The Free Internet Journal
for Organic Chemistry

Review

Archive for
Organic Chemistry

Arkivoc **2019**, part i, 106-138

Cobalt-, copper- and chromium–catalyzed carbon-carbon coupling reactions using a broad spectrum of Grignard reagents as reaction partners

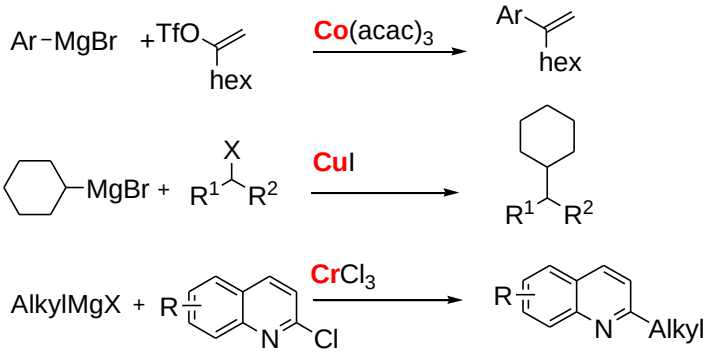
Adnan A. Dahadha

Biotechnology Department, Faculty of Science, Philadelphia University,
P. O. Box. 19392, Amman, Jordan
Email: adnan.dahadha_chem@yahoo.com

Received 12-31-2018 **Accepted** 03-14-2019 **Published on line** 06-04-2019

Abstract

The cobalt, copper and chromium catalyzed cross-coupling reaction of various Grignard reagents with electrophilic substrates is a powerful technique for the construction of carbon–carbon bonds, enabling the preparation of a wide variety of organic compounds that are employed in the pharmaceutical industry, as agricultural compounds, and for forming organic electronic materials. This review highlights major developments in carbon-carbon cross-coupling reactions catalyzed by cobalt, copper and chromium complexes over the past decade.



Keywords: Cobalt, copper, chromium, catalysis, Grignard reagents, C-C cross-coupling

Table of Contents

1. Introduction

Transition metal catalyzed cross-coupling reactions are widely used for the construction of carbon–carbon bonds.[1-5] Palladium and nickel-catalyzed cross-coupling reactions still play a prominent role in synthetic chemistry.[6-17] However, alternative cross-coupling protocols must be taken into consideration owing to the high cost of these transition metals, and their limited supply.[18-24] In addition to this, the development of broadly applicable, more environmental friendly and economical catalysts is a worthy target in catalytic cross-coupling reactions.[25,26]

Grignard reagents were discovered, by Victor Grignard at the University of Lyon in 1900, and for this significant finding Grignard was awarded the Nobel Prize in Chemistry in 1912.[27-30] Most of the Grignard reagents are prepared by the reaction of an organic halide with magnesium in ether solution under an inert atmosphere.[27] During the past century, Grignard reagents have been the most widely used organometallic reagents.[31-36] They remain desirable coupling partners owing to their stability and ease of preparation, with many representatives being commercially available.[37,38] Chromium is among the most abundant elements on earth.[21] Interestingly, it has recently proven to be an ideal alternative to palladium and nickel in cross-coupling reactions. In 1919, Hein described the formation of bis(arene)chromium species by reaction of a Grignard reagent with chromium(III) chloride.[39] From the middle of the 20th century, cobalt catalyzed carbon-carbon bond-forming reactions have received considerable attention. In 1943, Kharasch demonstrated the first example of cobalt catalyzed alkenylation of aromatic Grignard reagents by employing catalytic amounts of cobalt chloride and a stoichiometric amount of aromatic or aliphatic halides, affording good yields of homocoupling products.[40] Copper-catalyzed coupling reactions had been demonstrated several years before Pd and Ni-catalyzed reactions to form carbon–carbon bonds: in 1971, Kochi and Tamura carried out the coupling reaction of Grignard reagents and alkyl halides using alkylcopper(I) species.[41-43]

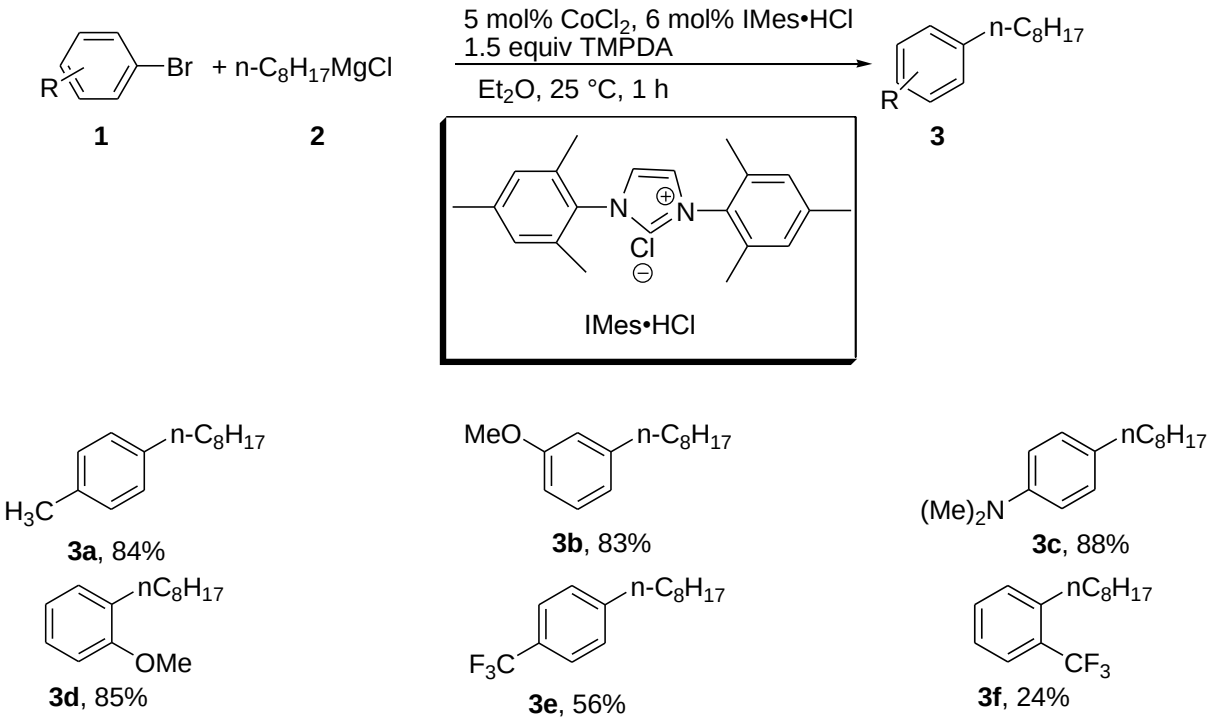
2. Metal Catalyzed C-C Cross-coupling Reactions Using Various Grignard Reagents

In this review, we classify the metal catalyzed cross-coupling reactions according to the metal present in the catalyst. Therefore, three major categories are discussed: the cobalt-catalyzed, the copper-catalyzed and the chromium-catalyzed reactions.

2.1 Cobalt catalyzed cross-coupling reactions

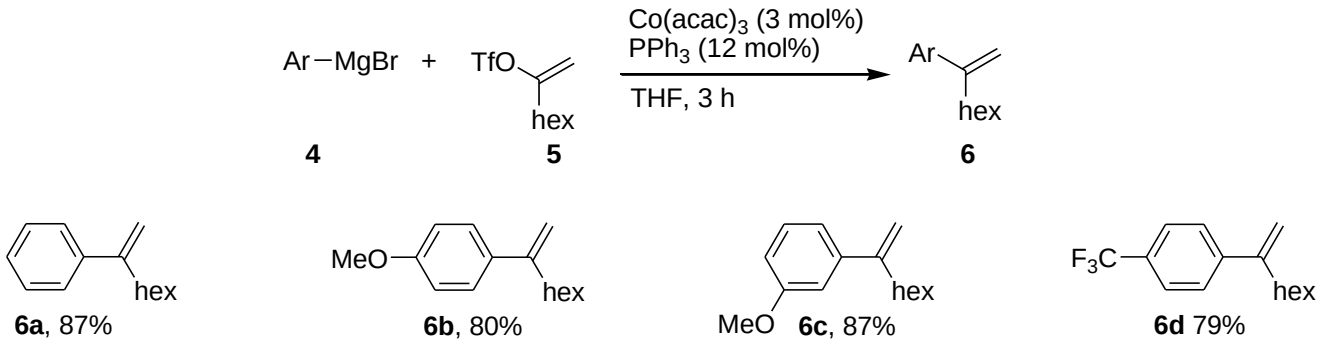
In 1943, Kharasch and Fuchs performed seminal research on the cobalt-catalyzed cross-coupling reactions for C–C bond formation using aliphatic Grignard reagents as a nucleophilic partner with various electrophiles.[40,44] Arising out of their work, cobalt complexes have proved to be very promising catalysts for cross-coupling reactions due to their relatively low cost, widespread availability, and low toxicity.[23,24]

In 2008, Oshima *et al.* reported cross-coupling reaction of alkyl Grignard reagents and aryl bromides in the presence of *N,N,N′,N′*-tetramethyl-1,3-propanediamine (TMPDA), catalytic amounts of cobalt(II) chloride and 1,3-dimesitylimidazolium salt (IMes·HCl) as the catalyst system. In this optimized cross-coupling methodology, aryl bromide substrates with electron donating groups such as methyl, 4-methoxy or 4-dimethylamino reacted with *n*-octylmagnesium chloride catalyzed by 5 mol% catalyst loading of $CoCl_2$ and 6 mol% IMes·HCl in diethyl ether at 25 ^oC to furnish the coupled products in very good yields (**3a-d**) (Scheme 1), while electron deficient substrates gave moderate to poor yields (**3e**,**f**).[45]



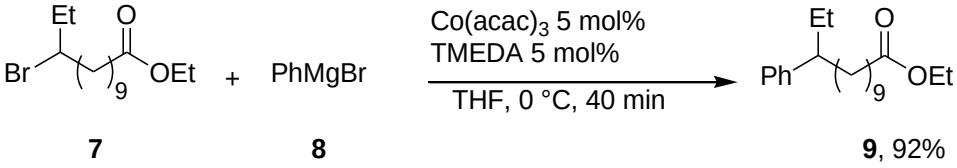
Scheme 1. Cross coupling reaction of arylbromide substrates with *n*-octylmagnesium bromide using $CoCl_2$.

In 2008, Hayashi *et al*. designed an efficient protocol for C(sp^2)-C(sp^2) coupling via cross-coupling reaction of alkenyl triflates with aryl and alkenyl Grignard reagents at low temperatures using a low cobalt loading catalyst and triphenylphosphine as free ligand to produce the corresponding alkenylarenes. Arylmagnesium bromides **4** cross-coupled with 1-octen-2-yl triflate **(5**) at 0 ^oC within 3 h to provide the desired products in high yields (**6a-d**) (Scheme 2). The reaction is compatible with aromatic Grignard reagents bearing electron-donating or electron withdrawing groups.[46]



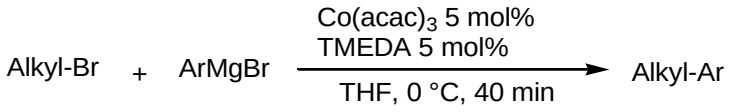
Scheme 2. Cobalt-catalyzed coupling of aryl Grignard reagents with alkenyl triflates.

Unactivated alkyl halides are often inactive substrates for metal catalyzed cross-coupling reactions because of their reluctance to undergo oxidative addition. In addition, metal alkyl intermediates are prone to induce unproductive β-hydrogen eliminations.[31,47] In 2009, Cahiez and his group developed a novel method to construct carbon-carbon bonds by chemoselective cobalt catalyzed cross-coupling of the functionalized nonactivated secondary alkyl bromide **7** with phenylmagnesium bromide **8** in the presence of TMEDA under mild reaction conditions to produce the cross-coupled products **9** (Scheme 3). Building upon this protocol, various functionalized primary alkyl bromides **10** were cross-coupled smoothly with arylmagnesium bromides **11** using $CoCl_2$/TMEDA (1:1) as an efficient catalyst system to afford the corresponding products **12** in excellent yields (Scheme 4). A wide range of sensitive groups such as acetate, ester, and ketone are fully tolerated in this coupling reaction.[48]

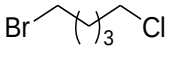
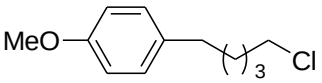
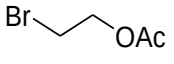
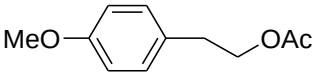
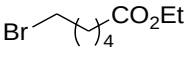
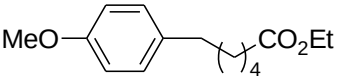
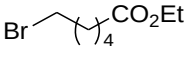
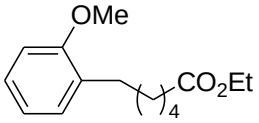
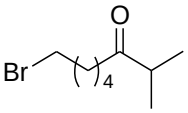
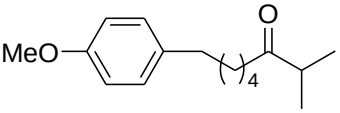


Scheme 3. Cross-coupling reaction of the functionalized nonactivated secondary alkyl bromide with phenylmagnesium bromide.

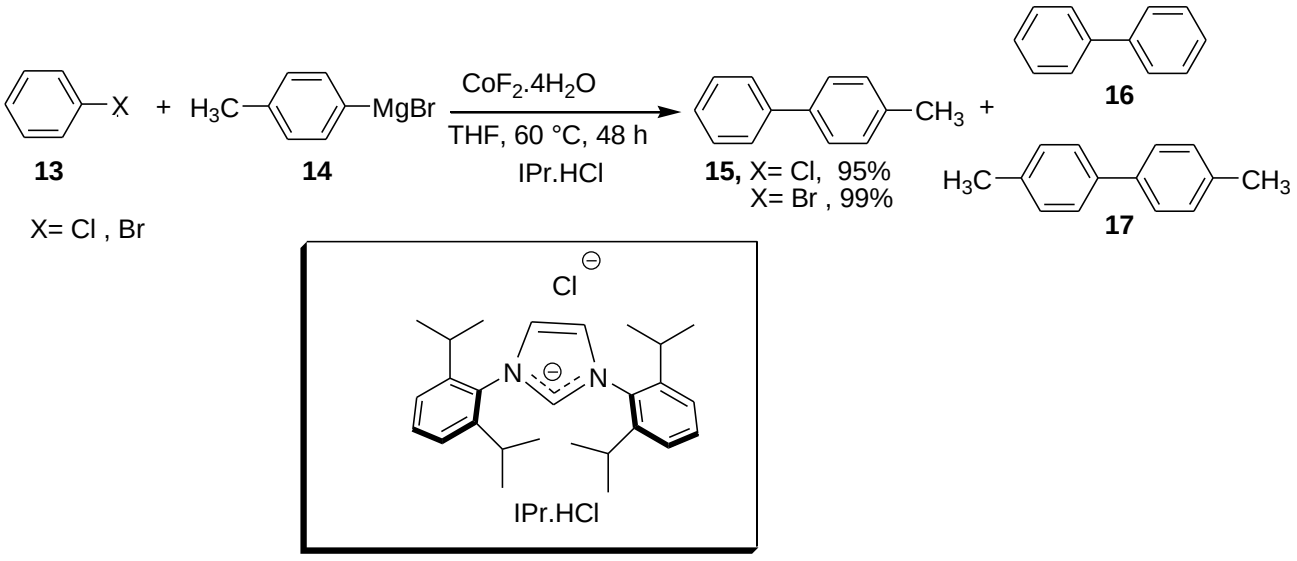
Biaryl compounds are widely used in many large-scale applications in the pharmaceutical, liquid crystal, functional polymer and electronic material industries.[49-51] Hence, the development of straightforward and selective methods for the preparation of biaryls has attracted much attention in recent years. In general, the cross-coupling reaction of aryl halides (Ar^1X) with arylmagnesium halide (Ar^2MgX) mediated by transition metals is one of the effective methodologies for the synthesis of biaryls.[52-54] Nevertheless, the ease of formation of Grignard reagents often indicates the likelihood of side reactions such as homocoupling to form undesired symmetrical biaryl compounds.[55] Nakamura and coworkers have designed a practical and selective method to form the wanted unsymmetrical biaryls in excellent yields (Ar^1-Ar^2) **15** with formation of much lower amounts of the homocoupling byproducts such as biphenyl (**16**) and 4,4'-dimethylbiphenyl (**17**) via cross-coupling reactions between phenyl halides **13** and aryl Grignard reagents **14** catalyzed by cobalt(II) fluoride tetrahydrate in combination with an imidazolium chloride salt as an effective preligand.[56]



10 **11** **12**

Entry	Alkyl bromide	Product	Yield %
1			89
2			88
3			90
4			88
5			90

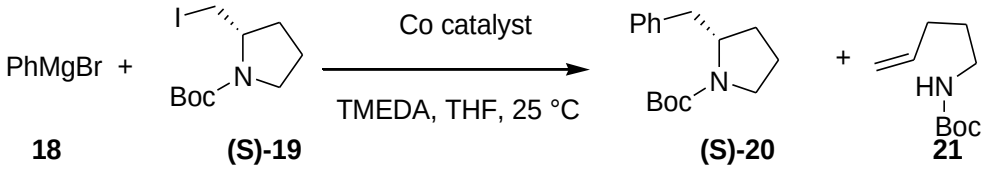
Scheme 4. Cross-coupling of aryl Grignard reagents with functionalized primary alkyl bromides.



Scheme 5. Cross-coupling of chlorobenzene/ bromobenzene with *p*-tolMgBr using CoF_2 catalyst in the presence of an imidazolium chloride salt.

Enantiopure pyrrolidines play a significant role in the synthesis of chiral organocatalysts, chiral ligands and building blocks for bioactive molecules. In 2011, Wu *et al*. described a novel protocol to form enantiopure functionalized pyrrolidines through a cobalt-catalyzed coupling reaction of phenylmagnesium bromide **18** and (*S*)-2-(iodomethyl)pyrrolidines with *tert*-butoxycarbonyl protecting group (Boc) (*S*)-**19**, in the presence of TMEDA at 25 ^{o}C, affording relatively good yields of enantiopure (*S*)-**20** and lower amounts of the byproduct

21.[57] The catalytic activity of various cobalt complexes such as $Co(OAc)_2$, $Co(acac)_3$, $CoCl(PPh_3)_3$, and $CoCl_2(PPh_3)_2$ was carefully investigated under optimal reaction conditions, the results in terms of catalyst loading and product yield of (*S*)-**20** are summarized in Scheme 6.



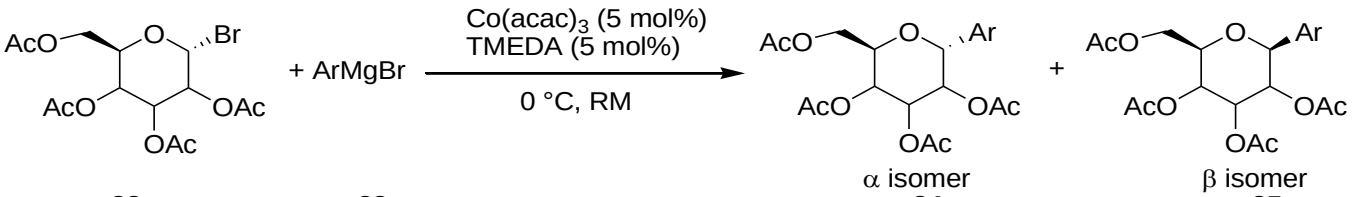
18 **(S)-19** **(S)-20** **21**

Entry	Catalyst (mol %)	Yield % of **20**
1	$Co(OAc)_2$ (5)	69
2	$Co(acac)_3$ (5)	76
3	$CoCl(PPh_3)_3$ (10)	79
4	$CoCl2(PPh_3)_2$ (10)	86
5	$CoCl2(PPh_3)_2$ (5)	76

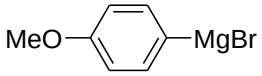
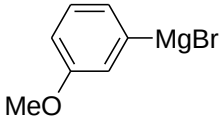
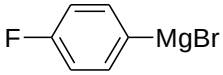
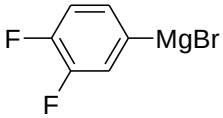
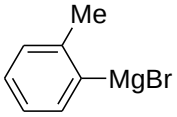
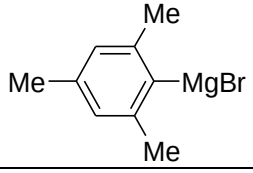
Scheme 6. Optimization of reaction conditions for the preparation of the chiral pyrrolidine (*S*)-**20.**

C-glycosides are prominent carbohydrate analogues with applications as efficacious pharmaceutical compounds.[58] In 2012, Cossy and coworkers designed an efficient diastereoselective cobalt catalyzed cross-coupling reaction of aryl Grignard reagents **23** and 1-bromoglycosides **22** to give an array of *C*-aryl glycosides with α selectivity (e.g. **24**) in synthetically useful yields. 1-Bromoglycoside as the electrophilic substrate reacted smoothly with various aryl Grignard reagents at either 0 ^{o}C or room temperature using $Co(acac)_3$ as a catalyst with the aid of tetramethylethylenediamine (TMEDA) (Scheme 7). Strikingly, aryl Grignard reagents with electron donating or electron withdrawing groups provided the coupling products in good yields with a higher α/β ratio (> 9:1) (entries 1-5). The use of a bulkier Grignard reagent furnished the product in about 37% yield (entry 6), the lower yield possibly being due to steric hindrance.[59]

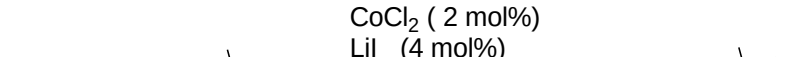
The Kumada cross-coupling reaction has become a powerful synthetic tool for the synthesis of carbon-carbon bonds, and recent advances have expanded the scope of this reaction to include tertiary alkyl Grignard reagents to give branched alkanes with quaternary carbon centers.[60] However, the use of tertiary alkyl Grignard reagents as nucleophiles in cross-couplings often affords low yields due to steric hindrance, facile β-hydrogen elimination and ease of isomerization of the tertiary metal alkyls. [1,61] In 2013, Kambe and his group demonstrated an efficient protocol for the coupling reaction of tertiary alkyl Grignard reagents and various alkyl halides in the presence of the mixed catalyst system including 2 mol% of $CoCl_2$, 4 mol% LiI and of isoprene as a ligand precursor to generate a wide spectrum of important organic molecules containing quaternary carbon centers. Accordingly, alkyl bromides **26** carrying an arene, olefin, alkyne, trifluoromethyl, ether, and amide groups cross-coupled effectively with tert-butylmagnesium chloride **27** to produce the corresponding coupled products in good to excellent yields without occurring side products arising from the isomerization of the *t*-Bu group (Scheme 8, **28a**-**g**).[62]



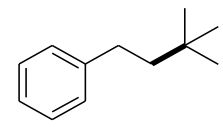
22 **23** **24** **25**

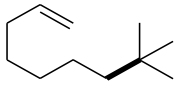
Entry	ArMgBr	Yield %	α/β
1		70	> 9:1
2		82	> 9:1
3		83	> 9:1
4		72	> 9:1
5		77	> 9:1
6		37	> 9:1

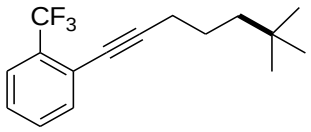
Scheme 7. Scope of the cobalt-catalyzed cross-coupling of ArMgX and 1-bromoglycosides.

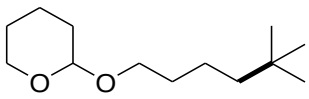


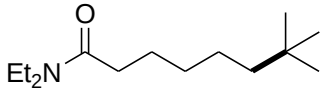
26 **27** **28**

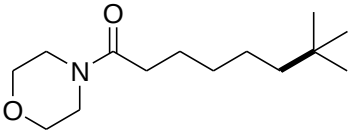

28a, 95%

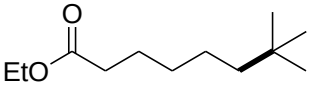

28b, 86%


28c, 84%

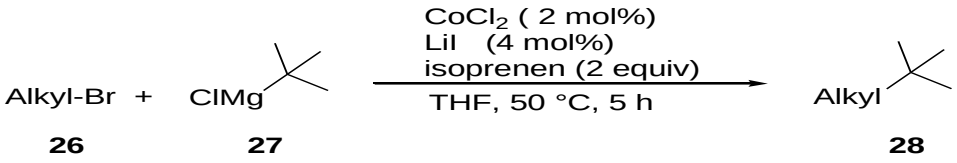

28d, 91%


28e, 79%

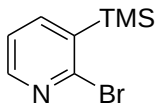
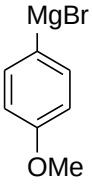
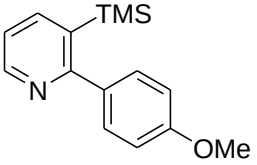
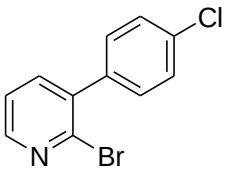
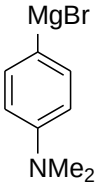
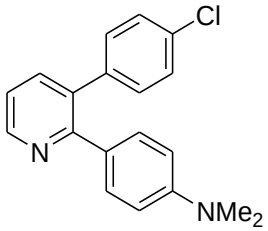
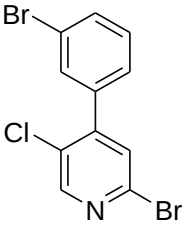
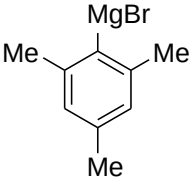
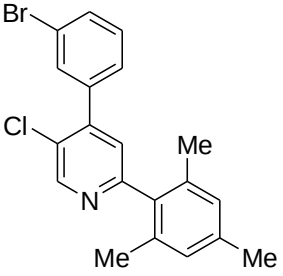
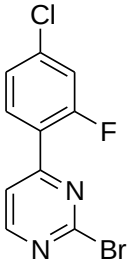
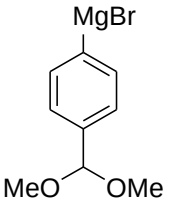
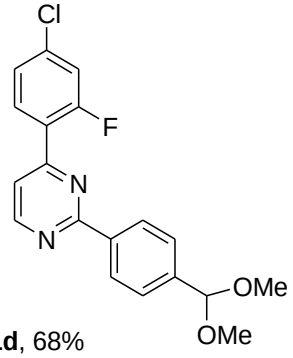
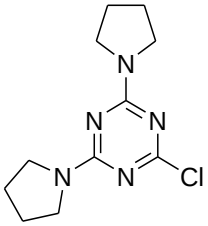
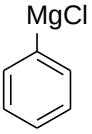
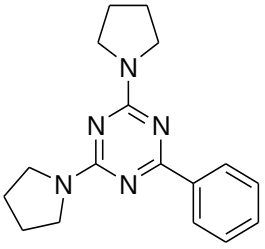

28f, 81%


28g, 78%

Scheme 8. Co-catalyzed alkylation of various alkyl halides.



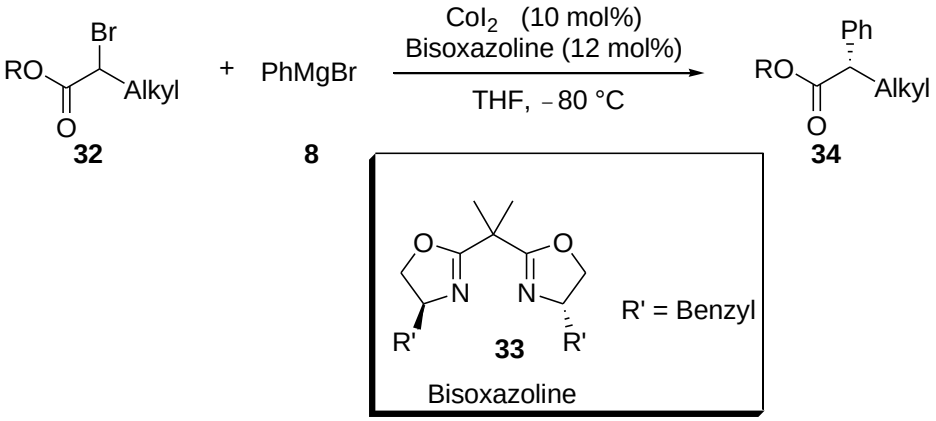
26 **27** **28**

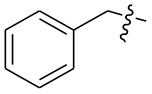
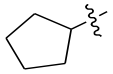
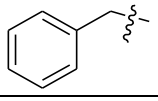
Entry	Starting material	Grignard reagent	Product (Yield %)
1			 **31a**, 85%
2			 **31b**, 77%
3			 **31c**, 82%
4			 **31d**, 68%
5			 **31e**, 76%

Scheme 9. Scope of Co-catalyzed cross-coupling reactions utilizing isoquinoline as a ligand.

Knochel and coworkers designed a novel catalyst system for fast and selective cross-coupling reaction of N-heteroaryl halides **29** and arylmagnesium reagents **30** using cobalt chloride in combination with an isoquinoline ligand. Moreover, the use of methyl *tert*-butyl ether as a co-solvent can minimize the formation of homocoupling byproducts. Interestingly, good yields of the selective coupled products **31** were obtained through cobalt catalyzed C-C coupling reaction of bromo- or chloro-substituted pyridines, pyrimidines and triazines with electron rich Grignard reagents (Scheme 9). In this way, even polyfunctional pyridine, pyrimidine and triazine derivatives cross-coupled with sterically hindered aryl Grignard reagents selectively.[63]

In 2014, Zhong *et al.* developed an efficient protocol for asymmetric cross-coupling of functionalized racemic α-bromo ester substrates **32** with phenyl Grignard reagents **8** in THF at −80 °C within 5 h, catalyzed by 10 mol % of CoI_2 and 12 mol % of bisoxazoline ligand **33** to produce a variety of chiral α-arylalkanoic esters **34** in excellent enantioselectivity and yield. Building upon this protocol, α-bromopropanoic and α-bromobutyric acid esters with various OR groups (R = methyl, ethyl, isopropyl, cyclopentyl or benzyl) were coupled efficiently with phenylmagnesium bromide to provide enantioselectivities ranging from 83 to 95% ee and yields in the 89−95% range (Scheme 10).[64]

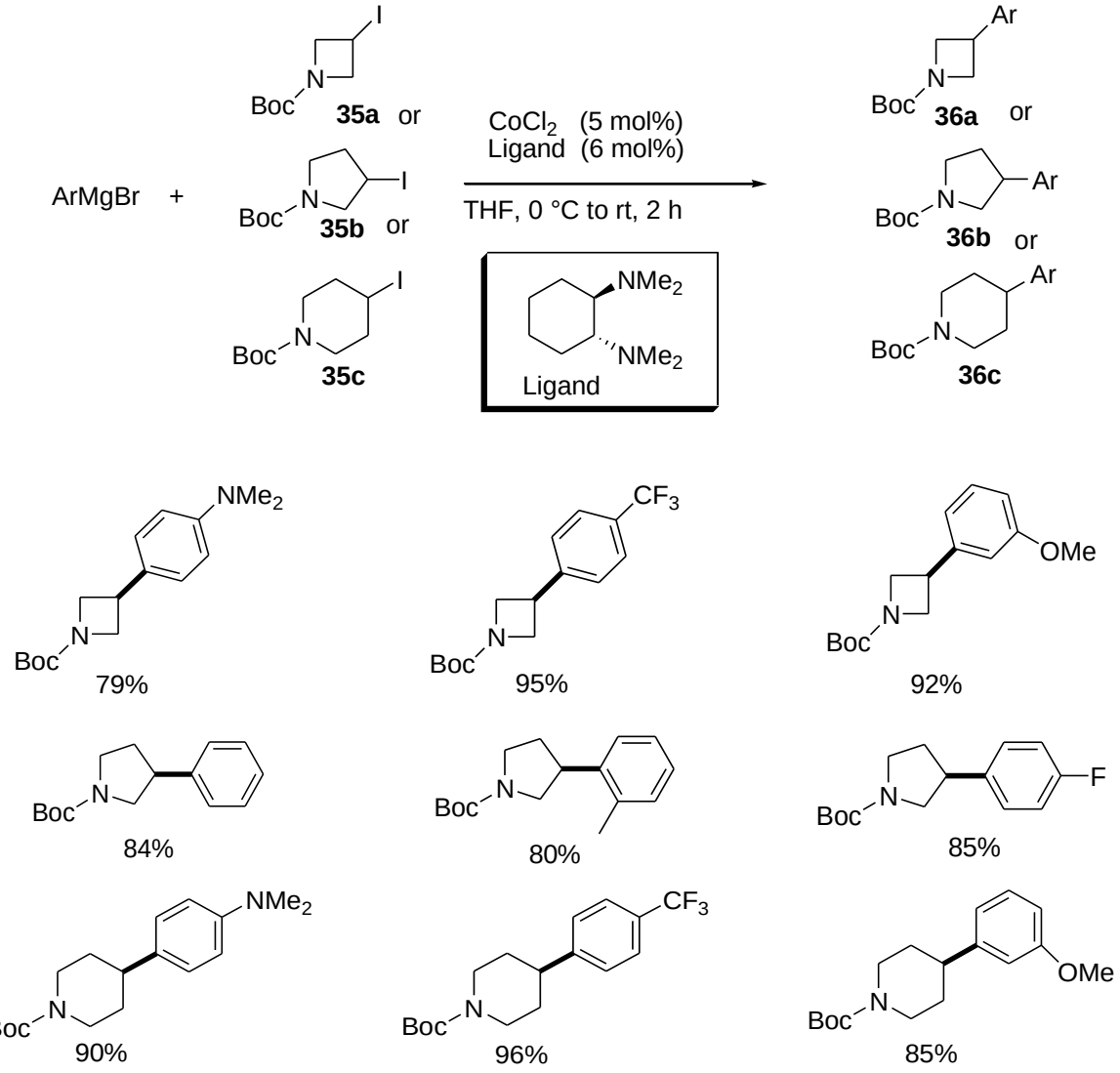


Entry	R group	Alkyl	Yield %	ee %
1	Et	Me	92	92
2	Me	Me	89	89
3	*i*-Pr	Me	93	95
4		Me	95	94
5		Me	83	91
6	Et	Et	92	92
7	*i*-Pr	Et	94	93
8	Me	Et	90	89
9		Et	90	93

Scheme 10. Phenylation of racemic α-bromo esters.

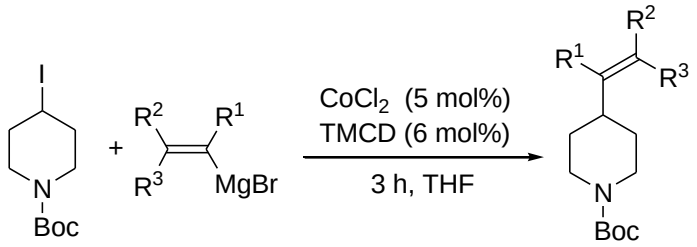
In 2014, Cossy *et al*. used the inexpensive $CoCl_2$ as an efficient catalyst for the cross-coupling reaction of iodinated N-heterocycles such as 3-iodoazetidine **35a**, 3-iodopyrrolidine **35b**, and 4-iodopiperidine **35c**, with

aryl Grignard reagents in the presence of (*R*,*R*)-tetramethylcyclohexanediamine (TMCD) as an essential ligand, to afford a broad spectrum of functionalized N-heterocyclic products **36a-c** in excellent yields (Scheme 11). Remarkably, the reaction was not sensitive to steric hindrance and tolerated a large variety of functional groups.[65]



Scheme 11. Cobalt catalyzed cross-coupling reactions of N-heterocycles iodides with aromatic Grignard reagents.

In 2015, Cossy and coworkers extended their protocol to couple 4-iodopiperidine **37** with alkenyl Grignard reagents **38**, catalyzed by $CoCl_2$ with the aid of (*R*,*R*)-tetramethylcyclohexanediamine (TMCD) in THF. The corresponding coupled products **39** were obtained in moderate yields (52-55%) when reaction of different alkenylmagnesium bromides with *N*-Boc-4-iodopiperidine in the temperature range between 0 ^{o}C and room temperature (entries 1-3, Scheme 12). On the other hand, lowering the temperature to -10 ^{o}C resulted in a significant improvement in the yield of the desired product (entry 4).[66]



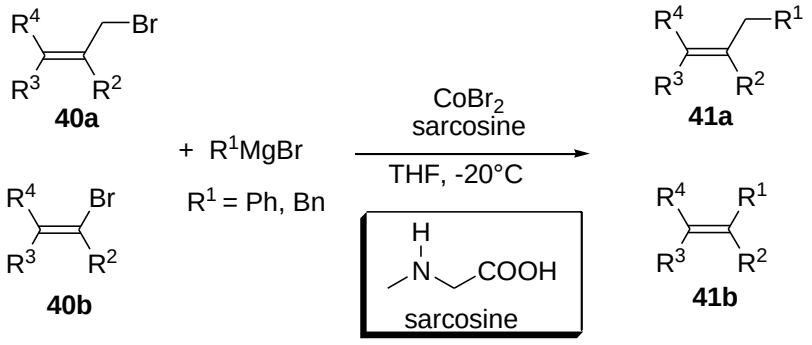
37 **38** **39**

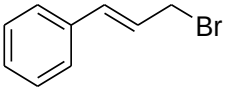
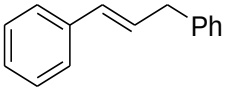
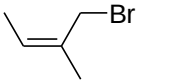
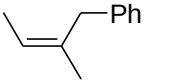
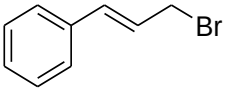
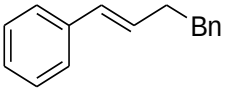
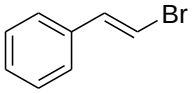
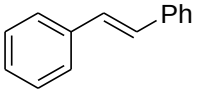
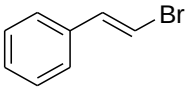
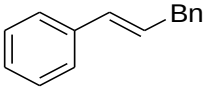
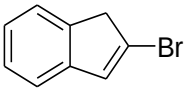
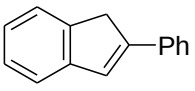
Entry	RMgBr	Temp (^{o}C)	Yield %
1		0 to RT	55
2		0 to RT	55
3		0 to RT	52
4		-10	70

Scheme 12. Cross-coupling with alkenyl Grignard reagents with *N*-Boc-4-iodopiperidine.

In the same year, Časar *et al*. made a significant contribution to the development of coupling reactions of Grignard reagent with allylic and vinylic bromides by virtue of the use of a $CoBr_2$/sarcosine catalyst system in THF at a low temperature. Consequently, phenyl and benzyl Grignard reagents were efficiently coupled with allylic **40a** and alkenyl **40b** bromides to generate a diverse array of the corresponding coupled products **41a,b** in good to excellent yields (Scheme 13). However, vinyl bromides afford slightly higher yields (entries 4-6) compared to cross-coupling reactions with allyl bromides (entries 1-3).[67]

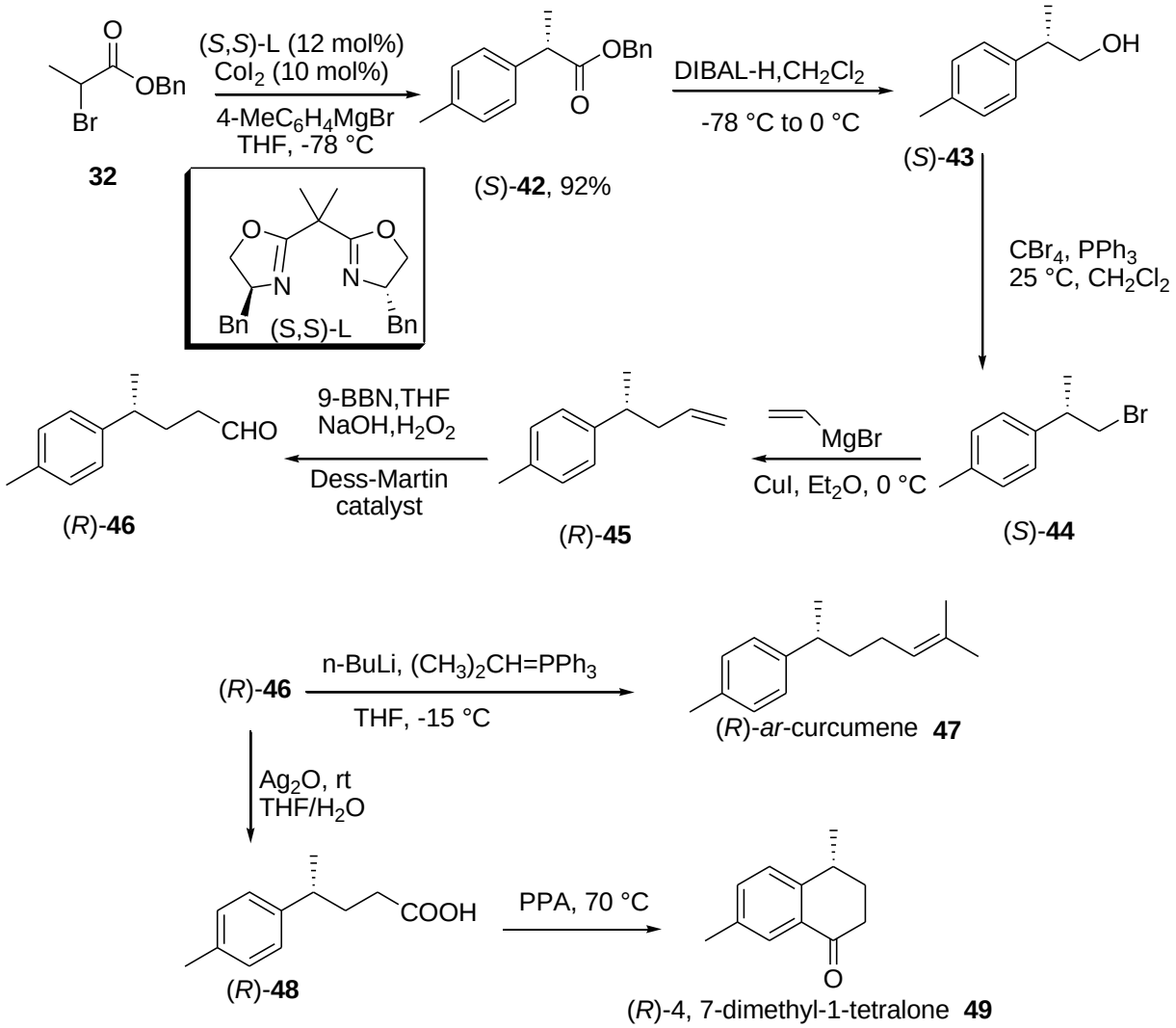
(*R*)-*ar*-Curcumene and 4,7-dimethyl-1-tetralone have been found in nature, and they have significant biological activity.[68] In 2015, Bian *et al*. reported the first cobalt-catalyzed asymmetric Kumada cross-coupling reaction in the synthesis of (*R*)-*ar*-curcumene, (*R*)-4,7-dimethylltetralone, and their enantiomers. Racemic α-bromopropanoate (*rac*-**32**) reacted with *p*-tolylmagnesium bromide catalyzed by CoI_2 and (*S*,*S*)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline) ligand to generate chiral α-arylcarboxylic ester **42**, which was reduced by diisobutylaluminum hydride to give chiral primary alcohol **43**. In turn, the primary alcohol was converted into primary bromide **44** with the help of triphenylphosphine and carbon tetrabromide. The desired terminal alkene (*R*)-**45** was obtained via CuI catalyzed cross-coupling (*S*)-**44** with vinylmagnesium bromide. The oxidation of (*R*)-**45** by Dess-Martin reagent led to the formation of the chiral aldehyde (*R*)-**46** which is an advantageous building block in the synthesis of (*R*)-*ar*-curcumene and (*R*)-4,7-dimethyl-1-tetralone. The reaction of aldehyde (*R*)-**46** with iso-propyltriphenylphosphonium iodide at low temperature afforded the desired (*R*)-*ar*-curcumene **47** in 79% yield, whereas the oxidation of aldehyde (*R*)-**46** with Ag_2O gave carboxylic acid (*R*)-**48** which was transformed into (*R*)-4,7-dimethyl-1-tetralone **49**.[69]



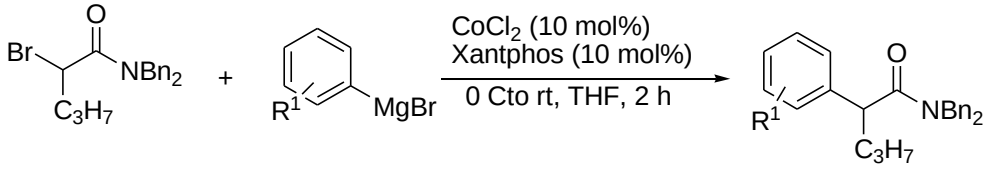
Entry	Allyl or alkenyl bromides	Products	Yield %
1			86
2			82
3			86
4			86
5			95
6			95

Scheme 13. $CoBr_2$/ Sarcosine-catalyzed carbon–carbon cross-coupling of allyl and alkenyl bromides with phenyl or benzyl Grignard reagents.

The scope of cobalt-catalyzed cross-coupling reactions has been considerably expanded by including a large variety of Grignard reagents and electrophilic substrates. In 2017, Cossy *et al.* have developed a protocol for the cross-coupling reaction of α-bromoamides **50** with aryl Grignard reagents **51** using $CoCl_2$ and Xantphos as an efficient catalyst system under mild reaction conditions. (Scheme 15, entries 1-6) Electron rich and electron poor Grignard reagents reacted efficiently with α-bromo amides with 10 mol % catalyst loading of $CoCl_2$ and Xantphos as ligand**,** furnishing α-aryl amides **52** in relatively good yields. On the other hand, the reaction was extremely sensitive to steric hindrance, as in the case of 2-MeC_6H_4MgBr (Scheme 15, entry 7).[70]



Scheme 14. Synthesis of (*R*)-*ar*-curcumene and (*R*)-4,7-dimethyl-l-tetralone.

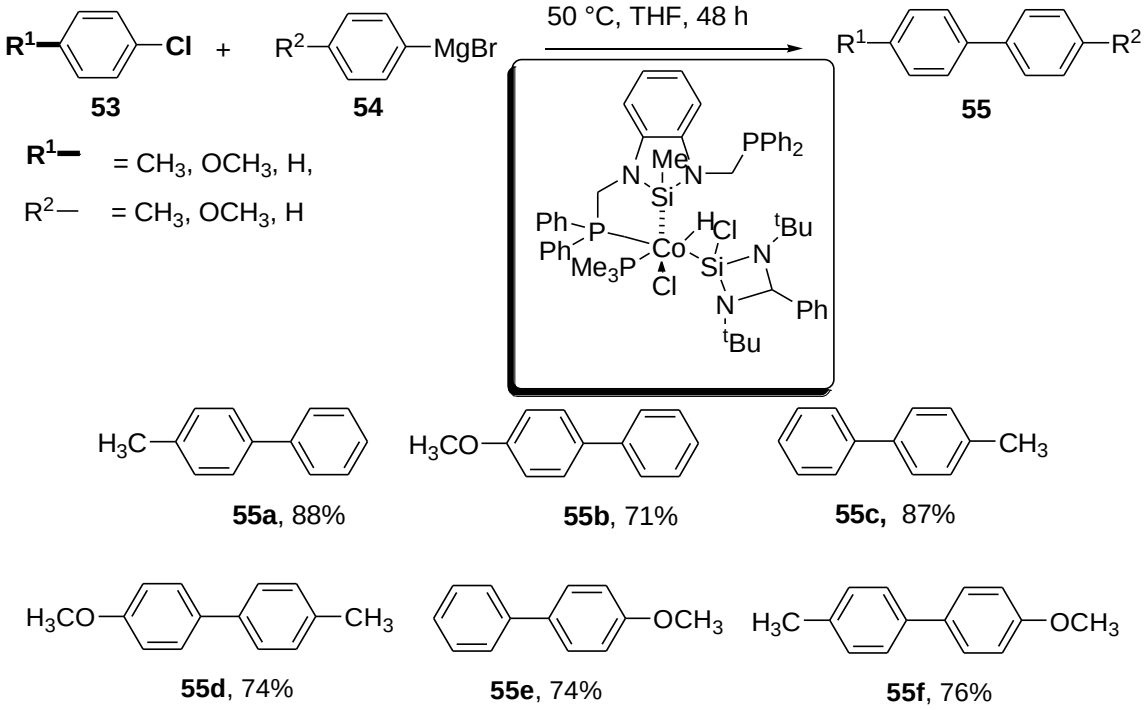


50 **51** **52**

Entry	R^1	Yield %
1	4-Me	68
2	4-MeO	69
3	4-NMe_2	64
4	4-CF_3	70
5	4-Cl	73
6	3-MeO	70
7	2-Me	0

Scheme 15. Cobalt catalyzed cross-coupling of α-bromo amides with aryl Grignard reagents.

The use of aryl chlorides as electrophilic substrates in cross-coupling reactions proved to be difficult, while their low cost and better availability compared to their iodo and bromo analogues makes them a highly attractive substrate class.[71] In 2018, Sun and coworkers have synthesized a powerful Co(III) hydride supported by a N-heterocyclic silylene ligand as a promising catalyst, which was successfully employed in cross-coupling of aryl chlorides **53** with aryl Grignard reagents **54**. Very good yields of coupled products were obtained at 50 ^{o}C within 48 h (Scheme 16, **55a**-**f**).[72]

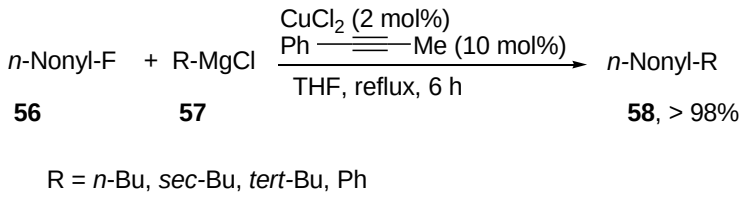


Scheme 16. Cross-coupling of aryl chlorides with Grignard reagents catalyzed by cobalt-silylene complex.

2.2 Copper catalyzed cross-coupling reactions

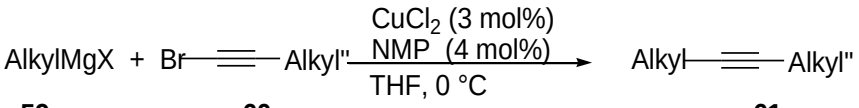
In recent years, copper reagents have emerged as applicable and powerful catalysts for cross-coupling reactions to construct C-C bonds.[73] The use of catalytic copper complexes in C-C bond formation had actually been demonstrated several years before the discovery of palladium and nickel as effective catalysts for these transformations. In 1971, Kochi *et al*. reported the first examples of copper-catalyzed cross-coupling reactions of Grignard reagents with alkyl halides.[74] However, during the last decade numerous methods have been developed for the formation of carbon-carbon bonds using copper-catalyzed cross-couplings of Grignard reagents with various electrophilic substrates, as will be discussed here.

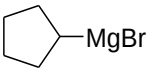
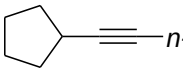
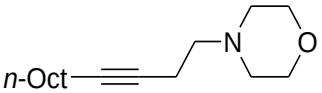
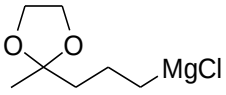
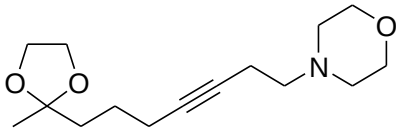
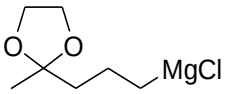
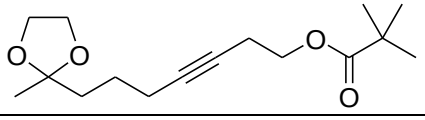
In 2007, Kambe and his group reported a method for constructing C-C bonds by the copper-catalyzed cross-coupling reaction of Grignard reagents and non-activated alkyl fluorides with the aid of 1-phenylpropyne as an additive under mild reaction conditions. Normally, alkyl fluorides were considered to be no suitable coupling partners in cross-couplings because of their low reactivity for oxidative addition.[75] In this optimized cross-coupling methodology, *n*-nonyl fluoride **56** reacted with Grignard reagents **57** in the presence of catalytic amounts of $CuCl_2$ (0.02 mmol) and 1-phenylpropyne in THF under reflux for 6 h, leading to cross-coupled products **58** in yields greater than 98% yield (Scheme 17).[76]



Scheme 17. Cross-coupling reaction of *n*-nonyl fluoride with Grignard reagents.

Cahiez *et al.* successfully prepared a broad spectrum of functionalized internal alkynes **61** by coupling alkyl Grignard reagents **59** with alkynyl halides **60** using $CuCl_2$ with σ-donor ligands like *N*-methylpyrrolidone (NMP) as an effective catalyst system at low temperatures in THF. Primary alkyl (Scheme 18, entries 1-2) and cyclic or acyclic secondary alkyl Grignard reagents (entries 3,4) coupled with 1-bromo-1-heptyne to afford the corresponding coupling products in good to excellent yields. Using this protocol, the catalyst system was also used to effect the coupling reaction of functionalized Grignard reagents with alkynyl bromides under mild reaction conditions, giving the desired products in satisfactory yields (entries 5-7).[77]

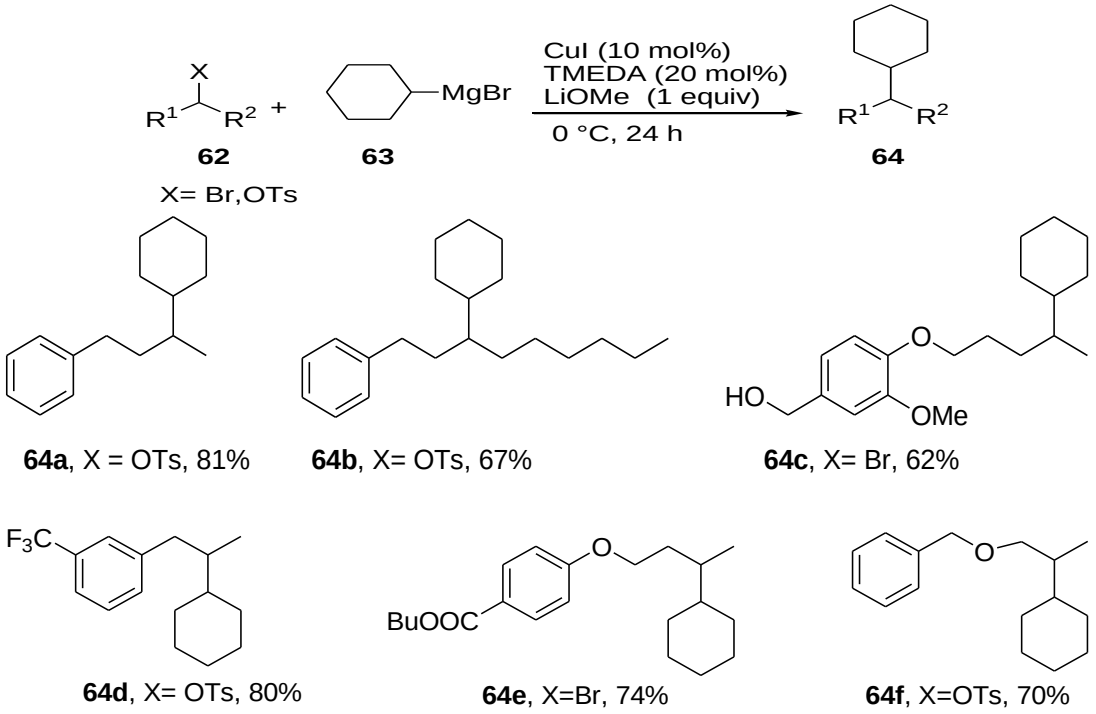


Entry	AlkylMgX	Product	Yield %
1	*n*-BuMgCl	*n*-Bu—≡—*n*-Pent	91
2	*n*-OctMgCl	*n*-Oct—≡—*n*-Pent	89
3	*sec*-BuMgCl	*sec*-But—≡—*n*-Pent	90
4			78
5	n-OctMgCl		92
6			89
7			81

Scheme 18. Copper-catalyzed cross-coupling of alkyl Grignard reagents with bromoalkynes.

As a rule, C(sp^3)-C(sp^3) cross-coupling is difficult owing to competing side reactions such as homocoupling, dehalogenation and β-elimination.[1,78,79] In 2012, Liu and coworkers developed a mixed catalyst system including CuI/ TMEDA/ LiOMe for the coupling reaction of functionalized nonactivated secondary alkyl halides or tosylates **62** with different chain lengths and cyclohexylmagnesium bromide **63** at 0 °C within 24 h,

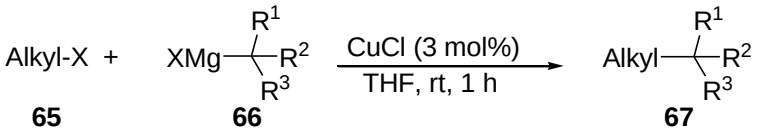
generating the desired products in synthetically useful yields (Scheme 19, **64a**-**f**). This coupling methodology tolerates a broad range of functional groups like hydroxyl, methoxy, trifluoromethyl and ester, although these functional groups are normally incompatible with Grignard reagents.[80]

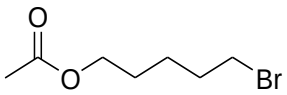
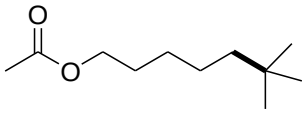
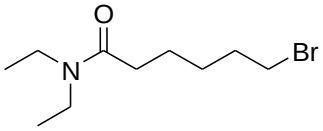
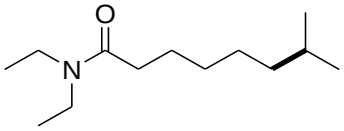
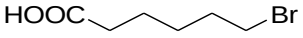
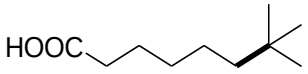
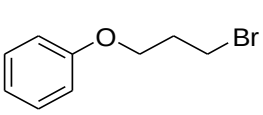
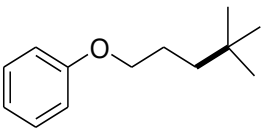
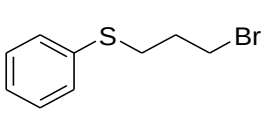
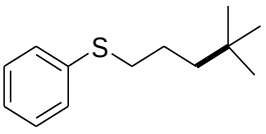
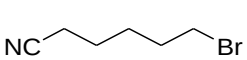
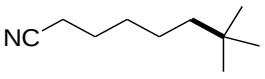
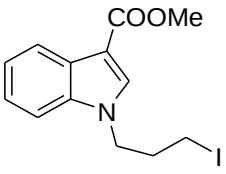
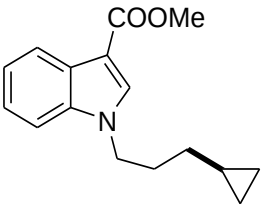
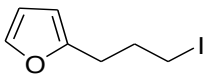
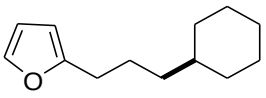
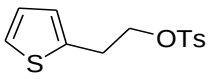
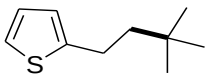
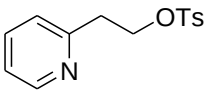
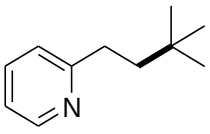


Scheme 19. Cross-coupling of unactivated secondary alkyl halides or tosylates with cyclohexylmagnesium bromide.

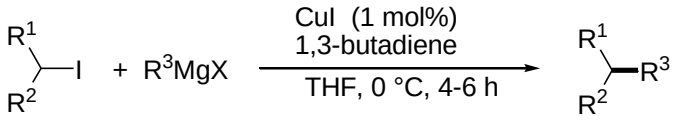
In 2012, Hu *et al*. designed a protocol to prepare a large array of organic compounds **67** by coupling a functionalized alkyl halide or tosylate **65** with a secondary or tertiary alkyl Grignard reagent **66** using 3 mol% CuCl as an efficient catalyst at room temperature. Electrophilic substrates containing ester, amide and carboxylic acid groups were fully tolerated (Scheme 20, entries 1-3). In this work, ether and thioether substrates were efficiently coupled in good yields (entries 4,5), likewise 6-bromohexanenitrile reacted smoothly with Grignard reagent under the same reaction conditions (entry 6). Heterocyclic substrates revealed exceptional reactivity, yielding the corresponding coupled products in good yields (entries 7-10).[81] Although the yields are similar, the coupling reaction is faster and more efficient in this case, compared to the previous cobalt catalyzed coupling tertiary alkyl Grignard reagents with alkyl halides developed by Kambe *et al*. as shown in scheme 8.

Kambe *et al*. have continued their efforts to develop the efficiency of copper catalysts in C-C coupling reactions. They carried out coupling of unactivated secondary alkyl iodides **68** with alkyl Grignard reagents **69** with loadings of the CuI catalyst as low as 1 mol% in the presence of 1,3-butadiene as an effective additive under mild reaction conditions. 2-Iodooctane and 4-iodoheptane coupled with *n*-BuMgCl to give alkyl–alkyl coupled products in very good yields (Scheme 21, entries 2, 3) Homoallylic iodides as substrates produced acceptable yields (entries 4, 6). In contrast, the sterically hindered 2,4-dimethylpent-3-yl iodide generated poor yields of the corresponding coupling products (entries 8-9).[82]



Entry	Alkyl halides/tosylates	Products	Yields %
1			82
2			77
3			76
4			81
5			82
6			75
7			82
8			84
9			87
10			74

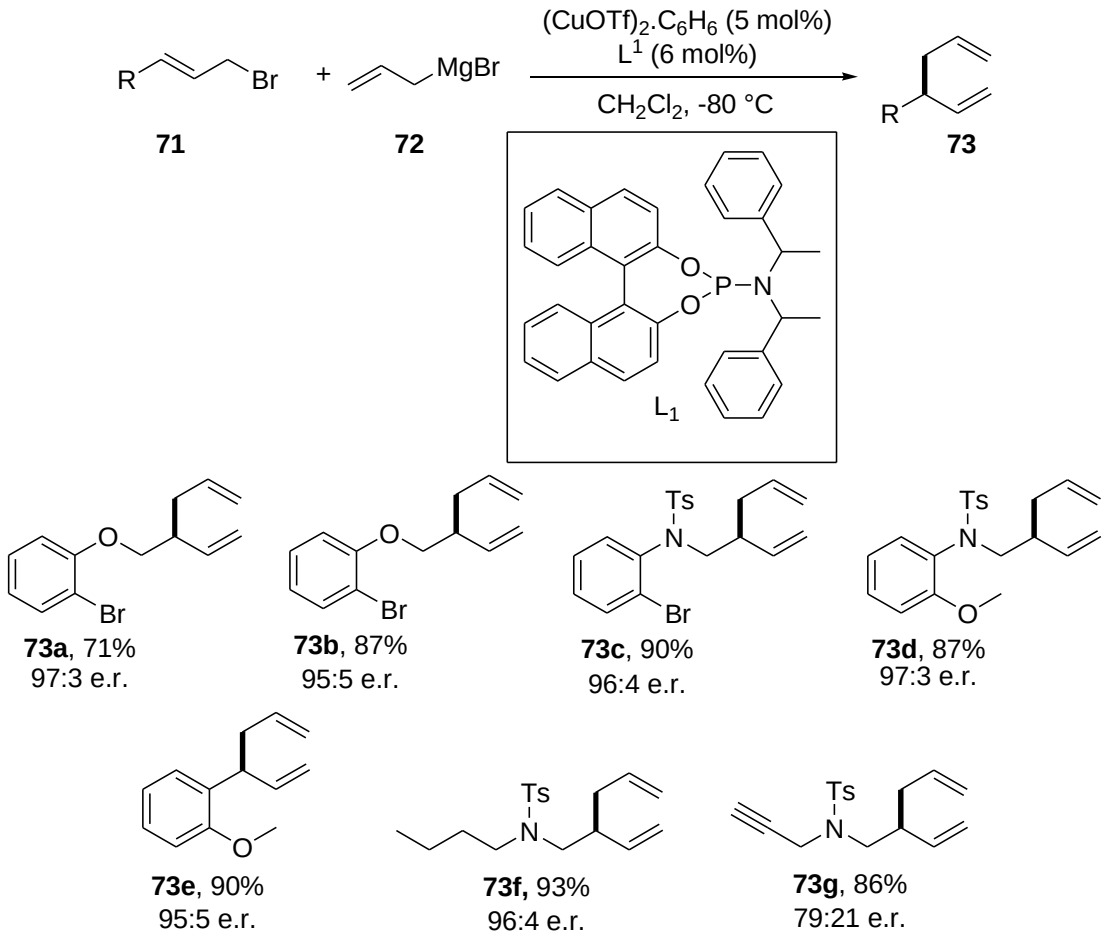
Scheme 20. Cu(I)-catalyzed coupling reactions of alkyl halides or tosylates with secondary and tertiary alkyl Grignard reagents.



68 **69** **70**

Entry	R^1	R^2	R^3MgX	Yield %
1	$PhCH_2CH_2$	*n*-Pr	*n*-BuMgCl	85
2	n-C_6H_{13}	Me	*n*-BuMgCl	87
3	*n*-Pr	*n*-Pr	*n*-BuMgCl	81
4	$PhCH_2CH_2$	Allyl	EtMgBr	70
5	$PhCH_2CH_2$	*n*-Pr	*n*-BuMgCl	80
6	$PhCH_2CH_2$	Allyl	*n*-BuMgCl	89
7	*n*-C_6H_{13}	Me	AllylMgCl	93
8	*i*-Pr	*i*-Pr	*n*-BuMgCl	42
9	*i*-Pr	*i*-Pr	NeopentylMgCl	17

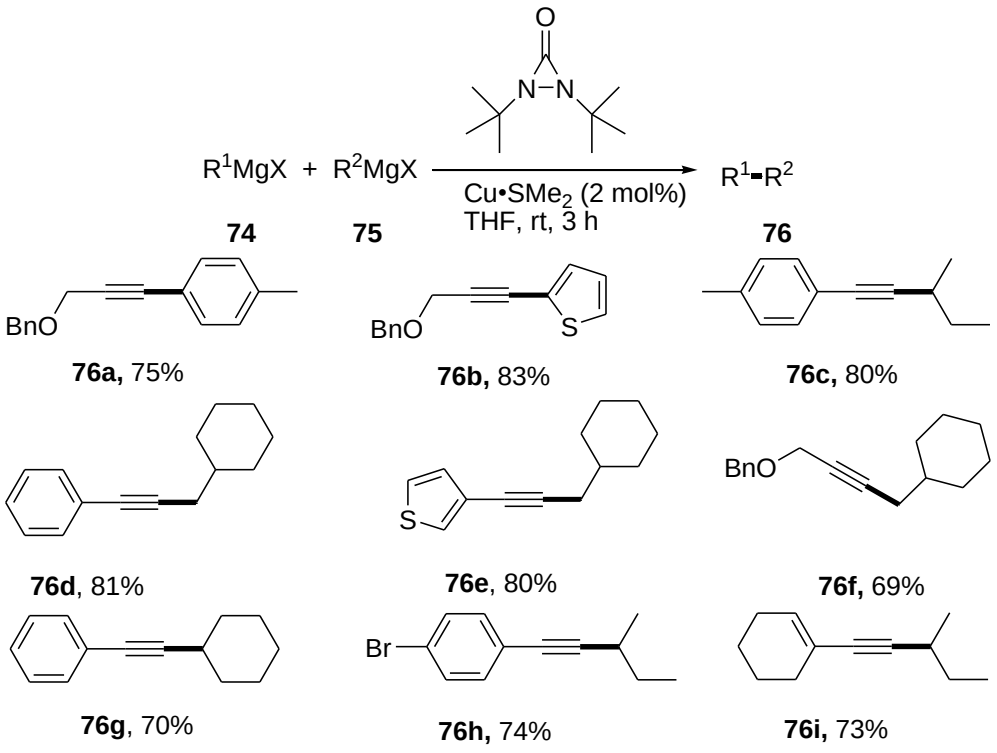
Scheme 21. Cross- coupling reaction of unactivated secondary alkyl iodides with alkyl Grignard reagents.



Scheme 22. Cu-catalyzed enantioselective allyl−allyl cross-coupling.

Recently, the copper-catalyzed reactions of allylic electrophiles with allyl Grignard reagents have seen impressive progress. In 2013, Feringa and coworkers reported the first copper-catalyzed enantioselective allyl–allyl coupling reaction of allyl bromides **71** and an allyl Grignard reagent **72** with the presence of phosphoramidite as efficient ligand (L^1) to afford a variety of the chiral 1,5-dienes **73** in good yields and high enantioselectivity. Nevertheless, the chiral 1,5-diene structures have served as building blocks for the chemical synthesis of complex natural products, including many terpenes. Several allylic substrates bearing various functional groups including protected alcohols, amines and alkenes coupled efficiently with allylmagnesium bromide to furnish the cross-coupled products in good yields with excellent enantioselectivities (Scheme 22, **73a**-**g**).[83]

In 2014, Shi *et al*. designed a novel oxidative copper catalyzed C-C coupling reaction of alkynyl Grignard reagents **74** with alkyl and alkenyl Grignard reagents **75** by using di-*tert*-butyldiaziridinone as an oxidant under mild reaction conditions. Remarkably, this oxidative coupling reaction was effective for C(*sp*)-C(sp^2) and C(*sp*)-C(sp^3) bond formations in the presence of 2 mol% of $CuBr{\cdot}SMe_2$ and 1.1 equiv of di-*tert*-butyldiaziridinone at room temperature for 3 h to afford the corresponding coupled products in good yields (Scheme 23, **76a**-**i**).[84]



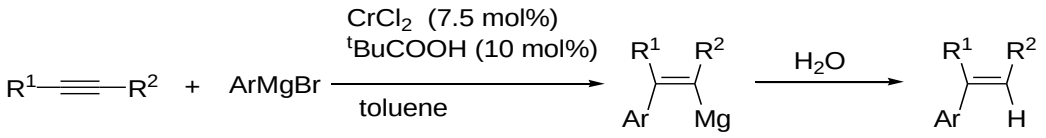
Scheme 23. Copper-catalyzed oxidative cross-coupling of Grignard reagents.

2.3 Chromium catalyzed cross-coupling reactions using various Grignard reagents

Cross-coupling reactions using chromium catalysts have rarely been investigated. Recently, the attention of researchers has been drawn towards the use of chromium salts in cross-couplings owing to their low cost and commercial availability, showing their ability to catalyze cross-couplings of C–X and C–H bonds with Grignard reagents.[21] In the last decade, Knochel and his group in pioneering studies have successfully developed chromium as a powerful catalyst for C-C bond formation via cross-coupling reactions.

In 2007, Oshima and co-workers reported the chromium-catalyzed arylmagnesiation of alkynes **77** using pivalic acid as co-catalyst. They found that aryl Grignard reagents added across the triple bond, forming the

arylmagnesium intermediate **78** using the $CrCl_2$/pivalic acid catalyst system at 110 ^oC, ultimately to generate the trisubstituted olefins **79**, predominantly with *E* configuration, in acceptable yields (Scheme 24).[85]

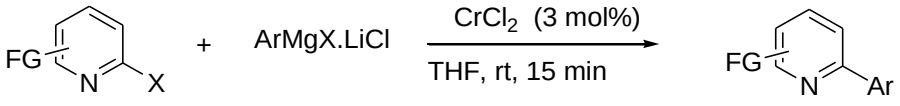


77 **78** **79**

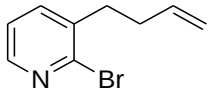
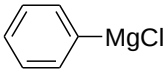
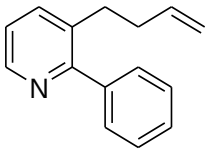
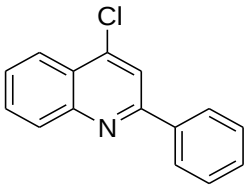
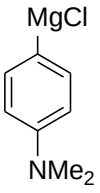
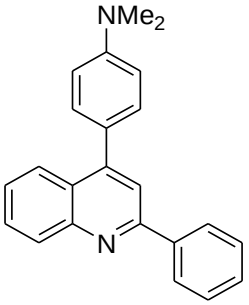
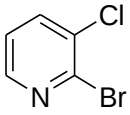
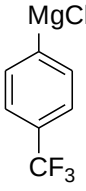
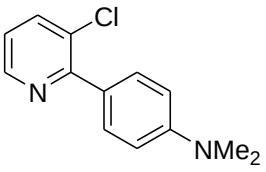
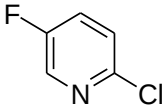
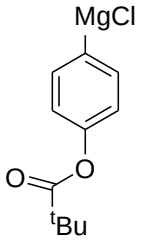
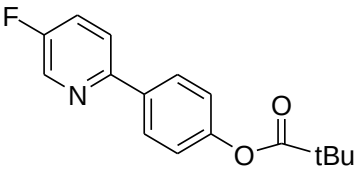
Entry	R^1	R^2	Ar	Time (h)	Yield %	*E*/*Z*
1	C_5H_{11}	C_5H_{11}	2-MeC_6H_4	10	55	99:1
2	C_5H_{11}	C_5H_{11}	3-MeC_6H_4	0.5	80	99:1
3	C_5H_{11}	C_5H_{11}	4-MeC_6H_4	0.5	81	99:1
4	C_5H_{11}	C_5H_{11}	4-ClC_6H_4	2	61	88:12
5	C_6H_{13}	Ph	Ph	2	68	92:8

Scheme 24. Chromium-catalyzed arylmagnesiation of alkynes.

Knochel *et al.* have made distinguished contributions to the development of a wide spectrum of chromium-mediated catalytic reactions to be used efficiently in cross-coupling reactions of a variety of Grignard reagents with various electrophilic substrates. In 2013, he and his group designed a method to construct C(sp^2)-C(sp^2) bonds (**82**, **84**) by fast cross-coupling reaction of the functionalized Grignard reagents bearing sensitive functionalities like ester, methoxy or halogens **81** with N-heterocyclic halides **80** or 2-chlorobenzophenone **83** using $CrCl_2$ as an efficient catalyst at room temperature within 15 min. Phenyl-magnesium bromide coupled smoothly with 2-bromo-3-(but-3-en-1-yl)pyridine, resulting in the 2,3-disubstituted pyridine in 95% yield (entry 1, Scheme 25), and cross-coupling of 4-(*N*,*N*-dimethylamino)phenyl-magnesium bromide with 4-chloroquinoline gave the desired product in good yield (entry 2). Similarly, the Grignard reagent containing a CF_3 group reacted with 2-bromo-3-chloropyridine to afford the product in 76% yield (entry 3). The sensitive ester-substituted Grignard reagent in entry 4 reacted with 2-chloro-5-fluoropyridine providing the expected product in a moderate yield.[86] Compared to the cobalt catalyzed arylation of N-heterocyclic halides by Grignard reagents previously illustrated in scheme 9, Knochel has successfully replaced cobalt chloride and isoquinoline ligand as catalyst system by equally efficient chromium chloride to give comparable results.

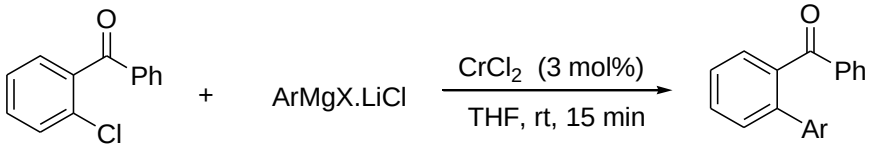


80 **81** **82**

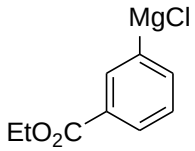
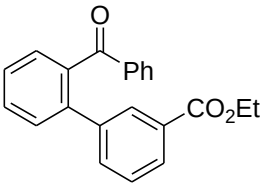
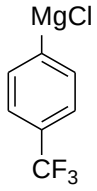
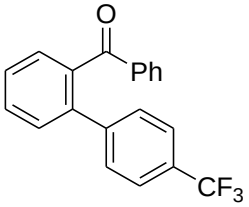
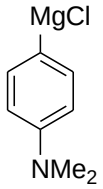
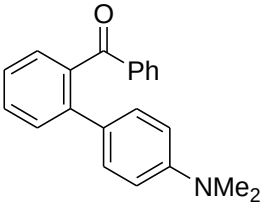
Entry	*N*-heterocyclic halide	Grignard reagent	Product	Yield %
1				95
2				78
3				76
4				66

Scheme 25. Cr-catalyzed reactions between N-heterocyclic halides and arylmagnesium reagents.

The same protocol was applied to Cr-catalyzed cross-coupling reactions between 2-chlorobenzophenone and phenylmagnesium reagents for the synthesis of the corresponding polyfunctional ketones in good to excellent yields (Scheme 26).[86]

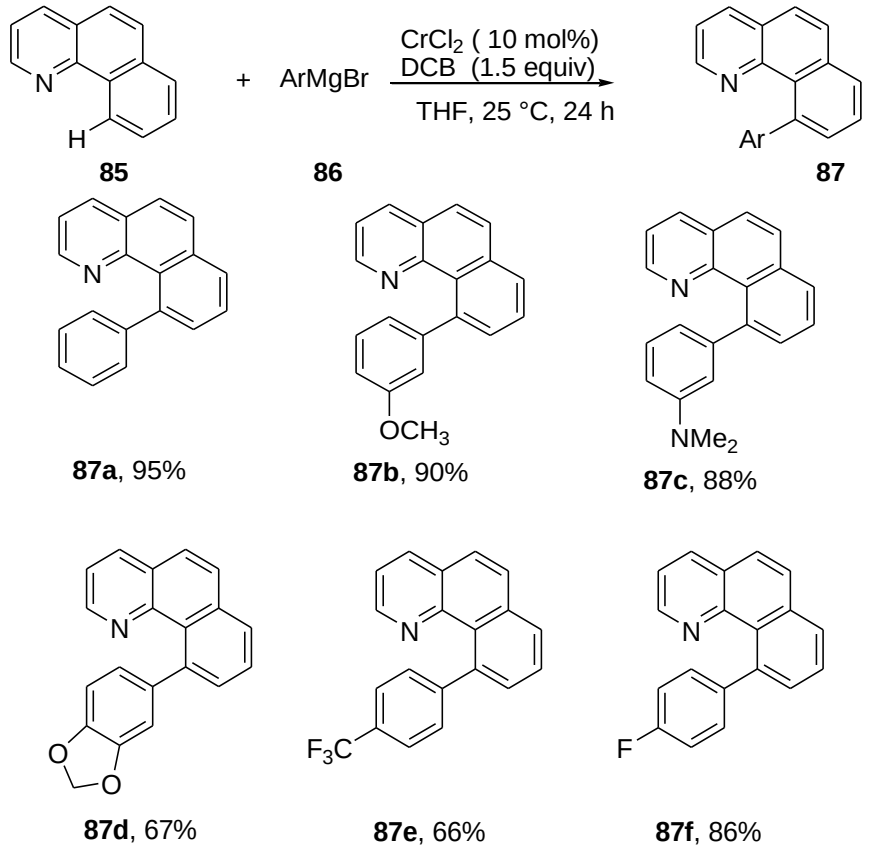


83 **84**

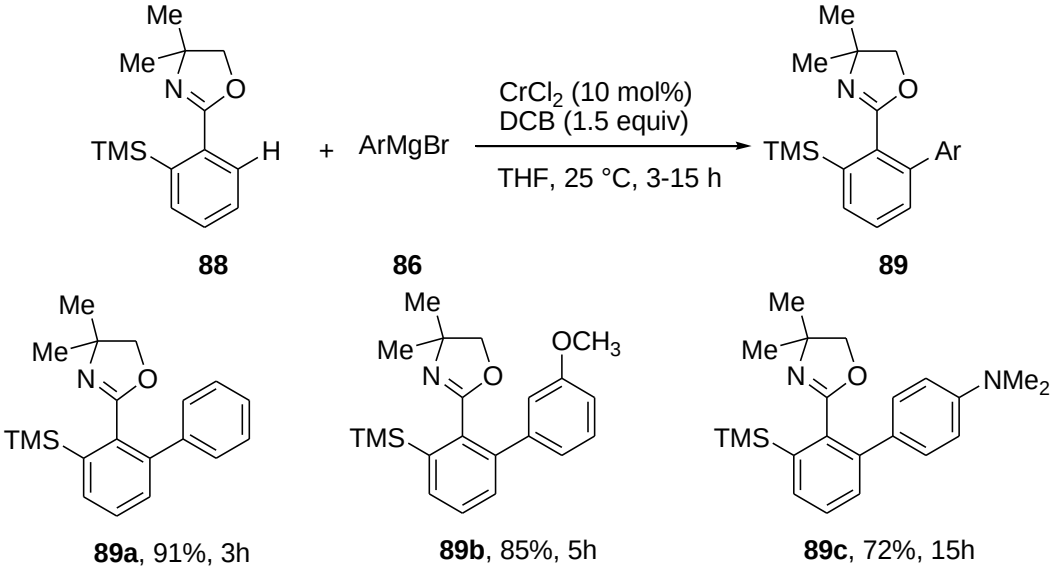
Entry	Grignard reagent	Product	Yield %
1			79
2			93
3			94

Scheme 26. Cr-catalyzed cross-coupling between 2-chlorobenzophenone and arylmagnesium reagents.

Knochel and coworkers have considerably extended the scope of chromium catalyzed C-C coupling reactions with Grignard reagents as coupling partners. In recent years, the formation of C-C bonds involving a transition-metal catalyzed C-H activation has been widely developed. [87-89] In 2014, Knochel *et al*. reported a novel chromium catalyzed direct arylation of pyridines and aryloxazolines by aryl Grignard reagents and 2,3-dichlorobutane (DCB) as an oxidant at room temperature. Direct arylation *via* activation of a C-H bond was efficiently accomplished by treatment of benzo[*h*]quinoline (**85**) with ArMgBr **86** catalyzed by $CrCl_2$ and DCB to give the arylated heterocycle **87a** in 95% yield (Scheme 27). Electron rich or -deficient Grignard reagents reacted effectively with benzo[*h*]quinoline, furnishing relatively high yields of products **87b**-**f**. 2-(2-Trimethyl-silylphenyl)oxazoline (**88**) has also been successfully coupled with various Grignard reagents providing the oxazoline *ortho*-arylated at the phenyl ring (**89a**-**c**) in 72-91 % yields (Scheme 28).[90] Compared to the previous methods developed by Knochel, chromium catalyzed direct arylations of aromatic C-H bonds by Grignard reagents have emerged as a promising alternative to classical cross-coupling reactions for the assembly of carbon–carbon bonds from simpler and more abundant starting materials.



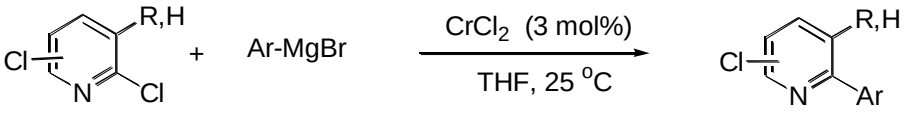
Scheme 27. Chromium-catalyzed arylation of benzo[*h*]quinoline.



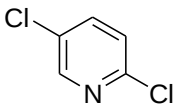
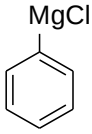
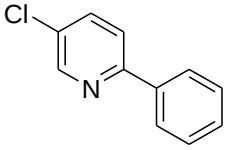
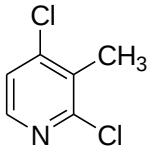
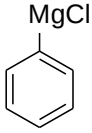
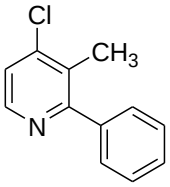
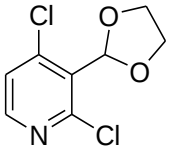
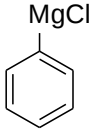
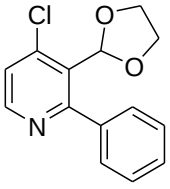
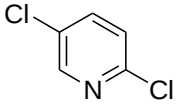
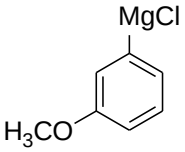
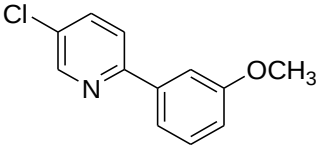
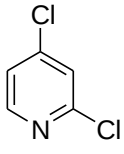
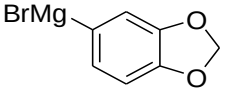
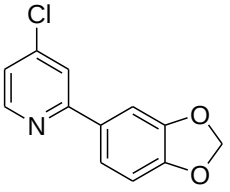
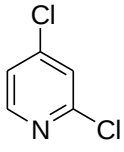
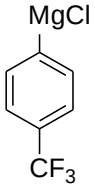
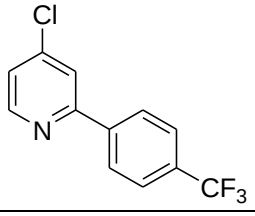
Scheme 28. Chromium-catalyzed arylation of 2-[2-(trimethylsilyl)phenyl]oxazoline.

Knochel and colleagues have continued to improve and extend chromium-mediated cross-coupling reactions involving functionalized Grignard reagents and substrates. They have reported selective coupling reactions of dichloropyridines **90** with a range of functionalized aryl Grignard reagents using $CrCl_2$ as the catalyst at room temperature leading to 2-arylated products **91**. In this optimized cross-coupling protocol, 2,5-dichloropyridine reacted selectively with a Grignard reagent within 15 minutes to form the product in 87%

yield (Scheme 29, entry 1). Similarly, 2,4-dichloro-3-methylpyridine coupled with phenylmagnesium bromide giving the cross-coupled product in good yield (entry 2). The reaction was also tolerant of steric hindrance: reaction of 2,4-dichloro-3-(1,3-dioxolan-2-yl)pyridine with a Grignard reagent afforded the expected product in moderate yield (entry 3). Electron-rich and electron-deficient Grignard reagents smoothly underwent coupling reactions with dichlorinated pyridines to provide the coupled products in satisfactory yields (entries 4-6).[91] Noteworthy, under the same cross-coupling conditions mentioned in the scheme 25, Knochel has demonstrated that the highly efficient regioselective coupling between dichlorinated pyridines and quinolines with aromatic Grignard reagents can be easily achieved using chromium salts. In accordance with a postulated mechanism, the selectivity is mainly attributed to pyridine-ring nitrogen which directs the attack of the phenyl–chromium intermediates into the proximal C-Cl bond.

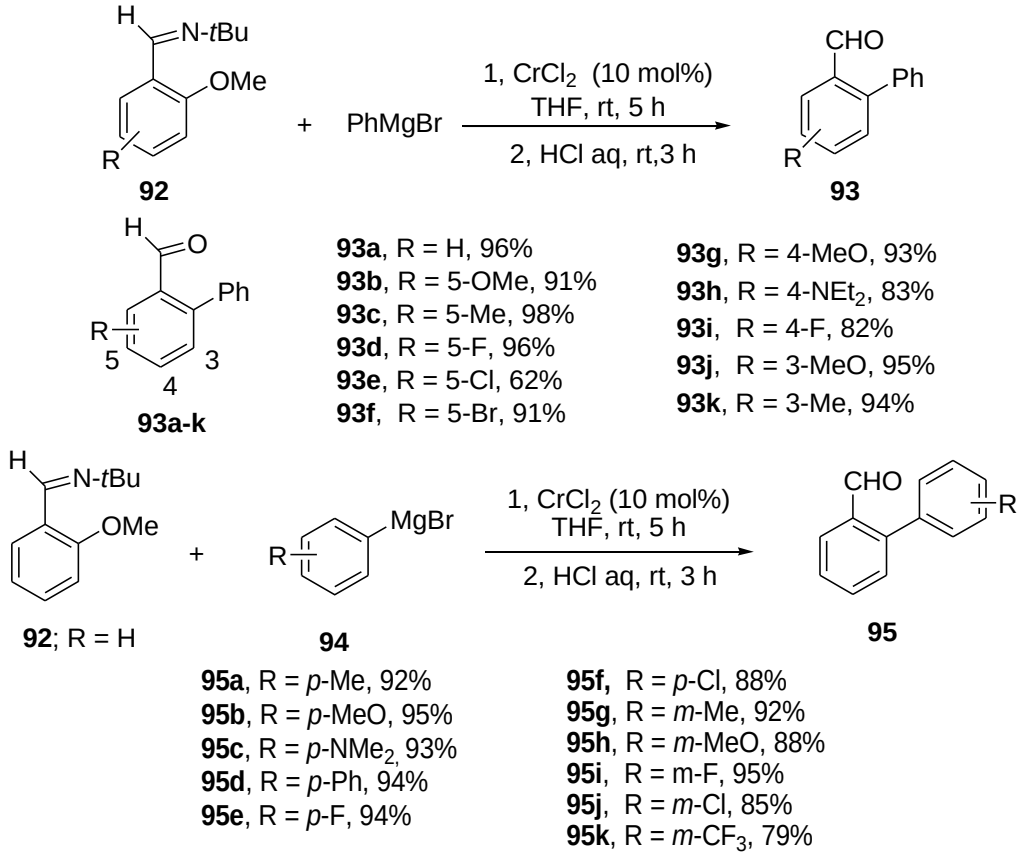


90 **86** **91**

Entry	Substrate	Grignard reagent	Product	Time min	Yield (%)
1				15	87
2				15	85
3				15	67
4				15	71
5				15	77
6				30	92

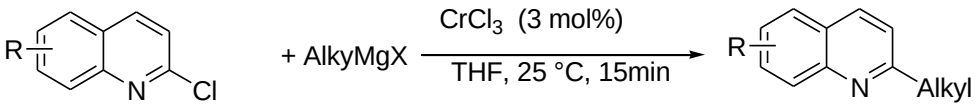
Scheme 29. Chemoselective reactions between dichlorinated pyridines and aromatic Grignard reagents.

Aryl ethers are considered one of the most attractive substrates in cross-coupling reactions in terms of availability, economics, and safety.[92,93] However, it is difficult to replace aryl ether groups in coupling reactions because of the robust nature of the C(aryl)-O bonds.[13] In 2015, Zeng *et al.* reported the first chromium catalyzed cross-coupling reactions of aryl ethers **92** with aryl Grignard reagents, giving excellent yields of functionalized aromatic aldehydes **93**. Both electron-rich and electron-deficient aryl ethers furnished the ortho-arylated aromatic aldehydes in good to excellent yields (62-98 %) (Scheme 30, **93a**-**k**). The electronic properties of electron-donating and electron-withdrawing groups on the Grignard reagents had little influence on the reaction: substituents like methoxy, fluoride, chloride, trifluoromethyl and amino were well tolerated in this coupling reaction (**95a-k**).[94]

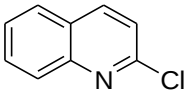
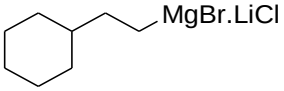
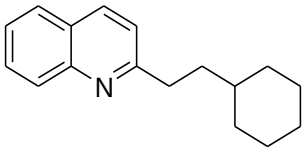
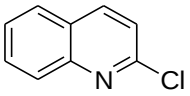
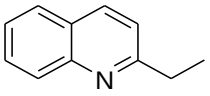
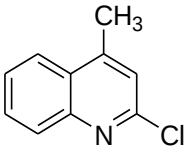
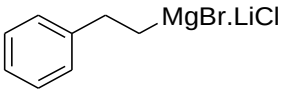
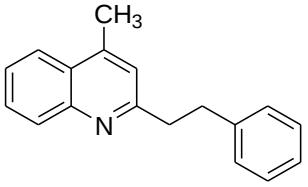
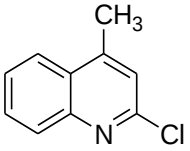
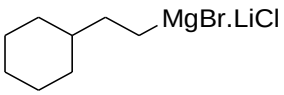
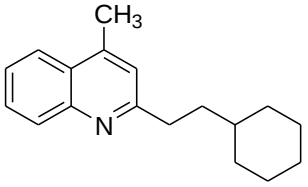
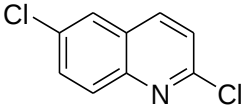
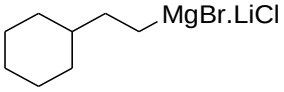
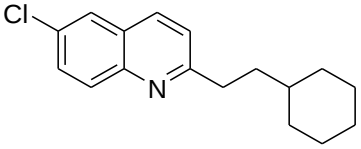
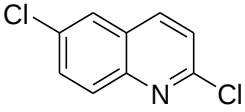
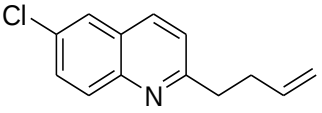


Scheme 30. Chromium catalyzed cross-coupling of aryl ethers with various aryl Grignard reagents.

In 2016, Knochel *et al*. demonstrated an efficient method for C(sp^2)-C(sp^3) bond formation via chromium catalyzed cross-coupling reactions of chloroquinolines **96** with Grignard reagents **97** under mild reaction conditions within 15 minutes. However, 2-chloroquinoline underwent a rapid coupling reaction with phenethylmagnesium and ethylmagnesium bromides using $CrCl_3$ as a catalyst in THF to produce the coupled products in good yields (Scheme 31, entries 1, 2). Under the same reaction conditions, 2-chloro-4-methyl-quinoline cross-coupled effectively with phenethylmagnesium and 2-(cyclohexyl)ethylmagnesium bromide, leading to alkylated quinolines in 82 and 79% yields respectively (entries 3, 4). Regioselective cross-coupling was achieved by treatment of 2,6-dichloroquinolines with various primary alkylmagnesium bromides, generating the 2-alkylated-6-chloroquinolines in very high yields (entries 5, 6).[95]



96 **97** **98**

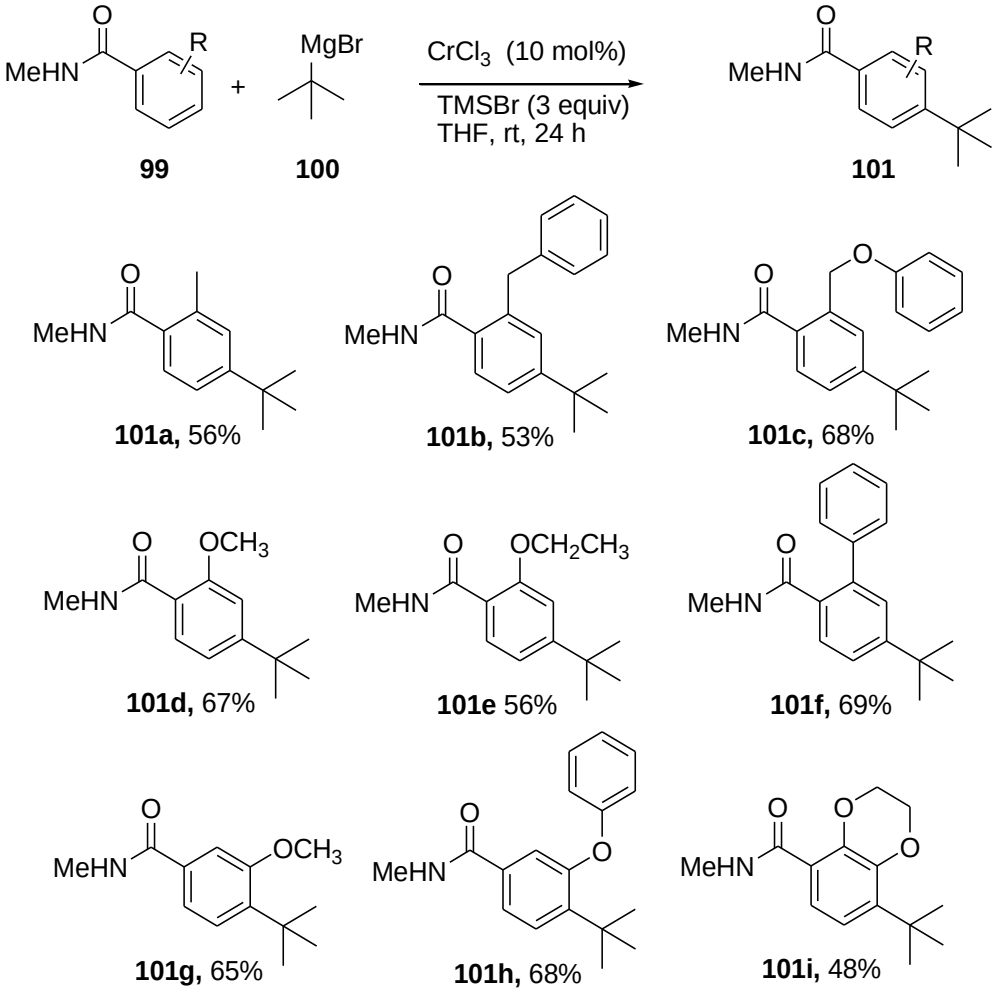
Entry	Electrophiles	Grignard reagents	Products	Yield %
1				79
2		EtMgBr.LiCl		65
3				82
4				79
5				77
6				84

Scheme 31. Chromium-catalyzed cross coupling reaction of Grignard reagents with chloroquinolines.

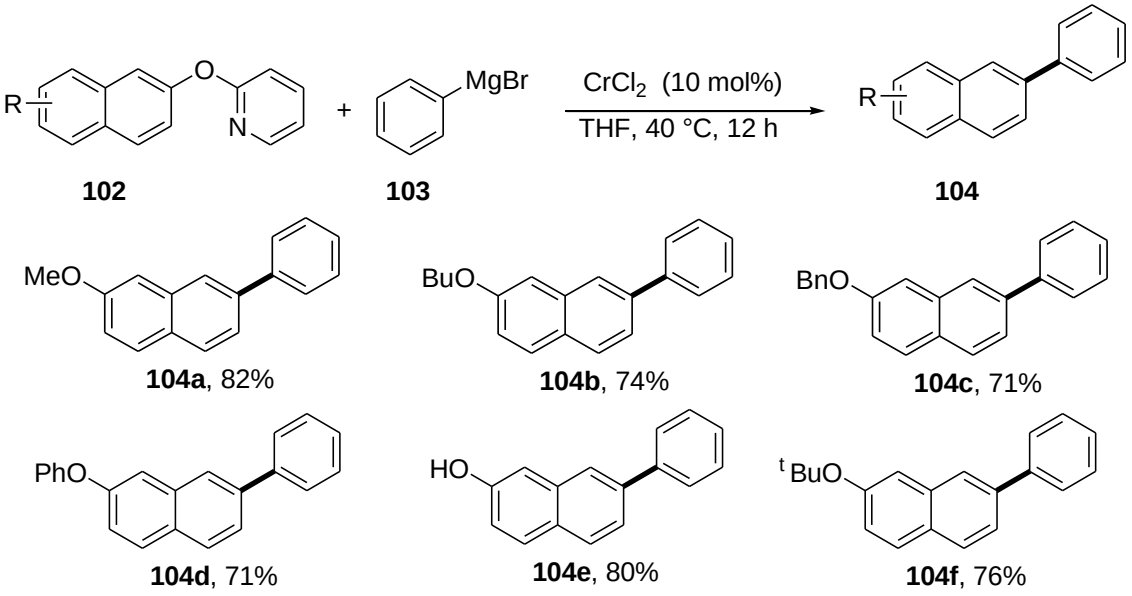
A surge of activity in the direct activation of C-H bonds has been witnessed in the last 20 years. In 2018, Zeng and coworkers have developed a chromium-catalyzed para-selective formation of quaternary carbon centers by direct alkylation of benzamide derivatives **99** using Grignard reagent **100**, in the presence of $CrCl_3$ with bromotrimethylsilane (TMSBr) as an efficient catalyst system at room temperature, to form alkylated benzamides **101** in good yields. Trimethylsilyl bromide may facilitate the formation of *tert*-butyl radicals and a trimethylsilyl-Cr intermediate through reaction with t-BuMgBr and low-valent Cr species in the catalytic cycle. The benzamide derivatives containing an *ortho*-methyl, benzyl, methoxy, ethoxy or phenoxymethyl substituent coupled with *t*-BuMgBr, generating acceptable yields of the corresponding *para*-*t*-butylated compounds **101a**-**f** (Scheme 32). Steric effects arising from *meta*-substitution of the benzamides did not exert much influence on the site selectivity of alkylation and product yields (**101g-i**).[96]

In the same year, Zeng *et al*. reported a novel methodology for C-C bond formation via chromium-catalyzed regioselective cross-coupling reaction of aryl 2-pyridyl ethers **102** with phenylmagnesium bromide **103**. The 2-pyridyl moiety played a crucial role in the cleavage of the C(aryl)-OPy bond to couple with the

Grignard reagent affording the selectively coupled products in good yields, while keeping the other C(aryl)-O bonds in the reaction system intact (Scheme 33, **104a**-**f**).[97]



Scheme 32. Cr-catalyzed *para*-selective alkylation of benzamides with *tert*-butyl Grignard reagent.



Scheme 33. Chromium-catalyzed selective arylative coupling of C(aryl)–N bonds in aryl 2-pyridyl ethers.

Conclusions

The metal catalyzed cross-coupling reactions provide one of the most straightforward protocols for carbon-carbon bond construction. These transformations are typically catalyzed by expensive and rare palladium and nickel complexes. Recently, the use of the abundant and inexpensive transition metals cobalt, copper and chromium in developing cost-effective synthetic strategies has attracted much attention. Grignard reagents remain desirable coupling partners owing to the ease of their preparation, and many of them are commercially available. Considerable effort has been devoted to developing novel and efficient methods using cobalt, copper and chromium-catalysts for the C-C coupling reaction of various organic halide substrates and related electrophiles with functionalized Grignard reagents, and significant achievements in this area have emerged during the past decade. This review highlights recent advances of carbon-carbon bond formation via cobalt, copper and chromium-catalyzed cross-coupling reactions of Grignard reagents with various electrophilic substrates to produce a wide variety of organic compounds.

References

1. Jana, R.; Pathak, T. P.; Sigman, M. S, *Chem. Rev.* **2011**, *111*, 1417-1492. http://dx.doi.org/10.1021/cr100327p
2. Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem. Int. Ed***. 2004**, *43*, 6180-6182. http://dx.doi.org/10.1002/anie.200460246
3. Vechorkin, O.; Hu, X. *Angew. Chem. Int. Ed*. **2009**, *48*, 2937-2940. http://dx.doi.org/10.1002/anie.200806138
4. Molnar. A. *Chem. Rev.* **2011**, *111*, 2251–2320. http://dx.doi.org/10.1021/cr100355b
5. Huang, J.; Nolan. S. *J. Am. Chem. Soc.* **1999,** *121,* 9889-9890. http://dx.doi.org/10.1021/ja991703n
6. Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc*. **2009**, *131*, 9756-9766. http://dx.doi.org/10.1021/ja9027378
7. Terao, J.; Kambe, N. *Acc. Chem. Res*. **2008**, *41*, 1545-1554. http://dx.doi.org/10.1021/ar800138a
8. Knochel, P.; Krasovskiy, A.; Sapountzis, I. *Handbook of Functionalized Organometallics*, Wiley-VCH: Weinheim, 2005, Vol. 1, pp 109 –172.
9. Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 1701-1703. http://dx.doi.org/10.1002/(SICI)1521-3773(19980703)37:12<1701::AID-ANIE1701>3.0.CO;2-U
10. Dahadha, A.; Aldhoun, M. *Arkivoc* **2018**, *(vi*), 234-253. http://dx.doi.org/10.24820/ark.5550190.p010.746
11. Zhang, X.; Wang, X. Z. *Synlett* **2013**, *24*, 2081-2084. http://dx.doi.org/10.1055/s-0033-1339653
12. Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717-1726. http://dx.doi.org/10.1021/acs.accounts.5b00051
13. Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, M. A.; Garg, N. K.; Percec, V. *Chem. Rev*. **2011**, *111*, 1346-1416. http://dx.doi.org/10.1021/cr100259t

14. Iglesias, J. M.; Prieto, A.; Nicasio, M. *Org. Lett.* **2012**, *14*, 4318-4321. http://dx.doi.org/10.1021/ol302112q
15. Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.*, **2005**, *127*, 17978-17979. http://dx.doi.org/10.1021/ja056327n
16. Han, J.; Zong, L.; Liu, C.; Wang, J.; Jian, X. *Polymer International* **2016**, *65*, 526-534. http://dx.doi.org/10.1002/pi.5086
17. Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 9590-9599. http://dx.doi.org/10.1021/ja903091g
18. Yanes, R. S.; Ceinos, M. G.; Buñuel, E.; Cárdenas, D. J. *Eur. J. Org. Chem.* **2014**, 6625-6629. http://dx.doi.org/10.1002/ejoc.201403007
19. Kuzminaa, O.; Steiba, A.; Moyeux, A.; Cahiez, G.; Knochel, P. *Synthesis* **2015**, *47*, 1696-1705. http://dx.doi.org/10.1055/s-0034-1380195
20. Sherry, D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500-1511. http://dx.doi.org/10.1021/ar800039x
21. Zeng, X.; Cong, X. *Org. Chem. Front*. **2015**, *2*, 69-72. http://dx.doi.org/10.1039/C4QO00272E
22. Barré, B.; Gonnard, L.; Guérinot, A.; Cossy. *Molecules* **2018**, *23*, 1449-1461. http://dx.doi.org/10.3390/molecules23061449
23. Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010,** *110,* 1435–1462. http://dx.doi.org/10.1021/cr9000786
24. Rérat, A.; Gosmini, C. *Physical Sci. Rev.* **2018**, *3*, 1-41. http://dx.doi.org/10.1515/psr-2016-0021
25. Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev*. **2004**, *104*, 6217-6254. http://dx.doi.org/10.1021/cr040664h
26. Asghar, S.; Tailor, S.; Elorriaga, D.; Bedford, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 16367-16370. http://dx.doi.org/10.1002/anie.201710053
27. Grignard, V. *Compt. Rend. Hebd. Séances Acad. Sci.* **1900**, *130*, 1322.
28. Guggenberger, L; Rundle, R. *J. Am. Chem. Soc*. **1964**, *86*, 5344-5345. http://dx.doi.org/10.1021/ja01077a068
29. Vallino, M. *J. Organomet. Chem*. **1969**, *20*, 1-10. http://dx.doi.org/10.1016/S0022-328X(00)80080-7
30. Seyferth, D. *Organometallics* **2009,** *28,* 1598–1605. http://dx.doi.org/10.1021/om900088z
31. Yonova, I.; Johnson, A.; Osborne, C.; Moore, C. *Angew. Chem*. **2014**. *53*, 2422-2427. http://dx.doi.org/10.1002/anie.201308666
32. Tamao, K.; Sumitani, K.; Kumada. M. *J. Am. Chem. Soc*. **1972**, *94*, 4374-4376. http://dx.doi.org/10.1021/ja00767a075
33. Trost, B. M. *Tetrahedron* **1977**, *33*, 2615-2649. http://dx.doi.org/10.1016/0040-4020(77)80284-6
34. Sugita, N.; Hayashi, S.; Hino, F.; Takanami, T. *J. Org. Chem*. **2012**, *77*, 10488-10497. http://dx.doi.org/10.1021/jo302122f
35. Dahadha, A.; Imhof, W. *Arkivoc* **2013**, (*iv*), 200-216. http://dx.doi.org/10.3998/ark.5550190.p008.044
36. Martin, R.; Buchwald, S. L. *Acc Chem Res*. **2008**, *41*, 1461-1473.

http://dx.doi.org/10.1021/ar800036s
37. Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.*, **2007**, *13*, 150-157. http://dx.doi.org/10.1002/chem.200601360
38. Martin, R.; Buchwald, S. L. *Acc. Chem. Res*. **2008**. *41*, 1461–1473. http://dx.doi.org/10.1021/ar800036s
39. Hein, F. Ber. *Dtsch. Chem. Ges*. **1919**, *52*, 195
40. Kharasch, M.; Fuchs, C. J. Am. Chem. Soc. **1943**, *65*, 504-507. http://dx.doi.org/10.1021/ja01244a006
41. Kochi, J.; Tamura, M. *J. Am. Chem. Soc*. **1971**, *93*, 1485-1487. http://dx.doi.org/10.1021/ja00735a028
42. Negishi, E. *Angew. Chem. Int. Ed.* **2011**, *50*, 6738-6764. http://dx.doi.org/10.1002/anie.201101380
43. Tamura. M.; Kochi, J. *J. Organomet. Chem*. **1972**, *42*, 205-228. http://dx.doi.org/10.1016/S0022-328X(00)81848-3
44. Gosmini, C.; Bégouin, J.-M.; Moncomble, A. *Chem. Commun.* **2008**, *28*, 3221-3233. http://dx.doi.org/10.1039/b805142a
45. Hamaguchi, H.; Uemura, M.; Yasui, H.; Yorimitsu, H.; Oshima. K. *Chemistry Letters* **2008**, *37*, 1178-1179. http://dx.doi.org/10.1246/cl.2008.1178
46. Shirakawa, E.; Imazaki, Y.; Hayashi, T. *Chemistry Letters* **2008**, *37*, 654-655. http://dx.doi.org/10.1246/cl.2008.654
47. Hu, X. *Chimia, Int. J. Chem.* **2010**, *64*, 231-234. http://dx.doi.org/10.2533/chimia.2010.231
48. Cahiez, G.; Chaboche, C.; Duplais, C.; Moyeux, A. *Org. Lett.* **2009**. *11*. 277-280. http://dx.doi.org/10.1021/ol802362e
49. Mitschke, U.; Bauerle, P. *J. Mater. Chem.* **2000**, *10*, 1471–1507. http://dx.doi.org/10.1039/A908713C
50. Yamamoto, T. *J. Organomet. Chem.* **2002**, *653*, 195–199. http://dx.doi.org/10.1016/S0022-328X(02)01261-5
51. Baudoin, O.; Gueritte, F. *Stud. Nat. Prod. Chem.* **2003**, *29*, 355–417. http://dx.doi.org/10.1016/S1572-5995(03)80011-X
52. Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 23–26. http://dx.doi.org/10.1016/S0022-328X(02)01159-2
53. Banno, T.; Hayakawa, Y.; Umeno, M. *J. Organomet. Chem.* **2002**, *653*, 288– 291. http://dx.doi.org/10.1016/S0022-328X(02)01165-8
54. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302–4320. http://dx.doi.org/10.1002/anie.200300579
55. Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265–555. http://dx.doi.org/10.1002/0471264180.or063.03
56. Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem.Soc.* **2009**, *131*, 11949–11963. http://dx.doi.org/10.1021/ja9039289
57. Hsu, S.; Ko, C.; Wu, Y. *Adv. Synth. Catal*. **2011**, *353*, 1756–1762. http://dx.doi.org/10.1002/adsc.201100220

58. Ghosh, R.; Chakraborty, A.; Maiti, S. *Arkivoc* **2004**, *(xiv*), 1-9. http://dx.doi.org/10.3998/ark.5550190.0005.e01
59. Nicolas, L.; Angibaud, P.; Stansfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J. *Angew. Chem. Int. Ed*. **2012**, *51*, 11101 –11104. http://dx.doi.org/10.1002/anie.201204786
60. Joshi-Pangu, A.; Wang, C.; Biscoe, M. *J. Am. Chem. Soc.*, **2011**, *133*, 8478–8481. http://dx.doi.org/10.1021/ja202769t
61. Rudolph, A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2656-2670. http://dx.doi.org/10.1002/anie.200803611
62. Iwasaki, T.; Takagawa, H.; Singh, S.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc,* **2013**, *135*, 9604–9607. http://dx.doi.org/10.1021/ja404285b
63. Kuzmina, O.; Steib, A.; Markiewicz, J.; Flubacher, D.; Knochel, P. *Angew. Chem. Int. Ed*. **2013**, *52*, 4945-4949. http://dx.doi.org/10.1002/anie.201210235
64. Mao, J.; Liu, F.; Wang, M.; Wu, L.; Zheng, B.; Liu, S.; Zhong, J.; Bian, Q.; Walsh, P. J. Am. Chem. Soc., **2014**, *136*, 17662-17668. http://dx.doi.org/10.1021/ja5109084
65. Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J. *Org. Lett*. **2014**, *16*, 6160–6163. http://dx.doi.org/10.1021/ol503043r
66. Gonnard, L.; Guerinot, A.; Cossy. J. *Chem. Eur. J.* **2015**, *21*, 12797–12803. http://dx.doi.org/10.1002/chem.201501543
67. Frlan, R.; Sova, M.; Gobec, S.; Stavber, G.; Časar, Z. *J. Org. Chem.* **2015**, *80*, 7803–7809. http://dx.doi.org/10.1021/acs.joc.5b01156
68. McBrien, H. L.; Millar, J. G.; Rice, R. E.; McElfresh, J. S.; Cullen, E.; Zalom, F. G. *J. Chem. Ecol.* **2002**, *28*, 1797–1818. http://dx.doi.org/10.1023/A:1020513218454
69. Wu, L.; Zhong, J.; Liu, S.; Liu, F.; Gao, Z.; Wang, M.; Bian, Q. *Tetrahedron: Asymmetry* **2016**, *27*, 78-83. http://dx.doi.org/10.1016/j.tetasy.2015.11.009
70. Barde, E.; Guérinot, A.; Cossy, J. *Org. Lett*. **2017**, *19*, 6068-6071. http://dx.doi.org/10.1021/acs.orglett.7b02848
71. Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Adv. Synth. Catal*. **2006**, *348*, 1301-1305. http://dx.doi.org/10.1002/adsc.200606060
72. Qi, X.; Sun, H.; Li, X.; Fuhr, O.; Fenske, D. *Dalton Trans.* **2018**, *47*, 2581-2588 http://dx.doi.org/10.1039/C7DT04155A
73. Corbet, J.; Mignani, G. *Chem. Rev*. **2006**, *106*, 2651−2710. http://dx.doi.org/10.1021/cr0505268
74. Kochi, J.; Tamura, M. *J. Am. Chem. Soc*., **1971**, *93*, 1485–1487 http://dx.doi.org/10.1021/ja00735a029
75. Amii, H.; Uneyama, K. *Chem. Rev.* **2009,** *109,* 2119-2183. http://dx.doi.org/10.1021/cr800388c
76. Terao, J.; Todo, H.; Begum, S.; Kuniyasu, H.; Kambe, N. *Angew. Chem. Int. Ed* **2007**, *46*, 2086-2089. http://dx.doi.org/10.1002/anie.200603451
77. Cahiez, G.; Gager, O.; Buendia, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 1278 –1281.

http://dx.doi.org/10.1002/anie.200905816
78. Qin, T.; Cornella, J.; Li, C.; Malins, L.; Edwards, J.; Kawamura, S.; Maxwell, B.; Eastgate, M.; Baran, P. *Science* **2016**, *352*, 801-805. http://dx.doi.org/10.1126/science.aaf6123
79. Johnston, C.; Smith, R.; Allmendinger, S.; MacMillan, D. *Nature* **2016**, *536*, 322-325. http://dx.doi.org/10.1038/nature19056
80. Yang, C.; Zhang, Z.; Liang, J.; Liu, J.; Lu, X.; Chen, H.; Liu, L. *J. Am. Chem. Soc*. **2012**, *134*, 11124−11127. http://dx.doi.org/10.1021/ja304848n
81. Ren, P.; Alexandre Stern, L.; Hu, X. *Angew. Chem. Int. Ed*. **2012**, *51*, 1–5. http://dx.doi.org/10.1002/anie.201204275
82. Shen, R.; Iwasaki, T.; Terao, J.; Kambe, N. *Chem. Commun.* **2012**, *48*, 9313–9315. http://dx.doi.org/10.1039/c2cc34847k
83. Hornillos, V.; Pérez, M.; Fañanás-Mastral, M.; Feringa, B. *J. Am. Chem. Soc.* **2013**, *135*, 2140−2143. http://dx.doi.org/10.1021/ja312487r
84. Zhu, Y.; Xiong, T.; Han, W.; Shi, Y. *Org. Lett*. **2014**, *16*, 6144−6147. http://dx.doi.org/10.1021/ol5030103
85. Murakami, K.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1569-1571. http://dx.doi.org/10.1021/ol0703938
86. Steib, A.; Kuzmina, O.; Fernandez, S.; Flubacher, D.; Knochel, P. *J. Am. Chem. Soc.* **2013**, *135*, 15346–15349. http://dx.doi.org/10.1021/ja409076z
87. Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731-1770. http://dx.doi.org/10.1021/cr0104330
88. Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev*. **2007**, *107*, 174-238. http://dx.doi.org/10.1021/cr0509760
89. Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed*. **2013**, *52*, 11726-11743. http://dx.doi.org/10.1002/anie.201301451
90. Kuzmina, O.; Knochel, P. *Org. Lett*., **2014**, *16*, 5208–5211. http://dx.doi.org/10.1021/ol502623v
91. Steib, A.; Kuzmina, O.; Fernandez, S.; Malhotra, S.; Knochel, P. *Chem. Eur. J.* **2015**, *21*, 1961–1965. http://dx.doi.org/10.1002/chem.201405275
92. Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081–8097. http://dx.doi.org/10.1039/C4CS00206G
93. Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717–1726. http://dx.doi.org/10.1021/acs.accounts.5b00051
94. Cong, X.; Tang, H.; Zeng, X. *J. Am. Chem. Soc*. **2015**, *137*, 14367–14372 http://dx.doi.org/10.1021/jacs.5b08621
95. Knochel, P.; Bellan, A.; Kuzmina, O.; Vetsova, V. *Synthesis* **2017**, *49*, 188–194. http://dx.doi.org/10.1055/s-0035-1561615
96. Liu, P.; Chen, C.; Cong, X.; Tang, J.; Zeng, X. *Nature Commun.* **2018**, *9*, 1-8. http://dx.doi.org/10.1038/s41467-018-07069-1
97. Fan, F.; Tang, J.; Luo, M.; Zeng, X. *J. Org. Chem*. **2018**, *83*, 13549–13559. http://dx.doi.org/10.1021/acs.joc.8b02104

Author's Biography

Adnan A. Dahadha was born in 1979 in Irbid, Jordan. He has received his B.Sc. and M.Sc. from the Applied Chemistry Department, Faculty of Science, Jordan University of Science and Technology, Jordan. In 2012 he obtained his Ph.D. degree in Organic Chemistry from the Friedrich Schiller University, Jena, Germany. He worked as an assistant professor at the Department of Chemistry, Faculty of Science, Sattam bin Abdul-Aziz University, Saudi Arabia during the period 2013-2015. He was then appointed to the Pharmacy Faculty, Philadelphia University, Jordan, from Sept. 2015- Aug. 2018. Currently, he is assistant professor of Organic Chemistry in the Faculty of Science, Biotechnology Department, Philadelphia University, Jordan.