

# Recent advances in Kumada-Tamao-Corriu cross-coupling reaction catalyzed by different ligands

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**Abstract** The formation of the carbon–carbon bond is a fundamental reaction in modern organic synthesis, which is mediated by transition-metal catalysts. Over the past 30 years, the carbon–carbon coupling reactions, particularly the Kumada-Tamao-Corriu coupling reaction, have been dramatically expanded providing a simple methodology for synthetic organic chemistry. So, this review highlights several recent and major developments of carbon–carbon bond-forming reactions by alkylation, alkenylation, arylation, and heteroarylation of Grignard compounds using different catalysts and ligands.

**Keywords** Carbon–carbon bond formation · Cross-coupling · Grignard reagent · Kumada-Tamao-Corriu reaction · Nickel catalyst · Transition metal

## Introduction

Transition-metal catalysis [1] can forge carbon–carbon bonds between functionalized and sensitive substrates which provide new opportunities [2], predominantly in total synthesis, medicinal and chemistry process, as well as in nanotechnology and chemical biology [3]. It is almost impossible nowadays to find an issue of a journal in the field of organic or organometallic chemistry without a donation dealing with some aspect of cross-coupling reactions [4].

The names of Heck [5], Suzuki [6], Stille [7], Sonogashira [8], Negishi [9], and Hiyama [10] are distinguished for their contribution to this chemistry [11] and among them the Kumada coupling has a predominant place which was reported in 1972 by Tamao et al. [12]. In the same year, Corriu independently reported the reaction of  $\beta$ -bromostyrene with phenylmagnesium bromide to afford *trans*-stilbene in the presence of Ni(acac)<sub>2</sub> as catalyst [13]. It is a protocol between an alkyl or aryl Grignard reagent and an aryl, alkyl, or vinyl halocarbon catalyzed based on nickel or palladium catalyst [14]. Palladium and nickel phosphine complexes accompanied by different ligands catalyze the selective cross-coupling reactions of Grignard reagents. This process has opened up the possibility of preparing a large variety of organic compounds by C–C bond formation especially from different organic halides and there have been reported numerous characteristic features of the reaction, such as asymmetric synthesis [15], stereochemical aspects [16], and heterocycle coupling [17].

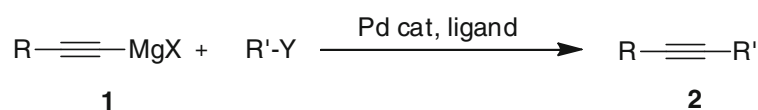
Cross-coupling reactions such as Kumada-Tamao-Corriu coupling, Suzuki–Miyaura coupling, Negishi coupling, Stille coupling, Hiyama coupling have been overviewed by A. C. Frisch and M. Beller specially for non-activated alkyl halides [18]. Also, a mechanistic perspective of nickel-catalyzed cross-coupling of non-activated alkyl halides was investigated [19]. But now, in the following sections, we discuss the application of different ligands and catalysts to form different carbon–carbon bonds by Kumada-Tamao-Corriu coupling reaction to synthesize organic compounds.

## Alkylation of Grignard compounds via alkyl halides

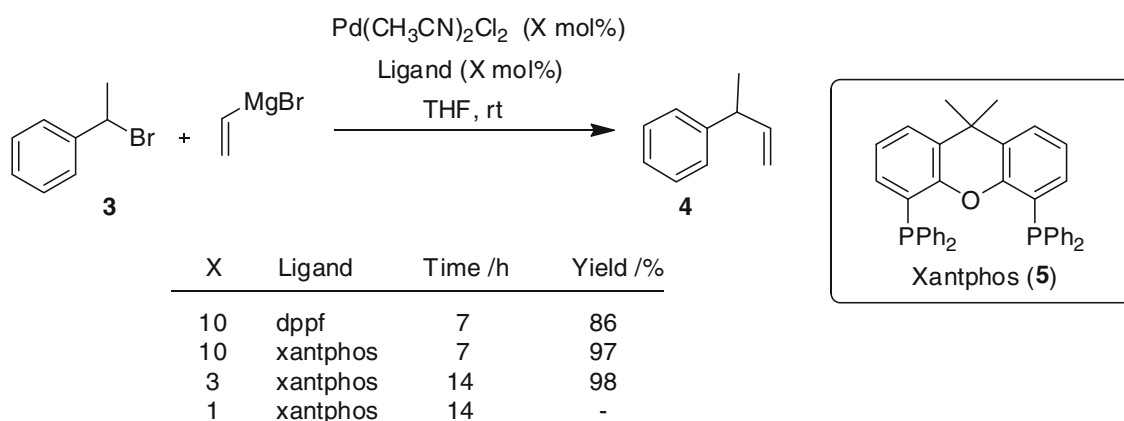
Alkyl halides are non-activated substrates for metal catalyzed C–C coupling reactions due to their reluctance to

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Scheme 1



Catalyst	Ligand	Yield /%
Pd(OAc) <sub>2</sub>	Me( <i>t</i> -Bu) <sub>2</sub> P	8
Pd(OAc) <sub>2</sub>	( <i>t</i> -Bu) <sub>3</sub> P	10
Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	12
Pd(dba) <sub>3</sub>	PPh <sub>3</sub>	40
Pd(dba) <sub>3</sub>	PPh <sub>3</sub>	83
Pd(dba) <sub>3</sub>	Cy <sub>3</sub> P	20
Pd(dba) <sub>3</sub>	Me( <i>t</i> -Bu) <sub>2</sub> P	30
Pd(dba) <sub>3</sub>	Me( <i>t</i> -Bu) <sub>2</sub> P	42
Pd(dba) <sub>3</sub>	Me( <i>t</i> -Bu) <sub>2</sub> P	14
Pd(dba) <sub>3</sub>	dppb	0
Pd(PPh <sub>3</sub> ) <sub>4</sub>		51
Pd(dba) <sub>3</sub>		0



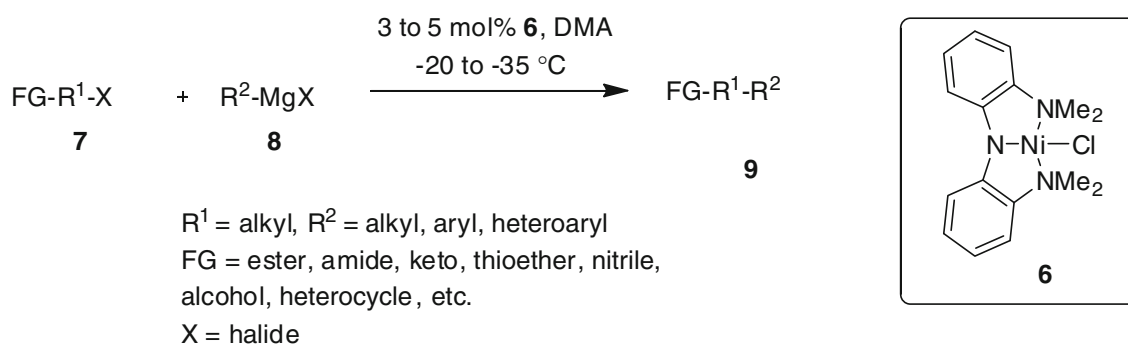
Scheme 2

undergo oxidative addition, and also metal alkyl intermediates are prone to unproductive  $\beta$ -hydride eliminations. However, significant advance as shown in the following paragraphs has been achieved in this field over the recent years to construct C–C bonds by cross-coupling reactions of alkyl halides and Grignard reagents using a nickel, palladium, or iron catalyst.

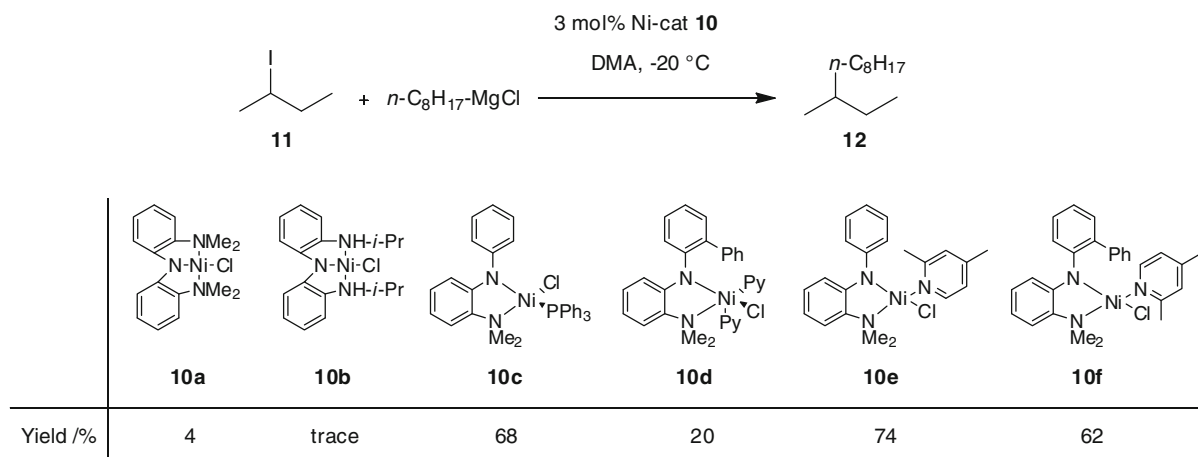
Yang et al. [20] have used a range of different catalysts and ligands for coupling of inactivated alkyl bromides or iodides with Grignard reagents **1** in Kumada-Tamao-Corriu coupling conditions. Palladium acetate in the presence of a phosphine ligand experimentally was not an effective catalyst. However, electron-donating trialkylphosphine ligands may accelerate the oxidative addition of low-valent palladium aliphatic carbon-halogen cross-couplings, but better

performance was observed by using triarylphosphine ligands compared to trialkylphosphine ligands. It was shown that the cross-coupling reaction may be a reductive elimination-controlled process. Thus, Pd<sub>2</sub>(dba)<sub>3</sub> and Ph<sub>3</sub>P appear to be essential for the catalytic process of Scheme 1.

A mild palladium-catalyzed Kumada-Tamao-Corriu coupling of secondary benzylic bromides **3** with aryl and alkenyl Grignard reagents has been developed by Lopez-Perez et al. [21]. In this protocol a catalytic system capable of minimizing the competitive  $\beta$ -hydride elimination pathway was tested by using Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> as catalyst and a collection of various ligands (Scheme 2). As a result, bidentate ligands with a large bite angle such as dppf (96°) and, especially, xantphos (**5**) (111°) turned out to be superb ligands due to their lower reaction time, high yields, and



Scheme 3

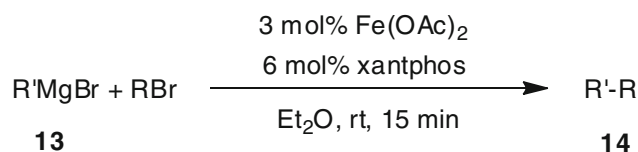


Scheme 4

minimized  $\beta$ -hydride elimination. In addition, no transformation was observed when the catalyst loading was reduced to 1 mol %.

Non-activated and functionalized alkyl halides **7** (alkyl halides containing ester, amide, ether, thioether, alcohol, pyrrole, indole, furan, nitrile, conjugated enone) coupled to alkyl, aryl, or heteroaryl Grignard reagents **8** catalyzed by a nickel(II) pincer complex  $[(^{\text{Me}}\text{NN}_2)\text{NiCl}]$  (**6**) in a Kumada-Tamao-Corriu cross-coupling reaction (Scheme 3) [22].

A structure-activity relationship has been studied that improved catalysts for Kumada-Tamao-Corriu cross-coupling of secondary alkyl halides such as a series of new nickel(II) complexes **10** including those with tridentate pincer bis(amino)amide ligands ( $^{\text{R}}\text{N}_2\text{N}$ ) and those with bidentate mixed amino-amide ligands ( $^{\text{R}}\text{NN}$ ) [23]. Analogous pincer complexes such as **10a** and **10b** were not efficient due to their inability to activate alkyl halides. The five-coordinate complex **10f** was moderately active. Also, the square-planar complexes **10e** and **10c** were active. But, complex  $[(^{\text{H}}\text{NN})\text{Ni}(2,4\text{-lutidine})\text{Cl}]$  (**10e**) specially was the



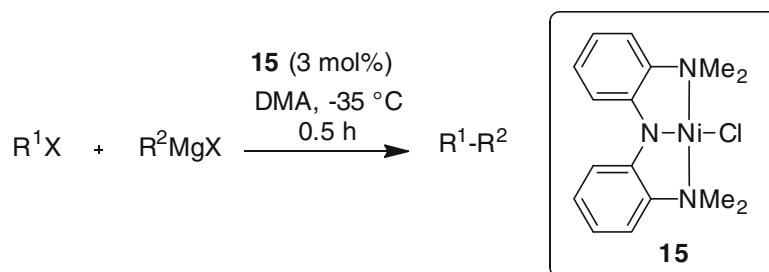
Scheme 5

most efficient catalyst. No significant isomerization products were formed using these catalysts, unlike pincer complex **10a** (Scheme 4).

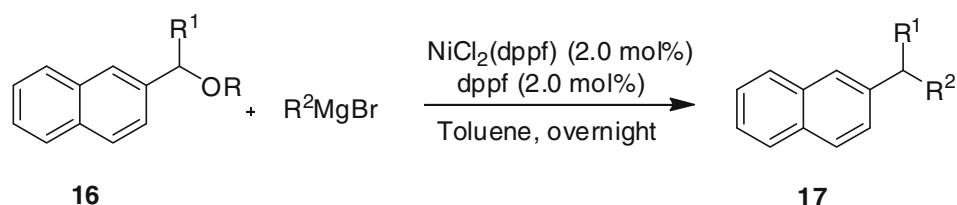
Primary and secondary alkyl halides (RX), depending on the nature of the R group, undergo  $\text{sp}^3\text{-sp}^3$  Kumada-Tamao-Corriu coupling with alkyl Grignard reagents by using an iron catalyst (Scheme 5) [24].

Alkyl halides containing ester, amide, ether, acetal, nitrile, thioether, and heterocyclic groups have undergone Kumada-Tamao-Corriu cross-coupling reaction with alkyl Grignard reagents by using  $[(^{\text{Me}}\text{NN}_2)\text{Ni}^{\text{II}}\text{-Cl}]$  complex **15** as nickel catalyst. The functional group of alkyl halides did

Scheme 6



Scheme 7



not participate in reaction with Grignard reagents (Scheme 6) [25].

#### Other alkylation of Grignard compounds

Much attention has also been paid to the activation of the relatively stable but commonly encountered C–O bonds in direct functionalizations by Grignard reagents.

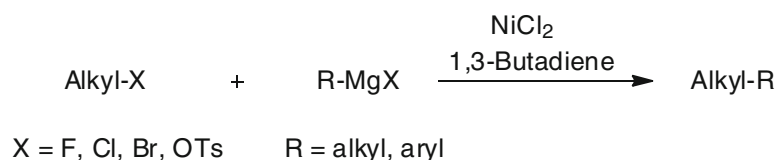
Ni-catalyzed alkylation of Grignard compounds via  $sp^3$  C–O bond activation in ethers was reported as a Kumada-Tamao-Corriu cross-coupling reaction. With dppe as the ligand, the methylation totally failed. The desired product **17** was isolated in good yield when dppf was applied as the ligand. However  $NiCl_2$  and hydrated  $NiCl_2$  were not very efficient. Finally,  $Ni(acac)_2$  showed a better catalytic ability in the presence of bidentated ligands other than dppe in this coupling reaction (Scheme 7) [26].

An effect of 1,3-butadienes was reported in the nickel-catalyzed cross-coupling reaction of Grignard reagents with alkyl halides and tosylates. The desired product was prepared in high yields by using 1,3-butadiene as an additive instead of phosphine ligands (Scheme 8) [27]. Cross-coupling reactions of organozinc reagents with alkyl halides catalyzed by nickel were also performed using the same protocol [28].

#### Alkenylation of Grignard compounds via alkyl halides

Electrophiles such as alkenyls have undergone useful Kumada-Tamao-Corriu couplings to emerge as powerful

Scheme 8

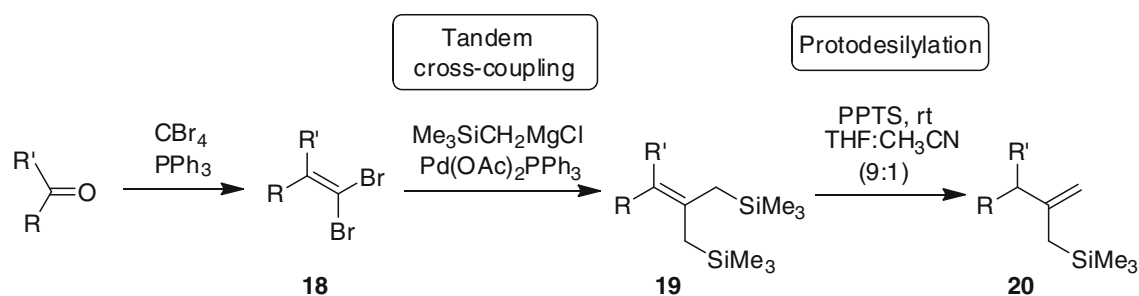


tools in synthetic organic chemistry for the construction of carbon–carbon bonds.

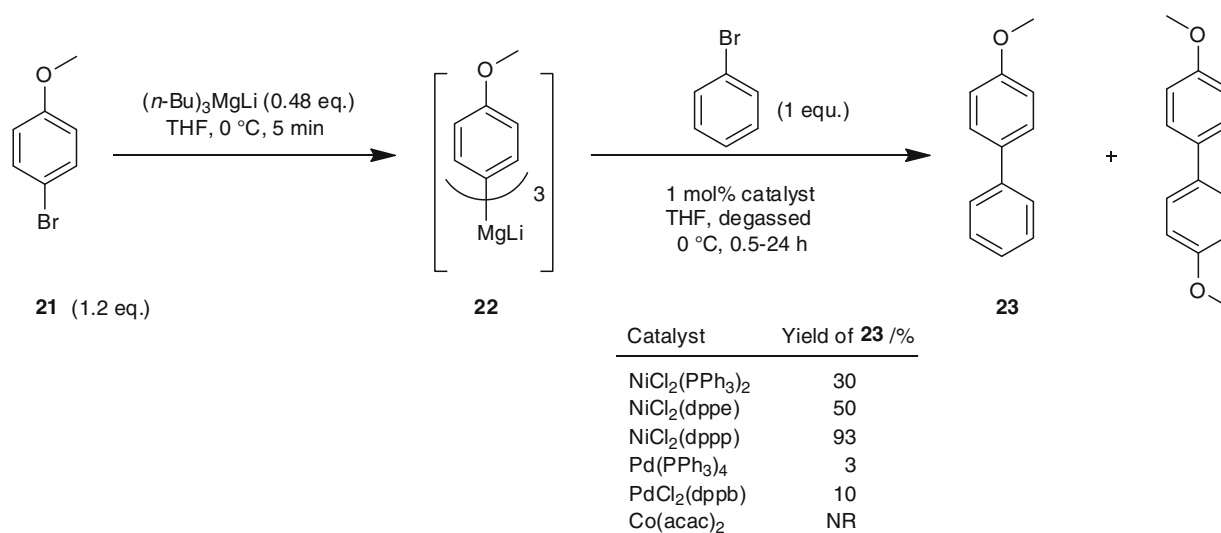
An interesting 3-step sequence for the preparation of exomethylene-type allylsilane **20** from aldehyde via 1,1-dibromo-1-alkene **18** has been investigated. 1,1-Dibromo-1-alkene **18** can be derived from the corresponding aldehyde. Then, the Pd-catalyzed tandem Kumada-Tamao-Corriu cross-coupling reaction of **18** was performed with an excess of trimethylsilylmethyl Grignard reagent to produce compound **19** in good to excellent yields. In the process,  $PPh_3$  was added to a mixture of  $Pd(OAc)_2$  and **18** in THF, stirring for 10 min at room temperature.  $Me_3SiCH_2MgCl$  was added at 0 °C, stirring for 2–12 h at room temperature. After quenching and purification, the desired bisallylsilane **19** was obtained. Finally, protodesilylation of bisallylsilanes **19** by using PPTS provided 2-(trimethylsilylmethyl)-1-alkenes **20** selectively (Scheme 9) [29].

Lithium triarylmagnesiates **22** are rapidly prepared by electron-rich aryl bromides **21**, which undergo nickel-catalyzed Kumada-Tamao-Corriu reactions with a diversity of aryl and alkenyl bromides, chlorides, tosylates, and triflates (Scheme 10) [30]. A variety of catalysts were evaluated. As reported by Kumada-type, the observed reactivity of nickel-phosphine catalysts followed this order:  $NiCl_2(dppp) > NiCl_2(dppe) > NiCl_2(PPh_3)_2$  [31]. In addition, when Pd catalysts were employed, isolated yields were low, and no reaction was observed with  $Co(acac)_2$ .

High yields of  $\alpha$ -fluorostyryls **26** and  $\alpha$ -fluorothiophenes **27** have been achieved by a Kumada-Tamao-Corriu cross-

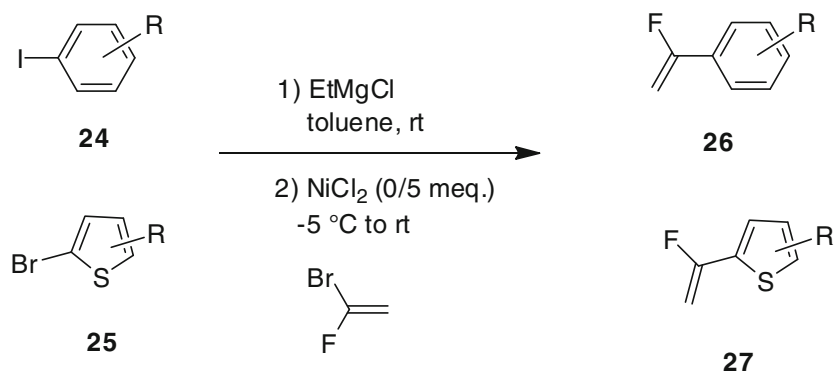


Scheme 9



Scheme 10

Scheme 11

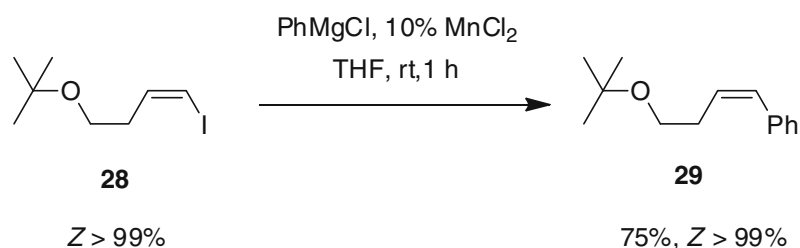


coupling reaction (Scheme 11). This reaction is useful in the synthesis of other fluorovinylsubstituted heterocycles of biological attention or in the industrial scale manufacture of fluorostyryl monomers or polymer chemistry [32].

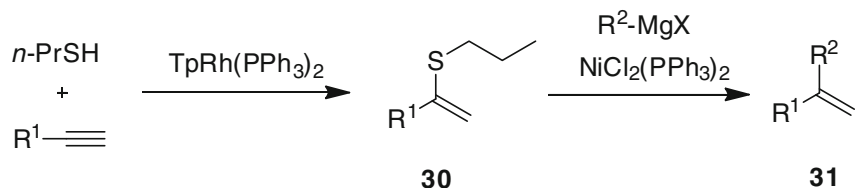
The first stereospecific Mn-catalyzed coupling reaction of aryl Grignard reagents with various alkenyl halides such as **28** was reported by Cahiez et al. (Scheme 12). In this

protocol stereospecific coupling was obtained except in the case of the (*Z*)-3-(2-bromoethenyl)pyridine due to the slow reaction rate of the reductive elimination step. Indeed, Mn(II) species are commonly stable at room temperature [33]. This manganese-catalyzed coupling reaction represents a more environmentally friendly alternative to nickel- or palladium-catalyzed reactions.

Scheme 12



Scheme 13



### Other alkenylation of Grignard compounds

As shown in Scheme 13, vinyl sulfides **30** undergo Kumada-Tamao-Corriu cross-coupling to prepare 1,1-disubstituted olefins **31**. Vinyl sulfides were afforded by regioselective catalytic alkyne hydrothiolation of both aromatic and aliphatic alkynes using  $\text{TpRh(PPh}_3)_2$  as catalyst. Then, cross-coupling reactions of alkyl vinyl sulfides with various Grignard reagents (alkyl, vinyl, and aryl) were performed using 10 mol %  $\text{NiCl}_2(\text{PPh}_3)_2$  as catalyst [34].

The 1,1-Disubstituted alkenes **33** were prepared by Kumada-Tamao-Corriu cross-coupling reaction of cyclic and acyclic vinyl phosphates **32** and magnesium reagents (Scheme 14) [35]. The reactions proceed by simple palladium salts such as  $\text{PdCl}_2$ , without the necessity of phosphine ligands [36].

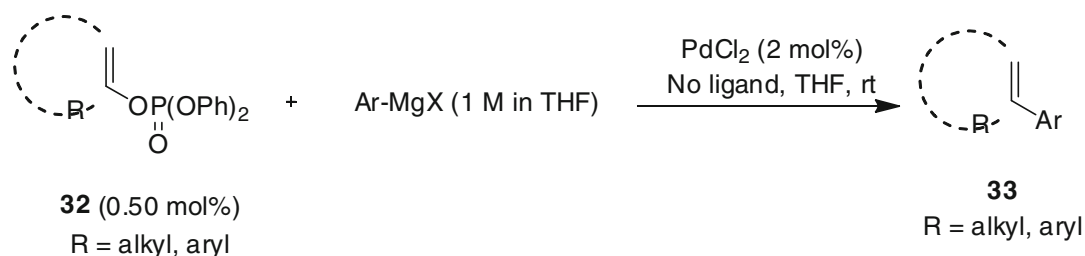
Cross-coupling of alkenyl/aryl carboxylates **34** with Grignard reagent **35** was performed via C–O bond activation by using  $\text{FeCl}_2$  as catalyst under mild conditions. Other catalysts were not useful in this protocol. Ligands such as heterocyclic NHC carbenes **37–39** improved the yield, while lower yields were obtained by using other mono- or bidentated phosphine and nitrogen ligands (Scheme 15) [37].

### Arylation of Grignard compounds via aryl halides

Aryl halide is another choice of organic precursors in Kumada-Tamao-Corriu cross-coupling reactions. With great efforts from different research groups in this field, significant achievements have been made to synthesize a broad range of organic compounds.

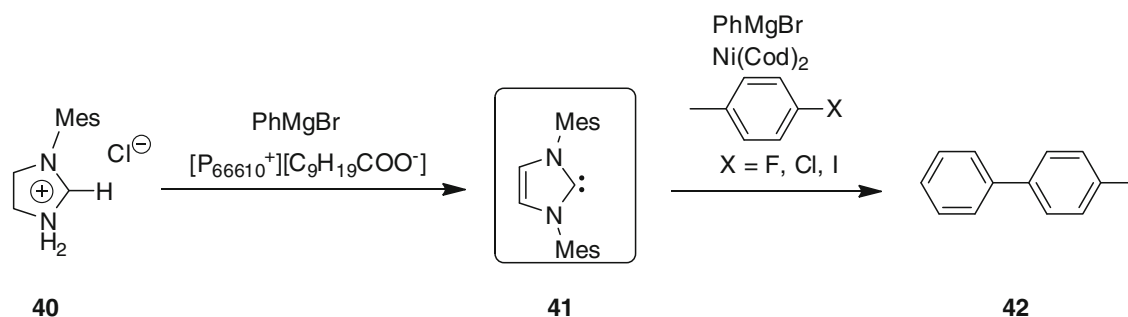
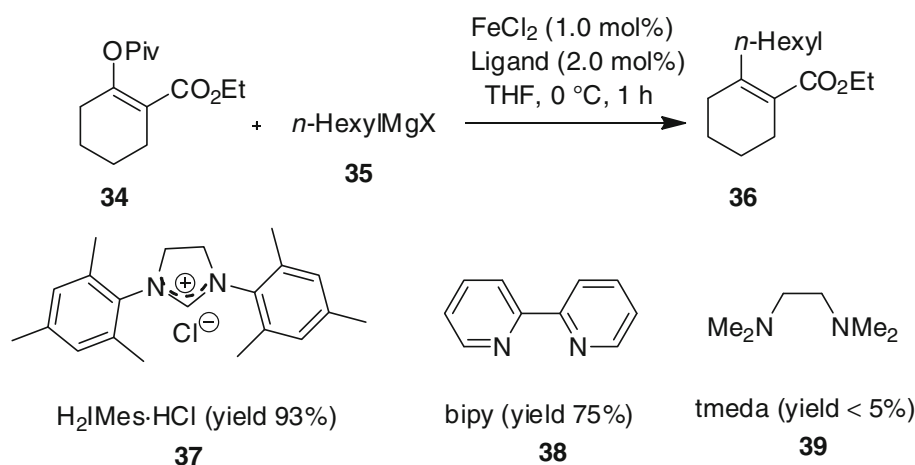
Compatibility of strongly basic carbon-center reagents like Grignard reagents with phosphonium ILs (phosILs) were reported first by Ramnial et al. (Scheme 16) [38]. The NHCs **41** produced in  $[\text{P}_{66610}^+][\text{C}_9\text{H}_{19}\text{COO}^-]$  in conjunction with  $\text{Ni}(\text{cod})_2$  ( $\text{cod} = 1,5\text{-cyclooctadiene}$ ) can successfully catalyze Kumada-Tamao-Corriu reactions [39].

Use of 3-Bromo-1-(trifluoromethyl)benzene (**43**) or its derivatives coupled with methylmagnesium chloride or ethyl magnesium chloride in the presence of  $\text{NiCl}_2/\text{xantphos}$  to prepare 3-methyl- or 3-ethyl-1-(trifluoromethyl)benzenes **44** resulted in good yields (Scheme 17). Also, 3-Chloro- and 3-bromo-1-(trifluoromethyl)benzene caused different behaviors in Kumada's coupling reaction with  $\text{NiCl}_2(\text{dppe})$ . As demonstrated in Scheme 17, the reaction between 3-bromo-1-(trifluoromethyl)benzene and ethyl magnesium bromide caused 3-ethyl-1-(trifluoromethyl)benzene in good yield, with a low level of biaryls.



Scheme 14

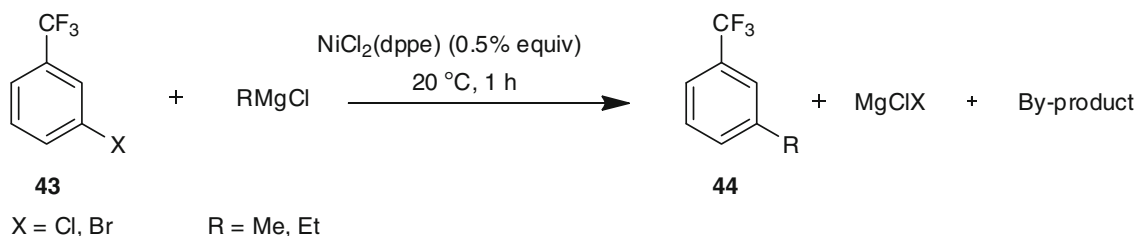
Scheme 15



Scheme 16

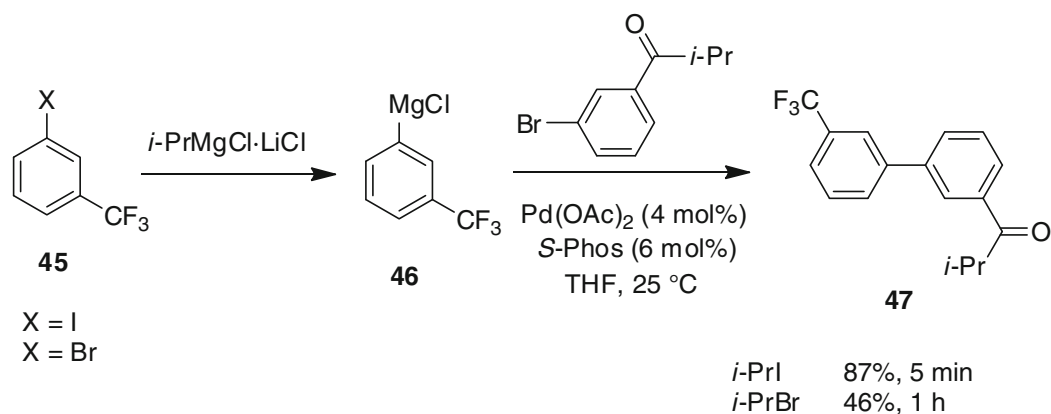
Parameters such as the nature of solvent, increase of temperature, and the nature of the metal catalyst did not affect the cross-coupling versus homocoupling or alkylation reaction. Therefore, the effect of nickel ligand was investigated. Finally, the best result was achieved by xantphos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene] as the nickel ligand [40].

Isopropyl iodide accelerated Kumada-Tamao-Corriu cross-coupling and led to a rapid radical catalysis reaction of a wide range of functionalized aryl- and heteroaryl-magnesium reagents **46** with aryl bromides (Scheme 18) [41]. Thus, functionalized biphenyl was obtained by the cross-coupling within 5 min at 25 °C as a single product in high yield.



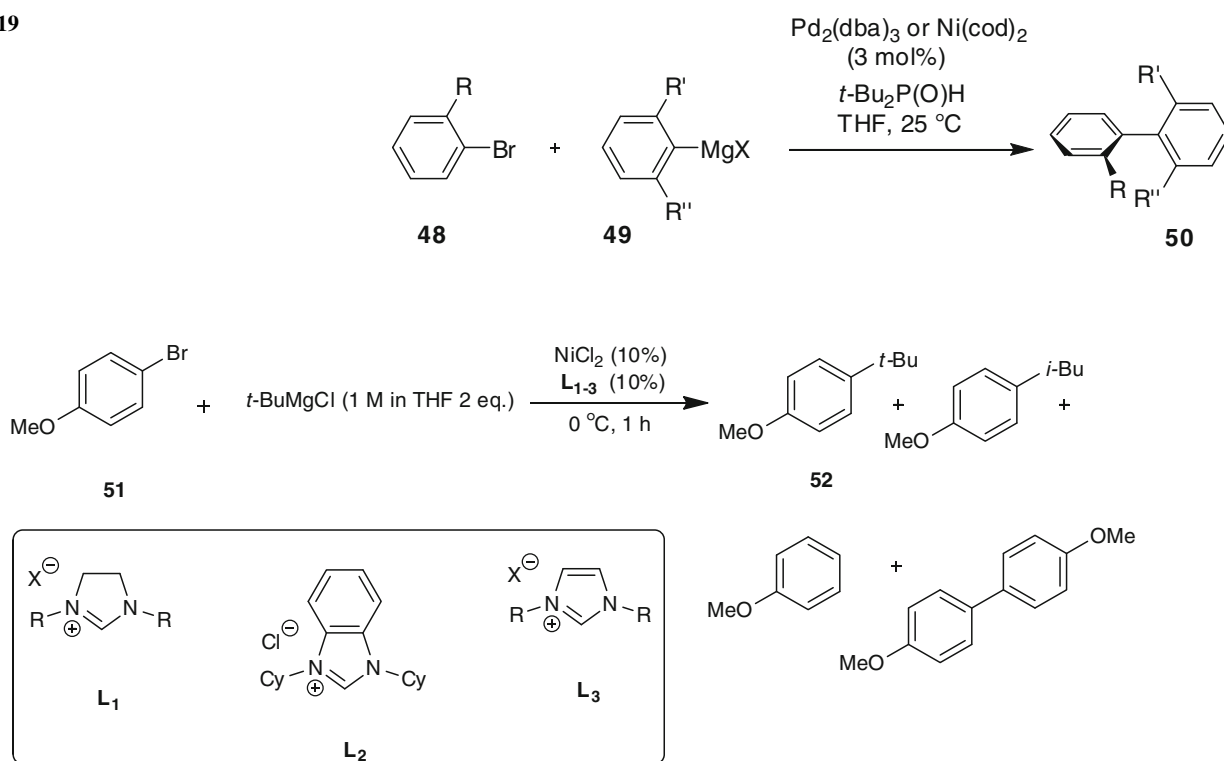
$\text{CF}_3\text{Ar-X, RMgCl}$	Yield $\text{CF}_3\text{Ar-R}$ / %	Yield $\text{CF}_3\text{Ar-H}$ / %	Yield biaryl / %
$\text{X = Br, R = Me}$	65	5	17
$\text{X = Br, R = Et}$	76	16	5
$\text{X = Cl, R = Me}$	18	2	3
$\text{X = Cl, R = Et}$	19	60	3

Scheme 17



Scheme 18

Scheme 19



Scheme 20

### Arylation of Grignard compounds via aryl bromides

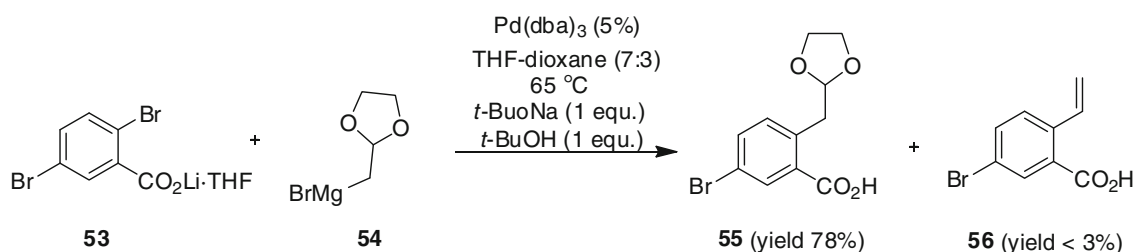
A palladium- and nickel-phosphinous acid catalyst performed a Kumada-Tamao-Corriu reaction with sterically hindered substrates under mild reaction conditions. Multifunctional biaryls **50** were formed in 87–98 % yield even when electron-rich aryl chlorides were used. Also, the reaction ensued with aryl iodides at  $-20$  °C (Scheme 19) [42].

The Kumada-Tamao-Corriu cross-coupling reactions of tertiary alkylmagnesium halide and aryl bromide **51** using nickel as catalyst have been developed. For this cross-

coupling reaction, NHCs were identified as the most promising ligand candidates. Thus, the effect of steric and electronic perturbations of the NHC backbone was examined. Increased formation of reduction product was observed, when new sources of  $\text{NiCl}_2$  were employed alongside ligand **L**<sub>3</sub> (Scheme 20). Aryl triflates, vinyl chlorides, and vinyl bromides as the electrophilic component also would undergo the same procedure [43].

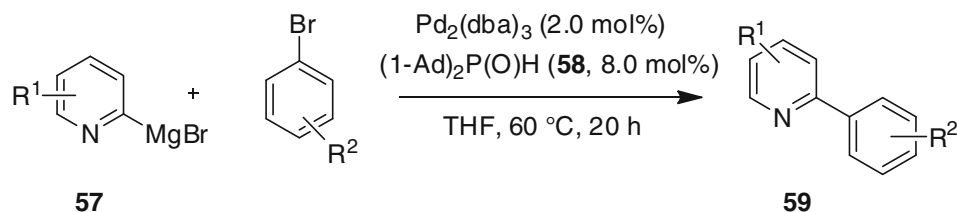
Kumada-Tamao-Corriu coupling of bromobenzoic acid derivatives **53** with the acetaldehyde enolate synthon (1,3-dioxolan-2-ylmethyl)magnesium bromide (**54**) proceeded



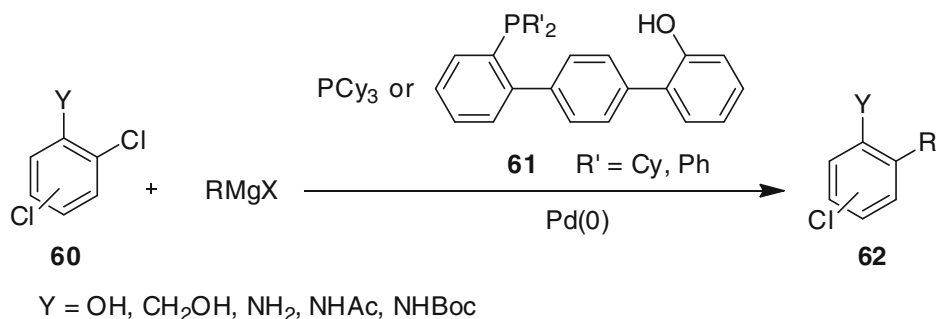


Scheme 21

Scheme 22



Scheme 23



under Pd catalysis with alkoxide additives to display an *ortho*-directing effect of the carboxylate functionality (Scheme 21) [44].

An applicable cross-coupling reaction of 2-pyridyl organomagnesium reagents **57** was performed by using alkyl-substituted secondary phosphine oxides preligand **58** (Scheme 22) [45]. A catalyst derived from more sterically hindered aryl-substituted preligand proved to be less efficient. Consequently, optimal result was obtained with sterically demanding, non-hygroscopic preligand **58**.

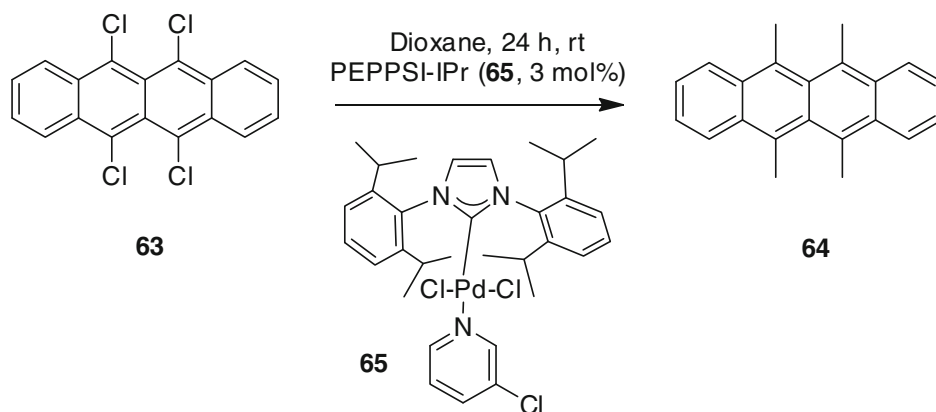
### Arylation of Grignard compounds via aryl chlorides

A new route to synthesize multisubstituted benzene derivatives was reported by Ishikawa et al. *Ortho*-selective cross-coupling of dichlorobenzene derivatives **60** was achieved by using Pd<sub>2</sub>(dba)<sub>3</sub> and PCy<sub>3</sub> and substrates with directing groups such as OH, CH<sub>2</sub>OH, NH<sub>2</sub>, NHAc, and NHBoc. The mechanism of selectivity remains unknown.

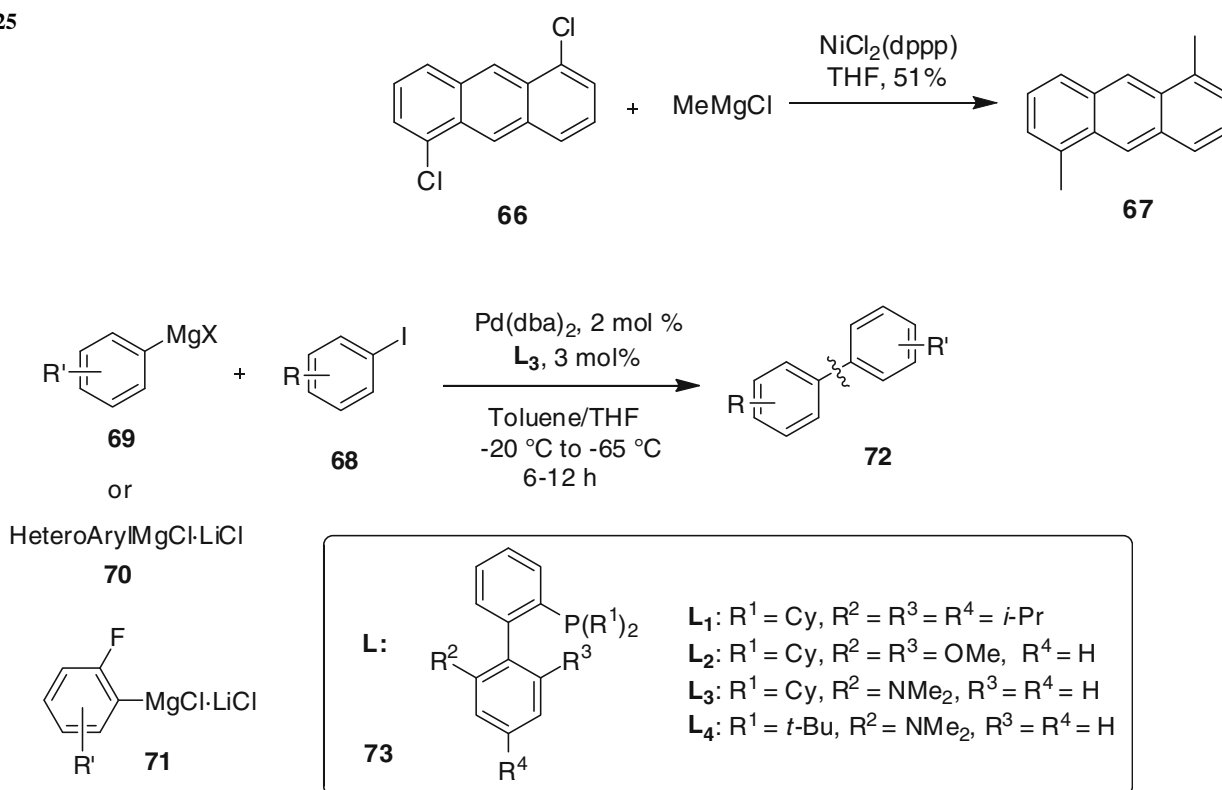
Use of hydroxylated terphenylphosphines (**61**) enhanced the reactions of dichlorophenol and dichloroaniline (Scheme 23) [46].

The functionalized linear acene **64** was achieved by using Kumada-Tamao-Corriu cross-coupling of polychlorinated acene **63** containing two *ortho* substituents with Grignard reagents at low temperature (Scheme 24). Tetramethyltetracene (**64**) was generated in excellent yield (98 %) by adding MeMgBr (3 equiv per chlorine) to a mixture of 5,6,11,12-tetrachlorotetracene (**63**) and PEPPSI-IPr (**65**) at room temperature in 1,4-dioxane. A brief solvent screen confirmed that dioxane gave better results. Lower yields were achieved by using more traditional cross-coupling catalysts such as Pd(OAc)<sub>2</sub> with X-Phos and Ru-Phos ligands. Using iron and nickel cross-coupling systems led to the ineffective decomposition of product to the starting material, resulting in no desired product formation. So, treatment of polychlorinated acenes with the PEPPSI-IPr catalyst (**65**) and MeMgBr produce distorted octamethylnaphthalene [47].

Scheme 24



Scheme 25



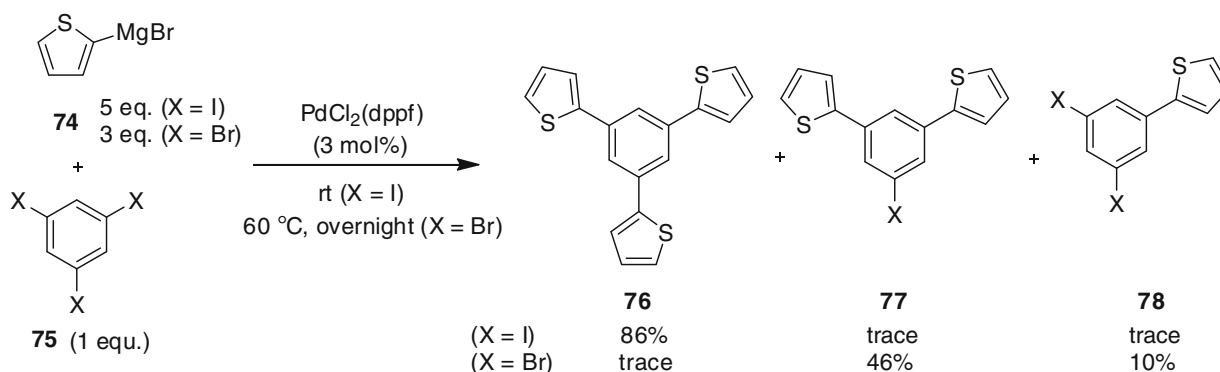
Scheme 26

Also, 1,5-Dimethylanthracene (**67**) was achieved in a moderate yield of 51 % by the reaction of 1,5-dichloroanthracene (**66**) with methylmagnesium chloride using nickel catalysts [48]. There are only a few examples for synthesis of compound **67** in the literature [49, 50] because of producing a mixture of 1,5- and 1,8-dimethylanthracene in the synthesis of these compounds. The reported procedures afforded a mixture of 1,5- and 1,8-dimethyl analogues, which has to be purified by crystallization. This problem was solved by the Kumada-Tamao-Corriu coupling reaction as illustrated in Scheme 25.

### Arylation of Grignard compounds via aryl iodides

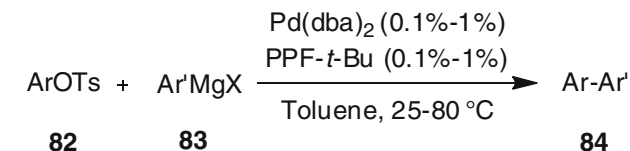
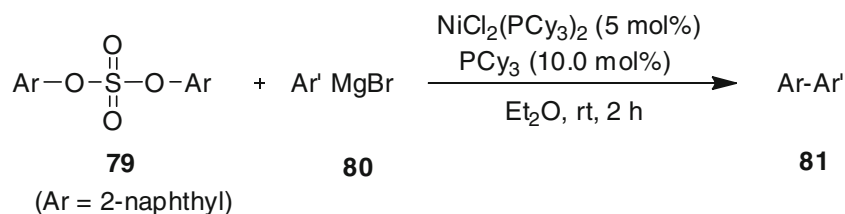
A Pd-catalyzed Kumada-Tamao-Corriu coupling was performed at temperatures ranging from  $-20$  to  $-65$  °C using polyfunctionalized Grignard reagents **69-71** to synthesize a broad spectrum of valuable compounds, including heterocyclic biaryls and polyfluoro biaryls (Scheme 26) [51].

Thienyl Grignard **74** and either 1,3- or 1,3,5-bromo- or iodobenzenes **75** were coupled to form *meta*-substituted thienylbenzenes in a Kumada-Tamao-Corriu reaction catalyzed by  $\text{PdCl}_2(\text{dppf})$  (Scheme 27) [52]. Iodo-substituted



Scheme 27

Scheme 28



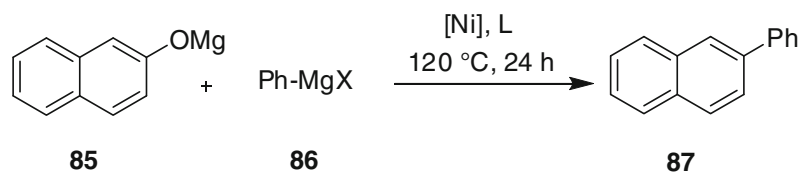
Scheme 29

benzenes gave the trisubstituted product under mild synthetic conditions (rt for 48 h) whereas bromo-substituted benzenes only gave mono- and disubstituted products under heating overnight (60 °C).

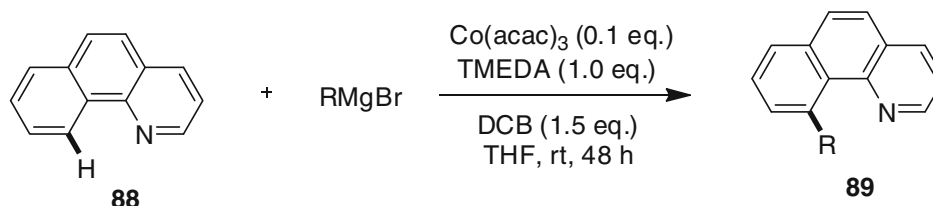
### Other arylation of Grignard compounds

A nickel-catalyzed Kumada-Tamao-Corriu coupling of diaryl sulfates **79** afforded the products **81** which caused a new synthetic procedure for constructing biaryls and showed the potential of using sulfates as a new kind of capable, green electrophiles in different cross-coupling reactions (Scheme 28) [53]. Ni-catalysts with different ligands were screened in this Kumada-Tamao-Corriu cross-coupling reaction, and  $\text{PCy}_3$  was proved to be the best one. In addition, other monodentate and bidentate phosphine ligands, such as  $\text{PPh}_3$ , *dppe*, *dppp*, and *dppf*, were not efficient. However, some common catalysts of Kumada-

Scheme 30



Scheme 31



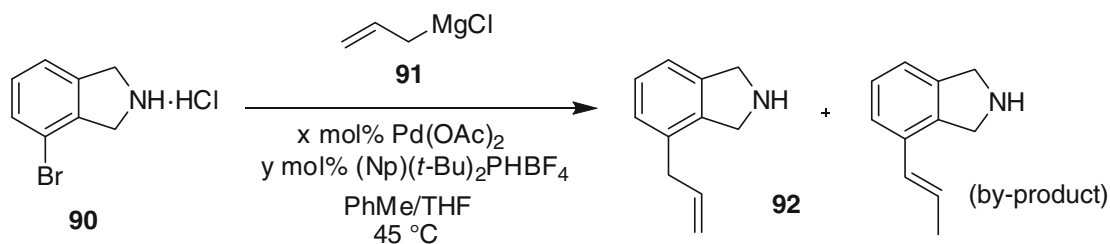
DCB = 2,3-dichlorobutane  
 TMEDA = *N,N,N',N'*-tetramethylethylenediamine

Tamao-Corriu couplings such as Pd, Fe, and Co complexes, entirely failed. Finally, a good yield of desired product **81** was obtained in the presence of Ni(PCy<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and the additional PCy<sub>3</sub> in Et<sub>2</sub>O after 2 h.

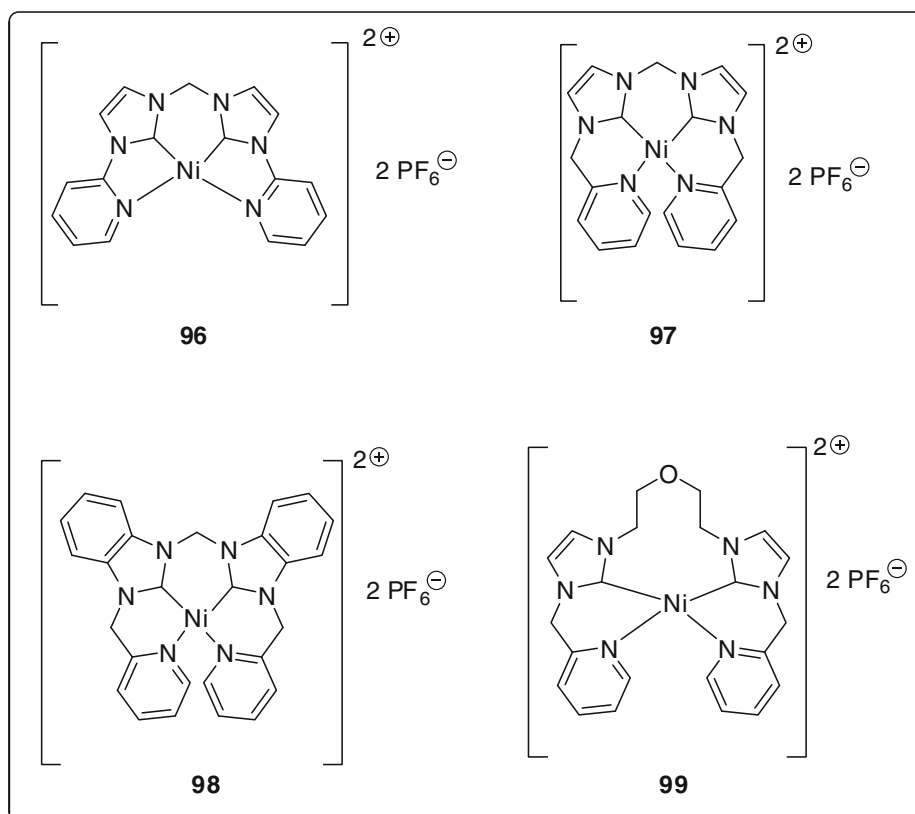
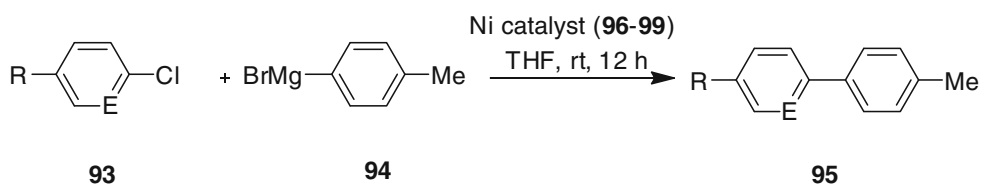
Low reactive aryl tosylates **82** have been coupled with aryl Grignard reagents **83** in the presence of 0.1–1.0 mol % Pd(dba)<sub>2</sub> and PPF-*t*-Bu in toluene at either room temperature

or 80 °C to produce the respective biaryls **84** in good yields (Scheme 29) [54].

Kumada-Tamao-Corriu cross-coupling reactions of magnesium phenolate **85** with Grignard reagents **86** to construct biaryl scaffolds **87** were afforded by Shi et al. This study suggested that MO<sup>-</sup> species could be a useful leaving group for different transformations. Screening of

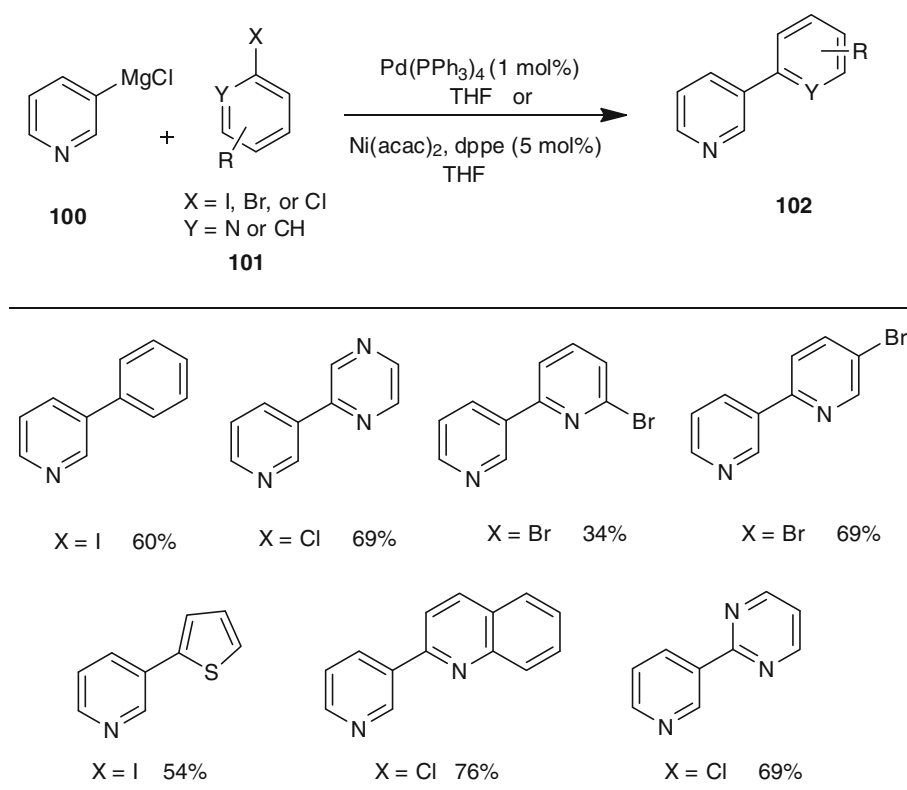


Scheme 32



Scheme 33

Scheme 34



the reaction conditions indicated that nonpolar solvents, a 3:1 mixture of toluene and diisopropyl ether (DIPE), were suitable for this transformation. This solvent system in the presence of  $\text{PCy}_3$  as a ligand showed the highest reactivity for this transformation (Scheme 30) [55].

Grignard reagents have been utilized as the coupling partners in direct cross-coupling of C–H bonds through cobalt catalysis. This was the first regioselective C–H transformation of benzo[*h*]quinolone (**88**) and phenylpyridine derivatives with Grignard reagents at room temperature that has a significant place in the field. In the absence of catalyst, direct nucleophilic attack by Grignard reagents at the 2-position of pyridine derivatives occurred due to decrease in the reactivity of  $\text{RMgBr}$ . Grignard reagents in a solution of THF, TMEDA, and 2,3-dichlorobutane were added to a Schlenk tube containing benzo[*h*]quinoline and  $\text{Co}(\text{acac})_3$ . The reaction mixture was stirred at rt for 48 h to produce **89** (Scheme 31) [56].

### Heteroarylation of Grignard compounds

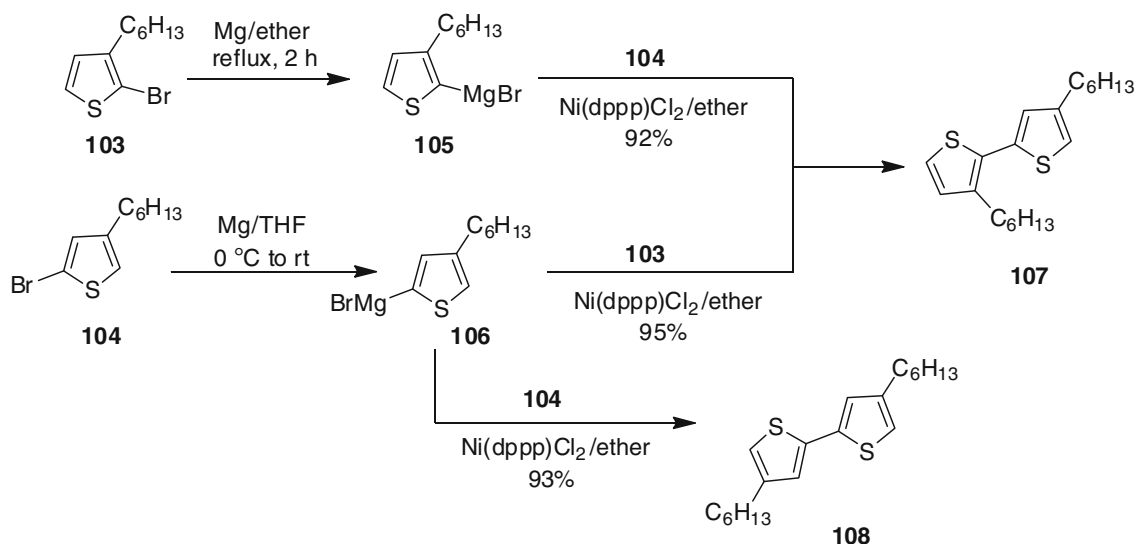
4-Allylisoindoline (**92**) has been prepared by a practical, cost-effective Kumada-Tamao-Corriu coupling reaction (Scheme 32). Olefin isomerization as a side reaction was suppressed by examination of various reaction parameters.

The first catalyst screen for this reaction with allylmagnesium reagents **91** is reported by Zacuto et al. [57]. A comparison between Pd sources of catalysts and readily available ligands led to the selection of (neopentyl)(*t*-Bu) $_2\text{P}\cdot\text{HBF}_4$  as the best one.

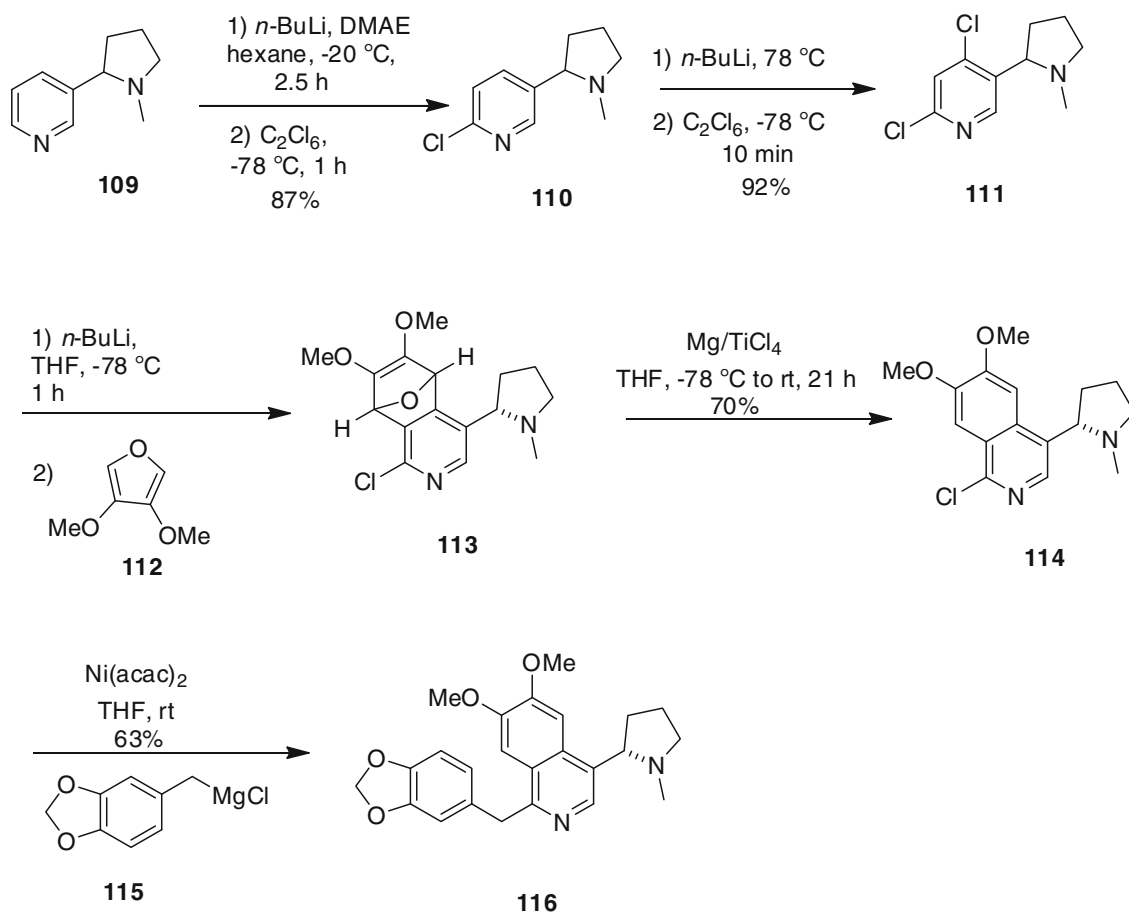
Room temperature Kumada-Tamao-Corriu cross-coupling of unactivated aryl chlorides, vinyl chlorides, and heteroaryl chlorides **93** catalyzed by *N*-heterocyclic carbene-based nickel(II) complexes **96–99** is reported by Zhenxing Xi et al. (Scheme 33). The stabilization effect of the NHC ligands provides high catalytic activities of these nickel complexes [58].

The significance of azine-containing biaryls **102** in pharmaceutical and material chemistry has impelled many methods such as Kumada-Tamao-Corriu coupling for their synthesis [59]. Kumada et al. [60] reported the use of 3-pyridylmagnesium chloride (**100**) in palladium-catalyzed Kumada-Tamao-Corriu couplings of aryl iodides. However, use of a  $\text{Ni}(\text{acac})_2/\text{dppe}$  catalyst was found to be optimal with aryl bromide substrates (Scheme 34). Only heterocyclic aryl bromide and chlorides are reported with 34–76 % yield.

A selective method for the synthesis of dihexyl-2,2'-bithiophenes **107**, **108** starting from 2-bromo-3-alkylthiophene **103** or 2-bromo-4-alkylthiophene **104** using catalytic amounts of  $\text{Ni}(\text{dppp})\text{Cl}_2$  was reported [61]. Then **107** and **108** were



Scheme 35

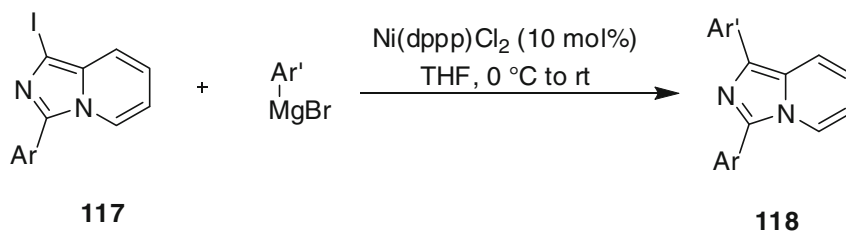


Scheme 36

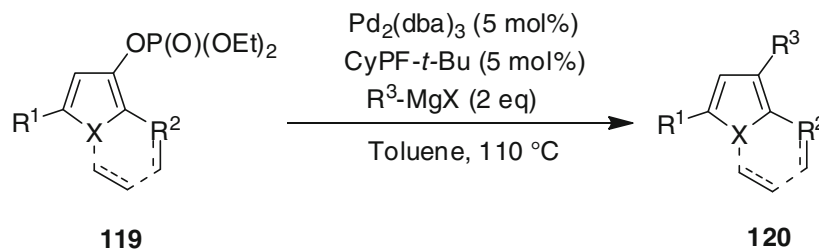
obtained as head-to-tail and tail-to-tail regioisomers in high yields and excellent selectivity using a Kumada-Tamao-Corriu cross-coupling reaction (Scheme 35).

Synthesis of (*S*)-macrostomine (**116**) has been skilled in five steps (Scheme 36). One step was a Kumada-Tamao-Corriu cross-coupling reaction on a 1-chloroisoquinoline

Scheme 37



Scheme 38



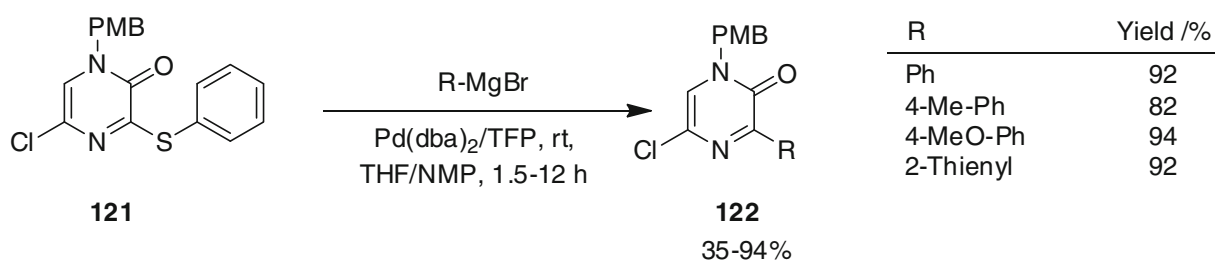
intermediate **114** that provided the plant alkaloid [62]. The appropriate catalyst and optimization of conditions have been investigated. Consequently, a ligand-free reaction with Ni(acac)<sub>2</sub> as catalyst was selected to afford the enantiopure natural product **116** in 63 % yield. Actually, the enantiopure natural product was obtained by separation of a diastereomeric mixture of **113**.

After halogenations of 3-arylimidazo[1,5-*a*]pyridines, Kumada-Tamao-Corriu cross-coupling of the produced 1-iodo-3-arylimidazo[1,5-*a*]pyridines **117** and aryl Grignard reagents was performed to prepare 1,3-diarylated imidazo[1,5-*a*]pyridines **118** (Scheme 37). Aryl Grignard reagent was added dropwise to a solution of 1-iodo-3-

arylimidazopyridine **117** and Ni(dppp)Cl<sub>2</sub> in THF at 0 °C under Ar atmosphere. After addition of Grignard reagent, the reaction mixture was stirred at room temperature to produce the desired product [63].

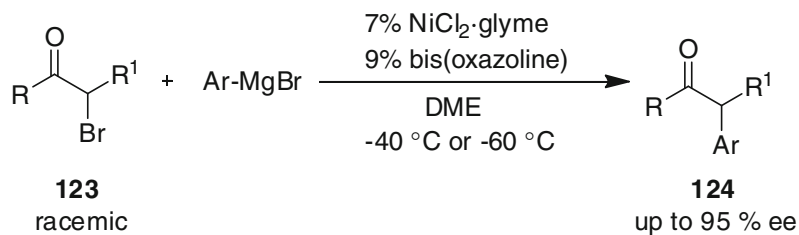
Phosphatyloxy-substituted heterocycles **119** undergo Kumada-Tamao-Corriu cross-coupling. This conversion proceeded most efficiently in the attendance of Pd<sub>2</sub>dba<sub>3</sub>/CyPF-*t*-Bu mixture. These heterocycles **120** were synthesized via migration/cycloisomerization approach by Schwier et al. [64] (Scheme 38).

Mild room temperature palladium-catalyzed C<sub>3</sub>-arylation of 2(1*H*)-pyrazinones **121** is reported via a desulfative Kumada-Tamao-Corriu cross-coupling reaction (Scheme 39).

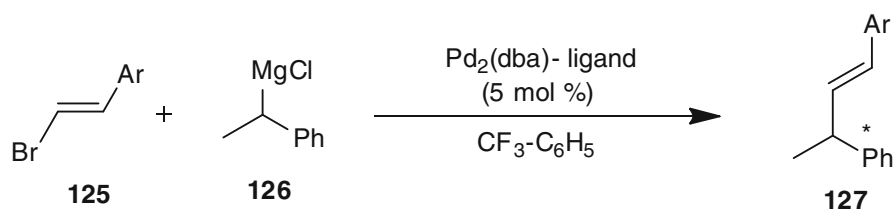


Scheme 39

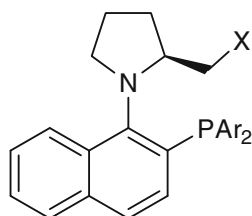
Scheme 40



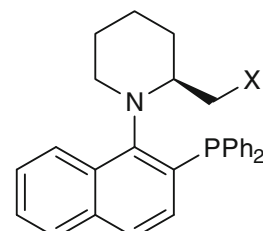
Scheme 41



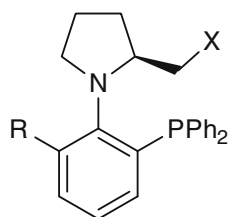
Ligands:

**128a**

Ar = Ph

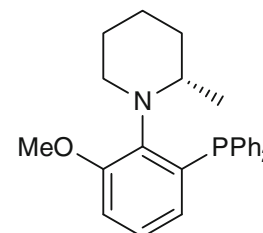
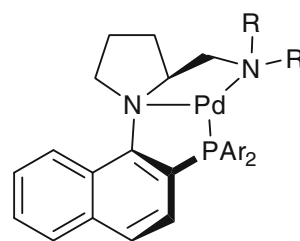
X = OMOM, OBn, O-*t*-Bu, pyrrolidinyl**128b**

X = pyrrolidinyl, piperidinyl

**128c**

X = OBn, R = Me

X = pyrrolidinyl, R = OMe

**128d****129**

In most cases, the desired cross-coupled products provide good to excellent yields [65]. First  $\text{Fe}(\text{acac})_3$  or  $\text{Ni}(\text{OAc})_2/\text{PPh}_3$  were examined as catalyst for the desulfurative cross-coupling. But an extensive amount of aryl-aryl homocoupling product was produced rather than the corresponding cross-coupled product. Thus, Pd was utilized as  $\text{Pd}(\text{dba})_2$  with TFP (tri-2-furylphosphine) as ligand and THF as solvent.

#### Asymmetric Kumada-Tamao-Corriu cross-coupling reactions

Catalytic asymmetric Kumada-Tamao-Corriu carbon-carbon bond formation is one of the most significant reactions in synthetic organic chemistry. The development of new chiral ligands for use in this field has continued to undergo rapid growth.



An asymmetric Kumada-Tamao-Corriu reaction of alkyl electrophiles is reported by Lou et al. (Scheme 40). In this protocol, racemic  $\alpha$ -bromoketones **123** coupled to aryl Grignard reagents [66]. Consequently, readily available bis(oxazolines) are shown for the first time to be effective ligands for cross-couplings of alkyl electrophiles.

Using  $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$  as catalyst and *N*-aryl axially chiral mimetic-type ligands **128a-128d** afforded good enantioselectivities in an asymmetric Kumada-Tamao-Corriu cross-coupling reaction (Scheme 41) [67]. Also, other palladium and nickel complexes have been investigated. Thus,  $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$  is the most effective complex. The ligands possessing a pendant oxygen group exhibited faster reaction rate than ligands possessing a pendant nitrogen group. Ligands possessing the pendant nitrogen substituent as a strong coordinating group perform the internal coordination of the pendant nitrogen group to palladium (**129**). Such a problem was solved by using a piperidine based ligand, because coordination of the pendant nitrogen group to the internal palladium seemed to be torsionally unfavorable.

## Conclusions

This review highlights recent developments of carbon-carbon bond formation of Kumada-Tamao-Corriu cross-coupling reactions. Several selected examples of alkylation, alkenylation, arylation, and heteroarylation of Grignard compounds and some examples of asymmetric Kumada-Tamao-Corriu cross-coupling reaction using various catalysts and ligands are discussed. Although many advances dealing with the Kumada-Tamao-Corriu coupling reaction have been made in the last few years, it will persist to be a fast-moving topic for the next several years. We hope this review will create strong interest among the wide-ranging readership of this journal.

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