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Deoxygenation of Ethers To Form Carbon–Carbon Bonds via Nickel Catalysis

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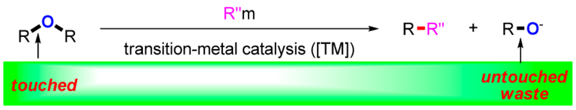
Supporting Information

ABSTRACT: In this article a successful protocol was developed to construct carbon–carbon bonds by the extrusion of the O atom of ethers via nickel catalysis in the presence of reductants. This methodology is featured as a highly economic route to construct sp^3–sp^3 C–C bonds through dual C–O activation of ethers with good functional group tolerance.

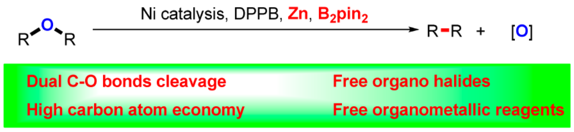
Ethers used as partners in cross-couplings exhibited a myriad of advantages due to their easy availability, stability, and nontoxicity. Recently, efforts to explore the potential utility of ethers, especially aryl ethers[1] and benzyl ethers,[2] in cross-couplings via transition-metal catalysis, have been made. However, in developed cross-couplings with ethers, only one part of ether was used and the remaining part was discarded with the second C–O bond untouched, to some extent showing the undesirable carbon atom economy (Scheme 1a).[3]

Scheme 1. Design of Reductive Deoxygenation of Ethers

a. Conventional transformation of ethers via tansition-metal catalysis



b. Reductive deoxygenation of ethers (This work)



To solve this problem, we recently focused on developing new protocols that apply both parts of ethers in organic synthesis through activation of both C–O bonds in one reaction. From this point of view, the deoxygenation of ethers to construct C–C bonds is an ideal choice, which was fundamentally important to investigate the activation of both etheric C–O bonds at different stages under the same conditions (Scheme 1b).

Our strategy toward the deoxygenation was based on the reductive couplings, which have been developed as powerful methods to construct carbon–carbon bonds.[4] At the current stage, the reductive coupling was used to carry out the transformation of organohalides. Recently, sporadic cases to elucidate the reductive coupling of ethers with organohalides were also reported.[5] To the best of our knowledge, there was no sufficient route of reductive coupling between two etheric C–O electrophiles presented,[4k] especially the proposed deoxygenation of acyclic ethers to date.[6] Compared to the developed reductive couplings, the deoxygenation of ethers faces the following predictable challenges: (1) the cleavage of both C–O bonds of ethers at different stages under the same conditions, especially the C–O bond in the formed alkoxide C–O at the latter stage; (2) the proper O-acceptor to remove the oxygen atom from the ethers.

To examine our concept, we chose 2,2′-oxybis(methylene)-dinaphthalene (**1a**) as the objective to investigate the designed deoxygenation. According to previous works in C–O activation and reductive coupling, Ni-catalysis was first considered in the presence of different ligand sets. As determined above, the proper reductant is required to provide the electrons to facilitate the reduction. The O-receptor was also required to remove the O atom in the ethers. In previous reports, metal powder was usually used in "reductive coupling" as an electron donor and a halogen scavenger.[4] After systematic examination of different parameters, such as nickel catalysts, ligands, reductants, and solvents, to our delight, the desired product 1,2-dinaphthylethane **2a** was obtained in 17% NMR yield when 10 mol % $NiBr_2$(glyme) was used as the catalyst in the presence of DPPB as the ligand and zinc powder as an reductant (Tables S1 and S2).

Considering the poor capability of zinc as an O-scavenger, B_2pin_2 (1.0 equiv) was used as the additive. To our satisfactory, the desired product (**2a**) was obtained in 75% isolated yield. Due to the Lewis acidity of B_2pin_2, it might be beneficial for reorganizing the electron density of C–O bond of the ethers and also facilitating the second oxidative addition by coordination. Other Lewis acids, such as $AlCl_3$ and B_2nep_2, were tested but failed. This result indicated another effect of B_2pin_2 rather than as a simple Lewis acid[7] (Table S2).

In the presence Zn and B_2pin_2, the effect of a ligand was further systematically investigated (Table 1). Monodentate phosphine ligands, including PCy_3 (**L2**), which exhibited excellent reactivity to promote the C–O activation in nickel catalysis, were not effective. Various bidentate phosphine

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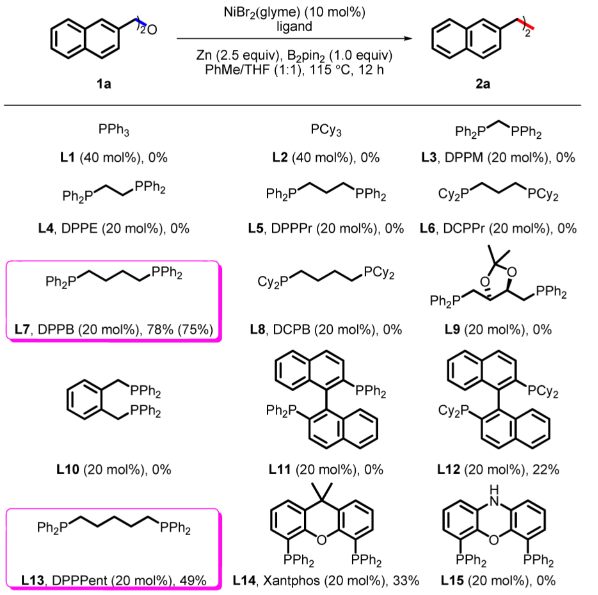
Table 1. Effects of Ligands in Deoxygenation Reactions[a]

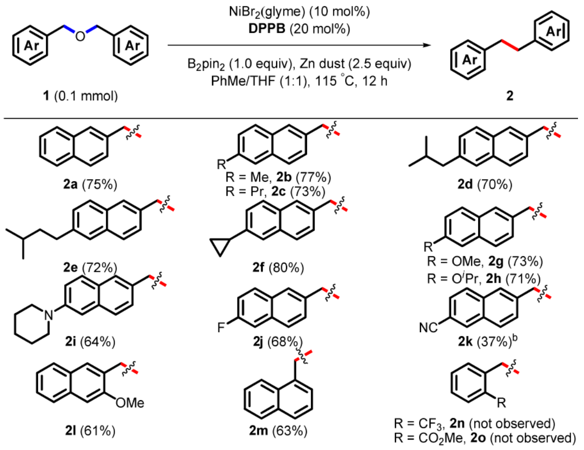


[a]Reaction conditions: a cocktail containing substrate **1a** (0.1 mmol), catalyst $NiBr_2$(glyme) (0.01 mmol), ligand, zinc dust (0.25 mmol), and B_2pin_2 (0.1 mmol) in PhMe/THF (1:1) was heated at 115 °C for 12 h. NMR yields were reported based on **1a**, and benzo[*d*][1,3]-dioxole was used as an internal standard; isolated yields of desired product was reported in parentheses.

ligands with different bite angles were submitted to the catalytic transformation, and the results indicated that bidentate phosphine ligands with a large bite angle promote the efficiency[8] (**L3**–**L7** and **L13**). For example, DPPB (**L7**) promoted the desired product **2a** formation in 78% NMR yield; only a 49% NMR yield was obtained when DPPent (**L13**) was employed as the ligand. Furthermore, variants of DPPB and DPPent, such as more electron-efficient DCPB (**L8**) and more rigid ligands (**L9**–**L12** and **L14**–**L15**), were tested. Unfortunately, none showed better reactivity.

Subsequently, the optimal conditions were applied to the deoxygenation of various diarylmethyl ethers (Table 2).

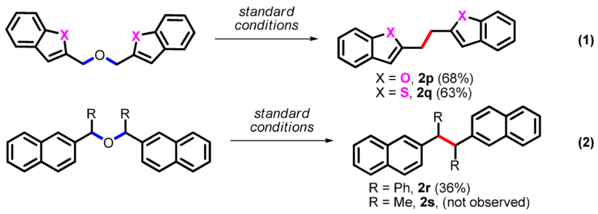
Table 2. Reductive Deoxygenation of Dibenzyl Ethers[a]



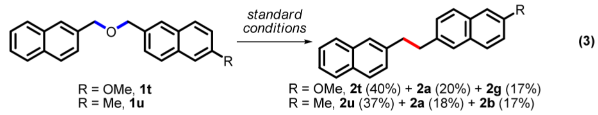
[a]Reaction conditions: a cocktail containing substrate **1** (0.1 mmol), catalyst $NiBr_2$(glyme) (0.01 mmol), ligand, zinc dust (0.25 mmol), and B_2pin_2 (0.1 mmol) in PhMe/THF (1:1) was heated at 115 °C for 12 h. Isolated yields were reported based on **1**. [b]NMR yield.

Initially, we tested the effect of substitutions on the naphthyl ring and found that both electron-donating and -withdrawing substituents did not affect the efficiency (**2a**–**j**). The substrates bearing different alkyl groups converted to the corresponding targeted products in good to excellent yields. Moreover, the cyclopropyl group (**1f**) survived well. Experiments to test the tolerance of sp^2 C–O and C–N bonds were conducted. Notably, various groups were tolerated, which provided another opportunity to diversify the products through nickel-catalyzed cross-couplings[1,9] (**2g**, **2h**, **2i**, and **2l**). A substrate bearing a cyano group also exhibited moderate reactivity under standard conditions (**2k**). Finally, this deoxygenation also proceeded smoothly with the sterically hindered *ortho*-substituent ethers (**2l** and **2m**), albeit in lower yields. Unfortunately, this catalytic system is unable to facilitate the reductive deoxygenation of simple dibenzyl ethers at this stage, even the ethers with an electron-withdrawing group (**2n**) or -directing group (**2o**) at the *ortho*-position.

To further explore the potential applications, we conducted the reductive deoxygenation of substrates containing heterocycles. Both 2,2′-oxybis(methylene)dibenzofuran (**1p**) and 2,2′-oxybis(methylene)dibenzo[*b*]thiophene (**1q**) gave the desired products in good yields (**2p** and **2q**) (eq 1). It is worth noting that product **2r** was obtained via the deoxygenation of highly steric hindered **1r** under the standard conditions in an acceptable yield (eq 2), while *β*-H elimination occurred in the presence of a methyl group at the *α*-position of ether and the desired product **2s** was not observed.

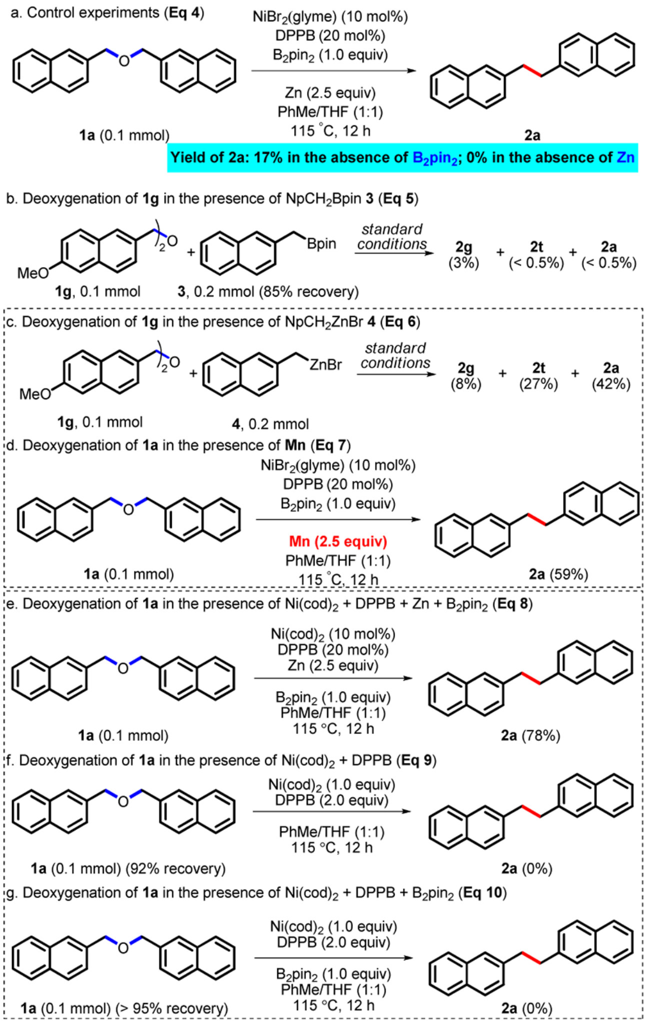


Besides symmetric ethers, asymmetric ether **1t** was submitted to this catalytic system, and the product **2t** was obtained as the major product in 40% yield, while byproducts **2a** and **2g** were observed in lower yields. A similar phenomenon was also observed in the deoxygenation of **1u**. This result indicated that this reaction occurs in an intermolecular manner (eq 3).



During the deoxygenation, a small amount of 2-napththylmethyl boronate was observed by GC-MS. In fact, the borylation of benzyl ethers was reported as we conducted these studies.[1m,10] To gain insight into the mechanism, we carefully reviewed the reaction system and conducted the additional experiments (Scheme 2). As mentioned above, in the absence of B_2pin_2, the desired product **2a** was indeed observed albeit in a low yield (17% NMR yield) (eq 4). This result clearly demonstrated the catalytic pathway could proceed in the absence of any B-based intermediates. To further understand the roles of the possible benzylboronate in the catalytic cycle, prepared aryl methyl boronate (2.0 equiv) was added in this deoxygenation (eq 5).[11] To our surprise, the additional naphthylmethyl boronate **3** was recovered in more than 80%

Scheme 2. Mechanism Studies

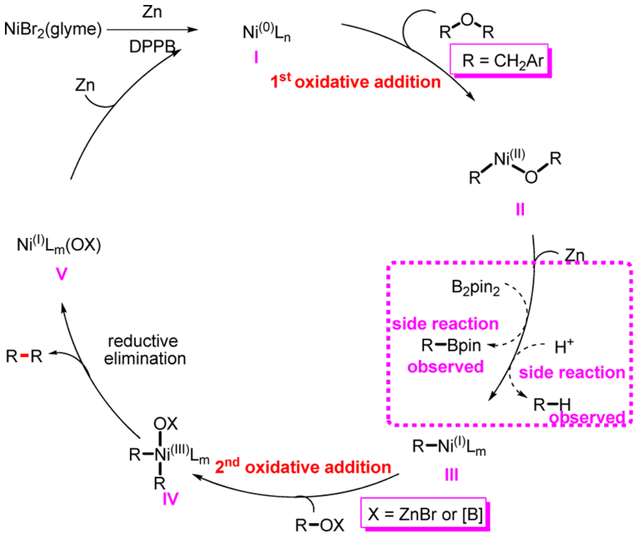


yield (the rest part was protonated to methylarene). The cross-coupling product between **1g** and **3** was detected in a trace amount by both the crude ^{1}H NMR spectra and GC-MS. This result ruled out the participation of benzylboronate as a key intermediate in the catalytic cycle. It is important to note that the additional benzylboronate suppressed this transformation, and the yields of desired products were severely decreased.

To determine the role of benzyl zinc reagent in the catalytic cycle, we conducted the deoxygenation reaction of **1g** in the presence of prepared benzylzinc **4** (eq 6); the desired product; the desired product **2g** was formed in only 8% yield. In this catalytic system, a coupling product between **1g** and **4** was observed in 27% yield. Furthermore, Mn was used to instead of Zn as the reductant to promote the deoxygenation of **1a**, and the target product was prepared in 59% yield (eq 7). By combining these results with those of the capturing experiments, we ruled out the role of the benzyl zinc reagent as an intermediate in the catalytic cycle (see Supporting Information (SI) for details).

To further elucidate the mechanism, other control experiments were performed (eqs 8−10). In the absence of the reductant Zn, the deoxygenation reaction was terminated despite the presence of a stoichiometric amount of Ni(cod)$_2$. Obviously, zinc played an essential role to fulfill the whole catalytic cycle. On the other hand, this result also indicated that the product was unlikely furnished via the transmetalation of two Ni(II) species **II**, which was generated from the first oxidative addition. Meanwhile, the recovery of **1a** indicated that the oxidative addition of the C−O bond to Ni(0) could not occur in the absence of Zn.[12] Moreover, this result also excluded the formation of Ni(IV) species in this catalytic reaction through double sequential oxidative addition of two types of C−O bonds from Ni(0) species (see SI for details). Otherwise, the coupling could take place in the presence of stoichiometric Ni(0) species and in the absence of any reductants.[13] Obviously, the involvement of reductant Zn was not limited to the catalytic cycle at the initial stage.

Scheme 3. Proposed Mechanism of Deoxygenation of Ethers



On the basis of the current results and previous reports, a plausible mechanism was depicted in Scheme 3. First, the nickel(II) species **II** was formed via the first oxidative addition of ether to Ni(0) species, which was reduced to the nickel(I) species **III** by zinc.[14] Subsequently, the second oxidative addition of another C−O bond took place on the Ni(I) species to form the Ni(III) species. Indeed, the proper reductant was very important to reduce the formed Ni(II) species. Because of the difficulty in forming the carbon-centered radical via the homologous section of the etheric C−O bond,[15] this oxidative addition probably took place through a concerted or S$_N$2 pathway, which should be different from the reported radical pathway.[5] Finally, the desired product was released through sp^3−sp^3 carbon−carbon bond reductive elimination on nickel(III) central to regenerating the Ni(I) species. Such a Ni(I) species was further reduced to Ni(0) by zinc to fulfill the catalytic cycle, thus showing the second role of the reductant. During this catalytic cycle, B$_2$pin$_2$ probably played a key role as a Lewis acid to promote the reactivity of the ethers and *in situ* generated alkoxide as well as the oxygen scavenger although other possibilities could not be determined at this stage.[7]

In summary, we for the first time developed a method to synthesize 1,2-diarylethanes via direct deoxygenation of diarylmethyl ethers. Challenges in this transformation were conquered toward the extrusion of the oxygen of ethers. This chemistry exhibited good atom and step economy and offered a complementary strategy in organic synthesis to produce C-based skeletons from O-linked molecules.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02326.

Experimental procedures and characterization data of products (PDF)

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Notes

The authors declare no competing financial interest.

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(12) The $ZnBr_2$ generated in the reduction of high valent nickel species could be acting as a Lewis acid, lowering the barrier for oxidative addition.

(13) In this case, if a reductant is not essential, the desired product can be observed and the yield can be equal to the loading of catalyst.

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