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Copper-catalyzed conversion of aryl and heteroaryl bromides into the corresponding chlorides†

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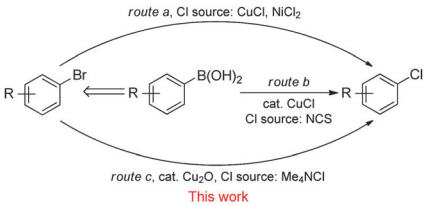
An efficient method for the synthesis of aryl and heteroaryl chlorides is described. The reactions of aryl and heteroaryl bromides with tetramethylammonium chloride proceeded smoothly in the presence of a copper catalyst under mild reaction conditions to produce the corresponding chlorides in satisfactory to excellent yields.

The development of convenient and efficient methods for the selective synthesis of aryl and heteroaryl chlorides has attracted considerable attention. Aryl and heteroaryl chlorides are widely utilized as intermediates in organic synthesis to prepare photoelectrical materials[1] and bioactive compounds.[2] They are also present in many pharmaceutical compounds as essential components.[3] The chlorination of arenes *via* direct electrophilic aromatic substitution has poor functional group tolerance and usually requires forcing conditions. In addition, the synthesis of chlorinated arenes through the Sandmeyer reaction entails complex procedures. For example, the direct chlorination of nitrobenzene to prepare 3-nitrophenyl chloride, which can be used as an intermediate in the preparation of the pharmaceuticals Ziprasidone hydrochloride[4] and Singulair,[5] produces a mixture of 3-nitrophenyl chloride, multi-chlorinated products, and denitrochlorination products. In contrast to direct chlorination, the direct bromination of arenes proceeds more smoothly under mild conditions to yield regio-selectively brominated products. Therefore, the production of the corresponding aryl chlorides *via* Finkelstein-type halide exchanges between aryl bromides and copper(I) chloride (CuCl) or nickel(II) dichloride ($NiCl_2$) has been thoroughly investigated and widely employed for this purpose (route a, Scheme 1).[6] However, these reactions require high temperatures (115 °C to 170 °C) and use excess CuCl or $NiCl_2$. The formation of chlorobenzene and 1-chloro-4-methylbenzene from bromobenzene or 1-bromo-4-methylbenzene using a catalytic amount of $NiCl_2$ in conjunction with lithium chloride (LiCl), or a five-fold excess of nickel powder in conjunction with potassium chloride (KCl), was attempted at high temperatures (210 °C and 150 °C, respectively). However, low conversions were observed (68% and 46%, respectively).[7] Recently, Hynes, Jr. and Wu have reported a mild and efficient Cu(I)-catalyzed method for the conversion of arylboronic acids to aryl chlorides using *N*-chlorosuccinimide as a chlorine source (route b, Scheme 1).[8] This protocol offers several advantages over previous methods.[9,10] The arylboronic acids used in this Cu(I)-catalyzed method are usually prepared from aryl bromides.



Scheme 1 Preparation of aryl chlorides.

We developed an efficient aryl bromide–chloride exchange reaction using copper(I) oxide (Cu_2O) and tetramethylammonium chloride (Me_4NCl) as catalyst and chlorine source, respectively (route c, Scheme 1). The results are reported in the current work.

In the initial studies conducted, the halogen exchange reaction of 1-bromo-4-methylbenzene (**1a**) was used as a model to optimize the reaction conditions. The results are shown in Table 1. Several Cu(I) salts, including CuCl, CuBr, CuI, and Cu_2O, were initially tested in ethanol (EtOH) at 110 °C using ethane-1,2-diamine (**L1**) and Me_4NCl as ligand and chlorine source, respectively (entries 2–5). Among the Cu(I) salts tested, Cu_2O exhibited a higher catalytic activity than all the others. No reaction was observed in the absence of a ligand (entry 1). The ligands were then screened using Cu_2O and Me_4NCl as the precatalyst and chlorine source, respectively (entries 5–10). Only trace amounts of the desired product, 1-chloro-4-methylbenzene (**2a**), were observed when the ligands pyridin-2-amine (**L2**), 1,10-phenanthroline (**L3**), quinolin-8-ol (**L4**), and 2-aminoacetic acid (**L5**) were examined. However, the yield of **2a** was dramatically increased to 74% when L-proline (**L6**) was used as a ligand (entry 10 *vs.* entries 5–9). The effect of catalyst loading on the yield of **2a** was evaluated (entries 10–12). The yield of **2a** increased with increasing catalyst loading. Product **2a** was obtained in 98% yield when 10 mol% Cu_2O and 20 mol% Me_4NCl were utilized. The chlorine source was finally screened, and Me_4NCl proved to be the best chlorine source (entries 12–15).

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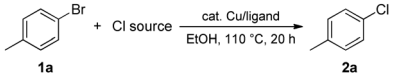
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for isolated compounds. See DOI: 10.1039/c2cc34944b

Table 1 Reaction condition screening[a]



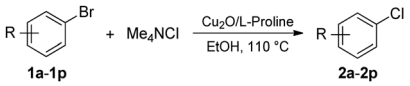
Entry	Cu salt (mol%)	Ligand (mol%)	Cl source	Yield[b] (%)
1	CuCl (10)	None	Me_4NCl	NR[c]
2	CuCl (10)	**L1** (10)	Me_4NCl	19
3	CuBr (10)	**L1** (10)	Me_4NCl	31
4	CuI (10)	**L1** (10)	Me_4NCl	39
5	Cu_2O (5)	**L1** (10)	Me_4NCl	49
6	Cu_2O (5)	**L2** (10)	Me_4NCl	Trace
7	Cu_2O (5)	**L3** (10)	Me_4NCl	Trace
8	Cu_2O (5)	**L4** (10)	Me_4NCl	Trace
9	Cu_2O (5)	**L5** (10)	Me_4NCl	Trace
10	Cu_2O (5)	**L6** (10)	Me_4NCl	74
11	Cu_2O (7)	**L6** (14)	Me_4NCl	82
12	Cu_2O (10)	**L6** (20)	Me_4NCl	98
13	Cu_2O (10)	**L6** (20)	NH_4Cl	NR[c]
14	Cu_2O (10)	**L6** (20)	KCl	17
15	Cu_2O (10)	**L6** (20)	NaCl	12

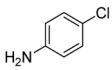
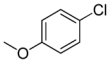
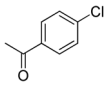
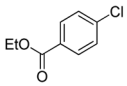
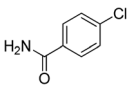
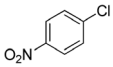
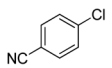
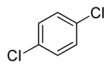
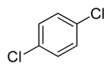
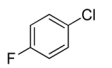
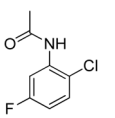
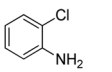
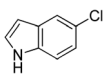
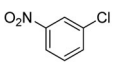
[a] Reaction conditions: 1-bromo-4-methylbenzene (**1a**, 0.2 mmol), chlorine source (2.0 equiv.), Cu salt (5–10 mol%), ligand (10–20 mol%), and EtOH (1.0 mL) in a sealed tube. [b] GC yield. Chlorobenzene was used as an internal standard. [c] No reaction.

The poor reactivities of NH_4Cl, KCl, and NaCl were considered due to their low solubility in the EtOH solvent. Therefore, the subsequent reactions of aryl (**1a–1p**) and heteroaryl (**3a–3g**) bromides with Me_4NCl were performed in the presence of Cu_2O and **L6** as a precatalyst and ligand, respectively, in EtOH at 110 °C.

The reactions of aryl bromides **1a–1p** with Me_4NCl were performed under optimized conditions, and the results are summarized in Table 2. The reaction of bromobenzene (**1b**), the simplest aryl bromide, was completed also within 20 h to offer its corresponding product, chlorobenzene (**2b**), in 87% yield (entry 2). Reactions of both electron-rich (**1a**, **1c**, and **1d**) and electron-deficient (**1e–1g**) aryl bromides proceeded smoothly to produce aryl chlorides **2a** and **2c–2g** in good to excellent yields (entries 1 and 3–7). The electronic properties of the substituents linked to the benzene ring did not strongly affect the reactivity of aryl bromide. The reason why the reaction of 1-chloro-4-nitrobenzene (**1h**) needs a relatively long time to complete remains unclear (entry 8, 65 h, 88% yield). 4-Chlorobenzonitrile (**2i**) was obtained along with an ester product, ethyl 4-chlorobenzoate (**2f**), in 65% and 23% yields, respectively, by reacting 4-bromobenzonitrile (**1i**) with Me_4NCl in the EtOH medium (entry 9). 1,4-Dichlorobenzene (**2j**) was produced when 1,4-dibromobenzene (**1j**) and 1-bromo-4-iodobenzene (**1k**) were reacted for a relatively long time (entries 10 and 11, 97% and 94% yields, respectively). As expected, the fluorine atom remained in the chlorinated product molecule when 1-bromo-4-fluorobenzene (**1l**) was examined (entry 12, 95% yield). Reactions of *N*-(2-bromo-5-fluorophenyl)acetamide (**1m**) and 2-bromoaniline (**1n**) required a relatively long reaction time to complete (entries 13 and 14, 92% and 97% yields, respectively). The relatively low reactivity of *ortho*-substituted aryl bromide was considered to be due to its steric effect. The reactions of 5-bromo-1*H*-indole (**1o**) and 1-bromo-3-nitrobenzene (**1p**) were finally investigated, and the corresponding products **2o** and **2p** were obtained in excellent yields (entries 15 and 16, 98% and 93% yields, respectively).

Table 2 Cu(I)-catalyzed aryl bromide–chloride exchange reactions[a]

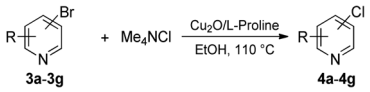


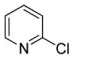
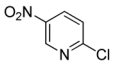
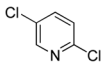
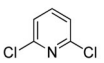
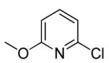
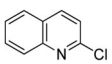
Entry	Bromide **1**	Chloride product **2**		Time (h)	Yield[b] (%)
1	**1a**		**2a**	20	98[c]
2	**1b**		**2b**	20	87[c]
3	**1c**		**2c**	15	94
4	**1d**		**2d**	18	80
5	**1e**		**2e**	17	86
6	**1f**		**2f**	20	86
7	**1g**		**2g**	20	98
8	**1h**		**2h**	65	88
9	**1i**		**2i**	20	65[d]
10	**1j**		**2j**	94	97[c,e]
11	**1k**		**2j**	94	94[c,e]
12	**1l**		**2l**	20	95[c]
13	**1m**		**2m**	50	92
14	**1n**		**2n**	36	97
15	**1o**		**2o**	30	98
16	**1p**		**2p**	20	93

[a] Reaction conditions: aryl bromide (**1a–1p**, 0.5 mmol), Me_4NCl (2.0 equiv.), Cu_2O (10 mol%), **L6** (20 mol%), and EtOH (3 mL) in a sealed tube at 110 °C for the period indicated in the table. [b] Isolated yield. [c] GC yield due to product volatility. [d] Ester product **2f** was also isolated in 23% yield. [e] 4.0 equiv. Me_4NCl was used.

The successful acquisition of aryl chlorides from Cu(I)- catalyzed aryl bromide–chloride exchange reactions encouraged the current authors to examine heteroaryl bromide–chloride exchange reactions. The results are summarized in Table 3. The reaction of

Table 3 Cu(I)-catalyzed heteroaryl bromide–chloride exchange reactions[a]

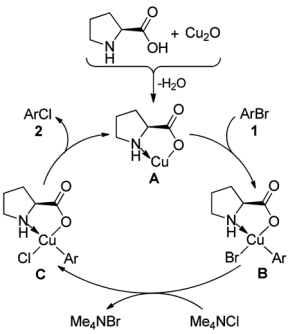


Entry	Bromide **3**	Chloride product **4**		Time (h)	Yield[b] (%)
1	**3a**		**4a**	20	93[c]
2	**3b**		**4b**	20	52[d]
3	**3c**		**4c**	96	81[e]
4	**3d**		**4d**	96	75[e]
5	**3e**		**4e**	24	70
6	**3f**		**4f**	36	89[c]
7	**3g**		**4g**	10	98

[a] Reaction conditions: heteroaryl bromide (**3a–3g**, 0.5 mmol), Me_4NCl (2.0 equiv.), Cu_2O (10 mol%), **L6** (20 mol%), and EtOH (3 mL) in a sealed tube at 110 °C for the period indicated in the table. [b] Isolated yield. [c] GC yield due to product volatility. [d] C–N coupling product **5** was isolated in 11% yield (for the structure of **5**, see ESI). [e] 4.0 equiv. Me_4NCl was used.

2-bromopyridine (**3a**) with Me_4NCl proceeded smoothly to produce the desired product, 2-chloropyridine (**4a**), in 93% yield (entry 1). 2-Chloro-5-nitropyridine (**4b**) was obtained along with C–N coupling product **5** in 52% and 11% yields, respectively, by reacting 2-bromo-5-nitropyridine (**3b**) with Me_4NCl (entry 2). This result indicated that the electron-deficient heteroaryl bromide could undergo a Cu(I)-catalyzed C–N coupling reaction. Similar to the reaction of dibromo-substituted aryl bromide **1j** described earlier, the reactions of 1,5-dibromopyridine (**3c**) and 2,6-dibromopyridine (**3d**) needed a long reaction time (96 h) to complete (entries 3 and 4). The desired products **4c** and **4d** were obtained in 81% and 75% yields, respectively. The reaction of 2-pyridinyl bromide **3e** bearing an electron-donating group MeO on the 6-position also proceeded smoothly to produce the corresponding chlorinated product **4e** in a satisfactory yield (entry 5, 70% yield). Compared with 2-bromopyridine (**3a**), 3-bromopyridine (**3f**) exhibited relatively low reactivity in this type of halogen exchange reaction. 3-Chloropyridine (**4f**) was obtained in 89% yield (entry 6). Finally, the reaction of 2-bromoquinoline (**3g**) was investigated under the same conditions. The Cu(I)-catalyzed halogen exchange reaction of **3g** with Me_4NCl proceeded quickly to produce the corresponding product, 2-chloroquinoline (**4g**), in 98% yield (entry 7).

The plausible mechanism for the Cu(I)-catalyzed halogen exchange reaction is shown in Scheme 2. The interaction between L-proline and Cu_2O would generate a Cu(I) complex **A**. The oxidative addition of **1** to Cu(I) species **A** would produce



Scheme 2 Proposed mechanism.

intermediate **B**. The halogen exchange reaction between **B** and Me_4NCl would occur to generate intermediate **C**, which would subsequently undergo reductive elimination reaction to produce aryl chloride **2** and regenerate Cu(I) catalyst **A**.

In conclusion, a new method for the direct conversion of aryl and heteroaryl bromides into the corresponding chlorides has been achieved using copper catalysis. The new method represents a significant improvement over previous methods: the reaction conditions are mild, the chlorine source (Me_4NCl) is cheap and readily available, and the substrate scope is broad. In addition, the new method has good functional group tolerance. To the best of our knowledge, this catalytic heteroaryl bromide–chloride exchange is the first example reported on such reactions.

We are grateful to the National Natural Science Foundation of China (No. 21073025 and 21072023) for their financial support.

Notes and references

1 (*a*) For a book, see: *Metal Catalyzed Cross Coupling Reactions*, ed. F. Dieterich and P. J. Stang, Wiley-VCH, New York, 1998. For selected reviews, see: (*b*) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082; (*c*) G. C. Fu, *Acc. Chem. Res.*, 2008, **41**, 1555; (*d*) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176.
2 For selected reviews, see: (*a*) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177; (*b*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054.
3 Of the top 10 products by U.S. spending of 2011 in the U.S., three were aryl chlorides, accounting for a combined sales revenue of $16.6 billion. IMS Health Inc. 2011 U.S. Spending Information: www.imshealth.com (accessed 04/06/2012).
4 (*a*) Y. Lai, L. Ma, W. Huang, X. Yu, Y. Zhang, H. Ji and J. Tian, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7349; (*b*) M. K. Gurjar, A. M. S. Murugaiah and D. S. Reddy, *Org. Process Res. Dev.*, 2003, **7**, 309. For selected patents, see: (*c*) Shashiprabha, K. Shridhara, M. Debkiron, B. Padmashree, K. R. Sundarraja and K. Nagarajan, *WO*2009116085, 2009; (*d*) C. Burgarolas Montero, J. Puig Serrano, C. Agnalot Aguilar and J. Bosch Illado, *WO*2006034964, 2006; (*e*) B. B. Molloy, *US*3882236, 1975.
5 (*a*) Y. Matsubara, S. Hirakawa, Y. Yamaguchi and Z.-i. Yoshida, *Angew. Chem., Int. Ed.*, 2011, **50**, 7670; (*b*) G. Sivaprasad, R. Rajesh and P. T. Perumal, *Tetrahedron Lett.*, 2006, **47**, 1783; (*c*) S. Suri, G. S. Sarin and M. Mahendru, *WO*2006021974, 2006.
6 For a review, see: (*a*) T. D. Sheppard, *Org. Biomol. Chem.*, 2009, **7**, 1043; (*b*) W. B. Hardy and R. B. Fortenbaugh, *J. Am. Chem. Soc.*, 1958, **80**, 1716.
7 (*a*) R. Cramer and D. R. Coulson, *J. Org. Chem.*, 1975, **40**, 2267; (*b*) S. H. Yang, C. S. Li and C. H. Cheng, *J. Org. Chem.*, 1987, **52**, 691.
8 H. Wu and J. Hynes Jr., *Org. Lett.*, 2010, **12**, 1192.
9 J. M. Murphy, X. Liao and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 15434.
10 R. H. Szumigala Jr., P. N. Devine, D. R. Gauthier Jr. and R. P. Volante, *J. Org. Chem.*, 2004, **69**, 566.