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Highly Efficient Synthesis of Phenols by Copper-Catalyzed Oxidative Hydroxylation of Arylboronic Acids at Room Temperature in Water

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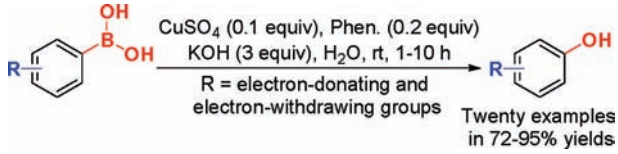
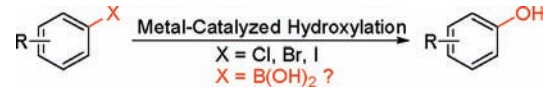
ABSTRACT



A general and efficient procedure for the preparation of phenols was developed by copper-catalyzed oxidative hydroxylation of arylboronic acids at room temperature in water.

Phenols have been found in numerous natural products in monomeric or polymeric forms. A number of them are pharmaceutically important compounds or widely serve as versatile synthetic intermediates.[1] In laboratory-scale synthesis, phenols are prepared routinely by a nucleophilic substitution of aryl halides activated by electron-withdrawing substituents or by a copper-catalyzed transformation of diazoarenes.[2] However, the former method requires harsh conditions for nonactivated substrates and is limited to the syntheses of electron-rich phenols. The latter one, which requires the conversion of amino groups to diazoarenes, is often not compatible with many other functional groups. In recent years, metal-catalyzed hydroxylation of aryl halides has emerged as an attractive alternative for the synthesis of phenols (Scheme 1). The aryl bromides and chlorides were converted into the corresponding phenols efficiently in the presence of Pd-based catalysts and phosphine ligands.[3] When iodides (or some bromides) were used as substrates, the same purpose was achieved by using cheap copper catalysts and nonphosphine ligands at higher temperature.[4]

Scheme 1



Investigation showed that arylboronic acids can be smoothly converted into phenols by oxidative hydroxylation,[5] in which

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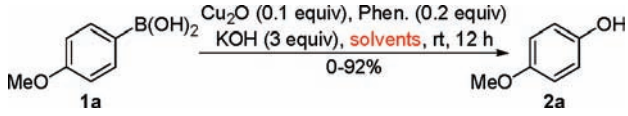
the amount of oxidants and reaction time needs to be controlled carefully because the products are sensitive to the oxidants. Although the phenols were observed as byproducts in many metal-catalyzed couplings of arylboronic acids,[6] there is no procedure that deals with the methodology for highly efficient metal-catalyzed hydroxylation of arylboronic acids to date.

Herein, we would like to report such a method by which highly efficient synthesis of phenols was achieved by an oxidative hydroxylation of arylboronic acids. The method proceeded at room temperature in water, and very cheap $CuSO_4$ and 1,10-phenanthroline were employed as catalyst and ligand, respectively.

Initially, Cu_2O was employed as a catalyst in our attempts for the hydroxylation of arylboronic acids. As shown in Table 1, when the mixture of 4-methoxyphenylboronic acid (**1a**),

Table 1. Effects of Solvents on the Hydroxylation of **1a**[a]



entry	catalyst	ligand	solvent	**2a**[b] (%)
1	Cu_2O		MeOH	0
2	Cu_2O		MeCN	0
3	Cu_2O		DMSO	0
4	Cu_2O		DMSO−H_2O	52
5	Cu_2O		H_2O	64
6	Cu_2O	Phen	H_2O	92
7		Phen	H_2O	0
8	Cu_2O	Phen	H_2O	35[c]

[a] Hydroxylation of **1a** (1 mmol) was performed in different solvents (5 mL) open to air. [b] The isolated yield was obtained. [c] The reaction was protected by N_2.

KOH (3 equiv), and Cu_2O (0.1 equiv) in MeOH, MeCN, or DMSO was stirred at room temperature for 12 h, no expected 4-methoxyphenol (**2a**) was obtained at all (entries 1−3). However, the same reaction gave **2a** in 52% or 64% yield by using DMSO−H_2O (1:1 by v/v) or pure H_2O as a solvent, respectively (entries 4 and 5). To our surprise, the yield of **2a** was elevated up to 92% in the presence of 1,10-phenanthroline (0.2 equiv) (entry 6). Since this excellent result had to be obtained by using the combination of Cu_2O and the ligand (entries 5−7), it strongly implied that Cu_2O may not be a real active catalytic species because it could not coordinated efficiently with the ligand. Further experiments (entry 8) proved that when the reaction was protected by nitrogen, its efficiency was decreased significantly. These phenomena suggested that a catalytic cycle between Cu(I) and Cu(II) may occur and Cu(II) may also be used as a catalyst for this reaction.

Thus, different Cu sources were tested as shown in Table 2. We observed that, in open air (without bubbling air), all tested Cu(I) salts showed satisfying catalytic activity (entries 1−3). Except for $Cu(OAc)_2{\cdot}H_2O$ which had relatively lower catalytic activity (entry 4), all the other tested Cu(II) salts gave good to excellent results (entries 5−8). By carefully monitoring the reaction time (**1a** was exhausted completely), the best result was obtained by using $CuSO_4$ as a catalyst (entry 8). The amount of $CuSO_4$ had a significant effect on the reaction efficiency (entries 9 and 10). When 0.2 equiv of $CuSO_4$ was used, the desired **2a** was obtained in 94% yield within 1 h (entry 10).

Table 2. Effects of Cu Catalysts on the Hydroxylation of **1a**[a]

entry	catalyst (equiv)	time[b] (h)	**2a**[c] (%)
1	CuBr (0.1)	5	84
2	CuI (0.1)	5	85
3	Cu_2O (0.1)	8	92
4	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	12	75
5	CuO (0.1)	8	93
6	$CuCl_2{\cdot}2H_2O$ (0.1)	2	90
7	$Cu_3(PO_4)_2$ (0.1)	2	85
8	$CuSO_4$ (0.1)	2	94
9	$CuSO_4$ (0.05)	7	87[d]
10	$CuSO_4$ (0.2)	1	94[e]
11	$CuSO_4$ (0.1)	12	30[f]

[a] A mixture of **1a** (1 mmol), Phen (0.2 equiv), KOH (3 equiv), and different Cu catalysts in H_2O was stirred at rt in open to air. [b] The time required for **1a** to be exhausted completely. [c] The isolated yield was obtained. [d] 0.1 equiv of Phen was used. [e] 0.2 equiv of Phen was used. [f] The reaction was protected by N_2.

Then, the ligands were scanned by using $CuSO_4$ as a catalyst (Table 3). As shown in entry 1, the reaction efficiency was decreased significantly without ligand. In comparison with the other popular ligands, such as L-proline, TMEDA, DMEDA, or 2,2′-bipyridine, 1,10-phenanthroline proved to be the best ligand for the hydroxylation of **1a** (entry 6).

As shown in Table 4, it seemed like that 3.0 equiv of KOH was good enough (entry 1). No improvement to the yield of **2a** was observed with 4.0 equiv of KOH (entry 2), while the yield of **2a** was reduced in 20% with 2.0 equiv of KOH (entry 3). The results of entries 4−8 clearly indicated that the basicity of the reagents played an important role for the reaction efficiency.

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Table 3. Effects of Ligands on the Hydroxylation of **1a**[a]

entry	ligand (0.2 equiv)	time[b] (h)	**2a**[c] (%)
1		12	61
2	L-proline	12	63
3	TMEDA	10	75
4	DMEDA	5	43
5	2,2′-bipyridine	5	55
6	Phen	2	94

[a] A mixture of **1a** (1 mmol), $CuSO_4$ (0.1 equiv), KOH (3 equiv), and different ligands in H_2O was stirred at rt in open to air. [b] The time required for **1a** to be exhausted completely. [c] The isolated yield was obtained.

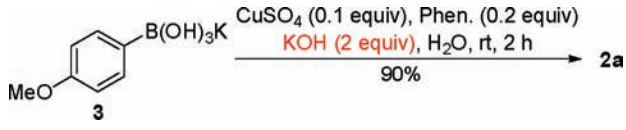
Table 4. Effects of Bases on the Hydroxylation of **1a**[a]

entry	base (3 equiv)	**2a**[b] (%)	entry	base (3 equiv)	**2a**[b] (%)
1	KOH	94[c]	5	*t*-BuOK	88
2	KOH (4 equiv)	94[c]	6	NaOH	65
3	KOH (2 equiv)	74	7	Cs_2CO_3	38
4	$CsOH.H_2O$	89	8	K_2CO_3	35

[a] A mixture of **1a** (1 mmol), $CuSO_4$ (0.1 equiv), Phen (0.2 equiv), and different bases in H_2O was stirred at rt in open to air. [b] Isolated yield was obtained. [c] The reaction time was 2 h.

Since the amount of KOH used was much less than expected, we hypothesized that the hydroxylation of **1a** may occur via a monopotassium trihydroxy(4-methoxy)-phenylborate salt intermediate (**3**),[7] by which **1a** was activated by only 1.0 equiv of KOH. To prove our hypothesis, the intermediate **3** was prepared by a known procedure.[8] As shown in Scheme 2, when **3** was treated

Scheme 2



with 2.0 equiv of KOH, the desired **2a** was obtained in 90% yield.

As shown in Figure 1, different arylboronic acid derivatives were tested under similar conditions. Phenylboronic acid (**1d**) was converted into phenol (**2d**) in 90% yield within 3 h. When potassium phenyltrifluoroborate (**4**) was used as a substrate, **2d** was obtained in 74% yield, in which **1d** may be an intermediate because it can be detected during the whole process. In fact, a reference has been reported that **4** was smoothly converted into **1d** in aqueous solution of NaOH.[8] As was expected, the cyclic esters of phenyboronic

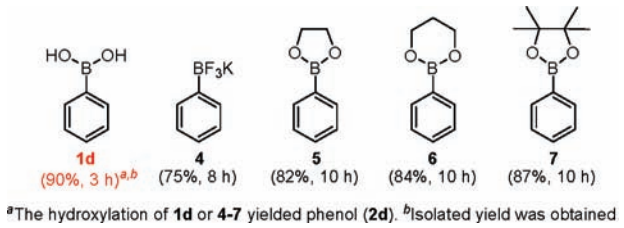
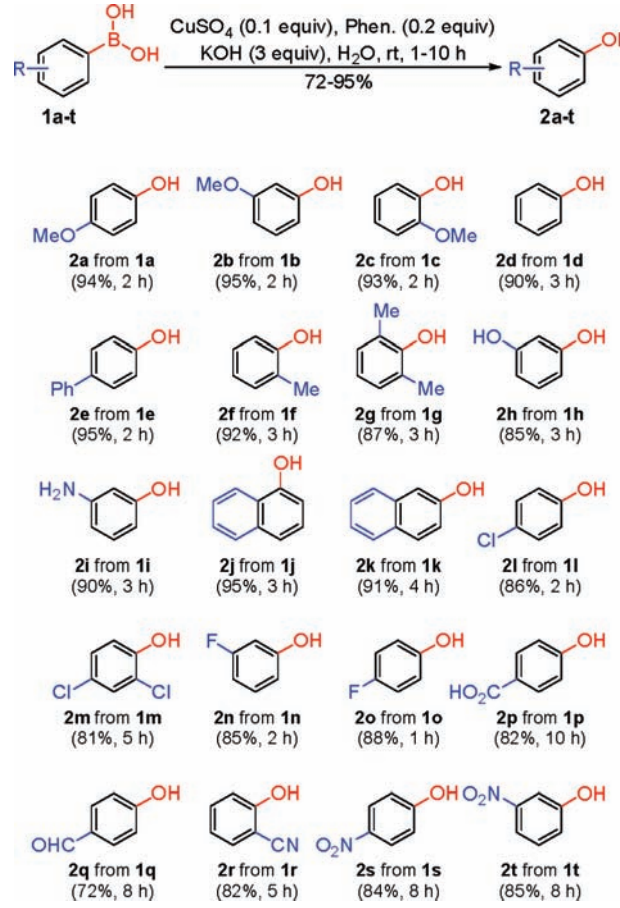


Figure 1. (a) Hydroxylation of **1d** or **4**−**7** yielded phenol (**2d**). (b) Isolated yield was obtained.

acid (**5**−**7**) gave satisfactory results. We interestingly observed that the most stable 2-phenyl-1,3,2-dioxaborolane (**5**) gave the lowest yield of **2d**. However, no evidence proved that **1d** was also an intermediate for the hydroxylations of **5**−**7**.

Incorporating the above measurements, a standard procedure was described in Scheme 3. By using different aryl-

Scheme 3



boronic acids **1a**−**t**, the method proved to be compatible with a wide range of substrates and **1a**−**t** were converted into the corresponding products **2a**−**t** in good to excellent yields. In contrast with the traditional nucleophilic substitution of

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aryl halides, the method preferred to offer the electron-rich phenols easily. For example, phenols **2a**−**k** were obtained in 85−95% yields during 2−4 h, and even 2,6-dimethylphenylboronic acid (**1g**) gave the corresponding **2g** in 87% yield within 3 h. Meanwhile, the electron-deficient phenols (**2p**−**t**) were also prepared in satisfactory yields, but relatively longer time was needed (5−10 h).

In conclusion, a general and efficient preparation of phenols was developed by a copper-catalyzed oxidative hydroxylation of arylboronic acids at room temperature in water. The method is characterized by the use of a cheap catalyst, mild conditions, short reaction time, and high yields. By using this method, the electron-rich, ortho-substituted, and functionalized phenols were prepared efficiently. To the best of our knowledge, this is the first highly efficient procedure for the synthesis of phenols by copper-catalyzed oxidative hydroxylation of arylboronic acids. Further mechanistic studies for this reaction are underway.

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Supporting Information Available: Experiments, characterization, and ^{1}H and ^{13}C NMR spectra for products **2a**−**t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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