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Highly Efficient Synthesis of Phenols by Copper-Catalyzed Hydroxylation of Aryl Iodides, Bromides, and Chlorides

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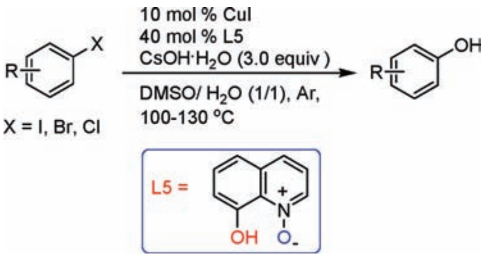
ABSTRACT



8-Hydroxyquinolin-*N*-oxide was found to be a very efficient ligand for the copper-catalyzed hydroxylation of aryl iodides, aryl bromides, or aryl chlorides under mild reaction conditions. This methodology provides a direct transformation of aryl halides to phenols and to alkyl aryl ethers. The inexpensive catalytic system showed great functional group tolerance and excellent selectivity.

Phenols are very useful intermediates for constructing pharmaceutical molecules, polymers, and natural compounds.[1] Traditional nonoxidative preparation of phenols includes nucleophilic substitution of activated aryl halides, copper-catalyzed transformation of diazoarenes, benzyne protocols, and aromatic boronic acids all of which were limited by harsh reaction conditions and the availability of starting materials.[2] While several iridium- or palladium-catalyzed conversions of different aryl halides to phenols have been reported in recent years,[3,4] which involved the use of rare and expensive metallic catalysts, and sophisticated supporting ligands, only a few examples of the copper-catalyzed hydroxylation of aryl iodides and electron-deficient aryl bromides were reported.[5,6] Significant limitations to this process were that aryl chlorides as well as electron-rich aryl bromides did not react. To reduce costs,

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it is highly desirable to use aryl chlorides directly coupled with hydroxide salt under mild reaction conditions in this process. In this paper, we describe an efficient and versatile method for the copper-catalyzed hydroxylation of electron-rich aryl bromides, and aryl chlorides that overcomes these problems, providing a considerably more practical and useful method for the conversion of aryl halides to phenols.

Based on several of our previously discovered new ligands (Figure 1) for the Cu-catalyzed Ullmann C–N coupling reactions under a low catalyst loading (1% [Cu] mol),[7,8] we are interested to explore a direct transformation of aryl halides especially aryl chlorides to the corresponding substituted phenols using these ligands, which, to the best of our knowledge, has never been reported. Herein, we report that the direct hydroxylation of a broad range of aryl halides especially aryl chlorides can be achieved in aqueous media under the catalysis of 10% CuI and 40% L5 ligand.

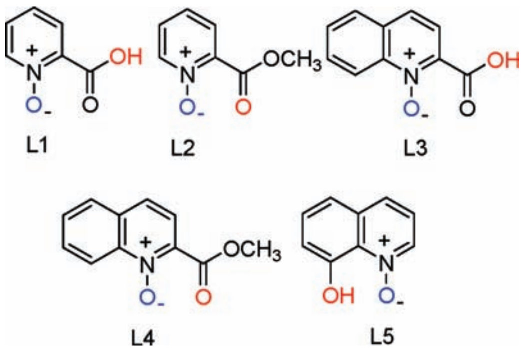
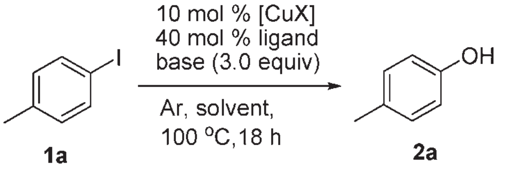


Figure 1. Structure of designed ligands.

We initially chose 4-methyl iodobenzene as the model substrate to evaluate the catalytic activity of the designed ligands at 100 °C (Table 1). Ligands (L1–L5) were tested in the mixed DMSO/H_2O (1:1) solvent system with 10 mol % CuI as the catalyst and CsOH as the base (entries 1–5), and L5 gave the highest yield (93%, entry 5), while no product formation was observed without addition of ligands under similar reaction conditions (entry 17). Using L5 as the ligand and CsOH as the base, different solvent systems such as THF/H_2O (1/1), DMF/H_2O (1/1), CH_3CN/H_2O (1/1), C_2H_5OH/H_2O (1/1), 1,4-dioxane/H_2O (1/1), DMSO/*t*-BuOH (1/1), and DMSO/H_2O (1/1) were tested, and DMSO/H_2O (1/1) provided the best result (Table 1, entries 5, 11–16). Copper salts also influenced the progress of the reaction, and CuI afforded the highest yield. Thus, after screening the ligands, bases, solvents, and catalysts, the optimal conditions were a combination of 10 mol % CuI, 40 mol % L5, and CsOH (3.0 equiv) in DMSO/H_2O (1/1) at 100 °C.

Table 1. Optimization of Cu-Catalyzed Hydroxylation of *p*-Iodotoluene[a]



entry	ligand	base	[Cu]	solvent (1/1)	yield (%)[b]
1	L1	CsOH	CuI	DMSO/H_2O	28
2	L2	CsOH	CuI	DMSO/H_2O	32
3	L3	CsOH	CuI	DMSO/H_2O	26
4	L4	CsOH	CuI	DMSO/H_2O	46
5	L5	CsOH	CuI	DMSO/H_2O	93
6	L5	KOH	CuI	DMSO/H_2O	54
7	L5	CsOH	CuBr	DMSO/H_2O	86
8	L5	CsOH	$CuBr_2$	DMSO/H_2O	75
9	L5	CsOH	CuCl	DMSO/H_2O	85
10	L5	CsOH	Cu	DMSO/H_2O	64
11	L5	CsOH	CuI	DMF/H_2O	14
12	L5	CsOH	CuI	THF/H_2O	15
13	L5	CsOH	CuI	CH_3CN/H_2O	20
14	L5	CsOH	CuI	C_2H_5OH/H_2O	57
15	L5	CsOH	CuI	1,4-dioxane/H_2O	47
16	L5	CsOH	CuI	DMSO/*t*BuOH	82
17	None	CsOH	CuI	DMSO/H_2O	0

[a] **1a** (1.0 mmol), 10 mol % [CuX], 40 mol % ligand, base (3.0 mmol), solvent (2 mL), Ar, 100 °C, 18 h. [b] Isolated yield.

The optimized reaction conditions were then applied to the conversion of a variety of aryl iodides, and the results are summarized in Scheme 1. Both electron-rich (**2a**–**2f**) and -deficient (**2g**–**2l**) aryl iodides provided the corresponding phenols in excellent yields. In addition, the reaction showed a great tolerance to a range of functional groups including alkoxy, acetyl, nitro, carboxylic acid, and amino moieties (**2d**–**2k**). Remarkably, sterically hindered aryl iodide also afforded the coupling products in excellent yields (**2b** and **2f**). When chloro or fluoro substituted aryl iodides were used, the coupling reaction took place selectively at the iodo part, leaving the fluoride and chloride substituents untouched (**2m**–**2o**).

When *o*-diiodobenzene, *p*-diiodobenzene, and 4-iodophenol were used, we observed the formation of the phenol in high yields, which is similar to that reported by Taillefer (**2p** from **1q**–**1s**).[5a] While Taillefer's group and You's group independently reported that hydroxylation of 4-bromo-iodobenzene using their catalytic systems produced

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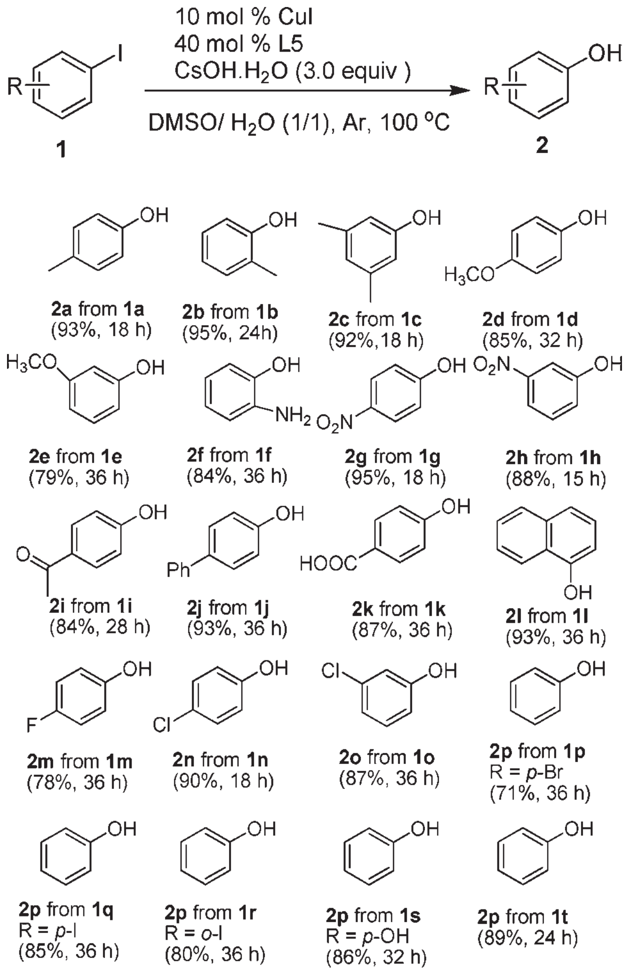
[7] (a) Yang, K.; Qiu, Y.; Li, Z.; Wang, Z.; Jiang, S. *J. Org. Chem.* **2011**, *76*, 3151. (b) Qiu, Y.; Liu, Y.; Yang, K.; Hong, W.; Li, Z.; Wang, Z.; Jiang, S. *Org. Lett.* **2011**, *13*, 3556.

[8] For recent contributions on Cu catalysis C–O coupling reactions, see: (a) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.—Eur. J.* **2006**, *12*, 3636. (b) Chen, Y.; Chen, H. *Org. Lett.* **2006**, *8*, 5609. (c) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (d) Zhao, Y.; Wang, Y.; Sun, H.; Li, L.; Zhang, H. *Chem. Commun.* **2007**, 3186. (e) Niu, J.; Zhou, H.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem.* **2008**, *73*, 7814. (f) Zhang, J.; Zhang, Z.; Wang, Y.; Zheng, X.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 5112. (g) Naidu, A. B.; Raghunath, O. R.; Prasad, D. J. C.; Sekar, G. *Tetrahedron Lett.* **2008**, *49*, 1057. (h) Naidu, A. B.; Jaseer, E. A.; Sekar, G. *J. Org. Chem.* **2009**, *74*, 3675.

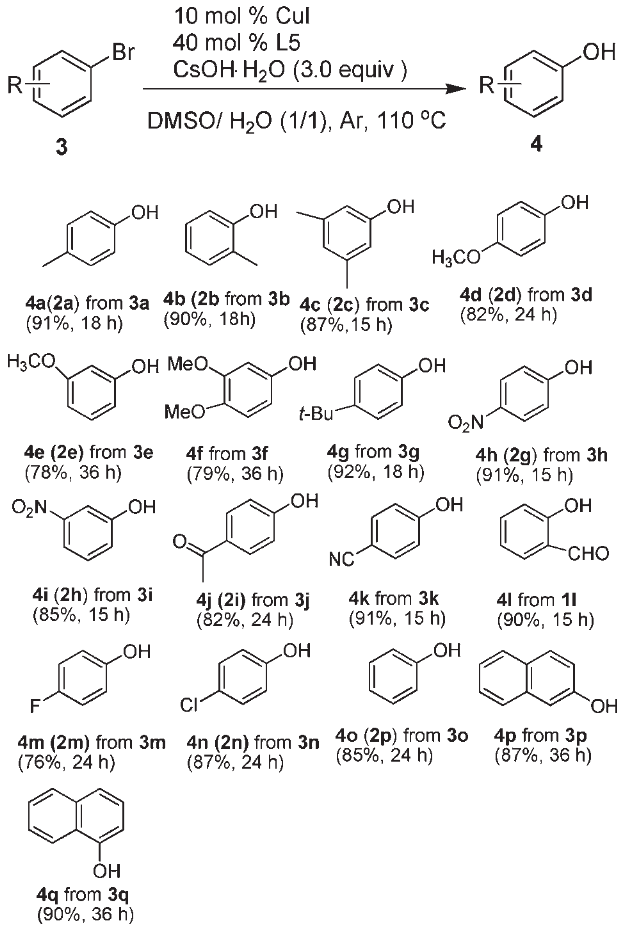
4-bromo-1-phenol,[5] we found hydroxylation of 4-bromo-1-iodobenzene using our catalytic system yielded phenol in 71% yield, which is totally different from those reported. We assumed that the initial monohydroxylation of 4-bromo-1-iodobenzene formed *p*-bromophenolate, which may be in favor of a radical mechanism by stabilizing the resulting phenolate radical anion ($OC_6H_4^{\bullet -}$). Then this radical intermediate could readily form phenol.

Scheme 1. Copper-Catalyzed Conversion of Aryl Iodides to Phenols

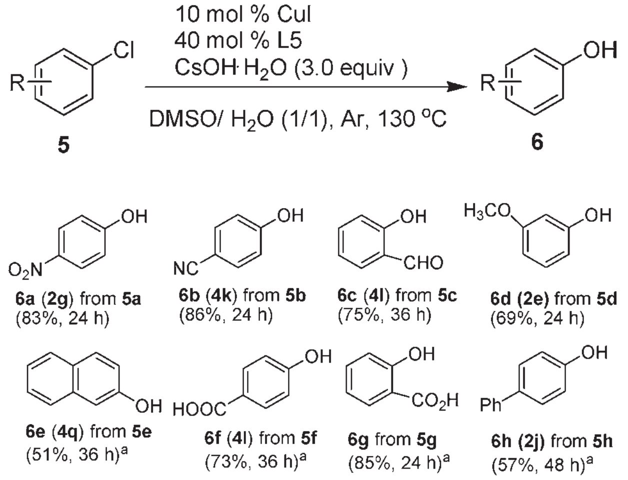


We then extended the CuI/L5 system to the hydroxylation of aryl bromides, and the results are shown in Scheme 2. All the examined aryl bromides coupled with CsOH in excellent yields at 110 °C. High yields were obtained for those aryl bromides with an electron-withdrawing group, regardless of the position of the substitution (**4h**–**4l**). In addition, bromobenzene, *β*-bromonaphthalene, 4-fluoro-1-bromobenzene, and electron-rich aryl bromides, such as 4-methoxy bromobenzene, 3-methoxy bromobenzene, and 4-methyl bromobenzene, had been highly challenging substrates for copper-catalyzed hydroxylation with hydroxide salts.[5] The CuI/L5 system was found to effectively catalyze the hydroxylation of these substrates in high yields at 110 °C (**4a**–**4g** and **4m**–**4p**).

Scheme 2. Copper-Catalyzed Conversion of Aryl Bromides to Phenols

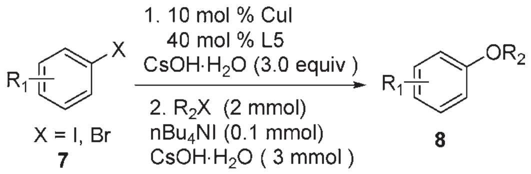


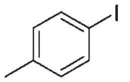
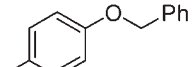
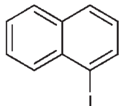
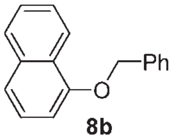
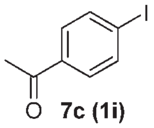
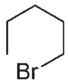
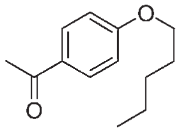
Scheme 3. Copper-Catalyzed Conversion of Aryl Chlorides to Phenols[a]

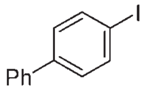
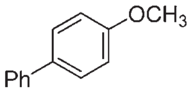
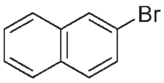
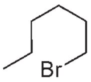
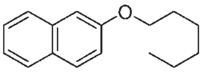
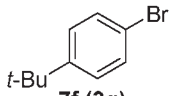
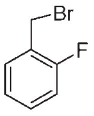
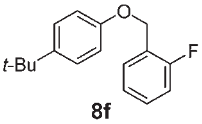


[a] 150 °C.

Table 2. One-Pot Synthesis of Alkyl Aryl Ethers from Aryl Halides[a,b]



entry	ArX	RX	product	yield (%)
1	 **7a (1a)**	BnBr (**3o**)	 **8a**	87
2	 **7b (1l)**	BnBr (**3o**)	 **8b**	84
3	 **7c (1i)**	 **3r**	 **8c**	79
4	CH₃I **1u** → see below			

entry	ArX	RX	product	yield (%)
4	 **7d (1j)**	CH_3I **1u**	 **8d**	92
5	 **7e (3p)**	 **3s**	 **8e**	85
6	 **7f (3g)**	 **3t**	 **8f**	85

[a] Reaction conditions: ArX (1.0 mmol), CuI (0.10 mmol, 10 mol %), L5 (0.4 mmol, 40 mol %), CsOH•H$_2$O (504 mg, 3.0 mmol) and DMSO/H$_2$O (1:1, 2 mL) at 100 °C for 24–36 h under argon. After the reaction mixture was cooled to ambient temperature, *n*-Bu$_4$NI (0.1 mmol, 10 mol %), CsOH•H$_2$O (504 mg, 3.0 mmol), and RX (2.0 mmol) were added, and the reaction system was then kept at 100 °C for 12 h. [b] Isolated yield.

Due to their low cost and ready availability, aryl chlorides are more highly desirable for industrial applications. Because of the low reactivity of aryl chlorides, the copper-catalyzed hydroxylation of aryl chlorides was indeed a challenge. We further extended the CuBr/L5 catalytic system to the conversion of aryl chlorides to phenols with CsOH. As shown in Scheme 3, aryl chlorides bearing either electron-donating or -withdrawing groups produced the corresponding phenols in good to excellent yields (**6a**–**6h**). Many functional groups, such as a nitro, methoxy, nitrile, aldehyde, and carboxylic acid, were well tolerated under the reaction conditions (**6a**–**6h**, **6f**, and **6g**). 2-Chloronaphthalene was also converted into the corresponding naphthol under these conditions (**6e**). Additionally, steric hindrance has no influence on the coupling reaction (**6f** vs **6g**). All of these results demonstrated the high efficiency of the CuBr/L5 catalyst system for the conversion of aryl halides to phenols.

To further extend the scope of this methodology, we developed a method for the conversion of aryl halides to alkyl aryl ethers in a one-pot fashion. Although You's group has reported copper-catalyzed formation of alkyl aryl ethers by a one-pot phenoxide/alkylation protocol, his method is limited to aryl iodides.[5b] As shown in Table 2, using the present catalytic system a variety of alkyl aryl ethers could be obtained from either aryl iodides or aryl bromides in excellent yields (**8a**–**8f**). Thus, the procedure provides a straightforward strategy for the catalytic synthesis of alkyl aryl ethers from the combination of both aryl halides and alkyl halides. Interestingly, this ether formation process requires two electrophilic components instead of one nucleophile and one electrophile.

In summary, a general, economical, and highly efficient method for the copper-catalyzed conversion of all kinds of aryl iodides, aryl bromides, and aryl chlorides to phenols was developed. To the best of our knowledge, the present catalytic system for copper-catalyzed hydroxylation of aryl chlorides or electron-rich aryl bromides is unprecedented. This inexpensive catalytic system showed great functional group tolerance and high selectivity at moderate temperatures. Furthermore, this protocol provides a one-pot procedure for the direct formation alkyl aryl ethers from aryl halides and alkyl halides.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.