Lithium pipecolinate as a facile and efficient ligand for copper-catalyzed hydroxylation of aryl halides in water[†]

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Direct hydroxylation of a wide scope of aryl halides was catalyzed by a combination of CuI and lithium pipecolinate in water with yields up to 92%.

Phenols are not only important structural motifs occurring in numerous pharmaceuticals, polymers, and natural products, but also serve as versatile synthetic intermediates in preparing oxygenated heterocycles¹ and aryl ethers.² The classical nonoxidative preparation of this class of compounds include transformation of arene diazonium salts in the presence of a copper complex, nucleophilic substitution of activated aryl halides and the benzyne synthetic route. However, in the former case, the presence of an amino group is necessary. In the latter case, the nucleophilic substitution reaction is often limited by the necessarily harsh reaction conditions or the electronic requirements of the substrate.^{2,3} A milder method based on an iridium phosphine catalyst for the preparation of non-ortho-substituted phenols involved two steps: C-H activation/borylation and oxidation.⁴ Recently, several palladium/phosphine-catalyzed processes have been developed for selective formation of phenols from different aryl halides and hydroxide salts.⁵ More recently, an iron-catalyzed method has been reported for conversion of aryl halides to phenols in water at 180 °C.⁶ Although copper has led to a resurgence of interest in an Ullmann-type coupling reaction from an economic and industrial point of view,⁷ the copper-mediated direct hydroxylation of aryl halides using hydroxide salts as nucleophiles is rare.⁸ On the other hand, water has attracted much attention as reaction media because of its low cost, availability, safety and environmentally benign nature.⁹ However, two additional challenges (e.g., water tolerance for the catalyst10 and the associated problem of substrate solubilities and reactivities) will be resulted in. Therefore, to explore other efficient copper-mediated and ligandassisted catalytic systems for direct conversion of aryl halides into phenols in water is still in demand and challenging.

In addition, although alkali metal salts of amino acids as efficient catalysts or ligands have been successfully applied in some asymmetric reactions,¹¹ studies of them in coupling reactions are less developed. To the best of our knowledge, there were only two reported examples, in which amino acid salts were used as the catalysts for the reaction of aryl halides or vinyl bromides with sulfinic acid salts.¹²

As part of our endeavours to develop environmentally friendly protocols,¹³ herein we disclose direct hydroxylation of aryl halides with sodium hydroxide as a nucleophile catalyzed by a combination of CuI and lithium pipecolinate in water.

Initially, iodobenzene 1 was chosen as a model substrate to optimize the reaction conditions, and the results are listed in Table 1. In general, all of the four ligands were effective to give moderate yields ranging from 50–66%, and lithium pipecolinate L4 was found to be a little better than the others (Table 1, entries 1–4). Control experiments confirmed that only 35%

Table 1 Optimization studies for the Cu-catalyzed direct hydroxyla-
tion of iodobenzene 1 in water^a



^a Unless otherwise noted, the reactions were carried out using iodobenzene (1.0 mmol), Cu source (10 mol%), ligand (20 mol%), base (3.0 mmol) and (*n*-Bu)₄NF (20 mol%) in water (3 mL) for 24 h.
^b Determined by GC-MS using 1,4-dichlrobenzene as internal standard.
^c Without addition of (*n*-Bu)₄NF.

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vield of the desired product 2a was detected without the aid of a ligand (Table 1, entry 15). Meanwhile, only 40% yield was obtained in the absence of $(n-Bu)_4NF$ (Table 1, entry 5). The catalytic activities of different copper sources were compared, and CuI was found to be superior to others (Table 1, entries 4 and 6–10). After screening a set of bases (e.g., K₂CO₃, NaOH and KOH), we found that both NaOH and KOH gave the best result of 76% yield (Table 1, entries 10 and 12). Meanwhile, weak bases such as K₂CO₃ provided an inferior result (Table 1, entry 11). Taking into consideration the cost, NaOH was chosen as the base for the further experiments. Reaction temperature was another important factor to affect the results. As shown in Table 1, higher temperature had a beneficial effect on product yield (entries 10, 13 and 14). Taking into consideration the base-sensitivity of some functional groups at high temperature, 130 °C was chosen as the appropriate temperature for this reaction. In summary, the optimal conditions for the direct hydroxylation of aryl halides in water consist of the combination of CuI (10 mol%), L4 (20 mol%), (n-Bu)₄NF (20 mol%) and NaOH (3 equiv.) at 130 °C for 24 h.

With the optimized reaction conditions in hand, the scope of aryl halides was then explored. As shown in Table 2, different aryl iodides, aryl bromides and even aryl chlorides were transformed into the corresponding phenols with moderate to excellent isolated yields ranging from 45% to 91%. The yields for reactions of aryl iodides were slightly superior to aryl bromides (Table 2, entries 1-8). Moreover, the good yields obtained in the reactions of p-chloroiodobenzene, p-bromoiodobenzene or p-chlorobromobenzene implied that there was good chemoselectivity between iodide, bromide or chloride (Table 2, entries 7-9). It was observed that steric hindrance of the substituent of the substrate had a significant effect on the reactions. For example, p-bromotoluene gave the desired product in 69% yield, o-bromotoluene afforded the corresponding product in 60% yield, while 2-bromo-m-xylene gave only 45% product under the same conditions (Table 2, entries 6 and 15-16). Similar phenomenons have been observed in recently reported iron-catalyzed hydroxylation of aryl halides.⁶ Meanwhile, the catalytic system could well tolerate a variety of functional groups, including nitro, hydroxy, carboxyl acid, aldehyde, methoxy, cyano and ketone groups (Table 2, entries 3-4, 10-13, 17-19, 22-23 and 26). Heterocyclic compounds, such as 2-bromopyridine and 3-bromopyridine could also afford the corresponding products in 75% and 74% yields, respectively (Table 2, entries 24 and 25). In addition, in most cases, aryl halides with electron-withdrawing groups could afford the corresponding products in good to excellent yields. It is noteworthy that aryl chloride with two strong electron-withdrawing groups, such as 2,4-dinitrochlorobenzene, could also give 2,4-dinitrophenol in 70% yield, though this class of reaction has not yet been investigated in detail (Table 2, entry 26).

In summary, we have developed a simple, efficient, economical and environmentally friendly protocol for copper-mediated and ligand-assisted direct hydroxylation of aryl halides in water. This method avoids the use of toxic organic solvents as well as inert reaction conditions. Moreover, the catalyst can be easily generated using a mixture of CuI and lithium

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Table 2Direct hydroxylation of aryl halides catalyzed by CuI/L4 inwater^aCul. L4

	ArX	(n-Bu) ₄ NF, NaOH, H ₂ O	ArOH	
		130 °C, 24h	20.0	
Entry	ArX	Product	<u>2a-v</u>	Yield (%)
1		Он	2a	85
2	→ Br	он	2a	72
3	0 ₂ N-{	О₂№→ОН	2b	91
4	O ₂ NBr	02NОН	2b	81
5	Me	Ме—ОН	2c	79
6	Me Br	Ме—————————————————————————————————————	2c	69
7	CI-	сі—	2d	72
8	CIBr	сі—	2d	67
9	Br-	BrОН	2e	80
10		OH NO ₂	2f	85
11	ССС	ОН	2g	76
12	ноос-	ноосон	2h	72
13		он	2i	70
14	NH ₂	OH NH2	2j	74
15	Br	OH	2k	60
	Me	Me		
16	⟨Br Me	Ме Ме	21	45
17	MeOBr	МеООН	2m	62
18	Br	Он	2n	60
19	Br	OH	20	50
20	FBr	FOH	2p	65
21	Br	OH	2q	62
22	NC-	№- ОН	2r	80
23	Me Br	о Ме	2s	75
24	⟨Br	́∩⊢он	2t	75
25	Br	OH N	2u	74
26			2v	70
	··· - 2			

^{*a*} Reactions were carried out using aryl halide (1.0 mmol), CuI (10 mol%), L4 (20 mol%), NaOH (3.0 mmol) and (*n*-Bu)₄NF (20 mol%) in water (3 mL) at 130 °C for 24 h. ^{*b*} Isolated yield after column chromatography.

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Notes and references

- 1 (a) J. H. P. Tyman, *Synthetic and Natural Phenols*, Elsevier, New York, 1996; (b) Z. Rappoport, *The Chemistry of Phenols*, Wiley-VCH, Weinheim, 2003.
- 2 C. A. Fyfe, in *The Chemistry of the Hydroxyl Group*, ed. S. Patai, Wiley-Interscience, New York, 1971, vol. 1, pp. 83–127.
- 3 (a) C. Hoarau and T. R. R. Pettus, *Synlett*, 2003, 127; (b) P. Hanson, J. R. Jones, A. B. Taylor, P. H. Walton and A. W. Timms, *J. Chem. Soc.*, *Perkin Trans.* 2, 2002, 1135; (c) T. George, R. Mabon, G. Sweeney, J. B. Sweeney and A. Tavassoli, *J. Chem. Soc.*, *Perkin Trans.* 1, 2000, 2529 and references cited therein.
- 4 R. E. Maleczka, F. Shi, D. Holmes and M. R. Smith, J. Am. Chem. Soc., 2003, 125, 7792.
- 5 (a) A. G. Sergeev, T. Schulz, C. Torborg, A. Spannenberg, H. Neumann and M. Beller, Angew. Chem., Int. Ed., 2009, 48, 7595; (b) T. Schulz, C. Torborg, B. Schäffner, J. Huang, A. Zapf, R. Kadyrov, A. Börner and M. Beller, Angew. Chem., Int. Ed., 2009, 48, 918; (c) M. C. Willis, Angew. Chem., Int. Ed., 2007, 46, 3402; (d) B. J. Gallon, R. W. Kojima, R. B. Kaner and P. L. Diaconescu, Angew. Chem., Int. Ed., 2007, 46, 7251; (e) G. S. Chen, A. S. C. Chan and F. Y. Kwong, Tetrahedron Lett., 2007, 48, 473; (f) K. W. Anderson, T. Ikawa, R. E. Tundel and S. L. Buchwald, J. Am. Chem. Soc., 2006, 128, 10694.

- 6 Y. L. Ren, L. Cheng, X. Z. Tian, S. Zhao, J. J. Wang and C. D. Hou, *Tetrahedron Lett.*, 2010, **51**, 43.
- 7 For recent reviews of copper-catalyzed cross-coupling reactions, see: (a) F. Monnier and M. Taillefer, Angew. Chem., Int. Ed., 2009, 48, 6954; (b) F. Monnier and M. Taillefer, Angew. Chem., Int. Ed., 2008, 47, 3096; (c) G. Evano, N. Blanchard and M. Toumi, Chem. Rev., 2008, 108, 3054; (d) I. P. Beletskaya and A. V. Cheprakov, Coord. Chem. Rev., 2004, 248, 2337; (e) S. V. Ley and A. W. Thomas, Angew. Chem., Int. Ed., 2003, 42, 5400; (f) K. Kunz, U. Scholz and D. Ganzer, Synlett, 2003, 2428.
- 8 For three systematic studies of copper-mediated direct hydroxylation of aryl halides, see: (a) C. M. Kormos and N. E. Leadbeater, *Tetrahedron*, 2006, **62**, 4728; (b) A. Tlili, N. Xia, F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 8725; (c) D. B. Zhao, N. J. Wu, S. Zhang, P. H. Xi, X. Y. Su, J. B. Lan and J. S. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 8729.
- 9 For recent reviews of organic reactions in water, see: (a) S. Kobayashi and K. Manabe, Acc. Chem. Res., 2002, 35, 209; (b) U. M. Lindstrom, Chem. Rev., 2002, 102, 2751; (c) C.-J. Li, Chem. Rev., 2005, 105, 3095; (d) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, Angew. Chem., Int. Ed., 2005, 44, 3275; (e) C.-J. Li and L. Chen, Chem. Soc. Rev., 2006, 35, 68; (f) L. Chen and C.-J. Li, Adv. Synth. Catal., 2006, 348, 1459; (g) M. Carril, R. SanMartin and E. Dominguez, Chem. Soc. Rev., 2008, 37, 639; (h) A. Chanda and V. V. Fokin, Chem. Rev., 2009, 109, 725.
- 10 D. Sinou, Adv. Synth. Catal., 2002, 344, 221.
- (a) M. Yamaguchi, N. Yokota and T. Minami, J. Chem. Soc., Chem. Commun., 1991, 1088; (b) M. Yamaguchi, Y. Igarashi, R. S. Reddy, T. Shiraishi and M. Hirama, Tetrahedron, 1997, 53, 11223; (c) X. H. Liu, B. Qin, X. Zhou, B. He and X. M. Feng, J. Am. Chem. Soc., 2005, 127, 12224; (d) A. Sato, M. Yoshida and S. Hara, Chem. Commun., 2008, 6242; (e) Z. L. Shen and S. J. Ji, Synth. Commun., 2009, 39, 775.
- (a) W. Zhu and D. W. Ma, J. Org. Chem., 2005, 70, 2696;
 (b) W. L. Bao and C. N. Wang, J. Chem. Res., 2006, 396.
- (a) L. Liang, Z. K. Li and X. G. Zhou, Org. Lett., 2009, 11, 3294;
 (b) Y. Wang, Z. Q. Wu, L. X. Wang, Z. K. Li and X. G. Zhou, Chem.-Eur. J., 2009, 15, 8971.