Biomimetic aerobic oxidative hydroxylation of arylboronic acids to phenols catalysed by a flavin derivative†

Hana Kotoučová,a,b Iveta Strnadová,b Martina Kovandová,a Josef Chudoba,c Hana Dvořákovác and Radek Cibulka*a

Flavin-catalysed oxidative hydroxylation of substituted arylboronic acids by molecular oxygen with the assistance of hydrazine or ascorbic acid resulted in phenols in high yields. This mild organocatalytic protocol is compatible with a variety of functional groups and it is alternatively usable for transformation of alkylboronic acids to alcohols. Reaction takes place also in water and fulfils criteria for a green procedure.

Introduction

Design of biomimetic systems inspired by enzymatic catalytic processes usually yields new efficient green methodologies in organic synthesis.1 Accordingly, oxygenation reactions occurring in flavin-dependent monoxygenases provided inspiration for artificial systems based on flavinium salts which are now used as powerful catalysts for chemoselective and stereoselective oxidations with oxygen or hydrogen peroxide.2–4 In monoxygenases, flavin cofactor Fl (FMN or FAD) reduced by NADPH reacts with oxygen to give flavin-4a-hydroperoxide FlOOH (Scheme 1), which oxidizes a substrate. After oxygen transfer, the cofactor is regenerated by water elimination.2,5

Artificial aerial oxidations catalysed by flavinium salts (e.g. by compound 1 in Scheme 1) in the presence of a sacrificial reducing agent proceed via the same mechanism.2,4 The use of 5-alkylflavinium salts instead of neutral flavin is necessary because the 5-alkyl group stabilizes hydroperoxide 1-OOH so that it can be utilized for oxidations.2b,6 Despite their considerable potential, flavinium catalysts have still been tested only in O2 oxidations of sulfides to sulfoxides,4a,f amines to N-oxides,4f and in Baeyer–Villiger (B.V.)4e and Dakin oxidations.4c Here, we report flavin-catalysed oxidative hydroxylation of arylboronic acids, thus extending the portfolio of flavin-mediated oxidations and bringing an organocatalytic procedure for the transformation of arylboronic acids to phenols. Analogous biocatalytic oxidation of C–B bonds with Baeyer–Villiger oxygenases employing the flavin cofactor has been reported,7 but with a substrate scope focused on alkylboronates.7b

Currently, the hydroxylation of arylboronic acid represents a useful alternative to classical phenol synthesis methods, i.e. nucleophilic aromatic substitution of aryl halides or hydrolysis of arene diazonium salts, which often suffer from low functional group compatibility and poor accessibility of the starting compounds. Arylboronic acids can be hydroxylated by strong
oxidizing agents such as hydrogen peroxide, oxone, or MCPBA which are usually used in stoichiometric amounts.\(^5\) Because there is a need for mild and environmentally friendly oxidation methods tolerating other functionalities, catalytic oxidative hydroxylations of boronic acids became a subject of intensive research in the last decade.\(^9\)–\(^12\) As a result, oxidations with molecular oxygen catalysed by copper(ii) or palladium(ii) salts,\(^9\) copper-promoted electrochemical hydroxylation,\(^10\)\(^a\)\(^b\) reaction with electrochemically generated superoxide anions,\(^10\)\(^b\) and photocatalytic aerobic oxidative hydroxylation mediated by a ruthenium or methylene blue sensitizer and visible light have been developed.\(^11\) Recently, the metal-free mild oxidation with N-oxides has been reported, but it requires a stoichiometric amount of organic oxidant.\(^12\) Unexpected phenol production from arylboronic acid in the presence of oxygen and naphthalquinone is still the only example of an organocatalytic aerobic process mentioned in the literature.\(^13\)

### Results and discussion

When searching for suitable conditions for the flavin-based oxidative hydroxylation of arylboronic acids, we evaluated a range of reducing agents and solvents from efficient protocols designed for aerobic sulfoxidations and B.V. oxidations.\(^4\)\(^e\)\(^d\)\(^f\) We used simple flavinium catalyst 2 (Scheme 2) which is readily available by a two-step procedure from commercial material.\(^4\)\(^d\) We initially employed the oxidation of phenylboronic acid (3a) with oxygen (1 atm., balloon) with 5 mol% of the catalyst as a model reaction (Table 1).

When hydrazine is used as a sacrificial reducing agent, the choice of solvent is essential (entries 1–4). In methanol, which dissolves phenylboronic acid well, only 5% conversion to phenol was observed after 10 min. Reaction in acetonitrile and in an acetonitrile–ethyl acetate–water mixture led to 35% and 12% conversions, respectively. Therefore we turned our attention to trifluoroethanol which is considered to be a suitable solvent for aerobic oxidations due to high solubility of oxygen.\(^6\) Addition of the methanol co-solvent was necessary to homogenize the reaction mixture. In the resulting trifluoroethanol–methanol (2:1) solvent system we observed the best result by far with a conversion of 95% after 10 min of oxidation (entry 4). As expected, lower catalyst loading as well as the use of air instead of oxygen led to deceleration of the process (entries 5 and 6). It is important to note that oxidation in the absence of the flavin catalyst does not take place (entry 7). Hydroxylation also proceeds with zinc or ascorbic acid as sacrificial reductants; however, the rates were lower than that with hydrazine under optimized conditions (entries 9–14). Reactions with zinc or ascorbic acid failed to accelerate either by changing the solvent or by adding sodium acetate to generate ascorbate with a higher reduction power and/or by generating the flavin hydroperoxide anion which is more powerful for nucleophilic oxidations\(^4\)\(^e\)\(^d\)\(^f\) (entries 11 and 13). Interestingly, flavin-based hydroxylations take place also in aqueous

![Scheme 2 Flavinium catalyst 2 and the corresponding hydroperoxide.](Image)

### Table 1 Oxidation of phenylboronic acid with oxygen catalyzed by alloxazinium salt 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reducing agent</th>
<th>Solvent + additives</th>
<th>Conv.(^b) 10 min. [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>N(_2)H(_2)H(_2)O</td>
<td>CH(_3)OH</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>N(_2)H(_2)H(_2)O</td>
<td>CH(_3)CN</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>N(_2)H(_4)H(_2)O</td>
<td>CH(_3)CN–EtOAc–H(_2)O(^d)</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>N(_2)H(_2)H(_2)O</td>
<td>CF(_2)CH(_2)OH–CH(_2)OH(^e)</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>2 (1 mol%)</td>
<td>N(_2)H(_4)H(_2)O</td>
<td>CF(_2)CH(_2)OH–CH(_2)OH(^e)</td>
<td>10</td>
</tr>
<tr>
<td>6(^e)</td>
<td>2</td>
<td>N(_2)H(_2)H(_2)O</td>
<td>CF(_2)CH(_2)OH–CH(_2)OH(^e)</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>—</td>
<td>N(_2)H(_2)H(_2)O</td>
<td>CF(_2)CH(_2)OH–CH(_2)OH(^e)</td>
<td>0(0)</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>N(_2)H(_2)H(_2)O</td>
<td>H(_2)O (pH = 7.8)</td>
<td>7(95)</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>Zn</td>
<td>CH(_3)OH</td>
<td>39</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>Zn</td>
<td>CH(_3)CN–EtOAc–H(_2)O(^e)</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>Zn</td>
<td>CH(_3)CN–EtOAc–H(_2)O(^d) + CH(_3)COONa (1 equiv.)</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>Ascorbic acid</td>
<td>CF(_2)CH(_2)OH–CH(_2)OH–H(_2)O(^f) + CH(_3)COONa (1 equiv.)</td>
<td>6</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>Ascorbic acid</td>
<td>CF(_2)CH(_2)OH–CH(_2)OH–H(_2)O(^f) + CH(_3)COONa (1 equiv.)</td>
<td>8</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>Ascorbic acid</td>
<td>H(_2)O (pH = 7.8)</td>
<td>27</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: phenylboronic acid (0.079 mmol), 2 (5 mol% unless otherwise indicated), reducing agent (0.106 mmol), oxygen (1 atm., balloon), solvent 0.6 mL, R.T. (for details see procedure A in the Experimental section). \(^b\) Conversion after 10 minutes (conversion after 3 hours in brackets) determined by \(^1\)H NMR. \(^c\) Air (1 atm., balloon) used instead of oxygen. \(^d\) 8:1:1. \(^e\) 2:1. \(^f\) 7:3:2.
solutions (entries 8 and 14). The reaction is slower compared to that in trifluoroethanol. Most probably, the reaction rate in water is negatively influenced by low solubility of oxygen which is approx. 10 times lower as compared with organic and fluorinated solvents.\textsuperscript{15} Even so, quantitative conversion was almost observed in aqueous medium with hydrazine as the reductant after extended time (3 h).

Series of boronic acids with an electron-withdrawing or electron-donating group were screened in preparative experiments to investigate the substrate scope of the reaction (Table 2; see the Experimental section and ESI\textsuperscript{†} for details). Most substituted phenols 4 were obtained in quantitative conversion and with good to excellent yields from arylboronic acids 3 using our optimized protocol, \textit{i.e.} the 2/O\textsubscript{2} (1 atm.)/hydrazine system in trifluoroethanol–methanol. It should be mentioned that the procedure is suitable also for \textit{ortho},\textit{ortho}-disubstituted derivatives with only longer reaction time being required. The reaction is slower also for \textit{ortho}- and \textit{para} nitro derivatives 3g and 3i. For oxidation of \textit{o}-nitrophenylboronic acid (3i), 51% conversion was only observed even after extended reaction time. This is probably caused (in addition to a steric effect in the case of 3i) by relatively high acidity of the resulting nitrophenols\textsuperscript{16} which are able to protonate hydrazine. Hydrazine acts as a flavin reducing agent and a base generating flavinhydroperoxide anion. Both these processes could be decelerated by hydrazinium/hydrazide equilibrium. Addition of a weak base,\textsuperscript{18} \textit{e.g.} sodium bicarbonate or sodium acetate, speeds up the reaction significantly: quantitative and 85% conversion was detected for 3g and 3i, respectively, in the presence of 5 equivalents of sodium acetate after 2 h.

Special attention has been paid to arylboronic acids possessing moieties sensitive to oxidation: aldehyde group, pyridine nitrogen, double bond and (hydroxymethyl)phenyl group. As expected, hydrazine is not compatible with aldehyde function and hydrazine 5 is formed by the original protocol from \textit{p}-formylnaphthylboronic acid (3p). On the other hand, the procedure with ascorbic acid gave \textit{p}-hydroxybenzaldehyde (4p) in an almost quantitative yield. This indicates that the 2/O\textsubscript{2}/ascorbic acid system is also useful on the preparative scale and, moreover, the procedure is chemoselective leaving the aldehyde function non-oxidized.\textsuperscript{19} The protocol with ascorbic acid was efficiently applied also to hydroxylation of \textit{o}-nitrophenylboronic acid (3i) and \textit{4}-vinylphenylboronic acid (3m). The hydrazine based procedure is excluded for 3m to avoid double bond reduction by diimide which can be formed from hydrazine by the action of flavinium salts.\textsuperscript{20} On the other hand, the procedure with hydrazine succeeded in producing corresponding hydroxy derivatives from pyridin-3-ylboronic acid (3n) and \textit{4}(hydroxymethyl)phenylboronic acid (3o) in quantitative conversion and with good yields. No side-oxidation of the double bond, pyridine nitrogen, as well as (hydroxymethyl)phenyl group was ever observed. Finally, cyclohexyl- (6a) and dodecyl-boronic acid (6b) were oxidized to the corresponding alcohols 7a and 7b by the unchanged protocol with hydrazine showing its applicability to alkylboronic acids.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Isolated yields and reaction times for oxidative hydroxylations of arylboronic (and alkylboronic) acids on a preparative scale\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aryl-B(OH)$_2$</td>
<td>2 (5 mol%), hydrazine, H$_2$O (1.3 equiv.), CF$_3$CH$_2$OH/CH$_3$OH (2:1, 6 mL), R.T. (see procedure B in the Experimental section). Conversion &gt;95%. Conversion 51%. 5 equiv. of sodium acetate added (see procedure D in the Experimental section). Conversion 85%. Ascorbic acid + sodium acetate instead of hydrazine (see procedure C in the Experimental section). Conversion 76%.</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conditions: boronic acid (0.79 mmol), catalyst 2 (5 mol%), hydrazine (1.06 mmol), oxygen (1 atm., balloon), CF$_3$CH$_2$OH–CH$_3$OH (2:1, 6 mL), R.T. (see procedure B in the Experimental section). Conversion >95%. Conversion 51%. 5 equiv. of sodium acetate added (see procedure D in the Experimental section). Conversion 85%. Ascorbic acid + sodium acetate instead of hydrazine (see procedure C in the Experimental section). Conversion 76%.
In a preliminary mechanistic study on the course of oxidative hydroxylation, we tried to vary the amount of hydrazine relative to the substrate. We observed the quantitative production of phenol with only 0.5 equivalent of hydrazine showing that, similar to sulfoxidations, one equivalent of hydrazine generates two equivalents of dihydroflavine (the precursor of flavin hydroperoxide) in the catalytic cycle. During the first reduction step, hydrazine is oxidized to diimide which is still strong enough to reduce the second molecule of flavinium salt while it itself is oxidized to molecular nitrogen. 

**Experimental**

**Materials and methods**

NMR spectra were recorded on a Varian Mercury Plus 300 (299.97 MHz for \(^1\)H, and 75.44 MHz for \(^13\)C) and a Bruker Avance DRX 500 (500.13 MHz for \(^1\)H, 125.77 MHz for \(^13\)C and 160.4 MHz for \(^11\)B) at 298 K unless otherwise indicated. Chemical shifts \(\delta\) are given in ppm using residual solvent or tetramethylsilane as an internal standard for \(^1\)H and \(^13\)C NMR and BF\(_3\)·Et\(_2\)O as an external standard for \(^11\)B. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240 analyser. High-resolution mass spectra were obtained on an LTQ Orbitrap Velos (Thermo Fisher Scientific), equipped with an orbitrap mass analyser. The mass spectrometer was operated in ESI mode (ESI source temperature 250 °C, potential 3000 V) with a mass range from 200 to 2000 a.m.u. TLC analyses were carried out on a DC Alufolien Kieselgel 60 F254 (Merck). Preparative column chromatography separations were performed on a silica gel Kieselgel 60 (0.040–0.063 mm) (Merck). Melting points were measured on a Boetius melting point apparatus and are uncorrected. Starting materials, reagents and substrates were obtained from...
commercial suppliers and used without further purification. The solvents were purified and dried using standard procedures. Catalyst 2 was prepared according to the modified protocol from the literature (see ESI† for details and characterization).

General procedures for oxidative hydroxylations

Oxidations carried out on an analytical scale – general procedure A. Boronic acid \((7.9 \times 10^{-5} \text{ mol})\) and a reducing agent \((10.6 \times 10^{-5} \text{ mol})\) were dissolved or suspended in 0.6 mL of solvent. Then catalyst 2 \((0.4 \times 10^{-5} \text{ mol})\) was added and the reaction mixture was shaken for 10 min in a small flask under oxygen (balloon, 1 atm.). The solvents were evaporated and the residue was dissolved in CD$_2$OD for NMR measurement.

Preparative oxidations – general procedure B (hydrazine hydrate used as a reducing agent). Boronic acid \((7.9 \times 10^{-4} \text{ mol})\) and hydrazine hydrate \((7.92 \text{ mL}, 10.6 \times 10^{-4} \text{ mol})\) were dissolved in trifluoroethanol \((4.0 \text{ mL})\) and methanol \((2.0 \text{ mL})\). Then catalyst 2 \((0.4 \times 10^{-4} \text{ mol})\) was added and the reaction mixture was shaken in a flask under oxygen (balloon, 1 atm.). The solvents were evaporated and the crude product was purified by column chromatography.

Preparative oxidations – general procedure C (ascorbic acid used as a reducing agent). Boronic acid \((7.9 \times 10^{-4} \text{ mol})\), natrium acetate \((131.2 \text{ mg}, 16.0 \times 10^{-4} \text{ mol})\) and ascorbic acid \((218.8 \text{ mg}, 16.0 \times 10^{-4} \text{ mol})\) were dissolved in trifluoroethanol \((3.5 \text{ mL})\), water \((1.0 \text{ mL})\) and methanol \((1.5 \text{ mL})\). Then catalyst 2 \((14.8 \text{ mg}, 0.4 \times 10^{-4} \text{ mol})\) was added and the reaction mixture was shaken in a flask under oxygen (balloon, 1 atm.). The solvents were evaporated and the residue was dissolved/suspended in water \((20 \text{ mL})\). The resulting mixture was extracted with dichloromethane \((3 \times 15 \text{ mL})\) and dried over magnesium sulfate. After evaporation of solvents, the crude product was purified by column chromatography.

Preparative oxidations – general procedure D (procedure B with the application of a base). Boronic acid \((7.9 \times 10^{-3} \text{ mol})\), natrium acetate \((162 \text{ mg}, 3.95 \times 10^{-3} \text{ mol})\) and hydrazine hydrate \((81.4 \text{ mg}, 16.0 \times 10^{-4} \text{ mol})\) were dissolved in trifluoroethanol \((4.0 \text{ mL})\) and methanol \((2.0 \text{ mL})\). Then catalyst 2 \((14.8 \text{ mg}, 0.4 \times 10^{-4} \text{ mol})\) was added and the reaction mixture was shaken in a flask under oxygen \((1 \text{ atm})\) for 2 hours. The solvents were evaporated, the residue was dissolved/suspended in water \((20 \text{ mL})\) and the mixture was acidified with hydrochloric acid \((\text{pH} = 1)\). The resulting mixture was extracted with dichloromethane \((3 \times 15 \text{ mL})\) and dried over magnesium sulfate. After evaporation of solvents, the crude product was purified by column chromatography.

Characterization of products of oxidative hydroxylations

Phenols 4a–4p and 5 and alcohols 7a and 7b resulting from oxidative hydroxylations of boronic acids were characterized by $^1$H and $^{13}$C NMR and the HR-MS technique. Spectral data correspond to those published in the literature (see ESI† for details).

Acknowledgements

This work was financially supported by the Czech Science Foundation (grant no. P207/12/0447).

Notes and references

2 Applications of flavinium salts in catalysis are reviewed in:
4 Papers on aerial oxidations catalyzed by flavinium salts:


16 pKₐ values for 3g, 3h, 3i and hydrazinium are 7.23, 8.40, 7.15 and 8.10, respectively; see ref. 17.


18 Stronger bases, e.g. sodium carbonate, caused decomposition of flavinium catalyst.

19 Oxidation of aromatic aldehydes to carboxylic acids or corresponding phenols (Dakin oxidation) mediated by flavins has been described; see ref. 3b and 4c.


21 Since hydrazine interaction with boronic acid results in signal broadening (see ESI†), we used ascorbic acid as a reducing agent.