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Hemilabile-coordinated copper promoted amination of aryl halides with ammonia in aqueous ethylene glycol under atmosphere pressure

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Direct amination of aryl iodides and bromides with ammonia under 1 atm pressure has been effected using *in situ*-generated hemilabile coordinated copper(I) species from copper(I) halides or copper metal in aqueous ethylene glycol, producing primary aromatic amines in good yields. Ammonia pressure and water were found to accelerate the copper-mediated reaction while strong chelating ligands showed a suppression effect. A rationale for the copper-mediated amination of aryl halides with ammonia is given based on a double-face role of chelating effect. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: copper; amination; aryl halides; atmosphere pressure; water

Introduction

Copper promoted $C_{Ar}-N$ coupling (the Ullmann reaction) has been known for over a hundred years for access to secondary and tertiary aryl amines.[1–4] Recent work has further proven that many simple organic molecules, such as aliphatic diamines,[5,6] salicylamide,[7] 1,10-phenanthroline,[8,9] amino acids,[10,11] amino alcohols[12,13] and β-diketones,[14] could dramatically accelerate the copper-promoted $C_{Ar}-N$ bond forming reaction of aryl halides with organic amines or amides. However, rather undeveloped is the corresponding $C_{Ar}-N$ coupling of ammonia to produce primary aryl amines, which are key intermediates in the manufacture of a wide range of fine chemicals, such as agrochemicals, pharmaceuticals, dyes and pigments.[15,16] Traditionally, the most common way to access primary aryl amines is reduction of the corresponding nitro precursors, which have to be prepared through nitration under harsh reaction conditions, and therefore has poor compatibility with many functional groups and many difficulties in handling and disposal. Although direct amination of simple aryl halides with ammonia under high pressure has been widely used in industrial processes, it is not convenient to conduct a high pressure reaction in traditional organic chemistry laboratory without autoclaves. In fact, functionalized primary aryl amines have been accessed through transition metal-catalyzed $C_{Ar}-N$ bond forming procedures with ammonia surrogates,[17–24] followed by additional steps to unmask the resulting protected primary amines. Recently, palladium-catalyzed amination of aryl halides with ammonia or metal amide ($LiNH_2$) has been achieved through a judicious choice of complicate supporting ligands for palladium catalysts.[25–27] Although copper-catalyzed amination of aryl halides with ammonia was reported under self-generated pressure (20–100 psi) in an autoclave,[28] to the best of our knowledge, no copper-mediated amination of aryl halides with ammonia under atmosphere pressure has been disclosed. We now describe an efficient copper-mediated amination of aryl iodides and bromides with ammonia in aqueous ethylene glycol under 1 atm pressure to produce primary aryl amines.

Experimental

All reactions were conducted under N_2 atomsphere unless otherwise indicated. All the commercially available chemicals were used as received. ^{1}HNMR spectra were recorded on a Bruker 500 spectrometer using the residue of deuterated solvents as the internal standard at the Center for Analysis of ECUST.

To a 25 ml flask equipped with a drop-funnel bearing a balloon to prevent gaseous ammonia from escaping were added CuI (1.0 mmol), aryl halide (1.0 mmol), 3 ml aqueous ammonia (25–27% w/w), Cu powder (0.2 mmol) and 5 ml ammonia ethylene glycol solution (6 M). The reaction mixture was heated at given temperature and monitored by TLC and, if necessary, additional 5–8 ml ammonia ethylene glycol solution was added from time to time. Then, the mixture was cooled to room temperature, diluted with water and extracted with CH_2Cl_2. Removal of the volatiles from the combined organic phase followed by flash chromatography on silica gel afforded the desired anilines, which were characterized by comparing physical data and ^{1}HNMR with authentic samples or those reported in literature.

Results and Discussion

Amination of *p*-bromoacetophenone with ammonia was chosen as the model to explore the copper-promoted coupling of aryl

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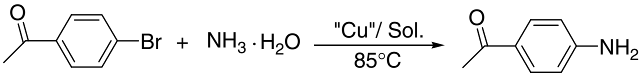
Table 1. Copper-promoted amination of *p*-bromoacetophenone with ammonia



Entry	Copper	Additive	Ammonia[a]	Solvent	Time(h)	Yield (%)[b]
1	1 equiv.CuI	3 equiv. EG	NH_3	^{i}PrOH	8	10
2	1 equiv. CuI	–	NH_3	EG	8	59
3	1 equiv. Cu	–	NH_3	EG	8	8
4	1 equiv. Cu	–	$NH_3 \cdot H_2O{-}NH_3$	EG	8	57
5	1 equiv. Cu_2O	–	$NH_3 \cdot H_2O{-}NH_3$	EG	8	50
6	1 equiv. CuI	–	$NH_3 \cdot H_2O{-}NH_3$	EG	8	77
7	1 equiv. CuI	0.2 equiv. Cu	$NH_3 \cdot H_2O{-}NH_3$	EG	8	78
8	1 equiv. CuCl	0.2 equiv. Cu	$NH_3 \cdot H_2O{-}NH_3$	EG	8	79
9	1 equiv. $CuCl_2$	0.2 equiv. Cu	$NH_3 \cdot H_2O{-}NH_3$	EG	8	50
10	1 equiv. CuI	0.2 equiv. Cu	$NH_3 \cdot H_2O{-}NH_3$	DMF	8	27
11	1 equiv. CuI	0.2 equiv. Cu	$NH_3 \cdot H_2O{-}NH_3$	ME	8	56
12	1 equiv. CuI	0.2 equiv. Cu	$NH_3 \cdot H_2O{-}NH_3$	DME	8	25
13	1 equiv. CuI	1 equiv. Cu	$NH_3 \cdot H_2O{-}NH_3$	EG	8	82
14	0.5 equiv. CuI	0.5 equiv. Cu	$NH_3 \cdot H_2O{-}NH_3$	EG	8	65
15	0.2 equiv. Cu	–	$NH_3 \cdot H_2O{-}NH_3$	EG	36	56
16	0.2 equiv. CuI	–	$NH_3 \cdot H_2O{-}NH_3$	EG	36	27
17	0.2 equiv. CuCl	–	$NH_3 \cdot H_2O{-}NH_3$	EG	40	54
18	0.2 equiv. Cu	0.2 equiv. TCA	$NH_3 \cdot H_2O{-}NH_3$	EG	36	20
19	0.2 equiv. Cu	0.2 equiv. CAT	$NH_3 \cdot H_2O{-}NH_3$	EG	24	26
20	0.2 equiv. Cu	0.2 equiv. Leu	$NH_3 \cdot H_2O{-}NH_3$	EG	36	40
21	0.2 equiv. CuI	H_2O[c]	NH_3[d]	EG	12	65
22	0.2 equiv. Cu	H_2O[c]	NH_3[d]	EG	12	70
23	0.2 equiv. Cu	H_2O[c]	NH_3[e]	EG	12	86

[a] Ammonia solution (*ca* 6 M) in EG for NH_3 and 25–27% aqueous solution for $NH_3 \cdot H_2O{-}NH_3$.
[b] Isolated yield (%).
[c] 30% volume to EG added.
[d] 3–4 atm in autoclave.
[e] 10–12 atm pressure in autoclave.

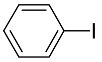
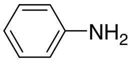
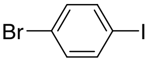
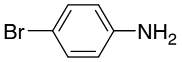
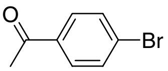
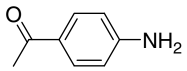
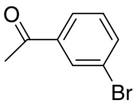
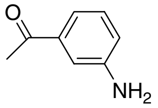
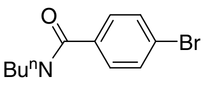
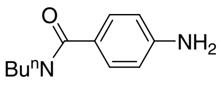
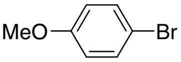
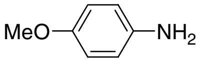
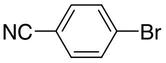
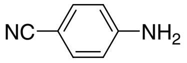
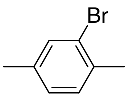
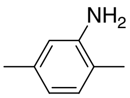
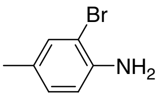
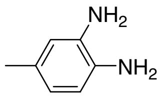
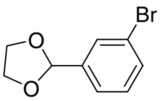
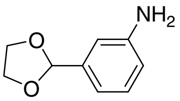
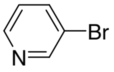
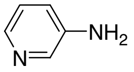
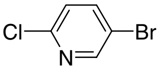
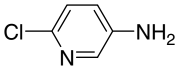
halides with ammonia considering easy monitoring and handling of the reaction (Table 1). It was reported that ethylene glycol (EG) could serve as an efficient supporting ligand for copper to catalyze amination of aryl halides with organic primary amines in isopropanol.[29] Therefore, the model reaction was initially conducted with 0.1 equiv. copper(I) iodide/0.3 equiv. ethylene glycol as catalyst in ^{i}PrOH under 1 atm pressure of gaseous ammonia under refluxing. Almost no reaction was detected by TLC in 8 h. However, the desired amination product *p*-aminoacetophenone could be isolated albeit in low yield (10%) when 1.0 equiv. CuI/3.0 equiv. EG was used. The yield further increased to 59% if the reaction was run in EG instead of ^{i}PrOH at 85 °C (Table 1, entries 1 and 2). A minor amount (*ca* 4%) of aryl ether, 4′-(2-hydroxyethoxyl)acetophenone, was also isolated due to the participation of ethylene glycol in the reaction. A poor yield (8%) was obtained in the amination of *p*-bromoacetophenone using copper powder in placement of CuI. Surprisingly, when some water or aqueous ammonia (3 ml) was added to the reaction mixture of ammonia solution in ethylene glycol (10 ml), the yields of *p*-aminoacetophenone significantly increased to 57 and 77% in the reactions using copper metal and copper iodide, respectively (Table 1, entries 4 and 6).[30] Interestingly, a cleaner reaction was observed by using a combination of copper iodide (1.0 equiv.) and metal (0.2 equiv.) as copper source than that with copper iodide alone, although yields of the reaction slightly increased (Table 1, entries 6, 7 and 13). Use of the methylation derivatives of EG, 2-methoxyethanol (ME) and 1,2-dimethoxyethane (DME),[31] as well as *N*,*N*-dimethylformamide (DMF) as solvent gave lower yields than EG in the model reaction under the otherwise identical conditions (Table 1, entries 10–12).

Since it is more convenient to use aqueous ammonia than ammonia EG solution we further explored the reaction with commercially available aqueous ammonia (25–27%, w/w). When aqueous ammonia–EG (1 : 1, v/v) was used as reaction medium and ammonia source the reaction became sluggish and solid *p*-bromoacetophenone separated from the solution. Therefore, considering both the convenience of handling and solubility of organic aryl halides a combination of 3 ml aqueous ammonia with 6 M ammonia solution in ethylene glycol (10 ml added in portion wise) was set as ammonia source and reaction medium for the copper-promoted amination reaction. Air-sensitive copper(I) chloride showed comparable efficacy to air-stable copper(I) iodide while copper(II) chloride $CuCl_2$ worked less efficiently than copper(I) halides CuX (X = I, Cl) in the model reaction (Table 1, entries 7–9).

To some extent, the amination reaction could proceed by using catalytic amount of copper although the catalytic efficiency is obviously not satisfactory under 1 atm pressure at present. For example, *p*-aminoacetophenone was obtained in 27–56% yields after heating *p*-bromoacetophenone with ammonia in aqueous EG

Table 2. Scope of the CuI–Cu-mediated amination of aryl halides with ammonia in aqueous ethylene glycol under atmosphere pressure

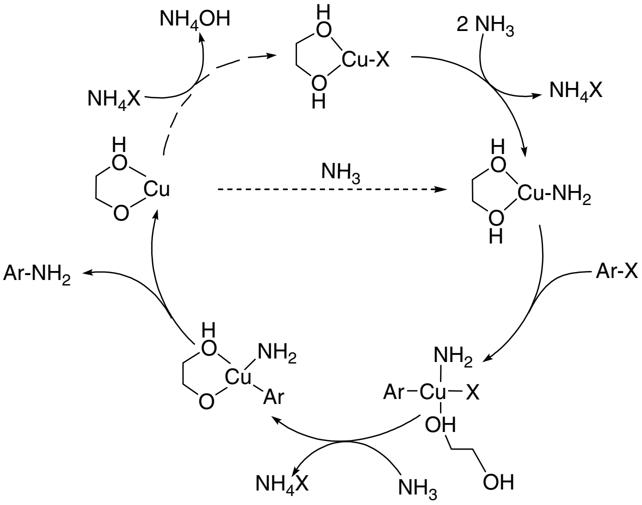
$$\text{Ar-X} + \text{NH}_3 \xrightarrow[\text{EG / H}_2\text{O, 1 atm}]{\text{1eq. CuI / 0.2eq. Cu}} \text{Ar-NH}_2$$

Entry	Ar-X	*T* (°C)	Time (h)	Anilines	Yield (%)[a]
1		50	10		67(42)[b]
2		50	10		69[c]
3		85	16		85
4		85	8		82
5		85	8		75
6		85	8		71
7		85	8		59
8		85	16		7
9		85	8		37[d]
10		85	8		70
11		85	8		65
12		85	8		77

[a] Isolated yield.
[b] Reaction run at 85 °C.
[c] Containing 10% *p*-iodoaniline.
[d] 1 equiv. copper powder added.

under 1 atm pressure for 36–40 h in the presence of 0.2 equiv. CuX or copper metal (Table 1, entries 15–17), although the catalytic efficiency increased significantly with the increase of ammonia pressure (Table 1, entries 21–23). Addition of strong chelating ligands, such as thiophene-2-carboxylic acid (TCA), leucine and catechol (CAT), led to a significant decrease in the yields of the amination reaction because ligation of ethylene glycol on copper could be competitively suppressed (Table 1, entries 18–20).

The scope of the copper-mediated amination reaction of aryl halides with ammonia under 1 atm pressure was explored under the optimal condition: 1.0 equiv. copper iodide with 0.2 equiv. copper metal in aqueous ammonia and ammonia solution in ethylene glycol (Table 2). For aryl iodides, such as iodobenzene, the amination reaction could proceed at 50 °C giving aniline in modest yield (67%). In fact, when the reaction was run at 85 °C aniline was isolated in lower yield (42%) due to deiodination (Table 2, entry 1). High chemical selectivity in the copper-promoted amination of aryl halides of iodide, bromide and chloride was observed (Table 2, entries 2 and 12). For example, reaction of *p*-bromobenzene iodide gave *p*-bromoaniline along with *p*-iodoaniline with 90 : 10 selectivity in 69% overall yield. The sole amination product 5-amino-2-chloropyridine was isolated in 77% yield from the reaction of 5-bromo-2-chloropyridine. No reaction occurred for *p*-chloroacetophenone even at 120 °C. A rather complicated mixture was obtained for *o*-bromoacetophenone while reaction of *m*-bromoacetophenone afforded *m*-aminoacetophenone in good yield (82%) (Table 2, entry 4). Electron-rich aryl halide, such as *p*-bromoanisole, reacted smoothly giving the corresponding aniline in good yield (Table 2, entry 6). The poor yield (7%) obtained in the reaction of 2-bromo-*p*-xylene indicated that the



Scheme 1. A rationale for the copper-mediated amination of aryl halides with ammonia in aqueous ethylene glycol.

copper-mediated amination is rather sensitive to steric hindrance. However, reaction of 2-bromo-4-methylaniline was quite clean, albeit 3,4-diaminotoluene was isolated just in 37% yield after flash chromatography on silica gel (Table 2, entry 9). Functional groups of amide, nitrile and aldehyde acetal survived while aldehyde and carboxylate (not shown) decomposed under the reaction condition (Table 2, entries 5, 7 and 10).

A rationale for the copper-promoted amination of aryl iodides and bromides in aqueous ethylene glycol possibly lies in the formation of chelating amido copper(III) alkoxide from a hemilabile coordinated copper precursor, $(HOCH_2CH_2OH)CuX$, which is clearly supported by the formation of 2-hydroxyethyl aryl ether in EG as well as the decreased yield of the reaction conducted in DME due to the failure in forming alkoxide (Scheme 1).

Chelating ligation of EG to copper ion could not only stabilize the copper(I) intermediates but also lead to the formation of aryl amido copper(III) alkoxide species, which are more ready to generate anilines through reductive elimination since alkoxide is a stronger electron-donator than bromide anion. The presence of water could accelerate the formation of amido copper(III) alkoxide by dissolving NH_4X. However, on the other hand, the high stability of the chelating copper alkoxide may hamper the transmetallation of copper alkoxide into amido copper, making the catalytic cycle rather slow without high pressure of ammonia. In other words, the chelating ligation of ethylene glycol to copper played a double-face role in the copper-mediated amination of aryl halides with ammonia under 1 atm pressure. The positive effects of high ammonia pressure and the negative effects of strong chelating ligands, such as TCA and catechol, on catalytic efficiency of copper were in consistent with the assumption.

Conclusion

In conclusion, copper promoted amination of aryl iodides and bromides with ammonia under 1 atm pressure has been found to proceed smoothly in aqueous ethylene glycol producing primary aromatic amines in good yields, providing a convenient procedure for the synthesis of primary aryl amines without using autoclaves. Water unexpectedly accelerated the copper-mediated reaction, probably through dissolving ammonium halides while strong chelating ligands showed a suppression effect by deactivating the copper alkoxide intermediate, which, in turn, could hamper the transmetallation of copper alkoxide into amido copper. Based on these investigations a double-face role of chealting effect of ethylene glycol was proposed in the copper-mediated amination.

Acknowledgments

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References

[1] S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.
[2] K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428.
[3] I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337.
[4] M. Kienle, S. R. Dubbaka, K. Brade, P. Knochel, *Eur. J. Org. Chem.* **2007**, 4166.
[5] A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727.
[6] J. C. Antilla, J. M. Baskin, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 5578.
[7] F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 793.
[8] R. K. Gujadhur, C. G. Bates, D. Venkataraman, *Org. Lett.* **2001**, *3*, 4315.
[9] R. A. Altman, S. L. Buchwald, *Org. Lett.* **2006**, *8*, 2779.
[10] D. Ma, Q. Cai, H. Zhang, *Org. Lett.* **2003**, *5*, 2453.
[11] H. Zhang, Q. Cai, D. Ma, *J. Org. Chem.* **2005**, *70*, 5164.
[12] Z. Lu, R. J. Twieg, S. D. Huang, *Tetrahedron Lett.* **2003**, *44*, 6289.
[13] Z. Lu, R. J. Twieg, *Tetrahedron* **2005**, *61*, 903.
[14] A. Shafir, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 8742.
[15] Z. Rappoport, *The Chemistry of Anilines*, Wiley: Chichester, **2007**.
[16] S. A. Lawrence, *Amines: Synthesis, Properties and Application*, Cambridge University Press: Cambridge, **2004**.
[17] J. P. Wolfe, J. Åhman, J. P. Sadighi, R. A. Singer, S. L. Buchwald, *Tetrahedron Lett.* **1997**, *38*, 6367.
[18] S. Jaime-Figueroa, Y. Liu, J. M. Muchowski, D. G. Putman, *Tetrahedron Lett.* **1998**, *39*, 1313.
[19] G. Mann, J. F. Hartwig, M. S. Driver, C. Fernandez-Rivas, *J. Am. Chem. Soc.* **1998**, *120*, 827.
[20] G. A. Grasa, M. S. Viciu, J. Huang, S. P. Nolan, *J. Org. Chem.* **2001**, *66*, 7729.
[21] X. Huang, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3417.
[22] S. Lee, M. Jorgensen, J. F. Hartwig, *Org. Lett.* **2001**, *3*, 2729.
[23] J. Barluenga, F. Aznar, C. Valdés, *Angew. Chem., Int. Ed.* **2004**, *43*, 343.
[24] D. Y. Lee, J. F. Hartwig, *Org. Lett.* **2005**, *7*, 1169.
[25] M. C. Willis, *Angew. Chem., Int. Ed.* **2007**, *46*, 3402.
[26] D. S. Surry, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 10354.
[27] Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 10028.
[28] F. Lang, D. Zewge, I. N. Houpis, R. P. Volante, *Tetrahedron Lett.* **2001**, *42*, 3251.
[29] F. Y. Kwong, A. Klapars, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 581.
[30] For a review on organic reactions accelerated by water see: C. J. Li, T. H. Chan, *Comprehensive Organic Reactions in Aqueous Media*, Wiley: New York, **2007**.
[31] A. A. B. Silva, A. L. F. Souza, O. A. C. Antunes, *Appl. Organometal. Chem.* **2008**, *22*, 2.