# A Simple Access to Symmetric Diarylamines via Copper(II)-catalyzed Coupling of Aqueous Ammonia with Arylboronic Acids

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A simple and efficient $Cu^{II}$-catalyzed coupling reaction of arylboronic acids with aqueous ammonia under air is described. The reaction was conducted under atmospheric pressure and no additional ligand was required. Benzoic acid was added to tune the basicity of the reaction system.

Direct access to aryl amines from ammonia is attractive not only because ammonia is one of the cheapest and most abundant nitrogen sources in chemical synthesis,[1] but also because aryl amines are useful intermediates in the pharmaceutical, agrochemical, and polymer industries.[2] However, examples of employing ammonia in such transformation have rarely been reported[3] which is at least partly due to the high N–H bond dissociation energy ($104 \pm 2\,\mathrm{kcal\,mol^{-1}}$).[4] Moreover, in coupling reactions, ammonia is an excellent ligand for many metals and will often bind to the metal center to form catalytically unactive species. The stability of the amido–metal complexes also inhibits the key reductive elimination to form C–N bonds.

Recently, the palladium-catalyzed amination of aryl halides with ammonia has been described by Surry and Buchwald[5a] and Shen and Hartwig[5b] in which bulky ferrocene or electron-rich phosphine ligands were used. The copper-catalyzed amination of aryl halides using ammonia was reported by Lang et al. and Thadani et al., respectively.[6] However, the reactions were performed under pressures along with a competitive C–O arylation of the ethylene glycol solvent in Lang's procedure. Very recently, a very simple copper-catalyzed coupling reaction of aqueous ammonia with aryl bromides was reported by Xia and Taillefer.[7]

Copper salts and complexes have been extensively utilized as catalysts for the Chan–Lam reaction between boronic acids and amines. However, to the best of our knowledge, the employment of aqueous ammonia in the Chan–Lam reaction has rarely been reported or studied.[8] We envisioned that the in situ formed copper(II)/$NH_3$ complex would be an efficient catalyst for such transformation. Recently, Fu described the coupling reaction of aromatic boronic and aqueous ammonia at room temperature affording primary arylamines.[9] Herein, we wish to report a simple and cheap copper(II)-catalyzed coupling reaction of aqueous ammonia with arylboronic acids, providing symmetric diarylamines in good to excellent yields.

Initial studies were conducted using aqueous ammonia (3 equiv) and phenylboronic acid (**1a**) (0.2 mmol) in 1,2-dichloroethane (DCE) as a model reaction under air in the presence of $Cu(OAc)_2 \cdot H_2O$ (20 mol %). Disappointingly, after the extensive screening of copper sources and solvents, no synthetically useful results were obtained. We realized that the distribution of the in situ formed copper species depended on the basicity of the reaction system and would have great effect on the reaction. Thus, benzoic acid was added to tune the basicity of the reaction system in a series of solvents. To our delight, in the presence of 0.5 equiv of benzoic acid, the yield increased to 50% in DCE (Table 1, Entry 1). Among the solvents tested, ethyl propionate was the best and the yield was sharply increased to 90% in the presence of 0.5 equiv of benzoic acid (Table 1, Entry 6). Trace aniline was obtained and no triaryl amines was detected under the procedure. Other acids, such as TsOH, acetic acid, and formic acid, were also efficient for such transformation and benzoic acid was the best (Table 1, Entries 6–9). Further investigations revealed that the amount of benzoic acid had a significant effect on the reaction. Several copper(II) sources were also examined, and $Cu(OAc)_2 \cdot H_2O$ turned out to be better than the others. No product was formed in the absence of $Cu^{II}$.

**Table 1.** Screening for the optimum conditions[a]

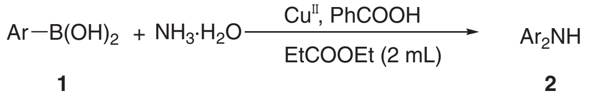
| Entry | Copper | Solvent | Acid/equiv | Yield/%[b] |
|---|---|---|---|---|
| 1 | $Cu(OAc)_2 \cdot H_2O$ | DCE | PhCOOH (0.5) | 50 |
| 2 | $Cu(OAc)_2 \cdot H_2O$ | Toluene | PhCOOH (0.5) | 60 |
| 3 | $Cu(OAc)_2 \cdot H_2O$ | THF | PhCOOH (0.5) | <5 |
| 4 | $Cu(OAc)_2 \cdot H_2O$ | $CH_3CN$ | PhCOOH (0.5) | 70 |
| 5 | $Cu(OAc)_2 \cdot H_2O$ | EtOAc | PhCOOH (0.5) | 65 |
| 6 | $Cu(OAc)_2 \cdot H_2O$ | EtCOOEt | PhCOOH (0.5) | 91 |
| 7 | $Cu(OAc)_2 \cdot H_2O$ | EtCOOEt | TsOH (0.5) | 70 |
| 8 | $Cu(OAc)_2 \cdot H_2O$ | EtCOOEt | HOAc (0.5) | 66 |
| 9 | $Cu(OAc)_2 \cdot H_2O$ | EtCOOEt | HCOOH (0.5) | 60 |
| 10 | $Cu(OAc)_2 \cdot H_2O$ | EtCOOEt | — | 24 |
| 11 | $Cu(OAc)_2 \cdot H_2O$ | EtCOOEt | PhCOOH (0.1) | 67 |
| 12 | $Cu(OAc)_2 \cdot H_2O$ | EtCOOEt | PhCOOH (2.0) | 69 |
| 13 | $Cu(OAc)_2 \cdot H_2O$ | EtCOOEt | PhCOOH (3.0) | 61 |
| 14 | $CuSO_4$ | EtCOOEt | PhCOOH (0.5) | 76 |
| 15 | $CuBr_2$ | EtCOOEt | PhCOOH (0.5) | 75 |
| 16 | CuO | $EtCOOEt_2$ | PhCOOH (0.5) | 29 |
| 17 | $Cu(OTf)_2$ | EtCOOEt | PhCOOH (0.5) | 84 |
| 18 | $CuF_2$ | EtCOOEt | PhCOOH (0.5) | 73 |
| 19 | — | EtCOOEt | PhCOOH (0.5) | <5 |

[a]All reactions were run with phenylboronic acid (**1a**) (0.2 mmol), $NH_3 \cdot H_2O$ (0.6 mmol), copper (20 mol %), indicated acid, EtCOOEt (2 mL), 80 °C, 24 h. [b]Isolated yields.

With the optimized conditions in hand, we turned our attention to study the substrate scope. The results are summarized in Table 2.

As expected, a series of arylboronic acids ran smoothly under the reaction conditions. Arylboronic acids possessing electron-donating groups delivered symmetric diaryl amines in good to excellent yields. For example, **2b**, **2c**, **2d**, and **2e** were isolated in 85, 75, 85, and 70% yields, respectively (Table 2, Entries 1–4). However, arylboronic acids possessing electron-withdrawing groups provided the products in lower yields, and primary amines were found to some extent. Fortunately, the yields for the arylboronic acids possessing electron-withdrawing

**Table 2.** Reaction of arylboronic acids with aqueous ammonia[a]



$$\underset{\mathbf{1}}{Ar{-}B(OH)_2} + NH_3{\cdot}H_2O \xrightarrow[\text{EtCOOEt (2 mL)}]{Cu^{II},\ PhCOOH} \underset{\mathbf{2}}{Ar_2NH}$$

| Entry | Ar | Product | Yield/%[b] |
|---|---|---|---|
| 1 | 4-$MeC_6H_4$– (**1b**) | **2b** | 85 |
| 2 | 3-$MeC_6H_4$– (**1c**) | **2c** | 75 |
| 3 | 3,5-di-$MeC_6H_3$– (**1d**) | **2d** | 85 |
| 4 | 4-$MeOC_6H_4$– (**1e**) | **2e** | 70 |
| 5 | 3-$MeOC_6H_4$– (**1f**) | **2f** | 57 |
| 6 | 4-$ClC_6H_4$– (**1g**) | **2g** | 80 |
| 7 | 4-$FC_6H_4$– (**1h**) | **2h** | 65 |
| 8 | 3-$CF_3$–$C_6H_4$– (**1i**) | **2i** | 60 |

[a] Reaction conditions: arylboronic acid (0.2 mmol), $NH_3{\cdot}H_2O$ (0.6 mmol), $Cu(OAc)_2{\cdot}H_2O$ (8 mg, 20 mol %), benzoic acid (12 mg, 0.1 mmol), EtCOOEt (2 mL). 80 °C, 24 h; Entries 6–8: $NH_3{\cdot}H_2O$ (0.4 mmol), $Cu(OTf)_2$ (7 mg, 10 mol %), benzoic acid (24 mg, 0.2 mmol). [b] Isolated yields.

groups were dramatically increased with the combination of $Cu(OTf)_2$ (10 mol %), aqueous ammonia (2 equiv), and benzoic acid (1 equiv). For example, bis(4-chlorophenyl)amine (**2g**) was formed in 80% yield (Table 2, Entry 6). Increasing the amount of $Cu(OTf)_2$ had little effect on the reaction. The procedure tolerated functional groups, such as methoxy, chloro, fluoro, and trifluoromethyl groups. It is worth noting that the in situ formed copper(II)/$NH_3$ complex is an efficient catalyst in our procedure, which obviates the use of expensive and air- and/or moisture-sensitive ligand. To the best of our knowledge, the present method is the simplest approach to diarylamines. However, the feasibility of monoarylation of aqueous ammonia failed since the arylamines are more reactive than ammonia.

Notably, the reaction was carried out at nearly atmosphere pressure, which permits the use of a common glass reactor. The benzoic acid may play a dual role in our reaction system. One is to tune the basicity of the reaction system. The other is to form a buffering system ($NH_4^+/NH_3$) to avoid dramatic change of basicity during the reaction.

In summary, we have successfully developed a simple and facile copper(II)-catalyzed coupling reaction of arylboronic acids with aqueous ammonia, providing the symmetric diarylamines in one-pot. The reaction was performed under atmosphere pressure and no additional ligand was required. It represents a practical method for the synthesis of symmetric diarylamines.[10]

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