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Thesis submitted for the award of the degree of

DOCTOR OF PHILOSOPHY

from

ECOLE POLYTECHNIQUE

in the field of

CHEMISTRY

by

Florin Marian ISTRATE

DEVELOPMENT OF NEW TRANSFORMATIONS CATALYZED BY GOLD(I) COMPLEXES

Presented on November 3rd, 2009 to a committee composed of:

Dr. Geneviève BALME – President of the committee
Dr. Benoît CROUSSE – Referee
Dr. Yvan SIX – Referee
Dr. Samir Z. ZARD – Examiner
Dr. Fabien L. GAGOSZ – Examiner

The work described in this thesis was carried out at the Laboratory of Organic Synthesis (DCSO), Ecole Polytechnique, Palaiseau (France) under the supervision of Dr. Fabien L. Gagosz and Prof. Dr. Samir Z. Zard.

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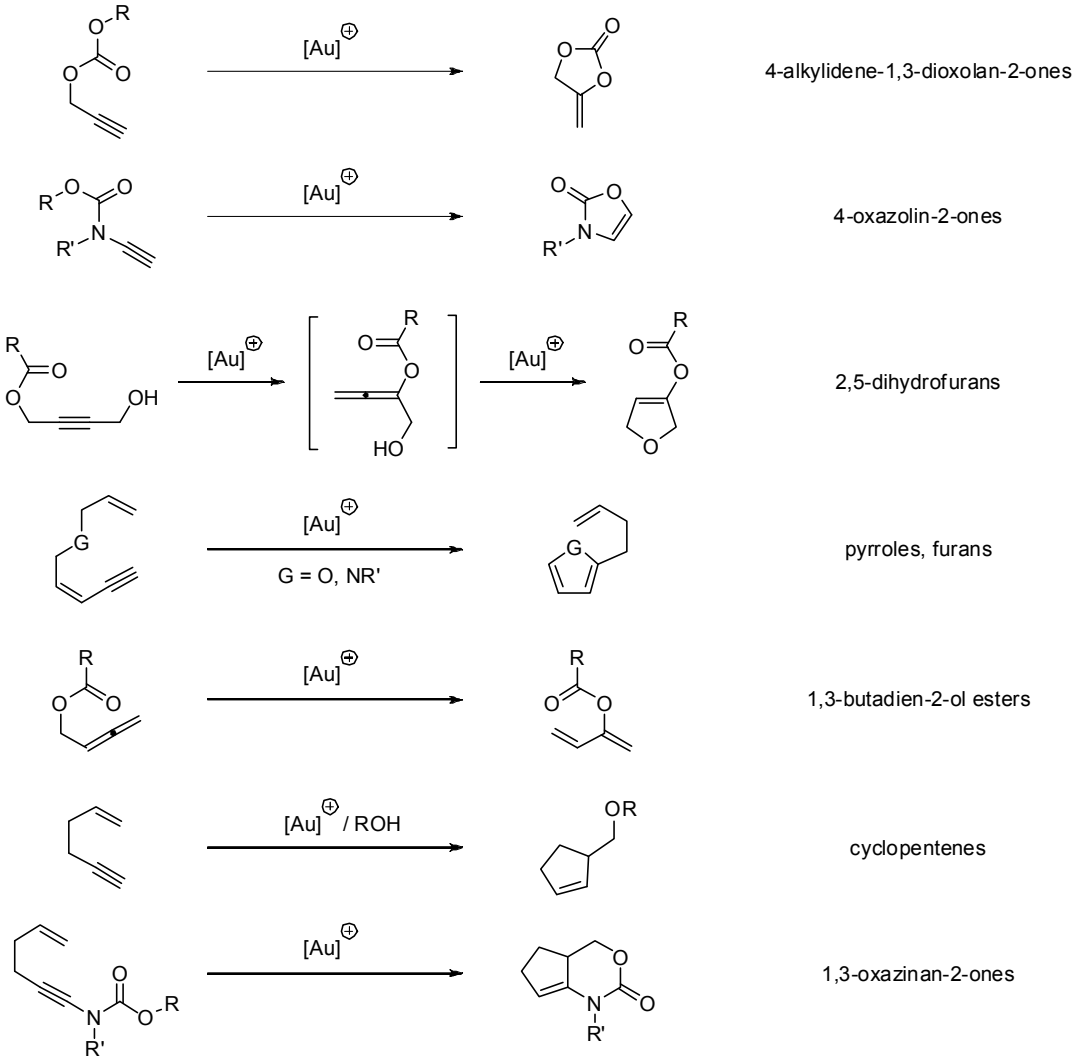
Abstract

Gold complexes have emerged in the last few years as excellent catalysts in numerous homogeneous transformations involving the activation of carbon-carbon multiple bonds towards the attack of a large variety of nucleophiles (Chapter 1). Following the discovery by Dr. Fabien L. Gagosz of a new type of air-stable, crystalline and highly reactive cationic gold(I)-catalysts possessing a triflimide counteranion (Chapter 2), our team took a keen interest in the development of new transformations catalyzed by these complexes.

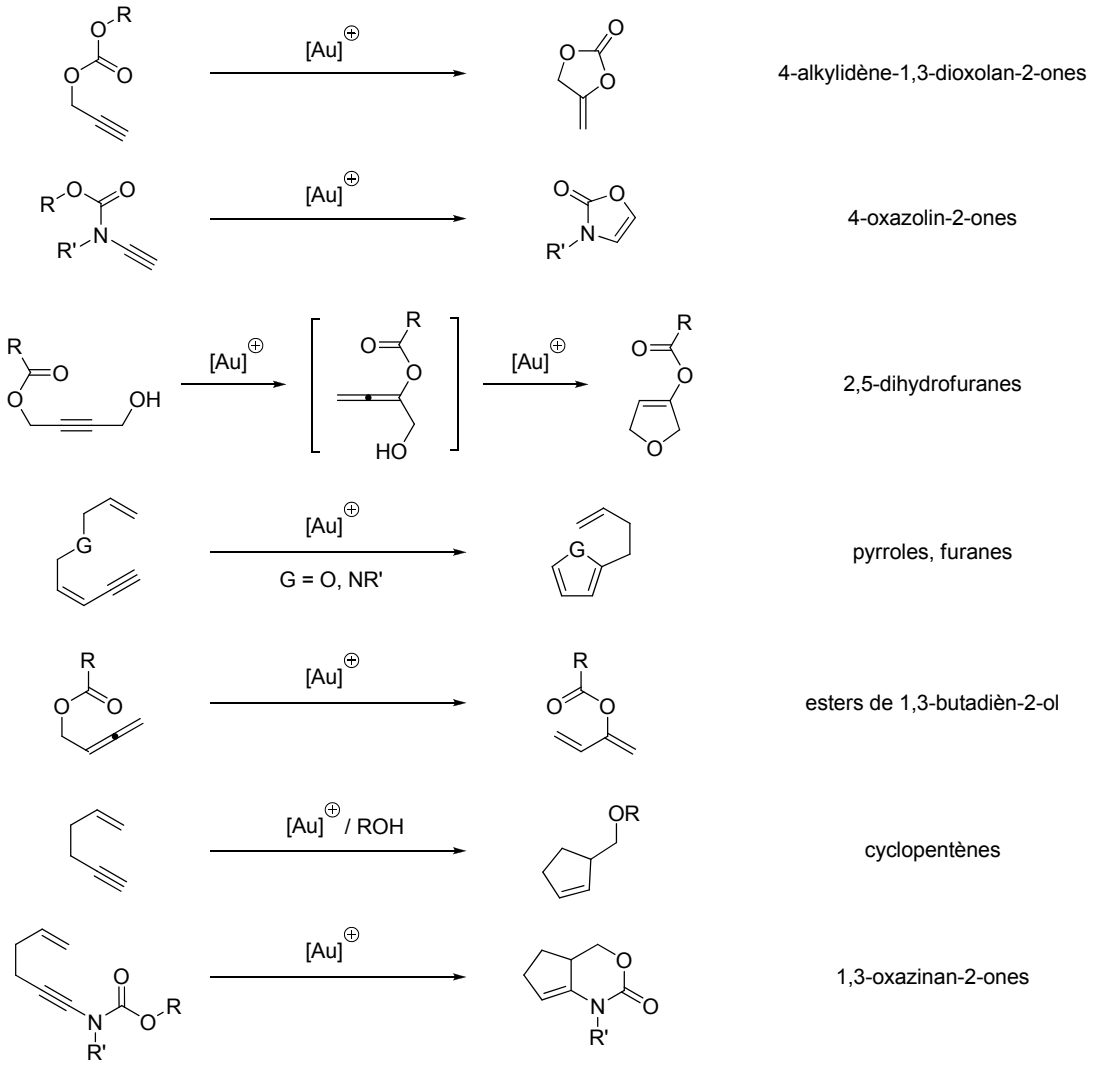
This manuscript presents some of the work carried out in this area, which led to the discovery of new methods for the synthesis of various heterocycle and carbocycle derivatives, such as 4-alkylidene-1,3-dioxolan-2-ones (Chapter 3), 4-oxazolin-2-ones (Chapter 4), 2,5-dihydrofurans (Chapter 5), pyrroles and furans (Chapter 6), 1,3-butadien-2-ol esters (Chapter 7), cyclopentenes (Chapter 8) and 1,3-oxazinan-2-ones (Chapter 9).



Résumé

Dans les dernières années, les complexes d'or se sont avérés des excellents catalyseurs pour des nombreuses transformations homogènes impliquant l'activation des liaisons carbon-carbon multiples vis-à-vis de l'attaque des différents nucléophiles (Chapitre 1). Suite à la découverte par le Dr. Fabien L. Gagosz d'une nouvelle classe de catalyseurs cationiques d'or(I), cristallins, stables à l'air et très réactifs, ayant un groupement triflimide comme contre-anion (Chapitre 2), notre équipe s'est intéressée au développement de nouvelles transformations catalysées par ces complexes.

Ce manuscrit présente une partie du travail effectué dans ce domaine qui a mené à la découverte de nouvelles méthodes pour la synthèse des différents dérivés hétéro- et carbocycliques, tels que les 4-alkylidène-1,3-dioxolan-2-ones (Chapitre 3), les 4-oxazolin-2-ones (Chapitre 4), les 2,5-dihydrofuranes (Chapitre 5), les pyrroles et les furanes (Chapitre 6), les esters de 1,3-butadièn-2-ol (Chapitre 7), les cyclopentènes (Chapitre 8) ou bien les 1,3-oxazinan-2-ones (Chapitre 9).



Acknowledgment

I would like to use this occasion to thank Prof. Dr. Samir Z. Zard, Head of the Chemistry Department at Ecole Polytechnique and Director of the Laboratory of Organic Synthesis (DCSO), for believing in me and for giving me the opportunity to work here during my Ph. D.

I wish to express my deepest gratitude to my advisor, Dr. Fabien L. Gagosz, for his support and guidance throughout all these years. His availability, dynamism, enthusiasm and encouragement have been of great value for me. Our extensive discussions around my work have been very helpful during this research project.

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Palaiseau August 26th, 2009

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CHAPTER

1

Gold Homogeneous Catalysis: an Introductory Overview

*"All that glitters may not be gold, but at least it contains free electrons" (**John Desmond Bernal**, Irish physicist)*

The gold homogeneous catalysis is a fascinating field of chemistry that underwent a tremendous development in the last years, a true "golden era". This chapter is intended to give a brief overview of this exceptional subject and to identify some of the most important applications of homogeneous gold catalysts in organic synthesis.

1. Gold – a precious metal

Gold has been present in the collective conscience of mankind since the beginning of known history. It always exerted a deep fascination, being associated with beauty, wealth, authority, or even magic.

Over the years, the desire to possess this metal led to many gold rushes, rivalries, wars, but also scientific discoveries. Alchemy in particular, whose main goal was to produce gold starting from other metals, is considered nowadays as the precursor of modern chemistry.

Gold's power of attraction probably comes from its aspect. It is one of the few metals to have in pure state a color different than gray or silver. Elementary gold has a bright yellow color and luster, maintained without oxidizing in air or water.

Due to its inertness it is estimated that some 80% of gold found on Earth is in its elemental state. The metal occurs as nuggets or grains in rocks, in veins and in alluvial deposits (Figure 1.1). However it is quite rare, which contributes as well to its power of attraction. Its average concentration in the Earth's crust is 0.004 parts per million.[1] It was estimated that just 161 000 t of gold were ever mined

[1] Earnshaw, A.; Greenwood, N. In *Chemistry of the Elements*; 2nd ed.; Butterworth-Heinemann: 1997.

so far in the whole world (at the end of 2007).[2] That's the weight of a gold cube with an edge length of just 20.28 m!

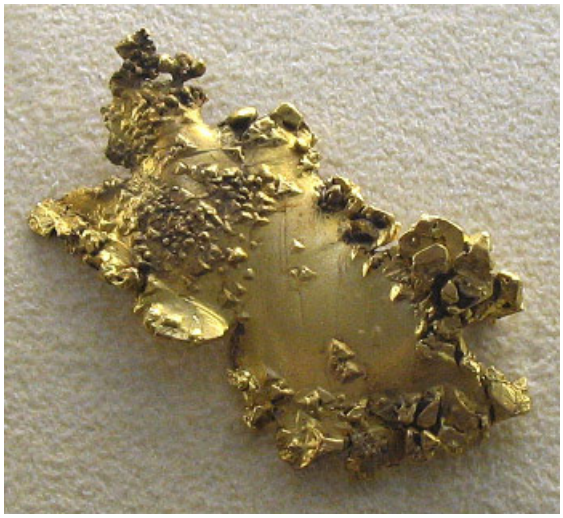


Figure 1.1. Gold nugget[3]

2. Uses of gold

The main use of gold was and still is in jewelry and decorative arts. Being unaffected by air, moisture and most corrosive reagents, gold is well suited either as base metal for various objects, or as a protective coating on other more reactive materials. Being the most malleable and ductile of all metals, gold can be beaten into very fine sheets (gold leafs for gilding) or made into thread (and used in embroidery). However, because of its softness in pure state, it is often mixed with other metals (such as silver, copper, aluminum, nickel, palladium etc.) in order to modify its physical properties.

Throughout the centuries gold was also used as a medium of monetary exchange (in the form of coins or bullions) and formed the basis for the gold standard up until the collapse of the Bretton Woods system in 1971. Even today many states hold gold in storage as a hedge against inflation or other economic disruptions. For instance the Federal Reserve Bank of New York has about 30 000 t of gold lying in its vaults (the largest gold reserve in the world).[4] Gold is also one of the most popular investments in the financial markets, either through direct ownership or indirectly through gold exchange-traded funds, certificates, accounts, spread betting, derivatives or shares.

Gold founds also numerous industrial applications. For instance, it is used as protective coating against radiation in the aeronautical and spatial industry, as heat shield in various high tech

[2] World Gold Council's website. Investing in gold. Demand and supply. http://www.invest.gold.org/sites/en/why_gold/demand_and_supply/ (accessed on July 1st, 2009)
[3] Source of the photo: Wikipedia.com website. Gold. Taken by Aram Dulyan at the Natural History Museum in London. http://en.wikipedia.org/wiki/File:Native_gold_nuggets.jpg (accessed on July 1st, 2009).
[4] Dube, R. K. *J. Mater. Process. Technol.* **2001**, *110*, 249-251.

industries (including in Formula 1 cars), as reflective layer on some optical devices, as coloring agent in special types of glass, or as toner in photography.

However, the most important industrial applications are found in electronics. Due to its excellent conductivity and its good general chemical resistance, gold is employed as a thin layer coating for electrical connectors, switch and relay contacts, connecting wires and connection strips of all kinds and for bondwiring semiconductors.

Gold is also used in medicine. Radioactive gold isotopes are sometimes utilized in diagnosis, while several gold complexes proved to be active against cancer[5] or arthritis.[6] In dentistry, gold alloys are often employed for fillings, crowns, bridges and orthodontic appliances.

High quality pure metallic gold is non-toxic and non-irritating and can be used in food, having the E175 label.[7] However, it is tasteless and it does not have any other nutritional effect, leaving the body unaltered.

Figure 1.2 shows a breakdown of the gold demand between 2003-2007 by first use (5 year average).[8]

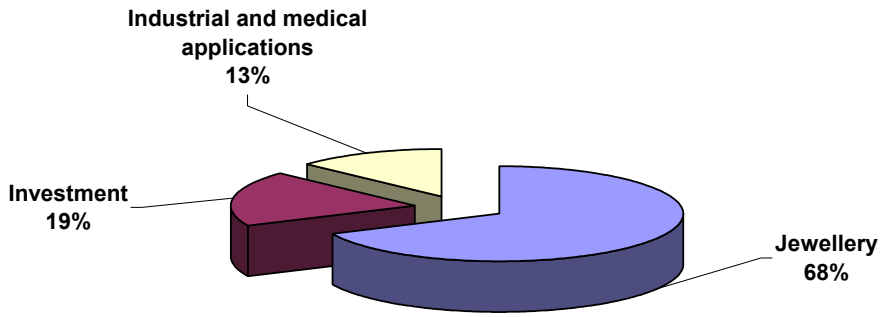


Figure 1.2. Gold demand by first use between 2003-2007 (5 year average)

3. Gold in organic chemistry

Unfortunately, in modern organic chemistry gold has lived in the shadow of other metals for a long time. It was the victim of several misconceptions, being considered for instance rare and expensive, but also chemically inert (especially with non-metals like carbon, hydrogen or oxygen).

[5] Casini, A.; Hartinger, C.; Gabbiani, C.; Mini, E.; Dyson, P. J.; Keppler, B. K.; Messori, L. *J. Inorg. Biochem.* **2008**, *102*, 564-575.
[6] Messori, L.; Marcon, G. In *Metal ions and their complexes in medication*; Sigel, A., Ed.; CRC Press: 2004, p 280-301.
[7] Food Standards Agency's web site. Current EU approved additives and their E Numbers. http://www.food.gov.uk/safereating/chemsafe/additivesbranch/enumberlist (accessed on July 1st, 2009)
[8] Source of the data: World Gold Council's website. Investing in gold. Demand and supply. http://www.invest.gold.org/sites/en/why_gold/demand_and_supply/ (accessed on July 1st, 2009

Of course, gold is a rare metal, but several other precious metals like ruthenium, palladium, rhodium, platinum, osmium or iridium are very rare as well (Figure 1.3). However they are widely used in organic chemistry.

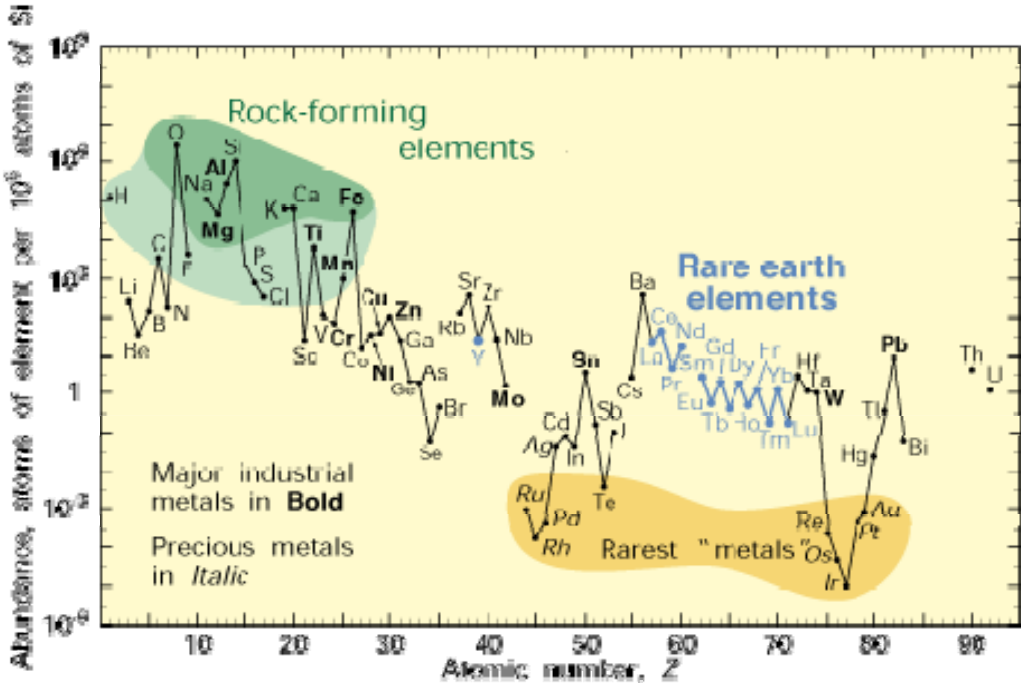


Figure 1.3. Relative abundance (atom fraction) of the chemical elements in Earth's upper continental crust as a function of atomic number.[9]

Furthermore, the price of gold is not as high as one might believe compared to the other precious metals. For instance platinum and rhodium are even more expensive (Figure 1.4).

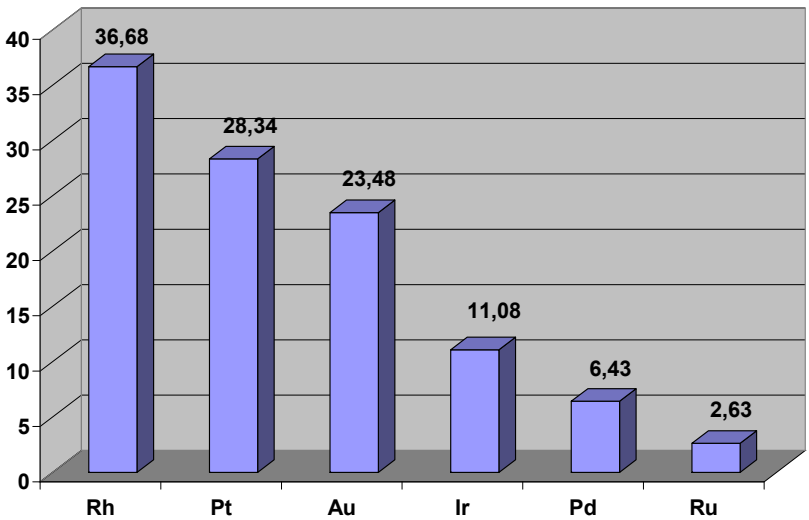


Figure 1.4. The prices of several precious metals on July 1st, 2009 (in €/g)[10]

[9] Source of the graph: U.S. Geological Survey's website. Fact Sheet 087-02. Rare Earth Elements - Critical Resources for High Technology. http://pubs.usgs.gov/fs/2002/fs087-02/ (accessed on July 1st, 2009)

Three additional factors have to be considered here. First of all, gold is not used in organic chemistry in its elementary state, but as a complex. These complexes are in most of the cases obtained from gold(I) or gold(III) salts, which can be sometimes cheaper to produce than the pure metal (e.g. $Na[AuCl_4]$). Second of all, in organometallic catalysis very often the price of the ligand is higher than the price of the metal itself. And finally, given the current supply of gold compared to the other precious metals (Figure 1.5), it is clear that a sudden increase in demand due to its large scale use in a new chemical industrial process would only marginally influence its current price (the same thing cannot be said about the other metals).

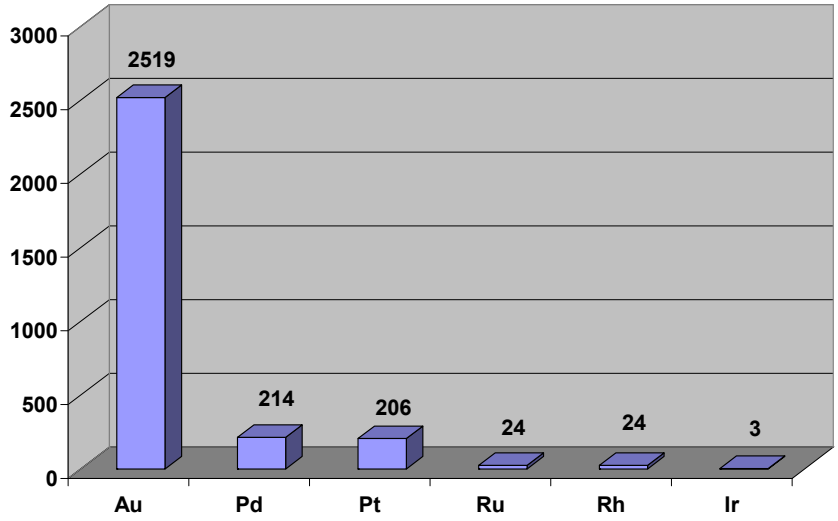


Figure 1.5. The production of several precious metals in 2005 (in tonnes)[11]

Concerning its reactivity, gold has a rich chemistry which includes a large number of fascinating compounds (complexes, organometallic derivatives, clusters, materials, alloys etc.) and various transformations (substitutions, oxidations, eliminations, thermical decompositions, isomerizations, hydrolysis or acidolysis reactions, insertions etc.).[12]

For economical reasons, the catalytical transformations involving gold are of course much more interesting than the stoechiometrical ones (even though some recycling methods for gold in stoechiometrical transformations are available). Examples of catalysis by gold salts are known since the beginning of the last century,[13] but, despite the evidence, the chemists continued to consider gold as "catalytically dead" because its stability in elementary state.

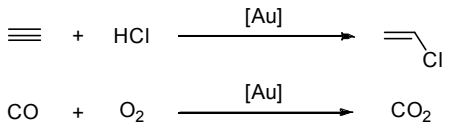
[10] Source of the data: Heraeus Precious Metal Portal web site. Prices and Charts. https://www.hmgcss.de/WCH2/HMG/edelpreis.nsf/EMPDat/$First?Open (accessed on July 1st, 2009)

[11] Source of the data: Folkerts-Landau, D. *A User Guide To Commodities*, Deutsche Bank, July 2006.

[12] For some reviews and books, see:
(a) Parish, R. V. *Gold Bull.* **1997**, *30*, 3-12.
(b) Parish, R. V. *Gold Bull.* **1997**, *30*, 55-62.
(c) Parish, R. V. *Gold Bull.* **1998**, *31*, 14-21.
(d) Elschenbroich, C. *Organometallics*; 3rd ed.; Wiley-VCH, 2006.
(e) Patai, S.; Rappoport, Z. *The Chemistry of Organic Derivatives of Gold and Silver*; Wiley, 1999.

[13] Bone, W. A.; Wheeler, R. V. *Philos. Trans. R. Soc. London, Ser. A* **1906**, *206*, 1-67.

All changed in the beginning of the 1970's when several successes in the area of *heterogeneous catalysis* fundamentally modified this perception. From that moment on, heterogeneous gold catalysis underwent an exceptional development.[14,15] Various applications such as the hydrochlorination of ethyne to vinyl chloride, or the low temperature oxidation of carbon monoxide have a huge industrial importance nowadays (Scheme 1.1).



Scheme 1.1. Two important industrial applications of heterogeneous gold catalysis

Closely related to the heterogeneous catalysis is the *nanoscale catalysis*. Gold also played an important role in the development of this discipline, with gold nanoparticles being probably the most frequently used after the silicon ones.[16]

However, the most interesting area of application of gold in organic chemistry may be the *homogeneous catalysis*.[14,17] It wasn't until about 10 years ago that this field started to come into

[14] For some reviews on gold catalysis in general, see:
(a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896-7936.
(b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180-3211.
(c) Hutchings, G. J.; Brust, M.; Schmidbaur, H. *Chem. Soc. Rev.* **2008**, *37*, 1759-1765.
(d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266-3325.

[15] For some reviews on gold heterogenenous catalysis, see:
(a) Hutchings, G. J. *Chem. Commun.* **2008**, 1148-1164.
(b) Thompson, D. *Gold Bull.* **1998**, *31*, 111-118.
(c) Thompson, D. *Gold Bull.* **1999**, *32*, 12-19.
(d) Bond, G. C. *Catal. Today* **2002**, *72*, 5-9.
(e) Schwank, J. *Gold Bull.* **1985**, *18*, 2-10.
(f) Bond, G. C. *Gold Bull.* **1972**, *5*, 11-13.

[16] For some reviews on gold nanocatalysis, see:
(a) Chen, M. S.; Goodman, D. W. *Catal. Today* **2006**, *111*, 22-33.
(b) Burda, C.; Chen, X.; Narayanan, R.; El-Sayed, M. A. *Chem. Rev.* **2005**, *105*, 1025-1102.
(c) Grzelczak, M.; Perez-Juste, J.; Mulvaney, P.; Liz-Marzan, L. M. *Chem. Soc. Rev.* **2008**, *37*, 1783-1791.
(d) Chen, M. S.; Goodman, D. W. *Chem. Soc. Rev.* **2008**, *37*, 1860-1870.
(e) Corma, A.; Garcia, H. *Chem. Soc. Rev.* **2008**, *37*, 2096-2126.

[17] For some reviews on homogeneous gold catalysis, see:
(a) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885-3903.
(b) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847-7870.
(c) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333-346.
(d) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51-65.
(e) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.
(f) Hoffmann-Roder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387-391.
(g) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3-9.
(h) Dyker, G. *Angew. Chem.* **2000**, *39*, 4237-4239.
(i) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326-3350.
(j) Hashmi, S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766-1775.
(k) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem. Int. Ed.* **2006**, *45*, 200-203.
(l) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2005**, *44*, 6990-6993.
(m) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271-2296.
(n) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, *2006*, 4555-4563.
(o) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916-5923.
(p) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431-436.

attention. Despite that, an impressive number of papers have appeared on this topic in the last few years, generating a true "gold rush".

Compared to heterogeneous catalysis, the homogeneous catalysis presents a certain number of advantages.

For instance, all the components of the reaction are in the same phase, which eliminates the previous problems related to the absorption / desorption processes from the surface of the catalyst. The transformations can be performed under very mild conditions (temperature, pressure etc.) and generally a better selectivity for the functional groups of the substrate can be observed.

The difficulties linked to the preparation of the heterogeneous catalysts (e.g. the deposition method of the active species on the support, the characteristics of the surface, the size of the nanoparticles etc.) are completely eliminated. The homogeneous catalysts are simple and well defined, which allows a better reproducibility of the experiments and facilitates the comparison between different catalytic systems.

Homogeneous gold catalysis proved also to be better adapted for complex transformations. Highly functionalized substrates can be used, making this type of reactions very interesting for the synthesis of fine chemicals.

4. Theoretical aspects of gold homogeneous catalysis

The unique properties of gold catalysts arise from the special nature of the metal center. Gold has the electronic configuration [Xe] $4f^{14}$ $5d^{10}$ $6s^{1}$. Its oxidation states can vary from −1 to +5, but the most common ones are by far +1 and +3.

The theories of frontier orbitals and of relativity[18] have helped rationalize some of these properties. They can account for instance for the strong contraction of the 6s and 6p orbitals, the electrons located in these orbitals (if present) being closer to the nucleus and having greater ionization energies. These theories can also explain the expansion of the 5d and 4f orbitals (which see a weaker nuclear attraction, being shielded by the 6s and 6p orbitals) and their fine splitting (a consequence of

(q) Echavarren, A. M.; Mendez, M.; Munoz, M. P.; Nevado, C.; Martin-Matute, B.; Nieto-Oberhuber, C.; Cardenas, D. J. *Pure Appl. Chem.* **2004**, *76*, 453-463.
(r) Marion, N.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2750-2752.
(s) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776-1782.
(t) Bruneau, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 2328-2334.
(u) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351-3378.
(v) Bongers, N.; Krause, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 2178-2181.

[18] For some reviews on the theoretical chemistry of gold, see:
(a) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395-403.
(b) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412-4456.
(c) Pyykkö, P. *Inorg. Chim. Acta* **2005**, *358*, 4113-4130.

the spin-orbit interaction). Pyykkö et al. estimated that these relativistic effects are more significant for gold than for any other transition metal.[19]

One direct consequence is that gold atoms are less electropositive and form stronger gold – ligand bonds compared to other group 11 metals. They can also interact with each other, forming Au-Au interactions of the same intensity as the hydrogen bonds ("aurophilicity").

Another even more important consequence is that gold complexes are excellent Lewis acids. However, because of their large diffuse orbitals, they prefer orbital instead of charge interactions. Thus they can be considered "soft" Lewis acids, reacting preferentially with "soft" species (such as π-systems) and being less oxophilic. They have a particular affinity for alkynes and allenes, even in the presence of other functional groups. This exceptional functional group tolerance allows the use of complex and highly functionalized substrates.

Gold has therefore the ability to selectively activate alkynes and allenes towards the attack of various nucleophiles, but its reactivity goes beyond that of a simple soft Lewis acid. Gold complexes can also stabilize the cationic reaction intermediates thus formed by backdonation. The non-classical nature of these intermediates together with a low propensity to give β-hydride eliminations frequently results in excellent reactivities and selectivities.

Gold complexes present sometimes a very particular reactivity, allowing transformations which are not possible with other transition metals. In the cases where several transition metals can catalyze the same transformation, gold usually gives faster and/or more selective transformations. This superior activity is also due to relativistic effects and cannot be explained merely by a faster ligand-exchange rate.[20]

Homogeneous gold catalysis usually allows a rapid increase in structural complexity starting from very simple substrates. Complicated skeletal rearrangements can be involved in these transformations. Unfortunately, this type of catalysis can be sometimes highly substrate dependant.

Gold(I) and gold(III) complexes have high oxidation potentials. Being also less oxophilic, they tolerate very well the presence of oxygen, air, water or alcohols, and have a higher stability in the reaction conditions. The reactions catalyzed by these complexes are therefore very easy to set up, being usually air and moisture tolerant, and can be performed in an "open flask". The insensitivity of gold complexes to various oxygenated solvents has been exploited sometimes to develop eco-friendly chemical reactions using water or alcohols as a solvent ("green chemistry").

The reaction conditions involved in homogeneous gold catalysis are usually very mild: room temperature or very gentle heating, low catalyst loadings, relatively short reaction times. The scale-up of transformations is relatively easy as well. The experiments can be followed by NMR since both gold(I) and gold(III) atoms are diamagnetic. Another advantage is the reduced toxicity of gold complexes compared to other transition metals.

The L-Au^+ fragment, often involved in homogeneous gold catalysis, is isolobal to H^+ and presents sometimes the behavior of a "big soft proton". Therefore gold catalysis can be applied, at least in

[19] Pyykko, P.; Desclaux, J. P. *Acc. Chem. Res.* **1979**, *12*, 276-281.
[20] Au(I) and Au(III) ligand exchange reactions follow an associative pathway and are very fast.

theory, to a large number of transformations known to be catalyzed by acidic conditions or Lewis acids.[21]

5. Classification of the homogeneous gold catalysts

Gold homogeneous catalysts mainly exist in +1 and +3 oxidations states. Complexes of both types proved to be active in a large number of transformations and were extensively used, as we shall see next.

Although providing a comprehensive list of all known gold complexes active in homogeneous catalysis is beyond the scope of this manuscript, the following paragraphs will contain a personal selection of the most popular ones.

5.1. Gold(III)-catalysts

Gold(III)-catalysts are d^8 complexes and have either the AuX_3, AuX_4^- or the $LAuX_3$ composition. Usually they prefer a square planar, tetracoordinated geometry. Their usage is less-frequent compared to the gold(I)-catalysts, fact that can be attributed to a reduced specificity and/or activity in some cases.

The most common gold(III) catalyst is probably the commercially available $AuCl_3$, which exists a as a dimer Au_2Cl_6 with two μ-Cl ligands (Figure 1.6).[22] Similarly, $AuBr_3$ or the cationic complex $Au(OTf)_3$ (formed *in situ* from $AuCl_3$ and AgOTf) have also been employed.

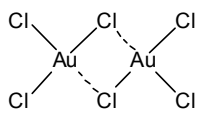


Figure 1.6. Dimeric Au_2Cl_6

Tetrachloroauric acid and its tetrachloroaurates derivatives are another type of gold(III)-catalysts (Figure 1.7). These complexes are probably the cheapest available source of Au(III) and were often used in the early years of homogeneous gold catalysis. Today however their use is limited because they can generate a large number of side-products.

$H[AuCl_4]$ $Na[AuCl_4]$ $[n\text{-}Bu_4N][AuCl_4]$

Figure 1.7. Tetrachloroauric acid and its tetrachloroaurates derivatives

[21] Hashmi, A. S. K. *Catal. Today* **2007**, *122*, 211-214.
[22] $AuCl_3$ can be either an homogeneous or a heterogeneous catalyst, depending on the solvent employed. It is well soluble especially in coordinating solvents (like H_2O, EtOH etc.).

Various anionic and neutral organometallic gold(III) compounds have been equally reported, but found few applications so far (Figure 1.8).[23]

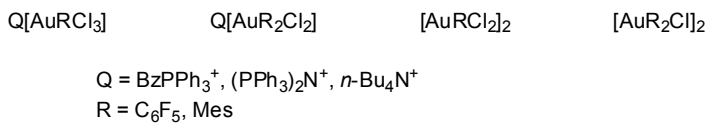


Figure 1.8. Various anionic and neutral organometallic gold(III) compounds

More appealing are the gold(III) complexes functionalized with a pyridine ligand.[24] Some examples are presented in Figure 1.9.

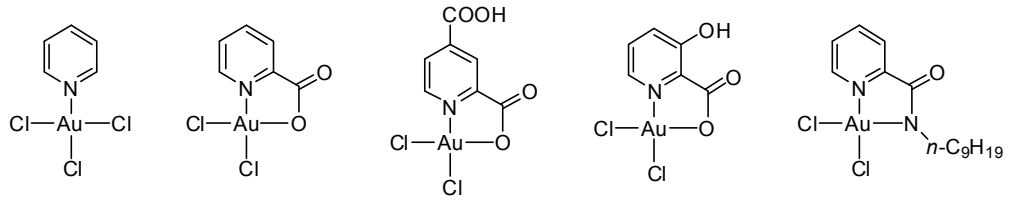


Figure 1.9. Gold(III) complexes functionalized with a pyridine ligand

Gold(III) complexes possessing an *N*-heterocyclic carbene ligand seem to be promising catalysts as well (Figure 1.10).[25]

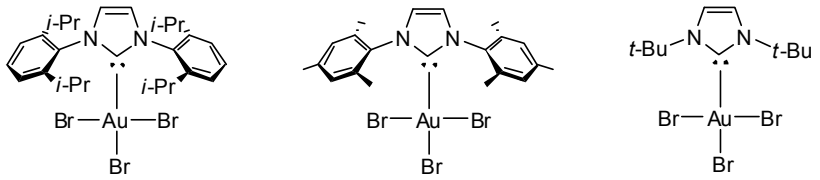


Figure 1.10. Gold(III) complexes possessing an *N*-heterocyclic carbene ligand

5.2. Gold(I)-catalysts

Gold(I)-catalysts are d^{10} complexes and have either the LAuX or the L_2Au^+ composition. They present a linear, bicoordinated geometry.

AuCl is the simplest commercially available source of Au(I). It exists in a polymeric form as a chain with μ-Cl ligands bridging between the gold atoms (Figure 1.11). Although it is bench stable, its use is rather limited due to its easy reduction to Au(0) and its modest activity in some reactions.

[23] Casado, R.; Contel, M.; Laguna, M.; Romero, P.; Sanz, S. *J. Am. Chem. Soc.* **2003**, *125*, 11925-11935.
[24] (a) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.
(b) Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem. Eur. J.* **2008**, *14*, 6672-6678.
[25] de Fremont, P.; Singh, R.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2007**, *26*, 1376-1385.

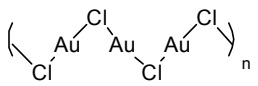


Figure 1.11. Polymeric chain of AuCl

Gold(I) complexes of LAuX composition usually need a strong σ-donor ligand in order to stabilize the metal center. The most common L ligands are phosphines or *N*-heterocyclic carbenes, although phosphites or arsines have been equally used. The X ligand generally has to be a weaker coordinating group, which can be easily displaced by the substrate during the catalysis reaction.

Depending on the nature of the Au-X bond, LAuX complexes can be either covalent (with X typically being a Cl) or cationic (for X = BF_4^-, PF_6^-, SbF_6^-, TfO^-, ClO_4^-, $(R_2O)P(O)O^-$ etc.). Figure 1.12 presents some of the most common gold(I) complexes with the LAuX composition, both covalent and cationic.

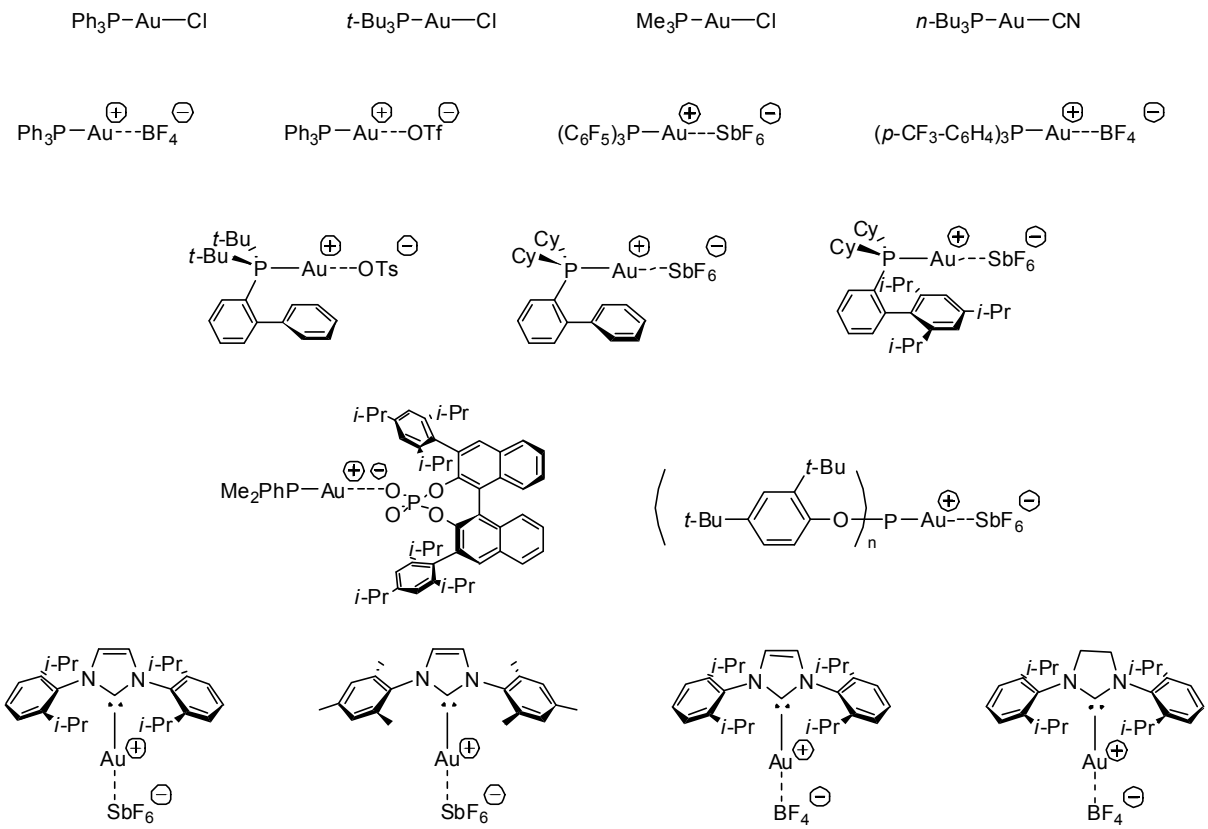


Figure 1.12. Some of the most common gold(I) complexes with LAuX composition

The gold(I) cationic complexes of this type are by far the most frequently used type of homogeneous gold catalysts. Despite their proven efficiency, these catalysts are sometimes quite unstable, especially when a fluorine-based counteranion is used,[26] and may not be isolable. As a consequence they are usually prepared *in situ*, as we shall see in the next chapter.

Recently, several dinuclear gold(I) catalysts have been successfully used in various transformations.[27]

[26] (a) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136.
(b) Baker, M. V.; Barnard, P. J.; Brayshaw, S. K.; Hickey, J. L.; Skelton, B. W.; White, A. H. *Dalton Transactions* **2005**, 37-43.
[27] (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260-11261.

They contain all a diphosphine ligand, being very similar with the mononuclear LAuX cationic gold(I) complexes previously described. Analogously, they are usually formed *in situ*. Excellent stereoselectivities were reported when chiral ligands and/or counteranions were used[28] (Figure 1.13).

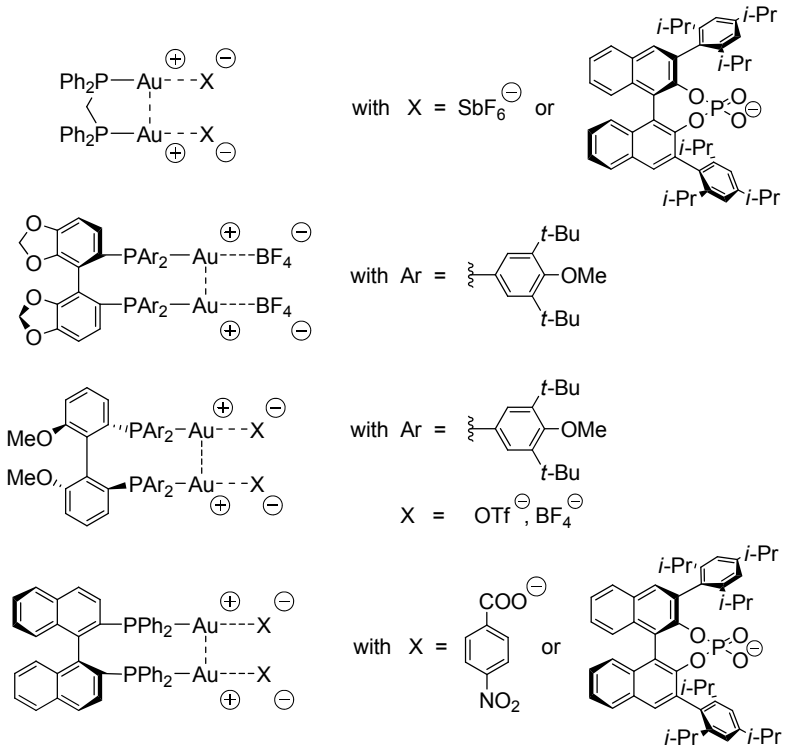


Figure 1.13. Dinuclear cationic gold(I)-phosphine catalysts

The catalysts of L_2Au^+ composition generally contain a gold(I) atom bicoordinated by two neutral ligands: a strong σ-donor one (typically a phosphine or an *N*-heterocyclic carbene) and a weakly coordinating one (usually a molecule of solvent such as acetonitrile, toluene or *p*-xylene, which can be easily displaced by the substrate during the catalysis reaction). These complexes are cationic and contain also a non-coordinating counteranion (usually SbF_6^- or PF_6^-) (Figure 1.14).

Being more stable than the previous LAuX cationic gold(I) complexes, they can be isolated and handled under ordinary conditions.[29] They proved very reactive in a variety of transformations and as a consequence were extensively used.[30] Their preparation will also be discussed in the next chapter.

(b) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452-2453.
(c) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496-499.

[28] Hashmi, A. S. K. *Nature* **2007**, *449*, 292-293.

[29] The stability of these complexes varies from one compound to another. NHC-substituted complexes seem to be less stable than the phosphine-substituted ones. See: de Fremont, P.; Stevens, E. D.; Fructos, M. R.; Diaz-Requejo, M. M.; Perez, P. J.; Nolan, S. P. *Chem. Commun.* **2006**, 2045-2047.

[30] (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148.
(b) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916-5923.
(c) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455-5459.

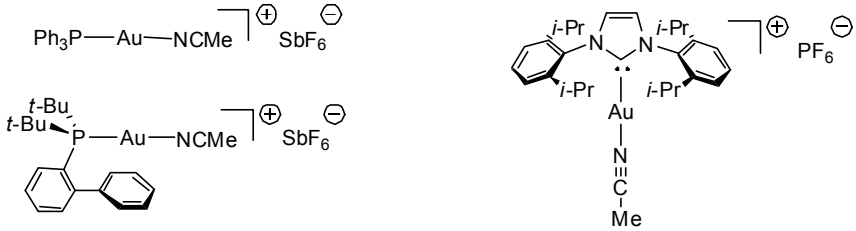


Figure 1.14. Some L_2Au^+ cationic gold(I) catalysts

Other polinuclear cationic gold(I) catalysts, stabilized by Au-Au interactions, have been reported as well, although their use remains rather limited so far.[31] Two examples are depicted in Figure 1.15.

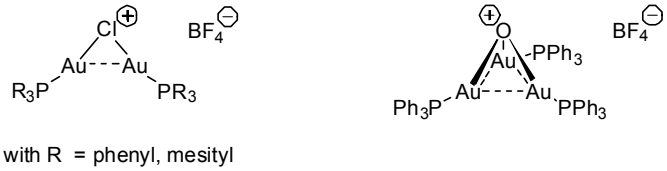


Figure 1.15. A few examples of polinuclear cationic gold(I) catalysts

6. Types of reactions involving homogeneous gold catalysts

6.1. General mechanism

Although there are many types of transformations catalyzed by homogeneous gold complexes, a vast majority of them proceed through some very similar mechanistic steps and involve the activation of a π-system (typically an alkyne or an allene, but sometimes even an alkene moiety) towards the attack of a nucleophile.

A general pathway for these transformations is given in Scheme 1.2.

The first step is always the formation of the catalyst's active species. While the precatalysts (typically gold(I) or gold(III) complexes) are well defined compounds, the exact nature of the active species is not entirely known.[32] Further investigations are needed in order to provide a definitive answer in this matter. This is the reason why the catalyst's active species will be denoted as [Au] for the rest of this manuscript.

(d) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.

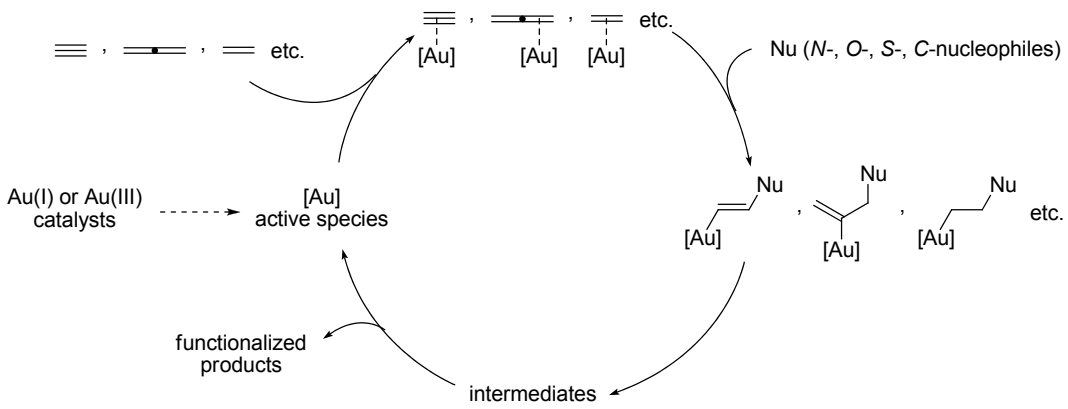
[31] (a) Hashmi, A. S. K.; Blanco, M. C.; Kurpejovic, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709-713.

(b) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132-8133.

(c) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978-15979.

[32] There are, for instance, studies suggesting that the active species of Au(III) catalysts are actually Au(I) complexes resulting from an *in situ* reduction. See for instance: Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, *2006*, 1387-1389.

The next step is the selective coordination of [Au] on the π-system, which renders this moiety more electrophilic and activates it for the nucleophilic attack.



Scheme 1.2. General mechanism encountered in many homogeneous gold-catalyzed transformations

The nucleophilic group can be nitrogenated (amines, imines etc.), oxygenated (alcohols, ethers, epoxides, aldehydes, ketones, esters etc.), sulfurated (thiols etc.) or carbonated (alkenes, alkynes, aryls, enols, enamines etc.). It can attack either in an inter- or in an intramolecular fashion. Given the excellent propensity of gold to undergo η^2 to η^1 migrations, the attack will result in the formation of two new C – [Au] and respectively C – Nu bonds.

What happens next depends on the exact nature of the organogold intermediate thus formed. As mentioned previously, it is stabilized by gold by back donation. Various rearrangements, transpositions, fragmentations, eliminations or further nucleophilic attacks are possible. The energetic differences between the various pathways are often quite small, which makes them difficult to predict, but also renders the gold chemistry so rich. Several additional new bonds may be formed and/or broken. The gold chemistry can also be easily combined with other transformations such as oxidations, reductions, concerted rearrangements etc.

The final step is always the regeneration of the active species and the formation of final products. This happens usually by protodemetallation from the organogold intermediates, although alternatively other electrophiles can be used to trap these derivatives or direct eliminations can take place.

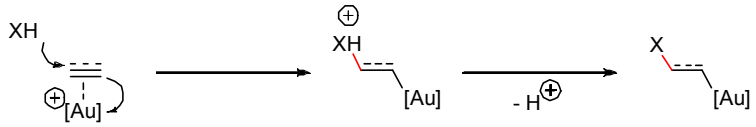
The rest of this chapter will try to show the extraordinary diversity of gold-catalyzed homogenous transformations. Although not intended to be a comprehensive review of the literature, the next sections contain a personal selection of some of the most representative examples, classified by the type of nucleophile and by mechanism.

6.2. Heteroatom attacks to C – C multiple bonds

C – C multiple bonds (alkyne, allene or even alkene moieties), in the presence of homogeneous gold catalysts, are usually good substrates for the attack of various heteroatom nucleophiles.

Simple heteroatom nucleophiles

The simplest case is when the heteroatom is sp^3-hybridized and bears a hydrogen atom. An *anti* attack takes place resulting in the formation of a gold intermediate and the loss of a proton (Scheme 1.3).



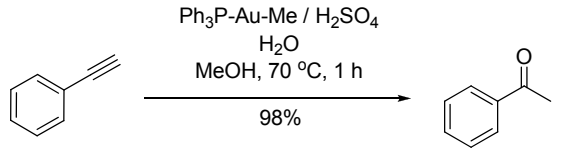
Scheme 1.3. Nucleophilic attack of a sp^3-hybridized heteroatom bearing a hydrogen atom (XH)

Although the gold intermediate can evolve in several ways, very often it undergoes an immediate protodeauration, giving the *trans* product corresponding to the formal addition of the XH group to the unsaturated C – C bond.

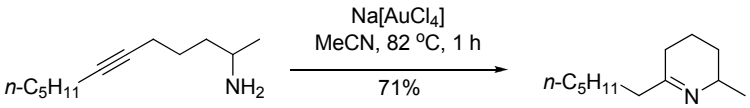
Various nucleophiles can react in this manner, including water, alcohols, ammonia, primary or secondary amines, thiols, primary and secondary amides and even carboxylic acids.

Intermolecular attacks lead to the formation of different ketones, enol ethers, ketals, enamines or imines. In the case of intramolecular attacks, different heterocycles are usually obtained, depending on the substitutions present on the substrate and on the size and nature of the linker joining the unsaturated C – C bond and the nucleophilic group. The 5-*endo*, 5-*exo* and 6-*exo* attacks are by far the most favorable and require usually very mild conditions.

Scheme 1.4 and Scheme 1.5 contain several examples involving various alkyne[33] and respectively allene[34] substrates.



(Eq. 1)

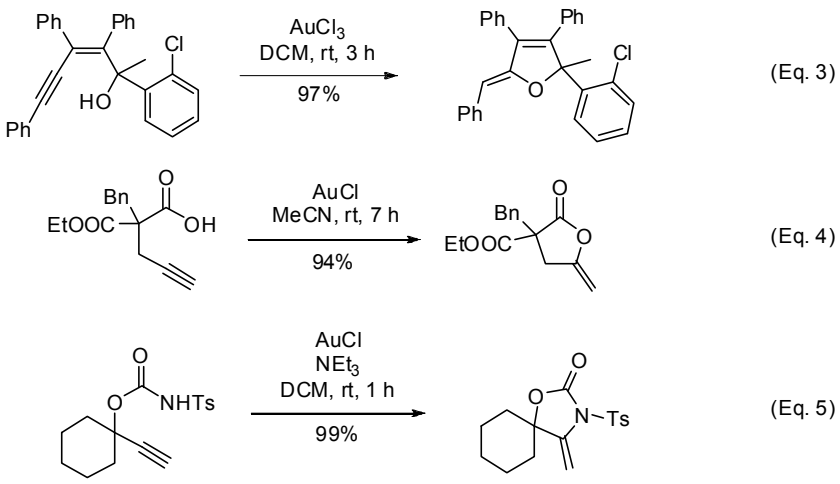


(Eq. 2)

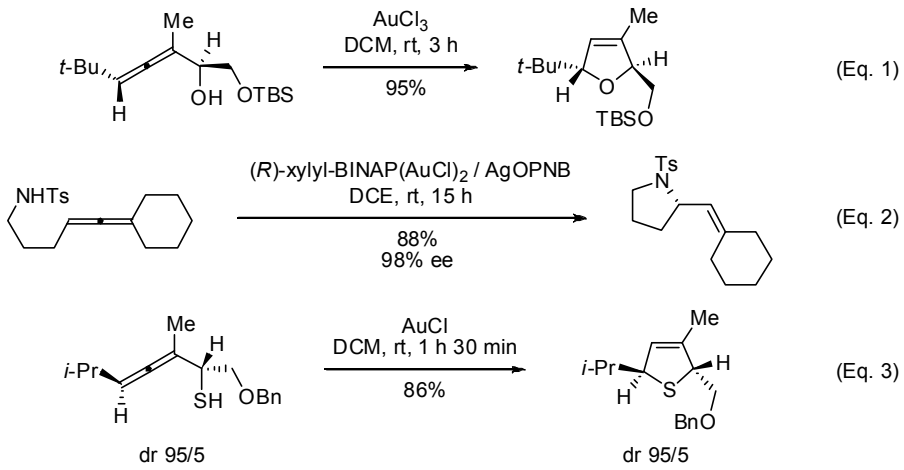
(continued on the next page)

[33] (a) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563-4565.
(b) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, *1991*, 975-978.
(c) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409-5412.
(d) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genet, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112-3113.
(e) Ritter, S.; Horino, Y.; Lex, J.; Schmalz, H.-G. n. *Synlett* **2006**, *2006*, 3309-3313.

[34] (a) Hoffmann-Roder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537-2538.
(b) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452-2453.
(c) Morita, N.; Krause, N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1897-1899.



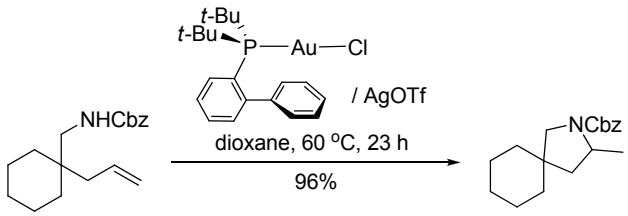
Scheme 1.4. A few gold-catalyzed nucleophilic attacks of XH groups onto alkyne substrates



Scheme 1.5. Some gold-catalyzed nucleophilic attacks of XH groups onto allene substrates

The regioselectivity of these reactions is often excellent and high enantioselectivities have been achieved in the case of cyclizations involving allenes.

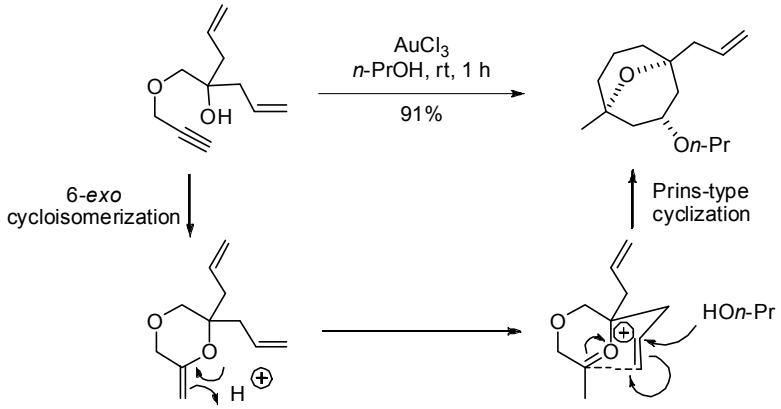
Other types of substrates containing C – C multiple bonds, like the alkene derivative presented in Scheme 1.6,[35] can be used as well, despite a somewhat lower reactivity.



Scheme 1.6. Example of a gold-catalyzed nucleophilic attack of an XH group onto an alkene substrate

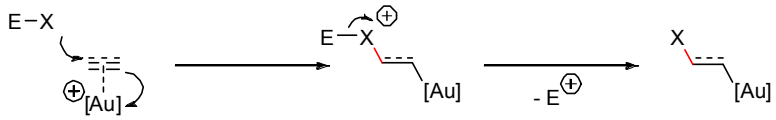
[35] Han, X.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1747-1749.

These reactions can of course be combined with other transformations. For example, a tandem process involving a 6-*exo* gold-catalyzed cycloisomerization followed by a Prins-type reaction is shown in Scheme 1.7.[36]



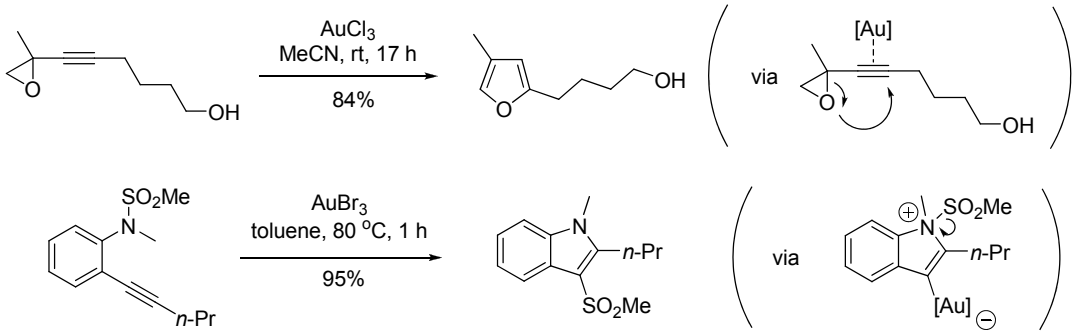
Scheme 1.7. Example of tandem process combining the XH group's nucleophilic attack on an alkyne moiety with Prins-type reaction

A very similar type of transformation involves sp^3-hybidrized heteroatoms substituted with an electrophilic group (Scheme 1.8). In this case the *anti* attack is followed by the fragmentation of the electrophilic moiety.



Scheme 1.8. Nucleophilic attack of an sp^3-hybridized heteroatom bearing an electrophilic group

The gold intermediate thus formed can rearrange directly (like in the example presented in Scheme 1.9, Eq. 1),[37a] or it can undergo an immediate demetallation by the E$^+$ group (as presented in Scheme 1.9, Eq. 2).[37b]



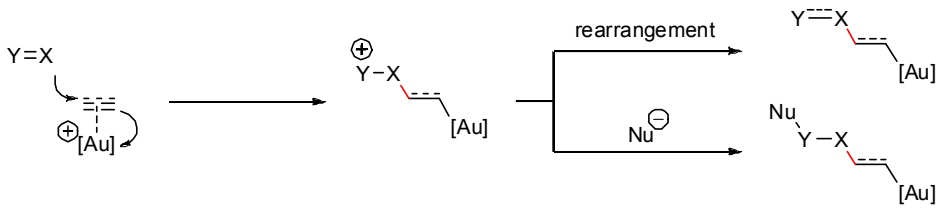
Scheme 1.9. Some examples of nucleophilic attacks of sp^3-hybridized heteroatoms bearing an electrophilic group

[36] Barluenga, J.; Diéguez, A.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2091-2093.

[37] (a) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432-438.
(b) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 2284-2287.

sp^2-Hybridized heteroatom nucleophiles

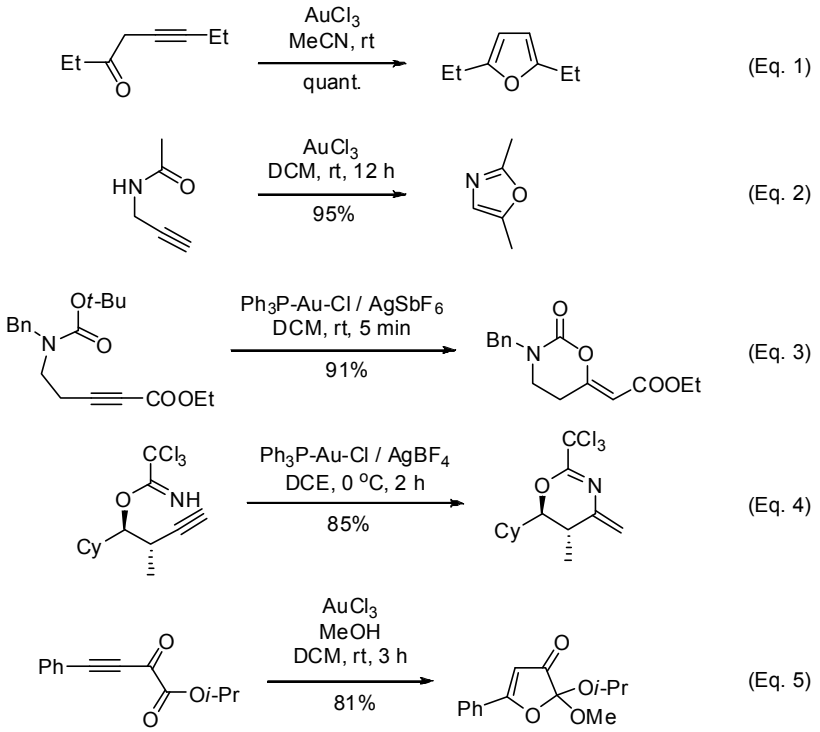
Another type of transformation involves sp^2-hybridized heteroatoms, such as carbonyl or imino groups. After the initial *anti* attack, a rearrangement or a second nucleophilic attack can take place (Scheme 1.10).



Scheme 1.10. Nucleophilic attack of a sp^2-hybridized heteroatom (Y=X)

Of particular interest is the intramolecular version of this transformation, which has been extensively used for the synthesis of a wide range of heterocycles. 5-*endo*, 5-*exo* and 6-*exo* attacks are the most common.

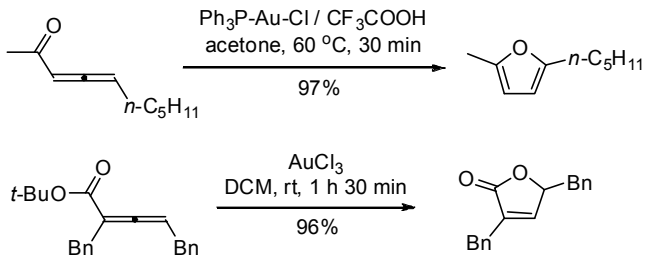
Scheme 1.11 presents a few intramolecular examples involving alkyne substrates and leading to the formation of furan (Eq. 1), oxazole (Eq. 2), oxazinone (Eq. 3), oxazine (Eq. 4) and furanone (Eq. 5) derivatives.[38]



Scheme 1.11. A few examples of nucleophilic attacks of sp^2-hybridized groups on alkyne moieties

[38] (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285-2288.
(b) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391-4394.
(c) Robles-Machin, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023-5026.
(d) Kang, J.-E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537-3540.
(e) Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445-3448.

Allenes derivatives can be used as well, as shown in Scheme 1.12.[39]



Scheme 1.12. A few examples of nucleophilic attacks of sp^2-hybridized heteroatoms on allene moieties

A special case of sp^2-hybridized nucleophiles is represented by ambidentate groups at the propargylic position.[40] The rearrangement in this case can be quite complex and involves either an *exo*-attack and the formation of carbenoid-gold intermediate[41] or an *endo*-attack giving an allene[42]. Both intermediates undergo further transformations afterwards (Scheme 1.13).

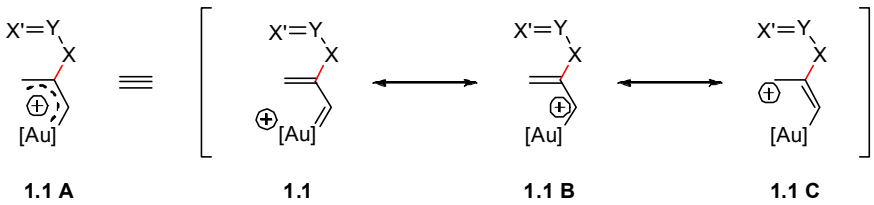
For instance, the example presented in Scheme 1.14 involves the formation of a carbenoid intermediate, which exhibits a carbene-type reactivity, reacting with an alkene and giving cyclopropane derivatives.[43]

---

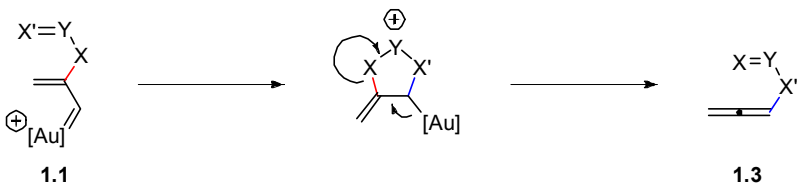
[39] (a) Zhou, C.-Y.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2005**, *8*, 325-328.
(b) Kang, J.-E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431-7433.

[40] For a review on propargylic esters in gold catalysis, see:
Marion, N.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2750-2752.

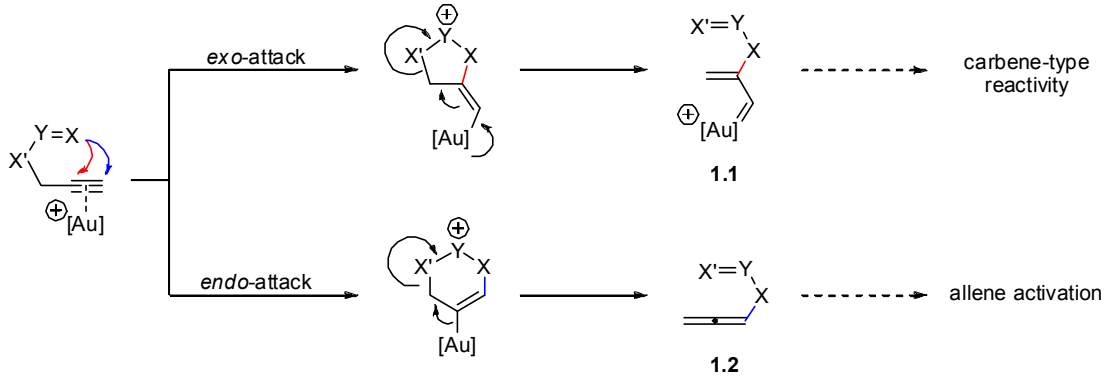
[41] The existence of a true gold carbene **1.1** (of Fischer type, as depicted in Scheme 1.13) is still debated. A non-classical carbenoid derivative **1.1 A** (with the positive charge delocalized on the gold atom and three other carbon atoms) can also be envisaged. Note that the carbene is one of its limit forms with a localized charge, the other two being an intermediate **1.1 B** with the positive charge at the vicinal carbon atom (stabilized by gold by backdonation) and another one **1.1 C** with the positive charge at the allylic carbon atom (resulting from the direct fragmentation of the C-X' bond). Depending on the transformation, one form might describe better than the others the exact nature of this intermediate. The carbene notation is used however for historical reasons and in order to insure the coherence with the literature.



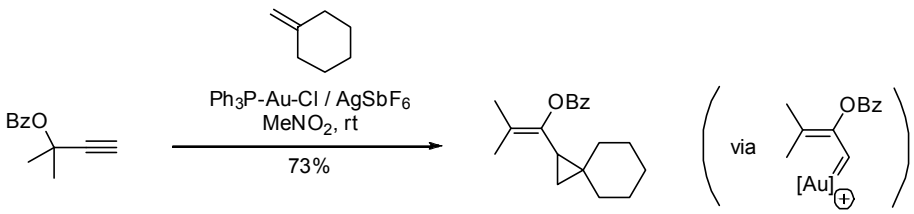
[42] An allene intermediate **1.3** can also be formed from the carbenoid intermediate **1.1** mentioned above via a second shift of the XYX' group. For a discussion see: Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718-721.



[43] Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

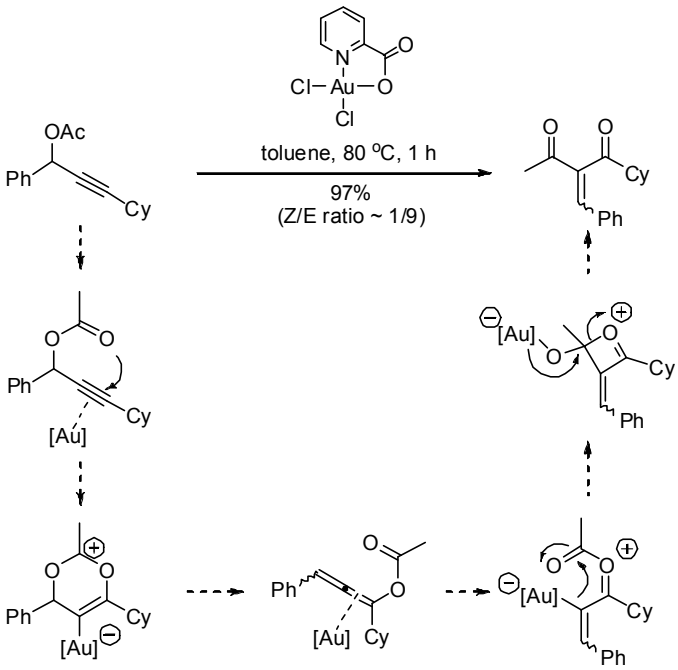


Scheme 1.13. Ambidentate groups at the propargylic position: a special case of nucleophilic attacks involving sp^2-hybridized heteroatoms



Scheme 1.14. Gold-catalyzed formation of cyclopropanes via carbenoid intermediates resulting from the rearrangement of propargylic benzoates

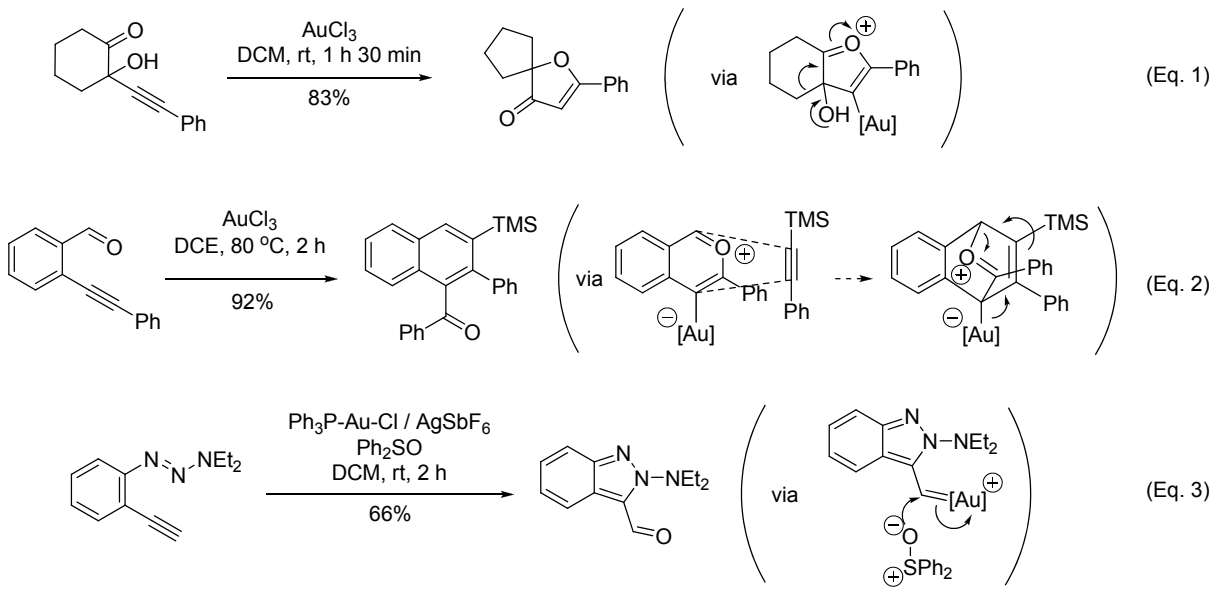
Scheme 1.15 shows another example in which an allene intermediate is formed. Subsequent activation by the gold catalyst leads to its rearrangement into an α-ylidene-β-diketone.[44]



Scheme 1.15. Gold-catalyzed formation of α-ylidene-β-diketones via allene intermediates resulting from the rearrangement of propargylic acetates

[44] Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414-8415.

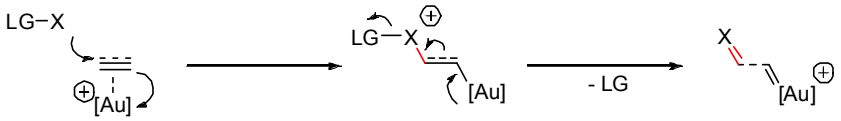
Various tandem reactions involving additional transformations, like 1,2-migrations (Scheme 1.16, Eq. 1), Diels-Alder cycloadditions (idem, Eq. 2) or oxidations (idem, Eq. 3) are also possible.[45]



Scheme 1.16. Tandem reactions involving nucleophilic attacks of sp^2-hybridized heteroatoms along with other transformations

Heteroatom nucleophiles bearing a leaving group

One last type of transformation involves heteroatom nucleophiles substituted with a leaving group. After the *anti* attack, the subsequent gold-assisted loss of the leaving group leads to the formation of a non-classical gold carbenoid intermediate which can evolve in several ways (Scheme 1.17).

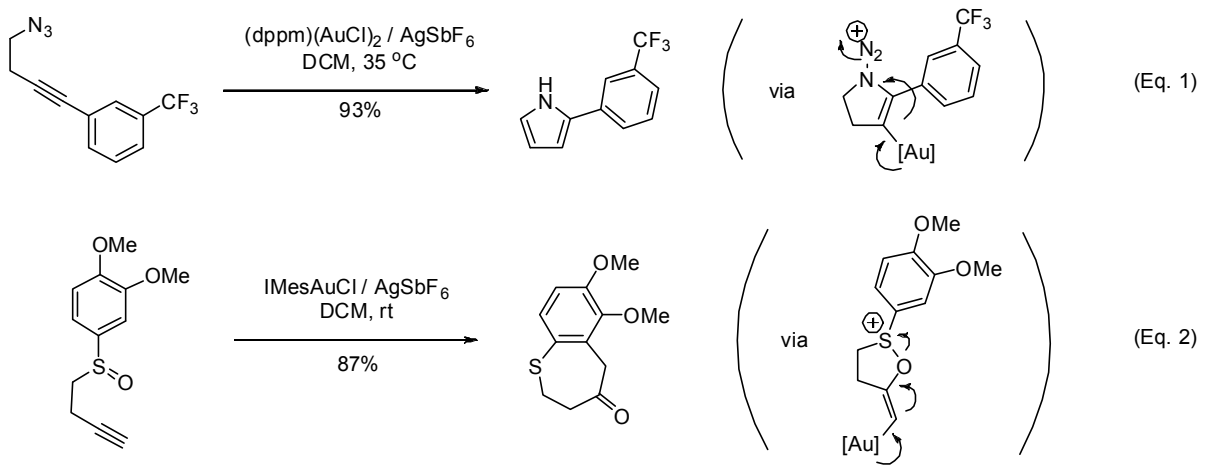


Scheme 1.17. Nucleophilic attack of heteroatoms bearing a leaving group (LG-X)

Scheme 1.18 shows two examples involving an azide (Eq. 1) and respectively a sulfoxide derivative (Eq. 2).[46]

[45] (a) Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 5878-5880.
(b) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650-12651.
(c) Witham, C. A.; Mauleon, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838-5839.

[46] (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260-11261.
(b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160-4161.



Scheme 1.18. Two examples of nucleophilic attacks involving leaving group-bearing heteroatoms

6.3. Carbon attacks to C – C multiple bonds

Various carbonated groups can serve as nucleophiles for the attack on multiple C – C bonds in the presence of homogeneous gold catalysts. These groups are usually sp^2- or sp-hybridized (e.g. alkenes, allenes, alkynes or aryls moieties), but can also be sp^3 (like the activated carbon atoms in 1,3-dicarbonylic compounds, for instance).

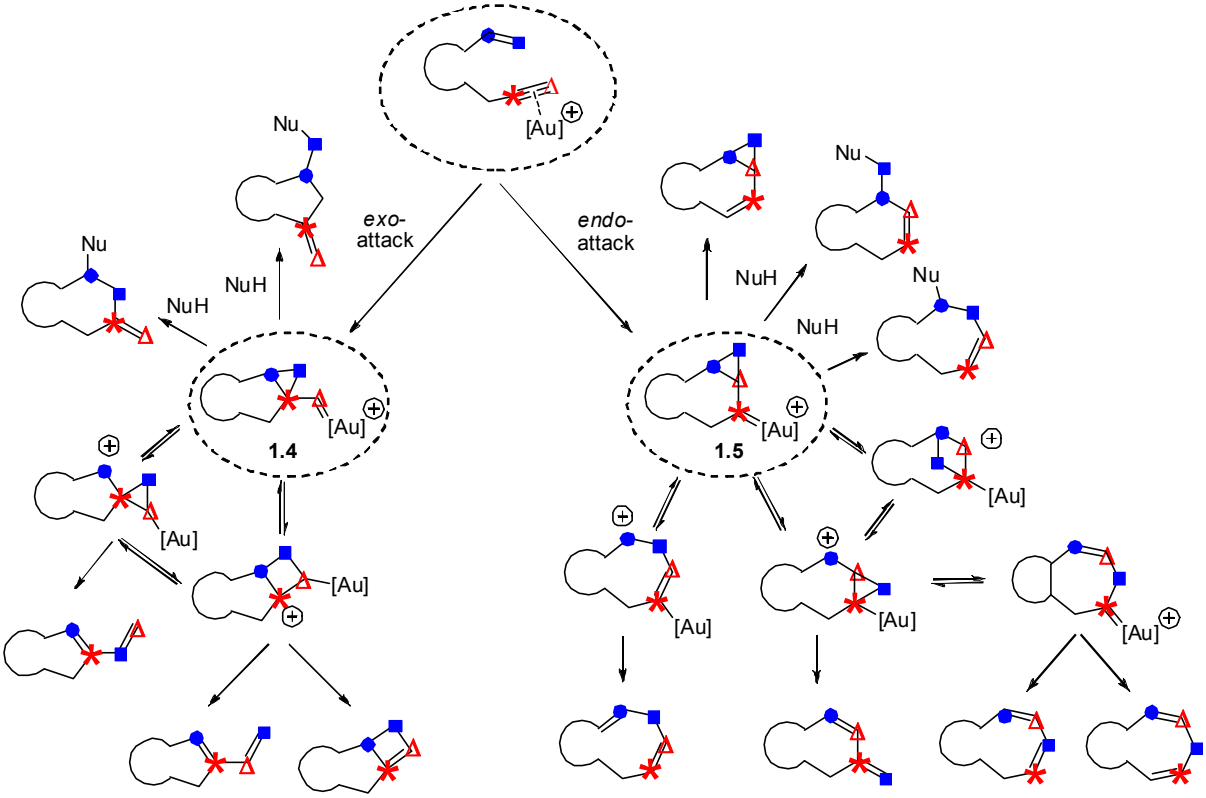
The vast majority of these transformations are intramolecular, leading to the formation of complex carbocycles starting from simple linear precursors.

Enyne cycloizomerizations

The cycloisomerization of enynes is probably one of the most fascinating areas of homogeneous gold catalysis. Gold complexes proved to be very effective in this kind of transformations, giving excellent selectivities and yields. On some occasions, they even surpassed the activity of other similar transition metals like Pt or Pd. Furthermore, they were able to catalyze reactions otherwise impossible with other catalysts, leading to new types of rearrangements.

The reaction outcome strongly depends on the nature of the substrate used (length of the linker between the alkene and the alkyne moieties, Thorpe-Ingold effects, substitutions present on the molecule etc.), but also on the conditions employed (type of catalyst, solvent, temperature, reaction time etc.).

Although extremely diverse, most of the gold-catalyzed enyne cycloisomerizations involve a similar mechanism, based on the selective activation of the alkyne moiety towards the nucleophilic attack of the double bond. Relative to the triple bond, either an *exo-dig* or an *endo-dig* attack can take place (Scheme 1.19).

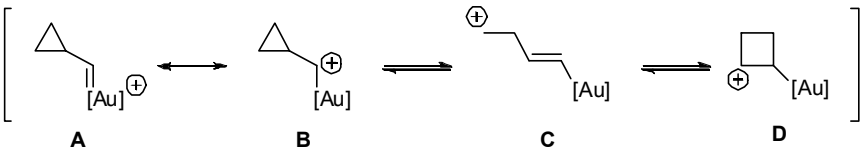


Scheme 1.19. Gold catalyzed cycloisomerization reactions involving enynes

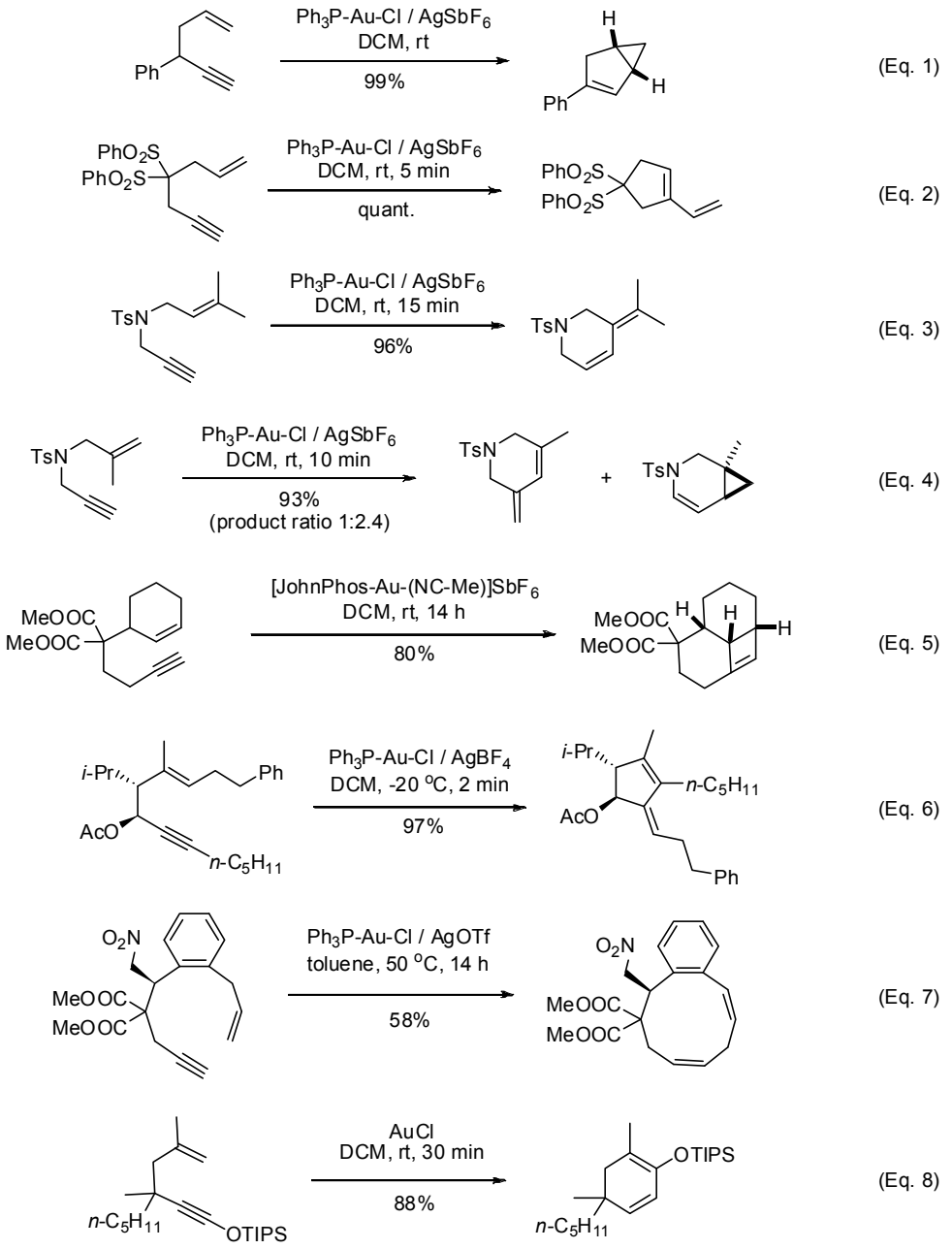
Two non-classical carbenoid gold cyclopropane intermediates **1.4** and respectively **1.5** are thus formed,[47] which can evolve in several ways. A few possibilities of evolution are presented in Scheme 1.19. The relative stability of the resulting carbocations will influence the type of rearrangement that will take place, just like in ionic chemistry.

The cyclizations of 1,5- and 1,6-enyes are the most common. Although less frequent, the cyclization of other 1,n-enynes is possible as well. Some examples are shown in Scheme 1.20.[48] Additional transformations involving the gold-catalyzed rearrangement of enynes into functionalized cyclopentenes can be found in Chapter 8, Section 1.2.

[47] For a discussion about the true electronic structure of these non-classical carbenoid gold cyclopropane intermediates (which can be represented as a sum of different mesomeric/tautomeric formulas **A–D**), see: Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 6754-6756. The carbene notation is used here however for historical reasons and in order to insure the coherence with the literature.



[48] (a) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859.
(b) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.
(c) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148.
(d) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129-4132.
(e) Comer, E.; Rohan, E.; Deng, L.; Porco, J. A. *Org. Lett.* **2007**, *9*, 2123-2126.
(f) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806-11807.

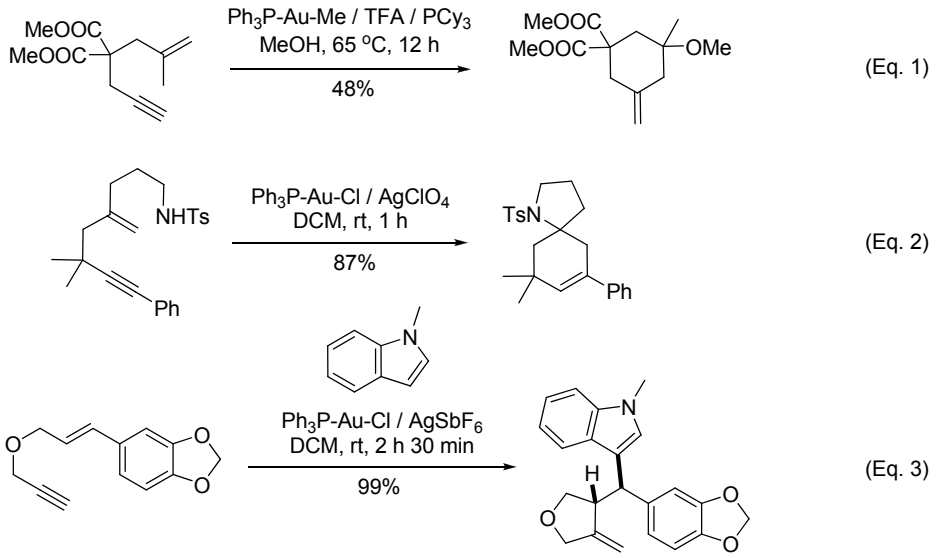


Scheme 1.20. A few examples of gold-catalyzed cycloisomerization of enynes

If another nucleophile (such as water, alcohols, amines, aryls, heteroaryls etc.) is present in the medium, the intermediates formed previously can be trapped. Several possible types of products are depicted in Scheme 1.19.

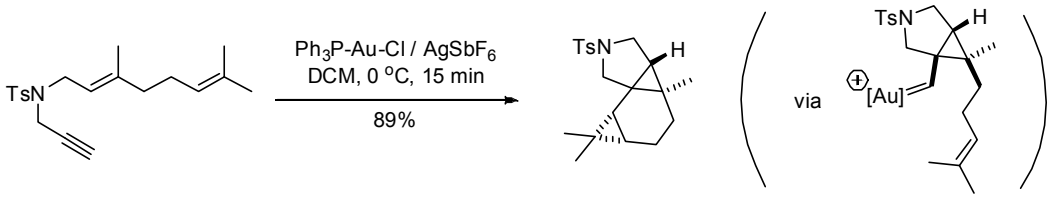
Scheme 1.21 shows three examples involving an alcohol (Eq. 1), an amine (Eq. 2) and an indole (Eq. 3) as nucleophiles.[48b,49]

[49] (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962-6963.
(b) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem. Int. Ed.* **2006**, *45*, 7427-7430.



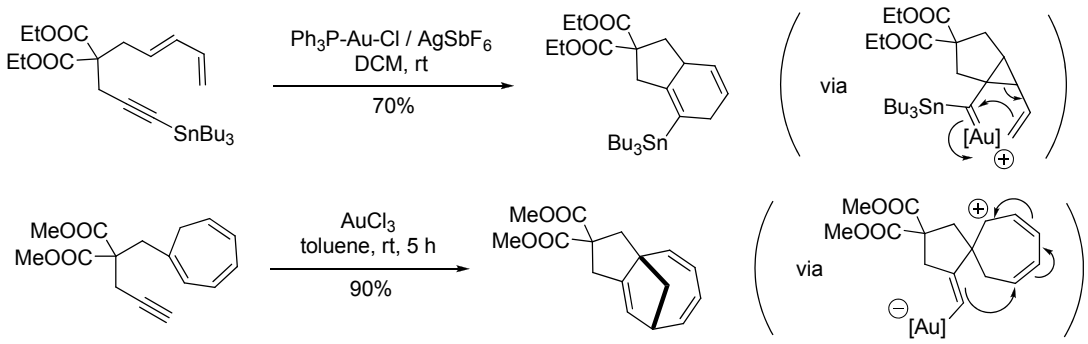
Scheme 1.21. Trapping of the intermediates formed during the gold-catalyzed cycloisomerization of enynes by another nucleophile present in the medium

A second double bond can also trap the carbenoid cyclopropyl intermediate formed in the initial cyclization step, leading to complex polycyclic structures (Scheme 1.22).[50]



Scheme 1.22. Trapping of the carbenoid cyclopropyl intermediate formed during the gold-catalyzed cycloisomerization of enynes by a second double bond

The presence of diene and polyene functionalities can lead to various conjugated additions, as shown in Scheme 1.23.[51]

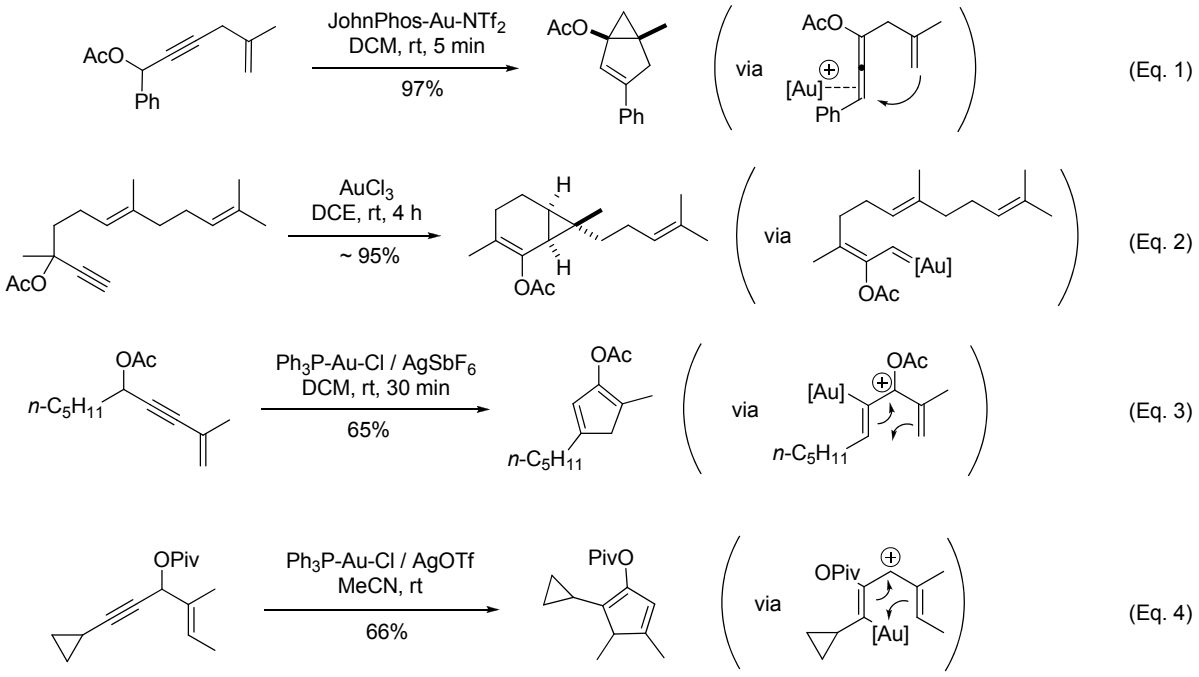


Scheme 1.23. Conjugated gold-catalyzed additions in the presence of diene and polyene functionalities

[50] Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1694-1702.

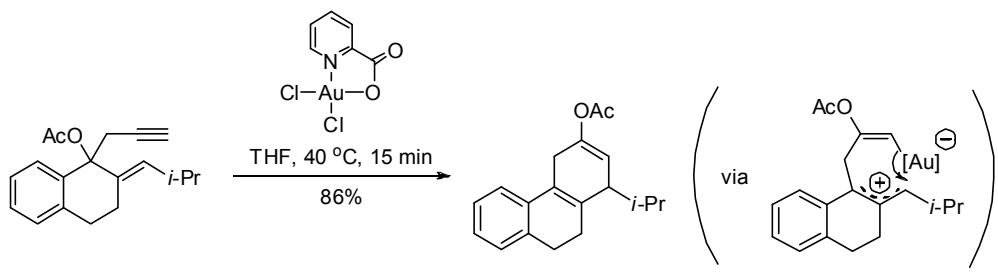
[51] (a) Fürstner, A.; Stimson, C. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 8845-8849.
(b) Tenaglia, A.; Gaillard, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 2454-2457.

If an acyloxy group is present in the propargylic position, the gold-catalyzed cycloisomerization of enynes usually follows a different pathway, involving the nucleophilic attack of the carbonyl group on the triple bond. This can lead to the formation of an allene intermediate, which can be reactivated by the gold catalyst for the attack of the double bond (Scheme 1.24, Eq. 1)[52a] It can also lead to the formation of a non-classical carbenoid intermediate, which can be trapped by the alkene moiety (idem, Eq. 2)[52b] Another possibility is represented by the formation of a cationic gold intermediate which can undergo a Nazarov-type rearrangement (idem, Eq. 3 and 4).[52c,d]



Scheme 1.24. Gold-catalyzed cycloisomerizations of enynes possessing an acyloxy group in the propargylic position

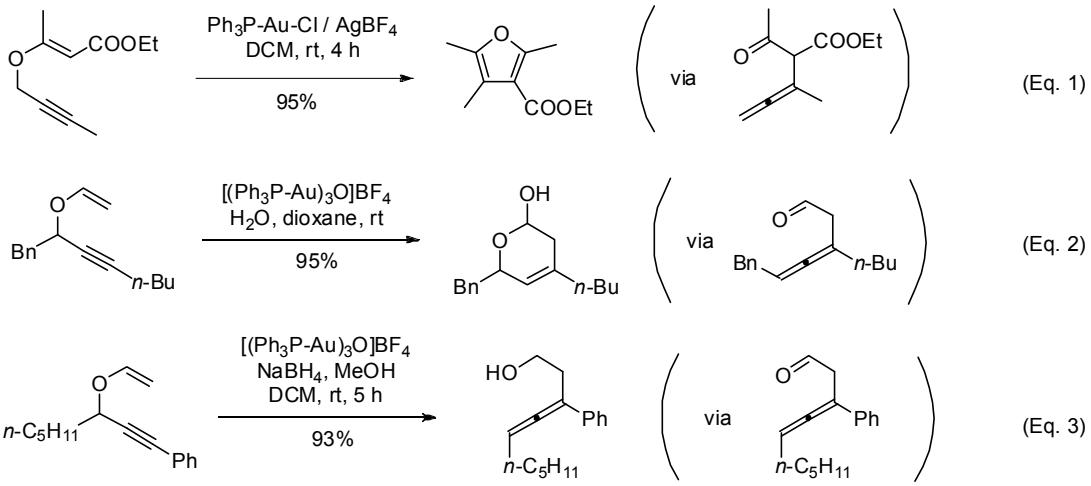
A similar nucleophilic attack of an acyloxy group on the triple bond can be observed sometimes for enynes substituted in the homopropargylic position, as shown in Scheme 1.25.[53]



Scheme 1.25. Cycloisomerizations of enynes possessing an acyloxy group in the homopropargylic position

[52] (a) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614-12615.
(b) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006-3019.
(c) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442-1443.
(d) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802-5803.
[53] Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 14274-14275.

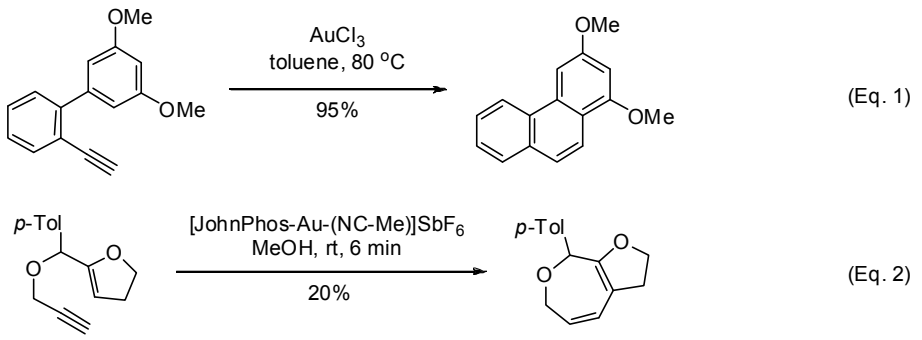
A special type of enyne rearrangement is given by vinyl propargyl ethers, which rearrange in the presence of gold to β-keto-allenes. These intermediates can undergo further transformations, like a cyclization giving a furan derivative (Scheme 1.26, Eq. 1), an additional nucleophilic attack of a water molecule yielding a dihydropyran (idem, Eq. 2) or an *in situ* reduction to the corresponding β-hydroxy allene (idem, Eq. 3).[54,31b,31c]



Scheme 1.26. Gold-catalyzed rearrangement of vinyl propargyl ethers

Other similar cycloisomerizations

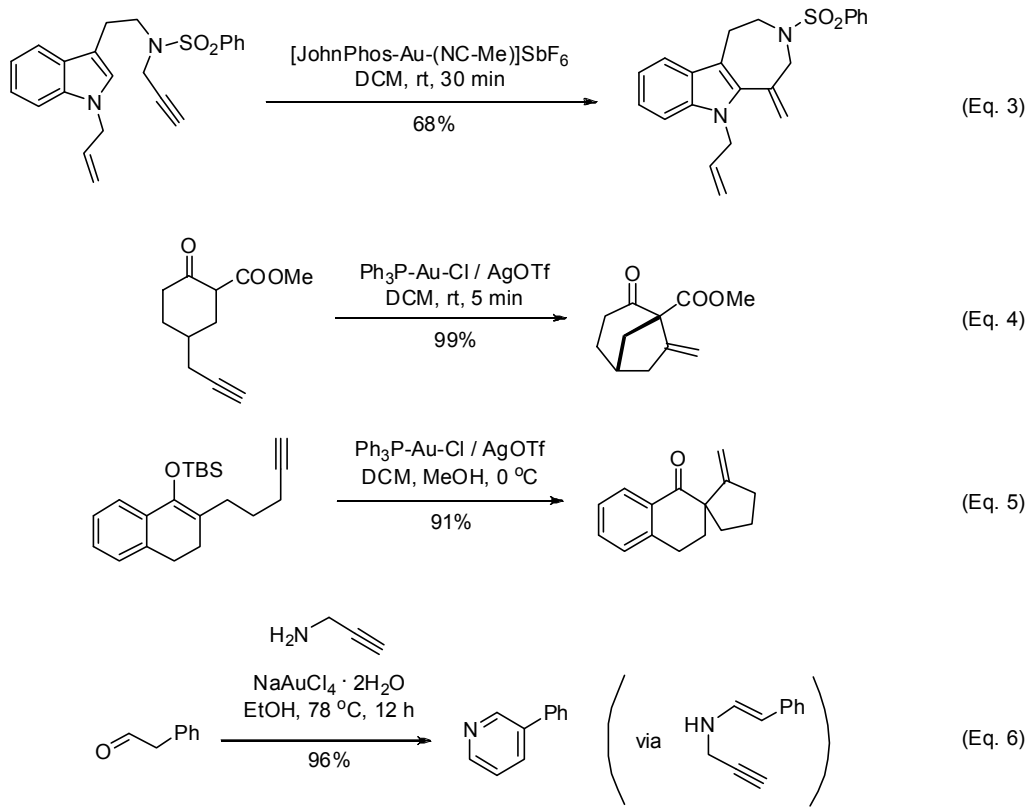
Alkyne derivatives possessing aryl, heteroaryl, 1,3-dicarbonylic, enol, silyl enol ether or imine functionalities can give rearrangements analogous to those described previously for the enyne derivatives. Scheme 1.27 contains a few representative examples.[55]



(continued on the next page)

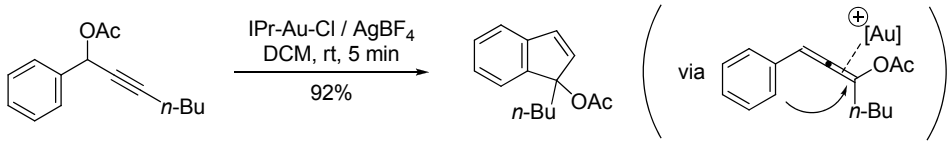
[54] Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925-3927.

[55] (a) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556-4575.
(b) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306-6316.
(c) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105-1109.
(d) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526-4527.
(e) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991-5994.
(f) Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959-6966.



Scheme 1.27. Analogous rearrangements of alkyne derivatives possessing various aryl, heteroaryl, 1,3-dicarbonylic, silyl enol ether or imine functionalities

Scheme 1.28 depicts the cycloisomerization of an aryl-yne derivative possessing an acetate group in the propargylic position. The initial 1,3-shift of the acetate group leads to the formation of aryl-allene intermediate. Upon a second activation by gold, this intermediate is attacked by the aryl group, leading to the formation of cyclized final product.[56]



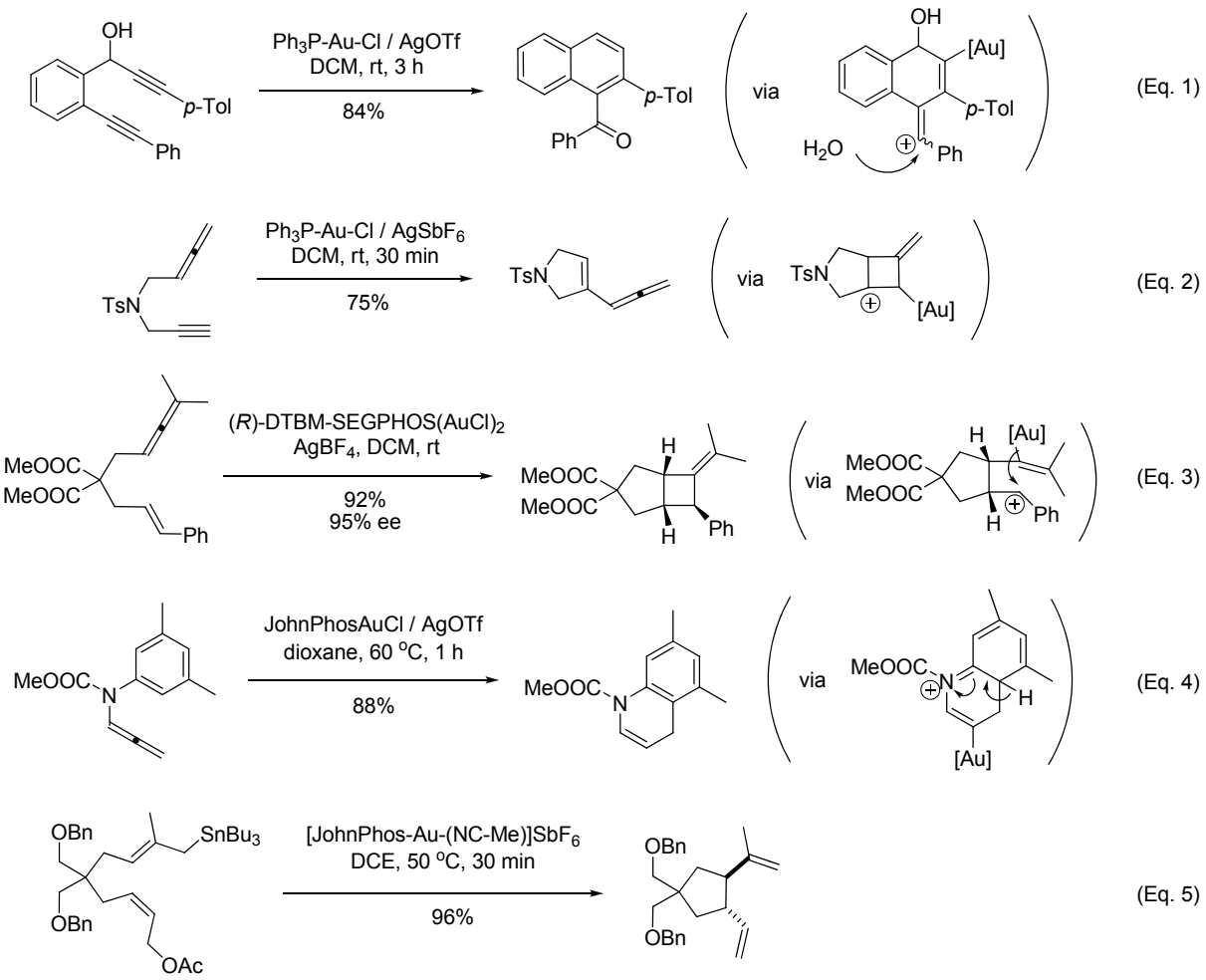
Scheme 1.28. Gold-catalyzed cycloisomerization of an aryl-yne derivative possessing an acetate group in the propargylic position

Various diyne (Scheme 1.29, Eq. 1), allenyne (idem, Eq. 2), allenene (idem, Eq. 3), aryl-ene (idem, Eq. 4) or diene (idem, Eq. 5) derivatives can also be cycloisomerized in the presence of gold catalysts.[57]

---

[56] Marion, N.; Díez-González, S.; Frémont, P. d.; Noble, A. R.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3647-3650.

[57] (a) Lian, J. J.; Liu, R. S. *Chem. Commun.* **2007**, 1337-1339.
(b) Lee, S. I.; Sim, S. H.; Kim, S. M.; Kim, K.; Chung, Y. K. *J. Org. Chem.* **2006**, *71*, 7120-7123.
(c) Luzung, M. R.; Mauleon, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402-12403.
(d) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821-4824.
(e) Porcel, S.; López-Carrillo, V.; García-Yebra, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 1883-1886.

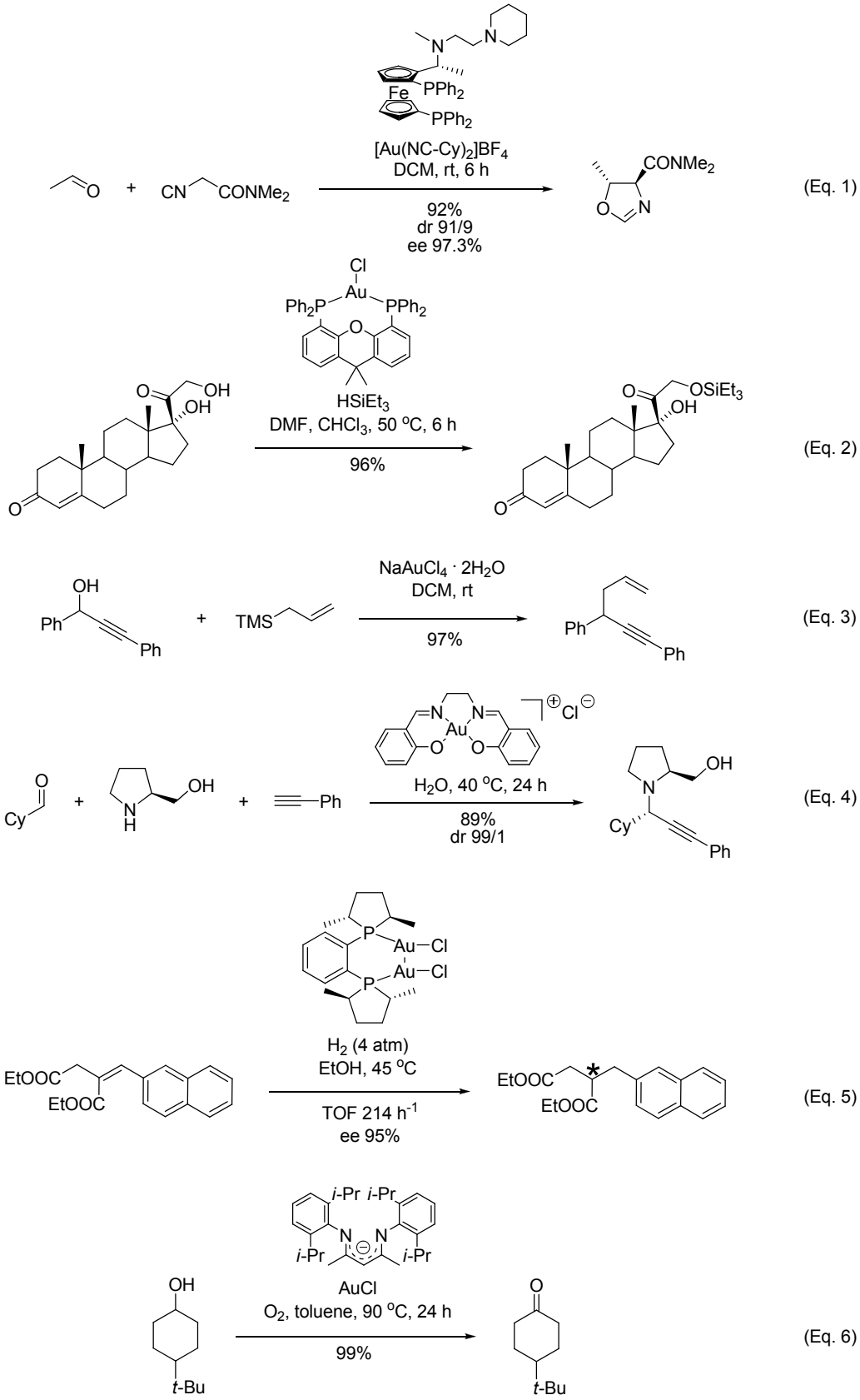


Scheme 1.29. Various cycloisomerizations involving diyne, allenyne, allenene, aryl-ene or diene derivatives

6.4. Other reactions

Homogeneous gold catalysts proved to be active in a certain number of other transformations. Scheme 1.30 contains a few representative examples involving asymmetric aldol reactions (Eq. 1),[58] selective silylations (Eq. 2),[59] nucleophilic substitutions (Eq. 3),[60] C_{sp} – H bond functionalizations (Eq. 4),[61] enantioselective hydrogenations (Eq. 5)[62] and oxidations (Eq. 6).[63]

[58] (a) Ito, Y.; Sawamura, M.; Kobayashi, M.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 6321-6324.
(b) Sawamura, M.; Ito, Y. *Chem. Rev.* **2002**, *92*, 857-871.
[59] Ito, H.; Takagi, K.; Miyahara, T.; Sawamura, M. *Org. Lett.* **2005**, *7*, 3001-3004.
[60] Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180-14181.
[61] Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529-1532.
[62] Gonzalez-Arellano, C.; Corma, A.; Iglesias, M.; Sanchez, F. *Chem. Commun.* **2005**, 3451-3453.
[63] Guan, B.; Xing, D.; Cai, G.; Wan, X.; Yu, N.; Fang, Z.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2005**, *127*, 18004-18005.



Scheme 1.30. Other types of reactions catalyzed by homogeneous gold complexes

7. Conclusion

Neglected for a long time, homogeneous gold catalysis has emerged in the last 10 years as one of the most promising fields in organometallic chemistry.

Its utility has been demonstrated on many occasions for the highly selective formation of new C – X (X = O, N, S etc.) and C – C bonds under very mild reaction conditions and with a broad substrate scope.

Gold complexes proved to be more effective than other transition metals in various transformations, leading to better yields and selectivities. They also showed some very particular properties, making possible new mechanistic pathways and exhibiting sometimes a distinct reactivity.

Homogeneous gold catalysis seems to be well suited for tandem reactions, resulting in a very rich chemistry which without any doubt will have soon an important impact in total synthesis and in industrial applications.

However, homogeneous gold catalysis faces also a certain number of challenges. For example, the advances in the area of chiral catalysis remain limited so far. Most of the transformations involving gold catalysts are highly substrate dependent and the control of closely related pathways is still insufficient.

Despite the proven efficiency of gold catalysts in intramolecular reactions for the preparation of numerous hetero- and carbocycles, the synthesis of larger rings is generally difficult. The development of general methods for intermolecular transformations is also needed.

Although the basic mechanistic pathways are better understood nowadays, numerous questions still remain unanswered concerning for instance the nature of the catalyst's active species or the factors favoring one pathway over another.

CHAPTER

2

The Catalytic System Used in Our Work

*"Two gold atoms are walking down the street when all of a sudden the first one turns to the second one and says 'Uh oh, I think I lost an electron'. The second gold atom says 'Are you sure?' The first one replies, 'Yeah, I'm positive!'" (**Unknown author**)*

This chapter describes the synthesis and some of the properties of a new type of gold(I) catalysts, developed by Dr. Fabien L. Gagosz and possessing a bis-(trifluoromethanesulfonyl) imidate (NTf_2^-) counteranion (Figure 2.1).

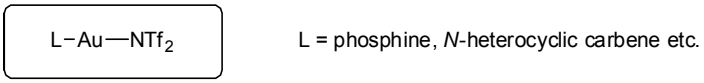


Figure 2.1. New type of gold(I) catalysts developed by Dr. Fabien L. Gagosz and used during our work for the development of new transformations in homogeneous gold(I) catalysis

The properties and the possible applications in organic synthesis of these complexes were extensively investigated by our team. The next chapters will detail the development of some of these new transformations.

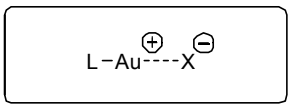
Among the advantages of this new type of catalyst we can name its stability (under air and with time), its easy preparation, storage and handling (both on small and large scale, the compound being crystalline), its solubility (in a wide variety of common solvents) and finally its remarkable activity.

In the first part of this chapter the preparation of two types of cationic gold(I)-catalysts, which are most commonly used, will be presented briefly and some of their shortcomings will be discussed as well (section 1). The second part will be dedicated to the synthesis, activity and some of the properties of gold(I) complexes possessing an NTf_2^- counteranion (section 2). This chapter will end with a short conclusion (section 3).

1. Cationic gold(I)-catalysts. Preparation and shortcomings

As we could see in the previous chapter, cationic gold(I)-complexes are the most frequently used homogeneous gold catalysts. Although various types of such catalysts have been reported and employed, in this section only the most important two classes will be discussed:

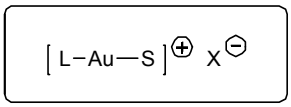
- those who contain a gold(I) atom bicoordinated by a strong ligand L and a weakly coordinating counteranion X^- (of LAuX composition, see Figure 2.2).



L = phosphine, phosphite, arsine, *N*-heterocyclic carbene etc.
X = NO_3^-, AcO^-, MsO^-, HSO_4^-, BF_4^-, PF_6^-, SbF_6^-, TfO^-, ClO_4^-, $(R_2O)P(O)O^-$ etc.

Figure 2.2. L-Au^+X^- cationic gold(I)-complexes

- those who have a gold(I) atom bicoordinated by a strong ligand L and a weakly coordinating ligand S, along with a non-coordinating SbF_6^- or PF_6^- counteranion (of L_2Au^+ composition, see Figure 2.3).



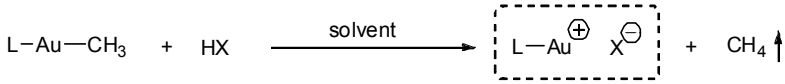
L = phosphine, *N*-heterocyclic carbene
S = MeCN, toluene, *p*-xylene
X = SbF_6^-, PF_6^-

Figure 2.3. [L-Au-S]$^+$X$^-$ cationic gold(I)-complexes

1.1. L-Au^+X^- cationic gold(I)-complexes

The first type of catalysts is generally unstable and has to be generated *in situ* by one of the several methods available.

One method of synthesis consists in protonating an alkyl gold(I) intermediate with a strong acid whose anion does not coordinate strongly to gold (e.g. CH_3SO_3H, H_2SO_4, HBF_4, $H_3PW_{12}O_{40}$, CF_3COOH etc.) (Scheme 2.1).[64] A Lewis acid such as BF_3 can also be used because it is rapidly hydrolyzed to HF under the reaction conditions.



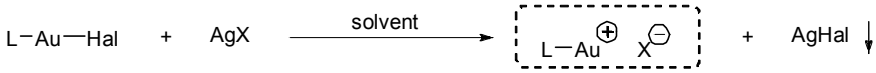
L = phosphine, phosphite, arsine etc.
X = MsO^-, HSO_4^-, BF_4^-, $H_2PW_{12}O_{40}^-$, CF_3COO^- etc.

Scheme 2.1. *In situ* generation of L-Au^+X^- cationic gold(I)-catalysts from an alkyl gold(I) intermediate by protonation with a strong acid

[64] (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.
(b) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.

Unfortunately, the scope of this method is rather limited, since these strong acidic conditions are not always compatible with the substrates employed.

Another method used to generate the first type of cationic gold(I)-catalysts makes use of a halide gold(I)-complex and a silver salt. This method is by far the most commonly used. The halogen can be either Cl or alternatively Br or I, while X is typically a weakly coordinating anion such as BF_4^-, PF_6^-, SbF_6^-, TfO^-, ClO_4^-, $(R_2O)P(O)O^-$ etc (Scheme 2.2).



L = phosphine, phosphite, arsine, *N*-heterocyclic carbene etc.
Hal = Cl, Br, I
X = BF_4^-, PF_6^-, SbF_6^-, TfO^-, ClO_4^-, $(R_2O)P(O)O^-$ etc.

Scheme 2.2. *In situ* generation of L-Au$^+$X$^-$ cationic gold(I)-catalysts from a halide gold(I)-complex and a silver salt

This method suffers from some limitations too. For instance, most of the silver salts are light sensitive and highly hygroscopic, a glovebox being required to properly weight them. Reactions on a small scale can be therefore rather difficult to set up. Upon hydrolysis, the silver salts can also acidify the reaction medium, leading to unwanted side reactions. Even the presence of the water can create problems, particularly when anhydrous conditions are required.

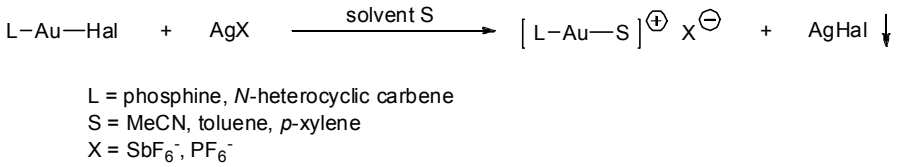
Furthermore, the active cationic gold(I) species can be quite unstable under the reaction conditions. The formation of [L-Au]$^+$ is sometimes irreversible. Once this cation is set free, it can only react with the substrate or enter catalyst deactivating pathways. This fact in turn can limit the activity of the catalytic system and reduce the turn-over numbers.

Other problems arise from the stability of the counteranion itself, especially when a fluorine-based counteranion is used. For instance, weakly coordinating anions such as BF_4^-, PF_6^- or SbF_6^- are Lewis acid/base conjugates of a superior nucleophile (e.g. $MF_{n+1}^- \rightarrow MF_n + F^-$). Because of this competitive side reaction, their ability to act as inert counterions is always limited. Furthermore the presence of a nucleophile (e.g. F^-) can cause unwanted side reactions, while the free Lewis acid (e.g. MF_n) can act as an oxidizing agent.[65]

1.2. [L-Au-S]$^+$X$^-$ cationic gold(I)-complexes

The second type of cationic gold(I)-catalysts can usually be isolated and handled under ordinary conditions. The desired complexes are prepared in a very similar fashion by treating a gold(I) halide complex with a silver salt in the corresponding solvent (Scheme 2.3). Despite being more convenient to work with, the limited stability of the counteranion can lead similarly to side-products, as discussed earlier.

[65] (a) Krossing, I.; Raabe, I. *Angew. Chem. Int. Ed.* **2004**, *43*, 2066-2090.
(b) Krossing, I.; Raabe, I. *Chem. Eur. J.* **2004**, *10*, 5017-5030.



Scheme 2.3. Synthesis of crystalline stable $[L\text{-}Au\text{-}S]^{+}X^{-}$ cationic gold(I)-catalysts

2. A new cationic gold(I) catalytic system

2.1. Gold(I) complexes possessing an NTf_2^- counteranion. The initial idea

We saw that current cationic gold(I) catalytic systems, despite being quite effective and widely used, suffer from a number of shortcomings. The development of new catalytic systems that might improve / solve some of these issues was therefore highly desirable.

During a study concerning the influence of the counteranions in cationic gold(I) catalysts, Dr. Fabien L. Gagosz envisaged the use of the weakly coordinating bis(trifluoromethanesulfonyl)imidate moiety (also known as triflimide or NTf_2^-) (Figure 2.4).

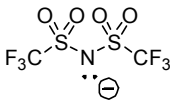


Figure 2.4. The bis(trifluoromethanesulfonyl)imidate (also known as triflimide or NTf_2^-) moiety

This group is used in numerous highly electrodeficient cationic complexes, which exhibit often strong Lewis acid catalytic proprieties.[66] By analogy with the stability of $AgNTf_2$ compared to the hygroscopic salts AgOTf, $AgBF_4$, $AgPF_6$ or $AgSbF_6$, Dr. Fabien L. Gagosz surmised that a new type of cationic gold(I)-catalyst possessing an NTf_2^- counteranion might be stable as well (Figure 2.5).

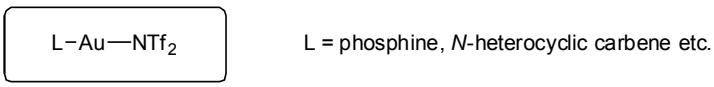
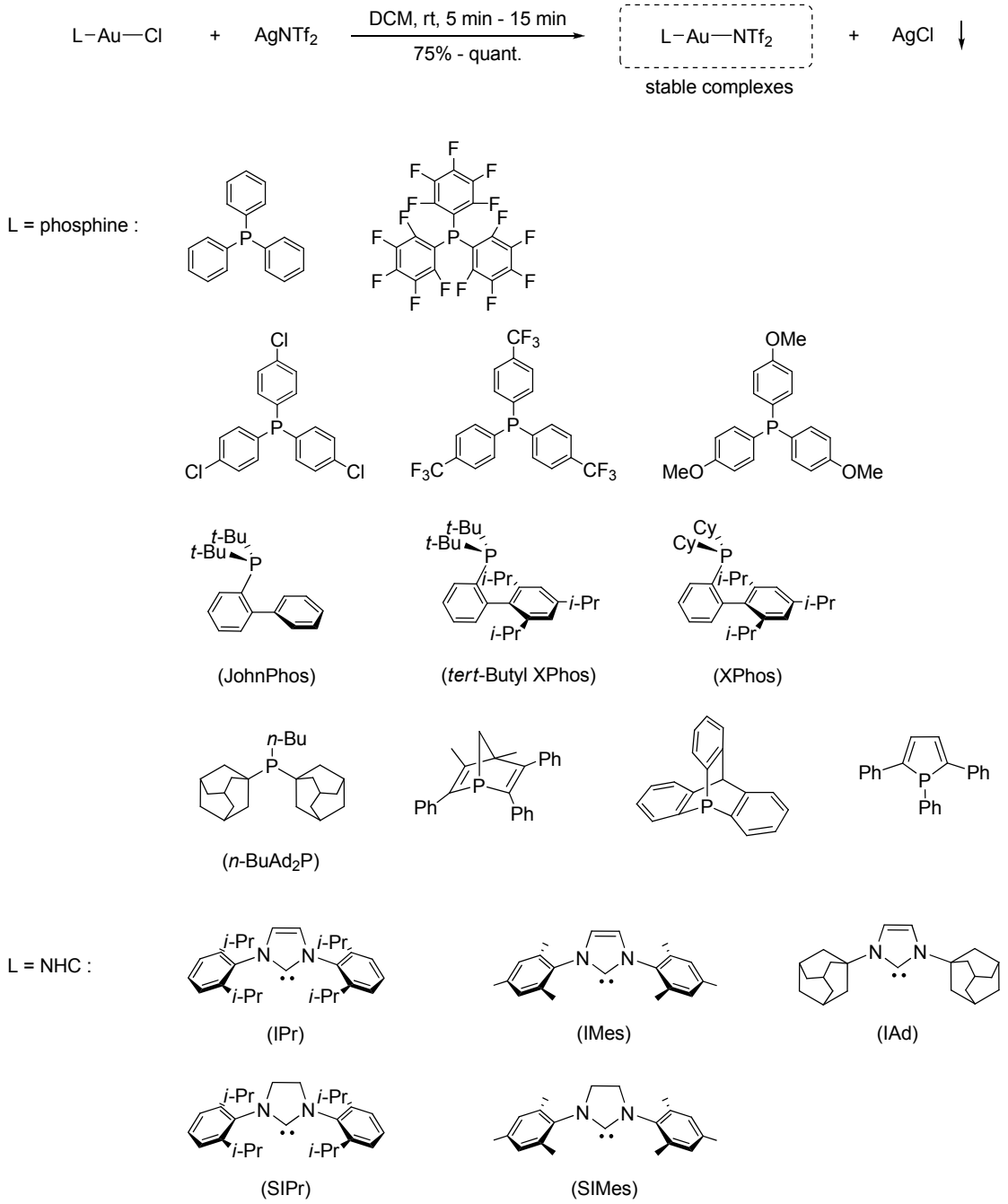


Figure 2.5. New type of cationic gold(I)-catalyst possessing an NTf_2^- counteranion

[66] For lithium, silver, magnesium, zinc, iron, scandium, yttrium and ytterbium, see:
(a) Sibi, M. P.; Petrovic, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2879-2882.
(c) Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, *1996*, 265-266.
(c) Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, *1996*, 839-841.
For tin, see:
(d) Vij, A.; Wilson, W. W.; Vij, V.; Corley, R. C.; Tham, F. S.; Gerken, M.; Haiges, R.; Schneider, S.; Schroer, T.; Wagner, R. I. *Inorg. Chem.* **2004**, *43*, 3189-3199.
For silicium, see:
(e) Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219-8226.

2.2. Synthesis of gold(I) complexes possessing an NTf_2^- counteranion

Gold(I) complexes possessing an NTf_2^- counteranion can be easily obtained in excellent yields starting from the corresponding gold(I) chloride and $AgNTf_2$. A large number of gold complexes, possessing various phosphine or *N*-heterocyclic carbene ligands were synthesized by Dr. Fabien L. Gagosz using this procedure (Scheme 2.4).[67]



Scheme 2.4. Synthesis of gold(I) complexes possessing an NTf_2^- counteranion

[67] (a) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136.
(b) Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704-4707.

The phosphine ligands can be substituted with aryls (plain, with electron withdrawing or with electron donating groups), biaryls,[68] alkyls, or can be cyclic. The *N*-heterocyclic carbenes can be both unsaturated or saturated.[69]

All complexes proved to be stable, including in the presence of air and moisture, and could be isolated. Being all crystalline, they are very easy to prepare (even on a 1 g scale), store and handle. Figure 2.6 shows the molecular structure of two representative examples, Ph_3P-Au-NTf_2 and IPr-Au-NTf_2, determined by X-ray crystallography.

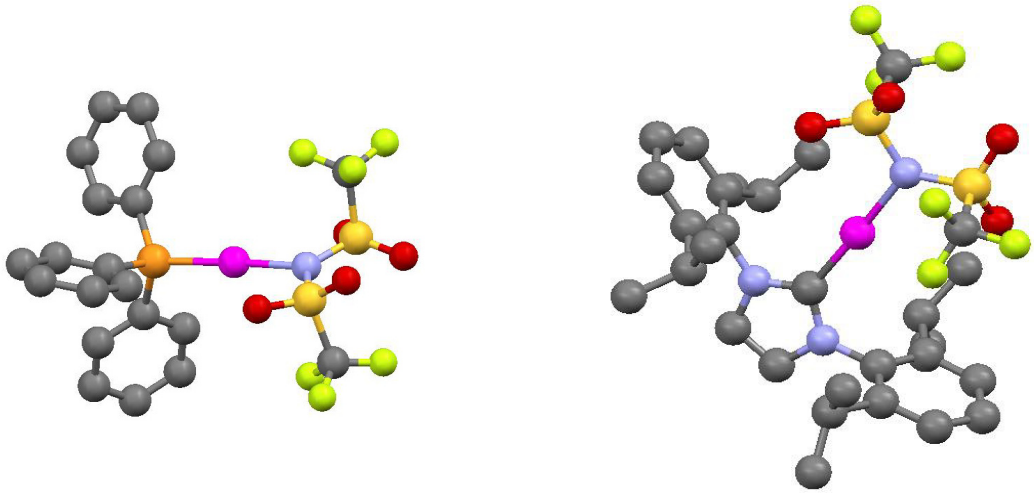


Figure 2.6. Molecular structure of Ph_3P-Au-NTf_2 (left) and IPr-Au-NTf_2 (right). Hydrogen atoms are omitted for clarity

2.3. Catalytic activity

Fortunately, a higher stability of this new class of gold(I)-complexes does not imply a reduced catalytic activity. Our catalysts bearing a NTf_2^- counteranion proved to be very active in numerous transformations.

Their use as catalysts in chemical transformations is also very convenient, especially on small scales, since no co-catalyst silver salts are needed. Open-flask reactions are possible and traces of air or moisture are usually well tolerated. They have also an excellent solubility in a variety of common organic solvents (such as dichloromethane, tetrahydrofuran, diethyl ether, toluene, methanol, acetonitrile etc.).

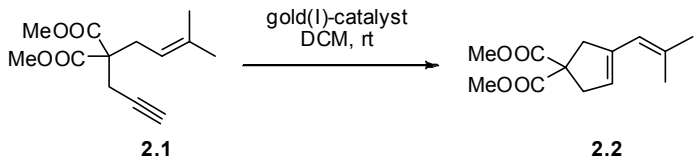
[68] For a review on Buchwald-type dialkyl(biaryl)phosphines, see:
(a) Mauger, C. C.; Mignani, G. A. *Aldrichimica Acta* **2006**, *39*, 17-24.
See also the following article and the references cited therein:
(b) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096-5101.

[69] For a review on *N*-heterocyclic carbenes in gold catalysis, see: Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776-1782.

Sometimes they even surpassed the activity of the previously employed gold(I) cationic catalysts by giving higher turn-over numbers, shorter reaction times, higher yields or less side-products. We suppose that the excellent catalytic activity of our gold catalytic system is due to a higher stability of its active species in the reaction conditions, which remain active a longer time compared to the other gold(I) cationic complexes.

Three experiments proving this point, performed by Dr. Fabien L. Gagosz, are presented below as an example.

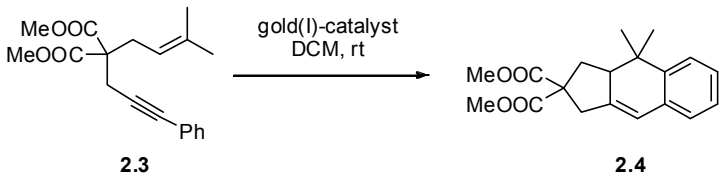
For instance, Echavarren et al. reported that the cycloisomerization of enyne **2.1** in the presence of 2% Ph_3P-Au-Cl / 2% $AgSbF_6$. afforded the diene **2.2** in less than 25 min and 91% yield.[70] Just by comparison, our catalyst Ph_3P-Au-NTf_2 gave similar results (30 min, 97% yield), but in a 0.01% loading.[67a] That's a 200 fold decrease in the amount of required catalyst! (Scheme 2.5).



catalyst	time	yield
2% Ph_3P-Au-Cl / 2% $AgSbF_6$	25 min	91%
0.01% Ph_3P-Au-NTf_2	30 min	97%

Scheme 2.5. Lower catalyst loadings may be required if gold(I) catalysts possessing a triflimide moiety are used

The formation of product **2.4** takes place in 12 h and 83% yield in the presence of 2% Ph_3P-Au-Cl / 2% $AgSbF_6$,[71] compared to 1 h and 98% with 2% Ph_3P-Au-NTf_2.[67a] Our catalytic system gives therefore a reaction time 12 times shorter and a better yield (Scheme 2.6).

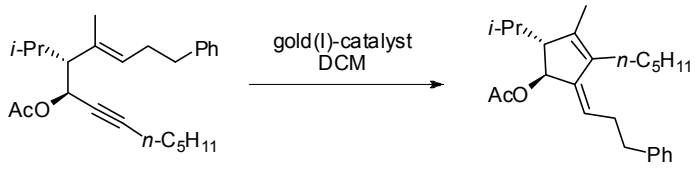


catalyst	time	yield
2% Ph_3P-Au-Cl / 2% $AgSbF_6$	12 h	83%
2% Ph_3P-Au-NTf_2	1 h	98%

Scheme 2.6. Gold(I) catalysts possessing a triflimide moiety can give higher yields and faster transformations

[70] Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.
[71] Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179.

Attempts to cycloisomerize **2.5** at 20 °C or at 0 °C in the presence of 2% Ph_3P-Au-Cl / 2% $AgSbF_6$ led to extensive decomposition of the substrate. Cooling down to -20 °C is necessary to obtain product **2.6** after 2 min in 90% yield. However, after 30 min at the same temperature, **2.6** can be isolated in less than 10% yield. This suggests that the final product decomposes under the reaction conditions. Just by comparison, **2.6** is formed in less than 5 min in the presence 2% Ph_3P-Au-NTf_2 at 20 °C in 95% yield. Letting the reaction run for 1 h at the same temperature gives a 90% yield, indicating that our catalyst system does not decompose significantly the final product (Scheme 2.7).[72]



2.5 **2.6**

catalyst	temp.	time	yield
2% Ph_3P-Au-Cl / 2% $AgSbF_6$	20 °C	5 min	degrad.
2% Ph_3P-Au-Cl / 2% $AgSbF_6$	0 °C	5 min	<10%
2% Ph_3P-Au-Cl / 2% $AgSbF_6$	-20 °C	2 min	90%
2% Ph_3P-Au-Cl / 2% $AgSbF_6$	-20 °C	30 min	<10%
2% Ph_3P-Au-NTf_2	20 °C	5 min	95%
2% Ph_3P-Au-NTf_2	20 °C	1 h	90%

Scheme 2.7. Gold(I) catalysts possessing a triflimide moiety can give less degradation products, even at higher temperatures or during longer times

2.4. Properties

The special properties of our gold(I) catalytic system are mainly due to the presence of the weakly coordinating group NTf_2^-.

Because it is a poor ligand, this moiety can be easily displaced by a molecule of substrate, which makes possible the catalytic activity of our gold complexes. It is believed however that the displacement is reversible, the triflimide group being able to complex again the gold center once the catalytic process took place. This ensures a higher stability of the catalyst's active species in the reaction conditions.

The affinity of gold for the NTf_2^- moiety and the steric and lipophilic effects of this group ensure also a higher stability of our gold complexes in pure state (stable crystalline complexes), as well as a tolerance to air or moisture.

The Au – NTf_2 bond's character is somewhere in between the mainly covalent nature of the Au - Cl bond (in a complex like L-Au-Cl) and the mainly ionic nature of the $Au^+\cdots SbF_6^-$ bond (in a cationic

[72] Gagosz, F. *Org. Lett.* **2005**, *7*, 4129-4132.

complex like L-Au$^+$SbF$_6^-$).

In solution, gold complexes possessing a stronger ionic character will have the tendency to be more dissociated. As a consequence, in weakly coordinating solvents such as DCM, a stronger ionic character can be correlated with a stronger alkynophilic character of the gold complex. Therefore L-Au-NTf$_2$ complexes will be less acidic and less alkynophilic than the L-Au$^+$SbF$_6^-$ ones, but more acidic and more alkynophilic than L-Au-Cl (Figure 2.7).

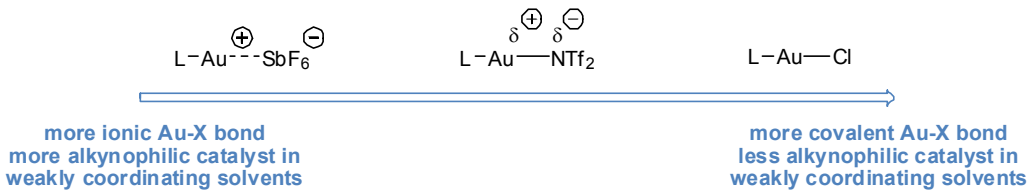


Figure 2.7. The alkynophilicity of L-Au-NTf$_2$ in weakly coordinating solvents compared with L-Au$^+$SbF$_6^-$ and L-Au-Cl

These remarks are only valid for weakly coordinating solvents. In more coordinating solvents such as MeOH, the solvation reduces the alkynophilicity of all cationic gold(I) catalysts because of a competitive equilibrium between the alkyne – gold complexes and the solvent – gold complexes.

In the case of more ionic complexes, the ion pair is more dissociated and the formation of the solvent – gold complexes is favored. In the case of less ionic complexes, the contact between the two ion pairs is closer and the formation of the solvent – gold complexes is less favored. Therefore a L-Au-NTf$_2$ complex can sometime exhibit a stronger alkynophilicity compared to a more ionic L-Au$^+$SbF$_6^-$ one in weakly coordinating solvents (Figure 2.8).

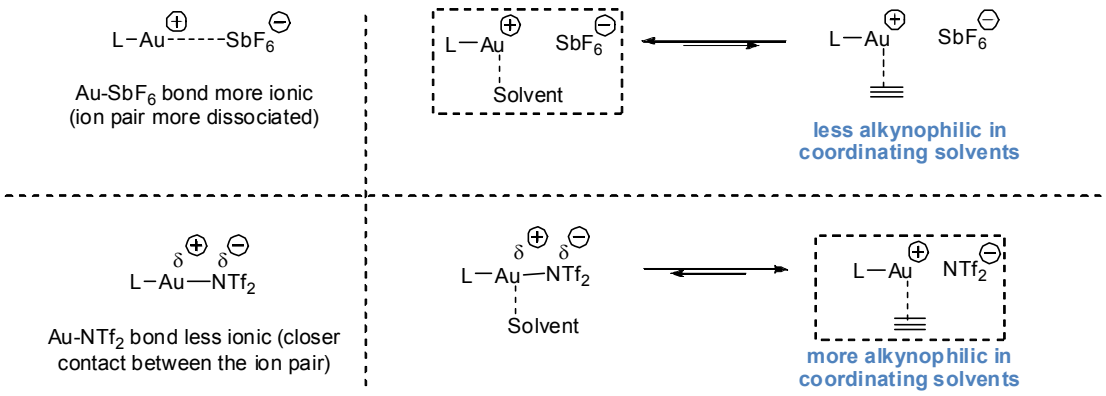


Figure 2.8. The alkynophilicity of L-Au-NTf$_2$ in more coordinating solvents compared with L-Au$^+$SbF$_6^-$

The properties of our gold(I) catalytic system can be fine-tuned by varying the nature of the ligand L.

The ligand's electronic effects play a crucial role, and involve σ-donor, π-acceptor, π-donor and/or secondary interactions (e.g. the interaction between the second aromatic ring of the Buchwald-type phosphines and the gold center). Although these electronic effects are very complex, as a general rule the more electron donating a ligand L will be, the less alkynophilic character the L-Au-NTf$_2$ complex will have.

Figure 2.9 contains an approximate relative scale of the electronic effects (all types combined) for several commonly used ligands L.

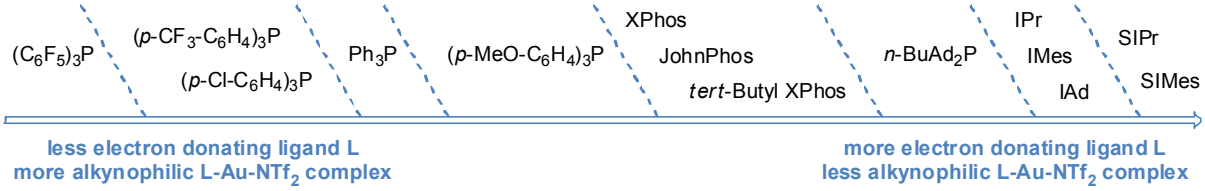


Figure 2.9. Approximate relative scale of the electronic effects for several ligands L and their influence on the alkynophilicity of the corresponding L-Au-NTf_2 complex

An equally important role is played by the steric effects, although their influence seems to vary from one type of transformation to another and even from one substrate to another.

3. Conclusion

Dr. Fabien L. Gagosz developed a new type of a cationic gold(I) catalyst containing a triflimide group as a weakly coordinating counteranion. Compared with the previously used cationic gold(I) catalytic systems, these complexes present several advantages.

They are crystalline and stable in the presence of air, moisture and with time (no need for *in situ* generation, no need for a silver co-catalyst), being convenient to prepare, store and handle even on a small scale.

They present also a very good catalytic activity. Their excellent solubility in most of the common organic solvents is complemented by their stability under the reaction conditions. Their use allows the development of new transformations in homogeneous gold(I) catalysis, otherwise difficult to perform, as we shall see in detail in the next chapters.

Currently, two gold catalysts of this family are commercially available at Sigma Aldrich (Figure 2.10).

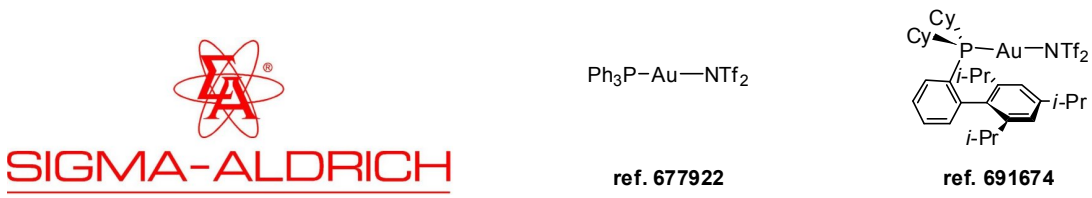


Figure 2.10. Two cationic gold(I) catalysts containing a triflimide group currently commercially available at Sigma Aldrich

CHAPTER

3

Gold(I)-Catalyzed Formation of 4-Alkylidene-1,3-dioxolan-2-ones

*"The most exciting phrase to hear in science, the one that heralds the most discoveries, is not 'Eureka!', but 'That's funny...' " (**Isaac Asimov**, American science-fiction writer and biochemistry professor)*

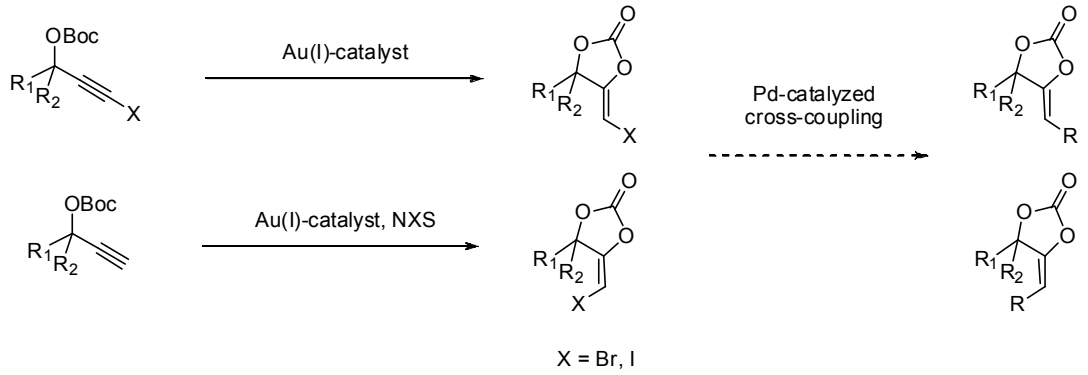
This chapter describes the formation of 4-alkylidene-1,3-dioxolan-2-ones starting form propargylic *tert*-butyl carbonates via a gold(I)-catalyzed rearrangement (Scheme 3.1).

Scheme 3.1. Gold(I)-catalyzed formation of 4-alkylidene-1,3-dioxolan-2-ones

Among the advantages of this transformation we can name the accessibility of the starting substrates (easily obtained from the corresponding propargylic alcohols), the reaction conditions (which are extremely mild), and the broad scope of this reaction (allowing the formation of a wide range of cyclic carbonates, otherwise difficult to obtain using classical methods).

This procedure was also extended to the stereoselective formation *Z*- or *E*-4-halo-methylene-1,3-dioxolan-2-ones, which are extremely versatile precursors of highly functionalized products. We have shown that these building blocks are particularly suitable for Pd-catalyzed cross-coupling reactions (Scheme 3.2).

In the first part of this chapter the importance of a particular class of 1,3-dioxolan-2-ones, the 4-alkylidene-1,3-dioxolan-2-ones, and some of the synthetic methods currently used to obtain them will be discussed briefly (section 1). The second part is dedicated to a more detailed look on our work concerning this topic and to some possible applications (section 2). Finally, this chapter ends with a few conclusions and perspectives (section 3).



Scheme 3.2. Stereoselective formation *Z*- or *E*-4-halo-methylene-1,3-dioxolan-2-ones

Disclaimer:

This work was conducted under the supervision of Dr. Fabien L. Gagosz. Although a part of the experiments presented in this chapter was carried out by Dr. Andrea K. Buzas and Dr. Fabien L. Gagosz, in order to preserve the coherence of the subject the totality of the work concerning this topic will be discussed here.

These results have been previously published in:

- Andrea K. Buzas, Fabien L. Gagosz* "Gold(I)-Catalyzed Formation of 4-Alkylidene-1,3-dioxolan-2-ones from Propargylic *tert*-Butyl Carbonates" *Org. Lett.* **2006**, *8*, 515–518 (Short Communication containing some initial results)
- Andrea K. Buzas, Florin M. Istrate, Fabien L. Gagosz* "Gold-catalyzed rearrangement of propargylic *tert*-butyl carbonates" *Tetrahedron* **2009**, *65*, 1889–1901 (Full Paper)

1. The 4-alkylidene-1,3-dioxolan-2-ones and their derivatives

1.1. The 1,3-dioxolan-2-one ring

The 1,3-dioxolan-2-one ring, a cyclic carbonate-type structure, is quite rare in natural products. Only a handful of such compounds possessing an interesting biological and/or pharmaceutical activity have been reported in the literature, such as neocarzinostatin,[73] aldgamycin E,[74] japoangelone,[75] phomoxin,[76] cytosporin E,[77] hololeucin[78] etc. (Figure 3.1).

[73] Myers, A. G.; Cohen, S. B.; Kwon, B.-M. *J. Am. Chem. Soc.* **1994**, *116*, 1670-1682.
[74] Hans Achenbach, W. K. *Chem. Ber.* **1975**, *108*, 772-779.

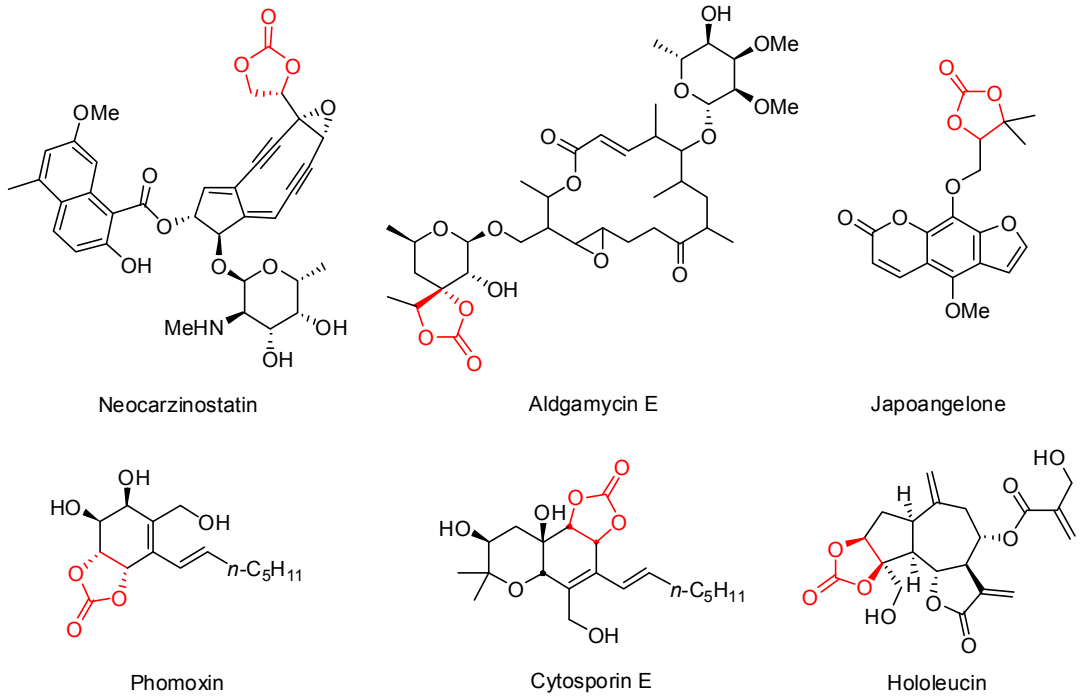


Figure 3.1. Some natural products containing a 1,3-dioxolan-2-one ring

Despite its scarcity in nature, the 1,3-dioxolan-2-one ring is very common in the chemical industry.[79] Cyclic carbonates of this type have found extensive use as aprotic polar solvents, and are common components of paint strippers, hydraulic fluids, electrolytes in high-energy density batteries and capacitors, and even cosmetics and personal care products. They are also precursors for polycarbonates and other polymeric materials.

1,3-Dioxolan-2-ones can react with alcohols, carboxylic acids, amines, halogens, isocyanates etc. and they are valuable intermediates in the production of pharmaceuticals and fine chemicals like dialkyl carbonates, glycols, carbamates, pyrimidines, purines etc.

These cyclic carbonates (typically obtained from CO_2 and an epoxide) have received a lot of attention lately as a practical way of converting waste CO_2 into a useful product. For instance a recent development involving the use of cyclic carbonates as anti-knocking agents in petrol might help reduce, if used on a wide scale, CO_2 emissions by 48 million tones (about 4%) in UK alone.[80]

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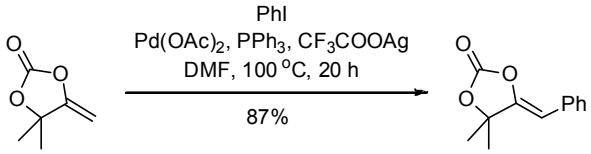
[75] Fujioka, T.; Furumi, K.; Fujii, H.; Okabe, H.; Mihashi, K.; Nakano, Y.; Matsunaga, H.; Katano, M.; Mori, M. *Chem. Pharm. Bull.* **1999**, *47*, 96-100.
[76] Liu, Z.; Jensen, P. R.; Fenical, W. *Phytochemistry* **2003**, *64*, 571-574.
[77] Ciavatta, M. L.; Lopez-Gresa, M. P.; Gavagnin, M.; Nicoletti, R.; Manzo, E.; Mollo, E.; Guo, Y.-W.; Cimino, G. *Tetrahedron* **2008**, *64*, 5365-5369.
[78] Rosselli, S.; Maggio, A.; Bellone, G.; Bruno, M. *Tetrahedron Lett.* **2006**, *47*, 7047-7050.
[79] For some reviews, see:
(a) Shaikh, A.-A. G.; Sivaram, S. *Chem. Rev.* **1996**, *96*, 951-976.
(b) Weissermel, K.; Arpe, H.-J. In *Industrial Organic Chemistry*; 3rd edition ed.; Wiley-VCH: Weinheim, NY, 1997, p 162–163.
(c) Sun, J.; Fujita, S.-i.; Arai, M. *J. Organomet. Chem.* **2005**, *690*, 3490-3497.
(d) Coates, G. W.; Moore, D. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 6618-6639.
[80] Newcastle University. Press Releases. Technological breakthrough in the fight to cut greenhouse gases. http://www.ncl.ac.uk/press.office/press.release/item/?ref=1209034169 (accessed on February 18th, 2009)

1.2. 4-Alkylidene-1,3-dioxolan-2-ones, an interesting subclass of 1,3-dioxolan-2-ones

4-Alkylidene-1,3-dioxolan-2-ones are a particular type of 1,3-dioxolan-2-ones possessing an exo-double bond in the 4-position of the heterocycle (Figure 3.2). The presence of this double bond gives them some new particularly interesting chemical properties which cannot be encountered in "classical" 1,3-dioxolan-2-ones and opens the way to a whole new range of synthetic applications.

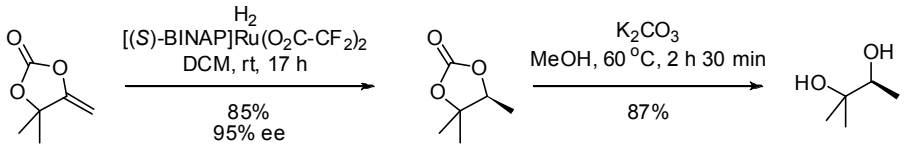
Figure 3.2. "Classical" 1,3-dioxolan-2-one ring (left) compared with the 4-alkylidene-1,3-dioxolan-2-one moiety (right)

For instance the exocyclic double bond can be used in a Heck coupling to introduce an extra substitution. Dixneuf et al.[81] reported a modified Heck protocol allowing the synthesis of *Z*-trisubstituted alkylidene cyclic carbonates from methylene carbonates and aryl iodides (Scheme 3.3).



Scheme 3.3. Heck reaction involving a 1,3-dioxolan-2-one derivative

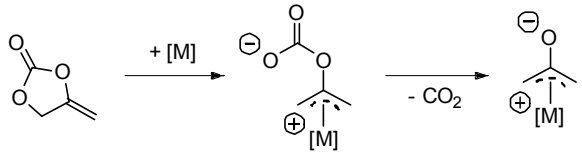
More importantly, the exocyclic double bond can be hydrogenated enantioselectively using chiral ruthenium catalysts. This allows the formation of optically active 1,3-dioxolan-2-ones, which can then be converted under classical conditions to chiral diols.[82] The authors of this transformation propose a chelation of the ruthenium to the oxygen atom in the 3-position in order to explain the excellent enantioselectivities observed (Scheme 3.4).



Scheme 3.4. Enantioselective hydrogenation of 1,3-dioxolan-2-ones

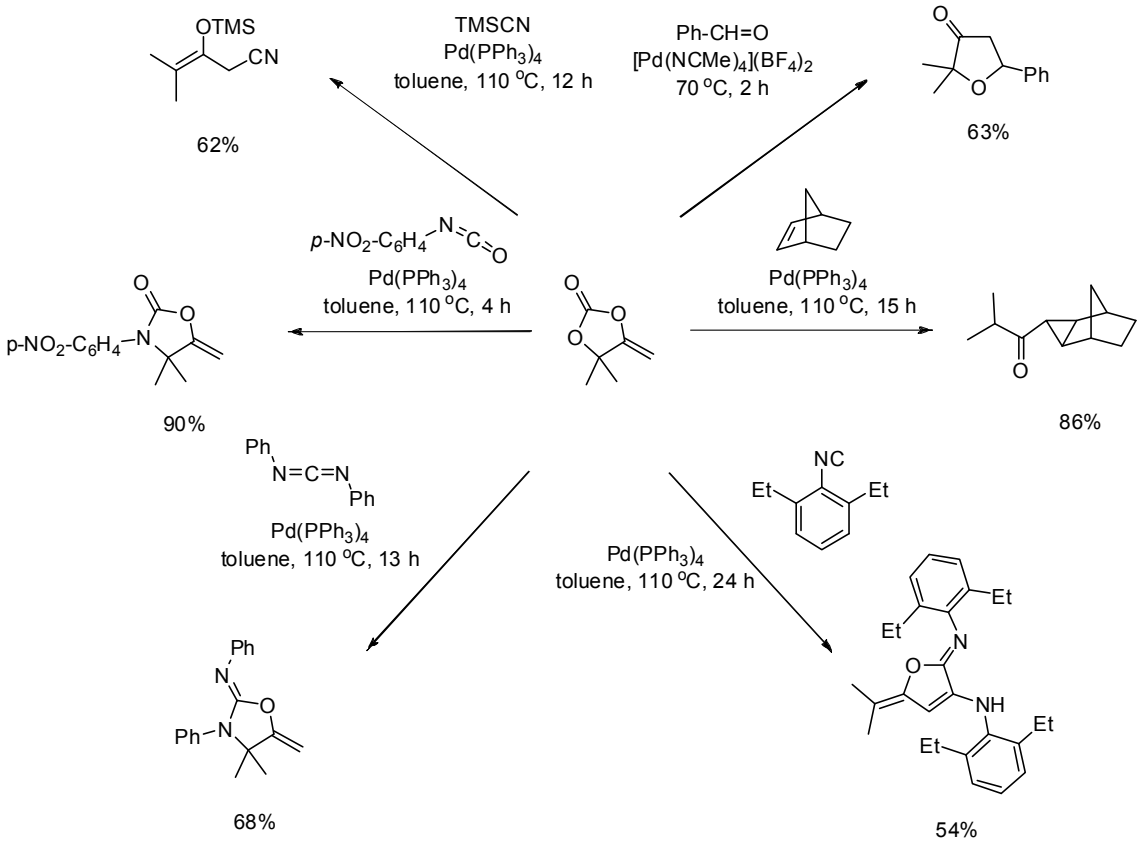
The allylic position to the double bond, substituted with a carbonate functionality, makes possible its activation by a palladium or a platinum catalyst and the formation of an oxa-π-allylmetal intermediate (Scheme 3.5).

[81] Toullec, P.; Carbayo Martin, A.; Gio-Batta, M.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **2000**, *41*, 5527-5531.
[82] Le Gendre, P.; Braun, T.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1996**, *61*, 8453-8455.



Scheme 3.5. Formation of the oxa-π-allylmetal intermediate

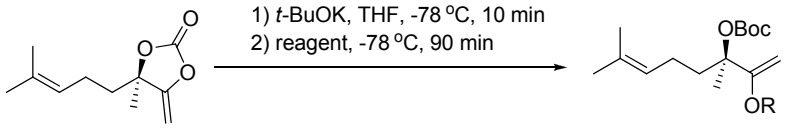
This intermediate can react with various ambiphilic species, such as aromatic aldehydes,[83] isonitriles, heterocumulenes, substituted alkenes or silylated nucleophiles[84] (Scheme 3.6).



Scheme 3.6. Reaction of the oxa-π-allylmetal intermediate with various ambiphilic species

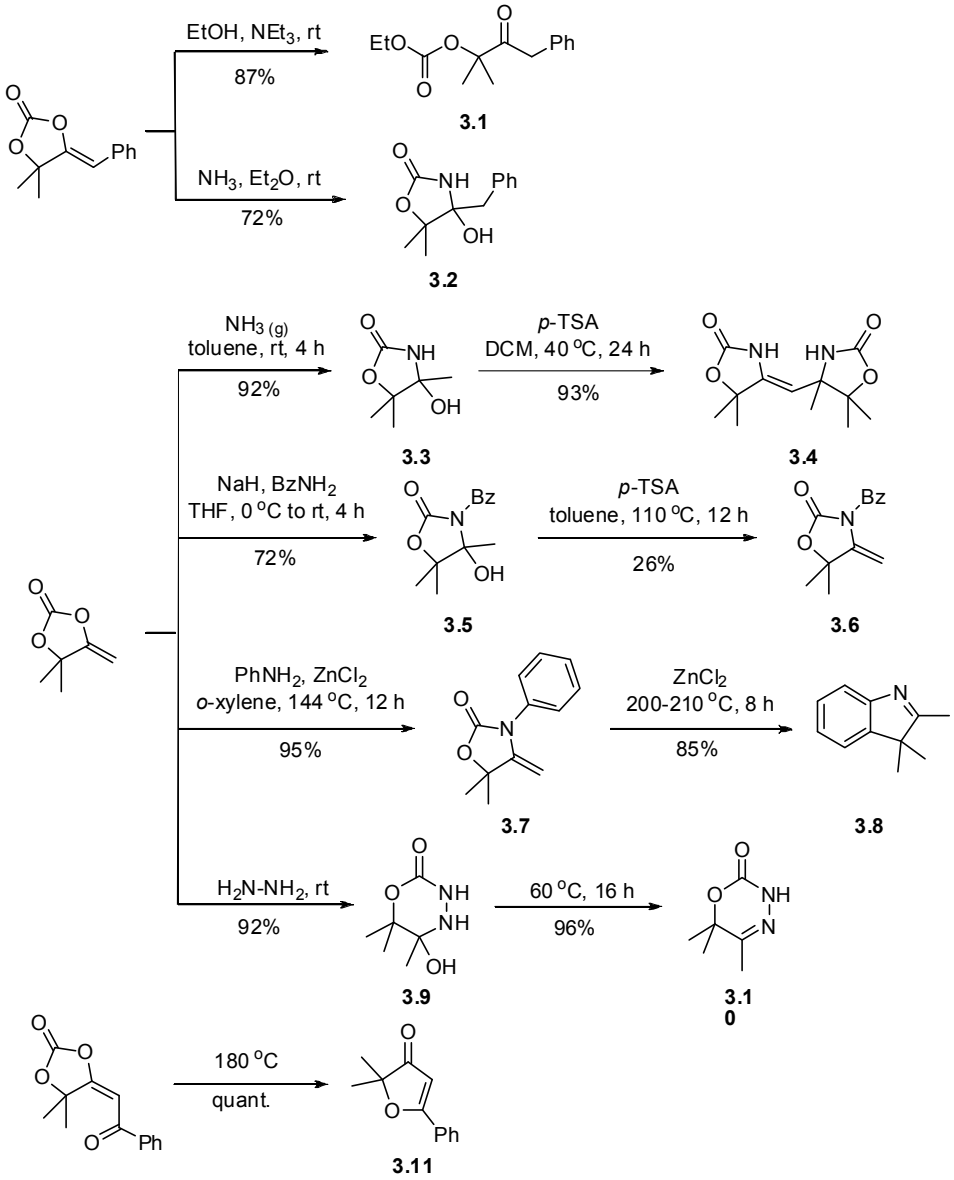
Unlike "classical" 1,3-dioxolan-2-ones, which can be viewed as a masked source of 1,2-diols, 4-alkylidene-1,3-dioxolan-2-ones represent a masked form of 1,2-hydroxyketones. Lautens et al. demonstrated that the reaction of these alkylidene cyclic carbonates with potassium *tert*-butoxide results in the *in situ* formation of a potassium enolate that can be trapped with silylating or triflating agents (Scheme 3.7).[85] These chiral 1,2-hydroxyketones derivatives can be used as highly valuable building blocks.

[83] Inoue, Y.; Matsushita, K.; Yen, I. F.; Imaizumi, S. *Chem. Lett.* **1991**, *20*, 1377-1378.
[84] (a) Ohe, K.; Matsuda, H.; Ishihara, T.; Ogoshi, S.; Chatani, N.; Murai, S. *J. Org. Chem.* **1993**, *58*, 1173-1177.
(b) Ohe, K.; Matsuda, H.; Morimoto, T.; Ogoshi, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 4125-4126.
(c) Joumier, J. M.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1992**, *1992*, 453-454.
[85] Maddess, M. L.; Lautens, M. *Synthesis* **2004**, *2004*, 1399-1408.



reagent	R	yield
$PhNTf_2$	Tf	94%
TBSOTf	TBS	96%

Scheme 3.7. 1,3-dioxolan-2-ones – a masked source of 1,2-hydroxyketones



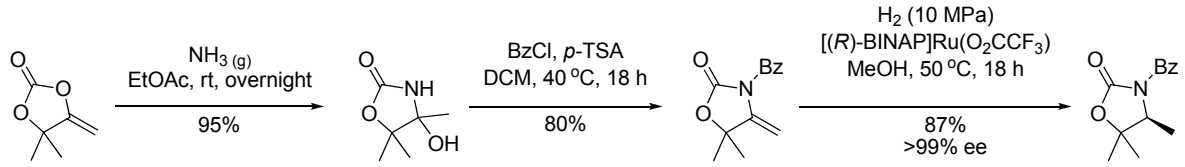
Scheme 3.8. Some typical examples of 4-alkylidene-1,3-dioxolan-2-ones undergoing a nucleophilic attack from *O*- and *N*-nucleophiles

The fact the 4-alkylidene-1,3-dioxolan-2-ones are a masked form of 1,2-hydroxyketones makes them excellent precursors for various classes of compounds. Upon attack by *O*- and *N*-nucleophiles, 4-

alkylidene-1,3-dioxolan-2-ones lead to acyclic β-ketocarbonates (**3.1**),[81,86] 4-hydroxy oxazolidin-2-ones (**3.2**, **3.3** and **3.5**),[81,87;88] *N*-substituted oxazolidin-2-ones (**3.7**),[89] 3,4-dihydro-5-hydroxy-1,3,4-oxadiazin-2-ones (**3.9**)[87] or even furanone derivatives (**3.11**)[90]etc. The nucleophiles can be both inter- or intramolecular. Scheme 3.8 shows some typical examples.

Of course, the nucleophilic attack step can be followed by another chemical transformation. For instance bis-oxazolidin-2-ones (**3.4**),[87] 4-alkylidene-oxazolidin-2-ones (**3.6**),[88] and 1,3,4-oxadiazin-2-ones **3.10**[87] can be obtained in very good yields by dehydration of the intermediate derivatives **3.3**, **3.5** and **3.9** respectively. 3*H*-indoles **3.8** can also be synthesized by cyclization of conveniently substituted 4-alkylidene-oxazolidin-2-ones **3.7**[89b] (see Scheme 3.8).

A nucleophilic attack can also be combined with a stereoselective hydrogenation step. Dixneuf et al. showed that optically active *N*-acyloxazolidinones can be readily prepared in 3 steps from 4-alkylidene-1,3-dioxolan-2-ones[88,91] (Scheme 3.9).



Scheme 3.9. Preparation of optically active *N*-acyloxazolidinones

1.3. Synthesis of 4-alkylidene-1,3-dioxolan-2-ones

Despite the vast synthetic potential of 4-alkylidene-1,3-dioxolan-2-ones, their use remains fairly limited in synthetic chemistry. This is due mainly to the limited number of general and efficient procedures to obtain them.

Indeed, most of the general methods used to obtain "regular" 1,3-dioxolan-2-ones (such as treatment of an epoxide with CO_2,[92] oxidative carboxylation of an olefin,[93] or the reaction between a 1,2-diol and a carbonylating agent[79a]) cannot be applied in the case of 4-alkylidene-1,3-dioxolan-2-ones. Instead, the latter are generally synthesized from a propargylic alcohol and CO_2 in the presence of a catalyst.

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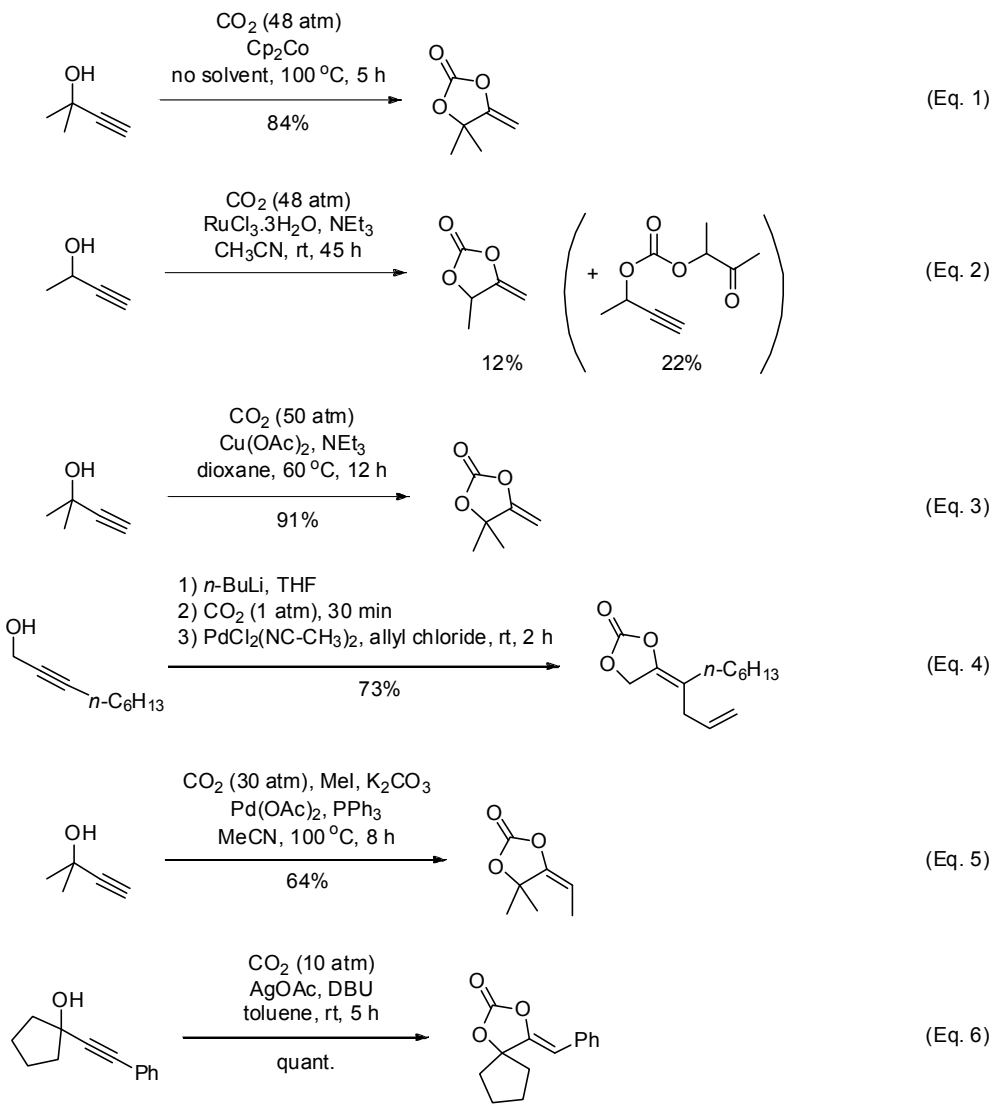
[86] Joumier, J. M.; Fournier, J.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3271-3274.
[87] Joumier, J.-M.; Grainger, R.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1993**, *1993*, 423-424.
[88] Le Gendre, P.; Thominot, P.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1998**, *63*, 1806-1809.
[89] (a) Fournier, J.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1990**, *31*, 1721-1722.
(b) Laas, H.; Nissen, A.; Nurrenbach, A. *Synthesis* **1981**, 958-959.
[90] Inoue, Y.; Ohuchi, K.; Imaizumi, S. *Tetrahedron Lett.* **1988**, *29*, 5941-5942.
[91] Le Gendre, P.; Jerome, F.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 533-534.
[92] For a review, see: Darensbourg, D. J.; Holtcamp, M. W. *Coord. Chem. Rev.* **1996**, *153*, 155-174. See also reference 79c and the references cited therein.
[93] (a) Aresta, M.; Dibenedetto, A. *J. Mol. Catal. A: Chem.* **2002**, *182-183*, 399-409.
(b) Aresta, M.; Dibenedetto, A.; Tommasi, I. *Appl. Organomet. Chem.* **2000**, *14*, 799-802.
(c) Sun, J.; Fujita, S.-i.; Bhanage, B. M.; Arai, M. *Catal. Commun.* **2004**, *5*, 83-87.

Synthesis from propargylic alcohols and CO_2

Such methods, although extensively investigated and commonly used (Scheme 3.10), present a certain number of shortcomings.

First of all, they have a rather limited scope, being usually restricted to a few tertiary terminal propargylic alcohols. Primary and secondary propargylic alcohols, as well as triple bond-substituted tertiary propargylic alcohols, generally exhibit a reduced reactivity or give other products.

Secondly, they require sometimes pretty harsh reaction conditions (temperatures usually in the range of 80-120 °C, high CO_2 pressures going from 10 to 138 atm, long reaction times, high loadings of catalyst 2-20% etc.) and the need for special laboratory equipment (such as autoclaves or high pressure reactors). This makes them suitable only for the synthesis of simple and robust molecules and restricts further their use for the synthesis of more functionalized and fragile compounds.



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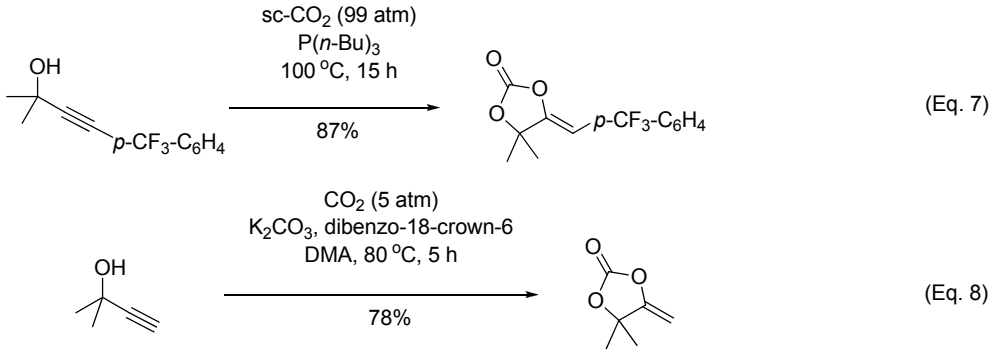

Scheme 3.10. Formation of 4-alkylidene-1,3-dioxolan-2-ones from propargylic alcohols and CO_2

The condensation of propargylic alcohols with carbon dioxide can be catalyzed by metallic species such as cobalt (Scheme 3.10, Eq. 1),[94] ruthenium (idem, Eq. 2),[95] copper (idem, Eq. 3),[96] palladium (idem, Eq. 4 and 5)[97] or silver complexes (idem, Eq. 6),[98] tertiary phosphines (idem, Eq. 7)[99] or strong bases (idem, Eq. 8).[97b] Palladium catalyzed condensations of propargyl alcohols with CO_2 are particularly interesting since they allow the formation of 4-alkylidene-1,3-dioxolan-2-ones tri- or even tetrasubstituted at the *exo*-double bond.

Synthesis from acyclic carbonates

These methods take advantage of the presence of a carbonate group in a latent form.

One approach to 4-alkylidene-1,3-dioxolan-2-ones is the use of an allylic propargylic carbonate as starting material. Palladium complexes are known to insert easily in allylic carbonates' C-O bond in order to give allylpalladium – carbonate species. However the latter decarboxylate quite easily, giving allylpalladium – alkoxyde species. In order to prevent this unwanted reaction, Uemura et al. had to perform their experiment under CO_2 pressure. Just like in the previous cases, the propargylic carbonates need to be tertiary. Secondary and primary propargyl carbonates give only modest yields (Scheme 3.11).[97b]

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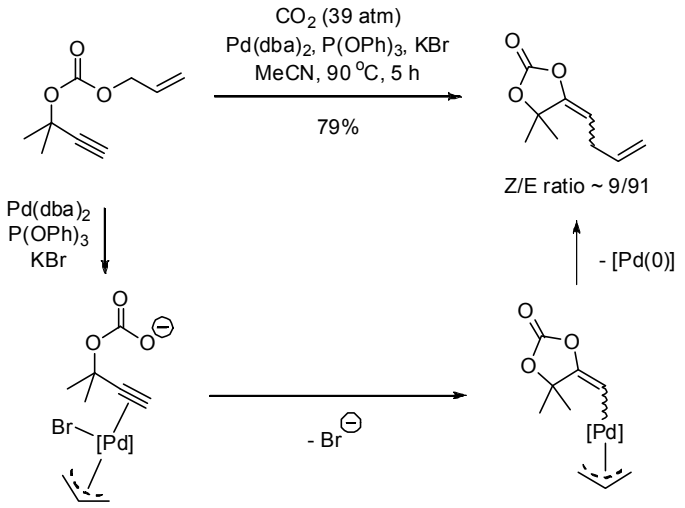
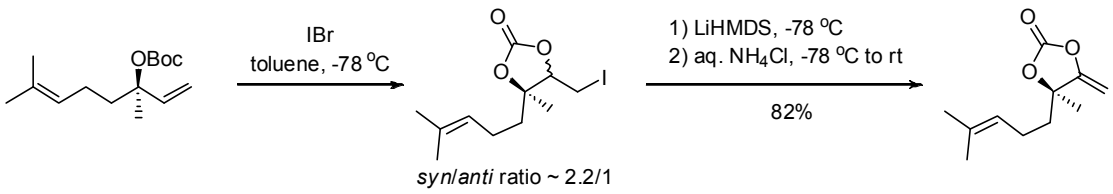
[94] Inoue, Y.; Ishikawa, J.; Taniguchi, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1204-1206.
[95] Sasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 1573-1574.
[96] (a) Dimroth, P.; Pasedach, H. *DE 1098953 B*, **1961**
(b) Schneider, K.; Best, W. *DE 3433403 A1*, **1986**
(c) Kim, H.-S.; Kim, J.-W.; Kwon, S.-C.; Shim, S.-C.; Kim, T.-J. *J. Organomet. Chem.* **1997**, *545-546*, 337-344.
(d) Kwon, S. C.; Cho, C. S.; Shim, S. C.; Kim, T. J. *Bull. Korean Chem. Soc.* **1999**, *20*, 103-105.
(e) Gu, Y.; Shi, F.; Deng, Y. *J. Org. Chem.* **2004**, *69*, 391-394.
(f) Jiang, H.-F.; Wang, A. Z.; Liu, H.-L.; Qi, C.-R. *Eur. J. Org. Chem.* **2008**, *2008*, 2309-2312.
[97] (a) Iritani, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.* **1986**, *51*, 5499-5501.
(b) Uemura, K.; Kawaguchi, T.; Takayama, H.; Nakamura, A.; Inoue, Y. *J. Mol. Catal. A: Chem.* **1999**, *139*, 1-9.
(c) Jiang, Z.-X.; Qing, F.-L. *J. Fluorine Chem.* **2003**, *123*, 57-60.
(d) Uemura, K.; Kawaguchi, T.; Takayama, H.; Nakamura, A.; Inoue, Y. *J. Mol. Catal. A: Chem.* **1999**, *139*, 1-9.
[98] Yamada, W.; Sugawara, Y.; Cheng, H. M.; Ikeno, T.; Yamada, T. *Eur. J. Org. Chem.* **2007**, *2007*, 2604-2607.
[99] (a) Fournier, J.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1989**, *30*, 3981-3982.
(b) Bruneau, C.; Dixneuf, P. H. *J. Mol. Catal.* **1992**, *74*, 97-107.
(c) Kayaki, Y.; Yamamoto, M.; Ikariya, T. *J. Org. Chem.* **2007**, *72*, 647-649.



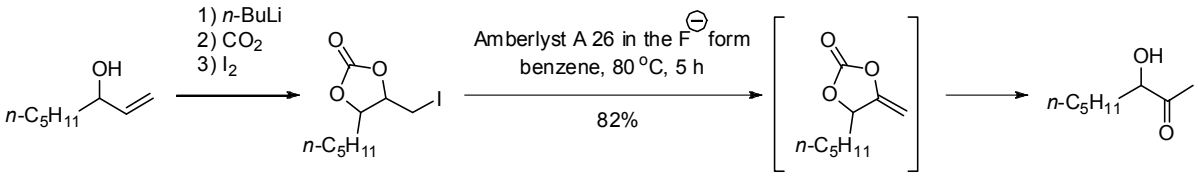
Scheme 3.11. Palladium-catalyzed rearrangement of allylic propargylic carbonates

A different approach consists in cyclizing *tert*-butyl allyl carbonates in the presence of IBr to afford saturated cyclic iodo-carbonates, from which iodide can be eliminated afterwards to afford the desired alkylidene-cyclic carbonates (Scheme 3.12).[85]



Scheme 3.12. Cyclization of *tert*-butyl allyl carbonates in the presence of IBr followed by iodide elimination

In a very similar approach, Cardillo et al. cyclized an allylic carbonate (obtained *in situ* from the corresponding allylic alcohol) using I_2. The iodo-carbonate thus obtained is treated with fluoride anion on polymeric support. The intermediate 4-alkylidene-1,3-dioxolan-2-ones derivative is not isolated, but further hydrolyzed to the corresponding α-hydroxy ketone (Scheme 3.13).[100]



Scheme 3.13. Formation of iodo-carbonates in the presence of I_2 followed by iodide elimination and hydrolysis

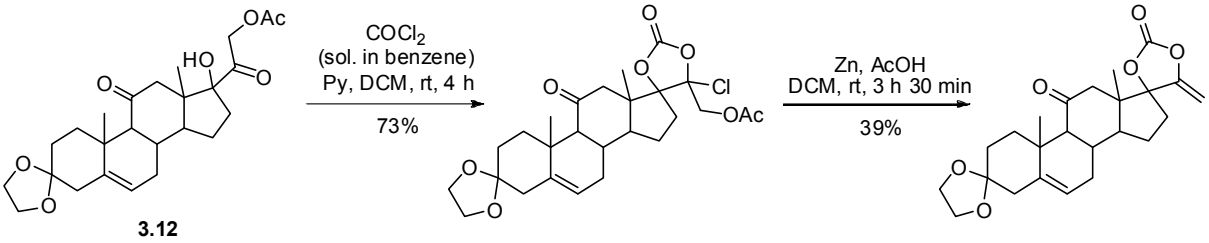
Other methods

There are also other methods which use two already existing vicinal groups on the target molecule, such as a 1,2-diol or a 1,2-ketoalcohol motif, to form the desired 4-alkylidene-1,3-dioxolan-2-one

[100] Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1984**, *49*, 701-703.

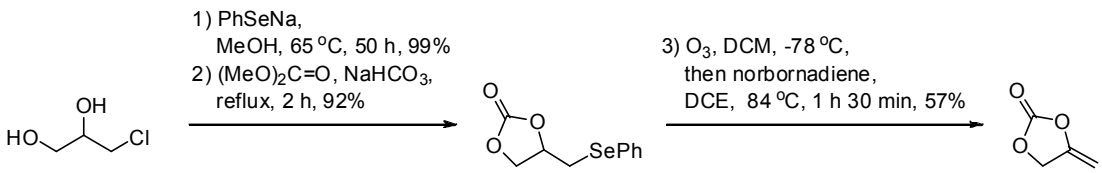
ring. Unfortunately these methods lack generality and are applicable only to particular substrates.

For example, Lewbart described the synthesis of a steroid derivative containing a 4-alkylidene-1,3-dioxolan-2-one ring starting from cortisone derivative **3.12**, which was treated with phosgene and then reduced in zinc / acetic acid conditions to afford the desired derivative alongside other degradation products (Scheme 3.14).[101]



Scheme 3.14. Formation of the 4-alkylidene-1,3-dioxolan-2-one ring starting from a 1,2-ketoalcohol

Trost et al. dedicated an entire paper to the synthesis of 4-methylene-1,3-dioxolan-3-one. The compound was prepared in a 52% overall yield in a 3 steps procedure. Its synthesis involves the oxidation of a phenylselenyl carbonate with ozone and the thermal elimination of the corresponding phenyl selenoxide to afford the *exo*-double bond. A large excess of norbornadiene (25 equiv) is needed to trap the resulting phenylselenenic acid which otherwise decomposes the final product (Scheme 3.15).[102]



Scheme 3.15. Synthesis of 4-methylene-1,3-dioxolan-3-one by Trost et al.

2. Our synthetic approach to functionalized pyrroles and furans

2.1. Precedents in the literature. The initial idea

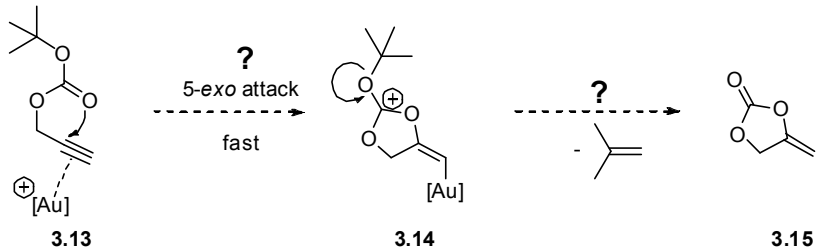
As we saw in the previous section, the current methods used to obtain 4-alkylidene-1,3-dioxolan-2-ones have a certain number of drawbacks. They apply only to very particular cases (usually tertiary terminal propargylic alcohols), demand sometimes rather energetic reaction conditions (for instance high CO_2 pressures and/or high temperatures) or require the handling of hazardous chemical products (such as phosgene, ozone, selenium compounds, mercury salts etc.).

[101] Lewbart, M. L. *J. Org. Chem.* **1976**, *41*, 78-84.
[102] Trost, B. M.; Chan, D. M. T. *J. Org. Chem.* **1983**, *48*, 3346-3347.

Given the restrictions of these methods and the potential applications of the 4-alkylidene-1,3-dioxolan-2-one moiety, we thought that a new synthetic route, which would allow an easy, effective and more general way to access this class of compounds, is highly desirable.

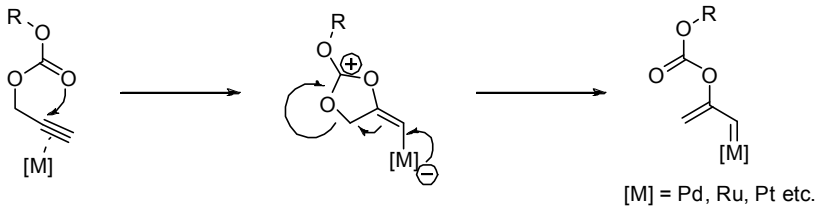
We saw in chapter 1 that gold catalysts are known for their ability to activate alkynes moieties towards the attack of a large variety of nucleophiles. A carbonyl group in particular is amongst the most common and useful ones.

Our initial idea was that a cationic gold(I)-complex could be used to promote the intramolecular 5-*exo* attack of the sp^2-oxygen on the triple bond in a propargylic *tert*-butyl carbonate precursor **3.13**. We surmised that the subsequent fragmentation of the intermediate **3.14** and the release of isobutene would provide the needed "pull-effect" for the rapid regioselective formation of 4-alkylidene-1,3-dioxolan-2-one **3.15** (Scheme 3.16).



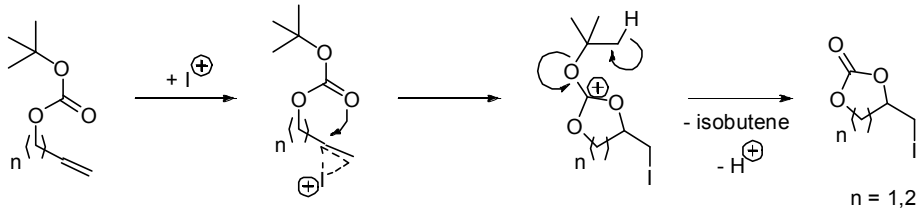
Scheme 3.16. Our initial idea for the formation of 4-alkylidene-1,3-dioxolan-2-ones

This transformation could be regarded as the beginning of a Rautenstrauch rearrangement,[103] interrupted by the fragmentation of the O – *t*-Bu bond (Scheme 3.17).



Scheme 3.17. The Rautenstrauch rearrangement

It also bears a lot of similarities with the well-known iodine-mediated cyclization of allylic and homoallylic *tert*-butyl carbonates[85,104] (Scheme 3.18; for a concrete example, see also Scheme 3.12).

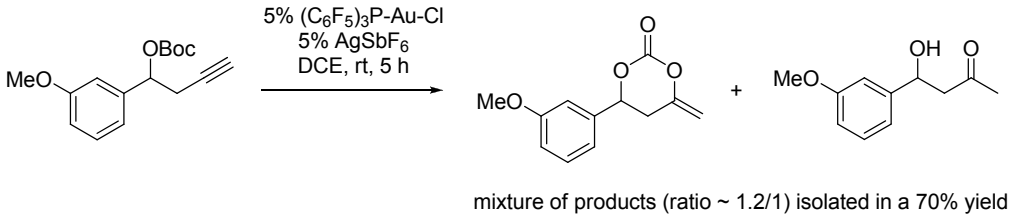


Scheme 3.18. Iodine-mediated cyclization of allylic and homoallylic *tert*-butyl carbonates

[103] Pd: (a) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950-952.
Ru, Pt: (b) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505-8513.
[104] Duan, J. J. W.; Smith, A. B. *J. Org. Chem.* **1993**, *58*, 3703-3711.

Compared to the previously described methods for the synthesis of 4-alkylidene-1,3-dioxolan-2-ones, our approach would have the advantage of using an already existing carbonate functionality on the precursor **3.13**, which in turn can be easily obtained from the corresponding propargylic alcohol using classical methods.

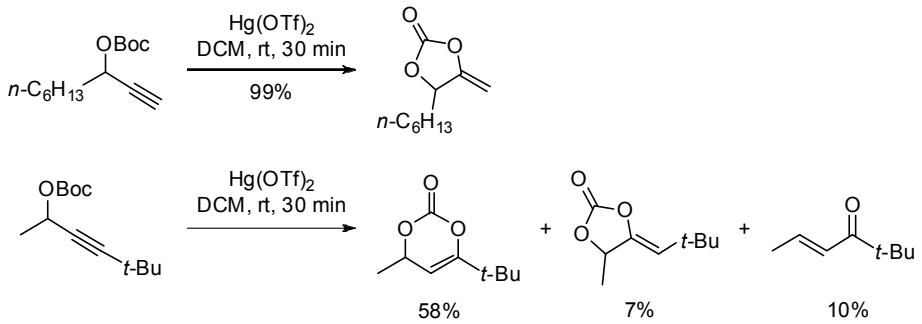
Shin already used a similar approach for the gold(I)-catalyzed cyclization of homopropargylic carbonates. His transformation is 6-*endo* regioselective, but unfortunately yields a mixture of dioxanones and hydrolyzed 1,3-hydroxyketones (Scheme 3.19).[105]



Scheme 3.19. Gold(I)-catalyzed cyclization of homopropargylic carbonates

After the publication of our group's initial report,[106] various other reports came to confirm that the *tert*-butyloxycarbonyl group can be used as an intramolecular nucleophile for the gold-catalyzed synthesis of numerous oxygenated heterocycles such as dioxolanones,[107] oxazolidinones,[108] and oxazolones.[109]

Of particular interest is also the method proposed by Nishizawa et al. which uses mercuric triflate to promote the cyclization of propargyl *tert*-butyl carbonates under very mild conditions. Unfortunately the reaction is selective only for the terminal alkynes, which give the expected 5-*exo* cyclization product. In the case of internal alkynes, mixtures of 5-*exo* and 6-*endo* isomers are obtained together with other side-products (Scheme 3.20).[110]



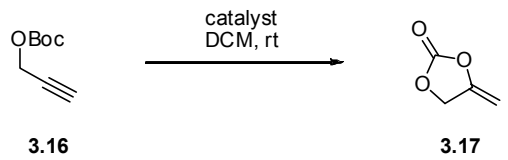
Scheme 3.20. Mercury-catalyzed rearrangement of *tert*-butyl propargylic carbonates

[105] Shin, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 1925-1926.
[106] Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515-518.
[107] Lim, C.; Kang, J.-E.; Lee, J.-E.; Shin, S. *Org. Lett.* **2007**, *9*, 3539-3542.
[108] (a) Robles-Machin, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023-5026.
(b) Buzas, A.; Gagosz, F. *Synlett* **2006**, *2006*, 2727-2730.
(c) Lee, E.-S.; Yeom, H.-S.; Hwang, J.-H.; Shin, S. *Eur. J. Org. Chem.* **2007**, *2007*, 3503-3507.
[109] (a) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Synlett* **2007**, *2007*, 1763-1766.
(b) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925-928.
[110] Yamamoto, H.; Nishiyama, M.; Imagawa, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, *47*, 8369-8373.

2.2. Preliminary results

In order to validate our approach, we decided to choose the simplest compound of its family, propargylic *tert*-butyl carbonate **3.16**, as a model substrate.

Tested in the presence of 1% of our Ph_3P-Au-NTf_2 catalyst (on a 1 mmol scale) at rt in DCM, compound **3.16** afforded the desired *exo*-methylene cyclic carbonate **3.17** in an 83% isolated yield (Table 3.1, Entry 1).

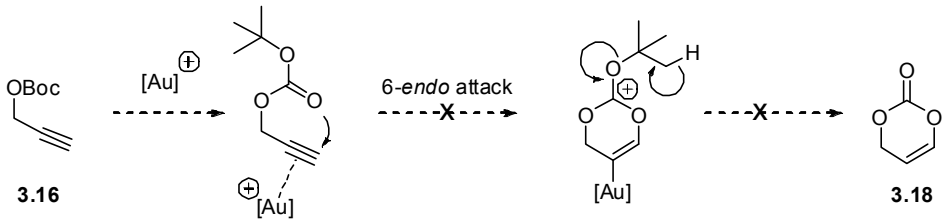


entry	catalyst	time	yield[a]
1	1% Ph_3P-Au-NTf_2	10 min	83%
2	0.1% Ph_3P-Au-NTf_2	5 h	81%
3	5% $HNTf_2$	1 h	-
4	5% $AgNTf_2$	1 h	-

Reaction conditions: substrate **3.16** (1 equiv), catalyst, DCM (0.5 M), rt. [a] Isolated yields.

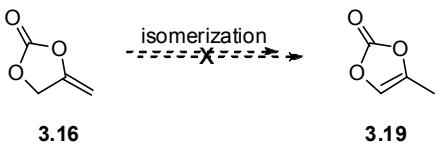
Table 3.1. Rearrangement of propargylic *tert*-butyl carbonate **3.16**

We were delighted to see that this rapid transformation (less than 10 min) is completely regioselective, no trace of **3.18** coming from a 6-*endo* cyclization being observed (Scheme 3.21).



Scheme 3.21. Hypothetical compound **3.18** coming form a 6-endo cyclization

No traces of product **3.19**, resulting from the isomerization of the double bond, were observed either (Scheme 3.22).



Scheme 3.22. Hypothetical compound **3.19** resulting from the isomerization of the double bond of compound **3.16**

We were pleased to see that the catalyst loading can be further reduced. Performing the same reaction with only 0.1% Ph_3P-Au-NTf_2 on a 12 mmol scale, the isolated yield remained practically

unchanged (81%), albeit the transformation's rate was somewhat lower (5 h reaction time) (Table 3.1, Entry 2).

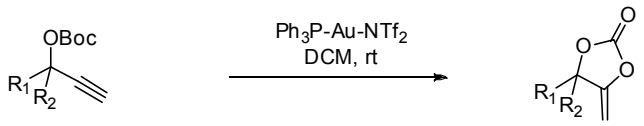
At this point it is maybe worth reminding that Trost's method[102] (see section 1.3, Scheme 3.15) used to obtain exactly the same product involved 3 steps, huge excesses of reagents (25 equiv of norbornadiene), a broad spectrum of temperatures (from -78 °C to 84 °C), the use of hazardous chemical products (like ozone or selenium derivatives etc.) and only a 52% global yield!

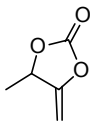
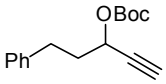
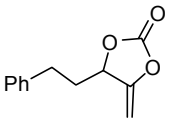
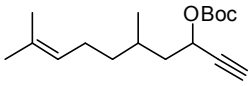
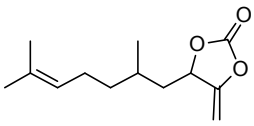
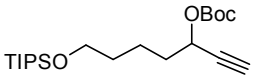
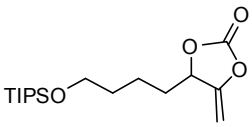
Control experiments meant to determine the exact nature of the catalytic active species led to the conclusion that $HNTf_2$ and $AgNTf_2$ are not suitable catalysts for this transformation (Table 3.1, Entries 3 and 4).

2.3. Reactivity of terminal propargylic carbonates

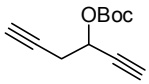
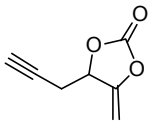
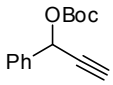
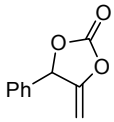
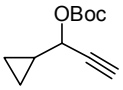
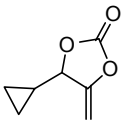
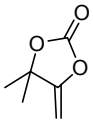
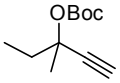
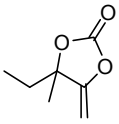
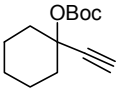
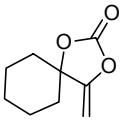
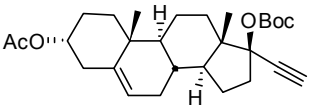
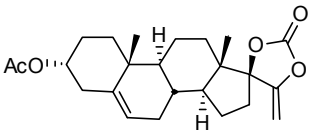
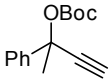
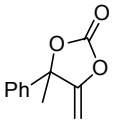
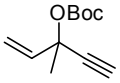
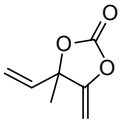
Encouraged by these preliminary results, we decided to explore the scope of the reaction. First a wide variety of propargylic carbonates possessing a terminal triple bond were tested under the conditions described in Table 3.1, Entry 1, which were retained as standard (1% Ph_3P-Au-NTf_2, DCM, rt).

The reaction proved to be quite general, since all terminal propargylic carbonates **3.20 a-f** and **h-m** gave total conversion, affording the desired 4-alkylidene-1,3-dioxolan-2-ones **3.21 a-f** and **h-m** with yields ranging from 40% to quant. (Table 3.2).



entry	substrate		product		time	yield[a]
1		**3.20 a**		**3.21 a**	15 min	94%
2		**3.20 b**		**3.21 b**	5 min	quant.
3	 dr ~ 1/1	**3.20 c**	 dr ~ 1/1	**3.21 c**	10 min	91%
4		**3.20 d**		**3.21 d**	5 min	96%

(continued on next page)

entry	substrate		product		time	yield[a]
5		**3.20 e**		**3.21 e**	5 min	95%
6		**3.20 f**		**3.21 f**	10 h	74%
7		**3.20 g**		**3.21 g**	5 h 1 h	49%[b] 49%[c]
8		**3.20 h**		**3.21 h**	5 min	85%
9		**3.20 i**		**3.21 i**	5 min	98%
10		**3.20 j**		**3.21 j**	30 min	96%
11		**3.20 k**		**3.21 k**	10 min	90%
12		**3.20 l**		**3.21 l**	17 h	76%
13		**3.20 m**		**3.21 m**	18 h	40%

Reaction conditions: substrate (1 equiv), Ph_3P-Au-NTf_2 (0.01 equiv), DCM (0.5 M), rt. [a] Isolated yields. [b] With 3% Ph_3P-Au-NTf_2. [c] With 1% [Ph_3P-Au-(NC-CH_3)]SbF_6.

Table 3.2. Reaction scope for the transformation of terminal alkynes **3.20 a-m**

The case of cyclopropyl substituted substrate **3.20 g** was particular, because it did not give full conversion under standard conditions (1% Ph_3P-Au-NTf_2). Its complete conversion required either a higher loading of catalyst (3% Ph_3P-Au-NTf_2) or the use of a more electrophilic gold complex (1% [Ph_3P-Au-(NC-CH_3)]SbF_6) and afforded final product **3.21 g** in both cases in a moderate 49% yield (Table 3.2, Entry 7).

Unlike previously reported methods, our transformation did not seem to be much influenced by the number of substitutions at the propargylic position. For example, primary (see compound **3.16**, Table 3.1, Entry 1), secondary (**3.20 a**, Table 3.2, Entry 1) and tertiary (**3.20 h**, Table 3.2, Entry 8) propargylic

carbonates exhibit all similar reactivities in our reaction conditions, giving similar reaction times (5 to 15 min) and yields (83 to 94%).

The nature of the substitutions however did play an important role. As a general rule the products substituted with phenyl, vinyl or cyclopropyl groups were isolated in lower yields and reacted with slower (40% - 76% and 1 h - 18 h for products **3.21 f, g, l, m** in Table 3.2, Entries 6, 7, 12 and 13) compared to those substituted with plain alkyl or functionalized alkyl groups (85% - 100% and 5 min - 30 min for products **3.21 a-e** and **h-k** in Table 3.2, Entries 1-5 and 8-11).

The lower isolated yield of alkylidene cyclic carbonates **3.21 f, g, l**, **m** substituted with phenyl, vinyl or cyclopropyl groups can be attributed to the competitive formation of various side-products. It should be noted that all these groups have a double bond (or a partial double bond) character and are all good carbocation stabilizing groups.

One hypothesis for the reason why those side-products are formed is that the gold catalyst, although very mild and selective, might be acidic enough to induce a competitive fragmentation of the C-O propargylic bond leading to undesired products. However it is curious that no such side products are observed in the case of tertiary alkyl substituted propargylic alcohols **3.20 h-k** (Table 3.2, Entries 8-11).

Another hypothesis is that cyclic carbonates products **3.21 f, g, l**, **m** are not stable enough and, once formed, partially decompose giving various side-products.

As we said earlier, products substituted with plain alkyl groups (either linear as **3.21 a** or **i**, branched as **3.21 c** or cyclic as **3.21 j**) or with functionalized alkyls groups (i.e. possessing various functionalities such as alkenes **3.21 c**, protected alcohols **3.21 d** and **k**, alkynes **3.21 e** etc.) present no such problems and give excellent yields (Table 3.2, Entries 1-5 and 8-11).

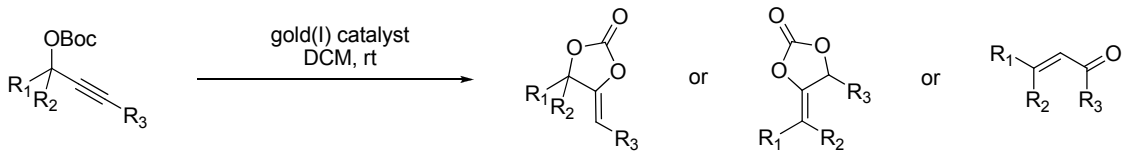
The androstene case (Table 3.2, Entry 11) was particularly interesting, since the final steroid derivative **3.21 k**, once formed, precipitates from the reaction medium and can be isolated by a simple filtration in a very good 90% yield. This example can be compared with the approach taken by Lewbart towards the synthesis of very similar alkylidene cyclic carbonate derived from a steroid (see ref. 101 and Scheme 3.14).

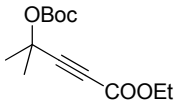
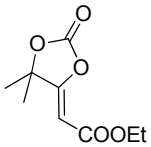
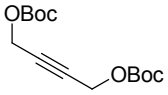
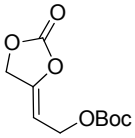
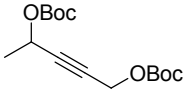
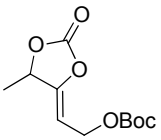
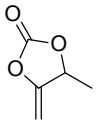
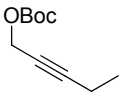
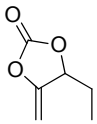
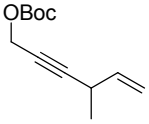
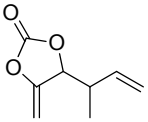
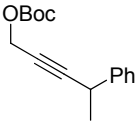
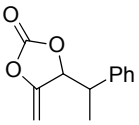
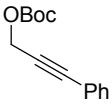
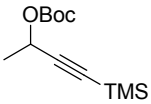
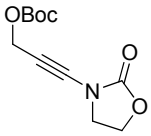
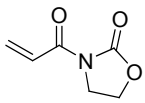
Another pleasant surprise was the regioselective rearrangement of diyne **3.20 e** (Table 3.2, Entry 5). The *tert*-butyl carbonate exclusively cyclizes on the α-triple bond giving the expected 5-*exo* compound **3.21 e** in an excellent 95% yield. No sign of 6-*exo* or 7-*endo* products resulting from a cyclization on the other triple bond are observed.

Our method seemed to compatible with a large number of functional groups: phenyl (products **3.21 b, f** or **l** in Table 3.2, Entries 2, 6 and 12), alkene (products **3.21 c, k** or **m** in Table 3.2, Entries 3, 11 and 13), alkyne (as we saw earlier, product **3.21 e** in Table 3.2, Entry 5), silyl ether (product **3.20 d** in Table 3.2, Entry 4) or ester (product **3.20 k** in Table 3.2, Entry 11).

2.4. Reactivity of internal propargylic carbonates

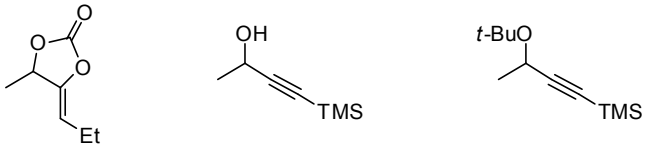
We next focused our attention on propargylic carbonates possessing an internal triple bond (Table 3.3).



entry	substrate		product		time	yield[a]
1		**3.22 a**		**3.23 a**	2 h	87%[b]
2		**3.22 b**		**3.23 b**	50 min	62%[b]
3		**3.22 c**		**3.23 c**	30 min	77%[b]
4		**3.22 d**		**3.23 d**	24 h	62%[c]
5		**3.22 e**		**3.23 e**	24 h	60%[c,d]
6		**3.22 f**	 dr ~ 1/1.6	**3.23 f**	20 h	68%[c]
7		**3.22 g**	 dr ~ 1/3.9	**3.23 g**	20 h	66%[c]
8		**3.22 h**	-		24 h	_[b,c,e]
9		**3.22 i**	-		3 h	_[b,c,f]
10		**3.22 j**		**3.23 j**	30 min	94%[b]

(continued on the next page)

Reaction conditions: substrate (1 equiv), gold(I) catalyst (0.01 equiv), DCM (0.5 M), rt. [a] Isolated yield. [b] With 1% Ph_3P-Au-NTf_2. [c] With 1% (p-CF_3-C_6H_4)$_3$P-Au-NTf_2. [d] Side-product **3.24** was isolated in a 10% yield [e] Mainly starting material was recovered at the end of this transformation. [f] Starting material was recovered at the end of this transformation along with side-products **3.25** (22%) and **3.26** (15%).



3.24 **3.25** **3.26**

Table 3.3. Reaction scope for the transformation of internal alkynes **3.22 a-j**

Substrates **3.22 a-c** were tested under standard conditions (1% Ph_3P-Au-NTf_2). We were delighted to observe the complete conversion of the substrates and the stereoselective formation of the expected alkylidene cyclic carbonates **3.23 a-c** exclusively with the *Z*-configuration (Table 3.3, Entries 1-3) (62% - 87% yields).

Cyclization of substrate **3.22 a** substituted with an ester group at the triple bond can be viewed as a gold-catalyzed Michael-addition (Table 3.3, Entry 1).

As expected, substrate **3.22 c** reacted faster and gave a better yield than substrate **3.22 b** due to the Thorpe-Ingold effect exerted by the methyl group (Table 3.3, Entries 2 and 3). The second *tert*-butyl carbonate group remains intact in both cases, proving once more the selectivity of this method.

It is also interesting to notice that once again, judging only from those 3 examples, the number of substituents at the propargylic position (**3.22 a** is a tertiary carbonate, **3.23 b** primary and **3.23 c** a secondary one) did not seem to influence that much this transformation.

This is one of the reasons we were extremely puzzled when substrates **3.22 d-g** showed a very low conversion under standard conditions (1% Ph_3P-Au-NTf_2). Using a more electrophilic gold complex (1% (p-CF_3-C_6H_4)$_3$P-Au-NTf_2) the rearrangement became effective, but we noticed that the isolated main products **3.23 d-g** were different from the expected products. To our surprise, the cyclic carbonate motif was shifted by one carbon resulting in structures with an *exo*-methylene functionality. The yields were generally smaller (60% - 68%) and the reaction times longer (between 20 and 24 hours) than in the case of propargylic carbonates giving the "normal" rearrangement.

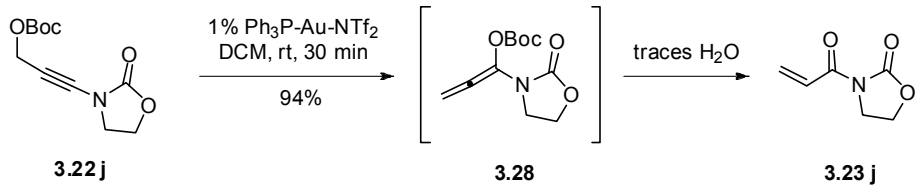
Although the factors favoring this unpredicted rearrangement cannot be fully rationalized, we can assume that it is competitive with the "normal" one. This assumption is supported by the isolation of a small quantity (10%) of **3.24**, resulting from the "normal" rearrangement, in the case of substrate **3.22 e**, along with 60% of **3.23 e** (Table 3.3, Entry 5).

Substrates **3.22 f** and **3.22 g**, containing an asymmetric center, gave diastereoisomeric mixtures of cyclic carbonates. Although the stereoselectivity remains modest, it seems to improve as the size of the group inducing the asymmetry increases (Table 3.3, Entries 6 and 7).

Disappointingly, compound **3.22 h** was unreactive, whatever conditions used (Table 3.3, Entry 8).

Substrate **3.22 i** on the other hand degraded in the presence of both gold catalysts (Table 3.3, Entry 9). Small amounts of side products **3.25** (22%) and **3.26** (15%) were isolated in this case.

Finally, substrate **3.22 j** produced under standard conditions **3.23 j** in an excellent 94% yield (Table 3.3, Entry 10). The formation of product **3.23 j** is analogous to the rearrangement of propargylic esters to α,β-unsaturated ketones described by Zhang et al.[111] It consists in a gold(I)-catalyzed rearrangement to the *tert*-butoxycarbonyloxyallene **3.28**[112] followed by hydrolysis by traces of water (Scheme 3.23).

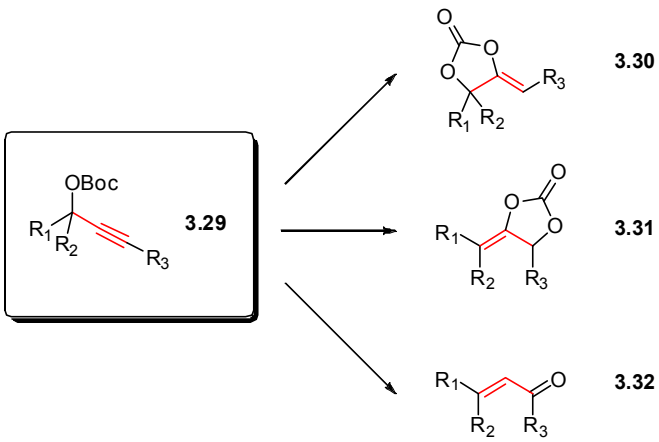


Scheme 3.23. Rearrangement of *tert*-butyl carbonate **3.22 j**

2.5. Mechanistic proposal

We saw in the last 3 sections that the outcome of the gold-catalyzed rearrangement of propargylic *tert*-butyl carbonates **3.29** is highly dependent on the structure of the initial substrate.

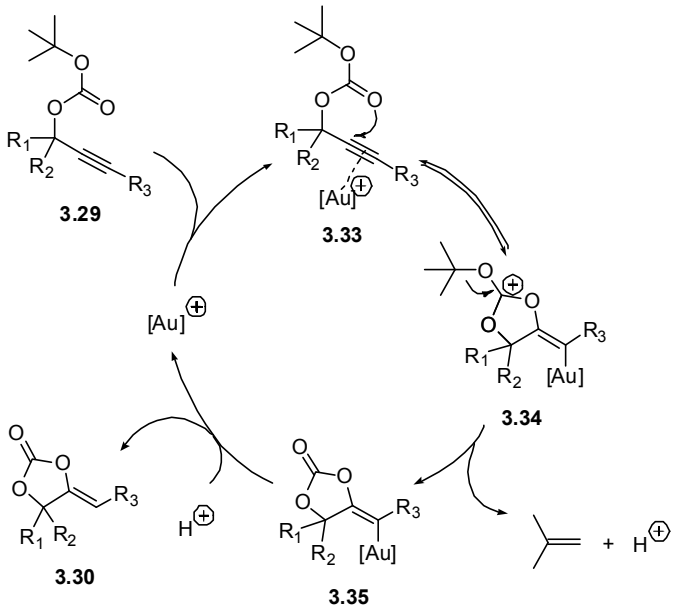
Terminal alkynes (R_3 = H and various R_1 and R_2 substitutions) always give the "normal" 4-alkylidene-1,3-dioxolan-2-one **3.30**. Internal alkynes ($R_3 \neq$ H) can give either the "normal" 4-alkylidene-1,3-dioxolan-2-one **3.30** of *Z* stereochemistry (typically for R_3 = electron withdrawing group and various R_1 and R_2 substitutions) or the "shifted" 4-alkylidene-1,3-dioxolan-2-one **3.31** (typically for R_3 = alkyl and $R_1 = R_2$ = H). There are also particular cases (such as substrate **3.23 j** with R_3 = oxazolidinone, $R_1 = R_2$ = H) which can give the α,β-unsaturated carbonylic compounds **3.32**.[111] Scheme 3.24 summarizes these possibilities.



Scheme 3.24. Various possibilities for the gold-catalyzed rearrangement of propargylic *tert*-butyl carbonates

[111] Yu, M.; Li, G.; Wang, S.; Zhang, L. *Adv. Synth. Catal.* **2007**, *349*, 871-875.
[112] This rearrangement can happen via a 1,3-shift or a double 1,2-shift. For a discussion of the possible mechanism, see the theoretical study about the gold-catalyzed rearrangement of propargylic esters: Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718-721.

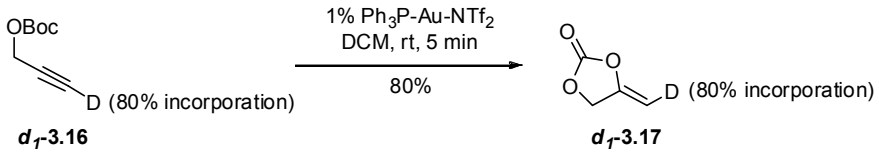
A mechanism meant to explain the formation of product **3.30** is proposed in Scheme 3.25. It starts with the activation of the alkyne moiety in substrate **3.29** by the active form of the gold catalyst. A nucleophilic attack of the sp^2-oxygen follows leading to the formation of the cationic intermediate **3.34**. A selective fragmentation of the *t*-Bu – O bond in the *tert*-butyl carbonate furnishes the neutral vinyl-gold intermediate **3.35** and releases isobutene that leaves the system (this is probably the "pull effect" which renders this transformation so effective). A final fast protodemetallation step gives cyclic carbonate **3.30** and regenerates the gold-catalyst.



Scheme 3.25. Mechanistic proposal explaining the formation of product **3.35**

The reaction is most likely under kinetic control, which combined with the fact that 5-*exo* attacks are generally faster that 6-*endo* ones, might explain the exclusive formation of the 5-*exo* regioisomer.

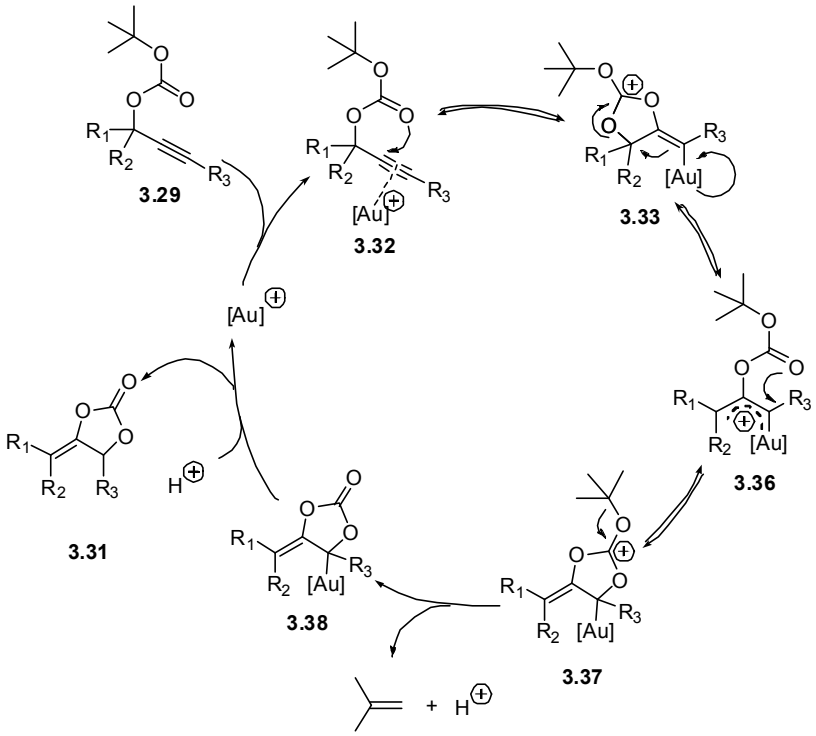
The *anti* addition of the Boc group on the activated alkyne combined with the stereoselective protodemetalation step are in agreement with the stereospecific formation of compounds **3.23 a-c**. An experiment involving the gold-catalyzed rearrangement of deuterated propargyl *tert*-butyl carbonate ***d₁*-3.16** which led to the exclusive formation of ***d₁*-3.17** further confirms this mechanistic proposal (Scheme 3.26).



Scheme 3.26. Rearrangement of deuterated propargyl *tert*-butyl carbonate ***d₁*-3.16**

This mechanistic pathway seems to be preferred by terminal alkynes, alkynes substituted with an electron withdrawing group and alkynes substituted with a $-CH_2$-Boc group.

For alkynes substituted at the triple bond with an alkyl group the pathway described in Scheme 3.25 is less favorable and another route seems to be preferred. Scheme 3.27 proposes such an alternative mechanism.

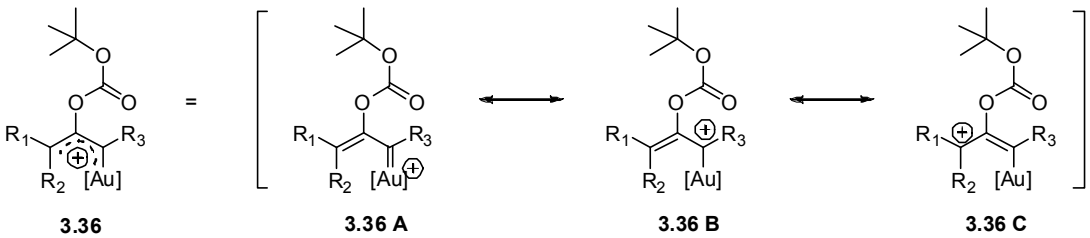


Scheme 3.27. Mechanistic proposal explaining the formation of product **3.39**

It begins just like in the previous case with the activation of the triple bond and the nucleophilic attack of the Boc group, leading to the formation of the **3.33**. The fragmentation of an internal C–O bond occurs in this case (as opposed to the fragmentation of the *t*-Bu–O bond in the previous case) which gives the cationic gold intermediate **3.36**.[113] A second attack of the Boc group furnishes **3.37**, followed by the fragmentation of the *t*-Bu–O bond and the release of isobutene. Vinyl gold intermediate **3.38** is then protodemetallated yielding cyclic carbonate **3.31**.

The mechanism depicted in Scheme 3.27 was proposed mainly because it is in accord with other mechanisms proposed in the literature. Note for instance that the sequence **3.29** – **3.36** is equivalent to a Rautenstrauch rearrangement[103] (see also Scheme 3.17). Of course, this is not the only possible mechanism that can be proposed. Other mechanisms can also be imagined, involving for example a

[113] We believe that the cationic gold intermediate **3.36** is probably best depicted as in Scheme 3.27, with the positive charge delocalized on the gold atom and three other carbon atoms. However, it can also be described by one of its three limit forms with a localized charge: the gold carbene **3.36 A** (very often in the literature it appears under this form, although it is not a true carbene derivative, but more of a carbenoid derivative), the form with a positive charge at the carbon atom linked to gold, stabilized by the metal by backdonation, **3.36 B** (which accounts for the regioselectivity of the second nucleophilic attack of the Boc group) or the homoallylic tertiary carbocation **3.36 C** (resulting from the fragmentation of the internal C–O bond). Depending on the transformation in which **3.36** is involved, one form might describe better than the others the observed reactivity.



direct 1,3-shift of the Boc group via a 6-*endo* nucleophilic attack on the activated alkyne. For a detailed discussion about 1,3-shifts vs. double 1,2-shifts in propargylic esters, see the journal cited in ref. 112.

2.6. Extension to the formation of 4-halomethylene-1,3-dioxolan-2-ones

Vinyl halides are one of the most important building blocks in organic chemistry. They are used in a large variety of synthetically useful applications, the most important being by far the metal catalyzed cross-couplings. Their efficient preparation, especially in a stereoselective fashion, is therefore an important objective.[114]

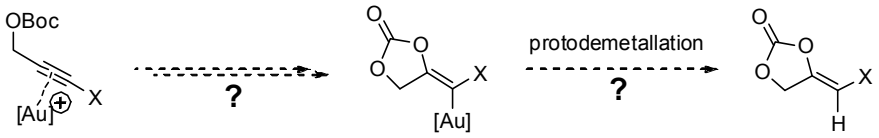
Vinyl halides are obtained mainly by olefination reactions, although the stoichiometric halogenation of carbon–metal bonds is very common as well. Lately the use of transition metal complexes as catalysts for the formation of vinyl halides starting from alkynes has become an area of growing interest.[115] This type of reactions generally leads to either the *Z* or the *E* isomer. A catalytic system that allows, stereoselectively, the formation of both isomers is of great interest, of course.

Our objective was therefore to extend our method to the formation of 4-halomethylene-1,3-dioxolan-2-ones. We also wanted to have selective access to either one of the two isomers and this in an efficient way (Figure 3.3).

Figure 3.3. 4-halomethylene-1,3-dioxolan-2-ones of *Z*- (left) and *E*-configuration (right)

Synthesis of 4-(*Z*-halomethylene)-1,3-dioxolan-2-ones

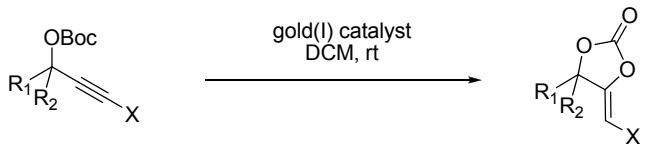
We saw in Section 2.4 that propargylic carbonates substituted with an electron withdrawing group have the tendency to give exclusively the *Z*-isomer. We surmised that the same approach applied to a halogen-substituted alkyne would lead to the stereoselective formation of 4-(*Z*-halomethylene)-1,3-dioxolan-2-ones (Scheme 3.28).

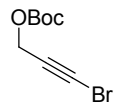
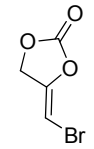
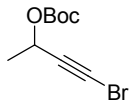
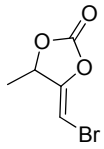
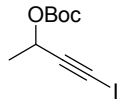
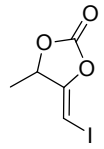
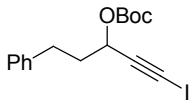
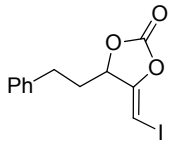
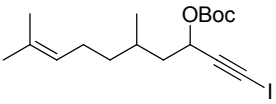
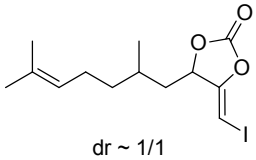
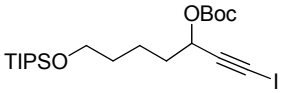
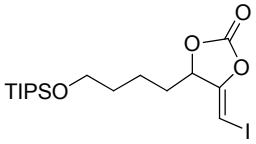
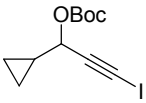
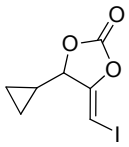
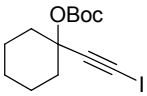
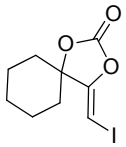


Scheme 3.28. Initial idea for the formation of 4-(*Z*-halomethylene)-1,3-dioxolan-2-ones

[114] See the editorial: Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1439-1439. See also the articles featured in that special issue of *Acc. Chem. Res.* dedicated to cross-couplings and the references cited therein.
[115] See for example: Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2002**, *124*, 7376-7389. and the references cited therein.

These substrates of *Z*-configuration are particularly important since they cannot be formed form similar propargylic carbonates using the methods previously reported in the literature: direct iodolactonization[85,104] would give the opposite *E*-isomer (Scheme 3.18), while Nishizawa's mercury-catalyzed reaction simply does not work in those cases (Scheme 3.20).[110]



entry	substrate		product		time	yield[a]
1		**3.40 a**		**3.41 a**	1 h	87%
2		**3.40 b**		**3.41 b**	20 min	87%
3		**3.40 c**		**3.41 c**	10 min	95%
4		**3.40 d**		**3.41 d**	5 min	99%
5	 dr ~ 1/1	**3.40 e**	 dr ~ 1/1	**3.41 e**	5 min	97%
6		**3.40 f**		**3.41 f**	5 min	69%
7		**3.40 g**		**3.41 g**	1 h	32%[b]
8		**3.40 h**		**3.41 h**	5 min	83%

Reaction conditions: substrate (1 equiv), Ph_3P-Au-NTf_2 (0.01 equiv), DCM (0.5 M), rt. [a] Isolated yields. [b] With 1% [Ph_3P-Au-(NC-CH_3)]SbF_6.

Table 3.4. Reaction scope for the formation of 4-(*Z*-halomethylene)-1,3-dioxolan-2-ones **3.41 a-h**

Several bromo- and iodoalkynes **3.40 a-h** were tested using the standard conditions (1% Ph_3P-Au-NTf_2). We were delighted to see the rapid formation of the expected haloalkynes **3.41 a-h** in the desired *Z*-configuration (Table 3.4).

It is interesting to observe that the presence of a halogen substituent on the alkyne moiety did not slow down the reaction. In fact the reaction times were strikingly similar to those observed in the case of the corresponding terminal alkynes (see Table 3.1 and Table 3.2). As before, primary, secondary and tertiary propargylic carbonates proved all to be reactive.

Bromoalkyne **3.40 b**, having an extra methyl substituent at the propargylic position, reacted faster than alkyne **3.40 a** (20 min vs. 1 h), although it gave same yield (87%). Its iodo- equivalent **3.40 c**, on the other hand, gave both a better rate and a better yield (10 min, 95%) (Table 3.4, Entries 1-3).

The reaction proved to be quite tolerant towards various functional groups. A phenyl group (Table 3.4, Entry 4), an alkene (Table 3.4, Entry 5) or a silyl ether (Table 3.4, Entry 6) reacted all in good yields (69%-99%).

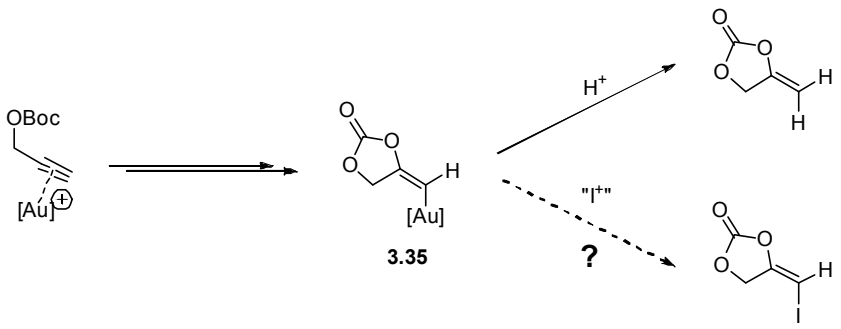
Just like in the case of the terminal alkyne **3.20 g** (Table 3.2, Entry 7), the cyclopropyl substituted compound **3.40 g** gave a disappointing result. Only traces of iodoalkene **3.41 g** were isolated when the reaction was performed under standard conditions (1% Ph_3P-Au-NTf_2). This transformation required a more electrophilic gold catalyst (1% [Ph_3P-Au-(NC-CH_3)]SbF_6) to reach full completion. The final product **3.41 g** was isolated in a modest 32% yield (Table 3.4, Entry 7). The formation of numerous side-products can be attributed to similar causes as for **3.20 g**.

Synthesis of 4-(*E*-iodomethylene)-1,3-dioxolan-2-ones

As we saw in section 2.5, the proposed last step of the rearrangement of terminal propargylic carbonates is the rapid protodemetallation of a vinyl gold derivative **3.35** of *E*-configuration (Scheme 3.27). This protodemetallation step is stereospecific and the newly introduced proton has also the *E*-configuration. We were wondering if another electrophile could be used to trap the same vinyl gold intermediate **3.35** (instead of the proton). The main issue was that the two processes, the protodemetallation and the electrophile-demetallation, would be competitive. Of course, if the electrophile-demetallation process could be rendered fast enough (before protodemetallation occurs), this would not be a problem any more.

In order to validate our hypothesis, NIS was chosen as an electrophilic iodine source.[108b,116] If viable, this approach was supposed to produce 4-(*E*-iodomethylene)-1,3-dioxolan-2-ones (Scheme 3.29).

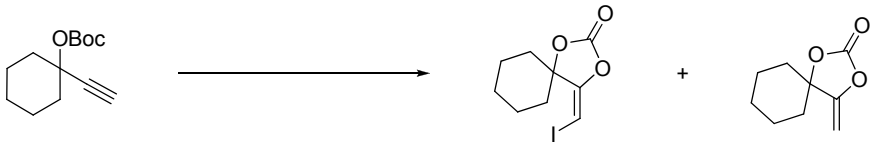
[116] (a) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 2310-2313.
(b) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147-2150.
(c) Crone, B.; Kirsch, S. F. *J. Org. Chem.* **2007**, *72*, 5435-5438.



Scheme 3.29. Initial idea for the formation of 4-(*E*-halomethylene)-1,3-dioxolan-2-ones

The formation of these compounds is theoretically possible even without the use of a gold-catalyst via iodine-mediated cyclization. Although never applied on propargylic carbonates, iodine-mediated cyclization is well documented for allylic or homoallylic *tert*-butyl carbonates.[85,104] Even an example on homopropargylic *tert*-butyl carbonates using IBr has been reported.[117]

Therefore, before trying the gold-catalyzed transformation, we decided to perform a control experiment on substrate **3.20 j** using just NIS (2 equiv) in acetone. The formation of *E*-iodoalkene **3.42** was rather slow, after 3 h just 5% of expected product being isolated (Table 3.5, Entry 1). Waiting for full consumption of the starting material required 48 h and afforded compound **3.42** in an 83% yield (Table 3.5, Entry 2).



3.20 j **3.42** **3.21 j**

entry	NIS	solvent	catalyst	time	product yield[a]	side-product yield[a]
1	2 equiv	acetone	-	3 h	5%	-
2	2 equiv	acetone	-	48 h	83%	-
3	1.2 equiv	DCM	1% Ph_3P-Au-NTf_2	5 min	48%	48%
4	1.2 equiv	acetone	1% Ph_3P-Au-NTf_2	5 min	95%	-

Reaction conditions: substrate (1 equiv), NIS (1.2 or 2 equiv, see table), Ph_3P-Au-NTf_2 (0.01 equiv only in some cases, see table), solvent (0.5 M), rt. [a] Isolated yields.

Table 3.5. Formation of *E*-iodoalkyne **3.42**

Next we wanted to see if the presence of a gold-catalyst could improve this transformation. The standard conditions used for the formation of propargylic carbonates were first tried (1% Ph_3P-Au-NTf_2 in DCM, rt) in the presence of a slight excess of NIS (1.2 equiv). The reaction was rapid (5 min), however a mixture of protodemetalleted derivative **3.21 j** and *E*-iodoalkene **3.42** was obtained (Table 3.5, Entry 3).

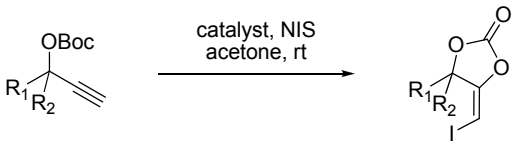
Hoping to improve the ratio of **3.42**, another experiment was performed using acetone as a solvent. We were hoping that a more polar solvent would slow down the protodemetallation and favor the

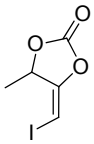
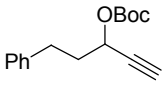
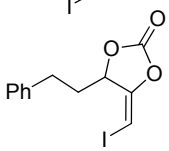
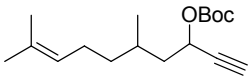
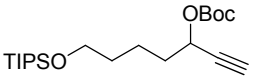
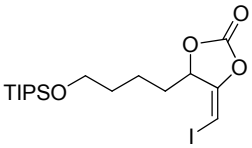
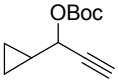
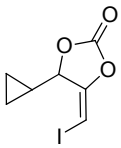
[117] Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798-3799.

trapping of the vinyl-gold intermediate by NIS. To our delight, this transformation led to the exclusive and stereoselective formation of *E*-iodoalkene **3.42** in 5 min and 95% yield (Table 3.5, Entry 4).

Even if this result does not prove that **3.42** is formed after an iododemetallation step of the vinyl-gold intermediate, it clearly shows that the gold complex plays a role in this transformation, fact proven by the huge difference in kinetics and the improved isolated yield (5 min vs. 48 h and 95% vs. 83%). As a further argument to support our hypothesis, several similar iododemetallation processes have been proposed in the literature.[108b,116]

Using these newly optimized conditions, diversely substituted propargylic carbonates **3.20 a-d, g** and **3.16** were tested. The results were rather surprising. While tertiary carbonate **3.20 j** gave an excellent yield, secondary derivatives **3.20 a, b, d** and **g** gave only moderate yields (35%-76%). Reaction times were also longer in the case of these secondary derivatives compared to the simple cyclization process (see Table 3.2), fact that can be a consequence of the lower activity of the gold complex in acetone (Table 3.6).



entry	substrate		product		time	yield[a]
1		**3.20 a**		**3.43 a**	5 min	35%
2		**3.20 b**		**3.43 b**	45 min	66%
3		**3.20 c**	-		5 min	-
4		**3.20 d**		**3.43 c**	15 min	64%
5		**3.20 g**		**3.43 d**	1 h	76%[b]
6		**3.16**	-		15 min	-

Reaction conditions: substrate (1 equiv), NIS (1.2 equiv), Ph_3P-Au-NTf_2 (0.01 equiv), acetone (0.5 M), rt. [a] Isolated yields. [b] With 1% [Ph_3P-Au-(NC-CH_3)]SbF_6.

Table 3.6. Reaction scope for the formation of 4-(E-iodomethylene)-1,3-dioxolan-2-ones **3.43 a-d**

This transformation therefore was not as general as the simple cyclization. In some cases, like that of the simple propargylic carbonate **3.20 a** substituted with a single methyl group, the formation of large number of side products was observed (Table 3.6, Entry 1). Other cases like **3.20 b** or **3.20 d** substituted with longer alkyl chains gave less side products (Table 3.6, Entries 2 and 4).

Substrate **3.20 c** completely degraded (Table 3.6, Entry 3). It is unclear if this can be attributed to the interaction of NIS with the alkene moiety.

Surprisingly, only limited desilylation occurred in the case of substrate **3.20 d**, product **3.43 c** being isolated in a 64% yield (Table 3.6, Entry 4). It was also unexpected to see that cyclopropyl derivative **3.20 g** furnished **3.43 d** in good yield (76%), although the use of a more electrophilic [Ph_3P-Au-(NC-CH_3)]SbF_6 was required just like in the case of simple cyclization (Table 3.6, Entry 5).

Primary propargylic derivative **3.16** degraded completely under standard conditions (Table 3.6, Entry 6).

2.7. Palladium cross-coupling reactions

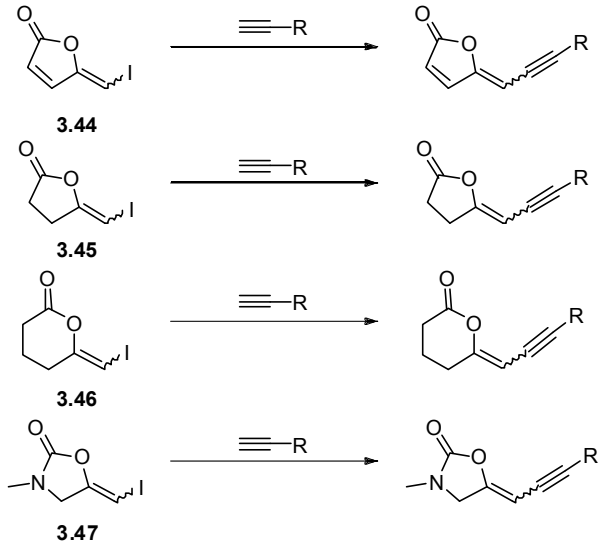
As we saw in section 1.3, there are currently very few methods available for the synthesis of 4-alkylidene-1,3-dioxolan-2-ones substituted at the *exo*-double bond. Most of them are based on the condensation of a substituted propargylic alcohol with CO_2 and give exclusively the *Z*-isomer, while others, catalyzed by palladium and producing the *E*-isomer, are limited in terms of functional groups that can be introduced.

This is why the 4-halomethylene-1,3-dioxolan-2-ones previously described were potentially valuable building blocks for accessing this type of structures. We wanted to validate this approach by engaging them in several palladium-catalyzed cross-coupling reactions.

Sonogashira coupling

Various 4-iodomethylene-heterocycles such as furanones **3.44**,[118] dihydrofuranones **3.45**,[119] tetrahydropyranones **3.46**[119,120] or oxazolidinones **3.47**[121] have already been used successfully in Sonogashira couplings (Scheme 3.30). For this reason we decided to focus our attention first on this transformation.

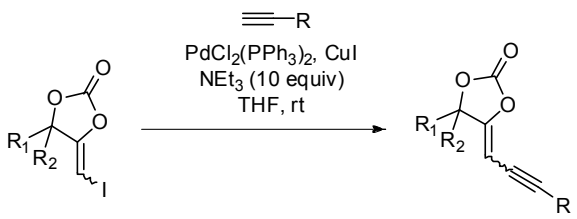
[118] Duchene, A.; Thibonnet, J.; Parrain, J.-L.; Anselmi, E.; Abarbri, M. *Synthesis* **2007**, *2007*, 597-607.
[119] (a) Spencer, R. W.; Tam, T. F.; Thomas, E.; Robinson, V. J.; Krantz, A. *J. Am. Chem. Soc.* **1986**, *108*, 5589-5597.
(b) Tam, T. F.; Spencer, R. W.; Thomas, E. M.; Copp, L. J.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 6849-6851.
[120] Zupan, L. A.; Weiss, R. H.; Hazen, S. L.; Parnas, B. L.; Aston, K. W.; Lennon, P. J.; Getman, D. P.; Gross, R. W. *J. Med. Chem.* **1993**, *36*, 95-100.
[121] (a) Tam, T. F.; Thomas, E.; Krantz, A. *Tetrahedron Lett.* **1987**, *28*, 1127-1130.
(b) Pinto, I. L.; Boyd, H. F.; Hickey, D. M. B. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2015-2017.

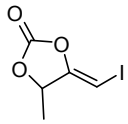
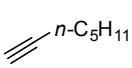
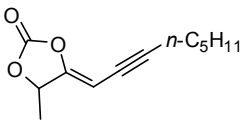
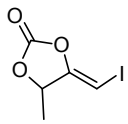
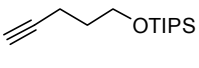
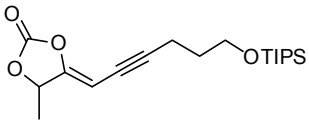
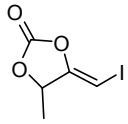
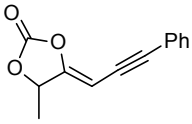


Scheme 3.30. Literature precedents for Sonogahira cross-coupling reactions involving substrates structurally related to 4-halomethylene-1,3-dioxolan-2-ones

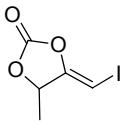
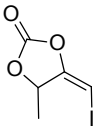
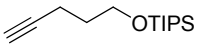
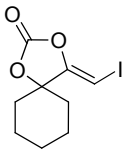
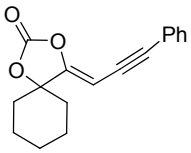
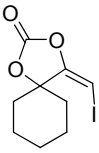
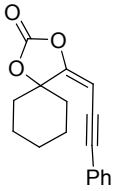
Various alkynes were coupled with the *Z*-iodoalkene **3.41 b** under standard Sonogashira conditions to give enynes **3.48 a-c** in yields comprised between 67% and 72%. Different substitutions on the alkyne partner were tolerated, such as plain alkyl, alkyl functionalized with silyl ether groups, or aryl (Table 3.7, Entries 1-3).

The reaction seemed to be sensitive to the amount of triethylamine present in the reaction mixture. With only 10 equiv of NEt_3 the reaction between **3.41 b** and phenylacetylene proceeded smoothly (Table 3.7, Entry 3). On the other hand, when NEt_3 was used as a solvent, a mixture of degradation products was obtained (Table 3.7, Entry 4).



entry	substrate		alkyne	product		time	yield[a]
1		**3.41 b**			**3.48 a**	1 h 30 min	67%
2		**3.41 b**			**3.48 b**	18 h	67%
3		**3.41 b**			**3.48 c**	20 min	72%

(continued on the next page)

entry	substrate	alkyne	product	time	yield[a]
4	 **3.41 b**		-	30 min	degrad.[b]
5	 **3.43 a**		-	30 min	degrad.
6	 **3.41 h**		 **3.48 d**	30 min	61%
7	 **3.42**		 **3.48 e**	20 min	94%

Reaction conditions: substrate (1 equiv), terminal alkyne (2 equiv), $PdCl_2(PPh_3)_2$ (0.2 equiv), CuI (0.04 equiv), and NEt_3 (10 equiv), THF (0.25 M), rt. [a] Isolated yield. [b] Reaction performed using NEt_3 as a solvent (0.25 M).

Table 3.7. Different Sonogashira couplings tested

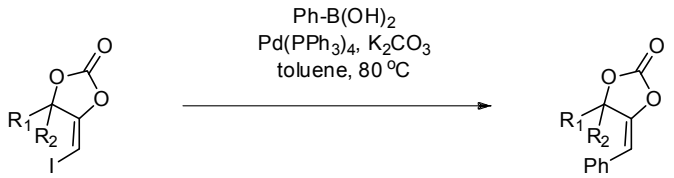
Curiously, under the classical reaction conditions, the *E*-isomer **3.43 a** degraded in the presence of triisopropyl-pent-4-ynyloxy-silane (Table 3.7, Entry 5).

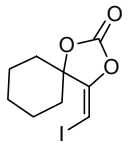
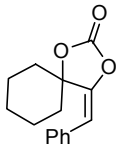
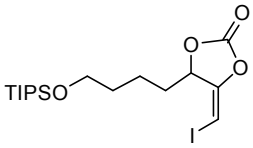
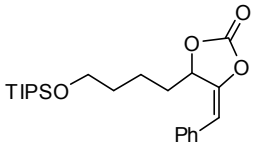
A similar difference in reactivity between the two *E*/*Z*-stereoisomers was observed in the case of substrates **3.41 h** and **3.42**. While the *E*-isomer **3.42** reacted nicely with phenylacetylene giving an excellent 94% yield of **3.48 e** (Table 3.7, Entry 7), the *Z*-isomer **3.41 h** furnished a modest 61% of **3.48 d** (Table 3.7, Entry 6).

Suzuki coupling

We were delighted to see that our attempts to perform Suzuki cross-coupling reactions were successful as well. 4-iodomethylene-1,3-dioxolan-2-ones **3.42** and **3.43 c** reacted with phenylboronic acid to give the phenyl substituted alkylidene carbonates **3.49 a** and **b** (70% and 40% yield respectively) (Table 3.8.).

The formation of several side products (probably due to the instability of the cyclic carbonate functionality in the reaction's basic conditions and high temperatures) is responsible for the average yields.



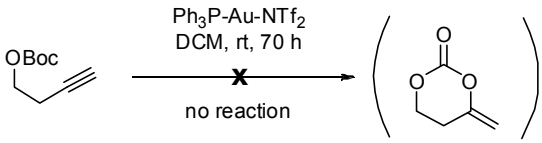
entry	substrate		product		time	yield[a]
1		**3.42**		**3.49 a**	3 h 30 min	79%
2		**3.43 c**		**3.49 b**	2 h 30 min	40%

Reaction conditions: substrate (1 equiv), phenylboronic acid (1.1 equiv), $Ph(PPh_3)_4$ (0.05 equiv) K_2CO_3 (2.5 equiv), toluene (0.5 M), 80°C [a] Isolated yield.

Table 3.8. Examples of Suzuki couplings tested

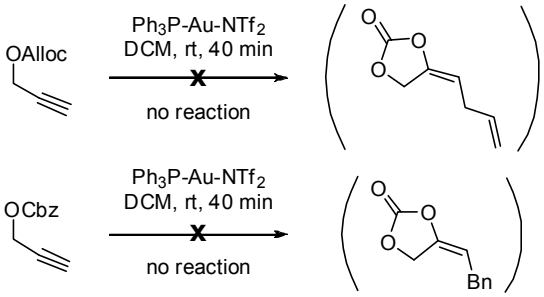
2.8. Other ideas tested

An extension of this method to the formation of 4-methylene-1,3-dioxan-2-ones from homopropargylic *tert*-butyl carbonates via a 6-*exo* gold-catalyzed cyclization was attempted. Unfortunately mainly unreacted starting material was recovered at the end of this trial (Scheme 3.31). Our method seems to be suitable only for 5-*exo* cyclizations (as we could observe also in the case of substrate **3.20 e**, see Table 3.2, Entry 5)



Scheme 3.31. Unsuccessful attempt to rearrange a homopropargylic *tert*-butyl carbonate

We also tried to vary the nature of the carbonate group. An allyloxycarbonate and an benzyloxycarbonate derivative were tested under standard conditions, but the results were disappointing, both substrates showing no reaction (Scheme 3.32).



Scheme 3.32. Unsuccessful attempts to rearrange propargylic allylcarbonates and benzylcarbonates

3. Conclusions and perspectives

In conclusion, we have shown that gold(I)-complexes efficiently catalyze the formation of 4-alkylidene-1,3-dioxolan-2-ones starting from readily available *tert*-butyl carbonates. These structures are otherwise difficult to obtain due to the lack of general methods for their synthesis.

Our method distinguishes itself by its wide scope, being compatible with nearly all types of substitutions at the propargylic position (primary, secondary or tertiary derivatives reacting with almost the same efficiency) and also with a good number of substitutions at the triple bond. The structure of the 4-alkylidene-1,3-dioxolan-2-ones formed depends on the nature of the group in the acetylenic position.

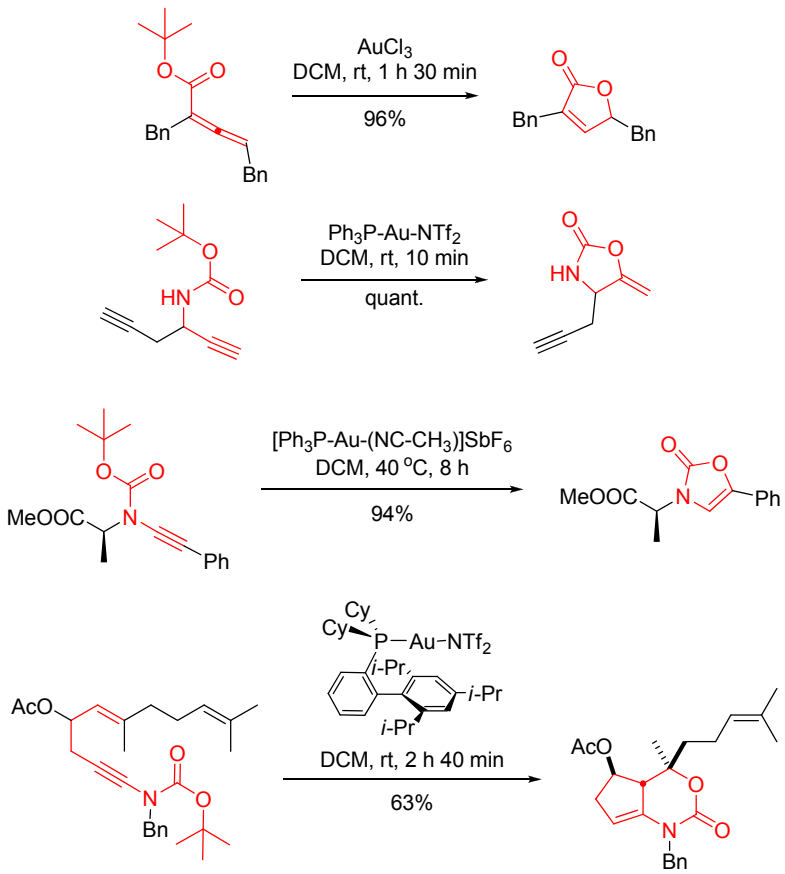
The reaction is tolerant towards a large number of functional groups (such as aromatics, alkynes, alkenes, esters, silyl ethers, functionalized alkyl groups etc.) and highly regio- and stereoselective (exclusive formation of the 5-*exo* cyclization product, substituted alkynes give only the *Z*-isomer etc.).

Other benefits include the low amounts of catalyst which is required for this transformation (even 0.1%) and the mild conditions used (room temperature, short reaction times etc.).

Our method was extended to the stereoselective formation of *Z*- and *E*-4-halomethylene-1,3-dioxolan-2-ones, which can be extremely useful building blocks. Their utility was proven by involving them in diverse Sonogashira and Suzuki cross-couplings, which led to the formation of various 4-alkylidene-1,3-dioxolan-2-ones substituted at the *exo*-double bond.

Similar approaches involving the gold(I)-catalyzed cyclization of a *tert*-butyloxycarbonyl group were later on successfully applied for the synthesis of other heterocycles, such as butenolides,[122] oxazolidinones,[108] oxazolones[109] or oxazinanones.[123] A few representative examples are given Scheme 3.33. Our work on the formation of oxazolones and oxazinanones will be detailed in chapters 4 and 9 respectively.

[122] Kang, J.-E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431-7433.
[123] Buzas, A.; Istrate, F.; Le Goff, X. F.; Odabachian, Y.; Gagosz, F. *J. Organomet. Chem.* **2009**, *694*, 515-519.



Scheme 3.33. Similar approaches involving the gold(I)-catalyzed cyclization of a *tert*-butyloxycarbonyl group

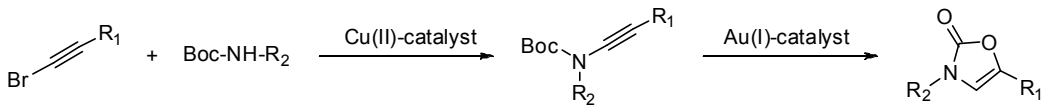
CHAPTER

4

Synthesis of Functionalized Oxazolones by a Sequence of Copper(II)- and Gold(I)-Catalyzed Transformations

*"If you're not part of the solution, then you're part of the precipitate." (**Stephen A. Wright**, American actor and writer, Academy Award winner in 1988)*

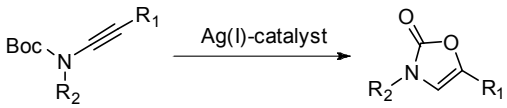
This chapter describes the formation of functionalized 4-oxazolin-2-ones (also known as 2(3*H*)-oxazolones) via an initial copper(II)-catalyzed coupling of a bromoalkyne with a secondary *tert*-butyloxycarbamate followed by a gold(I)-catalyzed cyclization of the *N*-alkynyl *tert*-butyloxycarbamate thus obtained (Scheme 4.1).



Scheme 4.1. Copper(II)- and gold(I)-catalyzed formation of functionalized 4-oxazolin-2-ones

This method constitutes an extremely easy and practical way to access fairly complex oxazolone-type structures starting from very simple starting compounds. The simplicity of the experimental techniques required, the mild reaction conditions, and the broad scope of this reaction, are among the advantages of this transformation.

In the most favorable cases, the gold(I) catalyst can be successfully replaced with a silver one. However the silver catalyzed process is not effective in all situations and therefore it does not constitute a substitute for the more active gold one; it is merely an alternative for some particular cases (Scheme 4.2).



Scheme 4.2. Alternative silver(I)-catalyzed transformation

In the first part of this chapter the importance of the oxazolone moiety in organic chemistry, a few of its applications and some current ways to access it will be discussed briefly (section 1). The second

part is dedicated to a more detailed look on our work concerning this topic (section 2). This chapter ends with a few conclusions and perspectives (section 3).

Disclaimer:

This work was conducted under the supervision of Dr. Fabien L. Gagosz. Although a part of the experiments presented in this chapter was carried out by Dr. Andrea K. Buzas, Igor Dias-Jurberg, Yann Odabachian and Dr. Fabien L. Gagosz, in order to preserve the coherence of the subject the totality of the work concerning this topic will be discussed here.

These results have been previously published in:

- Florin M. Istrate, Andrea K. Buzas, Igor Dias-Jurberg, Yann Odabachian, Fabien L. Gagosz* "Synthesis of Functionalized Oxazolones by a Sequence of Cu(II)- and Au(I)-Catalyzed Transformation" *Org. Lett.* **2008**, *10*, 925–928

1. The 4-oxazolin-2-ones

1.1. Importance and reactivity of the 4-oxazolin-2-one moiety

The 4-oxazolin-2-ones and their derivatives are a versatile class of heterocycles which received a lot of attention over the years due to their particular properties (Figure 4.1).[124]

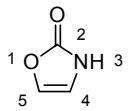


Figure 4.1. The 4-oxazolin-2-one (also known as 2(3*H*)-oxazolone) moiety

This moiety can be found in a good number of synthetic compounds exhibiting very interesting biological or pharmacological properties. For instance, the combretoxazolone family[125] shows cytotoxic and antitumor proprieties, 4-substituted 3-aryl-5-*tert*-butyl-4-oxazolin-2-ones like

[124] (a) Boyd, G. V. In *Comprehensive Heterocyclic Chemistry*; Alan, R. K., Rees, C. W., Potts, K. T., Eds.; Pergamon Press: 1984; Vol. 6, p 178-233.
(b) Hartner, F. W., Jr. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Shinkai, I., Eds.; Pergamon: 1996; Vol. 3, p 261-318.
(c) Kunieda, T.; Matsunaga, H. In *Oxazoles: Synthesis, Reactions, and Spectroscopy, Part B*; David, C. P., Ed.; Wiley: 2004, p 1-52.
(d) Dyen, M. E.; Swern, D. *Chem. Rev.* **1967**, *67*, 197-246.
[125] Nam, N.-H.; Kim, Y.; You, Y.-J.; Hong, D.-H.; Kim, H.-M.; Ahn, B.-Z. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3073-3076.

compound **4.1**[126] are potent herbicides, 3,4-diaryloxazolones like **4.2** [127] are antiinflammatory agents and derivative **4.3**[128] was found to have antimicrobial properties (Figure 4.2).

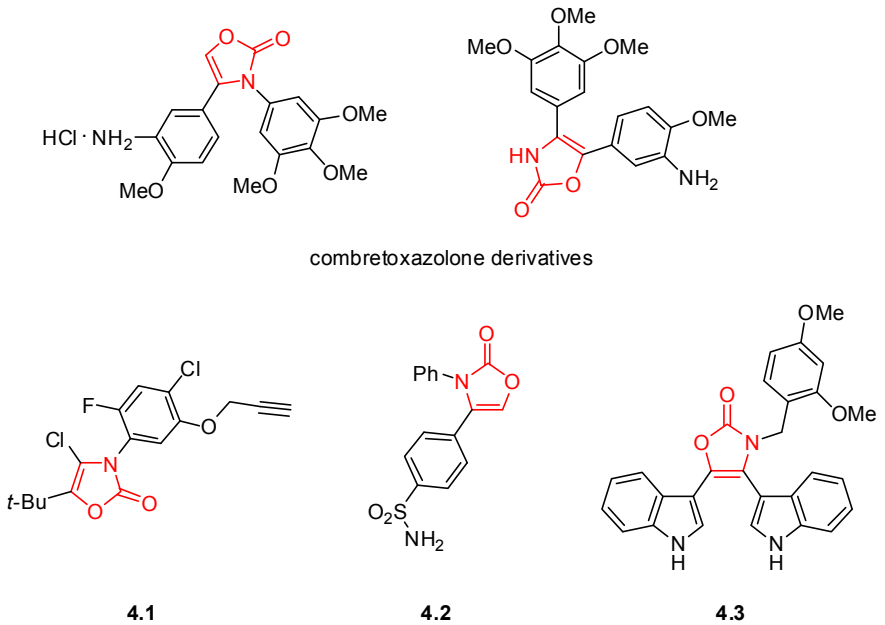


Figure 4.2. A few examples of biologically or pharmaceutically active compounds containing the 4-oxazolin-2-one moiety

The 4-oxazolin-2-ones contain in their structure a double bond, a ketone, and amino and alcohol groups under a masked form. They can be considered both enol and enamine derivatives, although they exist mainly in the keto form. Their dense functionalization ensures a very diverse reactivity and makes them very attractive building blocks.

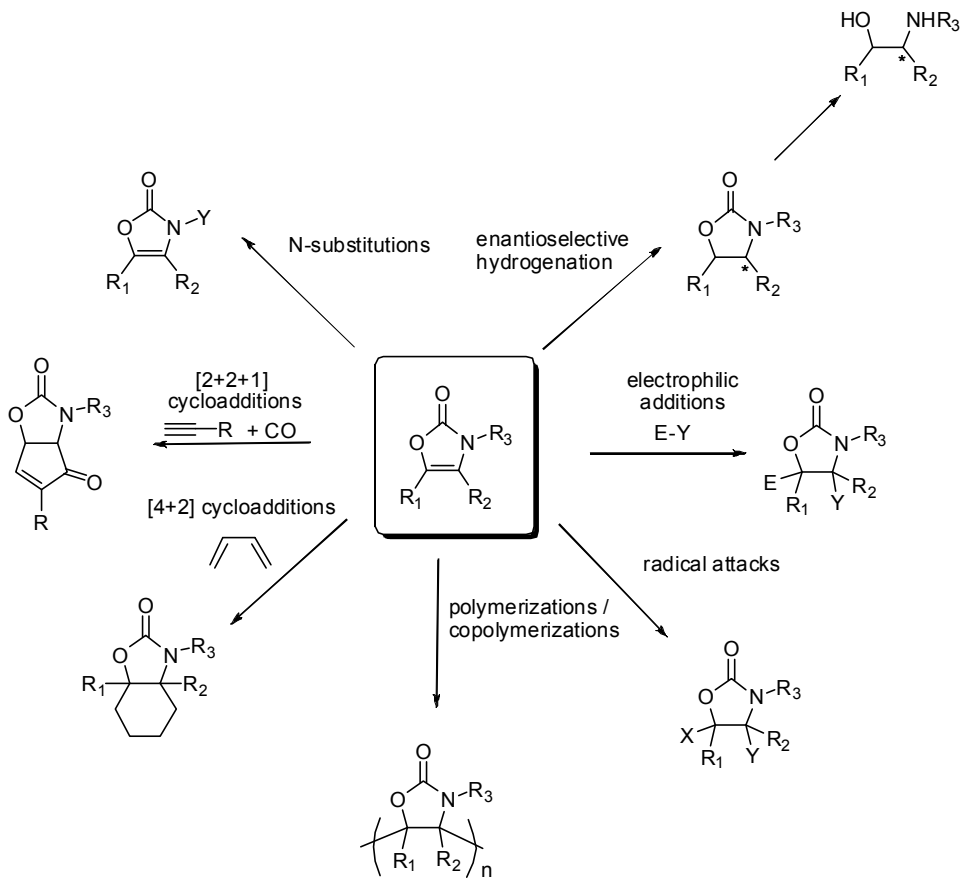
They proved to be excellent precursors for a large variety of compounds, including chiral 2-amino alcohols[129] (a structural unit found in a substantial number of bioactive compounds such as peptide enzyme inhibitors, amino sugar antibiotics, sympathomimetic amines, alkaloids etc.), optically active oxazolidinones[128b,130] (highly versatile chiral auxiliaries through numerous elegant syntheses) and even polymers.

On the other hand, the relatively good chemical stability of 4-oxazolin-2-ones allows their synthetic use as protecting[131] and leaving groups.[132]

---

[126] Kudo, N.; Taniguchi, M.; Furuta, S.; Sato, K.; Endo, T.; Honma, T. *J. Agric. Food. Chem.* **1998**, *46*, 5305-5312.
[127] Puig, C.; Crespo, M. I.; Godessart, N.; Feixas, J.; Ibarzo, J.; Jimenez, J.-M.; Soca, L.; Cardelus, I.; Heredia, A.; Miralpeix, M.; Puig, J.; Beleta, J.; Huerta, J. M.; Lopez, M.; Segarra, V.; Ryder, H.; Palacios, J. M. *J. Med. Chem.* **2000**, *43*, 214-223.
[128] Rodrigues Pereira, E.; Sancelme, M.; Voldoire, A.; Prudhomme, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2503-2506.
[129] (a) Nagamatsu, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 2375-2378.
(b) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **1997**, *53*, 1275-1294.
[130] Hoshimoto, S.; Matsunaga, H.; Wada, M.; Kunieda, T. *Chem. Pharm. Bull.* **2002**, *50*, 435-438.
[131] (a) Sheehan, J. C.; Guziec, F. S. *J. Am. Chem. Soc.* **1972**, *94*, 6561-6562.
(b) Sheehan, J. C.; Guziec, F. S. *J. Org. Chem.* **1973**, *38*, 3034-3040.
(c) Kanaoka, M.; Kurata, Y. *Chem. Pharm. Bull.* **1978**, *26*, 660-664.

Scheme 4.3 resumes some of their most important types of transformations.[133]



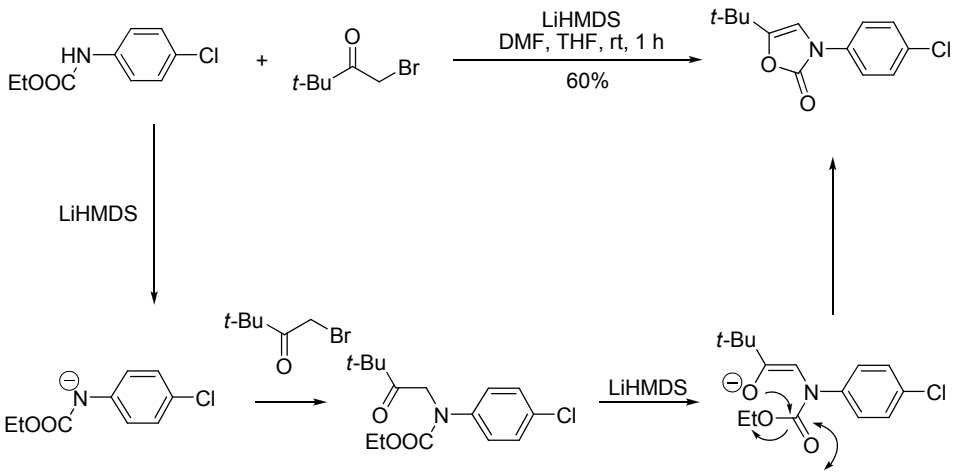
Scheme 4.3. Some typical transformations involving 4-oxazolin-2-ones

1.2. Synthesis of 4-oxazolin-2-ones

The first 4-oxazolin-2-one was synthesized more than a century ago by Maselli in 1905.[134] Since then, many other methods have been proposed in the literature.[124] A few of the most representative ones will be presented next.

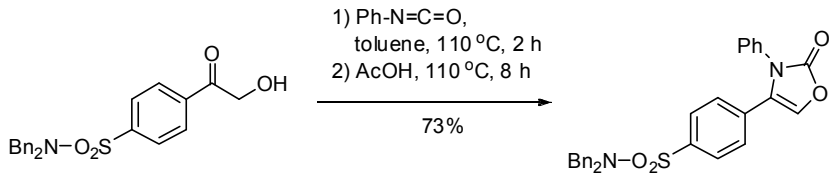
The 4-oxazolin-2-one ring is mainly constructed by cyclization reactions. β-Oxo acyclic carbamates have been widely used for this purpose. For instance Kudo et al. applied this strategy to the synthesis of functionalized oxazolones, employing as a key step the cyclization of an intermediate β-oxo acyclic carbamate in the presence of LiHMDS (Scheme 4.4).[135,126]

[132] (a) Kunieda, T.; Higuchi, T.; Abe, Y.; Hirobe, M. *Tetrahedron* **1983**, *39*, 3253-3260.
(b) Nagamatsu, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 2375-2378.
[133] For some specific examples, see the references cited in ref. 124.
[134] Maselli, C. *Gazz. Chim. Ital.* **1905**, *35*.
[135] Kudo, N.; Taniguchi, M.; Sato, K. *Chem. Pharm. Bull.* **1996**, *44*, 699-702.



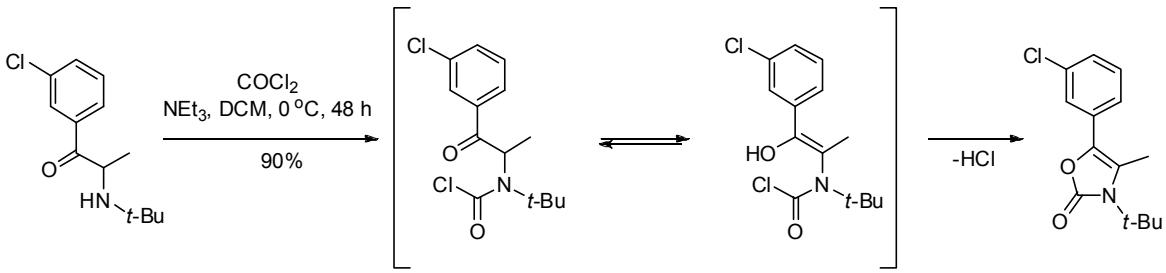
Scheme 4.4. Synthesis of 4-oxazolin-2-ones via the cyclization of an intermediate β-oxo acyclic carbamate

Isocyanates are another type of substrates often involved in the formation of 4-oxazolin-2-ones, as shown in the following example by Crespo et al. (Scheme 4.5).[127,125]



Scheme 4.5. Synthesis of 4-oxazolin-2-ones using isocyanates derivatives

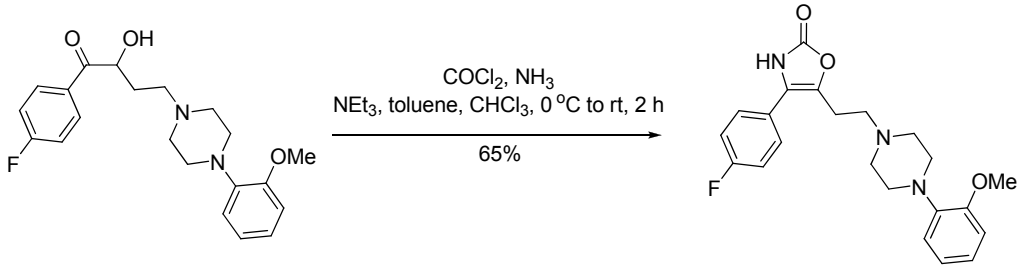
A common method to obtain 4-oxazolin-2-ones is also the direct carbonylation of an α-amino ketone in the presence of phosgene or other carbonylating agents (Scheme 4.6)[136]



Scheme 4.6. Synthesis of 4-oxazolin-2-ones by direct carbonylation of an α-amino ketone in the presence of phosgene

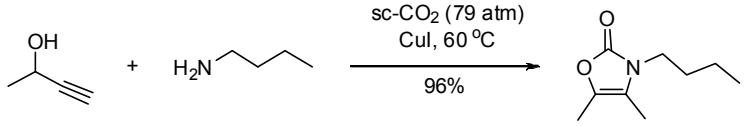
A variation of this reaction uses 2-hydroxy ketones, ammonia (or an amine) and phosgene, as demonstrated by Cascio et al. (Scheme 4.7).[137]

[136] Hamad, M. O.; Kiptoo, P. K.; Stinchcomb, A. L.; Crooks, P. A. *Biorg. Med. Chem.* **2006**, *14*, 7051-7061.
[137] Cascio, G.; Manghisi, E.; Fregnan, G. *J. Med. Chem.* **1989**, *32*, 2241-2247.



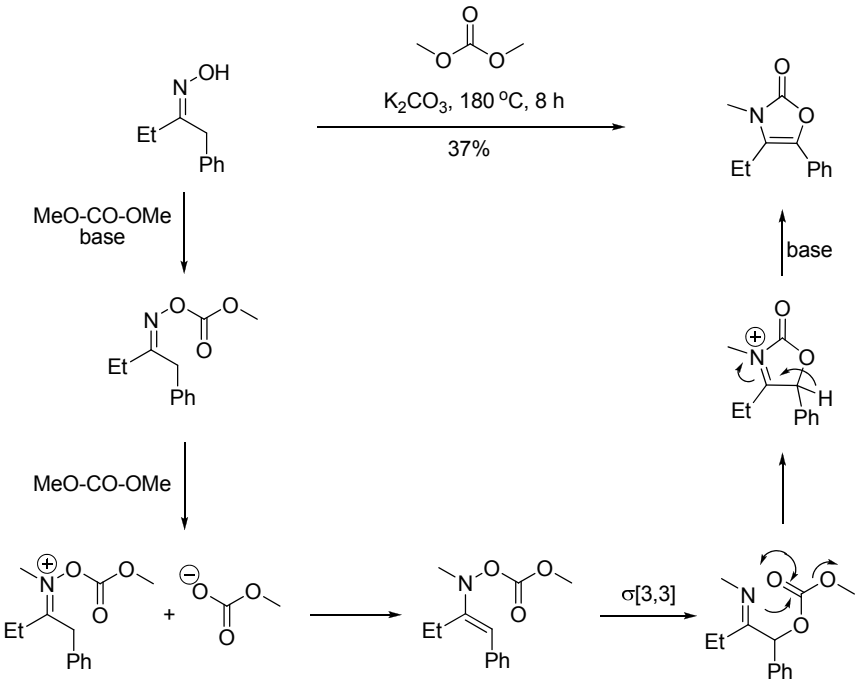
Scheme 4.7. Synthesis of 4-oxazolin-2-ones by direct carbonylation of an α-hydroxy ketone in the presence of phosgene and ammonia

Jiang et al. described a 3-component carbonylation making use of propargylic alcohols under high pressure of supercritical CO_2 and in the presence of an amine. This transformation is catalyzed by a copper catalyst (Scheme 4.8).[138]



Scheme 4.8. Synthesis of 4-oxazolin-2-ones via a 3-component carbonylation reaction

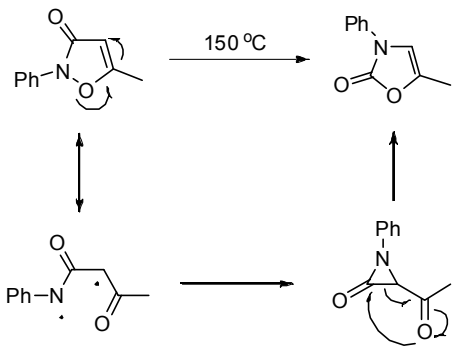
Oximes can also give 4-oxazolin-2-ones in the presence of dimethyl carbonates, as shown by Tundo et al.[139] This transformation proceeds via an intermediate oxime *O*-carbonate which affords an enamine in the presence of a base. A [3,3]-sigmatropic rearrangement and a cyclization step ensue to produce the desired heterocycle (Scheme 4.9).



Scheme 4.9. Synthesis of 4-oxazolin-2-ones starting form oximes

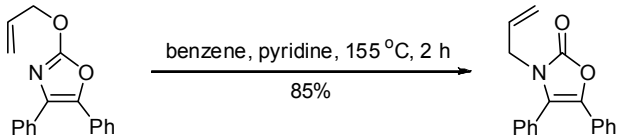
[138] Jiang, H. F.; Zhao, J. W.; Wang, A. H. *Synthesis* **2008**, 763-769.
[139] Marques, C. A.; Selva, M.; Tundo, P.; Montanari, F. *J. Org. Chem.* **1993**, *58*, 5765-5770.

The thermal[140] or photolytic[141] rearrangement of 4-isoxalin-3-ones yields 4-oxazolin-2-ones. In the case of the thermal rearrangement, the authors proposed the homolytic breaking of the N-O bond, the formation of a cyclopropane derivative and the subsequent rearrangement to the expected final product (Scheme 4.10).



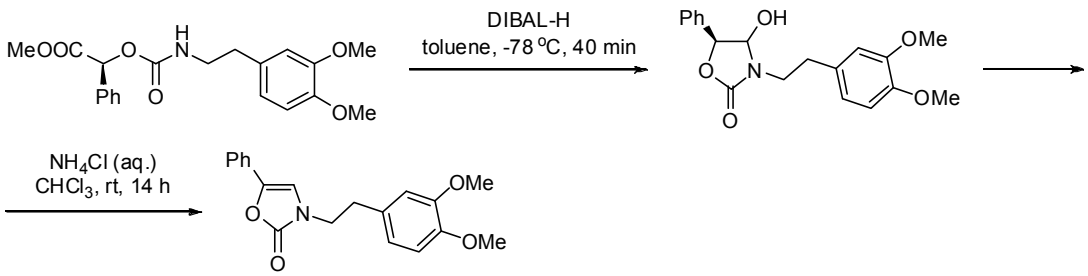
Scheme 4.10. Synthesis of 4-oxazolin-2-ones by thermal rearrangement of 4-isoxalin-3-ones

2-Allyloxy substituted oxazoles, upon heating, undergo easily an aza-Claisen sigmatropic [3,3] rearrangement to yield 3-allyl-4-oxazolin-2-ones (Scheme 4.11).[142]



Scheme 4.11. Synthesis of 4-oxazolin-2-ones by aza-Claisen rearrangement of 2-allyloxy substituted oxazoles

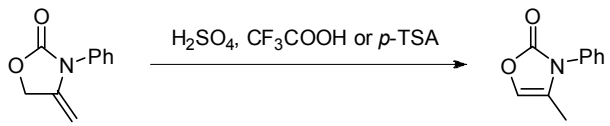
2-Oxazolidinones can be excellent precursors for 4-oxazolin-2-ones, provided they possess a suitable leaving group in the 4 or 5 positions. For instance, Kano et al. showed that 2-oxazolidinones can be easily obtained by treatment of an α-methoxycarbonylbenzyl carbamate with DIBAL-H an then dehydrated under extremely mild conditions with NH_4Cl to the expected oxazolone derivative (Scheme 4.12).[143]



Scheme 4.12. Synthesis of 4-oxazolin-2-ones from 2-oxazolidinones

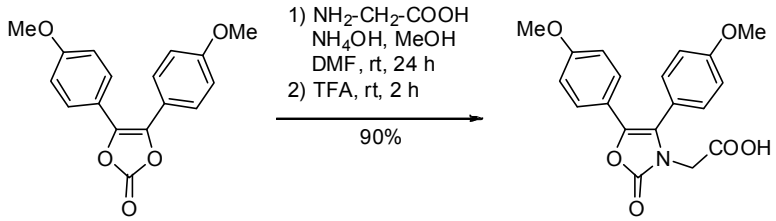
[140] Gagneux, A. R.; Göschke, R. *Tetrahedron Lett.* **1966**, *7*, 5451-5454.
[141] Nakagawa, M.; Nakamura, T.; Tomita, K. *Agric. Biol. Chem.* **1974**, *38*, 2205-2208.
[142] Padwa, A.; Cohen, L. A. *J. Org. Chem.* **1984**, *49*, 399-406.
[143] Kano, S.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1985**, *23*, 395-398.

5-Methylene-oxazolidin-2-ones isomerize easily in acidic conditions to the corresponding 4-methyl-4-oxazolin-2-ones (Scheme 4.13).[144]



Scheme 4.13. Synthesis of 4-oxazolin-2-ones from 5-methylene-oxazolidin-2-ones

Cyclic carbonates react with primary amines to give 4-oxazolin-2-ones. This procedure was extensively applied for the protection of amino acids and peptides since it has the advantage of protecting both hydrogen atoms of a primary amino group (Scheme 4.14).[131]



Scheme 4.14. Synthesis of 4-oxazolin-2-ones from cyclic carbonates

2. Our synthetic approach to functionalized 4-oxazolin-2-ones

2.1. The initial idea. Precedents in the literature

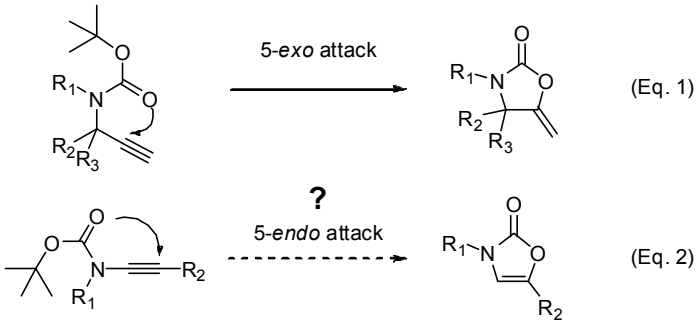
Despite the fact that a good number of methods have been proposed for the synthesis 4-oxazolin-2-ones, the access to this type of structures remains problematic, especially in the case of highly functionalized derivatives. Most of the methods previously described require high temperatures, high pressures, strong acidic or basic conditions or the use of toxic carbonylating reagents. This limits their compatibility with the substitution pattern of the substrates and restricts their usage to a few particular cases. Therefore the development of new efficient, mild, and general transformations leading to the formation of functionalized 4-oxazolin-2-ones remains an important goal in synthetic chemistry.

Due to the excellent ability of gold to catalyze the formation of various oxygen- or nitrogen-containing heterocycles via intramolecular attacks onto activated alkyne or allene moieties (see Chapter 1), we decided to focus our attention on the formation of 4-oxazolin-2-ones.

We already saw in the last chapter that the *tert*-butyloxycarbonyl moiety is particularly useful for this kind of transformations. For example, our group reported the formation of functionalized 5-methylene-oxazolidin-2-ones via a 5-*exo* cyclization of *N*-*tert*-butyloxycarbonyl-propargylic amines

[144] Stoffel, P. J.; Dixon, W. D. *J. Org. Chem.* **1964**, *29*, 978-979.

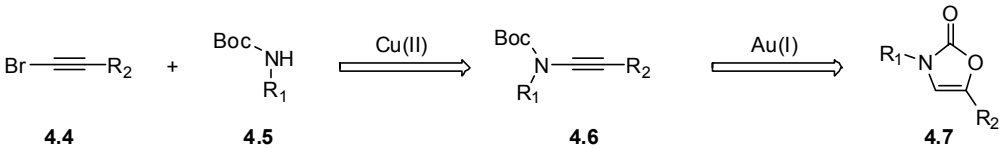
(Scheme 4.15, Eq. 1).[145] By analogy with this transformation we surmised that *N*-alkynyl *tert*-butyloxycarbamates could give 4-oxazolin-2-ones via a similar 5-*endo* transformation (Scheme 4.15, Eq. 2).



Scheme 4.15. The considered 5-*endo* gold-catalyzed rearrangement compared with the previously reported 5-*exo* transformation

Of course, we knew that such a process is less favorable that the 5-*exo* attack. However we were hoping that the special ability of gold catalysts to activate selectively alkyne groups might favor the desired transformation.

For the formation of the corresponding *N*-alkynyl *tert*-butyloxycarbamates **4.6** we decided to use a copper-catalyzed cross-coupling reaction between an alkynyl bromide **4.4** and a *tert*-butyloxycarbamate **4.5** (Scheme 4.16).

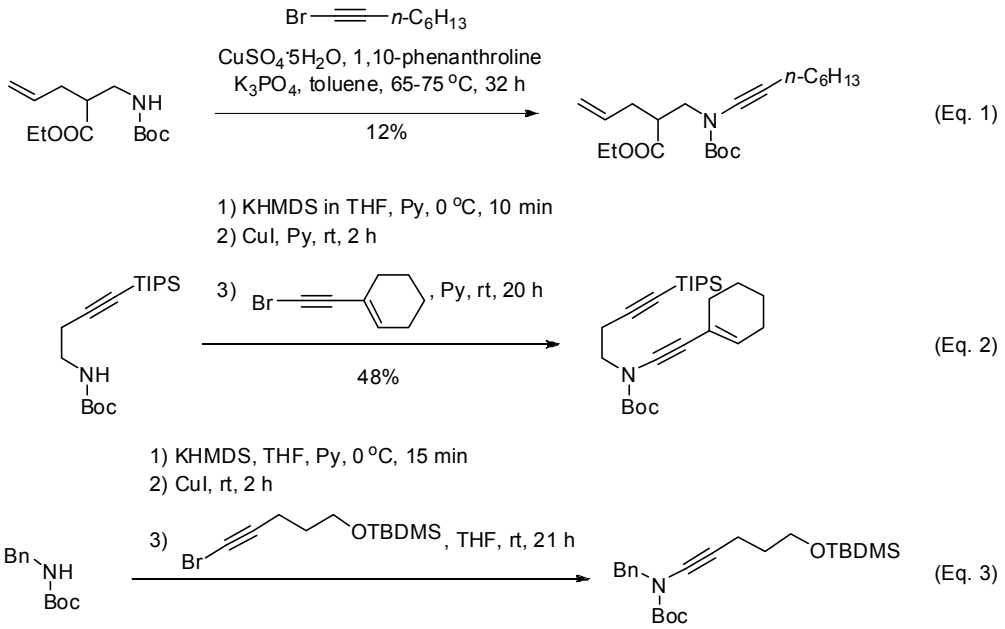


Scheme 4.16. Our initial 2-step approach for the formation of functionalized 4-oxazolin-2-ones

This is one of the most efficient methods leading to ynamides, a highly useful class of functionally rich organic building blocks that caught the attention of chemists during the last few years.[146] Numerous examples of this coupling between an alkynyl bromide and various sulfonamides, amides or carbamates have been reported in the literature, including a few which involve *tert*-butyloxycarbamates (Scheme 4.17).[147]

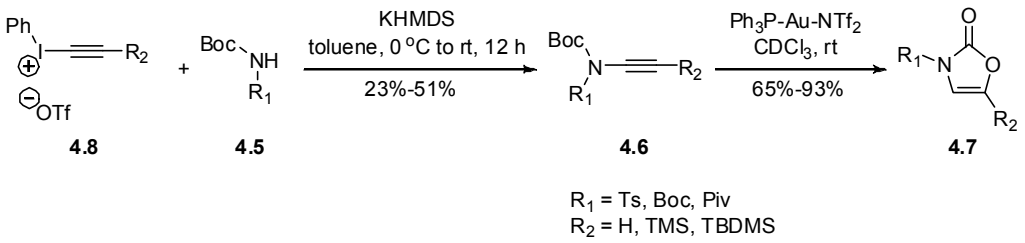
Our approach to 4-oxazolin-2-ones therefore consisted in a 2-step sequence involving a copper(II) catalyzed cross-coupling followed by a gold(I)-catalyzed rearrangement (Scheme 4.16).

[145] Buzas, A.; Gagosz, F. *Synlett* **2006**, *2006*, 2727-2730.
[146] For some reviews on the ynamide chemistry, see:
(a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575-7606.
(b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, *2003*, 1379-1390.
[147] (a) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170-4177.
(b) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776-5777.
(c) Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815-3822.



Scheme 4.17. A few examples of copper-catalyzed cross-couplings between an alkynyl bromide and a *tert*-butyloxycarbamate previously reported in the literature

While our work was in progress, Hashmi et al. reported the formation of 4-oxazolin-2-ones **4.7** in the presence of 5% Ph_3P-Au-NTf_2 under mild conditions (0°C to rt) and in relatively high yields (65-93%).[148] Unfortunately, his transformation seemed to be restricted to substrates **4.6** bearing a hydrogen or a silyl group on the alkyne moiety and an electron-withdrawing group (like Boc, Ts and Piv) on the nitrogen atom (Scheme 4.18).



Scheme 4.18. Similar gold-catalyzed formation of 4-oxazolin-2-ones reported by Hashmi et al.

In our opinion, this limitation was mainly due to the inefficient method used to obtain **4.6** and not to the gold-catalyzed step itself. The formation of substrate **4.6** involved the coupling between the iodonium salt **4.8** and the carbamate **4.5** in the presence of KHMDS, in yields varying between 27% and 51%. We supposed that the strong basic conditions of this reaction and the restricted access to the functionalized iodonium salt **4.8** reduced the tolerance for more functionalized substrates.

Given the limitations of Hashmi's procedure, we believed that our approach had a significant advantage. The copper-catalyzed coupling method we used was much more efficient and broadened the scope of the reaction, therefore increasing the utility of this transformation. Furthermore, a careful choice of the experimental conditions also improved the gold catalyzed step, by reducing for instance the catalyst loading.

[148] Hashmi, A. S. K.; Salathé, R.; Frey, W. *Synlett* **2007**, *2007*, 1763-1766.

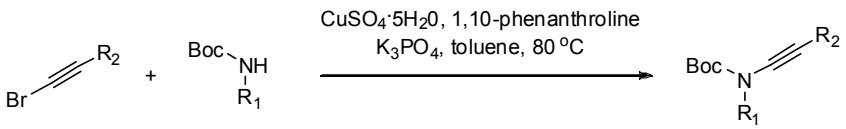
2.2. Copper(II)-catalyzed formation of *N*-alkynyl *tert*-butyloxycarbamates

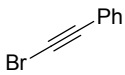
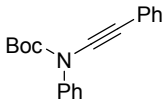
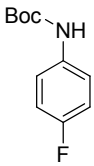
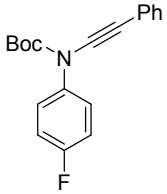
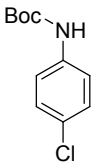
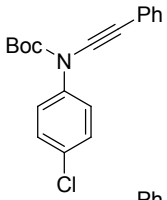
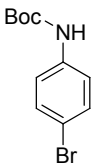
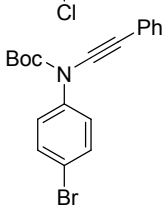
As we emphasized previously, the development of a general and mild method to access *N*-alkynyl *tert*-butyloxycarbamates was a crucial step in our investigation concerning the formation of functionalized 4-oxazolin-2-ones.

The copper-catalyzed cross-coupling between *tert*-butyloxycarbamates and alkynyl bromides was quickly retained as the preferred method. However, while the coupling with various sulfonamides, amides or carbamates is generally quite efficient and well documented, only a few examples with *tert*-butyloxycarbamates have been described and the reported yields are usually modest (see also Scheme 4.17).[147] This fact was usually attributed to steric hindrance.[147a]

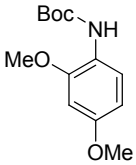
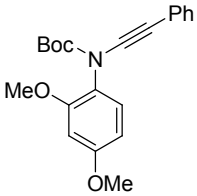
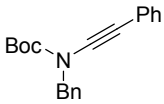
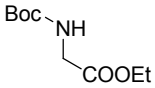
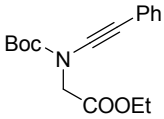
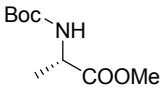
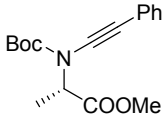
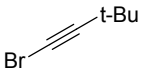
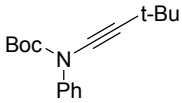
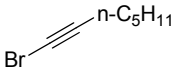
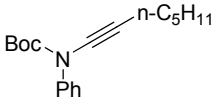
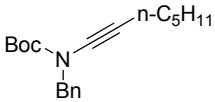
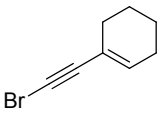
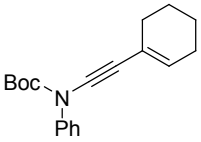
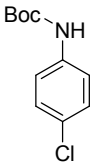
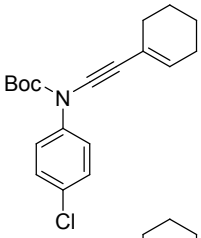
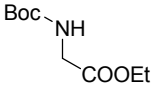
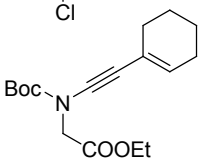
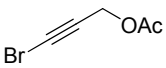
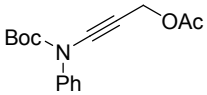
We decided therefore to investigate the scope of this copper-catalyzed coupling between various *tert*-butyloxycarbamates and alkynyl bromides. Using slightly modified reaction conditions[147a] (20% $CuSO_4{\cdot}5H_2O$, 40% 1,10-phenantroline and K_3PO_4 in toluene at 80 °C), we were delighted to observe that this transformation is generally much more efficient than initially reported.

Diversely substituted *N*-alkynyl *tert*-butyloxycarbamates **4.11 a-v** were obtained in yields varying from 22% to 88% (Table 4.1).

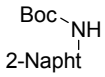
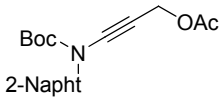
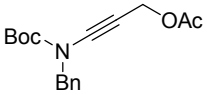
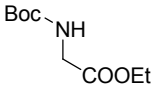
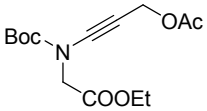
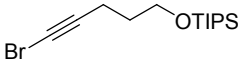
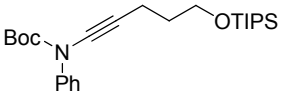
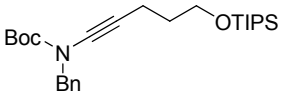
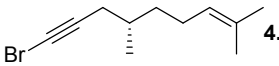
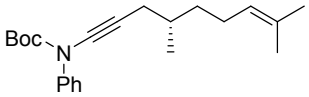
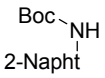
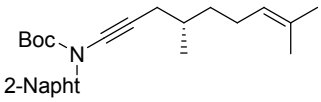


entry	bromoalkyne		carbamate		product		time	yield[a]
1		**4.9 a**		**4.10 a**		**4.11 a**	40 h	80%
2	"			**4.10 b**		**4.11 b**	16 h	65%
3	"			**4.10 c**		**4.11 c**	18 h	68%
4	"			**4.10 d**		**4.11 d**	16 h	48%

(continued on the next page)

entry	bromoalkyne		carbamate		product		time	yield[a]
5	"			**4.10 e**		**4.11 e**	48 h	22%
6	"			**4.10 g**		**4.11 f**	48 h	62%
7	"			**4.10 h**		**4.11 g**	36 h	70%
8	"			**4.10 i**		**4.11 h**	48 h	23%
9		**4.9 b**		**4.10 a**		**4.11 i**	38 h	24%
10		**4.9 c**		**4.10 a**		**4.11 j**	52 h	75%
11	"			**4.10 g**		**4.11 k**	48 h	69%
12		**4.9 d**		**4.10 a**		**4.11 l**	67 h	72%
13	"			**4.10 c**		**4.11 m**	67 h	80%
14	"			**4.10 h**		**4.11 n**	67 h	50%
15		**4.9 e**		**4.10 a**		**4.11 o**	65 h	55%

(continued on the next page)

entry	bromoalkyne	carbamate	product	time	yield[a]
16	"	 **4.10 f**	 **4.11 p**	48 h	49%
17	"	**4.10 g**	 **4.11 q**	72 h	49%
18	"	 **4.10 h**	 **4.11 r**	62 h	48%
19	 **4.9 f**	**4.10 a**	 **4.11 s**	45 h	88%
20	"	**4.10 g**	 **4.11 t**	62 h	72%
21	 **4.9 g**	**4.10 a**	 **4.11 u**	48 h	74%
22	"	 **4.10 f**	 **4.11 v**	48 h	65%

Reaction conditions: bromoalkyne (1 equiv), carbamate (1.2 equiv), $CuSO_4 \cdot 5H_2O$ (0.2 equiv), 1,10-phenantroline (0.4 equiv) and K_3PO_4 (2.4 equiv) in toluene (0.33 M), 80 °C. [a] Isolated yields.

Table 4.1. Scope of the copper(II)-catalyzed cross-coupling leading to the formation of *N*-alkynyl *tert*-butyloxycarbamates **4.11 a-v**

Bromoalkyne **4.9 a** reacted with different *tert*-butyloxycarbamates **4.10 a-e** and **g-i**, furnishing the expected products **4.11 a-h** (Table 4.1, Entries 1-8). A good number of substitutions patterns at the nitrogen were well tolerated, including various phenyl groups (plain or substituted with different electron withdrawing or donating groups), benzyl or amino acid-ester derivatives.

Rather disappointing results were obtained in the case of products **4.11 e** and **4.11 h** (22% and respectively 23% isolated yields; Table 4.1, Entries 5 and 8). These poor results may be attributed to a greater steric hindrance around the nitrogen center. All the other examples reacted with average to good yields (48%-80% isolated yields).

Product **4.11 i**, substituted with a *tert*-butyl group at the triple bond, also proved to be a disappointment, being isolated in only 24% yield. In this case the poor result is due to the volatility of the starting bromoalkyne **4.9 b** (Table 4.1, Entry 9).

Bromoalkyne **4.9 c**, substituted with a long alkyl chain, was coupled successfully with carbamates **4.10 a** and **4.10 g**, giving products **4.11 j** and **k** in 75% and respectively 69% yields (Table 4.1, Entries 10 and 11).

The coupling reaction seemed to be compatible with the presence of a double bond, as attested by the substrates **4.9 d** and **g**. They furnished the expected *N*-alkynyl *tert*-butyloxycarbamates **4.11 l-n** and **u-v** in average to good yields (50-80%; Table 4.1, Entries 12-14 and 21-22).

Oxygenated groups were well tolerated as well. Bromoalkyne **4.9 e**, possessing an ester moiety, exhibited an average reactivity towards various carbamates, affording products **4.11 o-r** in yields ranging from 48% to 55% (Table 4.1, Entries 15-18). Bromoalkyne **4.9 f**, containing a silyl ether moiety, was much more reactive, giving products **4.11 s** and **t** in 88% and 72% yields (Table 4.1, Entries 19 and 20).

Although we couldn't rationalize completely this ample variation in the isolated yields of the various products described, it seems that the nature of the substituents on both the bromoalkyne and the carbamate moieties plays a major role.

To the best of our knowledge, this is the first general study concerning the synthesis of *N*-alkynyl *tert*-butyloxycarbamates. It provides a general method of accessing these structures, which is highly tolerant to the presence of a large number of functional groups. Compatibility with alkyl, aryl, alkene, or protected alcohol groups at the triple bond position and with substituted phenyl, naphtyl, benzyl or amino acid esters at the nitrogen position was investigated and demonstrated.

Furthermore, relatively mild conditions were developed for this reaction. For instance, unlike similar copper catalyzed transformations, the presence of a strong base like LiHMDS is not required (see Scheme 4.17).

2.3. First gold(I)-catalyzed trials

Having developed an efficient method to the formation of *N*-alkynyl *tert*-butyloxycarbamates, we focused our attention on the gold(I)-catalyzed formation of 4-oxazolin-2-ones.

Substrate **4.11 j** was chosen as a model substrate and tested in the presence of 1% Ph_3P-Au-NTf_2 at rt. While Hashmi et al. obtained good results on his substrates using a 5% loading of the same catalyst (see Scheme 4.18),[148] our substrate gave an average 63% conversion in 7 h and a rather poor 29% isolated yield of **4.12 j** (Table 4.2, Entry 1).

The use of the more electrophilic (p-CF_3-C_6H_4)$_3$P-Au-NTf_2 (1% catalyst loading, rt) slightly increased both the conversion to 85% and the yield to 52%, but slowed down the reaction to 72 h (Table 4.2, Entry 2). By raising the temperature under the same conditions (1% (p-CF_3-C_6H_4)$_3$P-Au-NTf_2), 40 ^{o}C) full conversion was achieved in 2 h 30 min, but unfortunately the yield decreased to 40% (Table 4.2, Entry 3).

4.11 j **4.12 j**

entry	catalyst	temp.	time	conv.[a]	yield
1	1% Ph_3P-Au-NTf_2	rt	7 h	63%	28%[b]
2	1% (p-CF_3-C_6H_4)$_3$P-Au-NTf_2	rt	72 h	85%	52%[c]
3	1% (p-CF_3-C_6H_4)$_3$P-Au-NTf_2	40 °C	2 h 30 min	100%	40%[c]
4	1% [Ph_3P-Au-(NC-CH_3)]$^+SbF_6^-$	rt	4 h 30 min	100%	69%[c]
5	1% [Ph_3P-Au-(NC-CH_3)]$^+SbF_6^-$	40 °C	30 min	100%	74%[b]
6	10% $HNTf_2$	rt	1 h	100%	degrad.[c]
7	5% $AgSbF_6$	rt	20 min	100%	64%[b]
8	5% $AgNTf_2$	rt	1 h 30 min	100%	53%[c]

Reaction conditions: substrate **4.11 j** (1 equiv), catalyst, DCM (0.5 M), specified temperature. [a] Conversion of the starting material estimated by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield. [c] Yield estimated by ^{1}H NMR of the crude reaction mixture.

Table 4.2. Initial trials for the gold(I)-catalyzed formation of functionalized 4-oxazolin-2-ones

Finally the cationic complex [Ph_3P-Au-(NC-Me)]$^+SbF_6^-$ proved to be the catalyst of choice. The use of just 1% of the aforementioned catalyst at rt ensured a full conversion of the substrate in 4 h 30 min and a 69% yield (Table 4.2, Entry 4). Performing the same trial at 40 °C increases the reaction speed to less than 30 min and the yield to 74%, while maintaining the full conversion of the substrate (Table 4.2, Entry 5).

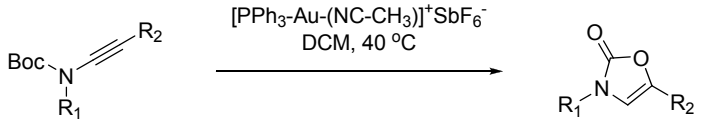
Several control experiments were performed as well. Brønsted acid $HNTf_2$ did not promote the reaction and led to the extensive degradation of the substrate (Table 4.2, Entry 6). Silver salts ($AgSbF_6$, $AgNTf_2$) did promote the reaction, but their efficiency proved to be limited (64% and 53% yields respectively; Table 4.2, Entries 7 and 8.).

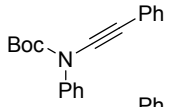
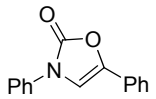
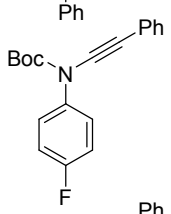
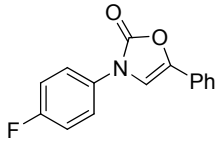
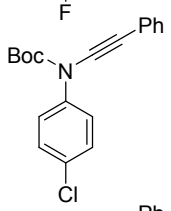
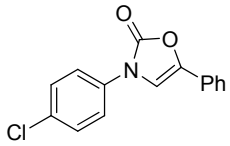
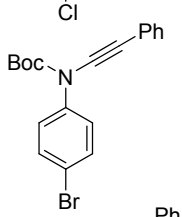
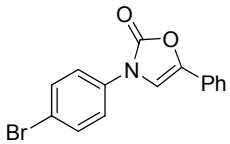
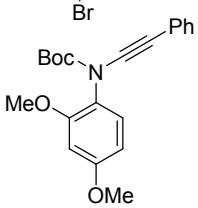
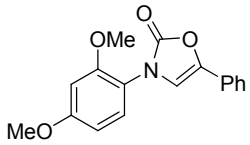
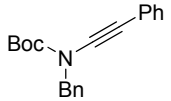
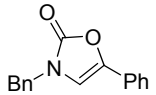
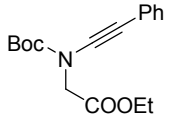
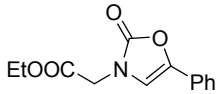
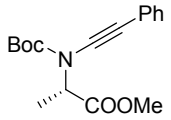
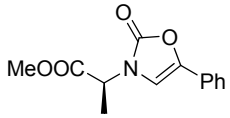
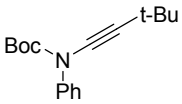
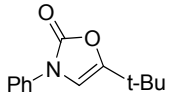
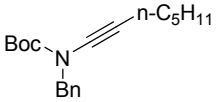
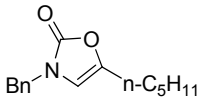
Finally the experimental conditions mentioned in Table 4.2, Entry 5 (1% [Ph_3P-Au-(NC-Me)]$^+SbF_6^-$, DCM, 40 °C) were retained as standard for the rest of this study.

2.4. Gold(I)-catalyzed formation of 4-oxazolin-2-ones

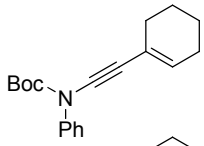
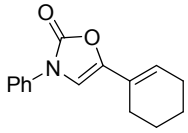
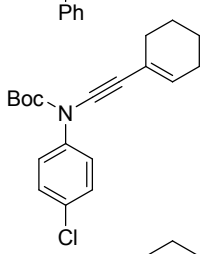
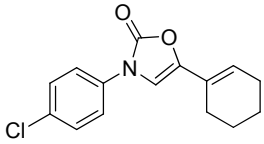
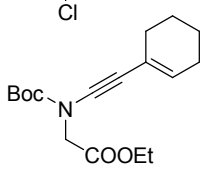
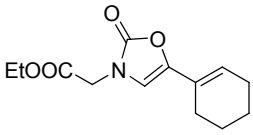
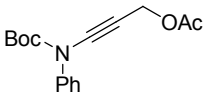
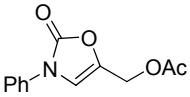
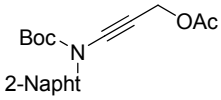
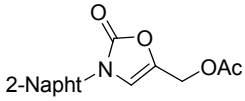
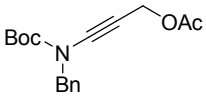
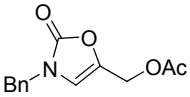
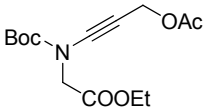
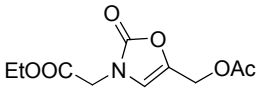
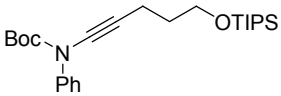
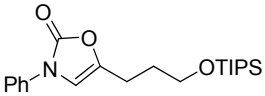
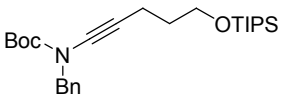
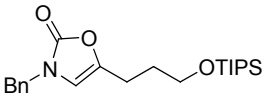
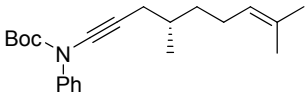
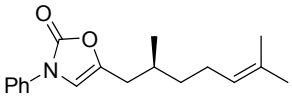
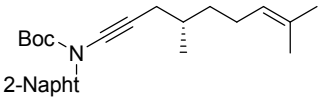
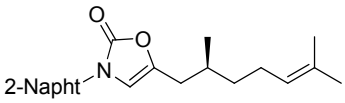
Several *N*-alkynyl *tert*-butyloxycarbamates previously synthesized by the copper(II)-catalyzed cross-coupling reaction were tested under the optimized conditions (Table 4.3).

The reaction proved to be general, oxazolones **4.12 a-i** and **k-v** being obtained in yields varying from 38% to 94%. The reaction times were usually shorter than 1 h, although in a few cases they could reach up to 16 h.



entry	substrate		product		time	yield[a]
1		**4.11 a**		**4.12 a**	25 min	83%
2		**4.11 b**		**4.12 b**	10 min	88%
3		**4.11 c**		**4.12 c**	10 min	88%
4		**4.11 d**		**4.12 d**	10 min	83%
5		**4.11 e**		**4.12 e**	16 h	85%
6		**4.11 f**		**4.12 f**	16 h	78%
7		**4.11 g**		**4.12 g**	12 h	93%
8		**4.11 h**		**4.12 h**	8 h	94%
9		**4.11 i**		**4.12 i**	2 h	58%
10		**4.11 k**		**4.12 k**	40 min	50%[b]

(continued on the next page)

entry	substrate		product		time	yield[a]
11		**4.11 l**		**4.12 l**	30 min	78%
12		**4.11 m**		**4.12 m**	10 min	94%
13		**4.11 n**		**4.12 n**	5 h	70%
14		**4.11 o**		**4.12 o**	40 min	71%
15		**4.11 p**		**4.12 p**	45 min	88%
16		**4.11 q**		**4.12 q**	20 min	50%[b]
17		**4.11 r**		**4.12 r**	20 min	49%
18		**4.11 s**		**4.12 s**	1 h	69%
19		**4.11 t**		**4.12 t**	40 min	38%[b]
20		**4.11 u**		**4.12 u**	30 min	71%
21		**4.11 v**		**4.12 v**	3 h	80%

Reaction conditions: substrate (1 equiv), $[Ph_3P\text{-}Au\text{-}(NC\text{-}CH_3)]^+SbF_6^-$ (0.01 equiv), DCM (0.5 M), 40 °C. [a] Isolated yield. [b] Yield estimated by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Table 4.3. Scope of the gold(I)-catalyzed rearrangement to 4-oxazolin-2-ones **4.12 a-i** and **k-v**

Various substituents were well tolerated at the nitrogen position, including simple and substituted phenyl (**4.11 a-e, i, l, m, o, s** and **u**), 2-naphtyl (**4.11 p** and **v**), benzyl (**4.11 f, k, q, t**) or ester derivatives (**4.11 g, h, n** and **r**). At the triple bond position, diverse functional groups showed an excellent compatibility as well, including alkyl (**4.11 i** and **k**), aryl (**4.11 a-h**), alkene (**4.11 l-n** and **u-v**), propargylic acetate (**4.11 o-r**) or silyl ether (**4.11 s-t**).

A particularly interesting aspect of this transformation was that most of the expected compounds (especially those substituted with an aryl groups, such as **4.12 a-h, l-n** and **p**) were extremely easy to purify (Table 4.3, Entries 1-8, 11-13 and 15). Once formed, they precipitated from the reaction medium and could be isolated by a simple filtration in very good yields (70%-88%). Surprisingly, this purification technique could not be applied to products **4.12 k, q** and **t**, substituted with a benzyl group at the nitrogen atom, which proved to be unstable and could not be isolated. The moderate yields (38%-50%), determined by ^{1}H NMR of the crude mixture, reflected this instability (Table 4.3, Entries 10, 16 and 19).

Substrates **4.11 a-h** (Table 4.3, Entries 1-8), substituted at the triple bond position with a phenyl substituent, were particularly reactive furnishing the expected final products in excellent yields (78%-94%). The reaction speeds on the other hand vary widely from one case to another. Substrates **4.11 a-d** give very fast reactions (10 to 25 min, Table 4.3, Entries 1-4), while substrates **4.11 e-h** required several hours to achieve full conversion (between 8 h and 16 h, see Table 4.3, Entries 5-8). It seems that electron withdrawing groups at the nitrogen atom tend to induce shorter reaction times.

Very good yields (70%-94%) are also obtained in the case of substrates **4.11 l-n**, substituted with a cyclohexenyl group (Table 4.3, Entries 11-13). Electron withdrawing groups at the nitrogen seem to give faster transformations in this case also.

Substrate **4.11 i**, substituted with a *tert*-butyl group at the triple bond converted to **4.12 i** only in an average 58% yield (Table 4.3, Entry 9). This modest result might be attributed to the steric hindrance exerted by *tert*-butyl during the cyclization of the Boc group onto the triple bond.

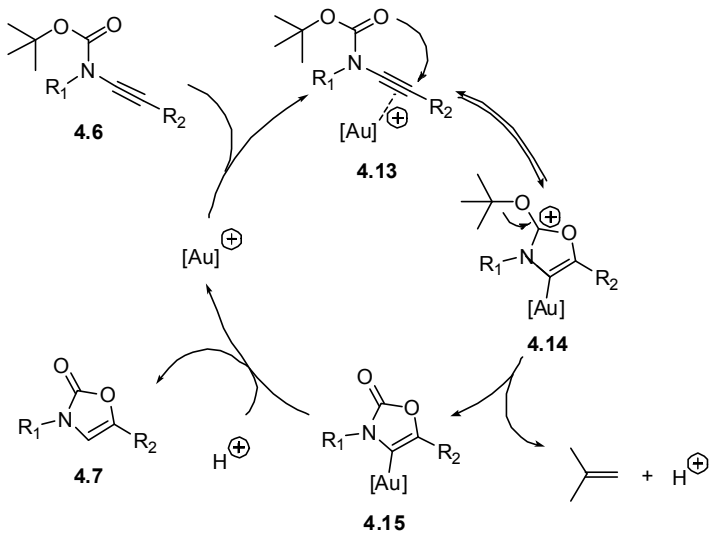
A pleasant surprise was the regioselective rearrangement of substrates **4.11 o-r** (Table 4.3, Entries 14-17). The *tert*-butyl carbonate exclusively cyclizes on the triple bond giving the expected 5-*endo* compounds **4.12 o-r** in yields varying form 49% to 88%. No sign of products resulting from a cyclization on the propargylic acetate was observed.

A protected alcohol does not interfere with the rearrangement of the Boc group either, as demonstrated in the case of compounds **4.11 s** and **t**, which furnish **4.12 s** and **t** in 69% and respectively 38% yields (Table 4.3, Entries 18 and 19).

The same goes for citronellal derivatives **4.11 u** and **v**, possessing a double bond. They furnish products **4.12 u** and **v** in good 71% and respectively 80% yields (Table 4.3, Entries 20 and 21).

2.5. Mechanistic proposal

A mechanism accounting for these experimental observations is proposed in Scheme 4.19.

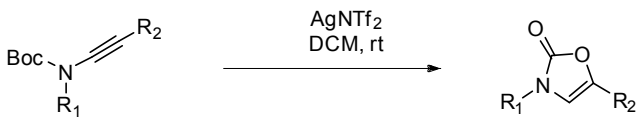


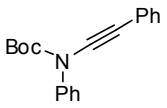
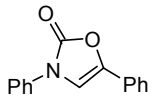
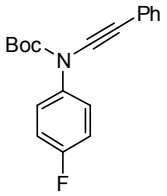
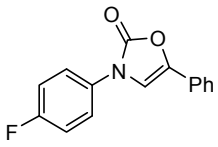
Scheme 4.19. Proposed mechanism explaining the formation of functionalized 4-oxazolin-2-ones **4.7**

The first step is the selective activation of the alkyne moiety by the gold catalyst's active species followed by the nucleophilic attack of the *tert*-butyloxycarbonyl group. Stabilized cationic intermediate **4.14** is thus formed. The fragmentation of the *t*-Bu – O bond in **4.14** leads to the formation of vinyl-gold intermediate **4.15** and the release of isobutene (gas). Finally, a fast protodemetallation step furnishes oxazolone **4.7** and regenerates the gold catalyst.

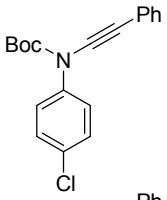
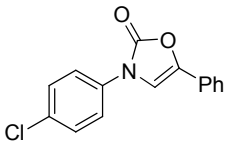
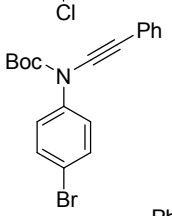
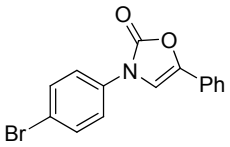
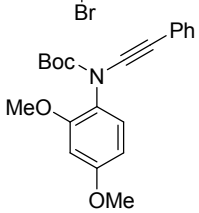
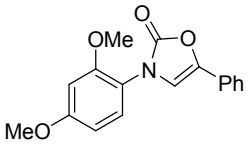
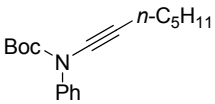
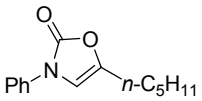
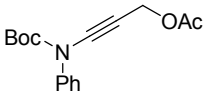
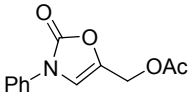
2.6. Extension to the silver(I)-catalyzed formation of 4-oxazolin-2-ones

For some of the substrates previously tested in the presence of 1% $[Ph_3P\text{-}Au\text{-}(NC\text{-}Me)]^+SbF_6^-$, the cyclization was attempted also in the presence of 5% $AgNTf_2$ at rt. We were delighted to observe the formation of 4-oxazolin-2-ones **4.12 a-e, j** and **o** under these conditions (Table 4.4).



entry	substrate		product		time	yield[a]
1		**4.11 a**		**4.12 a**	15 min	91%
2		**4.11 b**		**4.12 b**	25 min	95%

(continued on the next page)

entry	substrate		product		time	yield[a]
3		**4.11 c**		**4.12 c**	30 min	96%
4		**4.11 d**		**4.12 d**	20 min	88%
5		**4.11 e**		**4.12 e**	30 min	78%
6		**4.11 j**		**4.12 j**	1 h 30 min	53%
7		**4.11 o**		**4.12 o**	3 h	36%

Reaction conditions: substrate (1 equiv), $AgNTf_2$ (0.05 equiv), DCM (0.5 M), rt. [a] Yield estimated by ^1H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Table 4.4. Scope of the silver(I)-catalyzed rearrangement to 4-oxazolin-2-ones **4.12 a-e**, **j** and **o**

In the cases where the formation of 4-oxazolin-2-ones is extremely favorable (such as substrates **4.11 a-e**), the silver(I)-catalyst furnished excellent yields (88%-96%, see Table 4.4, Entries 1-5).

Unfortunately, when substrates for which the cyclization process is less favorable (such as **4.11 j** or **o**) were used, the silver catalyst proved to be less efficient (Table 4.4, Entries 6 and 7). For instance, substrate **4.11 j** gave **4.12 j** only in a 53% yield (compared to 74% for the gold-catalyzed transformation), while substrate **4.11 o**, substituted with a propargylic acetate functionality, furnished the expected product **4.12 o** in a meager 36% yield (versus 71% for the gold process).

In conclusion, although $AgNTf_2$ can be an excellent substitute for gold in some particular cases, it cannot completely replace it. This lack of generality can be explained by a lesser activity and specificity of silver complexes compared to gold ones for this type of transformation.

3. Conclusions and perspectives

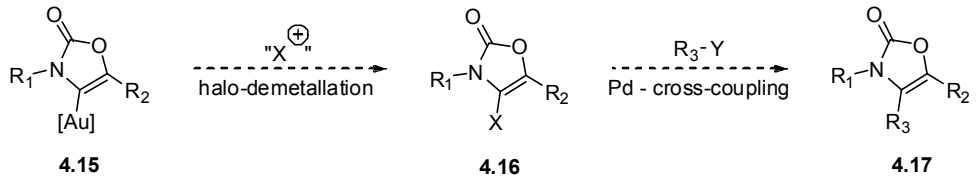
We have shown that 4-oxazolin-2-ones can be easily obtained in just two steps: first a copper(II) catalyzed coupling between a bromoalkyne and a secondary *tert*-butyloxycarbamate followed by a gold(I)-catalyzed cyclization of the *N*-alkynyl *tert*-butyloxycarbamate thus obtained.

The copper-mediated cross-coupling facilitates the access to *N*-alkynyl *tert*-butyloxycarbamates, otherwise difficult to obtain via classical methods.

The gold-catalyzed step distinguishes itself by its wide scope, being compatible with various substitutions at the triple bond and nitrogen atom positions. A large number of functional groups were tolerated as well, including alkene, silyl ether or ester functionalities. Other benefits include the low amounts of catalyst which is required for this transformation and the relatively mild conditions used. The easy purification of the final oxazolones in some cases is to be mentioned as well.

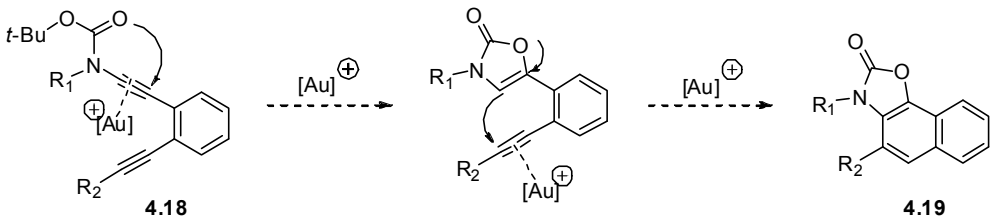
We have shown also that silver(I)-complexes can catalyze too the rearrangement *N*-alkynyl *tert*-butyloxycarbamates to 4-oxazolin-2-ones, although this only works in the most favorable cases. Still, the possibility of substituting gold with silver can be particularly appealing especially for large scale applications.

Potential perspectives of this methodology might include the access to trisubstituted 4-oxazolin-2-ones **4.17**. By analogy with the work described in the previous chapter, this could be done by trapping the intermediate vinyl gold intermediate **4.15** with a source of electrophilic halide. The vinyl halide derivative **4.16** thus obtained could then be involved for instance in various palladium couplings (Scheme 4.20).



Scheme 4.20. Potential access to 4-halo-4-oxazolin-2-ones **4.16** and trisubstituted 4-oxazolin-2-ones **4.17**

Other applications of this methodology might include the access to 1-hydroxy-2-amino naphtalenes derivatives **4.19** via a double gold(I)-cyclization process starting from substrates like **4.18** (Scheme 4.21).



Scheme 4.21. Potential access to 1-hydroxy-2-amino naphtalenes derivatives **4.19**

Finally, a different gold catalyzed process involving *N*-alkynyl *tert*-butyloxycarbamates and leading to oxazinanones will be presented later in chapter 9.

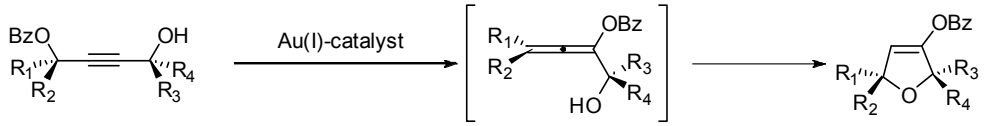
CHAPTER

5

Gold(I)-Catalyzed Stereoselective Formation of Functionalized 2,5-Dihydrofurans

"Chemistry is all about getting lucky..."
*(**Robert F. Curl, Jr.**, American chemist, Nobel Prize winner in 1996)*

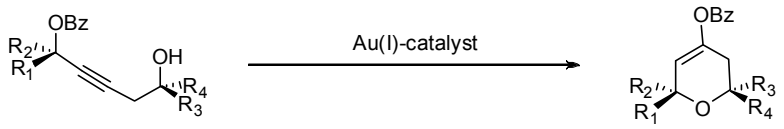
This chapter describes the stereoselective formation of functionalized 2,5-dihydrofurans starting form butynediol monobenzoates via a sequence of two gold(I)-catalyzed rearrangement steps (Scheme 3.1).



Scheme 5.1. Gold(I)-catalyzed formation of functionalized 2,5-dihydrofurans

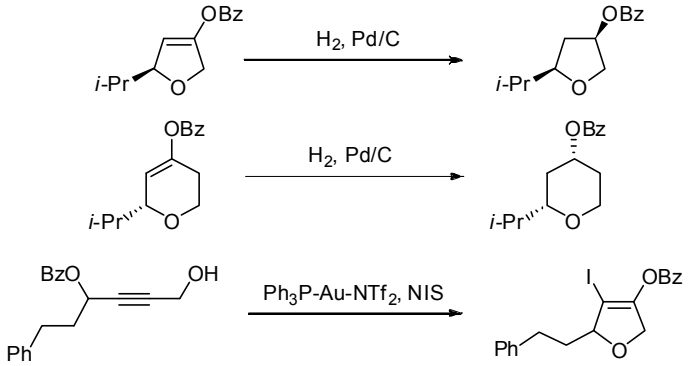
Among the advantages of this transformation we can name the accessibility of the starting substrates, the mild reaction conditions, the compatibility with a good number of functional groups and the excellent transfer of chiral information (if present in the starting substrate), allowing the formation of optically active 2,5-dihydrofurans otherwise difficult to obtain using classical methods.

The formation of functionalized dihydropyranes was also possible via this method, although in this case the stereocontrol was somewhat less effective (Scheme 3.2).



Scheme 5.2. Gold(I)-catalyzed formation of functionalized dihydropyranes

The potential of this method was highlighted by the formation of functionalized tetrahydrofurans, tetrahydropyranes or substituted 4-iodo-2,5-dihydrofurans (which can be versatile precursors of highly functionalized products) (Scheme 5.3).



Scheme 5.3. Possible transformations highlighting the potential of our method

In the first part of this chapter the importance of the 2,5-dihydrofuran moiety in organic chemistry and some of the synthetic methods currently used to obtain it will be discussed briefly (section 1). The second part is dedicated to a more detailed look on our work concerning this topic and also to some possible applications (section 2). This chapter ends with a few conclusions and perspectives (section 3).

Disclaimer:

This work was conducted under the supervision of Dr. Fabien L. Gagosz. Although a part of the experiments presented in this chapter was carried out by Dr. Andrea K. Buzas and Dr. Fabien L. Gagosz, in order to preserve the coherence of the subject the totality of the work concerning this topic will be discussed here.

These results have been previously published in:

- Andrea K. Buzas, Florin M. Istrate, Fabien L. Gagosz* "Gold(I)-Catalyzed Stereoselective Formation of Functionalized 2,5-Dihydrofurans" *Org. Lett.* **2006**, *8 (9)*, 1957–1959

1. The 2,5-dihydrofurans

1.1. Importance of the 2,5-dihydrofuran moiety

The 2,5-dihydrofuran ring (Figure 5.1) has received a lot of attention over the years due to its common presence in both natural and synthetic organic compounds.[149]

[149] (a) Kilroy, T. G.; O'Sullivan, T. P.; Guiry, P. J. *Eur. J. Org. Chem.* **2005**, *2005*, 4929-4949.
(b) Slavinskaya, V. A.; Karakhanov, R. A.; Brezhnev, L. Y.; Geiman, I. I.; Bulenkova, L. F.; Strautinya, A. K. *Chem. Heterocycl. Compd.* **1982**, *18*, 997-1008.
(c) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795-819.

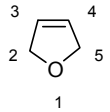


Figure 5.1. The 2,5-dihydrofuran moiety

Indeed, there are many classes of natural compounds containing a 2,5-dihydrofuran ring. Some of them exhibit interesting pharmaceutical and/or biological activities. For example, we can mention here tetronomycin[150] (a polyether antibiotic[151]), liatrin[152] (an antileukemic sesquiterpene lactone), bielschowskysin[153] and peribysin D[154] (marine natural products[155] with cytostatic proprieties) or (+)-furanomycin[156] (an antibiotic α-amino acid) etc. (Figure 5.2).

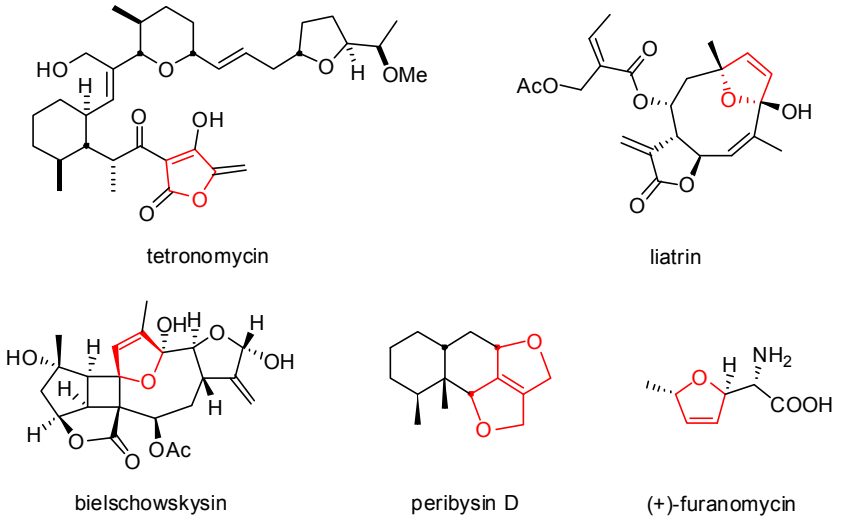


Figure 5.2. A few examples of natural products containing the 2,5-dihydrofuran ring

The 2,5-dihydrofuran moiety is also common in odorant compounds (such as etaspirene, isospirene or neocaspirene etc. [157]) and finds frequent applications in the flavor and fragrance industry.

(d) Wong, H. N. C.; Yeung, K. S.; Yang, Z.; Alan, R. K.; Christopher, A. R.; Eric, F. V. S.; Richard, J. K. T. In *Comprehensive Heterocyclic Chemistry III*; Elsevier: Oxford, 2008, p 407-496.

(e) Graening, T.; Thrun, F.; Alan, R. K.; Christopher, A. R.; Eric, F. V. S.; Richard, J. K. T. In *Comprehensive Heterocyclic Chemistry III*; Elsevier: Oxford, 2008, p 497-569.

(f) Livingstone, R. In *Rodd's Chemistry of Carbon Compounds*; 2nd ed.; Coffey, S., Ed.; Elsevier Scientific Publishing Company: 1973; Vol. IV, p 125-128.

[150] Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888-2902.

[151] Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407-2474.

[152] Kupchan, S. M.; Davies, V. H.; Fujita, T.; Cox, M. R.; Restivo, R. J.; Bryan, R. F. *J. Org. Chem.* **1973**, *38*, 1853-1858.

[153] Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G.; Sanchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661-1664.

[154] Yamada, T.; Iritani, M.; Minoura, K.; Kawai, K.; Numata, A. *Org. Biomol. Chem.* **2004**, *2*, 2131-2135.

[155] (a) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *23*, 26-78.

(b) Fernandez, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235-246.

[156] Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505-7510.

[157] Kraft, P.; Bajgrowicz, J. A.; Denis, C.; Fráter, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 2980-3010.

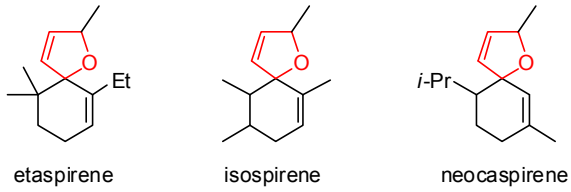


Figure 5.3. Odorant compounds containing a 2,5-dihydrofuran moiety

2,5-dihydrofurans are also valuable precursors in the synthesis of various useful chemicals[149b,158] (such as prostaglandins or polymers) and are frequent intermediates in various total synthesis.[159]

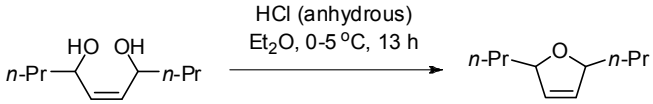
1.2. Synthesis of 2,5-dihydrofurans

The importance of the 2,5-dihydrofuran moiety in organic chemistry gave rise to a large number of studies concerning the access to this type of structure.[149] The development of new synthetic routes, more efficient and/or with a wider scope, remains a topic of major interest even today.

Although a complete list of the methods currently used to obtain 2,5-dihydrofurans is beyond the scope of this manuscript, some representative approaches will be presented next.

Synthesis by cyclization of diols

One of the most straightforward ways to form the 2,5-dihydrofuran ring is to cyclize directly a properly substituted but-2-en-1,4-diol. For instance, Werner et al. obtained 2,5-dipropyl-2,5-dihydrofuran by this approach (Scheme 5.4).[160]



Scheme 5.4. Synthesis of 2,5-dihydrofurans by cyclization of but-2-en-1,4-diols

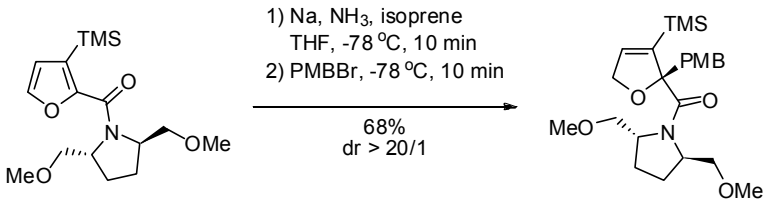
Although this method is widely used, even on an industrial scale (due to the easy access to but-2-ene-1,4-diols by partial reduction of but-2-yne-1,4-diols, which in turn can be obtained from acetylene and an aldehyde), the conditions employed are often quite harsh and can lead to the formation of various side-products, such as α,β-unsaturated carbonylic compounds [161] or polymers.[162]

[158] (a) Drury, R. F. *US 4231941*, **1980**
(b) Bacskai, R. *US 4011282*, **1977**
[159] (a) Trost, B. M.; Dirat, O.; Jr, J. D.; Hembre, E. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 3658-3660.
(b) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1996**, *118*, 3037-3038.
[160] Werner, R. E.; Reynolds, W. B. *J. Am. Chem. Soc.* **1947**, *69*, 633-634.
[161] Erace, N. O. *J. Am. Chem. Soc.* **1955**, *77*, 4157-4158.
[162] Gillis, B. T.; Beck, P. E. *J. Org. Chem.* **1963**, *28*, 1388-1390.

More gentle methods using for instance dicyclohexylcarbodiimide and copper(I) chloride have also been developed[163], but some of them still present significant drawbacks.

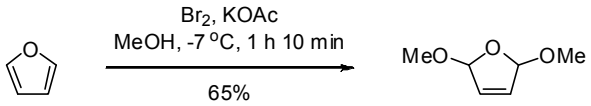
Synthesis by reduction of furans

Another way to obtain the 2,5-dihydrofuran structure is to start from a furan derivative. Donohoe et al. used a Birch reduction followed by the electrophilic attack of a benzylic bromide to synthesize stereoselectively a highly substituted 2,5-dihydrofuran derivative (Scheme 5.5).[164]



Scheme 5.5. Synthesis of 2,5-dihydrofurans by reduction of furans

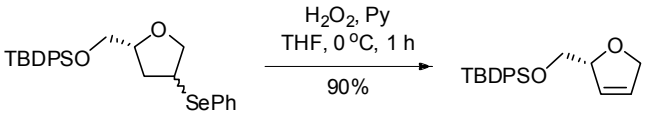
2,5-attacks to furans are also possible, as showed by Clauson-Kaas as early as 1948. He treated furan with bromine in methanol in the presence of weak bases (Scheme 5.6).[165]



Scheme 5.6. Synthesis of a 2,5-dihydrofuran by a 2,5-attack on a furan

Synthesis from other furan derivatives

Other furan derivatives can be used as well. An obvious method is the 3,4-elimination of a functional group in an appropriate tetrahydrofuran derivative (Scheme 5.7).[166]



Scheme 5.7. Synthesis of 2,5-dihydrofurans by a 3,4-elimination of a functional group in a tetrahydrofuran derivative

The Heck vinylation or arylation of 2,3-dihydrofurans is a very useful method to obtain substituted 2,5-dihydrofurans, as shown by Larock's[167] and Guiry's groups[168] (Scheme 5.8).

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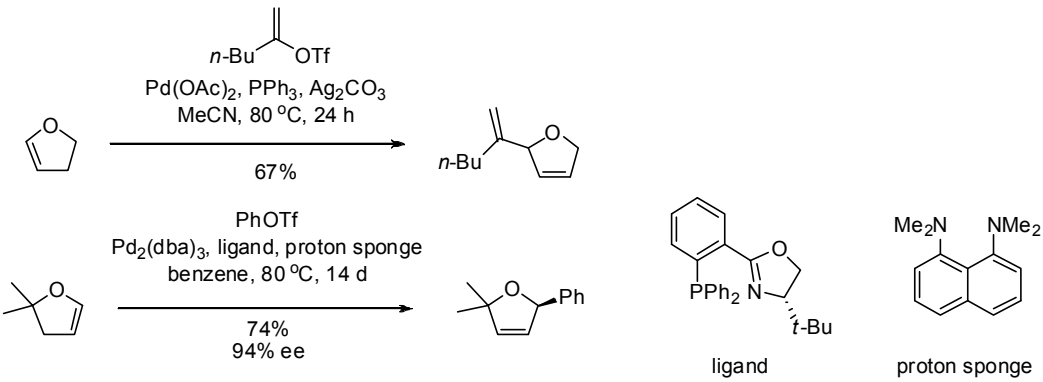
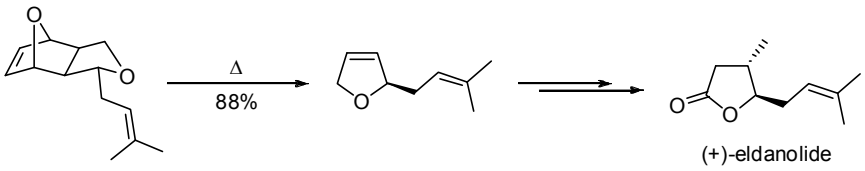
[163] Duffy, M. G.; Grayson, D. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1555-1563.
[164] Donohoe, T. J.; Fisher, J. W.; Edwards, P. J. *Org. Lett.* **2004**, *6*, 465-467.
[165] Clauson-Kaas, N.; Limborg, F.; Fakstorp, J. *Acta Chem. Scand.* **1948**, *2*, 109-115.
[166] Bravo, F.; Viso, A.; Castillon, S. *J. Org. Chem.* **2003**, *68*, 1172-1175.
[167] Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1989**, *54*, 2047-2050.
[168] Hennessy, A. J.; Connolly, D. J.; Malone, Y. M.; Guiry, P. J. *Tetrahedron Lett.* **2000**, *41*, 7757-7761.



Scheme 5.8. Synthesis of 2,5-dihydrofurans by Heck vinylation or arylation of 2,3-dihydrofurans

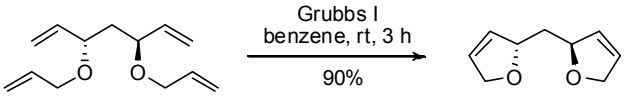
Modified furan – 2,5-dihydrofuran cycloadducts can also be employed to obtain optically active 2,5-dihydrofurans. Bloch and Seck used this approach for the total synthesis of (+)-eldanolide, a sexual pheromone of *Eldana Saccharina*, the African sugar-cane borer moth (Scheme 5.9).[169]



Scheme 5.9. Synthesis of 2,5-dihydrofurans by retro Diels-Alder reaction of furan – 2,5-dihydrofuran cycloadducts

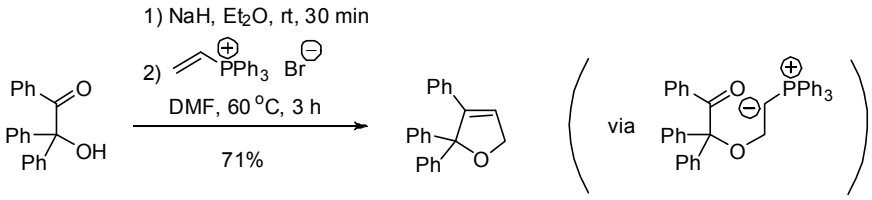
Formation of the C_3-C_4 double bond

The 2,5-dihydrofuran ring can also be constructed. Ring-closing metathesis of diallyl ethers allows the rapid formation of the C_3-C_4 double bond, as shown by Mioskowski et al. (Scheme 5.10).[170]



Scheme 5.10. Synthesis of 2,5-dihydrofurans by RCM of diallyl ethers

The double bond in the furan ring can also be formed by a Wittig cyclo-olefination reaction of a suitable β-oxaethylphosphorane (Scheme 5.11).[171]

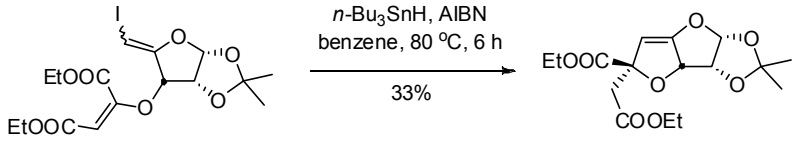


Scheme 5.11. Synthesis of 2,5-dihydrofurans by the Wittig cyclo-olefination reaction

[169] Bloch, R.; Seck, M. *Tetrahedron* **1989**, *45*, 3731-3740.
[170] Baylon, C.; Heck, M.-P.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3354-3360.
[171] Schweizer, E. E.; Liehr, J. G. *J. Org. Chem.* **1968**, *33*, 583-584.

Formation of the C_2-C_3 bond

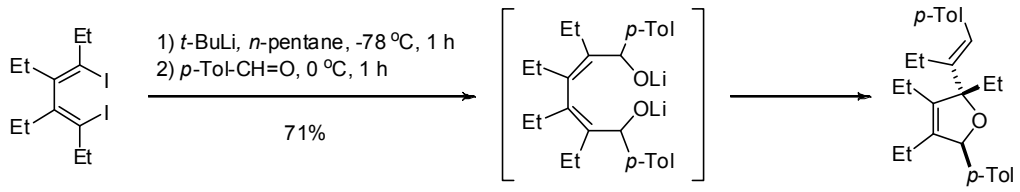
The main step in the synthesis of griseolic acid by Knapp et al. was a 5-*exo* radical cyclization which led to the stereoselective formation of a C_2-C_3 bond in a substituted 2,5-dihydrofuran moiety (Scheme 5.12).[172]



Scheme 5.12. Synthesis of 2,5-dihydrofurans by radical cyclization

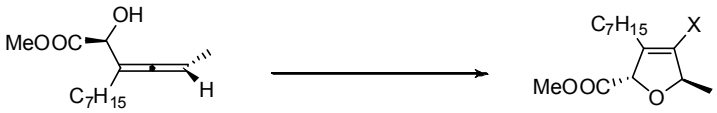
Formation of the C_2-O_1 bond

Xi et al. synthesized polysubstituted 2,5-dihydrofurans in good to high yields with perfect regio- and stereoselectivities by cyclizing hexa-2,4-diene-1,6-dialcoholate intermediates obtained from 1,4-diiodo-1,3-dienes (Scheme 5.13).[173]



Scheme 5.13. Synthesis of 2,5-dihydrofurans by cyclization of hexa-2,4-diene-1,6-dialcoholates

A very useful method for the stereoselective formation of 2,5-dihydrofurans is the cyclization of 2,3-allenols upon addition of various electrophiles (Scheme 5.14).[174] Several examples of acid- or base-catalyzed cyclization of allenic alcohols to 2,5-dihydrofurans have also been described, although their scope remains fairly limited.[175]



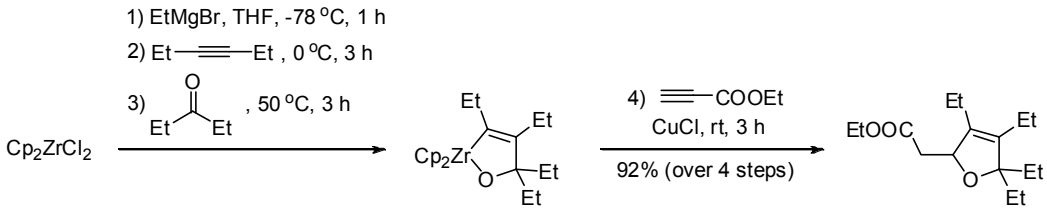
conditions	X	yield
PhSeCl, DCM, rt, 5 min	SePh	66%
NBS, DCM, rt, 48 h	Br	66%

Scheme 5.14. Synthesis of 2,5-dihydrofurans by cyclization of 2,3-allenols

Multicomponent reactions

[172] Knapp, S.; Madduru, M. R.; Lu, Z.; Morriello, G. J.; Emge, T. J.; Doss, G. A. *Org. Lett.* **2001**, *3*, 3583-3585.
[173] Chen, J.; Song, Q.; Li, P.; Guan, H.; Jin, X.; Xi, Z. *Org. Lett.* **2002**, *4*, 2269-2271.
[174] Marshall, J. A.; Wang, X. J. *J. Org. Chem.* **1990**, *55*, 2995-2996.
[175] See the articles cited in the introduction of reference 179a.

Takahasi et al. constructed substituted 2,5-dihydrofurans form several components in the presence zirconium derivatives via an oxazirconacyclopentene intermediate (Scheme 5.15).[176]



Scheme 5.15. Synthesis of 2,5-dihydrofurans via zirconocene complexes

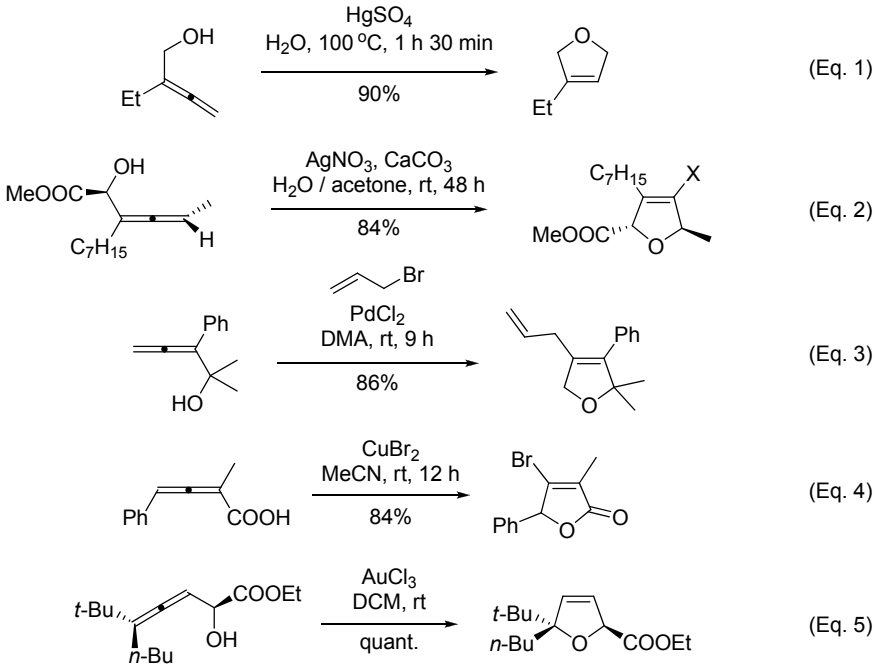
Metal-catalyzed rearrangements

Last, but not least, the transition-metal catalyzed rearrangement of various compounds into substituted 2,5-dihydrofurans has become one of the most versatile and elegant approaches towards this kind of structures.

Hydroxyallenes are amongst the most common precursors.[177] We have seen earlier that they can cyclize in the presence of electrophiles (and even acids or bases in some cases) to give substituted 2,5-dihydrofurans, although these transformations are rather limited in scope. The use of transition metals like mercury,[178] silver,[174,179] palladium,[180] copper[181] and more recently gold[182] improved dramatically both the yield and scope of these transformations.

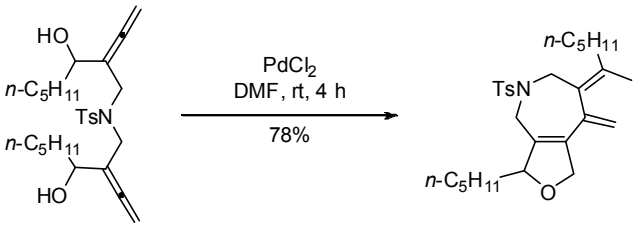
Scheme 5.16 shows some representative examples. We can see that the chirality of the starting allene can be nicely transferred to the final 2,5-dihydrofuran (Eq. 2 and 5). In the presence of a palladium catalyst, the rearrangement to 2,5-dihydrofurans can be combined with a cross-coupling reaction (Eq. 3). The copper-catalyzed rearrangement can lead to the 3-halosubstituted-2,5-dihydrofurans (Eq. 4).

[176] Xi, C.; Kotora, M.; Takahashi, T. *Tetrahedron Lett.* **1999**, *40*, 2375-2378.
[177] For some general reviews about the reactivity of allenes, see:
(a) Smadja, W. *Chem. Rev.* **1983**, *83*, 263-320.
(b) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067-3126.
(c) Ma, S. *Chem. Rev.* **2005**, *105*, 2829-2872.
[178] (a) Gelin, R.; Albrand, M.; Gelin, S. *C. R. Acad. Sci. Ser. C* **1969**, *269*, 241.
(b) Gelin, R.; Gelin, S.; Albrand, M. *Bull. Soc. Chim. Fr.* **1972**, 1946.
[179] (a) Olsson, L. I.; Claesson, A. *Synthesis* **1979**, 743-745.
(b) Nikam, S. S.; Chu, K. H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 745-747.
(b) Marshall, J. A.; Wang, X. J. *J. Org. Chem.* **1991**, *56*, 4913-4918.
(c) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966-5968.
(d) Lepage, O.; Kattnig, E.; Furstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970-15971.
[180] (a) Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933-8936.
(b) Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387-6389.
(c) Ma, S.; Duan, D.; Shi, Z. *Org. Lett.* **2000**, *2*, 1419-1422.
[181] Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314-9317.
[182] (a) Hoffmann-Roder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537-2538.
(b) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, *2006*, 1387-1389.



Scheme 5.16. Synthesis of 2,5-dihydrofurans by metal-catalyzed rearrangement of allenols

Of course, more complex variants of these transformation have been reported. For instance, Ma et al. reported a Pd-catalyzed transformation of 1,5-bisallenols leading to 2,5-dihydrofuran-fused bicyclic skeletons (Scheme 5.17).[183]

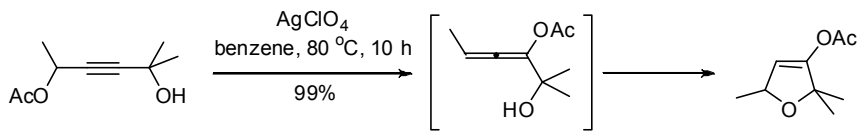


Scheme 5.17. Synthesis of 2,5-dihydrofuran-fused bicyclic skeletons by a metal-catalyzed rearrangement of 1,5-bisallenols

A very practical variant of this transformation has been developed by Hiyama et al. Given the instability of the allene moiety, the authors made use of a 4-hydroxypropargyl ester instead. The allene group was formed *in situ* under the influence of the silver catalyst, followed by the free hydroxyl group's cyclization (Scheme 5.18).[184] This approach has been successfully used for the total synthesis of compounds such as bullatenone, geiparvarin,[185] (*S*)-(-)-ascofuranone[186] or of muscarone

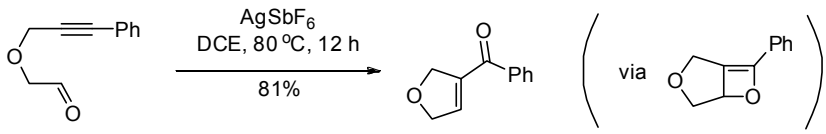
[183] Deng, Y.; Shi, Y.; Ma, S. *Org. Lett.* **2009**, *11*, 1205-1208.
[184] Saimoto, H.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1981**, *103*, 4975-4977.
[185] Saimoto, H.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3078-3087.
[186] (a) Shigemasa, Y.; Yasui, M.; Ohrai, S.; Sasaki, M.; Sashiwa, H.; Saimoto, H. *J. Org. Chem.* **1991**, *56*, 910-912.
(b) Saimoto, H.; Yasui, M.; Ohrai, S.; Oikawa, H.; Yokoyama, K.; Shigemasa, Y. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 279-284.

analogues.[187]



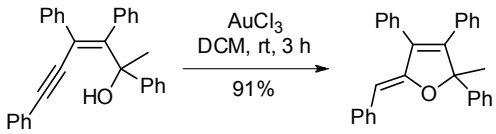
Scheme 5.18. Synthesis of 2,5-dihydrofurans from monoacylated butynediols via a double silver-catalyzed rearrangement

Rhee et al. reported a silver-catalyzed alkyne-carbonyl coupling leading to the formation of 3-carbonyl substituted 2,5-dihydrofurans (Scheme 5.19).[188]



Scheme 5.19. Synthesis of 2,5-dihydrofurans via a silver-catalyzed alkyne-carbonyl coupling

Liu et al. used gold(I) and gold(III) catalysts for the cyclization of *Z*-enynols offering a very efficient route to *Z*-5-ylidene-2,5-dihydrofurans (Scheme 5.20).[189]



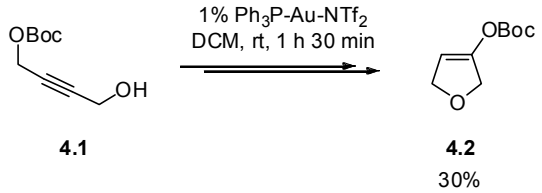
Scheme 5.20. Synthesis of 2,5-dihydrofurans via a gold-catalyzed rearrangement of *Z*-enynols

2. Our synthetic approach to functionalized 2,5-dihydorfurans

2.1. The initial idea. Precedents in the literature

During our work on the gold(I)-catalyzed formation of 4-alkylidene-1,3-dioxolan-2-ones (see Chapter 3), compound **5.1** was tested under standard conditions. To our surprise, the reaction led to the formation of an unexpected side-product, which was isolated (30% yield) and found to be the substituted 2,5-dihydrofuran **5.2** (Scheme 5.21).

[187] Wu, E. S. C.; Griffith, R. C.; Loch, J. T.; Kover, A.; Murray, R. J.; Mullen, G. B.; Blosser, J. C.; Machulskis, A. C.; McCreedy, S. A. *J. Med. Chem.* **1995**, *38*, 1558-1570.
[188] Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493-2495.
[189] Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409-5412.



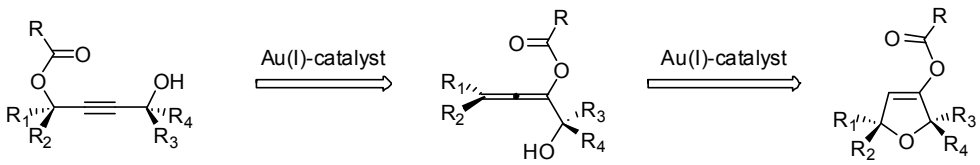
Scheme 5.21. Formation of 2,5-dihydrofuran **5.2** as a side product

Intrigued by this discovery, we decided to look further into it. A short survey of the literature revealed that similar silver-catalyzed rearrangements of monoacylated butynediols into 2,5-dihydrofurans had been previously reported.[184-187] They proceeded via an intermediate α-hydroxy allene intermediate formed *in situ* by the rearrangement of the propargylic ester group (see Scheme 5.18).

Unfortunately, these transformations seemed to be limited exclusively to tertiary alcohols. Furthermore, they required sometimes relatively important loadings of catalyst (between 5 and 15%), high temperatures (refluxing benzene for example), long reaction times and the protection of the reaction vessel from daylight. These rather harsh conditions were not always compatible with highly functionalized substrates. The counterion of the silver catalyst ($AgClO_4$, $AgBF_4$ etc.) could also lead to various side reactions.

Given the restrictions of these silver-catalyzed processes, we decided to develop a similar gold-catalyzed transformation. We were hoping that a gold catalyst, although theoretically more expensive than a silver one, might have the advantage of being more active and more specific.

By analogy, our transformation would consist in two gold-catalyzed steps: a migration of the acyloxy group to form the corresponding allene followed by cyclization of the free alcohol on the gold-activated allene (Scheme 5.22).

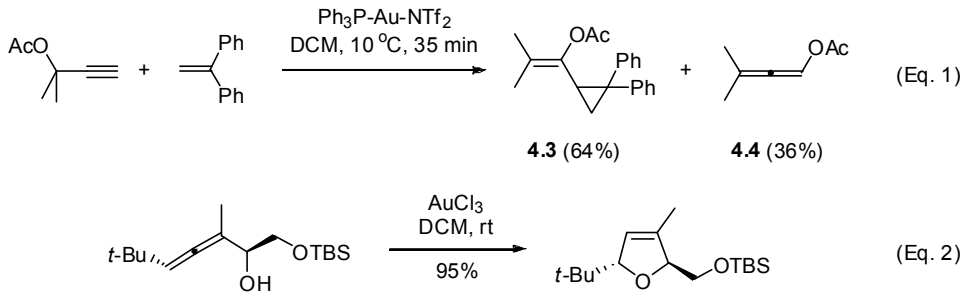


Scheme 5.22. Initial hypothesis for the formation of functionalized 2,5-dihydrofurans

Individually, both steps are well known in the literature and have been described to take place in the presence of a large number of transition metals, including gold.[190]

[190] For some examples describing the metal-catalyzed ester group shift, see the articles below plus the references cited therein:
- with copper: (a) Cookson, R. C.; Cramp, M. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1980**, 197-198.
- with silver: (b) Benn, W. R. *J. Org. Chem.* **1968**, *33*, 3113-3118. (c) Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hans-Jürgen; Schmid, H. H. *Helv. Chim. Acta* **1973**, *56*, 875-944. (d) Oelberg, D. G.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 1804-1806. (e) Bowden, B.; Cookson, R. C.; Davis, H. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2634-2637. (f) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 2280-2282.
- with palladium: (g) Cadran, N.; Cariou, K.; Herve, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408-3409. (h) Cariou, K.; Mainetti, E.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2004**, *60*, 9745-9755. (i) Anjum, S.; Marco-Contelles, J. *Tetrahedron* **2005**, *61*, 4793-4803.

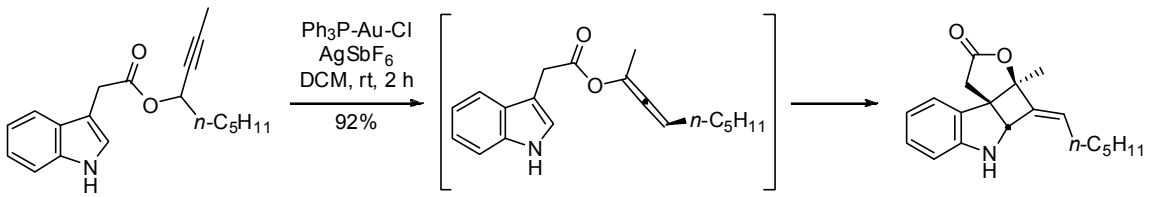
For example, the formation of allene **5.4** was observed as a side-reaction during the formation of cyclopropane **5.3** (Scheme 5.23, Eq. 1),[191] while Krause et al. described the stereoselective gold-catalyzed rearrangement of α-hydroxyallenes **5.5** to 2,5-dihydrofurans **5.6** (Scheme 5.23, Eq. 2).[182a]



Scheme 5.23. Examples of gold-catalyzed transformations similar with the individual steps of our transformation

Although the individual steps have each been previously described, to our best of knowledge no report combining the two in a single gold-catalyzed process has ever been made. Apart from the purely academic interest of showing that this 2-steps reaction can be done in the presence of a gold catalyst, we also wanted to develop a more effective and general transformation compared to the analogous silver-catalyzed rearrangements of monoacylated butynediols.[184-187]

Other gold-catalyzed processes using a similar principle (i.e. the rearrangement of a propargylic ester into an allene and the subsequent attack of an intramolecular nucleophile on the gold-activated allene) have also been reported. For instance, Zhang and coworkers obtained via this approach highly functionalized 2,3-indoline-fused cyclobutanes (Scheme 5.24).[190k]



Scheme 5.24. Similar gold-catalyzed process

2.2. First trials

We decided to start with the simplest substrates in order to validate our approach. Different monoesters of 2-butyl-1,4-diol **5.7 a-c** were tested in the presence of 1% Ph_3P-Au-NTf_2 in dichloromethane at rt (Table 5.1).

- with gold: (j) Marion, N.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2750-2752. (k) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804-16805. (l) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442-1443. (m) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271-2296.

For some examples describing the metal-catalyzed rearrangement of hydroxyallenes to 2,5-dihydrofurans, see the references 177 (general reviews), 178 (with mercury), 174, 179 (with silver), 180, 183 (with platinum), 181 (with copper), 182 (with gold), etc.

[191] Istrate, F. M.; Gagosz, F. L. *Unpublished results*.

Gratifyingly, in all three cases the formation of the expected 2,5-dihydrofurans **5.8 a-c** was observed. However, the acetate **5.7 a** and the pivalate **5.7 b** derivatives gave rather poor results (probably due to the volatility of the resulting final compound). On the other hand, the benzoate derivative **5.7 c** afforded the expected 2,5-dihydrofuran **5.8 c** in 83% yield. The benzoate group was therefore retained as a migrating group.

5.7 a-c **5.8 a-c**

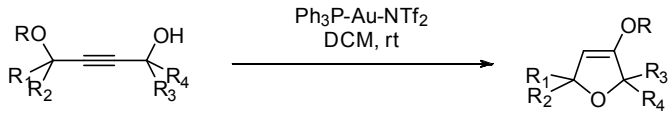
entry	R	substrate	time	yield[a]	product
1	Ac	**5.7 a**	1 h 30 min	<10%	**5.8 a**
2	Piv	**5.7 b**	1 h	23%	**5.8 b**
3	Bz	**5.7 c**	1 h 20 min	83%	**5.8 c**

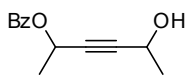
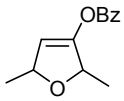
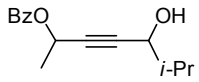
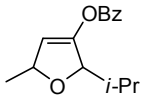
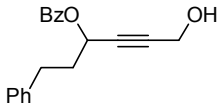
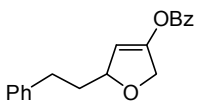
Reaction conditions: substrate (1 equiv), Ph_3P-Au-NTf_2 (0.01 equiv), DCM (0.5 M), rt. [a] Isolated yield.

Table 5.1. Initial trials for the formation of functionalized 2,5-dihydrofurans

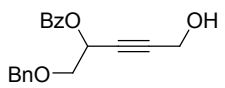
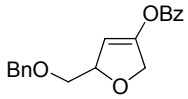
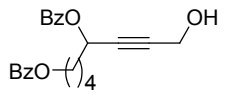
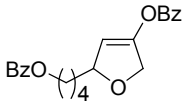
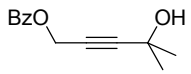
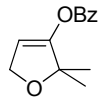
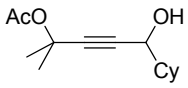
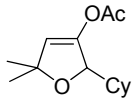
2.3. Reactivity in the racemic series

Encouraged by these preliminary results, we decided to prove first the scope of the reaction in the racemic series. The amount of catalyst was increased to 2% in order to insure a full conversion of the substrates in all cases. These conditions (2% Ph_3P-Au-NTf_2, 0.5 M DCM, rt) were retained as standard and various substituted monoester 2-butyn-1,4-diols **5.9 a-g** were tested (Table 5.2).

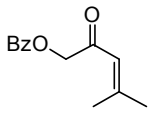


entry	substrate		product		time	yield[a]
1		**5.9 a**		**5.10 a**	15 min	95%
2		**5.9 b**		**5.10 b**	20 min	92%
3		**5.9 c**		**5.10 c**	5 min	95%

(continued on the next page)

entry	substrate		product		time	yield[a]
4		**5.9 d**		**5.10 d**	20 min	99%
5		**5.9 e**		**5.10 e**	10 min	99%
6		**5.9 f**		**5.10 f**	1 h	69%[b]
7		**5.9 g**		**5.10 g**	5 min	82%

Reaction conditions: substrate (1 equiv), Ph_3P-Au-NTf_2 (0.02 equiv), DCM (0.5 M), rt. [a] Isolated yield. [b] Compound **5.11** was also isolated as a side product in a 23% yield.



5.11

Table 5.2. Scope of the reaction in the achiral series

We were delighted to observe that this transformation was quite general. All substrates furnished the expected 2,5-dihydrofurans **5.10 a-g** in excellent yields (82%-99%) and very short reaction times (5 min to 20 min).

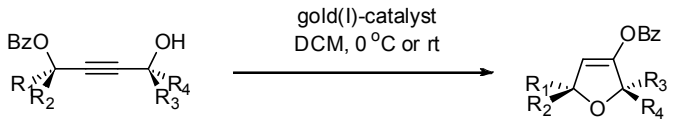
The only exception was the tertiary alcohol **5.9 f** which gave only an average yield (69%) and a slightly longer reaction time (1 h). The lower yield can be explained by the formation of enone **5.11** (23% isolated yield) via a competitive side reaction (Table 5.2, Entry 6). This result was quite surprising, knowing the fact that tertiary alcohol derivatives, in the case of the analogous silver-catalyzed rearrangements, gave the highest yields. This fact highlights furthermore the differences between gold and silver catalysts.

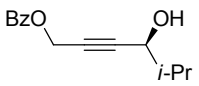
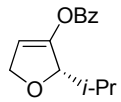
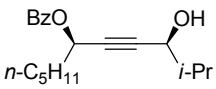
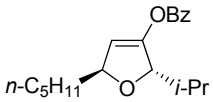
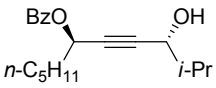
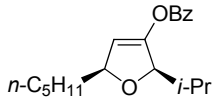
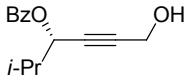
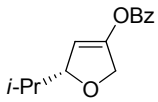
As one can notice from Table 5.2, our gold-catalyzed method is compatible with a large number of substitutions patterns at both vicinal ester and alcohol positions. Primary (substrate **5.7 c** in Table 5.1, Entry 3 and substrate **5.9 f** in Table 5.2, Entry 6), secondary (substrates **5.9 a-e** in Table 5.2, Entries 1-5) and tertiary propargylic esters (substrate **5.9 g** in Table 5.2, Entry 7) afford all the expected 2,5-dihydrofurans. The same goes for primary (substrates **5.9 c-e** in Table 5.2, Entries 3-5), secondary (substrates **5.9 a**, **b** and **g** in Table 5.2, Entries 1, 2 and 7) and tertiary alcohols (substrates **5.9 f** in Table 5.2, Entry 6). The presence of an aryl (substrates **5.9 c** in Table 5.2, Entry 3), ether (substrates **5.9 d** in Table 5.2, Entry 4) or ester group (substrates **5.9 e** in Table 5.2, Entry 5) is tolerated as well. In the case of less volatile compounds, an acetate derivative **5.9 g** may be used as well, as shown in Table 5.2, Entry 7.

With the exception of the tertiary alcohol **5.9 f** discussed above (Table 5.2, Entry 6), all the other compounds react with nearly identical reactivity, which might seem to indicate that the substitution pattern does not influence that much the outcome of this transformation.

2.4. Reactivity in the chiral series

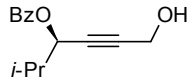
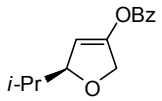
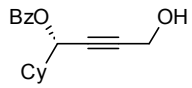
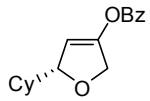
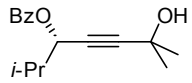
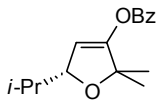
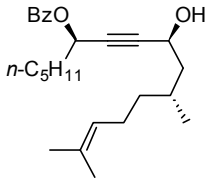
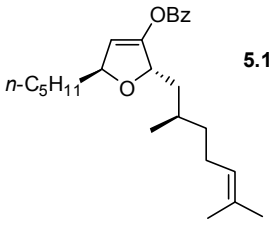
Next, we turned our attention to enantioenriched substrates. The procedure developed by Carreira et al.[192] allows the easy formation of various optically active 2-butyn-1,4-diols **5.12 a-h**, which were tested under standard catalytic conditions (Table 5.3).



entry	substrate		conditions	product		time	yield[a]
1	 87% ee	**5.12 a**	Ph_3P-Au-NTf_2, rt	 86% ee	**5.13 a**	3 h	83%
2	 93:7 dr, >98% ee	**5.12 b**	Ph_3P-Au-NTf_2, rt	 93:7 dr, >98% ee	**5.13 b**	40 min	97%
3	 94:6 dr, >98% ee	**5.12 c**	Ph_3P-Au-NTf_2, rt	 92:8 dr, >98% ee	**5.13 c**	35 min	99%
4	 94% ee	**5.12 d**	Ph_3P-Au-NTf_2, rt	 64% ee	**5.13 d**	10 min	99%

(continued on the next page)

[192] (a) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605-2606.
(b) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017-3020.
(c) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688.

entry	substrate		conditions	product		time	yield[a]
5		**5.12 e**			**5.13 e**		
	96% ee		i) Ph_3P-Au-NTf_2, rt	64% ee		15 min	99%
			ii) (p-CF_3-C_6H_4)$_3$P-Au-NTf_2, rt	66% ee		15 min	99%
			iii) Ad_2(n-Bu)P-Au-NTf_2, rt	74% ee		20 min	99%
			iv) Ph_3P-Au-NTf_2, 0 °C	84% ee		1 h 5 min	99%
			v) Ad_2(n-Bu)P-Au-NTf_2, 0 °C	90% ee		2 h	99%
6		**5.12 f**			**5.13 f**		
	94% ee		i) Ph_3P-Au-NTf_2, rt	42% ee		10 min	89%
			ii) Ad_2(n-Bu)P-Au-NTf_2, 0 °C	77% ee		2 h 25 min	91%
7		**5.12 g**	Ph_3P-Au-NTf_2, rt		**5.13 g**	50 min	95%
	81% ee			80% ee			
8		**5.12 h**	Ph_3P-Au-NTf_2, rt		**5.13 h**	15 min	99%
	~ 89.1:9.9:0.9:(<0.1) dr			~ 89.1:9.9:0.9:(<0.1) dr			

Reaction conditions: substrate (1 equiv), gold(I) catalyst (0.02 equiv, see table), DCM (0.5 M), 0 °C or rt (see table). [a] Isolated yield. dr and ee determined by chiral HPLC.

Table 5.3. Scope of the reaction in the chiral series

Just like in the case of the racemic substrates, the chiral ones furnished the expected 2,5-dihydrofurans **5.13 a-h** in excellent yields (83% - 99%) under standard conditions (2% Ph_3P-Au-NTf_2, rt). The transfer of the chiral information, on the other hand, seemed to vary according to the substitution pattern of the substrates.

The size or the number of the substitutions present at the propargylic ester position does not seem to play a major role, since primary (substrate **5.12 a** in Table 5.3, Entry 1) or secondary (substrates **5.12 b, c, g** and **h** in Table 5.3, Entries 2, 3, 7 and 8) derivatives react without loss of chirality under standard conditions.

At the other propargylic position, secondary (substrate **5.12 a-c** and **h** in Table 5.3, Entries 1-3 and 8) and tertiary (substrate **5.12 g** in Table 5.3, Entry 7) alcohols also react with complete retention of chirality. Primary alcohols on the other hand suffer from a partial loss of chiral information

(substrates **5.12 d-f** in Table 5.3, Entries 4-6). However, this loss can be limited thanks to a proper choice of the experimental conditions, as we shall see further along.

Enantio-enriched substrate **5.12 a** (87% ee), with a chiral center at its secondary alcohol position, furnishes product **5.13 a** in an 83% isolated yield without any loss of optical purity (86% ee) (Table 5.3, Entry 1).

Substrate **5.12 b**, possessing 2 stereocenters and obtained mainly as a single enantiomer (93:7 dr, >98% ee) rearranges to the *trans*-disubstituted dihydrofuran **5.13 b** in 97% yield. The dr and ee values of the final product (93:7 dr, >98% ee) indicate a complete transfer of chiral information (Table 5.3, Entry 2).

The diastereoisomer of **5.12 b**, substrate **5.12 c** (94:6 dr, 94% ee) gives very similar results, forming the *cis*-disubstituted dihydrofuran **5.13 c** in 99% yield, 92:8 dr and 94% ee (Table 5.3, Entry 3).

The two enantiomeric primary alcohol derivatives **5.12 d** and **e** (94% and respectively 96% ee) led under standard conditions (2% Ph_3P-Au-NTf_2, rt) to the formation of the corresponding enantiomers **5.13 d** and **e** in 99% yield, but with an important loss of optical purity (64% ee both, in Table 5.3, Entries 4 and 5-i).

The use of a more electrophilic catalyst (2% (p-CF_3-C_6H_4)$_3$P-Au-NTf_2, rt) for the formation of **5.13 e** does not improve the stereoselectivity (66% ee in Table 5.3, Entry 5-ii), however a catalyst with a more hindered and donor phosphine ligand (2% Ad_2(n-Bu)$_3$P-Au-NTf_2, rt) gives a slight improvement (66% ee in Table 5.3, Entry 5-iii). Lowering the temperature seems to be quite effective in reducing the chirality loss (2% Ph_3P-Au-NTf_2, 0 ^oC), although it also significantly slows down the reaction (84% ee in Table 5.3, Entry 5-iv). Finally a proper choice of the experimental conditions (i.e. a bulkier and less electrophilic catalyst combined with a lower reaction temperature: 2% Ad_2(n-Bu)$_3$P-Au-NTf_2, 0 ^oC) eliminates almost completely the loss of chiral information (90% ee in Table 5.3, Entry 5-v).

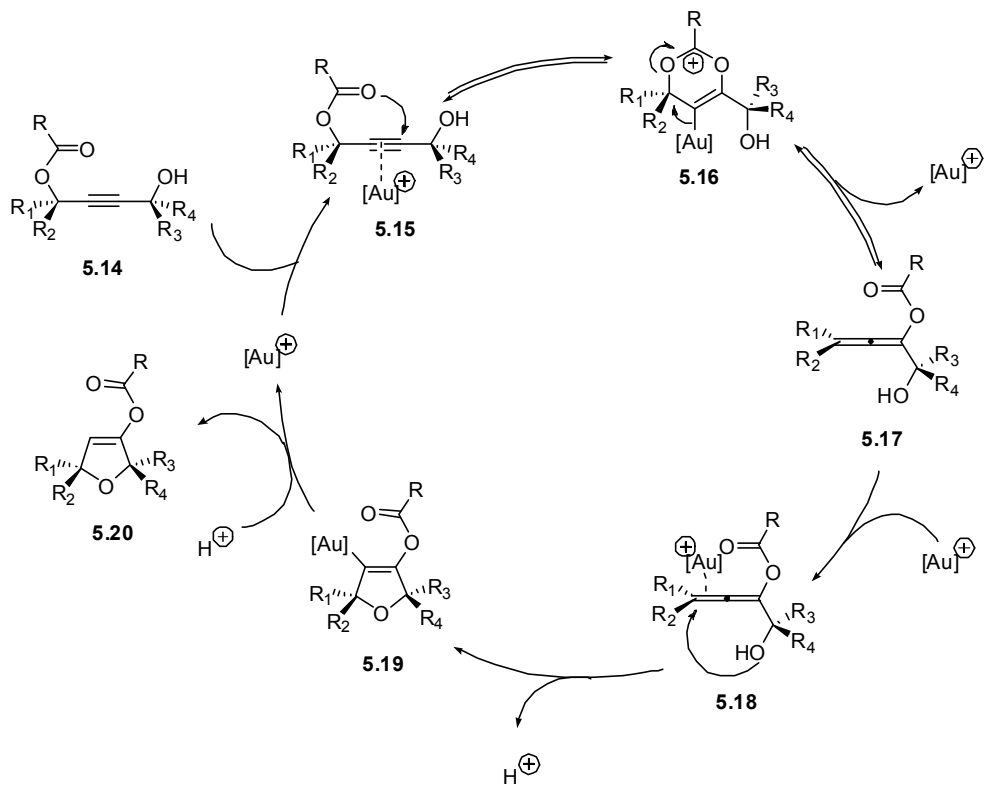
The chirality erosion seems to be more important as the substituent in the propargylic ester position gets bulkier. Compound **5.13 f**, bearing a cyclohexyl group, is obtained in an 89% yield, but only with an average 42% ee under standard conditions (Table 5.3, Entry 6-i). Using the newly optimized conditions (Table 5.3, Entry 6-ii), the loss of optical purity is considerably reduced, although not completely eliminated (91% yield and 77% ee).

Derivative **5.12 g**, tertiary at the propargylic alcohol position and secondary at the propargylic ester position (80% ee), gives a very efficient transformation, probably due to a Thorpe-Ingold effect favoring the cyclization process. Product **5.12 g** is obtained in 99% yield and the same 80% ee (Table 5.3, Entry 7).

The case of substrate **5.12 h**, possessing 3 asymmetric centers, was the most remarkable. It was obtained from optically pure (*R*)-citronellal and 99% ee (*R*)-benzoic acid-1-ethynyl-hexyl ester as a mixture of 4 non-superimposable diastereoisomers (~ 89.1:9.9:0.9:(<0.1) dr). Its rearrangement gave dihydrofuran **5.13 h**, also as a mixture of 4 non-superimposable diastereoisomers in 99% yield. The observed diastereoisomeric ratio (~ 89.1:9.9:0.9:(<0.1) dr) mirrors that of its precursor, suggesting a complete transfer of chirality. One should also notice that the presence of an alkene group in the side-chain was well tolerated (Table 5.3, Entry 8).

2.5. Mechanistic proposal

In order to account for the experimental observations presented earlier, a mechanism is proposed in Scheme 5.25.



Scheme 5.25. Proposed mechanism for the formation of functionalized 2,5-dihydrofurans

It starts with the selective activation of the triple bond by the active species of the catalyst. The attack of the carbonylic oxygen of the benzoate group onto the triple bond results in the formation of the stabilized cationic complex **5.16**. Fragmentation of the C-O bond leads to the formal 1,3-shift of the benzoate group, the formation of allene intermediate **5.17** and catalyst regeneration.

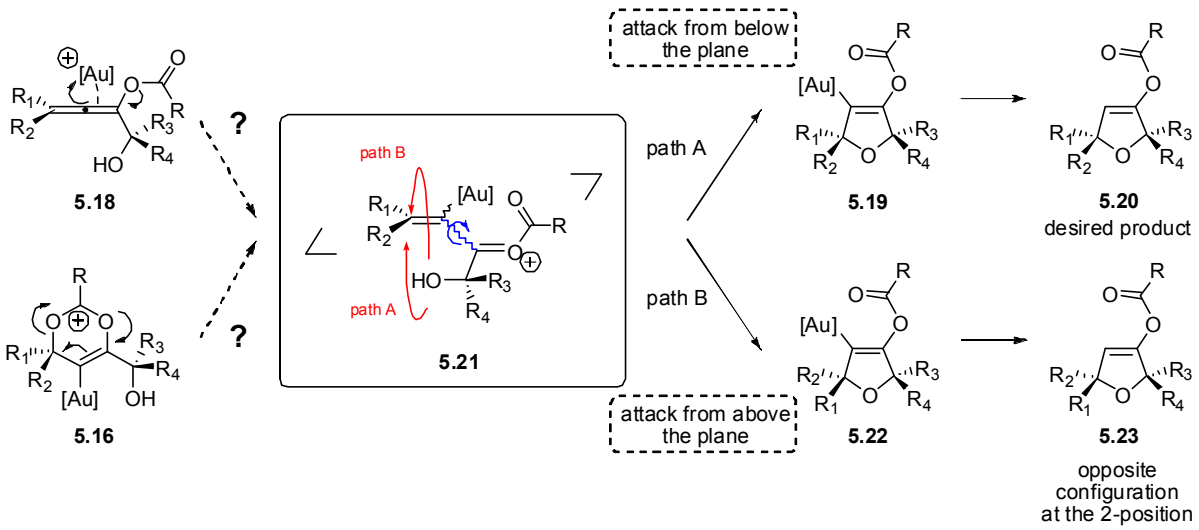
A second activation by the gold catalyst, this time of the allene moiety, promotes the nucleophilic attack of the free OH group. It is a 5-*endo-trig* attack and it follows the Baldwin's rules.[193] The vinyl-gold intermediate **5.19** is thus formed. Finally, a fast protodemetallation step affords the final 2,5-dihydrofuran **5.20**.

The observed stereoconfiguration of the final product **5.20** might be explained by a succession of stereoselective steps which conserve the chiral information of the starting substrate **5.19**. The configuration of the propargylic alcohol position is conserved throughout the whole transformation, while the configuration of the propargylic ester position is transferred first to the intermediate allene **5.17** (via a stereoselective rearrangement of the acyloxy group) and then to the final 2,5-dihydrofuran **5.20** (via a stereoselective cyclization of the free OH group).

[193] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

This mechanism is in accord with other reported gold-catalyzed transformations involving the rearrangement of propargylic esters into allenes[194] or the formation of 2,5-dihydrofurans from α-hydroxyallenes[195] and was proposed as a consequence of this fact. However, alternative mechanisms can be imagined as well.

The partial racemization observed in the case of primary alcohols might be due to the competitive involvement of a cationic intermediate **5.21**, derived either from **5.18** or directly from **5.16**. The free rotation around the vinylic carbon – oxocarbenium carbon σ-bond makes possible the attack of the free OH group either from below (Scheme 5.26, path A) or above the plane of the double bond (Scheme 5.26, path B). The first path leads to the formation of the intermediate **5.19** and of the desired product **5.20** (just like in Scheme 5.25), while the second path proceeds through intermediate **5.22** and gives diastereoisomer **5.23**, possessing an opposite configuration at the 2-position.[196]



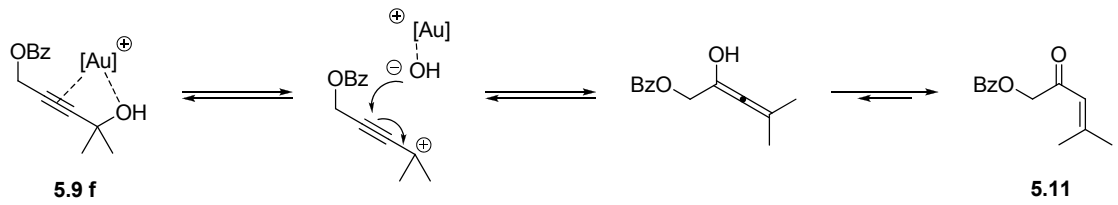
Scheme 5.26. Proposed mechanism for the partial racemization of the final 2,5-dihydrofuran **5.20**

The presence of substituents at the propargylic alcohol position (R_3 and/or $R_4 \neq H$) might speed up the direct cyclization of the OH group onto the allene moiety and favor the retention of chiral information. Therefore this Thorpe-Ingold effect is a possible explanation for the reason why no trace of racemization is observed for secondary and tertiary alcohols.

The formation of enone **5.11** can be explained by a Meyer-Schuster type rearrangement,[197] catalyzed

[194] This rearrangement can also happen via a double 1,2-shift. For a discussion regarding 1,3-shifts vs. double 1,2-shifts, see the theoretical study about the gold-catalyzed rearrangement of propargylic esters: Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718-721.
[195] During a study concerning the rearrangement of α-hydroxyallenes into 2,5-dihydrofurans in the presence of a gold(III)-catalyst, Hashmi et al. found evidence of gold (III) to gold(I) reduction. Although the article does not provide a definitive answer, according to Hashmi it can indicate the possibility of gold(I) active species involved in this transformation. This result is therefore in agreement with our proposed mechanism. See: Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, *2006*, 1387-1389.
[196] A similar racemization process of an allene was reported by Toste et al. during a study concerning a gold-catalyzed Claisen rearrangement: Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978-15979.
[197] Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429-438.

either by the gold itself[198] or by traces of acid (e.g. $HNTf_2$ formed for instance by hydrolysis of the catalyst in the presence of traces of water) (Scheme 5.27).



Scheme 5.27. Mechanistic proposal for the formation of enone **5.11** via a gold-catalyzed Meyer-Schuster rearrangement

2.6. Extension to the formation of functionalized dihydropyranes

Dihydropyranes are structural motifs found in a good number of organic compounds, both naturally occurring and synthetic, such as swinholide A[199] (cytotoxic macrolide), 20-deoxysalinomycin[200] (antibiotic) or kalafungin[201] (cytotoxic compound) (Figure 5.4).

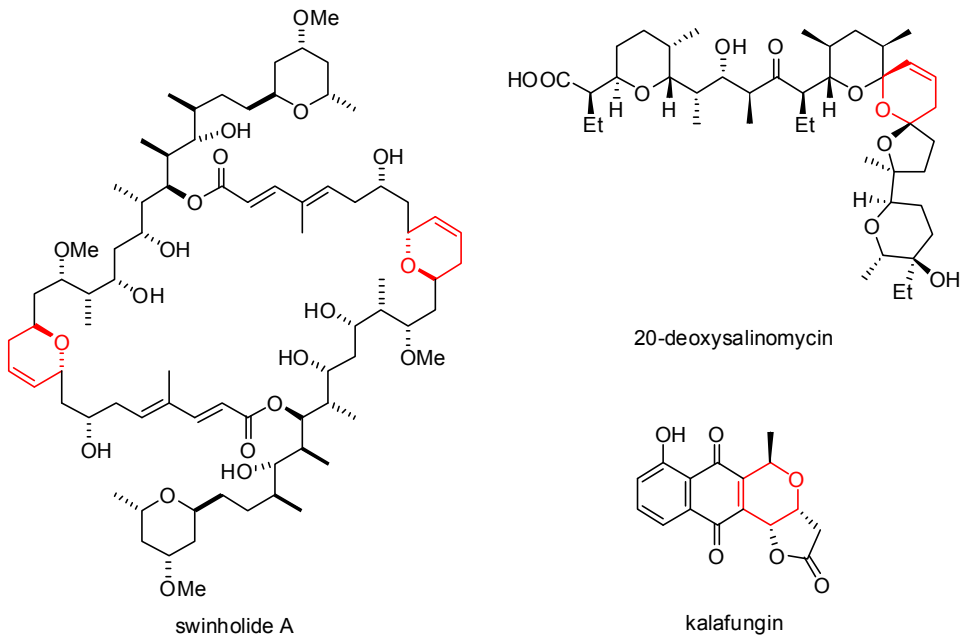


Figure 5.4. Natural products containing the dihydropyran moiety

[198] The first step of the proposed mechanism, is similar to the transformation described in: Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180-14181.
[199] (a) Bewley, C. A.; Holland, N. D.; Faulkner, D. J. *Experientia* **1996**, *52*, 716-722.
(b) Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M.; Tanaka, J.; Doi, M.; Ishida, T. *J. Am. Chem. Soc.* **1990**, *112*, 3710-3712.
[200] Miyazaki, Y.; Shibata, A.; Tsuda, K.; Kinashi, H.; Otake, N. *Agric. Biol. Chem.* **1978**, *42*, 2129-2132.
[201] Tsujibo, H.; Sakamoto, T.; Miyamoto, K.; Kusano, G.; Ogura, M.; Hasegawa, T.; Inamori, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2299-2300.

They are also very useful building blocks in the synthesis of many complex compounds (see for example the total synthesis of brevetoxin A[202] and ciguatoxin[203]).

Dihydropyrans are usually prepared by various anionic, cationic, radical and transition metal catalyzed cyclizations, Claisen rearrangements, allylation-Prins, hetero Diels–Alder or methatesis reactions.[204]

Encouraged by the promising results obtained for the formation of functionalized dihydrofurans, an extension of the same method, applied in this case to the formation of dihydropyranes, was attempted.

In order to validate our approach, three substrates **5.24 a-c** were subjected to the action of our gold catalyst (1% Ph_3P-Au-NTf_2). These tests clearly showed that although the formation of the 6-membered cycle is possible, it is definitely less favorable than the 5-membered ring formation (Table 5.4).

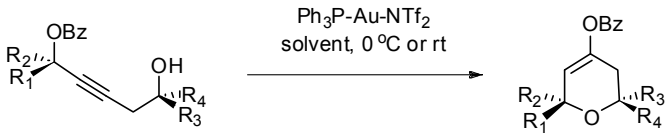
Achiral compound **5.24 a**, possessing a primary alcohol group, gave the expected dihydropyrane **5.25 a** only in an average 52% yield (Table 5.4, Entry 1). The formation of a large number of side products was observed as well. Performing the reaction at 0°C instead of room temperature did not seem to reduce the amount of degradation (Table 5.4, Entry 2).

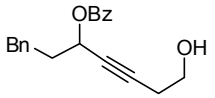
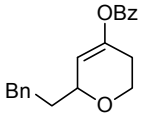
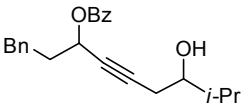
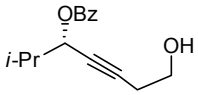
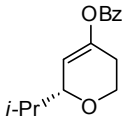
Achiral compound **5.24 b**, having a secondary alcohol moiety and substituted with a bulky isopropyl group, simply degraded (Table 5.4, Entry 3).

Finally chiral compound **5.24 c**, possessing a primary alcohol group, furnished dihydropyrane **5.25 c** in a 74% yield, but with a low retention of chirality (37% ee) (Table 5.4, Entry 4). Several other experimental conditions have been tried, like a lower temperature (Table 5.4, Entry 5), a less electrophilic and bulkier catalyst (Table 5.4, Entry 6) or a different solvent (Table 5.4, Entry 7-9), but the slight increase in the stereocontrol seemed to come at the price of a lower yield.

These experimental observations are in accord with the mechanism proposed in the last section, since a 6-*endo* cyclization would be less rapid and less favorable than a 5-*endo* one, therefore leaving enough time to the intermediate allene to racemize or to give other side reactions.

[202] Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 599-617.
[203] Sasaki, M.; Noguchi, T.; Tachibana, K. *J. Org. Chem.* **2002**, *67*, 3301-3310.
[204] See: Hong, B.-C.; Chen, Z.-Y.; Nagarajan, A.; Rudresha, K.; Chavan, V.; Chen, W.-H.; Jiang, Y.-F.; Zhang, S.-C.; Lee, G.-H.; Sarshar, S. *Tetrahedron Lett.* **2005**, *46*, 1281-1285. and the references cited therein.



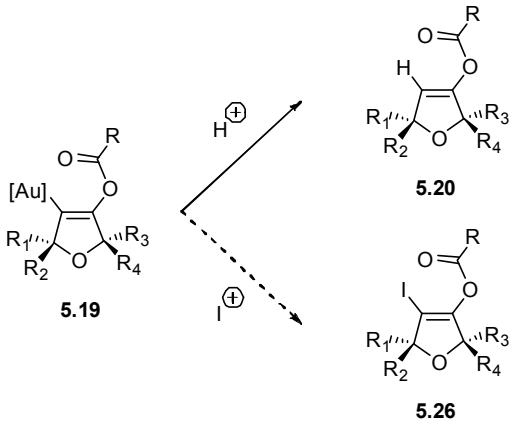
entry	substrate	solvent	temp.	product[a]	time	conv.[b]	yield[c]
	 **5.24 a**			 **5.25 a**			
1		DCM	rt		20 min	100%	52%
2		DCM	0 °C		3 h	100%	54%
	 **5.24 b**			-			
3		DCM	rt		1 h 30 min	100%	degrad.
	 **5.24 c**			 **5.25 c**			
4	89% ee	DCM	rt	37% ee	45 min	100%	74%
5		DCM	0 °C	45% ee	3 h 30 min	100%	58%
6		DCM[d]	rt	47% ee	40 min	100%	60%
7		MeCN/DCM 1/1	rt	45% ee	18 h	64%	34%
8		CF_3CH_2OH	rt	11% ee	6 h	81%	74%
9		PhMe	rt	73% ee	30 min	100%	29%

Reaction conditions: substrate (1 equiv), Ph_3P-Au-NTf_2 (0.01 equiv), solvent (0.33 M), 0°C or rt (see table). [a] ee determined by chiral HPLC. [b] Conversion of the starting material determined by ^{1}H NMR of the crude reaction mixture. [c] Isolated yield. [d] With 1% Ad_2(*n*-Bu)P-Au-NTf_2.

Table 5.4. Gold(I)-catalyzed rearrangement of substrates **5.24 a-c**

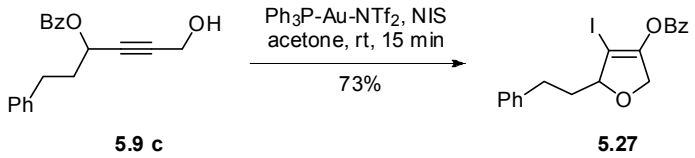
2.7. Other applications

By analogy with the formation of 4-(*E*-iodomethylene)-1,3-dioxolan-2-ones (described in Chapter 3, Section 2.6), we wanted to further highlight the potential of our method by synthesizing 4-iodo-substituted-2,5-dihydrofuran derivatives **5.26**. We surmised that such compounds could be easily formed by trapping the vinyl-gold intermediate **5.19** in the presence of a source of electrophilic iodide (instead of letting it undergo "classical" protodemetallation) (Scheme 5.28).



Scheme 5.28. Trapping of vinyl-gold intermediate **5.19** by a source of electrophilic iodide in competition with the "classic" protodemetallation step

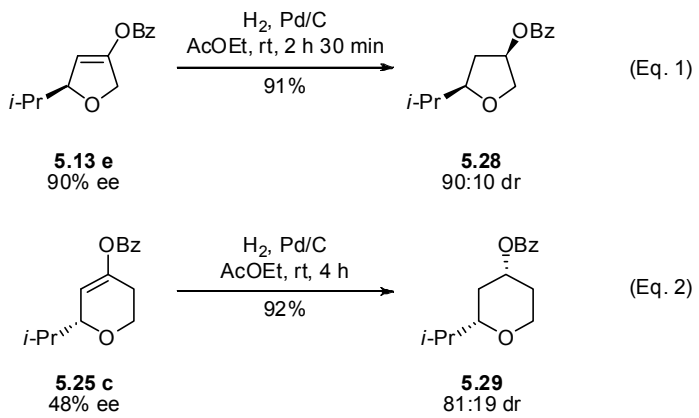
Substrate **5.9 c** was treated with 1% Ph_3P-Au-NTf_2 and 1.2 equivalents of NIS in acetone (0.5 M) at room temperature. We were delighted to observe that iodide derivative **5.27** was obtained in a 73% yield (Scheme 5.29).



Scheme 5.29. Gold(I)-catalyzed formation of vinyl iodide derivative **5.27**

This example shows that the formation of vinyl iodide derivatives is possible in this case also, opening the way for further functionalizations in the 4-position of the 2,5-dihydrofuran ring via various cross-coupling reactions.

In addition, the hydrogenation of two dihydrofuran and dihydropyran derivatives was attempted as well. Compounds **5.13 e** and **5.25 c** were transformed under standard conditions (10% Pd/C in AcOEt at room temperature) into the corresponding tetrahydofuran **5.28** and tetrahydropyran **5.29** compounds in good yields (91% and 92% respectively) and with a fairly good control of the relative stereochemistry (Scheme 5.30).



Scheme 5.30. Formation of tetrahydofuran and tetrahydropyran derivatives **5.28** and **5.29**

3. Conclusions and perspectives

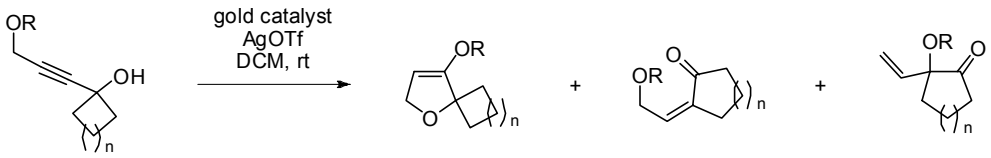
In conclusion, we've shown that gold(I) complexes catalyze stereoselectively the double rearrangement of monoacylated 2-butyn-1,4-diols to 2,5-dihydrofurans. This method, thanks to the easy access to the starting substrates, constitutes a very nice addition to the multitude of methods currently available for the synthesis of substituted 2,5-furans.

Compared to the previously reported silver-catalyzed rearrangements, our method increases the scope of this type of transformation since it is not limited to tertiary alcohols. The reaction conditions, extremely mild (0 °C or rt), and the selectivity of the catalyst insure the compatibility with a large number of functional groups. Due to the higher activity of the gold, the catalyst loading can be reduced and the reaction times are very short.

Although less effective than the formation of dihydrofurans, the synthesis of functionalized dihydropyranes is also possible via this method.

Concerning the potential applications of this process, the formation of a 4-iodo substituted 2,5-dihydrofuran was achieved, which makes possible the introduction of further fonctionalizations in the 4-position. The access to functionalized tetrahydrofurans and tetrahydropyranes is also feasible via a simple hydrogenation step.

An interesting extension of our method was proposed by Shin et al., who studied the rearrangement of spirocylic monoacylated 2-butyn-1,4-diols **5.30**.[205] They could show that, along with the expected spirocyclic 2,5-dihydrofurans **5.31**, other side products corresponding to various ring expansions can be obtained (Scheme 5.31).



5.30 **5.31** **5.32** **5.33**

n	R	catalyst	yield(5.31)	yield(5.32)	yield(5.33)
1	Ac	Ph_3P-Au-Cl	-	96%	-
2	Ac	Ph_3P-Au-Cl	16%	-	5%
2	Ac	JohnPhos-Au-Cl	61%	-	-
3	Bz	JohnPhos-Au-Cl	93%	-	-

Scheme 5.31. Extension of our method proposed by Shin et al. leading to the formation of spirocyclic 2,5-dihydrofurans and of other side-products

[205] Yeom, H.-S.; Yoon, S.-J.; Shin, S. *Tetrahedron Lett.* **2007**, *48*, 4817-4820.

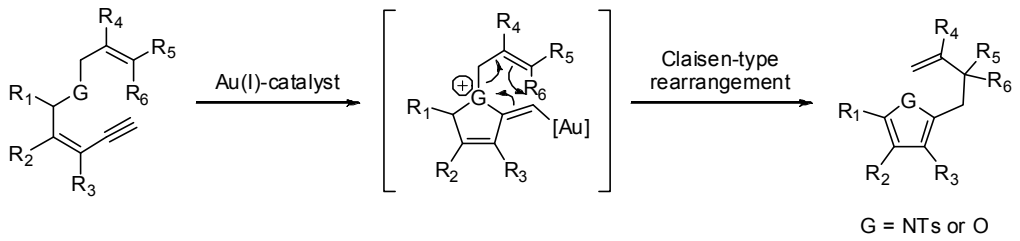
CHAPTER

6

Synthesis of Functionalized Pyrroles and Furans via a Gold(I)-Catalyzed Claisen-Type Rearrangement

"No amount of experimentation can ever prove me right; a single experiment can prove me wrong."
*(**Albert Einstein**, German-born theoretical physicist, Nobel Prize winner in 1921)*

This chapter describes the rearrangement of pentenynyl allyl tosylamides and ethers via a gold(I)-catalyzed Claisen-type mechanism leading to the formation of functionalized pyrroles and furans (Scheme 3.1).



Scheme 6.1. Synthesis of functionalized pyrroles and furans via a gold(I)-catalyzed Claisen-type rearrangement

This concerted rearrangement induces a complete selectivity of the process and allows the easy formation of quaternary centers. Our method is also characterized by its efficiency and the mild reaction conditions.

In the first part of this chapter the importance of pyrroles and furans in organic and some current methods used to access this type of structures will be discussed briefly (section 1). The second part is dedicated to a more detailed look on our work concerning this topic (section 2). This chapter ends with a few conclusions and perspectives (section 3).

Disclaimer:

This work was conducted under the supervision of Dr. Fabien L. Gagosz. Although a part of the experiments presented in this chapter was carried out by Dr. Fabien L. Gagosz, in order to preserve the coherence of the subject the totality of the work concerning this topic will be discussed here.

Some of these results have been previously published in:

- Florin M. Istrate, Fabien L. Gagosz* "Synthesis of Functionalized Pyrroles via a Gold(I)-Catalyzed aza-Claisen-Type Rearrangement" *Org. Lett.* **2007**, *9*, 3181-3184.

1. Pyrroles and furans

1.1. Importance and reactivity of pyrroles and furans

Pyrroles and furans are among the most common 5-membered ring heterocycles (Figure 6.1).[206]

Figure 6.1. The pyrrole (left) and furan (right) moieties

They can be found in a wide variety of natural or synthetic products and are also frequent intermediates in a good number of total syntheses. In industry, these heterocycles and their derivatives are used as solvents, demulsifying or pulping agents, antifreezes, textile and industrial dyes, and are involved in the production of resins, polymers, rubbers, photovoltaic cells, disinfectants, pharmaceuticals, fungicides, herbicides, etc.

A large number of studies have been dedicated over the years to the reactivity of pyrroles and furans and therefore numerous transformations implying these heterocycles have been described.

Among them, the substitutions by various electrophilic reagents are the most common. These reactions include protonations, nitrations, sulfonations, halogenations, acylations, alkylations, reactions with different carbonylic compounds, mercurations, diazo couplings, nitrosations etc.

Deprotonations at the carbon atom in the presence of a strong base are another common type of reaction involving the pyrrole and furans rings. The resulting anions have been reacted with a wide range of electrophiles.

Pyrroles and furans have also been involved in various cycloadditions in the presence of dienophiles, reductions, oxidations, electrophilic additions, ring-openings and even radical reactions.

[206] (a) Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry. The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*; Pergamon Press: Oxford, 1984; Vol. 4.
(b) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry. A Review of the Literature 1982-1995*; Pergamon Press: Oxford, 1996; Vol. 2.
(c) Davies, D. T. *Chimie des hétérocycles aromatiques*; De Boeck Université: Paris, 1997.
(d) Eicher, T.; Hauptmann, S.; Speicher, A. In *The Chemistry of Heterocycles (Second Edition)*; Wiley-VCH Verlag: 2004, p 52-121.

Of course, substituted pyrroles and furans can also give reactions specific for the functional group substituting the respective substrate.

1.2. Synthesis of pyrroles and furans

The rich chemistry involving pyrroles and furans led to a huge interest in the synthesis of these heterocycles. Even nowadays, the development of more selective and versatile approaches for their preparation remains an ongoing priority, especially in the case of highly functionalized products.

One of the most straightforward approaches to obtain pyrroles or furans is the cyclocondensations of carbonyl compounds. Methods such as the Paal-Knorr,[207,208] Feist-Benary[209] and its variants,[210] Hantzsch[211] or Knorr[212] syntheses have been widely used and are usually limited only by the availability of the corresponding starting substrates.

A large number of other strategies leading to the formation of pyrroles and furans have been reported as well. They include organometallic or radical cyclizations, Diels-Alder additions / retroadditions, the transformation of existing heterocycles via ring contractions / expansions, the functionalization of existing pyrrole or furans derivatives, etc. [206,213]

Lately, the cycloisomerizations of allene- or alkyne-containing substrates, usually in the presence of transition metals such as Cu, Rh, Pt, Pd, Ag or Au, have emerged as one of the most practical and versatile ways to access these heterocycles.[214]

Very well suited for the synthesis of highly functionalized products, these transformations present in most of the cases the advantage of being extremely regio- and stereoselective. As a consequence, they are highly tolerant towards various substitutions of the substrate and they generally give high yields. On the other hand, they present occasionally some limitations, mainly related to the difficulty of preparing the substrates needed for the cycloisomerization step.

Although this section does not provide an exhaustive literature survey of all metal-catalyzed rearrangements of alkene- or alkyne-containing substrates leading to pyrroles and furans, it is intended to offer a quick overview of the most interesting methods.

For instance, furans can be synthesized by the cyclization of α-ketoallenes.[215] Scheme 6.2 shows various examples involving rhodium (Eq. 1), silver (Eq. 2), gold (Eq. 3) or palladium catalysts (Eq. 4). In

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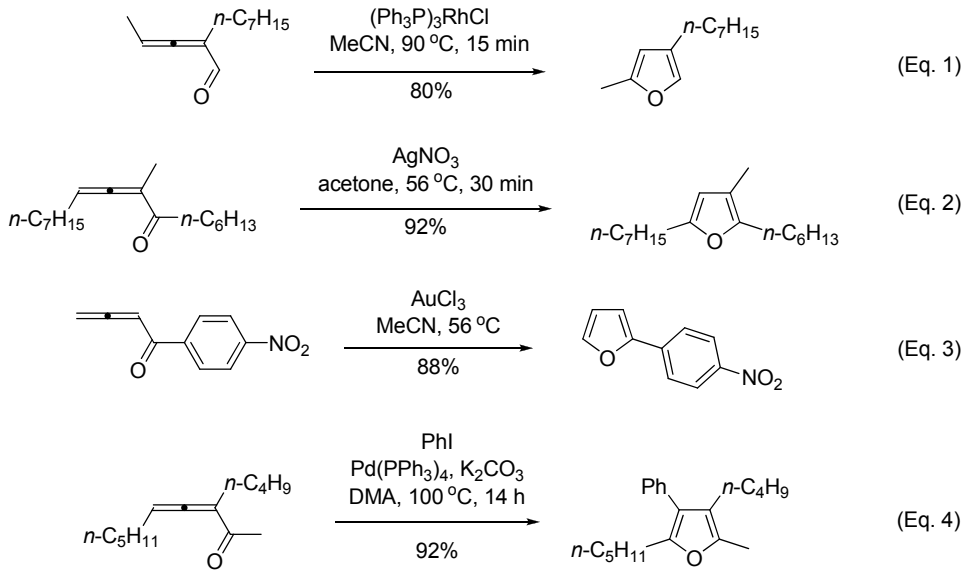
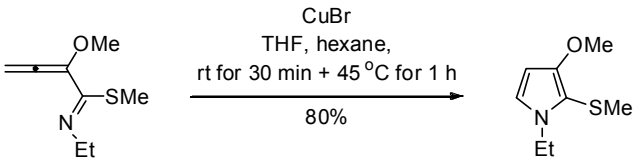
[207] Amarnath, V.; Amarnath, K. *J. Org. Chem.* **1995**, *60*, 301-307.
[208] Young, D. M.; Allen, C. F. H. *Org. Synth.* **1943**, *Coll. Vol. 2*, 219; **1936**, *Vol. 16*, 25.
[209] (a) Feist, F. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1537-1544.
(b) Benary, E. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 489-493.
[210] Bambury, R. E.; Yaktin, H. K.; Wyckoff, K. K. *J. Heterocycl. Chem.* **1968**, *5*, 95.
[211] Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474-1476.
[212] Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635-1642.
[213] (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491-2515.
(b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955-2020.
[214] Brown, R. C. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 850-852.

the last case tetrasubstituted furans can be obtained as well via a palladium cross-coupling reaction with an aryl iodide.



Scheme 6.2. Synthesis of functionalized furans from α-ketoallenes

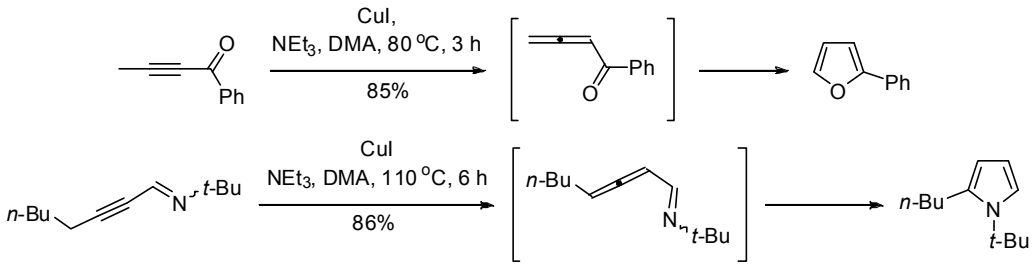
Analogously, nitrogen derivatives can give substituted pyrroles, although this type of transformation was less studied (Scheme 6.3).[216]



Scheme 6.3. Synthesis of functionalized pyrroles from α-iminoallenes

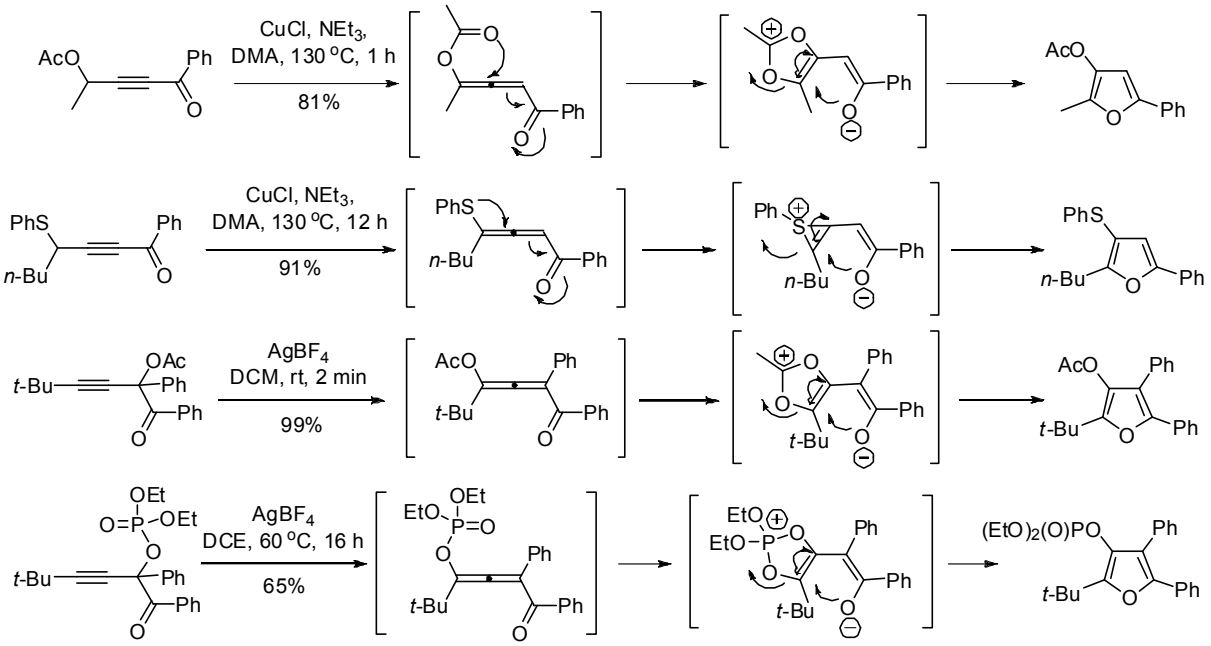
Alkynyl ketones and imines can undergo a similar cycloisomerization process giving furans and respectively pyrroles, via a proposed allene intermediate (Scheme 6.4).[217]

[215] (a) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450-3451.
(b) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169-7171.
(c) Marshall, J. A.; Wallace, E. M.; Coan, P. S. *J. Org. Chem.* **1995**, *60*, 796-797.
(d) Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729-5735.
(e) Hashmi, A. S. K. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1581-1583.
(f) Hashmi, A. S. K.; Ruppert, T. L.; Knofel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295-7304.
(g) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285-2288.
(h) Ma, S.; Zhang, J.; Lu, L. *Chem. Eur. J.* **2003**, *9*, 2447-2456.
(i) Ma, S.; Yu, Z. *Angew. Chem. Int. Ed.* **2002**, *41*, 1775-1778.
(j) Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941-944.
(k) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313-4320.
[216] Nedolya, N. A.; Brandsma, L.; Tarasova, O. A.; Verkruijsse, H. D.; Trofimov, B. A. *Tetrahedron Lett.* **1998**, *39*, 2409-2410.
[217] (a) Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95-98.
(b) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074-2075.



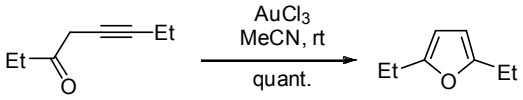
Scheme 6.4. Synthesis of functionalized furans and pyrroles from alkynyl ketones and imines via an α-keto- or α-iminoallene intermediate

Subsequent studies resulted in the discovery of a related transformation involving both the rearrangement of an intermediate α-ketoallene and the migration of a group located in the propargylic position, such as acetyl, phosphonate or thiol ether (Scheme 6.5).[218]



Scheme 6.5. Other synthesis of functionalized furans via an α-ketoallene intermediate

β-Ketoalkynes are other useful precursors for furan derivatives, rearranging easily in the presence of various transition metals (Scheme 6.6).[215g,219]

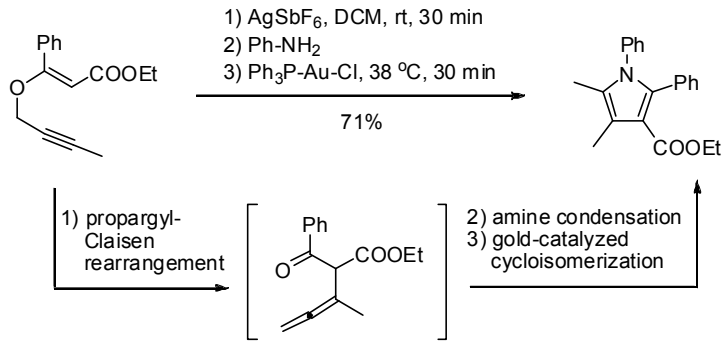


Scheme 6.6. Synthesis of functionalized furans from β-ketoalkynes

A very convenient one-pot process was proposed by Kirsch et al.[220] He converted easily accessed propargyl vinyl ethers and aromatic amines into substituted 5-methylpyrroles. The cascade reaction

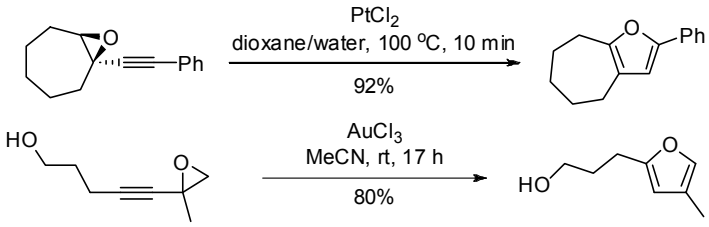
[218] (a) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 2280-2282.
(b) Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2003**, *42*, 98-101.
[219] Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816-5819.
[220] Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151-2153.

proceeds through a silver(I)-catalyzed propargyl-Claisen rearrangement, an amine condensation, and a gold(I)-catalyzed cycloisomerization (Scheme 6.7).



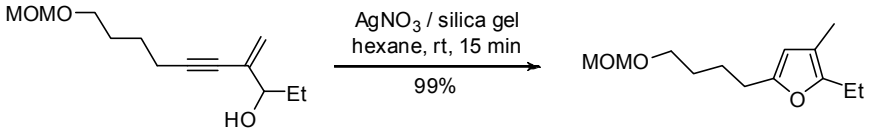
Scheme 6.7. Synthesis of functionalized pyrroles form propargyl vinyl ethers and aromatic amines

Alkynyl epoxides can also rearrange to substituted furans (Scheme 6.8).[221]



Scheme 6.8. Synthesis of functionalized furans from alkynyl epoxides

Furans can be obtained as well by the cycloisomerization of β-alkynyl allylic alcohols (Scheme 6.9).[222]

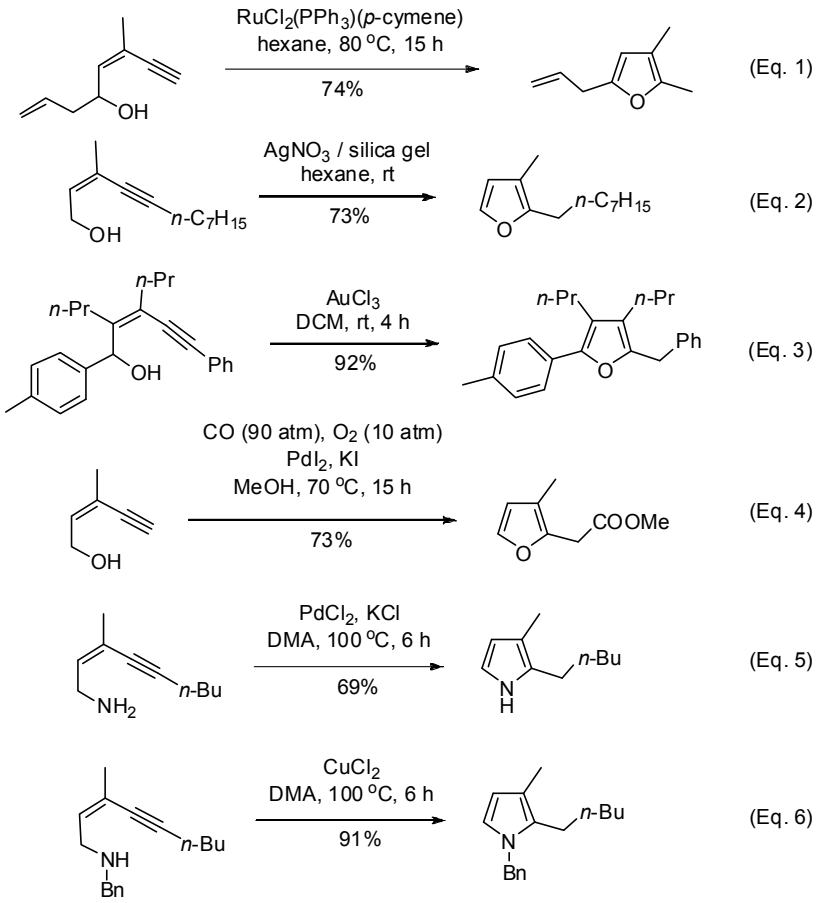


Scheme 6.9. Synthesis of functionalized furans from β-alkynyl allylic alcohols

Z-(2-En-4-ynyl) alcohols or amines have been widely studied as precursors for the formation of furans and pyrroles.[215g,222,223] Various transition metals can be used, including ruthenium, silver, palladium, copper or gold (Scheme 6.10). The cycloisomerization of both primary and secondary amines is possible, leading to the formation of free or *N*-substituted pyrroles (Scheme 6.10, Eq. 5 and 6). The

[221] (a) Miller, D. *J. Chem. Soc. C: Org.* **1969**, 12-15.
(b) Yoshida, M.; Al-Amin, M.; Matsuda, K.; Shishido, K. *Tetrahedron Lett.* **2008**, *49*, 5021-5023.
(c) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432-438.
[222] Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966-5968.
[223] (a) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089-13102.
(b) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409-5412.
(c) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687-7692.
(d) Gabriele, B.; Salerno, G.; De Pascali, F.; Costa, M.; Chiusoli, G. P. *J. Org. Chem.* **1999**, *64*, 7693-7699.
(e) Gabriele, B.; Salerno, G. *Chem. Commun.* **1997**, 1083-1084.
(f) Gabriele, B.; Salerno, G.; De Pascali, F.; Scianò, G. T.; Costa, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1997**, *38*, 6877-6880.
(g) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. R. *Tetrahedron Lett.* **2001**, *42*, 1339-1341.
(h) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853-7861.

cycloisomerization reactions can be combined with other transformations, as shown in Scheme 6.10, Eq. 4, where a palladium-catalyzed carboxylation process is also involved.



Scheme 6.10. Synthesis of functionalized furans and pyrroles form *Z*-(2-en-4-ynyl) alcohols and amines

2. Our synthetic approach to functionalized pyrroles and furans

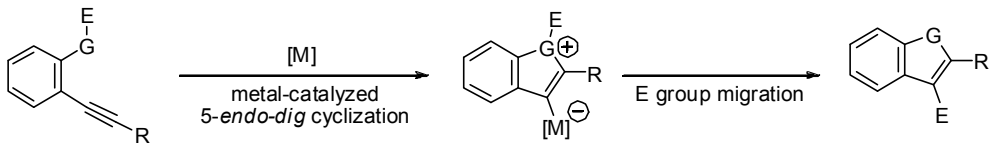
2.1. Precedents in the literature. The initial idea

Transition metals in general (and gold in particular) are extremely useful catalysts for the rearrangement of alkyne- and allene-containing substrates into various substituted heterocycles.

For instance, *ortho*-alkynyl-phenol, -aniline or -benzenethiol derivatives were extensively used for the synthesis of various functionalized benzofuran, indole or benzothiophene derivatives.[224] All these transformations involve the metal-catalyzed 5-*endo-dig* attack of the heteroatom on the triple bond. Recent developments in this type of transformations make use of *ortho*-alkynyl aryl substrates substituted at the heteroatom with an electrophilic moiety E (Scheme 6.11). This group migrates

[224] For a review, see: Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285-2310. and the references cited therein.

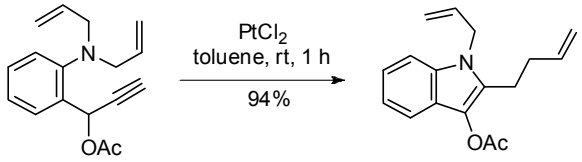
from the heteroatom to the vinylic carbon atom after the metal-catalyzed cyclization, allowing the easy formation of the corresponding heterocycles substituted in the 3-position.[225]



G = O, NR', S
E = allyl, benzyl, alkoxyalkyl, propargyl, acyl, sulfonyl etc.
M = Pt, Pd, Au, In etc.

Scheme 6.11. Metal-catalyzed 5-*endo-dig* attack of the heteroatom on the triple bond followed by migration of an electrophilic group

A similar process takes place in the case of related substrates containing an extra carbon atom between the alkyne moiety and the aromatic ring. This time a 5-*exo-dig* metal-catalyzed cyclization can be observed, followed by analogous migration of the electrophilic moiety, as shown by Malacria et al (Scheme 6.12).[226]



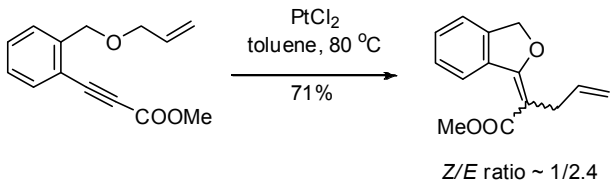
Scheme 6.12. Example of metal-catalyzed 5-*exo-dig* attack of the heteroatom on the triple bond followed by migration of an electrophilic group

Another possibility is represented by substrates containing an extra carbon atom between the heteroatom and the aromatic group. Fürstner et al. demonstrated that such compounds undergo

[225] Allyl group migrations:
(a) Furstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024-15025.
(b) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546-10547.
(c) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473-4475.
(d) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001-1011.
(e) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280-9288.
Benzyl group migrations:
(f) reference 225a.
(g) reference 225c.
Alkoxyalkyl group migrations:
(h) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022-15023.
(i) reference 225a.
(j) reference 225c.
Propargyl group migrations:
(k) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101-5104.
Acyl group migrations:
(l) reference 225b.
Sulfonyl group migrations:
(m) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 2284-2287.
(n) Furstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 4760-4763.

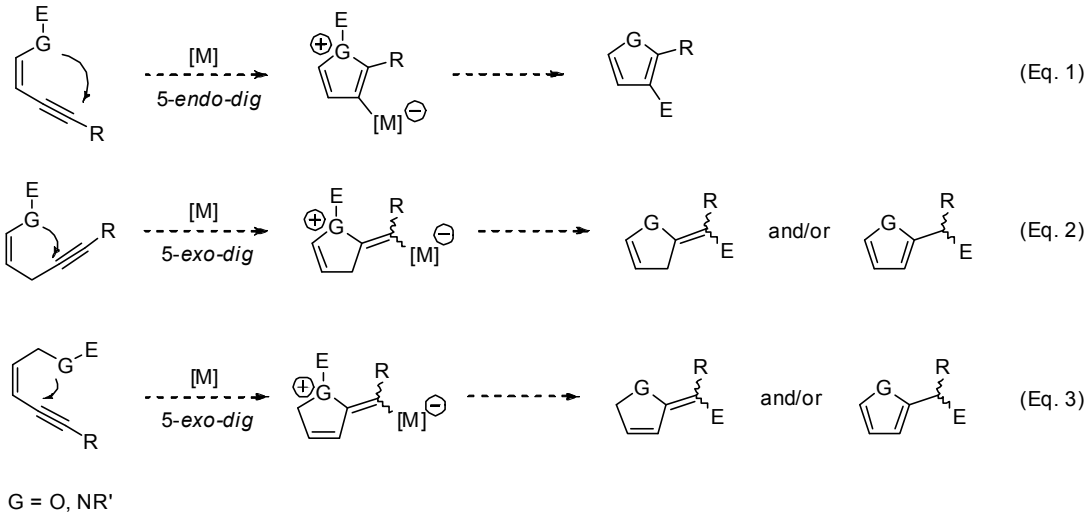
[226] Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1881-1884.

easily a 5-*exo-dig* cyclization followed by a similar migration of the electrophilic group on the heteroatom (Scheme 6.13).[227]



Scheme 6.13. Example of metal-catalyzed 5-*exo-dig* attack of the heteroatom on the triple bond followed by migration of an electrophilic group

All three approaches presented above can be considered as well for the synthesis of functionalized pyrroles and furans (Scheme 6.14).

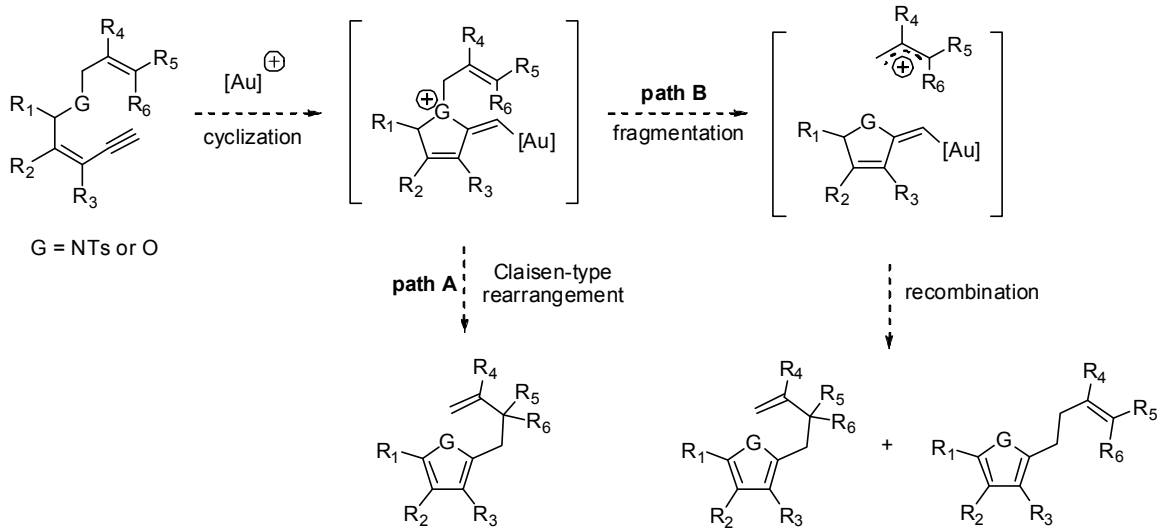


Scheme 6.14. Possible analogous approaches for the synthesis of functionalized pyrroles and furans

However, while the first two approaches seem limited due to the difficult and restricted access to the corresponding substrates (Eq. 1 and 2), the third one, on the other hand, appears to be more practical (Eq. 3). In fact we already saw in the previous section that simple *Z*-(2-en-4-ynyl) alcohols or amines (i.e. where E = H) were successfully rearranged to substituted furans and pyrroles[215g,222,223] (see Scheme 6.10).

By analogy with these previous results[215g,222,223] and with Fürstner's work,[227] we surmised that *Z*-pent-2-en-4-ynyl allyl tosylamides or ethers might lead to the formation of substituted pyrroles or furans via an initial gold-catalyzed cyclization followed by the migration of the allyl group (Scheme 6.15).

[227] (a) Furstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785-6786.
(b) Furstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863-11869.



Scheme 6.15. Our initial idea for the formation of substituted pyrroles or furans. Hypothesis of the two possible mechanisms for the migration of the allyl group

This strategy would lead to 2-butenyl pyrroles and furans, motifs that can be found in a wide variety of biologically active compounds, such as penochalasin A,[228] rubifolide,[229] curzerene,[230] or pumiloxide[231] (Figure 6.2).

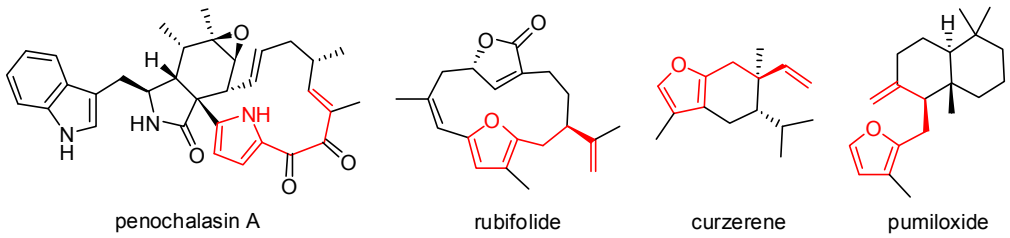


Figure 6.2. Natural compounds containing the 2-butenyl pyrrole or furan moiety

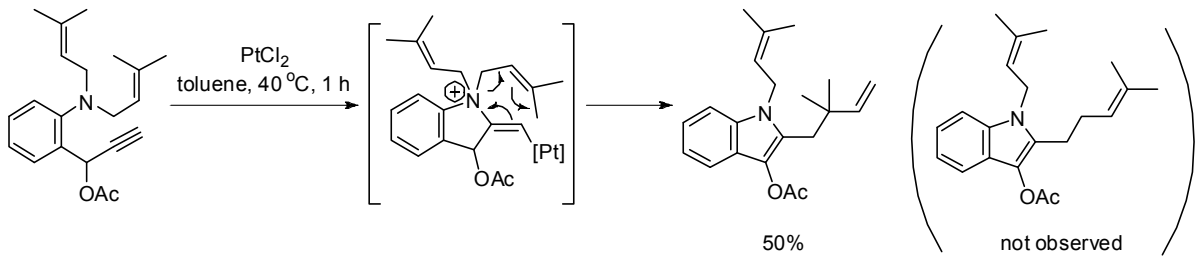
A particularly intriguing aspect of this transformation was the mechanism of the allyl group migration. Two mechanistic manifolds were theoretically possible. The first one (Scheme 6.15, path A) involved a concerted Claisen-type rearrangement and led to the formation of an unique product. The second one (Scheme 6.15, path B) consisted in an unselective shift of the allyl cation, leading to the possible formation of two regioisomers.

Both pathways have been previously proposed in the literature.

For instance, Malacria et al. suggested a concerted aza-Cope rearrangement in order to explain the allyl migration involved in the transformation presented in Scheme 6.12. Their crossover experiments (showing an intramolecular allyl shift) and the tests involving dissymmetrical allyl derivatives (where just one regioisomer is observed, see Scheme 6.16) seem to exclude a dissociative pathway.

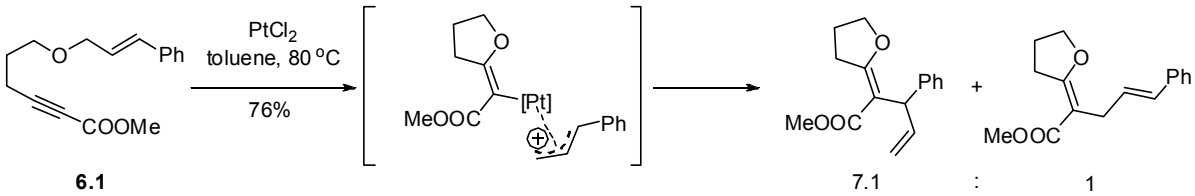
---

[228] Ding, G.; Song, Y. C.; Chen, J. R.; Xu, C.; Ge, H. M.; Wang, X. T.; Tan, R. X. *J. Nat. Prod.* **2006**, *69*, 302-304.
[229] Williams, D.; Andersen, R. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332-335.
[230] Saeed, M. A.; Sabir, A. W. *Fitoterapia* **2004**, *75*, 81-84.
[231] Tatsimo, S. J. N.; Tane, P.; Srinivas, P. V.; Sondengam, B. L.; Melissa, J.; Okunji, C. O.; Schuster, B. M.; Iwu, M. M.; Khan, I. A. *Planta Med* **2005**, *71*, 1145-1151.



Scheme 6.16. Migration of the allyl group by a sigmatropic rearrangement proposed by Malacria et al.

On the other hand, in Fürstner's case[227] (presented in Scheme 6.13), the authors suggested that a metal-complexed allyl cation equivalent was involved. Their conclusion is based on the formation of *E/Z*-mixtures of isomers (which rule out a stereoselective concerted mechanism) and on the lack of regioselectivity in the transformation involving the allyl pentynyl ester **6.1** (Scheme 6.17).



Scheme 6.17. Migration of allyl group via a metal-complexed allyl cation intermediate proposed by Fürstner et al.

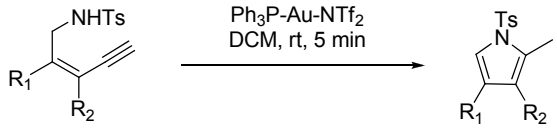
2.2. Preliminary results

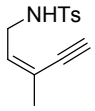
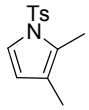
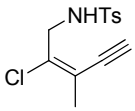
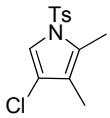
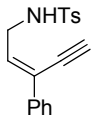
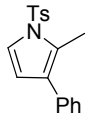
As discussed in the previous two sections, the cyclization of *Z*-(2-en-4-ynyl) alcohols or amines (primary or secondary) in the presence of transition metals such as ruthenium, silver, palladium or copper is well described in the literature. Unfortunately, albeit gold's excellent ability to catalyze this type of transformations, only two reports by the groups of Hashmi[215g] and Liu[223b] cover the cycloisomerization of *Z*-(2-en-4-ynyl) alcohols to functionalized furans in the presence of $AuCl_3$ (see for example Scheme 6.10, Eq. 3). To the best of our knowledge, no report involving the gold-catalyzed cycloisomerization of *Z*-(2-en-4-ynyl) amines has ever been published.

Before attempting the cyclization of *Z*-pent-2-en-4-ynyl allyl tosylamides or ethers, we decided to validate first our approach by showing that simple *Z*-pent-2-en-4-ynyl tosylamides can be cyclized in the presence of a gold catalysts as well.

Substrates **6.2 a-c** were tested in the presence of 1% Ph_3P-Au-NTf_2 at room temperature in DCM. As expected, they led to the rapid formation of pyrroles **6.3 a-c** in excellent yields (Table 6.1).

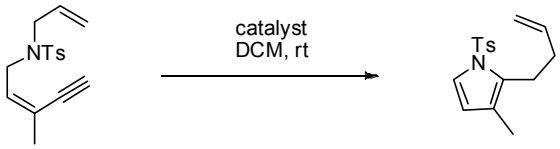
Encouraged by these preliminary results, we decided to pursue our investigation, moving on to allyl-substituted *Z*-pent-2-en-4-ynyl tosylamides. Compound **6.4 a** was chosen as a model substrate and tested in the same reaction conditions as before (Table 6.2, Entry 1). To our surprise, the reaction proceeded much slower (6 h versus 5 min). The starting material **6.4 a** gave only a partial conversion (84%), but furnished however the expected rearranged pyrrole **6.5 a** in a modest 62% isolated yield.



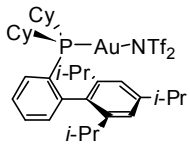
entry	substrate		product		yield[a]
1		**6.2 a**		**6.3 a**	97%
2		**6.2 b**		**6.3 b**	96%
3		**6.2 c**		**6.3 c**	94%

Reaction conditions: substrate (1 equiv), Ph_3P-Au-NTf_2 (0.01 equiv), DCM (0.1 M), rt, 5 min. [a] Isolated yield.

Table 6.1. Gold(I)-catalyzed cyclization of simple *Z*-pent-2-en-4-ynyl tosylamides



6.4 a **6.5 a**

entry	catalyst	time	conv.[a]	yield[b]
1	1% Ph_3P-Au-NTf_2	6 h	84%	62%
2	2% Ph_3P-Au-NTf_2	2 h	100%	80%
3	2% $(p\text{-}CF_3\text{-}C_6H_4)_3P$-Au-$NTf_2$	30 min	100%	94%
4	2%  **6.6**	16 h	51%	42%
5	5% $AuBr_3$	16 h	60%	21%
6	10% $AgNTf_2$	16 h	14%	0%

Reaction conditions: substrate (1 equiv), catalyst, DCM (0.1 M), rt. [a] Conversion of the starting material determined by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield.

Table 6.2. Rearrangement of allyl-substituted *Z*-pent-2-en-4-ynyl tosylamide **6.4 a**

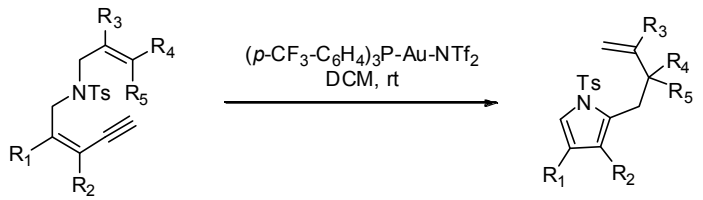
Doubling the catalyst loading led to a complete conversion of **6.4 a**, and improved both the reaction time and the isolated yield of **6.5 a** (2 h, 80% in Table 6.2, Entry 2).

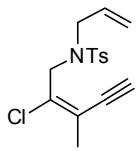
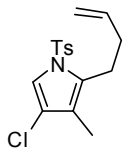
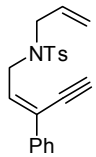
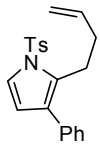
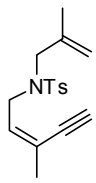
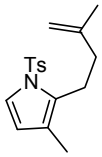
A rapid screening of various catalytic systems showed that the more electrophilic (p-CF_3-$C_6H_4)_3$P-Au-NTf_2 complex gives the best results, leading to the formation of **6.5 a** in an excellent yield of 94% in just 30 min (Table 6.2, Entry 3). Less electrophilic catalysts such as **6.6** (Table 6.2, Entry 4) gave the opposite results, leading to an incomplete conversion of the starting material (51%), a low isolated yield of **6.5 a** (42%) and a long reaction time (16 h).

Poor results were obtained as well with $AuBr_3$, the isolated yield of **6.5 a** dropping to 21% after 16 h (Table 6.2, Entry 5). Finally, $AgNTf_2$ did not promote the formation of pyrrole **6.5 a** (Table 6.2, Entry 6).

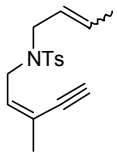
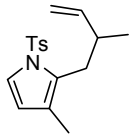
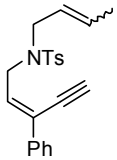
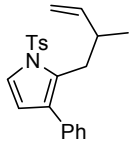
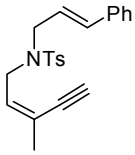
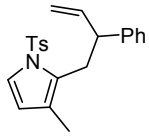
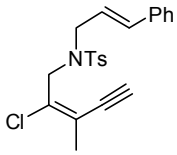
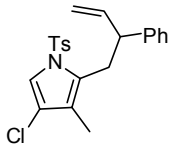
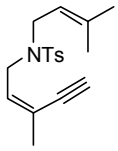
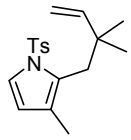
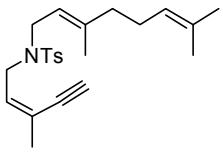
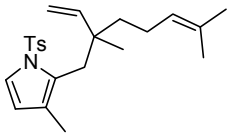
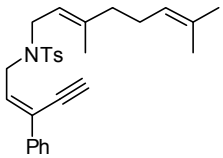
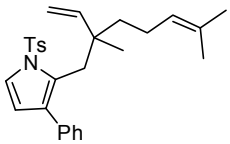
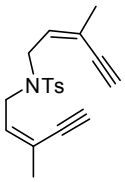
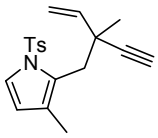
2.3. Gold(I)-catalyzed formation of functionalized pyrroles

Based on these preliminary findings, the conditions described in Table 6.2, Entry 3 were retained as standard (2% (p-CF_3-$C_6H_4)_3$P-Au-NTf_2 in DCM at rt). Several substrates **6.4 b-l** were synthesized and cycloisomerized in the presence of the aforementioned gold complex (Table 6.3).



entry	substrate		product		time	yield[a]
1		**6.4 b**		**6.5 b**	30 min	88%
2		**6.4 c**		**6.5 c**	45 min	72%
3		**6.4 d**		**6.5 d**	45 min	89%

(continued on the next page)

entry	substrate		product		time	yield[a]
4	 *Z*/*E* ratio ~ 1/3.5	**6.4 e**		**6.5 e**	15 min	91%
5	 *Z*/*E* ratio ~ 1/2.6	**6.4 f**		**6.5 f**	15 min	89%
6		**6.4 g**		**6.5 g**	15 min	97%
7		**6.4 h**		**6.5 h**	5 min	98%
8		**6.4 i**		**6.5 i**	15 min	90%
9		**6.4 j**		**6.5 j**	15 min	91%
10		**6.4 k**		**6.5 k**	15 min	93%
11		**6.4 l**		**6.5 l**	15 min	84%

Reaction conditions: substrate (1 equiv), (p-CF_3-C_6H_4)$_3$P-Au-NTf_2 (0.02 equiv), DCM (0.1 M), rt. [a] Isolated yield.

Table 6.3. Reaction scope for the formation of functionalized pyrroles

The reaction proved to be quite general, all starting compounds giving a full conversion and leading to the formation of pyrroles **6.5 b-l** in excellent yields ranging from 72% to 98%. A good number of substitutions patterns on the substrates **6.4 b-l** were well tolerated, both at the allyl moiety and at the double bond of the enyne fragment.

Simple allyl substituted substrates **6.4 b** and **c** afforded, just like substrate **6.4 a**, the expected pyrroles **6.5 b** and **c** in 88% and respectively 72% yields (Table 6.3, Entries 1 and 2). The reaction times were very similar too (30 min and 45 min respectively), the presence or the nature of substituents on the the double bond of the enyne fragment having a very limited influence on the outcome of this transformation.

Methallyl derivative **6.4 d** also led to the formation of the pyrrole **6.5 d** in 45 min and in an 89% isolated yield (Table 6.3, Entry 3).

Crotyl derivatives **6.4 e** and **f**, obtained as a mixture of *Z/E* isomers, rearranged in the presence of the gold catalyst leading to the formation of products **6.5 e** and **f** (91% and respectively 89% isolated yields). Both pyrroles were obtained exclusively as a sole regioisomer.[232] The cycloisomerization process seemed to be slightly faster in these two cases, full conversion of the starting material being achieved in just 15 min (Table 6.3, Entries 4 and 5).

The case of cinnamyl derivatives **6.4 g** and **h** was very similar, pyrroles **6.5 g** and **h** being formed rapidly (15 min and 5 min) and in excellent yields (97% and respectively 98%) (Table 6.3, Entries 6 and 7). No traces of other regioisomers were observed in this case either.[232]

Tosylamides **6.4 i-k**, bearing a prenyl or a geranyl group, reacted easily affording the expected pyrroles **6.5 i-k** (Table 6.3, Entries 8-10). It is interesting to notice that a new quaternary center is formed as a result of this cycloisomerization. However, the efficiency of the transformation is not affected by this increase in steric hindrance (reaction time 15 min, yields between 90%-95%).

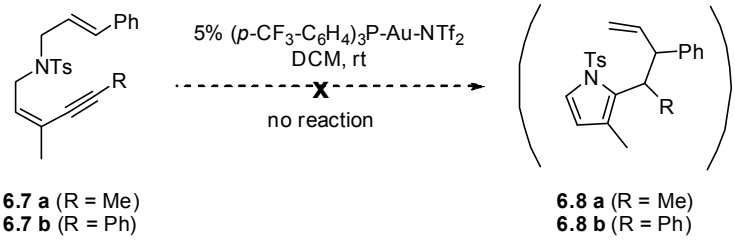
In the case of dienyne tosylamide **6.4 l**, pyrrole **6.5 l** is formed (15 min, 84%). The transformation proved to be highly selective, the second alkyne remaining unchanged. No products resulting from a hypothetical cyclization of this second triple bond on the pyrrole ring were detected[232] (Table 6.3, Entry 11).

The examples compiled in Table 6.3, Entries 4-11 seem to indicate a concerted aza-Claisen mechanism. In all these cases the branched products are exclusively formed. No linear regioisomer resulting from a dissociative mechanism and involving the formation of an allyl carbocation and the formal N to C shift of the allyl group was ever detected.[232]

Furthermore, from a reactivity point of view, allylic substrates bearing substituents at the terminal position react generally faster (**6.4 e-l**) than their unsubstituted counterparts (**6.4 a-d**). This fact is also in accord with the proposed aza-Claisen mechanism and excludes a dissociative mechanism (generally sensitive to steric hindrance).

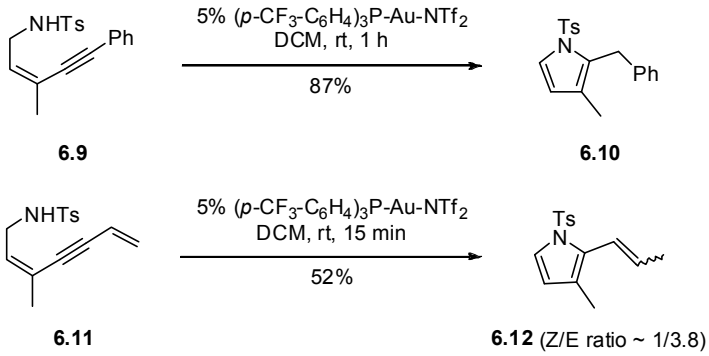
[232] Within the limits of detection by ^{1}H NMR.

Attempts to cyclize tosylamides bearing an internal alkyne were unfortunately unsuccessful. Cinamyl derivatives **6.7 a** and **b**, substituted at the triple bond with a phenyl or methyl group, failed to give the expected pyrroles **6.8 a** and **b** even in the presence of 5% (p-CF_3-C_6H_4)$_3$P-Au-NTf_2 (Scheme 6.18).



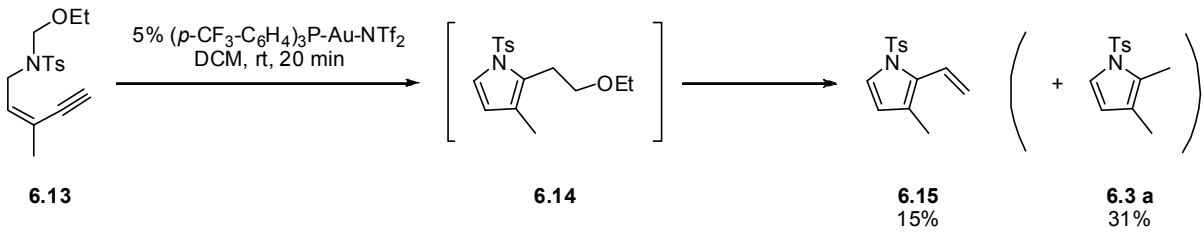
Scheme 6.18. Unsuccessful attempts to cyclize allyl-substituted tosylamides bearing an internal alkyne

This is very curious, especially since tosylamides **6.9** and **6.11**, lacking the allyl moiety, rearrange rapidly into pyrroles **6.10** and **6.12**[233] under the same conditions (87% and 52% isolated yields respectively, Scheme 6.19). The lack of reactivity of substrates **6.7 a** and **b** might therefore be attributed to an increased steric hindrance during the nucleophilic addition step of the tosylamide moiety onto the gold-activated alkyne.



Scheme 6.19. Gold(I)-catalyzed cyclization of simple *Z*-pent-2-en-4-ynyl tosylamides bearing an internal alkyne

The variation of the electrophilic group was considered as well. A single experiment, inspired by the work of Fürstner's and Yamamoto's groups,[225h-j] was performed involving the migration of an ethoxymethyl group (Scheme 6.20). Even though the reaction proved to be highly sensitive, vinyl pyrrole **6.15**, presumably derived from the expected pyrrole **6.14**, was isolated in a poor 15% yield. Side-product **6.3 a** was obtained as well (31% isolated yield).



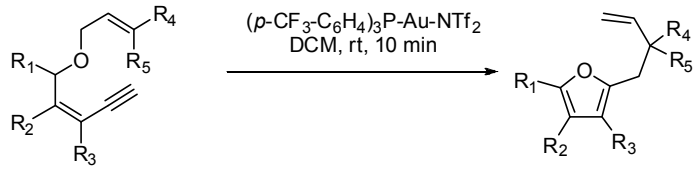
Scheme 6.20. Rearrangement of ethoxymethyl-substituted tosylamide **6.13**

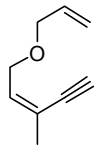
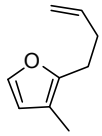
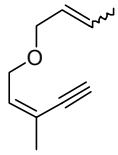
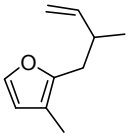
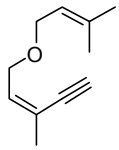
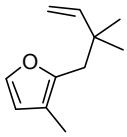
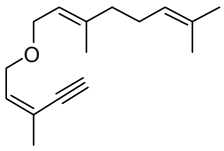
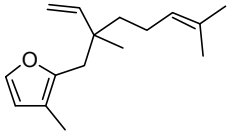
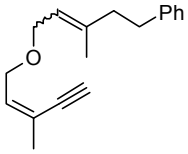
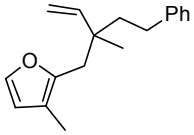
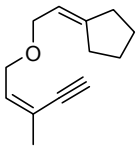
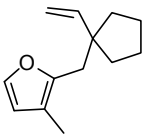
[233] Pyrrole **6.12** is obtained as a mixture of *Z/E* isomers, resulting from the isomerization of the double bond in the presence of gold or of traces of acid.

2.4. Gold(I)-catalyzed formation of functionalized furans

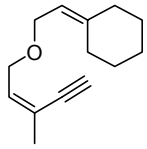
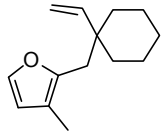
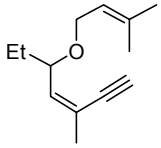
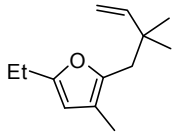
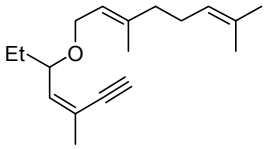
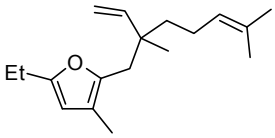
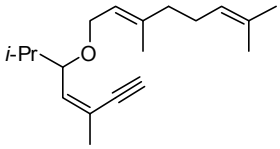
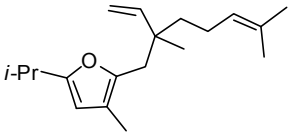
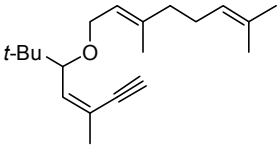
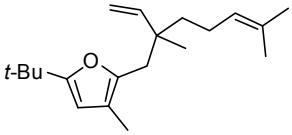
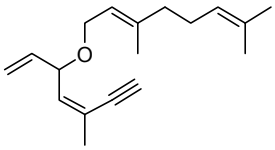
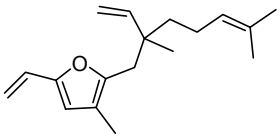
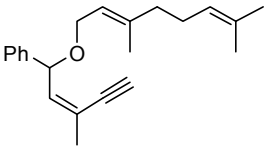
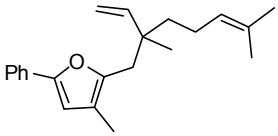
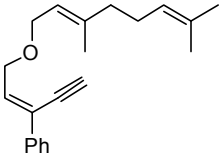
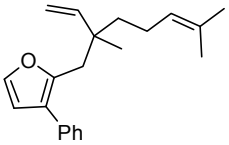
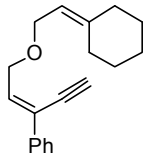
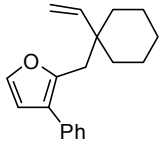
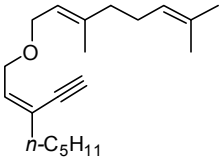
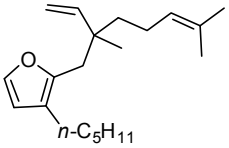
We pursued our investigation by applying the same strategy for the formation functionalized furans. Proving that this transformation works also with oxygen – instead of nitrogen – was important to confirm the initial mechanistic proposal, but also for extending the scope of this reaction.

The standard experimental conditions employed in the last section (2% (p-CF_3-C_6H_4)$_3$P-Au-NTf_2 in DCM at rt) were used for the cyclization of various *Z*-pent-2-en-4-ynyl allyl ethers **6.16 a-s**. We were delighted to observe the formation of the expected furans **6.17 a-s** (Table 6.4).

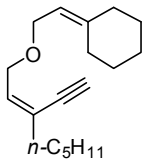
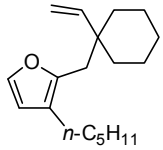
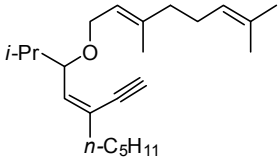
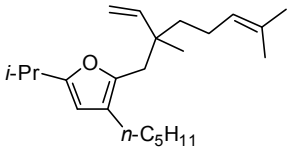
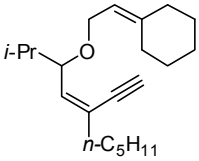
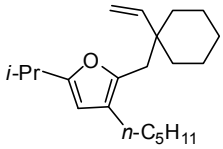


entry	substrate		product		conv.[a]	yield[b]
1		**6.16 a**		**6.17 a**	100%	18% (75%[c])
2	 *Z*/*E* ratio ~ 1/3	**6.16 b**		**6.17 b**	100%	39% (86%[c])
3		**6.16 c**		**6.17 c**	100%	59% (82%[c])
4		**6.16 d**		**6.17 d**	100%	81% (92%[c])
5	 *Z*/*E* ratio ~ 1/2.57	**6.16 e**		**6.17 e**	100%	66%
6		**6.16 f**		**6.17 f**	100%	71%

(continued on the next page)

entry	substrate		product		conv.[a]	yield[b]
7		**6.16 g**		**6.17 g**	100%	63%
8		**6.16 h**		**6.17 h**	100%	quant.
9		**6.16 i**		**6.17 i**	100%	quant.
10		**6.16 j**		**6.17 j**	100%	78%
11		**6.16 k**		**6.17 k**	100%	78%
12		**6.16 l**		**6.17 l**	100%	17%
13		**6.16 m**		**6.17 m**	100%	77%
14		**6.16 n**		**6.17 n**	100%	80%
15		**6.16 o**		**6.17 o**	100%	90%
16		**6.16 p**		**6.17 p**	100%	82%

(continued on the next page)

entry	substrate		product		conv.[a]	yield[b]
17		6.16 q		6.17 q	100%	86%
18		6.16 r		6.17 r	>84%[d]	73%
19		6.16 s		6.17 s	>62%[d]	36%

Reaction conditions: substrate (1 equiv), (p-CF_3-C_6H_4)$_3$P-Au-NTf_2 (0.02 equiv), DCM (0.1 M), rt, 10 min. [a] Conversion of the substrate determined by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield. [c] Yield determined by ^{1}H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal reference. [d] Reaction time: 40 min.

Table 6.4. Reaction scope for the formation of functionalized furans

All the examples presented in the Table 6.4, Entries 2-19 seem to be confirming the postulated Claisen-type rearrangement proposed in the last chapter. The exclusive formation of branched products is observed, no linear product resulting from an O to C shift of the allylic moiety being detected.[232] It is also interesting to notice that the ether derivatives reach full conversion generally faster (usually less than 10 min) than their tosylamides counterparts.

Increasing the substitution at the terminal allylic moieties of the starting ethers (monosubstitution in the case of **6.16 b**, disubstitution for **6.16 c-s**) makes no noticeable difference in terms of reaction's conversion rate or yield, even though the steric hindrance of the postulated oxy-Claisen intermediate increases.

The allyl (**6.16 a**), crotyl (**6.16 b**), prenyl (**6.16 c**) and geranyl (**6.16 d**) derivatives of the primary alcohol readily rearranged in the presence of the gold catalyst (Table 6.4, Entries 1-4). The isolation of the obtained furans **6.17 a-d** however proved to be quite challenging due to their volatility (isolated yields varied between 18%-81%). These reactions were therefore performed in CD_2Cl_2 in the presence of 1,3,5-trimethoxybenzene as internal reference and the yields assessed by ^{1}H NMR spectroscopy (75%-92%).

Compounds **6.16 b** and **6.16 e**, although obtained as a mixture of *Z/E* isomers, afforded an unique product **6.17 b** and respectively **6.17 e** (Table 6.4, Entries 2 and 5).

Substrates **6.16 f** and **g**, possessing an exocyclic allylic group gave the corresponding spirocompounds **6.17 f** and **g** in 71% and 63% yields (Table 6.4, Entries 6 and 7).

We next turned our attention to substrates substituted at the vicinal position to the alcohol group in the enyne moiety.

Interestingly, the rearrangement of the secondary alcohol derivative **6.16 h**, substituted with an ethyl group, was highly effective, furan **6.17 h** being obtained quantitatively (Table 6.4, Entry 8).

Substrates **6.16 h-m**, derived from the corresponding secondary alcohols and possessing a geranyl group, rearranged easily to afford the expected furans **6.17 h-m** (Table 6.4, Entries 9-13). The increased steric hindrance around the oxygen did not seem to affect the cyclization step (nucleophilic attack of the oxygen on the activated triple bond). The yields were generally very good (77%-quant.), a large variety of substitutions being tolerated: primary, secondary or tertiary alkyls and even phenyl groups. The only exception was compound **6.17 l**, which polymerized easily and therefore was isolated only in a poor yield (17%).

The substrate scope was then demonstrated by replacing the vinylic methyl on the enyne moiety with larger substituents (such as a phenyl group or a long alkyl chain) in the substrates **6.16 n-q** (Table 6.4, Entries 14-17). These substrates reacted in high yields (80%-90%), showing that furans substituted in 3 position with larger substituents (**6.17 n-q**) can also be easily obtained.

Unfortunately, ethers **6.16 r-s** (substituted simultaneously with 2 large groups at the enyne moiety) did not convert completely into the corresponding furans **6.17 r-s** (conversion of the starting material: >84% and respectively >62%, isolated yields: 73% and 36%). This fact is probably due to an unfavorable conformation of the transition state (Table 6.4, Entries 18 and 19).

2.5. Mechanistic proposal

In contrast with the results observed by Fürstner et al. during their study,[227] the experimental results obtained in our case suggest that no allyl cation is formed during the reaction. The substrates shown in Table 6.3, Entries 4-11 and in Table 6.4, Entries 2-19 serve as a mechanistic probe (since no linear products are observed, just the branched ones), excluding a dissociative mechanism and indicating a more concerted one.

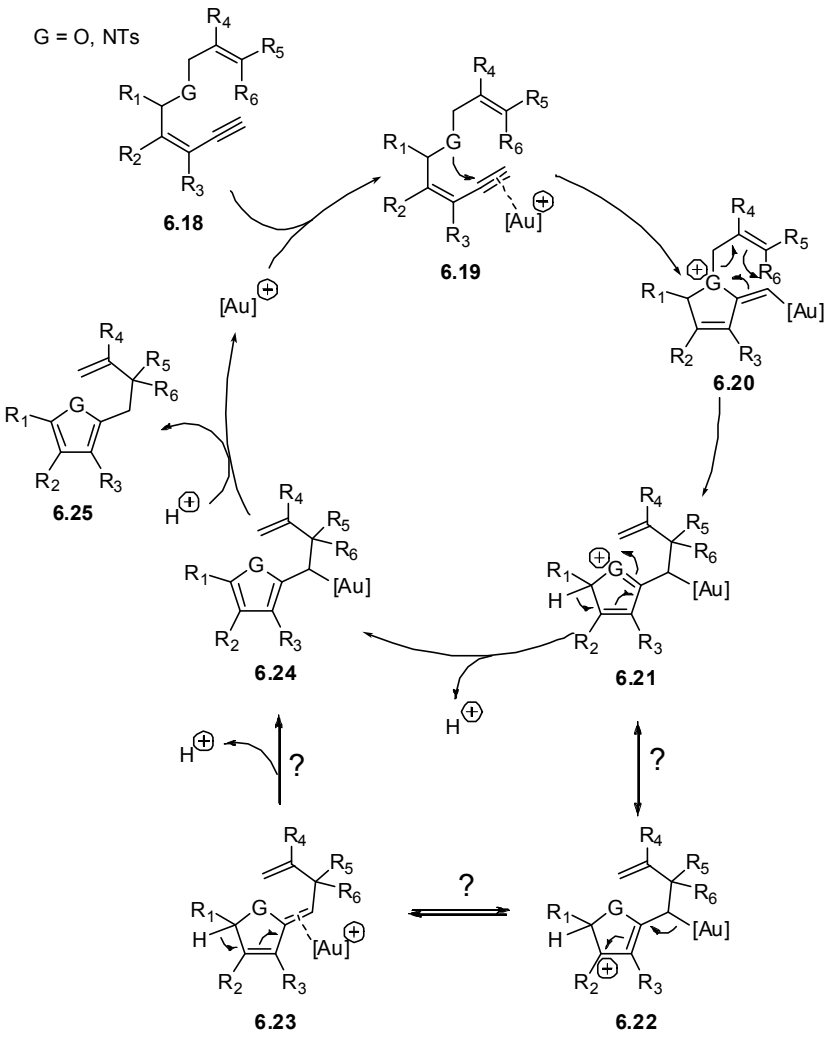
This hypothesis is partially supported by a crossover experiment in which an equimolar mixture of **6.4 f** and **g** were reacted under standard conditions. Pyrroles **6.5 f** and **g** were the only products formed during this reaction. No crossover derivatives were detected, thus proving the intramolecular transfer of the allyl groups.

The allyl group migration can be viewed therefore as a Claisen-type rearrangement, with or without the catalyst's participation. In the case where gold does play a role in this transformation, this would be, to the best of our knowledge, the first-ever reported gold-catalyzed Claisen-type rearrangement.

A curious behavior of the starting substrates is observed when the substitution at the terminal allylic moieties is increased (monosubstitution in the case of **6.4 e-h** and **6.16 b**, disubstitution for **6.4 i-l** and **6.16 c-s**). This does not penalize the reaction's conversion rate or yield and can lead even to a slight increase in reactivity, even though the steric hindrance of the postulated Claisen intermediate

increases. This observation strongly contrasts with generally less effective "classical" Claisen-type rearrangements of similarly substituted substrates, suggesting maybe the participation of gold.

In order to account for these experimental observations, a mechanism is proposed in Scheme 6.21.



Scheme 6.21. Mechanistic proposal for the formation of functionalized furans and pyrroles

It starts with the selective activation of the alkyne moiety in substrate **6.18** by the gold catalyst's active species, followed by the 5-*exo-dig* nucleophilic attack of the heteroatom. Cationic vinyl gold intermediate **6.20** is thus formed, which undergoes a Claisen-type rearrangement and leads to the formation of intermediate **6.21**, presumably in equilibrium with **6.22**. A proton loss from either one of these two intermediates leads to alkyl gold derivative **6.24**. Finally, a fast protodemetallation step leads to the expected final product **6.25** and regenerates the gold catalyst.

3. Conclusions and perspectives

In conclusion we have developed a new method for the formation of functionalized pyrroles and furans starting from pentenynyl allyl tosylamides and ethers. The complete selectivity observed in the structure of the final products is in agreement with the postulated Claisen-type rearrangement.

Unlike other methods used for the synthesis of functionalized pyrroles and furans from allene- or alkyne-containing substrates, which allow usually the formation of only one carbon - heteroatom bond, in our case two new carbon - carbon and carbon - heteroatom bonds are formed in just one step.

Thanks to its concerted mechanism, our approach allows the easy formation of quaternary center or the introduction of various substitutions in the side chain. The reaction conditions are extremely mild, hence the tolerance for a wide variety of substitutions. The starting pentenynyl allyl tosylamides and ethers are in most of the cases relatively easy to access via various methods.

As future perspectives for this work, further investigations of the involvement of gold(I) in this new process are needed. Tests on asymmetric substrates and the variation of the migrating group might help shed some light on this aspect.

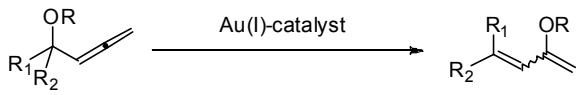
CHAPTER

7

Gold(I)-Catalyzed Isomerization of Allenyl Carbinol Esters: An Efficient Access to Functionalized 1,3-Butadien-2-ol Esters

*"Research is what I'm doing when I don't know what I'm doing." (**Wernher Von Braun**, German-American rocket physicist and astronautics engineer)*

This chapter describes the rearrangement of diversely substituted allenyl carbinol esters into functionalized 1,3-butadien-2-ol esters via a new 1,3-shift of the ester group onto the gold(I)-activated allene moiety (Scheme 3.1).



Scheme 7.1. Synthesis of functionalized 1,3-butadien-2-ol esters by isomerization of allenyl carbinol esters

Among the advantages of this method we can name its efficiency and its stereoselectivity, the mild conditions used, the short reaction times and the tolerance towards a large number of functional groups.

In the first part of this chapter the importance of 1,3-butadien-2-ol esters in organic chemistry, their reactivity and their synthesis will be discussed briefly (section 1). The second part is dedicated to our work concerning this topic (section 2). This chapter ends with a few conclusions and perspectives (section 3).

Disclaimer:

This work was conducted under the supervision of Dr. Fabien L. Gagosz. Although a part of the experiments presented in this chapter was carried out by Dr. Andrea K. Buzas and Dr. Fabien L. Gagosz, in order to preserve the coherence of the subject the totality of the work concerning this topic will be discussed here.

Some of these results have been previously published in:

- Andrea K. Buzas, Florin M. Istrate, Fabien L. Gagosz* "Gold(I)-Catalyzed Isomerization of Allenyl Carbinol Esters: An Efficient Access to Functionalized 1,3-Butadien-2-ol Esters" *Org. Lett.* **2007**, *9*, 985-988.

1. The 1,3-butadien-2-ol ester moiety

1.1. Importance and reactivity of functionalized 1,3-butadien-2-ol esters

Functionalized 1,3-butadien-2-ol esters (Figure 7.1) are versatile building blocks that are frequently employed in organic synthesis.

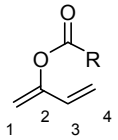
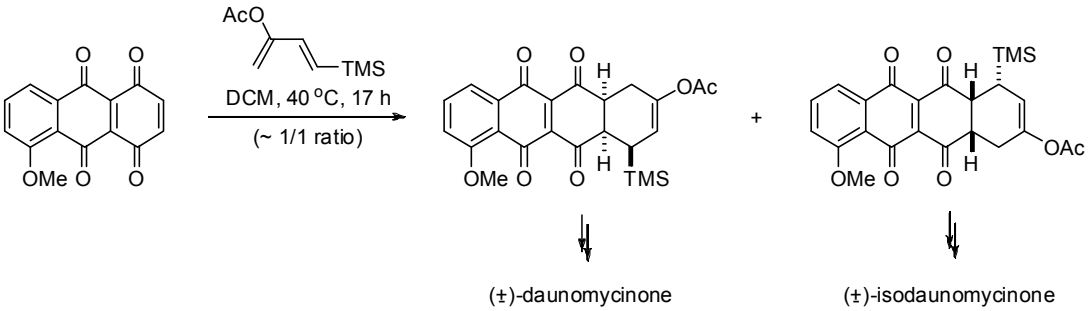


Figure 7.1. The 1,3-butadien-2-ol ester moiety

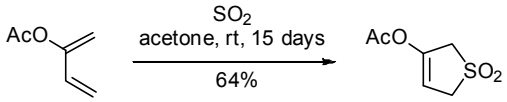
They have been involved in numerous Diels-Alder reactions, both intermolecular[234] and intramolecular.[235] For instance Hansen et al. used such a transformation for the total synthesis of two anthracyclinone derivatives, (±)-daunomycinone and (±)-isodaunomycinone (Scheme 7.2).[234d]



Scheme 7.2. Diels-Alder reaction involving a 1,3-butadien-2-ol ester during the total synthesis of (±)-daunomycinone and (±)-isodaunomycinone

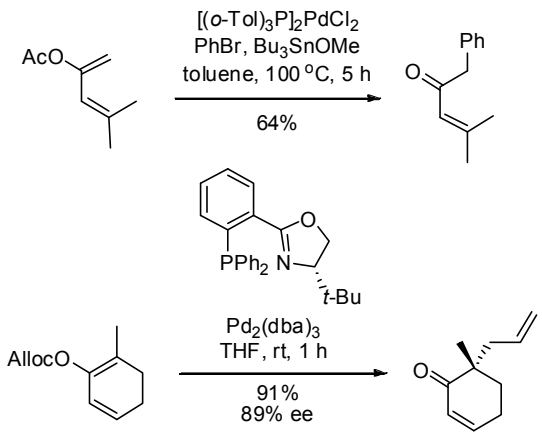
[234] (a) Danishefsky, S.; Kahn, M. *Tetrahedron Lett.* **1981**, *22*, 489-492.
(b) Kende, A. S.; Tsay, Y.-G.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967-1969.
(c) Potman, R. P.; Van Kleef, F. J.; Scheeren, H. W. *J. Org. Chem.* **1985**, *50*, 1955-1959.
(d) Hansen, D. W.; Pappo, R.; Garland, R. B. *J. Org. Chem.* **1988**, *53*, 4244-4253.
(e) Baylouny, R. A.; Danna, R. P.; Toth, K. H. *J. Org. Chem.* **1979**, *44*, 204-209.
[235] (a) Katsumura, S.; Kimura, A.; Isoe, S. *Tetrahedron* **1989**, *45*, 1337-1346.
(b) Pollini, G. P.; Bianchi, A.; Casolari, A.; De Risi, C.; Zanirato, V.; Bertolasi, V. *Tetrahedron: Asymmetry* **2004**, *15*, 3223-3231.
(c) Areces, P.; Jimenez, J. L.; Pozo, M. D. C.; Roman, E.; Serrano, J. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 754-762.

1,3-Butadien-2-ol esters have also been involved in [4+1] cycloadditions, as proven by Vogel et al. (Scheme 7.3).[236]



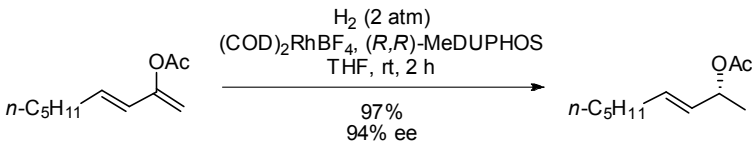
Scheme 7.3. [4+1] cycloaddition between a 1,3-butadien-2-ol ester and SO_2

They have been used as well in several transition-metal catalyzed transformations.[237] Scheme 7.4 illustrates two palladium-catalyzed couplings developed by the groups of Migita[237a] and respectively Stoltz.[237e]



Scheme 7.4. A few examples of palladium-catalyzed cross-coupling reactions involving functionalized 1,3-butadien-2-ol esters

1,3-Butadien-2-ol esters are also excellent precursors for chiral allylic esters via selective hydrogenation, as shown by Boaz (Scheme 7.5).[238]



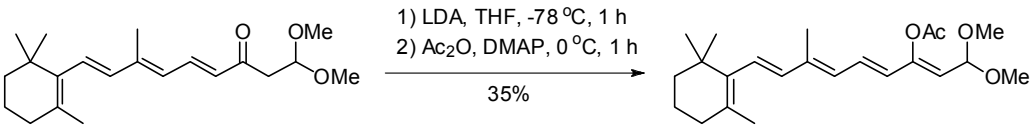
Scheme 7.5. Selective hydrogenation of a functionalized 1,3-butadien-2-ol ester

1.2. Synthesis of functionalized 1,3-butadien-2-ol esters

[236] Roversi, E.; Vogel, P. *Helv. Chim. Acta* **2002**, *85*, 761-771.
[237] (a) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242-246.
(b) Allard, A.; Levisalles, J. *Bull. Chem. Soc. Fr.* **1972**, 1926-1931.
(c) Larock, R. C.; Song, H. *Synth. Commun.* **1989**, *19*, 1463 - 1470.
(d) Novak, L.; Rohaly, J.; Kolonits, P.; Fekete, J.; Varjas, L.; Szantay, C. *Liebigs Ann. Chem.* **1982**, *1982*, 1173-1182.
(e) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045.
(f) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180-17181.
[238] Boaz, N. W. *Tetrahedron Lett.* **1998**, *39*, 5505-5508.

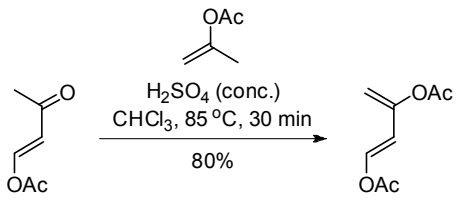
Despite their synthetic utility, this class of compounds is rather cumbersome to prepare. There are only a few methods used to access these structures and most of them start form the corresponding enones and involve either high temperatures or strong acidic or basic conditions. This raises of course the issue of functional group compatibility and limits the scope of such reactions.

For example, functionalized 1,3-butadien-2-ol esters are typically obtained by treatment of the enone with a base followed by the quenching of the formed enolate with an acyl derivative, as shown by Seltzer et al. during the synthesis of 13-acetoxy-13-desmethylretinal (Scheme 7.6).[239]



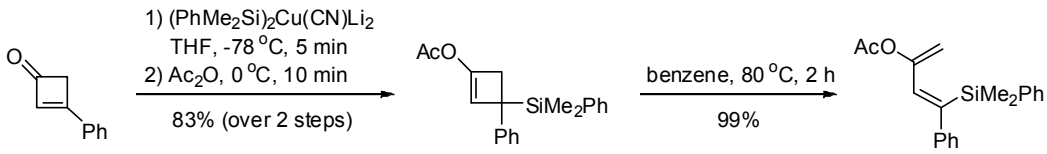
Scheme 7.6. Synthesis of a functionalized 1,3-butadien-2-ol ester from the corresponding enone under basic conditions

Another common method to obtain 1,3-butadien-2-ol esters is the transesterification reaction between an enol ester and the corresponding enone in acidic conditions (Scheme 7.7).[234c]



Scheme 7.7. Synthesis of a functionalized 1,3-butadien-2-ol ester from the corresponding enone under acidic conditions

A few alternative methods, involving precursors other than enone derivatives, have been developed as well. Ito et al. described the formation of functionalized 1,3-butadien-2-ol esters from cyclobutenone derivatives via a 1,4-addition of a cuprate followed by a stereoselective electrocyclic ring opening (Scheme 7.8).[240]

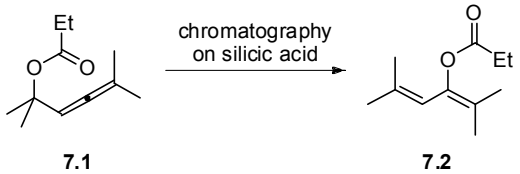


Scheme 7.8. Synthesis of functionalized 1,3-butadien-2-ol esters from cyclobutenone derivatives via a 1,4-addition of a cuprate followed by a stereoselective electrocyclic ring opening

Various allenyl and propargyl derivatives are known to be suitable precursors for the synthesis of functionalized 1,3-butadien-2-ol esters, although these transformations gave rather modest results.

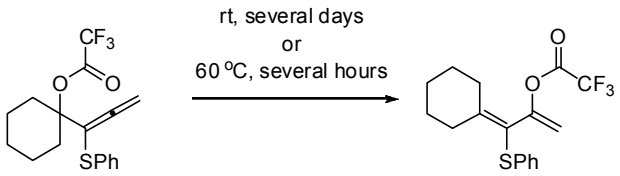
Meinwald et al. reported as early as 1965 that allenyl ester **7.1** degrades during chromatography on silicic acid to give 1,3-butadien-2-ol esters **7.2** (Scheme 7.9).[241]

[239] Seltzer, S. *J. Org. Chem.* **1995**, *60*, 1189-1194.
[240] Murakami, M.; Miyamoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6441-6442.
[241] Meinwald, J.; Wheeler, J. W.; Nimetz, A. A.; Liu, J. S. *J. Org. Chem.* **1965**, *30*, 1038-1046.



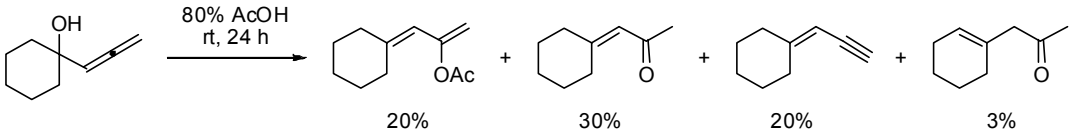
Scheme 7.9. Early example of an 1,3-butadien-2-ol ester formed from an allenyl carbinol ester

Bridges et al. showed that allenyl trifluoroacetates undergo a sigmatropic rearrangement when kept several days at room temperature (Scheme 7.10)[242]



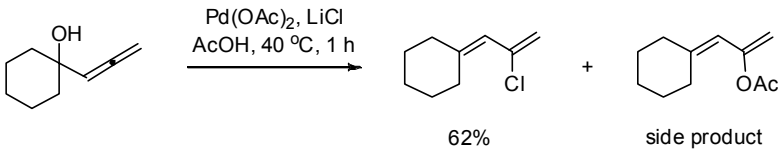
Scheme 7.10. Another example of an 1,3-butadien-2-ol ester formed from an allenyl carbinol ester

Olsson et al. discovered that α-allenic alcohols, in the presence of acetic acid, furnish 1,3-butadien-2-ol esters along with other rearrangement products (Scheme 7.11).[243]



Scheme 7.11. Formation of 1,3-butadien-2-ol esters from α-allenic alcohols in strong acid conditions

A similar reaction was observed by Bäckvall et al., which obtained a 2-acetoxy-1,3-diene derivative as a side product in the reaction of the corresponding acetylated allenic alcohol with $Pd(OAc)_2$ and LiCl (Scheme 7.12).[244] They surmised that the formation of the aforementioned side product is due to the presence of the acid.



Scheme 7.12. Formation of a 1,3-butadien-2-ol ester as a side product during the palladium-catalyzed transformation of α-allenic alcohols into chlorodienes

Several isomerizations of propargyl esters in the presence of a silver catalyst have been described, leading to the formation of 1,3-butadien-2-ol esters in mixtures with other products (Scheme 7.13).[245]

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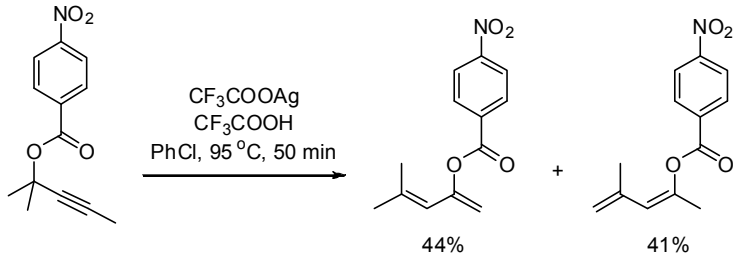
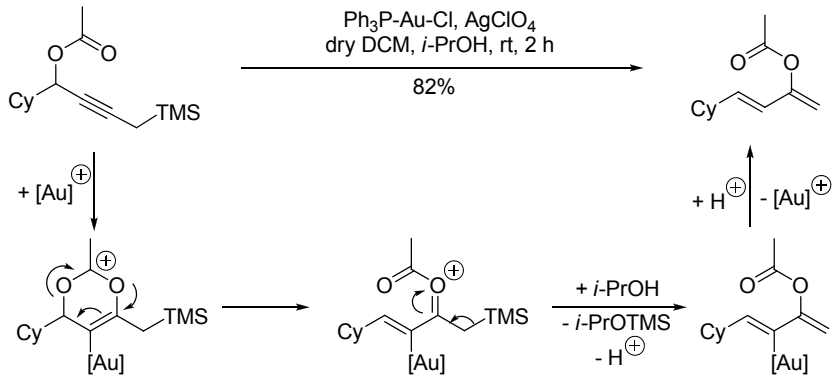
[242] Bridges, A. J.; Thomas, R. D. *J. Chem. Soc., Chem. Commun.* **1983**, 485-486.
[243] Olsson, L. I.; Claesson, A.; Bogentof, C. *Acta Chem. Scand.* **1973**, *27*, 1629-1636.
[244] Horvath, A.; Backvall, J.-E. *J. Org. Chem.* **2001**, *66*, 8120-8126.
[245] (a) Saucy, G.; Marbet, R.; Lindlar, H.; Isler, O. *Helv. Chim. Acta* **1959**, *42*, 1945-1955.
(b) Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hans-Jürgen; Schmid, H. H. *Helv. Chim. Acta* **1973**, *56*, 875-944.



Scheme 7.13. Silver-catalyzed rearrangement of propargyl esters into 1,3-butadien-2-ol esters

Zhang et al. reported a very efficient gold-catalyzed method for the preparation of 1,3-butadien-2-ol esters starting from trimethylsilylmethyl-substituted propargylic esters.[246] This transformation proceeds through an initial gold-catalyzed 1,3-shift of the acetate group resulting in the formation of an acyloxocarbenium intermediate followed by desilylation and protodemetallation of the vinyl-gold intermediate and formation of the desired product (Scheme 7.14).



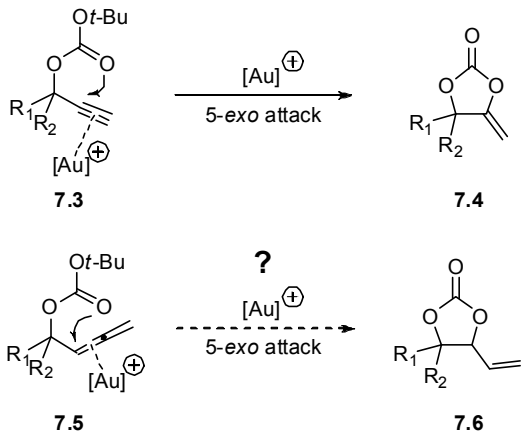
Scheme 7.14. Gold-catalyzed formation of functionalized 1,3-butadien-2-ol esters starting from trimethylsilylmethyl-substituted propargylic esters

2. Our synthetic approach to functionalized 1,3-butadien-2-ol esters

2.1. Precedents in the literature. The initial idea

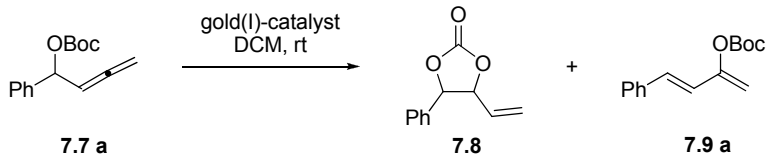
We saw in chapter 1 that gold complexes are excellent catalysts for the activation of alkyne- and allene-containing substrates for the attack of a wide range of nucleophiles. By analogy with our work concerning the rearrangement of propargyl *tert*-butyl carbonates **7.3** into vinylic cyclic carbonates **7.4** (described in Chapter 3), we surmised that an analogous rearrangement of allenyl-derivatives **7.5** might lead to the formation of allylic cyclic carbonates **7.6** (Scheme 7.15).

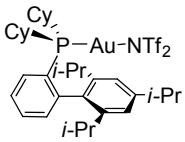
[246] Wang, S.; Zhang, L. *Org. Lett.* **2006**, *8*, 4585-4587.



Scheme 7.15. Initial idea regarding the gold-catalyzed rearrangement of allenyl derivatives **7.5** compared to the already described isomerization of propargyl *tert*-butyl carbonates **7.3** into vinylic cyclic carbonates **7.4**

In order to validate our hypothesis, the rearrangement of substrate **7.7 a** was attempted in the presence of 1% Ph_3P-Au-NTf_2 in DCM at rt. The substrate proved to be unreactive under these conditions, being recovered almost entirely after 34 h (Table 7.1, Entry 1). Gold-complex **7.10**, possessing a bulkier and more electron rich Buchwald-type phosphine, proved to be more active, leading to a 75% conversion of the starting material. However, to our surprise, no trace of the expected allylic cyclic carbonate **7.8** was observed. Instead, 1,3-butadien-2-ol derivative **7.9** a was isolated as a single *E*-isomer in a 69% yield (Table 7.1, Entry 2).



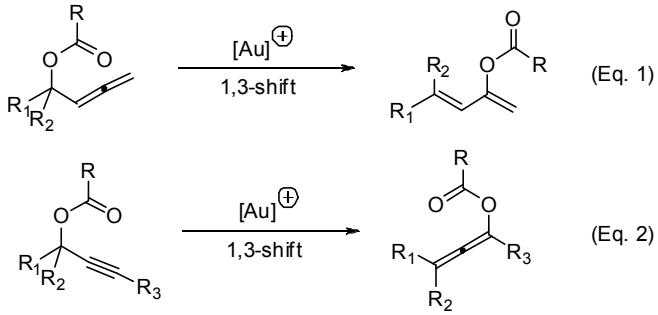
entry	catalyst	conversion[a]	time	yield of 7.8[b]	yield of 7.9 a[b]
1	Ph_3P-Au-NTf_2	<10%	34 h	-	-
2	 **7.10**	75%	20 h	-	69%

Reaction conditions: substrate (1 equiv), gold(I)-catalyst (0.01 equiv), DCM (0.25 M), rt. [a] Conversion of the starting material determined by ^{1}H NMR of the crude mixture. [b] Isolated yield.

Table 7.1. Unexpected gold-catalyzed rearrangement of allenyl-derivatives **7.7 a** into functionalized 1,3-butadien-2-ol derivative **7.9 a**

The formation of this product (**7.9 a**) proceeds through a formal gold-catalyzed 1,3-shift of the acyl group (Scheme 7.16, Eq. 1). While this type of rearrangement is well known for propargyl derivatives,

being used for the synthesis of a wide range of useful products (Scheme 7.16, Eq. 2),[247] it was never reported before for allene-containing substrates.



Scheme 7.16. Gold-catalyzed 1,3-shift of the acyl group for allenyl- (Eq. 1) and alkynyl-containing (Eq. 2) derivatives

Furthermore, our transformation allows the formation of functionalized 1,3-butadien-2-ol esters, a class of compounds for which the number of synthetic methods is quite limited, despite their importance as we saw in the previous section.

Compared with the gold-catalyzed reaction reported by Zhang et al. leading to the formation of similar products[246] (see also Scheme 7.14), we believe that our process presents some advantages. Indeed, the required allenic substrates **7.5** can be easily obtained by a Crabbé homologation[248] from the corresponding alkyne derivatives (requiring less expensive starting materials than the corresponding propargyltrimethylsilanes). Furthermore, the use of dry dichloromethane is not required since no water-sensitive acyloxycarbenium intermediate is involved.

2.2. Preliminary results

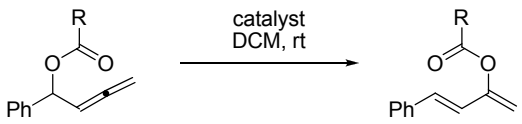
After the successful rearrangement of substrate **7.7 a** bearing a *tert*-butyl carbonate group in the presence of 1% of the biphenylphosphine-based catalyst **7.10**, we wanted to establish the influence of other ester groups on the outcome of the reaction. Allenyl substrates **7.7 b-d** possessing different acyl groups (such as acetate, benzoate or pivalate) were synthesized and tested under the same conditions (Table 7.2).

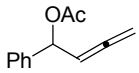
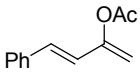
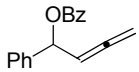
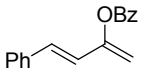
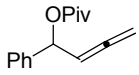
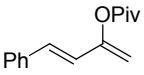
We were delighted to observe that all three substrates were fully converted, furnishing the expected 1,3-butadien-2-ol esters **7.9 b-d** of exclusive *E*-configuration in excellent yields ranging from 98% to quant. (Table 7.2, Entries 1, 5 and 8). It is also interesting to note that the acyl derivatives **7.7 b-d**

[247] See: (a) Marion, N.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2750-2752.
(b) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718-721.
and the references cited there in.

[248] (a) Crabbé, P.; Nassim, B.; Robert-Lopes, M.-T. *Org. Synth.* **1985**, *Vol. 63*, 203. *Org. Synth.* **1990**, *Coll. Vol. 7*, 276.
(b) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1968**, *90*, 4733-4734.
(c) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289-3292.

react faster (45 min – 3 h) and give better yields than the carbonate derivative **7.7 a** (see Table 7.2, Entry 2).



entry	substrate		catalyst	time	product		conv.[a]	yield
1		**7.7 b**	1% **7.10**	3 h		**7.9 b**	100%	98%[b]
2			1% Ph_3P-Au-NTf_2	24 h			15%	14%[c]
3			2% $AuBr_3$	24 h			<5%	0%[c]
4			10% $AgNTf_2$	24 h			15%	6%[c]
5		**7.7 c**	1% **7.10**	1 h 15 min		**7.9 c**	100%	quant.[b]
6			10% $HNTf_2$	24 h			<5%	0%[c]
7			-[d]	24 h			100%	<5%[c]
8		**7.7 d**	1% **7.10**	45 min		**7.9 d**	100%	quant.[b]

Reaction conditions: substrate (1 equiv), catalyst (see table), DCM (0.25 M), rt. [a] Conversion of the substrate estimated by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield. [c] Yield estimated by ^{1}H NMR of the crude reaction mixture. [d] Reaction performed in toluene (0.25 M) at 110 °C with no catalyst.

Table 7.2. Initial trials for the rearrangement of allenyl carbinol esters **7.7 b-d**

Additional reaction conditions were tested in order to get a better insight of this transformation.

Substrate **7.7 b** gave a poor conversion (15%) in the presence of 1% Ph_3P-Au-NTf_2 in DCM at rt, the desired compound **7.9 b** being obtained in just an estimated 14% yield (Table 7.2, Entry 2).

Even worse results were obtained when 2% $AuBr_3$ in DCM was used, the starting material remaining practically unreacted (less than 5% conversion) after 24 h (Table 7.2, Entry 3).

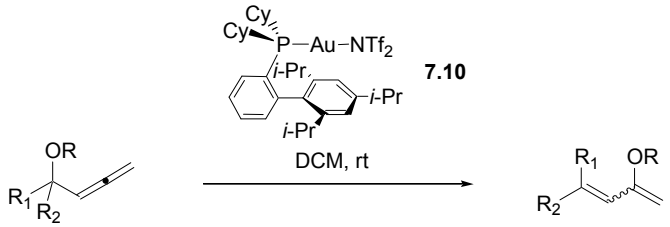
Silver was not a suitable catalyst for this reaction either, substrate **7.7 b** giving in the presence of 10% $AgNTf_2$ only a 15% conversion and a meager 6% estimated yield of **7.9 b** after 24 h (Table 7.2, Entry 4).

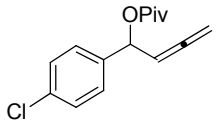
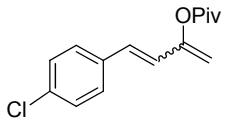
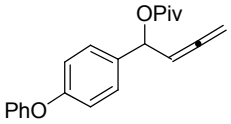
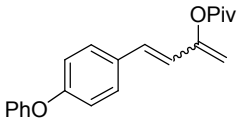
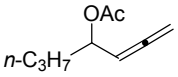
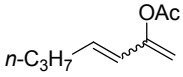
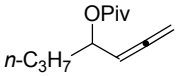
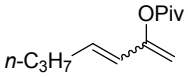
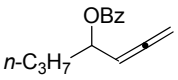
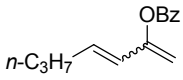
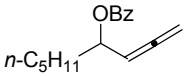
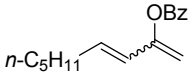
The transformation did not seem to take place in acidic or thermal conditions. Substrate **7.7 c** showed no conversion in the presence of 10% $HNTf_2$ in DCM for 24 h (Table 7.2, Entry 6). After reflux in toluene for 24 h, the decomposition of the **7.7 c** was observed (estimated yield of **7.9 c**: less than 5%; see Table 7.2, Entry 7).

In the light of these results, catalyst **7.10** was retained for the study of the scope of this transformation.

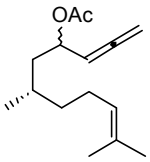
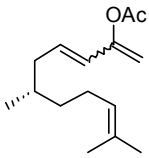
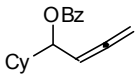
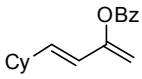
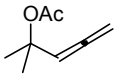
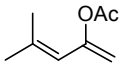
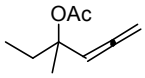
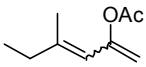
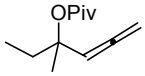
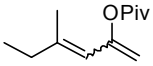
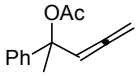
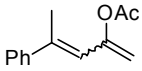
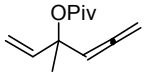
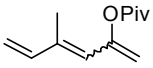
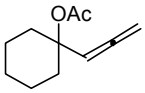
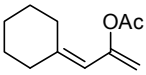
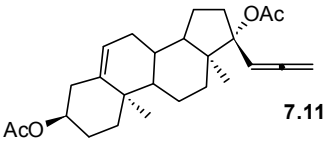
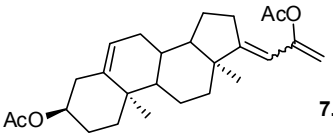
2.3. Gold-catalyzed formation of functionalized 1,3-butadien-2-ol esters

Different allenyl carbinol esters **7.11 a-o** were synthesized and tested under standard conditions (1% **7.10** in DCM at rt). The reaction proved to be quite general, the corresponding dienes **7.12 a-o** being obtained in generally good yields (53%-quant.) and *E*-selectivities. The time required to reach full completion was generally shorter than 2 h (Table 7.3).



entry	substrate		product		time	yield[a]
1		**7.11 a**	 *Z/E* ratio ~ 1/18	**7.12 a**	2 h	quant.
2		**7.11 b**	 *Z/E* ratio ~ 1/8	**7.12 b**	8 h	78%
3		**7.11 c**	 *Z/E* ratio ~ 1/7	**7.12 c**	3 h	quant.
4		**7.11 d**	 *Z/E* ratio ~ 1/9	**7.12 d**	1 h	quant.
5		**7.11 e**	 *Z/E* ratio ~ 1/19	**7.12 e**	5 min	quant.
6		**7.11 f**	 *Z/E* ratio ~ 1/15	**7.12 f**	40 min	quant.

(continued on the next page)

entry	substrate		product		time	yield[a]
7	 dr ~ 1/1	**7.11 g**	 *Z/E* ratio ~ 1/8	**7.12 g**	2 h	99%
8		**7.11 h**		**7.12 h**	9 h	quant.
9[c]		**7.11 i**		**7.12 i**	5 min	quant.[b]
10 11[d]		**7.11 j**	 *Z/E* ratio ~ 1/1.7	**7.12 j**	5 min 5 min	79% (quant.[b]) 88% (quant.[b])
12[d]		**7.11 k**	 *Z/E* ratio ~ 1/1.4	**7.12 k**	5 min	67% (89%[b])
13 14[e] 15[f]		**7.11 l**	 *Z/E* ratio ~ 1/1	**7.12 l**	24 h 3 h 3 h	0%[b] 46%[b] 59%[b]
16		**7.11 m**	 *Z/E* ratio ~ 1/2	**7.12 m**	10 min	53% (93%[b])
17		**7.11 n**		**7.12 n**	5 min	quant.
18		**7.11 o**	 *Z/E* ratio ~ 1/10	**7.12 o**	1 h	97%

Reaction conditions: substrate (1 equiv), **7.10** (0.01 equiv), DCM (0.25 M), rt. [a] Isolated yield. *Z/E* ratio determined by ^{1}H NMR. [b] Yield estimated by ^{1}H NMR of the crude reaction mixture. [c] Reaction performed in an NMR tube in CD_2Cl_2 (0.25 M). [d] Reaction performed at 0 °C. [e] Reaction performed at 40 °C. [f] Reaction performed in DCE (0.25 M) at 84 °C. Diene **7.12 l** was isolated in the mixture with the unreacted allene **7.11 l**.

Table 7.3. Scope of the gold-catalyzed rearrangement of allenyl carbinol esters **7.11 a-o** into functionalized 1,3-butadien-2-ol esters **7.12 a-o**

Various substituents were well tolerated, including simple or functionalized aryls, linear or branched alkyls, alkynes, or even moieties bearing halogen, ether or ester functionalities. Double substituted substrates at the α-allenic position (Table 7.3, Entries 9-17) reacted very effectively too, but a decrease in stereoselectivity was noticeable in these cases. The reaction times were generally shorter compared to the monosubstituted substrates (around 5 or 10 min).

Regarding the migrating group, benzoates and pivalates seemed to be slightly more reactive than the acetate derivatives, although the difference was very small. However, the nature of the migrating group played an important role in the selectivity of the final product. Although such an effect is difficult to rationalize, it seems that the benzoate group favors the formation of the *E*-isomer.

Substrate **7.11 a**, possessing a phenyl substituent functionalized with an electron-withdrawing group, seemed to be equally reactive as **7.7 d**, affording the expected functionalized 1,3-butadien-2-ol ester **7.12 a** in a quantitative yield and a *Z*/*E* ratio of 1/18 (Table 7.3, Entry 1).

On the other hand, *p*-phenoxy-phenyl allene **7.11 b** showed a slight decrease in both yield and selectivity (78% isolated yield of **7.12 b**, *Z/E* ratio ~ 1/8). The reaction time (8 h) was considerably longer too (Table 7.3, Entry 2).

The reaction was not limited to aryl substituted allenes, as shown in Table 7.3, Entries 3-8.

Substrates **7.11 c-e**, functionalized with a *n*-propyl group, furnished the corresponding dienes **7.12 c-e** quantitatively (Table 7.3, Entries 3-5). The acetate and pivalate derivatives **7.11 c** and **d** gave similar *Z/E* ratios of 1/7 and 1/9 respectively. The ratio increased up to 1/19 in the case of benzoate **7.11 e**.

Similarly, benzoate **7.11 f**, possessing a longer alky chain, furnished diene **7.12 f** quantitatively in a 1/15 *Z/E* ratio (Table 7.3, Entry 6).

The presence of an alkene group was compatible with our transformation, as proven by the citronellal derivative **7.11** g which isomerized into **7.12 g** in a 99% yield and a *Z/E* ratio of 1/8 (Table 7.3, Entry 7).

A sterically demanding group at the α-allenic position induced a complete stereocontrol of the reaction, product **7.12 h** being obtained exclusively as an *E*-isomer and in a quantitative manner (Table 7.3, Entry 8).

Substrate **7.11 i** isomerized rapidly and quantitatively into **7.12 i**. Unfortunately the final product was quite volatile, proving to be difficult to isolate. The reaction was therefore performed in deuterated dichloromethane in an NMR tube and the yield evaluated by ^{1}H NMR (Table 7.3, Entry 9).

Although **7.12 j** was obtained quantitatively starting from substrate **7.11 j** under standard conditions (according to the ^{1}H NMR spectrum of the crude mixture), it could only be isolated in a 79% yield (Table 7.3, Entry 10). Lowering the reaction temperature to 0 ^{o}C improved the isolated yield to 88% (Table 7.3, Entry 11). Similarly, diene **7.12 k** was obtained at 0 ^{o}C in an 89% estimated and 67% isolated yield (Table 7.3, Entry 12). The important decrease in stereoselectivity observed for products **7.12 j** and **k** (*Z/E* ratios ~ 1/1.7 and respectively 1/1.4) was a consequence of the low differentiation between the two substituents in the α-position.

Surprisingly, allene **7.11 l** was recovered unreacted after 24 h under standard conditions (Table 7.3, Entry 13). Performing the reaction in DCM at reflux for 3 h leads only to a partial conversion, **7.12 l** being formed only in a 46% yield (Table 7.3, Entry 14). Refluxing for 3 h in 1,2-dichloroethane was required to furnish diene **7.12 l** in a modest 59% yield along with unreacted substrate **7.11 l** (Table 7.3, Entry 15).

Beside dienes, trienes could also be obtained, as demonstrated by Table 7.3, Entry 16. Product **7.12 m** was obtained in a 93% yield (evaluated by ^{1}H NMR of the crude mixture) and a *Z/E* ratio of 1/2. The average isolated yield (53%) can be explained by a partial decomposition during the purification by flash chromatography.

Spiro substrate **7.11 n** rearranged rapidly and quantitatively into the corresponding product **7.12 n** (Table 7.3, Entry 16).

The reaction of androstene derivative **7.11 o** was exceptionally efficient and gave the expected 1,3-butadien-2-ol ester **7.12 o** in a 97% yield and an excellent stereoselectivity (*Z/E* ratio ~ 1/10) after a simple filtration of the crude reaction mixture (Table 7.3, Entry 17).

2.4. Mechanistic proposal

The formation of functionalized 1,3-butadien-2-ol esters described in previous sections proceeds through a new type of gold-catalyzed formal 1,3-shift of the acyl group.

The stereochemistry of the final products depends mainly on the relative size of the substituents located at the α-allenic position. If the size difference between the two substituents is large enough (like in case of monosubstituted derivatives), the *E*-isomer is mainly (even exclusively) obtained. Compounds **7.9 a-d**, **7.12 h** and **7.12 o** illustrate this fact (see Table 7.1, Table 7.2, and Table 7.3, Entries 8 and 17). On the other hand if the two substituents have similar sizes, *Z/E* mixtures are obtained (e.g. compounds **7.12 j-m** in Table 7.3, Entries 10-15).

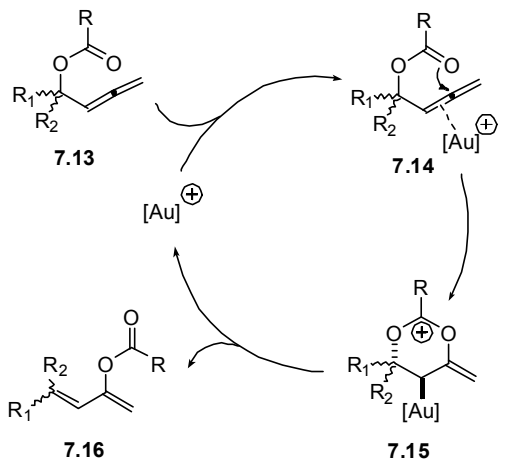
Another factor influencing the observed stereochemistry, although difficult to rationalize, is the nature of the migrating group. Compounds possessing a benzoate moiety seem to give a better *Z/E* ratio, as illustrated by examples **7.12 c-e** (Table 7.3, Entries 3-5).

It was proven that the gold catalyst **7.10** does not isomerize the final 1,3-butadien-2-ol esters products. Performing the rearrangement for a longer time or resubmitting the isolated dienes to the same reaction conditions did not change the *Z/E* ratios.

In order to account for these experimental observations, a mechanistic manifold is proposed in Scheme 7.17.

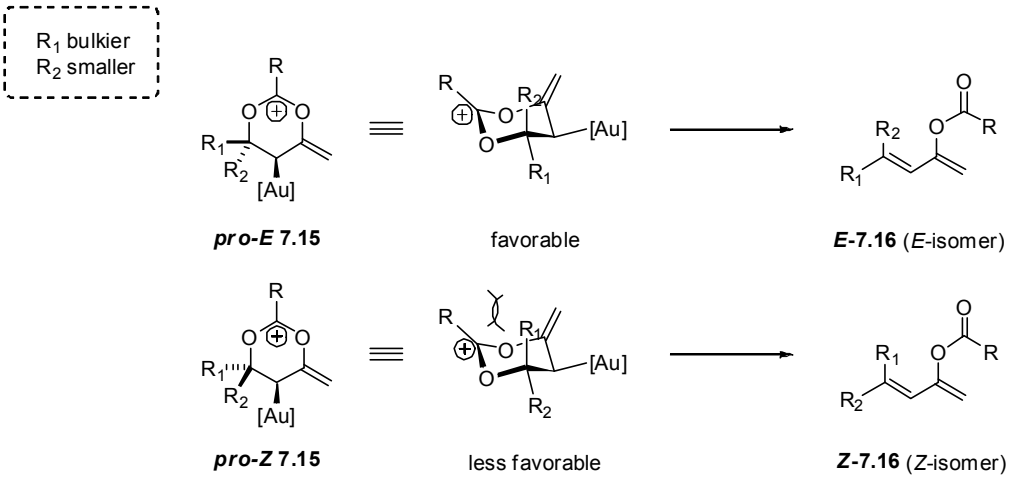
First the allene moiety of substrate **7.13** is regioselectively activated by the gold catalyst's active species. This promotes the nucleophilic attack of the carbonyl function of the ester group and leads to the formation of the 6-membered ring stabilized cationic intermediate **7.15**. Fragmentation of the

allylic Au-C bond and of the homoallylic C-O bond gives the expected rearranged 1,3-butadien-2-ol ester **7.16** and regenerates the gold catalyst.



Scheme 7.17. Mechanistic proposal for the formation of functionalized 1,3-butadien-2-ol esters

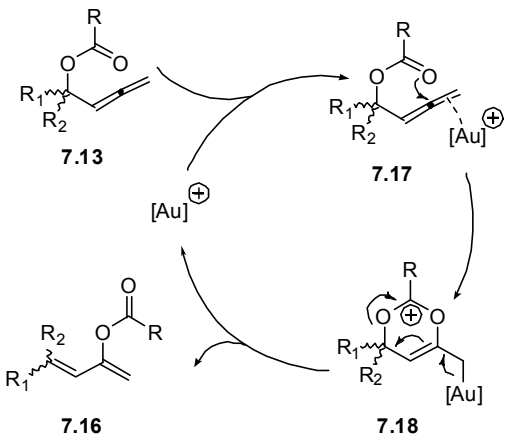
The stereoselectivity might be explained by the chair-like transition states ***pro-E* 7.15** and ***pro-Z* 7.15** presented in Scheme 7.18. In both cases the gold atom adopts a pseudoequatorial position, with the requisite antiperiplanar geometry between the homoallylic C-O bond and the allylic Au-C bond (needed for the fragmentation step). The bulkier group R_1 will be placed preferentially in the equatorial position, like depicted in the favored ***pro-E* 7.15** transition state, leading to the *E*-isomer ***E*-7.16**. On the contrary, in the less-favorable transition state ***pro-Z* 7.15**, giving the *Z*-isomer **Z-7.16**, the bulkier R_1 group adopts a pseudoaxial position, leading to a possible pseudo-1,3-diaxial interaction energetically unfavorable.



Scheme 7.18. Source of the *E/Z* selectivity for the formation of functionalized 1,3-butadien-2-ol esters

The proposed mechanism can explain the usually shorter reaction times (the fragmentation of the C-O bond is favored) or the reduced stereoselectivity (due to a smaller energy difference between the two transition states ***pro-Z* 7.15** and ***pro-E* 7.15** depicted in Scheme 7.18) observed in the case of disubstituted substrates at the α-position.

An alternative mechanism involving the activation of the terminal double bond of the allene moiety can be imagined as well (Scheme 7.19). It involves just like in the previously proposed mechanism the attack of the carbonyl group and the formation of a cationic intermediate **7.18**, followed by a fragmentation step in which the final product **7.16** is formed and the catalyst regenerated.



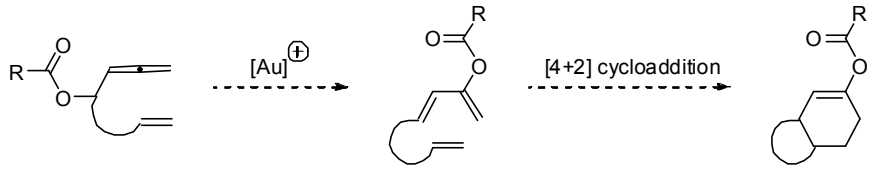
Scheme 7.19. Alternative mechanistic proposal for the formation of functionalized 1,3-butadien-2-ol esters

3. Conclusions and perspectives

In conclusion, we have shown that gold(I)-complexes efficiently catalyze the formation of functionalized 1,3-butadien-2-ol esters starting from readily available allenyl carbinol esters. Our transformation provides an interesting alternative to the already existing methods, most of them limited in scope.

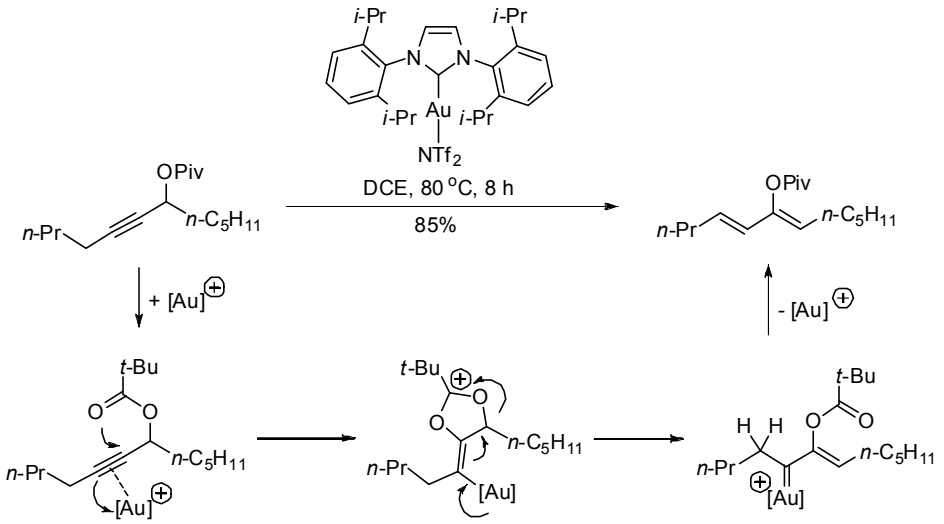
The reaction conditions are extremely mild, being less moisture sensitive compared to other methods and allowing the compatibility with a good number of substitutions patterns. Other benefits include the low amounts of catalyst required for this transformation (1%) and the facile and inexpensive method to form the starting allenes. The yields and the *E*-selectivities are generally good.

As perspectives for our work, the study of polysubstituted allene derivatives or the formation of bicyclic compounds via a sequence of gold-catalyzed rearrangements and [4+2] cycloadditions (Scheme 7.20) might be considered.



Scheme 7.20. A possible extension of our work

After the publication of our work, another gold-catalyzed transformation leading to the stereoselective formation of functionalized 1,3-butadien-2-ol esters was described by Zhang et al.[249] They showed that propargylic pivalates with electronically unbiased internal alkynes can undergo an 1,2-acyloxy migration selectively leading to the formation of an alkenyl gold carbenoid which inserts into the α-C–H bond (Scheme 7.21). Although limited in scope, this transformation proves once more the potential of gold homogeneous catalysis for the synthesis these particular diene structures.



Scheme 7.21. Another gold-catalyzed transformation leading to functionalized 1,3-butadien-2-ol esters proposed by Zhang et al.

[249] Li, G.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 3740-3741.

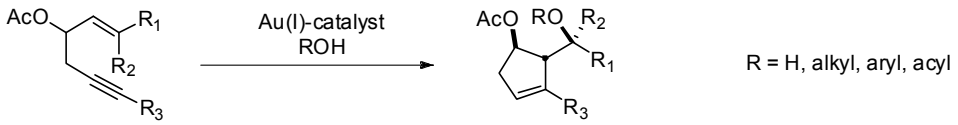
CHAPTER

8

Gold(I)-Catalyzed 5-*endo* Hydroxy- and Alkoxycyclization of 1,5-Enynes: an Efficient Access to Functionalized Cyclopentenes

*"A fact is a simple statement that everyone believes. It is innocent, unless found guilty. A hypothesis is a novel suggestion that no one wants to believe. It is guilty, until found effective." (**Edward Teller**, Hungarian-American theoretical physicist)*

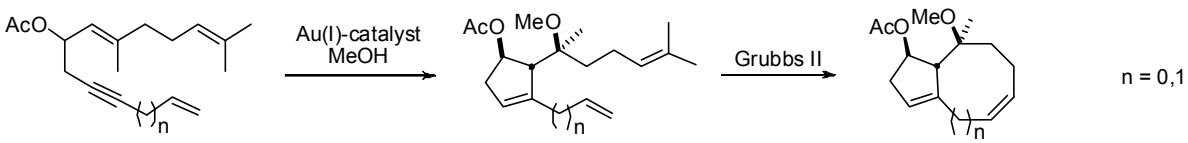
This chapter describes the rapid formation of highly functionalized cyclopentenes via a gold-catalyzed 5-*endo* hydroxy- or alkoxycyclization of 1,5-enynes (Scheme 3.1).



Scheme 8.1. Synthesis of highly functionalized cyclopentenes via a gold-catalyzed 5-*endo* hydroxy- or alkoxycyclization of 1,5-enynes

Our method constitutes an extremely practical and efficient way to access this type of structures, thanks to a very good control of the stereochemistry and to the mild reaction conditions. The broad scope of this reaction is another advantage, several types of oxygenated nucleophiles, as well as a good number of functional groups on the substrate, being well tolerated.

This method was extended to the formation of 5,7- and 5,8-fused bicyclic structures encountered frequently in natural products. These structures can be accessed easily by combining the cyclization reaction with a ring-closing metathesis (Scheme 8.2).



Scheme 8.2. Extension to the formation of 5,7- and 5,8-fused bicyclic compounds by combining the cyclization reaction with a ring-closing metathesis step

In the first part of this chapter the importance of the cyclopentene moiety and a few methods used for its synthesis will be discussed briefly (section 1). The second part is dedicated to a more detailed look on our work concerning this topic (section 2). This chapter ends with a few conclusions and perspectives (section 3).

Disclaimer:

This work was conducted under the supervision of Dr. Fabien L. Gagosz. Although a part of the experiments presented in this chapter was carried out by Dr. Andrea K. Buzas and Dr. Fabien L. Gagosz, in order to preserve the coherence of the subject the totality of the work concerning this topic will be discussed here.

Some of these results have been previously published in:

- Andrea K. Buzas, Florin M. Istrate, Fabien L. Gagosz* "Gold(I)-Catalyzed 5-*endo* Hydroxy-and Alkoxycyclization of 1,5-Enynes: an Efficient Access to Functionalized Cyclopentenes" *Angew. Chem. Int. Ed.* **2007**, *46*, 1141-1144.

1. The cyclopentene moiety

1.1. Occurrence in natural products and importance of functionalized cyclopentenes

The cyclopentene unit (Figure 8.1) is one of the most common types of carbon cycles. It can be encountered, along with its derivatives, in a wide range of biologically active compounds.

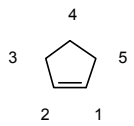


Figure 8.1. The cyclopentene moiety

For example 1-acetoxyvalerenic acid[250] (a valerenane sesquiterpenoid used both as a sedative and as an antispasmodic), thapsigargin[251] (a potent inhibitor for sarco/endoplasmic reticulum calcium ATPases - SERCA enzymes - which has become an indispensable tool for the study of cell physiology and might offer a new type of chemotherapeutics for treatment of prostate cancer), walsuronoids

[250] Stoll, A.; Seebeck, E. *Justus Liebigs Ann. Chem.* **1957**, *603*, 158-168.
[251] Liu, H.; Jensen, K. G.; Tran, L. M.; Chen, M.; Zhai, L.; Olsen, C. E.; Søhoel, H.; Denmeade, S. R.; Isaacs, J. T.; Brøgger Christensen, S. *Phytochemistry* **2006**, *67*, 2651-2658.

B[252] (a limonoid showing antimalarial activity) or tasumatrol P[253] (a cytotoxic taxane diterpene ester) contain all a functionalized cyclopentene unit (Figure 8.2).

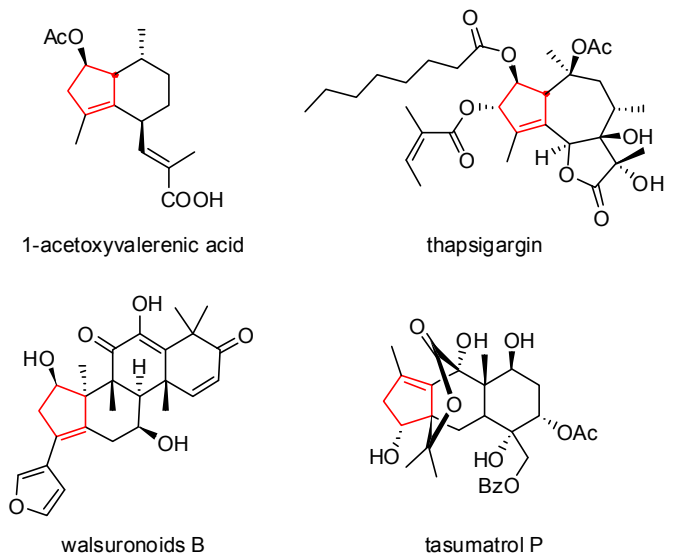


Figure 8.2. A few examples of biologically active compounds possessing a functionalized cyclopentene moiety

Cyclopentene derivatives are also valuable intermediates, being often involved in the total synthesis of a large number of useful compounds.

1.2. Synthesis of functionalized cyclopentenes

Due to the prevalence of functionalized cyclopentenes in both natural and synthetic compounds, a large number of strategies have been developed and employed for the synthesis of these compounds.[254] Commonly used methods include ring closing metathesis reactions, ionic and radical cyclizations, concerted cycloadditions, various condensations, derivatization of other five-member carbocycles etc.

Among this extraordinary variety of transformations, the metal-catalyzed 1,n-enyne rearrangements have emerged in the last 20 years as one of the most elegant approaches to functionalized cyclopentenes.[255,256]

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[252] Yin, S.; Wang, X.-N.; Fan, C.-Q.; Liao, S.-G.; Yue, J.-M. *Org. Lett.* **2007**, *9*, 2353-2356.
[253] Shen, Y.-C.; Lin, Y.-S.; Hsu, S.-M.; Khalil, A. T.; Wang, S.-S.; Chien, C.-T.; Kuo, Y.-H.; Chou, C.-H. *Helv. Chim. Acta* **2007**, *90*, 1319-1329.
[254] For some general works regarding the total synthesis of organic compounds in general and of cyclopentenes in particular, see:
(a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; Wiley-VCH, 1996.
(b) Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; 2007 ed.; Wiley-VCH: Weinheim, 2007.
[255] For some reviews on transition metal-catalyzed cycloisomerization of enynes, see:
(a) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.
(b) Bruneau, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 2328-2334.

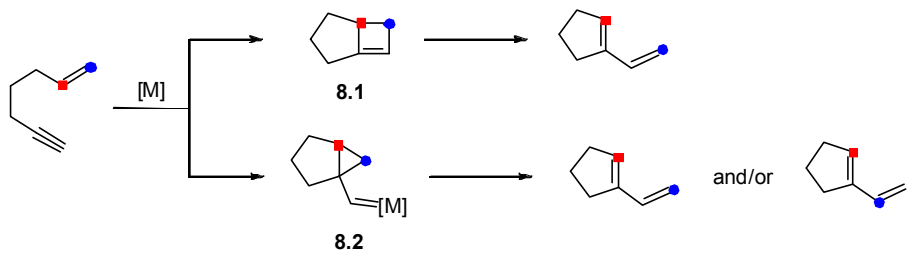
Their attractiveness comes mainly from the rapid increase in structural complexity (linear compounds are transformed into cyclic ones) and from the inherent atom-economy they entail. Furthermore, these transformations are in most of the cases easy to set up, safe and efficient.

Depending on the substitutions of the substrate and the experimental conditions, different final products may be obtained. Additional tandem reactions or rearrangements can be imagined as well, involving for instance inter- or intramolecular trapping agents, which can further increase the utility of these transformations.

Although providing a comprehensive list of all the possible metal-catalyzed rearrangements of 1,n-enynes leading to functionalized cyclopentenes is beyond the scope of this manuscript, this section will try to present a few representative examples.

Synthesis from 1,6-enynes

One of the most studied transformations of this type starting from 1,6-enynes involves the formation of conjugated vinyl cyclopentenes derivatives (Scheme 8.3). The mechanism of these transformations varies widely depending on the metal, the substrate or even the conditions used, but most of them involve either a cyclobutene intermediate **8.1** or a cyclopropyl carbenoid derivative **8.2**. Ring opening in the first case or a skeletal rearrangement in the second leads to the expected conjugated vinyl cyclopentenes derivatives.



Scheme 8.3. Metal-catalyzed formation of conjugated vinyl cyclopentenes derivatives from 1,6 enynes

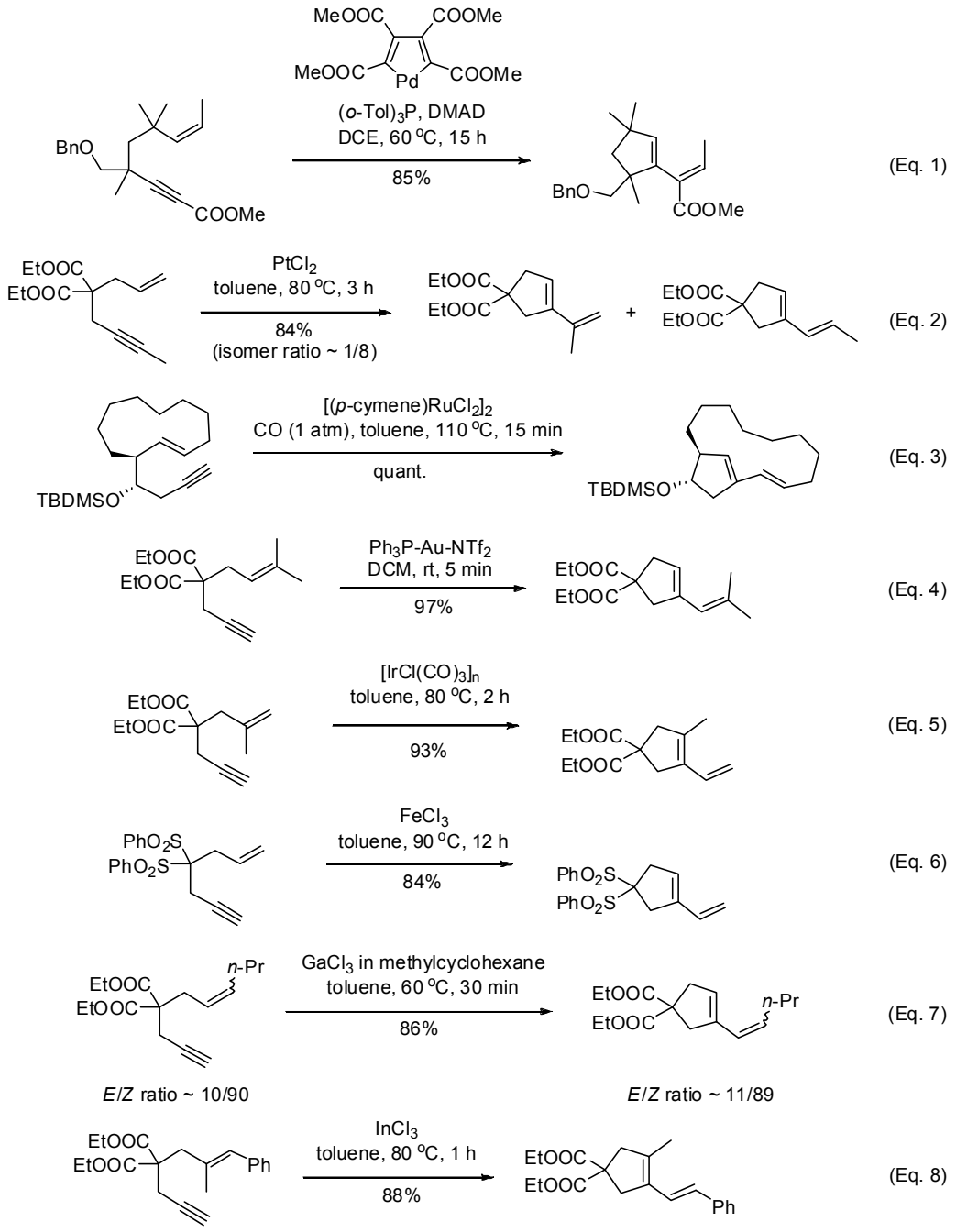
Scheme 8.4 illustrates some examples involving diverse metals such as palladium (Eq. 1),[257] platinum (Eq. 2 and 3),[258] ruthenium (Eq. 4),[259] gold (Eq. 5),[260] iridium (Eq. 6),[261] iron (Eq. 7),[262] gallium (Eq. 8),[263] or indium (Eq. 9).[264]

(c) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431-436.
(d) Añorbe, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Eur. J.* **2004**, *10*, 4938-4943.
(e) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813-834.
(f) Trost, B. M.; Krische, M. J. *Synlett* **1998**, *1998*, 1-16.
(g) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635-662.
(h) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215-236.

[256] For reviews on gold-catalyzed cycloisomerization of enynes, see:
(a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271-2296.
(b) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326-3350.
(c) Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030-5033.
(d) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847-7870.

[257] Trost, B. M.; Chang, V. K. *Synthesis* **1993**, *1993*, 824-832.

[258] Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901-903.

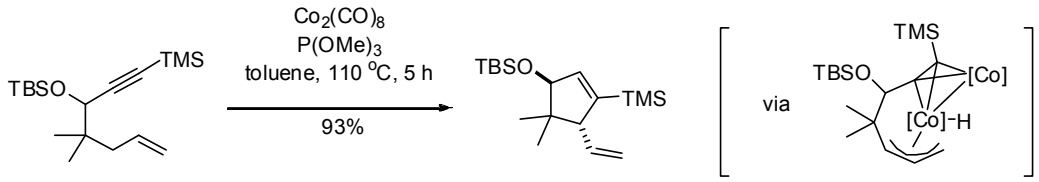


Scheme 8.4. Some examples illustrating the metal-catalyzed formation of conjugated vinyl cyclopentenes derivatives starting from 1,6 enynes

Various other reactions involving the cyclization of 1,6-enynes into functionalized cyclopentenes have been reported. Depending on the substitution of the substrate, the main process can be accompanied by other transformations.

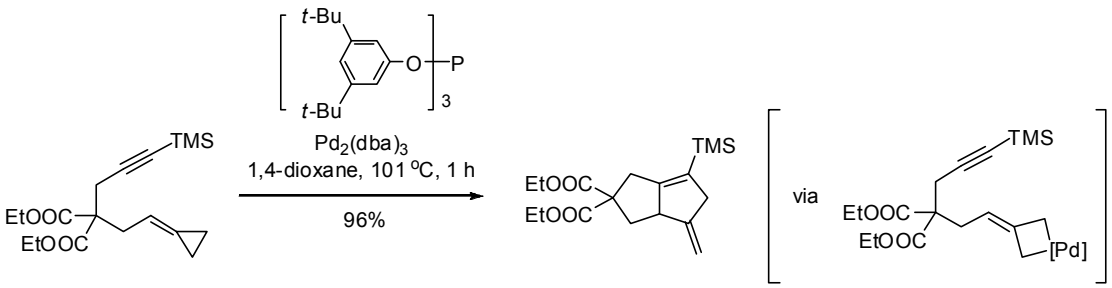
[259] Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801-3810.
[260] Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136.
[261] Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433-4436.
[262] Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.
[263] Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294-10295.
[264] Miyanohana, Y.; Chatani, N. *Org. Lett.* **2006**, *8*, 2155-2158.

For instance Scheme 8.5 describes a 5-*endo-dig* cyclization of a TMS-substituted enyne which proceeds via an allyl-cobalt derivative.[265]



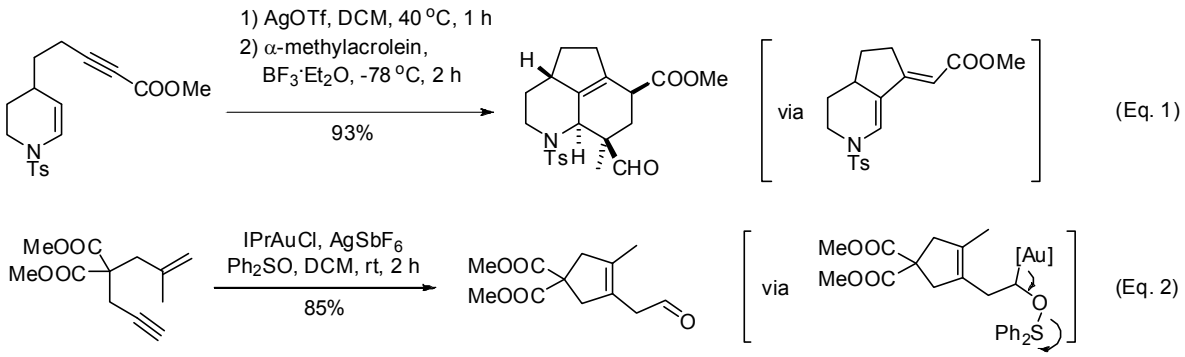
Scheme 8.5. Example of cobalt-catalyzed rearrangement of a 1,6-enyne leading to a functionalized cyclopentene

A similar substrate, but bearing an alkylidene cyclopropane moiety, gives another type of rearrangement leading to a bicyclic product (Scheme 8.6). The authors proposed a palladacyclobutane intermediate.[266]



Scheme 8.6. Another example of palladium-catalyzed rearrangement of a 1,6-enyne leading to a functionalized cyclopentene

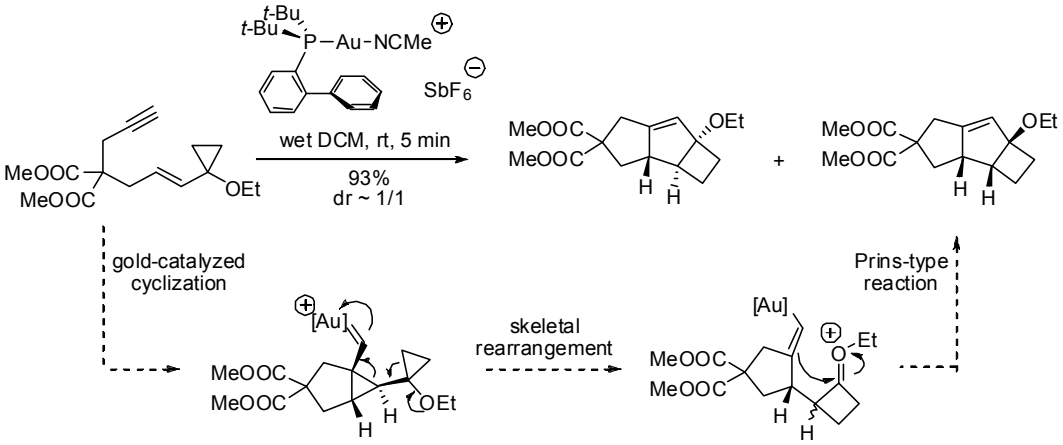
The efficacy of metal-catalyzed cycloisomerizations has prompted the development of tandem reactions, which associate the rearrangement process with another reaction, such as a Diels-Alder cycloaddition (Scheme 8.7, Eq. 1)[267] or an oxidation step (idem, Eq. 2).[268]



Scheme 8.7. Tandem reactions combining the metal-catalyzed rearrangement of 1,6-enynes with another transformation

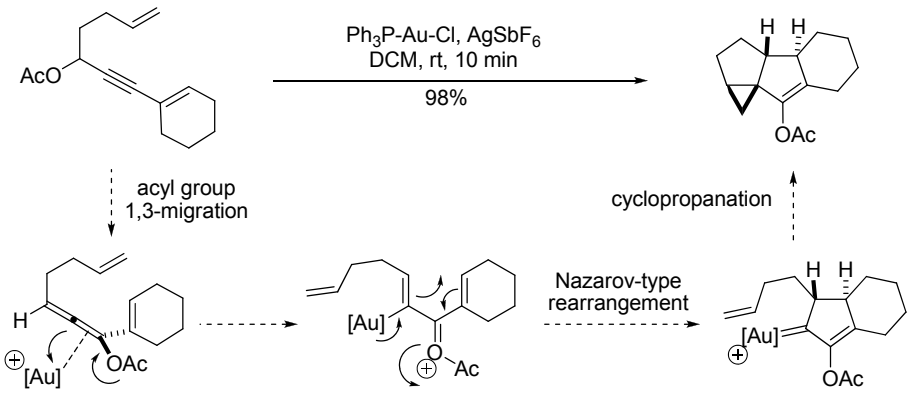
[265] Ajamian, A.; Gleason, J. L. *Org. Lett.* **2003**, *5*, 2409-2411.
[266] Duran, J.; Gulias, M.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2005**, *7*, 5693-5696.
[267] Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023-5026.
[268] Witham, C. A.; Mauleon, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838-5839.

Scheme 8.8 showcases a rather complex transformation consisting in an initial gold-catalyzed cyclization followed by a skeletal rearrangement and a Prins-type reaction.[269]



Scheme 8.8. Multi-step gold-catalyzed rearrangement of 1,6-enynes leading to functionalized cyclopentenes

Another multi-step transformation is shown in Scheme 8.9. It consists in an acetate group 1,3-migration, a Nazarov-type reaction and a cyclopropanation step.[270]



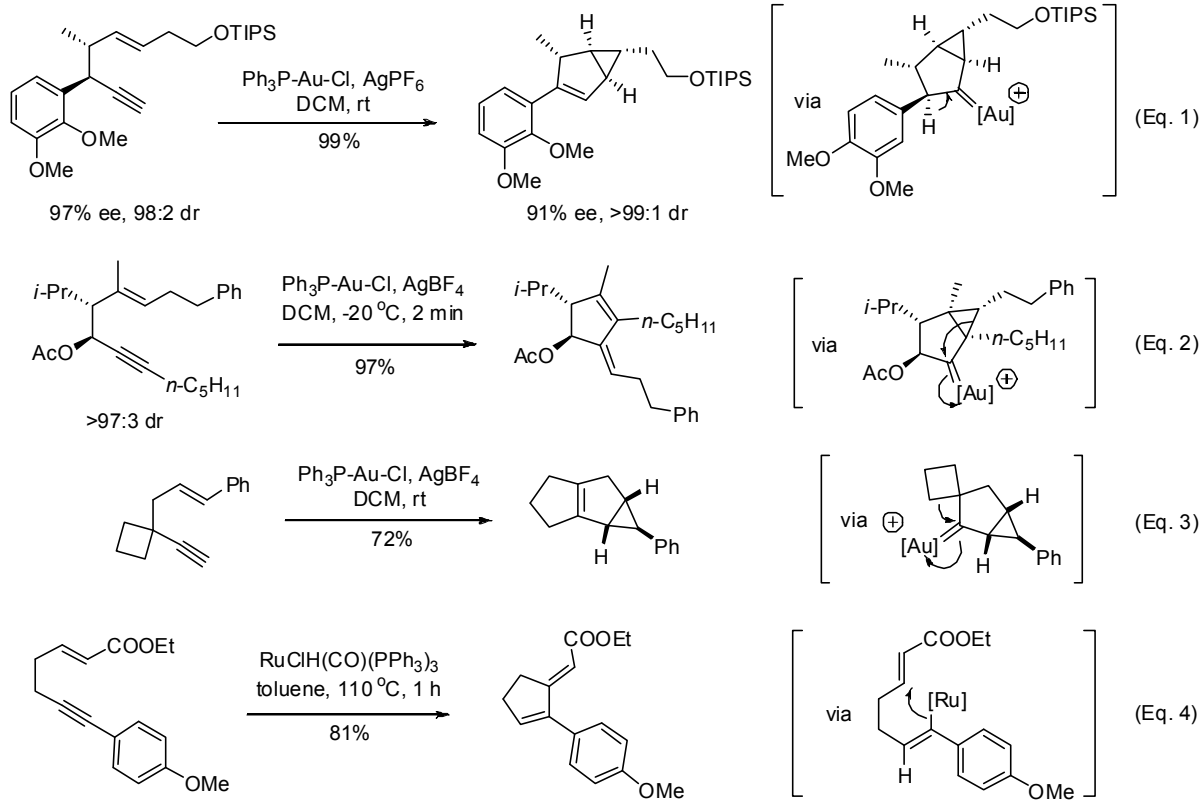
Scheme 8.9. Multi-step gold-catalyzed rearrangement of 1,6-enynes leading to functionalized cyclopentenes

Synthesis from 1,5-enynes

Metal-catalyzed 1,5-enyne cyclization offers another way to functionalized cyclopentenes. Equations 1-3 in Scheme 8.10 illustrate the formation of a cyclopropane carbenoid gold intermediate which can rearrange differently depending on the substitutions of the substrate. Eq. 4 shows a different process involving an initial hydroruthenation step followed by subsequent cyclization and β-hydrogen elimination.[271]

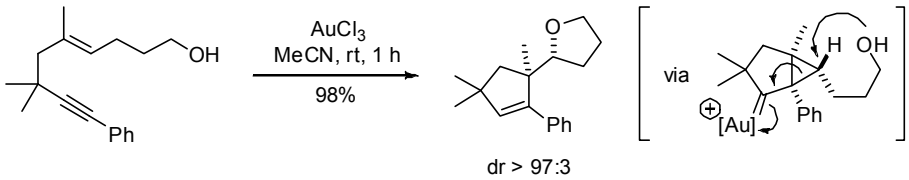
---

[269] Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452-5455.
[270] Lemiere, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207-2209.
[271] (a) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859.
(b) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129-4132.



Scheme 8.10. Metal-catalyzed cycloisomerizations of 1,5-enynes leading to various functionalized cyclopentenes

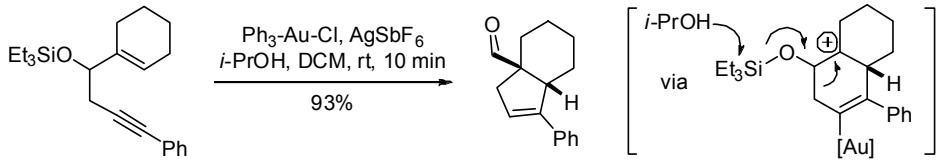
The presence of a nucleophile modifies the reaction outcome. Kozmin et al. observed for instance that an alcohol group can intramolecularly attack the cyclopropane functionality of the carbenoid gold intermediate giving stereoselectively a cyclopentene functionalized with a cyclic ether group (Scheme 8.11).[272]



Scheme 8.11. Gold-catalyzed cycloisomerization of a 1,5-enyne combined with the intramolecular attack of an alcohol group

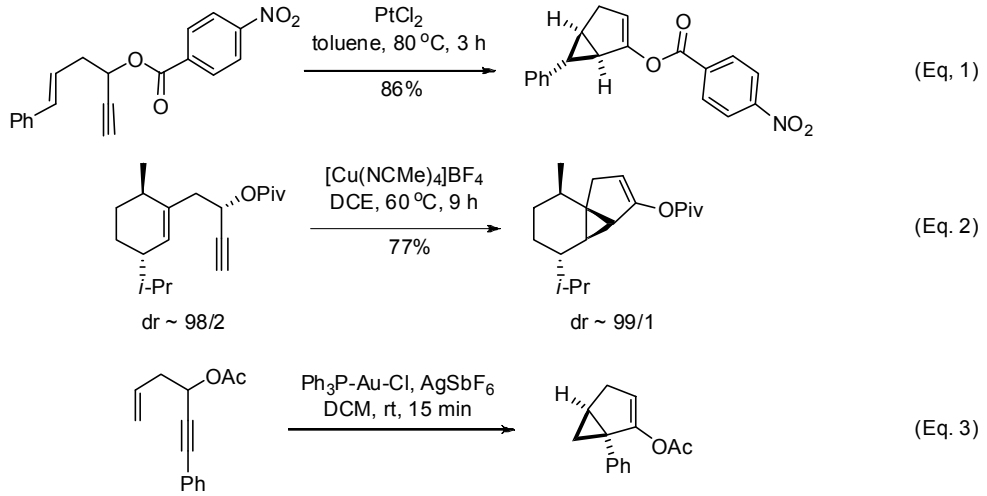
1,5-Enynes with a siloxy group at the allylic position can give cyclopentenes bearing an aldehyde substituent via a tandem cyclization and pinacol rearrangement, as shown by Kirsch et al. (Scheme 8.12).[273]

(c) Nishida, M.; Adachi, N.; Onozuka, K.; Matsumura, H.; Mori, M. *J. Org. Chem.* **1998**, *63*, 9158-9159.
[272] Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962-6963.
[273] Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 2310-2313.



Scheme 8.12. Another example of gold-catalyzed cycloisomerization of a 1,5-enyne leading to functionalized cyclopentenes

If an acyloxy functionality is placed in the propargylic position of a 1,5-enyne system, a 1,2-shift of the former group can take place leading to the formation of a carbenoid derivative which then reacts with the double bond to form a 3,5-fused bicyclic system (Scheme 8.13).[274]

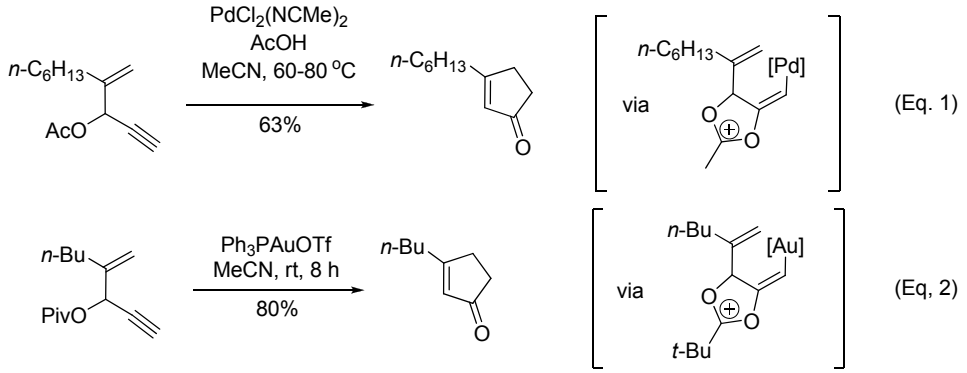


Scheme 8.13. Metal-catalyzed cycloisomerizations of 1,5-enynes with an acyloxy functionality in the propargylic position

Synthesis from 1,4-enynes

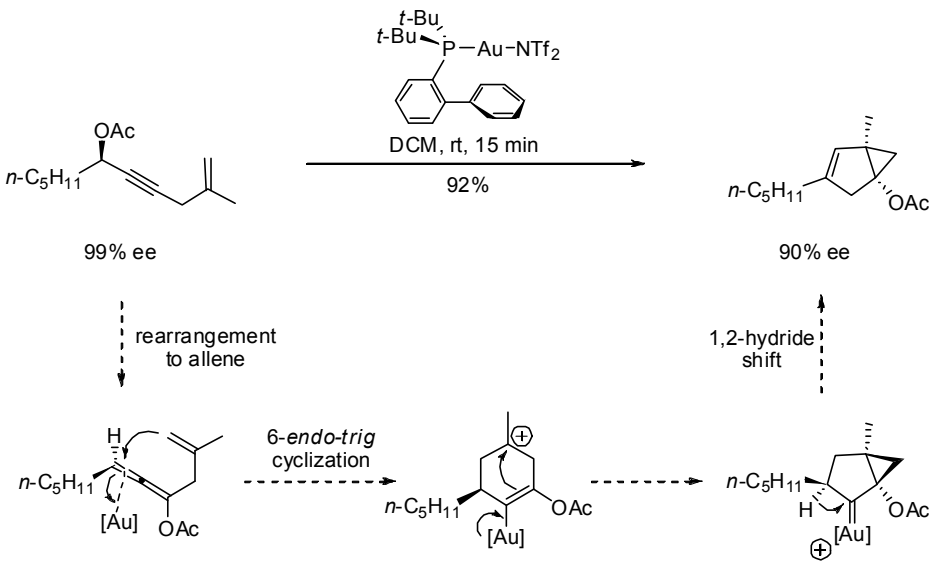
When an ester group is found between the alkyne and the alkene moieties of an 1,4-enyne, a Rautenstrauch-type rearrangement can occur leading to 2-cyclopentenones. The proposed mechanism involves the 1,2-shift of the ester group prior to the C-C bond formation (Scheme 8.14).[275]

[274] (a) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouries, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656-8657.
(b) Fehr, C.; Galindo, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2901-2904.
(c) Mamane, V.; Gress, T.; Krause, H.; Furstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654-8655.
[275] (a) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950-952.
(b) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802-5803.



Scheme 8.14. Metal-catalyzed rearrangement of 1,4-enynes leading to functionalized cyclopentenes

1,4-Enynes containing an ester group in the propargylic position distal to the alkene moiety undergo another cycloisomerization consisting in a rearrangement to allene followed by a 6-*endo-trig* cyclization and a 1,2-hydride shift. Cyclopentenes with a fused cyclopropane ring and two adjacent quaternary centers at the ring junction can be obtained this way (Scheme 8.15).[276]

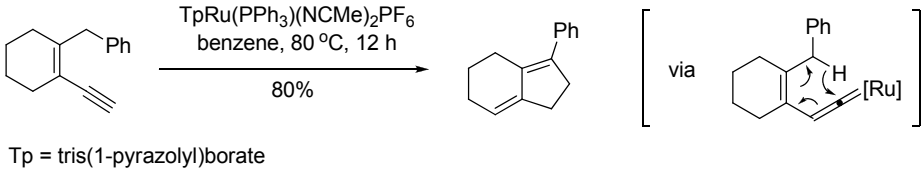


Scheme 8.15. Another type of metal-catalyzed rearrangement of 1,4-enynes leading to functionalized cyclopentenes

Synthesis from 1,3-enynes

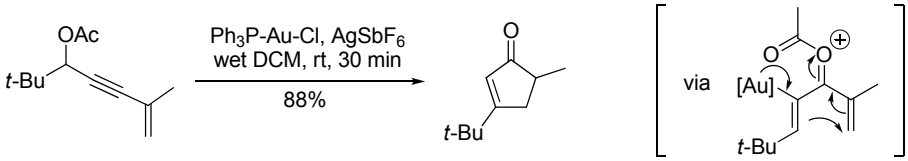
Liu et al. developed a ruthenium-catalyzed transformation for the formation of a cyclopentene ring from 1,3-enynes. This method probably involves a [1,5]-sigmatropic hydrogen shift of the ruthenium-vinylidene intermediates initially formed (Scheme 8.16).[277]

[276] Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614-12615.
[277] Datta, S.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 11606-11607.



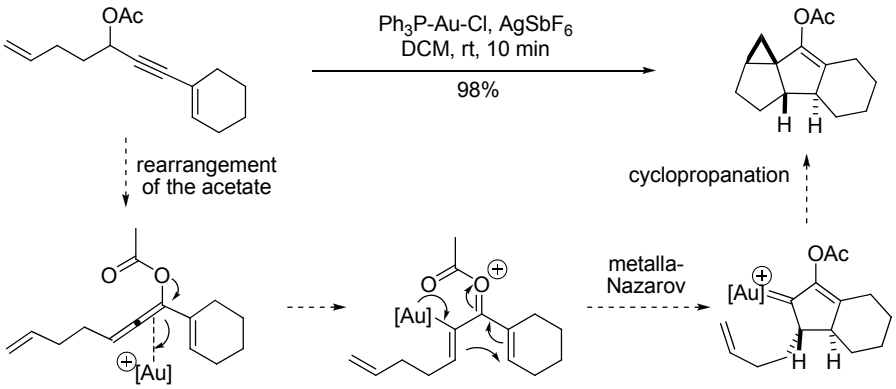
Scheme 8.16. Ruthenium-catalyzed formation of cyclopentene rings from 1,3-enynes

Zhang et al. proposed a convenient method to access cyclopentenones via a Nazarov-type reaction followed by hydrolysis of the vinyl ester group (Scheme 8.17).[278]



Scheme 8.17. Gold-catalyzed formation of functionalized cyclopentenes from 1,3-enynes

Malacria et al. extended this transformation to the synthesis of polycyclic compounds possessing a cyclopentene ring. Their tandem process includes the rearrangement of the acetate group in the presence of a gold catalyst, a metalla-Nazarov reaction and a cyclopropanation step (Scheme 8.18).[279]

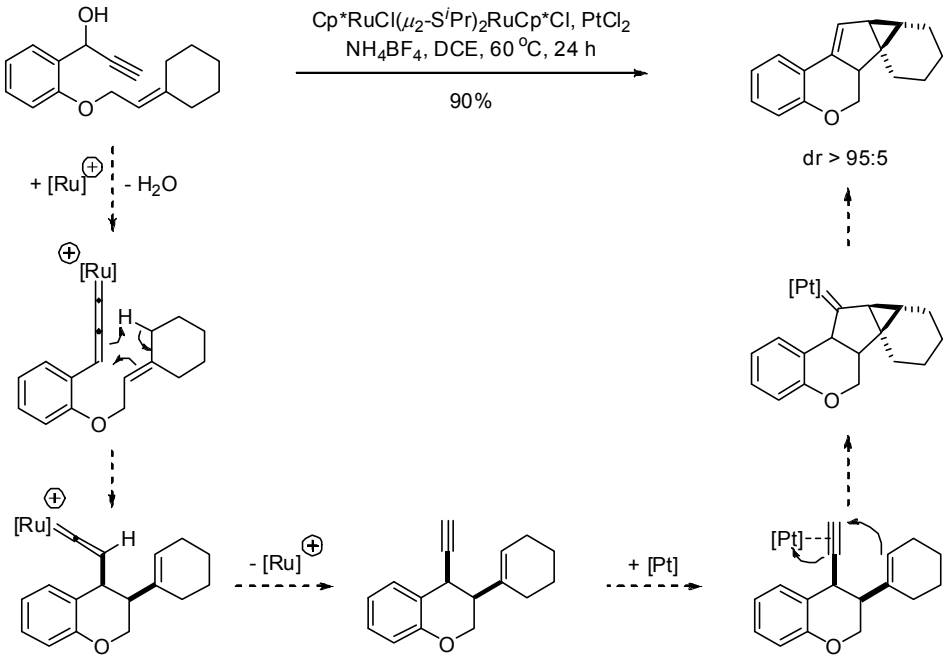


Scheme 8.18. Extension to the formation of polycyclic compounds containing a cyclopentene functionality

Synthesis from other 1,n-enynes

Transformation involving the rearrangement of longer 1,n-enynes (n>6) into functionalized cyclopentenes are quite rare. An interesting example was reported by Uemura et al.[280] A ruthenium and a platinum catalyst promoted a sequence of rearrangements of the starting 1,8-enyne leading to a polycyclic compound (Scheme 8.19).

[278] Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442-1443.
[279] Lemiere, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207-2209.
[280] Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2004**, *126*, 16066-16072.



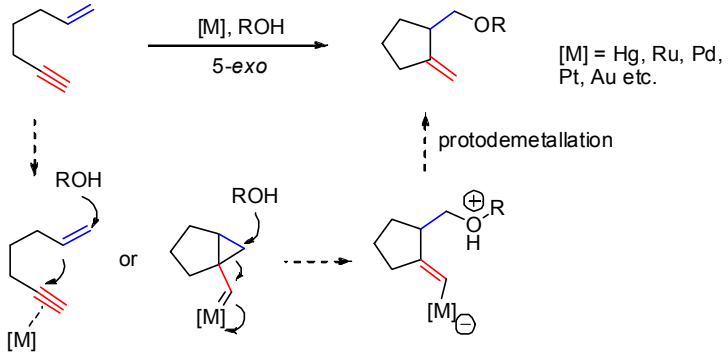
Scheme 8.19. Ru- and Pt-catalyzed sequence for the formation of functionalized cyclopentenes from 1,8-enynes

2. Our synthetic approach to functionalized cyclopentenes

2.1. Precedents in the literature. The initial idea

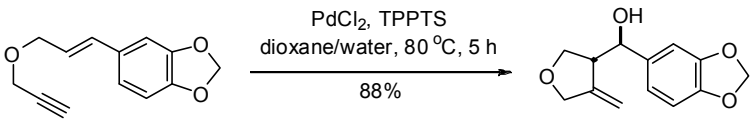
As we saw in the previous section, the potential of the transition metal-catalyzed rearrangement of 1,n-enynes has been highlighted by a large number of studies. Hydroxy- or alkoxycyclizations in particular are highly interesting since they combine the "classical" cyclization of an enyne with the nucleophilic attack of an oxygenated derivative. This allows not only the formation of a C-C bond, but also of a C-O bond in just one step.

One of the most common type of transition metal-catalyzed hydroxy- / alkoxycyclizations previously reported in the literature involves the 5-*exo* cyclization of an 1,6-enyne (Scheme 8.20). Depending on the metal and the reaction conditions, it has been proposed that the process might proceed either in a concerted manner (simultaneous attack of the alcohol on the alkene and of the alkene on the activated alkyne) or stepwise via a cyclopropane carbenoid intermediate (which is then stereoselectively opened by the alcohol).



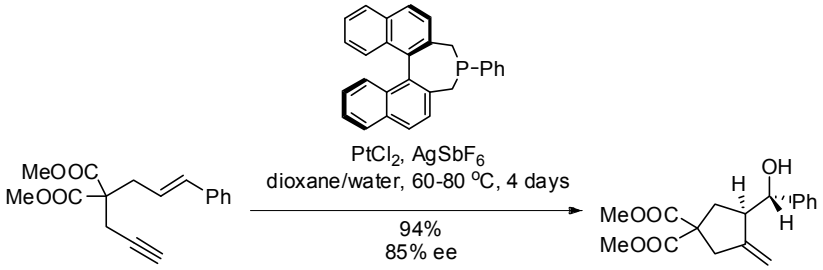
Scheme 8.20. Transition metal-catalyzed 5-*exo* alkoxycyclization of an 1,6-enyne

Various metals proved to be active in this transformation, including mercury,[281] ruthenium,[282] platinum,[283] palladium[284] and gold.[285] Oxygenated nucleophiles could be both inter- or intramolecular. Asymmetric versions have been developed as well. Scheme 8.21 shows a few representative examples.



(Eq. 1)

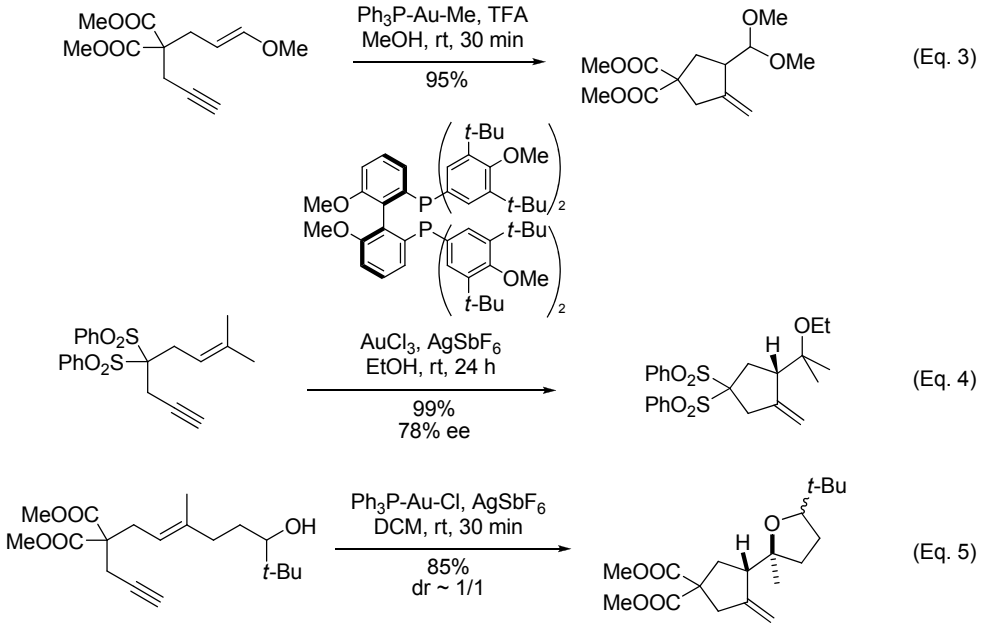
TPPTS = tris(m-sulfonatophenyl)phosphine trisodium salt



(Eq. 2)

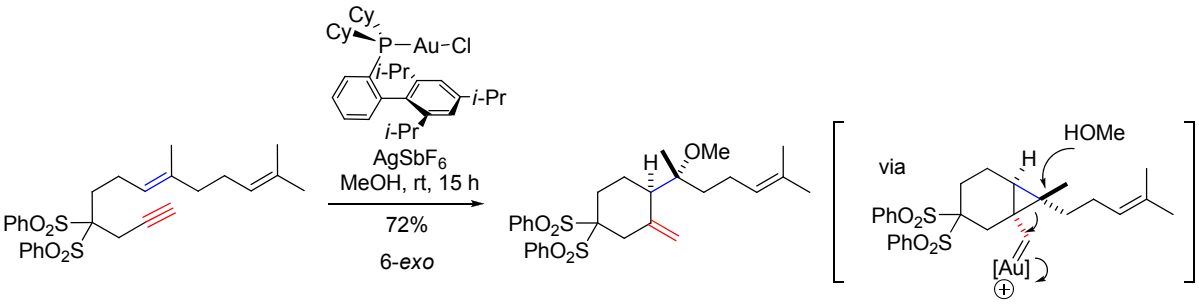
(continued on the next page)

[281] Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609-1611.
[282] Faller, J. W.; Fontaine, P. P. *J. Organomet. Chem.* **2006**, *691*, 1912-1918.
[283] Charruault, L.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2002**, *43*, 4757-4760.
[284] (a) Mendez, M.; Munoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549-11550.
(b) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627-2635.
(c) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M.-N.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, *2003*, 706-713.
(d) Mendez, M.; Munoz, M. P.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511-10520.
(e) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genet, J. P. *Chem. Commun.* **2004**, 850-851.
(f) Michelet, V.; Charruault, L.; Gladiali, S.; Genet, J. P. *Pure Appl. Chem.* **2006**, *78*, 397-407.
[285] (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.
(b) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179.
(c) Paz Munoz, M.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293-1300.
(d) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136.
(e) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.
(f) Chao, C.-M.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *J. Organomet. Chem.* **2009**, *694*, 538-545.

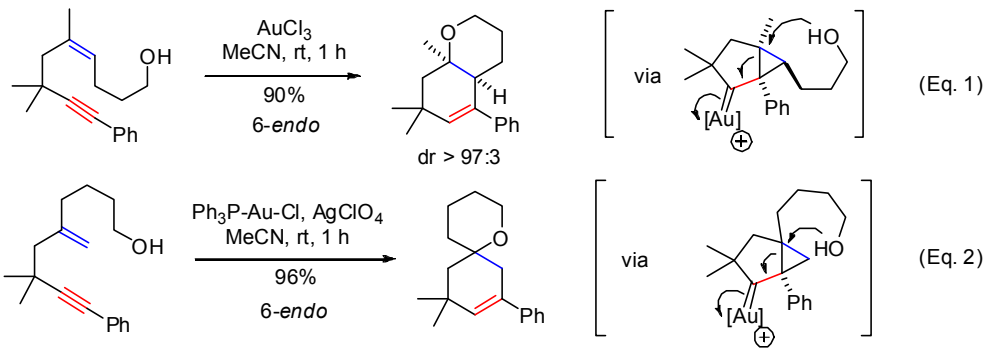


Scheme 8.21. A few examples of transition metal-catalyzed 5-*exo* hydroxy- / alkoxycyclization of 1,6-enynes

Hydroxy- / alkoxycyclization are not limited only to 1,6-enynes. Echavarren et al. showed that 1,7-enynes can undergo a gold-catalyzed 6-*exo* alkoxycyclization (Scheme 8.22),[286] while Kozmin et al. showed that 1,5-enynes can give a 6-*endo* one (Scheme 8.23).[272] Both transformations presumably proceed through a similar type of cyclopropane carbenoid intermediate.



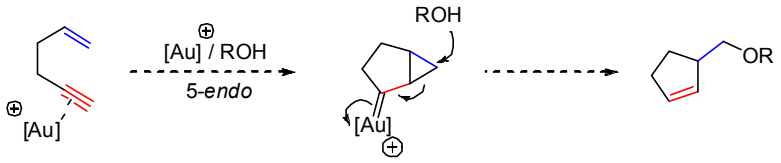
Scheme 8.22. Gold-catalyzed 6-*exo* alkoxycyclization of an 1,7-enyne



Scheme 8.23. Gold-catalyzed 6-*endo* alkoxycyclization of an 1,5-enyne

[286] Cabello, N.; Rodriguez, C.; Echavarren, A. M. *Synlett* **2007**, *2007*, 1753-1758.

Given the excellent ability of gold complexes to catalyze various cycloisomerizations and these literature precedents concerning the hydroxy- / alkoxycyclization of enynes, we surmised that a 5-*endo* alkoxycyclization of a suitably substituted 1,5-enyne would be possible. By analogy, we supposed that such an approach would lead to the formation of a cyclopropane carbenoid intermediate which upon attack of the oxygenated nucleophile would open to form a functionalized cyclopentene (Scheme 8.24).



Scheme 8.24. Our initial idea concerning the 5-*endo* alkoxycyclization of a suitably substituted 1,5-enyne

To the best of our knowledge, before the publication of our study only a single example of gold-catalyzed 5-*endo* alkoxycyclization of a 1,5-enyne had been reported by the group of Kozmin (see Scheme 8.11).[272,287] The authors attributed the curious outcome of this experiment to the strained nature of the alternative *trans*-oxabicyclo[4.4.0]decene product which was formed in all the other cases (see by comparison Scheme 8.23, Eq. 1).

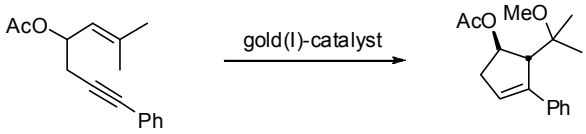
We anticipated this transformation to be highly substrate dependent, the substitution pattern in both the alkene and alkyne moieties playing a crucial role. For instance, we supposed that alkenes stabilizing a positive charge at the carbon attacked by the oxygenated nucleophile would favor our proposed 5-*endo* cyclization. Furthermore, whereas the 5-*exo* cyclization of 1,6-enynes is usually limited to terminal alkynes (see Scheme 8.20 and Scheme 8.21), we believed that in our case the transformation would be favored with internal alkynes. This approach would be very useful synthetically, as the cyclopentenes thus produced could serve as valuable precursors for the elaboration of more complex structures.

2.2. Preliminary results

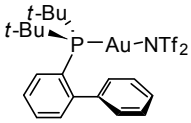
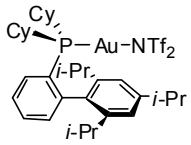
In order to validate these initial assumptions, compound **8.3**, substituted with a phenyl group at the terminal acetylenic position and trisubstituted at the double bond, was chosen as a model substrate (Table 8.1).

In a first attempt, **8.3** was treated with 1% Ph_3P-Au-NTf_2 in MeOH at rt (Table 8.1, Entry 1). The stereoselective formation of the expected cyclopentene was observed (58% isolated yield after 24 h), along with a couple of side products resulting probably from the direct methoxylation of the alkyne group.

[287] Two other gold-catalyzed 5-*endo* transformations have also been reported previously, although they involve the cyclization of alkynyl dicarbonyl compounds and respectively silyl enol ethers and not hydroxy-/ alkoxycyclization of 1,n-enynes:
(a) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 5350-5352.
(b) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991-5994.



8.3 **8.4 a**

entry	catalyst	solvent	time	yield[a]
1	Ph_3P-Au-NTf_2	MeOH	24 h	58%
2	Ad_2(*n*-Bu)P-Au-NTf_2	MeOH	24 h	64%
3	 **8.5**	MeOH	1 h	98%
4	 **8.6**	MeOH	40 min	98%
5		DCM/MeOH (10/1)	20 min	99%

Reaction conditions: substrate (1 equiv), gold(I)-catalyst (0.01 equiv), solvent (0.5 M), rt. [a] Isolated yield.

Table 8.1. Preliminary results for the gold(I)-catalyzed methoxycyclization of substrate **8.3**

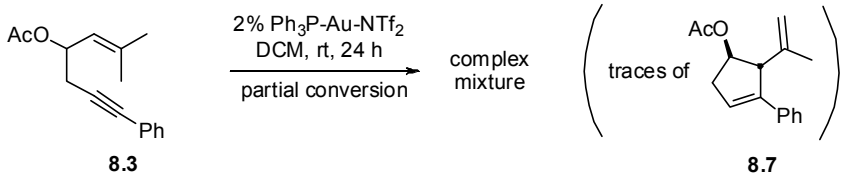
The use of the bulkier and more electron rich catalyst Ad_2(*n*-Bu)P-Au-NTf_2 led only to a slight improvement in the isolated yield of **8.4 a** (64% after 24 h, see Table 8.1, Entry 2).

Surprisingly, switching to the biphenylphosphine-based catalyst **8.5** allowed the clean and rapid formation of **8.4** in 1 h and 98% isolated yield (Table 8.1, Entry 3).

Conducting the reaction with another biphenylphosphine-based catalyst, **8.6**, gave the same isolated yield of 98% of **8.4**, while reducing the reaction time to just 40 min (Table 8.1, Entry 4). Finally performing the reaction in a DCM/MeOH 10/1 (v/v) mixture led to an even faster transformation (20 min) without any loss in efficiency (99% isolated yield, see Table 8.1, Entry 5).

In the light of these preliminary results, the experimental conditions described lastly were chosen as standard for the study of the scope of this transformation. Reducing the amount of nucleophile is advantageous not only from a reactivity point of view, but also for atom-economy considerations (especially in the case of more complicated - and more expensive - nucleophiles, as we shall see in the next section).

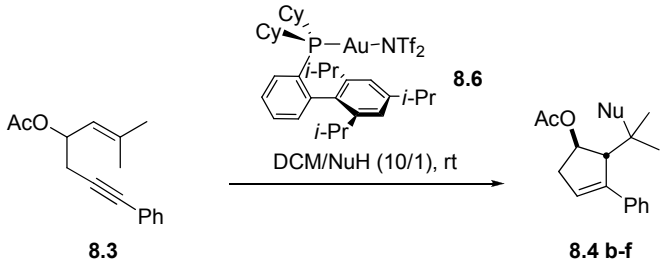
It is worth mentioning that substrate **8.3** was also tested in the absence of a nucleophile, using 2% Ph_3P-Au-NTf_2 in DCM at rt. Unfortunately, after 24 h a complex mixture of compounds was recovered, containing, amongst others, mainly starting material and traces of cyclized product **8.7** (Scheme 8.25).

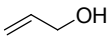
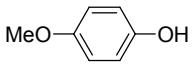
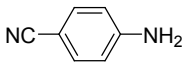


Scheme 8.25. Gold(I)-catalyzed isomerization of substrate **8.3** in the absence of a nucleophile

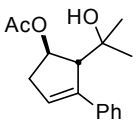
2.3. Variation of the nucleophile

We first focused our attention on the type of nucleophiles that are compatible with this transformation. Substrate **8.3** was chosen again as a model substrate and tested under the optimized conditions (1% **8.6**, DCM/nucleophile 10/1, rt). The reaction proved to be quite general, a good number of oxygenated nucleophiles being well tolerated (Table 8.2).



entry	nucleophile (NuH)	time	product	yield[a]
1		2 h	**8.4 b**	93%
2	*i*-PrOH	45 min	**8.4 c**	98%
3	CyOH	24 h	**8.4 d**	54%
4	*t*-BuOH	24 h	no reaction	-
5[b]		10 min	**8.4 e**	95%
6	AcOH	1 h 15 min	**8.4 f**	68%[c]
7[b]		24 h	no reaction	-

Reaction conditions: substrate **8.3** (1 equiv), catalyst **8.6** (0.01 equiv), DCM/nucleophile 10/1 (v/v) mixture as solvent (0.5 M), rt. [a] Isolated yield. [b] The reaction was carried out in DCM (0.5 M) with 2 equiv. of *p*-methoxyphenol. [c] Compound **8.4 g** was also isolated in 26% yield.



8.4 g

Table 8.2. Scope of the gold(I)-catalyzed alkoxycyclization of **8.3** in the presence of various nucleophiles

The reaction with allylic alcohol gave the desired functionalized cyclopentene **8.4 b** in under 2 h in a 93% isolated yield (Table 8.2, Entry 1). Excellent results were obtained also with a secondary alcohol like isopropanol, product **8.4 c** being isolated in an excellent 98% yield after just 45 min (Table 8.2, Entry 2). The transformation seems however to be sensitive to steric hindrance, since a bulkier secondary alcohol like cyclohexanol gave only a 54% yield of **8.4 d** after 24 h (Table 8.2, Entry 3). Tertiary alcohols like *tert*-butanol gave no reaction, due either to the steric hindrance or to the reduced nucleophilicity (Table 8.2, Entry 4).

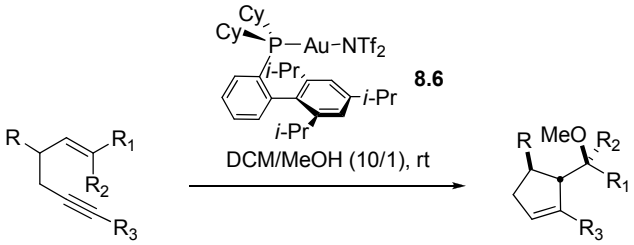
Phenols on the other hand proved to be extremely reactive, cyclopentene **8.4 e**, resulting from the reaction of **8.3** with *p*-methoxyphenol, being isolated in 10 min and an excellent 95% yield (Table 8.2, Entry 5). Since the nucleophile is crystalline in this case, DCM was used as a solvent together with 2 equivalents of *p*-methoxyphenol.

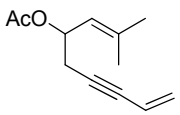
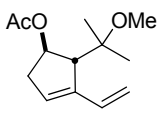
Interestingly, acetic acid was also compatible with our catalytic system, acetoxycyclopentene **8.4 f** being obtained after 1 h 15 min in 68% yield. Hydroxy-derivative **8.4 g** was also isolated in 26% yield, although its formation was probably due to adventitious water present in the acid (Table 8.2, Entry 6). Water therefore is an excellent nucleophile as well, however the gold(I)-catalyzed hydroxycyclization reactions will be discussed later in Section 2.5.

Unfortunately amines don't seem to be compatible with our catalytic system, substrate **8.3** being recovered unchanged when *p*-cyanoaniline was used a nucleophile (Table 8.2, Entry 7).

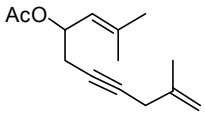
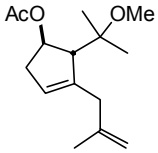
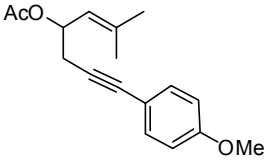
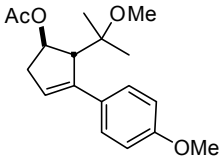
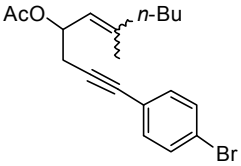
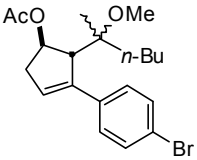
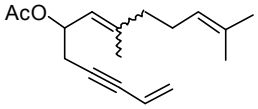
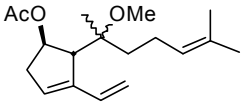
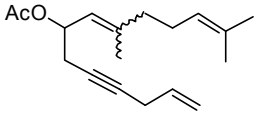
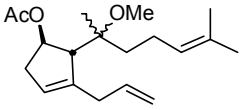
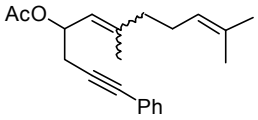
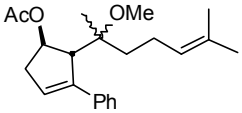
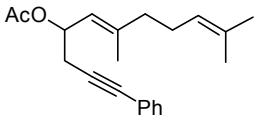
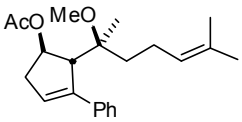
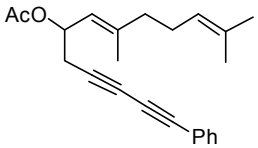
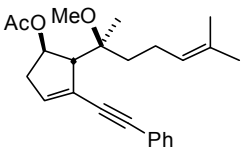
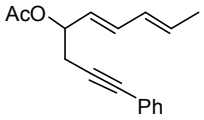
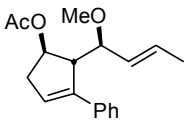
2.4. Variation of the enyne

Next we decided to continue our investigation by varying the enyne substrate. Diversely substituted enynes **8.8 a-k** were therefore synthesized and tested under the standard conditions previously developed (1% **8.6**, DCM/MeOH 10/1, rt) (Table 8.3).

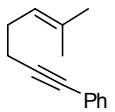
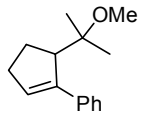


entry	substrate		product		time	yield[a]
1		**8.8 a**		**8.9 a**	1 h 20 min	77% (54%[b])

(continued in the next page)

entry	substrate		product		time	yield[a]
2		**8.8 b**		**8.9 b**	24 h	87% (75%[b])
3		**8.8 c**		**8.9 c**	20 min	93% (95%[b])
4	 *Z*/*E* ratio ~ 1/2	**8.8 d**	 dr ~ 1/2	**8.9 d**	1 h	65%
5	 *Z*/*E* ratio ~ 1/1.5	**8.8 e**	 dr ~ 1/1.5	**8.9 e**	6 h	78%
6	 *Z*/*E* ratio ~ 1/2	**8.8 f**	 dr ~ 1/1.5	**8.9 f**	6 h	64%
7	 *Z*/*E* ratio ~ 1/1.5	**8.8 g**	 dr ~ 1/1.5	**8.9 g**	1 h	90%
8		**8.8 h**		**8.9 h**	1 h	98%
9[c]		**8.8 i**		**8.9 i**	1 h	72%
10		**8.8 j**		**8.9 j**	1 h	87%

(continued on the next page)

entry	substrate		product		time	yield[a]
11		**8.8 k**		**8.9 k**	1 h	92%

Reaction conditions: substrate (1 equiv), catalyst **8.6** (0.01 equiv), DCM/MeOH 10/1 (v/v) mixture as solvent (0.5 M), rt. [a] Isolated yield. [b] Isolated yield when MeOH was used as a solvent (0.5 M). [c] Reaction performed at 40 °C.

Table 8.3. Scope of the gold(I)-catalyzed methoxycyclization of enynes **8.8 a-k**

We were delighted to observe that our transformation is not limited to phenyl-substituted alkynes or trisubstituted alkenes. Products **8.9 a-k** were obtained with a remarkable control of the stereochemistry and good yields varying from 64% to 98%. The reaction times varied between 20 min and 24 h.

Vinyl substituents at the triple bond were well compatible with our transformation. Substrates **8.8 a** and **e** led to the formation of 1,3-diene derivatives **8.9 a** and **e** with 77% and respectively 78% yields (Table 8.3, Entries 1 and 5). The same goes for the allyl (**8.8 f**) or methallyl (**8.8 b**) groups, which underwent alkoxycyclization to give cyclopentenes **8.9 f** and **b** in 87% and respectively 64% yields (Table 8.3, Entries 6 and 2).

Functionalized aryls, substituted with electron donating (**8.8 c**) or electron withdrawing groups (**8.8 d**), proved to be also excellent substituents for the alkyne moiety (Table 8.3, Entries 3 and 4). They furnished the expected cyclopentenes **8.9 c** and **d** in good yields, although the transformation of the *p*-bromophenyl-substitued derivative **8.8 d** seemed to be slightly less effective (64% isolated yield compared with 93% in the case of **8.8 c**).

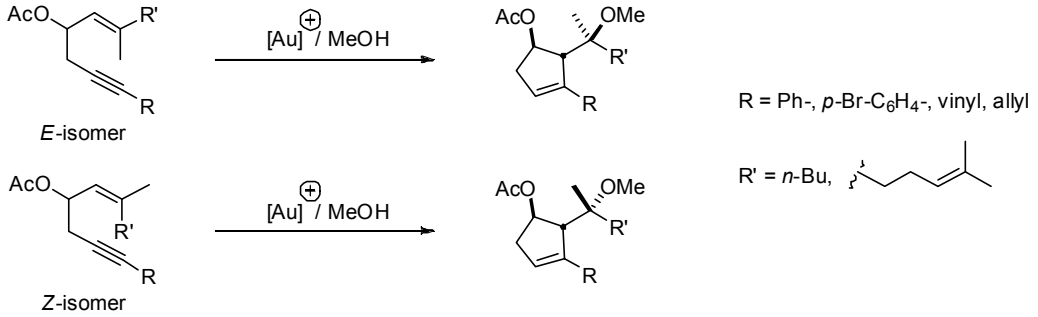
Plain phenyl-substituted derivative **8.8 g** converted cleanly into derivative **8.9 g** in a 90% yield (Table 8.3, Entry 7).

In the case of enynes **8.8 a-c**, the transformation was also attempted using MeOH directly as a solvent (Table 8.3, Entries 1-3). As expected, the isolated yields of the desired cyclopentenes **8.9 a-c** were generally lower or equivalent at the most with those obtained using the binary mixture DCM/MeOH 10/1 (v/v).

The stereoselectivity of this transformation was remarkable. NMR experiments proved that the acetate group and the side chain found in the vicinal position were always in a *trans*-relationship (Table 8.3, Entries 1-10).

Furthermore, the stereoisomeric *E*/*Z* ratio of the starting compounds **8.8 d-g** was found to be identical with the diastereoisomeric ratio of the final products **8.9 d-g** (Table 8.3, Entries 4-7). Each of the 2 diastereoisomers of cyclopentenes **8.9 d-g**, obtained in a mixture as mentioned previously, could also be separated and characterized.

Our assumption was that the *E*-isomer furnished exclusively one diastereoisomer, while the *Z*-isomer furnished exclusively the other (Scheme 8.26).



Scheme 8.26. Stereoselective transformation of the *E*- or *Z*-isomers into the corresponding diastereoisomers

In order to validate this hypothesis, enyne **8.8 h**, obtained as a pure *E*-isomer, was tested in the same reaction conditions. Gratifyingly, cyclopentene **8.9 h** was obtained as a single diastereoisomer with an excellent yield of 98% (Table 8.3, Entry 8).

An alkyne substituent is another type of substitution well tolerated at the triple bond. Diyne **8.8 i** furnished cyclopentene **8.9 i** as a single diastereoisomer in a 72% isolated yield, although the transformation needed reflux conditions to achieve full conversion (Table 8.3, Entry 9).

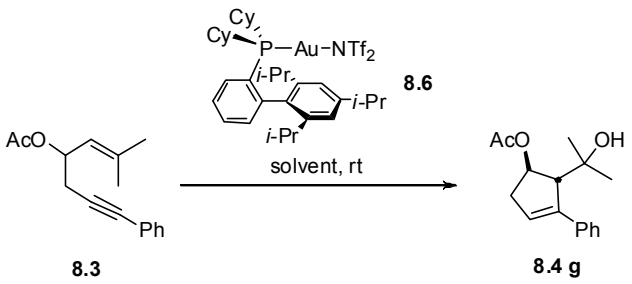
Next we focused our attention on the alkene moiety. As mentioned earlier, it was interesting to see whether a trisubstituted alkene was required for our transformation or a vicinal disubstituted one could be compatible as well. Substrate **8.8 j** was tested under standard conditions and afforded stereoselectively cyclopentene **8.9 j** (87% isolated yield, Table 8.3, Entry 10). No isomerization of the second double bond was observed.

Finally, given the importance of the acetate group (which seems to be directing the stereochemistry of the final product), we were wondering if its presence was really necessary. We were pleased to observe that simple enyne substrate **8.8 k** underwent rapid alkoxycyclization, giving the expected product **8.9 k** (Table 8.3, Entry 11).

2.5. Gold(I)-catalyzed hydroxycyclization reactions

We knew from the results presented in Table 8.2, Entry 6 that water can be an excellent nucleophile for this transformation, competing with less nucleophilic agents like acetic acid. Therefore we began exploring the scope of the hydroxycyclization transformation with a short optimization of the reaction conditions. Substrate **8.3** was chosen again as model substrate.

Using "wet" DCM (obtained by extraction of DCM from a binary DCM/H_2O mixture using a separatory funnel) in the presence of 1% **8.6** at rt led to the degradation of the starting material, a complex mixture of products being obtained (Table 8.4, Entry 1). Switching to an acetone/water 10/1 (v/v) mixture, the expected hydroxy derivative **8.4 g** was obtained in 24 h with a 99% isolated yield (Table 8.4, Entry 2). The best results were obtained with a ternary mixture DCM/acetone/water 8/2/1 (v/v/v), final product **8.4 g** being obtained quantitatively in less than 4 h 30 min (Table 8.4, Entry 3).

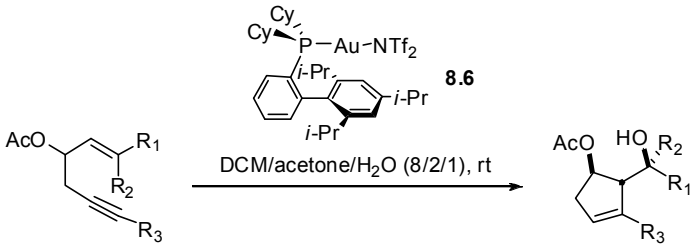


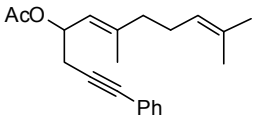
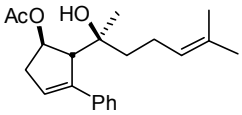
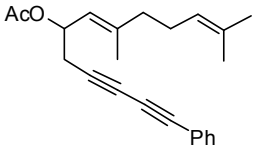
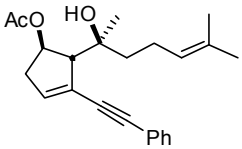
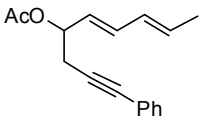
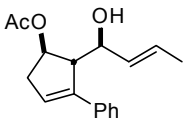
entry	solvent	time	yield[a]
1	"wet" DCM	24 h	complex mixture
2	acetone/water 10/1	24 h	99%
3	DCM/acetone/water 8/2/1	4 h 30 min	quant.

Conditions: substrate **8.3** (1 equiv), catalyst **8.6** (0.01 equiv), solvent (0.5 M), rt. [a] Isolated yields.

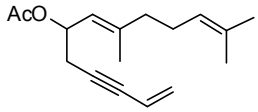
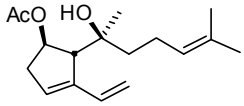
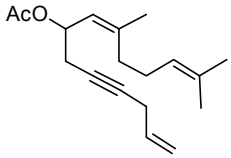
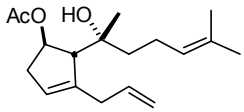
Table 8.4. Preliminary results for the gold(I)-catalyzed hydroxycyclization of substrate **8.3**

Enynes **8.8 h-j**, previously used to demonstrate the scope of the alkoxycyclization (see Table 8.3, Entries 8-10), were submitted to the optimized conditions described in the Table 8.4, Entry 3. The corresponding functionalized cyclopentenes **8.10 a-c** were obtained in excellent yields varying from 82% to 97% (Table 8.5, Entries 1-3).



entry	substrate		product		time	yield[a]
1		**8.8 h**		**8.10 a**	1 h	94%
2		**8.8 i**		**8.10 b**	2 h 30 min	97%
3		**8.8 j**		**8.10 c**	1 h	82%

(continued on the next page)

entry	substrate		product		time	yield[a]
4		**8.8 l**		**8.10 d**	2 h	91%[b]
5		**8.8 m**		**8.10 e**	24 h	92%[b,c]

Conditions: substrate (1 equiv), catalyst **8.6** (0.01 equiv), DCM/acetone/water 8/2/1 (v/v/v) mixture as a solvent (0.5 M), rt. [a] Isolated yields. [b] Reaction carried out using 2% **8.6**. [c] The reaction was heated at reflux.

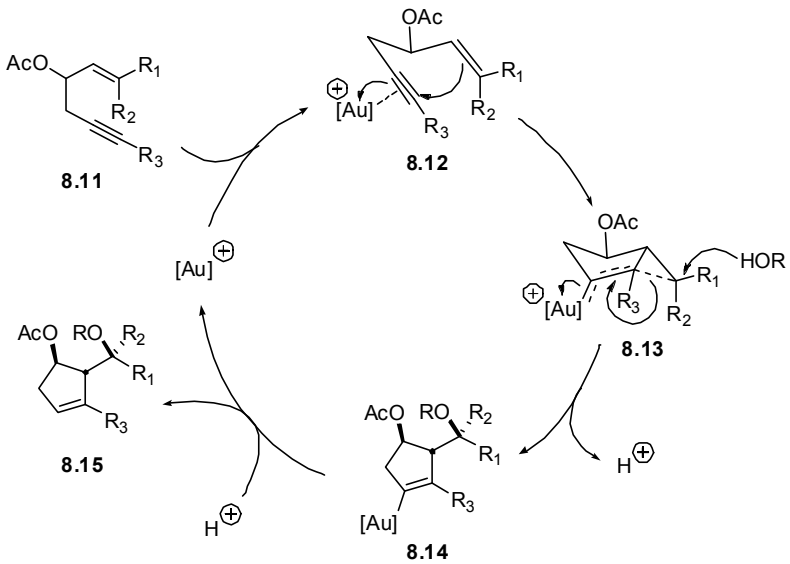
Table 8.5. Scope of the gold(I)-catalyzed hydroxycyclization reaction

Enynes **8.8 l** and **m**, on the other hand, needed a slightly higher loading of catalyst (2% of **8.6**) in order to achieve full conversion. Products **8.10 d** and **e** were obtained in 91% and respectively 92% yields (Table 8.5, Entries 4 and 5).

All these transformations proved to be highly stereoselective, products **8.10 a-e** being obtained as single diastereoisomers.

2.6. Mechanistic proposal

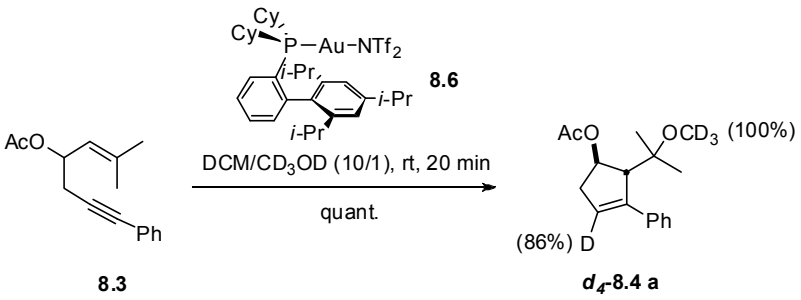
Based on these experimental observations, a mechanism accounting for the stereoselective formation of functionalized cyclopentenes is proposed in Scheme 8.27.



Scheme 8.27. Mechanistic proposal for the gold(I)-catalyzed formation of functionalized cyclopentenes **8.15**

First, the triple bond in enyne **8.11** is selectively activated by the gold catalyst's active species towards the nucleophilic addition of the alkene moiety. The cationic gold intermediate **8.13** is thus formed.[288] A subsequent regio- and stereoselective attack of the oxygenated nucleophile opens the cyclopropane ring, leading to the formation of vinyl gold intermediate **8.14**. Finally, a fast protodemetallation step gives the expected functionalized cyclopentene **8.15** and regenerates the gold catalyst.

This mechanism is supported by a deuterium-labeling experiment performed using substrate **8.3** in the presence of 1% **8.6** in a DCM/CD_3OD 10/1 (v/v) mixture at rt. The obtained product ***d*$_4$-8.4 a** shows incorporation of deuterium at the double bond position vicinal to the phenyl group (Scheme 8.28).

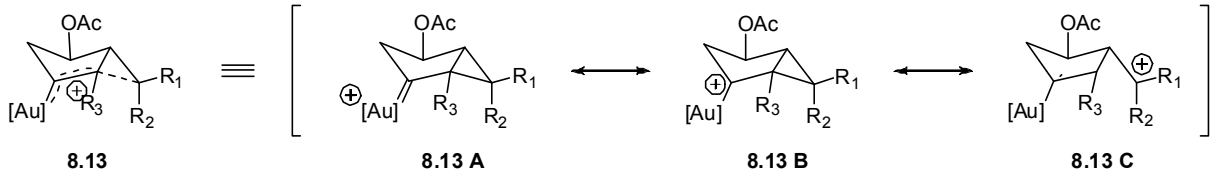


Scheme 8.28. Deuterium-labeling experiment supporting the proposed mechanism

The stereoselectivity of this transformation may be explained by a pseudo-chair transition state corresponding to **8.13**, in which the acetate group occupies a pseudoequatorial position. This induces the *trans*-relationship between the acetate and the vicinal side-chain observed in the final product **8.15**.

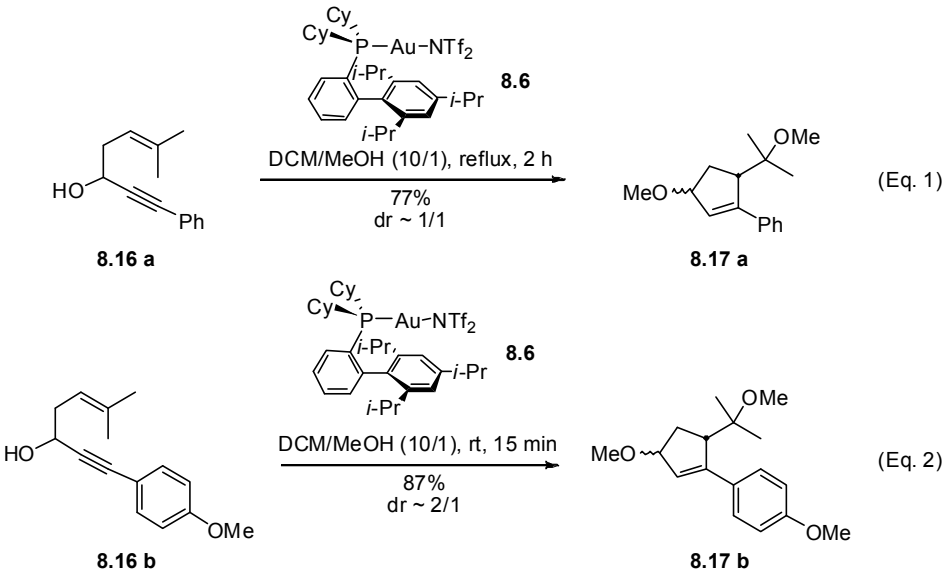
The exclusive formation of cyclopentenes could be attributed to the substitution pattern on the cyclopropane moiety in intermediate **8.13**. Upon the regioselective attack of the nucleophile at the terminal carbon of the alkene, the weakest bond in the cyclopropane ring will be cleaved. The attack takes place from the opposite side of the bond to be broken, with inversion of stereochemistry. The complete transfer of steric information from the *Z*- or *E*-substituted alkenes to the cyclopentene **8.15** arises from both the configurational stability of gold intermediate **8.13** and the rapid attack of the nucleophile.

[288] We believe that the cationic gold intermediate **8.13** is probably best depicted as in Scheme 8.27, with the positive charge delocalized on the gold atom and three other carbon atoms. However, it can also be described as one of its three limit forms with a localized charge: the cyclopropane gold carbene **8.13 A** (very often in the literature it appears under this form, although it is not a true carbene derivative, but more of a carbenoid derivative), the form **8.13 B** (which accounts for the existence of a positive charge at the carbon atom linked to gold, stabilized by the metal by backdonation), or the homoallylic tertiary carbocation **8.13 C** (which explains the regioselective attack of the oxygenated nucleophile at this position of the cyclopropane). Depending on the transformation in which **8.13** is involved, one form might describe better than the others the observed reactivity.



2.7. Other examples

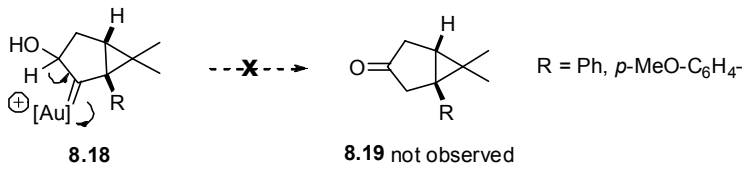
The methoxycyclization reaction was also applied to alcohols **8.16 a** and **b**. To our surprise, products **8.17 a** and **b**, possessing not one, but two methoxy groups, were obtained as a mixture of diastereoisomers in 77% and respectively 87% isolated yields (Scheme 8.29).



Scheme 8.29. Gold(I)-catalyzed methoxycyclization of substrates **8.16 a** and **b**

The introduction of an additional methoxy unit might result from a non-selective gold-catalyzed substitution of the intermediate acid-sensitive allylic alcohol by methanol. An alternative gold-catalyzed propargylic substitution might be envisaged as well.[289]

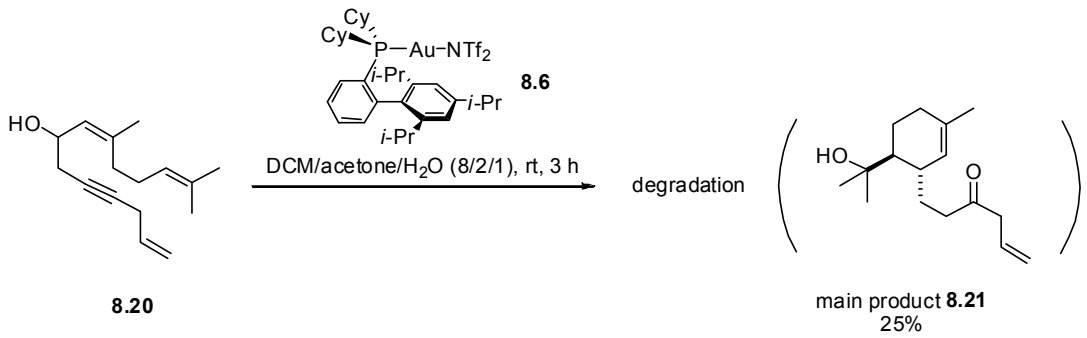
No competitive formation of the bicyclo[3.1.0]hexanone **8.19**, resulting from a 1,2-hydride shift of the intermediate cyclopropane gold carbenoid **8.18**, was observed.[290] This result confirms the rapid nucleophilic attack of the methanol (Scheme 8.30).



Scheme 8.30. The competitive formation of the bicyclo[3.1.0]hexanone **8.19** was not observed

Testing the unprotected alcohol **8.20** under standard hydroxycyclization conditions (1% **8.6**, DCM/acetone/water 8/2/1, rt) led to the degradation of the starting material. However, cyclohexene derivative **8.21** could be isolated as a main product in a modest 25% yield along with other side-products (Scheme 8.31).

[289] For a similar transformation, see: Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180-14181.
[290] For related transformations, see references 274 a and c.



Scheme 8.31. Unsuccessful attempt to hydroxycyclize substrate **8.20**

2.8. Extension to the formation of bicyclic products

5,7- and 5,8-fused bicyclic moieties are often encountered in natural products. Figure 8.3 shows two examples of terpenes containing such a structural motif.[291]

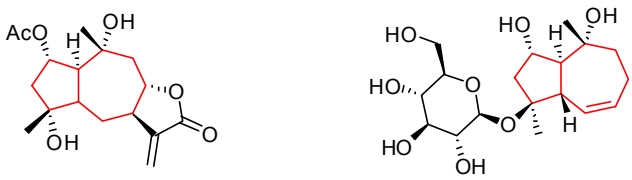


Figure 8.3. Two examples of natural terpenes containing a 5,7-fused bicyclic moiety

Given the fact that cyclopentenes such as **8.9 e**, **8.9 f** or **8.10 d** possess two side chains each containing an alkene functionality, we surmised that a ring-closing metathesis reaction might lead to the formation of bicyclic compounds.

On one hand, such an approach would confirm the relative configuration of the stereocenter bearing the methoxy substituent. On the other hand, this transformation would further extend the synthetic potential of our transformation.

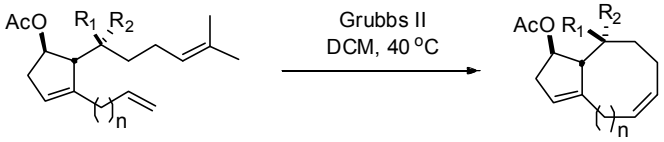
Ring-closing metathesis trials were conducted in classical conditions, using 10% of the Grubbs II catalyst in DCM at reflux (Table 8.6).

Gratifyingly, substrates **major 8.9 e**, **minor 8.9 e** and **major 8.9 f** converted quantitatively into bicyclic compounds **8.22 a-c** in less than 1 h (Table 8.6, Entries 1-3).

The cyclization of substrate **8.10 d**, possessing a free alcohol group, was considerably slower. Product **8.22 d** could however be isolated in a quantitative manner after 30 h (Table 8.6, Entry 4).

NMR analysis of the obtained bicyclic products **8.22 a-d** confirmed unequivocally their relative configuration.

[291] (a) Willuhn, G.; Skibinski, A.; Schmidt, T. J. *Planta Med.* **1998**, *64*, 635-639.
(b) Zhao, W.; Wolfender, J.-L.; Hostettmann, K.; Hong-Yu, L.; Stoeckli-Evans, H.; Rensheng, X.; Guowei, Q. *Phytochemistry* **1998**, *47*, 63-68.



entry	substrate	R_1	R_2	n	product	time	yield[a]
1	**major 8.9 e**	OMe	Me	0	**8.22 a**	1 h	quant.
2	**minor 8.9 e**	Me	OMe	0	**8.22 b**	1 h	quant.
3[b]	**major 8.9 f**	OMe	Me	1	**8.22 c**	1 h	quant.
4	**8.10 d**	OH	Me	0	**8.22 d**	30 h	quant.

Conditions: substrate (1 equiv), Grubbs II catalyst (0.1 equiv), DCM (0.03 M), rt. [a] Isolated yields. [b] Reaction carried out in DCM (0.0015 M).

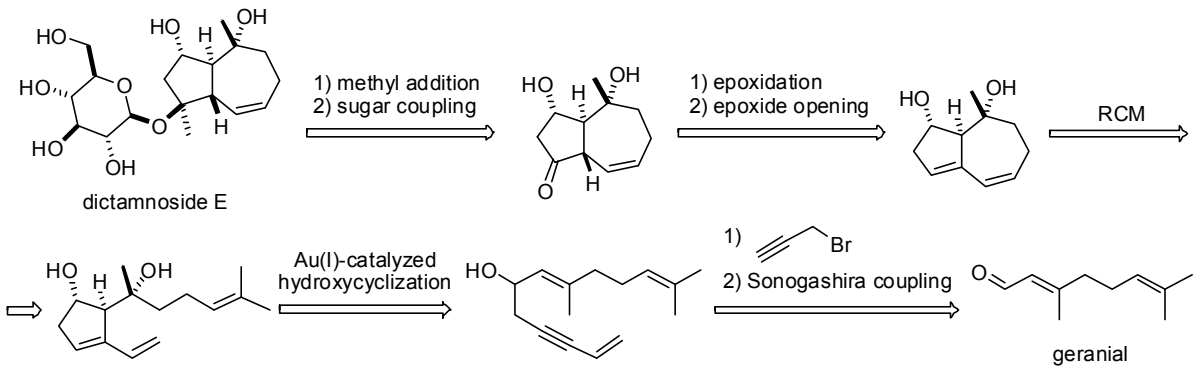
Table 8.6. Cyclization of different functionalized cyclopentenes via a ring-closing metathesis reaction

3. Conclusions and perspectives

In conclusion, we have developed an efficient and highly stereoselective process involving the 5-*endo* alkoxy- or hydroxycyclization of 1,5-enynes leading to the formation of functionalized cyclopentenes.

Among the advantages of this process we can list the low catalyst loadings employed, the mild reaction conditions, the broad reaction scope and excellent stereocontrol. Combining this cyclization with a ring-closing metathesis step increases its utility by providing complex structures frequently encountered in natural products.

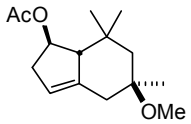
As a perspective for our work, an extension to the total synthesis of dictamnoside E, a novel sesquiterpene glycoside,[291b] is currently underway. Dr. Andrea K. Buzas and Dr. Fabien L. Gagosz have envisioned an approach starting from geranial and involving a gold(I)-hydroxycyclization of an 1,5-enyne derivative followed by a ring-closing metathesis step (see the full retrosynthetic analysis in Scheme 8.32).



Scheme 8.32. Retrosynthetic analysis for the total synthesis of dictamnoside E

Another extension of our work, concerning the formation of bicyclic oxazinanones via a gold(I)-catalyzed 1,5-enyne cyclization followed by internal nucleophilic trapping by a Boc group will be discussed in the next chapter.[292]

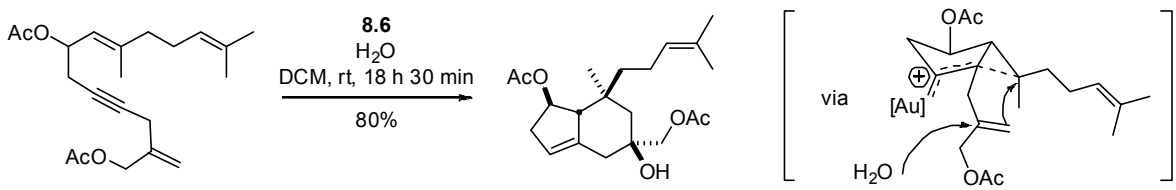
During the methoxycyclization of **8.8 b**, traces of a 5,6-fused bicyclic product **8.23** were also isolated (Figure 8.4).



8.23

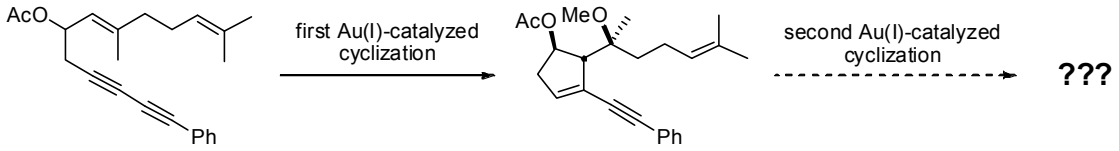
Figure 8.4. Side product observed during the methoxycyclization of enyne **8.8 b**

This led Sebastian Böhringer and Dr. Fabien L. Gagosz to the development of another transformation combining the same gold(I)-catalyzed 1,5-enyne cyclization with the internal nucleophilic trapping of the formed intermediate by the alkene moiety and the external trapping by another nucleophile (Scheme 8.33).[293]



Scheme 8.33. Extension to the formation of 5,6-fused bicyclic products

A future perspective for this transformation could be the formation of bicyclic products via a second gold(I)-catalyzed cyclization step starting from functionalized cyclopentenes like **8.9 i**, possessing both alkene and alkyne functionalities at their side chains (Scheme 8.34).



8.8 i **8.9 i**

Scheme 8.34. Extension to the formation of bicyclic products via a second gold(I)-catalyzed cyclization step

Other interesting perspectives might include the use of other nucleophiles (nitrogenated or carbonated ones for instance) or the development of an asymmetric version.

[292] Buzas, A.; Istrate, F.; Le Goff, X. F.; Odabachian, Y.; Gagosz, F. *J. Organomet. Chem.* **2009**, *694*, 515-519.
[293] Böhringer, S.; Gagosz, F. *Adv. Synth. Catal.* **2008**, *350*, 2617-2630.

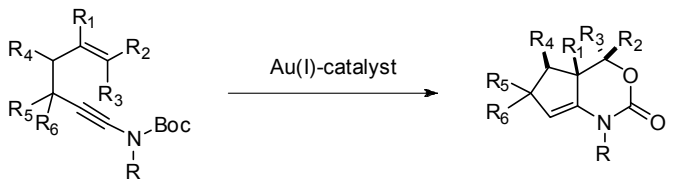
CHAPTER

9

Gold(I)-Catalyzed [4+2] Cycloaddition of *N*-(Hex-5-enynyl) *tert*-butyloxycarbamates

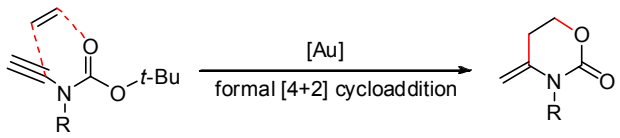
"If we knew what it was we were doing, it would not be called research, would it?"
*(**Albert Einstein**, German-born theoretical physicist, Nobel Prize winner in 1921)*

This chapter describes the formation of highly functionalized bicyclic 1,3-oxazinan-2-one derivatives via a gold(I)-catalyzed cyclization process starting from *N*-(hex-5-enynyl) *tert*-butyloxycarbamates (Scheme 3.1).



Scheme 9.1. Synthesis of highly functionalized bicyclic 1,3-oxazinan-2-one derivatives via a gold-catalyzed cyclization of *N*-(hex-5-enynyl) *tert*-butyloxycarbamates

This transformation can be described as a formal [4+2] cycloaddition between an *N*-alkynyl *tert*-butyloxycarbamate and an alkene (Scheme 9.2).



Scheme 9.2. Formal [4+2] cycloaddition between an *N*-alkynyl *tert*-butyloxycarbamate and an alkene

Although the efficiency of this transformation is rather moderate, the mild reaction conditions and the generally good stereoselectivity observed allow a rapid increase in structural complexity with the formation of two cycles, one new C-C and one new C-O bond and up to two new asymmetric centers.

In the first part of this chapter the importance of the 1,3-oxazinan-2-one moiety and a few methods used for its synthesis will be discussed briefly (section 1). The second part is dedicated to a more

detailed look on our work concerning this topic (section 2). This chapter ends with a few conclusions and perspectives (section 3).

Disclaimer:

This work was conducted under the supervision of Dr. Fabien L. Gagosz. Although a part of the experiments presented in this chapter was carried out by Dr. Andrea K. Buzas, Dr. Xavier F. Le Goff, Yann Odabachian and Dr. Fabien L. Gagosz, in order to preserve the coherence of the subject the totality of the work concerning this topic will be discussed here.

Some of these results have been previously published in:

- Andrea K. Buzas, Florin M. Istrate, Xavier F. Le Goff, Yann Odabachian, Fabien L. Gagosz* "Gold(I)-Catalyzed [4+2] Cycloaddition of *N*-(Hex-5-enynyl) *tert*-butyloxycarbamates" *J. Organomet. Chem.* **2009**, *694*, 515-519.

1. The 1,3-oxazinan-2-one moiety

1.1. Occurrence in natural products and importance of functionalized oxazinanones

Six-membered cyclic carbamate 1,3-oxazinan-2-ones (Figure 8.1) are important building blocks for the synthesis of biologically active compounds.

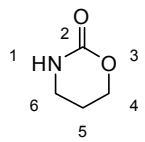
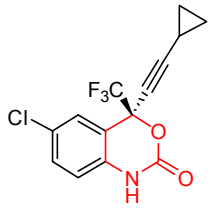


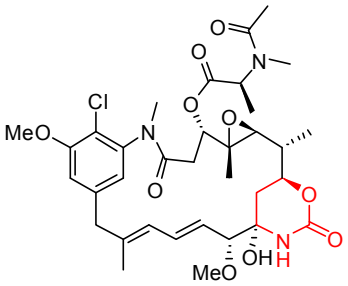
Figure 9.1. The 1,3-oxazinan-2-one moiety

These heterocycles can be encountered in a good number of natural products exhibiting a variety of pharmaceutical properties, such as efavirenz (HIV-1 inhibitor)[294] or maytansine[295] (antileukemic macrolide) and analogues (Figure 9.2).[296]

[294] Pierce, M. E.; Parsons, R. L.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C.-y.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G.; Grabowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536-8543.
[295] Larson, G. M.; Schaneberg, B. T.; Sneden, A. T. *J. Nat. Prod.* **1999**, *62*, 361-363.
[296] Cassady, J. M.; Chan, K. K.; Floss, H. G.; Leistner, E. *Chem. Pharm. Bull.* **2004**, *52*, 1-26.



efavirenz



maytansine

Figure 9.2. Two examples of natural products containing an 1,3-oxazinan-2-one moiety

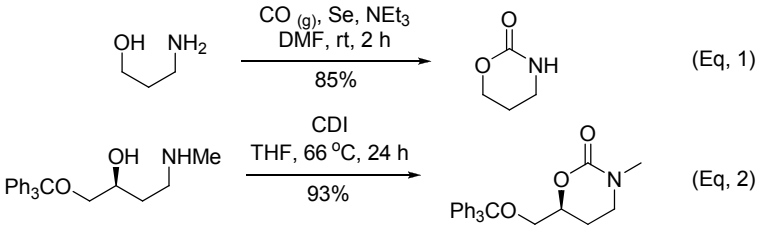
1,3-Oxazinan-2-ones can be viewed as precursors for 1,3-aminoacids and 1,3-aminoalcohols.[297] They have been employed successfully as key intermediates in Woodward's total synthesis of erythromycin A,[298] in the preparation of thrombolytics[299] and are used in liquid crystal devices.[300] Other heterocycles, such as oxazolidinones, can also be obtained starting from 1,3-oxazinan-2-ones.[301] Furthermore, they are also very useful as chiral auxiliaries[302] or protective groups in carbohydrate chemistry.[303]

1.2. Synthesis of functionalized 1,3-oxazinan-2-ones

Despite their potential applications, the number of synthetic methods used to access this type of structures is rather limited.

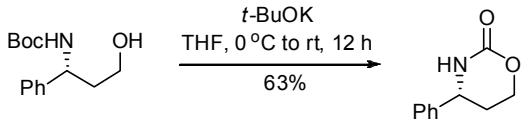
One of the most common strategies to obtain 1,3-oxazinan-2-ones involves an 1,3-aminoalcohol and a carbonylating agent, such as carbon monoxide, phosgene, diphosgene, triphosgene, 1,1'-carbonyldiimidazole etc. Scheme 9.3 shows two examples making use of CO[304] (Eq. 1) and respectively of 1,1'-carbonyldiimidazole, a less toxic and easier to handle reagent[305] (Eq. 2).

[297] Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Chem. Lett.* **1988**, 87-90.
[298] (a) Woodward, R. B.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Ward, D. E.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3213-3215.
(b) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2818-2820.
[299] Jin, F.; Confalone, P. N. 2000.
[300] Takiguchi, T.; Iwaki, T.; Tokanou, G.; Kosaka, Y.; Nakamura, S. 1997.
[301] Osa, Y.; Hikima, Y.; Sato, Y.; Takino, K.; Ida, Y.; Hirono, S.; Nagase, H. *J. Org. Chem.* **2005**, *70*, 5737-5740.
[302] Davies, S. G.; Garner, A. C.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Thomson, J. E. *Org. Biomol. Chem.* **2006**, *4*, 2753-2768.
[303] (a) Crich, D.; Wu, B. *Tetrahedron* **2008**, *64*, 2042-2047.
(b) Tanaka, H.; Ando, H.; Ishihara, H.; Koketsu, M. *Carbohydr. Res.* **2008**, *343*, 1585-1593.
[304] Sonoda, N.; Yamamoto, G.; Natsukawa, K.; Kondo, K.; Murai, S. *Tetrahedron Lett.* **1975**, *16*, 1969-1972.
[305] Ella-Menye, J.-R.; Sharma, V.; Wang, G. *J. Org. Chem.* **2005**, *70*, 463-469.



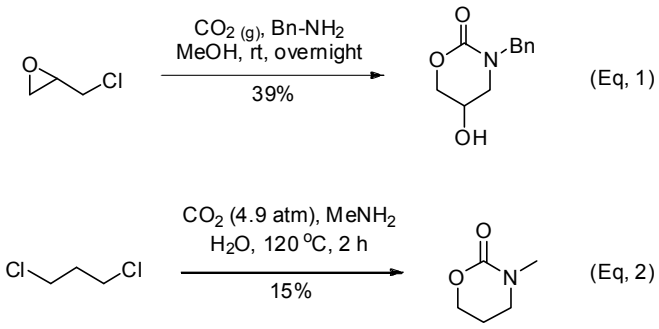
Scheme 9.3. Preparation of 1,3-oxazinan-2-ones from 1,3-aminoalcohols in the presence of a carbonylating agent

Another common strategy is based on the cyclization of *N*-carbamate 1,3-aminoalcohols.[306] Scheme 9.4 illustrates the cyclization of a *N*-*tert*-butyloxycarbonyl derivative under basic conditions.[302]



Scheme 9.4. Preparation of 1,3-oxazinan-2-ones by cyclization of *N*-carbamate 1,3-aminoalcohols

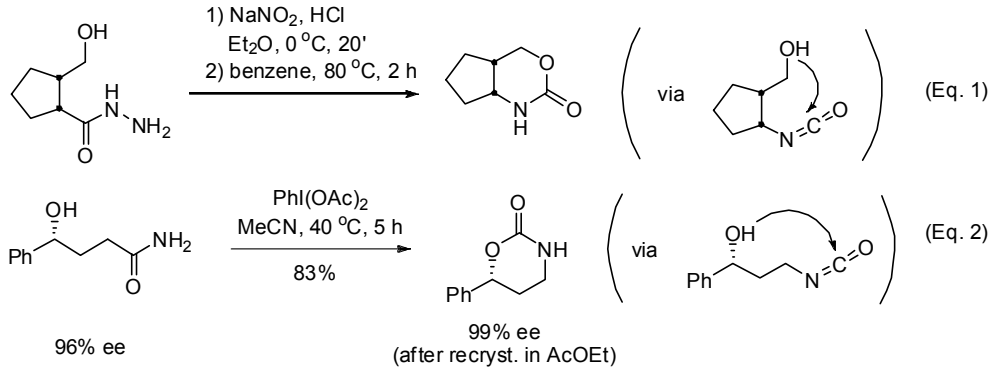
Various alternative methods, using less expensive or more eco-friendly reagents have been proposed. For instance, Nagase et al. showed that 1,3-oxazinan-2-ones can be obtained from halomethyloxiranes, primary amines, and carbon dioxide (Scheme 9.5, Eq. 1),[301] while Ikemoto proposed a large-scale process using dichloroderivatives, CO_2, and primary amines in water (idem, Eq. 2).[307]



Scheme 9.5. Other methods for the preparation of 1,3-oxazinan-2-ones

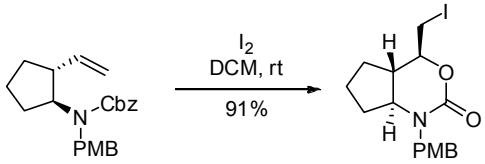
A very interesting approach consists in the intramolecular nucleophilic attack of an alcohol group on an isocyanate intermediate. These species can be obtained for instance via a Curtius (Scheme 9.6, Eq. 1)[308] or a Hofmann rearrangement (idem, Eq. 2).[309]

[306] (a) Lohray, B. B.; Baskaran, S.; Yadi Reddy, B.; Srinivas Rao, K. *Tetrahedron Lett.* **1998**, *39*, 6555-6556. (b) Ross, B. C. 1977.
[307] Ikemoto, K.; Mitsubishi Gas Chemical Co., Inc.: 2007.
[308] Cope, A. C.; LeBel, N. A. *J. Am. Chem. Soc.* **1960**, *82*, 4656-4662.
[309] Hilborn, J. W.; Lu, Z.-H.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919-8921.



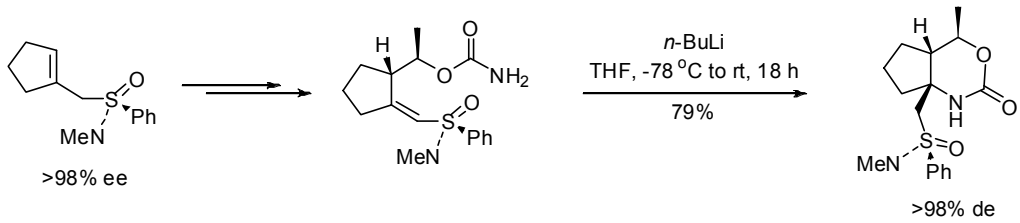
Scheme 9.6. Preparation of 1,3-oxazinan-2-ones via isocyanate intermediates

Very often employed, especially for the synthesis of chiral 1,3-oxazinan-2-ones, is also the iodocyclization of carbamate-protected homoallylic amines (Scheme 9.7).[310,297]



Scheme 9.7. Preparation of 1,3-oxazinan-2-ones by iodocyclization of carbamate-protected homoallylic amines

Finally, Gais et al. developed a stereoselective synthetic strategy based on the use of a sulfoximine auxiliary leading to highly functionalized chiral 1,3-oxazinan-2-ones (Scheme 9.8).[311]



Scheme 9.8. Stereoselective synthesis of chiral 1,3-oxazinan-2-ones

2. Our synthetic approach to functionalized 1,3-oxazinan-2-ones

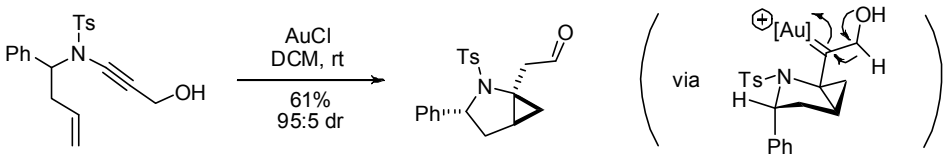
[310] (a) Jung, J.-W.; Shin, D.-Y.; Seo, S.-Y.; Kim, S.-H.; Paek, S.-M.; Jung, J.-K.; Suh, Y.-G. *Tetrahedron Lett.* **2005**, *46*, 573-575.
(b) Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7330-7335.
(c) Jordá-Gregori, J. M.; González-Rosende*, M. E.; Cava-Montesinos, P.; Sepúlveda-Arques, J.; Galeazzi, R.; Orena, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3769-3777.
[311] (a) Adrien, A.; Gais, H.-J.; Kohler, F.; Runsink, J.; Raabe, G. *Org. Lett.* **2007**, *9*, 2155-2158.
(b) Gais, H.-J.; Loo, R.; Roder, D.; Das, P.; Raabe, G. *Eur. J. Org. Chem.* **2003**, *2003*, 1500-1526.
(c) Kohler, F.; Gais, H.-J.; Raabe, G. *Org. Lett.* **2007**, *9*, 1231-1234.

2.1. Precedents in the literature. The initial idea

Ynamines and ynamides have become one of the most interesting types of alkyne derivatives, mainly due to their particular reactivity and their high synthetic potential.[146] As a consequence, a large number of transformations involving these special substrates have been developed. Most of them are catalyzed by various transition metal, such as ruthenium,[312] rhodium,[313] cobalt,[314] nickel,[313b] platinum,[315] palladium,[316] etc. and involve various cyclizations, couplings or rearrangements.

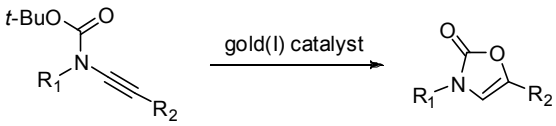
Despite the huge potential of gold catalysis in transformations involving alkyne derivatives, it is curious to see that only a couple of studies have appeared so far dealing with ynamines or ynamides in the presence of gold complexes.

The first report in this area belongs to Cossy et al., who described the diastereoselective cycloisomerization of ene-ynamides into 2-azabicyclo[3.1.0]hexanes (Scheme 9.9).[317]



Scheme 9.9. Gold-catalyzed diastereoselective cycloisomerization of ene-ynamides into 2-azabicyclo[3.1.0]hexanes

Later on, Hashmi et al.[109a] and our group[109b] described independently the formation of functionalized oxazolones starting form *N*-alkynyl *tert*-butyloxycarbamates (Scheme 9.10). This transformation has been discussed in detail in Chapter 4.



Scheme 9.10. Gold-catalyzed formation of functionalized oxazolones starting form *N*-alkynyl *tert*-butyloxycarbamates

More recently, the group of Hashmi also reported a highly effective gold-catalyzed dihydroindole formation starting from ynamides substituted with a furan ring (Scheme 9.11).[318]

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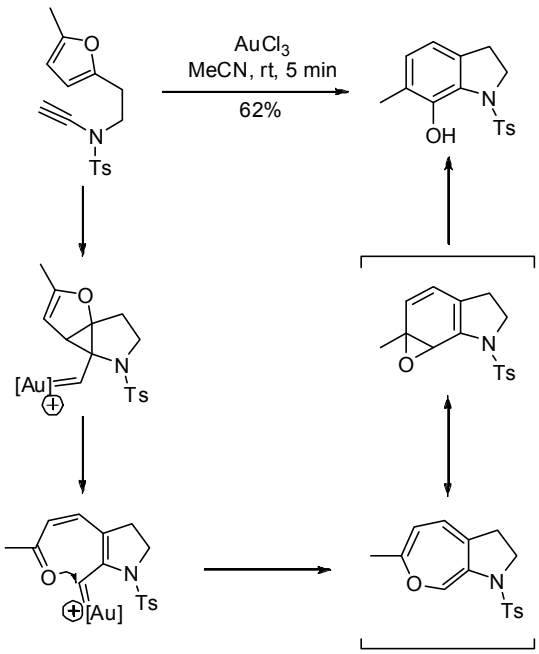
[312] (a) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681-3684.
(b) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417-2420.
(c) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803-805.
[313] (a) Witulski, B.; Alayrac, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3281-3284.
(b) Witulski, B.; Lumtscher, J.; Bergsträßer, U. *Synlett* **2003**, *2003*, 708-710.
[314] (a) Shen, L.; Hsung, R. P. *Tetrahedron Lett.* **2003**, *44*, 9353-9358.
(b) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037-2039.
[315] Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509-1511.
[316] Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Tetrahedron* **2006**, *62*, 3882-3895.
[317] Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6726-6730.
[318] Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem. Eur. J.* **2008**, *14*, 6672-6678.



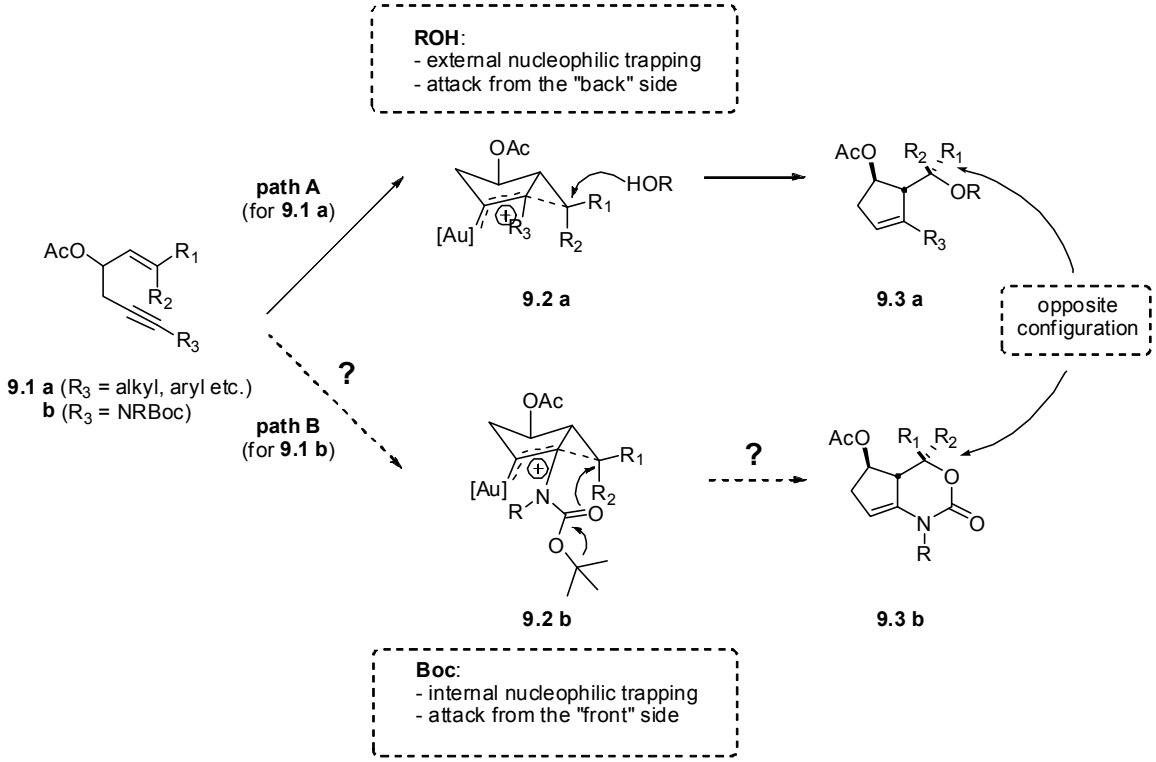
Scheme 9.11. Gold-catalyzed dihydroindole formation starting from ynamides substituted with a furan ring

Following our recent success with the alkoxy- or hydroxycyclization of 1,5-enynes into functionalized cyclopentenes described in the previous chapter,[319] we were looking for new ways to enhance the potential of this reaction. Given also our desire to develop new gold-mediated transformations involving ynamines / ynamides, we surmised that a *N*-hex-5-enynyl *tert*-butyloxycarbamate substrate **9.1 b**, possessing both an 1,5-enyne skeleton and a ynamide moiety, might be particularly interesting (Scheme 9.12).

We already saw that the previously described transformation involved the stereoselective cyclization of 1,5-enynes **9.1 a** in the presence of an external oxygenated nucleophile. It is this nucleophile that traps the cyclopropane gold intermediate **9.2 a** (here depicted as a gold-stabilized carbocationic derivative with the charge distributed over several atoms). The attack takes place from the opposite side of the bond to be broken (that is from the opposite side of the R_3 substituent) (Scheme 9.12, path A).

Our assumption was that in the case of the *N*-hex-5-enynyl *tert*-butyloxycarbamate substrate (**9.1 b**), the role of the nucleophile could be played by the Boc group. By analogy with the previously mentioned transformation, we supposed that a similar cationic intermediate **9.2 b** could be formed, which perhaps would be trapped internally by the oxygen atom of the *tert*-butyloxycarbonyl group (Scheme 9.12, path B). In this case the hypothetical nucleophilic attack can take place only from the same side as the Boc group, which means that the stereochemistry of the new stereocenter would be inverted in the final product **9.3 b** (compared with the previous final product **9.3 a**).

[319] Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1141-1144.

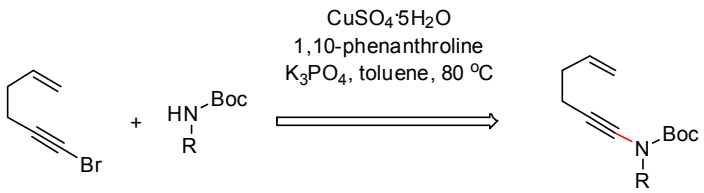


Scheme 9.12. Our initial idea (path B) compared to the previously reported formation of functionalized cyclopentenes (path A)

Such an approach would allow the stereoselective formation of bicyclic highly functionalized 1,3-oxazinan-2-one derivatives (**9.3 b**). The presence of an enamide functionality in these final cyclized products makes them very attractive building blocks and opens the way towards further transformations (such as reductions, hydrations or oxidations).

This approach would also be remarkable from a synthetic point of view, a fairly complex structure being created from a simple linear precursor. Indeed, this transformation would result in the formation of a C-C bond, a C-O bond, two cycles and up to two new stereocenters.

Furthermore, the ynamide precursors would be rather easy to access via the same copper-catalyzed coupling that was used for the formation of *N*-alkynyl *tert*-butyloxycarbamates (see Chapter 4, Section 2.2) and that proved to be well compatible with a large number of functional groups (Scheme 9.13).[320]

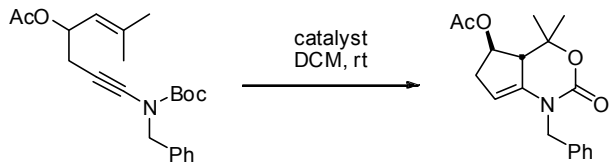


Scheme 9.13. General approach for the easy formation of our ynamide precursors

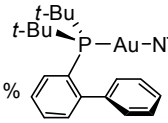
[320] The reaction conditions for this transformation are slightly modified compared to those previously reported by Hsung et al. See also ref. 147a.

2.2. Preliminary results

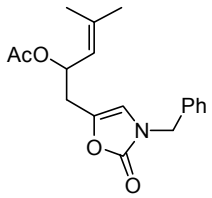
Substrate **9.4 a**, bearing a benzyl substituent at the nitrogen, was chosen as a model substrate in order to validate our approach (Table 9.1).



9.4 a **9.5 a**

entry	catalyst	time	yield[a]
1	1% Ph_3P-Au-NTf_2	30 min	68%
2	1%  **9.6**	1 h	78%
3	1% $HNTf_2$	15 min	degrad.
4	1% $AgNTf_2$	30 min	<10%[b]

Reaction conditions: substrate **9.3 a** (1 equiv), catalyst, DCM (0.1 M), rt. [a] Isolated yield. [b] Product **9.7** was also isolated in 85% yield.



9.7

Table 9.1. Preliminary results for the formation of product **9.5 a**

It was first tested in the presence of 1% Ph_3P-Au-NTf_2 in DCM at rt. We were pleased to observe the rapid formation of bicyclic product **9.5 a**, which was isolated in 68% yield after 30 min (Table 9.1, Entry 1). Using the biphenyl phosphine based catalyst **9.6,** the yield was improved to 78%, although the reaction time was slightly longer (1 h) (Table 9.1, Entry 2).

It is interesting to notice that the previously reported 5-*endo* cyclization of the *tert*-butyloxycarbonyl group on the alkyne moiety (see Scheme 9.10)[109b] did not significantly compete with this new transformation, only traces of oxazolone **9.7** being observed when gold complexes were used as catalysts. In those cases the nucleophilic attack of the alkene moiety onto the gold-activated alkyne seemed to be favored compared to the direct attack of Boc group.

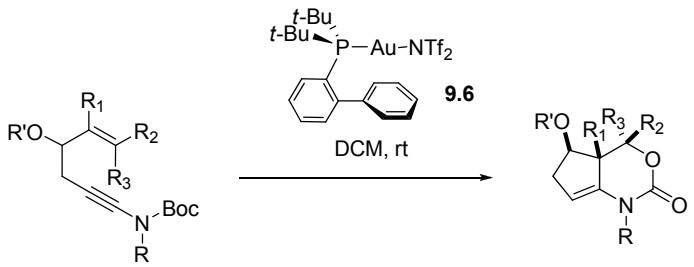
A control experiment in the presence of 1% $HNTf_2$ in DCM at rt led to the degradation of the starting material **9.4 a** in less than 15 min (Table 9.1, Entry 3). $AgNTf_2$ (1% in DCM, rt, 30 min) did not prove to

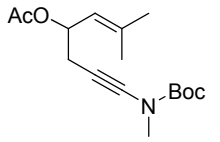
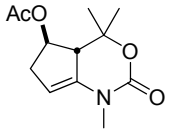
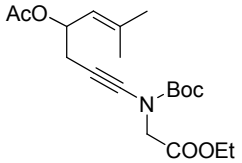
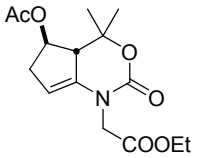
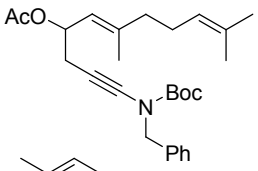
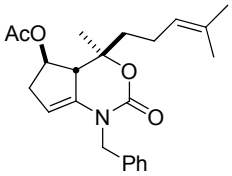
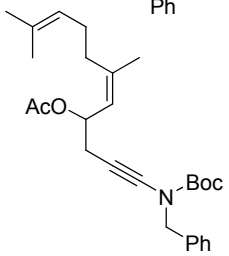
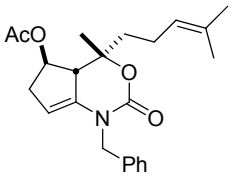
be a suitable catalyst for this transformation either, bicyclic product **9.5 a** being isolated only in a very low yield (< 10%). Oxalone **9.7** was surprisingly the major compound of this reaction, being isolated in an excellent 85% yield (Table 9.1, Entry 4).

In the light of these preliminary results, the conditions described in Table 9.1, Entry 2 (1% **9.6**, DCM, rt) were retained as standard for the study of the scope of this transformation.

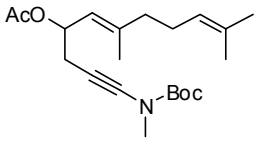
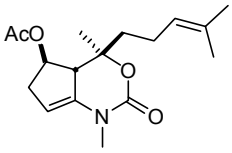
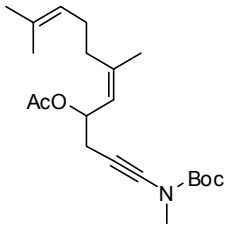
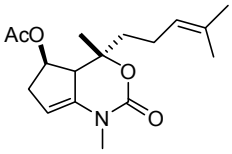
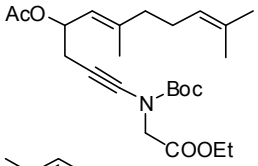
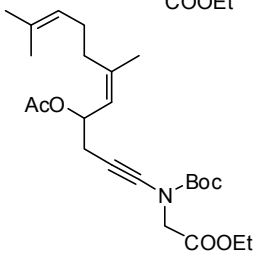
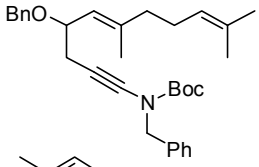
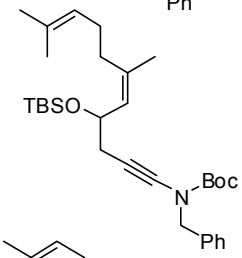
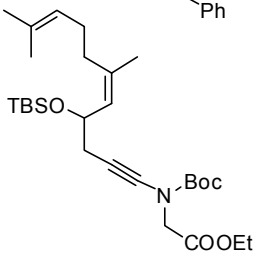
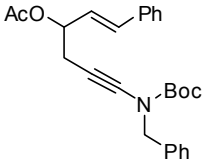
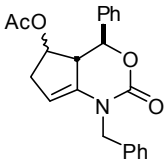
2.3. Variation of the substitutions at the nitrogen position and at the double bond

Diversely substituted *N*-hex-5-enynyl *tert*-butyloxycarbamates **9.4 b-u** were synthesized and tested under the previously optimized conditions (Table 9.2)

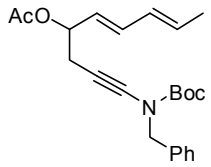
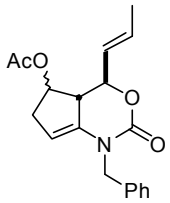
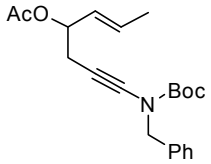
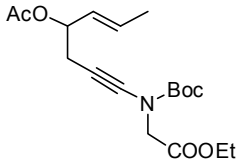
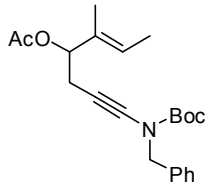
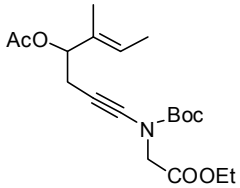
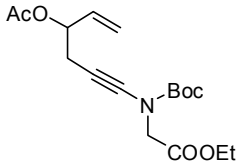


entry	substrate		product		time	yield[a]
1		**9.4 b**		**9.5 b**	22 h	68%
2		**9.4 c**		**9.5 c**	24 h	65%
3		**9.4 d**		**9.5 d**	2 h 40 min	63%
4		**9.4 e**		**9.5 e**	1 h 30 min	57%

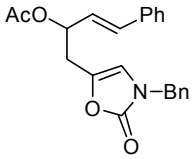
(continued on the next page)

entry	substrate		product		time	yield[a]
5		**9.4 f**		**9.5 f**	18 h	56%
6		**9.4 g**		**9.5 g**	22 h	56%
7		**9.4 h**	-		24 h	mainly SM
8		**9.4 i**	-		7 h	mainly SM
9		**9.4 j**	-		17 h	mainly SM
10		**9.4 k**	-		66 h	degrad.
11		**9.4 l**	-		24 h	degrad.
12		**9.4 m**	 dr ~1/1	**9.5 m**	15 min	47%[b]

(continued on the next page)

entry	substrate		product		time	yield[a]
13		**9.4 n**	 dr ~1.9/1	**9.5 n**	10 min	56%[c]
14		**9.4 o**	-		24 h	mainly SM
15		**9.4 p**	-		19 h	mainly SM
16		**9.4 q**	-		30 min	degrad.
17		**9.4 r**	-		7 h	mainly SM
18		**9.4 s**	-		24 h	mainly SM

Reaction conditions: substrate (1 equiv), catalyst **9.6** (0.01 equiv), DCM (0.1 M), rt. [a] Isolated yield. [b] Reaction performed using 3% **9.6**. Product **9.5 m** is obtained as a mixture of separable diastereoisomers. Side product **9.8** was also isolated in a 9% yield. [c] Reaction performed using 5% **9.6**. Product **9.5 n** is obtained as an inseparable mixture of 2 diastereoisomers, impurified with a third compound, yet unidentified. The yield and the dr are determined by ^{1}H NMR of the crude mixture.



9.8

Table 9.2. Scope of the gold(I)-transformation of *N*-hex-5-enynyl *tert*-butyloxycarbamate precursors **9.4 b-u**

Various bicyclic functionalized 1,3-oxazinan-2-ones **9.5 b-g** and **m-n** were obtained under very mild conditions with a generally good control of the stereochemistry. Unfortunately the isolated yields were rather modest (25%-68%) and the transformation proved to be compatible only with certain types of substrates.

For instance, substrates **9.4 b** and **c**, bearing a methyl group and respectively an ester derivative group at the nitrogen atom, reacted with relatively the same efficiency (Table 9.2, Entries 1 and 2) as substrate **9.4 a** (Table 9.1., Entry 2) in the presence of the gold catalyst **9.6**. The expected products **9.5 b** and **c** were isolated in respectively 68% and 65% yields, therefore proving that our transformations is tolerant towards various substitutions at the nitrogen. The reaction times, on the other hand, were considerably longer in these cases (22 h and 24 h respectively).

Just like the initial transformation of **9.4 a**, the rearrangements of **9.4 b** and **c** were highly stereoselective, affording exclusively only one diastereoisomer. The *cis* relationship between the acetoxy group and hydrogen atom at the ring junction was determined by NMR analysis and confirmed by X-ray crystallography of compound **9.5 b** (Figure 9.3).

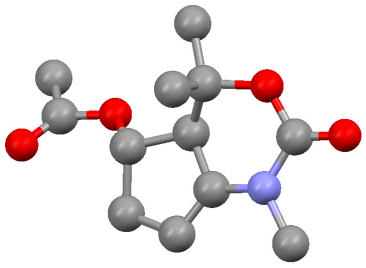


Figure 9.3. Molecular structure of **9.5 b**. Hydrogen atoms are omitted for clarity

The reaction could also be applied to substrates possessing variously trisubstituted alkene moieties. *E*/*Z*-Isomers **9.4 d** and **e**, possessing a geranyl and respectively a neryl moiety, furnished exclusively the expected bicyclic derivatives in **9.5 d** and **e** in 63% and respectively 57% yields (Table 9.2, Entries 3 and 4). The stereoselectivity of these transformations was remarkable, the original *E*/*Z*-configuration of the double bond being reflected in the configuration of the stereocenters newly formed in products **9.5 d** and **e**. Their relative configuration was determined by NMR analysis and confirmed by X-ray crystallography (Figure 9.4).

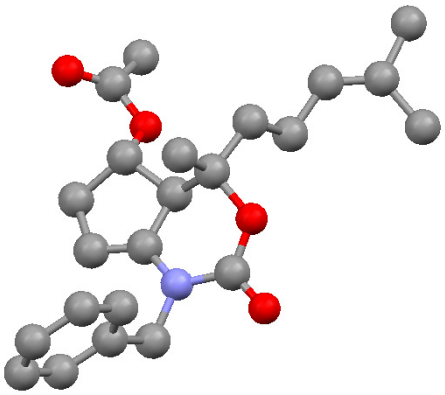


Figure 9.4. Molecular structure of **9.5 d**. Hydrogen atoms are omitted for clarity

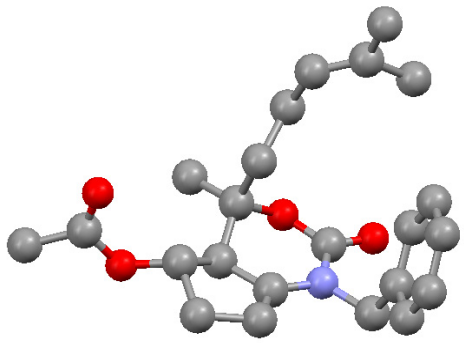


Figure 9.5. Molecular structure of **9.5 e**. Hydrogen atoms are omitted for clarity

The same goes for substrates **9.4 f** and **g**, substituted with a methyl instead of a benzyl at the nitrogen atom (Table 9.2, Entries 5 and 6). Products **9.5 f** and **g** were both isolated in a 56% yield, albeit the reaction times were also considerably longer compared to those needed for the formation of products **9.5 d** and **e** (18 h and 22 h vs. 2 h 40 min and 1 h 30 min).

Curiously, substrates **9.4 h** and **i**, possessing an ester derivative as substituent on the nitrogen atom, were recovered unreacted after 24 h and respectively 7 h (Table 9.2, Entries 7 and 8).

Our attempts to use other protective groups for the oxygen atom in the allylic position failed as well. Benzyl-protected derivative **9.4 j** gave no reaction (Table 9.2, Entry 9), while TBS-protected substrates **9.4 k** and **l** degraded (Table 9.2, Entries 10 and 11).

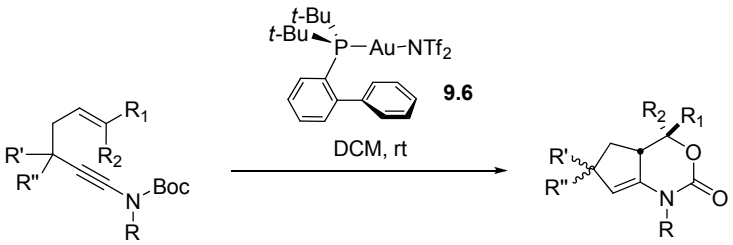
The transformation could also be performed with disubstituted alkenes possessing a cation-stabilizing substituent. For instance cinnamaldehyde derivative **9.4 m** afforded the bicyclic product **9.5 m** in 15 min and 47% estimated yield. However, the transformation needed a higher loading of catalyst (3% of **9.6**) in order to achieve full conversion of the starting material and was also less stereoselective, product **9.5 m** being obtained as a ~1/1 mixture of diastereoisomers (Table 9.2, Entry 12).

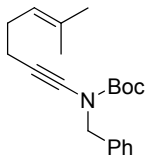
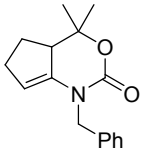
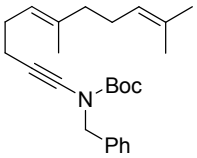
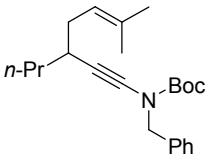
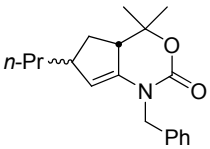
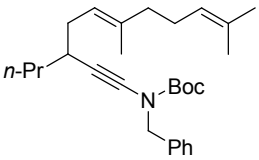
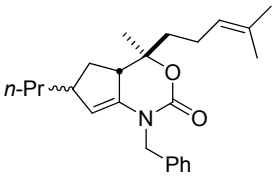
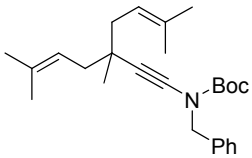
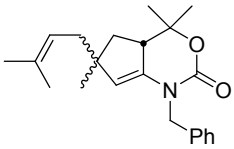
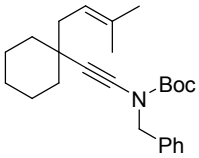
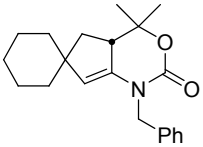
Similarly, sorbaldehyde derivative **9.4 n** gave in the presence of 5% **9.6** in less than 10 min the expected product **9.5 n** in a 56% estimated yield and a ~1/1.9 diasteroisomeric ratio (Table 9.2, Entry 13).

Sadly, the stabilization of the carbocation at the terminus of the triple bond seemed to be necessary to perform this transformation. Simply disubstituted crotyl derivatives **9.4 o** and **p** did not react under the optimized reaction conditions (Table 9.2, Entries 14 and 15). Trisubstituted tiglinaldehyde derivatives **9.4 q** and **r** are not suitable substrates either, giving degradation and respectively no reaction (Table 9.2, Entry 16 and 17). Monosubstituted alkene containing substrate **9.4 s** is also recovered unreacted at the end of the gold-catalyzed trial (Table 9.2, Entry 18).

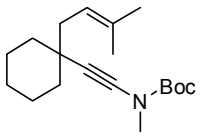
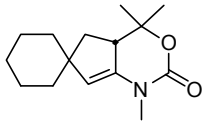
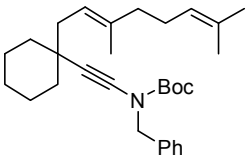
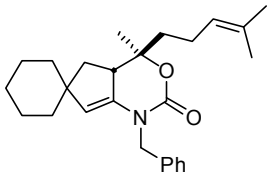
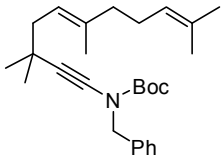
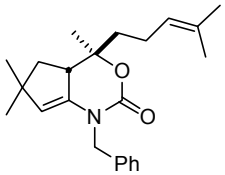
2.3. Variation of the substitutions at the propargylic positions

We next turned our attention to substrates bearing no oxygen substituent at the allylic position. Various substitutions at the propargylic position were tested (Table 9.3, Entries 1-9).

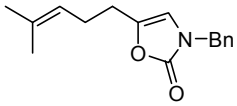


entry	substrate		product		time	yield[a]
1		**9.9 a**		**9.10 a**	1 h	40%[b]
2		**9.9 b**	-		7 h 30 min	degrad.
3		**9.9 c**	 dr ~1/1	**9.10 c**	4 h	36%[c]
4		**9.9 d**	 dr ~ 1/1.1	**9.10 d**	7 h 30 min	37%
5		**9.9 e**	 dr ~1/1.4	**9.10 e**	45 min	39%[d]
6		**9.9 f**		**9.10 f**	1 h	26%[e]

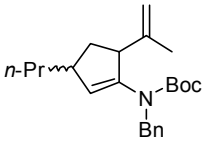
(continued on the next page)

entry	substrate		product		time	yield[a]
7		**9.9 g**		**9.10 g**	2 h	30%[f]
8		**9.9 h**		**9.10 h**	1 h 30 min	25%
9		**9.9 i**		**9.10 i**	1 h	39%

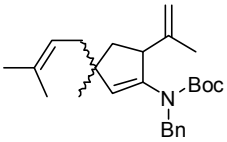
Reaction conditions: substrate (1 equiv), catalyst **9.6** (0.01 equiv), DCM (0.1 M), rt. [a] Isolated yield. dr determined by ^{1}H NMR. [b] Side product **9.11** was also isolated in a 5% yield. [c] Product **9.12 c** was also isolated in a 26% yield (dr ~ 1/2.3). [d] Product **9.12 e** was also isolated in a 16% yield (dr ~ 1/1). [e] Product **9.12 f** was also isolated in a 17% yield. [f] Product **9.12 g** was also isolated in a 36% yield.



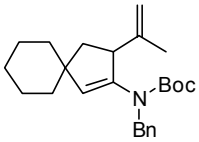
9.11



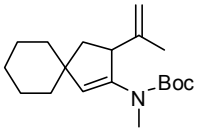
9.12 c



9.12 e



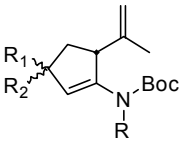
9.12 f



9.12 g

Table 9.3. Scope of the gold(I)-transformation of *N*-hex-5-enynyl *tert*-butyloxycarbamate precursors **9.10 a-i**

The expected final products **9.10 a-i** were formed in yields varying between 25% and 40% (45 min to 7 h 30 min reaction times). These rather modest results may be attributed, amongst other factors, to the competitive formation of monocyclic derivatives like **9.12** (Figure 9.6). Although traces of such products were sometimes (but not always) observed in the case of acetate substituted substrates **9.4 a-s** (Table 9.2), their formation seems to be favored in the case of substrates **9.9 a-i** (Table 9.3).



9.12

(R_1, R_2) = (H,H), (*n*-Pr, H), (prenyl, Me), cyclohexyl, (Me, Me)
R = Bn, Me

Figure 9.6. Side product observed sometimes during the gold catalyzed transformation of *N*-hex-5-enynyl *tert*-butyloxycarbamates

Simple derivative **9.9 a** gave the expected final product **9.10 a** in 1 h and 40% isolated yield (Table 9.3, Entry 1). In this case the formation of various side products was observed, including that of compound **9.11**, which was isolated in 5% yield.

Unfortunately derivative **9.9 b** degraded under the same reaction conditions, only traces of **9.10 b** being observed (Table 9.3, Entry 2).

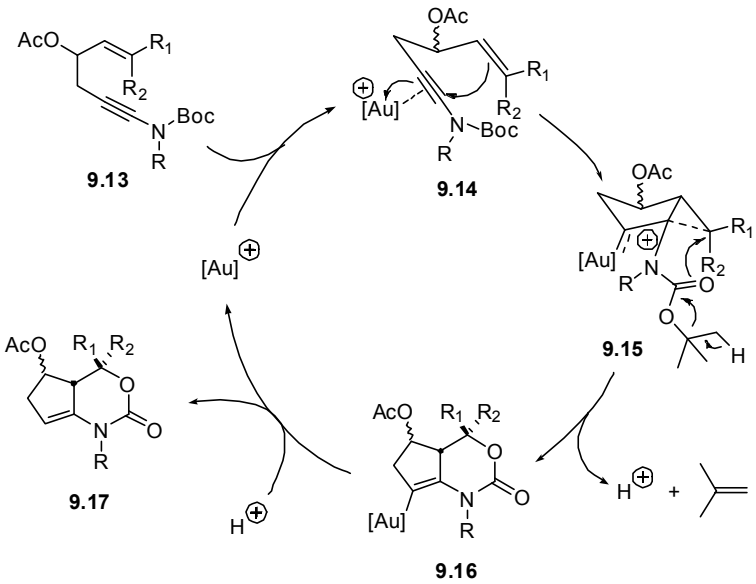
The substituent at the propargylic position exerted less stereocontrol on the stereochemistry of the final products. For instance, enynes **9.9 c** and **d**, monosubstituted with a *n*-propyl group, afforded the 1,3-oxazinan-2-ones **9.10 c** and **d** as ~1/1 and respectively ~1/1.1 mixtures of diastereoisomers (36% and respectively 37% isolated yields) (Table 9.3, Entries 3 and 4).

Similarly, substrate **9.9 e**, disubstituted with a methyl and a prenyl group, gave **9.10 e** as a ~1/1.4 mixture of diastereoisomers and 39% isolated yield (Table 9.3, Entry 5).

Finally, symmetrically substituted substrates **9.9 f-h** (with a cyclohexyl moiety) and **9.9 i** (with two methyl groups) afforded the expected products **9.10 f-i** in 26%, 30%, 25% and respectively 39% yields (Table 9.3, Entries 6-9).

2.4. Mechanistic proposal

In order to explain these experimental observations, a possible mechanism accounting for the formation of highly functionalized bicyclic 1,3-oxazinan-2-ones is proposed in Scheme 9.14.



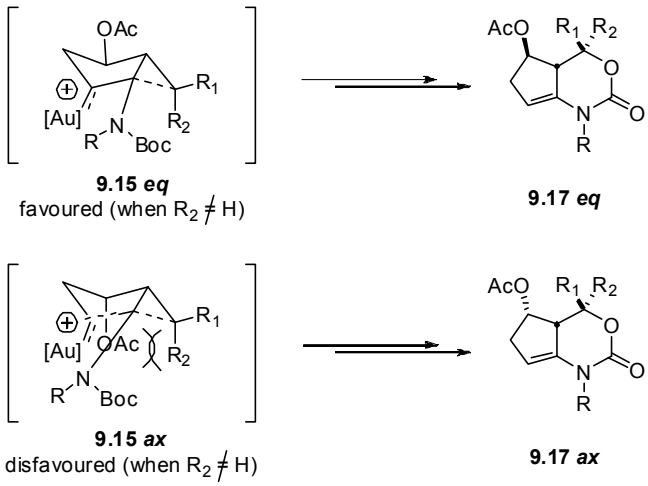
Scheme 9.14. Mechanistic proposal for the formation of highly functionalized bicyclic 1,3-oxazinan-2-ones

The active species of the gold(I) catalyst selectively activate the alkyne moiety of the starting *N*-hex-5-enynyl *tert*-butyloxycarbamate **9.13** towards the nucleophilic attack of the double bond. Cationic gold intermediate **9.15** is thus formed.[321] A subsequent nucleophilic attack of the carbonyl moiety of

[321] We believe that the cationic gold intermediate **9.15** is probably best depicted as in Scheme 9.14., with the positive charge delocalized on the gold atom and three other carbon atoms. However, it can also be described by one of its three limit forms with a localized charge: the cyclopropane gold carbene **9.15 A** (very often in the literature it appears under this form), the form **9.15 B** (with a positive charge at the carbon atom linked to gold,

the Boc group followed by fragmentation of the *tert*-butyl – oxygen bond gives the vinyl gold intermediate **9.16**. Finally, a fast protodemetallation step results in the formation of the expected functionalized 1,3-oxazinan-2-one **9.17** and regenerates the gold catalyst.

The stereoselectivity of this transformation can be explained by a pseudo-chair-like transition state, in which the acetate group can occupy either a pseudo-equatorial (as in **9.15 *eq*** in Scheme 9.15) or a pseudo-axial position (as in **9.15 *ax*** in Scheme 9.15).



Scheme 9.15. The two possible conformations of intermediate **9.15**

When the double bond is trisubstituted (R_1, R_2 ≠ H), an 1,3-diaxial steric hindrance between the acetoxy group and R_2 group disfavours the intermediate **9.15 *ax*** and favors **9.15 *eq***, leading to the exclusive formation of 1,3-oxazinan-2-one **9.17 *eq*** (with the acetate group and hydrogen atom at the ring junction in a *Z*-relationship).

When R_2 = H, the lack of a similar 1,3-diaxial interaction makes the transformation less selective and allows the competitive formation of two diastereoisomers **9.17 *eq*** and **9.17 *ax*** (for an example, see the products **9.5 m** and **n** in Table 9.2, Entries 12 and 13).

A similar argument can be proposed for the formation of products **9.10 c-e** (see Table 9.3, Entries 3-5). The absence of a strong steric interaction during the transition state of derivatives lacking an acetate group in the allylic position (and substituted at the propargylic position) makes possible the existence of two intermediates **9.18 a** and **b** and the unselective formation of two diastereoisomers **9.19 a** and **b** (Scheme 9.16).

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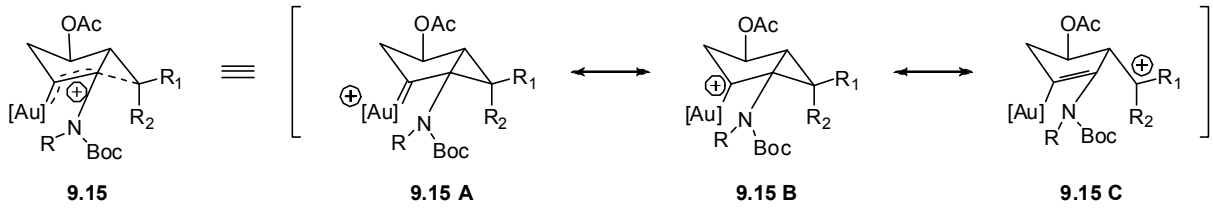
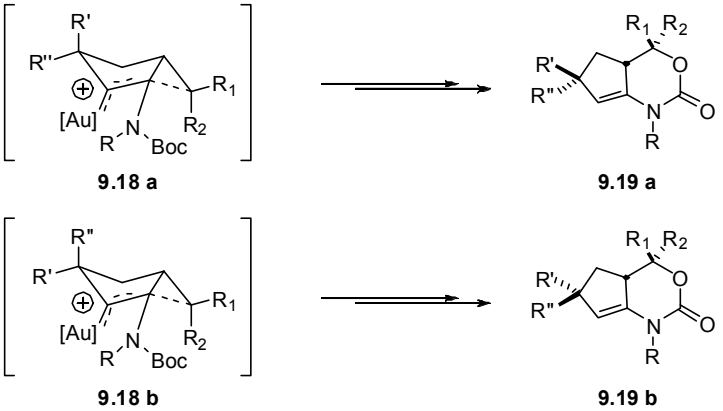
stabilized by the metal by backdonation), or the homoallylic tertiary carbocation **9.15 C** (which explains the regioselective attack of the Boc group at this position of the cyclopropane moiety). Depending on the transformation in which **9.15** is involved, one form might describe better than the others the observed reactivity.

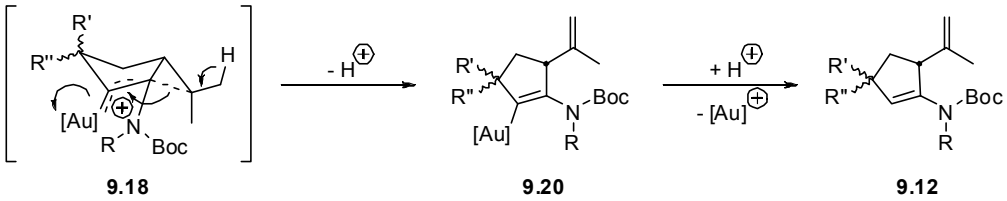




Scheme 9.16. Intermediates rationalizing the formation of the two diastereoisomers **9.19 a** and **b**

On the other hand, the nucleophilic attack of the carbonyl of the Boc group is regio- and stereoselective in all cases. It takes place exclusively at the terminal atom carbon of the alkene moiety from the same side as the carbamate group. Thanks to the configurational stability of the cationic gold intermediate **9.15** and to the rapid and stereoselective attack of the nucleophile, the steric information from the *Z*- or *E*-substituted alkenes **9.13** is completely transferred to the two newly formed stereocenters in product **9.17**.

The formation of side products **9.12** can be explained by a competitive elimination of a proton in intermediate **9.18** followed by a rapid protodemetallation step (Scheme 9.17). Further investigations are needed to fully understand the factors favoring this competitive reaction.

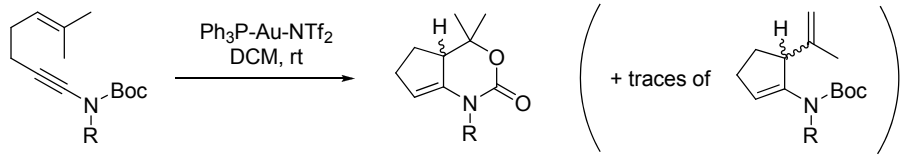


Scheme 9.17. Mechanistic proposal for the formation of side-product **9.12**

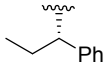
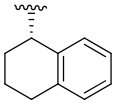
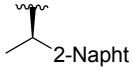
2.5. Attempts to induce asymmetry

The possibility of a diastereoselective version of this transformation, in which the asymmetry of the final product might be induced by a chiral fragment at the nitrogen atom, was also investigated.

Preliminary testing on the achiral substrate **9.9 a**, substituted at the nitrogen with a benzyl group, in the presence of 1% Ph_3P-Au-NTf_2 in DCM at rt showed that the cyclized product **9.10 a** can be obtained in a modest 46% yield (Table 9.4, Entry 1).



9.9 a, j-m **9.10 a, j-m** **9.12 a, j-m**

entry	R	substrate	time	yield[a]	dr[b]	product
1		**9.9 a**	45 min	46%	-	**9.10 a**
2		**9.9 j**	2 h 30 min	43%	~ 1/1.3	**9.10 j**
3		**9.9 k**	6 h	41%	~ 1/1.2	**9.10 k**
4		**9.9 l**	30 min	53%	~ 1/1.25	**9.10 l**
5		**9.9 m**	4 h	41%	~ 1/1.4	**9.10 m**

Reaction conditions: substrate (1 equiv), Ph_3P-Au-NTf_2 (0.01 equiv), DCM (0.1 M), rt. [a] Isolated yield. [b] dr determined by ^{1}H NMR.

Table 9.4. Attempts to develop an asymmetric version of our transformation

Unfortunately, switching to various optically pure substrates **9.9 j-m** did not improve the isolated yields of the expected 1,3-oxazinan-2-ones **9.10 j-m** (between 41%-53%). In all the cases traces of side-products **9.12 a** and **j-m** was also observed (Table 9.4, Entries 2-5).

Furthermore, the results were highly disappointing since the selectivity of the bicyclic products **9.10 j-m** was very poor (ranging form 1/1.2 to 1/1.4 for the most sterically hindered).

3. Conclusions and perspectives

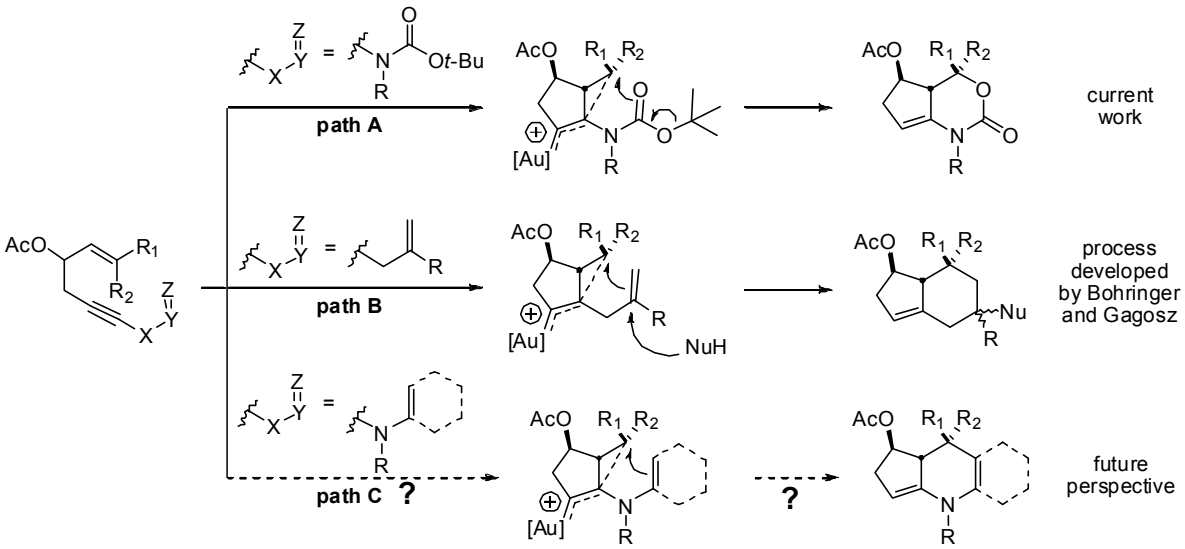
In conclusion, we have shown that highly functionalized bicyclic 1,3-oxazinan-2-one derivatives can be formed via a gold(I)-catalyzed cyclization process starting from *N*-(hex-5-enynyl) *tert*-butyloxycarbamates (Scheme 9.18, path A).

Even though the transformation is restricted only to certain types of substrates and the yields are moderate, the easily accessible substrates, the mild reaction conditions and the rapid increase in structural complexity (highly functionalized bicyclic products being obtained from linear substrates) render this transformation interesting from a synthetic point of view.

The bicyclic carbamates thus obtained can be valuable building blocks in total synthesis of more valuable compounds. Furthermore, the observed stereoselectivities are generally good, up to two new stereocenters being formed during this transformation.

From a more academic point of view, this transformation proved that a 1,5-enyne can undergo 5-*endo* cyclization and internal nucleophilic trapping, as opposed to the 5-*endo* cyclization and external nucleophilic trapping (alkoxy- and hydroxycyclization) discussed in the previous chapter (see also Scheme 9.12).

The same principle was further developed by Sebastian Böhringer and Dr. Fabien L. Gagosz into a process combining a 5-*endo* cyclization, an internal nucleophilic trapping and a second external nucleophilic trapping (Scheme 9.18, path B).[293] For an example see also Scheme 8.33.



Scheme 9.18. Current work (path A) compared to the process developed by Böhringer et Gagosz (path B) and an hypothetical future perspective (path C)

An interesting extension would also be a transformation involving the 5-*endo* cyclization of a 1,5-enyne followed by an internal nucleophilic trapping by an enamine or an aromatic amine present in the molecule (Scheme 9.18, path C).

CHAPTER

10

General Conclusion

"To gold they tend, / On gold depend, / All things!"
*(**Johann Wolfgang von Goethe**, German writer – from "Faust")*

This manuscript presents some of the results obtained by our group in the area of homogeneous gold catalysis (introduced briefly in Chapter 1).

Our work was essentially methodological and it had as primary objective the development of new transformations catalyzed by gold complexes. These transformations can lead to the formation of various structures frequently encountered in the synthesis of both natural products and of synthetic compounds having an interesting biological activity.

A central place in all these transformations is occupied by a new family of cationic gold(I)-catalysts, developed in our laboratory by Dr. Fabien L. Gagosz and possessing a bis(trifluoromethanesulfonyl)imidate counterion. Air-stable, crystalline and very easy to synthesize, store and handle, they proved to be also very reactive (Chapter 2). The secondary objective of our work was therefore to study their particular reactivity and to find new applications for them in organic synthesis.

In the last seven chapters, several synthetic approaches to functionalized 4-alkylidene-1,3-dioxolan-2-ones (Chapter 3), 4-oxazolin-2-ones (Chapter 4), 2,5-dihydrofurans (Chapter 5), pyrroles and furans (Chapter 6), 1,3-butadien-2-ol esters (Chapter 7), cyclopentenes (Chapter 8) and 1,3-oxazinan-2-ones (Chapter 9) have been presented.

They allow the efficient formation of these heterocycles or carbocycles starting from easily accessible precursors under very mild conditions and with an excellent stereocontrol. The wide scope of these methods and the excellent compatibility with a large number of functional groups are also remarkable.

In conclusion, we managed to show that gold complexes are highly suitable catalysts for a large number of homogeneous transformations involving the activation of carbon – carbon multiple bonds towards the attack of various nucleophiles. New stereocenters, carbon – carbon and/or carbon –

heteroatom bonds can thus be formed, leading to a variety of new structures highly useful in organic synthesis (Figure 10.1).

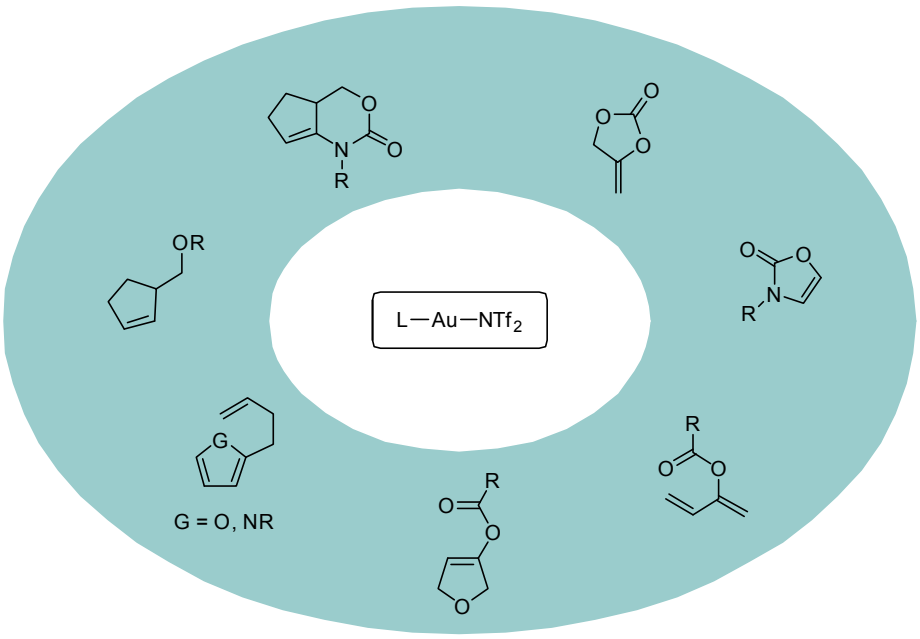


Figure 10.1. Schematic representation of our work, involving the development of new transformations catalyzed by gold(I)-complexes and leading to the formation of various structures frequently encountered in organic synthesis

Further studies on these gold-catalyzed processes and their application to the synthesis of natural products are currently underway.

APPENDIX

A

Acronym and Abbreviation List

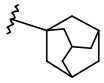
"Un bon chimiste est un chimiste radin…"
*(**Unknown author**)*

1. Units

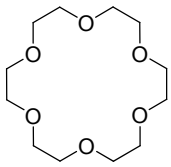
°C	Celsius degree
atm	Standard atmosphere
g	Gram
h	Hour
Hz	Hertz
kg	kilogram
L	Liter
M	Molar concentration
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mmol	Millimole
mol	Mole
m/z	Mass unit on elementary charge
N	Normal concentration
ppm	Parts per million
t	Tonne
€	Euro

2. Chemical groups and compounds

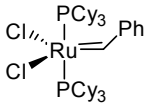
Ac	Acetyl
Ad	Adamantyl



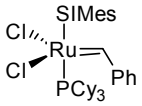
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
Cbz	Carbobenzyloxy (benzyloxycarbonyl)
CDI	1,1′-Carbonyldiimidazole
COD	1,5-Cyclooctadiene
Cp	Cyclopentadienyl
18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane



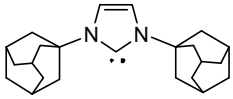
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DHP	3,4-Dihydro-2*H*-pyran
DIBAL-H	Diisobutylaluminun hydride
DIPA	Diisopropylamine
DMA	Dimethylacetamide
DMAD	Dimethyl acetylenedicarboxylate
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMEDA	*N*,*N*′-Dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppm	1,1-Bis(diphenylphosphino)methane
Et	Ethyl
Grubbs I	Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (1st generation Grubbs' catalyst)



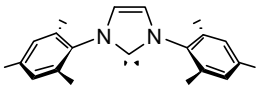
Grubbs II	Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (2nd generation Grubbs' catalyst)



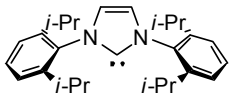
IAd	*N*,*N*′-bis(adamantyl)-imidazol-2-ylidene



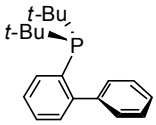
Im	Imidazole
IMes	*N*,*N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene



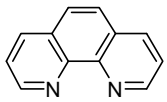
i-Pr	Isopropyl
IPr	*N*,*N'*-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene



JohnPhos	2-(Di-*tert*-butylphosphino)biphenyl

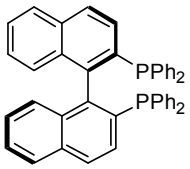


KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide (lithium bis(trimethylsilyl)amide)
Me	Methyl
Mes	Mesityl (2,4,6-trimethylphenyl)
m-CPBA	*meta*-Chloroperoxybenzoic acid
MOP	2-Methoxy-2-propyl
Ms	Mesyl (methanesulfonyl)
2-Napht	2-Naphtyl
n-Bu	*n*-Butyl
NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic carbene
NIS	*N*-Iodosuccinimide
n-Pr	*n*-Propyl
NXS	*N*-Halosuccinimide
PE	Petroleum ether
Ph	Phenyl
phen	1,10-phenanthroline

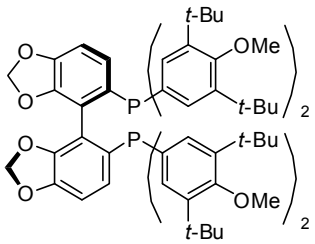


Piv	Pivalyl
PMB	*p*-Methoxybenzyl
PNB	*p*-Nitrobenzoyl
p-cymene	4-Isopropyltoluene

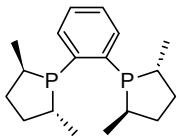
p-Tol	*p*-Tolyl
p-TSA	*p*-Toluensulphonic acid
Py	Pyridine
(*R*)-BINAP	(*R*)-(+)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl



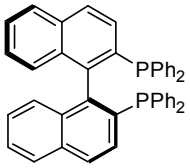
(*R*)-DTBM-SEGPHOS	(*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole



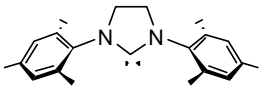
RedAl	Sodium bis(2-methoxyethoxy)aluminumhydride
(*R*,*R*)-Me-DUPHOS	(2*R*,2'*R*,5*R*,5'*R*)-2,2',5,5'-Tetramethyl-1,1'-(*o*-phenylene) diphospholane



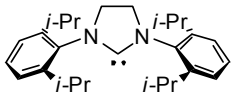
(*S*)-BINAP	(*S*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene



SIMes	1,3-dimesityl-imidazol-4,5-dihydro-2-ylidene

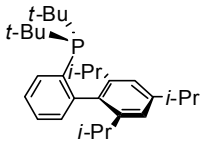


SIPr	1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene

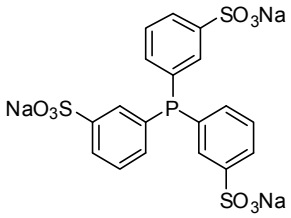


TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl

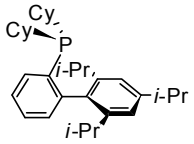
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
tert-Butyl XPhos	2-Di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl



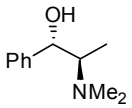
TIPS	Triisopropylsilyl
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
Tf	Trifluoromethansulfonyl
Tol	*p*-Tolyl
o-Tol	*o*-Tolyl
Tp	Tris(1-pyrazolyl)borate
TPPTS	3,3′,3″-Phosphinidynetris(benzenesulfonic acid) trisodium salt



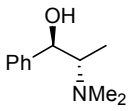
Ts	Tosyl (*p*-toluenesulfonyl)
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl



(+)-NME	(+)-*N*-Metylephedrine ((1*S*,2*R*)-(+)-2-Dimethylamino-1-phenylpropanol)



(-)-NME	(-)-*N*-Metylephedrine ((1R,2S)-(−)-2-Dimethylamino-1-phenylpropanol)



3. Other acronyms and abreviations

aq.	Aqueous
ax	Axial
bs	Broad singulet (in NMR)
cat.	Catalytic
CI^+	Positive chemical ionization (in MS)
conc.	Concentrated
conv.	Conversion
d	Doublet (in NMR)
de	Diastereoisomeric excess
degrad.	Degradation
dr	Diastereoisomeric ratio
E	Electrophile
ee	Enantiomerical excess
EI^+	Positive electron ionization (in MS)
eq	Equatorial
Eq.	Equation
equiv	Equivalent
EDG	Electron donating group
EWG	Electron withdrawing group
g	gas
hept	Heptuplet (in NMR)
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
IR	Infrared
J	Coupling constant (in NMR)
LG	Leaving group
m	Multiplet (in NMR)
m-	*meta-*
MF	Molecular formula
MS	Mass spectroscopy
MW	Molecular weight
NMR	Nuclear magnetic resonance
Nu	Nucleophile
o-	*ortho-*
p-	*para-*
q	Quadruplet (in NMR)
quant.	Quantitative
RCM	Ring closing metathesis
rt	Room temperature
s	Singulet
sc	Super critical
SM	Starting material
sol.	Solution
t	Triplet (in NMR)
temp.	Temperature
TLC	Thin layer chromatography
TOF	Turnover frequency

TON	Turnover number
UV	Ultraviolet
v/v	Volume to volume (about solutions)
v/v/v	Volume to volume to volume (about solutions)
wt.	Composition by mass (about solutions)
δ	Chemical shift (in NMR)
Δ	Heating
ν	Wavenumber (in IR)

APPENDIX

B

Experimental Section

"(Referring to a glass of water:) I mixed this myself.
Two parts H, one part O. I don't trust anybody!"
*(**Stephen A. Wright**, American actor and writer,*
Academy Award winner in 1988)

Disclaimer:

The work presented in this manuscript is the result of the collaboration between several members of our research group. As a consequence, only a part of the experiments described here was performed by the author of this manuscript.

The contribution of each member was acknowledged at the beginning of each chapter in the Main Section and will be restated here, together with the reference of the journal in which the results were initially published.

Section 3 of this appendix corresponds to Chapter 3 and was done in collaboration with Dr. Andrea K. Buzas and Dr. Fabien L. Gagosz.

- Andrea K. Buzas, Fabien L. Gagosz* "Gold(I)-Catalyzed Formation of 4-Alkylidene-1,3-dioxolan-2-ones from Propargylic *tert*-Butyl Carbonates" *Org. Lett.* **2006**, *8*, 515–518 (Short Communication containing some initial results)

- Andrea K. Buzas, Florin M. Istrate, Fabien L. Gagosz* "Gold-catalyzed rearrangement of propargylic *tert*-butyl carbonates" *Tetrahedron* **2009**, *65*, 1889–1901 (Full Paper)

Section 4 of this appendix corresponds to Chapter 4 and was done in collaboration with Dr. Andrea K. Buzas, Igor Dias-Jurberg, Yann Odabachian and Dr. Fabien L. Gagosz.

- Florin M. Istrate, Andrea K. Buzas, Igor Dias-Jurberg, Yann Odabachian, Fabien L. Gagosz* "Synthesis of Functionalized Oxazolones by a Sequence of Cu(II)- and Au(I)-Catalyzed Transformation" *Org. Lett.* **2008**, *10*, 925–928

Section 5 of this appendix corresponds to Chapter 5 and was done in collaboration with Dr. Andrea K. Buzas and Dr. Fabien L. Gagosz.

- Andrea K. Buzas, Florin M. Istrate, Fabien L. Gagosz* "Gold(I)-Catalyzed Stereoselective Formation of Functionalized 2,5-Dihydrofurans" *Org. Lett.* **2006**, *8 (9)*, 1957–1959

Section 6 of this appendix corresponds to Chapter 6 and was done in collaboration with Dr. Fabien L. Gagosz.

- Florin M. Istrate, Fabien L. Gagosz* "Synthesis of Functionalized Pyrroles via a Gold(I)-Catalyzed aza-Claisen-Type Rearrangement" *Org. Lett.* **2007**, *9*, 3181-3184.

Section 7 of this appendix corresponds to Chapter 7 and was done in collaboration with Dr. Andrea K. Buzas and Dr. Fabien L. Gagosz.

- Andrea K. Buzas, Florin M. Istrate, Fabien L. Gagosz* "Gold(I)-Catalyzed Isomerization of Allenyl Carbinol Esters: An Efficient Access to Functionalized 1,3-Butadien-2-ol Esters" *Org. Lett.* **2007**, *9*, 985-988.

Section 8 of this appendix corresponds to Chapter 8 and was done in collaboration with Dr. Andrea K. Buzas and Dr. Fabien L. Gagosz.

- Andrea K. Buzas, Florin M. Istrate, Fabien L. Gagosz* "Gold(I)-Catalyzed 5-*endo* Hydroxy-and Alkoxycyclization of 1,5-Enynes: an Efficient Access to Functionalized Cyclopentenes" *Angew. Chem. Int. Ed.* **2007**, *46*, 1141-1144.

Section 9 of this appendix corresponds to Chapter 9 and was done in collaboration with Dr. Andrea K. Buzas, Dr. Xavier F. Le Goff, Yann Odabachian and Dr. Fabien L. Gagosz.

- Andrea K. Buzas, Florin M. Istrate, Xavier F. Le Goff, Yann Odabachian, Fabien L. Gagosz* "Gold(I)-Catalyzed [4+2] Cycloaddition of *N*-(Hex-5-enynyl) *tert*-butyloxycarbamates" *J. Organomet. Chem.* **2009**, *694*, 515-519.

In order to preserve the coherence of the subject, a full description of the methods used to prepare both the precursors and the final products, together with the corresponding general procedures, will be given.

However, only the compounds synthesized by the author of this manuscript will be fully characterized. A list of these compounds is available below.

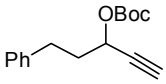
The characterization of the remaining compounds is available in the experimental section of the corresponding publications listed above. Additional informations can also be found in:

- Andrea K. Buzas "Etudes de nouvelles transformations catalysées par l'or(I)" *Ph. D. Thesis*, Ecole Polytechnique, Palaiseau (France), **2009**.

Compounds characterized in Section 3 (pp. 266-291)

3.16

3.20 a



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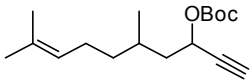

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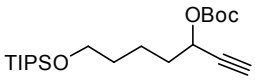

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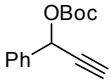

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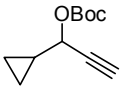

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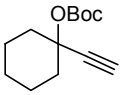

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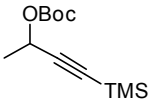

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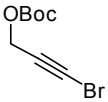

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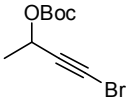

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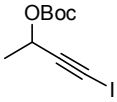

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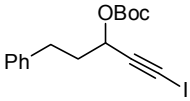

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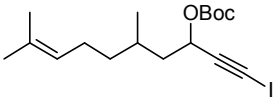

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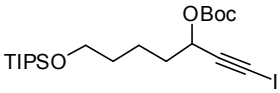

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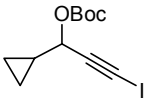

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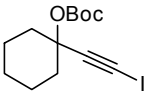

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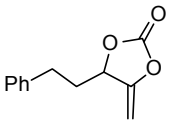

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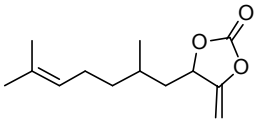

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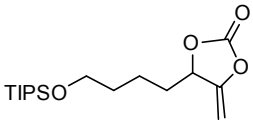

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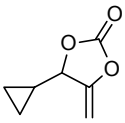

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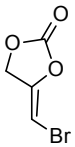

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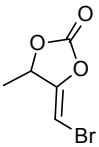

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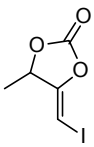

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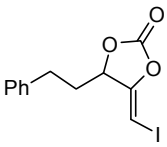

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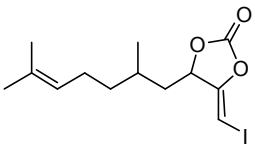

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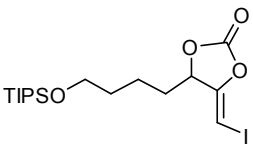

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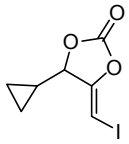

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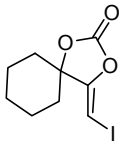

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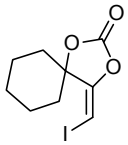

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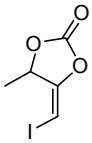

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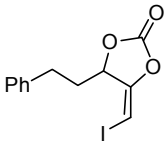

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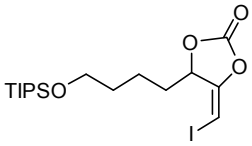

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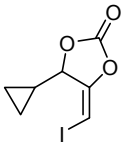

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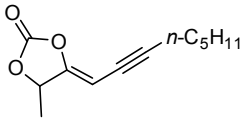

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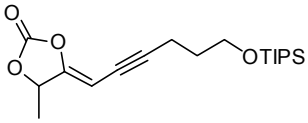

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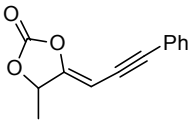

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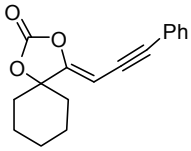

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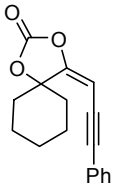

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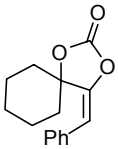

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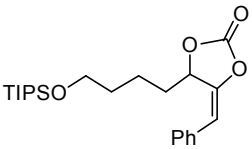
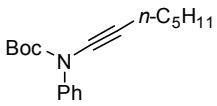


3.49 b

Compounds characterized in Section 4 (pp. 302-316)



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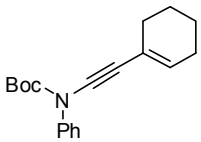

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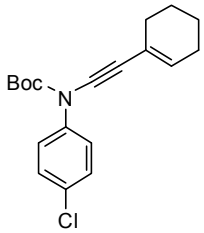

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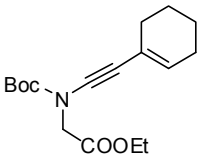

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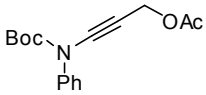

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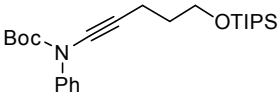

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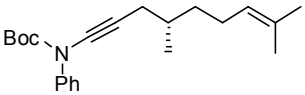

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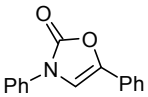

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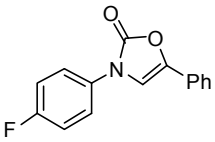

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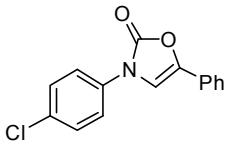

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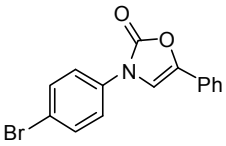

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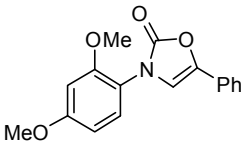

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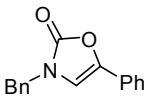

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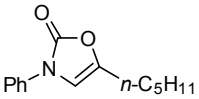

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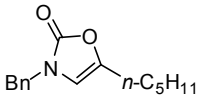

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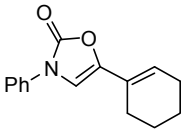

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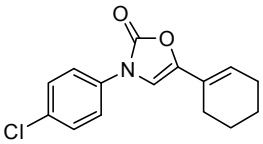

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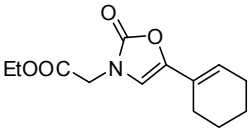

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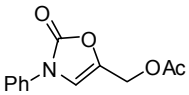

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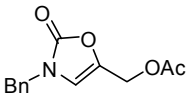

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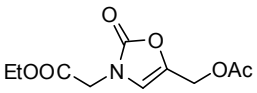

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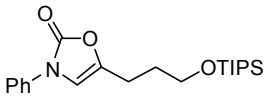

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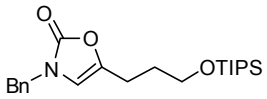

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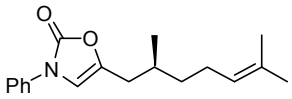
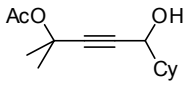
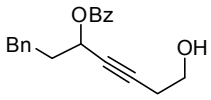


4.12 u

Compounds characterized in Section 5 (pp. 331-338)



5.9 g



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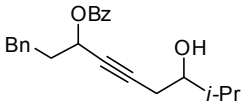

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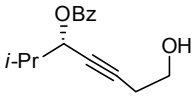

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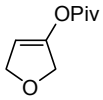

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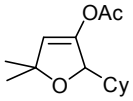

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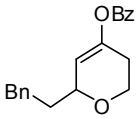

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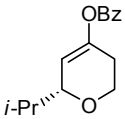

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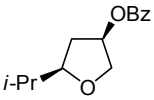

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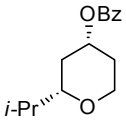
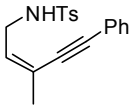


5.29

Compounds characterized in Section 6 (pp. 354-385)



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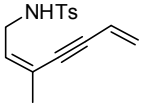

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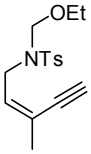

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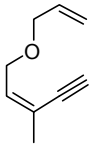
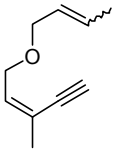


6.16 a



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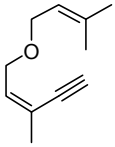

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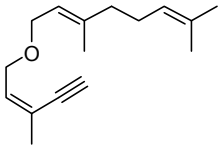

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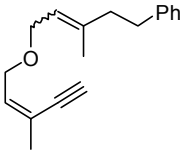

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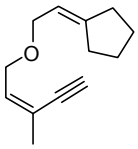

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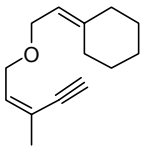

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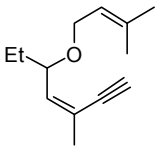

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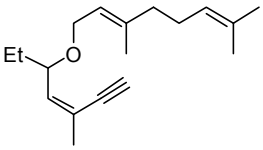

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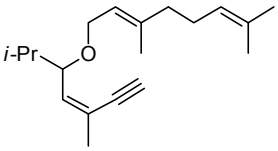

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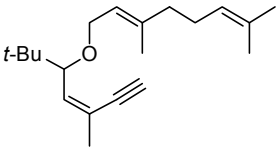

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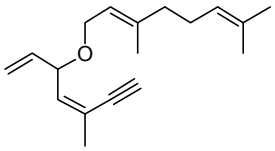

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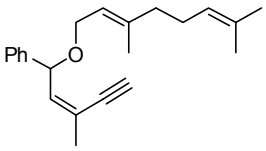

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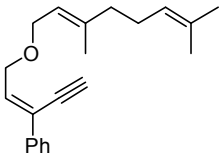

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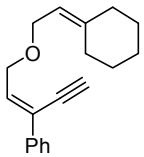

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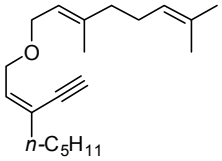

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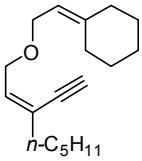

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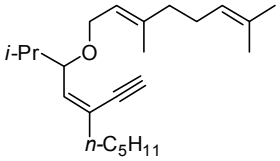

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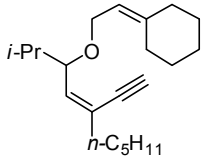

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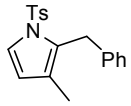

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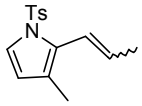

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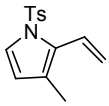

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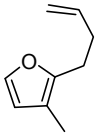

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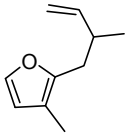

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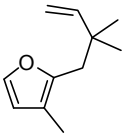

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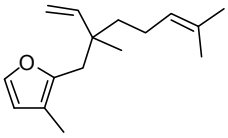

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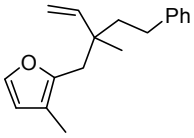

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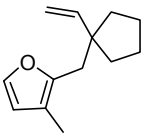

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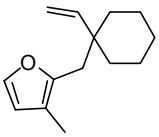

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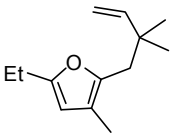

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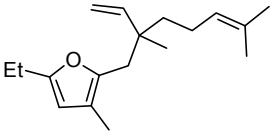
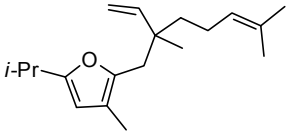
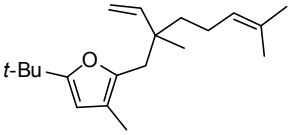


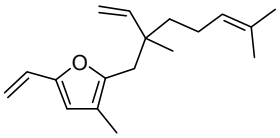
6.17 i



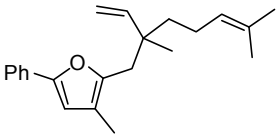
6.17 j



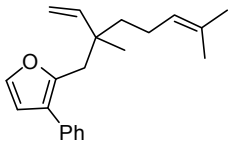
6.17 k



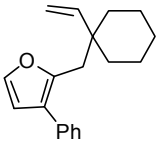
6.17 l



6.17 m



6.17 n



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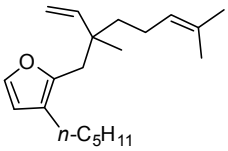
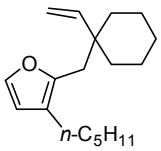


6.17 p



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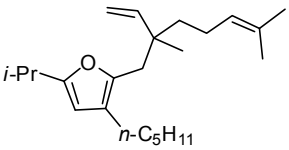
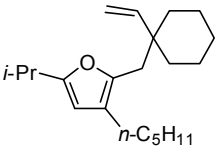
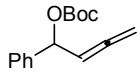


6.17 r

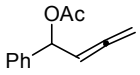


6.17 s

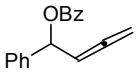
Compounds characterized in Section 7 (pp. 392-405)



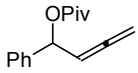
7.7 a



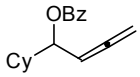
7.7 b



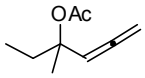
7.7 c



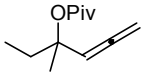
7.7 d



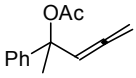
7.11 h



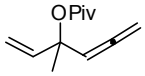
7.11 j



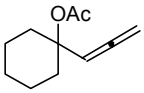
7.11 k



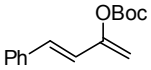
7.11 l



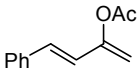
7.11 m



7.11 n



7.9 a



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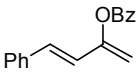
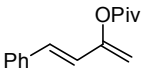
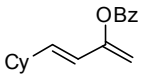


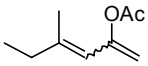
7.9 c



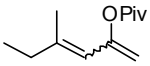
7.9 d



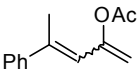
7.12 h



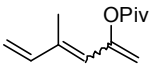
7.12 j



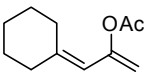
7.12 k



7.12 l

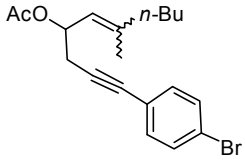


7.12 m

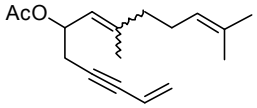


7.12 n

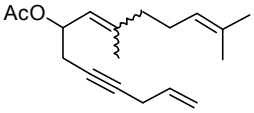
Compounds characterized in Section 8 (pp. 414-427)



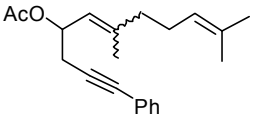
8.8 d



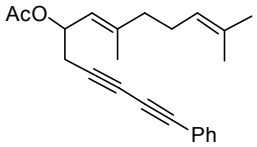
8.8 e



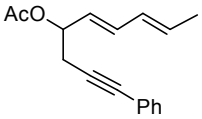
8.8 f



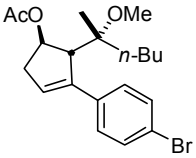
8.8 g



8.8 i



8.8 j



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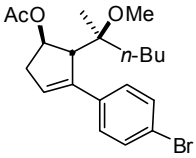
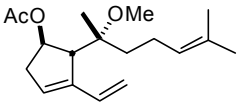


major 8.9 d



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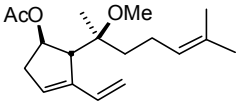
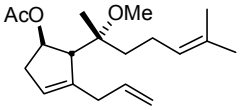


major 8.9 e



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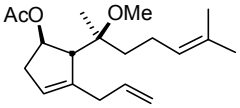
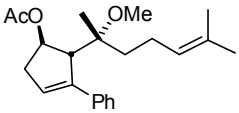


major 8.9 f



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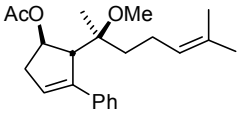
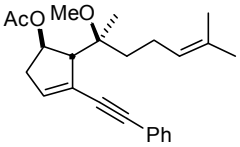
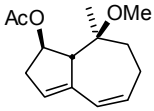


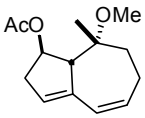
major 8.9 g



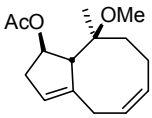
8.9 i



8.22 a

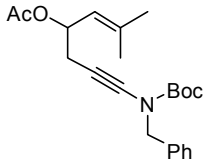


8.22 b

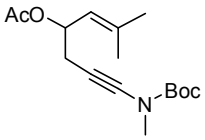


8.22 c

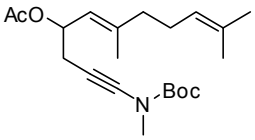
Compounds characterized in Section 9 (pp. 447-464)



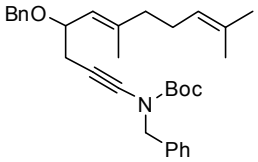
9.4 a



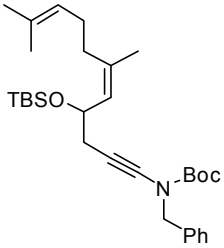
9.4 b



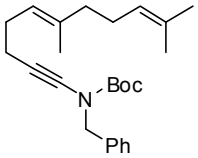
9.4 f



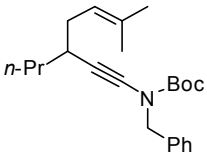
9.4 j



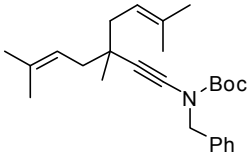
9.4 k



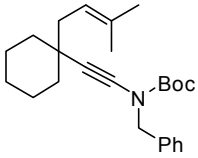
9.9 b



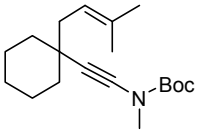
9.9 c



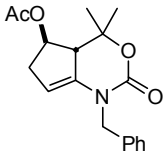
9.9 e



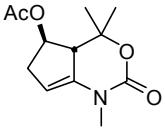
9.9 f



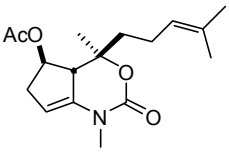
9.9 g



9.5 a



9.5 b



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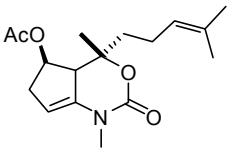

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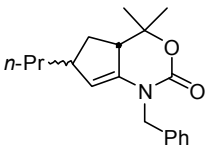
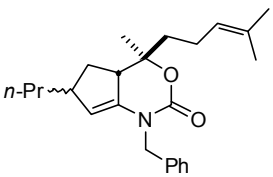


9.10 c



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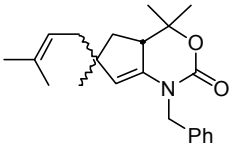

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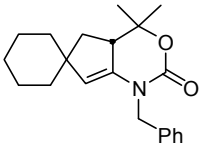
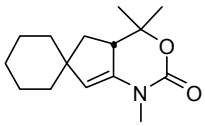
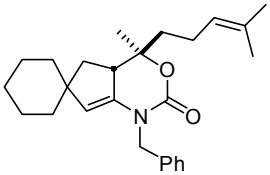


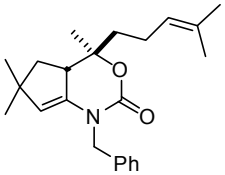
9.10 f



9.10 g



9.10 h



9.10 i

1. General Methods

1.1. Reagents and solvents

Commercially available **reagents** were used as received without further purification.

All **reaction solvents** correspond to SDS "pure for analysis" solvents and were used as received, with the exception of dry Et_2O and THF (which were obtained by distillation from Na/benzophenone) and of dry DCM and toluene (obtained by distillation from CaH_2).

Solvents for flash chromatographies correspond to the SDS "pure for synthesis" solvents and were used as received.

The same goes for **HPLC solvents**, which correspond to the SDS "HPLC grade".

1.2. Experimental procedures

All non-aqueous reactions were performed under dry Ar or N_2 atmosphere using standard syringe-cannula/septa techniques, unless specified otherwise.

Concentration under reduced pressure was performed by rotary evaporation at room temperature using a water jet pump.

Purified compounds were further dried on a high vacuum pump.

1.3. Chromatography

Thin-layer chromatographies (**TLC**) were done on Merck Silica Gel 60 F_{254} plates (aluminium plates coated with silica gel 60). They were visualized under UV light at 254 or 366 nm, then stained using $KMnO_4$ or anisaldehyde solution. **$KMnO_4$ solution** was prepared from 600 mL of water, 6 g $KMnO_4$, 40 g K_2CO_3 and 0.5 mL concentrated acetic acid. **Anisaldehyde solution** was prepared from 26 mL *p*-anisaldehyde, 950 mL ethanol 95%, 35 mL concentrated sulfuric acid and 10.5 mL concentrated acetic acid.

Flash chromatographies were done on SDS 60 CC 40-63 silica gel (pore size 60 Å, particle size 40-63 µm) using a forced flow of eluent at 0.1–0.5 bar pressure.

High pressure liquid chromatography (HPLC) analyses were performed on a Waters LC Module I Plus fitted with a chiral analytical column Chiralcel OD-H (amylose tris (3,5-dimethylphenyl carbamate) on a substrate of silica gel (5µm), lenght 150 mm, interior diameter 4.6 mm).

1.4. Analytical methods

NMR spectra were recorded on a Bruker Avance 400 operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C.

In **^{1}H NMR** chemical shifts (δ) are expressed in ppm using tetramethylsilane (δ=0 ppm) or the residual peak of the solvent (δ=7.27 ppm in the case of chloroform) as an internal reference. Coupling constants (J) are given in Hertz (Hz).

In **^{13}C NMR**, chemical shifts (δ) are expressed in ppm taking the solvent peak (δ=77 ppm in the case of the middle peak of the chloroform) as an internal reference.

IR spectra were recorded with a Perkin Elmer FT-1600 spectrophotometer. Oil or solid samples were dissolved in carbon tetrachloride, and then placed in a sodium chloride cell. The spectra values are reported as absorption maxima and expressed in cm^{-1}.

Mass spectra (**MS**) were recorded on a Hewlett Packard HP-5890 B using positive electron ionization (EI^{+}) or positive chemical ionization with ammonia (CI^{+}, NH_3) methods. Fragment signals are given as a mass-to-charge ratio (m/z).

High resolution mass spectra (**HRMS**) were recorded on a Jeol GCmate II spectrometer using positive electron ionization (EI^{+}) methods.

All analyses were performed at the DCSO Laboratory (Laboratoire de Synthèse Organique) of Ecole Polytechnique.

1.5. Software

The 1D and 2D NMR FID spectral data was processed and visualized using MestReC 4.7.0.0.

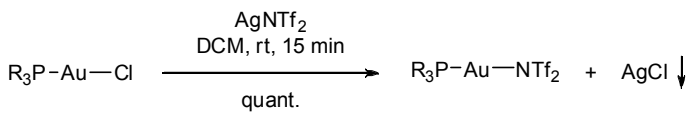
This manuscript was drafted using Microsoft Word, versions 2002 and 2007. Chemical formulas were edited in Cambridge Soft's Chemdraw Standard 6.0 and Chemdraw Ultra 10.0. The bibliography was managed using Thomson Endnote X1.

Finally, the name of the synthesized compounds was determined according to the CAS nomenclature using the Beilstein AutoNom 2000, version 4.01.305.

2. The catalysts used during our work

2.1. Synthesis of phosphine gold(I) bis(trifluoromethanesulfonyl)imidate complexes

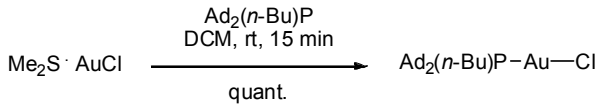
The phosphine gold(I) bis(trifluoromethanesulfonyl)imidate complexes used during our work were obtained according to the method developed by Dr. Fabien L. Gagosz[67] from the corresponding phosphine gold(I) chloride derivatives in the presence of $AgNTf_2$ in DCM at rt.



with R_3P = Ph_3P, $(p\text{-}CF_3\text{-}C_6H_4)_3P$, $Ad_2(n\text{-Bu})P$, JohnPhos, XPhos

General procedure 2.1: The phosphine gold(I) chloride complex (1 equiv) was dissolved in DCM (0.04 M) at rt and $AgNTf_2$ (1 equiv) was added solid resulting in the instantaneous formation of the expected silver chloride precipitate. The mixture was stirred for an additional 15 min and the formation of a single complex was checked by ^{31}P NMR of the crude mixture. Filtration over celite to remove the silver chloride salts, resulted in a pale colored solution. The expected complex was obtained quantitatively by evaporation to dryness under reduced pressure and drying under vacuum.

The $Ad_2(n\text{-Bu})P$-Au-Cl complex, which is not commercially available, can be prepared from $Me_2S{\cdot}AuCl$ in the presence of $Ad_2(n\text{-Bu})P$ by simple ligand exchange.

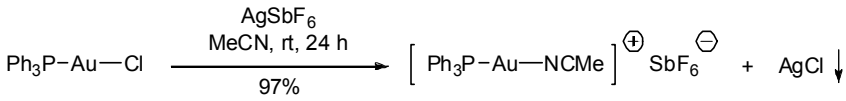


General procedure 2.2: $Me_2S{\cdot}AuCl$ (1 equiv) and the phosphine (1 equiv) were weighed in air then placed under nitrogen. DCM (0.04 M) was added, which resulted in the dissolution of the starting material and the formation of a pale yellow solution. The mixture was stirred at rt for 15 min and the complete formation of the desired gold chloride complex was checked by ^{31}P NMR. The volume of the solution reduced to 1 mL and then 5 mL of hexane were added, resulting in the precipitation of the complex. The solid was filtered, washed with hexane and dried under vacuum, resulting in the quantitative

isolation of the title product as a pale yellow solid. The complex was characterized only by its ^{31}P NMR spectrum and then directly used for the next step.

2.2. Synthesis of $[Ph_3P\text{-}Au\text{-}(NC\text{-}Me)]SbF_6$

$[Ph_3P\text{-}Au\text{-}(NC\text{-}Me)]SbF_6$ was obtained according to the methods described in the literature[322] starting from the commercially available $Ph_3P\text{-}Au\text{-}Cl$ complex and $AgSbF_6$ in acetonitrile at rt.



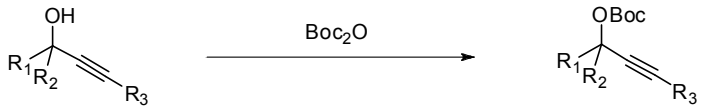
General procedure 2.3: To a mixture of $Ph_3P\text{-}Au\text{-}Cl$ (1 equiv) and $AgSbF_6$ (1 equiv), MeCN was added (0.125 M). The reaction mixture was stirred at rt for 24 h and then it was filtered through a pad of celite. The filtrate was evaporated under reduced pressure to give the expected cationic complex.

[322] Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.

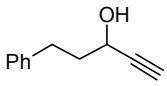
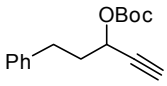
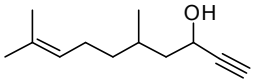
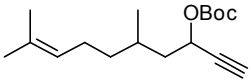
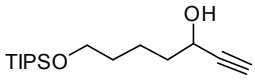
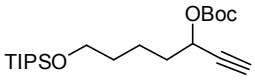
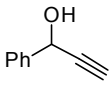
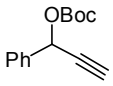
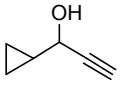
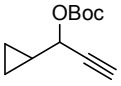
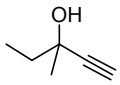
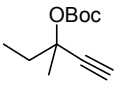
3. Gold(I)-catalyzed formation of 4-alkylidene-1,3-dioxolan-2-ones

3.1. Synthesis of the precursors

Propargylic *tert*-butylcarbonates **3.16**, **3.20 a-m** and **3.22 a-g** were synthesized from the corresponding alcohol and di-*tert*-butyldicarbonate following classical methods described in the literature.[323]

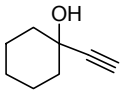
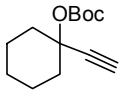
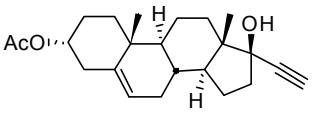
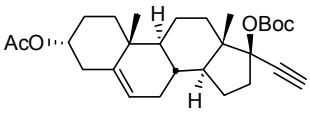
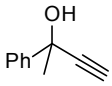
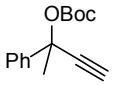
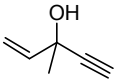
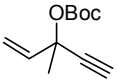
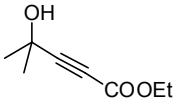
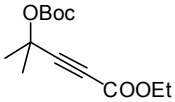
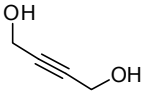
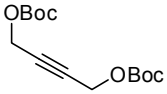
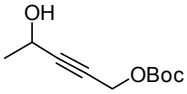
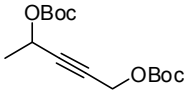
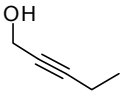
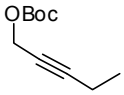
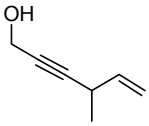
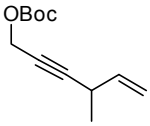
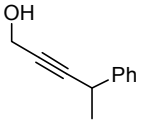
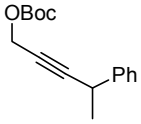


Conditions:
(a) Boc_2O, NEt_3, DMAP, DCM, rt
(b) Boc_2O, DMAP, MeCN, rt
(c) Boc_2O (1.2 equiv), Bu_4NHSO_4, NaOH (aq.), DCM, rt
(d) Boc_2O (2.4 equiv), Bu_4NHSO_4, NaOH (aq.), DCM, rt.

substrate		product		conditions	time	yield[a]
			3.16	a	1 h 30 min	84%
			3.20 a	a	1 h 30 min	66%
	**3.50 a**		**3.20 b**	a	1 h 30 min	92%
	**3.50 b**		**3.20 c**	a	3 h	87%
	**3.50 c**		**3.20 d**	a	2 h 30 min	95%
			**3.20 f**	b	2 h	97%
	**3.50 d**		**3.20 g**	a	1 h 30 min	89%
			3.20 h	b	42 h	49%
			**3.20 i**	b	17 h	83%

(continued on the next page)

[323] (a) Houlihan, F.; Bouchard, F.; Frechet, J. M. J.; Willson, C. G. *Can. J. Chem.* **1985**, *63*, 153-162.
(b) Eren, D.; Keinan, E. *J. Am. Chem. Soc.* **2002**, *110*, 4356-4362.
(c) Parker, K. A.; Coburn, C. A.; Johnson, P. D.; Aristoff, P. *J. Org. Chem.* **2002**, *57*, 5547-5550.

substrate		product		conditions	time	yield[a]
			**3.20 j**	b	26 h	95%
			**3.20 k**	b	68 h	46%
			**3.20 l**	b	72 h	96%
			**3.20 m**	b	72 h	80%
			**3.22 a**	b	72 h	30%
			**3.22 b**	d	2 h	70%
	**3.50 e**		**3.22 c**	a	3 h	51%
			3.22 d	c	2 h	48%
			**3.22 e**	c	1 h 30 min	50%
			**3.22 f**	a	2 h	83%
	**3.50 f**		**3.22 g**	a	2 h	90%

[a] Isolated yield.

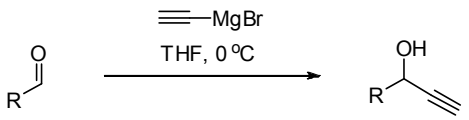
General procedure 3.1: Conditions a:[323a] To a solution of alcohol (1 equiv) in DCM (0.5 M) was added NEt_3 (1.1 equiv), Boc_2O (1 equiv) and DMAP (0.05 equiv). The mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was quenched with water and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the protected alcohol.

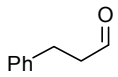
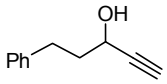
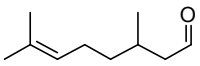
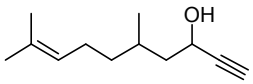
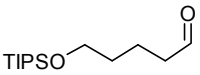
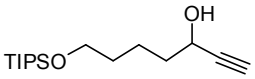
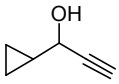
Conditions b:[323b] To a solution alcohol (1 equiv) in MeCN (0.1 M) was added Boc_2O (2.5 equiv) and DMAP (0.1 equiv). The mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was evaporated under reduced pressure and the residue diluted with aqueous HCl 1 N solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the protected alcohol.

Conditions c:[323c] To a solution of alcohol (1 equiv) in DCM (4 M) at 0 °C was added Boc_2O (1.2 equiv) and Bu_4NHSO_4 (0.3 equiv). To this mixture aqueous NaOH 30% solution (2 M relative to the alcohol) was added and the resulting suspension was stirred at rt and followed periodically by TLC. Upon completion, the reaction was quenched with water and extracted twice with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the protected alcohol.

Conditions d:[323c] The same as in Conditions c, but with 2.4 equiv of Boc_2O.

Alcohols **3.50 a-d** were prepared by nucleophilic addition of ethynylmagnesium bromide on the corresponding aldehyde.

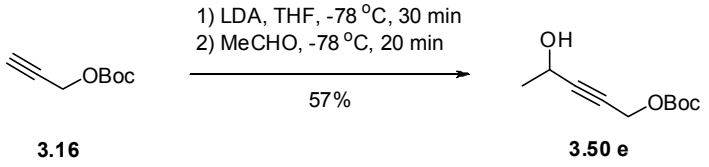


aldehyde	product		time	yield[a]
		**3.50 a**	30 min	85%
		**3.50 b**	30 min	97%
		**3.50 c**	2 h	94%
		**3.50 d**	30 min	61%

[a] Isolated yield.

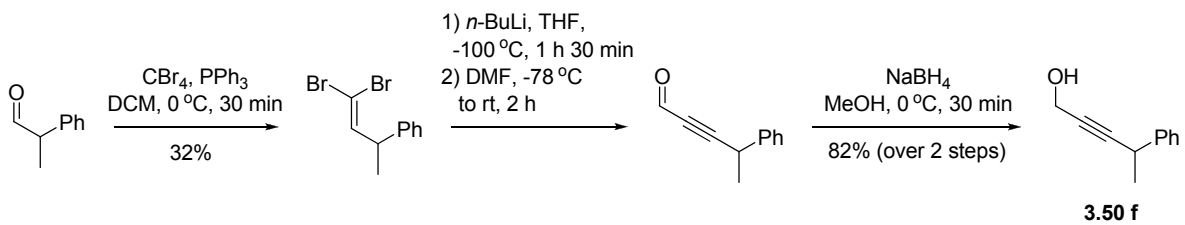
General procedure 3.2: To a solution of aldehyde (1 equiv) in THF (0.5 M) at 0 °C was added ethynylmagnesium bromide (1.1 equiv, 0.5 M in THF solution). The mixture was stirred at 0 °C and followed periodically by TLC. Upon completion, the reaction was quenched with saturated NH_4Cl aqueous solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected alcohol.

Alcohol **3.50 e** was prepared from terminal alkyne **3.16** by deprotonation in the presence of LDA followed by nucleophilic addition on acetaldehyde.



General procedure 3.3: The starting alkyne (1 equiv) was dissolved in THF (0.5 M) and cooled at -78 °C. Freshly prepared LDA (1.1 equiv) was added dropwise and the mixture was stirred at -78 °C for 30 min. Acetaldehyde (1.2 equiv) was added dropwise and the reaction mixture was stirred for another 30 min at -78 °C and followed periodically by TLC. Upon completion, the reaction was quenched with saturated NH_4Cl aqueous solution and extracted two times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected alcohol.

Alcohol **3.50 f** was obtained from 2-phenylpropionaldehyde (hydratropaldehyde) by conversion into the dibromoalkene derivative, treatment with *n*-BuLi to afford the lithiated alkyne followed by addition on DMF and reduction of the resulting aldehyde to the primary alcohol in the presence of $NaBH_4$.

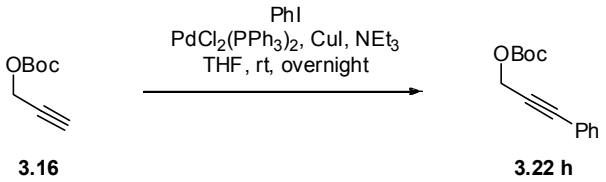


General procedure 3.4: To a solution of PPh_3 (4 equiv) in DCM (2 M) at 0 °C was added a solution of CBr_4 (2 equiv) in DCM (2 M). The mixture was stirred at 0 °C for 5 min, then a solution of 2-phenylpropionaldehyde (1 equiv) in DCM (1 M) was added dropwise. The mixture was allowed to react at 0 °C for 30 min. Upon completion, the reaction was quenched with water and extracted 2 times with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Petroleum ether was added to the residue, which was then filtered and reevaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether) to give the dibromoalkene.

The resulting dibromoalkene (1 equiv) was dissolved in THF (0.1 M) and cooled at -100 °C. *n*-BuLi (2.3 equiv, 1.6 M in hexane solution) was added dropwise and the mixture was stirred at -100 °C for 1 h 30 min. DMF (2 equiv) was the added dropwise and the resulting mixture was allowed to slowly warm to rt for 2 h. Upon completion, the reaction was quenched with saturated NH_4Cl aqueous solution and extracted 2 times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

The crude from the previous step was dissolved in MeOH (0.25 M) and cooled at 0 °C. $NaBH_4$ (1.2 equiv) was added and the resulting mixture was stirred at 0 °C for 30 min. Upon completion, the reaction was quenched with saturated NH_4Cl aqueous solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected alcohol.

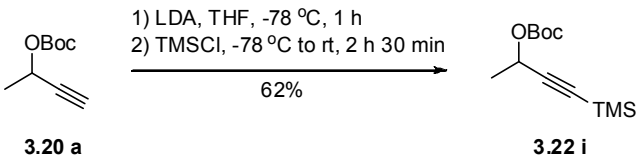
Substrate **3.22 h** was synthesized via a palladium-catalyzed Sonogashira coupling of alkyne **3.16** with iodobenzene.



General procedure 3.5: To a solution of alkyne (1 equiv) in THF (0.1 M), PhI (1.2 equiv), $PdCl_2(PPh_3)_2$ (0.03 equiv), CuI (0.05 equiv) and NEt_3 (10 equiv) were successively added. The reaction mixture was allowed to react at rt overnight. Upon completion, it was diluted with diethyl ether and filtered

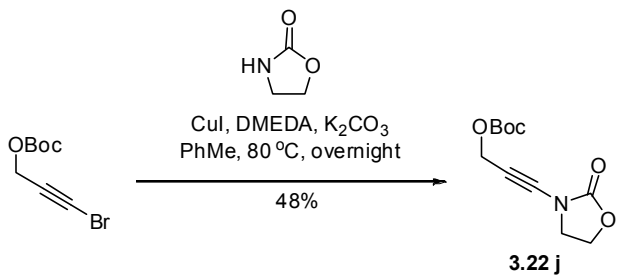
through silica, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to afford the desired product.

Substrate **3.22 i** was obtained from alkyne **3.20 a** by deprotonation in the presence of LDA followed by nucleophilic substitution on TMSCl.



General procedure 3.6: The starting alkyne (1 equiv) was dissolved in THF (1 M) and cooled at -78 °C. Freshly prepared LDA (1.1 equiv) was added dropwise and the mixture was stirred at -78 °C for 1 h. TMSCl (1.1 equiv) was then added dropwise and the reaction mixture was allowed to slowly warm from -78 °C to rt for 2 h 30 min. Upon completion, the reaction was quenched with saturated NH_4Cl aqueous solution and extracted 2 times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the desired compound.

Substrate **3.22 j** was synthesized by a copper(I)-catalyzed coupling of bromoalkyne **3.40 a** and oxazolidinone.[324]

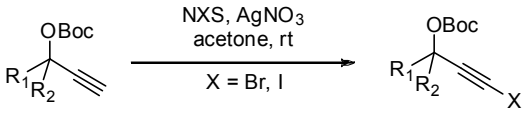


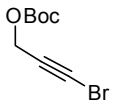
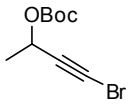
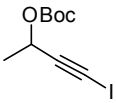
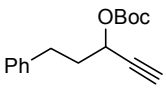
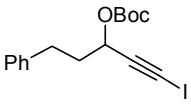
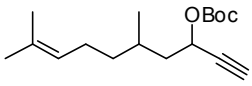
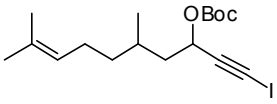
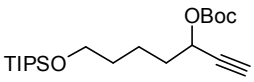
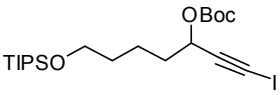
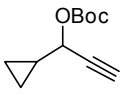
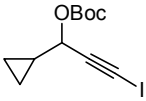
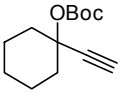
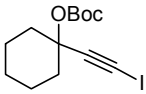
General procedure 3.7: To a solution of carbamate (1.3 equiv), K_2CO_3 (2.6 equiv) and CuI (0.05 equiv) in dry toluene (0.2 M), a solution of bromoalkyne (1 equiv) in toluene (0.2 M) was added. DMEDA (0.1 equiv) was also added and the

[324] Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368-2369.

reaction mixture was capped and heated at 80 °C overnight. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through silica, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether / ethyl acetate) to afford the desired product.

Halogenoalkynes **3.40 a-h** were synthesized by halogenation of the corresponding alkynes with NBS or NIS.[325]



substrate		product		time	yield[a]
	3.16		**3.40 a**	1 h	98%
	3.20 a		**3.40 b**	1 h	89%
	3.20 a		**3.40 c**	1 h 30 min	97%
	**3.20 b**		**3.40 d**	2 h	98%
	**3.20 c**		**3.40 e**	19 h	44%
	**3.20 d**		**3.40 f**	3 h 30 min	98%
	**3.20 g**		**3.40 g**	1 h	quant.
	**3.20 j**		**3.40 h**	1 h	51%

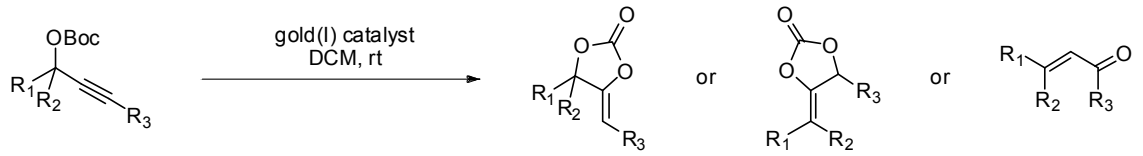
[a] Isolated yield.

[325] Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, *1994*, 485-486.

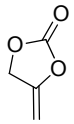
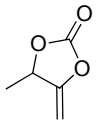
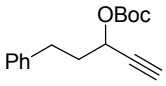
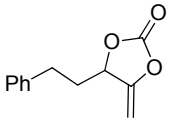
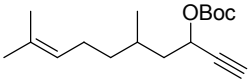
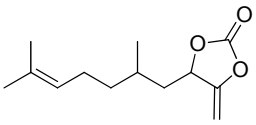
General procedure 3.8: To a solution of terminal alkyne (1 equiv) in acetone (0.15 M) at 0 °C were added NXS (1.1 equiv, X = Br or I) and $AgNO_3$ (0.05 equiv). The reaction vessel was wrapped in aluminum foil to avoid light exposure and the reaction mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was cooled again at 0 °C, quenched with cold water and extracted 3 times with diethyl ether. The combined organic layers were washed 2 times with water and once with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the halogenoalkyne.

3.2. Gold(I)-catalyzed transformations involving propargylic *tert*-butyl carbonates

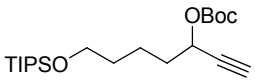
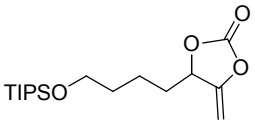
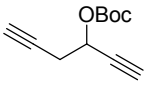
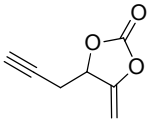
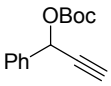
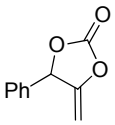
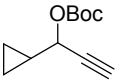
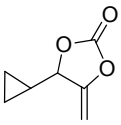
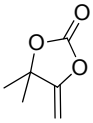
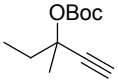
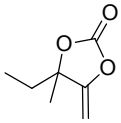
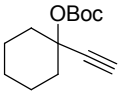
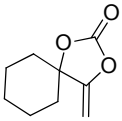
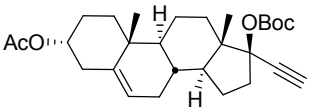
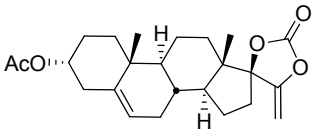
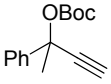
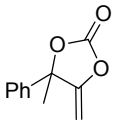
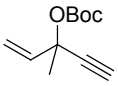
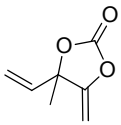
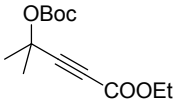
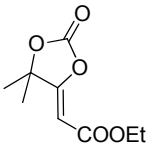
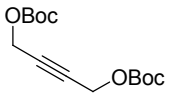
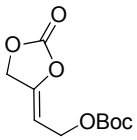
As we saw in Chapter 3, various terminal or internal propargylic *tert*-butyl carbonates were rearranged in the presence of a gold(I)-catalyst.



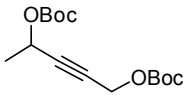
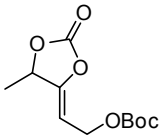
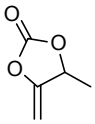
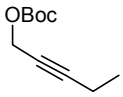
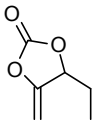
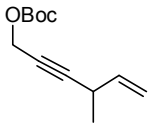
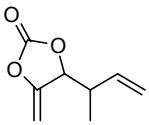
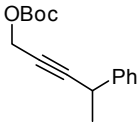
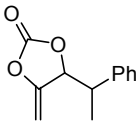
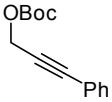
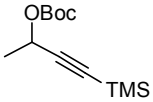
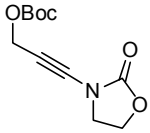
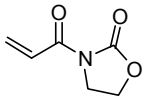
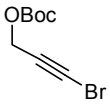
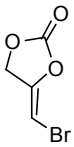
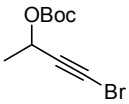
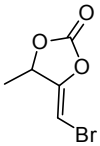
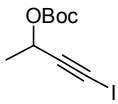
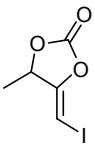
Conditions: (a) with 1% Ph_3P-Au-NTf_2
(b) with 3% Ph_3P-Au-NTf_2
(c) with 1% [Ph_3P-Au-(NC-CH_3)]SbF_6
(d) with 1% (p-CF_3-C_6H_4)$_3$P-Au-NTf_2

substrate		product		conditions	time	yield[a]
	3.16		**3.17**	a	10 min	83%
	3.20 a		**3.21 a**	a	15 min	94%
	**3.20 b**		**3.21 b**	a	5 min	quant.
 dr ~ 1/1	**3.20 c**	 dr ~ 1/1	**3.21 c**	a	10 min	91%

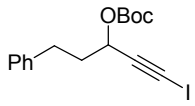
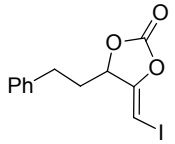
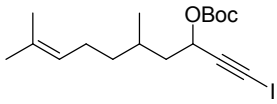
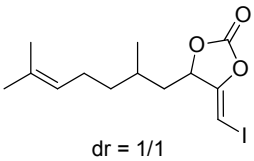
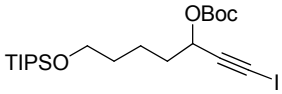
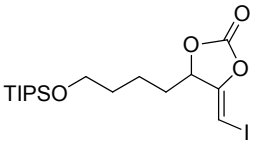
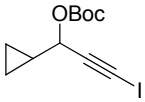
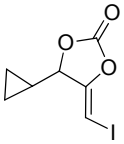
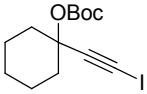
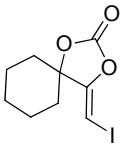
(continued on next page)

substrate		product		conditions	time	yield[a]
	**3.20 d**		**3.21 d**	a	5 min	96%
	**3.20 e**		**3.21 e**	a	5 min	95%
	**3.20 f**		**3.21 f**	a	10 h	74%
	**3.20 g**		**3.21 g**	b c	5 h 1 h	49% 49%
	3.20 h		**3.21 h**	a	5 min	85%
	**3.20 i**		**3.21 i**	a	5 min	98%
	**3.20 j**		**3.21 j**	a	30 min	96%
	**3.20 k**		**3.21 k**	a	10 min	90%
	**3.20 l**		**3.21 l**	a	17 h	76%
	**3.20 m**		**3.21 m**	a	18 h	40%
	**3.22 a**		**3.23 a**	a	2 h	87%
	**3.22 b**		**3.23 b**	a	50 min	62%

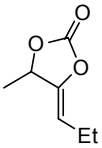
(continued on next page)

substrate		product		conditions	time	yield[a]
	**3.22 c**		**3.23 c**	a	30 min	77%
	3.22 d		**3.23 d**	d	24 h	62%
	**3.22 e**		**3.23 e**	d	24 h	60%[b]
	**3.22 f**		**3.23 f**	d	20 h	68%
		dr ~ 1/1.6				
	**3.22 g**		**3.23 g**	d	20 h	66%
		dr ~ 1/3.9				
	**3.22 h**	-		a,d	24 h	-[c]
	**3.22 i**	-		a,d	3 h	-[d]
	**3.22 j**		**3.23 j**	a	30 min	94%
	**3.40 a**		**3.41 a**	a	1 h	87%
	**3.40 b**		**3.41 b**	a	20 min	87%
	**3.40 c**		**3.41 c**	a	10 min	95%

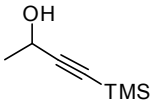
(continued on the next page)

substrate		product		conditions	time	yield[a]
	**3.40 d**		**3.41 d**	a	5 min	99%
 dr = 1/1	**3.40 e**	 dr = 1/1	**3.41 e**	a	5 min	97%
	**3.40 f**		**3.41 f**	a	5 min	69%
	**3.40 g**		**3.41 g**	c	1 h	32%
	**3.40 h**		**3.41 h**	a	5 min	83%

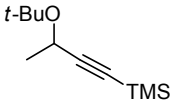
[a] Isolated yield. dr determined by ^{1}H NMR. [b] Side-product **3.24** was isolated with a 10% yield [c] Mainly starting material was recovered at the end of this transformation. [d] Starting material was recovered at the end of this transformation along with side-products **3.25** (22%) and **3.26** (15%).



3.24



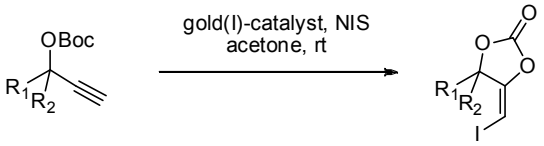
3.25



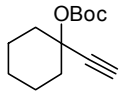
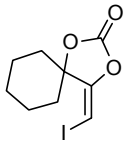
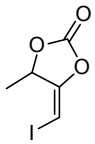
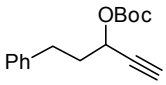
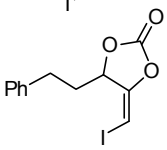
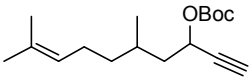
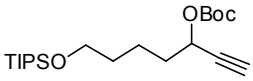
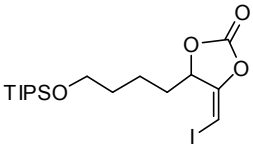
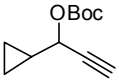
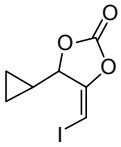
3.26

General procedure 3.9: To a solution of propargylic *tert*-butyl carbonate (1 equiv) in dichloromethane (0.5 M) at room temperature was added the corresponding amount of catalyst (conditions a: 0.01 equiv of Ph_3P-Au-NTf_2, conditions b: 0.03 equiv of Ph_3P-Au-NTf_2, conditions c: 0.01 equiv of $[Ph_3P\text{-Au-}(NC\text{-}CH_3)]SbF_6$, conditions d: 0.01 equiv of $(p\text{-}CF_3\text{-}C_6H_4)_3P$-Au-$NTf_2$). The mixture was stirred at room temperature and monitored periodically by TLC. Upon completion, the mixture was either directly filtered through a silica pad pre-impregnated with dichloromethane and then evaporated under reduced pressure or evaporated and then purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

4-(*E*-Iodomethylene)-1,3-dioxolan-2-ones **3.42** and **3.43 a-d** were obtained from the corresponding terminal propargylic *tert*-butyl carbonates in the presence of NIS and gold(I)-catalyst in acetone.



Conditions: (a) with 1% Ph_3P-Au-NTf_2
(b) with 1% [Ph_3P-Au-(NC-CH_3)]SbF_6

substrate		product		conditions	time	yield[a]
	**3.20 j**		**3.42**	a	5 min	95%
	3.20 a		**3.43 a**	a	5 min	35%
	**3.20 b**		**3.43 b**	a	45 min	66%
	**3.20 c**	-		a	5 min	-
	**3.20 d**		**3.43 c**	a	15 min	64%
	**3.20 g**		**3.43 d**	b	1 h	76%
	3.16	-		a	15 min	-

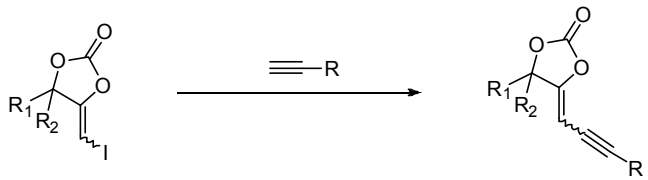
Reaction conditions: substrate (1 equiv), gold(I) catalyst (0.01 equiv), DCM (0.5 M), rt. [a] Isolated yield.

General procedure 3.10: To a solution of substrate (1 equiv) in acetone (0.5 M) at room temperature was added NIS (1.2 equiv) and the gold catalyst (conditions a: 0.01 equiv of Ph_3P-Au-NTf_2, conditions b: 0.01 equiv of [Ph_3P-Au-(NC-CH_3)]SbF_6). The mixture was stirred at room temperature and monitored periodically by TLC. Upon completion, the mixture was evaporated and then purified by flash column chromatography (silica gel, petroleum ether

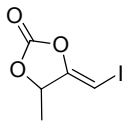
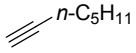
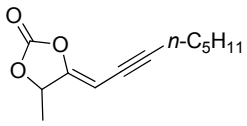
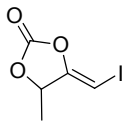
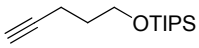
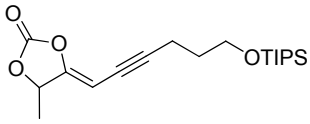
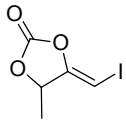
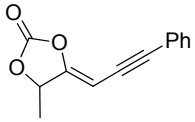
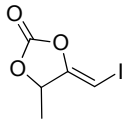
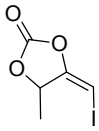
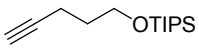
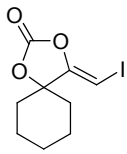
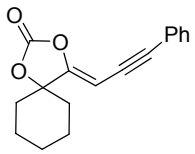
/ diethyl ether) to give the expected product.

3.3. Palladium catalyzed cross-coupling reactions

Substrates **3.48 a-e** were prepared via a Sonogashira coupling under classical conditions.[326]

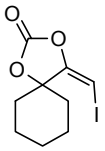
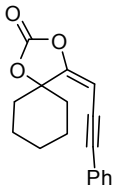


Conditions: (a) $PdCl_2(PPh_3)_2$, CuI, NEt_3 (10 equiv), THF, rt
(b) $PdCl_2(PPh_3)_2$, CuI, NEt_3 (solvent), rt

substrate		alkyne	product		conditions	time	yield[a]
	**3.41 b**			**3.48 a**	a	1 h 30 min	67%
	**3.41 b**			**3.48 b**	a	18 h	67%
	**3.41 b**			**3.48 c**	a	20 min	72%
	**3.41 b**		-		b	30 min	degrad.
	**3.43 a**		-		a	30 min	degrad.
	**3.41 h**			**3.48 d**	a	30 min	61%

(continued on the next page)

[326] Nakao, Y.; Hirata, Y.; Ishihara, S.; Oda, S.; Yukawa, T.; Shirakawa, E.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 15650-15651.

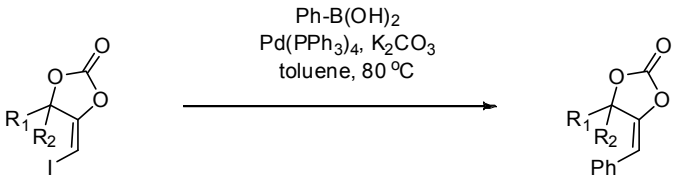
substrate	alkyne	product	conditions	time	yield[a]
 **3.42**		 **3.48 e**	a	20 min	94%

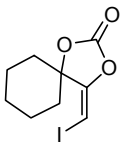
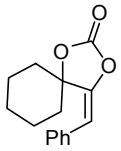
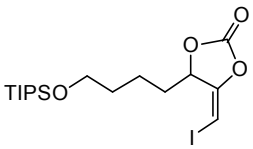
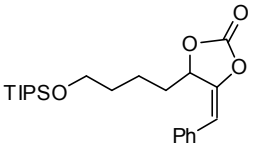
[a] Isolated yield.

General procedure 3.11: Conditions a:[326] To a solution of halogenated derivative (1 equiv) in THF (0.25 M) were added the corresponding terminal alkyne (2 equiv), $PdCl_2(PPh_3)_2$ (0.2 equiv), CuI (0.04 equiv), and NEt_3 (10 equiv). The mixture was stirred at room temperature and monitored periodically by TLC. Upon completion, it was quenched with a saturated aqueous solution of NH_4Cl, the aqueous layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under vacuum. The crude mixture was then purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

Conditions b: The same as in Conditions a, but with NEt_3 as solvent (0.25 M).

Substrates **3.49 a** and **b** were prepared via a Suzuki coupling under classical conditions.



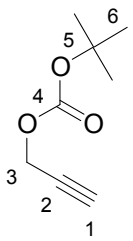
entry	substrate	product	time	yield[a]
1	 **3.42**	 **3.49 a**	3 h 30 min	79%
2	 **3.43 c**	 **3.49 b**	2 h 30 min	40%

[a] Isolated yield.

General procedure 3.12: To a solution of halogenated derivative (1 equiv) in toluene (0.5 M) was added K_2CO_3 powder (2.5 equiv), phenylboronic acid (1.1 equiv) and $Ph(PPh_3)_4$ (0.05 equiv). The mixture was stirred at 80 °C and monitored periodically by TLC. Upon completion, it was quenched with a saturated aqueous solution of NH_4Cl, the aqueous layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The crude mixture was then purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

3.4. Characterization of the prepared compounds

Carbonic acid *tert*-butyl ester prop-2-ynyl ester **3.16**



MF: $C_8H_{12}O_3$

MW: 156.17 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.1 a** (scale: 10 mmol).

Purification: Flash column chromatography (silica gel, PE/AcOEt 95/5).

Product: Colorless oil.

Yield: 84%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.66 (d, J = 2.45 Hz, 2H, *3*), 2.49 (t, J = 2.47 Hz, 1H, *1*), 1.50 (s, 9H, *6*).

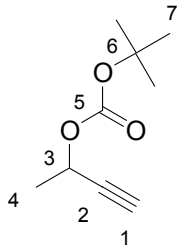
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 152.5 (*4*), 82.4 (*5*), 77.2 (*1* or *2*), 75.0 (*1* or *2*), 53.9 (*3*), 27.3 (*6*).

IR (ν, cm^{-1}) (CCl_4) 3293, 2982, 2938, 1809, 1745.

MS (CI^+, NH_3, m/z) 157 (MH^+).

HRMS (EI^+, m/z) Calculated for $C_8H_{12}O_3$: 156.0787.
Found for $C_8H_{12}O_3$: 156.0783.

Carbonic acid *tert*-butyl ester 1-methyl-prop-2-ynyl ester **3.20 a**



MF: $C_9H_{14}O_3$

MW: 170.20 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.1 a** (scale: 10 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 97/3).

Product: Pale yellow oil.

Yield: 66%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.15 (m, 1H, *3*), 2.42 (m, 1H, *1*), 1.42 (m, 12H, *4* and *7*).

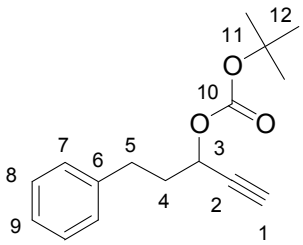
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.2 (*5*), 82.4 (*6*), 81.6 (*2*), 73.2 (*1*), 62.5 (*3*), 27.5 (*7*), 21.0 (*4*).

IR (ν, cm^{-1}) (CCl_4): 3312, 2984, 2937, 1744, 1154, 1313, 1271, 1168, 1101, 1020.

MS (CI^+, NH_3, m/z): 188 (MNH_4^+), 171 (MH^+), 156.

HRMS (EI^+, m/z): Calculated for $C_9H_{14}O_3$: 170.0943.
Found for $C_9H_{14}O_3$: 170.0934.

Carbonic acid *tert*-butyl ester 1-phenethyl-prop-2-ynyl ester 3.20 b



MF: $C_{16}H_{20}O_3$

MW: 260.33 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.1 a** (scale: 4.163 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

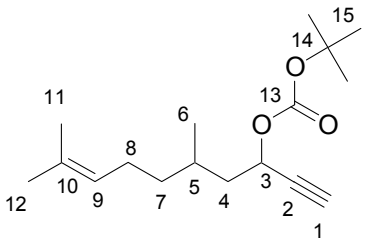
Product: Pale yellow oil.

Yield: 92%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.30 (m, 2H, *7* or *8*), 7.22 (m, 3H, *7* or *8* and *9*), 5.16 (td, J = 2.1, 6.7 Hz, 1H, *3*), 2.82 (t, J = 7.9 Hz, 2H, *5*), 2.55 (d, J = 2.1 Hz, 1H, *1*), 2.15 (m, 2H, *4*), 1.52 (s, 9H, *12*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.4 (*10*), 140.5 (*6*), 128.4 (*7* or *8*), 128.3 (*7* or *8*), 126.1 (*9*), 82.8 (*11*), 80.6 (*2*), 74.4 (*1*), 66.0 (*3*), 36.1 (*4*), 31.0 (*5*), 27.7 (*12*).
IR (ν, cm^{-1}) (CCl_4)	3310, 2978, 3064, 3027, 2978, 2934, 2865, 1745, 1455, 1366, 1347, 1266, 1162, 1092, 1034, 1014.
MS (EI^+, m/z)	260 (M^+), 217, 186, 162, 142.
HRMS (EI^+, m/z)	Calculated for $C_{16}H_{20}O_3$: 260.1413. Found for $C_{16}H_{20}O_3$: 260.1415.

Carbonic acid *tert*-butyl ester 1-ethynyl-3,7-dimethyl-oct-6-enyl ester **3.20 c**

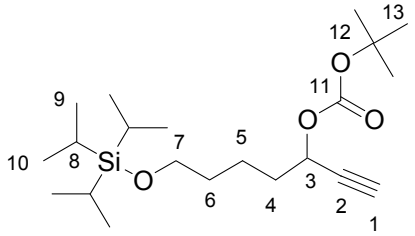


MF: $C_{17}H_{28}O_3$

MW: 280.40 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 3.1 a** (scale: 4.742 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 98/2).
Product:	Yellow oil (mixture of 2 diastereoisomers).
Yield:	87%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	For the mixture of diastereoisomers: 5.23 (m, 1H, *3*), 5.09 (thept, J = 1.2, 7.1 Hz, 1H, *9*), 2.48 (t, J = 2.2 Hz, 1H, *1*), 1.99 (m, 2H, *8*), 1.97-1.14 (m, 5H, *4*, *5*, and *7*), 1.68 (s, 3H, *11* or *12*), 1.60 (s, 3H, *11* or *12*), 1.50 (s, 9H, *15*), 0.95 (dm, J = 6.6 Hz, 3H, *6*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	For the mixture of diastereoisomers: 152.6 (*13*), 152.6 (*13*), 131.4 (*10*), 124.4 (*9*), 124.3 (*9*), 82.7 (*14*), 82.7 (*14*), 81.4 (*2*), 81.0 (*2*), 74.0 (*1*), 73.7 (*1*), 65.6 (*3*), 65.2 (*3*), 42.0 (*4*), 41.5 (*4*), 36.9 (*7*), 36.7 (*7*), 29.0 (*5*), 28.8 (*5*), 27.7 (*15*), 25.6 (*11* or *12*), 25.6 (*11* or *12*), 25.2 (*8*), 19.2 (*6*), 17.6 (*11* or *12*), 17.6 (*11* or *12*).
IR (ν, cm^{-1}) (CCl_4)	For the mixture of diastereoisomers: 3310, 2924, 1745, 1455, 1371, 1341, 1267, 1164, 1093, 1039.
MS (EI^+, m/z)	280 (M^+), 236, 224, 207.
HRMS (EI^+, m/z)	Calculated for $C_{17}H_{28}O_3$: 280.2039. Found for $C_{17}H_{28}O_3$: 280.2041.

Carbonic acid *tert*-butyl ester 1-ethynyl-5-triisopropylsilanyloxy-pentyl ester **3.20 d**



MF: $C_{21}H_{40}O_4Si$

MW: 384.63 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.1 a** (scale: 3.409 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product: Yellow oil.

Yield: 95%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.16 (td, J = 2.1, 6.8 Hz, 1H, *3*), 3.70 (t, J = 6.0 Hz, 2H, *7*), 2.47 (d, J = 2.1 Hz, 1H, *1*), 1.84 (m, 2H, *4*), 1.58 (m, 4H, *5* and *6*), 1.50 (s, 9H, *13*), 1.06 (m, 21H, *8*, *9* and *10*).

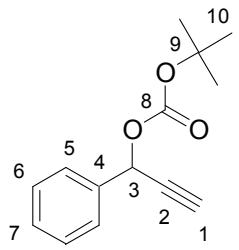
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.6 (*11*), 82.6 (*12*), 80.9 (*2*), 73.9 (*1*), 66.7 (*3*), 63.0 (*7*), 34.5 (*4*), 32.3 (*5* or *6*), 27.7 (*13*), 21.3 (*5* or *6*), 18.0 (*9* and *10*), 12.0 (*8*).

IR (ν, cm^{-1}) (CCl_4): 3311, 2945, 2893, 2865, 1744, 1463, 1370, 1346, 1265, 1165, 1109, 1038.

MS (EI$^+$, m/z): 384 (M^+), 318, 286, 267, 241, 223, 199.

HRMS (EI$^+$, m/z): Calculated for $C_{21}H_{40}O_4Si$: 384.2696.
Found for $C_{21}H_{40}O_4Si$: 384.2686.

Carbonic acid *tert*-butyl ester 1-phenyl-prop-2-ynyl ester — 3.20 f



MF: $C_{14}H_{16}O_3$

MW: 232.10 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.1 b** (scale: 10 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Pale yellow oil.

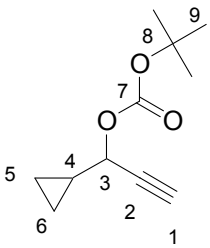
Yield: 97 %

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.58-7.55 (m, 2H), 7.42-7.33 (m, 3H) (*5*, *6* and *7*), 6.27 (d, J = 2.2 Hz, 1H, *3*), 2.71(d, J = 2.3 Hz, 1H, *1*), 1.51 (m, 9H, *10*).

^{13}C NMR (δ, ppm): 152.3 (*8*), 136.1 (*4*), 128.9 (*7*), 128.5 (*5* or *6*), 127.5 (*5* or *6*), 82.9 (*9*), 79.9

($CDCl_3$, 100 MHz)	(*1* or *2*), 75.9 (*1* or *2*), 68.0 (*3*), 27.6 (*10*).
IR (ν, cm^{-1}) (CCl_4)	3311, 2981, 2935, 1744, 1456, 1392, 1368, 1321, 1256, 1163, 1081, 1032.
MS (CI^+, NH_3, m/z)	304, 250 (MNH_4^+), 192, 132.
HRMS (EI^+, m/z)	Calculated for $C_{14}H_{16}O_3$: 232.1100. Found for $C_{14}H_{16}O_3$: 232.1105.

Carbonic acid *tert*-butyl ester 1-cyclopropyl-prop-2-ynyl ester **3.20 g**



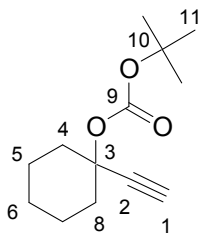
MF: $C_{11}H_{16}O_3$

MW: 196.24 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 3.1 a** (scale: 2.902 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 98/2).
Product:	Colorless oil.
Yield:	89%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.02 (dd, J = 2.1, 7.0 Hz, 1H, *3*), 2.46 (d, J = 2.2 Hz, 1H, *1*), 1.50 (s, 9H, *9*), 1.32 (m, 1H, *4*), 0.66-0.48 (m, 4H, *5* and *6*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.6 (*7*), 82.7 (*8*), 78.8 (*2*), 74.1 (*1*), 70.2 (*3*), 27.7 (*9*), 14.1 (*4*), 3.5, 2.1 (*5* and *6*).
IR (ν, cm^{-1}) (CCl_4)	3311, 3087, 2980, 2932, 2873, 1742, 1473, 1459, 1369, 1327, 1275, 1169, 1083, 1028.
MS (EI^+, m/z)	196 (M^+), 151, 140, 121.
HRMS (EI^+, m/z)	Calculated for $C_{11}H_{16}O_3$: 196.1100. Found for $C_{11}H_{16}O_3$: 196.1097.

Carbonic acid *tert*-butyl ester 1-ethynyl-cyclohexyl ester **3.20 j**



MF: $C_{13}H_{20}O_3$

MW: 224.29 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 3.1 b** (scale: 10 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 96/4).

Product: White crystals.

Yield: 88%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 2.60 (s, 1H, *1*), 2.16 (m, 2H), 1.81 (m, 2H), 1.70-1.50 (m, 6H) (*4*, *5*, *6*, *7* and *8*), 1.47 (s, 9H, *11*).

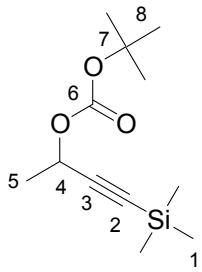
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.2 (*9*), 83.2, 82.0, 76.5, 74.4 (*1*, *2*, *3* and *10*), 36.8 (*4*, *5*, *6*, *7* and/or *8*), 27.8 (*11*), 25.0 (*4*, *5*, *6*, *7* and/or *8*), 22.5 (*4*, *5*, *6*, *7* and/or *8*).

IR (ν, cm^{-1}) (CCl_4): 3311, 2979, 2938, 2861, 1748, 1450, 1367, 1283, 1246, 1163, 1085, 1013.

MS (CI^+, NH_3, m/z): 242 (MNH_4^+), 225 (MH^+), 186, 181, 163, 143, 126.

HRMS (EI^+, m/z): Calculated for $C_{13}H_{20}O_3$: 224.1413.
Found for $C_{13}H_{20}O_3$: 224.1406.

Carbonic acid *tert*-butyl ester 1-methyl-3-trimethylsilanyl-prop-2-ynyl ester 3.22 i



MF: $C_{12}H_{22}O_3Si$

MW: 242.39 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 3.6** (scale: 3 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Colorless oil.

Yield: 62%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.27 (q, J = 6.7 Hz, 1H, *4*), 1.53 (d, J = 6.7 Hz, 3H, *5*), 1.50 (s, 9H, *8*), 0.17 (s, 9H, *1*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.3 (*6*), 103.1 (*3*), 89.9 (*2*), 82.5 (*7*), 63.5 (*4*), 27.7 (*8*), 21.4 (*5*), -0.2 (*1*).

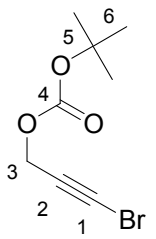
IR (ν, cm^{-1}) (CCl_4): 2979, 2902, 2872, 2177, 1742, 1474, 1452, 1369, 1340, 1312, 1268, 1268, 1169, 1125, 1099, 1039.

MS (EI^+, m/z): 242 (M^+).

HRMS (EI^+, m/z): Calculated for $C_{12}H_{22}O_3Si$: 242.1338.

Found for $C_{12}H_{22}O_3Si$: 242.1329.

Carbonic acid 3-bromo-prop-2-ynyl ester *tert*-butyl ester **3.40 a**



MF: $C_8H_{11}BrO_3$

MW: 235.07 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.8** (scale: 5 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Pale yellow oil.

Yield: 98%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 4.69 (s, 2H, *3*), 1.50 (s, 9H, *6*).

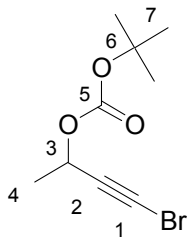
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 152.5 (*4*), 83.1 (*5*), 73.7 (*1* or *2*), 55.1 (*3*), 47.6 (*1* or *2*), 27.7 (*6*).

IR (ν, cm^{-1}) (CCl_4) 2981, 2936, 1748, 1430, 1370, 1271, 1163, 1092.

MS (EI$^+$, NH_3, m/z) 234 (M^+).

HRMS (EI$^+$, m/z) Calculated for $C_8H_{11}BrO_3$: 233.9892.
Found for $C_8H_{11}BrO_3$: 233.9898.

Carbonic acid 3-bromo-1-methyl-prop-2-ynyl ester *tert*-butyl ester **3.40 b**



MF: $C_9H_{13}O_3Br$

MW: 249.10 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.8** (scale: 2 mmol).

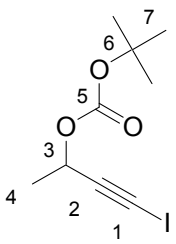
Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Yellow oil.

Yield: 89%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.27 (q, J = 6.7 Hz, 1H, *3*), 1.53 (d, J = 6.7 Hz, 3H, *4*), 1.50 (s, 9H, *7*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.3 (*5*), 82.8 (*6*), 78.1 (*1* or *2*), 63.7 (*3*), 46.0 (*1* or *2*), 27.7 (*7*), 21.2 (*4*).
IR (ν, cm^{-1}) (CCl_4)	2984, 2936, 2874, 2214, 1744, 1475, 1451, 1369, 1343, 1312, 1268, 1169, 1130, 1102, 1039.
MS (EI^+, m/z)	250, 248 (M^+).
HRMS (EI^+, m/z)	Calculated for $C_9H_{13}O_3Br$: 248.0048. Found for $C_9H_{13}O_3Br$: 248.0054.

Carbonic acid *tert*-butyl ester 3-iodo-1-methyl-prop-2-ynyl ester **3.40 c**



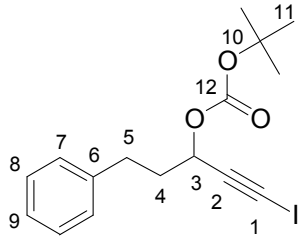
MF: $C_9H_{13}O_3I$

MW: 296.10 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 3.8** (scale: 2 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 95/5).
Product:	Pink oil.
Yield:	97%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.37 (q, J = 6.7 Hz, 1H, *3*), 1.53 (d, J = 6.7 Hz, 3H, *4*), 1.50 (s, 9H, *7*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.2 (*5*), 92.2 (*2*), 82.8 (*6*), 64.2 (*3*), 27.7 (*7*), 21.4 (*4*), 3.1 (*1*).
IR (ν, cm^{-1}) (CCl_4)	2981, 2935, 2868, 2189, 1745, 1474, 1452, 1370, 1343, 1311, 1266, 1168, 1122, 1101, 1037.
MS (EI^+, m/z)	296 (M^+), 268, 240.
HRMS (EI^+, m/z)	Calculated for $C_9H_{13}O_3I$: 295.9910. Found for $C_9H_{13}O_3I$: 295.9911.

Carbonic acid *tert*-butyl ester 3-iodo-1-phenethyl-prop-2-ynyl ester **3.40 d**



MF: $C_{16}H_{19}O_3I$

MW: 386.22 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.8** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil.

Yield: 98%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.30 (m, 2H, *7*), 7.21 (m, 3H, *8* and *9*), 5.28 (t, J = 6.7 Hz, 1H, *3*), 2.79 (t, J = 7.9 Hz, 2H, *5*), 2.13 (m, 2H, *4*), 1.51 (s, 9H, *11*).

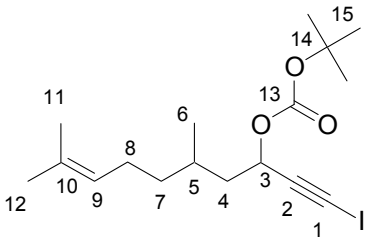
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.3 (*12*), 140.4 (*6*), 128.4 (*7* or *8*), 128.3 (*7* or *8*), 126.1 (*9*), 91.2 (*2*), 82.9 (*10*), 67.4 (*3*), 36.3 (*4*), 31.0 (*5*), 27.7 (*11*), 3.9 (*1*).

IR (ν, cm^{-1}) (CCl_4): 3027, 2977, 2931, 2863, 1745, 1453, 1370, 1271, 1161, 1118, 1090, 1037, 1009.

MS (EI$^+$, m/z): 386 (M^+), 330, 319, 285, 268, 241, 203.

HRMS (EI$^+$, m/z): Calculated for $C_{16}H_{19}O_3I$: 386.0379.
Found for $C_{16}H_{19}O_3I$: 386.0395.

Carbonic acid *tert*-butyl ester 1-iodoethynyl-3,7-dimethyl-oct-6-enyl ester 3.40 e



MF: $C_{17}H_{27}O_3I$

MW: 406.30 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.8** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

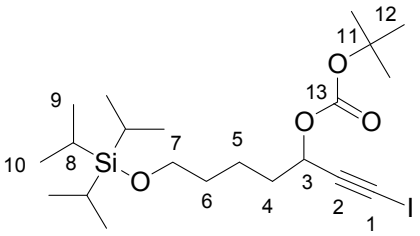
Product: Pale yellow oil (mixture of 2 diastereoisomers).

Yield: 44%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the mixture of diastereoisomers: 5.35 (m, 1H, *3*), 5.09 (m, 1H, *9*), 1.98 (m, 2H), 1.81 (m, 1H), 1.74-1.31 (m, 4H) (*4*, *5*, *7* and *8*), 1.69 (s, 3H), 1.61 (s, 3H) (*11* and *12*), 1.50 (s, 9H, *15*), 0.94 (dm, J = 6.4 Hz, 3H, *6*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	For the mixture of diastereoisomers: 152.5 (*13*), 152.4 (*13*), 131.4 (*10*), 131.4 (*10*), 124.4 (*9*), 124.3 (*9*), 91.9 (*2*), 91.6 (*2*), 82.7 (*14*), 82.7 (*14*), 67.1 (*3*), 66.6 (*3*), 42.1 (*4*), 41.7 (*4*), 36.8 (*7*), 36.6 (*7*), 28.9 (*5*), 28.8 (*5*), 27.7 (*15*), 25.7 (*11* or *12*), 25.2 (*8*), 19.3 (*6*), 19.3 (*6*), 17.6 (*11* or *12*), 17.6 (*11* or *12*), 3.4 (*1*), 3.1 (*1*).
IR (ν, cm^{-1}) (CCl_4)	For the mixture of diastereoisomers: 2966, 2925, 2871, 2191, 1742, 1456, 1370, 1341, 1275, 1165, 1088, 1034, 1005.
MS (EI^+, m/z)	406 (M^+), 342, 319, 306, 292, 271, 246, 221.
HRMS (EI^+, m/z)	Calculated for $C_{17}H_{27}O_3I$: 406.1005. Found for $C_{17}H_{27}O_3I$: 406.0997.

Carbonic acid *tert*-butyl ester 1-iodoethynyl-5-triisopropylsilanyloxy-pentyl ester **3.40 f**



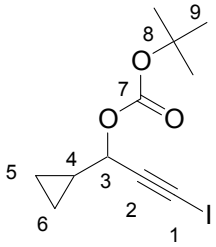
MF: $C_{21}H_{39}O_4SiI$

MW: 510.52 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 3.8** (scale: 1 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 80/20).
Product:	Orange oil.
Yield:	<98%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.29 (t, J = 6.7, 1H, *3*), 3.70 (t, J = 6.0 Hz, 2H, *7*), 1.82 (m, 2H, *4*), 1.56 (m, 4H, *5* and *6*), 1.50 (s, 9H, *12*), 1.07 (m, 21H, *8*, *9* and *10*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.5 (*13*), 91.5 (*2*), 82.7 (*11*), 68.1 (*3*), 62.9 (*7*), 34.7 (*4*), 32.3 (*5* or *6*), 27.7 (*12*), 21.3 (*5* or *6*), 18.0 (*9* and *10*), 12.0 (*8*), 3.3 (*1*).
IR (ν, cm^{-1}) (CCl_4)	2943, 2894, 2865, 1852, 1744, 1462, 1369, 1271, 1164, 1106.
MS (EI^+, m/z)	510 (M^+), 411, 368, 349.
HRMS (EI^+, m/z)	Calculated for $C_{21}H_{39}O_4SiI$: 510.1663. Found for $C_{21}H_{39}O_4SiI$: 510.1685.

Carbonic acid *tert*-butyl ester 1-cyclopropyl-3-iodo-prop-2-ynyl ester **3.40 g**



MF: $C_{11}H_{15}O_3I$

MW: 322.14 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.8** (scale: 0.5 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil.

Yield: Quant.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.11 (d, J = 7.1 Hz, 1H, *3*), 1.50 (s, 9H, *9*), 1.29 (m, 1H, *4*), 0.68-0.44 (m, 4H, *5* and *6*).

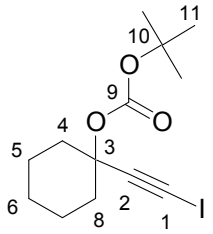
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.5 (*7*), 89.6 (*2*), 82.8 (*8*), 71.6 (*3*), 27.7 (*9*), 14.7 (*4*), 3.5 (*5* or *6*), 2.3 (*5* or *6*).

IR (ν, cm^{-1}) (CCl_4): 2978, 2930, 2865, 2193, 1742, 1458, 1370, 1328, 1271, 1166, 1081, 1045.

MS (EI$^+$, m/z): 322 (M^+), 265, 222, 204, 194.

HRMS (EI$^+$, m/z): Calculated for $C_{11}H_{15}O_3I$: 322.0066.
Found for $C_{11}H_{15}O_3I$: 322.0060.

Carbonic acid *tert*-butyl ester 1-iodoethynyl-cyclohexyl ester — 3.40 h



MF: $C_{13}H_{19}O_3I$

MW: 350.19 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.8** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Pale yellow oil.

Yield: 51%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 2.18 (m, 2H), 1.81 (m, 2H), 1.72-1.43 (m, 5H) (*4*, *5*, *6*, *7* and/or *8*), 1.50 (s, 9H, *11*), 1.31 (m, 1H, *4*, *5*, *6*, *7* or *8*).

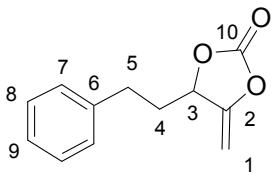
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.0 (*9*), 94.0 (*2* or *3*), 82.1 (*10*), 78.1 (*2* or *3*), 37.1 (*4*, *5*, *6*, *7* and/or *8*), 27.8 (*11*), 25.0 (*4*, *5*, *6*, *7* and/or *8*), 22.7 (*4*, *5*, *6*, *7* and/or *8*), 2.9 (*1*).

IR (ν, cm^{-1}) (CCl_4) 2977, 2937, 2861, 1748, 1450, 1368, 1283, 1246, 1161, 1083, 1014.

MS (EI^+, m/z) 350 (M^+), 292, 250, 230, 204, 190.

HRMS (EI^+, m/z) Calculated for $C_{13}H_{19}O_3I$: 350.0379.
Found for $C_{13}H_{19}O_3I$: 350.0388.

4-Methylene-5-phenethyl-1,3-dioxolan-2-one 3.21 b



MF: $C_{12}H_{12}O_3$

MW: 204.22 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 3.9 a** (scale: 0.25 mmol).

Purification: Filtration over silica gel (DCM).

Product: Yellow oil.

Yield: Quant.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.33 (m, 2H), 7.23 (m, 3H) (*7*, *8* and *9*), 5.15 (m, 1H, *3*), 4.89 (dd, J = 2.4, 4.0 Hz, 1H, *1*), 4.37 (dd, J = 2.0, 4.0 Hz, 1H, *1*), 2.84 (m, 2H, *5*), 2.15 (m, 2H, *4*).

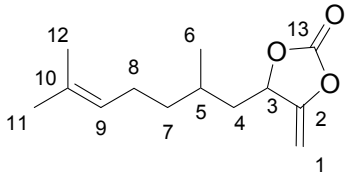
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 153.1 (*2*), 151.9 (*10*), 139.5 (*6*), 128.6 (*7* or *8*), 128.3 (*7* or *8*), 126.4 (*9*), 86.8 (*1*), 78.6 (*3*), 36.5 (*4*), 30.2 (*5*).

IR (ν, cm^{-1}) (CCl_4) 3065, 3028, 2950, 2930, 2862, 1842, 1705, 1681, 1497, 1452, 1341, 1282, 1131, 1085, 1045, 1004.

MS (EI^+, m/z) 204 (M^+), 160, 145, 117, 105.

HRMS (EI^+, m/z) Calculated for $C_{12}H_{12}O_3$: 204.0787.
Found for $C_{12}H_{12}O_3$: 204.0781.

4-(2,6-Dimethyl-hept-5-enyl)-5-methylene-1,3-dioxolan-2-one 3.21 c



MF: $C_{13}H_{20}O_3$

MW: 224.30 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 3.9 a** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil (mixture of 2 diastereoisomers).

Yield: 91%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the mixture of diastereoisomers: 5.20 (m, 1H, *3*), 5.09 (m, 1H, *9*), 4.84 (m, 1H, *1*), 4.33 (m, 1H, *1*), 2.02 (m, 2H, *8*), 1.94-1.13 (m, 5H, *4*, *5* and *7*), 1.69 (s, 3H, *11* or *12*), 1.61 (s, 3H, *11* or *12*), 1.00 (dm, J = 6.3 Hz, 3H, *6*).

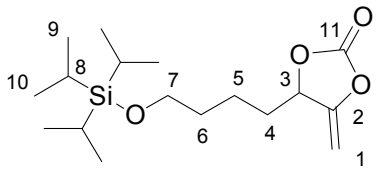
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the mixture of diastereoisomers: 154.0 (*2*), 154.0 (*2*), 152.0 (*13*), 131.8 (*10*), 131.8 (*10*), 123.9 (*9*), 123.9 (*9*), 86.6 (*1*), 86.5 (*1*), 78.6 (*3*), 78.1 (*3*), 42.5 (*4*), 42.5 (*4*), 37.2 (*7*), 36.1 (*7*), 29.2 (*5*), 28.6 (*5*), 25.6 (*11* or *12*), 25.2 (*8*), 25.1 (*8*), 19.8 (*6*), 18.7 (*6*), 17.6 (*11* or *12*), 17.6 (*11* or *12*).

IR (ν, cm^{-1}) (CCl_4): For the mixture of diastereoisomers: 2965, 2925, 2859, 1834, 1703, 1680, 1452, 1378, 1340, 1282, 1135, 1077, 1017.

MS (EI^+, m/z): 224 (M^+).

HRMS (EI^+, m/z): Calculated for $C_{13}H_{20}O_3$: 224.1413.
Found for $C_{13}H_{20}O_3$: 224.1420.

4-Methylene-5-(4-triisopropylsilanyloxy-butyl)-1,3-dioxolan-2-one 3.21 d



MF: $C_{17}H_{32}O_4Si$

MW: 328.52 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 3.9 a** (scale: 0.25 mmol).

Purification: Filtration over silica gel (DCM).

Product: Yellow oil.

Yield: 96%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.17 (m, 1H, *3*), 4.86 (dd, J = 2.4, 3.9 Hz, 1H, *1*), 4.35 (dd, J = 1.9, 3.9 Hz, 1H, *1*), 3.71 (t, J = 5.8 Hz, 2H, *7*), 1.89 (m, 2H, *4*), 1.60 (m, 4H, *5* and *6*), 1.06 (m, 21H, *8*, *9* and *10*).

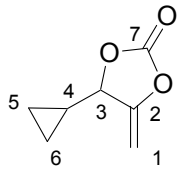
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.4 (*2*), 152.0 (*11*), 86.7 (*1*), 79.8 (*3*), 62.8 (*7*), 34.6 (*4*), 32.1 (*6*), 20.6 (*5*), 17.9 (*9* and *10*), 11.9 (*8*).

IR (ν, cm^{-1}) (CCl_4): 2945, 2865, 2727, 2251, 1842, 1746, 1704, 1681, 1462, 1383, 1338, 1280, 1105, 1011.

MS (EI^+, m/z): 328 (M^+), 286, 242, 223, 211, 199.

HRMS (EI^+, m/z): Calculated for $C_{17}H_{32}O_4Si$: 328.2070.
Found for $C_{17}H_{32}O_4Si$: 328.2083.

4-Cyclopropyl-5-methylene-1,3-dioxolan-2-one 3.21 g



MF: $C_7H_8O_3$

MW: 140.14 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.9 b** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Pale yellow oil.

Yield: 49%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.88 (dd, J = 2.5, 3.6 Hz, 1H, *1*), 4.57 (dd, J = 2.1, 8.4 Hz, 1H, *3*), 4.50 (dd, J = 2.0, 3.7 Hz, 1H, *1*), 1.23 (m, 1H, *4*), 0.78 (m, 2H, *5* or *6*), 0.57 (m, 1H, *5* or *6*), 0.50 (m, 1H, *5* or *6*).

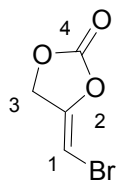
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.7 (*2* or *7*), 151.9 (*2* or *7*), 87.4 (*1*), 84.0 (*3*), 14.3 (*4*), 2.6 (*5* or *6*), 2.2 (*5* or *6*).

IR (ν, cm^{-1}) (CCl_4): 3088, 3013, 2966, 2927, 2860, 1843, 1681, 1378, 1320, 1277, 1181, 1130, 1045.

MS (EI^+, m/z): 140 (M^+).

HRMS (EI^+, m/z): Calculated for $C_7H_8O_3$: 140.0474.
Found for $C_7H_8O_3$: 140.0478.

Z-4-(Bromomethylene)-1,3-dioxolan-2-one **3.41 a**



MF: $C_4H_3BrO_3$

MW: 178.96 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.9 a** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/AcOEt 80/20).

Product: Colorless crystals.

Yield: 87%

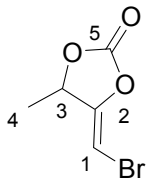
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.50 (t, J = 2.3 Hz, 1H, *1*), 5.02 (d, J = 2.1 Hz, 2H, *3*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.1 (*2* or *4*), 145.0 (*2* or *4*), 78.9 (*1*), 67.5 (*3*).

MS (CI^+, NH_3, m/z) 196 (MNH_4^+), 192, 188, 178, 169, 156.

HRMS (EI^+, m/z) Calculated for $C_4H_3BrO_3$: 177.9266.
Found for $C_4H_3BrO_3$: 177.9262.

4-(1-Bromo-meth-*Z*-ylidene)-5-methyl-1,3-dioxolan-2-one 3.41 b



MF: $C_5H_5O_3Br$

MW: 193.00 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.9 a** (scale: 1.698 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 80/20-50/50).

Product: Yellow crystals.

Yield: 87%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.44 (d, J = 2.0 Hz, 1H, *1*), 5.28 (qd, J = 2.0, 6.5 Hz, 1H, *3*), 1.62 (d, J = 6.5 Hz, 3H, *4*).

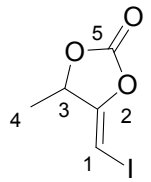
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 150.7 (*2* or *5*), 150.4 (*2* or *5*), 79.0 (*1* or *3*), 76.4 (*1* or *3*), 20.3 (*4*).

IR (ν, cm^{-1}) (CCl_4) 3098, 2989, 2933, 1857, 1689, 1379, 1325, 1288, 1164, 1140, 1103, 1078, 1035.

MS (EI^+, m/z) 194, 192 (M^+), 150, 148, 120, 122.

HRMS (EI^+, m/z) Calculated for $C_5H_5O_3Br$: 191.9422.
Found for $C_5H_5O_3Br$: 191.9419.

4-(1-Iodo-meth-*Z*-ylidene)-5-methyl-1,3-dioxolan-2-one 3.41 c



MF: $C_5H_5O_3I$

MW: 240.00 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.9 a** (scale: 1.847 mmol).

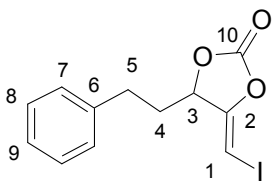
Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product: Brown crystals.

Yield: 95%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.38 (d, J = 1.9 Hz, 1H, *1*), 5.29 (qd, J = 1.9, 6.5 Hz, 1H, *3*), 1.61 (d, J = 6.5 Hz, 3H, *4*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	154.9 (*2*), 150.2 (*5*), 76.8 (*3*), 45.8 (*1*), 20.2 (*4*).
IR (ν, cm^{-1}) (CCl_4)	3086, 2988, 2933, 2867, 1844, 1675, 1447, 1379, 1324, 1276, 1140, 1103, 1076, 1033.
MS (EI^+, m/z)	240 (M^+).
HRMS (EI^+, m/z)	Calculated for $C_5H_5O_3I$: 239.9248. Found for $C_5H_5O_3I$: 239.9280.

4-(1-Iodo-meth-*Z*-ylidene)-5-phenethyl-1,3-dioxolan-2-one 3.41 d



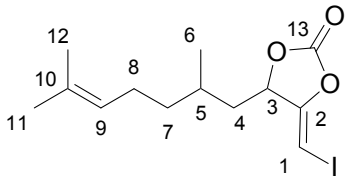
MF: $C_{12}H_{11}O_3I$

MW: 330.12 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 3.9 a** (scale: 0.25 mmol).
Purification:	Filtration over silica gel (DCM).
Product:	Yellow oil.
Yield:	99%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.33 (t, J = 7.0 Hz, 2H, *8*), 7.25 (t, J = 7.4 Hz, 1H, *9*), 7.20 (d, J = 6.9 Hz, 2H, *7*), 5.35 (d, J = 1.9 Hz, 1H, *1*), 5.15 (td, J = 1.8, 5.9 Hz, 1H, *3*), 2.83 (m, 2H, *5*), 2.15 (m, 2H, *4*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	153.6 (*2*), 150.3 (*10*), 139.1 (*6*), 128.7 (*7* or *8*), 128.3 (*7* or *8*), 126.6 (*9*), 79.3 (*3*), 45.9 (*1*), 36.3 (*4*), 30.1 (*5*).
IR (ν, cm^{-1}) (CCl_4)	3085, 3028, 2973, 2930, 2863, 1849, 1674, 1601, 1497, 1451, 1341, 1279, 1145, 1110, 1081, 1034.
MS (EI^+, m/z)	330 (M^+), 285, 267, 203.
HRMS (EI^+, m/z)	Calculated for $C_{12}H_{11}O_3I$: 329.9753. Found for $C_{12}H_{11}O_3I$: 329.9748.

4-(2,6-Dimethyl-hept-5-enyl)-5-(1-iodo-meth-*Z*-ylidene)-1,3-dioxolan-2-one 3.41 e



MF: $C_{13}H_{19}O_3I$

MW: 350.19 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.9 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Pink oil.

Yield: 97% (mixture of 2 diastereoisomers, dr ~ 1/1).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) For the mixture of diastereoisomers: 5.38 (d, J = 1.9 Hz, 1H, *1*), 5.26 (m, 1H, *3*), 5.12 (m, 1H, *9*), 2.04 (m, 3H, *4* and *8*), 1.85-1.17 (m, 4H, *4*, *5* and *7*), 1.74 (s, 3H, *11* or *12*), 1.65 (s, 3H, *11* or *12*), 1.04 (m, 3H, *6*).

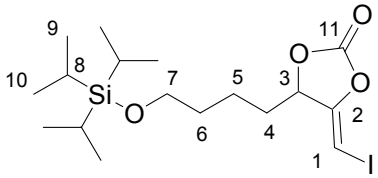
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) For the mixture of diastereoisomers: 154.4 (*2*), 154.3 (*2*), 150.3 (*13*), 131.9 (*10*), 123.8 (*9*), 123.8 (*9*), 79.2 (*3*), 78.8 (*3*), 45.7 (*1*), 45.5 (*1*), 42.2 (*4*), 37.0 (*7*), 36.1 (*7*), 29.0 (*5*), 28.5 (*5*), 25.6 (*11* or *12*), 25.1 (*8*), 25.0 (*8*), 19.7 (*6*), 18.7 (*6*), 17.6 (*11* or *12*), 17.6 (*11* or *12*).

IR (ν, cm^{-1}) (CCl_4) For the mixture of diastereoisomers: 3086, 2961, 2925, 2856, 1853, 1674, 1455, 1377, 1338, 1279, 1143, 1079.

MS (EI^+, m/z) 350 (M^+), 319, 264, 237, 223.

HRMS (EI^+, m/z) Calculated for $C_{13}H_{19}O_3I$: 350.0379.
Found for $C_{13}H_{19}O_3I$: 350.0388.

4-(1-Iodo-meth-*Z*-ylidene)-5-(4-triisopropylsilanyloxy-butyl)-1,3-dioxolan-2-one 3.41 f



MF: $C_{17}H_{31}O_4SiI$

MW: 454.42 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.9 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product: Yellow oil.

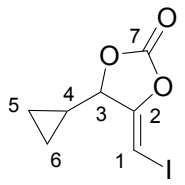
Yield: <69%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.35 (d, J = 1.8 Hz, 1H, *1*), 5.19 (m, 1H, *3*), 3.71 (t, J = 5.5 Hz, 2H, *7*), 1.88 (m, 2H, *4*), 1.59 (m, 4H, *5* and *6*), 1.06 (m, 21H, *8*, *9* and *10*).

^{13}C NMR (δ, ppm) 153.8 (*2*), 150.4 (*11*), 80.4 (*3*), 62.6 (*7*), 45.6 (*1*), 34.4 (*4*), 32.0 (*5* or *6*), 20.5

($CDCl_3$, 100 MHz)	(*5* or *6*), 17.9 (*9* and *10*), 11.9 (*8*).
IR (ν, cm^{-1}) (CCl_4)	3086, 2945, 2894, 2865, 1853, 1674, 1463, 1383, 1339, 1280, 1141, 1110, 1068, 1014.
MS (EI^+, m/z)	454 (M^+), 411, 368, 337.
HRMS (EI^+, m/z)	Calculated for $C_{17}H_{31}O_4SiI$: 454.1037. Found for $C_{17}H_{31}O_4SiI$: 454.1041.

4-Cyclopropyl-5-(1-iodo-meth-*Z*-ylidene)-1,3-dioxolan-2-one 3.41 g



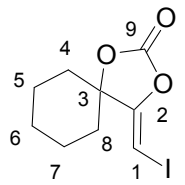
MF: $C_7H_7O_3I$

MW: 266.03 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 3.9 c** (scale: 0.176 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 96/4).
Product:	Orange oil.
Yield:	32%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.52 (d, J = 1.8 Hz, 1H, *1*), 4.53 (dd, J = 1.7, 8.7 Hz, 1H, *3*), 1.24 (m, 1H, *4*), 0.82 (m, 2H, *5* or *6*), 0.60 (m, 1H, *5* or *6*), 0.50 (m, 1H, *5* or *6*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	153.4 (*2*), 150.2 (*7*), 84.8 (*3*), 46.7 (*1*), 14.2 (*4*), 3.0 (*5* or *6*), 2.5 (*5* or *6*).
IR (ν, cm^{-1}) (CCl_4)	3089, 3012, 2926, 2855, 1855, 1674, 1320, 1274, 1142, 1107, 1037.
MS (EI^+, m/z)	266 (M^+), 222, 205, 192, 180.
HRMS (EI^+, m/z)	Calculated for $C_7H_7O_3I$: 265.9440. Found for $C_7H_7O_3I$: 265.9447.

4-(1-Iodo-meth-*Z*-ylidene)-1,3-dioxa-spiro[4.5]decan-2-one 3.41 h



MF: $C_9H_{11}IO_3$

MW: 294.09 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 3.9 a** (scale: 0.973 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: White solid.

Yield: 83%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.34 (s, 1H, *1*), 2.06 (br d, J = 9.2 Hz, 2H), 1.82–1.64 (m, 7H), 1.41–1.30 (m, 1H) (*4*, *5*, *6*, *7* and *8*).

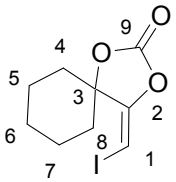
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 159.1 (*2* or *9*), 149.8 (*2* or *9*), 87.5 (*3*), 45.3 (*1*), 36.5 (*4*, *5*, *6*, *7* and/or *8*), 24.2 (*4*, *5*, *6*, *7* and/or *8*), 21.6 (*4*, *5*, *6*, *7* and/or *8*).

IR (ν, cm^{-1}) (CCl_4): 2943, 1846, 1668, 1192, 1048.

MS (CI^+,NH_3, m/z): 312 (MNH_4^+).

HRMS (EI^+, m/z): Calculated for $C_9H_{11}IO_3$: 293.9753.
Found for $C_9H_{11}IO_3$: 293.9751.

4-(1-Iodo-meth-*E*-ylidene)-1,3-dioxa-spiro[4.5]decan-2-one 3.42



MF: $C_9H_{11}IO_3$

MW: 294.09 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 3.10 a** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: White crystals.

Yield: 95%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.87 (s, 1H, *1*), 2.49 (td, J = 4.6, 13.9 Hz, 2H,), 1.95 (br d, J = 13.9 Hz, 2H), 1.83–1.66 (m, 5H), 1.44–1.27 (m, 1H) (*4*, *5*, *6*, *7* and *8*).

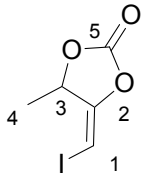
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.4 (*2* or *9*), 150.1 (*2* or *9*), 88.2 (*3*), 47.6 (*1*), 32.6 (*4*, *5*, *6*, *7* and/or *8*), 24.2 (*4*, *5*, *6*, *7* and/or *8*), 21.4 (*4*, *5*, *6*, *7* and/or *8*).

IR (ν, cm^{-1}) (CCl_4): 2944, 2864, 1841, 1658, 1264, 1204, 1128, 1057.

MS (CI^+,NH_3, m/z): 312 (MNH_4^+).

HRMS (EI^+, m/z): Calculated for $C_9H_{11}IO_3$: 293.9753.
Found for $C_9H_{11}IO_3$: 293.9753.

4-(1-Iodo-meth-*E*-ylidene)-5-methyl-1,3-dioxolan-2-one 3.43 a



MF: $C_5H_5O_3I$

MW: 240.00 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.10 a** (scale: 1.263 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil.

Yield: 35%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.91 (d, J = 2.2 Hz, 1H, *1*), 5.26 (qd, J = 2.2, 6.5 Hz, 1H, *3*), 1.73 (d, J = 6.5 Hz, 3H, *4*).

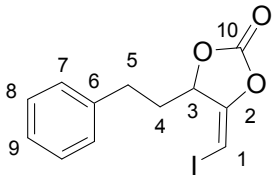
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.4 (*2* or *5*), 151.1 (*2* or *5*), 78.0 (*3*), 50.1 (*1*), 18.4 (*4*).

IR (ν, cm^{-1}) (CCl_4): 3085, 2988, 2933, 2866, 1841, 1673, 1450, 1376, 1318, 1279, 1139, 1119, 1073, 1035.

MS (EI^+, m/z): 240 (M^+), 196.

HRMS (EI^+, m/z): Calculated for $C_5H_5O_3I$: 239.9248.
Found for $C_5H_5O_3I$: 239.9272.

4-(1-Iodo-meth-*E*-ylidene)-5-phenethyl-1,3-dioxolan-2-one 3.43 b



MF: $C_{12}H_{11}O_3I$

MW: 330.12 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.10 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 96/4).

Product: Pink oil.

Yield: 66%

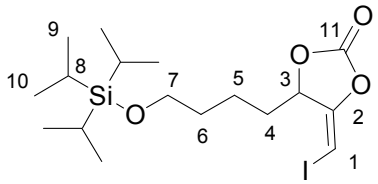
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.34 (m, 2H, *7*), 7.26 (m, 3H, *8* and *9*), 5.93 (d, J = 2.2 Hz, 1H, *1*), 5.16 (dt, J = 2.3, 8.3 Hz, 1H, *3*), 2.87 (m, 1H, *5*), 2.76 (m, 1H, *5*), 2.53 (m, 1H, *4*), 2.26 (m, 1H, *4*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.2 (*2* or *10*), 150.0 (*2* or *10*), 139.2 (*6*), 128.6 (*7* or *8*), 128.4 (*7* or *8*), 126.5 (*9*), 80.5 (*3*), 50.6 (*1*), 33.2 (*4*), 29.9 (*5*).

IR (ν, cm^{-1}) (CCl_4): 3085, 3029, 2954, 2927, 2859, 1843, 1670, 1498, 1453, 1332, 1281, 1144,

	1103, 1077, 1035, 1004.
MS (EI^+, m/z)	330 (M^+), 285, 220, 205.
HRMS (EI^+, m/z)	Calculated for $C_{12}H_{11}O_3I$: 329.9753. Found for $C_{12}H_{11}O_3I$: 329.9753.

4-(1-Iodo-meth-*E*-ylidene)-5-(4-triisopropylsilanyloxy-butyl)-1,3-dioxolan-2-one **3.43 c**

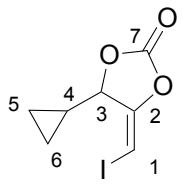


MF: $C_{17}H_{31}O_4SiI$

MW: 454.42 g.mol^{-1}

Reaction:	The reaction was carried out according to the **General Procedure 3.10 a** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 80/20).
Product:	Yellow oil.
Yield:	64%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.91 (d, J = 2.2 Hz, 1H, *1*), 5.20 (dt, J = 2.5, 7.5 Hz, 1H, *3*), 3.71 (t, J = 5.9 Hz, 2H, *7*), 2.19 (m, 1H, *4*), 2.00 (m, 1H, *4*), 1.60 (m, 4H, *5* and *6*), 1.06 (m, 21H, *8*, *9* and *10*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	151.3 (*11*), 150.4 (*2*), 81.5 (*3*), 62.6 (*7*), 50.3 (*1*), 32.1 (*6*), 31.5 (*4*), 20.1 (*5*), 18.0 (*9* and *10*), 11.9 (*8*).
IR (ν, cm^{-1}) (CCl_4)	3311, 3085, 2961, 2865, 2727, 2238, 1858, 1744, 1670, 1462, 1383, 1333, 1277, 1254, 1118, 1017.
MS (EI^+, m/z)	454 (M^+), 411, 368, 337, 325.
HRMS (EI^+, m/z)	Calculated for $C_{17}H_{31}O_4SiI$: 454.1037. Found for $C_{17}H_{31}O_4SiI$: 454.1036.

4-Cyclopropyl-5-(1-iodo-meth-*E*-ylidene)-1,3-dioxolan-2-one **3.43 d**



MF: $C_7H_7O_3I$

MW: 266.03 g.mol^{-1}

Reaction:	The reaction was carried out according to the **General Procedure 3.10 b** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 96/4).

Product: Pink oil.

Yield: 76%

^{1}H NMR (δ, ppm) (CDCl$_3$, 400 MHz): 6.00 (d, J = 2.1 Hz, 1H, *1*), 4.83 (dd, J = 2.0, 7.1 Hz, 1H, *3*), 1.36 (m, 1H, *4*), 0.84 (m, 2H, *5* or *6*), 0.72 (m, 1H, *5* or *6*), 0.58 (m, 1H, *5* or *6*).

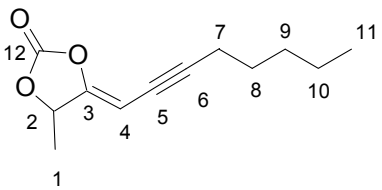
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz): 151.1 (*2* or *7*), 150.9 (*2* or *7*), 83.8 (*3*), 51.1 (*1*), 13.1 (*4*), 5.7 (*5* or *6*), 2.4 (*5* or *6*).

IR (ν, cm^{-1}) (CCl$_4$): 3085, 3015, 2927, 2856, 1839, 1670, 1311, 1270, 1139, 1103, 1031, 1020.

MS (EI$^+$, m/z): 266 (M$^+$), 222, 207, 192.

HRMS (EI$^+$, m/z): Calculated for $C_7H_7O_3I$: 265.9440.
Found for $C_7H_7O_3I$: 265.9434.

4-Methyl-5-oct-2-yn-*Z*-ylidene-1,3-dioxolan-2-one — 3.48 a



MF: $C_{12}H_{16}O_3$

MW: 208.25 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.11 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et$_2$O 90/10).

Product: Yellow oil.

Yield: 67%

^{1}H NMR (δ, ppm) (CDCl$_3$, 400 MHz): 5.30 (qm, J = 6.5 Hz, 1H, *2*), 4.82 (q, J = 2.2 Hz, 1H, *4*), 2.35 (td, J = 2.2, 7.1 Hz, 2H, *7*), 1.58 (d, J = 6.5 Hz, 3H, *1*), 1.53 (m, 2H, *8*), 1.35 (m, 4H, *9* and *10*), 0.91 (t, J = 7.1 Hz, 3H, *11*).

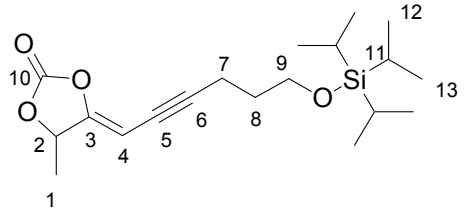
^{13}C NMR (δ, ppm) (CDCl$_3$, 100 MHz): 155.3 (*3*), 151.2 (*12*), 97.4 (*6*), 84.5 (*4*), 76.3 (*2*), 71.2 (*5*), 31.0 (*9* or *10*), 28.1 (*8*), 22.1 (*9* or *10*), 20.4 (*1*), 19.5 (*7*), 13.9 (*11*).

IR (ν, cm^{-1}) (CCl$_4$): 2932, 2863, 2222, 1853, 1690, 1457, 1375, 1355, 1330, 1307, 1214, 1140, 1103, 1078, 1031.

MS (EI$^+$, m/z): 208 (M$^+$), 161, 149, 121, 117, 107.

HRMS (EI$^+$, m/z): Calculated for $C_{12}H_{16}O_3$: 208.1100.
Found for $C_{12}H_{16}O_3$: 208.1104.

4-Methyl-5-(6-triisopropylsilanyloxy-hex-2-yn-*Z*-ylidene)-1,3-dioxolan-2-one — 3.48 b

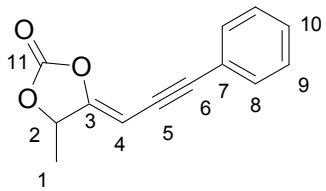


MF: $C_{19}H_{32}O_4Si$

MW: 352.54 g.mol^{-1}

Reaction:	The reaction was carried out according to the **General Procedure 3.11 a** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 90/10).
Product:	Brown oil.
Yield:	67%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.30 (qm, J = 6.4 Hz, 1H, *2*), 4.81 (q, J = 2.1 Hz, 1H, *4*), 3.78 (t, J = 6.0 Hz, 2H, *9*), 2.48 (td, J = 1.9, 7.0 Hz, 2H, *7*), 1.77 (m, 2H, *8*), 1.57 (d, J = 6.5 Hz, 3H, *1*), 1.06 (m, 21H, *11*, *12* and *13*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	155.4 (*3*), 151.1 (*10*), 97.0 (*6*), 84.4 (*4*), 76.3 (*2*), 71.3 (*5*), 61.7 (*9*), 31.7 (*8*), 20.4 (*1*), 17.9 (*12* and *13*), 16.0 (*7*), 11.9 (*11*).
IR (ν, cm^{-1}) (CCl_4)	2944, 2894, 2865, 1847, 1691, 1463, 1307, 1213, 1138, 1105, 1078, 1031.
MS (EI$^+$, m/z)	352 (M$^+$), 309, 265, 237, 223.
HRMS (EI$^+$, m/z)	Calculated for $C_{19}H_{32}O_4Si$: 352.2070. Found for $C_{19}H_{32}O_4Si$: 352.2071.

4-Methyl-5-(3-phenyl-prop-2-yn-*Z*-ylidene)-1,3-dioxolan-2-one 3.48 c



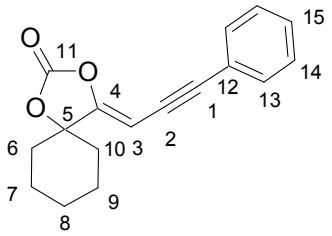
MF: $C_{13}H_{10}O_3$

MW: 214.22 g.mol^{-1}

Reaction:	The reaction was carried out according to the **General Procedure 3.11 a** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 90/10).
Product:	Yellow crystals.
Yield:	72%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.47 (m, 2H, *8*), 7.34 (m, 3H, *9* and *10*), 5.37 (qd, J = 2.0, 6.5 Hz, 1H, *2*), 5.07 (d, J = 2.0 Hz, 1H, *4*), 1.63 (d, J = 6.5 Hz, 3H, *1*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	156.1 (*3*), 151.0 (*11*), 131.5 (*8*), 128.6 (*10*), 128.3 (*9*), 122.6 (*7*), 95.6 (*5* or *6*), 84.1 (*4*), 80.1 (*5* or *6*), 76.5 (*2*), 20.3 (*1*).

IR (ν, cm^{-1}) (CCl_4)	3059, 2983, 2959, 2928, 2865, 1851, 1687, 1306, 1206, 1138, 1102, 1081, 1041.
MS (EI^+, m/z)	214 (M^+), 142, 141, 115.
HRMS (EI^+, m/z)	Calculated for $C_{13}H_{10}O_3$: 214.0630. Found for $C_{13}H_{10}O_3$: 214.0623.

4-(3-Phenyl-prop-2-yn-*Z*-ylidene)-1,3-dioxa-spiro[4.5]decan-2-one **3.48 d**



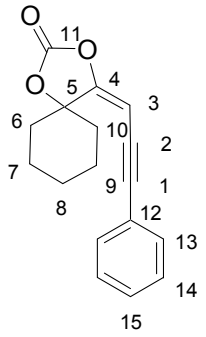
MF: $C_{17}H_{16}O_3$

MW: 268.31 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 3.11 a** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 92/8).
Product:	Yellow crystals.
Yield:	61%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.47 (m, 2H, *13*), 7.33 (m, 3H, *14* and *15*), 5.01 (s, 1H, *3*), 2.06 (d, J = 12.3 Hz, 2H), 1.80-1.58 (m, 7H), 1.34 (m, 1H) (*6*, *7*, *8*, *9* and *10*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	160.3 (*4*), 150.5 (*11*), 131.4 (*13* or *14*), 128.5 (*15*), 128.3 (*13* or *14*), 122.7 (*12*), 95.5 (*1* or *2*), 86.9 (*5*), 83.0 (*3*), 80.5 (*1* or *2*), 36.4 (*6* and *10*), 24.2 (*8*), 21.5 (*7* and *9*).
IR (ν, cm^{-1}) (CCl_4)	3056, 2943, 2863, 1844, 1679, 1492, 1447, 1346, 1260, 1191, 1126, 1052, 1007.
MS (EI^+, m/z)	268 (M^+), 196, 167, 149.
HRMS (EI^+, m/z)	Calculated for $C_{17}H_{16}O_3$: 268.1100. Found for $C_{17}H_{16}O_3$: 268.1097.

4-(3-Phenyl-prop-2-yn-*E*-ylidene)-1,3-dioxa-spiro[4.5]decan-2-one **3.48 e**



MF: $C_{17}H_{16}O_3$

MW: 268.31 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.11 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Yellow crystals.

Yield: 94%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.42 (m, 2H), 7.37 (m, 3H) (*13*, *14* and *15*), 5.86 (s, 1H, *3*), 2.42 (td, J = 3.5, 14.1 Hz, 2H), 2.01 (d, J = 13.9 Hz, 2H), 1.86-1.65 (m, 5H), 1.32 (m, 1H) (*6*, *7*, *8*, *9* and *10*).

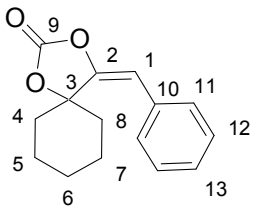
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 161.1 (*4*), 150.4 (*11*), 130.8 (*13* or *14*), 128.5 (*15*), 128.4 (*13* or *14*), 122.6 (*12*), 95.6 (*1* or *2*), 88.0 (*5*), 84.5 (*3*), 81.3 (*1* or *2*), 33.3 (*6* and *10*), 24.5 (*8*), 21.4 (*7* and *9*).

IR (ν, cm^{-1}) (CCl_4): 3060, 2942, 2860, 1842, 1670, 1492, 1446, 1352, 1264, 1213, 1177, 1126, 1072, 995.

MS (EI^+, m/z): 268 (M^+), 224, 196, 167.

HRMS (EI^+, m/z): Calculated for $C_{17}H_{16}O_3$: 268.1100.
Found for $C_{17}H_{16}O_3$: 268.1112.

4-(1-Phenyl-meth-*E*-ylidene)-1,3-dioxa-spiro[4.5]decan-2-one 3.49 a



MF: $C_{15}H_{16}O_3$

MW: 244.29 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 3.12** (scale: 0.25 mmol).

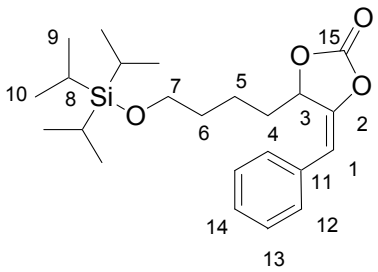
Purification: Flash column chromatography (silica gel, PE/Et_2O 96/4).

Product: Yellow crystals.

Yield: 79%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.34 (m, 3H, *12* and *13*), 7.22 (d, J = 7.2 Hz, 2H, *11*), 6.45 (s, 1H, *1*), 1.97 (m, 2H), 1.80-1.59 (m, 7H), 0.98 (m, 1H) (*4*, *5*, *6*, *7* and *8*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.3 (*2*), 151.3 (*9*), 132.0 (*10*), 129.3 (*11*), 128.3 (*12*), 127.7 (*13*), 105.4 (*1*), 87.2 (*3*), 35.2 (*4* and *8*), 24.2 (*6*), 21.3 (*5* and *7*).
IR (ν, cm^{-1}) (CCl_4)	3060, 3027, 2941, 2861, 1826, 1694, 1448, 1350, 1267, 1214, 1157, 1130, 1056, 1002.
MS (EI^+, m/z)	244 (M^+), 200, 185.
HRMS (EI^+, m/z)	Calculated for $C_{15}H_{16}O_3$: 244.1100. Found for $C_{15}H_{16}O_3$: 244.1096.

4-(1-Phenyl-meth-*E*-ylidene)-5-(4-triisopropylsilanyloxy-butyl)-1,3-dioxolan-2-one **3.49 b**



MF: $C_{23}H_{36}O_4Si$

MW: 404.62 $g.mol^{-1}$

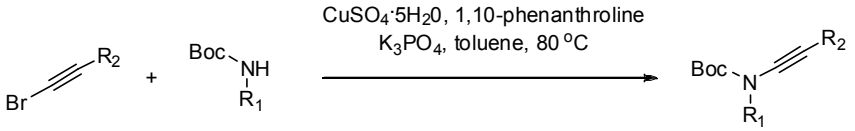
Reaction:	The reaction was carried out according to the **General Procedure 3.12** (scale: 0.143 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 93/7).
Product:	Yellow oil.
Yield:	40%

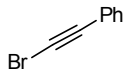
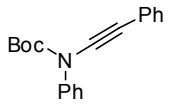
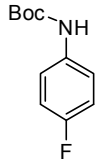
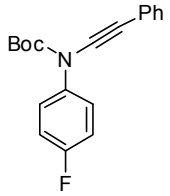
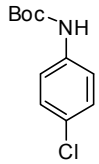
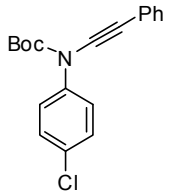
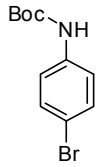
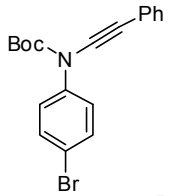
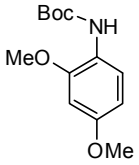
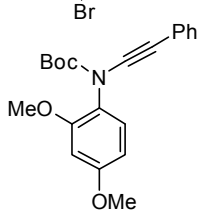
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.36 (t, J = 7.7 Hz, 2H, *13*), 7.27 (t, J = 8.0 Hz, 1H, *14*), 7.15 (d, J = 7.3 Hz, 2H, *12*), 6.37 (d, J = 2.2 Hz, 1H, *1*), 5.70 (dt, J = 2.6, 7.6 Hz, 1H, *3*), 3.61 (t, J = 5.7 Hz, 2H, *7*), 1.87 (m, 1H, *4*), 1.67 (m, 1H, *4*), 1.51 (m, 4H, *5* and *6*), 1.04 (m, 21H, *8*, *9* and *10*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	151.9 (*15*), 147.6 (*2*), 132.2 (*11*), 128.9 (*13*), 127.8 (*12*), 127.5 (*14*), 105.6 (*1*), 79.8 (*3*), 62.6 (*7*), 32.0 (*4*, *5* or *6*), 31.6 (*4*, *5* or *6*), 20.4 (*4*, *5* or *6*), 17.9 (*9* and *10*), 11.9 (*8*).
IR (ν, cm^{-1}) (CCl_4)	3062, 3028, 2945, 2893, 2865, 1838, 1691, 1462, 1381, 1344, 1225, 1179, 1123, 1070, 1018.
MS (EI^+, m/z)	404 (M^+), 359, 331.
HRMS (EI^+, m/z)	Calculated for $C_{23}H_{36}O_4Si$: 404.2383. Found for $C_{23}H_{36}O_4Si$: 404.2365.

4. Synthesis of functionalized oxazolones by a sequence of copper(II)- and gold(I)-catalyzed transformations

4.1. Synthesis of the precursors

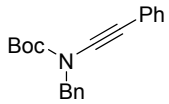
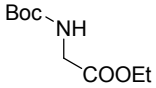
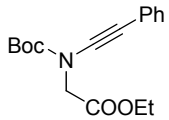
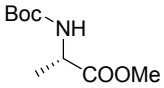
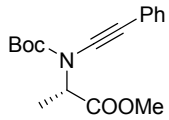
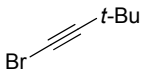
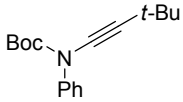
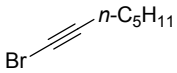
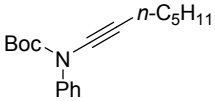
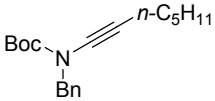
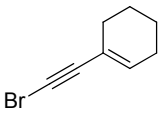
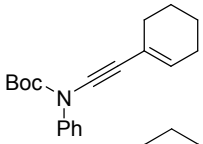
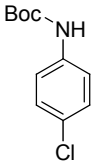
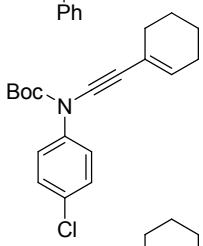
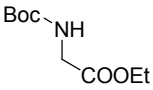
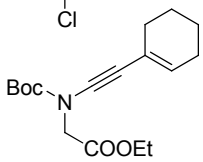
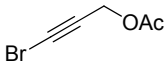
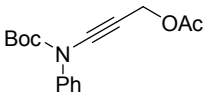
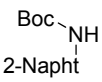
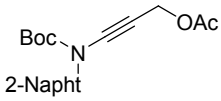
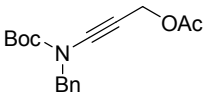
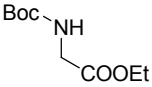
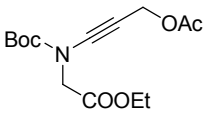
Substrates **4.11 a-v** were synthesized by a copper(II)-catalyzed coupling between bromoalkynes **4.9 a-g** and *tert*-butyloxycarbamates **4.10 a-i** following a slightly modified version of a procedure previously reported by Hsung and coworkers.[327]



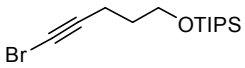
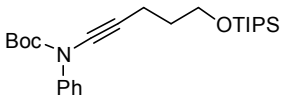
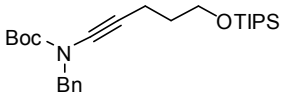
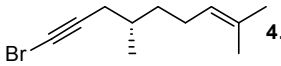
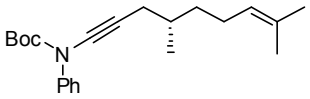
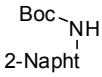
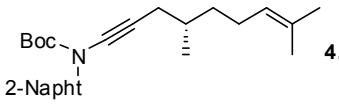
bromoalkyne		carbamate		product		time	yield[a]
	**4.9 a**		**4.10 a**		**4.11 a**	40 h	80%
"			**4.10 b**		**4.11 b**	16 h	65%
"			**4.10 c**		**4.11 c**	18 h	68%
"			**4.10 d**		**4.11 d**	16 h	48%
"			**4.10 e**		**4.11 e**	48 h	22%

(continued on the next page)

[327] (a) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170-4177.
(b) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151-1154.

bromoalkyne		carbamate		product		time	yield[a]
"			**4.10 g**		**4.11 f**	48 h	62%
"			**4.10 h**		**4.11 g**	36 h	70%
"			**4.10 i**		**4.11 h**	48 h	23%
	**4.9 b**		**4.10 a**		**4.11 i**	38 h	24%
	**4.9 c**		**4.10 a**		**4.11 j**	52 h	75%
"			**4.10 g**		**4.11 k**	48 h	69%
	**4.9 d**		**4.10 a**		**4.11 l**	67 h	72%
"			**4.10 c**		**4.11 m**	67 h	80%
"			**4.10 h**		**4.11 n**	67 h	50%
	**4.9 e**		**4.10 a**		**4.11 o**	65 h	55%
"			**4.10 f**		**4.11 p**	48 h	49%
"			**4.10 g**		**4.11 q**	72 h	49%
"			**4.10 h**		**4.11 r**	62 h	48%

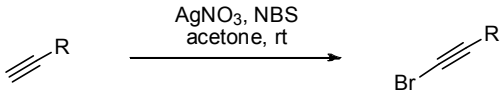
(continued on the next page)

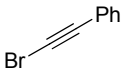
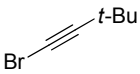
bromoalkyne		carbamate		product		time	yield[a]
	**4.9 f**		**4.10 a**		**4.11 s**	45 h	88%
"			**4.10 g**		**4.11 t**	62 h	72%
	**4.9 g**		**4.10 a**		**4.11 u**	48 h	74%
"			**4.10 f**		**4.11 v**	48 h	65%

[a] Isolated yield.

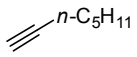
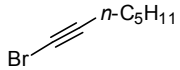
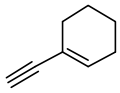
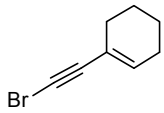
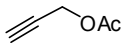
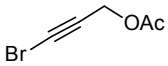
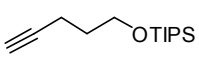
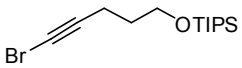
General procedure 4.1: To a solution of a bromoalkyne (1 equiv) in dry toluene (0.33 M) were sequentially added the carbamate (1.2 equiv), K_3PO_4 (2.4 equiv), $CuSO_4{\cdot}5H_2O$ (0.2 equiv) and 1,10-phenanthroline (0.4 equiv). The reaction mixture was capped and heated at 80 °C for 16 to 72 h while being monitored by TLC analysis. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite, and the filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to afford the desired carbamate.

Bromoalkynes **4.9 a-f** were prepared by bromination of the corresponding terminal alkyne under standard conditions.[325]



substrate	product		time	yield[a]
		**4.9 a**	1 h 30 min	95%
		**4.9 b**	4 h	8% (volatile)

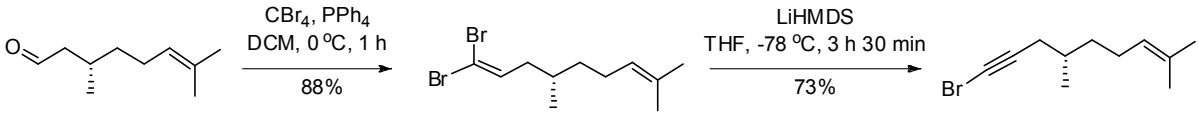
(continued on the next page)

substrate	product		time	yield[a]
		**4.9 c**	2 h 30 min	80%
		**4.9 d**	1 h	79%
		**4.9 e**	4 h	66%
		**4.9 f**	1 h	58%

[a] Isolated yield.

General procedure 4.2: To a solution of terminal alkyne (1 equiv) in acetone (0.15 M) at 0 °C were added the NBS (1.2 equiv) and $AgNO_3$ (0.25 equiv). The reaction vessel was wrapped in aluminum foil to avoid light exposure and the reaction mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was cooled again at 0 °C, quenched with cold water and extracted 3 times with diethyl ether. The combined organic layers were washed 2 times with water and once with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the bromoalkyne.

Bromoalkyne **4.9 g** was prepared by the Corey-Fuchs method[328] starting from (*S*)-(-)-citronellal.



(*S*)-(-)-citronellal **4.9 g**

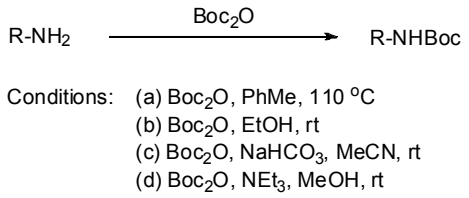
General procedure 4.3: To a solution of PPh_3 (4 equiv) in DCM (2 M) at 0 °C was added a solution of CBr_4 (2 equiv) in DCM (2 M). The mixture was stirred at 0 °C for 5 min, then a solution of (*S*)-(-)-citronellal (1 equiv) in DCM (1 M) was added dropwise. The mixture was allowed to react at 0 °C for 1 h. Upon

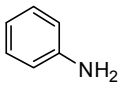
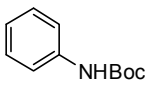
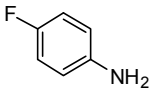
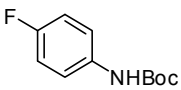
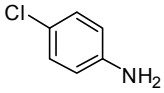
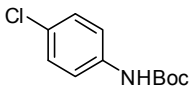
[328] (a) Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718-8719.
(b) Gung, B. W.; Dickson, H. *Org. Lett.* **2002**, *4*, 2517-2519.
(c) Simpkins, S. M. E.; Kariuki, B. M.; Arico, C. S.; Cox, L. R. *Org. Lett.* **2003**, *5*, 3971-3974.

completion, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted 2 times with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Petroleum ether was added to the residue, which was then filtered and reevaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether) to give the dibromoalkene.

The resulting dibromoalkene (1 equiv) was dissolved in THF (0.1 M) and cooled at -78 °C. LiHMDS (2 equiv, 1 M in THF solution) was added and the mixture was stirred at -78 °C for 3 h 30 min. Upon completion, the reaction was quenched with saturated NH_4Cl aqueous solution and extracted 2 times with petroleum ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether) to give the expected bromoalkyne.

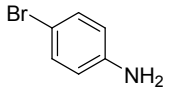
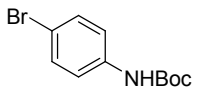
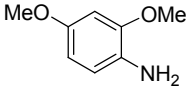
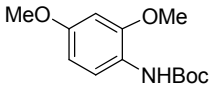
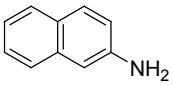
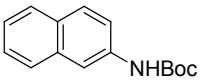
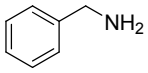
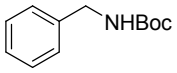
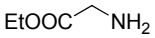
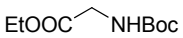
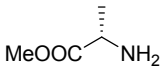
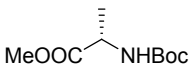
Carbamates **4.10 a-i** were obtained from the corresponding amines using classical methods described in the literature.[329]



substrate	product		conditions	time	yield[a]
		**4.10 a**	a	2 h	82%
		**4.10 b**	a	1 h	85%
		**4.10 c**	a	2 h	43%

(continued on the next page)

[329] (a) Schlosser, M.; Ginanneschi, A.; Leroux, F. *Eur. J. Org. Chem.* **2006**, *2006*, 2956-2969.
(b) Vilaivan, T. *Tetrahedron Lett.* **2006**, *47*, 6739-6742.
(c) Simpson, G. L.; Gordon, A. H.; Lindsay, D. M.; Promsawan, N.; Crump, M. P.; Mulholland, K.; Hayter, B. R.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 10638-10639.
(d) Yuste, F.; Ortiz, B.; Carrasco, A.; Peralta, M.; Quintero, L.; Sánchez-Obregón, R.; Walls, F.; García Ruano, J. L. *Tetrahedron: Asymmetry* **2000**, *11*, 3079-3090.

substrate	product		conditions	time	yield[a]
		**4.10 d**	a	3 h	70%
		**4.10 e**	a	1 h	95%
		**4.10 f**	a	2 h	83%
		**4.10 g**	b	5 min	83%
		**4.10 h**	c	24 h	47%
		**4.10 i**	d	24 h	90%

[a] Isolated yield.

General procedure 4.4: Conditions a:[329a] To a solution of amine (1 equiv) in toluene (1 M) was added Boc_2O (1.5 equiv). The mixture was stirred at reflux (110 °C) and, upon completion, concentrated under reduced pressure. The residue was recrystallized in petroleum ether / ethyl acetate to afford the pure final compound.

Conditions b:[329b] To a solution of amine (1 equiv) in EtOH (1 M) at rt was added Boc_2O (1.1 equiv). The mixture was stirred at rt for 5 min, then concentrated under reduced pressure. The residue was recrystallized in petroleum ether to afford the clean final product.

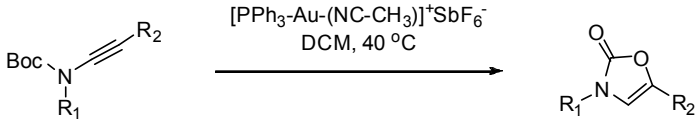
Conditions c:[329c] To a solution of amine (1 equiv) in MeCN (0.2 M) at 0 °C was added $NaHCO_3$ (3 equiv) and Boc_2O (1 equiv). The mixture was allowed to react at rt for 24 h, and then concentrated under reduced pressure. The residue was diluted with water and extracted 3 times with DCM. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / ethyl acetate) to give the expected final product.

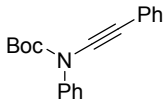
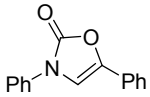
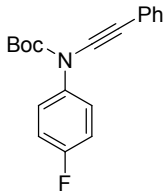
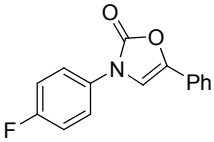
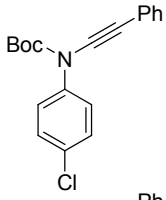
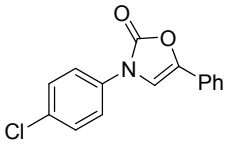
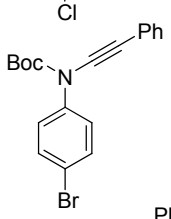
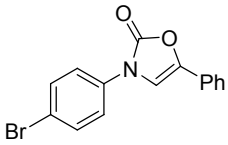
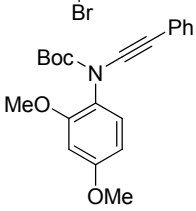
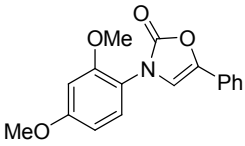
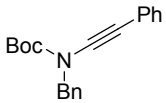
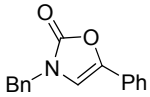
Conditions d:[329d] To a solution of amine (1 equiv) in MeOH (0.75 M) was added NEt_3 (1.5 equiv) and Boc_2O (1.05 equiv). The mixture was allowed to react at rt for 24 h, and then concentrated under reduced pressure. The residue was diluted with water and extracted 3 times with DCM. The

combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the pure final product.

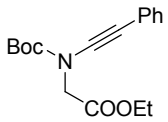
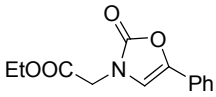
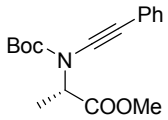
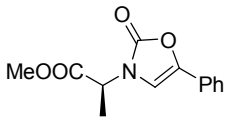
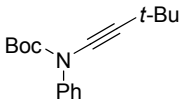
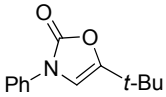
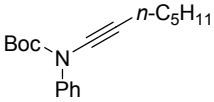
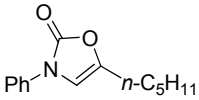
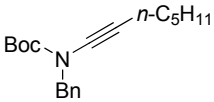
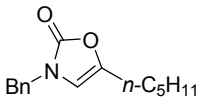
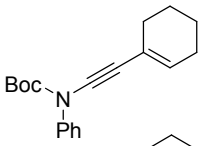
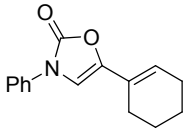
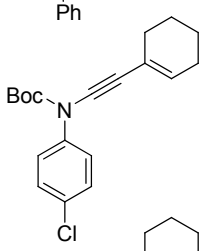
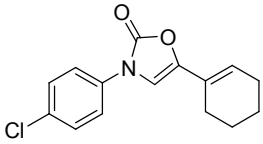
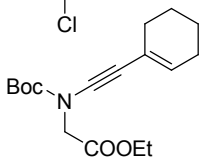
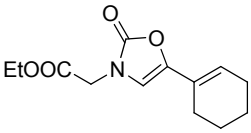
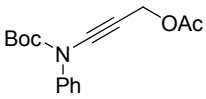
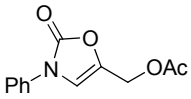
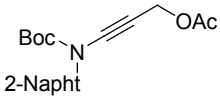
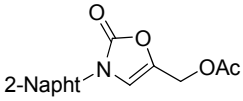
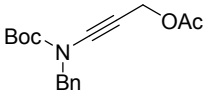
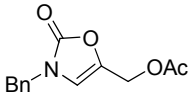
4.2. Gold(I)-catalyzed formation of 4-oxazolin-2-ones

As we saw in Chapter 4, the *N*-alkynyl *tert*-butyloxycarbamates **4.11 a-v** were rearranged in the presence of a gold(I)-catalyst into 4-oxazolin-2-ones **4.12 a-v**.

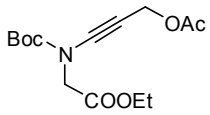
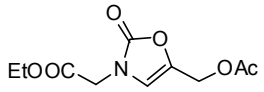
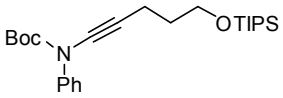
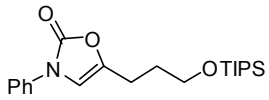
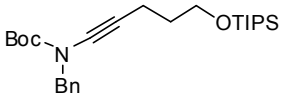
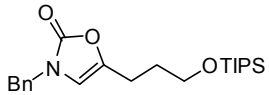
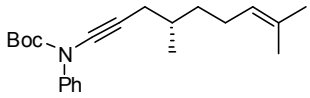
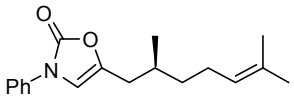
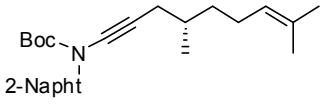
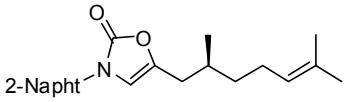


substrate		product		time	yield[a]
	**4.11 a**		**4.12 a**	25 min	83%
	**4.11 b**		**4.12 b**	10 min	88%
	**4.11 c**		**4.12 c**	10 min	88%
	**4.11 d**		**4.12 d**	10 min	83%
	**4.11 e**		**4.12 e**	16 h	85%
	**4.11 f**		**4.12 f**	16 h	78%

(continued on the next page)

substrate		product		time	yield[a]
	**4.11 g**		**4.12 g**	12 h	93%
	**4.11 h**		**4.12 h**	8 h	94%
	**4.11 i**		**4.12 i**	2 h	58%
	**4.11 j**		**4.12 j**	30 min	74%
	**4.11 k**		**4.12 k**	40 min	50%[b]
	**4.11 l**		**4.12 l**	30 min	78%
	**4.11 m**		**4.12 m**	10 min	94%
	**4.11 n**		**4.12 n**	5 h	70%
	**4.11 o**		**4.12 o**	40 min	71%
	**4.11 p**		**4.12 p**	45 min	88%
	**4.11 q**		**4.12 q**	20 min	50%[b]

(continued on the next page)

substrate		product		time	yield[a]
	**4.11 r**		**4.12 r**	20 min	49%
	**4.11 s**		**4.12 s**	1 h	69%
	**4.11 t**		**4.12 t**	40 min	38%[b]
	**4.11 u**		**4.12 u**	30 min	71%
	**4.11 v**		**4.12 v**	3 h	80%

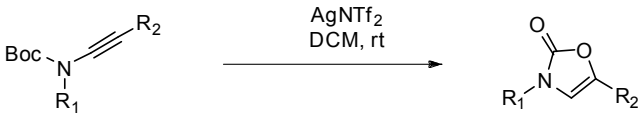
[a] Isolated yield. [b] Yield estimated by ^{1}H NMR of the crude mixture using 1,3,5-trimethoxybenzene as internal standard.

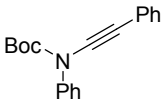
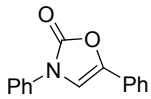
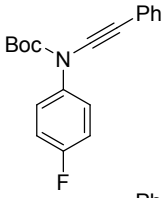
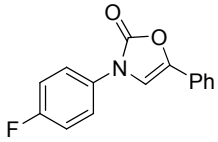
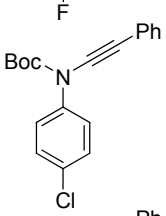
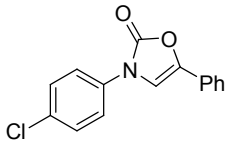
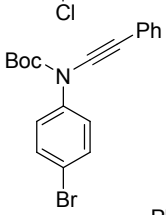
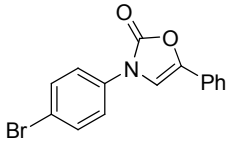
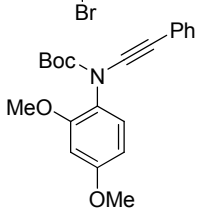
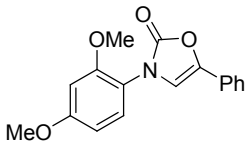
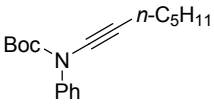
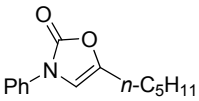
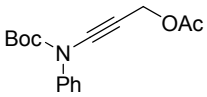
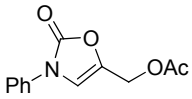
General procedure 4.5: To a solution of the substrate (1 equiv) in dry dichloromethane (0.5 M) was added $[Ph_3P\text{-}Au\text{-}(NC\text{-}CH_3)]^+SbF_6^-$ (0.01 equiv). The mixture was heated at 40 °C and monitored periodically by TLC. Upon completion, the mixture was evaporated and the crude mixture purified either by flash column chromatography (silica gel, petroleum ether / diethyl ether) or by recrystallization in petroleum ether to afford the desired oxazolones.

When the instability of the final oxazolone did not allow its isolation, the reaction was performed analogously in CD_2Cl_2. Upon completion, 1,3,5-trimethoxybenzene (1 equiv) was added as an internal standard and the yield was determined by ^{1}H NMR of the crude reaction mixture.

4.3. Silver(I)-catalyzed formation of 4-oxazolin-2-ones

Several *N*-alkynyl *tert*-butyloxycarbamates were also rearranged into 4-oxazolin-2-ones in the presence of a silver(I)-catalyst.



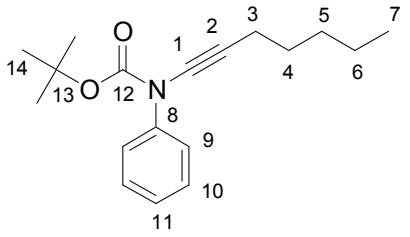
substrate		product		time	yield[a]
	**4.11 a**		**4.12 a**	15 min	91%
	**4.11 b**		**4.12 b**	25 min	95%
	**4.11 c**		**4.12 c**	30 min	96%
	**4.11 d**		**4.12 d**	20 min	88%
	**4.11 e**		**4.12 e**	30 min	78%
	**4.11 j**		**4.12 j**	1 h 30 min	53%
	**4.11 o**		**4.12 o**	3 h	36%

[a] Yield estimated by ^{1}H NMR of the crude mixture using 1,3,5-trimethoxybenzene as internal standard.

General procedure 4.6: To a solution of the substrate (1 equiv) in dry dichloromethane (0.5 M) was added $AgNTf_2$ (0.05 equiv). The mixture was stirred at room temperature and monitored periodically by TLC. Upon completion, the mixture was evaporated, and the yield of the desired oxazolone determined by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard (1 equiv).

4.4. Characterization of the prepared compounds

Hept-1-ynyl-phenyl-carbamic acid *tert*-butyl ester **4.11 j**



MF: $C_{18}H_{25}NO_2$

MW: 287.40 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 4.1** (scale: 3.953 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil.

Yield: 78%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.47 (d, J = 7.5 Hz, 2H, *9*), 7.36 (t, J = 7.5 Hz, 2H, *10*), 7.21 (t, J = 7.4 Hz, 1H, *11*), 2.33 (t, J = 7.0 Hz, 2H, *3*), 1.55 (m, 2H, *4*), 1.53 (s, 9H, *14*), 1.45-1.28 (m, 4H, *5* and *6*), 0.91 (t, J = 7.1 Hz, 3H, *7*).

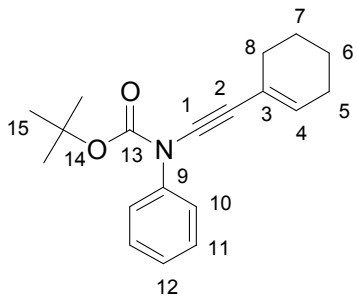
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.5 (*12*), 140.2 (*8*), 128.5 (*10*), 126.1 (*11*), 124.5 (*9*), 82.8 (*13*), 74.3 (*1*), 69.3 (*2*), 31.0 (*5* or *6*), 28.6 (*4*), 28.0 (*14*), 22.2 (*5* or *6*), 18.4 (*3*), 13.9 (*7*).

IR (ν, cm^{-1}) (CCl_4): 3067, 3038, 2958, 2931, 2862, 2266, 1731, 1594, 1494, 1459, 1366, 1295, 1256, 1161, 1048, 1015.

MS (EI^+, m/z): 287 (M^+), 228, 214, 186, 172, 159, 144, 130, 117, 105.

HRMS (EI^+, m/z): Calculated for $C_{18}H_{25}NO_2$: 287.1885.
Found for $C_{18}H_{25}NO_2$: 287.1889.

Cyclohex-1-enylethynyl-phenyl-carbamic acid *tert*-butyl ester **4.11 l**



MF: $C_{19}H_{23}NO_2$

MW: 297.39 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 4.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow crystals.

Yield: 72%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.48 (d, J = 7.5 Hz, 2H, *10*), 7.37 (t, J = 7.5 Hz, 2H, *11*), 7.23 (t, J = 7.4 Hz, 1H, *12*), 6.02 (m, 1H, *4*), 2.16 (m, 2H, *5* or *6*), 2.10 (m, 2H, *5* or *6*), 1.70-1.55 (m, 4H, *6* and *7*), 1.54 (s, 9H, *15*).

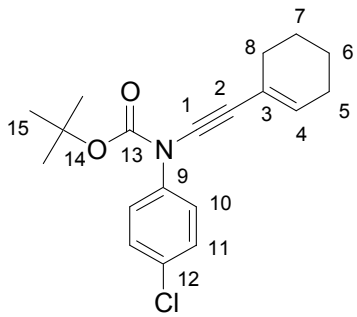
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.0 (*13*), 139.9 (*9*), 132.5 (*4*), 128.6 (*11*), 126.3 (*12*), 124.4 (*10*), 120.1 (*3*), 83.1 (*14*), 81.1 (*1* or *2*), 71.5 (*1* or *2*), 29.3 (*5* or *8*), 27.9 (*15*), 25.5 (*5* or *8*), 22.3 (*6* or *7*), 21.5 (*6* or *7*).

IR (ν, cm^{-1}) (CCl_4): 3066, 3032, 2978, 2933, 2862, 2243, 1733, 1594, 1495, 1453, 1369, 1287, 1159, 1102, 1008.

MS (EI^+, m/z): 297 (M^+), 266, 253, 241, 238, 224, 212.

HRMS (EI^+, m/z): Calculated for $C_{19}H_{23}NO_2$: 297.1729.
Found for $C_{19}H_{23}NO_2$: 297.1732.

(4-Chloro-phenyl)-cyclohex-1-enylethynyl-carbamic acid *tert*-butyl ester 4.11 m



MF: $C_{19}H_{22}NO_2Cl$

MW: 331.84 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: White crystals.

Yield: 80%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.44 (d, J = 8.9 Hz, 2H, *10* or *11*), 7.32 (d, J = 8.9 Hz, 2H, *10* or *11*), 6.03 (m, 1H, *4*), 2.15 (m, 2H, *5* or *8*), 2.10 (m, 2H, *5* or *8*), 1.69-1.56 (m, 4H, *6* and *7*), 1.54 (s, 9H, *15*).

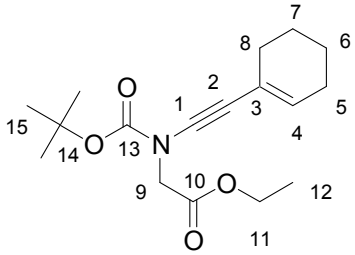
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.7 (*13*), 138.5 (*9* or *12*), 132.9 (*4*), 131.6 (*9* or *12*), 128.7 (*10* or *11*), 125.5 (*10* or *11*), 120.0 (*3*), 83.5 (*14*), 80.5 (*1* or *2*), 72.0 (*1* or *2*), 29.3 (*5* or *6*), 27.9 (*15*), 25.5 (*5* or *6*), 22.3 (*6* or *7*), 21.5 (*6* or *7*).

IR (ν, cm^{-1}) (CCl_4): 2979, 2933, 2862, 2838, 2243, 1734, 1491, 1369, 1286, 1258, 1157, 1095, 1006.

MS (EI^+, m/z): 331 (M^+), 318, 272, 231.

HRMS (EI^+, m/z) Calculated for $C_{19}H_{22}NO_2Cl$: 331.1339.
Found for $C_{19}H_{22}NO_2Cl$: 331.1343.

(*tert*-Butoxycarbonyl-cyclohex-1-enylethynyl-amino)-acetic acid ethyl ester **4.11 n**



MF: $C_{17}H_{25}NO_4$

MW: 307.38 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 97/3-96/4).

Product: White crystals.

Yield: 50%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.96 (m, 1H, *4*), 4.24 (q, J = 7.1 Hz, 2H, *11*), 4.14 (s, 2H, *9*), 2.09 (m, 4H, *5* and *8*), 1.67-1.54 (m, 4H, *6* and *7*), 1.52 (s, 9H, *15*), 1.29 (t, J = 7.1 Hz, 3H, *12*).

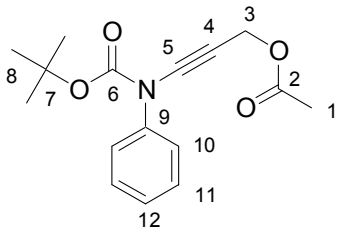
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 168.0 (*10*), 154.0 (*13*), 132.0 (*4*), 120.1 (*3*), 82.8 (*14*), 81.0 (*1* or *2*), 71.2 (*1* or *2*), 61.3 (*11*), 51.0 (*9*), 29.3 (*5* or *8*), 27.9 (*15*), 25.5 (*5* or *8*), 22.3 (*6* or *7*), 21.5 (*6* or *7*), 14.1 (*12*).

IR (ν, cm^{-1}) (CCl_4) 2980, 2933, 2862, 2240, 1755, 1726, 1397, 1369, 1319, 1243, 1199, 1160, 1101, 1027.

MS (EI^+, m/z) 307 (M^+), 266, 248, 235, 217, 212.

HRMS (EI^+, m/z) Calculated for $C_{17}H_{25}NO_4$: 307.1784.
Found for $C_{17}H_{25}NO_4$: 307.1784.

Acetic acid 3-(*tert*-butoxycarbonyl-phenyl-amino)-prop-2-ynyl ester **4.11 o**



MF: $C_{16}H_{19}NO_4$

MW: 289.33 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 92/8).

Product: Yellow oil.

Yield: 55%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.43 (d, J = 7.4 Hz, 2H, *10*), 7.38 (t, J = 7.4 Hz, 2H, *11*), 7.26 (t, J = 7.2 Hz, 1H, *12*), 4.86 (s, 2H, *3*), 2.10 (s, 3H, *1*), 1.53 (s, 9H, *8*).

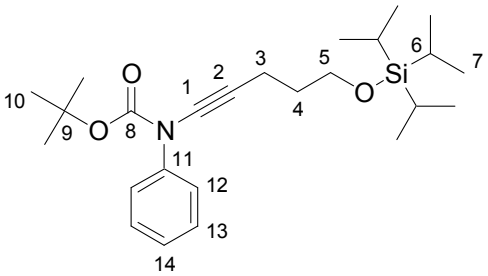
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.3 (*2*), 152.9 (*6*), 139.3 (*9*), 128.8 (*10* or *11*), 126.8 (*12*), 124.7 (*10* or *11*), 83.7 (*7*), 81.0 (*1*), 64.4 (*2*), 52.8 (*3*), 27.9 (*8*), 20.8 (*1*).

IR (ν, cm^{-1}) (CCl_4): 3067, 3039, 2980, 2935, 2261, 1742, 1594, 1495, 1369, 1287, 1224, 1158, 1048, 1019.

MS (EI^+, m/z): 289 (M^+), 189, 146, 129, 105.

HRMS (EI^+, m/z): Calculated for $C_{16}H_{19}NO_4$: 289.1314.
Found for $C_{16}H_{19}NO_4$: 289.1322.

Phenyl-(5-triisopropylsilanyloxy-pent-1-ynyl)-carbamic acid *tert*-butyl ester 4.11 s



MF: $C_{25}H_{41}NO_3Si$

MW: 431.68 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.1** (scale: 1.913 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 96/4).

Product: Yellow oil.

Yield: 88%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.45 (d, J = 7.6 Hz, 2H, *12*), 7.35 (t, J = 7.5 Hz, 2H, *13*), 7.22 (t, J = 7.8 Hz, 1H, *14*), 3.78 (t, J = 6.1 Hz, 2H, *5*), 2.45 (t, J = 6.9 Hz, 2H, *3*), 1.77 (pent, J = 6.8 Hz, 2H, *4*), 1.53 (s, 9H, *10*), 1.05 (m, 3H, *6*), 1.04 (d, J = 4.5 Hz, 18H, *7*).

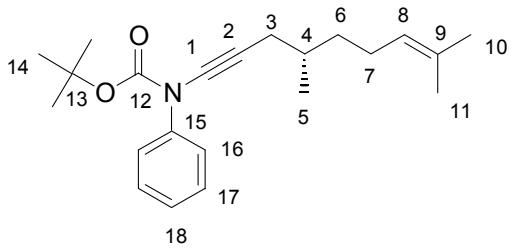
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.5 (*8*), 140.2 (*11*), 128.5 (*12* or *13*), 126.2 (*14*), 124.5 (*12* or *13*), 82.8 (*9*), 74.3 (*1*), 68.8 (*2*), 61.9 (*5*), 32.2 (*4*), 27.9 (*10*), 17.9 (*7*), 14.9 (*3*), 11.9 (*6*).

IR (ν, cm^{-1}) (CCl_4): 3067, 3038, 2943, 2865, 2264, 1731, 1594, 1494, 1462, 1366, 1296, 1254, 1160, 1109, 1068.

MS (EI^+, m/z): 431 (M^+), 375, 358, 344, 332.

HRMS (EI^+, m/z) Calculated for $C_{25}H_{41}NO_3Si$: 431.2856.
Found for $C_{25}H_{41}NO_3Si$: 431.2841.

((*S*)-4,8-Dimethyl-non-7-en-1-ynyl)-phenyl-carbamic acid *tert*-butyl ester 4.11 u



MF: $C_{23}H_{31}NO_2$

MW: 341.49 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil.

Yield: 74%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.48 (d, J = 7.5 Hz, 2H, *16*), 7.36 (t, J = 7.5 Hz, 2H, *17*), 7.21 (t, J = 7.5 Hz, 1H, *18*), 5.10 (t, J = 7.0 Hz, 1H, *8*), 2.32 (dd, J = 5.5, 16.4 Hz, 1H, *3*), 2.23 (dd, J = 6.8, 16.4 Hz, 2H, *3*), 2.00 (m, 2H, *7*), 1.71 (m, 1H, *4*), 1.69 (s, 3H, *10* or *11*), 1.61 (s, 3H, *10* or *11*), 1.54 (s, 9H, *14*), 1.47 (m, 2H, *6*), 1.01 (d, J = 6.7 Hz, 3H, *5*).

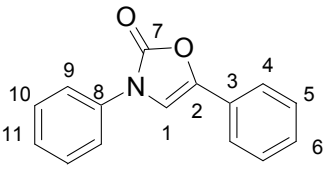
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 153.5 (*12*), 140.2 (*15*), 131.2 (*9*), 128.5 (*17*), 126.1 (*8*), 124.5 (*18*), 124.4 (*16*), 82.8 (*13*), 75.1 (*1*), 68.0 (*2*), 36.0 (*6*), 32.4 (*4*), 28.0 (*14*), 25.7 (*3*), 25.6 (*10* or *11*), 25.5 (*7*), 19.5 (*5*), 17.6 (*10* or *11*).

IR (ν, cm^{-1}) (CCl_4) 3066, 3037, 2969, 2921, 2263, 1731, 1594, 1494, 1454, 1368, 1269, 1160, 1016.

MS (EI^+, m/z) 341 (M^+), 286, 270, 242, 226, 209, 199.

HRMS (EI^+, m/z) Calculated for $C_{23}H_{31}NO_2$: 341.2355.
Found for $C_{23}H_{31}NO_2$: 341.2356.

3,5-Diphenyl-3*H*-oxazol-2-one 4.12 a



MF: $C_{15}H_{11}NO_2$

MW: 237.25 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

Purification: Recrystallization in PE.

Product: White crystals.

Yield: 83%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.63 (d, J = 7.6 Hz, 2H, *9*), 7.56 (d, J = 7.3 Hz, 2H, *4*), 7.48 (t, J = 7.6 Hz, 2H, *10*), 7.42 (t, J = 7.3 Hz, 2H, *5*), 7.34 (t, J = 7.4 Hz, 1H, *6*), 7.31 (t, J = 7.5 Hz, 1H, *11*), 7.18 (s, 1H, *1*).

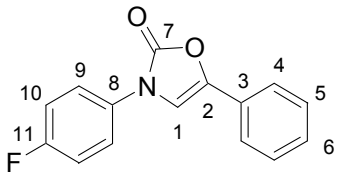
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.5 (*7*), 139.8 (*2*), 135.4 (*8*), 129.4 (*10*), 128.8 (*5*), 128.5 (*6*), 126.8 (*3*), 126.5 (*11*), 123.1 (*4*), 120.9 (*9*), 108.4 (*1*).

IR (ν, cm^{-1}) (CCl_4): 3153, 3055, 2958, 2927, 2860, 1773, 1595, 1503, 1450, 1393, 1212, 1114.

MS (EI^+, m/z): 237 (M^+), 218.

HRMS (EI^+, m/z): Calculated for $C_{15}H_{11}NO_2$: 237.0790.
Found for $C_{15}H_{11}NO_2$: 237.0793.

3-(4-Fluoro-phenyl)-5-phenyl-3*H*-oxazol-2-one 4.12 b



MF: $C_{15}H_{10}NO_2F$

MW: 255.24 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

Purification: Recrystallization in PE.

Product: Pale brown crystals.

Yield: 88%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.63-7.55 (m, 4H, *4* and *10*), 7.43 (t, J = 7.3 Hz, 2H, *5*), 7.35 (t, J = 7.4 Hz, 1H, *6*), 7.17 (dd, J = 8.2, 8.9 Hz, 2H, *9*), 7.13 (s, 1H, *1*).

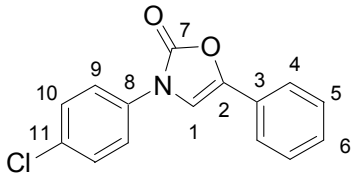
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 160.9 (d, J = 247.2 Hz, *11*), 152.6 (*7*), 140.0 (*2*), 131.5 (d, J = 3.0 Hz, *8*), 128.9 (*5*), 128.7 (*6*), 126.8 (*3*), 123.2 (*4*), 123.0 (d, J = 8.4 Hz, *10*), 116.4 (d, J = 23.0 Hz, *9*), 108.5 (*1*).

IR (ν, cm^{-1}) (CCl_4): 3060, 2926, 2855, 2359, 1770, 1515, 1451, 1397, 1234, 1112.

MS (EI^+, m/z): 255 (M^+), 211.

HRMS (EI^+, m/z): Calculated for $C_{15}H_{10}NO_2F$: 255.0696.
Found for $C_{15}H_{10}NO_2F$: 255.0699.

3-(4-Chloro-phenyl)-5-phenyl-3*H*-oxazol-2-one 4.12 c



MF: $C_{15}H_{10}NO_2Cl$

MW: 271.70 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

Purification: Recrystallization in PE.

Product: Yellow crystals.

Yield: 88%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.62-7.55 (m, 4H, *4* and *10*), 7.47-7.41 (m, 4H, *5* and *9*), 7.36 (t, J = 7.4 Hz, 1H, *6*), 7.16 (s, 1H, *1*).

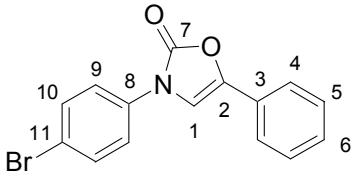
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.3 (*7*), 140.1 (*2*), 134.0 (*8* or *11*), 132.0 (*8* or *11*), 129.6 (*9* or *10*), 128.9 (*4* or *5*), 128.7 (*6*), 126.6 (*3*), 123.2 (*4* or *5*), 122.0 (*9* or *10*), 107.9 (*1*).

IR (ν, cm^{-1}) (CCl_4): 3117, 3062, 2975, 2928, 1731, 1654, 1498, 1449, 1393, 1279, 1203, 1095, 1052, 1016.

MS (EI$^+$, m/z): 271 (M$^+$), 227, 192.

HRMS (EI$^+$, m/z): Calculated for $C_{15}H_{10}NO_2Cl$: 271.0400.
Found for $C_{15}H_{10}NO_2Cl$: 271.0403.

3-(4-Bromo-phenyl)-5-phenyl-3*H*-oxazol-2-one 4.12 d



MF: $C_{15}H_{10}NO_2Br$

MW: 316.15 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.22 mmol).

Purification: Recrystallization in PE.

Product: White crystals.

Yield: 83%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.63-7.52 (m, 6H, *4*, *9* and *10*), 7.43 (t, J = 7.2 Hz, 2H, *5*), 7.36 (t, J = 7.3 Hz, 1H, *6*), 7.15 (s, 1H, *1*).

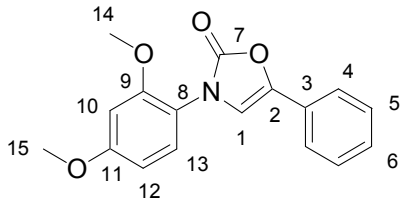
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 152.2 (*7*), 140.2 (*2*), 134.5 (*3*, *8* or *11*), 132.5 (*4*, *5*, *9* or *10*), 128.9 (*4*, *5*, *9* or *10*), 128.8 (*6*), 126.6 (*3*, *8* or *11*), 123.2 (*4*, *5*, *9* or *10*), 122.2 (*4*, *5*, *9* or *10*), 119.8 (*3*, *8* or *11*), 107.8 (*1*).

IR (ν, cm^{-1}) (CCl_4) 3128, 3060, 2926, 2856, 1768, 1732, 1653, 1589, 1495, 1449, 1392, 1277, 1203, 1051.

MS (EI^+, m/z) 315 (M^+), 288, 267, 212.

HRMS (EI^+, m/z) Calculated for $C_{15}H_{10}NO_2Br$: 314.9895.
Found for $C_{15}H_{10}NO_2Br$: 314.9890.

3-(2,4-Dimethoxy-phenyl)-5-phenyl-3*H*-oxazol-2-one 4.12 e



MF: $C_{17}H_{15}NO_4$

MW: 297.31 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

Purification: Recrystallization in PE.

Product: Orange crystals.

Yield: 85%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.53 (d, J = 7.2 Hz, 2H, *4*), 7.41-7.36 (m, 3H, *5* and *12*), 7.30 (t, J = 7.4 Hz, 1H, *6*), 6.96 (s, 1H, *1*), 6.57 (s, 1H, *10*), 6.56 (dd, J = 2.6, 10.8 Hz, 1H, *13*), 3.84 (s, 3H, *14* or *15*), 3.83 (s, 3H, *14* or *15*).

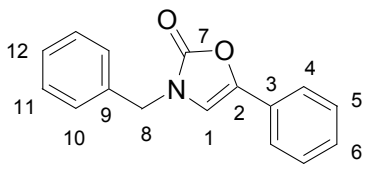
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 160.7 (*9* or *11*), 154.9 (*9* or *11*), 153.9 (*7*), 138.5 (*2*), 128.7 (*5*), 128.0 (*6* or *12*), 127.9 (*6* or *12*), 127.4 (*3*), 122.8 (*4*), 116.6 (*8*), 112.0 (*1*), 104.5 (*13*), 99.6 (*10*), 55.7 (*14* or *15*), 55.5 (*14* or *15*).

IR (ν, cm^{-1}) (CCl_4) 3061, 2927, 2854, 2360, 1768, 1611, 1518, 1460, 1287, 1212, 1162, 1109, 1039.

MS (EI^+, m/z) 297 (M^+), 253, 238, 223, 195.

HRMS (EI^+, m/z) Calculated for $C_{17}H_{15}NO_4$: 297.1001.
Found for $C_{17}H_{15}NO_4$: 297.0998.

3-Benzyl-5-phenyl-3*H*-oxazol-2-one 4.12 f



MF: $C_{16}H_{13}NO_2$

MW: 251.28 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

Purification: Recrystallization in PE.

Product: Pale yellow crystals.

Yield: 78%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.49-7.31 (m, 9H, *4*, *5*, *6*, *10*, *11* and/or *12*), 7.27 (t, J = 7.4 Hz, 1H, *6* or *12*), 6.65 (s, 1H, *1*), 4.80 (s, 2H, *8*).

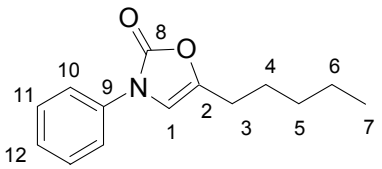
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.9 (*7*), 139.2 (*2*), 135.2 (*9*), 129.0 (*10* or *11*), 128.7 (*5*), 128.4 (*6* or *12*), 128.1 (*6* or *12*), 127.9 (*10* or *11*), 127.2 (*3*), 122.8 (*4*), 108.8 (*1*), 47.8 (*8*).

IR (ν, cm^{-1}) (CCl_4): 3134, 3064, 3032, 2927, 2856, 1767, 1449, 1396, 1362, 1262, 1179, 1082, 1019.

MS (EI^+, m/z): 251 (M^+), 193.

HRMS (EI^+, m/z): Calculated for $C_{16}H_{13}NO_2$: 251.0946.
Found for $C_{16}H_{13}NO_2$: 251.0937.

5-Pentyl-3-phenyl-3*H*-oxazol-2-one 4.12 j



MF: $C_{11}H_{17}NO_2$

MW: 231.29 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 92/8).

Product: White crystals.

Yield: 74%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.56 (d, J = 7.6 Hz, 2H, *10*), 7.43 (t, J = 7.5 Hz, 2H, *11*), 7.25 (t, J = 7.5 Hz, 1H, *12*), 6.59 (t, J = 1.1 Hz, 1H, *1*), 2.47 (td, J = 1.1, 7.8 Hz, 1H, *3*), 1.63 (m, 2H, *4*), 1.39-1.34 (m, 4H, *5* and *6*), 0.92 (t, J = 7.1 Hz, 3H, *7*).

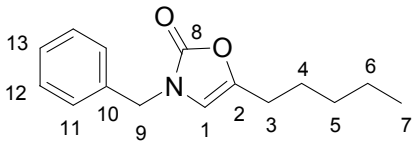
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.2 (*8*), 141.9 (*2*), 135.7 (*9*), 129.3 (*11*), 126.0 (*12*), 120.5 (*10*), 108.8 (*1*), 31.0 (*5*), 26.1 (*3*), 25.8 (*4*), 22.2 (*6*), 13.8 (*7*).

IR (ν, cm^{-1}) (CCl_4): 3154, 3069, 3048, 2955, 2930, 2863, 1764, 1677, 1596, 1503, 1461, 1393, 1296, 1212, 1113.

MS (EI^+, m/z): 231 (M^+), 186, 174, 158, 144, 130, 105.

HRMS (EI^+, m/z): Calculated for $C_{11}H_{17}NO_2$: 231.1259.
Found for $C_{11}H_{17}NO_2$: 231.1257.

3-Benzyl-5-pentyl-3*H*-oxazol-2-one **4.12 k**



MF: $C_{15}H_{19}NO_2$

MW: 245.32 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

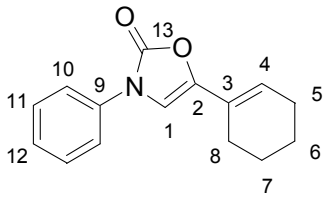
Purification: Difficult to isolate (unstable).

Product: -

Yield: 50% (determined by ^{1}H NMR of the crude mixture using 1,3,5-trimethoxybenzene as internal standard).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.40-7.21 (m, 5H, *11*, *12* and *13*), 6.02 (t, J = 1.2 Hz, 1H, *1*), 4.68 (s, 2H, *9*), 2.34 (td, J = 1.1, 7.8 Hz, 2H, *3*), 1.53 (m, 2H, *4*), 1.29 (m, 4H, *5* and *6*), 0.88 (m, 3H, *7*).

5-Cyclohex-1-enyl-3-phenyl-3*H*-oxazol-2-one **4.12 l**



MF: $C_{15}H_{15}NO_2$

MW: 241.29 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

Purification: Recrystallization in PE.

Product: Yellow crystals.

Yield: 78%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.58 (d, J = 7.6 Hz, 2H, *10*), 7.44 (t, J = 7.5 Hz, 2H, *11*), 7.27 (t, J = 7.4 Hz, 1H, *12*), 6.65 (s, 1H, *1*), 6.27 (m, 1H, *4*), 2.21 (m, 2H, *5* or *8*), 2.15 (m, 2H, *5* or *8*), 1.79-1.63 (m, 4H, *6* and *7*).

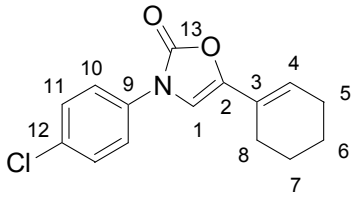
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 152.6 (*13*), 141.2 (*2*), 135.6 (*3* or *9*), 129.3 (*11*), 126.2 (*12*), 125.0 (*4*), 123.2 (*3* or *9*), 120.7 (*10*), 106.8 (*1*), 25.0 (*5* or *8*), 23.3 (*5* or *8*), 21.9 (*6* or *7*), 21.8 (*6* or *7*).

IR (ν, cm^{-1}) (CCl_4) 3153, 3117, 3053, 2932, 2861, 1770, 1596, 1504, 1390, 1290, 1214, 1114, 1016.

MS (EI$^+$, m/z) 241 (M$^+$), 217, 213.

HRMS (EI^+, m/z) Calculated for $C_{15}H_{15}NO_2$: 241.1103.
Found for $C_{15}H_{15}NO_2$: 241.1107.

3-(4-Chloro-phenyl)-5-cyclohex-1-enyl-3*H*-oxazol-2-one **4.12 m**



MF: $C_{15}H_{14}NO_2Cl$

MW: 275.73 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

Purification: Recrystallization in PE.

Product: Yellow crystals.

Yield: 94%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.54 (d, J = 9.0 Hz, 2H, *10* or *11*), 7.40 (d, J = 9.0 Hz, 2H, *10* or *11*), 6.62 (s, 1H, *1*), 6.27 (m, 1H, *4*), 2.21 (m, 2H, *5* or *8*), 2.14 (m, 2H, *5* or *8*), 1.78-1.63 (m, 4H, *6* and *7*).

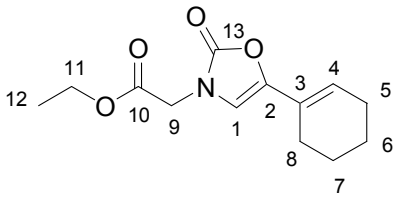
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 152.3 (*13*), 141.4 (*2*), 134.2 (*9*), 131.6 (*12*), 129.4 (*10* or *11*), 125.4 (*4*), 123.0 (*3*), 121.7 (*10* or *11*), 106.3 (*1*), 25.0 (*5* or *8*), 23.2 (*5* or *8*), 21.9 (*6* or *7*), 21.8 (*6* or *7*).

IR (ν, cm^{-1}) (CCl_4) 3140, 3051, 2930, 2865, 1755, 1596, 1499, 1393, 1203, 1142, 1095, 1016.

MS (EI^+, m/z) 275 (M^+), 266, 235, 231, 217.

HRMS (EI^+, m/z) Calculated for $C_{15}H_{14}NO_2Cl$: 275.0713.
Found for $C_{15}H_{14}NO_2Cl$: 275.0709.

(5-Cyclohex-1-enyl-2-oxo-oxazol-3-yl)-acetic acid ethyl ester **4.12 n**



MF: $C_{13}H_{17}NO_4$

MW: 251.28 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

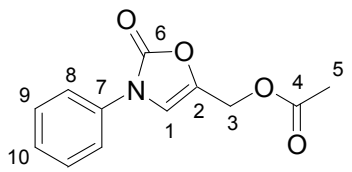
Purification: Recrystallization in PE.

Product: Yellow crystals.

Yield: 70%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	6.30 (s, 1H, *1*), 6.17 (m, 1H, *4*), 4.30 (s, 2H, *9*), 4.23 (q, J = 7.2 Hz, 2H, *11*), 2.16 (m, 2H, *5* or *8*), 2.07 (m, 2H, *5* or *8*), 1.73-1.58 (m, 4H, *6* or *7*), 1.29 (t, J = 7.2 Hz, 3H, *12*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	167.4 (*10*), 154.8 (*13*), 140.7 (*2*), 124.2 (*4*), 123.3 (*3*), 108.0 (*1*), 61.9 (*11*), 44.7 (*9*), 24.9 (*5* or *8*), 23.2 (*5* or *8*), 21.9 (*6* or *7*), 21.8 (*6* or *7*), 14.0 (*12*).
IR (ν, cm^{-1}) (CCl_4)	3147, 2981, 2935, 2862, 1763, 1425, 1377, 1260, 1206, 1098, 1022.
MS (EI^+, m/z)	251 (M^+), 223, 211.
HRMS (EI^+, m/z)	Calculated for $C_{13}H_{17}NO_4$: 251.1158. Found for $C_{13}H_{17}NO_4$: 251.1151.

Acetic acid 2-oxo-3-phenyl-2,3-dihydro-oxazol-5-ylmethyl ester **4.12 o**



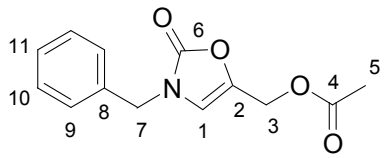
MF: $C_{12}H_{11}NO_4$

MW: 233.22 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 50/50).
Product:	Yellow crystals.
Yield:	71%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.53 (d, J = 7.6 Hz, 2H, *8*), 7.44 (t, J = 7.5 Hz, 2H, *9*), 7.29 (t, J = 7.5 Hz, 1H, *10*), 6.99 (s, 1H, *1*), 4.91 (s, 2H, *3*), 2.11 (s, 3H, *5*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	170.4 (*4*), 152.5 (*6*), 135.4 (*2*), 135.1 (*7*), 129.4 (*9*), 126.7 (*10*), 120.9 (*8*), 114.6 (*1*), 55.9 (*3*), 20.7 (*5*).
IR (ν, cm^{-1}) (CCl_4)	3049, 2959, 2927, 2862, 1777, 1748, 1597, 1505, 1398, 1218, 1108, 1024.
MS (EI^+, m/z)	233(M^+), 174, 163, 130, 118, 105.
HRMS (EI^+, m/z)	Calculated for $C_{12}H_{11}NO_4$: 233.0688. Found for $C_{12}H_{11}NO_4$: 233.0692.

Acetic acid 3-benzyl-2-oxo-2,3-dihydro-oxazol-5-ylmethyl ester **4.12 q**



MF: $C_{13}H_{13}NO_4$

MW: 247.25 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

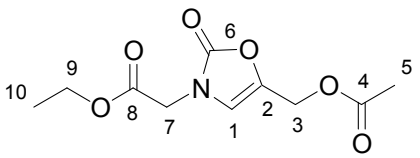
Purification: Difficult to isolate (unstable).

Product: -

Yield: 50% (determined by ^{1}H NMR of the crude mixture using 1,3,5-trimethoxybenzene as internal standard).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.43-7.22 (m, 5H, *9*, *10* and *11*), 6.47 (s, 1H, *1*), 4.79 (s, 2H, *3* or *7*), 4.71 (s, 2H, *3* or *7*), 2.07 (s, 3H, *5*).

(5-Acetoxymethyl-2-oxo-oxazol-3-yl)-acetic acid ethyl ester **4.12 r**



MF: $C_{10}H_{13}NO_6$

MW: 243.21 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

Purification: Washing with PE.

Product: Yellow oil.

Yield: 49%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.66 (s, 1H, *1*), 4.85 (s, 2H, *3*), 4.33 (s, 2H, *7*), 4.25 (q, J = 7.1 Hz, 2H, *9*), 2.09 (s, 3H, *5*), 1.30 (t, J = 7.1 Hz, 3H, *10*).

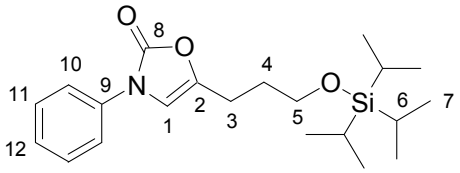
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.4 (*4*), 167.2 (*8*), 154.8 (*6*), 134.8 (*2*), 115.8 (*1*), 62.1 (*9*), 56.0 (*3*), 44.7 (*7*), 20.7 (*5*), 14.0 (*10*).

IR (ν, cm^{-1}) (CCl_4): 3152, 2982, 2934, 2869, 1773, 1753, 1708, 1424, 1376, 1215, 1165, 1088, 1022.

MS (EI^{+}, m/z): 243 (M^{+}), 216, 211, 201, 192.

HRMS (EI^{+}, m/z): Calculated for $C_{10}H_{13}NO_6$: 243.0743.
Found for $C_{10}H_{13}NO_6$: 243.0739.

3-Phenyl-5-(3-triisopropylsilanyloxy-propyl)-3*H*-oxazol-2-one **4.12 s**



MF: $C_{21}H_{33}NO_3Si$

MW: 375.58 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 94/6).

Product: White crystals.

Yield: 69%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.56 (d, J = 7.6 Hz, 2H, *10*), 7.43 (t, J = 7.5 Hz, 2H, *11*), 7.26 (t, J = 7.4 Hz, 1H, *12*), 6.61 (t, J = 1.1 Hz, 1H, *1*), 3.78 (t, J = 5.9 Hz, 2H, *5*), 2.62 (td, J = 1.1, 7.9 Hz, 2H, *3*), 1.87 (tt, J = 6.0, 7.7 Hz, 2H, *4*), 1.09 (m, 3H, *6*), 1.07 (d, J = 4.7 Hz, 18H, *7*).

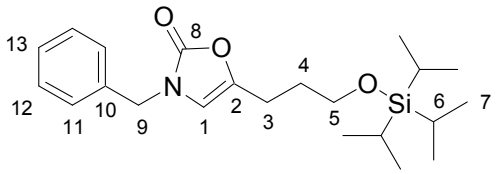
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 153.2 (*8*), 141.6 (*2*), 135.7 (*9*), 129.3 (*11*), 126.0 (*12*), 120.5 (*10*), 109.0 (*1*), 61.8 (*5*), 29.7 (*4*), 22.4 (*3*), 17.9 (*7*), 11.9 (*6*).

IR (ν, cm^{-1}) (CCl_4): 3069, 3047, 2944, 2894, 2865, 1769, 1597, 1505, 1462, 1391, 1108, 1068.

MS (EI$^+$, m/z): 375 (M$^+$), 350, 335, 332.

HRMS (EI$^+$, m/z): Calculated for $C_{21}H_{33}NO_3Si$: 375.2230.
Found for $C_{21}H_{33}NO_3Si$: 375.2245.

3-Benzyl-5-(3-triisopropylsilanyloxy-propyl)-3*H*-oxazol-2-one 4.12 t



MF: $C_{22}H_{35}NO_3Si$

MW: 389.60 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.25 mmol).

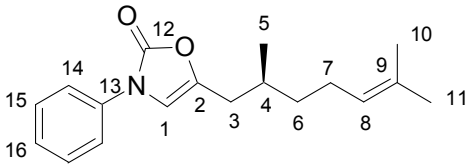
Purification: Difficult to isolate (unstable).

Product: -

Yield: 38% (determined by ^{1}H NMR of the crude mixture using 1,3,5-trimethoxybenzene as internal standard).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.40-7.20 (m, 5H, *11*, *12* and *13*), 6.05 (s, 1H, *1*), 4.68 (s, 2H, *9*), 3.69 (t, J = 6.0 Hz, 2H, *5*), 2.50 (t, J = 7.8 Hz, 2H, *3*), 1.77 (m, 2H, *4*), 1.04 (m, 21H, *6* and *7*).

5-((*S*)-2,6-Dimethyl-hept-5-enyl)-3-phenyl-3*H*-oxazol-2-one **4.12 u**



MF: $C_{18}H_{23}NO_2$

MW: 285.38 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 4.5** (scale: 0.12 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 94/6).

Product: Pale yellow oil.

Yield: 71%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.57 (d, J = 7.6 Hz, 2H, *14*), 7.44 (t, J = 7.5 Hz, 2H, *15*), 7.26 (t, J = 7.5 Hz, 1H, *16*), 6.61 (s, 1H, *1*), 5.10 (tm, J = 7.0 Hz, 1H, *8*), 2.47 (ddd, J = 1.0, 5.9, 15.2 Hz, 1H, *3*), 2.28 (ddd, J = 0.7, 7.8, 15.1 Hz, 1H, *3*), 2.02 (m, 2H, *7*), 1.85 (m, 1H, *4*), 1.70 (s, 3H, *10* or *11*), 1.62 (s, 3H, *10* or *11*), 1.43 (m, 2H, *6*), 0.97 (d, J = 6.7 Hz, 3H, *5*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 153.2 (*12*), 140.8 (*2* or *13*), 135.7 (*2* or *13*), 131.6 (*9*), 129.3 (*15*), 126.0 (*16*), 124.1 (*8*), 120.5 (*14*), 109.8 (*1*), 36.4 (*6*), 33.3 (*3*), 30.7 (*4*), 25.7 (*10* or *11*), 25.4 (*7*), 19.3 (*5*), 17.6 (*10* or *11*).

IR (ν, cm^{-1}) (CCl_4) 3155, 3047, 2962, 2923, 2856, 1767, 1597, 1504, 1456, 1392, 1213, 1196, 1111.

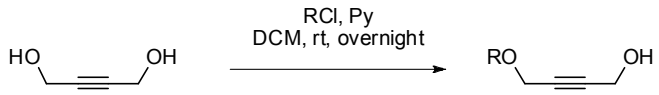
MS (EI^+, m/z) 285 (M^+), 226, 214, 201, 174, 148, 130, 105.

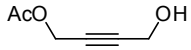
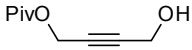
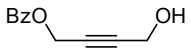
HRMS (EI^+, m/z) Calculated for $C_{18}H_{23}NO_2$: 285.1729.
Found for $C_{18}H_{23}NO_2$: 285.1729.

5. Gold(I)-catalyzed stereoselective formation of functionalized 2,5-dihydrofurans

5.1. Synthesis of the precursors

Substrates **5.7 a-c** were prepared by monoacylation of 1,4-butyndiol following the classical procedures described in the literature.[330]



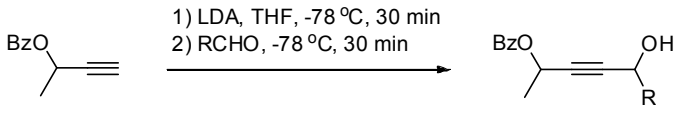
RCl	product		yield[a]
AcCl		**5.7 a**	51%
PivCl		**5.7 b**	49%
BzCl		**5.7 c**	52%

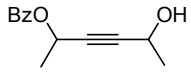
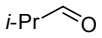
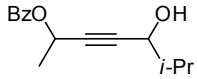
[a] Isolated yield.

General procedure 5.1: To a solution of a 1,4-butyndiol (1 equiv) in DCM (0.5 M) was added pyridine (1 equiv). The mixture was cooled at 0 °C and the corresponding acyl chloride (0.9 equiv) in DCM (0.5 M) was added dropwise for 3 h. The reaction mixture was then allowed to react at rt overnight. Saturated aqueous ammonium chloride was then added and the mixture was extracted twice with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the corresponding propargylic alcohol.

Substrates **5.9 a-b** were synthesized from benzoic acid 1-methyl-prop-2-ynyl ester by deprotonation with LDA followed by addition onto the corresponding aldehyde.

[330] Holt, K. E.; Swift, J. P.; Smith, M. E. B.; Taylor, S. J. C.; McCague, R. *Tetrahedron Lett.* **2002**, *43*, 1545-1548.



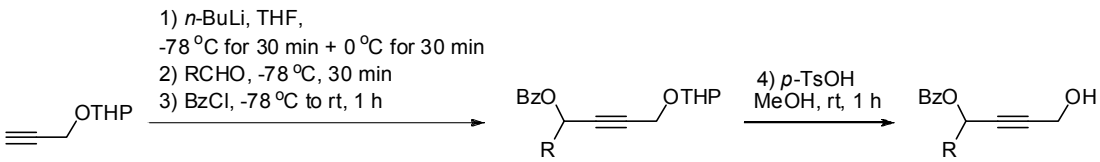
RCHO	product		yield[a]
		**5.9 a**	63%
		**5.9 b**	67%

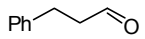
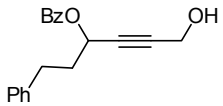
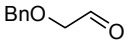
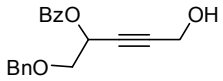
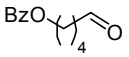
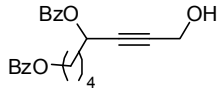
[a] Isolated yield.

General procedure 5.2: A lithium diisopropylamide solution (LDA) was prepared by adding *n*-BuLi (1.15 equiv, 1.6 M in hexanes) to diisopropylamine (1.2 equiv) in THF (0.4 M) at -20°C.

After 30 min, the LDA solution was cooled to -78 °C and benzoic acid 1-methyl-prop-2-ynyl ester (1 equiv) dissolved in THF (1 M) was added. After 30 min, the aldehyde (1.5 equiv) was added and the mixture was further stirred for 30 min. Saturated aqueous ammonium chloride was then added and the cooling bath was removed to allow the mixture to reach room temperature, before being extracted twice with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the corresponding propargylic alcohol.

Substrates **5.9 c-e** were obtained in a 4-step procedure from 2-prop-2-ynyloxy-tetrahydropyran by deprotonation with *n*-BuLi followed by addition on the corresponding aldehyde, acylation with BzCl and deprotection of the THP group in *p*-TSA / MeOH.



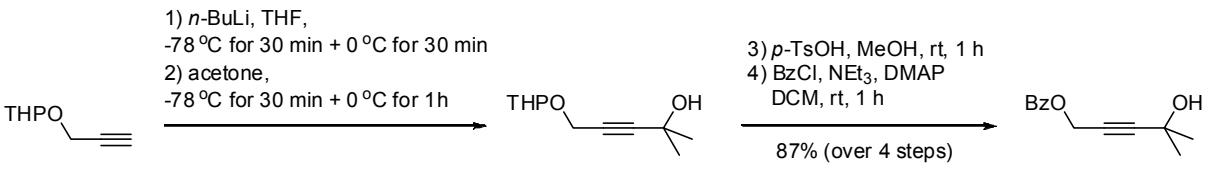
RCHO	product		yield[a]
		**5.9 c**	72%
		**5.9 d**	83%
		**5.9 e**	31%

[a] Isolated yield (over 4 steps).

General procedure 5.3: To a solution of 2-prop-2-ynyloxy-tetrahydropyran (1 equiv) in THF (0.5 M) at -78 °C was added dropwise *n*-BuLi (1 equiv, 1.6 M in hexanes). The reaction mixture was kept at this temperature for 15 min and further stirred for 30 min at 0 °C. It was then cooled to -78 °C and the corresponding aldehyde (1.1 equiv) was added dropwise. After 30 min, benzoyl chloride (1.24 equiv) was added and the reaction mixture was allowed to reach rt. It was stirred for 1 h and saturated aqueous ammonium chloride was added. The mixture was then extracted twice with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure.

The residue was dissolved in methanol (0.5 M), and a catalytic amount of *p*-TsOH was added. The mixture was stirred at rt for 1 h and concentrated under reduced pressure to remove the solvent. The residue was diluted with diethyl ether and washed with saturated aqueous sodium hydrogenocarbonate. The ethereal layer was dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The crude was finally purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the corresponding propargylic alcohol.

Substrate **5.9 f** was obtained in a similar way by deprotonation of 2-prop-2-ynyloxy-tetrahydropyran with *n*-BuLi followed by nucleophilic addition on acetone, deprotection of the THP group and selective benzoylation of the primary alcohol group.



5.9 f

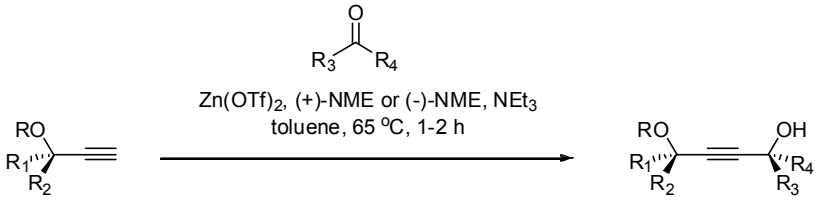
General procedure 5.4: To a solution of 2-prop-2-ynyloxy-tetrahydropyran (1 equiv) in THF (0.5 M) at -78 °C under argon, was added dropwise *n*-BuLi (1 equiv, 1.6 M in hexanes). The reaction mixture was kept at this temperature for 15 min and further stirred for 30 min at 0 °C. The reaction mixture was then cooled to -78 °C and acetone (2 equiv) was added. After 30 min, the reaction mixture was allowed to reach rt and was further stirred for 1 h. Saturated aqueous ammonium chloride was added. The mixture was then extracted twice with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure.

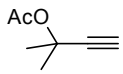
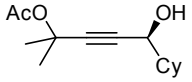
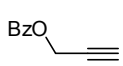
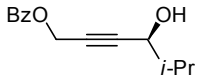
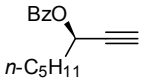
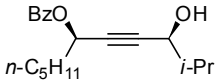
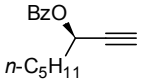
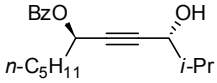
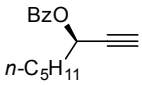
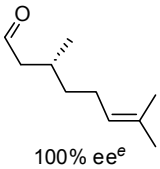
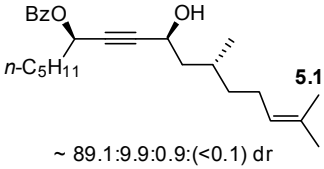
The residue was dissolved in methanol (0.5 M), and a catalytic amount of *p*-TsOH was added. The mixture was stirred at rt for 1 h and concentrated under reduced pressure to remove the solvent. The residue was diluted with diethyl ether and washed with a saturated aqueous sodium hydrogenocarbonate. The ethereal layer was dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure.

The residue was dissolved in dichloromethane (0.5 M) and triethylamine (1.2 equiv), benzoyl chloride (1.1 equiv) and a catalytic amount of DMAP were successively added. After 1 h, water was added and the mixture was then extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was finally purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the corresponding propargylic alcohol.

Substrates **5.9 g** and **5.12 a**, **b**, **c** and **h** were synthesized according to Carreira's procedure.[331]

[331] (a) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605-2606.
(b) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017-3020.
(c) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688.
(d) Sans Diez, R.; Adger, B.; Carreira, E. M. *Tetrahedron* **2002**, *58*, 8341-8344.



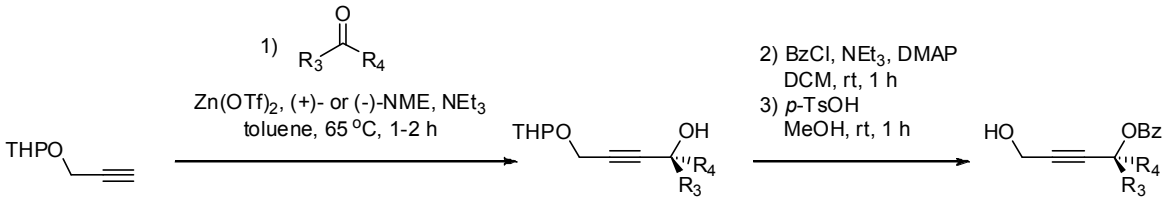
substrate	aldehyde	ligand	product[a]		yield[b]
		(-)-NME		**5.10 g**[c]	66%
		(-)-NME	 87% ee	**5.12 a**	93%
 99% ee[d]		(-)-NME	 93:7 dr, 98% ee	**5.12 b**	92%
 99% ee[d]		(+)-NME	 94:6 dr, 98% ee	**5.12 c**	94%
 99% ee[d]	 100% ee[e]	(-)-NME	 ~ 89.1:9.9:0.9:(<0.1) dr	**5.12 h**	84%

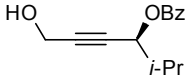
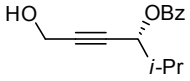
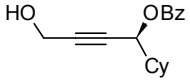
[a] dr and ee determined by chiral HPLC analysis. The absolute configuration was attributed on the basis of the work of Carreira et al. [b] Isolated yield. [c] The enantiomeric ratio of substrate **5.10 g** could not be determined by HPLC analysis due to the lack of chromophore group in its structure and was therefore considered to be racemic for the corresponding gold-catalyzed reaction. [d] 99% ee (*R*)-Benzoic acid-1-ethynyl-hexyl ester previously synthesized by benzoylation of the commercially available 99% ee (*R*)-1-octyn-3-ol. [e] Commercially available (*R*)-(+)-citronellal (optically pure).

General procedure 5.5: A flask was charged with $Zn(OTf)_2$ (1.1 equiv) and heated under vacuum using a heat gun for 5 min. (+) or (-)-*N*-methyl ephedrine (1.2 equiv) was added and the flask was purged with nitrogen for 15 min. Toluene (0.33 M) and triethylamine (1.2 equiv) were added. The resulting mixture was stirred at rt for 2 h before the corresponding alkyne (1 equiv) diluted in toluene (1 M) was added. After 30 min of stirring, the aldehyde (1.1 equiv) was added in one portion by syringe. The reaction was heated at 60 °C for 1 h to 2 h depending on the alkyne substrate and followed periodically by TLC. Upon completion, the mixture was quenched with a saturated

aqueous ammonium chloride solution and extracted twice with diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether).

Substrates **5.12 d-f** were synthesized in a 3-step procedure starting from 2-prop-2-ynyloxy-tetrahydro-pyran involving a Carreira asymmetric alkyne addition followed by benzoylation of the secondary alcohol group and deprotection of the primary one.



aldehyde	ligand	product[a]		yield[b]
	(-)-NME	 94% ee	**5.12 d**	82%
	(+)-NME	 94% ee	**5.12 e**	93%
	(-)-NME	 94% ee	**5.12 f**	88%

[a] ee and dr determined by chiral HPLC analysis. The absolute configuration was attributed on the basis of the work of Carreira et al. [b] Isolated yield (over 3 steps).

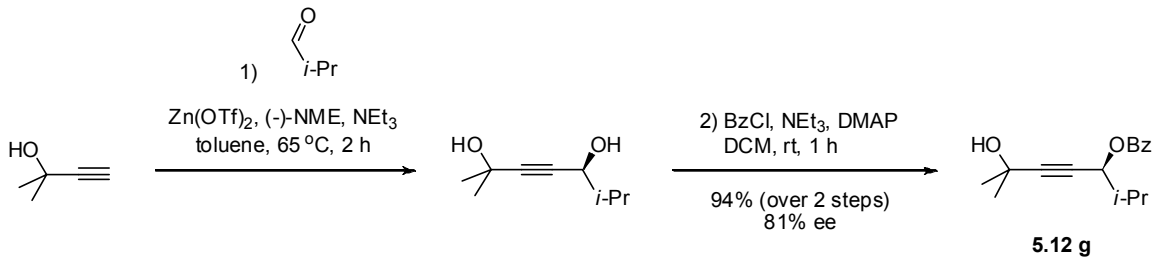
General procedure 5.6: A flask was charged with $Zn(OTf)_2$ (1.1 equiv) and heated under vacuum using a heat gun for 5 min. (+) or (-)-*N*-methyl ephedrine (1.2 equiv) was added and the flask was purged with nitrogen for 15 min. Toluene (0.33 M) and triethylamine (1.2 equiv) were added. The resulting mixture was stirred at rt for 2 h before 2-prop-2-ynyloxy tetrahydro-pyran (1 equiv) diluted in toluene (1 M) was added. After 30 min of stirring, the aldehyde (1.1 equiv) was added in one portion by syringe. The reaction was heated at 60 °C for 1 h to 2 h depending on the alkyne substrate and followed periodically by TLC. Upon completion, the mixture was quenched with a saturated aqueous ammonium chloride solution and extracted twice with diethyl ether. The combined organic layers were dried over magnesium

sulfate and concentrated under reduced pressure.

The residue was dissolved in dichloromethane (0.25 M) and triethylamine (1.5 equiv), benzoyl chloride (1.2 equiv) and a catalytic amount of DMAP were successively added. After 1 h, water was added and the mixture was then extracted twice with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure.

The residue was dissolved in methanol (0.2 M), and a catalytic amount of *p*-TsOH was added. The mixture was stirred at rt for 1 h and concentrated under reduced pressure to remove the solvent. The residue was diluted with diethyl ether and washed with a saturated aqueous sodium hydrogenocarbonate solution. The ethereal layer was dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether).

Substrate **5.12 g** was obtained in an analogous 2-step procedure starting from 2-methyl-but-3-yn-2-ol and involving a Carreira asymmetric alkyne addition followed by selective benzoylation of the secondary alcohol group.

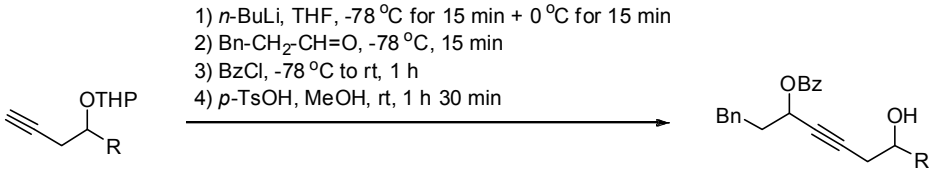


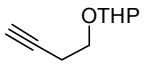
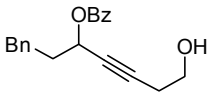
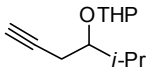
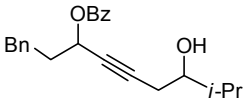
General procedure 5.7: A flask was charged with $Zn(OTf)_2$ (1.1 equiv) and heated under vacuum using a heat gun for 5 min. (-)-*N*-methyl ephedrine (1.2 equiv) was added and the flask was purged with nitrogen for 15 min. Toluene (0.33 M) and triethylamine (1.2 equiv) were added. The resulting mixture was stirred at rt for 2 h before 2-methyl-but-3-yn-2-ol (1 equiv) diluted in toluene (2 M) was added. After 30 min of stirring, the isobutyraldehyde (1.1 equiv) was added in one portion by syringe. The reaction was stirred and heated at 60 °C for 2 h. The mixture was quenched with a saturated aqueous ammonium chloride solution and extracted twice with diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure.

The residue was dissolved in dichloromethane (0.25 M) and triethylamine

(1.5 equiv), benzoyl chloride (1.2 equiv) and a catalytic amount of DMAP were successively added. After 1 h, water was added and the mixture was then extracted twice with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was finally purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give expected compound.

Substrates **5.24 a** and **b** were obtained starting from the terminal alkynes by deprotonation with *n*-BuLi, addition on hydrocinnamaldehyde, protection of the secondary alcohol group as a benzoate and deprotection of the THP group.



substrate	product	yield[a]
	 **5.24 a**	25%
 **5.34**	 **5.24 b**	29%

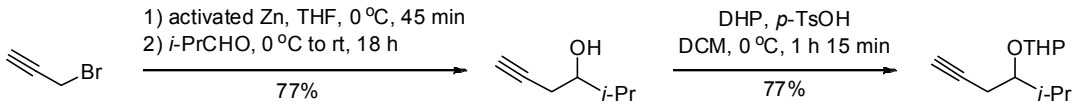
[a] Isolated yield (over 4 steps).

General procedure 5.8: To a solution of terminal alkyne (1 equiv) in dry THF (0.5 M) at -78 °C was added dropwise *n*-BuLi (1 equiv, 1.6 M in hexane). The reaction mixture was allowed to react at -78 °C for 15 min and at 0 °C for another 15 min. Then it was cooled down again at -78 °C and BzCl (1.3 equiv) was added and allowed to warm up to rt for 1 h. Upon completion, the reaction was quenched with a saturated aqueous NH_4Cl solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure.

The organic residue was dissolved in MeOH (0.5 M) and *p*-TsOH (0.01 equiv) was added. The mixture was stirred at rt for 1 h 30 min and upon completion the solvent was evaporated under reduced pressure. The crude was then directly purified by flash column chromatography (silica

gel, petroleum ether / diethyl ether) to give the desired compound.

Terminal alkyne **5.34** was prepared starting from propargyl bromide by addition onto isobutyraldehyde as an organozinc derivative followed by protection of the secondary alcohol with a THP group.



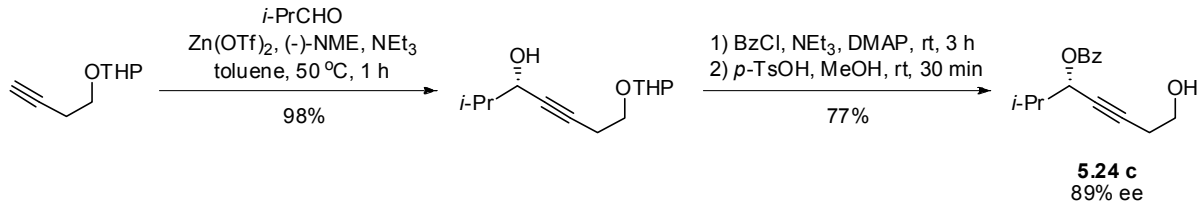
5.34

General procedure 5.9: Zn dust (15 g) was added to an aqueous HCl 2% solution (93.75 mL). The suspension was stirred at rt for 5 min and then filtered. The solid cake was successively washed with distilled water (5 x 75 mL), absolute ethanol (1 x 50 mL), acetone (1 x 100 mL), dry diethyl ether (1 x 50 mL) and dried under high vacuum.

To a suspension of previously activated Zn (2 equiv) in THF (1 M) at 0 °C was added propargyl bromide (1.5 equiv, 80% wt. toluene solution). The suspension was stirred at rt for 45 min, then isobutyraldehyde (1 equiv) was added and the suspension was stirred for another 2 h at 0 °C. More activated Zn (0.6 equiv) was added and the mixture was allowed to slowly reach rt (16 h). The reaction was quenched with saturated aqueous NH_4Cl solution, filtered and the filtrate extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether 90/10) to give 2-methyl-hex-5-yn-3-ol.

To a solution containing 2-methyl-hex-5-yn-3-ol (1 equiv) and *p*-TsOH (0.003 equiv) in DCM (0.66 M) at 0 °C was added dropwise DHP (1.12 equiv). The mixture was stirred at 0 °C and followed periodically by TLC. Upon completion (1 h 15 min), the solvent was evaporated under reduced pressure and the crude purified by flash column chromatography (silica gel, petroleum ether/diethyl ether 9/1) to give the expected product.

By analogy with the synthesis of substrated **5.12 d-f**, substrate **5.24 c** was prepared following Carreira's asymmetric alkyne addition followed by benzoylation of the secondary alcohol group and deprotection of the primary one.



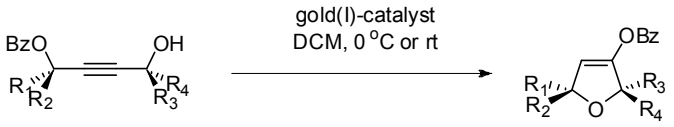
General procedure 5.10: A flask was charged with $Zn(OTf)_2$ (1.1 equiv) and heated under vacuum using a heat gun for 5 min. (-)-*N*-methyl ephedrine (1.2 equiv) was added and the flask was purged with nitrogen for 15 min. Toluene (0.5 M) and triethylamine (1.2 equiv) were added. The resulting mixture was stirred at rt for 2 h before the substrate (1 equiv) diluted in toluene (2 M) was added. After 30 min of stirring, the aldehyde (1.1 equiv) was added in one portion by syringe. The reaction was heated at 50 °C and followed periodically by TLC. Upon completion (1 h), the mixture was quenched with a saturated aqueous ammonium chloride solution and extracted twice with diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure.

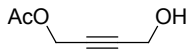
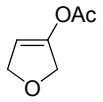
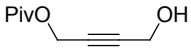
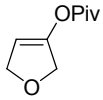
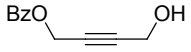
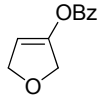
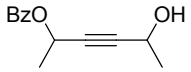
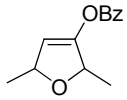
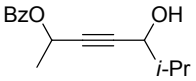
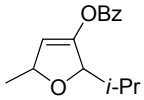
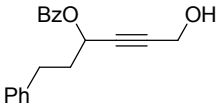
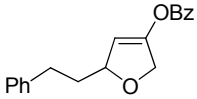
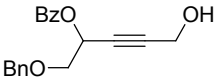
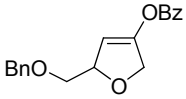
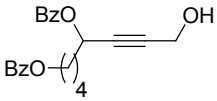
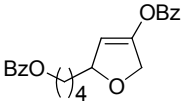
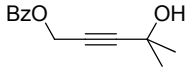
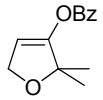
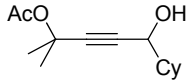
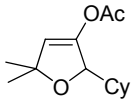
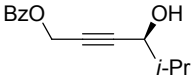
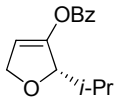
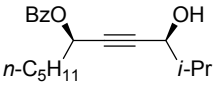
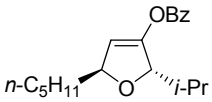
The residue was dissolved in dichloromethane (0.4 M) and triethylamine (1.3 equiv), benzoyl chloride (1.1 equiv) and DMAP (0.01 equiv) were successively added. The mixture was stirred at rt and followed periodically by TLC. After 3 h, water was added and the mixture was then extracted twice with diethyl ether. The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure.

The residue was dissolved in methanol (0.2 M), and *p*-TsOH (0.01 equiv) was added. The mixture was stirred at rt for 30 min and concentrated under reduced pressure to remove the solvent. The residue was diluted with diethyl ether and washed with a saturated aqueous sodium hydrogenocarbonate solution. The ethereal layer was dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether).

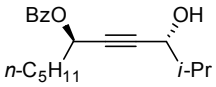
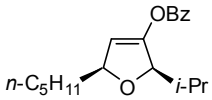
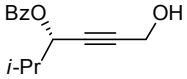
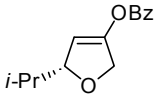
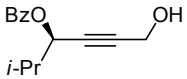
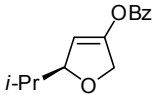
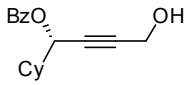
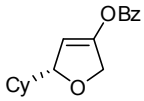
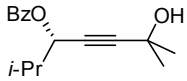
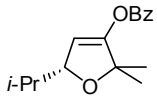
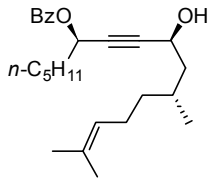
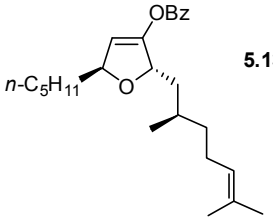
5.2. Gold(I)-catalyzed formation of functionalized dihydrofurans and dihydropyranes

As we saw in Chapter 5, functionalized 2,5-dihydropfurans **5.8 a-c**, **5.10 a-g** and **5.13 a-h** can be obtained stereoselectively from the corresponding precursors **5.7 a-c**, **5.9 a-g** and **5.12 a-h** in the presence of a gold(I)-catalyst.

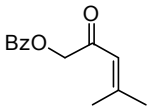


substrate		conditions	product		time	yield[a]
	**5.7 a**	1% Ph_3P-Au-NTf_2, rt		**5.8 a**	1 h 30 min	<10%
	**5.7 b**	1% Ph_3P-Au-NTf_2, rt		**5.8 b**	1 h	23%
	**5.7 c**	1% Ph_3P-Au-NTf_2, rt		**5.8 c**	1 h 20 min	83%
	**5.9 a**	2% Ph_3P-Au-NTf_2, rt		**5.10 a**	15 min	95%
	**5.9 b**	2% Ph_3P-Au-NTf_2, rt		**5.10 b**	20 min	92%
	**5.9 c**	2% Ph_3P-Au-NTf_2, rt		**5.10 c**	5 min	95%
	**5.9 d**	2% Ph_3P-Au-NTf_2, rt		**5.10 d**	20 min	99%
	**5.9 e**	2% Ph_3P-Au-NTf_2, rt		**5.10 e**	10 min	99%
	**5.9 f**	2% Ph_3P-Au-NTf_2, rt		**5.10 f**	1 h	69%[b]
	**5.9 g**	2% Ph_3P-Au-NTf_2, rt		**5.10 g**	5 min	82%
 87% ee	**5.12 a**	2% Ph_3P-Au-NTf_2, rt	 86% ee	**5.13 a**	3 h	83%
 93:7 dr, >98% ee	**5.12 b**	2% Ph_3P-Au-NTf_2, rt	 93:7 dr, >98% ee	**5.13 b**	40 min	97%

(continued on the next page)

substrate		conditions	product		time	yield[a]
	**5.12 c**	2% Ph_3P-Au-NTf_2, rt		**5.13 c**	35 min	99%
94:6 dr, >98% ee			92:8 dr, >98% ee			
	**5.12 d**	2% Ph_3P-Au-NTf_2, rt		**5.13 d**	10 min	99%
94% ee			64% ee			
	**5.12 e**			**5.13 e**		
96% ee		2% Ph_3P-Au-NTf_2, rt	64% ee		15 min	99%
		2% (p-CF_3-C_6H_4)$_3$P-Au-NTf_2, rt	66% ee		15 min	99%
		2% Ad_2(n-Bu)P-Au-NTf_2, rt	74% ee		20 min	99%
		2% Ph_3P-Au-NTf_2, 0 °C	84% ee		1 h 5 min	99%
		2% Ad_2(n-Bu)P-Au-NTf_2, 0 °C	90% ee		2 h	99%
	**5.12 f**			**5.13 f**		
94% ee		2% Ph_3P-Au-NTf_2, rt	42% ee		10 min	89%
		2% Ad_2(n-Bu)P-Au-NTf_2, 0 °C	77% ee		2 h 25 min	91%
	**5.12 g**	2% Ph_3P-Au-NTf_2, rt		**5.13 g**	50 min	95%
81% ee			80% ee			
	**5.12 h**	2% Ph_3P-Au-NTf_2, rt		**5.13 h**	15 min	99%
~ 89.1:9.9:0.9:(<0.1) dr			~ 89.1:9.9:0.9:(<0.1) dr			

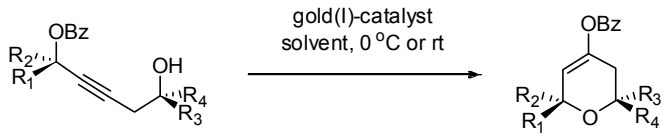
[a] Isolated yield. dr and ee determined by chiral HPLC analysis. [b] Compound **5.11** was also isolated as a side product in 23% yield.

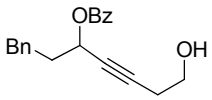
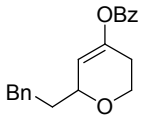
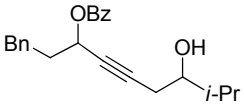
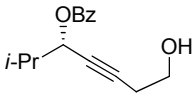
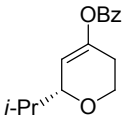


5.11

General procedure 5.11: To a solution of substrate (1 equiv) in dry dichloromethane (0.5 M) at the stated conditions of temperature (0 °C or rt) was added the gold catalyst (0.01 or 0.02 equiv of Ph_3P-Au-NTf_2, Ad_2(*n*-Bu)P-Au-NTf_2 or (*p*-CF_3-C_6H_4)$_3$P-Au-NTf_2 depending of the substrate). The reaction was stirred until full consumption of the starting material (as attested by TLC analysis). The resulting mixture was then filtered through a small pad of silica pre-impregnated with dichloromethane. The pad was washed with diethyl ether and the filtrate evaporated. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether).

Substrates **5.24 a-c** can also be rearranged sometimes in the presence of a gold(I)-catalyst to give substituted dihydropyrans.



substrate	conditions	product[a]	time	conv.[b]	yield[c]
 **5.24 a**		 **5.25 a**			
	1% Ph_3P-Au-NTf_2, DCM, rt		20 min	100%	52%
	1% Ph_3P-Au-NTf_2, DCM, 0 °C		3 h	100%	54%
 **5.24 b**		-			
	1% Ph_3P-Au-NTf_2, DCM, rt		1 h 30 min	100%	degrad.
 **5.24 c**		 **5.25 c**			
89% ee	1% Ph_3P-Au-NTf_2, DCM, rt	37% ee	45 min	100%	74%
	1% Ph_3P-Au-NTf_2, DCM, 0 °C	45% ee	3 h 30 min	100%	58%
	1% Ad_2(*n*-Bu)P-Au-NTf_2, DCM, 0 °C	47% ee	40 min	100%	60%
	1% Ph_3P-Au-NTf_2, MeCN/DCM 1/1, rt	45% ee	18 h	64%	34%
	1% Ph_3P-Au-NTf_2, CF_3CH_2OH, rt	11% ee	6 h	81%	74%
	1% Ph_3P-Au-NTf_2, toluene, rt	73% ee	30 min	100%	29%

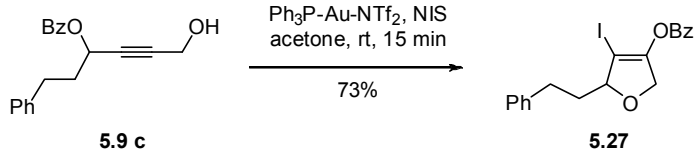
[a] ee determined by chiral HPLC analysis. [b] Determined by 1H NMR of the crude reaction mixture. [c] Isolated yield.

General procedure 5.12: To a solution of substrate (1 equiv) in the corresponding solvent (0.33 M) at the stated conditions of temperature (0 °C or rt) was added the gold catalyst (0.01 equiv. of Ph_3P-Au-NTf_2 or Ad_2(*n*-Bu)P-Au-NTf_2 depending of

the substrate). The reaction was monitored by TLC. The resulting mixture was then filtered through a small pad of silica pre-impregnated with dichloromethane. The pad was washed with diethyl ether and the filtrate evaporated. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether).

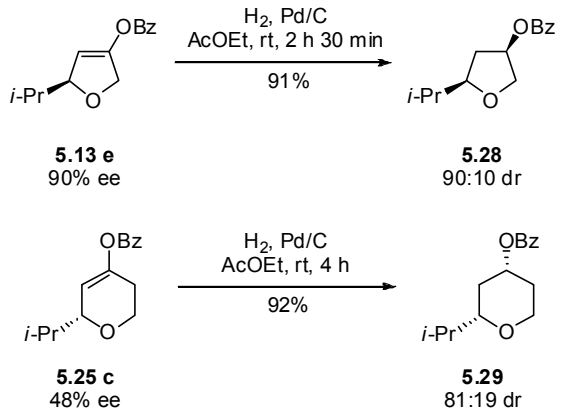
5.3. Other applications

4-Iodo-2,5-dihydrofuran **5.27** can be easily obtained from the corresponding substrate **5.9 c** via a gold(I)-catalyzed transformation in the presence of NIS.



General procedure 5.13: To a solution of substrate (1 equiv) in dry acetone (0.5 M) at rt were successively added NIS (1.2 equiv) and Ph_3P-Au-NTf_2 (0.02 equiv). The reaction mixture was stirred until the full consumption of the starting material was observed (for 15 min). The resulting mixture was then filtered through a small pad of silica pre-impregnated with diethyl ether. The pad was washed with more diethyl ether and the filtrate evaporated. The residue was directly purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected iodo-derivative.

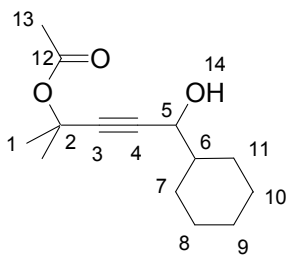
The dihydrofuran **5.13 e** and the dihydropyran **5.25 c** can be hydrogenated using Pd/C in classical conditions to afford the tetrahydrofuran **5.28** and the tetrahydropyran **5.29** respectively.



General procedure 5.14: To a solution of substrate (1 equiv) in ethyl acetate (0.1 M) at rt was added Pd/C (0.1 equiv, 10% over activated carbon). The reaction flask was purged twice with nitrogen before being filled with H_2 (1 atm pressure). The resulting mixture was stirred at rt, monitored periodically by TLC and upon completion filtered through a small pad of celite. The pad was washed with dichloromethane and the filtrate evaporated. The residue was directly purified by flash column chromatography (silica gel, petroleum ether / ethyl ether).

5.4. Characterization of the prepared compounds

Acetic acid 4-cyclohexyl-4-hydroxy-1,1-dimethyl-but-2-ynyl ester	**5.9 g**



MF: $C_{14}H_{22}O_3$

MW: 238.32 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 5.5** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 75/25-60/40).

Product: Colourless oil.

Yield: 66%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.21 (d, J = 6.0 Hz, 1H, *5*), 2.06 (s, 3H, *13*), 2.00 (bs, 1H, *14*), 1.89-1.65 (m, 5H, *7*, *8*, *9*, *10* and/or *11*), 1.69 (s, 6H, *1*), 1.63-1.53 (m, 1H, *6*), 1.34-1.03 (m, 5H, *7*, *8*, *9*, *10*, *11* and/or *12*).

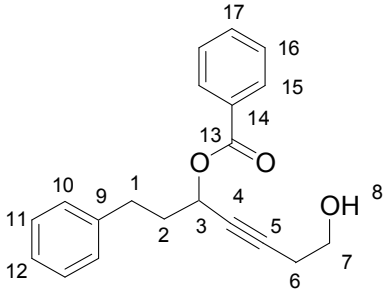
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 169.4 (*12*), 86.6 (*3*), 84.2 (*4*), 71.9 (*2*), 67.0 (*5*), 44.0 (*6*), 29.0 (*1*), 28.9 (*1*), 28.5 (*7*, *8*, *9*, *10*, *11* or *12*), 27.9 (*7*, *8*, *9*, *10*, *11* or *12*), 26.4 (*7*, *8*, *9*, *10*, *11* or *12*), 25.9 (*7*, *8*, *9*, *10*, *11* or *12*), 25.8 (*7*, *8*, *9*, *10*, *11* or *12*), 22.0 (*13*).

IR (ν, cm^{-1}) (CCl_4): 3618, 2927, 1778, 1658, 1451, 1366, 1302, 1205, 1116, 1101.

MS (CI^+, NH_3, m/z): 256 (MNH_4^+), 239 (MH^+).

HRMS (EI^+, m/z): Calculated for $C_{14}H_{22}O_3$: 238.1569.
Found for $C_{14}H_{22}O_3$: 238.1579.

Benzoic acid 5-hydroxy-1-phenethyl-pent-2-ynyl ester	**5.24 a**



MF: $C_{20}H_{20}O_3$

MW: 308.37 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 5.8** (scale: 5 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 60/40-50/50).

Product: Pale yellow oil.

Yield: 25% (over 4 steps).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.02 (d, J = 7.0 Hz, 2H, *15*), 7.56 (t, J = 7.4 Hz, 1H, *17*), 7.43 (t, J = 7.8 Hz, 2H, *16*), 7.17-7.31 (m, 5H, *10*, *11* and *12*), 5.57 (tt, J = 1.8, 6.4 Hz, *3*), 3.71 (t, J = 6.3 Hz, 2H, *7*), 2.85 (t, J = 7.9 Hz, 2H, *1*), 2.50 (td, J = 1.9, 6.3 Hz, 2H, *6*), 2.15-2.30 (m, 3H, *2* and *8*).

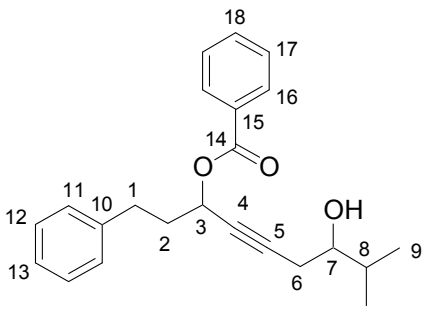
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 165.6 (13), 140.7 (*9* or *14*), 133.1 (*17*), 129.8 (*9* or *14*), 129.7 (*15*), 128.4 (*10*, *11*, *12* or *16*), 128.3 (*10*, *11*, *12* or *16*), 128.3 (*10*, *11*, *12* or *16*), 126.0 (*10*, *11*, *12* or *16*), 83.3 (*4* or *5*), 79.4 (*4* or *5*), 64.4 (*3*), 60.8 (*7*), 36.4 (*2*), 31.3 (*1*), 23.1 (*6*).

IR (ν, cm^{-1}) (CCl_4): 3633, 3535, 3065, 3029, 2953, 2875, 2240, 1724, 1600, 1451, 1317, 1282, 1103, 1049, 1025.

MS (CI^+, NH_3, m/z): 326 (MNH_4^+), 309 (MH^+), 291, 279, 270, 242, 226, 205, 188, 170.

HRMS (EI^+, m/z): Calculated for $C_{20}H_{20}O_3$: 308.1413.
Found for $C_{20}H_{20}O_3$: 308.1404.

Benzoic acid 5-hydroxy-6-methyl-1-phenethyl-hept-2-ynyl ester 5.24 b



MF: $C_{23}H_{26}O_3$

MW: 350.45 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 5.8** (scale: 5 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 75/25).

Product: Yellow oil.

Yield: 29% (over 4 steps).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.04 (d, J = 7.3 Hz, 2H, *16*), 7.57 (t, J = 7.3 Hz, 1H, *18*), 7.44 (t, J = 7.3 Hz, 2H, *17*), 7.15-7.33 (m, 5H, *11*, *12* and *13*), 5.58 (m, 1H, *3*), 3.49 (m, 1H, *7*), 2.86 (t, J = 7.9 Hz, 2H, *1*), 2.47 (m, 2H, *6*), 2.25 (m, 2H, *2*), 1.77 (hept, J = 5.6 Hz, 1H, *8*), 0.96 (dm, 6H, *9*).

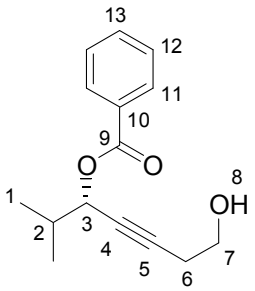
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 165.5 (*14*), 140.7 (*10* or *15*), 133.1 (*18*), 129.8 (*10* or *15*), 129.7 (*16*), 128.4 (*11*, *12*, *13* or *17*), 128.4 (*11*, *12*, *13* or *17*), 128.3 (*11*, *12*, *13* or *17*), 126.1 (*11*, *12*, *13* or *17*), 83.5 (*4* or *5*), 79.9 (*4* or *5*), 74.7 (*7*), 64.4 (*3*), 36.5 (*2*), 32.7 (*8*), 31.4 (*1*), 25.0 (*6*), 18.6 (*9*), 17.6 (*9*).

IR (ν, cm^{-1}) (CCl_4): 3591, 3539, 3065, 3028, 2959, 2871, 2240, 1724, 1601, 1453, 1316, 1263, 1175, 1104, 1023.

MS (CI^+, NH_3, m/z): 368 (MNH_4^+), 351 (MH^+), 246, 229, 211.

HRMS (EI^+, m/z): Calculated for $C_{23}H_{26}O_3$: 350.1882.
Found for $C_{23}H_{26}O_3$: 350.1883.

Benzoic acid (*S*)-5-hydroxy-1-isopropyl-pent-2-ynyl ester 5.24 c



MF: $C_{15}H_{18}O_3$

MW: 246.30 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 5.10** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 60/40).

Product: Yellow oil.

Yield: 75% (over 3 steps).

ee: 89%

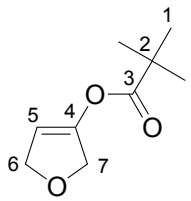
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.06 (d, J = 7.0 Hz, 2H, *11*), 7.57 (t, J = 7.4 Hz, 1H, *13*), 7.45 (t, J = 7.8 Hz, 2H, *12*), 5.42 (dt, J = 2.0, 5.6 Hz, 1H, *3*), 3.72 (t, J = 6.2 Hz, 2H, *7*), 2.51 (td, J = 2.0, 6.2 Hz, 2H, *6*), 2.12 (hept, J = 6.7 Hz, 1H, *2*), 1.80 (bs, 1H, *8*), 1.11 (dm, 6H, *1*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 165.6 (*9*), 133.0 (*13*), 130.0 (*10*), 129.7 (*11*), 128.3 (*12*), 83.2 (*5*), 78.5 (*4*), 69.8 (*3*), 60.9 (*7*), 32.6 (*2*), 23.1 (*6*), 18.2 (*1*), 17.8 (*1*).

IR (ν, cm^{-1}) (CCl_4): 3632, 3600, 3535, 3067, 3036, 2966, 3934, 2878, 2237, 1723, 1600, 1453,

	1262, 1177, 1100, 1050.
MS (CI^+, NH_3, m/z)	264 (MNH_4^+), 247 (MH^+), 237, 224, 163, 143, 126.
HRMS (EI^+, m/z)	Calculated for $C_{15}H_{18}O_3$: 246.1256. Found for $C_{15}H_{18}O_3$: 246.1248.
HPLC (Chiracel OD-H)	Eluent *n*-C_7H_{16}/*i*-PrOH 99.5/0.5, flow 1 mL / min, injection volume 10 µL. UV Detection at 220 nm. Retention time: 28.05 min (minor isomer), 30.47 min (major isomer).

2,2-Dimethyl-propionic acid 2,5-dihydro-furan-3-yl ester — 5.8 b

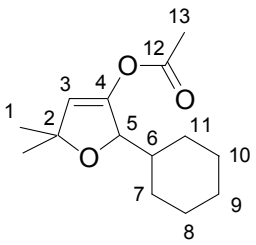


MF: $C_9H_{14}O_3$

MW: 170.21 g.mol^{-1}

Reaction:	The reaction was carried out according to the **General Procedure 5.11** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 96/4).
Product:	Pale yellow oil.
Yield:	23%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.74-5.72 (m, 1H, *5*), 4.77-4.74 (m, 1H, *7*), 4.66-4.63 (m, 1H, *6*), 1.30 (s, 9H, *1*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	175.3 (*3*), 145.7 (*4*), 106.6 (*5*), 73.7 (*7*), 70.9 (*6*), 39.2 (*2*), 27.0 (*1*).
IR (ν, cm^{-1}) (CCl_4)	2972, 2856, 1759, 1661, 1268, 1194, 1114.
MS (CI^+, NH_3, m/z)	188 (MNH_4^+), 171 (MH^+).
HRMS (EI^+, m/z)	Calculated for $C_9H_{14}O_3$: 170.0943. Found for $C_9H_{14}O_3$: 170.0936.

Acetic acid 2-cyclohexyl-5,5-dimethyl-2,5-dihydro-furan-3-yl ester — 5.10 g



MF: $C_{14}H_{22}O_3$

MW: 238.32 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 5.11** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 96/4).

Product: Pale yellow oil.

Yield: 82%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.77 (d, J = 2.0 Hz, 1H, *3*), 4.66 (dd, J = 2.0, 2.2 Hz, 1H, *5*), 2.20 (s, 3H, *13*), 1.80-1.78 (m, 2H, *7*, *8*, *9*, *10* and/or *11*), 1.71-1.69 (m, 2H, *7*, *8*, *9*, *10* and/or *11*), 1.57-1.47 (m, 1H, *6*), 1.38 (s, 3H, *1*), 1.37 (s, 3H, *1*), 1.35-1.12 (m, 6H, *7*, *8*, *9*, *10* and/or *11*).

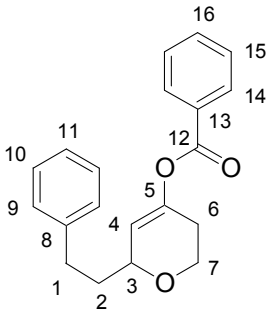
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 167.7 (*12*), 144.8 (*4*), 116.6 (*3*), 84.6 (*5*), 40.5 (*6*), 29.4 (*7*, *8*, *9*, *10* or *11*), 28.8 (*1*), 28.7 (*1*), 26.7 (*7*, *8*, *9*, *10* or *11*), 26.6 (*7*, *8*, *9*, *10* or *11*), 26.5 (*7*, *8*, *9*, *10* or *11*), 26.4 (*7*, *8*, *9*, *10* or *11*), 21.3 (*13*).

IR (ν, cm^{-1}) (CCl_4) 2928, 2855, 1744, 1449, 1366, 1242, 1134, 1012.

MS (CI^+, NH_3, m/z) 256 (MNH_4^+), 239 (MH^+).

HRMS (EI^+, m/z) Calculated for $C_{14}H_{22}O_3$: 238.1569.
Found for $C_{14}H_{22}O_3$: 238.1561.

Benzoic acid 6-phenethyl-3,6-dihydro-2*H*-pyran-4-yl ester 5.25 a



MF: $C_{20}H_{20}O_3$

MW: 308.37 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 5.12** (scale: 0.5 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product: Pale yellow oil.

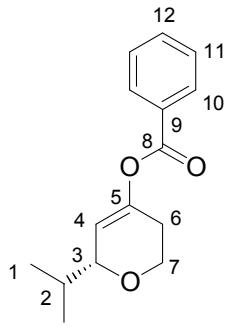
Yield: up to 54% (depending on the reaction conditions).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.06 (d, J = 7.0 Hz, 2H, *14*), 7.58 (t, J = 7.4 Hz, 1H, *16*), 7.45 (t, J = 7.8 Hz, 2H, *15*), 7.15-7.29 (m, 5H, *9*, *10* and *11*), 5.52 (s, 1H, *4*), 4.27 (m, 1H, *3*), 4.13 (ddd, J = 2.3, 5.7, 11.2 Hz, 1H, *7 eq*), 3.81 (td, J = 3.9, 9.9 Hz, 1H, *7 ax*), 2.77 (m, 2H, *1*), 2.62 (m, 1H, *6 ax*), 2.22 (dd, J = 2.8, 16.4 Hz, 1H, *6 eq*), 1.93 (m, 2H, *2*).

^{13}C NMR (δ, ppm) 164.5 (*12*), 146.5 (*5*), 141.8 (*8*), 133.3 (*16*), 129.8 (*14*), 129.5 (*13*), 128.4 (*9*, *10*, *11* and/or *15*), 128.3 (*9*, *10*, *11* or *15*), 125.7 (*9*, *10*, *11* or *15*), 116.4 (*4*),

($CDCl_3$, 100 MHz)	72.5 (*3*), 63.3 (*7*), 36.9 (*2*), 31.3 (*1*), 27.7 (*6*).
IR (ν, cm^{-1}) (CCl_4)	3065, 3028, 2933, 2861, 1736, 1692, 1600, 1496, 1452, 1355, 1261, 1176, 1140, 1060, 1021.
MS (CI^+, NH_3, m/z)	326 (MNH_4^+), 309 (MH^+), 270, 222, 205, 188.
HRMS (EI^+, m/z)	Calculated for $C_{20}H_{20}O_3$: 308.1413. Found for $C_{20}H_{20}O_3$: 308.1410.

Benzoic acid (*R*)-6-isopropyl-3,6-dihydro-2*H*-pyran-4-yl ester **5.25 c**

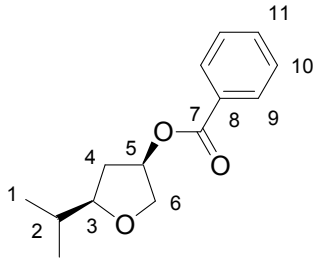


MF: $C_{15}H_{18}O_3$

MW: 246.30 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 5.12** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 98/2).
Product:	Pale yellow oil.
Yield:	up to 74% (depending on the reaction conditions).
ee:	up to 73% (depending on the reaction conditions).
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	8.08 (d, J = 7.0 Hz, 2H, *10*), 7.59 (t, J = 7.4 Hz, 1H, *12*), 7.47 (t, J = 7.8 Hz, 2H, *11*), 5.54 (s, 1H, *4*), 4.11 (ddd, J = 1.7, 5.9, 11.1 Hz, 1H, *7 eq*), 4.05 (d, J = 2.8 Hz, 1H, *3*), 3.80 (td, J = 3.7, 10.7 Hz, 1H, *7 ax*), 2.61 (m, 1H, *6 ax*), 2.16 (d, J = 16.5 Hz, 1H, *6 eq*), 1.86 (hept, J = 6.8 Hz, 1H, *2*), 0.97 (dm, 6H, *1*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	164.7 (*8*), 146.9 (*5*), 133.3 (*12*), 129.9 (*10*), 129.6 (*9*), 128.4 (*11*), 114.9 (*4*), 78.3 (*3*), 63.7 (*7*), 32.6 (*2*), 27.9 (*6*), 17.9 (*1*), 17.7 (*1*).
IR (ν, cm^{-1}) (CCl_4)	3066, 2963, 2927, 2866, 2815, 1736, 1692, 1456, 1260, 1135, 1062, 1021.
MS (CI^+, NH_3, m/z)	264 (MNH_4^+), 247 (MH^+), 237, 224, 220, 204, 191, 180, 163.
HRMS (EI^+, m/z)	Calculated for $C_{15}H_{18}O_3$: 246.1256. Found for $C_{15}H_{18}O_3$: 246.1261.
HPLC (Chiracel OD-H)	Eluent *n*-C_7H_{16}/*i*-PrOH 99.5/0.5, flow 0.5 mL / min, injection volume 10 µL. UV Detection at 220 nm. Retention time: 7.58 min (minor isomer), 8.56 min (major isomer).

(3*R*,5*R*)-Benzoic acid 5-isopropyl-tetrahydro-furan-3-yl ester **5.28**



MF: $C_{14}H_{18}O_3$

MW: 234.29 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 5.14** (scale: 0.245 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Yellow oil (mixture of diastereoisomers).

Yield: 91%

dr: 90:10

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) Major diastereoisomer: 8.08 (d, J = 7.8 Hz, 2H, *9*), 7.61 (t, J = 7.8 Hz, 1H, *11*), 7.48 (t, J = 7.8 Hz, 2H, *10*), 5.55-5.53 (m, 1H, *5*), 4.14 (d, J = 10.7 Hz, 1H, *6 cis*), 3.92 (dd, J = 10.7, 4.8 Hz, 1H, *6 trans*), 3.62 (ddd, J = 7.5, 7.5, 7.5 Hz, 1H, *3*), 2.50 (ddd, J = 14.4, 7.5, 7.5 Hz, 1H, *4 trans*), 1.96-1.81 (m, 2H, *2* and *4 cis*), 1.07 (d, J = 6.6 Hz, 3H, *1*), 0.97 (d, J = 6.6 Hz, 3H, *1*).

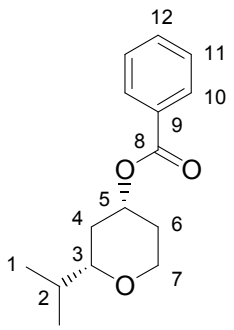
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) Major diastereoisomer: 166.4 (*7*), 133.0 (*11*), 130.1 (*8*), 129.6 (*9*), 128.4 (*10*), 84.6 (*3*), 75.7 (*5*), 72.9 (*6*), 36.0 (*4*), 32.8 (*2*), 19.2 (*1*), 18.5 (*1*).

IR (ν, cm^{-1}) (CCl_4) For the mixture of isomers: 2961, 2869, 1720, 1453, 1272, 1111, 1092.

MS (CI^+, NH_3, m/z) 235 (MH^+).

HRMS (EI^+, m/z) Calculated for $C_{14}H_{18}O_3$: 234.1256.
Found for $C_{14}H_{18}O_3$: 234.1250.

(3*R*,5*R*)-Benzoic acid 5-isopropyl-tetrahydro-furan-3-yl ester 5.29



MF: $C_{15}H_{20}O_3$

MW: 248.32 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 5.14** (scale: 0.15 mmol).

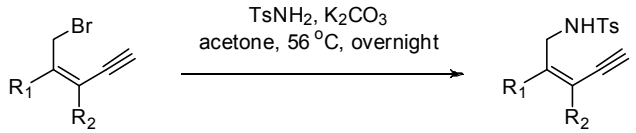
Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

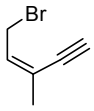
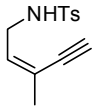
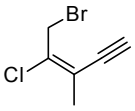
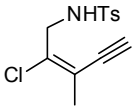
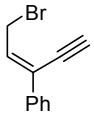
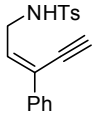
Product:	Yellow oil (mixture of diastereoisomers).
Yield:	92%
dr:	81:19
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	Major diastereoisomer: 8.03 (d, J = 7.0 Hz, 2H, *10*), 7.55 (t, J = 7.4 Hz, 1H, *12*), 7.44 (t, J = 7.8 Hz, 2H, *11*), 5.13 (m, 1H, *5*), 4.08 (ddd, J = 1.5, 4.9, 11.8 Hz, 1H, *7 eq*), 3.51 (td, J = 2.0, 12.3 Hz, 1H, *7 ax*), 3.13 (ddd, J = 1.7, 6.0, 11.3 Hz, 1H, *3*), 2.10 (dt, J = 2.2, 12.1 Hz, 1H, *4 eq*), 2.01 (ddd, J = 2.0, 4.6, 12.3 Hz, 1H, *6 eq*), 1.75 (m, 2H, *2* and *6 eq*), 1.46 (q, J = 11.4 Hz, 1H, *4 ax*), 0.97 (d, J = 6.8 Hz, 6H, *1*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	Major diastereoisomer: 165.9 (*8*), 132.8 (*12*), 130.4 (*9*), 129.5 (*10*), 128.3 (*11*), 81.0 (*3*), 71.5 (*5*), 65.7 (*7*), 34.3 (*4*), 32.9 (*2*), 32.2 (*6*), 18.4 (*1*), 18.2 (*1*).
IR (ν, cm^{-1}) (CCl_4)	For the mixture of isomers: 3065, 2960, 2927, 2854, 1715, 1453, 1312, 1271, 1168, 1110, 1026.
MS (CI^+, NH_3, m/z)	249 (MH+), 239, 157, 140, 128.
HRMS (EI^+, m/z)	Calculated for $C_{15}H_{20}O_3$: 248.1413. Found for $C_{14}H_{18}O_3$: 248.1407.

6. Synthesis of functionalized pyrroles and furans via a gold(I)-catalyzed Claisen-type rearrangement

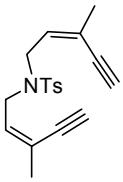
6.1. Synthesis of the precursors

Substrates **6.2 a-c** were synthesized by monoallylation of tosylamide following a procedure described in the literature.[332] During the formation of **6.2 a**, compound **6.4 l** was also obtained as a by-product (being formed by diallylation of tosylamide).



substrate		product		yield[a]
	**6.26 a**		**6.2 a**	61%[b]
	**6.26 b**		**6.2 b**	65%
	**6.26 c**		**6.2 c**	71%

[a] Isolated yield. [b] By-product **6.4 l** was also isolated in a 13% yield.



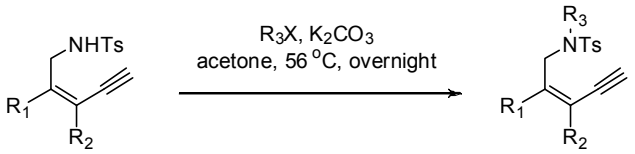
6.4 l

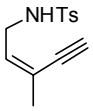
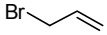
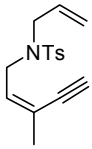
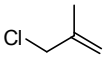
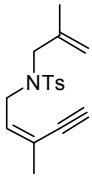
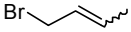
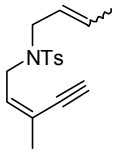
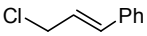
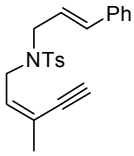
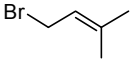
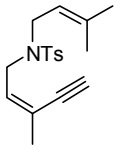
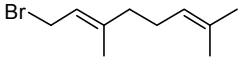
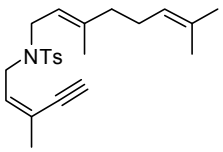
General procedure 6.1: To a solution containing the starting bromide (1 equiv) in acetone (0.5 M) were added *p*-tolylsulfonamide (1.5 equiv) and potassium carbonate (1.5 equiv). The mixture was heated overnight at reflux (56 °C). Upon completion, the acetone was removed under reduced pressure and the residue was dissolved in a diethyl ether / water mixture. The aqueous

[332] Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2000**, *2000*, 3007-3011.

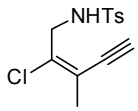
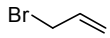
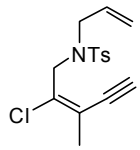
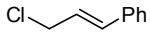
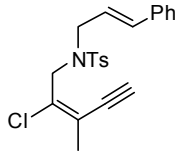
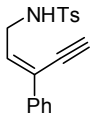
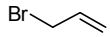
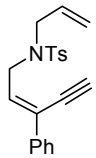
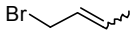
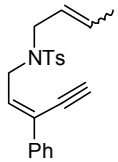
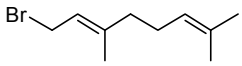
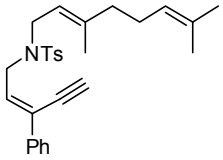
layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

Substrates **6.4 a-k** were obtained in similar conditions by allylation of the corresponding monosubstituted tosylamides **6.2 a-c**.[330]



substrate		R_3X	product		yield[a]
	**6.2 a**			**6.4 a**	96%
				**6.4 d**	94%
			 *Z/E* ratio ~ 1/3.5	**6.4 e**	89%
				**6.4 g**	92%
				**6.4 i**	76%
				**6.4 j**	82%

(continued on the next page)

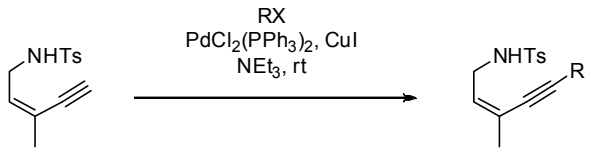
substrate		R_3X	product		yield[a]
	**6.2 b**			**6.4 b**	93%
				**6.4 h**	92%
	**6.2 c**			**6.4 c**	99%
			 *Z/E* ratio ~ 1/2.6	**6.4 f**	99%
				**6.4 k**	99%

[a] Isolated yield.

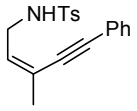
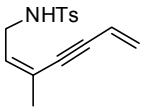
General procedure 6.2: To a solution of monosubstituted tosyl amide (1 equiv) in acetone (0.33 M) were added the corresponding allyl bromide (2 equiv) and potassium carbonate (1.5 equiv). (In the case of allyl chlorides (2 equiv), a catalytical amount of NaI (0.1 equiv) was also added). The mixture was heated overnight at reflux (56 ^{o}C). Upon completion, the acetone was removed under reduced pressure and the residue was dissolved in a diethyl ether / water mixture. The aqueous layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

The corresponding allylation agents **6.26 a-c** were obtained according to the procedures described by Gabriele, Salerno et al.[333]

Substrates **6.9** and **6.11** were obtained starting from the terminal alkyne **6.2 a** via a Sonogashira coupling.[326]



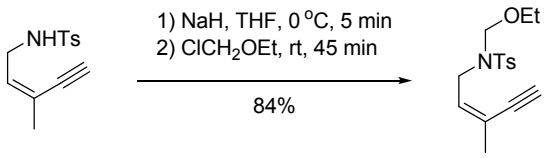
6.2 a

RX	product		time	yield[a]
Ph—Br		**6.9**	5 h	79%
		**6.11**	3 h	75%

[a] Isolated yield.

General procedure 6.3: To a solution containing the terminal alkyne (1 equiv) in NEt_3 (0.25 M) was added the corresponding halide (1.2 equiv), $PdCl_2(PPh_3)_2$ (0.02 equiv) and CuI (0.02 equiv). The mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected coupling product.

Substrate **6.13** was synthesized starting from **6.2 a** by deprotonation with NaH followed by alkylation with chloromethyl ethyl ether.

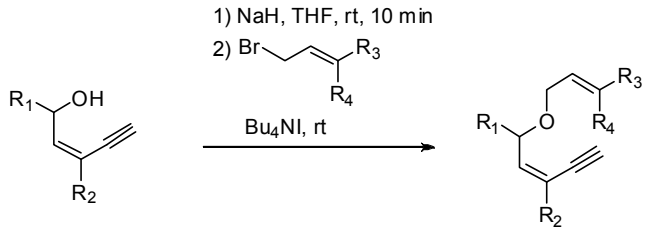


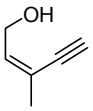
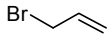
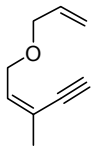
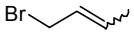
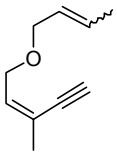
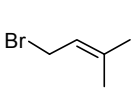
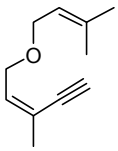
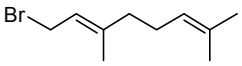
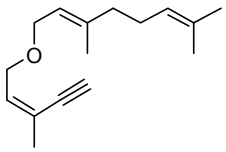
6.2 a **6.13**

[333] (a) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. R. *Tetrahedron Lett.* **2001**, *42*, 1339-1341.
(b) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687-7692.

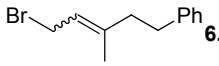
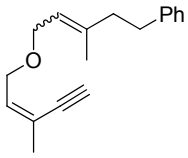
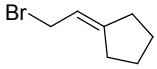
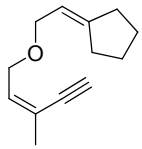
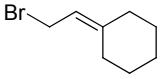
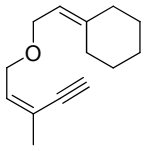
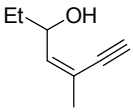
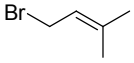
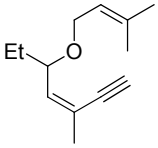
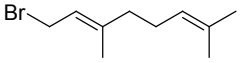
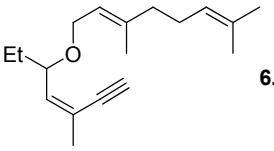
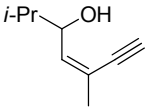
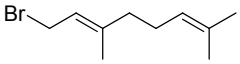
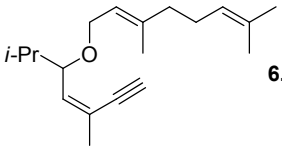
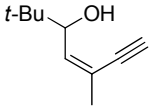
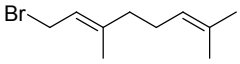
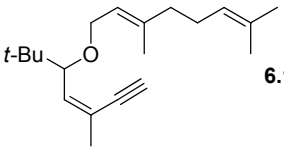
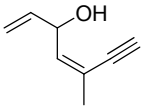
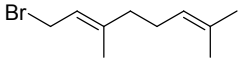
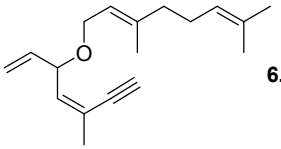
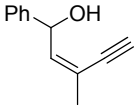
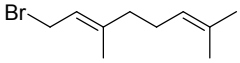
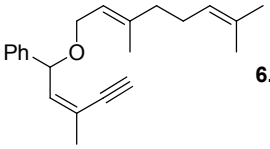
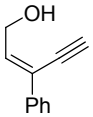
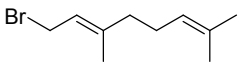
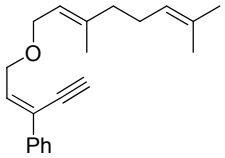
General procedure 6.4: To a solution of monosubstituted tosylamide (1 equiv) in THF (0.5 M) at 0 °C was added in portions NaH (2 equiv). The mixture was stirred at 0 °C for 5 min, then chloromethyl ethyl ether (2 equiv) was added dropwise. The reaction was allowed to react at rt and followed periodically by TLC. Upon completion (45 min), the reaction was quenched with saturated aqueous NH_4Cl solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

Substrates **6.16 a-s** were synthesized by allylation of the corresponding alcohol **6.27 a-i** under classical conditions.

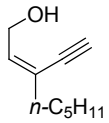
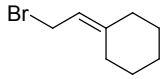
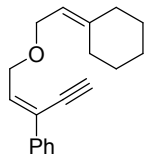
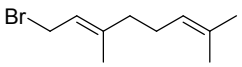
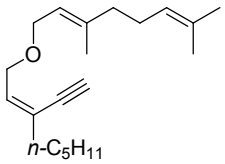
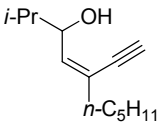
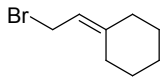
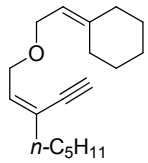
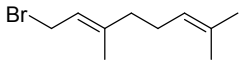
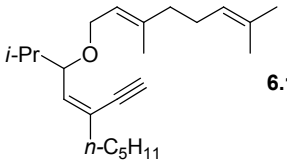
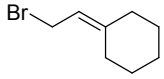
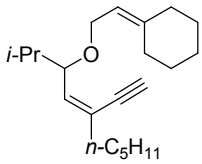


alcohol	bromide	product	time	yield[a]
 **6.27 a**		 **6.16 a**	1 h	45%
		 *Z/E* ratio ~ 1/3 **6.16 b**	1 h	65%
		 **6.16 c**	40 min	64%
		 **6.16 d**	40 min	69%

(continued on the next page)

alcohol	bromide	product	time	yield[a]
	 **6.28 a**	 *Z/E* ratio ~ 1/2.57 **6.16 e**	2 h	69%
	 **6.28 b**	 **6.16 f**	2 h	70%
	 **6.28 c**	 **6.16 g**	1 h	72%
 **6.27 b**		 **6.16 h**	4 h 30 min	44%
		 **6.16 i**	4 h	64%
 **6.27 c**		 **6.16 j**	4 h	50%
 **6.27 d**		 **6.16 k**	21 h	40%
 **6.27 e**		 **6.16 l**	2 h	57%
 **6.27 f**		 **6.16 m**	2 h	59%
 **6.27 g**		 **6.16 n**	2 h	68%

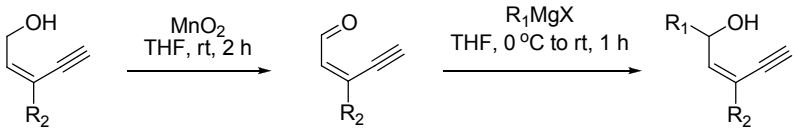
(continued on the next page)

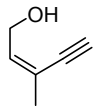
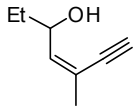
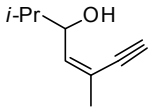
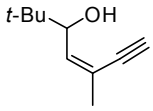
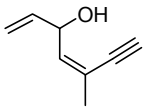
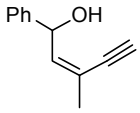
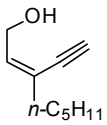
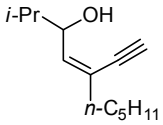
alcohol	bromide	product	time	yield[a]
 **6.27 h**	 **6.28 c**	 **6.16 o**	1 h	77%
		 **6.16 p**	2 h 30 min	84%
 **6.27 i**	 **6.28 c**	 **6.16 q**	1 h 30 min	75%
		 **6.16 r**	3 h	50%
	 **6.28 c**	 **6.16 s**	2 h	40%

[a] Isolated yield.

General procedure 6.5: To a solution of the alcohol (1 equiv) in THF (0.5 M) was added NaH (1.5 equiv, 60% dispersion in mineral oil) portionwise. The mixture was stirred at rt for a few minutes and then the corresponding bromide (1.2 equiv) and tetrabutylammonium iodide (0.1 equiv) were added. The mixture was allowed to react at rt and monitored periodically by TLC. Upon completion, it was quenched with a saturated solution of NH_4Cl, the aqueous layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

Secondary alcohols **6.27 b-f** and **i** were obtained by oxidation of the corresponding allylic alcohols followed by nucleophilic addition of the corresponding Grignard reagent.

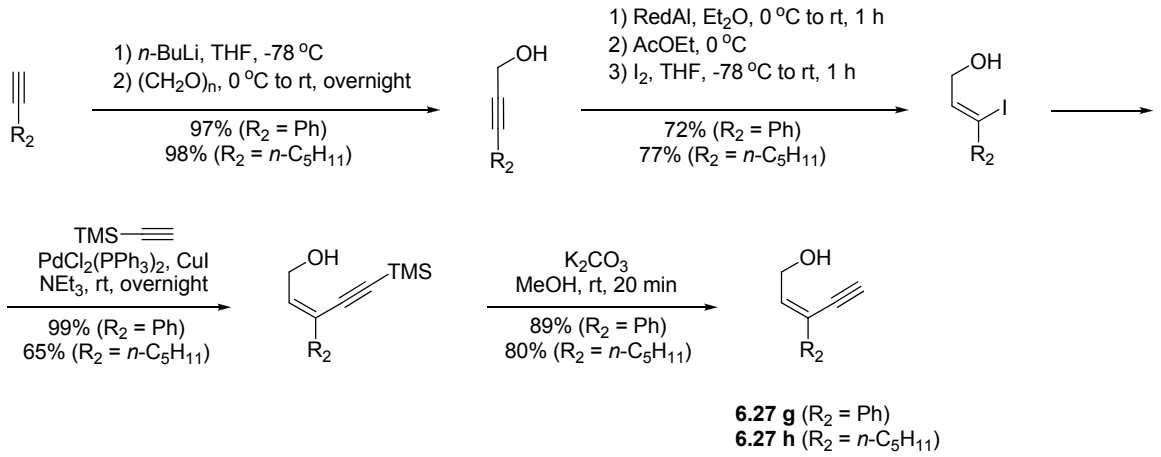


substrate		product		yield[a]
	**6.27 a**		**6.27 b**	67%
			**6.27 c**	22%
			**6.27 d**	20%
			**6.27 e**	46%
			**6.27 f**	22%
	**6.27 h**		**6.27 i**	29%

[a] Isolated yield (over 2 steps).

General procedure 6.6: To a solution of starting alcohol (1 equiv) in THF (0.33 M) was added MnO_2 (20 equiv). The mixture was stirred at rt for 2 h and then filtered through a celite pad. The filtrate was then cooled at 0 °C and the corresponding organomagnesium reagent (2 equiv) was added dropwise. The mixture was allowed to warm up at rt and monitored periodically by TLC. Upon completion, it was quenched with a saturated solution of NH_4Cl, the aqueous layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

Alcohols **6.27 g** and **h** were synthesized according to the methods described in the literature. The terminal alkyne was first deprotonated using *n*-BuLi then added to paraformaldehyde.[334] The cooresponding alcohol was reduced in the presence of RedAl / I_2 to afford an iododerivative.[335] Palladium-catalyzed Sonogashira coupling[336] followed by desilylation of the alkyne in K_2CO_3 / MeOH conditions[337] led to the desired final compounds.



General procedure 6.7: To a solution of terminal alkyne (1 equiv) in THF (1 M) at -78 °C was added *n*-BuLi (1.1 equiv). The mixture was allowed to reach 0 °C and then paraformaldehyde (2 equiv) was added. The reaction was stirred at rt overnight. Upon completion, it was quenched with a saturated solution of NH_4Cl, the aqueous layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected primary alcohol.

The primary alcohol (1 equiv) was dissolved in diethyl ether (0.5 M) at 0 °C and RedAl (1.8 equiv, 3.5 M solution in toluene) was added dropwise. The mixture was allowed to warm up from 0 °C to rt for 1 h. The reaction was then cooled back to 0 °C and ethyl acetate (3 M) was added dropwise. After that the mixture was further cooled to -78 °C and a solution of iodine (1.25 equiv) in THF (0.5 M) was added dropwise. The mixture was allowed to reach rt for 1 h. Upon completion, it was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and filtered through a silica pad impregnated with diethyl ether. The filtrate was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified

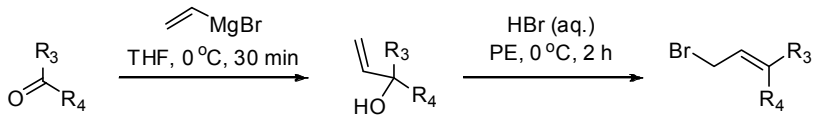
[334] Zachová, H.; Man, S.; Nečas, M.; Potáček, M. *Eur. J. Org. Chem.* **2005**, *2005*, 2548-2557.
[335] Furstner, A.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 1906-1907.
[336] Marx, K.; Eberbach, W. *Chem. Eur. J.* **2000**, *6*, 2063-2068.
[337] Musso, D. L.; Clarke, M. J.; Kelley, J. L.; Boswell, G. E.; Chen, G. *Org. Biomol. Chem.* **2003**, *1*, 498-506.

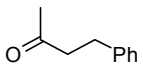
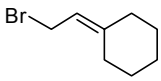
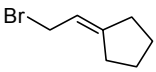
by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected iodide derivative.

The iodide previously obtained (1 equiv) was dissolved in NEt_3 (0.25 M), and ethynyl(trimethyl)silane (1.5 equiv), $PdCl_2(PPh_3)_2$ (0.02 equiv) and CuI (0.02 equiv) were successively added. The mixture was stirred overnight at rt. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected coupling product.

The TMS-protected alkyne (1 equiv) was then dissolved in MeOH (0.5 M) and K_2CO_3 (0.5 equiv) was added. The mixture was stirred at rt and followed periodically by TLC. Upon completion, it was quenched with a saturated solution of NH_4Cl, the aqueous layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

Finally, allyl bromides **6.28 a-c** were prepared in a 2-step procedure by addition of vinylmagnesium bromide on the corresponding ketone followed by a nucleophilic substitution on the alcohol in aqueous HBr solution.[338]



substrate	product		yield$_1$[a]	yield$_2$[a]
	Z/E ratio ~ 1/2	**6.28 a**	80%	78%
		**6.28 b**	53%	89%
		**6.28 c**	72%	68%

[a] Isolated yield.

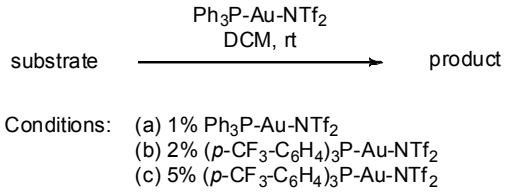
[338] Young, C. G.; James, B. R.; Rettig, S. J. *Can. J. Chem.* **1985**, *63*, 1035-1040.

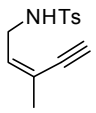
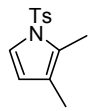
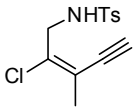
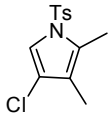
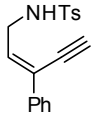
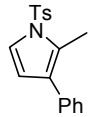
General procedure 6.8: To a solution of ketone (1 equiv) in THF (1 M) at 0 °C was added dropwise vinylmagnesium bromide (1.1 equiv). The mixture was stirred at 0 °C and followed periodically by TLC. Upon completion, it was quenched with a saturated solution of NH_4Cl, the aqueous layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected tertiary alcohol.

The alcohol thus obtained (1 equiv) was then dissolved in petroleum ether (0.5 M) at 0 °C and HBr (1.5 equiv, 48% aqueous solution) was added. The mixture was stirred at 0 °C for 1 h. Upon completion, the reaction was quenched with K_2CO_3 saturated aqueous solution. The aqueous layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to afford the clean allyl bromide derivative.

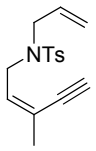
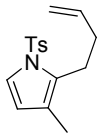
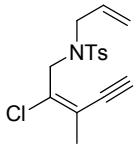
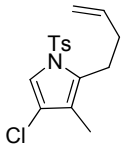
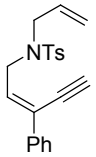
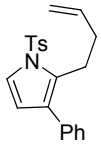
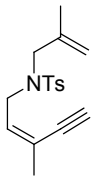
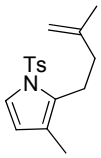
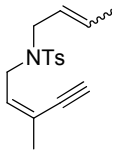
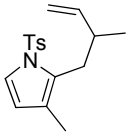
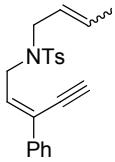
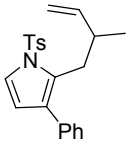
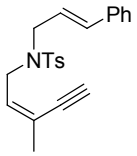
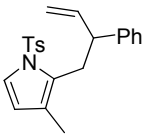
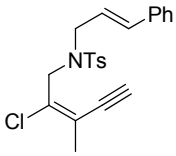
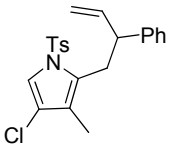
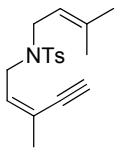
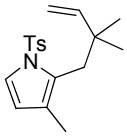
6.2. Gold(I)-catalyzed formation of functionalized pyrroles and furans

Various *Z*-pent-2-en-4-ynyl tosylamides derivatives **6.2 a-c**, **6.4 a-l**, **6.7 a-b**, **6.9**, **6.11** and **6.13** can be rearranged in the presence of a gold(I)-catalyst into the corresponding pyrroles **6.3 a-c**, **6.5 a-l**, **6.8 a-b**, **6.10**, **6.12** and **6.15**.

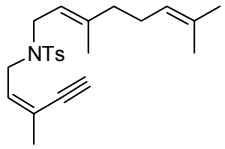
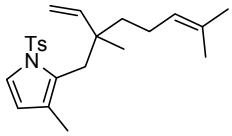
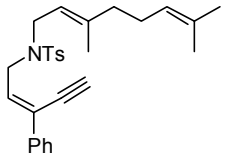
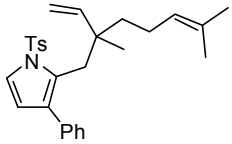
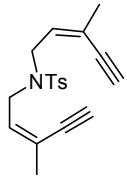
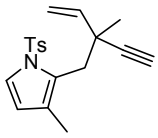
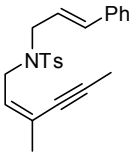
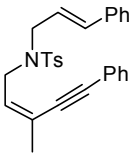
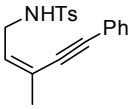
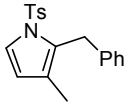
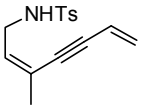
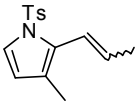
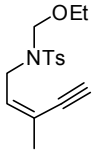
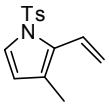


substrate		product		conditions	time	yield[a]
	**6.2 a**		**6.3 a**	a	5 min	97%
	**6.2 b**		**6.3 b**	a	5 min	96%
	**6.2 c**		**6.3 c**	a	5 min	94%

(continued on the next page)

substrate		product		conditions	time	yield[a]
	**6.4 a**		**6.5 a**	b	30 min	94%
	**6.4 b**		**6.5 b**	b	30 min	88%
	**6.4 c**		**6.5 c**	b	45 min	72%
	**6.4 d**		**6.5 d**	b	45 min	89%
 *Z/E* ratio ~ 1/3.5	**6.4 e**		**6.5 e**	b	15 min	91%
 *Z/E* ratio ~ 1/2.6	**6.4 f**		**6.5 f**	b	15 min	89%
	**6.4 g**		**6.5 g**	b	15 min	97%
	**6.4 h**		**6.5 h**	b	5 min	98%
	**6.4 i**		**6.5 i**	b	15 min	90%

(continued on the next page)

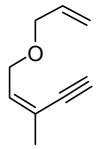
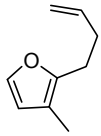
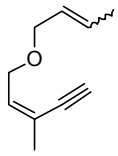
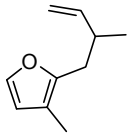
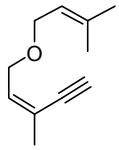
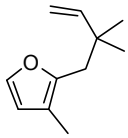
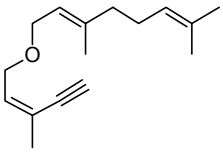
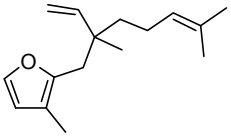
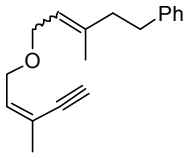
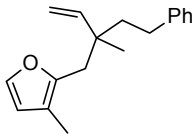
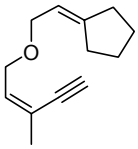
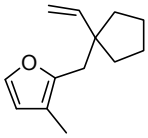
substrate		product		conditions	time	yield[a]
	**6.4 j**		**6.5 j**	b	15 min	91%
	**6.4 k**		**6.5 k**	b	15 min	93%
	**6.4 l**		**6.5 l**	b	15 min	84%
	**6.7 a**	-		c	-	-
	**6.7 b**	-		c	-	-
	**6.9**		**6.10**	c	1 h	87%
	**6.11**	 Z/E ratio ~ 1/3.8	**6.12**	c	15 min	52%
	**6.13**		**6.15**	c	20 min	15%[b]

[a] Isolated yield. [b] Compound **6.3 a** was also isolated with a 31% yield

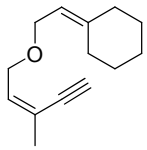
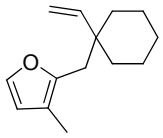
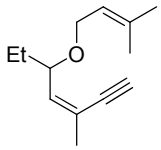
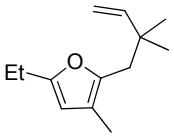
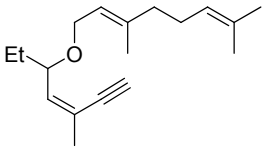
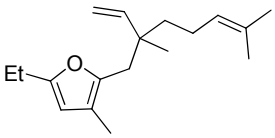
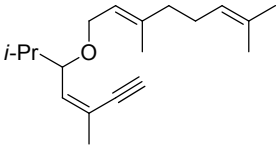
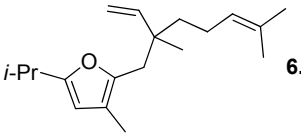
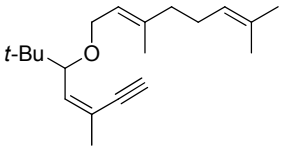
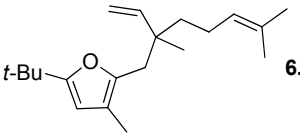
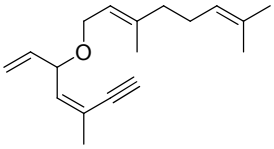
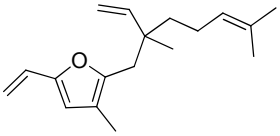
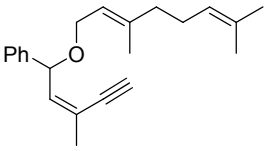
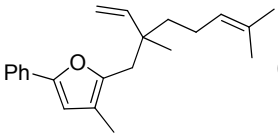
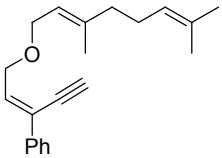
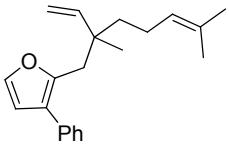
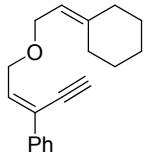
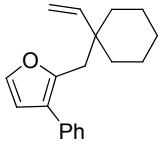
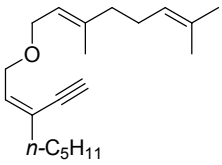
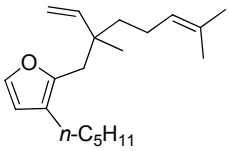
General procedure 6.9: To a solution of the substrate (1 equiv) in DCM (0.1 M) was added the catalyst (conditions a: 0.01 equiv of Ph_3P-Au-NTf_2 for substrates **6.2 a-c**, conditions b: 0.02 equiv. of (p-CF_3-C_6H_4)$_3$P-Au-NTf_2 for substrates **6.4 a-l**, conditions c: 0.05 equiv. of (p-CF_3-C_6H_4)$_3$P-Au-NTf_2 for substrates **6.7 a-b**,

6.9, **6.11** and **6.13**) The mixture was stirred at rt and monitored periodically by TLC. Upon completion, the mixture was evaporated under reduced pressure and purified by flash column chromatography (silica gel, petroleum ether / diethyl ether).

Z-pent-2-en-4-ynyl allyl ethers **6.16 a-s** were cycloisomerized analogously into the corresponding functionalized furans **6.17 a-s**.

substrate		product		time	conv.[a]	yield[b]
	**6.16 a**		**6.17 a**	10 min	100%	18% (75%[c])
 *Z/E* ratio ~ 1/3	**6.16 b**		**6.17 b**	10 min	100%	39% (86%[c])
	**6.16 c**		**6.17 c**	10 min	100%	59% (82%[c])
	**6.16 d**		**6.17 d**	10 min	100%	81% (92%[c])
 *Z/E* ratio ~ 1/2.57	**6.16 e**		**6.17 e**	10 min	100%	66%
	**6.16 f**		**6.17 f**	10 min	100%	71%

(continued on the next page)

substrate		product		time	conv.[a]	yield[b]
	**6.16 g**		**6.17 g**	10 min	100%	63%
	**6.16 h**		**6.17 h**	10 min	100%	quant.
	**6.16 i**		**6.17 i**	10 min	100%	quant.
	**6.16 j**		**6.17 j**	10 min	100%	78%
	**6.16 k**		**6.17 k**	10 min	100%	78%
	**6.16 l**		**6.17 l**	10 min	100%	17%
	**6.16 m**		**6.17 m**	10 min	100%	77%
	**6.16 n**		**6.17 n**	10 min	100%	80%
	**6.16 o**		**6.17 o**	10 min	100%	90%
	**6.16 p**		**6.17 p**	10 min	100%	82%

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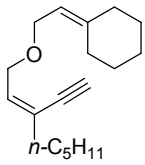
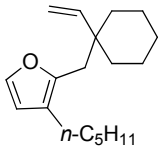
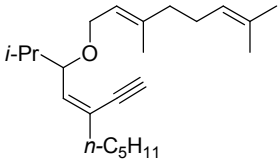
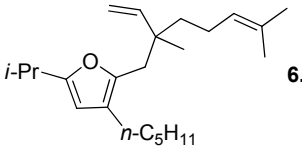
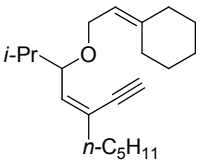
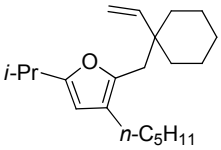
substrate		product		time	conv.[a]	yield[b]
	**6.16 q**		**6.17 q**	10 min	100%	86%
	**6.16 r**		**6.17 r**	40 min	>84%	73%
	**6.16 s**		**6.17 s**	40 min	>62%	36%

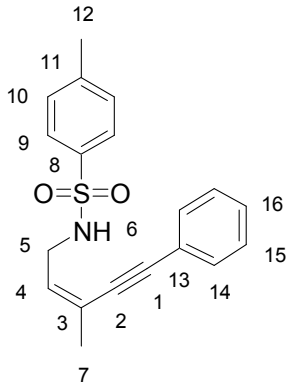
[a] Conversion of the substrate determined by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield. [c] Yield determined by ^{1}H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal reference.

General procedure 6.10: To a solution of the substrate (0.25 mmoles) in DCM (0.1 M) was added (p-CF_3-$C_6H_4)_3$P-Au-NTf_2 (0.02 equiv). The mixture was stirred at rt and monitored periodically by TLC. Upon completion, the mixture was evaporated and purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give to give the expected furan.

The reactions for which the yield was determined by ^{1}H NMR of the crude mixture were performed analogously in CD_2Cl_2 (0.1 M) as solvent. Upon completion, 1,3,5-trimethoxybenzene (1 equiv) was added and the yield of the desired product was assessed by NMR.

6.3. Characterization of the prepared compounds

4-Methyl-*N*-((*Z*)-3-methyl-5-phenyl-pent-2-en-4-ynyl)-benzenesulfonamide 6.9



MF: $C_{19}H_{19}NO_2S$

MW: 325.43 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.3** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 60/40).

Product: Yellow crystals.

Yield: 75%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.69 (d, J = 8.3 Hz, 2H, *9*), 7.23 (m, 5H, *14*, *15* and *16*), 7.17 (d, J = 8.0 Hz, 2H, *10*), 5.56 (tq, J = 1.5, 7.0 Hz, 1H, *4*), 4.66 (t, J = 6.0 Hz, 1H, *6*), 3.75 (t, J = 7.0 Hz, 2H, *5*), 2.30 (s, 3H, *12*), 1.78 (d, J = 1.2 Hz, 3H, *7*).

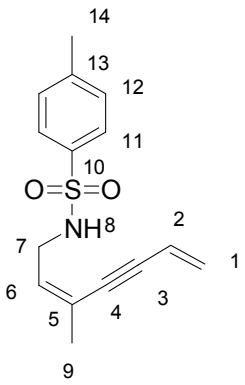
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 143.4 (*11*), 136.8 (*8*), 131.5 (*14* or *15*), 131.0 (*4*), 129.7 (*10*), 128.5 (*16*), 128.3 (*14* or *15*), 127.3 (*9*), 122.9 (*3* or *13*), 122.6 (*3* or *13*), 94.8 (*1*), 86.8 (*2*), 43.2 (*5*), 22.9 (*7*), 21.5 (*12*).

IR (ν, cm^{-1}) (CCl_4): 3396, 3261, 3059, 2958, 2925, 2861, 1727, 1596, 1489, 1441, 1407, 1341, 1162, 1117, 1093, 1038.

MS (CI^+, NH_3, m/z): 343 (MNH_4^+), 326 (MH^+), 309, 276, 261.

HRMS (EI^+, m/z): Calculated for $C_{19}H_{19}NO_2S$: 325.1136.
Found for $C_{19}H_{19}NO_2S$: 325.1137.

4-Methyl-*N*-((*Z*)-3-methyl-hepta-2,6-dien-4-ynyl)-benzenesulfonamide 6.11



MF: $C_{15}H_{17}NO_2S$

MW: 275.37 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.3** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 60/40).

Product: Orange crystals.

Yield: 79%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.77 (d, J = 8.3 Hz, 2H, *11*), 7.29 (d, J = 8.1 Hz, 2H, *12*), 5.84 (dd, J = 11.1, 17.5 Hz, 1H, *2*), 5.57 (tq, J = 1.3, 7.0 Hz, 1H, *6*), 5.54 (dd, J = 2.0, 17.5 Hz, 1H, *1*), 5.47 (dd, J = 2.0, 11.1 Hz, 1H, *1*), 5.02 (t, J = 6.0 Hz, 1H, *8*), 3.75 (t, J = 6.1 Hz, 2H, *7*), 2.41 (s, 3H, *14*), 1.77 (d, J = 1.1 Hz, 3H, *9*).

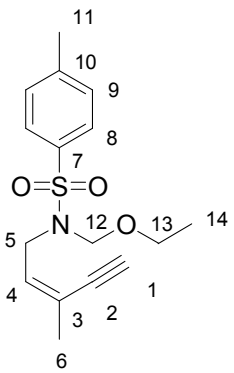
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 143.2 (*13*), 136.7 (*10*), 131.4 (*6*), 129.5 (*12*), 127.1 (*11*), 127.0 (*1*), 122.0 (*5*), 116.6 (*2*), 93.3 (*3*), 87.4 (*4*), 42.9 (*7*), 22.7 (*9*), 21.3 (*14*).

IR (ν, cm^{-1}) (CCl_4): 3396, 3274, 3014, 2956, 2923, 2874, 1597, 1406, 1338, 1162, 1094, 1044.

MS (CI^+, NH_3, m/z): 293 (MNH_4^+), 276 (MH^+), 189.

HRMS (EI^+, m/z): Calculated for $C_{15}H_{17}NO_2S$: 275.0980.
Found for $C_{15}H_{17}NO_2S$: 275.0979.

N-Ethoxymethyl-4-methyl-*N*-((*Z*)-3-methyl-pent-2-en-4-ynyl)-benzenesulfonamide **6.13**



MF: $C_{16}H_{21}NO_3S$

MW: 307.41 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.4** (scale: 0.277 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 90/10).

Product: Yellow oil.

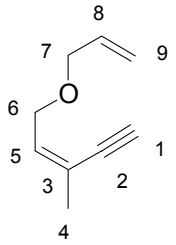
Yield: 84%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.67 (d, J = 8.3 Hz, 2H, *8*), 7.20 (d, J = 8.0 Hz, 2H, *9*), 5.60 (tq, J = 0.7, 6.3 Hz, 1H, *4*), 4.65 (s, 2H, *12*), 3.94 (d, J = 6.9 Hz, 2H, *5*), 3.41 (q, J = 7.0 Hz, 2H, *13*), 3.05 (s, 1H, *1*), 2.34 (s, 3H, *11*), 1.75 (d, J = 1.3 Hz, 3H, *6*), 1.07 (t, J = 7.0 Hz, 3H, *14*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 143.2 (*10*), 137.4 (*7*), 133.4 (*4*), 129.4 (*9*), 127.3 (*8*), 121.0 (*3*), 82.3 (*1*), 81.4 (*2*), 77.7 (*12*), 63.5 (*13*), 46.2 (*5*), 22.8 (*6*), 21.4 (*11*), 14.8 (*4*).

IR (ν, cm^{-1}) (CCl_4)	3308, 2977, 2927, 2878, 1445, 1350, 1191, 1162, 1084, 1012.
MS (CI^+, NH_3, m/z)	325 (MNH_4^+), 308 (MH^+), 262.
HRMS (EI^+, m/z)	Calculated for $C_{16}H_{21}NO_3S$: 307.1242. Found for $C_{16}H_{21}NO_3S$: 307.1242.

(*Z*)-5-Allyloxy-3-methyl-pent-3-en-1-yne **6.16 a**

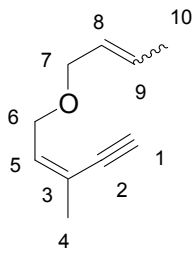


MF: $C_9H_{12}O$

MW: 136.19 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 6.5** (scale: 1 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 99/1).
Product:	Yellow oil.
Yield:	45%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.96-5.87 (m, 2H, *5* and *8*), 5.28 (dd, J = 1.6, 17.2 Hz, 1H, *9*), 5.17 (dd, J = 1.4, 10.4 Hz, 1H, *9*), 4.20 (dd, J = 0.9, 6.7 Hz, 2H, *6*), 3.97 (dt, J = 1.3, 5.7 Hz, 2H, *7*), 3.15 (s, 1H, *1*), 1.90 (d, J = 1.2 Hz, 3H, *4*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	135.1 (*5*), 134.6 (*8*), 120.4 (*4*), 116.9 (*9*), 82.0 (*1*), 81.8 (*2*), 71.1 (*7*), 68.2 (*6*), 22.9 (*4*).
IR (ν, cm^{-1}) (CCl_4)	3309, 3081, 3019, 2979, 2923, 2853, 1641, 1449, 1353, 1235, 1107, 1069, 991.
MS (CI^+, NH_3, m/z)	155 (MNH_4^+), 137 (MH^+), 105.
HRMS (EI^+, m/z)	Calculated for $C_9H_{12}O$: 136.0888. Found for $C_9H_{12}O$: 136.0889.

(*Z*)-5-[(But-2-enyl)oxy]-3-methyl-pent-3-en-1-yne **6.16 b**



MF: $C_{10}H_{14}O$

MW: 150.22 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil (*Z*/*E* mixture ~ 1/3).

Yield: 65%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) For the mixture of *Z*/*E* isomers: 5.90 (m, 1H, both isomers, *5*), 5.80-5.54 (m, 2H, both isomers, *8* and *9*), 4.21 (dd, J = 1.0, 6.8 Hz, 2H, minor isomer, *6*), 4.19 (dd, J = 1.0, 6.7 Hz, 2H, major isomer, *6*), 4.06 (d, J = 6.3 Hz, 2H, minor isomer, *7*), 3.91 (dm, J = 6.3 Hz, 2H, major isomer, *7*), 3.16 (s, 1H, minor isomer, *1*), 3.15 (s, 1H, major isomer, *1*), 1.91 (m, 3H, both isomers, *4*), 1.72 (dm, J = 6.4 Hz, major isomer, *10*), 1.68 (dm, J = 6.8 Hz, minor isomer, *10*).

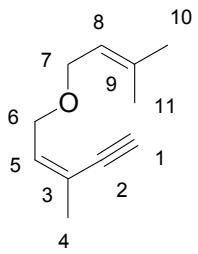
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) Major isomer: 135.4 (*5*), 129.8 (*8*), 127.4 (*9*), 120.2 (*3*), 82.0 (*1* or *2*), 81.9 (*1* or *2*), 70.9 (*7*), 68.1 (*6*), 22.9 (*4*), 17.7 (*10*).
Minor isomer: 135.4 (*5*), 127.9 (*8*), 126.7 (*9*), 120.3 (*3*), 82.0 (*1* or *2*), 81.9 (*1* or *2*), 68.3 (*6*), 65.5 (*7*), 22.9 (*4*), 13.1 (*10*).

IR (ν, cm^{-1}) (CCl_4) For the mixture of *Z*/*E* isomers: 3309, 3021, 2955, 2924, 2855, 1672, 1636, 1448, 1375, 1358, 1234, 1105, 1053, 968.

MS (CI^+, NH_3, m/z) 169 (MNH_4^+), 151 (MH^+).

HRMS (EI^+, m/z) Calculated for $C_{10}H_{14}O$: 150.1045.
Found for $C_{10}H_{14}O$: 150.1043.

(*Z*)-3-Methyl-5-(3-methyl-but-2-enyloxy)-pent-3-en-1-yne 6.16 c



MF: $C_{11}H_{16}O$

MW: 164.24 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

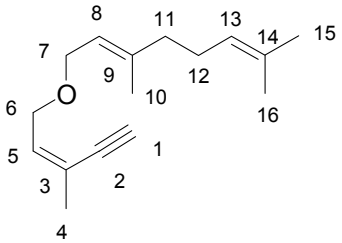
Product: Pale yellow oil.

Yield: 64%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.91 (t, J = 7.0 Hz, 1H, *5*), 5.37 (t, J = 7.0 Hz, 1H, *8*), 4.18 (d, J = 6.6 Hz, 2H, *6*), 3.97 (d, J = 7.0 Hz, 2H, *7*), 3.16 (s, 1H, *1*), 1.91 (d, J = 1.2 Hz, 3H, *4*), 1.75 (s, 3H, *10* or *11*), 1.69 (s, 3H, *10* or *11*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	137.2 (*9*), 135.6 (*5*), 120.9 (*8*), 120.1 (*3*), 81.9 (*2*), 81.9 (*1*), 68.2 (*6*), 66.6 (*7*), 25.7 (*10* or *11*), 22.9 (*4*), 18.0 (*10* or *11*).
IR (ν, cm^{-1}) (CCl_4)	3309, 2974, 2922, 2858, 1674, 1636, 1447, 1376, 1111, 1065.
MS (CI^+, NH_3, m/z)	183 (MNH_4^+), 165 (MH^+).
HRMS (EI^+, m/z)	Calculated for $C_{11}H_{16}O$: 164.1201. Found for $C_{11}H_{16}O$: 164.1196.

(*E*)-3,7-Dimethyl-1-((*Z*)-3-methyl-pent-2-en-4-ynyloxy)-octa-2,6-diene **6.16 d**

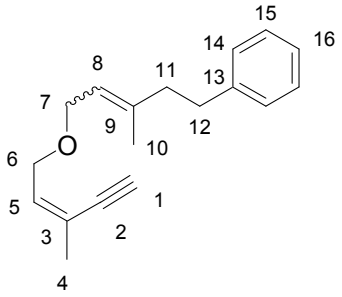


MF: $C_{16}H_{24}O$

MW: 232.36 g.mol^{-1}

Reaction:	The reaction was carried out according to the **General Procedure 6.5** (scale: 1 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 99/1).
Product:	Pale yellow oil
Yield:	69%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.91 (t, J = 6.6 Hz, 1H, *5*), 5.37 (t, J = 6.8 Hz, 1H, *8*), 5.11 (t, J = 6.6 Hz, 1H, *13*), 4.19 (d, J = 6.6 Hz, 2H, *6*), 4.00 (d, J = 6.8 Hz, 2H, *7*), 3.16 (s, 1H, *1*), 2.10 (m, 2H, *12*), 2.04 (m, 2H, *11*), 1.91 (d, J = 1.3 Hz, 3H, *4*), 1.68 (s, 6H, *10* and *15* or *16*), 1.61 (s, 3H, *15* or *16*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	140.4 (*9*), 135.6 (*5*), 131.6 (*14*), 123.9 (*13*), 120.6 (*8*), 120.2 (*3*), 81.9 (*2*), 81.9 (*1*), 68.2 (*6*), 66.7 (*7*), 39.6 (*11*), 26.3 (*12*), 25.6 (*15* or *16*), 22.9 (*4*), 17.6 (*15* or *16*), 16.4 (*10*).
IR (ν, cm^{-1}) (CCl_4)	3309, 2964, 2923, 2857, 1668, 1447, 1377, 1108, 1062.
MS (CI^+, NH_3, m/z)	251 (MNH_4^+), 233 (MH^+).
HRMS (EI^+, m/z)	Calculated for $C_{16}H_{24}O$: 232.1827. Found for $C_{16}H_{24}O$: 232.1834.

[3-Methyl-5-((*Z*)-3-methyl-pent-2-en-4-ynyloxy)-pent-3-enyl]-benzene **6.16 e**



MF: $C_{18}H_{22}O$

MW: 254.37 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Pale yellow oil (*Z*/*E* mixture ~ 1/2.57).

Yield: 69%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the mixture of *Z*/*E* isomers: 7.29 (m, 2H, both isomers, *15*), 7.20 (m, 3H, both isomers, *14* and *16*), 5.91 (m, 1H, both isomers, *5*), 5.41 (m, 1H, both isomers, *8*), 4.18 (dq, J = 1.1, 6.7 Hz, 2H, major isomer, *6*), 4.18 (dq, J = 1.1, 6.7 Hz, 2H, minor isomer, *6*), 4.00 (d, J = 6.7 Hz, 2H, major isomer, *7*), 3.82 (dq, J = 1.1, 0.8, 6.9 Hz, 2H, minor isomer, *7*), 3.16 (s, 1H, major isomer, *1*), 3.15 (s, 1H, minor isomer, *1*), 2.78-2.68 (m, 2H, *11*), 2.40-2.32 (m, 2H, *12*), 1.92 (d, J = 1.3 Hz, 3H, major isomer, *4*), 1.90 (d, J = 1.3 Hz, 3H, minor isomer, *4*), 1.80 (d, J = 1.1 Hz, 3H, minor isomer, *10*), 1.74 (s, 3H, major isomer, *10*).

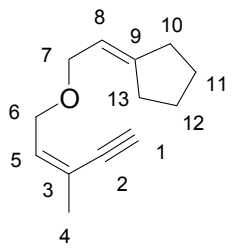
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): Minor isomer: 141.9 (*13*), 139.8 (*9*), 135.5 (*5*), 128.3 (*14* or *15*), 128.2 (*14* or *15*), 125.8 (*16*), 122.3 (*8*), 120.2 (*3*), 82.0 (*1* or *2*), 81.9 (*1* or *2*), 68.2 (*6*), 66.2 (*7*), 34.5 (*11* or *12*), 34.3 (*11* or *12*), 23.5 (*4* or *10*), 22.9 (*4* or *10*).
Major isomer: 142.1 (*13*), 139.8 (*9*), 135.5 (*5*), 128.3 (*14* or *15*), 128.2 (*14* or *15*), 125.7 (*16*), 121.1 (*8*), 120.2 (*3*), 82.0 (*1* or *2*), 81.9 (*1* or *2*), 68.2 (*6*), 66.6 (*7*), 41.4 (*12*), 34.3 (*11*), 23.0 (*4*), 16.6 (*10*).

IR (ν, cm^{-1}) (CCl_4): For the mixture of *Z*/*E* isomers: 3309, 3062, 3027, 2973, 2926, 2857, 1668, 1601, 1495, 1449, 1376, 1109, 1061.

MS (EI$^+$, m/z): 254 (M^+), 149, 131.

HRMS (EI$^+$, m/z): Calculated for $C_{18}H_{22}O$: 254.1671.
Found for $C_{18}H_{22}O$: 254.1672.

[2-((*Z*)-3-Methyl-pent-2-en-4-ynyloxy)-ethylidene]-cyclopentane 6.16 f



MF: $C_{13}H_{18}O$

MW: 190.28 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Pale yellow oil

Yield: 70%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.91 (t, J = 6.6 Hz, 1H, *5*), 5.47 (m, 1H, *8*), 4.19 (dq, J = 1.0, 6.6 Hz, 2H, *6*), 3.97 (d, J = 6.9 Hz, 2H, *7*), 3.16 (s, 1H, *1*), 2.33-2.24 (m, 4H, *10* and *13*), 1.91 (d, J = 1.3 Hz, 3H, *4*), 1.73-1.58 (m, 4H, *11* and *12*).

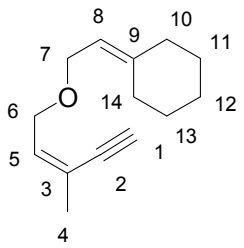
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 148.6 (*9*), 135.7 (*5*), 120.0 (*3*), 116.4 (*8*), 82.0 (*2*), 81.9 (*1*), 68.2 (*6*), 68.1 (*7*), 33.7 (*10* or *13*), 28.7 (*10* or *13*), 26.2 (*11* or *12*), 26.0 (*11* or *12*), 22.9 (*4*).

IR (ν, cm^{-1}) (CCl_4): 3309, 2953, 2866, 1678, 1636, 1449, 1361, 1233, 1170, 1104, 1053.

MS (EI^+, m/z): 190 (M^+), 161, 145, 137, 131, 121.

HRMS (EI^+, m/z): Calculated for $C_{13}H_{18}O$: 190.1358.
Found for $C_{13}H_{18}O$: 190.1363.

[2-((*Z*)-3-Methyl-pent-2-en-4-ynyloxy)-ethylidene]-cyclohexane **6.16 g**



MF: $C_{14}H_{20}O$

MW: 204.31 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil

Yield: 62%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.91 (t, J = 6.6 Hz, 1H, *5*), 5.30 (t, J = 7.0 Hz, 1H, *8*), 4.19 (dq, J = 1.1, 6.6 Hz, 2H, *6*), 3.99 (d, J = 7.0 Hz, 2H, *7*), 3.16 (s, 1H, *1*), 2.22-2.09 (m, 4H, *10* and *14*), 1.91 (d, J = 1.3 Hz, 3H, *4*), 1.57-1.53 (m, 6H, *11*, *12* and *13*).

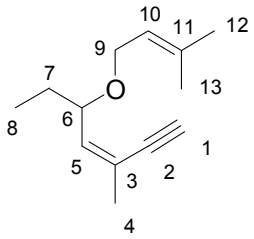
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 145.0 (*9*), 135.7 (*5*), 120.0 (*3*), 117.6 (*8*), 82.0 (*2*), 81.9 (*1*), 68.1 (*6*), 65.8 (*7*), 37.0 (*10* or *14*), 28.9 (*10* or *14*), 28.3 (*11*, *12* or *13*), 27.7 (*11*, *12* or *13*), 26.7 (*11*, *12* or *13*), 22.9 (*4*).

IR (ν, cm^{-1}) (CCl_4): 3309, 2929, 2854, 1668, 1446, 1100, 1065.

MS (EI^+, m/z) 204 (M^+), 189, 175, 161, 145, 137, 123, 109.

HRMS (EI^+, m/z) Calculated for $C_{14}H_{20}O$: 204.1514.
Found for $C_{14}H_{20}O$: 204.1505.

(*Z*)-3-Methyl-5-(3-methyl-but-2-enyloxy)-hept-3-en-1-yne 6.16 h



MF: $C_{13}H_{20}O$

MW: 192.30 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 0.693 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Pale yellow oil

Yield: 44%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.64 (dm, J = 0.7, 9.1 Hz, 1H, *5*), 5.35 (t, J = 6.9 Hz, 1H, *10*), 4.17 (dt, J = 6.7, 9.1 Hz, 1H, *6*), 3.98 (dd, J = 6.8, 11.4 Hz, 1H, *9*), 3.88 (dd, J = 7.1, 11.3 Hz, 1H, *9*), 3.11 (s, 1H, *1*), 1.92 (d, J = 1.4 Hz, 3H, *4*), 1.74 (s, 3H, *12* or *13*), 1.67 (s, 3H, *12* or *13*), 1.64 (m, 1H, *7*), 1.50 (m, 1H, *7*), 0.92 (t, J = 7.4 Hz, 3H, *8*).

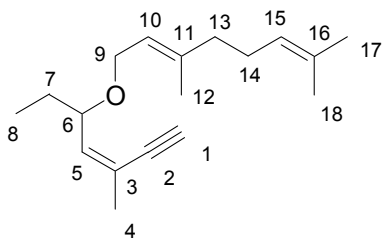
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 140.4 (*5*), 136.6 (*11*), 121.5 (*10*), 120.1 (*3*), 82.4 (*2*), 81.1 (*1*), 78.6 (*6*), 65.0 (*9*), 28.2 (*7*), 25.8 (*12* or *13*), 23.0 (*4*), 18.0 (*12* or *13*), 9.7 (*8*).

IR (ν, cm^{-1}) (CCl_4) 3309, 2970, 2926, 2866, 1668, 1634, 1447, 1378, 1111, 1056.

MS (CI^+, NH_3, m/z) 211 (MNH_4^+), 193 (MH^+), 175, 137, 124.

HRMS (EI^+, m/z) Calculated for $C_{13}H_{20}O$: 192.1514.
Found for $C_{13}H_{20}O$: 192.1520.

(*E*)-1-((*Z*)-1-Ethyl-3-methyl-pent-2-en-4-ynyloxy)-3,7-dimethyl-octa-2,6-diene 6.16 i



MF: $C_{18}H_{28}O$

MW: 260.41 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 0.660 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Pale yellow oil

Yield: 64%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.64 (dm, J = 0.7, 9.1 Hz, 1H, *5*), 5.36 (tq, J = 1.0, 6.9 Hz, 1H, *10*), 5.11 (thept, J = 1.4, 6.9 Hz, 1H, *15*), 4.18 (dt, J = 6.6, 9.1 Hz, 1H, *6*), 4.03 (dd, J = 6.5, 11.6 Hz, 1H, *9*), 3.92 (dd, J = 7.1, 11.6 Hz, 1H, *9*), 3.10 (s, 1H, *1*), 2.10 (m, 2H, *14*), 2.04 (m, 2H, *13*), 1.92 (d, J = 1.5 Hz, 3H, *4*), 1.69 (s, 3H, *17* or *18*), 1.67 (m, 1H, *7*), 1.66 (s, 3H, *12*), 1.61 (s, 3H, *17* or *18*), 1.48 (m, 1H, 7), 0.92 (t, J = 7.5 Hz, 3H, *8*).

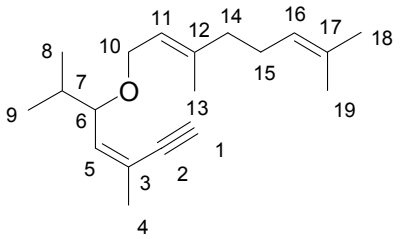
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 140.4 (*5*), 139.7 (*11*), 131.5 (*16*), 124.1 (*15*), 121.2 (*10*), 120.0 (*3*), 82.5 (*2*), 81.2 (*1*), 78.5 (*6*), 65.0 (*9*), 39.6 (*13*), 28.2 (*7*), 26.3 (*14*), 25.6 (*17* or *18*), 23.1 (*4*), 17.6 (*17* or *18*), 16.5 (*12*), 9.7 (*8*).

IR (ν, cm^{-1}) (CCl_4): 3309, 2970, 2927, 2872, 1674, 1632, 1448, 1377, 1110, 1059.

MS (CI^+, NH_3, m/z): 279 (MNH_4^+), 261 (MH^+), 243, 173, 154, 137.

HRMS (EI^+, m/z): Calculated for $C_{18}H_{28}O$: 260.2140.
Found for $C_{18}H_{28}O$: 260.2144.

(*E*)-1-((*Z*)-1-Isopropyl-3-methyl-pent-2-en-4-ynyloxy)-3,7-dimethyl-octa-2,6-diene 6.16 j



MF: $C_{19}H_{30}O$

MW: 274.44 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 0.434 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil

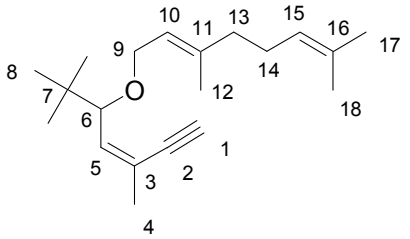
Yield: 50%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.65 (dm, J = 0.7, 9.4 Hz, 1H, *5*), 5.35 (tq, J = 1.3, 7.0 Hz, 1H, *11*), 5.11 (thept, J = 1.4, 6.9 Hz, 1H, *16*), 4.01 (dd, J = 6.4, 11.8 Hz, 1H, *10*), 3.94 (dd, J = 9.4, 7.1 Hz, 1H, *6*), 3.90 (dd, J = 7.0, 11.7 Hz, 1H, *10*), 3.08 (d, J = 0.6 Hz, 1H, *1*), 2.10 (m, 2H, *15*), 2.04 (m, 2H, *14*), 1.94 (d, J = 1.5 Hz, 3H, *4*), 1.75 (m, 1H, *7*), 1.69 (s, 3H, *18* or *19*), 1.66 (s, 3H, *13*), 1.61 (s, 3H, *18* or *19*), 0.97 (d, J = 6.7 Hz, 3H, *8* or *9*), 0.87 (d, J = 6.8 Hz, 3H, *8* or *9*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 139.6 (*12*), 139.1 (*5*), 131.4 (*17*), 124.1 (*16*), 121.4 (*11*), 120.7 (*3*), 82.7 (*2*), 82.2 (*1*), 81.0 (*6*), 65.1 (*10*), 39.6 (*14*), 32.9 (*7*), 26.3 (*15*), 25.6 (*18* or *19*), 23.2 (*4*), 18.8 (*8* or *9*), 18.1 (*8* or *9*), 17.6 (*18* or *19*), 16.5 (*13*).

IR (ν, cm^{-1}) (CCl_4)	3309, 2966, 2924, 2872, 1667, 1635, 1450, 1377, 1219, 1104, 1058.
MS (CI^+, NH_3, m/z)	275 (MH^+), 257, 248.
HRMS (EI^+, m/z)	Calculated for $C_{19}H_{30}O$: 274.2297. Found for $C_{19}H_{30}O$: 274.2287.

(*E*)-1-((*Z*)-1-*tert*-Butyl-3-methyl-pent-2-en-4-ynyloxy)-3,7-dimethyl-octa-2,6-diene 6.16 k

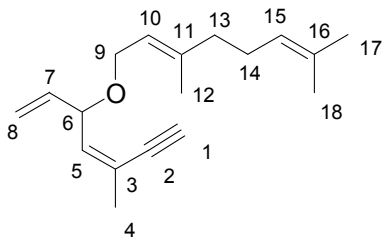


MF: $C_{20}H_{23}O$

MW: 288.47 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 6.5** (scale: 0.197 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 100/0).
Product:	Yellow oil
Yield:	40%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.70 (dm, J = 0.7, 9.7 Hz, 1H, *5*), 5.33 (tq, J = 1.2, 7.1 Hz, 1H, *10*), 5.12 (thept, J = 1.4, 6.9 Hz, 1H, *15*), 4.00 (dd, J = 6.1, 12.0 Hz, 1H, *9*), 3.88 (dd, J = 6.5, 12.4 Hz, 1H, *9*), 3.87 (d, J = 9.7 Hz, 1H, *6*), 3.07 (s, 1H, *1*), 2.10 (m, 2H, *14*), 2.04 (m, 2H, *13*), 1.94 (d, J = 1.4 Hz, 3H, *4*), 1.69 (s, 3H, *17* or *18*), 1.64 (s, 3H, *12*), 1.61 (s, 3H, *17* or *18*), 0.91 (s, 3H, *8*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	139.0 (*11*), 138.0 (*5*), 131.4 (*16*), 124.1 (*15*), 121.8 (*10*), 121.0 (*3*), 84.3 (*6*), 82.9 (*2*), 80.9 (*1*), 65.4 (*9*), 39.6 (*13*), 35.3 (*7*), 26.4 (*14*), 25.9 (*8*), 25.6 (*17* or *18*), 23.3 (*4*), 17.6 (*17* or *18*), 16.5 (*12*).
IR (ν, cm^{-1}) (CCl_4)	3309, 2959, 2926, 2866, 1667, 1449, 1379, 1107, 1057.
MS (EI^+, m/z)	288 (M^+), 273, 231.
HRMS (EI^+, m/z)	Calculated for $C_{20}H_{23}O$: 288.2453. Found for $C_{20}H_{23}O$: 288.2454.

(*E*)-3,7-Dimethyl-1-((*Z*)-3-methyl-1-vinyl-pent-2-en-4-ynyloxy)-octa-2,6-diene 6.16 l



MF: $C_{18}H_{26}O$

MW: 258.40 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 0.917 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil

Yield: 57%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.81 (ddd, J = 6.4, 10.4, 17.3 Hz, 1H, *7*), 5.72 (dm, J = 0.7, 8.8 Hz, 1H, *5*), 5.37 (tq, J = 1.3, 6.8 Hz, 1H, *10*), 5.30 (dt, J = 1.4, 17.2 Hz, 1H, *8*), 5.16 (ddd, J = 1.2, 1.6, 10.4 Hz, 1H, *8*), 5.11 (thept, J = 1.4, 6.9 Hz, 1H, *15*), 4.78 (dm, J = 7.7 Hz, 1H, *6*), 4.00 (d, J = 6.8 Hz, 2H, *9*), 3.16 (d, J = 0.6 Hz, 1H, *1*), 2.10 (m, 2H, *14*), 2.05 (m, 2H, *13*), 1.92 (d, J = 1.5 Hz, 3H, *4*), 1.68 (s, 3H, *17* or *18*), 1.66 (s, 3H, *12*), 1.60 (s, 3H, *17* or *18*).

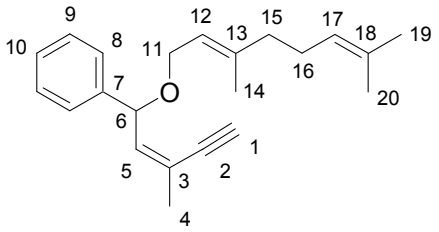
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 140.1 (*11*), 138.1 (*5*), 137.0 (*7*), 131.5 (*16*), 124.0 (*15*), 120.8 (*10*), 120.1 (*3*), 116.1 (*8*), 82.1 (*2*), 81.9 (*1*), 78.3 (*6*), 64.7 (*9*), 39.6 (*13*), 26.3 (*14*), 25.6 (*17* or *18*), 23.0 (*4*), 17.6 (*17* or *18*), 16.5 (*12*).

IR (ν, cm^{-1}) (CCl_4): 3309, 2972, 2922, 2859, 1668, 1640, 1445, 1378, 1111, 1054.

MS (EI^+, m/z): 258 (M^+), 187, 175, 159, 145, 135, 123, 106.

HRMS (EI^+, m/z): Calculated for $C_{18}H_{26}O$: 258.1984.
Found for $C_{18}H_{26}O$: 258.1991.

[(*Z*)-1-((*E*)-3,7-Dimethyl-octa-2,6-dienyloxy)-3-methyl-pent-2-en-4-ynyl]-benzene 6.16 m



MF: $C_{22}H_{28}O$

MW: 308.46 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 0.674 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil

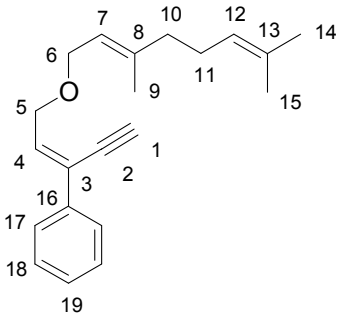
Yield: 59%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.42 (d, J = 7.1 Hz, 2H, *8*), 7.35 (t, J = 7.2 Hz, 2H, *9*), 7.27 (t, J = 7.2 Hz, 1H, *10*), 5.89 (dm, J = 0.7, 9.1 Hz, 1H, *5*), 5.42 (tq, J = 1.2, 6.8 Hz, 1H, *12*), 5.38 (d, J = 9.1 Hz, 1H, *6*), 5.12 (thept, J = 1.4, 6.9 Hz, 1H, *17*), 4.02 (t, J = 6.2 Hz, 2H, *11*), 3.21 (s, 1H, *1*), 2.10 (m, 2H, *16*), 2.06 (m, 2H, *15*), 1.90 (d, J = 1.4 Hz, 3H, *4*), 1.69 (s, 3H, *19* or *20*), 1.63 (s, 3H, *14*), 1.61 (s, 3H, *19* or *20*).

^{13}C NMR (δ, ppm): 141.5 (*13*), 140.2 (*7*), 139.6 (*5*), 131.5 (*18*), 128.4 (*9*), 127.5 (*10*), 126.4 (*8*),

($CDCl_3$, 100 MHz)	124.0 (*17*), 120.8 (*12*), 119.3 (*3*), 82.4 (*2*), 81.8 (*1*), 78.9 (*6*), 64.9 (*11*), 39.6 (*15*), 26.4 (*16*), 25.6 (*19* or *20*), 23.0 (*4*), 17.6 (*14*), 16.5 (*19* or *20*).
IR (ν, cm^{-1}) (CCl_4)	3309, 2970, 2922, 2859, 1668, 1600, 1448, 1377, 1102, 1055.
MS (CI^+, NH_3, m/z)	309 (MH^+), 171, 155.
HRMS (EI^+, m/z)	Calculated for $C_{22}H_{28}O$: 308.2140. Found for $C_{22}H_{28}O$: 308.2144.

[(*Z*)-3-((*E*)-3,7-Dimethyl-octa-2,6-dienyloxy)-1-ethynyl-propenyl]-benzene 6.16 n

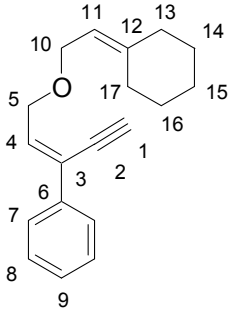


MF: $C_{21}H_{26}O$

MW: 294.43 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 6.5** (scale: 0.493 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 99/1).
Product:	Yellow oil
Yield:	68%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.64 (d, J = 7.0 Hz, 2H, *17*), 7.36 (t, J = 6.9 Hz, 2H, *18*), 7.31 (t, J = 7.0 Hz, 1H, *19*), 6.63 (t, J = 6.3 Hz, 1H, *4*), 5.41 (tq, J = 1.2, 6.8 Hz, 1H, *7*), 5.12 (thept, J = 1.3, 6.8 Hz, 1H, *12*), 4.46 (d, J = 6.4 Hz, 2H, *5*), 4.09 (d, J = 6.8 Hz, 2H, *6*), 3.41 (s, 1H, *1*), 2.12 (m, 2H, *11*), 2.06 (m, 2H, *10*), 1.71 (s, 3H, *9*), 1.69 (s, 3H, *14* or *15*), 1.62 (s, 3H, *14* or *15*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	140.7 (*8*), 136.7 (*3*), 135.9 (*4*), 131.6 (*13*), 128.4 (*18*), 128.1 (*19*), 126.0 (*17*), 124.0 (*16*), 123.9 (*12*), 120.5 (*7*), 84.5 (*1*), 79.9 (*2*), 68.8 (*5*), 66.9 (*6*), 39.6 (*10*), 26.3 (*11*), 25.6 (*14* or *15*), 17.6 (*14* or *15*), 16.5 (*9*).
IR (ν, cm^{-1}) (CCl_4)	3308, 2969, 2922, 2857, 1668, 1447, 1375, 1110, 1073.
MS (EI^+, m/z)	294 (M^+), 279, 251, 225, 211, 195, 183, 167, 157, 141, 128, 115, 109.
HRMS (EI^+, m/z)	Calculated for $C_{21}H_{26}O$: 294.1984. Found for $C_{21}H_{26}O$: 294.1977.

[(*Z*)-3-(2-Cyclohexylidene-ethoxy)-1-ethynyl-propenyl]-benzene 6.16 o



MF: $C_{19}H_{22}O$

MW: 266.38 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 0.8 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil

Yield: 77%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.64 (d, J = 7.1 Hz, 2H, *7*), 7.36 (t, J = 7.0 Hz, 2H, *8*), 7.30 (t, J = 7.1 Hz, 1H, *9*), 6.62 (t, J = 6.3 Hz, 1H, *4*), 5.34 (t, J = 7.0 Hz, 1H, *11*), 4.45 (d, J = 6.4 Hz, 2H, *5*), 4.07 (d, J = 7.0 Hz, 2H, *10*), 3.41 (s, 1H, *1*), 2.21 (m, 2H, *13* or *17*), 2.15 (m, 2H, *13* or *17*), 1.58-1.53 (m, 6H, *14*, *15* and *16*).

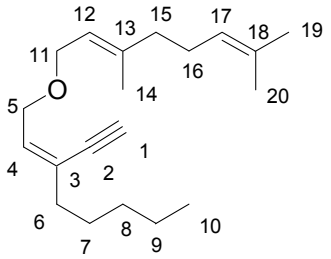
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 145.3 (*12*), 136.7 (*6*), 136.1 (*4*), 128.4 (*8*), 128.1 (*9*), 126.0 (*7*), 123.9 (*3*), 117.4 (*11*), 84.5 (*1*), 79.9 (*2*), 68.7 (*5*), 66.1 (*10*), 37.1 (*13*, *14*, *15*, *16* or *17*), 29.0 (*13*, *14*, *15*, *16* or *17*), 28.3 (*13*, *14*, *15*, *16* or *17*), 27.7 (*13*, *14*, *15*, *16* or *17*), 26.6 (*13*, *14*, *15*, *16* or *17*).

IR (ν, cm^{-1}) (CCl_4): 3308, 2930, 2854, 1711, 1668, 1495, 1446, 1360, 1239, 1085.

MS (EI^+, m/z): 266 (M^+), 235, 223, 207, 195.

HRMS (EI^+, m/z): Calculated for $C_{19}H_{22}O$: 266.1671.
Found for $C_{19}H_{22}O$: 266.1675.

(*E*)-1-((*Z*)-3-Ethynyl-oct-2-enyloxy)-3,7-dimethyl-octa-2,6-diene 6.16 p



MF: $C_{20}H_{32}O$

MW: 288.47 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 0.8 mmol).

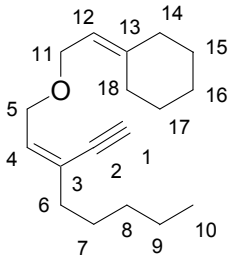
Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil

Yield: 84%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.90 (t, J = 6.5 Hz, 1H, *4*), 5.37 (tq, J = 1.2, 6.8 Hz, 1H, *12*), 5.11 (thept, J = 1.4, 6.9 Hz, 1H, *17*), 4.22 (d, J = 6.5 Hz, 2H, *5*), 4.00 (d, J = 6.8 Hz, 2H, *11*), 3.16 (s, 1H, *1*), 2.18-2.01 (m, 6H, *6*, *15* or *16*), 1.69 (s, 3H, *14*), 1.68 (s, 3H, *19* or *20*), 1.61 (s, 3H, *19* or *20*), 1.54 (m, 2H, *7*), 1.36-1.26 (m, 4H, *8* and *9*), 0.90 (t, J = 7.1 Hz, 3H, *10*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	140.4 (*13*), 135.0 (*4*), 131.6 (*18*), 125.1 (*3*), 124.0 (*17*), 120.7 (*12*), 82.4 (*1*), 81.3 (*2*), 68.1 (*5*), 66.6 (*11*), 39.6 (*15*), 36.8 (*6*), 31.1 (*8* or *9*), 27.6 (*7*), 26.3 (*16*), 25.6 (*14*, *19* or *20*), 22.4 (*8* or *9*), 17.6 (*14*, *19* or *20*), 16.4 (*14*, *19* or *20*), 13.9 (*10*).
IR (ν, cm^{-1}) (CCl_4)	3309, 2957, 2928, 2858, 1668, 1633, 1449, 1376, 1100, 1064.
MS (EI^+, m/z)	288 (M^+), 273, 257, 245, 230, 217, 205.
HRMS (EI^+, m/z)	Calculated for $C_{20}H_{32}O$: 288.2453. Found for $C_{20}H_{32}O$: 288.2458.

[2-((*Z*)-3-Ethynyl-oct-2-enyloxy)-ethylidene]-cyclohexane **6.16 q**



MF: $C_{18}H_{28}O$

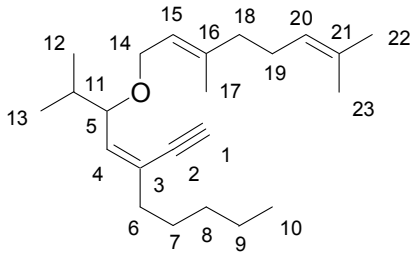
MW: 260.41 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 6.5** (scale: 0.8 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 99/1).
Product:	Yellow oil
Yield:	75%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.91 (t, J = 6.5 Hz, 1H, *4*), 5.30 (t, J = 7.0 Hz, 1H, *12*), 4.21 (d, J = 6.5 Hz, 2H, *5*), 3.99 (d, J = 7.0 Hz, 2H, *11*), 3.16 (s, 1H, *1*), 2.21-2.10 (m, 6H, *6*, *14* and *18*), 1.57-1.50 (m, 8H, *7*, *15*, *16* and *17*), 1.36-1.24 (m, 4H, *8* and *9*), 0.90 (t, J = 7.1 Hz, 3H, *10*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	145.0 (*13*), 135.1 (*4*), 125.0 (*3*), 117.6 (*12*), 82.4 (*1*), 81.4 (*2*), 68.1 (*5*), 65.8 (*11*), 37.0 (*6*, *7*, *8*, *9*, *14*, *15*, *16*, *17* or *18*), 36.8 (*6*, *7*, *8*, *9*, *14*, *15*, *16*, *17* or *18*), 31.1 (*6*, *7*, *8*, *9*, *14*, *15*, *16*, *17* or *18*), 28.9 (*6*, *7*, *8*, *9*, *14*, *15*, *16*, *17* or *18*), 28.3 (*6*, *7*, *8*, *9*, *14*, *15*, *16*, *17* or *18*), 27.7(*6*, *7*, *8*, *9*, *14*, *15*, *16*, *17* or *18*), 27.6 (*6*, *7*, *8*, *9*, *14*, *15*, *16*, *17* or *18*), 26.7 (*6*, *7*, *8*, *9*, *14*, *15*, *16*, *17* or *18*), 22.4 (*6*, *7*, *8*, *9*, *14*, *15*, *16*, *17* or *18*), 13.9 (*10*).
IR (ν, cm^{-1}) (CCl_4)	3309, 2930, 2856, 1668, 1447, 1373, 1233, 1091, 1050.

MS (EI^+, m/z) 260 (M^+), 245, 242, 229, 217, 204.

HRMS (EI^+, m/z) Calculated for $C_{18}H_{28}O$: 260.2140.
Found for $C_{18}H_{28}O$: 260.2147.

(*Z*)-3-((*E*)-3,7-Dimethyl-octa-2,6-dienyloxy)-5-ethynyl-2-methyl-dec-4-ene 6.16 r



MF: $C_{23}H_{38}O$

MW: 330.55 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 0.5 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99.5/0.5).

Product: Yellow oil

Yield: 50%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.64 (dd, J = 0.7, 9.4 Hz, 1H, *4*), 5.35 (tq, J = 0.7, 7.0 Hz, 1H, *15*), 5.11 (thept, J = 1.4, 6.9 Hz, 1H, *20*), 4.03 (dd, J = 6.4, 12.1 Hz, 1H, *14*), 3.98 (dd, J = 7.1, 9.4 Hz, 1H, *5*), 3.89 (dd, J = 7.0, 12.1 Hz, 1H, *14*), 3.08 (d, J = 0.6 Hz, 1H, *1*), 2.19 (td, J = 0.7, 7.5 Hz, 2H, *6*), 2.10 (m, 2H, *19*), 2.03 (m, 2H, *18*), 1.76 (hept, J = 6.7 Hz, 1H, *11*), 1.69 (s, 3H, *22* or *23*), 1.65 (s, 3H, *17*), 1.61 (s, 3H, *22* or *23*), 1.54 (m, 2H, *7*), 1.35-1.28 (m, 4H, *8* and *9*), 0.98 (d, J = 6.7 Hz, 3H, *12* or *13*), 0.90 (t, J = 6.9 Hz, 3H, *10*), 0.87 (d, J = 6.8 Hz, 3H, *12* or *13*).

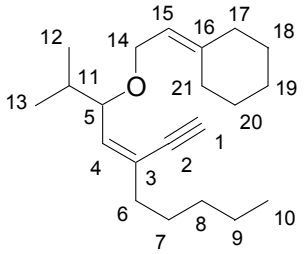
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 139.6 (*16*), 138.5 (*4*), 131.4 (*21*), 126.0 (*3*), 124.1 (*20*), 121.4 (*15*), 82.2 (*5*), 82.1 (*2*), 81.5 (*1*), 65.1 (*14*), 39.6 (*18*), 37.0 (*6*), 32.9 (*11*), 31.0 (*8* or *9*), 27.8 (*7*), 26.3 (*19*), 25.6 (*22* or *23*), 22.4 (*8* or *9*), 18.9 (*12* or *13*), 18.1 (*12* or *13*), 17.6 (*22* or *23*), 16.5 (*17*), 14.0 (*10*).

IR (ν, cm^{-1}) (CCl_4) 3309, 2960, 2928, 2863, 1457, 1378, 1114, 1058.

MS (EI^+, m/z) 330 (M^+), 315, 292, 288, 259, 247, 230, 218, 204.

HRMS (EI^+, m/z) Calculated for $C_{23}H_{38}O$: 330.2923.
Found for $C_{23}H_{38}O$: 330.2915.

[2-((*Z*)-3-Ethynyl-1-isopropyl-oct-2-enyloxy)-ethylidene]-cyclohexane 6.16 s



MF: $C_{21}H_{34}O$

MW: 302.49 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.5** (scale: 0.5 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil

Yield: 40%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.63 (dd, J = 0.7, 9.4 Hz, 1H, *4*), 5.29 (t, J = 6.9 Hz, 1H, *15*), 4.01 (dd, J = 6.7, 11.4 Hz, 1H, *14*), 3.95 (dd, J = 7.1, 9.4 Hz, 1H, *5*), 3.87 (dd, J = 7.1, 11.5 Hz, 1H, *14*), 3.08 (d, J = 0.7Hz, 1H, *1*), 2.20-2.06 (m, 6H, *6*, *17* and *21*), 1.76 (hept, J = 6.9 Hz, 1H, *11*), 1.58-1.51 (m, 8H, *7*, *18*, *19* and *20*), 1.36-1.26 (m, 4H, *8* and *9*), 0.98 (d, J = 6.7 Hz, 3H, *12* or *13*), 0.91 (t, J = 6.9 Hz, 3H, *10*), 0.87 (d, J = 6.8 Hz, 3H, *12* or *13*).

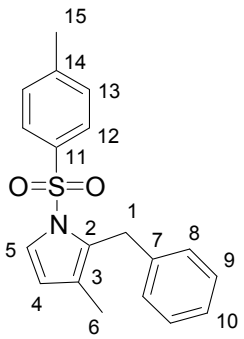
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 144.2 (*16*), 138.6 (*4*), 125.9 (*3*), 118.3 (*15*), 82.3 (*1* or *5*), 82.1 (*2*), 81.5 (*1* or *5*), 64.3 (*14*), 37.1 (*6*, *7*, *8*, *9*, *17*, *18*, *19*, *20* or *21*), 37.0 (*6*, *7*, *8*, *9*, *17*, *18*, *19*, *20* or *21*), 32.9 (*11*), 31.0 (*6*, *7*, *8*, *9*, *17*, *18*, *19*, *20* or *21*), 29.0 (*6*, *7*, *8*, *9*, *17*, *18*, *19*, *20* or *21*), 28.3 (*6*, *7*, *8*, *9*, *17*, *18*, *19*, *20* or *21*), 27.8 (*6*, *7*, *8*, *9*, *17*, *18*, *19*, *20* or *21*), 27.7 (*6*, *7*, *8*, *9*, *17*, *18*, *19*, *20* or *21*), 26.7 (*6*, *7*, *8*, *9*, *17*, *18*, *19*, *20* or *21*), 22.4 (*6*, *7*, *8*, *9*, *17*, *18*, *19*, *20* or *21*), 18.9 (*12* or *13*), 18.1 (*12* or *13*), 14.0 (*10*).

IR (ν, cm^{-1}) (CCl_4): 3309, 2928, 2857, 1705, 1667, 1448, 1377, 1066, 1049.

MS (EI^+, m/z): 302 (M^+), 287, 280, 272, 266, 259, 246, 229, 215, 204.

HRMS (EI^+, m/z): Calculated for $C_{21}H_{34}O$: 302.2610.
Found for $C_{21}H_{34}O$: 302.2606.

3-Methyl-2-propenyl-1-(toluene-4-sulfonyl)-1*H*-pyrrole 6.10



MF: $C_{19}H_{19}NO_2S$

MW: 325.43 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.9 c** (scale: 0.120 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Yellow oil.

Yield: 87%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.33 (d, J = 8.3 Hz, 2H, *12*), 7.29 (d, J = 3.3 Hz, 1H, *5*), 7.11 (m, 3H, *8* and *10*), 7.02 (d, J = 8.1 Hz, 2H, *13*), 6.89 (m, 2H, *9*), 6.18 (d, J = 3.3 Hz, 1H, *4*), 4.17 (s, 2H, *1*), 2.32 (s, 3H, *15*), 1.95 (s, 3H, *6*).

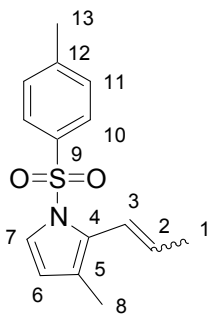
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 144.0 (*14*), 138.9 (*7*), 136.1 (*11*), 129.5 (*13*), 128.3 (*2*), 128.1 (*8* or *9*), 127.9 (*8* or *9*), 126.7 (*12*), 125.6 (*10*), 123.3 (*3*), 121.6 (*5*), 114.0 (*4*), 30.0 (*1*), 21.5 (*15*), 11.4 (*6*).

IR (ν, cm^{-1}) (CCl_4) 3031, 2958, 2925, 2864, 1742, 1597, 1493, 1452, 1372, 1322, 1260, 1180, 1132, 1093.

MS (CI^+, NH_3, m/z) 343 (MNH_4^+), 326 (MH^+).

HRMS (EI^+, m/z) Calculated for $C_{19}H_{19}NO_2S$: 325.1136.
Found for $C_{19}H_{19}NO_2S$: 325.1126.

3-Methyl-2-propenyl-1-(toluene-4-sulfonyl)-1*H*-pyrrole 6.12



MF: $C_{15}H_{17}NO_2S$

MW: 275.37 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.9 c** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

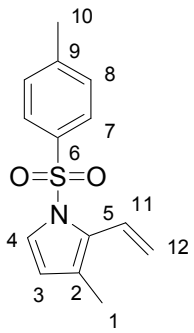
Product: Violet crystals.

Yield: 52% (isolated as a mixture of *Z*/*E* isomers ~ 1/3.8).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) For the mixture of *Z*/*E* isomers: 7.65 (d, J = 8.3 Hz, 2H, *E* isomer, *10*), 7.63 (d, J = 8.1 Hz, 2H, *Z* isomer, *10*), 7.27-7.18 (m, 3H, both isomers, *7* and *11*), 6.62 (d, J = 16.1 Hz, 1H, *E* isomer, *3*), 6.38 (d, J = 10.9 Hz, 1H, *Z* isomer, *3*), 6.12 (d, J = 3.3 Hz, 1H, *Z* isomer, *6*), 6.09 (d, J = 3.3 Hz, 1H, *E* isomer, *6*), 5.82 (dq, J = 6.0, 11.1 Hz, 1H, *Z* isomer, *2*), 5.64 (dq, J = 6.7, 15.9 Hz, 1H, *E* isomer, *2*), 2.39 (s, 3H, *E* isomer, *13*), 2.38 (s, 3H, *Z* isomer, *13*), 2.02 (s, 3H, *E* isomer, *8*), 1.87 (dd, J = 1.7, 6.6 Hz, 3H, *E* isomer, *1*), 1.81 (s, 3H, *Z*

	isomer, *8*), 1.27 (m, 3H, *Z* isomer, *1*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	For the *Z* isomer: 144.3 (*12*), 136.1 (*9*), 130.6 (*2*), 129.5 (*11*), 127.2 (*4*), 127.0 (*10*), 123.4 (*5*), 122.0 (*7*), 119.7 (*3*), 114.5 (*6*), 21.5 (*13*), 14.7 (*1*), 12.1 (*8*). For the *E* isomer: 144.5 (*12*), 136.2 (*9*), 130.2 (*2*), 129.6 (*11*), 129.2 (*4*), 127.0 (*10*), 122.4 (*5*), 120.8 (*7*), 120.1 (*3*), 115.2 (*6*), 21.6 (*13*), 18.8 (*1*), 13.0 (*8*).
IR (ν, cm^{-1}) (CCl_4)	For the mixture of *Z*/*E* isomers: 3149, 3033, 2924, 2860, 1596, 1447, 1374, 1190, 1171, 1140, 1099, 1051.
MS (CI^+, NH_3, m/z)	276 (MH^+).
HRMS (EI^+, m/z)	Calculated for $C_{15}H_{17}NO_2S$: 275.0980. Found for $C_{15}H_{17}NO_2S$: 275.0977.

3-Methyl-1-(toluene-4-sulfonyl)-2-vinyl-1*H*-pyrrole 6.15

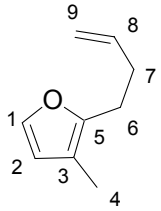


MF: $C_{14}H_{15}NO_2S$

MW: 261.34 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 6.9 c** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 95/5).
Product:	Yellow oil.
Yield:	15% (estimated, product isolated in mixture with pyrrole **6.3 a**)
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7 7.59 (d, J = 8.2 Hz, 2H, *7*), 7.21-7.13 (m, 3H, *4* and *8*), 6.93 (dd, J = 11.7, 17.8 Hz, 1H, *11*), 6.04 (d, J = 3.3 Hz, 1H, *3*), 5.25 (dd, J = 1.5, 11.6 Hz, 1H, *12*), 5.12 (dd, J = 1.5, 17.7 Hz, 1H, *12*), 2.31 (s, 3H, *10*), 2.00 (s, 3H, *1*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	144.7 (*9*), 136.1 (*6*), 129.7 (*8*), 129.1 (*5*), 126.9 (*7*), 125.9 (*11*), 123.9 (*2*), 121.7 (*4*), 117.2 (*12*), 115.4 (*3*), 21.5 (*10*), 13.3 (*1*).

2-But-3-enyl-3-methyl-furan 6.17 a



MF: $C_9H_{12}O$

MW: 136.19 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Pale yellow oil.

Yield: 18%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.23 (d, J = 1.7 Hz, 1H, *1*), 6.16 (d, J = 1.6 Hz, 1H, *2*), 5.84 (ddt, J = 6.6, 10.1, 17.1 Hz, 1H, *8*), 5.05 (dd, J = 1.4, 17.1 Hz, 1H, *9*), 4.98 (d, J = 10.2 Hz, 1H, *9*), 2.66 (t, J = 7.2 Hz, 2H, *6*), 2.36 (dt, J = 6.7, 8.0 Hz, 2H, *7*), 1.97 (s, 3H, *4*).

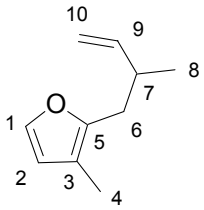
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 150.4 (*5*), 139.7 (*1*), 137.7 (*8*), 115.0 (*9*), 113.8 (*3*), 112.6 (*2*), 32.5 (*7*), 25.5 (*6*), 15.2 (*4*).

IR (ν, cm^{-1}) (CCl_4): 2926, 2857, 1640, 1451, 1150.

MS (CI^+, NH_3, m/z): 137 (MH^+), 122, 105.

HRMS (EI^+, m/z): Calculated for $C_9H_{12}O$: 136.0888.
Found for $C_9H_{12}O$: 136.0882.

3-Methyl-2-(2-methyl-but-3-enyl)-furan 6.17 b



MF: $C_{10}H_{14}O$

MW: 150.22 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

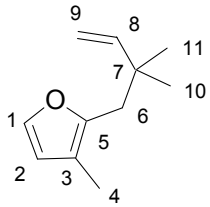
Product: Pale yellow oil.

Yield: 39%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.24 (d, J = 1.8 Hz, 1H, *1*), 6.17 (d, J = 1.7 Hz, 1H, *2*), 5.80 (ddd, J = 6.6, 10.4, 17.2 Hz, 1H, *9*), 4.99 (dt, J = 1.4, 17.2 Hz, 1H, *10*), 4.94 (dt, J = 0.8, 10.3 Hz, 1H, *10*), 2.64-2.48 (m, 3H, *6* and *7*), 1.96 (s, 3H, *4*), 1.00 (d, J = 6.4 Hz, 3H, *8*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	149.8 (*5*), 143.6 (*9*), 139.8 (*1*), 114.7 (*3*), 112.7 (*10*), 112.5 (*2*), 37.2 (*7*), 33.0 (*6*), 19.2 (*8*), 9.9 (*4*).
IR (ν, cm^{-1}) (CCl_4)	2960, 2926, 2867, 1640, 1512, 1456, 1374, 1149.
MS (CI^+, NH_3, m/z)	169 (MNH_4^+), 151 (MH^+), 137.
HRMS (EI^+, m/z)	Calculated for $C_{10}H_{14}O$: 150.1045. Found for $C_{10}H_{14}O$: 150.1048.

2-(2,2-Dimethyl-but-3-enyl)-3-methyl-furan 6.17 c



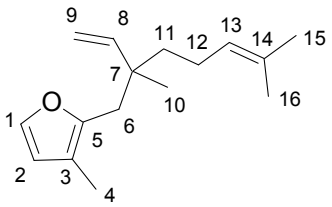
MF: $C_{11}H_{16}O$

MW: 164.24 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 100/0).
Product:	Pale yellow oil.
Yield:	59%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.24 (d, J = 1.7 Hz, 1H, *1*), 6.18 (d, J = 1.6 Hz, 1H, *2*), 5.91 (dd, J = 10.7, 17.5 Hz, 1H, *8*), 4.94 (dd, J = 1.2, 17.5 Hz, 1H, *9*), 4.91 (dd, J = 1.2, 10.7 Hz, 1H, *9*), 2.54 (s, 2H, *6*), 1.96 (s, 3H, *4*), 1.04 (s, 6H, *10* and *11*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	149.4 (*5*), 148.1 (*8*), 139.9 (*1*), 115.7 (*3*), 112.5 (*2*), 110.1 (*9*), 38.7 (*6*), 38.5 (*7*), 26.5 (*10* and *11*), 10.4 (*4*).
IR (ν, cm^{-1}) (CCl_4)	2961, 2927, 2869, 1639, 1511, 1460, 1377, 1150, 1075, 1001.
MS (CI^+, NH_3, m/z)	183 (MNH_4^+), 165 (MH^+).
HRMS (EI^+, m/z)	Calculated for $C_{11}H_{16}O$: 164.1201. Found for $C_{11}H_{16}O$: 164.1205.

2-(2,6-Dimethyl-2-vinyl-hept-5-enyl)-3-methyl-furan 6.17 d



MF: $C_{16}H_{24}O$

MW: 232.36 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.10**

(scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 81%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.24 (d, J = 1.8 Hz, 1H, *1*), 6.18 (d, J = 1.7 Hz, 1H, *2*), 5.84 (dd, J = 10.8, 17.5 Hz, 1H, *8*), 5.10 (thept, J = 1.4, 7.1 Hz, 1H, *13*), 5.01 (dd, J = 1.3, 10.8 Hz, 1H, *9*), 4.93 (dd, J = 1.3, 17.5 Hz, 1H, *9*), 2.57 (s, 2H, *6*), 1.96 (s, 3H, *4*), 1.93 (m, 2H, *12*), 1.69 (s, 3H, *15* or *16*), 1.61 (s, 3H, *15* or *16*), 1.36 (m, 2H, *11*), 1.03 (s, 3H, *10*).

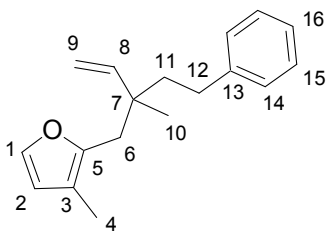
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 149.1 (*5*), 146.5 (*8*), 139.9 (*1*), 131.0 (*14*), 124.9 (*13*), 115.8 (*3*), 112.5 (*2*), 111.6 (*9*), 41.4 (*7*), 40.3 (*11*), 37.5 (*6*), 25.6 (*15* or *16*), 23.0 (*12*), 22.6 (*10*), 17.5 (*15* or *16*), 10.4 (*4*).

IR (ν, cm^{-1}) (CCl_4): 2965, 2924, 2868, 1636, 1511, 1452, 1376, 1149, 1069, 1002.

MS (CI^+, NH_3, m/z): 233 (MH^+), 216, 183.

HRMS (EI^+, m/z): Calculated for $C_{16}H_{24}O$: 232.1827.
Found for $C_{16}H_{24}O$: 232.1835.

3-Methyl-2-(2-methyl-2-phenethyl-but-3-enyl)-furan 6.17 e



MF: $C_{18}H_{22}O$

MW: 254.37 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 66%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.28-7.23 (m, 3H, *1* and *15*), 7.18-7.14 (m, 3H, *14* and *16*), 6.16 (d, J = 1.6 Hz, 1H, *2*), 5.87 (dd, J = 10.8, 17.5 Hz, 1H, *8*), 5.05 (dd, J = 1.2, 10.8 Hz, 1H, *9*), 4.98 (dd, J = 1.2, 17.5 Hz, 1H, *9*), 2.62 (d, J = 3.6 Hz, 2H, *6*), 2.57 (m, 2H, *12*), 1.95 (s, 3H, *4*), 1.64 (m, 2H, *11*), 1.09 (s, 3H, *10*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 148.9 (*5*), 146.3 (*8*), 143.1 (*13*), 140.0 (*1*), 128.3 (*14* or *15*), 128.2 (*14* or *15*), 125.5 (*16*), 116.0 (*3*), 112.6 (*2*), 112.0 (*9*), 42.3 (*11*), 41.6 (*7*), 37.3 (*6*), 30.8 (*12*), 22.9 (*10*), 10.5 (*4*).

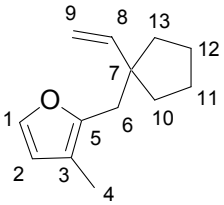
IR (ν, cm^{-1}) (CCl_4): 3082, 3027, 2930, 2866, 1636, 1602, 1502, 1455, 1374, 1204, 1149, 1071,

1003.

MS (EI^+, m/z) 254 (M^+), 159, 128, 117, 108.

HRMS (EI^+, m/z) Calculated for $C_{18}H_{22}O$: 254.1671.
Found for $C_{18}H_{22}O$: 254.1664.

3-Methyl-2-(1-vinyl-cyclopentylmethyl)-furan 6.17 f



MF: $C_{13}H_{18}O$

MW: 190.28 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 71%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.23 (d, J = 1.8 Hz, 1H, *1*), 6.17 (d, J = 1.7 Hz, 1H, *2*), 5.86 (dd, J = 10.8, 17.4 Hz, 1H, *8*), 4.95 (dd, J = 1.3, 10.8 Hz, 1H, *9*), 4.93 (dd, J = 1.3, 17.4 Hz, 1H, *9*), 2.65 (s, 2H, *6*), 1.96 (s, 3H, *4*), 1.68-1.54 (m, 8H, *10*, *11*, *12* and *13*).

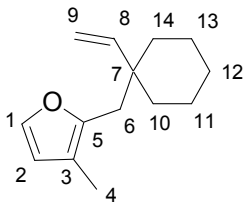
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 149.8 (*5*), 145.8 (*8*), 139.8 (*1*), 115.4 (*3*), 112.5 (*2*), 111.0 (*9*), 50.3 (*7*), 36.2 (*6*), 36.1 (*10*, *11*, *12* and/or *13*), 23.5 (*10*, *11*, *12* and/or *13*), 10.3 (*4*).

IR (ν, cm^{-1}) (CCl_4) 3080, 2953, 2868, 1635, 1511, 1454, 1377, 1217, 1149, 1073.

MS (EI^+, m/z) 190 (M^+), 121, 109.

HRMS (EI^+, m/z) Calculated for $C_{13}H_{18}O$: 190.1358.
Found for $C_{13}H_{18}O$: 190.1354.

3-Methyl-2-(1-vinyl-cyclohexylmethyl)-furan 6.17 g



MF: $C_{14}H_{20}O$

MW: 204.31 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 63%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.23 (d, J = 1.8 Hz, 1H, *1*), 6.17 (d, J = 1.7 Hz, 1H, *2*), 5.69 (dd, J = 11.0, 17.8 Hz, 1H, *8*), 5.08 (dd, J = 1.3, 11.0 Hz, 1H, *9*), 4.94 (dd, J = 1.3, 17.8 Hz, 1H, *9*), 2.54 (s, 2H, *6*), 1.95 (s, 3H, *4*), 1.68-1.20 (m, 10H, *10*, *11*, *12*, *13* and *14*).

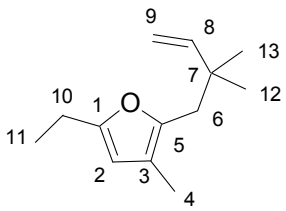
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 149.2 (*5*), 145.9 (*8*), 139.8 (*1*), 115.8 (*3*), 112.8 (*9*), 112.5 (*2*), 41.5 (*7*), 38.7 (*6*), 35.2 (*10*, *11*, *12*, *13* and/or *14*), 26.3 (*10*, *11*, *12*, *13* and/or *14*), 22.3 (*10*, *11*, *12*, *13* and/or *14*), 10.5 (*4*).

IR (ν, cm^{-1}) (CCl_4): 3080, 2924, 2857, 1634, 1563, 1511, 1449, 1211, 1149, 1094, 1071, 1000.

MS (EI^+, m/z): 204 (M^+), 121, 109.

HRMS (EI^+, m/z): Calculated for $C_{14}H_{20}O$: 204.1514.
Found for $C_{14}H_{20}O$: 204.1507.

2-(2,2-Dimethyl-but-3-enyl)-5-ethyl-3-methyl-furan — 6.17 h



MF: $C_{13}H_{20}O$

MW: 192.30 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.244 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Pale yellow oil.

Yield: Quant.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.91 (dd, J = 10.7, 17.5 Hz, 1H, *8*), 5.77 (s, 1H, *2*), 4.94 (dd, J = 1.4, 17.5 Hz, 1H, *9*), 4.91 (dd, J = 1.4, 10.7 Hz, 1H, *9*), 2.57 (qd, J = 0.8, 7.5 Hz, 2H, *10*), 2.50 (s, 2H, *6*), 1.91 (s, 3H, *4*), 1.23 (t, J = 7.0 Hz, 3H, *11*), 1.04 (s, 6H, *12* and *13*).

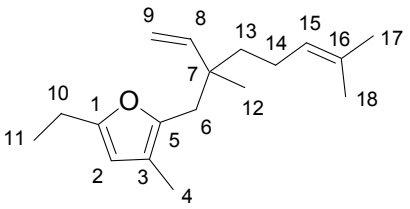
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 155.0 (*1*), 148.3 (*8*), 147.2 (*5*), 116.1 (*3*), 109.9 (*9*), 106.8 (*2*), 38.7 (*6*), 38.4 (*7*), 26.5 (*12* and *13*), 21.3 (*10*), 12.2 (*11*), 10.4 (*4*).

IR (ν, cm^{-1}) (CCl_4): 3083, 2964, 2930, 2874, 1637, 1572, 1459, 1375, 1221, 1087.

MS (CI^+, NH_3, m/z): 193 (MH^+), 123.

HRMS (EI^+, m/z): Calculated for $C_{13}H_{20}O$: 192.1514.
Found for $C_{13}H_{20}O$: 192.1514.

2-(2,6-Dimethyl-2-vinyl-hept-5-enyl)-5-ethyl-3-methyl-furan **6.17 i**



MF: $C_{18}H_{28}O$

MW: 260.41 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Pale yellow oil.

Yield: Quant.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.82 (dd, J = 10.8, 17.5 Hz, 1H, *8*), 5.76 (s, 1H, *2*), 5.10 (thept, J = 1.3, 7.1 Hz, 1H), 5.00 (dd, J = 1.3, 10.8 Hz, 1H, *15*), 4.93 (dd, J = 1.3, 17.5 Hz, 1H, *9*), 2.57 (q, J = 7.5 Hz, 2H, *10*), 2.53 (d, J = 2.6 Hz, 2H, *6*), 1.95 (m, 2H, *14*), 1.91 (s, 3H, *4*), 1.69 (s, 3H, *17* or *18*), 1.61 (s, 3H, *17* or *18*), 1.35 (m, 2H, *13*), 1.23 (t, J = 7.0 Hz, 3H, *11*), 1.02 (s, 3H, *12*).

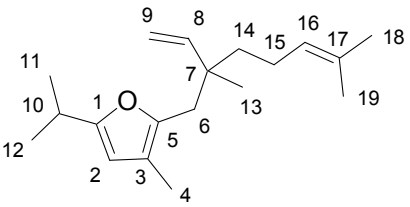
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 155.0 (*1*), 147.0 (*5*), 146.8 (*8*), 130.8 (*16*), 125.0 (*15*), 116.2 (*4*), 111.4 (*9*), 106.8 (*2*), 41.4 (*7*), 40.2 (*13*), 37.3 (*6*), 25.6 (*17* or *18*), 23.0 (*12*), 22.7 (*14*), 21.3 (*10*), 17.6 (*17* or *18*), 12.2 (*11*), 10.5 (*4*).

IR (ν, cm^{-1}) (CCl_4): 3082, 2923, 1636, 1572, 1452, 1376, 1218, 1119.

MS (CI^+, NH_3, m/z): 261 (MH^+), 123.

HRMS (EI^+, m/z): Calculated for $C_{18}H_{28}O$: 260.2140.
Found for $C_{18}H_{28}O$: 260.2132.

2-(2,6-Dimethyl-2-vinyl-hept-5-enyl)-5-isopropyl-3-methyl-furan **6.17 j**



MF: $C_{19}H_{30}O$

MW: 274.44 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.182 mmol).

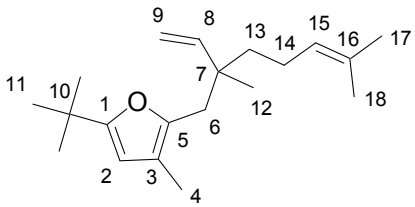
Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 78%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.82 (dd, J = 10.8, 17.5 Hz, 1H, *8*), 5.75 (s, 1H, *2*), 5.10 (thept, J = 1.3, 7.1 Hz, 1H, *16*), 4.99 (dd, J = 1.3, 10.8 Hz, 1H, *9*), 4.92 (dd, J = 1.3, 17.5 Hz, 1H, *9*), 2.85 (hept, J = 6.8 Hz, 1H, *10*), 2.53 (d, J = 2.5 Hz, 2H, *6*), 1.95 (m, 2H, *15*), 1.91 (s, 3H, *4*), 1.69 (s, 3H, *18* or *19*), 1.61 (s, 3H, *18* or *19*), 1.35 (m, 2H, *14*), 1.21 (d, J = 6.9 Hz, 6H, *11* and *12*), 1.01 (s, 3H, *13*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	159.0 (*1*), 146.9 (*5*), 146.8 (*8*), 130.9 (*17*), 125.0 (*16*), 116.0 (*3*), 111.4 (*9*), 105.5 (*2*), 41.4 (*7*), 40.2 (*14*), 37.3 (*6*), 27.6 (*10*), 25.6 (*18* or *19*), 23.0 (*15*), 22.7 (*13*), 21.0 (*11* or *12*), 21.0 (*11* or *12*), 17.6 (*18* or *19*), 10.5 (*4*).
IR (ν, cm^{-1}) (CCl_4)	3082, 2967, 2925, 2871, 1636, 1566, 1454, 1376, 1217, 1125, 1070, 1001.
MS (CI^+, NH_3, m/z)	275 (MH^+), 137.
HRMS (EI^+, m/z)	Calculated for $C_{19}H_{30}O$: 274.2297. Found for $C_{19}H_{30}O$: 274.2296.

5-*tert*-Butyl-2-(2,6-dimethyl-2-vinyl-hept-5-enyl)-3-methyl-furan **6.17 k**

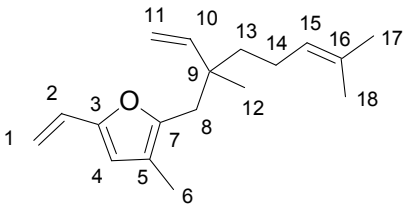


MF: $C_{20}H_{32}O$

MW: 288.47 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 6.10** (scale: 0.080 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 100/0).
Product:	Yellow oil.
Yield:	78%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.82 (dd, J = 10.8, 17.5 Hz, 1H, *8*), 5.73 (s, 1H, *2*), 5.09 (thept, J = 1.4, 7.1 Hz, 1H, *15*), 4.98 (dd, J = 1.4, 10.8 Hz, 1H, *9*), 4.91 (dd, J = 1.4, 17.5 Hz, 1H, *9*), 2.53 (d, J = 2.4 Hz, 2H, *6*), 1.96 (m, 2H, *14*), 1.91 (s, 3H, *4*), 1.68 (s, 3H, *17* or *18*), 1.60 (s, 3H, *17* or *18*), 1.35 (m, 2H, *13*), 1.24 (s, 9H, *11*), 1.01 (s, 3H, *12*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	161.4 (*1*), 146.8 (*5* or *8*), 146.8 (*5* or *8*), 130.8 (*16*), 125.1 (*15*), 115.8 (*3*), 111.3 (*9*), 104.6 (*2*), 41.4 (*7*), 40.3 (*13*), 37.2 (*6*), 32.2 (*10*), 28.9 (*11*), 25.6 (*17* or *18*), 23.0 (*14*), 22.8 (*12*), 17.6 (*17* or *18*), 10.5 (*4*).
IR (ν, cm^{-1}) (CCl_4)	3081, 2965, 2925, 2866, 1636, 1561, 1455, 1369, 1293, 1196, 1103, 1001.
MS (EI^+, m/z)	288 (M^+), 151, 136, 109.
HRMS (EI^+, m/z)	Calculated for $C_{20}H_{32}O$: 288.2453. Found for $C_{20}H_{32}O$: 288.2461.

2-(2,6-Dimethyl-2-vinyl-hept-5-enyl)-3-methyl-5-vinyl-furan 6.17 l



MF: $C_{18}H_{26}O$

MW: 258.40 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 17%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.41 (dd, J = 11.2, 17.5 Hz, 1H, *2*), 6.05 (s, 1H, *4*), 5.83 (dd, J = 10.8, 17.5 Hz, 1H, *10*), 5.53 (dd, J = 1.4, 17.5 Hz, 1H, *1*), 5.10 (thept, J = 1.3, 7.0 Hz, 1H, *15*), 5.05 (dd, J = 1.4, 11.2 Hz, 1H, *1*), 5.00 (dd, J = 1.3, 10.8 Hz, 1H, *11*), 4.93 (dd, J = 1.3, 17.5 Hz, 1H, *11*), 2.57 (d, J = 2.4 Hz, 2H, *8*), 1.94 (m, 2H, *14*), 1.92 (s, 3H, *6*), 1.68 (s, 3H, *17* and *18*), 1.60 (s, 3H, *17* and *18*), 1.38 (m, 2H, *13*), 1.04 (s, 3H, *12*).

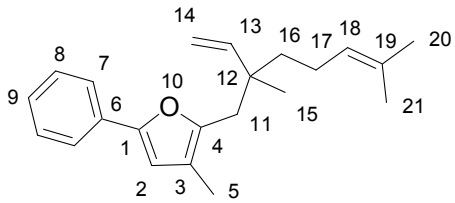
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 150.6 (*3*), 149.1 (*7*), 146.5 (*10*), 131.0 (*16*), 125.1 (*2* or *15*), 124.9 (*2* or *15*), 117.7 (*5*), 111.6 (*11*), 111.3 (*4*), 110.4 (*1*), 41.2 (*9*), 40.2 (*13*), 37.3 (*8*), 25.6 (*17* or *18*), 23.0 (*14*), 22.8 (*12*), 17.6 (*17* or *18*), 10.4 (*6*).

IR (ν, cm^{-1}) (CCl_4): 3083, 2964, 2924, 2860, 1639, 1606, 1531, 1451, 1375, 1297, 1122, 1028, 1001.

MS (EI^+, m/z): 258 (M^+), 205, 149, 135, 121.

HRMS (EI^+, m/z): Calculated for $C_{18}H_{26}O$: 258.1984.
Found for $C_{18}H_{26}O$: 258.1982.

2-(2,6-Dimethyl-2-vinyl-hept-5-enyl)-3-methyl-5-phenyl-furan 6.17 m



MF: $C_{22}H_{28}O$

MW: 308.46 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 77%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.63 (dd, J = 1.2, 8.2 Hz, 2H, *7*), 7.37 (t, J = 8.0 Hz, 2H, *8*), 7.23 (tt, J = 1.2, 7.4 Hz, 1H, *9*), 6.48 (s, 1H, *2*), 5.89 (dd, J = 10.8, 17.5 Hz, 1H, *13*), 5.14 (thept, J = 1.4, 7.0 Hz, 1H, *18*), 5.06 (dd, J = 1.3, 10.8 Hz, 1H, *14*), 4.98 (dd, J = 1.3, 17.5 Hz, 1H, *14*), 2.66 (d, J = 2.4 Hz, 2H, *11*), 2.03 (m, 2H, *17*), 2.01 (s, 3H, *15*), 1.72 (s, 3H, *20* or *21*), 1.64 (s, 3H, *20* or *21*), 1.45 (m, 2H, *16*), 1.11 (s, 3H, *15*).

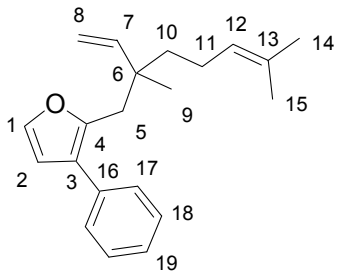
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.0 (*1*), 149.1 (*4*), 146.5 (*13*), 131.2 (*6*), 131.0 (*19*), 128.5 (*8*), 126.5 (*9*), 124.9 (*18*), 123.2 (*7*), 118.2 (*3*), 111.7 (*14*), 108.1 (*2*), 41.3 (*12*), 40.3 (*16*), 37.3 (*11*), 25.6 (*20* or *21*), 23.0 (*17*), 22.9 (*15*), 17.6 (*20* or *21*), 10.5 (*5*).

IR (ν, cm^{-1}) (CCl_4): 3079, 3031, 2967, 2923, 2866, 1636, 1600, 1550, 1484, 1448, 1376, 1182, 1121, 1068, 1001.

MS (CI^+, NH_3, m/z): 309 (MH^+), 171.

HRMS (EI^+, m/z): Calculated for $C_{22}H_{28}O$: 308.2140.
Found for $C_{22}H_{28}O$: 308.2147.

2-(2,6-Dimethyl-2-vinyl-hept-5-enyl)-3-phenyl-furan 6.17 n



MF: $C_{21}H_{26}O$

MW: 294.43 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 80%

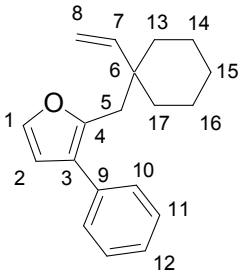
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.43-7.36 (m, 5H, *1*, *17* and *18*), 7.28 (m, 1H, *19*), 6.48 (d, J = 1.8 Hz, 1H, *2*), 5.77 (dd, J = 10.8, 17.5 Hz, 1H, *7*), 5.03 (thept, J = 1.4, 7.2 Hz, 1H, *12*), 4.95 (dd, J = 1.3, 10.8 Hz, 1H, *8*), 4.90 (dd, J = 1.3, 17.5 Hz, 1H, *8*), 2.85 (s, 2H, *5*), 1.87 (q, J = 8.2 Hz, 2H, *11*), 1.68 (s, 3H, *14* or *15*), 1.57 (s, 3H, *14* or *15*), 1.35 (m, 2H, *10*), 0.99 (s, 3H, *9*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 149.6 (*4*), 146.4 (*7*), 140.5 (*1*), 134.6 (*16*), 131.0 (*13*), 128.4 (*17* or *18*), 128.2 (*17* or *18*), 126.4 (*19*), 124.8 (*12*), 123.2 (*3*), 111.7 (*8*), 111.6 (*2*), 41.4 (*6*), 40.5 (*10*), 37.5 (*5*), 25.6 (*14* or *15*), 22.9 (*11*), 22.9 (*9*), 17.5 (*14* or *15*).

IR (ν, cm^{-1}) (CCl_4): 3079, 3028, 2966, 2921, 2862, 1611, 1515, 1449, 1376, 1202, 1143, 1057,

	1000.
MS (EI^+, m/z)	294 (M^+), 170, 157, 137, 129.
HRMS (EI^+, m/z)	Calculated for $C_{21}H_{26}O$: 294.1984. Found for $C_{21}H_{26}O$: 294.1988.

3-Phenyl-2-(1-vinyl-cyclohexylmethyl)-furan 6.17 o

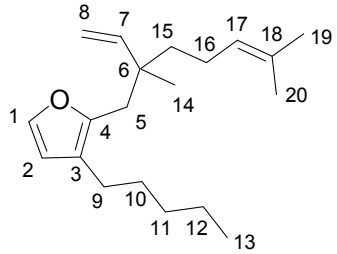


MF: $C_{19}H_{22}O$

MW: 266.38 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 100/0).
Product:	Yellow oil.
Yield:	90%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.40-7.32 (m, 5H, *1*, *10* and *11*), 7.25 (m, 1H, *12*), 6.44 (d, J = 1.9 Hz, 1H, *2*), 5.62 (dd, J = 11.0, 17.8 Hz, 1H, *7*), 4.97 (dd, J = 1.3, 10.9 Hz, 1H, *8*), 4.86 (dd, J = 1.3, 17.8 Hz, 1H, *8*), 2.79 (s, 2H, *5*), 1.58 (m, 2H, *13*, *14*, *15*, *16* and/or *17*), 1.47-1.32 (m, 8H, *13*, *14*, *15*, *16* and/or *17*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	149.6 (*4*), 145.7 (*7*), 140.4 (*1*), 134.7 (*9*), 128.3 (*10* or *11*), 128.2 (*10* or *11*), 126.3 (*12*), 123.1 (*3*), 112.9 (*8*), 111.5 (*2*), 41.5 (*6*), 38.6 (*5*), 35.5 (*13* and *17*), 26.2 (*15*), 22.2 (*14* and *16*).
IR (ν, cm^{-1}) (CCl_4)	3078, 3031, 2937, 2856, 1611, 1515, 1449, 1213, 1143, 1057.
MS (EI^+, m/z)	266 (M^+).
HRMS (EI^+, m/z)	Calculated for $C_{19}H_{22}O$: 266.1671. Found for $C_{19}H_{22}O$: 266.1671.

2-(2,6-Dimethyl-2-vinyl-hept-5-enyl)-3-pentyl-furan 6.17 p



MF: $C_{20}H_{32}O$

MW: 288.47 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 82%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.25 (d, J = 1.8 Hz, 1H, *1*), 6.22 (d, J = 1.8 Hz, 1H, *2*), 5.82 (dd, J = 10.8, 17.5 Hz, 1H, *7*), 5.11 (thept, J = 1.3, 7.1 Hz, 1H, *17*), 5.01 (dd, J = 1.3, 10.8 Hz, 1H, *8*), 4.93 (dd, J = 1.3, 17.5 Hz, 1H, *8*), 2.58 (s, 2H, *5*), 2.31 (t, J = 7.6 Hz, 2H, *9*), 1.94 (q, J = 7.5 Hz, 2H, *16*), 1.69 (s, 3H, *19* or *20*), 1.61 (s, 3H, *19* or *20*), 1.53 (m, 2H, *10*), 1.40-1.28 (m, 6H, *11*, *12* and *15*), 1.03 (s, 3H, *14*), 0.92 (t, J = 7.0 Hz, 3H, *13*).

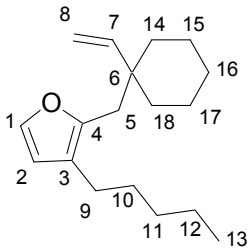
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 148.6 (*4*), 146.6 (*7*), 140.0 (*1*), 130.9 (*18*), 124.9 (*17*), 121.2 (*3*), 111.6 (*8*), 111.0 (*2*), 41.2 (*6*), 40.3 (*15*), 37.6 (*5*), 31.7 (*11* or *12*), 30.0 (*10*), 25.6 (*19* or *20*), 25.0 (*9*), 23.0 (*16*), 22.6 (*14*), 22.5 (*11* or *12*), 17.5 (*19* or *20*), 14.0 (*13*).

IR (ν, cm^{-1}) (CCl_4): 3081, 2923, 2860, 1637, 1511, 1456, 1376, 1188, 1147, 1051, 1002.

MS (EI^+, m/z): 288 (M^+), 245, 232, 219, 205.

HRMS (EI^+, m/z): Calculated for $C_{20}H_{32}O$: 288.2453.
Found for $C_{20}H_{32}O$: 288.2451.

3-Pentyl-2-(1-vinyl-cyclohexylmethyl)-furan 6.17 q



MF: $C_{18}H_{28}O$

MW: 260.41 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: mmol).

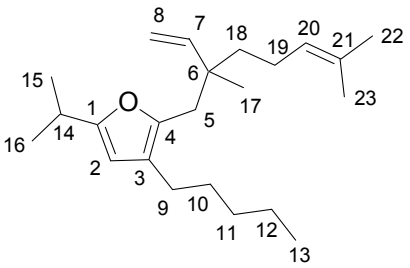
Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 86%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.24 (d, J = 1.8 Hz, 1H, *1*), 6.21 (d, J = 1.8 Hz, 1H, *2*), 5.68 (dd, J = 11.0, 17.8 Hz, 1H, *7*), 5.07 (dd, J = 1.3, 11.0 Hz, 1H, *8*), 4.94 (dd, J = 1.4, 17.8 Hz, 1H, *8*), 2.55 (s, 2H, *5*), 2.30 (t, J = 7.6 Hz, 2H, *9*), 1.63 (m, 2H, *10*, *11*, *12*, *14*, *15*, *16*, *17* and/or *18*), 1.57-1.26 (m, 14H, *10*, *11*, *12*, *14*, *15*, *16*, *17* and/or *18*), 0.92 (t, J = 7.0 Hz, 3H, *13*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	148.6 (*4*), 145.9 (*7*), 139.9 (*1*), 121.2 (*3*), 112.8 (*8*), 110.9 (*2*), 41.3 (*6*), 38.7 (*5*), 35.3 (*14* and *18*), 31.7 (*10*, *11*, *12* or *16*), 30.0 (*10*, *11*, *12* or *16*), 26.3 (*10*, *11*, *12* or *16*), 25.0 (*9*), 22.5 (*10*, *11*, *12* or *16*), 22.3 (*15* and *17*), 14.0 (*13*).
IR (ν, cm^{-1}) (CCl_4)	3080, 2934, 2859, 1635, 1511, 1452, 1377, 1149, 1114, 1050, 1001.
MS (EI^+, m/z)	260 (M^+), 220, 205.
HRMS (EI^+, m/z)	Calculated for $C_{18}H_{28}O$: 260.2140. Found for $C_{18}H_{28}O$: 260.2140.

2-(2,6-Dimethyl-2-vinyl-hept-5-enyl)-5-isopropyl-3-pentyl-furan 6.17 r



MF: $C_{23}H_{38}O$

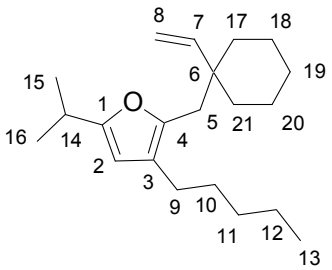
MW: 330.55 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 6.10** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 100/0).
Product:	Yellow oil.
Yield:	73%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.82 (dd, J = 10.8, 17.5 Hz, 1H, *7*), 5.79 (s, 1H, *2*), 5.10 (thept, J = 1.2, 7.1 Hz, 1H, *20*), 4.99 (dd, J = 1.3, 10.8 Hz, 1H, *8*), 4.92 (dd, J = 1.3, 17.5 Hz, 1H, *8*), 2.85 (hept, J = 6.8 Hz, 1H, *14*), 2.53 (d, J = 2.0 Hz, 2H, *5*), 2.26 (t, J = 7.7 Hz, 2H, *9*), 1.95 (m, 2H, *19*), 1.69 (s, 3H, *22* or *23*), 1.61 (s, 3H, *22* or *23*), 1.51 (m, 2H, *10*), 1.40-1.28 (m, 6H, *11*, *12* and *18*), 1.21 (d, J = 6.9 Hz, 6H, *15* and *16*), 1.02 (s, 3H, *17*), 0.92 (t, J = 7.0 Hz, 3H, *13*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	159.1 (*1*), 146.9 (*7*), 146.3 (*4*), 130.8 (*21*), 125.0 (*20*), 121.4 (*3*), 111.3 (*8*), 103.9 (*2*), 41.1 (*6*), 40.3 (*18*), 37.3 (*5*), 31.8 (*11* or *12*), 30.1 (*10*), 27.7 (*14*), 25.6 (*22* or *23*), 25.2 (*9*), 23.0 (*19*), 22.8 (*17*), 22.5 (*11* or *12*), 21.0 (*15* and *16*), 17.6 (*22* or *23*), 14.0 (*13*).
IR (ν, cm^{-1}) (CCl_4)	3081, 2931, 2862, 1636, 1565, 1457, 1376, 1337, 1216, 1125, 1060, 1001.
MS (EI^+, m/z)	330 (M^+), 292, 274, 242, 230, 218, 205.

HRMS (EI^+, m/z) Calculated for $C_{23}H_{38}O$: 330.2923.
Found for $C_{23}H_{38}O$: 330.2922.

5-Isopropyl-3-pentyl-2-(1-vinyl-cyclohexylmethyl)-furan **6.17 s**



MF: $C_{21}H_{34}O$

MW: 302.49 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 6.10** (scale: 0.175 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 100/0).

Product: Yellow oil.

Yield: 36%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.77 (s, 1H, *2*), 5.68 (dd, J = 10.9, 17.8 Hz, 1H, *7*), 5.04 (dd, J = 1.3, 11.0 Hz, 1H, *8*), 4.91 (dd, J = 1.4, 17.8 Hz, 1H, *8*), 2.85 (hept, J = 6.8 Hz, 1H, *14*), 2.49 (s, 2H, *5*), 2.24 (t, J = 7.7 Hz, 2H, *9*), 1.64-1.22 (m, 16H, *10*, *11*, *12*, *17*, *18*, *19*, *20* and *21*), 1.21 (d, J = 6.9 Hz, 6H, *15* and *16*), 0.91 (t, J = 7.0 Hz, 3H, *13*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 158.9 (*1*), 146.3 (*4* or *7*), 146.3 (*4* or *7*), 121.3 (*3*), 112.5 (*8*), 103.8 (*2*), 41.2 (*6*), 38.6 (*5*), 35.2 (*17* and *21*), 31.8 (*10*, *11*, *12* or *19*), 30.1 (*10*, *11*, *12* or *19*), 27.7 (*14*), 26.4 (*10*, *11*, *12* or *19*), 25.2 (*9*), 22.5 (*10*, *11*, *12* or *19*), 22.3 (*18* and *20*), 21.0 (*15* and *16*), 14.0 (*13*).

IR (ν, cm^{-1}) (CCl_4) 3080, 2928, 2858, 1635, 1566, 1454, 1378, 1218, 1118, 1065, 1000.

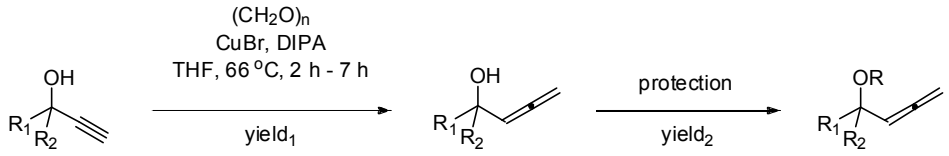
MS (EI^+, m/z) 302 (M^+), 206.

HRMS (EI^+, m/z) Calculated for $C_{21}H_{34}O$: 302.2610.
Found for $C_{21}H_{34}O$: 302.2612.

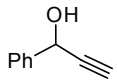
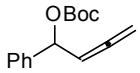
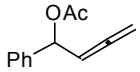
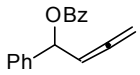
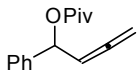
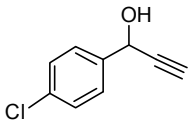
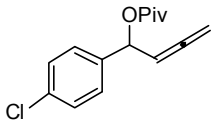
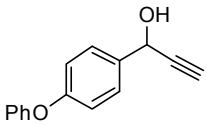
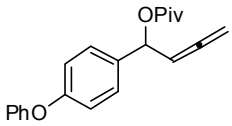
7. Gold(I)-catalyzed isomerization of allenyl carbinol esters: an efficient access to functionalized 1,3-butadien-2-ol esters

7.1. Synthesis of the precursors

Substrates **7.7 a-d** and **7.11 a-o** were all synthesized in a 2-step sequence starting from the corresponding propargylic alcohols via a Crabbe homologation[339] followed by protection of the resulting allenol using standard procedures.[330,340]

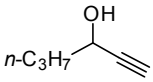
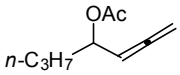
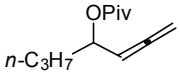
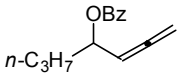
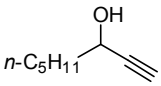
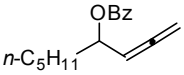
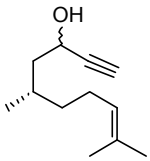
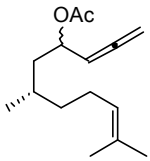
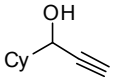
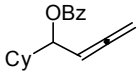
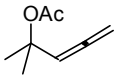
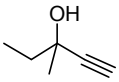
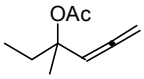
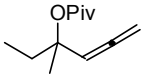
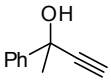
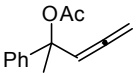
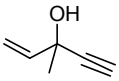
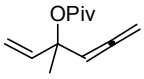
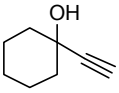
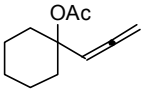
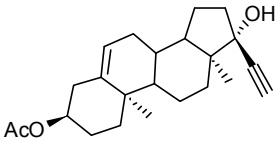
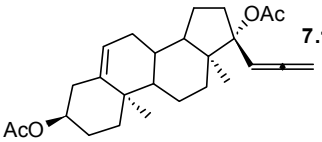


Protection conditions: (a) RCl or R_2O, NEt_3, DMAP, DCM, rt, 20 min - overnight (if R_2=H)
(b) RCl or R_2O, DMAP, Py, 60 °C, overnight (if $R_2 \neq H$)

propargylic alcohol	yield$_1$[a]	protection agent	protection conditions	product	yield$_2$[a]
	74%	Boc_2O	a	 **7.7 a**	80%
		Ac_2O	a	 **7.7 b**	97%
		BzCl	a	 **7.7 c**	quant.
		PivCl	a	 **7.7 d**	99%
 **7.19 a**	46%	PivCl	a	 **7.11 a**	25%
 **7.19 b**	44%	PivCl	a	 **7.11 b**	40%

(continued on the next page)

[339] (a) Kumareswaran, R.; Shin, S.; Gallou, I.; RajanBabu, T. V. *J. Org. Chem.* **2004**, *69*, 7157-7170.
(b) Crabbé, P.; Nassim, B.; Robert-Lopes, M.-T. *Org. Synth.* **1985**, *Vol. 63*, 203. *Org. Synth.* **1990**, *Coll. Vol. 7*, 276.
[340] Horvath, A.; Backvall, J.-E. *J. Org. Chem.* **2001**, *66*, 8120-8126.

propargylic alcohol		yield$_1$[a]	protection agent	protection conditions	product		yield$_2$[a]
		44%	Ac_2O	a		**7.11 c**	89%
			PivCl	a		**7.11 d**	99%
			BzCl	a		**7.11 e**	98%
		30%	BzCl	a		**7.11 f**	99%
 dr ~1/1	**7.19 c**	57%	Ac_2O	a	 dr ~ 1/1	**7.11 g**	88%
	**7.19 d**	30%	BzCl	a		**7.11 h**	95%
		21%	Ac_2O	b		**7.11 i**	60%
		19%	Ac_2O	b		**7.11 j**	58%
			PivCl	b		**7.11 k**	22%
		51%	Ac_2O	b		**7.11 l**	91%
		29%	PivCl	b		**7.11 m**	28%
		46%	Ac_2O	b		**7.11 n**	86%
		14%	Ac_2O	b		**7.11 o**	97%

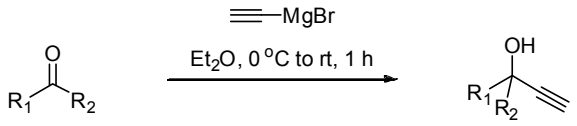
[a] Isolated yield.

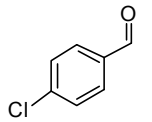
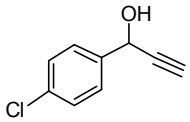
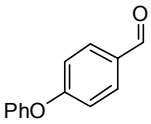
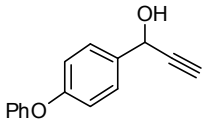
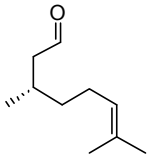
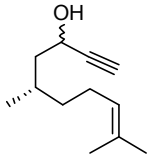
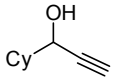
General procedure 7.1: Crabbe homologation: To a solution of propargylic alcohol (1 equiv) in THF (0.5 M) were added paraformaldehyde (2 equiv), cuprous bromide (0.5 equiv), and diisopropylamine (1.5 equiv). The resulting mixture was gently refluxed and upon completion cooled to rt and filtered through a celite plug. The filtrate was concentrated under reduced pressure and the resulting residue diluted with diethyl ether and HCl 1N solution. The ether layer was separated, and the aqueous solution was extracted twice with diethyl ether. The combined organic layers were then washed with saturated sodium chloride solution and dried over anhydrous $MgSO_4$. After removal of the ether by evaporation under reduced pressure, the crude was purified by flash column chromathography (silica gel, petroleum ether / diethyl ether) to give the expected allenol.

Acylation of the secondary alcohols: To a solution containing the secondary alcohol (1 equiv) in DCM (0.4 M) at 0 ^{o}C was added NEt_3 (2 equiv), the corresponding acylating agent (1.5 equiv of Ac_2O or 1.1 equiv of BzCl or PivCl or 1.0 equiv of Boc_2O respectively) and a catalytical amount of DMAP (0.05 equiv). The mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the protected alcohol.

Acylation of the tertiary alcohols: To a solution containing the tertiary alcohol (1 equiv) in pyridine (0.5 M) was added the corresponding acylating agent (2 equiv of Ac_2O or 1.5 equiv of PivCl respectively) and a catalytical amount of DMAP (0.1 equiv). The mixture was heated at 60 ^{o}C and followed periodically by TLC. Upon completion, the reaction was quenched with saturated aqueous HCl 1N solution and extracted twice with diethyl ether. The combined organic layers were washed with water and then brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the protected alcohol.

The propargylic alcohols **7.19 a-d** which were not commercially available were obtained by nucleophilic addition of ethynylmagnesium bromide to the corresponding carbonylic compounds under classical conditions.



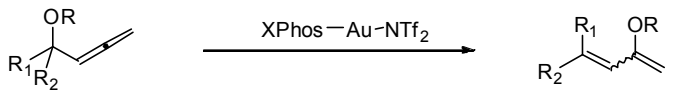
substrate	product		yield[a]
		**7.19 a**	quant.
		**7.19 b**	quant.
	 dr ~1/1	**7.19 c**	97%
		**7.19 d**	82%

[a] Isolated yield.

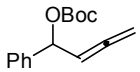
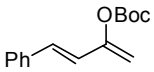
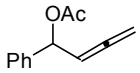
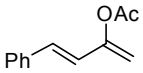
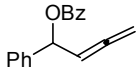
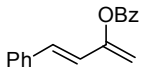
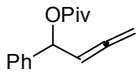
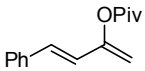
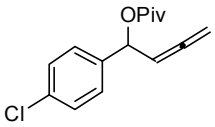
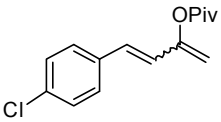
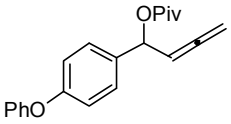
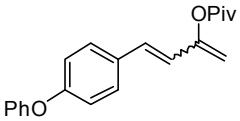
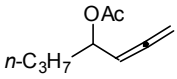
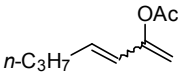
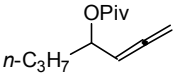
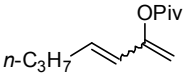
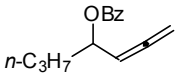
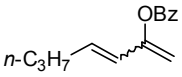
General procedure 7.2: To a solution of carbonylic compound (1 equiv) in Et_2O (0.33 M) at 0 °C was added dropwise ethynylmagnesium bromide (1.2 equiv, 0.5 M in THF solution). The mixture was allowed to slowly warm to rt and followed periodically by TLC. Upon completion (1 h), the reaction was quenched with saturated aqueous NH_4Cl solution and extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the propargylic alcohol.

7.2. Gold(I)-catalyzed formation of functionalized 1,3-butadien-2-ol esters

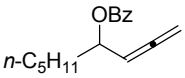
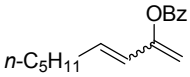
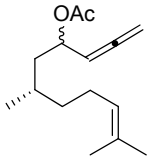
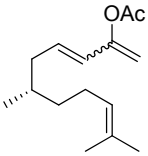
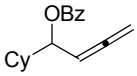
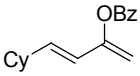
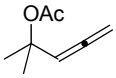
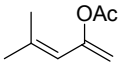
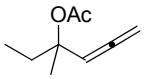
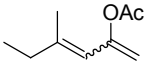
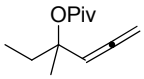
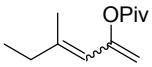
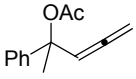
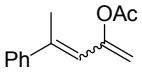
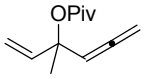
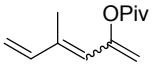
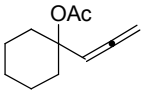
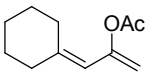
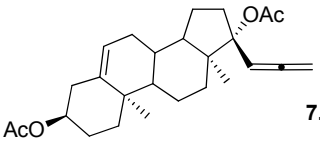
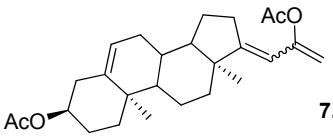
As we saw in Chapter 7, various allenyl carbinol esters **7.7 a-d** and **7.10 a-o** can be rearranged in the presence of a gold(I)-catalyst into the corresponding functionalized 1,3-butadien-2-ol esters **7.9 a-d** and **7.11 a-o**.



Conditions:
(a) DCM, rt
(b) CD_2Cl_2, rt
(c) DCM, 0 °C
(d) DCM, 40 °C
(e) DCE, 84 °C

substrate		product		conditions	time	yield[a]
	**7.7 a**		**7.9 a**	a	20 h	69%
	**7.7 b**		**7.9 b**	a	3 h	98%
	**7.7 c**		**7.9 c**	a	1 h 15 min	quant.
	**7.7 d**		**7.9 d**	a	45 min	quant.
	**7.11 a**	 *Z/E* ratio ~ 1/18	**7.12 a**	a	2 h	quant.
	**7.11 b**	 *Z/E* ratio ~ 1/8	**7.12 b**	a	8 h	78%
	**7.11 c**	 *Z/E* ratio ~ 1/7	**7.12 c**	a	3 h	quant.
	**7.11 d**	 *Z/E* ratio ~ 1/9	**7.12 d**	a	1 h	quant.
	**7.11 e**	 *Z/E* ratio ~ 1/19	**7.12 e**	a	5 min	quant.

(continued on the next page)

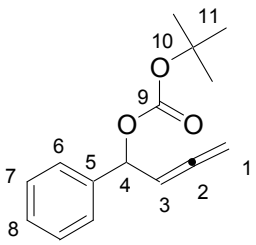
substrate		product		conditions	time	yield[a]
	**7.11 f**	 *Z/E* ratio ~ 1/15	**7.12 f**	a	40 min	quant.
 dr ~ 1/1	**7.11 g**	 *Z/E* ratio ~ 1/8	**7.12 g**	a	2 h	99%
	**7.11 h**		**7.12 h**	a	9 h	quant.
	**7.11 i**		**7.12 i**	b	5 min	quant.[b]
	**7.11 j**	 *Z/E* ratio ~ 1/1.7	**7.12 j**	a c	5 min 5 min	79% (quant.[b]) 88% (quant.[b])
	**7.11 k**	 *Z/E* ratio ~ 1/1.4	**7.12 k**	c	5 min	67% (89%[b])
	**7.11 l**	 *Z/E* ratio ~ 1/1	**7.12 l**	a d e	24 h 3 h 3 h	0%[b] 46%[b] 59%[b,c]
	**7.11 m**	 *Z/E* ratio ~ 1/2	**7.12 m**	a	10 min	53% (93%[b])
	**7.11 n**		**7.12 n**	a	5 min	quant.
	**7.11 o**	 *Z/E* ratio ~ 1/10	**7.12 o**	a	1 h	97%

[a] Isolated yield. *Z/E* ratio determined by ^{1}H NMR. [b] Yield estimated by ^{1}H NMR of the crude reaction mixture. [c] Diene **7.12 l** was isolated in the mixture with the unreacted allene **7.11 l**.

General procedure 7.3: To a solution of substrate (1 equiv) in the corresponding solvent (0.25 M: DCM for cond. a, c and d, CD_2Cl_2 for cond. b and DCE for cond. e) was added the XPhos-Au-NTf_2 (0.01 equiv). The reaction was stirred at the stated temperature (rt for cond. a and b, 0 °C for cond. c, 40 oC for cond. d and 84 °C for cond. e) and followed periodically by TLC. Upon completion, the resulting mixture was filtered through a small pad of silica pre-impregnated with dichloromethane. The pad was washed with ether and the filtrate evaporated. If necessary, the residue was purified by flash column chromatography.

7.3. Characterization of the prepared compounds

Carbonic acid *tert*-butyl ester 1-phenyl-buta-2,3-dienyl ester **7.7 a**



MF: $C_{15}H_{18}O_3$

MW: 246.30 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 96/4).

Product: Yellow oil.

Yield: 80%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.42-7.29 (m, 5H, *6*, *7* and *8*), 6.08 (dt, J = 2.2, 6.9 Hz, 1H, *4*), 5.47 (q, J = 6.8 Hz, 1H, *3*), 4.89 (m, 2H, *1*), 1.49 (s, 9H, *11*).

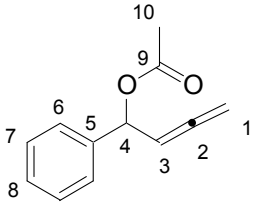
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 208.6 (*2*), 152.6 (*9*), 139.0 (*5*), 128.4 (*6* or *7*), 128.2 (*8*), 126.7 (*6* or *7*), 91.6 (*4*), 82.4 (*10*), 77.8 (*1*), 76.5 (*3*), 27.8 (*11*).

IR (ν, cm^{-1}) (CCl_4): 3066, 3033, 2981, 1958, 1742, 1473, 1456, 1367, 1270, 1165, 1084.

MS (CI^+, NH_3, m/z): 247 (MH^+), 235, 219, 203, 180, 147, 129, 90, 85, 71.

HRMS (EI^+, m/z) **:** Calculated for $C_{15}H_{18}O_3$: 246.1256.
Found for $C_{15}H_{18}O_3$: 246.1248.

Acetic acid 1-phenyl-buta-2,3-dienyl ester **7.7 b**



MF: $C_{12}H_{12}O_2$

MW: 188.22 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 96/4).

Product: Yellow oil.

Yield: 97%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.42-7.30 (m, 5H, *6*, *7* and *8*), 6.30 (dt, J = 2.3, 6.7 Hz, 1H, *4*), 5.44 (q, J = 6.6 Hz, 1H, *3*), 4.87 (m, 2H, *1*), 2.12 (s, 3H, *10*).

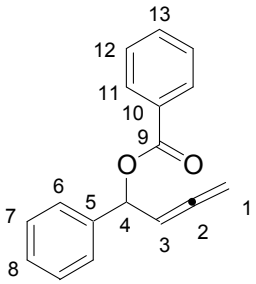
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 208.5 (*2*), 170.0 (*9*), 139.1 (*5*), 128.5 (*7*), 128.2 (*8*), 126.9 (*6*), 91.6 (*3*), 77.8 (*1*), 73.4 (*4*), 21.2 (*10*).

IR (ν, cm^{-1}) (CCl_4): 3029, 2929, 1766, 1642, 1605, 1369, 1200, 1017.

MS (CI^+, NH_3, m/z): 189 (MH^+), 164, 147, 146, 129, 119, 102.

HRMS (EI^+, m/z) **:** Calculated for $C_{12}H_{12}O_2$: 188.0837.
Found for $C_{12}H_{12}O_2$: 188.0838.

Benzoic acid 1-phenyl-buta-2,3-dienyl ester — 7.7 c



MF: $C_{17}H_{14}O_2$

MW: 250.29 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.1** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

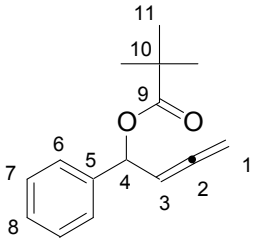
Product: Colorless oil.

Yield: Quant.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.11 (dd, J = 1.4, 7.1 Hz, 2H, *11*), 7.58 (tt, J = 1.3, 7.4 Hz, 1H, *13*), 7.48 (t, J = 7.5 Hz, 2H, *12*), 7.45 (d, J = 7.5 Hz, 2H, *6*), 7.40 (t, J = 7.0 Hz, 2H, *7*), 7.33 (t, J = 7.2 Hz, 1H, *8*), 6.56 (dt, J = 2.2, 6.7 Hz, 1H, *4*), 5.56 (q, J = 6.6 Hz, 1H, *3*), 4.90 (m, 2H, *1*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	208.7 (*2*), 165.5 (*9*), 139.3 (*5*), 133.0 (*13*), 130.3 (*10*), 129.7 (*11*), 128.5 (*7* or *12*), 128.3 (*7* or *12*), 128.2 (*8*), 126.8 (*6*), 91.7 (*3*), 77.9 (*1*), 74.0 (*4*).
IR (ν, cm^{-1}) (CCl_4)	3067, 3035, 1958, 1724, 1600, 1495, 1451, 1314, 1261, 1175, 1102, 1069, 1023.
MS (CI^+, NH_3, m/z)	251 (MH^+), 235, 219, 203, 180, 165, 146, 129, 122, 105.
HRMS (EI^+, m/z) **:**	Calculated for $C_{17}H_{14}O_2$: 250.0994. Found for $C_{17}H_{14}O_2$: 250.0985.

2,2-Dimethyl-propionic acid 1-phenyl-buta-2,3-dienyl ester **7.7 d**



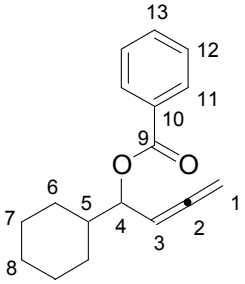
MF: $C_{15}H_{18}O_2$

MW: 230.30 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 7.1** (scale: 1 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 98/2).
Product:	Pale yellow oil.
Yield:	99%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.40-7.28 (m, 5H, *6*, *7* and *8*), 6.26 (dt, J = 2.4, 6.5 Hz, 1H, *4*), 5.41 (q, J = 6.5 Hz, 1H, *3*), 4.87 (m, 2H, *1*), 1.24 (s, 9H, *11*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	208.3 (*2*), 177.3 (*9*), 139.6 (*5*), 128.4 (*6* or *7*), 128.0 (*8*), 126.6 (*6* or *7*), 91.9 (*3*), 77.8 (*1*), 72.8 (*4*), 38.9 (*10*), 27.1 (*11*).
IR (ν, cm^{-1}) (CCl_4)	2965, 2931, 2870, 1958, 1731, 1477, 1458, 1393, 1366, 1275, 1147.
MS (CI^+, NH_3, m/z)	249 (MNH_4^+), 231 (MH^+), 219, 203, 180, 164, 146, 129, 119.
HRMS (EI^+, m/z) **:**	Calculated for $C_{15}H_{18}O_2$: 230.1307. Found for $C_{15}H_{18}O_2$: 230.1313.

Benzoic acid 1-cyclohexyl-buta-2,3-dienyl ester **7.11 h**



MF: $C_{17}H_{20}O_2$

MW: 256.34 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.1** (scale: 1.294 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil.

Yield: 95%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.07 (dd, J = 1.4, 8.0 Hz, 2H, *11*), 7.56 (tt, J = 1.4, 7.4 Hz, 1H, *13*), 7.49 (t, J = 7.9 Hz, 2H, *12*), 5.35 (tt, J = 1.7, 6.6 Hz, 1H, *4*), 5.25 (dt, J = 6.8, 7.0 Hz, 1H, *3*), 4.84 (m, 2H, *1*), 1.90-1.65 (m, 6H, *5*, *6*, *7* and/or *8*), 1.36-1.07 (m, 5H, *5*, *6*, *7* and/or *8*).

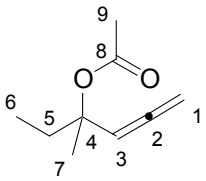
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 208.7 (*2*), 165.8 (*9*), 132.8 (*13*), 130.6 (*10*), 129.6 (*11*), 128.3 (*12*), 89.3 (*3*), 76.7 (*1*), 76.4 (*4*), 42.1 (*5*), 28.8 (*6*, *7*, or *8*), 28.4 (*6*, *7*, or *8*), 26.4 (*6*, *7*, or *8*), 26.0 (*6*, *7*, or *8*), 25.9 (*6*, *7*, or *8*).

IR (ν, cm^{-1}) (CCl_4): 2930, 2855, 1958, 1721, 1449, 1267, 1176, 1107, 1068, 1068, 1023.

MS (Cl^+, NH_3, m/z): 275 (MNH_4^+), 257 (MH^+), 249, 244, 239, 235, 227.

HRMS (EI^+, m/z) **:** Calculated for $C_{17}H_{20}O_2$: 256.1463.
Found for $C_{17}H_{20}O_2$: 256.1457.

Acetic acid 1-ethyl-1-methyl-buta-2,3-dienyl ester — 7.11 j



MF: $C_9H_{14}O_2$

MW: 154.21 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.1** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 97/3).

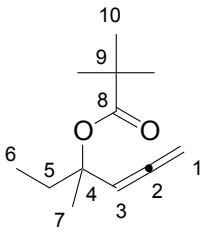
Product: Yellow oil.

Yield: 58%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.56 (t, J = 6.7 Hz, 1H, *3*), 4.88 (d, J = 3.1 Hz, 1H, *1*), 4.86 (d, J = 2.9 Hz, 1H, *1*), 2.00 (s, 3H, *9*), 1.97-1.78 (m, 2H, *5*), 1.50 (s, 3H, *7*), 0.91 (t, J = 7.4 Hz,

	3H, *6*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	207.2 (*2*), 170.1 (*8*), 95.7 (*3*), 81.8 (*4*), 77.8 (*1*), 32.8 (*5*), 23.5 (*7*), 22.2 (*9*), 8.2 (*6*).
IR (ν, cm^{-1}) (CCl_4)	2976, 2936, 1956, 1736, 1457, 1368, 1247, 1125, 1013.
MS (CI^+, NH_3, m/z)	155 (MH^+), 145, 143, 130, 127.
HRMS (EI^+, m/z) **:**	Calculated for $C_9H_{14}O_2$: 154.0994. Found for $C_9H_{14}O_2$: 154.0991.

Acetic acid 1-ethyl-1-methyl-buta-2,3-dienyl ester 7.11 k

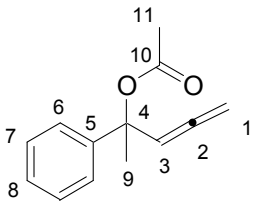


MF: $C_{12}H_{20}O_2$

MW: 196.29 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 7.1** (scale: 1 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 98/2).
Product:	Yellow oil.
Yield:	22%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.51 (t, J = 6.7 Hz, 1H, *3*), 4.87 (d, J = 6.8 Hz, 1H, *1*), 4.86 (d, J = 6.7 Hz, 1H, *1*), 1.98-1.77 (m, 2H, *5*), 1.49 (s, 3H, *7*), 1.17 (s, 9H, *10*), 0.91 (t, J = 7.5 Hz, 3H, *6*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	207.1 (*2*), 177.4 (*8*), 96.0 (*3*), 80.9 (*4*), 77.7 (*1*), 39.3 (*9*), 32.9 (*5*), 27.2 (*10*), 23.6 (*7*), 8.1 (*6*).
IR (ν, cm^{-1}) (CCl_4)	2974, 2934, 1956, 1810, 1726, 1477, 1458, 1283, 1165, 1120, 1037, 1005.
MS (CI^+, NH_3, m/z)	197 (MH^+), 183, 180, 169, 160, 143, 130, 127.
HRMS (EI^+, m/z) **:**	Calculated for $C_{12}H_{20}O_2$: 196.1463. Found for $C_{12}H_{20}O_2$: 196.1456.

Acetic acid 1-methyl-1-phenyl-buta-2,3-dienyl ester 7.11 l



MF: $C_{13}H_{14}O_2$

MW: 202.25 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 7.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O/NEt_3 98/2/2).

Product: Yellow oil.

Yield: 91%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.39 (dd, J = 1.6, 7.1 Hz, 2H, *6*), 7.35 (t, J = 7.2 Hz, 2H, *7*), 7.26 (tt, J = 1.6, 7.1 Hz, 1H, *8*), 6.01 (t, J = 6.7 Hz, 1H, *3*), 4.97 (d, J = 6.7 Hz, 1H, *1*), 4.96 (d, J = 6.6 Hz, 1H, *1*), 2.09 (s, 3H, *11*), 1.78 (s, 3H, *9*).

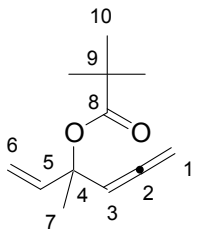
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 208.1 (*2*), 169.5 (*10*), 144.7 (*5*), 128.2 (*7*), 127.2 (*8*), 124.6 (*6*), 95.7 (*3*), 81.6 (*4*), 78.3 (*1*), 27.9 (*9*), 22.2 (*11*).

IR (ν, cm^{-1}) (CCl_4): 3062, 3029, 2989, 2936, 1956, 1744, 1493, 1445, 1367, 1240, 1061, 1011.

MS (CI^+, NH_3, m/z): 203 (MH^+).

HRMS (EI^+, m/z) **:** Calculated for $C_{13}H_{14}O_2$: 202.0994.
Found for $C_{13}H_{14}O_2$: 202.1000.

2,2-Dimethyl-propionic acid 1-methyl-1-vinyl-buta-2,3-dienyl ester 7.11 m



MF: $C_{12}H_{18}O_2$

MW: 194.27 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 7.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O/NEt_3 98/2/2).

Product: Yellow oil.

Yield: 28%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.06 (dd, J = 10.8, 17.4 Hz, 1H, *5*), 5.64 (t, J = 6.7 Hz, 1H, *3*), 5.26 (dd, J = 0.8, 17.4 Hz, 1H, *6*), 5.13 (dd, J = 0.8, 10.8 Hz, 1H, *6*), 4.91 (dd, J = 1.3, 6.8 Hz, 2H, *1*), 1.58 (s, 3H, *7*), 1.19 (s, 9H, *10*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 207.5 (*2*), 177.0 (*8*), 141.2 (*5*), 113.2 (*6*), 95.1 (*3*), 79.4 (*4*), 78.1 (*1*), 39.1 (*9*), 27.1 (*10*), 24.0 (*7*).

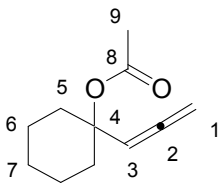
IR (ν, cm^{-1}) (CCl_4): 2975, 2933, 2872, 1956, 1730, 1477, 1368, 1283, 1156, 1091.

MS (CI^+, NH_3, m/z): 195 (MH^+), 179, 169, 157, 151, 137, 119.

HRMS (EI^+, m/z) **:** Calculated for $C_{12}H_{18}O_2$: 194.1307.

Found for $C_{12}H_{18}O_2$: 194.1309.

Acetic acid 1-propa-1,2-dienyl-cyclohexyl ester **7.11 n**



MF: $C_{11}H_{16}O_2$

MW: 180.24 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil.

Yield: 86%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.65 (t, J = 6.7 Hz, 1H, *3*), 4.86 (d, J = 6.7 Hz, 2H, *1*), 2.11 (m, 2H, *5*), 2.02 (s, 3H, *9*), 1.71 (m, 2H, *5*), 1.59-1.46 (m, 5H, *6* and *7*), 1.35 (m, 1H, *7*).

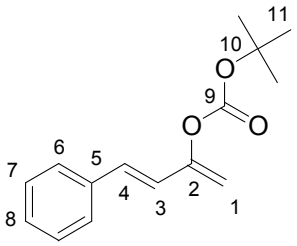
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 207.7 (*2*), 170.1 (*8*), 95.6 (*3*), 80.7 (*4*), 77.7 (*1*), 35.3 (*5*), 25.6 (*7*), 22.2 (*6* and *9*).

IR (ν, cm^{-1}) (CCl_4): 2936, 2859, 1954, 1735, 1447, 1365, 1257, 1237, 1133, 1016.

MS (CI^+, NH_3, m/z): 198 (MNH_4^+), 181 (MH^+).

HRMS (EI^+, m/z) **:** Calculated for $C_{11}H_{16}O_2$: 180.1150.
Found for $C_{11}H_{16}O_2$: 180.1159.

Carbonic acid tert-butyl ester (*E*)-1-methylene-3-phenyl-allyl ester **7.9 a**



MF: $C_{15}H_{18}O_3$

MW: 246.30 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.3 a** (scale: 0.25 mmol).

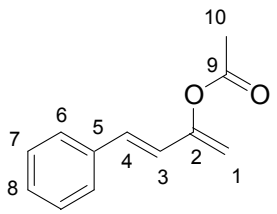
Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Colorless oil.

Yield: 69%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.41 (d, J = 7.1 Hz, 2H, *6*), 7.33 (t, J = 7.1 Hz, 2H, *7*), 7.26 (t, J = 7.1 Hz, 1H, *8*), 6.71 (d, J = 16.0 Hz, 1H, *4*), 6.63 (d, J = 16.0 Hz, 1H, *3*), 5.08 (d, J = 1.7 Hz, 1H, *1*), 5.06 (d, J = 1.7 Hz, 1H, *1*), 1.55 (s, 9H, *11*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.2 (*2*), 151.2 (*9*), 136.0 (*5*), 129.9 (*4*), 128.6 (*7*), 128.2 (*8*), 126.9 (*6*), 122.5 (*3*), 105.5 (*1*), 83.3 (*10*), 27.7 (*11*).
IR (ν, cm^{-1}) (CCl_4)	3063, 2981, 2929, 1799, 1746, 1635, 1453, 1370, 1247, 1153, 1122, 1082.
HRMS (EI^+, m/z) **:**	Calculated for $C_{15}H_{18}O_3$: 246.1256. Found for $C_{15}H_{18}O_3$: 246.1260.

Acetic acid (*E*)-1-methylene-3-phenyl-allyl ester **7.9 b**



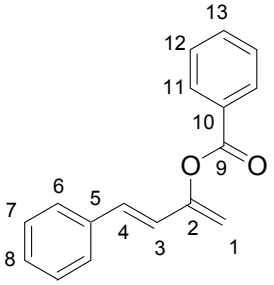
MF: $C_{12}H_{12}O_2$

MW: 188.22 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 7.3 a** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 96/4).
Product:	Pale yellow crystals.
Yield:	98%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.40 (d, J = 7.2 Hz, 2H, *6*), 7.32 (t, J = 7.1 Hz, 2H, *7*), 7.25 (t, J = 7.3 Hz, 1H, *8*), 6.64 (d, J = 16.0 Hz, 1H, *3*), 6.60 (d, J = 16.0 Hz, 1H, *4*), 5.12 (d, J = 1.5 Hz, 1H, *1*), 4.97 (d, J = 1.5 Hz, 1H, *1*), 2.29 (s, 3H, *10*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	168.7 (*9*), 151.8 (*2*), 135.9 (*5*), 129.8 (*4*), 128.6 (*7*), 128.2 (*8*), 126.8 (*6*), 122.5 (*3*), 106.1 (*1*), 20.9 (*10*).
IR (ν, cm^{-1}) (CCl_4)	3066, 3034, 1958, 1743, 1369, 1231, 1018.
MS (CI^+, NH_3, m/z)	189 (MH^+), 164, 147, 146.
HRMS (EI^+, m/z) **:**	Calculated for $C_{12}H_{12}O_2$: 188.0837. Found for $C_{12}H_{12}O_2$: 188.0835.

Benzoic acid (*E*)-1-methylene-3-phenyl-allyl ester **7.9 c**



MF: $C_{17}H_{14}O_2$

MW: 250.29 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.3 a** (scale: 0.25 mmol).

Purification: No purification necessary.

Product: White crystals.

Yield: Quant.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 8.22 (dd, J = 1.4, 7.1 Hz, 2H, *11*), 7.64 (tt, J = 1.1, 7.4 Hz, 1H, *13*), 7.52 (t, J = 7.8 Hz, 2H, *12*), 7.38 (d, J = 7.2 Hz, 2H, *6*), 7.30 (t, J = 7.0 Hz, 2H, *7*), 7.23 (t, J = 7.1 Hz, 1H, *8*), 6.76 (d, J = 16.0 Hz, 1H, *3*), 6.66 (d, J = 16.0 Hz, 1H, *4*), 5.24 (d, J = 1.3 Hz, 1H, *1*), 5.10 (d, J = 1.4 Hz, 1H, *1*).

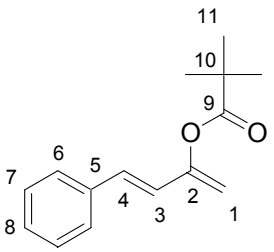
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 163.4 (*9*), 151.1 (*2*), 134.9 (*5*), 132.6 (*13*), 129.1 (*11*), 129.0 (*4*), 128.4 (*10*), 127.6 (*7* or *12*), 127.5 (*7* or *12*), 127.2 (*8*), 125.9 (*6*), 121.6 (*3*), 105.3 (*1*).

IR (ν, cm^{-1}) (CCl_4): 3063, 3035, 2927, 1741, 1641, 1604, 1450, 1239, 1175, 1088.

MS (CI^+, NH_3, m/z): 251 (MH^+), 219, 146.

HRMS (EI^+, m/z) **:** Calculated for $C_{17}H_{14}O_2$: 250.0994.
Found for $C_{17}H_{14}O_2$: 250.0994.

2,2-Dimethyl-propionic acid (*E*)-1-methylene-3-phenyl-allyl ester 7.9 d



MF: $C_{15}H_{18}O_2$

MW: 230.30 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.3 a** (scale: 0.25 mmol).

Purification: No purification necessary.

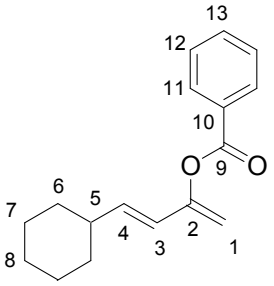
Product: White crystals.

Yield: Quant.

^{1}H NMR (δ, ppm): 7.37 (d, J = 7.2 Hz, 2H, *6*), 7.31 (t, J = 7.1 Hz, 2H, *7*), 7.24 (t, J = 7.1 Hz, 1H,

($CDCl_3$, 400 MHz)	*8*), 6.66 (d, J = 16.0 Hz, 1H, *3*), 6.58 (d, J = 16.0 Hz, 1H, *4*), 5.11 (d, J = 1.3 Hz, 1H, *1*), 4.92 (d, J = 1.5 Hz, 1H, *1*), 1.37 (s, 9H, *11*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	176.2 (*9*), 152.0 (*2*), 136.0 (*5*), 129.6 (*4*), 128.6 (*7*), 128.1 (*8*), 126.8 (*6*), 122.9 (*3*), 105.8 (*1*), 39.2 (*10*), 27.2 (*11*).
IR (ν, cm^{-1}) (CCl_4)	3028, 2974, 2932, 2872, 1809, 1753, 1641, 1608, 1479, 1454, 1260, 1121.
MS (CI^+, NH_3, m/z)	249 (MNH_4^+), 231 (MH^+), 219, 204, 180, 147, 146, 119, 102, 90.
HRMS (EI^+, m/z) **:**	Calculated for $C_{15}H_{18}O_2$: 230.1307. Found for $C_{15}H_{18}O_2$: 230.1299.

Benzoic acid (*E*)-3-cyclohexyl-1-methylene-allyl ester **7.12 h**



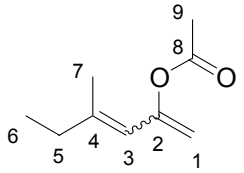
MF: $C_{17}H_{20}O_2$

MW: 256.34 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 7.3 a** (scale: 0.25 mmol).
Purification:	No purification necessary.
Product:	Pale yellow oil.
Yield:	Quant.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	8.17 (d, J = 7.3 Hz, 2H, *11*), 7.63 (t, J = 7.3 Hz, 1H, *13*), 7.51 (t, J = 7.8 Hz, 2H, *12*), 6.03 (dd, J = 0.8, 15.7 Hz, 1H, *3*), 5.80 (dd, J = 6.7, 15.7 Hz, 1H, *4*), 5.02 (d, J = 0.6 Hz, 1H, *1*), 4.91 (d, J = 0.9 Hz, 1H, *1*), 2.04 (m, 1H, *5*), 1.80-1.60 (m, 5H, *6*, *7* and/or *8*), 1.35-1.03 (m, 5H, *6*, *7* and/or *8*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	164.4 (*9*), 152.3 (*2*), 138.3 (*4*), 133.3 (*13*), 130.0 (*11*), 129.6 (*10*), 128.5 (*12*), 121.6 (*3*), 103.8 (*1*), 40.2 (*5*), 32.4 (*6* or *7*), 26.0 (*8*), 25.9 (*6* or *7*).
IR (ν, cm^{-1}) (CCl_4)	2927, 2853, 1656, 1606, 1449, 1239, 1176, 1090, 1023.
MS (CI^+, NH_3, m/z)	275 (MNH_4^+), 257 (MH^+), 249, 243, 239, 235, 232, 226, 223.
HRMS (EI^+, m/z) **:**	Calculated for $C_{17}H_{20}O_2$: 256.1463. Found for $C_{17}H_{20}O_2$: 256.1470.

Acetic acid 3-methyl-1-methylene-pent-2-enyl ester **7.12 j**



MF: $C_9H_{14}O_2$

MW: 154.21 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.3 c** (scale: 0.25 mmol).

Purification: No purification necessary.

Product: Yellow oil.

Yield: 88% (isolated as a mixture of *Z*/*E* isomers ~ 1/1.7).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) For the mixture of *Z*/*E* isomers: 5.62 (s, 1H, *E* isomer, *3*), 5.60 (s, 1H, *Z* isomer, *3*), 4.83 (m, 2H, both isomers, *1*), 2.28 (q, J = 7.6 Hz, 2H, *Z* isomer, *5*), 2.16 (s, 3H, *E* isomer, *9*), 2.15 (s, 3H, *Z* isomer, *9*), 2.08 (d, J = 7.4 Hz, 2H, *E* isomer, *5*), 1.85 (d, J = 0.9 Hz, 3H, *E* isomer, *7*), 1.79 (d, J = 1.4 Hz, 3H, *Z* isomer, *7*), 1.04 (t, J = 7.8 Hz, 3H, *Z* isomer, *6*), 1.02 (t, J = 7.5 Hz, 3H, *E* isomer, *6*).

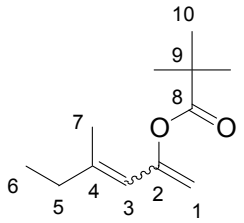
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) *Z* isomer: 169.0 (*8*), 151.6 (*2*), 144.9 (*4*), 118.8 (*3*), 104.1 (*1*), 26.1 (*5*), 23.8 (*7*), 21.1 (*9*), 12.6 (*6*).
E isomer: 169.1 (*8*), 152.1 (*2*), 144.3 (*4*), 118.7 (*3*), 104.4 (*1*), 33.4 (*5*), 21.1 (*9*), 18.0 (*7*), 12.2 (*6*).

IR (ν, cm^{-1}) (CCl_4) For the mixture of *Z*/*E* isomers: 2968, 2934, 2877, 1760, 1651, 1369, 1202, 1161, 1016.

MS (CI^+, NH_3, m/z) 155 (MH^+), 130, 113.

HRMS (EI^+, m/z) **:** Calculated for $C_9H_{14}O_2$: 154.0994.
Found for $C_9H_{14}O_2$: 154.0998.

Acetic acid 3-methyl-1-methylene-pent-2-enyl ester 7.12 k



MF: $C_{12}H_{20}O_2$

MW: 196.29 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.3 c** (scale: 0.183 mmol).

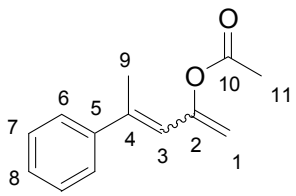
Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil.

Yield: 67% (isolated as a mixture of *Z*/*E* isomers ~ 1/1.4).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	For the mixture of *Z*/*E* isomers: 5.56 (s, 1H, *E* isomer, *3*), 5.54 (s, 1H, *Z* isomer, *3*), 4.80 (m, 2H, both isomers, *1*), 2.31 (q, J = 7.6 Hz, 2H, *Z* isomer, *5*), 2.09 (d, J = 7.4 Hz, 2H, *E* isomer, *5*), 1.86 (d, J = 1.1 Hz, 3H, *E* isomer, *7*), 1.79 (d, J = 1.4 Hz, 3H, *Z* isomer, *7*), 1.27 (s, 9H, *E* isomer, *10*), 1.26 (s, 9H, *Z* isomer, *10*), 1.04 (t, J = 7.6 Hz, 3H, *Z* isomer, *6*), 1.03 (t, J = 7.4 Hz, 3H, *E* isomer, *6*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	*Z* isomer: 176.9 (*8*), 152.1 (*2*), 145.0 (*4*), 118.9 (*3*), 103.5 (*1*), 38.9 (*9*), 27.0 (*10*), 26.1 (*5*), 23.6 (*7*), 12.6 (*6*). *E* isomer: 176.8 (*8*), 152.6 (*2*), 144.6 (*4*), 117.9 (*3*), 104.0 (*1*), 38.8 (*9*), 33.3 (*5*), 27.1 (*10*), 18.3 (*7*), 12.3 (*6*).
IR (ν, cm^{-1}) (CCl_4)	For the mixture of *Z*/*E* isomers: 2970, 2933, 2874, 1745, 1647, 1477, 1458, 1394, 1369, 1262, 1213, 1127, 1030.
MS (CI^+, NH_3, m/z)	197 (MH^+).
HRMS (EI^+, m/z) **:**	Calculated for $C_{12}H_{20}O_2$: 196.1463. Found for $C_{12}H_{20}O_2$: 196.1471.

Acetic acid 1-methylene-3-phenyl-but-2-enyl ester 7.12 l



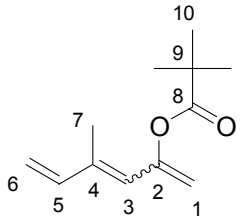
MF: $C_{13}H_{14}O_2$

MW: 202.25 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 7.3 e** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 98/2).
Product:	Product isolated in mixture with the unreacted allene **10l**.
Yield:	59% (estimated, mixture of *Z*/*E* isomers ~ 1/1).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	For the mixture of *Z*/*E* isomers: 7.48-7.20 (m, 5H, both isomers, *6*, *7* and *8*), 6.16 (s, 1H, *E* isomer, *3*), 6.05 (s, 1H, *Z* isomer, *3*), 5.04 (s, 2H, *E* isomer, *1*), 4.89 (s, 1H, *Z* isomer, *1*), 4.72 (s, 1H, *Z* isomer, *1*), 2.30 (s, 3H, *E* isomer, *9*), 2.22 (s, 3H, *Z* or *E* isomer, *11*), 2.09 (s, 3H, *Z* isomer, *9*), 1.32 (s, 3H, *Z* or *E* isomer, *11*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	For the mixture of *Z*/*E* isomers: 169.0 (*Z* or *E* isomer, *10*), 168.7 (*Z* or *E* isomer, *10*), 151.9 (*E* isomer, *2*), 151.4 (*Z* isomer, *2*), 143.2 (*E* isomer, *4*), 141.7 (*Z* isomer, *4*), 140.4 (*E* isomer, *5*), 140.3 (*Z* isomer, *5*), 128.2 (*Z* or *E* isomer, *6* or *7*), 127.9 (*Z* or *E* isomer, *6* or *7*), 127.7 (*Z* or *E* isomer, *6* or *7*), 127.6 (*Z* or *E* isomer, *8*), 126.8 (*Z* or *E* isomer, *8*), 126.0 (*Z* or *E* isomer, *6* or *7*), 121.5 (*E* isomer, *3*), 120.0 (*Z* isomer, *3*), 106.4 (*E* isomer, *1*), 105.8 (*Z* isomer, *1*), 27.6 (*Z* isomer, *9*), 21.1 (*Z* or *E* isomer, *11*), 19.6 (*Z* or *E* isomer, *11*), 17.7 (*Z* isomer, *9*).

2,2-Dimethyl-propionic acid 3-methyl-1-methylene-penta-2,4-dienyl ester **7.12 m**



MF: $C_{12}H_{18}O_2$

MW: 194.27 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 7.3 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil.

Yield: 53% (isolated as a mixture of *Z*/*E* isomers ~ 1/2).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the mixture of *Z*/*E* isomers: 7.07 (ddd, J = 0.8, 10.9, 17.5 Hz, 1H, *E* isomer, *5*), 6.38 (ddd, J = 0.7, 10.6, 17.3 Hz, 1H, *Z* isomer, *5*), 5.81 (s, 1H, *Z* isomer, *3*), 5.75 (d, J = 0.7 Hz, 1H, *E* isomer, *3*), 5.35 (d, J = 17.5 Hz, 1H, *E* isomer, *6*), 5.31 (d, J = 17.3 Hz, 1H, *Z* isomer, *6*), 5.21 (dt, J = 1.5, 10.9 Hz, 1H, *E* isomer, *6*), 5.14 (d, J = 10.6 Hz, 1H, *Z* isomer, *6*), 4.95 (d, J = 5.8 Hz, 1H, *Z* isomer, *1*), 4.91 (d, J = 5.8 Hz, 1H, *E* isomer, *1*), 1.98 (d, J = 1.2 Hz, 3H, *Z* isomer, *7*), 1.91 (d, J = 1.4 Hz, 3H, *E* isomer, *7*), 1.29 (s, 9H, *Z* isomer, *10*), 1.27 (s, 9H, *E* isomer, *10*).

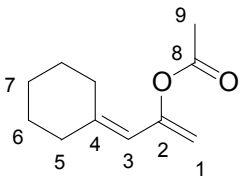
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): *Z* isomer: 176.7 (*8*), 151.9 (*2*), 141.0 (*5*), 138.3 (*4*), 125.0 (*3*), 114.7 (*6*), 106.4 (*1*), 38.9 (*9*), 27.1 (*10*), 13.2 (*7*).
E isomer: 176.6 (*8*), 151.4 (*2*), 137.8 (*4*), 134.6 (*5*), 123.1 (*3*), 116.4 (*6*), 106.3 (*1*), 39.0 (*9*), 27.0 (*10*), 13.3 (*7*).

IR (ν, cm^{-1}) (CCl_4): For the mixture of *Z*/*E* isomers: 2974, 2932, 2872, 1748, 1639, 1479, 1262, 1239, 1124.

MS (CI^+, NH_3, m/z): 203 (MNH_4^+), 195 (MH^+), 188, 180, 169, 162.

HRMS (EI^+, m/z) **:** Calculated for $C_{12}H_{18}O_2$: 194.1307.
Found for $C_{12}H_{18}O_2$: 194.1306.

Acetic acid 1-cyclohexylidenemethyl-vinyl ester **7.12 n**



MF: $C_{11}H_{16}O_2$

MW: 180.27 g.mol^{-1}

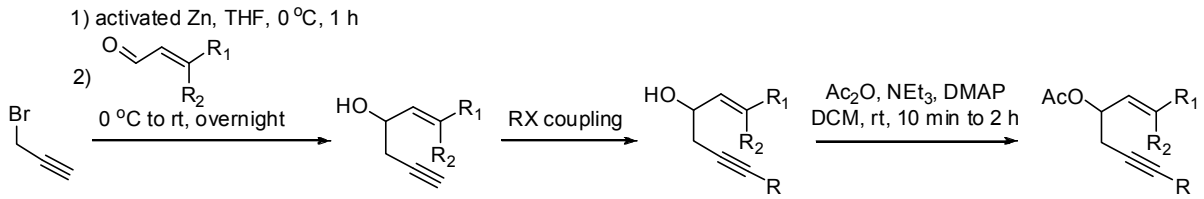
Reaction: The reaction was carried out according to the **General Procedure 7.3 a** (scale: 0.25 mmol).

Purification:	No purification necessary.
Product:	Yellow oil.
Yield:	Quant.
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.59 (d, J = 6.7 Hz, 1H, *3*), 4.82 (d, J = 1.2 Hz, 1H, *1*), 4.80 (s, 1H, *1*), 2.40 (m, 2H, *5*), 2.15 (s, 3H, *9*), 2.13 (m, 2H, *5*), 1.60-1.55 (m, 6H, *6* and *7*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	169.0 (*8*), 151.7 (*2*), 147.1 (*4*), 116.0 (*3*), 104.5 (*1*), 37.7 (*5*), 29.9 (*5*), 28.4 (*6* or *7*), 27.6 (*6* or *7*), 26.4 (*6* or *7*), 21.0 (*9*).
IR (ν, cm^{-1}) (CCl_4)	2931, 2855, 1760, 1688, 1654, 1619, 1445, 1368, 1201, 1169, 1015.
MS (CI^+, NH_3, m/z)	198 (MNH_4^+), 181 (MH^+), 169, 153, 145, 139, 127.
HRMS (EI^+, m/z) **:**	Calculated for $C_{11}H_{16}O_2$: 180.1150. Found for $C_{11}H_{16}O_2$: 180.1144.

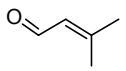
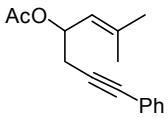
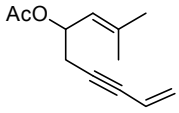
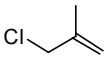
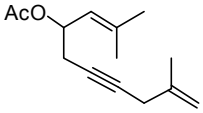
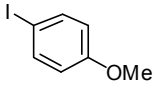
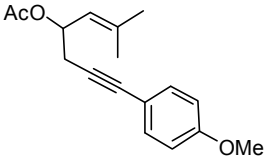
8. Gold(I)-catalyzed 5-*endo* hydroxy-and alkoxycyclization of 1,5-enynes: an efficient access to functionalized cyclopentenes

8.1. Synthesis of the precursors

Substrates **8.3**, **8.8 a-j** and **8.8 l-m** were all prepared in a 3-step sequence involving: (i) a zinc mediated propargylation of an α,β-unsaturated aldehyde,[341] (ii) a Sonogashira coupling[326] (in the case of vinylic, alkynic or arylic halides) or a copper(I)-mediated allylation[342] (in the case of allylic halides) and (iii) an acetylation of the secondary alcohol under classical conditions. It is also worth mentioning that the last 2 steps (the RX coupling and the acetylation step) can usually be performed in any order, with the exception of substrates **8.8 f** and **m**, where it seems to be important to perform the copper(I)-allylation on the free alcohol in order to prevent the isomerization of the nearby double bond.

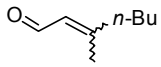
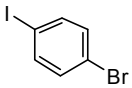
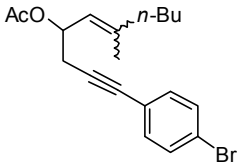
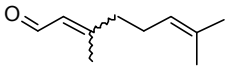
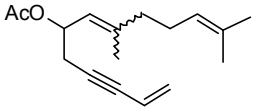
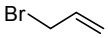
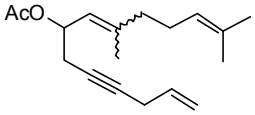
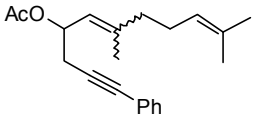
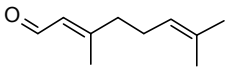
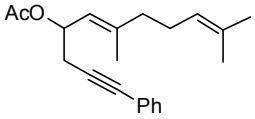
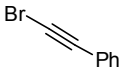
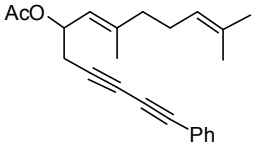
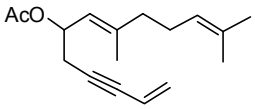
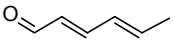
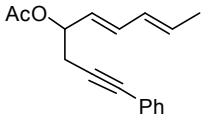
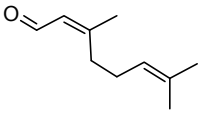
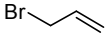
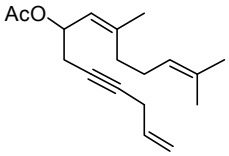


Coupling conditions: (a) $PdCl_2(PPh_3)_2$, CuI, NEt_3, rt, overnight (if RX = vinylic, alkynic or arylic halide)
(b) CuI, TBAB, K_2CO_3, NaI, DMF, rt, overnight (if RX = allylic halide)

aldehyde	RX	conditions for RX coupling	product		yield[a]
	PhI	**a**		**8.3**	47%
		a		**8.8 a**	57%
		**b**		**8.8 b**	60%
		**a**		**8.8 c**	58%

(continued on the next page)

[341] Yang, Z.-Q.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 9602-9603.
[342] Betancort, J. M.; Martin, T.; Palazon, J. M.; Martin, V. S. *J. Org. Chem.* **2003**, *68*, 3216-3224.

aldehyde	RX	conditions for RX coupling	product		yield[a]
		**a**	 *Z*/*E* ratio ~ 1/2	**8.8 d**	40%
		**a**	 *Z*/*E* ratio ~ 1/1,5	**8.8 e**	46%
		**b**	 *Z*/*E* ratio ~ 1/2	**8.8 f**	49%
	PhI	**a**	 *Z*/*E* ratio ~ 1/1.5	**8.8 g**	54%
	PhI	**a**		**8.8 h**	56%
		**a**		**8.8 i**	42%
		a		**8.8 l**	41%
	PhI	**a**		**8.8 j**	60%
		**b**		**8.8 m**	56%

[a] Isolated yield (over 3 steps).

General procedure 8.1: Zn(II)-mediated propargylation: To a suspension of previously activated Zn

(2 equiv) in THF (1 M) at 0 °C was added propargyl bromide (1.5 equiv, 80% wt. toluene solution). The suspension was stirred at 0 °C for 1 h, then the α,β-unsaturated aldehyde (1 equiv) was added and the suspension was allowed to slowly reach rt overnight. The reaction was quenched with saturated aqueous NH_4Cl solution, filtered and the filtrate extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected coupling product.

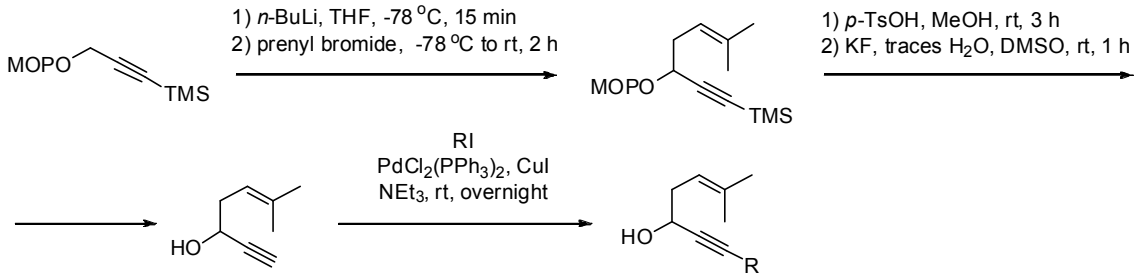
Pd(II)-catalyzed Sonogashira coupling: To a solution containing the terminal alkyne (1 equiv) in NEt_3 (0.25 M) were added the corresponding halide derivative (1.2 equiv), $PdCl_2(PPh_3)_2$ (0.02 equiv) and CuI (0.02 equiv). The mixture was stirred overnight at rt. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected coupling product.

Cu(I)-mediated allylation: To a solution containing the terminal alkyne (1 equiv) in DMF (1 M) were added K_2CO_3 (2.8 equiv), TBAB (0.15 equiv) and CuI (0.10 equiv) and the mixture was stirred at rt for 1 h. The corresponding allylic halide was then added (5 equiv) along with NaI (0.2 equiv). The reaction was allowed to react at rt overnight. Upon completion, the reaction was quenched with water and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the coupling product.

Acetylation of the secondary alcohol group: To a solution of secondary alcohol (1 equiv) in DCM (0.4 M) were added NEt_3 (2 equiv), Ac_2O (1.5 equiv) and DMAP (0.1 equiv). The mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected acetylated product.

Substrate **8.8 k** is obtained from enyne **8.3** by carbocation reduction in $Et_3SiH/HNTf_2$ conditions.

Enynes **8.16 a** and **b** were synthesized in four step according to a procedure developed by Malacria et al.,[343] by allylation of the starting [3-(1-methoxy-1-methyl-ethoxy)-prop-1-ynyl]-trimethyl-silane followed by removal of the protecting MOP and TMS groups and Sonogashira coupling with the corresponding aryl iodide.

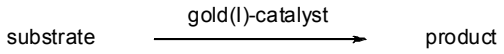


8.16 a (R = Ph) : 22% (over 4 steps)
8.16 b (R = *p*-MeO-C_6H_4) : 30% (over 4 steps)

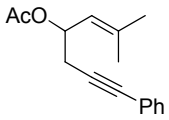
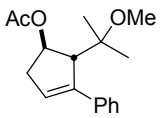
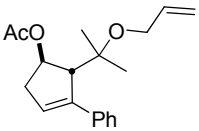
Enyne **8.20** is the intermediate formed during the synthesis of substrate **8.8 m** after the first two steps (the zinc mediated propargylation and the copper-catalyzed cross-coupling).

8.2. Gold(I)-catalyzed formation of functionalized cyclopentenes

As we saw in Chapter 8, various functionalized cyclopentenes can be obtained from the corresponding 1,5-enynes via a gold catalyzed 5-*endo* hydroxy-and alkoxycyclization.

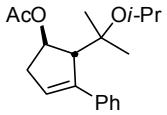
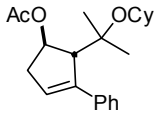
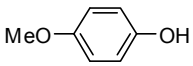
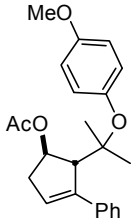
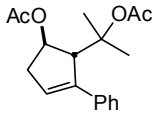
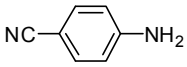
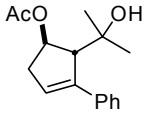
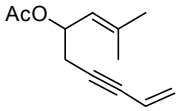
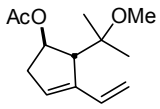
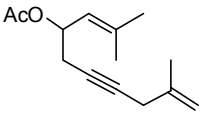
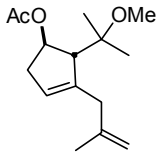
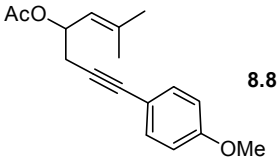
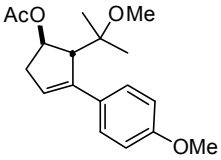


Conditions:
(a) 1% XPhos-Au-NTf_2, DCM/NuH (10/1), rt
(b) 1% XPhos-Au-NTf_2, NuH (2 equiv), DCM, rt
(c) 1% XPhos-Au-NTf_2, DCM/acetone/H_2O (8/2/1), rt
(d) 1% XPhos-Au-NTf_2, DCM/NuH (10/1), reflux
(e) 2% XPhos-Au-NTf_2, DCM/acetone/H_2O (8/2/1), rt
(f) 2% XPhos-Au-NTf_2, DCM/acetone/H_2O (8/2/1), reflux

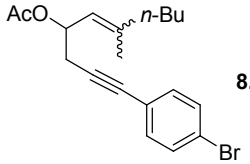
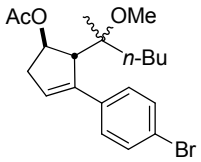
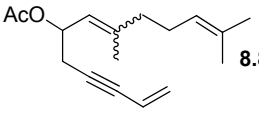
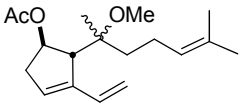
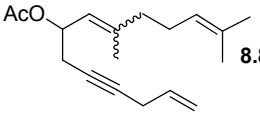
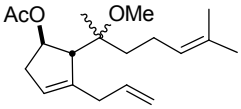
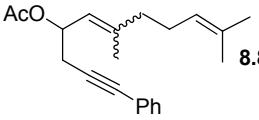
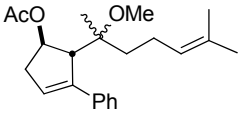
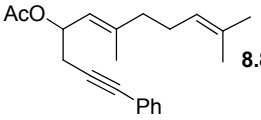
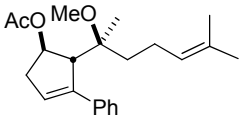
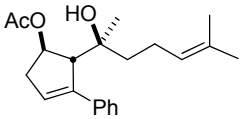
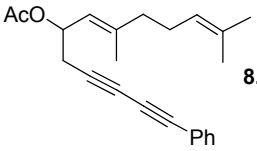
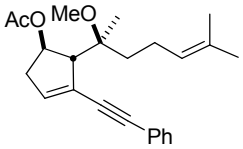
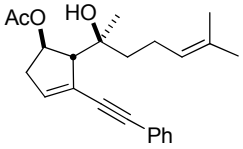
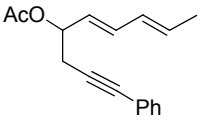
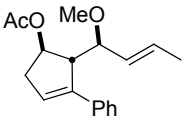
substrate		nucleophile	product		conditions	time	yield[a]
	**8.3**	MeOH		**8.4 a**	a	20 min	99%
				**8.4 b**	a	2 h	93%

(continued on the next page)

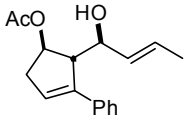
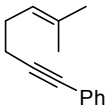
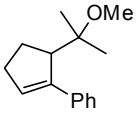
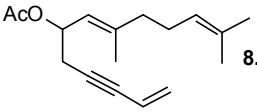
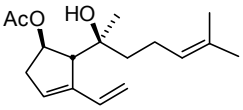
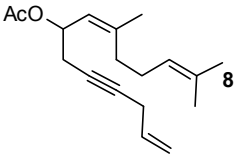
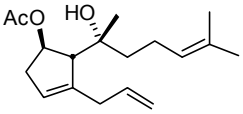
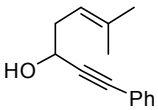
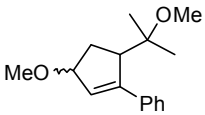
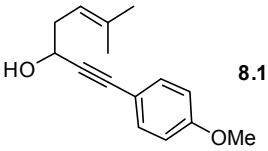
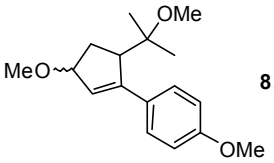
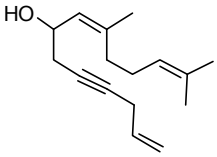
[343] Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouries, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656-8657.

substrate	nucleophile	product	conditions	time	yield[a]
	i-PrOH	 **8.4 c**	a	45 min	98%
	CyOH	 **8.4 d**	a	24 h	54%
	t-BuOH	no reaction	a	24 h	-
		 **8.4 e**	b	10 min	95%
	AcOH	 **8.4 f**	a	1 h 15 min	68%[b]
		no reaction	b	24 h	-
	H_2O	 **8.4 g**	c	4 h 30 min	quant.
 **8.8 a**	MeOH	 **8.9 a**	a	1 h 20 min	77%
 **8.8 b**	MeOH	 **8.9 b**	a	24 h	87%
 **8.8 c**	MeOH	 **8.9 c**	a	20 min	93%

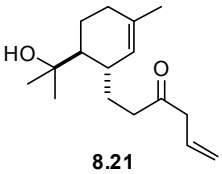
(continued on the next page)

substrate	nucleophile	product	conditions	time	yield[a]
 **8.8 d**	MeOH	 **8.9 d**	a	1 h	65%
Z/*E* ratio ~ 1/2		dr ~ 1/2			
 **8.8 e**	MeOH	 **8.9 e**	a	6 h	78%
Z/*E* ratio ~ 1/1.5		dr ~ 1/1.5			
 **8.8 f**	MeOH	 **8.9 f**	a	6 h	64%
Z/*E* ratio ~ 1/2		dr ~ 1/1.5			
 **8.8 g**	MeOH	 **8.9 g**	a	1 h	90%
Z/*E* ratio ~ 1/1.5		dr ~ 1/1.5			
 **8.8 h**	MeOH	 **8.9 h**	a	1 h	98%
	H_2O	 **8.10 a**	c	1 h	94%
 **8.8 i**	MeOH	 **8.9 i**	d	1 h	72%
	H_2O	 **8.10 b**	c	2 h 30 min	97%
 **8.8 j**	MeOH	 **8.9 j**	a	1 h	87%

(continued on the next page)

substrate	nucleophile	product	conditions	time	yield[a]
	H_2O	 **8.10 c**	c	1 h	82%
 **8.8 k**	MeOH	 **8.9 k**	a	1 h	92%
 **8.8 l**	H_2O	 **8.10 d**	e	2 h	91%
 **8.8 m**	H_2O	 **8.10 e**	f	24 h	92%
 **8.16 a**	MeOH	 **8.17 a** dr ~ 1/1	d	2 h	77%
 **8.16 a**	MeOH	 **8.17 b** dr ~ 2/1	a	15 min	87%
 **8.20**	H_2O	degrad.	c	3 h	-[c]

[a] Isolated yield. [b] Compound **8.4 g** was also isolated in 26% yield [c] Side product **8.21** was isolated in 25% yield.

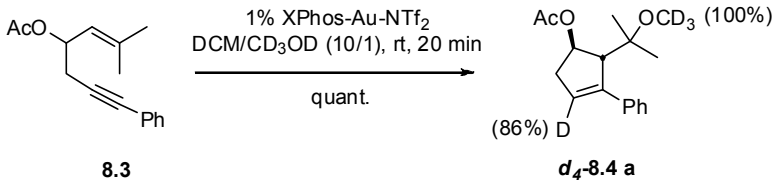


8.21

General procedure 8.2: The 1,5-enyne (1 equiv) was dissolved in the apropiate volume (0.5 M) of solvent or solvent / nucleophile mixture: a DCM/NuH 10/1 (v/v) mixture for conditions (a) and (d), a solution of NuH (2 equiv) in DCM for conditions (b) or a DCM/acetone/H_2O 8/2/1 (v/v/v) mixture for conditions (c), (e) and (f). The corresponding amount of XPhos-Au-NTf_2 was added

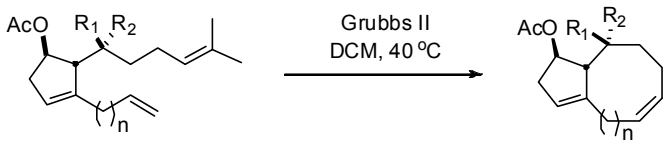
(0.01 equiv for conditions (a)-(d), 0.02 equiv for conditions (e) and (f)). The mixture was stirred at the corresponding temperature (rt for conditions (a)-(c) and (e), reflux for conditions (d) and (f)) and monitored periodically by TLC. Upon completion of the reaction, the mixture was evaporated under reduced pressure and purified by flash chromatography (silica gel, petroleum ether / diethyl ether) to give the hydroxy- or alkoxycyclized product.

A deuterium labeling experiment was performed on substrate **8.3** in analogous conditions (using CD_3OD instead of MeOH for the DCM/CD_3OD 10/1 (v/v) mixture, 0.5 M).



8.3. Extension to the formation of bicyclic products

Bicyclic compounds **8.22 a-d** were obtained by a RCM reaction in classical conditions starting from derivatives **major 8.9 e**, **minor 8.9 e**, **major 8.9 f** and respectively **8.10 d**.

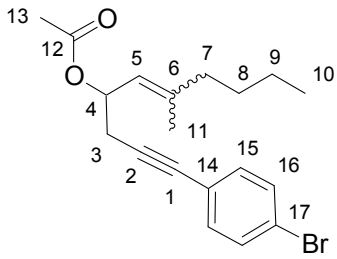


substrate	R_1	R_2	n	product	time	yield[a]
major 8.9 e	OMe	Me	0	**8.22 a**	1 h	quant.
minor 8.9 e	Me	OMe	0	**8.22 b**	1 h	quant.
major 8.9 f	OMe	Me	1	**8.22 c**	1 h	quant.
8.10 d	OH	Me	0	**8.22 d**	30 h	quant.

General procedure 8.3: To a solution of the substrate (1 equiv) in degassed DCM (0.03 M for **major 8.9 e**, **minor 8.9 e** and **8.10 d** and 0.0015 M for **major 8.9 f**) was added the Grubbs II catalyst (0.1 equiv). The mixture was stirred under reflux and under argon. Upon completion of the reaction, the mixture was evaporated under reduced pressure and purified by flash chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

8.4. Characterization of the prepared compounds

Acetic acid 1-[3-(4-bromo-phenyl)-prop-2-ynyl]-3-methyl-hept-2-enyl ester **8.8 d**



MF: $C_{19}H_{23}BrO_2$

MW: 363.29 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.1** (scale: 1.070 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil.

Yield: 40% (isolated as a mixture of *Z*/*E* isomers ~ 1/2).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the mixture of *Z*/*E* isomers: 7.42 (d, J = 8.5 Hz, 2H, both isomers, *15* or *16*), 7.23 (d, J = 8.5 Hz, 2H, both isomers, *15* or *16*), 5.72 (m, 1H, both isomers, *4*), 5.27 (m, 1H, both isomers, *5*), 2.70 (m, 2H, both isomers, *3*), 2.07 (s, 3H, both isomers, *13*), 2.06-2.02 (m, 2H, both isomers, *7*), 1.76 (s, 3H, both isomers, *11*), 1.42-1.23 (m, 4H, both isomers, *8* and *9*), 0.88 (t, J = 7.2 Hz, 3H, both isomers, *10*).

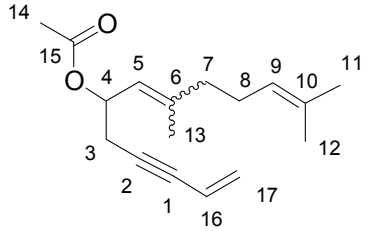
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the *Z* isomer: 170.1 (*12*), 143.1 (*6*), 133.1 (*15* or *16*), 131.4 (*15* or *16*), 122.5 (*14* or *17*), 122.2 (*5*), 122.0 (*14* or *17*), 86.8 (*1* or *2*), 81.1 (*1* or *2*), 68.8 (*4*), 32.4 (*7*), 30.4 (*8*), 26.2 (*3*), 23.4 (*11*), 22.7 (*9*), 21.2 (*13*), 14.0 (*10*). For the *E* isomer: 170.2 (*12*), 142.4 (*6*), 133.0 (*15* or *16*), 131.4 (*15* or *16*), 122.5 (*14* or *17*), 121.9 (*14* or *17*), 121.7 (*5*), 86.7 (*1* or *2*), 81.1 (*1* or *2*), 69.3 (*4*), 39.2 (*7*), 29.7 (*8*), 26.0 (*3*), 22.2 (*9*), 21.2 (*13*), 16.9 (*11*), 13.9 (*10*).

IR (δ, cm^{-1}) (CCl_4): For the mixture of *Z*/*E* isomers: 2958, 2930, 1739, 1668, 1486, 1370, 1236, 1071, 1014.

MS (CI^+, NH_3, m/z): 382 (MNH_4^+), 364 (MH^+), 322, 303, 289, 279, 263, 247, 235.

HRMS (EI^+, m/z): Calculated for $C_{19}H_{23}BrO_2$: 362.0881.
Found for $C_{19}H_{23}BrO_2$: 362.0865.

Acetic acid 3,7-dimethyl-1-pent-4-en-2-ynyl-octa-2,6-dienyl ester **8.8 e**



MF: $C_{17}H_{24}O_2$

MW: 260.37 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.1** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Pale yellow oil.

Yield: 46% (isolated as a mixture of *Z*/*E* isomers ~ 1/1.5)

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) For the mixture of *Z*/*E* isomers: 5.76 (qdd, J = 1.9, 11.0, 17.5 Hz, 1H, both isomers, *16*), 5.63 (dt, J = 6.3, 9.0 Hz, 1H, both isomers, *4*), 5.57 (dt, J = 2.4, 17.5 Hz, 1H, both isomers, *17*), 5.41 (dd, J = 2.3, 11.0 Hz, 1H, both isomers, *17*), 5.23 (tm, J = 10.1 Hz, 1H, both isomers, *5*), 5.08 (m, 1H, both isomers, *9*), 2.61 (m, 2H, both isomers, *3*), 2.18-2.06 (m, 4H, both isomers, *7* and *8*), 2.06 (s, 3H, *E* isomer, *14*), 2.05 (s, 3H, *Z* isomer, *14*), 1.77 (d, J = 1.4 Hz, 3H, *Z* isomer, *13*), 1.76 (d, J = 1.3 Hz, 3H, *E* isomer, *13*), 1.68 (s, 3H, both isomers, *11* or *12*), 1.61 (s, 3H, *Z* isomer, *11* or *12*), 1,60 (s, 3H, *E* isomer, *11* or *12*).

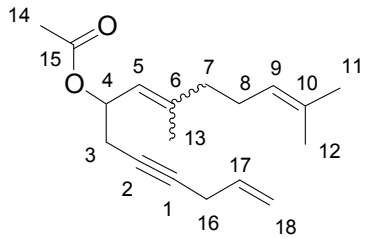
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) For the *Z* isomer: 170.1 (*15*), 142.2 (*6* or *10*), 132.1 (*6* or *10*), 126.2 (*17*), 123.8 (*9*), 122.6 (*5*), 117.3 (*16*), 86.1 (*1* or *2*), 81.0 (*1* or *2*), 68.9 (*4*), 32.6 (*7* or *8*), 26.6 (*3*), 26.0 (*7* or *8*), 25.7 (*11* or *12*), 23.4 (*13*), 21.2 (*14*), 17.6 (*11* or *12*).
For the *E* isomer: 170.2 (*15*), 142.8 (*6* or *10*), 131.8 (*6* or *10*), 126.2 (*17*), 123.7 (*9*), 122.0 (*5*), 117.3 (*16*), 86.0 (*1* or *2*), 80.9 (*1* or *2*), 69.3 (*4*), 39.5 (*7* or *8*), 26.3 (*3*), 25.9 (*7* or *8*), 25.7 (*11* or *12*), 21.2 (*14*), 17.7 (*11* or *12*), 17.0 (*13*).

IR (ν, cm^{-1}) (CCl_4) For the mixture of *Z*/*E* isomers: 2969, 2919, 2857, 1739, 1669, 1608, 1442, 1371, 1236, 1017.

MS (CI^+, NH_3, m/z) 261 (MH^+), 233, 218, 201, 161.

HRMS (EI^+, m/z) Calculated for $C_{17}H_{24}O_2$: 260.1776.
Found for $C_{17}H_{24}O_2$: 260.1765.

Acetic acid 1-hex-5-en-2-ynyl-3,7-dimethyl-octa-2,6-dienyl ester 8.8 f



MF: $C_{18}H_{26}O_2$

MW: 274.40 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.1** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Pale yellow oil.

Yield: 49% (isolated as a mixture of *Z*/*E* isomers ~ 1/2).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) For the mixture of *Z*/*E* isomers: 5.81 (m, 1H, both isomers, *17*), 5.62 (dt, J = 6.2, 9.1 Hz, 1H, both isomers, *4*), 5.31 (dm, J = 16.9 Hz, 1H, both isomers, *18*), 5.23 (tm, J = 11.9 Hz, 1H, both isomers, *5*), 5.13-5.07 (m, 2H, both isomers, *9* and *18*), 2.93 (m, 2H, both isomers, *16*), 2.50 (m, 2H, *3*), 2.17-2.08 (m, 4H, both isomers, *7* and *8*), 2.05 (s, 3H, *E* isomer, *14*), 2.04 (s, 3H, *Z* isomer, *14*), 1.76 (d, J = 1.3 Hz, 3H, *Z* isomer, *13*), 1.74 (d, J = 1.3 Hz, 3H, *E* isomer, *13*), 1.68 (s, 3H, both isomers, *11* or *12*), 1.61 (s, 3H, *Z* isomer, *11* or *12*), 1.60 (s, 3H, *E* isomer, *11* or *12*).

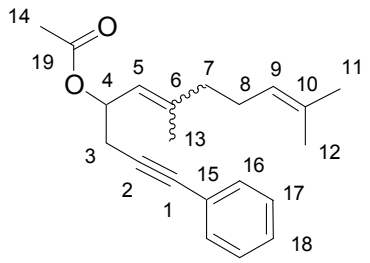
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) For the *Z* isomer: 170.1 (*15*), 142.0 (*6* or *10*), 132.9 (*17*), 132.0 (*6* or *10*), 123.8 (*9*), 122.8 (*5*), 115.7 (*18*), 78.5 (*1* or *2*), 78.0 (*1* or *2*), 69.1 (*4*), 39.5 (*7* or *8*), 26.6 (*7* or *8*), 25.6 (*11* or *12*), 25.4 (*3*), 23.4 (*13*), 23.1 (*16*), 21.2 (*14*), 17.6 (*11* or *12*).
For the *E* isomer: 170.2 (*15*), 141.6 (*6* or *10*), 132.9 (*17*), 131.7 (*6* or *10*), 123.7 (*9*), 122.1 (*5*), 115.7 (*18*), 78.4 (*1* or *2*), 77.9 (*1* or *2*), 69.5 (*4*), 32.6 (*7* or *8*), 26.3 (*7* or *8*), 25.6 (*11* or *12*), 25.3 (*3*), 23.0 (*16*), 21.2 (*14*), 17.7 (*11* or *12*), 17.0 (*13*).

IR (ν, cm^{-1}) (CCl_4) For the mixture of *Z*/*E* isomers: 2970, 2917, 2857, 1738, 1669, 1643, 1439, 1371, 1237, 1016.

MS (CI^+, NH_3, m/z) 275 (MH^+), 255, 232, 215, 173.

HRMS (EI^+, m/z) Calculated for $C_{18}H_{26}O_2$: 274.1933.
Found for $C_{18}H_{26}O_2$: 274.1925.

Acetic acid 3,7-dimethyl-1-(3-phenyl-prop-2-ynyl)-octa-2,6-dienyl ester 8.8 g



MF: $C_{21}H_{26}O_2$

MW: 310.43 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 8.1** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Pale yellow oil.

Yield: 54% (isolated as a mixture of *Z*/*E* isomers ~ 1/1.5).

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) For the mixture of *Z*/*E* isomers: 7.38 (m, 2H, both isomers, *17*), 7.29 (m, 3H, both isomers, *16* and *18*), 5.73 (dt, J = 6.5, 9.0 Hz, 1H, both isomers, *4*), 5.29 (m, 1H, both isomers, *5*), 5.10 (m, 1H, both isomers, *9*), 2.70 (m, 2H, both isomers, *3*), 2.18-2.08 (m, 4H, both isomers, *7* and *8*), 2.08 (s, 3H, both isomers, *14*), 1.79 (m, 3H, both isomers, *13*), 1.68 (s, 3H, *Z* isomer, *11* or *12*), 1.66 (s, 3H, *E* isomer, *11* or *12*), 1.60 (s, 3H, both isomers, *11* or *12*).

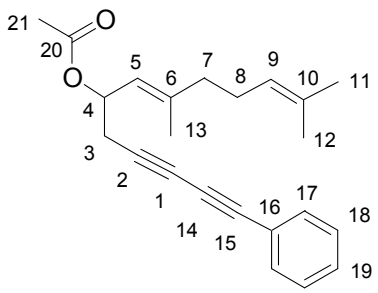
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) For the *Z* isomer: 170.1 (*19*), 142.2 (*6* or *15*), 132.1 (*10*), 131.6 (*17*), 128.2 (*18*), 127.8 (*19*), 123.7 (*9*), 123.6 (*6* or *15*), 122.7 (*5*), 85.4 (*1* or *2*), 82.4 (*1* or *2*), 69.0 (*4*), 39.5 (*3*, *7* or *8*), 26.6 (*3*, *7* or *8*), 26.1 (*3*, *7* or *8*), 25.7 (*11* or *12*), 23.4 (*13*), 21.3 (*14*), 17.6 (*11* or *12*).
For the *E* isomer: 170.2 (*19*), 141.8 (*6* or *15*), 131.7 (*10*), 131.5 (*17*), 128.1 (*18*), 127.8 (*19*), 123.7 (*9*), 123.6 (*6* or *15*), 122.0 (*5*), 85.3 (*1* or *2*), 82.1 (*1* or *2*), 69.4 (*4*), 39.5 (*3*, *7* or *8*), 26.3 (*3*, *7* or *8*), 26.0 (*3*, *7* or *8*), 25.6 (*11* or *12*), 21.2 (*14*), 17.7 (*11* or *12*), 17.0 (*13*).

IR (ν, cm^{-1}) (CCl_4) For the mixture of *Z*/*E* isomers: 3055, 2969, 2919, 1738, 1669, 1596, 1490, 1442, 1371, 1237, 1017.

MS (CI^+, NH_3, m/z) 328 (MNH_4^+), 311 (MH^+), 268, 251.

HRMS (EI^+, m/z) Calculated for $C_{21}H_{26}O_2$: 310.1933.
Found for $C_{21}H_{26}O_2$: 310.1932

Acetic acid (*E*)-3,7-dimethyl-1-(5-phenyl-penta-2,4-diynyl)-octa-2,6-dienyl ester 8.8 i



MF: $C_{23}H_{26}O_2$

MW: 334.45 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 8.1** (scale: 1 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

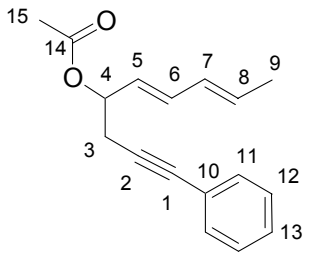
Product: Yellow oil.

Yield: 42%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.47 (dd, J = 1.4, 7.8 Hz, 2H, *18*), 7.31 (m, 3H, *17* and *19*), 5.64 (dt, J = 6.0, 9.1 Hz, 1H, *4*), 5.24 (dq, J = 1.2, 9.1 Hz, 1H, *5*), 5.09 (tm, J = 7.0 Hz, 1H, *9*), 2.67 (d, J = 5.9 Hz, 2H, *3*), 2.12-2.01 (m, 4H, *7* and *8*), 2.06 (s, 3H, *21*), 1.76 (d, J = 1.3 Hz, 3H, *13*), 1.69 (s, 3H, *11* or *12*), 1.60 (s, 3H, *11* or *12*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	170.0 (*20*), 142.1 (*6*), 132.4 (*10*), 131.7 (*18*), 128.8 (*19*), 128.2 (*17*), 123.5 (*9*), 121.7 (*16*), 121.5 (*5*), 79.5 (*1*), 75.1 (*15*), 74.1 (*14*), 68.7 (*4*), 66.7 (*2*), 39.4 (*7*), 26.1 (*8*), 26.1 (*3*), 25.6 (*11* or *12*), 21.1 (*21*), 17.6 (*11* or *12*), 16.9 (*13*).
IR (ν, cm^{-1}) (CCl_4)	3058, 2969, 2921, 2856, 1740, 1491, 1442, 1371, 1235, 1017.
MS (CI^+, NH_3, m/z)	352 (MNH_4^+), 292, 275.
HRMS (EI^+, m/z)	Calculated for $C_{23}H_{26}O_2$: 334.1933. Found for $C_{23}H_{26}O_2$: 334.1919.

Acetic acid (2E,4E)-1-(3-phenyl-prop-2-ynyl)-hexa-2,4-dienyl ester **8.8 j**

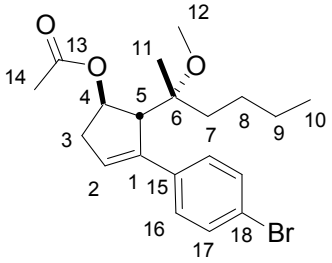


MF: $C_{17}H_{18}O_2$

MW: 254.32 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 8.1** (scale: 1.5 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 98/2).
Product:	Yellow oil.
Yield:	60%
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.39 (m, 2H, *12*), 7.28 (m, 3H, *11* and *13*), 6.32 (dd, J = 15.2, 10.4 Hz, 1H, *6*), 6.05 (m, 1H, *7*), 5.81 (m, 1H, *8*), 5.64 (dd, J = 15.2, 7.9 Hz, 1H, *5*), 5.46 (m, 1H, *4*), 2.76 (dd, J = 6.1, 3.3 Hz , 2H, *3*), 2.10 (s, 3H, *15*), 1.77 (dd, J = 6.8, 1.3 Hz , 3H, *9*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	170.1 (*14*), 133.8 (*5*, *6*, *7*, *8*, or *13*), 131.7 (*5*, *6*, *7*, *8*, or *13*), 131.6 (*11* or *12*), 130.4 (*5*, *6*, *7*, *8*, or *13*), 128.2 (*11* or *12*), 127.8 (*5*, *6*, *7*, *8*, or *13*), 126.6 (*5*, *6*, *7*, *8*, or *13*), 123.4 (*10*), 85.0 (*1* or *2*), 82.6 (*1* or *2*), 72.5 (*4*), 25.8 (*3*), 21.2 (*15*), 18.2 (*9*).
IR (ν, cm^{-1}) (CCl_4)	2915, 1742, 1661, 1490, 1439, 1369, 1233, 1018.
MS (CI^+, NH_3, m/z)	255 (MH^+), 212, 195.
HRMS (EI^+, m/z)	Calculated for $C_{17}H_{18}O_2$: 254.1307. Found for $C_{17}H_{18}O_2$: 254.1303.

***Racemic* - acetic acid (1*R*,2*R*)-3-(4-bromo-phenyl)-2-((*R*)-1-methoxy-1-methyl-pentyl)-cyclopent-3-enyl ester** **minor 8.9 d**



MF: $C_{20}H_{27}BrO_3$

MW: 395.33 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2-90/10).

Product: Yellow oil.

Yield: 29%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.42 (d, J = 8.5 Hz, 2H, *17*), 7.24 (d, J = 8.5 Hz, 2H, *16*), 5.90 (s, 1H, *2*), 5.44 (d, J = 6.1 Hz, 1H, *4*), 3.48 (d, J = 0.9 Hz, 1H, *5*), 3.00 (s, 3H, *12*), 2.89 (dd, J = 6.2, 18.9 Hz, 1H, *3*), 2.36 (dd, J = 3.0, 19.2 Hz, 1H, *3*), 2.07 (s, 3H, *14*), 1.44-1.36 (m, 2H, *7*), 1.32-1.15 (m, 4H, *8* and *9*), 0.92 (s, 3H, *11*), 0.86 (t, J = 7.0 Hz, 3H, *10*).

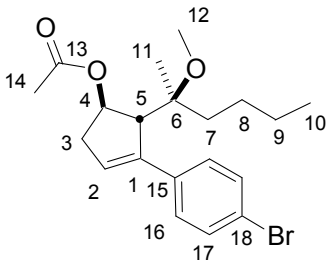
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 170.7 (*13*), 143.2 (*1*), 137.6 (*18*), 130.9 (*17*), 128.8 (*2*), 128.6 (*16*), 120.6 (*15*), 78.4 (*6*), 77.1 (*4*), 59.7 (*5*), 48.9 (*12*), 40.8 (*3*), 35.6 (*7*), 25.2 (*8*), 23.2 (*9*), 21.4 (*14*), 21.0 (*11*), 14.1 (*10*).

IR (ν, cm^{-1}) (CCl_4) 3049, 2936, 2869, 2829, 1738, 1485, 1463, 1371, 1242, 1166, 1076, 1017, 987.

MS (CI^+, NH_3, m/z) 397, 395 (MH^+), 382, 380, 365, 363, 322, 320, 305, 303.

HRMS (EI^+, m/z) Calculated for $C_{20}H_{27}BrO_3$: 394.1144.
Found for $C_{20}H_{27}BrO_3$: 394.1132.

***Racemic* - acetic acid (1*R*,2*R*)-3-(4-bromo-phenyl)-2-((*S*)-1-methoxy-1-methyl-pentyl)-cyclopent-3-enyl ester** **major 8.9 d**



MF: $C_{20}H_{27}BrO_3$

MW: 395.33 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2-90/10).

Product: Yellow oil.

Yield: 36%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.49 (d, J = 8.4 Hz, 2H, *17*), 7.28 (d, J = 8.4 Hz, 2H, *16*), 5.95 (s, 1H, *2*), 5.62 (d, J = 5.7 Hz, 1H, *4*), 3.47 (s, 1H, *5*), 3.18 (s, 3H, *12*), 2.96 (dd, J = 5.9, 18.9 Hz, 1H, *3*), 2.42 (dd, J = 3.0, 18.9 Hz, 1H, *3*), 2.13 (s, 3H, *14*), 1.32-1.08 (m, 6H, *7*, *8* and *9*), 1.00 (s, 3H, *11*), 0.84 (t, J = 7.2 Hz, 3H, *10*).

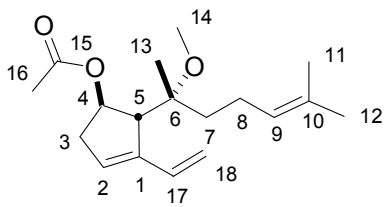
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.7 (*13*), 143.0 (*1*), 137.7 (*18*), 131.2 (*17*), 129.7 (*2*), 128.2 (*16*), 120.8 (*15*), 78.5 (*6*), 77.4 (*4*), 59.3 (*5*), 49.0 (*12*), 41.0 (*3*), 36.3 (*7*), 25.2 (*8*), 22.9 (*9*), 21.5 (*14*), 20.2 (*11*), 13.9 (*10*).

IR (ν, cm^{-1}) (CCl_4): 3048, 2939, 2869, 2828, 1737, 1485, 1463, 1371, 1243, 1170, 1076, 1018, 987.

MS (CI^+, NH_3, m/z): 397, 395 (MH^+), 382, 380, 365, 363, 322, 320, 305, 303.

HRMS (EI^+, m/z): Calculated for $C_{20}H_{27}BrO_3$: 394.1144.
Found for $C_{20}H_{27}BrO_3$: 394.1163.

***Racemic* - acetic acid (1*R*,2*R*)-2-((*R*)-1-methoxy-1,5-dimethyl-hex-4-enyl)-3-vinyl-cyclopent-3-enyl ester** **minor 8.9 e**



MF: $C_{18}H_{28}O_3$

MW: 292.41 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2-90/10).

Product: Yellow oil.

Yield: 31%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.41 (dd, J = 10.9, 17.5 Hz, 1H, *17*), 5.85 (s, 1H, *2*), 5.38 (d, J = 17.5 Hz, 1H, *18*), 5.27 (d, J = 6.4 Hz, 1H, *4*), 5.06 (t, J = 7.1 Hz, 1H, *9*), 5.03 (d, J = 11.1 Hz, 1H, *18*), 3.17 (s, 3H, *14*), 3.12 (s, 1H, *5*), 2.83 (dd, J = 6.0, 19.0 Hz, 1H, *3*), 2.22 (d, J = 19.0 Hz, 1H, *3*), 2.03 (s, 3H, *16*), 1.98 (m, 2H, *8*), 1.68 (s, 3H, *11* or *12*), 1.60 (s, 3H, *11* or *12*), 1.56-1.41 (m, 2H, *7*), 1.06 (s, 3H, *13*).

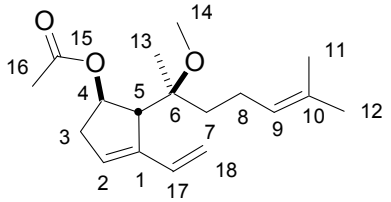
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.6 (*15*), 142.2 (*1*), 134.0 (*17*), 131.3 (*10*), 126.9 (*2*), 124.4 (*9*), 114.4 (*18*), 78.2 (*6*), 77.3 (*4*), 58.5 (*5*), 48.8 (*14*), 39.9 (*3*), 35.5 (*7*), 25.7 (*11* or *12*), 21.7 (*8*), 21.3 (*6*), 20.2 (*13*), 17.6 (*11* or *12*).

IR (ν, cm^{-1}) (CCl_4): 2971, 2930, 2858, 2828, 1737, 1453, 1372, 1296, 1243, 1178, 1091, 1024, 987.

MS (CI^+, NH_3, m/z): 310 (MNH_4^+), 293 (MH^+), 278, 261, 251, 236, 219, 201, 194, 180.

HRMS (EI^+, m/z) Calculated for $C_{18}H_{28}O_3$: 292.2039.
Found for $C_{18}H_{28}O_3$: 292.2039.

***Racemic* - acetic acid (1*R*,2*R*)-2-((*S*)-1-methoxy-1,5-dimethyl-hex-4-enyl)-3-vinyl-cyclopent-3-enyl ester** **major 8.9 e**



MF: $C_{18}H_{28}O_3$

MW: 292.41 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2-90/10).

Product: Yellow oil.

Yield: 47%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.38 (dd, J = 10.9, 17.5 Hz, 1H, *17*), 5.88 (s, 1H, *2*), 5.44 (d, J = 5.9 Hz, 1H, *4*), 5.33 (d, J = 17.5 Hz, 1H, *18*), 5.07 (t, J = 6.9 Hz, 1H, *9*), 5.08 (d, J = 10.6 Hz, 1H, *18*), 3.19 (s, 3H, *14*), 3.08 (s, 1H, *5*), 2.83 (dd, J = 5.6, 19.2 Hz, 1H, *3*), 2.24 (dd, J = 2.9, 19.2 Hz, 1H, *3*), 2.03 (s, 3H, *16*), 2.00 (m, 2H, *8*), 1.69 (s, 3H, *11* or *12*), 1.62 (s, 3H, *11* or *12*), 1.61-1.46 (m, 2H, *7*), 1.03 (s, 3H, *13*).

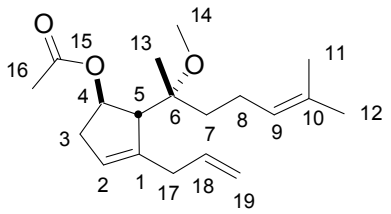
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 170.7 (*15*), 142.1 (*1*), 133.8 (*17*), 131.5 (*10*), 128.3 (*2*), 124.3 (*9*), 114.5 (*18*), 78.3 (*6*), 77.5 (*4*), 58.4 (*5*), 49.0 (*14*), 40.2 (*3*), 36.4 (*7*), 25.7 (*11* or *12*), 22.0 (*8*), 21.4 (*16*), 20.0 (*13*), 17.6 (*11* or *12*).

IR (ν, cm^{-1}) (CCl_4) 2974, 2630, 2859, 2830, 1736, 1449, 1372, 1244, 1180, 1088, 1023, 987.

MS (CI^+, NH_3, m/z) 310 (MNH_4^+), 293 (MH^+), 278, 261, 253, 236, 219, 201, 194.

HRMS (EI^+, m/z) Calculated for $C_{18}H_{28}O_3$: 292.2039.
Found for $C_{18}H_{28}O_3$: 292.2034.

***Racemic* - acetic acid (1*R*,2*R*)-3-allyl-2-((*R*)-1-methoxy-1,5-dimethyl-hex-4-enyl)-cyclopent-3-enyl ester** **minor 8.9 f**



MF: $C_{19}H_{30}O_3$

MW: 306.44 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1-95/5).

Product: Yellow oil.

Yield: 21%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.93 (m, 1H, *18*), 5.49 (s, 1H, *2*), 5.16 (dt, J = 2.0, 6.8 Hz, 1H, *4*), 5.10-5.03 (m, 3H, *9* and *19*), 3.17 (s, 3H, *14*), 3.04 (ddd, J = 1.1, 6.8, 16.9 Hz, 1H, *17*), 2.98 (s, 1H, *5*), 2.88 (dm, J = 16.9 Hz, 1H, *17*), 2.75 (dd, J = 6.8, 17.9 Hz, 1H, *3*), 2.13 (d, J = 17.9 Hz, 1H, *3*), 2.04 (s, 3H, *16*), 2.00 (t, J = 7.1 Hz, 2H, *8*), 1.68 (s, 3H, *11* or *12*), 1.61 (s, 3H, *11* or *12*), 1.59-1.46 (m, 2H, *7*), 0.99 (s, 3H, *13*).

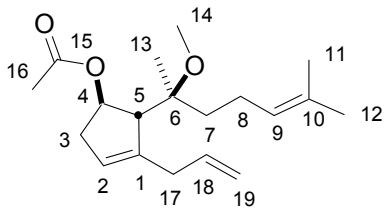
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 170.7 (*15*), 142.8 (*1*), 136.6 (*18*), 131.4 (*10*), 124.7 (*2*), 124.4 (*9*), 115.6 (*19*), 78.5 (*6*), 77.4 (*4*), 59.0 (*5*), 48.6 (*14*), 39.6 (*3*), 35.9 (*17*), 35.1 (*7*), 25.7 (*11* or *12*), 21.4 (*8*), 21.3 (*16*), 19.6 (*13*), 17.6 (*11* or *12*).

IR (ν, cm^{-1}) (CCl_4) 3073, 3053, 2972, 2929, 2857, 1736, 1640, 1437, 1373, 1243, 1175, 1087, 1025.

MS (CI^+, NH_3, m/z) 324 (MNH_4^+), 307 (MH^+), 292, 275, 250, 233, 222, 206.

HRMS (EI^+, m/z) Calculated for $C_{19}H_{30}O_3$: 306.2195.
Found for $C_{19}H_{30}O_3$: 306.2198.

***Racemic* - acetic acid (1*R*,2*R*)-3-allyl-2-((*S*)-1-methoxy-1,5-dimethyl-hex-4-enyl)-cyclopent-3-enyl ester** **major 8.9 f**



MF: $C_{19}H_{30}O_3$

MW: 306.44 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1-95/5).

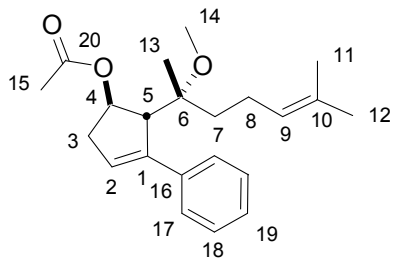
Product: Yellow oil.

Yield: 43%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.90 (m, 1H, *18*), 5.47 (s, 1H, *2*), 5.27 (d, J = 6.5 Hz, 1H, *4*), 5.10-5.04 (m, 3H, *9* and *19*), 3.20 (s, 3H, *14*), 3.04 (dd, J = 5.2, 17.1 Hz, 1H, *17*), 2.96 (s, 1H, *5*), 2.86 (dd, J = 6.6, 16.9 Hz, 1H, *17*), 2.76 (dm, J = 18.1 Hz, 1H, *3*), 2.14 (d, J = 18.1 Hz, 1H, *3*), 2.04 (s, 3H, *16*), 1.99 (m, 2H, *8*), 1.68 (s, 3H, *11* or *12*), 1.61 (s, 3H, *11* or *12*), 1.55-1.46 (m, 1H, *7*), 1.40-1.26 (m, 1H, *7*), 1.13 (s, 3H, *13*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	170.7 (*15*), 142.2 (*1*), 136.3 (*18*), 131.4 (*10*), 125.7 (*2*), 124.5 (*9*), 115.8 (*19*), 78.1 (*6*), 77.7 (*4*), 59.5 (*5*), 49.1 (*14*), 39.7 (*3*), 36.3 (*17*), 35.5 (*7*), 25.7 (*11* or *12*), 21.8 (*8*), 21.4 (*6*), 20.5 (*3*), 17.6 (*11* or *12*).
IR (ν, cm^{-1}) (CCl_4)	3074, 3052, 2973, 2929, 2856, 1735, 1639, 1436, 1373, 1243, 1181, 1138, 1073, 1024.
MS (CI^+, NH_3, m/z)	324 (MNH_4^+), 307 (MH^+), 292, 275, 254, 250, 236, 215, 193.
HRMS (EI^+, m/z)	Calculated for $C_{19}H_{30}O_3$: 306.2195. Found for $C_{19}H_{30}O_3$: 306.2182.

***Racemic* - acetic acid (1*R*,2*R*)-2-((*R*)-1-methoxy-1,5-dimethyl-hex-4-enyl)-3-phenyl-cyclopent-3-enyl ester** **minor 8.9 g**



MF: $C_{22}H_{30}O_3$

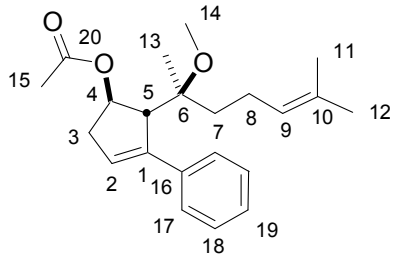
MW: 342.47 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 8.2** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 98/2-90/10).
Product:	Yellow oil.
Yield:	39%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.37 (d, J = 7.1 Hz, 2H, *17*), 7.30 (d, J = 7.2 Hz, 2H, *18*), 7.25 (t, J = 7.2 Hz, 1H, *19*), 5.87 (s, 1H, *2*), 5.49 (d, J = 6.0 Hz, 1H, *4*), 5.00 (tt, J = 1.3, 7.1 Hz, 1H, *9*), 3.57 (d, J = 0.5 Hz, 1H, *5*), 3.05 (s, 3H, *14*), 2.92 (dd, J = 6.2, 18.9 Hz, 1H, *3*), 2.38 (dd, J = 2.9, 18.9 Hz, 1H, *3*), 2.08 (s, 3H, *15*), 2.00 (m, 1H, *8*), 1.89 (m, 1H, *8*), 1.66 (s, 3H, *11* or *12*), 1.57 (s, 3H, *11* or *12*), 1.40 (m, 2H, *7*), 0.93 (s, 3H, *13*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	170.7 (*20*), 144.1 (*1*), 138.5 (*16*), 131.3 (*10*), 128.2 (*2*), 127.9 (*18*), 127.0 (*17*), 126.9 (*19*), 124.6 (*9*), 78.2 (*6*), 77.2 (*4*), 59.6 (*5*), 49.0 (*14*), 40.9 (*3*), 35.9 (*7*), 25.7 (*11* or *12*), 21.8 (*8*), 21.4 (*15*), 21.3 (*13*), 17.6 (*11* or *12*).
IR (ν, cm^{-1}) (CCl_4)	2971, 2929, 2857, 1737, 1598, 1493, 1446, 1372, 1244, 1166, 1074, 1025.
MS (CI^+, NH_3, m/z)	343 (MH^+), 311, 251, 141.
HRMS (EI^+, m/z)	Calculated for $C_{22}H_{30}O_3$: 342.2195. Found for $C_{22}H_{30}O_3$: 342.2198.

***Racemic* - acetic acid (1*R*,2*R*)-2-((*S*)-1-methoxy-1,5-dimethyl-hex-4-enyl)-3-** **major 8.9 g**

phenyl-cyclopent-3-enyl ester



MF: $C_{22}H_{30}O_3$

MW: 342.47 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2-90/10).

Product: Yellow oil.

Yield: 51%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.36-7.23 (m, 5H, *17*, *18* and *19*), 5.88 (s, 1H, *2*), 5.60 (d, J = 5.9 Hz, 1H, *4*), 4.78 (tt, J = 1.4, 7.1 Hz, 1H, *9*), 3.48 (s, 1H, *5*), 3.16 (s, 3H, *14*), 2.92 (dd, J = 5.9, 18.8 Hz, 1H, *3*), 2.38 (dd, J = 3.0, 18.9 Hz, 1H, *3*), 2.07 (s, 3H, *15*), 1.91 (m, 2H, *8*), 1.61 (s, 3H, *11* or *12*), 1.53 (s, 3H, *11* or *12*), 1.32-1.14 (m, 2H, *7*), 0.97 (s, 3H, *13*).

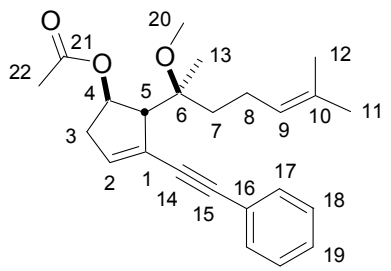
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.7 (*20*), 144.0 (*1*), 138.6 (*16*), 131.2 (*10*), 129.0 (*2*), 128.2 (*18*), 127.1 (*19*), 126.6 (*17*), 124.2 (*9*), 78.4 (*6*), 77.5 (*4*), 59.1 (*5*), 48.9 (*14*), 41.0 (*3*), 36.3 (*7*), 25.6 (*11* or *12*), 21.8 (*8*), 21.5 (*15*), 20.0 (*13*), 17.6 (*11* or *12*).

IR (ν, cm^{-1}) (CCl_4): 2973, 2931, 2829, 1736, 1597, 1493, 1445, 1371, 1244, 1176, 1092, 1073, 1024.

MS (CI^+, NH_3, m/z): 343 (MH^+), 311, 251, 195.

HRMS (EI^+, m/z): Calculated for $C_{22}H_{30}O_3$: 342.2195.
Found for $C_{22}H_{30}O_3$: 342.2187.

***Racemic* - acetic acid (1*R*,2*R*)-2-((*S*)-1-methoxy-1,5-dimethyl-hex-4-enyl)-3-phenylethynyl-cyclopent-3-enyl ester** **8.9 i**



MF: $C_{24}H_{30}O_3$

MW: 366.49 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5-90/10).

Product: Yellow oil.

Yield: 72%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.41 (m, 2H, *18*), 7.30 (m, 3H, *17* and *19*), 6.22 (s, 1H, *2*), 5.48 (d, J = 6.2 Hz, 1H, *4*), 5.12 (tm, J = 6.9 Hz , 1H, *9*), 3.21 (s, 3H, *20*), 3.17 (s, 1H, *5*), 2.90 (ddt, J = 2.0, 6.3, 19.8 Hz, 1H, *3*), 2.33 (dd, J = 2.7, 19.8 Hz, 1H, *3*), 2.24-2.00 (m, 2H, *8*), 2.04 (s, 3H, *22*), 1.99-1.74 (m, 2H, *7*), 1.66 (s, 3H, *11* or *12*), 1.59 (s, 3H, *11* or *12*), 1.07 (s, 3H, *13*).

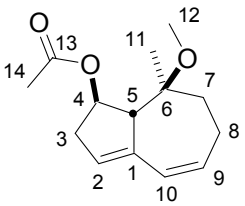
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.6 (*21*), 138.5 (*2*), 131.4 (*10*), 131.3 (*18*), 128.2 (*17*), 128.1 (*19*), 124.4 (*9*), 123.8 (*1*), 123.2 (*16*), 91.3 (*15*), 86.7 (*14*), 77.8 (*6*), 76.0 (*4*), 60.7 (*5*), 48.9 (*20*), 40.9 (*3*), 35.5 (*7*), 25.6 (*11* or *12*), 21.8 (*8*), 21.3 (*22*), 19.4 (*13*), 17.6 (*11* or *12*).

IR (ν, cm^{-1}) (CCl_4): 3056, 29.70, 2931, 1738, 1445, 1372, 1243, 1091, 1069, 1026.

MS (CI^+, NH_3, m/z): 367 (MH^+), 335, 275.

HRMS (EI^+, m/z): Calculated for $C_{24}H_{30}O_3$: 366.2195.
Found for $C_{24}H_{30}O_3$: 366.2210.

***Racemic* - acetic acid (1*R*,8*S*,8a*R*)-8-methoxy-8-methyl-1,2,6,7,8,8a-hexahydro-azulen-1-yl ester** **8.22 a**



MF: $C_{14}H_{20}O_3$

MW: 236.31 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: 0.034 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 80/20).

Product: Yellow oil.

Yield: Quant.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 6.18 (d, J = 11.4 Hz, 1H, *10*), 5.69 (dt, J = 5.2, 11.4 Hz, 1H, *9*), 5.58 (s, 1H, *2*), 5.44 (m, 1H, *4*), 3.23 (s, 4H, *5* and *12*), 2.85 (dd, J = 6.0, 18.4 Hz, 1H, *3*), 2.43 (m, 1H, *8*), 2.27 (d, J = 18.3 Hz, 1H, *3*), 2.10 (m, 1H, *8*), 2.05 (s, 3H, *14*), 1.96 (td, J = 2.6, 13.8 Hz, 1H, *7*), 1.78 (m, 1H, *7*), 1.30 (s, 3H, *11*).

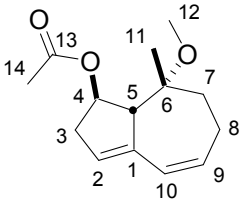
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.7 (*13*), 139.7 (*1*), 131.7 (*9*), 127.9 (*2*), 126.2 (*10*), 77.8 (*6*), 76.6 (*4*), 60.4 (*5*), 49.0 (*12*), 39.4 (*3*), 37.3 (*7*), 24.9 (*8*), 21.3 (*14*), 18.7 (*11*).

IR (ν, cm^{-1}) (CCl_4): 2931, 2853, 1737, 1444, 1370, 1244, 1174, 1141, 1100, 1068, 1038, 983.

MS (CI^+, NH_3, m/z): 237 (MH^+), 222, 215, 205, 186, 176, 161, 145.

HRMS (EI^+, m/z) Calculated for $C_{14}H_{20}O_3$: 236.1413.
Found for $C_{14}H_{20}O_3$: 236.1401.

***Racemic* - acetic acid (1*R*,8*R*,8a*R*)-8-methoxy-8-methyl-1,2,6,7,8,8a-hexahydro-azulen-1-yl ester** **8.22 b**



MF: $C_{14}H_{20}O_3$

MW: 236.31 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: 0.021 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Yellow crystals.

Yield: Quant.

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 6.22 (d, J = 11.4 Hz, 1H, *10*), 5.72 (dt, J = 5.2, 11.3 Hz, 1H, *9*), 5.62 (s, 1H, *2*), 5.51 (m, 1H, *4*), 3.21 (s, 3H, *12*), 2.94 (dd, J = 7.4, 19.0 Hz, 1H, *3*), 2.87 (s, 1H, *5*), 2.23-2.18 (m, 3H, *3* and *8*), 2.05 (s, 3H, *14*), 2.02-1.95 (m, 1H, *7*), 1.84-1.78 (m, 1H, *7*), 1.30 (s, 3H, *11*).

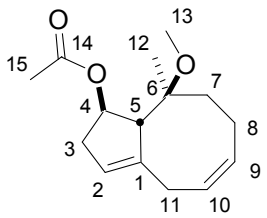
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 170.7, 140.1, 131.4, 128.4, 126.7, 77.4, 77.2, 62.8, 49.8, 39.2, 38.2, 25.0, 22.8, 21.4.

IR (ν, cm^{-1}) (CCl_4) 2927, 2854, 1735, 1460, 1372, 1243, 1177, 1142, 1091, 1023, 985.

MS (CI^+, NH_3, m/z) 237 (MH^+), 219, 205, 183, 161, 145.

HRMS (EI^+, m/z) Calculated for $C_{14}H_{20}O_3$: 236.1413.
Found for $C_{14}H_{20}O_3$: 236.1407.

***Racemic* - acetic acid (*Z*)-(1*R*,9*S*,9a*R*)-9-methoxy-9-methyl-2,4,7,8,9,9a-hexahydro-1*H*-cyclopentacycloocten-1-yl ester** **8.22 c**



MF: $C_{15}H_{22}O_3$

MW: 250.33 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 8.2** (scale: mmol).

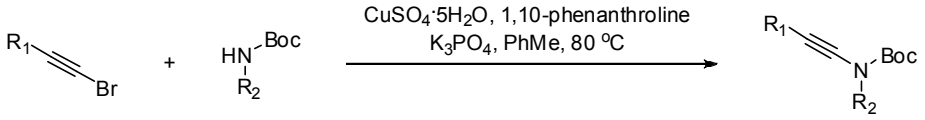
Purification: Flash column chromatography (silica gel, PE/Et_2O 80/20).

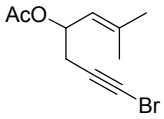
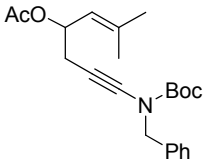
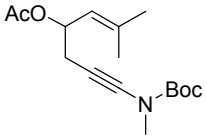
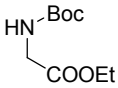
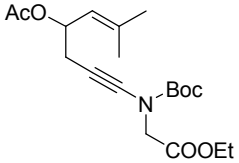
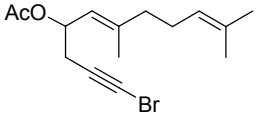
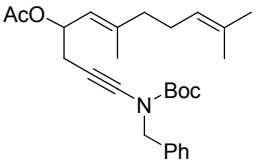
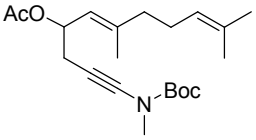
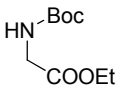
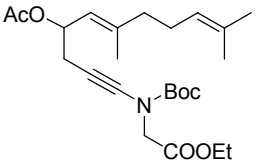
Product:	Yellow oil.
Yield:	Quant.
^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.63-5.56 (m, 2H, *9* and *10*), 5.51 (m, 1H, *2*), 4.91 (m, 1H, *4*), 3.19 (s, 3H, *13*), 3.10 (dd, J = 2.3, 19.2 Hz, 1H, *11*), 3.01 (d, J = 19.4 Hz, 1H, *11*), 2.66 (dm, J = 15.4 Hz, 1H, *3*), 2.60 (d, J = 5.9 Hz, 1H, *5*), 2.19 (m, 1H, *3*), 2.06 (s, 3H, *15*), 2.04-1.94 (m, 2H, *8*), 1.73 (dd, J = 6.8, 18.3 Hz, 1H, *7*), 1.61 (m, 1H, *7*), 1.11 (s, 3H, *12*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	170.6 (*14*), 133.4 (*1*), 129.3 (*9* or *10*), 124.0 (*2*), 122.6 (*9* or *10*), 78.1 (*4*), 75.3 (*6*), 49.0 (*13*), 48.4 (*5*), 40.8 (*11*), 29.0 (*3*), 28.1 (*7*), 22.7 (*8*), 21.5 (*15*), 20.7 (*2*).
IR (ν, cm^{-1}) (CCl_4)	3047, 2981, 2934, 1734, 1425, 1371, 1261, 1210, 1167, 1107, 1077, 1022, 987.
MS (CI^+, NH_3, m/z)	279 (MNH_4^+), 251 (MH^+), 219, 208, 191, 176, 159.
HRMS (EI^+, m/z)	Calculated for $C_{15}H_{22}O_3$: 250.1569. Found for $C_{15}H_{22}O_3$: 250.1578.

9. Gold(I)-catalyzed [4+2] cycloaddition of *N*-(hex-5-enynyl) *tert*-butyloxycarbamates

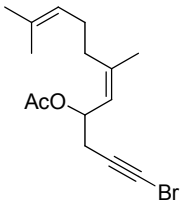
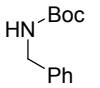
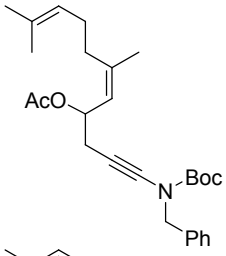
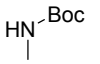
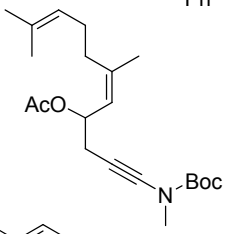
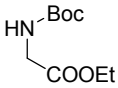
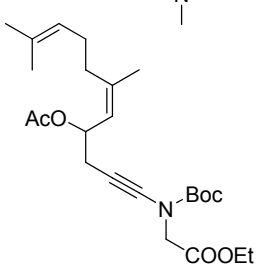
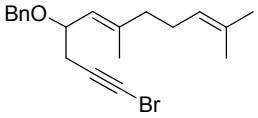
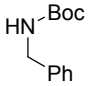
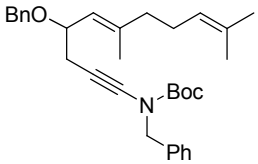
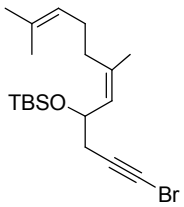
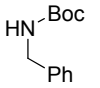
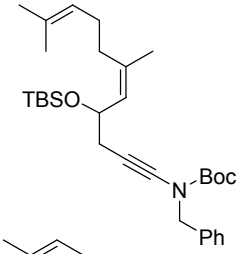
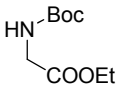
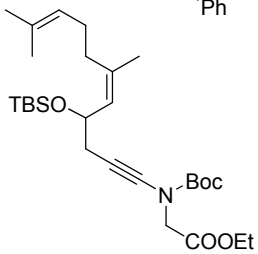
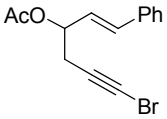
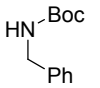
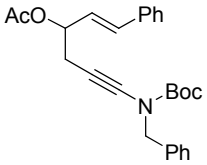
9.1. Synthesis of the precursors

Substrates **9.4 a-s** and **9.9 a-m** were synthesized by a copper(II)-catalyzed coupling between bromoalkynes **9.21 a-r** and *tert*-butyloxycarbamates **9.22 a-g** following a slightly modified version of a procedure previously reported by Hsung and coworkers.[327]

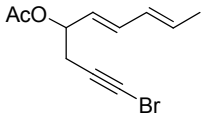
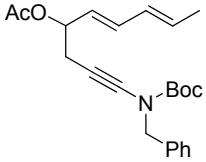
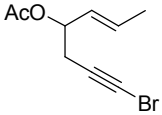
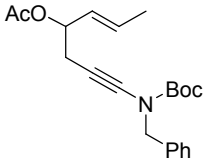
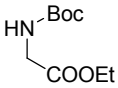
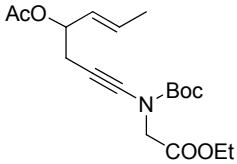
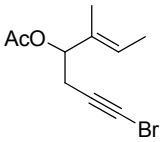
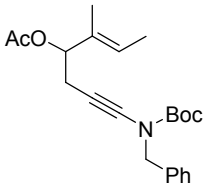
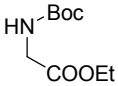
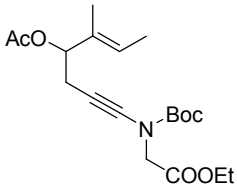
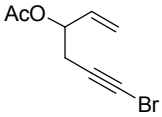
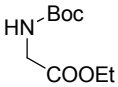
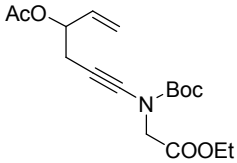
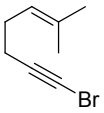
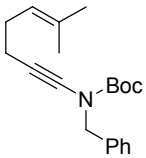
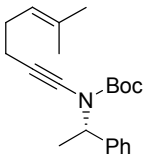
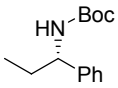
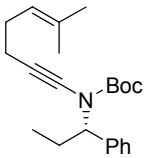


bromoalkyne		carbamate		product		time	yield[a]
	**9.21 a**		**9.22 a**		**9.4 a**	72 h	69%
			9.22 b		**9.4 b**	94 h	16%
			**9.22 c**		**9.4 c**	72 h	31%
	**9.21 b**		**9.22 a**		**9.4 d**	72 h	61%
			9.22 b		**9.4 f**	96 h	38%
			**9.22 c**		**9.4 h**	72 h	51%

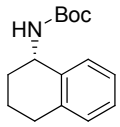
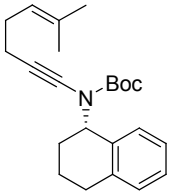
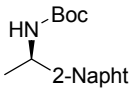
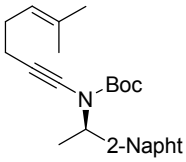
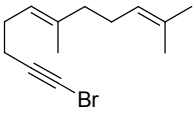
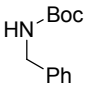
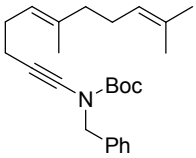
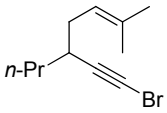
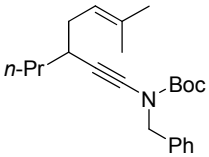
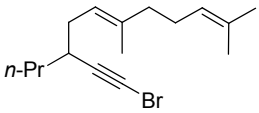
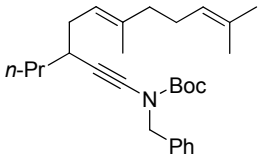
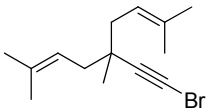
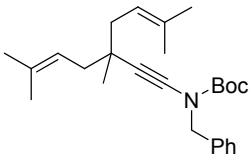
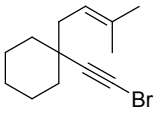
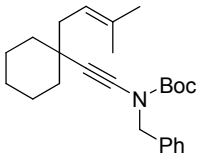
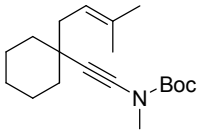
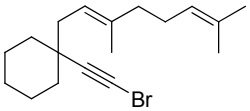
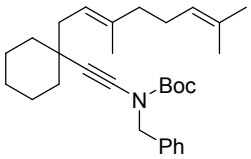
(continued on the next page)

bromoalkyne		carbamate		product		time	yield[a]
	**9.21 c**		**9.22 a**		**9.4 e**	120 h	45%
			**9.22 b**		**9.4 g**	120 h	37%
			**9.22 c**		**9.4 i**	72 h	63%
	**9.21 d**		**9.22 a**		**9.4 j**	88 h	58%
	**9.21 e**		**9.22 a**		**9.4 k**	66 h	47%
			**9.22 c**		**9.4 l**	48 h	64%
	**9.21 f**		**9.22 a**		**9.4 m**	120 h	31%

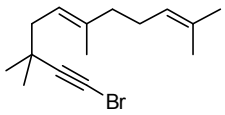
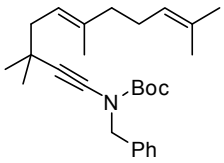
(continued on the next page)

bromoalkyne		carbamate		product		time	yield[a]
	**9.21 g**		**9.22 a**		**9.4 n**	48 h	43%
	**9.21 h**		**9.22 a**		**9.4 o**	72 h	25%
			**9.22 c**		**9.4 p**	96 h	26%
	**9.21 i**		**9.22 a**		**9.4 q**	72 h	20%
			**9.22 c**		**9.4 r**	72 h	23%
	**9.21 j**		**9.22 c**		**9.4 s**	96 h	31%
	**9.21 k**		**9.22 a**		**9.9 a**	96 h	56%
			9.22 d		**9.9 j**	96 h	25%
			**9.22 e**		**9.9 k**	72 h	29%

(continued on the next page)

bromoalkyne	carbamate	product	time	yield[a]
	 **9.22 f**	 **9.9 l**	72 h	19%
	 **9.22 g**	 **9.9 m**	72 h	68%
 **9.21 l**	 **9.22 a**	 **9.9 b**	67 h	18%
 **9.21 m**	**9.22 a**	 **9.9 c**	87 h	64%
 **9.21 n**	**9.22 a**	 **9.9 d**	72 h	51%
 **9.21 o**	**9.22 a**	 **9.9 e**	67 h	66%
 **9.21 p**	**9.22 a**	 **9.9 f**	67 h	36%
	9.22 b	 **9.9 g**	67 h	30%
 **9.21 q**	**9.22 a**	 **9.9 h**	120 h	20%

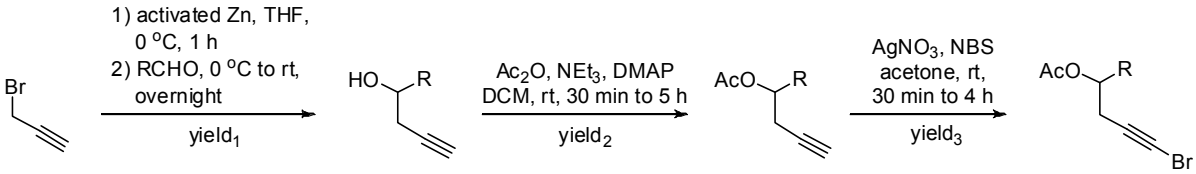
(continued on the next page)

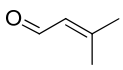
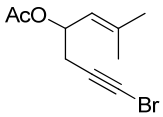
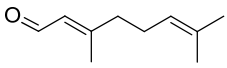
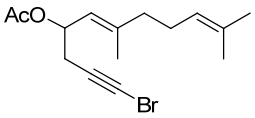
bromoalkyne	carbamate	product	time	yield[a]
 **9.21 r**	**9.22 a**	 **9.9 i**	96 h	18%

[a] Isolated yield.

General procedure 9.1: To a solution of a bromoalkyne (1 equiv) in dry toluene (0.33 M) were sequentially added the carbamate (1.2 equiv), K_3PO_4 (2.4 equiv), $CuSO_4 \cdot 5H_2O$ (0.2 equiv) and 1,10-phenanthroline (0.4 equiv). The reaction mixture was capped and heated at 80 °C while being monitored by TLC periodically. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to afford the desired carbamate.

Bromoalkynes **9.21 a-c** and **f-j** were prepared in a 3-step sequence involving a zinc mediated propargylation of an α,β-unsaturated aldehyde,[341] an acetylation of the secondary alcohol under classical conditions and a bromination of the corresponding terminal acetylene.[325]



aldehyde	product		yield$_1$[a]	yield$_2$[a]	yield$_3$[a]
		**9.21 a**	80%	93%	quant.
		**9.21 b**	84%	72%	80%

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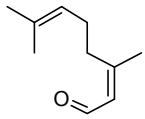
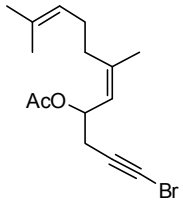
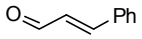
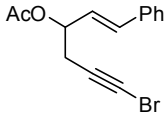
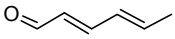
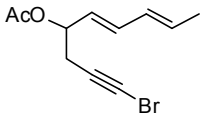
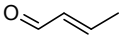
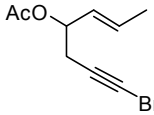
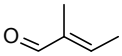
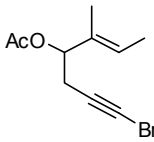
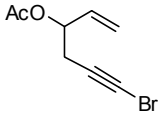
aldehyde	product		yield$_1$[a]	yield$_2$[a]	yield$_3$[a]
		**9.21 c**	80%	99%	70%
		**9.21 f**	77%	43%	99%
		**9.21 g**	76%	91%	85%
		**9.21 h**	75%	73%	92%
		**9.21 i**	85%	quant.	97%
		**9.21 j**	55%	81%	70%

[a] Isolated yield.

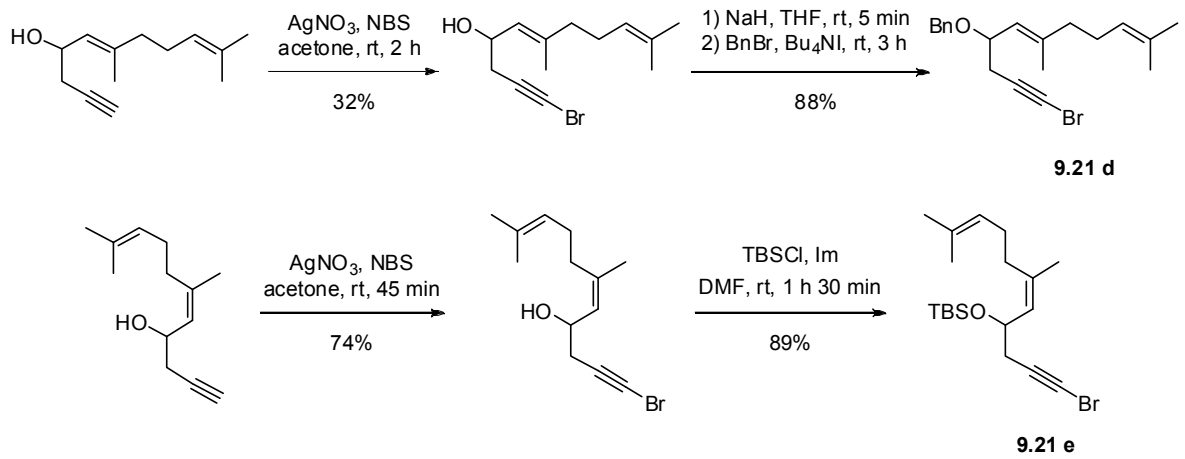
General procedure 9.2: Zn(II)-mediated propargylation: To a suspension of previously activated Zn (2 equiv) in THF (1 M) at 0 °C was added propargyl bromide (1.5 equiv, 80% wt. toluene solution). The suspension was stirred at 0 °C for 1h, then the α,β-unsaturated aldehyde (1 equiv) was added and the suspension was allowed to slowly reach rt overnight. The reaction was quenched with saturated aqueous NH_4Cl solution, filtered and the filtrate extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected coupling product.

Acetylation of the secondary alcohol group: To a solution of secondary alcohol (1 equiv) in DCM (0.5 M) was added NEt_3 (2 equiv), Ac_2O (1.5 equiv) and DMAP (0.1 equiv). The mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$,

and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected acetylated product.

Bromination of the terminal alkyne: To a solution of terminal alkyne (1 equiv) in acetone (0.15 M) at 0 °C were added NBS (1.1 equiv) and $AgNO_3$ (0.05 equiv). The reaction vessel was wrapped in aluminum foil to avoid light exposure and the reaction mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was cooled again at 0 °C, quenched with cold water and extracted three times with diethyl ether. The combined organic layers were washed two times with water and once with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the bromoalkyne.

Bromoalkynes **9.21 d** and **e** were prepared in a very similar way by bromination of the corresponding enyne (obtained by the method previously described) followed by protection of the secondary alcohol group.

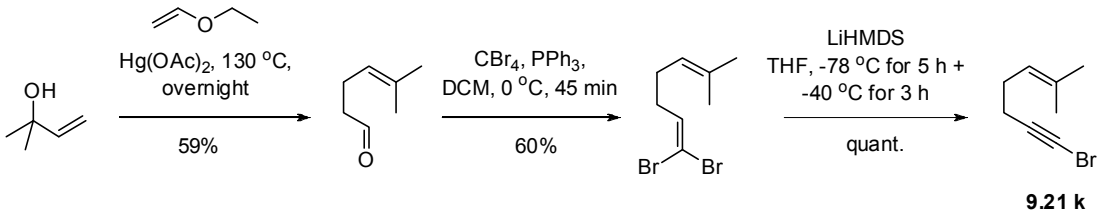


General procedure 9.3: Protection of the secondary alcohol with a Bn group: To a solution of secondary alcohol (1 equiv) in THF (0.5 M) was added NaH (1.2 equiv, 60% dispersion in mineral oil). The mixture was allowed to react for 5 min, then BnBr (1.1 equiv) and Bu_4NI (0.1 equiv) were added. The mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica

gel, petroleum ether / diethyl ether) to give the expected product.

Protection of the secondary alcohol with a TBS group: To a solution of secondary alcohol (1 equiv) in dry DMF (0.25 M) was added imidazole (3 equiv) and TBSCl (1.5 equiv). The mixture was stirred at rt and followed periodically by TLC. Upon completion, the reaction was quenched with water and extracted twice with diethyl ether. The combined organic layers were washed twice with water and once with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected product.

Substrate **9.21 k** was prepared starting from 2-methyl-but-3-en-2-ol and ethyl vinyl ether by a Claisen rearrangement[344] of the intermediate allylic vinyl ether into the corresponding γ,δ-unsaturated aldehyde, followed by its transformation into the final bromoalkyne by the Corey-Fuchs method.[345,328b,328c]



General procedure 9.4: A mixture of 2-methyl-but-3-en-2-ol (1 equiv), ethyl vinyl ether (3 equiv), and freshly recrystallized $Hg(OAc)_2$ (0.2 equiv) were capped and heated at 130 °C overnight. The reaction mixture was concentrated under reduced pressure to remove volatiles and then purified via flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the rather volatile γ,δ-unsaturated aldehyde.

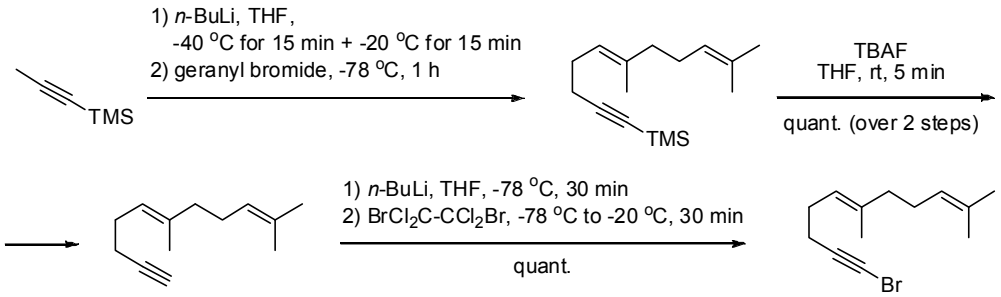
To a solution of PPh_3 (4 equiv) in DCM (2 M) at 0 °C was added a solution of CBr_4 (2 equiv) in DCM (2 M). The mixture was stirred at 0 °C for 5 min, then a solution of γ,δ-unsaturated aldehyde (1 equiv) in DCM (1 M) was added dropwise. The mixture was allowed to react at 0 °C for 45 min. Upon completion, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted two times with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Petroleum ether was added to the residue, which was then filtered and reevaporated under reduced pressure. The crude was purified by flash column chromatography (silica

[344] Kraus, G. A.; Kim, J. *Org. Lett.* **2004**, *6*, 3115-3117.
[345] Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1994**, *35*, 3529-3530.

gel, petroleum ether) to give the dibromoalkene.

The resulting dibromoalkene (1 equiv) was dissolved in THF (0.1 M) and cooled at -78 °C. LiHMDS (2 equiv, 1 M in THF solution) was added dropwise and the mixture was stirred at -78 °C for 5 h and at -40 °C for 3 h. Upon completion, the reaction was quenched at -40 °C with HCl 1N aqueous solution and extracted two times with petroleum ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether) to give the expected bromoalkyne.

Substrate **9.21 l** was prepared from trimethyl(prop-1-yn-1-yl)silane by deprotonation with *n*-BuLi in the propargylic position, allylation with geranyl bromide, deprotection of the TMS group and bromination of the terminal alkyne thus obtained. Bromoalkyne **9.21 l** is obtained in mixture with $BrCl_2C\text{-}CCl_2Br$, however this impurity does not hinder the coupling reaction with the corresponding carbamate.



9.21 l

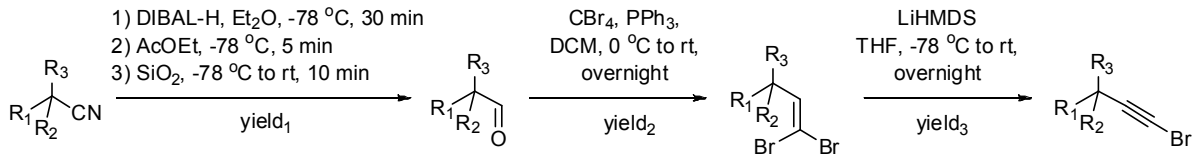
General procedure 9.5: To a solution of trimethyl(prop-1-yn-1-yl)silane (1 equiv) in THF (0.5 M) at -40 °C was added *n*-BuLi (1 equiv, 1.6 M in hexane) dropwise. The reaction was stirred at -40 °C for 15 min and at -20 °C for another 15 min, then it was cooled back to -78 °C and geranyl bromide (1 equiv) was added dropwise. The resulting mixture was stirred at -78 °C for 1h, and then it was quenched with water and extracted two times with petroleum ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether) to give the TMS-protected enyne.

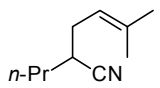
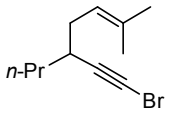
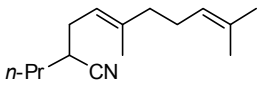
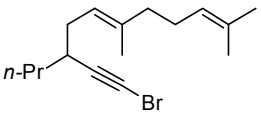
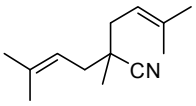
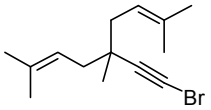
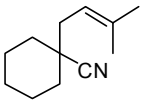
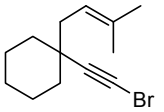
The resulting TMS-protected enyne (1 equiv) was dissolved in THF (1 M) and to this solution was added TBAF (1 equiv, 1 M solution in THF) dropwise. The reaction was stirred at rt for 5 min. Upon completion, the reaction was quenched with water and extracted two times with

petroleum ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether) to give expected enyne.

To a solution of the enyne previously obtained (1 equiv) in THF (0.5 M) was added *n*-BuLi (1.05 equiv, 1.6 M in hexane) dropwise. The reaction was stirred at -78 °C for 30 min, and then 1,2-dibromo-1,1,2,2-terachloroethane (1.1 equiv) was added dropwise. The resulting mixture was allowed to warm up slowly from -78 °C to -20 °C for 30 min, and then it was quenched with water and extracted twice with petroleum ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether) to give final product in a mixture with 1,2-dibromo-1,1,2,2-terachloroethane.

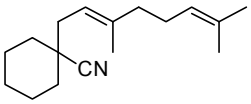
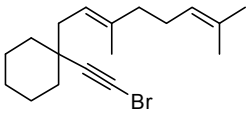
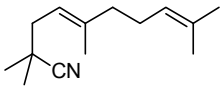
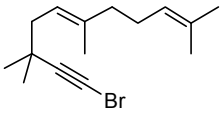
Substrates **9.21 m-r** were obtained from the cyano derivatives **9.23 a-f** by DIBAL-H reduction[346] to the corresponding aldehyde followed by conversion to the corresponding bromoalkyne via the Corey-Fuchs method.[345,328b,328c]



substrate		product		yield$_1$[a]	yield$_2$[a]	yield$_3$[a]
	**9.23 a**		**9.21 m**	61%	70%	96%
	**9.23 b**		**9.21 n**	80%	87%	94%
	**9.23 c**		**9.21 o**	84%	72%	94%
	**9.23 d**		**9.21 p**	84%	41%	97%

(continued on the next page)

[346] Boyer, F. D.; Hanna, I. *Eur. J. Org. Chem.* **2006**, *2006*, 471-482.

substrate		product		yield$_1$[a]	yield$_2$[a]	yield$_3$[a]
	**9.23 e**		**9.21 q**	70%	38%	84%
	**9.23 f**		**9.21 r**	70%	43%	94%

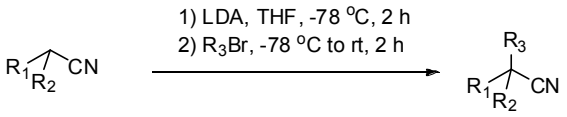
[a] Isolated yield.

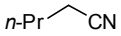
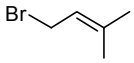
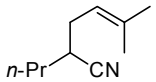
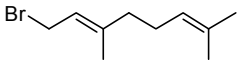
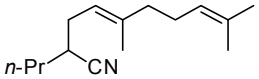
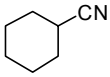
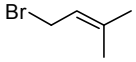
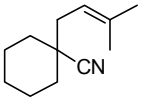
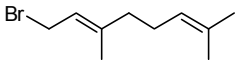
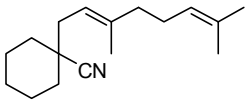
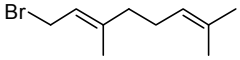
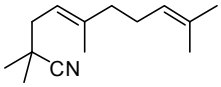
General procedure 9.6: To a solution of cyano derivative (1 equiv) in diethyl ether (0.4 M) at -78 °C DIBAL-H (1.5 equiv, 1 M solution in hexane) was added dropwise. The reaction was stirred at -78 °C for 30 min, then AcOEt was added dropwise and the resulting mixture was stirred for another 5 min at -78 °C. Silica was further added and the resulting suspension stirred for 5 min at -78°C. The mixture was warmed to 0 °C, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the desired aldehyde.

To a solution of PPh_3 (4 equiv) in DCM (2 M) at 0 °C was added a solution of CBr_4 (2 equiv) in DCM (2 M). The mixture was stirred at 0 °C for 5 min, then a solution of previously obtained aldehyde (1 equiv) in DCM (1 M) was added dropwise. The mixture was allowed to slowly warm to rt overnight. Upon completion, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted two times with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Petroleum ether was added to the residue, which was then filtered and reevaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether) to give the dibromoalkene.

The resulting dibromoalkene (1 equiv) was dissolved in THF (0.1 M) and cooled at -78 °C. LiHMDS (2 equiv, 1 M in THF solution) was added dropwise and the mixture was allowed to warm up from -78 °C to rt overnight. Upon completion, the reaction was quenched with HCl 1N aqueous solution and extracted two times with petroleum ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected bromoalkyne.

Cyano derivatives **9.23 a-e** were prepared by monoallylation from the corresponding starting nitriles under classical conditions.[347]



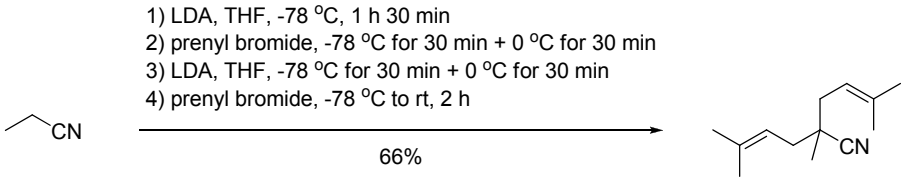
nitrile	allyl bromide	product		yield[a]
			**9.23 a**	31%
			**9.23 b**	43%
			**9.23 c**	97%
			**9.23 d**	95%
			**9.23 e**	65%

[a] Isolated yield.

General procedure 9.7: To a solution of nitrile (1 equiv) in THF (4 M) at -78 °C a solution of freshly prepared LDA (1.05 equiv, 4M in THF) was added dropwise. The reaction was stirred at -78 °C for 2 h, then the allyl bromide (1 equiv) was added dropwise. The resulting mixture was allowed to warm up from -78 °C to rt for 2 h. Upon completion, the reaction was quenched with saturated NH_4Cl aqueous solution and extracted two times with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected cyano derivative.

Cyano derivative **9.23 f** was prepared analogously by bisallylation of the corresponding nitrile.

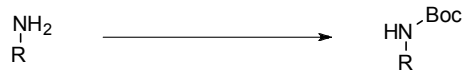
[347] Horrillo Martinez, P.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221-2223.



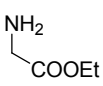
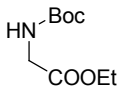
9.23 f

General procedure 9.8: To a solution of nitrile (1 equiv) in THF (1 M) at -78 °C a solution of freshly prepared LDA (1.05 equiv, 1M in THF) was added dropwise. The reaction was stirred at -78 °C for 1 h 30 min, then prenyl bromide (0.95 equiv) was added dropwise and the resulting mixture was stirred at -78 °C for 30 min and at 0 °C for 30 min. The reaction was cooled down to -78 °C and more freshly prepared LDA solution (1.05 equiv, 1 M in THF) was added. After 30 min of stirring at -78 °C and another 30 min at 0 °C, prenyl bromide (1.15 equiv) was added dropwise and the resulting mixture was allowed to warm up from -78 °C to rt for 2 h. Upon completion, the reaction was quenched with saturated NH_4Cl aqueous solution and extracted two times with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to give the expected cyano derivative.

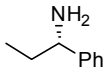
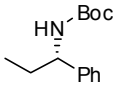
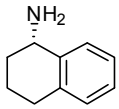
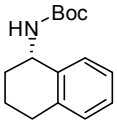
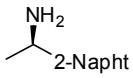
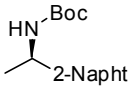
Carbamates **9.22 a-g** were obtained from the corresponding amines using classical methods described in the literature.[329b,329d]



Conditions: (a) Boc_2O, EtOH, rt, 5 min - 30 min
(b) Boc_2O, MeOH, rt, 5 min
(c) Boc_2O, NEt_3, MeOH, rt, 24 h

amine	product		conditions	time	yield[a]
		9.22 a	a	5 min	81%
		9.22 b	b	5 min	86%
		**9.22 c**	c	24 h	95%

(continued on the next page)

amine	product		conditions	time	yield[a]
		9.22 d	a	5 min	96%
		**9.22 e**	a	5 min	93%
		**9.22 f**	a	30 min	quant.
		**9.22 g**	**a**	5 min	90%

[a] Isolated yield.

General procedure 9.9: Conditions a:[329b] To a solution of amine (1 equiv) in EtOH (1 M) at rt was added Boc_2O (1.05 equiv). The mixture was stirred at rt, then concentrated under reduced pressure. The residue was recrystallized in petroleum ether to afford the clean final product.

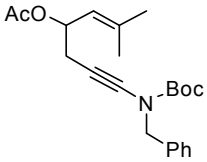
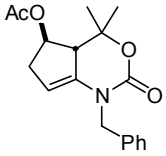
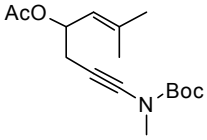
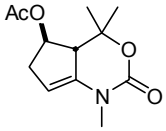
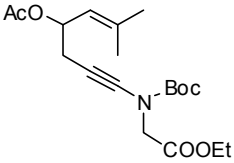
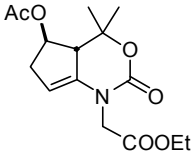
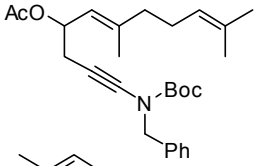
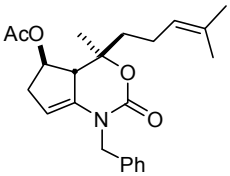
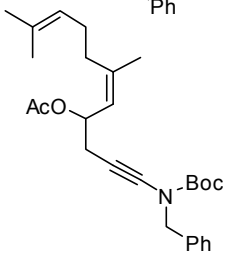
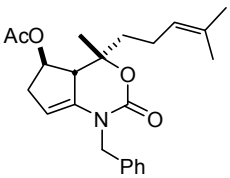
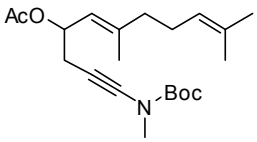
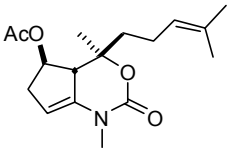
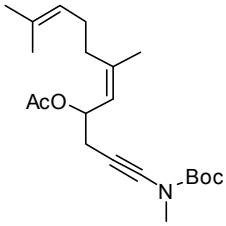
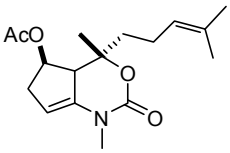
Conditions b:[329b] To a solution of amine (2 equiv) in MeOH (~10% vol.) at rt was added slowly Boc_2O (1 equiv). The mixture was stirred at rt for 5 min, then concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to afford the clean final product.

Conditions c:[329d] To a solution of amine (1 equiv) in MeOH (0.75 M) was added NEt_3 (1.5 equiv) and Boc_2O (1.05 equiv). The mixture was allowed to react at rt for 24 h, and then concentrated under reduced pressure. The residue was diluted with water and extracted three times with DCM. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the pure final product.

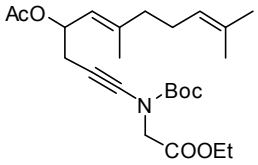
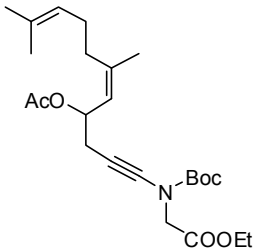
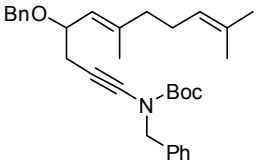
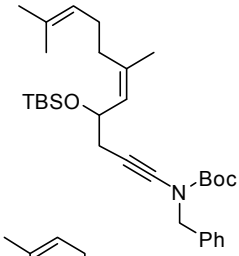
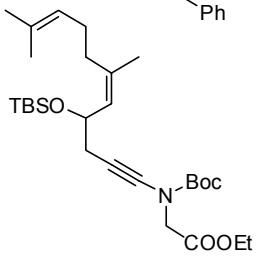
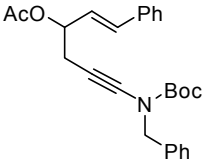
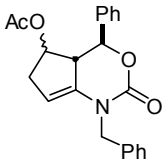
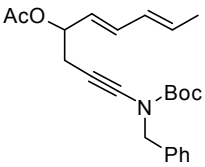
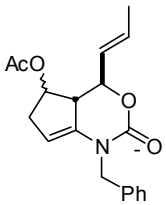
9.2. Gold(I)-catalyzed formation of functionalized 1,3-oxazinan-3-ones

As we saw in Chapter 9, various functionalized 1,3-oxazinan-2-ones derivatives can be obtained from the corresponding *N*-hex-5-enynyl *tert*-butyloxycarbamates.

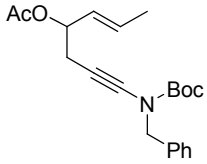
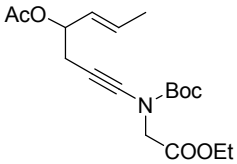
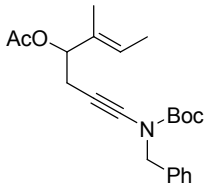
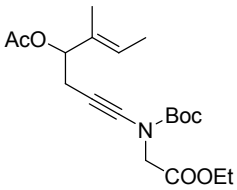
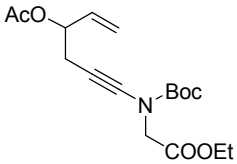
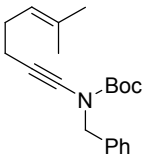
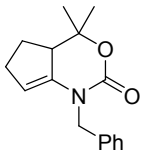
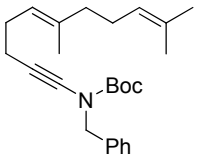
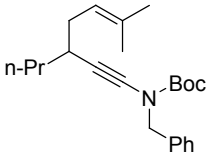
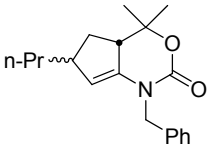
Conditions: (a) 1% JohnPhos-Au-NTf_2
(b) 3% JohnPhos-Au-NTf_2
(c) 5% JohnPhos-Au-NTf_2
(d) 1% Ph_3P-Au-NTf_2

substrate		product		conditions	time	yield[a]
	**9.4 a**		**9.5 a**	a d	1 h 30 min	78% 68%
	**9.4 b**		**9.5 b**	a	22 h	68%
	**9.4 c**		**9.5 c**	a	24 h	65%
	**9.4 d**		**9.5 d**	a	2 h 40 min	63%
	**9.4 e**		**9.5 e**	a	1 h 30 min	57%
	**9.4 f**		**9.5 f**	a	18 h	56%
	**9.4 g**		**9.5 g**	a	22 h	56%

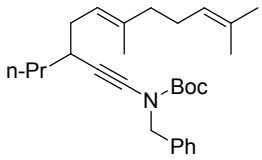
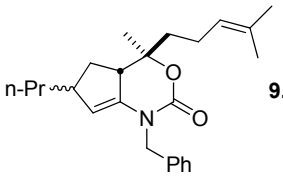
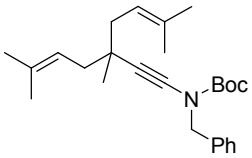
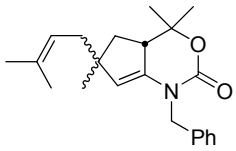
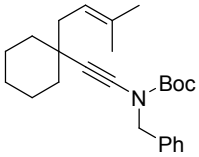
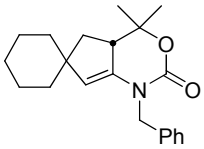
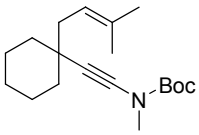
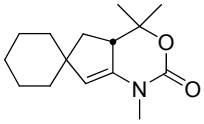
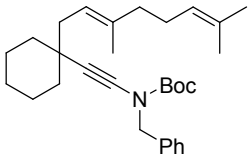
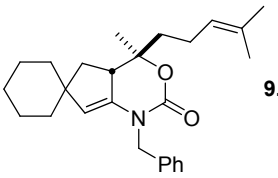
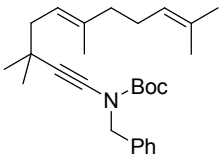
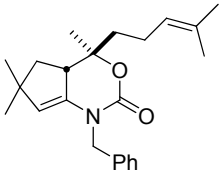
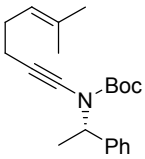
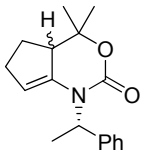
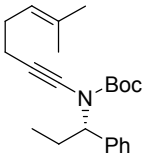
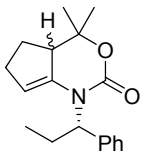
(continued on the next page)

substrate		product		conditions	time	yield[a]
	**9.4 h**	-		a	24 h	mainly SM
	**9.4 i**	-		a	7 h	mainly SM
	**9.4 j**	-		a	17 h	mainly SM
	**9.4 k**	-		a	66 h	degrad.
	**9.4 l**	-		a	24 h	degrad.
	**9.4 m**	 dr ~1/1	**9.5 m**	b	15 min	47%[b]
	**9.4 n**	 dr ~1.9/1	**9.5 n**	c	10 min	56%[c]

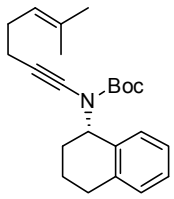
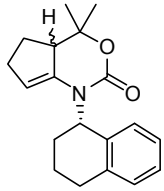
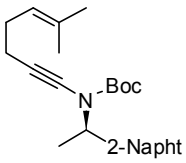
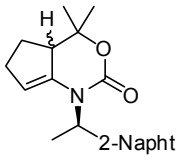
(continued on the next page)

substrate		product		conditions	time	yield[a]
	**9.4 o**	-		a	24 h	mainly SM
	**9.4 p**	-		a	19 h	mainly SM
	**9.4 q**	-		a	30 min	degrad.
	**9.4 r**	-		a	7 h	mainly SM
	**9.4 s**	-		a	24 h	mainly SM
	**9.9 a**		**9.10 a**	a d	1 h 45 min	40%[d] 46%[e]
	**9.9 b**	-		a	7 h 30 min	degrad.
	**9.9 c**	 dr ~1/1	**9.10 c**	a	4 h	36%[f]

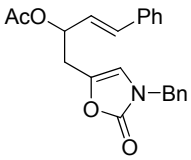
(continued on the next page)

substrate		product		conditions	time	yield[a]
	**9.9 d**	 dr ~ 1/1.1	**9.10 d**	a	7 h 30 min	37%
	**9.9 e**	 dr ~1/1.4	**9.10 e**	a	45 min	39%[g]
	**9.9 f**		**9.10 f**	a	1 h	26%[h]
	**9.9 g**		**9.10 g**	a	2 h	30%[i]
	**9.9 h**		**9.10 h**	a	1 h 30 min	25%
	**9.9 i**		**9.10 i**	a	1 h	39%
	**9.9 j**	 dr ~ 1/1.3	**9.10 j**	d	2 h 30 min	43%[j]
	**9.9 k**	 dr ~ 1/1.2	**9.10 k**	d	6 h	41%[k]

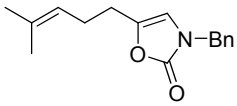
(continued on the next page)

substrate		product		conditions	time	yield[a]
	**9.9 l**	 dr ~ 1/1.25	**9.10 l**	d	30 min	53%[l]
	**9.9 m**	 dr ~ 1/1.4	**9.10 m**	d	4 h	41%[m]

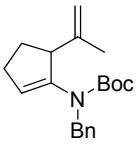
[a] Isolated yield. dr determined by ^{1}H NMR [b] Product **9.5 m** is obtained as a mixture of separable diastereoisomers. Side product **9.8** was also isolated in a 9% yield. [c] Product **9.5 n** is obtained as an inseparable mixture of 2 diastereoisomers, impurified with a third compound, yet unidentified. The yield and the dr are determined by ^{1}H NMR of the crude mixture. [d] Side product **9.11** was also isolated in a 5% yield. [e] The formation of traces of product **9.12 a** was also observed. [f] Product **9.12 c** was also isolated with a 26% yield (dr ~ 1/2.3). [g] Product **9.12 e** was also isolated with a 16% yield (dr ~ 1/1). [h] Product **9.12 f** was also isolated with a 17% yield. [i] Product **9.12 g** was also isolated with a 36% yield. [j] The formation of traces of product **9.12 j** was also observed. [k] The formation of traces of product **9.12 k** was also observed. [l] The formation of traces of product **9.12 l** was also observed. [m] The formation of traces of product **9.12 m** was also observed.



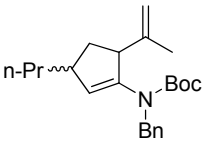
9.8



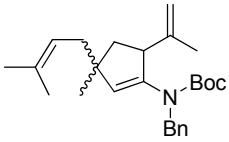
9.11



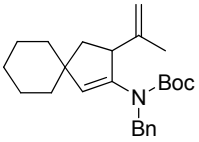
9.12 a



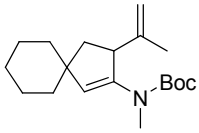
9.12 c



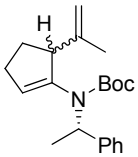
9.12 e



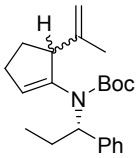
9.12 f



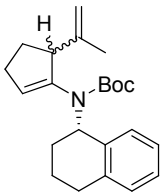
9.12 g



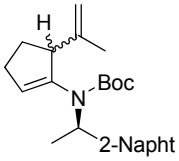
9.12 j



9.12 k



9.12 l

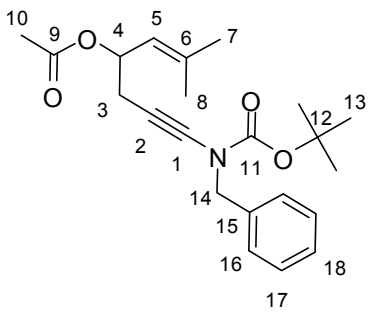


9.12 m

General procedure 9.10: To a solution of substrate (1 equiv) in DCM (0.1 M) the corresponding amount of catalyst was added (0.01 equiv of JohnPhos-Au-NTf_2 for conditions (a), 0.03 equiv of JohnPhos-Au-NTf_2 for conditions (b), 0.05 equiv of JohnPhos-Au-NTf_2 for conditions (c) and 0.01 equiv of Ph_3P-Au-NTf_2 for conditions (d)). The reaction was stirred at rt while being monitored periodically by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether / diethyl ether) to afford the desired product.

9.3. Characterization of the prepared compounds

Acetic acid 1-[3-(benzyl-*tert*-butoxycarbonyl-amino)-prop-2-ynyl]-3-methyl-but-2-enyl ester **9.4 a**



MF: $C_{22}H_{29}NO_4$

MW: 371.47 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Yellow oil.

Yield: 69%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.37-7.26 (m, 5H, *16*, *17* and *18*), 5.54 (m, 1H, *4*), 5.18 (dhept, J = 1.3, 9.1 Hz, 1H, *5*), 4.54 (s, 2H, *14*), 2.56 (d, J = 5.5 Hz, 2H, *3*), 2.00 (s, 3H, *10*), 1.72 (d, J = 1.2 Hz, 3H, *7* or *8*), 1.70 (d, J = 1.2 Hz, 3H, *7* or *8*), 1.49 (s, 9H, *13*).

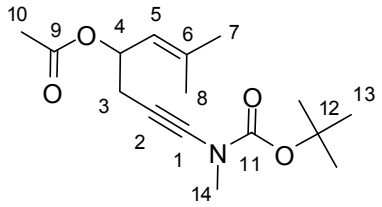
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.1 (*9*), 154.3 (*11*), 138.2 (*6*), 136.7 (*15*), 128.3 (*16* or *17*), 128.3 (*16* or *17*), 127.6 (*18*), 122.3 (*5*), 82.2 (*12*), 77.2 (*1*), 69.5 (*4*), 64.9 (*2*), 53.0 (*14*), 28.0 (*13*), 25.7 (*7* or *8*), 25.0 (*3*), 21.2 (*10*), 18.5 (*7* or *8*).

IR (ν, cm^{-1}) (CCl_4): 3065, 3031, 2977, 2932, 2263, 1724, 1446, 1390, 1369, 1296, 1239, 1163, 1017.

MS (EI$^+$, m/z): 371 (M^+), 318, 311, 273, 255, 228, 212.

HRMS (EI^+, m/z) Calculated for $C_{22}H_{29}NO_4$: 371.2097.
Found for $C_{22}H_{29}NO_4$: 371.2094.

Acetic acid 1-[3-(*tert*-butoxycarbonyl-methyl-amino)-prop-2-ynyl]-3-methyl-but-2-enyl ester **9.4 b**



MF: $C_{16}H_{25}NO_4$

MW: 295.37 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.1** (scale: 2 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Yellow oil.

Yield: 16%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.59 (m, 1H, *4*), 5.23 (d, J = 9.4 Hz, 1H, *5*), 3.06 (s, 3H, *14*), 2.58 (m, 2H, *3*), 2.05 (s, 3H, *10*), 1.76 (s, 3H, *7* or *8*), 1.75 (s, 3H, *7* or *8*), 1.49 (s, 9H, *13*).

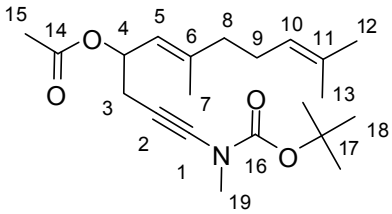
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 170.2 (*9*), 154.7 (*11*), 138.3 (*6*), 122.3 (*5*), 81.9 (*12*), 77.2 (*1*), 69.6 (*4*), 63.6 (*2*), 37.1 (*14*), 28.0 (*13*), 25.7 (*7* or *8*), 25.0 (*3*), 21.2 (*10*), 18.6 (*7* or *8*).

IR (ν, cm^{-1}) (CCl_4) 2977, 2931, 2263, 1725, 1449, 1426, 1370, 1314, 1239, 1158, 1016.

MS (EI^+, m/z) 295 (M^+), 235, 197.

HRMS (EI^+, m/z) Calculated for $C_{16}H_{25}NO_4$: 295.1784.
Found for $C_{16}H_{25}NO_4$: 295.1779.

Acetic acid (*E*)-1-[3-(*tert*-butoxycarbonyl-methyl-amino)-prop-2-ynyl]-3,7-dimethyl-octa-2,6-dienyl ester **9.4 f**



MF: $C_{21}H_{33}NO_4$

MW: 363.49 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.1** (scale: 1.66 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 95/5).

Product: Yellow oil.

Yield: 38%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.59 (m, 1H, *4*), 5.21 (d, J = 9.9 Hz, 1H, *5*), 5.08 (t, J = 6.9 Hz, 1H, *10*), 3.05 (s, 3H, *19*), 2.58 (m, 2H, *3*), 2.09 (m, 2H, *9*), 2.05 (s, 3H, *15*), 2.03 (m, 2H, *8*), 1.75 (s, 3H, *7*), 1.68 (s, 3H, *12* or *13*), 1.60 (s, 3H, *12* or *13*), 1.49 (s, 9H, *18*).

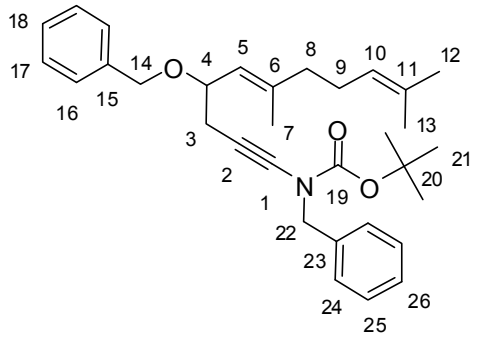
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.2 (*14*), 154.7 (*16*), 141.5 (*6*), 131.7 (*11*), 123.7 (*10*), 122.1 (*5*), 81.9 (*17*), 77.2 (*1*), 69.5 (*4*), 66.8 (*2*), 39.4 (*8*), 37.1 (*19*), 28.0 (*18*), 26.3 (*9*), 25.6 (*12* or *13*), 25.0 (*3*), 21.2 (*15*), 17.6 (*12* or *13*), 16.9 (*7*).

IR (ν, cm^{-1}) (CCl_4): 2974, 2926, 2859, 2263, 1725, 1674, 1447, 1372, 1314, 1238, 1158, 1122, 1017.

MS (EI^+, m/z): 363 (M^+), 318, 303, 265, 262, 248, 234, 220.

HRMS (EI^+, m/z): Calculated for $C_{21}H_{33}NO_4$: 363.2410.
Found for $C_{21}H_{33}NO_4$: 363.2406.

Benzyl-((*E*)-4-benzyloxy-6,10-dimethyl-undeca-5,9-dien-1-ynyl)-carbamic acid *tert*-butyl ester **9.4 j**



MF: $C_{32}H_{41}NO_3$

MW = 487.67 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 9.1** (scale: 0.794 mmol).

Purification : Flash column chromatography (silica gel, PE/Et_2O 96/4).

Product : Yellow oil.

Yield : 58%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.34-7.24 (m, 10H, *16*, *17*, *18*, *24*, *25* and *26*), 5.14 (dm, J = 9.2 Hz, 1H, *5*), 5.11 (thept, J = 1.3, 7.0 Hz, 1H, *10*), 4.56 (d, J = 12.1 Hz, 1H, *14*), 4.53 (s, 2H, *22*), 4.37 (d, J = 12.1 Hz, 1H, *14*), 4.19 (m, 1H, *4*), 2.59 (m, 1H, *3*), 2.49 (m, 1H, *3*), 2.10 (m, 2H, *8* or *9*), 2.05 (m, 2H, *8* or *9*), 1.69 (s, 3H, *7*, *12* or *13*), 1.62 (s, 3H, *7*, *12* or *13*), 1.58 (d, J = 1.2 Hz, 3H, *7*, *12* or *13*), 1.47 (s, 9H, *21*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.4 (*19*), 140.5 (*15*), 138.8 (*6* or *11*), 135.9 (*23*), 131.6 (*6* or *11*), 128.3 (*16*, *17*, *18*, *24*, *25* and/or *26*), 128.2 (*16*, *17*, *18*, *24*, *25* and/or *26*), 127.6 (*16*, *17*, *18*, *24*, *25* and/or *26*), 127.5 (*16*, *17*, *18*, *24*, *25* and/or *26*), 127.3

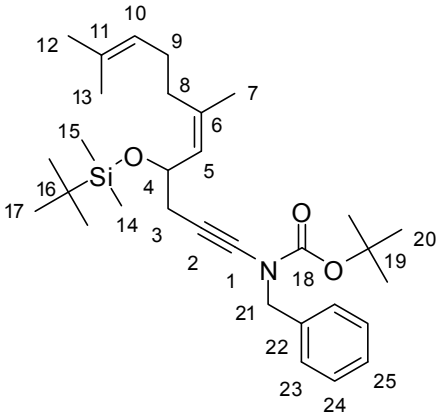
(*16*, *17*, *18*, *24*, *25* and/or *26*), 124.8 (*5* or *10*), 123.9 (*5* or *10*), 82.1 (*20*), 77.2 (*1* or *2*), 73.6 (*4*), 69.6 (*14*), 66.4 (*2*), 53.8 (*22*), 39.6 (3, 8 or 9), 28.0 (*21*), 26.3 (3, 8 or 9), 25.8 (3, 8 or 9), 25.7 (*7*, *12* or *13*), 17.7 (*7*, *12* or *13*), 16.7 (*7*, *12* or *13*).

IR (ν, cm^{-1}) (CCl_4) 3064, 3031, 2976, 2926, 2859, 2263, 1718, 1449, 1388, 1297, 1252, 1231, 1164, 1089, 1071, 1025.

MS (EI^+, m/z) 487 (M^+), 430, 418, 386, 378, 362.

HRMS (EI^+, m/z) **:** Calculated for $C_{32}H_{41}NO_3$: 487.3086.
Found for $C_{32}H_{41}NO_3$: 487.3099.

Benzyl-[(*Z*)-4-(*tert*-butyl-dimethyl-silanyloxy)-6,10-dimethyl-undeca-5,9-dien-1-ynyl]-carbamic acid *tert*-butyl ester **9.4 k**



MF: $C_{31}H_{49}NO_3Si$

MW = 511.81 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 9.1** (scale: 1.427 mmol).

Purification : Flash column chromatography (silica gel, PE/Et_2O 99/1-98/2).

Product : Yellow oil.

Yield : 47%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.36-7.27 (m, 5H, *19*, *20* and *21*), 5.14 (dm, J = 8.7 Hz, 1H, *5*), 5.09 (m, 1H, *10*), 4.59-4.40 (m, 3H, *4* and *21*), 2.39 (m, 2H, *3*), 2.04 (m, 4H, *8* and *9*), 1.68 (s, 6H, 7 and *12* or *13*), 1.60 (s, 3H, *12* or *13*), 1.48 (s, 9H, *20*), 0.87 (s, 9H, *17*), 0.03 (s, 3H, *14* or *15*), 0.01 (s, 3H, *14* or *15*).

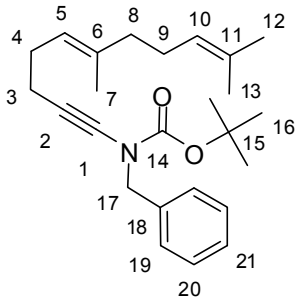
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 154.4 (*18*), 136.9 (*22*), 136.0 (*7*), 131.7 (*11*), 128.8 (*6*), 128.3 (*23* and *24*), 127.5 (*25*), 124.0 (*10*), 82.0 (*19*), 77.2 (*1* or *2*), 68.4 (*4*), 65.8 (*1* or *2*), 53.0 (*21*), 32.5 (*8* or *9*), 28.8 (*3*), 28.0 (*20*), 26.5 (*8* or *9*), 25.8 (*17*), 25.6 (*7*, *12* or *13*), 23.1 (*7*, *12* or *13*), 18.1 (*16*), 17.6 (*7*, *12* or *13*), -4.2 (*14* or *15*), -4.6 (*14* or *15*).

IR (ν, cm^{-1}) (CCl_4) 3067, 3031, 2955, 2930, 2856, 2261, 1718, 1453, 1388, 1297, 1252, 1164, 1071.

MS (EI^+, m/z) 511 (M^+), 478, 454, 440, 428, 411.

HRMS (EI^+, m/z) **:** Calculated for $C_{31}H_{49}NO_3Si$: 511.3482.
Found for $C_{31}H_{49}NO_3Si$: 511.3483.

Benzyl-((*E*)-6,10-dimethyl-undeca-5,9-dien-1-ynyl)-carbamic acid *tert*-butyl ester 9.9 b



MF: $C_{25}H_{35}NO_2$

MW = 381.55 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 9.1** (scale: 2 mmol).

Purification : Flash column chromatography (silica gel, PE/Et_2O 97/3).

Product : Yellow oil.

Yield : 18%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.37-7.27 (m, 5H, *19*, *20* and *21*), 5.15 (tm, J = 6.8 Hz, 1H, *10*), 5.10 (tm, J = 6.9 Hz, 1H, *5*), 4.54 (s, 2H, *17*), 2.26 (m, 2H, *8*), 2.18 (m, 2H, *9*), 2.06 (m, 2H, *4*), 1.97 (m, 2H, *3*), 1.69 (s, 3H, *7*), 1.60 (s, 6H, *12* and *13*), 1.49 (s, 9H, *16*).

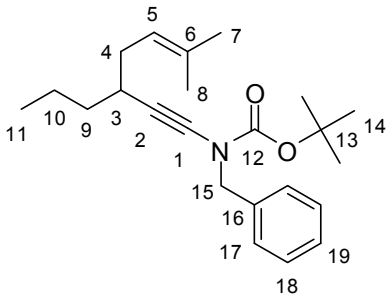
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 154.5 (*14*), 136.9 (*18*), 136.1 (*6* or *11*), 131.3 (*6* or *11*), 128.3 (*19*, *20* and/or *21*), 127.5 (*19*, *20* and/or *21*), 124.2 (*5* or *10*), 122.9 (*5* or *10*), 82.1 (*15*), 53.1 (*17*), 39.6 (*3*), 28.0 (*16*), 27.7 (*9*), 26.7 (*4* or *8*), 25.6 (*7*), 18.9 (*4* or *8*), 17.6 (*12* or *13*), 16.0 (*12* or *13*).

IR (ν, cm^{-1}) (CCl_4) 3064, 3031, 2974, 2925, 2856, 2260, 1718, 1447, 1388, 1294, 1164, 1252, 1230, 1164, 1025.

MS (EI^+, m/z) 381 (M^+), 325, 310, 279, 266, 241, 233, 212, 199, 190.

HRMS (EI^+, m/z) **:** Calculated for $C_{25}H_{35}NO_2$: 381.2668.
Found for $C_{25}H_{35}NO_2$: 381.2652.

Benzyl-(6-methyl-3-propyl-hept-5-en-1-ynyl)-carbamic acid *tert*-butyl ester 9.9 c



MF: $C_{22}H_{33}NO_2$

MW: 355.51 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.1** (scale: 2.334 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil.

Yield: 64%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.39-7.27 (m, 5H, *17*, *18* and *19*), 5.17 (thept, J = 1.2, 7.1 Hz, 1H, *5*), 4.54 (s, 2H, *15*), 2.41 (m, 1H, *3*), 2.11 (m, 2H, *4*), 1.70 (s, 3H, *7* or *8*), 1.59 (s, 3H, *7* or *8*), 1.50 (s, 9H, *14*), 1.46-1.26 (m, 4H, *9* and *10*), 0.87 (t, J = 6.8 Hz, 3H, *11*).

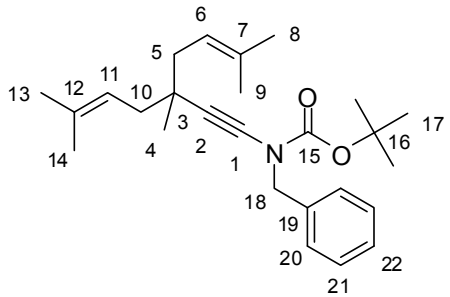
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.6 (*12*), 136.8 (*16*), 132.4 (*6*), 128.3 (*17*, *18* and/or *19*), 127.6 (*17*, *18* and/or *19*), 122.3 (*5*), 81.9 (*13*), 77.2 (*1* or *2*), 73.2 (*1* or *2*), 53.0 (*15*), 37.0 (*9* or *10*), 33.9 (*4*), 31.8 (*3*), 28.0 (*14*), 25.7 (*7* or *8*), 20.5 (*9* or *10*), 17.9 (*7* or *8*), 13.9 (*11*).

IR (ν, cm^{-1}) (CCl_4): 3065, 3032, 2964, 2928, 2869, 2256, 1717, 1450, 1391, 1365, 1293, 1228, 1163, 1077, 1028.

MS (EI^+, m/z): 355 (M^+), 299, 286, 255, 240, 229, 212.

HRMS (EI^+, m/z): Calculated for $C_{22}H_{33}NO_2$: 355.2511.
Found for $C_{22}H_{33}NO_2$: 355.2516.

Benzyl-[3,6-dimethyl-3-(3-methyl-but-2-enyl)-hept-5-en-1-ynyl]-carbamic acid *tert*-butyl ester — 9.9 e



MF: $C_{26}H_{37}NO_2$

MW: 395.58 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.1** (scale: 3.205 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1).

Product: Yellow oil.

Yield: 66%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.42-7.27 (m, 5H, *20*, *21* and *22*), 5.23 (t, J = 6.7 Hz, 1H, *6* and *11*), 4.54 (s, 2H, *18*), 2.06 (m, 4H, *5* and *10*), 1.71 (s, 6H, *8*, *9*, *13* and/or *14*), 1.58 (s, 6H, *8*, *9*, *13* and/or *14*), 1.51 (s, 9H, *17*), 1.05 (s, 3H, *4*).

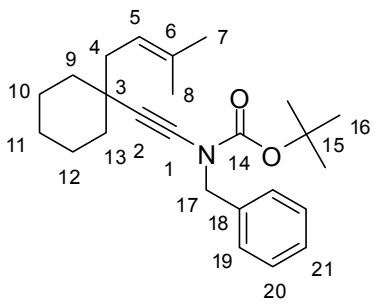
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.6 (*15*), 136.8 (*19*), 132.8 (*7* or *12*), 132.8 (*7* or *12*), 128.3 (*20* and *21*), 127.5 (*22*), 121.2 (*6* and *11*), 81.8 (*16*), 76.1 (*1*), 67.2 (*2*), 53.0 (*18*), 39.8 (*3*), 35.8 (*5* and *10*), 28.1 (*17*), 26.3 (*4*), 25.9 (*8*, *9*, *13* and/or *14*), 18.0 (*8*, *9*, *13* and/or *14*).

IR (ν, cm^{-1}) (CCl_4): 3063, 3031, 2975, 2925, 2727, 2255, 1719, 1448, 1385, 1306, 1255, 1160, 1076, 1027.

MS (EI^+, m/z): 395 (M^+), 339, 326, 308, 270, 226.

HRMS (EI^+, m/z): Calculated for $C_{26}H_{37}NO_2$: 395.2824.
Found for $C_{26}H_{37}NO_2$: 395.2820.

Benzyl-[1-(3-methyl-but-2-enyl)-cyclohexylethynyl]-carbamic acid *tert*-butyl ester — 9.9 f



MF: $C_{25}H_{35}NO_2$

MW: 381.55 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 9.1** (scale: 3.424 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 98/2).

Product: Yellow oil.

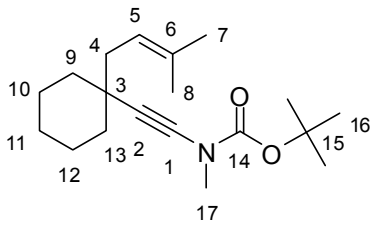
Yield: 36%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.40-7.27 (m, 5H, *19*, *20* and *21*), 5.25 (t, J = 7.3 Hz, 1H, *5*), 4.56 (s, 2H, *17*), 2.05 (d, J = 7.1 Hz, 2H, *4*), 1.70 (s, 3H, *7* or *8*), 1.67-1.03 (m, 10H, *9*, *10*, *11*, *12* and *13*), 1.59 (s, 3H, *7* or *8*), 1.51 (s, 9H, *16*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 154.7 (*14*), 136.8 (*18*), 132.7 (*6*), 128.3 (*19* and *20*), 127.5 (*21*), 120.9 (*5*), 81.8 (*15*), 74.9 (*1* and/or *2*), 53.0 (*17*), 41.5 (*4*), 37.7 (*9*, *10*, *11*, *12* and/or *13*), 37.2 (*3*), 28.1 (*16*), 26.1 (*9*, *10*, *11*, *12* and/or *13*), 25.9 (*7* or *8*), 23.0 (*9*, *10*, *11*, *12* and/or *13*), 18.0 (*7* or *8*).

IR (ν, cm^{-1}) (CCl_4)	3065, 3031, 2922, 2854, 2254, 1712, 1447, 1391, 1363, 1308, 1158, 1125, 1077, 1030.
MS (EI^+, m/z)	381 (M^+), 325, 312, 281, 268, 257, 213.
HRMS (EI^+, m/z)	Calculated for $C_{25}H_{35}NO_2$: 381.2668. Found for $C_{25}H_{35}NO_2$: 381.2677.

Methyl-[1-(3-methyl-but-2-enyl)-cyclohexylethynyl]-carbamic acid *tert*-butyl ester **9.9 g**



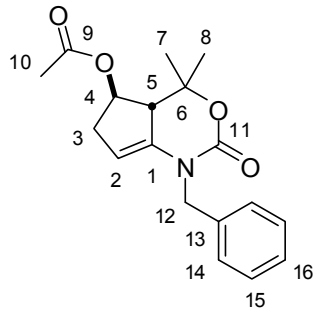
MF: $C_{19}H_{31}NO_2$

MW: 305.45 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 9.1** (scale: 2 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 98/2).
Product:	Pale yellow oil.
Yield:	30%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	5.33 (thept, J = 1.3, 7.4 Hz, 1H, *5*), 3.06 (s, 3H, *17*), 2.10 (d, J = 7.4 Hz, 2H, *4*), 1.73 (s, 3H, *7* or *8*), 1.71-1.05 (m, 10H, *9*, *10*, *11*, *12* and *13*), 1.62 (s, 3H, *7* or *8*), 1.49 (s, 9H, *16*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	155.0 (*14*), 132.9 (*6*), 120.8 (*5*), 81.5 (*15*), 78.5 (*1*), 73.1 (*2*), 41.5 (*4*), 37.8 (*9*, *10*, *11*, *12* and/or *13*), 37.2 (3 and *17*), 28.1 (*16*), 26.2 (*9*, *10*, *11*, *12* and/or *13*), 25.9 (*7* or *8*), 23.1 (*9*, *10*, *11*, *12* and/or *13*), 18.0 (*7* or *8*).
IR (ν, cm^{-1}) (CCl_4)	2975, 2930, 2854, 2255, 1713, 1450, 1379, 1348, 1316, 1254, 1157, 1070, 1033.
MS (EI^+, m/z)	305 (M^+), 270, 249, 236, 226, 204, 192.
HRMS (EI^+, m/z)	Calculated for $C_{19}H_{31}NO_2$: 305.2355. Found for $C_{19}H_{31}NO_2$: 305.2360.

***Racemic* - acetic acid (4a*R*,5*R*)-1-benzyl-4,4-dimethyl-2-oxo-1,2,4,4a,5,6-hexahydro-cyclopent[*d*][1,3]oxazin-5-yl ester** **9.5 a**



MF: $C_{18}H_{21}NO_4$

MW: 315.36 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.10 a** (scale: 0.243 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 60/40).

Product: Yellow oil.

Yield: 68%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.36-7.24 (m, 5H, *14*, *15* and *16*), 5.14 (q, J = 7.0 Hz, 1H, *4*), 4.90 (d, J = 15.5 Hz, 1H, *12*), 4.77 (d, J = 15.5 Hz, 1H, *12*), 4.73 (m, 1H, *2*), 3.17 (dd, J = 1.7, 7.5 Hz, 1H, *5*), 2.87 (dddd, J = 1.5, 2.9, 8.1, 15.6 Hz, 1H, *3*), 2.28 (ddt, J = 2.0, 6.7, 15.5 Hz, 1H, *3*), 2.07 (s, 3H, *10*), 1.41 (s, 3H, *7* or *8*), 1.31 (s, 3H, *7* or *8*).

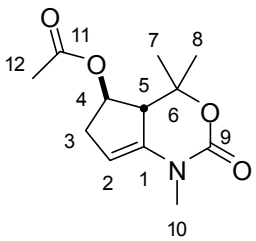
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.5 (*10*), 151.3 (*11*), 136.3 (*1* or *13*), 135.3 (*1* or *13*), 128.5 (*14* or *15*), 127.4 (*16*), 127.1 (*14* or *15*), 100.0 (*2*), 81.1 (*6*), 73.8 (*4*), 53.7 (*5*), 48.7 (*12*), 36.6 (*3*), 27.0 (*7* or *8*), 21.5 (*7* or *8*), 20.9 (*10*).

IR (ν, cm^{-1}) (CCl_4): 3085, 3031, 2978, 2933, 2860, 1721, 1655, 1439, 1398, 1367, 1272, 1228, 1163, 1100, 1050.

MS (EI$^+$, m/z): 315 (M$^+$), 255, 240, 211.

HRMS (EI$^+$, m/z): Calculated for $C_{18}H_{21}NO_4$: 315.1471.
Found for $C_{18}H_{21}NO_4$: 315.1473.

Racemic - acetic acid (4a*R*,5*R*)-1,4,4-trimethyl-2-oxo-1,2,4,4a,5,6-hexahydro-cyclopent[*d*][1,3]oxazin-5-yl ester — 9.5 b



MF: $C_{12}H_{17}NO_4$

MW: 239.27 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.10 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 60/40).

Product: Pale yellow crystals.

Yield: 68%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.17 (q, J = 7.0 Hz, 1H, *4*), 4.73 (m, 1H, *2*), 3.16 (s, 3H, *10*), 3.13 (dd, J = 1.7, 7.6 Hz, 1H, *5*), 2.94 (dddd, J = 1.5, 2.9, 8.1, 15.5 Hz, 1H, *3*), 2.34 (ddt, J = 2.0, 6.9, 15.5 Hz, 1H, *3*), 2.08 (s, 3H, *12*), 1.38 (s, 3H, *7* or *8*), 1.27 (s, 3H, *7* or *8*).

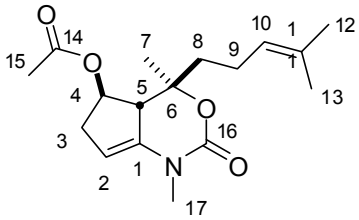
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.5 (*11*), 151.0 (*9*), 136.5 (*1*), 98.8 (*2*), 80.9 (*6*), 74.1 (*4*), 53.4 (*5*), 36.6 (*3*), 31.5 (*10*), 27.0 (*7* or *8*), 21.3 (*7* or *8*), 20.9 (*12*).

IR (ν, cm^{-1}) (CCl_4): 3083, 2978, 2937, 2859, 1724, 1656, 1430, 1343, 1270, 1233, 1162, 1105, 1036.

MS (EI^+, m/z): 239 (M^+), 220, 205, 194, 189.

HRMS (EI^+, m/z): Calculated for $C_{12}H_{17}NO_4$: 239.1158.
Found for $C_{12}H_{17}NO_4$: 239.1156.

Racemic - Acetic acid (4*R*,4a*R*,5*R*)-1,4-dimethyl-4-(4-methyl-pent-3-enyl)-2-oxo-1,2,4,4a,5,6-hexahydro-cyclopent[*d*][1,3]oxazin-5-yl ester **9.5 f**



MF: $C_{17}H_{25}NO_4$

MW: 307.38 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 9.10 a** (scale: 0.184 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 70/30).

Product: Yellow oil.

Yield: 56%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.14 (q, J = 7.0 Hz, 1H, *4*), 5.05 (t, J = 7.1 Hz, 1H, *10*), 4.74 (m, 1H, *2*), 3.31 (dd, J = 1.6, 7.5 Hz, 1H, *5*), 3.16 (s, 3H, *17*), 2.97 (dddd, J = 1.5, 2.9, 8.1, 15.6 Hz, 1H, *3*), 2.33 (ddt, J = 2.0, 6.8, 15.5 Hz, 1H, *3*), 2.20 (m, 2H, *9*), 2.07 (s, 3H, *15*), 1.74-1.51 (m, 2H, *8*), 1.68 (s, 3H, *12* or *13*), 1.61 (s, 3H, *12* or *13*), 1.25 (s, 3H, *7*).

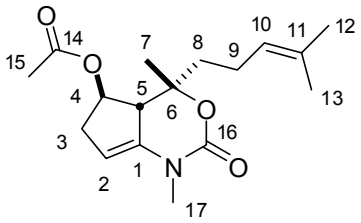
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 170.5 (*14*), 151.2 (*16*), 136.5 (*1*), 132.2 (*11*), 123.2 (*10*), 98.9 (*2*), 82.5 (*6*), 74.2 (*4*), 50.4 (*5*), 39.3 (*8*), 36.8 (*3*), 31.5 (*17*), 25.6 (*12* or *13*), 21.3 (*9*), 20.9 (*15*), 20.4 (*7*), 17.6 (*12* or *13*).

IR (ν, cm^{-1}) (CCl_4): 3082, 2969, 2926, 2858, 1722, 1656, 1430, 1380, 1347, 1235, 1148, 1073, 1040.

MS (EI^+, m/z): 307 (M^+), 266, 247, 232, 220.

HRMS (EI^+, m/z) Calculated for $C_{17}H_{25}NO_4$: 307.1784.
Found for $C_{17}H_{25}NO_4$: 307.1780.

***Racemic* - acetic acid (4*S*,4a*R*,5*R*)-1,4-dimethyl-4-(4-methyl-pent-3-enyl)-2-oxo-1,2,4,4a,5,6-hexahydro-cyclopent[*d*][1,3]oxazin-5-yl ester**	**9.5 g**



MF: $C_{17}H_{25}NO_4$

MW: 307.38 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 9.10 a** (scale: 0.205 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 70/30).

Product: Yellow oil.

Yield: 56%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) 5.24 (q, J = 7.8 Hz, 1H, *4*), 5.04 (t, J = 7.1 Hz, 1H, *10*), 4.70 (m, 1H, *2*), 3.18 (dd, J = 1.7, 7.6 Hz, 1H, *5*), 3.14 (s, 3H, *17*), 2.92 (dddd, J = 1.5, 2.9, 8.1, 15.5 Hz, 1H, *3*), 2.32 (ddt, J = 2.0, 6.7, 15.5 Hz, 1H, *3*), 2.12 (m, 2H, *9*), 2.07 (s, 3H, *15*), 1.65 (s, 3H, *12* or *13*), 1.57 (s, 3H, *12* or *13*), 1.48 (m, 2H, *8*), 1.36 (s, 3H, *7*).

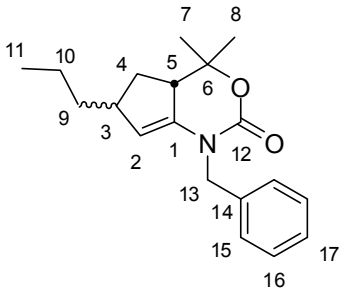
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) 170.5 (*14*), 150.9 (*16*), 136.5 (*1*), 132.6 (*11*), 123.0 (*10*), 98.7 (*2*), 82.1 (*6*), 73.6 (*4*), 54.4 (*5*), 36.6 (*3*), 34.0 (*8*), 31.4 (*17*), 25.5 (*12* or *13*), 24.1 (*7*), 21.3 (*9*), 20.9 (*15*), 17.5 (*12* or *13*).

IR (ν, cm^{-1}) (CCl_4) 3082, 2968, 2927, 2859, 1736, 1656, 1432, 1346, 1241, 1173, 1078, 1040.

MS (EI^+, m/z) 307 (M^+), 247, 232, 220.

HRMS (EI^+, m/z) Calculated for $C_{17}H_{25}NO_4$: 307.1784.
Found for $C_{17}H_{25}NO_4$: 307.1781.

1-Benzyl-4,4-dimethyl-6-propyl-4,4a,5,6-tetrahydro-1*H*-cyclopenta[*d*][1,3]oxazin-2-one	**9.10 c**



MF: $C_{19}H_{25}NO_2$

MW: 299.41 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.10 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1-80/20).

Product: Yellow oil (isolated as a mixture of two *Z*/*E* isomers ~ 0.49/0.51).

Yield: 36%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): For the mixture of *Z*/*E* isomers: 7.37-7.21 (m, 5H, both isomers, *15*, *16* and *17*), 4.99 (d, J = 15.5 Hz, 1H, minor isomer, *13*), 4.87 (m, 1H, minor isomer, *2*), 4.86 (d, J = 15.5 Hz, 1H, major isomer, *13*), 4.79 (d, J = 15.5 Hz, 1H, major isomer, *13*), 4.78 (m, 1H, major isomer, *2*), 4.69 (d, J = 15.5 Hz, 1H, minor isomer, *13*), 3.08 (dd, J = 8.3, 9.2 Hz, 1H, minor isomer, *5*), 2.97 (dd, J = 8.0, 10.0 Hz, 1H, major isomer, *5*), 2.67 (m, 1H, both isomers, *3*), 2.17 (m, 1H, major isomer, *4*), 1.69 (m, 2H, minor isomer, *4*), 1.39 (s, 3H, both isomers, *7* or *8*), 1.35-1.16 (m, 4H, both isomers, *9* and *10*), 1.25 (s, 3H, minor isomer, *7* or *8*), 1.23 (s, 3H, major isomer, *7* or *8*), 1.01 (m, 1H, major isomer, *4*), 0.87 (m, 3H, both isomers, *11*).

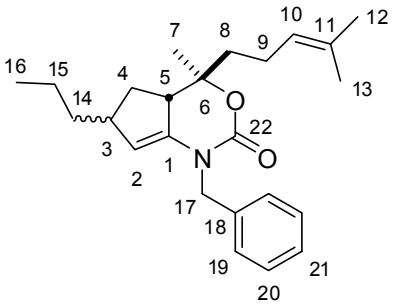
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): For the mixture of *Z*/*E* isomers: 151.9 (*12*), 138.1 (*1* or *18*), 138.0 (*1* or *18*), 136.8 (*1* or *18*), 136.7 (*1* or *18*), 128.4 (*15*, *16* and/or *17*), 128.4 (*15*, *16* and/or *17*), 127.2 (*15*, *16* and/or *17*), 127.1 (*15*, *16* and/or *17*), 108.6 (*2*), 82.5 (*6*), 82.0 (*6*), 49.4 (*13*), 49.4 (*5*), 49.1 (*13*), 48.3 (*5*), 42.9 (*3*), 42.6 (*3*), 39.0 (*9* or *10*), 38.3 (*9* or *10*), 32.0 (*4*), 30.6 (*4*), 27.3 (*7* or *8*), 27.3 (*7* or *8*), 20.9 (*7* or *8*), 20.7 (*9* or *10*), 20.7 (*7* or *8*), 20.6 (*9* or *10*), 14.1 (*11*), 14.1 (*11*).

IR (ν, cm^{-1}) (CCl_4): For the mixture of *Z*/*E* isomers: 3068, 3032, 2959, 2928, 2867, 1710, 1653, 1497, 1444, 1395, 1369, 1328, 1298, 1226, 1191, 1127, 1096.

MS (EI^+, m/z): 299 (M^+), 284, 256, 240, 230, 212.

HRMS (EI^+, m/z): Calculated for $C_{19}H_{25}NO_2$: 299.1885.
Found for $C_{19}H_{25}NO_2$: 299.1876.

1-Benzyl-4-methyl-4-(4-methyl-pent-3-enyl)-6-propyl-4,4a,5,6-tetrahydro-1*H*-cyclopent[*d*][1,3]oxazin-2-one **9.10 d**



MF: $C_{24}H_{33}NO_2$

MW: 367.52 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.10 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1-80/20).

Product: Yellow oil (isolated as a mixture of two *Z*/*E* isomers ~ 0.47/0.53).

Yield: 37%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) For the mixture of *Z*/*E* isomers: 7.40-7.21 (m, 5H, both isomers, *19*, *20* and *21*), 5.09 (t, J = 7.0 Hz, 1H, both isomers, *10*), 5.00 (d, J = 15.4 Hz, 1H, minor isomer, *17*), 4.87 (m, 1H, minor isomer, *2*), 4.86 (d, J = 15.4 Hz, 1H, major isomer, *17*), 4.80 (d, J = 15.4 Hz, 1H, major isomer, *17*), 4.78 (m, 1H, major isomer, *2*), 4.69 (d, J = 15.4 Hz, 1H, minor isomer, *17*), 3.15 (dd, J = 8.4, 8.8 Hz, 1H, minor isomer, *5*), 3.05 (dd, J = 8.0, 10.1 Hz, 1H, major isomer, *5*), 2.67 (m, 1H, both isomers, *3*), 2.18 (m, 2H-both isomers, *9* + 1H-major isomer, *4*), 1.77-1.14 (m, 6H-both isomers, *8*, *14* and *15* + 2H-minor isomer, *4*), 1.69 (s, 3H, both isomers, *12* or *13*), 1.63 (s, 3H, both isomers, *12* or *13*), 1.24 (s, 3H, both isomers, *7*), 0.99 (m, 1H, major isomer, *4*), 0.87 (m, 3H, both isomers, *16*).

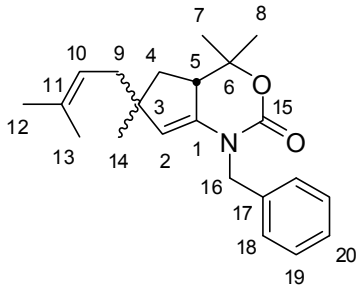
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) For the major isomer: 152.1 (*22*), 138.0 (*1* or *18*), 136.8 (*1* or *18*), 132.2 (*11*), 128.5 (*19*, *20* and/or *21*), 127.2 (*19*, *20* and/or *21*), 123.4 (*10*), 108.5 (*2*), 83.6 (*6*), 49.1 (*17*), 47.3 (*5*), 43.0 (*3*), 40.0 (*4*, *8*, *9*, *14* or *15*), 39.1 (*4*, *8*, *9*, *14* or *15*), 32.2 (*4*, *8*, *9*, *14* or *15*), 25.6 (*12* or *13*), 21.5 (*4*, *8*, *9*, *14* or *15*), 20.6 (*4*, *8*, *9*, *14* or *15*), 19.6 (*7*), 17.7 (*12* or *13*), 14.2 (*16*).
For the minor isomer: 152.1 (*22*), 138.1 (*1* or *18*), 136.9 (*1* or *18*), 132.2 (*11*), 128.4 (*19*, *20* and/or *21*), 127.2 (*19*, *20* and/or *21*), 123.5 (*10*), 108.5 (*2*), 84.2 (*6*), 49.5 (*17*), 46.3 (*5*), 42.7 (*3*), 40.0 (*4*, *8*, *9*, *14* or *15*), 38.4 (*4*, *8*, *9*, *14* or *15*), 30.8 (*4*, *8*, *9*, *14* or *15*), 25.6 (*12* or *13*), 21.5 (*4*, *8*, *9*, *14* or *15*), 20.7 (*4*, *8*, *9*, *14* or *15*), 19.4 (*7*), 17.7 (*12* or *13*), 14.1 (*16*).

IR (ν, cm^{-1}) (CCl_4) For the mixture of *Z*/*E* isomers: 3066, 3031, 2962, 2926, 2867, 1758, 1710, 1654, 1496, 1446, 1395, 1374, 1296, 1223, 1171, 1118, 1071, 1028.

MS (EI$^+$, m/z) 367 (M^+), 324, 279, 230.

HRMS (EI$^+$, m/z) Calculated for $C_{24}H_{33}NO_2$: 367.2511.
Found for $C_{24}H_{33}NO_2$: 367.2501.

1-Benzyl-4,4,6-trimethyl-6-(3-methyl-but-2-enyl)-4,4a,5,6-tetrahydro-1*H*-cyclopent[*d*][1,3]oxazin-2-one **9.10 e**



MF: $C_{22}H_{29}NO_2$

MW: 339.47 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.10 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1-80/20).

Product: Yellow oil (isolated as a mixture of two *Z*/*E* isomers ~ 0.41/0.59).

Yield: 39%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz) For the mixture of *Z*/*E* isomers: 7.34-7.22 (m, 5H, both isomers, *18*, *19* and *20*), 5.00 (tm, J = 7.4 Hz, 1H, major isomer, *10*), 4.99 (d, J = 15.5 Hz, 1H, major isomer, *16*), 4.93 (tm, J = 7.5 Hz, 1H, minor isomer, *10*), 4.88 (d, J = 15.5 Hz, 1H, minor isomer, *16*), 4.75 (d, J = 15.4 Hz, 1H, minor isomer, *16*), 4.68 (m, 1H, both isomers, *2*), 4.65 (d, J = 15.5 Hz, 1H, major isomer, *16*), 3.10 (td, J = 2.1, 9.8 Hz, 1H, major isomer, *5*), 3.00 (td, J = 2.1, 9.2 Hz, 1H, minor isomer, *5*), 2.08-1.84 (m, 3H, both isomers, *4* and *9*), 1.67-1.34 (m, 1H, both isomers, *4*), 1.65 (s, 3H, major isomer, *12* or *13*), 1.64 (s, 3H, minor isomer, *12* or *13*), 1.51 (s, 3H, major isomer, *12* or *13*), 1.47 (s, 3H, minor isomer, *12* or *13*), 1.37 (s, 3H, both isomers, *7* or *8*), 1.25 (s, 3H, minor isomer, *7* or *8*), 1.22 (s, 3H, major isomer, *7* or *8*), 1.06 (s, 3H, minor isomer, *14*), 1.02 (s, 3H, major isomer, *14*).

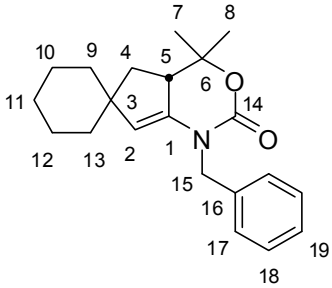
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz) For the major isomer: 151.8 (*15*), 136.8 (*1* or *17*), 136.6 (*1* or *17*), 133.2 (*11*), 128.4 (*18*, *19* or *20*), 127.2 (*18*, *19* or *20*), 127.0 (*18*, *19* or *20*), 121.1 (*10*), 113.6 (*2*), 82.3 (*6*), 49.3 (*16*), 48.3 (*5*), 47.6 (*3*), 40.4 (*9*), 37.1 (*4*), 28.4 (*7*, *8*, *12*, *13* or *14*), 27.3 (*7*, *8*, *12*, *13* or *14*), 25.9 (*7*, *8*, *12*, *13* or *14*), 20.9 (*7*, *8*, *12*, *13* or *14*), 17.8 (*7*, *8*, *12*, *13* or *14*).
For the minor isomer: 151.9 (*15*), 136.8 (*1* or *17*), 136.7 (*1* or *17*), 133.3 (*11*), 128.4 (*18*, *19* or *20*), 127.2 (*18*, *19* or *20*), 127.1 (*18*, *19* or *20*), 120.8 (*10*), 113.5 (*2*), 82.1 (*6*), 49.3 (*5*), 49.1 (*16*), 47.8 (*3*), 39.9 (*9*), 37.9 (*4*), 28.4 (*7*, *8*, *12*, *13* or *14*), 26.9 (*7*, *8*, *12*, *13* or *14*), 25.9 (*7*, *8*, *12*, *13* or *14*), 20.8 (*7*, *8*, *12*, *13* or *14*), 17.6 (*7*, *8*, *12*, *13* or *14*).

IR (ν, cm^{-1}) (CCl_4) For the mixture of *Z*/*E* isomers: 3065, 3032, 2971, 2928, 2867, 1710, 1656, 1446, 1394, 1371, 1308, 1227, 1102, 1054.

MS (EI^+, m/z) 339 (M^+), 324, 298, 280, 271, 248, 227, 205.

HRMS (EI^+, m/z) Calculated for $C_{22}H_{29}NO_2$: 339.2198.
Found for $C_{22}H_{29}NO_2$: 339.2193.

1'-benzyl-4',4'-dimethyl-4a',5'-dihydro-1'*H*-spiro[cyclohexane-1,6'-cyclopenta[*d*][1,3]oxazin]-2'(4'*H*)-one **9.10 f**



MF: $C_{21}H_{27}NO_2$

MW: 325.44 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.10 a** (scale: 0.25 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1-80/20).

Product: Yellow oil.

Yield: 26%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.35-7.20 (m, 5H, *17*, *18* and *19*), 4.87 (d, J = 1.5 Hz, 1H, *2*), 4.86 (d, J = 15.5 Hz, 1H, *15*), 4.77 (d, J = 15.5 Hz, 1H, *15*), 3.06 (dd, J = 7.6, 9.6 Hz, 1H, *5*), 1.96 (dd, J = 8.0, 12.6 Hz, 1H, *4*), 1.54-1.24 (m, 10H, *9*, *10*, *11*, *12* and *13*), 1.38 (s, 3H, *7* or *8*), 1.24 (s, 3H, *7* or *8*), 1.15 (dd, J = 9.4, 12.6 Hz, 1H, *4*).

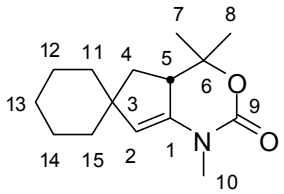
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.8 (*14*), 136.7 (*1* or *16*), 136.7 (*1* or *16*), 128.4 (*17*, *18* and/or *19*), 127.1 (*17*, *18* and/or *19*), 113.3 (*2*), 82.1 (*6*), 49.2 (*15*), 48.0 (*5*), 47.5 (*3*), 39.5 (*9*, *10*, *11*, *12* or *13*), 37.0 (*9*, *10*, *11*, *12* or *13*), 36.9 (*4*), 27.2 (*7* or *8*), 25.7 (*9*, *10*, *11*, *12* or *13*), 23.5 (*9*, *10*, *11*, *12* or *13*), 23.2 (*9*, *10*, *11*, *12* or *13*), 20.7 (*7* or *8*).

IR (ν, cm^{-1}) (CCl_4): 3066, 3032, 2977, 2927, 2856, 1710, 1655, 1497, 1445, 1394, 1372, 1311, 1265, 1227, 1161, 1106, 1072.

MS (EI$^+$, m/z): 325 (M$^+$), 310, 282, 266, 252, 238, 225, 205, 190.

HRMS (EI$^+$, m/z): Calculated for $C_{21}H_{27}NO_2$: 325.2042.
Found for $C_{21}H_{27}NO_2$: 325.2033.

1',4',4'-trimethyl-4a',5'-dihydro-1'*H*-spiro[cyclohexane-1,6'-cyclopenta[*d*][1,3]oxazin]-2'(4'*H*)-one **9.10 g**



MF: $C_{15}H_{23}NO_2$

MW: 249.35 g.mol^{-1}

Reaction: The reaction was carried out according to the **General Procedure 9.10 a**

(scale: 0.173 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1-80/20).

Product: Yellow oil.

Yield: 30%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.87 (d, J = 1.2 Hz, 1H, *2*), 3.15 (s, 3H, *10*), 3.04 (dd, J = 8.0, 9.6 Hz, 1H, *5*), 1.98 (dd, J = 8.0, 12.6 Hz, 1H, *4*), 1.77-0.99 (m, 11H, *4*, *11*, *12*, *13*, *14* and *15*), 1.36 (s, 3H, *7* or *8*), 1.20 (s, 3H, *7* or *8*).

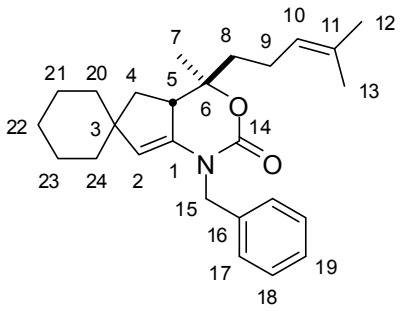
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz): 151.7 (*9*), 138.0 (*1*), 112.1 (*2*), 81.9 (*6*), 47.7 (*5*), 47.5 (*3*), 39.8 (*11*, *12*, *13*, *14* or *15*), 37.4 (*11*, *12*, *13*, *14* or *15*), 37.2 (*4*), 32.1 (*10*), 27.3 (*7* or *8*), 25.8 (*11*, *12*, *13*, *14* or *15*), 23.6 (*11*, *12*, *13*, *14* or *15*), 23.3 (*11*, *12*, *13*, *14* or *15*), 22.6 (*7* or *8*).

IR (ν, cm^{-1}) (CCl_4): 3063, 2918, 2855, 1717, 1654, 1456, 1383, 1342, 1314, 1266, 1228, 1157, 1109, 1076, 1037, 1016.

MS (EI^+, m/z): 249 (M^+), 234, 220, 205, 190.

HRMS (EI^+, m/z): Calculated for $C_{15}H_{23}NO_2$: 249.1729.
Found for $C_{15}H_{23}NO_2$: 249.1731.

Racemic-(4'*R*,4a'*S*)-1'-benzyl-4'-methyl-4'-(4-methylpent-3-enyl)-4a',5'-dihydro-1'*H*-spiro[cyclohexane-1,6'-cyclopenta[*d*][1,3]oxazin]-2'(4'*H*)-one — 9.10 h



MF: $C_{26}H_{35}NO_2$

MW: 393.56 $g.mol^{-1}$

Reaction: The reaction was carried out according to the **General Procedure 9.10 a** (scale: 0.146 mmol).

Purification: Flash column chromatography (silica gel, PE/Et_2O 99/1-80/20).

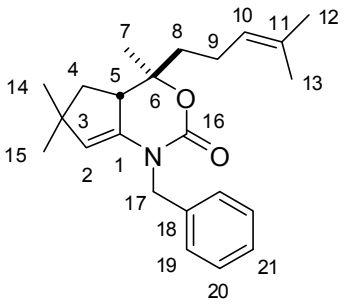
Product: Yellow oil.

Yield: 25%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.36-7.19 (m, 5H, *17*, *18* and *19*), 5.09 (thept, J = 1.2, 7.2 Hz, 1H, *10*), 4.88 (m, 2H, *2* and *15*), 4.77 (d, J = 15.5 Hz, 1H, *15*), 3.13 (dd, J = 7.5, 9.7 Hz, 1H, *5*), 2.18 (m, 2H, *9*), 1.92 (dd, J = 8.0, 12.8 Hz, 1H, *4*), 1.75-1.53 (m, 2H, *8*), 1.69 (s, 3H, *12* or *13*), 1.63 (s, 3H, *12* or *13*), 1.53-1.18 (m, 10H, *20*, *21*, *22*, *23* and *24*), 1.23 (s, 3H, *7*), 1.14 (dd, J = 9.4, 12.6 Hz, 1H, *4*).

^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.1 (*14*), 136.8 (*1* or *16*), 136.7 (*1* or *16*), 132.2 (*11*), 128.4 (*17*, *18* or *19*), 127.2 (*17*, *18* or *19*), 127.1 (*17*, *18* or *19*), 123.5 (*10*), 113.2 (*2*), 83.7 (*6*), 49.2 (*15*), 47.6 (*3*), 46.0 (*5*), 40.0 (*4*, *8*, *20*, *21*, *22*, *23* and/or *24*), 39.6 (*4*, *8*, *20*, *21*, *22*, *23* and/or *24*), 37.1 (*4*, *8*, *20*, *21*, *22*, *23* and/or *24*), 25.7 (*4*, *8*, *20*, *21*, *22*, *23* and/or *24*), 25.6 (*12* or *13*), 23.5 (*4*, *8*, *20*, *21*, *22*, *23* and/or *24*), 23.3 (*4*, *8*, *20*, *21*, *22*, *23* and/or *24*), 21.5 (*9*), 19.4 (*7*), 17.7 (*12* or *13*).
IR (ν, cm^{-1}) (CCl_4)	3066, 3031, 2972, 2855, 1712, 1655, 1498, 1446, 1395, 1374, 1314, 1266, 1226, 1166, 1099, 1067.
MS (EI^+, m/z)	393 (M^+), 348, 306.
HRMS (EI^+, m/z)	Calculated for $C_{26}H_{35}NO_2$: 393.2668. Found for $C_{26}H_{35}NO_2$: 393.2657.

Racemic - (4*R*,4a*S*)-1-Benzyl-4,6,6-trimethyl-4-(4-methyl-pent-3-enyl)-4,4a,5,6-tetrahydro-1*H*-cyclopenta[*d*][1,3]oxazin-2-one **9.10 i**



MF: $C_{23}H_{31}NO_2$

MW: 353.50 $g.mol^{-1}$

Reaction:	The reaction was carried out according to the **General Procedure 9.10 a** (scale: 0.25 mmol).
Purification:	Flash column chromatography (silica gel, PE/Et_2O 99/1-80/20).
Product:	Yellow oil.
Yield:	39%

^{1}H NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.36-7.20 (m, 5H, *19*, *20* and *21*), 5.09 (thept, J = 1.3, 7.0 Hz, 1H, *10*), 4.90 (d, J = 15.5 Hz, 1H, *17*), 4.73 (m, 2H, *2* and *17*), 3.20 (dd, J = 7.6, 9.7 Hz, 1H, *5*), 2.18 (m, 2H, *9*), 1.79 (dd, J = 7.8, 12.4 Hz, 1H, *4*), 1.73-1.52 (m, 2H, *8*), 1.69 (s, 3H, *12* or *13*), 1.63 (s, 3H, *12* or *13*), 1.31 (dd, J = 9.6, 12.4 Hz, 1H, *4*), 1.23 (s, 3H, *7*), 1.09 (s, 3H, *14* or *15*), 1.02 (s, 3H, *14* or *15*).
^{13}C NMR (δ, ppm) ($CDCl_3$, 100 MHz)	152.0 (*16*), 136.7 (*1* or *18*), 136.3 (*1* or *18*), 132.1 (*11*), 128.4 (*19* or *20*), 127.1 (*21*), 127.1 (*19* or *20*), 123.4 (*10*), 114.7 (*2*), 83.6 (*6*), 49.2 (*17*), 46.6 (*5*), 43.4 (*3*), 40.3 (*4*), 40.0 (*8*), 30.1 (*14* or *15*), 28.5 (*14* or *15*), 25.6 (*12* or *13*), 21.5 (*9*), 19.5 (*7*), 17.6 (*12* or *13*).
IR (ν, cm^{-1}) (CCl_4)	3065, 3031, 2956, 2931, 2865, 1710, 1655, 1497, 1447, 1395, 1372, 1306, 1224, 1171, 1108, 1071, 1026.
MS (EI^+, m/z)	353 (M^+), 338, 294, 270, 240, 236, 218, 206.

HRMS (EI^+, m/z) Calculated for $C_{23}H_{31}NO_2$: 353.2355.
Found for $C_{23}H_{31}NO_2$: 353.2366.