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Direct Arylation/Alkylation/Magnesiation of Benzyl Alcohols in the Presence of Grignard Reagents via Ni-, Fe-, or Co-Catalyzed sp^3 C–O Bond Activation

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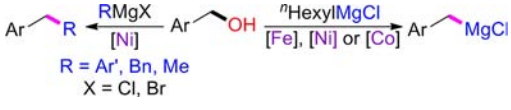
Supporting Information

ABSTRACT: Direct application of benzyl alcohols (or their magnesium salts) as electrophiles in various reactions with Grignard reagents has been developed via transition metal-catalyzed sp^3 C–O bond activation. Ni complex was found to be an efficient catalyst for the first direct cross coupling of benzyl alcohols with aryl/alkyl Grignard reagents, while Fe, Co, or Ni catalysts could promote the unprecedented conversion of benzyl alcohols to benzyl Grignard reagents in the presence of ^{n}hexylMgCl. These methods offer straightforward pathways to transform benzyl alcohols into a variety of functionalities.

Alcohols broadly exist in nature and can also be easily synthesized from carbonyl compounds or alkenes. Owing to their low toxicity and cost, direct transformations of alcohols to valuable chemicals has attracted much attention in organic synthesis.[1] In classical organic chemistry, alcohols (or their salts) always act as the nucleophiles and reductants. Recent advances have demonstrated that alcohols could be applied as efficient electrophiles in not only Brønsted/Lewis acid-promoted Friedel–Crafts reaction[2] but also transition metal-catalyzed hydrogen-borrowing reactions.[3] Meanwhile, Brønsted/Lewis acid-promoted and/or transition metal-catalyzed reductions of alcohols have also been reported.[4] Herein, we demonstrate that benzyl alcohols (or their magnesium salts) can not only act as electrophiles in Ni-catalyzed cross coupling but also undergo Fe-, Ni-, or Co-catalyzed direct magnesiation with different Grignard reagents via sp^3 C–O bond activation (Scheme 1).

Scheme 1. Catalytic Transformations of Benzyl Alcohols with Different Grignard Reagents via Fe-, Ni-, or Co-Catalyzed sp^3 C–O Bond Activation



Transition metal-catalyzed cross-coupling reactions are important and powerful tools to construct carbon–carbon bonds.[5] Compared with the reactions of aryl/alkenyl electrophiles,[6,7] application of alkyl electrophiles in cross couplings has been less investigated, which may arise from their difficult oxidative addition and reductive elimination as well as other competitive side reactions (e.g., β-H elimination).[8] Compared with alkyl halides, alcohols are much more desirable because of their low toxicity and easy availability. However, due to the high bond dissociation energy of the C–O bond,[9] good coordinative ability and low leaving ability of the OH^- group, and easy oxidation through β-H elimination, protection of the hydroxyl group and simultaneous activation of the C–O bond are commonly required. For example, alkyl sulfonates have been applied in various cross-coupling reactions.[10]

Obviously, direct transformation of alcohols is much more step- and atom-economic as well as environmentally benign. With the efforts to achieve this goal, highly active alcohols, such as allylic, allenic, and propargylic alcohols, have been directly employed in cross-coupling reactions by several groups.[11] Recently, in a significant contribution, Yi reported the Ru-catalyzed C–H alkylation of alkenes and phenols with general alcohols.[12] To date, direct cross coupling of benzyl alcohols has never been achieved, although benzyl carbonates, carboxylates, phosphates, and ethers have been applied in various cross couplings by several groups, including ours.[13]

With the success of activation of sp^2 C–O bond in naphthoxides via Ni catalysis,[14] we planned to apply this idea to sp^3 C–O bond cleavage of alkoxides. The choice of benzyl alcohol at the initial stage was inspired by the relatively higher reactivity of such an sp^3 C–O bond[9] and the importance of diarylmethanes, which are a common structural motif in biologically active drugs[15] and supramolecular structures,[16] as desired products.

2-Naphthylmethanol **1a** was chosen as the standard substrate, and relatively inexpensive MeMgBr was used as the base to

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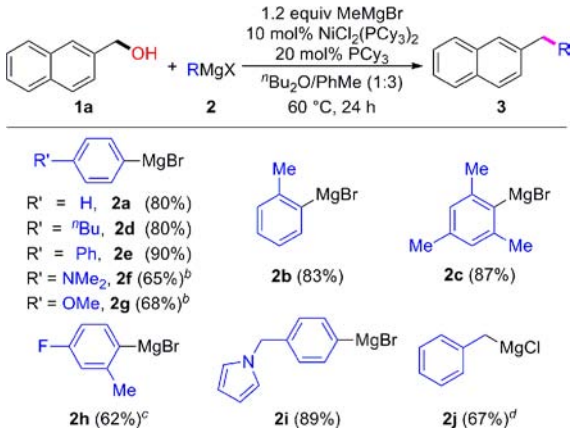
generate magnesium naphthylmethoxide for the subsequent coupling. Recent studies indicated that Ni catalysts had a great potential to activate both sp^2 and sp^3 C–O bonds.[7,13,14,17–19] After much screening, we found that $NiCl_2(PCy_3)_2$ was efficient for cross coupling **1a** with PhMgX (X = Br, Cl) to afford 2-benzylnaphthalene **3aa** (Table S1).

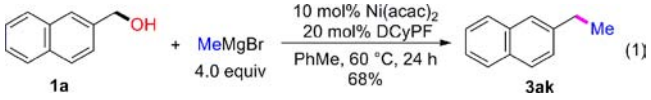
With the optimized conditions, we investigated the scope of Grignard reagents (Table 1). Various arylmagnesium bromides,

Table 1. Cross Coupling of 1a with Grignard Reagents 2[a]



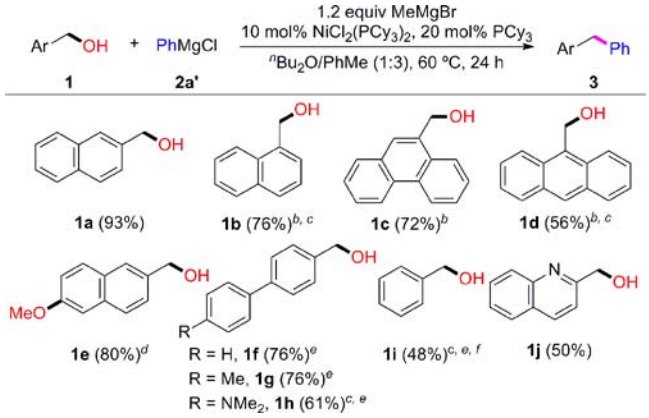
[a]Reaction conditions: 0.2 mmol of **1a**, 2.0 equiv of **2**, 1.2 equiv of MeMgBr, 10 mol% of $NiCl_2(PCy_3)_2$, 20 mol% of PCy_3 in a mixture of 0.75 mL of PhMe and 0.25 mL of $^nBu_2O$ at 60 °C under N_2 for 24 h. [b]30 °C. [c]22 h. [d]48 h.

including those with steric hindrance (**2b**, **2c**, **2h**), showed good efficiency. Moreover, Grignard reagents with electron-donating groups (**2f**, **2g**) showed good reactivity even at 30 °C. It is important to note that both sp^2 C–OMe (**2g**) and C–F bonds (**2h**) can survive in the reaction and can further undergo orthogonal cross coupling with different organometallic reagents.[19,20] Heterocycles such as pyrrole (**2i**) can also be tolerated. Besides aryl Grignard reagents, benzylmagnesium chloride (**2j**) also showed good reactivity. Unfortunately, alkyl and alkenyl Grignard reagents were not suitable for this transformation. In some cases, some coupling products were observed, accompanied by a small amount of reductive product 2-methylnaphthalene (**4a**). To our delight, in the presence of a bidentate phosphine ligand, 1,1′-bis(dicyclohexylphosphino)-ferrocene (DCyPF),[18a] $Ni(acac)_2$ showed good activity in methylation of **1a** under similar reaction conditions (eq 1). The product **3ak** was obtained in 68% yield, along with 9% of **4a** (please refer to Table 3).



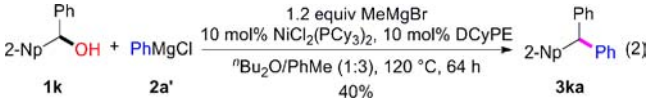
The substrate scope of benzylic alcohols was further surveyed with PhMgCl (**2a′**) as the coupling partner (Table 2). Benzylic alcohols involving fused rings, such as **1b–1d**, afforded the desired products in moderate to good yields. When **1e** was applied in the reaction, both C–O bonds were cleaved and the diphenylated product was obtained with good efficiency. Although the simple benzylic alcohol showed low reactivity under identical conditions, the conversion and yield could be significantly promoted by using a bidentate ligand, 1,2-bis(dicyclohexylphosphino)ethane (DCyPE),[17b] to replace the

Table 2. Cross Coupling of Benzyl Alcohols 1 with 2a′ [a]



[a]Reaction conditions same as in Table 1. [b]30 °C. [c]48 h. [d]Both of the C–O bonds were phenylated. [e]10 mol% of DCyPE was used instead of 20 mol% of PCy_3. [f]GC yield with *n*-decane as an internal standard.

additional PCy_3. Under this modified condition, 4-biphenylmethanols **1f–h** with different substituents and even simple benzyl alcohol **1i** showed credible reactivity. Notably, quinolin-2-ylmethanol (**1j**) is also applicable, albeit with relatively low conversion and yield. α-Arylated benzylic alcohols also worked but showed lower reactivity. For example, **1k** could only afford **3ka** in 40% yield (eq 2).



As mentioned above, reductive products were observed when alkyl Grignard reagents were used. Inspired by this observation, we searched for efficient methods to reduce benzyl alcohols. Previously, Pd, Ru, Au, Rh, and other metals showed activity in catalytic reduction of benzyl alcohols.[2,4] However, iron catalysts, which are much less expensive and nontoxic, have never been applied in this reaction.[21] After systematic screening, we were pleased to find that various iron catalysts exhibited good reactivity to afford the reductive product in the presence of ^{n}hexylMgCl (**2k**) (Table S2). Moreover, several cobalt and nickel salts, such as $CoCl_2$ and $Ni(acac)_2$ (Table 3, entries 2 and 3), also showed good activity, while copper salts gave a very low efficiency (Table S2), which indicated that the contaminant from copper might not be the active catalyst in this reaction.[22]

Under the optimized conditions, reduction of different benzyl alcohols was conducted (Table 3). Beside benzylic alcohols involving fused rings (**1a**, **1c**, and **1e**), biphenylmethanol derivatives **1f–m** and even simple benzyl alcohol **1n** (Table 3, entries 6–10) could be reduced well. It is noteworthy that many functional groups, such as amino group and sp^2 C–OMe and C–F bonds, are well tolerated (Table 3, entries 5–10).

In the initial mechanistic investigation, we hypothesized that reduction arose from β-H elimination of an alkyliron complex and reductive elimination. Two possible catalytic cycles with different active catalysts were proposed (Scheme S1). As we know, the alkene would be generated in the process of β-H elimination. To prove these hypotheses, we applied 1-tetradecylmagnesium chloride in the reaction. As expected, the tetradecene was detected as a byproduct (Scheme S2). Moreover, several deuterium-labeled alkyl Grignard reagents were synthesized to confirm the source of "H" in final products

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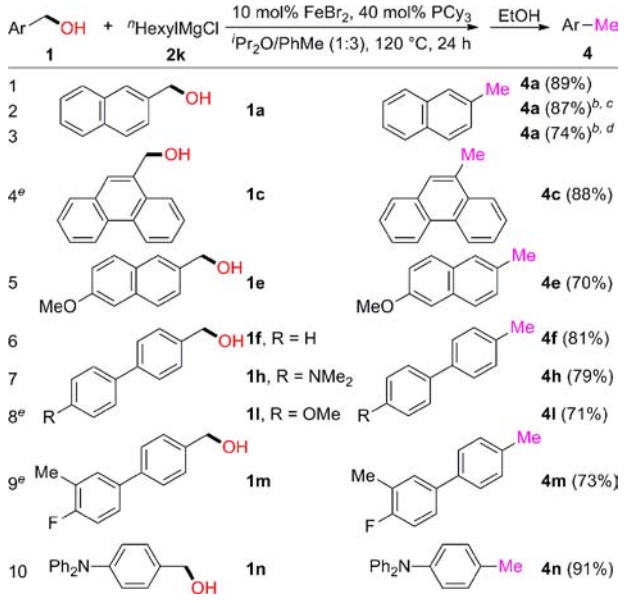
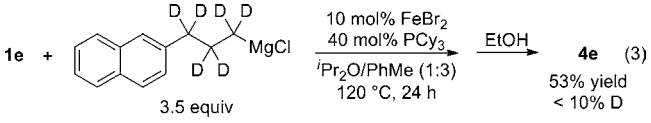
Table 3. "Reduction" of Different Benzyl Alcohols 1[a]

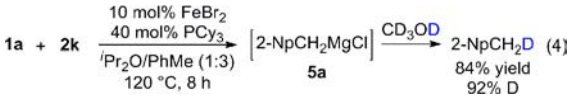


[a]Reaction conditions: 0.2 mmol of **1**, 3.5 equiv of **2k**, 10 mol% of $FeBr_2$, 40 mol% of PCy_3 in a mixture of 0.75 mL of PhMe and 0.25 mL of $^iPr_2O$ at 120 °C under N_2 for 24 h. [b]GC yields with *n*-decane as an internal standard. [c]10 mol% of $CoCl_2$ as the catalyst. [d]10 mol% of $Ni(acac)_2$ as the catalyst. [e]48 h.

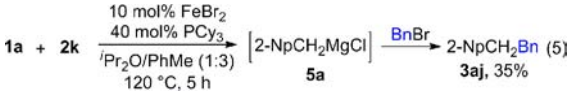
(Scheme S3). To our surprise, no D-incorporation was observed in **4e** when the hexa-deuterium-labeled alkyl Grignard reagent was used (eq 3), which indicated that the "H" did not come from Grignard reagent and excluded these two proposed mechanisms (Scheme S1).



To unveil the real source of "H", we did several isotopic tracking experiments. We tested **1e**-d_2 as the substrate, toluene-d_8 as solvent, and exchange with THF-d_8, but no D-incorporation was observed (Scheme S3). In a pleasant surprise, we found that mono-deuterium-labeled product **4a**-d_1 (92% D) was obtained in 84% yield when the reaction of **1a** was quenched with CD_3OD after 8 h (eq 4), in strong support of benzylic C–M bond



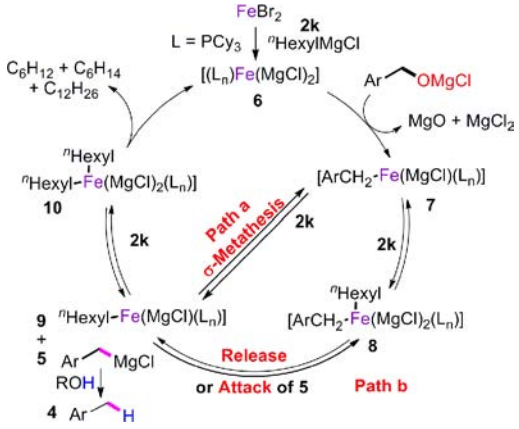
formation. Due to the catalytic amount of $FeBr_2$, we concluded that benzyl Grignard reagent **5a** was formed. Beside protons, carbon-based electrophiles were used to trap the generated **5a** to construct C–C bonds.[23] For example, when BnBr was used as the electrophile, the desired product **3aj** was obtained, albeit with relatively low efficiency (eq 5). Although formations of new



Grignard reagents via transition metal-catalyzed hydromagnesiation or carbomagnesiation of alkynes and alkenes have been disclosed,[24] to our knowledge, this is the first example of transition metal-catalyzed magnesiation of a C–O bond in alcohols.[25]

Based on our results and previous mechanistic studies of iron catalysis,[21] we put forward a new possible mechanism (Scheme 2). An inorganic Grignard reagent $[(L_n)Fe(MgCl)_2]$ (**6**), formed

Scheme 2. Proposed Catalytic Cycle for Magnesiation of Benzylic Alcohols in the Presence of 2k



in situ in the presence of **2k** and PCy_3, was the active catalytic species and underwent the following catalytic cycle.[21e] Oxidative addition of benzylic C–O bond and release of magnesium salts generated **7**, which underwent transmetalation with **2k** to generate a more stable benzyl Grignard reagent **5** and iron complex **9**.[24] The latter was attacked by **2k** to afford **10**, which further underwent β-H elimination and/or reductive elimination to regenerate the active catalyst **6**.[21e] Transmetalation of **7** with **2k** can proceed through σ-metathesis (Path a), or attack of **2k** followed by release of **5** (Path b), both of which are hypothesized to be reversible.

In conclusion, we have developed the first nickel-catalyzed cross coupling and an unprecedented iron-, nickel-, or cobalt-catalyzed magnesiation of benzylic alcohols in the presence of different Grignard reagents via sp^3 C–O bond activation. The coupling affords an atom- and step-economic transformation of benzylic alcohols to construct important diarylmethanes under mild conditions. The new pathway to directly generate benzyl Grignard reagent from alcohols is theoretically important, offering the potential for generation of organometallic reagents from alcohols via transition metal catalysis. Further investigations to understand the reaction mechanism, expand the substrate scope, and carry out other novel transformations of alcohols are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Brief experimental details; spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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