Cobalt-catalyzed carbon-carbon bond formation by activation of carbon-halogen or carbon-hydrogen bonds

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Contents

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List of abbreviations

Ac	Acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aromatic group
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bipy	bipyridine
Bn	Benzyl
Boc	t-butyloxycarbonyl
B(pin)	pinacolatoboron
Bu	butyl
Cbz	carboxybenzyl
CDC	cross-dehydrogenative coupling
cod	1,5-cyclooctadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DCB	2,3-dichlorobutane
DCE	1,2-dichloroethane
DFCT	3,5-di(trifluoromethyl)phenyl(cyano)iodonium triflate
DMAc	*N,N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
DPEphos	bis[(2-diphenylphosphino)phenyl]methane
dppe	1,2-bis(diphenylphosphino)ethane
dppm	1,2-bis(diphenylphosphino)methane
dppp	1,2-bis(diphenylphosphino)ethane
DTBP	di-*tert*-butyl peroxide
***ee*.**	enantiomeric excess
equiv.	equivalent
Et	ethyl
GC	gas chromatography
glyme	dimethoxyethane
HR	high resolution
***i*Pr**	iso-propyl
Me	methyl
MS	mass spectrometry

NEP	*N*-ethyl-2-pyrrolidone
NHC	*N*-heterocyclic carbine
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NP	nanoparticles
OAc	acetate
OTf	triflate
OTs	toyslate
Ph	phenyl
phen	1,10-phenantroline
PMP	*p*-methylphenyl
ppm	part per million
PTA	1,3,5-triaza-7-phosphaadamantane
PTS	polyoxyethanyl α-tocopheryl sebacate
py	pyridine
Pyphos	2-[2-(diphenylphosphanyl)ethyl]pyridine
pym	pyrimidine
Q	quinoline
r.t.	room temperature
s	singlet
SET	single electron transfer
t	triplet
TBAB	tetra-*n*-butylammonium bromide
TBHP	*tert*-butyl hydroperoxide
***t*Bu**	tert-butyl
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TFP	tri(2-furyl)phosphine
TMEDA	tetramethylethylenediamine
TMEPO	2,2,6,6-tetramethylpiperine-1-oxyl
TMSCl	trimethylsilylchloride
Tol	toluene
Ts	Tosyl
Xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

Résumé Français

La formation de liaisons carbone-carbone est l'un des outils les plus importants en synthèse organique largement utilisé pour la synthèse de produits pharmaceutiques, de produits chimiques agricoles et de produits naturels. Au cours des dernières décennies, la formation de liaisons carbone-carbone catalysée par un métal de transition s'est considérablement développée comme le couplage de Negishi, le couplage de Kumada, le couplage de Suzuki-Miyaura et le couplage de Heck.

Le palladium et le nickel sont bien connus comme catalyseurs efficaces pour ce type de réaction pour construire des liaisons carbone-carbone. Néanmoins, ces métaux sont chers et/ou toxiques. En outre, des ligands sophistiqués et coûteux sont toujours nécessaires pour obtenir de bons rendements. Par conséquent, le développement de méthodes efficaces utilisant des catalyseurs métalliques bons marchés sont en forte demande. Récemment, l'intérêt de l'utilisation des métaux de transition de la première rangée dans la formation de liaisons carbone-carbone s'est accru.

Parmi les métaux de transition de la première rangée, le cobalt est un bon catalyseur utilisé en chimie organique. Dans les premiers temps, Otto Roelen a découvert que le cobalt a été capable de catalyser l'hydrocarbonylation de l'éthylène en phase organique, et ce fut la naissance de la catalyse homogène.[1] Pour la construction de liaisons carbone-carbone, le cobalt joue également un rôle important. Après les premières réactions de couplage catalysées par le cobalt dans les années 1940 développées par Kharasch,[2] la formation de liaisons carbone-carbone par la catalyse au cobalt a récemment montré un intérêt croissant.[3]

De plus, les réactifs organométalliques ont également reçu de nombreuses attentions. Parmi ceux-ci, les organozinciques sont parmi les plus largement utilisées, en particulier dans le

[1] F. Hebrard, P. Kalck, *Chem. Rev.*, **2009**, *109*, 4272–4282.

[2] a) M. S. Kharasch, E. K. Fields, *J. Am. Chem. Soc*. **1941**, *63*, 2316; b) M. S. Kharasch, C. F. Fuchs, *J. Am. Chem. Soc*. **1943**, *65*, 504.

[3] a) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435-1462; b) W. Hess, J. Treutwein, G. Hilt, *Synthesis-Stuttgart* **2008**, 3537-3562; c) C. Gosmini, J.-M. Begouin, A. Moncomble, *Chem. Commun.* **2008**, *28*, 3221-3233; d) C. E. I. Knappke, S. Grupe, D. Gartner, M. Corpet, C. Gosmini, *Chem. Eur. J.* **2014**, *20*, 6828-6842; e) Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208-1219; f) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498-525.

couplage de Negishi. Outre les méthodes reportées par Rieke et par Knochel,[4] notre groupe a développé une méthode plus simple et efficace pour la synthèse d'arylzinciques en utilisant la catalyse au cobalt. Il est à noter que le cobalt utilisé dans la synthèse d'arylzinciques peut catalyser la réaction de couplage ultérieure, ce qui est plus économique.

Pour notre part, nous avons établi une nouvelle réaction de cyanation électrophile catalysée au cobalt, d'arylzinciques, avec une source de cyanure bénigne et non-toxique, le *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS). L'addition d'une quantité catalytique de zinc métallique dans la seconde étape est nécessaire pour obtenir une bonne efficacité de la réaction. Cette méthode montre une excellente tolérance des groupements fonctionnels dans des conditions très douces. En particulier, plusieurs groupements chélatants tels que cétone et nitrile, peuvent être permis en utilisant le complexe de cobalt associé au ligand bipyridine [$CoBr_2$(bipy)]. C'est une bonne alternative aux voies de cyanation électrophiles précédemment décrits. En outre, une variété d'autres composés de type N-CN a été examinée.

Les réactions de couplage croisé réducteurs sont des approches simples pour obtenir des liaisons carbone-carbone. Depuis une dizaine d'années, notre groupe a établi une variété de couplages réducteurs impliquant des carbones *sp*2 et des carbones *sp*3.[3d] En général, ces méthodes sont efficaces et se font dans des conditions douces, et des ligands sophistiqués ne sont pas nécessaires. Ainsi, nous continuons d'utiliser ce système catalytique à plusieurs types de réactions de couplage croisé.

Dans le deuxième chapitre, sur la base des réactions des couplages croisées réducteurs précédentes développées dans notre laboratoire, nous avons étudié la formation de liaison C_{sp3}-C_{sp3} par homocouplage reducteur catalysé au cobalt. Une variété de bromures d'alkyle primaires et secondaires portant des groupements fonctionnels ont pu être tolérée offrant les produits d'homocouplage avec des rendements modérés à d'excellents dans des conditions douces. Par ailleurs, les iodures d'alkyle, les chlorures de benzyle, ainsi que les acétates d'allyliques donnent également de bons rendements. Avec des chlorures d'alkyle moins réactifs, de modérés à de bons rendements sont obtenus par addition d'iodures de sodium, d'augmentation de la température et de temps de réaction. L'iodure de sodium est également

[4] a) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445-1453; b) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem., Int, Ed.* **2006**, *45*, 6040-6044; c) P. Knochel, J. J. A. Perea, P. Jones, *Tetrahedron*. **1998**, *54*, 8275-8319.

utilisé pour la dimérisation de toyslates alkyle. L'étude mécanistique suggère l'implication d'un intermédiaire radicalaire dans la réaction.

Suite à ces résultats nous avons ensuite exploré le couplage croisé entre 2 halogénures d'alkyles différents. L'homocouplage concurrentiel de chacun des halogénures d'alkyle est observé. Cependant, après modification des conditions de réaction, il est apparu que le cobalt associé à la quinoléine comme ligand et qu'en opérant à des températures plus élevées, permet d'obtenir de bons rendements. Cependant, la méthode n'est pas généralisable à tous les halogénures d'alkyle.

Dans le troisième chapitre, nous avons reporté une nouvelle approche de couplage croisé vinyle-benzyle catalysée au cobalt. Contrairement aux couplages croisés réducteurs précédents catalysés par le cobalt reportés par notre groupe, la pyridine et l'acide trifluoroacetique (TFA) ne sont plus nécessaires. Au lieu de cela, le TMSCl est choisi pour activer le manganèse et l'iodure de sodium est indispensable pour cette réaction. Des halogénures de vinyles et de benzyles portant de groupements electrodonneurs ou electroattrateurs peuvent ainsi être couplés efficacement. En générale, il est nécessaire de chauffer à 50 °C, avec des produits de départ portant des groupements electroattrateurs. La stéréochimie de la double liaison carbone-carbone reste inchangée. Comme l'homocouplage d'alkyle-alkyle, un intermédiaire radicalaire est impliqué dans la réaction.

Ensuite, nous avons essayé d'étendre cette méthode à d'autres types de substrats tels que les halogénures et les acétates allyliques. Toutefois, seuls les halogénures d'allyliques conduisent à des rendements modérés par couplage avec des bromures de vinyle.

Egalement, au cours des cinq dernières années, l'activation d'une liaison C-H catalysée par le cobalt a été développé par différents groupes.[4e-f] Notamment, les organométalliques permettent l'activation d'une liaison C-H par la catalyse au cobalt. Jusqu'à présent, seuls les réactifs de Grignard ont été utilisés. Etant donné que les organozinciques sont moins nucléophiles, il est plus difficile de les employer pour l'activation d'une liaison C-H.

Pour notre part, nous avons essayé d'activer d'une liaison C-H de la 2-phénylpyridine avec des réactifs d'arylzinciques grâce à la catalyse au cobalt. Après des modifications importantes des conditions de réaction, nous avons obtenu un rendement modéré au produit d'arylation. Le principal problème est faible taux de conversion de 2-phénylpyridine. L'optimisation de la réaction doit être poursuivie.

En conclusion, nous avons développé plusieurs réactions de formation des liaisons carbone-carbone catalysée par le cobalt. Les réactions se font généralement dans des conditions douces. L'utilisation du catalyseur au cobalt, qui est économique, éco-compatible et efficace, est une bonne alternative aux autres métaux de transition.

General Introduction

Carbon-carbon bond formation has been one of the most significant synthetic tools in chemistry, which has been widely applied in pharmaceuticals, agricultural chemicals and natural products.[5] With great efforts by chemists during the past few decades, considerable development of transition-metal-catalyzed carbon-carbon bond formation has been achieved such as Negishi reaction, Kumada reaction and Suzuki-Miyaura reaction and Heck reaction.

It is well known that late transition metals are efficient catalyst for these types of reaction to construct carbon-carbon bonds. Nevertheless, these metals are expensive and/or toxic. Moreover, sophisticated and expensive ligands are always necessary to obtain good yields. Therefore, efficient methods using low-cost metal catalysts are in high demand. Recently, the application of the first-row transition metals in catalysis and organic synthesis has attracted increasing interest and remarkable advances have been achieved.

Among those first-row transition metals, cobalt is widely used for various reactions. In early times, Otto Roelen discovered that cobalt was able to catalyze the hydrocarbonylation of ethylene in organic phase, and it was the birth of homogeneous catalysis.[6] For construction of carbon-carbon bonds, cobalt also plays an important role. After Kharasch pioneered the first cobalt-catalyzed coupling reactions in 1940s,[7] the cobalt-catalyzed carbon-carbon bond formation has emerged increasingly.[8]

Cross-coupling reactions are straightforward approaches to obtain carbon-carbon bonds. The development of sustainable cobalt-catalyzed cross-coupling is still progressing impressively. In our group, we have established a variety of cross-coupling involving *sp*2-carbon and *sp*3-carbon.[4d] In general, these methods are efficient and simply operated under mild conditions,

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[5] (a) J. Tsuji, *Palladium in Organic Synthesis; Topics in Organometallic Chemistry*, Vol. 14; Springer: Berlin, **2005**. (b) G. Franció, W. Leitner, *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) A. C. Spivey, C. J. G. Gripton, J. P. Hannah, *Curr. Org. Synth*. **2004**, *1*, 211-226.

[6] F. Hebrard, P. Kalck, *Chem. Rev.*, **2009**, *109*, 4272–4282.

[7] a) M. S. Kharasch, E. K. Fields, *J. Am. Chem. Soc*. **1941**, *63*, 2316; b) M. S. Kharasch, C. F. Fuchs, *J. Am. Chem. Soc*. **1943**, *65*, 504.

[8] a) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435-1462; b) W. Hess, J. Treutwein, G. Hilt, *Synthesis-Stuttgart* **2008**, 3537-3562; c) C. Gosmini, J.-M. Begouin, A. Moncomble, *Chem. Commun.* **2008**, *28*, 3221-3233; d) C. E. I. Knappke, S. Grupe, D. Gartner, M. Corpet, C. Gosmini, *Chem. Eur. J.* **2014**, *20*, 6828-6842; e) Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208-1219; f) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498-525.

and moreover, sophisticated ligands are not necessary. Thus, we continue to extend such catalytic system to more kinds of cross-coupling reactions. In the following parts, alkyl-alkyl homo- and cross-coupling, as well as vinyl-benzyl cross-coupling will be described.

In the other hand, organometallic reagents have also received numerous attentions. Among these, organozinc compounds are one of the most widely used, in particular, in Negishi coupling reactions. Apart from the Rieke and Knochel methods,[9] our group has developed a more simple and efficient way to prepare arylzinc compounds in the presence of cobalt catalyst. It is noteworthy that the cobalt used in synthesis of arylzinc species could catalyze next coupling reaction, which is more economical. Based on the development of cobalt-catalyzed cross-coupling,[4d] we disclose the functionalization of arylzinc reagents. In this thesis, a cyanation of arylzinc compounds will be discussed.

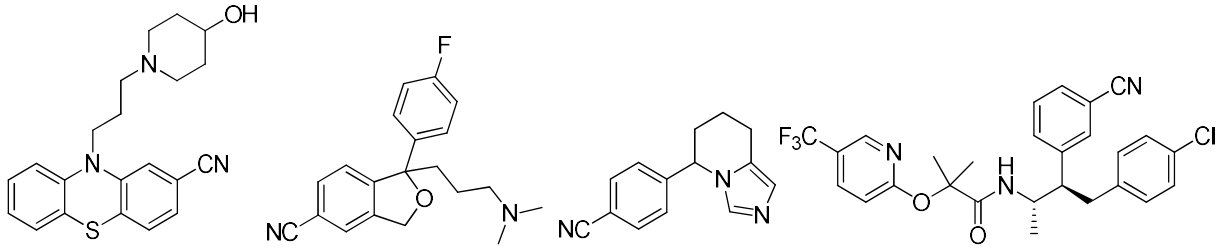
In addition, cobalt-catalyzed C-H activation has achieved considerable progress in the last five years. [4e-f] Notably, organometallic compounds are a great promoter for cobalt-catalyzed C-H activation. So far, Grignard reagents are most useful in these reactions. Since organozinc compounds are less nucleophilic, it is more difficult to employ them to assist C-H activation. To expand the application of cobalt catalytic system in our group, series of trials about cobalt-catalyzed C-H activation with arylzinc reagents will be discussed.

[9] a) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445-1453; b) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem., Int, Ed.* **2006**, *45*, 6040-6044; c) P. Knochel, J. J. A. Perea, P. Jones, *Tetrahedron*. **1998**, *54*, 8275-8319.

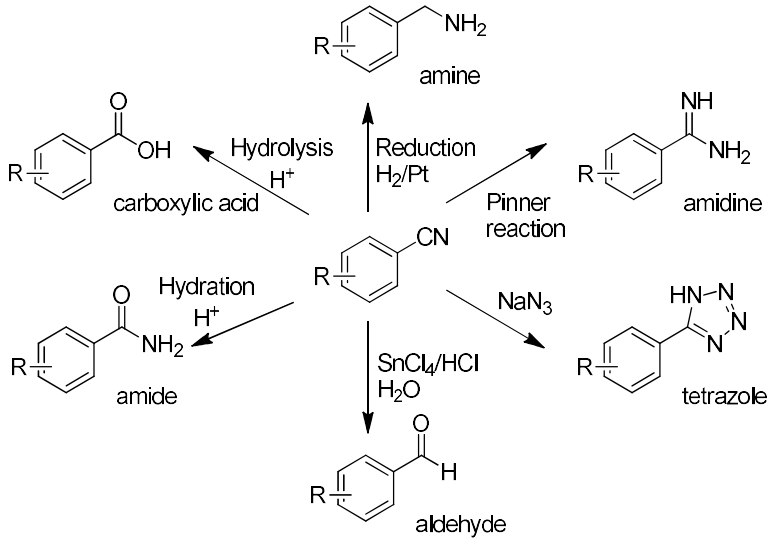
Chapter 1 Cobalt-catalyzed Electrophilic Cyanation of Arylzincs with N-cyano-N-phenyl-p-methyl-benzenesulfonamide (NCTS)

I. Introduction

Benzonitriles are ubiquitous organic compounds in natural products, pharmacy, dyes and electronic materials (Scheme 1-1).[10] Meanwhile the nitrile group plays an important role in organic synthesis since it allows a multitude of transformations to other functional groups, such as amines, amidines, tetrazoles, aldehydes, amides (Scheme 1-2).[11] As a result, the synthesis of aryl-CN has attracted great attention of chemists.



Scheme 1-1 Examples of pharmaceutical, dyes and electronic materials benzonitrile structures



Scheme 1-2 Representative synthetic applications of benzonitriles

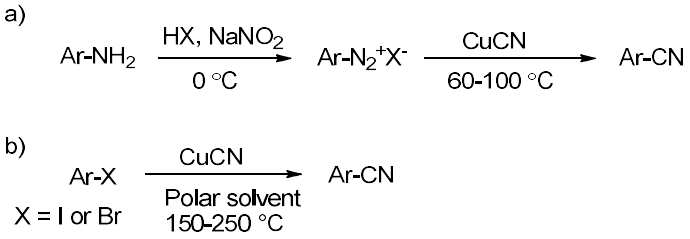
In the early years, the Sandmeyer reaction after diazotization of anilines[12] and Rosenmund-von Braun reaction of aryl halides[13] were the two most traditional methods for the preparation

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

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

[12] C. Galli, *Chem. Rev.* **1988,** *88*, 765-792.

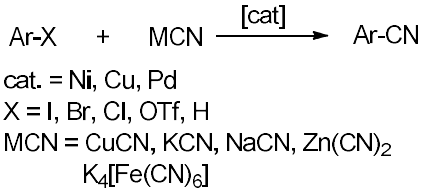
of benzonitriles (Scheme 1-3). However, both of them suffered from significant drawbacks: a stoichiometric amount of very toxic copper cyanide was required and not wide scope of substrates was tolerated. Moreover, the conditions of Rosenmund-von Braun reaction were relatively harsh such as high temperature.



Scheme 1-3 a) Sandmeyer reaction; b) Rosenmund-von Braun Reaction

I-1 Metal cyanide s as "CN" source

An alternative way to obtain the benzonitriles is transition-metal catalyzed nucleophilic cyanation reactions of aryl-X (X = halides, OTf, H) using commercial and cheap metal cyanides as "CN" source. In the presence of transition metal, Pd, Cu, or Ni catalysts, various cyanide sources, such as CuCN,[14] KCN,[15] NaCN,[16] $Zn(CN)_2$,[17] or $K_4[Fe(CN)_6]$[18] react with functionalized aryl halides to provide the corresponding aryl nitriles (Scheme 1-4). They have been applied in both academic research and industry. However, due to the high affinity of the



Scheme 1-4 Transition metal-catalyzed cyanation reactions with metal cyanides

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[13] a) K. W. Rosenmund, E. Struck, *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1919,** *52*, 1749-1756; b) D. T. Mowry, *Chem. Rev.* **1948,** *42*, 189-283.

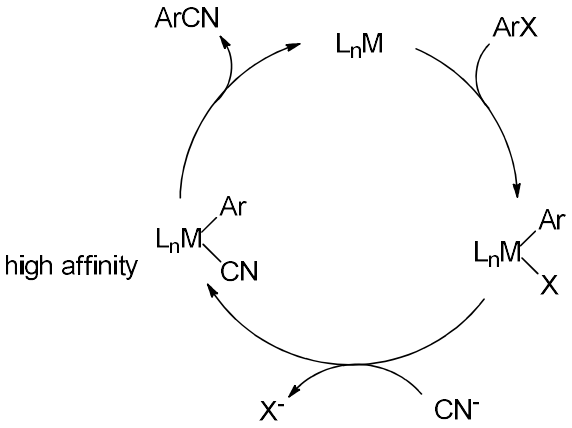
[14] J. Chen, Y. Sun, B. Liu, D. Liu, J. Cheng, *Chem. Commun.* **2012,** *48*, 449-451.

[15] a) K. Takagi, T. Okamoto, Y. Sakakibara, S. Oka, *Chem. Lett.* **1973**, 471-474; b) M. Sundermeier, A. Zapf, M. Beller. J. Sans, *Tetrahedron Lett.* **2001**, *42*, 6707-6710; c) Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2005,** *11*, 2483-2492.

[16] a) J. R. Dalton and S. L. Regen, *J. Org. Chem.* **1979**, *44*, 4443–4444; b) A. V. Ushkov, V. V. Grushin, *J. Am. Chem. Soc.* **2011,** *133*, 10999-11005.

[17] a) A. Littke, M. Soumeillant, R. F. Kaltenbach III, R. J. Cherney, C. M. Tarby, S. Kiau, *Org. Lett.* **2007**, *9*, 1711-1714; b) F. G. Buono, R. Chidambaram, R. H. Mueller, R. E. Waltermire, *Org. Lett.* **2008**, *10*, 5325-5328; c) M. Shevlin, *Tetrahedron Lett.* **2010**, *51*, 4833-4836.

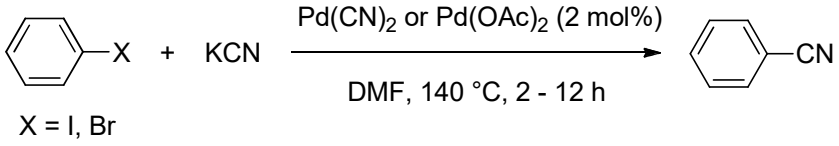
[18] a) T. Schareina, A. Zapf, M. Beller, *Chem. Commun.* **2004**, 1388-1389; b) T. Schareina, R. Jackstell, T. Schulz, A. Zapf, A. Cotté, M. Gotta, M. Beller, *Adv. Syn. Catal.* **2009**, *351*, 643-648; c) P. Y. Yeung, C. M. So, C. P. Lau, F. Y. Kwong, *Angew. Chem. Int. Ed.* **2010**, *49*, 8918-8922; d) T. D. Senecal, W. Shu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 10035 - 10039.



Scheme 1-5 General mechanism of transition metal catalyzed nucleophilic cyanation reactions

cyanide ion towards the metal catalysts, high catalyst loading is required (Scheme 1-5).

In 1973, Takagi and coworkers reported the first palladium-catalyzed cyanation of aryl halides with KCN as a cyanating reagent (Scheme 1-6).[15a] However, this method still required high temperature and the group did not extend this method to other functionalized aryl halides. Some efforts were spared to make progress of this kind of cyanation such as changing the ligands, using different solvent and employing additives,[19] though most of these protocols need harsh reaction conditions. In 2004, employing KCN as a cyanating reagent, Yang and coworkers developed a palladium-catalyzed cyanation reaction of aryl halides promoted by trace levels of tri-n-butyltin chloride (Scheme 1-7).[20] A variety of functionalized aryl halides were well tolerated affording good to excellent yields, with low catalyst loading under mild reaction conditions. Tri-*n*-butyltin chloride plays a role similar to a phase transfer catalyst to generate a tin-ate complex,[21] which was proposed to be the key to this approach.

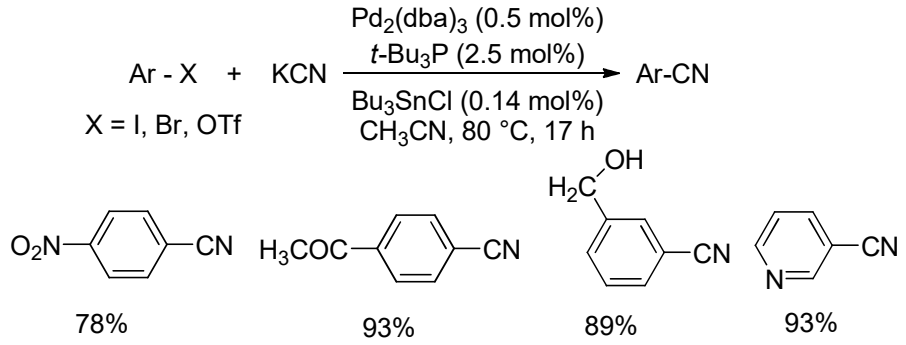


Scheme 1-6 Palladium-catalyzed cyanation reaction of aryl halides with KCN

[19] a) K. Takagi, T. Okamoto, Y. Sakakibara, A. Ohno, S. Oka, N. Hayama, *Bull. Chem. Soc. Jpn*. **1975**, *48*, 3298-3301; b) M. Sundermeier, A. Zapf, M. Beller, J. Sans, *Tetrahedron Lett.* **2001**, *42*, 6707-6710; c) M. Sundermerier, A. Zapf, S. Mutyala, W. Baumann, J. Sans, S. Weiss, M. Beller, *Chem. Eur. J.* **2003**, *9*, 1828-1836.

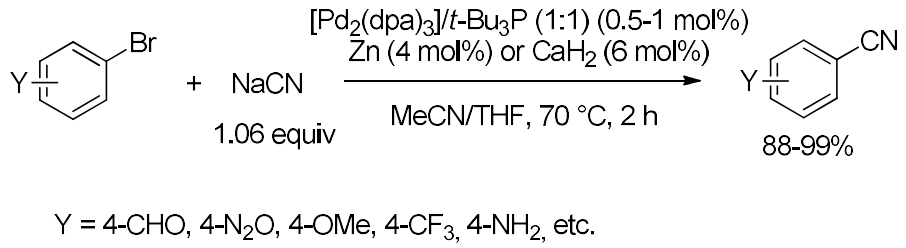
[20] C. Yang, J. M. Williams, *Org. Lett.* **2004**, *6*, 2837-2840.

[21] S. E. Johnson, C. B. Knobler, *Organometallics* **1992**, *11*, 3684-3690.



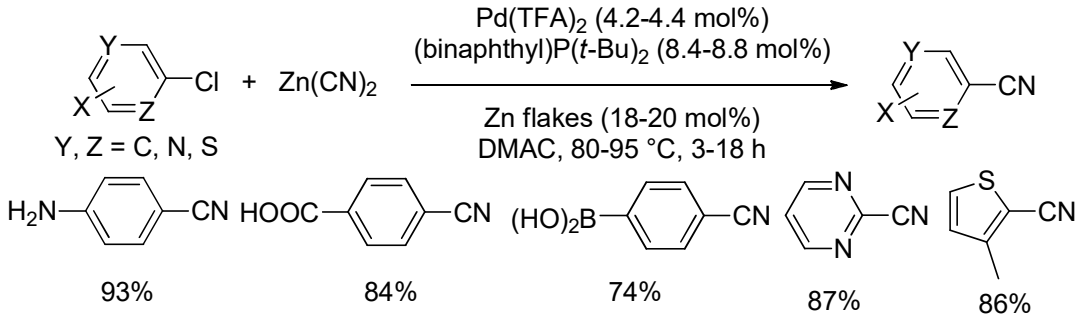
Scheme7 Palladium-catalyzed cyanation reaction of aryl halides promoted by organotin compound

Recently, Grushin and coworkers established a highly efficient and general cyanation reaction with NaCN catalyzed by palladium (Scheme 1-8).[12b] The method exhibited good functional group tolerance such as nitro, ketone, amine and methoxy group affording full conversions and excellent yields. Catalytic amount of zinc dust or CaH_2 was used accompanied with 0.5-1 mol% of palladium as the catalyst. The role of the additives was assumed to reactivate the poisoned catalyst in order to facilitate the reaction.[22]



Scheme 1-8 Palladium-catalyzed cyanation reaction of aryl halides with NaCN

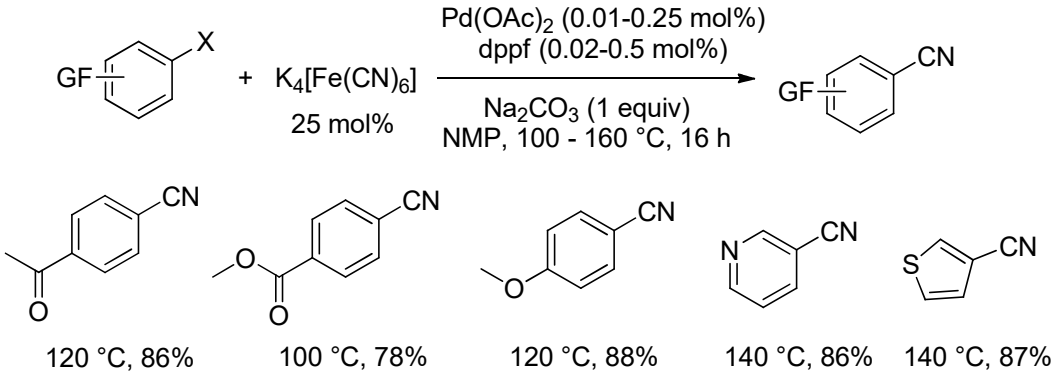
Compared with the simple alkali metal cyanides, zinc cyanide is less toxic and served as one of the most widely used cyanide source. For example, in 2007, Kiau and coworkers developed a general method for cyanation of aryl and heteroayl chlorides with palladium catalyst (Scheme 1-9).[8a]



Scheme 1-9 Palladium-catalyzed cyanation reaction of aryl halides with $Zn(CN)_2$

[22] F. G. Buono, R. Chidambaram, R. H. Mueller, R. E. Waltermire, *Org. Lett.* **2008**, *10*, 5325-5328.

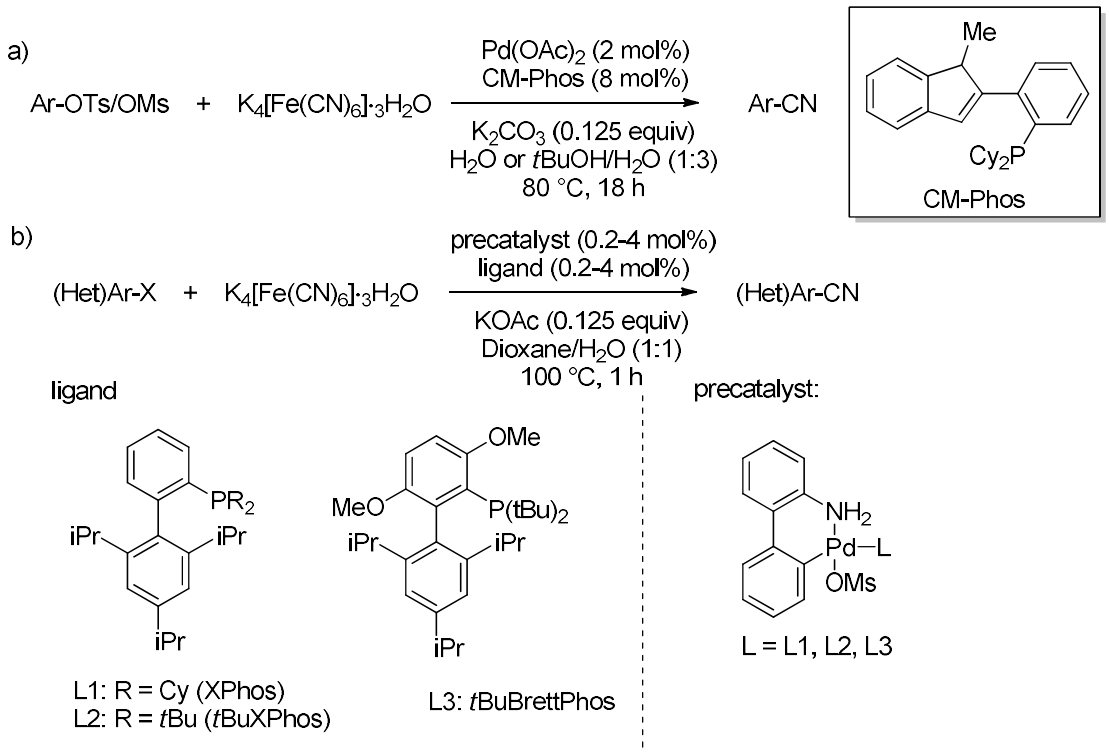
Potassium hexacyanoferrate(II) has attracted attention of chemist in the last decade. As a non-toxic cyanide, it could be handled without additional precaution. Beller and coworkers first utilized this compound to develop a palladium-catalyzed cyanation reaction (Scheme 1-10).[14a] With all six cyanide ions available for reaction, good yields of cyanation of various functionalized aryl bromides were obtained under optimized reaction conditions. High catalyst productivities were observed due to the slow release of cyanide ions. Next the same group proved that this kind of reaction could be performed by copper catalyst.[23]



Scheme 1-10 Palladium-catalyzed cyanation reaction of aryl halides with $K_2[Fe(CN)_6]$

Several extension of the palladium-catalyzed cyanation reaction has been made by the same and other groups. For example, Beller and coworkers replaced the catalyst by $Pd(TFA)_2$ with a bulky ligand to undergo a cyanation of aryl chlorides bearing electron-donating groups.[14b] Kwong *et al.* employed aryl tosylates or mesylates as the starting materials in water (Scheme 1-11-a)[14c] and Buchwald *et al.* also used water as a co-solvent to undergo the cyanation reaction (Scheme 1-11-b).[14d]

[23] T. Schareina, A. Zapf, M. Beller, *Tetrahedron Lett.* **2005**, *46*, 2585-2588.



Scheme 1-11 Palladium-catalyzed cyanation reaction of aryl halides with $K_2[Fe(CN)_6]$ in water

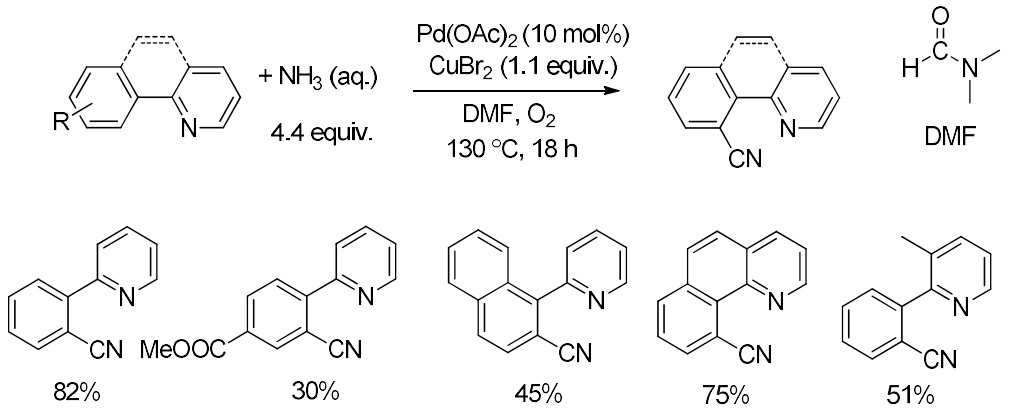
After the development over 40 years, metal cyanide has been widely employed for the synthesis of functionalized benzonitriles. Nevertheless, some limitations still remain. Most of these cyanide reagents are toxic and need to be careful handled, moreover, at least one equivalent of inorganic salt waste is produced during the reaction. When utilizing potassium ferrocyanide, most of the reactions require precious palladium catalyst as well as expensive sophisticated ligands, while cheap metal catalysts have been poorly investigated.

I-2 Combined "CN" source

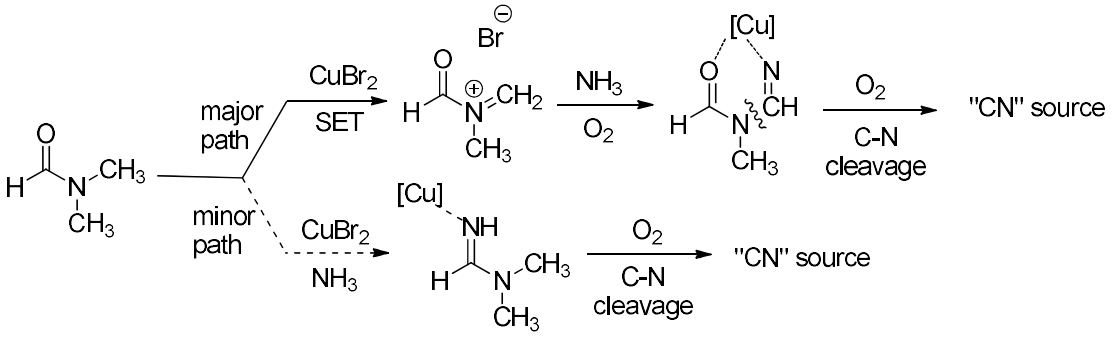
To avoid using toxic metal cyanides, combined "CN" source has been attracting attention in recent years. A variety of these kinds of reaction has emerged in succession during the past few years. In this kind of cyanation reaction, the "CN" unit is formed *in situ* from one or two small molecules. The detailed mechanism of these reactions is not known, which is mainly due to the complexity of the reaction mixture. Chang and coworkers first employed two different simple molecules, ammonia and DMF to generate "CN" for the cyanation of arenes (Scheme 1-12).[24] An isotope study disclosed that the carbon atom of CN originates from dimethyl group of DMF and the nitrogen atom from ammonia. It was proposed that the

[24] J. Kim, S. Chang, *J. Am. Chem. Soc.* **2010,** *132*, 10272-10274.

palladium was only involved in the C-H activation step while copper played an important role to form the "CN" unit with the oxidation of oxygen (Scheme 1-13). This method was not applied to a wide scope of substrates. With electron-withdrawing group substituted 2-phenylpyridine, only moderate yield was obtained.



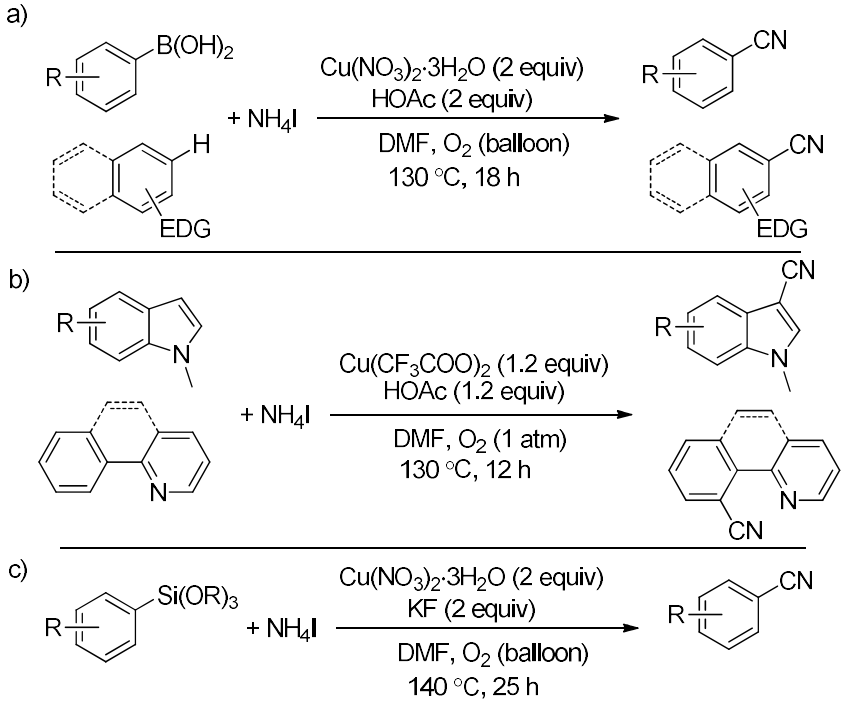
Scheme 1-12 Combined "CN" source from NH_3 and DMF in the palladium-catalyzed cyanation of aryl C−H bonds



Scheme 1-13 Proposal mechanism for the "CN" formation

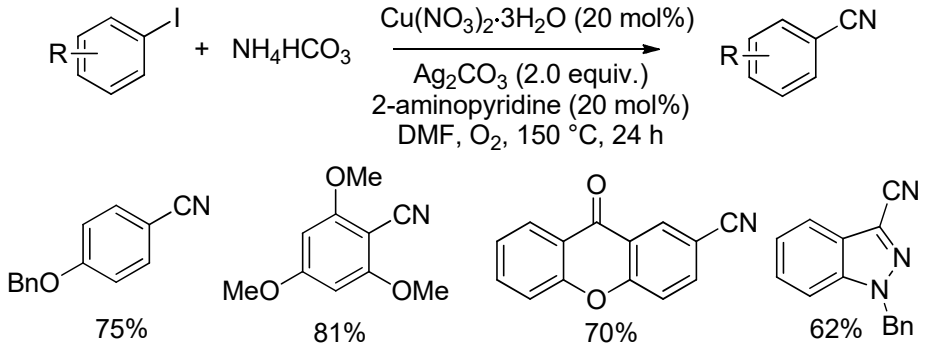
Subsequently, Chang and coworkers demonstrated copper-mediated cyanation of aryl boronic acid or electron-rich benzenes using ammonium iodide and DMF under "Pd-free" conditions (Scheme 1-14-a).[25] Aryl boronic compounds bearing electron-withdrawing or electron-donating groups reacted well affording good to excellent yields. From electron-rich benzenes, iodoarene was confirmed to be the key intermediate to undergo the cyanation. With simple modification of conditions, this method was extended to more substrates (Scheme 1-14-b, c).[26,27]

[25] J. Kim, J. Choi, K. Shin, S. Chang, *J. Am. Chem. Soc.* **2012**, *134*, 2528-2531.
[26] J. Kim, H. Kim, S. Chang, *Org. Lett.* **2012,** *14*, 3924-3927.
[27] Z. Wang, S. Chang, *Org. Lett.* **2013,** *15*, 1990-1993.



Scheme 1-14 Combined "CN" source from NH_4I and DMF in the copper-mediate aryl cyanation

The above copper-mediated cyanation had a significant drawback: more than stoichiometric amounts of copper species were required. In 2014, Chang's group found that a combination of silver carbonate and oxygen could facilitate copper-catalyzed cyanation reaction of aryl iodides with ammonium bicarbonate and DMF as cyano source (Scheme 1-15).[28] In this reaction, silver salts reoxidized the copper(I) species to regenerate the activated copper(II) catalyst. However, it was less economic owing to the requirement of 2 equivelant of silver.



Scheme 1-15 copper-catalyzed cyanation of aryl iodides with NH_4HCO_3 and DMF

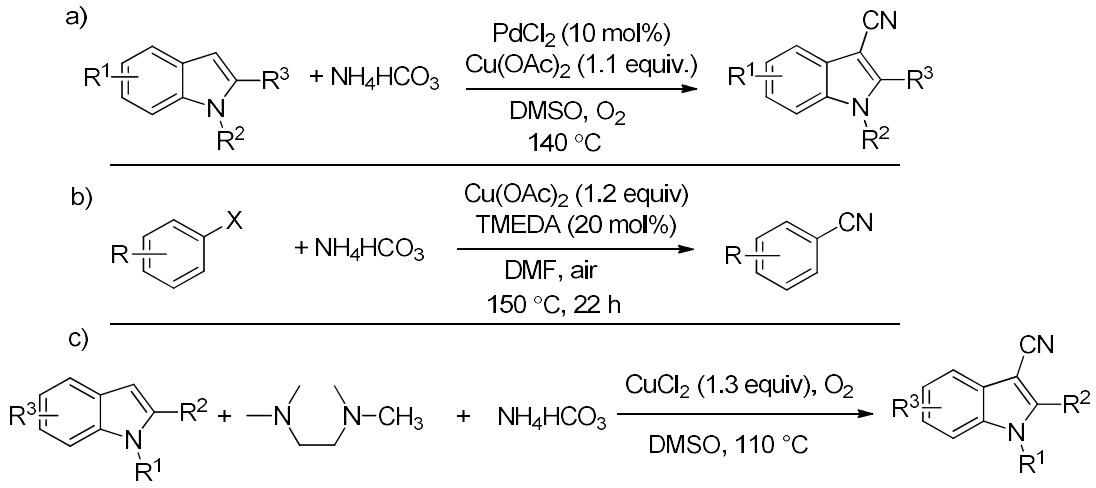
Cheng and coworkers established similar methods using DMSO and ammonium bicarbonate as a combined cyano source for the cyanation of indoles (Scheme 1-16-a).[29] Later, they

[28] A. B. Pawar, S. Chang, *Chem. Commun.* **2014**, *50*, 448-450.

[29] X. Ren, J. Chen, F. Chen, J. Cheng, *Chem. Commun.* **2011,** *47*, 6725-6727.

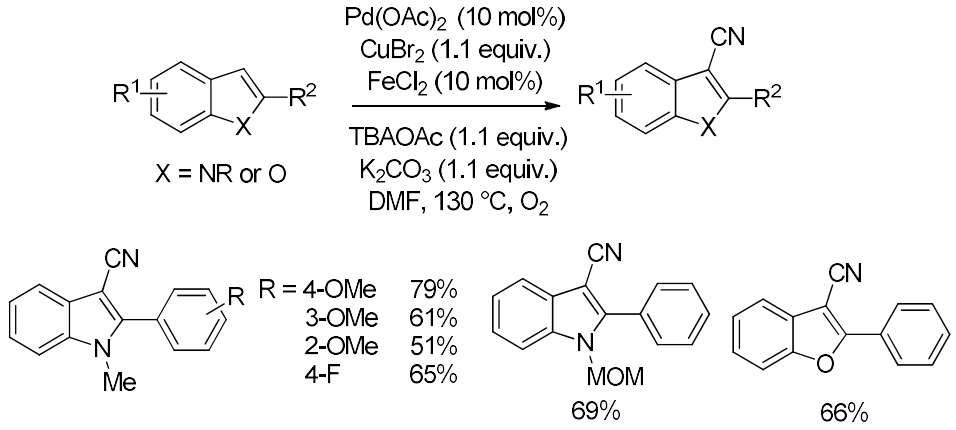
developed a palladium-free protocol, which combined ammonium bicarbonate and DMF as a cyano-source, and allowed the cyanation of a series of electron-rich aryl halides (Scheme 1-16-b).[30] Then they utilized TMEDA as the carbon donator while DMSO did not provide carbon to form "CN" (Scheme 1-16-c).[31]

Without ammonia or ammonium salts, Jiao and coworkers demonstrated a palladium-catalyzed cyanation with DMF as the only provider of both carbon and nitrogen atom which incorporated into the cyano group (Scheme 1-17).[32] This protocol was limited to electron-rich compounds and in some cases aldehyde products were produced as the side products. They next extended this method to cyanation of 2-phenylpyridine under "palladium-free" condition.[33] Wang *et al.* and Han *et al.* developed similar approaches mediated by copper, respectively.[34]



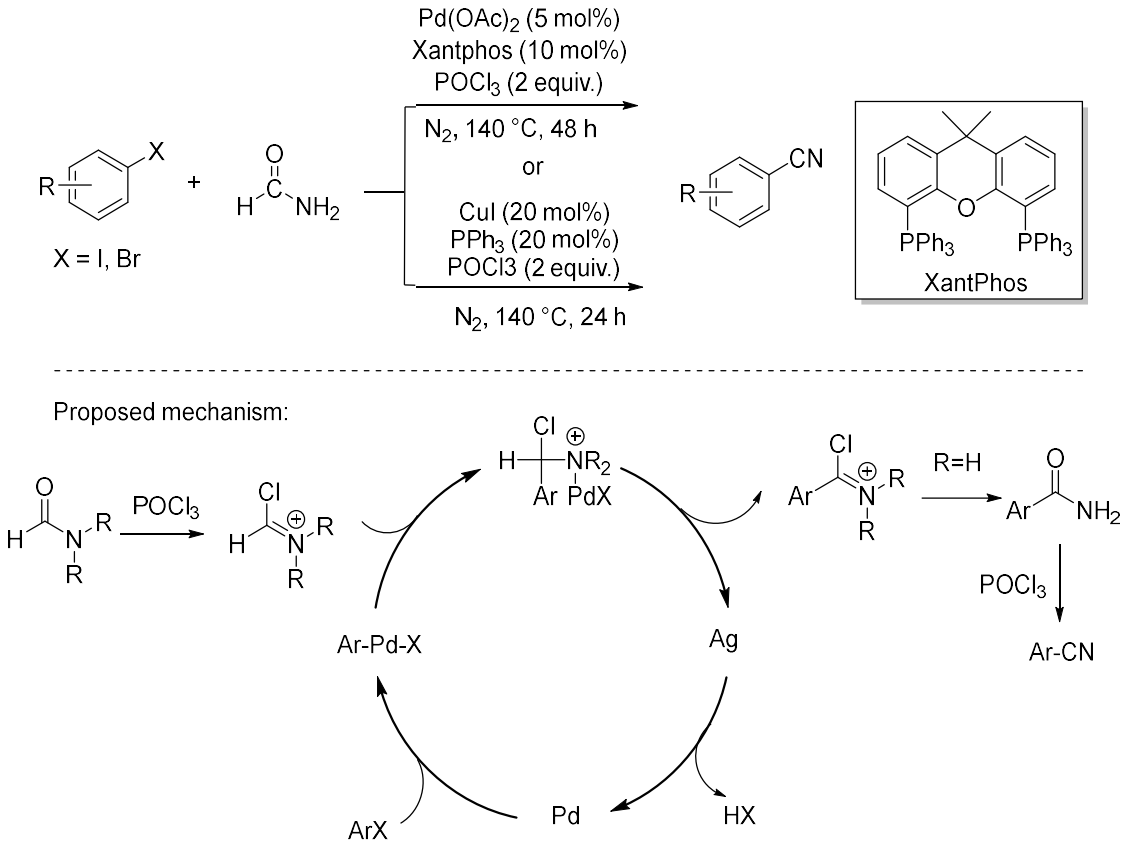
Scheme 1-16 "CN" source from NH_4HCO_3 and DMSO/DMF in the palladium-catalyzed cyanation

[30] G. Zhang, X. Ren, J. Chen, M. Hu, J. Cheng, *Org. Lett.* **2011,** *13*, 5004-5007.
[31] B. Liu, J. Wang, B. Zhang, Y. Sun, L. Wang, J. Chen, J. Cheng, *Chem. Commun.* **2014,** *50*, 2315-2317.
[32] S. Ding, N. Jiao, *J. Am. Chem. Soc.* **2011,** *133*, 12374-12377.
[33] Y. Yan, Y. Yuan, N. Jiao, *Org. Chem. Front.* **2014**, *1*, 1176-1179.
[34] a) L. Zhang, P. Lu, Y. Wang, *Org. Biomol. Chem.* **2015**, *13*, 8322-8329; b) J. Xiao, Q. Li, T. Chen, L-B. Han, *Tetrahedron Lett.* **2015**, *56*, 5937-5940.



Scheme 1-17 Copper-catalyzed cyanation using DMF as the "CN" source

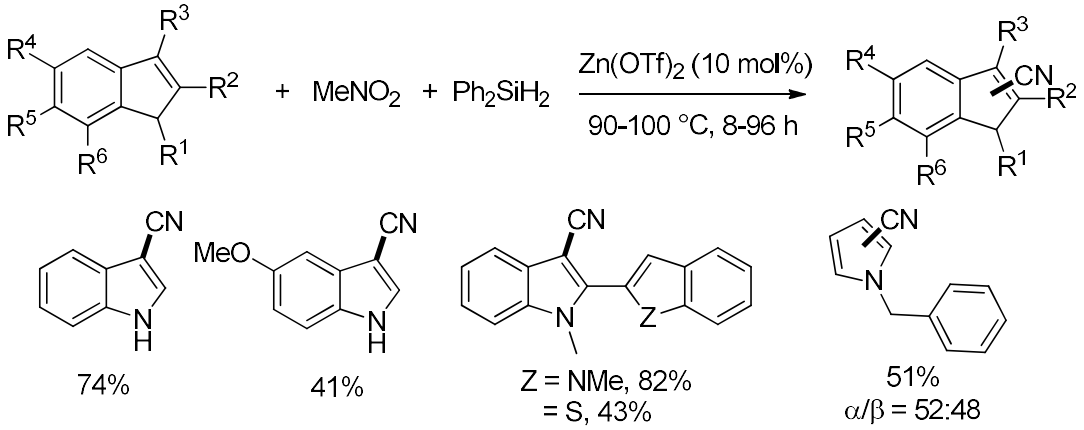
Bhanage and coworkers employed formamide as the single cyano surrogate, which is more atomic economical, to form benzonitriles from aryl iodides and bromides in the presence of palladium or copper iodide catalyst (Scheme 1-18).[35] Both electron-donating and electron-withdrawing groups could be well tolerated. $POCl_3$ undergoes a Vilsmeier-type procedure twice to form the corresponding benzonitriles.



Scheme 1-18 Pd or Cu-catalyzed aryl cyanation with formamide as the "CN" source

[35] a) D. N. Sawant, Y. S. Wagh, P. J. Tambade, K. D. Bhatte, B. M. Bhanage, *Adv. Synth. Catal.* **2011,** *353*, 781-787; b) A. B. Khemnar, B. M. Bhanage, *RSC Adv.* **2014**, *4*, 13405-13408.

Tsuchimoto and coworkers first demonstrated that a Lewis acid could participate as a catalyst in the cyanation reaction with nitromethane as the cyanide source (Scheme 1-19).[36] $MeNO_2$ here not only served as a cyanide source but also a reaction medium. The author showed that Si-H moiety of Ph_2SiH_2 was essential to the reaction, which might involve in the formation of silylated complex followed by sequential elimination of two molecules of "*HOSi"*. When applied to cyanation of pyrroles, it had no regioselectivity.



Scheme 1-19 Zinc-catalyzed cyanation of indoles and pyrroles with nitromethane as cyano source

To date the cyanation reactions using combined "CN" sources have been well investigated. Among these sources, DMF and ammonia or ammonium salts were most employed. In several cases, a non negligible drawback is the requirement of more than stoichiometric metal (copper). Moreover, early-transition-metal have been poorly explored to catalyze such cyanation reactions using combined "CN" sources.

I-3 Organic compounds containing a "CN" unit

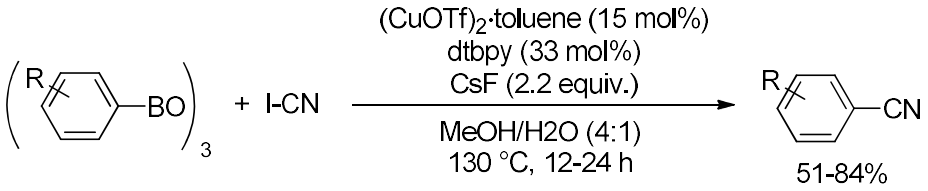
Recently, a variety of organic compounds containing a CN unit has been successfully explored as efficient cyano source in metal-catalyzed cyanation reactions. In this way, deactivation of catalyst due to the high cyanide-metal affinity could be highly reduced. Furthermore, metal wastes could be possibly avoided.

I-3-1 Cyanogen Halides

Cyanogen halides were one of the cyanating reagents that were used in early times. 100 years ago, Grignard employed cyanogen chloride to form aryl nitriles with Grignard reagents.[37]

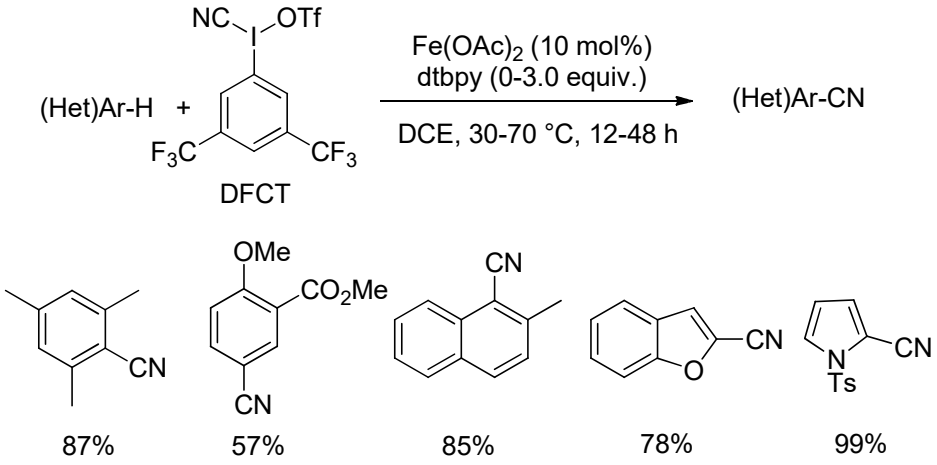
[36] Y. Nagase, T. Sugiyama, S. Nomiyama, K. Yonekura, T. Tsuchimoto, *Adv. Synth. Catal.* **2014**, 356, 347-352.
[37] V. Grignard, E. Bellet, *Compt. Rend.* **1914**, *158*, 457.

Later cyanogen bromide and iodide were disclosed to be cyano sources for similar reactions.[38] Very recently Ohe and coworkers reported a copper-catalyzed cyanation of arylboronic reagents with cyanogen iodide (Scheme 1-20).[39] Series of functionalized arylboronic acids reacted efficiently affording good to excellent yields. However, cyanogen halides are highly toxic, which limits the synthetic application.



Scheme 1-20 Copper-catalyzed cyanation of arylboronic acids with cyanogen iodide

In 2014, Wang and coworkers first demonstrated that aryl(cyano)iodonium triflates are a good cyano source to undergo an iron-catalyzed direct cyanation of arenes (Scheme 1-21).[40] This reaction was applicable to various electron-donating group substituted heteroarenes or arenes.



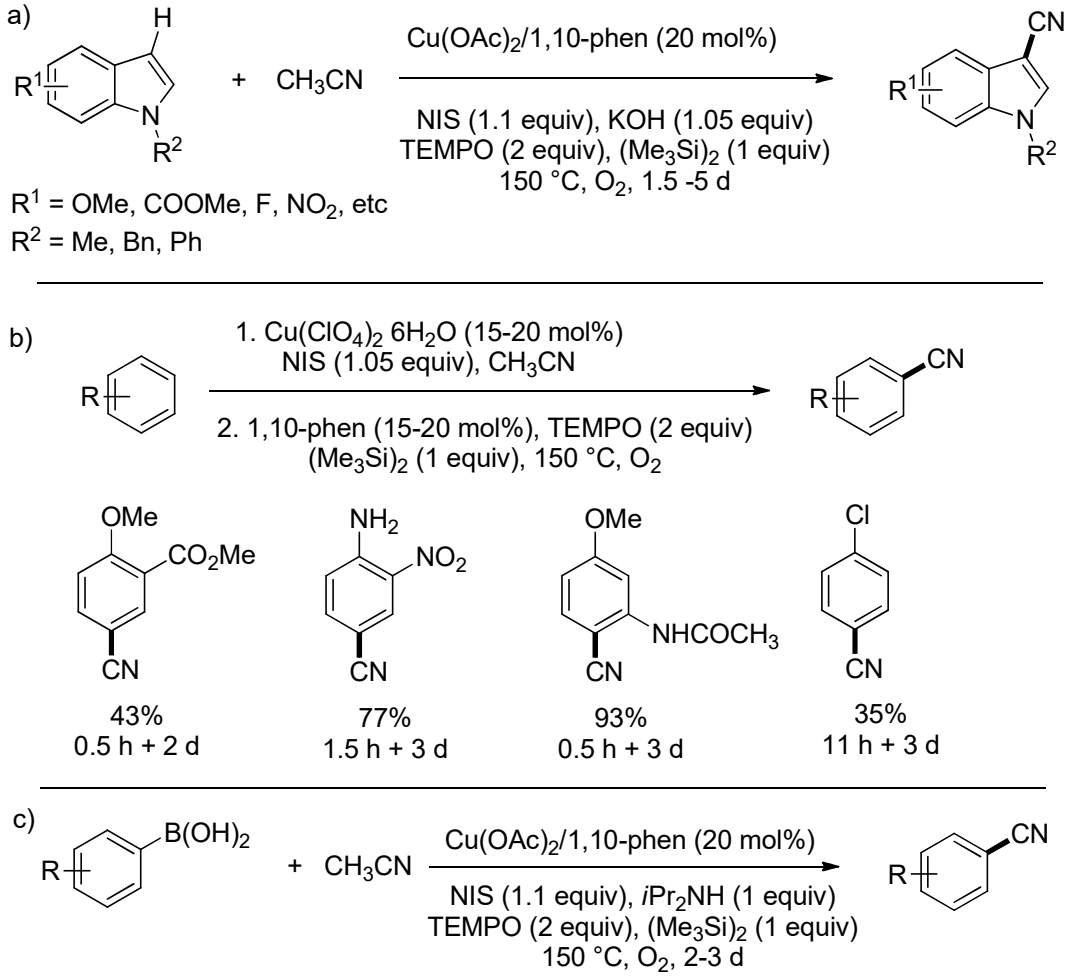
Scheme 1-21 Iron-catalyzed direct cyanation of arenes with DFCT

I-3-2 C-CN Compounds

In 1998, Cheng and coworkers established a palladium-catalyzed cyanation of aryl halides in the presence of zinc species.[41] Due to the analysis of the side products, an alkyl-zinc complex was proposed to have been generated. Later in 2013, acetonitrile was used for the cyanation of

[38] a) V. Grignard, E. Bellet, C. Courtot, *Ann. Chim. (Paris, Fr.)* **1915**, *4*, 28. b) V. Grignard, E. Bellet, C. Courtot, *Ann. Chim. (Rome,Italy)* **1920**, *12*, 364.
[39] K. Okamoto, N. Sakata, K. Ohe, *Org. Lett.* **2015**, *17*, 4670−4673.
[40] Z. Shu, W. Ji, X. Wang, Y. Zhou, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 1-5.
[41] F-H. Luo, C-I. Chu, C-H. Cheng, *Organometallics* **1998**, *17*, 1025-1030.

indoles developed by Zhu's group.[42] More recently, Shen and coworkers reported a series of sequential iodination/cyanation reaction with acetonitriles (Scheme 1-22).[43] TEMPO played an important dual role in this reaction. First, it acted as an oxidant to enable the reactivation of copper catalyst. Second, mechanistic study revealed that a TEMPO-CH_2CN was generated as an active cyanating reagent. Nevertheless, all these reactions required very long reaction time.

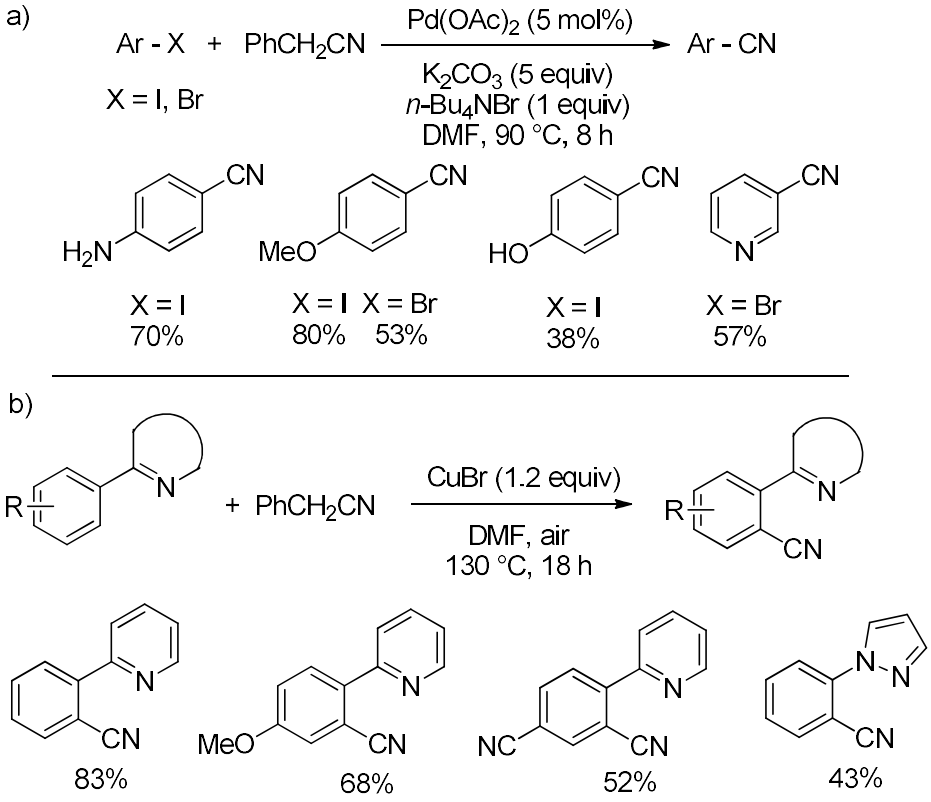


Scheme 1-22 Copper-catalyzed cyanation using acetonitrile as cyano source

Wang and coworkers developed a palladium-catalyzed cyanation of aryl halides using simple benzyl cyanide as the cyanating reagent (Scheme 1-23-a).[44] Both K_2CO_3 and *n*-Bu_4NBr were essential. No electron-withdrawing group substituted aryl halides were used in this protocol.

[42] C. Pan, H. Jin, P. Xu, X. Liu, Y. Cheng, C. Zhu, *J. Org. Chem.* **2013**, *78*, 9494-9498.
[43] a) Y. Zhu, M. Zhao, W. Lu, L. Li, Z. Shen, *Org. Lett.* **2015**, *17*, 2602−2605; b) M. Zhao, W. Zhang, Z. Shen, *J. Org. Chem.* **2015**, *80*, 8868−8873 ; c) Y. Zhu, L. Li, Z. Shen, *Chem. Eur. J.* **2015**, *21*, 13246 – 13252.
[44] Q. Wen, J. Jin, B. Hu, P. Lu, Y. Wang, *RSC Adv.* **2012**, *2*, 6167-6169.

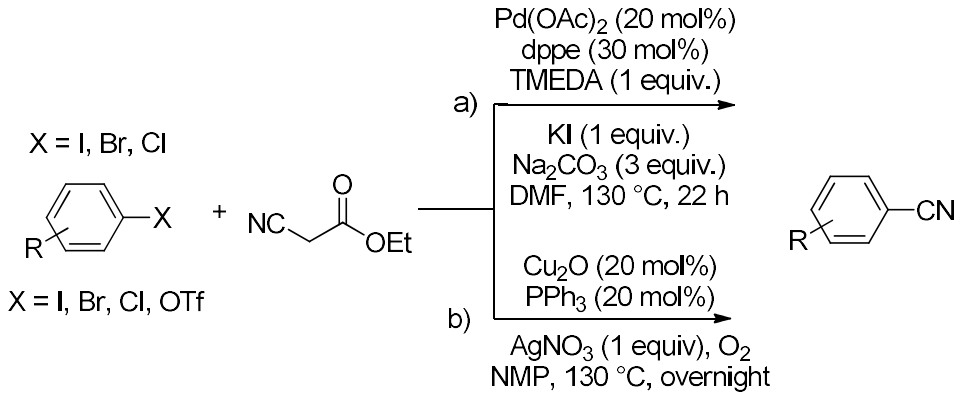
Then the group demonstrated copper-mediated cyanation of aryl halides [45] and 2-phenylpyridines with benzyl cyanide (Scheme 1-23-b)[46].



Scheme 1-23 Cyanation of aryl halides and 2-phenylpyridine using benzyl cyanide as cyano source

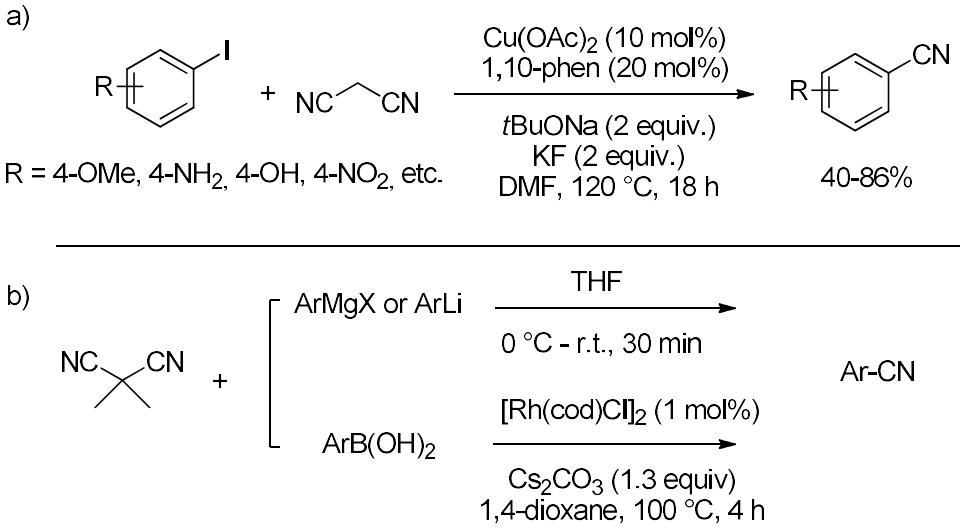
Ethyl cyanoacetate, which is more reactive than acetonitrile, was proved to be a good cyano source by Shen *et al.* (Scheme 1-24-a)[47] and Huang *et al.* (Scheme 1-24-b)[48]respectively. A variety of electron-rich or electron-deficient aryl halides were efficiently converted into corresponding benzonitriles.

[45] Q. Wen, J. Jin, Y. Mei, P. Liu, Y. Wang, *Eur. J. Org. Chem.* **2013**, 4032–4036.
[46] J. Jin, Q. Wen, P. Lu, Y. Wang, *Chem. Commun.* **2012**, *48*, 9933-9935.
[47] S. Zheng, C. Yu, Z. Shen, *Org. Lett.* **2012**, *14*, 3644-3647.
[48] S-L. Zhang, L. Huang, *Org. Biomol. Chem.* **2015**, *13*, 9963-9969.



Scheme 1-24 Cyanation of aryl halides and aryl halides/pseudohalides using ethyl cyanoacetate as cyano source

In 2011, Zhou and coworkers disclosed a transnitrilation from malonitrile to aryl iodides in the presence of copper catalyst (Scheme 1-25-a).[49] The key intermediate copper-cyano [Cu(phen)$(CN)_2$] was generated *in situ* followed by transnitrilation. Very recently, Senanayake and coworkers then chose dimethylmalononitrile as the cyanating reagent, which reacted with aryl Grignard, lithium and boronic reagents to form benzonitriles (Scheme 1-25-b).[50] No catalysts were necessary when aryl Grignard or lithium compounds were employed while large scope of substrates could be well tolerated. They also demonstrated that several variations of malononitriles could give excellent yields with aryl Grignard or boronic reagents.



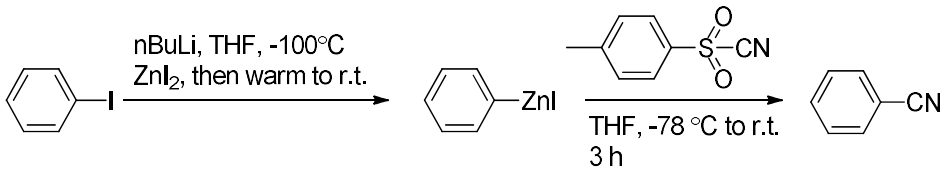
Scheme 1-25 transnitrilation from malononitriles to aryl halides or arylmetallic compounds

I-3-3 O-CN and S-CN compounds

[49] Z. Jiang, Q. Huang, S. Chen, L. Long, X. Zhou, *Adv. Synth. Catal.* **2012**, *354*, 589.

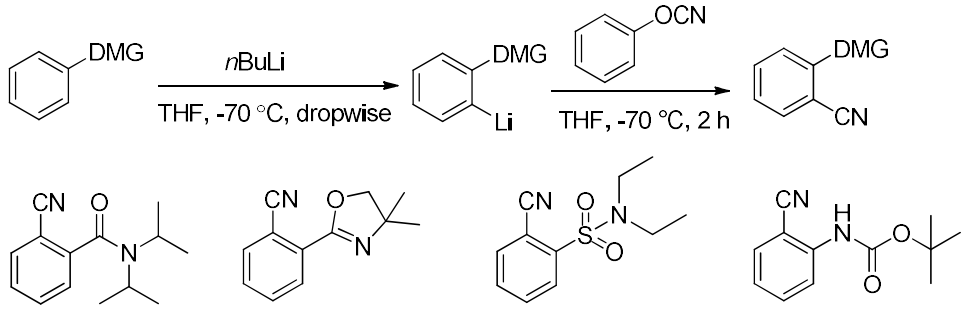
[50] a) J. T. Reeves, C. A. Malapit, F. G. Buono, K. P. Sidhu, M. A. Marsini, C. A. Sadar, K. R. Fandrick, C. A. Busacca, C. H. Senanayake, *J. Am. Chem. Soc.* **2015**, *137*, 9481−9488; b) C. A. Malapit, J. T. Reeves, C. A. Busacca, A. R. Howell, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2016**, *55*, 326 –330.

In 1993, Knochel and coworkers developed an efficient method for the cyanation of a wide range of organozinc compounds with *p*-toluenesulfonyl cyanide (Scheme 1-26).[51] It is a transition-metal free procedure. However, the scope of arylzinc species was not well explored. Moreover, the preparation of this organozinc compound required very low temperatures and used TsCN, which is dangerous to prepare or ship.



Scheme 1-26 Cyanation reaction of arylzinc compound with TsCN

In 1996, Lee found out that 2-pyridyl cyanate was a useful cyanating reagent and several benzonitriles were synthesized from Grignard reagents.[52] Later Sato developed an efficient synthesis of *ortho*-cyanoarenes *via* directed lithiation followed by electrophilic cyanation with cyanatobenzene (Scheme 1-27).[53] 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. However, the synthesis of cyanate required cyanogen halides, which is highly toxic.

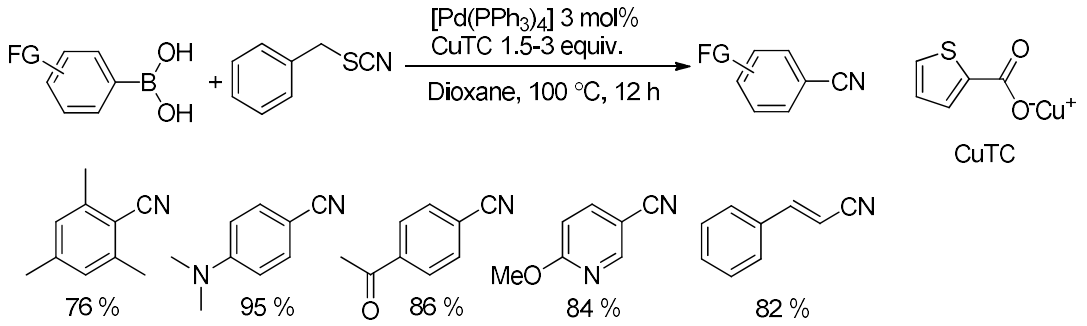


Scheme 1-27 Cyanation reaction of aryl lithium reagent

Liebeskind and coworker reported the first Pd-catalyzed, Cu-mediated (CuTC: Copper(I)-thiophene-2-carboxylate) cyanation of boronic acid with benzylthiocyanate (Scheme 1-28).[54] Using this protocol, a variety of functionalized aryl nitriles was formed in high yields. It is a

[51] I. Klement, K. Lennick, C. E. Tucker, P. Knochel, *Tetrahedron Lett.* **1993,** *34*, 4623-4626.
[52] J. S. Koo, J. I. Lee, *Synth. Commun.* **1996**, *26*, 3709-3713.
[53] (a) N. Sato, Q. Yue, *Tetrahedron* **2003,** *59*, 5831-5836; (b) N. Sato, *Tetrahedron Lett.* **2002,** *43*, 6403-6404.
[54] Z. Zhang, L. S. Liebeskind, *Org. Lett.* **2006,** *8*, 4331-4333.

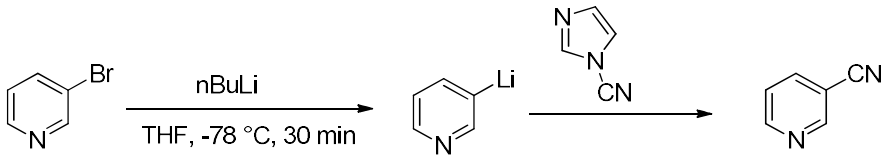
useful complementary method compared to that employing aryl halides/pseudo-halides with cyanide sources in the presence of a transition-metal catalyst.



Scheme 1-28 Palladium-catalyzed, copper(I)-mediated coupling of boronic acids and benzylthiocyanate

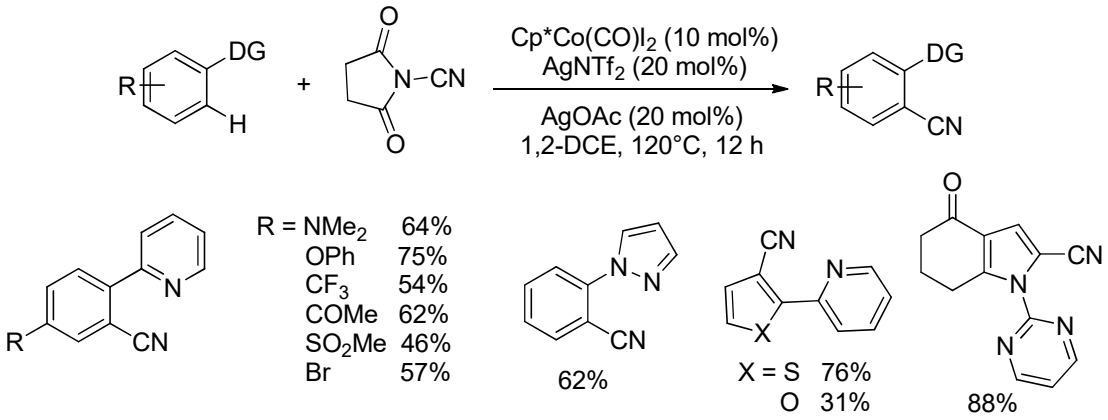
I-3-4 N-CN compounds

Hamilton and coworkers disclosed that 1-cyanoimidazole is a mild and efficient electrophilic cyanating agent with different nucleophilic reagents (amine, sulfur, and carbanion) (Scheme 1-29), but only one arylnitrile example was obtained from the aryl lithium reagent.[55]



Scheme 1-29 Cyanation reaction of aryl lithium reagent

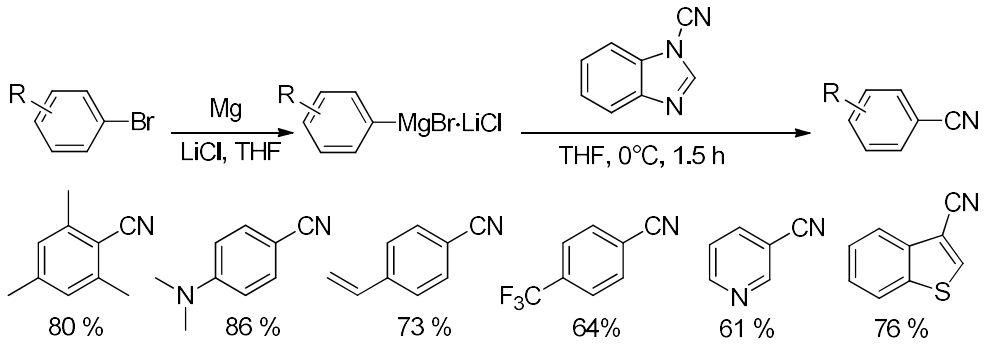
In 2015, Chang and coworkers developed a cobalt-catalyzed C-H cyanation of (hetero)arenes with *N*-cyanosuccinimide (Scheme 1-30).[56] The new cyanating reagent was facile to prepare and bench stable. A cyano group could be efficiently introduced into a variety of functionalized 2-phenylpyridines as well as several hereoarenes.



[55] Y-Q. Wu, D. C. Limburg, D. E. Wilkinson, G. S. Hamilton, *Org. Lett.* **2000**, *2*, 795-797.
[56] A. B. Pawar, S. Chang, *Org. Lett.* **2015**, *17*, 660−663.

Scheme 1-30 Cobalt-catalyzed cyanation reaction of (hetero)arenes with *N*-cyanosuccinimide

In 2010, Beller and coworkers reported the electrophilic cyanation of aryl/heteroaryl Grignard reagents (Scheme 1-31).[57] 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 to excellent 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 was prepared from toxic cyanogen bromide.



Scheme 1-31 Electrophilic cyanation of aryl/heteroaryl Grignard reagents

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 1-32).[58] NCTS was readily synthesized by the reaction of phenylurea with *p*-toluenesulfonyl chloride in pyridine in good yield.[59] 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.[60] This method tolerated both electronically rich/poor groups. Methoxy, diphenylamine, thioether, chloro, dioxane, amide, nitrile and heteroaryl substituted arene were cyanated in high yields. Therefore, this methodology is cost-effective and environmentally-friendly.

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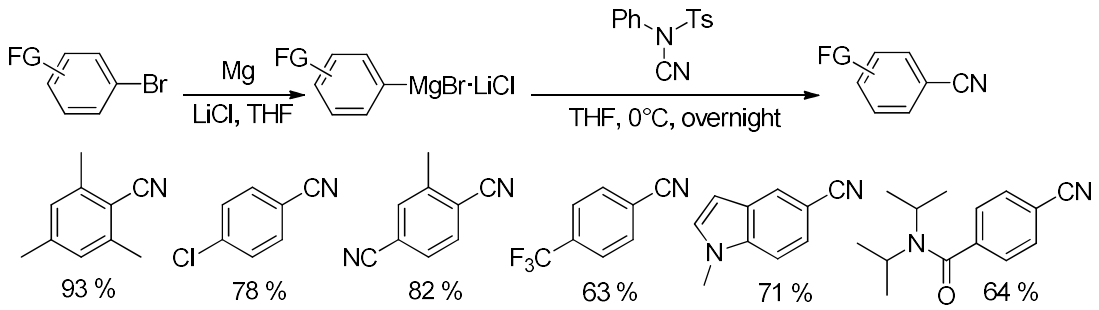
[57] P. Anbarasan, H. Neumann, M. Beller, *Chem.-Eur. J.* **2010**, *16*, 4725-4728.

[58] P. Anbarasan, H. Neumann, M. Beller, M. *Chem.-Eur. J.* **2011,** *17*, 4217-4222.

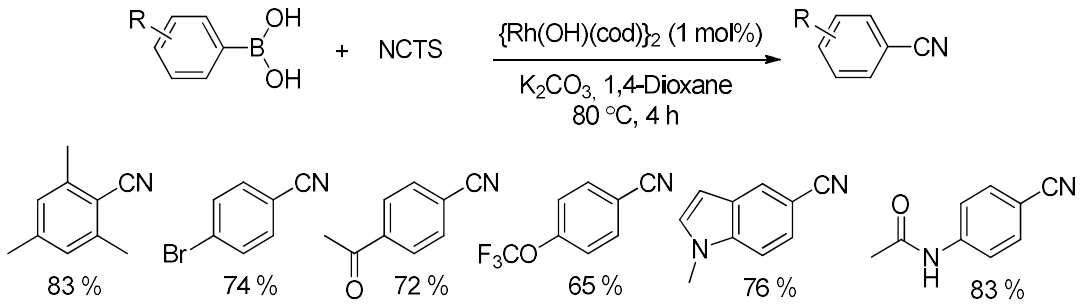
[59] Kurzer, F. *J. Chem. Soc. (Resumed)* **1949**, 1034-1038.

[60] a) P. Knochel, A. Krasovskiy, I. Sapountzis, In *Handbook of Functionalized Organometallics*; P. Knochel, Wiley-VCH: Weinheim, **2005**; *Vol. 1*, pp 109-172; b) L. Boymond, M, Rottlander, G. Cahiez, P. Knochel, *Angew. Chem., Int. Ed*. **1998**, *37*, 1701–1703; c)P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem., Int. Ed*. **2003**, *42*, 4302–4320; c) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem., Int. Ed*. **2008**, *47*, 6802–6806.



Scheme 1-32 Electrophilic cyanation of aryl/heteroaryl Grignard reagents with NCTS

In 2011, Beller and coworkers demonstrated the first Rh-catalyzed cyanation of aryl boronic acids with NCTS under mild condition (Scheme 1-33).[61] 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.

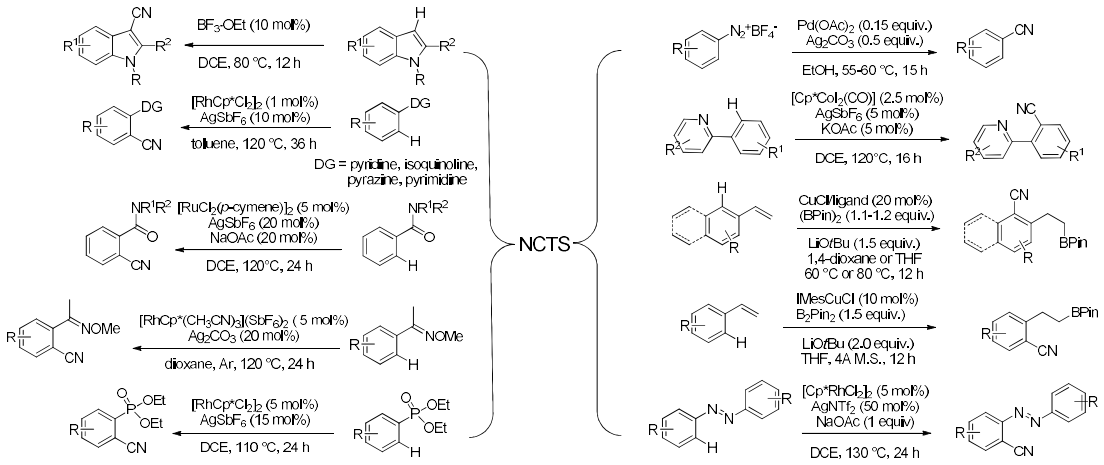


Scheme 1-33 Rh-catalyzed electrophilic cyanation of aryl boronic acids

Later on, NCTS has been widely used to aryl cyanation by several groups, most of which are via C-H activation (Scheme 1-34).[62]

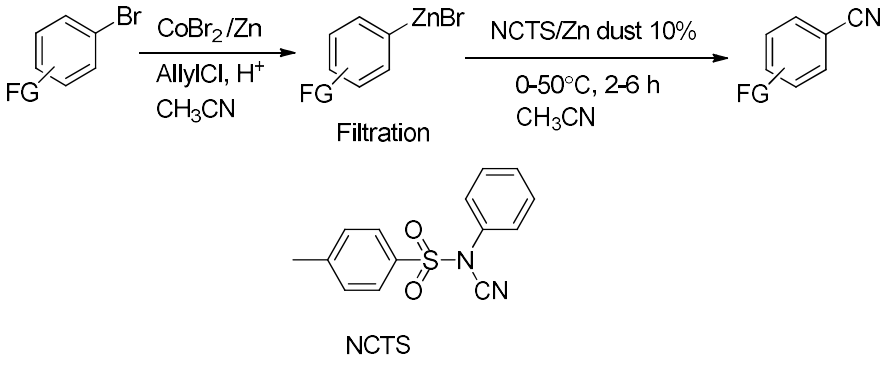
[61] P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem., Int. Ed.* **2011**, *50*, 519-522.

[62] a) Y, Yang, Y. Zhang, J. Wang, *Org. Lett.* **2011**, *13*, 5608-5611 ; b) M. Chaitanya, D. Yadagiri, P. Anbarasan, *Org. Lett.* **2013**, *15*, 4960-4963; c) T-J. Gong, B. Xiao, W-M, Cheng, W. Su, J. Su, Z-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 10630-10633 ; d) L-J. Gu, C. Jin, R. Wang, H-Y. Ding, *ChemCatChem* **2014**, *6*, 1225 - 1228; e) J. Han, C. Pan, X. Jia, C. Zhu, *Org. Biomol. Chem.* **2014**, *12*, 8603-8606; f) Y. Yang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2014**, *53*, 8677 –8681; g) W. Liu, L. Ackermann, *Chem. Commun.* **2014**, *50*, 1878-1831; h) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 3635-3638; i) W. Zhao, J. Montgomery, *Angew. Chem. Int. Ed.* **2015**, *54*, 12683 –12686; j) J. Li, W. Xu, J. Ding, K-H. Lee, *Tetrahedron Lett.* **2016**, 57, 1205-1209.



Scheme 1-34 Methodologies for synthesis of aryl nitriles using NCTS

In conclusion, these methodologies have made important contributions to the synthesis of aryl nitriles. 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 toxic 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 in our laboratory, are good candidates as nucleophilic partners. Since NCTS is a good electrophilic cyano source, and it has never been employed with arylzinc compounds, we developed the cyanation of arylzinc reagents using NCTS (Scheme 1-35). A variety of functionalized arylzinc species was transformed to the corresponding arylnitriles as will be discussed in the next section.

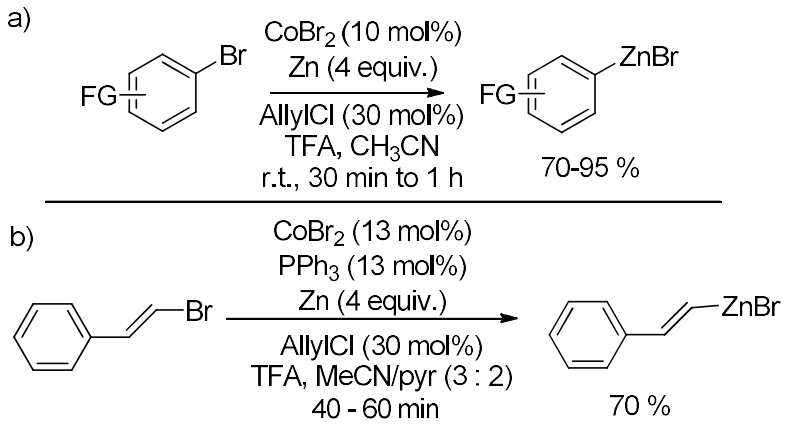


Scheme 1-35 Cobalt-catalyzed electrophilic cyanation of arylzinc species

II. Results and discussions

II-1Formation of arylzinc and vinylzinc reagents

Organozinc reagents are one of the most useful organometallic compounds, which are widely used in organic synthesis.[63] The preparation of organozinc compounds has also been well developed, particularly by Rieke *et al.* and Knochel *et al*.[54c, 64] These methods were efficient and had good tolerance of functional groups. However, they were not simply operated owing to the use of active zinc or lithium salts as promoter. In our lab, Gosmini and coworkers established an efficient approach to synthesize arylzinc compounds in the presence of cobalt catalyst (Scheme 1-36-a).[65] This reaction has a very wide scope of substrates with good to excellent yields under very mild conditions in one hour. Moreover, this reaction could be operated in round-bottom flask without nitrogen protection. Later, with addition of PPh_3 ligand and pyridine as a co-solvent, zinc insertion could occur with β-bromostyrene affording excellent yield.



Scheme 1-36 Cobalt-catalyzed synthesis of arylzinc and vinylzinc compounds

[63] selected reviews, see : a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117-2188; b) L. Pu, H. B. Yu, *Chem. Rev.* **2001**, *101*, 757-824 ; c) P. Knochel, J. J. A. Perea, P. Jones, *Tetrahedron*. **1998**, *54*, 8275-8319; d) V. B. Phapale, D. J. Cardenas, *Chem. Soc. Rev.* **2009**, *38*, 1598-1607; e) J. H. Kim, Y. O. Ko, J. Bouffard, S. Lee, *Chem. Soc. Rev.* **2015**, *44*, 2489-2507.

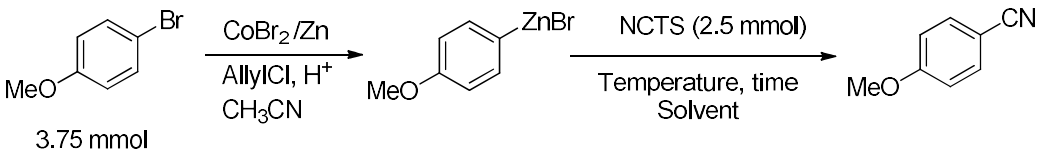
[64] a) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445-1453; b) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem., Int, Ed.* **2006**, *45*, 6040-6044.

[65] a) H. Fillon, C. Gosmini, J. Périchon, *J. Am. Chem. Soc.* **2003,** *125*, 3867-3870; b) I. Kazmierski, C. Gosmini, J-M. Paris, J. Périchon, *Tetrahedron Lett.* **2003**, *44*, 6417-6420; c) C. Gosmini, M. Amatore, S. Claudel, J. Périchon, *Synlett* **2005**, 2171-2174.

II-2 Optimization of the reaction conditions

Using the method that our lab developed to synthesize arylzinc bromides with a $CoBr_2$/Zn catalytic system, we first examined the reaction of 4-methoxyphenylzinc bromide, formed by cobalt catalyst, with NCTS to allow a preliminary optimization of the procedure (Table 1-1). This crude solution of arylzinc bromide was directly added to a solution of NCTS (0.67 equiv *versus* ArBr, 2.5 M) in CH_3CN without further addition of cobalt catalysis. NCTS was consumed within 3 h at room temperature and 41% of the corresponding cyanation product was isolated (Table 1-1, entry 1). We found that the excess of Zn dust in the crude solution would consume NCTS quickly. Previously we have shown that zinc dust could be easily removed by filtration, however, in this reaction, adding filtrate to NCTS, 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 1-1, entries 2 and 3). Since arylzinc compounds could be easily dimerize under these conditions, we tried to slow down the reaction by adding THF. In this way, the selectivity might be increased. However, THF in the medium played a negative role in the reaction, and both the conversion of the arylzinc species and NCTS were decreased, affording very poor yield even at 50 °C (Table 1-1, entries 4 and 5). In some described nucleophilic cyanation methodologies, Zn dust was used to avoid Co catalyst poisoning by cyanide ions.[66] Therefore, the reaction was conducted as usual, after filtration of the Zn dust, 10 mol% Zn dust was added into the reaction medium. To our delight, good yield was obtained (Table 1-1, entry 6) at room temperature with only 10 % NCTS left. Furthermore, increasing the temperature to 50 °C led a total conversion of NCTS within 4 h and gave an excellent yield of 84% (Table 1-1, entry 7).[67] Next we tested different amount of zinc dust added in the second step and proved that 10 mol% of zinc dust was optimum (Table 1-1, entries 8 and 9).

Table 1-1 Optimization of the reaction conditions



[66] (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.

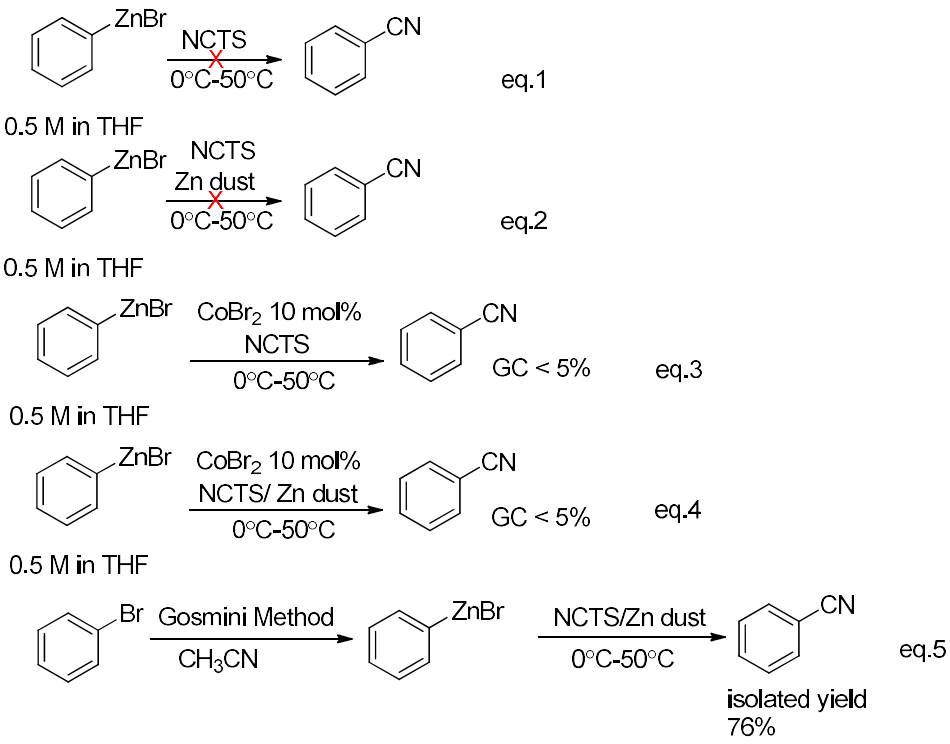
[67] The consummation of Zn dust is diverse depending on the different arylbromides. That's why we do not use less Zu dust in the formation of arylzinc species step.

Entry	Condition	Yield %[a]
1	Without filtration, 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, 4 h**	**84[b]**
8	Filter all the Zn dust, then add 5 mol% Zn, 50 °C, 4 h	(43)
9	Filter all the Zn dust, then add 20 mol% Zn, 50 °C, 4 h	(50)

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

II-3 Necessity of $CoBr_2$

Some controlled reactions were conducted to demonstrate that $CoBr_2$ has a catalytic role in this cyanation process (Scheme 1-37). 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 1-37, equation.1). 10 mol% Zn dust was introduced in the reaction medium, but no arylnitrile formed either (Scheme 1-37, equation.2). Introducing $CoBr_2$ and Zn dust to this phenylzinc bromide solution in the cyanation step provide only traces of arylnitrile (Scheme 1-37, 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 1-37, equation.5).



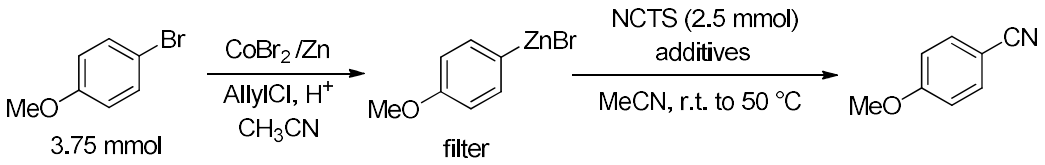
Scheme 1-37 Control experiments to demonstrate that cobalt is required for the cyanation process

II-4 Investigation on the role of zinc dust in second step

In order to understand the role of the catalytic amount of zinc dust in the second step, we have replaced it by 10 mol% of other metals such as Mg, Fe, Mn and CuI and lower GC yields were obtained 31, 0, 53 and 14% , respectively (Table 1-2, entries 5-8). Replacement of Zn by a Lewis acid such as $ZnBr_2$ to facilitate the desired cyanation gave no cyanated product (Table 1-2, entry 9). Therefore, we thought that Zn dust should help the release the cobalt catalyst from the cyano group due to possible affinity between Zn and cyano group, since the electrophilic amination with RR'N-Cl carried out under the same conditions (acetonitrile) works well without zinc.[68] This was further confirmed by preparing the arylzinc bromide with [$CoBr_2$(bipy)] which is able to "protect" the cobalt from the cyano group (Table 1-2, entry 10). In this case, an excellent yield was obtained without supplementary addition of zinc dust in the second step. However, we preferred to use commercially available $CoBr_2$ as catalyst without ligands and add zinc dust in the second step for economic reasons.

Table 1-2 investigation of the additives in second step

[68] X. Qian, Z. Yu, A. Auffrant, C. Gosmini, *Chem. Eur. J.* **2013**, *19*, 6225–6229.



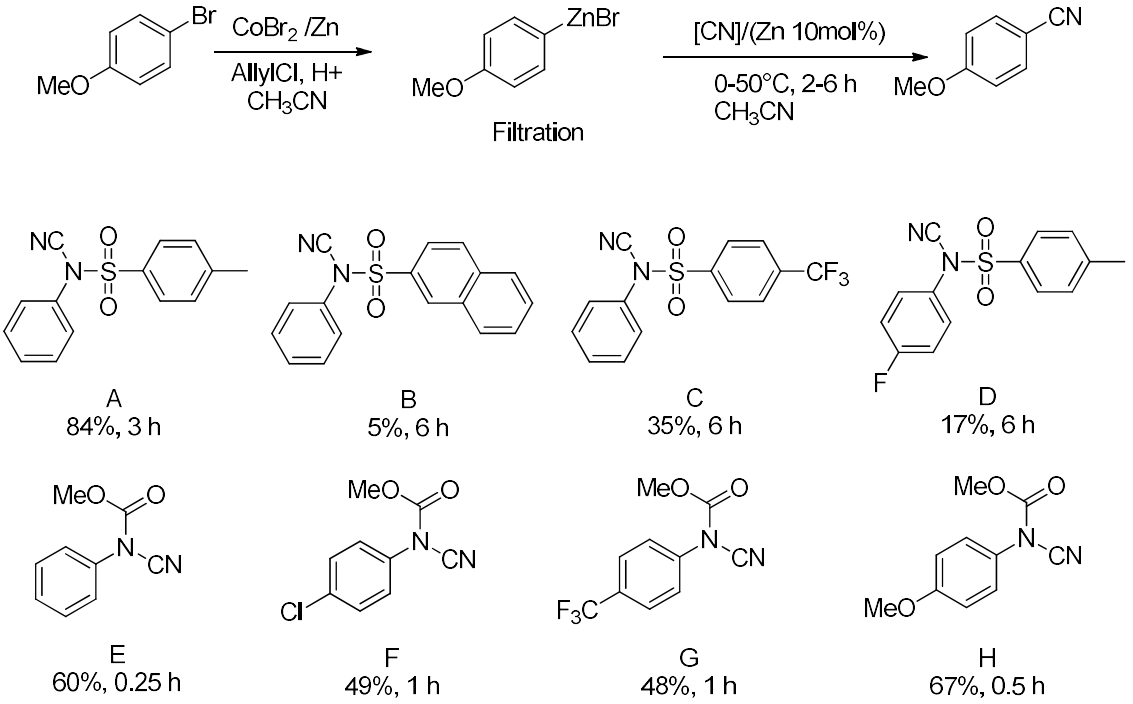
entry	Additives in Step 2	Yield(%)[a]
1	None	38
2	5 mol% Zn	43
3	**10 mol% Zn**	**82[b]**
4	20 mol% Zn	50
5	10 mol% Mg	31
6	10 mol% Fe	0
7	10 mol% CuI	14
8	10 mol% Mn	53
9	10 mol% $ZnBr_2$	0
10[a]	None	77

[a]arylzinc bromide was synthesized with $CoBr_2(bpy)_2$

II-5 Investigation on the reactivity of analogous cyanide resources

Different substituted arylsulphonylcyanamides were investigated (Scheme 1-38, **A**, **B**, **C**, **D**), which 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**, the more bulky naphthyl analogue **B** displayed lower activity and gave only very poor yield of cyanation product. Electron-withdrawing group on the aryl moiety might make the $ArNSO_2Ar'$ fragment a better leaving group, but only poor yields of cyanation were obtained. From the reactivities of **C** and **D**, it indicated that the electron-withdrawing group on the *N*-phenyl group had higher effect than that on the sulphonyl group. Other N-CN compounds, in which arylsulphonyl group was replaced by ester, were also tested. *N*-carbomethoxy-*N*-arylcyanamides (Scheme 1-38, **E**, **F**, **G**, **H**) were synthesized by Alice in three steps from the corresponding commercial benzonitriles to see the influence of the groups on nitrogen and to compare them with arylsulfonylcyanamides. These cyano sources were much more reactive than arylsulfonylcyanamides and the reaction time could be reduced to 15 min. Good yields of cyanated products were obtained from **E** and **H** bearing an electron-donating substituent, whereas compounds **F** and **G** within electron-withdrawing groups on the

N-phenyl group were less efficient. However, these compounds were relatively unstable, so that the yields could not be increased under the optimized reaction conditions for cyanation with NCTS. Therefore, we focused our study on the NCTS.



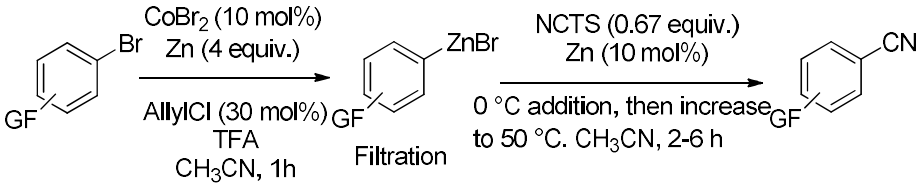
Scheme 1-38 Analogous cyanide resources

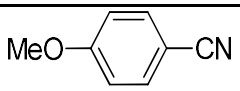
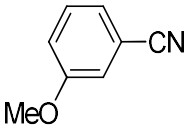
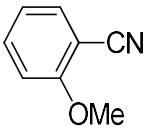
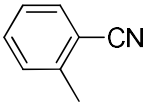
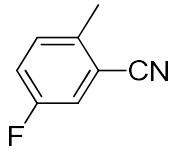
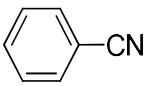
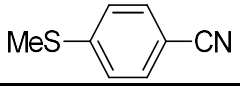
II-6 Scope of aryl halides

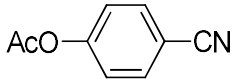
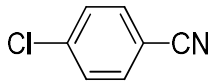
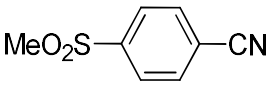
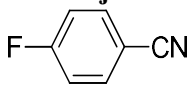
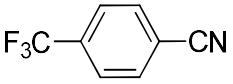
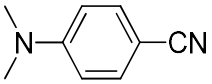
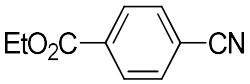
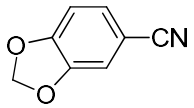
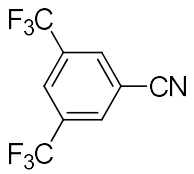
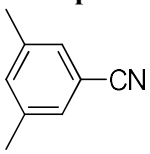
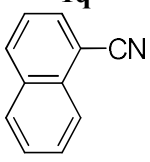
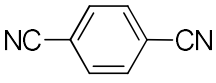
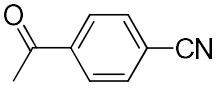
We next explored the scope of arylzinc bromides under the optimized conditions in collaboration with Xin (Table 1-2). In general, moderate to excellent yields were obtained with a variety of substrates. Methoxy group on the *para*-position of the arene was more favorable than that on the *meta*- or *ortho*- position. (Table 1-3, entries 1 to 3). An alkyl group such as methyl group in *ortho*- position still provided excellent yields (Table 1-3, entries 4 and 5). Unfunctionalized phenyl bromide also reacted efficiently (Table 1-3, entry 6). Other aryl bromides bearing functional groups, such as thioether, acetate, chloro-, sulfone-, fluoro-, trifluomethane-, dimethylamine-, ester, dioxane, afforded moderate to excellent yields (Table 1-3, entries 6 to 15). It is noteworthy that some of them were quite difficult to obtain by the electrophilic cyanation of Grignard reagents, since ArMgX are too nucleophilic to tolerate them. Di-substituted, electron-withdrawing or donating group substituted arylzinc bromides also reacted nicely (Table 1-3, enties 16 and 17), naphthylzinc gave an excellent yield product (Table 1-3, entry 18). However, we found that the presence of a strong chelating group (ketone or nitrile) on arylzinc species inhibited the reaction. In these cases, only trace of

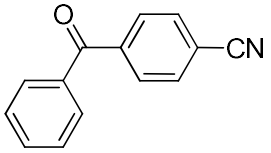
products were observed (identified by HRMS) and not all the NCTS was consumed. Adding more $CoBr_2$ slightly improved the yields. If chelation of cobalt is the problem, the use of [$CoBr_2$(bipy)] instead of $CoBr_2$ to form the corresponding ArZnBr as well as catalyze the cyanation reaction should solve it. To out delight, this worked, under these conditions moderate yields of aryl nitriles were obtained (Table 1-3, entries 19–21). Moreover, we have performed a new method to form vinylzinc species from β-bromosrytene, however, we encountered some problems to couple this zinc species with NCTS. The additional pyridine may hamper the cyanation step. Heteroarylzinc bromides (thiophene and furyl derivatives) gave only some traces of the expected nitrile derivatives.

Table 1-2 Scope of aryl halides



Entry	FG [a]	Product	Reaction time	Yield [b]
1	*p*-OMe	 **1a**	2.5 h	84
2	*m*-OMe	 **1b**	2.5 h	57
3	*o*-OMe	 **1c**	6 h	58
4	*o*-Me	 **1d**	6 h	98
5	2-F,5-Me	 **1e**	6 h	82
6	H	 **1f**	6 h	76
7	*p*-SMe		6 h	76

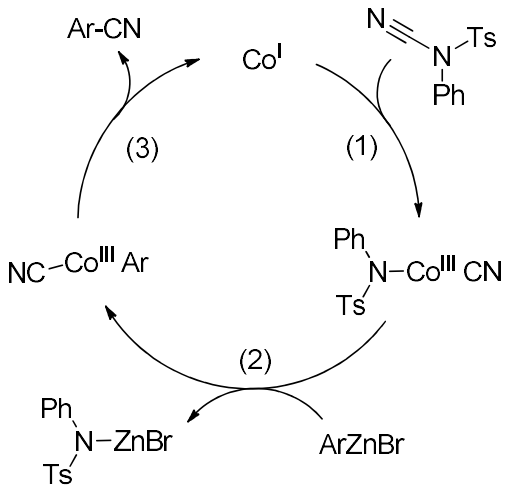
		1g		
8	*p*-OCOMe	 **1h**	6 h	40
9	*p*-Cl	 **1i**	6 h	63
10	*p*-SO_2Me	 **1j**	6 h	47[c]
11	*p*-F	 **1k**	6 h	74
12	*p*-CF_3	 **1l**	6 h	68
13	*p*-NMe_2	 **1m**	6 h	68
14	*p*-CO_2Et	 **1n**	6 h	72
15	1,2-(methylenedioxy)	 **1o**	6 h	79
16	3,5-diCF_3	 **1p**	6 h	40[d]
17	3,5-diMe	 **1q**	6 h	56
18	1-naphthyl	 **1r**	6 h	79
19[e]	*p*-CN	 **1s**	6 h	50
20[e]	*p*-COMe	 **1t**	6 h	34

21[e]	*p*-COPh	 **1u**	6 h	45

[a] Ratio of ArBr to NCTS is 1.5:1. [b] Isolated yields. [c] ^{1}H NMR yield. [d] GC yield.[e]$CoBr_2$(bpy) as catalyst instead of $CoBr_2$.

II-7 Postulated mechanism

A plausible mechanism for this reaction is shown in Scheme based on our previous works involving arylzinc compounds. In Scheme 1-39, (1) oxidative addition of NCTS to the active Co^I catalyst to form the TsPhN-Co^{III}-CN complex. (2) Transmetalation of arylzinc species with TsPhN-Co-CN to furnish Ar-Co^{III}-CN complex followed by (3) the final reductive elimination to generate the Ar-CN product as well as the Co(I) catalyst.



Scheme 1-39 Postulated mechanism

III Conclusions and perspectives

In summary, this new cobalt-catalyzed cyanation of arylzinc bromides with NCTS allows an easy access to various benzonitriles, and complements nicely known methodologies. This reaction tolerates a large number of functional groups and the yields range from modest to excellent. Particularly, with [$CoBr_2$(bipy)] instead of $CoBr_2$, the ketone and nitrile group could be tolerated. The presence of catalytic amount of zinc dust in the cyanation reaction is necessary to achieve good efficiency when $CoBr_2$ is used as the catalyst. The low price of the catalyst, and the mild and bench-friendly conditions for the synthesis of the reagents make this reaction an interesting alternative to more classical methodologies and those via C-H activation.

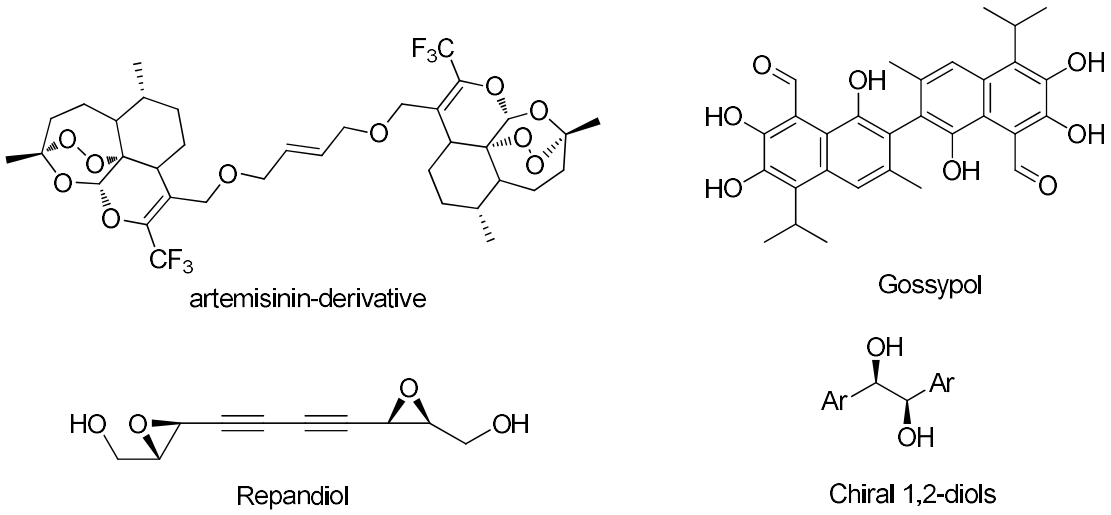
Nevertheless, several issues still remain to be solved. Although some sensitive functional groups and important chelating groups, such as nitrile, ketone are tolerated in this reaction, heteroaromatic substituted groups are not compatible. Efforts have been made in vain to solve these limitations. The scope has still to be broadened with modification of the reaction conditions, including changing the ligands and additives. Besides, the cyanation of vinylzinc compounds should be developed. Moreover, further mechanistic investigations should be conducted to provide with a better understanding, especially concerning the effect of the diversely substituted NCTS derivatives. In addition, the *N*-carbomethoxy-*N*-arylcyanamides may be potential cyano donors if more derivatives and reaction conditions could be examined, since they are consumed faster than NCTS with good yields of cyanation products. Now the electrophilic C-CN bond formation from the arylzinc species obtained under cobalt catalysis has been well established, however, some other electrophiles may be investigated to form new C-C or C-heteroatom bonds, such as C-F and C-CF_3 bond formation, which are also challenging.

Chapter 2 Cobalt-Catalyzed C_{sp3}-C_{sp3} Reductive Coupling

I Cobalt-catalyzed Reuctive C_{sp3}-C_{sp3} Homocoupling

I-1 Introduction

With the progress of biological science, the demand for efficient homocoupling processes increases, since many natural products are dimers or pseudodimers (Scheme 2-1).[69] The homocoupling of olefins,[70] alkynes,[71] carbonyls[72] and aryl halides[73] have been well developed in the last decades and a variety of efficient methodologies has been reported. However, compared to the methods mentioned above, the homocoupling of alkyl halides has been relatively poorly investigated. The traditional Wurtz coupling was an important tool but it suffers from limited functional group tolerance



Scheme 2-1 Representive examples of organic symmetric compounds

[69] a) F. Grellepois, B. Crousse, D. Bonnet-Delpon, J.-P. Bégué, *Org. Lett.,* **2005**, *7*, 5219; b) M. C. de la Torre, A. M. Deometrio, E. Álvaro, I. García, M. A. Sierra, *Org. Lett.,* **2006**, *8*, 593; c) L. Li, B. Xu, *Curr. Pharm. Des.* **2005**, *11*, 3111; d) K. A. Ahrendt, J. A. Olsen, M. Wakao, J. Trias, J. A. Ellman, *Bioorg. Med. Chem. Lett.,* **2003**, *13*, 1683–1686.

[70] a) K. Itami, Y. Ushiogi, T. Nokami, Y. Ohashi, J. Yoshida, *Org. Lett.*, **2004**, *21*, 3695; b) M. Michalak, L. Gulajski, K. Grela, *Sci. Synth.*, **2010**, *47a*, 327; c) Y.M. Wen, J.Y. Xie, C.M. Deng, Y.L. Wu, *synlett*, **2015**, *26*, 1755.

[71] a) A. S. Batsanov, J.C. Collings, I. J. S. Fairlamb, J. P. Holland, J. A. K. Howad, Z. Lin, T. B. Marder, A. C. Parsons, R. M. Ward, J. Zhu, *J. Org. Chem.*, **2005**, *70*, 703; b) X. Jia, K. Yin, C. Li, J. Li, H. Bian, *Green Chem.*, **2011**, *13*, 2175; c) X. Niu, C. Li, J. Li, X. Jia, *tetrahedron lett.*, **2012**, *53*, 5559.

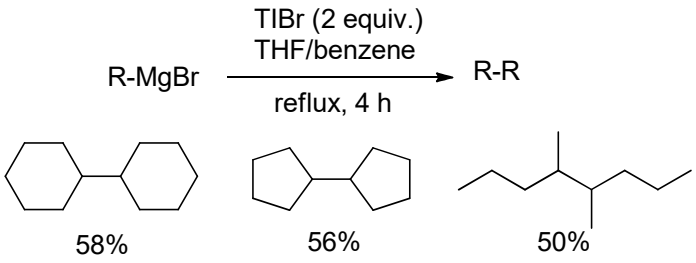
[72] a) S. Ogoshi, H. Kamada, H. Kurosawa, *Tetrahedron*, **2006**, *62*, 7583; b) A. Chatterjee, N. N. Joshi, *Tetrahedron*, **2006**, *62*, 12137; c) T. Takeda, A. Tsubouchi, *Sci. Synth.* **2010**, *47a*, 247;

[73] a) G. Cahiez, A. Moyeux, J. Buendia, C. Duplais, *J. Am. Chem. Soc.*, **2007**, *129*, 13788; b)N. Kirai, Y. Yamamoto, *Eur. J. Org. Chem.*, **2009**, 1864; c)T. Matsuda, T. Asai, S. Shiose, K. Kato, *Tetrahedron Lett.*, **2011**, *52*, 4779; d) C.A. Contreras-Celedon, J.A. Rincon-Medina, D. Mendoza-Rayo, L. Chacon-Garcia, *appl. Organometal. Chem.*, **2015**, *29*, 439.

due to the harsh reaction conditions.[74] Moreover, the competing elimination reaction and rearrangement processes lead to low yields. Another drawback is the requirement of stoichiometric quantity of highly reactive metals (*e.g.* Na). Thus, the design of more practical and efficient methods needs to be developed.

I-1-1 C_{sp3}-C_{sp3} homocoupling of organometallic compounds

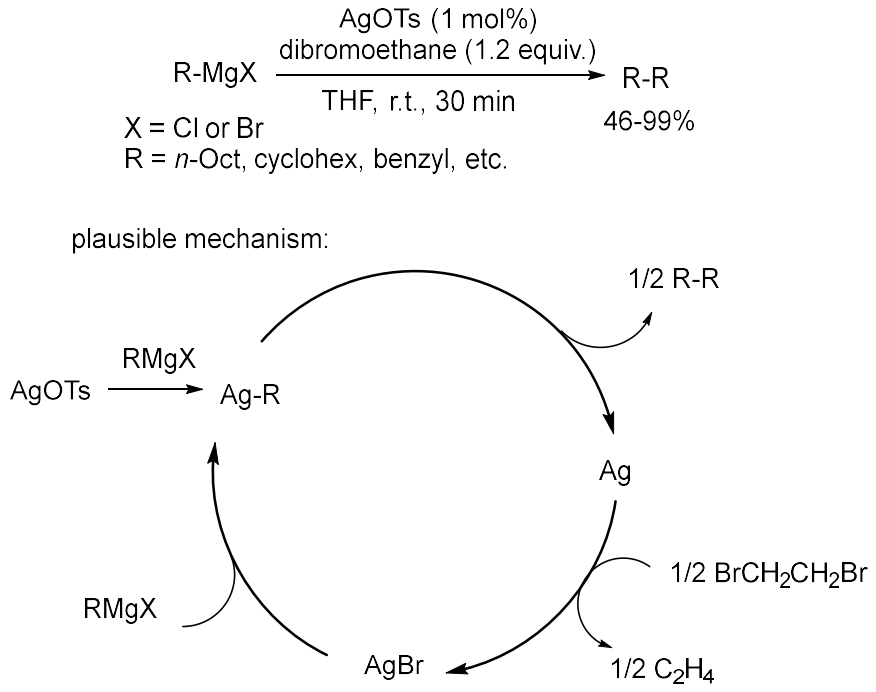
Alkyl-alkyl oxidative homocoupling employing organometallic compounds was one way to achieve dimers. Grignard reagents were utilized to one of the first alkyl oxidative reactions which was reported in 1968 (Scheme 2-2).[75] 2 equivalents of thallium bromide were used to form organothallium compounds which could dimerize or couple with organo halides. In this reaction, primary aliphatic Grignard reagents only afforded traces amount of homocoupling products.



Scheme 2-2 Homocoupling of Grignard reagents in the presence of TlBr

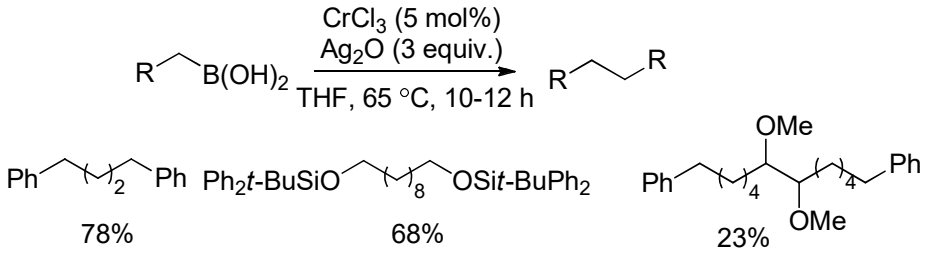
In 2005, Hayashi and coworkers employed Grignard reagents to establish an alkyl-alkyl homocoupling reaction using silver catalyst (Scheme 2-3).[76] With dibromoethane as the reoxidant, a variety of unfunctionalized alkyl and benzyl Grignard reagents were tolerated under mild conditions yielding moderate to excellent yields. However, scope of functional groups was not well displayed. Recently, in some aryl-aryl homocoupling reactions using Grignard compounds, very limited alkyl examples were also examined.[77]

[74] A. Wurtz, *Ann. Chem. Pharm.*, **1855**, *96*, 364.
[75] A. MacKillop, L. F. Elsom, C. E. Taylor, *J. Am. Chem. Soc.* **1968**, *90*, 2423-2424.
[76] T. Nagano, T. Hayashi, *Chem. Lett.* **2005**, *34*, 1152-1153.
[77] a) S.-K. Hua, Q.-P. Hu, J. Ren, B.-B. Zeng, *Synthesis* **2013**, *45*, 518–526; b) T. Korenaga, K. Nitatori, H. Muraoka, S. Ogawa, K. Shimada, *Org. Lett.* **2015**, *17*, 5500-5503.



Scheme 2-3 Silver-catalyzed homocoupling of alkyl Grignard reagents

Besides Grignard reagents, other organometallic compounds were also applicable to undergo dimerization. Falck and coworkers demonstrated a chromium-catalyzed oxidative homocoupling of organoboronic acids in the presence of Ag_2O (Scheme 2-4).[78] Several examples of alkylboronic acids were exhibited, and it showed good tolerance of primary alkylboronic acids. Silver salts were crucial for the reaction when chromium chloride was the catalyst.

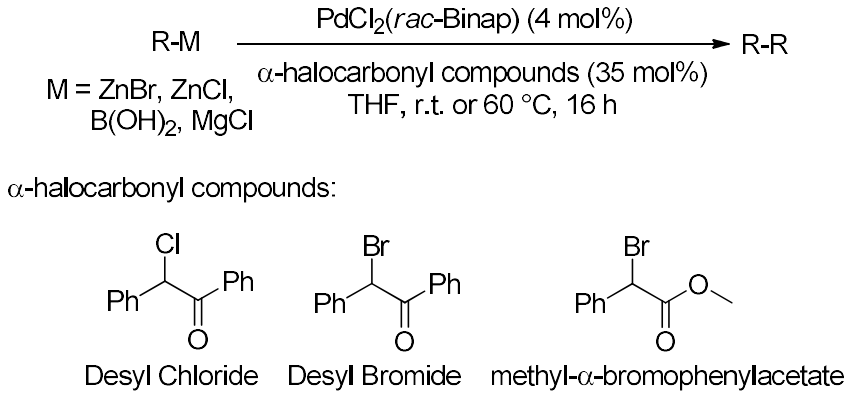


Scheme 2-4 Chromium-catalyzed homocoupling of alkylboronic acids

In 2002, Zhang and Lei disclosed that alkylzinc compounds could be efficiently homocoupled as well as alkylboronic acids and Grignard reagents (Scheme 2-5).[79] Palladium catalyst efficiently delivered dimers of benzylmetallic compounds in the

[78] J. R. Falck, S. Mohapatra, M. Bondlela, S. K. Venkataraman, *Tetrahedron Lett.* **2002**, *43*, 8149
[79] A. Lei, X. Zhang, *Org. Lett.* **2002**, *4*, 2285-2288.

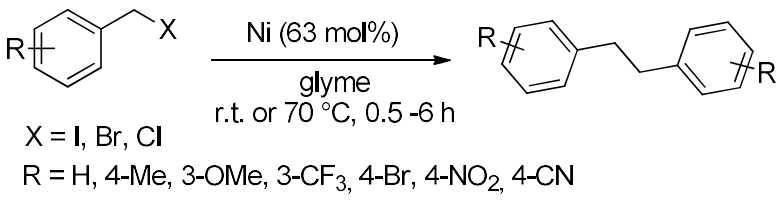
presence of α-halocarbonyl compounds as oxidants. The authors showed good toletance of different kinds of organometallic compounds as well as functional groups. Nevertheless, this method suffered from the competitive β-elimination when alkylmetallic compounds bearing β-H atoms were employed.



Scheme 2-5 Palladium-catalyzed homocoupling of alkylmetallic compounds

I-1-2 C_{sp3}-C_{sp3} reductive homocoupling

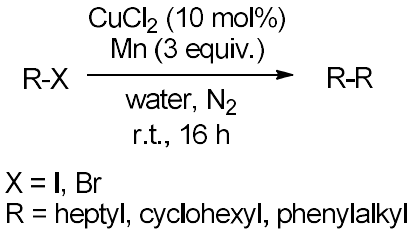
The C_{sp3}-C_{sp3} reductive homocoupling was mostly focused on metal-mediated or catalyzed benzyl-benzyl homocoupling. In 1970, Hashimoto and coworkers developed a nickel-mediated dimerization of benzyl halides.[80] Methyl and methoxy group could be well tolerated affording excellent yields while cyano group favored to give reduction product. Later Rieke and coworkers disclosed that highly reactive metallic nickel promoted homocoupling of benzylic halides efficiently (Scheme 2-6).[81] Not only different halides were examined but also a broad scope of functional groups was displayed. Besides, the homocoupling of benzyl halides could also be promoted by titanium[82] or indium[83], however, both of the methods did not exhibit good tolerance of substrates.



[80] I. Hashimoto, N. Tsuruta, M. Ryang, S. Tsutsumi, *J. Org. Chem.* **1970**, *35*, 3748-3752.
[81] S. Inaba, H. Matsumoto, R. D. Rieke, *J. Org. Chem.* **1984**, *49*, 2093-2098.
[82] A. F. Barrero, M. M. Herrador, J. F. Quilez del Moral, P. Arteaga, M. Akssira, F. El Hanbali, J. F. Arteaga, H. R. Dieguez, E. M. Sanchez, *J. Org. Chem.* **2007**, *72*, 2251-2254.
[83] B. C. Ranu, P. Dutta, A. Sarkar, Tetrahedron Lett. 1998, 39, 9557-9558.

Scheme 2-6 Nickel-mediated homocoupling of benzyl halides

Homocoupling of alkyl halides bearing β-H atoms were less investigated. Apart from dimerization of specific alkyl halides,[84] homocoupling of unfunctionalized alkyl halides were first developed. In 1981, Nakajima and coworkers reported a palladium-catalyzed homocoupling of primary iodoalkanes.[85] The iodoalkanes with a longer chain afforded better yields, while iodohexane only gave 0.7% yield. Large amount of strong base (NaOH) was used, which may limit the application. In 1998 Chan and coworkers established a copper-catalyzed homocoupling of alkyl halides with manganese as reductant (Scheme 2-7).[86] Series of primary and secondary alkyl iodides and bromides homocoupled efficiently in water under mild conditions. In addition to an allyl bromide bearing acid group, no functionalized alkyl halides were examined.

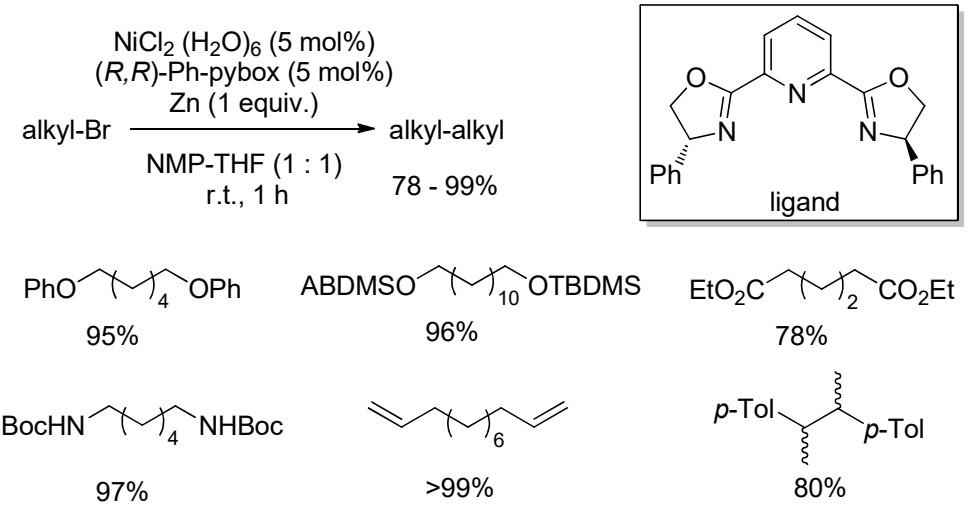


Scheme 2-7 Coppe-catalyzed homocoupling of unfunctionalized alkyl halides

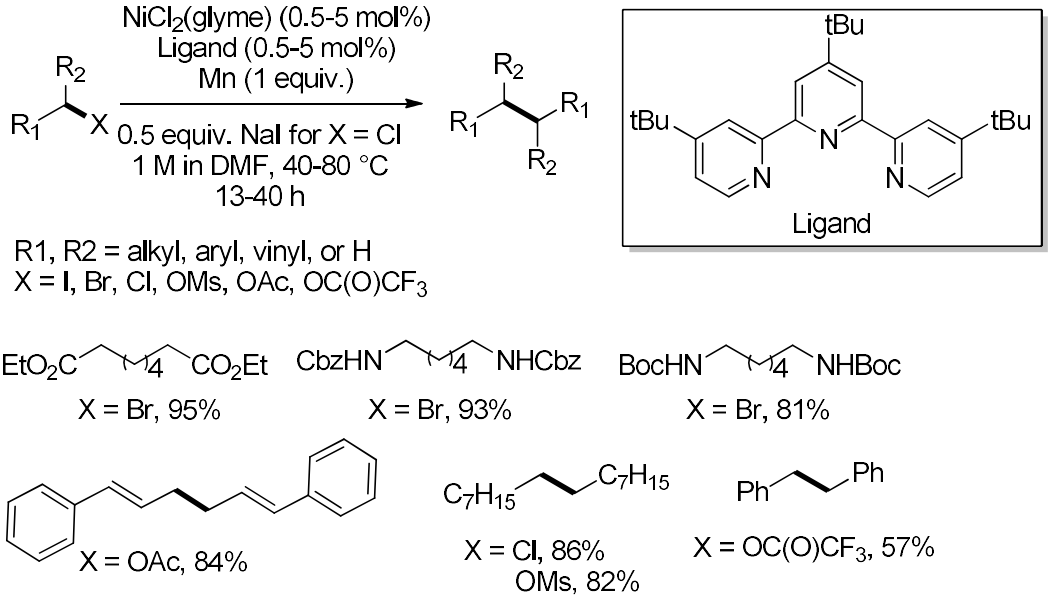
In 2010, Leigh and coworkers first described tridentate nitrogen-donor atom ligands-assisted Ni-catalyzed homocoupling of alkyl bromides under mild reaction conditions (Scheme 2-8).[87] It was highly yielding and operationally simple but the scope of substrates was not broadly applied. Almost at the same time, Weix and coworkers published a more general method for reductive dimerization of alkyl halides/pseudohalides, using a Ni/terpy-catalyzed system (Scheme 2-9).[88] A variety of functionalized substrates was tolerated affording moderate to excellent yields, including primary and secondary alkyl halides, benzyl chlorides and allylic acetates. With the presence of sodium iodide (50 mol%), unactivated alkyl chloride, alkyl

[84] examples, see: a) F. Ginah, T. Donovan, S. Suchan, D. Pfennig, G. Ebert, *J. Org. Chem.* **1990**, *55*, 584-589; b) X. Xu, D. Cheng, W. Pei, *J. Org. Chem.* **2006**, *71*, 6637-6639; c) P. Poizot, V. Jouikov, J. Simonet, *Tetrahedron Lett.* **2009**, *50*, 822-824.
[85] R. Nakajima, K. Morita, T. Hara, *Bull.Chem.Soc. Jpn.* **1981**, *54*, 3599-3600.
[86] J. Ma, T.-H. Chan, *Tetrahedron Lett.* **1998**, *39*, 2499-2502.
[87] S. M. Goldup, D. A. Leigh, R. T. McBurney, P. R. McGonigal, A. Plant, *Chem. Sci.*, **2010**, *1*, 383.
[88] M. R. Prinsell, D. A. Everson, D. J. Weix, *Chem. Commun.*, **2010**, *46*, 5743.

sulfonate ester and alkyl trifluoroacetate ester dimerized with moderate to excellent yields. The role of sodium iodide is likely (1) enhancement of the reductive coupling, possibly by facilitating reduction of the nickel catalyst[89] or the formation of a nickelate species.[90] (2) generation of reactive alkyl iodides from the corresponding alkyl substrates (alkyl chlorides, mesylates or trifluoroacetates) *in situ* by "leaving group /I" exchange.



Scheme 2-8 Nickel-catalyzed reductive homocoupling of unactivated alkyl bromides

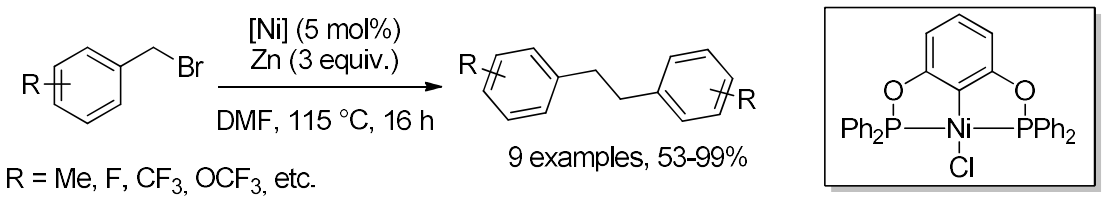


Scheme 2-9 Nickel-catalyzed reductive homocoupling of alkyl/allylic halides/pseudohalides

[89] I. Colon, D. R. Kelsey, *J. Org. Chem.* **1986**, *51*, 2627–2637.

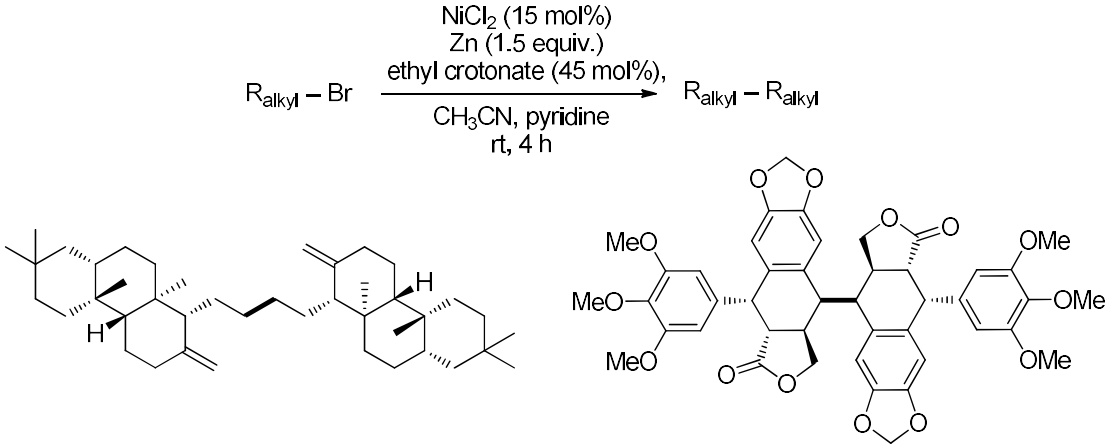
[90] J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc*. **2002**, *124*, 4222–4223.

Nickel was also chosen as the catalyst to conduct a homocoupling of benzyl halides in the presence of zinc as the reductant (Scheme 2-10). [91] Electron-donating or withdrawing groups could be well tolerated in high temperature resulting in moderate to excellent yields. However, the scope of substrates was not broadened.



Scheme 2-10 Nickel-catalyzed reductive homocoupling of benzyl halides

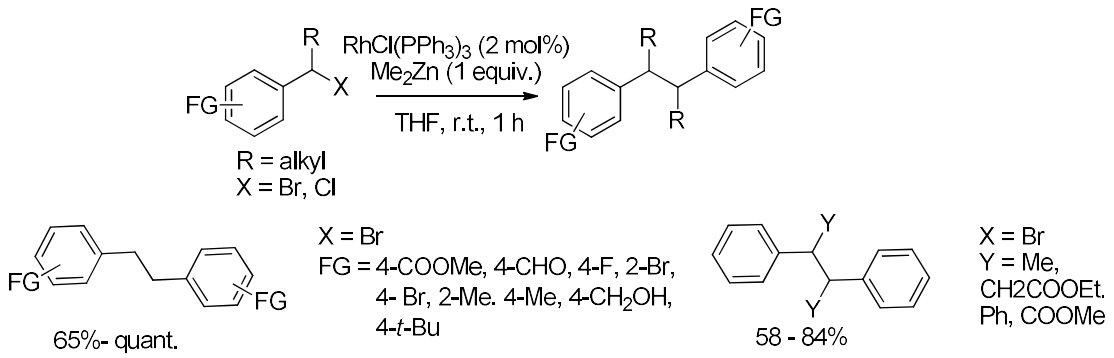
Later, Wang and coworkers established another method for alkyl-alkyl homocoupling with a Ni/Ethyl crotonate or Ni/bipy system, which could be employed for sophisticated substrates.[92] The dimerization of primary, secondary as well as tertiary alkyl bromides was efficiently established, and it was applied to the highly stereoselective homocoupling of podophyllotoxin-derived bromide (Scheme 2-11).



Scheme 2-11 Nickel-catalyzed reductive homocoupling of alkyl bromides and its application

More recently, Ando and coworkers showed that a Rh-catalyzed C_{sp3}-C_{sp3} homocoupling reaction of benzyl halides could be involved instead of a nickel catalyst (Scheme 2-12). [93] Reactive substituents such as an uncovered formyl or hydroxymethyl group were tolerated under veryl mild reaction conditions.

[91] T. Chen, L. Yang, L. Li, K.-W. Huang, *Tetrahedron* **2012**, *68*, 6152-6157.
[92] Y. Peng, L. Luo. S-C. Yan, J-J. Zhang, Y-W. Wang, *J. Org. Chem.*, **2013**, *78*, 10960.
[93] K. Sato, Y. Inoue, T. Mori, A. Ando, *Org. Lett.*, **2014**, *16*, 3756.



Scheme 2-12 Rhodium-catalyzed reductive homocoupling of benzyl halides

For few years, our group has already reported efficient Co-catalyzed reductive cross couplings, such as aryl-aryl, aryl-alkyl, allyl-alkyl cross coupling, [94] and homocoupling of aryl halides.[95] Therefore, we investigated an alternative C_{sp3}-C_{sp3} homocoupling reaction using simple Co catalyst with the objective to develop a more practical method, since cobalt is more environmentally friendly than nickel, much cheaper than rhodium, and Co-catalyzed reactions often do not need additional ligands.

I-2 Results and discussions

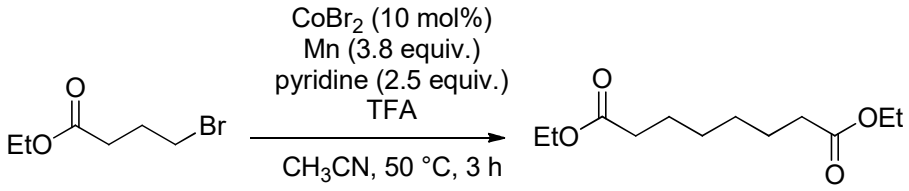
I-2-1 Optimization of reaction conditions

We first carried out a model study using ethyl 4-bromobutyrate as the starting reagent (Table 2-1). We identified that a combination of $CoBr_2$/Mn/pyridine in CH_3CN, as previously reported for the allyl-alkyl coupling reaction, [96] afforded the desired coupling product in 84% yield (Table 2-1, entry 1). Without pyridine, the reduction product was rapidly the main product (Table 2-1, entry 2). Increasing pyridine reduced the catalytic ability and decreased the yield (Table 2-1, entry 3). We assumed that pyridine stablized the reactive Co(I) species while too much pyridine may blocked the reaction. It is noteworthy that when 2-picoline was used instead of pyridine, the same yield was obtained (Table 2-1, entry 4). Decreasing either the catalyst loading or the amount of Mn led to lower yields (Table 2-1, entry 5-6), while increasing the catalyst loading gave no positive effect (Table 2-1, entry 7). Low yield

[94] C. E. I. Knappke, S. Grupe, D. Gartner, M. Corpet, C. Gosmini, A. Jacobi von Wangelin, *Chem. Eur. J.*, **2014**, *20*, 6828.
[95] A. Moncomble, P. Le Floch, C. Gosmini, *Chem. Eur. J.*, **2009**, *15*, 4770
[96] X. Qian, A. Auffrant, A. Felouat, C. Gosmini, *Angew. Chem. Int. Ed.*, **2011**, *50*, 10402.

was obtained at room temperature (Table 2-1, entry 8). Addition of allyl chloride in a first step had no positive effect in this homocoupling reaction whereas the reduction product decreased in cobalt-catalyzed reductive aryl-aryl homocoupling reactions in its presence.[14] In contrast, more reduction product was observed and the reaction rate was diminished (Table 2-1, entry 9).

Table 2-1. Optimization of reaction conditions



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

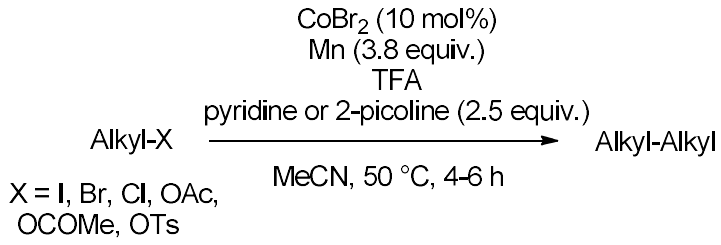
[a] Isolated yield. [b] Conversion is 40 % after 18 h.

I-2-2 Scope of substrates in C_{sp3}-C_{sp3} homocoupling reaction

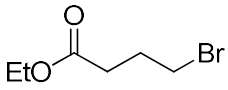
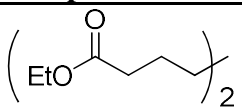
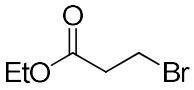
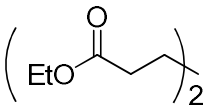
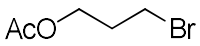
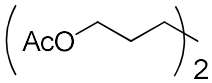
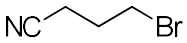
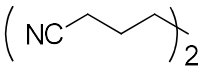
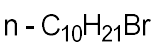
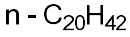
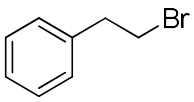
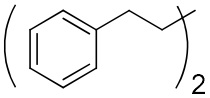
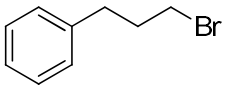
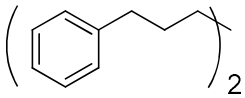
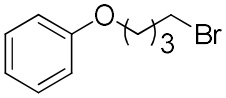
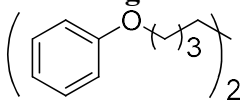
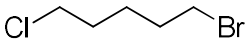
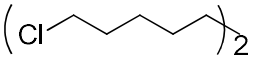
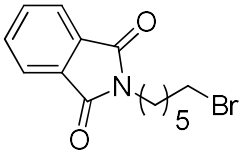
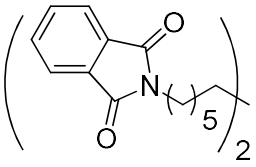
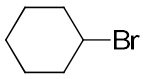
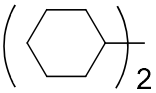
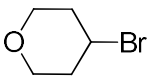
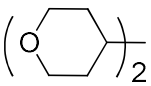
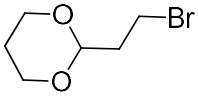
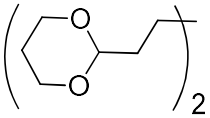
With this optimized conditions in hand, we next investigated the scope of alkyl halides (Table 2-2). Primary alkyl bromides were well tolerated; good to excellent yields were obtained with or without functionalities (Table 2-2, entries 1-10). In most cases, 2-picoline gave better yields than pyridine. Alkyl bromides bearing electron-donating groups and electron-withdrawing groups, such as ester (Table 2-2, entries 1-2), acetate (Table 2-2, entry 3), nitrile (Table 2-2, entry 4), phenyl (Table 2-2, entry 6-7), ether (Table 2-2, entry 8), chloride (Table 2-2, entry 9), ketal (Table 2-2, entry 13) efficiently reacted. Interestingly, whereas isoindol-1,3-dione and ketone groups were not tolerated in the cobalt-catalyzed allyl-alkyl cross-coupling reactions,[15] they provided moderate to good yields in this homocoupling reaction (Table 2-2, entry 10,

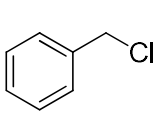
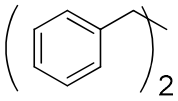
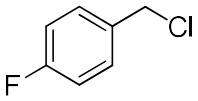
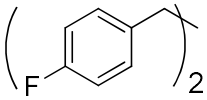
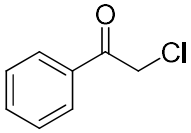
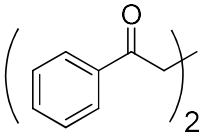
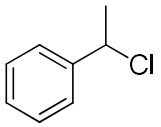
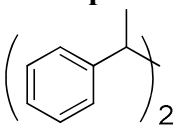
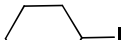
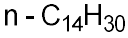
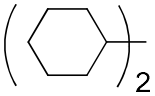
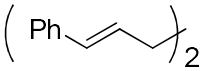
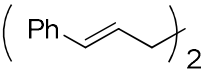
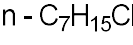
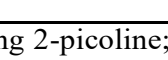
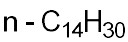
16). Unfortunately, some sensitive functional groups, such as acid, alcohol, inhibited this reaction. Benzyl chloride, which is more reactive, could also be used in this reaction (Table 2-2, entry 14-15). Moreover, the dimerization of secondary benzyl chloride proceeded efficiently (Table 2-2, entry 17). However, the coupling of more reactive functionalized benzyl chlorides bearing electron-withdrawing groups, such as 4-(chloromethyl)benzonitrile and 4-methylsulfonyl benzyl chloride, only afforded reduction product. No better result was obtained at room temperature. Moreover, when vinyl group was substituted on benzyl chloride, a mixture of trimers and polymers was detected. The result may imply that a radical intermediate was generated in the reaction. Unreactive alkyl chlorides did not react under these conditions. However, as already reported in some Ni-catalyzed reductive couplings,[8,97] addition of sodium iodide led to the coupling product. In our case, alkyl chloride dimerized smoothly at higher temperature in longer reaction time in the presence of NaI (Table 2-2, entry 22). This additive also had a positive influence on the homocoupling of alkyl tosylates, which did not react under standard reaction conditions (Table 2-2, entry 23). Nevertheless, more unreactive alkyl chloride seemed to difficult to dimerize under the modified condition. Some secondary alkyl bromides, such as cyclohexyl bromide and 4-bromotetrahydropyran, coupled smoothly under these conditions (Table 2-2, entry 11-12), but *t*Butyl 4-bromopiperidine-1-carboxylate was not homocoupled and only reduction product was isolated. Besides, primary and secondary alkyl iodides reacted and led to moderate yields (Table 2-2, entry 18-19), while tertiary alkyl bromides did not react on this condition. To our delight, cinnamyl acetate and carbonate were well dimerized in this protocol (Table 2-2, entry 20-21). However, an hindered substituted allylic acetate, e.g. (E)-hex-2-en-1-yl acetate did not react.

Table 2-2 scope of substrates

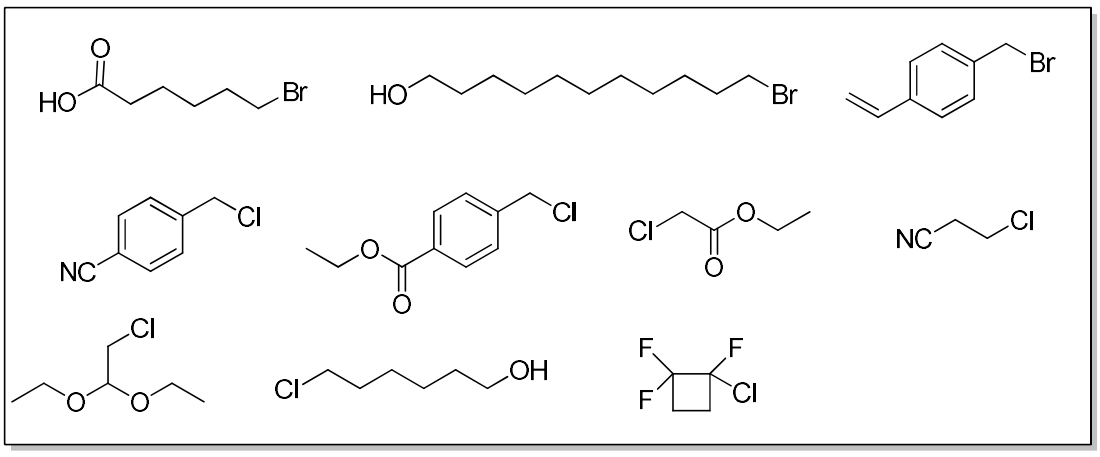


[97] a) I. Colon, D. R. Kelsey, *J. Org. Chem*., **1986**, *51*, 2627; b) A.H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2014**, *136*, 14365.

entry	substrate	product	yield
1		 **2a**	84[a,b]
2		 **2b**	66[b]
3		 **2c**	83[a]
4		 **2d**	88[b] (65[a])
5		 **2e**	87
6		 **2f**	74[b] (37[a])
7		 **2g**	70[b] (57[a])
8		 **2h**	76[b]
9		 **2i**	56[b] (80[a,e])
10		 **2j**	79[a]
11		 **2k**	68[a] (48[b,e])
12		 **2l**	95[b] (49[a,e])
13		 **2m**	87[b]

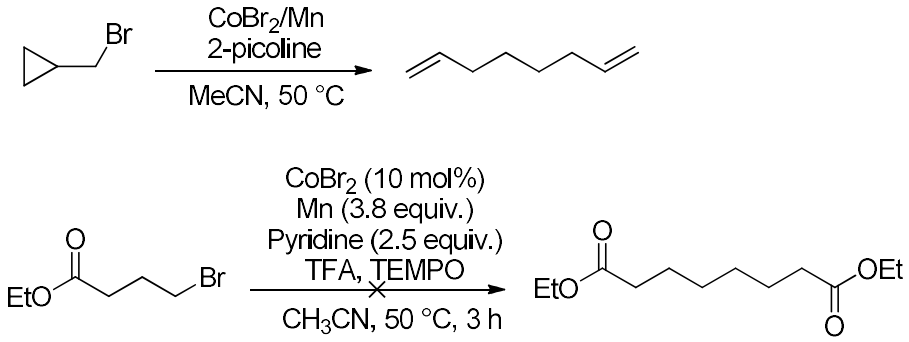
14		 **2n**	82[a]
15		 **2o**	79[b] (68[a,e])
16		 **2p**	50[a] (trace[b])
17		 **2q**	78[a]
18		 **2r**	60[a]
19		 **2k**	53[a,b]
20		 **2s**	82[a]
21		 **2s**	72[a]
22		**2r**	70[a,c] (37[b,c])
23		 **2r**	80[a,d]

[a]using pyridine; [b] using 2-picoline; [c] add 0.5 equiv. of NaI, at 80 °C, 72h; [d]add 0.5 equiv. of NaI. [e] yield on GC



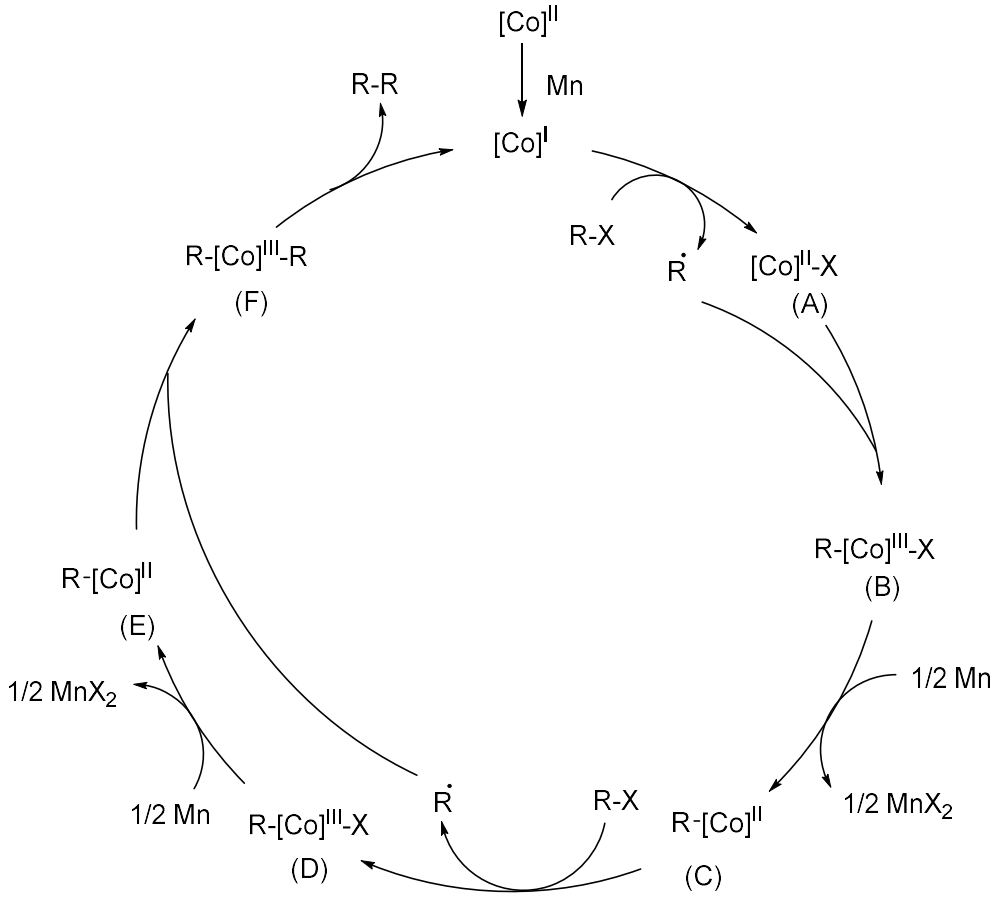
I-2-3 Investigation of mechanism

A few experiments were conducted to provide some insights into the mechanism of this homocoupling reaction (Scheme 2-13). When bromomethylcyclopropane was used as starting material, the dimer of the ring-opened product was the sole product identified by NMR. Moreover, the addition of a free radical scavenger such as 2,2,6,6-tetramethylpiperine-1-oxyl (TEMPO) after the activation of manganese inhibited the homocoupling reaction. These results suggest that a radical intermediate is involved in this reaction.



Scheme 2-13 Mechanism study

Therefore we proposed a mechanism of the reaction as shown in Scheme 2-14. First, cobalt(II) is reduced by manganese. Then, an alkyl radical is generated from alkyl halide by its reaction with this low valent cobalt and a cobalt complex (A) is formed. This last complex (A) reacts with the alkyl radical to form another cobalt complex (B). After reduction of the complex (B) by manganese, a similar procedure leads to a cobalt-bialkyl complex (F). Finally the reductive elimination gives the desired homocoupling product and regenerates the catalyst.



Scheme 2-14 Proposed mechanism

I-3 Conclusions and perspectives

In conclusion, a novel approach for C_{sp3}-C_{sp3} homocoupling has been developed using a simple cobalt bromide as catalyst in acetonitrile/pyridine as solvent. This method is very easy to implement and no additional ligand is needed. A large variety of functionalities on the alkyl halides was tolerated and good to excellent yields were obtained even with reactive benzyl chlorides and allyl acetate/carbonate. Primary and secondary alkyl bromides and iodides undergo the dimerization with good yields while tertiary alkyl bromides could not be tolerated. However, the addition of sodium iodide is required to obtain the homocoupling product of unactivated alkyl chlorides and tosylates with good yields. Mechanistic study suggests that the reaction involves a radical intermediate, while the catalytic cycle needs to be elucidated after further investigations.

II Cobalt-catalyzed reductive C_{sp3}-C_{sp3} cross-coupling

II-1 Introduction

Efficient transition-metal catalyzed C_{sp3}-C_{sp3} cross-coupling reaction is a valuable tool to achieve important nature products and pharmaceuticals. However, it remains a challenge compared to C_{sp2} or C_{sp} analoges, because it is unwilling to undergo oxidative addition of the nonactivated alkyl halides with a metal catalyst and prone to β-H elimination. Recently, a variety of strategies forward to C_{sp3}-C_{sp3} cross-coupling has been developed. We first summerize transition-metal-catalyzed cross-coupling of primary and secondary alkyl electrophiles with primary alkyl nucleophiles.[98] Then cross-dehydrogenative coupling will be introduced followed by 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.

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

II-1-1-1 Kumada type alkyl-alkyl reactions

Conventional Kumada type has been applied to alkyl-alkyl cross-coupling since several decades.[99] However, very limited substrated was employed. 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 2-15).[100] 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. Then the same group extended this reaction with Pd catalysts,[101] and revealed that Pd catalysts showed higher chemoselectivities in favour of tosylates against bromides and chlorides under the same reaction conditions.

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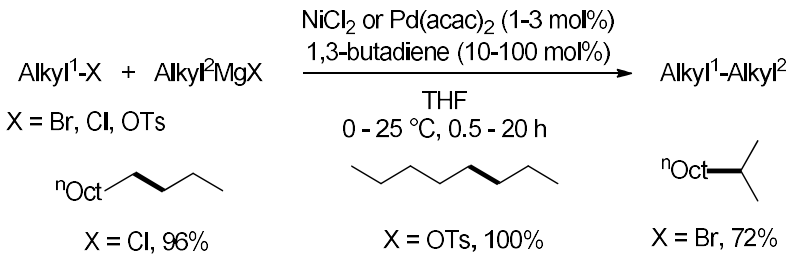
[98] Hu, X. *Chem. Sci.* **2011**, *2*, 1867-1886.

[99] a) M. Tamura, J.K. Kochi, *Synthesis*, **1971**, *93*, 303-305; b) K. Yuan, W. J. Scott, *Tetrahedron Lett.* **1991**, *32*, 189-192; c) G. Cahiez, C. Chaboche, M. Jézéquel, *Tetrahedron*, **2000**, *56*, 2733-2737.

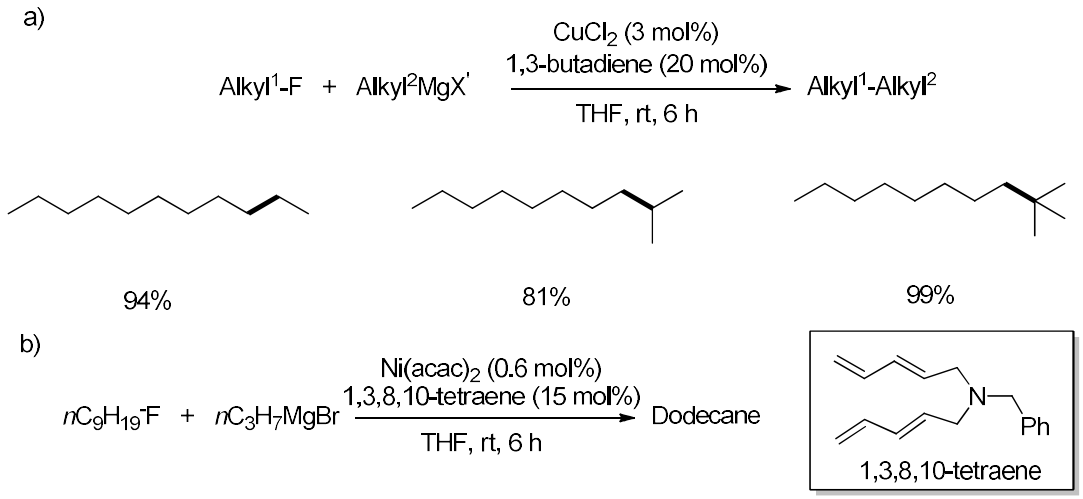
[100] J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2002**, *124*, 4222-4223.

[101] a) J. Terao, Y. Naitoh, H. Kuniyasu, N. Kambe, *Chem. Lett.* **2003**, *32*, 890-891; b) S. P. Singh, T. Iwasaki, J. Terao, N. Kambe, *Tetrahedron Lett.* **2011**, *52*, 774-776.



Scheme 2-15 Nickel-catalyzed Kumada type alkyl-alkyl cross-coupling reactions

Kambe and coworkers later reported an efficient system for the cross-coupling reaction of alkyl fluorides with alkyl Grignard reagents catalyzed by $CuCl_2$ with 1,3-butadiene as the ligand (Scheme 2-16-a)[102] or catalyzed by $Ni(acac)_2$ with 1,3,8,10-tetraenes as additives (Scheme 2-16-b).[103] Primary unfunctionalized 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. The high reactivity of alkyl fluorides are proposed to rely on their transformation into the corresponding alkyl bromides in the presence of $MgBr_2$.[104]

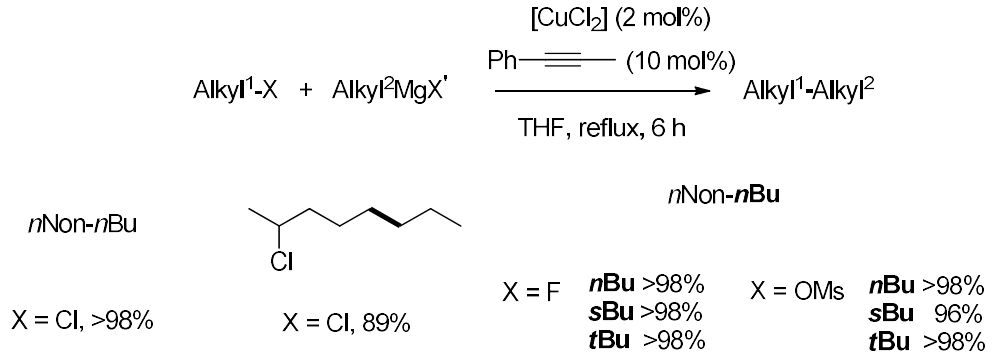


Scheme 2-16 Copper-catalyzed Kumada type alkyl-alkyl cross-coupling reactions.

Later, they overcame the difficulties for the coupling of alkyl chlorides with Grignard reagents catalysed by copper chlorides (Scheme 2-17).[105] In the presence of 1-

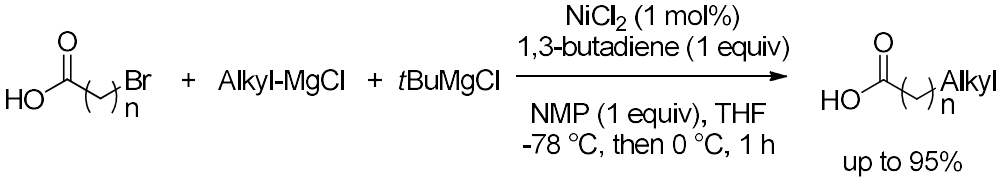
[102] Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646-5647.
[103] J. Terao, H. Todo, H. Watanabe, A. Ikumi, N. Kambe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6180-6182.
[104] Begum, S. A.; Terao, J.; Kambe, N. *Chem. Lett*. **2007**, *36*, 196-197.
[105] J. Terao, H. Todo, S. A. Begum, H. Kuniyasu, N. Kambe, *Angew. Chem. Int. Ed.* **2007**, *46*, 2086-2089.

phenylpropyne as an additive, alkyl chlorides reacted with alkyl Grignard reagents under reflux and provided good to excellent coupling yields. This protocol was also used for alkyl fluorides and mesylates. Again, the functional compatibilities and substrate scope were not demonstrated. Furthermore, they disclosed that in the copper-diene or copper-alkyne system the catalyst loading could be decreased to ppm scale.[106]



Scheme 2-17 Copper-catalyzed Kumada type alkyl-alkyl cross-coupling reactions.

Next improvement of the nickel-butadiene catalytic system was cross-coupling of bromoalkonoic acids with alkyl Grignard reagents (Scheme 2-18).[107] It required 1 equivelant of *t*BuMgCl as base to deprotonate the carboxylic acid group. Low temperature was nesserasy when addint the Grignard reagents.



Scheme 2-18 Nickel-catalyzed Kumada type alkyl-alkyl cross-coupling reactions employing bromoalkanoic acids

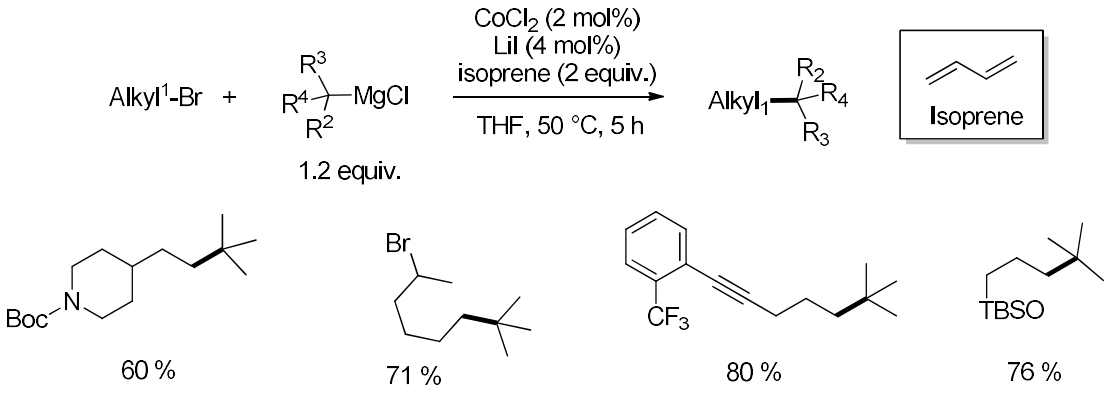
Recently, Kambe's group reported the first cobalt-catalyzed cross-coupling of primary alkyl halides with tertiary alkyl Grignard reagents (Scheme 2-19).[108] This protocol constructed sterically congested quaternary carbon centers and tolerates various functional groups. Both 1,3-butadiene and LiI played important roles to achieve high

[106] T. Iwasaki, R. Imanishi, R. Shimizu, H. Kuniyasu, J. Terao, N. Kambe, *J. Org. Chem.* **2014**, *79*, 8522−8532.

[107] T. Iwasaki, K. Higashikawa, V. P. Reddy, W. W. S. Ho, Y. Fujimoto, K. Fukase, J. Terao, H. Kunisayu, N. Kambe, *Chem. Eur. J.* **2013**, *19*, 2956 – 2960.

[108] a) Iwasaki, T.; Takagawa, H.; Singh, S. P.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2013**; b) T. Iwasaki, H. Takagawa, K. Okamoto, S. P. Singh, H. Kuniyasu, N. Kambe, *Synthesis*, **2014**, *46*, 1583-1592.

yields, though the role of LiI was not clear. Mechanistic studies rules out a single electron transfer procedure, which is well-known in cobalt-catalyzed cross-coupling reactions of alkyl halides.[109]



Scheme 2-19 Cobalt-catalyzed cross-coupling of alkyl halides with tertiary alkyl Grignard reagents

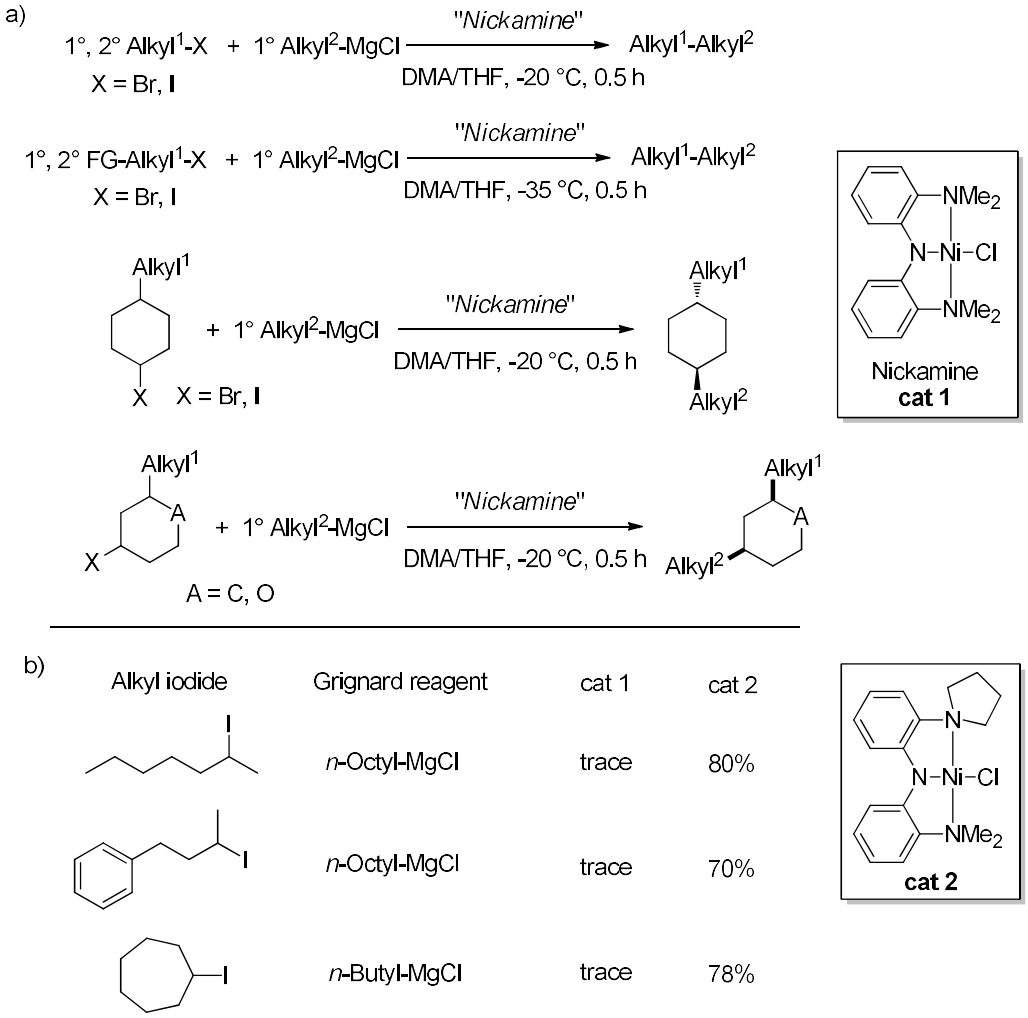
Hu and coworkers developed a method of alkyl-alkyl Kumada-type cross-coupling catalyzed by a well-defined nickel complex, "*Nickamine*" [$(Me_2N)_2NNi^{II}Cl$] (Scheme 2-20-a).[110] A variety of nonactivated nonfunctionalized and functionalized alkyl bromides and iodides were coupled with primary alkyl Grignard reagents in good to excellent yields. However, acyclic secondary alkyl iodide could not be tolerated. The problem was solved by modification of the ligand (Scheme 2-20-b).[111] Furthermore, mechanistic studies suggest radical intermediates were involved in this reaction.[112]

[109] a) X. Qian, A Auffrant, A. Felouat, C. Gosmini, *Angew. Chem. Int. Ed.* **2011**, *50*, 10402-10405; b) Y. Cai, X. Qian, C. Gosmini, **2016**, doi: 10.1002/adsc.201600213.

[110] a) O. Vechorkin, X. Hu, *Angew. Chem. Int. Ed.* **2009**, *48*, 2937-2940; b) O. Vechorkin, Z. Csok, R. Scopelliti, X. Hu, *Chem. Eur. J.* **2009**, *15*, 3889-3899; c) P. M. Perez Garcia, T. Di Franco, A. Orsino, P. Ren, X. Hu, *Org. Lett.* **2012**, *14*, 4286-4289.

[111] P. M. Perez Garcia, T. Di Franco, A. Epenoy, R. Scopelliti, X. Hu, *ACS Catal.* **2016**, *6*, 258-261.

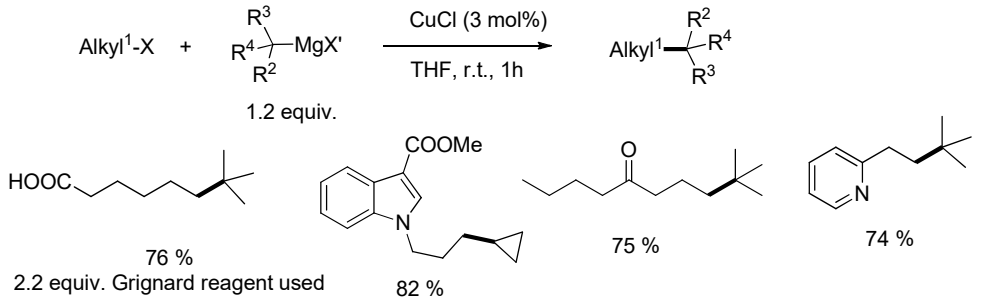
[112] J. Breitenfeld, J. Ruiz, M. D. Wodrish, X. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 12004-12012.



Scheme 2-20 Kumada type alkyl-alkyl cross-coupling reactions catalyzed by "Nickamine"

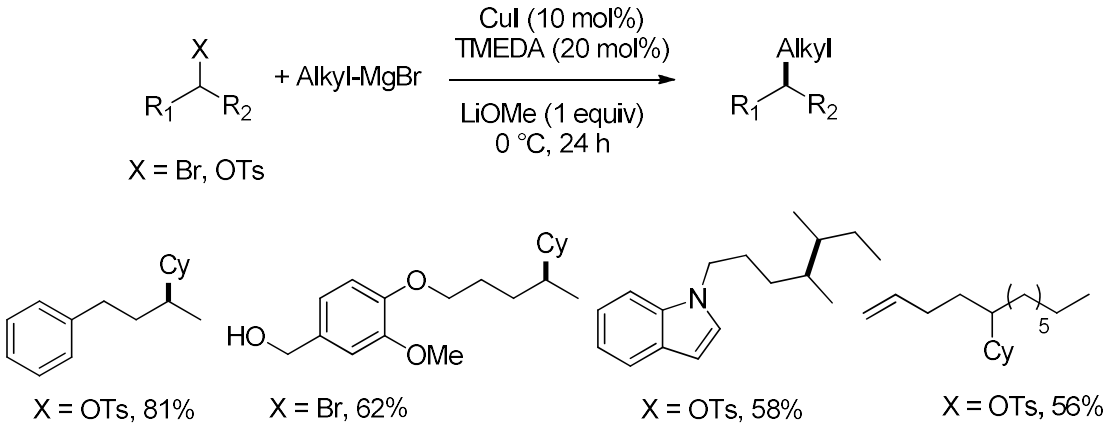
Later, Hu and coworkers developed a highly efficient copper-catalyzed approach for the cross-coupling of nonactivited functionalized alkyl halides/tosylates with secondary and tertiary alkyl Grignard reagents (Scheme 2-21).[113] The method was remarkably practical and general. Moreover, its wide scope, highly chemoselectivity and functional group tolerance made the protocol attractive for the streamlined synthesis of functional molecules. Unlike Nickamine-catalyzed cross-coupling reaction, a radical chain mechanism was ruled out according to the mechanistic studies.

[113] P. Ren, L-A. Stern, X. Hu, *Angew. Chem., Int. Ed.* **2012**, *51*, 9110-9113.



Scheme 2-21 Copper-catalyzed alkyl-alkyl cross-coupling reaction of primary alkyl halides and tosylates with secondary and tertiary alkyl Grignard reagents

In 2012, Liu and coworkers also employed a copper catalyst to develop a cross-coupling reaction of secondary alkyl halides/tosylates with secondary or even tertiary alkyl Grignard reagents in the presence of LiOMe (Scheme 2-22).[114] This method not only tolerated a large number of important yet sensitive functional groups, but also solved the coupling of primary alkyl chlorides, which was a challenge in Kumada type reaction for a long time. Copper formed an active species $(Alkyl)_2Cu^-MgCl^+$,[115] and the reaction was confirmed to occur *via* S_N2 mechanism with inversion of configuration by X-ray crystal analysis. Therefore, it could provide a general approach for the stereocontrolled formation of C-C bonds in high *ee* value from the corresponding chiral secondary tosylates.

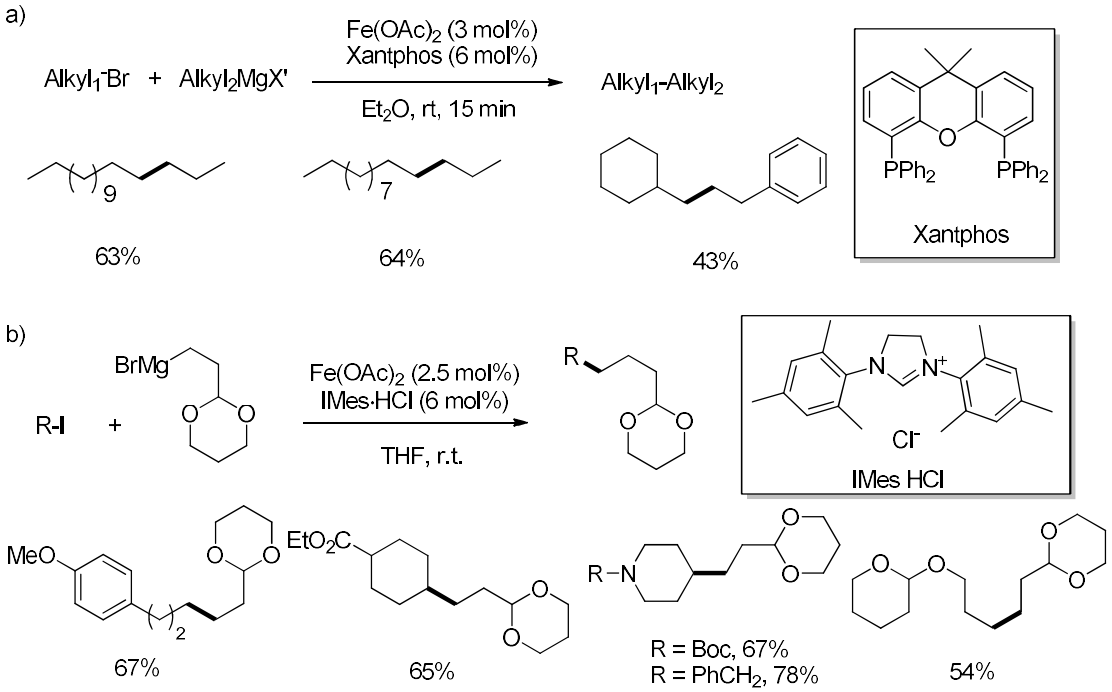


Scheme 2-22 Copper-catalyzed alkyl-alkyl cross-coupling reaction of secondary alkyl halides and tosylates with secondary alkyl Grignard reagents

Compared to nickel and copper, efficient methods for iron-catalyzed Kumada-type C_{sp3}-C_{sp3} coupling reactions are rarely reported. In 2007, Chai and coworkers first

[114] C-T. Yang, Z-Q. Zhang, J. Liang, J-H. Liu, X-Y. Lu, H-H. Chen, L. Liu, *J. Am. Chem. Soc.* **2012**, *134*, 11124−11127.
[115] J. Terao, H. Todo, S. A. Begum, H. Kuniyasu, N. Kambe, *Angew. Chem. Int. Ed.* **2007**, *46*, 2086-2089.

demonstrated that $Fe(OAc)_2$ in combination with Xantphos was effective in coupling alkyl halides with alkyl Grignard reagents (Scheme 2-23-a).[116] The yields were generally low to medium. However, the functional compatibility was very limited. Using the same catalyst, Cárdenas and coworkers established another alkyl-alkyl cross-coupling method between alkyl iodides and Grignard reagents with IMes HCl as the ligand (Scheme 2-23-b).[117] This approach could be applied to series of functionalized alkyl iodides while only one Grignard reagent was used. In this reaction, Grignard reagent served not only as the coupling partner but also the reductant to form Fe(I) species.



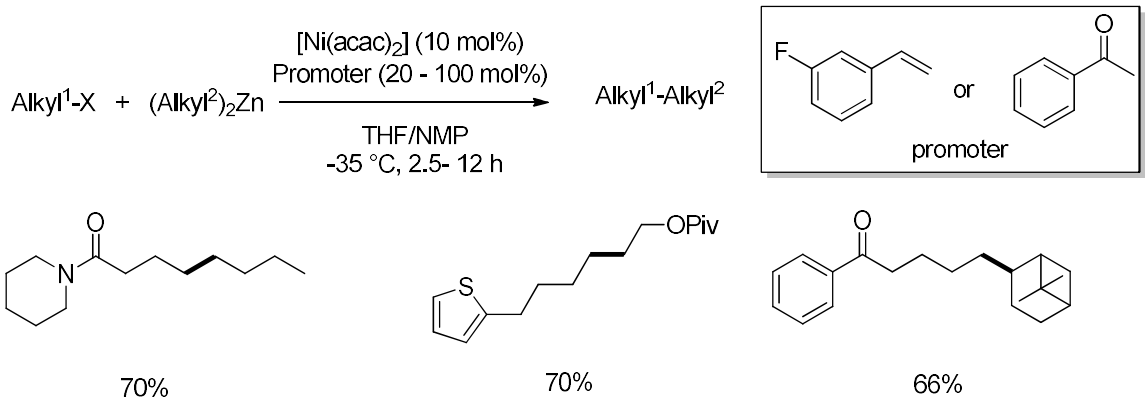
Scheme 2-23 Iron-catalyzed Kumada type alkyl-alkyl cross-coupling reactions

II-1-1-2 Negishi type alkyl-alkyl reactions

Organozinc compound is another widely used organometallic reagent to undergo the formation of C-C bonds. Knochel and coworkers 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

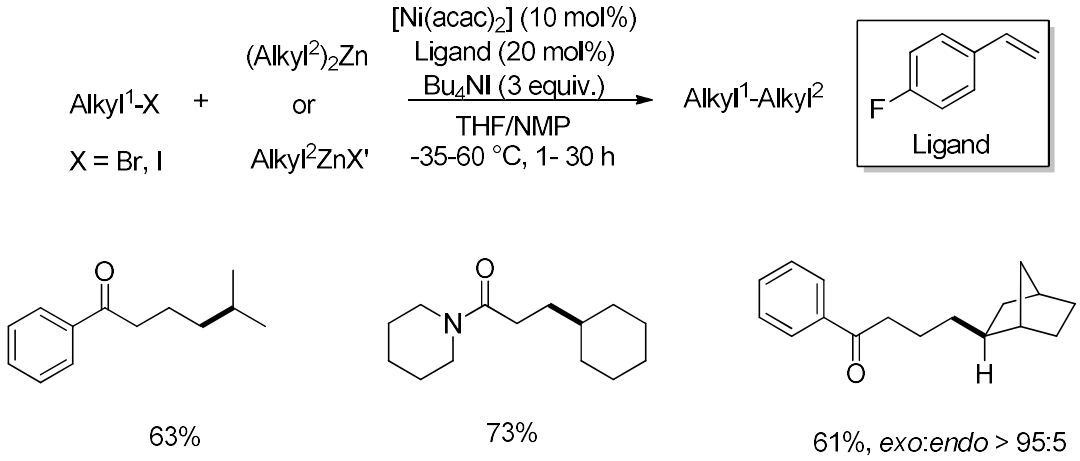
[116] K. G. Dongol, H. Koh, M. Sau, C. L. L. Chai, *Adv. Synth. Catal.* **2007**, *349*, 1015-1018.
[117] M. Guisán-Ceinos, F. Tato, E. Buñuel, P. Calle, D. J. Cárdenas, *Chem. Sci.* **2013**, *4*, 1098-1104.

diorganozinc compounds cross-coupling reactions (Scheme 2-24).[118] 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.



Scheme 2-24 Nickel-catalyzed Negishi type alkyl-alkyl cross-coupling reactions

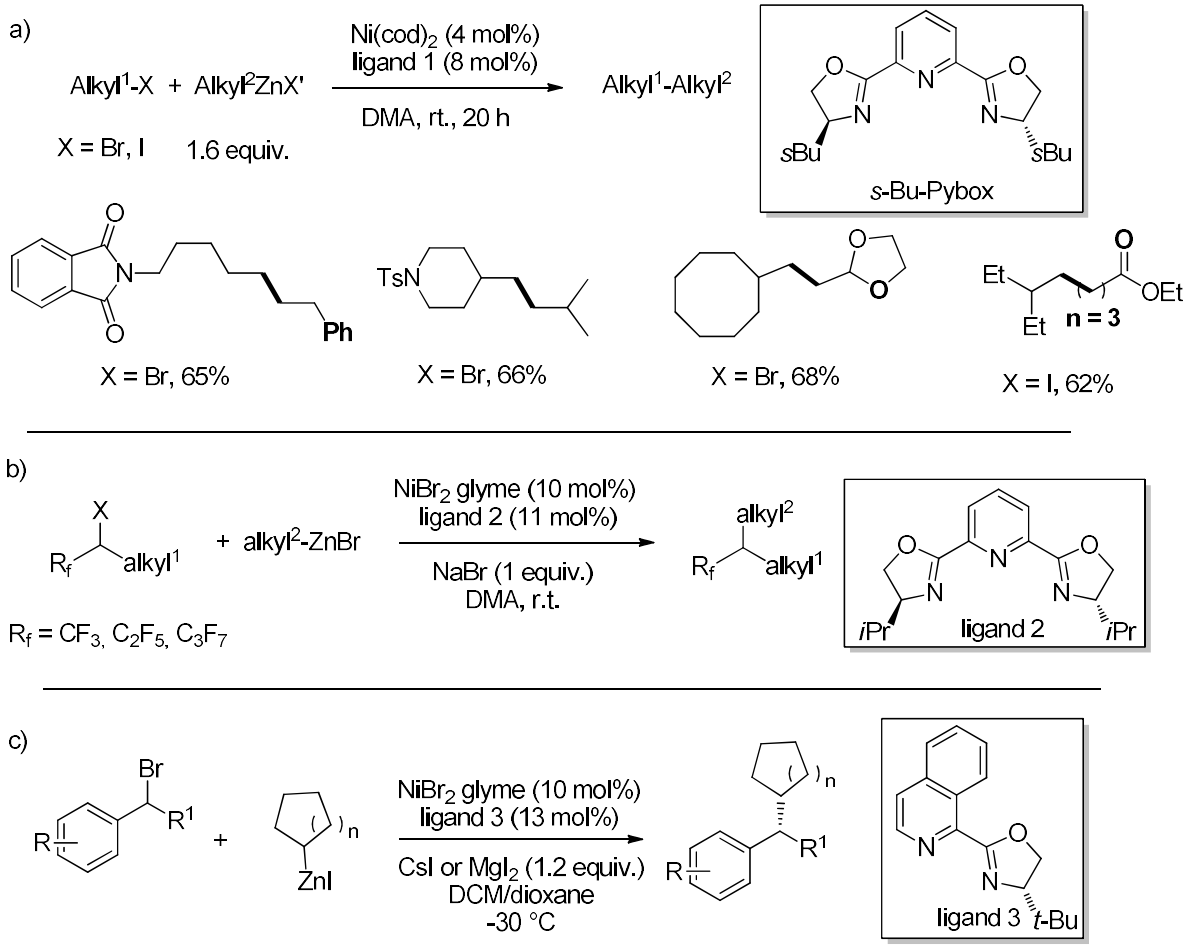
Later, Knochel and coworkers modified the reaction condition by adding Bu_4NI, which allowed broadening the substrate scope.[119] The new system was applied for the coupling of primary and secondary organozinc reagents with primary alkyl halides (Scheme 2-25). The effect of Bu_4NI was not clear, but it is crucial to obtain high yields of the cross-coupling reactions.



Scheme 2-25 Nickel-catalyzed Negishi type alkyl-alkyl cross-coupling reactions

[118] R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 2387-2390.
[119] A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002,** *67,* 79-85.

The Fu's group developed an efficient Negishi type alkyl-alkyl cross-coupling reaction catalyzed by nickel (Scheme 2-26-a).[120] A variety of secondary 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. Recently the group extended this system to cross-coupling of fluorinated secondary electrophiles (Scheme 2-26-b)[121] and eneantioselective cross-coupling between racemic secondary benzylic bromides and achiral secondary cycloalkylzinc reagents (Scheme 2-26-c).[122]

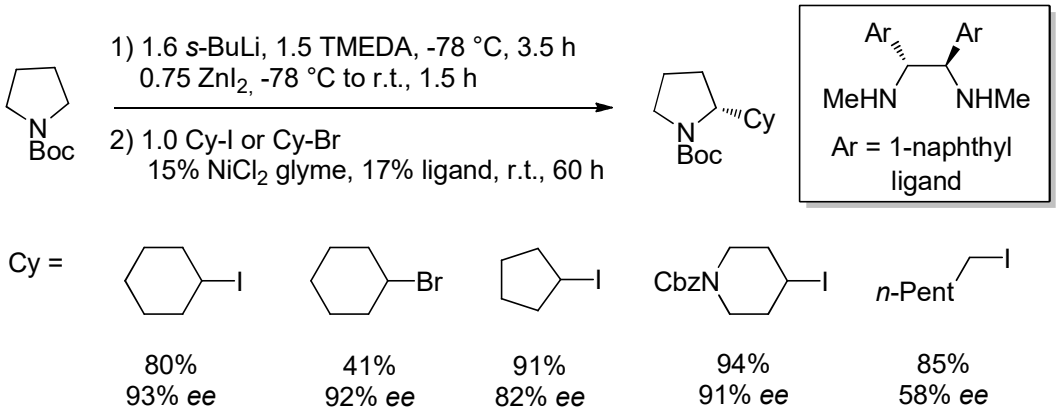


Scheme 2-26 Nickel-catalyzed Negishi type alkyl-alkyl cross-coupling reactions

Fu and coworkers later established an enantioconvergent cross-coupling of racemic α-zincated *N*-Boc-pyrrolidine (prepared in situ from *N*-Boc-pyrrolidine) with unactivated alkyl halides to generate 2-alkylpyrrolidine with good yields and ee

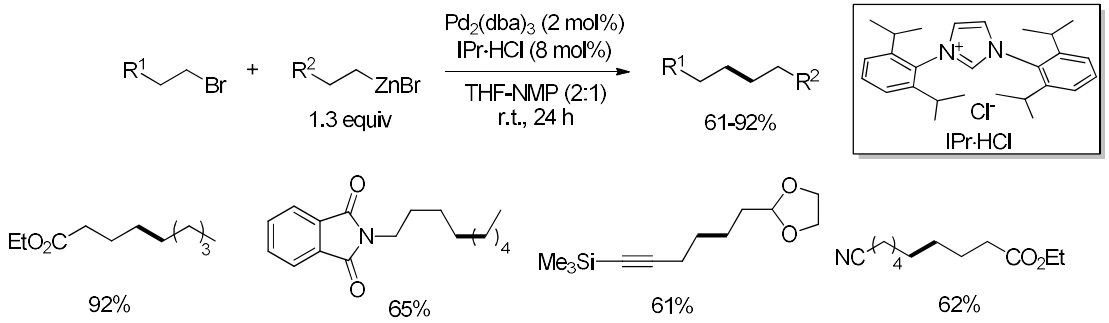
[120] J. R. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 17426-17427.
[121] Y. Liang, G. C. Fu, *Angew. Chem. Int. Ed.* **2015**, *54*, 9047-9051.
[122] J. T. Binder, C. J. Cordier, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 17003-17006.

(Scheme 2-27).[123] High yield and enantioselectivity was obtained with secondary alkyl iodide, whereas primary alkyl iodide led to high yield but low ee and secondary alkyl bromides afforded high *ee* but moderate to good yields. Mechanistic studies suggest that the selectivity was dependent primarily on the chiral ligand rather than organozinc nucleophile.



Scheme 2-27 Nickel-catalyzed enantioconvergent Negishi *α*-alkylations of *N*-Boc-pyrrolidine

Organ and coworkers developed the first high-yielding Negishi-type alkyl-alkyl cross-coupling in a Pd-NHC system (Scheme 2-28).[124] The tolerance of functional groups was wide under mild reaction conditions. Next the group proved that LiBr could enhance the reactivity of alkylzinc compound, and suggested that higher-order zincates were served as transmetalators in this Negishi-type reaction.[125]

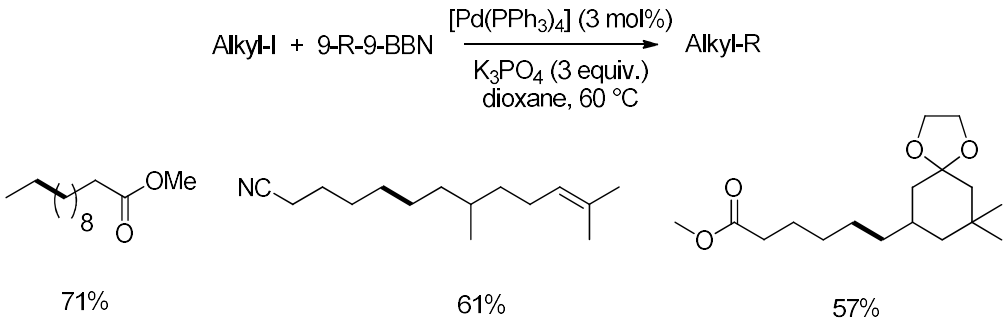


Scheme 2-28 Palladium-catalyzed Negishi-type alkyl-alkyl cross-coupling

[123] C. J. Cordier, R. J. Lundgren, G. C. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 10946-10949.
[124] a) N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Org. Lett.* **2005**, *7*, 3805-3807; b) N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *J. Org. Chem.* **2005**, *70*, 8503-8507.
[125] a) G. T. Achouduh, N. Hadei, C. Valente, S. Avola, C. J. O'Brien, M. G. Organ, *Chem. Comm.* **2010**, *46*, 4109-4111; b) H. N. Hunter, N. Hadei, V. Blagojevic, P. Patschinski, G. T. Achouduh, S. Avola, d. K. Bohme, M. G. Organ, *Chem. Eur. J.* **2011**, *7*, 7845-7851; c) L. C. McCann, H. N. Hunter, J. A. C. Clyburne, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 7024-7027.

II-1-1-3 Suzuki type alkyl-alkyl reactions

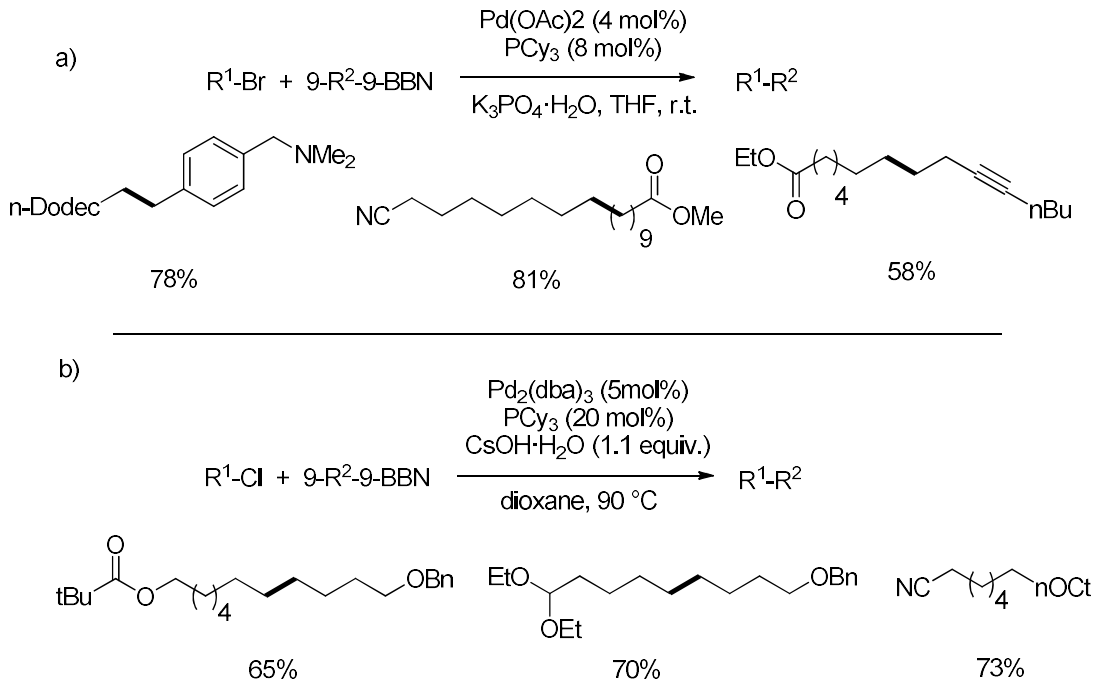
Suzuki and coworkers reported the first palladium-catalyzed Suzuki-type alkyl-alkyl cross-coupling reactions in 1992.[126] In the presence of $[Pd(PPh_3)_4]$ and K_3PO_4, alkyl iodides react with 9-alkyl-9-BBN smoothly and provide moderate to good cross-coupling yields (Scheme 2-29). However, the alkyl bromides or secondary alkyl halides did not react. The reaction was identified as a radical process.



Scheme 2-29 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 2-30-a).[127] 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 $K_3PO_4 \bullet 3H_2O$, the non-activated alkyl halides (I or Br) coupled with 9-alkyl-9-BBN at room temperature and provided good to excellent yields .

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



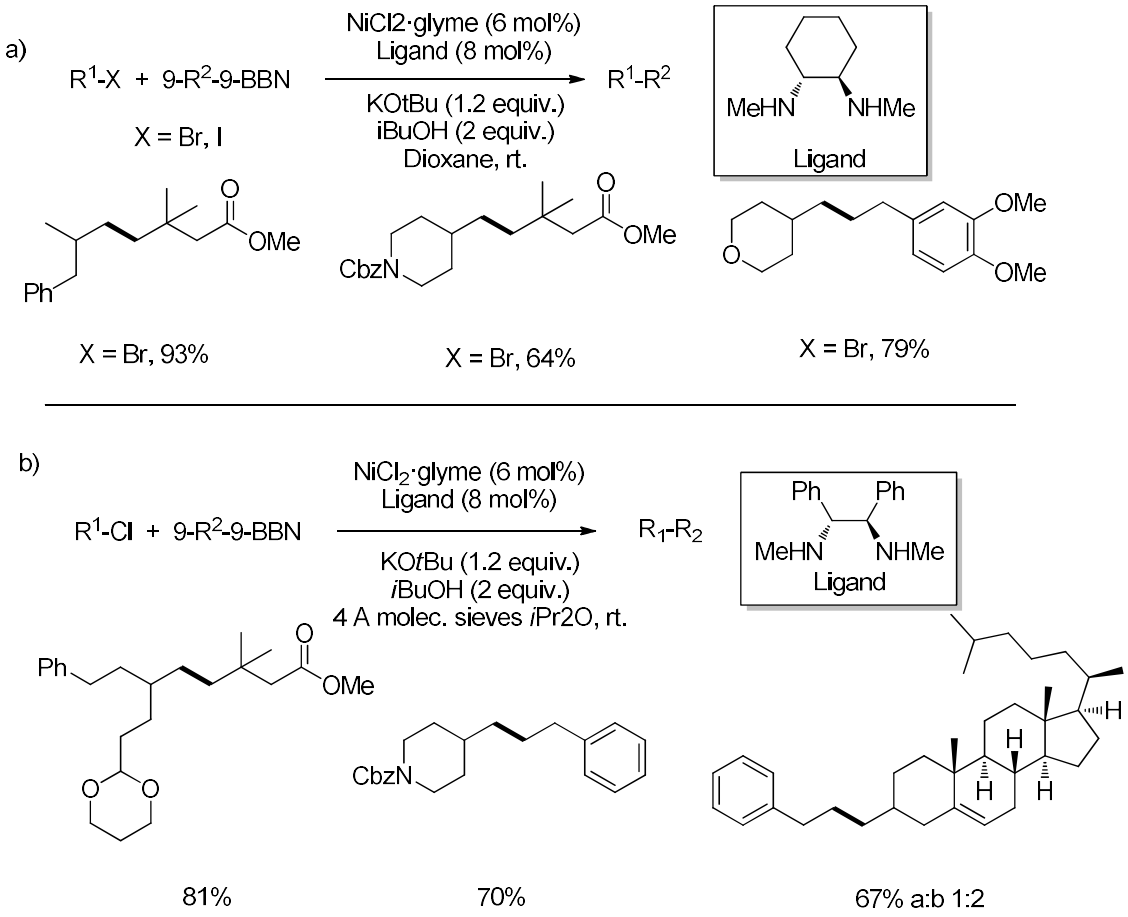
Scheme 2-30 Pd-catalyzed Suzuki-type alkyl-alkyl cross-coupling reactions with alkyl halides

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 such as substituted unactivited alkyl chlorides (Scheme 2-30-b).[128]

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 2-31-a **Scheme 2-**).[129] 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.

Subsequently, 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 2-31-b).[130] This protocol was very efficient in the coupling of functionalized alkyl electrophiles, including alkyl chlorides, bromides and iodides under mild conditions.

[128] Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1945-1947.
[129] Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602-9603.
[130] Lu, Z.; Fu, G. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6676-6678.

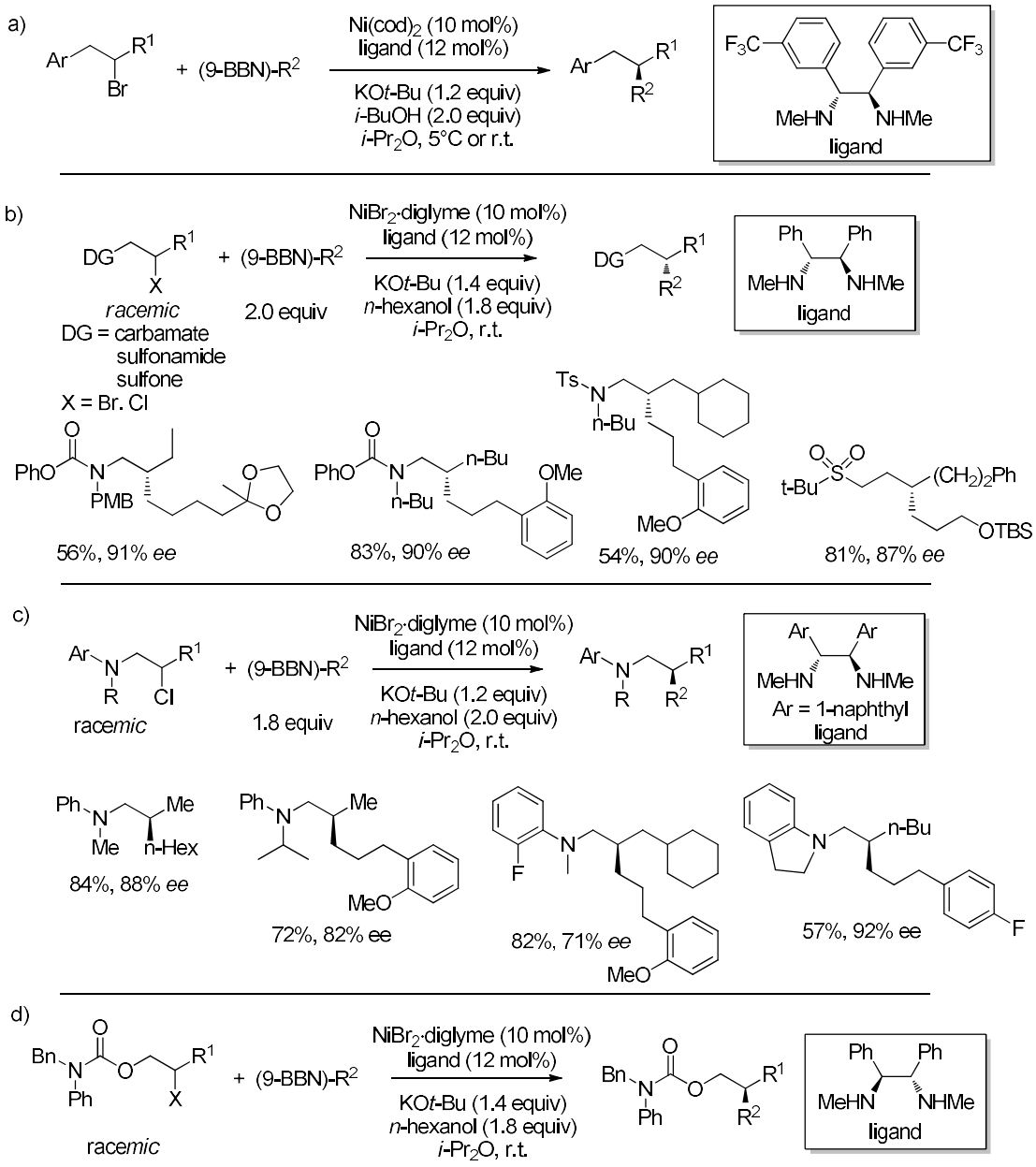


Scheme 2-31 Ni-catalyzed Suzuki-type alkyl-alkyl cross-coupling reactions of alkyl halides

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 2-32-a).[131] After, the same group developed series of stereoconvergent alkyl-alkyl Suzuki-

[131] B. Saito, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 6694-6695.

type reactions by employing the similar systems (Scheme 2-32-b, c, d).[132]A variety of



Scheme 2-32 Nickel-catalyzed Suzuki-type enantioselective cross-couplings of unactivated alkyl electrophiles

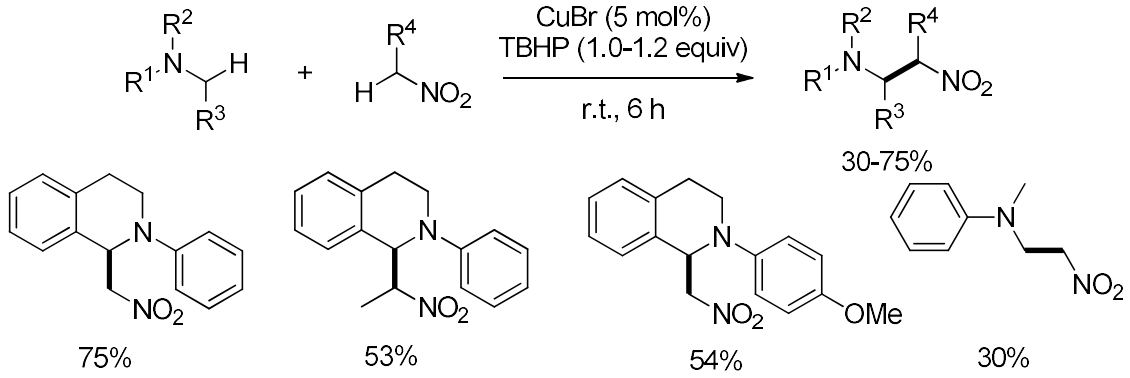
starting reagents bearing different functional groups were well tolerated with good yields and good *ee*. The stereochemistry of the chiral catalyst demonstrated the stereochemial outcome of the asymmetric alkyl-alkyl cross-coupling.

II-1-2 C_{sp3}-C_{sp3} Cross dehydrogenative coupling (CDC)

[132] a) N. A. Owston, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 11908-11909; b) Z. Lu, A. Wilsily, G. C. Fu, *J. Am. Chem. Soc.* **2011**, *133*, 8154-8157; c) A. Wilsily, F. Tramutola, N. A. Owston, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 5794-5797.

In recent years, a direct C-C bond formation using a simple C-H starting material has emerged as an attractive and challenging topic for chemists. Compared with cross-coupling employing an organometallic reagent, which generates a stoichiometric salt waste as product, CDC is more environmentally friendly and atom economic. The C_{sp3}-C_{sp3} CDC reactions have been achieved with various strategies, here we focus on transition-metal-catalyzed C_{sp3}-C_{sp3} CDC reactions.

In 2005, Li and coworkers reported the first general aza-Henry-type C_{sp3}-C_{sp3} CDC reactions using copper bromide as catalyst (Scheme 2-33).[133] Several *N*-arylated tetrahydroisoquinolines were successfully coupled with an excess of nitroalkanes in the presence of TBHP as an oxidant at room temperature. Nitromethane proved to be more reactive than nitroethane since nitroethane is less electron-deficient than nitromethane. The yields were increased by employing oxygen as oxidant and water as solvent.[134] The amount of nitroalkanes was also reduced, while heating and longer reaction time was necessary.



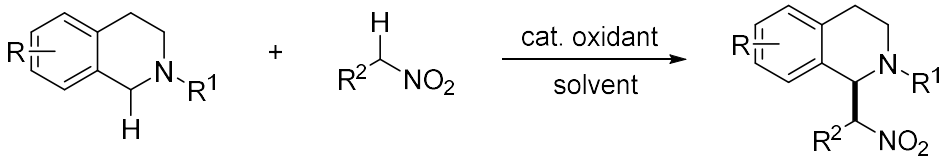
Scheme 2-33 Copper-catalyzed aza-Henry-type C_{sp3}-C_{sp3} CDC reaction

Similar results were obtained by Xiang's group, Liang's group, Zhu's group and Prabhu's group independently using different metal catalysts (Scheme 2-34).[135]

[133] Z. Li, C-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672 - 3673

[134] O. Baslé, C.-J. Li, *Green Chem.* **2007**, *9*, 1047 - 1050

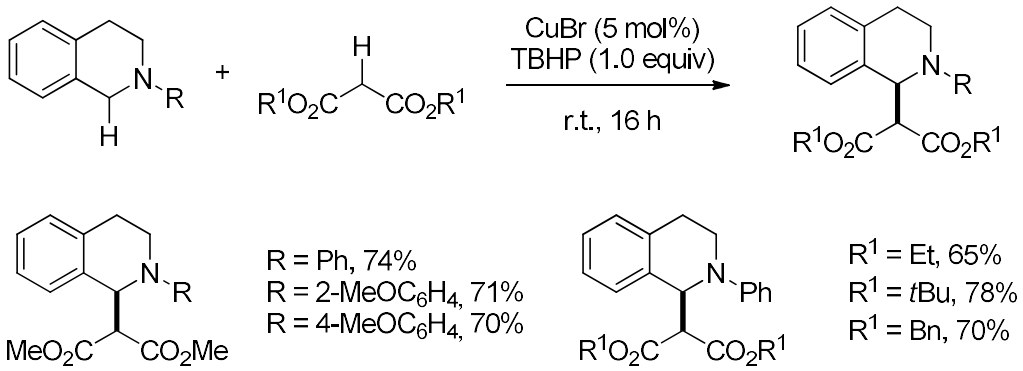
[135] a) A. Yu, Z. Gu, D. Chen, W. He, P. Tan, J. Xiang, *Catal. Commun.* **2009**, *11*, 162 - 166; b) X.-Z. Shu, Y.-F. Yang, X.-F. Xia, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, *Org. Biomol. Chem.* **2010**, *8*, 4077 - 4079; c) J. Xie, H. Li, J. Zhou, Y. Cheng, C. Zhu, *Angew. Chem. Int. Ed.* **2012**, *51*, 1252 - 1255; d) K. Alagiri, K. R. Prabhu, *Org. Biomol.Chem.* **2012**, *10*, 835- 842.



a) $RuCl_3$ (2.5 mol%), O_2 (1 atm), MeOH, 55 °C, 4-24 h yield: 64%-94%
b) $PtCl_2$ (2.5 mol%), 4A M.S., H_2O, 85 °C, 10-30 h yield: 44%-96%
c) $[(ipy)AuCl_2]AuCl_4$ (3 mol%), air (1 atm), MeOH, 60 °C, 1.5-30 h yield: 52%-95%
d) V_2O_5 (5 mol%), O_2 (1 atm), 60 °C, 24 h yield: 85%-99%

Scheme 2-34 metal-catalyzed aza-Henry-type C_{sp3}-C_{sp3} CDC reactions

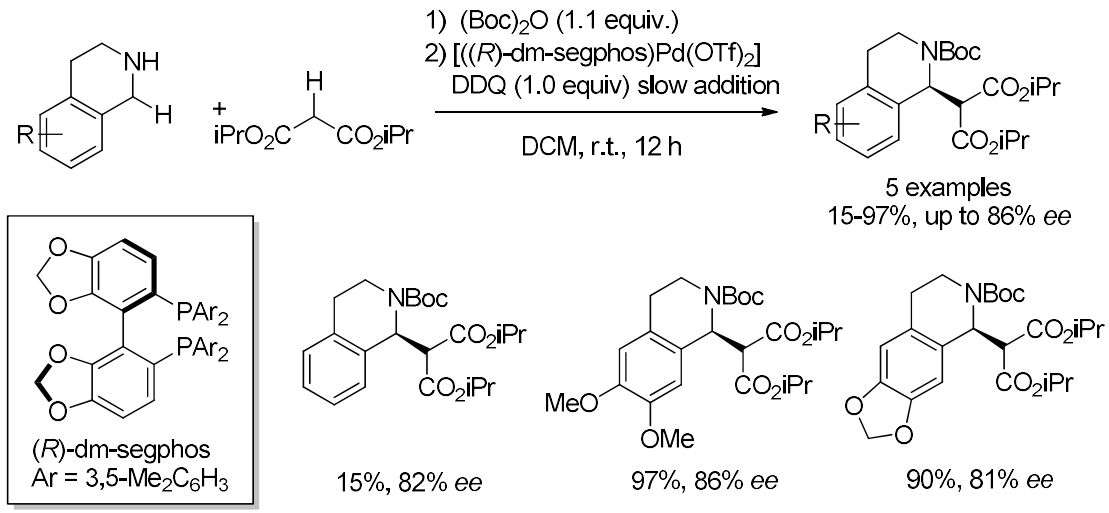
In 2005, Li and coworkers published another pioneering work employing readily enolizable malonates as the coupling partner (Scheme 2-35).[136] This cooper-catalyzed Mannich-type reaction proceeded smoothly under mild solventless conditions affording good yields. The use of malonitrile in place of malonates only led to a moderate yield of corresponding product while a cyanation side product was generated. Moreover, the excess of TBHP had a negative influence due to a possible oxidative degradation of malonitrile.



Scheme 2-35 copper-catalyzed Mannich-type C_{sp3}-C_{sp3} CDC reactions

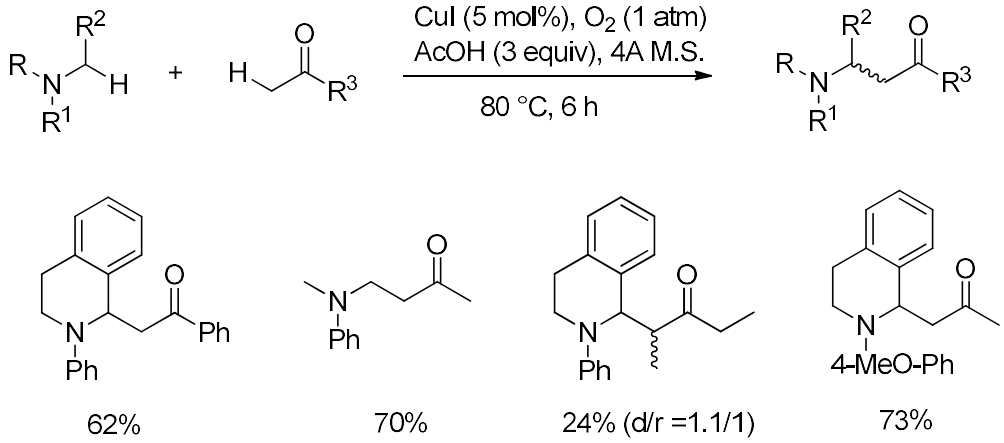
Later an enantioselective palladium-catalyzed approach was established by Sodeoka and coworkers (Scheme 2-36).[137] The imines were efficiently coupled with malonates in the presence of [((*R*)-dm-segphos)$Pd(OTf)_2$] complex and DDQ as the oxidant. It is necessary to add DDQ slowly to obtain the excellent results.

[136] Z. Li, C.-J. Li, *Eur. J. Org. Chem.* **2005**, 3173 - 3176
[137] C. Dubs, Y. Hamashima, N. Sasamoto, T. M. Seidel, S. Suzuki, D. Hashizume, M. Sodeoka, *J. Org. Chem.* **2008**, *73*, 5859 - 5871.



Scheme 2-36 Palladium-catalyzed enantioselective Mannich-type C_{sp3}-C_{sp3} CDC reaction

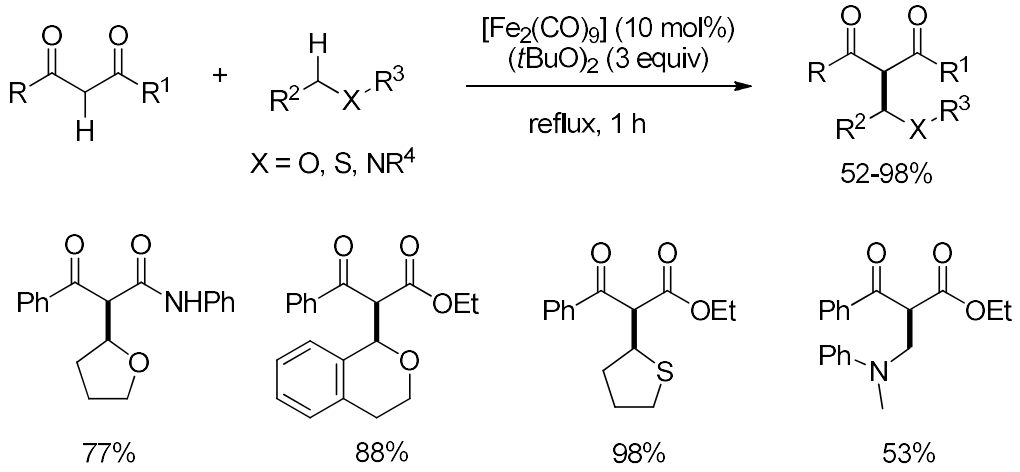
Aldehyde or ketone, which has less acidic hydrogen, could also undergo a Mannich-type CDC with tertiary amines. Guo and coworkers developed the first general work catalyzed by copper iodide (Scheme 2-37).[138] The addition of acetic acid was the key to obtain good yield while molecular sieves slightly increased the yield.



Scheme 2-37 Copper-catalyzed Mannich-type C_{sp3}-C_{sp3} CDC reaction with acetic acid

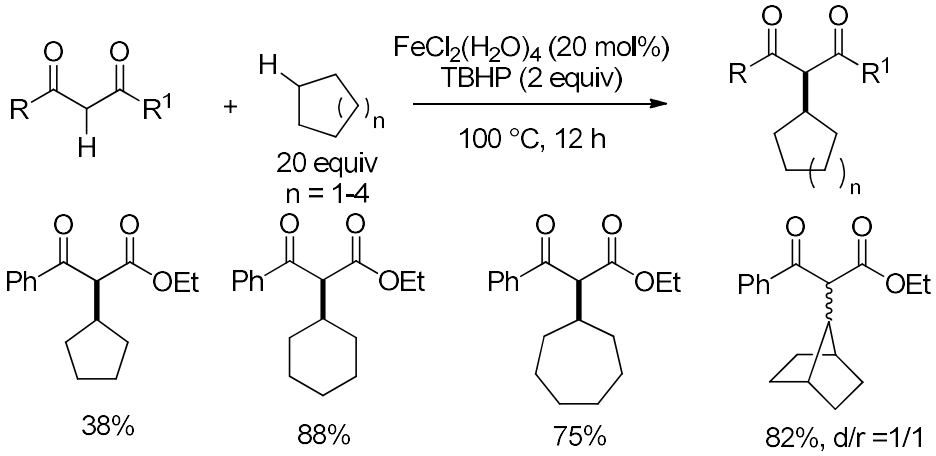
Li and coworkers reported an iron-catalyzed CDC reactions between 1,3-diketones and cyclic or alicyclic saturated heterocycles (Scheme 2-38). [139] The reaction proceeded efficiently without additional solvent, while the heterocycles served both as reagent and solvent. A variety of 1,3-diketones could efficiently couple with various ethers and tetrahydrothiophene affording good to excellent yields.

[138] Y. Shen, M. Li, S. Wang, T. Zhan, Z. Tan, C.-C. Guo, *Chem.Commun.* **2009**, 953 - 955.
[139] Z. Li, R. Yu, H. Li, *Angew. Chem. Int. Ed.* **2008**, *47*, 7497 - 7500.



Scheme 2-38 Iron-catalyzed C_{sp3}-C_{sp3} CDC reaction between 1,3-diketones and heterocyles

Li and coworkers developed another iron-catalyzed CDC reactions between 1,3-dicarbonyl compounds and simple nonfunctionalized cycloalkanes in the presence of TBHP as the oxidant (Scheme 2-39).[140] Series of simple cycloalkanes were tolerated affording moderate to excellent yields, however, a large excess (20 equiv.) of cycloalkanes was required.



Scheme 2-39 Iron-catalyzed C_{sp3}-C_{sp3} CDC reaction using simple cycloalkanes

II-1-3 Transition-metal catalyzed reductive alkyl-alkyl cross-coupling reaction

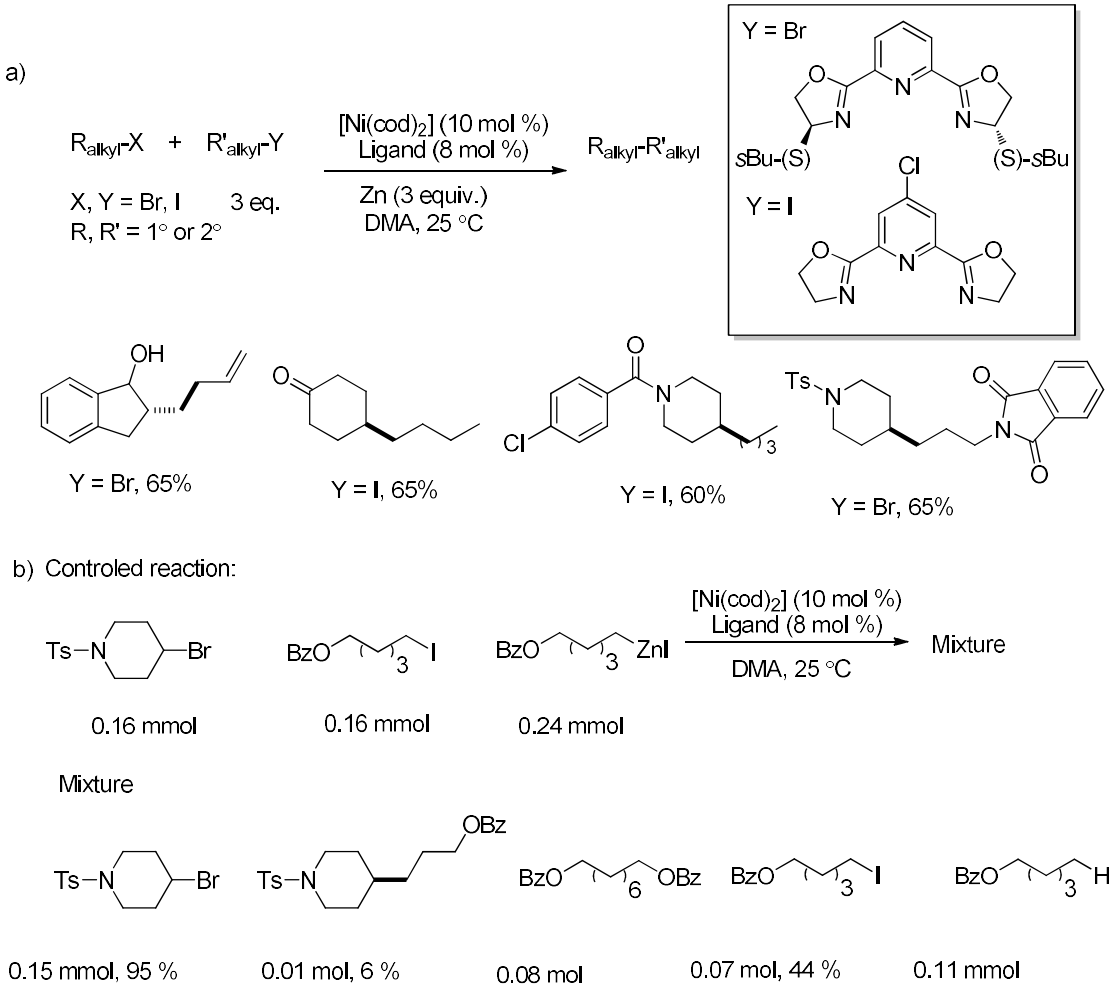
Reductive C_{sp3}-C_{sp3} cross-coupling has been poorly investigated. The concept dated back to tranditional Wurtz reactions.[141] However, these reactions have limited tolerance of functional groups due to harsh reaction conditions such as the use of

[140] Y. Zhang, C.-J. Li, *Eur. J. Org. Chem.* **2007**, 4654 - 4657.

[141] a) A. Wurtz, *Ann. Chim. Phys.*, **1855**, *44*, 275 - 312; b) A. Wurtz, *Ann. Chem. Pharm.*, **1855**, *96*, 364 -375.

sodium. The challenges to undergo an efficient reductive C_{sp3}-C_{sp3} cross-coupling still remain, because of low chemoselectivity of structurally similar coupling partners. To ensure the selectivity, one solution is to employ excess of one coupling partner. In 2011, Gong and coworkers established the first effective cross-coupling of two alkyl halides via a nickel-catalyzed reductive process (Scheme 2-40-a).[142] To turn the Negeshi reaction process to a reductive coupling process whereby an organozinc reagent is replaced with an alkyl halide and a reductant such as Zn. In this way the protocol avoids the use of organometallic reagents, and exhibits a high group tolerance, including nitrogen heterocycles, keto or even alcohol groups. Moreover, both cyclic and acyclic secondary alkyl bromides (limiting reagents) demonstrated good reactivities. The pybox ligands were found necessary to suppress the homocoupling reactions. 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 2-40-b) 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 necessity 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.

[142] X. Yu, T. Yang, S. Wang, H. Xu, H. Gong, *Org. Lett.* **2011**, *13*, 2138 – 2141.

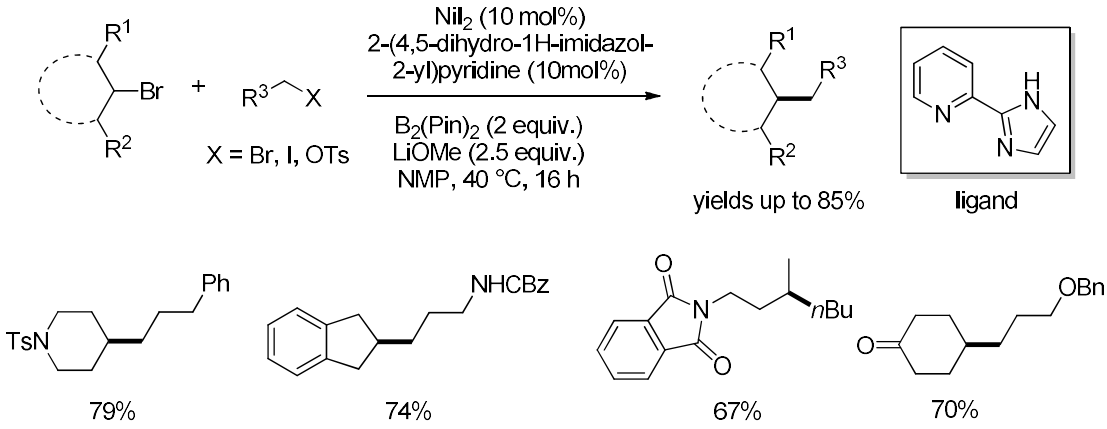


Scheme 2-40 Nickel-catalyzed reductive cross-coupling of unactivated alkyl halides using a pybox ligand

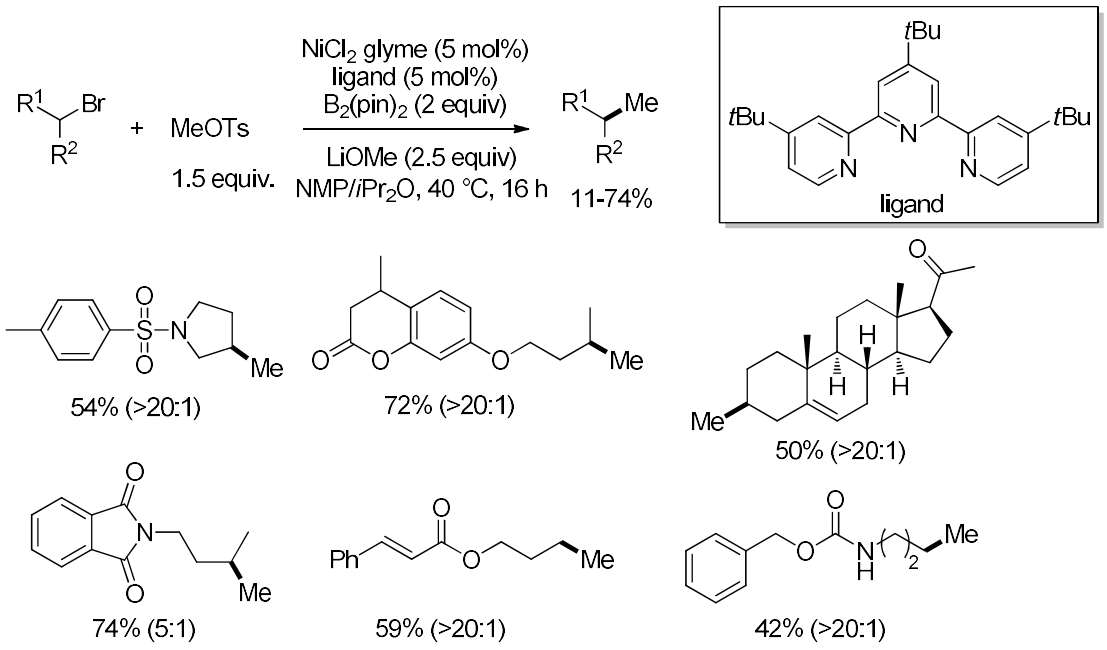
To reduce the amount of one alkyl halide due to the highly competitive homocoupling in the nickel-catalyzed alkyl-alkyl cross-coupling, Gong and coworkers then employed bis(pinacolato)diboron as the reductant in the presence of LiOMe as the base (Scheme 2-41).[143] LiOMe was crucial to obtain good yields and Li^+ was assumed to play an important role. The use of primary bromides was decreased to 1.5 equivalents, with good yields of cross-coupling product. A broad range of functionalized primary and secondary alkyl bromides were well tolerated affording moderate to excellent yields, including substrates containing NH proton, β-leaving groups, ketone and silyl ester. Furthermore, cross-coupling involving alkyl iodides and tosylates was successfully achieved with primary and secondary alkyl bromides. However, unfunctionalized alkyl bromides and alkyl chlorides were not effective,

[143] H. Xu, C. Zhao, Q. Qian, W. Deng, H. Gong, *Chem. Sci.* **2013**, *4*, 4022-4029.

while primary with primary and secondary and secondary cross-coupling only gave moredate yields.



Scheme 2-41 Nickel-catalyzed reductive cross-coupling of unactivated alkyl halides with $B_2(Pin)_2$



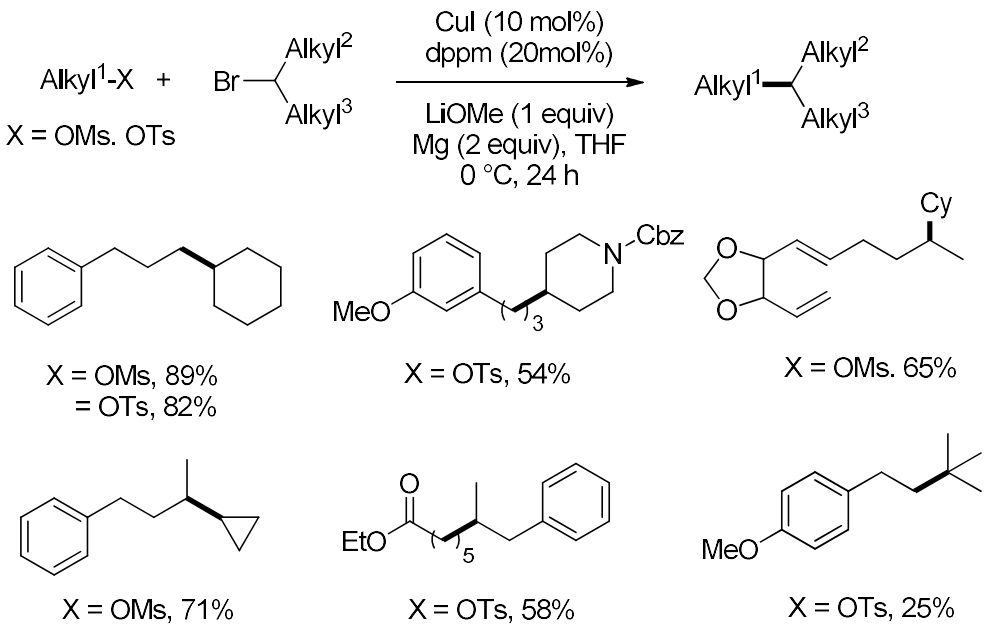
Scheme 2-42 Nickel-catalyzed methylation of unactivated alkyl halides with methyl tosylate

In 2014, Gong and coworkers identified methyl tosylate as an excellent reagent to reductive cross-coupling reaction with unactivated alkyl halides under similar conditions as cross-coupling of unactivated alkyl halides with $B_2(Pin)_2$ (Scheme 2-42).[144] This protocol took the advantage of distinctive reactivities of alkyl toyslates and alkyl halides, which could lead to a chemoselectivity. Series of functional groups were well tolerated, though the yields of most cross-coupling products were not

[144] Z. Liang, W. Xue, K. Lin, H. Gong, *Org. Lett.* **2014**, *16*, 5620-5623.

excellent. Moreover, in general, secondary alkyl bromides coupled with methyl tosylate better than primary alkyl bromides. This approach only focuses on methylation, whereas it provides a possibility to a more general method for cross-coupling between alkyl halides and alkyl tosylates.

In the same year, Liu and coworkers established a copper-catalyzed reductive cross-coupling of nonactivated alkyl tosylates and mesylates with alkyl and aryl bromides (Scheme 2-43).[145] In the first trial, a similar yield of cross-coupling product was obtained when an alkyl tosylate and an alkyl bromide were used compared to cross-coupling between two alkyl bromides, while the homocoupling products were highly suppressed. A variety of functionalized primary and secondary alkyl tosylates and mesylates could be efficiently coupled with various primary and secondary alkyl bromides. Tertiary alkyl bromide only led to a modest yield. This reaction represents an alternative general approach to reductive alkyl-alkyl cross-coupling.



Scheme 2-43 Copper-catalyzed Reductive Cross-coupling between Unactivated Alkyl Halides and alkyl mesylate or tosylate

As introduced above, cross-coupling reactions between organomellic compounds have been successully established and broadly applied, however, it requires the handling of organicmetallic reagents, which are moisture-sensitive and always need a

[145] J-H. Liu, C-T. Yang, X-Y. Lu, Z-Q. Zhang, L. Xu, M. Cui, X. Lu, B. Xiao, Y. Fu, L. Liu, *Chem. Eur. J.* **2014**, *20*, 15334-15338.

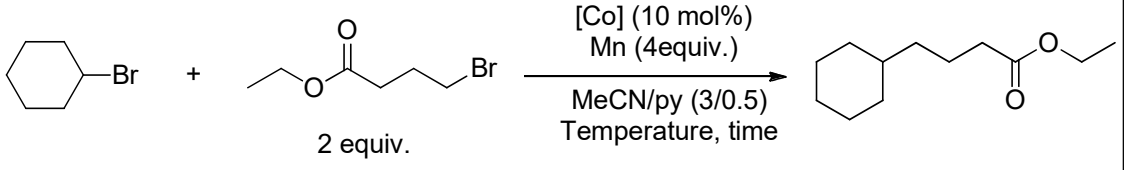
separate prefunctionalization step. This drawback may limit the application, especially for large-scale use. Cross-dehydrogenative coupling has been recently explored in the past decade, with various strategies for C_{sp3}-C_{sp3} CDC reaction achieved. But so far a C-H bond in close to aromatic cycle and an acidic C-H is always required, otherwise a large excess of one starting material is necessary. C_{sp3}-C_{sp3} reductive reactions have been investigated only in the few past years. The successful results indicated potential achievement in this area. Thus, we try to develop a cobalt-catalyzed reductive alkyl-alkyl cross-coupling reaction, which do not employ an organometallic reagent.

II-2 Results and discussions

II-2-1 Model reaction 1

To begin, we chose bromocyclohexane and ethyl-4-bromobutyrate as the coupling partners to undergo a model reaction (Table 2-3). By employing the reaction condition for alkyl-alkyl homocoupling, only 6% of yield was obtained after 16 h and the starting materials were not all consumed (Table 2-3, entry 1). Increasing the temperature to 80 °C led to a higher yield in shorter reaction time (Table 2-3, entry 2). When PPh_3 was added as a ligand, it did not assist to improve the result (Table 2-3, entry 3). Moreover, biquinoline performed less efficiently than PPh_3 (Table 2-3, entry 4). Using a preformed cobalt-phenanthroline complex, the yield was slightly higher (Table 2-3, entry 5). Next we confirmed that heating to 80 °C was necessary even with $CoBr_2$(phen) (Table 2-3, entries 6-7). More catalyst loading did not give a better yield, and less amount of catalyst had a negative effect, with which the starting materials could not be all consumed (Table 2-3, entries 8-9).

Table 2-3 : Optimization of condition for model reaction 1



Entry	Catalyst/ligand (10 mol%)	Temperature	Time	GC yield[a]/%
1	$CoBr_2$	50	16 h	6
2	$CoBr_2$	80	3 h	16
3	$CoBr_2$/PPh_3	80	3 h	16

4	$CoBr_2$/biquinoline	80	3 h	11
5	$CoBr_2$(phen)	80	2 h 30	22
6	$CoBr_2$(phen)	r.t.	16 h	0
7	$CoBr_2$(phen)	50	6 h 30	18
8	$CoBr_2$(phen) (15 mol%)	80	5 h	18
9	$CoBr_2$(phen) (6 mol%)	80	5 h 30	9

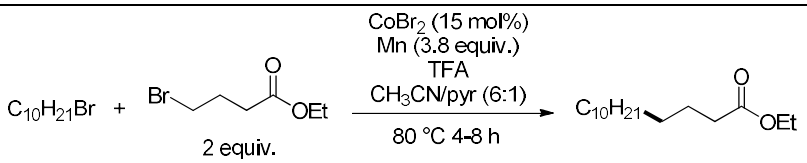
a: using dodecane as internal standard

II-2-2 preliminary optimization of conditions for model reaction 2

After series optimizations of reaction conditions, we did not obtain even a moderate yield. These two coupling partners favored to undergo a homocoupling or reduction reaction. Thus, we next changed the model reaction with two primary alkyl bromides (Table 2-4). 1-bromodecane ($Alkyl^1$) and ethyl 4-bromobutanoate ($Alkyl^2$) were chosen to undergo the model reactions (Table 2-4). Again, first we used the conditions similar to that of the alkyl-alkyl homocoupling reaction with an excess of ethyl 4-bromobutanoate but at higher temperature and using more cobalt catalyst. Unlike model reaction 1, the combined $CoBr_2$/Mn catalytic system in acetonitrile with pyridine gave a good yield (Table 2-4, entry 1). 50 °C turned out not to be an effective temperature since lower yield was observed as well as some unconsumed starting materials (Table 2-4, entry 2). Using 3 equivalents of the more reactive alkyl bromides ($Alkyl^2$) provided a slightly better result (Table 2-4, entry 3). However, taking the "green chemistry" into account, the excess loading of one coupling partner was a disadvantage. Therefore, we continued to optimize the conditions with keeping the ratio of coupling partners in 2:1. Pyridine was crucial to afford the cross-coupling product in good yield, without it the reaction gave the reduction product rapidly (Table 2-4, entry 4). According to the previous work in our group, DMF may be used as an efficient solvent. Nevertheless, in this reaction, employing DMF instead of acetonitrile, the reaction was inhibited (Table 2-4, entry 5). In DMF, a triphenylphosphine or bipyridine ligand only provided with traces of cross-coupling product (Table 2-4, entries 6-7). 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 $Alkyl^2$. However, both of them only led to the rapid consuming of $Alkyl^2$ and did not increase the cross-coupling product (Table 2-4, entries 8 and 9). When zinc was used as reductant instead of manganese, it had a

negative effect on the reaction (Table 2-4, entry 10). Quinoline was examined as a pyridine derivative, yet it only delivered largely lower yield (Table 2-4, entry 11).

Table 2-4 Preliminary optimization of conditions for model reaction 2



Entry	Deviation from Standard Conditions	GC Yield[a] %
1	None	61
2[b]	10 mol% of $CoBr_2$	34
3	$Alkyl^1$:$Alkyl^2$ = 1:3	63[c]
4	Without pyridine	47
5	DMF instead of MeCN	traces
6	DMF+PPh_3	traces
7	DMF+Bpy	traces
8	AllylCl (40 mol%)	traces
9	$ClCH_2CH_2Cl$ (1 equiv.)	traces
10	Zn instead of Mn	traces
11	Quinoline instead of pyridine	15

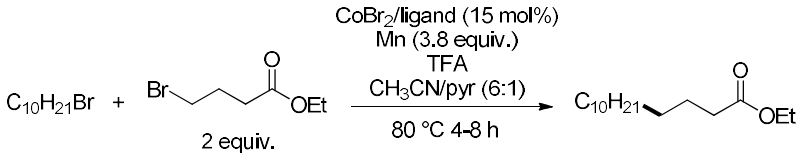
a : using dodecane as internal standard ; b : starting material not all converted c: isolated yield

II-2-3 Effect of ligands

For alkyl-alkyl cross-coupling, the competitive homocoupling of each coupling partners is always the main problem. Careful screen of ligands is necessary to improve the selectivity of cross-coupling. Herein, series of ligands were examined (Table 2-5). Bidentate phosphine ligands only gave traces of cross-coupling products (Table 2-5, entries 2-3). A cobalt-dppp complex did not have a positive effective, either (Table 2-5, entry 4). Since bidentate phosphine ligand might be too bulky for this reaction, we also tested with momodentate phosphine ligand. However, both $P(cy)_3$ and $P(i\text{-}Pr)_3$ performed similar to bidentate phosphine ligands, with only traces of desired product obtained (Table 2-5, entries 5-6). Then several nitrogen ligands were displayed. Using a preformed cobalt-phenantroline complex, we obtained a

decreasing yield compared with that without ligands (Table 2-5, entry 7). Another cobalt complex with pyridine as a ligand, proved to be less effective (Table 2-5, entry 8). Next, we employed quinoline as a ligand, and slightly increased yield was afforded (Table 2-5, entry 9). Furthermore, with quinoline, the reaction performed better at a lower temperature 60°C in longer reaction time (Table 2-5, entry 10). As an analogue to quinoline, isoquinoline also had a positive effect, though a slightly lower yield was obtained compared to quinoline (Table 2-5, entry 11). In addition, the reaction was conducted in lower yield with quinaldine as a ligand (Table 2-5, entry 12). So far, after an extensive screen of ligands, the progress was achieved with higher yield and lower temperature.

Table 2-5 Screen of ligands for model reaction 2



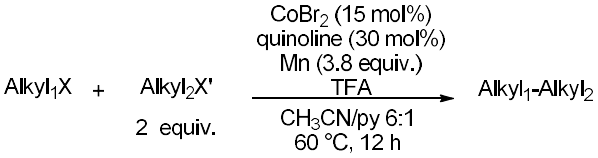
Entry	Ligand or Cobalt-ligand complex	GC Yield[a] %
1	none	61[b]
2	dppe	traces
3	dppp	traces
4	[$CoBr_2$(dppp)]	traces
5	$P(cy)_3$	traces
6	P(*i*-Pr)$_3$	traces
7	[$CoBr_2$(phen)]	46
8	[$CoBr_2$ $(Py)_2$]	14
9	2*quinoline	65[b]
10[c]	2*quinoline	75
11[c]	2*isoquinoline	71[b]
12[c]	2*quinaldine	50

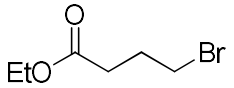
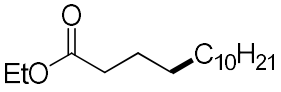
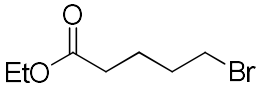
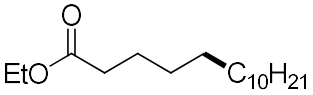
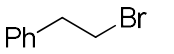
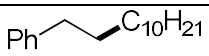
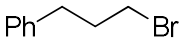
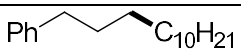
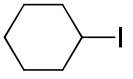
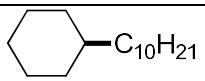
a : using dodecane as internal standard ; b: isolated yield; c: 60 °C, 12 h

II-2-4 Examples of substrates

After optimization of these parameters, we used the conditions of Table 2-5, entry 10 as standard conditions to explore the scope of alkyl halides (Table 2-6). When ethyl 5-bromovalerate was used to couple with bromododecane, we only obtained a moderate yield (Table 2-6, entry 2). 1-Bromo-2-phenylethane reacted less efficiently, with a small amount of desired product (Table 2-6, entry 3). A less reactive 1-bromo-3-phenylpropane performed better, though a moderate yield was obtained (Table 2-6, entry 4). Besides, cyclohexyl iodide was coupled with bromododecane in these conditions; however, cyclohexyl iodide favored to dimerize while only small quantity of cross-coupling products (Table 2-6, entry 5).

Table 2-6 Examples of alkyl-alkyl cross-coupling



Entry	Alkyl[1]	Alkyl[2]	product	Yield (%)[a]
1	$C_{10}H_{21}Br$		 3a	75
2	$C_{10}H_{21}Br$		 3b	40 %[b]
3	$C_{10}H_{21}Br$		 3c	< 20 %
4	$C_{10}H_{21}Br$		 3d	40 %[b]
5	$C_{10}H_{21}Br$		 3e	<10%

a: GC yields; b: isolated yields.

II-3 Conclusions and perspectives

In conclusion, after series of modification of reaction conditions for alkyl-alkyl cross-coupling, we built a catalytic system for model reaction 2, affording a good yield. However, the homocoupling still remains a challenge. When the same conditions are

applied to other substrates, no good yields are obtained. Therefore, a further optimization requires to be undertaken, in particular, the elaboration of ligands is in high demand. Moreover, under these reaction conditions, the secondary alkyl halides were not tolerated. From this point of view, an efficient method to undergo secondary alkyl-alkyl homocoupling could be investigated first. In addition, the using two different leaving groups is also an alternative to achieve good selectivity of cross-coupling rather than homocoupling.

Chapter 3 Cobalt-Catalyzed Reductive Cross-Coupling of Vinyl Halides with Benzyl Halides

I Introduction

Methods for transition-metal-catalyzed C_{sp2}-C_{sp3} bond formation have been well investigated during the last decades, which have been one of the most significant tools for organic synthesis.[146] Meanwhile, 1,3-diarylpropenes are important molecular structures or intermediates in the synthesis of natural or biological products (Scheme 3-1).[147] A variety of strategies has been developed towards the synthesis of 1,3-diarylpropenes, such as allylic selective defunctionalization (Scheme 3-2, route a),[148] alkylation of benzene (Scheme 3-2, route b),[149] olefination of benzaldehydes via decarboxylation (Scheme 3-2, route c).[150] C_{sp2}-C_{sp3} cross-coupling also provides a route to achieve such compounds. Apart from the heterogeneous catalytic Suzuki-Miyaura type reaction with allylic acetate and $NaBPh_4$ (Scheme 3-2, route d), aryl-allyl and vinyl-benzyl cross-couping are the two main ideas that we will describe in the next part.

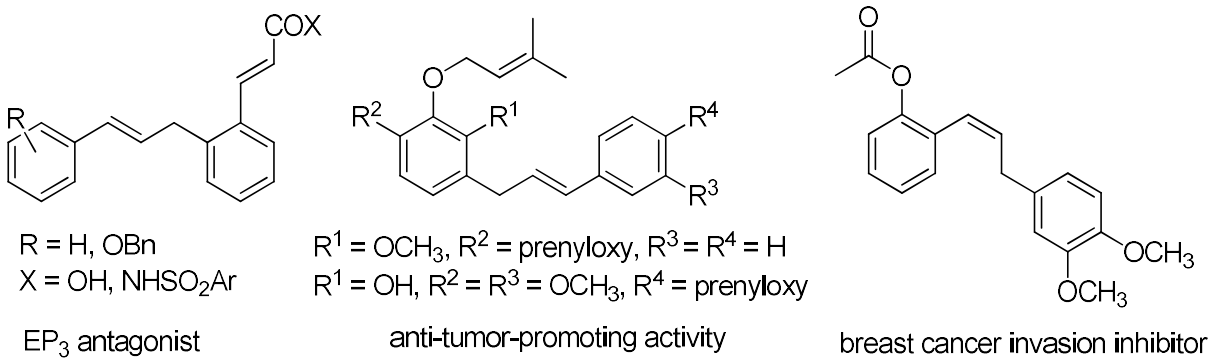
[146] For selected reviews, see: a) T-Y. Luh, M-K. Leung, K-T. Wong, *Chem. Rev.* **2000**, *100*, 3187-3204; b) E. Nakamura, N. Yoshikai, *J. Org. Chem.* **2010**, 75, 6061-6067; c) A. C. Frisch, M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 674–688; *Angew. Chem.* **2005**, *117*, 680-695; d) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; e) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435-1462; f) C. C. C. J. Seechurn, M. O. Kitching, T. J . Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085; *Angew. Chem.* **2012**, *124*, 5150-5174; g) C. Cassani, G. Bergonzini, C-J. Wallentin, *ACS Catal.* **2016**, *6*, 1640-1648; h) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587-9652 ; i) A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 2656-2670; *Angew. Chem.* **2009**, *121,* 2694-2708.

[147] a) M. Belley, C. C. Chan, Y. Gareau, M. Gallant, H. Juteau, K. Houde, N. Lachance, M. Labelle, N. Sawyer, N. Tremblay, S. Limontage, M. C. Carrière, D. Denis, G. M. Greig, D. Slipez, R. Gordon, N. Chauret, C. Lo, R. J. Zamboni and K. M. Metters, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5639-5642; b) C. Ito, M. Itoigawa, T. Kanematsu, Y. Imamura, H. Tokuda, H. Nishino and H. Furukawa, *Eur. J. Med. Chem.* **2007**, *42*, 902-909; c) F. M. Abdel Bar, M. A. Khanfar, A. Y. Elnagar, F. A. Badria, A. M. Zaghloul, K. F. Ahmad, P. W. Sylvester and K. A. El Sayed, *Bioorg. Med. Chem.* **2010**, *18*, 496-507; d) M. Namara and M. Yvonne, *Bioorg. Med. Chem.* **2011**, *19*, 1328–1348.

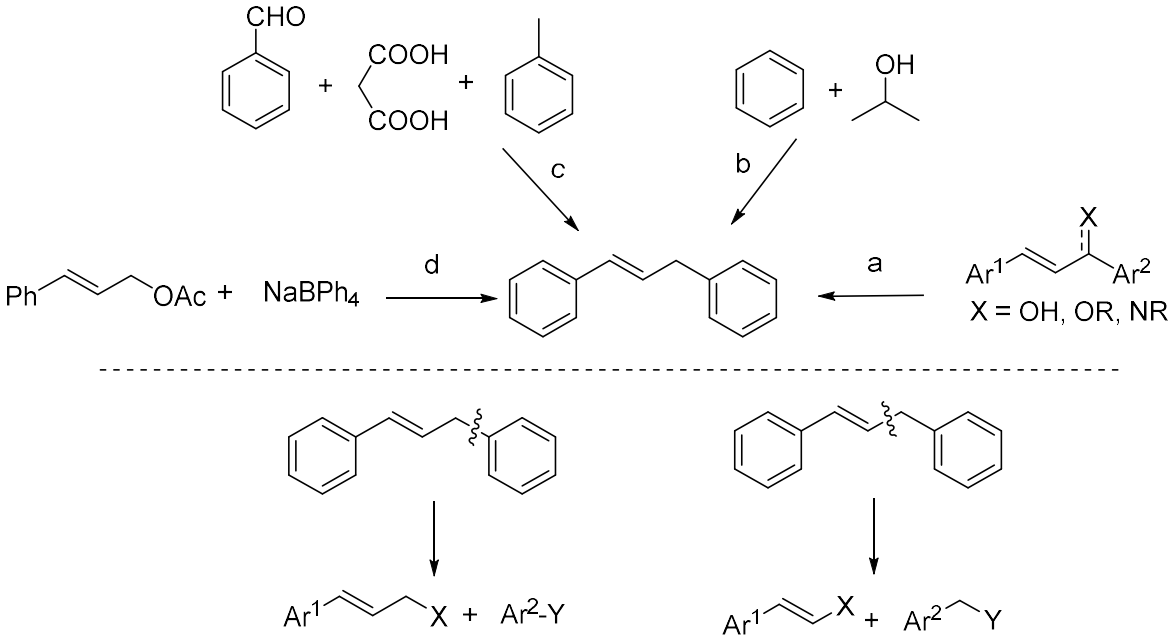
[148] a) S. Yasui, K. Nakamura, M. Fujii, A. Ohno, *J. Org. Chem.* **1985**, *50*, 3283-3287; b) J. Wang, W. Huang, Z. Zhang, X. Xu, R. Liu, X. Zhou, *J. Org. Chem.* **2009**, *74*, 3299-3304; c) B-L. Yang, S-K. Tian, *Chem. Commun.* **2010**, *46*, 6180-6182; d) X. Fan, X-M. Cui, Y-H. Guan, L-A. Fu, H. Lv, K. Guo, H-B. Zhu, *Eur. J. Org. Chem.* **2014**, 498-501.

[149] P. Makowski, R. Rothe, A. Thomas, M. Niederberger, F. Goettmann, *Green Chem.* **2009**, *11*, 34-37.

[150] a) G. Hamasaka, F. Sakurai, Y. Uozomi, *Tetrahedron* **2015**, *71*, 6437-6441 ; b) Y. M. A. Yamada, T. Watanabe, K. Torii, Y. Uozumi, *Chem. Commun.* **2009**, *37*, 5994-5996.



Scheme 3-1 Examples of 1,3-diarylpropenes



Scheme 3-2 Strategies towards the synthesis of 1,3-diarylproprenes

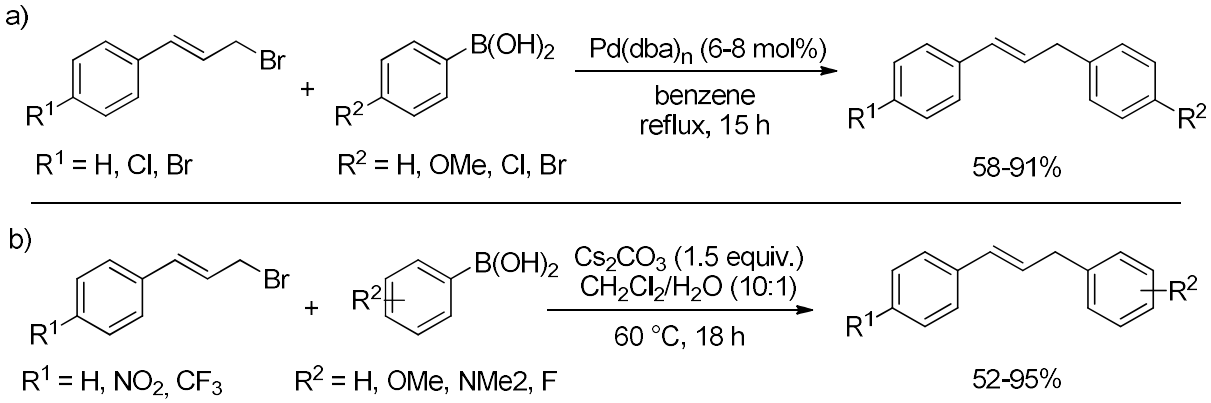
I-1 Aryl-allyl cross-coupling

I-1-1 Aryl-allyl redox-neutral cross-coupling employing organometallic compounds

In 1994, Moreno-Mañas pioneered a palladium-catalyzed Suzuki-type coupling with allylic bromides and arylboronic acids (Scheme 3-3-a).[151] Next they employed another palladium catalyst with a macrocycle ligand, but the scope of substrates was not broadened.[152] Later Ueda and coworkers developed a transition-metal-free cross-

[151] M. Moreno-Mañas, F. Pajuelo, R. Pleixats, *J. Org. Chem.* **1995**, *60*, 2396-2397.
[152] J. Cortés, M. Moreno-Mañas, R. Pleixats, *Eur. J. Org. Chem.* **2000**, 239-243.

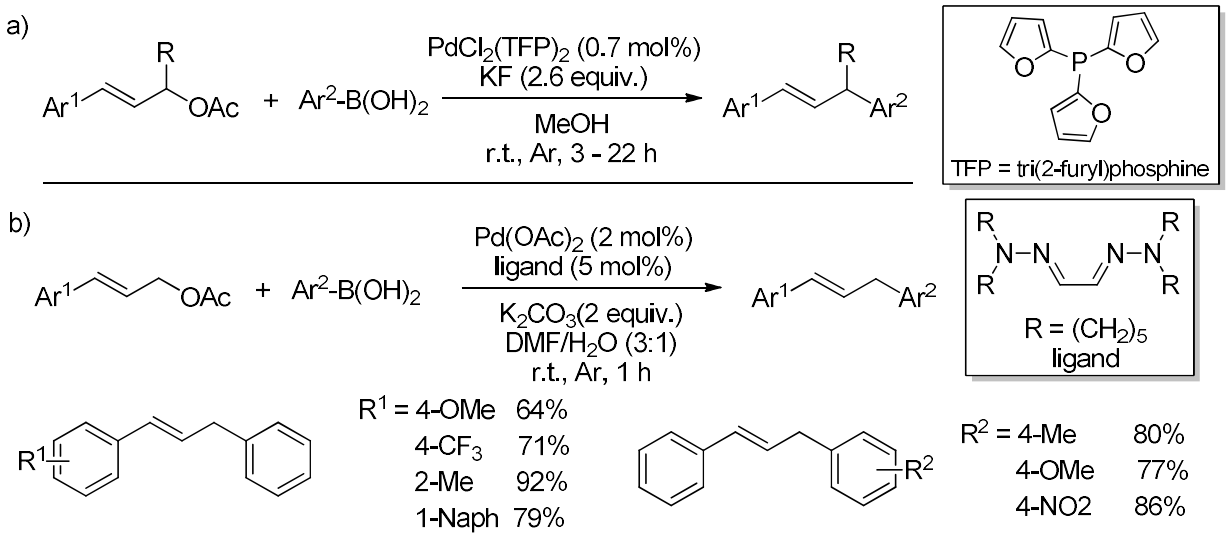
coupling between allylic bromides and arylboronic acids (Scheme 3-3-b).[153] This reaction had a broader scope under milder conditions. Moreover, they proved that no radical intermediates were involved in the reaction.



Scheme 3-3 Cross-coupling of allylic bromides with arylboronic acids

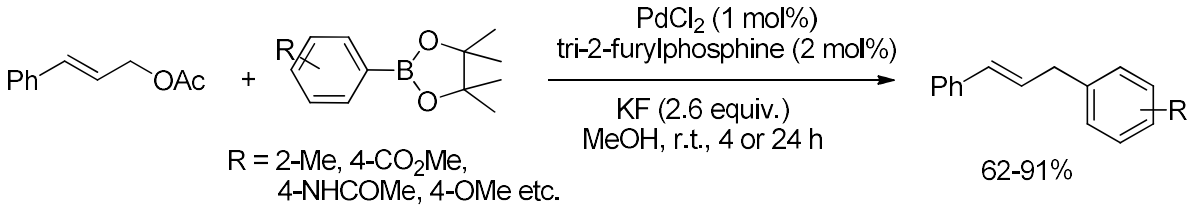
More Suzuki-Miyaura type reactions were developed *via* C-O activation. In 2002, Balme and coworkers reported a palladium-catalyzed cross-coupling of allylic acetate with arylboronic acids under mild conditions (Scheme 3-4-a).[154] The method displayed excellent regio- and stereoselectivity since only *E*-product was obtained. A variety of functionalized arylboronic acids well coupled while no functional groups on allylic acetate were tested. Mino *et al.* developed another palladium-catalyzed cross-coupling using a phosphine-free hydrozones ligand, and exhibited that it tolerated both electron-donating and electron-withdrawing groups on either allylic acetate or arylboronic acids affording good to excellent yields (Scheme 3-4-b).[155]

[153] M. Ueda, K. Nishimura, R. Kashima, I. Ryu, *Synlett* **2012**, *23*, 1085-1089.
[154] D. Bouyssi, V. Gerusz, G. Balme, *Eur. J. Org. Chem.* **2002**, 2445-2448.
[155] T. Mino, K. Kajiwara, Y. Shirae, M. Sakamoto, T. Fujita, *Synlett* **2008**, *17*, 2711-2715.



Scheme 3-4 Palladium-catalyzed cross-coupling of allylic acetate with arylboronic acids

Following Balme's work[9], Ortar employed pinacol arylboronates as the coupling partner with allylic acetates in a similar manner (Scheme 3-5).[156]

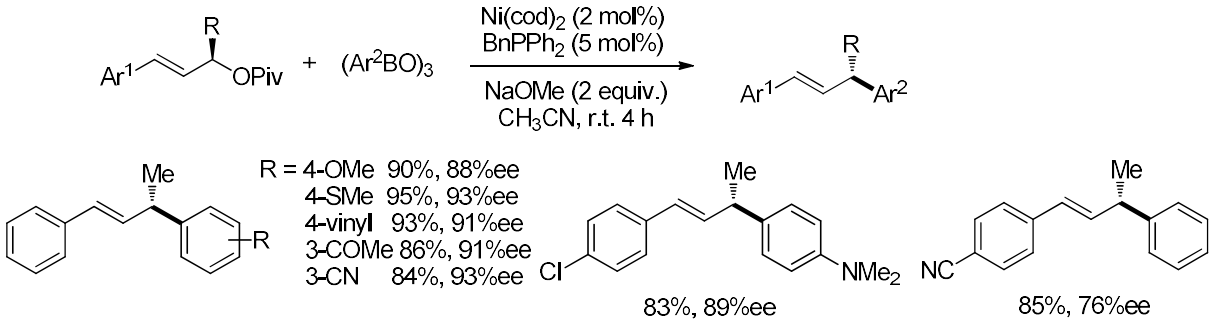


Scheme 3-5 Palladium-catalyzed cross-coupling of allylic acetate with pinacol arylboronates

In 2014, Watson and coworkers reported an enantiospecific cross-coupling of 1,3-disubstituted allylic pivalates with arylboroxines catalyzed by nickel(0) (Scheme 3-6).[157] The ligand $BnPPh_3$ was essential for the enantiospecificity, while the reaction also had *E*/*Z* selectivity. The method featured mild conditions that allowed broad functional group tolerance on both allylic pivalate and arylboroxine. It is noteworthy that the catalyst could be replaced by $NiBr_2$ and Zn, which generated Ni(0) *in situ*.[12]

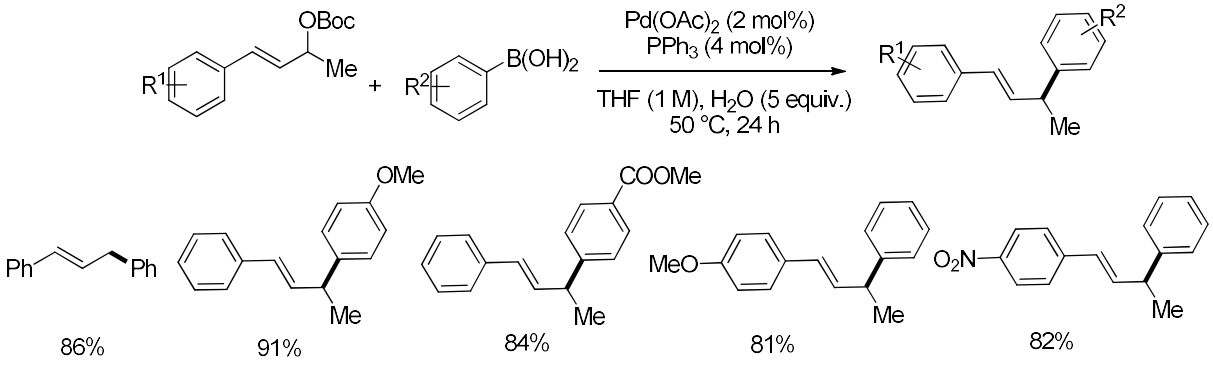
[156] G. Ortar, *Tetrahedron Lett.* **2003**, *44*, 4311-4314.

[157] H. D. Srinivas, Q. Zhou, M. P. Watson, *Org. Lett.* **2014**, *16*, 3596−3599.



Scheme 3-6 Nickel-catalyzed cross-coupling of allylic pivalates with arylboroxines

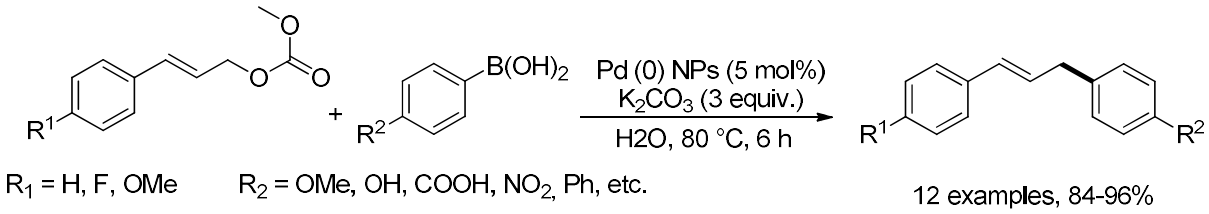
In 2012, Zhang and coworkers established a palladium-catalyzed Suzuki-Miyaura coupling reaction between allylic carbonates and arylboronic acids under mild conditions (Scheme 3-7).[158] This method was conducted in a wet solvent under a base-free system. Series of functionalized allylic carbonates and arylboronic acids were efficiently coupled with high level of isolated yields as well as complete regio- and *E*/*Z* selectivities.



Scheme 3-7 Palladium-catalyzed cross-coupling of allylic carbonates with arylboronic acids

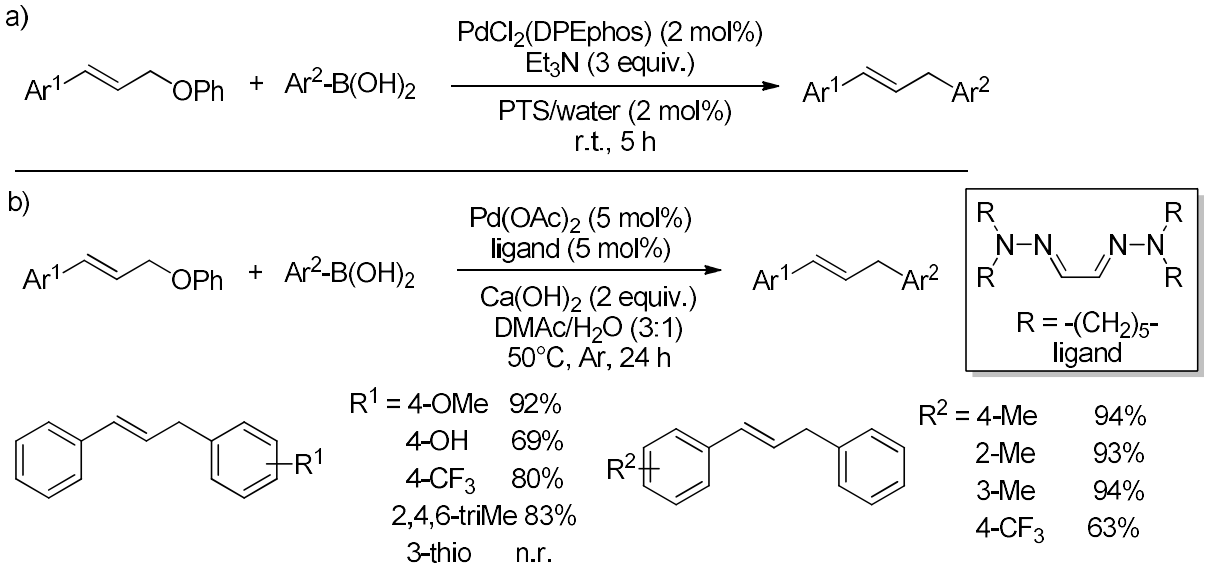
Very recently, Rhee and coworkers demonstrated the allylic arylation of cinnamyl carbonates by palladium(0) nanoparticles (Scheme 3-8).[159] The reaction could be conducted under mild conditions in water and no ligands were necessary. Arylboronic acids bearing functional groups, including alcohol and acid, reacted very well affording excellent yields.

[158] C. Li, J. Xing, J. Zhao, P. Huyhn, W. Zhang, P. Jiang, Y. J. Zhang, *Org. Lett.* **2012**, *14*, 390-393.
[159] Y. Lee, S. Shabbir, S. Lee, H. Ahn, H. Rhee, ***Green Chem.*** **2015**, *17*, 3579-3583.



Scheme 3-8 Cross-coupling of allylic carbonates with arylboronic acids catalyzed by palladium nanoparticles

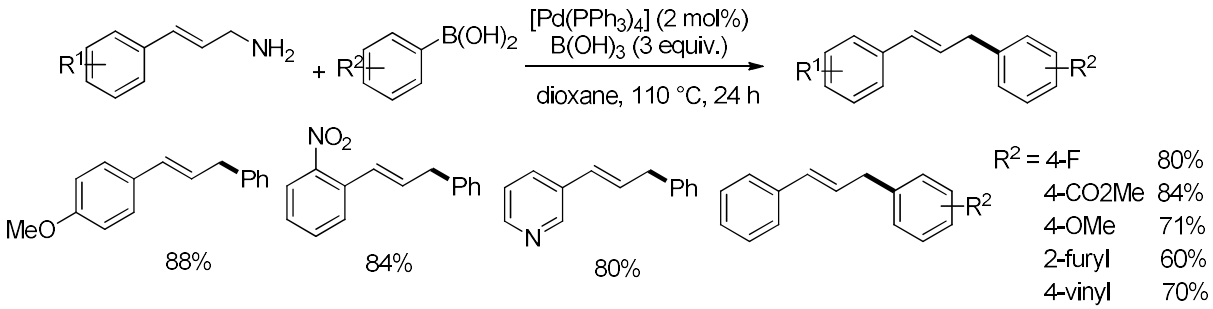
In 2009, Lipshutz and coworkers disclosed the first palladium-catalyzed Suzuki-Miyaura couping employing allylic phenyl ethers and arylboronic acids in the presence of nonionic amphiphile PTS in water (Scheme 3-9-a). [160] Several functionalized 1,3-diarylpropenes could also be synthesized under the conditions. Mino and coworkers developed a similar reaction which was applied to more wide scope of substrates (Scheme 3-9-b). [161] Notably, using 4-trifluoromethyl group substituted arylboronic acid or trifluoromethyl group substituted cinnamyl ether, the carbon-carbon double bond would be slightly rearranged. No more electron-withdrawing groups were tested.



Scheme 3-9 Palladium-catalyzed cross-coupling between allylic phenyl esters and arylboronic acids

[160] T. Nishikata, B. H. Lipshutz, *J. Am. Chem. Soc.* **2009**, *131*, 12103-12105.
[161] T. Mino, T. Kogure, T. Abe, T. Koizumi, T. Fujita, M. Sakamoto, *Eur. J. Org. Chem.* **2013**, 1501–1505.

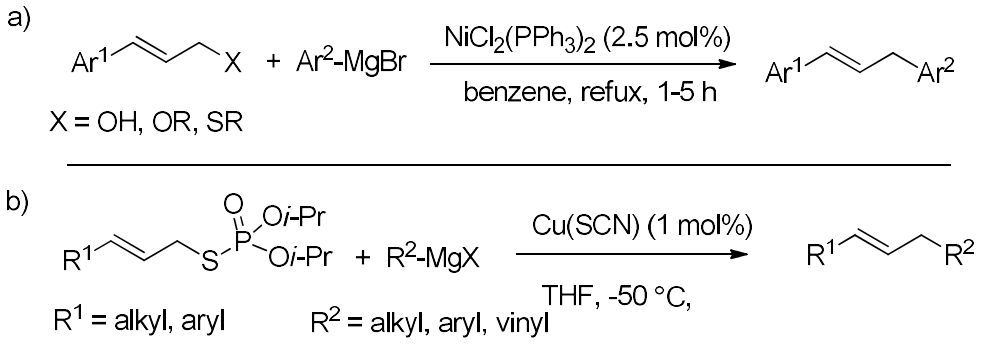
Allylic amines, which is more rare to use as a coupling partner, was employed to a palladium-catalyzed regioselective and stereospecific cross-coupling with arylboronic acids and boronates developed by Tian, wherein the NH_2 group served as an effective leaving group (Scheme 3-10).[162] A range of primary allylic amines bearing β and γ substitutents smoothly couple with functionalized boronic acids in an excellent α-selective fashion to give alkenes in good to excellent yields and with excellent *E* selectivity.



Scheme 3-10 Palladium-catalyzed cross-coupling of allylic amines with arylboronic acids

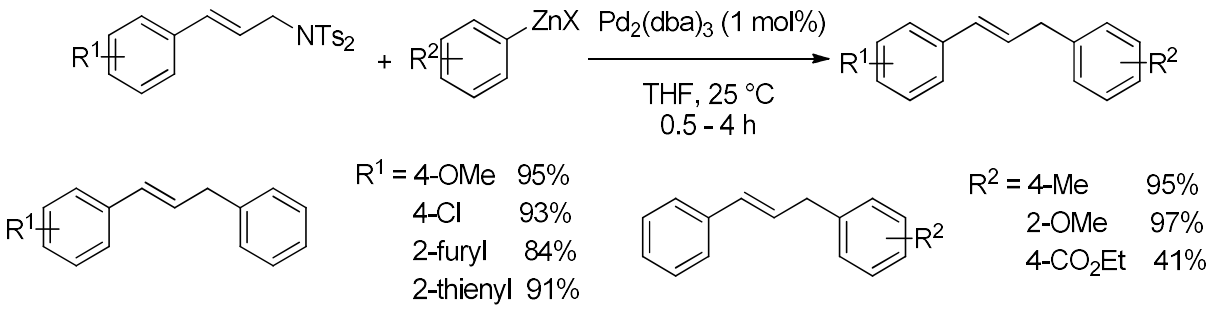
Compared to arylborate compounds, other organometallic reagents have been less investigated to couple with allylic electrophiles. Thirty years ago, Wenkert and coworkers developed a methodology using aryl Grignard reagents and allylic alcohol, ethers or thioethers (Scheme 3-11-a).[163] Though several leaving groups were tolerated, very limited functional groups were examined. In 1998, Knochel and coworkers synthesized ferrocenyl ligands and used them to undergo enantioselective preparation of several unfunctionalized 1,3-diarylpropenes.[164] Recently, Wu and coworkers reported a copper-catalyzed allylic alkylation reaction between phosphorothioate esters and organomagnesium reagents, in which arylmagnesium reagents could also be coupled to obtain 1,3-diarylpropenes (Scheme 3-11-9).[165]

[162] M-B. Li, Y. Wang, S-K. Tian, *Angew. Chem. Int. Ed.* **2012**, *51*, 2968 –2971.
[163] E. Wenkert, J. B. Fernandes, E. L. Michelotti, C. S. Swindell, *Synthesis* **1983**, *9*, 701-703.
[164] L. Schwink, P. Knochel, *Chem. Eur. J.* **1998**, *4*, 950-968.
[165] A. M. Lauer, F. Mahmud, J. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 9119–9123.



Scheme 3-11 Cross-coupling between allylic compounds and Grignard reagents

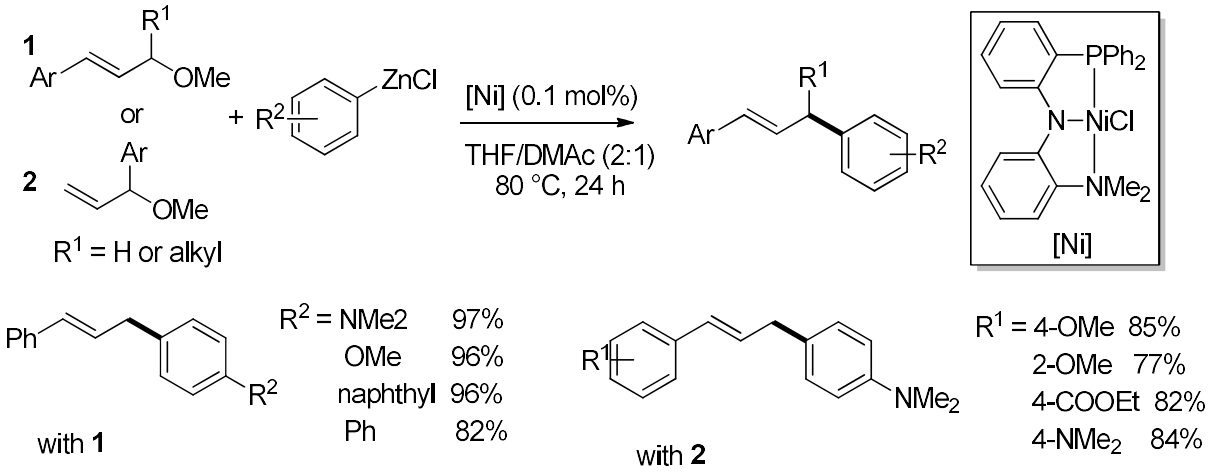
In 2012, Tian and coworkers utilized *N*-allylic sulfonimides to couple with organozinc compounds (Scheme 3-11).[166] In the presence of palladium catalyst, a range of functionalized *N*-allylic sulfonimides smoothly coupled with various organozinc compounds under mild conditions. With electron-donating groups on the starting materials, the yields were excellent. However, it seems that the method did not well tolerate electron-withdrawing groups, only one examples was tested with modest yield.



Scheme 3-11 Palladium-catalyzed cross-coupling of *N*-allylic sulfonimides with organozinc compounds

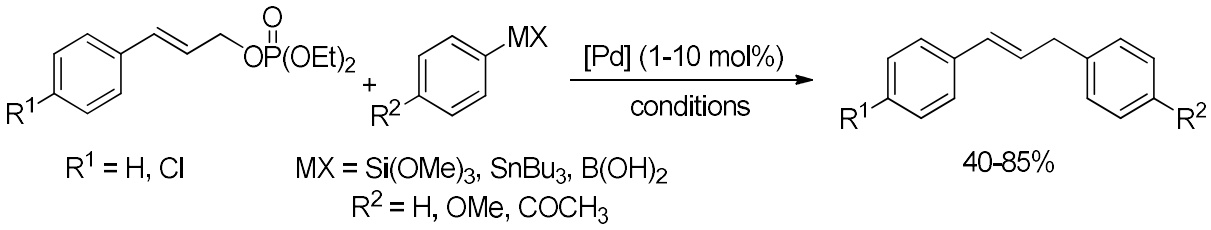
More recently, Wang and coworkers employed a pincer-nickel catalyst to undergo allyl-aryl cross-coupling between allyl methyl ethers and arylzinc chlorides (Scheme 3-12).[167] Both (1-methoxyallyl)arenes and (3-methoxypro-1-en-1-yl)arenes could couple with arylzinc chlorides to afford 1,3-diarylpropenes with a very low catalyst loading. However, functional groups on arylzinc chlorides were limited. Electron-poor arylzinc chlorides or heteroarylzinc chlorides only led to failures due to possible difficult reductive elimination.

[166] X.-L. Tang, Z. Wu, M-B. Li, Y. Gu, S-K. Tian, *Eur. J. Org. Chem.* **2012**, 4107–4109.
[167] J-L. Tao, B. Yang, Z-X. Wang, *J. Org. Chem.* **2015**, *80*, 12627−12634.



Scheme 3-12 Cross-coupling of allylic ethers with arylzinc chlorides catalyzed by nickel

In 2009, Saicic utilized allylic phosphates as the electrophiles to couple with various organometallic compounds, including arylsilicons, arylstannanes and arylborates (Scheme 3-13).[168] However, the scope of substrates was not broadened yet.

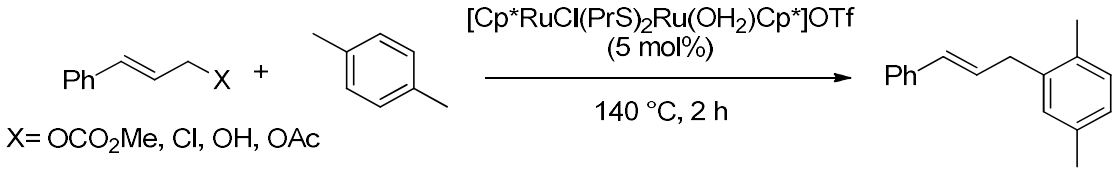


Scheme 3-13 Palladium catalyzed cross-coupling of allylic phosphates with organometallic compounds

I-1-2 Aryl-allyl oxidative cross-coupling

Oxidative aryl-allyl cross-couplings have been seldom reported. Hidai and coworkers reported a diruthenium-catalyzed oxidative cross-coupling with allylic compounds and arenes,[169] however, it had very limited scope of substrates (Scheme 3-14). Even unfunctionalized benzene afforded 11% of yield.

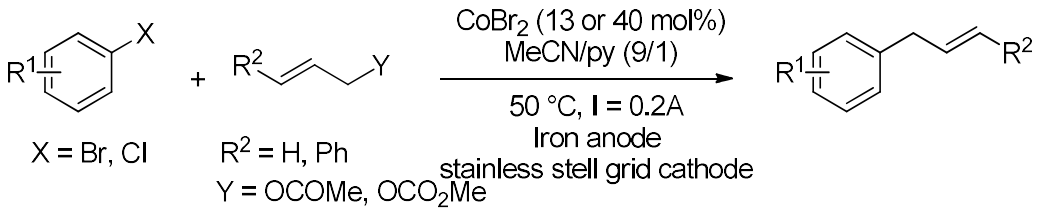
[168] V. Maslak, Z. Tokic-Vujosevic, R. N. Saicic, *Tetrahedron Lett.* **2009**, *50*, 1858-1860.
[169] Y. Nishibayashi, M. Yamanashi, Y. Takagi, M. Hidai, *Chem. Commun.* **1997**, *9*, 859-860.



Scheme 3-14 Ruthenium-catalyzed cross-coupling of allylic compounds with arenes

I-1-3 Aryl-allyl reductive cross-coupling

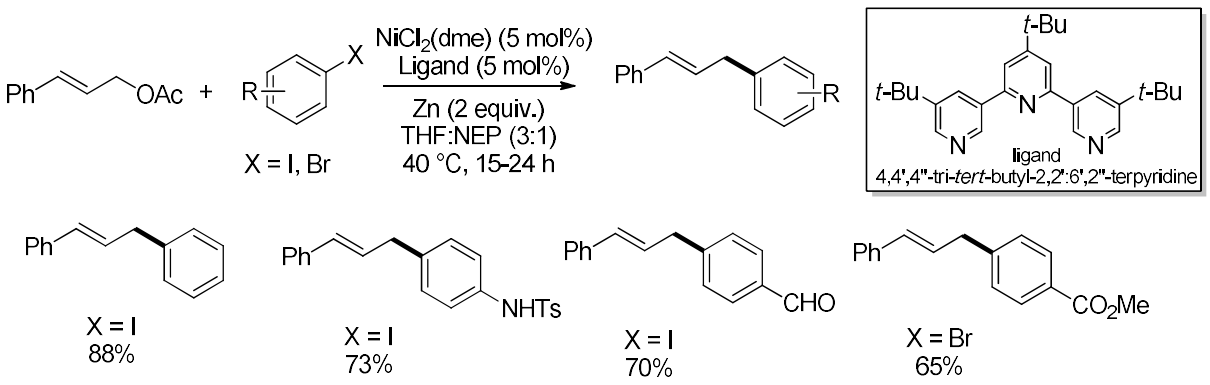
Reductive aryl-allyl cross-coupling to form 1,3-diarylpropenes has been poorly investigated. In 2003, Gosmini and coworkers reported an electrochemical method to conduct allylic-vinyl reductive cross-coupling under cobalt catalysis (Scheme 3-15).[170] It showed good tolerance of functional groups. However, electrochemical synthesis was not simply operated.



Scheme 3-15 Cobalt-catalyzed electrochemical cross-coupling of aryl halides with allylic acetates or carbonates

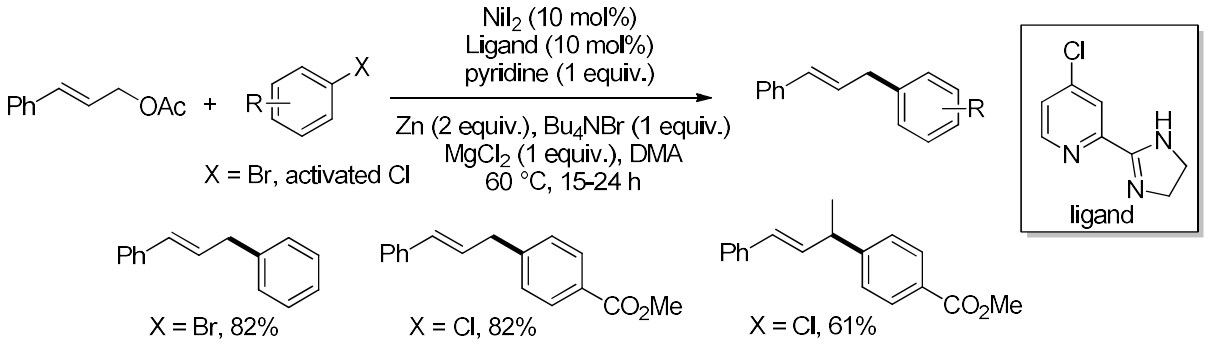
In 2012, Weix and coworkers developed a nickel-catalyzed general cross-coupling of allylic acetate with aryl and alkyl halides (Scheme 3-16).[171] With a tridentate ligand, the reaction could suppress the dimerization of aryl halides compared with bidentate ligands. A variety of aryl halides, including aryl halides and electron-deficient substituted aryl bromides, were well tolerated affording good to excellent yields. However, functionalized cinnamyl acetate were not tested to couple with aryl halides.

[170] P. Gomes, C. Gosmini, J. Perichon, *J. Org. Chem.* **2003**, *68*, 1142-1145.
[171] L. L. Anka-Lufford, M. R. Prinsell, D. J. Weix, *J. Org. Chem.* **2012**, *77*, 9989-10000.



Scheme 3-16 Nickel-catalyzed cross-coupling of allylic acetate with aryl iodides and bromides

Later, Gong and coworkers also utilized a nickel catalyst to establish a similar cross-coupling, which were used for aryl bromides and activated aryl chlorides (Scheme 3-17).[172] $MgCl_2$ and Bu_4NBr were crucial to obtain excellent yields, owing to the possible activation of zinc powder by removal salts on its surface.[173]



Scheme 3-17 Nickel-catalyzed cross-coupling of allylic acetate with aryl bromides and chlorides

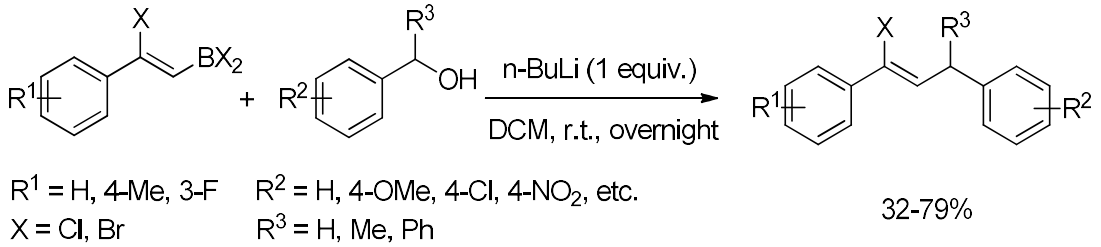
I-2 Vinyl-benzyl cross-coupling

Vinyl-benzyl cross-coupling represents an attractive alternative. However, compared with the aryl-allyl cross-coupling, vinyl-benzyl cross-coupling has been poorly investigated, though several alkenylation or benzylation reactions were reported, which were applied to very limited scope of substrates.[174]

[172] X. Cui, S. Wang, Y. Zhang, W. Deng, Q. Qian, H. Gong, *Org. Biomol. Chem.* **2013**, *11*, 3094-3097.
[173] S. Wang, Q. Qian, H. Gong, *Org. Lett.* **2012**, *14*, 3352-3355.
[174] several recent examples, see: a) D. Leboeuf, M. Presset, B. Michelet, C. Bour, S. Bezzenine-Lafollée, V. Gandon, *Chem*, *Eur. J.* **2015**, *21*, 11001-11005; b) M. Ohsumi, R. Kuwano, *Chem. Lett.* **2008**, *37*, 796-797; c) Y. Baba, A. Toshimitsu,S. Matsubara, *Synlett.* **2008**, *13*, 2061-2063.

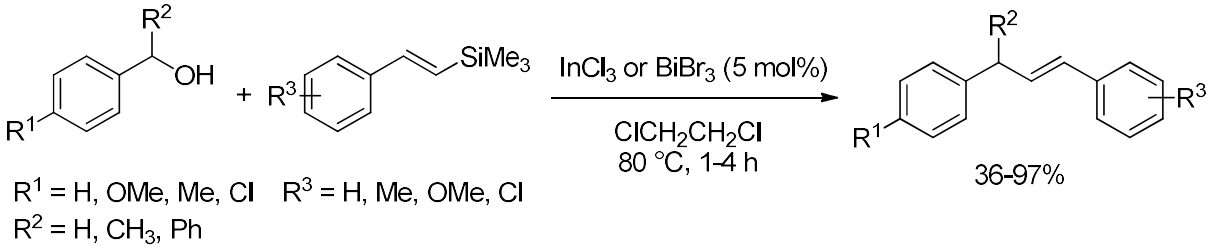
I-2-1 Vinyl-benzyl cross-coupling involving organometallic compounds

In 2005, Wu developed a lithium-mediated cross-coupling between benzylic alcohols and vinylboron dihalides (Scheme 3-18).[175] Several functionalized secondary benzylic alcohols coupled efficiently with vinyldibromides or vinyldichlorides, affording only *Z*-isomers under mild conditions. However, the corresponding benzylic alcohol gave no cross-coupling product.



Scheme 3-18 Lithium-mediated cross-coupling of vinyldihalides with benzylic alcohols

Benzylic alcohols have been chosen to couple with vinylsilanes, which was displayed by Baba and coworkers (Scheme 3-19).[176] They utilized indium or bismuth salts, which were Lewis acids, as catalysts to perform the reactions. Several functional groups on either benzylic alcohols or vinylsilanes were tolerated with stereospecificity. However, *Z*-vinylsilanes could not proceed the reaction at all.

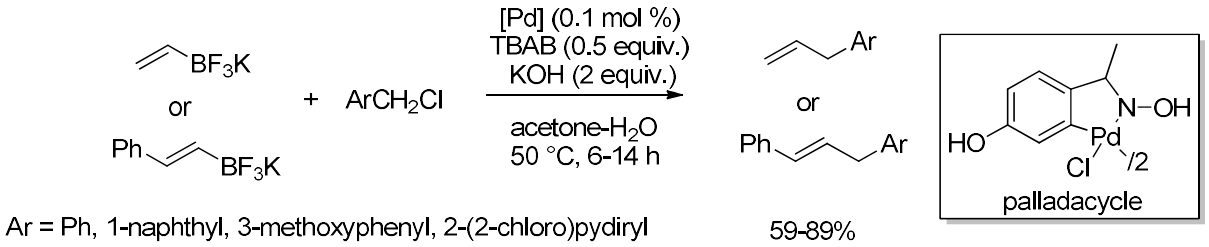


Scheme 3-19 Indium or bismuth-catalyzed cross-coupling of vinylsilanes with benzylic alcohols

In 2008, Nájera and coworkers developed a palladium-catalyzed cross-coupling of potassium alkenyltrifluoroborates with organic halides (Scheme 3-20).[177] A variety of organic halides could be effective coupling partners such as aryl bromides, allylic halides and benzyl halides. They examined four functionalized benzyl chlorides coupling with potassium styrenyltrifluoroborates and obtained excellent yields under mild conditions. Moreover, retention of carbon-carbon double bond was observed in

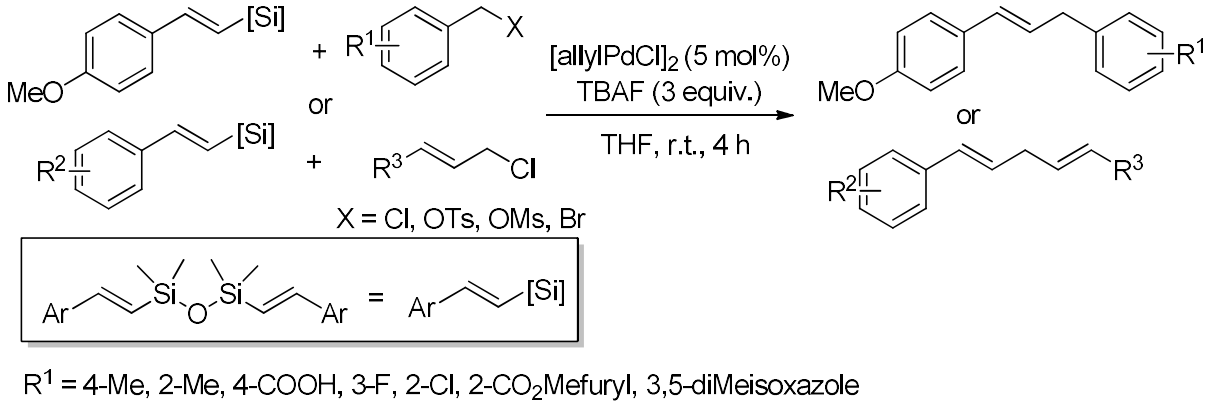
[175] G. W. Kabalka, M-L. Yao, S. Borella, Z-Z. Wu, *Org. Lett.* **2005**, *7*, 2865-2867.
[176] Y. Nishimoto, M. Kajioka, T. Saito, M. Yasuda, A. Baba*, Chem. Commun.* **2008**, 6396-6398.
[177] E. Alacid, C. Nájera, *J. Org. Chem.* **2009**, *74*, 2321-2327.

this reaction. The same system was also effective for vinylboronic acids though only one example was exhibited.[178]



Scheme 3-20 Palladium-catalyzed cross-coupling of vinyldisiloxanes with benzylic and allylic halides

R. Spring's group developed a Pd-catalyzed cross-coupling of vinyldisiloxanes with benzylic and allylic halides and sulfonates (Scheme 3-21).[179] A wide variety of functional groups on benzyl chlorides was tolerated under mild conditions, nevertheless, only methoxy group substituted vinyl disiloxane were coupled with various benzylic halides.



Scheme 3-21 Palladium-catalyzed cross-coupling of vinyldisiloxanes with benzylic or allylic halides

On the other side, although preparation of various benzylic organometallic compounds have been well developed in the past decades,[180] they have scarcely been used with an aromatic electrophile to synthesize 1,3-diarylpropenes.

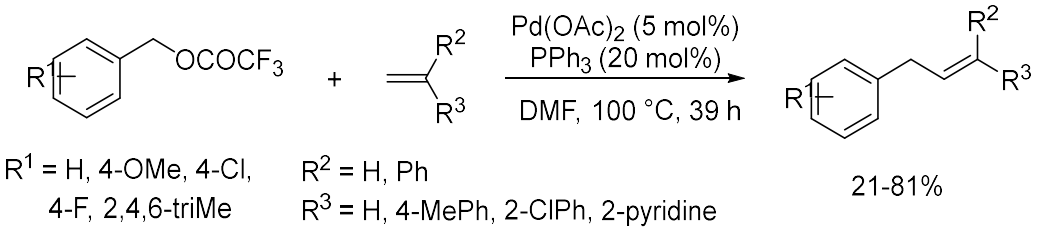
[178] E. Alacid, C. Nájera, *J. Organometallic. Chem.* **2009**, *694*, 1658-1665.

[179] E. C. Frye, C. J. O'Connor, D. G. Twigg, B. Elbert, L. Laraia, D. G. Hulcoop, A. R. Venkitaraman, D. R. Spring, *Chem. Eur. J.* **2012**, *18*, 84-89.

[180] Several examples, see: a) M. J. Gallagher, S. Harvey, C. L. Raston, R. E. Sue, *J. Chem. Soc., Chem. Commun.* **1988**, 289-290; b) H. G. Chen, C. Hoechstetter, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 4795-4798; c) S. C. Berk, M. C. P. Yeh, N. Jeong, P. Knochel, *Organometallics* **1990**, *9*, 3053-3064; d)

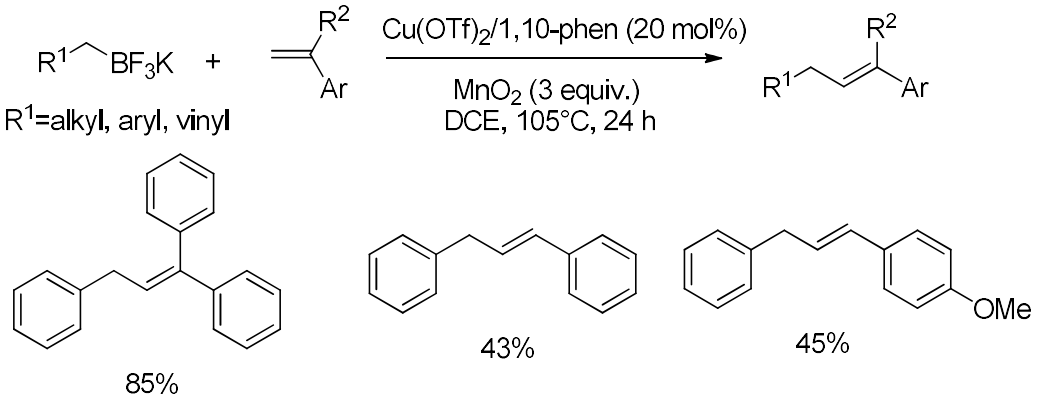
I-2-2 Heck-type vinyl-benzyl Cross-coupling

In 2004, Shimizu developed a Heck-type benzylation of olefins with benzyl trifluoroacetates catalyzed by palladium (Scheme 3-22).[181] Benzyl trifluoroacetates bearing functional groups could be converted into the corresponding products with low to excellent yields. However, it seems that this methods strictly went for electron-withdrawing groups on benzyl trifluoroacetaes and electron-donating groups on vinyl arenes.



Scheme 3-22 Palladium-catalyzed Heck-type cross-coupling of vinyl arenes with potassium benzyltrifluoroacetates

In 2013, Chemler and coworkers reported a copper-catalyzed oxidative Heck-type reaction with vinyl arenes and potassium benzyltrifluoroborates or alkyltrifluoroborates (Scheme 3-23). [182] This methods applied much better for disubstituted vinyl arenes than styrenes. Moreover, it occurred that the carbon-carbon double bond migrated when disubstituted vinyl arenes were used possibly due to the involving radical intermediates which were confirmed.



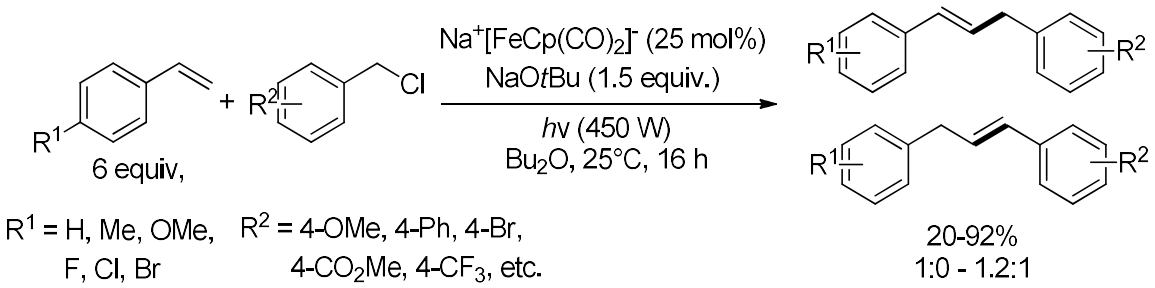
A. Metzger, M. A. Schade, G. Manolikakes, P. Knochel, *Chem. Asian J.* **2008**, *3*,1678 – 1691 ; e) T. D. Blumke, K. Groll, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2011**, *13*, 6440-6443.

[181] H. Narahashi, A. Yamamoto, I. Shimizu, *Chem. Lett.* **2004**, *33*, 348-349.

[182] T. W. Liwosz, S. R. Chemler, *Org. Lett.* **2013**, *15*, 3034-3037.

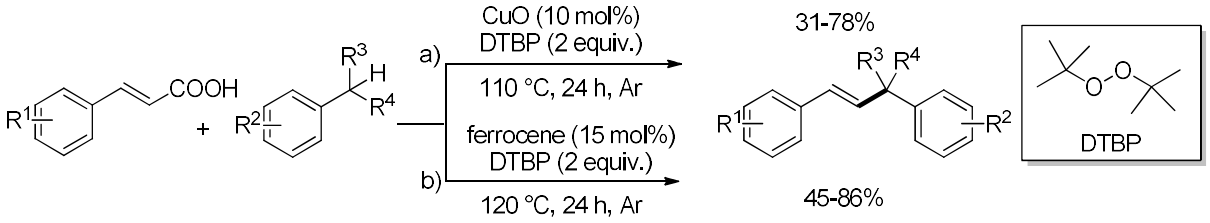
Scheme 3- 23 Copper-catalyzed Heck-type cross-coupling of vinyl arenes with potassium benzyltrifluoroborates

More recently, Mankad and coworkers chose benzyl chlorides as the Heck-type coupling partners with vinyl arenes in the presence of iron catalyst (Scheme 3-24).[183] It had a broader tolerance of functional groups; however, the yields were low to modest for most of the substrates. Furthermore, a minor product was always generated resulting from alkene migration. Besides, another drawback was the use of a large excess of vinyl arenes.



Scheme 3- 24 Iron-catalyzed Heck-type cross-coupling of vinyl arenes with benzyl chlorides

Apart from Heck-type coupling reaction, Mao and coworkers established another kind of oxidative cross-coupling via decarboxylation process (Scheme 3-25).[184] Copper or iron was the catalyst and di-*tert*-butyl peroxide (DTBP) as the oxidant. In general, iron had a better catalytic activity and allowed more substrates than copper. Furthermore, electron-donating groups substituted starting materials afforded higher yields.

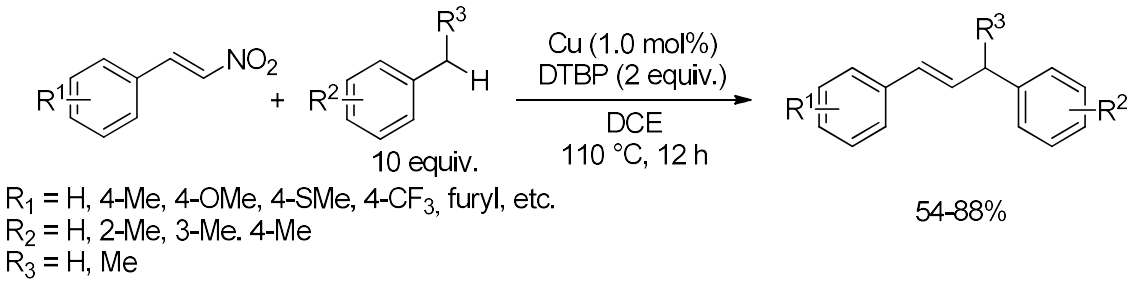


R1 = 4-OMe, 3,4,5-triMe, 4-F, 4-CN, 4-COOMe, 3-OCOMe, 3-pyridine, etc.
R2 = 4-Me, naphthyl, 4-Cl, 4-I, 4-COMe, 4-CH2Cl, etc.
R3 , R4 = H, Me

[183] G. W. Waldhart, N. P. Mankad, *J. Organomet. Chem.* **2015**, *793*, 171-174.
[184] a) H. Yang, H. Yan, P. Sun, Y. Zhu, L. Lu, D. Liu, G. Rong, J. Mao, *Green. Chem.* **2013**, *15*, 976-981; b) H. Yang, P. Sun, Y. Zhu, H. Yan, L. Lu, X. Qu, T. Li, J. Mao, *Chem. Commun.* **2012**, *48*, 7847-7849.

Scheme 3-25 Decarboxylative cross-coupling of cinnamic acids and benzylic hydrocarbons

Very recently, Yuan and coworkers disclosed the benzyl addition to β-nitrostyrenes in the presence of simple copper powder with DTBP as the oxidant (Scheme 3-26).[185] This system showed great tolerance of functional groups on nitrostyrenes, on the contrary, no functionalized toluene derivatives could react. Mechanistic study revealed that a radical intermediate was involved in the reaction.



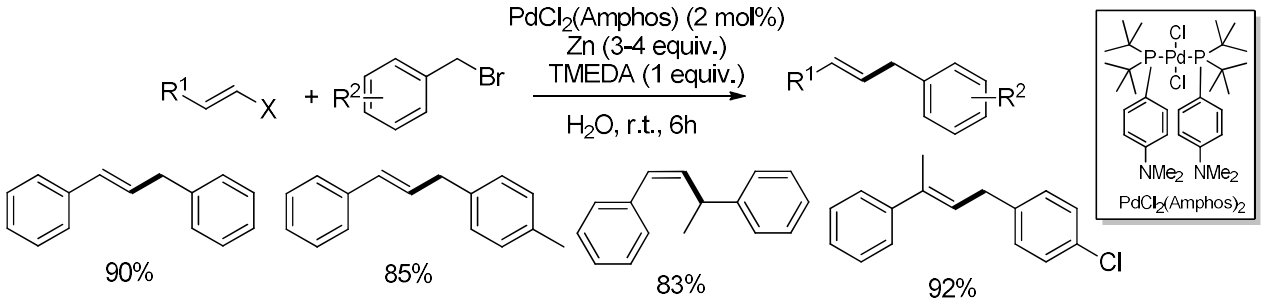
R_1 = H, 4-Me, 4-OMe, 4-SMe, 4-CF_3, furyl, etc.
R_2 = H, 2-Me, 3-Me. 4-Me
R_3 = H, Me

Scheme 3-26 Copper-catalyzed benzyl radical addition to β-nitrostyrenes

I-2-3 Reductive vinyl-benzyl cross-coupling

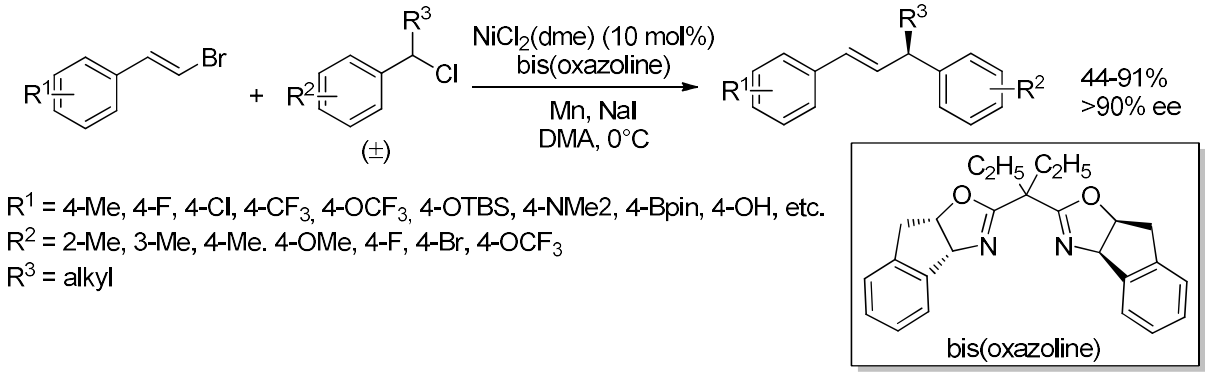
In 2011, Lipshutz and coworkers disclosed vinyl-benzyl reductive cross-coupling in the presence of palladium catalyst and zinc dust in water (Scheme 3-27).[186] They first displayed the system on aryl-benzyl cross-coupling[187] and then extended it to vinyl-benzyl cross-coupling. It is assumed that organozinc species were generated *in situ* and TMEDA stabilized them. Several 1,3-diarylpropenes were synthesized with excellent yields with the retention of alkene stereochemistry. Secondary benzyl halides and disubstituted vinyl bromides were well tolerated, while not broad scope of functional groups were examined. Furthermore, due to competitive zinc-insertion and subsequent proton-quenching by water, three equivalents of electron-poor benzylic chlorides were necessary.

[185] a) S. Guo, Y. Yuan, J. Xiang, *New. J. Chem.* **2015**, *39*, 3093-3097; b) S-R. Guo, Y-Q. Yuan, *Synlett* **2015**, *26*, 1961-1968.
[186] V. Krasovskaya, A. Krasovskiy, A. Bhattacharjya, B. H. Lipshutz, *Chem. Commun.* **2011**, *47*, 5717-5719.
[187] C. Duplais, A. Krasovsky, A. Wattenberg, B. H. Lipshutz, *Chem. Commun.* **2010**, *46*, 562-564.



Scheme 3-27 Palladium-catalyzed vinyl-benzyl cross-coupling in water

More recently, Reisman and coworkers established an efficient nickel-catalyzed enantioselective reductive cross-coupling between vinyl bromides and secondary benzyl chlorides (Scheme 3-28).[188] This method was efficient to various functional groups on both of the starting materials including some sensitive groups such as amine and alcohol. However, while *Z*-vinyl bromide only afforded *E*-product in low yield and the scope of electron-withdrawing groups on benzyl chlorides was not well explored.



Scheme 3-28 Nickel-catalyzed enantioselective vinyl-benzyl cross-coupling

In summary, series of C_{sp2}-C_{sp3} cross-coupling reactions for the synthesis of 1,3-diarylpropenes are introduced. Among those methodologies, cross-coupling employing organometallic compounds have been best developed. However, a separated step for preparation of organometallic compounds cannot be avoided. Moreover, the moisture-sensitivity of organometallic compounds requires careful operation. Oxidative cross-coupling uses simple starting materials and is more atomic economic, but the scope of functional groups is always limited owing to harsh

[188] A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2014**, *136*, 14365-14368.

reaction conditions such as high temperature and long reaction time. Besides, a large excess of one starting material is often required. Reductive cross-coupling, as a straightforward and effective method, has been much less investigated. And the published reductive cross-coupling methods also have drawbacks, including the use of expensive palladium catalyst or toxic nickel catalyst. To the best of our knowledge, no general cobalt-catalyzed vinyl-benzyl reductive cross-coupling reactions have been reported. Our group has already reported several successful C_{sp2}-C_{sp3} reductive cross-coupling catalyzed by cobalt, including aryl-allyl,[189] aryl-alkyl,[190] aryl-benzyl cross-coupling.[191] Following these results, here we establish the first cobalt-catalyzed vinyl-benzyl reductive cross-coupling involving vinyl bromides and benzyl chlorides.

II Results and discussions

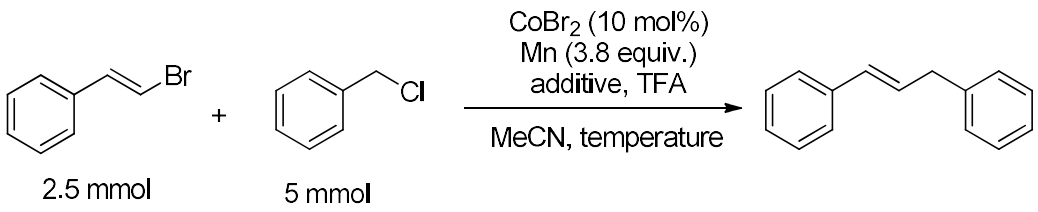
II-1 optimization of reaction conditions

To begin with, we investigated the cross-coupling between β-bromostyrene and benzyl chloride, using $CoBr_2$/Mn/pyridine system without ligands and TFA to activate manganese, in MeCN as solvent (Table 3-1, entry 1). This catalytic system has been successfully employed in our previous work,[40, 192] however, under the initial condition, the desired cross-coupling product was obtained with only 14% yield, while more dimers of both starting materials were generated. Sodium iodide, which has been used to promote cobalt-catalyzed alkyl-alkyl homocouping since it could possibly facilitate the reduction of cobalt catalyst,[47b] was added to the medium. To our delight, the yield was highly increased (Table 3-1, entry 2). Without pyridine, the reaction performed less effectively in the presence of sodium iodide (Table 3-1, entry 3). Next we utilized zinc dust as the reductant instead of manganese and it turned out that zinc only had a negative effect on the cross-coupling (Table 3-1, entry 4) with or without pyridine. When we used PPh_3 as ligand, the yield was much higher without pyridine (Table 3-1, entry 5-6), which was always required in our previous cross-coupling reaction using Co/Mn system. Decreasing the temperature to 30 °C led to unconsumed β-bromostyrene (Table 3-1, entry 7), while increasing the temperature to 70 °C

[189] P. Gomes, C. Gosmini, J. Périchon, *Org. Lett.* **2003**, *5*, 1043-1057.
[190] M. Amatore, C. Gosmini, *Chem. Commun*. **2008**, 5019-5021.
[191] S. Pal, S. Chowdhury, E. Rozwadowski, A. Auffrant, C. Gosmini, published.
[192] a) X. Qian, A. Auffrant, A. Felouat, C. Gosmini, *Angew. Chem. Int. Ed.* **2011**, *50*, 10402-10405 ; b) Y. Cai, X. Qian, C. Gosmini, *Adv. Synth. Catal.* **2016**, DOI: 10.1002/adsc.2016 00213.

promoted homocoupling instead of cross-coupling, which slightly decreased the yield (Table 3-1, entry 8). Thus, 50 °C proved to be the best temperature. 0.25 and 1 equivalent of sodium iodides were also tested. With less sodium iodide, only traces of cross-coupling product were detected on GC, while more reduction product of β-bromostyrene was observed (Table 3-1, entry 9). More sodium iodide did not destroy the cross-coupling and slightly decreased the yield (Table 3-1, entry 10). Lower catalyst loading gave lower yield though both of the starting materials were consumed (Table 3-1, entry 11).Then the reaction conditions were optimized with a screen of phosphine ligands, and PPh_3 was identified to be the best one (Table 3-1, entry 5, 11-17). It is worth noting that the preformed $CoBr_2(PPh_3)_2$ complex, instead of adding $CoBr_2$ and PPh_3 separately, slightly improved the yield (Table 3-1, entry 18) . With $CoBr_2(PPh_3)_2$ as the catalyst, sodium iodide was confirmed to be necessary and the most effective after we examined other additives such as TMSCl and KBF_4 (Table 3-1, entry 19-21). When TMSCl was used as an additive, a similar phenomenon occurred as activation by TFA. Therefore, next TMSCl[193] was tested to activate smoothly the manganese instead of TFA, and we were pleased to observe an excellent NMR yield of 84% (Table 3-1, 22). Furthermore, TMSCl also lowered the reaction temperature to 0 °C to room temperature (Table 3-1, entry 23-24). However, when we used $CoBr_2$ and PPh_3 instead of the preformed complex and activation of manganese with TMSCl, no cross-coupling product was obtained (Table 3-1, entry 25).

Table 3-1. Optimization of reaction conditions



entry	catalyst	ligand	T (°C)	Additive (0.5equiv.)	Yield(%)[a]
1[b]	$CoBr_2$	/	50	/	14
2[b]	$CoBr_2$	/	50	NaI	60

[193] J. Augé, N. Lubin-Germain, A. Thiaw-Woaye, *Tetrahedron. Lett.* **1999**, *40*, 9245-9247.

3	$CoBr_2$	/	50	NaI	37
4[b, c]	$CoBr_2$	/	50	NaI	16
5[b]	$CoBr_2$	2*PPh_3	50	NaI	38[d]
6	$CoBr_2$	2*PPh_3	50	NaI	70[d]
7	$CoBr_2$	2*PPh_3	30	NaI	/
8	$CoBr_2$	2*PPh_3	70	NaI	60
9	$CoBr_2$	2*PPh_3	50	NaI (0.25 equiv)	trace
10	$CoBr_2$	2*PPh_3	50	NaI (1.0 equiv)	64
11	$CoBr_2$ (6%)	2*PPh_3	50	NaI	54[d]
12	$CoBr_2$ (6%)	2* (*p*-MeO-Ph)$_3$P	50	NaI	14
13	$CoBr_2$ (6%)	2* (*p*-F-Ph)$_3$P	50	NaI	51
14	$CoBr_2$ (6%)	2* (5F-Ph)$_3$P	50	NaI	9
15	$CoBr_2$ (6%)	2* (*p*-Me-Ph)$_3$P	50	NaI	/
16	$CoBr_2$	2*(*i*-Bu-Ph)$_2$PH	50	NaI	10
17	$CoBr_2$	1*dppe	50	NaI	25
18	$CoBr_2(PPh_3)_2$	/	50	NaI	77[d]
19	$CoBr_2(PPh_3)_2$	/	50	/	53
20	$CoBr_2(PPh_3)_2$	/	50	TMSCl	61[d]
21	$CoBr_2(PPh_3)_2$	/	50	KBF4	61[d]
22[e]	$CoBr_2(PPh_3)_2$	/	50	NaI	84[d]
23[e]	$CoBr_2(PPh_3)_2$	/	r.t.	NaI	84[d]
24[e]	**$CoBr_2(PPh_3)_2$**	**/**	**0-r.t.**	**NaI**	**86[d]**

25[e]	$CoBr_2$	2*PPh_3	50	NaI	0

[a]: GC yield calculated with dodecane as an internal standard ; [b]: adding 0.5 mL of pyridine; [c]: using Zn instead of Mn; [d]: yield calculated by NMR with mesitylene as internal standard; [e]: using TMSCl (30mol%) for activation

L1 : tri(*p*-methoxyphenyl)phosphine

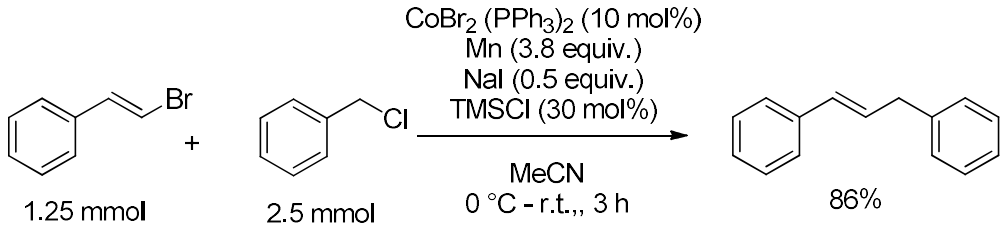
L2 : tri(*p*-fluorophenyl)phosphine

L3 : tri(pentafluorophenyl)phosphine

L4 : tri(*p*-methylphenyl)phosphine

L5 : biisobutylphenylphosphine

The optimized conditions are:



II-2 Scope of substrates

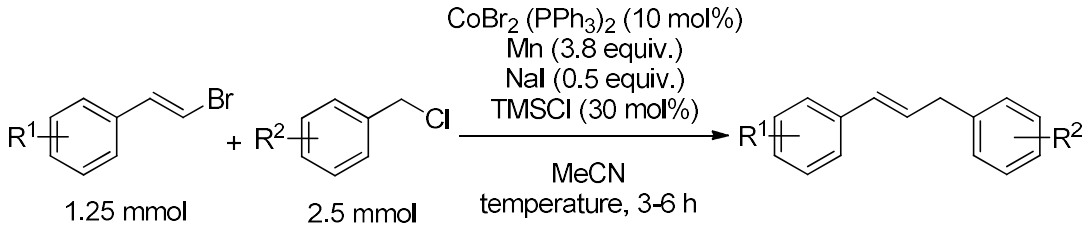
II-2-1 Scope of vinyl bromides

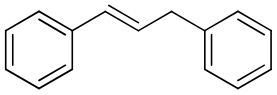
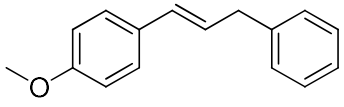
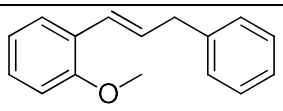
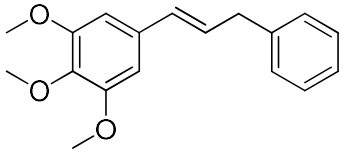
With the optimized reaction conditions in hand, we next explored the scope of substrates. First the benzyl chloride reacted with various functionalized vinyl bromides. Both the styrenyl bromides bearing an electron-donating group on the aromatic ring were coupled with benzyl chlorides affording moderate to excellent yields. Methoxy group, either on *para*- or *ortho*- position, was well tolerated ended to high yields (Table 3-2, entries 2-3). With three methoxy groups on the arene, we found that heating to 50 °C gave the best yield while at room temperature less amount of product was obtained (Table 3-2, entry 4). Moreover, a fluorine substitute on the styrenyl bromide gave cross-coupling product in good yield (Table 3-2, entry 5). Moreover, this method tolerated amine, though only moderate yield was obtained (Table 3-2, entry 6).

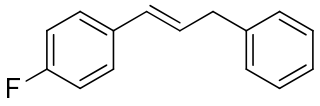
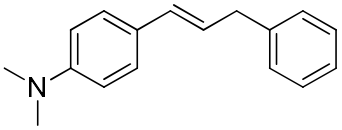
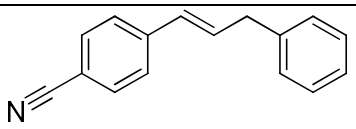
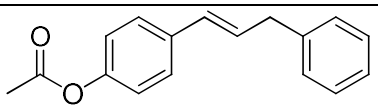
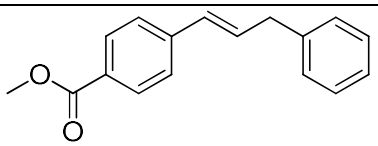
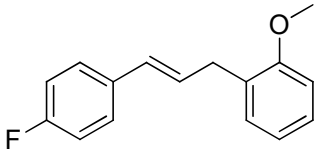
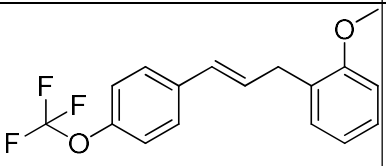
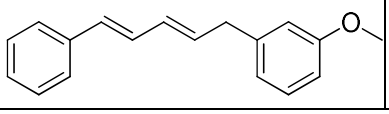
Styrenyl bromides bearing electron-withdrawing groups on the aromatic ring were also tolerated in this method. Nevertheless, in general, the yields were higher with substitution of electron-donating groups than electron-withdrawing groups.

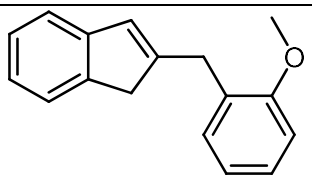
Furthermore, it was required to heat to 50 °C when a vinyl bromide bearing electron-withdrawing group was employed such as ester because it was less reactive (Table 3-2, entries 8-9). However, 4-(2-bromovinyl)benzontrile only gave a low yield despite the temperature (Table 3-2, entry 7). Several vinyl bromides bearing weakly electron-donating groups on the aromatic ring were coupled with benzyl chloride most efficiently at 50 °C (Table 3-2, entries 8, 11) while at room temperature the vinyl bromides were not all consumed. It is interesting that the reaction proceeded very well with 4-bromo-(buta-1,3-dienyl)benzene affording excellent yield (Table 3-2, entry 12). In addition, secondary vinyl bromide also served as a good coupling partner in this reaction (Table 3-2, entry 13). However, when 2-bromopropene was used, no cross-coupling product was detected.

Table 3-2. Scope of vinyl bromides



Entry	R^1	R^2	Temperature	product	yield (%)
1	H (4a)	H (5a)	0 °C – r.t.	 6aa	86[a]
2	4-OMe (4b)	H (5a)	0 °C – r.t.	 6ba	80
3	2-OMe (4c)	H (5a)	r.t.	 6ca	90
4	3,4,5-triOMe (4d)	H (5a)	50 °C		89

				6da	
5	4-F (4e)	H (5a)	r.t.	 6ea	62[a]
6	4-NMe_2 (4f)	H (5a)	0 °C – r.t.	 6fa	47
7	4-CN (4g)	H (5a)	r.t.	 6ga	29
8	4-OCOMe (4h)	H (5a)	50 °C	 6ha	80
9	4-CO_2Me (4i)	H (5a)	50 °C	 6ib	68
10	4-F (4d)	2-OMe (5b)	0 °C – r.t.	 6db	80
11	4-OCF_3 (4j)	2-OMe (5b)	50 °C	 6jb	75
12	PhCHCHCHCH- (4k)	3-OMe (5c)	0 °C – r.t		74

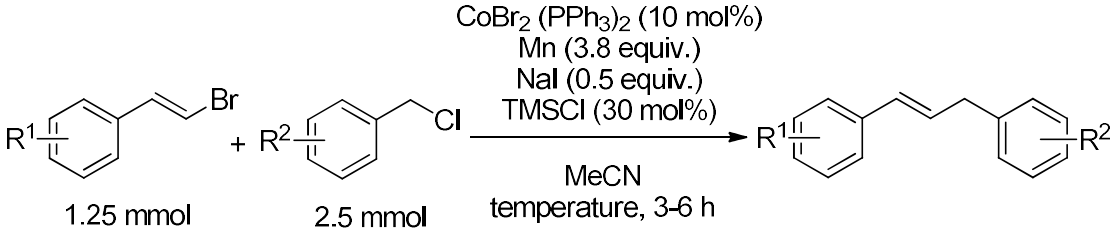
				6kc	
13	2-indene (4l)	2-OMe (5b)	0 °C – r.t	 6lb	77
[a] yield calculated by NMR with mesitylene as internal standard.					

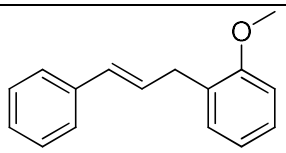
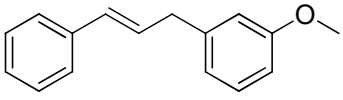
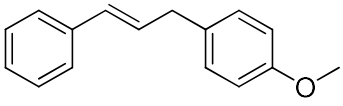
II-2-2 Scope of benzyl bromides

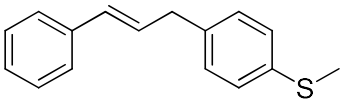
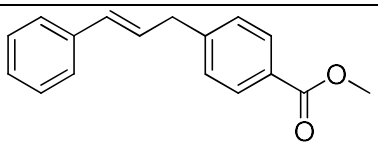
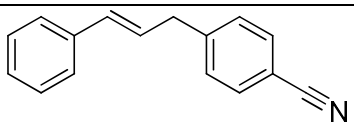
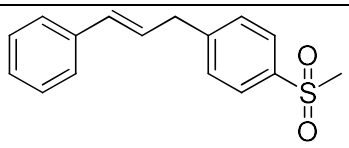
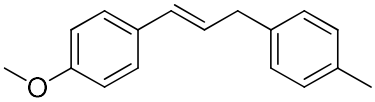
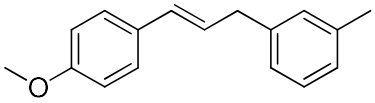
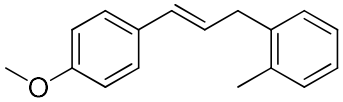
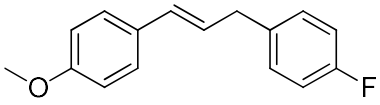
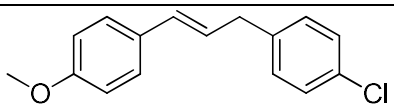
A variety of functional groups on the side of benzyl chloride were next investigated. Electron-donating groups and electron-withdrawing groups were well tolerated with good to excellent yields. Benzyl chlorides bearing methoxy group on *ortho*- and *meta*-position both afforded high yield (Table 3-3, entries 1-2). However, to our surprise, methoxy group on *para*- position largely affected the reactivity, which led to faster dimerization of benzylic chloride and low amount of desired production (Table 3-3, entry 3). We supposed that lower temperature (-20 °C) could decrease the reaction rate of dimerization, in fact, this modification did not help. Heating to 50 °C, which was assumed to make the cross-coupling more competitive, also failed to increase the yield. Some other trials, such as decreasing the catalyst loading and changing the solvent, had no positive influence. A similar result was observed when using *p*-thiomethyl substituted benzyl chloride (Table 3-3, entry 4). In reverse, the reaction was successfully carried out with benzyl chloride bearing methyl group on *para*-position as well as *meta*- and *ortho*- positions (Table 3-3, entries 8-10). Moreover, halogen substituted benzyl chlorides were well coupled with vinyl bromide (Table 3-3, entry 11-13). It is noteworthy that vinyl group was well tolerated without polymerization (Table 3-3, entry 15), which was a problem when we conducted alkyl-alkyl homocoupling.[47b] Besides, 2-(chloromethyl)naphthalene proceeded the reaction with good yield (Table 3-3, entry 16). Like functionalized styrenyl bromides, heating to 50 °C was necessary when benzyl chlorides bearing electron-withdrawing groups such as ester, cyano, trifluoromethyl and methylsulfonyl group were employed, however, excellent yields were obtained (Table 3-3, entry 5-7, 14). Too strong

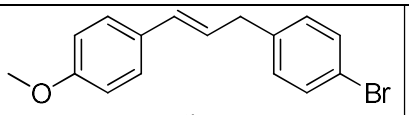
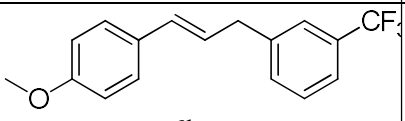
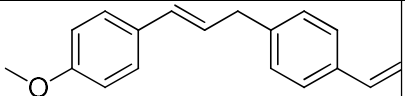
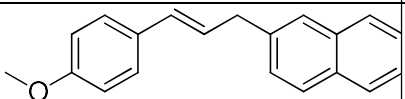
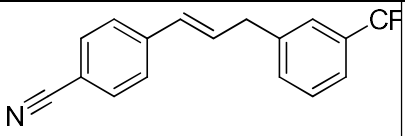
electron-withdrawing group such as nitro group could not be tolerated with only starting material left unconsumed. In addition, carboxy acid group did not react probably owing to the reactive proton. When we used (*E*)-4-(2-bromovinyl)benzonitrile and 3-trifluorobenzyl chloride to undergo a more challenging cross-coupling, the desired product was obtained with moderate yield (Table 3-3, entry 17). The cross-coupling of secondary benzyl chloride and β-bromostyrene was examined. Surprisingly, only dimer of β-bromostyrene was detected while secondary benzyl chloride kept intact. Series of modification of conditions was applied to improve the yield, including using DMF as solvent instead of acetonitrile, TFA instead of TMSCl, heating to 50 °C, adding pyridine (see experimental part). Finally, only moderate yield of 40% was obtained with TFA as the activation reagent and pyridine as a co-solvent. We also tried alkyl substituted vinyl bromides such as 1-bromo-2-methyl-1-propene, however, no cross-coupling products were deteted while the starting materials were all consumed.

Table 3-3. Scope of benzyl chlorides



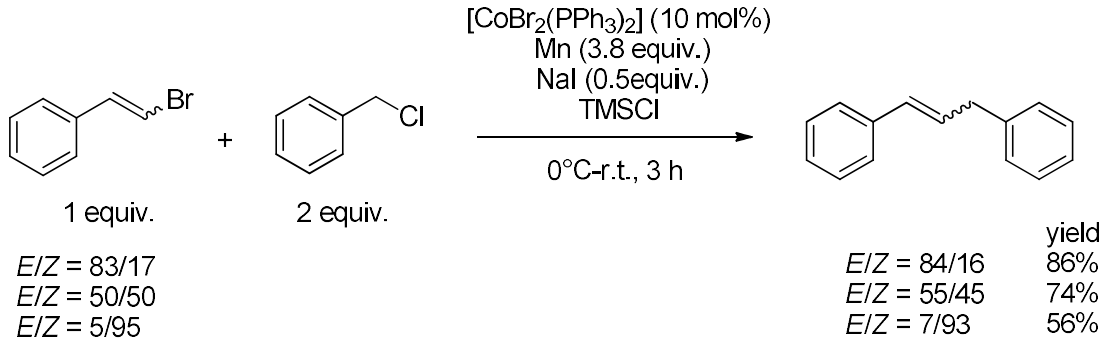
Entry	R^1	R^2	temperature	product	yield (%)
1	H (4a)	2-OMe (5b)	r.t.	 6ab	80
2	H (4a)	3-OMe (5c)	0 °C - r.t.	 6ac	77
3	H (4a)	4-OMe (5d)	r.t.		37

				6ad	
4	H (4a)	4-SMe (5e)	0 °C - r.t.	 6ae	40
5	H (4a)	4-CO_2Me (5f)	50 °C	 6af	65
6	H (4a)	4-CN (5g)	50 °C	 6ag	73
7	H (4a)	4-SO_2Me (5h)	50 °C	 6ah	90
8	4-OMe (4b)	4-Me (5i)	0 °C - r.t.	 6bi	73
9	4-OMe (4b)	3-Me (5j)	50 °C	 6bj	97
10	4-OMe (4b)	2-Me (5k)	0 °C - r.t.	 6bk	79
11	4-OMe (4b)	4-F (5l)	r.t.	 6bl	61
12	4-OMe (4b)	4-Cl (5m)	0 °C - r.t.	 6bm	63

13	4-OMe (4b)	4-Br (5n)	0 °C - r.t.	 6bn	67
14	4-OMe (4b)	3-CF_3 (5o)	50 °C	 6bo	77
15	4-OMe (4b)	4-vinyl (5p)	0 °C - r.t.	 6bp	77
16	4-OMe (4b)	2-naphthyl (5q)	r.t.	 6bq	71
17	4-CN (1g)	3-CF_3 (5r)	50 °C	 6gr	39

II-3 Stereochemical study

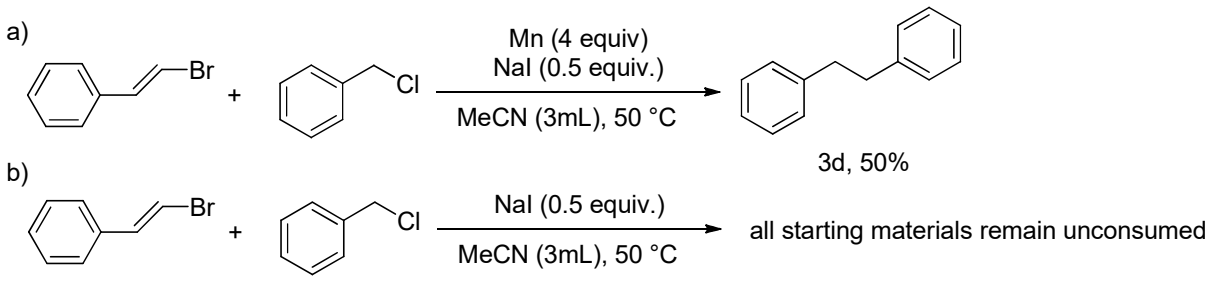
To probe the stereospecificity or stereoselectivity of the method, several experiments were conducted with *Z*/*E*-β-bromostyrene coupling with benzyl chloride. The results showed that the corresponding products had the same configuration as the starting reagents (Scheme 3-29). Therefore, it suggests that the reaction occurs with the retention of the carbon-carbon double bond configuration. It implies that no single electron transfer process is occurred with vinyl bromides. Furthermore, the lower ratio of *E*/*Z* afforded lower overall yields of cross-coupling product. This remark implied that *E*-β-bromostyrene reacted faster than the *Z*-isomer.



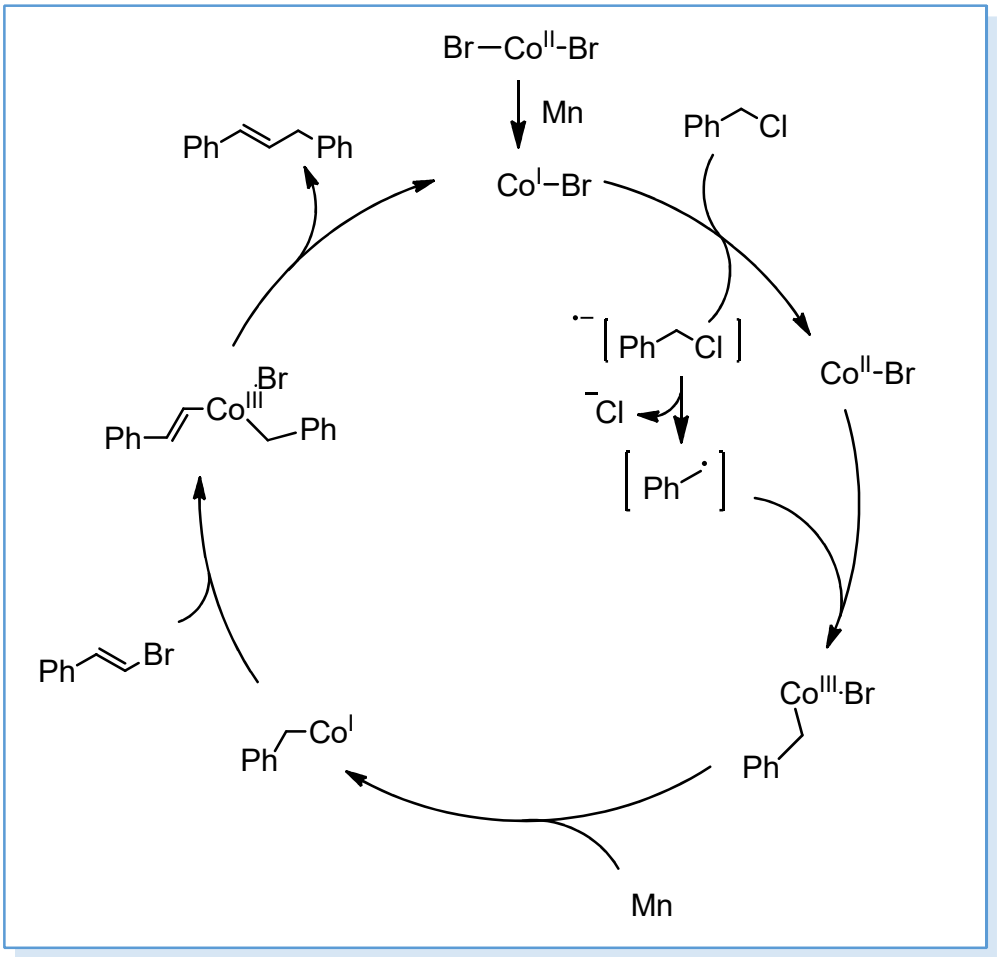
Scheme 3-29 Stereochemical studies

II-4 Mechanistic investigations

In this reaction, 4-vinylbenzyl chloride could react affording high yield, while it could not undergo a benzyl-benzyl homocoupling as previously described in chapter 2.[47b] Nevertheless, a radical intermediate could not be ruled out. With the addition of TEMPO which is a free radical scavenger, the reaction was completely inhibited. It indicated that a single electron transfer (SET) process may occur with benzyl chlorides. In addition, the same reaction was conducted without cobalt catalyst under the optimized reaction conditions. After three days, only dimer of benzyl chloride was detected while β-bromostyrene did not react (Scheme 3-30-a). Therefore, cobalt catalyst was necessary in this method. We also wondered the role of sodium iodide. Without cobalt and manganese, sodium iodide did not undergo a simple Finkelstein-type reaction since no iodostyrene or benzyl iodide was generated in the medium (Scheme 3-30-b). According to the result and general transition metal catalytic mechanism, with taken the stereochemistry into account, a mechanism was proposed as follows (Scheme 3-31). First Co(II) was reduced by Mn to generate Co(I), which undergoes an oxidative addition with vinyl bromide to form a Co(III) complex, followed by another reduction by Mn. A single electron transfer process from Co(I) to benzyl chloride resulted in a benzyl radical. Subsequent radical recombination delivered a Co(II) complex, which is then reduced by Mn. The desired product is formed as well as the generation of Co(I) after the final reductive elimination. Here we proposed that sodium iodide could facilitate the reductive elimination of cobalt.



Scheme 30 a) necessity of cobalt catalyst; b) investigation of sodium iodide



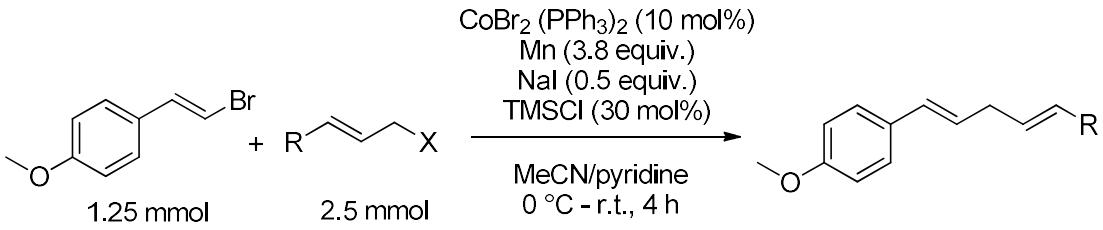
Scheme 3-31 Proposed mechanism

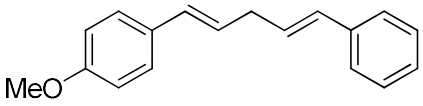
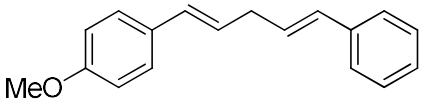
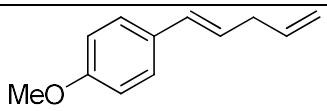
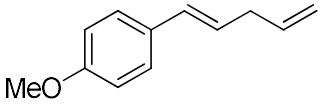
II-5 Extension of this method

II-5-1 Cross-coupling between vinyl halides and allyl halides

In some of the previous work for vinyl-benzyl cross-coupling, allylic halides were also chosen as the coupling partners with the same vinyl reagents under the same reaction condition. Thus, we expected to expand this method to vinyl-allyl cross-coupling using allylic halides. We employed cinnamyl chloride to couple with 4-(2-bromovinyl)anisole under the same reaction condition and obtained the desired product in 32% yield (not shown). With pyridine, the yield was increased to 48% (Table 3-4, entry 1). Allyl chloride was even less reactive, affording only 29% yield (Table 3-4, entry 3). Using cinnamyl bromide or allyl bromide, only low to moderate yields were obtained (Table 3-4, entry 2, 4).

Table 3-4. Scope of vinyl bromides

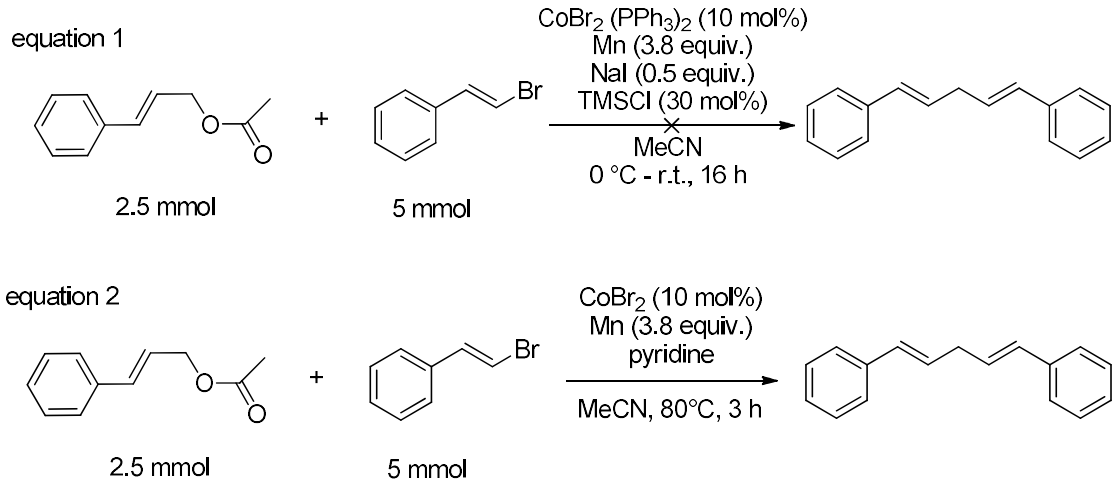


Entry	R	X	product	yield (%)
1	Ph	Cl	 7a	48
2	Ph	Br	 7a	30
3	H	Cl	 7b	29
4	H	Br	 7b	45

II-5-2 Cross-coupling between vinyl halides and allyl acetates

Cinnamyl acetate was also chosen as a coupling partner with β-bromostyrene. Under the same condition, no reaction occurred (Table 3-5, equation 1). Since our group has already developed an allylic-alkyl cross-coupling using a Co/Mn/pyridine system, we next used that system to conduct this reaction (Table 3-5, equation 2). To our delight, it delivered a moderate yield (Table 3-5, entry 1). Increasing the amount of pyridine to 1 mL had a positive effect, while 2 mL highly decreased the yield (Table 3-5, entries 2-3). Moreover, lower or higher temperature led to a low yield (Table 3-5, entries 4-5). Decreasing the catalyst loading had a negative effect on the cross-coupling (Table 3-5, entry 6). However, 15 mol% did not give a higher yield (Table 3-5, entry 7). Then different pyridine derivatives were examined. With 2-picoline, which has more electron density on nitrogen, was less effective than pyridine (Table 3-5, entry 8). On the other hand, 2-fluoropyridine did not show advantages over pyridine (Table 3-5, entry 9).

Table 3-5 : optimization of reaction conditions



Entry	Amount of catalyst	Bromostyrene : allyl acetate	Temperature	pyridine	GC yield
1	10%	2 : 1	80	0.5 mL	55
2	10%	2 : 1	80	1 mL	64
3	10%	2 : 1	80	2 mL	25

4	10%	2 : 1	60	1 mL	12
5	10%	2 : 1	100	1 mL	39
6	6%	2 : 1	80	1 mL	31
7	15%	2 : 1	80	1 mL	64
8	10%	2 : 1	80	2-picoline 1 mL	38
9	10%	2 : 1	80	2-fluoropyridine 1 mL	56

a: using dodecane as internal standard

A screen of ligands was displayed after preliminary optimization (Table 3-6). With PPh_3, the reaction rate was increased yet affording a lower yield (Table 3-6, entry 2). Bidentate phosphine ligand dppe almost inhibited the cross-coupling (Table 3-6, entry 3). 1,3,5-Triaza-7-phosphaadamantane (PTA), a combined phosphine and nitrogen ligand, decreased the yield (Table 3-6, entry 4). When isoquinoline was employed, we obtained a slightly higher yield (Table 3-6, entry 5), while an analogue quinoline afforded slightly lower yield (Table 3-6, entry 6). Another monodentate nitrogen ligand, acridine, had a negative effect (Table 3-6, entry 7). Bidentate nitrogen ligand, such as 1,10-phenantroline and biquinoline, gave decreasing yields (Table 3-6, entries 8-9). After these optimizations of conditions, we still did not obtain an excellent yield. Further modification is in demand.

Table 3-6 : Effect of ligands

Entry	**catalyst**	**ligand**	**pyridine**	**GC yield**
1	$CoBr_2$	/	1 mL	64
2	$CoBr_2$	PPh_3	1 mL	49[a]
3	$CoBr_2$	dppe	1 mL	9

4	$CoBr_2$	PTA	1 mL	25
5	$CoBr_2$	isoquinoline	1 mL	67
6	$CoBr_2$	quinoline	1 mL	60
7	$CoBr_2$	acridine	1 mL	28
8	$CoBr_2$(phen)		1 mL	28
9	$CoBr_2$	biquinoline	1 mL	27

a: reaction time 1.5 h

III Conclusions and perspectives

In conclusion, a novel and efficient method of vinyl-benzyl reductive cross-coupling using cobalt as a catalyst has been developed. It is simply operated and environmentally friendly. A broad scope of substrates couples efficiently under very mild conditions affording moderate to excellent yields. Both electron-donating and electron-withdrawing groups on both vinyl bromides and benzyl chlorides are well tolerated, though sometimes heating to 50 °C is necessary. Furthermore, both *Z*- and *E*- isomers can be utilized with the retention of carbon-carbon double bond configuration. A radical chain mechanism is ruled out since the reaction proceeds well in the presence of radical scavenger TEMPO.

Nevertheless, as described before, several problems still remain to be solved. First, this method does not tolerate secondary benzyl chlorides well, only moderate yield was obtained so far. Further optimization should be done such as different ligands and additives. In addition, the enantiochemistry should be investigated and a chiral ligand might be useful to afford enantioselectivity. Second, the mechanism is still not clear. Particularly, the role of sodium iodide and TMSCl needs to be investigations with more control reactions or some useful techniques to analyse the intermediates. Third, it is intriguing to develop a vinyl-allyl cross-coupling, which is seldom reported. Allylic halides or acetates have been used as coupling partners and a couple of initial results are obtained with moderate yields at the best. We should pursue in this direction. Besides, some other leaving groups might be tried such as amides and tosylates.

Chapter 4 Cobalt-Catalyzed Aryl C-H Activation with Arylzinc Reagents

I Introduction

In recent years, remarkable progress for C-H functionalization has been achieved; thereby a variety of C-C and C-X bond formation via unreactive C-H cleavage has been established.[194] Among those methods, most of them rely on precious late transition metal catalysts such as Pd,[195] Rh,[196] Ru[197], while cost-efficient early transition metals also have the property to allow C-H activation such as Ni,[198] Fe[199] and Cu.[200] Cobalt, as an environmental benign relatively earth-abundant metal, plays an important role on series of catalytic reactions.[201] In the past few years, it has also attracted interest to undertake C-H activation and considerable advances have been obtained. Here we summarize the development of C-H activation catalyzed by cobalt and try to design a possible approach for C-H activation based on our previous work.

I-1 Early exploration

[194] a) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879-2932; b) C. G. Jia, T. Kitamura, Y. Fujiwara, *Chem. Soc. Rev.* **2001**, *34*, 633-639; c) V. Ritleng, C. Sirlin, M. Preffer, *Chem. Rev.* **2002**, *102*, 1731-1769; d) L. Ackerman, R. Vincente, A. R. Kapdi, *Angew. Chem., Int. Ed.* **2009**, *48*, 9792-9826; e) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315-1345; f) J. Wencel-Delord, T. Droge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740-4761; g) J. Yamaguchi, A. D. Yamagushi, K. Itami, *Angew. Chem., Int. Ed.* **2012**, *51*, 8960-9009.

[195] a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147-1169; b) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2009**, *48*, 5094-5115; c) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074-1086; d) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936-946; e) B.-J. Li, S.-D. Yang, Z.-J. Shi, *synlett* **2008**, *7*, 949-957.

[196] a) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624-655; b) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3654-3678; c) T. Sotoh, M. Miura, *Chem. Eur. J.* **2010**, *37*, 11212-11222; d) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013-1025; e) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814-825.

[197] a) T. Naota, H. Takaya, S-I. Murahashi, *Chem. Rev.* **1998**, *98*, 2599-2660; b) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879-5918; c) M. Seki, *Org. Process Res. Dev.* **2016**, *20*, 867–877; d) L. Ackermann, R. Vicente, *Top. Curr. Chem.* **2010**, *292*, 211-229.

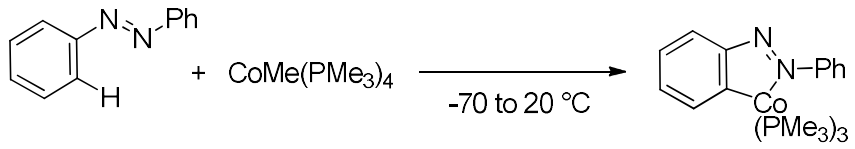
[198] a) J. J. Mousseau, A. B. Charette, *Acc. Chem. Res.* **2013**, *46*, 412-424; b) M. S. Khan, A. Haque, M. K. Al-Suti, P. R. Raithby, *J. Organometallic Chem.* **2015**, *793*, 114-133; c) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299-309.

[199] a) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem., Int. Ed.* **2009**, *48*, 9792-9826; b) A. A. Kulkarni, O. Daugulis, *Synthesis* **2009**, *24*, 4087-4109.

[200] a) X.-X. Guo, D.-W. Gu, Z. Xu, W. Zhang, *Chem. Rev.* **2015**, *115*, 1622-1651; b) J. Liu, G. Chen, Z. Tan, *Adv. Syn. Catal.* **2016**, *358*, 1174-1194; c) W.-H. Rao, B.-F. Shi, *Org. Chem. Front.* **2016**, 10.1039/C6QO00156D.

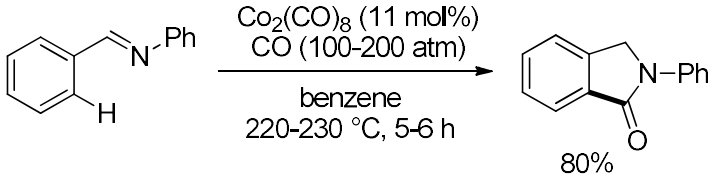
[201] a) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435-1462; b) W. Hess, J. Treutwein, G. Hilt, *Synthesis-Stuttgart* **2008**, 3537-3562; c) M. Jeganmohan, C.-H. Cheng, *Chem. Eur. J.* **2008**, *14*, 10876-10886; d) C. E. I. Knappke, S. Grupe, D. Gartner, M. Corpet, C. Gosmini, *Chem. Eur. J.* **2014**, *20*, 6828-6842; e) Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208-1219; f) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498-525.

In 1993, Klein and coworkers synthesized a cobalt-azobenzene complex by using stoichiometric $CoMe(PMe_3)_4$ to insert into the *ortho* C-H bond of azobenzene at low temperature(Scheme 4-1).[202] Later, series of azobenzenes bearing different directing groups such as nitrogen,[203] oxygen,[204] sulfur[205] and phosphorus[206] groups were examined to undergo a similar procedure. These cyclocobaltations indicated the possibility to undergo cobalt-mediated C-H activation in the presence of a directing group.



Scheme 4-1 Cyclocobaltation compounds using $CoMe(PMe_3)_4$

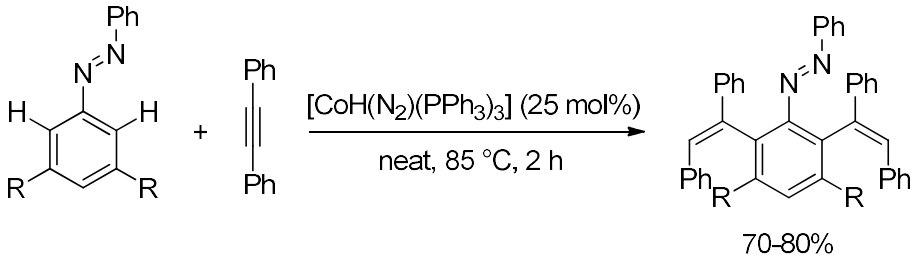
First example of cobalt-catalyzed C-H activation was revealed before the discovery stoichiometric cyclocobaltation. In 1955, Murahashi disclosed a carbonylative cyclization of azobenzene with $Co_2(CO)_8$ (Scheme 4-2).[207] Later a similar procedure was applied to indazolones.[208] Both of the reactions required quite harsh conditions, though, it still implied the broader potential development of cobalt-catalyzed C-H activation.



Scheme 4-2 Cobalt-catalyzed carboxylative cyclization of azobenzene

[202] H. F. Klein, M. Helwig, U. Koch, U. Florke, H. J. Z. Haupt,.*Naturforsch., B: J. Chem. Sci.* **1993**, *48*, 788-784.
[203] H.-F Klein, S. Camadanli, R. Beck, D. Leukel, U. Flo rke, *Angew. Chem., Int. Ed.* **2005**, *44*, 975–977.
[204] S. Camadanli, R. Beck, U. Florke, H.-F. Klein, *Dalton. Trans.* **2008**, 5701–5704.
[205] R. Beck, H. Sun, X. Li, S. Camadanli, H.-F. Klein, *Eur. J. Inorg. Chem.* **2008**, 3253–3257.
[206] a) H.-F. Klein, S. Schneider, M. He, U. Floerke, H.-J. Haupt, *Eur. J. Inorg. Chem.* **2000**, 2295–2301.
b) H.-F. Klein, R. Beck, U. Flo rke, H.-J. Haupt, *Eur. J. Inorg. Chem.* **2003**, 1380–1387.
[207] S. Murahashi, *J. Am. Chem. Soc.* **1955**, *77*, 6403-6404.
[208] S. Murahashi, S. J. Horiie, *J. Am. Chem. Soc.* **1956**, *78*, 4816-4817.

However, the next cobalt-catalyzed C-H activation was displayed until 1994 by Kisch and coworkers, and consisted of a hydroarylation of alkynes using azobene derivatives (Scheme 4-3). [209] Here the reactive catalyst was generated via substitution of N_2 ligand by nitrogen on the substrates. Moreover, it turned out that $CoH(H_2)(PMe_3)_3$ was also an effective catalyst.

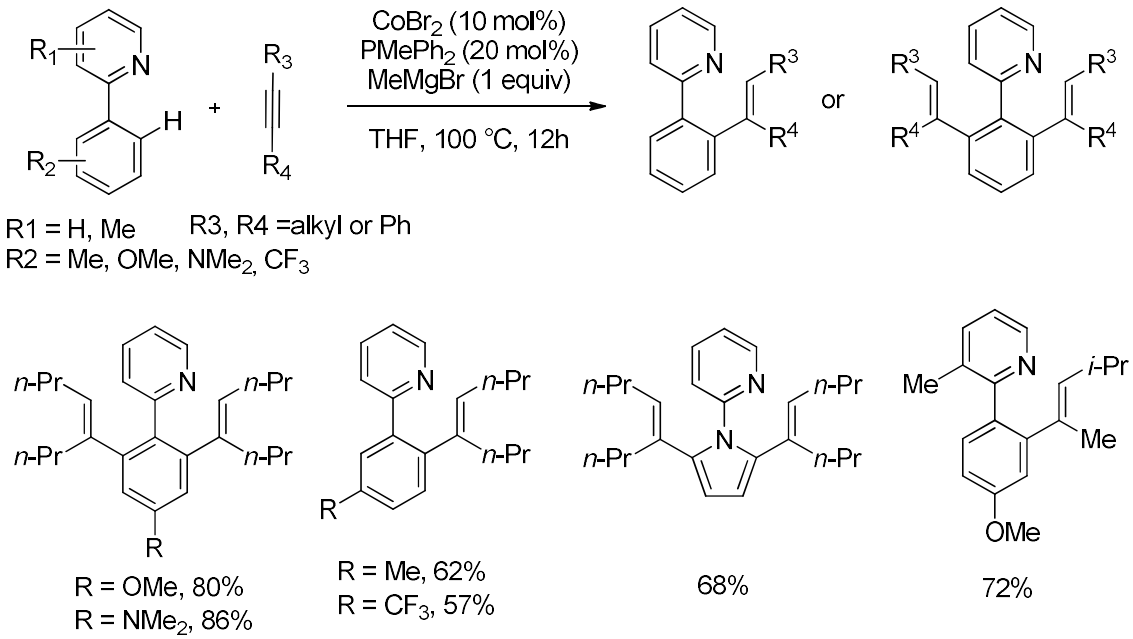


Scheme 4-3 Cobalt-catalyzed hydroarylation of alkynes

I-2 Hydroarylation of alkynes

Building upon the creative finding, Yoshikai and coworkers have gained outstanding achievement about cobalt-catalyzed C-H bond activation since 2010. Thus, Yoshikai and coworkers employed a ternary catalytic system which consisted of a simple $CoBr_2$ as a precatalyst, a phosphine ligand and stoichiometric Grignard reagents, to conduct a hydroarylation of alkynes with 2-arylpyridines (Scheme 4-4).[210] Several functional groups such as an electron-donating methoxy group and an electron-withdrawing trifluoromethyl group were examined affording good to excellent yields. The role of Grignard reagents was not clear now. The necessity of a larger amount (>40%) of Grignard reagents than required for reduction Co(II) to Co(0) suggested possible involvement of an organocobalt(0) species.

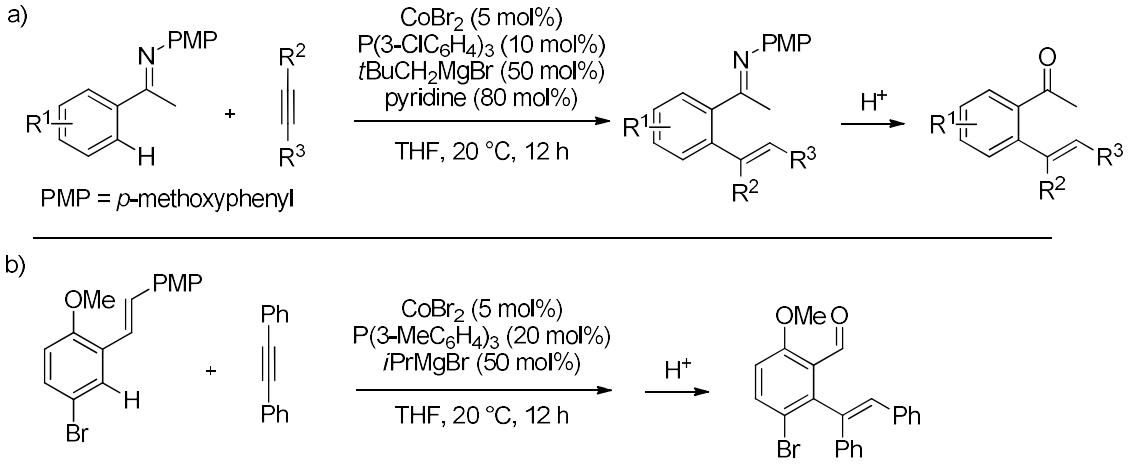
[209] G. Halbritter, F. Knoch, A. Wolski, H. Kisch, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1603-1605.
[210] K. Gao, P.-S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2010**, *132*, 7609-7612.



Scheme 4-4 Cobalt-catalyzed hydroarylation of alkynes with 2-arylpyridines

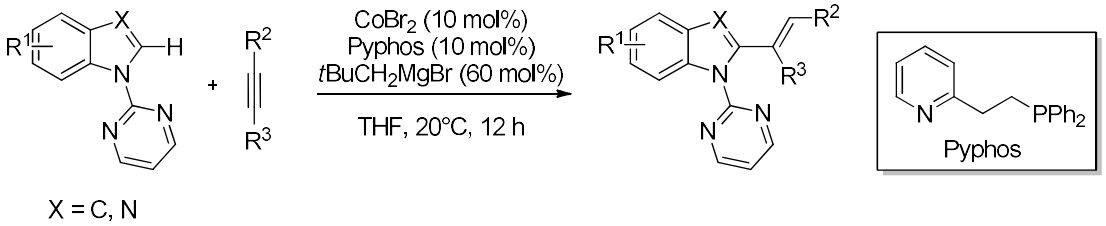
Aryl ketimines were disclosed to be applicable substrates for the addition of alkynes (Scheme 4-5-a).[211] A similar catalytic system was used with lower catalyst loading and less Grignard reagents at room temperature. In this reaction, pyridine was necessary. The ketimines bearing *meta*- methoxy, cyano, fluoro and chloro groups could be well tolerated, while bromo-substituted ketimines only afforded 20% yield. Notably, with unsymmetric alkynes, the addition proceeded with regioselectivity. Moreover, the imine directing group could be easily converted into ketone with acid, which may expand the application of this method. Nevertheless, aldimines were not well performed under the same conditions, herein re-optimization provided the access to the C-H activation of aldimines using P(3-MePh)$_3$ and *i*-PrMgBr without pyridine (Scheme 4-5-b).[212]

[211] P.-S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2011**, *133*, 17283-17295.
[212] T. Yamakawa, N. Yoshikai, *Tetrahedron* **2013**, *69*, 4459-4465.



Scheme 4-5 Cobalt-catalyzed hydroarylation of alkynes with aryl ketimines and aldimines

The catalytic system was further investigated (Scheme 4-6)[213] based on the findings of Ackerman and coworkers about C-H functionalization using 2-pyrimidyl group as a removable directing group.[214] As the previous work, the key to success was the careful choice of a phosphine ligand and a Grignard reagent. This work provided with a complementary scope of cobalt-catalyzed hydroarylation of alkynes.



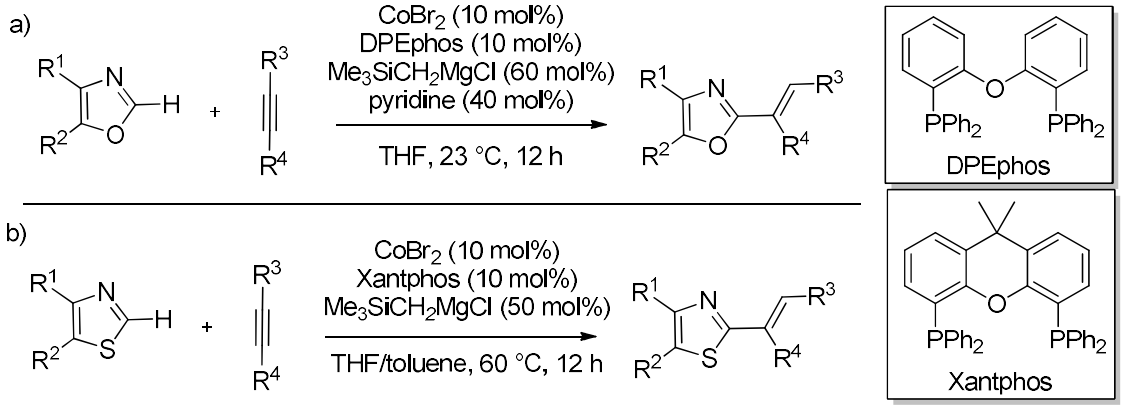
Scheme 4-6 Cobalt-catalyzed hydroarylation of alkynes with indoles and benzimidazoles

In addition, the addition of alkynes could be achieved for azoles and thiazoles without directing groups after modification of ligands and Grignard reagents (Scheme 4-7).[215] When R^1 or R^2 contained an aromatic ring, the site selectivity of C-H cleavage depended on the C-H acidities, and Me_3SiCH_2MgCl allowed the *syn*-addition of azoles and thioazoles onto internal alkynes.

[213] Z. Ding, N. Yoshikai, *Angew. Chem., Int. Ed.* **2012**, *51*, 4698-4701.

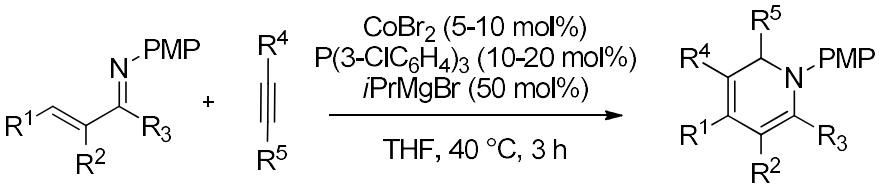
[214] L. Ackermann, A.V. Lygin, *Org. Lett.* **2012**, *14*, 764-767.

[215] a) Z. Ding, N. Yoshikai, *Org. Lett.* **2010**, *12*, 4180-4183; b) Z. Ding, N. Yoshikai, *Synthesis* **2011**, 2561-2566.



Scheme 4-7 Cobalt-catalyzed hydroarylation of alkynes with azoles and thioazoles

Besides aromatic substrates, the hydroarylative procedure also occurred with olefins via vinylic C-H activation, followed by an intramolecular annulation of *α,β*-unsaturated imines,[216] to form dihydropyridine derivatives (Scheme 4-8).[217]

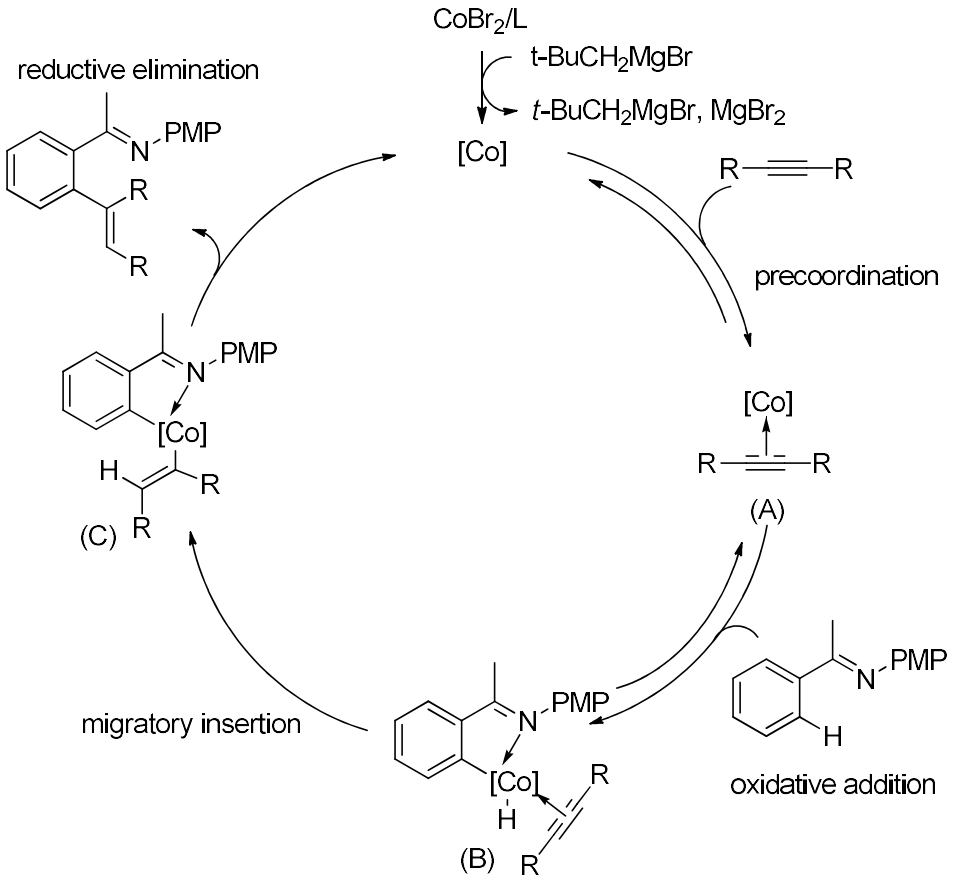


Scheme 4-8 Cobalt-catalyzed annulation of *α,β*-unsaturated imines with alkynes

Yoshikai *et al.* proposed a catalytic cycle as follows (Scheme 4-9). It involved (1) reduction of cobalt(II) precatalyst by Grignard reagent to generate a low-valent cobalt species, (2) precoordination of alkyne to the low-valent active cobalt to form a cobalt complex (A), (3) oxidative addition of ortho- C-H bond followed by migratory insertion of alkyne into the Co-H bond to generate an intermediate (C), and (4) reductive elimination to afford the desired product and regenerate the active low-valent cobalt. Based on the results about kinetic isotope effect (KIE), the C-H activation step was assumed to be the turnover-limiting step.

[216] a) D. A. Colby, R.G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645-3651; b) K. Parthasarathy, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2008**, *10*, 325-328.

[217] T. Yamakawa, N. Yoshikai, *Org. Lett.* **2013**, *15*, 196-199.



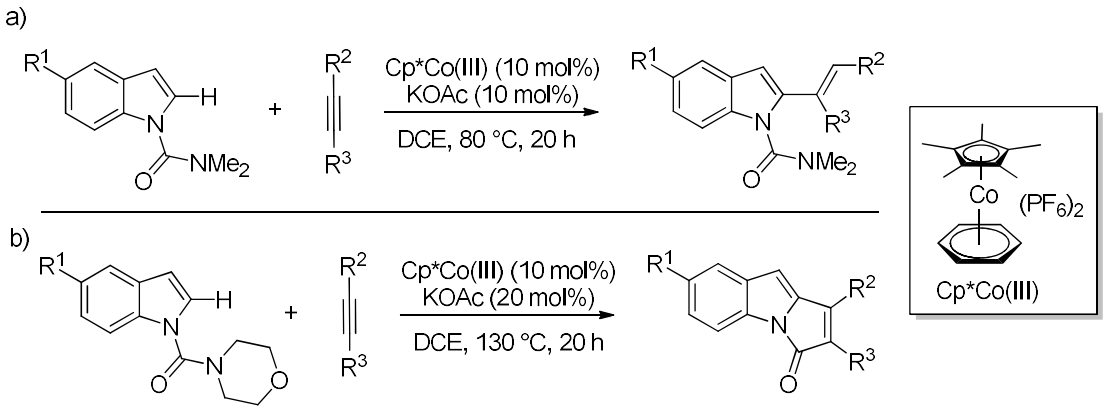
Scheme 4-9 Proposed mechanism for cobalt-catalyzed hydroarylation of alkynes via C-H activation

Inspired by the rhodium-catalyzed C-H activation,[218] in 2014, Matsunaga/Kanai and coworkers developed a high valent cobalt-catalyzed hydroarylation via C-H activation (Scheme 4-10).[219] They employed a Cp^*Co^{III} complex[220] as catalyst with catalytic amount of KOAc to promote the reaction. Both electron-donating and electron-withdrawing groups afforded excellent yields. However, a drawback was the low regioselectivity when sterically pure alkynes were used. It is intrigued that the intermediate after hydroarylation of alkynes could lead to an annulation to form pyrroloindolones without additional steps (Scheme 4-10-b). In the hydroarylation/annulations domino reaction, higher temperature and more KOAc were required.

[218] a) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212; b) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31;(c) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; d) S. Chiba, *Chem. Lett.* **2012**, *41*, 1554.

[219] H.Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2014**, *136*, 5424−5431

[220] T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem., Int. Ed.* **2013**, *52*, 2207-2211.



Scheme 4-10 Cp*Co^{III}-catalyzed hydroarylation and annulations of alkynes

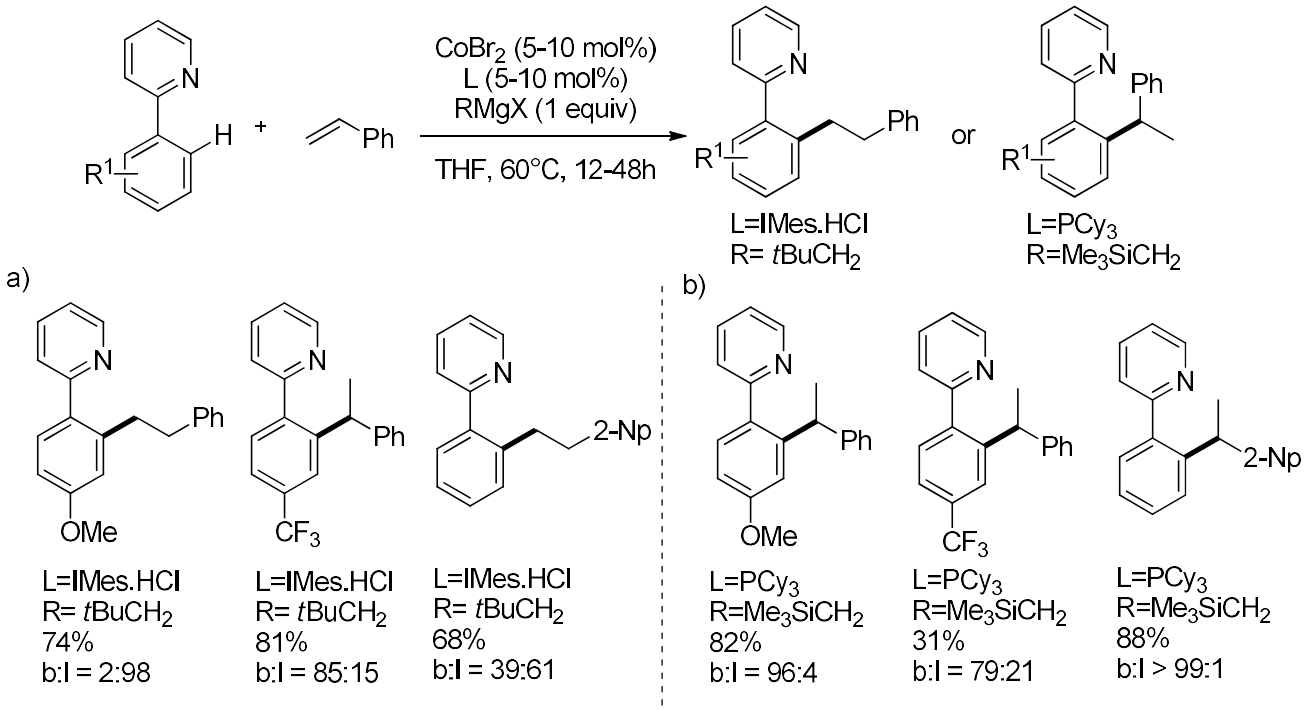
Later, a variety of such hydroarylation/annulation reactions via C-H bond activation was developed, using amides,[221] sulfonamides,[222] amidines,[223] nitrosoanilines,[224] phosphinic amides,[225] pyridines[226] and esters[227] as substrates, with a cobalt(III) catalyst or a cobalt(II) precatalyst/oxidant ($Mn(OAc)_3$, O_2) combination. In these catalytic systems, acetates were always required to promote the deprotonation.

I-3 Hydroarylation of alkenes

In the meantime of development of cobalt-catalyzed hydroarylation of alkynes, Yoshikai and coworkers also paid attention to analogous hydroarylation of more challenging olefins. They first chose 2-phenylpyridine and styrene as the starting materials (Scheme 4-11).[228] Employing different ligands and Grignard reagents, they obtained regiodivergent results. With a *N*-heteocyclic carbene (NHC) ligand IMes•HCl the reaction favored more linear addition than branched one, while a phosphine ligand led to more branched products than linear ones. Furthermore, the electron features of substrates also had effect on the regioselectivity of the reaction. With IMes•HCl and neo-pentylmagnesium, methoxy group substituted 2-

[221] a) L. Kong, S. Yu, X. Zhou, X. Li, *Org. Lett.* **2016**, *18*, 588-591; b) R. Mei, H. Wang, S. Warratz, S. A. Macgregor, L. Ackermann, *Chem. Eur. J.* **2016**, *22*, 6759-6763; c) G. Sicakumar, A. Vijeta, M. Jeganmohan, *Chem. Eur. J.* **2016**, *22*, 5899-5903.
[222] a) D. Kalsi, B. Sundaraju, *Org. Lett.* **2015**, *17*, 6118-6121; b) O. Planas, C. J. Whiteoak, A. Company, X. Ribas*, Adv. Synth. Catal.* **2015**, *357*, 4003-4012.
[223] J. Li, M. Tang, L. Zhang, X. Zheng, Z. Zhang, L. Ackermann, *Org. Lett.* **2016**, *18*, 2742-2745.
[224] Y. Liang, N. Jiao, *Angew. Chem., Int. Ed.* **2016**, *55*, 4035-4039.
[225] T. T. Nguyen, L. Grigorjeva, O. Daugulis, *ACS catal.* **2016**, *6*, 551-554.
[226] S. Prakash, K. Muralirajan, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2016**, *55*, 1844-1848.
[227] W. Yu, W. Zhang, Z. Liu, Y. Zhang, *Chem. Commun.* **2016**, *52*, 6837-6840.
[228] K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2011**, *133*, 400-402.

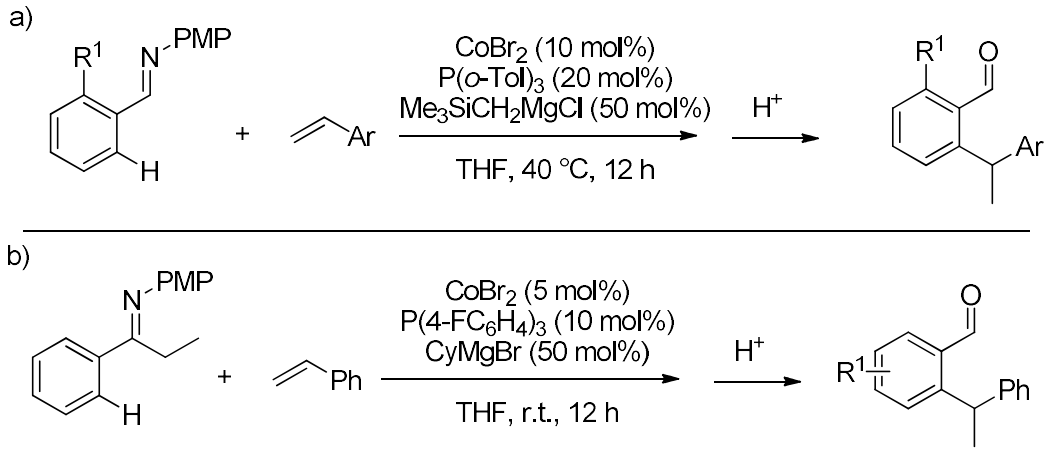
phenylpyridine afforded linear product but trifluoromethyl group tended to give more branched product (Scheme 4-11-a). In the same condition, 2-vinylnaphtalene just decreased the regioselectivity. Better regioselectivity was gained by the choice of phosphine ligand. Both Electron-donating groups and electron-withdrawing group gave much more branched products than linear ones, though trifuoromethyl group resulted in moderate yield (Scheme 4-11-b).



Scheme 4-11 Cobalt-catalyzed regiodivergent hydroarylation of styrenes

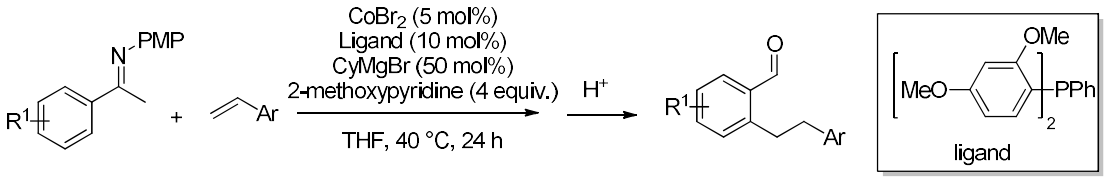
The branched-selective method was extended to aldimines using an analogous phosphine ligand (Scheme 4-12-a).[229] A variety of functionalized aldimines could couple with styrenes under mild conditions in good regioselectivity. It is noteworthy that a substituent on the *ortho*- position was necessary to achieve monoadditive product, otherwise, the reaction favored a dialkylation product. A similar catalytic system was applied to ketimines after changing the phosphine ligand and Grignard reagent (Scheme 4-12-b).[230] Interestingly, the dialkylation of arenes did not occur, possibly due to the increased steric bulk of ethyl group.

[229] P.-S. Lee, N. Yoshikai, *Angew. Chem., Int. Ed.* **2013**, *52*, 1240-1244.
[230] J. Dong, P.-S. Lee, N. Yoshikai, *Chem. Lett.* **2013**, *42*, 1140−1142.



Scheme 4-12 Cobalt-catalyzed branched-selective hydroarylation of styrenes with aldimines and ketimines

More recently, Yoshikai and coworkers developed a linear regioselective hydroarylation of styrenes through extensive tuning of elaborated phosphine ligands (Scheme 4-13).[231] 2-methoxypyridine served as Lewis base to accelerate the reaction. It is interesting that with one 2,4-dimethoxyphenyl group on phosphine, the regioselectivity was totally inversed. NHC ligand also afforded excellent linear selectivity; however, the catalytic reactivity was much lower. Nevertheless, in the exploration of scope of substrates, 2-vinylnaphthalene afforded to traces amount of products and no regioselectivity as before.[22] Moreover, they did not provided with the results of the ketimines bearing electron-withdrawing groups.

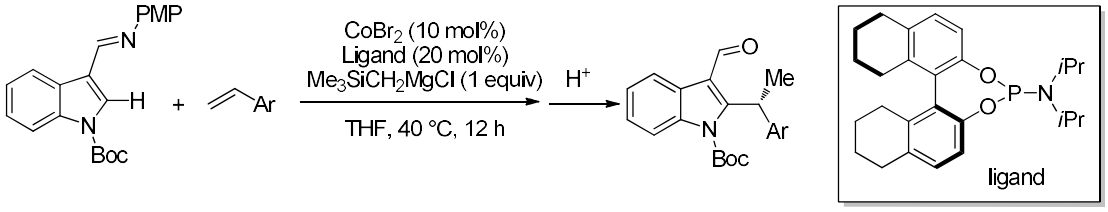


Scheme 4-13 Cobalt-catalyzed linear-selective hydroarylation of styrenes with ketimines

Subsequently, Yoshikai and coworkers reported the first enantioselective hydroarylation of styrenes with indoles using a chiral phosphoramidate ligand (Scheme 4-14).[232] Series of functionalized substrates were efficiently tolerated delivering branched products with good enantioselectivity. According to the deuterium experiments, it was suggested that the enantioselectivity was controlled by

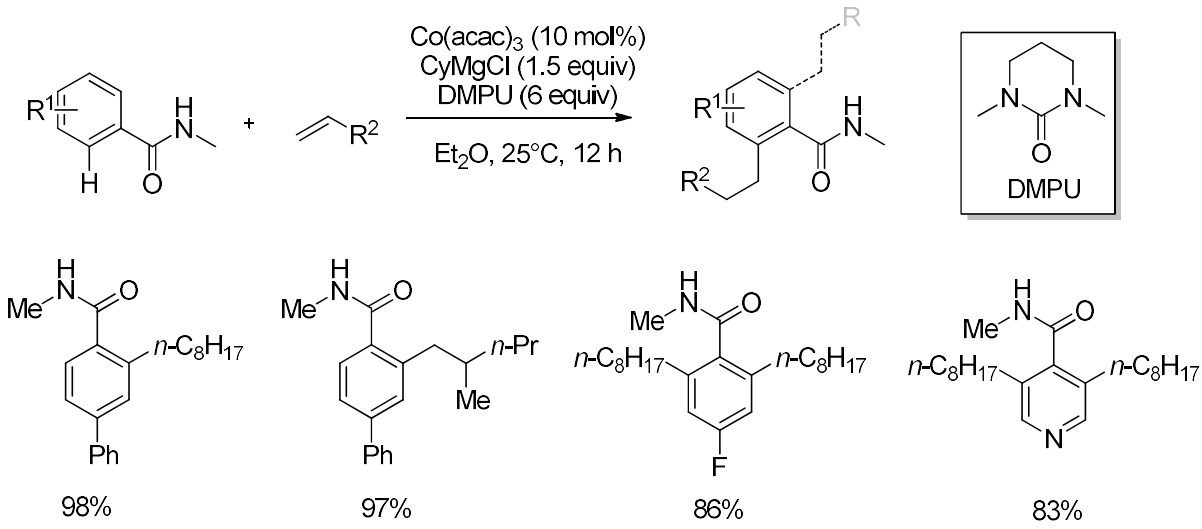
[231] W. Xu, N. Yoshikai, *Angew. Chem., Int. Ed.* **2014**, *53*, 14166−14170.
[232] P.-S. Lee, N. Yoshikai, *Org. Lett.* **2015**, *17*, 22-25.

both the styrene insertion and the C-C reductive elimination. Furthermore, the Boc group on *N*-position was proved to be essential to undergo this reaction.



Scheme 4-14 Cobalt-catalyzed enantioselective hydroarylation of styrenes indoles

Apart from styrenes, aliphatic alkenes were also employed in the cobalt-catalyzed hydroarylation. In 2011, Nakamura and coworkers utilized amides as directing groups to undergo a vinyl hydroarylation, using Grignard reagent and more polar solvent under mild conditions (Scheme 4-15).[233] DMPU was crucial for the reaction, and it may serve more than a ligand. Good tolerance of functional groups as well as different structures of olefins was displayed.

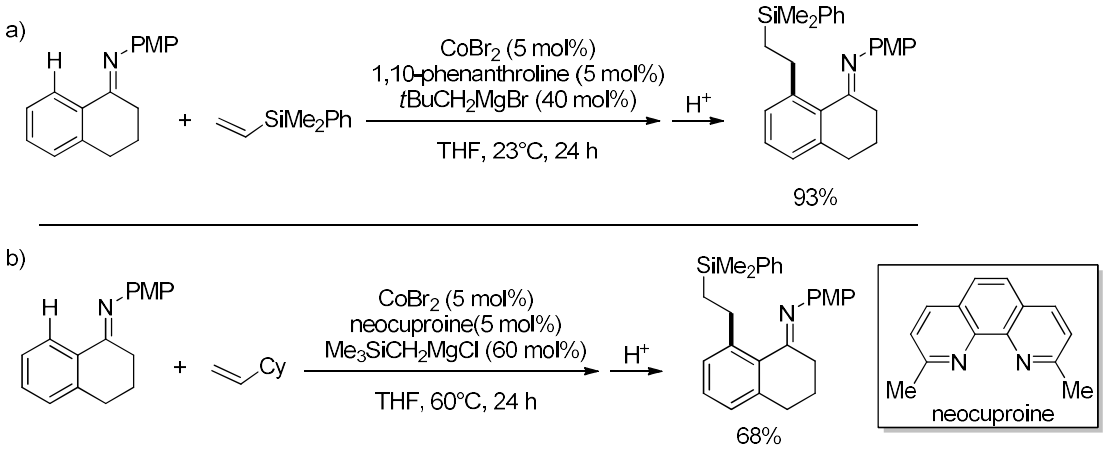


Scheme 4-15 Cobalt-catalyzed hydroarylation of alkenes

Yoshikai and coworkers also extended their catalytic system to vinylsilanes and aliphatic alkenes (Scheme 4-16).[234] The success resulted from judicious choice of ligand. Here, the cobalt-phosphine or cobalt-carbene was not effective, and was

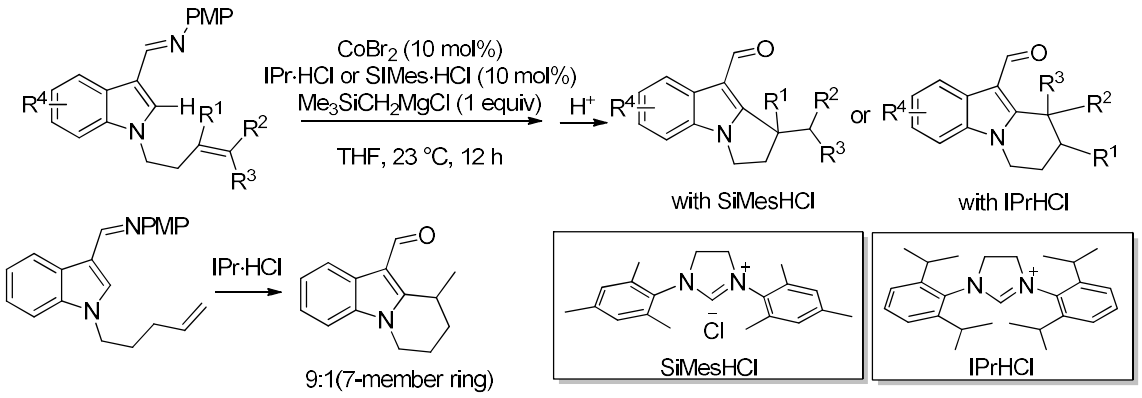
[233] L. Ilies, Q. Chen, X. Zeng, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 5221-5223.
[234] Gao, K.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6888−6892.

replaced by a bidentent phenanthroline-type ligand. Aliphatic alkenes required higher temperature than vinylsilanes (Scheme 4-16-b).



Scheme 4-16 Cobalt-catalyzed hydroarylation of vinylsilanes and aliphatic alkenes

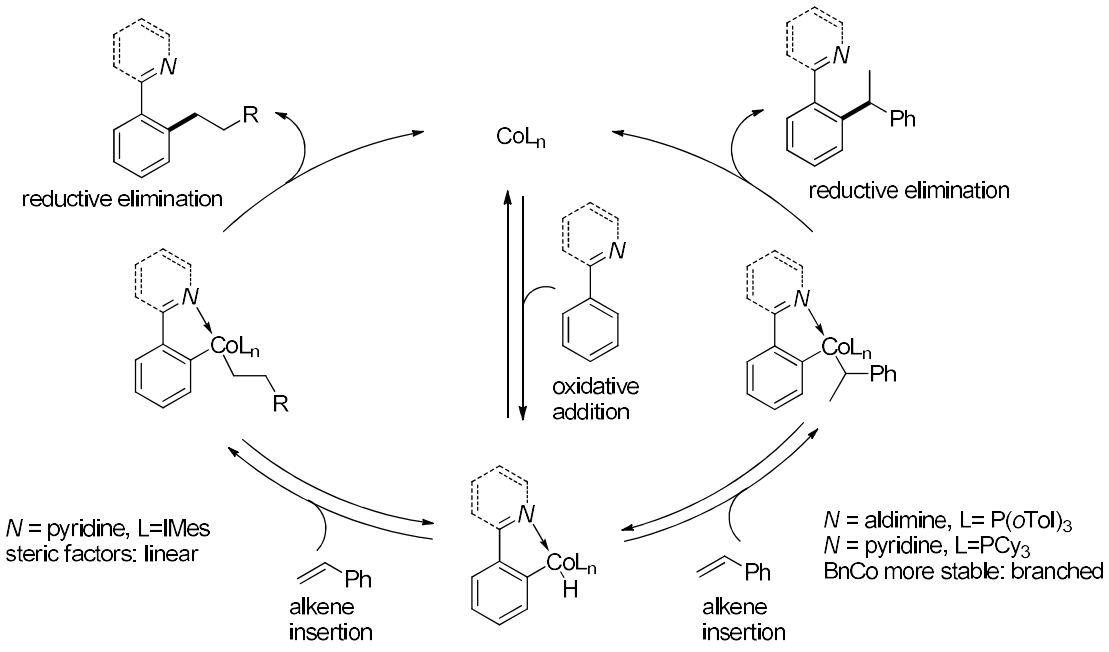
Further investigation of hydroarylation of alkenes was undertaken by the same group. The first example of an intramolecular cobalt-catalyzed hydroarylation of alkenes via C-H activation with indoles was demonstrated (Scheme 4-17).[235] The cobalt-NHC systems could promote regiodivergent cyclization via hydroarylation. While SiMes•HCl led to dihydropyrroloindoles, IPr•HCl afforded tetrahydropyridoindole isomers. Besides the steric properties of NHC ligands, the structure of alkene tethers also had effect on the regioselectivity. For example, a bis(homoallyl) group on the tether of indoles favored a six-member ring rather than seven-member, when IPr•HCl was used as ligand. This approach could tolerate various substrates, moreover, it also enabled the formation of a quaternary carbon center and a bicyclic [3.3.1]-moiety.



Scheme 4-17 Cobalt-catalyzed cyclization of indoles via intramolecular hydroarylation of alkenes

235

The deuterial experiments indicated that H/D exchange between the *ortho*- position of arenes and the olefinic C-H bond takes place prior to the C-C formation. Based on this finding and other observations, a simple mechanism was proposed as follows (Scheme 4-18).[236] A reversible oxidative addition of the *ortho*- C-H bond to low-valent cobalt occurred before an alkene insertion leading to a linear or branched intermediate. Next a reductive elimination afforded the hydroarylation product as well as the regeneration of active cobalt species.

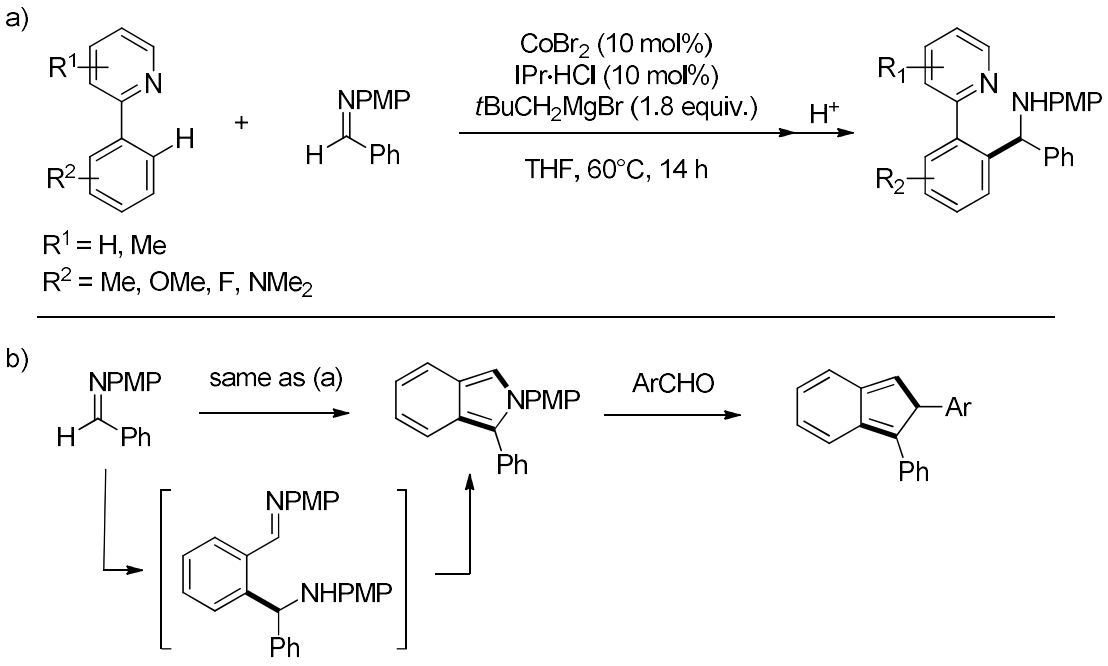


Scheme 4-18 Proposed mechanism of cobalt-catalyzed hydroarylation of alkenes

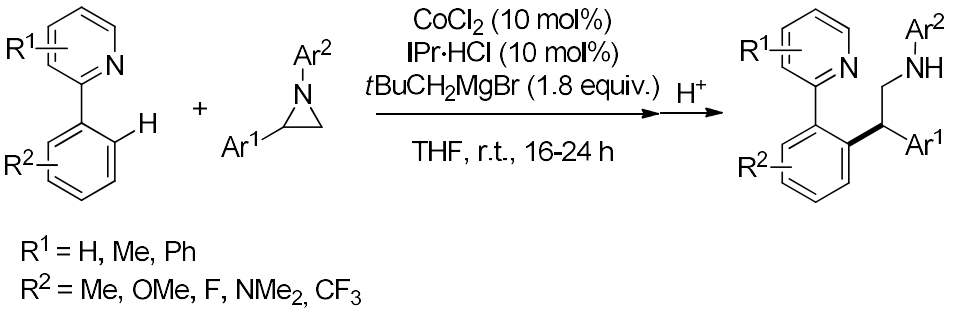
Various substrates for cobalt-catalyzed hydrarylation via C-H activation were displayed by Yoshikai's group such as aldimines[237] and aziridines.[238] The cobalt-IPr catalyst and *t*-BuCH_2MgBr were employed to yield hydroarylation of aldimines (Scheme 4-19-a). In this reaction more than stoichiometric amount of Grignard reagents was used to serve as a reducing reagent and a base. Interestingly, the same conditions could be applied to self-coupling of aldimines, affording a phenylisoindole product, which could be transferred into 2,3-diarylindenone derivatives by aldehydes (Scheme 4-19-b). By changing the precatalyst to $CoCl_2$ instead of $CoBr_2$, the catalytic was employed to aziridines (Scheme 4-20) under lower temperature. Nevertheless, the

[236] K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208-1219.
[237] K. Gao, N. Yoshikai, *Chem. Commun.* **2012**, *48*, 4305−4307.
[238] K. Gao, R. Paira, N. Yoshikai, *Adv. Synth. Catal.* **2014**, *356*, 1486−1490.

systems did not perform efficiently, only moderate to good yields were obtained for most substrates. Moreover, the method was sensitive to steric hindrance since substituted on *ortho*-position of phenyl ring or on the 3-position of pyridine ring gave no products.



Scheme 4-19 Cobalt-catalyzed hydroarylation of aldimines and self-coupling of aldimines



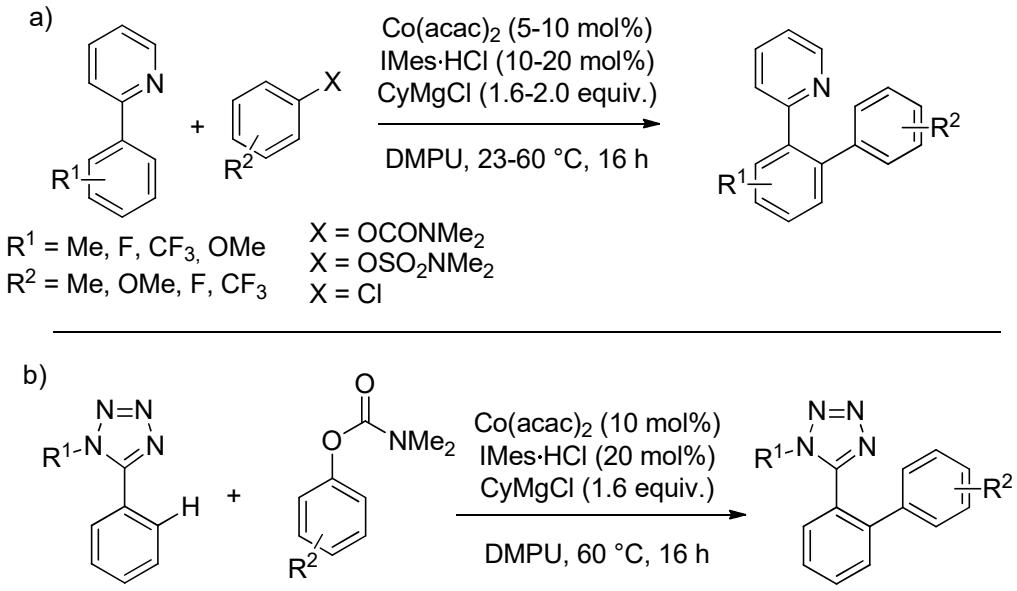
Scheme 4-20 Cobalt-catalyzed alkylation of 2-phenylpyridines with aziridines

I-4 C-H Arylation

Later than the development of cobalt-catalyzed addition reactions via C-H activation, arylation with aryl electrophiles were also disclosed. In 2012, Ackerman and Song reported the first example using a $Co(acac)_2$/NHC/RMgCl system (Scheme 4-21-a).[239] They chose aryl carbamates and sulfamades to couple with 2-phenylpyridines

[239] W. Song, L. Ackermann, *Angew. Chem., Int. Ed.* **2012**, *51*, 8251-8254.

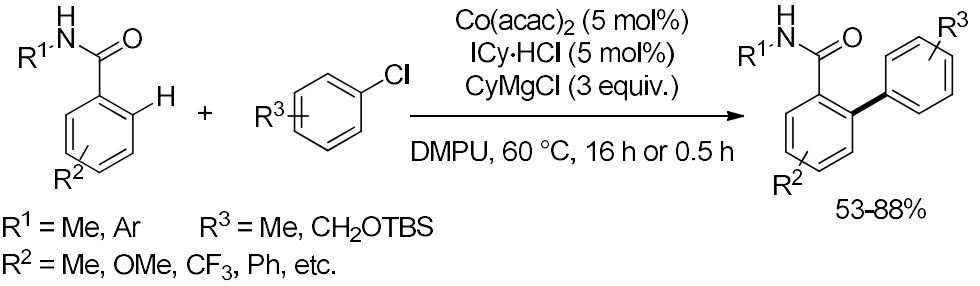
efficiently under mild conditions. The controlled experiments with TEMPO ruled out the radical chain mechanism. Later, the same group extended the scope of aryl electrophiles to aryl chlorides, which could even tolerate a broader scope of substrates.[240] Interestingly, with aryl chlorides, the arylation occurred at the more sterically hindered position when bearing a methoxy group on *meta*- postision of arene. Next, they found out that tetrazoles could be the directing group to undergo arylation with aryl carbamates under the same conditions (Scheme 4-21-b).[241]



Scheme 4-21 Cobalt-catalyzed arylation of 2-phenylpyridines with aryl carbamates, sulfamades and chlorides

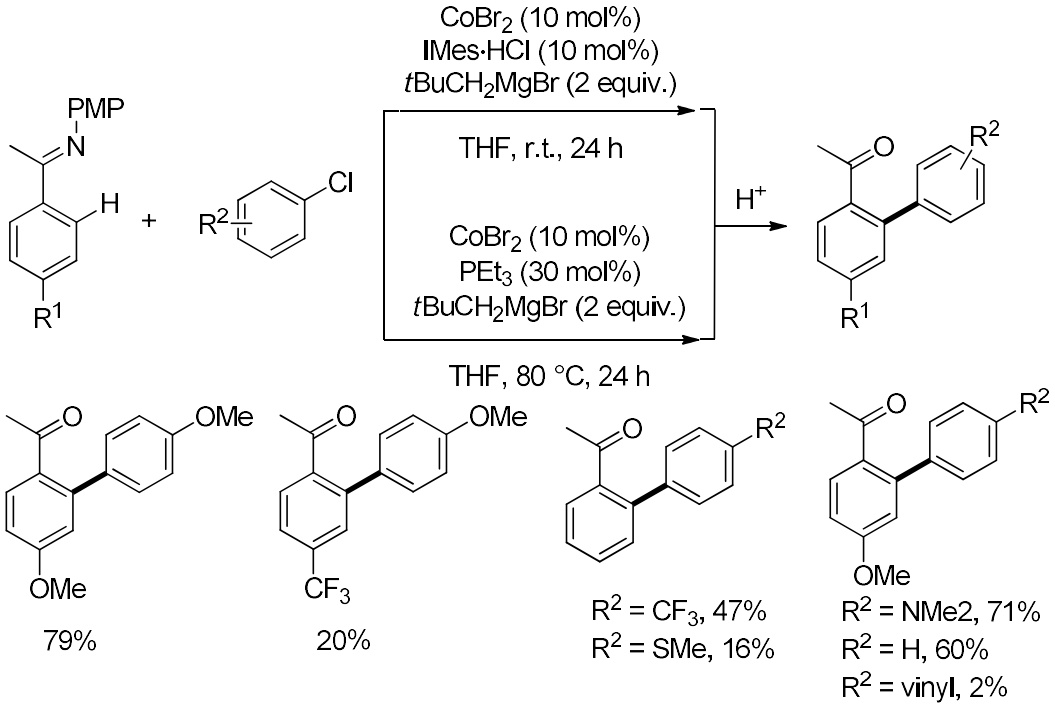
With another carbene ligand, the catalytic system was employed to C-H arylation of benzamides with aryl chlorides (Scheme 4-22).[35] This method displayed a wide scope of substrates bearing either electron-donating or electron-withdrawing groups affording moderate to excellent yields. A set of intermolecular competition experiments revealed that electron-poor benzamides and electron-poor aryl chlorides were more reactive than their electron-rich counterparts.

[240] B. Punji, W. Song, G. A. Shevchenko, L. Ackermann, *Chem. -Eur. J.* **2013**, *19*, 10605-10610.
[241] J. Li, L. Ackermann, *Chem. - Eur. J.* **2015**, *21*, 5718-5722.



Scheme 4-22 Cobalt-catalyzed arylation of benzamides with aryl chlorides

In 2012, Yoshikai and coworkers used their catalytic systems to C-H arylation of ketimines (Scheme 4-23).[242] Both NHC ligand and phosphine ligand were efficient, but higher temperature was required with phosphine ligand. However, this approach was more sensitive than Ackerman's procedure. With ketimines bearing a trifluoromethyl group, low yield was obtained. Some other groups such as thiomethyl and vinyl group were not tolerated.

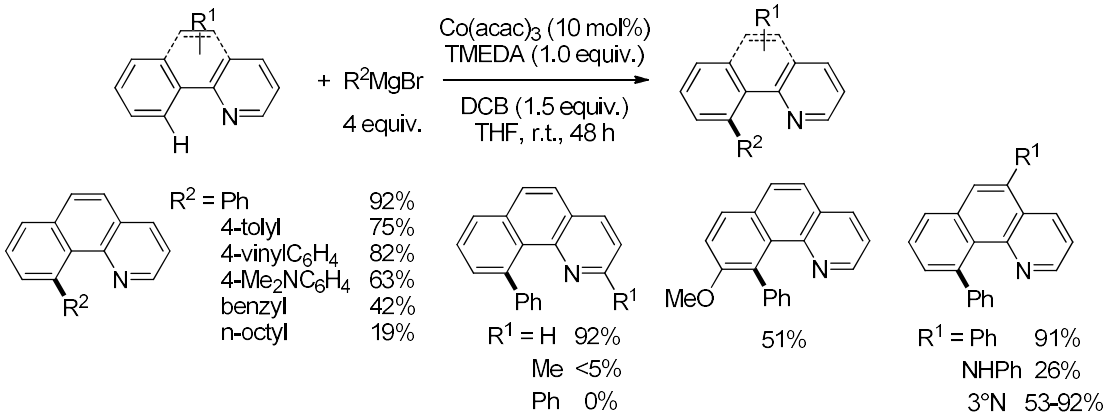


Scheme 4-23 Cobalt-catalyzed arylation of aryl ketimines with aryl chlorides

Although Grignard reagents were widely employed in the cobalt-catalyzed C-H activation, it was rarely reported to use Grignard reagents as the coupling partners in C-H activation. In 2011, Shi and coworkers first demonstrated an *ortho*-arylation of

[242] K. Gao, P.-S. Lee, C. Long, N. Yoshikai, *Org. Lett.* **2012**, *14*, 4234-4237.

benzo[h]quinolines with Grignard reagents (Scheme 4-24).[243] A high-valent cobalt salt was chosen as the catalyst, and 2,3-dichlorobutane as an oxidant was essential to generate a high-valent cobalt complex intermediate by oxidation. In this reaction, Grignard compounds were not reductant to generate a low-valent active cobalt, but served as a sacrifice to eliminate hydrogen. A large number of electron-donating groups substituted arylmagnesium compounds was well tolerated, moreover, functional groups in different positions of benzo[h]quinolones, or 2-phenylpyridines could also afford good yields.

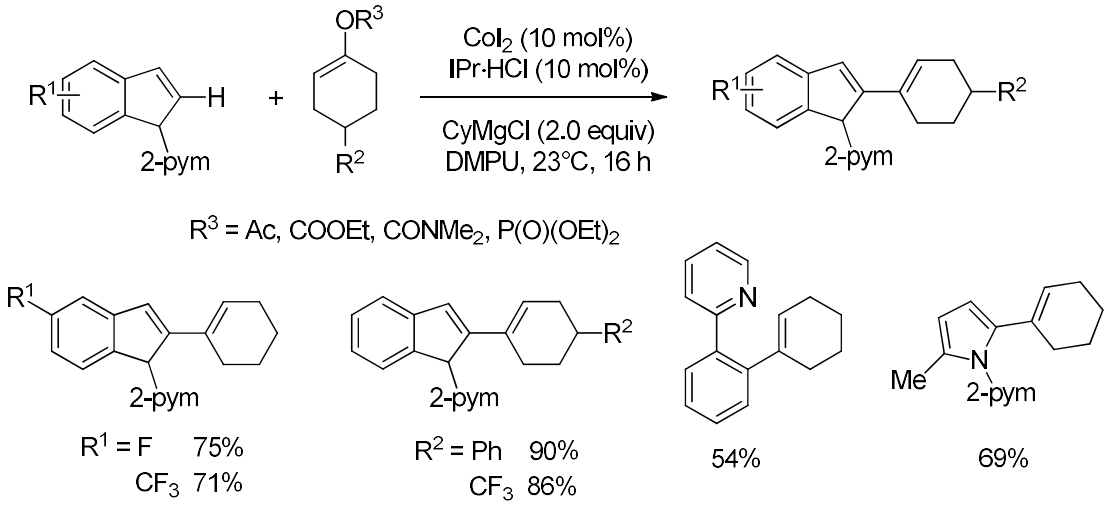


Scheme 4-24 Cobalt-catalyzed arylation of benzo[h]quinolines with aryl Grignard reagents

I-5 C-H alkenylation

The cobalt-catalyzed C-H functionalization with electrophiles was not restricted to aryl electrophiles. Very recently, Ackermann and coworkers designed a protocol of C-H alkenylation of indoles using a Co/NHC catalytic system (Scheme 4-25). [244] Unactivated alkenyl acetates, carbonates, carbamates and phosphates were allowed to couple with indoles, pyrroles and pyridines affording moderate to excellent yields. It is noteworthy that cyclic alkenylation could not be achieved by hydroarylation of alkynes. Furthermore, with acyclic unsymmetric alkenyl acetates, only E-configuration of products was observed.

[243] B. Li, Z. Wu, Y. Gu, C. Sun, B. Wang, Z.-J. Shi, *Angew. Chem., Int. Ed.* **2011**, *50*, 1109-1113.
[244] M. Moselage, N. Sauermann, S. C. Richter, L. Ackermann, *Angew. Chem., Int. Ed.* **2015**, *54*, 6352−6355.

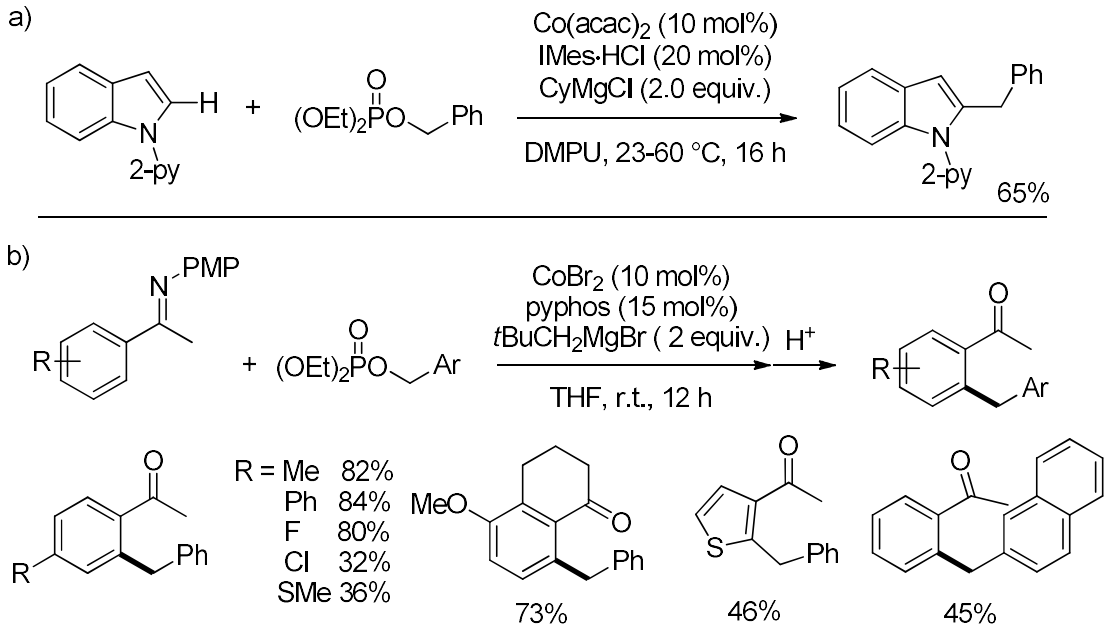


Scheme 4-25 Cobalt-catalyzed alkenylation of indoles with aryl Grignard reagents

I-5 C-H alkylation

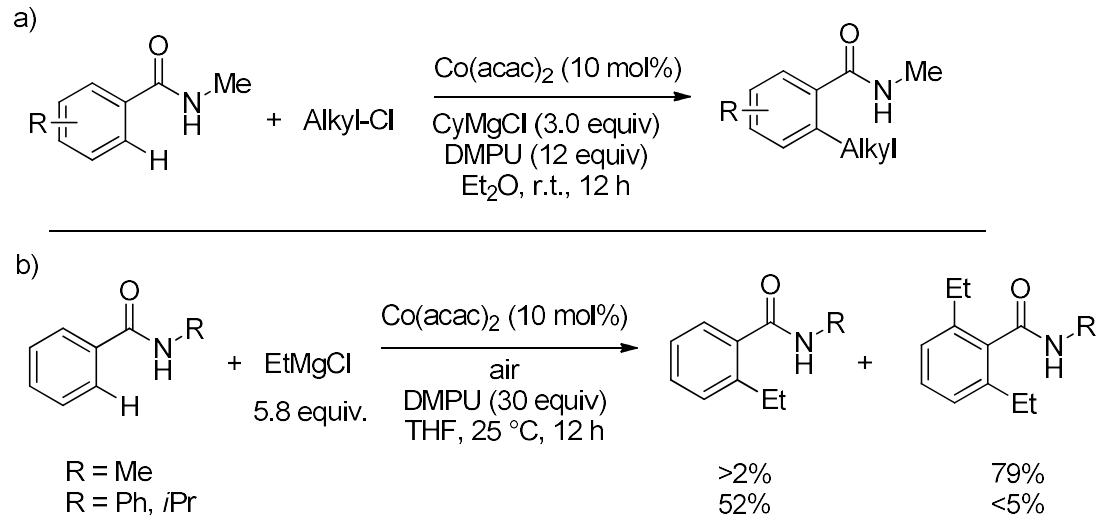
In the cobalt-catalyzed arylation of indoles reported by Ackermann and Song,[33] an example of benzylation using phosphate was also examined with good yield (Scheme 4-26-a). This result indicated the possibility to undergo a benzylation of arenes via cobalt-catalyzed C-H activation. In 2015, Yoshikai and coworkers employed benzylic phosphates as the electrophiles to couple with aryl ketimines in *ortho*- position (Scheme 4-26-b).[245] The phosphine/pyridine bidentate ligand pyphos performed much better than NHC or phosphine ligands, in which the phosphine part was assumed to play a more important role than the pyridine part. Series of functionalized benzylic phosphates as well as imine derivatives were well tolerated, though no electron-withdrawing groups substituted substrates were exhibited.

[245] W. Xu, R. Paira, N. Yoshikai, *Org. Lett.* **2015**, *17*, 4192−4195.



Scheme 4-26 Cobalt-catalyzed benzylation of indoles and aryl ketimines

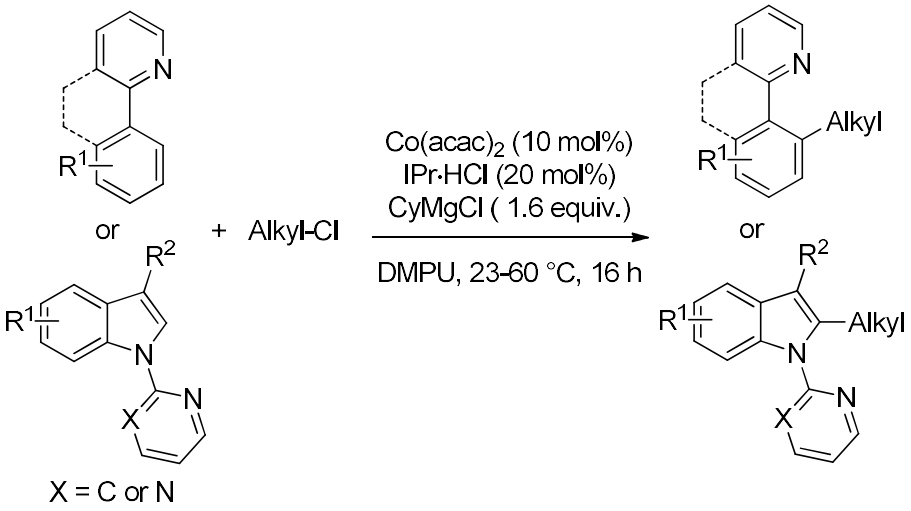
Besides benzylation, cobalt-catalyzed alkylation via C-H activation has been developed. The first example was reported by Nakamura and coworkers (Scheme 4-27-a). [246] With CyMgCl as the reductant, alkylation of benzamides with alkyl chlorides was possible with $Co(acac)_2$ as a catalyst. Interestingly, no ligands were necessary. Under similar conditions, alkylmagnesium reagents could be employed as the coupling partners (Scheme 4-27-b).[247]



Scheme 4-27 Cobalt-catalyzed alkylation of benzamides

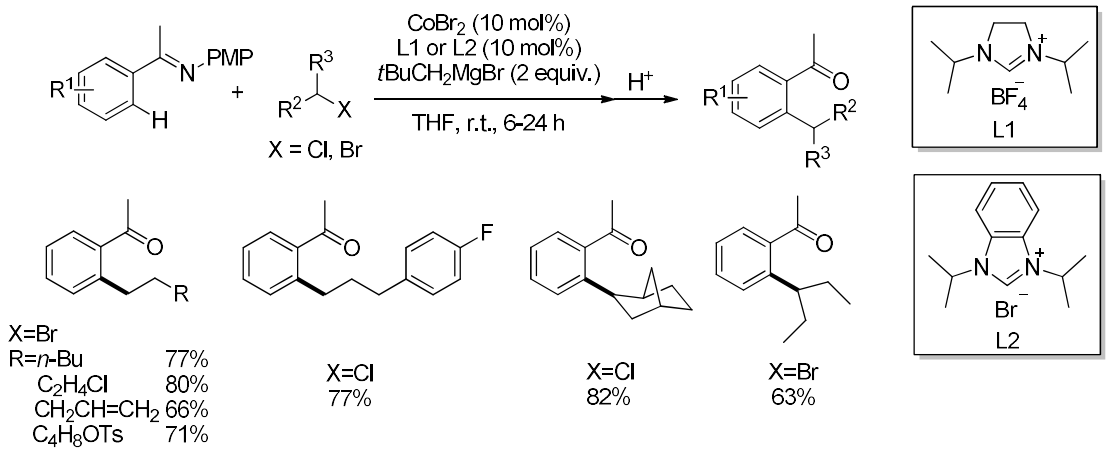
[246] Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428−429.
[247] Q, Chen, L. Ilies, N. Yoshikai, E. Nakamura, *Org. Lett.* **2011**, *13*, 3232-3234.

In addition to the arylation of 2-phenylpyridines with aryl chlorides reported by Ackermann,[34] alkyl chlorides were also applied in this method with changing the ligand to IPr•HCl (Scheme 4-28). Chloromethyltrimethylsilane, unfunctionalized primary and secondary alkyl chlorides reacted efficiently and delivered moderate to excellent yields.



Scheme 4-28 Cobalt-catalyzed alkylation of benzamides

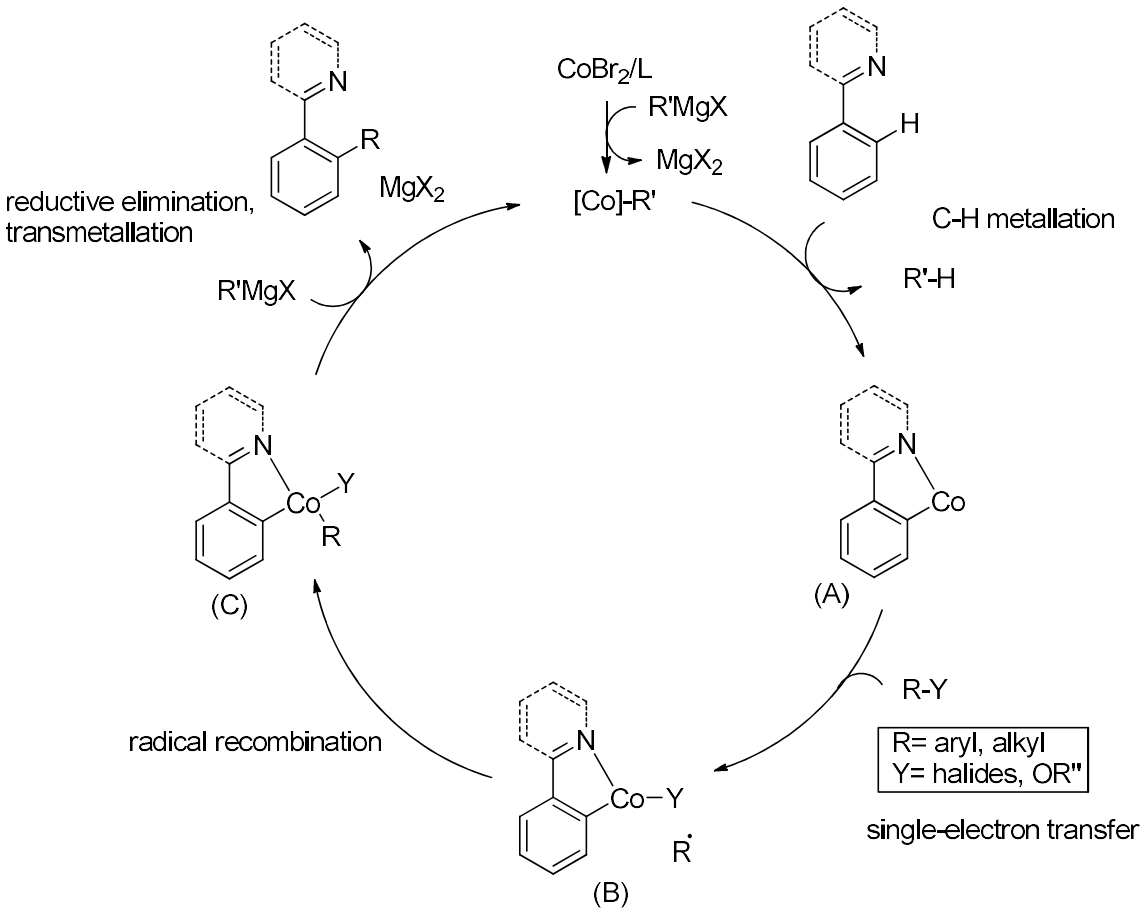
Independently, Yoshikai and Gao established direct alkylation of aryl ketimines with their catalytic system (Scheme 4-29).[248] Different NHC ligands were applied to give the best yields. Functionalized primary and secondary alkyl bromides and chlorides les to moderate to excellent yields except with alkyl halides bearing a pyridine or amide group. However, tertiary alkyl halides were not compatible.



Scheme 4-29 Cobalt-catalyzed alkylation of aryl ketimines

[248] K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2013**, *135*, 9279−9282.

Despite the remarkable development of cobalt-catalyzed arylation and alkylation, the mechanism has not been elucidated yet. Based on the work of Ackermann's group and Yoshikai's group, several clues about the catalysis mode were obtained. With addition of TEMPO as a radical scavenger, the catalytic activity was significantly reduced. In addition, when enantiomerically pure secondary alkyl halides were employed, a racemization was observed. Thus, a single-electron transfer (SET) process was proved to be involved. The proposed mechanism was described as follows (Scheme 4-30): After reduction by Grignard reagents to generate active low-valent cobalt, a cyclometallation of arenes forms cobalt complex (A). Then a SET process leads to cobalt complex (B) and an aryl or alkyl radical, followed by a recombination to generate a cobalt complex (C). The final step of reductive elimination and transmetallation affords the desired product as well as active low-valent cobalt.



Scheme 4-30 Proposed mechanism for cobalt-catalyzed arylation and alkylation

In summary, during the past few years the cobalt-catalyzed C-H activation has emerged as a significant tool for organic synthesis. The cobalt exhibits unique catalytic reactivity and selectivity with careful choice of ligands to undergo a variety

of transformations via C-H activation. Moreover, series of directing groups turn out to be suitable for cobalt-catalysis. Nevertheless, most of low-valent cobalt-catalyzed C-H activation requires specific Grignard reagents, which may limit the functional groups. When a high-valent cobalt was used, high temperature (80-130 °C) and bases (MOAc) are always necessary. Since our group has well established synthesis of arylzinc compounds in a simple and efficient way, it is interesting to try with arylzinc compounds to play a similar role as Grignard reagent and also as coupling partners.

II Results and discussions

II-1 Initial researches

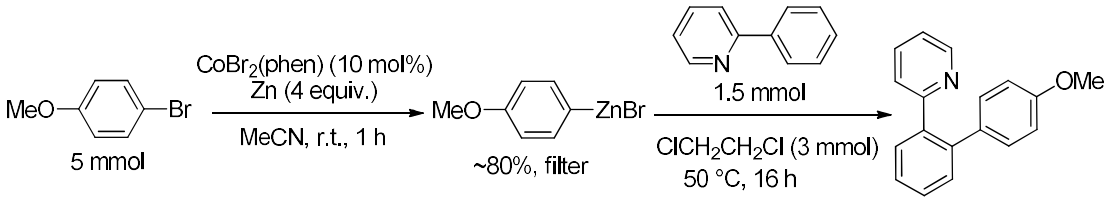
To begin, we emulated the reaction of Shi's group, who employed Grignard reagents to couple with benzo[h]quinolines.[47] 2-Phenylpyridine and the arylzinc species from bromoanisole were utilized as starting materials to undergo a model reaction (Table 4-1). By the method of cobalt-catalyzed synthesis of arylzinc reagents in our laboratory, 4-methoxy phenylzinc bromide was efficiently prepared using [$CoBr_2$(phen)] with excellent GC yield of 80%. Next the crude mixture was filtered to remove the extra zinc dust. Then, 2-phenylpyridine and 1,2-dichloroethane as oxidant were added and the medium was heated to 50 °C. After 16 hours, traces amount of the desired product was observed while almost all of the 2-phenylpyridine was recovered (Table 4-1, entry 1). Arylzinc compounds were mostly converted to dimers and hydrolysis products. Thus, the initial reaction conditions were not suitable for the expected C-H activation.

Then we tried to optimize the reaction conditions by changing different parameters. First we replaced 1,10-phenanthroline by triphenylphosphine as a ligand, lower conversion was obtained (Table 4-1, entry 2). We assumed that nitrogen-ligands performed better than phosphorus-ligands. When the reaction was conducted at room temperature, almost no conversion of 2-phenylpyridine was identified while the arylzinc compounds were still dimerized and hydrolyzed (Table 4-1, entry 3). A higher temperature did not improve the yield either (Table 4-1, entry 4). Without filtration, zinc dust only inhibited the reaction, no matter the oxidant was added or not (Table 4-1, entries 5-6). It was assumed that zinc dust could prevent C-H insertion by cobalt. In the previous low-valent cobalt-catalyzed C-H activation, Grignard reagents showed distinguished influence on the reactions. Thus, we proposed if the electron

properties of arylzinc compounds would affect the catalytic system. Therefore, 4-bromobenzoate was chosen to form the arylzinc species in replacement of bromoanisole. A slightly decreasing of the conversion was obtained (Table 4-1, entry 7). Despite the non-improved performance, it might imply the potential tolerance of functional groups. Since a variety of directing groups have been proved excellent for cobalt to undergo C-H insertion, while different directing groups require different reaction conditions. Benzamide was examined under the initial conditions, however, it performed worse than 2-phenylpyridine with no desired products detected (Table 4-1, entry 8). The preparation of arylzinc species was in acetonitrile; we added THF with expectation to lower the rate of consumption of arylzinc species (Table 4-1, entry 9). The conversion of 2-phenylpyridine was slightly increased and a yield of 10% was achieved. The result indicated that the nonpolar THF may be a more suitable solvent than acetonitrile. Several preliminary screens of the oxidants were attempted (Table 4-1, entries 10-12). Air turned out to have negative effect, while no addition of oxidant led to a slight decreasing of conversion (Table 4-1, entries 10-11). Furthermore, when 2,3-dichlorobutane was employed, a higher yield was isolated, though it was still very low (entries 12).

From the results of initial optimization of reaction conditions, although we did not achieve a satisfying yield, a number of positive information could be concluded. Compared with the starting conditions, we would still keep the first step, which was the synthesis of 4-methoxyphenylzinc bromide, as well as the filtration of zinc dust. 2-phenylpyridine was also kept as a starting material, while the oxidant was changed to 2,3-dichlorobutane. Moreover, the addition of THF in the second step was a preference.

Table 4-1 Initial optimization of reaction conditions



entry	Deviation from starting conditions	Yield (%)	Conversion[a] (%)

1	none	trace	10
2	$CoBr_2$ instead of $CoBr_2$(phen); add PPh_3 in step 2	trace	5
3	r.t.	trace	2
4	80 °C	trace	7
5	Without filtration	none	/
6	Without filtration, no oxidant	none	/
7	Using 4-bromobenzoate instead of 4-bromoanisole	trace	9
8	Using Ph-CONH-Ph as starting material	none	/
9	Add 1 mL THF in step 2	10	11
10	Air instead of $ClCH_2CH_2Cl$	trace	3
11	No oxidant	trace	8
12	2,3-dichlorobutane instead of 1,2-dichloroethane	20	18

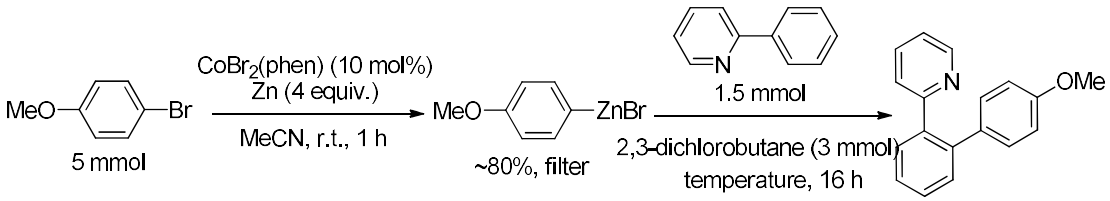
[a]: conversion=product/(product + starting material)

II-2 Optimization of temperature, solvent and amount of 2-phenylpyridine

Next we focused on the modification of temperature, solvent as well as the amount of starting materials (Table 4-2). In the initial optimization of reaction conditions, different temperatures were examined. Owing to the very low conversion, not large differences were observed. Thus, with 2,3-dichlorobutane as the oxidant and the addition of THF after filtration, the reactions were conducted at different temperatures (Table 4-2, entries 1-3). At room temperature only traces amount of product was detected, while at higher temperature no significant improvement was observed. Therefore, 50 °C was the best one. Due to the positive effect of THF as we observed in initial optimization, we tried with more quantity of THF in the second step (not shown in the table). However, no increasing yields were obtained possibly because the diluted concentration of the medium lowered the reaction rate. Then we replaced

acetonitrile to THF by evaporation of acetonitrile after filtration of zinc dust (Table 4-2, entry 4). It is noteworthy that after evaporation the arylzinc species were not destroyed. Unfortunately, it did not give better result. To our delight, an increasing conversion was obtained when the medium was heated to 70 °C (Table 4-2, entry 5). When Shi's group conducted the coupling between Grignard reagents and benzo[h]quinolines, a large excess of Grignard reagents were used. Here the amount of arylzinc was less than 3 equivalents of 2-phenylpyridine, which might be not enough. Thus, we decreased the amount of 2-phenylpyridine, surprisingly, we did not observe an increasing conversion, no matter at lower or higher temperature (Table 4-2, entries 6-8). Herein, after the continuous optimization, we concluded that the reaction of cobalt-catalyzed C-H activation performed more efficiently in THF than in acetonitrile.

Table 4-2 Optimization of solvent, temperature and amount of starting materials

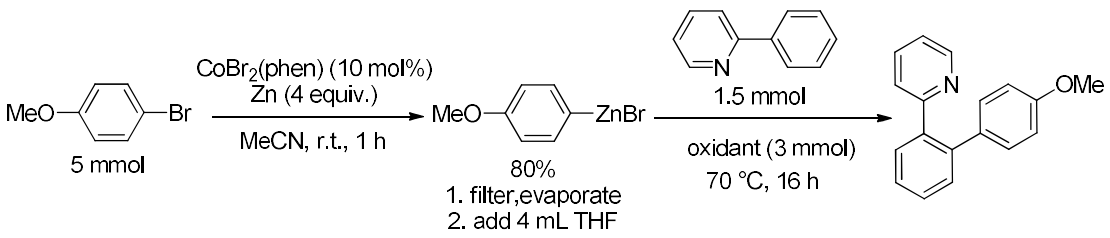


entry	Deviation from starting condition	Temperature	Yield (%)	Conversion
1	+1 mL THF after filtration	50	20	18
2	+1 mL THF after filtration	r.t.	trace	trace
3	+1 mL THF after filtration	80		18
4	Filter, evaporate, +4 mL THF	50	trace	8
5	Filter, evaporate, +4 mL THF	70	28	33
6	Filter, evaporate, +4 mL THF, 1 mmol 2-phenylpyridine	70		32
7	Filter, evaporate, +4 mL THF, 1 mmol 2-phenylpyridine	90		7
8	Filter, evaporate, +4 mL THF, 1 mmol 2-phenylpyridine	50		18

II-3 Optimization of oxidant and temperature

In the preliminary optimization, the largest difference was made by changing the oxidant from 1,2-dichloroethane to 2,3-dichlorobutane. Therefore, we next explored the effect of oxidants (Table 4-3). With the commercial inorganic oxidant Oxone, 2-phenylpyridine was less converted (Table 4-3, entry 2). A less strong inorganic oxidant such as silver nitrate inhibited the reaction (Table 4-3, entry 3). The silver atom may have negative effect on the C-H activation. Later, we employed benzo[h]quinoline as a mild organic oxidant, and lower conversion was observed (Table 4-3, entry 4). Moreover, small quantity of arylation of benzo[h]quinoline was detected by GC. In the previous optimization, 2 equivalents (*vs.* 2-phenylpyridine) of oxidants were used. When adding more oxidants, the conversion was decreased (Table 4-3, entry 5). We had tried this reaction without oxidant before and slightly decreasing conversion was observed (Table 4-1, entry 11). Here, after changing the solvent and temperature, an experiment without oxidant was conducted affording better yield than that with oxidant (Table 4-3, entry 6). It is assumed that the oxidation of a cobalt intermediate to form high-valent cobalt was not necessary. A C-H insertion of low-valent cobalt and *ortho*- C-H bond might be possible. Furthermore, oxidants could promote the dimerization of arylzinc compounds;[249] therefore, the rate of side reaction would be reduced without oxidants. Then higher temperature was examined without oxidants (Table 4-3, entries 7-8). Improved yield was obtained at 100 °C (Table 4-3, entry 7), while heating to 120 °C did not deliver a better yield (Table 4-3, entry 8).

Table 4-3 Optimization of oxidant



[249] Y. Bourne-Branchu, A. Moncomble, M. Corpet, G. Danoun, C. Gosmini, *Synthesis*, **2016**, *48*, 3352-3356.

entry	**Oxidant （2 equiv. vs 2-phenylpyridine）**	**temperature**	**Isolated Yield (%)**	**Conversion**
1	2,3-dichlorobutane	70	28	32
2	Oxone (1 equiv.)[a]	70	19	24
3	$AgNO_3$	70	/	/
4	Benzo[h]quinoline	70		16
5	2,3-dichlorobutane (3 equiv.)	70		11
6	None	70	42	38
7	None	100	47	47
8	None	120	40	48

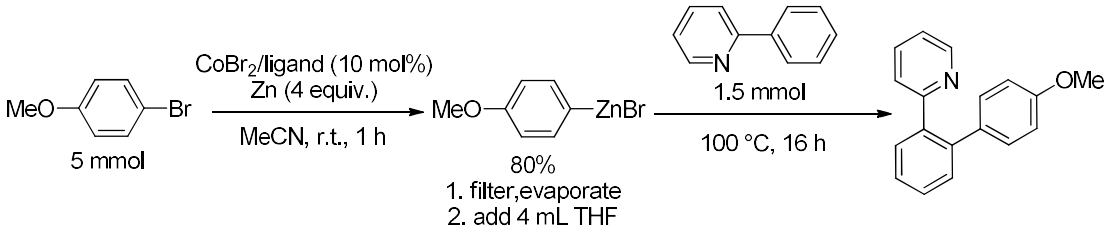
[a] Oxone = $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$

II-4 Optimization of ligands and bases

From the literature, it is obvious that ligands played a significant role on the metal-catalyzed C-H activation. In the initial optimization, we showed that 1,2-phenanthroline afforded higher conversion than triphenylphosphine (Table 4-1, entry 2). Next a broader screen of ligands was conducted (Table 4-4). The synthesis of arylzinc species did not require ligands, however, without ligands the C-H activation was largely restrained (Table 4-4, entry 2). When the $CoBr_2$ and 1,10-phenanthroline were added separately instead of $CoBr_2$(phen) complex, a slightly decreased yield was obtained (Table 4-4, entry 3). Similar results was afforded using $CoBr_2$(bipy), as an analogue of $CoBr_2$(phen) (Table 4-4, entry 4). Here, again we employed phosphine ligands. Either monodentate or bidentate phosphine ligands lowered the yields (Table 4-4, entries 5-6). Monodentate nitrogen ligands were also tested, nevertheless, both of them only delivered very low yields (Table 4-4, entries 7-8). It seemed that a bidentate nitrogen ligand could conduct the reaction more efficiently. Thus, we utilized a simple bidentate nitrogen ligand tetramethylethylenediamine (TMEDA) and a lower yield was obtained (Table 4-4, entry 9). Moreover, when additional TMEDA was added in the second step, the yield was even lower (Table 4-4, entry 10). Since

TMEDA could strongly coordinate to cobalt center compared to 1,10-phenanthroline, the cobalt might less favor to undergo a C-H insertion. Next bipyridine derivatives were examined. 4,4'-dimethyl-2,2'-bipyridine slightly increased the yield, while a more electron-donating 4,4'-dimethoxy-2,2'-bipyridine afforded lower yield (Table 4-4, entries 11-12). Sterically bulky ligand biquinoline highly blocked the reaction, giving a very low yield (Table 4-4, entry 13). In this reaction, we proposed that part of arylzinc species was a sacrifice to remove hydrogen on C-H bond. Thus, we wondered if bases could assist to eliminate the hydrogen. Several trials with amines or pyridines indicated that bases did not have a positive effect (Table 4-4, entries 14-16). In addition, inorganic bases such as Cs_2CO_3 could not increase the yield (Table 4-4, entry 17).

Table 4-4 Optimization of ligands and bases



Entry	Catalyst/ligand	Base	Yield （%）
1	$CoBr_2$(phen)	/	47
2	$CoBr_2$	/	5
3	$CoBr_2$/phen	/	40
4	$CoBr_2$(bipy)	/	40
5	$CoBr_2$/PPh_3	/	13
6	$CoBr_2$/dppe	/	10
7	$CoBr_2$/isoquinoline	/	5
8	$CoBr_2$/acridine	/	7
9	$CoBr_2$/TMEDA	/	21
10	$CoBr_2$/TMEDA	TMEDA (20 mol%)	9
11	$CoBr_2$/4,4'-dimethyl-2,2'-	/	50

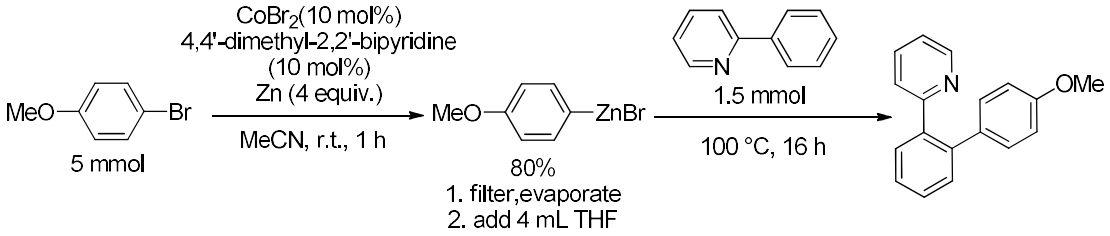
	bipyridine		
12	$CoBr_2$/4,4'-dimethoxy-2,2'-bipyridine	/	39
13	$CoBr_2$/biquinoline	/	10
14	$CoBr_2$(phen)	TMEDA (2 equiv.)	27
15	$CoBr_2$(phen)	trimethylamine (2 equiv.)	37
16	$CoBr_2$(phen)	2-picoline (2 equiv.)	35
17	$CoBr_2$/4,4'-dimethyl-2,2'-bipyridine	Cs_2CO_3 (0.33 equiv.)	40

II-5 Optimization with additives

The reaction conditions were continued to be optimized (Table 4-5). Next we examined several additives, which could possible promote the reaction, though the role was not very clear. The acetate group may coordinate to cobalt to facilitate the elimination of hydrogen. However, the yields were decreased with addition of metal acetate (Table 4-5, entries 2-3). Iron(II) salts, which could be a reductant and a Lewis acid, led to a much lower yield (Table 4-5, entry 4). In the cobalt-catalyzed electrophilic cyanation of arylzinc reagents, a catalytic amount of zinc was added after filtration, which was the key to the excellent yield. On the contrary, in this case zinc inhibited the reaction (Table 4-5, entry 5). Next we tested several starting materials. Unfunctionalized phenylzinc bromide performed with the same efficiency of 4-methoxyphenylzinc bromide (Table 4-5, entry 6). Besides, ester group on arylzinc compounds could also conduct C-H activation reaction, though the conversion was lower (Table 4-5, entry 7). In addition, amides were tested as directing groups. However, both benzanilide and 8-benzoylaminoquinoline were not tolerated in this system (Table 4-5, entries 8-9). When benzo[h]quinoline was employed as starting material, similar results as 2-phenylpyridine were obtained (Table 4-5, entry 10). These results suggested that this system was more sensitive to directing groups than to arylzinc species. Moreover, lowering the reaction rate by decreasing the temperature only had negative influence (Table 4-5, entry 11).

Interestingly, with additional $CoBr_2$ and ligand in the second step, the yield was increased (Table 4-5, entry 12). It implied that the turnover frequency (TOF) of cobalt was not enough and cobalt seemed to be easy to lose catalytic reactivity.

Table 4-5 Optimization of additives and starting materials



Entry	Derivatives	yield（%）	conversion
1	none	50	55
2	Add 33 mol% KOAc in step 2	40	45
3	Add 33 mol% $Cu(OAc)_2$ in step 2	32	31
4	Add 33 mol% $FeBr_2$ in step 2	20	18
5	Add 10 mol% Zinc in step 2		traces
6	Ph-Br as starting material for arylzinc		55
7	EtOCO-PhBr as starting material for arylzinc		40
8	Ph-CONH-Ph as starting material		traces
9	Ph-CONH-Q as starting material		traces
10	Benzo[h]quinoline		41
11	40 °C 2d	23	33
12	Add 10 mol% $CoBr_2$/4,4-dimethyl-	61	73

	2,2'-bipyridine in step 2		

III Conclusions and perspectives

Although considerable progress of cobalt-catalyzed C-H activation has been achieved, this topic still remains challenging. Particularly, with arylzinc species as the coupling partner as well as the reductant, it had never been investigated. Since arylzinc species are less electrophilic than Grignard reagents, it is difficult to undergo such C-H functionalization. After extensive modification of reaction conditions, including solvents, temperature, ligands, oxidants and additives, we have made a progress from none to modest yield of desired product. Bromoanisoles and 2-phenylpyridine proved to be suitable starting materials, which could be employed in the further optimization of conditions.

The main problem is the low conversion of 2-phenylpyridine, since almost no side reactions occur. Furthermore, the conversion depends on the catalytic activity of cobalt. Ligand has an important effect on the active cobalt. So far we find that 4,4'-dimethyl-2,2'-bipyridine is the best ligand, however, a further careful elaboration of ligand is required. In addition, it is worthy trying with a large excess of arylzinc species. Nevertheless, the amount of cobalt catalysis relies on that of arylzinc compounds; thus, a large quantity of cobalt/ligand versus 2-phenylpyridine is not evitable, which is not a catalysis mode. Herein, commercial phenylzinc compounds could be an alternative. From the crude results with different group substituted phenylzinc reagents, it implies a potential tolerance of functionalized arylzinc species.

General conclusion

First, we established a novel cobalt-catalyzed electrophilic cyanation of arylzinc species, employing benign and non-toxic NCTS as the cyano source. The addition of catalytic amount of zinc dust in the second step proved to be necessary to achieve good efficiency with $CoBr_2$ as catalyst. This method exhibited an excellent tolerance of functional groups under very mild conditions. In particular, several chelated groups such as ketone and cyano groups, could be tolerated with changing the catalyst to [$CoBr_2$(bipy)]. It is a good alternative to the previous electrophilic cyanation pathways. Moreover, a variety of N-CN type compounds were examined, some of which showed possibility to be developed as good cyano source.

In the second chapter, based on previous cross-coupling reactions in our laboratory, we demonstrated a simple and efficient C_{sp3}-C_{sp3} homocoupling reaction catalyzed by cobalt. A variety of primary and secondary alkyl bromides bearing functional groups was well tolerated affording moderate to excellent yields under mild conditions. Besides, alkyl iodides, benzyl chlorides as well as allylic acetates also gave good yields. Furthermore, less reactive alkyl chlorides, with addition of sodium iodides, moderate to good yields were obtained, though higher temperature and longer reaction time were required. In addition, sodium iodide was also useful for the dimerization of alkyl toyslates.

Following the results we next explored the alkyl-alkyl cross-coupling. It is more challenging owing to the competitive homocoupling of each alkyl halides. After series of modification of reaction conditions, it turned out that more cobalt catalysts and higher temperature were necessary to afford good yields. A screen of ligands could not lead to a better yield. Furthermore, when primary and secondary alkyl halides were used, the results were more unsatisfying.

In the third chapter, we disclosed a novel approach to undergo cobalt-catalyzed vinyl-benzyl cross-coupling. Unlike previous cobalt-catalyzed cross-coupling in our group, pyridine and TFA were no more required. Instead, TMSCl was chosen to activate manganese smoothly and sodium iodide was essential for this reaction. Various electron-donating and electron-withdrawing functional groups on benzyl chlorides or styrenyl bromides on aromatic ring were efficiently tolerated under mild conditions.

In general, it is required to heat to 50 °C when using starting materials bearing electron-withdrawing groups. Then we tried to extend this method to more kinds of substrates. However, only allylic halides delivered moderate yields with vinyl bromides.

Last chapter was about the progress on cobalt-catalyzed arylation of 2-phenylpyridine via C-H activation with arylzinc species. After extensive modification of reaction conditions, we obtained moderate yield of arylation product. The main problem was low conversion of 2-phenylpyridine. A further optimization needs to be undertaken.

In conclusion, we have achieved several progresses on cobalt-catalyzed carbon-carbon bond formation. The reactions are simply operated under mild conditions. The use of cobalt catalyst, which is economic, eco-compatible and efficient, has been proved to be an alternative to other transition metals.

Experimental Sections

General Information

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. [$CoBr_2$(bpy)], [$CoBr_2$(phen)] and [$CoBr_2(PPh_3)_2$] were synthesized according to published procedure.[250,251] Nuclear magnetic resonance spectra were recorded on a Bruker AC-300 SY spectrometer operating at 300.0 MHz for ^1H, 75.0 MHz for ^{13}C and 282.0 MHz for ^{19}F. Solvent peaks are used as internal references relative to ^1H ($CDCl_3$ = 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. 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 chromatography Varian (25-m CPSIL5CB/MS capillary column). Column chromatography was performed on silica gel with 60, 70-230 mesh with petroleum ether/ethyl acetate as eluent. Filtration of arylzinc containing solutions was carried on using Whatman PTFE syringe filter ReZist-30 0.45 µm.

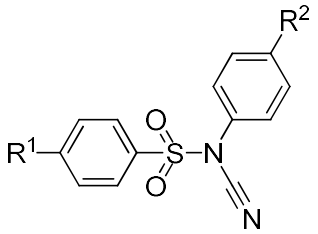
I Cobalt-catalyzed Electrophilic Cyanation of Arylzincs with N-cyano-N-phenyl-p-methyl-benzenesulfonamide (NCTS)

I-1 Procedure for the formation of arylsulfonylcyanamides (A-D)

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

[250] L. Polleux, E. Labbe, O. Buriez, J. Périchon, *Chem; Eur. J.*, **2005**, *11*, 4678-4685.
[251] F. A. Cotton, O. D. Faut, D. M. L. Goodgame, R. H. Holm, *J. Am. Chem. Soc.* **1961**, *83*, 1780–1785.

tosyl chloride was converted into corresponding ethyl ester). *N*-cyano-*N*-phenyl-4-methylbenzenesulfonamide was provided as white power (17.4 g, 76%).



R^1= Me, R^2 = H**:** HRMS (EI+): calculated: 272.0619; found: 272.0616. ^{1}H-NMR (300MHz, $CDCl_3$) δ/ppm: 7.55 (d, *J* = 8.5 Hz, 2H), 7.37-7.23 (m, 5H), 7.14-7.09 (m, 2H), 2.39 (s, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 146.7, 134.5, 132.3, 130.2, 130.0, 129.8, 128.4, 126.5, 108.6, 21.8.[252]

B, C, and D were synthesized by a similar procedure changing the tosylchloride or the phenylurea.

B, R^1= naphtyl, R^2 = H**:** HRMS (EI+): calculated: 308.0619; found: 308.0621. ^{1}H-NMR (300MHz, $CDCl_3$) δ/ppm: 8.63 (d, *J* = 9.0 Hz, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.74-7.64 (m, 2H), 7.50-7.45 (t,1H), 7.36-7.23 (m, 3H), 7.07 (d, *J* = 9.0 Hz, 2H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 137.0, 134.2, 133.0, 130.6, 130.0, 129.8, 129.6, 128.3, 127.7, 126.6, 124.4, 124.0, 108.5.

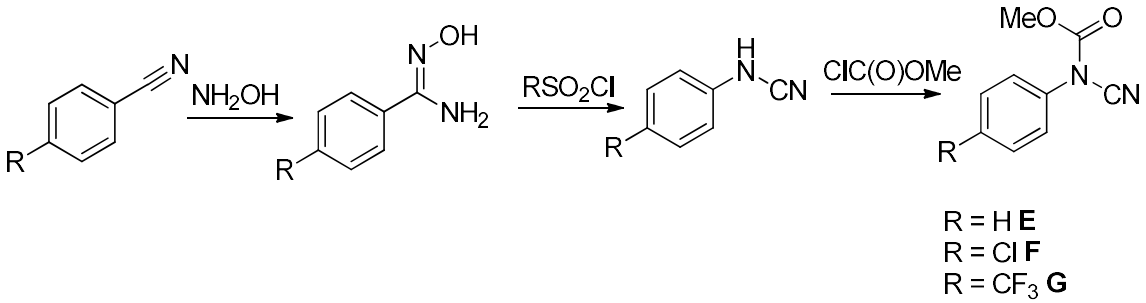
C, R^1= CF_3, R^2 = H**:** δ/ppm: 7.91 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.41-7.49 (m, 3H), 7.22 (br. d, *J* = 8.0 Hz, 2H), 2.39 (s, 3H).

D, R^1= Me, R^2 = F**:** δ/ppm: 7.63 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H).

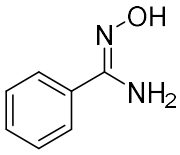
[252] P. Anbarasan, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 4725-4728.

I-2 Procedure for the formation of *N*-carbomethoxy-*N*-arylcyanamides (E-G)

(Performed by Alice Rérat)

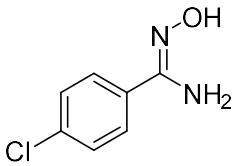


I-2-1 First step: synthesis of benzamidoxime derivatives



Typical procedure for the synthesis of benzamidoxine ($C_7H_8N_2O$):

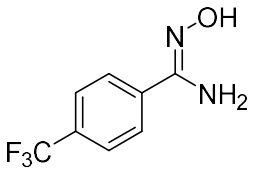
To a stirred solution of benzonitrile (2.06 mL, 20 mmol) in EtOH (200 mL) was added a 50*wt*% aqueous hydroxylamine solution (2.38 mL, 40 mmol) under nitrogen. The reaction mixture was stirred at 100 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated under vacuum. Purification was performed using silica gel column chromatography, with a gradient from 2:1 to 1:1 petroleum ether/ethyl acetate, affording benzamidoxime as white powder (2.69 g, 98%). HRMS (EI+) ($C_7H_8N_2O$): calculated m/z: 136.0637, found: 136.0636. ^{1}H-NMR (300 MHz, DMSO) δ/ppm: 9.63 (s, 1H), 7.67 (m, 2H), 7.38 (m, 3H), 5.80 (s, 2H). ^{13}C-NMR (75 MHz, DMSO) δ/ppm: 150.8, 133.4, 128.9, 128.1, 125.4.[18]**253**



Synthesis of 4-chlorobenzamidoxime ($C_7H_7ClN_2O$):

[253] B. V. Rokade, S. K. Malekar, K. R. Prabhu *Chem. Commun.*, **2012**,*48*, 5506-5508.

4-chlorobenzamidoxime was synthesized similarly using 4-chlorobenzonitrile (2.74 g, 20 mmol) in EtOH (200 mL), a 50*wt*% aqueous hydroxylamine solution (2.38 mL, 40 mmol) Purification was performed by recrystallization in pentane/ethyl acetate, affording 4-chlorobenzamidoxime as white powder (2.76 g, 81%). HRMS (EI+) ($C_7H_7ClN_2O$): calculated m/z: 170.0247, found: 170.0247. ^{1}H-NMR (300 MHz, DMSO) δ/ppm: 9.74 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 5.87 (s, 2H). ^{13}C-NMR (75 MHz, DMSO) δ/ppm: 149.9, 133.4, 132.2, 128.1, 127.1. [18]4

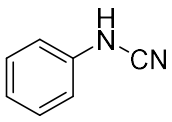


Synthesis of 4-trifluoromethylbenzamidoxime ($C_8H_7F_3N_2O$):

4-trifluoromethylbenzamidoxime was synthesized following the same protocole using 4-trifluoromethylbenzonitrile (3.42 g, 20 mmol) and a 50*wt*% aqueous hydroxylamine solution (2.38 mL, 40 mmol) under nitrogen. Purification was performed by recrystallization in pentane/ethyl acetate, affording 4-trifluoromethylbenzamidoxime as white solid (3.42 g, 84%). HRMS (EI+) ($C_8H_7F_3N_2O$): calculated m/z: 204.0510, found: 204.0511. ^{1}H-NMR (300 MHz, DMSO) δ/ppm: 9.94 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H,), 5.98 (s, 2H). ^{13}C-NMR (75 MHz, DMSO) δ/ppm: 149.8, 137.7, 129.1 (q, *J* = 32.0 Hz), 126.1, 125.1 (q, *J* = 4.0 Hz), 124.2 (q, *J* = 272.1 Hz). ^{19}F-NMR (282 MHz, DMSO, bis(trifluoromethane)sulfonimide as external reference) δ/ppm: -61.1.[18]4

I-2-2 Second step: synthesis of *N*-arylcyanamide ($C_7H_6N_2$):

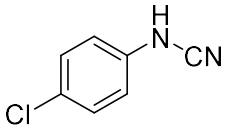
Synthesis of *N*-phenylcyanamide



To a stirred solution of benzamidoxime (2.45 g, 18 mmol) in pyridine (18 mL) at 0 °C was added tosyl chloride (3.6 g, 18.9 mmol) under nitrogen. The mixture was stirred at 0 °C for 10 min then at room temperature for 5 h. The reaction mixture was concentrated under vacuum. Purification was performed using silica gel column

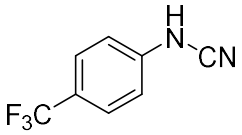
chromatography, with a gradient from 5:1 to 4:1 petroleum ether/ethyl acetate, affording *N*-phenylcyanamide as yellow solid (1.61 g, 76%). HRMS (EI+) ($C_7H_6N_2$): calculated m/z: 118.1390, found: 118.0526. ^{1}H-NMR (300 MHz, DMSO) δ/ppm: 9.93 (s, 1H), 7.32 (t, *J* = 8.0 Hz, 2 H), 7.00 (m, 3H). ^{13}C-NMR (75 MHz, DMSO) δ/ppm: 138.7, 129.7, 122.5, 115.0, 112.1.[18] 4

Synthesis of *N*-(4-chlorophenyl)cyanamide ($C_7H_5ClN_2$):



To a stirred solution of 4-chlorobenzamidoxime (2.70 g, 15.8 mmol) in dichloromethane (160 mL) at 0 °C was added N,N-diisopropylethylamine (2.8 mL, 16.6 mmol) and 2-nitrobenzenesulfonylchloride (3.68 g, 16.6 mmol) under nitrogen. The mixture was stirred at 0 °C for 10 min then at 45 °C for 1 h. After cooling to room temperature, the reaction mixture was concentrated under vacuum. Purification was performed using silica gel column chromatography with dichloromethane, affording *N*-(4-chlorophenyl)cyanamide as white solid (1.51 g, 63%). HRMS (EI+) ($C_7H_5ClN_2$): calculated m/z: 152.0141, found: 152.0141. ^{1}H-NMR (300 MHz, DMSO) δ/ppm: 7.38 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H). ^{13}C-NMR (75 MHz, DMSO) δ/ppm: 137.7, 129.6, 126.3, 116.7, 117.7.[18]4

Synthesis of N-(4-trifluoromethylphenyl)cyanamide ($C_8H_5F_3N_2$):

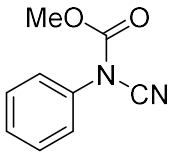


The above procedure was used to prepare *N*-(4-trifluoromethylphenyl)cyanamide employing 4-trifluoromethylbenzamidoxime (3.00 g, 14.7 mmol) in dichloromethane (150 mL), DIPEA (2.6 mL, 15.4 mmol), and *o*-NsCl (3.41 g, 15.4 mmol). Purification was achieved similarly affording *N*-(4-trifluoromethylphenyl)cyanamide as white solid (957 mg, 35%). HRMS (EI+) ($C_8H_5F_3N_2$): calculated m/z: 186.0405, found: 186.0401. ^{1}H-NMR (300 MHz, DMSO) δ/ppm: 10.72 (s, 1H), 7.68-7.65 (d, *J* = 8.4 Hz, 2H), 7.14-7.11 (d, *J* = 8.5 Hz, 2H). ^{13}C-NMR (75 MHz, DMSO) δ/ppm: 142.6, 127.1 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 272.0 Hz), 123.0 (q, *J* = 32.0 Hz), 115.4, 111.1.

^{19}F-NMR (282 MHz, DMSO, bis(trifluoromethane)sulfonimide as external reference) δ/ppm: -60.5.[18] 4

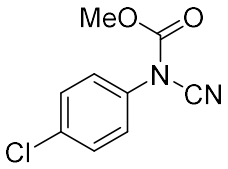
I-2-3 Third step: synthesis of *N*-carbomethoxy-*N*-arylcyanamide $C_9H_8N_2O_2$ (E-G)

Typical procedure: Synthesis of *N*-carbomethoxy-*N*-phenylcyanamide (E) ($C_9H_8N_2O_2$) :



To a stirred solution of *N*-phenylcyanamide (500 mg, 4.2 mmol) in acetonitrile (11 mL) at 0 °C was added triethylamine (0.63 mL g, 4.6 mmol). Methyl chloroformate (0.35 mL, 4.6 mmol) was slowly added to the reaction mixture and the solution was then stirred at 0 °C for 10 min then at room temperature overnight. The reaction was quenched with a saturated solution of NH_4Cl (30 mL). The aqueous layer was extracted three times with dichloromethane (3*30 mL), 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 7:1 to 6:1 petroleum ether/ethyl acetate, affording *N*-carbomethoxy-*N*-phenylcyanamide as a white solid (517 mg, 78%). M.p.: 73.4 °C. HRMS (EI+) ($C_9H_8N_2O_2$): calculated m/z: 176.0586, found: 176.0585. ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.44 (m, 5H), 3.97 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 152.2, 134.9, 129.8, 129.0, 124.9, 108.5, 55.6.

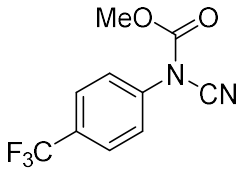
Synthesis of *N*-carbomethoxy-*N*-(4-chlorophenyl)cyanamide (F) ($C_9H_7ClN_2O_2$):



N-carbomethoxy-N-(4-chlorophenyl)cyanamide was prepared similarly using *N*-(4-chlorophenyl)cyanamide (500 mg, 3.3 mmol) in acetonitrile (10 mL), triethylamine

(0.49 mL g, 3.6 mmol), and methyl chloroformate (0.28 mL, 3.6 mmol). Purification was performed using silica gel column chromatography, with a gradient from 5:1 to 4:1 petroleum ether/ethyl acetate, affording *N*-carbomethoxy-*N*-(4-chlorophenyl)cyanamide as a white solid (580 mg, 84%). M.p.: 90.2 °C. HRMS (EI+) ($C_9H_7ClN_2O_2$): calculated m/z: 210.0196, found: 210.0198. ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.40 (m, 4H), 3.95 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 151.8, 134.7, 133.3, 129.9, 126.0, 108.0, 55.7.

Synthesis of *N*-carbomethoxy-*N*-(4-trifluoromethylphenyl))cyanamide (G) ($C_{10}H_7F_3N_2O_2$):



N-carbomethoxy-*N*-(4-trifluoromethylphenyl))cyanamide was prepared similarly using of *N*-(4-trifluoromethylphenyl)cyanamide (500 mg, 2.7 mmol) in acetonitrile (8 mL), triethylamine (0.40 mL g, 3.0 mmol), and Methyl chloroformate (0.23 mL, 3.0 mmol) Purification was performed using silica gel column chromatography, with a 4:1 petroleum ether/ethyl acetate, affording *N*-carbomethoxy-*N*-(4-trifluoromethylphenyl)cyanamide as a white solid (574 mg, 87%). M.p.: 94.0 °C. HRMS (EI+) ($C_{10}H_7F_3N_2O_2$): calculated m/z: 244.0460, found: 244.0458. ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.74 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 4.01 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 151.5, 137.9, 130.7 (q, J = 33.5 Hz), 127.0 (q, J = 4.0 Hz), 124.4, 123.5 (q, J = 272.0 Hz), 107.61, 55.92. ^{19}F-NMR (282 MHz, DMSO, bis(trifluoromethane)sulfonimide as external reference) δ/ppm: -62.7.

I-3 General procedure for formation of arylzinc and vinylzinc reagents

To a solution of $CoBr_2$ (13 mol %, 0.5 mmol, 110 mg) and zinc powder (10 mmol, 0.65 g, 2.5 equiv.) in acetonitrile (4 mL) were successively added at room temperature under vigourous stirring allylchloride (1.5 mmol, 125 μL, 30%) and trifluoroacetic acid (50 μL), causing an immediate rise in temperature and color change to dark gray.

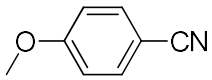
Once the orange tinge of the reaction mixture had disappeared, arylbromide (3.75 mmol, 1 equiv.) was added. The medium was then stirred at room temperature and the reaction was followed by GC on iodolyzed aliquots. When the arylbromide had totally reacted, stirring was stopped and the reaction was taken through a syringe filter. An internal standard was added to this cobalt-containing arylbromide solution, with was titrated by GC on an iodolyzed aliquot.

To a solution of $CoBr_2$ (13 mol %, 0.5 mmol, 110 mg) and zinc powder (10 mmol, 0.65 g, 2.5 equiv.) in acetonitrile (3 mL) were successively added at room temperature under vigourous stirring allylchloride (1.5 mmol, 125 μL, 30%) and trifluoroacetic acid (50 μL), causing an immediate rise in temperature and color change to dark gray. Once the orange tinge of the reaction mixture had disappeared, PPh_3 (13 mol%, 0.5 mmol), pyridine (2 mL) and β-bromostyrene (3.75 mmol, 1 equiv.) were added. The medium was then stirred at room temperature and the reaction was followed by GC on iodolyzed aliquots. When the β-bromostyrene had totally reacted, stirring was stopped and the reaction was taken through a syringe filter. An internal standard was added to this cobalt-containing arylbromide solution, with was titrated by GC on an iodolyzed aliquot.

I-4 General procedures for the cyanation of arylzinc derivatives

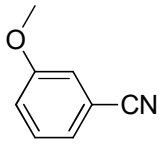
The arylzinc solution prepared as mentioned above was added to a mixture of NCTS and zinc dust in acetonitrile which was placed in a schlenk flask under N_2 at 0°C. Stirring was pursued once the cold bath has melted; the reaction mixture was gently heated to 50°C. The reaction was followed by GC on iodolyzed aliquots untill the total consumption of the arylzinc. Aqueous HCL (ca 2M, 20 mL) and diethyl ether (20 mL) were then added and stirring was then continued for 5 min. The phased were separated and the aqueous phase was washed with ether (3x20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to afford the crude material. Purification was performed using silica gel column chromatography (petroleum ether /ethyl acetate).

I-5 Characterization data for arylnitriles



4-methoxybenzonitrile C_8H_7NO (1a): 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 (300MHz, $CDCl_3$) δ/ppm: 7.57 (d, *J* = 9.0 Hz, 2H); 6.93 (d, *J* = 9.0 Hz, 2H); 3.84 (*s*, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 162.8; 133.9; 119.2; 114.7; 103.8; 55.5.[254]

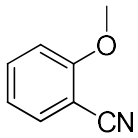


3-methoxybenzonitrile C_8H_7NO (1b): CAS# 1527-89-5**.**

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 (300MHz, $CDCl_3$) δ/ppm: 7.39 (m, 1H), 7.27 (m, 1H), 7.16 (m, 2H), 3.87 (s, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 159.6, 130.3, 124.5, 119.3, 118.7, 116.8, 113.1, 55.5.[3][255]

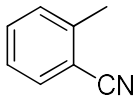
[254] S. S. Deshmukh, S. N. Huddar, R. R. Jadhav, K. G. Akamanchi, *Tetrahedron Lett.* **2011,** *52*, 4533-4536.

[255] W. Zhou, J. Xu, L. Zhang, N. Jiao, *Org. Lett.* **2010,** *12*, 2888-2891.



2-methoxybenzonitrile C_8H_7NO (1c): 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 (300MHz, $CDCl_3$) δ/ppm: 7.62 (m, 2H), 7.05 (m, 2H), 3.96 (s, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 160.2, 133.4, 132.6, 119.7, 115.4, 110.3, 100.5, 55.0.[4]256

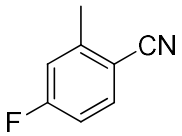


2-methylbenzonitrile C_8H_7N (1d): CAS# 529-19-1**.**

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 (300MHz, $CDCl_3$) δ/ppm: 7.60 (dd, J = 9.0 Hz, J = 3.0 Hz, 1H), 7.51 (dt, J = 9.0 Hz, J = 3.0 Hz, 1H), 7.36 (m, 2H), 2.54 (s, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 142.0, 132.7, 132.5, 130.2, 126.2, 118.2, 112.8, 20.5.[5]257

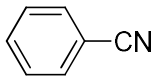
[256] P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 519-522.

[257] L. Liu, J. Li, J. Xu, J.-T. Sun *Tetrahedron Lett.* **2012,** *53*, 6954-6956

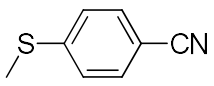


4-fluoro-2-methylbenzonitrile C_8H_6FN (1e): CAS# 147754-12-9**.**

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-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 (300MHz, $CDCl_3$) δ/ppm: 7.33-7.18 (m, 3H), 2.54 (s, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 160.3 (d, *J* = 247.5 Hz), 137.9 (d, *J* = 4.0 Hz), 131.9 (d, *J* = 8.5 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.[6] [258]



Benzonitrile C_7H_5N (1f): 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 (300MHz, $CDCl_3$) δ/ppm: 7.71-7.61 (m, 3H), 7.54-7.49 (m, 2H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 133.3, 132.7, 129.7, 119.3, 113.0.[7][259]

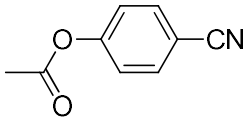


[258] Z. Zhang, M. B. Wallace, J. Feng, J. A. Stafford, J. A.; R. J. Skene, L. Shi, B. Lee, K. Aertgeerts, A. Jennings, R. Xu, D. B. Kasse, lS. W. Kaldor, M. Navre, D. R. Webb, S. L. Gwaltney *J. Med. Chem.* **2010,** *54*, 510-524.

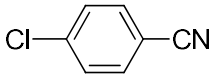
[259] S. Zheng, C. Yu, Z. Shen *Org. Lett.* **2012,** *14*, 3644-3647.

4-(methylthio)benzonitrile C_8H_7NS (1g): 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 (300MHz, $CDCl_3$) δ/ppm: 7.57 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 9.0 Hz, 2H), 2.54 (s, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 146.1, 132.2, 125.5, 119.0, 107.7, 14.7.[8]260



4-cyanophenyl acetate $C_9H_7NO_2$ (1h): 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 (300MHz, $CDCl_3$) δ/ppm: 7.73 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 1H), 2.34 (s, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 169.1, 154.5, 134.2, 123.3, 118.7, 110.2, 21.4.[9]261

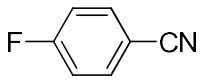


4-chlorobenzonitrile C_7H_4ClN (1i): CAS# 623-03-0**.**

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

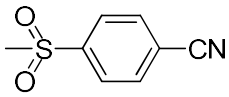
[260] S. Laulhé, S. S. Gori, M. H. Nantz, *J. Org. Chem.* **2012,** *77*, 9334-9337.
[261] S. T. Kadam S. S. Kim *Synthesis* **2008**, 267-271.

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 (300MHz, $CDCl_3$) δ/ppm: 7.64 (d, *J* = 9.0 Hz, 2H), 7.51 (d, *J* = 9.0 Hz, 2H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 139.7, 133.9, 130.0, 118.3, 111.3.[10]262



4-fluorobenzonitrile C_7H_4FN (1j): 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+) ($C_{10}H_9NO_2$): calculated m/z: 121.0328, found: 121.0322. ^{1}H-NMR (300MHz, $CDCl_3$) δ/ppm: 7.74 (m, 2H), 7.21 (m, 2H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 165.0 (*J* = 130.0 Hz), 134.7 (*J* = 10.0 Hz), 118.0, 116.8 (*J* = 2.0 Hz), 108.6.[11]263

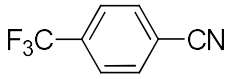


4-(methylsulfonyl)benzonitrile $C_8H_7NO_2S$ (1k): CAS# 22821-76-7**.**

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 on silica gel with petroleum ether-diethyl ether (9:1) afforded the title compound in 47% (213 mg) yield 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

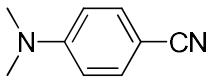
[262] G. Ishii, R. Harigae, K. Moriyama, H. Togo, *Tetrahedron* **2013,** *69*, 1462-1469.
[263] G. Ishii, K. Moriyama, H. Togo, *Tetrahedron Lett.* **2011,** *52*, 2404-2406.

(EI+) ($C_8H_7NO_2S$): calculated m/z: 181.0198, found: 181.0205. ^{1}H-NMR (300MHz, $CDCl_3$) δ/ppm: 7.83 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 2.76 (s, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 151.4, 133.0, 124.3, 117.7, 114.8, 43.8.[12]264



4-(trifluoromethyl)benzonitrile $C_8H_4F_3N$ (1l): 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 (300MHz, $CDCl_3$) δ/ppm: 7.85-7.77 (m, 4H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 134.6 (q, *J* = 34.0 Hz), 132.7, 126.2 (q, *J* = 3.5 Hz), 123.1 (q, *J* = 271.0 Hz), 117.5, 116.1.[13]265

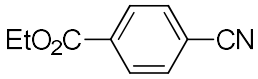


4-(dimethylamino)benzonitrile $C_9H_{10}N_2$ (1m): CAS# 1197-19-9**.**

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 (300MHz, $CDCl_3$) δ/ppm: 7.46 (d, *J* = 9.0 Hz, 2H), 6.63 (d,

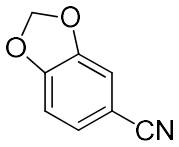
[264] B. Yu, A.-H. Liu, L.-N. He, B. Li, B.; Diao, Z.-F.; Li, Y.-N. *Green Chem.* **2012,** *14*, 957-962.
[265] Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012,** *134*, 9034-9037.

J = 9.0 Hz, 2H), 3.03 (s, 6H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 152.4, 133.4, 120.8, 111.4, 97.3, 39.9.[14]266



Ethyl 4-cyanobenzoate $C_{10}H_9NO_2$ (1n): CAS# 7153-22-2**.**

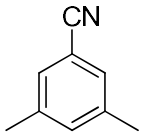
The arylzinc derivative was prepared in acetonitrile (4 mL) from ethly-4-bromobenzoate (0.62 mL, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.81 g, 3 mmol) and Zn dust (24 mg, 0.375 mmol). Purification 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 (300MHz, $CDCl_3$) δ/ppm: 8.15 (d, *J* = 9 Hz, 2H), 7.78 (d, *J* = 9 Hz, 2H), 4.41 (q, *J* = 7.0 Hz, 2H), 1.42 (t, *J* = 6.0 Hz, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 165.4, 134.9, 132.8, 130.4, 118.6, 116.7, 62.3, 14.5.[15] 267



Benzo[d][1,3]dioxole-5-carbonitrile $C_8H_5NO_2$ (1o): CAS# 4421-09-4**.**

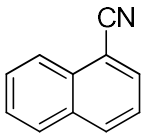
The arylzinc derivative was prepared in acetonitrile (4 mL) from 5-bromobenzo[d][1,3]dioxole (0.755 g, 3.75 mmol) as described in the general procedure. It was obtained in 80% GC yield (3.0 mmol). It was obtained in 80% GC yield (3.0 mmol). This solution was filtered and added to a solution of NTCS (0.68 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 (300MHz, $CDCl_3$) δ/ppm: 7.62 (dd, *J* = 9.0 Hz, 3 Hz, 1H), 7.07 (d, *J* = 3.0 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 6.10 (s, 2H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 151.5, 148.0, 128.2, 118.9, 111.4, 109.1, 104.9, 102.2.[10]

266 P. Anbarasan, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 4725-4728.
267 I.A. Azath, P. Suresh, K. Pitchumani, K. *New J. Chem.* **2012,** *36*, 2334-2339.



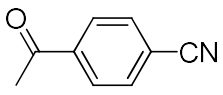
3,5-dimethylbenzonitrile C_9H_9N (1q): CAS# 22445-42-7**.**

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 (300MHz, $CDCl_3$) δ/ppm: 7.26 (s, 2H), 7.22 (s, 1H), 2.35 (s, 6H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 138.9, 134.4, 129.4, 119.0, 111.9, 20.8.[14] 17



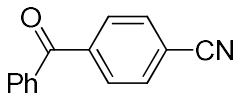
1-naphthonitrile $C_{11}H_7N$ (1r): CAS# 86-53-3**.**

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 (300MHz, $CDCl_3$) δ/ppm: 8.23 (d, J = 9.0 Hz, 1H), 8.07, (d, J = 9.0 Hz, 1H), 7.92-7.89 (m, 2H), 7.67-7.49 (m, 3H). ^{13}C-NMR (75MHz, $CDCl_3$) δ/ppm: 133.2, 132.9, 132.6, 132.3, 128.6, 128.6, 127.5, 125.1, 124.9, 117.8, 110.1.[18]



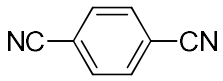
4-acetyl-benzonitrile C_9H_7NO (1s): CAS# 1443-80-7**.**

The arylzinc derivative was prepared in acetonitrile (4 mL) from benzonitrile (0.746 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 NTCS (0.41 g, 1.5 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 34% (0.074 g) yield as a white powder. HRMS (EI+) (C_9H_7NO): calculated m/z: 145.0528, found: 145.0521.^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.97 (d, *J* = 9.0 Hz, 2H), 7.70, (d, *J* = 6.0 Hz, 2H), 2.57 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 196.4, 139.9, 132.5, 128.7, 117.9, 116.4, 26.7. [16]268



4-cyanophenyl phenyl ketone $C_{14}H_9NO$ (1t): CAS# 1443-80-7

The arylzinc derivative was prepared in acetonitrile (4 mL) from benzonitrile (0.979 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 NTCS (0.41 g, 1.5 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 47% (0.146 g) yield as a white powder. HRMS (EI+)($C_{14}H_9NO$):calculated m/z: 207.0684, found: 207.0685.^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.82-7.79 (m, 2H), 7.73-7.70 (m, 4H), 7.60-7.55 (m, 1H), 7.47-7.42 (t, *J* = 15 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 195.0, 141.2, 136.4, 133.3, 132.2, 130.2, 130.0, 128.6, 118.0, 115.7.[17] 269



para-dicyanobenzene $C_8H_4N_2$ (1u): CAS# 1443-80-7

The arylzinc derivative was prepared in acetonitrile (4 mL) from benzonitrile (0.683 g, 3.75 mmol) as described in the general procedure with $CoBr_2$(bipy) instead of $CoBr_2$. It was obtained in 90% GC yield (3.4 mmol). This solution was filtered and added to a

[268] D. Shen, C. Miao, S. Wang, C. Xia, W. Sun, Org. Lett., **2014** , *16*, 1108-1111.
[269] Y. Fu, Y. Yang, H. M. Hügel, Z. Du, K. Wang, D. Huang, Y. Hu., *Org. Biomol. Chem.*, **2013**,*11*, 4429-4432.

solution of NTCS (0.41 g, 1.5 mmol) and Zn dust (24 mg, 0.375 mmol). Purification on silica gel with petroleum ether-diethyl ether (95:5-90:10) afforded the title compound in 52% (0.100 g) yield as a white powder. HRMS (EI+) ($C_8H_4N_2$): calculated m/z: 128.0374, found: 128.0374.^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm: 7.74 (s, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 132.8, 117.0, 116.7.[18]

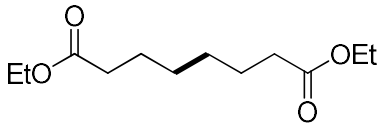
II Cobalt-Catalyzed C_{sp3}-C_{sp3} Reductive Coupling

II-1 Cobalt-Catalyzed C_{sp3}-C_{sp3} homocoupling

II-1-1 General General procedure for the homocoupling of alkyl halides

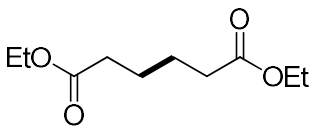
To a solution of $CoBr_2$ (10 mol%, 0.25 mmol, 55 mg) and manganese powder (3.8 equiv., 9.5 mmol, 500 mg) in CH_3CN (3 mL) was added at room temperature the alkyl halide (2.5 mmol). Manganese powder was activated by traces of trifluoroacetic acid (50 µL) and the medium was then stirred at room temperature for 5 minutes until smoke disappeared. At this time, pyridine or 2-picoline (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 quenched with a solution of 2M HCl (30 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 or solid by flash chromatography over silica with petroleum ether/diethyl ether (or ethyl acetate) mixtures afforded the pure compounds.

II-1-2 Characterization data for homocoupling products



Diethyl octanedioate $C_{12}H_{22}O_4$ (2a): CAS# 2050-23-9.

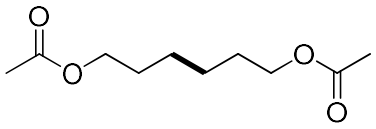
Prepared according to the general procedure from ethyl 4-bromobutanoate (487 mg, 2.50 mmol). Eluated from the column with petroleum ether-diethyl ether (10:1) in 84 % (244 mg) yield as a colorless oil. **HRMS** (EI+) **($C_{12}H_{22}O_4$):** calculated m/z: 230.1518, found: 230.1522. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 4.10 (q, *J* =7.1 Hz, 4H), 2.28 (t, *J* =7.5 Hz, 4H), 1.68-1.63 (m, 4H), 1.38-1.26 (m, 4H), 1.18 (t, *J* =7.1 Hz, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.7, 60.2, 34.2, 28.7, 24.7, 14.2.[270]



[270] M. R. Prinsell, D. A. Everson, D. J. Weix, *Chem. Commun*, **2010**, *46*, 5743-5745.

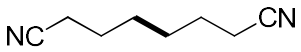
Diethyl adipate $C_{10}H_{18}O_4$ (2b): CAS# 141-28-6.

Prepared according to the general procedure using twice amount of all the reagents and solvent from ethyl 3-bromopropionate (0.64 mL, 5 mmol). Eluated from the column with petroleum ether-diethyl ether (10:1) in 65 % (330 mg) yield as a colorless oil. **HRMS** (EI+) **(**$C_{10}H_{18}O_4$**):** calculated m/z: 202.1205, found: 202.1209. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 4.09 (q, *J* =6.7 Hz, 4H), 2.28 (t, *J* =6.5 Hz, 4H), 1.72-1.55 (m, 4H), 1.22 (t, *J* =7.1 Hz, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 173.2, 60.2, 33.9, 24.4, 14.1.[271]



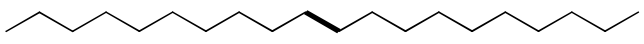
Hexane-1,6-diyl diacetate $C_{10}H_{18}O_4$ (2c): CAS# 6222-17-9.

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. **HRMS (**$C_{10}H_{18}O_4$**):** calculated m/z: 202.1205, found: $[M+H]^+$ 202.1204. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 4.04 (t, *J* =6.7 Hz, 4H), 2.03 (s, 6H), 1.67-1.56 (m, 4H), 1.42-1.33 (m, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 171.2, 64.4, 28.4, 25.6, 21.0.[272]



Octanedinitrile $C_8H_{12}N_4$ (2d): CAS# 629-40-3.

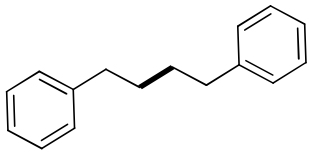
Prepared according to the general procedure from 4-bromobutanenitrile (0.50 mL, 5.0 mmol). Eluated from the column with petroleum ether-diethyl ether (9:1) in 88 % (300 mg) yield as a colorless oil. **HRMS** (EI+) **(**$C_8H_{12}N_4$**):** calculated m/z: 164.1062, found: 164.1064. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 2.33 (t, *J* =7.0 Hz, 4H), 1.72-1.57 (m, 4H), 1.53-1.37 (m, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 117.7, 27.8, 25.5, 17.5.[273]



[271] J. Yan, B. R. Travis, B. Borhan, *J. Org. Chem.*, **2004**, *69*, 9299-9302.
[272] D. Pfaff, G. Nemecek, J. Podlech, *Belstein. J. Org. Chem.* **2013,** *9*, 1572-1577.
[273] M. Ghiaci, M. E. Sedaghat, R. J. Kalbasi, A. Abbaspur, *Tetrahedron*, **2005**, *61*, 5529-5534.

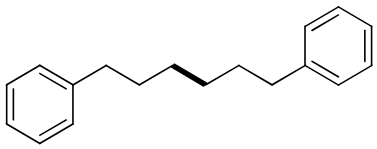
eicosane $C_{20}H_{42}$ (2e): CAS# 112-95-8.

Prepared according to the general procedure from 1-bromodecane (0.52 mL, 2.50 mmol). Eluated from the column with petroleum ether in 87 % (307 mg) yield as a colorless solid. **HRMS (**$C_{10}H_{18}O_4$**):** calculated m/z: 282.3286, found: 282.3301. $[M+H]^+$ 203. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 1.26 (s, 36H), 0.88 (t, *J* =6.7 Hz, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 31.9, 29.7, 29.4, 22.7, 14.1.



4-phenylbutylbenzene $C_{16}H_{18}$ (2f): CAS# 1083-56-3.

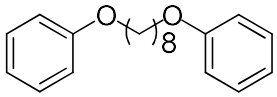
Prepared according to the general procedure using twice amount of all the reagents and solvent from (2-bromoethyl)benzene (0.68 mL, 5 mmol). Eluated from the column with petroleum ether in 74 % (340 mg) yield as a colorless oil. **HRMS** (EI+) **(**$C_{16}H_{18}$**):** calculated m/z: 210.1408, found: 210.1408. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.37-7.25 (m, 4H), 7.26-7.14 (m, 6H), 2.67 (t, *J* =7.0 Hz, 4H), 1.80-1.61 (m, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 142.6, 128.4, 128.3, 125.6, 35.8, 31.1.[1]



1,6-diphenylhexane $C_{18}H_{22}$ (2g): CAS# 1087-49-6.

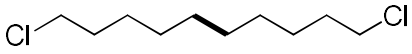
Prepared according to the general procedure using twice amount of all the reagents and solvent from 1-bromo-3-phenylpropane (0.76 mL, 5 mmol). Eluated from the column with petroleum ether in 72 % (430 mg) yield as a colorless oil. **HRMS** (EI+) **(**$C_{16}H_{18}$**):** calculated m/z: 238.1721, found: 238.1720. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.38-7.28 (m, 4H), 7.27-7.18 (m, 6H), 2.66 (t, *J* =7.7 Hz, 4H), 1.78-1.58 (m, 4H), 1.51-1.35 (m, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 142.8, 128.4, 128.2, 125.6, 36.0, 31.4, 29.2.[274]

[274] H. Yoshikazu, T. Yu, K. Kaori, A. Hitoshi, T. Kiyoshi, *Org. Lett.,* **2014**, *16*, 3184-3187.



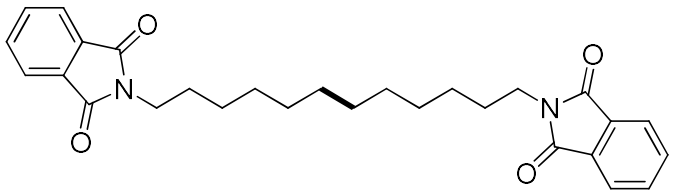
1,8-diphenoxyoctane $C_{20}H_{26}O_2$ (2h): CAS# 61575-01-7.

Prepared according to the general procedure using twice amount of all the reagents and solvent from 4-phenoxybutyl bromide (1.15 g, 5 mmol). Eluated from the column with petroleum ether in 77 % (430 mg) yield as a white solid. **HRMS** (EI+) **(**$C_{20}H_{26}O_2$**):** calculated m/z: 298.1933, found: 298.1938. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.44-7.21 (m, 4H), 7.13-6.86 (m, 6H), 4.01 (t, *J* =6.5 Hz, 4H), 1.85 (p, *J* = 6.5 Hz, 4H), 1.64-1.39 (m, 8H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 159.2, 129.4, 120.5, 114.6, 67.9, 29.3, 26.0.[275]



1,10-dichlorodecane $C_{10}H_{20}Cl_2$ (2i): CAS# 2162-98-3.

Prepared according to the general procedure from 1-bromo-5-chloropentane (927 mg, 5.0 mmol). Eluated from the column with petroleum ether in 56 % (307 mg) yield as a colourless oil. **HRMS** (EI+) **(**$C_{14}H_{14}$**):** calculated m/z: 210.0942, found: 210.0935. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 3.53 (t, *J* = 6.7 Hz, 4H), 1.77 (p, *J* = 6.8 Hz, 4H), 1.45-1.40 (m, 4H), 1.30 (s, 8H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 45.1, 32.6, 29.3, 28.8, 26.8.

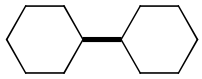


2,2'-(dodecane-1,12-diyl)bis(isoindoline-1,3-dione) $C_{28}H_{32}N_2O_4$ (2j): CAS# 27646-76-0.

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

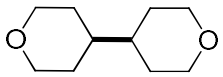
[275] M. Lamsa, J. Pursiainen, K. Rissanen, J. Huuskonen, *Acta Chemica Scandinavica,* **1998**, *52*, 563-570.

(dd, *J* = 5.5, 3.0 Hz, 4H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 4H), 3.66 (t, *J* =7.3 Hz, 4H), 1.65 (p, *J* = 7.2 Hz, 4H), 1.30-1.23 (m, 16H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 168.5, 133.8, 132.2, 123.1, 38.1, 29.5, 29.4, 29.1, 28.6, 26.8.



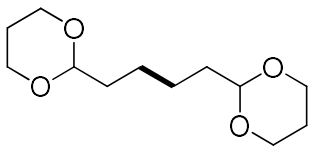
bicyclohexyl $C_{12}H_{22}$ (2k): CAS# 92-51-3.

Prepared according to the general procedure from cyclohexyl iodide (1050 mg, 5.0 mmol) or bromocyclohexane (0.62 mL, 5.0 mmol). Eluated from the column with petroleum ether in 53 % (130 mg) yield (68% yiled with bromocyclohexane) as a colourless oil. **HRMS** (EI+) **($C_{14}H_{14}$):** calculated m/z: 166.1721, found: 166.1719. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 1.76-1.44 (m, 10H), 1.32-0.69 (m, 12H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 43.4, 30.1, 26.9. [276]



octahydro-2H,2'H-4,4'-bipyran $C_{10}H_{18}O_2$ (2l):.

Prepared according to the general procedure from 4-bromotetrahydropyran (0.28 mL, 2.5 mmol). Eluated from the column with petroleum ether-diethyl ether (10:1) in 95 % (202 mg) yield as a colorless solid. **HRMS** (EI+) **($C_{10}H_{18}O_2$):** calculated m/z: 170.1307, found: 170.1257. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 3.97 (d, *J* =10.1 Hz, 4H), 3.33 (t, *J* =11.9 Hz, 4H), 1.61 (d, *J* =9.6 Hz, 4H), 1.28 (s, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 68.2, 40.2, 30.0.

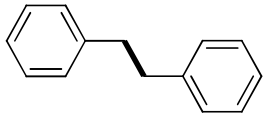


2-[4-(1,3-dioxan-2-yl)butyl]-1,3-dioxane $C_{10}H_{18}O_2$ (2m): CAS# 111865-42-0.

Prepared according to the general procedure from 2-(2-bromoethyl)-1,3-dioxane (0.42 mL, 2.5 mmol). Eluated from the column with petroleum ether-ethyl acetate (10:1-5:1) in 87 % (310 mg) yield as a colorless oil. **HRMS** (EI+) **($C_{10}H_{18}O_2$):** calculated m/z:

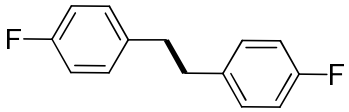
[276] X. Xu, D. Cheng, P. Wen, *J. Org. Chem.,* **2006**, *71*, 6637-6639.

230.1518, found: 230.1440. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 4.49 (t, *J* = 5.2 Hz, 2H), 4.11-4.05 (m, 4H), 3.86-3.57 (m, 4H), 2.13-2.02 (m, 2H), 1.57 (dd, *J* = 5.0, 2.3 Hz, 4H), 1.40-1.29 (m, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 102.2, 66.8, 35.1, 25.8, 23.8.[277]



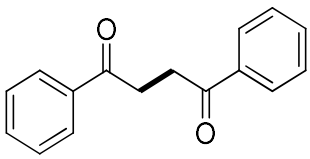
1,2-diphenylethane $C_{14}H_{14}$ (2n): CAS# 103-29-7.

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: 7.40−7.32 (m, 4H), 7.30−7.22 (m, 6H), 2.99 (s, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 141.8, 128.5, 128.4, 125.9, 38.0.[278]



4,4'-difluorobibenzyl $C_{14}H_{12}F_2$ (2o): CAS# 458-76-4.

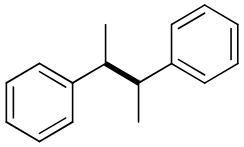
Prepared according to the general procedure using twice amount of all the reagents and solvent from 4-fluorobenzyl chloride (0.60 mL, 5 mmol). Eluated from the column with petroleum ether in 79 % (420 mg) yield as a colorless oil. **HRMS** (EI+) **($C_{10}H_{18}O_4$):** calculated m/z: 256.0875, found: 256.0870. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.12-7.07 (m, 4H), 6.99-6.94 (m, 4H), 2.88 (s, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 161.4 (d, J = 243.6 Hz), 136.9 (d, *J* = 3.3 Hz), 129.8 (d, *J* = 7.8 Hz), 115.0 (d, *J* = 21.1 Hz), 37.1.[279]



[277] M. Guisán-Ceinos, F. Tato, E. Buñuel, B. Calle, D. J. Cárdenas, *Chem. Sci.* **2013**, *4*, 1098-1104.
[278] C. E. Hartmann, V. Jurcik, O. Songis, C. S. J. Cazin, *Chem. Commun.* **2013**, *49*, 1005-1007.
[279] K. Sato, Y. Inoue, T. Mori, A. Anto, *et al. Org. Lett.* **2014**, *16*, 3756-3759.

1,4-diphenylbutane-1,4-dione $C_{16}H_{14}O_2$ (2p): 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: 8.04 (d, *J* = 7.1 Hz, 4H), 7.63-7.54 (m, 2H), 7.48 (t, *J* =7.4 Hz, 4H), 3.46 (s, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 198.7, 136.7, 133.1, 128.6, 128.1, 32.6.[280]

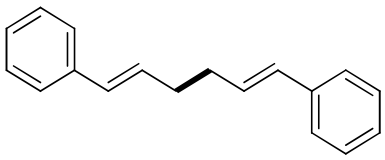


2,3-diphenylbutane $C_{16}H_{18}$ (2q): CAS# 2726-21-8.

Prepared according to the general procedure using twice amount of all the reagents and solvent from 4-fluorobenzyl chloride (0.60 mL, 5 mmol). Eluated from the column with petroleum ether in 79 % (420 mg) yield as a colorless oil. **HRMS** (EI+) **($C_{10}H_{18}O_4$):** calculated m/z: 256.0875, found: 256.0870. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.41-7.28 (m, 4H), 7.27-7.22 (m, 6H), 2.89-2.78 (m, 2H), 1.09-1.02 (m, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 146.5, 128.3, 127.6, 126.0, 77.4, 77.0, 76.6, 47.3, 21.0.[10]

tetradecane $C_{14}H_{30}$ (2r): CAS# 629-59-4.

Prepared according to the general procedure from 1-iodoheptane (0.76 mL, 5.0 mmol). Eluated from the column with petroleum ether in 60 % (296 mg) yield as a colourless oil. **HRMS** (EI+) **($C_{14}H_{14}$):** calculated m/z: 198.2347, found: 198.2345. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 1.19 (s, 24H), 0.81 (t, *J*=6.6 Hz, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 31.9, 29.7, 29.6, 29.3, 22.6, 14.0.[281]

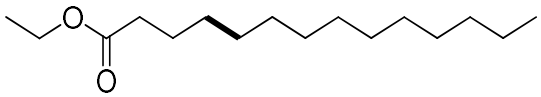


[280] L. Zhang, G. Y. Ang, S. Chiba, *Org. Lett.* **2011**, *13*, 1622-1625.
[281] Y. Imada, T. Kitagawa, T. Ohno, H. Iida, T. Naota, T. *Org. Lett.* **2010**, *12*, 32-35

(1*E*,5*E*)-1,6-diphenylhexa-1,5-diene $C_{18}H_{18}$ (2s): 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 in 72 % (293 mg) yield as a white powder. **HRMS** (EI+) **($C_{14}H_{14}$):** calculated m/z: 234.1409, found: 234.1409. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.49-7.28 (m, 8H), 7.29-7.20 (m, 2H), 6.49 (d, *J* =15.8 Hz, 2H), 6.42-6.24 (m, 2H), 2.44 (t, *J* = 6.4 Hz, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 137.8, 130.4, 130.0, 128.5, 127.0, 126.0, 33.0.[282]

II-1 Cobalt-Catalyzed C_{sp3}-C_{sp3} reductive cross-coupling



Ethyl tetradecanoate $C_{16}H_{32}O_2$ (3a): 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 (974 mg, 5.0 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), isoquinoline (10 mol%, 0.25 mmol, 0.09 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 2M HCl (50 mL). The mixture was stirred vigorously until layers turned clear. The solution was extracted with ethyl acetate (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 70 % (170 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 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.[283]

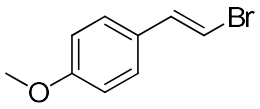
[282] T. Sprott, K.; Corey, E.J. *Org. Lett.* **2005**, *5*, 2465-2467.
[283] G. Cahiez, C. Chaboche, C. Duplais, A. Giulliani, A. Moyeux, *Adv. Syn. Cat.* **2008,** *350*, 1484-1488.

III Cobalt-Catalyzed Reductive Cross-Coupling of Vinyl with Benzyl Halides

III-1 General procedures for preparation of vinyl bromides

III-1-1 Synthesis of (2-bromovinyl)-4-methoxybenzene

To a solution of 4-methoxy cinnamic acid (20 mmol) in DCM (200 mL) was added Et_3N (1 mmol). After stirred for 5 min, NBS (25 mmol) was added in one portion. The resulting mixture was stirred for 14 h and the solvents were removed under reduced pressure. The solid residue was washed repetitively with petroleum ether and combined organic layers were evaporated under vacuum. The residue was purified by column chromatography over silica gel to give the desired (2-bromovinyl)-4-methoxybenzene as white solid.



(*E*)-1-(2-bromovinyl)-4-methoxybenzene (4b): CAS# 6303-59-9.

HRMS (EI+) **(**C_9H_9BrO**):** calculated m/z: 211.9837, found: 211.9832. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.24 (d, *J* =8.7 Hz, 2H), 7.05 (d, *J* =14.0 Hz, 1H), 6.86 (d, *J* =8.8 Hz, 2H), 6.62 (d, *J* =13.9 Hz, 1H), 3.81 (s, 3H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 159.63, 136.53, 128.73, 127.35, 114.17, 103.99, 55.30.[284]

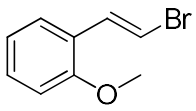
III-1-2 Synthesis of functionalized vinyl bromides from aldehydes

To an oven-dried flask was added aldehyde (1 equiv.), CBr_4 (1.5 equiv.), Zn dust (1 equiv.) and DCM. The flask was cooled to 0 °C and a solution of PPh_3 in DCM was added dropwise via addition funnel over 30 min. The solution was stirred at 0 °C to room temperature until the aldehyde was consumed. Then the solution was diluted with DCM and washed with water and brine. After drying over $MgSO_4$, the mixture was filtered and concentrated under vacuum. A large quantity of petroluem ether was added to the concentrated solution and white solid precipitated. After, the filtrate was

[284] D. Chang, Y. Gu, Q. Shen. *Chem. Eur. J.*, **2015**, *21*, 6074-6078

evaporated under vacuum. The residue was purified by colomn chromatography over silica gel to get the dibromoalkene.

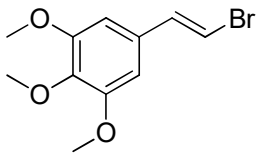
To a solution of dibromoalkene (1 equiv.) in DMF was added diethyl phosphite (3.0 equiv.). The solution was cooled to 0 °C and Et3N (3.0 equiv.) was added dropwise. The mixture was allowed to be warmed to room temperature and kept stirred overnight. The mixture was diluted with water and extracted with DCM. The organic layer was washed with water and brine. After drying over MgSO4, the mixture was filtered and evaporated. The residue was purified by colome chromatography over silica gel to get the desired vinyl bromide.



(*E*)-1-(2-Bromovinyl)-2-methoxybenzene (4c):

Prepared from 2-methoxybenzaldehyde (2.72 g, 20.0 mmol) according to general procedure B. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate =98/2) to yield 1-(2-Bromovinyl)-2-methoxybenzene (1.86 g, 44%) as colorless liquid.

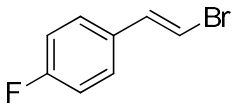
HRMS (EI+) **(**C_9H_9BrO**):** calculated m/z: 211.9837, found: 211.9832. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.35-7.25 (m, 3H), 6.95 -6.93 (m, 3H), 3.86 (s, 3H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 156.57, 133.03, 129.25, 127.94, 124.75, 120.70, 110.96, 107.86, 55.40.



(*E*)-1-(2-Bromovinyl)-3,4,5-trimethoxybenzene (4d):

Prepared from 3,4,5-trimethoxybenzaldehyde(3.92 g, 20.0 mmol) according to general procedure B. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate =9/1) to yield 1-(2-Bromovinyl)-3,4,5-trimethoxybenzene (2.61 g, 48%) as colorless liquid.

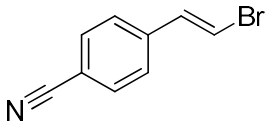
HRMS (EI+) **(**$C_{11}H_{13}BrO_3$**):** calculated m/z: 272.0048, found: 272.0050. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.00 (d, *J* = 13.9 Hz, 1H), 6.67 (d, *J* = 13.9 Hz, 1H), 6.49 (s, 2H), 3.84 (s, 6H), 3.83 (s, 3H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 153.39, 138.35, 137.02, 131.57, 105.80, 103.29, 60.83, 56.09.



(*E*)-1-(2-Bromovinyl)-4-fluorobenzene (4e): CAS# 870122-74-0.

Prepared from 4-fluorobenzaldehyde (2.1 mL, 20.0 mmol) according to general procedure B. The crude residue was purified by column chromatography over silica gel (petroleum ether) to yield 1-(2-Bromovinyl)-4-fluorobenzene (1.82 g, 46%) as colorless liquid.

HRMS (EI+) **(**C_8H_6BrF**):** calculated m/z: 199.9637, found: 199.9642. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.35-7.21 (m, 2H), 7.13-6.96 (m, 3H), 6.69 (d, *J* =14 Hz, 1H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 162.58 (d, *J* = 248.3 Hz), 135.96, 132.12 (d, *J* = 3.4 Hz), 127.70 (d, *J* = 8.1 Hz), 115.93, 115.79 (d, J = 21.8 Hz), 106.09 (d, *J* = 2.5 Hz).

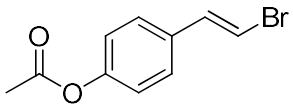


(*E*)-4-(2-Bromovinyl)benzonitrile (4g): CAS# 60606-71-5

Prepared from 4-cyanobenzaldehyde(1.31 g, 10.0 mmol) according to general procedure B. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate =95/5) to yield 4-(2-Bromovinyl)benzonitrile (1.30 g, 62%) as white solid.

HRMS (EI+) **(**C_9H_6BrN**):** calculated m/z: 206.9684, found: 206.9686. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.61 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* =

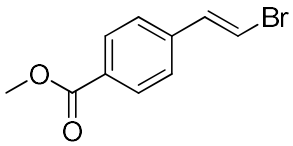
14.1 Hz, 1H), 6.96 (d, *J* = 14.1 Hz, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 140.03, 135.64, 132.62, 126.55, 118.58, 111.61, 110.84.[285]



(*E*)-4-(2-Bromovinyl)phenyl acetate (4h):

Prepared from 4-acetoxybenzaldehyde (1.41 mL, 10.0 mmol) according to general procedure B. The crude residue was purified by column chromatography over silica gel (petroleum ether) to yield 4-(2-Bromovinyl)phenyl acetate (0.70 g, 29%) as white solid.

HRMS (EI+) **($C_{10}H_9BrO_2$):** calculated m/z: 239.9786, found: 239.9787. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.30 (d, *J* = 8.5 Hz, 2H), 7.12-7.03 (m, 3H), 6.73 (d, *J* = 14.0 Hz, 1H), 2.30 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 169.21, 150.50, 136.17, 133.65, 127.09, 121.96, 106.66, 21.10.[1]

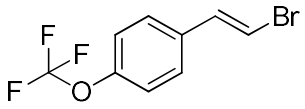


(*E*)-Methyl-4-(2-bromovinyl)benzoate (4i):

Prepared from 4-formylbenzoate (1.64 g, 10.0 mmol) according to general procedure B. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 95/5) to yield methyl-4-(2-bromovinyl)benzoate (1.31 g, 54%) as white solid.

HRMS (EI+) **($C_{10}H_9BrO_2$):** calculated m/z: 239.9786, found: 239.9787. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.96 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 14.1 Hz, 1H), 6.89 (d, *J* = 14.0 Hz, 1H), 3.89 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 166.53, 140.00, 136.28, 130.07, 129.59, 125.93, 109.43, 52.16.[1]

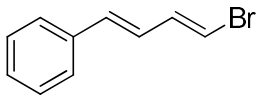
[285] L-Y. He, M. Shulz-Senft, B. Thiedemann, J. Linshoeft, P. J. Gates, A. Staubitz. *Eur. J. Org. Chem.*, **2015**, 2498-2502



(*E*)-1-(2-Bromovinyl)-4-trifluoromethoxybenzene (4j):

Prepared from 4-trifluoromethoxybenzaldehyde (1.43 mL, 10.0 mmol) according to general procedure B. The crude residue was purified by column chromatography over silica gel (petroleum ether) to yield 1-(2-Bromovinyl)-4-triluofomethoxybenzene (1.07 g, 40%) as yellow liquid.

HRMS (EI+) **(**$C_9H_6BrF_3O$**):** calculated m/z: 265.9554, found: 265.9563. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.32 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 14.0 Hz, 1H), 6.78 (d, *J* = 14.0 Hz, 1H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 148.94 (q, *J* = 1.6 Hz), 135.71, 134.59, 127.36, 121.21, 120.39 (q, *J* = 257.5 Hz), 107.46.[286]



(4-bromobuta-1,3-dien-1-yl)benzene (4k): CAS# 77150-87-9

Prepared from cinnamaldehyde (2.52 g, 20.0 mmol) according to general procedure B. The crude residue was purified by column chromatography over silica gel (petroleum ether) to yield methyl-4-(2-bromovinyl)benzoate (1.52 g, 36%) as white solid. To a vial containing (4-bromobuta-1,3-dien-1-yl)benzene (1.52 g, 7.2 mmol) was added NaOH (0.85 equiv.) and isopropanol (15 mL). The mixture was stirred at reflux for 2h and cooled to room temperature. Then the mixture was diluted with pentane and water. The organic layer was washed with HCl, water and brine, and dried with $MgSO_4$. After filtration, the filtrate was concentrated under vacuum and the residue was purified with column chromatography over silica gel (petroleum ether) to obtain ((*1E*, *3E*)-(4-bromobuta-1,3-dien-1-yl))benzene (1.45 g, 34%).

HRMS (EI+) **(**$C_{10}H_9BrO_2$**):** calculated m/z: 207.9888, found: 207.9880. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: δ 7.47 – 7.38 (m, 2H), 7.38 – 7.22 (m, 3H), 6.90 (dd, *J* = 13.4, 10.2 Hz, 1H), 6.77 – 6.53 (m, 2H), 6.44 (d, *J* = 13.4 Hz, 1H). ^{13}**C-NMR** (75

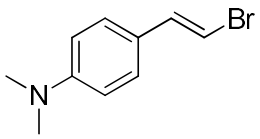
[286] A.H. Cherney, S. E. Reisman. *J. Am. Chem. Soc*., **2014**, *136*, 14365-14368

MHz, $CDCl_3$) δ/ppm: 137.68, 136.58, 133.37, 128.72, 128.06, 126.52, 126.04, 108.94.[287]

III-1-3 Synthesis of 4-(2-bromovinyl)-N,N-dimethylaniline

To a stirred solution of 4-dimethylaminobenzaldehyde (2.98 g, 20.0 mmol) and malonic acid (2.29 g, 22.0 mmol) in pyridine (10 mL) was added piperidine (0.20 mL, 2.0 mmol) at romm temperature. The reaction mixture was heated to 80 °C for 25 h. After cooling down to room temperature, the reaction mixture was poured into ice-cooled aqueous hydrochloric acid (50 mL, 1 N) and yellow solid precipitated. The yellow precipitate was filtered and washed with cooled water and acetone to afford product (2.0 g, 53%) as yellow solid.

To a stirred suspension of tetraethylammonium bromide (2.30 g, 11.0 mmol) in DCM (100 mL) was added iodosobenzene diacetate (3.54 g, 11.0 mmol). The reaction mixture was stirred at room temperature for 5 min and then (*E*)-3-(4-(dimethylamino)phenyl)acrylic acid (1.91 g, 10.0 mmol) was added in one portion and stirred at room temperature for 19 h. The reaction mixture was diluted with DCM (100 mL) and washed successively with aqueous $NaHSO_3$ (10%, 3 x 80 mL), aqueous $NaHCO_3$ (10%, 3 x 80 mL), H_2O (2 x 80 mL) and brine (1x 100 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue obtained was purified by column chromatography over silica gel (petroleum ether / ethyl acetate: 9 / 1) to afford the product (0.53 g, %), as a colorless solid.



(*E*)-4-(2-bromovinyl)-*N*,*N*-dimethylaniline (4f):

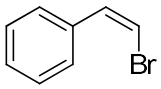
HRMS (EI+) **(**$C_{10}H_{12}BrN$**):** calculated m/z: 225.0153, found: 225.0159. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.21 (d, *J* =8.7 Hz, 2H), 7.02 (d, *J* =13.9 Hz, 1H), 6.68 (d, *J* =8.9 Hz, 2H), 6.53 (d, *J* =13.9 Hz, 1H), 2.98 (s, 6H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 150.34, 136.98, 127.16, 124.31, 112.26, 101.51, 40.37.[2]

III-1-4 Synthesis of (*Z*)-(2-bromovinyl)benzene

[287] M. Qian, Z. Huang, E. Negeshi, *Org. Lett.* **2004**, *6*, 1531-1534

To a mixture of cinnamic acid (5.34 g, 30 mmol) and AcOH (15 mL) was added bromine (1.78 mL, 33 mmol) dropwise and the resulting solution was stirred at room temperature until cinnamic acid was consumed (1-2 h). The reaction was quenched by a solution of Na2S2O3 (1 M, 15 mL). The precipitate was filtered and washed with water and chloroform (6 mL) to give the crude product 2,3-dibromo-3-phenylpropanoic acid (8.6g), which was used in the next step without purified.

Triethylamine (8.1mL) was added dropwise to the mixture of 2,3-dibromo-3-phenylpropanoic acid and dry DMF (35mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 5 h. Water (20mL) was added to quench the reaction. The mixture was extracted with pentane (3 x 40mL). The organic layers were combined, washed with water (2 x 40mL) and brine(40mL), dried over $MgSO_4$ and concentrated in vacuum, purified by column chromatography over silica gel with petroleum ether/ethyl acetate=20/1 to give 4.23g of (Z)-(2-bromovinyl)benzene (77% yield).



(*Z*)-(2-bromovinyl)benzene: CAS#41380-64-7

HRMS (EI+) **(**C_8H_7Br**):** calculated m/z:, found:. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.73 (d, *J* =8.3 Hz, 2H), 7.50-7.30 (m, 3H), 7.11 (d, *J* =8.1 Hz, 1H), 6.47 (d, *J* =8.1 Hz, 1H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 134.64, 132.37, 129.00, 128.35, 128.26, 106.39.[288]

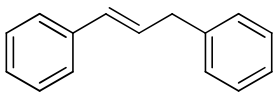
III-2 General procedure for cross-coupling of vinyl bromide and benzyl chloride

To an oven-dried flask were added $CoBr_2(PPh_3)_2$ (0.125 mmol), Mn (4.75 mmol), NaI (0.675 mmol) and MeCN (2 mL). Then TMSCl (30 mmol%) was added to activate Mn. After the mixture was cooled down to room temperature (around 5 min), vinyl bromide (1.25 mmol) and benzyl chloride (2.5 mmol) was added. The medium was stirred until the starting materials were all consumed (around 4 h). The medium was cooled to 0 °C or heated to 50 °C depending on the starting materials. The reaction

[288] C. Kuang, Q. Yang, H. Senboku, M. Tokuda. *Tetrahedron,* **2005**, *61*, 4043-4052

was quenched with HCl and extracted with ethyl acetate. The organic layer was washed with brine and dried over MgSO4. After evaporation, the residue was purified by column chromatography over silica gel.

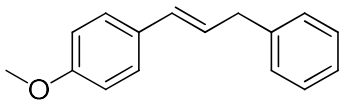
III-3 Characterization of cross-coupling products



(*E*)-1,3-diphenylpropene (6aa): CAS#2412-44-0

Prepared from β-bromostyrene (2.5 mmol) and benzyl chloride (5 mmol) according to general procedure III-2 using twice amount of reagents at 0 °C - r.t. The yield was calculated by adding mesitylene as internal standard on NMR (86%) after filtration over silica gel.

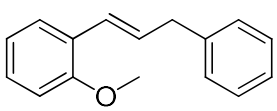
HRMS (EI+) **(**$C_{10}H_9BrO_2$**):** calculated m/z: 194.1096, found:194.1092.



(*E*)-1-(4-Methoxyphenyl)-3-phenylpropene (6ba):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (2.5 mmol) and benzyl chloride (5 mmol) according to general procedure III-2 using twice amount of reagent at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield 1-(4-Methoxyphenyl)-3-phenylpropene (0.447 g, 80%) as colorless oil.

HRMS (EI+) **(**$C_{16}H_{16}O$**):** calculated m/z: 224.1201, found: 224.1208. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.43-7.27 (m, 7H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.39-6.23 (m, 1H), 3.85 (s, 3H), 3.61 (d, *J* = 6.8 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 158.90, 140.49, 130.48, 130.36, 128.69, 128.49, 127.27, 127.09, 126.14, 113.97, 55.29, 39.38.[289]

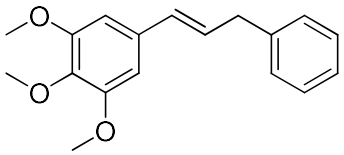


[289] H. Yang, P. Sun, Y. Zhu, J. Mao, *et al. Chem. Commun.*, **2012**, *48*, 7847-7849

(*E*)-1-(2-Methoxyphenyl)-3-phenylpropene (6ca): CAS# 1246889-00-6

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (1.25 mmol) and benzyl chloride (2.5 mmol) according to general procedure III-2 at r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield 1-(2-Methoxyphenyl)-3-phenylpropene (0.251 g, 90%) as colorless oil.

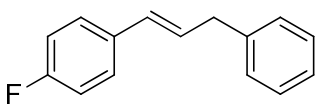
HRMS (EI+) **($C_{16}H_{16}O$):** calculated m/z: 224.1201, found: 224.1205. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.49 (d, *J* = 9.1 Hz, 1H), 7.40-7.21 (m, 6H), 7.00-6.83 (m, 3H), 6.51-6.33 (m, 1H), 3.89 (s, 3H), 3.64 (d, *J* = 7.0 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 156.50, 140.59, 129.83, 128.68, 128.48, 128.16, 126.67, 126.57, 126.10, 125.84, 120.67, 110.87, 55.48, 39.92.[5]



(*E*)-1-(3,4,5-Trimethoxyphenyl)-3-phenylpropene (6da):

Prepared from (*E*)-1-(2-bromovinyl)-3,4,5-trimethoxybenzene (1.25 mmol) and benzyl chloride (2.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 95/5) to yield 1-(3,4,5-trimethoxyphenyl)-3-phenylpropene (0.317 g, 89%) as white solid.

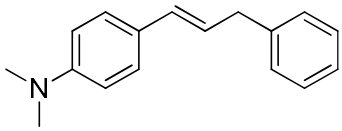
HRMS (EI+) **($C_{18}H_{20}O_3$):** calculated m/z: 284.1412, found: 284.1417. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.37-7.21 (m, 5H), 6.60 (s, 2H), 6.45-6.21 (m, 2H), 6.44-6.36 (m, 1H), 3.87 (s, 6H), 3.85 (s, 3H), 3.56 (d, *J* = 6.4 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 153.29, 140.08, 137.51, 133.23, 130.93, 128.81, 128.72, 128.52, 126.24, 103.20, 60.91, 56.06, 39.28.[5]



(*E*)-1-(4-fluorophenyl)-3-phenylpropene (6ea):

Prepared from (*E*)-1-(2-bromovinyl)-4-fluorobenzene (2.5 mmol) and benzyl chloride (5 mmol) according to general procedure III-2 using twice amount of reagent at r.t. The yield was calculated by adding mesitylene as internal standard on NMR (62%) after filtration over silica gel.

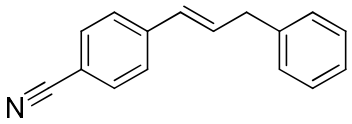
HRMS (EI+) **(**$C_{15}H_{13}F$**):** calculated m/z: 212.1001, found: 212.0999.



(*E*)-1-(4-(*N*,*N*-(dimethylamino)phenyl)-3-phenylpropene (6fa) :

Prepared from (*E*)-1-(2-bromovinyl)-*N*,*N*-dimethylaniline (1.25 mmol) and benzyl chloride (2.5 mmol) according to general procedure III-2 at 0 °C – r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 98/2) to yield N,N-dimethyl-4-(3-phenylprop-1-en-1-yl)aniline (0.140 g, 47%) as white solid.

HRMS (EI+) **(**$C_{17}H_{19}N$**):** calculated m/z: 237.1517, found: 237.1522. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.37-7.21 (m, 7H), 6.70 (d, *J* = 8.9 Hz, 2H), 6.41 (d, *J* = 15.7 Hz, 1H), 6.22-6.12 (m, 1H), 3.55 (d, *J* = 6.7 Hz, 2H), 2.96 (s, 6H).[290] ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 149.84, 140.89, 130.92, 128.66, 128.40, 127.01, 126.26, 126.00, 124.98, 112.62, 40.63, 39.43.



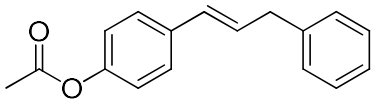
(*E*)-4-(3-phenylprop-1-enyl)benzonitrile (6ga):

Prepared from (*E*)-4-(2-bromovinyl)benzonitrile (1.25 mmol) and benzyl chloride (2.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 97/3) to yield (*E*)-4-(3-phenylprop-1-enyl)benzonitrile (0.079 g, 29%) as white solid.

HRMS (EI+) **(**$C_{16}H_{13}N$**):** calculated m/z: 219.1148, found: 219.1074. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.57 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* =

[290] Reference only for ^{1}H NMR: Y. Shen, J. Yao. *J. Org. Chem.*, **1996**, *61*, 8659-8661

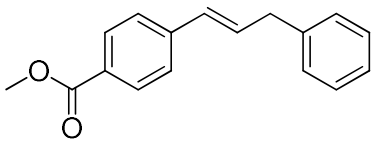
7.2 Hz, 2H), 7.25 (t, *J* = 6.6 Hz, 3H), 6.59-6.39 (m, 2H), 3.59 (d, *J* = 5.8 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 141.94, 139.17, 133.59, 132.34, 129.54, 128.68, 128.65, 126.58, 126.48, 119.04, 110.30, 39.37.[291]



(*E*)-4-(3-phenylprop-1-enyl)phenyl acetate (6ha):

Prepared from (*E*)-4-(2-Bromovinyl)phenyl acetate (1.25 mmol) and benzyl chloride (2.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 96/4) to yield (*E*)-4-(3-phenylprop-1-enyl)phenyl acetate (0.250 g, 80%) as white solid.

HRMS (EI+) **($C_{17}H_{16}O_2$):** calculated m/z: 252.1150, found: 252.1152. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.36 (dd, *J* = 15.4, 7.9 Hz, 4H), 7.26 (d, *J* = 7.3 Hz, 3H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.47 (d, *J* = 15.4 Hz, 1H), 6.41-6.25 (m, 1H), 3.57 (d, *J* = 6.5 Hz, 2H), 2.31 (s, 3H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 169.46, 149.70, 140.04, 135.32, 130.11, 129.53, 128.66, 128.52, 127.04, 126.23, 121.59, 39.30, 21.12.



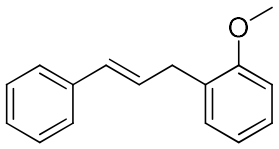
(*E*)-methyl-4-(3-phenylprop-1-enyl)benzoate (6ia): CAS#1012036-96-2

Prepared from methyl 4-(2-Bromovinyl)benzoate (1.25 mmol) and benzyl chloride (2.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 96/4) to yield (*E*)-methyl-4-(3-phenylprop-1-enyl)benzoate (0.213 g, 68%) as colorless oil.

HRMS (EI+) **($C_{17}H_{16}O_2$):** calculated m/z: 252.1150, found: 252.1150. ^{1}**H-NMR** (300 MHz, $CDCl_3$): 7.99 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.38-7.31 (m, 2H), 7.27 (d, *J* = 6.7 Hz, 3H), 6.51(t, *J* = 4.1 Hz, 2H), 3.92 (s, 3H), 3.59 (d, *J* = 4.9 Hz, 2H).

[291] H. Yang, H. Yan, P. Sun, J. Mao, *et al, Green Chem.*, **2013**, *15*, 976-981

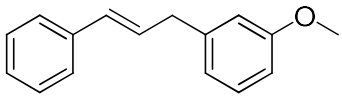
^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm: 166.93, 141.97, 139.57, 132.22, 130.21, 129.90, 128.71, 128.60, 128.56, 126.37, 125.99, 52.04, 39.44.[292]



(*E*)-3-(2-Methoxylphenyl)-1-phenylpropene (6ab):

Prepared from β-bromostyrene (2.5 mmol) and 2-methoxy benzylchloride (5.0 mmol) according to general procedure III-2 at r.t. using twice amount of reagents. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-3-(2-methylphenyl)-1-phenylpropene (0.320g, 80%) as colorless oil.

HRMS (EI+) **($C_{16}H_{16}O$):** calculated m/z: 224.1201, found: 224.1200. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.44 (d, *J* = 7.0 Hz, 2H), 7.40-7.24 (m, 5H), 6.98 (dd, *J* = 18.9, 7.9 Hz, 2H), 6.66-6.35 (m, 2H), 3.91 (s, 3H), 3.64 (d, *J* = 5.2 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 157.35, 137.85, 130.76, 129.92, 128.98, 128.73, 128.50, 127.48, 126.95, 126.14, 120.61, 110.43, 55.42, 33.48.[293]



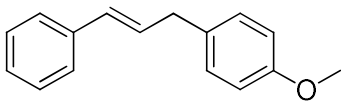
(*E*)-3-(2-Methxoylphenyl)-1-phenylpropene (6ac):

Prepared from β-bromostyrene (2.5 mmol) and 3-methoxy benzylchloride (5.0 mmol) according to general procedure 3. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-3-(3-methoxylphenyl)-1-phenylpropene (0.308g, 77%) as colorless oil.

HRMS (EI+) **($C_{16}H_{16}O$):** calculated m/z: 224.1201, found: 224.1200. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ/ppm: δ 7.50 – 7.15 (m, 6H), 6.97 – 6.76 (m, 3H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.47-6.32 (m, 1H), 3.84 (s, 3H), 3.57 (d, *J* = 6.5 Hz, 2H). **^{13}C-NMR** (75 MHz,

[292] G. Hamasaka, F. Sakurai, Y. Uozumi, *Chem. Commun.*, **2015**, *51*, 3886-3888
[293] L. L. Anka-Lufford, M. R. Prinsell, D. J. Weix, *J. Org. Chem*., **2012**, *77*, 9989-10000.

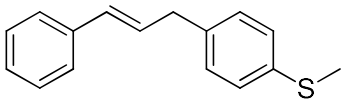
$CDCl_3$) δ/ppm: 159.80, 141.84, 137.49, 131.19, 129.49, 129.05, 128.54, 127.16, 126.18, 121.10, 114.42, 111.56, 55.21, 39.43.[294]



(*E*)-3-(4-Methylphenyl)-1-phenylpropene (6ad):

Prepared from β-bromostyrene (2.5 mmol) and 4-methoxy benzylchloride (5.0 mmol) according to general procedure III-2 at r.t. using twice amount of reagents. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-3-(4-Methylphenyl)-1-phenylpropene (0.210g, 37%) as colorless oil.

HRMS (EI+) **(**$C_{16}H_{16}O$**):** calculated m/z: 224.1201, found: 224.1200. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.44 – 7.31 (m, 4H), 7.23 (dd, *J* = 14.0, 7.9 Hz, 3H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.57 – 6.31 (m, 2H), 3.84 (s, 3H), 3.54 (d, *J* = 6.2 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 158.10, 137.56, 132.19, 130.76, 129.70, 129.62, 128.51, 127.06, 126.13, 113.94, 55.29, 38.48.[295]



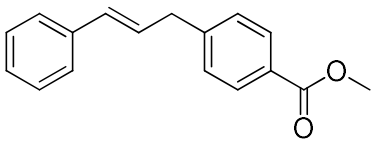
(*E*)-3-(4-Methylthiophenyl)-1-phenylpropene (6ae):

Prepared from β-bromostyrene (1.25 mmol) and 2-methoxy benzylchloride (2.5 mmol) according to general procedure III-2 at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-3-(4-methylthiophenyl)-1-phenylpropene (0.121g, 40%) as colorless oil.

HRMS (EI+) **(**$C_{16}H_{16}S$**):** calculated m/z: 240.0973, found: 240.0972. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.41-7.28 (m, 4H), 7.21 (q, *J* = 8.3 Hz, 5H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.40-6.28 (m, 1H), 3.52 (d, *J* = 6.4 Hz, 2H), 2.49 (s, 3H). ^{13}**C-NMR** (75

[294] E. Alacid, C. Nájera, *J. Org. Chem.* **2009**, *74*, 2321-2327.
[295] T. Nishikata, B. H. Lipshutz, *J. Am. Chem. Soc.*, **2009**, *131*, 12103–12105

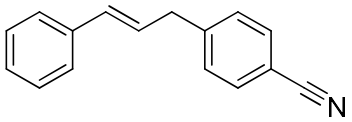
MHz, $CDCl_3$) δ/ppm: 137.39, 137.22, 135.84, 131.15, 129.20, 129.01, 128.50, 127.22, 127.13, 126.11, 38.76, 16.30.[296]



(*E*)-3-(4-methylsulfonylphenyl)-1-phenylpropene (6af):

Prepared from β-bromostyrene (1.25 mmol) and 4-(methylsulfonyl)benzyl chloride (2.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 98/2) to yield (*E*)-3-(4-methylsulfonylphenyl)-1-phenylpropene (g, 90%) as colorless oil.

HRMS (EI+) **(**$C_{16}H_{16}O$**):** calculated m/z: 272.0871, found: 272.0877. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 8.00 (d, *J* = 8.2 Hz, 2H), 7.41 - 7.27 (m, 6H), 7.27 – 7.20 (m, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.42-6.27 (m, 1H), 3.92 (s, 3H), 3.61 (d, *J* = 6.6 Hz, 2H).^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 167.05, 145.61, 137.19, 131.82, 129.84, 128.68, 128.55, 128.21, 128.02, 127.32, 126.16, 52.00 , 39.27.

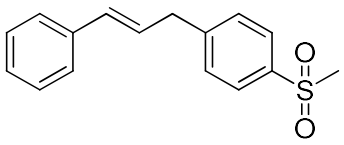


(*E*)-3-(4-cyanophenyl)-1-phenylpropene (6ag):

Prepared from β-bromostyrene (1.25 mmol) and 4-(2-chloromethyl)benzonitrile (1.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 98/2) to yield (*E*)-3-(4-cyanophenyl)-1-phenylpropene (0.200 g, 73%) as colorless oil.

HRMS (EI+) **(**$C_{16}H_{13}N$**):** calculated m/z: 219.1048, found: 219.1074. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.61 (d, *J* = 8.3 Hz, 2H), 7.44-7.21 (m, 7H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.39-6.24 (m, 1H), 3.61 (d, *J* = 6.7 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 145.81, 136.91, 132.41, 132.31, 129.44, 128.60, 127.52, 127.14, 126.18, 119.00, 110.14, 39.30.[10]

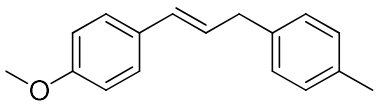
[296] H. Tsukamoto, M. Sato, Y. Kondo, *Chem. Commun.*, **2004**, 1200-1201



(*E*)-3-(4-methylsulfonylphenyl)-1-phenylpropene (6ah):

Prepared from β-bromostyrene (1.25 mmol) and 4-(methylsulfonyl)benzyl chloride (2.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 98/2) to yield (*E*)-3-(4-methylsulfonylphenyl)-1-phenylpropene (0.314 g, 90%) as colorless oil.

HRMS (EI+) **(**$C_{16}H_{16}O$**):** calculated m/z: 272.0871, found: 272.0877. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.89 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.21 (m, 5H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.42 – 6.22 (m, 1H), 3.64 (d, *J* = 6.8 Hz, 2H), 3.05 (s, 3H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 146.78, 138.50, 136.90, 132.37, 129.58, 128.58, 127.62, 127.51, 127.21, 126.16, 44.58, 39.12.

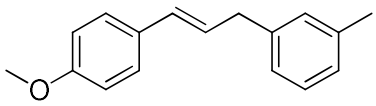


(*E*)-1-(4-methoxyphenyl)-3-(4-methylphenyl)-propene (6bi):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (2.5 mmol) and 4-methylbenzyl chloride (5.0 mmol) according to general procedure III-2 at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-1-(4-methoxylphenyl)-3-(4-methylphenyl)-propene (0.435 g, 73%) as colorless oil.

HRMS (EI+) **(**$C_{17}H_{18}O$**):** calculated m/z: 238.1358, found: 238.1353. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.18 (d, *J* = 8.7 Hz, 2H), 7.02 (s, 4H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.29 (d, *J* = 15.8 Hz, 1H), 6.18 – 6.01 (m, 1H), 3.67 (s, 3H), 3.38 (d, *J* = 6.8 Hz, 2H), 2.23 (s, 3H).^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 158.86, 137.40, 135.61, 130.44, 130.26, 129.19, 128.58, 127.40, 127.26, 113.96, 55.29, 38.97, 21.07.[297]

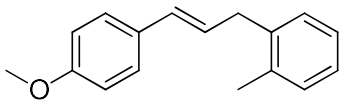
[297] Y. Zhao, L. Sun, T. Zeng, J. Wang, Y. Peng, G. Song, *Org. Biomol. Chem.*, **2014**, *23*, 3493



(*E*)-1-(4-methoxyphenyl)-3-(3-methylphenyl)-propene (6bj):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (1.25 mmol) and 3-methyl benzylchloride (2.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-1-(4-methoxylphenyl)-3-(3-methylphenyl)-propene (0.290 g, 97%) as colorless oil.

HRMS (EI+) **(**$C_{17}H_{18}O$**):** calculated m/z: 238.1358, found: 238.1350. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.38 (d, *J* = 8.7 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.17-7.09 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.37-6.23 (m, 1H), 3.86 (s, 3H), 3.58 (d, *J* = 6.8 Hz, 2H), 2.43 (s, 3H).^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 158.90, 140.44, 138.08, 130.42, 130.37, 129.47, 128.41, 127.28, 127.24, 126.91, 125.72, 113.98, 55.29, 39.36, 21.46.[298]



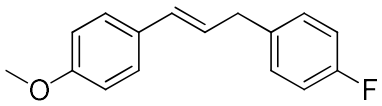
(*E*)-1-(4-methoxyphenyl)-3-(2-methylphenyl)-propene (6bk):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (1.25 mmol) and 2-methyl benzylchloride (2.5 mmol) according to general procedure III-2 at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-1-(4-methoxylphenyl)-3-(2-methylphenyl)-propene (0.234 g, 79%) as colorless oil.

HRMS (EI+) **(**$C_{17}H_{18}O$**):** calculated m/z: 238.1358, found: 238.1350. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.30 (d, *J* = 8.7 Hz, 2H), 7.26-7.14 (m, 4H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.35 (d, *J* = 15.9 Hz, 1H), 6.28 – 6.14 (m, 1H), 3.82 (s, 3H), 3.53 (d, *J* = 6.1 Hz, 2H), 2.36 (s, 3H).^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 158.81, 138.50, 136.39, 130.40,

[298] S. Guo, Y. Yuan, J. Xiang, *New J. Chem.*, **2015**, *39*, 3093-3097

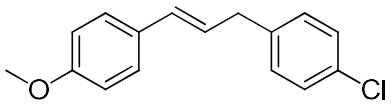
130.25, 130.18, 129.18, 127.16, 126.35, 126.32, 126.06, 113.91, 55.28, 36.84, 19.44.[299]



(*E*)-1-(4-methoxyphenyl)-3-(4-fluorophenyl)-propene (6bl):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (2.5 mmol) and 4-fluoro benzylchloride (5.0 mmol) according to general procedure III-2 at r.t. using twice amount of reagents. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-1-(4-methoxylphenyl)-3-(4-fluorophenyl)-propene (0.370 g, 61%) as colorless oil.

HRMS (EI+) **(**$C_{16}H_{15}F$**):** calculated m/z: 242.1107, found: 242.1105. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.30 (d, *J* = 8.7 Hz, 2H), 7.20 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.39 (d, *J* = 15.8 Hz, 1H), 6.28-6.12 (m, 1H), 3.81 (s, 3H), 3.50 (d, *J* = 6.8 Hz, 2H).^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 158.92, 130.58, 130.14, 130.02, 129.92, 127.22, 126.80, 115.29, 115.01, 113.94, 55.27, 38.45.[300]



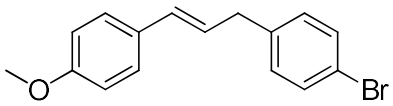
(*E*)-1-(4-methoxyphenyl)-3-(4-chlorophenyl)-propene (6bm):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (1.25 mmol) and 4-chloro benzylchloride (2.5 mmol) according to general procedure III-2 at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-1-(4-methoxylphenyl)-3-(4-chlorophenyl)-propene (0.212 g, 63%) as colorless oil.

HRMS (EI+) **(**$C_{16}H_{15}Cl$**):** calculated m/z: 258.0810, found: 258.0805. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.34-7.27 (m, 4H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.26 – 6.09 (m, 1H), 3.81 (s, 3H), 3.50 (d, *J* = 6.8 Hz,

[299] E. C. Frye, C. J. O'Connor, D. G. Twigg, D. R. Spring, *et al*, *Chem. Eur. J.*, **2012**, *18*, 8774-8779
[300] G. Li, L. Wu, G. Lv, Z. Tang, *et al*, *Chem. Commun.*, **2014**, *50*, 6246-6248

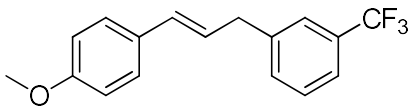
2H).[13]**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 158.94, 138.87, 131.85, 130.84, 130.05, 130.00, 128.52, 127.25, 126.35, 113.95, 55.28, 38.61.[12]



(*E*)-1-(4-methoxyphenyl)-3-(4-bromophenyl)-propene (6bn):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (1.25 mmol) and 4-bromobenzyl chloride (2.5 mmol) according to general procedure III-2 at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-1-(4-methoxylphenyl)-3-(4-bromophenyl)-propene (0.255 g, 67%) as colorless oil.

HRMS (EI+) **(**$C_{16}H_{15}Cl$**):** calculated m/z: 302.0306, found: 302.0291. [1]**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.45 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.41 (d, *J* = 15.8 Hz, 1H), 6.29 – 6.09 (m, 1H), 3.82 (s, 3H), 3.49 (d, *J* = 6.8 Hz, 2H).[13]**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 159.00, 139.43, 131.50, 130.94, 130.43, 130.08, 127.28, 126.25, 119.92, 113.99, 55.29, 38.68.[5]

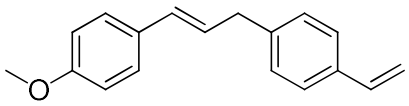


(*E*)-1-(4-methoxyphenyl)-3-(3-trifluoromethylphenyl)-propene (6bo):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (1.25 mmol) and 3-(trifluoromethyl)benzyl chloride (2.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-1-(4-methoxylphenyl)-3-(3-trifluoromethylphenyl)-propene (0.280 g, 77%) as colorless oil.

HRMS (EI+) **(**$C_{17}H_{15}F_3O$**):** calculated m/z: 292.1075, found: 292.1075. [1]**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.58 – 7.42 (m, 4H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 15.7 Hz, 2H), 6.30 – 6.14 (m, 1H), 3.83 (s, 3H), 3.61 (d, *J* = 6.9 Hz, 2H). [13]**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 159.10, 141.43, 132.04, 131.32,

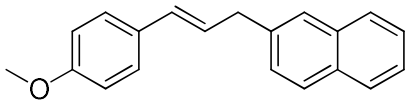
130.99, 130.56, 129.97, 128.84, 127.52 (q, *J* = 251.2 Hz), 127.33, 126.07, 125.77, 125.30 (q, J = 3.8 Hz), 123.02 (q, J = 3.8 Hz), 114.00, 55.24, 39.06.



(*E*)-1-(4-methoxyphenyl)-3-(4-vinylphenyl)-propene (6bp):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (1.25 mmol) and 4-vinylbenzyl chloride (2.5 mmol) according to general procedure III-2 at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (*E*)-1-(4-methoxylphenyl)-3-(4-bromophenyl)-propene (0.270 g, 77%) as colorless oil.

HRMS (EI+) **(**$C_{18}H_{18}O$**):** calculated m/z: 250.1358, found: 250.1354. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.25 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.60 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.29 (d, *J* = 15.8 Hz, 1H), 6.16-6.01 (m, 1H), 5.61 (d, *J* = 17.6 Hz, 1H), 5.10 (dd, *J* = 10.9, 0.8 Hz, 1H), 3.66 (s, 3H), 3.40 (d, *J* = 6.7 Hz, 2H).^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 158.95, 140.20, 136.71, 135.64, 130.59, 130.35, 128.90, 127.30, 126.92, 126.40, 114.00, 113.23, 55.31, 39.11.

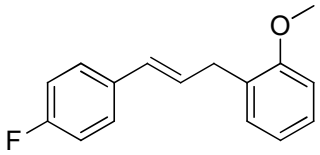


(*E*)-1-(4-methoxyphenyl)-3-β-naphthalenylpropene (6bq):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (1.25 mmol) and 2-(Chloromethyl)naphthalene (2.5 mmol) according to general procedure III-2 at r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0 - 99/1) to yield (*E*)-1-(4-methoxylphenyl)-3-β-naphthalenylpropene (0.244 g, 71%) as white solid.

HRMS (EI+) **(**$C_{20}H_{18}O$**):** calculated m/z: 274.1358, found: 274.1353. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.85 (t, *J* = 8.0 Hz, 3H), 7.72 (s, 1H), 7.52 - 7.46 (m, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.42 – 6.27 (m, 1H), 3.83 (s, 3H), 3.73 (d, *J* = 6.6 Hz, 2H). ^{13}**C-NMR**

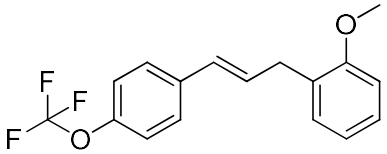
(75 MHz, $CDCl_3$) δ/ppm: 158.94, 137.98, 133.72, 132.20, 130.73, 130.35, 128.02, 127.66, 127.53, 127.51, 127.30, 126.92, 126.71, 125.98, 125.31, 113.99, 55.29, 39.48.[5]



(*E*)-1-(4-fluorophenyl)-3-(2-methoxyphenyl)-propene (6db):

Prepared from (*E*)-1-(2-bromovinyl)-4-fluorobenzene (1.25 mmol) and 2-methoxybenzyl chloride (2.5 mmol) according to general procedure III-2 at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/diethyl ether = 100/0-99/1) to yield (*E*)-1-(4-methoxylphenyl)-3-(4-bromophenyl)-propene (0.242 g, 80%) as colorless oil.

HRMS (EI+) **(**$C_{16}H_{15}FO$**):** calculated m/z: 242.1107, found: 242.1108. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.32 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.22 (dd, *J* = 14.5, 7.0 Hz, 2H), 7.04 – 6.85 (m, 4H), 6.45 – 6.22 (m, 2H), 3.86 (s, 3H), 3.54 (d, *J* = 6.2 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 161.90 (d, *J* = 245.6 Hz), 157.24, 133.90 (d, *J* = 3.3 Hz), 129.83, 129.42, 128.67 (d, *J* = 2.2 Hz), 128.52, 127.46 (t, *J* = 3.9 Hz), 120.53, 115.39, 115.11, 110.35, 55.37, 33.37.

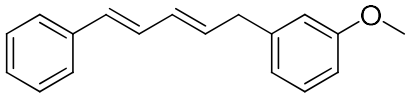


(*E*)-1-(4-trifluoromethoxyphenyl)-3-(2-methoxyphenyl)-propene (6jb):

Prepared from methyl 1-(2-Bromovinyl)-4-trifluoromethoxybenzene (1.25 mmol) and 2-methoxybenzyl chloride (2.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 100/0-99/1) to yield (0.290 g, 75%) as colorless oil.

HRMS (EI+) **(**$C_{17}H_{15}O_2F$**):** calculated m/z: 308.1024, found: 308.1035. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.37 (d, *J* = 8.7 Hz, 2H), 7.28 – 7.10 (m, 4H), 6.98 – 6.86 (m, 2H), 6.48 – 6.33 (m, 2H), 3.87 (s, 3H), 3.56 (d, *J* = 5.1 Hz, 2H). ^{13}**C-NMR** (75

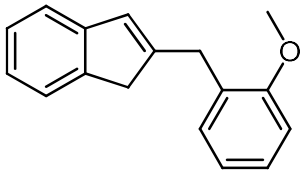
MHz, $CDCl_3$) δ/ppm: 157.27, 147.98, 136.58, 130.13, 129.85, 129.16, 128.30, 127.55, 127.20, 120.97, 120.56, 110.39, 55.35, 33.42.



1-Phenyl-5-(3-methoxyphenyl)-1,3-pentadiene (6kc):

Prepared from ((*1E*, *3E*)-(4-bromobuta-1,3-dien-1-yl))benzene (1.25 mmol) and 3-methoxybenzyl chloride (2.5 mmol) according to general procedure 3 at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/diethyl ether = 100/0-99/1) to yield (*1E*, *3E*)-1-Phenyl-5-(3-methoxyphenyl)-1,3-pentadiene (0.231 g, 74%) as colorless oil.

HRMS (EI+) **(**$C_{18}H_{18}O$**):** calculated m/z: 242.1107, found: 242.1108. ^{1}**H-NMR** (300 MHz, $CDCl_3$): 7.46 - 7.21 (m, 6H), 6.91 – 6.73 (m, 4H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.30 (dd, *J* = 14.4, 10.8 Hz, 1H), 6.06 - 5.93 (m, 1H), 3.83 (s, 3H), 3.49 (d, *J* = 6.9 Hz, 2H). δ/ppm^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 159.78, 141.77, 137.48, 133.49, 131.81, 131.04, 129.48, 128.97, 128.60, 127.30, 126.23, 121.04, 114.35, 111.53, 55.19, 39.25.

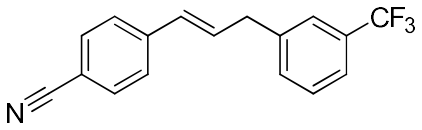


2-(2-Methoxybenzyl)-indene (6lb):

Prepared from 2-bromoindene (1.25 mmol) and 2-methoxybenzyl chloride (2.5 mmol) according to general procedure III-2 at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether) to yield 2-(2-Methoxybenzyl)-indene (0.223 g, 77%) as white solid.

HRMS (EI+) **(**$C_{17}H_{16}O$**):** calculated m/z: 236.1201, found: 287.0920. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.36 (d, *J* = 7.3 Hz, 1H), 7.28 – 7.16 (m, 4H), 7.09 (td, *J* = 7.2, 1.5 Hz, 2H), 6.91 (t, *J* = 7.8 Hz, 2H), 6.47 (s, 1H), 3.85 (s, 3H), 3.83 (s, 2H), 3.32 (s, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 157.31, 149.36, 145.60, 143.44, 130.34,

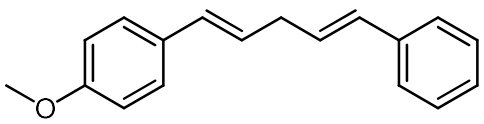
128.58, 127.48, 127.31, 126.14, 123.58, 123.37, 120.48, 119.98, 110.47, 55.38, 41.10, 31.61.[301]



(*E*)-1-(4-cyanophenyl)-3-(3-trifluoromethylphenyl)-propene (6gr):

Prepared from (*E*)-4-(2-bromovinyl)benzonitrile (1.25 mmol) and 3-trifluoromethylbenzyl chloride (2.5 mmol) according to general procedure III-2 at 50 °C. The crude residue was purified by column chromatography over silica gel (petroleum ether/diethyl ether = 100/0-97/3) to yield (*E*)-1-(4-cyanophenyl)-3-(3-trifluoromethylphenyl)-propene (0.139 g, 39%) as white solid.

HRMS (EI+) **(**$C_{17}H_{12}F_3N$**):** calculated m/z: 287.0922, found: 287.0920. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.58 (d, *J* = 8.4 Hz, 2H), 7.54 – 7.40 (m, 6H), 6.52-6.41 (m, 2H), 3.64 (d, *J* = 4.3 Hz, 2H) ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 141.54, 140.13, 132.37, 132.25, 132.08 (d, *J* = 1.2 Hz), 131.16, 129.07, 127.43 (q, *J* = 242.8 Hz), 126.66, 125.34 (q, J = 3.8 Hz), 123.39 (q, *J* = 3.8 Hz), 118.93, 110.59, 39.05.



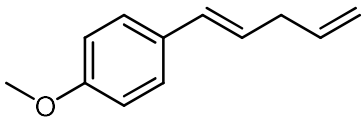
(*E*)-Cinnamyl-4-methoxystyrene (7a):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (1.25 mmol) and cinnamyl chloride (2.5 mmol) according to general procedure III-2 with addition of pyridine (0.25 mL) at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/diethyl ether = 100/0-99/1) to yield (*E*)-Cinnamyl-4-methoxystyrene (0.150 g, 48%) as colorless oil.

HRMS (EI+) **(**$C_{18}H_{18}O$**):** calculated m/z: 250.1358, found: 252.1149. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.46 – 7.39 (m, 2H), 7.39 – 7.30 (m, 4H), 7.30 – 7.20 (m, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.48 (t, *J* = 15.3 Hz, 2H), 6.40 – 6.27 (m, 1H), 6.25 – 6.17 (m, 1H), 3.83 (s, 3H), 3.14 (t, *J* = 6.5 Hz, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm:

[301] T. Ishimaru, N. Shibata, T. Horikawa, M. Shiro, *et al, Angew. Chem. Int. Ed.* **2008**, *47*, 4157-4161

158.89, 137.65, 130.87, 130.44, 128.53, 127.20, 127.06, 126.09, 126.00, 113.98, 55.28, 36.22.[14]



(*E*)-4-Methoxycinnamylethene (7b):

Prepared from (*E*)-1-(2-bromovinyl)-4-methoxybenzene (1.25 mmol) and allyl bromide (2.5 mmol) according to general procedure III-2 with addition of pyridine (0.25 mL) at 0 °C - r.t. The crude residue was purified by column chromatography over silica gel (petroleum ether/diethyl ether = 100/0-99/1) to yield (E)-4-Methoxycinnamylethene (0.100 g, 45%) as colorless oil.

HRMS (EI+) **(**$C_{12}H_{14}O$**):** calculated m/z: 174.1045, found: 174.1044. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 7.30 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.18-6.04 (m, 1H), 6.00 – 5.82 (m, 1H), 5.18 – 5.01 (m, 2H), 3.81 (s, 3H), 3.01-2.85 (m, 2H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) δ/ppm: 158.78, 136.75, 130.45, 130.19, 127.11, 125.97, 115.43, 113.90, 55.25, 37.00.[14]

IV Cobalt-Catalyzed Aryl C-H Activation with Arylzinc Reagents

IV-1 Synthesis of starting materials

IV-1-1 Synthesis of *N*-benzoylaniline

The synthesis of N-benzolaniline is based on Godfroid's method.[302] To a cold solution of aniline (77.6 mmol, 9.0 mL) in dichloromethane (20 mL) was added dropwise benzoyl chloride (165 mmol, 15 mL) in dichloromethane (40 mL). After stirring for 2 h at room temperature, water (30 mL) and HCl (20 mL, 37%) were added. The mixture was filtered and the solid product was washed with water and then with acetone to afford *N*-benzoylaniline (12.0 g, 60.8 mmol) in 78% yield.

IV-1-2 Synthesis of *N*-benzoylaminoquinoline

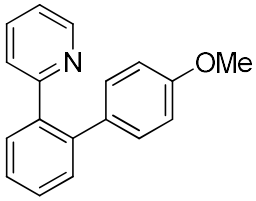
8-Aminoquinoline (1.0 g, 7 mmol) and *N*,*N*-dimethyl-4-aminopyridine (DMAP) (27 mg, 0.32 mmol) were placed in a 50 mL Schlenk tube flushed with nitrogen. Dichloromethane (7 mL) and Et_3N (1.0 mL, 8 mmol) were added and the resulting solution was cooled to 0 °C. To this solution benzoyl chloride (0.76 mL, 6.7 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 15 h. The mixture was quenched with water and extracted with dichloromethane, and the combined organic layer was dried over magnesium sulfate and concentrated in vacuum. Colloum chromatography over silica gel with petroleum ether/ethyl acetate (5/1) gave *N*-benzoylaminoquinoline (0.80 g, 3.2 mmol) in 48% yield.

IV-2 General procedure for arylation of 2-phenylpyridine with arylzinc species

The arylzinc (5 mmol of arylbromide, 80% yield, 4 mmol of arylzinc) was prepared as mentioned in I-3 with CoBr2/4,4'-dimethyl-2,2'-bipyridine (10 mol%, 0.5 mmol) as catalyst. The crude solution of arylzinc species was carefully filtered with a syringe filter. Next the filtrate was evaporated under vacuum and a very concentrated orange medium was obtained, which was dissolved by adding 4 mL of THF. Then the arylzinc/THF solution was transferred to a Schlenk tube under nitrogen and it was kept stirring. After adding 2-phenylpyridine (1.5 mmol), the medium was heated to

[302] G. L. Bilan, F. Rondu, A. Pelé-Tounian, J-J. Godfroid, *et al*., *J. Med. Chem.* **1999**, *42*, 1587-1603.

100 °C with reflux. The reaction was followed by GC on iodolyzed aliquots untill the total consumption of the arylzinc. Aqueous saturated NH_4Cl (20 mL) and ethyl acetate (20 mL) were then added. The organic layer was separated and the aqueous phase was washed with ethyl acetate (3x20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to afford the crude material. Purification was performed by column chromatography on silica gel with petroleum ether /ethyl acetate as elunte.



2-(4-Methoxy-[1,1-biphenyl]-2-yl)pyridine ($C_{18}H_{15}NO$) :

HRMS (EI+) **(**$C_{18}H_{15}NO$**):** calculated m/z: 261.1154, found: 261.1152. ^{1}**H-NMR** (300 MHz, $CDCl_3$) δ/ppm: 8.66 (d, *J* = 4.5 Hz, 1H), 7.78 – 7.63 (m, 1H), 7.51 – 7.35 (m, 4H), 7.21-7.02 (m, 3H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H).[303]

[303] G. M. Reddy, N. S. S. Rao, P. Satyanarayana, H. Maheswaran, RSC Advances, 2015 , 5, 105347-105352.

université PARIS-SACLAY

ÉCOLE DOCTORALE
Sciences chimiques : molécules, matériaux, instrumentation et biosystèmes

Titre : Formation de Liaisons Carbone-Carbone Catalysée par le Cobalt par Activation de Liaisons Carbone-Halogène ou Carbone-Hydrogène.

Mots clés : cobalt; catalyse; couplages croisés; organozinciques; cyanation; C-H activation

Résumé : Ce travail de thèse présente le développement de nouvelles réactions de formation de liaisons carbone-carbone. Le premier chapitre décrit la cyanation d'arylzinciques par catalyse au cobalt à partir d'une source non toxique et bénigne, le *N*-cyano-*N*-phenyl-p-methylbenzenesulfonamide (NCTS), et conduit à de bons rendements en benzonitriles correspondants. Dans cette réaction, le cobalt sert de catalyseur non seulement pour la formation des arylzinciques mais aussi pour la formation de liaisons C-CN. Les groupements fonctionnels, cétone et nitrile, sont permis lorsque le complexe de cobalt associé au ligand bipyridine est utilisé. Le deuxième chapitre porte sur l'homocouplage C_{sp3}-C_{sp3}. Un simple halogénure de cobalt permet de catalyser la dimérisation des halogénures d'alkyles et des acétates d'allyles avec de bons à d'excellents rendements. L'ajout d'iodure de sodium permet d'étendre cette réaction aux chlorures et tosylates d'alkyles. Le couplage croisé entre 2 halogénures d'alkyle différents a également été testé mais les conditions doivent être optimisées. Dans le troisième chapitre, le couplage croisé catalysé au cobalt entre des bromures vinyliques et des chlorures benzyliques est présenté. Des halogénures de vinyles et de benzyles porteurs de groupements electrodonneurs ou electroattrateurs peuvent ainsi être couplés efficacement avec rétention de la configuration de la double liaison. Un mécanisme radicalaire semble être impliqué. Enfin, le dernier chapitre décrit l'arylation d'une 2-phenylpyridine avec un arylzincique par catalyse au cobalt par activation d'une liaison C-H et conduit à de premiers résultats encourageants.

Title : Cobalt-Catalyzed Carbon-Carbon Bond Formation by Avtivation of Carbon-Halogen or Carbon-Hydrogen bonds

Keywords : cobalt; catalysis; cross-coupling; organozinc reagents; cyanation; C-H activation

Abstract: This thesis presents the development of cobalt-catalyzed carbon-carbon bonds formation. The first chapter describes a novel cobalt-catalyzed electrophilic cyanation of arylzinc species, employing benign and non-toxic *N*-cyano-*N*-phenyl-p-methylbenzenesulfonamide (NCTS) as the cyano source. In this reaction, cobalt catalyzes both the formation of arylzinc species and the cyanation reaction. Various benzonitriles are synthesized affording good to excellent yields. Using cobalt-bipyridine complexes instead of $CoBr_2$, ketone and nitrile groups can be tolerated. The second chapter reports cobalt-catalyzed C_{sp3}-C_{sp3} homocoupling reaction. A simple catalytic system could deliver dimers of a number of alkyl halides/pseudohalides and allylic acetates. Sodium iodide is crucial for the homocoupling of unactivated alkyl chlorides and tosylates. This method is extended to alkyl-alkyl cross-coupling; however, the conditions still need to be optimized. The third chapter describes a cobalt-catalyzed vinyl-benzyl cross-coupling. A variety of functionalized vinyl bromides and benzyl chlorides are efficiently coupled under mild conditions in good to excellent yields, with retention of *Z*/*E* configuration. A few mechanistic experiments indicate a single electron transfer involved. The last chapter discusses the progress on the cobalt-catalyzed arylation of 2-phenylpyridine with an arylzinc species by C-H activation and promising results are obtained.