



Visible light induced oxidative hydroxylation of boronic acids

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ABSTRACT

We report herein a visible light-induced aerobic oxidative hydroxylation of boronic acids. The reaction employed 7H-benzo[c]thioxanthen-7-one as metal-free catalyst and dimethyl carbonate as green solvent. Scale-up experiment was achieved using 0.1 mol% catalyst in a good yield with column-free purification. This reaction showed great green chemistry features and potential in synthetic applications.

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Oxidative hydroxylation of boronic acids into phenols or alcohols is a hot topic in organic synthesis [1–6]. Strong oxidants, such as high-valence halogen compounds [7–10], peroxide [11–14], ozone [15], and N-oxide [16], are efficient reagents in such transformations. However, these methods are not environmentally friendly, since lots of wastes are formed. Oxygen in air is considered as green and abundant oxidant. Methods employing oxygen have been well studied. Some Ru [17,18], Pd [19], Fe [20], Cu [21–24] complexes or Cu [25], Fe [26], Au [27] nanoparticles were proved to be effective catalysts in this field. However, the synthesis of catalysts is complicated and transitional metals were harmful to the environment (Scheme 1a).

Photoredox oxidative hydroxylation of boronic acids has attracted much attention in the past decade. Transition metal catalysts [28–31] and metal free catalysts [32–37] showed nice catalytic activities in such transformations. Mechanistic studies showed that superoxide radical anion was generated by single electron transfer from highly reductive photocatalyst to oxygen. Then superoxide radical anion coordinated with boron atom and rearranged to a boronic ester. After hydrolysis, phenol or alcohol would be formed as the final product (Scheme 1b) [28–37].

With our continues research interest in aerobic photo oxidation reactions [38–41], we turned our interest to study thioxanthone as catalyst for this transformation. Thioxanthone was normally used

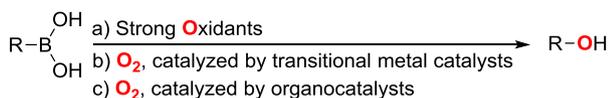
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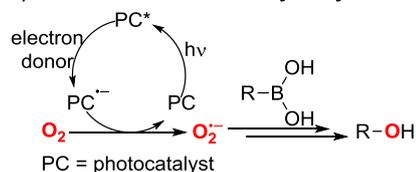
as photo initiator in polymer chemistry. The photophysical properties of thioxanthone also allows it to be a photocatalyst for organic transformations [42]. Thus, we proposed an alternative energy or electron transfer way to generate the superoxide radical anion, which is the key intermediate in the whole reaction procedure (Scheme 1c). In such a process, the photo catalyst may involve in electron transfer and/or energy transfer process. It activated oxygen superoxide radical anion, which is considered as key intermediate in oxidative hydroxylation. Herein, we wish to report our recent observation in aerobic oxidative hydroxylation of boronic acids using thioxanthone derivatives as catalyst.

In the beginning, (4-fluorophenyl)boronic acid (**2a**) was chosen as the model substrate. Our initial attempt was carried out under an oxygen atmosphere at rt using commercially available thioxanthone (**1a**) as the photosensitizer, *i*-Pr₂NEt as the electron donor, and dimethyl carbonate (DMC) as the solvent. An 84% NMR yield of the desired product 4-fluorophenol (**3a**) was formed after irradiation under a purple LED for 8 h (entry 1, Table 1). With this result in hand, modification of the catalyst was carried out aiming at promoting efficiency (entries 1–6, Table 1). A methoxy group was attached at different positions of thioxanthone. Only 4-methoxythioxanthone (**1d**) gave a better performance than **1a** (entry 4, Table 1). A phenyl group was also introduced, and the yield was slightly increased (entry 5, Table 1). Next, we expanded the conjugated system using a naphthalene ring instead of one benzene ring (**1f**). Full conversion was achieved within 3.5 h in a 99% NMR yield (entry 6, Table 1). Thus, **1f** was chosen as the optimal catalyst for further optimization. With the optimal catalyst in

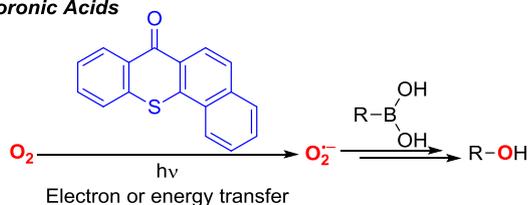
a) Thermo Oxidative Hydroxylation of Boronic Acids



b) Photo Redox Oxidative Hydroxylation of Boronic Acids



c) This work: Photochemically Aerobic Oxidative Hydroxylation of Boronic Acids



Scheme 1. Oxidative hydroxylation of boronic acids.

hand, optimization of the reaction conditions was conducted. A survey of solvents was carried out using only green solvents (entries 6–10, Table 1). Reactions in methyl *tert*-butyl ether (MTBE) gave much lower yield than DMC (entry 7, Table 1). Reactions in

methanol or acetone resulted in similar excellent yields (entries 8 and 9, Table 1). Another ester, ethyl acetate, was also tested, yielding 97% of **3a** (entry 10, Table 1). Thus, among the selected green solvents, DMC remained the best one. Next, the screening of electron donors was carried out. Another tertiary amine (NEt₃) gave slightly lower efficiency (entry 11, Table 1). A secondary amine (*i*-Pr₂NH) showed a dramatically decreased yield (entry 12, Table 1). Ammonia could also serve as an electron donor but gave a poor yield (entry 13, Table 1). A decrease of the amount of *i*-Pr₂NEt led to decreased yields (entries 14 and 15, Table 1). Finally, we attempted to reduce the catalyst loading (entries 16 and 17, Table 1). 1 mol% of **1f** catalyzed the reaction smoothly, affording **3a** in an excellent yield (entry 17, Table 1).

Oxygen in the air also served as an external oxidant with slightly increased reaction time (entry 18, Table 1). Control experiments were also carried out showing both catalyst (entry 19, Table 1) and light (entry 20, Table 1) were necessary for this transformation. Notably, we compared our method with traditional Brown oxidation [43] (entries 18 and 21, Table 1). These results indicated that this photochemically oxidation showed higher yield. Thus, Condition A (1 mol% of **1f**, 2 equivalents of *i*-Pr₂NEt, DMC, air atmosphere, purple LED, and rt) was considered as the standard reaction condition for further studies.

With the optimal conditions in hand, the scope of this oxidative hydroxylation was explored (Fig. 1). A wide range of phenols were obtained in excellent yields. Substrate with strong electron donating group, including methoxy, showed excellent reactivity as well as excellent yield (**3b–d**). Weak electron-donating groups, such as methyl (**3e–g**), ethyl (**3h**) and phenyl (**3i**), were also employed

Table 1
Optimization of the reaction conditions.^a

Entry	Solvent	1 (mol%)	<i>e</i> - donor (equiv.)	Time (h)	Yield (%) ^b
1	DMC	1a (5)	<i>i</i> -Pr ₂ NEt (2)	8	84
2	DMC	1b (5)	<i>i</i> -Pr ₂ NEt (2)	12	70 (8) ^c
3	DMC	1c (5)	<i>i</i> -Pr ₂ NEt (2)	12	41 (56) ^c
4	DMC	1d (5)	<i>i</i> -Pr ₂ NEt (2)	5	91
5	DMC	1e (5)	<i>i</i> -Pr ₂ NEt (2)	6	94
6	DMC	1f (5)	<i>i</i> -Pr ₂ NEt (2)	3.5	>99
7	MTBE	1f (5)	<i>i</i> -Pr ₂ NEt (2)	4.5	85
8	MeOH	1f (5)	<i>i</i> -Pr ₂ NEt (2)	6	93
9	Acetone	1f (5)	<i>i</i> -Pr ₂ NEt (2)	4.5	94
10	EA	1f (5)	<i>i</i> -Pr ₂ NEt (2)	5	97
11	DMC	1f (5)	NEt ₃ (2)	5	97
12	DMC	1f (5)	<i>i</i> -Pr ₂ NH (2)	8	59 (33) ^c
13	DMC	1f (5)	NH ₃ ·H ₂ O (2 mL)	8	22 (76) ^c
14	DMC	1f (5)	<i>i</i> -Pr ₂ NEt (1)	8	87 (10) ^c
15	DMC	1f (5)	<i>i</i> -Pr ₂ NEt (0.5)	8	67 (29) ^c
16	DMC	1f (3)	<i>i</i> -Pr ₂ NEt (2)	5.5	99
17	DMC	1f (1)	<i>i</i> -Pr ₂ NEt (2)	6.5	96
18 ^d	DMC	1f (1)	<i>i</i> -Pr ₂ NEt (2)	8.5	96 (96) ^e
19 ^d	DMC	–	<i>i</i> -Pr ₂ NEt (2)	10	0 (96) ^c
20 ^{d, f}	DMC	1f (1)	<i>i</i> -Pr ₂ NEt (2)	16	0 (99) ^c
21 ^g	DMC	–	–	8.5	71

^a The reactions were carried out using **2a** (0.5 mmol) in solvent (5 mL), irradiated by purple LED under O₂ (1 atm) atmosphere at rt.

^b Yield determined by ¹⁹F NMR analysis using trifluoromethylbenzene as internal standard.

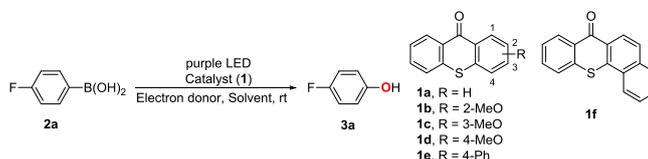
^c Recovered yield of **2a** determined by ¹⁹F NMR analysis using trifluoromethylbenzene as internal standard.

^d The reaction was carried out in the open air.

^e Isolated yield of **3a**.

^f The reaction was carried out without light.

^g The reaction was carried out using 30% H₂O₂ aq. (1.2 equiv) and 3 M NaOH aq. (3 equiv).



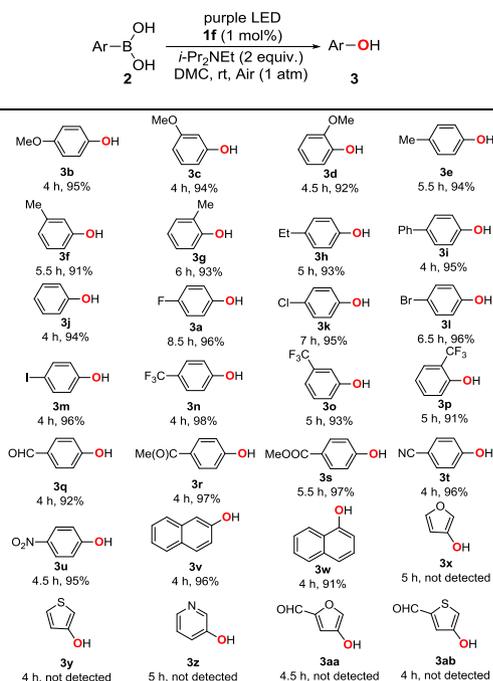


Figure 1. The oxidative hydroxylation of alkylboronic acid, alkenylboronic acid and arylboronic acid ester **4** under Condition A.^a

and gave similar excellent yields. Nice reactivity was also obtained with halogen atom- substituted arylboronic acids (**3a** and **3k-m**). *o*-, *m*-, and *p*- (trifluoromethyl)phenylboronic acids were also examined and showed similar excellent yields (**3n-p**). Reactants with other strong electron-withdrawing groups, such as formyl (**3q**), acetyl (**3r**), methoxy carbonyl (**3s**), nitrile (**3t**) and nitro (**3u**), were also tolerant in this reaction. These results also indicated that this reaction showed nice functional group tolerance. We further expanded the aromatic system to naphthyl group. Both α - and β - naphthol (**3v** and **3w**) were afforded in excellent yields. Some heteroaromatic boronic acids were also tested. Disappointingly, the resulting reaction mixtures were complicated. A competition experiment was carried out using **2b** as an electron-rich substrate. As monitored by ¹H NMR analysis of the crude reaction mixture, no obvious rate difference was observed. (for details, see [Supplementary Material Table S1](#))

Further studies demonstrated that alkyl- or alkenylboronic acids as well as arylboronic acid ester were also suitable substrates for this reaction (Fig. 2). Cyclohexanol (**5a**) was afforded from cyclohexylboronic acid (**4a**) in a 64% isolated yield. Considering the boiling point of cyclohexanol was relatively low, we assumed

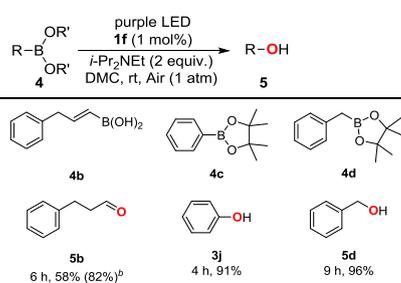
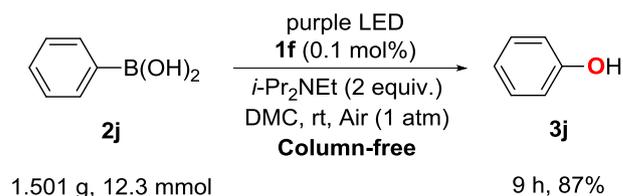


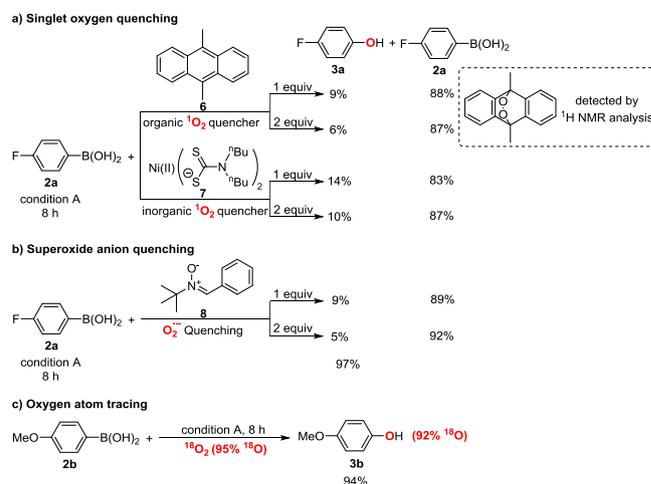
Figure 2. The oxidative hydroxylation of alkyl boronic acid, alkenyl boronic acid and aryl boronic acid ester **4a-d** under Condition A.^a

that the yield loss might have occurred during the isolation process, especially in rotary evaporation and drying in vacuum. So we monitored the yield by ¹H NMR analysis of the crude reaction mixture. An 81% NMR yield of **5a** was observed. This data validated that the low isolated yield was mainly due to the loss during isolation. A similar result was observed for the reaction of (3-phenylprop-1-en-1-yl)boronic acid (**4b**). In this case, 3-phenylpropanal (**5b**) was formed. When phenylboronic acid pinacol ester (**4c**) was tested under Condition A, an excellent yield of phenol (**3j**) was generated. Primary alkyl boronic acid pinacol ester **4d** was also tested and showed excellent yield. A gram scale reaction was also carried out using **2j** as a probe (Scheme 2). The loading of catalyst could be decreased to 0.1 mol%. After simple work-up and recrystallization, 87% of **3j** was afforded with promising purity. The scale-up reaction showed the potential in practical applications.

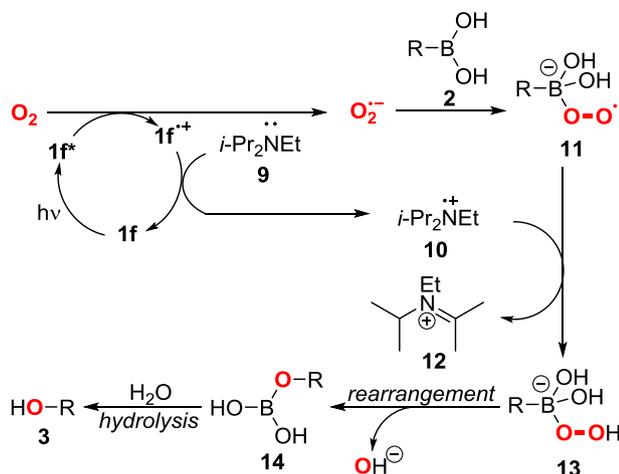
To gain insights into the reaction mechanism, several control experiments were carried out, focusing on the involved oxygen species (Scheme 3). 9,10-Dimethylantracene (**6**) was added to the reaction system as an organic singlet oxygen quencher (Scheme 3a).^[44–46] Severe inhibition was observed with both 1 and 2 equivalents of **6**. The [4 + 2]-trapping product (9,10-dimethyl-9,10-dihydro-9,10-epidioxyanthracene) [44] was also observed from ¹H NMR analysis of the crude reaction mixture. Bis((dibutylcarbamothioyl)th-io) nickel(II) (**7**) was also tried as an inorganic singlet oxygen quencher (Scheme 3a) [47]. Severe inhibition was also observed with both 1 and 2 equivalents of **7**. *N*-tert-Butyl-1-phenylmethanimine oxide (**8**) is considered as a superoxide radical anion quencher according to literature reports (Scheme 3b) [48–50]. With the addition of 1 or 2 equivalents of **8**, the reaction was efficiently inhibited. The results above suggested that both singlet oxygen and superoxide radical anion were likely involved in this reaction. The reaction of **2b** under Condition A using ¹⁸O₂ (95% ¹⁸O) gave ¹⁸O-labelled product **3b** (92% ¹⁸O) in a 94% isolated



Scheme 2. Gram scale reaction.



Scheme 3. Mechanism studies.



Scheme 4. Proposed Mechanism.

yield. This result indicated the oxygen atom in the product was completely from oxygen in the air (Scheme 3c).

With the information above and literature precedence [28–37], a possible mechanism was proposed in Scheme 4. Upon photo irradiation, the excited **1f** donate an electron to oxygen gave superoxide radical anion [32,51]. It would further react with the boronic acid **2** to generate intermediate **11** [28], which could abstract a hydrogen atom from **10** to form intermediate **13** [35]. Further rearrangement of **13** and hydrolysis of **14** furnished the final product **3** [30,33,52].

In conclusion, we developed a photochemically aerobic oxidative hydroxylation of boronic acids. This method employed 7H-benzo[c]thioxanthen-7-one as the metal-free catalyst and DMC as the green solvent. This reaction showed excellent yield and broad substrate tolerance. A gram scale reaction could be easily conducted without column chromatography. These features meet the requirements of green chemistry well. Mechanism studies indicated that both singlet oxygen and superoxide radical anion might be key intermediates in this transformation. Further application and mechanism validation are in progress in our laboratory.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tetlet.2019.01.052>.

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