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Mild and Rapid Hydroxylation of Aryl/Heteroaryl Boronic Acids and Boronate Esters with *N*-Oxides

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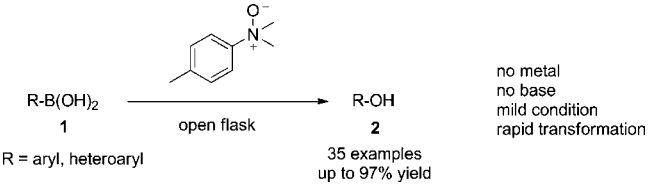
ABSTRACT



Aryl and heteroaryl boronic acids and boronate esters are rapidly, often within minutes, transformed into the corresponding phenols by *N*-oxides in an open flask at ambient temperature. This transformation has broad compatibility with a variety of functional groups.

Phenol is a ubiquitous structural unit found in a vast array of natural products and pharmaceuticals.[1] Moreover, it frequently serves as the key synthetic intermediate for construction of more complex structures. Consequently, establishing mild and efficient access to phenols, especially in the presence of polyfunctional groups, is of great significance.

Arylboronic acids and related aromatic/heteroaromatic boronate esters are readily available and have found broad applications in synthetic chemistry.[2] Their transformation into phenols is typically accomplished through transition-metal-catalyzed hydroxylation or oxidative hydroxylation, but it continues to remain an area of active investigation. For example, Wang et al. and Fu et al. have recently reported copper-catalyzed hydroxylations of arylboronic acids at room temperature,[3,4] albeit using a stoichiometric strong base (KOH or NaOH) (Scheme 1 (a)). Subsequently, alternative base-free or palladium-catalyzed conditions were developed.[5] However, these approaches required several hours to complete the conversions. The hydroxylation of arylboronic acids has been achieved without transition metal catalysis, but this requires strong oxidants such as hydrogen peroxide and oxone for success (Scheme 1 (b)).[6,7] Moreover, the amount of oxidant needed and the reaction conditions (time, temperature) often must be carefully controlled to avoid overoxidation of sensitive functionality. From a practical point of view, nonmetal-mediated processes are much preferred in the pharmaceutical industry, since metal contamination can induce severe concerns and metal removal can be expensive. Herein, we reveal the first *N*-oxide mediated transformation of arylboronic acids to

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(5) (a) Inamoto, K.; Nozawa, K.; Yonemoto, M.; Kondo, Y. *Chem. Commun.* **2011**, *47*, 11775. (b) Kaboudin, B.; Abedi, Y.; Yokomatsu, T. *Eur. J. Org. Chem.* **2011**, 6656. (c) Chowdhury, A. D.; Mobin, S. M.; Mukherjee, S.; Bhaduri, S.; Lahiri, G. K. *Eur. J. Inorg. Chem.* **2011**, 3232.

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(7) For other hydroxylations of boronic acids, see: (a) Kianmehr, E.; Yahyaee, M.; Tabatabai, K. *Tetrahedron Lett.* **2007**, *48*, 2713. (b) Hosoi, K.; Kuriyama, Y.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2010**, *46*, 1284. (c) Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R.-L.; Jørgensen, K. A.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 784.

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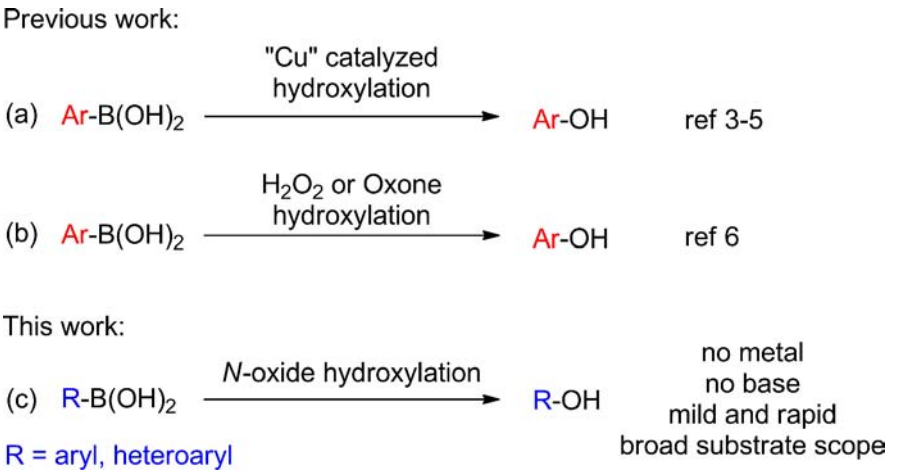
Scheme 1. Hydroxylation of Boronic Acids



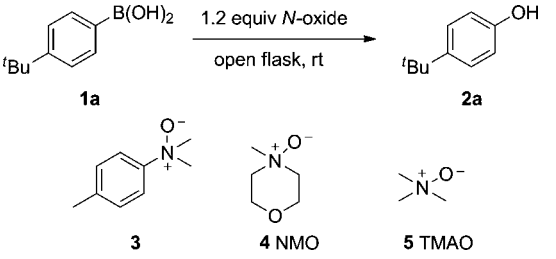
phenols (Scheme 1 (c)). The reaction proceeds rapidly, mostly within a few minutes at ambient temperature and without base. Another notable feature is the compatibility of heteroaryl boronic acids which remains a challenge and has rarely been demonstrated.[8]

This report is based on unexpected findings during the exploration of cross-coupling reactions between *N*,*N*-dimethyl-4-toluidine *N*-oxide and boronic acids. Specifically, simple addition together of *N*-oxide **3** and 4-*tert*-butylphenylboronic acid **1a** resulted in an exothermic reaction that led to the corresponding phenol **2a** (Table 1, entry 1). Both are solids at room temperature. Given the nearly complete conversion, we assumed that the temperature rose high enough to melt one or both reagents. The reaction can be conducted at 0.2 M in DCM without compromising efficiency, giving the desired product in high chemical yield (Table 1, entry 2). We also examined other commercially available *N*-oxides, e.g., NMO and TMAO. Compared with **3**, the reactions of **4** and **5** were patently sluggish (Table 1, entries 3 and 4). Notably, the reaction could also be carried out in water with prolonged reaction time, providing a potentially green process (Table 1, entry 5).

The optimized reaction parameters from Table 1 were utilized to explore the substrate scope (Scheme 2). These transformations demonstrated excellent compatibility with a wide range of functional groups, e.g., halide, aldehyde, nitrile, sulfide, ester, nitro, etc. Superior results were observed irrespective of electronic or steric properties of the arylboronic acids. Generally, the conversion of electron-rich arylboronic acids was complete within 1 min, while electron-deficient arylboronic acids took about 5 min or less. Importantly, oxidation-sensitive substituents such as sulfide **2e** and aldehydes **2k**, **2x** tolerated the conditions without suffering overoxidation. The transformation in the presence of aryl bromides **2g**, **2q**, **2u** and iodide **2h** is

(8) An example of hydroxylation of organotrifluoroborates, see: Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2011**, *76*, 623.

Table 1. Reaction Parameters

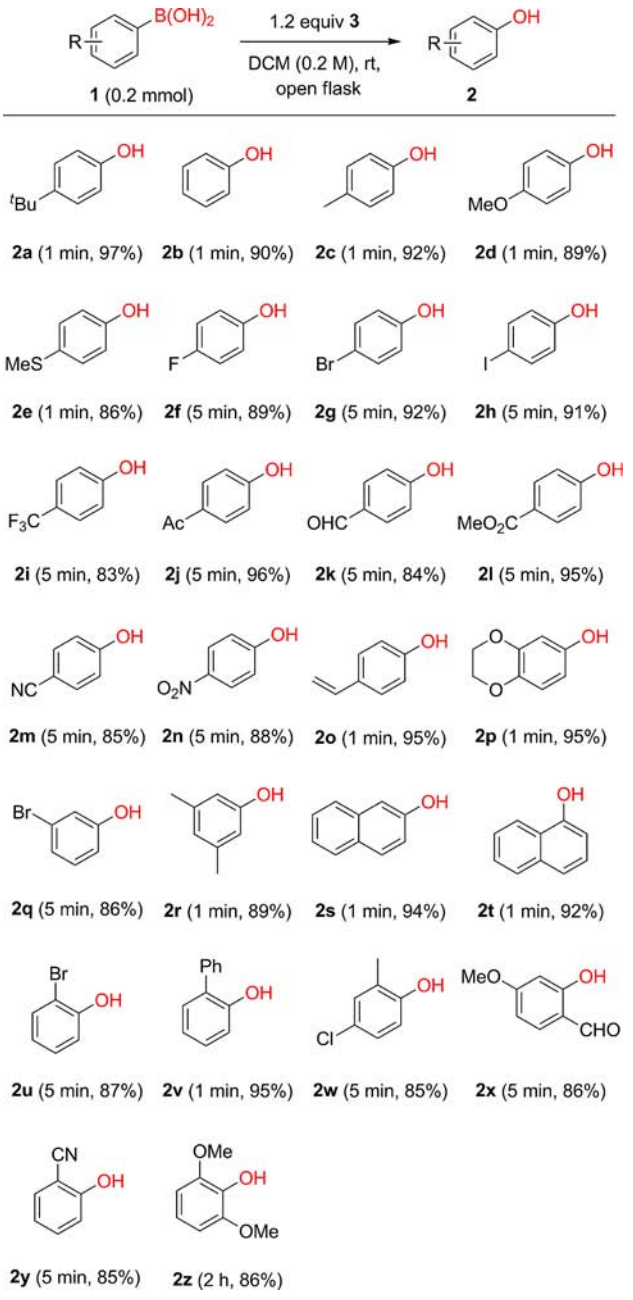


entry	oxidant	condition	result
1	**3**	no solvent	highly exothermic, conversion >99%
2	**3**	DCM (0.2 M)	1 min, conversion >99%, isolated yield 97%
3	**4**	DCM (0.2 M)	10 min, conversion <10%; 50 °C for 12 h, isolated yield 90%
4	**5**	DCM (0.2 M)	10 min, conversion <10%; 50 °C for 12 h, isolated yield 86%
5	**3**	H_2O (0.2 M)	10 h, isolated yield 85%

noteworthy, as the bromide and iodide can be exploited for subsequent functionalization. The chemoselective hydroxylation of boronic acid **2o** instead of olefinic epoxidation displayed another undeniable advantage of this methodology. Even the highly crowded 2,6-dimethoxyboronic acid furnished the corresponding phenol **2z** in useful yield by extension of the reaction time.

Encouraged by these results, we next investigated the hydroxylation of heteroaryl boronic acids (Scheme 3). Both pyridinyl and quinolinyl boronic acids were readily converted into the corresponding phenols **7a** and **7b** in good chemical yields. Hydroxylation of pyrrolyl boronic acid **6c** followed by tautomerization efficiently generated a usefully synthetic building block 3-pyrrolin-2-one **7c**.[9] In addition to nitrogen-containing boronic acids, oxygen- and

Scheme 2. Hydroxylation of Arylboronic Acids



sulfur-containing heteroarenes such as benzofuran **6d** and benzothiophene **6e** were apt substrates.

Remarkably, not only boronic acids but other popular boronic acid surrogates proved suitable for hydroxylation (Scheme 4). Under the standard conditions, various phenyl boronic esters **8a**–**c** as well as potassium phenyltrifluoroborate **8d** afforded phenol **2b** in satisfactory yield and with slightly slower reaction rates.

(9) For selected examples, see: (a) Shepherd, N. E.; Tanabe, H.; Xu, Y.; Matsungaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 3666. (b) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2011**, *13*, 788. (c) Lin, L.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.* **2011**, *13*, 6410. (d) Huang, H.; Jin, Z.; Zhu, K.; Liang, X.; Ye, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3232.

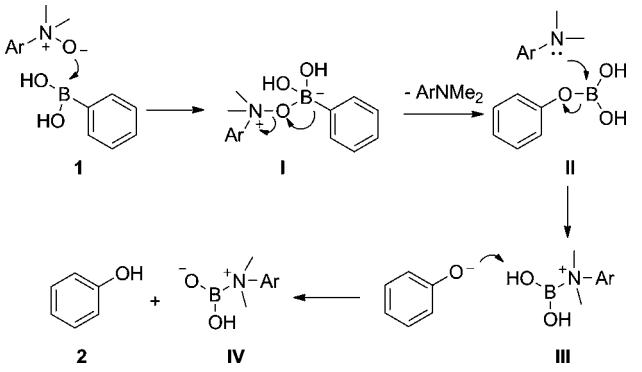
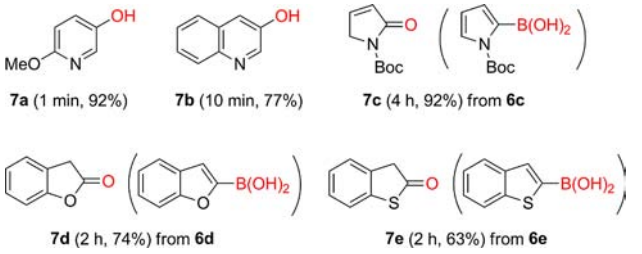


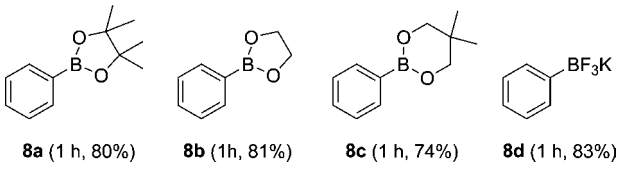
Figure 1. Plausible mechanism.

Scheme 3. Hydroxylation of Heteroaryl Boronic Acids[a]



[a] Standard conditions: boronic acid **6** (0.2 mmol) and *N*-oxide **3** (0.24 mmol) in DCM (1 mL), rt, open flask.

Scheme 4. Hydroxylation of Other Boronic Compounds[a]



[a] Standard conditions: boronic compound **8** (0.2 mmol) and *N*-oxide **3** (0.24 mmol) in DCM (1 mL), rt, open flask.

A postulated mechanistic pathway is depicted in Figure 1.[10] We speculate that nucleophilic attack of the *N*-oxide on boronic acid **1** generates key intermediate **I**. Subsequent migration of the aryl group from boron to oxygen generates boronate ester II. Simultaneous departure of the quaternary ammonium cation provides an important driving force for the N–O bond cleavage. The newly released tertiary amine attacks the boronic ester, facilitating the release of phenoxide anion, which abstracts a proton from the nitrogen–boron complex **III** furnishing phenol **2** and zwitterion **IV** that precipitates from solution.[11]

(10) For similar mechanism, see: Kabalka, G. W.; Wadgaonkar, P. P.; Shoup, T. M. *Organometallics* **1990**, *9*, 1316.

(11) The hydrolyzed product $ArNMe_2$ of zwitterion **IV** can be observed in the reaction.

In conclusion, a *N*-oxide mediated, mild, and practical hydroxylation of boronic acids and boronate esters has been developed. The reactions are conducted in an open flask at room temperature, and most of them are complete within a few minutes. This transformation has broad functional group compatibility for both electron-rich and -deficient substituents. In addition to arylboronic acids, heteroaryl boronic acids are also tolerated in this methodology.

Significantly, this transformation provides a mechanistic inspiration which prompted us to pursue other transition-metal-free functionalizations of boronic acids based upon the same concept. These results will be revealed in due course.

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Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.