## Ammonium salts as an inexpensive and convenient nitrogen source in the Cu-catalyzed amination of aryl halides at room temperature<sup>†</sup>

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Convenient and inexpensive ammonium salts such as  $NH_4Cl$  and aqueous  $NH_3$  solution are found to be readily utilized in the Cu-catalyzed room temperature *N*-arylation of aryl halides, providing *N*-unprotected aniline derivatives in high yields.

Cu-catalyzed C–N cross-coupling reactions are powerful tools to prepare N-containing compounds which have high utilities in synthetic, biological, pharmaceutical, and materials science.<sup>1</sup> Traditional protocols such as Ullmann<sup>2</sup> or Goldberg<sup>3</sup> reactions often require stoichiometric amounts of copper reagents at high temperatures.<sup>2</sup> Mainly due to the recent introduction of effective ligands, the Cu-catalyzed N-arylation has significantly expanded its scope in coupling amino compounds to include aniline,<sup>4</sup> amide,<sup>5</sup> imidazole,<sup>6</sup> indole,<sup>7</sup> hyda-zide,<sup>8</sup> and hydroxyamine.<sup>9</sup> Notable examples of such efficient ligands are bisamines,<sup>5,7</sup> ethylene glycols,<sup>10a</sup> N,N-diethylsali-cylamides,<sup>10b</sup> oximes,<sup>11</sup> N-hydroxylimides,<sup>12</sup> 1,10-phenanthroline.4b,13 or thiophencarboxylates.<sup>14</sup> In addition, Ma demonstrated that certain amino acids, in particular proline and N,N-dimethylglycine, exhibit remarkable accelerating effects not only in the Cu-catalyzed N-arylation<sup>15</sup> but also in the C–C,  $^{16}$  C–O $^{17}$  and C–S $^{18}$  coupling reactions.

Buchwald group reported that benzophenone imine<sup>19</sup> or LiN(SiMe<sub>3</sub>)<sub>2</sub> (LiHMDS)<sup>20</sup> could serve as ammonia equivalents in the Pd-catalyzed *N*-arylation.<sup>21</sup> Although their protocols were useful to prepare primary aryl amines with a range of aryl (pseudo)halides in respectable yields, an extra step for the cleavage of protecting groups is required in order to obtain desired aniline products. Alternatively, more direct arylations of aryl halides for primary aryl amines were achieved using either ammonia gas or liquid ammonia.<sup>22</sup> Although the reaction affords acceptable yield and selectivity, the requirement of high pressure and elevated temperature makes their synthetic utility difficult.

Ammonium chloride (NH<sub>4</sub>Cl), a cheap and stable solid,<sup>23</sup> has been usually used in the Cu-catalyzed reaction to quench the copper reagents. We wondered whether NH<sub>4</sub>Cl might be utilized as an ammonia surrogate in the Cu-catalyzed *N*-arylation.<sup>24</sup> For the identification of optimal conditions such as suitable copper source and ligands, 4'-iodoacetophenone was chosen as a test substrate, allowing to react with equivalent NH<sub>4</sub>Cl (Table 1). To our delight, the cross-coupling

reaction took place under the initial conditions to provide the desired product, 4-aminoacetophenone, and, not surprisingly, efficiency of the reaction was revealed to be dependent on the modified conditions.<sup>25</sup>

Among various copper sources examined, while Cu(II) species displayed little activity (entry 1), the CuI catalyst was especially effective in DMSO when it was used in combination with certain ligands of amino acids (entry 3). In particular, Ma's L-proline system turned out to be the best ligand (entry 4). On the other hand, different types of chelating species were less effective under the otherwise same conditions (entries 5–8). Among various bases screened (*e.g.* EtN(*i*-Pr)<sub>2</sub>, Et<sub>3</sub>N, K<sub>3</sub>PO<sub>4</sub>, KOH, or KO*t*Bu), K<sub>2</sub>CO<sub>3</sub> was most effective in DMSO solvent. In different solvents other than DMSO, efficiency of the coupling was decreased significantly (*e.g.* entry 9). It is noteworthy to observe that addition of small amounts of water resulted in an improved yield of the *N*-arylation (compare entries 4 and 10).<sup>16a</sup> It is reasoned that water might increase

Table 1 Cu/ligand-catalyzed N-arylation of 4'-iodoacetophenone with  $\rm NH_4 Cl^{\it a}$ 



<sup>*a*</sup> Reaction conditions: 4<sup>*l*</sup>-iodoacetophenone (0.5 mmol), NH<sub>4</sub>Cl (0.5 mmol), [Cu] catalyst (10 mol%), ligand (20 mol%), and K<sub>2</sub>CO<sub>3</sub> (1.5 mmol) in solvent (1 mL) under Ar. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> H<sub>2</sub>O (50  $\mu$ L) was added. <sup>*d*</sup> CuI (20 mol%), ligand (40 mol%) and NH<sub>4</sub>Cl (0.65 mmol) were used.

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Table 2 CuI/proline-catalyzed N-arylation of aryl iodides with  $NH_4Cl^a$ 

<sup>*a*</sup> Reaction conditions: aryl iodide (0.5 mmol), NH<sub>4</sub>Cl (0.65 mmol), CuI (20 mol%), L-proline (40 mol%), K<sub>2</sub>CO<sub>3</sub> (1.5 mmol) in DMSO (1 mL) and H<sub>2</sub>O (50  $\mu$ L) under Ar at 25 °C. <sup>*b*</sup> Isolated yield.

solubility of NH<sub>4</sub>Cl reagent, thus accelerating the reaction rates. Finally, we were pleased to observe that the cross-coupling readily took place even at room temperature, although slightly larger amounts of CuI/L-proline were needed to obtain satisfactory product yield (entry 11).

Under the optimized conditions, the scope of aryl iodides was investigated for the *N*-arylation reaction with the convenient NH<sub>4</sub>Cl reagent (Table 2). In general, the corresponding N-unprotected aniline derivatives could be obtained in good yields. In addition, the reaction was tolerant with a range of functional groups including hydroxyl, keto, ester, nitro or cyano moiety (entries 1–9). It should be mentioned that the coupling takes place selectively at an iodo part in the presence of a bromo group (entry 10). On the other hand, the present protocol using NH<sub>4</sub>Cl exhibits a limitation for certain types of substrates. For instance, reactions of aryl iodides bearing electron-donating groups or *ortho*-substituents provided rather poor product yields (entries 11 and 12, respectively).

Due to the fact that the coupling of aryl iodides with  $NH_4Cl$  proceeds with higher efficiency in the presence of water, we

**Table 3** CuI/proline-catalyzed *N*-arylation of aryl iodides with aqueous  $NH_3$  solution<sup>*a*</sup>



<sup>*a*</sup> Reaction conditions: aryl halide (0.5 mmol), NH<sub>3</sub> (aqueous 28%, 0.75 mmol), CuI (20 mol%), L-proline (40 mol%), K<sub>2</sub>CO<sub>3</sub> (1.5 mmol) in DMSO (1 mL) under Ar at 25 °C. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> NH<sub>3</sub> (28% aqueous, 2.5 mmol) was employed at 80 °C.

were intrigued by the possibility of using aqueous  $NH_3$  solution as a source of the amino group in the Cu-catalyzed crosscoupling reaction. We were pleased to observe that the reaction did indeed take place even with aqueous  $NH_3$  (28% solution, 1.5 equiv) at room temperature under otherwise identical conditions compared to those of  $NH_4Cl$  (Table 3).

Interestingly, reaction rates of the *N*-arylation of aryl halides were quite similar between two reagents of ammonium salts,  $NH_4Cl$  and aqueous  $NH_3$ .<sup>26</sup> In addition, functional group tolerance was also wide even with the latter reagent. It should be noted that reactions of aryl halides bearing electron-rich substituents, which are problematic with  $NH_4Cl$ , could be carried out with much higher efficiency when aqueous  $NH_3$  solution was employed. For example, while 32% product yield was obtained from the reaction of 4-iodomethoxybenzene with  $NH_4Cl$  (entry 11, Table 2), it was significantly improved up to 77% with aqueous  $NH_3$  solution (entry 1, Table 3). However, reactions of aryl iodides bearing *ortho*-substituents exhibited still rather low reactivity with aqueous  $NH_3$  solution as shown in the preparation of 2-methylaniline (entry 7, Table 3).

In addition to iodobenzenes, heterocyclic iodides and aryl bromides could also be utilized as efficient substrates under the present mild *N*-arylation protocol (Table 4). Comparison between two nitrogen sources,  $NH_4Cl$  and aqueous  $NH_3$ solution, was tried to reveal that higher product yields were obtained with the latter reagent in each substrate. Heterocyclic iodides such as thiophene or pyridine derivatives smoothly

ArX	+ $NH_4CI$ + or $NH_3$ (aq)	cat. Cul / L-proline	ArNH <sub>2</sub>
		K <sub>2</sub> CO <sub>3</sub> , DMSO, H <sub>2</sub> O, RT, 12 h	
Entry	Aryl halide	Product	Yield (%)
$\frac{1}{2^{c}}$	Г <sup>S</sup> —I	₩NH <sub>2</sub>	45 50
3 4 <sup>c</sup>	S ↓	NH <sub>2</sub>	61 70
5 6 <sup>c</sup>	CI-		75 90
$7^d$ $8^{cd}$	NC-	n NC-NH2	75 88
$9^{d}$ $10^{cd}$	°→−Б	r O	80 91
11 <sup>d</sup> 12 <sup>cd</sup>	MeO-	Br MeO-NH2	10 44

<sup>*a*</sup> Reaction conditions: aryl halide (0.5 mmol), NH<sub>4</sub>Cl (0.65 mmol), CuI (20 mol%), L-proline (40 mol%), K<sub>2</sub>CO<sub>3</sub> (1.5 mmol) in DMSO (1 mL) and 50  $\mu$ L of H<sub>2</sub>O (when NH<sub>4</sub>Cl was used) under Ar at 25 °C. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> NH<sub>3</sub> (aqueous 28%, 0.75 mmol) was used for 24 h. <sup>*d*</sup> Run at 80 °C.

reacted with both ammonium salts at room temperature to furnish the corresponding coupled products in good yields (entries 1–6). Moreover, it was observed that aryl bromides bearing electron-withdrawing groups were viable substrates although elevated temperatures were required for satisfactory yields (entries 7–10). On the other hand, aryl bromides bearing electron-donating substituents were less effective (entries 11–12). In addition, the reaction of aryl chlorides was much more sluggish under the present system.<sup>27</sup>

In summary, we have developed an efficient protocol of room temperature Cu-catalyzed coupling of aryl halides with inexpensive and convenient ammonium salts. Although both reagents,  $NH_4Cl$  and aqueous  $NH_3$  solution, can be employed as ammonia equivalents in the Cu-catalyzed aminations, the latter species was more effective for the coupling reaction to afford higher product yields. The present procedure is mild and tolerant of a variety of functional groups, thus allowing for the practical new route to primary aryl amines.

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## Notes and references

- 1. M. Negwar, in *Organic-Chemical Drugs and their Synonyms:* (An International Survey), Akademie, Berlin, Germany, 7th edn, 1994.
- (a) F. Ullmann, Ber. Dtsch. Chem. Ges., 1903, 36, 2382; (b) J. Lindley, Tetrahedron, 1984, 40, 1433.
- 3. I. Goldberg, Ber. Dtsch. Chem. Ges., 1906, 39, 1619.
- (a) R. Gujadhur, D. Venkataraman and J. T. Kintigh, *Tetrahedron Lett.*, 2001, 42, 4791; (b) R. K. Gujadhur, C. G. Bates and D. Venkataraman, *Org. Lett.*, 2001, 3, 4315.

- A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, J. Am. Chem. Soc., 2001, 123, 7727.
- (a) A. Kiyomori, J.-F. Marcoux and S. L. Buchwald, *Tetrahedron Lett.*, 1999, **40**, 2657; (b) J. C. Antilla, J. M. Baskin, T. E. Barder and S. L. Buchwald, *J. Org. Chem.*, 2004, **69**, 5578.
- J. C. Antilla, A. Klapars and S. L. Buchwald, J. Am. Chem. Soc., 2002, 124, 11684.
- M. Wolter, A. Klapars and S. L. Buchwald, Org. Lett., 2001, 3, 3803.
- K. L. Jones, A. Porzelle, A. Hall, M. D. Woodrow and N. C. O. Tomkinson, *Org. Lett.*, 2008, 10, 797.
- (a) F. Y. Kwong, A. Klapars and S. L. Buchwald, Org. Lett., 2002, 4, 581; (b) F. Y. Kwong and S. L. Buchwald, Org. Lett., 2003, 5, 793.
- H.-J. Cristau, P. P. Cellier, J.-F. Spindler and M. Taillefer, *Eur. J.* Org. Chem., 2004, 695.
- 12. H-C. Ma and X. -Z. Jiang, J. Org. Chem., 2007, 72, 8943.
- (a) D. V. Allen and D. Venkataraman, J. Org. Chem., 2003, 68, 4590; (b) A. Shafir, P. A. Lichtor and S. L. Buchwald, J. Am. Chem. Soc., 2007, 129, 3490.
- S. Zhang, D. Zhang and L. S. Liebeskind, J. Org. Chem., 1997, 62, 2312.
- (a) D. Ma, Q. Cai and H. Zhang, Org. Lett., 2003, 5, 2453;
  (b) X. Pan, Q. Cai and D. Ma, Org. Lett., 2004, 6, 1809;
  (c) W. Zhu and D. Ma, Chem. Commun., 2004, 888;
  (d) H. Zhang, Q. Cai and D. Ma, J. Org. Chem., 2005, 70, 5164;
  (e) B. Zou, Q. Yuan and D. Ma, Angew. Chem., Int. Ed., 2007, 46, 2598;
  (f) B. Zou, Q. Yuan and D. Ma, Org. Lett., 2007, 9, 4291;
  (g) D. Ma, Y. Zhang, J. Yao, S. Wu and F. Tao, J. Am. Chem. Soc., 1998, 120, 12459.
- (a) D. Ma and F. Liu, Chem. Commun., 2004, 1934; (b) X. Xie, G. Cai and D. Ma, Org. Lett., 2005, 7, 4693; (c) B. Lu and D. Ma, Org. Lett., 2006, 8, 6115; (d) X. Xie, Y. Chen and D. Ma, J. Am. Chem. Soc., 2006, 128, 16050; (e) Y. Chen, X. Xie and D. Ma, J. Org. Chem., 2007, 72, 9329.
- (a) Q. Cai, B. Zou and D. Ma, Angew. Chem., Int. Ed., 2006, 45, 1276; (b) Q. Cai, G. He and D. Ma, J. Org. Chem., 2006, 71, 5268.
- (a) W. Zhu and D. Ma, J. Org. Chem., 2005, 70, 2696;
  (b) H. Zhang, W. Cao and D. Ma, Synth. Commun., 2007, 37, 25.
- (a) J. P. Wolfe, J. Ahman, J. P. Sadighi, R. A. Singer and S. L. Buchwald, *Tetrahedron Lett.*, 1997, **38**, 6367; (b) G. Mann, J. F. Hartwig, M. S. Driver and C. Fernandez-Rivas, *J. Am. Chem. Soc.*, 1998, **120**, 827.
- (a) S. Lee, M. Jørgensen and J. F. Hartwig, Org. Lett., 2001, 3, 2729; (b) X. Huang and S. L. Buchwald, Org. Lett., 2001, 3, 3417; (c) D.-Y. Lee and J. F. Hartwig, Org. Lett., 2005, 7, 1169.
- For the use of other ammonia equivalents, see: (a) S. Jaime-Figueroa, Y. Liu, J. M. Muchowski and D. G. Putman, *Tetrahedron Lett.*, 1998, **39**, 1313; (b) C. W. Lim and S. Lee, *Tetrahedron*, 2000, **56**, 5131; (c) C. Bolm and J. P. Hildebrand, *Tetrahedron Lett.*, 1998, **39**, 5731.
- (a) Q. Shen and J. F. Hartwig, J. Am. Chem. Soc., 2006, 128, 10028; (b) D. S. Surry and S. L. Buchwald, J. Am. Chem. Soc., 2007, 129, 10354; (c) F. Lang, D. Zewge, I. N. Houpis and R. P. Volante, Tetrahedron Lett., 2001, 42, 3251; (d) M. C. Willis, Angew. Chem., Int. Ed., 2007, 46, 3402.
- R. Yamaguchi, S. Kawagoe, C. Asai and K.-i. Fujita, Org. Lett., 2008, 10, 181.
- 24. For selected examples of using NH<sub>4</sub>Cl in Cu-catalyzed reactions other than N-arylation, see: (a) H. Hayashi, K. Kawasaki and T. Murata, *Chem. Lett.*, 1974, 1079; (b) P. Capdevielle, A. Lavigne and M. Maumy, *Synthesis*, 1989, 451.
- For previous reports on the related cross-coupling recations from this laboratory, see: (a) S. Ko, C. Lee, M.-G. Choi, Y. Na and S. Chang, J. Org. Chem., 2003, 68, 1607; (b) Y. Na, S. Park, S. B. Han, H. Han, S. Ko and S. Chang, J. Am. Chem. Soc., 2004, 128, 250; (c) S. Park, M. Kim, D. H. Koo and S. Chang, Adv. Synth. Catal., 2004, 346, 1638; (d) S. Ko, B. Kang and S. Chang, Angew. Chem., Int. Ed., 2005, 44, 455; (e) L. K. Hwang, Y. Na, J. Lee, Y. Do and S. Chang, Angew. Chem., Int. Ed., 2005, 44, 6166.
- 26. See the Electronic Supplementary Information (ESI).
- 27. For example, the reaction of 4'-chloroacetophenone with aqueous NH<sub>3</sub> solution afforded 26% conversion and 5% product yield using the Cu/proline system at 90 °C. No further attempts to optimize this reaction have been made.