C–O Bond Activation

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Direct Application of Phenolic Salts to Nickel-Catalyzed Cross-Coupling Reactions with Aryl Grignard Reagents**

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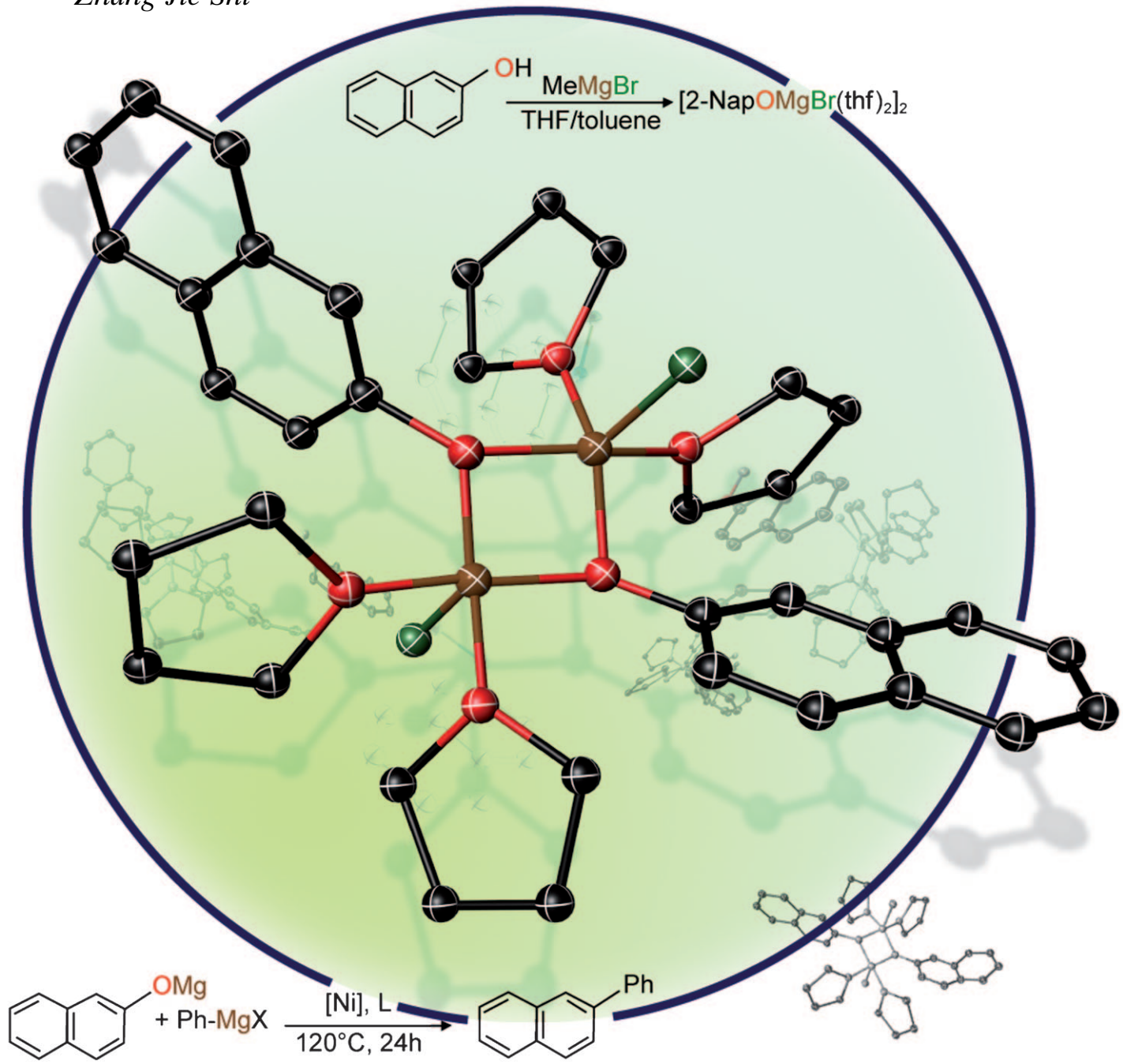

Since the 1970s, much attention has been paid to cross-coupling reactions. Many reactions have been named, which demonstrates the importance of these developments.[1] Undoubtedly, the cross-coupling reaction has already become one of the most powerful tools in organic synthesis.[2] Amongst these developments, the construction of biaryl scaffolds have been particular extensively investigated because of its diversified applications in drug discovery, material chemistry, and the construction of natural products.[3]

In the early stages of this development, aryl iodides and bromides were successfully employed as electrophiles in cross-coupling reactions because of their relatively high reactivities.[1a–b] With the development of efficient catalytic systems, the less-reactive aryl chlorides and fluorides were also successfully used as coupling partners.[2a,4] However, the relatively high cost of aryl halides and their toxicity to the environment have limited their applications. Furthermore, most organic halides are difficult to prepare, which might result in an economic and ecological problem in large scale syntheses.[5]

More recently, a variety of cross-coupling reactions involving direct C–H transformation have been rapidly developed. Towards the key target of constructing C–C bonds, the direct functionalization of C–H bonds has the advantages of lower costs, less waste production, and higher step economy.[6] Although great progress has been made in this area, many challenges remain. For example, relatively harsh conditions, high catalyst loading, as well as the requirement for directing groups or specific substrates make such chemistry less desirable for practical application.[7]

Compared with the above-mentioned electrophiles, readily available phenol substrates and their derivatives provide an alternative route to C–C bond formation (Figure 1). Previous work using phenol as a coupling partner involved initial transformation into a more active species. For instance, aryl triflates have long been successfully used as an efficient electrophile because of their relatively high reactivity.[8] Subsequent studies developed other, less-reactive sulfonates and phosphates in cross-coupling reactions.[9] Notably, recent advances indicated that aryl carboxylates, carbamates, and anisole derivatives are also potential substrates.[10] However, the use of such groups limits their efficiency for overall yields and step economy. Obviously, a direct transformation from phenol itself or its inorganic salt would be the best choice to solve such a problem as it avoids the extra steps of group transfer and the generation of organic wastes.

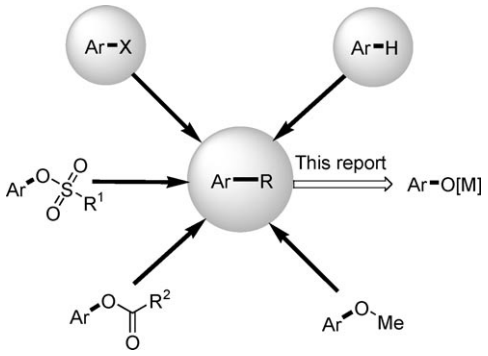

Figure 1. Design of cross-coupling from a phenol or phenolate using organometallic reagents. X = I, Br, Cl; R = aryl, alkenyl, alkyl; $R^1 = R^2$ = alkyl, aryl, NR'_2; [M] = metal complex.

Obviously, such a design faces a formidable, and yet to be overcome, enthalpy barrier. The bond dissociation energy (BDE) seemed to indicate that direct cleavage of the aryl C–O bond on phenol is impossible. 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.[11] Previous reports have demonstrated the difficulty of such transformations, although the cross-coupling product was occasionally observed in some cases.[10f,h] Contrary to this traditional analysis, herein we report the first successful example of the cross-coupling reactions of magnesium phenolate with Grignard reagents to construct biaryl scaffolds.

Starting from the phenolic salt, we envisioned that metal ions could act as Lewis acids that are tightly coordinated by the oxygen atom of the phenoxide. Presumably, the oxygen atom lone pair coordinates with different metal centers to form regular frameworks. With inorganic salts, we proposed that such coordination might induce the reorganization of the electronic structure of the phenolic C–O bond. The reorganization of the electron density might then activate the C–O bond for further cross-coupling reactions. In this proposed reaction, the metal ions would act as electron-withdrawing groups. With this in mind, 2-NapOMgBr (Nap = naphthyl) was prepared and its single crystal was grown in a tetrahydrofuran/toluene solution (Figure 2).[13] Analysis of the X-ray structure revealed two features. 1) A dimer was formed in which both oxygen atoms coordinated with two magnesium ions to form a four-membered-ring core. Bromine and thf ligands were also ligated to each magnesium ion. 2) With the assistance of both Mg^{2+} centers, the activated phenol C–O bond length was 1.336 Å, as predicted, and thus has the

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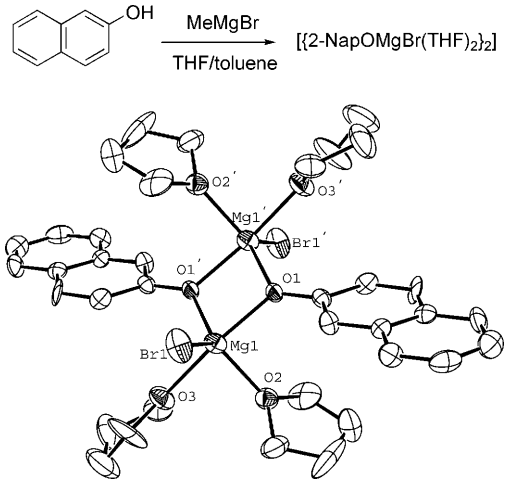


Figure 2. Preparation and structural determination of a magnesium phenolate complex. Ellipsoids set at 30% probability. Hydrogen atoms removed for clarity.

potential to be cleaved in the cross-coupling reaction as it is as long as that of the corresponding naphthol C–O bond.

With this confirmation, we tested the cross-coupling reaction of phenoxide with phenyl Grignard reagent PhMgBr. Different metal counterions were also tested. When 2-NapOLi and 2-NapOK were submitted to the cross-coupling conditions in the presence of NiF_2 and additional PCy_3, the desired coupling product was observed, albeit with a very low efficiency. Interestingly, a better result was obtained when 2-NapONa was used as a substrate. Satisfactorily, both the prepared $(2\text{-NapO})_2Mg$ and 2-NapOMgBr showed much improved reactivity and the desired product was obtained in moderate yields in both cases, with partial substrate recovery. It is important to note that the halide substituent on the Grignard reagent is critical to the reaction and Br^- was found to be the best (Figure 3).

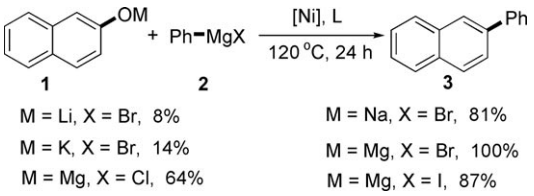
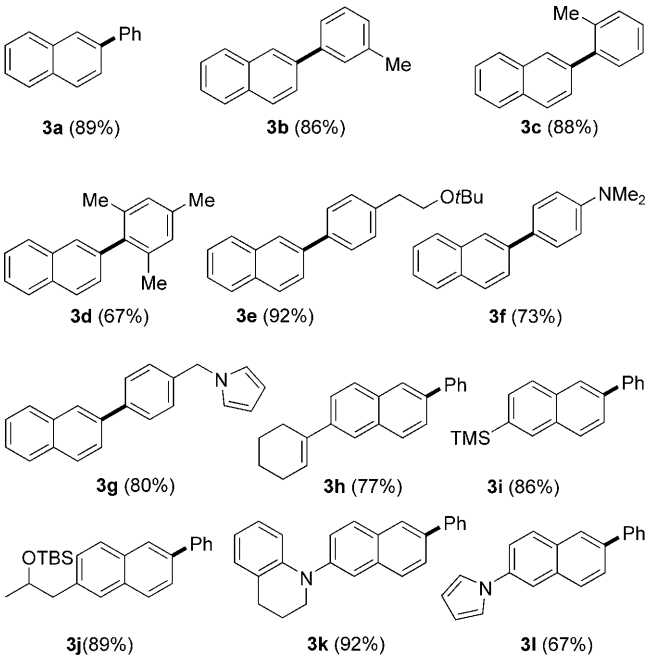


Figure 3. Coupling reaction of 2-naphtholate and PhMgX (GC yield). TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl.

Screening of the reaction conditions indicated that nonpolar solvents were suitable for this transformation; the best solvent system was a 3:1 mixture of toluene and diisopropyl ether (DIPE). This solvent system might retain the core framework owing to their low coordinating ability. NiF_2 in the presence of PCy_3 as a ligand showed the highest reactivity for this transformation.

To simplify the reaction process, we prepared 2-NapOMgBr in situ, as the Grignard reagents were used as the reaction partners. Fortunately, increasing the number of equivalents of PhMgBr to 5.0 equivalents induced complete conversion of 2-naphthol into 2-phenyl naphthalene. As some arylMgBr reagents are hard to prepare and relatively expensive, the commercially available MeMgBr was used to deprotonate the naphthol to reduce costs and increase the carbon-atom economy. When 1.2 equivalents of MeMgBr were used, followed by the cross-coupling with PhMgBr, the desired product was isolated in 89% yield.

We then tested different aryl Grignard reagents (Scheme 1). Steric effect did not have a significant influence on the reactivity (**3a**, **3b** and **3c**); however, high steric



Scheme 1. Biaryl products synthesized from naphthol with various aryl Grignard reagents by nickel catalysis. Reaction conditions: **1** (0.2–0.4 mmol), NiF_2 (10 mol%), PCy_3 (40 mol%), MeMgBr (120 mol%), and ArMgBr **2** (200 mol%) in toluene (0.75 mL) and DIPE (0.25 mL), 120°C, 24 hours. All reported yields are the avarage yields of at least two experiments.

hindrance decreased the rate of reaction and the desired product was produced in relatively low yield (**3d**). The *tert*-butyl-protected alcohol **3e** was also compatible with this transformation. Notably, the dialkylamino group (**3f**) tolerated this transformation and the cross-coupling reaction proceeded smoothly. Furthermore, heterocyclic groups at the benzylic position, such as pyrrole (**3g**), tolerated the reaction conditions.

Various substituted naphthols were subsequently investigated. Alkyl, aryl, and alkenyl substituents did not hinder the transformation (**3h**), and importantly, the C–Si group (**3i**), which is then available for further elaboration, was also tolerated successfully. Similarly, the TBS-protected hydroxy group (**3j**) was compatible with the reaction. N-containing groups, such as *N*-tetrahydroquinilinyl (**3k**) and *N*-pyrrolyl (**3l**), also performed well. Those products might have potential application in drug discovery and materials chemis-

try. Unfortunately, at present, phenol derivatives do not successfully undergo this transformation.

Preliminary studies were conducted to understand the reaction mechanism. The solid [{2-NapOMgBr(thf)$_2$}$_2$] was suspended in the mixed solvent system and heated to the reaction conditions that resulted in the salt being partial dissolved. After removal of the solvent under vacuum and recovery of the salts, the ^{1}H NMR and ^{13}C NMR spectroscopy of the solid residue did not show significant changes from the original data. Further IR and powder X-ray diffraction (PXRD) analysis of the recovered material suggested that the structure of the magnesium salts did not decompose under the reaction conditions (see the Supporting Information). Therefore, we considered that such a scaffold of the dimer was directly involved in cross-coupling.

The transformation was thought to go through the Ni^0/Ni^{II} catalytic cycle (Figure 4). NiX$_2$ was first reduced to Ni^0 species **4** with the support of the PCy$_3$ ligand. In the presence of MeMgBr, magnesium phenoxide salt **5** was generated. With

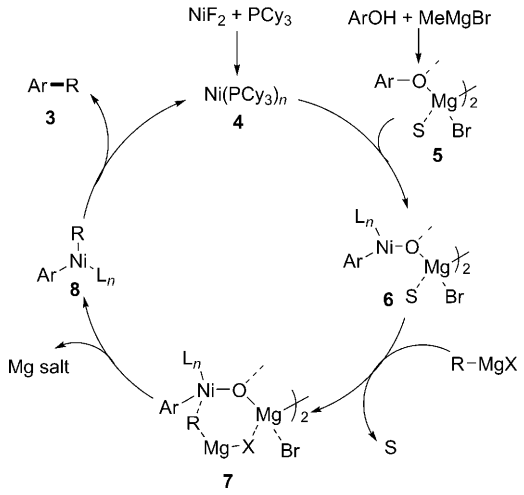


Figure 4. Catalytic Pathway of the cross-coupling between phenolic salt and Grignard reagents. Ar = substituted naphthyl, S = solvent, L = ligand, X = halide, n = 0–2.

the assistance of Mg^{2+} in the complex, the phenoxide C–O bond was slightly activated, and further underwent oxidative addition to the Ni^0 species. After transmetalation with RMgX, through the proposed 6-membered transition state (**7**), the biaryl Ni^{II} species **8** was formed. Finally, reductive elimination released the desired product **3**, concurrently regenerating the Ni^0 species **4** to facilitate the catalytic cycle. However, in the presence of NiF$_2$, the catalytic efficacy was highly promoted. Therefore, the potential Ni^{II}/Ni^{IV} cycle that involved a nickel fluoride ate complex could not be elucidated as in the previous report.[12]

In conclusion, we have demonstrated the first successful cross-coupling reaction of 2-naphthol derivatives with various aryl Grignard reagents. This study suggested that MO$^-$ species might be a useful leaving group for different transformations. Not only did this unprotected process offer significant enhancement in process economy and atom economy, it also decreases the expense of the design and preparation of complex scaffolds by using readily available phenol derivatives. Most importantly, 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. Further expansion of substrate scope, mechanistic investigation, and extension of this idea to other synthetic transformations are underway.

Experimental Section

Typical procedure for the Kumada-Tamao-Corriu coupling of naphthol derivatives: 2-naphthol (**1a**; 57.6 mg, 0.4 mmol), NiF$_2$ (3.9 mg, 0.04 mmol), and PCy$_3$ (44.8 mg, 0.16 mmol) were added to an oven-dried Schlenk tube that contained a stirrer bar. The tube was degassed 3 times and 0.5 mL of freshly distilled THF was added. Then, MeMgBr (0.48 mmol) was added by syringe at room temperature, and the mixture was stirred at room temperature for 5 minutes. After addition of PhMgBr (0.8 mmol), the solvent was removed with a cold trap under reduced pressure. Next, toluene (0.75 mL) was added and the solution was stirred at room temperature for a further 5 minutes. After iPr$_2$O (0.25 mL) was added, the solution was stirred at room temperature for another 10 minutes. The mixture was then stirred at 120 °C for 24 hours under a N$_2$ atmosphere. The mixture was cooled to room temperature, quenched with EtOH, and filtered through a short silica column. The solvent was removed and the product was purified by column chromatography on silica gel. All reactions were carried out on a 0.4 mmol scale, apart from **3j** and **3l** (0.2 mmol). **3f** and **3k** were obtained after 36 and 34 hours, respectively).

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[13] CCDC 769550 ([{2-NapOMgBr(thf)$_2$}$_2$]) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

