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# Copper promoted C–N and C–O bond cross-coupling with phenyl and pyridylboronates

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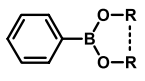
**Abstract**—Acyclic and cyclic esters, as well as anhydride (boroxine) of phenylboronic acids are efficient phenylating agents in copper promoted C–N and C–O bond cross-coupling reactions. The first successful C–N cross-coupling of a heterocyclic boronate with heteroarenes, such as indazole, has been demonstrated. 

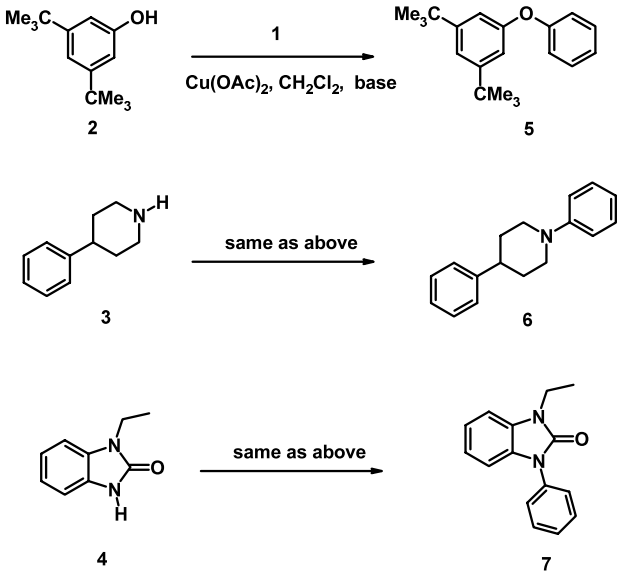
Copper promoted cross-coupling with arylboronic acids is emerging as a popular protocol in the preparation of aryl ethers, aryl amines, and arylated heterocycles due to its mild conditions and tolerance of base-sensitive functionalities.[1,2] The technology is especially suited for expeditious parallel or solid state synthesis of arylated analogs from the parent NH or OH compounds using the large library of boronic acids currently available commercially.[3] Since our initial reports,[1] significant progress has been made in broadening the scope,[4] as well as extending the methodology to include the use of other organometalloids such as arylstannanes,[5c] arylsiloxanes,[5] and aryl iodonium salts.[6]

In a continuing effort to identify other efficient arylating agents and to better understand the controlling factors of these boronic acid reactions, we undertook a systematic study on the efficiency of various boronic acid derivatives (**1**) in participating in these arylations. For this investigation we purposely chose phenylboronic acid as the prototypical system because of the ready availability of its anhydride form (boroxine) and its ester derivatives, as well as its relative inefficiency in the *N*- and *O*-cross coupling reactions which provides the necessary latitude for comparison.[7] *We also used only 1 equiv. of* ***1*** *for comparison although 2 equiv. of phenylboronic acid are needed for optimum yields.*[1]




**1**

Three substrates: a phenol, a basic amine and a urea were chosen to represent different functional groups (OH and NH) and relative reactivity. They are 3,5-di-*tert*-butyphenol (**2**), 4-phenylpiperidine (**3**), and 1-ethyl-2-benzimidazolinone (**4**) (Scheme 1). For consistency, we employed identical reaction conditions and the corresponding phenylated products **5**, **6**, **7** were isolated by




**Scheme 1.** Phenylation with boronic acid derivatives.

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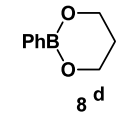
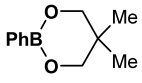
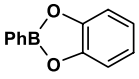
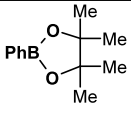
flash chromatography under similar fashion. The results are summarized in Table 1.

It is apparent from this study that the ancillary oxo-ligand on the boron has a dramatic influence on these cross-coupling reactions. In general, the boron esters are more efficient than phenylboronic acid itself. The exception being the catechol derivative **11** (entry 7), which appears to be unstable and readily hydrolyzes back to the acid, and the pincolate **12** (entry 8) presumably due to steric hindrance. However, there appears to be no significant difference in efficiency among these boronates. The overall superior performance of triphenylboroxine (entry 2), the cyclic anhydride form of phenylboronic acid, is noteworthy. This observation is consistent with the report by Evans in the study of phenol arylation.[1b] It should also be mentioned that we have observed $PhB(OH)_2$ readily converts to $(PhBO)_3$ in methylene chloride at room temperature by $^1H$ NMR.[8] This dynamic behavior of boronic acid implies that the active arylating agent in our earlier study could indeed be the anhydride form and not the free acid. It is interesting to speculate that one purpose for the addition of molecular sieves in Evans' improvement[1b] is to promote the formation of the boroxine form.

**Table 1.** Phenylation with 1 equiv. boronic acid derivatives **1**

| | | % Isolated yields of products [a] | | |
|---|---|---|---|---|
| *Entry* | **1** | **5** | **6** | **7** |
| *1* | $PhB(OH)_2$ [b] | 17 (35) | 22 (16) | 30 (17) |
| *2* | $(PhBO)_3$ [c] | 43 (46) | 40 (40) | 62 (29) |
| *3* | $PhB(OiPr)_2$ [d] | 39 | 29 | 61 |
| *4* |  **8** [d] | 29 | 42 | 52 |
| *5* |  **9** [e] | 21<br>30 [f] | 43<br>76 [f] | 26<br>46 [f] |
| *6* |  **10** [d] | 32 | 30 | 52 |
| *7* |  **11** [e] | 18 | 28 | 32 |
| *8* |  **12** [e] | 4 | 23 | 6 |

Conditions: **1** (1.0 equiv.), anhydrous $Cu(OAc)_2$ (1.0 equiv.), $Et_3N$ or pyridine (2.0 equiv.), $CH_2Cl_2$, rt, 24 h.

[a] Yields are for $Et_3N$, yields for pyridine are in parentheses.

[b] $PhB(OH)_2$ was purified by recrystallization of commercial material from water.

[c] $(PhBO)_3$ was prepared by azeotropic refluxing of $PhB(OH)_2$ in hexane or toluene for 2–3 h. It typically contains <5% of $PhB(OH)_2$. 0.33 equiv. was used in this case.

[d] Diisopropoxyphenyl borane and 2-phenyl-1,3,2-dixoaborinane (**8**) were obtained commercially from Aldrich Chem. Co.

[e] Boron esters **9**, **10**, **11** and **12** were prepared by azeotropic refluxing of $PhB(OH)_2$ and the appropriate diol in toluene.

[f] 2 equiv. of **9** were used in this run.

Although the current study is performed with the parent phenylboronic acid system and with a limited range of substrates, it is likely that our conclusion should be applicable to other substituted arylboronic acid systems and other substrates in general. The increasing commercial availability of arylboronic esters, and the ease in which they can be generated from the corresponding aryl halide precursors using Grignard or palladium-catalyzed diboron chemistry make these attractive reagents for *N*- and *O*-arylations.

The application of cyclic boronates as arylating agents has been extended to a heterocyclic boronic acid system—3-pyridylboronic acid. Since the majority of drugs on the market contain heterocycles, we are interested in connecting two heterocyclic units together via our copper-promoted C–N cross-coupling reaction. Indeed 3-pyridylboronic acid and its corresponding 1,3-propanediol cyclic ester (**13**)[9] both produce the *N*-pyridyl products with benzimidazole in reasonable yields, with the boronate ester being a better arylating agent (Scheme 2).[10] *This constitutes the first successful copper promoted C–N cross-coupling involving a heterocyclic boronic acid system.*

In summary, we have demonstrated that borate esters **1**, together with the previously reported boroxine,[1b] are effective arylating agents in the copper-promoted C–N and C–O bond cross-coupling reactions. We have successfully applied this new discovery in the cross-coupling of a 3-pyridyl moiety to a variety of NH-containing heteroarenes. We continue to expand the scope of our copper-promoted cross-coupling reaction.

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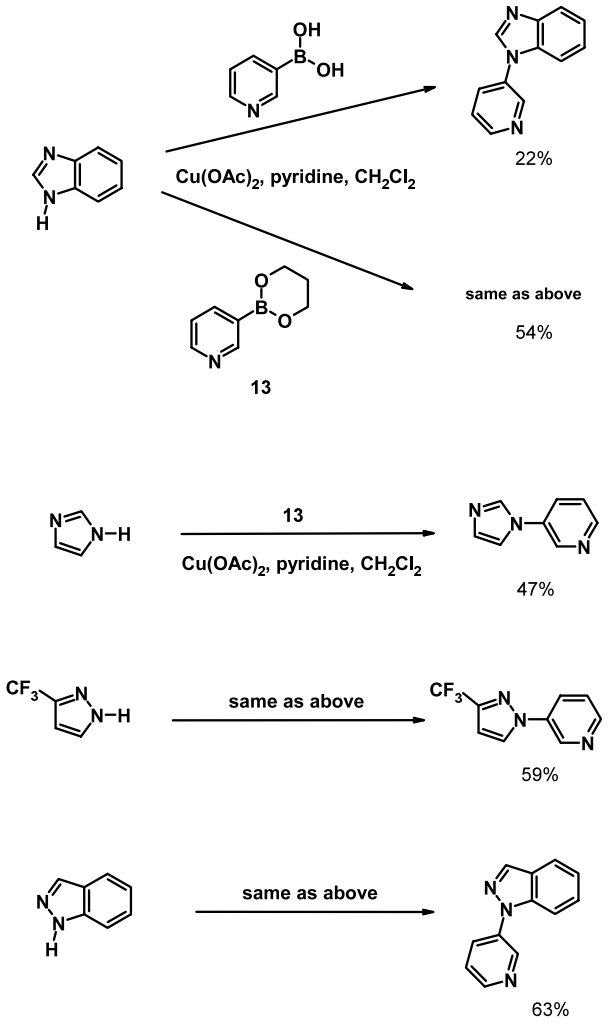


**Scheme 2.** Copper promoted cross-coupling of heteroarenes with **13**.[11,12]

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7. It should be noted that the parent phenyl system is probably one of the least effective arylating agents in our chemistry, see Refs. 1a and 4a. Most substituted systems give much more respectable yields.
8. Interestingly $PhB(OH)_2$ is perfectly stable in $d^6$-DMSO, the OH protons show up as singlet at $\delta$ 8.3 ppm.
9. Obtained commercially from Lancaster Synthesis Inc.
10. No cross-coupling occurs between 4-pyridylboronic acid and the ethyl ester of 3-methyl-5-pyrazole carboxylic acid. This pyrazole was previously shown to be a good substrate for *N*-arylation. We thank Dr. Yun-Long Li for this observation.
11. A representative procedure is illustrated in the synthesis of 1-(3-pyridyl)-benzimidazole: A 20 mL vial was charged with a magnetic stir bar, **12** (109 mg, 0.667 mmol, 2.0 equiv.), benzimidazole (39 mg, 0.333 mmol, 1.0 equiv.), anhydrous $Cu(OAc)_2$ (91 mg, 0.500 mmol, 1.5 equiv.), pyridine (1.0 mL of 0.67 M solution in dichloromethane, 0.67 mmol, 2.0 equiv.), and 3 mL dichloromethane. The reaction was stirred under air at ambient temperature for 12 h. A solution of 3 mL of 4 M $NH_3$ in MeOH was added. The mixture was filtered through a layer of glass wool on Celite and purified by silica gel chromatography (ethyl acetate) to give 35 mg (54%) of 1-(3-pyridyl)-benzimidazole.
12. *The physical data of 1-(3-pyridyl)-benzimidazole*: $^1$H NMR ($CDCl_3$) $\delta$ 8.87 (s, 1H), 8.76 (d, $J=1.4$ Hz, 1H), 8.14 (s, 1H), 7.92–7.86 (m, 2H), 7.58–7.51 (m, 2H), 7.41–7.31 (m, 2H). MS(ES) $m/z$ 196.2 (100%) $(M+H)^+$. Elemental anal. ($C_{12}H_9N_3$) theoretical: C, 73.83%; H, 4.656; N, 21.52; found: C, 73.49%; H, 4.78; N, 21.67.