

A Simple and Practical Copper-Catalyzed Approach to Substituted Phenols from Aryl Halides by Using Water as the Solvent

Daoshan Yang and Hua Fu*^[a]

Phenols are important building blocks in numerous pharmaceuticals, polymers, and natural products,^[1] and their preparation usually uses an oxidative strategy, for example, the cumene-phenol process (Hock process), based on the decomposition of cumene hydroperoxide with sulfuric acid to give phenol and acetone, is the current method for phenol synthesis used worldwide.^[2] Unfortunately, the method shows low efficiency (only 5 % overall yield). Smith, Maleczka, and co-workers have developed a novel approach to non-*ortho*-substituted phenols involving a one-pot, iridium-catalyzed aromatic C–H bond borylation/oxidation sequence under milder conditions.^[3] Clearly, the direct hydroxylation of readily available aryl halides is an appealing approach to substituted phenols.^[4,5] In the past, the nonoxidative preparation of this class of compounds involving nucleophilic aromatic substitution of activated aryl halides was often performed under harsh reaction conditions.^[6] Recently, several research groups have developed efficient palladium-catalyzed hydroxylation reactions of aryl halides with hydroxide salts under mild conditions,^[5,7] even at room temperature.^[8] Considering the ready availability and low toxicity of copper catalysts and their ligands,^[9] the development of a cheaper copper-catalyzed system enabling the direct hydroxylation of aryl halides has become an important goal. Very recently, the efficient copper-catalyzed synthesis of phenols from aryl halides was reported under milder conditions (100–130 °C), and research showed that a well-defined ratio of water/organic solvent was the key factor for the success of the method, however, water alone was inefficient.^[10] It is well known that water is the most economical and envi-

ronmentally friendly solvent in the world,^[11] and the wide applications of substituted phenols found in many fields have stimulated research into the development of new strategies for their synthesis in water. However, synthesis of organic molecules in water entails the additional challenges of water tolerance for the catalyst/ligand systems and the associated problems of substrate solubility and reactivity.^[12] Kormos and Leadbeater attempted the direct conversion of aryl halides to phenols in water with microwave heating, unfortunately, high temperatures (200–300 °C) were required, and the resulting yields were very low.^[13] In a continuation of our endeavors to develop copper-catalyzed cross-coupling reactions in organic solvents^[14] and in neat aqueous medium^[15] we, herein, report a simple, practical and efficient copper-catalyzed synthesis of substituted phenols from aryl halides by using environmentally benign water as the solvent under mild conditions.

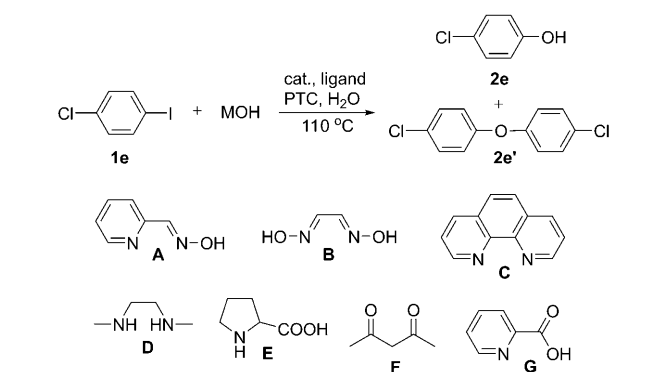
First, 1-chloro-4-iodobenzene (**1e**) was chosen as the model substrate to optimize the reaction conditions, including catalysts, ligands, and bases under a nitrogen atmosphere. As shown in Table 1, tetrabutylammonium hydroxide was used as the base and phase transfer catalyst (PTC) at 110 °C with CuI (10 mol %) as the catalyst and pyridine-2-aldoxime (PAO; 20 mol %) as the ligand (relative to the amount of **1e**) in water (Table 1, entry 1), and the reaction provided 4-chlorophenol (**2e**) in 45 % yield with the corresponding symmetric ether appearing in 15 % yield. Other bases, namely, KOH and CsOH (Table 1, entries 2 and 3, respectively), were tested by using tetrabutylammonium bromide (TBAB; 20 mol %) as the PTC, and CsOH showed better activity. Other copper salts were screened (Table 1, entries 4–6), and Cu₂O proved to be the best choice (Table 1, entry 6). No target product was observed in the absence of ligand (Table 1, entry 7), and **2e** was afforded in 32 % yield without addition of PTC (Table 1, entry 8). Other ligands were also investigated, and the ligand for copper catalysis, pyridine-2-aldoxime (PAO), afforded the highest efficiency (Table 1, entry 6 vs. entries 9–14).

The scope of copper-catalyzed hydroxylation of aryl halides was investigated under our optimized conditions (Cu₂O

[a] D. Yang, Prof. Dr. H. Fu
Key Laboratory of Bioorganic Phosphorus Chemistry and
Chemical Biology (Ministry of Education)
Department of Chemistry, Tsinghua University
Beijing 100084 (China)
Fax: (+86) 10-62781695
E-mail: fuhua@mail.tsinghua.edu.cn

Supporting information for this article is available on the WWW
under <http://dx.doi.org/10.1002/chem.200903468>.

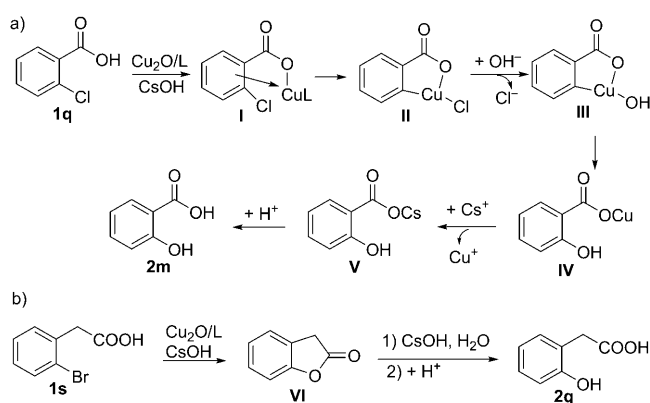
Table 1. Copper-catalyzed hydroxylation of **1e** to form **2e** in water: optimization of conditions.^[a]



Entry	Cat.	L	MOH	Yield (2e) [%] ^[b]	Yield (2e') [%] ^[b]
1 ^[c]	CuI	A	<i>n</i> Bu ₄ NOH	45	15
2	CuI	A	KOH	61	13
3	CuI	A	CsOH	66	13
4	CuBr	A	CsOH	75	10
5	CuCl	A	CsOH	60	7
6	Cu ₂ O	A	CsOH	82	5
7	Cu ₂ O	–	CsOH	0	0
8 ^[c]	Cu ₂ O	A	CsOH	32	0
9	Cu ₂ O	B	CsOH	trace	0
10	Cu ₂ O	C	CsOH	35	0
11	Cu ₂ O	D	CsOH	12	0
12	Cu ₂ O	E	CsOH	17	0
13	Cu ₂ O	F	CsOH	5	0
14	Cu ₂ O	G	CsOH	22	0

[a] Reaction conditions: **1e** (1 mmol), MOH (3 mmol), catalyst (0.05 mmol for Cu₂O, 0.1 mmol for others), ligand (0.1 mmol), TBAB (0.2 mmol), water (1 mL) under a nitrogen atmosphere. Reaction time (48 h). [b] Yield of the isolated product. [c] In the absence of TBAB.

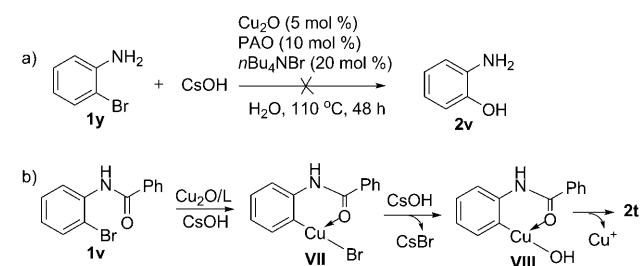
(5 mol%) as the catalyst, PAO (10 mol%) as the ligand, TBAB (20 mol%) as the phase-transfer catalyst, CsOH (3 equiv) as the base, and water as the solvent). As shown in Table 2, most of the substrates examined provided good to excellent yields at 100 or 110 °C. For the aryl iodides, the substrates containing electron-withdrawing groups showed higher reactivity than ones containing electron-donating groups (compare Table 2, entries 1–13). Aryl bromides containing activated groups (such as carboxyl, nitro, and aldehyde) afforded high yields (Table 2, entries 14–16, 20 and 21). Interestingly, 2-chlorobenzoic acid (**1q**) and 2-chloropyridine-3-carboxylic acid (**1r**) also exhibited higher activity (Table 2, entries 17 and 18). In fact, aryl chlorides were weak substrates in the previous copper-catalyzed Ullmann-type couplings,^[9] and the results showed an *ortho*-substituent effect^[16] of the carboxyl group during hydroxylation, as shown in Scheme 1a. Coordination of **1q** with Cu₂O first forms **I** in the presence of base (CsOH). Oxidative addition of **I** provides the coordination complex **II**, and exchange of OH[–] from CsOH with the Cl[–] of **II** gives **III**. Reductive elimination of **III** leads to **IV**, treatment of **IV** with CsOH gives **V** with release of the copper catalyst, and acidification of **V** affords the target product (**2m**). Unactivated 2-(2'-bromophenyl)acetic acid (**1s**) almost quantitatively transformed



Scheme 1. A possible mechanism for the hydroxylation of 2-chlorobenzoic acid (**1q**) and 2-(2'-bromophenyl)acetic acid (**1s**).

into the target product (**2q**) (Table 2, entry 19), and the pathway can undergo formation of the intra-ester (**VI**) and the hydrolysis sequence as shown in Scheme 1b.

Compounds **1v** and **1w** also provided the corresponding products (**2t** and **2u**) in moderate yields with minor products 2-aminophenol and 2-amino-5-methylphenol from hydrolysis of the amide (–NHCOPh) appearing (Table 2, entries 22 and 23). However, unactivated 2-bromobenzeneamine (**1y**) did not work under our standard conditions (Scheme 2a), and the results above showed an *ortho*-substituent effect^[16] of the –NHCOPh group in **1v** during hy-



Scheme 2. a) Attempted reaction of compound **1y** under our standard conditions; b) Possible mechanism for the hydroxylation of *N*-(2-bromophenyl)benzamide (**1v**).

droxylation as shown in Scheme 2b. Coordination of *N*-(2-bromophenyl)benzamide (**1v**) with Cu₂O and subsequent oxidative addition forms **VII**, and treatment of **VII** with CsOH gives **VIII**. Reductive elimination of **VIII** affords the target product (**2t**) with release of the copper catalyst. However, *N*-(2-bromophenyl)acetamide (**1x**) afforded hydrolysis product 2-aminophenol (**2v**) as the major product under our standard conditions (Table 2, entry 24), which can provide a new approach to substituted 2-aminophenol derivatives. Cyclization of **2t** in the presence of PCl₅ provided compound **3a** (Scheme 3), and the protocol gives a novel method for the synthesis of 2-arylbenzoxazoles.

The hydroxylation reactions above could tolerate various functional groups, including C–Cl bonds (Table 2, entries 5

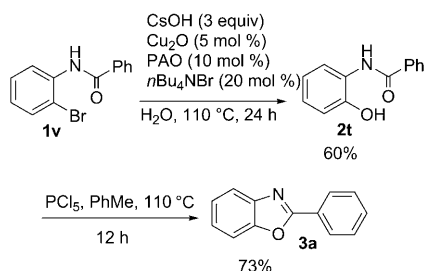
Table 2. Copper-catalyzed synthesis of substituted phenols by hydroxylation of aryl halides with CsOH in water.^[a]

Entry	1	T [°C]/t [h]	2	Yield [%] ^[b]	Entry	1	T [°C]/t [h]	2	Yield [%] ^[b]
1		110/36		95	13		100/24		92
2		110/48		78	14		100/48		96
3		110/48		61	15		100/48		81
4		110/48		87	16		100/48		84
5		110/48		82	17		110/48		66
6		110/48		71	18		110/48		63
7		110/48		91	19		110/36		98
8		110/48		86 ^[c]	20		110/48		87
9		110/36		92	21		110/48		62
10		110/48		45	22		110/24		60
11		110/48		73	23		110/24		52
12		100/24		95	24		110/48		53 ^[d]

[a] Reaction conditions: aryl halide (1 mmol), CsOH (3 mmol for entries 1–11 and 21–24; 5 mmol for entries 12–20), Cu₂O (0.05 mmol), PAO (0.1 mmol), TBAB (0.2 mmol), and water (1 mL) under a nitrogen atmosphere. [b] Yield of the isolated product. [c] 0.8 mmol of TBAB was used. [d] Product **2v** from hydrolysis of amide -NHCOCH₃ in *N*-(2-hydroxyphenyl)acetamide.

and 6) and C–F bond (Table 2, entry 7) in aryl iodides, nitro groups (Table 2, entries 8, 9, and 16), an aldehyde (Table 2, entry 21), carboxyl groups (Table 2, entries 12–20), hydroxyl

group (Table 2, entry 21), and amide groups (Table 2, entries 22 and 23) in aryl halides.

Scheme 3. Cyclization of **2t** to form compound **3a**.

In summary, we have developed a simple and efficient copper-catalyzed method for the synthesis of substituted phenols. The protocol uses pyridine-2-aldoxime as the ligand of the copper catalyst and environmentally friendly water as the solvent. By using this protocol, the hydroxylation of aryl halides proceeded well under mild conditions. The method is of high tolerance towards various functional groups in the substrates, and the synthesis of these compounds will attract much attention in academic and industrial research because of their wide applications in numerous pharmaceuticals, polymers, and natural products.

Experimental Section

General procedure for the synthesis of substituted phenols (2a–2v): A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with Cu_2O (0.05 mmol, 7 mg), CsOH (3 mmol or 5 mmol), PAO (0.1 mmol, 12 mg), TBAB (0.2 mmol, 65 mg) (note: 0.8 mmol, 260 mg for substrate **1h**), and aryl halide, if a solid (1 mmol). The tube was evacuated twice and backfilled with nitrogen. Aryl halide, if a liquid (1 mmol) and water (1 mL) were sequentially added by syringe at RT under a stream of nitrogen and the tube was sealed and put into a preheated oil bath at 100 or 110 °C for 24–48 h under a positive pressure of nitrogen (it is necessary to occasionally shake the tube during the reactions of substrate **1h** because it can sometimes stick to the vessel wall above the solution). After the resulting solution was cooled to RT, HCl (1 N, 2 mL) was added to acidify the solution (pH 2–3) and the solution was extracted with ethyl acetate (3 × 2 mL). The combined organic phases were concentrated, and the remaining residue was purified by column chromatography on silica gel to provide the desired product.

Acknowledgements

Financial support was provided by the National Natural Science Foundation of China (grant nos. 20672065, 20972083), the Chinese 863 Project (grant no. 2007AA02Z160), and the Key Subject Foundation from Beijing Department of Education (XK100030514).

Keywords: aryl halides • copper • hydroxylation • phenols • water chemistry

ladium Chemistry for Organic Synthesis (Ed.: E.-I. Negishi), Wiley-Interscience, New York, **2002**.

- [2] a) H. Hock, S. Lang, *Ber. Dtsch. Chem. Ges. B* **1944**, 77, 257; b) W. Jordan, H. van Barneveld, O. Gerlich, M. K. Boymann, J. Ullrich in *Ullmann's Encyclopedia of Industrial Organic Chemicals*, Vol. A9, Wiley-VCH, Weinheim, **1985**, pp. 299–312.
- [3] R. E. Maleczka, F. Shi, D. Holmes, M. R. Smith III, *J. Am. Chem. Soc.* **2003**, 125, 7792.
- [4] For typical methods for the preparation of phenols, see: D. A. Whiting in *Comprehensive Organic Chemistry: The Synthesis and Reactions of Organic Compounds*, Vol. 1 (Eds.: D. Barton, W. D. Ollis), Pergamon Press, Oxford, **1979**, pp. 717–730.
- [5] For a highlight of the palladium-catalyzed synthesis of phenols, see: M. C. Willis, *Angew. Chem.* **2007**, 119, 3470; *Angew. Chem. Int. Ed.* **2007**, 46, 3402.
- [6] a) C. A. Fyfe in *The Chemistry of the Hydroxyl Group*, Vol. 1 (Ed.: S. Patai), Wiley-Interscience, New York, **1971**, pp. 83–127; b) C. Hoarau, T. R. R. Pettus, *Synlett* **2003**, 127; c) P. Hanson, J. R. Jones, A. B. Taylor, P. H. Walton, A. W. Timms, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1135; d) T. George, R. Mabon, G. Sweeney, J. B. Sweeney, A. J. Tavassoli, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2529, and references therein.
- [7] a) K. W. Anderson, T. Ikawa, R. E. Tundel, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, 128, 10694; b) G. Chen, A. S. C. Chan, F. Y. Kwong, *Tetrahedron Lett.* **2007**, 48, 473; c) B. J. Gallon, R. W. Kojima, R. B. Kaner, P. L. Diaconescu, *Angew. Chem.* **2007**, 119, 7389; *Angew. Chem. Int. Ed.* **2007**, 46, 7251; d) T. Schulz, C. Torborg, B. Schäffner, J. Huang, A. Zapf, R. Kadyrov, A. Börner, M. Beller, *Angew. Chem.* **2009**, 121, 936; *Angew. Chem. Int. Ed.* **2009**, 48, 918.
- [8] A. G. Sergeev, T. Schulz, C. Torborg, A. Spannenberg, H. Neumann, M. Beller, *Angew. Chem.* **2009**, 121, 7731; *Angew. Chem. Int. Ed.* **2009**, 48, 7595.
- [9] For recent reviews on copper-catalyzed cross couplings, see: a) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, 123, 7727; b) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, 41, 1450; c) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428; d) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, 115, 5558; *Angew. Chem. Int. Ed.* **2003**, 42, 5400; e) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, 248, 2337; f) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, 108, 3054; g) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, 121, 7088; *Angew. Chem. Int. Ed.* **2009**, 48, 6954, and references therein.
- [10] a) D. Zhao, N. Wu, S. Zhang, P. Xi, X. Su, J. Lan, J. You, *Angew. Chem.* **2009**, 121, 8885; *Angew. Chem. Int. Ed.* **2009**, 48, 8729; b) A. Tlili, N. Xia, F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, 121, 8881; *Angew. Chem. Int. Ed.* **2009**, 48, 8725.
- [11] a) For organic synthesis in water, see: a) *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie A&P London, **1998**; b) M. Siskin, A. R. Katritzky, *Chem. Rev.* **2001**, 101, 825; c) U. M. Lindström, *Chem. Rev.* **2002**, 102, 2751; d) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, 35, 209; e) N. Akiya, P. E. Savage, *Chem. Rev.* **2002**, 102, 2725; f) J. M. DeSimone, *Science* **2002**, 297, 799; g) M. Poliakov, J. M. Fitzpatrick, T. R. Farren, P. T. Anastas, *Science* **2002**, 297, 807; h) C.-J. Li, *Chem. Rev.* **2005**, 105, 3095; i) D. G. Blackmond, A. Armstrong, V. Coomber, A. Wells, *Angew. Chem.* **2007**, 119, 3872; *Angew. Chem. Int. Ed.* **2007**, 46, 3798; j) S. Minakata, M. Komatsu, *Chem. Rev.* **2008**, 108, 825; k) Y.-C. Teo, G.-L. Chua, *Chem. Eur. J.* **2009**, 15, 3072; l) Y.-C. Teo, *Adv. Synth. Catal.* **2009**, 351, 720.
- [12] D. Sinou, *Adv. Synth. Catal.* **2002**, 344, 221.
- [13] C. M. Kormos, N. E. Leadbeater, *Tetrahedron* **2006**, 62, 4728.
- [14] For selected papers on copper-catalyzed cross couplings in organic solvents, see: a) H. Rao, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2005**, 70, 8107; b) H. Rao, Y. Jin, H. Fu, Y. Jiang, Y. Zhao, *Chem. Eur. J.* **2006**, 12, 3636; c) D. Jiang, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2007**, 72, 672; d) X. Guo, H. Rao, H. Fu, Y. Jiang, Y. Zhao, *Adv. Synth. Catal.* **2006**, 348, 2197; e) L. Zeng, H. Fu, R. Qiao, Y. Jiang, Y. Zhao, *Adv. Synth. Catal.* **2009**, 351, 1671; f) X. Gao, H. Fu, R. Qiao, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, 73, 6864; g) C.

Huang, X. Tang, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2006**, *71*, 5020; h) C. Huang, Y. Fu, H. Fu, Y. Jiang, Y. Zhao, *Chem. Commun.* **2008**, 6333; i) D. Yang, H. Fu, L. Hu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 7841; j) F. Wang, H. Liu, H. Fu, Y. Jiang, Y. Zhao, *Org. Lett.* **2009**, *11*, 2469; k) D. Yang, H. Liu, H. Yang, H. Fu, L. Hu, Y. Jiang, Y. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 1999; l) L. Wang, H. Fu, Y. Jiang, Y. Zhao, *Chem. Eur. J.* **2008**, *14*, 10722; m) X. Liu, Y. Zhang, L. Wang, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 6207; n) M. Niu, Z. Yin, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 3813; o) Y. Zhang, H. Fu, Y. Jiang, Y. Zhao, *Org. Lett.* **2007**, *9*, 3813; p) M. Niu, H. Fu, Y. Jiang, Y. Zhao, *Chem. Commun.* **2007**, 272; q) H. Rao, H. Fu, Y. Jiang, Y. Zhao, *Angew. Chem.* **2009**, *121*, 1134; *Angew. Chem. Int. Ed.* **2009**, *48*, 1114; r) X. Liu, H. Fu, Y. Jiang, Y. Zhao, *Angew. Chem.* **2009**, *121*, 354; *Angew. Chem. Int. Ed.* **2009**, *48*, 348.

- [15] For copper-catalyzed cross couplings in neat aqueous medium, see:
a) F. Wang, H. Fu, Y. Jiang, Y. Zhao, *Green Chem.* **2008**, *10*, 452;
b) F. Wang, H. Fu, Y. Jiang, Y. Zhao, *Adv. Synth. Catal.* **2008**, *350*, 1830.
[16] a) K. C. Nicolaou, C. N. C. Boddy, S. Natarajar, T.-Y. Yue, H. Li, S. Bräse, J. M. Ramanjulu, *J. Am. Chem. Soc.* **1997**, *119*, 3421; b) J. Lindley, *Tetrahedron* **1984**, *40*, 1433; c) A. V. Kalinin, J. F. Bower, P. Riebel, V. Snieckus, *J. Org. Chem.* **1999**, *64*, 2986; d) Q. Cai, B. Zou, D. Ma, *Angew. Chem.* **2006**, *118*, 1298; *Angew. Chem. Int. Ed.* **2006**, *45*, 1276.

Received: December 18, 2009

Please note: Minor changes have been made to this publication in *Chemistry—A European Journal* Early View. The Editor.

Published online: January 27, 2010