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Nickel-Catalyzed Formal Homocoupling of Methoxyarenes for the Synthesis of Symmetrical Biaryls via C−O Bond Cleavage

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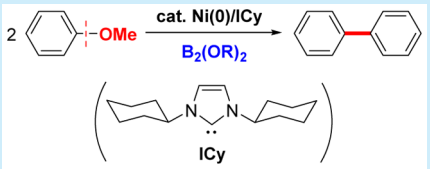
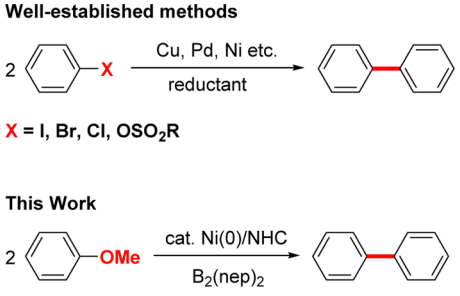
Supporting Information

ABSTRACT: A new method has been developed for the nickel-catalyzed homocoupling of methoxyarenes via C−O bond cleavage using a diboron reagent. The use of 1,3-dicyclohexylimidazol-2-ylidene as a ligand was found to be critical to the success of the reaction. This new method allows the synthesis of a wide range of biaryl compounds.



Given the numerous applications of biaryl substructures across a broad range of fields, including pharmaceuticals and organic materials, the development of catalytic methods for their efficient synthesis has turned into an intense area of research.[1] Despite the outstanding progress made in metal-catalyzed cross-coupling technologies in the past few decades, the homocoupling reactions of aryl halides and their equivalents continue to serve as powerful methods for the synthesis of symmetrical biaryl compounds.[2] Since Ullmann reported the first homocoupling of aryl halides using stoichiometric copper salts,[3] a variety of advanced procedures have been developed for this transformation, which have culminated in the widespread use of homocoupling methods, as exemplified by the syntheses of natural products[4] and conjugated polymers.[5] In terms of the scope of the aryl electrophiles used in the catalytic homocoupling reactions reported to date, aryl halides and sulfonates have been used extensively (Scheme 1, top). Herein

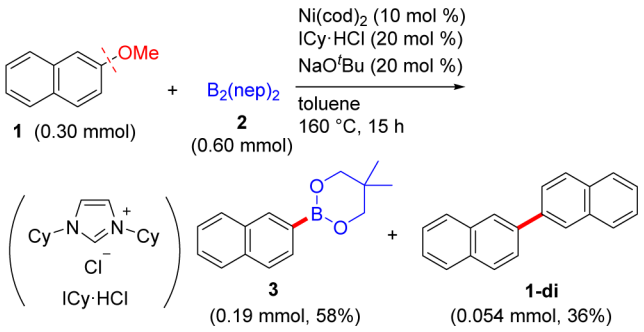
Scheme 1. Catalytic Homocoupling of Aryl Electrophiles Leading to Biaryls



we report the first catalytic homocoupling of aryl ethers via the nickel-catalyzed activation of strong C(aryl)−O bonds (Scheme 1, bottom).[6,7] In addition to the ready availability and low toxicity of aryl ether substrates, the use of an inert methoxy group as a handle for homocoupling would allow for the rapid extension of the π system through sequential cross-/homocoupling processes.

Our ongoing interest in the catalytic transformation of aryl ethers[7b,8] led us to investigate the borylation of **1** using the diboron reagent **2**. When $Ni(cod)_2$ was used as a catalyst in conjunction with 1,3-dicyclohexylimidazol-2-ylidene (ICy),[9] the expected borylated product **3** was obtained in 58% yield. Interestingly, however, we also obtained the homocoupling product **1-di** in 36% yield (Scheme 2). Although we were

Scheme 2. Ni-Catalyzed Reaction of 1 with 2



unable to obtain **3** selectively using the $Ni(cod)_2$/ICy system, we developed a keen interest in the optimization of this reaction for the selective formation of **1-di**. We were especially interested in the novelty of this transformation as a means of satisfying the growing demands for new homocoupling methodologies from the synthetic chemistry community.[4,5] It is noteworthy that Martin and co-workers recently reported the successful development of a nickel-catalyzed C−O borylation of aryl ethers using a $Ni(cod)_2/PCy_3$ system.[10] Interestingly, no homocoupling product was formed under the $Ni(cod)_2/PCy_3$ conditions, highlighting the profound effect of the ligand on the product selectivity of this process.

After a series of screening experiments, we found that decreasing the amount of **2** to 0.80 equiv relative to the aryl

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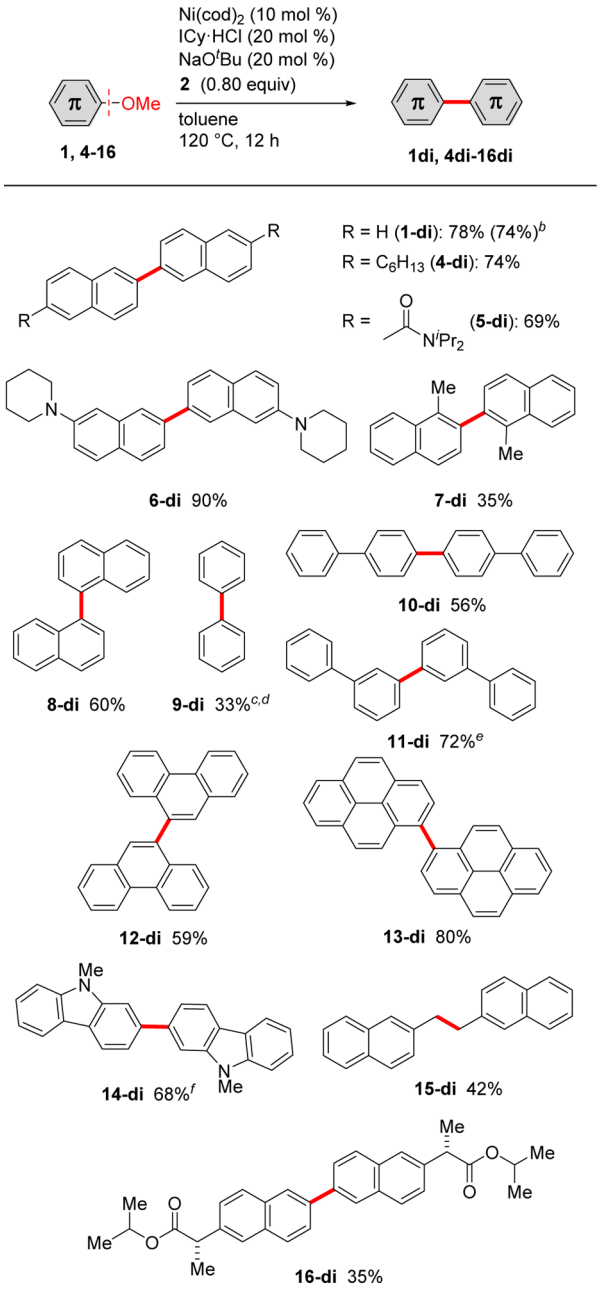
ether substrate led to the selective formation of the homocoupling product.[11] For example, aryl ether **1** formed **1-di** in 90% NMR yield (78% isolated yield) under these nickel-catalyzed conditions, and neither **3** nor **1** was observed by GC analysis of the crude reaction mixture (Scheme 3). The reaction could be conducted on a 10 mmol scale with 5 mol % catalyst without a noticeable loss of the yield of **1-di**. A series of 2,2′-binaphthalene derivatives, including those bearing alkyl (**4-di**), amide (**5-di**), and amine (**6-di**) groups, were successfully synthesized under these conditions. This catalytic homocoupling was found to be sensitive to the steric environment of the aryl ether substrate, since an increase in the steric hindrance of the substrate leads to a 2-fold increase in the steric hindrance developed in the transition state for the C−C bond-forming event (e.g., **7-di**). Nevertheless, this method allowed the synthesis of the sterically demanding 1,1′-binaphthalene system, as in **8-di**. The extent of the π conjugation in the substrate had a significant impact on its reactivity toward this homocoupling reaction. For example, anisole afforded the homocoupling product **9-di** in 33% yield under these conditions, along with PhB(nep) (16%) and **9** (41%). These results indicate that the C−O bond activation of anisole is less efficient than that of naphthalene derivatives, which is consistent with the reactivity trend observed in the nickel-catalyzed cross-coupling reactions of aryl ethers with relatively less nucleophilic reagents.[7b] Methoxybiphenyls were determined to be suitable substrates for this nickel-catalyzed homocoupling process, providing quaterphenyls **10-di** and **11-di**. Further π-extended methoxyarenes such as phenanthrene **12** and pyrene **13** were also homocoupled under these conditions, allowing facile access to much larger aromatic molecules. This homocoupling method also worked well for heteroarenes, as exemplified by the formation of **14-di**. Importantly, 2-naphthylmethyl methyl ether (**15**) also afforded a dimerized product via the activation of its C(sp^3)−O bond.[9a,10] This method was also found to be suitable for the homocoupling of biologically active methoxyarenes. For example, the dimeric derivative of naproxen (**16**) was successfully synthesized using our homocoupling protocol.

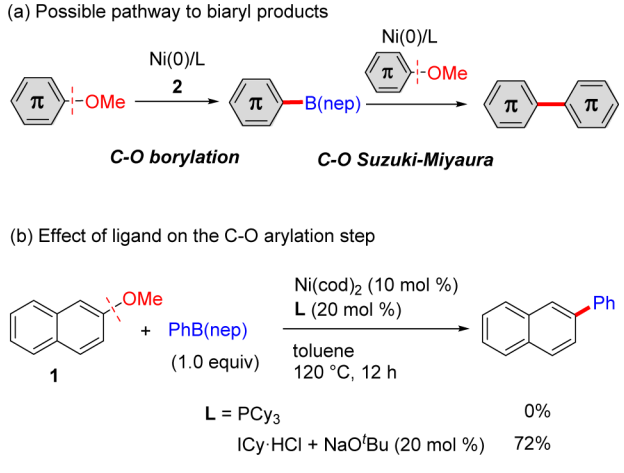
Of all the additives evaluated in the current study, only the diboron reagent **2** produced a homocoupling product.[11] The yield of the homocoupling product reached its highest level when 0.80 equiv of **2** relative to the methoxyarene substrate was added to the reaction, with the use of excess **2** leading to the formation of the C−O borylated product (Scheme 2). Taken together, all of these observations suggested that the homocoupling product is formed through two sequential nickel-catalyzed C−O activation reactions, including borylation of the methoxyarene with **2**[10] followed by cross-coupling of the borylated arene with the starting methoxyarene (Scheme 4a).[9a] The catalytic homocoupling of aryl halides via a similar pathway has been reported previously.[12] This mechanistic hypothesis led us to question why the use of PCy_3 as a ligand instead of ICy failed to provide any of the desired homocoupling product even

Scheme 3. Ni/ICy-Catalyzed Homocoupling of Aryl Ethers[a]



[a]Reaction conditions: aryl ether (0.50 mmol), **2** (0.40 mmol), $Ni(cod)_2$ (0.050 mmol), ICy·HCl (0.10 mmol), and NaO^{t}Bu (0.10 mmol) in toluene (1.5 mL) at 120 °C for 12 h. [b]Isolated yield on a 10 mmol scale using 5.0 mol % catalyst. [c]Yield determined by GC because of the volatility of the product. [d]PhB(nep) (16%) and anisole (41%) were also observed. [e]**2** (0.50 mmol) was used. [f]At 140 °C.

Scheme 4. Possible Pathway and Ligand Effect



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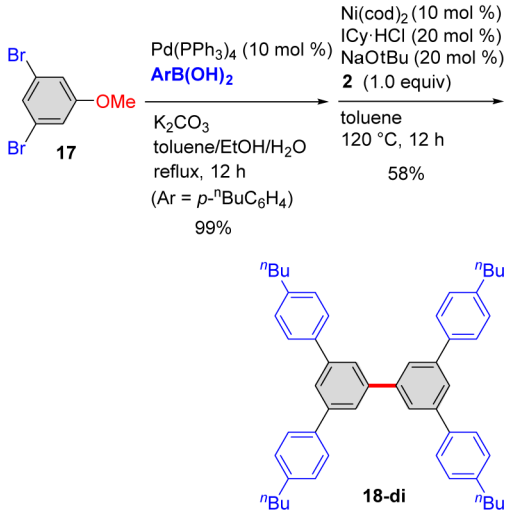
though PCy_3 and ICy are capable of promoting the borylation[10] and Suzuki–Miyaura-type cross-coupling reactions of methoxynaphthalenes.[9a,13] To develop a deeper understanding of the differences between these two ligands, we investigated the cross-coupling of **1** with phenylboronic ester (Scheme 4b). When PCy_3 was used as the ligand in the absence of an extra base, we found that none of the arylated product was formed, which was consistent with the results of our previous study.[13] In contrast, the use of ICy as the ligand for this reaction led to the cross-coupling product in good yield, even in the absence of a stoichiometric base.[14,15] These results therefore provide a clear explanation for the unique activity of ICy toward the nickel-catalyzed homocoupling of methoxyarenes. It is noteworthy that the superior activity of ICy toward the activation of C(aryl)–OMe bonds allowed the successful reaction of the less reactive non-naphthalene substrates **9**, **10**, and **11**, which did not react with the Ni/PCy_3 system.[9a]

The robust nature of the methoxy group under the conditions commonly used for organic synthesis allows this homocoupling to be conducted at the later stage of synthesis. For example, the rapid assembly of highly π-extended molecules was achieved by implementing sequential cross-/homocoupling processes with halogenated methoxyarenes (Scheme 5).

Scheme 5. Rapid Expansion of π Systems via Sequential Cross-/Homocoupling Reactions of Halogenated Aryl Ethers



In summary, we have developed a nickel-catalyzed homocoupling of methoxyarenes using diboron reagent **2**. The homocoupling most likely proceeds through sequential nickel-catalyzed C–O borylation and C–O/C–B cross-coupling. The use of ICy as a ligand was found to be critical to the success of this homocoupling because of its ability to promote the C–O/C–B cross-coupling process in the absence of a stoichiometric amount of base. This new homocoupling protocol is distinct from the classical homocoupling methods in the sense that it involves the cleavage of an inert C–O bond. On the basis of its unique features, we envision that this method will find numerous applications in organic synthesis, especially for π-conjugated molecules. Further studies toward the development of new catalytic methods involving the transformation of inert C–O bonds are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03151.

Detailed experimental procedures and characterization of products (PDF)

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Notes

The authors declare no competing financial interest.

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