

## All-Purpose Copper Catalyst for Coupling of Ammonium Salts and 1° and 2° Amines with Boronic Acid

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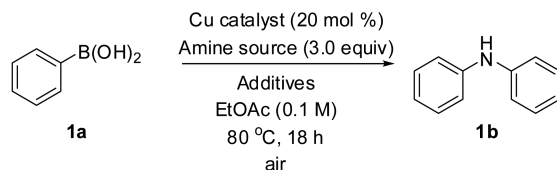
Received January 20, 2012, Accepted February 7, 2012

**Key Words** : Copper acetate, Ammonium carbonate, Aromatic amines, Chan-Lam coupling

The high demand for aromatic amines in pharmaceutical and other industries leads to intensive studies on developing catalytic methods for *N*-arylation of amines.<sup>1-7</sup> The most attractive metal-promoted coupling conditions for affording aromatic amines are the copper-catalyzed cross couplings of arylboronic acid and amines, in which inexpensive Cu(II) and Cu(I) complexes are used in the presence of ligands, acids, or bases under aerobic conditions.<sup>8,9</sup> Since the first report on copper-mediated cross-coupling of arylboronic acid and amines by Chan and Lam, numerous modifications of copper catalysts, acid or base additives, and solvents have been conducted with the aim of realizing efficient arylation of amines. [Cu(OH)·TMEDA]<sub>2</sub>Cl<sub>2</sub> in the presence of oxidants (O<sub>2</sub>, TEMPO, and pyridine-*N*-oxide) was reported as a first catalytic system for amine arylation.<sup>9a,b</sup> Subsequently, Cu(OAc)<sub>2</sub>-catalyzed conditions involving various additives (acid, base, molecular sieves) were applied for the coupling of amines with boronic acids and borate salts.<sup>9</sup> In addition to the regular amine derivatives, aqueous NH<sub>3</sub> solution was used with boronic acids under copper-catalyzed coupling conditions. Depending on the copper complexes, monoaryl-amines with Cu<sub>2</sub>O and diarylamines with Cu(OAc)<sub>2</sub> were obtained from the NH<sub>3</sub> aqueous solution.<sup>9l,m</sup> Depending on the substituents of amines and boronic acids, copper salts with diverse ligands and additives are required to perform efficient coupling of different types of amines with boronic acids. Therefore, we have explored an all-purpose copper catalyst system that can be employed to realize the coupling of a variety of amines, including ammonium salts, primary amines, and secondary amines, for *N*-arylation. In this study, Cu(OAc)<sub>2</sub> with the combination of benzoic acid and carbonate ions showed versatile reactivity for the arylation of amines, regardless of the substitution and electronic properties of amines under aerobic conditions.

Initially, optimization of arylation of ammonium salts was conducted, as listed in Table 1. Based on Cheng's report regarding the coupling of aqueous ammonia with arylboronic acid,<sup>9m</sup> copper(II) complexes with benzoic acid were used for the coupling of (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> with phenyl boronic acid **1a** to afford diphenylamine **1b** in 75% yield (entry 1). Previously reported ammonia arylation using Cu<sub>2</sub>O catalyst in MeOH produced the arylated product from ammonium salts in low yields (0-8%).<sup>9l,m</sup> The addition of acetic acid was

**Table 1.** *N*-Arylation of ammonium salts

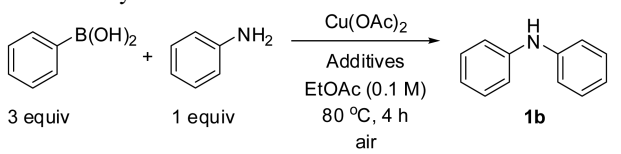


Entry	Cu source	N-source	Additives (equiv)	Yield
1	Cu(OAc) <sub>2</sub>	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>	PhCO <sub>2</sub> H (0.5)	75%
2	Cu(OAc) <sub>2</sub>	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>	HOAc (0.5)	21%
3	Cu(OAc) <sub>2</sub>	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub> (0.5)	N.R.
4	Cu(OAc) <sub>2</sub>	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>	PhCO <sub>2</sub> H (0.2)	49%
5	Cu(OAc) <sub>2</sub>	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>	PhCO <sub>2</sub> H (1)	42%
6	Cu(OAc) <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub>	PhCO <sub>2</sub> H (0.5)	33% <sup>a</sup>
7	Cu(OAc) <sub>2</sub>	NH <sub>4</sub> OAc	PhCO <sub>2</sub> H (0.5)	64% <sup>a</sup>
8	Cu(OAc) <sub>2</sub>	NH <sub>4</sub> Cl	PhCO <sub>2</sub> H (0.5)	N.R.

<sup>a</sup>6 eq of amine source

detrimental to the yield, and a base additive (K<sub>2</sub>CO<sub>3</sub>) completely prevented product formation (entries 2 and 3). Different loadings of benzoic acid (0.2 equivalents and 1 equivalent) also produce **1b** in low yield (entries 4 and 5). For the coupling of amines with boronic acids, carboxylic acid was assumed to coordinate to a copper ion or to tune the basicity/acidity of the solution to increase the yield of the coupling product, as discussed in previous papers by Buchwald and Cheng.<sup>9d,m</sup> In addition to (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub>, NH<sub>4</sub>HCO<sub>3</sub> and NH<sub>4</sub>OAc participate in the coupling reaction to produce **1b** in 33% and 64% yield, respectively (entries 6 and 7). Unlike above-mentioned ammonium salts, NH<sub>4</sub>Cl is not converted to **1b**, indicating that the presence of the basic anion is necessary (entry 8).

The optimized conditions for arylation of (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> were applied to carry out the arylation of aniline to produce **1b** in 17% yield, as shown in entry 1 of Table 2. On the basis of the results of *N*-arylation of ammonium salts (Table 1), the counter anion of ammonium salts is assumed to be a base or promoter for transmetalation of arylboronic acid to the copper catalyst. As illustrated in entries 2-4, 3, 1, and 0.5 equivalents of K<sub>2</sub>CO<sub>3</sub> were employed for the arylation of aniline, and the yield dramatically changed to 76%, 98%, and 73%, respectively. The reaction time of *N*-arylation of

**Table 2.** *N*-Arylation of aniline


Entry	Cu source (mol %)	Base (equiv)	Acid (eq)	Yield
1	Cu(OAc) <sub>2</sub> (20)	-	PhCO <sub>2</sub> H (0.5)	17%
2	Cu(OAc) <sub>2</sub> (20)	K <sub>2</sub> CO <sub>3</sub> (3)	PhCO <sub>2</sub> H (0.5)	76%
3	Cu(OAc) <sub>2</sub> (20)	K <sub>2</sub> CO <sub>3</sub> (1)	PhCO <sub>2</sub> H (0.5)	98%
4	Cu(OAc) <sub>2</sub> (20)	K <sub>2</sub> CO <sub>3</sub> (0.5)	PhCO <sub>2</sub> H (0.5)	73%
5	Cu(OAc) <sub>2</sub> (20)	K <sub>2</sub> CO <sub>3</sub> (1)	PhCO <sub>2</sub> H (0.5)	82% <sup>a</sup>
6	Cu(OAc) <sub>2</sub> (10)	K <sub>2</sub> CO <sub>3</sub> (1)	PhCO <sub>2</sub> H (0.5)	81%
7	Cu(OAc) <sub>2</sub> (5)	K <sub>2</sub> CO <sub>3</sub> (1)	PhCO <sub>2</sub> H (0.5)	77%

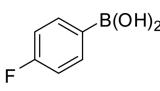
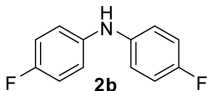
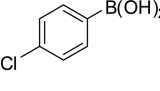
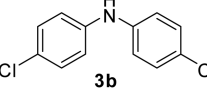
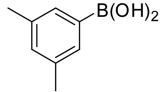
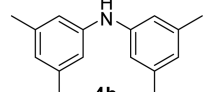

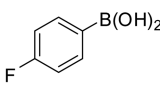
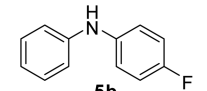

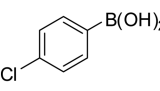
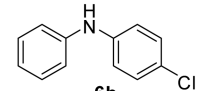

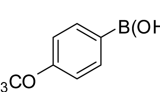
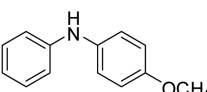

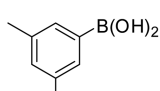
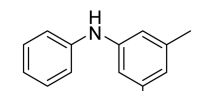

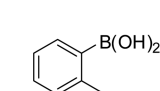
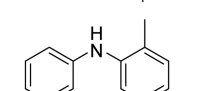
<sup>a</sup>reaction at ambient temperature, reaction time: 48 h

aniline was generally less than 4 h at 80 °C. At ambient temperature, the yield of **1b** remained 82%, but a significantly longer reaction time (48 h) was required (entry 5). Next, reduced loadings (10 and 5 mol %) of Cu(OAc)<sub>2</sub> were used, and **1b** was produced in 81% and 77% yield, respectively (entries 6 and 7).

The results of arylation of ammonium salts and aniline (Tables 1 and 2) show that Cu(OAc)<sub>2</sub>, benzoic acid, and carbonate ions are necessary for *N*-arylation of amine derivatives. Arylation of ammonium salts and aniline were conducted in the ethyl acetate solution of Cu(OAc)<sub>2</sub> (20 mol %), benzoic acid (0.5 or 1 equivalent), and K<sub>2</sub>CO<sub>3</sub> (1 equivalent in the case of aniline) at 80 °C (Table 3) by using a series of substituted boronic acids. As shown in entries 1-3, *para*-fluoro-, -chloro-, and 3,5-dimethyl-substituted phenyl boronic acids readily participated in the arylation of ammonium carbonate to afford diaryl compounds in modest yields. Like ammonium carbonate, aniline was arylated in the presence of a variety of boronic acid derivatives, and good yields were obtained (entries 4-8). In particular, *ortho*-methyl-substituted phenyl boronic acid, a previously reported not facile substrate due to the steric hindrance underwent the coupling with aniline to afford **9b** in 92% yield (entry 8). In the case of alkyl boronic acids, cyclohexylboronic acid was tested, showing no desired product formation.

Next, a wide range of amines including 1° and 2° aromatic and aliphatic amines, a heterocyclic amine, and a sulfonamide were subjected to the reaction conditions listed in Table 4. The electron-donating and electron-withdrawing group-substituted anilines reacted with phenyl boronic acid to yield aromatic amines having different aromatic substituents (entries 1-3). *N*-Methylaniline also underwent arylation and afforded **13b** in good yield (74%) without Cu-promoted dealkylation (entry 4).<sup>9e</sup> The heterocyclic amine (benzimidazole) participated in the reaction to afford the *N*-arylation product in 96% yield (entry 5). The arylation yield of *p*-toluenesulfonamide was somewhat lower (48%) than other amines (entry 6). The arylation of alkylamine was explored. Benzylamines and morpholine showed great reactivity for arylation (entries 7 and 8). Overall, the Cu-

**Table 3.** *N*-Arylation of ammonium carbonate and anilines with various boronic acid

Entry	Amine	Boronic acid	Product (Yield)
1	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>		 42% <sup>a</sup>
2	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>		 49% <sup>b</sup>
3	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>		 50% <sup>a</sup>
4			 71% <sup>c</sup>
5			 72% <sup>c</sup>
6			 99% <sup>c</sup>
7			 76% <sup>c</sup>
8			 92% <sup>c</sup>

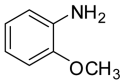
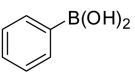
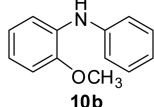
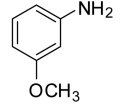
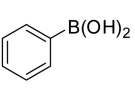
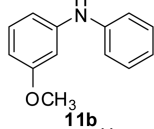
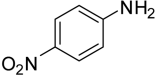
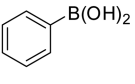
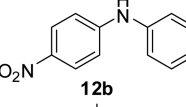
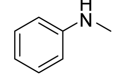
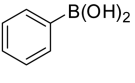
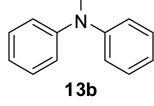
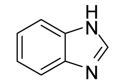
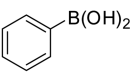
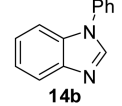
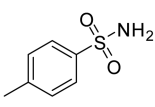
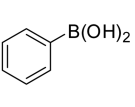
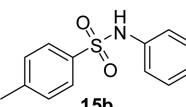
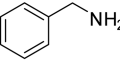
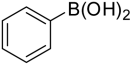
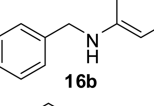

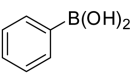
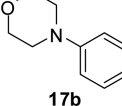
<sup>a</sup>Cu(OAc)<sub>2</sub> (20 mol %), PhCO<sub>2</sub>H (0.5 equiv). <sup>b</sup>Cu(OAc)<sub>2</sub> (20 mol %), PhCO<sub>2</sub>H (1 equiv). <sup>c</sup>Cu(OAc)<sub>2</sub> (20 mol %), PhCO<sub>2</sub>H (1 equiv), K<sub>2</sub>CO<sub>3</sub> (1 equiv)

catalyzed conditions proposed in this work provide an efficient and general protocol for the arylation of a wide range of amine derivatives.

In conclusion, we have studied the copper-catalyzed coupling of amines and boronic acids to develop a general, versatile, and practical protocol. Under the copper-catalyzed conditions, a variety of amines, including ammonium salts, 1° and 2° aromatic- and aliphatic amines, benzimidazole, and sulfonamide, were efficiently arylated in the presence of a series of phenyl boronic acids as aryl donors. Remarkably, the cleavage of the C-N bond of aliphatic amines, which produces the major side product of copper-catalyzed arylation of aliphatic amines, was not observed in compounds **13b**, **16b** and **17b**. By utilizing this all-purpose copper catalyst, ammonium salts and 1° and 2° amines were successfully converted to monoarylamines, and symmetrical- and unsymmetrical diarylamines in good yield.

**Experimental.** To a premixed ethyl acetate solution of Cu(OAc)<sub>2</sub> (20 mol %), benzoic acid (indicated mol %), and K<sub>2</sub>CO<sub>3</sub> (0 mol % for ammonium carbonate, 100 mol % for other amines) was added the amine and boronic acid at room

**Table 4.** N-Arylation of various amines with phenyl boronic acid

Entry	Amine	Boronic acid	Product (Yield)
1			 72% <sup>a</sup>
2			 87% <sup>a</sup>
3			 94% <sup>b</sup>
4			 74% <sup>a</sup>
5			 96% <sup>b</sup>
6			 48% <sup>b</sup>
7			 72% <sup>a</sup>
8			 95% <sup>a</sup>

<sup>a</sup>Cu(OAc)<sub>2</sub> (20 mol %), PhCO<sub>2</sub>H (1 equiv), K<sub>2</sub>CO<sub>3</sub> (1 equiv). <sup>b</sup>Cu(OAc)<sub>2</sub> (20 mol %), PhCO<sub>2</sub>H (0.5 equiv), K<sub>2</sub>CO<sub>3</sub> (1 equiv)

temperature. The resulting mixture was allowed to run at 80 °C until the starting material is consumed completely. The solvent was removed using a rotary evaporator to produce a residue that was purified by column chromatography on silica gel eluting with hexane and ethyl acetate to yield the final desired product.

**Acknowledgments.** This study was supported by the Korea Research Foundation (grant No. 2011-0030745 and 2011-0005996) and Korea CCs R&D Center, funded by the Ministry of Education, Science and Technology of Korean government (grant No. 2011-0031994).

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