

# Cross-coupling of aryl/heteroaryl bromides with ammonia using a copper-carbene catalyst†

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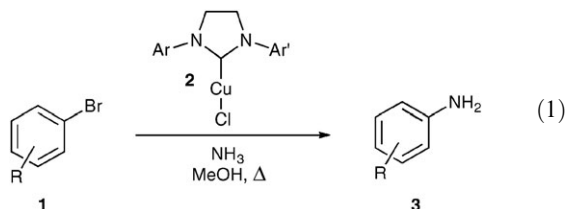
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**A variety of aryl and heteroaryl bromides were cross-coupled with ammonia in good to high yields in the presence of a copper-NHC catalyst.**

Ammonia (NH<sub>3</sub>) is an inexpensive commodity chemical that is manufactured world-wide on a multi-ton basis annually.<sup>1</sup> Consequently, it would be highly desirable for downstream amines to be directly synthesized from NH<sub>3</sub>. In particular, aromatic amines are highly useful and valuable compounds that have numerous applications in the pharmaceutical, agrochemical and polymer industries.<sup>2</sup> Thus, any new methodology that could allow for rapid access to a variety of aromatic amines from simple precursors would be an attractive development.

During the course of an ongoing program into carbon-nitrogen bond formations,<sup>3</sup> we observed a cross-coupling between an aryl bromide (**1**) and NH<sub>3</sub> in the presence of copper complex **2**, which had been introduced into the reaction to accomplish an unrelated transformation (eqn (1)).



Cu salts and complexes have been extensively utilized as catalysts for the cross-coupling reaction between aryl halides and 1°/2° amines (the Ullmann condensation).<sup>4,5</sup> In contrast, scant attention has been applied to their use in similar cross-couplings with ammonia.<sup>6</sup> As such, we sought to expand on the initial discovery shown in eqn (1) to develop a new Cu-based catalyst for the cross-coupling of aryl halides and ammonia. Cu-*N*-heterocyclic carbene (Cu-NHC) complexes have previously been demonstrated to be efficient catalysts for a range of other organic transformations.<sup>7–9</sup> In addition, it should be noted that unrelated Pd-based catalysts are also effective for the reaction shown in eqn (1).<sup>10,11</sup>

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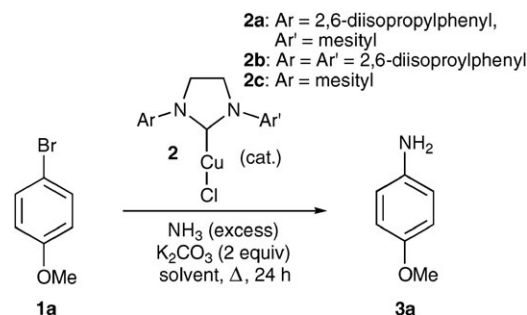
† Electronic supplementary information (ESI) available: Optimization studies, full experimental and characterization data of **2a** and **3**, NMR spectra of **3** and CIF file for **2a**. CCDC 701641. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b815757j

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We initiated optimization studies by studying the reaction between 4-bromoanisole (**1a**) and ammonia in the presence of several Cu-NHC complexes (**2**) (Table 1).<sup>12</sup> A variety of other parameters were varied including the catalyst loading, stoichiometry, base, solvent, temperature and reaction time, the full details of which are included in the electronic supplementary information (ESI†). The results from Table 1 show that both Cu-NHC complexes **2a** (see Fig. 1 for X-ray structure<sup>13,14</sup>) and **2b** were the catalysts of choice (entries 1, 3), although a minimum of 5 mol% of the catalyst was required in order to achieve satisfactory isolated yield of the product (entry 2). In addition, a 1 : 1 mixture of MeOH/NMP (entries 1, 7, 8) and K<sub>2</sub>CO<sub>3</sub> were determined to be optimal solvent and base respectively (see ESI†), while elevated reaction temperatures (entries 1, 5, 6) and an excess of ammonia (see ESI†) were also crucial for a successful outcome.<sup>15</sup>

We next sought to investigate the substrate scope of the Cu-NHC catalyzed cross-coupling by examining aryl bromides under the following optimized reaction conditions: **1** (0.2 M) in MeOH/NMP (1 : 1) saturated with NH<sub>3</sub>, **2a** (5 mol%), K<sub>2</sub>CO<sub>3</sub> (2 equiv), 90 °C, 24 h (Table 2). The results indicate that electron-rich aromatic substrates (entries 1–3) generally

**Table 1** Optimization studies on the cross-coupling of 4-bromoanisole (**1a**) and ammonia in the presence of Cu-NHC catalysts (**2**)



Entry	Cu-NHC <b>2</b>	(mol%)	Temperature/°C	Solvent <sup>a</sup>	Yield of <b>3a</b> (%) <sup>b</sup>
1	<b>2a</b>	5	90	MeOH/NMP	79
2	<b>2a</b>	1	90	MeOH/NMP	24
3	<b>2a</b>	0	90	MeOH/NMP	0
4	<b>2b</b>	5	90	MeOH/NMP	79
5	<b>2c</b>	5	90	MeOH/NMP	63
6	<b>2a</b>	5	20	MeOH/NMP	<5
7	<b>2a</b>	5	40	MeOH/NMP	19
8	<b>2a</b>	5	90	MeOH	66
9	<b>2a</b>	5	90	NMP	60

<sup>a</sup> MeOH/NMP = 1 : 1 mixture of NMP/MeOH; 0.2 M in **1a**.

<sup>b</sup> Isolated yield (average of two runs).

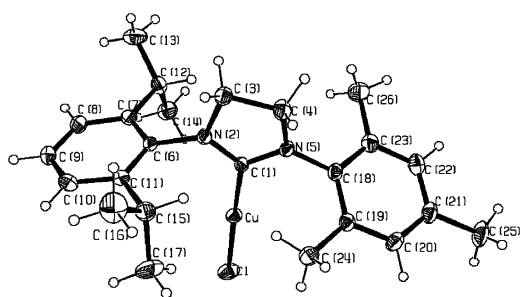
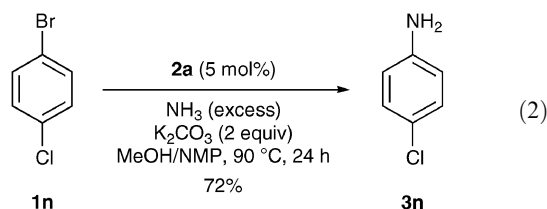


Fig. 1 X-Ray crystal structure of **2a**.<sup>14</sup>

reacted more sluggishly and afforded the aniline derivative **3** in lower yields. In contrast, excellent yields of **3** were obtained when the more reactive electron deficient aryl bromides (entries 7–12) were utilized in the aforementioned reaction. The reaction conditions were also tolerant of functional groups such as the nitro (entry 10), cyano (entry 11), trifluoromethyl (entry 12), amide (entries 3, 9) and ketone (entries 7, 8). A significant limitation of the current methodology is that sterically hindered aryl bromides **1** consistently afforded very low isolated yields of **3** (entry 13). It should also be noted that aryl chlorides did not react under the standard conditions as highlighted by the reaction shown in eqn (2).



We did manage to further expand the substrate scope of the methodology to include heteroaromatic bromides as listed in Table 3. The data show that thiophene (entries 1, 2), quinoline (entry 3), and benzothiazole (entry 4) bromides successfully reacted to afford the corresponding primary amine **3** in good to high yields.

Table 2 Cu-NHC catalyzed cross-coupling of aryl bromides and ammonia

Entry	Ar	Yield (%) <sup>a</sup>
1	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>1a</b> )	79 ( <b>3a</b> )
2	2,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>1b</b> )	66 ( <b>3b</b> )
3	2-CH <sub>3</sub> C(O)NHC <sub>6</sub> H <sub>4</sub> ( <b>1c</b> )	73 ( <b>3c</b> )
4	2-MeC <sub>6</sub> H <sub>4</sub> ( <b>1d</b> )	80 ( <b>3d</b> )
5	2-PhC <sub>6</sub> H <sub>4</sub> ( <b>1e</b> )	81 ( <b>3e</b> )
6	2-Naphthyl ( <b>1f</b> )	75 ( <b>3f</b> )
7	4-CH <sub>3</sub> C(O)C <sub>6</sub> H <sub>4</sub> ( <b>1g</b> )	97 ( <b>3g</b> )
8	2-CH <sub>3</sub> C(O)C <sub>6</sub> H <sub>4</sub> ( <b>1h</b> )	92 ( <b>3h</b> )
9	4-H <sub>2</sub> NC(O)C <sub>6</sub> H <sub>4</sub> ( <b>1i</b> )	93 ( <b>3i</b> )
10	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ( <b>1j</b> )	91 ( <b>3j</b> )
11	4-CNC <sub>6</sub> H <sub>4</sub> ( <b>1k</b> )	93 ( <b>3k</b> )
12	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>1l</b> )	95 ( <b>3l</b> )
13	2,6-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>1m</b> )	7 ( <b>3m</b> ) <sup>b</sup>

<sup>a</sup> Isolated yield (average of two runs). <sup>b</sup> Run at 120 °C for 48 h (10 mmol scale).

Table 3 Cross-coupling of heteroaryl bromides and ammonia catalyzed by Cu-NHC catalyst **2a**

Entry	R	Yield (%) <sup>a</sup>
1		88 ( <b>3o</b> )
2		84 ( <b>3p</b> )
3		80 ( <b>3q</b> )
4		73 ( <b>3r</b> )

<sup>a</sup> Isolated yield (average of two runs).

In conclusion, we have demonstrated that copper-*N*-heterocyclic carbene complexes are effective catalysts for the cross-coupling reaction between aryl and heteroaryl bromides and ammonia. The resulting aromatic primary amines were obtained in good to excellent yields. The substrate scope of the methodology is broad and a variety of functional groups are tolerated. The low cost of ammonia makes the current methodology an attractive addition to the repertoire of strategies for the synthesis of aniline derivatives.

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## Notes and references

§ General experimental procedure for the cross-coupling of aryl and heteroaryl bromides with ammonia in the presence of Cu-NHC catalyst (**2a**): *CAUTION: The procedure described below is conducted in closed reaction apparatus that is under pressure. The reaction apparatus should be placed behind a blast shield in a well-ventilated fume hood.*

To a solution of MeOH/NMP (1 : 1, 4 mL) saturated with ammonia in a Parr<sup>®</sup> reactor that was previously purged with argon was added the aryl/heteroaryl bromide (1 mmol) and K<sub>2</sub>CO<sub>3</sub> (276 mg, 2.00 mmol). A solution of the Cu-NHC catalyst **2a** (22.5 mg, 0.05 mmol) in MeOH/NMP (1 : 1, 1 mL) was subsequently added. The Parr<sup>®</sup> reactor was connected to a cylinder of ammonia, purged extensively with ammonia, and heated to 90 °C for 24 h while still connected to the ammonia cylinder. The ultimate pressure generated in the reactor was ca. 100 psi. The Parr<sup>®</sup> reactor was then cooled to rt and immersed in a dry-ice acetone bath. The ammonia cylinder was disconnected from the reactor and excess ammonia was carefully vented into the fume hood while the reactor was allowed to warm to rt. The contents of the bomb were transferred to a round bottom flask and all volatiles were removed *in vacuo*. The residue was then chromatographed on silica gel (hexanes/EtOAc, 0.5% Et<sub>3</sub>N) to afford primary aromatic amine **3**.

- 1 M. Appl, in *Ammonia: Principles and Industrial Practice*, Wiley-VCH, Weinheim, 1999.
- 2 (a) S. A. Lawrence, in *Amines: Synthesis, Properties and Application*, Cambridge University Press, Cambridge, 2004; (b) M. Negwer, in *Organic Drugs and their Synonyms*, Akademie Verlag GmbH, Berlin, 7th ed., 1994; (c) *Pigment Handbook*, ed. P. A. Lewis, John Wiley, New York, 1988; (d) B. Schlummer and U. Scholz, *Adv. Synth. Catal.*, 2004, **346**, 1599–1626.
- 3 (a) B. Dhudshia, J. Tiburcio and A. N. Thadani, *Chem. Commun.*, 2005, 5551–5553; (b) R. Ntaganda, T. Milovic, J. Tiburcio and A. N. Thadani, *Chem. Commun.*, 2008, 4052–4054.
- 4 For reviews on copper-catalyzed *N*-arylations, see: (a) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400–5449; (b) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428–2439; (c) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337–2364; (d) J. P. Finet, A. Y. Fedorov, S. Combes and G. Boyer, *Curr. Org. Chem.*, 2002, **6**, 597–626; (e) S. R. Chemler and P. H. Fuller, *Chem. Soc. Rev.*, 2007, **36**, 1153–1160; (f) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2008, **47**, 3096–3099; (g) M. Carril, R. SanMartin and E. Domínguez, *Chem. Soc. Rev.*, 2008, **37**, 639–647.
- 5 For select recent examples of Cu-catalyzed *N*-arylations/alkenylations, see: (a) J. W. Tye, Z. Weng, A. M. Johns, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 9971–9983; (b) A. Minatti and S. L. Buchwald, *Org. Lett.*, 2008, **10**, 2721–2724; (c) R. A. Altman, A. M. Hyde, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 9613–9620; (d) C. He, C. Chen, J. Cheng, C. Liu, W. Liu, Q. Li and A. Lei, *Angew. Chem., Int. Ed.*, 2008, **47**, 6414–6417; (e) L. M. Huffman and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 9196–9197; (f) Z. Zhang, Y. Yu and L. S. Liebeskind, *Org. Lett.*, 2008, **10**, 3005–3008; (g) C. Worch and C. Bolm, *Synthesis*, 2008, 739–742; (h) Y. Bolshan and R. A. Batey, *Angew. Chem., Int. Ed.*, 2008, **47**, 2109–2112.
- 6 (a) J. Kim and S. Chang, *Chem. Commun.*, 2008, 3052–3054; (b) F. Lang, D. Zewge, I. N. Houpis and R. P. Volante, *Tetrahedron Lett.*, 2001, **42**, 3251–3254.
- 7 For a recent review on the catalytic use of Cu-NHC complexes in organic synthesis, see: S. Díez-González and S. P. Nolan, *Aldrichimica Acta*, 2008, **41**, 43–51, and references therein.
- 8 For recent examples on the catalytic use of Cu-NHC complexes in organic synthesis, see: (a) S. Díez-González, E. D. Stevens and S. P. Nolan, *Chem. Commun.*, 2008, 4747; (b) T. Ohishi, M. Nishiura and Z. Hou, *Angew. Chem., Int. Ed.*, 2008, **47**, 5792–5795; (c) O. Winkelmann, C. Näther and U. Lüning, *J. Organomet. Chem.*, 2008, **693**, 923–932; (d) J. A. Bull, M. G. Hutchings, C. Luján and P. Quayle, *Tetrahedron Lett.*, 2008, **49**, 1352–1356.
- 9 For an example on the use of a Cu-NHC complex in cross-coupling of aryl halides and azoles, see: C. Tubaro, A. Biffis, E. Scattolin and M. Basato, *Tetrahedron*, 2008, **64**, 4187–4195.
- 10 (a) Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 10028–10029; (b) D. S. Surry and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 10354–10355.
- 11 For select examples of the use of ammonia surrogates in cross-coupling reactions, see: (a) J. P. Wolfe, H. Tomori, J. P. Sadighi, J. J. Yin and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1158–1174; (b) X. H. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 6653–6655; (c) G. A. Grasa, M. S. Viciu, J. K. Huang and S. P. Nolan, *J. Org. Chem.*, 2001, **66**, 7729–7737; (d) J. Barluenga, F. Aznar and C. Valdes, *Angew. Chem., Int. Ed.*, 2004, **43**, 343–345; (e) S. Lee, M. Jorgensen and J. F. Hartwig, *Org. Lett.*, 2001, **3**, 2729–2732; (f) D.-Y. Lee and J. F. Hartwig, *Org. Lett.*, 2005, **7**, 1169–1172.
- 12 Control experiments (omission of catalyst **2a** under otherwise identical conditions) were performed for all the substrates examined in this study. <sup>1</sup>H NMR of the crude reaction mixtures revealed < 5% of product formation in all cases.
- 13 The structure of **2a** is similar to the reported structures of **2b** and **2c**, see: (a) S. Díez-González, E. D. Stevens and S. P. Nolan, *Chem. Commun.*, 2008, 4747; (b) S. Díez-González, H. Kaur, F. K. Zinn, E. D. Stevens and S. P. Nolan, *J. Org. Chem.*, 2005, **70**, 4674–4796.
- 14 *Crystal data*, **2a**: C<sub>24</sub>H<sub>32</sub>Cu<sub>1</sub>N<sub>2</sub>, *M* = 447.51, triclinic, space group P $\bar{1}$ , *a* = 9.3700(17) Å, *b* = 9.4399(17) Å, *c* = 14.913(3) Å,  $\alpha$  = 81.078(2)°,  $\beta$  = 85.418(2)°,  $\gamma$  = 64.894°, *V* = 1179.9(4) Å<sup>3</sup>, *Z* = 2, *T* = 223(2) K,  $\mu$ (Mo-K $\alpha$ ) = 1.05 mm<sup>-1</sup>, 13374 reflections collected, 5232 unique (*R*<sub>int</sub> = 0.060), *F*<sup>2</sup> refinement, *R*<sub>1</sub> = 0.059, *wR*<sub>2</sub> = 0.145, (3409 reflections, *I* > 2 $\sigma$ *I*). Goodness-of-fit = 1.012. Data were collected on a Bruker APEX CCD instrument and solutions performed using the SHELXTL 5.03 Program Library, Siemens Analytical Instrument Division, Madison, WI, USA, 1997. CCDC 701641.
- 15 The ultimate pressure generated in the Parr<sup>®</sup> reactor was *ca.* 100 psi.