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Synthesis of symmetrical diaryl ethers from arylboronic acids mediated by copper(II) acetate

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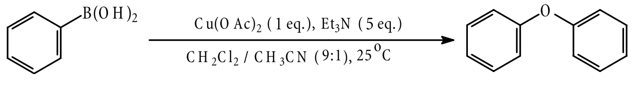
Abstract—Copper promoted generation of phenols in situ through arylation of water and their subsequent arylation with arylboronic acids affords a wide range of symmetrical diaryl ethers in good to high yield. The reaction is rapid, mild, convenient and tolerant of a wide range of functionalities on the arylboronic acid.

Many synthetic methods have been developed for the synthesis of diaryl ethers which are important building blocks for a large number of natural products and pharmaceuticals. Despite recent improvements,[1] the Ullmann ether synthesis[2] requires elevated temperatures (>100°C) in the presence of base and can lead to inconsistent results for functionalised systems.[3]

The chemistry of arylboronic acids continues to be a growth area in synthetic methodology. Oxidative cleavage, usually with hydrogen peroxide, is a well known reaction of arylboronic acids leading to the formation of phenols.[4] More useful in synthesis are C–O and C–N coupling reactions of arylboronic acids with phenols,[5,6] amines,[7] *N*-hydroxyphthalimides,[8] amides and imides,[9] and *N*-heterocycles,[10,11] to give the corresponding *N*- or *O*-arylated products. Formation of unsymmetrical thioethers,[12] from arylboronic acids and alkylthiols, promoted by copper(II) acetate has also been described.

Evans et al.[5] reported a useful boronic acid-phenol cross-coupling reaction mediated by copper(II) acetate for the expedient synthesis of thyroxine. In this study, while optimising the reaction conditions for the cross coupling between 4-*tert*-butylphenol and phenylboronic acid in methylene dichloride, the formation of phenol and diphenyl ether as unwanted side products, in significant amounts, was observed. This formation of these side products was attributed to the competitive arylation of water, released from the phenylboronic acid and coupling of the phenol with the phenylboronic acid. This was supported by the fact that the addition of 4 Å molecular sieves to the reaction mixture completely suppressed the formation of these side products. We reasoned that, formation of the side product, diphenyl ether, as observed by Evans et al. could be exploited to synthesise symmetrical diaryl ethers from arylboronic acids. We sought to develop this procedure for the formation of symmetrical diaryl ethers and report herein the success of this approach.[13,14]



Scheme 1.

The initial conditions explored were those of Evans et al. but without the 4 Å molecular sieves. Phenylboronic acid (1 equiv.), Cu(OAc)$_2$ (1 equiv.) and triethylamine (5 equiv.) were allowed to react in methylene dichloride at room temperature for 18 h to give diphenyl ether in 50% yield with only traces of phenol. Attempts to increase the yield of product by lengthening the reaction time, up to 24 h, were unsuccessful.

Since, in this case, the water was being released from the phenylboronic acid via triphenyl boroxine formation we thought that the presence of sufficient water in the reaction medium would enhance the rate of the reaction as well as the yield of product. Therefore, we decided to carry out the reaction in a methylene dichloride–acetonitrile system assuming that acetonitrile contains some water. Interestingly, diphenyl ether was

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Keywords: arylation; arylboronic acids; copper; symmetrical diaryl ethers.

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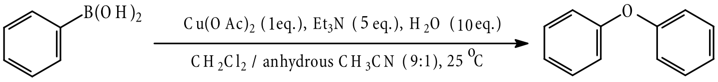
Table 1. Effect of added water in the synthesis of diphenyl ether from phenyl boronic acid[a]

Entry	Amount of water added (equiv.)	Time (h)	Yield of the product (%)
1	2	6	55
2	4	6	67
3	6	6	72
4	8	6	85
5	10	6	95
6	12	24	97

[a] All the reactions were performed in methylene dichloride–anhydrous acetonitrile (1:9).



Scheme 2.

obtained in 95% yield within 6 h under these reaction conditions as outlined in Scheme 1.

It was assumed that the use of acetonitrile in the reaction media as a source of water improved the yield of the diphenyl ether. In support of this postulate, it was found that the use of acetonitrile freshly distilled from P_2O_5 directly into the reaction flask, furnished a similar yield of diphenyl ether as in the previous experiments without acetonitrile. This finding confirmed the need for water in the reaction media to enhance the rate of the reaction as well as the yield of the product, and ruled out the possibility that acetonitrile itself plays some role in the reaction.

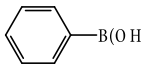
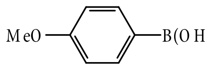
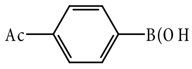
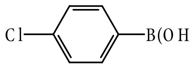
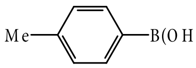
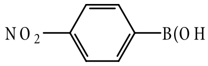
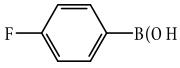
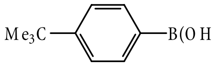
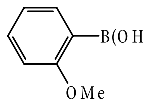
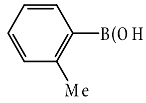
We next turned our attention to find the optimum amount of water for the maximum yield of product. We performed a series of experiments with phenylboronic acid as a model substrate adding known amounts of water to the methylene dichloride–anhydrous acetonitrile system. We found that the maximum yield of the product was obtained with 10 equiv. of water (Table 1). Further addition of water resulted in no significant improvement in the yield despite the reaction being continued for 24 h.

These studies revealed that the optimum conditions for the reaction were 1 equiv. of phenylboronic acid, 1 equiv. of copper(II) acetate, 5 equiv. of triethylamine and 10 equiv. of water in methylene dichloride–anhydrous acetonitrile at room temperature (Scheme 2).

We speculate that the water in the reaction medium must be playing the dual roles of activating the boronic acid[15] and enhancing the rate of phenol formation.

Using conditions outlined in Scheme 2, a variety of arylboronic acids were successfully converted into the corresponding symmetrical diaryl ethers in good to high yield (Table 2). The reactions proceed with both elec-

Table 2. Copper-catalyzed synthesis of symmetrical diaryl ethers

Entry	Boronic acid	Yield of Product[a,b] (%)
1		95
2		94
3		92
4		67
5		97
6		85
7		89
8		94
9		83
10		94

[a] The yield refers to the pure isolated product.[b] All the products were characterised by spectral characteristics (^{1}H NMR, IR, elemental microanalyses) and by comparison with authentic samples.

tron-rich and electron-deficient arylboronic acids and work in the presence of other functional groups including halide, nitro, alkoxy, acyl, etc (Table 2). Unfortunately, in the case of the chloro substituted boronic acid the yield decreased significantly (Table 2, entry 4). It should be noted that a rationale for the enhancement of the reaction rate by oxygen has been offered by Lam et al.[10] for the *N*-arylation of saturated heterocycles and by Evans et al. for the *O*-arylation of phenols[5] but in our case, the mere presence of water in the reaction medium resulted in a dramatic rate enhancement (stirring at room temperature for 18 h against 6 h) thereby precluding the need for an oxygen atmosphere, although the possibility of further enhancement of the reaction rate using an oxygen atmosphere cannot be ruled out. The relatively low toxicity and environmental impact of boronic acids,[16] precluding the need for anhydrous conditions, are noteworthy features of this method.

In conclusion, we have used the results of Evans et al. to develop a copper catalyzed, protocol for the synthesis of symmetrical diaryl ethers from commercially available arylboronic acids.

General procedure:

Arylboronic acid (2 mmol), $Cu(OAc)_2$ (2 mmol, 1 equiv.) and triethylamine (5 equiv.) were dissolved in 20 ml of anhydrous acetonitrile–methylene dichloride (1:9). Water (10 equiv.) was added and the mixture stirred vigorously at room temperature for 6 h. After completion of the reaction (TLC), the reaction mixture was filtered, washed with saturated $NaHCO_3$, and brine, and the organic layer was separated. After drying over anhydrous Na_2SO_4 the solvent was evaporated under reduced pressure to give the product. The crude product was purified on a short silica gel column (ethyl acetate, petroleum ether: 1:9).

Acknowledgements

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