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Aerobic oxidative C–B bond cleavage of arylboronic acids mediated by methylhydrazines†

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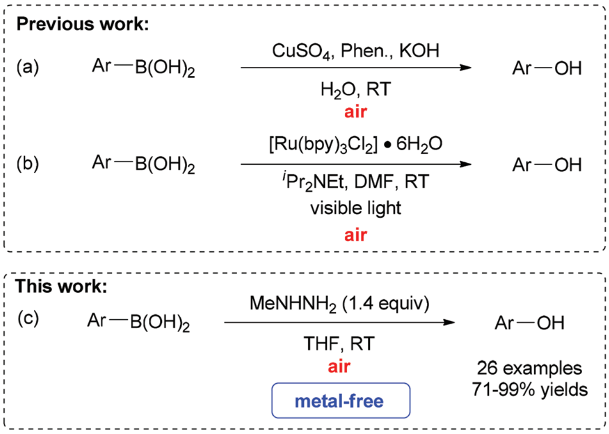
The aerobic oxidative C–B bond cleavage and *ipso*-hydroxylation of arylboronic acids mediated by methylhydrazine have been developed under metal-free conditions. This transformation affords structurally diverse phenols in good to excellent yields (26 examples, 71–99%).

Boronic acids are valuable synthetic precursors and have attracted considerable research interest from chemical society.[1] Among the various transformations of boronic acids, the oxidative C–B bond cleavage and the *ipso*-hydroxylation of arylboronic acid have recently been extensively investigated to prepare synthetically useful and biologically important phenols.[2] In this context, great efforts have been devoted to the search for new and more efficient terminal oxidants for this transformation. Representative examples include aqueous hydrogen peroxide,[3] sodium perborate,[4] oxone,[5] hydroxylamine,[6] *N*-oxide,[7] *m*-chloroperoxybenzoic acid,[8] and *tert*-butyl hydroperoxide.[9]

Compared to these oxidants, molecular oxygen and air have been well established as highly environmentally friendly and inexpensive oxidants for oxidation reactions.[10] Notably, oxygen and air have been successfully employed as oxidants for the oxidation reaction of C–B bonds.[11] For instance, Wang, Hu and co-workers have documented an elegant example of the $CuSO_4$-catalyzed aerobic oxidative hydroxylation of arylboronic acids in the presence of KOH (Scheme 1a).[11g] Thereafter, other metal catalysts, such as a variety of copper or palladium complexes, have been utilized in this kind of transformation under air or oxygen atmospheres.[11c–f] Alternatively, our group has recently developed a visible light induced aerobic oxidative cleavage of arylboronic acids to phenols with $[Ru(bpy)_3Cl_2]·6H_2O$ as a photoredox catalyst (Scheme 1b).[11a] In this reaction, the key intermediate superoxide radical anion, generated from oxygen by photoredox catalysis, was proposed to act as the highly active terminal oxidant. Although impressive advances have been achieved, these procedures usually need to use transition-metals as the catalysts. Therefore, the search for more efficient and milder methods for the conversion of structurally diverse arylboronic acids into their corresponding phenols with oxygen or air as the oxidant remain highly desirable.[11b] As part of our continuing research program on the chemistry of arylboronic acids[11a] and hydrazones,[12] we recently developed a novel protocol for the oxidative cleavage of aryl C–B bonds mediated by methylhydrazine in an open flask at room temperature under metal-free conditions. Herein, we describe the preliminary results in this communication (Scheme 1c).[13]



Scheme 1 Oxidative cleavage of arylboronic acid to phenol under an air atmosphere.

Initially, 4-methoxyphenylboronic acid **1a** was chosen as the model substrate for examining the feasibility of the aerobic oxidation reaction and optimizing the reaction conditions (Table 1). To our delight, the desired product 4-methoxyphenol **2a** could be obtained in a 90% yield under an oxygen atmosphere in the presence of $MeNHNH_2$ (40% aq., 1.4 equiv.)[14,15] (Table 1, entry 1). Notably, the reaction could also proceed

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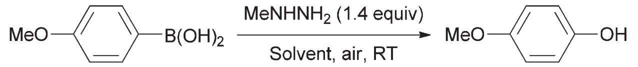
Table 1 Screening of solvents and control experiments[a]



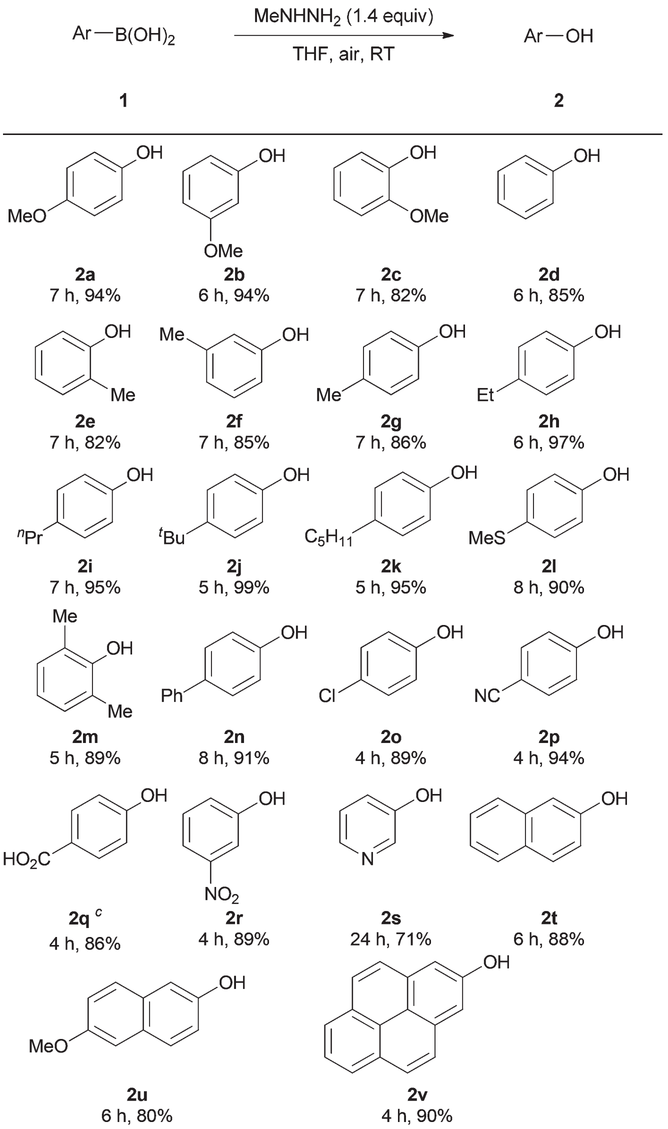
1a

2a

Entry	Solvent	Time (h)	Yield[b] (%)
1[c]	Dioxane	7	90
2	Dioxane	7	89
3	CH_2Cl_2	24	65
4	MeOH	24	59
5	EtOH	24	55
6	DMF	7	67
7	Toluene	24	72
8	**THF**	**7**	**94**
9	Et_2O	24	81
10	TBME	24	91
11	$^{i}Pr_2O$	24	81
12[d]	THF	12	n.r.
13[e]	THF	12	Trace

[a] Unless otherwise noted, the reaction of **1a** (0.5 mmol) with $MeNHNH_2$ (40% aq., 1.4 equiv.) was carried out in the solvent (30 mL) at room temperature under an air atmosphere. [b] Isolated yield. [c] The reaction was carried out under an O_2 atmosphere. [d] Performed without $MeNHNH_2$. [e] Performed under an N_2 atmosphere. n.r. = no reaction.

Table 2 Substrate scope of methylhydrazine mediated aerobic oxidative cleavage of arylboronic acids[a,b]



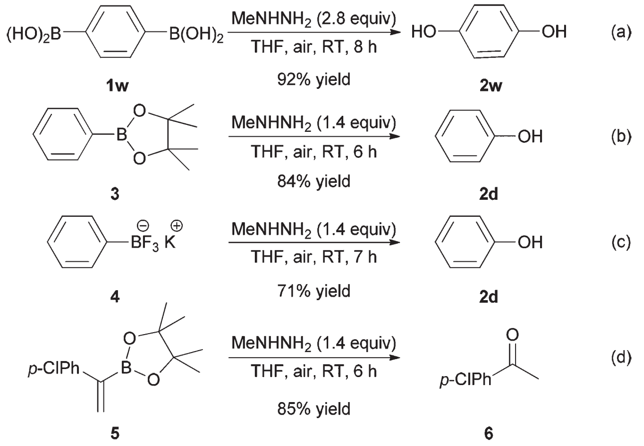
[a] Unless otherwise noted, the reaction of **1** (0.5 mmol) with $MeNHNH_2$ (1.4 equiv.) was carried out in the THF (30 mL) at room temperature under air atmosphere. [b] Isolated yield. [c] 2.8 equiv. of $MeNHNH_2$ was used.

smoothly in an open flask (under an air atmosphere) with a comparative yield within 7 h (Table 1, entry 2). Encouraged by these results, we then examined other reaction parameters to further improve the chemical yield. It was found that this transformation could proceed well in many commonly used organic solvents (Table 1, entries 3–11). Complete conversion was achieved in THF after 7 h to give the product **2a** in a 94% isolated yield (Table 1, entry 8). Control experiments showed that both $MeNHNH_2$ and air were essential for this process; otherwise, no desired product was observed when either of them was omitted from the reaction system (Table 1, entries 12–13). Screening of other reaction parameters led to no further improvement.[16] Accordingly, the optimal reaction conditions were identified as follows: **1a** (0.5 mmol) and $MeNHNH_2$ (40% aq; 1.4 equiv.) in THF (0.017 M) at room temperature under an air atmosphere (Table 1, entry 8).

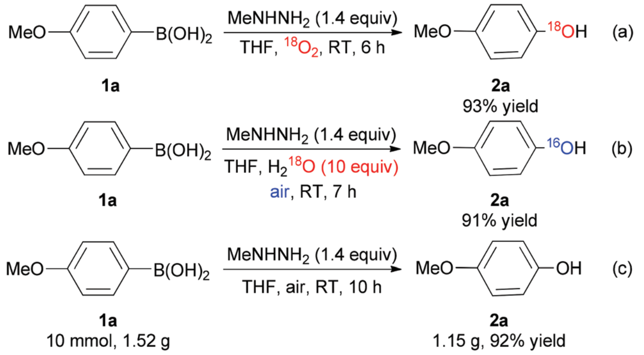
With the optimal reaction conditions in hand, we then examined the substrate scope of this transformation. As shown in Table 2, the reaction appears to be very general with respect to a variety of arylboronic acids and gives their corresponding phenols in good to excellent yields. Variation of the electronic properties and the position of the substituents on the aromatic ring of arylboronic acids has little effect on this transformation, affording the corresponding products **2a–r** in 82–99% yields (Table 2). Compared to the traditional procedures for phenol preparation *via* the nucleophilic aromatic substitution of activated aryl halides,[17] the present metal-free method showed a higher efficiency in the cases of electron-rich phenols **2a–m**. In addition, the heteroaryl boronic acid **1s** and polycyclic substrates **1t–v** were also well tolerated to afford their corresponding phenols **2s–v** in 71–90% isolated yields.

Notably, 1,4-phenylenediboronic acid **1w** proved to be suitable for this process, generating hydroquinone **2w** in a 92% yield (Scheme 2a). Both phenylboronic pinacol ester **3** and potassium phenyltrifluoroborate **4** could also undergo the desired oxidative cleavage easily to provide the product **2d** in 84% and 71% yields, respectively (Scheme 2b and c). Interestingly, under the standard conditions, the vinylboronic ester **5** was readily transformed into the ketone **6** through an oxidative cleavage/*ipso*-hydroxylation/isomerization sequence in an 85% yield (Scheme 2d).

To gain more insight into the possible mechanism, we also carried out two ^{18}O-labelling experiments by using $^{18}O_2$ and



Scheme 2 Methylhydrazine mediated hydroxylation of representative boronic compounds.



Scheme 3 ^{18}O labelling experiments and gram scale reaction.

$H_2{}^{18}O$ (Scheme 3a and b). These results show that the oxygen atom of the hydroxyl oxygen atom in the product originated from molecular oxygen rather than water. Moreover, the reaction could be carried out on a gram scale without any loss of efficiency (Scheme 3c).

In conclusion, we have developed a methylhydrazine-mediated aerobic oxidative cleavage of arylboronic acids to their corresponding phenols.[18] This mild and metal-free strategy shows a wide substrate scope and high functional group tolerance with respect to arylboronic acids. Further detailed mechanistic investigations into this reaction as well as applications of this system to other processes are currently underway in our laboratory.

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18 Methylhydrazine-mediated aerobic oxidative cleavage of arylboronic acids. General procedure: a 50 mL round-bottom flask was charged with aryl boronic acid **1** (0.5 mmol), $MeNHNH_2$ (40% aq. 1.4 equiv., 80 μL) (*potentially dangerous, please be careful!!!*) and THF (0.017 M, 30 mL). Then, the reaction mixture was stirred at room temperature in an open flask. After the reaction was completed (monitored by TLC analysis), the mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel (eluted with ethyl acetate–petroleum ether = 1 : 5) to give the desired product **2**. Analytical data of 4-methoxyphenol (**2a**): colorless solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 6.80–6.76 (4 H, m), 4.65 (1 H, s), 3.77 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.39, 149.45, 116.07, 114.88, 55.83. MS: m/z = 124.1 (M^+).