ORGANIC LETTERS

2001
Vol. 3, No. 13
2077−2079

Copper-Catalyzed Coupling of Arylboronic Acids and Amines

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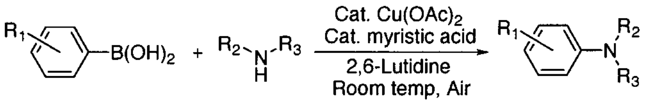
Received April 27, 2001

ABSTRACT



A general catalytic coupling of arylboronic acids and amines is reported. This room-temperature coupling was realized through the use of catalytic copper(II) acetate, 2,6-lutidine as base, and myristic acid as an additive. Functionalized aniline substrates provided the diarylamine coupling products in good yield (58–91%). A variety of alkylamines were also successfully coupled to give *N*-alkyl anilines in moderate yield (50–64%).

Aromatic amines are important compounds found throughout the pharmaceutical[1] and agrochemical[2] industries. Uses for aromatic amines can range from conducting polymers[3] in material science to ligands for asymmetric homogeneous chemistry.[4] It therefore follows that catalytic aromatic carbon−nitrogen bond forming reactions that are practical, relatively inexpensive, and viable over a broad range of substrates would be valued in organic synthesis.

The most successful C−N coupling methods in the literature to date have utilized the palladium- or nickel-catalyzed coupling of amines with aryl halides.[5] Copper-catalyzed or -mediated systems for the coupling of amines with aryl halides are typically performed under Ullmann-type[6] conditions where heating, often above 130 °C, is common.[7] Copper-mediated coupling of amines using alternate transmetallating agents such as aryllead triacetate[8] and arylbismuth[9] reagents have also been employed. A recent series of developments by Chan and Lam[10] and others[11] has shown that the amination of arylboronic acids,[10a−c,11] arylsiloxanes,[10d] or arylstannanes[10e] can be effective when stoichiometric quantities of $Cu(OAc)_2$ were used. An important discovery by Collman[12] has demonstrated that this reaction can be rendered catalytic for the arylation of imidazoles when $[Cu(OH)\cdot TMEDA]_2Cl_2$ is used as the copper source. After the submission of this work a new publication by Lam[13] has shown that the cross-coupling of amines, N−H heterocycles, and phenols with arylboronic acids can be catalyzed by $Cu(OAc)_2$ when a variety of oxidants are employed.

Collman found that the catalytic coupling of arylboronic acids with imidazoles was possible when an O_2 or air atmosphere was present. We therefore decided that a screening of copper salts for catalytic activity (20 mol % Cu) in the coupling of *p*-tolylboronic acid with aniline under an air atmosphere at ambient temperature could provide a general catalytic system. It was initially found that CuOAc, $Cu(OAc)_2$, and copper(II) isobutyrate could provide 2−3 turnovers (40−55% conversion). The reaction was found to proceed smoothly to 35−45% conversion in the first 4−5 h, and catalytic activity rapidly diminished over the next 20

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(1) Negwer, M. In *Organic-Chemical Drugs and their Synonyms: (An International Survey)*, 7th ed.; Akademie Verlag GmbH: Berlin, 1994.

(2) Montgomery, J. H. In *Agrochemicals Desk Reference: Environmental Data*; Lewis Publishers: Chelsea, MI 1993.

(3) D'Aprano, G.; Leclerc, M.; Zotti, G.; Schiavon, G. *Chem. Mater.* **1995**, *7*, 33−42.

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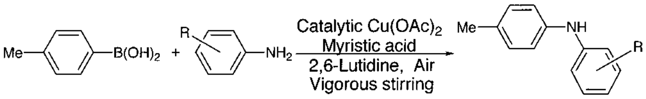
(5) For reviews see: (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*(1−2), 125−146. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (c) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046−2067.

(6) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382−2384. (b) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670−674. For a general Ullmann review, see: (c) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456.

10.1021/ol0160396 CCC: $20.00

Table 1. Copper-Catalyzed Coupling of Anilines with *p*-Tolylboronic Acid[a]



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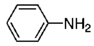
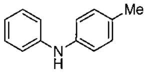
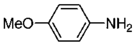
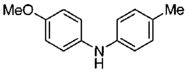
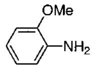
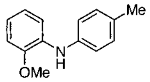
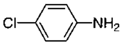
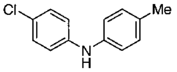
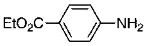
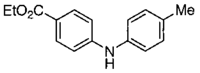
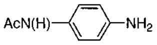
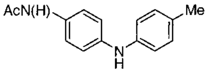
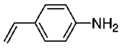
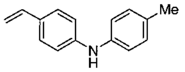
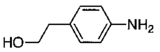
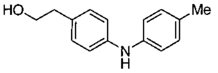
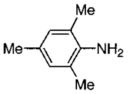
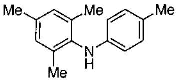
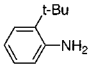
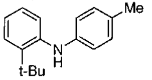
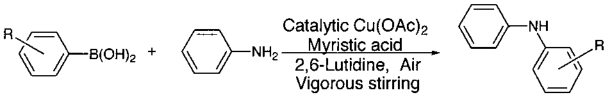
1		5	10		91
2		5	10		82
3		5	10		78
4		5	10		72
5		10	20		78
6		10	20		58
7		10	20		71
8		5	10		77
9		10	20		89
10		10	20		79

[a] Reaction conditions: 1.0 equiv of the aniline, 1.5 equiv of the boronic acid, 1.0 equiv of 2,6-lutidine, ambient temperature (22 °C) with 2 mL of toluene (0.5 M in amine) for 24 h. [b] Isolated yields are the average of two runs and are estimated to be >95% pure by ^1H NMR and GC analysis. All previously unknown compounds gave satisfactory ^1H NMR, ^{13}C NMR, IR, and compustion analysis data.

h. It was then discovered that by using vigorous stirring in flasks with a large volume (100 mL) relative to that of the solvent volume (2 mL) the complete conversion of aniline could be achieved. Presumably, these conditions allowed improved oxygen uptake and therefore more efficient oxidation of a reduced copper intermediate.[14] A second discovery was that the addition of myristic acid to the reaction mixture provided an enhanced reaction rate. This additive may operate by coordination to the copper center, thereby increasing the solubility of the catalyst.

Using conditions outlined in Table 1, a series of substituted anilines were subjected to the copper-catalyzed arylation with *p*-tolylboronic acid.[15] It was initially found that 5−10 mol % of $Cu(OAc)_2$ was sufficient to promote full conversion to arylated product. We were pleased to find that both electron-withdrawing and -donating substituents in the *para* position are tolerated in the reaction (entries 2−6). Substrates containing functional groups that have been problematic in the palladium-catalyzed amination chemistry[16] such as amides (entry 6) and alcohols (entry 8) were successfully transformed. Sterically demanding anilines (entries 9 and 10) required 10 mol % copper but were also efficiently arylated.

Table 2. Copper-Catalyzed Coupling of Amines with Arylboronic Acids[a]



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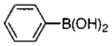
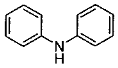
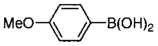
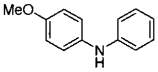
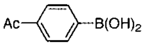
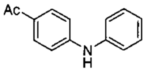
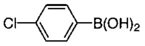
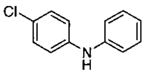
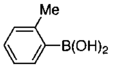
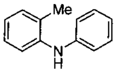
1		5	10		79
2		5	10		70
3		10	20		62
4		10 1 equiv	20 none		<10 (GC) 50 (GC)
5		20	40		50

[a,b] See Table 1.

A series of substituted arylboronic acids, shown in Table 2, were subjected to these cross-coupling conditions to further explore the reaction scope. Substitution in the *para* position gave satisfactory coupling when methoxy or acetyl groups (entries 2 and 3) were used, but the yields dropped off precipitously with the analogous chloride (entry 4). It was soon discovered that substitution *ortho* to boron had a dramatic influence on the reaction rate. The relatively unhindered 2-methyl-phenylboronic acid (entry 5) gave only a 50% yield when 20 mol % catalyst was used. Cundy[11a] reported a similar drop-off in yield for the coupling of 2-, 3-, and 4-substituted arylboronic acids with *p-tert*-butyl aniline, with only the reaction of phenyl- and *p*-tolylboronic acids being moderately successful.

The application of this reaction to the coupling of alkylamines with arylboronic acids was also briefly explored. Such coupling was found to give the desired *N*-alkyl aniline products in moderate yield, as depicted in Table 3. Branched and unbranched primary and secondary amines were suc-

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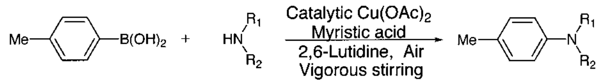
(7) For an Ulmann-type coupling of heterocyclic amines and aryl halides under relatively mild conditions, see: Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657−2640.

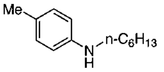
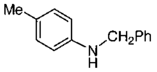
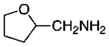
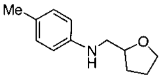
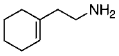
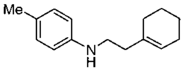
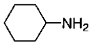
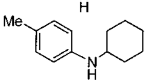
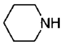
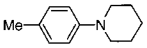
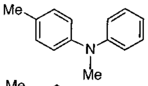
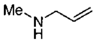
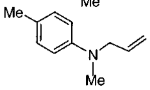
(8) Elliott, G. I.; Konopelski, J. P. *Org. Lett.* **2000**, *20*, 3055−3057 and references therein.

(9) Sorenson, R. J. *J. Org. Chem.* **2000**, *65*, 7747−7749 and references therein.

(10) (a) Chan, D. M. T.; Monaca, K. L.; Wanag, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933−2936. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941−2944. (c) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, 1623−1626. (d) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600−7601. (e) Lam, P. Y. S.; Clark, C. G.; Subern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, *5*, 674−676.

Table 3. Copper-Catalyzed Coupling of Amines with *p*-Tolylboronic Acids[a]



entry	amine	mol % $Cu(OAc)_2$	mol % myristic acid	product	isolated % yield[b]
1	n-$C_6H_{13}NH_2$	10	20		50
2	$PhCH_2NH_2$	10	20		64
3		10	20		55
4		10	20		55
5		10	20		57
6		10	20		56
7	Ph(Me)NH	10	20		64
8		10	20		54

[a,b] See Table 1.

cessful as substrates. It was found that substrates containing olefin moieties could also be cleanly arylated (entries 4 and 8).

It should be noted that bis-arylated products were never detected during the course of the reported reactions. It is also of interest that in the reaction of *p*-tolylboronic acid and aniline with excess base (neat in 2,6-lutidine or pyridine) a side product, *p*-tolylamine, was observed in up to a 29% GC yield. This side product was possibly formed by arylation of aniline followed by C−N bond scission.

In summary, we have built on the results of Chan and Lam and of Collman and have developed a copper-catalyzed coupling of arylboronic acids and amines in moderate to good yields. This method shows good substrate generality while using relatively nontoxic, inexpensive reagents under mild conditions.

Acknowledgment. This work was supported by the NIH (grant GM46059). We thank Pfizer and Merck for additional unrestricted support. J.C.A. was partially supported as a postdoctoral trainee of the National Cancer Institute (NCI training grant CI T32CA09112).

Supporting Information Available: Experimental procedures and characterization data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) **Typical Experimental Procedure.** Arylboronic acid (1.5 mmol), Cu(OAc)$_2$ (5−20 mol %), and myristic acid (10−40 mol %) were combined in a 100-mL round-bottom flask with a large stir bar. A rubber septum was attached, and dry toluene (2 mL), 2,6-lutidine (1.0 mmol), and the amine (1.0 mmol) were successively added by syringe. The resulting mixture was stirred at a high rate for 24 h, diluted with ethyl acetate (10 mL), filtered through a plug of silica gel, and then purified by column chromatography to give the desired product (see Supporting Information).

(16) Brief attempts to arylate imidazoles with this method resulted in low yields (32%) of the desired product.