

Hydroxylation

Synthesis of Phenol, Aromatic Ether, and Benzofuran Derivatives by Copper-Catalyzed Hydroxylation of Aryl Halides**

Dongbing Zhao, Ningjie Wu, Shuai Zhang, Peihua Xi, Xiaoyu Su, Jingbo Lan, and Jingsong You*

Phenols are not only important building blocks for constructing pharmaceuticals, polymers, and natural compounds, but also serve as versatile synthetic intermediates in preparing oxygenated heterocycles.^[1] The classical non-oxidative preparative routes of these compounds include transformation of diazoarenes in the presence of a copper complex as well as nucleophilic substitution of activated aryl halides and benzyne. However, these methods generally suffer from limitations with regard to substrate generality, the availability of starting materials, and sometimes the harsh reaction conditions.^[2] A milder method of the preparation of non-*ortho*-substituted phenols has been achieved in two steps: C–H activation/borylation and oxidation in the presence of iridium phosphine complexes.^[3]

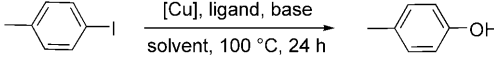
In contrast to well-established palladium- or copper-catalyzed formation of aryl ethers,^[4,5] the direct hydroxylation of aryl halides has proved to be challenge in coupling chemistry. Recently, several palladium-catalyzed processes have allowed the cross-coupling of aryl halides with hydroxide salts to proceed under relatively mild reaction conditions.^[6,7] Although the economic attractiveness of copper has led to remarkable progress in the development of copper-catalyzed coupling reactions,^[8] the copper-mediated hydroxylation of aryl halides with hydroxide salts (e.g., KOH and NaOH) as nucleophiles to directly form phenols under mild conditions is less developed.^[9] Drawing from recent experiences in the field of copper-catalyzed cross-coupling reactions,^[10] we herein disclose that aryl halides can directly couple with potassium hydroxide under mild reaction conditions, namely in the presence of CuI and 1,10-phenanthroline (phen)—which is inexpensive and commercially available. The process constitutes a practical, general, and efficient method for the synthesis of phenols.

It was determined during a preliminary survey of the reaction conditions that we should use *p*-iodotoluene as the

model substrate in the presence of copper(I) iodide (Table 1). As KOH was used as the nucleophile, initial reaction screening led to disappointing results in the absence of a ligand (Table 1, entry 1). We subsequently screened a variety of ligands, solvents, and bases. 1,10-Phenanthroline proved to be an excellent ligand (Table 1, entries 2–6), and the mixed DMSO/H₂O (1:1) solvent system was clearly the best choice (Table 1, entries 6–10). When the base was altered to potassium carbonate, cesium carbonate, or potassium phosphinate, only poor yields were obtained (Table 1, entries 11–13). In addition, other sources of the copper salt were inferior to CuI (compare Table 1, entry 6 to entries 14–17). Although not yet investigated in detail, the hydroxylation of *p*-iodotoluene could occur in 38% yield even with a substantially low CuI loading of 0.1 mol% (Table 1, entry 20).

With the optimized conditions now determined, a variety of substituted aryl halides were examined and the results are summarized in Table 2. Gratifyingly, various phenol derivatives were obtained with both non-activated and activated

Table 1: Optimization of the hydroxylation of *p*-iodotoluene.^[a]

					
Entry	Ligand	Solvent (1:1)	Base	[Cu]	Yield [%] ^[b]
1	–	DMSO/H ₂ O	KOH	CuI	45
2	Hacac	DMSO/H ₂ O	KOH	CuI	76
3	L-Pro	DMSO/H ₂ O	KOH	CuI	66
4	TMEDA	DMSO/H ₂ O	KOH	CuI	86
5	DMEDA	DMSO/H ₂ O	KOH	CuI	89
6	phen	DMSO/H ₂ O	KOH	CuI	96
7	phen	DMSO	KOH	CuI	< 10
8	phen	H ₂ O	KOH	CuI	n.r.
9	phen	DMF/H ₂ O	KOH	CuI	n.r.
10	phen	1,4-dioxane/H ₂ O	KOH	CuI	35
11	phen	DMSO/H ₂ O	K ₂ CO ₃	CuI	16
12	phen	DMSO/H ₂ O	Cs ₂ CO ₃	CuI	25
13	phen	DMSO/H ₂ O	K ₃ PO ₄	CuI	20
14	phen	DMSO/H ₂ O	KOH	CuSO ₄	48
15	phen	DMSO/H ₂ O	KOH	Cu(OAc) ₂	52
16	phen	DMSO/H ₂ O	KOH	CuCl	92
17	phen	DMSO/H ₂ O	KOH	Cu(acac) ₂	87
18 ^[c]	phen	DMSO/H ₂ O	KOH	CuI	84
19 ^[d]	phen	DMSO/H ₂ O	KOH	CuI	85
20 ^[e]	phen	DMSO/H ₂ O	KOH	CuI	38

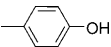
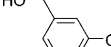
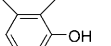
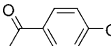
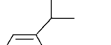
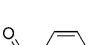
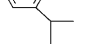
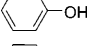
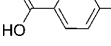
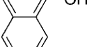
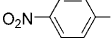
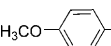
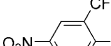
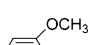
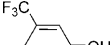
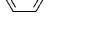
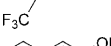
[a] Reactions were carried out using CuI (10 mol%), base (3.0 equiv), ligand (20 mol%), and *p*-iodotoluene (1 mmol) in a 1.25 M solution at 100 °C for 24 h. [b] Yield of isolated product. [c] Reaction was carried out for 15 h. [d] CuI (5 mol%). [e] CuI (0.1 mol%). DMEDA = *N,N'*-dimethylethanedi-amine, DMF = *N,N*-dimethylformamide, DMSO = dimethyl sulfoxide, Hacac = acetylacetonate, L-Pro = L-proline, n.r. = no reaction, TMEDA = *N,N,N',N'*-tetramethylethanedi-amine.

[*] D. Zhao, N. Wu, S. Zhang, P. Xi, Dr. X. Su, Prof. Dr. J. Lan, Prof. Dr. J. You
Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry and State Key Laboratory of Biotherapy, West China Medical School, Sichuan University
29 Wangjiang Road, Chengdu 610064 (China)
Fax: (+86) 28-8541-2203
E-mail: jsyou@scu.edu.cn

[**] This work was supported by grants from the National Natural Science Foundation of China (grant nos 20772086, 20872101, and 20702035). We also thank the Center of Testing and Analysis, Sichuan University for NMR measurements.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200903923>.

Table 2: Copper-catalyzed synthesis of phenols from aryl halides.^[a]

		$\text{R}-\text{C}_6\text{H}_4-\text{X} \xrightarrow[\text{H}_2\text{O/DMSO (1:1)}]{\text{Cul (10 mol\%)}, \text{1,10-phenanthroline (20 mol\%)}, \text{KOH (2.0–6.0 mmol)}}$					
		X = I, Br				3a–s	
Entry	X	Product	Yield [%] ^[b]	Entry	X	Product	Yield [%] ^[b]
1	I	3a 	96	11	I	3k 	84
2	I	3b 	94	12	I	3l 	87
3	I	3c 	85	13	I	3m 	75
4	I	3d 	92	14	I	3n 	82
5	I	3e 	89	15	I	3o 	95
6	I	3f 	97	16	Br	3p 	86
7	I	3g 	94	17	Br	3q 	92
8	I	3h 	93	18	Br	3r 	76
9	I	3i 	95	19	I	3s 	70
10	I	3j 	86				

[a] Reactions were carried out using Cul (10 mol%), 1,10-phenanthroline (20 mol%), KOH (2.0–6.0 mmol; for details see the Supporting Information), and aryl halide (1.0 mmol) in DMSO/H₂O (1:1; 1.25 M concentration) at 100 °C for 24 h. [b] Yield of isolated product. MOM = methoxymethyl.

aryl iodide derivatives. No matter if the aryl iodides were electron-rich, electron-poor, or sterically bulky, all of them afforded good to excellent yields (**3a–n**; Table 2, entries 1–14). The high yields observed in the reaction of 4-chlorophenyl iodide or 4-bromophenyl iodide implied that there was good chemoselectivity between aryl iodide, bromide, or chloride (**3h** and **3i**; Table 2, entries 8 and 9). Moreover, high-yielding hydroxylation was possible with aryl bromides bearing electron-withdrawing groups: although the reaction has not yet been investigated in detail (**3o–q**; Table 2, entries 15–17). It is important to stress that the reaction conditions were compatible with the presence of functional groups such as hydroxy, hydroxymethyl, ketone, aldehyde, carboxyl acid, and nitro groups, which could all then be subject to further synthetic transformations (**3j–p**; Table 2, entries 10–16).

The value of this methodology is evident from its application to the synthesis of 2,2',3,3'-tetrahydroxy-1,1'-

binaphthyl (**3s**; Table 2, entry 19) from 2,2'-dihydroxy-3,3'-diiodo-1,1'-binaphthyl in one synthetic step in 86% yield. As building blocks, 2,2',3,3'-tetrahydroxy-1,1'-binaphthyls have already shown promise in the area of supramolecular chemistry. The previously reported route toward these products employed a multi-steps process involving borylation and oxidation.^[11]

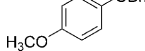
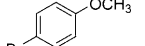
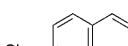
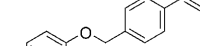
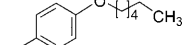
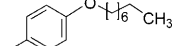
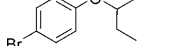
This methodology has been combined with the Williamson ether synthesis leading to the formation of alkyl aryl ethers in one-pot from aryl iodides.^[12] Aryl iodides first formed phenoxides, and subsequent treatment with alkyl halides gave alkyl aryl ethers, which was expedited by tetrabutylammonium iodide as the phase-transfer catalyst.^[6a] As shown in Table 3, a variety of alkyl aryl ethers could be obtained in good yields. Thus, the procedure offers an alternative route in the synthesis of alkyl aryl ether from aryl iodides and alkyl halides.

Benzofuran-containing molecules are frequently found in a variety of biologically active compounds.^[13] Although these bioactive properties have motivated the development of efficient methods for constructing the benzofuran framework,^[14] exploring new improved routes is still a very active and prolific field of research.^[15] Herein, we utilize our catalytic protocol to prepare a

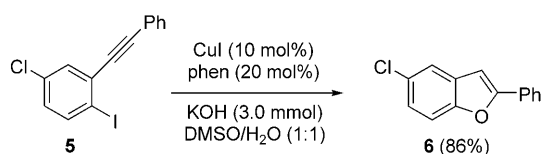
substituted benzofuran directly from 2-iodoaryl alkyne by a sequential one-pot reaction. For example, 2-iodoaryl alkyne **5** underwent the domino reactions involving hydroxylation coupling and subsequent intramolecular hydroalkoxylation to provide the benzofuran **6** in good yield (Scheme 1).

In conclusion, we have developed a copper-catalyzed hydroxylation that allows the direct transformation of aryl halides into phenols in one step. The process is not only simple and convenient in terms of the reaction conditions and purification, but is also tolerant of a variety of functional groups, thus constitutes a practical route to give phenols. Although aryl bromides or iodides rather than chlorides are required in this copper-catalyzed system, the scope, experimental ease, and reliability of a system are often much more important factors in terms of practical application.^[16] We have also demonstrated that alkyl halides can be converted into alkyl aryl ethers by a one-pot phenoxide/alkylation protocol. In addition, a benzofuran was prepared smoothly by treat-

Table 3: One-pot synthesis of alkyl aryl ethers from aryl iodides.^[a]

1) KOH (3.0–6.0 mmol) Cul (10 mol%) 1,10-phenanthroline (20 mol%) 2) R'–X (2.0 mmol) <i>n</i> Bu ₄ NI (10 mol%) KOH (0–3.0 mmol)			
Entry	R'X	Product	Yield [%] ^[b]
1		4a 	89
2	CH ₃ I	4b 	84
3		4c 	81
4		4d 	82
5		4e 	80
6		4f 	81

[a] Reactions were carried out using Cul (10 mol%), KOH (3.0–6.0 mmol; for details see the Supporting Information), ligand (20 mol%), and aryl iodide (1 mmol) in a 1.25 M DMSO/H₂O (1:1) at 100 °C for 24 h. After the reaction mixture was cooled to ambient temperature, *n*Bu₄NI (0.1 mmol), KOH (0–3.0 mmol; for details see the Supporting Information), and R'X (2.0 mmol) were added, and the reaction system was then kept at 100 °C for 12 h. [b] Yield of isolated product. Bn = benzyl.


Scheme 1. Synthesis of a benzofuran from 2-iodoaryl alkyne.

ment of *ortho*-iodoaryl alkynes with KOH under relatively mild reaction conditions. We believe that this simple procedure outlined here will find wide applications in various fields of synthetic chemistry.

Received: July 17, 2009

Published online: September 22, 2009

Keywords: aryl ethers · benzofurans · copper · hydroxylation · phenols

- [1] J. H. P. Tyman, *Synthetic and Natural Phenols*, Elsevier, New York, 1996.
- [2] For pertinent review for synthesis of phenols, see: a) T. George, R. Mabon, G. Sweeney, J. B. Sweeney, A. Tavassoli, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2529; b) P. Hanson, J. R. Jones, A. B. Taylor, P. H. Walton, A. W. Timms, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1135; c) C. Hoarau, T. R. R. Pettus, *Synlett* **2003**, 127; d) J. B. Sweeney, *Contemp. Org. Synth.* **1997**, 4, 435.

- [3] R. E. Maleczka, Jr., F. Shi, D. Holmes, M. R. Smith III, *J. Am. Chem. Soc.* **2003**, 125, 7792.
- [4] Selected examples for palladium-mediated synthesis of diaryl ether: a) C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem.* **2006**, 118, 4427; *Angew. Chem. Int. Ed.* **2006**, 45, 4321; b) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, 121, 4369; c) G. Mann, C. Incarvito, A. L. Rheigold, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, 121, 3224.
- [5] Selected examples for copper-catalyzed synthesis of diaryl ether: a) H. Rao, Y. Jin, H. Fu, Y. Jiang, Y. Zhao, *Chem. Eur. J.* **2006**, 12, 3636; b) Q. Cai, B. Zou, D. Ma, *Angew. Chem.* **2006**, 118, 1298; *Angew. Chem. Int. Ed.* **2006**, 45, 1276; c) D. Ma, Q. Cai, *Org. Lett.* **2003**, 5, 3799; d) A. Ouali, R. Laurent, A.-M. Caminade, J.-P. Majoral, M. Taillefer, *J. Am. Chem. Soc.* **2006**, 128, 15990.
- [6] a) K. W. Anderson, T. Ikawa, R. E. Tundel, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, 128, 10694; b) M. C. Willis, *Angew. Chem.* **2007**, 119, 3470; *Angew. Chem. Int. Ed.* **2007**, 46, 3402; 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.
- [7] 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] For reviews, see: a) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, 115, 5558; *Angew. Chem. Int. Ed.* **2003**, 42, 5400; b) F. Monnier, M. Taillefer, *Angew. Chem.* **2008**, 120, 3140; *Angew. Chem. Int. Ed.* **2008**, 47, 3096; c) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, 41, 1450; d) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, 108, 3054; e) G. Evano, M. Toumib, A. Costea, *Chem. Commun.* **2009**, 4166.
- [9] For copper-mediated direct conversion of aryl halides into phenols using high temperature (as high as 300 °C) or near-critical water and microwave heating, see: C. M. Kormos, N. E. Leadbeater, *Tetrahedron* **2006**, 62, 4728.
- [10] a) J. Lan, L. Chen, X. Yu, J. You, R. Xie, *Chem. Commun.* **2004**, 188; b) W. Chen, Y. Zhang, L. Zhu, J. Lan, R. Xie, J. You, *J. Am. Chem. Soc.* **2007**, 129, 13879; c) L. Zhu, P. Guo, G. Li, J. Lan, R. Xie, J. You, *J. Org. Chem.* **2007**, 72, 8535; d) L. Zhu, L. Cheng, Y. Zhang, R. Xie, J. You, *J. Org. Chem.* **2007**, 72, 2737; e) L. Zhu, G. Li, L. Luo, P. Guo, J. Lan, J. You, *J. Org. Chem.* **2009**, 74, 2200; f) D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao, J. You, *Angew. Chem.* **2009**, 121, 3346; *Angew. Chem. Int. Ed.* **2009**, 48, 3296.
- [11] H. Danjo, K. Hirata, S. Yoshigai, I. Azumaya, K. Yamaguchi, *J. Am. Chem. Soc.* **2009**, 131, 1638.
- [12] For selected examples for palladium-catalyzed couplings of alkoxides with aryl halides, see: a) M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, 119, 3395; b) G. Mann, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, 118, 13109; c) A. V. Vorogushin, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, 127, 8146; d) Q. Shelby, N. Kataoka, G. Mann, J. Hartwig, *J. Am. Chem. Soc.* **2000**, 122, 10718.
- [13] a) Z. Tomaszewski, M. P. Johnson, X. Huang, D. E. Nichols, *J. Med. Chem.* **1992**, 35, 2061; b) M. Sauter, W. Adam, *Acc. Chem. Res.* **1995**, 28, 289; c) G. A. Kraus, I. Kim, *Org. Lett.* **2003**, 5, 1191; d) S. M. Bakunova, S. A. Bakunov, T. Wenzler, T. Barszcz, K. A. Werbovetz, R. Brun, J. E. Hall, R. R. Tidwell, *J. Med. Chem.* **2007**, 50, 5807.
- [14] a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, 104, 3079; b) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, 106, 4644.
- [15] For selected examples, see: a) C. G. Bates, P. Saejueng, J. M. Murphy, D. Venkataraman, *Org. Lett.* **2002**, 4, 4727; b) Y. Liao, J. Smith, R. Fathi, Z. Yang, *Org. Lett.* **2005**, 7, 2707; c) X. Cheng, X. Liu, *J. Comb. Chem.* **2007**, 9, 906; d) M. Carril, R. S. Martin, I. Tellitu, E. Domínguez, *Org. Lett.* **2006**, 8, 1467; e) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn, B. DeBoef, *Org. Lett.* **2007**, 9,

- 3137; f) C. Martínez, R. Álvarez, J. M. Aurrecoechea, *Org. Lett.* **2009**, *11*, 1083; g) X.-C. Huang, Y.-L. Liu, Y. Liang, S.-F. Pi, F. Wang, J.-H. Li, *Org. Lett.* **2008**, *10*, 1525.
- [16] For selected examples, see: a) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727; b) L. Rout, T. K. Sen, T. Punniyamurthy, *Angew. Chem.* **2007**, *119*, 5679; *Angew. Chem. Int. Ed.* **2007**, *46*, 5583; c) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404; d) O. Bistri, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 596; *Angew. Chem. Int. Ed.* **2008**, *47*, 586; e) M. Carril, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 4940; *Angew. Chem. Int. Ed.* **2008**, *47*, 4862; f) A. Correa, M. Carril, C. Bolm, *Angew. Chem.* **2008**, *120*, 2922; *Angew. Chem. Int. Ed.* **2008**, *47*, 2880.
-