ORGANIC LETTERS

2003
Vol. 5, No. 6
793−796

Mild and Efficient Copper-Catalyzed Amination of Aryl Bromides with Primary Alkylamines

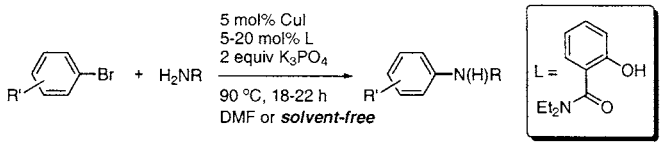
Fuk Yee Kwong and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

sbuchwal@mit.edu

Received November 22, 2002

ABSTRACT



An efficient copper-catalyzed amination of aryl bromides with primary alkylamines was developed that uses commercially available diethylsalicylamide as the ligand. This amination reaction can be performed at 90 °C in good yield. A variety of functional groups are compatible with these reaction conditions. Preliminary results show that this reaction can be carried out under solvent-free conditions with comparable yields.

Traditional copper-catalyzed Ullmann coupling protocols necessitate the use of high temperatures and often require the use of stoichiometric amounts of copper reagents, which, on scale, leads to problems of waste disposal.[1] Additionally, they have been plagued by poor substrate scope. Recently, milder Ullmann-type processes for C−N bond formation such as N-arylation of anilines,[2] amides,[3] imidazole,[4] indoles,[3] and hydrazines[5] have been reported. Progress in the arylation of aliphatic amines, however, has been realized only in the context of chelating substrates[6] such as α- and β-amino acids[7] and β-amino alcohols[8] or in strategies utilizing less convenient or more costly arylating agents.[9,10] Thus, a simple and general procedure for the copper-catalyzed coupling of alkylamines and aryl halides has remained elusive. Recently, we disclosed that ethylene glycol serves as an excellent ligand in the Cu-catalyzed amination of aryl iodides.[11] In this report, we noted that using phenolic ligands, aryl bromides could be utilized if the reaction was conducted using a large excess of the amine as the solvent. While this is satisfactory in some instances, the success of these

(1) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382−2384. For review, see: (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1470.

(2) (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*, 4135−4138. (c) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670−674. (d) Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett.* **2002**, *43*, 7143−7146. (e) For preparation of primary anilines using copper catalysis in liquid ammonia, see: Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251−3254.

(3) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428. (c) Antilla, J. C.; Klapars, A. Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684−11688. (d) Kang, S.-K.; Kim, D.-H.; Park, J.-N. *Synlett* **2002**, 427−430.

(4) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657−2640.

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

(6) (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.

(7) (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.

(8) Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3703−3706.

(9) (a) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077−2079. (b) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233−1236. (c) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528−1531. (c) Lam, P. Y. S.; Vincent, G.; Clark, C. G, Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415−3418. (d) Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* **2000**, 1022−1024.

10.1021/ol0273396 CCC: $25.00 © 2003 American Chemical Society
Published on Web 02/21/2003

processes prompted us to examine whether other anionic O-donor ligands could be used for the amination of aryl bromides without necessitating the use of a large excess of the amine substrate.[12] Herein, we report a mild and practical Cu-catalyzed coupling of primary amines to functionalized aryl bromides using air-stable CuI as the catalyst and structurally simple salicylamides as ligands.

In our initial screening experiments, 5-bromo-*m*-xylene and *n*-hexylamine were used as the prototypical substrates for discovery of suitable reaction conditions (Figure 1). The

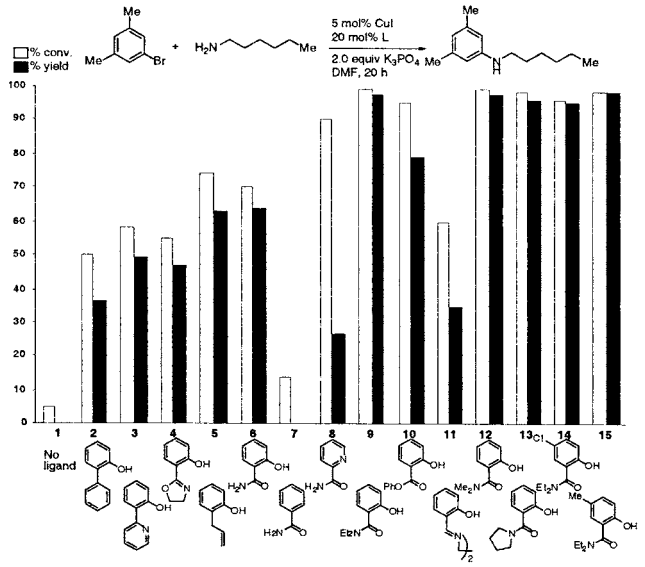


Figure 1. Ligand comparison in Cu-catalyzed amination of aryl bromide. Reaction conditions: ArBr (1.0 mmol), amine (1.5 mmol), CuI (0.05 mmol), ligand (0.2 mmol), and K_3PO_4 (2.0 mmol) were added to a screw-capped test tube with a Teflon septum followed by the addition of anhydrous DMF. The reaction was stirred for at 90 °C for 20 h under argon. Conversion (GC) and yield (GC) were calibrated with dodecane as a standard.

use of the hindered phenol, 2-phenylphenol, which we previously employed,[12] gave a 50% conversion of the aryl bromide and 38% yield of the product (Figure 1, bar 2); no desired products were observed in the absence of a substituted phenol ligand. Reactions in which a group capable of chelation was incorporated *ortho* to the phenolic hydroxyl proceeded with slightly higher conversion and yield (Figure 1, bars 3−6). That the phenolic group plays an important role is evident by comparing the results in bars 6 and 7.[13] With picolinamide, although a good conversion of aryl bromide was observed, competitive amidation of the ligand led to a low yield of the product (Figure 1, bar **8**). We wondered whether N,N-dialkylated salicylamides might be efficient ligands. To our delight, the use of commercially available *N*,*N*-diethylsalicylamide gave excellent conversion to and yield of the product (Figure 1, bar 9). Variation of the *N*,*N*-dialkyl group and the electronic character of the aromatic moiety produced ligands whose use gave similar results. Both K_3PO_4 and K_2CO_3 were found to be effective as bases; however, amine bases such as DBU or DABCO gave inferior results. The use of DMF gave the best results among the several solvents that were screened.[14]

The optimized reaction conditions, 5 mol % CuI, 20 mol % *N*,*N*-diethylsalicylamide, and 2.0 equiv of K_3PO_4 in DMF at 90 °C, were applied to the amination of a number of functionalized aryl bromides (Table 1).[15] As can be seen, the presence of a free $-NH_2$ group did not diminish the efficiency of the coupling of 3-bromoaniline with *n*-hexylamine (Table 1, entry 2). This result is important since this aryl bromide is not a good substrate using Pd-based systems. It is also interesting that the δ-amino alcohol, 4-aminobutan-1-ol, was selectively N-arylated in excellent yield (Table 1, entry 3).[8] Functional groups that are compatible with this Cu-catalyzed amination protocol include thioether, hydroxy, nitrile, keto, and nitro.[16]

The selective N-arylation of the primary amine moiety was observed when 4-aminomethylpiperidine was used as the substrate (Table 1, entry 11). No racemization of the product was observed when (*R*)-α-methylbenzylamine was used as the substrate (Table 1, entry 12).[17] In contrast to palladium-catalyzed couplings, no significant electronic effects were observed in the reaction of *para*-substituted aryl bromides.

(10) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett*. **1998**, *39*, 2933−2936. (b) Cundy, D. J.; Forsyth, S. A. *Tetrahedron Lett*. **1998**, *39*, 7979−7982. (c) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winter, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett*. **1998**, *39*, 2941−2944. (d) Lam, P. Y. S.; Deudon, S.; Hauptman, E.; Clark, C. G. *Tetrahedron Lett*. **2001**, *42*, 2427−2429. (e) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. P. *Synlett* **2000**, 674−676. (f) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett*. **1999**, *40*, 1623−1626. (g) Combs, A. P.; Tadesse, S.; Rafalski, M.; Haque, T. S.; Lam, P. Y. S. *J. Comb. Chem*. **2002**, *4*, 179−182. (h) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett*. **2002**, *43*, 3091−3094. (i) 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. (j) Sorenson, R. J. *J. Org. Chem*. **2000**, *65*, 7747−7749. (k) Arnauld, T.; Barton, D. H. R.; Doris, E. *Tetrahedron* **1997**, *53*, 4137−4144. (l) Fedorov, A. Y.; Finet, J.-P.; *Tetrahedron Lett*. **1998**, 39, 7979−7982. Lopez-Alvarado, P.; Avendano, C.; Menendez, J. C. *J. Org. Chem.* **1995**, *60*, 5678−5682.

(11) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 581−584.

(12) Hindered phenols could be used as ligands if the amine was used both as the substrate and the solvent (approximately an 8-fold excess with respect to aryl halide was used). See ref 11.

(13) *N*,*N*-Diethyl-2-methoxybenzamide, *N*,*N*-diethyl-2-aminobenzamide, and *N*,*N*-dimethylpicolinamide as ligands provided less than 1% yield (GC) of the product. We thank the referees for suggesting these control experiments.

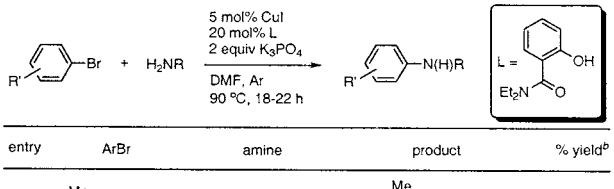
(14) GC yields of the desired product for the screening reactions using other solvents: toluene (53%), DME (69%), dioxane (79%), Et_3N (33%).

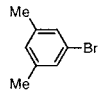
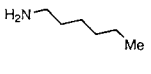
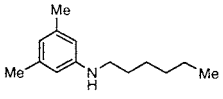
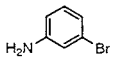
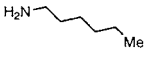
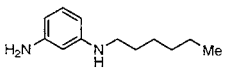
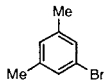
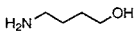
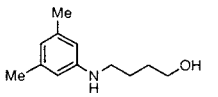
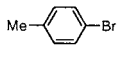
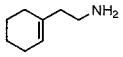
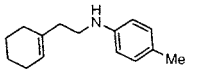
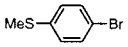
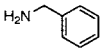
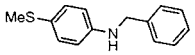
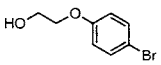
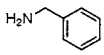
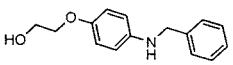
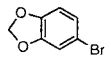
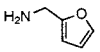
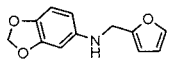
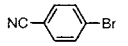
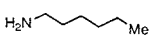
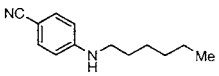
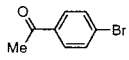
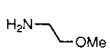
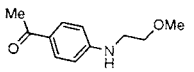
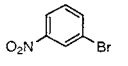
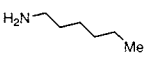
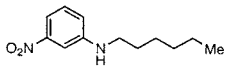
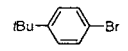
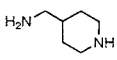
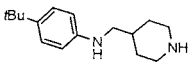
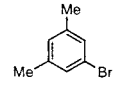
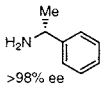
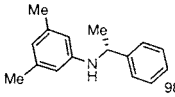
(15) Typical procedures: CuI (10 mg, 0.05 mmol), *N*,*N*-diethylsalicylamide (39 mg, 0.20 mmol), aryl bromide (if solid, 1.0 mmol), and K_3PO_4 (425 mg, 2.0 mmol) were added to a screw-capped test tube with a Teflon-lined septum. The tube was then evacuated and backfilled with argon (3 cycles). Aryl bromide (if liquid, 1.0 mmol), amine (1.5 mmol), and dry DMF (0.5 mL) were added by syringe at room temperature. The reaction mixture was stirred at 90 °C for 18−22 h. The reaction mixture was allowed to reach room temperature. Ethyl acetate (∼2 mL), water (∼10 mL), ammonium hydroxide (∼0.5 mL), and dodecane (227 μL, GC standard) were added. The organic phase was analyzed by GC or GC-MS. The reaction mixture was further extracted with ethyl acetate (4 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel to afford the desired product.

(16) For a recently described improvement in Pd-catalyzed amination of functionalized aryl halides using $LiN(TMS)_2$ as the base, see: Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 2885−2888.

(17) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 8451−8458.

Table 1. Cu-Catalyzed Amination of Aryl Bromides[a]



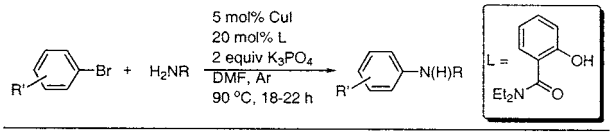
entry	ArBr	amine	product	% yield[b]
1				91
2				80
3				91
4				95
5				89
6				84
7				87
8				73
9				81
10				79
11				80
12[c]				71

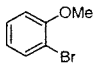
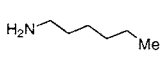
[a] Reaction conditions: CuI (0.05 mmol, 5 mol %), *N*,*N*-diethylsalicylamide (0.2 mmol, 20 mol %), ArBr (1.0 mmol), amine (1.5 mmol), and K_3PO_4 (2.0 mmol) in DMF at 90 °C under argon. [b] Isolated yield (average of two experiments). [c] Reaction temperature: 100 °C.

This newly developed Cu-catalyzed amination protocol was also applied to *ortho*-substituted and heterocyclic aryl halide substrates (Table 2). As shown, *ortho*-substituted aryl bromides often required the use of a slightly higher reaction temperature (100 °C). Heteroaryl bromides, including bromopyridine, -pyrimidine, and -benzothiophene, were efficiently transformed to the desired products in excellent yield.

Although this new protocol works well when primary amines are employed as substrates, a similar process with secondary amines has provided poor results. We are continuing work to overcome this limitation.

Table 2. Copper-Catalyzed Amination of *ortho*-Substituted and Heteroaryl Bromides[a]



entry	ArBr	amine	product	% yield[b]
1[c]				88
2				81
3[c]				79
4				92
5				91
6				85
7				85

[a] Reaction conditions: CuI (0.05 mmol, 5 mol %), *N*,*N*-diethylsalicylamide (0.2 mmol, 20 mol %), ArBr (1.0 mmol), amine (1.5 mmol), and K_3PO_4 (2.0 mmol) in DMF at 90 °C under argon. [b] Isolated yield (average of two experiments). [c] Reaction temperature: 100 °C.

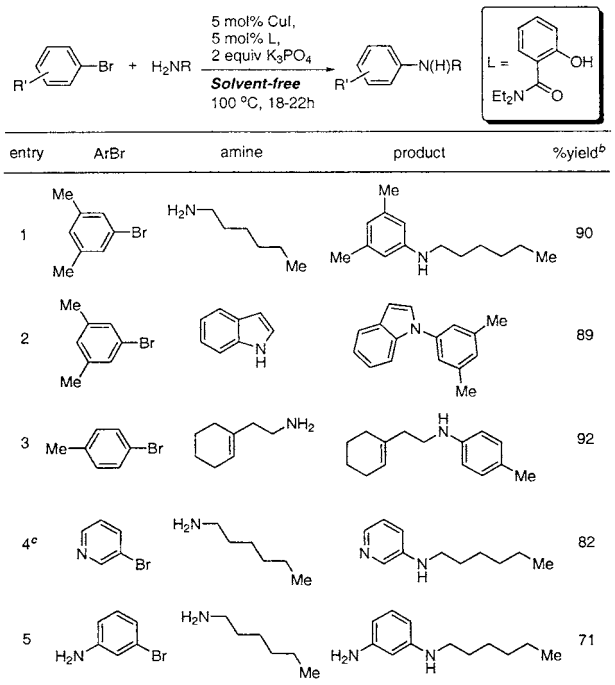
The intramolecular amination of aryl halides can also be carried out using a similar protocol under quite mild reaction conditions (Table 3).[18] Both five- and six-membered ring

Table 3. Intramolecular Copper-Catalyzed Amination of Aryl Halides[a]

entry	X	n	temp (°C)	time (h)	% yield[b]
1[c]	Br	1	35	12	88
2	Br	2	40	18	80
3[d]	Cl	1	50	48	78
4	Cl	1	100	14	74

[a] Reaction conditions: intramolecular amine-ArBr/Cl substrate (1.0 mmol), CuOAc (0.05 mmol, 5 mol %), *N*,*N*-diethylsalicylamide ligand (0.2 mmol, 20 mol %), and K_3PO_4 (2.0 mmol) in DMF at the specified temperature. [b] Isolated yield (average of two experiments). [c] Control experiment in the absence of ligand revealed a 32% conversion of ArBr and 26% GC yield of the desired product. [d] Control experiment in the absence of ligand revealed a 5% conversion of ArCl and 0% GC yield of the desired product.

Table 4. Solvent-Free Cu-Catalyzed Amination of Aryl Bromides[a]



[a] Reaction conditions: CuI (0.05 mmol, 5 mol %), *N*,*N*-diethylsalicylamide (0.05 mmol, 5 mol %), ArBr (1.0 mmol), amine (1.5 mmol), and K_3PO_4 (2.0 mmol) at 100 °C under argon (no solvent added). [b] Isolated yield (average of two experiments). [c] Reaction temperature: 90 °C.

formations can be accomplished with aryl bromide substrates at 35−40 °C (Table 3, entries 1 and 2). Even an aryl chloride can be efficiently transformed, although longer reaction times or higher reaction temperatures were required (Table 3, entries 3 and 4). That these reactions proceed under such mild reaction conditions suggests that the amino group binds to copper prior to effecting an intramolecular oxidative addition.[19]

The use of inexpensive precatalysts and a simple ligand make this reaction of potential practical utility. We sought to enhance its attractiveness further by developing solvent-free reaction conditions. We found that using 5 mol % CuI, 5 mol % ligand, and 2 equiv of K_3PO_4 at 100 °C, with the substrates being adsorbed on the combination of solid components of the reaction mixture, gave the desired products in excellent yield (Table 4).[20]

In summary, we have developed an efficient, mild, and inexpensive Cu-catalyzed coupling of primary alkylamines and aryl bromides at 90 °C that utilizes commercially available components. A variety of functional groups are compatible with these reaction conditions. Preliminary results show that this reaction can be performed under solvent-free conditions with comparable yields. Further studies of this and related Cu-salicylamide-catalyzed chemistry are in progress.

Acknowledgment. We thank the National Institutes of Health (GM 58160). Pfizer, Merck, and Bristol-Myers Squibb are acknowledged for support in the form of unrestricted funds. F.Y.K. is grateful to Croucher Foundation for a postdoctoral fellowship.

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

OL0273396

(18) CuOAc complex was used as the precatalyst since it is more soluble at lower temperatures. A lower yield of the desired product was observed when CuI complex was used as the precatalyst instead of CuOAc for the reaction shown in Table 3, entry 1.

(19) Intramolecular amination: Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231−234.

(20) Color of the solid (base, CuI, and *N*,*N*-diethylsalicylamide ligand) changed from white to green upon addition of the amine substrate at room temperature. The color of the solid then changed to brown when the reaction mixture was heated to 100 °C for <5 min. The reaction mixture maintains its appearance as a solid after heating for 18−22 h.