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LETTERS

# Copper-catalyzed amination of aromatic halides with 2-*N*,*N*-dimethylaminoethanol as solvent☆

Zhikuan Lu, Robert J. Twieg* and Songping D. Huang

*Department of Chemistry, Kent State University, Kent, OH 44242-0001, USA*

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**Abstract**—A copper-catalyzed amination of aromatic halides under mild conditions using *N*,*N*-dimethylaminoethanol as solvent is described. We have studied this reaction in some detail varying the copper source, base, water content and other parameters including the scope of useful amine and aromatic halide structures. A variety of 4-halo-*N*,*N*-cycloalkylanilines and 2-*N*,*N*-cycloalkylaminothiophenes were synthesized for further elaboration into chromophores for optoelectronic applications.

Transition metal-catalyzed aryl amination has been extensively explored in recent years.[1–3] Many of these studies have involved palladium, but copper catalysis has also been pursued due to potential cost advantages.[4] Often the traditional copper-mediated Ullmann condensation has limitations due to the high reaction temperatures required.[5] Mild amination conditions have been reported with arylboronic acids,[6] hypervalent aryl siloxanes,[7] aryllead triacetates,[8] triphenylbismuth derivatives[9] and arylstannanes.[10] The direct amination of aromatic halides is highly desirable due to their ready availability. Venkataraman reported a mild aryl-nitrogen, aryl-oxygen, and aryl-carbon bond formation from aryl halides catalyzed by a predefined copper based catalyst.[11] Buchwald has described a mild copper catalyzed amination reaction with ethylene glycol as ligand.[12] However, more work still needs to be done to find new ligands and to expand the scope of the substrates and reactions that may be catalyzed by copper species. We herein report a mild and practical copper-catalyzed amination in *N*,*N*-dimethylaminoethanol. This method has been successfully applied to some heterocycles such as 2-iodo or 2-bromothiophene and difunctional molecules such as 1,4-diiodobenzene.

The enhancement of Ullmann condensations by ligands such as crown ethers and ethylene oxide oligomers is well known.[13,14] One goal is to increase solubility of the copper species so the reaction can be carried out in a more homogeneous environment.[15] In contrast to palladium catalysts, phosphines were only occasionally used as ligands for copper catalysts.[16] Three main types of bidentate ligands with nitrogen and/or oxygen as copper chelating atoms have been explored. First are the nitrogen-containing ligands: 1,10-phenanthroline, 2,2-dipyridyl, and other diamine complexes that were explored for formation of amines, ethers, sulfones and aryl sulfides.[11,17–20] Second are the oxygen-coordinated ligands: diester impurities in the diglyme reaction solvent enhance copper-catalyzed aryl ether formation,[21,22] carboxylic acid,[23] 2,2,6,6-tetramethylheptane-3,5-dione,[24] diol,[12] and even ethyl acetate and 2-phenylphenol were found to accelerate such reactions.[25,26] Third, the use of ligands with mixed nitrogen/oxygen sites are more rare.[27] In the Ullmann ether condensation, 8-hydroxyquinoline and some of its derivatives were effective and 2-dimethylaminomethyl-3-hydroxypyridine was significantly more efficient than parent 3-hydroxypyridine.[4] The reactivity of some functionalized amines is enhanced relative to simple parent amines. Hida and co-workers found that the Ullmann condensation of bromoanthroquinone with 2-aminoethanol was much faster than with simple aliphatic amines such as butylamine.[28] But, Ma found that coupling reaction of (*S*)-valinol with bromobenzene only afforded 5% conversion at 110°C after 32 h using DMA as solvent and $K_2CO_3$ as base.[29] Buchwald recently investigated selective *N*-aryl and *O*-aryl reactions of β-amino alcohols as reactants with different solvents and bases.[30] While diamines and diols have been explored as acceleration ligands for copper-catalyzed amination, to our knowledge amino alcohols have

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* Corresponding author. Tel.: +1-330-672-2791; fax: +1-330-672-3816; e-mail: rtwieg@lci.kent.edu

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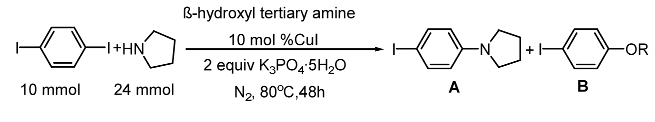
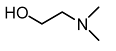
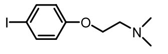
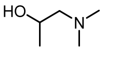
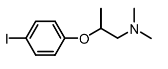
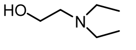
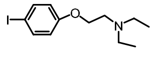
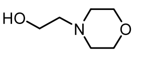
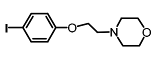
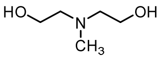
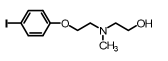
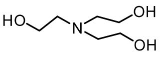
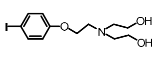
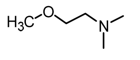
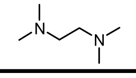
only been used as reactants and their use as ligands has not been systematically explored for this type of amination reaction outside of mention in the patent literature.[27] Here, we demonstrate that some amino alcohols also serve as accelerating ligands for copper catalyzed aminations.

The use of amino alcohol ligands with primary or secondary amine functional groups are complicated by the possibility of formation of ether and amine products so we have concentrated on the utility of amino alcohols with tertiary amine functionality. A variety of β-hydroxy substituted tertiary amines were examined as ligands and solvents for amination of 1,4-diiodobenzene with pyrrolidine. While 1,4-diiodobenzene is not an ideal substrate for this study due to its bifunctionality, we were interested in these specific products and we decided to continue our exploration using it. Table 1 summarizes an evaluation of 2-aminoethanol derivatives as ligands.

From this survey (Table 1) we identified 2-*N*,*N*-dimethylaminoethanol (deanol) as the most effective solvent. Many copper salts are completely dissolved in deanol and this is very favorable to the catalytic reaction. The common pyrrolidine *N*-arylation product and the specific *O*-arylation byproducts (derived from competing reaction at the alcohol of the different solvents) were separated and characterized. Although the reactions were not carried out under individually optimized conditions, it is clear that deanol gave the best results relative to the other β-hydroxylamines examined. The number of hydroxyl groups is not the main cause of the different ratio of aryl ether byproducts. Instead, any bulky ligands coordinated to the relatively small copper ion prevent access of the amine to the catalytically active copper center. The amine parts of monohydroxy amines *N*,*N*-diethylethanolamine (entry 3) and 4-morpholinoethanol (entry 4) are larger than that found in deanol. When these aminoalcohols were used as solvent the aryl ethers were the major products and the catalytic activity is much less than that of deanol. To our surprise, aminoether *N*,*N*-dimethyl-2-methoxy-ethylamine (entry 7) has no accelerating effect and the diamine TMEDA (entry 8), which was previously utilized as a ligand for arylboronic acid amination, is not an effective ligand.[6] A control reaction using triethylamine and ethanol was carried out under the same conditions and only a trace of the desired amination product was obtained.

**Table 1.** β-Hydroxy tertiary amine solvents examined for amination of 1,4-diiodobenzene with pyrrolidine



| *entry* | *β-hydroxyl amine* | *yield of **A** (%)* | *aryl ether product* | *yield of **B** (%)* |
|---|---|---|---|---|
| 1[a] |  | 73 |  | 8.2 |
| 2[a] |  | 53 |  | 27 |
| 3[a] |  | 14 |  | 66 |
| 4[b] |  | 8.8 |  | 38 |
| 5[b] |  | 19 |  | 72 |
| 6[b] |  | 9.0 |  | 74 |
| 7[b] |  | < 3 | N/A | - |
| 8[b] |  | < 3 | N/A | - |

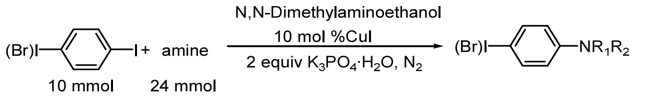
a. Isolated yield, 10mmol scale. b. Run on 1 mmol scale. GC yield, products were separated and characterized

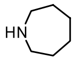
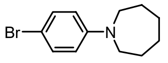
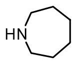
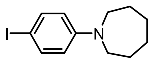
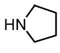
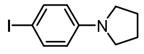
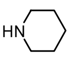
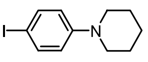
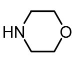
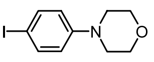
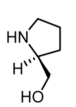
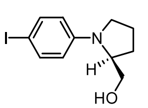
Potassium phosphate is the most effective base amongst those examined for this reaction. The amination rates are influenced by the water content in the reaction system in a complicated way: reactions with thoroughly dried base were sluggish, addition of even a trace of water (up to 2 equiv.) to the anhydrous reaction system gave the fastest reaction rate but additional water seems to decrease the reaction rate. However, while the reaction rate decreased at higher water concentration ($K_3PO_4·5H_2O$) the ether-forming side reactions were also suppressed. Other factors, such as the exact sources and particle size of the $K_3PO_4$ hydrates did not seem to play a major role in the reaction.[18] The $K_3PO_4$ monohydrate is the most active commercial available base amongst all the bases examined. Other bases such as anhydrous $K_2CO_3$, KOH and triethylamine were ineffective in this system.

Copper metal, copper(I) oxide and copper salts are often utilized for Ullmann condensation.[31,32] Since the copper metal catalyzed 'homogeneous' reactions generally proceed 'very slowly',[15] copper salts were used in the recently developed ligand accelerated mild amination reactions.[1,12] This study reveals that copper metal is often the best catalyst precursor (affording the best amination yield and the least byproducts). Another advantage of Cu metal is that the reaction flask was simply sealed with a septum and kept under a nitrogen positive pressure. When the reaction is worked up, there is no Cu(0) left in the reaction system in most cases. Many copper salts are also effective catalyst precursors for the these amination reactions including CuI, CuCl, CuBr, $Cu(OAc)_2$, $CuCl_2$, $CuBr_2$, $Cu_2(OH)_2CO_3$, $Cu_2O$ and $CuSO_4$ but not CuO. It should be noted that while metallic copper catalyst combined with $K_3PO_4·H_2O$ often affords the best results, some earlier examples presented here involve other catalysts or bases.

The reactions of dihalobenzenes with a variety of cyclic amines are shown in Table 2.[†] We tried to distinguish the two halogens in 1,4-dihalobenzene so as to retain an active halide site for later synthetic manipulation. The amination of 1,4-diiodobenzene with hexamethyleneimine provided almost the same result as with 4-bromoiodobenzene although now up to 10% of diamination product resulted. Later reactions were run only on 1,4-diiodobenzene. The reaction temperatures were varied depending on the specific aryl halide and amine. The halide remaining in the monoaminated product was deactivated by the *para* amino group but it can be converted to either amino or the deanol ether functionality with more forcing conditions. In order to obtain an optimal yield of monoamination product the stoichiometry, temperature and time must be adjusted and the reaction progress must be monitored. Usually, the reaction should be terminated when the conversion of diiodobenzene was >97% as further reaction will only increase the amount of byproducts. The isolated yield of the monoamination product from 1,4-diiodobenzene is lower than that of the corresponding monoiodide amination reactions (entry 4 in Table 2 and entry 11 in Table 3). Pyrrolidine afforded the best results amongst the cyclic amines examined. Reaction at 45°C, 24 h gave 3.7% *O*-arylation, 71.4% monoamination and 6.5% diamination. Longer reaction times

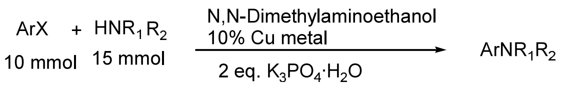
**Table 2.** Copper-catalyzed amination of dihalobenzenes with cyclic amines in deanol

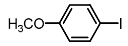
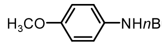
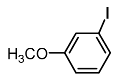
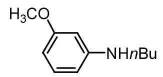
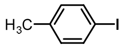
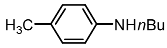
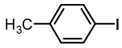
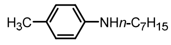
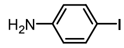
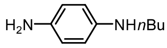
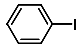
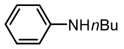
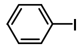
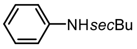
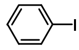
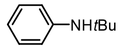
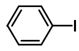
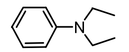
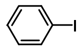
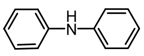
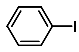
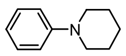
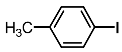
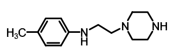
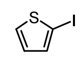
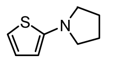
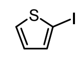
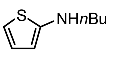
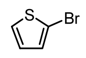
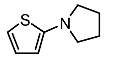
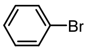
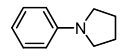
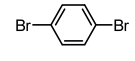
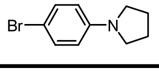


| entry | amine | products | reaction temp. and time(°C/h) | yield (%)[a] |
|---|---|---|---|---|
| 1 |  |  | 60/40 | 47 |
| 2 |  |  | 50/48 | 50 |
| 3 |  |  | 45/20 | 78 |
| 4 |  |  | 45/40 | 68 |
| 5 |  |  | 55/36 | 54 |
| 6[b] |  |  | r.t /48 | 34 |
| | | | r.t/20 then 40/28 | 49 |

a. Isolated yield. b. ratio of $p$-$C_6H_4I_2$:amine is 2:1 for this reaction.

**Table 3.** Copper-catalyzed amination reactions with a variety of amines and aryl halides with deanol as solvent



| entry | ArX | products | reaction temp. and time(°C/h) | yield (%)[a] |
|---|---|---|---|---|
| 1 |  |  | 70/9 | 87 |
| 2 |  |  | 70/9 | 89 |
| 3 |  |  | 60/12 | 93 |
| 4 |  |  | 60/40 | 88 |
| 5 |  |  | 85/11 | 66 |
| 6 |  |  | 70/14 | 94 |
| 7 |  |  | 80/26 | 68 |
| 8 |  |  | 90/48 | 3[b] |
| 9 |  |  | 90/48 | 2[b] |
| 10 |  |  | 80/38 | 30 |
| 11 |  |  | 75/30 | 72 |
| 12 |  |  | 75/30 | 84 |
| 13 |  |  | 60/11 | 91 |
| 14 |  |  | 60/11 | 62 |
| 15 |  |  | 80/49 | 81[c] |
| 16 |  |  | 80/48 | 61 |
| 17 |  |  | 80/48 | 28 |

a. Isolated yield. b. Most of the missing yield was the aryl ether of deanol or unreacted starting material. c. Scale was 160 mmol.

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[†] **General procedure**: The aromatic halide (10 mmol), amine (15–24 mmol), Cu metal or CuI (10% mol), $K_3PO_4 \cdot H_2O$ (20 mmol) and deanol (10 ml) were placed in a round-bottom flask fitted with a magnetic stir bar, condenser and sealed with a septum. For the CuI catalyst, the flask was cooled, evacuated and backfilled with nitrogen. For the Cu metal catalyst, the system was simply sealed with a septum and kept the reaction under nitrogen positive pressure. The reaction mixture was stirred at the temperature and time indicated in the tables. After the reaction was cooled to room temperature 100 ml of water was added and the organic products extracted with diethyl ether or ethyl acetate (3×100 ml). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel to afford the products. Note: For entries 13, 14 and 15 in Table 3, the products are unstable on silica gel and were further purified by Kugelrohr distillation.

increased the conversion of starting material but the byproduct(s) ratios increased accordingly.

The reaction conditions for a variety of haloaromatics and amines with 10% copper metal catalyst, $K_3PO_4 \cdot H_2O$ base and deanol solvent are listed in Table 3. About 1–5% of the ether byproducts of deanol were detected for less sterically hindered substrates. Primary aliphatic amines and small cyclic secondary amines were readily coupled with unhindered aryl iodides. Acyclic secondary amines worked poorly (entry 9) and substrates containing both primary and secondary amines gave predominant reaction at the primary site (entry 12). Increasing the hindrance of the primary butyl amines led to a decrease in amination yield (entries 6, 7, 8). Aniline is not a good substrate as it afforded only 30% of amination product (entry 10). Amination of the heterocycle 2-iodothiophene with pyrrolidine afforded an excellent yield (entry 13) and a good yield with *n*-butylamine (entry 14).[33] Notably, palladium-mediated amination of 2-halothiophenes with primary amines was not successful due to diarylation[34] or poor yield.[35] A very good yield was also obtained from the Cu mediated amination of 2-bromothiophene with pyrrolidine on a 160 mmol scale (entry 15, an important result as such aminothiophenes are useful in optoelectronic materials).[36] For bromides, selectivity between the amine and ether products was generally lower than for the comparable iodide. For instance, in the reaction of bromobenzene with pyrrolidine only a 61% isolated yield of the amine adduct was obtained and the selectivity between C–N and C–O is about 3:1 when the reaction temperature is 80°C. Reaction of 1,4-dibromobenzene with pyrrolidine gave only 28% yield of the monoaminated product. If more forcing conditions were applied none of the products dominated.

We have demonstrated deanol is an alternative solvent and copper metal is a useful catalyst precursor for amination of aromatic halides. Non-hindered primary amines are the most reactive while acyclic secondary amines are very unreactive so that it is possible to differentiate them. This process has been successfully applied to some heterocycles such as 2-iodo or 2-bromothiophene and difunctional molecules such as 1,4-diiodobenzene.

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