

Kumada–Tamao–Corriu cross-coupling reaction of O-based electrophiles with Grignard reagents *via* C–O bond activation

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Kumada–Tamao–Corriu coupling reaction catalyzed by transition-metal has been widely used in organic synthesis. Organic halides are mostly used as electrophiles in this reaction. Compared with organic halides, O-based electrophiles are less explored. In this review, we summarized the Kumada–Tamao–Corriu coupling reaction of O-based electrophiles, including sulfonates, phosphates, ethers, and carboxylates.

1. Introduction

Transition-metal-catalyzed cross-coupling reactions play an important role in organic synthesis, medicinal and chemistry processes, nanotechnology and chemical biology.¹ Their significance has attracted more and more attention since the 2010 Chemistry Nobel prizes “for palladium-catalyzed cross couplings in organic synthesis”. Among these cross-coupling reactions, Kumada coupling reaction, which was reported independently in 1972 by the groups of Makoto Kumada² and Robert Corriu,³ occupies a special place.

Organic halides with relatively high reactivity are frequently used as electrophiles in Kumada–Tamao–Corriu coupling reaction. Alternatively, O-based electrophiles are gaining increasing interest in recent years. The advantages of O-based

electrophiles include: (1) easy to synthesise, cheaper and environmentally benign, (2) decrease the production of halide waste, (3) the potential orthogonal reactivity exposed to organic halides.^{4a} However, there are still several challenges in the application of O-based electrophiles in cross-coupling reactions, such as the difficulty of differentiating the two bonds linked to oxygen atom and the cleavage of “inert” C–O bond with relatively high bond dissociation energy (BDE).^{4b} Nevertheless, promoted by the great application prospect, much progress has been made in this area. In some cases, high yield could be obtained under the appropriate conditions.

In this review, we summarize the Kumada–Tamao–Corriu cross-coupling reaction of O-based electrophiles with Grignard reagents in the past few years. Phosphate, tosylates, ethers and carboxylates will be discussed. As far as we know, Kumada coupling^{4a–g} of alkyl electrophiles through C–O bond activation is rarely discussed. Herein, both alkyl electrophiles and aryl/vinyl electrophiles participated Kumada reaction will be discussed.

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2. Kumada–Tamao–Corriu coupling of C(sp²)-O based electrophiles

2.1. Alkenyl/aryl phosphates as electrophiles in Kumada–Tamao–Corriu coupling

As early as the 1980s, the cross-coupling of phosphates has been achieved.⁵ For example, in the presence of NiBr₂ as a catalyst, the cross-coupling between alkenyl phosphates and Grignard reagent was realized by Kumada and co-workers in high yields (Scheme 1).^{5c} Due to the excellent reactivity and readily available alkenyl phosphates, this reaction was applied to synthesize many other interesting molecules.⁶

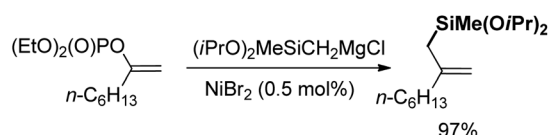
In comparison with alkenyl phosphates, aryl phosphates are less reactive. Thus, electron-donating ligands are required in most cases. The first cross-coupling of aryl phosphates with Grignard reagents was reported by Kumada and co-workers in the presence of nickel catalyst with moderate to high yields (Scheme 2).⁷

Hydroxyphosphine ligands (PO ligands) were found to accelerate nickel-catalyzed cross-coupling reactions of aryl phosphates significantly. Experiments and theoretical calculations indicate that through reduction of Ni(II) to Ni(0) and deprotonation of the PO ligand, the Ni(II) pre-catalyst, PO ligand and Grignard reagent could form a nickel/magnesium bimetallic catalytic species and then this catalytic species carried out push–pull, cooperative activation of the aryl phosphates (Scheme 3).^{8a}

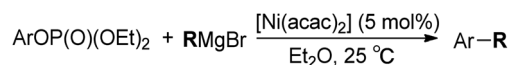
Through analysis of kinetic isotope effects and theoretical calculations,^{8b} mechanism of Ni-catalyzed Kumada–Tamao–Corriu reactions was proposed: first, oxidative addition occurs to afford the Ni(II) intermediate, after transmetalation with RMgY, the desired products will be formed through reductive elimination. In addition, the ligand exchange process may be the first irreversible step and may affect the turnover efficiency and the selectivity of the reaction (Scheme 3).

The first enantioselective coupling of alkenyl phosphate was achieved by Hayashi and co-workers⁹ *via* the merge of (*R*)-*N*, *N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine ((*R,S*)-PPFA) as chiral ligand and PdCl₂ as a catalyst. But the enantioselectivity was not very high.

The direct conversion of enolizable ketones to alkylated or arylated olefins was realized through the reaction between *in situ*-generated enol phosphate intermediates and Grignard reagents. When PdCl₂(PPh₃)₂ was used as a catalyst, moderate to high yields can be obtained.¹⁰ In 2009, Skrydstrup and co-workers found that cross-couplings of nonactivated cyclic and acyclic vinyl phosphates with aryl magnesium reagents could proceed at room temperature by using simple palladium salt (PdCl₂) and phosphine ligands were not necessary. This system



Scheme 1 Nickel-catalyzed Kumada coupling of vinyl phosphates.



Scheme 2 Nickel-catalyzed Kumada coupling of aryl phosphates.

was environmentally friendly because of the avoidance of expensive ligands and thermal energy (Scheme 4).¹¹

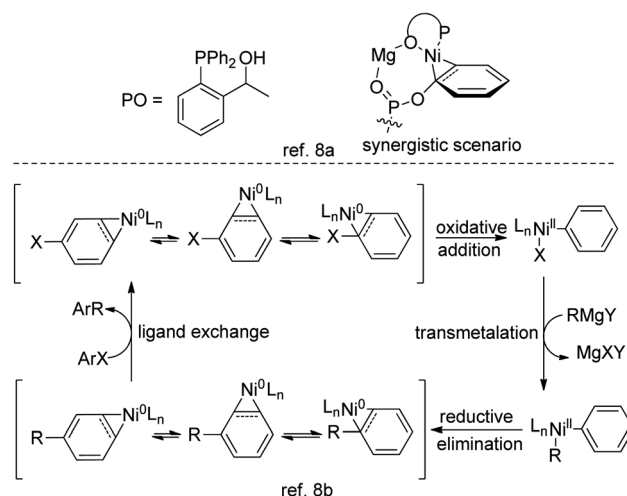
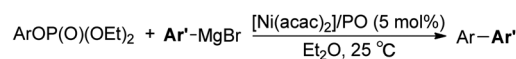
Heteroaromatic phosphates were also found to react with Grignard reagents to afford the desired products with good to high yields (Scheme 5). A strong electron-donating, chelating diphosphine ligand was required to accelerate this palladium-catalyzed reaction.¹²

Besides palladium and nickel, iron could also catalyze the cross-coupling of enol phosphates with Grignard reagents (Scheme 6). In the presence of Fe(acac)₃, stereospecific trisubstituted olefins could be easily obtained.¹³ Terminal conjugated dienes could also be prepared under similar reaction conditions.¹⁴ This method was subsequently adopted for the synthesis of the pheromone of *Diparopsis castanea*.

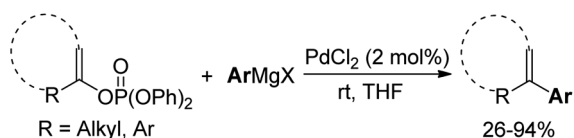
2.2. Alkenyl/aryl sulfonates as electrophiles in Kumada–Tamao–Corriu coupling

In the presence of nickel as a catalyst, Snieckus and co-workers¹⁵ described the coupling of aryl O-sulfamate with aryl Grignard reagents. The new reactions extended directed *ortho*-metalation (DoM) concept and protocols for application in organic synthesis (Scheme 7). This concept was then exploited by Bois and co-workers¹⁶ to synthesize functionalized biaryls. Both alkyl and aryl Grignard reagents were tolerated in this system.

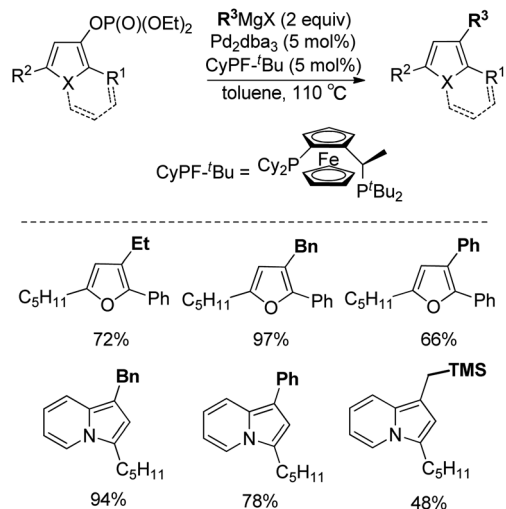
In 2010, diaryl sulfates were applied as electrophiles in Kumada coupling by Shi group.¹⁷ Biaryls could be obtained in high efficiency with the emission of harmless inorganic salts (Scheme 8). Polyarenes could be synthesized efficiently using this method.



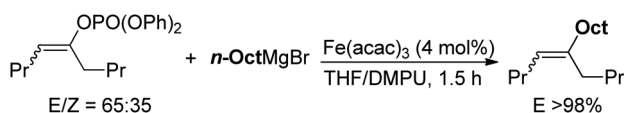
Scheme 3 Nickel-catalyzed Kumada coupling of aryl phosphates.



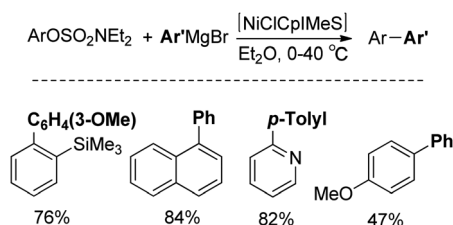
Scheme 4 Palladium-catalyzed Kumada coupling of vinyl phosphates.



Scheme 5 Palladium-catalyzed Kumada coupling of vinyl phosphates.



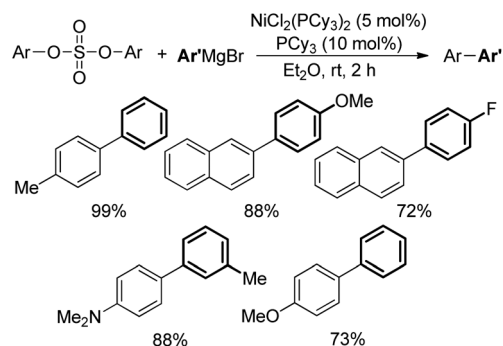
Scheme 6 Iron-catalyzed Kumada coupling of vinyl phosphates.



Scheme 7 Kumada coupling of aryl sulfamates, Cp = cyclopentadienyl, Imes = 1,3-dimesitylimidazol-2-ylidene.

Recently, a new class of air-stable diaminophosphine oxides was developed by Jin, Fang *et al.*¹⁸ When they were applied to Kumada coupling reaction, good to high yields were obtained. A cooperative Ni/Mg bimetallic action mode maybe incorporated in this system (Scheme 9).

Compared with aryl/alkenyl tosylates, aryl mesylates were rarely studied. In 1995, Percec and co-workers¹⁹ described the nickel-catalyzed Kumada coupling of aryl mesylated with aryl Grignard reagents. But the yields and selectivity were not very high. Of note, except for this example, no report of aryl mesylates with Grignard reagents is available for the Kumada



Scheme 8 Construction of biaryls through Ni-catalyzed Kumada coupling.

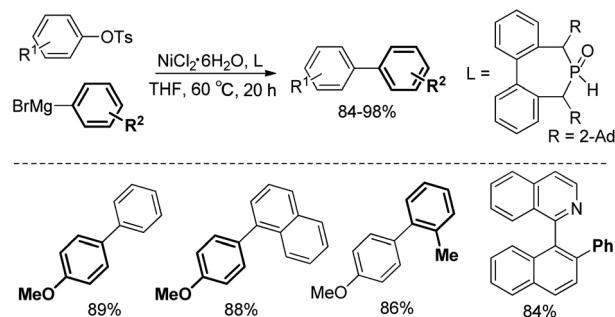
coupling reaction. Further studies are required to expand the substrate scope and potential applications (Scheme 10).

In the presence of electron-rich, sterically bulky chelating diphosphine as ligand, Hartwig and co-workers observed the oxidative addition of aryl tosylate to palladium center and successfully isolated the key intermediate.²⁰ Inspired by this progress, they achieved the palladium-catalyzed coupling of aryl and alkenyl tosylates with aryl, alkenyl and alkyl Grignard reagents. The desired products were obtained with good to high yields at room temperature (Scheme 11).²¹

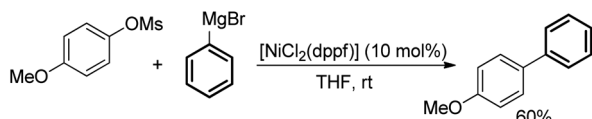
Ackermann and co-workers²² found that an air-stable and easily accessible PinP(O)H was an efficient ligand for palladium-catalyzed Kumada cross-coupling reactions of aryl tosylates substrates, including electron-rich and electron-poor carbocyclic tosylates as well as heterocyclic tosylates were well tolerated in this system (Scheme 12).

Iron was also an efficient catalyst for this coupling reaction. Fürstner and co-workers disclosed the iron-catalyzed Kumada coupling of aryl tosylates with alkyl Grignard reagents (Scheme 13).²³ Various sensitive functional groups were tolerated in this reaction because of the mild reaction conditions. Whereas, nonactivated aryl tosylates were not well tolerated in this system. This was a major advance in the area of Kumada coupling reaction of tosylates. A low-valent iron intermediate may be incorporated in this reaction.²⁴

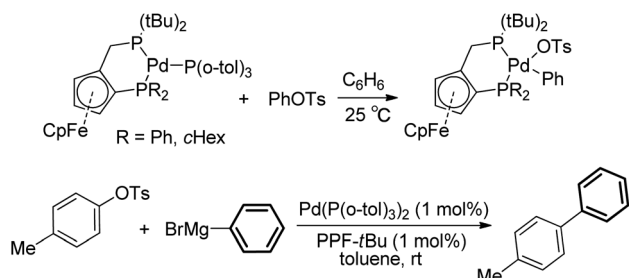
Heteroaromatic sulfonates also showed high reactivity in iron-catalyzed Kumada reaction. The reaction proceeded at low temperature, thus many functional groups were well tolerated in this reaction (Scheme 14).^{25a}



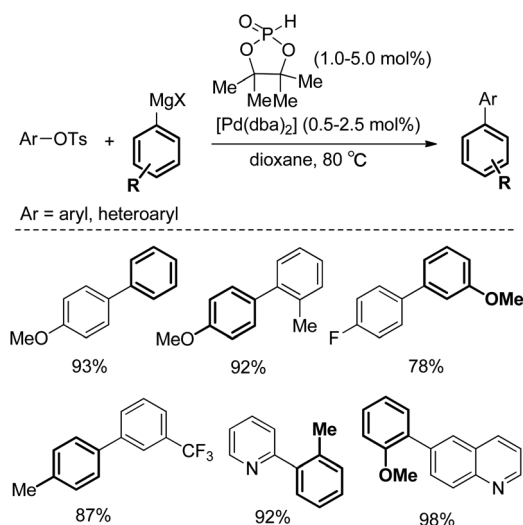
Scheme 9 Nickel-catalyzed cross-coupling of aryl tosylates with ArMgBr.



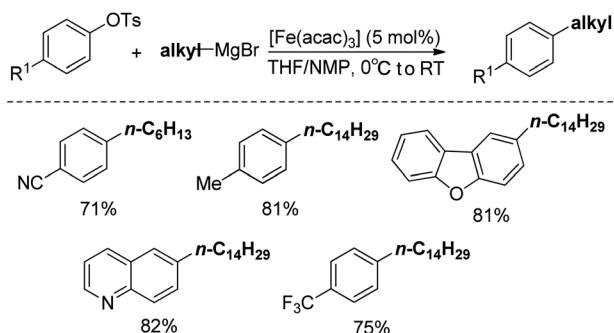
Scheme 10 Ni-catalyzed Kumada coupling of aryl mesylates, dppf = 1,1'-bis(diphenylphosphino)ferrocene.



Scheme 11 Palladium-catalyzed Kumada coupling, Ts = tosyl, tol = tolyl.

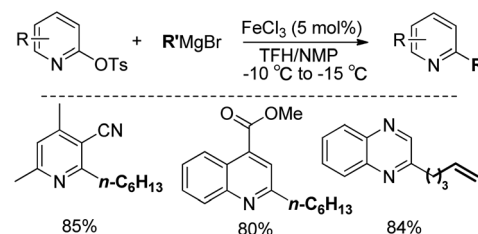


Scheme 12 Palladium-catalyzed Kumada coupling.



Scheme 13 Iron-catalyzed Kumada coupling.

The coupling of aryl sulfamates and carbamates with Grignard reagents using iron catalysis was disclosed by Garg and co-workers.^{25b} This reaction provided a versatile means for



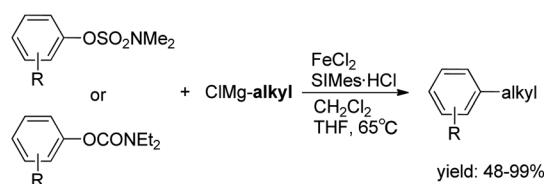
Scheme 14 Heteroaromatic tosylates in iron-catalyzed cross-couplings.

the construction of sp^2 - sp^3 carbon-carbon bonds. This methodology would be useful in multistep synthesis (Scheme 15).

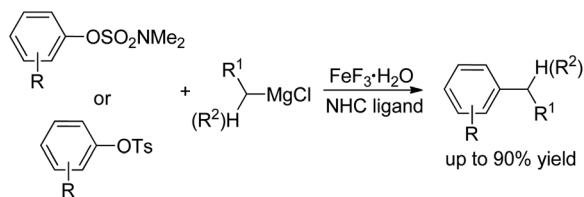
Cook and co-workers^{25c} achieved iron-catalyzed cross-coupling of aryl sulfamates and tosylates. While a variety of iron sources were competent in the reaction, the use of $FeF_3 \cdot 3H_2O$ was critical to minimize nucleophile isomerization. Organoiron compounds were prepared by Fürstner and co-workers.^{25d} Investigations showed that iron-catalyzed cross coupling reactions may occur along more than one pathway: $Fe(+1)/Fe(+3)$, $Fe(0)/Fe(+2)$, and $Fe(-2)/Fe(0)$. The attractive features of C-O electrophiles, combined with cheap and environmentally friendly iron catalysis, made these methodologies attractive in organic synthesis (Scheme 16).

2.3. Ethers as electrophiles in Kumada-Tamao-Corriu coupling

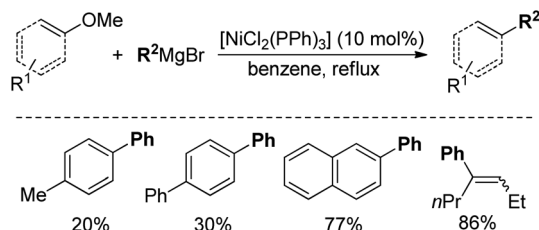
Due to the high bonding energy of C-O bonds and the selectivity between two C-O bonds of ethers, application of ethers in Kumada coupling is a great challenge. However, through the development of efficient catalyst systems, much progress has been obtained in the Kumada coupling of ethers with Grignard reagents. Kumada coupling reaction of enol ethers with Grignard reagents has been discovered as early as the 1950s.²⁶ After that, aryl methyl ether was also used as an electrophile in Kumada reaction.²⁷ The first nickel-catalyzed Kumada coupling of enol ethers and aryl ethers with Grignard reagents was demonstrated by Wenkert and co-workers.²⁸ Using nickel as a catalyst, only moderate yields were obtained and the substrate scope was limited (Scheme 17). The enol ethers in benzofuran showed higher reactivity than that of aryl ethers. However, in some instances, isomerization of the double-bond geometry occurred (Scheme 18). Additionally, furan was also a good electrophile for Kumada coupling reaction.²⁹ Secondary alkyl Grignard reagents were not suitable for Kumada coupling reaction, because the reduction of enol ethers usually occurred in such a situation.³⁰



Scheme 15 Iron-catalyzed coupling reactions.



Scheme 16 Iron-catalyzed coupling reactions.



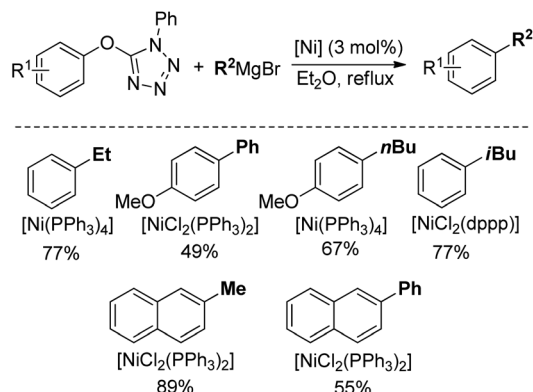
Scheme 17 Nickel-catalyzed cross-couplings of alkenyl/aryl methyl ethers.



Scheme 18 Nickel-catalyzed coupling of benzofuran with Grignard reagents.

Johnstone and Mclean³¹ found that aryl tetrazolyl ethers were also good electrophiles for Kumada coupling reaction. In the presence of nickel as a catalyst, the desired products with good to excellent yields were obtained. Both aryl and alkyl Grignard reagents could react efficiently in this system. It is important to note that the methoxy group was well tolerated in this reaction (Scheme 19).

When Ni(II) phosphane complexes were applied as a catalyst for Kumada coupling reaction, the desired biaryl compounds can be obtained in high yields. Nonpolar solvents were essential for this transformation. Functional groups, such as alcohols, the hydroxy groups of phenols, amines, enamines, and *N*-heterocycles in the aromatic ether substrate, could survive in this reaction (Scheme 20).³²



Scheme 19 Nickel-catalyzed coupling of aryl tetrazolyl ethers with Grignard reagents.

Based on the use of the (IPr)Ni(allyl)Cl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidene) complex as a catalyst, the coupling of anisoles with Grignard reagents proceeded well. Products with high yields were obtained under fairly mild reaction conditions (Scheme 21).^{33a} Wang and co-workers^{33b} also showed nickel-catalyzed Kumada coupling of aryl/alkenyl ethers with Grignard reagents. This reaction had a wide substrate scope and leads to the formation of the products in good to excellent yields.

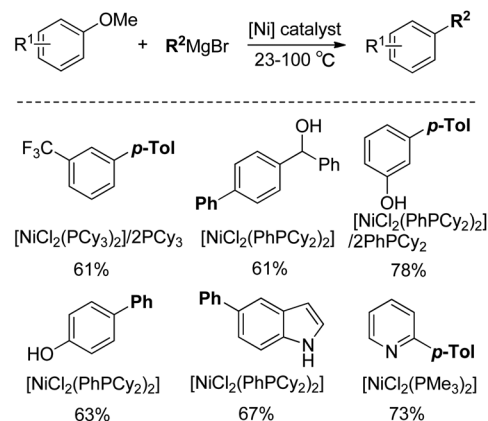
Recently, Shi group^{34a} described nickel-catalyzed coupling of aryl methyl ethers with methyl Grignard reagents under mild conditions. Both fused and nonfused aryl alkyl ethers could react efficiently and gave the desired products with high yields. Interestingly, alkenyl groups and free phenols could survive in this reaction (Scheme 22).

Then the reaction was used by the Shi group^{34b} to synthesize phloroglucinol derivatives. Based on the rational design and analysis of the reactivity of different kinds of C–O bonds, a general strategy toward multiarylated benzenes was developed via Pd-catalyzed C–OTs, Ni-catalyzed C–OC(O)NEt₂, and C–OMe bond activation (Scheme 23).

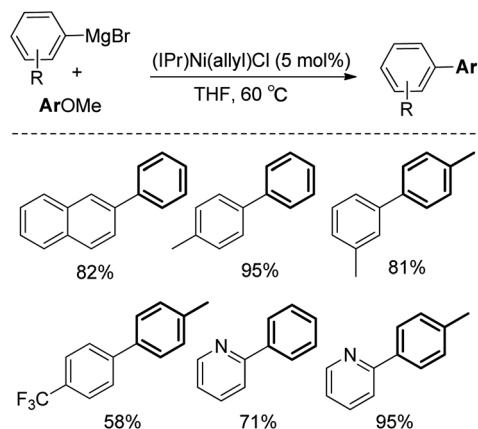
Wenkert and co-workers^{28a} reported the nickel-catalyzed coupling of enol silyl ethers with Grignard reagents, but the yields of this reaction were not very high. After systematic research on this reaction, Kumada and co-workers^{35a} realized the first general and practical method for coupling of enol silyl ethers with Grignard reagents. Long-chain alkyl Grignard reagents were tolerated well in this reaction and high stereo-selectivity with respect to the alkene geometry was obtained (Scheme 24). Recently, Shi group^{35b} also showed the reaction of aryl/alkenyl silyl ethers with Grignard reagents. This reaction provided a new strategy of silyl protection/C–C bond formation sequence in organic synthesis.

2.4. Carboxylates and carbamates as electrophiles in Kumada–Tamao–Corriu coupling

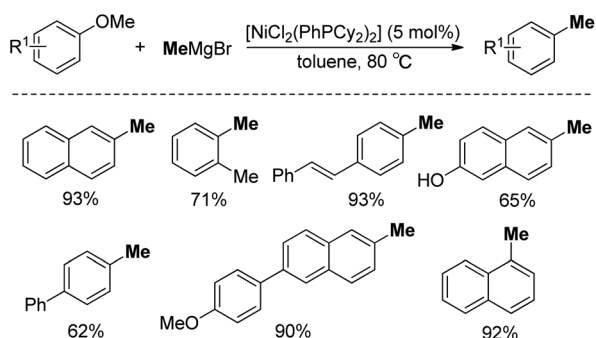
In 1989, the first nickel-catalyzed coupling of enol carbamates with Grignard reagents was disclosed by Kocienski and Dixon, albeit the substrate scope was limited.³⁶ The groups of Betzer and F  rezou found that alkenyl, aryl and acetylenyl Grignard



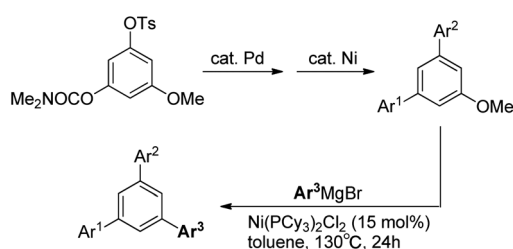
Scheme 20 Nickel-catalyzed coupling of anisole with Grignard reagents.



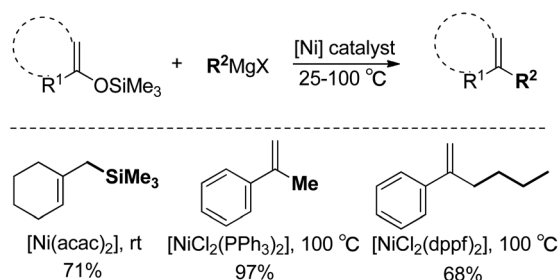
Scheme 21 Cross-coupling of aryl ethers with ArMgBr catalyzed by (IPr)Ni(allyl)Cl.



Scheme 22 Nickel-catalyzed coupling of anisole with methyl Grignard reagents.



Scheme 23 Synthesis of phloroglucinol derivatives.



Scheme 24 Nickel-catalyzed coupling of enol silyl ethers with methyl Grignard reagents.

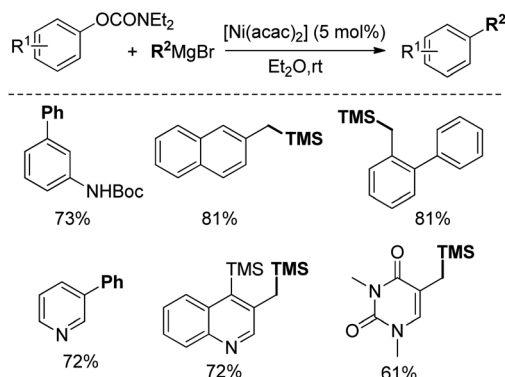
reagents were also suitable for this coupling reaction.³⁷ In 1992, Snieckus and co-workers achieved the Kumada reaction of aryl O-carbamate in the presence of [Ni(acac)₂] as a catalyst. The scope of the substrates was greatly expanded. Carbamates with both electron-donating and electron-withdrawing groups could react smoothly to give the final products. However, the scope of Grignard reagents was limited. When allyl, benzyl and long-chain alkyl Grignard reagents were used, the reaction did not proceed very well (Scheme 25).³⁸

Hydroxyphosphine ligands (PO ligands) could also accelerate the nickel-catalyzed Kumada reaction of aryl carbamates with aryl Grignard reagents. With low catalyst loading, the reaction proceeded well to afford the desired products with good to high yields (Scheme 26).⁸

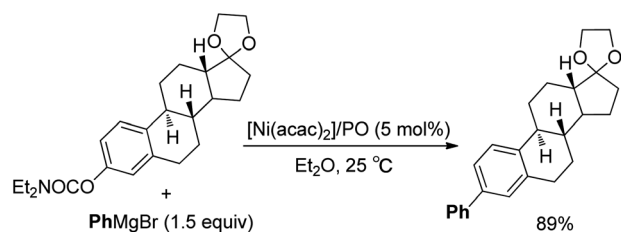
Besides nickel, iron was also a good catalyst for Kumada coupling reaction of carboxylates. Shi and co-workers³⁹ demonstrated the iron-catalyzed cross-coupling reaction of alkenyl/aryl pivalate with Grignard reagent under mild conditions. Products with good to excellent yields can be afforded. Various carboxylates could be tolerated in this transformation, leaving carbonyl groups such as ketones and lactones untouched (Scheme 27). Garg and co-workers^{25b} also realized Fe-catalyzed Kumada coupling of carbamates with Grignard reagents (Scheme 15).

2.5. Naphthol as electrophiles in Kumada–Tamao–Corriu coupling

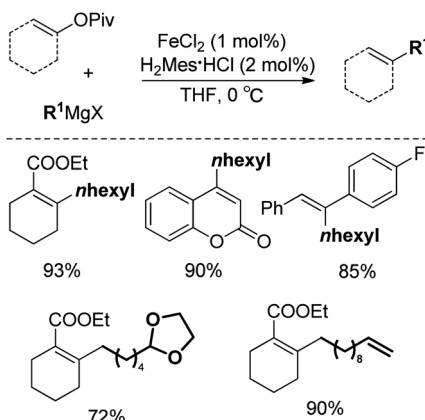
All the O-based electrophiles used above needed a protecting group prior to the cross-coupling reaction. The usage of such groups limits their efficiency and step economy. If the phenols or phenolates could be used directly in the cross coupling reactions to construct C–C bonds, a protecting group will not be needed. However, such a design will meet formidable challenges. First, the BDE seemed to indicate that direct cleavage of the aryl C–O bond on phenol is impossible. Second, the phenolic anion is a good σ -donor ligand, which could bind to the metal catalyst and impede the transition-metal-induced cleavage of the C–O bond. Furthermore, formation of the phenolic salt enhances the BDE to completely nullify any potential cleavage.⁴⁰



Scheme 25 Nickel-catalyzed cross-coupling of aryl O-carbamates with Grignard reagents.



Scheme 26 Cross-coupling of aryl carbamates with Grignard reagents.



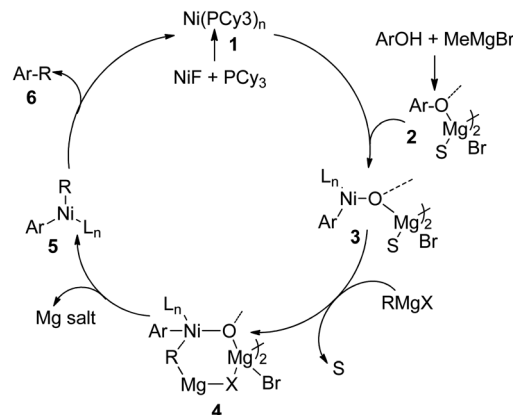
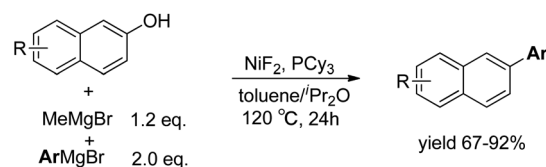
Scheme 27 Cross-coupling of carboxylates with Grignard reagents.

Shi and co-workers⁴¹ thought the cleavage of the phenol C–O bond might be achieved by the combination of Lewis acid and transition metal catalyst (Scheme 28). Lewis acid might act as an electron-withdrawing group to reorganize the electron of the C–O bond, and the metal oxide might function as a good leaving group. Then, cleavage of the C–O bond in the phenolic salt would be achieved with a proper transition metal catalyst. With this in mind, they realized the first successful cross-coupling reaction of 2-naphthol derivatives with various aryl Grignard reagents. These studies challenge the traditional consideration of the stability of phenol and its phenolic species, thus opening a direct route to useful core structures from phenol derivatives through cross-coupling reactions.⁴¹

Mechanism of this reaction was thought to go through the Ni⁰/Ni^{II} catalytic cycle. With the aid of PCy₃, NiX₂ was reduced to Ni⁰. Magnesium phenoxide salt **2** generated from the reaction of ArOH and MeMgBr. The phenoxide C–O bond was slightly activated with the assistance of Mg²⁺ in the complex. It then underwent oxidative addition to the Ni⁰ species affording the intermediate **3**. After transmetalation with RMgX, through the proposed 6-membered transition state **4**, the biaryl Ni^{II} species **5** was formed. Finally, the desired product **6** was formed through reductive elimination.

3. Kumada–Tamao–Corriu coupling of C(sp³)-O based electrophiles

Compared with alkenyl/aryl electrophiles, alkyl electrophiles are not well studied in Kumada coupling reaction. The reasons



Scheme 28 Kumada reaction of naphtholic salts with ArMgBr, S = solvent.

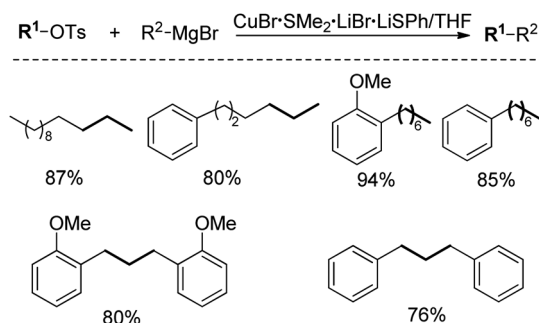
include : (1) an sp³ C–O bond possesses relatively higher BDE than that of sp² C–O bond; (2) the coupling reaction with other reagents to construct C–C bonds is hard to control after the cleavage of sp³ C–O bonds.⁴² Until now, there are only several examples of transition-metal-catalyzed Kumada cross-coupling of O-based alkyl electrophiles with Grignard reagents. It is noteworthy that allyl O-based electrophiles are relatively reactive and there has been a review⁴³ on the reaction of allyl O-based electrophiles with Grignard reagents. So O-based allyl electrophiles will not be discussed here.

3.1. Alkyl sulfonates as electrophiles in Kumada–Tamao–Corriu coupling

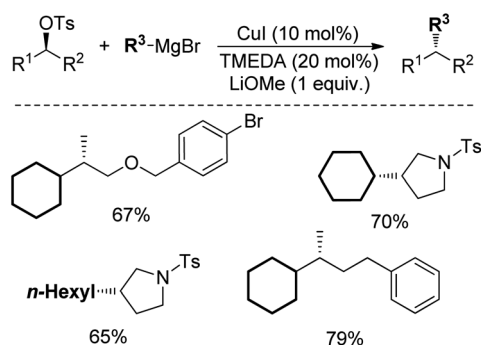
A new soluble copper catalyst [CuBr–LiSPh–LiBr–THF] which comprised equal amounts of CuBr–SMe₂, LiBr, and LiSPh was found to be efficient at Kumada coupling reaction of alkyl sulfonates. ¹H NMR signals demonstrated that the catalyst solution consisted of several species, which most likely were composed of copper ligated with thiophenol, THF, and LiBr in aggregated forms (Scheme 29).⁴⁴

In the presence of copper as a catalyst, Kumada coupling of secondary alkyl electrophiles with secondary alkyl nucleophiles was realized by Liu and co-workers.⁴⁵ The addition of TMEDA and LiOMe was crucial for this reaction. X-ray crystal analysis of the products revealed that the reaction occurs *via* an S_N2 mechanism with inversion of configuration. This reaction represents a rare example of transition-metal-catalyzed cross-coupling between two tertiary alkyl carbons (Scheme 30). Hu and co-workers⁴⁶ found that the cross-coupling of alkyl tosylates with tertiary alkyl Grignard reagents could also proceed efficiently in the presence of CuCl as a catalyst (Scheme 31).

Besides copper, nickel could also catalyze Kumada reaction of alkyl tosylates with Grignard reagents. With the aid of Ni catalyst, cross-coupling reaction of Grignard reagents with alkyl



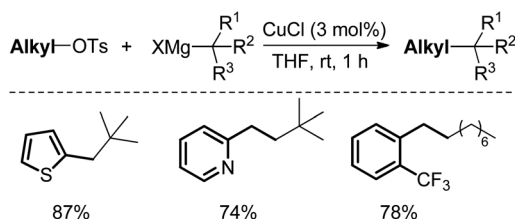
Scheme 29 Copper-catalyzed cross-coupling of alkyl tosylates with Grignard reagents.



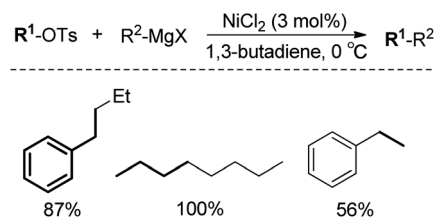
Scheme 30 Copper-catalyzed cross-coupling of secondary alkyl tosylates with alkyl Grignard reagents.

tosylates was developed by Kambe and co-workers.⁴⁷ The use of 1,3-butadiene as an additive instead of phosphine ligands was crucial to attain high yields of the cross-coupling products (Scheme 32). Later, the same group⁴⁸ found nickel and palladium-containing perovskites, $\text{LaFe}_{0.8}\text{Ni}_{0.2}\text{O}_3$ (LFNO) and $\text{LaFe}_{0.95}\text{Pd}_{0.05}\text{O}_3$ (LFPO), could also be employed as effective catalyst sources for the cross-coupling of alkyl tosylates and Grignard reagents in the presence of conjugated dienes. In addition, the catalyst could be reused three times without considerable loss of activity.

A mild selective synthesis of alkenes and modified arylketones through the $\text{NiI}_2(\text{PPh}_3)_2/\text{PCy}_3$ catalyzed Kumada coupling of tosylalkanes with Grignard reagents was disclosed by Li and co-workers.⁴⁹ This is the first example of alkene synthesis from alkyl electrophiles with Grignard reagents using the Kumada reaction strategy and the carbonyl group of the tosylalkane was well tolerated in this reaction (Schemes 33 and 34).



Scheme 31 Copper-catalyzed cross-coupling of alkyl tosylates with tertiary alkyl Grignard.



Scheme 32 Nickel-catalyzed cross-coupling of alkyl tosylates with Grignard reagents.

3.2. Alkyl ethers as electrophiles in Kumada–Tamao–Corriu coupling

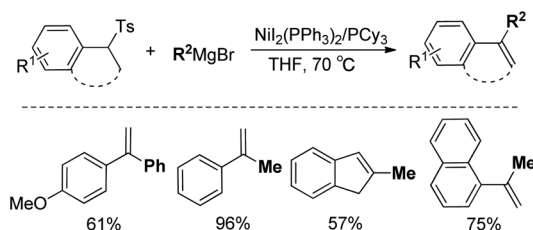
An unprecedented Ni-catalyzed cross-coupling of relatively stable benzyl ethers with Grignard reagents were reported by Shi group.^{42a} Interestingly, sp^2 C–OMe and benzylic sp^3 C–OMe in the same molecule could be differentiated by the methylation tuned by the ligand in this system, which offered new tools for synthesizing complex molecules (Scheme 35).

Stereospecific nickel-catalyzed cross-coupling reactions of alkyl ethers were realized by Jarvo and co-workers.⁵⁰ Enantioenriched 1,1-diarylalkanes, which are important pharmacophores in medicinal chemistry, were synthesized using this method. This reaction afforded the desired products with inversion of configuration and high stereochemical fidelity (Scheme 36).

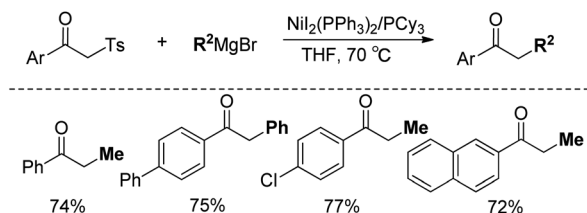
The first iron-catalyzed cross coupling of homobenzylic methyl ethers with alkyl Grignard reagents was realized by Shi and co-workers.^{42b} The reaction presumably proceeded through dehydroalkoxylation to form vinyl-intermediate, followed by carbometalation to form benzylic Grignard reagents and quenching with protons (Scheme 37). A possible mechanism was proposed: olefin **3** coming from the dehydroalkoxylation of dialkyl ether **1** reacted with alkyl-Fe species **2** to afford benzylic iron species **4**, followed by transmetalation with alkyl Grignard reagent **6** to produce alkyl-Fe species **2** and benzylic Grignard reagent **7**. Final products **8** will be obtained by the treatment of **7** with EtOH. Additionally, the by-product **5** would be generated from the β -H elimination of the benzylic metal species **4** or **7**.

3.3. Alkyl alcohols as electrophiles in Kumada–Tamao–Corriu coupling

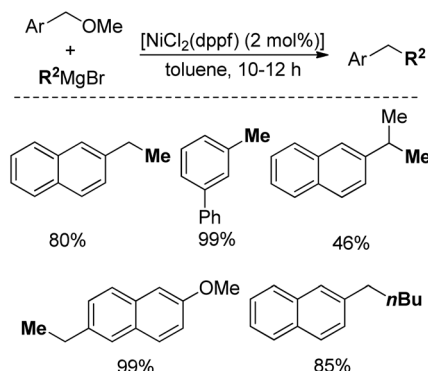
The first nickel-catalyzed cross coupling of benzylic alcohols in the presence of different Grignard reagents was developed by Shi and co-workers. These methods offered straightforward



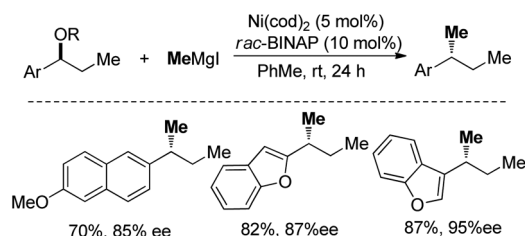
Scheme 33 $\text{NiI}_2(\text{PPh}_3)_2/\text{PCy}_3$ catalyzed synthesis of alkenes.



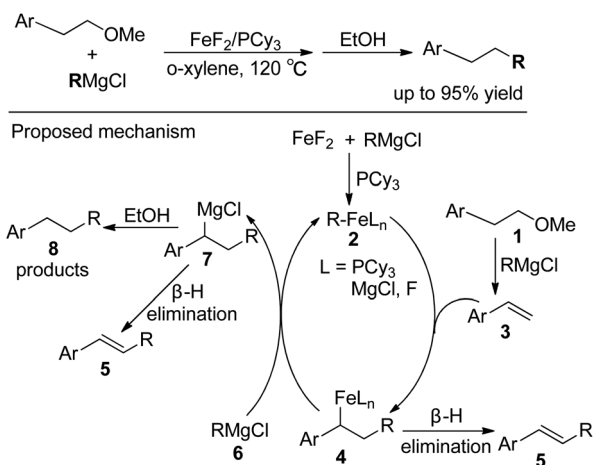
Scheme 34 $\text{NiCl}_2(\text{PPh}_3)_2/\text{PCy}_3$ catalyzed Kumada coupling of 1-aryl-2-tosylethanones.



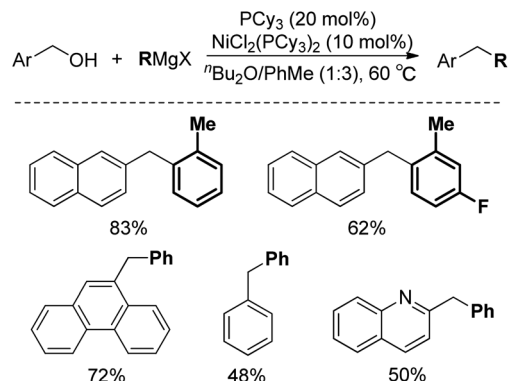
Scheme 35 Nickel-catalyzed Kumada cross-coupling reaction.



Scheme 36 Stereospecific Kumada cross-coupling reactions.



Scheme 37 Reaction between homobenzylic methyl ethers with alkyl Grignard reagents.



Scheme 38 Nickel-catalyzed Kumada coupling reactions.

pathways to transform benzyl alcohols into a variety of functionalities, offering the potential method for generation of organometallic reagents from alcohols *via* transition metal catalysis (Scheme 38). Of note, except for this example, there is no example of Kumada reactions of alkyl alcohols.⁵¹

4. Conclusions and Outlook

This review highlights recent advances in Kumada–Tamao–Corriu cross-coupling reaction of O-based electrophiles with Grignard reagents, which have demonstrated excellent functional group compatibility and good chemo- and stereo-selectivities in organic transformation. Although outstanding progress has been achieved at present, further research on Kumada coupling reaction is still required to obtain a higher achievement. At present, nickel is the most used catalyst in Kumada coupling reactions of O-based electrophiles. How to make full use of other transition metals, such as Fe, Cu, Co *et al.*, is yet to be further studied. The category and scope of $\text{C}(\text{sp}^3)\text{-O}$ based electrophiles and Grignard reagents, especially secondary and tertiary alkyl Grignard reagents, still need to be further explored. Asymmetric Kumada reaction of O-based electrophiles in the presence of chiral ligands also deserved our attention.

It would be a pleasure for us to see that this review will create keen interest among the wide readership of this journal and result in further focused research to meet some of these challenges in the future.

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