Cobalt-Catalyzed C-C and C-N Coupling reactions

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THESE

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XIN QIAN

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君子生非异也，善假于物也。

不积跬步，无以致千里；不积小流，无以成江海。

荀子

Les gentilshommes ne sont pas si differents des autres de par leur naissance, mais eux savent saisir toutes les occasions qu’ils presentent.

Petit à petit, l'oiseau fait son nid; Pas à pas, on va loin.

Xun Zi 312–230 BC

Dedicated with love and appreciation to my grandmother

Yufeng Li

Contents

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Foremost, I would like to express my gratitude to my parents, families and boyfriend Peng for their support and encouragement during my study. Your love brightened my life.

List of symbols and abbreviations

Ac	Acetyl
acac	acetylacetonate
aq.	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	t-butyloxycarbonyl
B(pin)	pinacolatoboron
br	broad
Bu	butyl
Bz	benzyl
calc.	calculated
cat.	catalyst
cbz	Carboxybenzyl
cod	1,5-cyclooctadiene
cy	cyclohexyl
cyp	cyclopentyl
d	doublet
dd	doublet of doublets
DFT	density functional theory
DMA	*N*,*N*-dimethylacetamide
DMBA	2,6-dimethylbenzoic acid
DME	1,2-dimethoxyethane
dmeda	*N*,*N*'-dimethylethane-1,2-diamine
DMI	1,3-dimethyl-2-imidazolidinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppbz	1,2-Bis(diphenylphosphino)benzene
dq	doublet of quartets
dt	doublet of triplets
***ee*.**	enantiomeric excess
eq.	equation
equiv.	equivalent
Et	ethyl
Et_3N	triethylamine
GC	gas chromatography
HR	high resolution
HPLC	high-performance liquid chromatography
***i*Bu**	iso-butyl
***i*Pr**	iso-propyl
LiHMDS	Lithium bis(trimethylsilyl)amide
Me	methyl
MHZ	mega-hertz
MS	mass spectrometry
Ms	mesylate
NaOMe	sodium methoxide
***n*Bu**	normal-butyl

NMI	*N*-methylimidazole
NMR	nuclear magnetic resonance
OAc	acetate
Oct.	octyl
OTf	triflate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
Ph	phenyl
ppm	part per million
PTA	1,3,5-triaza-7-phosphaadamantane
pybox	2,6-bis[(4R)-4-phenyl-2-oxazolinyl]pyridine
r.t.	room temperature
s	singlet
***s*Bu**	sec-butyl
t	triplet
TBS	tButyldimethylsilyl
***t*Bu**	tert-butyl
td	triplet of doublets
THF	tetrahydrofuran
tmeda	tetramethylethylenediamine
tmepo	2,2,6,6-tetramethylpiperine-1-oxyl
TMS	trimethylsilyl
xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

Background introduction

Transition metal-catalyzed C-C or C-heteroatom (F, N, S, P …) bond formation reactions are very important tools in organic synthesis, allowing the construction of complex molecules from simple precursors.[1] Many efficient methodologies have been built and applied in natural products and pharmaceuticals synthesis, or in material science.[2]

Palladium-catalyzed processes started in the early 1970s, with the work of Negishi, Kumada and Suzuki and had a deep impact in organic synthesis. This toolbox was enriched after 1994, with the Pd-catalyzed C-N couplings concomitantly developed by Buchward and Hartwig (Figure 1). If palladium is the metal of choice for this type of reactions, alternative methodologies employing less expensive metals have also emerged. Nickel-catalyzed processes can be very efficient in some instances.[3] However, both these metals are toxic and/or expensive. Moreover, sophisticated, expensive and sensitive ligands are generally necessary to obtain good yields.

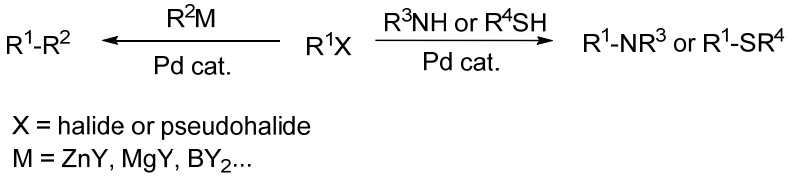

Figure 1 Common Pd-catalyzed C-C and C-heteroatom coupling reactions

1 (a) de Meijere, A., Diederich, F., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH: Weinheim, Germany, **2004**. (b) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. *Polyfunctional zinc organometallics for organic synthesis. In Handbook of Functionalized Organometallics: Applications in Synthesis*; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, **2005**; Vol.1.

2 (a) Tsuji, J. *Palladium in Organic Synthesis; Topics in Organometallic Chemistry*, Vol. 14; Springer: Berlin, **2005**. (b) Franció, G.; Leitner, W. *Organic synthesis with transition metal complexes using compressed carbon dioxide as reaction medium. Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*; Wiley: New York, **2004**; Vol. 2. (c) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth*. 2004, 1, 211-226.

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Therefore, in the last ten years, organic chemists have been looking for more eco-compatible and cheaper transition metal-catalyzed procedures. A growing number of Mn-,[4] Fe-,[5] Co-[6] and Cu-[7] catalyzed reactions are proposed to replace the older palladium and nickel catalyzed cross-coupling procedures.

Among of them, cobalt catalysis is attractive because it is specific and sometimes very efficient. Moreover, in these reactions, alternative mechanisms have been evidenced, for example in cobalt-catalyzed C-C cross-coupling reactions of alkyl halides, the oxidative addition is accomplished through a single-electron transfer.[8] This not only avoid side reactions (β-H elimination), which may be problematic in the Pd- and Ni-catalyzed cross-coupling reactions, but also showed advantages in the coupling reaction of secondary or even tertiary alkyl halides, which remain quite difficult with the other metals. Furthermore, extensive studies have also been done in cobalt-catalyzed cycloaddition reactions[9] and cobalt-catalyzed directly reductive C-C coupling reactions (It will be discussed in chapter 1).

The cost-effective, high efficiency and mild reaction conditions make cobalt-catalyzed cross coupling reactions a powerful method for C-C and C-heteroatom bonds construction. In this thesis, some progresses in cobalt-catalyzed C-C and C-heteroatom bonds formation reactions will be presented.

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9 Selected examples: (a) Geny, A.; Agenet, N.; Iannazzo, L.; Malacria, M.; Aubert, C.; Gandon, V. *Angew. Chem., Int. Ed*. **2009**, *48*, 1810-1813. (b) Chen, K. C.; Rayabarapu, D. K.; Wang, C. C.; Cheng, C.-H. *J. Org. Chem*. **2001**, *66*, 8804-8810.

Chapter 1 Cobalt-Catalyzed Reductive Coupling of Alkyl Halides or Allylic Acetate/Carbonates

I Cobalt-catalyzed Reductive Allylation of Alkyl Halides with Allylic Acetates or Carbonates

I-1 Introduction

I-1-1 Transition metal catalyzed alkyl-allyl cross-coupling reactions employing organometallic reagents

Transition metal-catalyzed allylic alkylations, using a broad range of metal complexes, have been intensively studied in order to synthesize new olefinic compounds, in particular for the synthesis of important intermediates in natural products (Scheme 1).[10] Many late transition metals, such as Pd-,[10] Mo-,[11] Ir-,[12] Ru-,[13] Rh-,[14] Pt-,[15] and even Fe-[16] are able to catalyze allylic substitutions by soft nucleophiles. The nucleophiles can be carbon-, nitrogen- or oxygen- based, such as alcohols, enolates, phenols and enamines. Protocols providing high *chemo-*, *regio-*, and enantioselectivities have been developed. In contrast, some non-precious metals, such as Co,[17] Ni[18] and Cu[19] catalysts allow the use of hard nucleophiles such as alkylzinc or Grignard reagents to obtain the alkyl-allyl products. Therefore, this chapter will first discuss the literature data concerning the first row transition metal catalyzed alkyl-allyl cross-coupling reactions and also summarize the development of the transition metal catalyzed reductive Csp^3-

10 (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003,** *103*, 2921-2944; (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008,** *47*, 258-297; (c) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011,** *111*, 1417-1492.
11 (a) Trost, B. M.; Hung, M. H. *J. Am. Chem. Soc.* **1983,** *105*, 7757-7759; (b) Trost, B. M.; Tometzki, G. B.; Hung, M. H. *J. Am. Chem. Soc.* **1987,** *109*, 2176-2177; (c) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1995,** *34*, 462-464; (d) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007,** *129*, 14548-14549.
12 (a) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741-742; (b) Takeuchi, R.; Shiga, N. *Org. Lett.* **1999,** *1*, 265-268.
13 (a) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.-a.; Takahashi, S. *J. Am. Chem. Soc.* **2001,** *123*, 10405-10406; (b) Onitsuka, K.; Matsushima, Y.; Takahashi, S. *Organometallics* **2005,** *24*, 6472-6474.
14 Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003,** *5*, 1713-1715.
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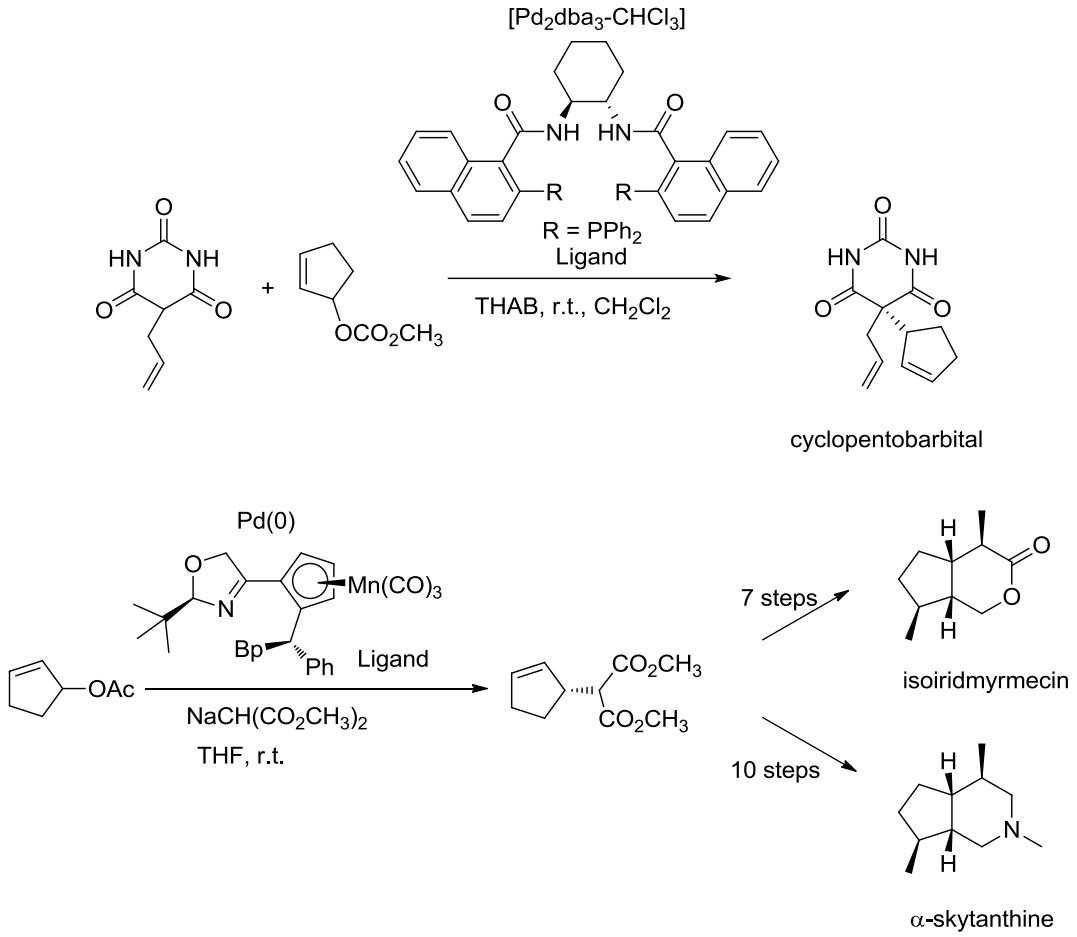
17 (a) Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed.* **1996,** *35*, 1700-1701; (b) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002,** *41*, 4137-4139; (c) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. – Eur. J.* **2004,** *10*, 5640-5648.
18 (a) Nomura, N.; RajanBabu, T. V. *Tetrahedron Lett.* **1997,** *38*, 1713-1716; (b) Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008,** *130*, 2756-2757.
19 (a) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004,** *43*, 2426-2428; (b) Falciola, C. A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006,** *45*, 5995-5998; (c) Lauer, A. M.; Mahmud, F.; Wu, J. *J. Am. Chem. Soc.* **2011,** *133*, 9119-9123.

Csp^3 coupling reactions. Then ours results concerning a cobalt-catalyzed reductive allylation of alkyl halides with allylic acetates or carbonates method will be presented.

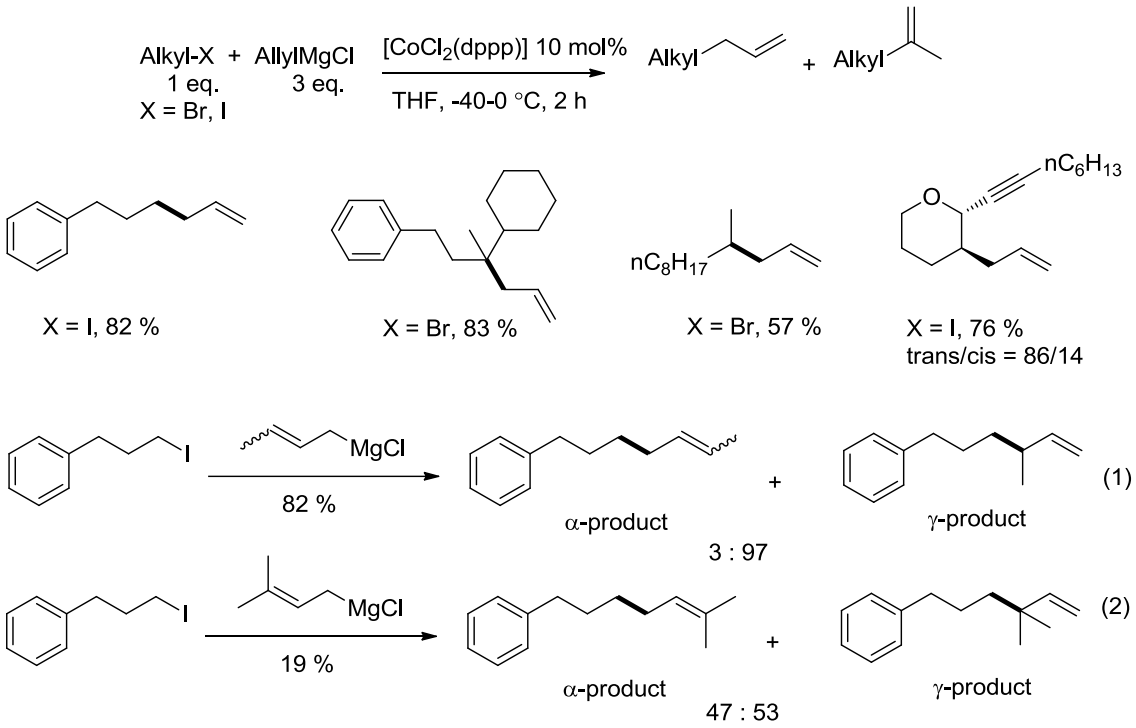


Scheme 1 Palladium-catalyzed allyl-alkyl cross-coupling reaction for the synthesis of natural products.

I-1-1-1 Cobalt-catalyzed alkyl-allyl cross-coupling reactions

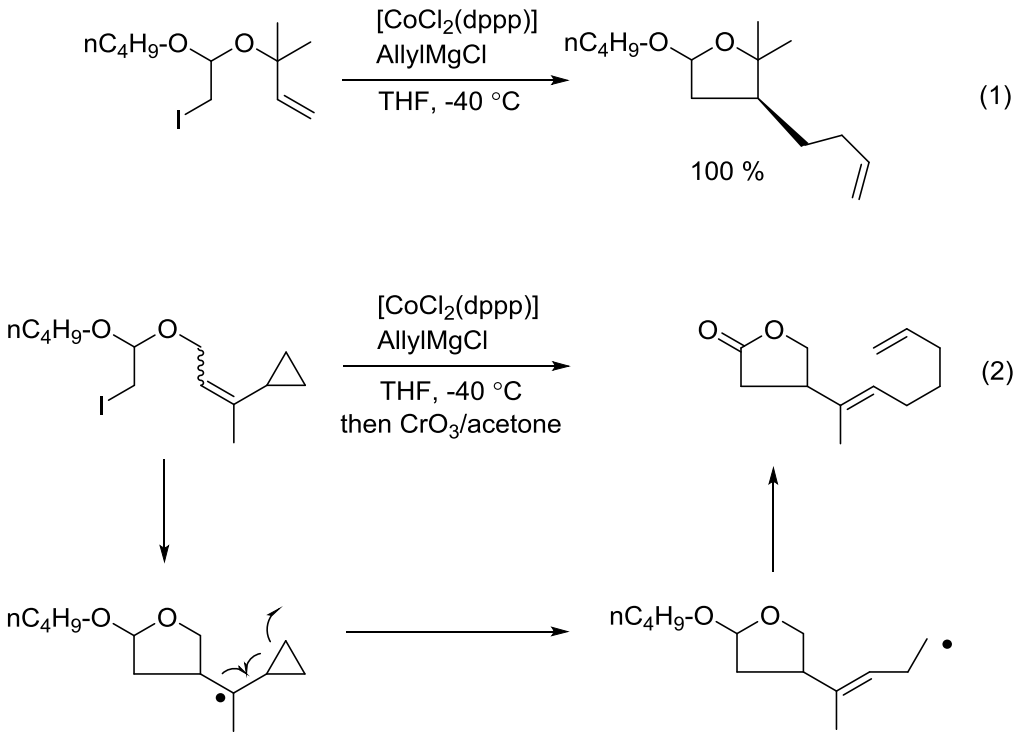
Oshima and coworkers reported the first cobalt-catalyzed coupling reaction of alkyl halides with allylic Grignard reagents (Scheme 2).[17b] The choice of the bidentate ligand and the reaction temperature proved to be crucial to achieve high yields of coupling product. Not only primary and secondary alkyl halides, but also tertiary alkyl halides react smoothly with allyl Grignard reagents. Such sterically hindered electrophiles are difficult to couple under palladium, nickel or copper catalysis. Primary and secondary bromides were less reactive compared to the tertiary alkyl bromides. Some other allylic Grignard reagents were also employed, yielding mainly the branched product (γ-selective). The reaction with prenyl (*E*-but-2-en-1-yl) Grignard reagent was

unsuccessful. Moreover, in this pioneer report, the exploration of the functional group tolerance was quite limited.



Scheme 2 Cobalt-catalyzed Kumada type alkyl-allyl cross-coupling reactions

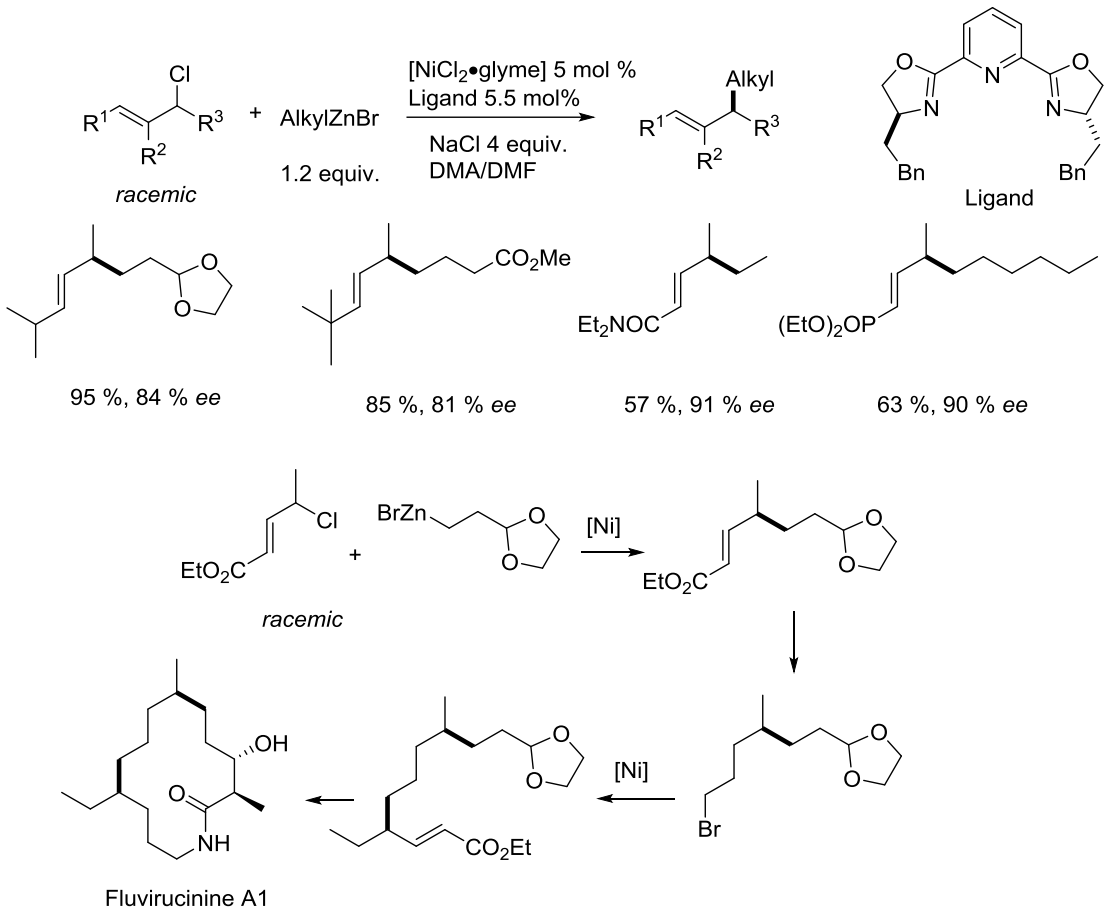
Motivated by this early success, they have continued to explore the scope of the method and initiate a mechanistic study (Scheme 3).[17c] Functional groups such as amide, ester, and carbonate groups did not survive in the reaction conditions. The Grignard reagents react with the carbonyl groups even at -78 °C, with none of the desired products being obtained. Some reactions were also conducted in order to get insight into the mechanism. Tandem cyclization confirmed a single-electron transfer mechanism and the existence of radical intermediates (Scheme 3). Single electron transfer allows a facile oxidative addition and the reductive elimination may occur rapidly enough to avoid β-H elimination side products.



Scheme 3 Cobalt-catalyzed Kumada type alkyl-allyl cross-coupling reactions

I-1-1-2 Nickel catalyzed alkyl-allyl cross-coupling reactions

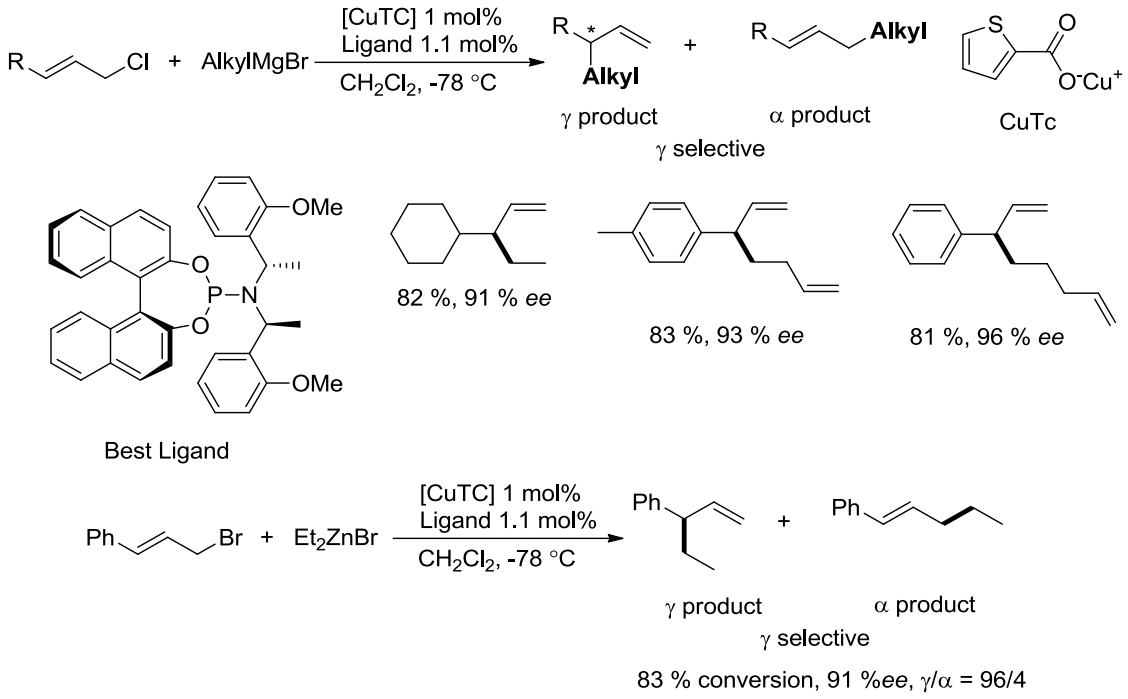
Fu and coworkers developed an effective nickel/Pybox catalyst for a regioselective asymmetric Negishi cross-coupling of racemic secondary allylic chlorides with primary alkylzinc compounds (Scheme 4).[18b] A variety of substituted alkylzinc compounds and secondary allylic chlorides was coupled in high yields (favoring α-product) and enantioselectivity with good functional group tolerance. This method was also applied to realize two key steps in the formal total synthesis of fluvirucinine A_1.



Scheme 4 Nickel-catalyzed Negishi type asymmetric alkyl-allyl cross-coupling reactions

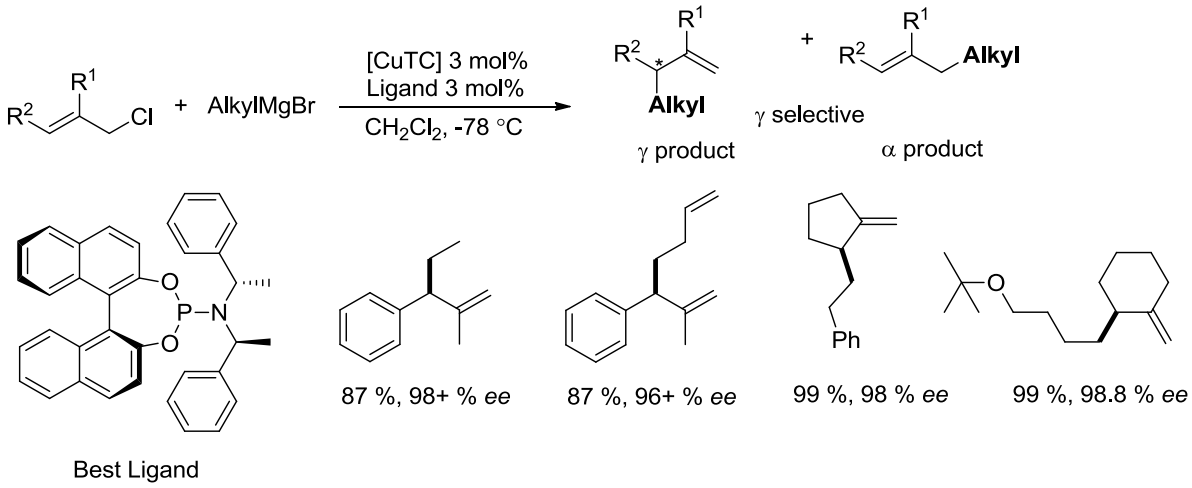
I-1-1-3 Copper-catalyzed alkyl-allyl cross-coupling reactions

Kumada type asymmetric coupling reaction is highly efficient to provide *chiral* olefinic compounds, which combined transition metal catalysis and a *chiral* ligand. For example, Alexakis and coworkers developed a series of novel and highly efficient phosphoramidite ligands applied in the alkylation of allylic halides using copper catalysis (Scheme 5).[19a] In this report, both alkyl Grignard reagents and alkylzinc compounds were used as coupling partners. The methods showed highly *regio*-(favoring γ-product) and enantioselectivity (92 %-96 % *ee*)



Scheme 5 Copper-catalyzed Kumada/Negishi type asymmetric alkyl-allyl cross-coupling reactions

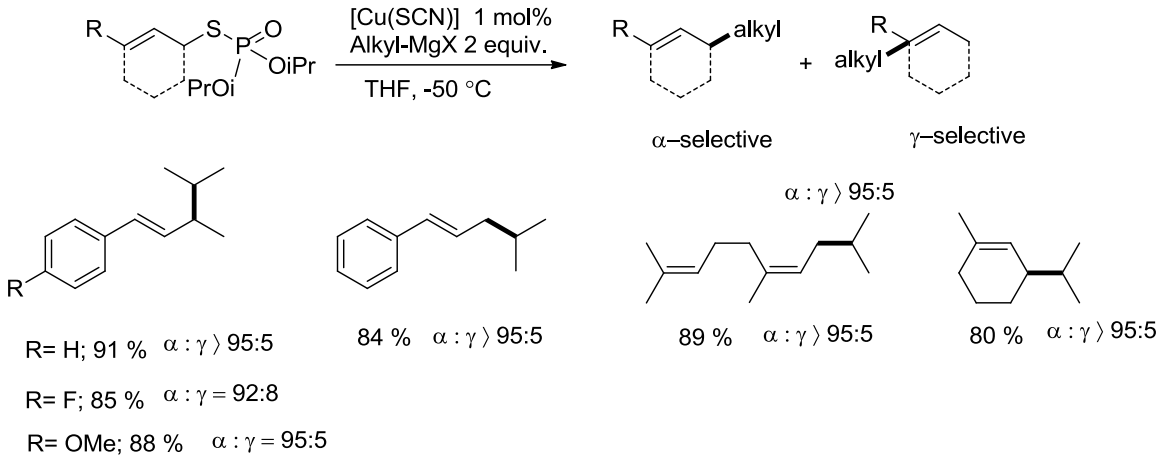
Later, the Alexakis group expended this methodology to the coupling of alkyl Grignard reagents with *β*-disubstituted allylic chlorides (Scheme 6).[19b] By employing a low copper catalyst loading and a phosphoramidite ligand, the *chiral* olefins were obtained in high yields with high *ee* values. This reaction favors *γ*-product (γ/α ratio from 72:28 to 98:2). Again, the choice of the ligand is essential to obtain both high *regio*- and enantioselectivities.



Scheme 6 Copper-catalyzed Kumada type asymmetric alkyl-allyl cross-coupling reactions

The alkylation of substituted allylic electrophiles with hard nucleophiles usually furnish both α and γ selective products. The use of transition metals and ligands improve the regioselectivity, while it overwhelmingly favors γ selective products under copper catalysis.[20] In 2011, Wu and coworkers reported a copper-catalyzed allylic alkylation of alkyl Grignard reagents utilizing phosphorothioate ester leaving groups (Scheme 7).[19c] This method showed a highly α-selective alkylation and the coupling of both secondary substrates partners was realized, which remains rare in the literature. Both primary and secondary alkyl Grignard reagents react with primary or secondary allylic phosphorothioate esters in high yields with high regioselectivity. The protocol was also extended to generate allylic phosphorothioate *in situ* by using allylic chlorides and sodium diethylphosphorothioate.

20 (a) Kar, A.; Argade, N. P. *Synthesis* **2005**, 2995-3022. (b) Breit, B.; Derrel, P. In *Modern Organocopper Chemistry*; Krause, N., Ed.; WileyVGH: Weinheim, **2002**, pp 210-223. (c) Knochel, P.; Gavryushin, A.; Brade, K. in the *Chemistry of Organomagnesium Compounds*; Rappoport, Z., Marek, I., Eds.; *The Chemistry of Functional Groups*; John Wiley & Sons: Chichester, **2008**; Part 2, pp 557-558. (d) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem*. **2008**, 3765-3780.



Scheme 7 Copper-catalyzed Kumada type asymmetric alkyl-allyl cross-coupling reactions

I-1-2 Transition-metal catalyzed reductive alkyl-allyl coupling reactions

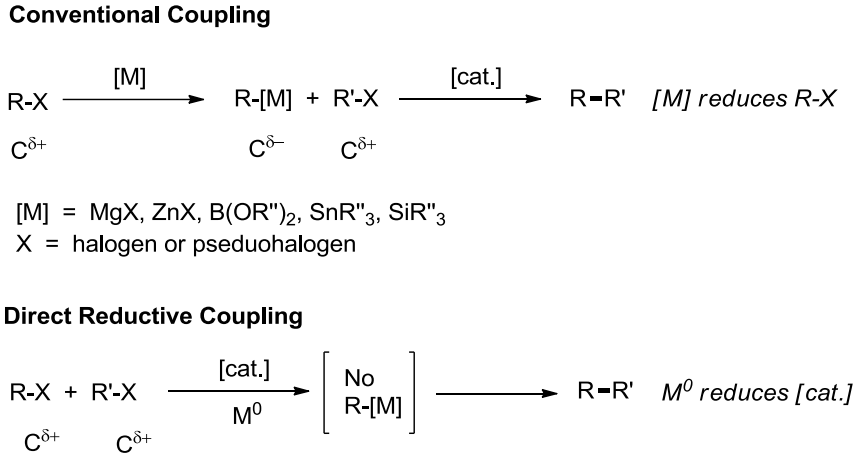
Conventional transition-metal catalyzed cross-coupling reactions, which combine a nucleophilic carbon ($C^{\delta-}$ or "R−[M]") with an electrophilic carbon ($C^{\delta+}$ or"R−X") have been extensively studied and many of them have been efficiently applied in both academic research and industry. In 2010, the importance of this chemistry was recognized by the award of the Nobel Prize to Heck, Negishi, and Suzuki for "Palladium-catalyzed cross-couplings in organic synthesis". However, avoiding a stoichiometric organometallic species, the direct coupling of two electrophilic carbons has been much less investigated (Scheme 8), although such catalytic coupling reactions have many important advantages compared to the conventional ones:

1. Availability: Many organometallic reagents (R-MgX, R-ZnX, R-$B(OH)_2$ *etc*.) are good coupling partners, however, limited functionalized organometallic reagents are commercially available, therefore, people have to prepare them. Moreover, some organometallic are impossible to obtain because incompatibility between the nucleophilic group and the functional group (*e.g.* aldehyde substituted arylhalide is difficult to transform in the corresponding aryl Grignard reagent or organozinc compound).

2. Cost-efficient: To obtain one equivalent of organometallic reagent, two, three, or more equivalents of organo-halide (or other organo-precursor) may be necessary, which is not economical.

3. Stability and handling: Generally, most organometallic reagents are oxygen or moisture sensitive and generally require special techniques and equipments to use them. Moreover, they may require to be freshly prepared to guarantee a good reactivity.

4. Substrate scope and functional group compatibility: Some substrates are difficult to transform into the corresponding organometallic reagents as mentioned above. More importantly, many sensitive but important functional groups such as aldehyde, ketone, acidic protons, or heterocyclic are not compatible with Grignard reagents or organozinc compounds. Organo-boronic acids are less reactive and can tolerate relatively more functional groups, but in the most efficient method, the Suzuki coupling reactions, a stoichiometric base is required, which may also react with some reactive functional groups.



Scheme 8 Conventional coupling *vs*. Reductive coupling

To break these limitations, direct reductive coupling reactions appear as efficient alternatives. With the right combination of catalyst and reductor, two organo-electrophiles are coupled directly, without generating stoichoimetric organometallic reagent/intermediate *in situ*. In 2003 Gosmini *et al*. developed the first reductive allyl-aryl[21] coupling reaction in this field, since then many efficient synthetic methodologies have been developed especially after 2008, including aryl-aryl,[22] aryl-vinyl,[23] alkyl-

21 Gomes, P.; Gosmini, C.; Périchon, J. *Org. Lett.* **2003,** *5*, 1043-1045.

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23 (a) Amatore, M.; Gosmini, C.; Périchon, J. *Eur. J. Org. Chem.* **2005**, 989-992. (b) Moncomble, A.; Floch, P. L.; Lledos, A.; Gosmini, C. *J. Org. Chem.* **2012,** *77*, 5056-5062.

aryl,[24], alkyl-alkyl,[25] alkyl-allyl,[26] allyl-aryl[21, 26c, 27] and alkyl-acyl[28] coupling reactions. A variety of sophisticated molecules was synthesized from bench stable, easy-to-handle materials under simple conditions. Importantly, many of them could not be obtained by a conventional coupling approach. Some of those methodologies have been extended to be applied to asymmetric synthesis[29] and materials chemistry.[30] In this section, the bibliography reports will focus on the transition metal catalyzed reductive Csp^3-Csp^3 coupling reactions, including alkyl-alkyl and alkyl-allyl coupling reactions, which was relative to my research field.

Following our work (see I-2),[26a] Gong and coworkers developed the nickel-catalyzed allylation of various functionalized alkyl halides with substituted allylic carbonates by using Zn powder as the reductant (Scheme 9).[26b] This protocol is simple and highly-regioselective. *E*-alkenes were provided in good to excellent yields with a high degree of functional-group tolerance, such as amide, ketal, ether, nitrile and even alcohol groups. The addition of CuI or $MgCl_2$ increases the yield of the cross-coupling product significantly. Perhaps they can increase the polarity of the medium, which accelerate the reaction. The mechanistic study showed that the process do not follow a Negishi pathway.

24 (a) Amatore, M.; Gosmini, C. *Chem. – Eur. J.* **2010,** *16*, 5848-5852. (b) Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010,** *132*, 920-921. (c) Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.* **2012,** *134*, 6146-6159. (d) Wang, S.; Qian, Q.; Gong, H. *Org. Lett.* **2012,** *14*, 3352-3355. (e) Yan, C.-S.; Peng, Y.; Xu, X.-B.; Wang, Y.-W. *Chem. – Eur. J.* **2012,** *18*, 6039-6048.

25 (a) Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. *Org. Lett.* **2011,** *13*, 2138-2141. (b) Prinsell, M. R.; Everson, D. A.; Weix, D. J. *Chem. Commun.* **2010,** *46*, 5743-5745.

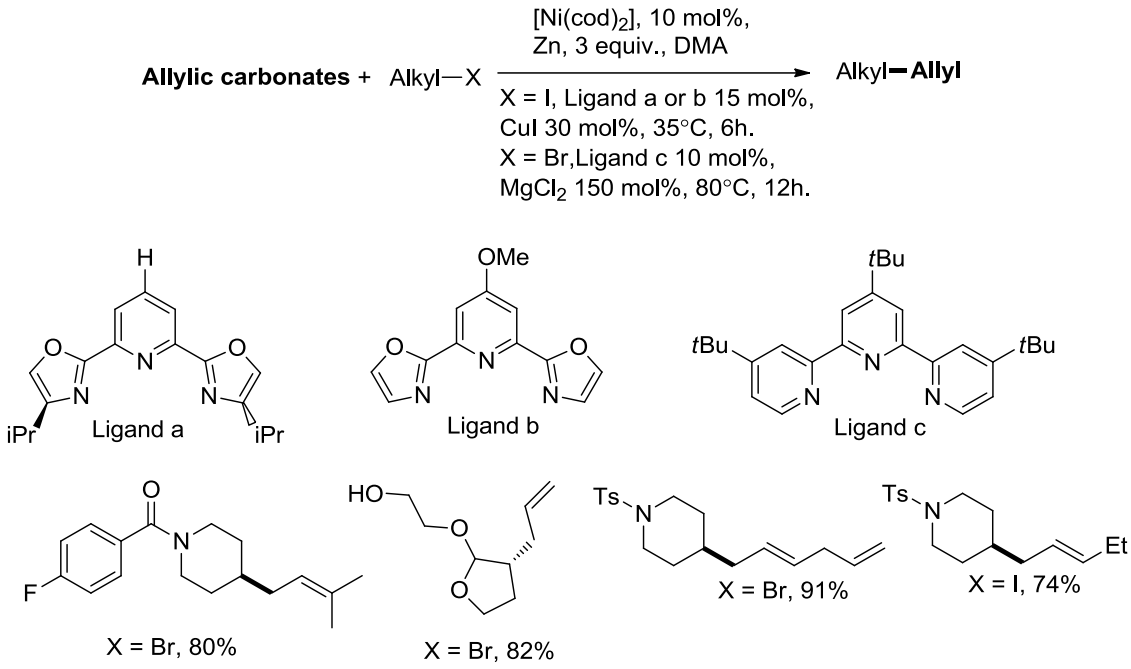
26 (a) Qian, X.; Auffrant, A.; Felouat, A.; Gosmini, C. *Angew. Chem., Int. Ed.* **2011,** *50*, 10402-10405. (b) Dai, Y.; Wu, F.; Zang, Z.; You, H.; Gong, H. *Chem. – Eur. J.* **2012,** *18*, 808-812. (c) Anka-Lufford, L. L.; Prinsell, M. R.; Weix, D. J. *J. Org. Chem.* **2012,** *77*, 9989-10000.

27 Cui, X.; Wang, S.; Zhang, Y.; Deng, W.; Qian, Q.; Gong, H. *Org. Bio. Chem.* **2013,** *11*, 3094-3097.

28 (a) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett.* **2012,** *14*, 3044-3047. (b) Yin, H.; Zhao, C.; You, H.; Lin, K.; Gong, H. *Chem. Commun.* **2012,** *48*, 7034-7036. (c) Wotal, A. C.; Weix, D. J. *Org. Lett.* **2012,** *14*, 1476-1479.

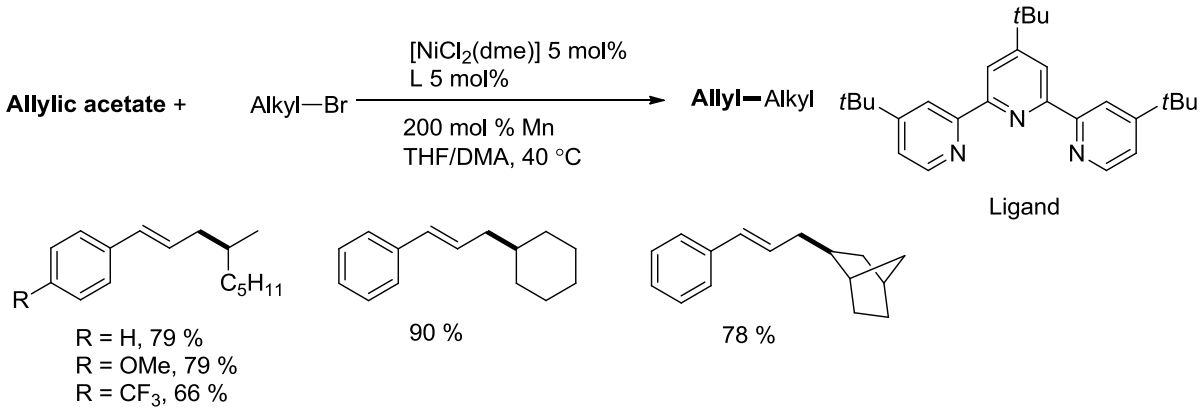
29 Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem.Soc.* **2013**

30 (a) Goldup, S. M.; Leigh, D. A.; McBurney, R. T.; McGonigal, P. R.; Plant, A. *Chem. Sci.* **2010,** *1*, 383-386. (b) Lu, S.; Jin, T.; Bao, M.; Yamamoto, Y. *J. Am. Chem.Soc.* **2011,** *133*, 12842-12848.



Scheme 9 Nickel-catalyzed reductive allylation of unactivated Alkyl Halides

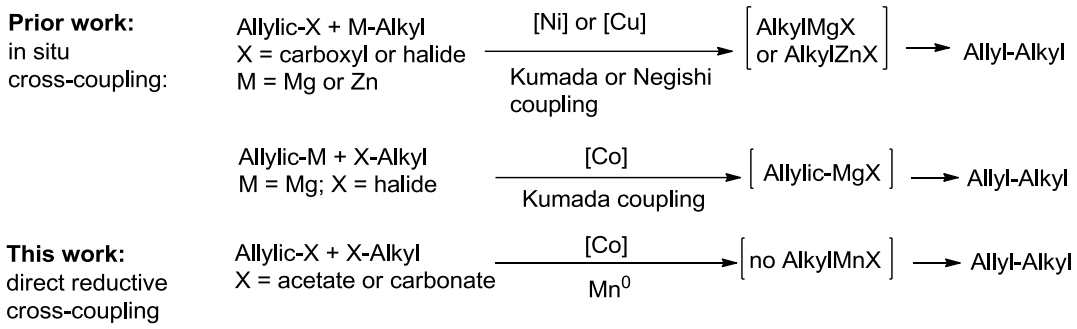
Very recently, Weix and coworkers reported a nickel-catalyzed reductive allyl-alkyl coupling reactions (Scheme 10).[26c] Their conditions are very similar to Gong's report, but without the addition of $MgCl_2$. However, this method works efficiently only for the coupling of secondary alkyl bromides. Primary alkyl bromides rapidly dimerize.



Scheme 10 Nickel-Catalyzed Reductive Allylation of secondary Alkyl bromides

In summary, few methods catalyzed by first-row transition metals for alkyl-allyl cross-coupling reactions have been developed, nevertheless functional group compatibility and/or good regioselectivity required to carefully design the catalytic system. To avoid the handling of air- and moisture-sensitive organomagnesium and organozinc reagents, straightforward procedures, which do not require organometallic reagents, are highly desirable and many have now been developed as summarized above. To the best of our

knowledge, direct transition-metal-catalyzed alkyl–allyl cross-couplings without using *in situ* generated catalytic organometallic reagents were still unknown in 2011 (Scheme 11). However, a few years ago, our group reported a related cobalt-catalyzed coupling reaction of aryl halides with allylic acetates;[21] these reactions in the presence of an appropriate reducing reagent, gave allylaromatic compounds. Such allylic carboxylates, are less reactive than allyl halides, and more environmentally friendly. Given the experience of our group in the direct cobalt-catalyzed functionalization,[21, 22a,c, 23, 24a] we were interested to take the chemistry further, and developed a new and general method for direct reductive cross-coupling of allylic acetates with alkyl halides.



Scheme 11 New synthetic routes for alkyl-allyl cross-coupling reactions

I-2 Results and discussions

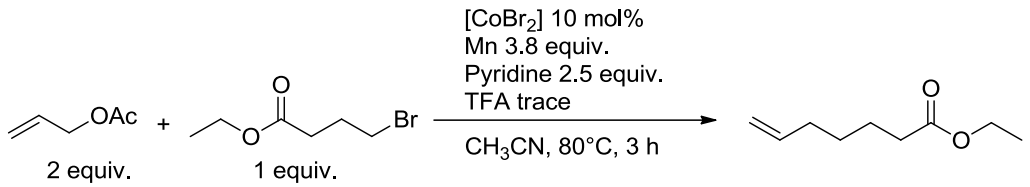
I-2-1 Optimization of the reaction conditions

First, we investigated the use of the readily available ethyl 4-bromobutanoate with non-substituted allyl acetate as the electrophile. The major challenge here lies in promoting cross-coupling rather than the formation of reduction and homocoupling products. A combination of factors enabled us to overcome these difficulties (Table 1).

$CoBr_2$ (10 mol%) and Mn (3.8 equivalents) were used in an acetonitrile/pyridine solvent mixture at 80 °C, this represents the standard conditions, which afforded an excellent yield within 3 hours (Table 1, entry 1). A 5 mol% catalyst loading gave the same result but over a period of 16 hours (Table 1, entry 2), and a 20 mol% $CoBr_2$ loading accelerated the reaction (2 hours) but gave a higher quantity of the alkyl dimer according to GC analysis (Table 1, entry 3). [$Co(acac)_2$] showed no catalytic activity. The starting materials in the reactions kept untouched (Table 1, entry 4). Reducing the amount of Mn dust decreased the reaction rate and the yield (Table 1, entry 5), while replacing Mn by Zn dust resulted in no cross-coupling product. Only trace reduction

product of alkyl halide was observed by GC (Table 1, entry 6). Equally, no cross-coupling product was detected upon changing CH_3CN for DMF (Table 1, entry 7). An excess of the allyl acetate was required to drive the reaction to completion, which is probably due to the formation of a π-allyl-cobalt complex (Table 1, entry 8). The pyridine appears to be important in stabilizing the low-valent Co intermediate because cross-coupling yields decreased in its absence (Table 1, entry 9). Replacing pyridine by bipyridine or triphenylphosphine gave poor yields, with more than 50% alkyl halide remaining unconsumed (Table 1, entries 11 and 12). The Co/Mn system requires activation by trifluoroacetic acid (TFA) for the formation of the low-valent Co intermediate, and attempts to run the reaction in the absence of this activator gave no cross-coupling product. The starting materials remain intact (Table 1, entry 13). At 35 °C, almost no reaction occurred (Table 1, entry 14) and conversion remained low at 50 °C, with the alkyl halide being only partially consumed even after 16 h (Table 1, entry 15).

Table 1 Optimized Reaction Conditions



Entry	Deviation from Standard Conditions	GC Yield %[a]
1	**None**	**90**
2	$[CoBr_2]$ 5 mol%	43/(91)[b]
3	$[CoBr_2]$ 20 mol%	77
4	$[Co(acac)_2]$ 10 mol%	None
5	Mn 1.9 equiv.	17
6	Zn 3.8 equiv. instead of Mn	None
7	DMF instead of CH_3CN	Trace
8	1 equiv. Allyl acetate	47(67)[c]
9	No pyridine	27
10	2 ml pyridine	67
11	Bipyridine instead of pyridine	18[b]
12	PPh_3 instead of pyridine	Trace[b]
13	No TFA	None
14	T = 35°C	Trace
15	T = 50°C	43

[a] Yields were calculated by GC analysis using dodecane as an internal standard. [b] The reaction time is 16 h. After 16 h, there may be still some starting material. [c] Used 1.1 equivalents of allyl acetate. acac=acetoacetonate, DMF=*N*,*N*'-dimethylformamide, TFA=trifluoroacetic acid.

I-2-2 Scope of alkyl bromides

With these results in hand, we first screened various alkyl halides with allyl acetate. The results reported in Table 2 and Table 3 demonstrate that the reaction has a good functional group tolerance. Functional groups such as nitriles, esters, a dioxane, a carbamate, and chlorine are nicely tolerated (Table 2 and Table 3).

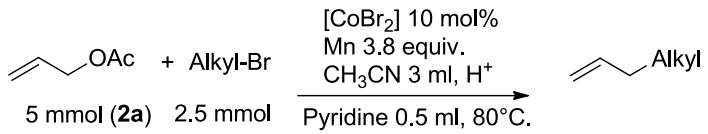
Ketone group is not tolerated in this method, no matter where it is positioned in the alkyl halide. The isolated product could not be identified. Proton NMR spectroscopy showed that the ketone group remains intact, without formation of any cross-coupling product. Moreover, alkyl halides bearing an isoindoline-1,3-dione, diisopropylamine and amine group were not coupled. The starting materials remain intact. The alkyl halide bearing a tosylate group was not coupled either. It seemed that the tosylate may also act as a leaving group, since there is no reduction product or dimerization product of the bromo alkyltosylate was observed

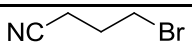
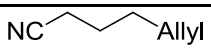
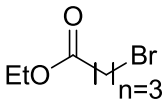
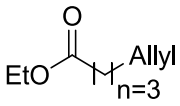
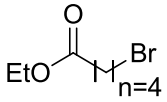
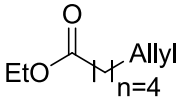
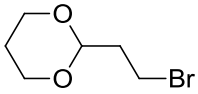
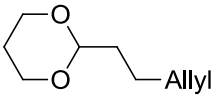
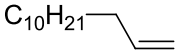
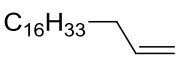
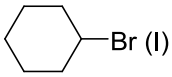
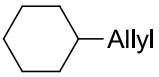
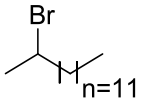
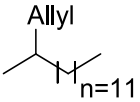
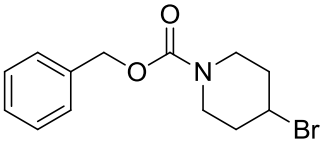
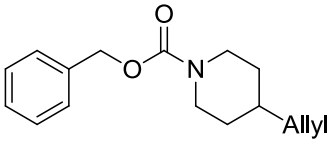
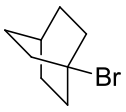
The reaction also proceeded well with long-chain alkyl bromides (Table 2, entries 5 and 6). Unreactive alkyl chloride ($C_{10}H_{21}Cl$) failed to couple. The coupling of 1,3-dibromopropane also failed, which may be related to its oxidative ability.

The coupling of secondary alkyl bromides (either cyclic or acyclic) was achieved in high yields (Table 2, entries 7–9) and even the tertiary alkyl bromide **1j** afforded the product **3j** in moderate quantities (Table 2, entry 10). Generally, the reactions reach completion within 4–6 h, although coupling with tertiary alkyl halides required longer reaction time (till 18 h). The results are therefore in agreement with the suggestion by Oshima17[b, c] that cobalt catalysts are superior to Ni[31] and Cu[32] for the coupling of quaternary carbon centers. However, the coupling of 2-bromo-1-chloro-2-methylpropane was not realized and only gave the reduction product of the alkyl halide.

Table 2 Scope of alkyl bromides.

31 (a) Joshi-Pangu, A.; Wang, C.-Y.; Biscoe, M. R. *J. Am. Chem. Soc.* **2011,** *133*, 8478-8481. (b) Lohre, C.; Dröge, T.; Wang, C.; Glorius, F. *Chem. – Eur. J.* **2011,** *17*, 6052-6055.
32 Hintermann, L.; Xiao, L.; Labonne, A. *Angew. Chem., Int. Ed.* **2008,** *47*, 8246-8250.



Entry	Alkyl-X	Product 3	Yield %[a]
1	 **1a**	 **3a**	90
2	 **1b**	 **3b**	88
3	 **1c**	 **3c**	90
4	 **1d**	 **3d**	70
5	$C_{10}H_{21}Br$ **1e**	 **3e**	75[b,c]
6	$C_{16}H_{33}Br$ **1f**	 **3f**	71[b,c]
7	 **1g**	 **3g**	81[a](85)[d]
8	 **1h**	 **3h**	85[b]
9	 **1i**	 **3i**	70[c, e, f]
10	 **1j**	 **3j**	60[b, c, e]

[a] Yield of the isolated product. [b] The yields were determined by corrected GC using dodecane as an internal standard. [c] The reaction time was 10 h. [d] Yield from the cyclohexyliodide, as calculated

using GC. [e] Mixture of alkyl–H and alkyl–alkyl. [f] The yields were determined by ^{1}H NMR spectroscopy.

I-2-3 Scope of allylic acetates

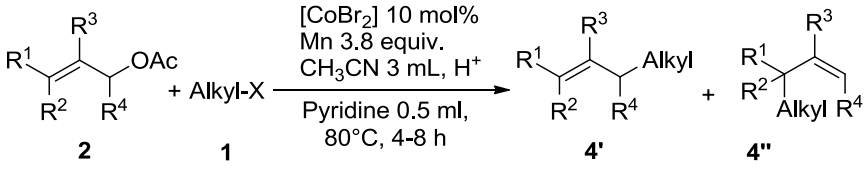
Next we investigated the scope of allyl acetates (Table 3). *Trans*-crotyl acetate (**2b**) coupled with primary and secondary alkyl halides in good albeit slightly lower yields than those obtained with unsubstituted allyl acetate (Table 3, entries 1–3)

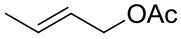
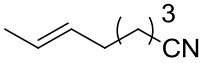
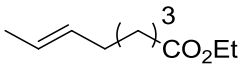
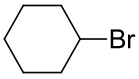
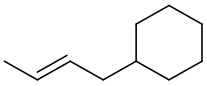
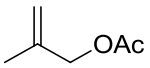
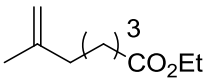
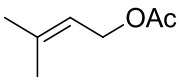
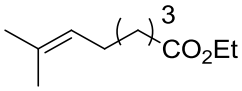
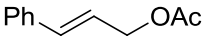
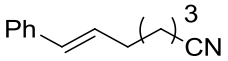
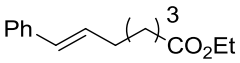
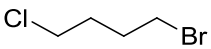
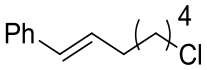
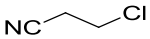
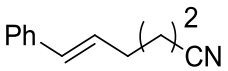
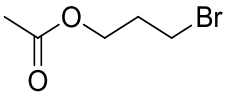
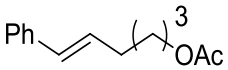
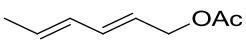
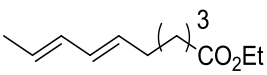
The formation of the isomeric α and γ products from substituted allyl acetate in allyl–alkyl cross-coupling reactions is known to occur in cobalt-catalyzed[17] or copper-catalyzed[19] processes and both products were detected in our reactions. However, the linear product **4'** always dominated (with a minimal proportion of 78%; Table 3, entry 5). The **4'**/**4''** ratio was determined by ^{1}H NMR spectroscopy. But-3-en-2-yl acetate (**2c**) reacted with the primary alkyl bromide **1b** (Table 3, entry 4) but not the secondary alkyl bromide **1g**. More sterically hindered acetates, such as prenyl acetate (**2d**), reacted with **1b** to give the cross-coupling product in good yield (Table 3, entry 5), but again no coupling product was observed with secondary alkyl bromide **1g**. Excellent yields were also obtained using (*E*)-cinnamyl acetate (**2e**; Table 3, entries 6–9). The alkylation reaction of 1-bromo-4-chlorobutane resulted in a selective attack at the bromide, thus affording (*E*)-7-chlorohept-1-en-1-ylbenzene (**4h**) in good yield (Table 3, entry 8). Interestingly, when a chloro group was at the β position relative to the nitrile, an excellent yield of the cross-coupled product **4i** was obtained (Table 3, entry 9). But when an amide group is located β position the chloride, no coupling occurred. No cross-coupling occurs with bromo alkylalcohols, which may due to the low solubility of the formed hydroxy salt in CH_3CN. We employed the corresponding acylated alcohol **1l** with success (Table 3, entry 10). Importantly, no branched coupling product was detected with the phenyl-substituted allylic acetate **2e**. The conjugated allylic acetate **2f** was also used, giving lower yields compared to those obtained from allyl or cinnamyl acetates (Table 3, entry 11). Next we investigated the reactivity of secondary allylic acetates. The cyclohex-2-en-1-yl acetate (**2g**) reacted with **1b** to give the product in poor yield; the high reactivity of the primary alkyl halide leads to the formation of by-products (Table 3, entry 12). The acyclic secondary allylic acetate **2h** reacted with both primary and tertiary alkyl halides to give mainly the linear coupling product in moderate yield (Table 3, entries 13 and 14). Unsurprisingly, double alkylation of *cis*-1,4-diacetoxy-2-butene (**2i**) with **1a** was the main reaction observed; the reaction proceeded

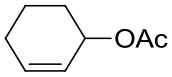
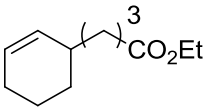
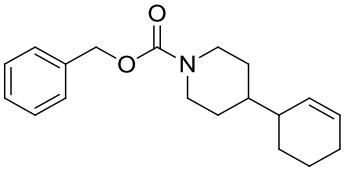
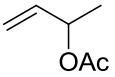
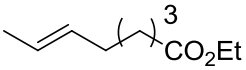
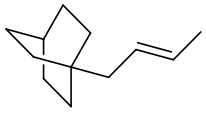
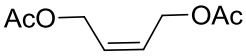
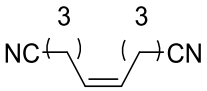
with retention of stereochemistry to give the *Z* product in good yield (Table 3, entry 15).

Other substrates were tested in place of allylic acetate, including allyl alcohol, alkyl acetates (benzyl acetate included), aryl acetates/carbonates, and prop-2-yn-1-yl acetate. Unfortunately, no reaction was observed in any of these cases. Finally, secondary alkyl halides fail to react with γ-disubstituted or β-substituted allylic acetate due to steric effect. The reduction product and homocoupling of alkyl halides were observed.

Table 3 Scope of allylic acetates



Entry	Allylic acetate	Alkyl-X	Product 4 (Ratio 4'/4'')	Yield %[a]
1	 **2b**	**1a**	 **4a** (85/15)	63
2	**2b**	**1b**	 **4b** (89/11)	72
3	**2b**	 **1g**	 **4c** (95/5)	75[b]
4	 **2c**	**1b**	 **4d**	88
5	 **2d**	**1b**	 **4e** (78/22)	67
6	 **2e**	**1a**	 **4f** (>99/1)	71
7	**2e**	**1b**	 **4g** (>99/1)	81
8	**2e**	 **1j**	 **4h** (>99/1)	77
9	**2e**	 **1k**	 **4i** (>99/1)	98
10	**2e**	 **1l**	 **4j** (>99/1)	68
11	 **2f**	**1b**	 **4k** (92/8)[c]	52

12	 **2g**	**1b**	 **4l**	38
13	**2g**	**1i**	 **4m**	50[d]
14	 **2h**	**1b**	 **4b** (12/88)	56
15	**2h**	**1j**	 **4n** (15/85)	66
16	 **2i**	**1a**	 **4o**[e]	76

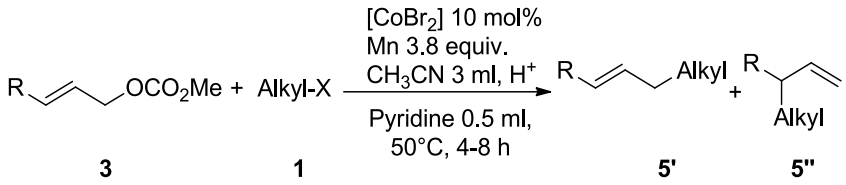
[a] Yield of isolated **4** and **4'**. [b] The yield was determined by ^{1}H NMR spectroscopy. [c] In this case the minor product comes from an attack at the methyl-substituted carbon atom (ε position). [d] GC yield. [e] Mixture of bis and mono g-alkylated products bearing an acetate group in an 81:19 ratio.

I-2-4 Scope of allylic carbonates and alkyl halides

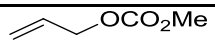
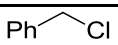
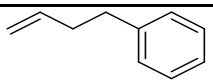
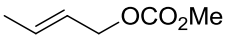
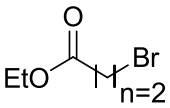
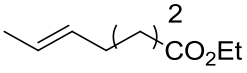
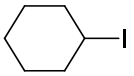
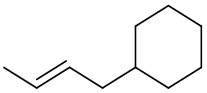
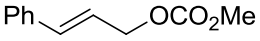
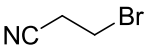
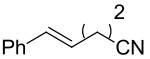
During the screening of more reactive alkyl halides, we found that both the presence of electron-withdrawing substituents, such as nitrile or ester groups, in the β position relative to the reactive bromo functionality and the use of benzyl chloride prevented the coupling reaction. They only provided the reduction product and dimer products of alkyl halides rapidly. This prompted us to employ the more reactive series of allyl carbonates. After minor modifications of the standard protocol ($CoBr_2$ (10 mol%)/Mn (3.8 equivalents) in an acetonitrile/pyridine solvent mixture at 50 °C), allyl carbonates including crotyl carbonate and cinnamyl carbonate, were successfully coupled to such halides (Table 4). In the case of trans-crotyl carbonate, the reaction with a primary alkyl halide gave primarily the terminal coupling product (Table 4, entry 2). Note that with bulkier cinnamyl carbonates, only the linear product was detected (Table 4, entry 4). The reaction also worked efficiently with secondary alkyl halide, such as cyclohexyl iodide (Table 4, entry 3). However, the more-reactive α-substituted alkyl halides, such as ethyl 2-chloro/bromo acetate, were not coupled. Only the reduction products of alkyl

halides were detected. To our best of our knowledge, very few reports deal with C-C coupling of these reactive alkyl halides.[24, 33]

Table 4 Scope of allylic carbonates and alkyl halides



3 **1** **5'** **5"**

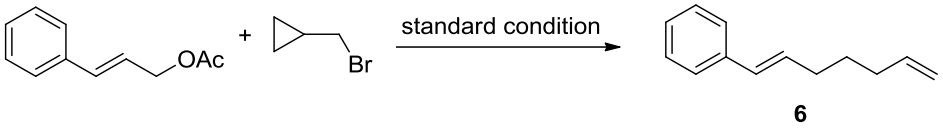
Entry	Allylic carbonate	Alkyl-X	Product (5'/5'')	Yield %
1	 **3a**	 **1l**	 **5a**	95[a]
2	 **3b**	 **1m**	 **5b** (87/13)[c]	82[b]
3	**3b**	 **1n**	 **4c (**89/11)	70[a]
4	 **3d**	 **1o**	 **4i** >99/1[c]	93[b]

[a] Yield determined by GC using dodecane as an internal standard. [b] Combined yield of isolated **5**' and **5**''. [c] Ratio of linear/branched.

I-2-5 Mechanistic investigations

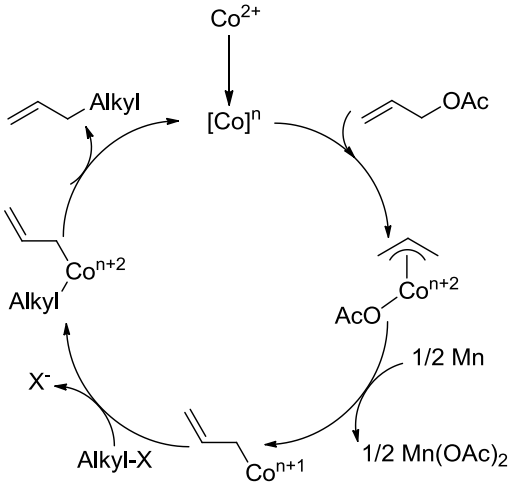
A few experiments were conducted to provide some insights into the mechanism of this allyl–alkyl cross coupling reaction. When bromomethylcyclopropane was reacted with (*E*)-cinnamyl acetate, the ring-opened product (*E*)-hepta-1,6- dien-1-ylbenzene was detected by GC as the sole cross coupling product (Equation 1). Moreover, the addition of the free radical 2,2,6,6-tetramethylpiperine-1-oxyl (TEMPO) before the alkyl halides inhibited the cross-coupling reaction. These results point towards the involvement of an alkyl radical intermediate in the activation process of the alkyl halide.

33 Durandetti, M.; Gosmini, C.; Périchon, J. *Tetrahedron* **2007,** *63*, 1146-1153.



Equation 1 Radical clock reaction

Our current mechanistic hypothesis is presented in Scheme 12. Initial reduction of the Co^{II} precatalyst should furnish a catalytically active low-valent Co species. Subsequent oxidative addition to the allyl acetate forms an allyl Co intermediate that is again subjected to reduction by manganese dust. This allyl Co complex reacts with an alkyl halide to give an allyl-alkyl-Co complex through the formation of an alkyl radical. Then reductive elimination occurs to furnish the cross-coupling product along with the regeneration of the active species.



Scheme 12 Postulated mechanism for the direct allylation of alkyl halides.

I-2-6 Conclusions and perspectives

In summary, a new route for the direct allylation of various alkyl halides catalyzed by cobalt(II) bromide was developed. This method is very straightforward and efficient for the coupling of a large variety of alkyl halides (primary, secondary, and tertiary) with substituted allylic acetates and carbonates and provides good to excellent yields with a good functional group tolerance. Moreover, in the case of substituted allyl acetates, the reaction affords the linear product as the major or the sole product. Both sterically hindered secondary allyl acetates and secondary and tertiary alkyl halides are acceptable as substrates. It is worth to note that after the publication of these results, another two nickel-catalyzed direct reductive coupling allylic acetate/carbonate with

alkyl halides were reported by Gong[26b] and Weix[26c] respectively (as mentioned in I-1-2).

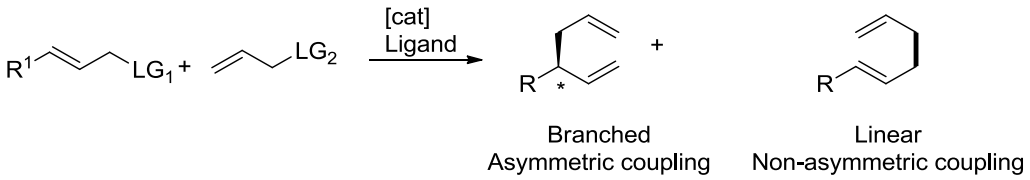
As described here, some progress has been made in cobalt-catalyzed direct reductive allyl-alkyl cross-coupling reactions. However, there are several issues that still remain to be resolved: (1) The coupling of unreactive alkyl chlorides still remains a challenge. Alkyl chlorides are desirable alkylation reagents because of their wide availability and low cost relative to their iodo and bromo analogues, however they are less reactive due to the strong C-Cl bond compared to C-Br and C-I bonds. Thus, high functional group-tolerant reductive couplings of non-activated alkyl chlorides should be developed. (2) As primary benzyl chloride well coupled with allyl acetate, it will be advantageous to investigate the reactivity of secondary benzyl halides with allylic acetates/carbonates, and especially the enantioselectivity of the products with a proper *chiral* ligand. (3) Reductive intramolecular cross-coupling reactions are very rarely reported.[24e] It will be interesting to develop a cobalt-mediate reductive intramolecular allyl-alkyl coupling reaction, which may be a new route to synthesis cyclic-alkenes. (4) Cross-coupling reactions of two secondary/tertiary electrophiles remain undeveloped,[34] whereas they allow more flexibility in the synthesis of sophisticated carbon skeletons. However, in our medium we found that secondary allylic acetate **2g** reacted with secondary alkyl halide **1j**, secondary allylic acetate **2h** react with tertiary alkyl halide **1i** providing moderate to good yields. Study in this direction should be pursued.

34 Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012,** *134*, 11124-11127.

II. Cobalt-catalyzed Allyl-Allyl Cross-Coupling Reactions

II-1 Introduction

Transition-metal catalyzed allyl-allyl cross-coupling reactions reprensents a very important way to access to the 1,5-diene motif, which is present in naturally occurring terpenes,[35] versatile intermediates and other synthetic building blocks (Scheme 13).[36]



Scheme 13 Catalytic allyl-allyl coupling reaction

When the transformation provides the branched product as the main product, the control of the enantioselectivity of the *chiral* 1,5-diene structure is highly desirable. Many efficient catalytic systems have been designed, based on Pd,[37] Au,[38] and Cu[39] to realize the asymmetric allyl-allyl coupling reaction with high enantioselectivity (Scheme 14).

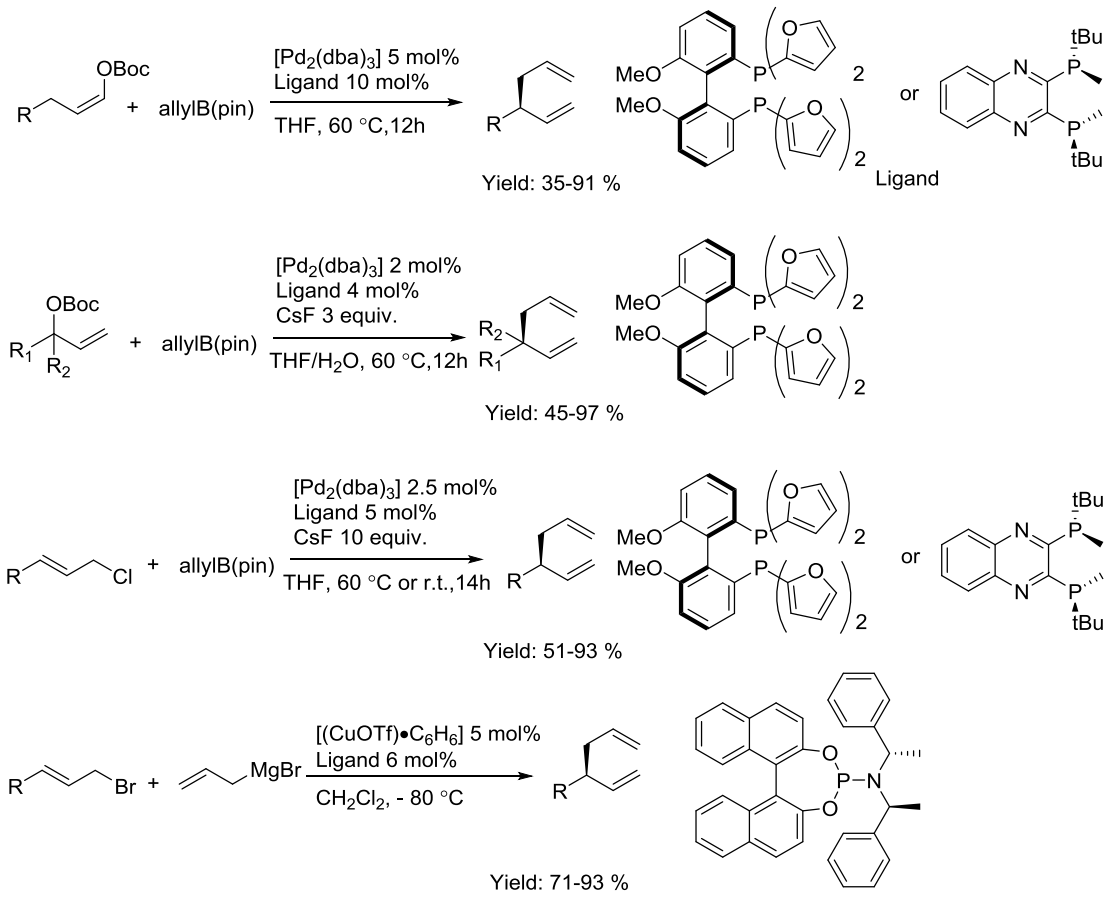
35 (a) Breitmaier, E. *Terpenes, Flavors, Fragrances, Pharmaca, Pheromones*; Wiley-VCH:Weinheim, **2006**. (b) *Medicinal Natural Products: A Biosynthetic Approach*; Dewick, P. M., Ed.; Wiley: Chichester, **2002**. (c) Nicolaou, K. C. and Montagnon, T. *Molecules that Changed the World*; Wiley: Chichester, **2008**.

36 (a) Nakamura, H.; Yamamoto, Y. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley Interscience: West Lafayette, **2002**; Vol. 2. (b) Feducia, A. J.; Gagne, M. R. *J. Am. Chem. Soc.***2008**, 130, 4, 405-409.

37 (a) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686-10688. (b) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716-9719. (c) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778-16781.

38 Porcel, S.; López-Carrillo, V.; García-Yebra, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* 2008, *47*, 1883-1886.

39 Hornillos, V.; Pérez, M.; Fañanás-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2013**, *135*, 2140-2143.



Scheme 14 Represented examples on asymmetric allyl-allyl coupling reaction

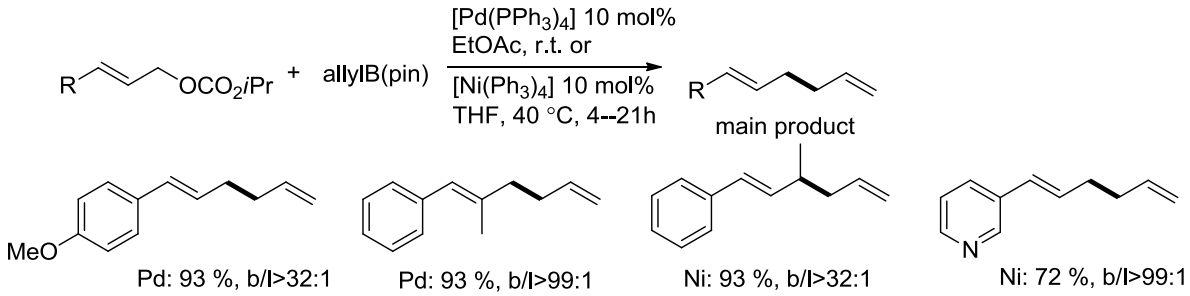
However, the transition-metal catalyzed reactions giving selectively the non-asymmetrical linear allyl-allyl coupling products are significantly more challenging but less investigated until now.[40] Stoichiometric π-allyl-palladium complex was used to catalyze the allyl-allyl C-C coupling reaction. However, the undesired *β*-H elimination occurred under palladium catalysis. In addition, these non-asymmetrical allyl-allyl couplings also suffered from the homocoupling and unsatisfactory regioselectivities, which lead to low yields and limited scope.

Kobayashi developed the first Suzuki type allyl-allyl nonsymmetrical coupling reactions (Scheme 15).[41] In the presence of Pd(0) or Ni(0) precatalyst, substituted allyl carbonates and allyl boronic esters are coupled efficiently and yield linear diene products selectively. This novel protocol overcomes the previous reports' drawbacks,

40 Negishi, E.-i.; Liao, B. *Handbook of Organopalladium Chemistry for Organic Synthesis*, *Vol. 1* (Eds.: E.-i. Negishi, A. de Meijere), Wiley-Interscience, West Lafayette, **2002**, p. 591.

41 Ferrer Flegeau, E.; Schneider, U.; Kobayashi, S. *Chem. – Eur. J.* **2009**, *15*, 12247-12254.

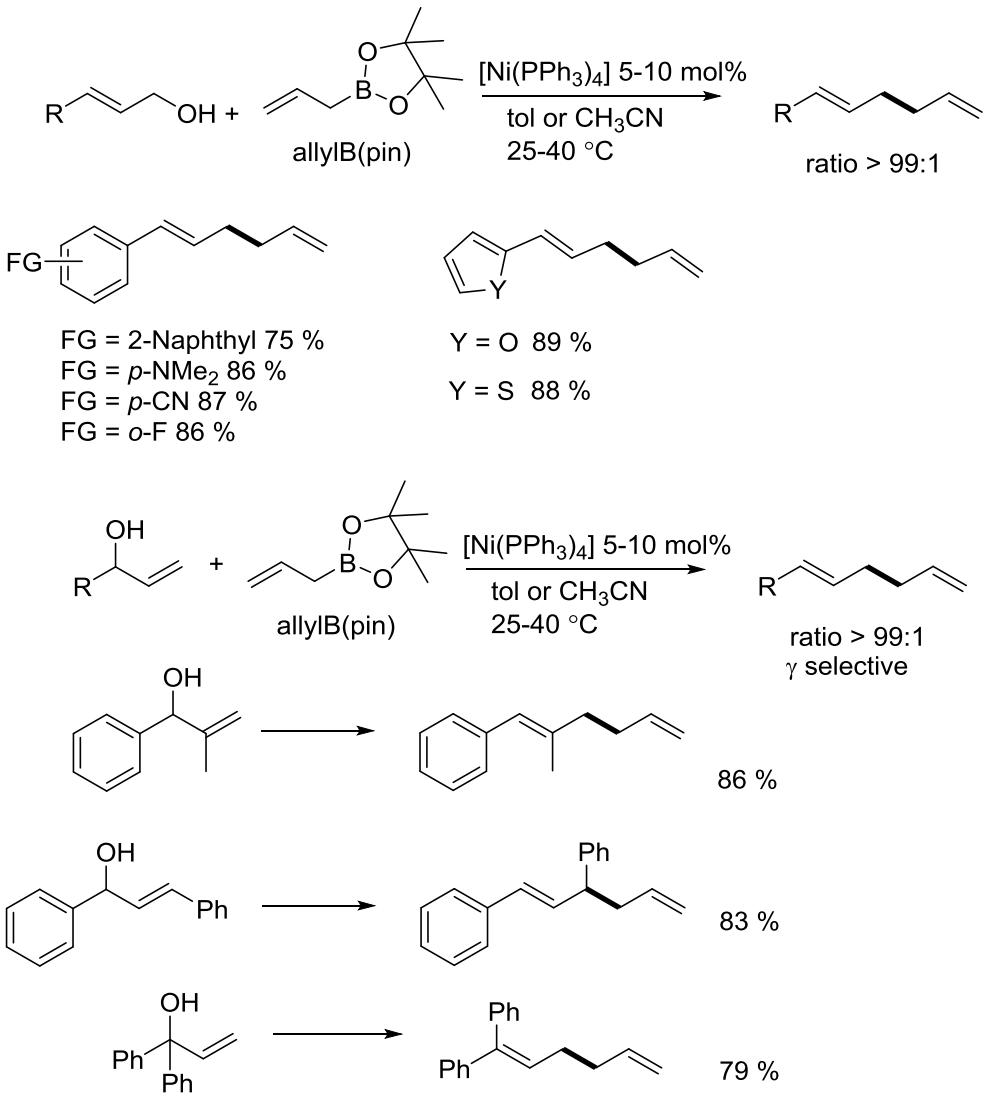
such as the use of toxic/harmful reagents and harsh conditions. However, the scope of the substrates and functional group tolerance was poorly explored.



Scheme 15 Palladium/Nickel-catalyzed allyl-allyl cross-coupling reaction

In 2011, Kobayashi and coworkers continued in this field and developed a very efficient nickel-catalyzed allyl-allyl cross-coupling reaction using directly allyl alcohols and allyl boronates (Scheme 16).[42] The linear-, γ-selective 1,5-dienes were obtained in excellent yield (75 – 94 %) and regioselectivity (l:b >99:1). Not only primary allyl alcohols, but also secondary and tertiary allyl alcohols were coupled efficiently. Besides, this procedure tolerated several important functional groups, such as dimethylamine, nitrile, trifluomethane, and heterocycles. The key to easily achieve the C-O bond activation is to take the advantage of the Lewis acidity of the trivalent boron atom. The Lewis basic allyl alcohols may coordinate to the *Lewis acidic* boron atom and then transform this hydroxyl moiety into an easier leaving group.

42 Jimenez-Aquino, A.; Ferrer Flegeau, E.; Schneider, U.; Kobayashi, S. *Chem. Comm.* **2011,** *47*, 9456-9458.

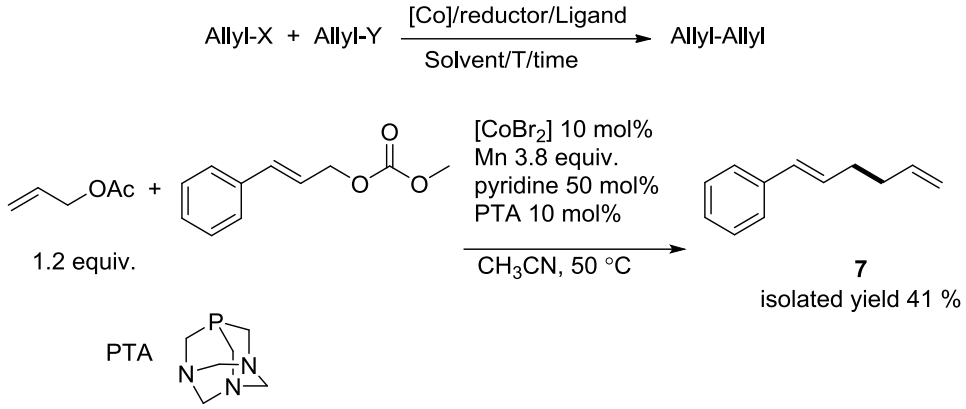


Scheme 16 Nickel-catalyzed allyl-allyl cross-coupling reaction

II-2 Results and discussions

II-2-1 Reaction conditions optimization

Given these reports and our experience in the field of cobalt-catalyzed different coupling of allylic substrates, it is interesting to build a catalytic system to couple two allylic electrophilies directly. We try to find the right combination of $CoBr_2$/reductor/ligand to couple the allyl acetate and cinnamyl carbonate as the model reaction. Various parameters were optimized, at the end, $CoBr_2$, with Mn as the reductor, 1, 3, 5-triaza-7-phosphaadamantane, (PTA) /pyridine *bi*-ligand system was found to be the most efficient until now (Scheme 17). Non-asymmetric linear diene product was isolated in moderate yield. The optimical process will be detailed below.

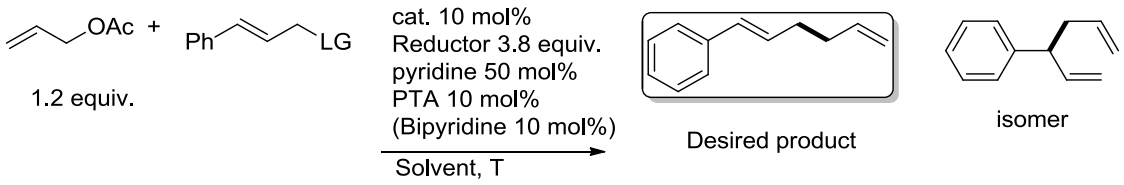


Scheme 17 Cobalt-catalyzed allyl-allyl cross-coupling reaction

II-2-1-1 Parameter optimization 1: catalyst, reductor, solvent, allyl substrate, temperature

First, the catalyst, reductor, solvent, allyl substrate and reaction temperature were tuned. The standard conditions are shown in Table 5, entry 1, which is the best result obtained until now. By using a $CoBr_2$/Mn system with an acetonitrile/pyridine solvent mixture, allyl acetate reacts with cinnamyl carbonate directly and provides 41 % isolated yield. The main side product is the dimer of cinnamyl carbonate. $CoBr_2$ cannot be substituted by $[Co(acac)_2]$ or $[Co(OAc)_3]$ (Table 5, entries 2 and 3), which showed no catalytic ability in this reaction. Interestingly, Zn dust also showed some reductive ability in this case (Table 5, entry 4), however, the branch product was formed. The major challenge here lies in promoting cross-coupling rather than the formation of homocoupling products. Increasing the difference of reactivity of the two substrates is one possible solution. While employing cinnamyl chloride, bromide or acetate only provided poor cross-coupling results (Table 5, entries 5 to 7). Conducting the reaction in DMF gave no reaction (Table 5, entry 8). Increasing the temperature to 80 °C did not improve the coupling reaction (Table 5, entry 9). Moreover, higher temperature decomposed the cinnamyl carbonate into phenol quickly in the presence of pyridine. The reaction did not work well at 30 °C (Table 5, entry 10), the conversion is low (no more than 30 %) even after 18 h.

Table 5 Parameter optimization 1: catalyst, reductor, solvent, allyl substrate, temperature



Entry	Cat.	Reductor	Solvent	$Allyl_2$	T/ °C	GC Yield
1	$[CoBr_2]$	Mn	CH_3CN	cinnamyl carbonate	50	50 %[a]
2	$[Co(acac)_2]$	Mn	CH_3CN	cinnamyl carbonate	50	0
3	$[Co(OAc)_3]$	Mn	CH_3CN	cinnamyl carbonate	50	0
4	$[CoBr_2]$	Zn	CH_3CN	cinnamyl carbonate	50	isomer 23 %
5	$[CoBr_2]$	Mn	CH_3CN	cinnamyl chloride	50	16 %
6	$[CoBr_2]$	Mn	CH_3CN	cinnamyl bromide	50	7%
7	$[CoBr_2]$	Mn	CH_3CN	cinnamyl acetate	50	19 %
8	$[CoBr_2]$	Mn	DMF	cinnamyl carbonate	50	0
9	$[CoBr_2]$	Mn	CH_3CN	cinnamyl carbonate	80	5 %
10	$[CoBr_2]$	Mn	CH_3CN	cinnamyl carbonate	30	14 %

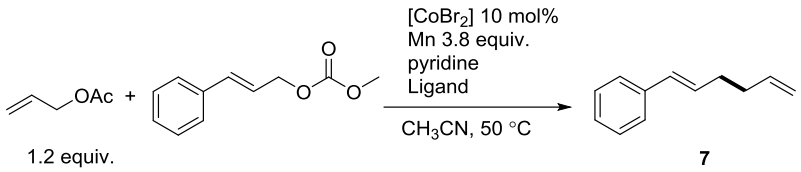
[a]41% isolated yield.

II-2-1-2 Parameter optimization 2: Ligand effect

Next we keep the parameters in table 12, entry 1 as constants, but we changed the ligands. It showed that the reaction needs a ligand (Table 6, entry 2). PTA was crucial in the recent conditions, without it the yield decreases sharply (Table 6, entry 3). Bipyridine may be not necessary, because the GC results are similar (Table 6, entry 4). Pyridine seemed essential for the transformation (Table 6, entries 5 and 6). Reducing pyridine amount to 25 mol%, only led to a weak decrease of the yield (Table 6, entry 5). However, the conversion is 60 % after 24 h if the reaction went without pyridine (Table 6, entry 6). Increasing the amounts of pyridine has no positive effect (Table 6, entry 7). When only pyridine is present, 29 % coupling product was obtained (Table 6,

the yield was even poorer (Table 6, entries 9 to 11). However, it is worth to note that when employing 50 mol% PTA, the branched product was detected and no dimer of cinnamyl carbonate was detected by GC. NEt_3 instead of PTA provided the branched product in low yield (Table 6, entry 12). PPh_3 also provided a mixture of both (ratio=3:2) in poor yield (Table 6, entry 13). Bidentate ligand dppp gave the lowest efficiency (Table 6, entry 14).

Table 6 Parameter optimization 2: Ligand effect



Entry	Ligand 1	Pyridine	Yield
1[a]	PTA 10 mol%	50 mol%	50 % (41 %)
2	PTA 0	0	No reaction
3[a]	PTA 0	50 mol%	19
4	PTA 10 mol%	50 mol%	44
5	PTA 10 mol%	25 mol%	41
6	PTA 10 mol%	0	22[b]
7	PTA 10 mol%	250 mol%	38
8	PTA 0	50/250/100 mol%	29/19/22
9	PTA 20 mol%	50 mol%	39
10[a]	PTA 50 mol%	50 mol%	11[c]
11	PTA 50 mol%	100 mol%	27[d]
12	NEt_3 10 mol%	50 mol%	15[e]
13	PPh_3 10 mol%	50 mol%	30[f]
14	dppp 10 mol%	50 mol%	8

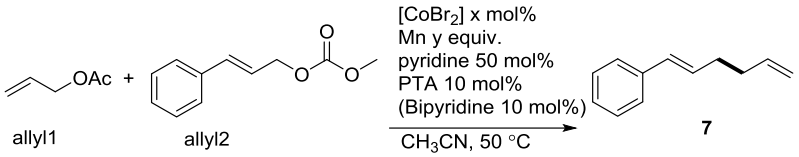
[a] Bipyridine 10 mol% [b] Conversion is 60 %. [c] Branch product, conversion is 50 %. [d] Branch product, conversion is 40 %. [e] Branch product. [f] A mixture of linear and branch product.

II-2-1-3 Parameter optimization 3: Quantity effect

The *ratio*s between allyl acetate and cinnamyl carbonate, catalyst loading, reductor quantity were also modified (Table 7). Allyl acetate should be in slight excess (1.2 equiv.) compared to cinnamyl carbonate, while 2 equivalents is not useful to increase the yield (Table 7, entry 2). Switch the quantity of allyl acetate and cinnamy carbonate decrease the yield (Table 7, entry 3). Decreasing the catalyst loading to 5 mol% gave lower yield of coupling product (Table 7, entry 4). While increasing the catalyst loading to 20 mol% only increase the yield of the cinnamyl dimer (Table 7, entry 5). In addition,

to 20 mol% only increase the yield of the cinnamyl dimer (Table 7, entry 5). In addition, reducing the quantity of Mn by two also decreased the coupling product (Table 7, entry 6).

Table 7 Parameter optimization 3: Quantity effect



Entry	Catalyst	Reductor	Allyl 1 : Allyl 2	GC Yield %
1	[$CoBr_2$] 10 mol%	Mn 3.8 equiv.	1.2 :1	50 (41)[a]
2	[$CoBr_2$] 10 mol%	Mn 3.8 equiv.	2 :1	44
3	[$CoBr_2$] 10 mol%	Mn 3.8 equiv.	1 :1.2	30
4	[$CoBr_2$] 5 mol%	Mn 3.8 equiv.	2 :1	27
5	[$CoBr_2$] 20 mol%	Mn 3.8 equiv.	2 :1	25
6	[$CoBr_2$] 10 mol%	Mn 1.9 equiv.	2 :1	19

[a]Isolated yield in parentheses.

II-2-2 Conclusions and future work

In conclusion, efforts were made to build a novel cobalt-catalyzed reductive allyl-allyl coupling reaction. Although the conditions were not finally optimized efficiently, some suggestions were found. The next step may focus on investigating new allylic substrates with different leaving groups, to decrease the competitive dimerization homocoupling product. Meanwhile, some other ligands should be screened. It seems that the ligands have important effect on the chemoselectivity and regioselectivity of the coupling product. Moreover, well-defined cobalt complexes may be designed and employed as the catalysts for this reaction. This will help us to understand and control the reactivity in a rational manner.

III. Cobalt-catalyzed Reductive Cross-Coupling of Alkyl Halides

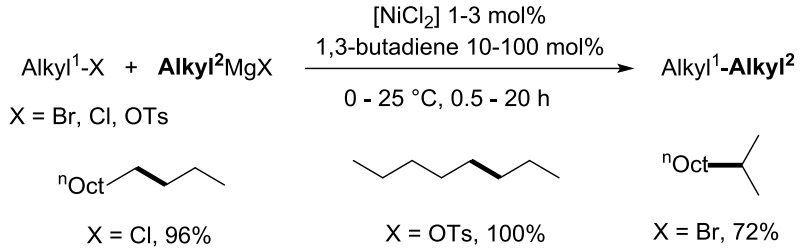
III-1 Introduction

Efficient transition-metal catalyzed C_{sp}^3-C_{sp}^3, alkyl-alkyl cross-coupling reactions are difficult to achieve compared to their C_{sp}^2 or C_{sp} analoges, because they are prone to side reaction, such as β-H elimination and unwilling to undergo oxidative addition. Many transition-metal catalysts can now promote the coupling of primary and secondary alkyl electrophiles with primary alkyl nucleophiles.[43] This section will first summarize the transition-metal catalyzed alkyl-alkyl cross-coupling reactions with organometallic reagents, and then will introduce the nickel-catalyzed reductive alkyl-alkyl cross-coupling reactions. Finally our work concerned a cobalt-catalyzed reductive alkyl-alkyl cross-coupling reaction will be preliminary studied.

III-1-1 Transition-metal catalyzed alkyl-alkyl cross-coupling reactions employing organometallic reagents

III-1-1-1 Kumada type alkyl-alkyl reactions

In 2002, Kambe and coworkers developed the first efficient Ni-catalyzed Kumada-type cross-coupling reactions of primary and secondary Grignard reagents with primary alkyl chlorides, bromides, and tosylates under mild conditions (Scheme 18).[44] The use of 1,3-butadiene as a ligand is crucial to obtain high yields. However, the functional compatibilities and substrates scope were little explored.

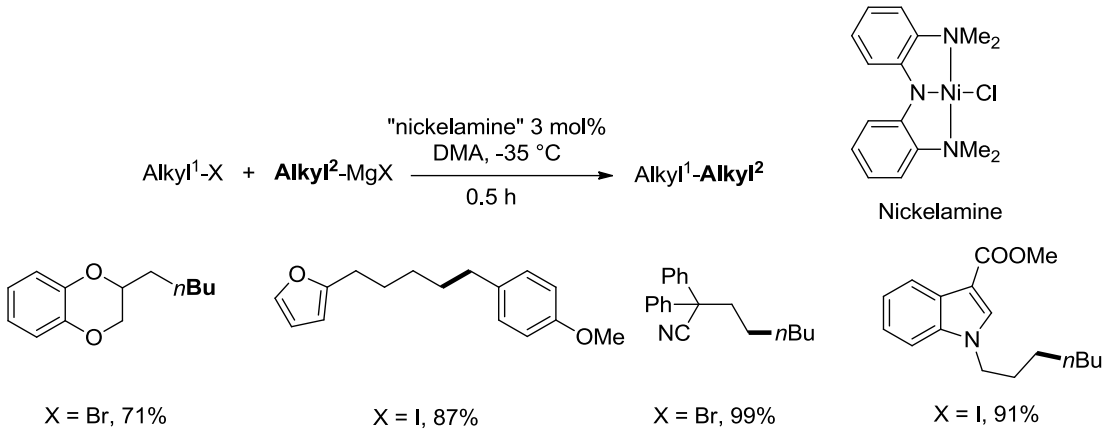


Scheme 18 Nickel-catalyzed Kumada type alkyl-alkyl cross-coupling reactions

Hu and coworkers reported a method of alkyl-alkyl Kumada coupling catalyzed by a well-defined nickel complex, "nickelamine" [($^{Me}N_2N$)Ni^{II}Cl] (Scheme 19).[45] A variety of non-activated and functionalized alkyl bromides and iodides were coupled with alkyl

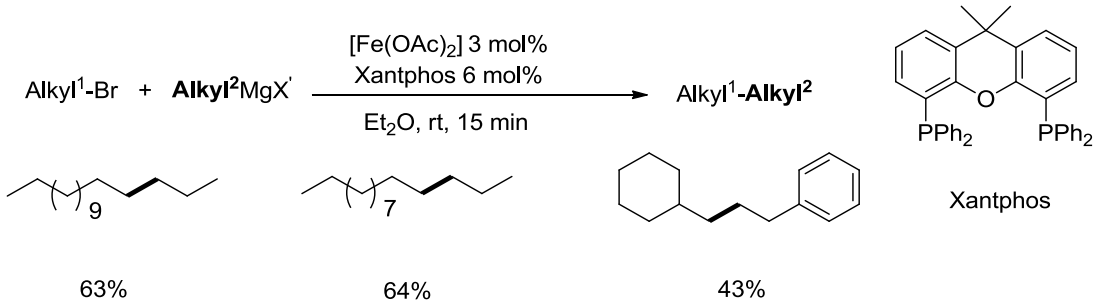
43 Hu, X. *Chem. Sci.* **2011**, *2*, 1867-1886.
44 Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222-4223.
45 Vechorkin, O.; Hu, X. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 2937-2940.

Grignard reagents in good to excellent yields. The low temperature is necessary to obtain high coupling yields.



Scheme 19 Kumada type alkyl-alkyl cross-coupling reactions catalyzed by "Nickelamine"

Efficient methods for iron-catalyzed Kumada-type C(sp^3)-C(sp^3) coupling reactions are rarely reported. In 2006, Chai *et al*. demonstrated that [$Fe(OAc)_2$] in combination with Xantphos was effective in coupling alkyl halides with alkyl Grignard reagents (Scheme 20).[46] The yields were generally low to medium. However, the functional compatibility was very limited.

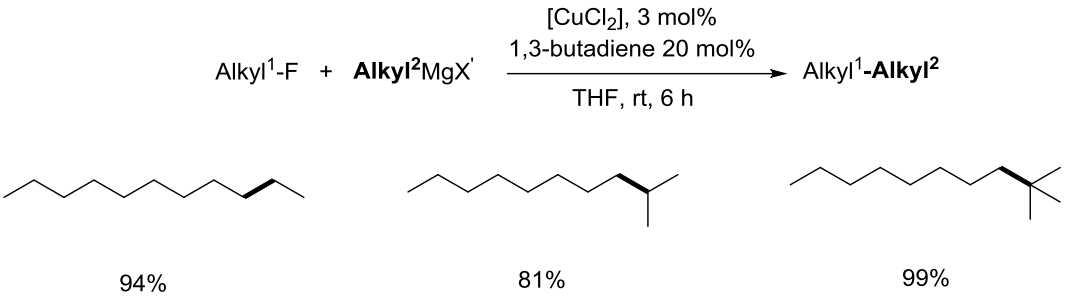


Scheme 20 Iron-catalyzed Kumada type alkyl-alkyl cross-coupling reactions

Kambe *et al.* reported an efficient system for the cross-coupling reaction of alkyl fluorides with alkyl Grignard reagents catalyzed by $NiCl_2$ or $CuCl_2$ salts with 1,3-butadiene as the ligand (Scheme 21).[47] Primary alkyl fluorides and various Grignard reagents (primary, secondary, and tertiary alkyl and phenyl Grignard reagents) were coupled in good to excellent yields under mild conditions. The reactivity of alkyl halides was also examined and observed to be in the order chloride < fluoride < bromide.

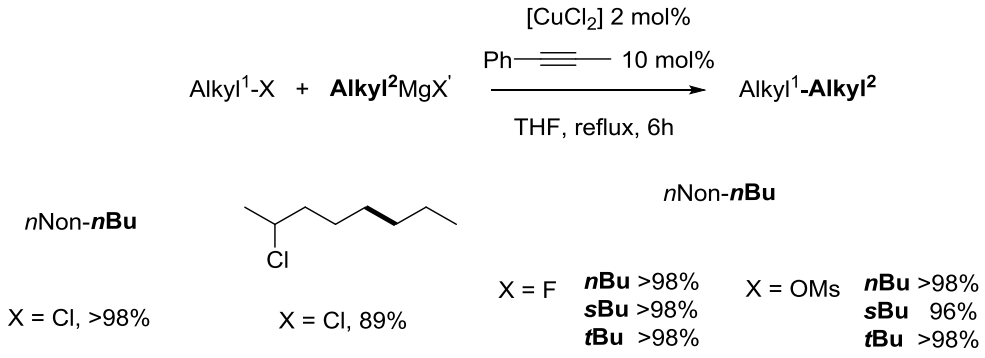
46 Dongol, K. G.; Koh, H.; Sau, M.; Chai, C. L. L. *Adv. Synth. Catal.* **2007**, *349*, 1015-1018.
47 Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646-5647.

The high reactivity of alkyl fluorides are proposed to rely on their transformation into the corresponding alkyl bromides in the presence of $MgBr_2$.[48] However, the functional group tolerance was not thoroughly investigated.



Scheme 21 Copper-catalyzed Kumada type alkyl-alkyl cross-coupling reactions.

Later, they overcame the difficulties for the coupling of alkyl chlorides (**Scheme** 22).[49] With 1-phenylpropyne as an additive, alkyl chlorides reacted with alkyl Grignard reagents and provided good to excellent coupling yields in the presence of copper catalyst. This protocol was also used for alkyl fluorides and mesylates. Again, the functional compatibilities and substrate scope were not demonstrated.

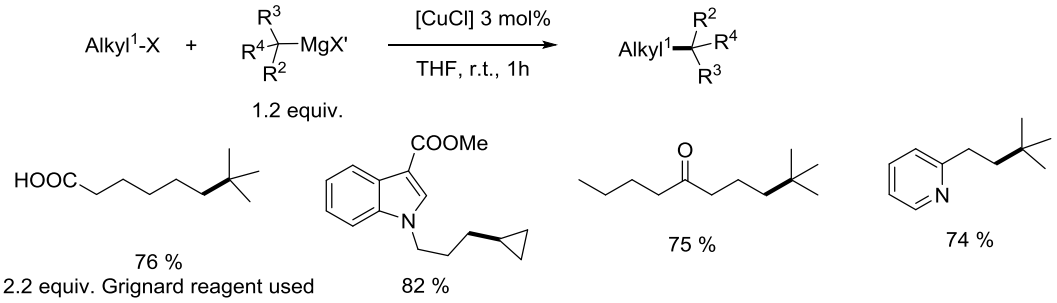


Scheme 22 Copper-catalyzed Kumada type alkyl-alkyl cross-coupling reactions.

Nevertheless, the creation of quaternary carbon centers remains highly challenging. Until now, there are only three high activity, broad substrate scope and high functional group tolerance methods reported concerning the creating of quaternary carbon centers from two alkyl substrates.

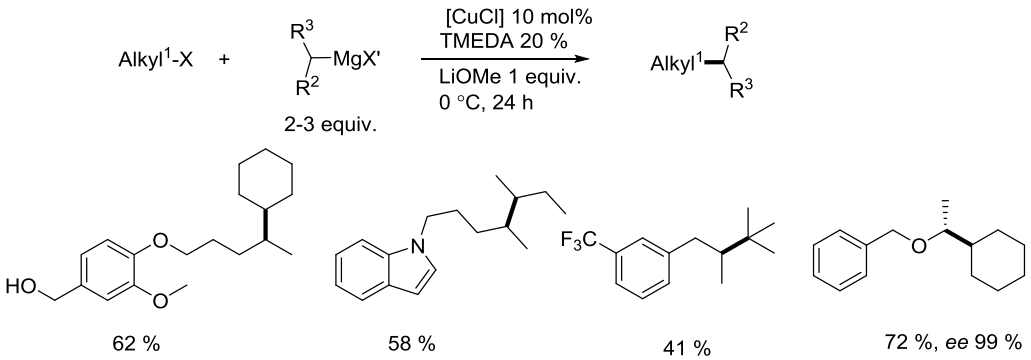
48 Begum, S. A.; Terao, J.; Kambe, N. *Chem. Lett.* **2007**, *36*, 196-197.
49 Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 2086-2089.

Hu and coworkers developed a highly efficient method for the cross-coupling of non-activited functionalized alkyl halides/tosylates with secondary and tertiary alkyl Grignard reagents catalyzed by a copper salt (Scheme 23).[50] The method is remarkably practical and general. Moreover, its wide scope, highly chemo-selective and functional group tolerance make the protocol attractive for the streamlined synthesis of functional molecules.



Scheme 23 Copper-catalyzed alkyl-alkyl cross-coupling reaction of primary alkyl halides and tosylates with secondary and tertiary alkyl Grignard reagents

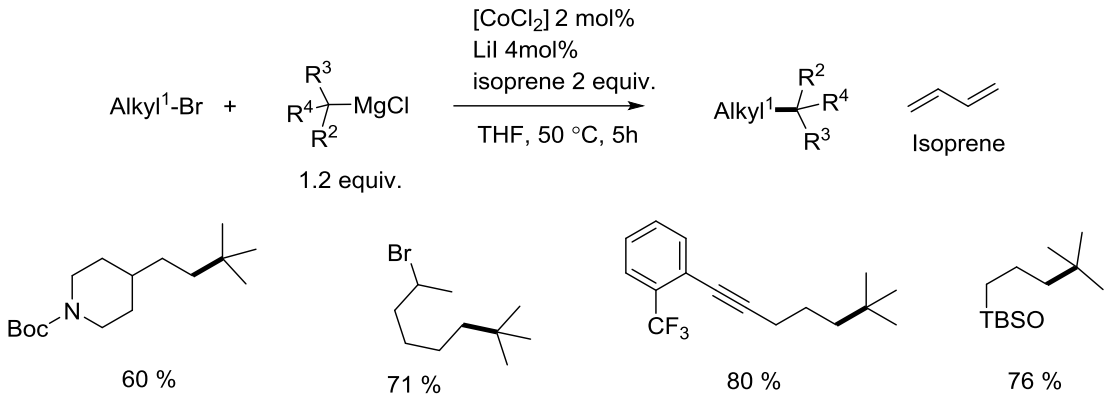
Later, Liu and coworkers developed a copper-catalyzed cross-coupling reactions of secondary alkyl halides/tosylates with secondary or even tertiary alkyl Grignard reagents (Scheme 24).[34] This method not only tolerates a large number of important yet sensitive functional groups, but also solves the coupling of primary alkyl chlorides, which is a challenge in Kumada type reaction for a long time. Besides, the reaction was confirmed to occur *via* S_N2 mechanism with inversion of configuration by X-ray crystal analysis. Therefore, it can provide a general approach for the stereocontrolled formation of C-C bonds in high *ee* value from the corresponding chiral secondary tosylates.



Scheme 24 Copper-catalyzed alkyl-alkyl cross-coupling reaction of secondary alkyl halides and tosylates with secondary alkyl Grignard reagents

50 Ren, P.; Stern, L.-A.; Hu, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 9110-9113.

Very recently, the Kambe's group reported a cobalt-catalyzed cross-coupling of primary alkyl halides with tertiary alkyl Grignard reagents (Scheme 25).[51] This protocol constructs sterically congested quaternary carbon centers and tolerates various of functional groups. The use of 1,3-butadiene and LiI was crucial to achieve high yields. A plausible mechanism suggested that this reaction proceeds *via* an ionic mechanism: the formation of an anionic π-cobalt complex is crucial.

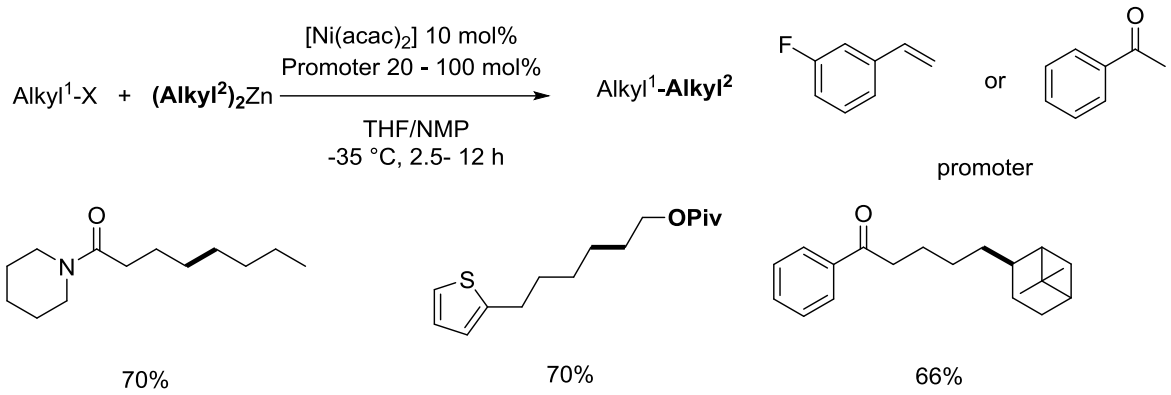


Scheme 25 Cobalt-catalyzed cross-coupling of alkyl halides with tertiary alkyl Grignard reagents

III-1-1-2 Negishi type alkyl-alkyl reactions.

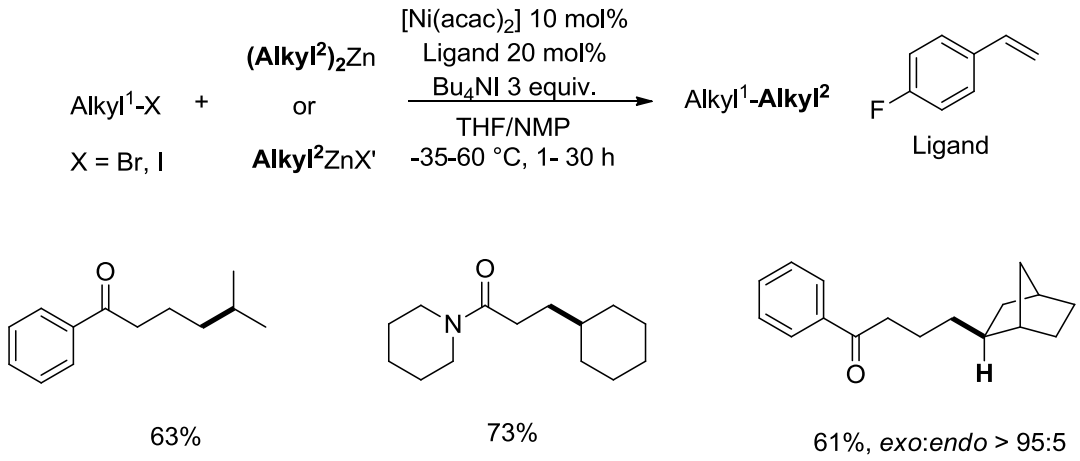
Knochel *et al.* pioneered the development of transition-metal catalyzed Negishi type alkyl–alkyl cross-coupling reactions. In 1998, they reported an efficient nickel-catalyzed primary iodoalkanes and primary diorganozinc compounds cross-coupling reactions (Scheme 26).[52] The promoter, *m*-trifluoromethylstyrene or acetophenone is crucial to obtain the cross-coupling products. It is proposed that the main effect of these two promoters is that they facilitate the reductive elimination of the intermediate Ni(II) complex $(Alkyl^1)(Alkyl^2)NiL_n$ by removing electron density from the metal centre.

51 Iwasaki, T.; Takagawa, H.; Singh, S. P.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2013**.
52 Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2387-2390.



Scheme 26 Nickel-catalyzed Negishi type alkyl-alkyl cross-coupling reactions

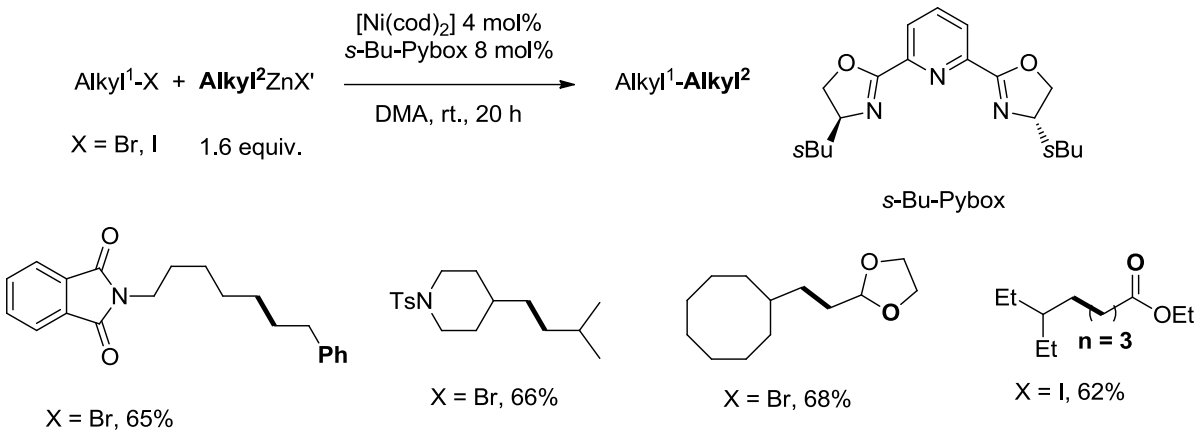
Later, Knochel and coworkers modified the reaction condition by adding Bu_4NI, which allowed broadening the substrate scope.[53] The new system was applied for the coupling of primary and secondary organozinc reagents with primary alkyl halides (Scheme 27). The effect of Bu_4NI is not clear, but it is crucial to obtain high yields of the cross-coupling reactions.



Scheme 27 Nickel-catalyzed Negishi type alkyl-alkyl cross-coupling reactions

The Fu's group developed an efficient Negishi type alkyl-alkyl cross-coupling reaction catalyzed by nickel.[54] A variety of secondary (and primary) alkyl bromides and iodides reacted with alkylzinc halides and provided the coupling product in moderate to good yield with high functional group tolerance under mild conditions (Scheme 28).

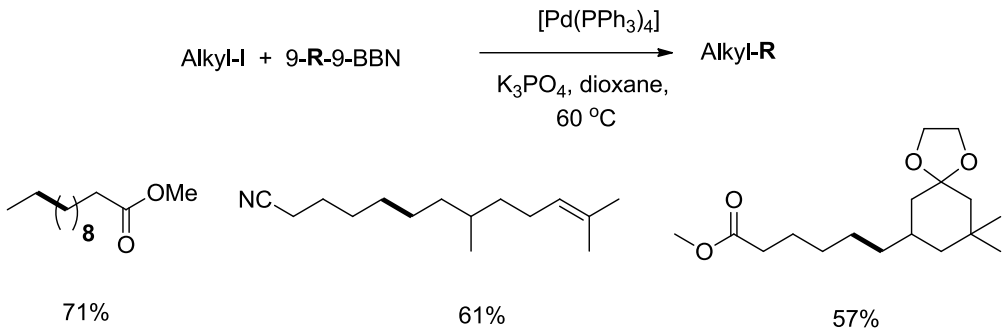
53 Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002,** *67*, 79-85.
54 Zhou, J. R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 17426-17427.



Scheme 28 Nickel-catalyzed Negishi type alkyl-alkyl cross-coupling reactions

III-1-1-3 Suzuki type alkyl-alkyl reactions.

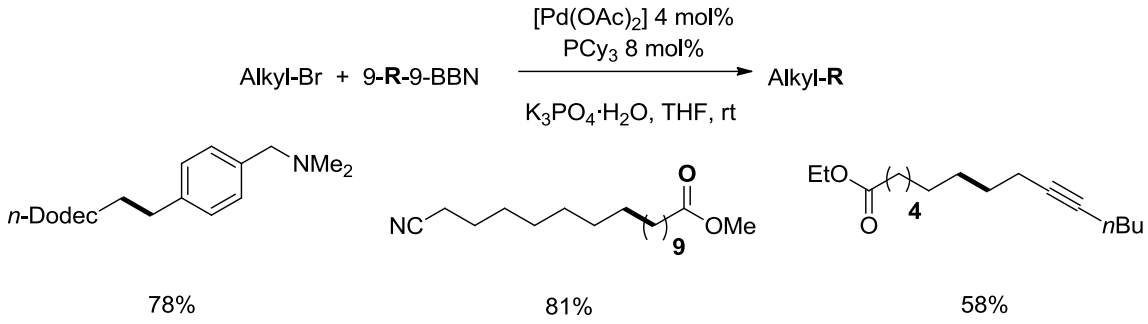
Suzuki and coworkers reported the first palladium-catalyzed Suzuki-type alkyl-alkyl cross-coupling reactions in 1992.[55] In the presence of $[Pd(PPh_3)_4]$ and K_3PO_4, alkyl iodides react with 9-alkyl-9-BBN smoothly and provide moderate to good cross-coupling yields (Scheme 29). However, the alkyl bromides or secondary alkyl halides did not react. The reaction was also identified as a radical process.



Scheme 29 The first Pd-catalyzed Suzuki-type alkyl-alkyl cross-coupling reactions

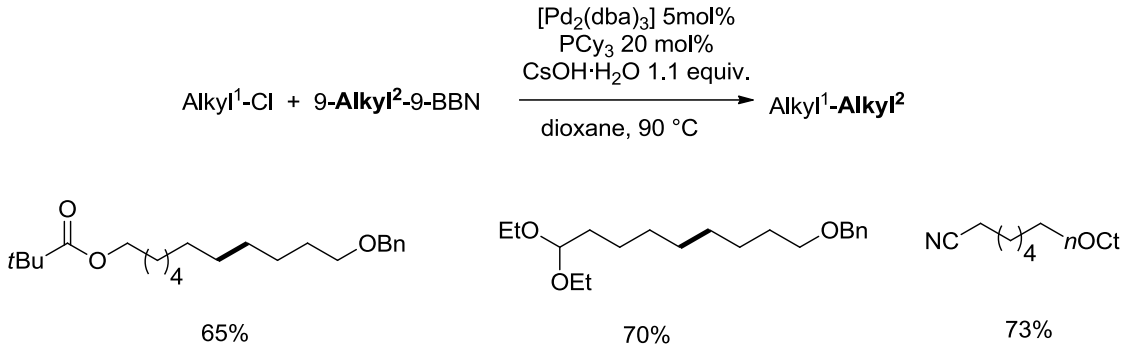
Fu and coworkers established the first efficient Suzuki reactions of unactivited alkyl bromides (Scheme 30).[56] This work represents a significant expansion in the scope of the Suzuki reaction. Using $Pd(OAc)_2/PCy_3$ (1:2) in the presence of $K_3PO_4 \cdot 3H_2O$, the non-activated alkyl halides (I or Br) coupled with 9-alkyl-9-BBN at room temperature and provided good to excellent yields .

55 Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691-694.
56 Netherton, M. R.; Dai, C.; Neuschuetz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099-10100.



Scheme 30 Pd-catalyzed Suzuki-type alkyl-alkyl cross-coupling reactions with alkyl bromides

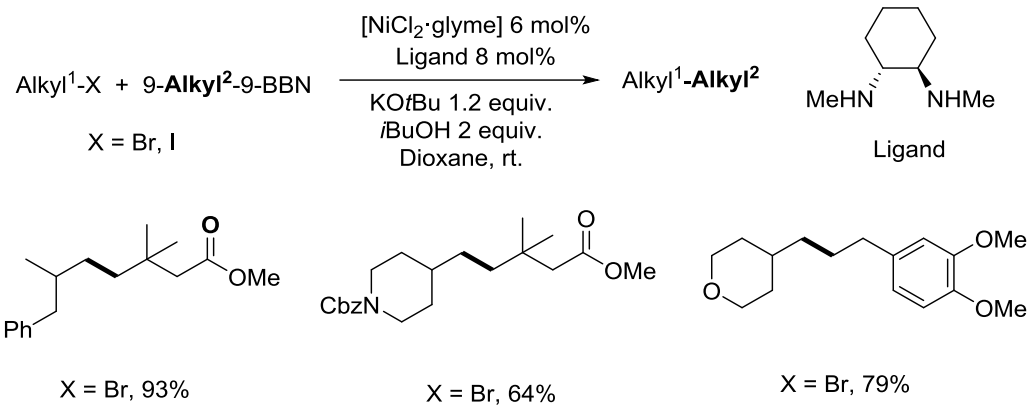
Later, they modified the reaction conditions, and employed a combined $[Pd(dba)_3]$ and PCy_3 in the presence of $CsOH•3H_2O$, which can overcome the difficulty of coupling the more challenging functional groups substituted unactivited alkyl chlorides (Scheme 31).[57]



Scheme 31 Pd-catalyzed Suzuki-type alkyl-alkyl cross-coupling reactions with alkyl chlorides.

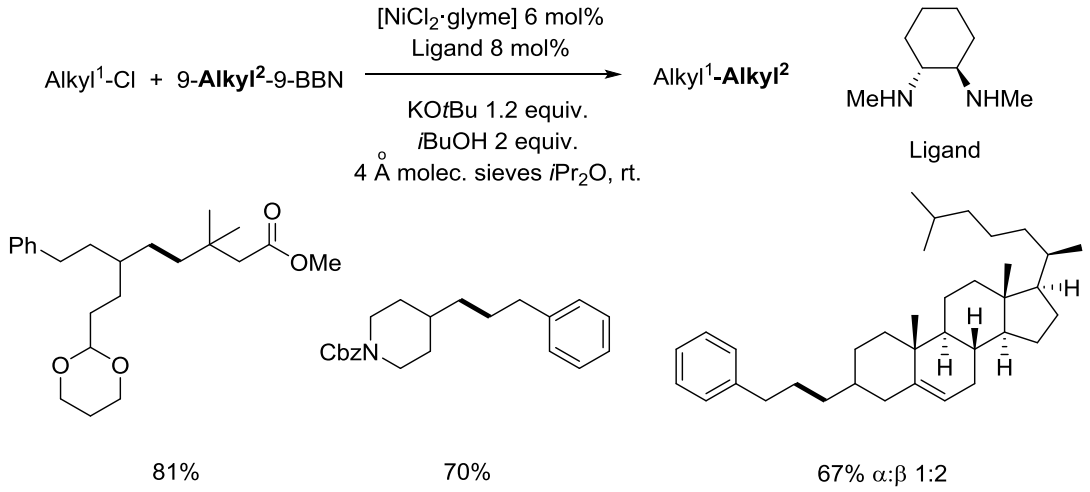
In 2007, Fu *et al.* described the first method for achieving Suzuki type alkyl-alkyl coupling of unactivated secondary alkyl halides with alkylboranes catalyzed by nickel (Scheme 32).[58] The simple, readily available diamine ligand is the key point to obtain high cross-coupling yields. KO*t*Bu and *i*BuOH are also necessary, they are proposed to activate the alkylborane for transmetalation with nickel.

57 Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1945-1947.
58 Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602-9603.



Scheme 32 Ni-catalyzed Suzuki-type alkyl-alkyl cross-coupling reactions of alkyl bromides and iodides

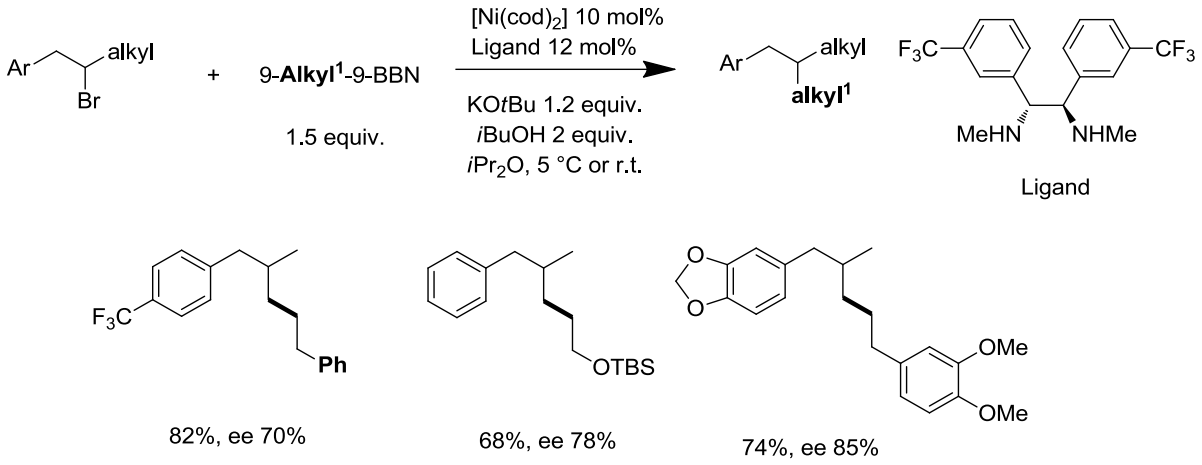
In 2010, Fu and coworkers extended the above method and developed the first Ni-catalyzed alkyl–alkyl Suzuki reaction of unactivated secondary alkyl chlorides under a similar system (Scheme 33).[59] This protocol was very efficient in the coupling of functionalized alkyl electrophiles, including alkyl chlorides, bromides and iodides under mild conditions.



Scheme 33 Ni-catalyzed Suzuki-type cross-coupling reactions of secondary alkyl chlorides

By using $Ni(cod)_2$/chiral diamine as catalyst, the system was also applied to asymmetric cross-couplings of non-activated alkyl electrophiles. This was the first example of enantioselective Suzuki coupling of alkyl electrophiles (Scheme 34).[60]

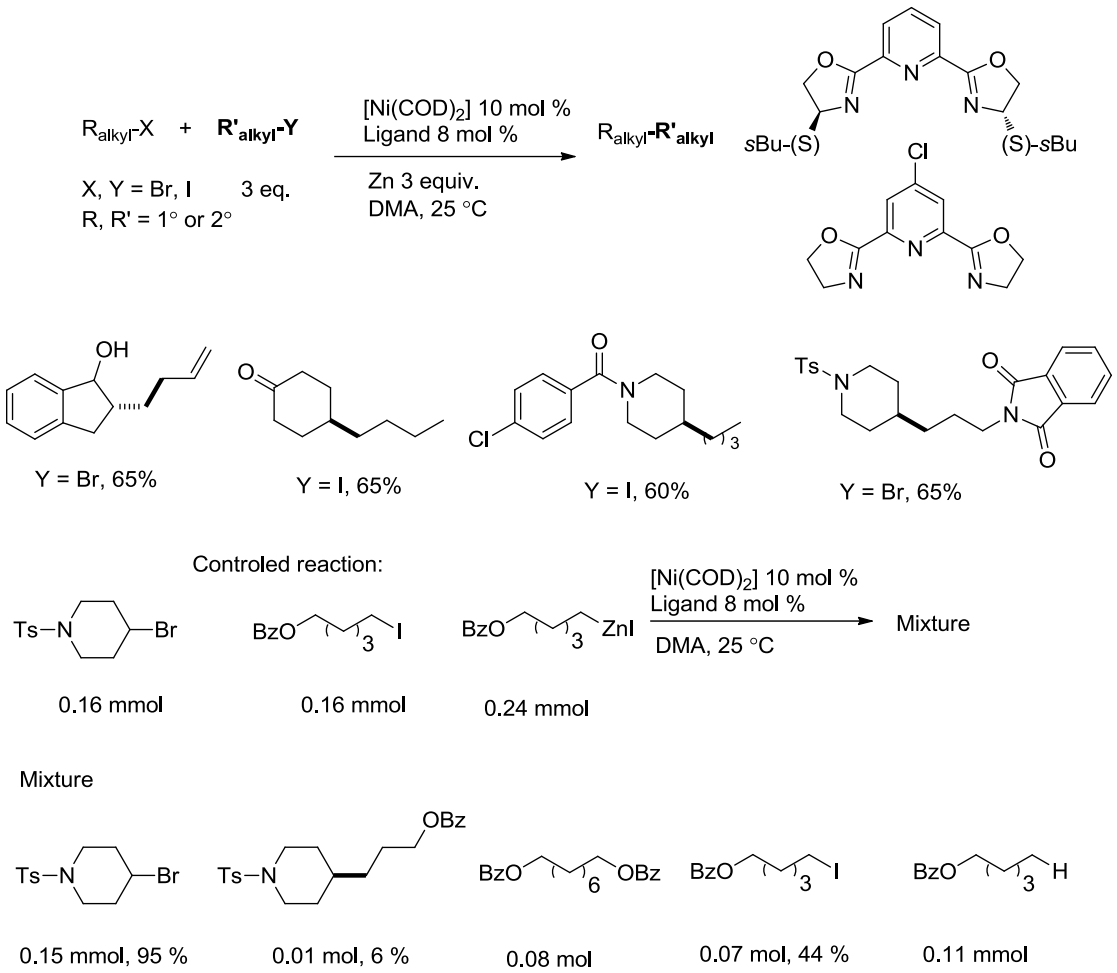
59 Lu, Z.; Fu, G. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6676-6678.
60 Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482-10483.



Scheme 34 Nickel-catalyzed Suzuki-type asymmetric cross-couplings of unactivated alkyl electrophiles

III-1-2 Transition-metal catalyzed reductive alkyl-alkyl cross-coupling reaction

Gong and coworkers established the first effective cross-coupling of two alkyl halides via a nickel-catalyzed reductive process (Scheme 35).[25a] The pybox ligands were found necessary to suppress the homocoupling reactions. This protocol avoids the use of organometallic reagents, and exhibits a high group tolerance, including nitrogen heterocycles, keto or even alcohol groups. Stoichiometric reactions showed that alkyl bromides are not transformed into the corresponding alkylzinc bromide *in situ* (contrary to a Negishi process), while alkyl iodides might be converted into the organozinc compounds. However, a mixture of 4-bromo-1-tosylpiperidine, 5-iodopentyl benzoate and its organozinc reagent in the presence of $Ni(COD)_2$/ligand (Scheme 35) delivered only trace of cross-coupling product when an alkylzinc reagent is used instead of Zn dust, which suggest that a non-Negishi process appears to be kinetically favored. The main problem of this method is the necessary of excess of one coupling partner (3 equivalents of the relatively more reactive alkyl halides are required), which will limit its application in large scale production.



Scheme 35 Nickel-catalyzed Reductive Cross-coupling of Unactivated Alkyl Halides using a Pybox Ligand

As introduced above, these reactions are efficient methods but all of them require the handling of Grignard reagents, which have to be prepared. Thus, we try to develop a cobalt-catalyzed reductive alkyl-alkyl cross-coupling reaction, which do not employ an organometallic reagent.

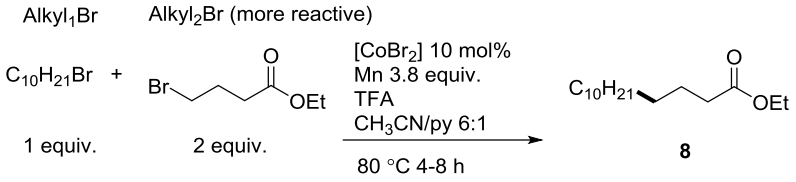
III-2 Results and discussions

III-2-1 Conditions optimization

To begin with, we chose the coupling of 1-bromodecane (Alkyl[1]) and ethyl 4-bromobutanoate (Alkyl[2]) as the model reactions (Table 8). First we used the conditions similar to the ones of the allyl-alkyl coupling reaction. Thus, the more reactive alkyl[2] halide was employed in excess, with a combined $CoBr_2$/Mn system in acetonitrile/pyridine mixture to give a good yield (Table 8, entry 1). Using 3 equivalents of the more reactive alkyl bromides (Alkyl[2]) provided a better result (Table 8, entry 2). However, the excess loading of one coupling partner remains a drawback. Some other

efforts were made to optimize the reaction. Pyridine is essential to obtain the cross-coupling in high yield, without that the reaction gave the reduction product rapidly (Table 8, entry 3). Preformed cobalt (II) complexes [$CoBr_2(Py)_2$] or [$CoBr_2$(dppp)] only provided little or no yield of coupling product (Table 8, entries 4 and 5). Ligand such as 3,3'-dimethyl-2,2'-bipyridine, dppp, dppe, tricyclohexylphosphine and triisopropylphosphine was also screened, however, none of them has positive effect on the reaction (Table 8, entry 6, Figure 2). The starting materials almost remained intact except trace reduction products were obtained from alkyl^2. Refluxing the reaction at 100 °C provided a yield similar to entry 2. However, the reaction in this condition is difficult to reproduce (Table 8, entry 7). According to the group's previous reports, DMF may be used as an efficient solvent.[22a, 24a] However in this reaction, employing DMF independently, or with a triphenylphosphine or bipyridine ligand only provided trace of coupling product (Table 8, entries 8 to 10). Trace of product was obtained when Zn instead of Mn was used (Table 8, entry 11). Some additives, such as allyl chloride or 1,2-dichloroethane were used as "sacrificial species" which was proposed to be consumed first and then decrease the side reactions of Alkyl^2 (Table 8, entries 12 and 13). However, both of them only led to the rapid consuming of Alkyl^2 and did not increase the cross-coupling product.

Table 8 Reaction conditions optimization



Entry	Deviation from Standard Conditions	GC Yield %
1	None	61
2	**Alkyl^1:Alkyl^2 = 1:3**	**72(63)[a]**
3	Without pyridine	47
4	[$CoBr_2(Py)_2$] 10 mol%	14
5	[$CoBr_2$(dppp)] 10 mol%	No product
6	Ligand (Figure 1)	Trace or none
7	100 °C	68
8	DMF as solvent (with pyridine)	Trace
9	DMF+PPh_3	Trace
10	DMF+ Bpy	Trace
11	Zn instead of Mn	Trace

12	AllylCl 40 mol%	Trace
13	$ClCH_2CH_2Cl$ 1 equiv.	Trace

[a]Isolated yield in parentheses.

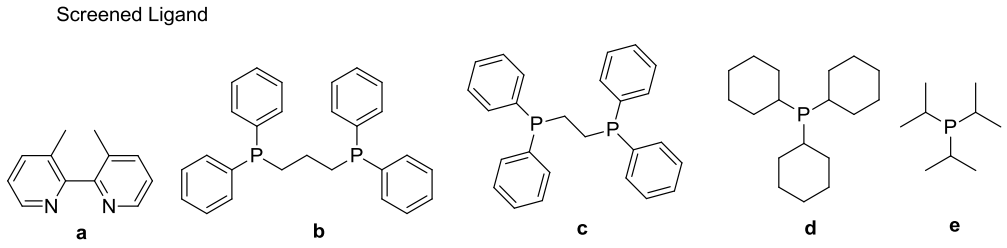
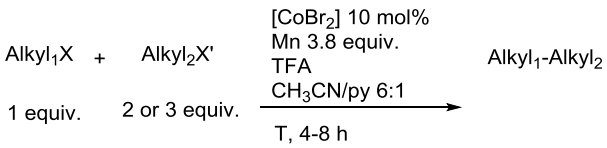


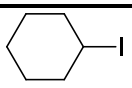
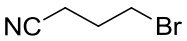
Figure 2 Ligands screened in the cobalt-catalyzed alkyl-alkyl cross-coupling reactions

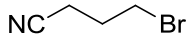
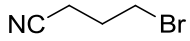
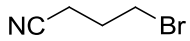
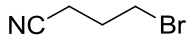
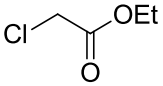
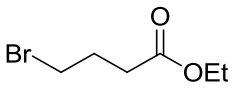
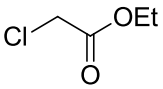
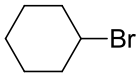
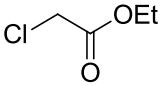
III-2-2 The scope of alkyl halides in alkyl-alkyl cross-coupling reactions.

After optimization of these parameters, we used the conditions of table 4, entry 2 as standard conditions to explore the scope of alkyl halides (Table 9). Cyclohexyl iodide was coupled in these conditions (Table 9, entry 1). However, with stronger electron-withdrawing groups, we had difficulties. 4-bromobutanenitrile did not couple well with 1 bromodecane, conversion stopped at 70 % even in the presence of 3 equivalents 4-bromo cyanobutane (Table 9, entries 2 to 5). The main problem is that the reactive alkyl halide ($alkyl^2$) rapidly gave reduction product and dimer product. Dropwise addition of the more reactive alkyl halide over 30 min did not improve the conversion (Table 9, entry 4). Adding 1 equivalent chloroacetate, this is more reactive and may act as "sacrificial species" in the medium, totally inhibits the reaction (Table 9, entry 5). The starting material remained intact. Decreasing the reaction temperature only led to poorer conversion (Table 9, entry 6). The α-substituted alkyl chloride failed to react with unreactive alkyl halides under this condition (Table 9, entries 7 to 9). The starting materials remained intact.

Table 9 The exploration of alkyl halides



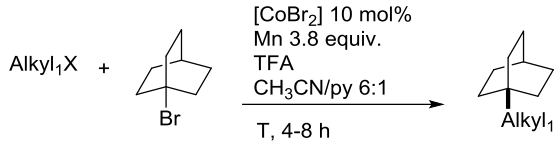
Entry	$Alkyl^1$	$Alkyl^2$	Temperature	Yield[a]
1	$C_{10}H_{21}Br$ 1 equiv.	 2 equiv.	40 °C	55 %[b]
2	$C_{10}H_{21}Br$		80 °C	< 20 %[c]

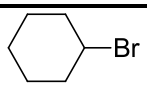
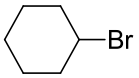
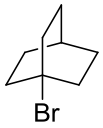
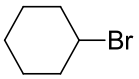
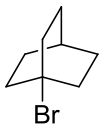
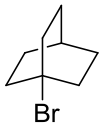
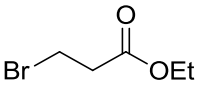
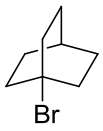
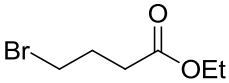
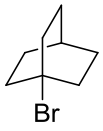
	1 equiv.	2 equiv.		
3	$C_{10}H_{21}Br$		80 °C	40 %[d]
	1 equiv.	3 equiv.		
4	$C_{10}H_{21}Br$		80 °C	< 20 %[c]
	1 equiv.	3 equiv.		
		dropwise in 30 min		
5	$C_{10}H_{21}Br$		80 °C	0
	1 equiv.	3 equiv.		
		With 1 equiv.		
		chloroacetate		
6	$C_{10}H_{21}Br$		60 °C	< 20 %[c]
	1 equiv.	3 equiv.		
7	$C_{10}H_{21}Br$		80 °C	0
	1 equiv.	3 equiv.		
8			80 °C	0
		3 equiv.		
9			80 °C	0
		3 equiv.		

[a] GC yields. [b] 3 equiv. alkyl[2] gave a similar GC yield, while higher temperature (65 or higher) would decrease the yield. [c] In these cases, the conversions of alkyl[1] were no more than 60 % according dodecane as the internal standard. [d] The conversion of alkyl[1]Br is 70%.

Several reactions were also attempted for the reductive alkyl-alkyl cross-coupling of tertiary alkyl bromide under the conditions established in table 4, entry 2. However, none of them worked (Table 10). The reaction between cyclohexyl bromide and 1-bromobicyclo[2.2.2]octane only yielded the dimer of cyclohexane bromide under 50 or 80 °C (Table 10, entries 1 and 2). Adding 40 mol% of allylTMS, which may form the allyl-cobalt complex, led to a mixture of bicyclohexane and bi-bicyclo[2.2.2]octane (Table 10, entry 3). When it was coupled with less reactive primary alkyl bromides under 50 °C, only the dimer of alkyl[1] bromide was detected by GC (Table 10, entry 4). The same result was obtained when it reacts with more reactive primary alkyl halide (Table 10, entry 5). However, under 80 °C, trace of bi-bicyclo[2.2.2]octane was detected by GC (Table 10, entry 6). Unfortunately, there was no cross-coupling product formed under the tested conditions.

Table 10 Attempts for the cross-coupling of tertiary alkyl halides



Entry	Alkyl[1]	Alkyl[2]	Temperature	Result
1			50 °C	Only dimer of alkyl[1]
2			80 °C	Only dimer of alkyl[1]
3			80 °C	Dimer of alkyl[1] and alkyl[2a]
4	$C_{10}H_{21}Br$		50 °C	Only dimer of alkyl[1]
5			50 °C	Only dimer of alkyl[1]
6			80 °C	Dimer of alkyl[1] and alkyl[2]

[a] 40 mol% AllylTMS was added.

However, an α-substituted tertiary alkyl chloride was found to couple in the modified conditions (Table 11). This promoted us to investigate the coupling of 1-chloro-1,2,2-trifluorocyclobutane,[61] which rarely used in transition metal coupling reactions, while it is present in many natural compounds, pharmaceutical and biologically active

61 Park, J. D.; Holler, H. V.; Lacher, J. R. *J. Org. Chem*. **1960,** *25*, 990-993.

compounds (Figure 3),[62] such as, fungicides (Figure 3, a)[63], antiparasitic agents (Figure 3, b)[64] and epidepride (Figure 3, c and d)[65].

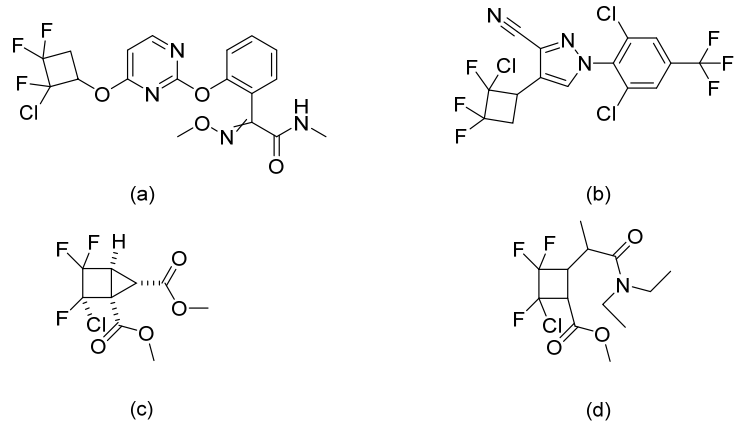
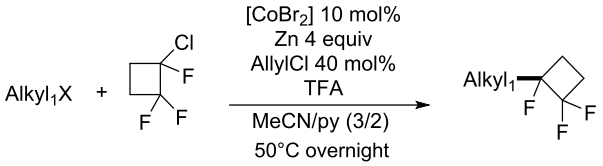


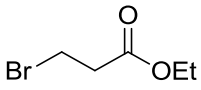
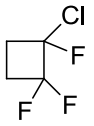
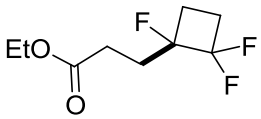
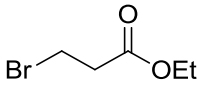
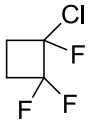
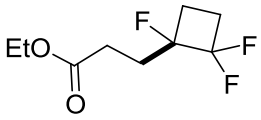
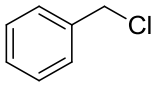
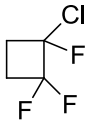
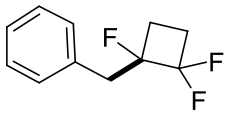
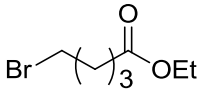
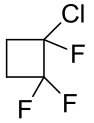
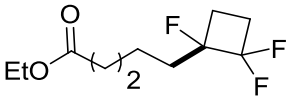
Figure 3 1-chloro-1,2,2-trifluorocyclobutane derivatives

With $CoBr_2$ as catalyst and Zn as reductor in CH_3CN/pyridine mixture, the coupling was realized with 30 % isolated yield. Allyl chloride was employed to reduce the consummation of alkyl[1] bromide (Table 11, entry 1). Replacing Zn by Mn gave no result (Table 11, entry 2). This may be due to the difference of their standard reduction potentials; the reduction potentials of Mn (-1.185), being lower than Zn (-0.7618). Changing the nature of alkyl[1] halides were disappointing (Table 11, entries 3 and 4). In these cases, alkyl[2] were consumed to reduction products rapidly.

62 Kissa, E. *Fluorinated Surfactants and Repellents*. 2nd ed, **2001**, **New York**: Marcel Dekker.
63 **Patent:** US6348471 B1, **2002**; **Patent Family:** WO1999/5122 A1; EP1000037 A1; US6348471 B1.
64 **Patent:** US6077859 A1, **2000**; **Patent Family**: EP959071 A1; US6077859 A1; JP2004/262944 A; EP959071 B1.
65 (a) Plancquaert, M.-A.; François, P.; Merényi, R.; Viehe, H. G. *Tetrahedron Lett.* **1991**, *32*, 7265-7268. (b) Plancquaert, M.-A.; Janousek, Z.; Viehe, H. G. *J. Prak. Chem. Chem. ZTG*. **1994**, *336*, 19-28.

Table 11 The coupling reaction of 1-chloro-1,2,2-trifluorocyclobutane



Entry	Alkyl[1]	Alkyl[2]	Product	Yield
1	 2 equiv.	 1 equiv.	 **9**	isolated yield : 30 %
2	 2 equiv.	 1 equiv.		Trace[a]
3	 2 equiv.	 1 equiv.		Trace
4	 2 equiv.	 1 equiv.		0

[a] Mn instead of Zn as reductant.

III-2-3 Conclusions and future work

In conclusion, some progress has been made in cobalt-catalyzed reductive alkyl-alkyl cross-coupling reactions. Primary optimized conditions were built (Table 4, entry 2). However, they did not allow the coupling of more reactive alkyl halides. The coupling of tertiary alkyl halide was studied. It is supposed that an allylic-cobalt complex and higher temperature may promote the reductive coupling of tertiary alkyl halides. However, the coupling of α-substituted alkyl halide, 1-chloro-1,2,2-trifluorocyclobutane with relative reactive alkyl halide only provided poor yield. This has to be further studied.

IV. Cobalt-catalyzed Reductive Homocoupling of Alkyl Halides

IV-1 Introduction

Dimerization of organic units has to be developped even if it seems rather intuitive, as many natural products are dimers or pseudodimers. Especially along with the progress of biological science, the demand for efficient organic synthesis of dimerization of a variety of natural products [66] and pharmaceutics [67] is even increasing (Figure 4). Efficient methods for the dimerization of olefins (olefin metathesis [68]), alkyne (oxidative terminal alkyne pathway[69]), carbonyls (pinacol coupling[70] and McMurry coupling[71]), and aryl halides (oxidative[72]/reductive[22c] pathway) have been proposed during the last decades and a variety of efficient methodologies has been built.

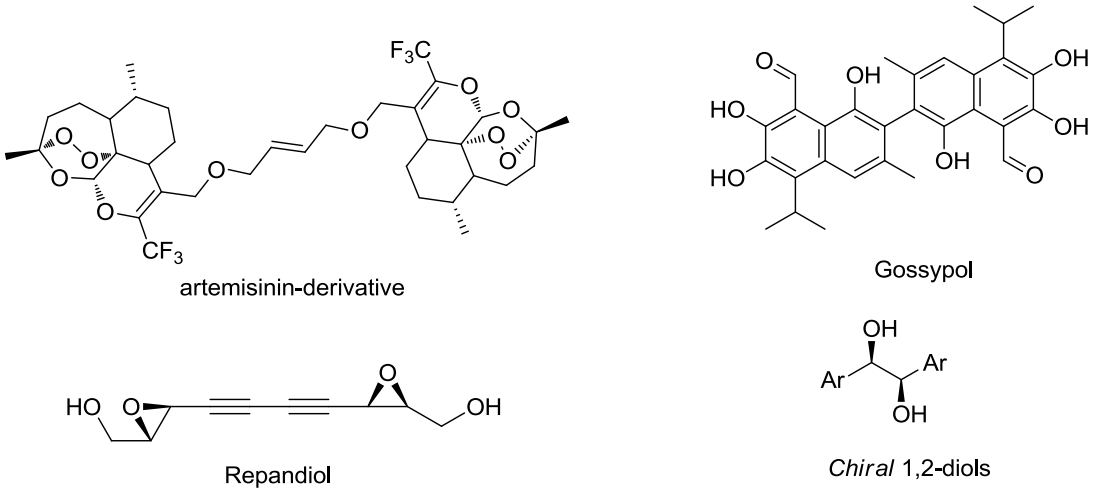
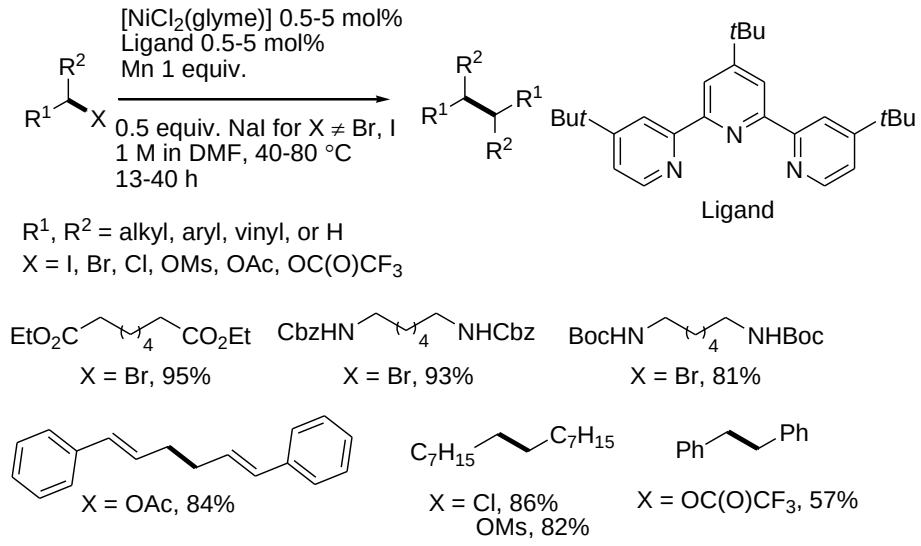


Figure 4 Representive examples of organic dimer compounds

However, a general and efficient method for the direct dimerization of alkyl halides is less investigated. Weix and coworkers established a novel catalytic system for the dimerization of alkyl halides/pseudohalides and allylic acetates. Ni/pybox ligand/Mn

66 (a) Grellepois, F.; Crousse, B.; Bonnet-Delpon, D. ; Bégué, J.-P. *Org. Lett.* **2005**, *7*, 5219–5222. (b) de la Torre, M. C.; Deometrio, A. M.; Álvaro, E.; García, I. ; Sierra, M. A. *Org. Lett.* **2006**, *8*, 593–596.
67 (a) Li, L.; Xu, B. *Curr. Pharm. Des.* **2005**, *11*, 3111–3124. (b) Ahrendt, K. A.; Olsen, J. A.; Wakao, M.; Trias. J.; Ellman, J. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1683–1686.
68 Michalak, M.; Gulajski, L.; Grela, K.; *Sci. Synth.* **2010**, *47a*, 327–437.
69 Recent examples (a) Jia, X.; Yin, K.; Li, C.; Li, J.; Bian, H. *Green Chem.* **2011**, *13*, 2175-2178; (b) Wang, D.; Li, J.; Li, N.; Gao, T.; Hou, S.; Chen, B. *Green Chem.* **2010**, *12*, 45-48.
70 (a) Chatterjee, A.; Joshi, N. N. *Tetrahedron* **2006**, *62*, 12137-12158. (b) Hirao, T.; *Top. Curr. Chem.*, **2007**, *279*, 53–75.
71 Takeda, T.; Tsubouchi, A. *Sci. Synth.* **2010**, *47a*, 247–325
72 Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788-13789.

was found to form the two Csp^3-Csp^3 bonds efficiently (Scheme 36).[25b] A variety of alkyl fragments was used, including primary/secondary alkyl halides, benzyl chloride and linear/cyclic allylic acetates. It generally provides high yields, nevertheless a catalytic amount of sodium iodide may be necessary to give good yields. The role of the added sodium iodide is likely: (1) Enhancement of the reductive coupling, possibly by facilitating reduction of the nickel catalyst[73] or the formation of a nickelate species.[74] (2) The coupling perhaps occurs after the alkyl substrates (alkyl chlorides, mesylates or trifluoroacetates) are converted into their corresponding iodides *in situ* by "leaving group /I" exchange. The reaction is easy to conduct and unaffected by air or moisture. The functional-group compatibility of this dimerization reaction is excellent. Ketone and unprotected hydroxyl carbamate, which are rarely compatible with traditional organometallic reagents transformation, are well-tolerated. When scaling up the reaction, good yields were obtained until 96%, more than 4 g of the dimerization of bromooctane, $C_{16}H_{34}$. Interested by these results, we try to develop an efficient method using cobalt, which is less toxic than nickel.



Scheme 36 Nickel-Catalyzed Reductive Dimerization of Alkyl Halides/Pseudohalides and Allylic Acetates

73 Colon, I.; Kelsey, D. R. *J. Org. Chem.* **1986**, *51*, 2627–2637.

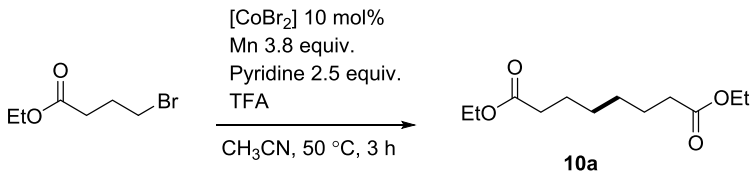
74 Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc*. **2002**, *124*, 4222–4223.

IV-2 Results and discussions

IV-2-1 Reaction conditions optimization

To begin with, we chose the dimerization of ethyl 4-bromobutanoate as the model reaction (Table 12). We identified that a combination of $CoBr_2$/Mn/Pyridine in CH_3CN, which a similar manner to the previous reort for the allyl-alkyl coupling reaction, gave the desired coupling product in 84 % (Table 12, entry 1). Pyridine is essential for this reaction, without it the reduction product formed rapidly (Table 12, entry 2). Increasing pyridine reduced the catalytic ability and decreased the yield (Table 12, entry 3). Decreasing the catalyst loading led to a lower yield even after longer time (18 h) (Table 12, entry 4). Likely, dropping the Mn in half also led to a lower yield (Table 12, entry 5). Increasing the catalyst loading gave no positive effect (Table 12, entry 6).[75] Low yield was obtained at room temperature, while it is satisfactory at 50 °C (Table 12, entry 7). Allyl chloride is an efficient additive to reduce the reduction side product in cobalt-catalyzed reductive aryl-aryl homocoupling reactions.[25b] However, in the alkyl-alkyl homocoupling reactions, it did not have any positive effect, but slowed down the reaction rate and formed even more reduction product (Table 12, entry 8). Besides, the combination of more $CoBr_2$ with allylCl has no positive effect (Table 12, entry 9).

Table 12 Reaction conditions optimization



Entry	Deviation from Standard Conditions	GC Yield %
1	None	(84)[a]
2	No pyridine	< 10
3	Pyridine 5 equiv.	42
4	[$CoBr_2$] 5 mol%	53
5	Mn 1.9 equiv.	56
6	[$CoBr_2$] 20 mol%	50
7	r.t.	20[b]
8	Adding 40 mol% AllylCl before TFA	30
9	[$CoBr_2$] 20 mol%, AllylCl 40 mol%	20[c]

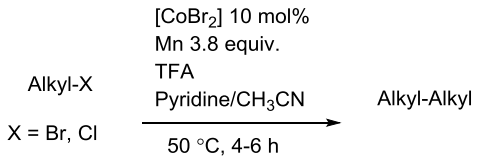
75 In this case, increasing the amount of pyridine at the same time may be necessary.

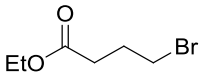
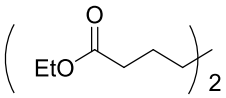
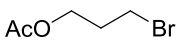
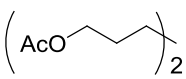
[a] Isolated yield. [b] Conversion is 40 % after 18 h. [c] Conversion is 70 % after 18 h.

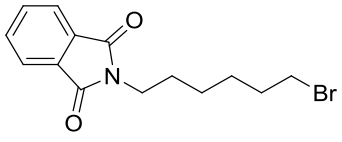
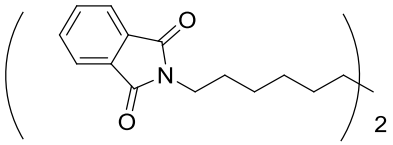
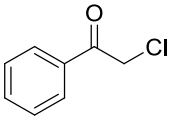
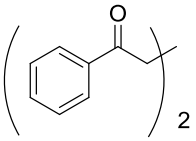
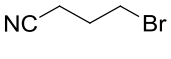
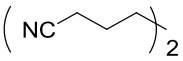
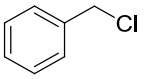
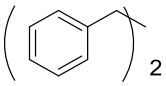
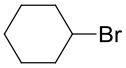
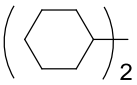
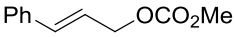
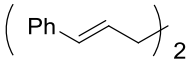
IV-2-2 The scope of alkyl halides in alkyl-alkyl homo-coupling reactions.

With this optimized conditions in hand, we next investigated more functionalized alkyl halides (Table 13). Ester and acetate substituted alkyl bromides are well coupled in high yields (Table 13, entries 1 and 2). Interestingly, the substrates, isoindo-1,3-dione and ketone substituted alkyl bromides in entry 3 and 4 did not work in the cobalt-catalyzed allyl-alkyl cross-coupling reactions, however, they provide moderate to good yields in this homocoupling reaction. The α-keto group was well tolerated, but α-amide alkyl chloride could not be used with this method and only provide reduction product. Primary alkyl bromide with nitrile group was coupled efficiently (Table 13, entry 5). More reactive alkyl halide such as benzyl chloride could also be used in this reaction (Table 13, entry 6). However, the coupling of more reactive 4-(chloromethyl)benzonitrile only gave reduction product. No better result was obtained at room temperature. Cyclohexyl bromide proceed smoothly under this condition (Table 13, entry 7), but *N*-Boc group substituted cyclohexyl bromide (*t*Butyl 4-bromopiperidine-1-carboxylate) was not homocoupled. Only reduction product was isolated. Primary long chain alkyl bromide proceeds smoothly (Table 13, entry 8). Besides, the cinnamyl carbonate was also dimerized in this protocol (Table 13, entry 9). However, hindered substituted allylic acetate, *e.g.* (*E*)-hex-2-en-1-yl acetate was not dimierized in the recent method. The starting material remained intact.

Table 13 The scope of alkyl halides in alkyl-alkyl cross-coupling reactions.



Entry	Alkyl-X	Alkyl	Yield/%[a]
1		 **10a**	84
2		 **10b**	83

3			79
		10c	
4			50
		10d	
5			65
		10e	
6			82
		10f	
7			68
		10g	
8	$C_{10}H_{21}Br$	$C_{20}H_{22}$	87
		10h	
9			72
		10i	

[a] Isolated yields.

Although during the past decades, transition-metal catalyzed coupling reaction of alkyl electrophiles have been extensively studied, except several sporadic reports concerning the coupling of tertiary alkyl substrates, almost all of them have focused on the couplings of primary and secondary alkyl partners.[76, 10c] The difficulties mainly concern the oxidative addition of steric carbon centre and the rearrangement of tertiary carbon intermediate.

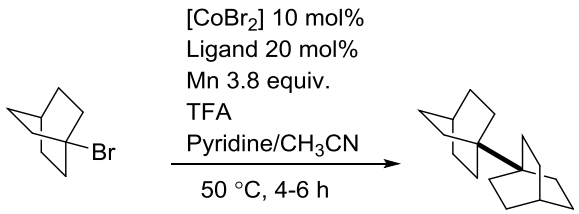
However, according to our experience on the allyl-alkyl coupling reactions, we found that the tertiary alkyl halide 1-bromobicyclo[2.2.2]octane, coupled with allyl acetate or but-3-en-2-yl acetate. As mentioned above, cobalt has some unique catalytic ability in

76 (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532. (c) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.*, **2005**, *44*, 674–688.

the coupling of tertiary alkyl electrophiles, it will be of great interest to investigate its catalytic ability in coupling tertiary alkyl halide with some other substrates.

Some initial ideas were attempted (Table 14). Under the standard conditions, only reduction product was formed (Table 14, entry 1). Trace of product was formed when conducting the reaction under 80 °C (Table 14, entry 2). Moreover, in the presence of allylic substrates (Table 14, entries 3-5), traces of the dimer of bicyclo[2.2.2]octane were observed. AllylOAc and allylCl may act as the coupling partner and the reaction preferred the allyl-alkyl coupling pathway. Addition of allylTMS (Allyltrimethylsilane**)** also gave trace of product. This implied that the formation of π-allyl cobalt complexes may promote the coupling of tertiary alkyl halide. Another allylic substrate, (*E*)-hex-2-en-1-yl acetate was also chosen to act as ligand, since it does not couple with alkyl halides. However, in this case only reduction product was found (Table 14, entry 6). Another π-ligand, 1,5-Cyclooctadiene did not show positive effect and again only reduction product was formed (Table 14, entry 7). Finally, $Co(acac)_2$ failed as a catalyst. The starting material remained intact (Table 14, entry 8).

Table 14 Attempts for the homo-coupling for tertiary alkyl halides



Entry	Ligand	Result
1	No ligand	0
2	80 °C	GC < 5%
3	Allyl acetate	GC < 10 %
4	Allyl chloride	GC < 10 %
5	Allyltrimethylsilane	GC < 10 %
6	(*E*)-hex-2-en-1-yl acetate	0
7	1,5-Cyclooctadiene	0
8	$[Co(acac)_2]$	0

IV-2-3 Conclusions and future work

In conclusion, an efficient cobalt-catalyzed reductive homocoupling of alkyl halides have been developed. Functionalized alkyl bromides and reactive alkyl chlorides were coupled in high yields under very mild conditions. Functional groups such as ester, acetate, isoindo-1,3-dione, ketone, and nitrile were well tolerated. Primary and secondary alkyl halides as well as benzyl chloride are all coupled efficiently. Further study is desired to focus on the dimerization of tertiary alkyl substrates, which is few reported.

Chapter 2 Electrophilic C-N and C-S Bonds Formation Reaction with Arylzinc Species

I. Cobalt-catalyzed Electrophilic Amination of Arylzinc species with N-chloroamines

I-1 Introduction

Aromatic C-N bond-forming reactions are important for the synthesis of biologically-active substructures and medicinal-chemistry targets (Figure 4).[77] In modern organic chemistry, efficient metal catalyzed methodologies for C-N bond formation have been developed. They are mainly divided into three types: nucleophilic amination of electrophilic aryl halides, which is also named as Buchwald-Hartwig coupling reactions (Scheme 37, equation 1); Chan-Lam type C-N coupling of nucleophilic aryl boronic acid and N-H substrates (Scheme 37, equation 2); electrophilic amination coupling of organometallic reagents with $R_1R_2N^+$ synthons (Scheme 37, equation 3). All of these three types of methods constitute significant progress in constructing new C-N bond. In this chapter, first, the development of metal-catalyzed aromatic C-N bond-formation methods will be reviewed, and then our results concerning a cobalt-catalyzed electrophilic amination of arylzinc species with *N*-chloroamines will be presented.

77 (a) Weissermel, K.; Arpe, H.J.; *Industrial Organic Chemistry*, Wiley-VCH, Weinheim, **1997**; (b) Lawrence, S.A. *Amines : Synthesis Properties and Applications*, University Press, Cambridge, **2004**; (c) R. Hili, A.K. Yudin, *Nat. Chem. Biol*. **2006**, *2*, 284-287. (d) Barker, T. J.; Jarvo, E. R. *Synthesis* **2011,** 3954-3964.

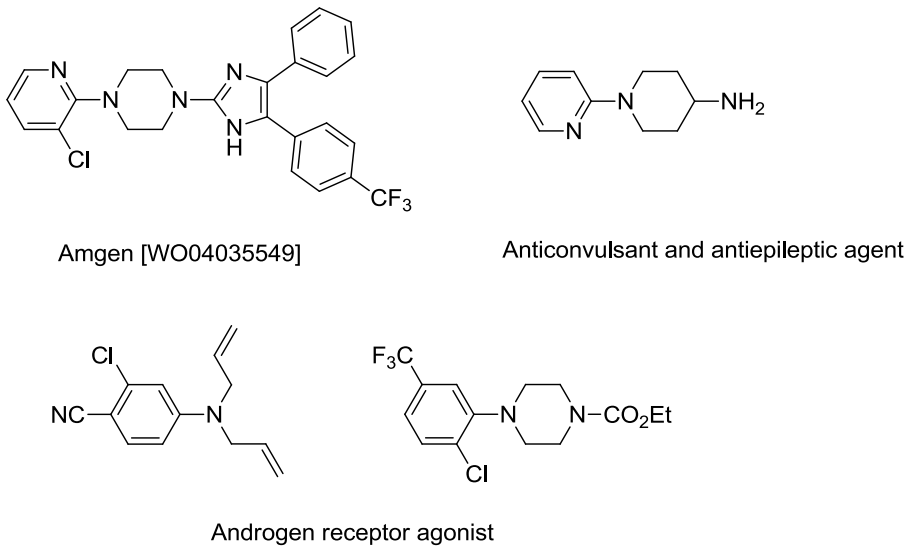
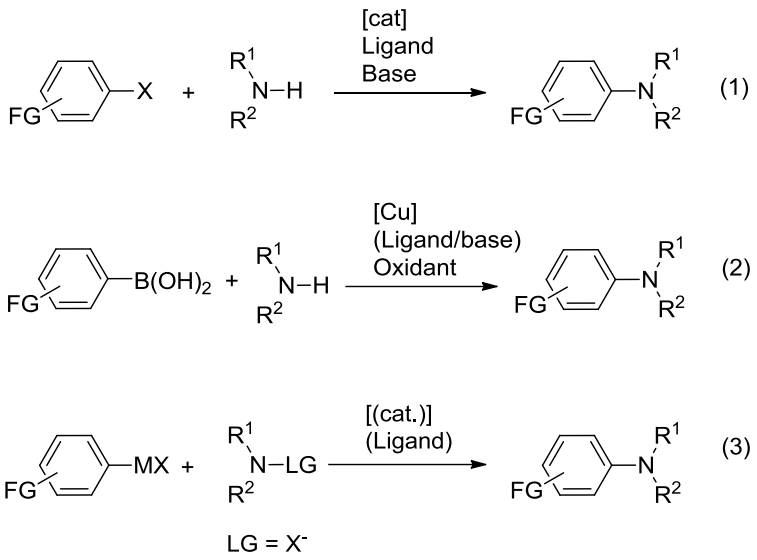


Figure 5 Examples of the arylamine structures in biologically-active substructures and medicinal targets



Scheme 37 Modern synthetic routes of arylamines

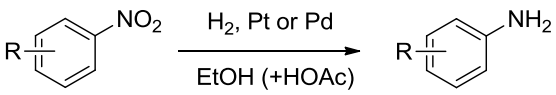
I-1-1 Nucleophilic amination

The functionalized aromatic amines are key units for the synthesis of pharmaceuticals, herbicides, polymers and materials. In the early years, this class of compound was prepared *via* classical methods (Scheme 38), such as nitration-reduction or reductive amination, copper-mediated Ullmann[78] and Goldberg[79] coupling reactions, addition to

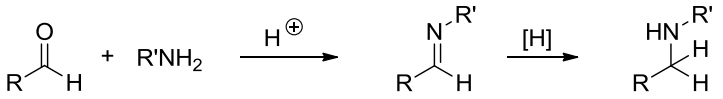
78 (a) Ullmann, F.; Sponagel, P., Ueber die Phenylirung von Phenolen. *Berichte der deutschen chemischen Gesellschaft* **1905,** *38*, 2211-2212. (b) Monnier, F.; Taillefer, F. *Angew. Chem., Int. Ed.* **2009,** *48*, 6954-6971.

79 Goldberg, I., Ueber Phenylirungen bei Gegenwart von Kupfer als Katalysator. *Berichte der deutschen chemischen Gesellschaft* **1906,** *39*, 1691-1692.

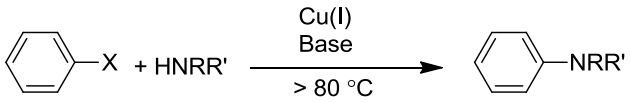
benzyne intermediates and direct nucleophilic substitution on particularly electron-poor aromatic halides. These types of reactions imply harsh conditions, limited scope and non-cost-efficiency.



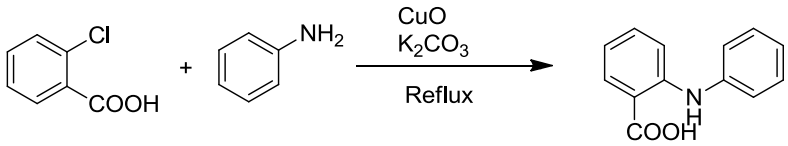
(a) Nitration- Reduction



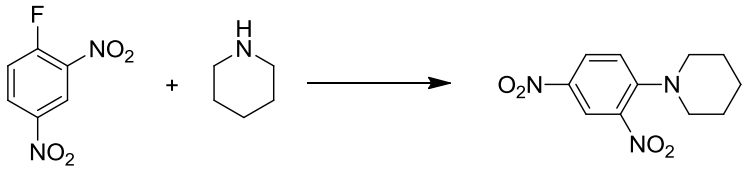
(b)Reductive amination



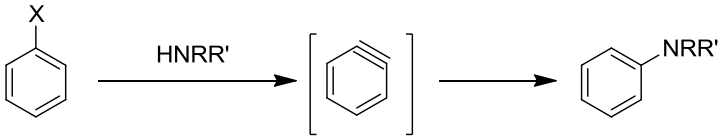
(c) Ullmann type C-N coupling reaction



(d) Goldberg type C-N coupling reaction



(e) Nucleophilic substitution on the aryl halide



(f) Addition to benzyne intermediates

Scheme 38 Classical method for C-N formation reaction

Palladium-catalyzed C-N coupling reactions supplant rapidly those early methods and are now widely applied in modern chemistry industries (Figure 6). This section will

summarize the development of nucleophilic synthesis of arylamine, mostly with palladium catalysts.[80]

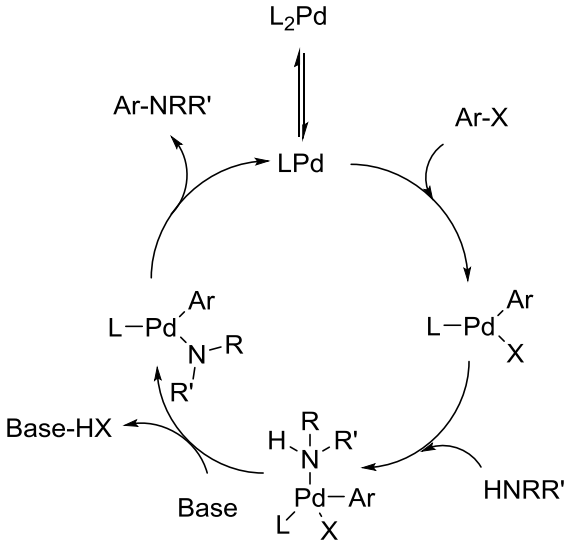
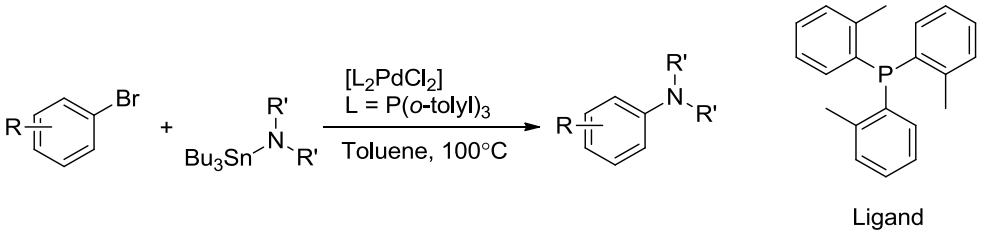


Figure 6 General mechanism of Pd-catalyzed C-N coupling reactions

The first palladium-catalyzed amination of aryl halides reactions was reported by Migita and coworkers (Equation 2).[81]



Equation 2 Pd-catalyzed amination of aryl halides with aminostannane reagents

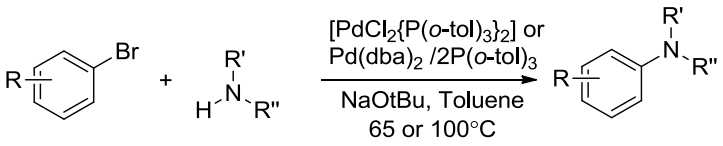
Inspired by this initial study, Buchwald's [82] and Hartwig's groups[83] independently reported the palladium-catalyzed coupling of aryl halides with secondary amines in the presence of base in 1995. Both these protocols avoid the utilization of toxic and relatively unstable aminostannane reagents. They involve palladium complexes featuring bulky phosphine ligands and constitute the first generation catalysts (Equation 3 and Equation 4).

80 (a) Hartwig, J. F. *Acc. Chem. Res.* **2008,** *41*, 1534-1544; (b) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011,** *2*, 27-50.

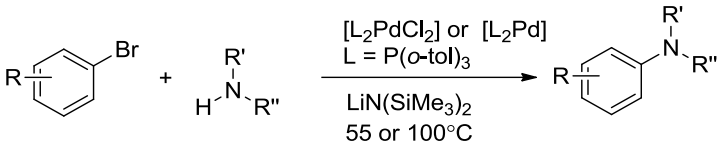
81 Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983,** *12*, 927-928.

82 Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1995,** *34*, 1348-1350.

83 Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995,** *36*, 3609-3612.

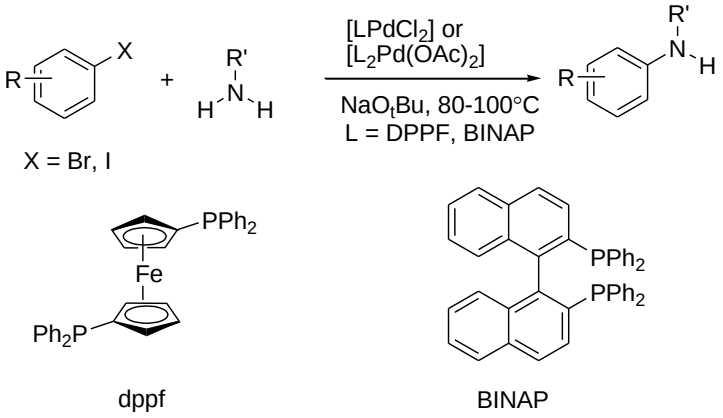


Equation 3 Pd-catalyzed coupling of aryl halides with secondary amines reported by Buchwald *et al.*



Equation 4 Pd-catalyzed coupling of aryl halides with secondary amines reported by Hartwig *et al.*

Later, Buchwald and Hartwig groups again both turn towards bidentate ligands BINAP[84] or dppf[85] respectively for the palladium-catalyzed amination of aryl halides. The presence of a strong metallic base is also necessary. These "secondary generation catalysts" were designed in order to allow the coupling of primary amines (Equation 5).



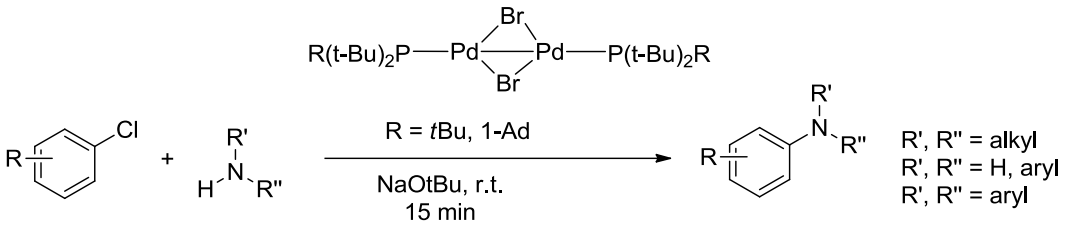
Equation 5 Pd-catalyzed coupling of aryl halides with primary amines

Then the remaining challenge consists in coupling aryl chlorides under mild conditions. A spectacular success was obtained in Hartwig's group by using palladium(I) dimers, such as $[Pd\text{-}P(t\text{Bu})_3Br]_2$ and $\{Pd[P(t\text{Bu})_2(1\text{-Ad})]Br\}_2$, (1-Ad = 1-adamantyl) featuring one bulky phosphine ligand on each palladium center. With such reactive catalysts, aryl

84 (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996,** *118*, 7215-7216; (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000,** *65*, 1144-1157.

85 Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996,** *118*, 7217-7218.

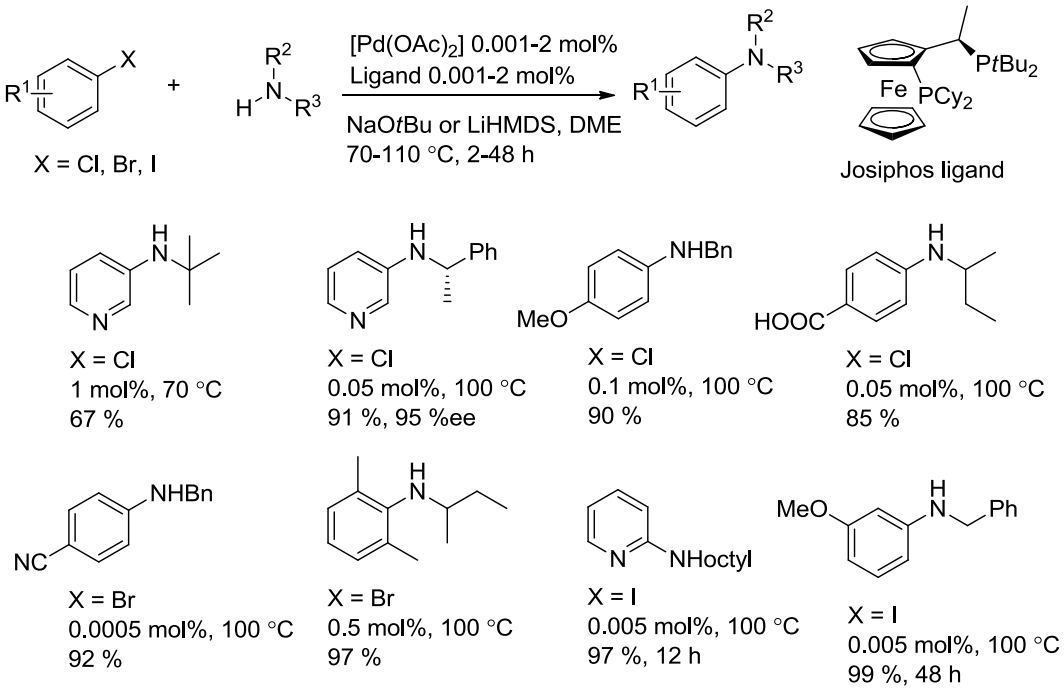
chlorides react with secondary amines at room temperature very quickly.[86] Within 15 min, tertiary amines are formed in high yields (Equation 6).



Equation 6 Pd-catalyzed coupling of aryl chlorides with amines

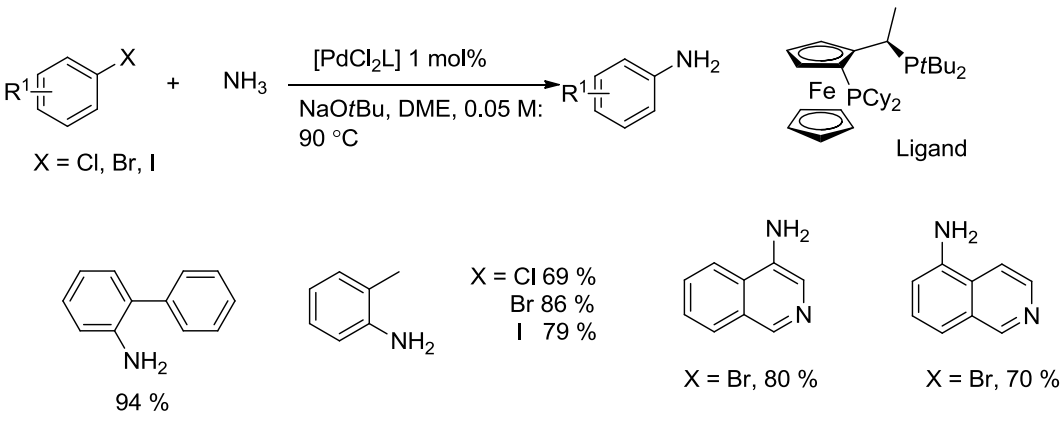
Although the first three generations catalysts have been efficient for the coupling of aryl halides with secondary amines, the coupling of primary amines still suffers from limitations, such as the existence of side-products and a high loading of palladium. Other generations of catalysts have been developed to overcome these difficulties. Currently the most reactive catalyst is generated from palladium salts and a sterically hindered version of the Josiphos family of ligands[87] that exhibits a ferrocenyl-1-ethyl backbone, a hindered di-*tert*-butylphosphino group, and a hindered dicyclohexylphosphino group. It is worth to note that these Josiphos ligands are commercially available. It combines the chelation of a biphosphine of the second generation catalysts of with the steric properties and the strong electron donation of the hindered alkylphosphines of the third-generation systems. The fourth generation catalyst enables the coupling of aryl chlorides, bromides, and iodides with primary amines,[88] N-H imines, and hydrazones[89] in high yields. The reaction has a broad scope, presents a highly functional group tolerance, and a high *chemo*-selectivity. It also requires the lowest levels of palladium that was ever used for C-N coupling (Scheme 39).

86 Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002,** *41*, 4746-4748.
87 Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Cat.* **2002**, *19*, 3-16.
88 Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008,** *130*, 6586-6596.
89 Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005,** *44*, 1371-1375.



Scheme 39 The synthesis of secondary amines from aryl halides and primary amines by using the fourth generation catalysts.

Besides, in a similar manner, the new generation catalytic system is able to catalyze the coupling of ammonia with aryl halides to form the primary aryl amines (Scheme 40).[90]

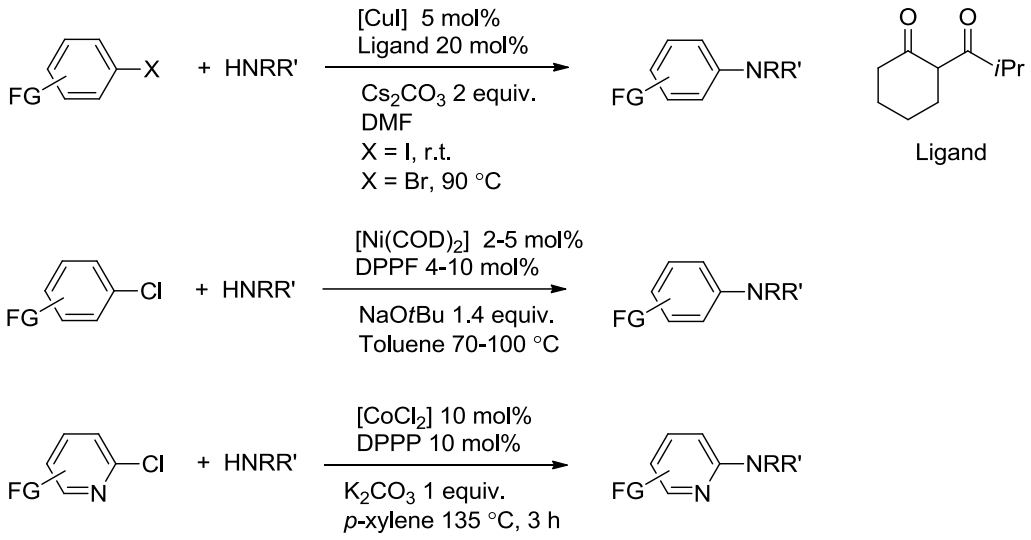


Scheme 40 The synthesis of primary amines from aryl halides and ammonia by using the fourth generation catalysts.

Although the discovery of efficient palladium-catalyzed amination reactions by Buchwald and Hartwig has been a major breakthrough in creating C-N bonds and forming functionalized arylamines, they still present some limitations such as handling of air and moisture sensitive species, functional-group tolerance, high cost of palladium

90 Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006,** *128*, 10028-10029.

and use of sophisticated ligands. Therefore chemists turn to other metals, such as Cu,[91] Ni, [92] and Co [93] (Scheme 41). However, these reactions generally also require sophisticated ligands. Moreover, stoichiometric amounts of base or high reaction temperatures (usually around 100 °C) are often necessary to achieve the reactions. Some more reactive arylating reagents, involving organo-bismuth, lead, stannane, and siloxane derivatives or hypervalent iodonium salts have been also employed in forming C-N bonds. [94] Obviously, these reagents are relatively toxic and unstable, and sometimes are expensive to prepare, which limit their application. Therefore, some other synthetic routes are desired as complementary pathways.



Scheme 41 Represented examples of copper/nickel/cobalt catalyzed nucleophilic C-N coupling reactions

I-1-2 Chan-Lam type C-N coupling

In 1998, Chan [95] and Lam [96] independently reported at the same time that copper mediated the oxidative coupling of arylboronic acids with N-H containing compounds

91 (a) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006,** *128*, 8742-8743; (b) Diao, X.; Xu, L.; Zhu, W.; Jiang, Y.; Wang, H.; Guo, Y.; Ma, D. *Org. Lett.* **2011,** *13*, 6422-6425.

92 (a) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997,** *119*, 6054-6058; (b) Tasler, S.; Lipshutz, B. H. *J. Org. Chem.* **2003,** *68*, 1190-1199.

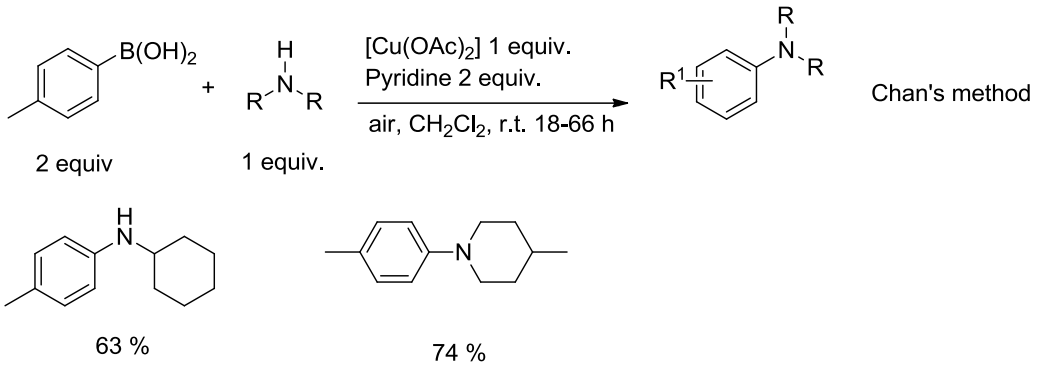
93 (a) Teo, Y.-C.; Chua, G.-L. *Chem. –Eur. J.* **2009,** *15*, 3072-3075; (b) Toma, G.; Fujita, K.-i.; Yamaguchi, R. *Eur. J. Org. Chem.* **2009,** *27*, 4586-4588.

94 (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003,** *42*, 5400-5449; (b) Elliott, G. I.; Konopelski, J. P. *Tetrahedron* **2001,** *57*, 5683-5705; (c) Finet, J. P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002,** *6*, 597-626.

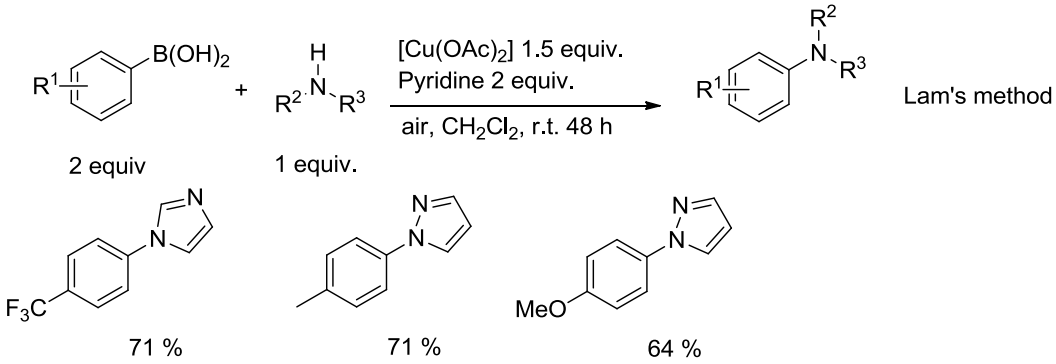
95 Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998,** *39*, 2933-2936.

96 Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998,** *39*, 2941-2944.

(Scheme 42 and Scheme 43, Figure 7). With the stoichiometric amount of copper salts, boronic acids react with an impressive range of N–H nucleophiles at room temperature efficiently.



Scheme 42 Chan C-N coupling method



Scheme 43 Lam C-N coupling method

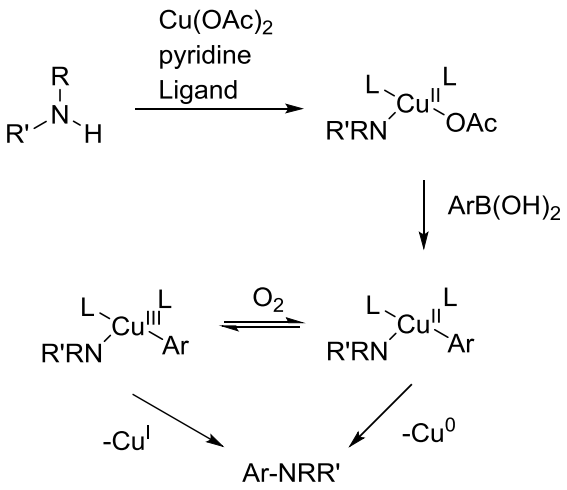
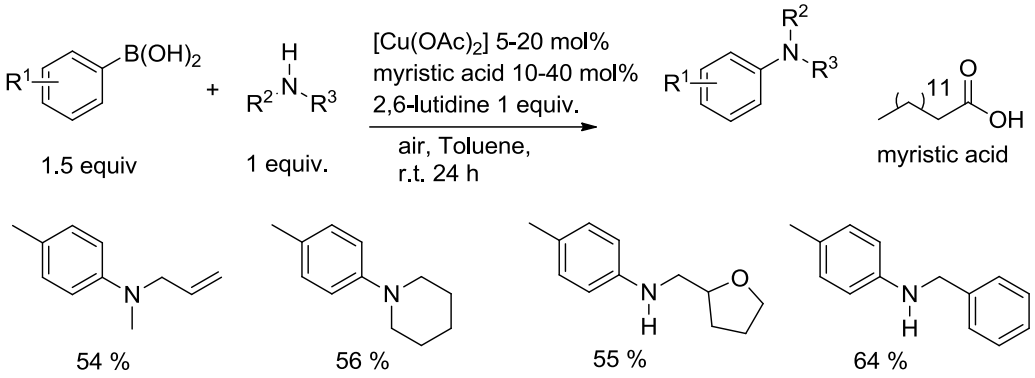


Figure 7 General mechanism of Chan-Lam type C-N coupling reactions

In the beginning, the Chan-Lam type reactions employ stoichiometric metal salts and amine additives. It is the main drawback of this method. In 2001, inspired by Collman's

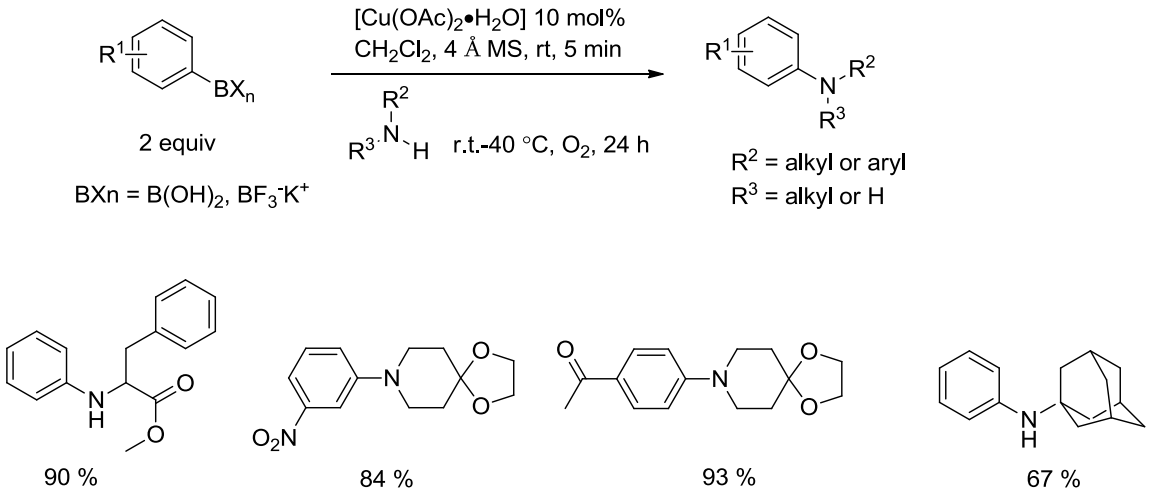
report,[97] Buchwald and coworkers built a copper-catalyzed coupling of arylboronic acids and amines in moderate to good yields (Scheme 44).[98] This method shows a broad substrate scope. However, in this case, a stoichiometric base is still required. The addition of myristic acid to the reaction mixture provided an enhanced reaction rate by promoting the solubility of the catalyst. Besides, investigations on functionalized boronic acid and alkyl amine were limited.



Scheme 44 Copper-catalyzed coupling of arylboronic acid and amines

In 2003, Batey and coworkers reported a very efficient Chan-Lam type amination of arylboronic acids (Scheme 45).[99] This protocol has the advantage to be ligand- and base-free. It employs the copper(II) acetate salt, proceeds under mild conditions, and tolerates a broad range of functional groups on both of the cross-coupling partners.

97 (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000,** *2*, 1233-1236; (b) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001,** *66*, 1528-1531.
98 Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001,** *3*, 2077-2079.
99 Quach, T. D.; Batey, R. A. *Org. Lett.* **2003,** *5*, 4397-4400.



Scheme 45 Ligand- and base- free copper-catalyzed coupling of arylboronic acid and amines

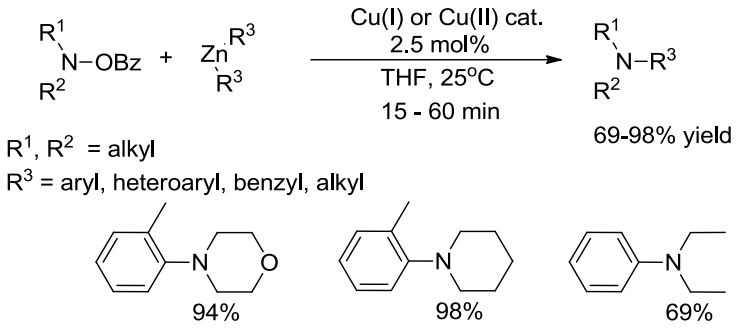
In summary, the Chan-Lam type methods have now made significant progress. Compared to the nucleophilic amination reaction, they use inexpensive reagents, exhibit higher functional group tolerance and comparable mild conditions. Its main drawbacks are: the long reactions time (generally 24 h or longer); the use of arylboronic acids that are generally more expensive than the corresponding aryl halides. Meanwhile, the toxicity of aryl boronic acid deriviatives cannot be ignored.[100]

I-1-3 Electrophilic amination

In order to overcome the drawbacks of the nucleophilic type or the Chan-Lam type C-N bond construction, the alternative electrophilic amination of organometallic reagents with electrophilic nitrogen sources (containing a weak N-X bond, where X is equal or more electronegative than nitrogen) has been developed. In general, these methods are cost-effective (*e.g.* employing cheap metals and no sophisticated ligands) and work in mild conditions (*e.g.* lower reaction temperature and shorter reaction time), which make them complementary to the nucleophilic type or Chan-Lam type C-N coupling reactions. This section will summarize the representative examples of the electrophilic synthesis of alkyl-arylamines according to the report time. The achievements and potential improvement will also be discussed.

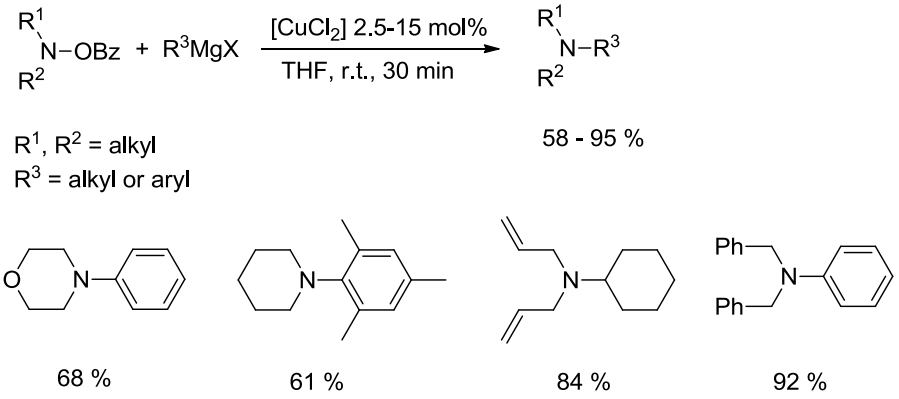
100 Hall, D. G. *Structure, Properties, and Preparation of Boronic Acid Derivatives. Overview of Their Reactions and Applications, in Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*, Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2006**.

The first example using an electrophilic N_{sp3} source with a transition metal catalyst was reported by Johnson and coworkers in 2004 (Scheme 46).[101] They successfully prepared a wide range of tertiary arylamines *via* the copper-catalyzed electrophilic amination of diorganozinc reagents with *O*-acyl hydroxylamine derivatives. The reaction was not slowed by the presence of a methyl group at the *ortho*- position of the phenyl ring. The exploration of the functional scope of the substrates was nevertheless limited, for example, no nucleophile bearing electron-withdrawing group was presented.



Scheme 46 Copper-catalyzed electrophilic amination of diorganozinc reagents

Later, the same authors extended the method and realized the amination of Grignard reagents with the same electrophilic amine partners in a similar manner (Scheme 47).[102] The slow addition of Grignard reagents is necessary to obtain reproducible results.

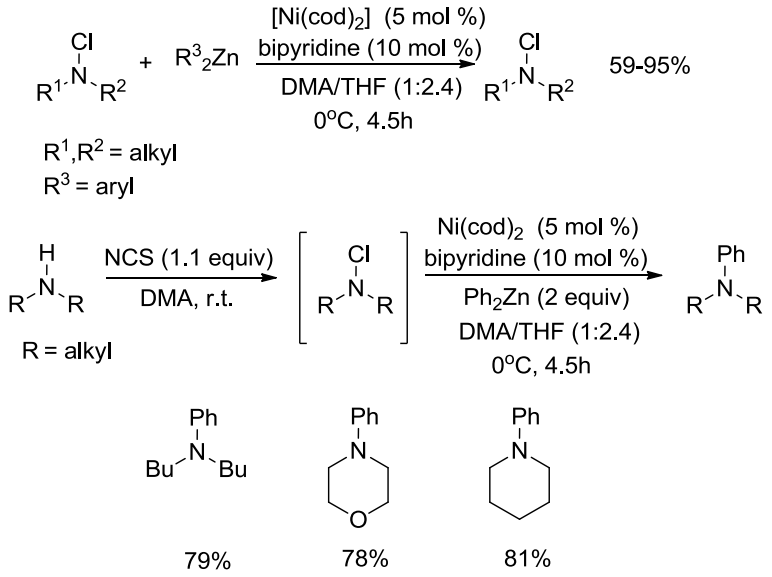


Scheme 47 Copper-catalyzed electrophilic amination of Grignard reagents

Jarvo's research group reported the first nickel-catalyzed cross-coupling reactions of *N*-chloroamines and diphenylzinc reagents to give the tertiary arylamine products in good to excellent yields with both cyclic and acyclic amines (Scheme 48).[103] Substrates

101 Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004,** *126*, 5680-5681.
102 Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007,** *9*, 1521-1524.
103 Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009,** *131*, 15598-15599.

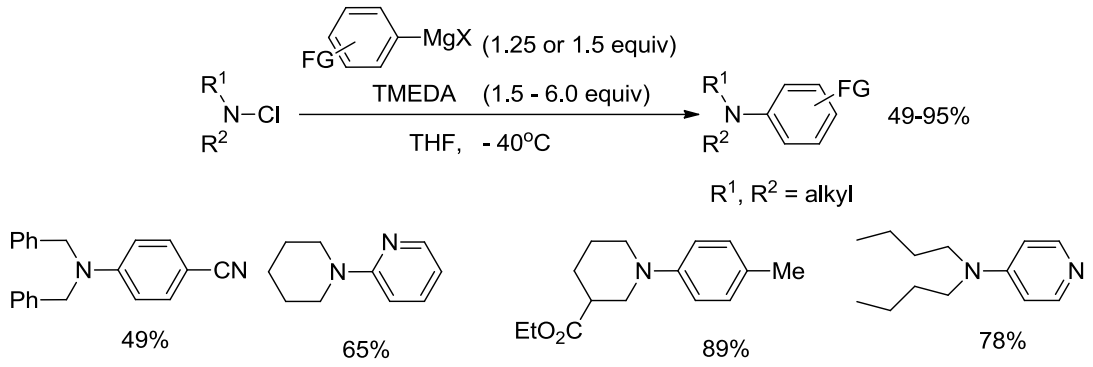
with a terminal alkene or a free amide group on the nitrogen as well as a heterocyclic organozinc reagent were tolerated. No electronic effect was found since a *meta*-substituted phenyltriflates was also efficiently coupled. It is worth to note that a *one-pot* procedure avoiding the isolation of the *N*-chloroamine was successfully developed.



Scheme 48 Nickel-catalyzed electrophilic amination of diorganozinc reagents

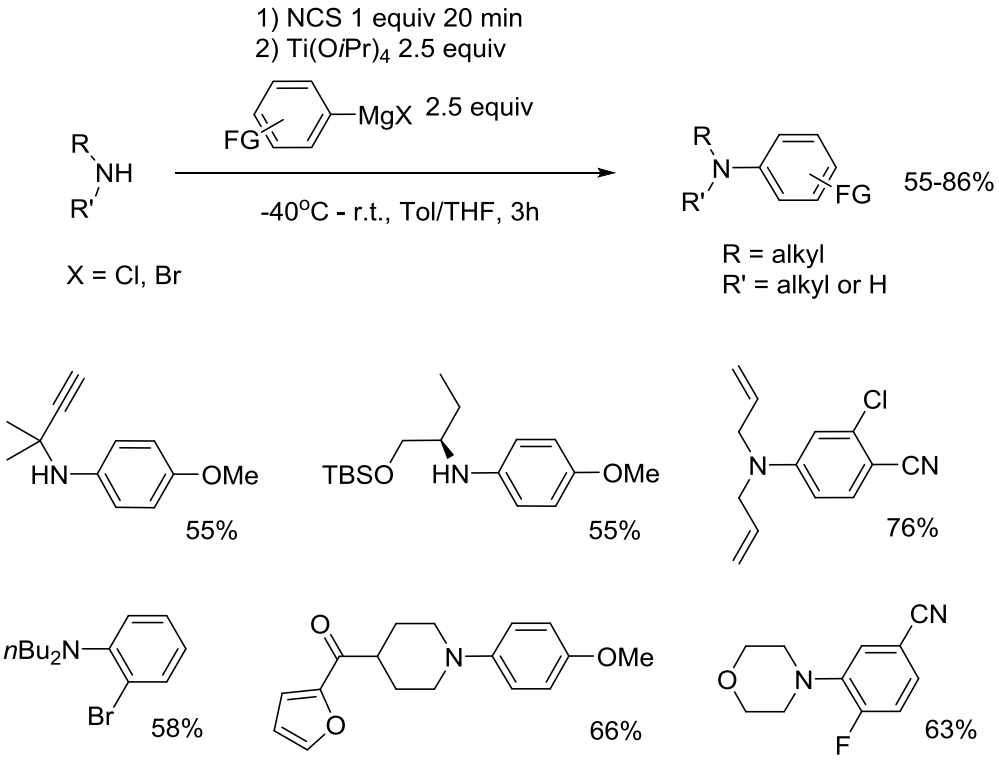
Avoiding the use of a transition metal may offer practical synthesis of natural products and pharmaceutical targets. Thus, Nakamura and coworkers reported a transition-metal free electrophilic amination reaction between aryl Grignard reagents and *N*-chloroamines (Scheme 49).[104] Using TMEDA as additive, a variety of tertiary arylamines was produced in good to excellent yields. A broad scope of secondary *N*-chloroamines was coupled, while a limited scope for aryl Grignard reagents was presented. For some chelating substituted Grignard reagents, up to 6.0 equivalents of TMEDA were essential to obtain good yields. Besides, this reaction required the freezing medium of the at – 40 ^{0}C temperature.

104 Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010,** *12*, 1516-1519.



Scheme 49 Transition-metal-free electrophilic amination of aryl Grignard reagents

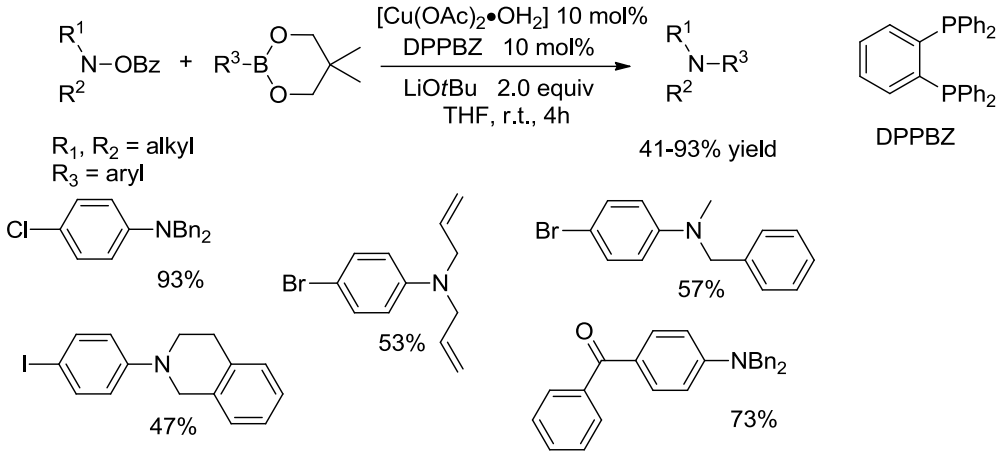
In 2011, Jarvo and coworkers established a new method for the amination of Grignard reagents, [105] employing a stoichiometric amount of [Ti(O*i*Pr)$_4$], a variety of functionalized secondary and tertiary arylamines was prepared in moderate to good yields (Scheme 50). This Ti(O*i*Pr)$_4$-mediated *one-pot* reaction successfully extended the scope to primary *N*-chloroamines, which are challenging substrates. Besides, it also showed that the *chiral* information is preserved when starting from a chiral amine.



Scheme 50 Titanium-mediated electrophilic amination of Grignard reagents

105 Barker, T. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011,** *50*, 8325-8328.

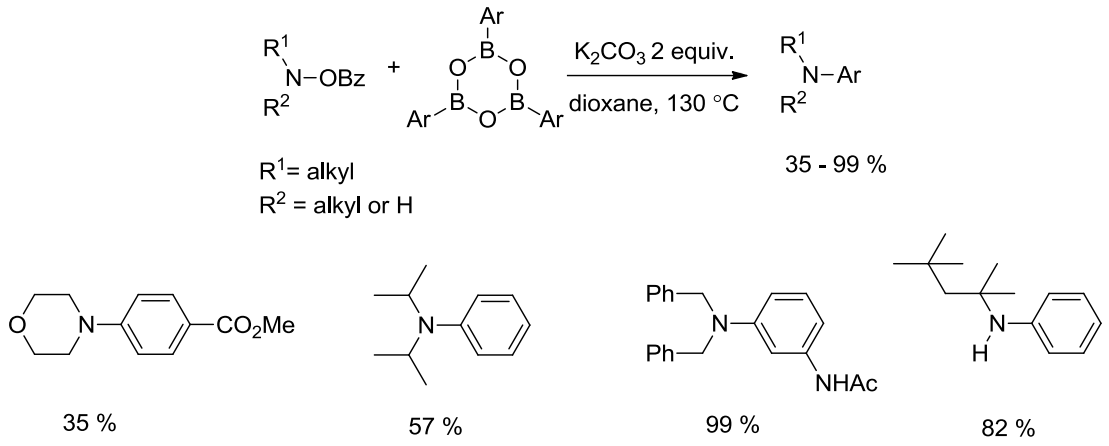
Recently, Hirano and Miura reported a copper-catalyzed system for the amination of dialkylhydroxylamines (Scheme 51). [106] Instead of employing aryl Grignard or diarylzinc reagents, they used the arylboronate reagents as nucleophiles. In this case, various functional groups, such as halides, aldehydes, ketones and esters are tolerated. The halide-substituted arylamines can be further functionalized by traditional coupling reactions. Lithium *tert*-butoxide is crucial to generate the Cu*O*t*B*u species and the diarylcuprate ate complex, which are the intermediates in the catalytic cycle.



Scheme 51 Copper-catalyzed electrophilic amination of aryl boronic esters

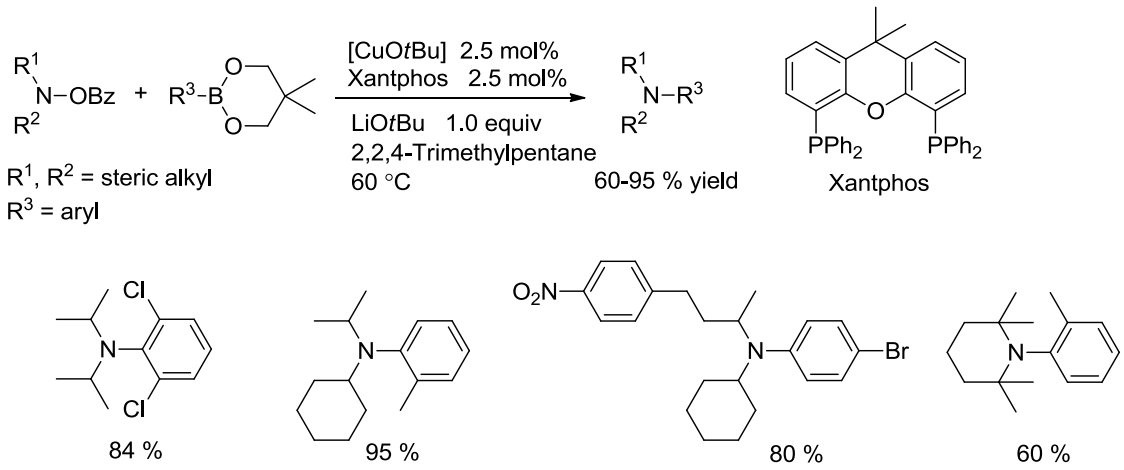
In 2012, Wang's group reported a novel methodology of transition-metal free electrophilic amination of arylboroxines with *O*-benzoyl hydroxylamines (Scheme 52).[107] This transformation provides a useful method to access to various functionalized aromatic amines, including sterically hindered amines and secondary arylamines. The authors were able to exclude the possible effect of trace transition metal in the medium by ICP-MS analysis of the substrates.[108] It is worth to note that, compared to other electrophilic amination pathways, this method required high reaction temperature (130 °C) and long reaction time (24 h). Besides, although the *ratio* between the two substrates is 1:1, there is only one Ar unit of arylboroxines that is transferred, while the other two Ar units are lost. Thus, this method is not really "cost-effective" as claimed by the authors.

106 Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012,** *51*, 3642-3645.
107 Xiao, Q.; Tian, L.; Tan, R.; Xia, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Org. Lett.* **2012,** *14*, 4230-4233.
108 ICP-MS is an analytical technique used for elemental determinations.



Scheme 52 Transition-metal-free electrophilic amination of arylboroxines

Very recently, Lalic and coworkers developed a copper-catalyzed reaction for the synthesis of sterically hindered anilines from aryl and heteroaryl boronic esters under very mild conditions (Scheme 53).[109] This method is compatible with a wide range of functional groups, including chloro, bromo, iodo, carbomethoxy, nitro, hydroxyl, formyl and methoxy groups. The synthesis of hindered and iodo/bromo substituted anilines made this method really competitive compared to other reports.



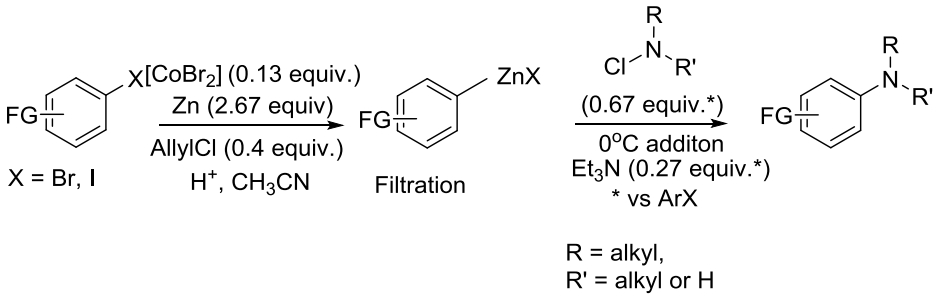
Scheme 53 Copper-catalyzed electrophilic amination of aryl boronic esters

In summary, significant progresses have been made in the electrophilic amination of aryl substrates while some drawbacks still exist. A cost-efficient, easy-handled and inexpensive procedure requiring milder condition remains desirable. Consider atom-economic, *N*-chloroamines are among the most desirable amination reagents in the

109 Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *Angew. Chem., Int. Ed.* **2012,** *51*, 3953-3956.

alternative amination strategy because of their availability and scalability.[110] Moreover, arylzinc reagents,[111] whose synthesis is well understood, are good candidates as reaction partners, but their amination with electrophilic amines such as chloroamines is underdeveloped. A few years ago, we described the cobalt-catalyzed formation of functionalized-arylzinc species from the corresponding halides or triflates, and the presence of cobalt salts in these arylzinc solutions should catalyze formation of C-N bonds through an electrophilic pathway. We already have some related precedent for the cross-coupling of cobalt-generated organozinc species with a range of electrophiles that is catalyzed by the residual cobalt salts in the medium.[112]

Having recently reported a cross-coupling of aniline derivatives and 2-chloropyrimidines in the presence of tolylzinc bromide as a base,[113] we develop a complementary approach to C-N bond formation that allows the coupling of *in situ* generated arylzinc species with *N*-chloroamines, again using cobalt salts as catalysts (Equation 7).



Equation 7 Cobalt-catalyzed electrophilic amination of arylzincs with *N*-chloroamines.

110 Zhong, Y.-L.; Zhou, H.; Gauthier, D. R.; Lee, J.; Askin, D.; Dolling, U. H.; Volante, R. P. *Tetrahedron Lett.* **2005,** *46*, 1099-1101.

111 (a) Stathakis, C. I.; Bernhardt, S.; Quint, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2012,** *51*, 9428-9432; (b) Fillon, H.; Gosmini, C.; Périchon, J. *J. Am. Chem. Soc.* **2003,** *125*, 3867-3870; (c) Kazmierski, I.; Gosmini, C.; Paris, J.-M.; Périchon, J. *Tetrahedron Lett.* **2003,** *44*, 6417-6420; (d) Gosmini, C.; Amatore, M.; Claudel, S.; Périchon, J. *Synlett* **2005**, 2171-2174; (e) Kazmierski, I.; Gosmini, C.; Paris, J.-M.; Périchon, J. *Synlett* **2006**, 881-884.

112 (a) Gosmini, C.; Begouin, J.-M.; Moncomble, A. *Chem. Commun.* **2008**, 3221-3233; (b) Gosmini, C.; Moncomble, A. *Israel J. Chem.* **2010,** *50*, 568-576.

113 Delvos, L. B.; Begouin, J.-M.; Gosmini, C. *Synlett* **2011**, 2325-2328.

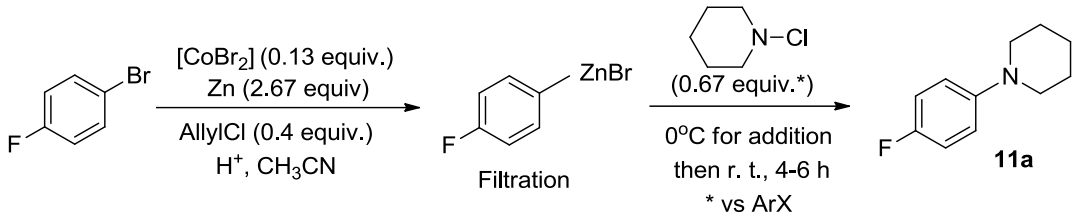
I-2 Results and discussions

I-2-1 Optimization of the reaction conditions

Our first investigations concentrated on the cobalt-catalyzed coupling of 4-fluorophenylzinc bromide with *N*-chloropiperidine in order to achieve a preliminary optimization of the procedure (Table 15). The arylzinc species is prepared from the corresponding arylbromide (ArBr) in presence of cobalt in acetonitrile as previously reported.[111b-e] When this reaction mixture was filtered and added to the *N*-chloroamine (0.33 equiv with respect to ArBr) without further addition of cobalt, 44 % of the cross-coupling product was obtained according to GC (Table 15 entry 1). Gratifyingly, this GC yield was improved to 90 % by concentrating the medium (Table 15 entry 2). Decreasing the excess of ArBr to 1.5 equivalent (instead of 3 equiv.), did not affect the yield (Table 15 entry 3), but an excess of *N*-chloroamine relative to aryl bromide was detrimental (Table 15, entry 4). Filtration of the arylzinc compound was found to be necessary (Table 15, entry 5). To establish that cobalt plays a crucial role in this coupling reaction, a few experiments were conducted (Table 15, entries 6-8). MVK (methyl vinyl ketone) is known to bind cobalt and to largely reduce or annihilate its catalytic activity, while keeping the aryl zinc species intact.[114] Under the optimized conditions (Table 15, entry 3) with the addition of one equivalent of MVK to the arylzinc solution, only traces of the C-N product was found after 2 h or overnight stirring. Commercial ArZnBr (in THF or after replacing THF by CH_3CN) or electrochemically generated ArZnBr in acetonitrile were shown to give no coupling product when reacted with *N*-chloropiperidine (Table 15, entry 7). Moreover, the addition of THF in the medium gave poor yield of cross-coupling product (Table 15, entry 8), THF is therefore detrimental to this reaction.

114 Amatore, M.; Gosmini, C. *Synlett* **2009**, 1073 – 1076.

Table 15 Initial studies for C-N bond formation of *p*-FC_6H_4ZnBr.



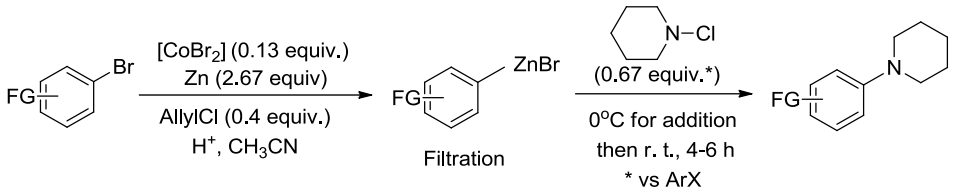
Entry	FG	ArBr/N-Cl	[ArZnBr]	Yield [a]
1	*p*-F	3/1	0.75M.	(44)
2	*p*-F	3/1	1.2M.	(90)
3	*p*-F	1.5/1	0.6M.	80 (91)
4	*p*-F	1/1.5	0.6M.	(32)
5	*p*-F [b]	1.5/1	0.6M.	(30)
6	*p*-F [c]	1.5/1	0.6M.	(5)
7	*p*-F [d],[e],[f]	1.5/1	0.6M	0
8	*p*-F [g]	1.5/1	0.6M.	(10)

[a] Yields given are for isolated products, (except those in parentheses which give crude yields as established by is GC, with decane as internal standard.) [b] No filtration of ArZnBr [c] 0.5 mmol (equal to the amount of $CoBr_2$) MVK (methyl vinyl ketone) was added to the arylzinc species before injected to the NCl solution. [d] Commercial ArZnBr in THF. [e] Commercial ArZnBr in THF and subsequent replacement of THF by CH_3CN [f] electrochemically prepared ArZnBr in CH_3CN [g] formation of ArZnX in CH_3CN (2mL) and addition of THF (3 mL)

I-2-2 The scope of aryl zinc species

We then extended the scope of the reaction to various aryl bromides (Table 16) using the optimized conditions (Table 15, entry 3). Moderate to excellent yields were obtained. However, the initial conditions were not satisfactory for all substrates. For example, only traces of cross-coupling product were observed when coupling *N*-chloropiperidine and *p*-$MeCOC_6H_4ZnBr$ or PhZnBr. Moreover, with other *N*-chloroamines such as the *N*-chloropyrrolidine, the major observed products resulted from chlorination or protonation of the arylzinc specie.

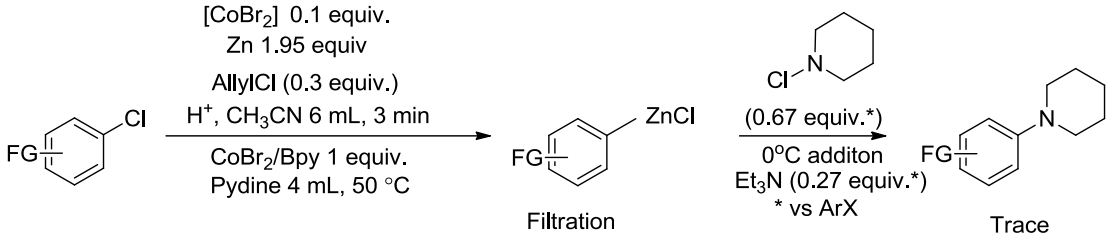
Table 16 The scope of cobalt-catalyzed electrophilic amination of various arylzinc bromides



Entry	FG	ArZnX (mmol)	Temperature	Product	Yield [a]
1	*p*-CF_3	3.2	0°C to r.t.	**11b**	79
2	*m*-CF_3	3.2	0°C to rt	**11c**	55
3	*p*-CO_2Et	2.8	0°C to 50 °C	**11d**	65
4	*p*-CN	3.2	0°C to 50 °C	**11e**	82
5	*p*-OMe	3.0	0°C to 50 °C	**11f**	71
6	*p*-Me	3.0	0°C to 50 °C	**11g**	53
7	*o*-OMe	2.6	0°C to 50 °C	**11h**	42[b]

[a] Isolated yield based on *N*-chloroamines (2.5 mmol).[b] 42% yield as determined by ^{1}H NMR of the mixture of Ar-N and traces of Ar-are obtained after chromatography, see the experimental section for details.

We also tried to extend this methodology to arylchloride derivatives. We have previously established that cobalt catalysis allows the simple and high-yielding preparation of a broad range of functionalised arylzinc species from readily available aryl chlorides (Equation 8), nevertheless this step requires the presence of pyridine which then hampers the amination. Therefore, only traces of C-N product were observed with aryl chlorides after several attempts. Amination of heteroaromatic substrates, such as thiophene and pyridine halides also failed, only providing poor C-N coupling yield (GC < 30 %).

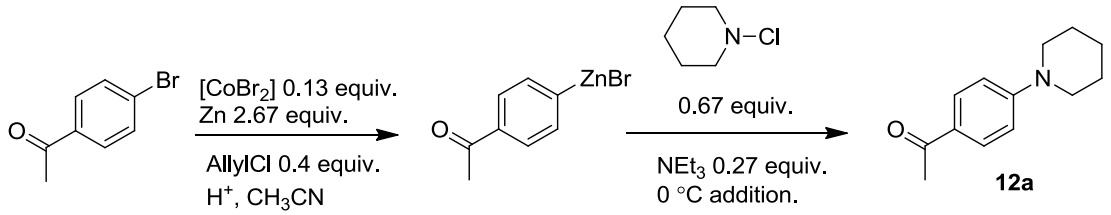


Equation 8 The formation of arylzinc species from aryl chlorides under cobalt catalyst

I-2-3 The scope of aryl halides and *N*-chloroamines.

As amines were found to limit side reactions,[104] triethylamine was added to the reaction medium. We found that the optimal *ratio* is 1: 0.4 for NCl : NEt_3 (Table 17). With this modification, we were pleased to observe the disappearance of the side-products and the successful formation of arylamines in cases where previously no reaction occurred. More importantly, the reaction rate was enhanced in all cases; with all reactions being finished at room temperature after only two hours *vs* 4 to 6 h without additive (compare tables 16 and 18)

Table 17 The effect of triethylamine to C-N coupling reaction



Entry	Loading of NEt_3 %	Temperature	Time[a]	GC Yield %
1	0	r.t. or 50 °C	2 h	< 5
2	20	r.t.	2 h	59
3	40	r.t.	2 h	81[b]
4	60	r.t.	2 h	26
5	80	r.t.	2 h	22
6	100	r.t.	2 h	9

[a] No improvement was seen after longer reaction time [b] Isolated yields

Having established this general protocol, we explored the scope of the reaction using various aryl halides and a variety of *N*-chloroamines. Aryl derivatives bearing many functional groups such as ketone, acetate, sulfone, chlorine, fluorine, nitrile, trifluoromethyl, methoxy, thioether or dioxane groups in *ortho, meta* or *para* positions were all successfully coupled at room temperature. However, the dimethylamine group is not tolerated in this method, although the arylzinc species was formed successfully. During the secondary step, when transfering the *N*-chloroamine into the medium, the

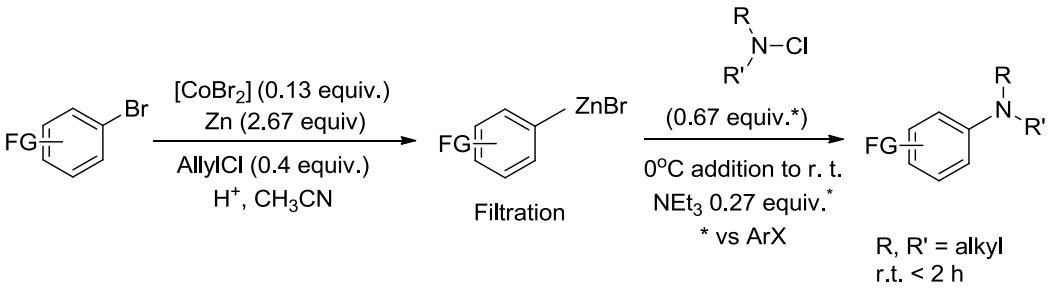
whole solution became dark purple colour. There is no effect by adding more triethylamine in this case. Since we have shown that in the large quantity of NEt_3, the catalyst would lose reactivity, it was proposed that the dimethylamine group similarly inhibited the reaction.

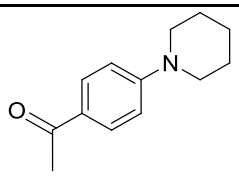
Cyclic *N*-chloroamines such as *N*-chloromorpholine, *N*-chloropyrrolidine and *N*-chloropiperidine bearing an ester group provide good to excellent yields when reacted with various arylzinc species bearing either electron-donating or withdrawing groups (Table 18, entries 1 to 14). The reaction was also successfully extended to acyclic functionalized amines (Table 18, entries 15 to 18).

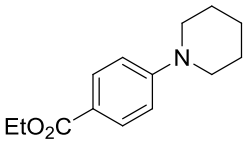
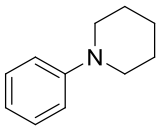
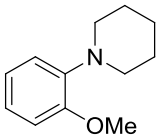
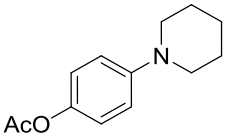
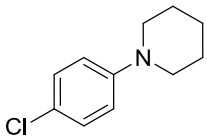
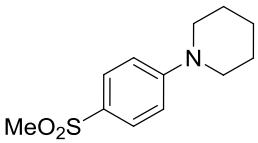
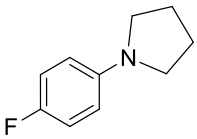
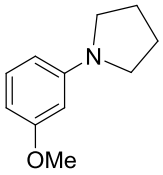
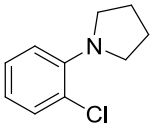
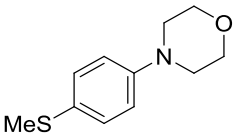
Some other $R_1R_2N^+$ synthons were also investigated. Electron-poor *N*-chlorosuccinimide (NCS) did not undergo coupling under the current reaction conditions, similarly to Jarvo's report. *N*-bromoamine was also explored as the nitrogen source partner. Since the electro-negativity of bromide (2.96) is slightly lower than nitrogen (3.04), arylzinc species cannot react with *N*- bromoamine to provide the C-N product. Only trace C-N coupling product was detected by GC, while quantity of ArBr was formed. Adding triethylamine decreased the bromination of arylzinc species, but did not improve the formation of the C-N coupling product.

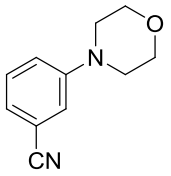
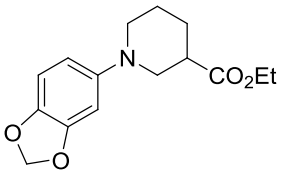
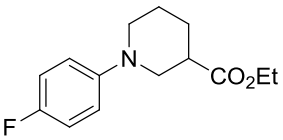
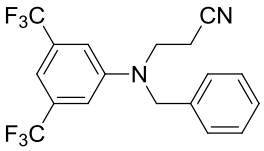
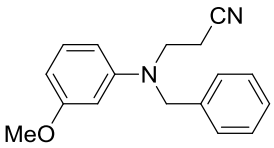
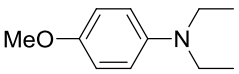
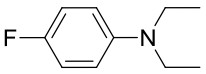
Besides, aniline and its derivatives, either primary aniline or secondary aniline cannot be chlorinated by *N*-chlorosuccinimide.

Table 18 The scope of aryl bromides/iodides and *N*-chloroamines.



Entry	FG	ArZnX/mmol	Product	Yield[a]
1	*p*-COMe	2.8	 **12a**	81

2	*p*-CO_2Et	2.8	 **11d**	75
3	H	3.0	 **12b**	82
4	*o*-OMe	2.6	 **11h**	39
5	*p*-OCOMe	3.2	 **12c**	71
6	*p*-Cl	3.4	 **12d**	80
7	*p*-SO_2Me	3.0	 **12e**	64[b]
8	*p*-F	3.2	 **12f**	53
9	*m*-OMe	3.2	 **12g**	88
10	*o*-Cl	2.8	 **12h**	51
11	*p*-SMe	3.0	 **12i**	67

12	*m*-CN	3.0	 **12j**	72
13	1,2-(methylenedioxy)	3.0	 **12k**	68
14	*p*-F	3.2	 **12l**	52
15	3,5-diCF_3	3.4	 **12m**	61
16	*m*-OMe	3.2	 **12n**	71 [c]
17	*p*-OMe	3.0	 **12o**	80
18	*p*-F	3.2	 **12p**	53

[a] Isolated yield based on NCl. [b] 64% yield as determined by ^{1}H NMR of the mixture of Ar-N and traces of Ar-Ar obtained after chromatography, see experimental section S3 for details [c] 71% yield as determined by ^{1}H NMR of the mixture of Ar-N and traces of Ar-Ar obtained after chromatography, see experimental section for details.

I-2-4 Amination with non- isolated *N*-chloroamines.

Exploring the scope of the reaction showed that some *N*-chloroamines are difficult to isolate, especially those prepared from primary amines and allylic amine.[115] Thus, we developed a protocol that avoids the isolation of the *N*-chloroamine.[103, 105] The key lies in eliminating the succinimide by-product, which would otherwise consume a large quantity of the arylzinc species. Therefore the preparation of the *N*-chloroamine was achieved in toluene, which allowed the expedient removal of the insoluble succinimide

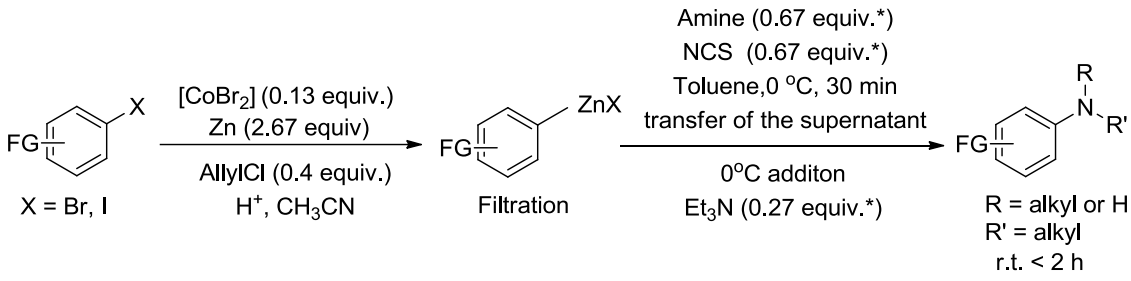
115 Guillemin, J. C.; Denis, J. M. *Synthesis* **1985,** *1985*, 1131-1133.

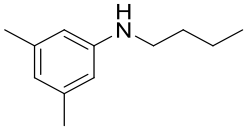
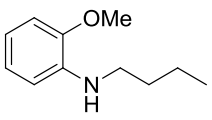
by filtration using a syringe filter. The succinimide free chloroamine solution was then added to the arylzinc solution. Under these conditions, the C-N bond formation was observed even from primary amines (Table 19).

Both linear (Table 19, entries 1 and 2) and branched amines (Table 19, entries 3 and 4) yielded the desired products. More importantly, the introduction of the primary benzylamine fragment worked well (Table 19, entry 5), which is unusual for electrophilic amination procedures. Allyl substituents are also tolerated (Table 19, entry 6). A *N*-Boc group and an aryl-Cl moiety remain untouched in these amination conditions, which opens up possibilities for further functionalization by traditional cross coupling methods (Table 19, entry 7).

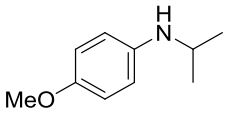
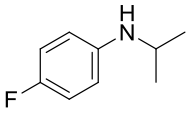
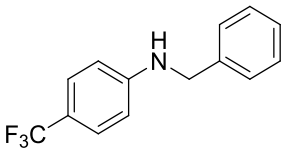
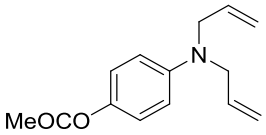
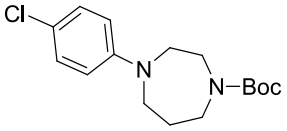
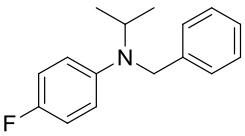
The cross-coupling reaction also worked well with one sterically hindered substituent on the nitrogen (Table 19, entry 8), whereas no coupling product was obtained with two bulky groups on the N atom.[116] In this case, the formation of *N*-chloroamine is realized, however, in the second step, the arylzinc species cannot react with the *N*-chloroamine efficiently. After the reaction, only trace C-N coupling product was found, with unreacted *N*-chloroamine.

Table 19 Amination with non- isolated *N*-chloroamines.



Entry	FG	ArZnX/mmol	Product	Yield [a]
1	3,5-dimethyl	3.0	 **13a**	70 [b]
2	*o*-OMe	2.8		80

116 *N*-chloro-*N*-isopropylpropan-2-amine and (2*R*, 6*S*)-2, 6-dimethylpiperidine were attempted.

			13b	
3	*p*-OMe	2.8		78
			13c	
4	*p*-F	3.2		58
			13d	
5	*p*-CF_3	3.2		78
			13e	
6	*p*-OCOMe	3.0		39
			13f	
7	*p*-Cl	3.0		58
			13g	
8	*p*-F	3.2		58
			13h	

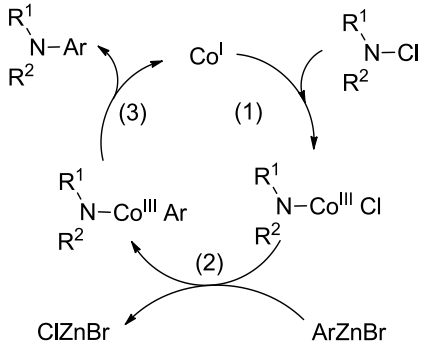
[a] Isolated yield based on amine. [b] 70% yield as determined by ^{1}H NMR of the mixture of Ar-N and traces of Ar-Ar obtained after chromatography, see experimental sectionfor details.

I-2-5 Postulated mechanism

Concerning the mechanism, some previous work about the cobalt catalyzed formation of the arylzinc species in acetonitrile allows a pathway to be proposed.[117] The *in-situ* formed Co^I catalyzes the formation of the arylzinc compounds in acetonitrile. It was also shown that cobalt remains in the solution after filtration of the zinc dust which allows further reactivity.[118] The Co^I center is proposed to undergo an oxidative addition with the electrophilic *N*-chloroamine to afford a Co^{III} species (1). In a second step (2), this latter species is transmetalated with the arylzinc halides to furnish R^1R^2N-Co^{III}-Ar

117 Seka, S.; Buriez, O.; Nédélec, J.-Y.; Périchon, J. *Chem. -Eur. J.* **2002,** *8*, 2534-2538.
118 Amatore, M.; Gosmini, C. *Chem. Commun.* **2008**, 5019-5021.

and the cycle is completed by a reductive elimination (3) which produces the C-N product and regenerates Co^{I}. This putative mechanism is presented in Scheme 54.



Scheme 54 Postulated mechanism

I-2-6 Conclusions and perspectives

In summary, we have developed a mild and highly efficient procedure for the amination of functionalized arylzinc reagents by secondary and tertiary *N*-chloroamines using cobalt catalysis. This simple and convenient protocol displays a wide substrate scope, and a tolerance to a large number of important sensitive functional groups. In some cases, triethylamine dramatically improved the reaction of the arylzinc species with the *N*-chloroamine and prevents the formation of by-products. This method is attractive for the streamlined synthesis of functional molecules.

As described here, some progress has been made. However, there are several issues that still remain to be resolved: (1) Coupling of *N*-chloroamides with organozinc is less studied. *N*-chloroamides is desirable amination reagents because of the ease of preparation, however they are rarely reported in catalytic electrophilic amination reactions.[110, 119] In 2008, Lei and coworkers developed an efficient copper-catalyzed electrophilic amination of arylboronic acids by *N*-chloroamides under mild conditions.[120] While these reagents failed to be applied in the nickel-catalyzed electrophilic amination of diarylzinc compounds claimed by Jarvo.[103] It should be possible to develop some C-N coupling reactions to form diarylamides under cobalt-catalyzed systems. (2) Numerous C_{sp}^{2}-Nc_{sp}^{3} bond forming reactions have been

119 (a) Kovacic, P.; Lowery, M. K.; Field, K. W. *Chem. Rev*. **1970**, *70*, 639-665. (c) Armesto, X. L.; Canle L, M.; Garcia, M. V.; Santaballa, J. A. *Chem. Soc. Rev*. **1998**, *27*, 453 – 460.

120 He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008,** *47*, 6414-6417.

developed in both nucleophilic and electrophilic pathways, but it remains a challenge to realize the electrophilic C_{sp}^2-Nc_{sp}^2 bond forming reactions. The reaction between arylzinc species and aniline derivatives under cobalt-catalysis is a possible solution. However, it is worth to note that the chlorinated-anilines are extremely unstable.[121] Some other electrophilic reagents, such as N-O derivatives may be feasible.[101,102] (3) Since a variety of secondary and tertiary alkyl-aryl amine was formed from this efficient method, with catalysts possessing *chiral* ligands could result in the formation of C-N products with some enantioselectivity, and should be explored.

121 Chapman, K.; Dyall, L. *Aust. J. Chem.* **1976,** *29*, 367-374.

II. The Synthesis of Aryl Thioether Employing the Arylzinc Species

II-1 Introduction

Aromatic C-S bond-forming reactions are important for the synthesis of biological activity and pharmaceutical applications (Figure 8),[122] therefore, many protocols have been developed. Classical synthetic methods (Scheme 55), including the Chan-Lam coupling,[95,96] Sandmeyer-type reaction[123] and Ullmann-type treaction[124] have been extensively studied and applied in industry for years. Their main drawbacks are the requirements of stoichiometric amount of copper salts, base or oxidant and relative harsh conditions.

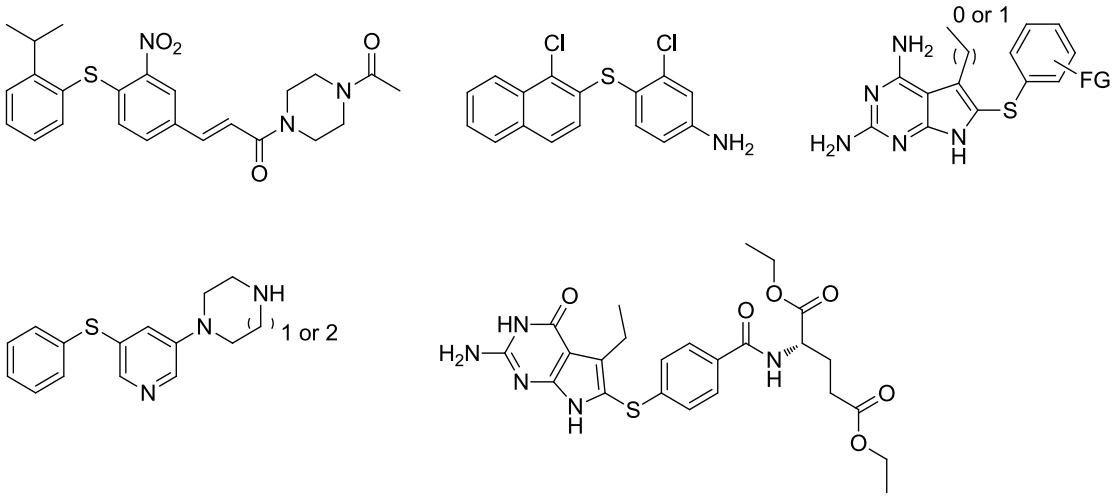
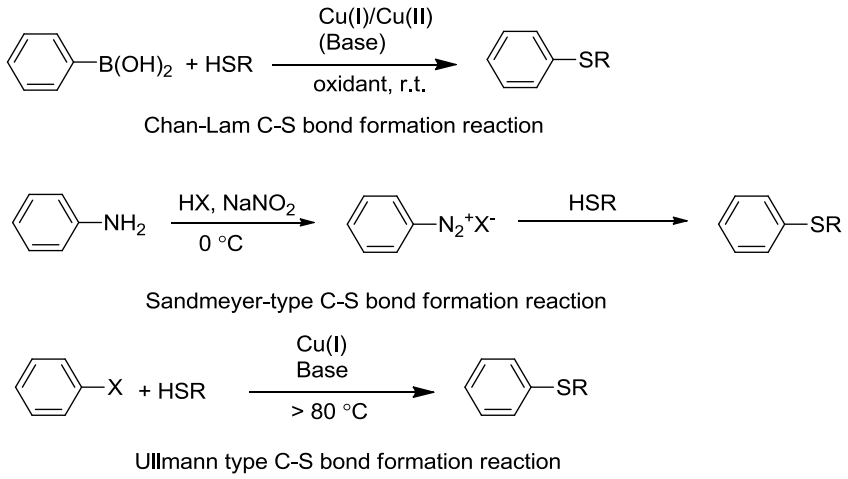


Figure 8 Biologically active molecules / pharmaceutical comprising the diaryl thioether framework

122 (a) Nielsen, S. F.; Nielsen, E. Ø.; Olsen, G. M.; Liljefors, T.; Peters, D. *J. Med. Chem*. **2000**, *43*, 2217-2226. (b) Liu, G.; Huth, J. R.; Olejniczak, E. T.; Mendoza, F.; Fesik, S. W.; von Geldern, T. W. *J. Med. Chem*. **2001**, *44*, 1202-1210. (c) DeMartino, G.; Edler, M. C.; LaRegina, G.; Coluccia, A.; Barbera, M. C.; Barrow, D.; Nicholson, R. I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 947-954. (d) Gangjee, A.; Zeng, Y.; Talreja, T.; McGuire, J. J.; Kisliuk, R. L.; Queener, S. F. *J. Med. Chem*. **2007**, *50*, 3046-3053.

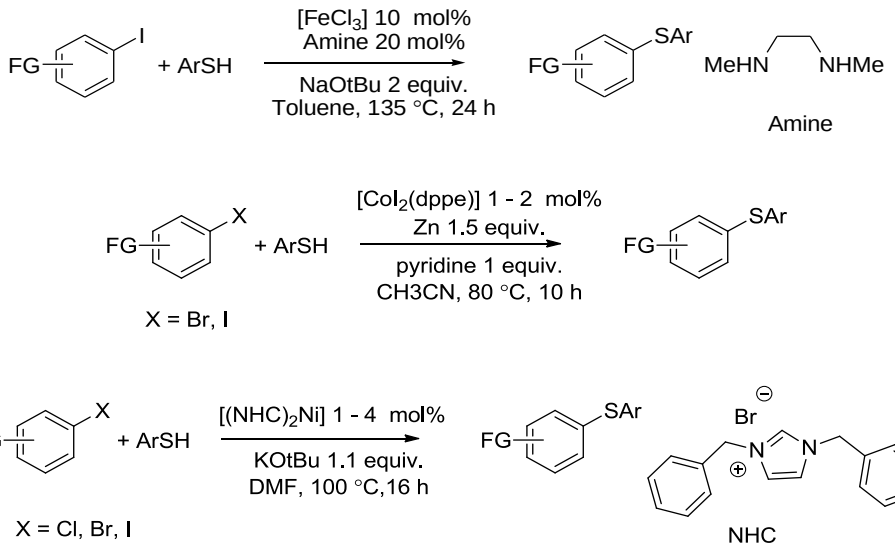
123 Hodgson, H. H., The Sandmeyer Reaction. *Chem. Rev.* **1947,** *40*, 251-277.

124 (a) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002,** *4*, 2803 -2806; (b) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006,** *8*, 5609-5612.

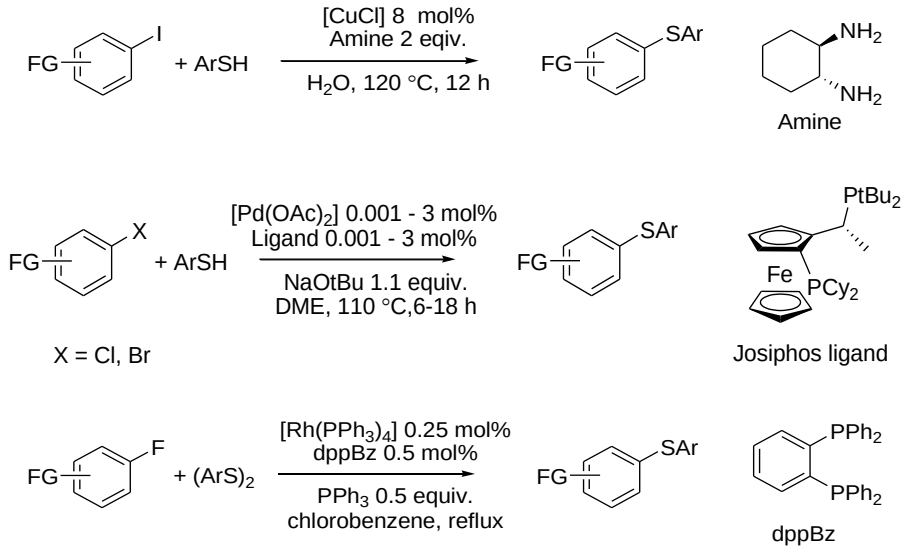


Scheme 55 Classical methods for the synthesis of aryl thioethers

Since the past decades transition-metal catalysis has dramatically changed the face of modern organic chemistry. Transition-metal catalyzed cross-coupling reactions of thiols with aryl halides or pseudo halides appear efficient to form C-S bonds (Scheme 56).[125] However, the efficient and selective construction of C-S bonds in transition-metal-catalyzed transformations remained relatively limited compared to the methods developed for other C-C or other C-heteroatom (N, O and P) bonds, mainly because of the catalyst poisoning by sulfur species. Moreover, all of these methods generally required either high temperatures, several equivalents of base, or oxidant, or reducing agents. Furthermore, from the view of pharmaceutical industry, transition-metal free C-S bond construction is also interesting.



125 Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011,** *111*, 1596-1636.



Scheme 56 Representive examples of transition-metal catalyzed synthesis of arylthioethers[126]

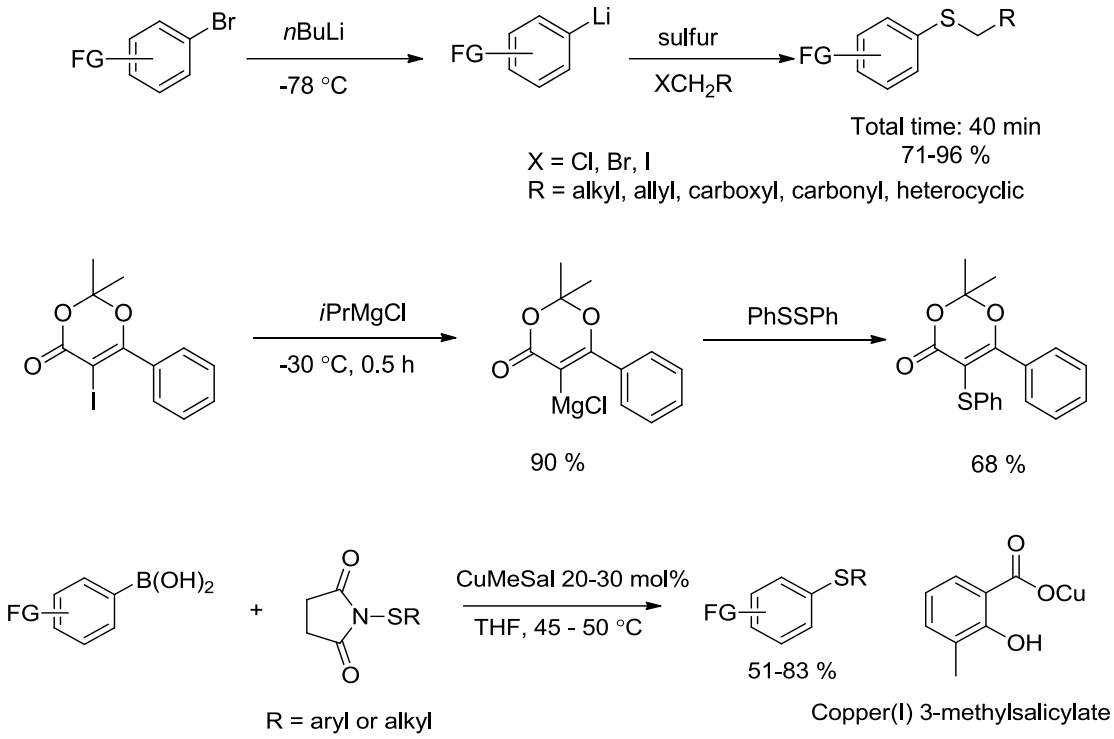
The construction of C-S bonds was also achieved by employing the organometallic reagents (Scheme 57), such as aryllithium,[127] Grignard reagents[128] or arylboronic acids[129] with diphenyldisulfides, thiosulfonates, sulfur, or *N*-thioimides. In this case, the conditions are usually milder, base-free and sometimes even transition-metal free. These reactions have shown some advantages such as shorter reaction time, low temperature and no base, no sophisticated ligands or expensive metal catalyst. However, there are still some drawbacks, which limit their applications, such as the unconvenient handling of organometallic reagents, few substrates scope exploration and high loading of expensive catalyst. Therefore, the development of inexpensive, straightforward, mild and convenient protocol is desirable in this field.

126 (a) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed*. **2008**, *47*, 2880-2883. (b) Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5613-5316. (c) Zhang, Y.; Ngeow, K. N.; Ying, J. Y. *Org. Lett*. **2007**, *9*, 3495-3598. (d) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Chem.-Eur. J*. **2007**, *13*, 5100-5105. (e) Fernandez Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc*. **2006**, *128*, 2180-2181. (f) Arisawa, M.; Suzuki, T.; Ishikawa, T.; Yamaguchi, M. *J. Am. Chem. Soc*. **2008**, *130*, 12214-12215.

127 Ham, J.; Yang, I.; Kang, H. *J. Org. Chem.* **2004,** *69*, 3236-3239.

128 Vu, V. A.; Bérillon, L.; Knochel, P. *Tetrahedron Lett.* **2001,** *42*, 6847-6850.

129 Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002,** *4*, 4309-4312.



Scheme 57 The synthesis of aryl thioethers employing organometallic reagents

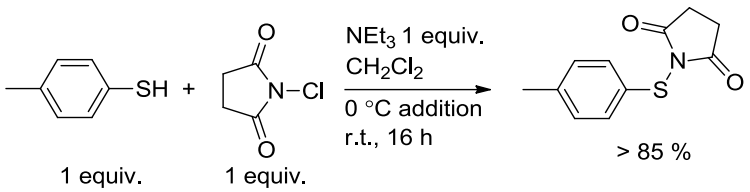
Arylzinc species, whose synthesis is well understood,[111] are good candidates as reaction partners, but their application in the synthesis of thioether with electrophilic sulfur source is underdeveloped. Based on the methodology we developed for the electrophilic amination of arylzinc derivatives. Thus, we tried to find the proper electrophilic sulfur source to form the new arylthio ethers from arylzinc species.

II-2 Results and discussions

First we chose *N*-thioimides as the electrophilic sulfur source,[130] because the synthesis of them has been well described in the literature (Equation 9),[131] and more importantly, they are stable and easy to control in the reaction. In the presence of triethylamine as the base, the thiol reacts with *N*-chlorosuccinimide and provides the correspongding *N*-thioimide in excellent yield.

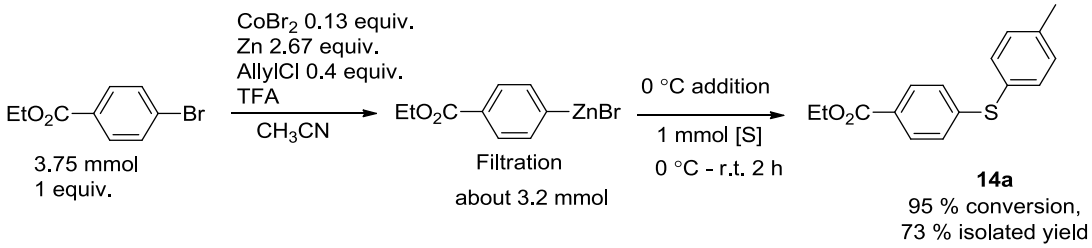
130 The electronegativity of N is 3.04, while S is 2.98.

131 Furukawa, M.; Fujino, Y.; Kojima, Y.; Ono, M.; Hayashi, S. *Chem. Pharm. Bull*. **1972**, *26*, 2024-2028.



Equation 9 The formation of *N*-thioimides

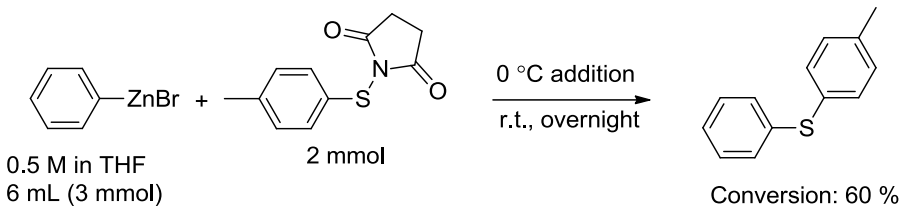
The arylzinc species is prepared from the corresponding arylbromide (ArBr) in presence of cobalt in acetonitrile as previously reported.[111] When this reaction mixture was filtered and added to the sulfur source directly at 0 °C, 73 % (isolated yield) of aryl thioether product was obtained (Equation 10). However, even in the presence of large excess of arylzinc species (3.2 mmol), the conversion of *N*-thioimide (1 mmol) remains at 95%. Meanwhile, no side reaction was observed for the *N*-thioimide by GC. However, it seemed that the *N*-thioimide showed oxidative ability in the presence of cobalt catalyst, since a large quantity of dimer of arylzinc species was formed. Thus, decreasing the *ratio* between arylzinc compound and sulfur source and increasing the chemoselectivity are the key points of this reaction.



Equation 10 C-S bond formation reaction employing arylzinc species obtained under cobalt catalyst

Then we used the commercial phenylzinc compound, which is solved in THF (0.5 M), instead of the arylzinc species that was formed under cobalt catalysis to see whether the cobalt salt plays a catalytic role in this reaction (Equation 11). When performing the reaction with the two substrates in the *ratio* of 1.5: 1, after stirring overnight at room temperature, about 60 % sulfur source was converted to the corresponding aryl thioether. No dimer of arylzinc conpound was formed in this case. It implies that this reaction may be a transition-metal free reaction. Without catalyst, nucleophilic arylzinc species can react with the electrophilic sulfur source directly and give the aryl thioether product. However, it seems that the arylzinc species is not nucleophilic enough to convert all the electrophilic reagents in the *ratio* of 1.5:1.

Nevertheless, we found that without cobalt catalysis in the medium, no dimer of arylzinc compound was formed. This gave us a clue that by introducing some additives into the medium, which may trap the cobalt catalyst, avoid the consumation of arylzinc species for the dimerization and increase the chemoselectivity of the reaction.



Equation 11 C-S bond formation reaction employing commercial arylzinc compound

Then we optimized the reaction conditions, at different temperatures or by introducing some additives, which tried to decrease the amount of arylzinc species (Table 20). Conducting the reaction at 50 ^{0}C only promoted the dimerization of arylzinc species and gave poor yield (Table 20, entry 1). Excellent yield was obtained when the reaction temperature was kept at – 10-0 ^{0}C. In this case, the conversion of *N*-thioimide was 100 % with 2.8 equivalents arylzinc species (Table 20, entry 2). However, decreasing the arylzinc species to 2.2 equivalents at this temperature, led to lower conversion (Table 20, entry 3).

According to our previous experience, adding THF into the medium may inhibit the catalytic ability of cobalt and decrease the side reation of this C-S coupling reaction (Table 20, entry 4). However, the yield of aryl thioether was not increased in this case. Introducing MVK (methyl vinyl ketone**)** into the medium, which is known to bind cobalt and to largely reduce or annihilate its catalytic activity (Table 20, entry 5), while keeping the aryl zinc species intact, may decrease the dimer of arylzinc species. However, by adding MVK to the medium, there was still large quantity of dimer of arylzinc species. A very recently report has found that even in the presence of trace metal catalyst,[132] the organometallic reagent are prone to dimerize easily with the proper oxidant. Introducing pyridine to the medium led to trace of C-S coupling product and dimer product (Table 20, entry 6). The yield of dimer of arylzinc species was

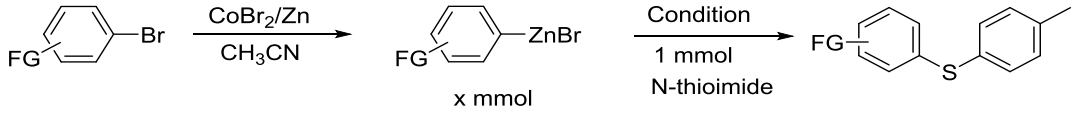
132 Kiefer, G.; Jeanbourquin, L.; Severin, K. *Angew. Chem., Int. Ed.* **2013,** *52*, 6302-6305. Among of these results, when $CoCl_2$ catalyst was using in as low as 0.004 mol%, the dimerization of Grignard reagents was still in 91 % yield in the presence of N_2O as an oxidant.

decreased apparently when NEt_3 was employed as the additive, however, it did not promote the conversion of *N*-thioimide (Table 20, entry 7).

Another idea is to usethe sterically hindered arylzinc species, which should be less prone to dimerize. 2-ethyl benzoate was attempted (Table 20, entry 8), however, the reaction still produced the dimer product as the main product.

Thus, some efforts were made to obtain high yield of aryl thioether by using less arylzinc species. However, it is still required 2.8 equivalents to obtain good results.

Table 20 C-S bond formation reaction employing arylzinc species



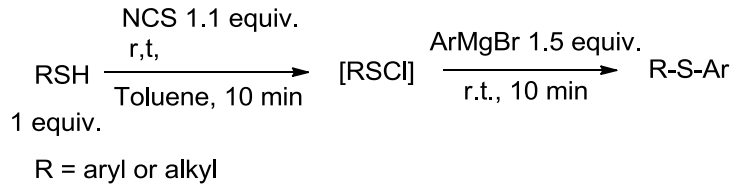
Entry	FG	X mmol	Condition	GC Yield
1	*p*-CO_2Et	3.2	0 to 50 °C	< 30 %
2	*p*-CO_2Et	2.8	-10 to 0 °C[a]	85 %[b]
3	*p*-CO_2Et	2.2	-10 to 0 °C[a]	50 %
4	*p*-CO_2Et	2.2	-10 to 0 °C[a, c]	50 %
5	*p*-CO_2Et	2.2	Pyridine 6 equiv. 0 °C	Trace
6	*p*-CO_2Et	2.2	MVK 40 mol%, 0 °C	40 %
7	*p*-CO_2Et	2.2	NEt_3 40 mol%, 0 °C	65 %
8	*o*-CO_2Et	2.2	0 °C	Trace

[a] NH_4Cl:ice = 3:1. [b] Conversion is 100 %. [c] THF as co-solvent.

During the course of these experiments, Lee's group reported the synthesis of aryl thioethers through the coupling of thiols with Grignard reagents in the presence of *N*-chlorosuccinimide (Equation 12).[133] NCS was used for the preparation of sulfenylchlorides. The corresponding sulfenylchlorides reacted with Grignard reagents quickly and provided good to excellent cross-coupling arylthioether products. Functional groups such as ester, fluoro and chloro are tolerated under this reaction conditions. This protocol seems very convenient since it was handled as "*one pot*" reaction. The succinimide which was formed in the first step has not to be removed. Unlike some previous "*one pot*" reports,[103,105] in which the diphenylzinc compounds or Grignard reagents are required to be in large excess (2.2 equiv. and 2.5 equiv.

133 Cheng, J.-H.; Ramesh, C.; Kao, H.-L.; Wang, Y.-J.; Chan, C.-C.; Lee, C.-F. *J. Org. Chem.* **2012,** *77*, 10369-10374.

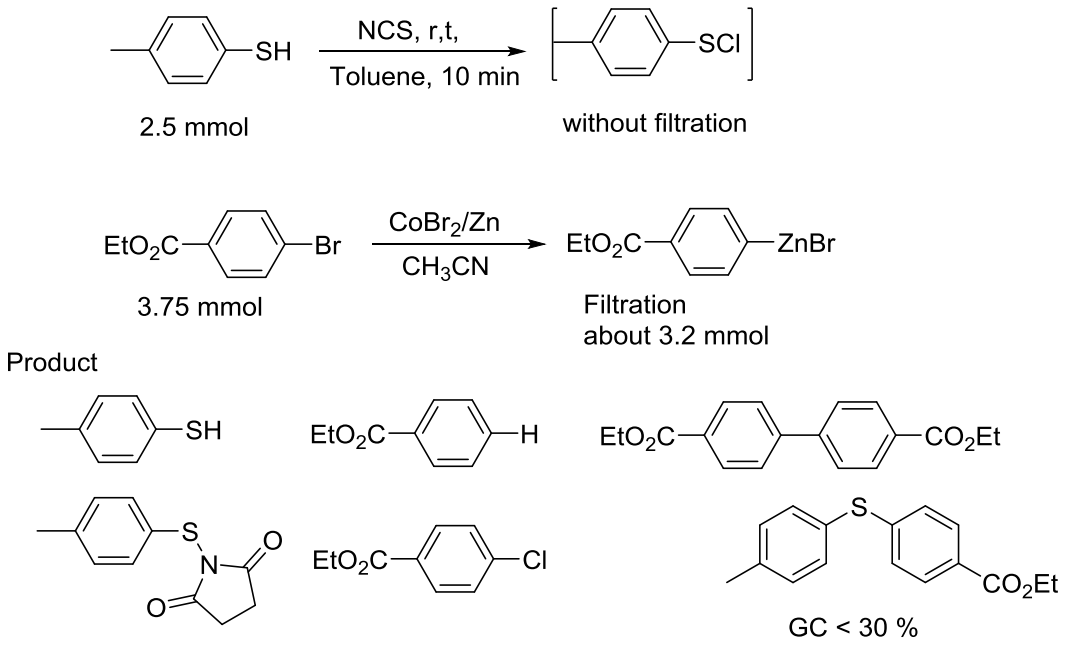
respectively) to achieve the high yields in the presence of succinimide, this report only employed 1.5 equivalent Grignard reagent and obtained good to excellent yields.



Equation 12 C-S coupling reaction with Grignard reagents.

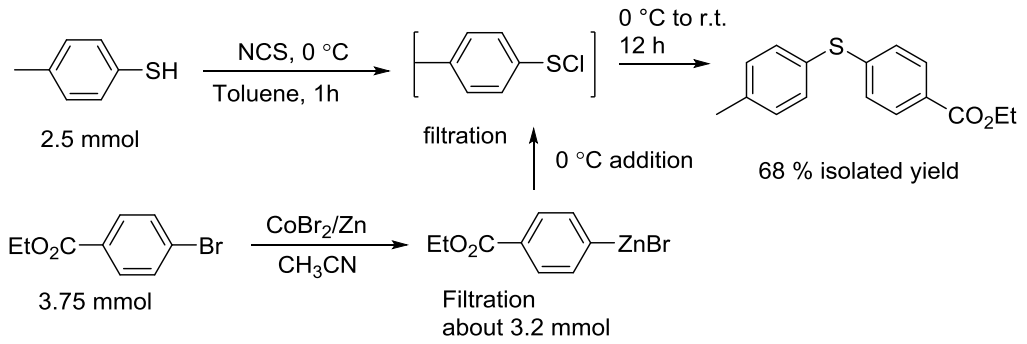
Therefore, it is quite interesting to extend this reaction, by employing arylzinc species instead of Grignard reagents to construct new C-S bond with sulfenylchlorides (Scheme 58). First, we followed the procedure of Lee's report, forming the sulfenylchloride in toluene without removing the succinimide, and then transfering the arylzinc species which obtained from Gosmini's method into this solution at room temperature. However, after several attempts, it only provided a mixture, which including the unreacted thiol, *N*-thioimide, chlorination product, reduction product, dimerization of arylzinc species, and poor yield of arylthioether product. It is proposed that the removing of succinimid is necessary, which avoids the protonated of arylzinc species. Besides, although the authors claimed that the sulfenylchlorides could be obtained from NCS under mild conditions as the literatures described,[134] the cited literatures always used polar solvent dichloromethane, but not with toluene. Moreover, sometimes very low temperature (-78 ^{0}C) is necessary.

134 (a) Schlosser, K. M.; Krasutsky, A. P.; Hamilton, H. W.; Reed, J. S.; Sexton, K. *Org. Lett*. **2004**, *6*, 819-822. (b) Kroll, F.; Morphy, R.; Rees, D.; Gani, D. *Tetrahedron Lett*. **1997**, *38*, 8573-8576. (c) Yadav, J. S.; Reddy, B. V. S.; Jain, R.; Baishya, G. *Tetrahedron Lett*. **2008**, *49*, 3015-3018.



Scheme 58 C-S coupling reaction of arylzinc species and sulfenylchlorides

Thus, we modified the condition of the synthesis of sulfenylchlorides by decreasing the temperature to 0 °C and increasing the reaction time to 1 hour (Scheme 59). Before introducing the arylzinc species, we removed the succinimide by syringe filtration. In this case, good yield was obtained when coupling 4-methylbenzenethiol with 4-(ethoxycarbonyl)phenyl zinc bromide. It is worth noting that the arylzinc species was in little excess (1.3 equivalents).



Scheme 59 C-S coupling reaction of arylzinc species and sulfenylchlorides

However, when explored some other arylzinc species (ketone and fluoride substituted), the side reactions, such as the chlorination of arylzinc compounds, or the formation of *N*-thioimide occurred seriously again. Only moderate yields were obtained (33 % and 38 % isolated yields respectively). It implied that the sulfenylchloride is not stable enough. Moreover, even without the triethylamine base, the reaction between thiol and

NCS still provides *N*-thioimide. Thus, it is not an ideal route to form the sulfenylchloride under this condition.

II-3 Conclusions and perspectives

In conclusion, N-thioimides can be used as an electrophilic sulfur source which reacts with the arylzinc species to provide the corresponding aryl thioether, although large quantity of arylzincs is necessary to obtain high yield. Moreover, the sulfenylchloride can be also employed as a sulfur source. However, the results are difficult to reproduce. The process seems a transition-metal free reaction. Future work should continue in the employment of N-thioimide as the electrophilic source. Some base may be helpful to increase the nucleophility of the arylzinc species, which may promote the C-S bond formation reaction.

Chapter 3 Cobalt-catalyzed Electrophilic Cyanation of Arylzincs with N-cyano-N-phenyl-p-methyl-benzenesulfonamide (NCTS)

I. Introduction

Benzonitriles represents an important role in natural products, pharmacy, dyes and electronic materials (Figure 9).[135] Meanwhile the nitrile group allows a multitude of transformations to other important functional groups, such as amines, amidines, tetrazoles, aldehydes, amides (Figure 10).[136]

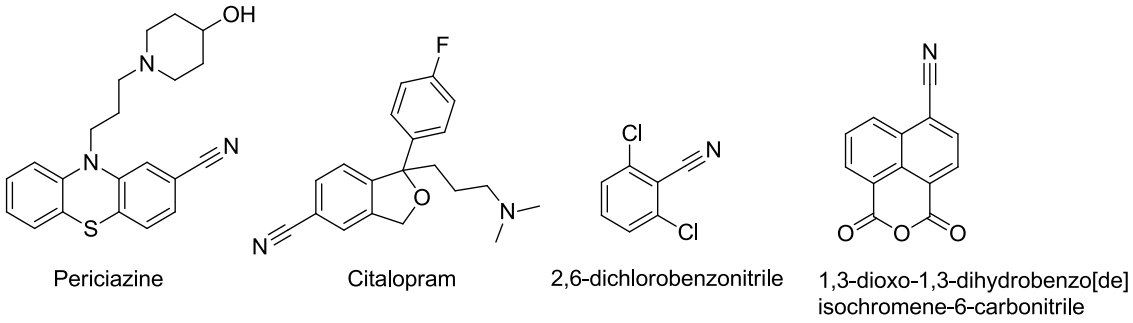


Figure 9 Examples of pharmaceutical, dyes and electronic materials benzonitrile structures

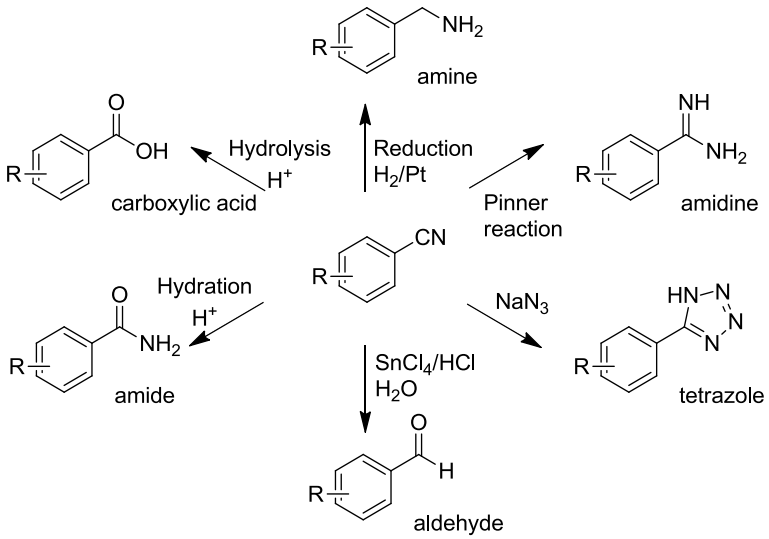
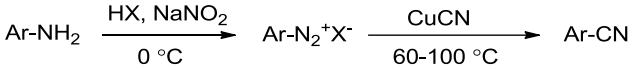


Figure 10 Representative synthetic applications of benzonitriles.

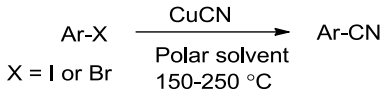
135 (a) Fatiadi, A. J. In *Preparation and Synthetic Applications of Cyano Compounds*; Patai, S., Rappaport, Z., Ed.; Wiley: New York, **1983**; (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, **1989**; (c) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Synthesis, Patents, Applications*, 4th ed.; Thieme: Stuttgart, Germany, **2001**; (d) Miller, J. S.; Manson, J. L. *Accounts Chem. Res.* **2001,** *34*, 563-570; (e) Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003,** *103*, 2035-2078; (f) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Wiley: Hoboken, NJ, **2007**.

136 (a) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011,** *40*, 5049-5067. (b) Kim, J.; Kim, H. J.; Chang, S. *Angew. Chem., In. Ed.* **2012,** *51*, 11948-11959.

In the early years, the Sandmeyer[123, 137] and Rosenmund-von Braun[138] reactions were the two most employed methods for the introduction of a cyano group onto the arenes (Equation 13 and Equation 14). However, both of them suffer from significant drawbacks: a stoichiometric amount of copper cyanide and relatively harsh conditions. Moreover, these methodologies are not applicable to most functionalized benzonitriles.



Equation 13 Sandmeyer reaction



Equation 14 Rosenmund-von Braun Reaction

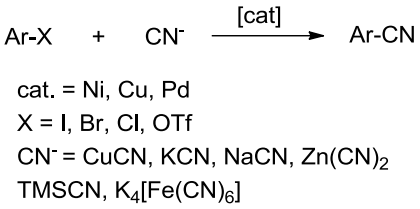
I-1 Nucleophilic cyanation reaction

In recent decades, transition-metal catalyzed nucleophilic cyanation reactions of aryl substrates have emerged as powerful alternatives to achieve the formation of the C-CN bond. In the presence of transition metal, Pd, Cu, or Ni catalysts, various cyanide sources, such as CuCN, [139] KCN, [140] NaCN, [141] $Zn(CN)_2$, [142] TMSCN, [143] or $K_4[Fe(CN)_6]$[144] react with functionalized aryl halides to provide the corresponding aryl nitriles (Scheme 60, Figure 11). They have been applied in both academic research and industry.

However, some limitations remain: 1) The concentration of cyanide has to be carefully controlled because of the high affinity of the cyanide ion towards the catalyst, high catalyst loading is generally required. 2) Most of these cyanide reagents are toxic and

137 Galli, C. *Chem. Rev*. **1988,** *88*, 765-792.
138 (a) Rosenmund, K. W.; Struck, E. *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1919,** *52*, 1749-1756; (b) Mowry, D. T. *Chem. Rev.* **1948,** *42*, 189-283.
139 Chen, J.; Sun, Y.; Liu, B.; Liu, D.; Cheng, J. *Chem. Commun.* **2012,** *48*, 449-451.
140 Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem. –Eur. J.* **2005,** *11*, 2483-2492.
141 Ushkov, A. V.; Grushin, V. V. *J. Am. Chem. Soc.* **2011,** *133*, 10999-11005.
142 Buono, F. G.; Chidambaram, R.; Mueller, R. H.; Waltermire, R. E. *Org. Lett.* **2008,** *10*, 5325-5328.
143 Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003,** *684*, 50-55.
144 Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2011,** *13*, 648-651.

need to be careful handled in order to avoid the generation of HCN. 3) Moreover, one equivalent of metal waste is produced during the reaction.



Scheme 60 Transition metal-catalyzed nucleophilic cyanation reactions

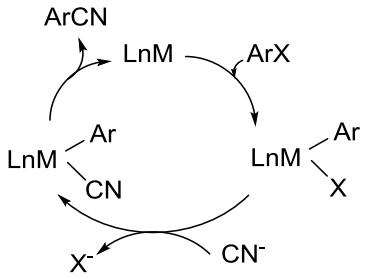
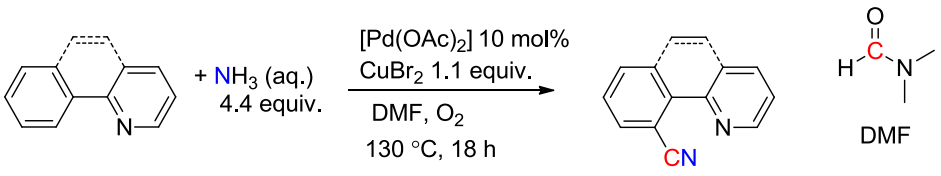


Figure 11 General mechanism of transition metal catalyzed nucleophilic cyanation reactions

I-2 Cyanation reaction without "CN" unit cyano-source

Before discussing electrophilic cyanation reaction, it is worth giving a brief introduction on the cyanation reactions which employ "non-CN-unit" cyano-source. The detailed mechanism of these reactions is not known, which is mainly due to the complexity of the reaction mixture. Nevertheless they generally require a stoichiometric amount of metal salt and harsh conditions.

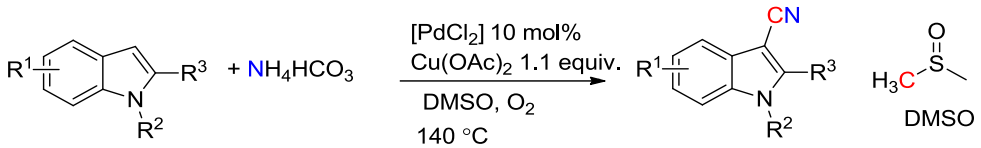
Chang and coworkers first found that DMF and aqueous ammonia may be used as a cyano-source. The process consists in a palladium-catalyzed C-H activation with copper mediated oxidation. Various 2-phenylpyridine and derivatives were cyanated directly (Equation 15).[145]



Equation 15 Combined "CN" source from NH_3 and DMF in the palladium-catalyzed cyanation of aryl C−H bonds

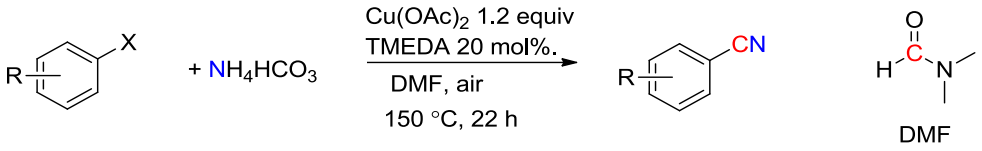
145 Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010,** *132,* 10272-10274.

Then Cheng's group used DMSO and ammonium bicarbonate as a combined cyano-source in a similar manner for the cyanation of indoles (Equation 16).[146]



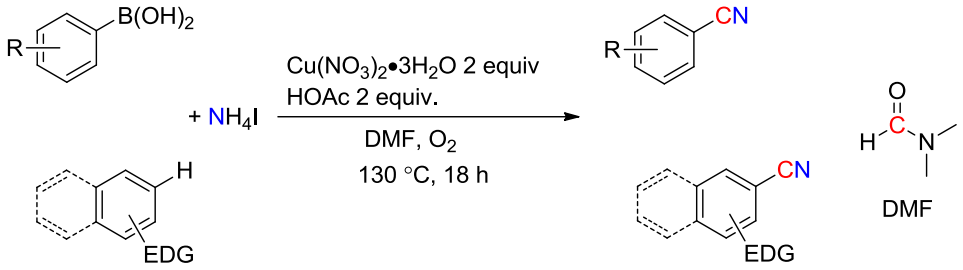
Equation 16 Combined "CN" source from NH_4HCO_3 and DMSO in the palladium-catalyzed cyanation of indole C−H bonds

Subsequently, they developed a palladium-free protocol, which combines ammonium bicarbonate and DMF as a cyano-source, and allows the cyanation of a series of electron-rich aryl halides (Equation 17).[147]



Equation 17 Combined "CN" source from NH_4HCO_3 and DMF in the copper-mediate cyanation of aryl halides

More recently, Chang and coworkers realized the cyanation of both aryl boronic acid and electron-rich benzenes using ammonium iodide and DMF in the presence of $Cu(NO_3)_2 \cdot 3H_2O$ (Equation 18).[148]

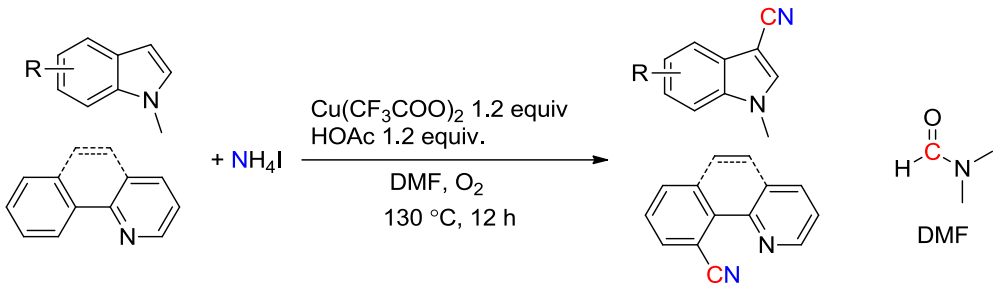


Equation 18 Combined "CN" source from NH_4I and DMF in the copper-mediate cyanation of boronic acid and electron-rich benzenes

Then they found more cost-efficient cyanation systems employing the same combined cyano-source. When performing the cyanation with NH_4I and DMF, the iodination of

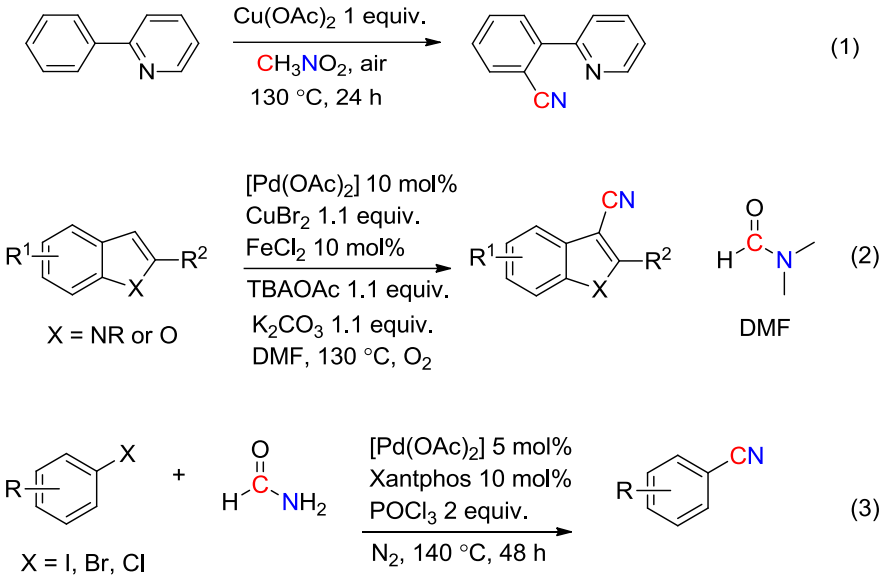
146 Ren, X.; Chen, J.; Chen, F.; Cheng, J. *Chem. Commun.* **2011,** *47*, 6725-6727.
147 Zhang, G.; Ren, X.; Chen, J.; Hu, M.; Cheng, J. *Org. Lett.* **2011,** *13*, 5004-5007.
148 Kim, J.; Choi, J.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2012,** *134*, 2528-2531.

the aromatic ring occurs first. [149] Then they were able to suppress the palladium catalyst, which represents an important economy to achieve the cyanation of indoles and 2-phenylpyridine derivatives (compared to Equation 15, Equation 19).[150]



Equation 19 Combined "CN" source from NH_4I and DMF in the copper-mediate cyanation of indoles and aryls C-H bonds

$MeNO_2$,[151] DMF[152] and formamide[153] are also efficient cyano-sources for the cyanation of 2-phenylpyridine derivatives, indoles and aryl halides respectively (Scheme 61, eq. 1-3), but all these reactions demand high temperatures.



Scheme 61 Independent "CN" source

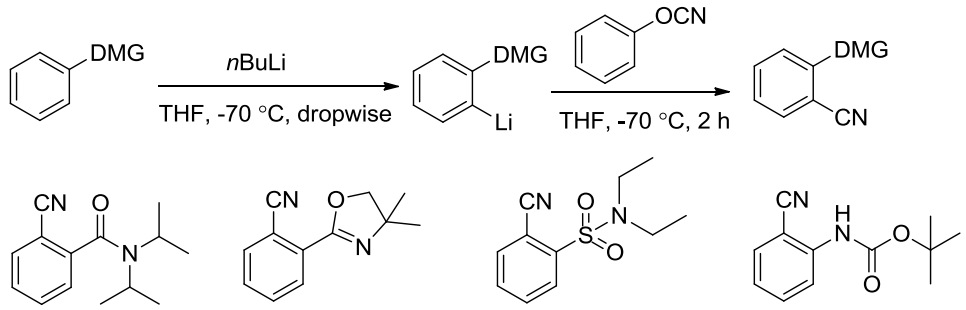
149 Krishna Mohan, K. V. V.; Narender, N.; Kulkarni, S. J. *Tetrahedron Lett.* **2004,** *45*, 8015-8018.
150 Kim, J.; Kim, H.; Chang, S. *Org. Lett.* **2012,** *14*, 3924-3927.
151 Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006,** *128*, 6790-6791.
152 Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011,** *133*, 12374-12377.
153 Sawant, D. N.; Wagh, Y. S.; Tambade, P. J.; Bhatte, K. D.; Bhanage, B. M. *Adv. Synth. Catal.* **2011,** *353*, 781-787.

I-3 Electrophilic cyanation reaction

Electrophilic cyanations have been less studied compared to nucleophilic ones. However, they represent useful complementary alternatives, which sometimes overcome the above mentioned drawbacks. In this section the cyanation reactions of different aryl-organometallic reagents with a variety of cyano-source will be summarized.

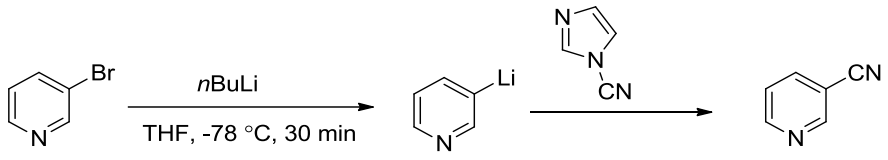
I-3-1 Aryl Lithium Reagents

Sato developed an efficient synthesis of *ortho*-cyanoarenes *via* directed lithiation followed by electrophilic cyanation with cyanatobenzene (Scheme 62).[154] This methodology requires the presence of a directed metalation group (DMG). Note that the fine controlling of the reaction temperature is necessary to ensure good yields. This method is a very efficient way for the synthesis of *ortho*-functional cyanoarenes.



Scheme 62 Cyanation reaction of aryl lithium reagent

Hamilton and coworkers demonstrated that 1-cyanoimidazole is a mild and efficient electrophilic cyanating agent with different nucleophilic reagents (amine, sulfur, and carbanion) (Scheme 63), but only one arylnitrile example was obtained from the aryl lithium reagent.[155]



Scheme 63 Cyanation reaction of aryl lithium reagent

154 (a) Sato, N.; Yue, Q. *Tetrahedron* **2003,** *59*, 5831-5836; (b) Sato, N. *Tetrahedron Lett.* **2002,** *43*, 6403-6404.

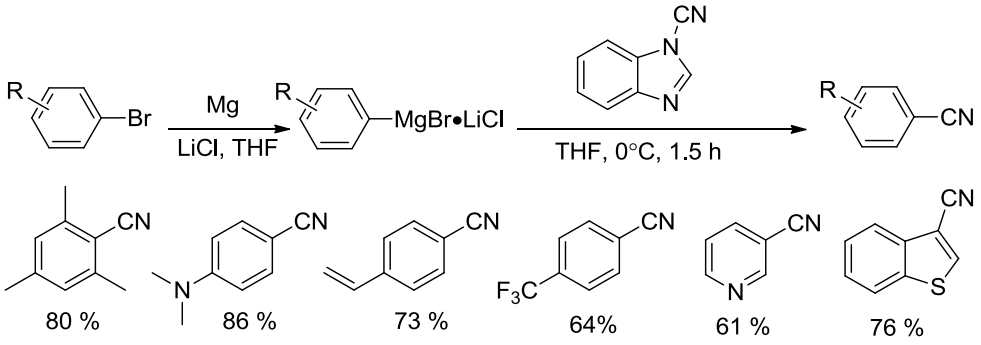
155 Wu, Y.-Q.; Limburg, D. C.; Wilkinson, D. E.; Hamilton, G. S. *Org. Lett.* **2000,** *2*, 795-797.

I-3-2 Aryl Stannanes Reagents

ClCN react with aryltrimethylstannanes in the presence of $AlCl_3$.[156] Only phenyl and toluene trimethylstannanes were investigated and provided moderate yields. Besides, the reaction of BrCN with aryl stannanes gave aryl bromides. Considering the toxicity of the organostannanes reagents,[157] the authors turned to a less hazard reagent, an organosilane derivative. However, they reported that phenyltrimethylsilane did not react with cyanogen chloride in this condition.

I-3-3 Grignard Reagents

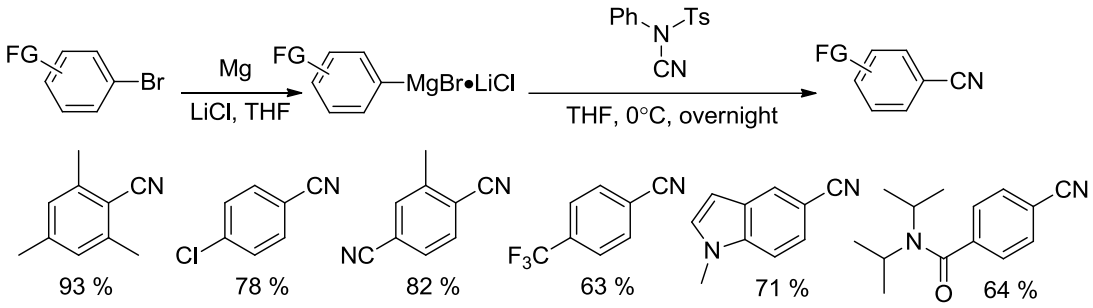
In the early years, the nucleophilic displacement of *p*-toluenesulfonyl cyanide[158] or 2-pyridyl cyanate[159] with phenylmagnesium bromide has been investigated. However, the scope of the Grignard reagents was not explored. Only in 2010, Beller and coworkers reported the electrophilic cyanation of aryl/heteroaryl Grignard reagents (Scheme 64).[160] After screening a series of nitrogen-bound cyano-group sources, they found that *N*-cyanobenzimidazole exhibited the highest reaction efficiency. Both electron-rich and electron-poor substrates were efficiently cyanated in good isolated yields, as well as sterically demanding molecules. This methodology was also applied in domino Grignard-coupling-cyanation sequence. The main drawback of this method is that the cyano-reagent is prepared from cyanogen bromide, which is quite toxic and dangerous.



Scheme 64 Electrophilic cyanation of aryl/heteroaryl Grignard reagents

156 Bartlett, E. H.; Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1972,** *46*, 267-269.
157 Gajda, M.; Jancso, A. (2010). "*Organotins, formation, use, speciation and toxicology*". *Metal ions in life sciences* (Cambridge: RSC publishing). *7*, Organometallics in environment and toxicology.
158 (a) van Leusen, A. M.; Jagt, J. C. *Tetrahedron Lett.* **1970,** *11*, 967-970; (b) van Leusen, A. M.; Iedema, A. J. W.; Strating, J. *Chem. Commun.* **1968,** 440-441.
159 Koo, J. S.; Lee, J. I. *Synthetic Commun.* **1996,** *26*, 3709-3713.
160 Anbarasan, P.; Neumann, H.; Beller, M. *Chem.-Eur. J.* **2010,** *16*, 4725-4728.

Later, Beller's group developed a novel and convenient synthesis of benzonitriles through aryl/heteroaryl Grignard reagents using a benign cyanating reagent, *N*-cyano-*N*-phenyl-*p*-methyl-benzenesulfonamide (NCTS) (Scheme 65).[161] NCTS was readily synthesized by the reaction of phenylurea with *p*-toluenesulfonyl chloride in pyridine in good yield.[162] It is a bench-stable, easy to handle and environmentally-benign electrophilic cyanating agent. Compared to the previous established electrophilic cyanating source, its synthesis does not require the highly toxic cyanogen halides, or similar cyanating precursors. The Grignard reagents were prepared *via* Knochel's procedure.[163] This method tolerates both electronically rich/poor groups at any place of the arene. Methoxy, diphenylamine, thioether, chloro, dioxane, amide, nitrile and heteroaryl substituted arene were cyanated in high yields. This methodology is cost-effective and environmentally-friendly.



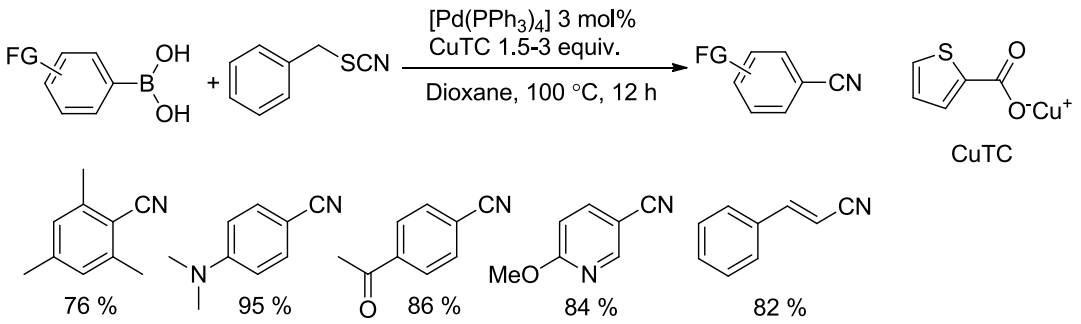
Scheme 65 Electrophilic cyanation of aryl/heteroaryl Grignard reagents

I-3-4 Aryl Boronic Acid Compounds

Liebeskind and coworker reported the first Pd-catalyzed, Cu-mediated (CuTC: Copper(I)-thiophene-2-carboxylate) cyanation of boronic acid with benzylthiocyanate. (Scheme 66)[164] Using this protocol, a variety of functionalized aryl nitriles was formed in high yields. It is a useful complementary method compared to that employing aryl

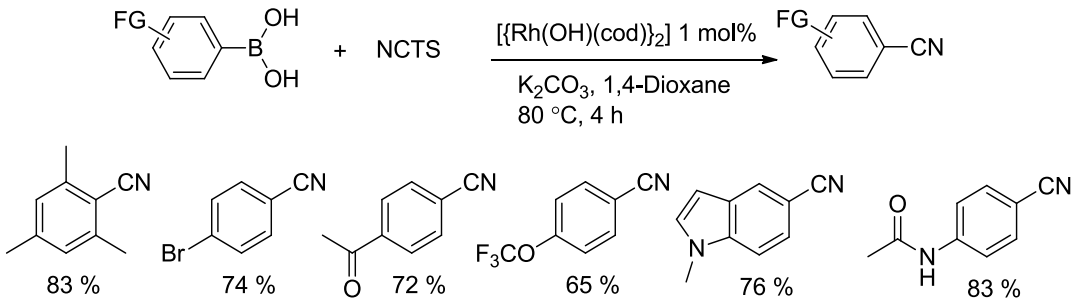
161 Anbarasan, P.; Neumann, H.; Beller, M. *Chem.-Eur. J.* **2011,** *17*, 4217-4222.
162 Kurzer, F. *J. Chem. Soc. (Resumed)* **1949**, 1034-1038.
163 (a) Knochel, P.; Krasovskiy, A.; Sapountzis, I. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, **2005**; Vol. 1, pp 109-172. (b) Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed*. **1998**, *37*, 1701–1703. (c) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed*. **2003**, *42*, 4302–4320. (c) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P.*Angew. Chem., Int. Ed*. **2008**, *47*, 6802–6806.
164 Zhang, Z.; Liebeskind, L. S. *Org. Lett.* **2006,** *8*, 4331-4333.

halides/pseudo-halides with cyanide sources in the presence of a transition-metal catalyst.



Scheme 66 Palladium-Catalyzed, copper(I)-mediated coupling of boronic acids and benzylthiocyanate

In 2011, Beller and coworkers demonstrated the first Rh-catalyzed cyanation of aryl boronic acids with NCTS under mild condition (Scheme 67).[165] A variety of interesting and important functional groups is tolerated, such as ketone, bromide, chloride, heterocycles and acidic protons. Sterically demanding aryl boronic acids were also cyanated efficiently under these conditions. Besides, this procedure was combined with some direct borylations of arenes to give the corresponding nitriles in a straightforward manner.



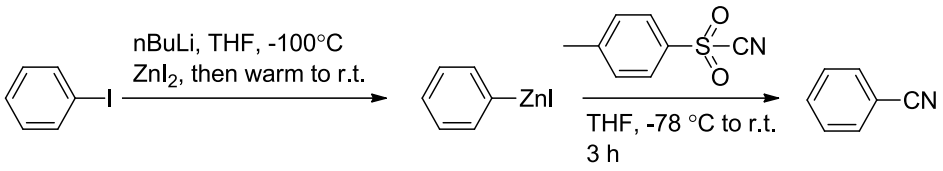
Scheme 67 Rh-catalyzed electrophilic cyanation of aryl boronic acids

I-3-5 Arylzinc Compounds

In 1993, Knochel and coworkers developed an efficient method for the cyanation of a wide range of organozinc compounds with *p*-toluenesulfonyl cyanide (Scheme 68).[166] It is a transition-metal free procedure. Various alkyl, alkenyl, alkynyl, benzylic, aromatic and heterocyclic organozinc halides bearing functional groups such as ester,

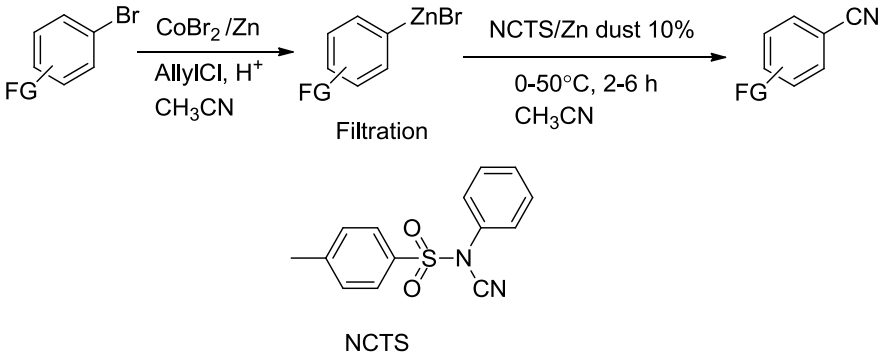
165 Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011,** *50*, 519-522.
166 Klement, I.; Lennick, K.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1993,** *34*, 4623-4626.

boronic ester, nitrile, halide and trialkoxysilyl groups. However, not much variety in the arylzinc species was presented. Moreover, the preparation of this organozinc compound required very low temperatures and used TsCN, which is dangerous to prepare or shipping.



Scheme 68 Cyanation reaction of arylzinc compound with TsCN

In summary, these umpolung procedures have made important contributions to the synthesis of arylnitriles. Many efficient methodologies have been developed. However, these methods also suffer from some drawbacks in that they require either the use of stoichiometric co-catalyst or additives, or expensive catalyst, or dangerous CN sources. Moreover, high or very low temperatures are often necessary to ensure a good yield. Thus, despite impressive recent progress, the development of a mild, inexpensive, and simple procedure remains highly desirable. Arylzinc reagents, whose synthesis is well understood, are good candidates as nucleophilic partners. Following our results concerning the amination of arylzinc compounds with *N*-chloroamines, we developed the cyanation of arylzinc reagents using NCTS as the electrophilic CN source (Equation 20). A variety of functionalized arylzinc species was transformed to the corresponding arylnitriles as will be discussed in the next section.



Equation 20 Cobalt-catalyzed electrophilic cyanation of arylzinc species

II. Results and discussions

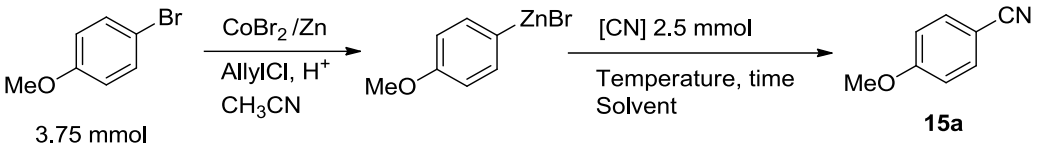
II-1 Optimization of the reaction conditions

First investigations concerned the cobalt-catalyzed coupling of 4-methoxyphenylzinc bromide with NCTS to allow a preliminary optimization of the procedure (Table 21). The arylzinc species is prepared from the corresponding arylbromide (ArBr) in presence of cobalt in acetonitrile as developed in our group.[111b-e] This reaction mixture was directly added to a solution of NCTS (0.67 equiv with respect to ArBr, 2.5 M) in CH_3CN without further addition of cobalt. NCTS was quickly consumed within 3 h at room temperature and 41 % of the cross-coupling product was isolated (Table 21 entry 1). We found that the extra Zn dust would consume NCTS quickly. Therefore, filtration of the arylzinc compound should improve the yields. However, after 12 h, the conversion of NCTS did not exceed 50 % and this conversion was improved to 70 % by increasing the temperature to 50 °C (Table 21 entries 2 and 3). As the transformation of the arylzinc compound seems to be poorly selective giving cyanation and dimerization products, we tried to increase the selectivity by slowing the reaction which can be achieved by adding THF. However, adding THF in the medium would decrease both the conversion of the arylzinc species as well as NCTS and only gave very poor yield (Table 21 entries 4 and 5). In some described nucleophilic cyanation methodologies, Zn dust was used to avoid catalyst poisoning by cyanide.[167] Therefore, the reaction was conducted as usual, with filtration of the unreacted Zn dust and then addition of 10 mol% Zn dust into the reaction medium. It accelerates the reaction efficiently (Table 21, entry 6) at room temperature with only 10 % NCTS left. Increasing the temperature induced a total conversion of the cyano- source within 4 h and provided an excellent yield of 84% (Table 21, entry 7).[168]

167 (a) Wang, X.; Zhi, B.; Baum, J.; Chen, Y.; Crockett, R.; Huang, L.; Eisenberg, S.; Ng, J.; Larsen, R.; Martinelli, M.; Reider, P. *J. Org. Chem.* **2006,** *71*, 4021-4023; (b) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011,** *111*, 2177-2250.

168 The consummation of Zn dust is diverse depending on the different arylbromides. That's why we donot use less Zu dust in the formation of arylzinc species step.

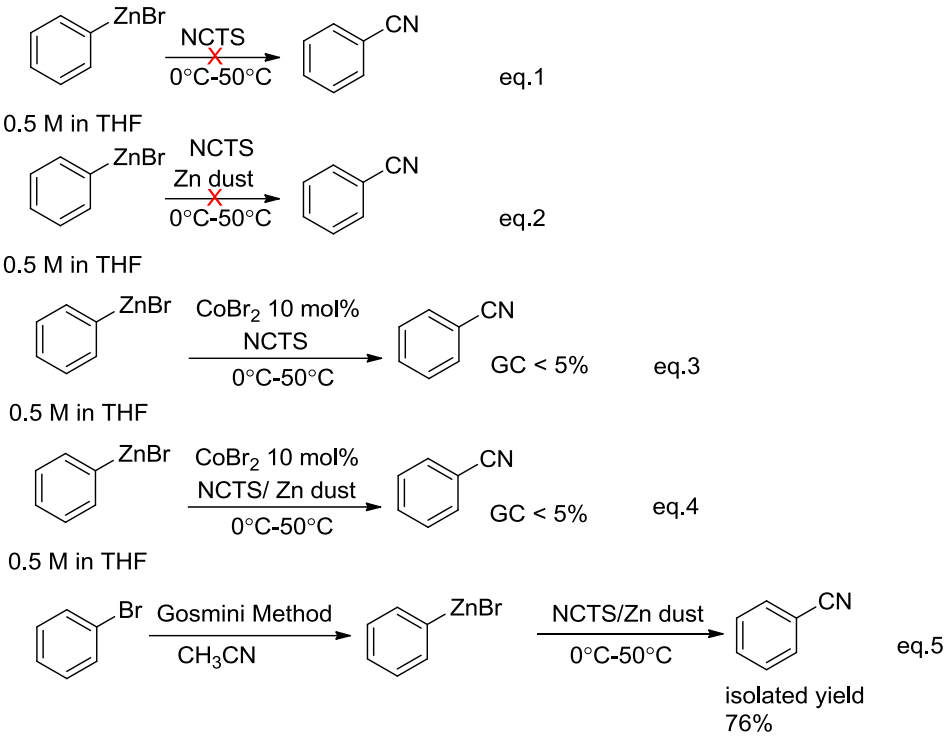
Table 21 Optimization of the reaction conditions



Entry	Condition	Yield %[a]
1	Without filteration, r.t., 3 h	41[b]
2	Filter all the Zn dust, r. t., 12 h	(30)
3	Filter all the Zn dust, 50 °C, 12 h	(50)
4	Filter the Zn dust, add THF 3 ml, 12 h, 50 °C	(< 10 %)
5	Filter the Zn dust and add THF 1 ml, 48 h	(< 10 %)
6	Filter all the Zn dust, then add 10 mol% Zn, r.t., 16 h	(67)
7	**Filter all the Zn dust, then add 10 mol% Zn, 50 °C, 6h**	**84[b]**

[a]Yields in parentheses are corrected GC results. (Decane as internal standard). [b] Isolated yields.

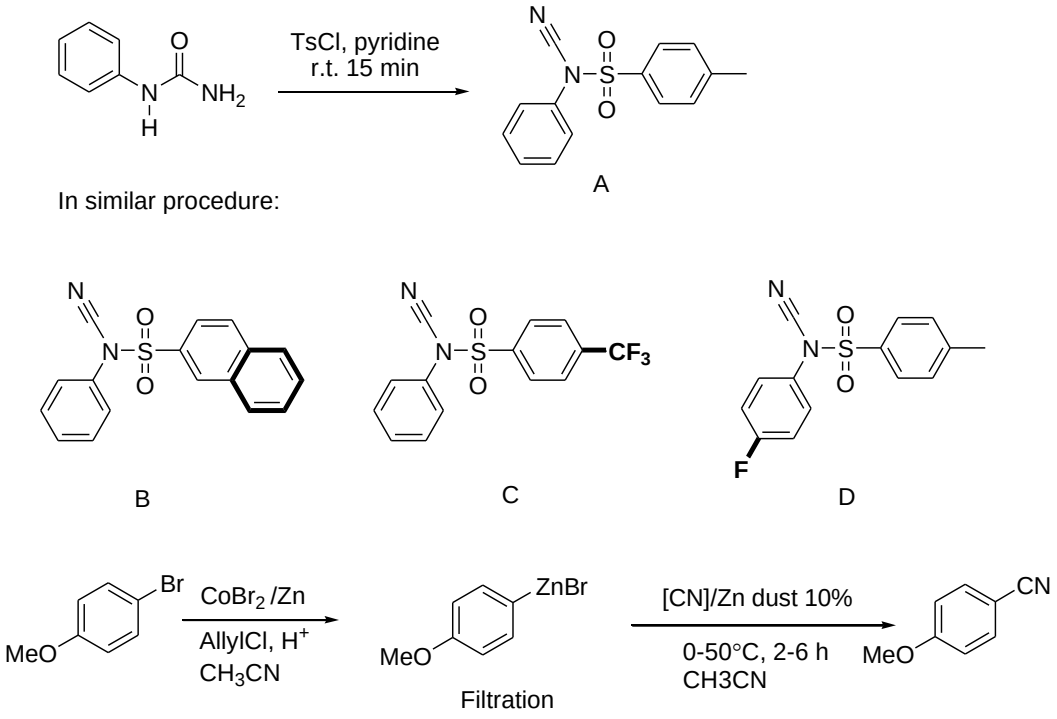
Some controlled reactions were also conducted to demonstrate that $CoBr_2$ has a catalytic role in this cyanation process (Scheme 69). A commercial phenylzinc bromide solution in THF was added to a solution of NCTS in THF at 0 °C. The reaction mixture was heated to 50 °C. After overnight stirring at this temperature, no arylnitrile product was detected by GC (Scheme 69, equation.1). 10 mol% Zn dust was introduced in the reaction medium, but no arylnitrile formed either (Scheme 69, equation.2). Introducing $CoBr_2$ and Zn dust to this phenylzinc bromide solution in the cyanation step provide only traces of arylnitrile (Scheme 69, equation.3 and 4). As mentioned above, the addition of THF in the medium gave poor yield of C-CN product. Finally, by employing Gosmini's method that form the phenylzinc in the presence of $CoBr_2$ in CH_3CN, under the standard condition, good yield of phenylnitrile was only obtained when forming the PhZnBr reagent in situ using the method developed by our group, which supposes to have $CoBr_2$ and Zn at the beginning of the reaction (Scheme 69, equation.5).



Scheme 69 Control experiments to demonstrate that cobalt is required for the cyanation process

II-2 Investigation the reactivity of analogous cyanide resources

The effect of different substituted arylsulphonylcyanamides was also investigated (Figure 12). They were synthesized by a similar procedure. The reaction of substituted arylsulphonyl chlorides with substituted arylureas in pyridine at room temperature deliver **B**, **C** and **D**. Compared to **A**, hindered naphthyl analogue **B** displays lower activity and gave only very poor yields of cyanation product. Although electron-withdrawing group on the aryl moity should make the $ArNSO_2Ar'$ fragment a better leaving group, only poor yields of cyanation were obtained, when reacting **B**, **C** and **D** with ArZnBr. Comparing reagents **C** and **D** it seems that the electron-withdrawing group on the *N*-phenyl group has higher effect than that on the sulphonyl group. It may due to the sulfonyl group shield some electron effect from the trifluoromethane group.



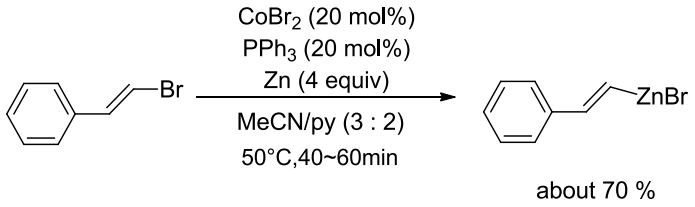
A: 84 % (isolated)
B: 5 %
C: 35 %
D: 17 % (all corrected GC)

Figure 12 analogous cyanide resources

II-3 The scope of aryl halides

We then extended the scope of aryl bromides (Table 22) using the optimized conditions. Moderate to excellent yields were obtained. Methoxy group on the *para*-position of the arene is the more favorable substrate, the yields are lower when it is located the *meta*- or *ortho*- position. (Table 22, entries 1 to 3). Small group like methyl- on the *ortho*-position still provided excellent yields (Table 22, entries 4 and 5). Aryl halide without any substitutent (Table 22, entry 6), or with a variety of functional groups, such as thioether, acetate, chloro-, sulfone-, fluoro-, trifluomethane-, dimethylamine-, ester, dioxane all provide moderate to excellent yields (Table 22, entries 6 to 15). Some of them are quite difficult to obtain by the electrophilic cyanation of Grignard reagents, since ArMgX are too strong nucleophiles to tolerate them. However, we found that the presence of a strong chelating group (ketone or nitrile) on arylzinc species inhibit the reaction. The main problem may be the chelation of the metal center, which lose its catalytic ability. In these cases, only trace products were observed (identified by HRMS). Moreover, as mentioned in chapter 2, when preparing the arylzinc chloride, pyridine and bipyridine are necessary, then they hamper the cyanation step. Only poor

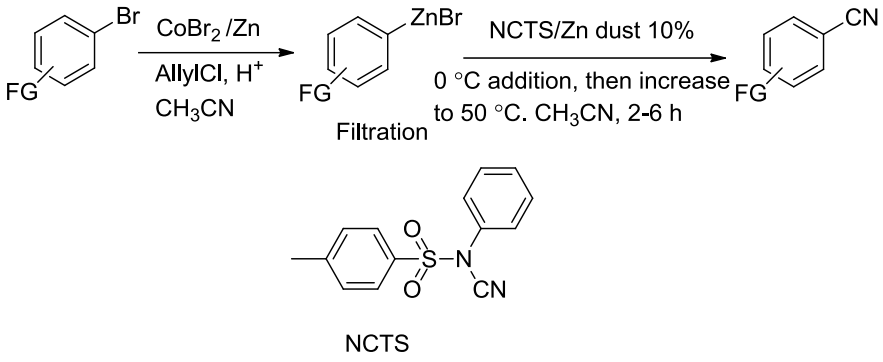
yield of arylnitrile product was observed with aryl chlorides after several attempts. The cyanation of bromostyrene suffered from the same problem since the formation of vinylzinc bromide required pyridine (Equation 21). Heterocyclic (pyridine and thiophene) arylzinc species did not work very well either (GC yield is up to 30 %).

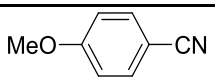
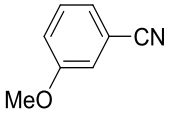
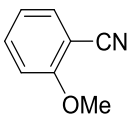
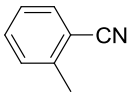


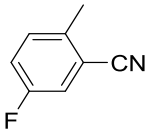
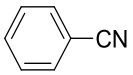
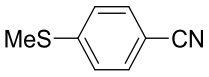
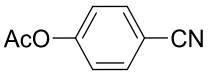
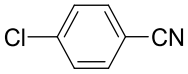
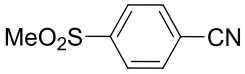
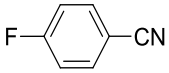
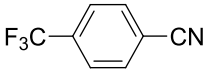
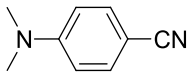
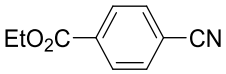
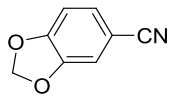
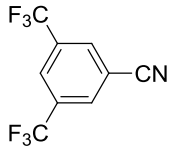
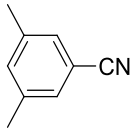
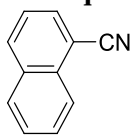
Equation 21 The formation of styrinezinc bromide under cobalt catalyst

Di-substituted, electron-withdrawing or donating group substituted arylzinc compounds also reacted nicely (Table 22, enties 16 and 17), naphthyl arylzinc gave an excellent yield product (Table 22, entry 18).

Table 22 The scope of aryl halides



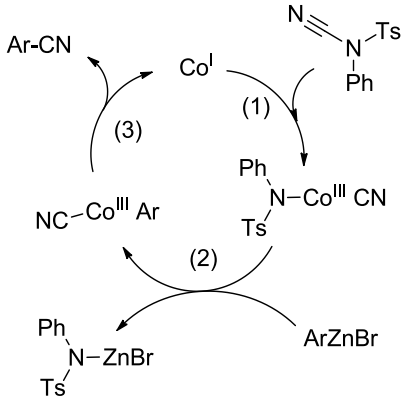
Entry	FG [a]	Product	Reaction time	Yield [b]
1	*p*-OMe	 **15a**	2.5 h	84
2	*m*-OMe	 **15b**	2.5 h	57
3	*o*-OMe	 **15c**	6 h	58
4	*o*-Me	 **15d**	6 h	98

5	2-F,5-Me	 **15e**	6 h	82
6	H	 **15f**	6 h	76
7	*p*-SMe	 **15g**	6 h	76
8	*p*-OCOMe	 **15h**	6 h	40
9	*p*-Cl	 **15i**	6 h	63
10	*p*-SO_2Me	 **15j**	6 h	47[c]
11	*p*-F	 **15k**	6 h	74
12	*p*-CF_3	 **15l**	6 h	68
13	*p*-NMe_2	 **15m**	6 h	68
14	*p*-CO_2Et	 **15n**	6 h	72
15	1,2-(methylenedioxy)	 **15o**	6 h	79
16	3,5-diCF_3	 **15p**	6 h	40[d]
17	3,5-diMe	 **15q**	6 h	56
18	1-naphthyl	 **15r**	6 h	79

[a] Ratio of ArBr to NCTS is 1.5:1. [b] Isolated yields. [c] ^1H NMR yield. [d] GC yield.

II-4 Postulated mechanism

A plausible mechanism for the present transformation is shown in Scheme 70 on the basis of our experience on electrophilic reaction with arylzinc compounds and other related reports.[120, 165,] In Scheme 70, (1) reaction of NCTS (electrophile) with the metal catalyst (Co^1) would introduce the cyano- group on the metal center to form TsPhN-Co-CN. (2) Transmetalation of arylzinc species with TsPhN-Co-CN to furnish Ar-Co-CN and (3) final reductive elimination to form the Ar-CN product.



Scheme 70 Postulated mechanism

II-5 Conclusions and perspectives

In conclusion, we developed the first cobalt-catalyzed electrophilic cyanation reactions of arylzinc compounds. By using a safe and efficient CN source, a variety of aromatic nitriles with different functional groups, such as ester, acetate, sulfone, chlorine, fluorine, trifluoromethyl, methoxy, thioether, dimethylaniline, dioxane were obtained with moderate to excellent yields under mild conditions. We also investigate the reactivity of analogous cyanide resources.

However, there are several issues that still remain to be resolved: (1) Although some sensitive functional groups are tolerated in this medium, several other important chelating groups, such as nitrile, ketone or heteroaromatic substituted groups are not compatible. Efforts were made to solve these limitations but without effect. The scope has still to be broadened. (2) Further mechanistic investigations should allow to understand why electron-withdrawing group substituted cyano-source is less reactive. (3) Since we have developed the electrophilic C-N and C-CN bond formation of the arylzinc species obtained under cobalt catalysis, some other electrophiles may be

investigated to realize the new C-C or C-heteroatom bond, such as C-F and C-CF_3 bond formation.

General conclusion

First, a novel and simple procedure for the direct coupling of alkyl halides and allylic acetates or carbonates was developed. It is the first report for the metal-catalyzed allyl-alkyl coupling reactions without handling air and moisture sensitive stoichiometric organometallic reagents. The cobalt/Mn system was able to couple various alkyl halides and allyl-acetates or-carbonates efficiently. This method has a broad substrate scope and a high degree functional group tolerance.

The protocol was also tentatively extended to the direct allyl-allyl coupling reactions. However, after a series of optimization experiments, only moderate yield was obtained. Direct reductive coupling of two different alkyl halides remain also disappointing. Only alkyl-alkyl homocoupling reactions proceed well under the developed conditions. Both primary and secondary alkyl halides were coupled efficiently and many functional groups were tolerated, among which some are difficult to dimerize by other metal-mediated protocoles.

The second chapter deals with a highly efficient method for the synthesis of new aryl-alkyl amines. Arylzinc compounds, whose synthesis is well mastered in our group, react with N-chloroamine to give the C-N coupling product. A variety of polyfunctionalized aryl-alkylamine was synthesized in good to excellent yields under very mild conditions. It is attractive for the synthesis of functionalized arylamines compared to some other procedures.

Following the results of the cobalt-catalyzed electrophilic amination reactions of arylzinc compounds, extension to C-S bond formation was attempted. *N*-thioimide was employed as an electrophilic sulfur source. Good yield of C-S product was obtained, but it required a large excess of arylzinc species, which is not cost-efficient. Besides, the reaction was found to be a cobalt-catalyst free reaction. This work required further studies to decrease the loading of arylzinc compounds.

The third chapter described a novel cobalt-catalyzed electrophilic cyanation of arylzinc species. Employing a safe and non-toxic cynano-source, N-cyano-N-phenyl-p-methyl-benzenesulfonamide (NCTS), various functionalized benzonitriles were obtained under very mild conditions. This method showed some advantages compared to some other

electrophilic cyanation reactions. Moreover, it is complementary to nucleophilic cyanation pathways.

In general conclusion, some progresses were made in the cobalt-catalyzed C-C and C-N bonds formation reactions. The procedures are easy-handled, cost-effective and highly efficient and therefore attractive for the synthesis of new functionalized molecules.

Experimental Sections

General Informations.

All reactions were carried out in the air unless otherwise precised. All glasswares were oven dried before use. All solvents and chemicals were obtained commercially and used as received unless otherwise mentioned. Nuclear magnetic resonance spectra were recorded on a Bruker AC-300 SY spectrometer operating at 300.0 MHz for ^{1}H, 75.0 MHz for ^{13}C and 282.0 MHz for ^{19}F. Solvent peaks are used as internal references relative to ^{1}H ($CDCl_3$ = 7.26 ppm) and ^{13}C ($CDCl_3$ = 77.0 ppm) chemical shifts (ppm). Coupling constants are given in hertz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quadruplet, quint, quintet, m, multiplet. IR spectra were recorded on a Perkin Elmer spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Gas Liquid Chromatography (GLC) was performed on a Perichrom PR 2100 2317 Series gas chromatograph equipped with a split-mode, capillary injection system and flame ionisation detectors using a SGE apolar ID-BP1 (25 m x 0.32 mm) column. Mass spectra were recorded with a GCQ Thermoelectron spectrometer coupled to a gas chromatograph Varian (25-m CPSIL5CB/MS capillary column). Column chromatography was performed on silica gel with 60, 70-230 mesh with petroleum ether/diethyl ether as eluent. Filtration of arylzinc containing solutions was carried on using Whatman PTFE syringe filter ReZist-30 0.45 µm.

I Cobalt-Catalyzed Reductive Coupling of Alkyl Halides or Allylic Acetate/Carbonates

I-1 Cobalt-catalyzed reductive allyl-alkyl crosscoupling reactions

I-1-1 General procedure for allylic acetate synthesis

The allylic alcohol (0.125 mol) and the acetic anhydride (0.125 mol) were introduced in a 100 mL round bottom flask with a catalytic amount of DMAP (dimethylaminopyridine). Then a mixture of pyridine (10 ml) and dichloromethane (10 ml) was added dropwise at 0 °C over 30 min. After the addition, the reaction mixture was stirred at room temperature until allylic alcohol was consumed (5 hours). The amount of the corresponding AllylOAc was measured by GC. The reaction mixture was poured into HCl (2 M) and the organic layer was extracted, neutralized by a saturated $NaHCO_3$ solution and dried by $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel afforded the allylic acetate.

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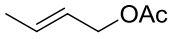
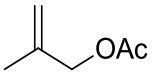
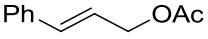
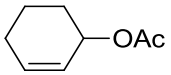
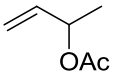
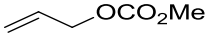
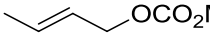
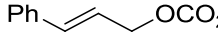
				

I-1-2 General procedure for allylic carbonate synthesis

A solution of the allylic alcohol (0.05 mol) and pyridine (10 mL) in dry ether (10 mL) was cooled to 0 °C under nitrogen. [169] To this solution, methyl chloroformate (0.05 mol) was added dropwise through a dropping funnel over 30 min. White precipitate appeared and the resultant suspension was stirred for 5 h at room temperature until the reaction was complete, (GC analysis). Then the solution was quenched by HCl (2 M), the organic layer was extracted, washed by saturated $CuSO_4$ solution to remove excess pyridine and dried by $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel afforded the allylic carbonate.

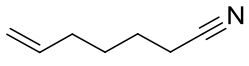
CAS: 35466-83-2	CAS : 87802-95-7	CAS : 85217-69-2
		

I-1-3 Cross-coupling of alkyl halides with allylic acetate

General Procedure: To a solution of $CoBr_2$ (10 mol%, 0.25 mmol, 55 mg) and manganese powder (3.8 equiv., 9.5 mmol, 500 mg) in CH_3CN (3 mL) was added at room temperature the corresponding allylic acetate (5 mmol). Manganese powder was activated by traces of trifluoroacetic acid (50 µL) and the medium was then stirred at room temperature for 5 minutes until smoke disappeared. At this time, pyridine, (0.5 mL) and alkyl halide (2.5 mmol) were added and the medium was stirred at 80 °C for allylic acetate until alkyl halide was consumed (3 to 12 h). The mixture was then poured into a solution of 2 M HCl (50 mL). The mixture was stirred vigorously until layers turned clear. The solution was extracted with Et_2O (3 x 50 ml), washed with brine (1 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification of the resulting oil by flash chromatography over silica with petroleum ether/diethyl ether mixtures afforded the pure compounds.

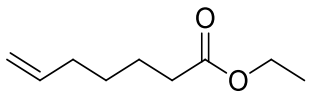
169 Minami, I.; Tsuji, J. *Tetrahedron* **1987**, *43*, 3903-3915.

I-1-4 Cross-coupling compounds



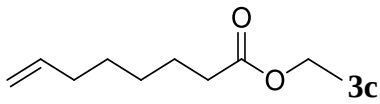
3a

Hept-6-ene nitrile $C_7H_{11}N$: CAS: 5048-25-9: Prepared according to the general procedure from 4-bromobutyronitrile (370 mg, 2.50 mmol). Purification on silica gel petroleum ether-diethyl ether (9:1) afforded the title compound as clear colorless oil (246 mg, 90% yield). **IR** (cm^{-1}) 2950, 2252, 1644; 1450, 1430, 1009. **HMRS** (EI+) ($C_7H_{11}N$) calculated m/z: 109.0891, found m/z: 109.0890. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.76 (vdt, *J* =16.5, 6.5, and 10.0 Hz, 1H), 4.98 (m, 2H), 2.33 (m, 2H), 2.06 (t, *J* =7.1 Hz, 2H), 1.65 (m, 2H), 1.53 (m, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 137.5, 118.9, 115.3, 32.7, 27.6, 24.6, 16.9.[170]



3b

Ethyl hept-6-enoate $C_9H_{16}O_2$: CAS: 25118-23-4. Prepared according to the general procedure from ethyl 4-bromobutanoate (487 mg, 2.50 mmol). Purification on silica gel petroleum ether-diethyl ether (9:1) afforded the title compound as clear colorless oil (343 mg, 88% yield). **IR** (cm^{-1}) 2940, 1735, 1260, 1160, 903. **HRMS** (EI+) ($C_9H_{16}O_2$) calculated m/z: 156.1150, found m/z: 156.1152. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.77 (ddt, *J* =17.0, 7.0, and 10.0 Hz, 1H), 4.95 (m, 2H), 4.11 (q, *J* =7.0 Hz, 2H), 2.27 (t, *J* =7.0 Hz, 2H), 2.06 (vq, *J* =7.0 Hz, 2H), 1.64 (vqt, *J* =7.0 Hz, 2H), 1.44-1.24 (m, 5H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.2, 137.9, 114.3, 59.7, 41.0, 33.8, 28.0, 22.2, 13.9.[171]



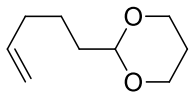
3c

Ethyl oct-7-enoate $C_{10}H_{18}O_2$: Prepared according to the general procedure from ethyl 5-bromopentanoate (523 mg, 2.50 mmol). Purification on silica gel petroleum ether-diethyl ether (9:1) afforded the title compound as clear colorless oil (425 mg, 90%

170 Nishiyama, H.; Sakuta, K.; Osaka, N.; Arai, H.; Matsumoto, M.; Itoh, K.*Tetrahedron* **1988**, *44*, 2413-2426.

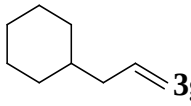
171 Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790-8795.

yield). **IR** (cm^{-1}) 2858, 1741; 1382, 1350, 1235, 1073. **HRMS** (EI+) ($C_{10}H_{18}O_2$) calculated m/z: 170.1307, found m/z 170.1310. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.75 (ddt, *J* =17.0, 6.5, and 10.0 Hz,, 1H), 4.92-5.00 (m, 2H), 4.10 (q, *J* =7.0 Hz, 2H), 2.26 (t, *J* =7.0 Hz, 2H), 2.01 (m, 2H), 1.58 (qt, *J* =7.0 Hz, 2H), 1.38-1.18 (m, 7H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 174.1, 138.5, 114.2, 60.2, 34.11 (CH2), 33.3, 28.34 (CH2), 24.6, 14.0.[172]



3d

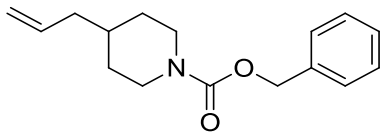
2-(pent-4-en-1-yl)-1,3-dioxane $C_9H_{16}O_2$: Prepared according to the general procedure from 2-(2-bromoethyl)-1,3-dioxane (488 mg, 2.50 mmol). After drying from $MgSO_4$, evaporate the solvent (diethyl ether) carefully and keep the rescue of 70% yield. **IR** (cm^{-1}) 1640, 1140, 1172, 1215, 996, 908. **HRMS** (EI+) **(**$C_9H_{16}O_2$**):** calculated m/z: 156.1150, found: 156.1149. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.70 (ddt, *J* =17.0, 6.5, and 10.5 Hz, 1H), 4.90 (dm, *J* =17.0 Hz, 2H), 4.49 (t, *J* =5.0 Hz, 1H), 4.08 (vdd, *J* =10.0; 5.0 Hz 2H), 3.74 (vdd, *J* =10.0, 5.0 Hz, 2H), 2.05 (m, 2H), 1.53, 1.19 (m, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 138.2, 114.5, 110.3, 66.7, 34.2, 33.3, 25.5, 20.5.[173]



3g

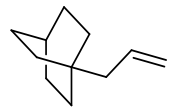
Allylcyclohexane C_9H_{16}: CAS: 2114-42-3. Prepared according to the general procedure from bromocyclohexane (408 mg, 2.5 mmol). Eluated from the column with petrol etherdiethyl ether (99:1) together with some bicyclohexane, the yield was estimated from proton NMR: yield 81%.). **IR** (cm^{-1}) 2940, 1638; 1260, 1160, 905. **HRMS** (EI+) (C_9H_{16}) calculated m/z: 124.1252, found m/z; 124.1250. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.78 (m, 1H), 5.01 (m, 2H), 1.96 (t, *J*= 6.2 Hz, 2H), 1.40-1.29 (m, 11H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 137.6, 115.2, 41.6, 33.3, 29.3, 27.9, 26.5, 22.6, 20.7.[174]

172 Wnuk, S. F.; Rios, J. M.; Khan, J. K.; Hsu, Y.-L. *J. Org. Chem*. **2000**, *65*, 4169–4174.
173 Widenhoefer, R. A., A. Vadehra *Tetrahedron Lett*. **1999**, *40*, 8499-8502.
174 Brown, H. C.; Rangaishenvi, M. V. *Tetrahedron Lett*. **1990**, *31*, 7115-7118.



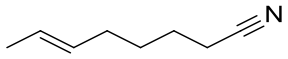
3i

Benzyl 4-allylpiperidine-1-carboxylate $C_{16}H_{21}NO_2$: Prepared according to the general procedure from benzyl 4-bromopiperidine-1-carboxylate (745 mg, 2.50 mmol). Eluated from the column with petrol ether-diethyl ether (1:1) as a yellow oil (635 mg). (Crude, mixed with some reduction product, the yield was calculated by the integration of proton NMR, in 70%, 444 mg.) **HRMS** (EI+) **(**$C_{16}H_{21}NO_2$**):** calculated m/z: 259.1572, found: 259.1571. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.36-7.28 (m, 5H), 5.75 (m, H), 5.15 (s, 2H), 5.04 (m, 2H), 3.98-3.38 (m, 4H), 2.78 (m, 2H), 1.13-2.07 (m, 5H).



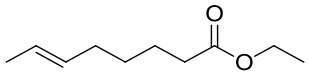
3j

1-allylbicyclo[2.2.2]octane $C_{11}H_{18}$: CAS: 22922-62-9. Prepared according to the general procedure from 1-bromobicyclo[2.2.2]octane (472 mg, 2.50 mmol). Mixed with some bicyclo[2.2.2]octane. GC yield is 60% according to the corrected internal standard. HRMS (EI+) ($C_{11}H_{18}$): calculated m/z: 150.1409, found: 150.1411.



4a

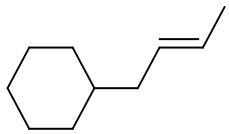
(*E*)-oct-6-enenitrile $C_8H_{13}N$: CAS: 25143-91-3. Prepared according to the general procedure from (*E*)-crotyl acetate (570 mg, 5 mmol) and 4-bromobutyronitrile (370 mg, 2.50 mmol). Eluated from the column with petrol ether-diethyl ether (9:1) in 63% (194 mg) yield as a colorless oil. **IR** (cm^{-1}) 2940, 2250, 1260, 1161, 964. **HRMS** (EI+) ($C_8H_{13}N$) calculated m/z: 123.1048, found m/z; 123.104. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.40 (m, 2H), 2.31 (m, 3H), 2.01 (q, *J* =7.0 Hz, 2H), 1.63 (m, 4H), 1.48 (p, *J* =7.0 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 130.0, 125.8, 119.8, 31.6, 28.4, 24.7, 17.9, 17.0.



4b

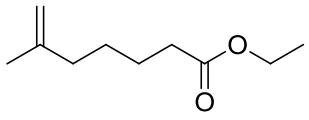
(*E*)-ethyl oct-6-enoate $C_{10}H_{18}O_2$: CAS: 25143-92-4. Prepared according to the general procedure from (E)-crotyl acetate (570 mg, 5 mmol) and ethyl 4-bromobutanoate (487

mg, 2.50 mmol). Purification on silica gel petroleum ether-diethyl ether (9:1) afforded the title compound in 72% (306 mg) yield as a colorless oil. **IR** (cm^{-1}) 2932, 1735; 1460, 1160, 967. **HRMS** (EI+) **(**$C_{10}H_{18}O_2$**):** calculated m/z: 170.1307, found: 170.1308. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.42-5.36 (m, 2H), 4.13 (q, *J* =7.0 Hz, 2H), 2.29 (t, *J* =7.0 Hz, 2H), 2.0 (vq, *J* =7.0 Hz, 2H), 1.62 (d, *J* =5.0 Hz, 3H), 1.35 (m, 2H), 1.23 (t, *J* =7.0 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.6, 130.7, 124.9, 60.0, 34.0, 31.9, 28.8, 24.2, 17.7, 14.0.[175]



4c

(E)-but-2-en-1-ylcyclohexane $C_{10}H_{18}$: CAS: 5860-28-6. Prepared according to the general procedure from (E)-crotyl acetate (570 mg, 5 mmol) and bromocyclohexane (408 mg, 2.5 mmol). Eluated from the column with petrol ether-diethyl ether (99:1) together with some bicyclohexane. Yield determined by **^{1}H-NMR** at 75% yield. **IR** (cm^{-1}) 2922, 1663; 1596, 1447, 962. **HRMS** (EI+) ($C_{10}H_{18}$): calculated m/z: 138.1409, found: 138.1407. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.39 (m, 2H), 1.84 (t, *J* =6.7 Hz, 3H), 1.69-1.17 (m, 13H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 130.0, 125.5, 40.7, 38.1, 33.1, 30.2, 26.7, 26.6, 26.4, 17.9.

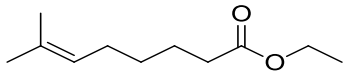


4d

Ethyl 6-methylhept-6-enoate $C_{10}H_{18}O_2$: CAS: 166533-72-8. Prepared according to the general procedure from 2-methylallyl acetate (570 mg, 5 mmol) and ethyl 4-bromobutanoate (487 mg, 2.50 mmol). Eluated from the column with petrol ether-diethyl ether (9:1) together with some remaining allylic acetate, the yield was caculated from proton NMR: yield 88% as a colorless oil. **IR** (cm^{-1}) 3071, 2920, 1728, 1647, 1450, 1354. **HRMS** (EI+) **(**$C_{10}H_{18}O_2$**):** calculated m/z: 170.1307, found: 170.1307. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 4.69 (m, 1H), 4.65 (m, 1H), 4.12 (q, *J* =7.0 Hz, 2H), 2.32 (t, *J* =7.0 Hz, 2H), 2.04 (t, *J* =7.0 Hz, 2H), 1.69 (s, 3H), 1.61 (qt, *J* =7.0 Hz, 2H),

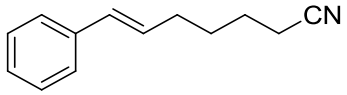
175 Kirihara, M.; Yokoyama, S.; Kakuda, H.; Momose, T. *Tetrahedron.* **1998**, *54*, 13943-13954.

1.24 (t, *J* =7.0 Hz, 3H), 1.46 (m, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.7, 145.5, 110.0, 60.2, 37.4, 34.2, 27.0, 24.6, 22.3, 14.3.[176]



4e

Ethyl 7-methyloct-6-enoate $C_{11}H_{20}O_2$: CAS: 109976-58-1. Prepared according to the general procedure from prenyl acetate (640 mg, 5 mmol) and ethyl 4-bromobutanoate (487 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (9:1) in 67% (308 mg) yield as a colorless oil**. IR** (cm^{-1}) 2911, 1731, 1649, 1458, 1435, 1205, 964. **HRMS** (EI+) **(**$C_{11}H_{20}O_2$**):** calculated m/z: 184.1463, found: 184.1460. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.09 (m, 1H), 4.12 (q, *J* =7.0 Hz, 2H), 2.28 (t, *J* =7.5 Hz, 2H), 1.99 (q, *J* =7.0 Hz, 2H), 1.67 (s, 3H), 1.64-1.59 (m, 5H), 1.34(qt, *J* =7.5 Hz, 2H), 1.24 (t, *J* =7.0 Hz, 3H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.8, 131.7, 124.2, 60.1, 34.3, 29.32, 27.6, 25.7, 24.6, 17.6, 14.3.[177]

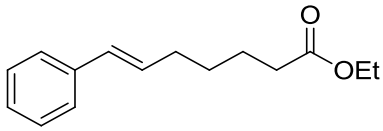


4f

(*E*)-7-phenylhept-6-enenitrile $C_{13}H_{15}N$: CAS: 119220-49-4. Prepared according to the general procedure from E-cinnamyl acetate (880 mg, 5 mmol) and 4-bromobutyronitrile (370 mg, 2.50 mmol). First eluated from the column with pure pentane to wash the by-product dimer of cinammyl acetate, then eluated from the column with pentane-diethyl ether (1:1) in 71% (329 mg) yield as a colorless oil. . **IR** (cm^{-1}) 3035, 2923, 2256, 1604, 1503, 1456, 960. **HRMS** (EI+) ($C_{13}H_{15}N$): calculated m/z: 185.1204, found: 185.1200. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.41-7.32 (m, 5H), 6.48 (d, *J* =16.0 Hz, 1H), 6.22 (td, *J* =16.0, 7.0 Hz, 1H), 2.37 (t, *J* =7.0 Hz, 2H), 2.30 (q, *J* =6.0 Hz, 2H), 2.14 (m, 2H), 1.71 (m, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 137.2, 130.5, 129.2, 128.3, 126.9, 125.8, 119.5, 31.9, 30.0, 24.6, 16.8.[170]

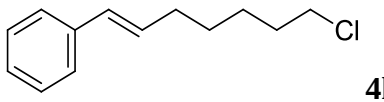
176 Bauta , W. E.; Booth, J.; Bos, M. E.; DeLuca, M.; Diorazio, L.; Donohoe, T. J.; Frost, C.; Magnus, N.; Magnus, P.; Mendoza, J.; Pye, P.; Tarrant, J. G.; Thom, S.; Ujjainwalla F. *Tetrahedron*. **1996**, *52*, 14081-14102.

177 Sim, T. B.; Choi, J.; Joung, M. J.; Yoon, N. M. *J. Org. Chem*. **1997**, *62*, 2357-2361.



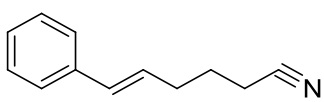
4g

(*E*)-ethyl 7-phenylhept-6-enoate $C_{15}H_{20}O_2$: CAS: 13159-25-6. Prepared according to the general procedure from E-cinnamyl acetate (880 mg, 5 mmol) and ethyl 4-bromobutanoate (487 mg, 2.50 mmol). First eluated from the column with pure pentane to wash the byproduct dimer of cinammyl acetate, then eluated from the column with pentane-diethyl ether (1:1) in 81% (470 mg) yield as a colorless oil. **IR** (cm^{-1}) 3035, 2944, 1730, 1602, 1451, 964. **HRMS** (EI+) ($C_{15}H_{20}O_2$): calculated m/z: 232.1463, found: 232.1460. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.40-7.23 (m, 5H), 6.46 (d, *J* =16.0 Hz, 1H), 6.25 (qt, *J* =16.0; 7.0 Hz, 1H), 4.19 (q, *J* =7.0 Hz, 2H), 2.37 (t, *J* =7.5 Hz, 2H), 2.24 (vq, *J* =7.0 Hz, 2H), 1.77 (vqt, *J* =7.1 Hz, 2H), 1.58 (vqt, *J* =7.0 Hz, 2H), 1.30 (t, *J* =7.0 Hz, 3H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.6, 137.5, 130.1, 130.0, 128.3, 126.7, 125.8, 60.1, 34.0, 32.6, 29.6, 28.7, 24.4, 14.1.



4h

(*E*)-(7-chlorohept-1-en-1-yl)benzene $C_{13}H_{17}Cl$: CAS: 86542-33-8. Prepared according to the general procedure from E-cinnamyl acetate (880 mg, 5 mmol) and 1-bromo-4chlorobutane (429 mg, 2.50 mmol). First eluated from the column with pure pentane to wash the byproduct dimer of cinammyl acetate, then eluated from the column with pentane-diethyl ether (1:1) in 77% (401 mg) yield as a white solid. **IR** (cm^{-1}) 3025, 2911, 1594, 1490, 1446, 962. **HRMS** (EI+) ($C_{13}H_{17}Cl$): calculated m/z: 208.1019, found: 208.1019. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.38-7.24 (m, 5H), 6.46 (d, *J* =16.0 Hz, 1H), 6.26 (td, *J* =16.0, 7.0 Hz, 1H), 3.59 (vtd, *J* =7.0, 1.0 Hz, 2H), 2.27 (m, 2H), 1.85 (m, 2H), 1.55 (m, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 137.7, 130.5, 130.1, 128.5, 126.8, 125.9, 45.0, 32.8, 32.5, 28.6, 26.4.[178]

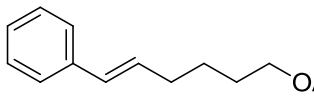


4i

(*E*)-6-phenylhex-5-enenitrile $C_{12}H_{13}N$: CAS: 16424-52-5**.** Prepared according to the

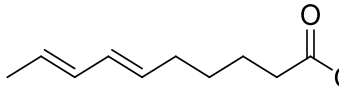
178 Terao, J.; Watabe, H.; Miyamoto, M.; Kambe, N. *Bull. Chem. Soc. Jpn*, **2003**, *76*, 2209-2214.

general procedure from E-cinnamyl acetate (880 mg, 5 mmol) and 3-chloropropanenitrile (224 mg, 2.50 mmol). First eluated from the column with pure pentane to wash the by-product dimer of cinammyl acetate, then eluated from the column with pentane-diethyl ether (1:1) in 98% yield as a color oil.**IR** (cm^{-1}) 3032, 2250, 1502, 965. **HRMS** (EI+) ($C_{12}H_{13}N$**):** calculated m/z: 171.1048, found: 171.1050. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.41-7.26 (m, 5H), 6.53 (d, *J* =16.0 Hz, 1H), 6.17 (dt, *J* =16.0, 7.0 Hz, 1H), 2.40 (t, *J* =7.0 Hz, 4H), 1.86 (qt, *J* =7.0 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 136.9, 131.8, 128.4, 127.5, 127.2, 125.9, 119.5, 31.5, 24.8, 16.3.[179]



4j

(*E*)-6-phenylhex-5-en-1-yl acetate $C_{14}H_{18}O_2$: CAS: 92655-06-6. Prepared according to the general procedure from E-cinnamyl acetate (880 mg, 5 mmol) and 3-bromopropyl acetate (452 mg, 2.50 mmol). First eluated from the column with pure petrol ether to wash the byproduct dimer of cinammyl acetate, then eluated from the column with petrol ether-diethyl ether (1:1) in 68% (370 mg) yield as a colorless oil. **IR** (cm^{-1}) 2858, 1700; 1646, 1617, 1556, 1455, 1232, 1040. **HRMS** (EI+) ($C_{14}H_{18}O_2$**):** calculated m/z: 218.1307, found: 218.1307. **^{1}H-NMR** (300 MHz, $CDCl_3$) d/ppm: 7.34-7.20 (m, 5H), 6.38 (d, *J* =15.8 Hz, 1H), 6.23 (dt, *J* =15.8, 7.0 Hz, 1H), 4.09 (t, *J* =6.6 Hz, 2H), 2.27 (m, *J* =7.0 Hz, 2H), 2.06 (s, 3H), 1.70 (p, *J* =7.1 Hz, 2H), 1.55 (p, *J* =7.1 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) d/ppm: 171.2, 137.6, 130.3, 130.2, 128.5, 126.9, 125.9, 64.4, 32.5, 28.1, 25.6, 21.0.[180]

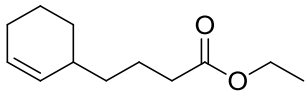


4k

(6*E*, 8*E*)-ethyl deca-6,8-dienoate $C_{12}H_{20}O_2$: Prepared according to the general procedure from (2E,4E)-hexa-2,4-dien-1-yl acetate (700 mg, 5 mmol) and ethyl 4-bromobutanoate (487 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (95:5) in 52% (255 mg) yield as a colorless oil. **IR** (cm^{-1}): 2978, 2803, 1734, 1381, 1350, 1184, 1076. **HRMS** (EI+) **(**$C_{12}H_{20}O_2$**):** calculated m/z: 196.1463,

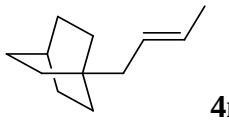
179 Giese, B.; Gebhardt, T. *Helv. Chim. Acta*, **1991**, *74*, 1143–1155.
180 Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc*. **2010**, *132*, 13981-13983.

found: 196.1460. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.97 (d, *J* =15.0 Hz, 2H), 5.63-5.42 (m, 2H), 4.08 (qt, *J* =7.0 Hz, 2H), 2.24 (dt, *J* =7.5, 4.0 Hz, 2H), 2.03 (m, 2H), 1.68 (d, *J* =6.0 Hz, 3H), 1.58 (vqt, *J* =8.0 Hz, 2H), 1.38 (dt, *J* =8.0, 7.0 Hz, 2H), 1.20 (t, *J* =7.0 Hz, 3H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.5, 131.4, 131.1, 130.5, 126.8, 60.0, 34.0, 32.0, 28.7, 24.3, 17.9, 14.0.



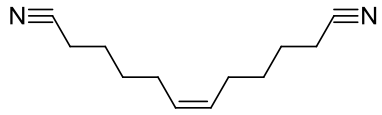
4l

Ethyl 4-(cyclohex-2-en-1-yl)butanoate $C_{12}H_{20}O_2$: Prepared according to the general procedure from cyclohex-2-en-1-yl acetate (700 mg, 5 mmol) and ethyl 4-bromobutanoate (487 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (9:1) in 38% (186 mg) yield as a colorless oil. **IR** (cm^{-1}): 2979, 2868, 1742.00, 1297, 1188, 1073. **HRMS** (EI+) **(**$C_{12}H_{20}O_2$**):** calculated m/z: 196.1463, found: 196.1454. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.68-5.52 (m, 2H), 4.12 (q, *J* =7.01 Hz, 2H), 2.27 (vt, *J* =7.5 Hz, 2H), 1.68-1.60 (m, 3H), 1.27-1.13 (m, 6H), 0.89-0.86 (m, 5H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 174.1, 132.1, 127.4, 60.6, 36.6, 36.2, 35.2, 35.0, 28.1, 25.7, 21.8, 14.7.



4n

(*E*)-1-(but-2-en-1-yl)bicyclo[2.2.2]octane $C_{12}H_{20}$: Prepared according to the general procedure from but-3-en-2-yl acetate (570 mg, 5 mmol) and 1-bromobicyclo[2.2.2]octane (472 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (99:1) in 66% (271 mg) yield as a colorless oil. . **IR** (cm^{-1}) 2908, 1624, 1450, 1214, 1157, 950. **HRMS** (EI+) ($C_{12}H_{20}$): calculated m/z: 164.1565, found: 164.1572. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.40 (m, 2H), 1.93 (m, 3H), 1.77-1.27 (m, 15H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 127.0, 126.8, 47.7, 42.4, 37.7, 37.1, 28.8, 28.3, 18.0.

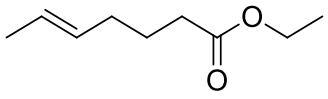


4o

(Z)-dodec-6-enedinitrile $C_{12}H_{18}N_2$: Prepared according to the general procedure from (Z)-but-2-ene-1,4-diyl diacetate (430 mg, 5 mmol) and 4-bromobutyronitrile (370 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (9:1) in 76% (361 mg) yield as a colorless oil. **IR** (cm^{-1}): 2947, 2862, 2246, 1384, 1351, 1214. **HRMS** (EI+) **(**$C_{12}H_{18}N_2$**):** calculated m/z: 190.1470, found: 190.1472. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.38 (vtt, *J* =4.0, 1.5 Hz, 2H), 2.33 (m, 4H), 2.03 (m, 4H), 1.65 (m, 4H), 1.49 (m, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 130.0, 119.7, 31.5, 28.3, 24.2, 17.0.

I-1-5 Cross-coupling of alkyl halides with allylic carbonates

General Procedure: To a solution of $CoBr_2$ (10 mol%, 0.25 mmol, 55 mg) and manganese powder (3.8 equiv., 9.5 mmol, 500 mg) in CH_3CN (3 mL) was added at room temperature the corresponding allylic carbonate (5 mmol). Manganese powder was activated by traces of trifluoroacetic acid (50 µL) and the medium was then stirred at room temperature for 5 minutes until smoke disappeared. At this time, pyridine, (0.5 mL) and alkyl halide (2.5 mmol) were added and the medium was stirred at 50 °C for allylic carbonate until alkyl halide was consumed (4 to 12 h). The mixture was then poured into a solution of 2 M HCl (50 mL). The mixture was stirred vigorously until layers turned clear. The solution was extracted with Et_2O (3 x 50 ml), washed with brine (1 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification of the resulting oil by flash chromatography over silica with petroleum ether/diethyl ether mixtures afforded the pure compounds.



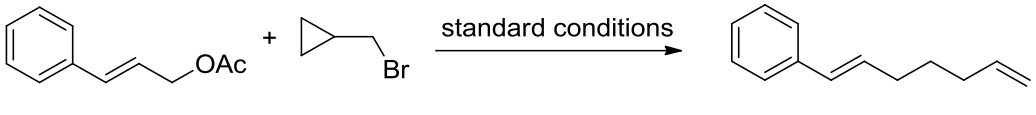
5b

(*E*)-ethyl hept-5-enoate $C_9H_{16}O_2$: CAS: 54340-69-1. Prepared according to the general procedure from E-crotyl carbonate (650 mg, 5 mmol) and ethyl 3-bromopropanoate (453 mg, 2.50 mmol). **IR** (cm^{-1}) 2922, 1732, 1720, 1651, 1159, 962. **HMRS** (EI+) ($C_9H_{16}O_2$) calculated m/z: 156.1150, found m/z; 156.1148. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 5.40 (m, 2H), 4.12 (q, *J* =7.0 Hz, 2H), 2.27 (dt, *J* =7.5, 5.0 Hz, 2H), 2.01 (m, 2H), 1.64 (m, 5H), 1.24 (t, *J* =7.0 Hz, 3H). ^{13}**C-NMR** (75 MHz,

$CDCl_3$) δ/ppm: 173.7, 130.1, 125.8, 60.1, 33.6, 31.8, 24.6, 17.8, 14.1.[181]

I-1-6 Mechanistic experiments

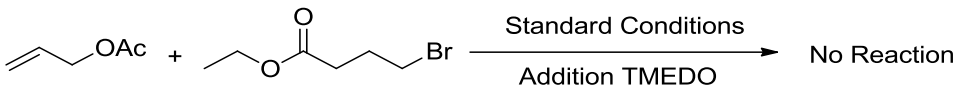
(a) Reaction between bromomethylcyclopropane and (*E*)-cinnamyl acetate :



6

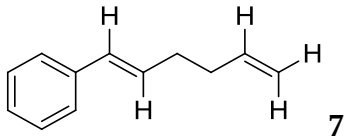
The general procedure described in part III was employed for the reaction between bromomethylcyclopropane (0.24 mL, 2.5 mmol) and (E)-cinnamyl acetate (880 mg, 5 mmol). The formation of 1-Phenyl-1,6-heptadiene was ascertained by ^{1}H NMR, (no peak was observed below 1.0 ppm). ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.40-7.20 (m, 5H), 6.39 (d, *J* =16.0 Hz, 1H), 6.25 (dt, *J* =16.0 Hz, 7.5 Hz, 1H), 5.85 (br. t, *J* = 16.0 Hz, 1H), 5.04-4.96 (m, *2*H), 2.20 (dt, *J* =8.0 Hz, 7.0 Hz 2H), 2.12 (m, 2H), 1.60 (m, 2H).

(b) **Reaction in the presence of TEMPO**:



For the reaction with TEMPO the general procedure was slightly modified with the introduction of the TEMPO reagent (78 mg, 0.5 mmol) before the addition of ethyl 4-bromobutanoate (0.35 mL, 2.5 mmol).

I-2 Cobalt-catalyzed reductive allyl-allyl cross-coupling reaction



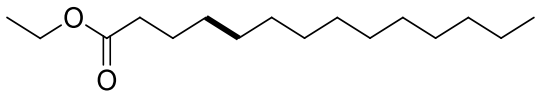
7

(*E*)-hexa-1,5-dien-1-ylbenzene $C_{12}H_{14}$: CAS# 56644-04-3. To a solution of $CoBr_2$ (10 mol%, 0.25 mmol, 55 mg) and manganese powder (3.8 equiv., 9.5 mmol, 500 mg) in CH_3CN (3 mL) was added at room temperature the allyl acetate (300 mg, 3 mmol). Manganese powder was activated by traces of trifluoroacetic acid (50 µL) and the

181 Thomas, H. G.; Thoennessen, F. *Chem. Ber*. **1979**, *112*, 2786-2797.

medium was then stirred at room temperature for 5 minutes until smoke disappeared. At this time, pyridine, (0.5 mL), PTA (10 mol%) and the other cinnamyl carbonate (440 mg, 2.5 mmol) were added and the medium was stirred at 50 °C (12 h). The mixture was then poured into a solution of 2 M HCl (50 mL). The mixture was stirred vigorously until layers turned clear. The solution was extracted with Et_2O (3 x 50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification of the resulting oil by flash chromatography over silica with petroleum ether/diethyl ether (99/1) mixtures afforded the white powder in 41 % (162 mg). **HRMS** (EI+) **(**$C_{12}H_{14}$**):** calculated m/z: 158.1096, found: 158.1098. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.42-7.23 (m, 4H), 6.47 (d, *J* = 15 Hz, 1H), 6.32 (dt, *J* =15.8, 7.0 Hz, 1H), 5.95 (m, 1H), 5.11 (m, 2H), 2.34 (m, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 138.1, 137.8, 130.2, 130.1, 128.5, 126.9, 126.0, 114.9, 33.6, 32.4.[182]

I-3 Cobalt-catalyzed reductive alkyl-alkyl cross-coupling reactions

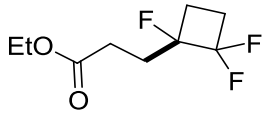


8

Ethyl tetradecanoate $C_{16}H_{32}O_2$: CAS# 124-06-1. To a solution of $CoBr_2$ (10 mol%, 0.25 mmol, 55 mg) and manganese powder (3.8 equiv., 9.5 mmol, 500 mg) in CH_3CN (3 mL) was added the 4-bromobutanoate (1461 mg, 7.50 mmol) at room temperature. Manganese powder was activated by traces of trifluoroacetic acid (50 µL) and the medium was then stirred at room temperature for 5 minutes until smoke disappeared. At this time, pyridine, (0.5 mL) and 1-bromodecane (550 mg, 2.5 mmol) were added and the medium were stirred at 80 °C until alkyl halide was consumed (6 h). The mixture was then poured into a solution of 2 M HCl (50 mL). The mixture was stirred vigorously until layers turned clear. The solution was extracted with Et_2O (3 x 50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification of the resulting oil by flash chromatography over silica with petroleum ether/diethyl ether (10/1) mixtures afforded the syringe crystal in 63 % (151 mg) yield. **HRMS** (EI+) **(**$C_{16}H_{32}O_2$**):** calculated m/z: 256.2402, found: 256.2404. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 4.14 (q, *J* = 7.4 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.63 (m, 2H), 1.27 (s, 23H), 0.9 (t, J = 6.9

182 Li, M.-B.; Wang, Y.; Tian, S.-K. *Angew. Chem., Int. Ed.* **2012,** *51*, 2968-2971.

Hz, 3H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.8, 60.1, 34.3, 31.9, 29.6, 29.6, 29.4, 29.3, 29.2, 29.1, 22.6, 14.2, 14.05.[183]



9

(R)-ethyl 3-(1,2,2-trifluorocyclobutyl)propanoate $C_9H_{13}F_3O_2$. CAS# no found. To a solution of $CoBr_2$ (10 mol%, 0.25 mmol, 55 mg), Zn dust (10 mmol, 600 mg) and allyl chloride (0.13 mL, 1.5 mmol) in CH_3CN (3 mL) was added at room temperature ethyl 3-bromopropanoate (0.91 g, 5 mmol). Zn dust was activated by traces of trifluoroacetic acid (50 µL) and the medium was then stirred at room temperature for 5 minutes until smoke disappeared. At this time, pyridine, (0.5 mL) and 1-chloro-1,2,2-trifluorocyclobutane (2.5 mmol) were added and the medium were stirred at 50 °C (18 h). The mixture was then poured into a solution of 2 M HCl (50 mL). The mixture was stirred vigorously until layers turned clear. The solution was extracted with Et_2O (3 x 50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the resulting oil by flash chromatography over silica with petroleum ether/diethyl ether mixtures (9:1) afforded the pure compounds. Eluated from the column with petroleum ether-diethyl ether (10:1) in 30 % (151 mg) yield as pale yellow oil. **HRMS** (EI+) **(**$C_9H_{13}F_3O_2$**):** calculated m/z: 210.0868, found: 210.0864. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 4.17 (q, *J* = 7.4 Hz, 2H), 2.55-1.97 (m, 8H), 1.27 (t, *J* = 6 Hz, 3H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.1 (d, *J* = 75.8 Hz), 119.7 (td, *J* = 210 Hz, *J* = 15 Hz), 98.5 (dq, *J* = 172.5 Hz, *J* = 15 Hz), 60.5 (d, *J* = 30 Hz), 28.6 (dt, *J* = 15.8 Hz), 27.4 (dt, *J* = 15.8 Hz), 25.0 (dq, *J* = 9.75 Hz), 20.2 (d, *J* = 30 Hz), 14.1.

I-4 Cobalt-catalyzed reductive homocoupling of alkyl halides

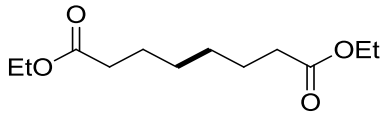
I-4-1 General procedure of the homocoupling of alkyl halides

To a solution of $CoBr_2$ (10 mol%, 0.25 mmol, 55 mg) and manganese powder (3.8 equiv., 9.5 mmol, 500 mg) in CH_3CN (3 mL) was added at room temperature the alkyl halide (2.5 mmol). Manganese powder was activated by traces of trifluoroacetic acid (50 µL) and the medium was then stirred at room temperature for 5 minutes until smoke

183 Cahiez, G.; Chaboche, C.; Duplais, C.; Giulliani, A.; Moyeux, A. *Adv. Syn. Cat.* **2008,** *350*, 1484-1488.

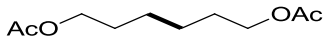
disappeared. At this time, pyridine, (0.5 mL) was added and the medium was stirred at 50 °C until the alkyl halide was consumed (3 to 6 h). The mixture was then poured into a solution of 2 M HCl (50 mL) and was stirred vigorously until layers turned clear. The solution was extracted with Et_2O or EtOAc (3 x 50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification of the resulting oil by flash chromatography over silica with petroleum ether/diethyl ether mixtures afforded the pure compounds.

I-4-2 Homocoupling compounds



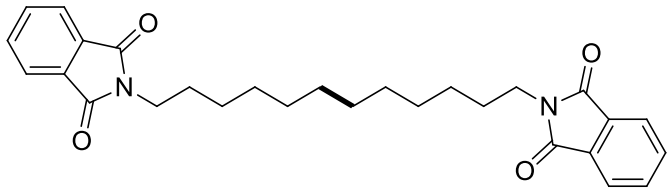
10a

Diethyl octanedioate $C_{12}H_{22}O_4$: CAS# 2050-23-9. Prepared according to the general procedure from ethyl 4-bromobutanoate (487 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (10:1) in 85 % (244 mg) yield as a colorless oil. **HRMS** (EI+) **($C_{12}H_{22}O_4$):** calculated m/z: 230.1518, found: 230.1522. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 4.05 (q, *J* =7.1 Hz, 4H), 2.22 (t, *J* =7.1 Hz, 4H), 1.56 (m, 4H), 1.27 (m, 4H), 1.18 (t, *J* =7.1 Hz, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.9, 60.3, 34.4, 28.9, 24.9, 14.4.[25b]



10b

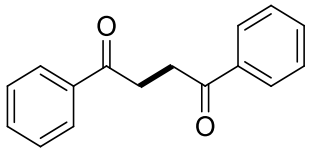
Hexane-1,6-diyl diacetate $C_{10}H_{18}O_4$: CAS# 6222-17-9. Prepared according to the general procedure from 3-bromopropyl acetate (453 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (10:1) in 83 % (210 mg) yield as a colorless oil. **MS ($C_{10}H_{18}O_4$):** calculated m/z: 202.1, found: $[M+H]^+$ 203. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 4.04 (q, *J* =7.1 Hz, 4H), 2.03 (t, *J* =7.1 Hz, 4H), 1.62 (m, 4H), 1.37 (m, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 170.3, 64.9, 28.9, 25.5, 20.7.[184]



10c

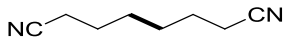
184 Miyamoto, K.; Tada, N.; Ochiai, M. *J. Am. Chem. Soc.* **2007,** *129*, 2772-2773.

2,2'-(dodecane-1,12-diyl)bis(isoindoline-1,3-dione) $C_{28}H_{32}N_2O_4$: CAS# 27646-76-0. Prepared according to the general procedure from 2-(6-bromohexyl)isoindoline-1,3-dione (775 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (10:1) in 79 % (455 mg) yield as a white powder. **HRMS** (EI+) **(**$C_{28}H_{32}N_2O_4$**):** calculated m/z: 460.2362, found: 460.2370. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.83 (q, *J* = 3 Hz, 4H), 7.70 (q, *J* = 3 Hz, 4H), 3.66 (t, *J* =7.1 Hz, 4H), 1.65 (m, 4H), 1.29 (m, 16H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 168.4, 133.8, 132.2, 123.1, 38.1, 29.5, 29.4, 29.1, 28.6, 26.8.



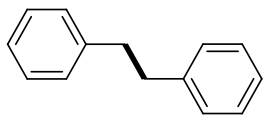
10d

1,4-diphenylbutane-1,4-dione $C_{16}H_{14}O_2$: CAS# 495-71-6. Prepared according to the general procedure from 2-chloro-1-phenylethanone (386 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (10:1) in 50 % (151 mg) yield as syringe crystal. **HRMS** (EI+) **(**$C_{16}H_{14}O_2$**):** calculated m/z: 238.0994, found: 238.0998. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 8.07 (d, *J* = 7.4 Hz, 4H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.50 (t, *J* =7.1 Hz, 4H), 3.49 (s, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 198.7, 136.7, 133.1, 128.6, 128.1, 32.6.[185]



10e

Octanedinitrile $C_8H_{12}N_4$: CAS# 629-40-3. Prepared according to the general procedure from 4-bromobutanenitrile (370 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (9:1) in 65 % (111 mg) yield as a colorless oil. **HRMS** (EI+) **(**$C_8H_{12}N_4$**):** calculated m/z: 164.1062, found: 164.1064. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 2.37 (t, *J* =7.0 Hz, 4H), 1.66 (m, 4H), 1.49 (m, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 117.7, 27.8, 25.5, 17.5.[186]

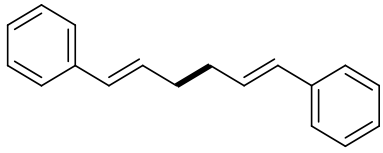


10f

185 Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2011,** *13*, 1622-1625

186 Ghiaci, M.; Sedaghat, M. E.; Kalbasi, R. J.; Abbaspur, A. *Tetrahedron* **2005,** *61*, 5529-5534.

1,2-diphenylethane $C_{14}H_{14}$: CAS# 103-29-7. Prepared according to the general procedure from benzyl chloride (320 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (99:1) in 82 % (187 mg) yield as a colorless oil. **HRMS** (EI+) **(**$C_{14}H_{14}$**):** calculated m/z: 182.1096, found: 182.1092. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.30−7.26 (m, 4H), 7.21−7.17 (m, 6H), 2.92 (s, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 141.8, 128.5, 128.4, 125.9, 38.0.[187]



10i

(1*E*,5*E*)-1,6-diphenylhexa-1,5-diene $C_{18}H_{18}$: CAS# 58463-02-8. Prepared according to the general procedure from cinnamy carbonate (480 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (99:1) in 72 % (293 mg) yield as a white powder. **HRMS** (EI+) **(**$C_{18}H_{18}$**):** calculated m/z: 234.1409, found: 234.1409. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.35 (m, 4H), 7.30 (m, 4H), 7.20 (m, 2H), 6.44 (d, *J* =15.8 Hz, 2H), 6.28 (d, *J* =15.8 Hz, 2H), 2.40 (m, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 137.9, 130.5, 130.1, 128.6, 127.1, 126.1, 33.1.[25b]

187 Hartmann, C. E.; Jurcik, V.; Songis, O.; Cazin, C. S. J. *Chem. Commun.* **2013,** *49*, 1005-1007.

II. Electrophilic C-N and C-S Bonds Formation Reaction with Arylzinc Species

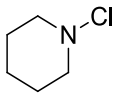
II-1 Cobalt-catalyzed Electrophilic Amination of Arylzinc species with N-chloroamines

II-1-1 General procedures for the formation of arylzinc reagents

To a solution of $CoBr_2$ (0.5 mmol, 110 mg) and zinc powder (10 mmol, 0.65 g) in acetonitrile (4 mL), allylchloride (1.5 mmol, 125 μL) and trifluoroacetic acid (50 μL) were successively added at room temperature, causing an immediate rise in temperature and a color change to dark gray. For aryl bromide and aryl iodide precursors, after stirring the resulting mixture for 3 min, aryl bromide or iodide (3.75 mmol) was added. The medium was then stirred at room temperature until the aryl halide was consumed (30-60 min, iodonalysis). In the case of aryl chloride precursor, the protocol has to be modified: pyridine (2 mL) and 2,2'-bipyridine (78 mg, 0.5 mmol) were introduced into the solution before the addition of ArCl and the reaction mixture was stirred at 50 °C until the total consumption of the aryl chloride. After 30 min – 60 min stirring, 0.5 mL of the arylzinc solution is added to a 10 mL tube containing a granule of I_2 (about 50 mg), which was sublimated using a heatgun. Then it was quenched with a saturated solution o8f $Na_2S_2O_3$ (2 mL). The organic layer was diluted with diethylether and then used directly for GC analysis.

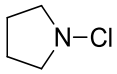
II-1-2 Representative procedures for the formation of *N*-chloroamines

To a 25 mL round-bottom flask, acetonitrile (4 mL), piperidine (0.5 mL, 5 mmol,) and *N*-chlorosuccinimide (0.7 g, 5.5 mmol,) were added. The reaction was stirring at 0 °C. After 30 min, the solution was hydrolyzed with NH_4Cl and extracted with diethylether. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum. The product which is a pale yellow oil, was used without purification.

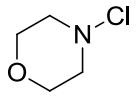


^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 3.11 (s, 4H), 1.76-1.59 (m, 4H), 1.41 (s, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 63.9, 27.6, 22.9.[188]

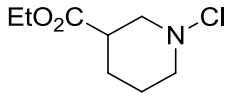
188 Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2011,** *14*, 656-659.



^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 3.11-3.0 (m, 4H), 1.91-1.71 (m, 4H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 62.6, 22.3.[189]



^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 3.73 (s, 4H), 3.15 (s, 4H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 67.6, 62.9.[188]



^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 4.11 (q, *J* = 7.1 Hz, 2H), 3.53 (m, 1H), 3.29 (m, 1H), 3.10-2.60 (m, 3H), 1.98-1.82 (m, 1H), 1.82-1.65 (m, 2H), 1.59-1.34 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 172.6, 77.4, 63.8, 62.6, 60.8, 25.7, 14.2.[188]

II-1-3 Cobalt-catalyzed amination of arylzinc species

II-1-3-1 Method A: General procedures for amination of arylzinc reagents without Et_3N

The arylzinc solution prepared as mentioned above, was carefully filtered with a syringe filter and injected into a solution of freshly prepared *N*-chloroamine (2.5 mmol,) in acetonitrile (1 mL), which was placed in a Schlenk flask under N_2 and cooled to 0 °C. The ice bath was allowed to melt, allowing the reaction to slowly warm to room temperature. After 2h to 20h, the reaction was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted three times with diethylether or ethyl acetate and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification was performed using silica gel column chromatography, with a gradient from 99:1 to 8:2 petroleum ether/diethylether and several drops of NEt_3, affording the corresponding arylamine cross-coupling product.

189 Scarpino Schietroma, D. M.; Monaco, M. R.; Bucalossi, V.; Walter, P. E.; Gentili, P.; Bella, M. *Org. Bio. Chem.* **2012,** *10*, 4692-4695.

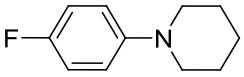
II-1-3-2 Method B: General procedures for amination of arylzinc reagents with Et_3N

Method B: differs from method A in that the arylzinc solution was added to a solution of *N*-chloroamine (2.5 mmol) and triethylamine (1 mmol). All other conditions are identical.

II-1-3-3 Method C: General Procedure for the reaction with non-isolated *N*-chloroamine

The amine (2.5 mmol, 1 equiv) and *N*-chlorosuccinimide (0.41 g, 2.75 mmol, 1.1 equiv) and toluene (3 mL) were stirred at 0 °C. After 30 min, the precipitated succinimid was filtrated off leading to a toluene solution of chloroamine, which was placed at 0°C, before adding NEt_3 (1 mmol) and the filtered arylzinc in acetonitrile. The ice bath was allowed to melt, so that the reaction mixture slowly warm to room temperature. After 2 h, the reaction was quenched with saturated solution of NH_4Cl. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification was performed using silica gel column chromatography, with a gradient from 99:1 to 8:2 petroleum ether/diethylether and several drops of NEt_3, affording the corresponding arylamine cross-coupling product.

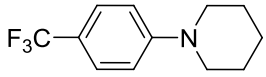
II-1-4 Characterization Data for Arylamines



11a

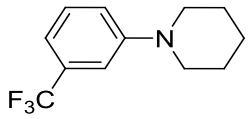
1-(4-fluorophenyl)piperidine $C_{11}H_{14}FN$: CAS# 4280-36-8. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-fluorobenzene (0.41 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) see general procedure (method A). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 80% (0.356 g) yield as a pale yellow oil. **HRMS** (EI+) **(**$C_{11}H_{14}FN$**):** calculated m/z: 179.1110, found: 179.1109. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.99-6.90 (m, 4H), 3.07 (t, *J* =5.4 Hz, 4H), 1.78-1.1.70 (quint, *J* =5.4 Hz, 4H), 1.60-1.52 (quint, *J* =5.4 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 157.3 (d, *J* = 232.4 Hz), 148.3, 118.7 (d, *J* = 7.5 Hz), 115.4

(d, *J* = 21.8 Hz), 52.1, 25.7, 23.9. **^{19}F-NMR** (182 MHz, $CDCl_3$, fluorobenzene as external reference) δ/ppm: -12.0. [190]



11b

1-(4-(trifluoromethyl)phenyl)piperidine $C_{12}H_{14}F_3N$: CAS# 10338-55-3. The arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromobenzotrifluoride (0.52 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) see general procedure (method A). Purification on silica gel with petroleum ether-diethyl ether (99:1) afforded the title compound in 79% (0.452 g) yield as a pale yellow oil. **HRMS** (EI+) **(**$C_{12}H_{14}F_3N$**):** calculated m/z: 229.1078, found: 229.1080. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.51 (d, *J* =9.0 Hz, 2H), 6.96 (d, *J* =9.0 Hz, 2H), 3.30 (t, *J* =4.8 Hz, 4H), 1.77-1.66 (m, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 153.7, 126.2, 124.8 (q, *J* = 246.5 Hz), 119.4 (q, *J* = 32.3 Hz), 114.5, 49.2, 25.3, 24.1. ^{19} F-NMR (182 MHz, $CDCl_3$, BF_3 as external reference) δ/ppm: -63.3. [190]

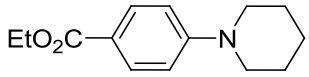


11c

1-(3-(trifluoromethyl)phenyl)piperidine $C_{12}H_{14}F_3N$: CAS# 189065-47-2. The arylzinc derivative was prepared in acetonitrile (4 mL) from 3-bromobenzotrifluoride (0.53 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 mg, 2.50 mmol) see general procedure (method A). Purification on silica gel with petroleum ether-diethyl ether (99:1) afforded the title compound in 55% (0.315 g) yield as a pale yellow oil. **HRMS** (EI+) ($C_{12}H_{14}F_3N$): calculated m/z: 229.1078, found: 229.1077. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.36 (t, *J* =7.5 Hz, H), 7.17 (s, 1H), 7.1- 7.0(t, 2H), 3.24 (t, *J* =5.4 Hz, 4H), 1.75 (quint, *J* =5.4 Hz, 4H), 1.64

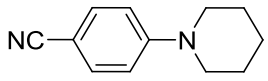
190 (a) Conesa Lerma, I.; Cawley, M. J.; Cloke, F. G. N.; Arentsen, K.; Scott, J. S.; Pearson, S. E.; Hayler, J.; Caddick, S. *J. Organomet. Chem.* **2005,** *690*, 5841-5848. (b) Zakrzewska, A.; Kolehmainen, E.; Osmialowski, B.; Gawinecki, R. *J. Fluorine. Chem.* **2001,** *111*, 1-10.

(quint, *J* =5.4 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 152.2, 131.3 (q, *J* = 27.8 Hz), 129.5, 128.7 (q, *J* = 272 Hz), 119.2, 115.2, 112.5, 50.1, 25.6, 24.1. ^{19} F-NMR (182 MHz, $CDCl_3$, BF_3 as external reference) δ/ppm: -63.2. [191]



11d

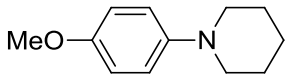
Ethyl 4-(piperidin-1-yl)benzoate $C_{14}H_{19}NO_2$: CAS# 101038-65-7. The arylzinc derivative was prepared in acetonitrile (4 mL) from ethly-4-bromobenzoate (0.62 mL, 3.75 mmol) as described in the general procedure. It was obtained in 75% GC yield (2.8 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 75% (0.446 g) yield as a white powder. **HRMS** (EI+) **($C_{14}H_{19}NO_2$):** calculated m/z: 233.1416, found: 233.1416. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.90 (d, *J* =9.0 Hz, 2H), 6.82 (d, *J* =9.0 Hz, 2H), 4.31 (q, *J* =7.2 Hz, 2H), 3.29 (t, *J* =4.8 Hz, 4H), 1.68-1.52 (m, 6H), 1.35 (t, *J* =7.2 Hz 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 166.7, 154.3, 131.0, 118.9, 113.5, 60.1, 48.8, 25.2, 24.2, 14.4.



11e

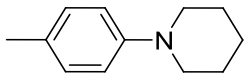
4-(piperidin-1-yl)benzonitrile $C_{12}H_{14}N_2$: CAS# 1204-85-9. The arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromobenzonitrile (0.70 g, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) see general procedure (method A). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 82% (0.381 g) yield as a pale yellow oil. **HRMS** (EI+) **($C_{12}H_{14}N_2$):** calculated m/z: 186.1157, found: 186.1155. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.46 (d, *J* =9.0 Hz, 2H), 6.83 (d, *J* =9.0 Hz, 2H), 3.31 (t, *J* =6.0 Hz, 4H), 1.65 (m, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 153.4, 133.3, 120.3, 114.0, 98.8, 48.3, 25.1, 24.1. [104]

191 Fang, Y.; Zheng, Y.; Wang, Z. *Eur. J. Org. Chem.* **2012,** *8*, 1495-1498.



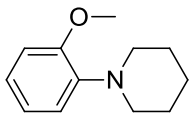
11f

1-(4-methoxyphenyl)piperidine $C_{12}H_{17}NO$: CAS# 5097-25-6. The arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromo-anisole (0.47 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) see general procedure (method A). Purification on silica gel with pentane-diethyl ether (98:2) afforded the title compound in 71% (0.339 g) yield as a pale yellow oil. **HRMS** (EI+) **(**$C_{12}H_{17}NO$**):** calculated m/z: 191.1310, found: 191.1313. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.96 (d, *J* =9.2 Hz, 2H), 6.87 (d, *J* =9.2 Hz, 2H), 3.80 (s, 3H), 3.07 (t, *J* =5.4 Hz, 4H), 1.77 (quint, *J* =5.4 Hz, 4H), 1.58 (quint, *J* =5.4 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 153.5, 146.8, 118.6, 114.2, 55.4, 52.2, 26.0, 24.1. [190]



11g

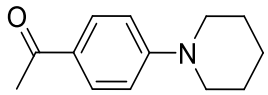
1-*p*-tolylpiperidine $C_{12}H_{17}N$: CAS# 31053-03-9. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-methylbenzene (0.65 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) see general procedure (method A). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 53% (0.232 g) yield as a pale yellow oil. **HRMS** (EI+) **(**$C_{12}H_{17}N$**):** calculated m/z: 175.1361, found: 175.1360. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.10 (d, *J* =9 Hz, 2H), 6.92 (d, *J* =9 Hz, 2H), 3.13 (t, *J* =5.4 Hz, 4H), 2.30 (s, 3H), 1.76 (quint, *J* =5.4 Hz, 4H), 1.59 (quint, *J* =5.4 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 149.8, 129.5, 129.0, 117.0, 51.5, 25.7, 24.1, 20.4.[190]



11h

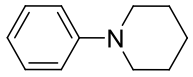
1-(2-methoxyphenyl)piperidine $C_{12}H_{17}NO$: CAS# 5181-06-6. The arylzinc derivative was prepared in acetonitrile (4 mL) from 2-bromoanisole (0.69 mL, 5 mmol) as described in the general procedure. It was obtained in 70% GC yield (3.5 mmol).

This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) see general procedure (method A). Purification on silica gel with petroleum ether-diethyl ether (100:5) afforded the title compound in 42% (0.204 g) yield as a pale yellow oil (the weight of the mixture was 0.234 g including 0.03 g of Ar-Ar calculated by ^{1}H NMR). **HRMS** (EI+) **(**$C_{12}H_{17}NO$**):** calculated m/z: 191.1310, found: 191.1315. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.02-6.84 (m, 4H), 3.87 (s, 3H), 3.00 (t, *J* =4.8 Hz, 4H), 1.77 (quint, *J* =5.4 Hz, 4H), 1.58 (quint, *J* =5.4 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 152.3, 142.6, 122.6, 120.8, 118.3, 111.0, 55.3, 52.4, 26.3, 24.4.



12a

1-(4-(piperidin-1-yl)phenyl)ethan-1-one $C_{13}H_{17}NO$: CAS# 10342-85-5. The arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromoacetophenone (0.75 g, 3.75 mmol) as described in the general procedure. It was obtained in 75% GC yield (2.8 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (4:1) afforded the title compound in 81% (411 mg) yield as a white solid. **HRMS** (EI+) **(**$C_{13}H_{17}NO$**):** calculated m/z: 203.1310, found: 203.1308. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.83 (d, *J* =9.0 Hz, 2H), 6.83 (d, *J* =9.0 Hz, 2H), 3.40-3.30 (m, 4H), 2.49 (s, 3H), 1.65-1.58 (m, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 196.3, 154.2, 130.3, 126.4, 113.1, 48.5, 26.0, 25.2, 24.2. [192]

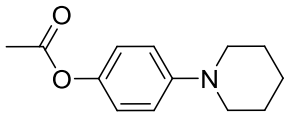


12b

***N*-phenylpiperidine $C_{11}H_{15}N$:** CAS# 4096-20-2. The arylzinc derivative was prepared in acetonitrile (4 mL) from bromobenzene (0.4 mL, 3.75 mmol) as described in the general procedure. It was obtained in 81% GC yield (3.0 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (100:1) afforded the title compound in 82%

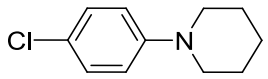
192 Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2009,** *74*, 7464-7469.

(0.331 g) yield as a pale yellow oil. **HRMS** (EI+) **(**$C_{11}H_{15}N$**):** calculated m/z: 161.1204, found: 161.1204. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.32 (t, *J* =7.5 Hz, 2H), 7.01 (t, *J* =7.5 Hz, 2H), 6.89 (t, *J* =7.5 Hz, H), 3.21 (t, *J* =4.8 Hz, 4H), 1.78 (quint, *J* =5.4 Hz, 4H), 1.63 (quint, *J* =5.4 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 152.2, 128.9, 119.1, 116.5, 50.6, 25.8, 24.3. [190]



12c

4-(piperidin-1-yl)phenyl acetate $C_{13}H_{17}NO_2$: CAS# 1064704-94-4. The arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromophenyl acetate (0.54 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (8:2) afforded the title compound in 71% (0.389 g) yield as a pale yellow oil. **MS** (EI+) **(**$C_{13}H_{17}NO_2$**):** calculated m/z: 219, found: 219. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.96 (q, *J* =6.0 Hz, 4H), 3.13 (t, *J* =5.7 Hz 4H), 2.28 (s, 3H), 1.73 (quint, *J* =5.4 Hz, 4H), 1.58 (quint, *J* =5.4 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 169.9, 150.1, 143.3, 121.6, 117.3, 51.1, 25.7, 24.1, 21.0. [193]

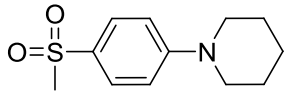


12d

1-(4-chlorophenyl)piperidine $C_{11}H_{14}ClN$: CAS# 40832-73-3. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-chloro-4-iodobenzene (0.904 g, 3.75 mmol) as described in the general procedure. It was obtained in 90% GC yield (3.4 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (99:1) afforded the title compound in 80% (0.388 g) yield as a white powder. **HRMS** (EI+) **(**$C_{11}H_{14}ClN$**):** calculated m/z: 195.0815, found: 195.0814. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.19 (d, *J* =9.0 Hz, 2H), 6.85 (d, *J* =9.0 Hz, 2H), 3.12 (t, *J* =5.5 Hz, 4H), 1.71 (quint, *J* =5.4

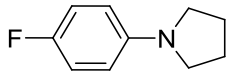
193 Osorio-Lozada, A.; Tovar-Miranda, R.; F.Olivo, H. *J. Mol. Catal. B-Enzym*. **2008**, *55*, 30-36.

Hz, 4H), 1.58 (quint, *J* =5.4 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 150.7, 128.8, 123.8, 117.6, 50.6, 25.6, 24.1. [194]



12e

1-(4-(methylsulfonyl)phenyl)piperidine $C_{12}H_{17}NO_2S$: CAS# 150221-20-8. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-(methylsulfonyl)benzene (0.90mg, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of *N*-chloropiperidine (0.30 mg, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B) Purification on silica gel with petroleum ether-diethyl ether (9:1) afforded the title compound in 64% (380 mg) yield as as white solid (the weight of the mixture was 396 mg including 16 mg of Ar-Ar calculated by ^{1}H NMR). **HRMS** (EI+) **(**$C_{12}H_{17}NO_2S$**):** calculated m/z: 239.0980, found: 239.0981. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.63 (d, *J* =8.7 Hz, 2H), 6.82 (d, *J* =8.7 Hz, 2H), 3.26 (m, 4H), 2.91 (s, 3H), 1.56 (m, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 154.0, 128.7, 126.8, 113.3, 48.1, 44.5, 24.7, 23.8.

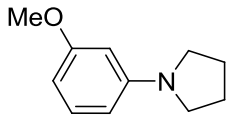


12f

1-(4-fluorophenyl)pyrrolidine $C_{10}H_{12}FN$: CAS# 4280-34-6. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-fluorobenzene (0.41 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of *N*-chloropyrrolidine (0.264 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (9:1) afforded the title compound in 53% (0.218 g) yield as a pale yellow oil. **HRMS** (EI+) **(**$C_{10}H_{12}FN$**):** calculated m/z: 165.0954, found: 165.0950. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.97 (vt, *J* = 9 Hz, 2H), 6.50 (dd, *J* = 9 Hz, *J* = 3 Hz, 2H), 3.27 (t, *J* =6.6 Hz, 4H), 2.03 (quint, *J* =7.1 Hz, 4H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 154.5 (d, *J* = 232.5 Hz), 144.7,

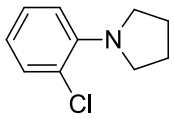
194 Yang, H.; Xi, C.; Miao, Z.; Chen, R. *Eur. J. Org. Chem.* **2011,** *18*, 3353-3360.

115.4 (J = 22.5 Hz) , 112.0 , (d, J = 7.5 Hz) 48.0, 25.4. **^{19}F-NMR** (182 MHz, $CDCl_3$, fluorobenzene as external reference) δ/ppm: **-**17.6. [190]



12g

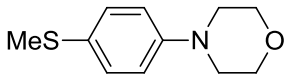
1-(3-methoxyphenyl)pyrrolidine $C_{11}H_{15}NO$: CAS# 32040-07-6. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-3methoxybenzene (0.48 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of *N*-chloropyrrolidine (0.264 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B) Purification on silica gel with petroleum ether-diethyl ether (9:1) afforded the title compound in 88% (0.389 g) yield as a brown oil. **HRMS** (EI+) **(**$C_{11}H_{15}NO$**):** calculated m/z: 177.1154, found: 177.1156. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.27 (t, J =8.4 Hz, 1H), 6.36 (dd, J =9 and 3 Hz, 2H), 3.27 (t, J =3 Hz, 1H), 3.92 (s, 3H), 3.40 (t, J =6.6 Hz 4H), 2.10 (t, J =6.6 Hz, 4H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 160.5, 148.9, 129.4, 104.6, 100.2, 97.6, 54.6, 47.3, 25.1. [195]



12h

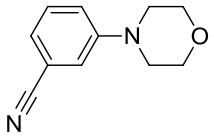
1-(2-chlorophenyl)pyrrolidine $C_{10}H_{12}ClN$: CAS#105516469. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-2-chlorobenzene (0.718 mL, 3.75 mmol) as described in the general procedure. It was obtained in 75% GC yield (2.8 mmol). This solution was filtered and added to a solution of *N*-chloropyrrolidine (0.264 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (100:1) afforded the title compound in 51% (0.223 g) yield as a yellow oil. **HRMS** (EI+) **(**$C_{10}H_{12}ClN$**):** calculated m/z: 181.0658, found: 181.0656. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.36 (dd, J =9 and 3 Hz, 1H), 7.20 (td, J =9 and 3 Hz, 1H), 6.94 (d, J =9 Hz, 1H), 6.84 (td, J =9 and 3 Hz, H), 3.44 (t, J =6.6 Hz, 4H), 2.00 (t, J =6.6 Hz, 4H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 147.0, 131.1, 127.1, 123.2, 120.0, 117.0, 50.8, 25.1. [196]

195 Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. *Adv. Synth. Catal.* **2008,** *350*, 395-398.
196 Shim, S. C.; Huh, K. T.; Park, W. H. *Tetrahedron* **1986,** *42*, 259-263.



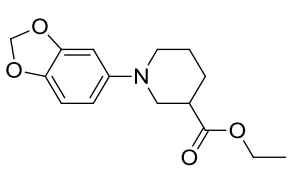
12i

4-(4-(methylthio)phenyl)morpholine $C_{11}H_{15}NOS$: CAS# not found. The arylzinc derivative was prepared in acetonitrile (4 mL) from (4-bromophenyl)(methyl)sulfane (0.762 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of *N*-chloromorpholine (0.304 g, 2.50 mmol and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (4:1) afforded the title compound in 67% (0.351 g) yield as a white solid. **HRMS** (EI+) **(**$C_{11}H_{15}NOS$**):** calculated m/z: 209.0874, found: 209.0868. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.28 (d, *J* =7.5 Hz, 2H), 6.88 (d, *J* =7.5 Hz, 2H), 3.87 (t, *J* =7.1 Hz 4H), 3.15 (t, *J* =7.1 Hz 4H), 2.46 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 149.6, 129.9, 128.0, 116.3, 86.3, 66.8, 49.3, 17.9.



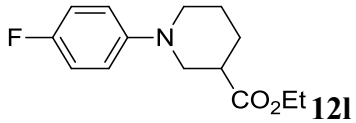
12j

3-morpholinobenzonitrile $C_{11}H_{12}N_2O$: CAS#204078-31-9. The arylzinc derivative was prepared in acetonitrile (4 mL) from 3-bromobenzonitrile (0.683 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of *N*-chloromorpholine (304 mg, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (3:1) afforded the title compound in 72% (338 mg) yield as a white solid. **HRMS** (EI+) **(**$C_{11}H_{12}N_2O$**):** calculated m/z: 188.0950, found: 188.0953. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.33 (t, *J* = 9 Hz, H), 7.13-7.08 (m, 3H), 3.85 (t, *J* =7.1 Hz, 4H), 3.17 (t, *J* =7.1 Hz, 4H), **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 151.3, 129.9, 122.8, 119.5, 119.2, 118.1, 113.0, 66.5, 48.4. [107]



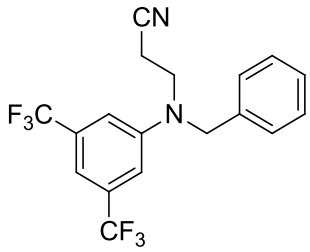
12k

Ethyl 1-(benzo[d][1,3]dioxol-5-yl)piperidine-3-carboxylate $C_{15}H_{19}NO_4$: CAS# not found. The arylzinc derivative was prepared in acetonitrile (4 mL) from 5-bromobenzo[d][1,3]dioxole (0.755 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of ethyl 1-chloropiperidine-3-carboxylate (0.480 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (4:1) afforded the title compound in 68% (0.471 g) yield as a white solid. **HRMS** (EI+) **(**$C_{15}H_{19}NO_4$**):** calculated m/z: 277.1314, found: 277.1313. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.71 (d, *J* = 9 Hz, H), 6.58 (d, *J* = 3 Hz, H), 6.39 (dd, *J* = 9 and 3 Hz, H), 5.88 (s, *2*H), 4.16 (q, *J* =7.8 Hz, 2H), 3.53 (dd, *J* = 7.0 and 3 Hz, H), 3.27 (d, *J* = 7.0 Hz, H), 2.92 (t, J = 7.0, H), 2.75-2.65 (m, 2H), 2.02-1.96 (m, H), 1.82-1.53 (m, 3H), 1.25 (t, *J* =7.8 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.8, 148.1, 147.7, 141.6, 109.9, 108.0, 100.8, 60.4, 54.0, 51.6, 41.6, 26.7, 24.4, 14.2.



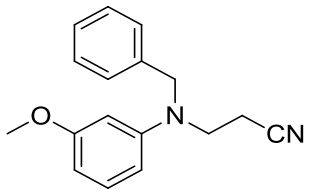
12l

Ethyl 1-(4-fluorophenyl)piperidine-3-carboxylate $C_{14}H_{18}FNO_2$: CAS# not found. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo 4 fluorobenzene (0.42 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of ethyl 1-chloropiperidine-3-carboxylate (0.480 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (85:15) afforded the title compound in 52% (0.326 g) yield as a white solid. **HRMS** (EI+) **(**$C_{14}H_{18}FNO_2$**):** calculated m/z: 251.1322, found: 251.1317. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.00-6.88 (m, 4H), 4.17 (q, *J* =7.8 Hz, 2H), 3.57 (d, *J* = 7.0 Hz, H), 3.34 (d, *J* = 7.0 Hz, H), 2.98 (t, *J* = 7.0, H), 2.80-2.65 (m, 2H), 2.05-1.90 (m, H), 1.85-1.65 (m, 3H), 1.27 (t, *J* =7.8 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.8, 157.2 (*J* = 240 Hz), 148.3, 118.8 (d, *J* = 8.3 Hz), 115.4 (d, *J* = 21.8 Hz), 60.5, 53.4, 50.1, 41.6, 26.6, 24.3, 14.2. **^{19}F-NMR** (182 MHz, $CDCl_3$, BF_3 as external reference) δ/ppm: -124.9.



12m

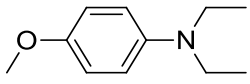
3-(benzyl(3,5-bis(trifluoromethyl)phenyl)amino)propanenitrile $C_{18}H_{14}F_6N_2$: CAS# not found. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-brome-3,5-di(trifluoromethane)benzene (0.65 mL, 3.75 mmol) as described in the general procedure. It was obtained in 90% GC yield (3.4 mmol). This solution was filtered and added to a solution of 3-(benzylchloroamino)propanenitrile (0.490 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (85:15) afforded the title compound in 61% (0.567 g) yield as a white solid. **HRMS** (EI+) ($C_{18}H_{14}F_6N_2$)**:** calculated m/z: 372.1061, found: 372.1050. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.40-7.20 (m, 6H), 7.10 (s, 2H), 4.75 (s, *2*H), 3.88 (t, *J* = 6 Hz, 2H), 2.68 (t, *J* = 6 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 147.9, 135.9, 133.8 (q, *J*, = 32.5 Hz), 129.1, 127.9, 126.5, 123.4 (q, *J* = 270.0 Hz), 117.5, 111,9, 111.0, 54.6, 46.9, 15.9. **^{19}F-NMR** (182 MHz, $CDCl_3$, BF_3 as external reference) δ/ppm: -63.6.



12n

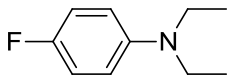
3-(benzyl(3-methoxyphenyl)amino)propanenitrile $C_{17}H_{18}N_2O$: CAS# not found. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-methoxy-3-bromobenzene (0.47 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of 3-(benzylchloroamino)propanenitrile (0.49 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (9:1) afforded the title compound afforded 74% (0.49 g) pale brown oil. **HRMS** (EI+) ($C_{17}H_{18}N_2O$)**:** calculated m/z: 266.1419, found: 266.1419. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.38-7.15 (m, 6H), 6.39 (dd, J = 9 and 3 Hz 2H), 6.33-6.30 (m, H),4.64 (s, *2*H), 3.82-3.74 (m, 5H), 2.64 (t, J = 6 Hz, 2H). **^{13}C-NMR** (75

MHz, $CDCl_3$) δ/ppm: 160.9, 148.4, 137.7, 130.3, 128.7, 127.2, 126.6, 118.2, 105.9, 102.6, 99.8, 55.1, 54.8, 47.1, 15.7.



12o

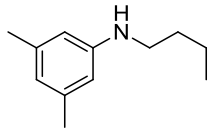
***N,N*-diethyl-4-methoxyaniline $C_{11}H_{17}NO$:** CAS# 15144-80-6. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-methoxy-4-bromobenzene (0.47 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of *N*-chloro-*N*-diethylamine (0.27 g, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (96:4) afforded the title compound in 80% yield (0.358 g) as a pale yellow oil. **HRMS** (EI+) **(**$C_{11}H_{17}NO$**):** calculated m/z: 179.1310, found: 179.1310. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.87 (d, *J* =9.0 Hz, 2H), 6.74 (d, *J* =9.0 Hz, 2H)，3.79 (s, 3H), 3.29 (q, *J* =7.2 Hz, 4H), 1.14 (t, *J* =7.2 Hz 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 151.4, 142.3, 115.2, 114.7, 55.6, 45.3, 12.3. [190]



12p

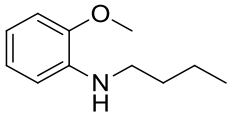
***N,N*-diethyl-4-fluoroaniline $C_{10}H_{14}FN$:** CAS# 347-39-7. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-fluorobenzene (0.41 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of *N*-chloro-*N*-diethylamine (0.27 mg, 2.50 mmol) and triethylamine (0.15 mL, 1.0 mmol) see general procedure (method B). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 53% (0.221 g) yield as a pale yellow oil. **HRMS** (EI+) **(**$C_{10}H_{14}FN$**):** calculated m/z: 167.1110, found: 167.1109. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.93 (t, *J* = *J* = 9 Hz, 2H), 6.64 (dd, *J* = 9 Hz, *J* = 3 Hz, 2H), 3.30 (q, *J* =7.2 Hz, 4H), 1.14 (t, *J* =7.2 Hz 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 154.6 (d, *J* = 232.5 Hz), 144.5, 115.5 (d, *J* = 22.5 Hz), 113.5 (d, *J* = 6.8 Hz), 44.9, 12.3. **^{19}F-NMR** (182 MHz, $CDCl_3$, fluorobenzene as external reference) δ/ppm: **-**16.8. [190,197]

197 Saitoh, T.; Ichikawa, J. *J. Am. Chem. Soc.* **2005,** *127*, 9696-9697.



13a

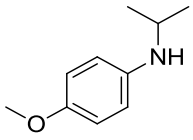
***N*-butyl-3,5-dimethylaniline $C_{12}H_{19}N$:** CAS# 13442-26-2. On one hand, *N*-chlorobutylamine was prepared from the corresponding amine (0.24 mL, 2.5 mmol) and NCS (0.4 g, 2.8 mmol) in toluene (3 mL) at 0 °C. The obtained suspension was filtered using Whatman PTFE syringe filter ReZist-30 0.45 μm and introduced to another dried flask. Triethylamine (0.15 mL, 1 mmol) was then added and the flask was placed in an ice-water bath. On the other hand, the arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-3,5-dimethylbenzene (0.51 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This arylzinc solution was added, after filtration, to the flask containing the *N*-chloroamine. The reaction mixture was stirred for 90 min, see general procedure (method C). Purification on silica gel with petroleum ether-diethyl ether (100:1) afforded the title compound in 70% (0.31 g) as a pale yellow oil (the weight of the mixture was 344 mg including 34 mg of Ar-Ar calculated by ^{1}H NMR). **HRMS** (EI+) ($C_{12}H_{19}N$): calculated m/z: 177.1517, found: 177.1518. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.46 (s, H), 6.34 (s, 2H)，3.49 (s, H), 3.17 (t, *J* = 7.1 Hz, 2H), 2.34 (s, 6H), 1.67 (quint, *J* = 7.1 Hz, 2H), 1.48 (quint, *J* = 7.1 Hz, 2H), 1.05 (t, *J* = 6 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 148.4, 138.7, 119.0, 110.6, 43.6, 31.6, 21.4, 13.8.



13b

***N*-butyl-2-methoxyaniline $C_{11}H_{17}NO$:** CAS# 65570-20-9. On one hand, *N*-chlorobutylamine was prepared from the corresponding amine (0.24 mL, 2.5 mmol) and NCS (0.4 g, 2.8 mmol) in toluene (3 mL) at 0 °C. The obtained suspension was filtered using Whatman PTFE syringe filter ReZist-30 0.45 μm and introduced to another dried flask. Triethylamine (0.15 mL, 1 mmol) was then added and the flask was placed in an ice-water bath. On the other hand, the arylzinc derivative was prepared in acetonitrile (4 mL) from 2-bromoanisole (0.69 mL, 5 mmol) as described in the general procedure. It was obtained in 80% GC yield (4.0 mmol). This arylzinc solution was added, after filtration, to the flask containing the *N*-chloroamine. The reaction mixture

was stirred for 90 min, see general procedure (method C). Purification on silica gel with petroleum ether-diethyl ether (100:1) afforded the title compound in 80% (0.358 g) yield as a pale yellow oil. **HRMS** (EI+) ($C_{11}H_{17}NO$): calculated m/z: 179.1310, found: 179.1312. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.93 (t, *J* = 9 Hz, H), 6.82 (d, *J* = 6 Hz, H), 6.74-6.65 (m, 2H), 4.21 (broad s, H)，3.89 (s, 3H), 3.18 (t, *J* = 6 Hz, 2H), 1.73 (quint, *J* = 7.1 Hz, 2H), 1.52 (quint, *J* = 7.1 Hz, 2H), 1.03 (t, *J* = 6 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 146.6, 138.4, 121.2, 115.9, 109.6, 109.1, 55.2, 43.3, 31.5, 20.3, 13.8. [198]

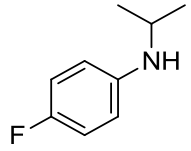


13c

***N*-isopropyl-4-methoxyaniline $C_{10}H_{15}NO$ (Method C):** CAS# 16495-67-3. On one hand, *N*-chloropropan-2-amine was prepared from the corresponding amine (0.31 mL, 2.5 mmol) and NCS (0.4 g, 2.8 mmol) in toluene (3 mL) at 0 °C. The obtained suspension was filtered using Whatman PTFE syringe filter ReZist-30 0.45 μm and introduced to another dried flask. Triethylamine (0.15 mL, 1 mmol) was then added and the flask was placed in an ice-water bath. On the other hand, the arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromoanisole (0.47 mL, 3.75 mmol) as described in the general procedure. It was obtained in 75% GC yield (2.8 mmol). This arylzinc solution was added, after filtration, to the flask containing the *N*-chloroamine. The reaction mixture was stirred for 90 min, see general procedure (method C). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 78% (0.322 g) yield as a pale yellow oil. **HRMS** (EI+) ($C_{10}H_{15}NO$): calculated m/z: 165.1154, found: 165.1154. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.82 (d, *J* = 9 Hz, 2H), 6.61 (d, *J* = 9 Hz, 2H)，3.77 (s, 3H), 3.57 (m, *2*H), 1.21 (d, *J* = 6 Hz, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 151.7, 141.5, 114.9, 114.7, 55.5, 45.1, 22.8. [199]

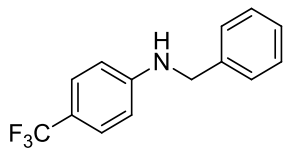
198 Nacario, R.; Kotakonda, S.; Fouchard, D. M. D.; Tillekeratne, L. M. V.; Hudson, R. A. *Org. Lett.* **2005,** *7*, 471-474.

199 Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2009,** *48*, 7375-7378.



13d

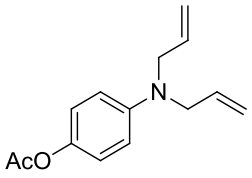
4-fluoro-*N*-isopropylaniline $C_9H_{12}FN$ (Method C): CAS# 70441-63-3. One one hand, *N*-chloropropan-2-amine was prepared from the corresponding amine (0.31 mL, 2.5 mmol) and NCS (0.4 g, 2.8 mmol) in toluene (3 mL) at 0 °C. The obtained suspension was filtered using Whatman PTFE syringe filter ReZist-30 0.45 µm and introduced to another dried flask. Triethylamine (0.15 mL, 1 mmol) was then added and the flask was placed in an ice-water bath. On the other hand, the arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-fluorobenzene (0.41 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This arylzinc solution was added, after filtration, to the flask containing the *N*-chloroamine. The reaction mixture was stirred for 90 min, see general procedure (method C). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 58% (0.229 g) yield as a pale yellow oil. **HRMS** (EI+) ($C_9H_{12}FN$): calculated m/z: 153.0954, found: 153.0952. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.89 (t, *J* = 9 Hz, 2H), 6.53 (dd, *J* = 9 Hz, *J*= 3 Hz, 2H), 3.56 (hept, *J* = 6 Hz, H), 3.16 (s, H), 1.20 (d, *J* = 6 Hz, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 155.5 (d, *J* = 232.5 Hz), 143.8, 115.6 (d, *J* = 21.8 Hz), 114.1 (d, *J* = 6.8 Hz), 48.9, 22.9. **^{19}F-NMR** (182 MHz, $CDCl_3$, BF_3 as external reference) δ/ppm: -128.0. [199]



13e

***N*-benzyl-4-(trifluoromethyl)aniline $C_{14}H_{12}F_3N$:** CAS# 405-81-2. On one hand, *N*-chlorobenzylamine was prepared from the corresponding amine (0.27 mL, 2.5 mmol) and NCS (0.4 g, 2.8 mmol) in toluene (2 mL) at 0 °C. The obtained suspension was filtered using Whatman PTFE syringe filter ReZist-30 0.45 µ and introduced to another dried flask. Triethylamine (0.15 mL, 1 mmol) was then added and the flask was placed in an ice-water bath. On the other hand, the arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromobenzotrifluoride (0.52 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This arylzinc

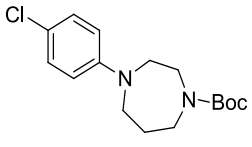
solution was added, after filtration, to the flask containing the *N*-chloroamine. The reaction mixture was stirred for 90 min, see general procedure (method C). Purification on silica gel with petroleum ether-diethyl ether (100:1) afforded the title compound in 78% (0.49 g) yield as a pale yellow oil. **HRMS** (EI+) ($C_{14}H_{12}F_3N$): calculated m/z: 251.0922, found: 251.0925. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.53-7.35 (m, 7H), 6.68 (d, *J* = 9 Hz, 2H)，4.42 (broad s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 150.4, 138.4, 128.7, 127.4, 127.3, 126.6, 124.6 (q, *J* = 245 Hz), 118.8 (q, *J* = 32.3 Hz), 111.9, 47.6. **^{19}F-NMR** (182 MHz, $CDCl_3$, BF_3 as external reference) δ/ppm: -61.4. [200]



13f

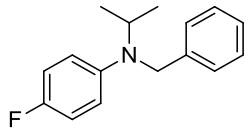
4-(diallylamino)phenyl acetate $C_{14}H_{17}NO_2$: CAS# not found. On one hand, *N*,*N*-chlorodiallylamine was prepared from the corresponding amine (0.31 mL, 2.5 mmol) and NCS (0.4 g, 2.8 mmol) in toluene (2 mL) at 0 °C. The obtained suspension was filtered using Whatman PTFE syringe filter ReZist-30 0.45 μm and introduced to another dried flask. Triethylamine (0.15 mL, 1 mmol) was then added and the flask was placed in an ice-water bath. On the other hand, the arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromophenyl acetate (0.54 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This arylzinc solution was added, after filtration, to the flask containing the *N*-chloroamine. The reaction mixture was stirred for 90 min, see general procedure (method C). The solution was first quenched by satureated NH_4Cl solution and extracted the organic layer by diethyl ether. Purification on silica gel with petroleum ether-diethyl ether (9:1) afforded the title compound in 39% (0.226 g) yield as a pale yellow oil. **HRMS** (EI+) ($C_{14}H_{17}NO_2$): calculated m/z: 231.1259, found: 231.1263. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 6.90 (d, *J* = 9 Hz, 2H), 6.67 (d, *J* = 9 Hz, 2H)，5.92-5.75 (m, 2H), 5.22-5.15 (m, 4H), 3.90 (d, *J* = 4.8 Hz, 4H), 2.26 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 170.3, 146.6, 141.1, 133.7, 121.7, 116.0, 112.6, 53.0, 21.1.

200 Blank, B.; Madalska, M.; Kempe, R. *Adv. Synth. Catal.* **2008,** *350*, 749-758.



13g

Tert-butyl 4-(4-chlorophenyl)-1,4-diazepane-1-carboxylate $C_{16}H_{23}ClN_2O_2$: CAS# Not found. On one hand, *N*-chloroamine was prepared from the corresponding amine (0.5 mL, 2.5 mmol) and NCS (0.4 g, 2.8 mmol) in toluene (2 mL) at 0 °C. The obtained suspension was filtered using Whatman PTFE syringe filter ReZist-30 0.45 µm and introduced to another dried flask. Triethylamine (0.15 mL, 1 mmol) was then added and the flask was placed in an ice-water bath. On the other hand, the arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromobenzene chloride (0.72 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This arylzinc solution was added, after filtration, to the flask containing the *N*-chloroamine. The reaction mixture was stirred for 90 min, see general procedure (method C). The solution was stirred for 90 min. Purification on silica gel with petroleum ether-diethyl ether (85:15) afforded the title compound in 58% (0.45 g) yield as a pale brown oil. **HRMS** (EI+) **(**$C_{16}H_{23}ClN_2O_2$**):** calculated m/z: 310.1448, found: 310.1445. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.10 (d, J = 7.1 Hz, 2H), 6.58 (d, J = 7.1 Hz, H)， 3.55-3.44 (m, 6H), 3.27 (t, *J* = 6 Hz, H), 3.17 (t, J = 6 Hz, H), 1.91 (quint, *J* = 7.1 Hz, 2H), 1.41 and 1.29 (2s, 9H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 155.3, 154.9, 145.7, 145.6, 129.2, 129.2, 120.7, 112.9, 112.7, 79.5, 50.5, 50.2, 48.9, 48.0, 46.1, 46.0, 45.6, 28.4, 28.2, 24.9, 24.6. (2 stereoisomers (55:45) are seen on the ^{1}H NMR spectra)



13h

***N*-benzyl-4-fluoro-*N*-isopropylaniline $C_{16}H_{18}FN$:** CAS# not found. On one hand, *N*-benzyl-*N*-chloropropan-2-amine was prepared from the corresponding amine (0.42 mL, 2.5 mmol) and NCS (0.4 g, 2.8 mmol) in toluene (2 mL) at 0 °C. The obtained suspension was filtered using Whatman PTFE syringe filter ReZist-30 0.45 µm and introduced to another dried flask. Triethylamine (0.15 mL, 1 mmol) was then added and the flask was placed in an ice-water bath. On the other hand, the arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-fluorobenzene (0.41 mL, 3.75

mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This arylzinc solution was added, after filtration, to the flask containing the *N*-chloroamine. The reaction mixture was stirred for 90 min, see general procedure (method C). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 58% (0.353 g) yield as a pale yellow oil. **HRMS** (EI+) **(**$C_{16}H_{18}FN$**):** calculated m/z: 243.1423, found: 243.1425. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.39 (d, *J* =6 Hz, 4H), 7.35-7.25 (m, 1 H)， 6.96 (t, *J* = 9 Hz, 2H), 6.72 (dd, *J* = 9 Hz, *J* = 3 Hz, 2H), 4.45 (s, 2H), 4.22 (quint, *J* = 6 Hz, H), 1.30 (d, *J* =6 Hz, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 155.3 (*J* = 232.5 Hz), 145.7, 140.5, 128.4, 126.4, 126.2, 115.3 (d, *J* = 21.8 Hz), 114.7 (d, *J* = 6.8 Hz), 49.1, 48.7, 19.7. **^{19}F-NMR** (182 MHz, $CDCl_3$, BF_3 as external reference) δ/ppm: -129.6.

II-1-5 Control experiments to demonstrate that cobalt is required for the amination process

(a) With commercial ArZnBr

4-Fluorophenylzinc bromide solution (0.5 M in THF, 4 mL, 2 mmol) was added on a solution of freshly prepared *N*-chloropiperidine (0.24 g, 2 mmol, 1 equiv) in THF (1 mL), which was placed in a Schlenk flask under N_2 and cooled to 0 °C. The ice bath was allowed to melt, so that the reaction mixture slowly warm to room temperature. After overnight stirring, no C-N product was seen by GC.

(b) With commercial ArZnBr (THF was replaced by CH_3CN)

4-Fluorophenylzinc bromide solution (0.5 M in THF, 4 mL, 2 mmol) was placed in a 25-mL Schlenk flask under N_2. The solvent was evaporated. Then, acetonitrile (4 mL) was added (The solution is prepared immediately prior to use). The reaction was followed by GC on iodolysed aliquots to verify that ArZnX is present in the medium. This solution was injected into a solution of freshly prepared *N*-chloropiperidine (0.24 g, 2 mmol) in CH_3CN (1 mL), which was placed in a Schlenk flask under N_2 and cooled to 0 °C. The ice bath was allowed to melt, so that the reaction mixture slowly warm to room temperature. After overnight stirring, no C-N product was seen by GC.

(c) Formation of 4-Fluorophenylzinc bromide by electrochemistry in CH_3CN

The disproportionation of Co(I) occurs in the case of electrochemical formation of ArZnBr, so that this reaction is slower than the chemical one. Therefore, once the ArZnX is formed there is no more Co(I) in the mixture.

4-Fluorophenylzinc bromide solution (4 mL, 2.5 mmol), which was obtained from the electrochemical procedure,[1] was injected into a solution of freshly prepared *N*-chloropiperidine (0.24 g, 2 mmol) in CH_3CN (1 mL), which was placed in a Schlenk flask under N_2 and cooled to 0 °C. The ice bath was allowed to melt, so that the reaction mixture slowly warm to room temperature. After overnight stirring, no C-N product was seen by GC.

(d) Formation of 4-Fluorophenylzinc bromide in CH_3CN and addition of catalytic amount of methylvinylketone (MVK)

MVK is known to bind cobalt and to largely reduce or annihilate its catalytic activity, but keeps the arylzinc species intact.[114]

Allylchloride (1.5 mmol, 125 μL) and trifluoroacetic acid (50 μL) were successively added to a solution of $CoBr_2$ (0.11 g, 0.5 mmol) and zinc powder (0.65 g, 10 mmol) in acetonitrile (4 mL) at room temperature, causing an immediate rise in temperature and color change to dark gray. 4-fluorobenzene bromide (0.41 mL, 3.75 mmol) was added. The medium was then stirred at room temperature until the aryl halide was consumed (about 40 min). Methyl vinyl ketone (0.05 mL, 0.5 mmol) was added to this solution. This solution was then injected after filtration into a solution of freshly prepared *N*-chloropiperidine (0.3 g, 2.5 mmol,) in acetonitrile (1 mL placed in a Schlenk flask under N_2 and cooled to 0 °C. The ice bath was allowed to melt, so that the reaction mixture slowly warm to room temperature. After 2 h or overnight stirring, only traces (GC yield< 5%) of C-N product were found.

II-2 The synthesis of aryl thioether employing the arylzinc species

II-2-1 Preparation of *N*-(*p*-tolylthio)succinimide

To a CH_2Cl_2 (15 mL) solution of *N*-Chlorosuccinimide (1.01 g, 7.53 mmol) were added *p*-tolylthio (0.77 ml, 7.53 mmol) and then triethylamine (1.05 mL, 7.53 mmol) dropwise at 0 °C. The reaction mixture was stirred for 18 h at room temperature. After the reaction mixture being partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl,

column chromatography of the organic layer gave the *N*-(*p*-tolylthio)succinimide (1.3 g, 84 %).[201]

II-2-2 Representative procedure for the C-S bond formation reaction with *N*-(*p*-tolylthio)succinimide

The arylzinc solution prepared as mentioned above, was carefully filtered with a syringe filter and injected (3.2 mmol) into a solution of *N*-(*p*-tolylthio)succinimide (1 mmol) in acetonitrile (1 mL), and cooled to 0 °C. The ice bath was allowed to melt, allowing the reaction to slowly warm to room temperature. After 18 h, the reaction was quenched with HCl (2 M). The aqueous layer was extracted three times with diethylether or ethyl acetate and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification was performed using silica gel column chromatography, with a gradient from 95/5 petroleum ether/diethylether, affording the corresponding arylthioether product 73% (0.199 g).

II-2-3 Representative procedure for the C-S bond formation reaction *via* commercial zinc compound

The phenylzinc bromide solution (0.5 M in THF, 6 mL, 3 mmol) was injected into a solution of *N*-(*p*-tolylthio)succinimide (2 mmol) in acetonitrile (1 mL), and cooled to 0 °C. The ice bath was allowed to melt, allowing the reaction to slowly warm to room temperature. After 18 h, the reaction was quenched with HCl (2 M). The conversion of *N*-thioimide was monitored by GC.

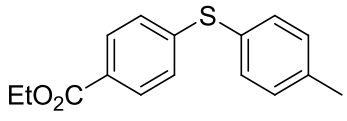
II-2-4 Representative procedure for the C-S bond formation reaction via *one-pot* approach

A 25 mL flask was charged with 4-methylbenzenethiol (2.5 mmol), *N*-chlorosuccinimide (2.75 mmol), and toluene (3 mL). After the mixture was stirred for 20 min at 0 °C, the succinimide was removed by the syringe filter. The soluction was collected. Then the arylzinc bromide (0.8 M CH_3CN solution, 4 mL, 3.2 mmol) were added in this solution by syringe filter. After being stirred for another 12 h (after all the starting materials consumed, monitored by GC), the reaction mixture was quenched with 15 mL HCl (2.0 M) and diluted with ethyl acetate (3 x 5 mL). the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification

201 Shimada, H.; Kikuchi, S.; Okuda, S.; Haraguchi, K.; Tanaka, H. *Tetrahedron* **2009,** *65*, 6008-6016.

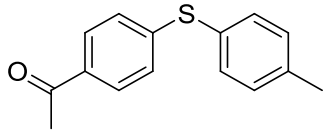
was performed using silica gel column chromatography, with a gradient from 95/5 petroleum ether/diethylether, affording the corresponding arylthioether product 69 % (0.47 g)

II-2-5 Characterization of arylthio ethers



14a

Ethyl 4-(p-tolylthio)benzoate $C_{16}H_{16}O_2S$: CAS# No found. The arylzinc derivative was prepared in acetonitrile (4 mL) from ethly-4-bromobenzoate (0.62 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of *N*-(*p*-tolylthio)succinimide (0.2 g, 1 mmol). Purification on silica gel with petroleum ether-ethyl acetate (95:5) afforded the title compound in 73% (0.199 g) yield as a white crystal. **HRMS** (EI+) **(**$C_{16}H_{16}O_2S$**):** calculated m/z: 272.0871, found: 272.0874. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.88 (d, *J* = 8 Hz, 2H), 7.40 (d, *J* = 8 Hz, 2H), 7.21 (d, *J* = 7.1 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 1.36 (t, *J* = 8 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 166.1, 145.1, 139.1, 134.2, 130.4, 129.9, 128.2, 127.3, 126.7, 60.9, 21.3, 14.4.[202]

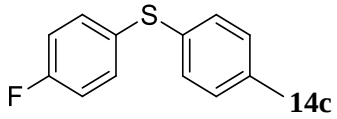


14b

1-(4-(p-tolylthio)phenyl)ethanone $C_{15}H_{14}OS$: CAS# 99433-27-9. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-(4-bromophenyl)ethanone (0.75 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). A 25 mL flask was charged with 4-methylbenzenethiol (2 mmol), *N*-chlorosuccinimide (2.5 mmol), and toluene (3 mL). After the mixture was stirred for 40 min at 0 °C, the succinimide was removed by the syringe filter. Then the arylzinc soluction was added in this mixture at 0 °C. Purification on silica gel with petroleum ether-ethyl acetate (9:1) afforded the title compound in 33% (0.167 g) yield as a white crystal. **HRMS** (EI+) **(**$C_{15}H_{14}OS$**):** calculated m/z: 242.0765, found: 242.0759. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.82 (d, *J* = 8 Hz, 2H), 7.43 (d, *J* = 8 Hz, 2H), 7.25

202 Mo, J.; Eom, D.; Kim, S. H.; Lee, P. H. *Chem. Lett.* **2011,** *40*, 980-982.

(d, *J* = 7.1 Hz, 2H), 7.17 (d, *J* = 8 Hz, 2H), 2.56 (s, 3H), 2.42 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 197.3, 146.1, 139.5, 134.7, 134.2, 130.7, 129.0, 128.0, 126.7, 26.6, 21.4.[203]



14c

(4-fluorophenyl)(p-tolyl)sulfane $C_{13}H_{11}FS$: CAS# 42917-47-5. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-fluorobenzene (0.41 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). A 25 mL flask was charged with 4-methylbenzenethiol (2 mmol), *N*-chlorosuccinimide (2.5 mmol), and toluene (3 mL). After the mixture was stirred for 40 min at 0 °C, the succinimide was removed by the syringe filter. Then the arylzinc soluction was added in this mixture at 0 °C. Purification on silica gel with petroleum ether-ethyl acetate (95:5) afforded the title compound in 38% (0.165 g) yield as a pale yellow oil. **HRMS** (EI+) **(**$C_{13}H_{11}FS$**):** calculated m/z: 218.0566, found: 218.0572. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.25 (m, 2H), 7.24 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 6.99 (m, 2H), 2.39 (s, 3H),. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 162.0 (*J* = 130 Hz), 137.3 (*J* = 10.0 Hz), 132.8, 132.2, 131.5, 131.2, 130.0, 116.2 (*J* = 2.2 Hz), 21.7. **^{19}F-NMR** (282 MHz, $CDCl_3$) δ/ppm: -104.6.[204]

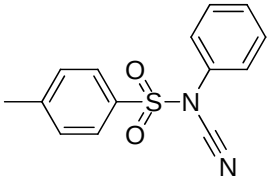
203 Prasad, D. J. C.; Sekar, G. *Org. Lett.* **2011,** *13*, 1008-1011.

204 (a) Still, I. W. J.; Toste, F. D. *J. Org. Chem.* **1996,** *61*, 7677-7680. (b) Dayal, S. K.; Taft, R. W. *J. Am. Chem. Soc.* **1973,** *95*, 5595-5604.

III Cobalt-catalyzed Electrophilic Cyanation of Arylzincs with N-cyano-N-phenyl-p-methyl-benzenesulfonamide (NCTS)

III-1 Procedure for the formation of NCTS

Dry 250 mL round bottom flask was charged with phenylurea (10.9 g, 8 mmol) and pyridine was added (54 mL). The flask was immersed in room temperature water bath. *P*-Toluenesulfonyl chloride (52.8 g, 27.7 mmol) was added potion wise over 3 min. The reaction mixture was stirred for additional 15 min and poured into to ice-cooled water (400 mL) with mechanical stirring. Precipitate formed during mechanical stirring was filtered and washed with water. The crude product was treated with 40 mL of ethanol and precipitated from the same. (During ethanol treatment unreacted tosyl chloride was converted into corresponding ethyl ester). *N*-cyano-*N*-phenyl-4-methylbenzenesulfonamide was provided as white power (17.4 g, 76%).

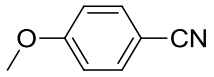


HRMS (EI+): calculated: 272.0619; found: 272.0616. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.55 (d, *J* = 8.4 Hz, 2H), 7.37-7.23 (m, 5H), 7.14-7.09 (m, 2H), 2.39 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 146.7, 134.5, 132.3, 130.2, 130.0, 129.8, 128.4, 126.5, 108.6, 21.8.[161]

III-2 Representative procedure for the cyanation reaction

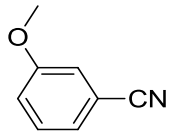
The arylzinc solution prepared as mentioned above, was carefully filtered with a syringe filter and injected into a solution of NCTS (2.5 mmol), Zn dust (0.02 g, 0.25 mmol) in acetonitrile (1 mL), which was placed in a Schlenk flask under N_2 and cooled to 0 °C. The ice bath was allowed to melt, allowing the reaction to slowly warm to 50 °C. After 4-6 h, the reaction was quenched with HCl (2 M). The aqueous layer was extracted three times with diethylether or ethyl acetate and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification was performed using silica gel column chromatography, with a gradient from 99:1 to 8:2 petroleum ether/diethylether, affording the corresponding arylnitrile product.

III-3 Characterization data for arylnitriles



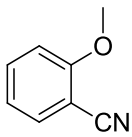
15a

4-methoxybenzonitrile C_8H_7NO: CAS# 874-90-8. The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-methoxy-4-bromobenzene (0.47 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.50 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 84% yield (0.336 g) as a white solid. **HRMS** (EI+) **(**C_8H_7NO**):** calculated m/z: 133.0528, found: 133.0527. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.57 (d, *J* = 9 Hz, 2H); 6.93 (d, *J* = 9 Hz, 2H); 3.84 (*s*, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 162.8; 133.9; 119.2; 114.7; 103.8; 55.5.[205]



15b

3-methoxybenzonitrile C_8H_7NO: CAS# 1527-89-5**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 3-**bromoanisole** (0.52 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.50 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 57% (0.19 g) yield as a white solid. **HRMS** (EI+) (C_8H_7NO): calculated m/z: 133.0527, found: 133.0526. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.39 (m, 1H), 7.27 (m, 1H), 7.16 (m, 2H), 3.87 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 159.6, 130.3, 124.5, 119.3, 118.7, 116.8, 113.1, 55.5.[206]

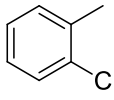


15c

205 Deshmukh, S. S.; Huddar, S. N.; Jadhav, R. R.; Akamanchi, K. G. *Tetrahedron Lett.* **2011,** *52*, 4533-4536.

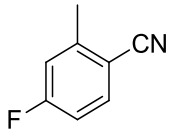
206 Zhou, W.; Xu, J.; Zhang, L.; Jiao, N. *Org. Lett.* **2010,** *12*, 2888-2891.

2-methoxybenzonitrile C_8H_7NO: CAS# 6609-56-9**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 2-bromoanisole (0.52 mL, 3.75 mmol) as described in the general procedure. It was obtained in 70% GC yield (2.6 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.50 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 58% (0.193 g) yield as a white solid. **HRMS** (EI+) **(**C_8H_7NO**):** calculated m/z: 133.0527, found: 133.0526. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.62 (t, *J* = 6 Hz, 2H), 7.05 (t, *J* = 6 Hz, 2H), 3.96 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 160.2, 133.4, 132.6, 119.7, 115.4, 110.3, 100.5, 55.0.[165]



15d

2-methylbenzonitrile C_8H_7N: CAS# 529-19-1**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-2-methylbenzene (0.45 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (9:1) afforded the title compound in 98% (0.286 g) yield as a colorless oil. **HRMS** (EI+) (C_8H_7N): calculated m/z: 117.0578, found: 117.0578. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.60 (dd, *J* = 9 Hz, *J* = 3 Hz, 1H), 7.51 (dt, *J* = 9 Hz, *J* = 3 Hz, 1H), 7.36 (m, 2H), 2.54 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 142.0, 132.7, 132.5, 130.2, 126.2, 118.2, 112.8, 20.5.[207]

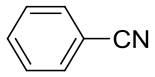


15e

4-fluoro-2-methylbenzonitrile C_8H_6FN: CAS# 147754-12-9**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-fluoro-2-methylbenzene (0.709 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-

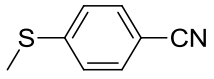
207 Liu, L.; Li, J.; Xu, J.; Sun, J.-T. *Tetrahedron Lett.* **2012,** *53*, 6954-6956.

diethyl ether (95:5) afforded the title compound in 81% (0.274 g) yield as a white powder. **HRMS** (EI+) (C_8H_6FN): calculated m/z: 135.0484, found: 135.0485. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.33-7.18 (m, 3H), 2.54 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 160.3 (d, *J* = 247.5 Hz), 137.9 (d, *J* =3.8 Hz), 131.9 (d, *J* =8.3 Hz), 122.2 (d, *J* = 21.0 Hz), 118.9 (d, *J* = 24.0 Hz), 116.9, 113.8 (d, *J* =9 Hz), 19.7.[208]



15f

Benzonitrile C_7H_5N: CAS# 100-47-0**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from bromobenzene (0.4 mL, 3.75 mmol) as described in the general procedure. It was obtained in 81% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 76% (0.196 g) yield as a white powder. **HRMS** (EI+) (C_7H_5N): calculated m/z: 104.0422, found: 104.0419. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.71-7.61 (m, 3H), 7.54-7.49 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 133.3, 132.7, 129.7, 119.3, 113.0.[209]



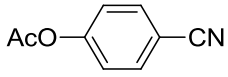
15g

4-(methylthio)benzonitrile C_8H_7NS: CAS# 21382-98-9**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from (4-bromophenyl)(methyl)sulfane (0.762 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 76% (0.282 g) yield as a white powder. **HRMS** (EI+) (C_8H_7NS): calculated m/z: 149.0299, found: 149.0297. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.57 (d, *J* = 9 Hz, 2H), 7.31 (d, *J* = 9 Hz, 2H), 2.54 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 146.1, 132.2, 125.5, 119.0, 107.7, 14.7.[210]

208 Zhang, Z.; Wallace, M. B.; Feng, J.; Stafford, J. A.; Skene, R. J.; Shi, L.; Lee, B.; Aertgeerts, K.; Jennings, A.; Xu, R.; Kassel, D. B.; Kaldor, S. W.; Navre, M.; Webb, D. R.; Gwaltney, S. L. *J. Med. Chem.* **2010,** *54*, 510-524.

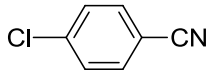
209 Zheng, S.; Yu, C.; Shen, Z. *Org. Lett.* **2012,** *14*, 3644-3647.

210 Laulhé, S.; Gori, S. S.; Nantz, M. H. *J. Org. Chem.* **2012,** *77*, 9334-9337.



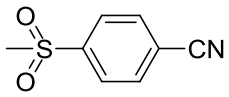
15h

4-cyanophenyl acetate $C_9H_7NO_2$: CAS# 13031-41-9**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromophenyl acetate (0.806 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-EtOAc (9:1) afforded the title compound in 40% (0.161 g) yield as a colorless oil. **HRMS** (EI+) ($C_9H_7NO_2$): calculated m/z: 161.0480, found: 161.0477. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.73 (d, *J* = 9 Hz, 3 Hz, 1H), 7.28 (d, *J* = 9 Hz, 1H), 2.34 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 169.1, 154.5, 134.2, 123.3, 118.7, 110.2, 21.4.[211]



15i

4-chlorobenzonitrile C_7H_4ClN: CAS# 623-03-0**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-chloro-4-iodobenzene (0.904 g, 3.75 mmol) as described in the general procedure. It was obtained in 90% GC yield (3.4 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.50 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 63% (0.216 g) yield as a white powder. **HRMS** (EI+) (C_7H_4ClN): calculated m/z: 137.0032, found: 137.0033. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.64 (d, *J* = 9 Hz, 2H), 7.51 (d, *J* = 9 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 139.7, 133.9, 130.0, 118.3, 111.3.[212]

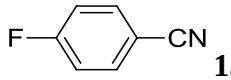


15j

4-(methylsulfonyl)benzonitrile $C_8H_7NO_2S$: CAS# 22821-76-7**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-(methylsulfonyl)benzene (0.90mg, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification

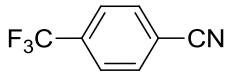
211 Kadam, S. T.; Kim, S. S. *Synthesis* **2008**, 267-271.
212 Ishii, G.; Harigae, R.; Moriyama, K.; Togo, H. *Tetrahedron* **2013,** *69*, 1462-1469.

on silica gel with petroleum ether-diethyl ether (9:1) afforded the title compound in 47% (213 mg) yield as as white solid (the weight of the mixture was 460 mg including 247 mg of 4-methyl-N-phenylbenzenesulfonamide calculated by ^{1}H NMR). **HRMS** (EI+) ($C_8H_7NO_2S$): calculated m/z: 181.0198, found: 181.0205. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.83 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H), 2.76 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 151.4, 133.0, 124.3, 117.7, 114.81, 43.8.[213]



15k

4-fluorobenzonitrile C_7H_4FN: CAS# 1194-02-1**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-4-fluorobenzene (0.41 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.81 g, 3 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (9:1) afforded the title compound in 74% (0.269 g) yield as a colorless oil. **HRMS** (EI+) (C_7H_4FN): calculated m/z: 121.0328, found: 121.0322. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.74 (m, 2H), 7.21 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 165.0 (*J* = 130 Hz), 134.7 (*J* = 10.0 Hz), 118.0, 116.8 (*J* = 2.2 Hz), 108.6. **^{19}F-NMR** (282 MHz, $CDCl_3$) δ/ppm: -104.6.[214 215]

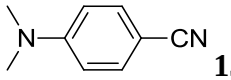


15l

4-(trifluoromethyl)benzonitrile $C_8H_4F_3N$: CAS# 455-18-5**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromobenzotrifluoride (0.52 mL, 3.75 mmol) as described in the general procedure. It was obtained in 85% GC yield (3.2 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 68% (0.291 g) yield as a colorless oil. **HRMS** (EI+) ($C_8H_4F_3N$): calculated m/z: 171.0296, found: 171.0299. **^{1}H-NMR** (300 MHz,

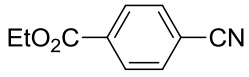
213 Yu, B.; Liu, A.-H.; He, L.-N.; Li, B.; Diao, Z.-F.; Li, Y.-N. *Green Chem.* **2012,** *14*, 957-962.
214 Ishii, G.; Moriyama, K.; Togo, H. *Tetrahedron Lett.* **2011,** *52*, 2404-2406.
215 Massachusetts Institute of Technology Patent**:** US2011/15401 A1,**2011.**

$CDCl_3$) δ/ppm: 7.85-7.77 (m, 4H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 134.6 (q, *J* = 34 Hz), 132.7, 126.2 (q, *J* = 3.7 Hz), 123.1(q, *J* = 271 Hz), 117.5, 116.1. **^{19}F-NMR** (282 MHz, $CDCl_3$) δ/ppm: -63.1. [216]



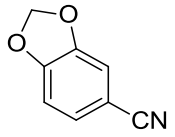
15m

4-(dimethylamino)benzonitrile $C_9H_{10}N_2$: CAS# 1197-19-9**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 4-bromo-N,N-dimethylaniline (0.75 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-EtOAc (9:1) afforded the title compound in 68% (0.248 g) yield as a white solid. **HRMS** (EI+) ($C_9H_{10}N_2$): calculated m/z: 146.0844, found: 146.0851. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.46 (d, *J* = 9 Hz, 2H), 6.63 (d, *J* =9 Hz, 2H), 3.03 (s, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 152.4, 133.4, 120.8, 111.4, 97.3, 39.9.[160]



15n

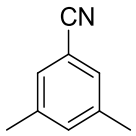
Ethyl 4-cyanobenzoate $C_{10}H_9NO_2$: CAS# 7153-22-2**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from ethly-4-bromobenzoate (0.62 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.81 g, 3 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (9:1) afforded the title compound in 72% (0.378 g) yield as a white crystal. **HRMS** (EI+) ($C_{10}H_9NO_2$): calculated m/z: 175.0634, found: 175.0633. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 8.15 (d, *J* = 9 Hz, 2H), 7.78 (d, *J* = 9 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 6 Hz, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 165.4, 134.9, 132.8, 130.4, 118.6, 116.7, 62.3, 14.5.[217]



15o

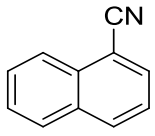
216 Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012,** *134*, 9034-9037.

Benzo[d][1,3]dioxole-5-carbonitrile $C_8H_5NO_2$: CAS# 4421-09-4**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 5-bromobenzo[d][1,3]dioxole (0.755 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 79% (0.291 g) yield as a white powder. **HRMS** (EI+) ($C_8H_5NO_2$): calculated m/z: 147.0320, found: 147.0320. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.62 (dd, *J* = 9 Hz, 3 Hz, 1H), 7.07 (d, *J* =3 Hz, 1H), 6.92 (d, *J* = 9 Hz, 1H), 6.10 (s, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 151.5, 148.0, 128.2, 118.9, 111.4, 109.1, 104.9, 102.2.[212]



15q

3,5-dimethylbenzonitrile C_9H_9N: CAS# 22445-42-7**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromo-3,5-dimethylbenzene (0.51 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 g, 2.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 58% (0.111 g) yield as a white powder. **HRMS** (EI+) (C_9H_9N): calculated m/z: 131.0735, found: 131.0749. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.26 (s, 2H), 7.22(s, 1H), 2.35 (s, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 138.9, 134.4, 129.4, 119.0, 111.9, 20.8.[161]



15r

1-naphthonitrile $C_{11}H_7N$: CAS# 86-53-3**.** The arylzinc derivative was prepared in acetonitrile (4 mL) from 1-bromonaphthalene (0.779 g, 3.75 mmol) as described in the general procedure. It was obtained in 90% GC yield (3.4 mmol). This solution was filtered and added to a solution of NTCS (0.81 g, 3 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5) afforded the title compound in 79% (0.365 g) yield as a white powder. **HRMS** (EI+) ($C_{11}H_7N$):

calculated m/z: 153.0583, found: 153.0578. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 8.23 (d, *J* = 9 Hz, 1H), 8.07, (d, *J* =9 Hz, 1H), 7.92-7.89 (m, 2H), 7.67-7.49 (m, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 133.2, 132.9, 132.6, 132.3, 128.6, 128.6, 127.5, 125.1, 124.9, 117.8, 110.1.[217]

217 Azath, I. A.; Suresh, P.; Pitchumani, K. *New J. Chem.* **2012,** *36*, 2334-2339.