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Regioselective Conversion of Arylboronic Acids to Phenols and Subsequent Coupling to Symmetrical Diaryl Ethers

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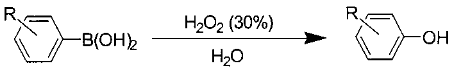
The development of mild methods for the synthesis of diaryl ethers[1] has recently gained increased attention in several research groups,[2−9] mainly due to their important roles in antibiotics and other biologically active compounds.[10,11] Furthermore, poly(aryl ethers) are important commercial polymers.[12] However, synthesis through conventional methods tends to be problematic, especially in the case of unactivated aromatic substrates. Although modifications of the classical Ullmann diaryl ether synthesis[13,14] have lead to improvements,[5−9] harsh reaction conditions are usually required. For most applications, milder reaction conditions are desirable. Recently, Chan and Evans independently reported the copper(II)-promoted arylation of phenols with arylboronic acids under mild conditions.[2,3]

As part of our ongoing research on regioselective substitutions of arylboronic acids, we have reported the ipso-halogenation[15] and ipso-nitration[16] of arylboronic acids. We now report the conversion of arylboronic acids to phenols and subsequent coupling to form symmetrical diaryl ethers in one pot.

Results and Discussion

In our reaction sequence, we first converted arylboronic acids to phenols. To the best of our knowledge, there are only few methods described in the literature[17−20] for this transformation. By simply adding an aqueous hydrogen peroxide solution, we were able to obtain the phenols in good yields (Table 1) with the desired regioselectivity. A variety of substituents are tolerated on the aromatic substrate, and even strongly deactivating substituents give satisfying results (entry 7).

Table 1. Regioselective Oxidation of Arylboronic Acids to Phenols



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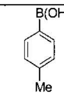
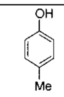
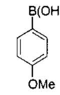
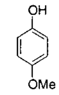
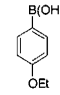
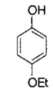
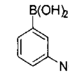
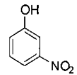
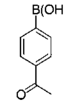
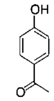
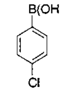
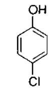
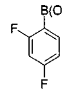
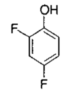
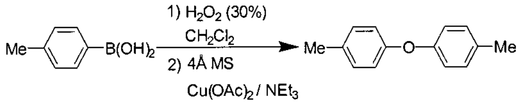
Entry	Substrate	Product	Isolated yield (%)
1			85
2			72
3			88
4			76
5			63
6			71
7			60

Table 2. Effect of H_2O_2 Ratio on Overall Product Yields



H_2O_2 equivalents	solvent	isolated yield (%)[a]
0.40	H_2O/no MS	–
0.15	CH_2Cl_2/MS	65
0.25	CH_2Cl_2/MS	90
0.31	CH_2Cl_2/MS	61
0.40	CH_2Cl_2/MS	45
0.45	CH_2Cl_2/MS	28

[a] Based on H_2O_2 (limiting reagent) employed.

On the basis of these results, we developed a one-pot coupling sequence for the symmetrical diaryl ethers in

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dichloromethane. Partial conversion of the arylboronic acid to phenol yields the precursors for the coupling sequence. To absorb water from the aqueous 30% H_2O_2 solution and water that is produced during triaryl boroxine formation,[21,22] powdered molecular sieves (MS) were added. We found that the H_2O_2/arylboronic acid ratio is critical for the outcome of the reaction. As illustrated in Table 2, 0.25 equiv of H_2O_2 furnish the highest overall yields in the reaction sequence.

Upon reaction with the hydrogen peroxide solution and addition of molecular sieves, the copper(II) catalyst and the amine base are introduced and the desired symmetrical diaryl ethers are formed without isolation of the intermediate phenols. This one-pot synthesis is easily carried out under very mild conditions and tolerates a great variety of substituents (Table 3). The reaction produces best results for electron rich substrates. However, satisfying results were obtained for deactivated aromatics. Unreacted substrate and phenol, when present, can also be recovered in high yield.

In summary, we have successfully carried out the conversion of arylboronic acids to phenols in good yields and have illustrated a sequence for a one-pot synthesis of symmetrical diaryl ethers from arylboronic acids in good to excellent yields.

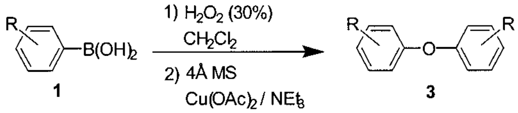
Experimental Section

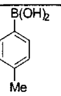
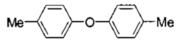
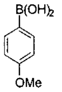
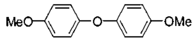
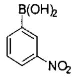
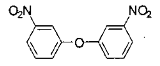
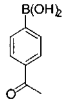
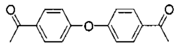
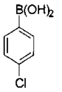
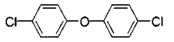
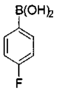
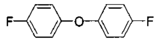
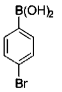
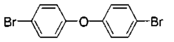
Arylboronic acids were obtained from Aldrich Chemical Co. and Frontier Scientific and used as such. Flash chromatography purification was performed on silica gel 60 (230−400 mesh). All products are known compounds and characterized by comparison of their physical and NMR data with published information. NMR spectra were taken at 300 MHz.

Conversion of Arlyboronic Acids to Phenols. A reaction flask was charged with 3.0 mmol of arylboronic acid (1.0 equiv), 1.0 equiv of H_2O_2 (30% solution), and additional 10 mL of H_2O and stirred at rt for several hours. CH_2Cl_2 (40 mL) was added, and the layers were separated. The aqueous layer was washed with 20 mL of CH_2Cl_2, and the combined organic layers were washed with H_2O and brine. The solvent was removed under reduced pressure, and the compound was purified by flash chromatography and Kugelrohr distillation (if necessary).

One-Pot Coupling to Symmetrical Diaryl Ethers. A reaction flask is charged with 3.0 mmol of arylboronic acid (1.0 equiv), 20 mL of CH_2Cl_2, and 0.25 equiv of H_2O_2 (30% solution) and allowed to stir at rt for several hours. To this mixture are added powdered 4 Å molecular sieves, 0.5 equiv of $Cu(OAc)_2$, and 3.0 equiv of NEt_3. The resulting colored reaction mixture is stirred overnight, and the diaryl ether is isolated by direct column chromatography of the crude mixture with preabsorption on silica gel.

Table 3. One-Pot Synthesis of Symmetrical Diaryl Ethers from Arylboronic Acids



Entry	Substrate	Product	Isolated yield (%)[a]
1			90
2			79
3			55
4			84
5			85
6			58
7			77

[a] Based on H_2O_2 employed. The rest is substrate and phenol.

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