RSC Advances

Unexpected Hydrazine Hydrate-Mediated Aerobic Oxidation of Aryl/ Heteroaryl Boronic Acids to Phenols with Ambient Air‡

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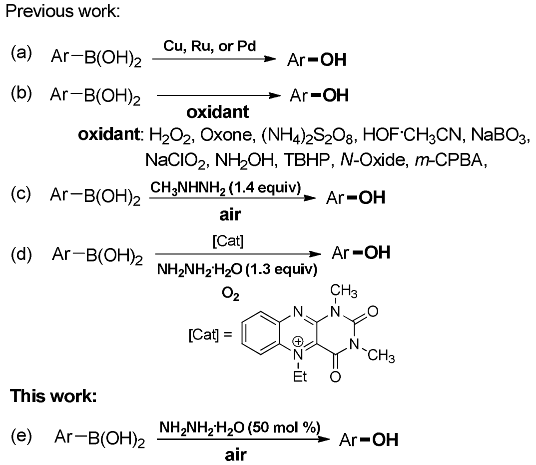
Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X
First published on the web Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

The expedient and efficient sub-stoichimetric hydrazine hydrate-mediated aerobic hydroxylation of boronic acids that proceeds in poly(ethylene glycol) (PEG-400) has been successfully developed, providing diverse phenols in high yields. And heteroaryl boronic acids are also amenable to this protocol.

The phenol motif is widespread in a vast array of polymers, pharmaceuticals, and naturally occurring compounds.[1] Moreover, it often serves as the key building block for construction of more complex structures. As a result, establishing practical, general, and efficient catalytic methods for the synthesis of phenols remain an area of tremendous research efforts.

Among the methods developed to prepare phenols, the oxidative *ipso*-hydroxylation of arylboronic acids has attracted considerable interest because arylboronic acids are readily available, thermally-, air- and water-stable, and easily separated from products. Furthermore, classical phenol synthesis methods, *i.e.* nucleophilic aromatic substitution of aryl halides, hydrolysis of arene diazonium salts, and benzyne protocols,[2] frequently suffer from low functional group compatibility, poor accessibility of the starting materials, and harsh reaction conditions. Transition-metal-catalysis as a powerful tool has been widely applied in organic synthesis and also introduced to oxidative hydroxylation of arylboronic acids. For instance, a variety of copper, ruthenium, or palladium catalysts have been developed for this transformation and achieved effective catalysis for a broad substrate scope (Scheme 1a)[3] under air or oxygen atmosphere. From a practical point of view, it is highly desirable to develop nonmetal-catalyzed processes in the pharmaceutical industry, since metal contamination can cause severe concerns and metal removal can be cumbersome. Although numerous nonmetal-mediated processes have been utilized in hydroxylation of arylboronic acids, most of them require stoichiometric strong oxidants, as shown in the Scheme 1b[4-13] and often lead to poor functional group tolerance, safety issues and /or stoichiometric amounts of unwanted byproducts. Compared to these oxidants, air and molecular oxygen are the ideal oxidants with low cost and lack of toxic byproducts.[14]

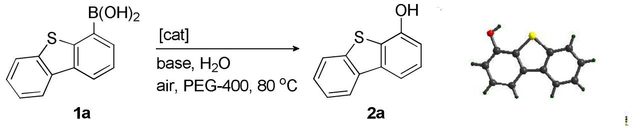
During the preparation of this manuscript, Xiao and co-workers reported a stoichiometric methylhydrazine-mediated hydroxylation of arylboronic acids using air as oxidant (Scheme 1c).[15] And subsequently, a complicated organic catalyst was reported to catalyzed this transformation with the assistant of stoichiometric hydrazine hydrate in the presence of molecular oxygen (Scheme 1d).[16] And, in the both methods toxic and volatile solvents were used as reaction media. Herein, we disclose the first inexpensive sub-stoichimetric hydrazine hydrate-mediated oxidative *ipso*-hydroxylation of arylboronic acids to phenols by using ambient air as the sole oxidant in green solvent poly(ethylene glycol) (Scheme 1e). A remarkable feature of this protocol is the compatibility of heteroaryl boronic acids which remains elusive.[12]



Scheme 1 Oxidative *ipso*-hydroxylation of boronic acids

Recently, we have smoothly launched ligand-free catalytic systems for cross-coupling reactions,[17] utilizing PEG-400 [poly(ethylene glycol) with an average molecular weight of 400 Da][18] as a solvent. This report is based on unexpected findings during the exploration of carbon-nitrogen bond-forming reactions of hydrazine hydrate with arylboronic acids in PEG-400. During the exploration, we observed hydrazine hydrate promoted *ipso*-hydroxylation of arylboronic acids to phenols in the absence of a transiton-metal catalyst under air atmosphere. Encouraged by this observation, we first investigated hydrazine hydrate-promoted aerobic oxidation of dibenzothiophen-4-ylboronic acid (**1a**) to dibenzothiophen-4-ol (**2a**) in the absence of a metal catalyst. The structure of **2a** was proved by single-crystal X-ray diffraction.[19] Selected results from our screening experiments are presented in Table 1. The bases affected the reaction. For example, K_3PO_4, and K_2CO_3 gave moderate results (Table 1, entries 1 and 5), whereas Na_2CO_3, KOH, NaF, TBAF, and Et_3N were found to be ineffective (Table 1, entries 4, 6, 7, 8, and 9).

Table 1 Aerobic oxidation of **1a** in PEG-400[a]

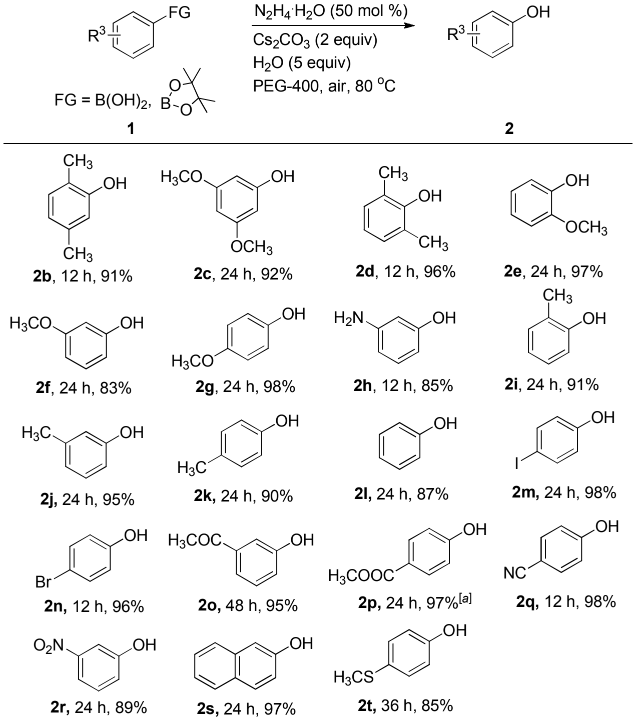


Entry	[cat] (mol %)	base	water (equiv)	Yield[b] of **2a**/%
1	$N_2H_4·H_2O$ (200)	K_3PO_4	-	54
2	$N_2H_4·H_2O$ (200)	Cs_2CO_3	-	79
3	$N_2H_4·H_2O$ (200)	CH_3COOK	-	70
4	$N_2H_4·H_2O$ (200)	Na_2CO_3	-	<5
5	$N_2H_4·H_2O$ (200)	K_2CO_3	-	52
6	$N_2H_4·H_2O$ (200)	KOH	-	trace
7	$N_2H_4·H_2O$ (200)	NaF	-	38
8	$N_2H_4·H_2O$ (200)	TBAF	-	<5
9	$N_2H_4·H_2O$ (200)	Et_3N	-	trace
10	$N_2H_4·H_2O$ (200)	Cs_2CO_3	H_2O (1)	83
11	$N_2H_4·H_2O$ (200)	Cs_2CO_3	H_2O (3)	87
12	$N_2H_4·H_2O$ (200)	Cs_2CO_3	H_2O (5)	91
13	$N_2H_4·H_2O$ (200)	Cs_2CO_3	H_2O (10)	78
14	-	Cs_2CO_3	H_2O (5)	29
15	$N_2H_4·H_2O$ (50)	Cs_2CO_3	H_2O (5)	43
16[c]	$N_2H_4·H_2O$ (50)	Cs_2CO_3	H_2O (5)	86
17[c]	$N_2H_4·H_2O$ (20)	Cs_2CO_3	H_2O (5)	83
18[c]	$N_2H_4·H_2O$ (50)	-	H_2O (5)	41
19[d]	$N_2H_4·H_2O$ (50)	Cs_2CO_3	H_2O (5)	96
20[c]	$C_6H_5NHNH_2$ (50)	Cs_2CO_3	H_2O (5)	10
21[c]	$C_6H_5NH_2$ (50)	Cs_2CO_3	H_2O (5)	10
22[c]	$NH_3·H_2O$ (50)	Cs_2CO_3	H_2O (5)	trace

[a] *Reaction conditions* (unless otherwise stated): **1a** (0.5 mmol), base (1.0 mmol), PEG-400 (2.0 g), air, 80 °C, 6 h. [b] Isolated yield after flash chromatography. [c] 24 h. [d] O_2 (balloon).

Comparatively, Cs_2CO_3 gave a better result (Table 1, entry 2). The effect of water on the reaction was also evaluated. The best result was obtained when 5.0 equiv of water was used (Table 1, entry 12). However, in the absence of hydrazine hydrate, the yield was decreased to 29% (Table 1, entry 14). Gratifyingly, a sub-stoichimetric amount of hydrazine hydrate (50 mol %) and (20 mol %) also gave a satisfactory yield (86%) and (83%) in 24 h, respectively (Table 1, entries 16 and 17). Under otherwise equal reaction conditions this transformation was performed under an oxygen atmosphere and afforded **2a** in 96% yield in 6 h (Table 1, entry 18). Considering operability and practicability, we chose air as oxidant. Other catalysts such as phenylhydrazine, aniline, and $NH_3·H_2O$ were ineffective with this reaction (Table 1, entries 20–22).

Having identified the optimal conditions, we next explored the efficacy of hydrazine hydrate-mediated aerobic oxidation of various arylboronic acids to phenols (Scheme 2). A wide array of arylboronic acids could be oxidized to phenols in good to excellent yields. The electronic properties of the arylboronic acids was found to be only loosely correlated with their reactivity and had little effect on this transformation. Sterically hindered arylboronic acids (*e.g.*, **2b**, **2d**, **2e**, and **2i**) were well-tolerated. Base-sensitive functional groups methyl ketone and ester also proceeded successfully, leading to desire products **2o** and **2p** in 95% and 97% yields, respectively. Notably, an oxidation-sensitive free aniline group proved to be a compatible functional group (*e.g.*, **2h**), which was rarely reported in this type of transformation.[20] And, the product 3-aminophenol (**2h**) is a key intermediate for the synthesis of fluorescent dye Rhodamine B. Furthermore, iodo and bromo substitutes that have been widely applied in cross-coupling reactions were well tolerated with this method (*e.g.*, **2m** and **2n**). To our delight, not only boronic acids but a boronic ester smoothly converted to corresponding phenol **2p** in 97 % yield. We were also pleased to find that 2-naphthylboronic acid underwent an efficient aerobic oxidative *ipso*-hydroxylation (*e.g.*, **2s**). Significantly, sulfide **2t**, an oxidation-sensitive substrate, can tolerate the normal conditions without suffering overoxidation.



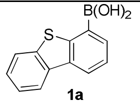
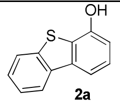
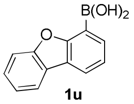
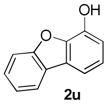
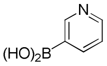
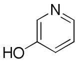
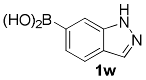
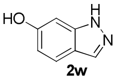
Scheme 2 Hydrazine hydrate-mediated aerobic oxidation of arylboronic acid. [a] *Reaction conditions* (unless otherwise stated): **1** (0.5 mmol), Cs_2CO_3 (1.0 mmol), H_2O (2.5 mmol), $N_2H_4·H_2O$ (0.25 mmol), PEG-400 (2.0 g), 80 °C, air. Isolated yield after flash chromatography. [b] With 4-carbomethoxy_ phenylboronic acid pinacol ester.

Notably, heteroarylboronic acids are also amenable to this protocol. Various heteroaryl systems were explored, including dibenzothiophenyl, dibenzofuranyl, thiophenyl, pyridinyl, and indazolyl derivatives. And, the corresponding heteroarylboronic acids delivered desired products with superior yields (Table 2).

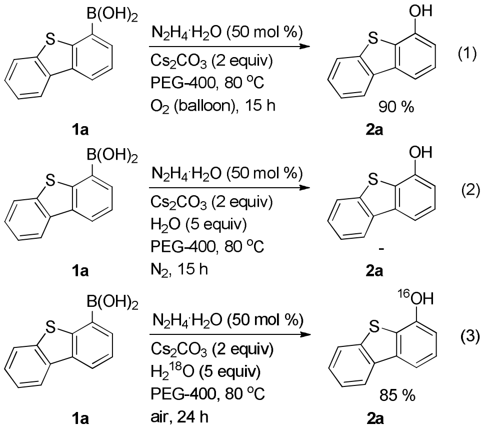
To gain insight into the possible mechanism, control experiments were carried out. When the model reaction was performed in anhydrous conditions under oxygen atmosphere, a excellent yield of **2a** can be obtained [eqn (1)]. Whereas the same reaction proceeded in oxygen-free system, **2a** can not be detected [eqn (2)]. Furthermore, under normal conditions H_2O was replaced by $H_2{}^{18}O$ and as a result, the product was still the **2a** [eqn (3)]. These results suggest that molecular oxygen rather than water is the donor of the oxygen atom in the oxidative hydroxylation reactions. Recently, Berkessel et al.

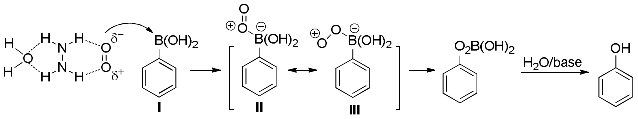
reported multiple H-bond dramatically accelerating olefin epoxidation.[21] On the basis of above results and previous studies,[4b,21,22] the reaction presumably involves hydrazine hydrate firstly activating oxygen molecule through hydrogen bonding. Subsequently the activated oxygen molecule undergoes nucleophilic attack on boronic acid **I** to form a key intermediate **II** (or **III**). Finally, phenyl migration and hydrolysis provide the final product (Scheme 3).

Table 2 Hydrazine hydrate-mediated aerobic oxidation of heteroaryl boronic acids[a]

Entry	boronic acid	product	time/h	yield/%
1	 **1a**	 **2a**	24	86
2	 **1u**	 **2u**	12	83
3	 **1v**	 **2v**	24	91
4	 **1w**	 **2w**	12	96

[a] *Reaction conditions* (unless otherwise stated): **1** (0.5 mmol), Cs_2CO_3 (1.0 mmol), H_2O (2.5 mmol), $N_2H_4 \cdot H_2O$ (0.25 mmol), PEG-400 (2.0 g), 80 °C, air. Isolated yield after flash chromatography.





Scheme 3 Plausible mechanism for hydrazine hydrate-mediated oxidative *ipso*-hydroxylation of aryl/heteroaryl boronic acids

In summary, a general, practical and efficient hydrazine hydrate-mediated hydroxylation of boronic acids and a boronate ester has been developed.[23] The use of air as the sole oxidant makes the process both safely and environmentally sound. Substrates bearing electron-withdrawing or electron-donating functionality, active groups, as well as ortho-substitution underwent smoothly, delivering phenols in high yields. Additionally, heteroaryl boronic acids are also well tolerated in this protocol.

Notes and references

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/

‡ The work was sponsored by the Natural Science Foundation of China (21302099), the Natural Science Foundation of Jiangsu Province (BK2012449), the Natural Science Foundation of Jiangsu Provincial Colleges and Universities (12KJB150014), the Scientific Research Start-up Foundation of Nanjing Normal University (2011103XGQ0250), the SRF for ROCS, SEM, and the Priority Academic Program Development of Jiangsu Higher Education Institutions. We thank Prof. Yaqian Lan and Dr. Shunli Li for assistance with X-ray structure analysis.

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19 CCDC 996231 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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23 **General Procedure for aerobic oxidation of aryl/heteroaryl boronic acids to phenols with ambient Air**: a flask was charged with aryl/heteroaryl boronic acid **1** (0.5 mmol), $N_2H_4 \cdot H_2O$ (0.25 mmol, 14.4 μL), Cs_2CO_3 (1.0 mmol, 329.1 mg), H_2O (2.5 mmol, 45.0 μL), and PEG-400 (2.0 g). Then, the flask was stirred at 80 °C in open air for the indicated time. At the end of the reaction, the reaction mixture was acidified with dilute aqueous HCl and extracted with ethyl acetate (3 × 15 mL). The organic phases were combined, and the volatile components were evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate).