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# Copper-Catalyzed Coupling of Alkylamines and Aryl Iodides: An Efficient System Even in an Air Atmosphere

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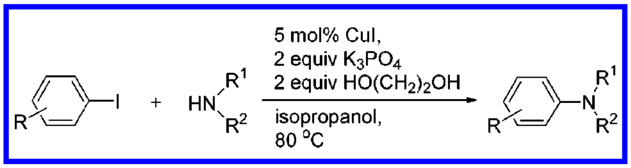
## ABSTRACT



**A mild method for the copper-catalyzed amination of aryl iodides is reported. This operationally simple C–N bond-forming protocol uses CuI as the catalyst and ethylene glycol as ligand in 2-propanol. A variety of functionalized aryl iodides as well as several amines were efficiently coupled using this method. This catalytic amination procedure is relatively insensitive to moisture and can be performed under an air atmosphere with comparable yield. Preliminary results on the amination of aryl bromides are also described.**

The formation of carbon−nitrogen bonds via cross-coupling reactions represents a powerful means for the preparation of numerous products important in pharmaceutical and material sciences.[1] Efficient palladium-catalyzed aminations of aryl halides have been developed in recent years and have proven useful in both academic and industrial laboratories.[2] Despite substantial improvements in the past few years, however, significant limitations still exist. For example, substrates containing certain functional groups such as free NH and OH directly bound to the aryl halide have proven to be problematic. Additionally, Pd-based methods can often be relatively sensitive to exogenous oxygen and moisture. Moreover, the use of Pd[3] and phosphine or related ligands limit the attractiveness of these methods for certain applications. Thus, less costly alternatives and operationally simple procedures are desirable.

Copper-mediated Ullmann[4] and Goldberg[5] couplings are attractive for large and/or industrial-scale applications;[6] however, the use of high temperatures, poor substrate scope, and the need to use stoichiometric amounts of copper reagents have limited the utility of these reactions in some cases.[4] Recently, milder Ullmann-type methodologies for the *N*-arylation of anilines,[7] imidazoles,[8] amides,[9] nitrogen heterocycles,[9] and hydrazides[10] as well as the preparation of diaryl ethers[11] have been reported. Progress in the arylation

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

[2] 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.

[3] For the price of palladium, see: www.kitco.com.

[4] (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382−2384. For reviews, see: (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456.

[5] Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1619.

[6] (a) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043−5051. (b) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670−674.

[7] (a) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791−4793. (b) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315−4317.

[8] Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657−2640.

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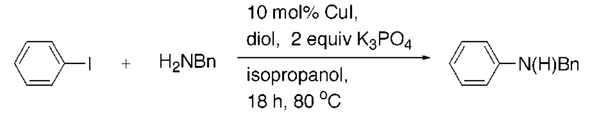
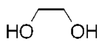
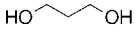
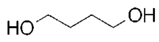
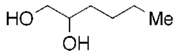
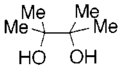
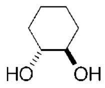
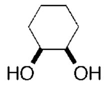
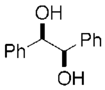
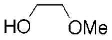
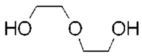
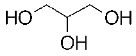
of aliphatic amines, however, has been realized only in the context of chelating substrates[12] such as α- and *β*-amino acids[13] or in strategies utilizing less convenient or more costly arylating agents.[14,15,16] Thus, a simple and general procedure for the copper-catalyzed coupling of alkylamines and aryl halides has remained elusive. We previously disclosed that *trans*-1,2-diaminocyclohexane serves as an excellent supporting ligand in the Cu-catalyzed amidation of aryl halides and the *N*-arylation of nitrogen heterocycles.[9] The success of these processes as well as a recent report by a Merck group[17] prompted us to examine whether *O*-donor ligands could be used for C−N bond formation reactions. Herein, we report a mild, practical Cu-catalyzed amination of functionalized aryl iodides using air-stable CuI as the catalyst, ethylene glycol as ligand and unpurified 2-propanol as the solvent; these reactions can be performed without protection from air or moisture.

A variety of diol ligands were examined using iodobenzene and benzylamine as model substrates (Table 1). Neat ethylene glycol can be used as solvent instead of 2-propanol (Table 1, entry 5). However, the highly viscous ethylene glycol made stirring difficult, and the solubility of certain substrates in ethylene glycol was poor. Moreover, the yield of the reaction was higher when 2-propanol was used as solvent as compared to the reaction performed in ethylene glycol (entry 5).

Dramatic differences in yield were observed in reactions using ethylene, propylene and butylene glycols as ligands (Table 1, entries 5−7). Presumably, ethylene glycol acts as a ligand that is more effective in stabilizing or solubilizing the copper complex. Control experiments revealed that no reaction was observed in the absence of ethylene glycol. Substituted diols such as pinacol and cis- and *trans*-1,2-cyclohexanediol gave poor conversions and yields compared with ethylene glycol (Table 1, entries 8−12). 2-Methoxyethanol, diethyleneglycol, and glycerol proved to be significantly less effective (Table 1, entries 13−15).

**Table 1.** Copper-Catalyzed Amination: Effect of Diol Ligand[a]



| entry | diol | equiv of diol | conv, % | yield, %[b] |
|---|---|---|---|---|
| 1 |  | 0.1 | 27 | 5 |
| 2 | | 0.2 | 34 | 10 |
| 3 | | 0.5 | 52 | 42 |
| 4 | | 1.0 | 80 | 77 |
| 5 | | 2.0 | 98 | 93 (87[c]) |
| 6 |  | 2.0 | 20 | trace |
| 7 |  | 2.0 | 21 | trace |
| 8 |  | 2.0 | 53 | 34 |
| 9 |  | 2.0 | 29 | trace (42[c]) |
| 10 |  | 2.0 | 44 | 31 |
| 11 |  | 2.0 | 49 | 33 |
| 12 |  | 2.0 | 52 | 27 |
| 13 |  | 2.0 | 20 | 7 (38[c]) |
| 14 |  | 2.0 | 32 | 17 (31[c]) |
| 15 |  | 2.0 | 29 | 18 (14[c]) |
| 16 | sucrose | 2.0 | 5 | trace |

[a] Reaction conditions: 1.0 mmol of iodobenzene, 1.2 mmol of benzylamine, 10 mol % CuI, 2.0 mmol of diol, 2.0 mmol of K$_3$PO$_4$, *i*-PrOH (1 mL), 80 °C under Ar. [b] Calibrated GC yield. [c] Diol used as solvent.

Preliminary results showed that Cu salts such as CuI, CuBr, CuCl, and CuOAc were effective precatalysts. Among the copper(I) sources investigated, CuI and CuOAc were the most efficient. Air-stable and inexpensive CuI was used in experiments designed to examine the effect of base and solvent in the amination reaction. Both K$_3$PO$_4$ and Cs$_2$CO$_3$ proved effective, however, some *O*-arylated ethylene glycol was obtained (~9%) when Cs$_2$CO$_3$ was used. 2-Propanol and *n*-butanol were found to be the solvents of choice, while toluene, dioxane, and DMF were much less effective. That the process is fairly insensitive to water is demonstrated by the observation that a small decrease in reaction rate occurred when 2 equivalents of water (relative to aryl iodide) was added to the reaction mixture. Thus, no special precautions to exclude small amounts of moisture from this reaction are required.

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(10) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803−3805.

(11) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539−10540.

(12) (a) Arai, S.; Yamagishi, T.; Ototake, S.; Hida, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 547−548. (b) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986−2987. (c) Vedejs, E.; Trapencieris, P.; Suna, E. *J. Org. Chem.* **1999**, *64*, 6724−6729. (d) Arterburn, J. B.; Pannala, M.; Gonzalez, A. M. *Tetrahedron Lett.* **2001**, *42*, 1475−1477.

(13) (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459−12466. (b) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583−2586. (c) Clement, J.-B.; Hayes, J. F.; Sheldrake, H. M.; Sheldrake, P. W.; Wells, A. S. *Synlett* **2001**, 1423−1427.

(14) (a) Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* **2000**, 1022−1024. (b) Elliott, G. I.; Konopelski, J. P. *Tetrahedron* **2001**, *57*, 5683−5705. (c) 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. (d) Lam, P. Y. S.; Clark, C. G.; Subern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674−676.

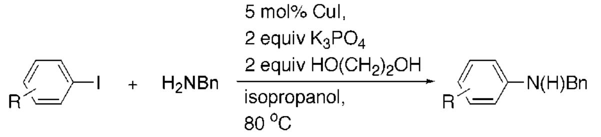
(15) (a) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077−2079, and references therein. (b) Lam, P. Y. S.; Vincent, G.; Clark, C. G, Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415−3418.

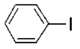
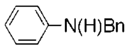
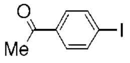
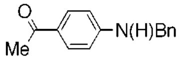
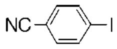
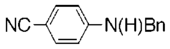
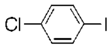
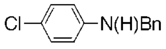
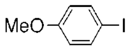
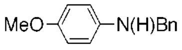
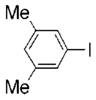
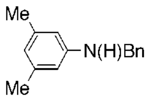
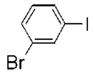
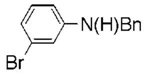
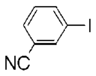
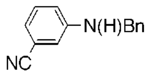
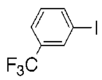
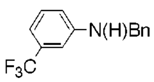
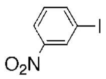
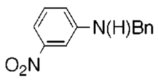
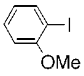
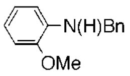
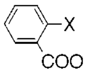
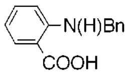
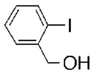
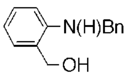
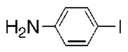
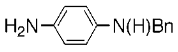
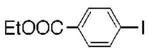
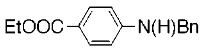
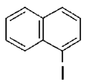
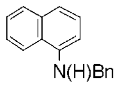
(16) For the use of *stoichiometric* Cu reagents, see: (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1988**, *39*, 2933−2936. (b) Cundy, D. J.; Forsyth, S. A. *Tetrahedron Lett.* **1988**, *39*, 7979−7982. (c) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233−1236. (d) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528−1531.

(17) Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251−3254.

The optimized reaction conditions[18] were used to examine C−N bond couplings involving functionalized aryl iodides as well (Table 2). In general, 5 mol % of copper(I) iodide and 2.0 equiv of ethylene glycol in 2-propanol were used, but 1 mol % of the catalyst was also found to be effective (Table 2, entries 3, 4, and 12). Keto, cyano, nitro, amino, carboxylate, methoxy, bromo, and chloro groups are tolerated on the aryl iodide component. No significant electronic effects were observed for para- and meta-substituted aryl iodides; the rates and yields of reactions were comparable. Ortho-substituted aryl halides typically gave lower yields and required higher catalyst loadings (Table 2, entry 17). *o*-Iodo benzyl alcohol and *o*-iodobenzoic acid can be efficiently reacted; good to excellent yields were observed (Table 2, entries 18 and 21). The amination of 4-iodoaniline proved to be successful; this result is important since this substrate is not efficiently coupled using palladium-based systems (Table 2, entry 22). It was also possible to couple bromo- and chlorobenzoic acids (Table 2, entries 19 and 20). Transesterification of ester containing substrates was observed; ethyl 4-iodobenzoate was transformed in 58% yield, however, when ethanol was used as solvent (Table 2, entry 23). It is noteworthy that this Cu-catalyzed amination can be performed in an ambient atmosphere without sacrificing yield (Table 2, entries 2, 10, and 13).

**Table 2.** Copper-Catalyzed Amination of Functionalized Aryl Iodides with Benzylamine



| entry | ArI | products | time, h | yield, %$^a$ |
|---|---|---|---|---|
| 1<br>2 |  |  | 8<br>$18^d$ | 91<br>89 |
| 3<br>4 |  |  | $5^b$<br>$18^b$ (70 °C) | 90<br>87 |
| 5 |  |  | 12 | 79 |
| 6 |  |  | 12 | 84 |
| 7 |  |  | 18 | 89 |
| 8<br>9 |  |  | 12<br>$18^d$ | 82<br>85 |
| 10<br>11<br>12 |  |  | 6<br>$30^b$<br>$18^d$ | 83<br>87<br>86 |
| 13 |  |  | 12 | 80 |
| 14<br>15 |  |  | 12<br>$18^d$ | 91<br>85 |
| 16 |  |  | $12^f$ | 72 |
| 17 |  |  | $72^e$ | 73 |
| 18<br>19<br>20 |  X = I<br>X = Br<br>X = Cl |  | 18<br>$48^e$<br>$72^e$ | 71<br>53<br>48 |
| 21 |  |  | 24 | 95 |
| 22 |  |  | $38^g$ (90 °C) | 62 |
| 23 |  |  | $12^h$ | 58 |
| 24 |  |  | 12 | 70 |

$^a$ Isolated yield (average of two runs). $^b$ 1 mol % CuI. $^c$ 10 mol % CuI. $^d$ Performed under air. $^e$ *n*-BuOH as solvent, 10 mol % CuI, 100 °C. $^f$ 1.0 mmol of $BnNH_2$, 1.4 mmol of ArI was used. $^g$ 2 equiv of $BnNH_2$ was used. $^h$ EtOH as solvent; 1.4 mmol of ArI and 1.0 mmol of $BnNH_2$ were used.

Other aliphatic amines can be utilized in the Cu−ethylene glycol catalyzed amination reaction (Table 3). The *N*-arylation of most aliphatic amines can be effected with 1 mol % CuI under air (Table 3, entries 2, 3, 5, 6, 11, and 12). Notably, optically active (*R*)-α-methylbenzylamine can be transformed to the desired product without loss of enantiomeric purity[19] (Table 3, entry 7). Cyclic secondary amines such as piperidine, morpholine, and *N*-methylpiperazine usually give slightly lower yields of the corresponding arylated products, however, pyrrolidine reacted efficiently (Table 3, entries 10−15). Under the same conditions, 3-iodopyridine[20] can be cleanly transformed (Table 3, entry 17). Additionally, aliphatic amines are chemoselectively *N*-arylated over an aniline group (Table 3, entry 18). Moreover, the amination protocol cleanly effects the selective arylation of the primary amine in spermidine with no reaction observed at the secondary amine moiety (Table 3, entry 19). In all reactions involving primary amines, diarylation products were minimal. Interestingly, amides and anilines were poor substrates in this Cu-catalyzed protocol.[21]

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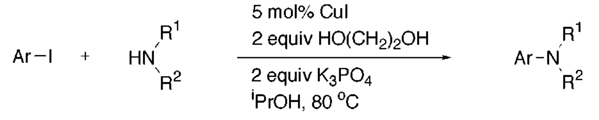
(18) **Typical Procedure.** CuI (10 mg, 0.05 mmol, 5 mol %) and $K_3PO_4$ (425 mg, 2.0 mmol) were added to a screw-capped test tube with a Teflon-lined septum. The tube was evacuated and back-filled with argon three times. (For reactions under *air*, the evacuation/back-fill step was not performed.) 2-Propanol (1.0 mL), ethylene glycol (111 $\mu$L, 2.0 mmol), iodobenzene (112 $\mu$L, 1.0 mmol), and benzylamine (131 $\mu$L, 1.2 mmol) were added by syringe at room temperature. The reaction mixture was heated at 80 °C to furnish a pale yellow suspension. The reaction mixture was allowed to cool to room temperature after heating for the time specified. Water (ca. 5 mL) was added, and the mixture was extracted with diethyl ether (4 × 10 mL). The combined organic phases were washed with brine and dried over $Na_2SO_4$. The solvent was removed in vacuo to yield the crude product as a deep yellow residue that was purified by column chromatography on silica gel.

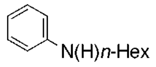
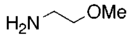
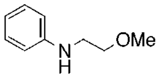
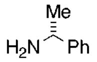
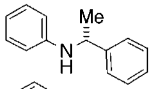
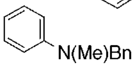
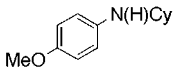
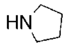
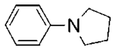
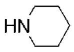
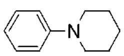
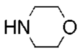
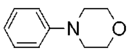
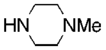
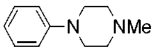
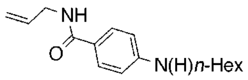
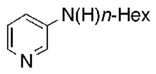
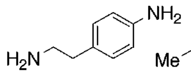
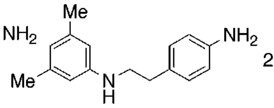
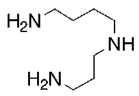
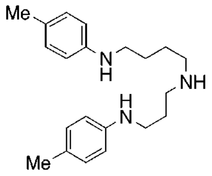
(19) Racemization in the intermolecular *N*-arylation of enantiomerically enriched amines can be avoided by using a $Pd_2(dba)_3$/BINAP catalyst. See: Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 8451−8458.

(20) For Pd-catalyzed reactions involving halopyridines, see: Wagaw, S.; Buchwald, S. L. *J. Org. Chem*. **1996**, *61*, 7240−7241.

(21) Under the optimized conditions, the reaction of iodobenzene with 2-pyrrolidinone and aniline proceeds in 41% and 50% yield, respectively.

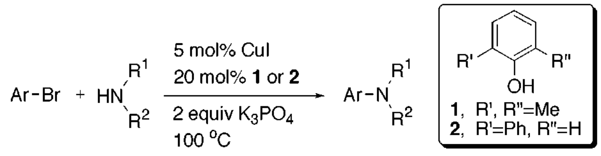
**Table 3.** Amination of Aryl Iodides with Different Amines

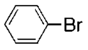
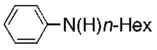
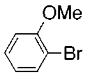
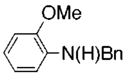
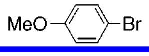
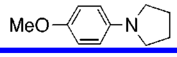


| entry | amine | product | time, h | yield, %[a] |
|---|---|---|---|---|
| 1 | $H_2N$-*n*-Hex |  | 12 | 84 |
| 2 | | | 30[b] | 80 |
| 3 | | | 18[d] | 82 |
| 4 |  |  | 18 | 91 |
| 5 | | | 30[b] | 87 |
| 6 | | | 18[d] | 85 |
| 7 |  98%ee |  | 24 | 76 (99%ee) |
| 8 | HN(Me)Bn |  | 24 | 70 (74[e]) |
| 9 | $H_2N$-Cy |  | 14 | 72[f] |
| 10 |  |  | 18 | 90 |
| 11 | | | 30[b] | 89 |
| 12 | | | 18[d] | 84 |
| 13 |  |  | 18 | 80 |
| 14 |  |  | 10 | 76 |
| 15 |  |  | 10 | 71 |
| 16 | $H_2N$-*n*-Hex |  | 24 | 88 |
| 17 | $H_2N$-*n*-Hex |  | 40 | 85 |
| 18 |  |  | 22 | 65 |
| 19 |  |  | 23 | 72 |

[a] Isolated yield (average of two runs). [b] 1 mol % CuI. [c] 10 mol % CuI. [d] Performed under air. [e] 10 mol % CuI, *n*-BuOH as solvent at 90 °C. [f] *n*-BuOH as solvent.

**Table 4.** Copper-Catalyzed Amination of Aryl Bromides



| entry | ArBr | ligand | products | time, h | conv, % | yield, %[a] |
|---|---|---|---|---|---|---|
| 1 |  | **1** |  | 18 | 100 | 87[b] |
| 2 | | **2** | | 22 | >99 | 90[b] |
| 3 | | **2** | | 22 | 81 | 61[b,c] |
| 4 | | **2** | | 22 | 56 | 31[c,d] |
| 5 |  | **2** |  | 22 | 100 | 83[b] |
| 6 |  | **2** |  | 22 | 100 | 73[b] |

[a] Isolated yield (average of two runs). Reaction conditions: 1.0 mmol PhBr, *n*-Hex$NH_2$ as solvent. [b] Under argon. [c] 1.0 mmol of PhBr, 1.2 mmol of *n*-Hex$NH_2$ in toluene. [d] Under air.

Extension of this amination process to aryl bromide substrates has yielded promising results (Table 4). Interestingly, hindered phenols **1** and **2** proved more efficient ligands than ethylene glycol;[22] *N*-phenylhexylamine was obtained in good yield if the reaction was performed in *n*-hexylamine as the solvent. It is interesting that both bidentate and monodentate *O*-donor ligands accelerate the copper-catalyzed arylation of alkylamines. Studies to understand these ligand effects will be useful in the understanding of the reaction mechanism(s) and the development of improved catalyst systems.

In summary, we have developed an operationally simple CuI-ethylene glycol catalyzed amination reaction. This method enjoys relatively mild reaction conditions and broad functional group tolerance on the aryl iodide coupling partner. This amination protocol can be performed under air without loss of yield. We have also disclosed promising results in the Cu-catalyzed amination of aryl bromides. Explorations into the scope and mechanism of these Cu-catalyzed aminations are in progress.

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**Supporting Information Available:** Detailed experimental procedures and characterization data of each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0171867

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[22] In a preliminary experiment, the coupling of iodobenzene with *n*-hexylamine in toluene proceeds in 41% GC yield using the CuI/**1** system. No attempts to optimize this reaction have been performed.