Copper-Mediated Aryl Amination: In Situ Generation of an Active Copper(I) Species

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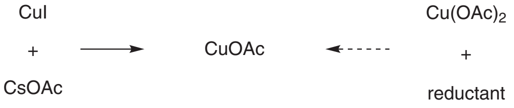
Abstract: We have developed novel conditions for copper-mediated aryl amination by using a combination of easy-to-handle and inexpensive $Cu(OAc)_2 \cdot H_2O$ and phenylhydrazine.

Key words: amine, aryl amination, copper, phenylhydrazine, reductant

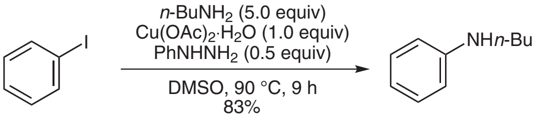
Aryl aminations have received considerable attention by synthetic community in recent years because aromatic C–N bonds are constituents of many biologically active compounds.[1] While the Ullmann–Goldberg reaction is a classic method of aryl amination,[2] the harsh reaction conditions tend to preclude its applications to the synthesis of complex molecules. To overcome this drawback, Buchwald,[3–5] Hartwig,[6] and Ma[7] have independently developed palladium- or copper-mediated aryl amination reactions, which could be performed under mild conditions and thus broaden the substrate scope. More recently, a novel amination reaction catalyzed by CuI and CsOAc has been developed in our laboratory.[8] This copper-mediated reaction is so mild that a wide range of functional groups are shown to survive especially in the case of intramolecular reactions.[9] In this paper, we describe the development of an alternative method for copper-mediated aryl aminations using $Cu(OAc)_2 \cdot H_2O$.

In our previous report, we described that the active copper species was considered to be CuOAc generated in situ by exchange between CuI and CsOAc (Scheme 1). Because CuOAc is expensive and too hygroscopic and air sensitive to be handled in air, it was more practical to use the combination of CuI and CsOAc. We envisioned that CuOAc could also be generated by reduction of $Cu(OAc)_2$, which is much easier to handle in air.



Scheme 1 Generation of copper(I) acetate

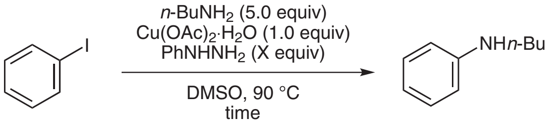
Based on this hypothesis, the amination reaction using $Cu(OAc)_2 \cdot H_2O$ was attempted. In the event, iodobenzene was treated with five equivalents of *n*-butylamine in the presence of a copper reagent, which was generated in situ by treatment of one equivalent of $Cu(OAc)_2 \cdot H_2O$ in DMSO with 0.5 equivalent of phenylhydrazine (Scheme 2).[10] The reaction proceeded efficiently by heating at 90 °C for nine hours to afford the corresponding aniline in 83% yield. This result was comparable to yields achieved by using our previous procedure.[8]



Scheme 2 Aryl amination using a copper reagent generated in situ by reduction of $Cu(OAc)_2$ with phenylhydrazine

The effect of the amount of phenylhydrazine on this transformation was evaluated (Table 1). Unexpectedly, the reaction proceeded to afford the desired product in the absence of phenylhydrazine.[11,12] Nevertheless, the reaction was clearly accelerated by addition of phenylhydrazine. Addition of phenylhydrazine in quantities greater than 0.50 molar equivalent did not further accelerate the reaction rate but instead caused the undesired formation of azobenzene. This by-product was presumably produced by aryl amination of iodobenzene with phenylhydrazine, followed by oxidation of the resultant 1,2-diphenylhydrazine by copper(II) acetate. These results would indirectly support the evidence that a copper(I) species was generated under these conditions.

Table 1 Effect of Phenylhydrazine



X	Time (min)	Ratio (PhI/PhNHBu)[a]
0	40	1:0.25
0.25	40	1:5
0.50	40	1:49
0.50	20	1:23
0.75	20	1:70[b]
1.00	20	1:50[b]

[a] Determined by ^1H NMR.
[b] Formation of azobenzene was observed.

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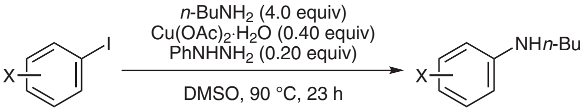
After extensive investigation, we found that catalyst loading could be reduced to 40 mol% without affecting the yields of the desired product. The optimal conditions were found to include use of 4.0 equivalents of amine, 0.4 equivalent of $Cu(OAc)_2 \cdot H_2O$, and 0.2 equivalent of phenylhydrazine.[13]

We next investigated the scope of the reaction by examining a variety of iodobenzenes (Table 2). It was found that *m*- or *p*-substituted iodobenzenes bearing either electron-withdrawing or electron-donating substituent groups were suitable substrates to give the corresponding disubstituted anilines in moderate to good yields. On the other hand, *o*-substituted iodobenzenes gave the corresponding anilines in low yield. Selective monoamination reactions were possible when *m*- or *p*-diiodobenzene was used. These tendencies were similar to those described in our previous report.[8a–c]

Table 2 Substitution Effects on the Aryl Amination

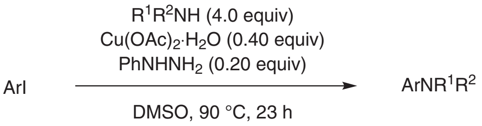


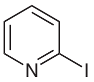
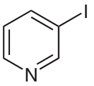
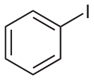
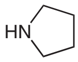
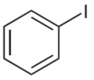
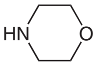
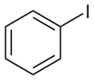
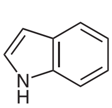
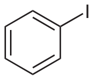
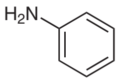
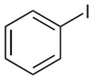
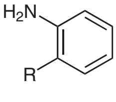
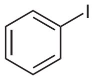
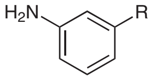
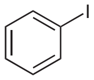
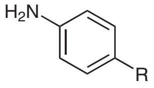
Entry	X	Yield (%)[a]	Reported yield (%)[b]
1	*o*-NO_2	20	78
2	*m*-NO_2	66	95
3	*p*-NO_2	94	99
4	*o*-Me	30	21
5	*m*-Me	93	99
6	*p*-Me	74	86
7	*o*-OMe	26	49
8	*m*-OMe	87	89
9	*p*-OMe	50	84
10	*m*-I	52	50
11	*p*-I	64	76
12	*o*-F	17	37

[a] Isolated yields unless otherwise noted.
[b] See ref. 8.

We next examined the generality of the amination reaction by evaluating a variety of aryl iodides and amines (Table 3). It was found that 2- and 3-iodopyridine were suitable substrates for the amination. While acyclic secondary amines such as diethylamine afforded the corresponding products in trace amounts, cyclic secondary amines gave the corresponding anilines in moderate yields. In the case of aniline or indole, these conditions appeared to be less effective, providing low yields of the products.

Table 3 Aryl Amination of Various Substrates



ArI	R^1R^2NH	Yield (%)[a]	Reported yield (%)[b]
	*n*-$BuNH_2$	88	70
	*n*-$BuNH_2$	84	96
		71	68
		34	73
		28	68
		24	24
		R = OMe; 26 R = NO_2; 20	44 63
		R = OMe; 27 R = NO_2; 13	4 12
		R = OMe; 31 R = NO_2; 16	38 64

[a] Isolated yield.
[b] See ref. 8.

In summary, we have developed novel conditions for the copper-mediated aryl amination by combining easy-to-handle and inexpensive $Cu(OAc)_2 \cdot H_2O$ and phenylhydrazine. Although the yields are generally lower than the previous conditions, this work provides an alternative method for aryl aminations.

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(11) We reported that the aryl amination reaction with $Cu(OAc)_2$ did not proceed in DMF (ref. 8). DMSO might work as a reductant under these conditions.

(12) A possibility that amines might work as a reductant has been reported: Qin, W.; Kakusawa, N.; Wu, Y.; Yasuike, S.; Kurita, J. *Chem. Pharm. Bull.* **2009**, *57*, 436.

(13) **Typical Procedure**: A solution of copper(II) acetate monohydrate (0.40 mmol) and amine (4.0 mmol) in DMSO (1 mL) was stirred for 30 min at r.t., whereupon phenylhydrazine (0.20 mmol) was added. After stirring for 30 min, aryl iodide (1.0 mmol) was added to the solution. The reaction mixture was stirred for 30 min, and the solution was warmed to 90 °C. After stirring for 23 h at the same temperature, the solution was cooled to r.t. and diluted with EtOAc. The solution was washed with aq ammoniacal sodium chloride (3 ×). The combined aqueous layer was extracted with EtOAc (3 ×). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to give the corresponding aniline.