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Boronic Acid-Catalyzed Selective Oxidation of 1,2-Diols to α-Hydroxy Ketones in Water

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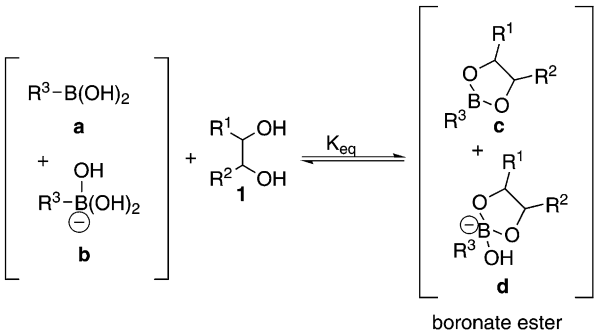
Abstract: The activation of 1,2-diols through formation of boronate esters was found to enhance the selective oxidation of 1,2-diols to their corresponding α-hydroxy ketones in aqueous medium. The oxidation step was accomplished using dibromoisocyanuric acid (DBI) as a terminal chemical oxidant or an electrochemical process. The electrochemical process was based on the use of platinum electrodes, methylboronic acid [$MeB(OH)_2$] as a catalyst and bromide ion as a mediator. Electro-generated OH^- ions (EGB) at the cathode acted as a base and "Br^+" ion generated at the anode acted as an oxidant. Various cyclic and acyclic 1,2-diols as substrates were selectively oxidized to the corresponding α-hydroxy ketones *via* their boronate esters by the two oxidative methods in good to excellent yields.

Keywords: boronic acids; 1,2-diols; α-hydroxy ketones; selective oxidation; water

Green chemistry has become a central paradigm, in both academia and industry. Without this approach, industrial chemistry is not sustainable.[1] The development of environmentally benign synthetic methods for the oxidation of alcohols is important for organic synthesis.[2] In particular, the selective synthesis of α-hydroxy ketones from 1,2-diol precursors is an important research focus in the pharmaceutical industry. α-Hydroxy ketone units are common in antitumor antibiotics like olivomycin A,[3] and natural products such as kurasoin A and B.[4] In addition, α-hydroxy ketones can conveniently be converted to amino alcohols. The effective synthetic generation of hydroxyl ketones has thus been a long standing research focus for many organic chemists. Various oxidants and Lewis acids have been used to activate the 1,2-diol moiety.[5–10] Unfortunately, some of the methods developed suffer drawbacks, such as relatively low yields and side reactions associated with C–C bond cleavage.[9] In this regard, our group has selectively oxidized 1,2-diols using both chemical[11] and electrochemical[11a,12] methods with Me_2SnCl_2 and $CuCl_2$ catalysts in organic solvents. The current clean synthesis paradigm prefers the use of aqueous media. Since water is non-toxic and non-flammable, its application results in safer and cheaper processes.[13] In an effort to make this process more environmentally benign, we recently achieved the selective oxidation of 1,2-diols in water using both chemical[14] and electrochemical oxidation[15] mediated by Me_2SnCl_2 catalyst. The catalyst activates the 1,2-diol moiety through stannylene acetal formation in addition to enhancing selectivity for both oxidation and benzoylation reactions.[16] However, serious issues have been raised on the toxicity of organotin catalysts to humans and the environment.[17] Thus, there is urgent need to search for safer alternatives to organotin catalysts.

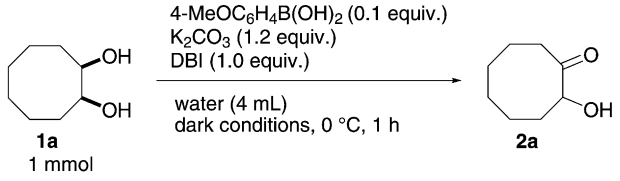
Boronic acids, widely used in the Suzuki cross-coupling,[18–20] are known to bind with compounds containing diol moieties with high affinities through reversible ester formation (Scheme 1).[21]

Such a tight binding of boronic acids to diols allows their useful application in saccharide sensing.[22] Recently, our group has utilized boronic acids to activate



Scheme 1. Boronate ester formation.

Table 1. Optimization study for the selective oxidation of **1a**.

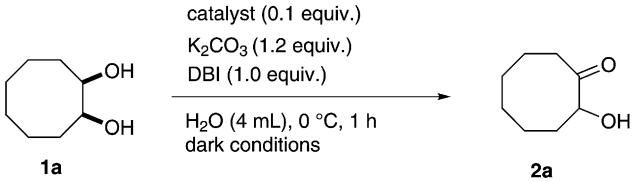


1a 1 mmol **2a**

Entry	Variation from the "standard" conditions	Yield [%][a]
1	none	99
2	absence of 4-$MeOC_6H_4B(OH)_2$	<1
3	0.05 equiv. of 4-$MeOC_6H_4B(OH)_2$	88
4	absence of K_2CO_3	52
5	DBDMH[b] (1.5 equiv.) instead of DBI	40
6	NBS (2.0 equiv.) instead of DBI	15
7	Br_2 (1.5 equiv.) instead of DBI	<1

[a] Isolated yield.
[b] 1,3-Dibromo-5,5-dimethylhydantoin.

Table 2. Screening of boronic acid catalysts.



1a 1 mmol **2a**

Entry	R in R-$B(OH)_2$	Yield [%][a]
1	4-$MeOC_6H_4$	99
2	2-$MeOC_6H_4$	97
3	3-$MeOC_6H_4$	98
4	3,4-$(MeO)_2C_6H_3$	93
5	4-FC_6H_4	88
6	4-MeC_6H_4	94
7	4-CNC_6H_4	82
8	3-$NO_2C_6H_4$	80
9	3-BrC_6H_4	91
10	3-ClC_6H_4	90
11	4-$CF_3C_6H_4$	87
12	Ph	91
13	4-dibenzothiophene	31
14	2-naphthalene	85
15	3-biphenyl	61
16	3-quinoline	77
17	3-methyl-2-buten-2-yl	99
18	Me	99

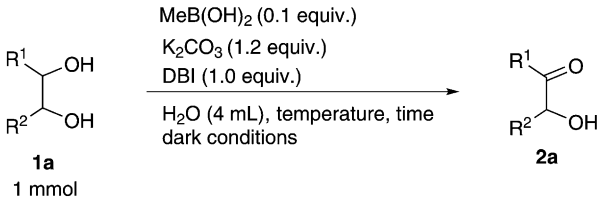
[a] Isolated yield.

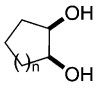
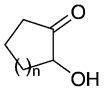
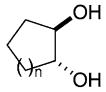
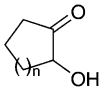
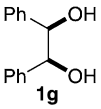
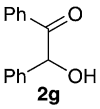
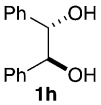
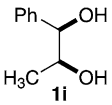
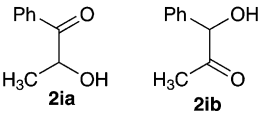
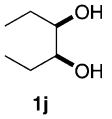
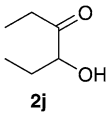
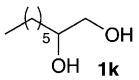
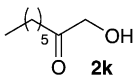
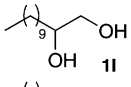
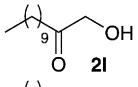
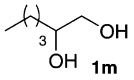
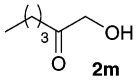
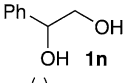
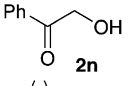
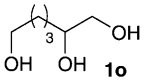
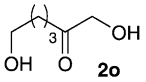
the 1,2-diol moiety in the monolkylation of 1,2-diols in organic solvent.[23] The safety of boronic acids, their ease in handling, good solubility in water and the availability of a wide variety of boronic acid catalysts, prompted us to test them for the activation of 1,2-diols in water. To the best of our knowledge, no previous report on the selective oxidation of 1,2-diols in water aided by boronic acid catalysts has been presented. We began our investigation on the catalytic selective oxidation of 1,2-diols in water using *cis*-cyclooctane-1,2-diol **1a** as a model substrate and halogen cation "source" oxidants. After a series of optimization studies, we found that selective oxidation of **1a** in water proceeded efficiently in the presence of 10 mol% of 4-$MeOC_6H_4B(OH)_2$, 1.0 equiv. of potassium carbonate, and 1.0 equiv. of DBI[24] at a low temperature (0 °C) under dark conditions within 1 h to afford **2a** in 99% yield (entry 1, Table 1).

Selective oxidation did not proceed in the absence of the catalyst (entry 2). This demonstrates the important role played by the catalyst in the activation of the 1,2-diol moiety. Reducing the catalyst loading to 0.05 equiv. as well as performing the reaction in the absence of base led to a drop in yields (entries 3 and 4). Other oxidants screened, including 1,3-dibromo-5,5-dimethyl-hydantoin (DBDMH), *N*-bromosuccinimide (NBS) and Br_2, were not efficient in effecting this oxidation (entries 5–7). We next screened various boronic acid catalysts to determine their suitability for selective oxidation in water. The results are summarized in Table 2. Among the substituted phenylboronic acid catalysts screened, the MeO-substituted one gave the best yields (entries 1–4). Phenylboronic acids having Me-, F-, CN-, Br-, Cl- and CF_3- substituents at *ortho* or *para* positions as well as unsubstitued $PhB(OH)_2$ afforded good yields though lower than their MeO-substituted counterparts (entries 5–12). Dibenzothiophene-, naphthalene-, biphenyl- and quinolineboronic acids were also tried, but resulted in low yields of the desired products (entries 13–16). Interestingly, simple alkyl and alkenylboronic acids, such as 3-methyl-2-buten-2-ylboronic acid and $MeB(OH)_2$ gave excellent yields, comparable to those obtained with 4-$MeOC_6H_4B(OH)_2$ (entries 17 and 18).

With the three best catalysts namely, $MeB(OH)_2$, 4-$MeOC_6H_4B(OH)_2$ and 3-methyl-2-buten-2-ylboronic acid, we next explored the substrate applicability to the oxidation system involving K_2CO_3 as a base and DBI as a terminal oxidant. Generally, both $MeB(OH)_2$ and 4-$MeOC_6H_4B(OH)_2$ catalysts gave comparable yields for *cis*-cyclic 1,2-diol substrates. On the other hand, for *trans*-cyclic 1,2-diols and acyclic diols with bulky alkyl chains, $MeB(OH)_2$ and 3-methyl-2-buten-2-ylboronic acid catalysts gave superior results (see the Supporting Information). The relatively high cost of 3-methyl-2-buten-2-ylboronic acid restricted much of this study to 4-$MeOC_6H_4B(OH)_2$ and $MeB(OH)_2$ catalysts. The results are summarized in Table 3. All *meso*- and *trans*-cyclic 1,2-diols, underwent selective oxidation affording mono-oxidized products in good to excellent yields, with $MeB(OH)_2$ as a catalyst of choice except for 1,2-diols **1a** and **1d** (entries 1–4) in which higher yields were obtained

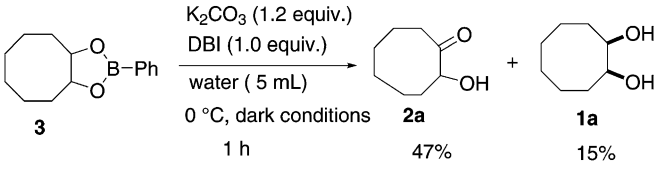
Table 3. Substrate scope of the 1,2-diols.



Entry	1,2-Diol	Temperature (Time)	Product	Yield [%][a]
1	 **1b, c**	0 °C (2 h)	 **2b, c**	**b**: $n=3$: 97, (98)[b] **c**: $n=2$: 68
2		0 °C (8 h)		
3	 **1d–f**	0 °C (4 h)	 **2a–c**	**a**, **d**: $n=4$: 81, (85)[b] **b**, **e**: $n=3$: 94
4		0 °C (5 h)		
5		0 °C (8 h)		**c**, **f**: $n=2$: 62
6	 **1g**	50 °C (7 h)	 **2g**	87
7	 **1h**	50 °C (7 h)	**2g**, **2h**	89
8	 **1i**	r.t. (5 h)	 **2ia** **2ib** (mixture)	94
9	 **1j**	r.t. (5 h)	 **2j**	96
10	 **1k**	0 °C (5 h)	 **2k**	91, (96)[c]
11	 **1l**	r.t. (3 h)	 **2l**	84, (85)[c]
12	 **1m**	0 °C (4 h)	 **2m**	88
13	 **1n**	r.t. (5 h)	 **2n**	80
14	 **1o**	r.t. (6 h)	 **2o**	86

[a] Isolated yield.
[b] 4-$MeOC_6H_4B(OH)_2$ was used.
[c] 3-Methyl-2-buten-2-ylboronic acid was used.

with 4-$MeOC_6H_4B(OH)_2$ catalyst. Acyclic 1,2-diols were also tolerated with substrates **1g** and **1h** being oxidized at an elevated temperature of 50 °C[25] to obtain the corresponding α-hydroxy ketones in excellent yields (entries 6 and 7). 1,2-Diol **1i** underwent oxidation non-selectively at room temperature to give



Scheme 2. Oxidation of boronate esters in water.

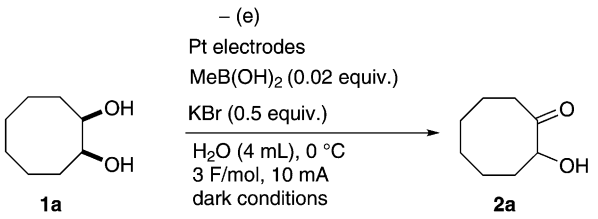
almost an equal mixture of α-hydroxy ketones **2ia** and **2ib** (entry 8). On the other hand, *meso* **1j** smoothly underwent selective oxidation affording **2j** in excellent yield (entry 9). Next, we carried out the selective oxidation of 1,2-diols having both primary and secondary alcohol functions. When 1,2-diols **1k**, **1l**, **1m**, and **1n** were treated under these catalytic conditions, the secondary alcohols were selectively oxidized affording products **2k**, **2l**, **2m**, and **2n**, respectively, in high yields (entries 10–13). Additionally, 1,2,6-hexanetriol **1o** underwent selective oxidation at the secondary hydroxy group of the 1,2-diol moiety affording **2o** in satisfactory yield (entry 14).

Narasaka and Sharpless designed a process for the dihydroxylation of olefins by use of phenylboronic acid as a diol captor leading to the formation of phenylboronate ester.[26,27,28] This method has proved useful for the synthesis of water-soluble diols. In order to get some insight on whether a boronate ester plays the role of the intermediate in our reaction, we syntheized boronate ester **3** using the Narasaka procedure,[27] and subjected it to our oxidation conditions in water. The reaction gave a 47% yield of α-hydroxy ketone **2a** and was accompanied by the hydrolysis of the boronate ester to the corresponding *cis*-1,2-cyclooctanediol **1a** (Scheme 2).

This reaction, although not unequivocally, hints that the boronate ester intermediate is involved in our reaction.

With the success of chemical oxidation using boronic acid catalysts, we envisaged that we can make the process cleaner by developing an electrochemical oxidation process. Electrochemical oxidation avoids the use of chemical oxidants and the need for bases, some of which are toxic to people and the environment. Our earlier reported method on the electrochemical oxidation of 1,2-diols in water catalyzed by Me_2SnCl_2[15] faces drawbacks such as low yields and requires large amounts of electrolyte for some substrates. The key to a chemical oxidation reaction is the activation of 1,2-diols with boronic acid leading to the formation of a boronate intermediate. This is followed by oxidation of the boronate intermediate with DBI as a terminal oxidant. Therefore, we realized that if the boronate was exposed to electrochemical oxidation conditions, selective oxidation would be achieved. We began this investigation with KBr as a bromide ion source, $MeB(OH)_2$ as the catalyst and *cis*-cyclooctan-1,2-diol **1a** as a model substrate using

Table 4. Optimization of the electrochemical oxidation of **1a**.



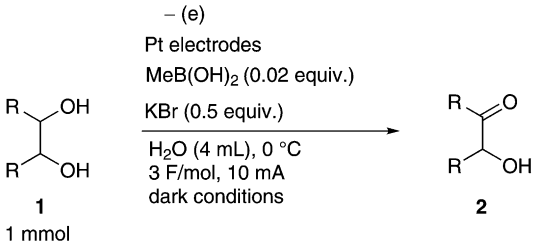
Entry	Optimization study	Yield [%][a]
1	0.02 equiv. of $MeB(OH)_2$	98
2	0.02 equiv. of 4-$MeOC_6H_4B(OH)_2$	81
3	0.01 equiv. of $MeB(OH)_2$	94
4	0.25 equiv. of KBr	61
5	NaBr instead of KBr	86

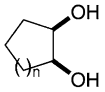
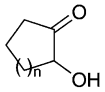
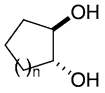
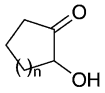
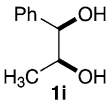
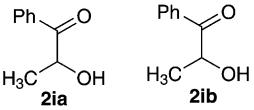
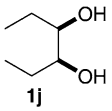
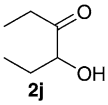
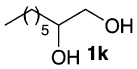
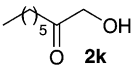
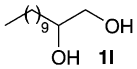
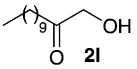
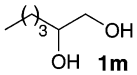
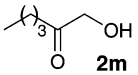
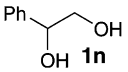
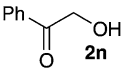
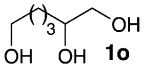
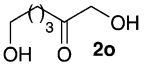
[a] Isolated yield.

platinum electrodes. The results are summarized in Table 4. After optimization, we found that KBr (0.5 equiv.) and $MeB(OH)_2$ (0.02 equiv.) afforded an excellent yield of 98% (entry 1). Using 4-$MeOC_6H_4B(OH)_2$ instead of $MeB(OH)_2$ lead to a drop in yield (entry 2). Lowering the amount of $MeB(OH)_2$ to 0.01 equiv, as well as the amount of KBr to 0.25 equiv, also led to drops in yields (entries 4 and 5). With the optimum conditions in hand, substrate applicability was next explored. The results are summarized in Table 5. All *meso*- and *trans*-cyclic 1,2-diols, underwent selective oxidation affording monooxidized products in moderate to excellent yields (entries 1–5). Acyclic 1,2-diol **1i** underwent selective oxidation at room temperature to give a mixture of α-hydroxy ketones **2ia** and **2ib** in good yield (entry 6).

Acyclic 1,2-diol **1j** was converted to the desired product **2j** in excellent yield at room temperature (entry 7). Next, we carried out selective oxidation of 1,2-diols having both primary and secondary alcohol functions. When 1,2-diols **1k**, **1l**, **1m**, and **1n** were treated under these catalytic conditions, the secondary alcohols were selectively oxidized preferentially to give products **2k**, **2l**, **2m**, and **2n**, respectively, in good yield (entries 8–11). Additionally, 1,2,6-hexanetriol **1o** underwent selective oxidation at the secondary hydroxy group of the 1,2-diol moiety affording **2o** in good yield (entry 12). In this electrochemical oxidation, the 1,2-diol is activated by the boronic acid catalyst to generate a boronate ester intermediate. The "Br^+" ion, generated at the anode, plays the oxidant role. The OH^- ion electro-generated at the cathode plays the role of the base.[15] A proposed reaction pathway for selective oxidation of 1,2-diol **1** in water is shown in Scheme 3. Boronate ester **A** or nucleophile **A′** (activated intermediates), could be oxidized

Table 5. Electrochemical oxidation of various 1,2-diols mediated by $MeB(OH)_2$.

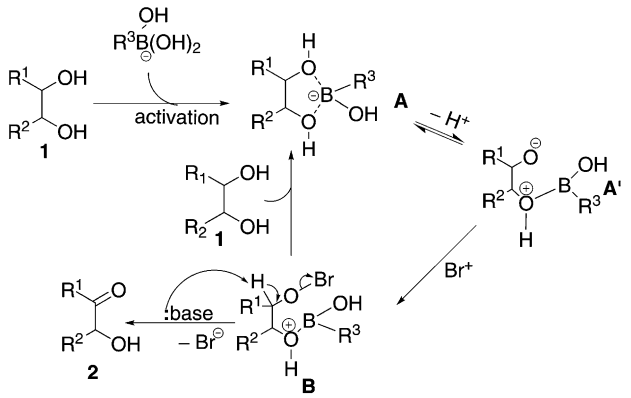


Entry	1,2-Diol		Product	Yield [%][a]
1	 **1a–c**	**a**: $n=4$	 **2a–c**	98
2		**b**: $n=3$		97
3		**c**: $n=2$		61
4	 **1d, e**	**a**, **d**: $n=4$	 **2a, b**	81
5		**b**, **e**: $n=3$		93
6[c]	 **1i**		 **2ia** **2ib** (mixture)	67[b]
7[c]	 **1j**		 **2j**	90[b]
8[c]	 **1k**		 **2k**	70
9[d]	 **1l**		 **2l**	80[b]
10[c]	 **1m**		 **2m**	68[b]
11[d]	 **1n**		 **2n**	77[b]
12	 **1o**		 **2o**	71

[a] Isolated yield.
[b] Reaction done at room temperature.
[c] 1.0 equiv. of KBr was used.
[d] Mixture of 0.5 equiv. of $MgBr_2$ and 0.5 equiv. of Et_4NBr was used.

by Br^+ generated from the terminal oxidant or electrochemically generated in water leading to **2**.

In conclusion, we have successfully designed high yielding and safer chemical and electrochemical methods for the oxidation of 1,2-diols in water using a boronic acid catalyst to activate the 1,2-diol moieties. Various cyclic and acyclic 1,2-diols have been selectively oxidized to afford α-hydroxy ketones in good to excellent yields. This oxidation provides an efficient and an environmentally friendly process, except for a few challenges like low solubility of some substrates in water, which required the reaction to be conducted at elevated temperature. We are currently studying this mode of activation in oxidation of sugars and the possibility of achieving enantioselective oxidation with water-soluble boronic acid catalysts.



Scheme 3. Proposed reaction pathway for selective oxidation in water.

Experimental Section

General Procedure for Chemical Oxidation of 1,2-Diols in Water using DBI as an Oxidant

DBI (1.0 mmol) was added to a solution of 1,2-diol **1a** (1.0 mmol), methylboronic acid (0.1 mmol), and K_2CO_3 (1.2 mmol) in water (4 mL) at 0 °C under shielding from light conditions. After the reaction mixture had been stirred for 1 h, aqueous saturated $Na_2S_2O_3$ solution (10 mL) was added. The organic portion was extracted with AcOEt (3× 40 mL) and then dried over $MgSO_4$. The solvent was removed under vacuum and the residue was subjected to silica gel column chromatography (*n*-hexane/AcOEt 5:1) to afford product **2a**; yield: 141 mg (99%).

General Procedure for Electrochemical Oxidation of 1,2-Diols

A solution of 1,2-diol **1a** (1.0 mmol) and methylboronic acid (0.02 mmol) in water (4 mL) was stirred at room temperature for 10 min before electrolysis. The resulting solution was transferred into a glass cell equipped with a platinum anode and cathode (1×2 cm). KBr (0.5 mmol) was added to the solution as an electrolyte. Then, the mixture was subjected to constant current electrolysis (10 mA) at 0 °C shielded from light (dark conditions) until **1a** had disappeared, as monitored by TLC. After completion of the reaction, aqueous saturated $Na_2S_2O_3$ solöution (10 mL) was added. The organic portion was extracted with AcOEt (3×40 mL) and then dried over $MgSO_4$. The solvent was removed under vacuum and the residue was subjected to silica gel column chromatography (*n*-hexane/AcOEt = 5:1) to afford product **2a**; yield: 139.8 mg (98%).

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