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Exploration of New C—O Electrophiles in Cross-Coupling Reactions

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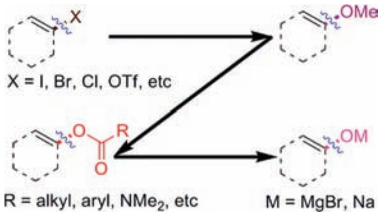

Since their development in the 1970s, cross-coupling reactions catalyzed by transition metals have become one of the most important tools for constructing both carbon—carbon and carbon—heteroatom bonds. Traditionally, organohalides were widely studied and broadly used as the electrophile, both in the laboratory and in industry. Unfortunately, the high cost, environmental toxicity, and sluggish preparation often associated with aryl halides can make them undesirable for the large-scale syntheses of industrial applications. However, with the further development of catalytic systems, and particularly of the ligands contained therein, a variety of electrophiles have now been successfully applied to cross-coupling reactions.

Oxygen-based electrophiles have attracted much attention due to their ready availability from phenol and carbonyl compounds. Initially, aryl and alkenyl triflates were used in cross-coupling reactions due to their high reactivity; however, low moisture stability and high cost hampered their application. Later, with the development of highly efficient catalytic systems, the less reactive sulfonates and phosphates were successfully employed in cross-coupling reactions. Although they have higher stability and can be easily prepared, low atom economy remains an obstacle to their broader utility.

Our group has worked to directly apply the abundant and readily available oxygen-containing compounds, such as phenols, alcohols, ethers, and carbonyl compounds, to cross-coupling reactions. In this Account, we describe our recent efforts in transition-metal-catalyzed cross-coupling reactions of new O-based electrophiles via C—O bond activation.

We began by developing the methylation of aryl methyl ethers and benzyl methyl ethers via Ni-catalyzed selective C—O bond cleavage. With the refined Ni-based catalytic system, we further applied aryl/alkenyl carboxylates and carbamates to Suzuki—Miyaura, Negishi, and Kumada—Tamao—Corriu reactions to construct various biaryl scaffolds and highly substituted alkenes. To further improve the carbon atom economy, we developed the diaryl sulfates as one-by-one electrophiles (that is, both aryl groups are used in the reaction). Most recently, we have achieved the first successful cross-coupling reaction of magnesium naphtholates with aryl Grignard reagents. These results extend aryl and benzyl ethers, aryl and alkenyl carboxylates/carbamates, and magnesium naphtholates as novel electrophiles in cross-coupling reactions. More importantly, these studies contribute to our better understanding the intrinsic nature of C—O bonds, which were traditionally considered "inert" but clearly show enormous synthetic potential with the proper catalysts.

1. Introduction

Since the development of the transition-metal-catalyzed cross-coupling reactions in 1970s, numerous efforts have been made to make the cross-coupling reactions more reliable and applicable.[1] Among these developments, one major improvement is to extend the diversity of organoelectrophiles.[2] At the early stage, organo iodides/bromides were found as good coupling partners due to their high reactivity. However, the high cost and limited availability limit their application in industry. Through the development of highly efficient catalytic systems, various electrophiles including less reactive aryl chlorides[3] as well as fluorides[4] were also successfully applied into cross-coupling reactions.

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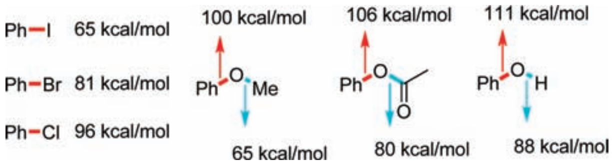


FIGURE 1. Bond dissociation energy (BDE) of C−X bonds and C−O bonds.

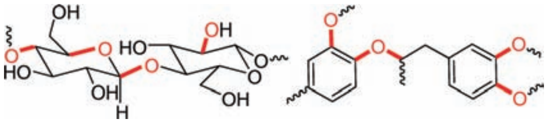


FIGURE 2. The representative structures of biomass.

Due to the broad existence of O-containing organic compounds in nature and the synthetic world, they have drawn the chemists' attention even at the early stage of cross-coupling reactions. Initially, alkenyl/aryl triflates were used due to their high reactivity.[5] Other sulfonates and phosphonates were also successfully applied in various transformations through catalyst development.[6] However, other widely existing O-containing compounds, including ethers, esters, phenols, alcohols, and carbonyl compounds, are rarely used as coupling partners directly.

The application of O-containing organic compounds as electrophiles in cross-coupling reactions faces three major challenges. First, in general, the bond dissociation energy (BDE) of the C−O bond is relatively high. For example, the BDE of C_{Ar}−O of aryl ether is comparable with that of the corresponding C_{Ar}−Cl (Figure 1), which indicates that the cleavage of such an "inert" C−O bond is thermodynamically difficult.[7] Second, the differentiation of two different bonds linked to the oxygen atom is also difficult. Finally, the selective activation of one of several O-containing groups in a complex molecule is considerably challenging. Up to now, most of the transformations were focused on the active carbonyl compounds, while less work was reported on the activation of the "inert" C−O bonds, which is the bottleneck of direct transformation of various abundant O-containing compounds.

Obviously, research in this field is highly demanded. As we know, many kinds of ethers, esters, and alcohols are produced in large amounts in industry and are primarily used as solvents. The use of these fine chemicals as carbon sources may offer more environmentally benign and atom-economical processes. In addition, the selective cleavage of the C−O bond also provides the basis for the application of biomass, a promising alternative to the fossil fuel (Figure 2). Take lignin as an example: it was isolated in the paper industry as a byproduct on the scale of 50 million tons per year. However, it was mainly burned to reduce the pollution. If we could directly transform these compounds to more useful molecules, we could not only reduce the cost but also alleviate the pollution. Therefore, such studies can provide the solution for the economical and ecological as well as environmental problems. Our focus in this field is to develop novel transformations of the O-containing compounds based on the understanding the intrinsic feature of "inert" C−O bonds, thereby providing the "bricks and mortar" for organic synthesis. This Account summarizes our recent progress in applying ethers, carboxylates, and carbamates, as well as naphtholic salts, as electrophiles in cross-coupling reactions via transition-metal-catalyzed C−O bond activation.

2. Ethers as Electrophiles

As one of the most common structural units in the natural and synthetic worlds, ethers are traditionally used as solvents in organic synthesis. They are rarely applied in organic synthesis as electrophiles due to their low reactivity, except the relatively active allyl ethers.[8,9] How to differentiate two similar C−O bonds of the ethers is another big challenge.

2.1. Aryl Alkyl Ethers as Electrophiles in Kumada−Tamao−Corriu Reaction. The pioneering work was carried out by Wenkert in 1979, in which aryl/alkenyl methyl ethers were applied as electrophiles in Ni-catalyzed Kumada−Tamao−Corriu reaction.[10] Surprisingly, this important observation has been ignored for almost 20 years. In 1998, Milstein and coworkers reported a stoichiometric cleavage of C_{Ar}−OMe with various transition metal complexes through a directing group assisted strategy.[11] Later on, Kakiuchi and co-workers realized the Ru-catalyzed Suzuki−Miyaura coupling of anisoles directed by the carbonyl group.[12] During this period, Dankwardt made a significant contribution to extend the substrate scope of aryl alkyl ethers in the Ni-catalyzed Kumada−Tamao−Corriu coupling with aryl Grignard reagents.[13] However, methylation of aryl ethers seemed to completely fail. Although Johnstone's studies showed that aryl tetrazolyl ethers could undergo alkylation smoothly, low atom efficiency was a big problem.[14] Following these studies, we initiated our studies in the field of C−O activation of ethers in late 2004.

Initially, we focused on the Ni-based catalytic system since Ni catalysts showed high efficiency in the presence of Grignard reagents. Obviously, the high nucleophilicity of Grignard reagents was not only beneficial for the transmetalation but also for maintaining the reductive reaction conditions to stabilize the low-valent Ni species. Interestingly, we investigated the catalytic system and found that aryl alkyl ethers could efficiently undergo methylation in the presence of $NiCl_2(PCy_3)_2$[60]

TABLE 1. Kumada$-$Tamao$-$Corriu Reaction of Aryl Methyl Ethers with MeMgBr

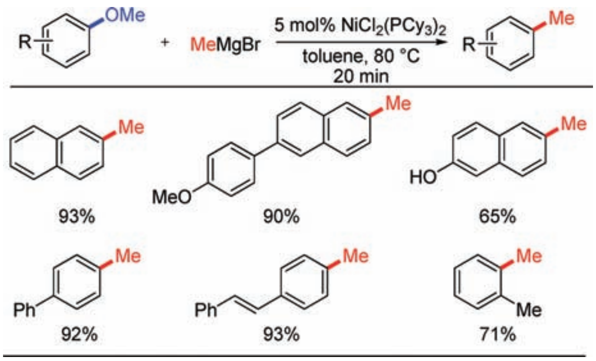
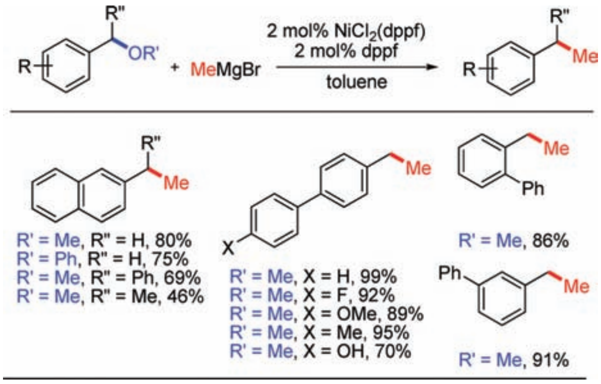
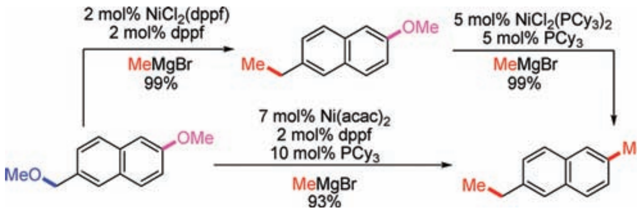


TABLE 2. Kumada$-$Tamao$-$Corriu Reaction of Benzyl Alkyl Ethers with MeMgBr



SCHEME 1. Sequential or Simultaneous Methylation of C$-$O Bonds of Different Ethers

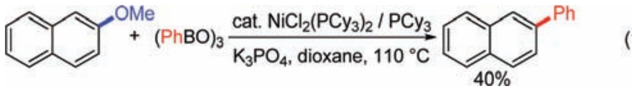


(Table 1).[15] Various aryl methyl ethers could undergo methylation in high yields, with alkene and free hydroxyl groups of phenol tolerated. Steric hindrance slightly lowered the yield. Interestingly, the naphthyl C$-$O bond showed higher reactivity than the phenyl C$-$O bond. Unfortunately, the coupling of other alkyl Grignard reagents gave complex mixtures.

2.2. Benzyl Alkyl Ethers as Electrophiles in Kumada$-$Tamao$-$Corriu Reaction. In contrast with aryl and alkenyl ethers, cross coupling of dialkyl ethers has been less investigated due to the difficulty of differentiating two similar sp^3 C$-$O bonds. Although the reactions of relatively active allylic ethers were known,[8,9] selective activation of C$-$O bonds of benzylic ethers had never been reported. We successfully developed the Ni-catalyzed methylation of benzyl methyl ethers with methyl Grignard reagent at room temperature.[16] Among various ligands, dppf was the most efficient one (Table 2). To our interest, when benzyl phenyl ether was subjected to the reaction, selective sp^3 C$-$O bond activation was achieved without cleavage of the sp^2 C$-$O bond. The yields of substrates bearing hydrogen beta to the C$-$O bond dramatically decreased with the observation of stryene derivatives, arising from the β-H elimination. The steric effect on the aromatic ring did not show a strong impact on the yields. Many functional groups, such as fluoride, methoxyl, and free phenol, were tolerated. Among different Grignard reagents tested, EtMgBr showed high reactivity while PhMgBr and ^{i}PrMgBr gave low yields. With the combination of the two developed methylation systems, methylation of two types of C$-$O bonds could take place in high efficiency either stepwise or in one pot (Scheme 1).

3. Aryl and Alkenyl Carboxylates and Carbamates as Electrophiles

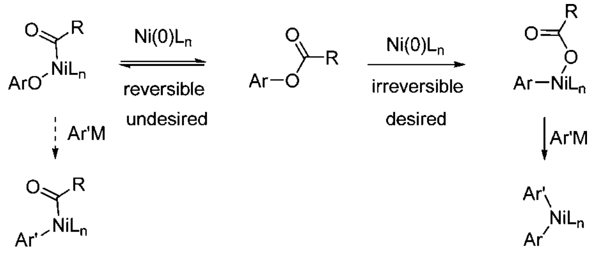
3.1. Suzuki$-$Miyaura Coupling of Aryl Carboxylates. We further planned to extend aryl methyl ethers in Suzuki$-$Miyaura coupling. With much effort, we found that, the cross coupling of naphthyl methyl ether with phenylboroxine indeed took place with moderate efficiency by using K_3PO_4 as the base (eq 1).[17] During the course of our work, Chatani and co-workers made a significant contribution in this field and reported the successful Suzuki$-$Miyaura coupling of anisoles with phenylboronic ester using CsF as the base.[18] Then, we turned our attention to search for other new O-containing electrophiles.



(1)

In organic synthesis, carboxylates are easily available and have been used as the protecting groups of phenols and alcohols for long time. The carboxylate group can be easily removed by hydrolysis, which implies the high reactivity of the acyl C$-$O bonds. The most successful transformation using carboxylates as the leaving group is the transition-metal-catalyzed reactions of allylic and benzylic carboxylates.[19] In contrast, transformation via selective cleavage of the aryl and alkenyl C$-$O bond of aryl and alkenyl carboxylates is unprecedented, although transition-metal-catalyzed cleavage of the acyl C$-$O bond in carboxylates was reported.[2b] For example, an important clue was found from an early report of Yamamoto, in which Ni could cleave both the phenyl C$-$O and the

SCHEME 2. Rational Design of the Cross Coupling of Aryl Carboxylates



acyl C—O of phenyl acetate under different conditions.[20] Although the decarbonylation generated stable alkyl—Ni species, an equilibrium of oxidative addition of the acyl C—O toward Ni(0) and reductive elimination might exist. Therefore, enhancement of the transmetalation of the aryl—Ni species and inhibition of decarbonylation of the acyl—Ni complex are crucial for the desired coupling reaction (Scheme 2). Such a mechanistic scenario was later supported by DFT calculation carried out by Liu and co-workers.[21] With this in mind, we started to search for the proper catalytic system for the direct application of the inexpensive and environmentally benign aryl carboxylates in cross-coupling reactions.

We found that 2-naphthol derivatives showed higher reactivity in previous studies. Gratifyingly, 2-naphthyl acetate underwent the Suzuki—Miyaura coupling with phenylboroxine using $NiCl_2(PCy_3)_2$ as the catalyst and K_3PO_4 as the base in dioxane at 110 °C.[22] Addition of 0.88 equiv of H_2O was essential, which may arise from the good balance by promoting the reactivity of boron reagents and lowering the hydrolysis of the starting materials. Benzoates also showed moderate reactivity. The reactions of various naphthyl acetates and arylboroxines gave the biaryl products in good yields (Table 3). Many functional groups, such as C—F bonds, ketones, and esters, survived. It was important to note that phenyl, benzylic, MOM-protected, and even free phenols were tolerated, which offered great opportunity for further functionalization.

Under the same conditions, however, cross coupling of phenyl acetate was not successful. The yields could be increased when phenyl pivalates were subjected (Table 4). The coupling of pivalates with electron-withdrawing groups and arylboroxines with electron-donating groups gave higher yields. Almost at the same time, the Garg group also reported similar results.[23]

3.2. Alkenyl Carboxylates as Electrophiles in Suzuki—Miyaura Reaction. Cross-coupling reactions are one of the most efficient methods to synthesize highly substituted alkenes. Generally, alkenyl halides, sulfonates, and phosphates are good electrophiles. After the success of the cross coupling of aryl carboxylates, we turned our attention to the alkenyl carboxylates, which can be easily synthesized from the corresponding carbonyl compounds by ester exchange. During the course of our work, Kuwano and co-workers reported a Rh-catalyzed Suzuki—Miyaura coupling of specific alkenyl acetates.[24]

In our study,[25] we found that $NiCl_2(PCy_3)_2$ was the best catalyst. Arylboroxines were the best cross-coupling partners, while aryl boronic acid showed lower reactivity. Similarly, the addition of the proper amount of water was also essential. The mixture of toluene/dioxane was important for efficient transformation. Various aryl boroxines as well as alkenyl acetates with functional groups such as methoxyl, C—F, and C—Cl bonds underwent the reactions efficiently (Table 5).

Through the cross couplings of aryl and alkenyl carboxylates, we can efficiently functionalize estrone under different conditions. For example, arylation of the phenol part could proceed through a pivalation—coupling sequence. On the other hand, the ketone part could be selectively arylated through the ester exchange—coupling sequence (Scheme 3).

3.3. Aryl and Alkenyl Carboxylates as Electrophiles in Negishi Reaction. In the Suzuki—Miyaura reactions of aryl and alkenyl carboxylates, fairly harsh conditions, high temperature, and high catalyst loading limited their potential applications. Such pitfalls might arise from the low reactivity of aryl boronic acid derivatives in both the generation of active catalytic species and the transmetalation steps. Thus, the use of more reactive organometallic reagents might overcome these problems. Organozinc reagent is a good choice since it is more reactive and, at the same time, exhibits good functional group tolerance.

We first successfully developed the Negishi reaction of aryl/alkenyl carboxylates under mild conditions.[26] When naphthyl acetate was tested, the desired product was obtained in low yield. Most of the starting material was hydrolyzed through the direct attack of aryl zinc reagent to the ester group. Increasing the steric hindrance of the carboxylates improved the yield. When naphthyl pivalate was used, high efficiency was obtained in 2 h even when the catalyst loading was reduced to 1.0 mol % or the temperature was lowered to 30 °C. Various naphthyl and activated phenyl pivalates underwent the reaction smoothly (Table 6). The reactions of both acyclic and cyclic alkenyl pivalates gave good yields. In our later studies, we also demonstrated that alkenyl acetates could also be applied in similar reaction conditions.[25]

The Suzuki—Miyaura and Negishi coupling of aryl/alkenyl carboxylates may proceed through a similar mechanism (Scheme 4). First, active Ni(0) catalyst was generated *in situ*

TABLE 3. Suzuki−Miyaura Reaction of Naphthyl Acetates with Arylboroxines

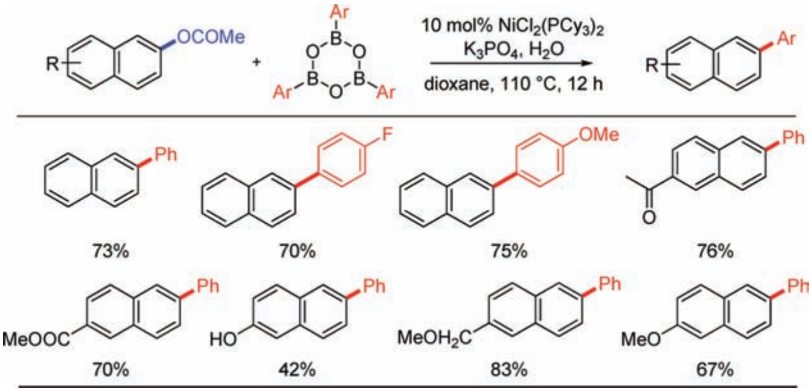


TABLE 4. Suzuki−Miyaura Reaction of Phenyl Pivalates with Arylboroxines

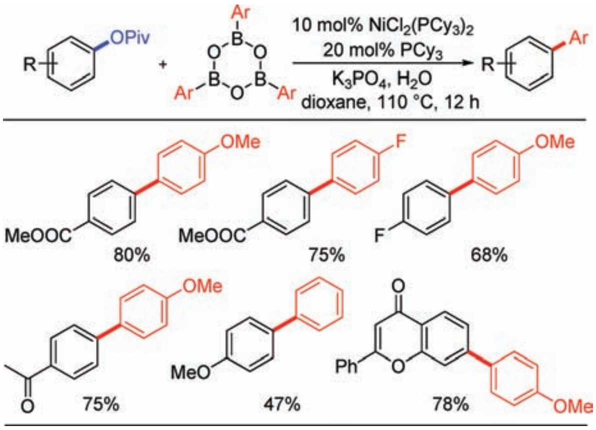
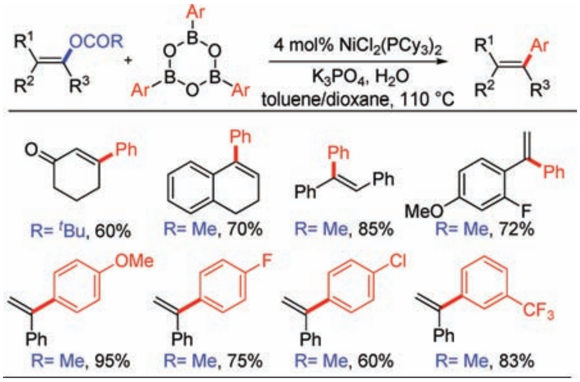


TABLE 5. Suzuki−Miyaura Reaction of Alkenyl Acetates with Arylboroxines



SCHEME 3. Selective Arylation of C_{sp^2}−O bond of Different Carboxylates

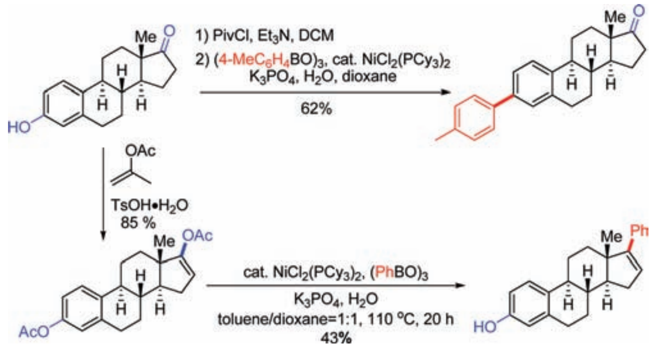
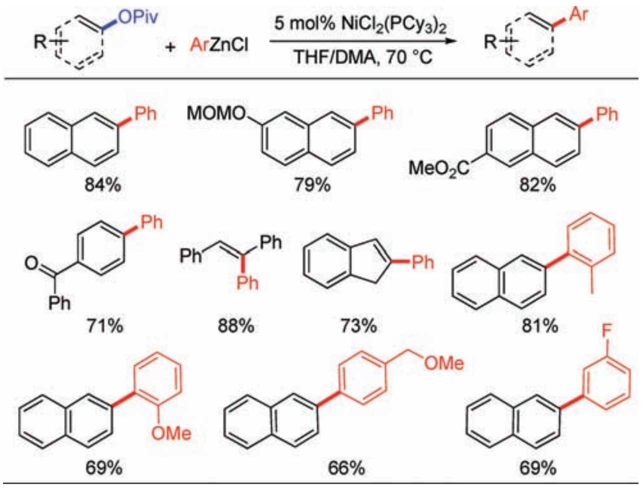


TABLE 6. Negishi Reaction of Aryl/Alkenyl Pivalates with ArZnCl



through reduction of Ni(II) by organometallic reagents or ligands. Oxidative addition of the aryl/alkenyl C−O bond to the Ni(0) species afforded the aryl/alkenyl Ni(II) complex, which underwent transmetalation with aryl organometallic reagents to produce the diaryl or aryl/alkenyl Ni(II) intermediates. Reductive elimination produced the desired coupling products and facilitated the catalytic cycle by regenerating Ni(0) catalyst.

3.4. Alkenyl/Aryl Pivalates and Carbamates as Electrophiles in Kumada−Tamao−Corriu Reaction. After the success of the cross coupling of aryl/alkenyl carboxylates with organoboron and organozinc reagents, we further explored the coupling of aryl/alkenyl carboxylates with Grignard

SCHEME 4. Proposed Catalytic Cycle of the Cross Coupling of Aryl/Alkenyl Carboxylates

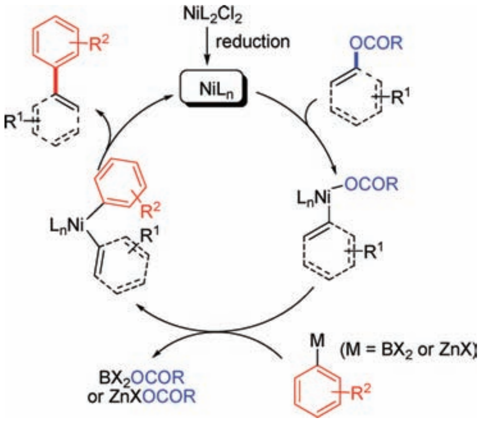


TABLE 7. Kumada−Tamao−Corriu Reaction of Alkenyl Pivalates with RMgCl

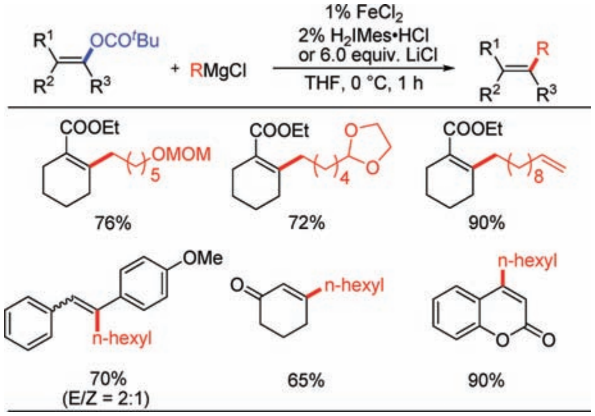
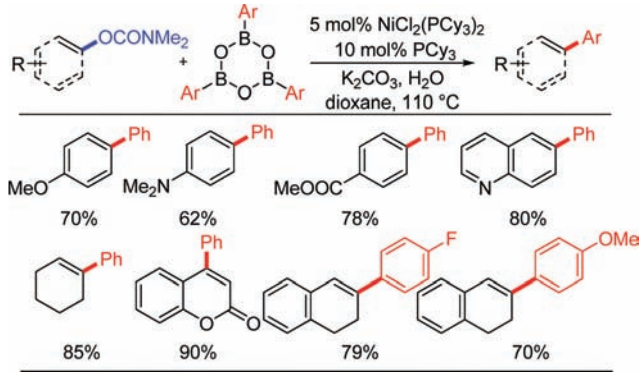


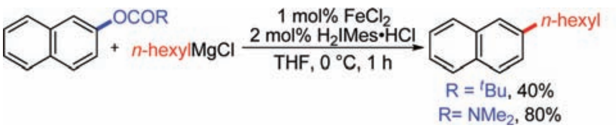
TABLE 8. Suzuki−Miyaura Reaction of Aryl/Alkenyl Carbamates with Arylboroxines



reagents. It is well-known that the reaction of Grignard reagent with carboxylate proceeds through direct nucleophilic attack to the carbonyl group. To achieve the cross coupling of aryl/alkenyl carboxylates with Grignard reagents, a suitable catalyst is necessary to selectively cleave the C_{sp^2}−O bond. Iron species attracted our attention since they exhibited excellent reactivity in the cross coupling of O-based electrophiles such as aryl triflates and tosylates.[27]

With much effort, we developed the first Kumada−Tamao−Corriu reaction of alkenyl pivalates with alkyl Grignard reagents via iron catalysis.[28] A catalyst system composed of $FeCl_2$ and H_2IMes was highly efficient, allowing the coupling to proceed with 1.0 mol % iron catalyst in 1 h at 0 °C. Alkyl Grignard reagents bearing functional groups such as alkene, ether, and acetal gave the cross coupling products in high yields. Notably, the presence of β-H is essential for this transformation. Activated cyclic alkenyl pivalates underwent the reaction in good to excellent yields (Table 7). The reaction of acyclic alkenyl pivalates provided a mixture of stereoisomers, suggesting that an alkenyl radical intermediate might be involved.[29]

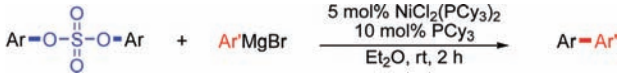
Under this reaction condition, aryl pivalate also showed moderate efficiency. Notably, aryl carbamate was a better choice and underwent the reaction to afford the product in a high yield (eq 2). These results suggested that the carbamates might be good electrophiles in other cross-coupling reactions.



(2)

3.5. Aryl/Alkenyl Carbamates as Electrophiles in Suzuki−Miyaura Coupling. Compared with aryl carboxylates, aryl carbamates are more stable and, more importantly, have potential application in directed *ortho* metalation (D*o*M).[30] Previously, aryl carbamates were only applied in nickel-catalyzed Kumada−Tamao−Corriu reaction.[4,31] Since we have found that aryl carbamates exhibited superior reactivity to aryl carboxylates in the iron-catalyzed coupling with alkyl Grignard reagents, we further investigated the application of aryl carbamates in the Suzuki−Miyaura coupling. We succeeded in the development of this reaction.[32] Good to excellent yields were obtained when *N*,*N*-dimethyl aryl carbamates were used as substrates with 5 mol % of nickel catalyst (Table 8). Most importantly, deactivated aryl carbamates, such as *p*-methoxyl- and *p*-*N*,*N*-dimethylamino-substituted phenylcarbamates underwent the reaction smoothly. Unactivated alkenyl carbamates were also suitable substrates. The reactions with low catalyst loading or on 10 mmol scale proceeded without obvious decrease of the yields, demonstrating the potential application. During the preparation of the

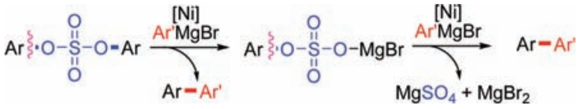
TABLE 9. Kumada−Tamao−Corriu Reaction of Diaryl Sulfates with ArMgBr



entry	Ar	Ar′	yield (%)
1	2-naphthyl	Ph	85
2	2-naphthyl	4-MeOC$_6$H$_4$	88
3	2-naphthyl	2,4,6-(Me)$_3$C$_6$H$_2$	91
4	2-naphthyl	4-FC$_6$H$_4$	72
5	2-naphthyl	4-ClC$_6$H$_4$	43
6	2-tolyl	Ph	88[a]
7	4-MeOC$_6$H$_4$	2-tolyl	75
8	2-MeOC$_6$H$_4$	4-tolyl	75
9	4-Me$_2$NC$_6$H$_4$	Ph	83
10	4-Me$_2$NC$_6$H$_4$	1-C$_{10}$H$_7$	61

[a] GC yield.

SCHEME 5. Proposed Mechanism

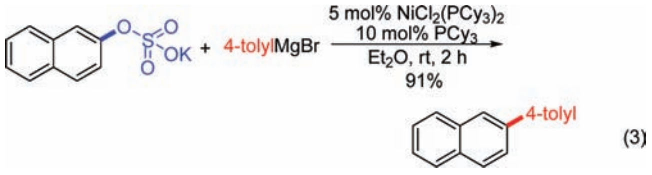


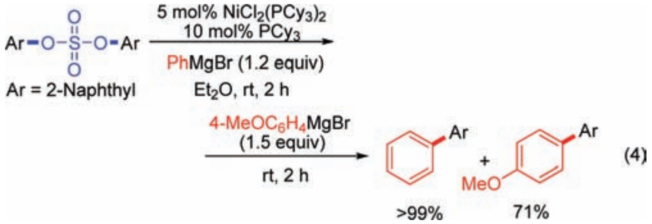
manuscript, the Garg and Snieckus groups simultaneously reported similar results.[33]

4. Diaryl Sulfates as Electrophiles in Kumada−Tamao−Corriu Coupling

In the new classes of electrophiles such as ethers, carboxylates, and carbamates, the carbon atom economy is not ideal because all the leaving groups contain certain carbon atoms. Thus, the identification of O-containing electrophiles that proceed without generating C-containing byproduct would be highly appealing. Based on the previous studies on the cross coupling of sulfonates including triflates, tosylates, mesylates, and sulfamates,[6] we felt that diaryl sulfates might be a good candidate if both aryl groups could be utilized.

Diaryl sulfates are quite stable and could be easily prepared in good yields even on a large scale. After systematic studies, we developed the first Kumada−Tamao−Corriu reaction of diaryl sulfates, in which both aryl groups were incorporated to the product with inorganic salts as the only byproduct.[34] The cross coupling reaction occurred in high efficiency in the presence of 5 mol % nickel catalyst at room temperature (Table 9). Deactivated diaryl sulfates with methoxyl or dimethylamino groups underwent the reaction smoothly. The independently prepared potassium 2-naphthyl monosulfate could also undergo the cross-coupling reaction (eq 3), indicating that the two C_{sp^2}−O bonds were cleaved sequentially (Scheme 5). Interestingly, due to the lower reactivity of the monosulfate, two different biaryls were obtained in good yields by adding two different Grignard reagents sequentially (eq 4).





5. Magnesium Naphtholates as Electrophiles in Kumada−Tamao−Corriu Coupling

Although much progress has been achieved in the transformations of inexpensive and easily synthesized phenol derivatives, such as anisoles, carboxylates, and carbamates, as well as diaryl sulfates, introduction of a protecting group is always necessary prior to the cross-coupling reaction, thereby lowering the carbon-atom economy and step economy. Undoubtedly, direct application of phenols or phenolates into cross-coupling reactions to construct C−C bonds is an ideal process. However, the successful implementation of this process meets formidable challenges. First, high bond dissociation energy makes the OH and MO$^-$ poor leaving groups. Second, transformation of phenols to phenolic salts further enhances the bond energy of the C−O bond. Furthermore, the phenolic anion always acts as a good ligand to bind the transition metals, which impedes the cleavage of the C−O bond. Although little product was observed by Wenkert in the cross-coupling reaction of magnesium β-naphthoxide with Grignard reagent,[10] successful transformations have never been achieved prior to our work.[2c,35]

Inspired by the successful transformation of the phenol derivatives with good leaving groups, we hypothesized that the cleavage of the phenol C−O bond might be practical by combining Lewis acid and a transition metal catalyst. 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.[36]

With this in mind, we first prepared 2-NaphOMgBr in THF, and its single crystal was grown in toluene solution. Analysis of the X-ray structure (Figure 3) showed that a dimer was

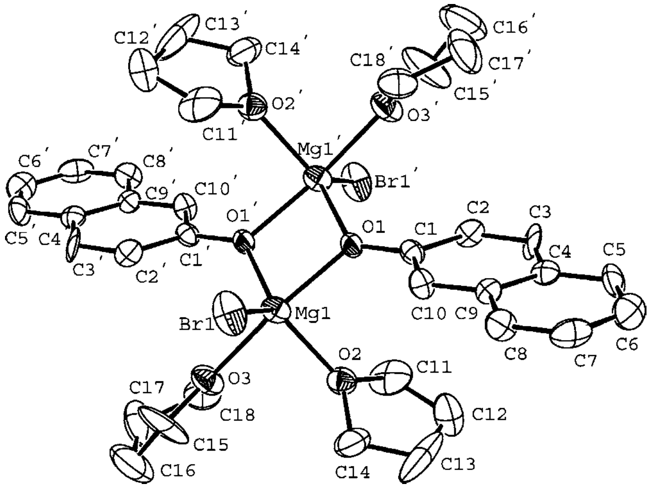


FIGURE 3. Crystal structure of [2-NaphOMgBr(THF)$_2$]$_2$

formed in which both oxygen atoms were coordinated to two magnesium ions. The C−O bond length is the same as that in naphthol. This observation is consistent with our hypothesis. Later, preliminary mechanistic studies showed that the crystal of [2-NaphOMgBr(THF)$_2$]$_2$ is stable under the reaction conditions so that no significant difference was detected. We proposed that the dimer of magnesium naphtholate could be directly involved in the cross coupling via C−O bond activation.

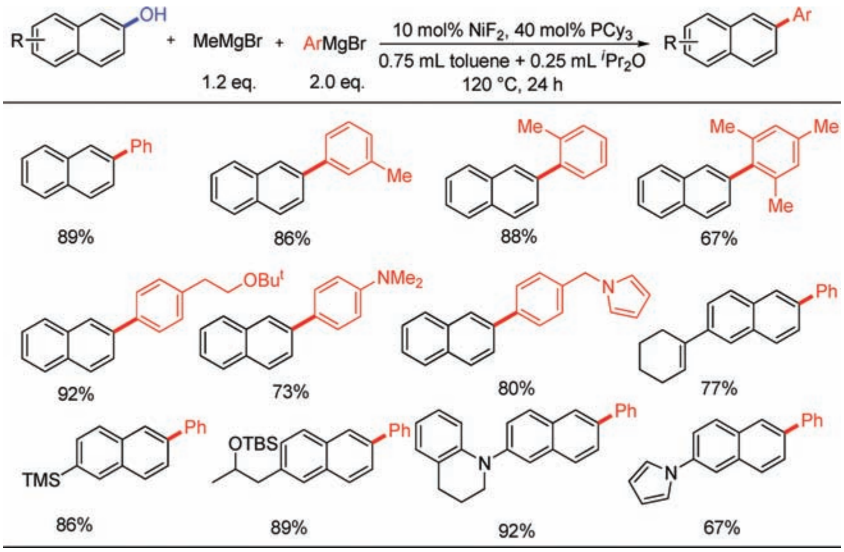
Prompted by the information, we explored the Kumada−Tamao−Corriu reaction of naphtholic salts. We tested various naphtholic salts, among which (2-NaphO)$_2$Mg and 2-NaphOMgBr gave the best results. The combination of NiF$_2$ and PCy$_3$ showed the highest efficiency in mixtures of toluene and diisopropyl ether. The optimized reaction condition was applicable to various aryl Grignard reagents and naphthol derivatives. Functional groups, such as alkenyl, TMS, ^{t}Bu, and TBS-protected alcohol were tolerated (Table 10).

6. Conclusion and Outlook

During the last several years, we have developed the cross-coupling reactions of various O-based electrophiles via C−O bond activation. We started our research from the activation of sp^2 C−O bonds of anisoles, which possibility had been demonstrated by other pioneers. With our efforts, methylation reactions of both anisoles and benzylic alkyl ethers via selective C−O bond activation have been achieved. Furthermore, we have achieved the selective cleavage of the C$_{Ar}$−O bond in aryl carboxylates in preference to the more active acyl C−O. Various cross-coupling reactions, including Suzuki−Miyaura, Negishi, and Kumada−Tamao−Corriu reactions, of the carboxylates and carbamates have been developed. In addition, diaryl sulfates were applied as one-by-one electrophiles in Kumada−Tamao−Corriu reaction, with magnesium salts as the sole byproduct. As one of the final goals, we successfully demonstrated that naphtholic salts could act as electrophiles in the Kumada−Tamao−Corriu reaction. These studies provide novel processes to efficiently construct C−C bonds. More importantly, they are beneficial to understand the intrinsic feature of C−O bonds, which were traditionally considered "inert" motif of ethers, carboxylates, and phenolic salts.

Although much progress has been achieved, high catalyst loading and the use of air-sensitive electron-rich phosphines are required in some cases, which limited the application. The development of a more efficient catalyst system is highly desirable. Furthermore, selective activation of sp^3 C−O bonds

TABLE 10. Kumada−Tamao−Corriu Reaction of Naphtholic Salts with ArMgBr



in common dialkyl ethers, alkyl esters, and alcohols is still a great challenge. The understanding of intrinsic characteristics of C—O bonds and the huge potential for application will promote more and more research interests in this fertile area. We believe that these goals will be realized in near future.

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FOOTNOTES

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