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Ligand- and Base-Free Copper(II)-Catalyzed C–N Bond Formation: Cross-Coupling Reactions of Organoboron Compounds with Aliphatic Amines and Anilines

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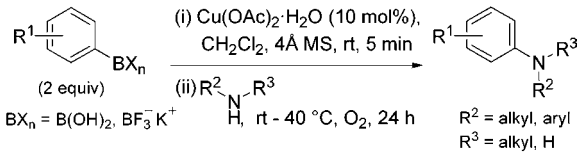
ABSTRACT



A ligandless and base-free Cu-catalyzed protocol for the cross-coupling of arylboronic acids and potassium aryltrifluoroborate salts with primary and secondary aliphatic amines and anilines is described. The process utilizes catalytic copper(II) acetate monohydrate and 4 Å molecular sieves in dichloromethane at slightly elevated temperatures under an atmosphere of oxygen. A broad range of functional groups are tolerated on both of the cross-coupling partners.

Copper-mediated C−N bond formation via the cross-coupling of arylboronic acids and nitrogen-based nucleophiles has become an important synthetic strategy since the initial reports by Chan and Lam.[1] Under their conditions, the *N*-arylation[2] of nitrogen-based nucleophiles by arylboronic acids occurs using a stoichiometric amount of Cu salt, and several equivalents of an external base/ligand. A variety of amines, anilines, and nitrogen heterocycles have been *N*-arylated under these conditions, both in the liquid phase and on solid support.[3] Most recently, Lam reported the arylation of amino acid ester hydrochloride salts under these now "classical" conditions.[4] Catalytic variants have also been developed. Collman has employed a catalytic amount of $[Cu(OH)\cdot TMEDA]_2Cl_2$ complex in the arylation of imidazoles with arylboronic acids. Unfortunately, the substrate scope of this protocol is limited to the use of imidazole derivatives.[5] Lam has shown that stoichiometric chemical oxidants (including molecular oxygen, TEMPO, and pyridine-*N*-oxide) can be used to regenerate the Cu catalyst. However, the optimal oxidants vary with the choice of the nucleophilic amine component; furthermore, an appreciable amount of competitive oxidation of the boronic acid also occurs.[6]

(1) (a) Chan, D. M. T.; Monaco, K. L.; Wang, 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.

(2) An alternative protocol for C−N bond formation is the amination of arylhalides catalyzed by Cu(I) salts developed by Buchwald. This highly efficient method tolerates a broad range of substrates, but reactions are performed at elevated temperatures, and in the presence of several equivalents of base. See: Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793−796 and references therein.

(3) For a recent review on $Cu(OAc)_2$-mediated arylation of heteroatomic nucleophiles using aryl-B, Bi, Pb, Si, and Sn and hypervalent iodonium reagents, see: Finet, J. P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597−626.

(4) Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett.* **2003**, *44*, 1691−1694.

(5) (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233−1236. (b) Collman, J. P.; Zhong, M.; Zeng, L.; Costano, S. *J. Org. Chem.* **2001**, *66*, 1528−1531. (c) Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892−7897.

(6) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415−3418.

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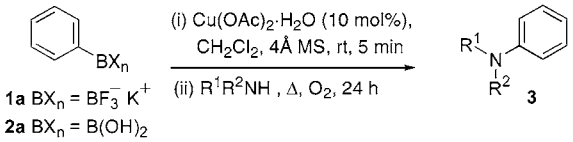
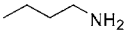
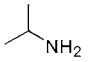
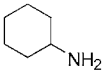
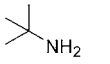
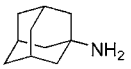
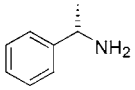
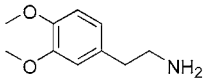
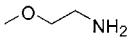
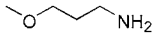
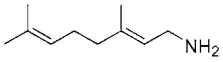
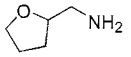
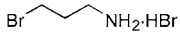
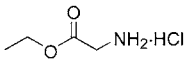
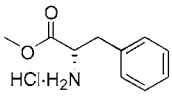
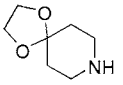
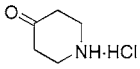
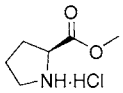
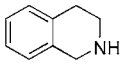
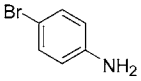
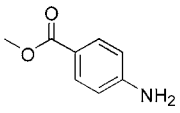
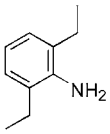
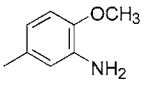
Table 1. Cu(II)-Catalyzed *N*-Phenylation of Aliphatic Amines, Ammonium Salts, and Anilines[a]



1a $BX_n = BF_3^- K^+$
2a $BX_n = B(OH)_2$

entry	R^1R^2NH	temp. (°C)	prod.	yield (%) from **1a**[b]	yield (%) from **2a**[b]
1		rt	**3a**	89	92
2		rt	**3b**	98	98
3		rt 40	**3c**	79 -	- 85
4		rt 40	**3d**	26 -	- 39
5		40	**3e**	57	67
6		rt	**3f**	91[c]	-
7		rt 40	**3g**	90 -	- 95
8		rt 40	**3h**	32 79	- 94
9		rt 40	**3i**	78 -	- 85
10		40	**3j**	80	89
11		40	**3k**	83	91
12		40	**3l**	-	86[d]
13		40	**3m**	-	84[d]
14		40	**3n**	-	90[c,d]
15		rt 40	**3o**	78 -	- 86
16		40	**3p**	81	90
17		40	**3q**	87	86
18		40	**3r**	-	83[d]
19		40	**3s**	-	74[c,d]
20		rt	**3t**	72	72
21		40	**3u**	80	89
22		40	**3v**	30	53
23		40	**3w**	35	40
24		40	**3x**	34	49
25		40	**3y**	51	66

[a] Reaction times are not optimized for individual substrates. [b] Isolated yields. [c] Epimerization of the stereocenter did not occur under the reaction conditions. [d] Ammonium salt was pretreated with Amberlyst A-21 in MeCN for 30 min prior to addition to the reaction mixture; yield reported is over both steps.

Buchwald has reported a Cu-catalyzed cross-coupling of arylboronic acids employing myristic acid as ligand, and 2,6-lutidine as base.[7] This protocol uses oversized reaction vessels in an air/O_2 atmosphere. Excellent yields of the arylated product were obtained using anilines as the cross-coupling partners, but with poorer results shown with aliphatic amines. This trend is also observed for the aforementioned stoichiometric Cu protocols. Following our recent report on the Cu-catalyzed cross-coupling of potassium organotrifluoroborate salts and boronic acids with aliphatic alcohols,[8] we now report a new set of reaction conditions, optimized for the cross-coupling of primary and secondary aliphatic amines with arylboron compounds.

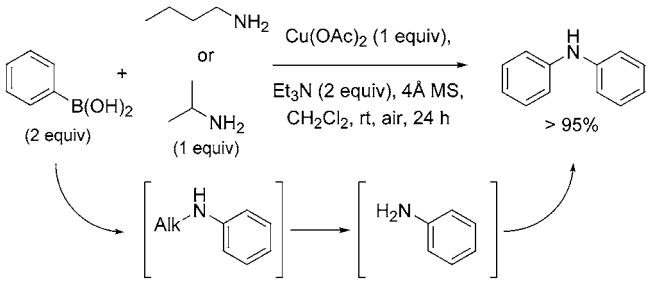
Previous attempts at the arylation of aliphatic amines under stoichiometric Cu conditions have reported low yields of the

(7) (a) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077−2079. (b) Sasaki, M.; Dalili, S.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 2045−2047.

(8) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381−1384.

cross-coupled product from primary amines and moderate yields from secondary amines, though no further descriptions of the outcome of those reactions have been offered.[1a,3,6] In our hands, the treatment of 1 equiv of *n*-butylamine or isopropylamine with 2 equiv of $PhB(OH)_2$ under Chan and Lam's original conditions gave diphenylamine as the sole product in almost quantitative yield (Scheme 1). In this

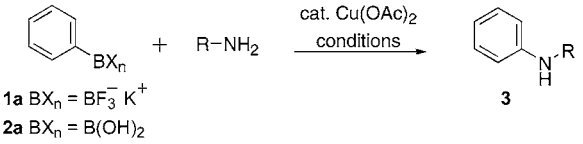
Scheme 1. Reaction of Primary Amines Using Stoichiometric Cu(II) Salts

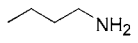
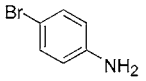


manner, simple aliphatic amines can be used as a surrogate for ammonia, in symmetrical diarylation reactions. Presumably, primary amines undergo the expected cross-coupling reaction to form the alkylarylamine, which then undergoes subsequent Cu-promoted *N*-dealkylation. The resultant aniline then participates in a second cross-coupling with another equivalent of the arylboronic acid, thereby affording the diarylated product. This hypothesis is supported by the results of Tolman, who observed that bis(μ-oxo)dicopper complexes promote the oxidative C−N bond scission of aliphatic amines.[9]

We concluded from these results that *N*-dealkylation is a potentially serious side reaction, a feature which undoubtedly negatively impacted earlier attempts at *N*-arylations of aliphatic amines using arylboronic acids. *N*-Dealkylation side reactions could be minimized by preventing bis(μ-oxo)-dicopper complex formation, either by dilution of the reaction mixture, or by decreasing the amount of Cu present (i.e., rendering the reaction catalytic in Cu salts). Application of our earlier reported conditions for the cross-coupling of aliphatic alcohols, to the reaction of 1 equiv of the model amine, *n*-$BuNH_2$, with 2 equiv of $PhBF_3^-K^+$, 10 mol % Cu-$(OAc)_2 \cdot H_2O$, 20 mol % DMAP, and powdered 4 Å MS in CH_2Cl_2 under an atmosphere of dry O_2 at room temperature for 24 h, gave an excellent yield of the monoarylated product (89%). No trace of the diarylated product, *n*-butyldiphenylamine, or the *N*-dealkylated product, diphenylamine, was observed. Further optimization revealed that the presence of the DMAP ligand (required for *O*-arylation) was unnecessary for the cross-coupling of aliphatic amines. This is probably because the amine nucleophile is a much better ligand for Cu. The presence of molecular sieves was again found to be essential for efficient cross-coupling to occur.

Table 2. Comparison of Cu(II)-Catalyzed Methods



entry	R—NH_2	conditions[a]	prod.	yield (%) from **1a**[b]	yield (%) from **2a**[b]
1		A	**3a**	89	92
		B		0	47
2		A	**3v**	30	53
		B		0	91

[a] Reaction conditions: A = $Cu(OAc)_2 \cdot H_2O$ (10 mol %), CH_2Cl_2, 4 Å MS, 40 °C, O_2, 24 h; B = $Cu(OAc)_2$ (10 mol %), myristic acid (20 mol %), 2,6-lutidine (1 equiv), toluene, rt, air (ref 7a). [b] Isolated yields.

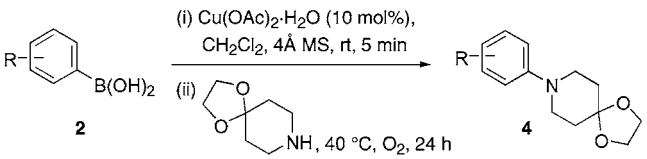
The scope and limitations of this protocol were examined using a series of primary and secondary amines, and anilines with both $PhBF_3^-K^+$[10] and $PhB(OH)_2$ (Table 1).[11] In general, phenylboronic acid **1a** gave slightly greater yields than potassium phenyltrifluoroborate **2a**. This may be due to its greater solubility in CH_2Cl_2, although we observed the reverse behavior in the cross-coupling reactions of aliphatic alcohols.[8] When compared to their alcohol analogues, aliphatic amines give greater yields; in fact, whereas tertiary alcohols do not undergo cross-coupling, tertiary alkyl substituted amines undergo arylation, albeit in low yields (Table 1, entries 2−5). A variety of functional groups on the amines are tolerated, including alkenes, esters, ketones and ketals. Interestingly, both alkyl and aryl halide functionality is also tolerated, without nucleophilic displacement or cross-coupling being observed (Table 1, entries 12 and 22). Substrates bearing chelating substituents on the aliphatic chain typically did not undergo complete conversion at room temperature but gave better results when heated to 40 °C (Table 1, entry 8). α-Amino acid derivatives underwent reaction without detectable epimerization (Table 1, entries 14 and 19). In the case of ammonium salts, in situ activation of the ammonium salt with 1 equiv of Et_3N or pyridine as per Lam's conditions,[4] afforded only low yields of the arylated product. However, pretreatment of the ammonium salt with the weakly basic resin, Amberlyst A-21, prior to addition to the reaction mixture overcomes this problem (Table 1, entries 12−14, 18, and 19).

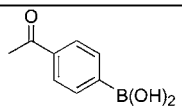
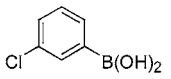
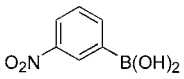
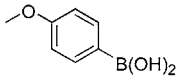
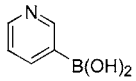
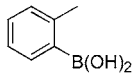
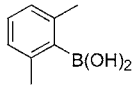
Anilines proved to be poorer cross-coupling partners under these conditions, affording only low to moderate yields of the unsymmetrical diarylamine products (Table 1, entries 22−25). Additionally, competitive oxidative homocoupling of the anilines to azobenzene derivatives occurred under these conditions.[12] A comparison of our conditions with those of Buchwald's revealed that the two are complementary (Table

(9) (a) Mahapatra, S.; Halfen, J. A.; Wilkinson, E. C.; Pan, G.; Wang, X.; Young, V. G.; Cramer, C. J.; Que, L.; Tolman, W. B. *J. Am. Chem. Soc.* **1996**, *118*, 11555−11574. (b) Mahapatra, S.; Halfen, J. A.; Tolman, W. B. *J. Am. Chem. Soc.* **1996**, *118*, 11575−11586.

(10) Potassium organotrifluoroborate salts are readily synthesized from their boronic acid derivatives by treatment with KHF_2, and several are now commercially available. See: Vedejs, E.; Fields, S. C.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 11612−11613.

Table 3. Cu(II)-Catalyzed *N*-Arylation of 1,4-Dioxa-8-azaspiro[4.5]decane[a]



entry	boronic acid	product	yield (%)[b]
1		**4a**	93
2		**4b**	85
3		**4c**	84
4		**4d**	95
5		**4e**	55
6		**4f**	61
7		-	trace

[a] Reaction times are not optimized for individual substrates. [b] Isolated yields.

2). While Buchwald's conditions give excellent yields of the arylated anilines, the arylation of *n*-butylamine produces only 47% of the product. The lower yields obtained under the Buchwald protocol using aliphatic amines is due, at least in part, to the fact that the higher concentration of Cu present results in undesired *N*-dealkylation side reactions. Indeed, in our hands, 26% of diphenylamine was isolated in the reaction of butylamine under Buchwald's conditions. The failure of the $PhBF_3^-K^+$ salt to react under Buchwald's conditions is due to its insolubility in toluene at room temperature.

Finally, the nature of the boronic acid component of the reaction was examined using 1,4-dioxa-8-azaspiro[4.5]decane as a model amine (Table 3). The reaction tolerates both electron-donating and electron-withdrawing substituents in the meta or para positions of the arylboronic acid (Table 3, entries 1−4). Electron-poor heterocyclic boronic acids, such as 3-pyridylboronic acid, also participate in the reaction (Table 3, entry 5). Substitution at the ortho positions of the aryl boronic acids has a profound effect on the outcome of the reaction. 2-Methylphenylboronic acid gave only a moderate yield of cross-coupled product; whereas, the more sterically hindered 2,6-dimethylphenylboronic acid generated only trace amounts of the arylated amine (identified through crude ^{1}H NMR) (Table 3, entries 6 and 7).

In conclusion, we have developed an efficient Cu-catalyzed protocol for the arylation of primary and secondary aliphatic amines, a class of nucleophiles that have been problematic under previous cross-coupling protocols with arylboronic acids. The transformation can be affected under an atmosphere of molecular oxygen without the need of a ligand for the Cu-catalyst or base to activate the amine. This procedure further extends the utility of the Cu catalyzed cross-coupling protocols in the rapidly growing field of *N*-arylations, and we anticipate its use in a diverse range of synthetic applications. Further studies along these lines, including a mechanistic investigation probing the influence of additives and molecular sieves, will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all compounds isolated. ^{1}H and ^{13}C spectra of all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **Typical Experimental Procedure.** A suspension of $PhBX_n$ (2.0 mmol), $Cu(OAc)_2·H_2O$ (10 mol %), and powdered 4 Å MS (0.75 g) in CH_2Cl_2 (8.0 mL) was stirred for 5 min at room temperature. To this mixture was added the amine (1.0 mmol). The reaction vessel was then sealed with a rubber septum and stirred at room temperature (or 40 °C) under O_2 for 24 h. The reaction mixture was then filtered through a plug of Celite and the product isolated by column chromatography (see the Supporting Information).

(12) (a) Kinoshita, K. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 777−780. (b) Kinoshita, K. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 780−783. (c) Kinoshita, K. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 783−787.