## **Copper-Catalyzed Aromatic C–H Bond Halogenation Using Lithium Halides as Halogenating Reagents**

Yongzhong Lu,<sup>a</sup> Ruiping Wang,<sup>a</sup> Xixue Qiao,<sup>a</sup> Zengming Shen<sup>\*b</sup>

<sup>a</sup> Department of Chemistry, College of Life and Environment Sciences, Shanghai Normal University, 100 Guilin Road, Shanghai 200234, P. R. of China

<sup>b</sup> School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. of China

Fax +86(21)54741297; E-mail: shenzengming@sjtu.edu.cn

Received 30 November 2010

Dedicated to Prof. Xi-Yan Lu and Prof. Li-Xin Dai for their great contributions to organic chemistry

**Abstract:** The copper-catalyzed C–H halogenation of 2-arylpyridines containing a variety of electron-withdrawing and electron-donating substituents was described. It is worth noting that cheap and easy-to-handle lithium halides were utilized as the halogen sources.

Key words: copper, C–H activation, halogenation, lithium halide, arylpyridines

The development of transition-metal-catalyzed C–H functionalization with the assistance of directing groups has made great progress in the past decades.<sup>1</sup> Of particular interest are Pd-, Pt-, Rh-, and Ru-catalyzed C–H activation reactions. In contrast, less attention has been paid to investigating the Cu-catalyzed C–H activation.<sup>2,3</sup> Copper is one of the most abundant metals on the earth, and one of the most inexpensive and environmentally friendly ones. Consequently, in recent years, increasing effort has been directed toward the copper-catalyzed functionalization of C–H bonds for the efficient construction of C–C bonds,<sup>2</sup> and C–heteroatom bonds.<sup>3</sup>

Halogenated aromatics are not only important structural motifs in natural products and synthetic drugs, but also remarkably useful precursors that are widely employed in organic synthesis, for example, in cross-coupling reactions.<sup>4</sup> The classical approach to halogenated arenes is the direct electrophilic halogenations using Cl<sub>2</sub> and Br<sub>2</sub> as halogenating reagents, however, this method suffers from the inherent disadvantage, including low regioselectivity as well as tedious and dangerous procedures.<sup>5</sup> Recently, palladium-catalyzed halogenations of aromatic sp<sup>2</sup> C-H bond were achieved with the assistance of directing groups, such as amides,<sup>6</sup> pyridines,<sup>7</sup> pyrimidine,<sup>8</sup> carboxylic acids,<sup>9</sup> and oxazolines,<sup>7</sup> whereas their broad utility remains limited by the requirement of the stoichiometric amount of CuCl<sub>2</sub>, NXS (X = Cl, Br, I), or IOAc as halogen sources. More recently, Yu presented a copper-catalyzed ortho C-H chlorination on the aryl ring with pyridine as directing group and large excess of Cl<sub>2</sub>CHCHCl<sub>2</sub> as chlorinating reagent.<sup>10</sup> Notably, cheap lithium halides were

SYNLETT 2011, No. 7, pp 1038–1042 Advanced online publication: 10.03.2011 DOI: 10.1055/s-0030-1259729; Art ID: W34510ST © Georg Thieme Verlag Stuttgart · New York successfully applied in the copper-catalyzed C–H halogenations of electron-rich arenes with dioxygen as the terminal oxidant,<sup>11</sup> while these methods could not extend to electron-deficient arenes. Inspired by these pioneering studies, we launched our effort to develop a simple method for the halogenation of aryl C–H bonds using cheap halogen sources. Herein, we wish to demonstrate an approach to constructing C–X (X = Cl, Br) bonds through copper-catalyzed C–H halogenation of 2-arylpyridines by the use of cheap and easy to handle lithium halides as the halogen sources.

In our initial studies, 2-phenylpyridine (1) was chosen as a model substrate to test the halogenation of aryl C-H bond directed by a pyridyl group. Gratifyingly, the reaction of 2-phenylpyridine (1) with LiCl in the presence of 20 mol% Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O and MnO<sub>2</sub> acting as an oxidant in acetic acid gave the ortho-monochlorinated product 1a in 49% isolated yield and the ortho-dichlorinated product 1b in 25% yield (Table 1, entry 1). This observation indicated that good conversion could be achieved by performing this reaction in the presence of a proper oxidant. Further screening of different oxidants showed that 30%  $H_2O_2$ , (PhCOO)<sub>2</sub>, KMnO<sub>4</sub>, and Ce(SO<sub>4</sub>)<sub>2</sub> could provide the mono- and dichlorinated products in low to good yields, however, these oxidants could not give a good selectivity (Table 1, entries 2-5). Other oxidants, such as TBHP, BQ, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, and Oxone were observed to be ineffective for this reaction (Table 1, entries 6–9). It should be noted that the use of  $CrO_3$  as an oxidant provided the dichlorinated product 1b in 88% yield as well as 8% of the monochlorinated product 1a after prolonging the reaction time to 3 days (Table 1, entry 10). Finally, the dichlorinated product 1b could be obtained in 71% isolated yield in the presence of five equivalents of Ac<sub>2</sub>O as an additive without using Ph<sub>3</sub>P ligand (Table 1, entry 11).

Next, we screened different types of Cu(II) and Cu(I) catalysts, such as Cu(OAc)<sub>2</sub>, CuCl<sub>2</sub>, Cu(OTf)<sub>2</sub>, CuO (nano), CuCl, CuI, and Cu<sub>2</sub>O, and found these Cu species could mediate this reaction to provide the chlorinated products, but with lower ratios and yields of **1a** and **1b** compared to that of Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (Table 2). Notably, the reaction did not occur in the absence of a copper catalyst (Table 2, entry 9). Instead of LiCl, both NaCl and KCl could also promote the chlorination of 2-phenylpyridine (**1**) under

Table 1 Screening of Oxidants for the C-H Halogenation<sup>a</sup>



1b

Entry	Oxidant	Time (h)	Yield of $1a$	Yield of $1b$
1¢	MnO	19	49	25
1 2 <sup>d</sup>	$H_2O_2$	48	26	46
3 <sup>d</sup>	(PhCOO) <sub>2</sub>	36	42	36
4	KMnO <sub>4</sub>	24	40	12
5	$Ce(SO_4)_2$	48	26	4
6 <sup>d</sup>	TBHP	36	7	_
7 <sup>d</sup>	BQ	36	n.r.	n.r.
8	$K_2S_2O_8$	48	n.r.	n.r.
9	Oxone	48	7	_
10	CrO <sub>3</sub>	72	8	88
11 <sup>e</sup>	CrO <sub>3</sub>	48	_	71 <sup>f</sup>

<sup>a</sup> Reaction conditions: **1** (30 mg, 0.19 mmol), LiCl (33 mg, 0.77 mmol), Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (9.4 mg, 20 mol%), Ph<sub>3</sub>P (20.3 mg, 40

mol%), AcOH (1.5 mL), 150 °C, oxidant (4 equiv), in a sealed tube. <sup>b</sup> GC yield with *n*-dodecane as an internal standard.

<sup>c</sup> Isolated yield.

<sup>d</sup> Cu(NO<sub>3</sub>)<sub>2</sub>· $^{3}H_{2}O$  (14 mg, 30 mol%), Ph<sub>3</sub>P (30.4 mg, 60 mol%), oxidant (1.2–1.5 equiv).

 $^{\rm e}$  CrO<sub>3</sub> (2 equiv), Ac<sub>2</sub>O (5 equiv) as an additive without using Ph<sub>3</sub>P.  $^{\rm f}$  Compound **1b** was isolated.

the standard conditions, whereas the lower selectivities were observed as compared to that of LiCl (with NaCl, 71% yield, 14:86 ratio of **1a** and **1b**; with KCl, 78% yield, 1:1 ratio of **1a** and **1b**). From the viewpoint of organic synthesis, we expected to achieve high monoselectivity of the aromatic C–H chlorination by the addition of ligand. Disappointingly, a wide range of ligands, such as 2,2-bipyridine, TMEDA, dppe, dppf, and 1,10-phenanthroline did not play a positive role in improving the selectivity of this reaction (for details, see Supporting Information).

With these conditions in hand, we examined the scope of this reaction by varying substituents on the aryl and/or pyridyl rings. As shown in Table 3, a variety of substrates 1-13 bearing electron-withdrawing or electron-donating substituents afforded the chlorinated products in moderate yields, albeit with poor selectivity. The methyl group at the *para* position on the phenyl ring in compound **2** pro-

 Table 2
 Copper-Mediated C-H Halogenation<sup>a</sup>



			10	
Entry	[Cu]	Yield of $1a (\%)^b$ Yield of $1b (\%)^b$		
1 <sup>c</sup>	Cu(OAc) <sub>2</sub>	42	22	
2	CuCl <sub>2</sub>	25	2	
3 <sup>d</sup>	CuCl	26	_	
4 <sup>d</sup>	CuI	27	_	
5	Cu <sub>2</sub> O	44	9	
6	Cu(OTf) <sub>2</sub>	36	11	
7	Cu(PPh <sub>3</sub> ) <sub>2</sub> NO <sub>3</sub>	20	51	
8	CuO (nano)	36	7	
9	none	trace	-	

<sup>a</sup> Reaction conditions: 1 (31 mg, 0.2 mmol), LiCl (34 mg, 0.8 mmol), CrO<sub>3</sub> (24 mg, 0.24 mmol), AcOH (1.5 mL), Cu complex (20 mol%), 150 °C, 2 d, in a sealed tube.

<sup>b</sup> GC yield with *n*-dodecane as an internal standard.

° Isolated yield.

<sup>d</sup> Only monochlorinated product **1a** was observed by GC.

vided the ortho-chlorinated products 2a and 2b in 62% total yields (52:48 ratio, Table 3, entry 2). Interestingly, the electron-withdrawing CF<sub>3</sub> group also gave the orthodichlorinated product 4b (58% yield) as a major product together with the monochlorinated product 4a (23% yield, Table 3, entry 4). In the presence of the ortho substitutent on the pyridine (Table 3, entry 9), the monochlorinated product 9a was observed as a single product in 32% yield, which indicates that the steric hindrance around the N atom of the pyridyl group prevents further chlorination. The analogous result was observed in compound 11 with isoquinoline as a directing group (Table 3, entry 11). When the electron-donating methoxyl group is attached to the pyridine, the chlorination on the pyridyl ring was observed (Table 3, entries 7, 8, and 10). The bromination reactions using LiBr afforded mixtures of brominated products in 70-83% total yields with low regioselectivity (Table 3, entries 14–16). At the same time, it is observed that the reaction turned red-brown in color upon heating, possibly implicating the formation of molecular bromine in solution.<sup>12</sup> Although the mechanism of copper-catalyzed halogenation of 2-arylpyridines is not clear so far, it can be suggested that a free-radical mechanism is likely to operate in these systems, and electrophilic halogenation

Synlett 2011, No. 7, 1038–1042 © Thieme Stuttgart · New York

pathway is also possible. Mechanistic aspects of this reaction are under investigation.

### Table 3 Copper-Mediated C-H Halogenation<sup>a</sup> Entry Substrate Time Product Yield (%)<sup>b</sup> (d) 2 1 71 1b 1 2a 32 2 6 30 2 2b MeC Ċ 3a 24 0.8 3 35 MeO 3 MeC ĊI 3b F<sub>3</sub>C 4a 23 2 4 58 F<sub>3</sub>C 4 F<sub>3</sub>C 4b MeC MeC 0.8 5 38 5





10c

Synlett 2011, No. 7, 1038-1042 © Thieme Stuttgart · New York

5a

Table 3 Copper-Mediated C-H Halogenation<sup>a</sup> (continued)



 Table 3
 Copper-Mediated C-H Halogenation<sup>a</sup> (continued)



<sup>a</sup> Reaction conditions:  $Cu(NO_3)_2 \cdot 3H_2O$  (20 mol%),  $CrO_3$  (2.0 equiv), LiX (X = Cl or Br, 4.0 equiv),  $Ac_2O$  (5.0 equiv), AcOH, in a sealed tube.

<sup>b</sup> Isolated yield.

 $^{\rm c}$  Reaction conditions: Cu(NO\_3)\_2'3H\_2O (20 mol%), MnO\_2 (4.0 equiv), LiCl (4.0 equiv), AcOH, in a sealed tube.

<sup>d</sup> *Conditions*: CuO (nano) (20 mol%),  $CrO_3$  (2.0 equiv), LiBr (4.0 equiv),  $Ac_2O$  (5.0 equiv), AcOH, in a sealed tube.

In summary, we developed a method for the copper-mediated C–H chlorination and bromination of 2-arylpyridines substituted with both electron-donating and electronwithdrawing groups by the use of cheap LiX (X = Cl, Br) as the halogen sources. Further investingations to improve the regioselectivity and probe the mechanism of this reaction are in progress in our lab.

# Copper-Catalyzed Aromatic C–H Bond Halogenation; Typical Procedure

In a sealed tube, a solution of substrate 2 (67.6 mg, 0.4 mmol), LiCl (67.2 mg, 1.6 mmol), Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (19.4 mg, 0.08 mmol), CrO<sub>3</sub> (80 mg, 0.8 mmol), Ac<sub>2</sub>O (204 mg, 2 mmol) in AcOH (3 ml) was stirred at 150 °C for 6 d. Then the mixture was neutralized with NaHCO<sub>3</sub> (sat. solution) and extracted with EtOAc ( $3 \times 15$  mL). The combined organic layers was washed with brine  $(2 \times 15 \text{ mL})$  and dried over Na2SO4. After evaporation, the residue was purified via TLC with PE–Et<sub>2</sub>O [2:1 (v/v)] as the eluent to provide oily product **2a** in 32% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 2.38$  (s, 3 H), 7.17 (d, J = 7.6 Hz, 1 H), 7.26 (d, J = 6.0 Hz, 1 H), 7.30 (s, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.74 (t, *J* = 8.0 Hz, 1 H), 8.71 (d, J = 5.2 Hz, 1 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 20.9$ , 122.1, 124.8, 127.8, 130.5, 131.3, 131.7, 135.7, 136.2, 139.9, 149.4, 156.8. IR (KBr): v = 2924, 1609, 1585, 1463, 1430, 874, 783 cm<sup>-1</sup>. MS (EI):  $m/z = 205.1 [M^+ ({}^{37}Cl)] (19.72), 203.1 [M^+ ({}^{35}Cl)] (66.28),$ 169.1, 168.1, 167.1, 153.1. HRMS (EI): *m/z* calcd for C<sub>12</sub>H<sub>10</sub>ClN: 203.0502; found: 203.0505.

#### 2-(2,6-Dichloro-4-methylphenyl)pyridine (2b)<sup>10</sup>

Oil; 30% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.30 (s, 3 H), 7.16 (s, 2 H), 7.31–7.35 (m, 2 H), 7.73 (td, *J* = 1.6, 7.6 Hz, 1 H), 8.68 (d, *J* = 4.8 Hz, 1 H). IR (KBr): v = 2923, 1731, 1600, 1494, 1452, 736, 696 cm<sup>-1</sup>. MS (EI): *m/z* = 241.0 [M<sup>+</sup> (<sup>37</sup>Cl<sup>37</sup>Cl)] (3.10), 239.0 [M<sup>+</sup> (<sup>37</sup>Cl<sup>35</sup>Cl)] (19.70), 237.0 [M<sup>+</sup> (<sup>35</sup>Cl<sup>35</sup>Cl)] (30.51), 205.0, 204.0, 202.0, 167.1, 166.1, 139.1, 138.0.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

**Primary Data** for this article are available online at http:// www.thieme-connect.com/ejournals/toc/synlett and can be cited using the following DOI: 10.4125/pd0009th. FID data and associated files for the <sup>1</sup>H and <sup>13</sup>C NMR spectra are available.

#### Acknowledgment

This work was supported by the National Natural Sciences Foundation of China (20852004, 20902058), Shanghai Pujiang Program (09PJ1408100), Shanghai Education Committee (ssd09018), and Shanghai Jiao Tong University.

#### References

- For reviews, see: (a) Dyker, G. Angew. Chem. Int. Ed. 1999, 38, 1698. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. Chem. Rev. 2002, 102, 1731; and references cited therein. (c) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. Chem. Soc. Rev. 2009, 38, 3242. (d) Lyons, T. W.; Sanford, M. S. Chem. Rev. 2010, 110, 1147. (e) Bellina, F.; Rossi, R. Chem. Rev. 2010, 110, 1082. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Chem. Rev. 2010, 110, 624.
- (2) For representative examples of the copper-catalyzed C–C bond formation, see: (a) Tang, B. X.; Song, R. J.; Wu, C. Y.; Liu, Y.; Zhou, M. B.; Wei, W. T.; Deng, G. B.; Yin, D. L.; Li, J. H. J. Am. Chem. Soc. 2010, 132, 8900. (b) Mousseau, J. J.; Bull, J. A.; Charette, A. B. Angew. Chem. Int. Ed. 2010, 49, 1115. (c) Do, H. Q.; Daugulis, O. Org. Lett. 2010, 12,

2517. (d) Kawano, T.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 1764. (e) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2009**, *11*, 1511. (f) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

- (3) For representative examples of the copper-catalyzed C-heteroatom bond formation, see: (a) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. J. Am. Chem. Soc. 2010, 132, 6900.
  (b) Zhang, L. N.; Ang, G. Y.; Chiba, S. Org. Lett. 2010, 12, 3682. (c) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. Angew. Chem. Int. Ed. 2009, 48, 8078. (d) Wang, W. H.; Luo, F.; Zhang, S. H.; Cheng, J. J. Org. Chem. 2010, 75, 2415. (e) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. J. Am. Chem. Soc. 2010, 132, 12068.
- (4) (a) Ullmann's Encyclopedia of Industrial Chemistry, 6th ed.;
   Wiley-VCH: Weinheim, 2002. (b) Davos, S. G.
   Organotransition Metal Chemistry: Application to Organic Synthesis; Pergamon Press: Oxford, 1982.
- (5) (a) Sasson, Y. In *The Chemistry of Functional Group: The Chemistry of Halides, Pseudo-halides and Azides*, Part 1, Suppl. D2; Patai, S.; Rappoport, Z., Eds.; John Wiley and Sons: Chichester, **1995**. (b) de la Mare, P. D. B. *Electrophilic Halogenation*; Cambridge University Press: New York, **1976**.
- (6) Wan, X. B.; Ma, Z. X.; Li, B. J.; Zhang, K. Y.; Cao, S. K.; Zhang, S. W.; Shi, Z. J. J. Am. Chem. Soc. 2006, 128, 7416.
- (7) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. Org. Lett. 2006, 8, 2523.
- (8) (a) Song, B. R.; Zheng, X. J.; Mo, J.; Xu, B. Adv. Synth. Catal. 2010, 352, 329. (b) Zheng, X. J.; Song, B. R.; Li, G. F.; Liu, B. X.; Deng, H. M.; Xu, B. Tetrahedron Lett. 2010, 51, 6641.
- (9) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. Angew. Chem. Int. Ed. 2008, 47, 5215.
- (10) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J.-Q. J. Am. *Chem. Soc.* **2006**, *128*, 6790.
- (11) (a) Yang, L. J.; Lu, Z.; Stahl, S. S. *Chem. Commun.* 2009, 6460. (b) Menini, L.; Gusevskaya, E. V. *Chem. Commun.* 2006, 209. (c) Menini, L.; Parreira, L. A.; Gusevskaya, E. V. *Tetrahedron Lett.* 2007, 48, 6401.
- (12) Barnes, J. C.; Hume, D. N. Inorg. Chem. 1963, 2, 444.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.