Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine

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Abstract: Diaryl ethers are readily synthesized in high yield at room temperature through the copper(II)-promoted coupling of arylboronic acids and phenols. The reaction is tolerant of a wide range of substituents on both coupling partners. These reaction conditions permit the racemization-free arylation of phenolic amino acids, methodology that has been applied to an efficient synthesis of thyroxine. © 1998 Elsevier Science Ltd. All rights reserved.

The macrocyclic diaryl ethers in vancomycin antibiotics[1] are important architectural constituents that play an critical structural role in constraining the heptapeptide backbone. Accordingly, mild methods for the construction of diaryl ethers that are compatible with racemization-prone amino acid residues is an ongoing objective of a number of research groups[2] whose goal is the synthesis of this family of natural products.[3] Even with recent improvements,[4] the Ullmann ether synthesis[5] requires elevated temperature (>100 °C) in the presence of base and can give inconsistent results for functionalized systems.[6] In the preceding Letter, Chan and co-workers report the coupling of arylboronic acids with various nitrogen-containing substrates to yield the corresponding N-arylated products at ambient temperatures.[7] In this study, the arylation of a several phenols in moderate yield is also disclosed. As a consequence of our interest in applications of this reaction to complex peptidic substrates, this Letter outlines an investigation to improve the utility of this process (eq 1) and describes a concise synthesis of thyroxine (T$_4$) from the illustrated phenol and boronic acid precursors (eq 2).
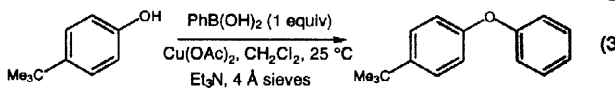

$$ (1) $$

$$ (2) $$

Thyroxine
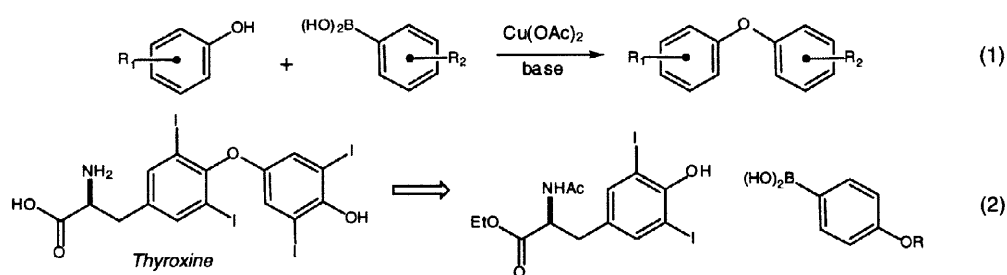
Initial reaction optimization was conducted on 4-*tert*-butylphenol and phenylboronic acid in methylene chloride (eq 3). An evaluation of Cu(II) sources revealed that, in accord with Chan's observations, Cu(OAc)$_2$ was the optimal Cu(II) source for promoting arylation.[8] Analysis of the unpurified reaction mixtures by GC/MS revealed the formation of phenol and diphenyl ether as unwanted reaction products. It was assumed that the side reaction resulting in diminished yields was the competitive arylation of water and the subsequent competition of phenol with the phenolic substrate. Since significant quantities of both side products were generated even under seemingly anhydrous conditions, we concluded that water was being generated from the phenylboronic acid, through triphenylboroxine formation.[9] The preceding analysis was confirmed by the addition of powdered 4 Å molecular sieves to the reaction mixture which suppressed phenol and diphenyl ether formation and increased product yields. In support of the preceding postulate, it was also found that phenylboronic acid could be replaced by triphenylboroxine (0.33 equiv) to furnish similar yields of desired product. Reaction yields were found to increase upon using several equivalents of amine base (Table 1, entries 1-5) with 5 equivalents being

optimal. During the optimization process, it was discovered that exposure of the reaction to oxygen was also advantageous (entries 6-12). It was further noted that a dry, pure oxygen atmosphere was unnecessary, as running the reaction under an ambient atmosphere gave identical results (entries 9, 11). Under these conditions, both copper(I) acetate and elemental copper successfully promoted the phenolic arylation, albeit in low yield. Under inert atmosphere, however, only Cu(II) salts yielded the diaryl ether. Finally, while methylene chloride proved to be the optimal solvent, the reaction is tolerant of a range of solvents with both acetonitrile and toluene affording acceptable yields of the desired diaryl ether.

A number of structurally and electronically diverse substrates were then evaluated (Table 2). While yields were generally good, electron-rich phenols underwent arylation most efficiently (entries 10-13). The reaction is tolerant of proximal substitution, as ortho-substituted phenols were arylated in good yield (entries 7-14, 25). With several exceptions, the reaction is also general with respect to the boronic acid component. Although ortho alkyl substituents appear to be tolerated (entries 14, 19), yields are depressed with ortho-heteroatom substituted boronic acids (entries 20, 21).[10] In the more sluggish reactions, a second equivalent of boronic acid was required for synthetically useful product yields. In all cases, the boronic acid was consumed during the reaction.
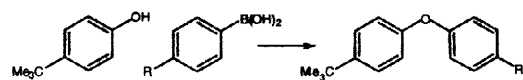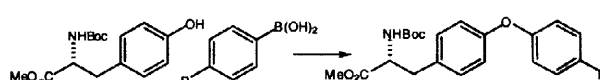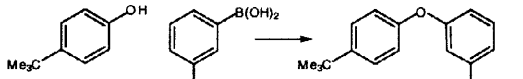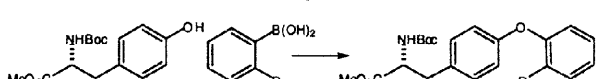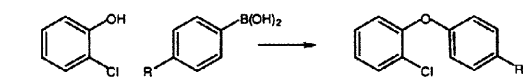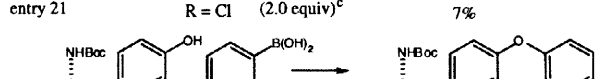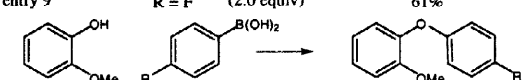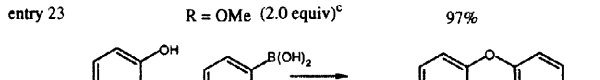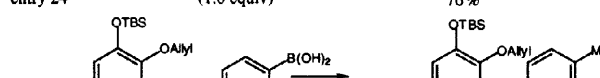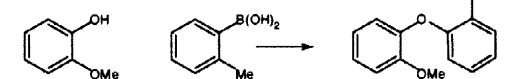
Table 1. Arylation of 4-tert-butylphenol with $PhB(OH)_2$

$$PhB(OH)_2 \ (1 \ equiv)$$
$$Cu(OAc)_2, \ CH_2Cl_2, \ 25 \ ^\circ C$$
$$Et_3N, \ 4 \ \text{Å sieves}$$

(3)

entry	equiv $Cu(OAc)_2$	atmosphere	equiv base	yield[a]
1	1.0	Argon	0	16%
2	1.0	Argon	1	22%
3	1.0	Argon	2	26%
4	1.0	Argon	4	33%
5	1.0	Argon	10	34%
6	0.10	Argon	5	9%
7	0.10	Oxygen	5	30%
8	1.0	Argon	5	34%
9	1.0	Oxygen	5	71%
10	1.0	Ambient	1	41%
11	1.0	Ambient	5	71%
12	1.0	Ambient	10	71%

[a] Entries 1-5 are GC/MS yields. Entries 6-12 are isolated yields.

Table 2. Synthesis of Diaryl Ethers through the $Cu(OAc)_2$-Promoted Arylation of Phenols with Arylboronic Acids[a]

| entry 1 | R = H | (1.5 equiv)[b] | 95% |
entry 2	R = Me	(2.0 equiv)[b]	87%
entry 3	R = F	(2.0 equiv)[b]	42%
entry 4	R = OMe	(2.0 equiv)[b]	85%

| entry 5 | R = OMe | (1.0 equiv)[b] | 68% |
| entry 6 | R = NO_2 | (2.0 equiv)[b] | 68% |

entry 7	R = H	(2.0 equiv)[b]	95%
entry 8	R = Me	(1.0 equiv)[b]	70%
entry 9	R = F	(2.0 equiv)[b]	61%

entry 10	R = H	(1.0 equiv)[b]	92%
entry 11	R = Me	(1.0 equiv)[b]	95%
entry 12	R = F	(1.0 equiv)[b]	97%
entry 13	R = OMe	(2.0 equiv)[b]	82%

| entry 14 | (1.0 equiv)[b] | 52% |

entry 15	R = H	(2.0 equiv)[c]	95%
entry 16	R = Me	(2.0 equiv)[c]	98%
entry 17	R = F	(2.0 equiv)[c]	97%
entry 18	R = OMe	(2.0 equiv)[c]	96%

entry 19	R = Me	(2.0 equiv)[c]	98%
entry 20	R = OMe	(2.0 equiv)[c]	37%
entry 21	R = Cl	(2.0 equiv)[c]	7%

| entry 22 | R = NO_2 | (2.0 equiv)[c] | 98% |
| entry 23 | R = OMe | (2.0 equiv)[c] | 97% |

| entry 24 | (1.0 equiv)[b] | 76% |

| entry 25 | (1.0 equiv)[b] | 81% |

[a] Yields represent isolated product. [b] Amine base: triethylamine (5 equiv). [c] Amine base: pyridine (5 equiv).

In contrast, no side products were observed with respect to the phenol component which, when still present, could be recovered in high yield.

Following initial success with simple phenols, attention was directed to the arylation of more complex phenolic amino acid derivatives. The illustrated (R)-tyrosine N-Boc methyl ester underwent coupling with a variety of boronic acids in high yield (entries 15-21). The arylation process may also be successfully extended to the racemization-prone[11] 3- and 4-hydroxyphenylglycine derivatives (entries 24-25). Neither competing N-arylation nor racemization was detected with either family of substrates.

The impact of steric hindrance on the phenolic constituent was evaluated in the context of a short formal synthesis of thyroxine (eq 4).[12] (S)-N-acetyl-3,5-diiodo-4-p-methoxyphenoxyphenylalanine ethyl ester (**3a**), an intermediate in Hems' synthesis of L-thyroxine[13] was chosen as the target. Phenol **1**[14] readily reacted with either phenylboronic acid **2a** or **2b**[15] (3 equiv) under the General Reaction Procedure to afford **3a** and **3b** in 81% and 84% yield respectively. As was seen with the arylation reactions of tyrosine derivatives (Table 2, entries 15-23), pyridine increased the yield for this transformation. For this substrate, optimized yields were obtained with a mixture of pyridine (5 equiv) and triethylamine (5 equiv). At the present time, the selection of the optimal base (triethylamine or pyridine) for a given reaction has been empirical. Although evidence is currently lacking, we speculate that this reaction component could have a dual role as both a base and/or ligand for one of the organocopper intermediates.

2a, R = Me
2b, R = Si-*t*-BuMe₂

3a, R = Me   81%
3b, R = Si-*t*-BuMe₂   84%

(4)
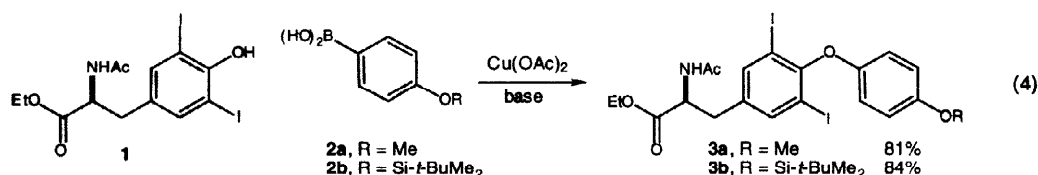
General Reaction Procedure. A flask is charged with phenol (1.0 equiv), Cu(OAc)₂ (1.0 equiv), arylboronic acid (1.0-3.0 equiv), and powdered 4 Å molecular sieves. The reaction mixture is diluted with CH₂Cl₂ to yield a solution approximately 0.1 M in phenol, and the amine base (5.0 equiv) is added. After stirring the colored heterogeneous reaction mixture for 18 h at 25 °C under ambient atmosphere, the resulting slurry is filtered and the diaryl ether is isolated from the organic filtrate by flash chromatography.

Mechanistic Observations. We speculate that the present process (Path A, M = B(OH)₂) and the Ullmann reaction[4,5] (Path B) intersect at the plausible arylcopper phenoxide intermediate(s) **4** or **5** which undergo subsequent reductive elimination to the diaryl ether (Scheme 1). The unresolved issue is the oxidation state of this intermediate in either process prior to breakdown to product. The improvement in the present reaction when exposed to atmospheric oxygen lends support to the possibility that **4** could be oxidized to **5** under the reaction conditions prior to reductive elimination. In a closely related transformation, the use of other arylmetaloid reagents such as triarylbismuth diacetate in the Cu(OAc)₂-promoted arylation of phenols (Path A, M = BiAr₂(OAc)₂) has also been reported.[16] It is evident that aryltrialkylstannanes might also participate in this transformation. While we have demonstrated that this is the case, the yields for this transformation do not yet match those found for the present reaction. In addition, we have also not yet extended the arylation process to alcohols; however, further studies in this area are ongoing.

Scheme 1
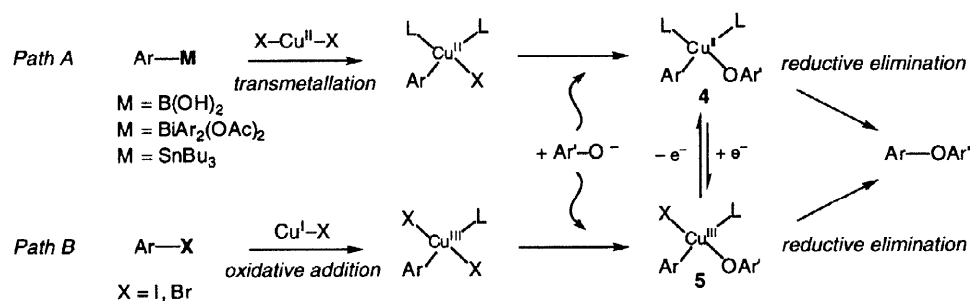
Applications relevant to the synthesis of vancomycin-related targets will be reported in due course.

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