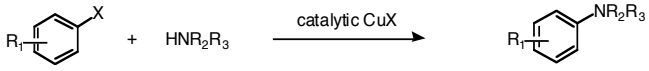
Recent Developments in Copper-Catalyzed *N*-Arylation with Aryl Halides

Carol A. Mulrooney

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, PA 19104, USA

cmulroon@sas.upenn.edu

ABSTRACT



An overview of current advancements in the copper-catalyzed *N*-arylation of aryl halides is presented. Improvements in the Ullmann condensation include the use of catalytic copper instead of stoichiometric quantities, the use of ligands to optimize yields, the tuning of selectivities to allow for the presence of a variety of functional groups, and the development of mild reaction conditions.

Aryl-nitrogen bonds are prevalent in many compounds that are of pharmaceutical and materials interest. The development of synthetic methods to form these bonds has been widely studied. The Ullmann condensation has been a powerful method for the coupling of aryl halides with amines.[1] Typically, Ullmann reactions require the use of copper metal or copper salts, base, and reaction temperatures in excess of 150 °C. Recently the palladium catalyzed aryl amination has gained attention as a synthetically powerful tool due to the lower temperatures required.[2] The drawbacks to this methodology include the cost of the reagents, the removal of trace palladium from late stage synthetic intermediates, and the difficulty of coupling electron-rich or *ortho*-substituted aryl halides. The use of catalytic copper to replace palladium is an attractive research goal for many groups.

Copper-catalyzed couplings of aryl metals such as boronic acids, stannanes, siloxanes, and other species with amines have been achieved and have been recently reviewed.[3] Couplings of aryl halides carry many advantages, including greater functional group compatibilities and the commercial availability of a wide variety of substrates. The cross-couplings of amines, amides (Goldberg reaction),[4] anilines and nitrogen heterocycles with aryl iodides, bromides, and chlorides have been achieved with high yields and mild reaction conditions. This review will highlight some of the recent examples and discuss the benefits and drawbacks of this methodology.

While investigating the synthesis of benzolactam-V8, a protein kinase C activator, Ma and co-workers developed a copper catalyzed arylation of amino acids.[5] The coupling of bromobenzene and L-valine could be achieved in 81% yield by the use of catalytic copper with K_2CO_3, in dimethyl acetamide at 90 °C for 48 hours. Other amino acids, including D-valine, L-proline, L-phenylalanine and L-methionine also coupled in greater than 70% yield. Despite the presence of base and heat, significant racemization was observed in only one substrate, a thiomethyl ether which was isolated in 71% optical purity after the coupling.

Amino acids without hydrophobic groups or with hydrophilic groups such as glycine, glutamic acid, and serine could not be coupled. Both electron rich and electron deficient aryl bromides were effective, but aryl chlorides

(1) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. Reviews: (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) Reviews: (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**; *31*, 852. (d) Hartwig, J.F. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2046. (e) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.

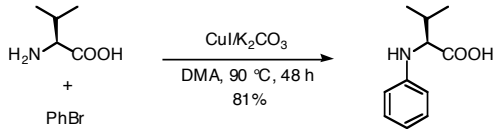
(3)Finet, J. P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597.

(4) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.

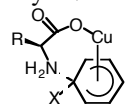
(5) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

were not. Sterically hindered aromatic rings such as 2,6-dimethylbromobenzene gave low yields (4-15%). For the optimum substrates, yields ranged from 46-92%.

Figure 1. Coupling of L-Valine with Bromobenzene.



Benzylamine coupled to bromobenzene in only 5% yield. The authors propose that the acid present in the substrate coordinated to the copper salt, which then coordinated to the aryl halide and allowed for intramolecular nucleophilic substitution to form the aryl-N bond.



Lang et al. reported a copper catalyzed aryl amination with ammonia that was milder than similar aminations previously reported.[6] Their proposed synthesis of muscarinic (M3) antagonist required a selective amination of a bromopyridine in the presence of a protected alkyl amine. Figure 2 gives the results of their optimized reaction. The bromopyridyl intermediate was treated with an 8 M solution of ammonia in ethylene glycol with catalytic Cu_2O at 100 °C in a pressure tube (100 psi) for 24 hours. An ether side product resulting from the coupling of the solvent with the bromopyridine was observed. The yield was 91%, with a 94:6 ratio of amine:ether. H_2O and MeOH were also effective solvents for the reaction, but with reduced yields (65% and 70%). This reaction was extended to a variety of bromopyridines and also to iodobenzene. Some amination products and yields of the corresponding coupling reaction (run at 80 °C for 16 hours) are listed in Table 1. Chloropyridines are not effective coupling partners, with the exception of 2-chloro-5-nitropyridine that was aminated in 85% yield with 100% selectivity.

Figure 2. Amination of a Bromopyridine.

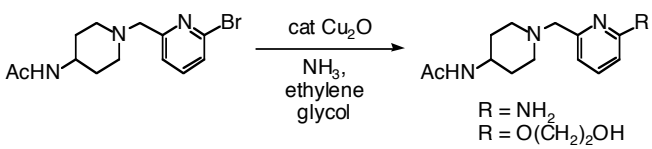
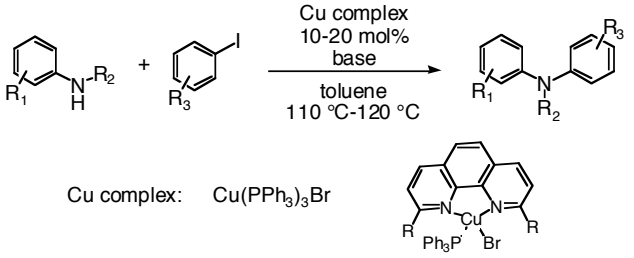


Table 1. Application of the Amination Reaction. (Figure 2.)

product	Yield (%)	Selectivity (amine:ether)
2-Aminopyridine	65	80:20
2-Amino-6-methoxypyridine	75	92:8
2-Amino-5-nitropyridine	99	100:0
3-Aminopyridine	85	95:5
4-Aminopyridine	81	97:3
4'Aminoacetophenone	65	91:9
Aniline	74	86:14

The coupling of anilines with aryl iodides has been investigated by Venkataraman and co-workers.[7] The $Cu(PPh_3)_3Br$ complex was used as catalyst with $CsCO_3$ base in toluene at 110-120 °C for 24-32 hours. Various substituted arylamines and iodides underwent reaction to form di- and triaryl substituted amines with yields from 25-88%. Another type of copper-ligand complex, $Cu(phen)(PPh_3)Br$ and its derivative $Cu(neocup)(PPh_3)Br$ were utilized by this group. The bispyridyl ligand was necessary for the coupling reaction. These copper-ligand complexes were stable to air and soluble in organic solvents. These provide an advantage over organic soluble Cu(I) salts such as CuOTf that had been applied to coupling reactions. Interestingly, the base, amine, and catalyst needed to be stirred together at 110 °C for 5 minutes before the addition of aryl bromide, or decomposition occurred. Table 2 lists examples of triarylamines synthesized by this method.

Table 2. Reactions of Arylmines with Aryl Iodides.



Cu complex: $Cu(PPh_3)_3Br$

R = H Cu(phen)(PPh3)Br
R = Me Cu(neocup)(PPh3)Br

R_1	R_2	R_3	ligand	%Yield
H	H	H	$Cu(PPh_3)_3Br$	75
H	Ph	H	$Cu(PPh_3)_3Br$	70
p-CH_3	H	H	$Cu(PPh_3)_3Br$	88
H	Ph	H	$Cu(neocup)(PPh_3)Br$	78
H	Ph	*o*-CH_3	$Cu(neocup)(PPh_3)Br$	88

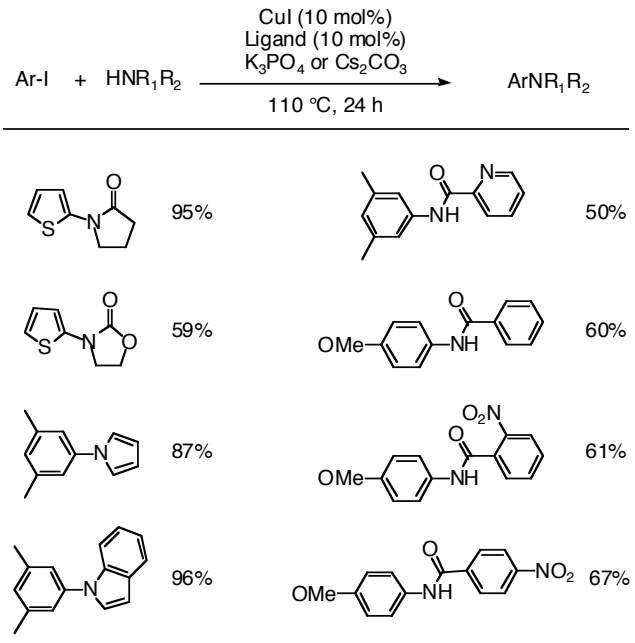
(6) Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251.

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

Further studies of the utility of ligand additives on *N*-arylation were carried out by Kang and co-workers.[8] A variety of aryl iodides were coupled with amides and nitrogen heterocycles using 10 mol% CuI with 10 mol% ethylenediamine. The base used was K_3PO_4 or $CsCO_3$, and the reactions are run in dioxane at 110 °C for 24 hours and the yields range from 41-95%. Some examples are listed in Table 3. Many of these substrates synthesized have functionalities that can coordinate to Cu(I) without affecting the reaction products.

Other ligands that were screened include 1,3-propylenediamine, TMEDA and 1,2-phenylenediamine. Yields from 61% to 94% were achieved for the coupling of 2-iodothiophene and pyrrolidinone.

Table 3. Substrates Synthesized by Kang et al.



The aryl-aryl cross-coupling of imidazoles and aryl iodides or bromides has been investigated by the Buchwald group.[9] Catalytic $Cu(OTf)_2$, $CsCO_3$, 1,10-phenanthroline and *trans,trans*-dibenzylideneacetone in refluxing xylenes couples substituted imidazoles and aryl iodides.[9a] Buchwald has since reported further significant advances in this area.[9b-d] The copper-catalyzed coupling of imidazoles, indoles, and amides with aryl halides is applicable to a wide variety of substrates with CuI, (0.2-10 mol%), a diamine ligand (*N,N'*-dimethylethylenediamine or *trans-N,N'*-dimethyl-1,2-diaminocyclohexane) and K_3PO_4, $CsCO_3$, or K_2CO_3 as base.

(8) Kang, S.-K; Kim, D.-H.; Park, J.-N. *Synlett* **2002**, 427.

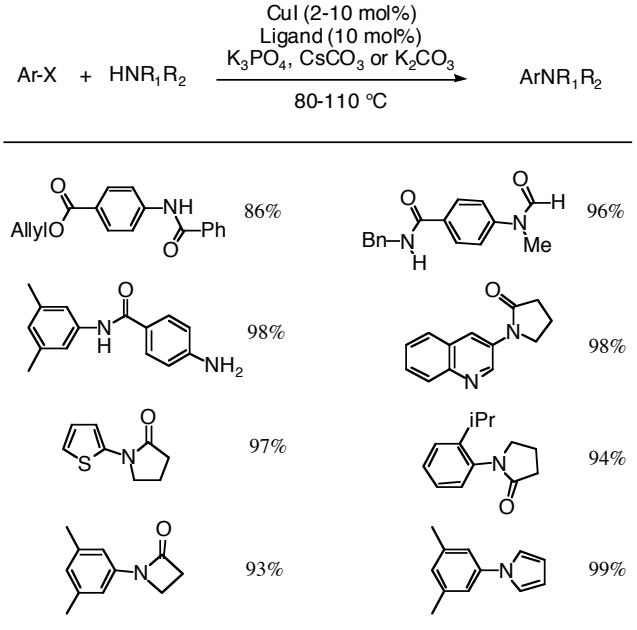
(9) (a) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett*. **1999**, *40*, 2657-2660. (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2001**, *123*, 7727. (c) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 7421. (d) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett*. **2001**, *3*, 3803.

Aryl iodides, bromides, and even some *para*-substituted aryl chlorides coupled in high yields (51-95% for aryl chloride examples). Both electron withdrawing and electron donating substituents on the aryl ring were tolerated. Primary and secondary amides were coupled in good yields with aryl iodides (ranges of 69-99% for primary amides, 63-99% for secondary). Reaction temperatures ranged from 60-110 °C, in dioxane or toluene. Benzamide coupled to 3,5-dimethyl iodobenzene at room temperature in 90% yield. Addition of water was not always detrimental; for this case, when the solvent used was THF, the addition of water gave coupling in 99% yield, presumably because of the resulting greater solubilization of the base.

The ligands and copper sources were screened, with secondary diamines and CuI giving the overall optimum yields, although CuCl and Cu_2O also gave good yields. Some substrates coupled by this protocol are listed in Table 4. Functional groups that were tolerated include alcohols, anilines, esters, and amines. Selectivity for one methyl substituted amide over a benzyl substituted amide is observed.

The advantages of this method include a greater substrate scope, lower reaction temperatures (60-110 °C), requirement of only one ligand additive, and application to amides as well as nitrogen heterocycles. A few hydrazides were coupled according to this protocol.[9d] The coupling of hydrazides to aryl halides was addressed in another study, with attention paid to the tuning of coupling for each nitrogen in the system.

Table 4. Substrates Coupled with CuI-Diamine Ligands.

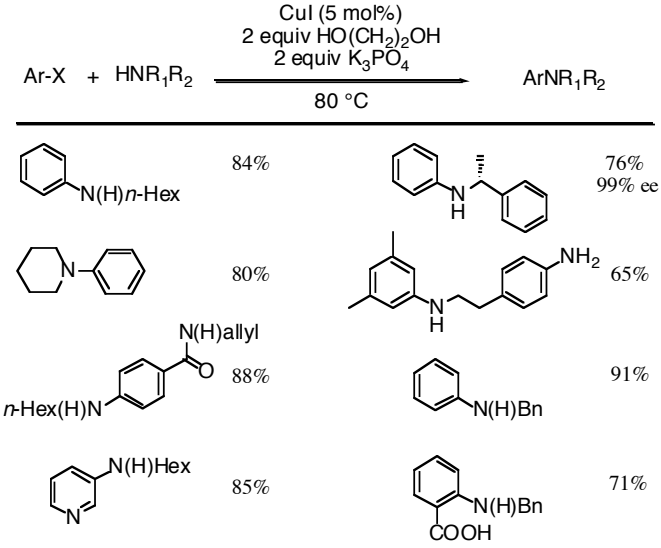


A set of *N,N'*-substituted 1,2-diaminocyclohexane ligands was also screened towards the *N*-arylation of

indoles.[10] *N,N'*-Dimethyldiamine ligands provided yields over 90%. Copper sources were also examined, with CuI and Cu (bronze) lending to the highest yields for *para*-substituted aryl bromides, however Cu (bronze) was not as effective for coupling with an *ortho*-substituted aryl bromide. Reaction conditions were similar to those previously listed, but toluene was used a solvent. The reaction was selective for arylating indoles in the presence of alkylamines, arylamines and amides. The couplings were sensitive to the presence of phenol or carboxylic acid functionalities. The selectivity of *N*-coupling over *O*-coupling was 5:1 with 5-hydroxyindole, and no coupling was observed with 4- or 2-bromobenzoic acid. The authors propose either loss of solubility of the reagent due to the polar group, or a coordination of the carboxylate anion to the copper rendering the catalyst inactive.

A copper-catalyzed coupling of alkylamines and aryl iodides was developed by using 5 mol% CuI with K_3PO_4 and ethylene glycol additive.[11] The reaction was performed in *i*PrOH at 80 °C without the need for an inert atmosphere. Again, a wide variety of functional groups including alcohols, carboxylic acids, and anilines were tolerated. Both primary and secondary amines would couple, but selectivity of coupling for primary over secondary amines was observed. Table 5 lists some examples.

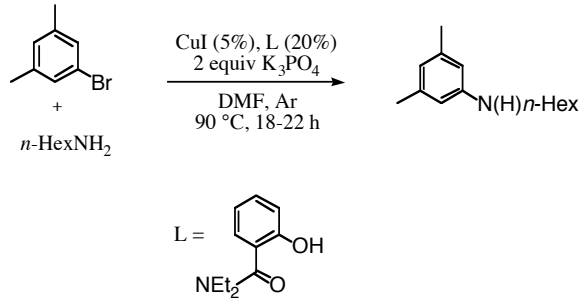
Table 5. Substrates Coupled with CuI-Ethylene Glycol.



β-Amino alcohols were coupled with this catalyst system, with good selectivities and yields for *N*-arylated products.[12] Retention of stereochemistry was observed for all chiral substrates. Selectivity could be shifted to the *O*-arylated products by changing the solvent to butyronitrile

Aryl bromides were also coupled to primary alkylamines in good yields.[13] Previous studies had been performed using ethylene glycol as ligand. This application required the use of the amine as solvent under an inert atmosphere for the reaction to proceed in good yield. A variety of alternative ligands were screened for this coupling including substituted phenol and pyridyl derivatives. The optimum ligands were found to be salicylamides (Figure 3). With diethylsalicylamide, the coupling of aryl bromides was achieved with 1.5 equivalents of amine in high yields. The reactions were run with 5 mol% CuI, 20 mol% ligand, 2 equivalents K_3PO_4 and DMF as solvent at 90 °C for 18-22 hours. *Ortho*-substituted aryl bromides and heteroaryl bromides are effective coupling partners. As in previous examples, a wide variety of functional groups are tolerated. A solvent free coupling is reported, with a mixture of 5 mol% CuI, 5 mol% ligand and 2 equivalents K_3PO_4 and the substrates heated to 100 °C for 18-22 hours. Yields of 71-92% are reported.

Figure 3. Aminations of Aryl Bromides with CuI and Salicylamide**.**



As the application of new ligands towards the Ullmann coupling progresses, the reaction temperatures have been lowered, the substrate scope has increased, and the selectivity has been fine-tuned. The copper-catalyzed aryl amination has already proven to be a general method to form carbon-nitrogen bonds and the recent achievements point toward the development of even milder reaction conditions and greater functional group compatibility. As the arylamine moiety is prevalent in so many compounds of interest, this research has a direct impact on the rapid synthesis of many new useful structures.

(10) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684.

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

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

(13) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793.