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REVIEW

Advances in Kumada–Tamao–Corriu cross-coupling reaction: an update

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Abstract

The formation of the C–C bond is a major and important reaction in synthetic organic chemistry and frequently catalyzed by transition-metal catalysts. Among them, Kumada–Tamao–Corriu coupling reaction is providing a simple methodology and extensively employed in the art of organic synthesis. In this review, we try to highlight the recent advances in the applications of Kumada–Tamao–Corriu coupling reaction by updating of our previous review from 2012 up to date.

Graphical abstract

$$\mathrm{RX} + \mathrm{R'MgX} \xrightarrow{\text{Pd or Ni or Fe}} \mathrm{R\text{-}R'}$$

R = alkyl, alkenyl, aryl, heteroaryl

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

Introduction

Carbon–carbon bond formation is the closet reaction to the heart of organic synthetic chemists. Metal-catalyzed cross coupling reactions are of great importance in the art of organic synthesis. They are frequently used for the synthesis of new polymeric materials, pharmaceutically active complex molecules and total synthesis of virtually all natural products, from commercially available or readily accessible starting materials. Thus, metal-catalyzed cross-coupling reactions are considered as a powerful and vital tool in the C–C bond forming step (steps) in multi-step organic synthesis [1].

These metal-catalyzed reactions also play a significant role in medicinal chemistry, nanotechnology, and bioorganic chemistry [2–6]. Undoubtedly, the most important metal-catalyzed cross coupling reactions are the various Pd-catalyzed cross coupling reactions since the 2010 Chemistry Nobel prize was awarded to Heck, Negishi, and Suzuki "for their achievements in palladium-catalyzed cross-couplings in organic synthesis". They have revolutionized the way that chemists assemble carbon–carbon (C–C) bonds. These reactions typically involve halogenated aromatic electrophiles, which represent a small subset of the reaction partners used in organic synthesis.

Name reactions in organic chemistry are referred to those reactions which are well-recognized and reached to such status for being called as their explorers, discoverers, or developers. Examples are including the Diels-Alder reaction, the Claisen condensation [7], Wittig reaction [8], the Grignard reaction [9], and the Friedel-Crafts alkylation and acylation reaction [10]. The name is simply a reminder. The important and distinguished name reactions for the Pd-catalyzed cross couplings are Suzuki [11], Sonogashira [12],

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Heck [13], Negishi [14], Stille [15], and Hiyama [16] reactions. Indeed, these reactions have revolutionized the art of organic synthesis and their contribution to organic chemistry is undisputable [17].

The above mentioned protocols have been found extremely beneficial in the art of organic synthesis as well as materials science. However, most strategies involve the use of Pd-based catalysts, which are toxic, expensive, or actually both. Furthermore, these cross coupling reactions use only those substrates containing sp^2- or sp-hybridized carbons. Reactions involving sp^3-hybridized substrates are uncommon, although, nowadays some significant progress has been made [18–20].

The most effective and commonly employed catalysts for cross coupling reactions are actually based on noble metals [21] and in particular, Pd and its complexes are widely reported as superior catalysts. The mechanistic details of Pd-based catalysts are well recognized [22]. Several pharmaceuticals, agrochemicals, and polymers are produced in industrial scale using Pd-catalyst in their C–C bond formation step. However, due to the high cost and low abundance of Pd sources, the development of alternative catalytic systems based on earth-abundant and less expensive metals, such as nickel and iron, has always been in much demand. Thus, Ni(0), Ni(I), Ni(II), and Ni(III) complexes attracted the attention of synthetic organic chemists as potential replacement for Pd to catalyze the cross coupling reaction for the construction of C–C bond [23–25].

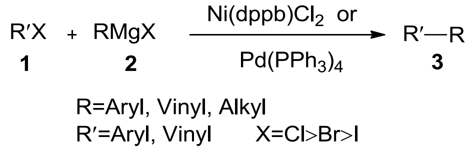
Ni-catalyzed cross-coupling reactions have also emerged as efficient methods for the construction of C–C bonds, and many mechanistic studies have been conducted to understand the factors controlling the reactivity and selectivity of Ni-catalyzed reactions. Ni catalysts not only enable to catalyze the cross coupling reactions of primary alkyl electrophiles but also sterically hindered secondary and tertiary alkyl electrophiles bearing beta-hydrogens with different organometallic reagents to construct carbon–carbon bonds.

Another type of cross coupling reaction was achieved and reported by Tamao et al. [26]. The Kumada and Tamao cross-coupling reaction involves the reaction of an appropriate organohalide with an organomagnesium compound (a Grignard reagent), to provide the corresponding cross-coupled products in the presence of Pd or Ni as catalysts. In the same year, Corriu research group, independently reported the successful reaction of *β*-bromostyrene with phenylmagnesium bromide to obtain *trans*-stilbene in the presence of $Ni(acac)_2$ as catalyst [27].The Kumada cross coupling reaction initially was achieved in 1972 using either Pd or Ni as catalyst [26]. The cross coupling reaction of Grignard reagents with alkyl, vinyl, or aryl halides was accomplished in the presence of Ni as a less expensive catalyst in comparison to the conventional Pd catalyst providing a more economic transformation especially when it was performed in chemical industry. An operational and current example is mass production of useful styrene derivatives, in which for their low-cost synthesis the Ni-catalyzed Kumada coupling of unsymmetrical biaryls is employed. However, the Ni-catalyzed cross coupling reaction is limited to the utilization of those halide partners which can not react with organomagnesium reagents (Grignard reagents). On the hand, the advantage of this Ni-catalyzed cross coupling reaction is the direct cross coupling of Grignard reagents, which evades furtherQuery unwanted possible additional reaction such as the transformations of Grignard reagents to the corresponding of zinc reagents used as the starting materials in the Negishi cross coupling reactions [28] (Scheme 1).

A plausible mechanism for a Ni-catalyzed cross coupling reaction has been suggested. It most probably starts with oxidative addition of the organohalide to the Ni(0) to form a Ni(II) complex. Then, the transmetalation with the Grignard reagent takes place, where the R group of the Grignard reagent substitutes the halide anion on the Ni complex, generating a magnesium(II) halide salt. Eventually a reductive elimination occurs giving raise to the final cross coupled product, while recreating the catalyst, which enables to begin another catalytic cycle (Fig. 1) [26].

Kumada, Tamao, and Corriu cross-coupling reaction is a type of cross-coupling which has been found beneficial for

Scheme 1



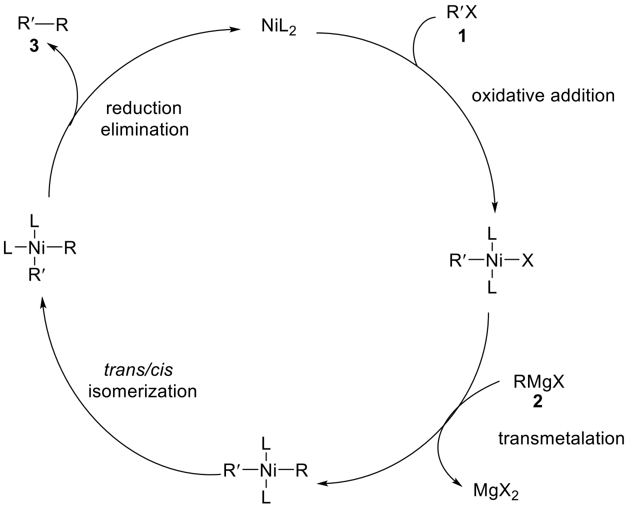


Fig. 1 A plausible mechanism for a Ni-catalyzed cross coupling reaction

the formation of carbon–carbon bonds through the reaction of a Grignard reagent and an organic halide (for the recent surveys on Grignard reagents) [29–32]). This kind of cross coupling has been found beneficial for a wide range of aryl or vinyl halides, as well as pseudo-halides (e.g. tosylates and triflates) and various Grignard reagents (with aryl, vinyl, or alkyl residues), which nowadays dominated by using Ni instead of Pd catalysts. Notably, several other effective catalysts for this reaction have been developed and reported [33].

Besides, other types of cross-coupling reactions of organometallic reagents with organic electrophiles which have found extensive industrial applications. The initial cross-coupling reactions reported by Kumada or Corriu made use of organomagnesium bromides in the presence of nickel catalysts, such as [Ni(dppe)Cl_2] and $Ni(acac)_2$ [26, 27]. In the Ni-catalyzed cross-coupling reactions of aryl halides using *trans*-$ArNiBr(PEt_3)_2$, the generation of Ni(I) as well as Ni(III) species were suggested as reactive intermediates [34]. Interestingly, Ni is significantly more nucleophilic in comparison with Pd and Pt because its atomic size is smaller than Pd and Pt. Thus, due to their higher nucleophilicity, Ni catalysts promote the reactions under milder reaction conditions and therefore catalyze the reaction of more challenging electrophiles easier than Pd catalysis.

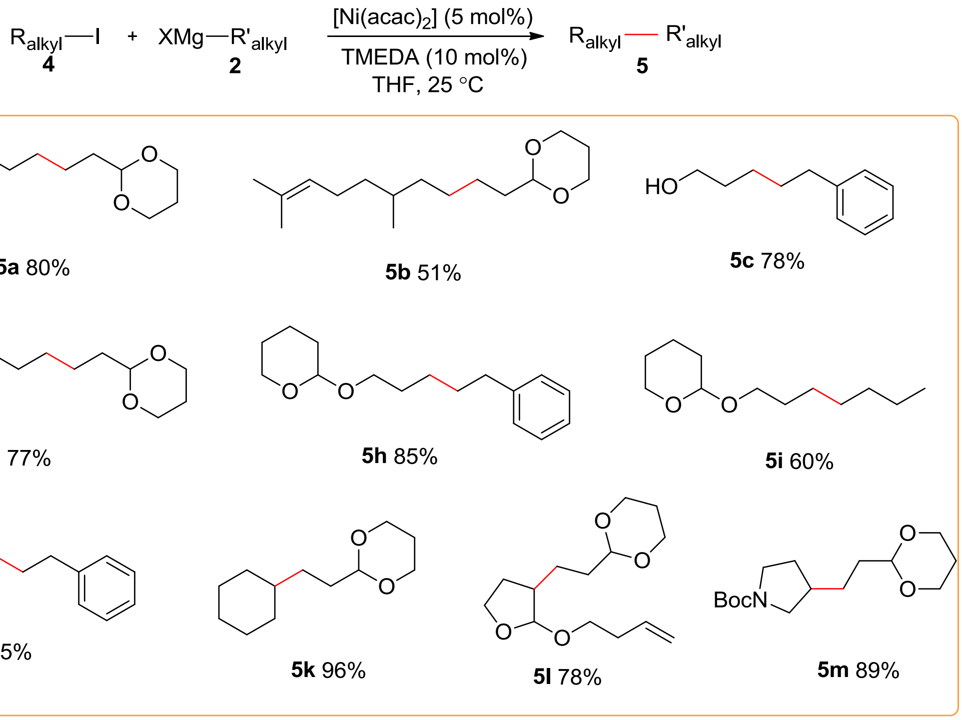
In 2012, we reviewed the advances in Kumada–Tamao–Corriu cross-coupling reaction catalyzed by different ligands [35]. In continuation of our interest in name reactions [36–48], as well as Ni-catalyzed reaction [49], due to importance of Kumada–Tamao–Corriu cross-coupling by different ligands, approved by a plethora of related references, appeared in chemical literature, in this review we try to update our previous work published in 2012 [35]. Thus, this review covers the applications of different ligands and catalysts by Kumada–Tamao–Corriu coupling reaction in organic synthesis reported from 2012 till date.

Alkylation of Grignard compounds via alkyl halides

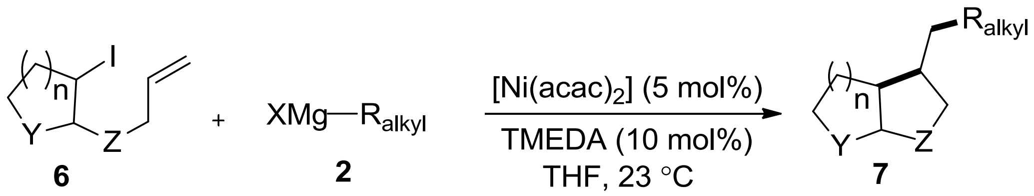
Nickel-mediated alkyl–alkyl Kumada coupling reactions (Scheme 2) and cascade cyclization-coupling reaction for the construction of two alkyl–alkyl bonds (Scheme 3) has been established by Guisn-Ceinos et al. [50]. The generality of this reaction was explored using various functional groups involving esters, carbamates, nitriles, and ketals. Noticeably, mechanistic examination exhibited the intermediacy of radical species, and also the catalytic cycle of Ni^{I}–Ni^{II}–Ni^{III} [50].

The paramagnetic organoiron system, dimesityliron(II) complex $[Fe(II)Mes_2\text{-}(SciOPP)]_3$ (**10**) has been applied as catalyst in Kumada–Tamao–Corriu-type cross-coupling in 2015 by Takaya et al. [51] Significantly, the reaction of **8** and phenylmagnesium bromide (**9**) afforded 16% of **11** and 50% of 1-decylbenzene (DecylPh, **12**), together with 10% debrominated side-products and 15% of the starting bromoalkane **8** (Scheme 4).

Scheme 2

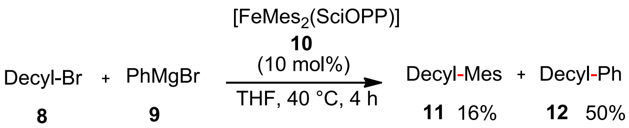


Scheme 3



$Z=CH_2, O, NTS, C(CO_2Et)_2; Y=CH_2; n=0, 1$

Scheme 4



A series of Fe systems having chelating amine ligands as pre-catalysts was applied in the cross-coupling reaction of 4-tolylmagnesium bromide (4-tolylMgBr, **13**) and cyclohexyl bromide (**14**) [52]. The systems **16–18**, as well as the species obtained spontaneously from iron(II) chloride and tetramethylethylenediamine (TMEDA) in tetrahydrofuran have been used as pre-catalysts in the cross-coupling reaction of 4-tolylMgBr and cyclohexylbromide using two methods. In the method (A), the reaction has been accomplished at 0 °C with slow addition of the Grignard reagent. While in the method (B), the Grignard reagent has been added quickly and the reaction was heated to 40 °C. The lability of the amine ligands of the systems **16–18** using excess benzyl Grignard reflects decreasing catalytic property in the coupling reaction of 4-tolylMgBr with cyclohexylbromide, with the least labile systems demonstrating the poorest catalytic property. Particularly, whereas the systems **17** and **18** treat with benzyl Grignard, the amine ligands are not displaced by excess Grignard, unlike the amine ligands in the other complexes tested. Remarkably, these two systems exhibited only very low efficiency as catalysts in the cross-couplings (Scheme 5, Table 1) [52].

A simple and direct approach for the synthesis of deuterated methyleugenol was performed in three steps starting from veratraldehyde. Methyleugenol monodeuterated on the benzylic position, 4-(1-deuteroprop-2-enyl)-1,2-dimethoxybenzene, was provided in 88% isotopic enrichment in a method in which the introduction of deuterium was accomplished using lithium aluminium deuteride ($LiAlD_4$) as deuteride source and presenting a nickel-mediated Kumada–Corriu type coupling reaction of a deuterated benzyl chloride derivative with vinyl magnesium bromide [53]. Hence, based on this method, the coupling reaction of compound **19** and vinyl magnesium bromide **20** has been examined through Kumada–Corriu cross-coupling in the

Scheme 5

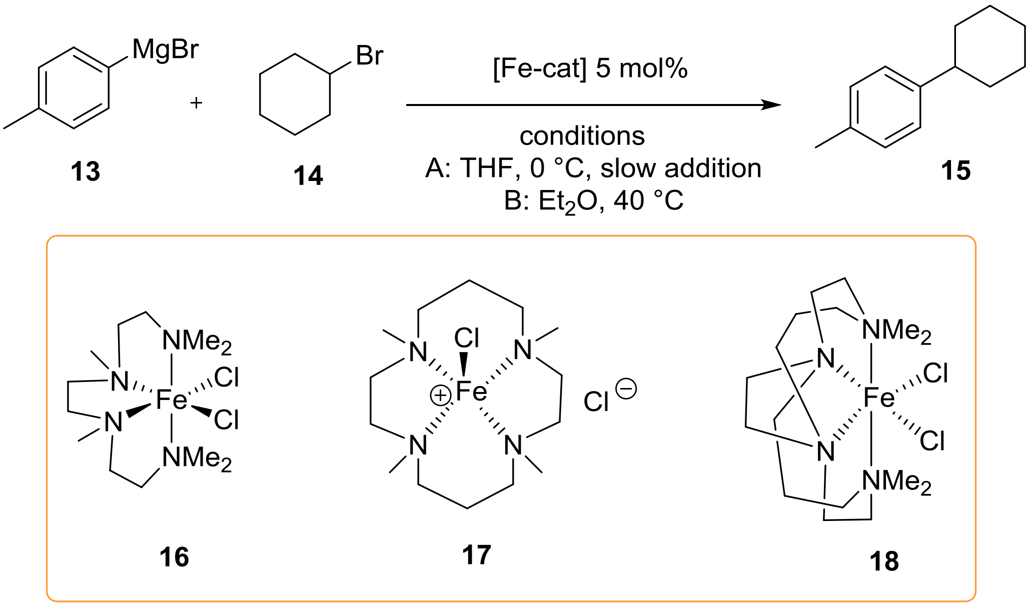


Table 1 Fe-mediated Kumada cross-coupling reaction

Entry	[Fe-cat]	Conditions	Conversion to **15**/%
1	$FeCl_2$ + excess TMEDA	A	93
2	$FeCl_2$ + 2 TMEDA	B	77
3	**16**	A	19
4	**16**	B	53
5	**17**	A	15
6	**17**	B	3
7	**18**	A	1
8	**18**	B	3

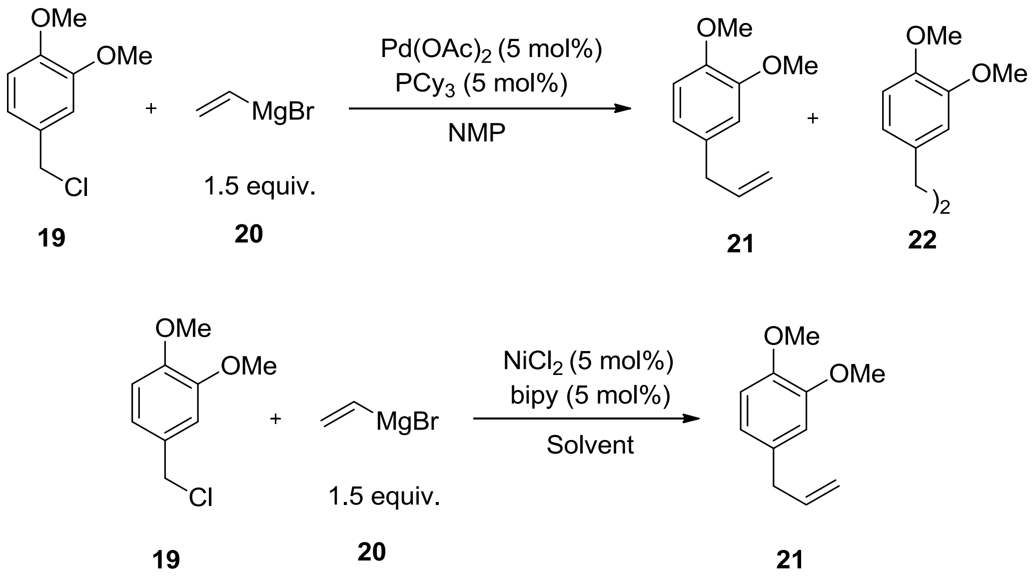
presence of $Pd(OAc)_2$ [54]. Noticeably, the construction of undesirable side-product **22** has been detected. Various efforts to increase the selectivity in favour of **21** have been accomplished. Next, this group examined a nickel-mediated coupling inspired from previous methods for the coupling reaction of alkyl Grignard's reagents to halides [55] and aryl Grignard's reagents to benzyl chlorides [56]. Pleasantly, this modified method permitted a better control of the construction of **22** and the desired product **21** were provided in 51% yield (Scheme 6).

Various Ni NNN pincer systems with variance only in the groups of the side arm amino substituents were formed in 2016 by Hu et al. [57]. Remarkably, a structure-activity investigation of these systems in alkyl–alkyl Kumada coupling reaction was accompanied. Four novel Ni pincer systems **28**–**31** with moderate to high activity in alkyl–alkyl Kumada coupling reaction of primary alkyl halides were synthesized. Noticeably, among them, complex **28** was effective for the coupling reaction of secondary alkyl halides. The effect of the groups on the catalytic activity of the Ni systems in alkyl–alkyl Kumada cross-coupling reaction was explored. It should be mentioned that the catalytic property displays no noticeable relationship with the redox potential, Lewis acidity, or a key structural parameter (C–N–C angle) of the systems (Scheme 7) [57].

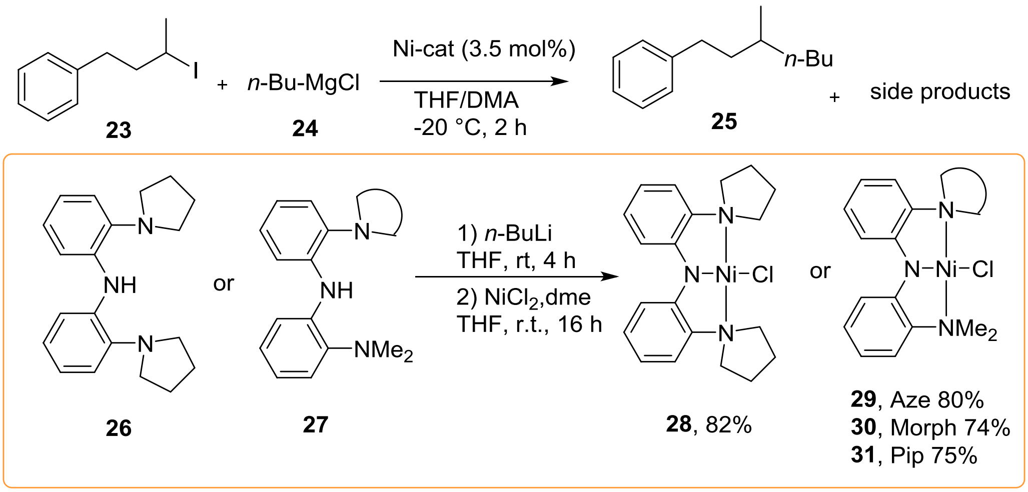
A particularly useful instance of cross coupling reactions for example Kumada reaction was demonstrated by Nakamura et al. [58] using alkynyl Grignard reagents. Based on this method, the mixture of bulky alkynyl Grignard reagents **33** and $FeCl_2$(SciOPP) precatalyst **35** afforded excellent yields of ethynylated cyclic and primary alkanes **34** developing from alkyl bromides, chlorides, and *pseudo*-halides **32** over moderately short reaction times (Scheme 8).

This group suggested a radical-based mechanism for this catalysis in which a doubly alkynylated Fe(II)-SciOPP species works as the active catalyst resting state. The proposed cycle was performed through homolytic removal of the C–X bond of the electrophile using the alkynylated Fe(II)-SciOPP active species to form a transient Fe(III) intermediate from which cross-coupled product is eventually provided. Next, the resultant monoalkynylated Fe(II)-SciOPP species could undergo transmetalation using additional equivalents of Grignard reagent to reproduce the active catalyst. Besides, alkynylated ferrate species provided through over-alkynylation of Fe(II)-SciOPP centers were suggested to be responsible for the construction of by-products. It should be mentioned that up to now (2017), none of the proposed Fe intermediates have been directly

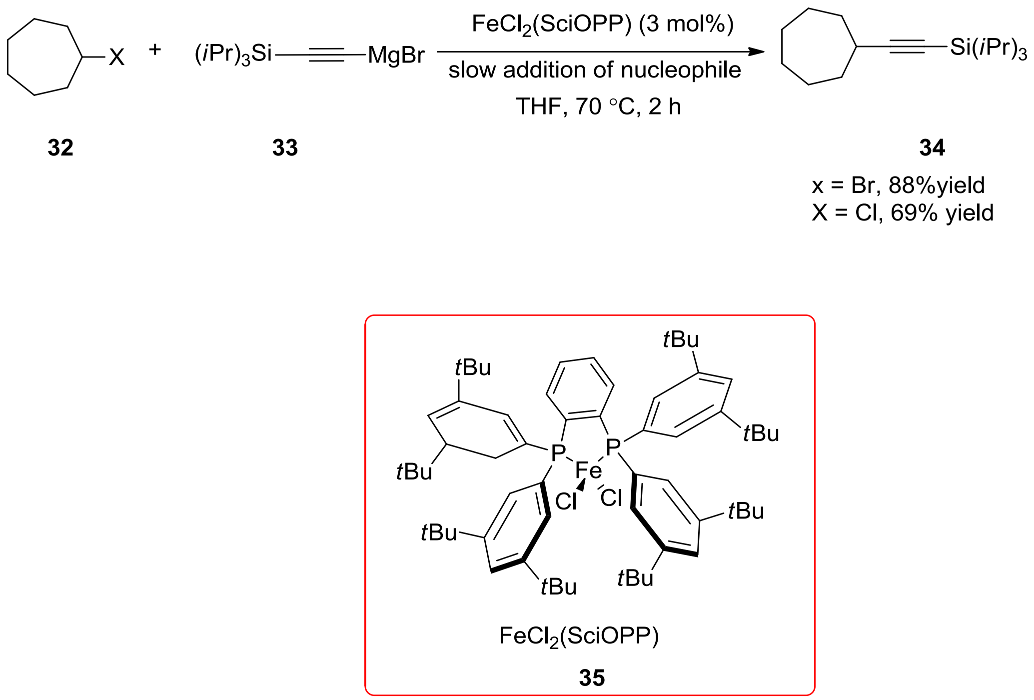
Scheme 6



Scheme 7



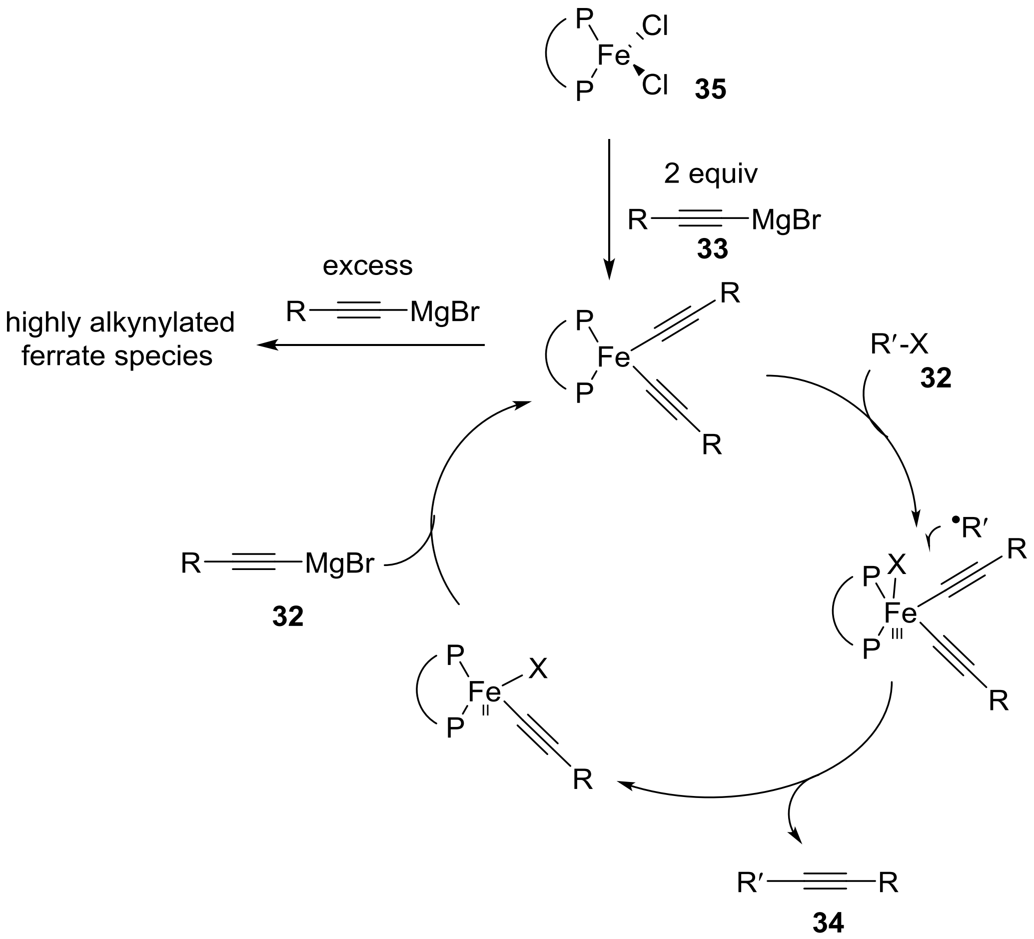
Scheme 8



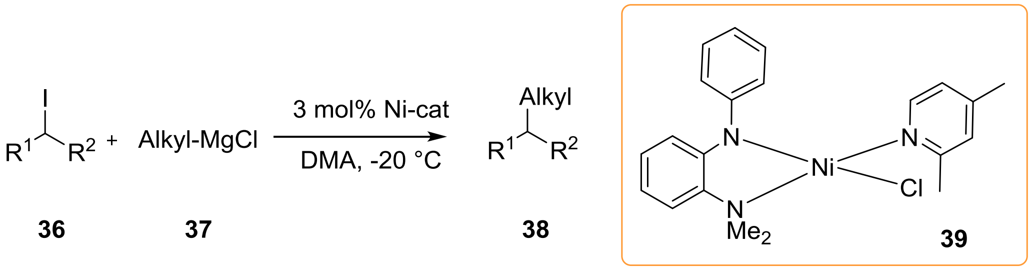
detected or identified and the nature of potential off-cycle species was not evaluated (Scheme 9) [59].

A structure-activity investigation has been occurred for nickel mediated alkyl–alkyl Kumada-type cross coupling reactions. A novel Ni(II) system involving tridentate pincer bis(amino)amide ligands ($^{R}N_2N$) and bidentate mixed amino-amide ligands (^{R}NN) were formed and structurally identified. The best two catalysts were [(^{H}NN)Ni(PPh$_3$)Cl] and [(^{H}NN)Ni(2,4-lutidine)Cl]. The complex **39** was tested as precatalysts for cross-coupling reaction of nonactivated alkyl halides, principally secondary alkyl iodides, with alkyl Grignard reagents. A transmetalation position in the precatalyst is essential for the catalysis. The coordination geometries and spin-states of the pre-catalysts have a minor or no effect. Noticeably, the investigation resulted in the identification of various well-defined nickel catalysts that are considerably more potent and effective than the pincer system [($^{Me}N_2N$)NiCl] for the coupling reaction of secondary alkyl halides (Scheme 10) [60].

Scheme 9



Scheme 10



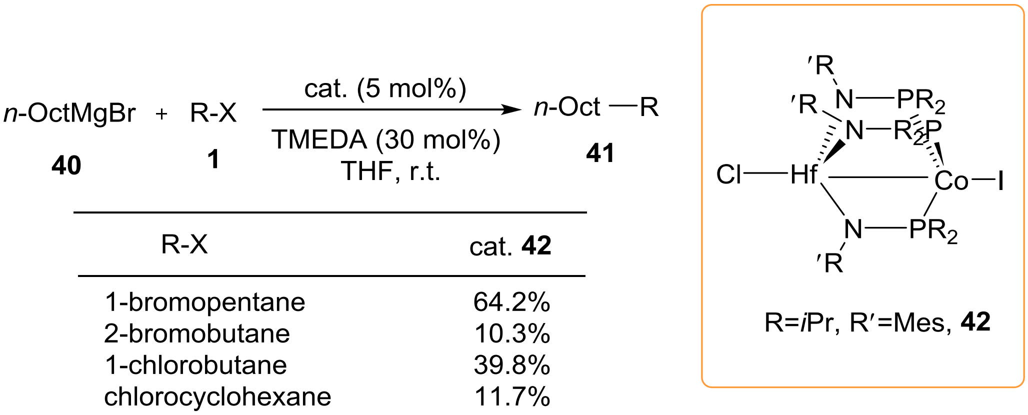
The phosphinoamide-linked Co/Hf complex ICo(iPr$_2$PNMes)$_3$HfCl (**42**) were formed from the relevant tris(phosphinoamide)HfCl systems for comparison with the previously described tris(phosphinoamide) cobalt/zirconium systems [61]. The activity of **42** toward Kumada coupling reaction has been explored, finding considerably decreased activity in comparison to cobalt/zirconium systems [62]. Whereas these hafnium/cobalt systems have not yet demonstrated advantageous over zirconium/cobalt systems (Scheme 11).

Takuji et al. in 2011 established an extremely efficient Fe-mediated cross-coupling reaction of alkyl halides and aryl Grignard reagents using *ortho*-phenylene-tethered bisphosphine ligand containing bulky groups at the 3,5-positions of the diphenylphosphino groups (SciOPPs). An FeCl$_2$ system containing a sterically demanding *ortho*-phenylene-tethered bisphosphine ligand demonstrated an excellent catalytic performance in the Kumada–Tamao–Corriu coupling reaction of aryl Grignard reagents and nonactivated alkyl halides. Noticeably, in this approach, primary, secondary, and also tertiary alkyl halides were used as an electrophilic coupling partner (Scheme 12) [63].

In 2014, Cárdenas et al. reported the quick Nickel-mediated Kumada-type cross-coupling reaction of substituted allyl and benzyl chlorides with alkylmagnesium reagents. The application of Ni(acac)$_2$-TMEDA (acac = acetylacetonate, TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine) permitted the presence of reactive functional substituents on the electrophile (Scheme 13) [64].

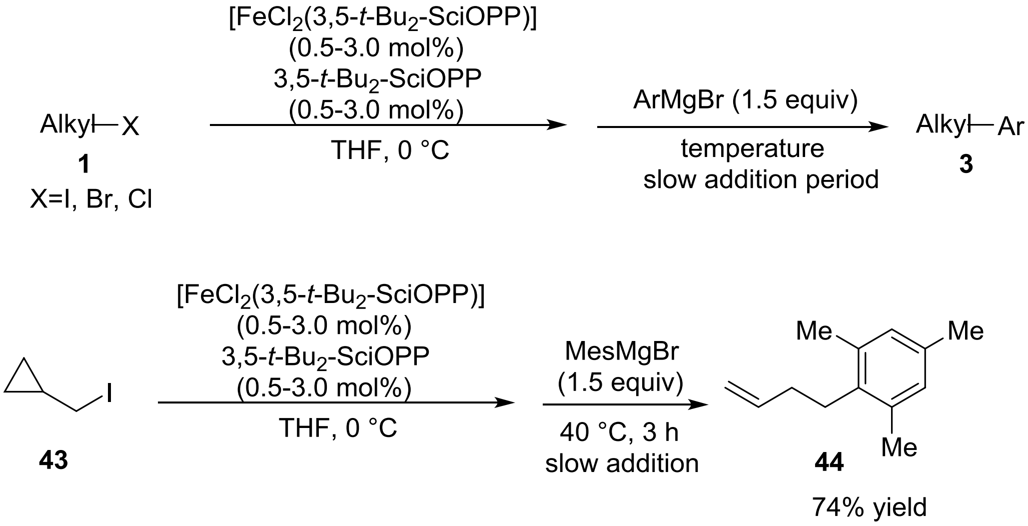
A divalent cobalt iodine system having 1,3-bis(mesityl) imidazol-2-ylidene and pyridine ligands was formed in 2013 by Matsubara et al. [65]. Catalytic performance of this Co system using bromoalkanes and Grignard reagents exhibited high-yield construction of alkenes because of β-hydrogen removal; in sharp contrast, the activation of alkyl halides

Scheme 11

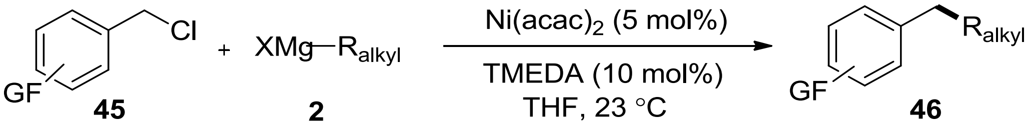


R-X	cat. **42**
1-bromopentane	64.2%
2-bromobutane	10.3%
1-chlorobutane	39.8%
chlorocyclohexane	11.7%

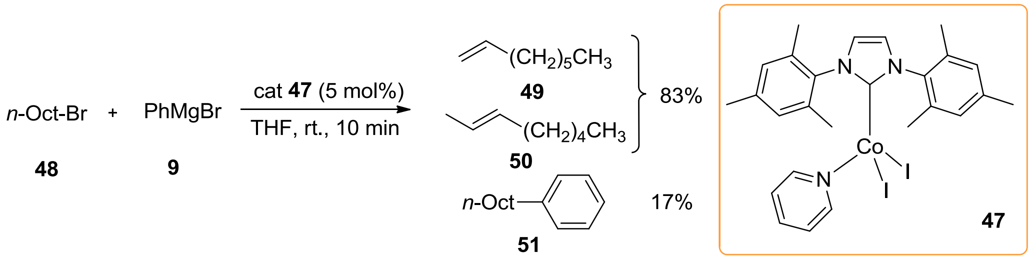
Scheme 12



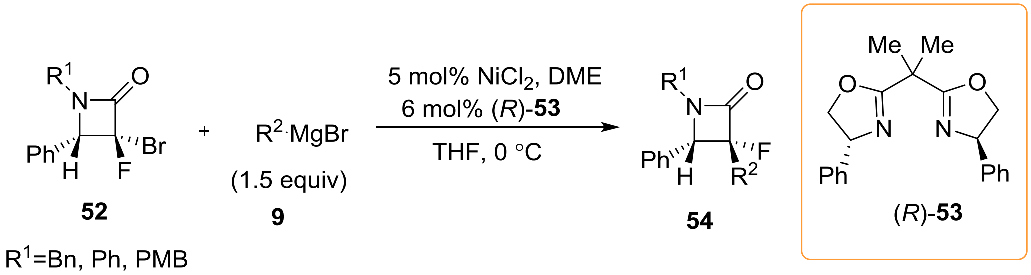
Scheme 13



Scheme 14



Scheme 15



with the larger *N*-heterocyclic carbene ligand, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene was not effective (Scheme 14).

Ando et al. in 2013 reported the Kumada cross-coupling reaction of α-bromo-α-fluoro-β-lactam **52** that is a fluorinated second-aryl carbonyl substrate, with the Ni/bis(oxazoline) as catalyst. Excellent yields and d.e.s were provided with a variety of of arylMgBr substrates. Remarkably, several hetero-aromatic derivatives **54** were provided in moderate yields (Scheme 15) [66].

A bimetallic oxidative addition mechanism including radical intermediates was demonstrated for alkyl–alkyl Kumada cross-coupling using the Ni(II) pincer complex ([(N_2N)Ni-Cl]) **55** as catalyst. Hu et al. in 2013 [67]. The coupling reaction was performed via a radical method, including two Ni centers for the oxidative addition reaction of alkyl halide. The main intermediate species for the activation of alkyl halide is the complex [(N_2N)Ni-alkyl^2](alkyl^2-MgCl); the construction of this type is the turnover-limiting stage of the catalysis. One or more nitrogen donors in the pincer N_2N ligand is suggested to help the catalysis in binding to the Mg^{2+} ion in the Grignard reagents (Fig. 2).

Hu et al. in 2016 replaced a dimethyl amino group of the amidobis(amine) Ni(II) pincer system **55a**, [($^{Me}N_2N$)-Ni−Cl], by a pyrrolidino group to make a unique Ni(II) pincer system **55b**, [($^{Pyr}N^{Me}NN$)Ni−Cl]. Noticeably, complex **55b** was used as a significant catalyst for Kumada cross-coupling reaction of nonactivated secondary alkyl halides, whereas complex **55a** was not effective (Scheme 16) [68].

Hu et al. in 2015 reported Fe pincer complexes as catalysts and intermediates in alkyl–aryl Kumada coupling reactions. This group used a bis(oxazolinylphenyl)amido pincer ligand (Bopa) to stabilize the catalytically active iron center, leading to isolation and identification of well-defined Fe systems in which catalytic activities were explored. By using the strongly chelating pincer ligand Bopa, this group provided and isolated ligated iron systems that are genuine catalysts and intermediates in iron-mediated alkyl–aryl Kumada couplings (Scheme 17) [69].

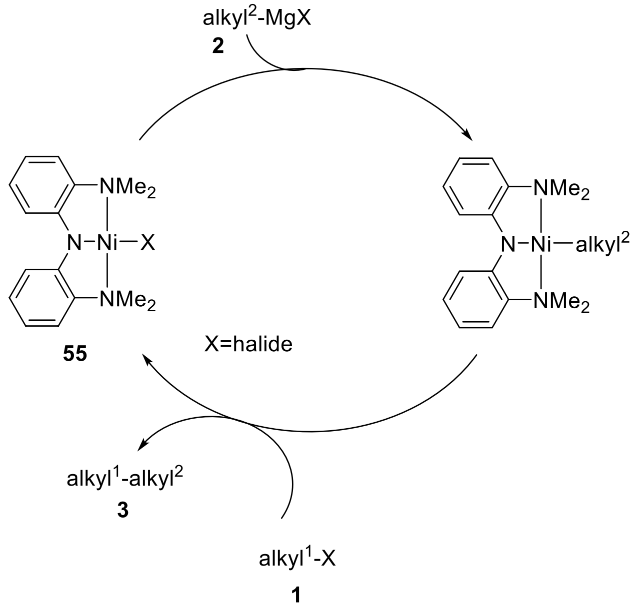
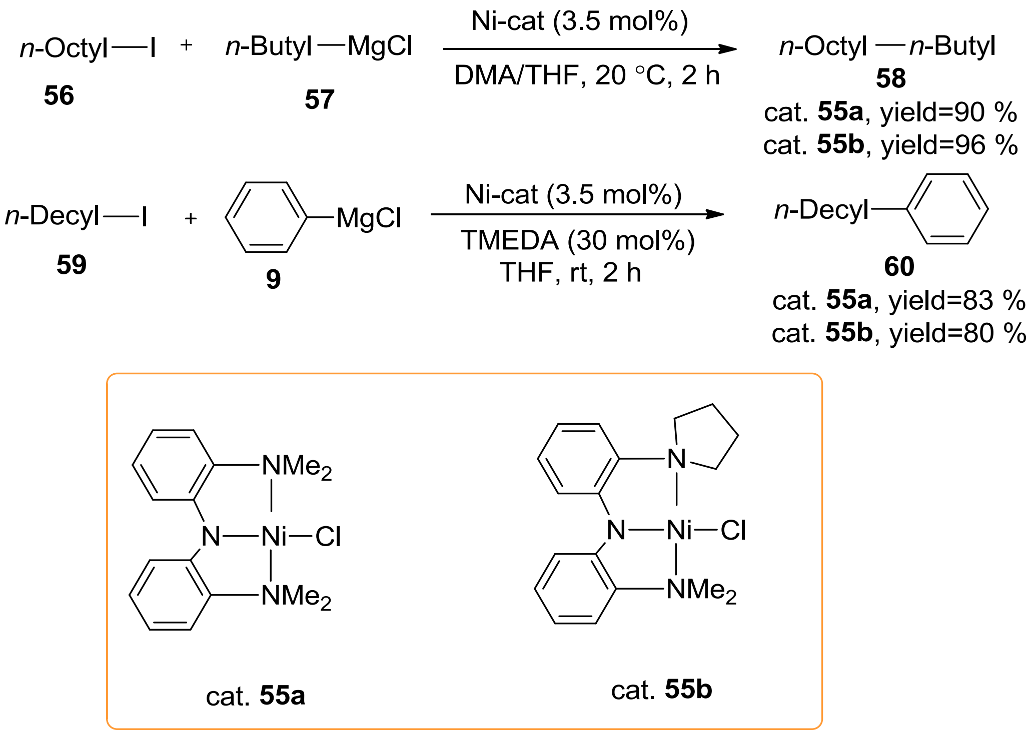
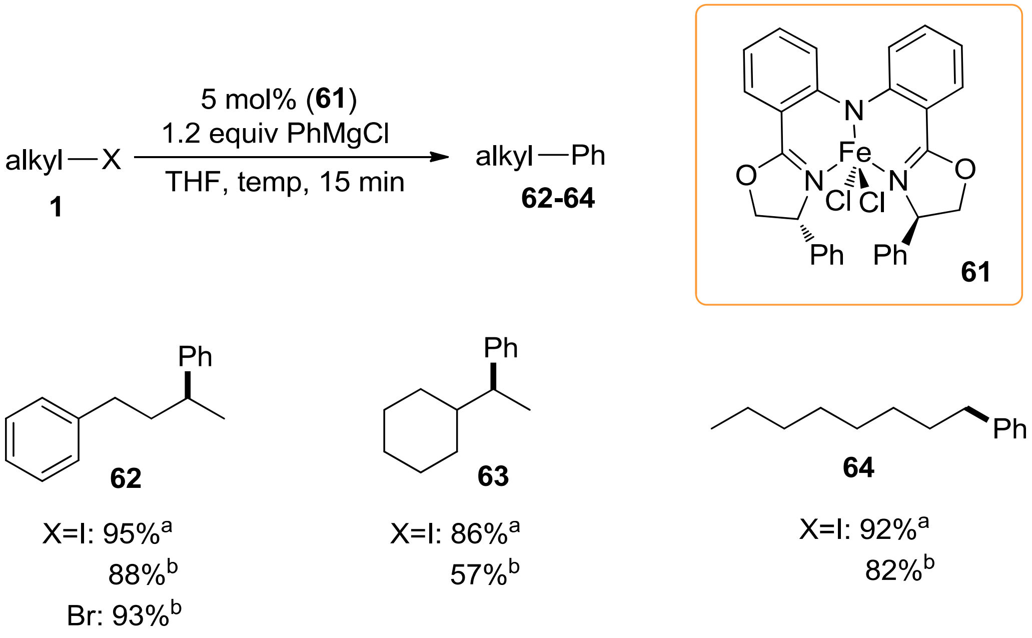


Fig. 2 Suggested reaction sequence for alkyl–alkyl Kumada coupling reactions using Ni(II) pincer systems

Scheme 16



Scheme 17

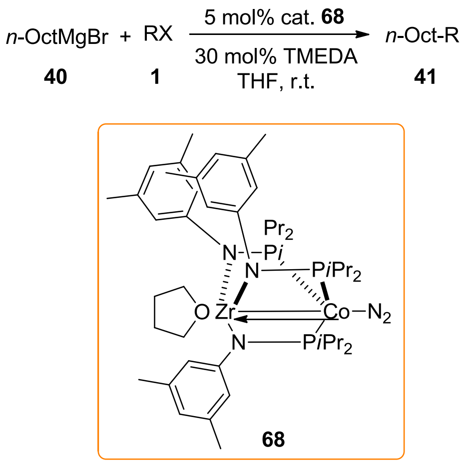


A unique Fe-NHC catalytic complex permits the alkyl–alkyl cross coupling of alkyl halides with alkylmagnesium reagents was established. Remarkably, this is the first iron-mediated Kumada-type coupling reaction for the construction of C(sp^3)–C(sp^3) bonds with functional groups. This method was achieved through mild conditions, preventing the construction of β-elimination products. Mechanistic investigations propose the intermediacy of iron(I) systems, provided by reduction with the Grignard reagent, as the active species. In this route, it was examined useful ligands for the Fe-mediated cross-coupling of 1-iodo-3-phenylpropane (**65**) with (1,3-dioxan-2-ylethyl)magnesium bromide. Firstly, iron(II) acetate was considered as the Fe source. In the absence of ligands, the construction of the corresponding cross-coupling product **67** was not detected. In the model reaction, the application of this ligand gave **67** in poor yield (27%), even when the reaction was accomplished by slow addition of the Grignard reagent to a tetrahydrofuran solution of iron(II) acetate, ligand, and alkyl iodide. It looks that the presence of a large excess of Grignard reagent in the reaction medium inactivates the catalytic system. Moreover, different pyridine-based ligands including bipyridine, terpyridine, and phenantroline afforded poor yields, demonstrating that sp^2-nitrogen ligands are not appropriate for the construction of an active Fe system. The yield did not increase either when the reaction was occurred using bidentate N,P ligands for example *i*Pr-phox or QUINAP, that gave 15% and 19% yield of the cross-coupled product **67**, respectively [70]. Lastly, the stronger σ-donor NHC ligands [71], that were provided spontaneously from the deprotonation of imidazolidinium salts with the Grignard reagent were tested. Among a number of NHC ligands used in the cross-coupling reaction, SIMes·HCl gave the best result (42% yield). It should be mentioned that L7 is the best ligand resulting in highest yield, while all other ligands gave yields between 8 and 27% (Scheme 18).

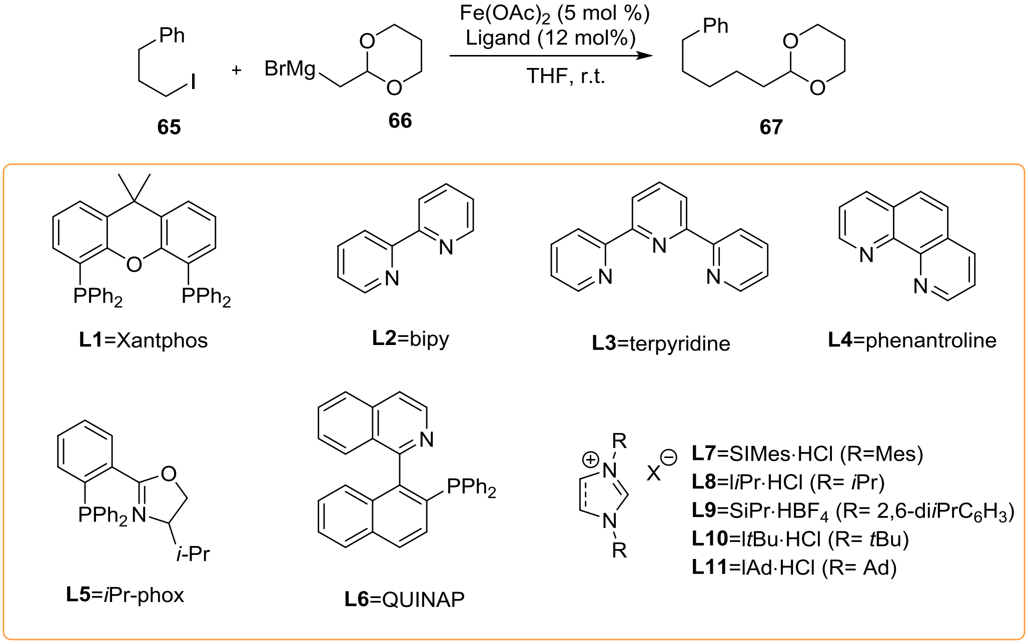
The influence of modifying the *N*-aryl group (aryl = mesityl vs. *m*-xylyl) of the phosphinoamide ligands linking zirconium and cobalt in tris(phosphinoamide)-linked heterobimetallic systems was explored in 2014 by Thomas et al. The addition of alkyl halide to $N_2Co(iPr_2PNXyl)_3Zr(THF)$ (**68**) led to homo-coupling products providing from alkyl radicals rather than the alkyl-bridged or intramolecular C–H activation products provided after addition of RX to **40** (Scheme 19) [72].

Fe(III) bisoxazolinylphenylamido (bopa) pincer systems are effective precatalysts for the cross-coupling reaction of nonactivated primary and secondary alkyl halides with phenyl Grignard reagents. The reactions were performed at ambient temperature in good to high yields. A wide range of functional groups were examined in this reaction. Remarkably, the enantioselectivity of the coupling reaction of secondary alkyl halides is low. The coupling reaction was

Scheme 19



Scheme 18



performed easily in the absence of any additives. Moreover, the chelating bopa ligand remains on the Fe center during catalysis. The synthetic efficacy of this catalyst system was exhibited through the coupling reaction of various substituted substrates (Scheme 20) [73].

Other alkylation of Grignard compounds

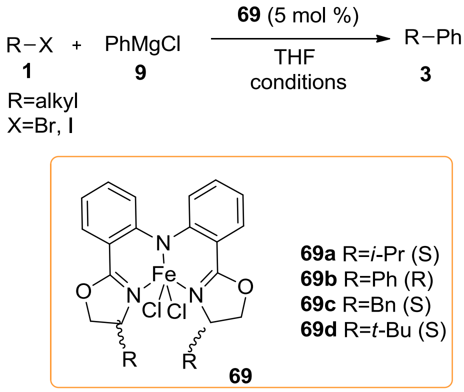
Sandfort et al. in 2017 demonstrated that a wide range of aryl coupling partners could be applied in RAE (redox-active ester) coupling reactions. Kumada coupling reactions were performed with the simple iron/DMPU (DMPU=1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) catalytic system. Decarboxylative cross-coupling reaction using redox-active esters makes carbon–carbon bonds with boronic acids, organozinc, and organomagnesium species with simplicity comparable to amide bond construction [74] (Scheme 21).

Baran et al. [75] reported cross-coupling reactions of redox-active esters (both isolated and obtained spontaneously from carboxylic acids) and organomagnesium and organozinc species using iron-based catalyst system has been accomplished with a wide range of primary, secondary, and tertiary compounds (Scheme 22).

Morandi et al. [76] established an operationally facile, extremely chemoselective catalytic approach for the C(sp^3)–C(sp^3) Kumada-type cross-coupling reaction of polyols and alkyl Grignard reagents to afford substituted alcohols (Scheme 23).

A useful synthesis of (*Z*)-9-tricosene, the sex pheromone of the housefly, was performed by the addition of one-carbon core from the easily accessible (*Z*)-erucic acid. This synthetic method contains three sequential steps, $LiAlH_4$, reduction of erucic acid, tosylation of the resultant alcohol, and Cu-mediated Kumada-type cross-coupling reaction of the tosylate with MeMgBr as the main stage [77]. Based on this method, reduction of (*Z*)-erucic acid (**81**) with $LiAlH_4$ in Et_2O at ambient temperature afforded erucyl alcohol in 96% yield. Then, alcohol **82** using tosyl chloride and pyridine in CH_2Cl_2 at room temperature was transformed into erucyl *p*-toluenesulfonate **83** in 94% yield. The last step was accomplished through Cu-mediated Kumada-type cross-coupling of the tosylate with methyl Grignard. Noticeably, CuI was used for the cross-coupling reaction of **83** with MeMgBr to provide (*Z*)-9-tricosene (**84**) in 90% yield (Scheme 24).

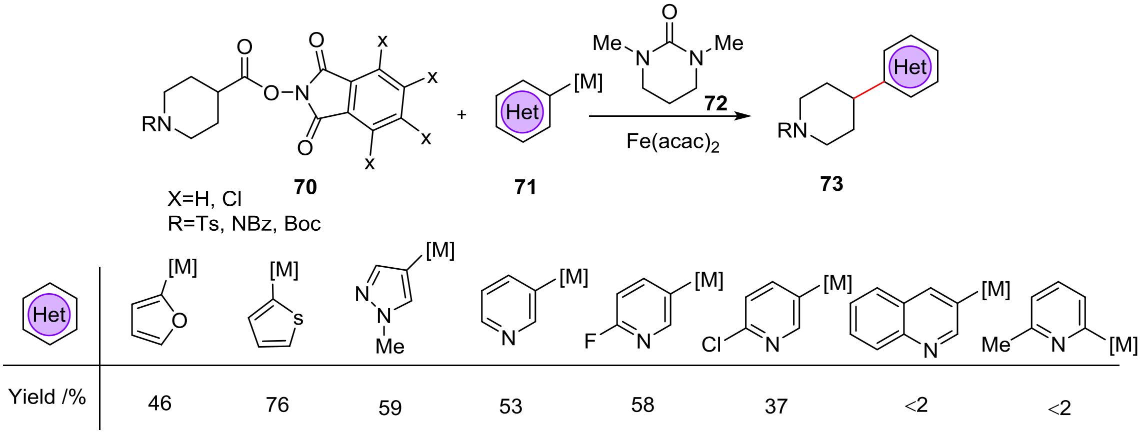
Scheme 20



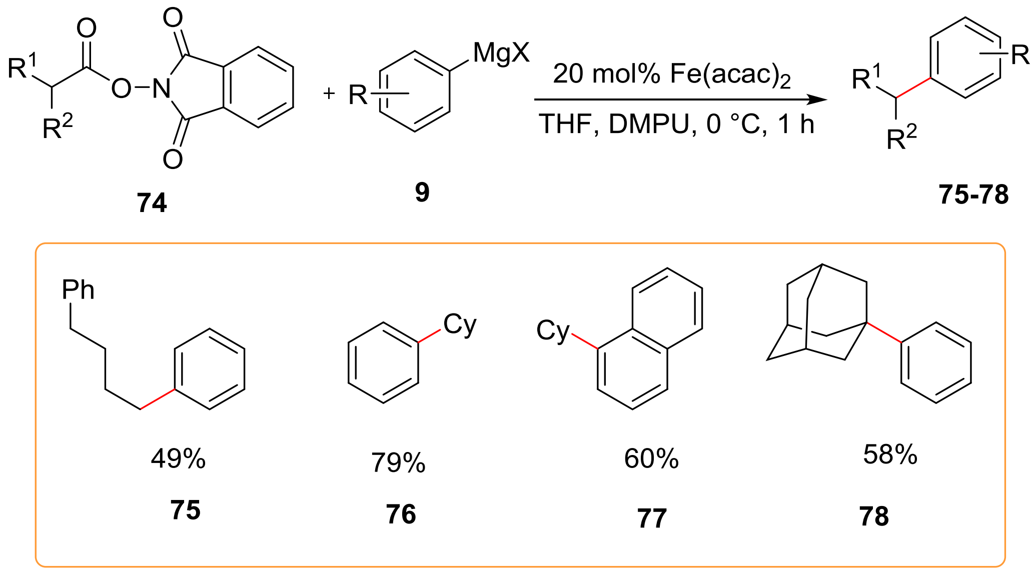
Alkenylation of Grignard compounds via alkyl halides

A unique and short synthesis of 1,3-diacetoxy-2-[2′-(2″,4″-difluorophenyl)prop-2′-en-1′-yl]propane was established in four stages from 2,3-dichloropropene (**85**) and diethyl malonate (**86**) in an overall yield of 60%. The main cross-coupling reaction of 2,4-difluorophenylmagnesium bromide with 2-(2′-chloroprop-2′-en-1′-yl)-1,3-diacetoxypropane using $Fe(acac)_3$ as catalyst afforded the target product **87** in high yield. This approach is a valuable method for the

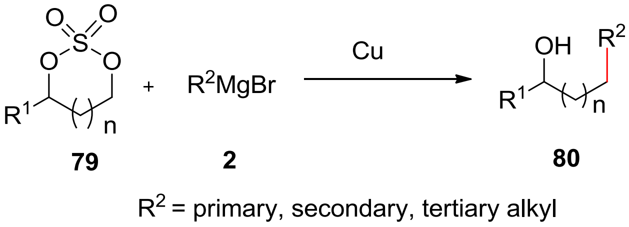
Scheme 21



Scheme 22



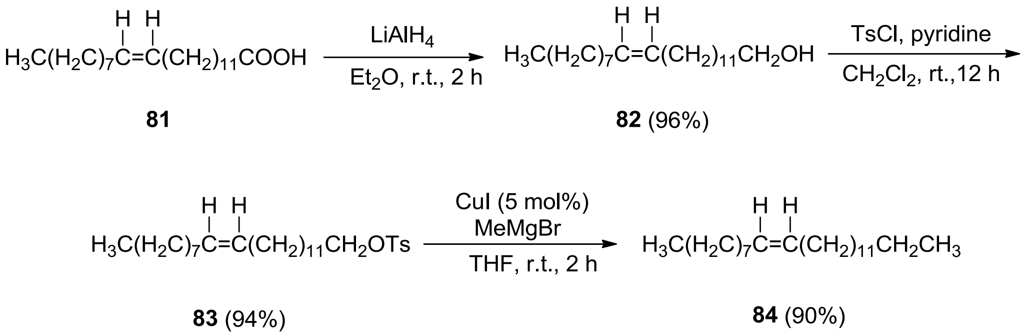
Scheme 23



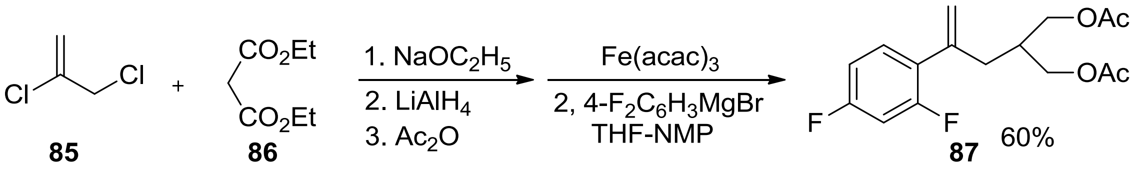
formation of its 2-(2- functionalized prop-2-en-1-yl)-1,3-diactoxypropanes (Scheme 25) [78].

C(sp^2)–C(sp^2) cross-coupling reactions between "unmasked" (oligo) olefinic precursors were the noticeable method to provide the dendralenes directly. The only preceding synthesis of [5] dendralene was the 3-sulfolene protecting method that had delivered a paltry 0.7 mg of the hydrocarbon. Since no branched triene (or higher) was market purchasable, it looked like a natural select to apply

Scheme 24



Scheme 25

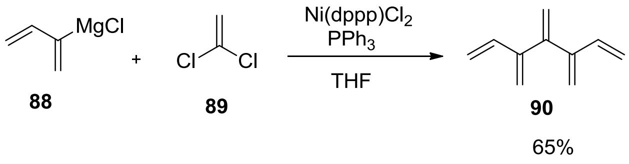


1,1-dichloroethylene as a double electrophile and the chloroprene Grignard reagent as nucleophile. The two carbons of 1,1-dichloroethylene would end up as the central C=C bond of the [5] dendralene structure and the four chloroprene carbons would become the two terminal 1,3-butadienyl residues of the hydrocarbon. The direct Kumada-type cross-coupling served very well, providing 5 g batches of the hydrocarbon (Scheme 26) [79, 80].

A useful, Ni-mediated Kumada type double cross-coupling reaction of *gem*-difluoroalkenes and 1,4- or 1,5-di-Grignard reagents was reported in 2016 by Cao et al. Based on this method, a wide range of cyclization compounds, arylmethylenecyclopentanes and arylmethylenecyclohexanes, were provided in high yields. It should be mentioned that because different *gem*-difluoroalkene derivatives can be readily synthesized from market purchasable reagents including methyl 2,2-difluoro-2-(fluorosulfonyl)-acetate (MDFA) and difluoromethyl 2-pyridyl sulfone, this approach provides an efficient method to exocyclic trifunctionalized alkenes (Scheme 27) [81].

The *trans* bromide of 2,2-dibromo-1-(2,4,6-tri-*t*-butylphenyl)-1-phosphaethene (Mes*P=CBr$_2$; Mes*=2,4,6-*t*Bu$_3$C$_6$H$_2$) was effectively functionalized with an aryl substituent through Pd Kumada–Tamao–Corriu cross-coupling method. Main construction of the 2-aryl-2-bromo-1-phosphae-thene [(*Z*)-Mes*P=C(Br)Ar] needed appropriate conditions involving optimization of the ancillary phosphine ligand, thereby retarding the dual elimination of bromides providing phos-phaalkyne (Mes*CP). Scheme 28 demonstrates the formation of 2,2-diaryl-1-phosphaethenes through palladium-catalyzed coupling reactions. Using the Kumada–Tamao–Corriu-type coupling reaction (Scheme 28(a)), the relevant phosphaethene **95** was provided in good yields. Then, compound **94a** has been treated with *p*-methoxyphenyl Grignard reagent with Pd(PPh$_3$)$_4$, to provide product **96** has been provided as a single isomer (Scheme 28(c)). Moreover, the steric inversion method was identified in the Kumada–Tamao–Corriu-type coupling reaction of **94b** and PhMgBr to provide **97** as the stereoisomer of **96** (Scheme 28(d)) [82, 83].

Scheme 26



The regioselective catalytic monoarylation reaction of the sterically encumbered *gem*-dibromophosphaethene **98** was reported through the Pd type of the Kumada–Tamao–Corriu cross-coupling approach gave 2-bromo-2-aryl-1-phosphaethenes (Scheme 29) [84].

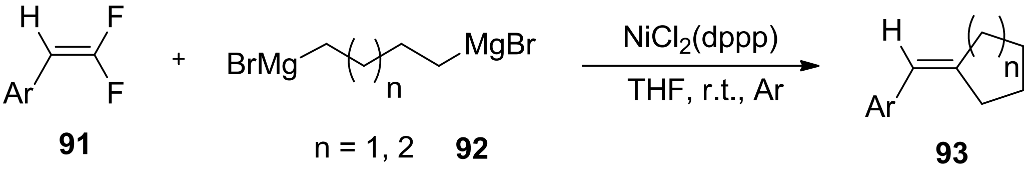
Also, arylation reaction of the 2-alkynyl-2-bromo-1-phosphaethenes using Pd type of the Kumada–Tamao–Corriu cross-coupling afforded the relevant 2-alkynyl-2-aryl-1-phosphaethenes via an inversion of the configuration. Noticeably, the bromine atom in **100** was valuable for providing *π*-functional groups into the product. All of these substrates afforded the relevant arylated compounds **101** in satisfactory yields (Scheme 30) [84].

The Pd mediated cross-coupling reaction of 3,6-dihydro-2*H*-pyran **102** and Grignard reagent in tetrahydrofuran in the presence of a catalytic quantity of Pd(PPh$_3$)$_4$ afforded the Kumada product **104** in 57% yield (Scheme 31) [85].

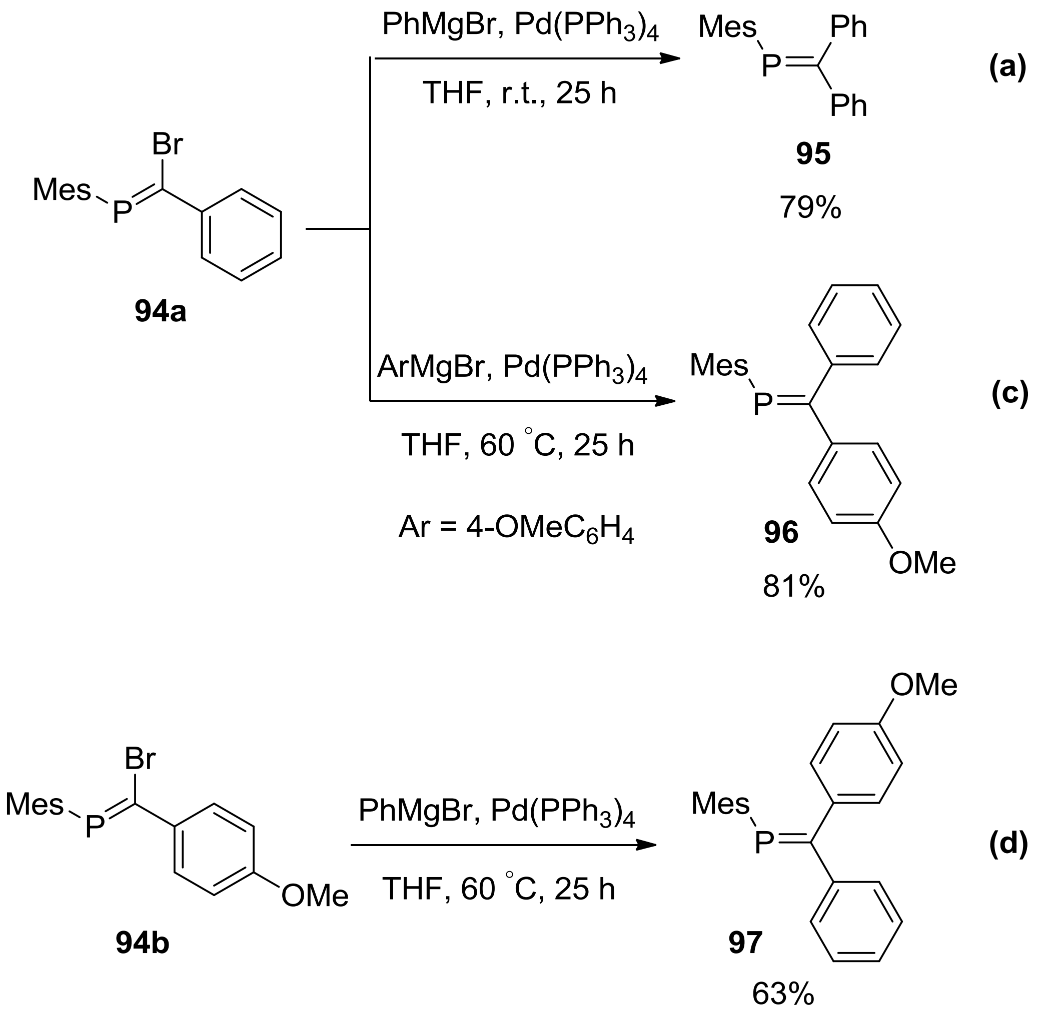
Wu et al. in 2014 reported an efficient Kumada–Tamao–Corriu cross-coupling of *gem*-di- or mono-fluoroalkenes with Grignard reagents, with or without β-hydrogen atoms, using a catalytic quantity of Pd- or Ni-based catalysts. This method afforded di-cross- or mono-cross-coupled compounds in moderate to excellent yields (Scheme 32) [86].

A probable mechanism for the nickel-mediated coupling of fluoroalkene and Grignard reagents having β-hydrogen atoms **106f**–**106j** is shown in Scheme 33. The nickel-mediated coupling reaction includes three elementary stages including oxidative addition of RF, transmetalation of RMgX, and also reductive removal of the nickel system. The mechanism of the palladium-mediated coupling of fluoroalkene and Grignard reagents without β-hydrogen atoms **106a**–**106e** is almost the same as that of the nickel-mediated coupling reaction. It was demonstrated that once primary and secondary alkyl Grignard reagents that contain β-hydrogen atoms were applied as coupling partners with organic halides, that aside from their relevant cross-coupling

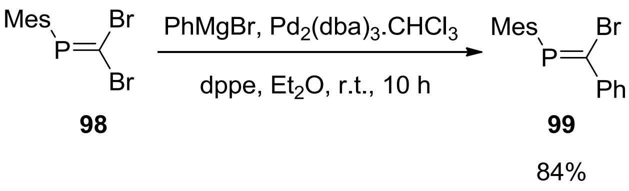
Scheme 27



Scheme 28



Scheme 29



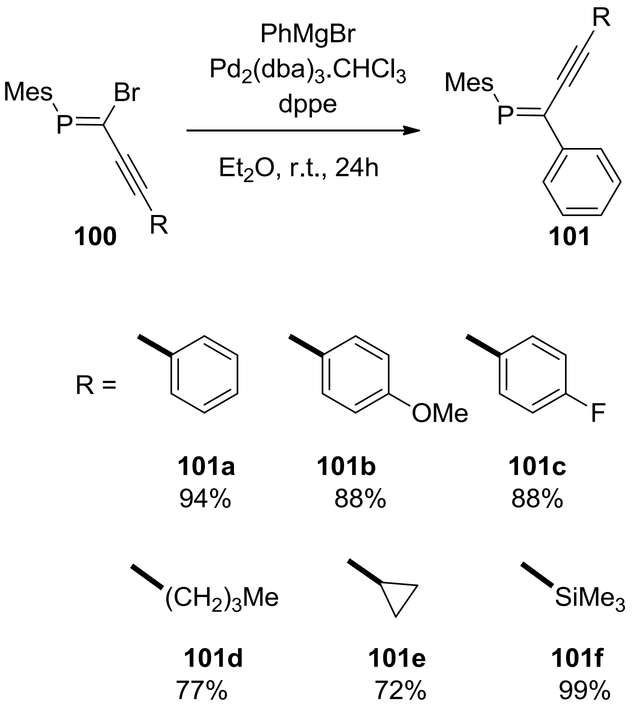
products, a small quantity of reduction product was detected (Scheme 33) [87–89].

Gangula et al. [90] reported the formation of (2*R*,7*R*,*E*)-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-*N*,*N*,8-trimethylnon-4-enamide (**110**) through Kumada cross-coupling reaction (Scheme 34).

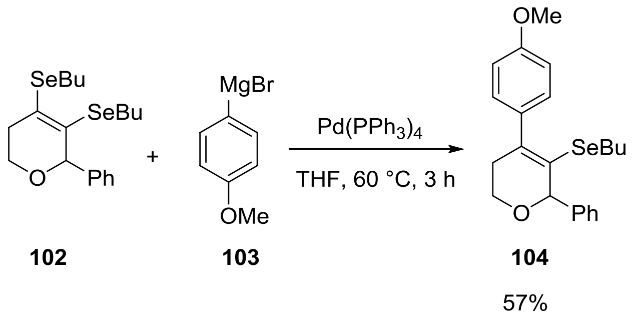
As shown Scheme 35, in this coupling reaction upon addition of R^2Cl solution, the Fe(acac)$_3$ and NMP catalyst spontaneously treat with Grignard regent and make the active catalyst Ar[Fe^0(MgCl)]. Then, the active catalyst treats with R^2Cl and transmetalation followed by reductive removal reactions occur giving the coupling product **110**. In this cycle the active iron catalyst recreates and is continuously included in the coupling reaction provides the coupling product **110** [90].

Short and effective syntheses of (7*Z*,11*Z*,13*E*)-hexadecatrienal, a sex-pheromone component of the citrus leaf miner, and (8*E*,10Z)-tetradecadienal, the sex pheromone of the horse-chestnut leaf miner were demonstrated in 2012 by Tao et al. [91]. In this method, Kumada cross-coupling reaction was known as one of the essential reactions for the formation of (7*Z*,11*Z*,13*E*)-hexadecatrienal. This synthetic method afforded excellent overall yield (26% of the former and 23% for the latter) and excellent isomeric purity (97% for the former and 99% for the latter). Asymmetric synthesis of (7*Z*,11*Z*,11*E*)-hexadecatrienal (**115**)

Scheme 30



Scheme 31

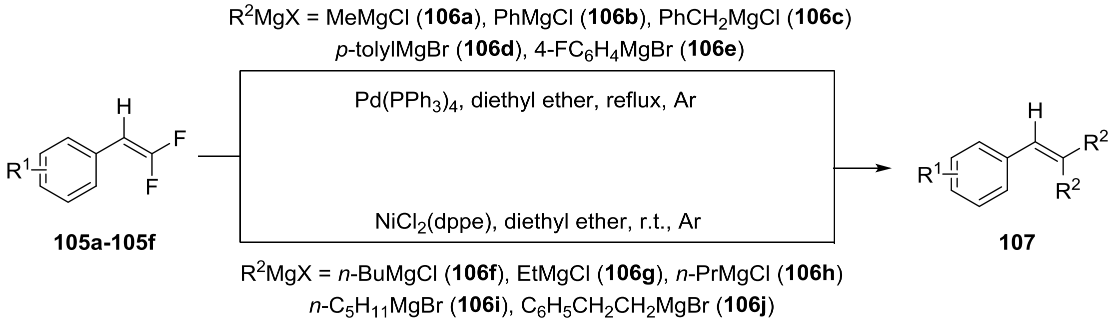


has been initiated from 7-bromo-(4*Z*,6*E*)-heptadienal (**111**). The ylide, synthesized from phosphonium salt **112** by reaction with potassium bis(trimethylsilyl) amide as base in dry tetrahydrofuran, treated with aldehyde **111** to provide tetraene **113** in 85% yield and 98% isomeric purity [92]. Kumada cross-coupling reaction of tetraene **113** with EtMgBr through catalysis of NiCl$_2$(dppp) in dry tetrahydrofuran at ambient temperature afforded tetraene **114** in 93% yield and 97% isomeric purity [93]. Then, upon two steps, the target product **115** has been synthesized in 52% yield (Scheme 36).

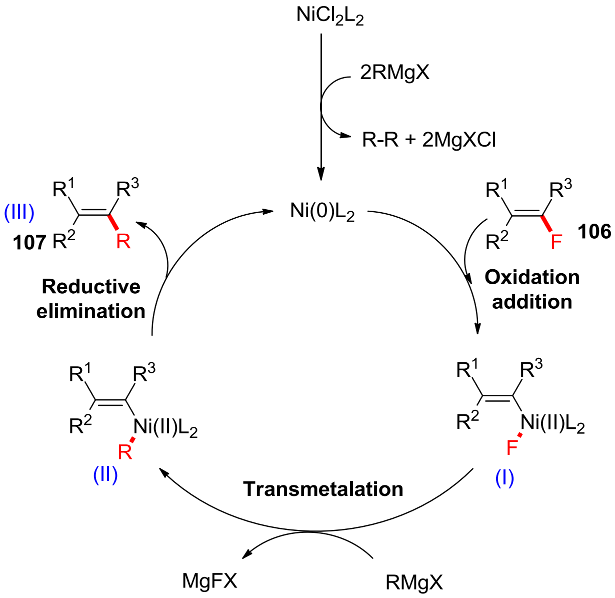
On the other hand, for the synthesis of (8*E*,10*Z*)-tetradecadienal, aldehyde **116** has been reacted with Zn-modified cyanoborohydride and (*p*-tolylsulfonyl)hydrazine in MeOH to provide diene **117** in 72% yield [94]. Kumada cross-coupling reaction of diene **117** with (6-hepten-1-yl) magnesium bromide synthesized from bromide in dry tetrahydrofuran at ambient temperature afforded triene **118** in 91% yield and 99% isomeric purity [93]. Upon two steps, (8*E*,10*Z*)-tetradecadienal (**119**) has been synthesized in 47% overall yields from aldehyde **116** (Scheme 37).

Useful and improved methods for the construction of 7-bromo-(*Z*,*E*)-4,6-heptadienal by palladium(II)-mediated coupling reaction were established in 2013 by Tao et al. [95]. A significant and asymmetric synthesis of (*Z*,*E*)-9,11-hexadecadienal, the main pheromone component of the sugarcane borer, Diatraea saccharalis, was performed in 38% overall yield. Relied on this approach, masking of aldehyde **116** with trimethyl orthoformate-sulfuric acid at ambient temperature gave the relevant acetal **120** in 95% yield [96]. Next, Kumada cross-coupling reaction of acetal **120** and 1-BuMgBr in dry tetrahydrofuran (THF) at ambient temperature gave acetal **121** in 92% yield and > 98% isomeric purity [97]. Upon several steps, (*Z*,*E*)-9,11-hexadecadienal (**122**) has been synthesized in 38% overall yield from aldehyde **116** (Scheme 38).

Scheme 32



Scheme 33



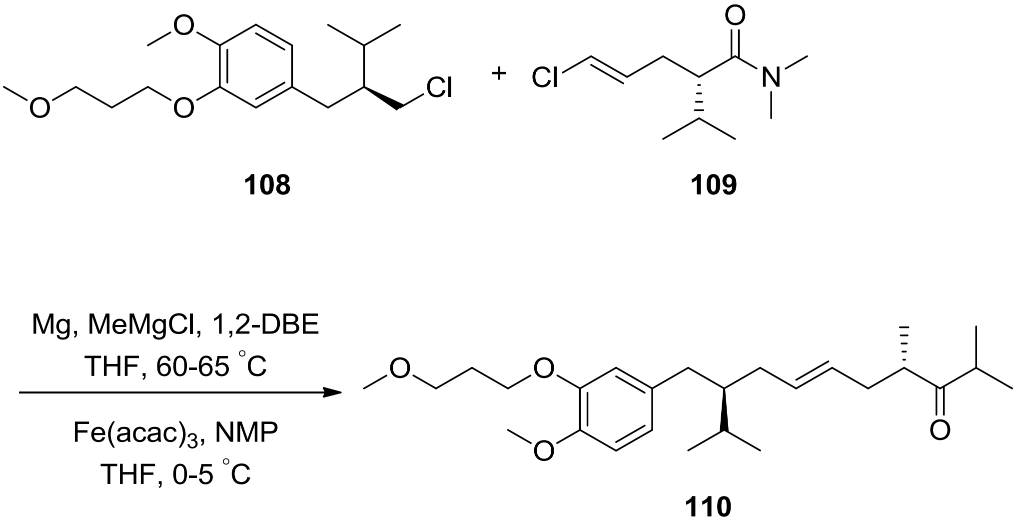
Other alkenylation of Grignard compounds

Using Pd-mediated Kumada–Corriu cross-coupling reactions the desired 4-functionalized 1,2-oxazines were synthesized in moderate yields. They exhibit the synthetic potential of the newly synthesized enantiopure 4-functionalized 1,2-oxazines [98]. Then, this group tried on the functionalization of nonaflates and enol phosphates **123** through Pd-mediated cross-coupling reactions. Firstly, it was selected two previous methods of Begtrup [99, 100] and Skrydstrup [101] demonstrating the application of enol phosphates in Pd-mediated Kumada-Corriu coupling reactions. Reaction of *syn*-**123** with PhMgCl using PdCl$_2$(PPh$_3$)$_2$ under reflux in tetrahydrofuran afforded the 4-phenyl-functionalized 1,2-oxazine derivative *syn*-**124** in only 30% yield. Under ligand-free palladium(II) chloride-mediated conditions no better result has been detected and the desired product *syn*-**124** was provided in 25% yield (Scheme 39).

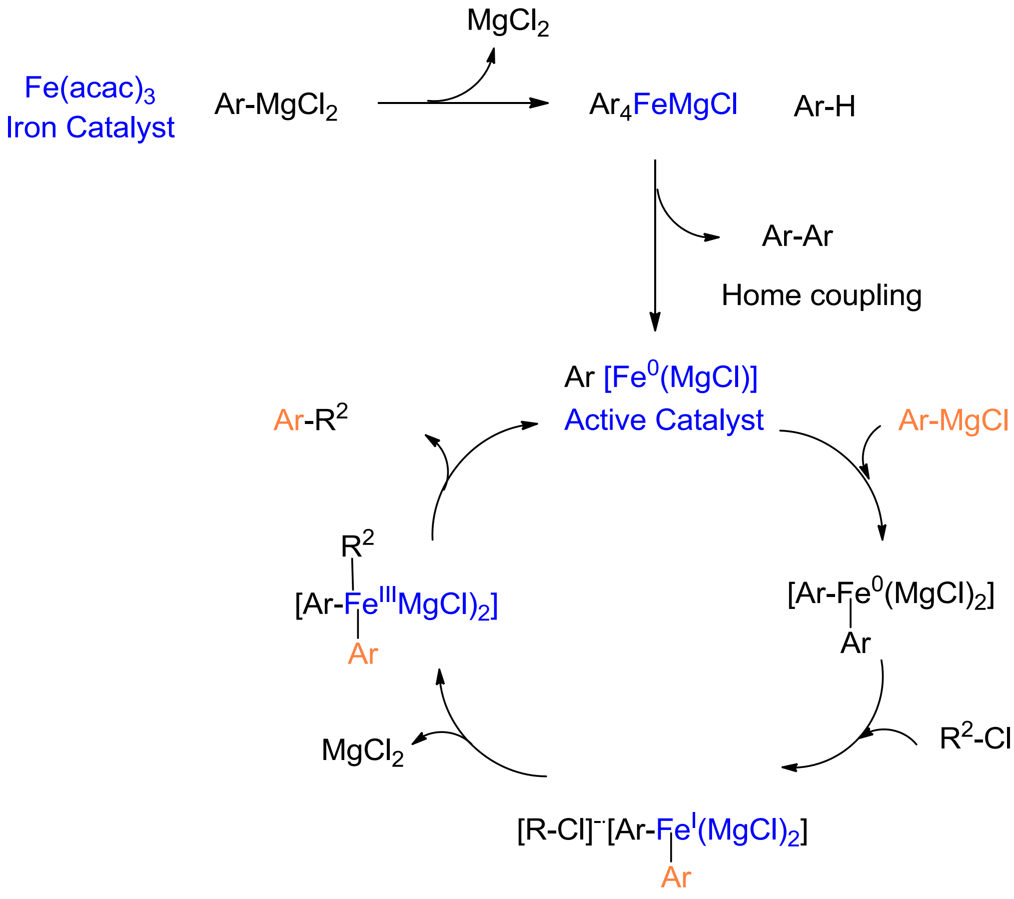
The Kumada–Corriu coupling reaction was successfully improved under MWI [102]. 1,2-Oxazine *syn*-**125** and phenylmagnesium chloride or 4-MeOC$_6$H$_4$MgBr using Pd(PPh$_3$)$_4$ under MWI giving *syn*-**126** and *syn*-**127**, respectively, in 46–57% yield. A control test occurred with *syn*-**125** and phenylmagnesium chloride afforded a considerably poorer yield (35%) of the anticipated product *syn*-**126**, demonstrating that conventional heating in tetrahydrofuran under reflux for one day is less effective. Moreover, diastereomer *anti*-**125** was subjected to the microwave-assisted coupling conditions and it supplied the relevant 4-aryl-functionalized *anti*-**126** and *anti*-**127** in good yields (55–64%). Efforts to perform the Kumada–Corriu reaction with Ni catalysts were inadequately unsatisfactory; they afforded the desired 4-aryl-functionalized 1,2-oxazines in less than 10% yield (Scheme 40) [103–105].

Alkenyl and (hetero)aryl nonaflates are well developed constituents in a wide range e of Pd-mediated conversions [106]. Hence, it was examined one of the 1,2-oxazin-4-yl nonaflates as substrate in the Kumada–Corriu coupling reaction. Pleasantly, nonaflate *syn*-**128** and 4-MeOC$_6$H$_4$MgBr using PdCl$_2$(PPh$_3$)$_2$ treated even at ambient temperature to give the cross-coupling compound *syn*-**129** in 61% yield (Scheme 41).

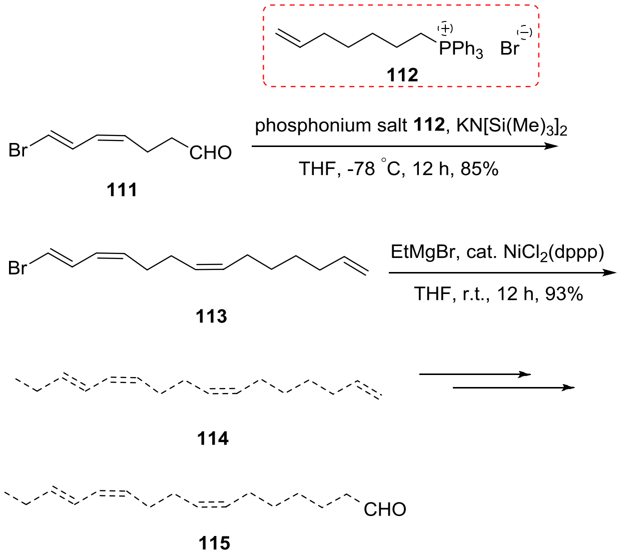
Scheme 34



Scheme 35



Scheme 36



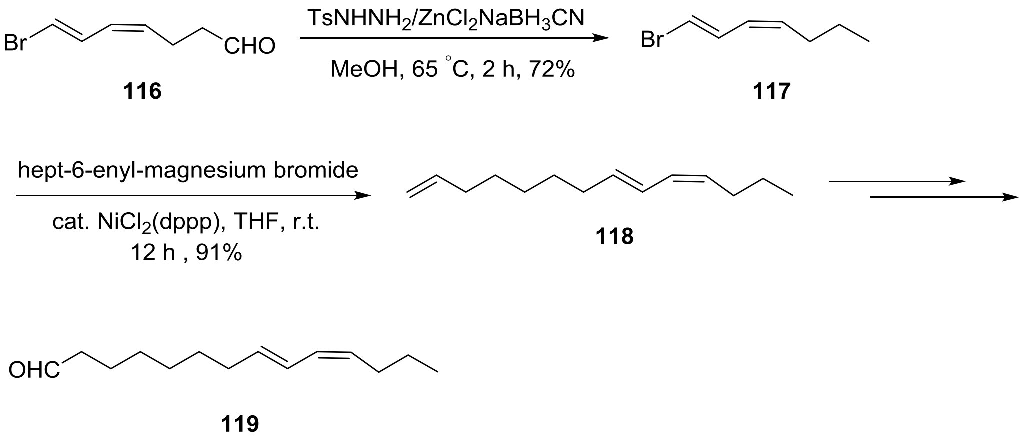
Arylation of Grignard compounds via aryl halides

Arylation of Grignard compounds via aryl bromides

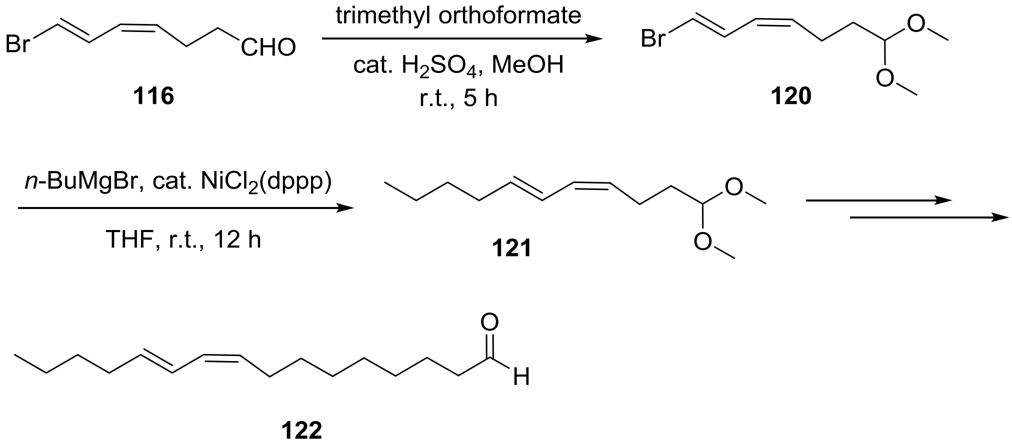
Ni-mediated couplings of arylhalides with *tert*-alkyl Grignard reagents were achieved in 2016 by Ando et al. This original bicyclic NHC ligands reduced the construction of isomerized products, and it was known that that NMP as a co-solvent suppressed the reduction method. Based on the optimized reaction conditions, the catalyst loading was decreased to 0.5 mol%, and catalyst loading using *ortho*-functionalized aryl bromides was also applicable at the level of 2.0 mol%. This group demonstrated the Kumada–Tamao–Corriu coupling reaction of aryl bromides with *tert*-alkyl Grignard reagents in the presence of the original NHC-Ni catalyst. DHASI-type NHC ligands successfully suppressed the ways providing the isomerized product (Scheme 42) [107].

Two dichlorido-tetrakis-(*N*-*R*-imidazole)nickel(II) systems (R = 2,6-diisopropylphenyl; methyl) were formed in

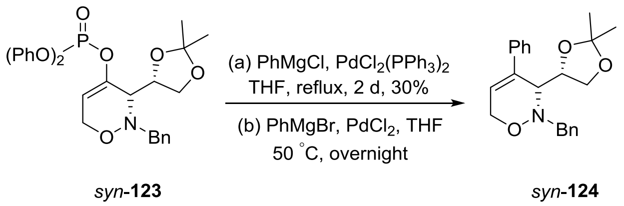
Scheme 37



Scheme 38



Scheme 39

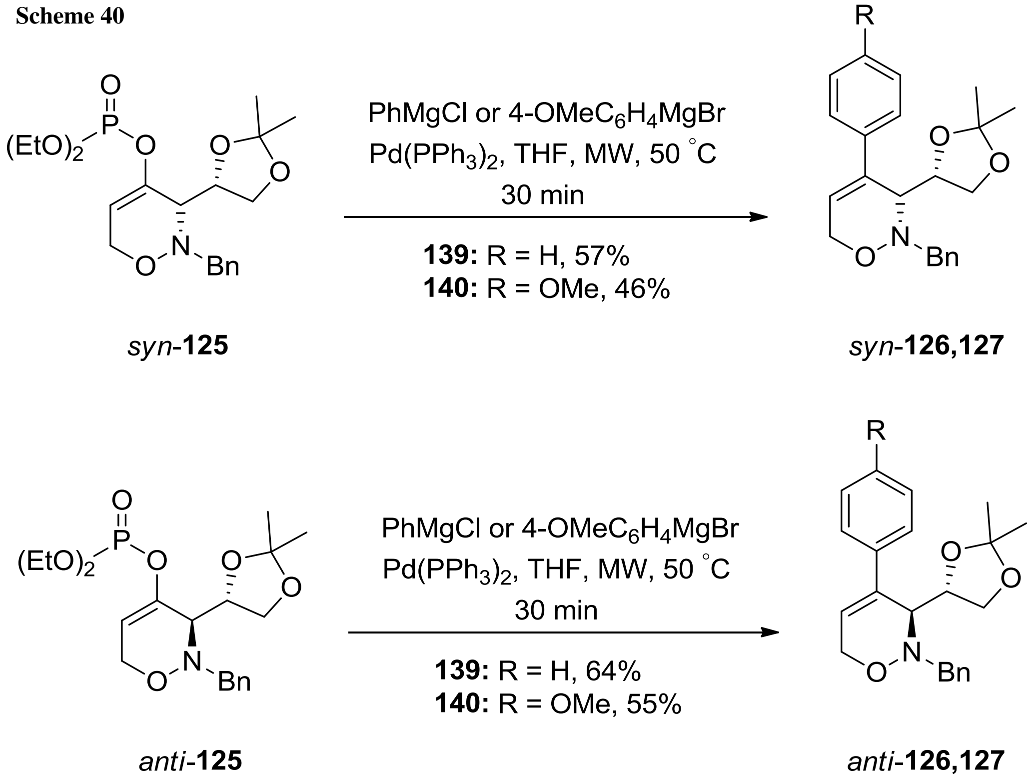


2011 by Matt et al. [108]. Both systems exhibited excellent properties in Kumada–Tamao–Corriu cross-coupling reaction of arylhalides and arylgrignards (Scheme 43).

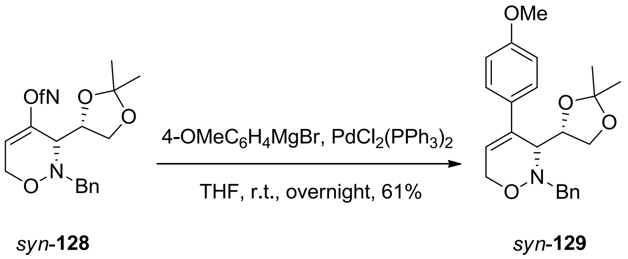
Generally, complex **137** exhibited very satisfactory property for Kumada–Corriu-type cross-coupling. It was realized that NHSi–NHC supported nickel(II) complex **137** can successfully mediate the cross-couplings of 4-MeC$_6$H$_4$MgCl and aromatic halides (yields: >99%) (Scheme 44) [109].

The initial instance of ligand-controlled site-selective Kumada–Tamao–Corriu coupling reaction has been reported by Manabe and Ishikawa [26] and used dihaloarene substrates with Grignard reagents [110]. Reaction of 2,4-dibromophenol with excess Grignard reagent using Pd$_2$(dba)$_3$ and hydroxy-functionalized terphenylphosphine (Ph-HTP) [111] improved coupling ortho to the hydroxy group to provide **139** with high selectivity. Since electron-donating hydroxy substituents that are transformed into more electron-donating oxido groups using a strong base, commonly retard oxidative addition of ortho C–X bonds, it is significant that Ph-HTP improved this conversion to reach completion in 2 h. Changing the Ph-HTP ligand with DPPF reversed the siteselectivity toward the para C–X bond to make

Scheme 40



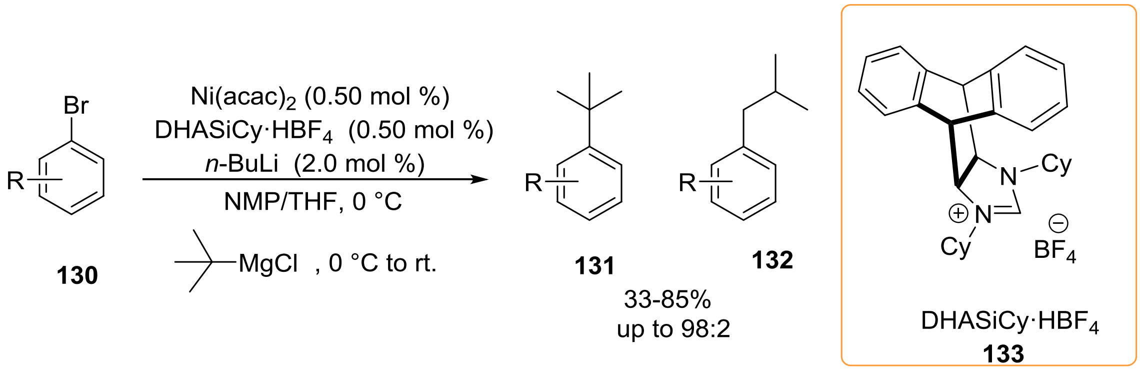
Scheme 41



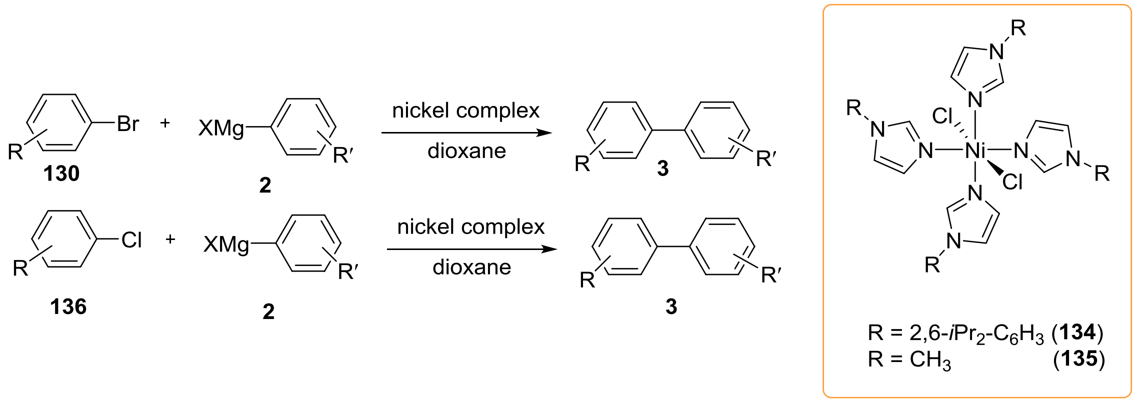
isomer **140**. It should be mentioned that the di-cross-coupled product, in which both bromo substituents were substituted with 4-methoxyphenyl substituents, has been provided in just less than 5% yield despite the presence of excess Grignard reagent. The para-selectivity showed in the DPPF-based catalytic system can be related to steric effects; that is, oxidative addition happens preferentially at the less sterically hindered position *para* to the hydroxy group. Instead, this reasoning does not clarify the high reactivity and exclusive *ortho*-selectivity of the Ph-HTP-based catalytic system (Scheme 45) [112].

A unique copolymer obtained from 2,7-carbazole with thiophene was reported in 2013 by Pablo Soto et al.

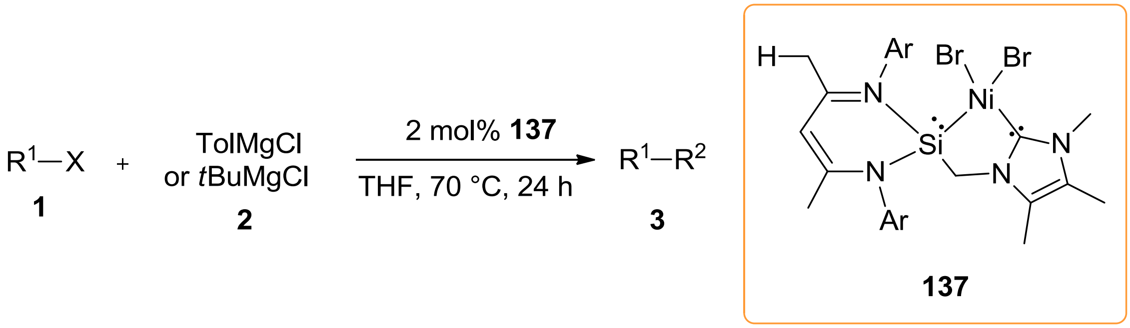
Scheme 42



Scheme 43



Scheme 44



[113]. This copolymer was provided via the formation of 2,7-dibromo-*N*-methylcarbazole and 2-bromothiophene through a Kumada-type reaction to link both rings and with two various types of palladium catalysts, [Pd(OAc)$_2$] and [Pd(PPh$_3$)$_4$], with important variances in their yields. The consequences provided for the coupling reaction of this product and the Grignard reactant provided from the Kumada coupling display 83.0% for Pd(PPh$_3$)$_4$ and 18.3% for Pd(OAc)$_2$. Relied on these yield values, the best catalyst for bonding these systems is [Pd(PPh$_3$)$_4$] (Scheme 46).

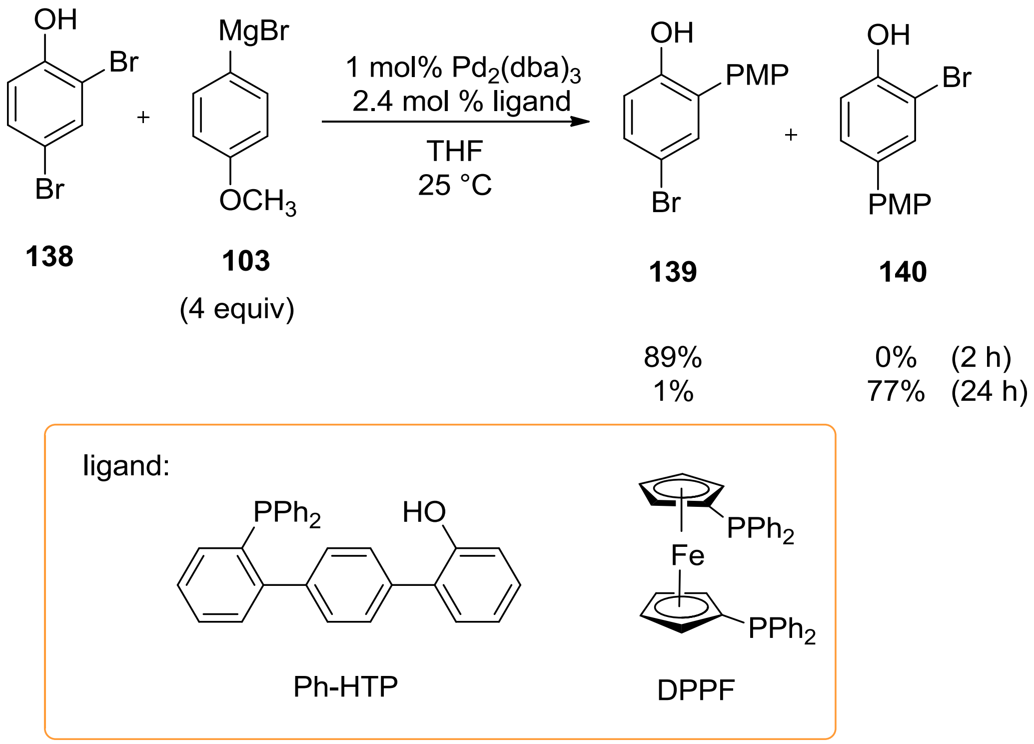
Nolan et al. in 2014 reported the application of [Pd(IPr*$^{\text{OMe}}$)(cin)-Cl] as a significant and useful catalyst in the Kumada–Corriu coupling. In spite of the great activity of this catalyst, some challenges remain in cross-couplings, predominantly concerning the application of aryl chlorides in the formation of tetra-ortho-functionalized biaryls and the coupling reaction of tri- and tetra-functionalized vinyl Grignard reagents (Scheme 47) [114].

Kumada coupling reaction of the 2,6-dibromobiphenyls with phenylethynylmagnesium bromides in THF easily afforded the 2,6-bis(phenylethynyl)biphenyls **148**. The catalyst (Ph$_3$P)$_2$PdCl$_2$ was applied for compounds **147a** and **147b** (Scheme 48) [115].

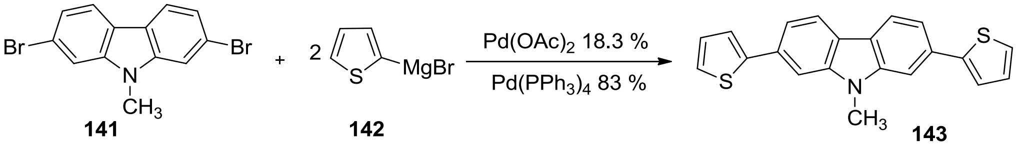
N-Heterocyclic carbene ligands obtained from C2-symmetric diamine having naphthyl side chains were introduced as chiral monodentate ligands, and their Pd systems (NHC)Pd(cin)Cl were synthesized in 2013 by Dorta et al. These compounds were applied in the enantioselective Kumada coupling to produce chiral biaryls in excellent yield and good selectivity. [(*Sa*,*Sa*)-**149**] was examined in the enantioselective Kumada coupling that provided chiral biaryls in excellent yields and poor to good e.e.s. It should be mentioned that precatalysts [(*Ra*,*Ra*)-**149**] and [(*Ra*,*Ra*)-**150**] were failed in this reaction [116]. Next, precatalyst (*Sa*,*Sa*)-**149** improved the enantioselective Kumada coupling easily affording the chiral biaryls in moderate yields but moderately poor selectivity (Scheme 49).

The formation of some nickel(II) systems **150a–150j** with H$_2$L tridentate (ONO) Schiff-base ligand [2-[(2-oxybenzylidene)amino]phenolate] were achieved by Kuchtanin et al. [117]. Some complexes were applied as catalysts for Kumada–Corriu cross-couplings and demonstrated a good catalytic property in the formation of biaryls. The catalytic property of nickel(II) systems **150a–150d**, **150g**, and **150j** was easily tested in Kumada-Corriu cross-coupling [22], which is still one of the most striking approaches for the construction of biphenyls [118–122]. 4-Bromoanisole and

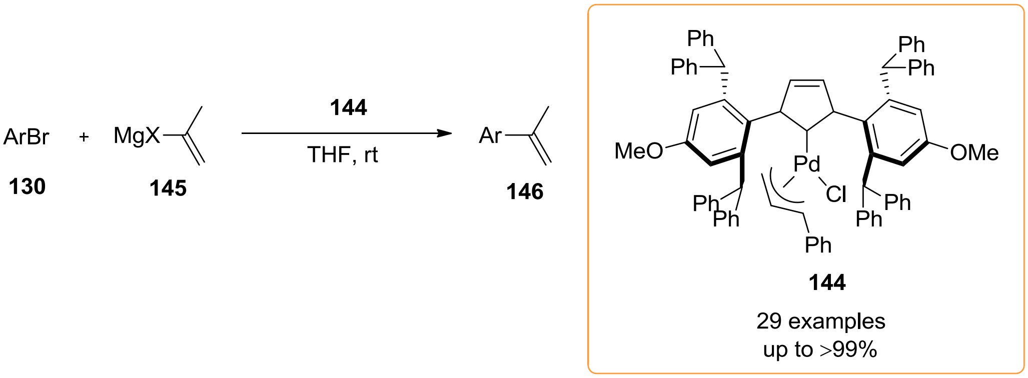
Scheme 45



Scheme 46

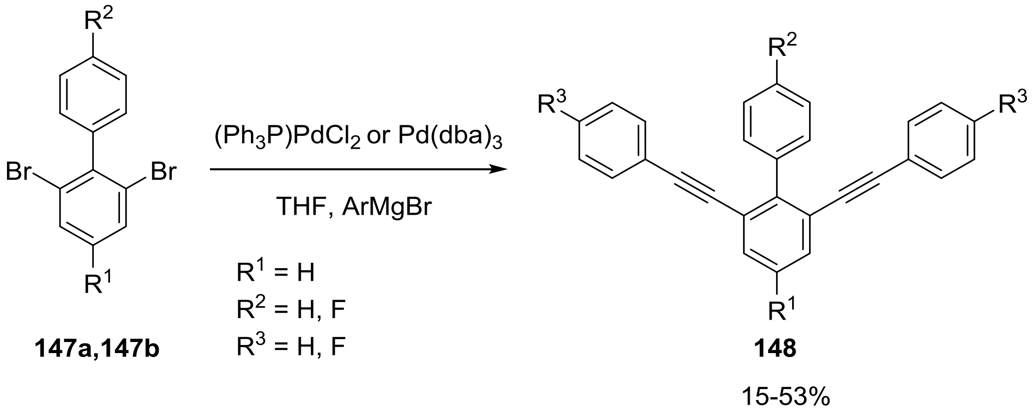


Scheme 47

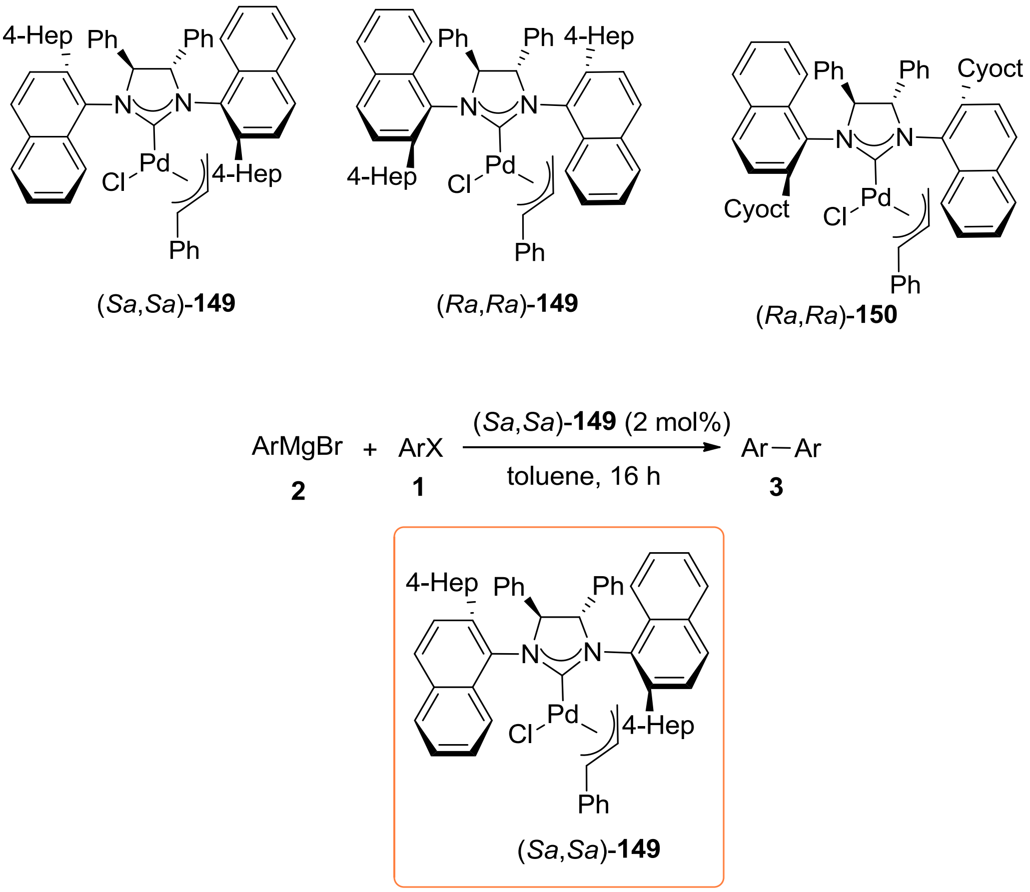


PhMgBr (**9**) have been selected as initial model substrates. Three of the examined systems **150a**, **150c**, and **150d** demonstrated moderate catalytic property, and the corresponding product 4-methoxybiphenyl was provided in 65–70% yields, in spite of various ligands applied. Besides, the yields were even higher than that with Ni(dppp)Cl_2 (57%). On the

Scheme 48



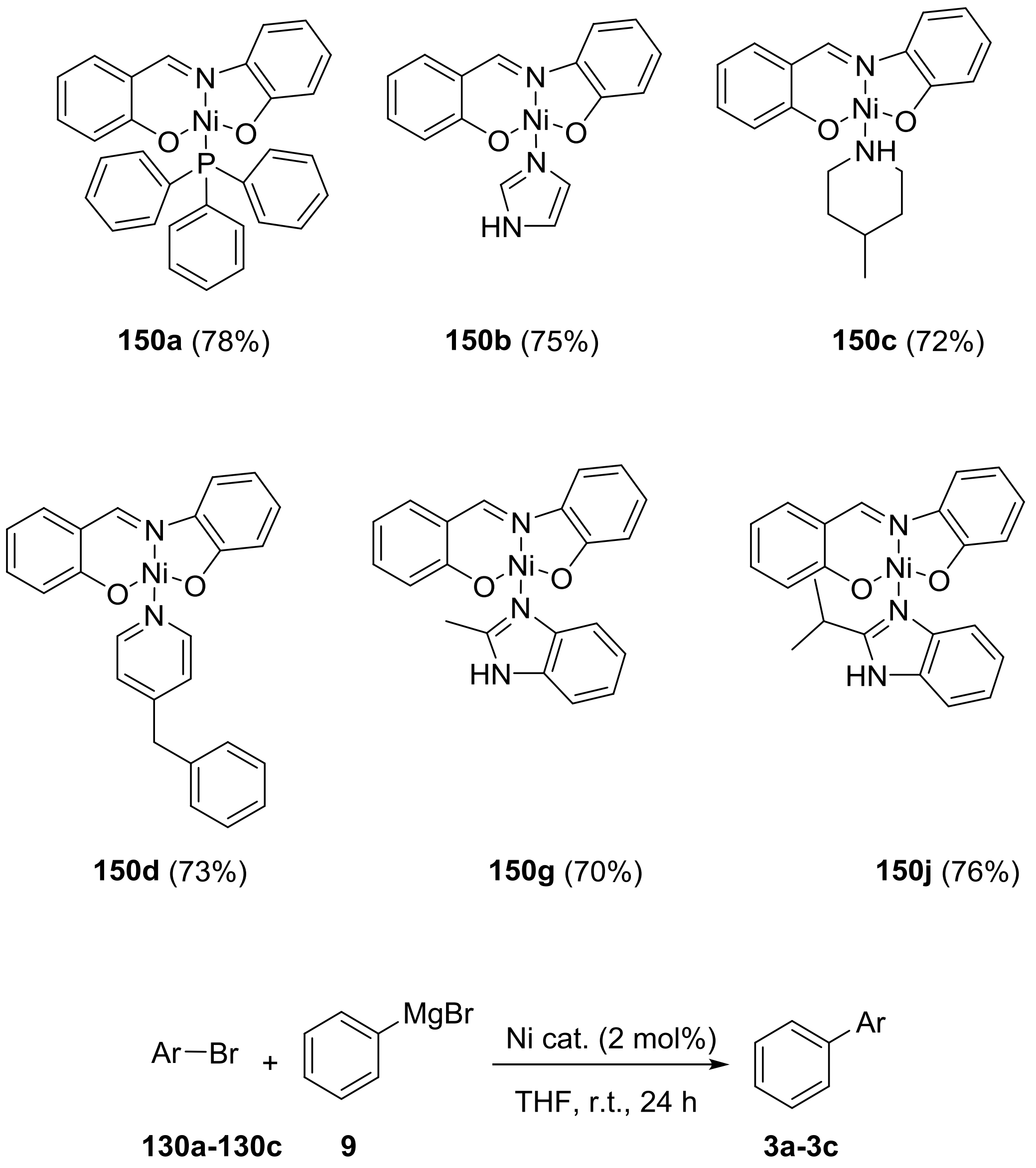
Scheme 49



other hand, complexes **150b**, **150g** , and **150j**, having the imidazole and the benzimidazole ligands were less active (Scheme 50).

A common synthesis of systems [Ni(Cp)(X)(NHC)] from a Ni halide, CpLi, and a carbene solution was demonstrated in 2016 by Buchowicz et al. [123]. This method gives unprecedented systems with ring-expanded NHC ligands (RE-NHC) of six- **154a**, **154b**, seven- **154c**, and eight-membered **154d** heterocycles. Complexes **154a**–**154e** were efficient pre-catalysts in Kumada–Tamao–Corriu coupling

Scheme 50

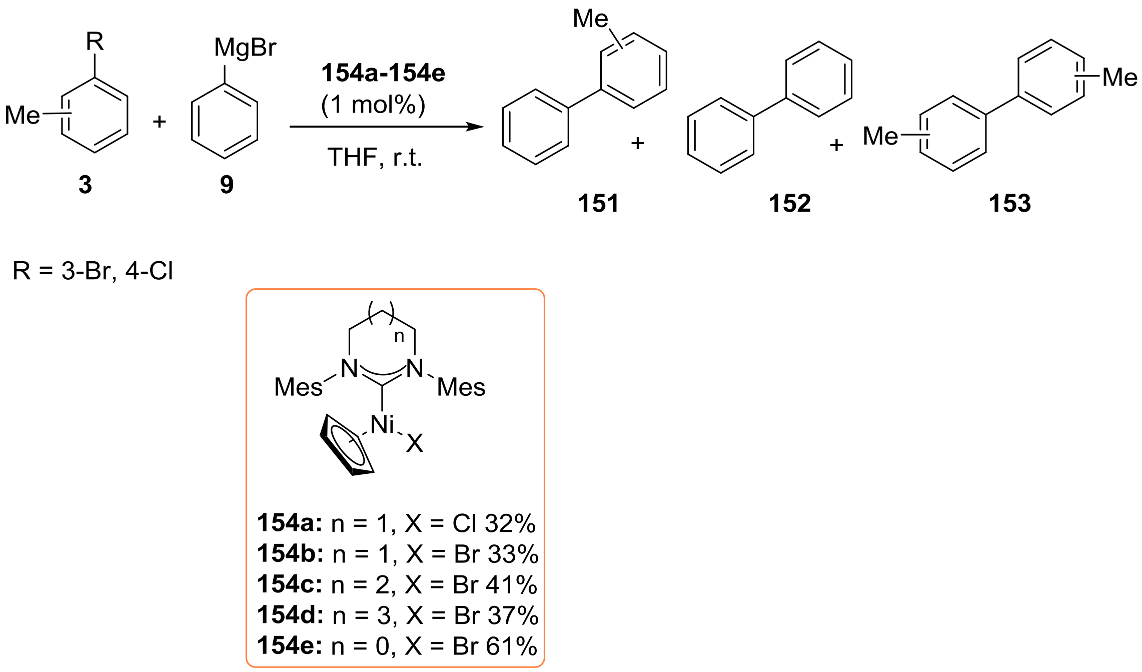


reaction with maximum activity detected for complexes having the six-membered NHC. In order to attain insight the effect of NHC ring expansion on the activity of [Ni(Cp)(X)(NHC)] in Kumada–Tamao–Corriu coupling, this group examined complexes **154a**–**154e** in reactions of phenylmagnesium bromide with halotoluenes (3-bromotoluene, 4-chlorotoluene). Expansion of the NHC ligand from a five- to six-membered ring demonstrated to be useful for the catalytic property. Catalyst loading of only 1% mol of **154a** or **154b** is appropriate to accomplish conversions over 95% with very moderate selectivity at ambient temperature (Scheme 51) [124].

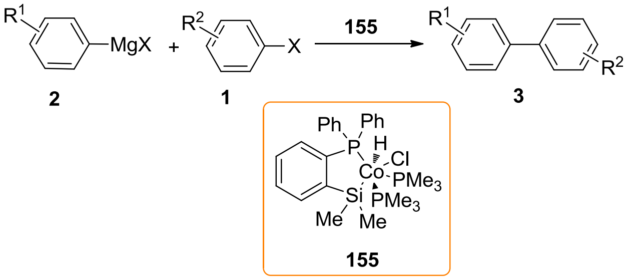
Sun et al. in 2017 reported the construction of silyl [P,Si]-chelate cobalt complex **155**. The catalytic activity of silyl Co(III) hydride, $CoHCl(PMe_3)_2(1\text{-}Si(Me)_2\text{-}2\text{-}(PPh_2)C_6H_4)$ (**155**) was examined for the Kumada couplings. Using a load of 2 mol% of catalyst, system **155** exhibited moderate to high catalytic activity for the treatments of aryl bromides or aryl chlorides with Grignard reagents (Scheme 52) [125].

Three resorcinarene-cavitands having a 3-R-1-imidazolylium group (*R* = alkyl) grafted to the wider rim of the cavitand **156a**–**156c** were used in the Kumada–Tamao–Corriu cross-coupling reaction of aryl halides and arylmagnesium halides. Their mixture with $[Ni(cod)_2]$ (cod = 1,5-cyclooctadiene; 1:1 stoichiometry) led to extremely effective catalysts, the activities of which varied in the following order: *R* = *n*-propyl (**156a**) isopropyl (**156b**) ≈ benzyl (**156c**).

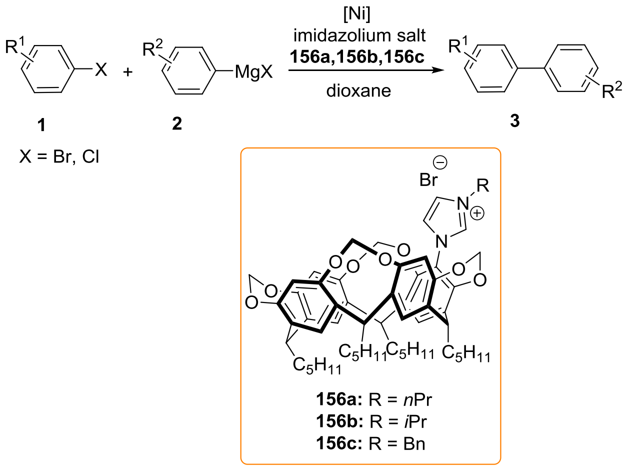
Scheme 51



Scheme 52



Scheme 53

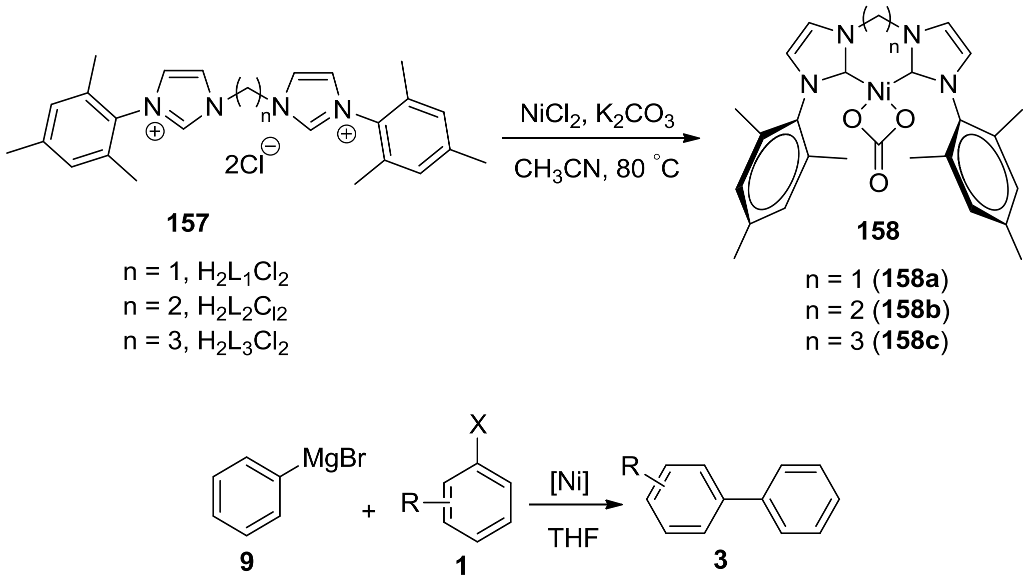


Catalytic Kumada–Tamao–Corriu cross-coupling reactions were performed with a series of aryl halides (chlorides and bromides), and two aryl Grignard reagents, phenylmagnesium bromide and *o*-TolMgCl. The catalytic complexes that were anticipated to include NHC systems, were all provided spontaneously by mixing the imidazolium salt with a suitable Ni precursor (Scheme 53) [126].

Reactions of alkane-bridged ($n = 3$) di-NHC precursor, bisimidazolium chlorides with the nickel(II) chloride using potassium carbonate in CH_3CN afforded the relevant 16-electron binuclear complex of the type Ni(di-NHC)(μ-O)$_2$CO in good yield. The catalytic activities of the systems were examined in the Kumada reaction for cross-coupling reaction of PhMgBr with a wide range of aryl halides. The complex **158c** displays the best catalytic property in these reactions. In this route, alkyl halides (bromides and chlorides) having various electronic and steric properties were selected in the reactions with complex **158c** as catalyst. The consequences exhibited that the complex **158c** can mediate the reaction with more reactive aryl bromides, but also can mediate the reaction in moderate to excellent yield with less reactive aryl chlorides. Although, the reaction with aryl bromides usually went completion quicker and afforded increased yield than that with aryl chlorides (Scheme 54) [127].

Air stable nickel(II) and palladium(II) systems viz. [Ni(LS)(P(OEt)$_3$)] (**159**), [Ni(LN)(P(OEt)$_3$)], [Pd(LS)(P(OEt)$_3$)] (**160**), and [Pd(LN)(P(OEt)$_3$)] (where LS and LN are dianions of *N*-(2-mercaptophenyl)

Scheme 54



157

n = 1, $H_2L_1Cl_2$
n = 2, $H_2L_2C_{l2}$
n = 3, $H_2L_3Cl_2$

158

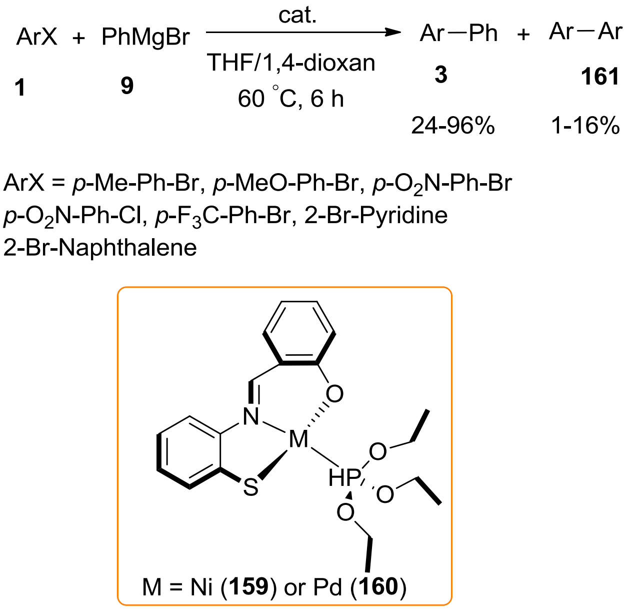
n = 1 (**158a**)
n = 2 (**158b**)
n = 3 (**158c**)

9 **1** **3**

salicylideneimine and *N*-(2-mercaptophenyl)naphthylideneimine, respectively) were formed in 2012 by Karvembu et al. [128]. These nickel(II) and palladium(II) systems showed moderate catalytic property in Kumada–Tamao–Corriu coupling reaction. Complex **159** was used in the Kumada–Tamao–Corriu coupling reaction. The catalytic activity of the nickel(II) **159** and palladium(II) **160** systems for Kumada–Tamao–Corriu reaction was examined. It was realized that nickel(II) complex **159** display improved activity in comparison with palladium(II) system **160**. Among the two nickel(II) complex **159** was effective and applied for Kumada–Tamao–Corriu reactions with various aryl halides. Complex **159** produced 91% conversion of 4-bromoanisole in Kumada–Tamao–Corriu reaction. Using 0.5 mol% of **159**, 1-bromo-4-(trifluoromethyl) benzene, 2-bromopyridine, and 2-bromonaphthalene were transformed into relevant biaryl compounds with 89, 97, and 82% conversion, respectively (Scheme 55).

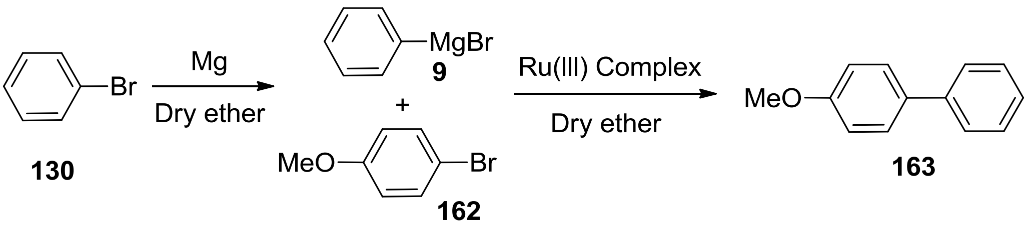
Ru(III) Schiff base systems with 2-acetylpyridine thiosemicarbazone/semicarbazone were formed in 2012 by Viswnathamurthi et al. These systems were realized to be significant catalyst for transfer hydrogenation and Kumada–Corriu coupling reactions. In this method, the coupling of PhMgBr and 4-bromoanisole afforded 4-phenylanisole as the product. Bromobenzene was first transformed into the relevant Grignard reagent. Next, 4-bromoanisole provided 28–48% yield of 4-phenylanisole. The current catalyst systems are able to couple aryl bromides with aryl Grignard reagents at ambient temperature in a low catalyst loading for moderate yields (Scheme 56) [129].

Scheme 55

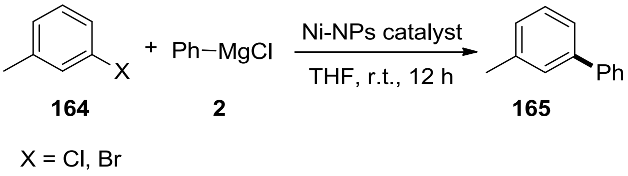


In 2013, Kobayashi et al. established heterogeneous polymer-incarcerated Ni nanoparticles (NPs) that mediate cross-coupling reactions. The Ni-NPs were effectively used to Corriu–Kumada–Tamao reactions with a wide substrate scope involving functional group tolerance. Under the optimal condition, the generality of the Corriu–Kumada–Tamao reaction was investigated. Based on this method, both electron-rich and electron-deficient aryl substrates for aryl halides served well in this reaction (Scheme 57) [130].

Scheme 56



Scheme 57



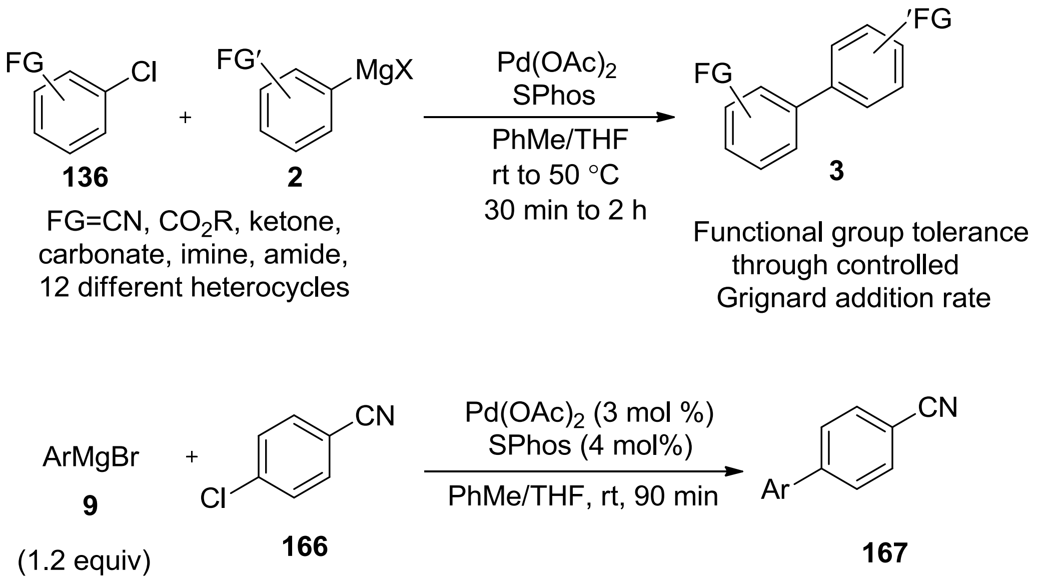
Arylation of Grignard compounds via aryl chlorides

Newman et al. in 2016 demonstrated that high-yielding coupling reactions can happen using various electrophilic and heterocyclic functional groups [131]. This method signifies the most thorough demonstration of palladium-mediated Kumada–Corriu coupling reaction of aryl chlorides and the most in-depth study of chemoselectivity issues with Grignard reagents. It is complementary to existing approaches for base metal-mediated chemoselective coupling, predominantly of alkyl halides (Scheme 58) [132, 133].

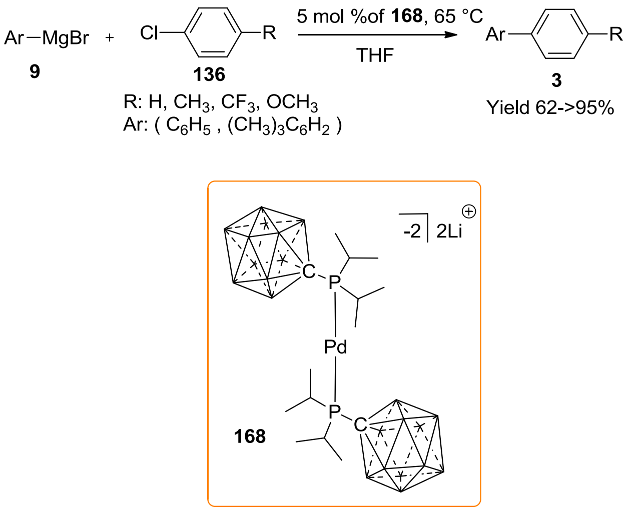
A stable dianionic 14-electron palladium(0) system supported by monoanionic carboranyl phosphines was reported in 2016 by Lavallo et al. This system quickly undergoes the oxidative addition reaction of Cl–C_6H_5 at ambient temperature and is a competent catalyst for Kumada cross-coupling reaction. The excellent reactivity of the dianionic palladium(0) system toward chloroarenes can be elucidated by electrostatic influences, which improve both construction of monophosphine-ligated LPd^0 and stabilization of the transition state during oxidative addition. In order to exhibit that complex **168** is a competent catalyst for palladium mediated cross-coupling, the application of complex was explored using various simple Kumada cross-coupling reactions (Scheme 59) [134].

Carbene ligands having a pyridyl substituent and an ethylenedioxyl scaffold were established, and applied as effective ligands for the Ni-mediated Kumada–Tamao–Corriu coupling reaction. An extensive range of aryl chlorides were applied for the cross-coupling with aryl Grignard reagents to provide the relevant products in excellent yields. Carbene precursor **169** were used to the Ni-mediated coupling

Scheme 58



Scheme 59



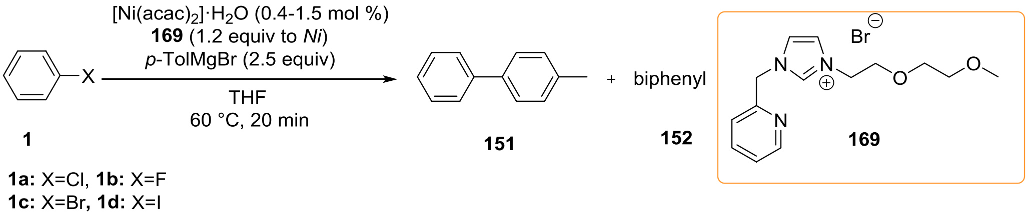
reaction of chlorobenzene with *p*-tolyl Grignard reagent. Using a catalytic quantity of [Ni(acac)$_2$].H$_2$O and **169**, the cross-coupling reaction of chlorobenzene and *p*-tolylmagnesium bromide was performed and afforded 4-methylbiphenyl (**151**) in 94% yield (Scheme 60) [135].

A unique palladium-*N*-heterocyclic carbene (Pd-NHC) system with pyrazine **170** has been formed in 2013 by Türkmen et al. This group exhibited that complex **170** is very adept at re-forming the Kumada–Tamao–Corriu cross-coupling reaction. The Kumada–Tamao–Corriu cross-coupling of phenylmagnesium bromide and 4-chlorotoluene using complex **170** was explored. The coupling product was provided at 78% yield. Arylmagnesium bromide was coupled with various aryl chlorides in the presence of **170** as the catalyst to provide the corresponding products in excellent yields (Scheme 61) [136].

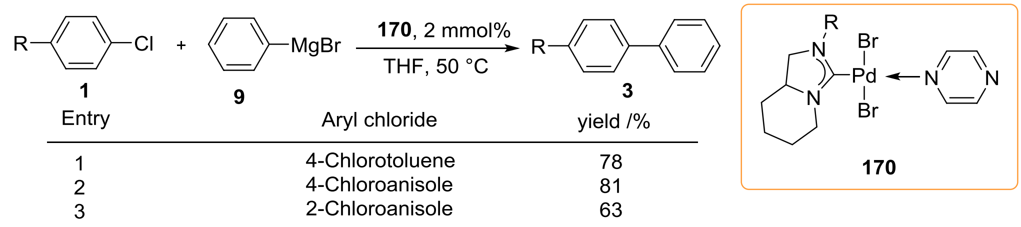
Tumkevicius et al. in 2015 reported the formation of 2-(2-thienyl)benzoic acid **174** from the treatment of 2-chlorobenzonitrile (**171**) with 2-thienylmagnesium bromide (**172**) via the Kumada-type nickel(0)-mediated cross-coupling reaction. Based on the optimal conditions, it was found that the success of the cross-coupling reaction depends on the quantity of catalyst. When 2 mol% NiCl$_2$(PPh$_3$)$_2$ were applied only 10% conversion of nitrile **171** to the corresponding product **173** was detected. Increase of catalyst loading up to 4 mol% improved the conversion to 30%, and 2-chlorobenzonitrile (**171**) was wholly consumed in 8 h once 8 mol% NiCl$_2$(PPh$_3$)$_2$ was used in the reaction. Construction of compound **173** was confirmed, and transformation of the starting precursor has been estimated by GC/MS. Distillation of the crude product under reduced pressure afforded a mixture containing of 2-(2-thienyl)-benzonitrile (**173**) and triphenylphosphine. This mixture was applied in the next stage without any additional purification. Hydrolysis of compound **173** with potassium hydroxide in ethylene glycol provided 2-(2-thienyl)benzoic acid (**174**) in overall two-step yield 44% (Scheme 62) [137].

Kang et al. in 2016 reported nickel-mediated cross coupling reaction of aryl Grignard reagents and aryl halides in toluene. The reaction was used for the formation of different biaryls in moderate yields without the introduction of a large steric ligand. The Kumada–Tamao–Corriu reaction in toluene was effectively modified to proceed under neat

Scheme 60

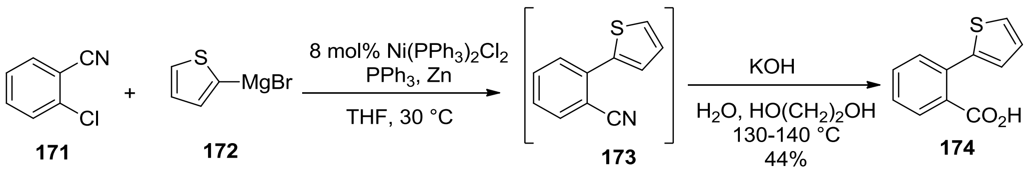


Scheme 61

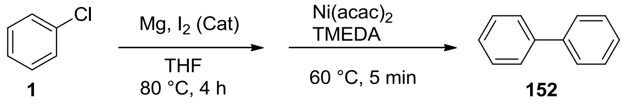


Entry	Aryl chloride	yield /%
1	4-Chlorotoluene	78
2	4-Chloroanisole	81
3	2-Chloroanisole	63

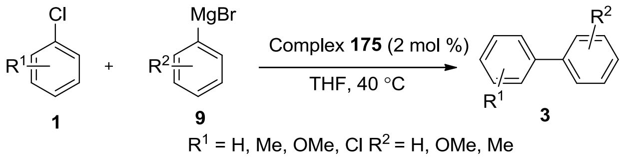
Scheme 62

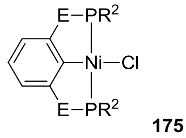


Scheme 63



Scheme 64





R \ E	CH_2	NH	O
Ph	1	5	3
*i*Pr		4	2

conditions for the effective syntheses of symmetrical biaryls, mostly in large-scale preparations. Unactivated aryl chlorides display greater reactivity than aryl bromides, mainly under neat conditions. The construction of the Grignard reagent from an aryl chloride exhibits one of the merit of the neat conditions since it is very difficult, if not impossible, to provide the Grignard reagents directly from an aryl chloride and magnesium either in toluene or in tetrahydrofuran. Additives could improve the Kumada–Tamao–Corriu reaction under neat conditions, of which tetramethylethylenediamine (TMEDA) exhibited the maximum yield of 82% of **152**. Next, 84% and 81% yields of **152** were provided once the catalyst loading was decreased to 2.5% and 1%, respectively. The neat reactions were more quick than those in toluene, finished in 5 min as monitored by GC analysis. Mechanistic investigations suggest a radical method for the catalytic cycle, and the origin of the radical intermediates being aryl halides (Scheme 63) [138].

A broad range of pincer nickel(II) systems were synthesized and applied in the Kumada cross-coupling of nonactivated aryl chlorides and Grignard reagents. Complex **175** ([Ph-PNCNP-Ph]-Ni-Cl) exhibited the uppermost catalytic property for the cross-coupling using 2 mol% catalyst based on mild reaction condition. Air-stable pincer Ni(II) systems are very significant catalysts for the cross-coupling reaction of non-activated aryl chlorides with aryl Grignard reagents with the catalyst loading of 2 mol%. The catalytic reaction might proceed through transmetalation at the beginning and the subsequent ligand substitution (Scheme 64) [139].

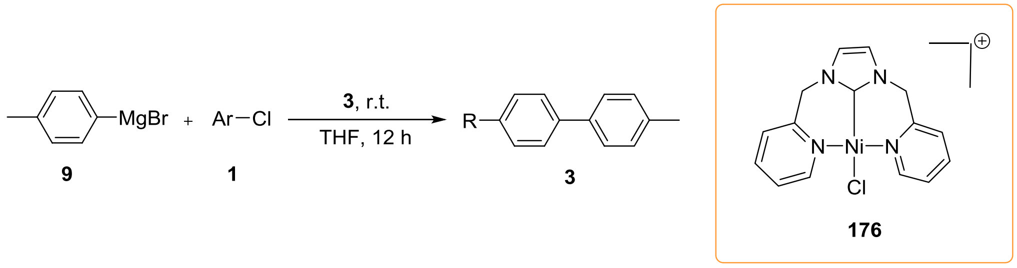
In 2012, Qiu et al. exhibited that the transmetalations with Cu(I)-NHC system as the carbene source can be used for the synthesis of Ni systems. The Cu-NHC systems can be readily synthesized from imidazolium salts and Cu_2O or Cu powder. Therefore, the transmetalation reaction gives novel synthetic approach for Ni NHC systems. The pincer Ni mono(NHC) systems display moderate catalytic property in Kumada–Corriu couplings based on mild conditions. In this route, the catalytic property of **176** for cross coupling reaction of aryl halides and arylmagnesium bromides at ambient temperature was performed. Complex **176** was realized to be active for the coupling reaction of tolylmagnesium bromide and different aryl chlorides affording the corresponding products in moderate to high yields. Moreover, the catalyst is appropriate for heteroaryl chlorides, and the target products could be provided in nearly quantitative yields (Scheme 65) [140].

A ligand-free Pd/$Al(OH)_3$ nano-catalyst synthesized via one-pot three-component approach using $Pd(PPh_3)_4$, tetra(ethylene glycol) and aluminum tri-*sec*-butoxide displays high catalytic property in Kumada coupling reactions of (Het)aryl chlorides and different Grignard reagents. To exhibit the generality of this nanoparticles palladium catalyst, an investigation of Kumada cross-couplings of a wide range of (hetero)aryl chlorides and Grignard reagents was accomplished. Substrates having an electron-withdrawing or electron-donating substituent, the reactions gave the corresponding products in excellent yields (Scheme 66) [141].

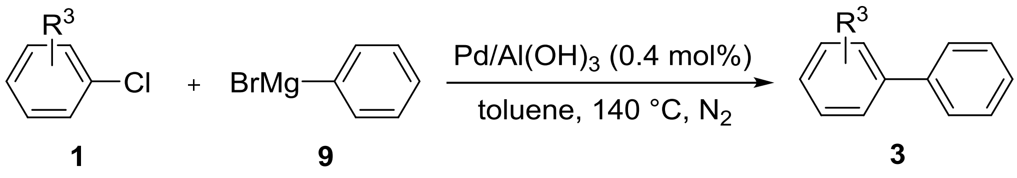
Unique tridentate silyl pincer cobalt system was synthesized through Si–H bond activation. Using a catalyst loading of 5 mol%, complex **178** exhibited effective catalytic property for Kumada cross-couplings of aryl bromides and aryl chlorides with Grignard reagents (Scheme 67) [142].

The formation of NiCl(*o*-tolyl)(TMEDA) (**179**) and its usage in couplings was described in 2015 by Monfette et al. In combination with an appropriate ligand, precatalyst **179** was used to Kumada coupling reaction. Complex **179** is the first extremely useful nickel source which combines the

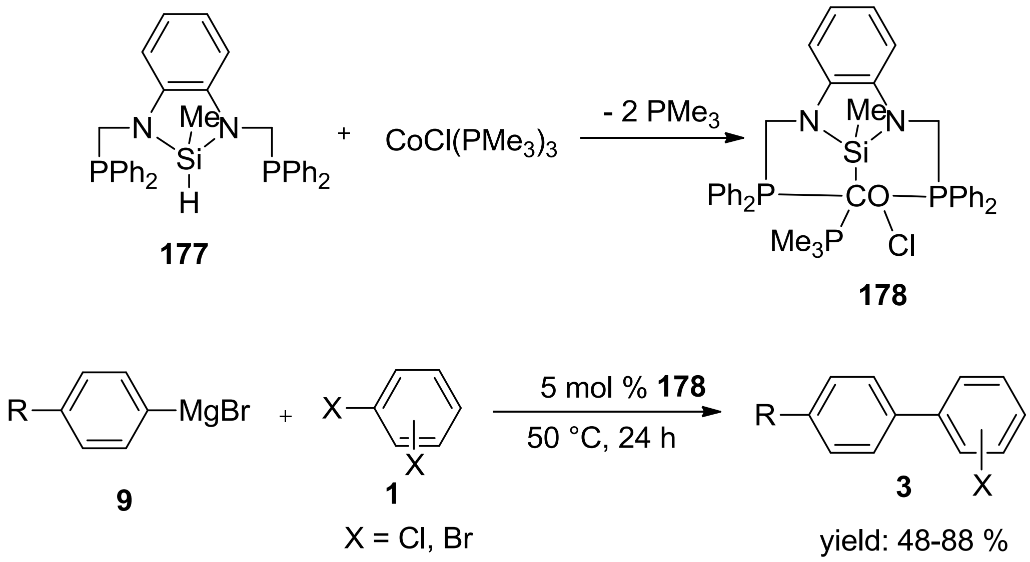
Scheme 65



Scheme 66



Scheme 67

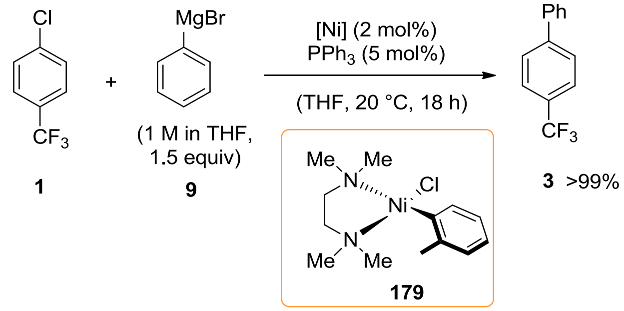


broad applicability of **1** with the air stability of **9**. Kumada coupling of 4-(trifluoromethyl)chlorobenzene with phenylmagnesium bromide afforded near quantitative yield of the corresponding biphenyl product with **179** (Scheme 68) [143].

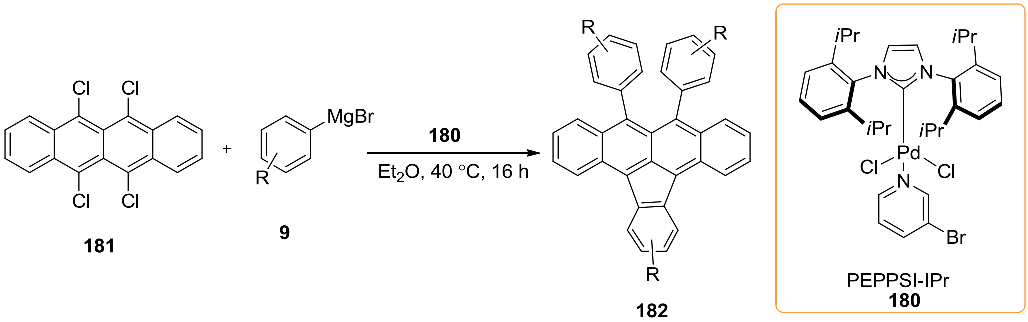
A direct synthesis of unique donor materials for organic photovoltaic cells was reported in 2012 by Douglas et al. Diaryindenotetracene derivatives were formed using a Kumada–Tamao–Corriu cross-coupling reaction of *peri*-substituted tetrachlorotetracene with spontaneous indene annulation through C–H activation (Scheme 69) [144].

1,8-Bis(phenylethynyl)anthracene (1,8-BPEA) (**185**) was formed through a two-fold Kumada cross-coupling, using

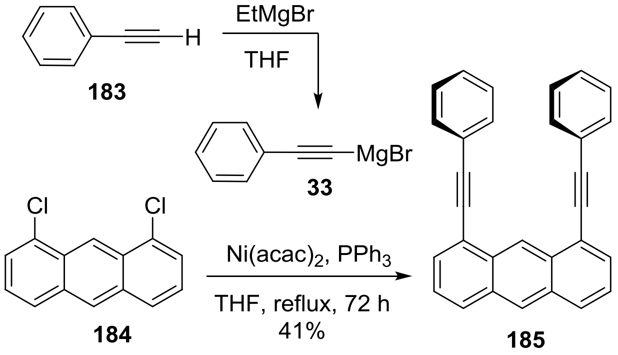
Scheme 68



Scheme 69



Scheme 70

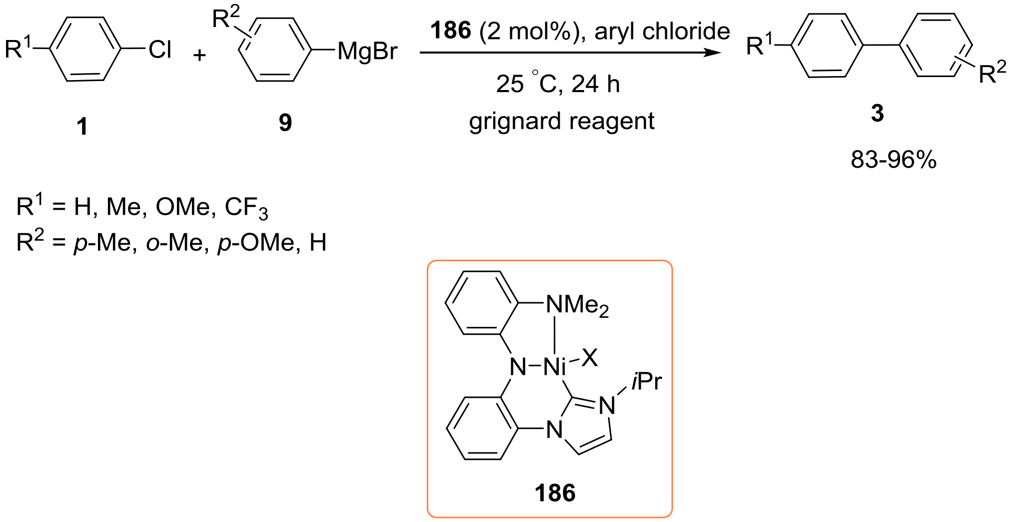


(phenylethynyl)magnesium bromide and 1,8-dichloroanthracene that was freshly synthesized by transformation of phenylacetylene with EtMgBr (Scheme 70) [145].

[CNN]-pincer nickel(II) complex with NHC-amine arms were formed in three steps by Sun and et al. in 2014. Complex **186** was used as an effective catalyst for the Kumada coupling reaction of aryl chlorides or aryl dichlorides. Using a catalyst loading of 2 mol%, complex **186** exhibited high property and was able to successfully mediate the cross-coupling reaction of aryl chlorides or dichlorides with aryl Grignard reagents. Fascinatingly, activated aryl chlorides having an electron-with-drawing substituent (CF_3) afforded moderately poorer yields compared to the unactivated aryl chlorides involving *p*-$MeOC_6H_4Cl$ and *p*-MeC_6H_4Cl (Scheme 71) [146].

2,9-Diethynylanthracenes having trialkylsilyl substituents were easily formed from 2-chloro-9-anthrone in two steps: the addition of an ethynyllithium and the Kumada–Tamao coupling reaction with tri-*tert*-butylphosphine as ligand. These disilylated compounds were applied for the formation of different 2,9-diethynylanthracenes: full desilylation followed by Sonogashira coupling reaction afforded 2,9-bis(phenylethynyl)anthracenes, whereas selective desilylation followed by oxidative coupling afforded di(2-anthryl)butadiynes [147]. The starting precursor, 2-chloro-9-anthrone (**187**) [148] was reacted with (trimethylsilyl)-ethynyllithium, synthesized from trimethylsilylethyne and

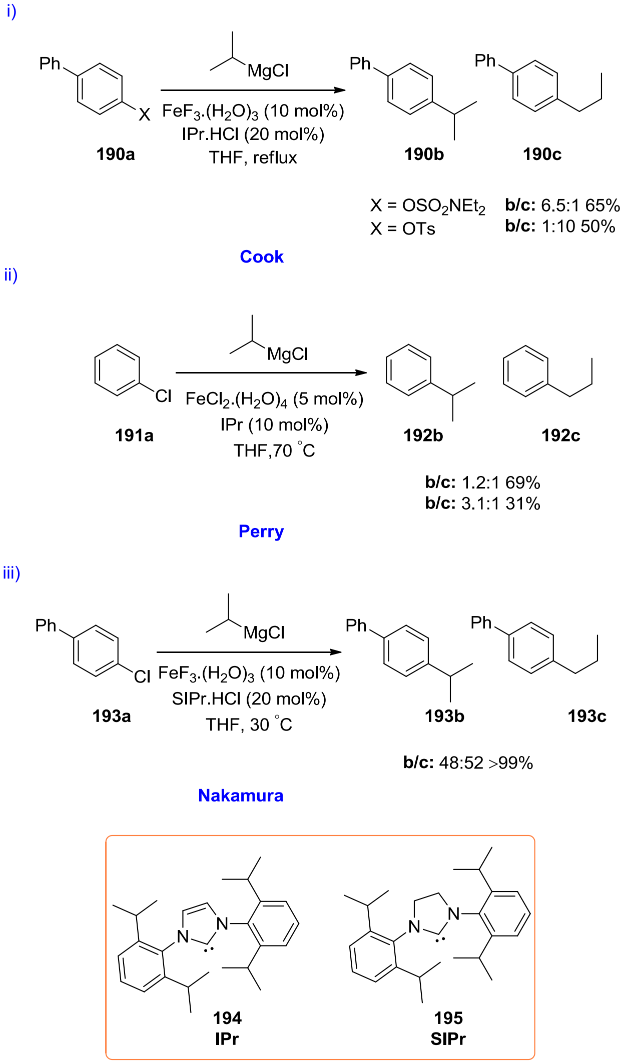
Scheme 71



R^1 = H, Me, OMe, CF$_3$
R^2 = *p*-Me, *o*-Me, *p*-OMe, H

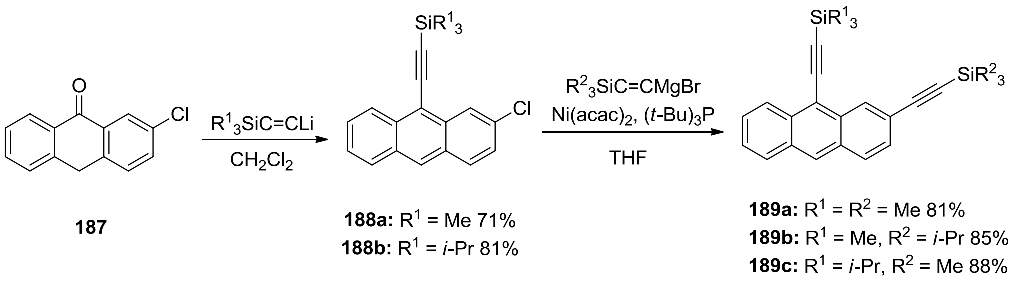
butyllithium, in Et_2O or THF through the normal method [149, 150]. Although, those reactions afforded only a trace quantity of **188a**. Upon various efforts, it was realized that the reaction was performed well in CH_2Cl_2, albeit this solvent is not common for reactions with organolithium reagents. The thus-synthesized addition product spontaneously dehydrated during workup and purification to afford **188a**. The yield of **188a** was improved with an increasing quantity of the lithium reagent: 29% (2.0 equiv), 48% (3.0 equiv), and 71% (4.0 equiv). Similarly, triisopropylsilyl derivative **188b** was formed in 81% yield with (triisopropylsilyl)ethynyllithium. The ethynyl group was introduced at the 2-position through the Kumada–Tamao coupling. The reaction conditions were optimized for the formation of **189a** from **188a** and (trimethylsilyl)ethynylmagnesium bromide. The reaction with 5.0 equivalents of the Grignard reagent, but, afforded the corresponding compound in 48% yield. The yield was more improved to 81% with tri-*tert*-butylphosphine inplace of triphenylphosphine; this bulky trialkylphosphine is valuable for various metal-mediated coupling reactions. This method was used to the formation of **189b** and **189c** from the relevant reagents to afford the corresponding products in moderate yields (**189b**: 85%, **189c**: 88%). Remarkably, these formed compounds are useful starting precursors for the synthesis of substituted 2,9-diethynylanthracenes (Scheme 72).

Scheme 73



Very few samples of the Fe-mediated coupling reaction of secondary alkyl Grignard reagents were demonstrated. Cook et al. [151] exhibited the isopropylation of aryl sulfamates and sulfonamides in 2012. However noteworthy isopropyl to *n*-propyl isomerization was detected [i (Scheme 73)] [152]. The application of a FeF_3 pre-catalyst was exhibited to afford a higher isopropyl to *n*-propyl ratio than $FeCl_2$. Also, Perry et al. [153] examined the application of isopropylmagnesium chloride as part of a wider study into the usage of NHC ligands in Fe-mediated reactions. It was mentioned that a higher isopropyl to *n*-propyl ratio could be accomplished via the application of a large excess (six equivalents) of Grignard reagent, although at the expense of yield [ii (Scheme 73)]. Furthermore, Nakamura et al. used an Fe/NHC complex to couple electron-rich aryl chlorides with both primary and secondary alkyl Grignard reagents [154]. Although, attempted coupling reactions with isopropylmagnesium chloride resulted in the broad construction of isomerized side-products [iii, (Scheme 73)] [155] the application of an FeF_3 pre-catalyst was demonstrated to be essential for a productive reaction in this case. Generally, the

Scheme 72



Fe/NHC catalyst complexes afforded high levels of isopropyl to *n*-propyl isomerization, possibly caused by the increased temperatures needed for effective cross-coupling reaction [152–154].

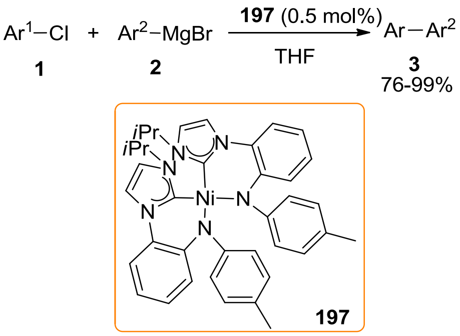
A catalyst system containing $Fe_2(OtBu)_6$ and an *N*-heterocyclic carbene ligand provided effective construction of (hetero)biaryls from the reactions of aryl Grignard reagents having a different (hetero)aryl chlorides. Remarkably, *tert*-butoxide was the most significant in inhibiting the homocoupling of arylmagnesiums. Based on the optimal conditions, great yielding syntheses of biaryls were performed with various arylmagnesiums differing in electronic and steric properties. A wide series of (hetero)aryl chlorides was evaluated in the reaction with *p*-tolylmagnesium bromide. Aryl chlorides having electron withdrawing or either electron-donating groups were successfully transformed into the corresponding biaryl compounds (Scheme 74) [155].

A novel amine substituted double chelate NHC Ni system **197** was formed. Catalytic activity of Ni system **197** was examined in Kumada coupling reaction. Complex **197** exhibited the greatest catalytic property among them. Using only 0.5 mol% of system **197**, the coupling reaction of aryl chlorides and Grignard reagents provided moderate yields (Scheme 75) [156].

Yamaguchi et al. demonstrated a simple three-step synthesis of 2,5,7-trifunctionalized indoles from *N*-acetyl-2,4,6-trichloroaniline, with the first step introducing palladium/dihydroxyterphenylphosphine (DHTP)-mediated ortho-selective Sonogashira coupling followed by cyclization reaction to provide 2-functionalized 5,7-dichloroindoles. Subsequent introduction of aryl or alkenyl substituents at the C7 position was performed by palladium/DHTP-mediated site-selective Kumada–Tamao–Corriu coupling reaction, with more substitution of the chlorine at the C5 position (Suzuki–Miyaura coupling or Buchwald–Hartwig amination) giving 2,5,7-trifunctionalized indoles (Scheme 76) [157].

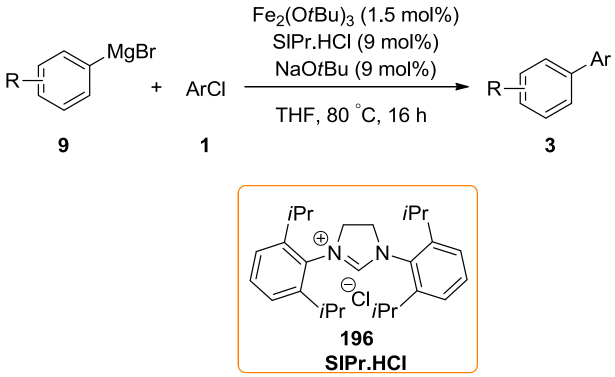
Moreover, this group reported C7-selective Kumada–Tamao–Corriu coupling reaction of 5,7-dichloroindole and Grignard reagents [158]. It was anticipated 2,5,7-trifunctionalized indoles having various groups to be readily available from 2,4,6-trichloroaniline using palladium/dihydroxyterphenylphosphine (DHTP)-mediated *ortho*-selective Sonogashira coupling reaction that was followed by C7-selective Kumada–Tamao–Corriu coupling reaction and additional conversion of the remaining chloro group (Scheme 77).

Scheme 75

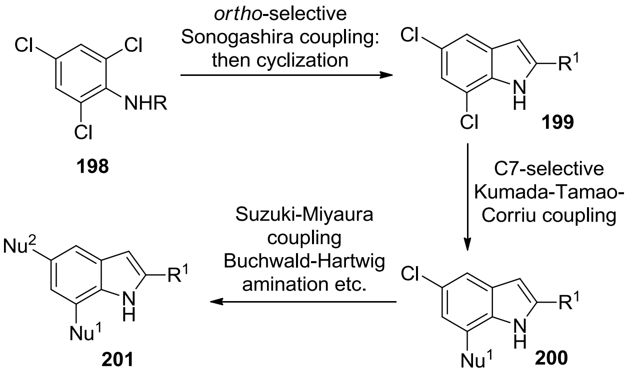


Therefore, it was anticipated C7-selective cross-coupling reaction of 2- functionalized 5,7-dichloroindoles to be possible, with dichloroindole **203** and 4-methylphenylmagnesium bromide (**13**) as model substrates. Inappropriately, catalysis by palladium/PCy_3 gave the corresponding product **204** in poor yield. It was guessed that the steric hindrance of the 4-methoxyphenyl substituent at the C2 position of **203** led to poor yield of **204**. Although, the application of **206b** dramatically improved the reaction and site-selectively gave **204** in excellent yield. Also, ligand **206c** was realized to be effecinet in this reaction, with monohydroxylated terphenylphosphine **206a**·HBF_4 giving the corresponding product in a slightly poorer yield, and tri-*tert*-butylphosphine demonstrating low performance. In the case of XPhos, only a small quantity of **204** was provided. In all cases, no reaction was detected at the C5 position. It should be mentioned that **206b** gave the best results (Scheme 78).

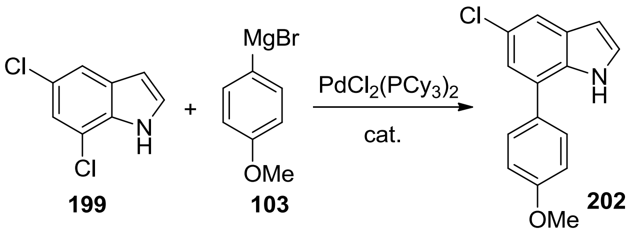
Scheme 74



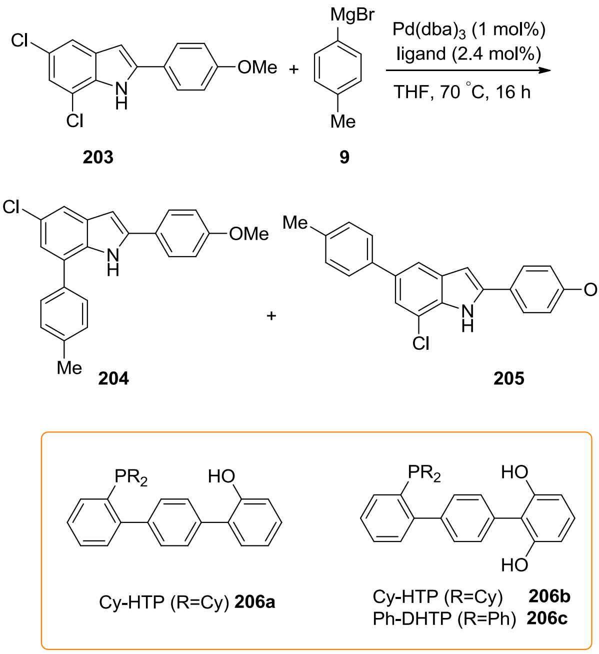
Scheme 76



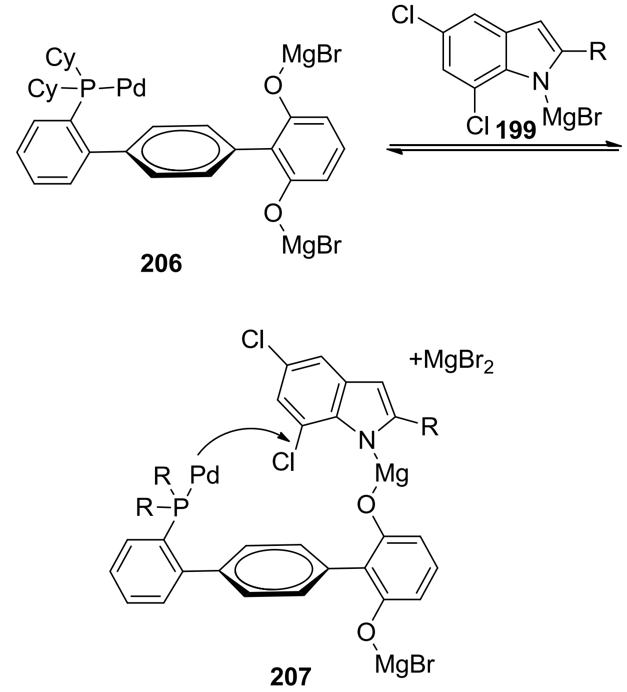
Scheme 77



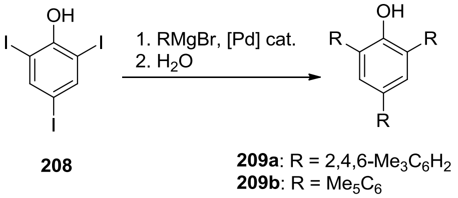
Scheme 78



Scheme 79



Scheme 80



Consequently, oxidative addition reaction to the palladium center is improved at the *ortho* position. In the case of Kumada–Tamao–Corriu coupling reaction of 2-functionalized 5,7-dichloroidoles, Grignard reagent deprotonates **206b** and the substrate, and the resultant Mg salts form heteroaggregate **207**. Hence, oxidative addition reaction to the palladium atom selectively happens at the C7 position of indole (Scheme 79).

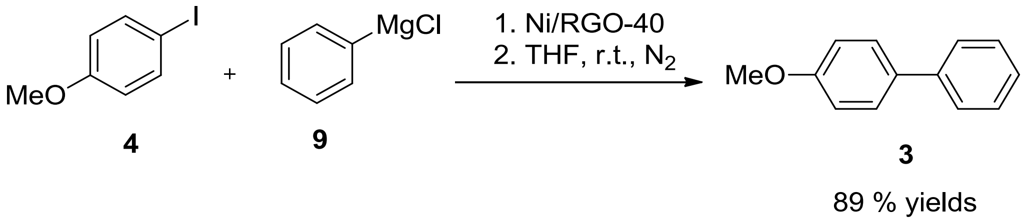
Arylation of Grignard compounds via aryl iodides

Functionalized phenols having a *m*-terphenyl scaffold 2,4,6-$R_3C_6H_2OH$ [R = 2,4,6-$Me_3C_6H_2$), Me_5C_6] have been formed through Kumada cross-coupling of 2,4,6-$I_3C_6H_2OH$ and the relevant Grignard reagent in 2015 by Rat et al. The compounds **209a** and **209b** have been provided using 2,4,6-$I_3C_6H_2OH$ and 5 equivalents of the relevant Grignard reagent. The complexes [(IPr)$PdCl_2$(3-ClC_5H_4N)] (IPr=1,3-bis-(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene) and [(IPr)PdCl(μ-Cl)]$_2$, respectively, have been applied as catalysts. Also, product **209a** was provided using [(IPr)PdCl(μ-Cl)]$_2$ as catalyst, and 2,4,6-$X_3C_6H_2OH$ as starting precursors, in 28% (X = Br) and 50% (X = I) yields (Scheme 80) [159].

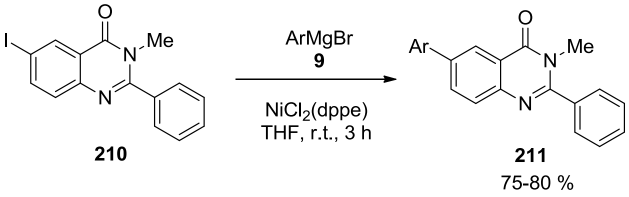
Basu et al. in 2014 reported the Kumada–Corriu cross-coupling reactions using reduced graphene oxide (RGO) supported 40 wt% nickel nanoparticles (Ni/RGO-40) as a heterogeneous catalyst. The reaction conditions have been performed by performing the cross-coupling of 4-iodoanisole and PhMgCl using a catalytic quantity of Ni/RGO-40. It should be mentioned that a detailed investigation of the catalysis has been performed by changing the haloarenes and Grignard reagents under the optimal reaction conditions with yields of 91–72% (Scheme 81) [160].

Ni mediated Kumada cross coupling, for the formation of 6-aryl-2-phenyl-3-methylquinazolin-4(3*H*)-ones **211** has been achieved by the reaction of 6-iodo-2-phenyl-3-methylquinazolin-4(3*H*)-one (**210**) and different 6-aryl/heteroaryl Grignard reagents. The Kumada cross coupling reaction of 6-iodo-2-phenylquinazolin-4-(3*H*)-one (**210**) has been

Scheme 81



Scheme 82



achieved using various aryl/heteroaryl Grignard reagents and $NiCl_2$(dppe) (10 mol%) as a catalyst in tetrahydrofuran at ambient temperature. This reaction afforded the carbon–carbon coupled products **211** in excellent yields (Scheme 82) [161].

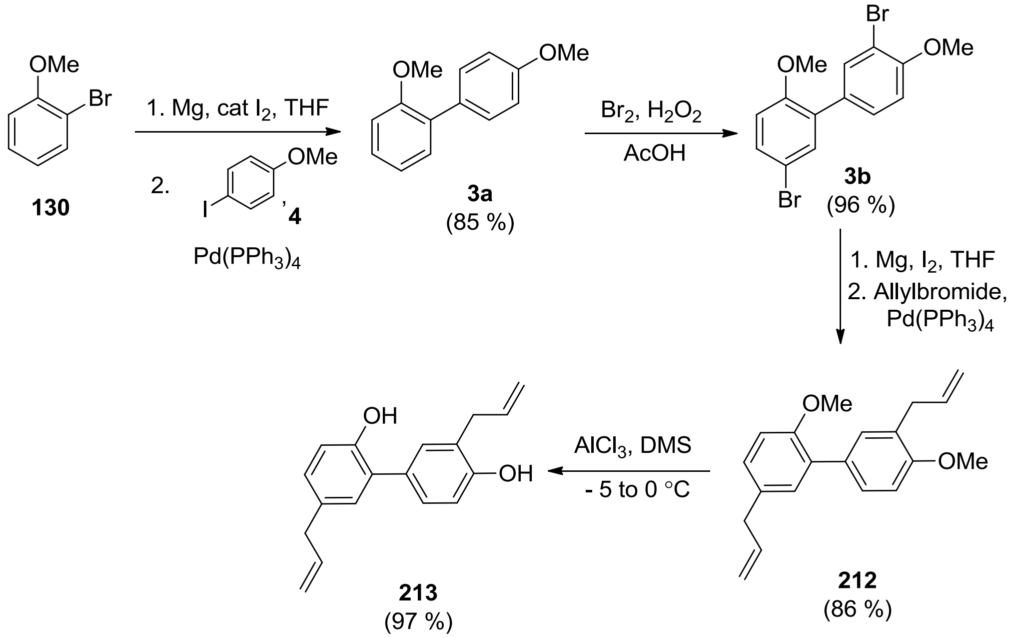
A short and four-step effective synthesis of honokiol (**213**) in 68% overall yield was reported in 2014 by Kumar et al. This method includes tetrakis(triphenylphosphine)palladium [Pd(Ph_3)$_4$] mediated Kumada coupling reaction in two key steps. First coupling reaction provides biaryl scaffold intermediate **3a** and second provides 2,4′-*O*-dimethylhonokiol (**212**). Lastly, demethylation using aluminium chloride/dimethyl sulfide (DMS) condition gave honokiol (**213**) in quantitative yield. Based on this method, initially, the 2-bromoanisole **130** was transformed into organomagnesium intermediate and then reacted with second coupling partner 4-iodoanisole (**4**) through Kumada carbon–carbon bond construction condition in which tetrakis (triphenylphosphine) palladium {Pd(Ph_3)$_4$} has been applied as a source of palladium catalyst. This coupling reaction makes the biaryl backbone intermediate **3a** in 85% yields. Next, the biaryl intermediate **3a** has been reacted with Br_2 using H_2O_2 in HOAc to afford unsymmetrical biaryl, 3′,5-dibromo-2,4′-dimethoxybiphenyl (**3b**) in 96% yield. In the following, biphenyl **3b** transformed to organomagesium species and then reacted with allyl bromide through Kumada coupling condition mediated by Pd(PPh_3)$_4$ afforded 86% of coupled product, 3′,5-diallyl-2,4′-dimethoxybiphenyl (**212**). Lastly honokiol (**213**) has been provided in near quantitative yields of 97% through demethylation of compound **212** using aluminium chloride/DMS [162] (Scheme 83).

An examination of the Pd-mediated Kumada cross-coupling of phenylmagnesium bromide and (pseudo-*ortho*) 4,12-diiodo-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane demonstrated that in addition to the desired cross-coupled product, an unexpected major product was provided. The product was identified to be 9,9,10,10-tetrafluoro-1,2,4,12-tetraphenyl[2.2]paracyclophan-1-ene and is suggested to be generated through reductive defluorination using a Grignard reagent. Based on this method, it has been identified that using dropwise addition of the Grignard reagent under reflux in tetrahydrofuran improved the yields of the cross-coupled compounds **215** and **216** to 30%. Although, this examination led to the construction of an additional, undesired compound that in fact was the main extracted product of this reaction. The construction of product **217** probably initiated with the originally corresponding double Pd- mediated Kumada coupling reaction of diiodide **214** and phenylmagnesium bromide to make the expected cross-coupled product **216**. It looks likely that the additional phenylmagnesium bromide then serves as a reductant, promoting reductive defluorination of **216** to form the relevant paracyclophan-1-ene, and in turn the remaining excess phenylmagnesium bromide then makes two sequential vinylic groups of the fluorines to yield the target product **217** (Scheme 84) [163].

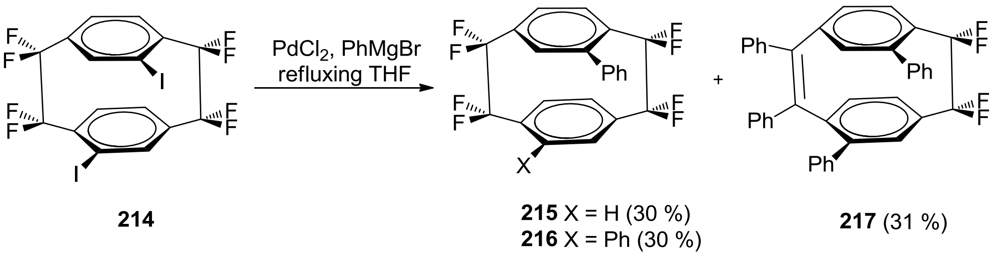
An examination of Pd-mediated Kumada type reactions of different Grignard reagents with mono-functionalized octafluoroparacyclophanes demonstrated that by changing the reaction temperature, and mode of addition of the Grignard reagent, it was probable to affect whether the main product was the cross-coupled, or the homo-coupled (reductive dimer) paracyclophane product. This way gave an improved approach to provide aryl functionalized paracyclophanes, and additionally an alternate method to the unusual and rare di-cyclophane scaffold. Similar reactions using alkyl lithium reagents leading to the construction of various formerly unreported octafluoroparacyclophane compounds [164].

The first effort was on the reaction of phenylmagnesium bromide with OFP-Halides and palladium(II) chloride in tetrahydrofuran. As expected, it was rapidly developed that OFP-I_2 was the preferred starting precursor for these reactions, always providing the maximum yield. OFP-Cl_3 did not treat under the common reaction conditions, while OFP-Br_4

Scheme 83



Scheme 84

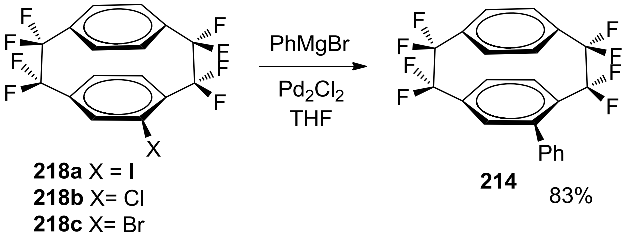


treat, but always with poorer yields of corresponding product, because of an increase in the quantity of reduction product, and poorer conversion (Scheme 85).

Then, the treatment of phenylmagnesium bromide with **218a** was further examined. This reaction using palladium(II) chloride, under reflux in tetrahydrofuran resulted in the corresponding OFP-Ph$_5$ cross-coupled compound in 49% yield, reaction without any palladium(II) chloride catalyst, only led to the construction of reduction product in excellent yield. It should be mentioned that the yield was affected by the rate of addition of the PhMgBr. By adding the organometallic reagent slowly into the refluxing tetrahydrofuran solution, the yield of the cross-coupled product was improved up to 83% [164].

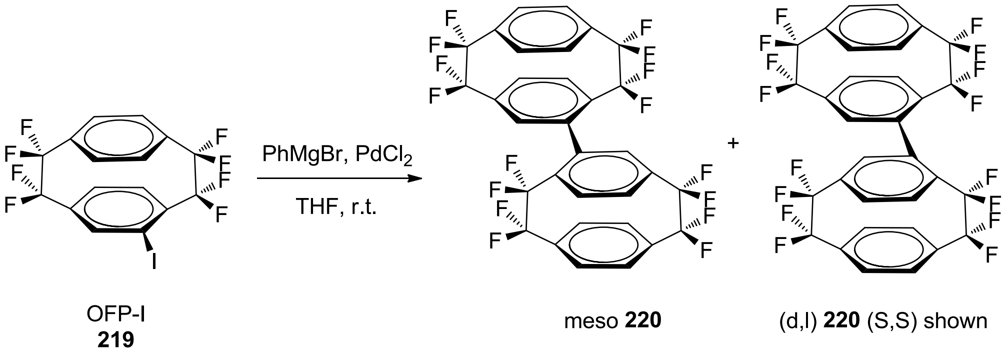
Although more astonishingly, it was known that once the reaction was accomplished at ambient temperature, in addition to the desired cross-coupled and reduction products, another product was provided. The novel undesired product was recognized as bis(OFP)$_6$ (Scheme 86) [164].

Scheme 85

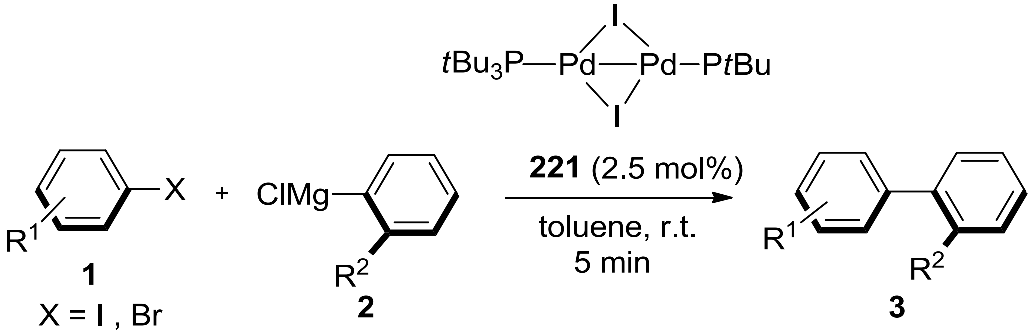


In 2015, Schoenebeck et al. revealed a systematic additive/activity study for the two structurally analogous palladium(I) dimers, [Pd(μ-X)(P*t*Bu$_3$)]$_2$ (*X* = I). Extremely effective Kumada couplings of a series of aryl bromides and iodides were performed in 5 min at ambient temperature

Scheme 86



Scheme 87

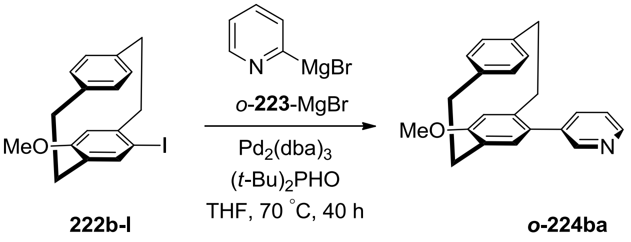


using 2.5 mol% of palladium(I) dimer **221** and a slight excess of coupling partner (1.5 equiv). This method demonstrated to be compatible with electron-poor and electron-rich aryl halides in addition to heterocyclic, ether, ester, and silyl functionalities (Scheme 87) [165].

Pyridyl-functionalized [2.2]paracyclophanes form a multifunctional structural scaffold that is valuable in material chemistry, catalysis and for luminescent structures. The coupling reaction of substituted [2.2]paracyclophanes with different functionalized and substituted pyridyls was performed through Kumada coupling reactions for the synthesis of pyridyl-functionalized [2.2]paracyclophanes. Hence, Bräse et al. have used from the more reactive iodinated [2.2]paracyclophane **222b-I** that has an additional MeO substituent for synthetic reasons. They were able to provide *o*-**224ba** through a Kumada coupling reaction upon in situ magnesiation of ***o*-223a**-Br in poor yield (16%) using bis(*tert*-butyl)phosphine oxide as ligand (Scheme 88) [166].

Arisawa et al. in 2016 established a theoretically and methodologically novel self-assembled multilayer Ni nanoparticle (NP) catalyst-sulfur-modified Au-supported NiNPs (SANi) for organic synthesis. The SANi catalyst was readily synthesized via a three-step method including instantaneous spontaneously metal NP and nanospace organization. SANi mediated C–C bond-forming cross-coupling, Kumada coupling reactions through ligand-free condition and can be applied frequently for this reaction. Moreover, this group examined the scope of SANi use by performing liquid-phase combinatorial synthesis using different iodobenzenes and Grignard reagents (Scheme 89) [167].

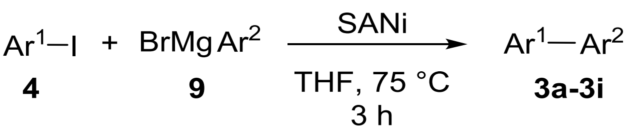
Scheme 88



The unique nickel(II) system [Ni{$(Ph_2P)_2N(CH_2)_3Si(OCH_3)_3$-P,P}$Cl_2$] (**225**) in which the square-planar NiP_2Cl_2 coordination sphere includes a four-membered Ni–P–N–P ring was established in 2015 by Kyritsis et al. Direct anchoring of **225** onto SBA-15 molecular sieves via the trimethoxysilyl end-group of the ligand gave heterogeneous catalyst **225**/SBA-15. Both **225** and **225**/SBA-15 mediated Kumada cross-couplings. The Grignard reagent used is likely to induce leaching of the catalyst that retains its activity in solution (Scheme 90) [168].

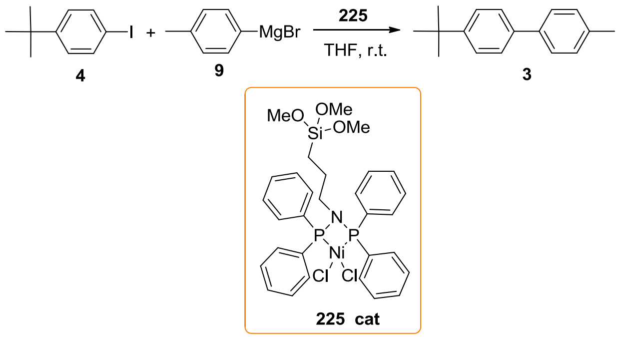
Well-recognized Kumada cross-coupling reactions include preformed Grignard reagents in dry ethereal solvent,

Scheme 89

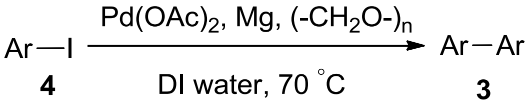


$$\underset{\mathbf{4}}{\mathrm{Ar^1{-}I}} + \underset{\mathbf{9}}{\mathrm{BrMgAr^2}} \xrightarrow[\text{THF, 75 °C, 3 h}]{\text{SANi}} \underset{\mathbf{3a\text{-}3i}}{\mathrm{Ar^1{-}Ar^2}}$$

Scheme 90



Scheme 91

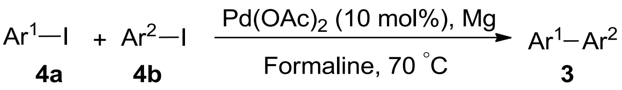


$$\underset{\mathbf{4}}{\mathrm{Ar{-}I}} \xrightarrow[\text{DI water, 70 °C}]{\mathrm{Pd(OAc)_2,\ Mg,\ (\text{-}CH_2O\text{-})_n}} \underset{\mathbf{3}}{\mathrm{Ar{-}Ar}}$$

which usually treat for example with aryl halide derivatives through palladium catalysis to provide products of net substitution. Exposure of aromatic halides to catalytic quantities of palladium(II) and excess Mg metal in pure water resulted in symmetrical/unsymmetrical biaryls, indicative of a net Kumada-like biaryl coupling reaction. Evidence is presented demonstrating that Grignard reagents, provided spontaneously in water, may be included [169] (Scheme 91).

Moreover, hetero cross-coupling reactions of aryl iodides have been examined under these aqueous conditions. Generally, yields were modest. A greater loading of $Pd(OAc)_2$ (10 mol%) was needed than that needed for homo-coupling reactions, as was additional Mg. Also, the combination that looks to be least favorable includes aryl iodides once each partner includes an electron-withdrawing substituent. Best results were provided using the combination of electron-rich and electron-deficient groups. Formalin is essential for hetero-coupling reactions, whereas paraformaldehyde is the additive of choice for homo-coupling reactions [169] (Scheme 92).

Scheme 92



$$\underset{\mathbf{4a}}{\mathrm{Ar^1{-}I}} + \underset{\mathbf{4b}}{\mathrm{Ar^2{-}I}} \xrightarrow[\text{Formaline, 70 °C}]{\mathrm{Pd(OAc)_2\ (10\ mol\%),\ Mg}} \underset{\mathbf{3}}{\mathrm{Ar^1{-}Ar^2}}$$

Control reactions exhibited that both metals, together with paraformaldehyde, are essential for these cross-coupling reactions to happen (path A). Reaction of an aryl halide and Mg under otherwise identical conditions in tetrahydrofuran (THF) afforded a small quantity of the protio-quenched arene and no homocoupling (path B). Once $Pd(OAc)_2$ (5 mol%) plus excess magnesium were added, without formaldehyde, the main product was the same reduced arene (path C). Conducting the coupling in D_2O afforded the desired biaryl, whereas the side-product arene exhibited 100% deuterium incorporation (path A), confirming H_2O as the source of hydrogen that is mechanistically important (vide infra) (Scheme 93) [169].

Other arylation of Grignard compounds

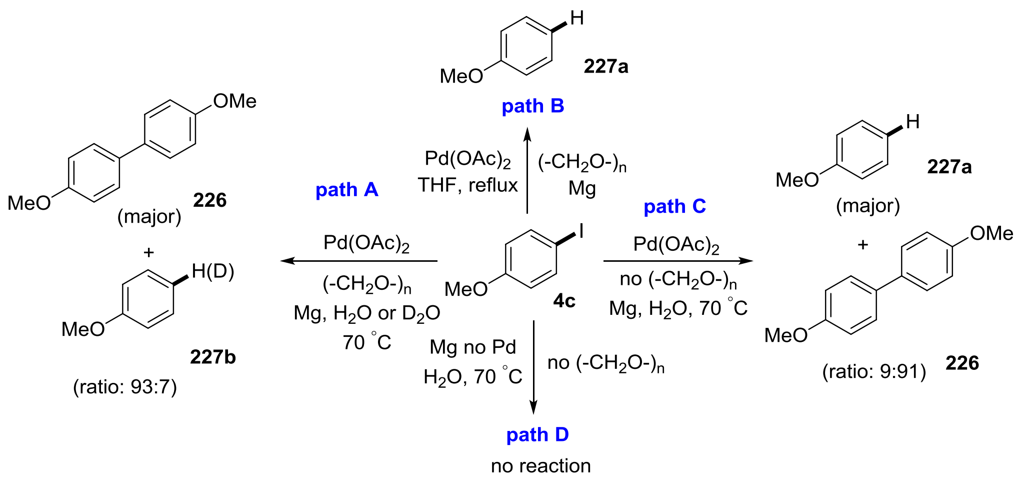
Aryl and heteroaryl sulfoxides underwent *ortho* allylation after reaction with trifluoromethanesulfonic anhydride (Tf_2O) and allylsilanes. This approach supplements the application of sulfoxides to provide *ortho*-metalation and reaction with electrophiles as it permits allylic carbon nucleophiles to be added *ortho* to the directing group in a metal-free method. The useful sulfide products can be selectively employed through different approaches involving Kumada-Corriu cross coupling reaction of the organosulfanyl group (Scheme 94) [170].

Using the reaction conditions of Wenkert [171, 172], *ortho* allyl aryl sulfides **231** through effective Kumada–Corriu coupling reaction applying a wide series of Grignard reagents under nickel catalysis afforded products **232** (Scheme 95).

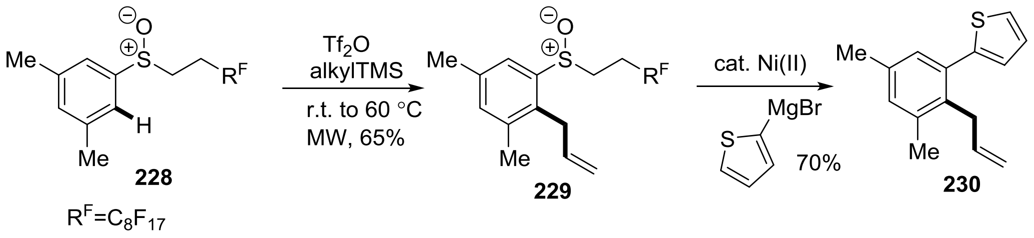
Extremely active dinuclear Ni(I) systems having bulky N-heterocyclic carbene ligands were applied in the catalytic cycle of the Kumada–Tamao–Corriu cross-coupling of aryl halides. Compound **233** mediated the Kumada cross-coupling reaction of weakly active aryl halides. Noticeably, compounds **233** and **234** demonstrated vibrant variances in their catalytic properties (Scheme 96, Table 2) [173].

The paramagnetic systems $Ni^I(IMes)_2X$ (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) were synthesized from the treatment of aryl halides and $Ni(IMes)_2$. Products that would be produced from oxidative addition were not detected. In sharp contrast, $Ni^{II}(tmiy)_2$ (X)(Ar) systems were provided from the oxidative addition reaction of aryl halide derivatives to nickel bound using a sterically less hindered NHC ligand, tetramethylimidazol-2-ylidene (tmiy). $Ni^I(Mes)_2X$ systems **235** and **236** were examined as possible cross-coupling catalysts for Kumada cross-couplings. Specially, mesitylmagnesium bromide and chlorobenzene were exposed to 3 mol% nickel catalyst and permitted to treat

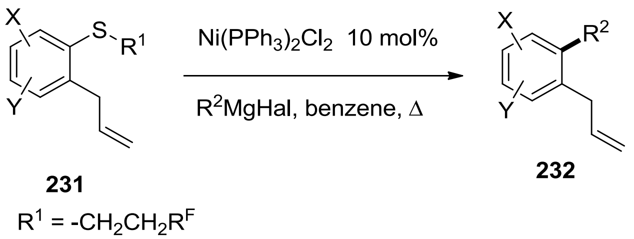
Scheme 93



Scheme 94



Scheme 95



at ambient temperature for 20 h. Once reactions were performed in tetrahydrofuran, all nickel systems demonstrated analogous catalytic property. Remarkably, both nickel(I) systems (**235** and **236**) mediated the Kumada cross-coupling reaction and provided the biaryl product with identical yields (73–77%). Not astonishingly, the $Ni^{I}(IMes)_2Br$ (**235**)-mediated Kumada coupling reaction of bromobenzene efficiently gave the biaryl product in increased yield (Scheme 97) [174].

Shi and et al. in 2012 reported a systematic approach of the Kumada–Tamao–Corriu coupling using Ni-mediated CO bond activation of aryl/alkenyl silyl ethers. The Kumada–Tamao–Corriu reaction was accomplished using $[Ni(PCy_3)_2Cl_2]$ as the catalyst and 2-trimethylsiloxynaphthalene (**237**) as substrate. Using phenylmagnesium bromide (**9**) as the nucleophile, the corresponding cross-coupling served well in arene or ether as solvents. Actually, toluene and tetrahydrofuran afforded the best results under mild conditions and moderate to high yields of the product **3** were provided in 1 h at 30 °C. Various Grignard reagents were examined under the normal conditions and most of the aryl Grignard reagents afforded moderate to high yields (Scheme 98) [175].

In 2012, Jin et al. established a novel class of air-stable diaminophosphine oxides from 1,1′-biphenyl-2,2′-diamine. The Ni system of the sterically encumbered diaminophosphine oxide **239** showed greater reactivity in the cross-coupling reaction of Grignard reagents with electronically deactivated aryl fluorides, chlorides, and tosylates. The activity of the systems provided spontaneously from these diaminophosphine oxides in the Ni-mediated Kumada cross-coupling considerably attributed to the functionalized method on the heteroatom adjacent to phosphorus atom. Moreover, the Ni catalyst provided from diaminophosphine oxide **239** demonstrated appropriate to electronically deactivated aryl tosylates (Scheme 99) [176].

The two bulky adamantyl groups in **239** were not only useful to the reductive removal stage in the catalytic cycle, but also improved the ligand-exchange method from the coupling product to the haloarene as the first irreversible stage

Scheme 96

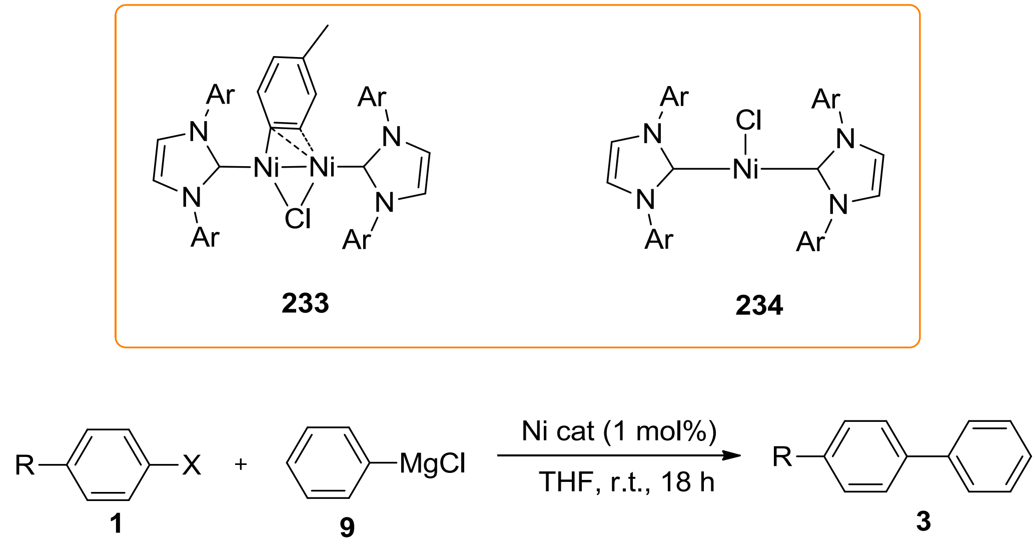


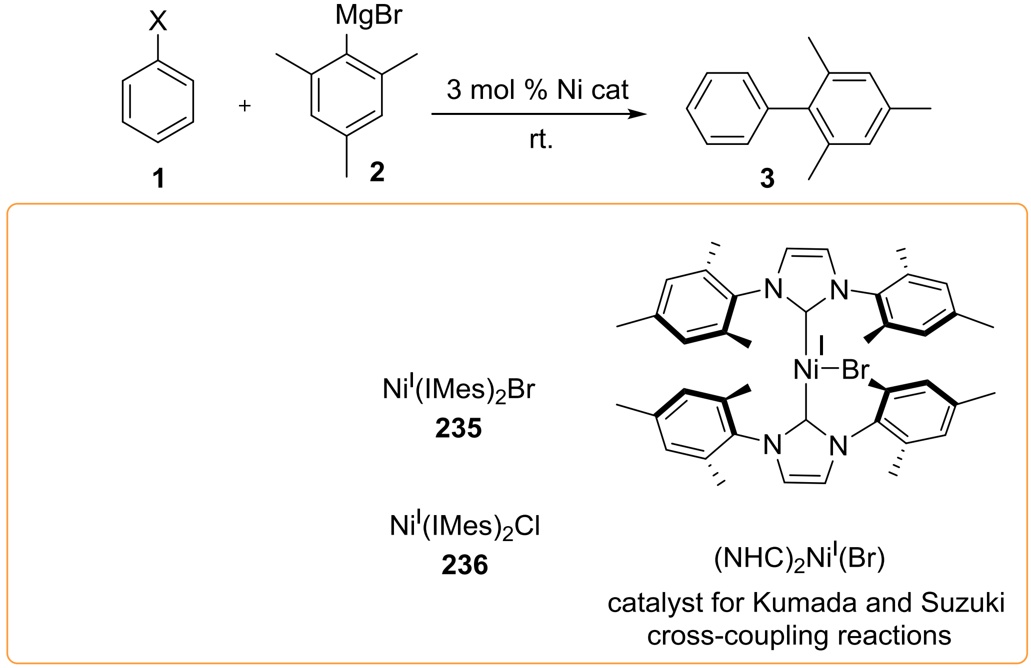
Table 2 Kumada cross-coupling reaction of aryl halides catalyzed by nickel(I) complexes

Entry	Cat.	R	X	Additive	Yield/%
1	**233**	OMe	Cl		85
2	**233**	OMe	F		42
3	**234**	OMe	Cl	IPr (5 mol%)	33
4	**234**	OMe	Br	IPr (5 mol%)	93
5	**234**	Ph	Br	IPr (5 mol%)	89

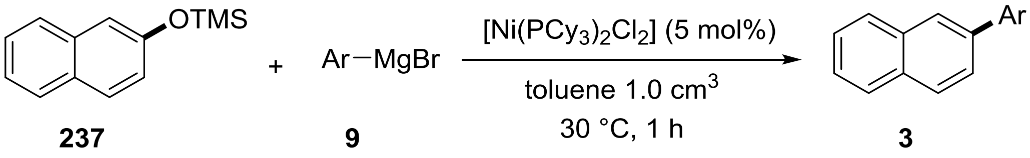
in the Ni-mediated cross-couplings [177], that significantly increase the turnover effectiveness (Scheme 100).

The $[Ni\{(Ph_2P)_2N\text{-}S\text{-}CHMePh\text{-}P,P'\}Br_2]$ system was synthesized through a ligand-exchange reaction of $[Ni(dme)Br_2]$ (dme = 1,2-dimethoxyethane) and the P–N–P ligand $(Ph_2P)_2N(S\text{-}CHMePh)$. The catalytic performance of $[Ni\{(Ph_2P)_2N\text{-}S\text{-}CHMePh\text{-}P,P'\}X_2]$, X = Cl or Br, in Kumada coupling was examined and compared with the property of $[Ni(dppp)Cl_2]$. Both

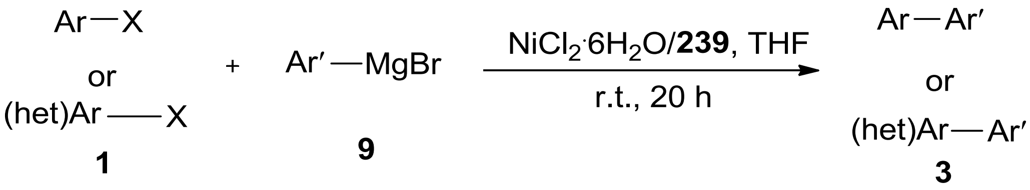
Scheme 97



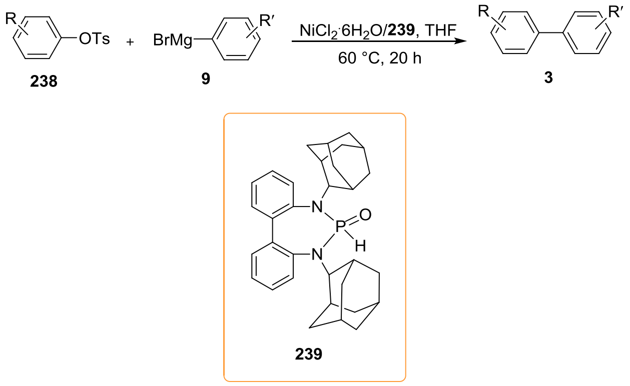
Scheme 98



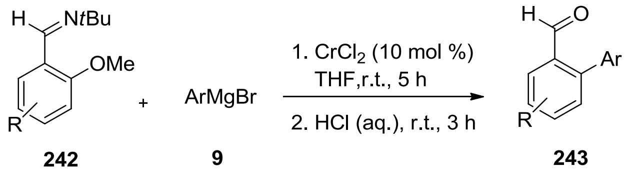
Scheme 99



Scheme 100



Scheme 102

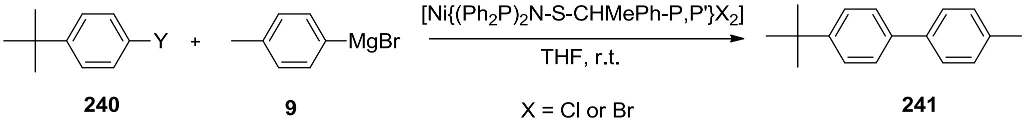


[Ni{(Ph$_2$P)$_2$N-S-CHMePh-P,P′}X$_2$] (X = Cl or Br) mediated Kumada coupling reactions, in which the effectiveness of the dibromo system is somewhat lower than that of its dichloro counterpart [178] (Scheme 101).

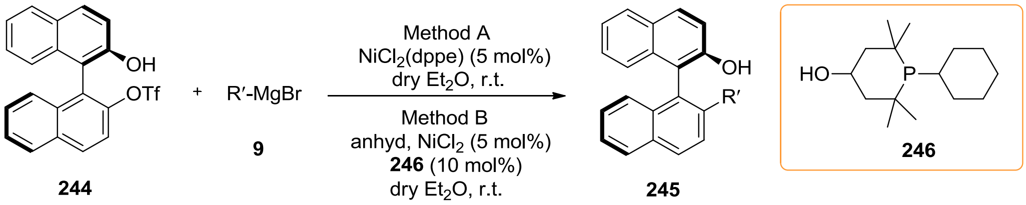
Zeng et al. in 2015 reported the first Cr mediated selective cross-couplings of aryl ethers and Grignard reagents through the removal of C–O (alkyl) bonds. Various conversions of C–O (alkyl) bonds, involving arylation, alkylation, and ring-opening/cross-coupling reactions, have been performed with CrCl$_2$ as the pre-catalyst combining with a Grignard reagent. It gives a new way for accumulation substituted aromatic aldehydes with excellent activity and selectivity. An unprecedented chromium mediated chemo- and regioselective functionalization of aromatic ethers via the removal of unactivated C–O (alkyl) bonds was established. For the first time, the unique ability of activating C–O (alkyl) bonds with chromium is exhibited with the aid of amino substituents which gives an extremely selective approach to provide fundamental aryl and alkyl moieties at the ortho position of aromatic aldehydes through the conversion of C–O (alkyl) bonds (Scheme 102) [179].

Two complementary Kumada couplings for the conversion of monotriflated 1,1′-binaphthalene-2,2′-diol (BINOL) into 2′-functionalized binaphthyl monoalcohols based on mild conditions were achieved in 2013 by Slaughter et al. A method using NiCl$_2$(dppe), in combination with an improved preparation of the monotriflate, is effective for 1,1′-binaphthalene-2-ols **244** with unfunctionalized or electron-poor aryl or benzyl 2′-substituents. Another method, using a potentially hemilabile-bidentate phosphinan-4-ol ligand, is superior for products having neopentyl or electron-rich aryl 2′-groups. These binaphthyl alcohols signify potentially valuable synthons for chiral ligands and auxiliaries. Remarkably, based on an optimized condition, including NiCl$_2$(dppe) catalyst and an improved synthesis of **244**, is effective for attachment of unfunctionalized or electron-deficient aryl

Scheme 101



Scheme 103



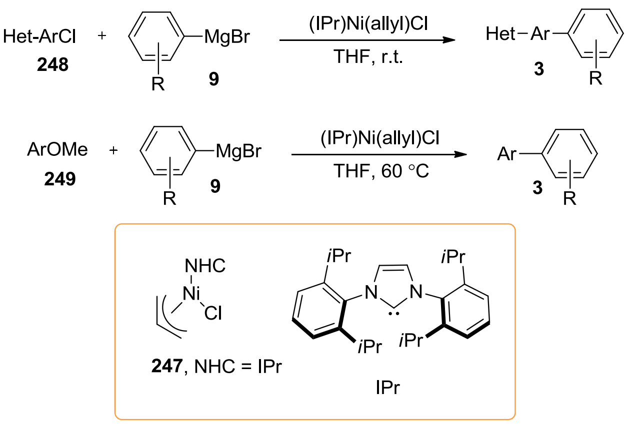
or benzyl groups at the binaphthyl 2′-position. An efficient Kumada cross-coupling approach, using a potentially hemilabile-bidentate phosphinan-4-ol ligand in combination with Ni, gave improved yields for binaphthyl alcohols having alkyl or electron-rich aryl 2′-groups (Scheme 103) [180].

The complex (IPr)Ni(allyl)Cl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidene) mediated the cross-couplings of heteroaromatic chlorides and aryl Grignard reagents. Catalyst loadings as low as 0.1 mol% were applied to provide the corresponding products in high yields. Prieto et al. in 2012 reported an approach for the Kumada–Tamao–Corriu reaction of electrophiles including heteroaryl chlorides and anisoles relied on the application of the (IPr)Ni(allyl)Cl system as the catalyst. Besides, this Ni-based catalytic complex improved the activation of the $C_{Ar}O$ bond of anisoles in the Kumada–Tamao–Corriu reaction using fairly mild conditions (Scheme 104) [181].

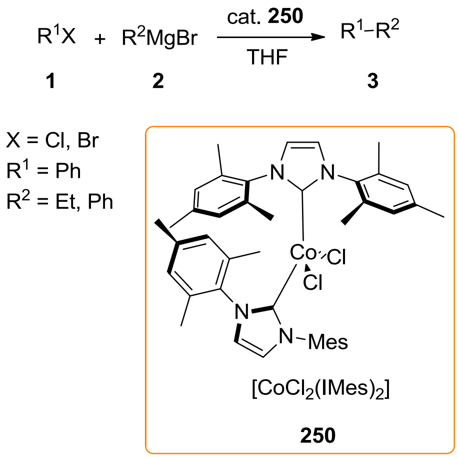
Alkyl compounds of Co(II) having aryl functionalized N-heterocyclic carbene ligands were synthesized by reaction of the precursor chloro systems [$CoCl_2(IMes)_2$] and [$Co_2Cl_2(\mu\text{-}Cl)_2(IPr)_2$] (IMes = 1,3-dimesityl-imidazol-2-ylidene; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) with Grignard reagents. The catalytic activity of [$CoCl_2(IMes)_2$] in Kumada coupling reactions was tested, as is the chemistry of the alkyl complexes toward CO [182] (Scheme 105).

Fe-mediated Kumada coupling reactions of aryl carbamates and sulfamates for the assembly of sp^2–sp^3 carbon–carbon bonds was reported by Garg and et al. A broad examining of reaction parameters were explored, to improve the corresponding sp^2–sp^3 cross-coupling reactions. This included the application of iron(II) chloride as the pre-catalyst, SIMes·HCl **251** as the ligand, tetrahydrofuran as the solvent, and substoichiometric amounts of dichloromethane as an additive. Various heterocyclic substrates underwent the corresponding alkylative process, however sulfamates demonstrated problematic in some cases. With respect to the alkyl Grignard reagent, alternatives to hexyl Grignard could be used, involving reagents with pendant heterocycles, and those with α-or β-branching (Scheme 106) [183].

Scheme 104

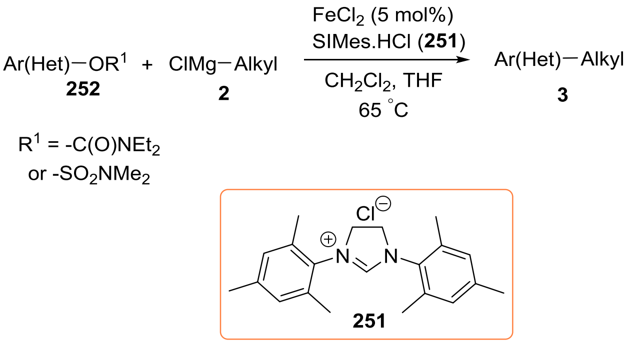


Scheme 105

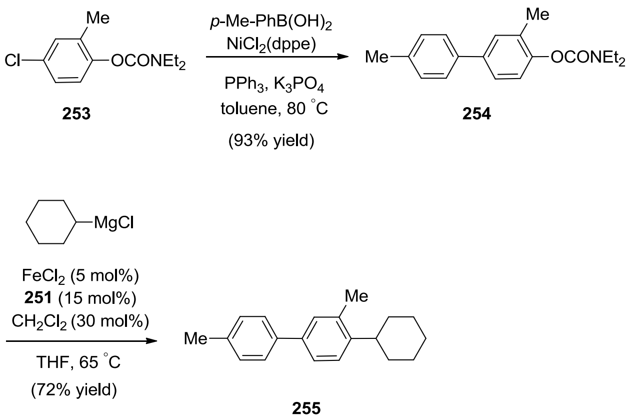


This group examined the efficiency of this approach to steric hindrance and orthogonal reactivity by performing the reaction sequence [184]. Chlorocarbamate **253** that has been synthesized by ortho lithiation/methylation of the relevant carbamate, was subjected to Percec's conditions for nickel-mediated Suzuki–Miyaura coupling [185]. The corresponding carbon–carbon bond construction was performed chemoselectively to afford carbamate **254** in 93% yields. With the carbamate remaining undisturbed, subsequent Fe-mediated Kumada coupling reaction of **254** with cyclohexyl magnesium chloride easily provided product **255**. This latter transformation exhibits the ability of this approach to assemble

Scheme 106



Scheme 107

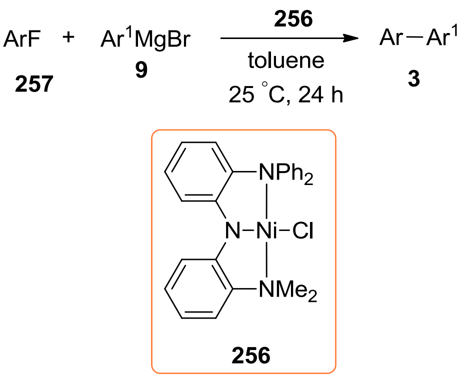


congested carbon–carbon bond linkages in a significant and selective route (Scheme 107).

A wide range of organonickel(II) systems incorporating an amido phosphine ligand tethered with an amino pendant were synthesized in 2012 by Liang et al. Alkylation or arylation reaction of [PNN]NiCl with suitable Grignard reagents in tetrahydrofuran yields [PNN]NiR (R = Me, Et, *i*-Bu, *n*-hexyl, CH_2Ph, Ph). The chloride system [PNN]NiCl was known to be a potent catalyst precursor for Kumada couplings of PhX (X = I, Br, Cl) with alkyl or aryl Grignard reagents, involving those with β-hydrogen atoms (Scheme 108) [186].

P,N,N-Pincer Ni systems $[Ni(Cl)\{N(2\text{-}R_2PC_6H_4)(2'\text{-}Me_2NC_6H_4)\}]$ (R = Ph,; R=Pri, R=Cy,) were used in the Kumada cross-coupling of aryl chlorides and fluorides. Complex **256** successfully mediated the cross-coupling reaction of (hetero)aryl fluorides and aryl Grignard reagents at ambient temperature. Also, complex **256** successfully mediated cross-coupling reaction of various activated, unactivated and deactivated aryl fluoride derivatives and 2- or 3-fluoropyridines with aryl Grignard reagents, providing biaryls in 54–99% yields. Complex **256** is one of the most active Ni catalysts for the Kumada cross-coupling reaction of aryl fluorides (Scheme 109) [187].

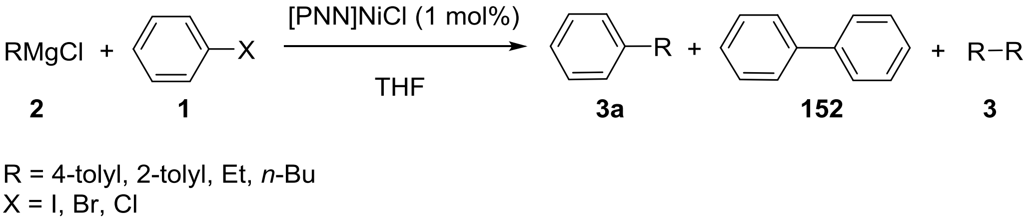
Scheme 109



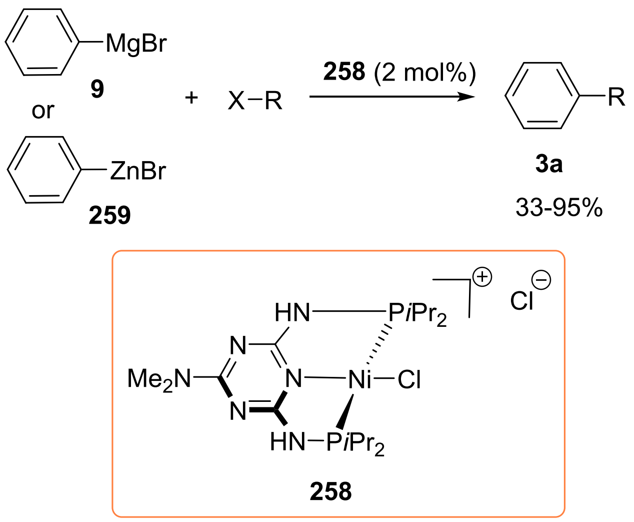
Kirchner et al. in 2017 reported Kumada–Corriu cross-couplings using a Ni(II) PNP pincer system having a triazine scaffold. The catalyst is capable to treat with both activated and inactivated aryl halide derivatives involving chlorides as well as phenols for example mesylates and tosylates to afford the relevant cross-coupling products in moderate to high yields. Catalyst **258** was tested in the coupling reaction of different aryl and heteroaryl halides (chlorides) and *pseudo*-halides (tosylates, triflates) with PhMgBr. Generally, moderate to high yields were detected for most substrates comprising electron donating substituents (OMe) or electron withdrawing substituents (acyl) (Scheme 110) [188].

Ni(II) systems having thiosemicarbazone ligands $[Ni(L)_2]$ (**260** and **261**) (L = 9,10-phenanthrenequinone-thiosemicarbazone (HL **260**), 9,10-phenanthrenequinone-*N*-methylthiosemicarbazone (HL **261**) were introduced in 2015 by Viswanathamurthi et al. The catalytic

Scheme 108



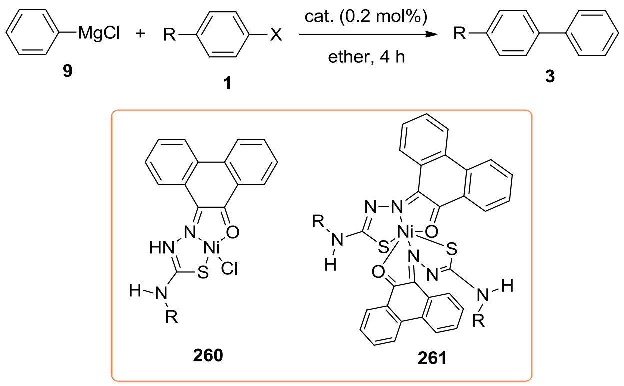
Scheme 110



performance of systems to carbon–carbon Kumada–Corriu coupling reactions was explored. These systems behave as significant catalysts in the Kumada–Corriu coupling reaction [189]. Based on the optimal conditions, it was examined the Kumada–Corriu coupling reactions using different aryl halides. The coupling products were provided in good to high yields. Aryl halide having electron withdrawing groups were known to proceed slightly increased yield than those with electron-donating groups. Furthermore, hetero aromatic halides undergo coupling reactions and afforded the coupled products in increased yield. The coupling of aryl halide containing *ortho* groups afforded good yields (Scheme 111) [189].

Fe-mediated Kumada cross-couplings of pyrimidin-2-yl-phosphates and Grignard reagents were achieved in 2015 by Wang et al. This reaction was performed at ambient temperature in a short reaction time, and the relevant products were synthesized with good to excellent yields. An extensive range of C2- substituted pyrimidine derivatives were synthesized in good yields and various functional groups are well tolerated. The generality of this reaction was examined using different pyrimidin-2-yl phosphates **262** and a wide range of Grignard reagents **9**. Generally, good yields of 50–89% were provided with [Fe(acac)$_3$] as the catalyst **263**. The yield with aliphatic Grignard reagents was upper than with aromatic Grignard reagents since the activity of aliphatic Grignard reagents is higher. It was known that the reactions of pyrimidin-2-yl phosphates having electron-withdrawing substituents (4-Br, 4-Cl, or 4-F) on the aromatic ring afforded upper yields than those having electron-donating substituents (4-methyl or 4-methoxy). Grignard reagents having electron-donating substituents afforded higher yields than those having electron-withdrawing substituents (Scheme 112) [190].

Scheme 111

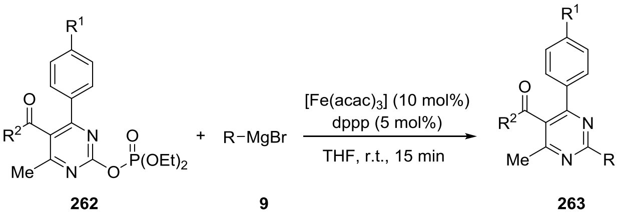


Moreover, Quan et al. tested (5-methyl-pyridin-2-yl)-phosphate and [6-methyl-2-(phenylamino)pyrimidin-4-yl]-phosphate as substrates in the Kumada coupling with *n*-hexylMgBr or phenylmagnesium bromide. The reactions of both substrates afforded the corresponding products **265a–265c** in 63–78% yield (Scheme 113) [190].

Stein et al. in 2015 reported the synthetic potential of organoselenides to cross-coupling with Grignard reagents. The reaction of vinyl, alkynyl, and heteroaryl selenides and 4-methoxyphenylmagnesium bromide mediated by Pd(PPh$_3$)$_4$ in tetrahydrofuran afforded the cross-coupled compounds in moderate yields [191]. They exhibited that vinyl, aryl, alkynyl, and heteroaryl selenides are appropriate substrates to Pd cross-coupling reactions. Generally, Pd(PPh$_3$)$_4$, in dimethylformamide exhibited to be effective for the coupling reaction of organoselenides and Grignard reagents (Scheme 114).

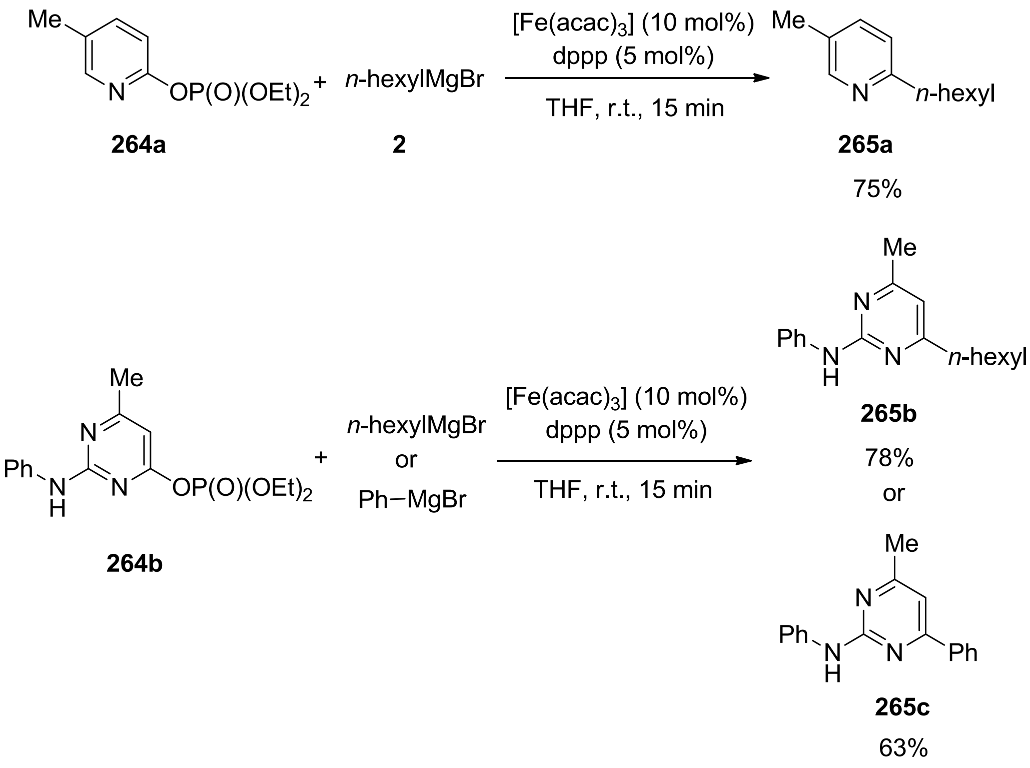
Scheme 115 demonstrates the metal-mediated cross-coupling reaction of the dimethylamino group. For example, Reeves et al. in 2010 reported a one-pot Pd-mediated Kumada coupling reaction with aryl trimethylammonium salts at ambient temperature [192]. The quaternization of the amine **268** with methyl triflate followed by Pd-mediated Kumada coupling reaction with PhMgBr provided the biaryl **269** that demonstrates the synthetic efficacy of the dialkylamino scaffold [193].

Scheme112

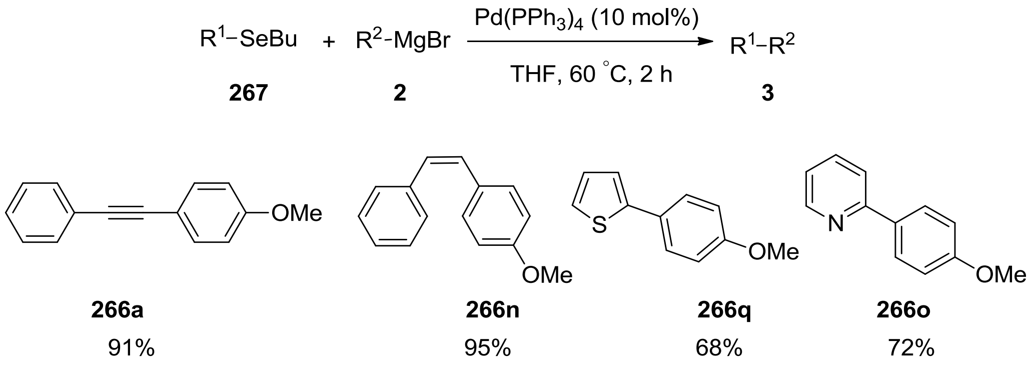


R^1 = H, Me, OMe, Br, Cl, F
R^2 = OEt, OMe

Scheme 113



Scheme 114



Scheme 115

Imidazole and imidazoline (dihydroimidazole) derivatives can be used as facile and effective ligands for the Ni-mediated Kumada–Tamao–Corriu coupling reaction. Among them, the 2-phenyllimidazoline-nickel(II) chloride system showed the maximum catalytic property. The combination of nickel(II) chloride and 2-phenylimidazoline (**270**), it has been tested the reaction of a wide range of functionalized haloarenes and PhMgCl. The functionalized haloarenes containing both of electron withdrawing substituent and electron donating substituent served as a substrate to afford the corresponding coupling compounds in 60–88% yield. Although, inappropriately, in all cases unexpected homo-coupling compounds were provided in 5–25% yield (Scheme 116) [194].

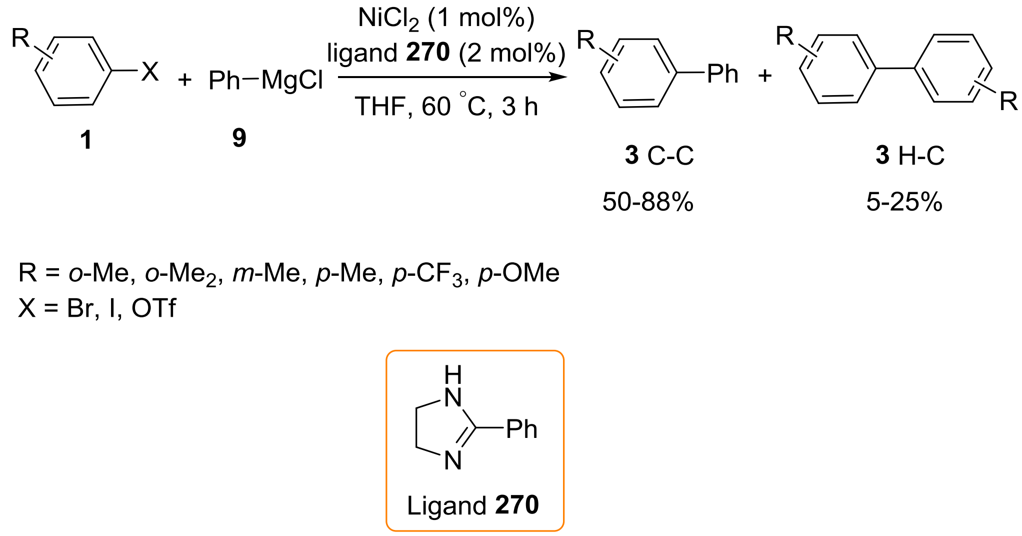
A wide range of 2,4-diarylquinazolines were efficiently provided through the nickel-mediated cross-coupling of quinazoline-4-tosylates and aryl Grignard reagents that afforded alternative straightforward methods for the introduction of aryl substituents to quinazoline derivatives at C-4 position. Lastly, the optimal reaction conditions for the coupling reaction were developed by using Ni(DPPF)Cl_2 and PPh_3 as the catalyst at 60 °C in tetrahydrofuran (Scheme 117) [195].

Also, substrates **273**, having both OTs and aryl chloride **273** (Cl) or bromide **273** (Br) scaffold, have been used based on the identical conditions. Once Grignard **2** treated with 2-(4-Br-phenyl)quinazoline-4-OTs **273** (Br), both of the OTs substituent and the Br substituent can be coupled in a one-pot reaction, giving the corresponding product **275** as the sole product. A low yield (30%) of **275** was provided once equal molecular ratio of **2** : **273** (Br) was applied; although, the yield of compound **275** can be increased to 67% when 4.0 equiv of Grignard **2** was added. For the treatment of Grignard **2** with 2-(4-Cl-phenyl)quinazoline-4-OTs **273** (Cl), the chloride- functionalized product **274** (Cl) and compound **275** can be isolated in 57 and 14% yield when equal molecular ratio of **2** : **273** (Cl) has been utilized, respectively. Although, this situation can be changed once increasing the a mount of the Grignard reagent **2**, since the yield of compound **274** (Cl) reduced slowly and eventually, no product **274** (Cl) can be identified when the amount of Grignard **2** has been improved to 4.0 equiv; the product **275** was extracted in 65% yield (Scheme 118) [195].

Susanto et al. in 2012 explored the application of an oxime-based palladacycle to mediate the Kumada cross-coupling reaction. A precatalyst loading of 0.05 mol% palladium was applied for this reaction. Based on the optimal conditions, it has been extended the reaction to various combinations of Grignard reagents and halides that gave moderate yields of the corresponding product (Scheme 119) [196].

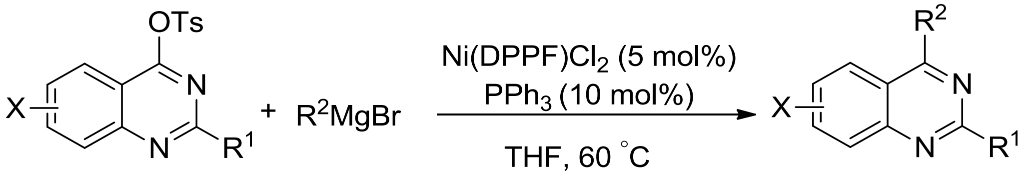
A Ni(II) system $[L^{me}Ni(II)Cl]^{+}(BPh_4)^{-}$ was generated in 2017 by Messerle et al. The catalytic property of this system has been examined in the Kumada cross coupling of PhMgBr and aromatic halogen functionalized substrates. A complex $[L^{me}Ni(II)Cl]^{+}(BPh_4)^{-}$ demonstrated to be the most active catalyst for the cross couplings of chlorobenzene and bromobenzene. Remarkably, it was

Scheme 116



R = *o*-Me, *o*-Me_2, *m*-Me, *p*-Me, *p*-CF_3, *p*-OMe
X = Br, I, OTf

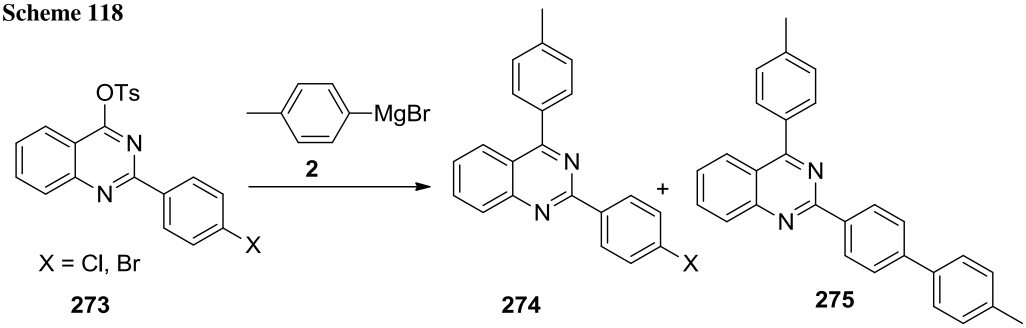
Scheme 117



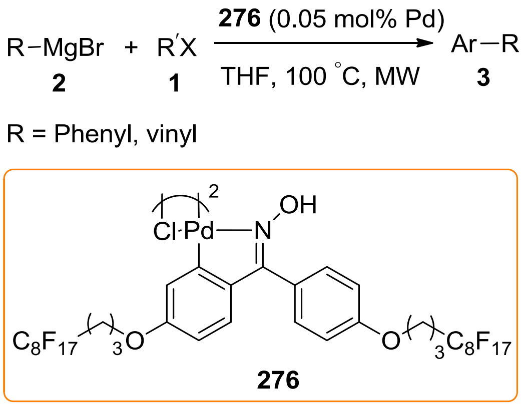
271 **2** **272**

64-88%

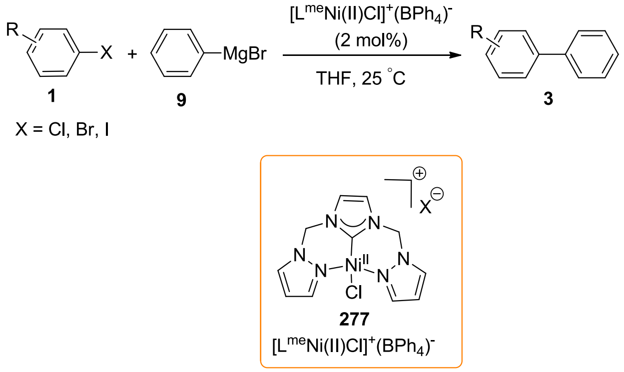
Scheme 118



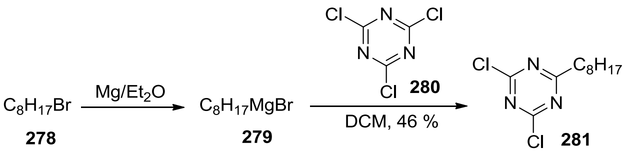
Scheme 119



Scheme 120



Scheme 121



examined as a catalyst for the conversion of a number of substrates with PhMgBr. It was selected to use a catalyst loading of 2 mol%, as this afforded the best yield. Obviously, iodobenzene afforded quantitative transformation to biphenyl product (Scheme 120) [197].

Heteroarylation of Grignard compounds

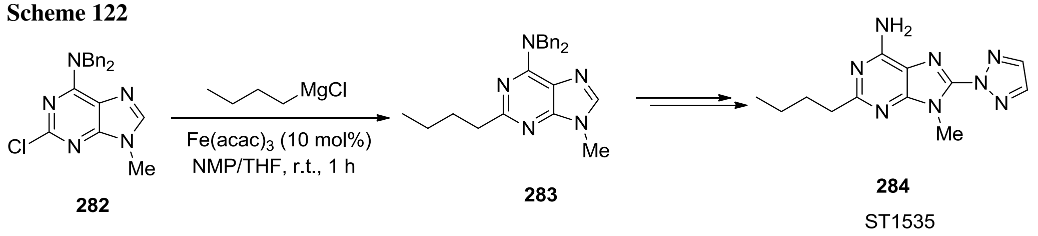
Using 2,4,6-trichloro-1,3,5-triazine as starting precursor, a substituted triazine derivative, 4-(naphthalen-1-yl)-6-octyl-1,3,5-triazin-2-amine (NOTA) has been provided in 4% yield via three steps: Kumada cross-coupling, Suzuki coupling and amination. 2,4-Dichloro-6-octyl-1,3,5-triazine (**281**) has been provided in 46% yield through Kumada coupling reaction with Grignard reagent of 1-bromooctane and 2,4,6-trichloro-1,3,5-triazine in dry dichloromethane (Scheme 121) [198].

A simple, useful, and eco-friendly method to ST1535 (**284**) using a Fe- mediated cross-coupling and BuMgCl was reported. The treatment of 2-chloropurine (**282**) with the *n*-butyl Grignard reagent in tetrahydrofuran was performed using 10 mol% of iron(III) tris(acetylacetonate) [Fe(acac)$_3$] as the precatalyst in tetrahydrofuran/*N*-methyl-2-pyrrolidone (NMP) at ambient temperature to afford **283** in 91% yield. Outstandingly, this stage was found as a main step in the formation of ST1535. Competitive reactions with the alkyl organometallics (for example spontaneous decomposition through β-elimination or by proto-demetalation, isomerization or homocoupling) did not happen (Scheme 122) [199].

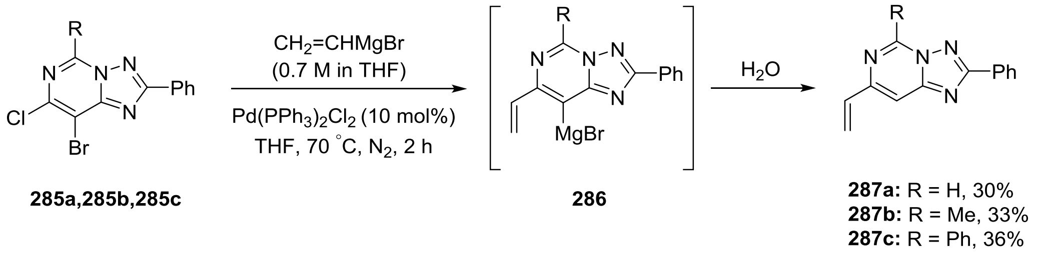
8-Bromo-7-chloro [1, 2, 4] triazolo[4,3-*c*]pyrimidine derivatives were synthesized through bromine-catalyzed oxidative cyclization reaction of the aldehyde-derived hydrazones. The Kumada coupling reaction of compounds **285** with vinylmagnesium bromide with 10 mol% Pd(PPh$_3$)$_2$Cl$_2$ as catalyst was effective. The Kumada cross-coupling reaction occurred at C-7 giving the 7-vinyl-functionalized and C-8 debrominated product **287** in satisfactory yields. An original magnesium-bromine exchange method and subsequent protonation of the intervening species **286** tentatively clarify the detected debromination (Scheme 123) [200].

The application of low-valent Fe^0 and Fe^I systems in aryl-heteroaryl Kumada cross-coupling reaction was examined, and it is found that the zerovalent Fe^0 species was applied successfully as a precursor in this reaction, while the Fe^I oxidation state does not display any reactivity. The iron salts are effective catalysts in Kumada couplings [201, 202]. They

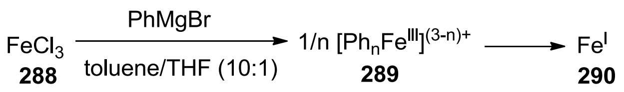
Scheme 122



Scheme 123



Scheme 124

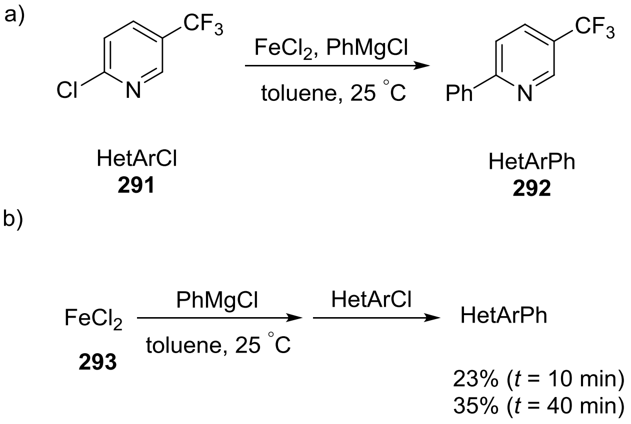


$$\underset{\mathbf{288}}{FeCl_3} \xrightarrow[\text{toluene/THF (10:1)}]{PhMgBr} \underset{\mathbf{289}}{1/n\,[Ph_nFe^{III}]^{(3-n)+}} \longrightarrow \underset{\mathbf{290}}{Fe^{I}}$$

do not benefit from the presence of stabilizing acac-ligands and are more electron-deficient, being thus more readily reduced by phenylmagnesium bromide. Unlike the reduction of Fe(acac)$_3$, the reduction of iron(III) chloride using 1 equiv of phenylmagnesium bromide gives a combination of a low-spin Fe^{I} system and high-spin Fe^{III} unidentified species. These results support the construction of transient polyphenyl-Fe^{III} species [203] that can evolve to the construction of Fe^{I} (Scheme 124) [204].

The reactivity of these complexes was examined in aryl-heteroaryl Kumada cross-coupling reactions. 2-Chloro-5-(trifluoromethyl)pyridine (HetArCl) was applied as an electrophilic partner in catalytic reactions: chloropyridines demonstrated indeed to be significant cross-coupling partners in co-ligand-free Fe-mediated approaches (Scheme 125) [201, 202].

Scheme 125

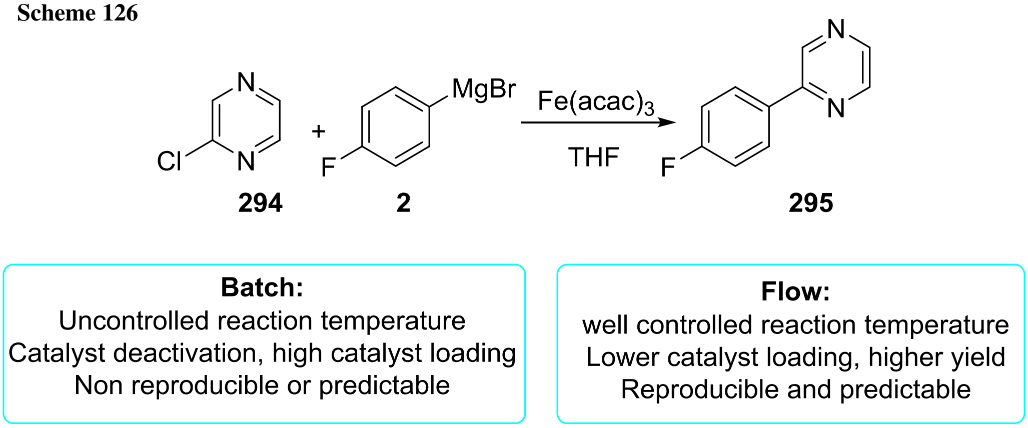


An effective continuous flow Fe-mediated Kumada cross-coupling reaction was established for the coupling reaction of 2-chloropyrazine and different aryl Grignard reagents using low catalyst loadings (0.5 mol%). Compared to batch mode, the continuous flow method overcomes the exothermicity that permitted longer catalyst lifetime, assisted scale-up and considerably increased the yield. Buono et al. in 2016 reported the development of a continuous flow process which solved these challenges and permitted an Fe-mediated cross-coupling reaction of 2-chloropyrazine with Grignard reagents in excellent yields at low catalyst loadings (Scheme 126) [205].

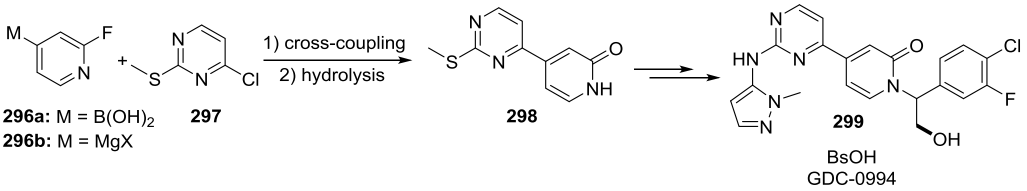
Pyridone **298**, a key intermediate in the construction of ERK inhibitor GDC-0994, was provided through a cross-coupling/hydrolysis sequence from market purchasable precursors. Carbon–carbon bond construction was accomplished through an effective Pd-mediated Kumada-Corriu cross-coupling (Scheme 127) [206].

Due to the lack of extremely sensitive functional groups in the target compound, this group guessed that a metal mediated Kumada–Corriu cross-coupling could permit admittance to **301** [207–211]. The 4-pyridylmagnesium halide reagent **296** was provided via a halogen-metal exchange with *i*-PrMgCl·LiCl in tetrahydrofuran [212]. The Kumada–Corriu cross-coupling was accomplished by introducing **296** into a combination of 2-chloropyrimidine **297** and a particular

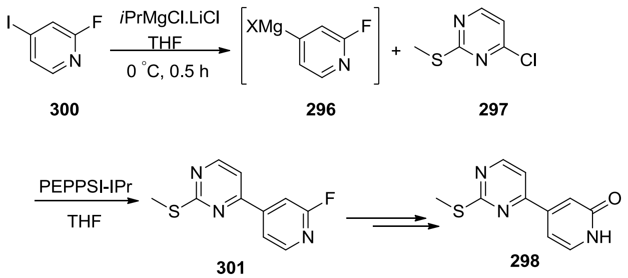
Scheme 126



Scheme 127



Scheme 128



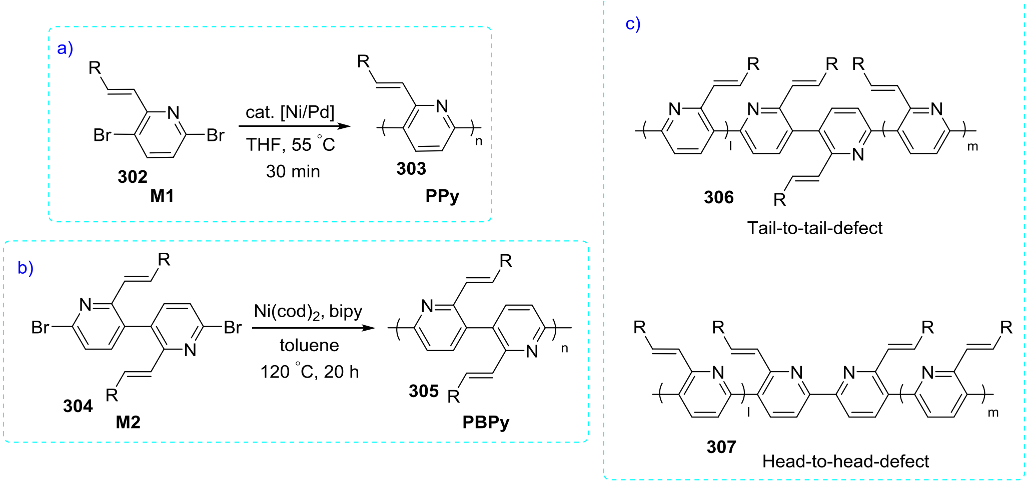
catalyst in tetrahydrofuran. A brief catalyst screen demonstrated that the palladium-mediated cross-couplings afforded improved transformations in comparison with other transition metal catalysts. The screen demonstrated PEPPSI-IPr [213] as an effective catalyst for the Kumada–Corriu cross-coupling reaction (Scheme 128) [214].

Grandl et al. in 2015 reported the formation of head-to-tail regioregular poly[6-(1-tridecenyl)-pyridine-2,5-diyl] (PPy) and its post-functionalization through hydroboration. For the construction of the polymeric substrate, it was selected Kumada-coupling polycondensation, of in situ provided AB-bifunctional monomers [215]. This type of cross-coupling polymerization was extremely efficient in the synthesis of an extensive range of polyarenes, alkyl, and alkoxy-functionalized polypyridines [216–219]. Polymerization of M1 **302** to polypyridine PPy **303** was accomplished through Ni - and Pd-mediated Kumada-type cross- coupling reaction of in situ provided 9-MgCl with various catalytic systems (Scheme 129).

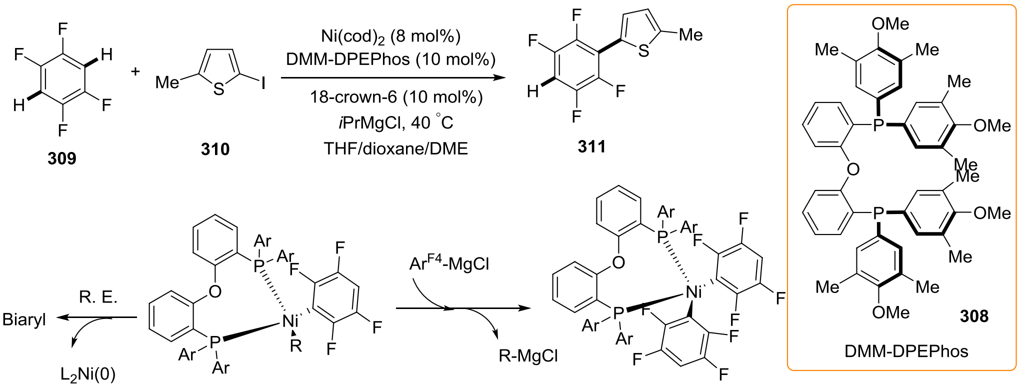
In 2017, Wang et al. reported a unique selective monoarylation method for effective synthesis of polyfluorinated biaryl, combining a Ni catalyst and highly electron-deficient Grignard reagents Ar^{Fn}-MgCl provided spontaneously from relevant fluoroarenes. The examination of this novel synthetic method was initiated from the isolation of the catalysis arrest state, an unexpected stable cis $[(Ar^{F4})_2Ni(DPEPhos)]$ system (Ar^{F4} = 2,3,5,6-tetrafluorophenyl), which originated from the second transmetalation that went undiscovered for a long time in Kumada–Tamao–Corriu coupling reaction of intermediate Ar–Ni–Ar^{F4} and excess Ar^{F4}-MgCl. In the presence of newly developed DMM-DPEPhos and necessary additives, an effective and common Ni catalysis is built up to provide different significant poly fluorinated biaryls in both high yield and monoselectivity (monos) with a serial of aryl, heteroaryl, and vinyl triflates, as well as thiophene iodides based on mild conditions (Scheme 130) [220].

The development of extremely selective mono-arylation reaction of tetrafluorobenzene demonstrated the probable directions in arylation reaction of tetrafluorobenzene through Kumada–Tamao–Corriu coupling. It was reasoned that selective monoarylation reaction of 1,2,4,5-tetrafluorobenzene with two equal acidic C–H bonds might be attainable by using spontaneously-provided Ar^{F4}-MgCl as a coupling partner, if the coupling could be found with an effective Ni catalyst based on mild conditions. First, in situ-provided species A is stabilized using three coordinated solvents via

Scheme 129



Scheme 130



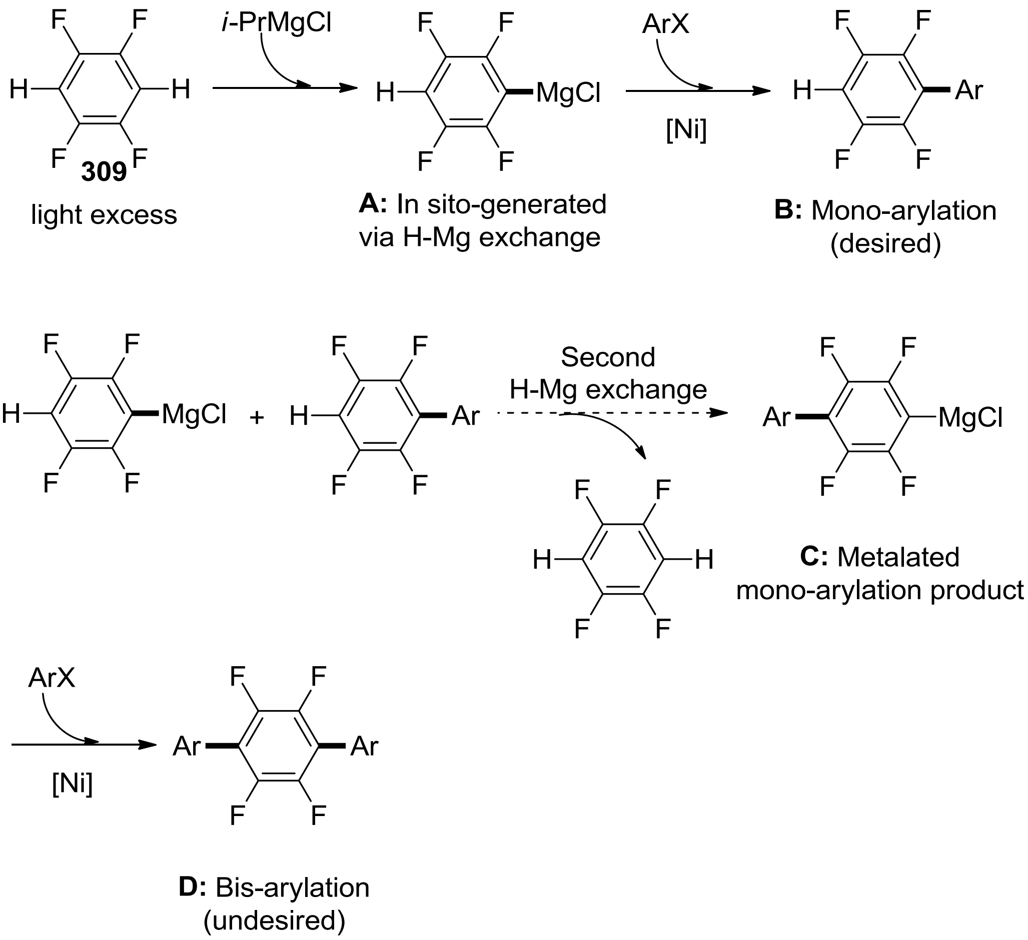
X-ray crystallography and astonishingly has a long half-time as tracked by ^{19}F nuclear magnetic resonance (NMR) at ambient temperature that leaves adequate time for the Ni catalyst to fully transform aryl electrophiles. Second, the lower basicity of species A relative to that of *i*-PrMgCl would retard secondary H-Mg exchange between A and monoarylated product B particularly were dioxane applied as a co-solvent, consequently dramatically diminishing the extent of construction of C and bisarylated byproduct D. Finally, the good functional group tolerance of A would be beneficial with respect to practical synthesis (Scheme 131) [220].

Asymmetric Kumada–Tamao–Corriu cross-coupling reactions

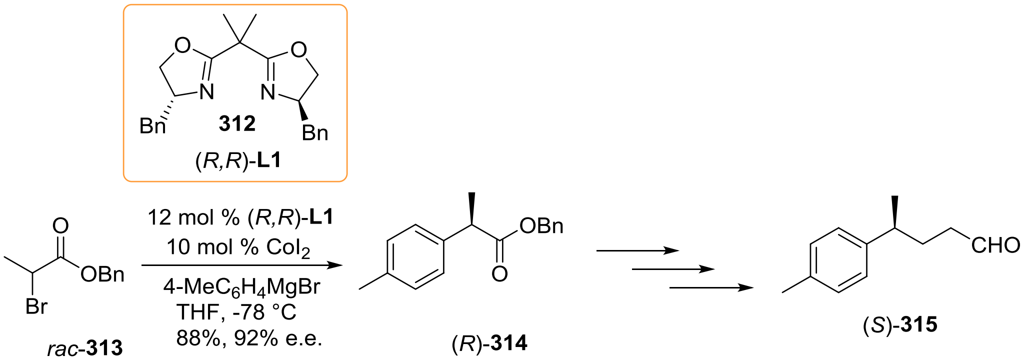
A significant and short enantioselective synthesis of (*R*)-(+)-ar-curcumene, (*R*)-4,7-dimethyl-l-tetralone, and their enantiomers was performed in 2016 et al. [221]. The main stage to create the stereogenic benzylmethyl centers of these naturally occurring compounds is the Co-mediated enantioselective Kumada cross-coupling of a racemic α-bromo ester. The great deal of attention on the asymmetric Kumada coupling stems from its capacity to produce tertiary or quaternary carbon centers [222]. This group established the first Co-mediated enantioselective Kumada cross-coupling with high e.e. (up to 97% e.e.) and yield (96% yield) that could make a stereogenic benzylmethyl center directly. Remarkably, this group reported an expanded usage of this approach to a significant and short enantioselective synthesis of (*R*)-(+)-ar-curcumene, (*R*)-4,7-dimethyl-l-tetralone, and their enantiomers. The main strategies of this method include the Co-mediated enantioselective Kumada cross-coupling of racemic α-bromo ester, the Wittig olefination of the aldehyde, and also the intramolecular Friedel-Crafts acylation reaction of carboxylic acid (Scheme 132).

Nickel-mediated Kumada coupling reaction of symmetric cyclic sulfates is a significant approach for developing enantioselective carbon centers. Using the catalyst system **316**, the reaction happened with moderate selectivity for the formation of tertiary hydrocarbon centers. These reactions are

Scheme 131



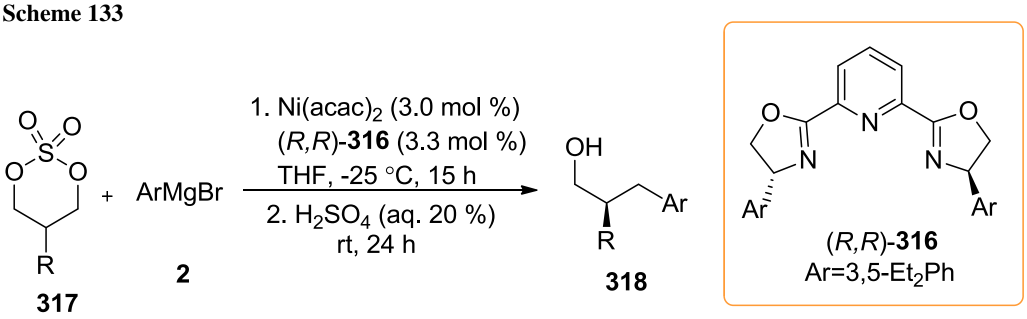
Scheme 132



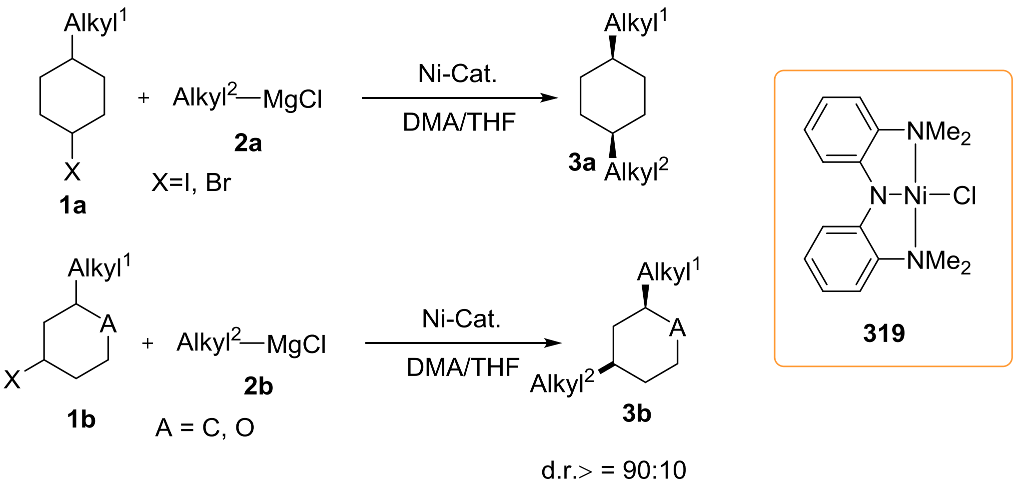
effective with a wide range of functionalized cyclic sulfates and provide the corresponding products with enantioselective tertiary carbon centers (Scheme 133) [223].

In 2012, Hu et al. established a Ni-mediated diastereoselective alkylalkyl Kumada coupling for 1,3- and 1,4-functionalized cyclohexyl halides and tetrahydropyrans. High d.e. was provided using the Ni pincer catalyst **319**. The d.e. is controlled by the conformational preference of the Ni-alkyl intermediates. Fortuitously, it was provided proof for the reversible activation of alkyl halide in the Ni catalysis that gave important data for mechanistic considerations of

Scheme 133



Scheme 134

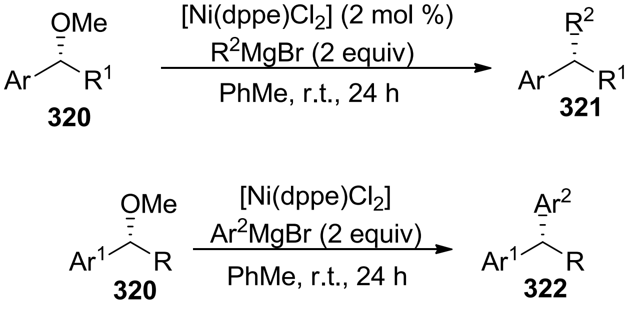


the Ni-mediated cross-coupling reaction of nonactivated alkyl halides (Scheme134) [224].

Jarvo et al. in 2014 established a stereospecific Ni-mediated Kumada cross-coupling reaction, which tolerates Grignard reagents with extended alkyl chains. Besides, this catalytic system is appropriate to reactions of aryl and heteroaryl magnesium reagents for the formation of 1,1-diarylalkane derivatives. Reactions usually were performed with improved e.e. at lower catalyst loadings, and mechanistic tests are consistent with racemization of the *p*-benzyl Ni intermediate (Scheme 135) [225].

Jarvo et al. reported their investigations in establishing Ni-mediated stereospecific cross-couplings of secondary electrophiles. These approaches afforded a unique method for the formation of enantioenriched medicinal agents having properties against a wide series of targets. In Kumada couplings, a full complement of Grigard reagents, involving methyl, aryl, *n*-alkyl, and Grignard reagents were used. In the current reactions using MeMgI, ligation of the Ni catalyst using *rac*-BINAP or DPEphos gave the maximum yield and stereospecificity. For all other Grignard reagents, $Ni(dppe)Cl_2$ has appeared as the greatest catalyst (Scheme 136) [226].

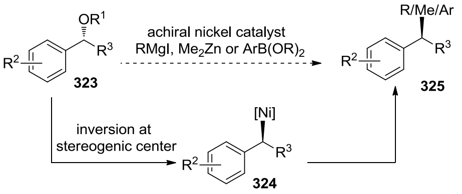
Scheme 135



Jarvo et al. in 2015 reported the potential of stereospecific Ni-mediated cross-couplings for usages in the medicinal industry. Using a cheap and sustainable Ni catalyst, they reported a gram-scale Kumada cross-coupling reaction. Remarkably, cross-couplings of benzylic ethers were performed in excellent yields and stereospecificity on gram-scale (Scheme 137) [227].

In 2014, Jarvo et al. reported the stereospecific ring-opening of *O*-heterocycles to afford acyclic alcohols and carboxylic acids with controlled construction of a novel carbon–carbon bond. Remarkably, these reactions afforded novel approaches for synthesis of acyclic polyketide analogs

Scheme 136



with complex stereochemical arrays. Stereoselective synthesis of the cyclic template was used to control relative configuration; subsequent stereospecific Ni-mediated ring-opening gave the acyclic product. Aryl-functionalized tetrahydropyrans and tetrahydrofurans undergo Ni-mediated Kumada-type coupling reaction having a wide series of Grignard reagents to provide acyclic alcohols with excellent d.e. Enantioenriched lactones undergo Negishi-type cross-coupling reaction with dimethylzinc to provide enantioenriched carboxylic acids. Application in a two-step asymmetric synthesis of an antidyslipidemia agent was exhibited (Scheme 138) [228].

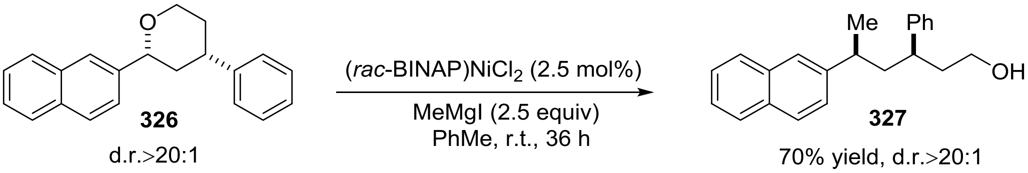
The first Co-mediated enantioselective Kumada cross-coupling reaction with excellent e.e. was established in 2014 by Zhong et al. The reaction gave a novel method for the asymmetric arylation reaction of α-bromo esters mediated using a Co-bisoxazoline system. A broad range of chiral α-arylalkanoic esters were synthesized in high e.e. (up to 97% e.e.*)* and yield (96%). The arylated products were converted to α-arylcarboxylic acids and primary alcohols without erosion of enantioselectivity. The novel enantioenriched α-arylpropionic esters provided are possibly valuable in the establishment of nonsteroidal anti-inflammatory drugs. This approach was performed on gram-scale and used to the formation of extremely enantioenriched (*S*)-arturmerone and (*S*)-fenoprofen (Scheme 139) [229].

Nakamura in 2015 reported the first instance of asymmetric Fe-mediated cross-coupling reactions of α-chloroesters **334** and aryl Grignard reagents with chiral bisphosphine ligand P* **333** (Scheme 140) [230].

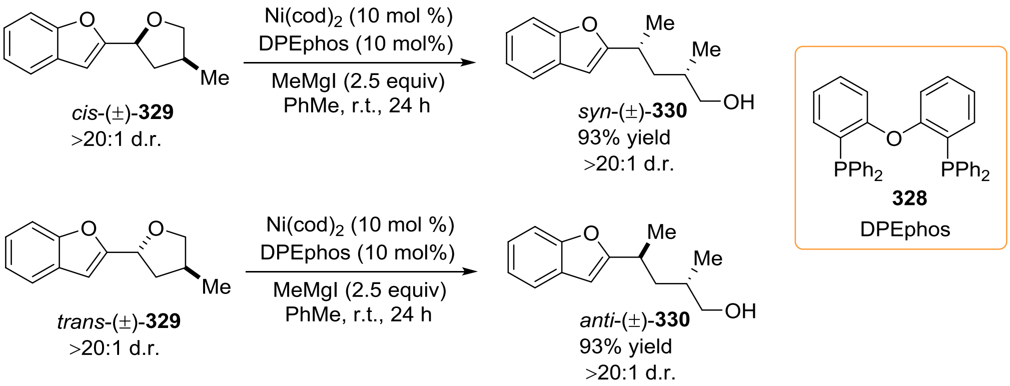
Stereoselective Pd-mediated Kumada–Corriu reactions of substituted alkenyl halide derivatives and a wide range of Grignard reagents, containing β-hydrogen atoms and sensitive functional substituents were performed at ambient temperature with a new mixture of reagents. The sterically hindered bidentate diphosphine ligands dtbpf and DPEPhos, using TMEDA, make a significant combination leading to effective palladium-mediated Kumada–Corriu couplings of alkenyl halides in tetrahydrofuran at ambient temperature. In the case of cross-coupling reaction of the Grignard reagents containing reactive functionalities, DPEPhos/TMEDA demonstrated to be an improved system affording the corresponding products in increased yields (Scheme 141) [231].

This approach compares favorably with the methods and consequences stated by Oshima [232] (Scheme 142, path A; CyOMe = cyclopentyl methyl ether) and Cahiez [233] (Scheme 142, path B). Fascinatingly, in this case once again both DPEPhos and dtbpf ligands gave corresponding product **339** with very analogous conversions and isolated yields. Similarly, direct comparison with the conventional report of Hayashi [234], e.g., transformation of Grignard **340** and

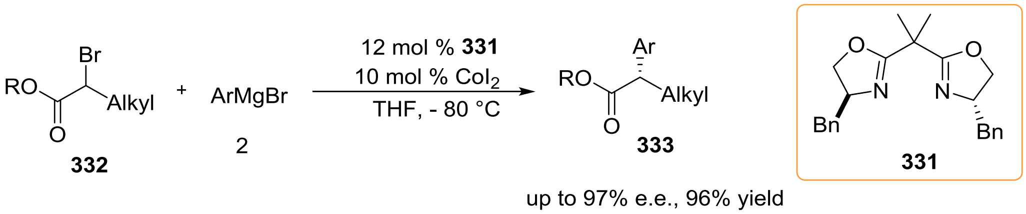
Scheme 137



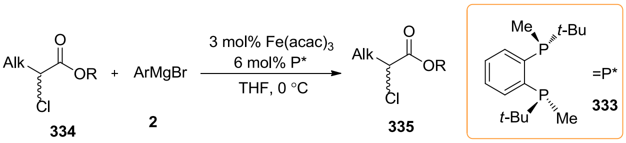
Scheme 138



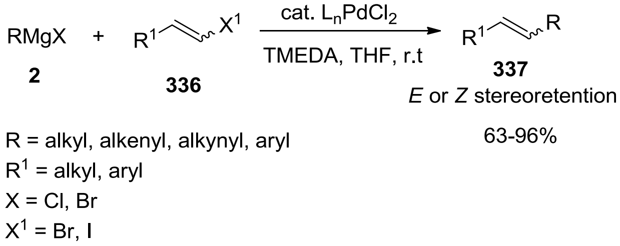
Scheme 139



Scheme 140



Scheme 141

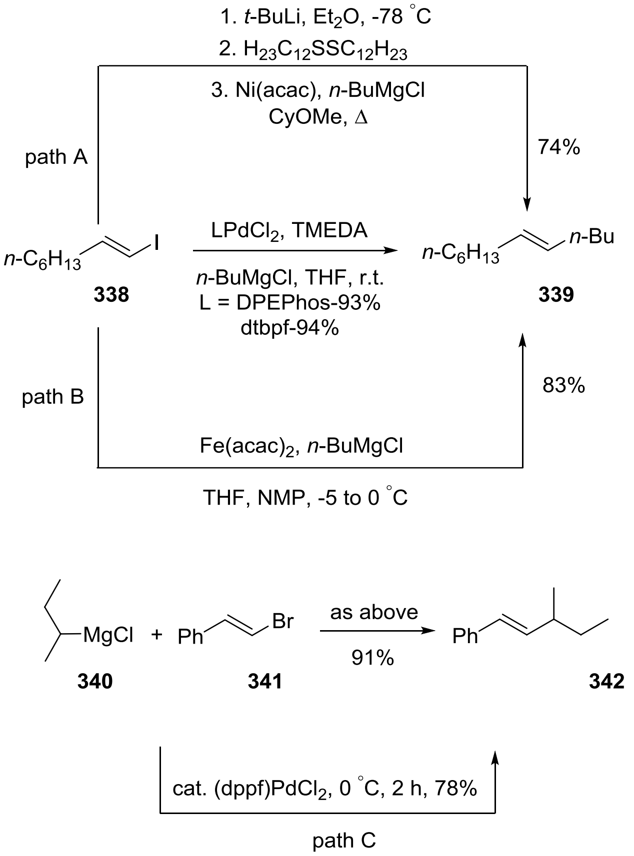


alkenyl halide **341** to product **342** (Scheme 142 path C), is again indicative of the positive influence of both the change in ligand, as well as the application of TMEDA.

Conclusion

In summary, in this review, we tried to update our previous review published in 2012 on the developments in Kumada–Tamao–Corriu Ni-catalyzed cross-coupling reactions for the formation of C–C bond, till date. Several selected recently reported examples such alkylation, alkenylation, arylation, and heteroarylation of Grignard compounds were described. In addition some examples of asymmetric Kumada–Tamao–Corriu cross-coupling reaction, employing different chiral catalysts and ligands were also discussed. Much attention has been paid on replacing expensive and toxic Pd by Ni in recent years. Thus, Ni-catalyzed Kumada–Tamao–Corriu cross-coupling reaction and particularly its asymmetric variant are expected, being a fast-moving topic, persistently in the future. We hope this review attracts the attention of synthetic organic chemists, worldwide and stirring up the strong interest among the wide-ranging readership of this journal.

Scheme 142



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