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Photoinduced hydroxylation of arylboronic acids with molecular oxygen under photocatalyst-free conditions

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Photoinduced hydroxylation of boronic acids with molecular oxygen under photocatalyst-free conditions is reported, providing a green entry to a variety of phenols and aliphatic alcohols in a highly concise fashion. This new protocol features photocatalystfree conditions, wide substrate scope and excellent functional group compatibility.

Phenols and their derivatives represent an important class of compounds because they are structural motifs in many in natural products and biologically active compounds, and versatile synthetic intermediates.¹ For this reason, considerable attention has been aroused in the construction of phenols and their derivatives.² One of the most effective established strategies toward their synthesis phenols is the hydroxylation of arylboronic acids. Pioneering work on the conditions for the hydroxylation of arylboronic acids focused on the use of transition metals³ with the requirement of a strong base in some case. Alternatively in the absence of transition metals, the use of stoichiometric strong oxidants such as hydrogen peroxide,⁴ PhI(OAc)₂,⁵ benzoquinone,⁶ mCPBA,⁷ TBHP,⁸ NaBO₃,⁹ oxone¹⁰ and amine oxide¹¹ enabled directly hydroxylation of arylboronic acids to access phenols. In addition, organic electrochemistry as an efficient synthetic technology has been applied in the hydroxylation of boronic acids.12

On the other hand, photoredox catalysis has emerged as a powerful strategy for construction of C-C and C-heteroatom bonds in the organic synthesis.¹³ Groundbreaking effort on light-promoted aerobic oxidative hydroxylation of arylboronic acids to phenols in the presence of Ru(bpy)₃Cl₂ was made by Xiao's group.¹⁴ Subsequently, much attention has been focused in the development of photocatalysts for photocatalytic oxidative hydroxylation of arylboronic acids.¹⁵ Nevertheless, most of these photocatalysts suffered from tedious synthesis and expensive cost. In this regard, these

Table 1 Optimization of reaction conditions^a



entry	light source	additive	solvent	yield(%)
1	UV lamp		DMF	23
2	UV lamp	Et ₃ N	DMF	87
3	UV lamp	Et ₃ N	dioxane	40
4	UV lamp	Et ₃ N	THF	53
5	UV lamp	Et ₃ N	CH₃CN	77
6	UV lamp	Et ₃ N	toluene	41
7	UV lamp	Et ₃ N	DCM	23
8	UV lamp	Et ₃ N	DMSO	33
9	UV lamp	Et ₃ N	2-MeTHF	92
10	UV lamp	DIPEA	2-MeTHF	82
11	UV lamp	(Me)₂EtN	2-MeTHF	83
12	UV lamp	(Me) ₂ ⁿ BuN	2-MeTHF	65
13 ^b	UV lamp	Et ₃ N	2-MeTHF	58
14 ^c	UV lamp	Et_3N	2-MeTHF	0
15	filament lamp	Et ₃ N	2-MeTHF	10
16	green LED	Et ₃ N	2-MeTHF	83
17	blue LED	Et ₃ N	2-MeTHF	80
18	dark	Et ₃ N	2-MeTHF	0

^aReaction conditions: **1a** (0.3 mmol), O_2 (1 atm), light source (15 W), additive (0.45 mmol), solvent (4 mL), rt, 24 h, isolated yields. ^bUnder the air atmosphere. ^cUnder the N₂ atmosphere.

issues can be solved by photocatalyst-free aerobic hydroxylation of arylboronic acids, which represents an attractive and cost-effective strategy for building phenols. Herein, we disclosed a photocatalyst-free method for lightpromoted aerobic hydroxylation of arylboronic acids for the first time, with triethylamine being used as an additive.

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^aReaction conditions: a (0.3 mmol), O₂ (1 atm), UV lamp (15 W), Et₃N (0.45 mmol), 2-MeTHF (4 mL), rt, 24 h, isolated yields. ^b48 h.

We set out to screen the optimal reaction conditions by selecting [1,1'-biphenyl]-4-ylboronic acid 1a as model substrate (Table 1). It was observed that the model reaction carried out in DMF under O2 atmosphere at room temperature with UV irradiation in the absence of a photocatalyst furnished the expected product 1b in 23% yield (entry 1). To our delight, the addition of Et_3N as an additive resulted in a remarkably increased yield (entry 2). Screening of solvents indicated that 2-MeTHF served as the optimal solvent, affording the desired product in 92% yield (entries 3-9). Switching the Et₃N to other additives such as DIPEA, (Me)₂EtN or (Me)₂ⁿBuN gave the expected products in relatively lower yields (entries 10-12).

The similar result was obtained when the reaction was performed under air atmosphere (entry 13). The replacement of the O_2 with the N_2 atmosphere shut down this transformation (entry 14), indicating that oxygen played an essential role in the reaction. Further investigation of light sources showed that visible light also successfully enabled this transformation in the absence of a photocatalyst, albeit in relatively lower yields (entries 15-17). Control experiment in dark conditions failed to deliver the desired product, confirming the necessity of continuous UV irradiation (entry 18). Therefore, the reaction conditions of entry 9 proved to be optimal.

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With the optimized reaction conditions in hand, we next investigated the substrate scope of boronic acids including arylboronic acids and alkylboronic acids (Table 2). Arylboronic acids containing various functional groups on the aromatic ring have proved to be compatible in the standard conditions and afforded hydroxylated products (2b-50b). Arylboronic acids bearing various substitutions at the para-position of the aromatic ring ranging from electron-donating groups such as alkyl (2a and 3a), alkoxy (8a-10a), methylthio (12a) and TMS (13a) to electron-withdrawing groups such as halogens (4a-7a), trifluoromethyl (14a), nitro (16a), acetyl (18a) and ester (19a), reacted well to provide the desired products under the standard conditions. Among these, the resulting products bearing halogens such as Cl, Br and I could be further utilized for the synthesis of more complex organic compounds. It is worth noting that these sensitive groups including phenolic hydroxyl (11a), aldehyde (17a) and vinyl (20a) groups were also amenable to the reaction conditions, offering the desired product in 91%, 94% and 58% yields respectively. Thus, it can be inferred from these results that electronic properties of substitution had little effect on reaction efficiency. In addition, the optimized reaction conditions were compatible with a range of substitutions at the ortho and meta-positions of the aromatic ring (21a-33a). These observations revealed that the substitutions at the meta and para-positions led to higher yields compared with that at the ortho-position. Hindered 2,6substituted arylboronic acids have proved to be suitable substrates (35a-38a). The substrates with multiple strong electron-donating groups was successfully converted to the desired products in good yields (38b-40b). Unfortunately, heterocyclic boronic acids were ineffective under the standard reaction conditions to provide the desired products (41b and 42b). The substrates bearing a fused ring smoothly underwent the photocatalyst-free aerobic hydroxylation, affording the corresponding products with 50%-85% yields (43b-49b). In the case of (9,9-dimethyl-9H-fluoren-2-yl)boronic acid, the reaction delivered the product 50b in 85% yield. Remarkably, the scope could be expanded to alkylboronic acids under the standard reaction conditions, providing the desired products in 71% and 99% yields respectively (51b and 52 b).



Scheme 1. Some control experiments.

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To shed light on the mechanism of this photochemical hydroxylation of boronic acids, some Debittion 3 2000 - 20000 - 20000 were conducted (Scheme 1). First, The model reaction performed under ¹⁸O₂ atmosphere successfully offered the ¹⁸O-labeled product (Scheme 1a), demonstrating the oxygen atom of the phenol product was derived from O2. Then we intended to exam the effect of photocatalysts on the reaction efficiency. Surprisingly, it was found that the presence of photocatalysts such as RuCl₂(bpy)₃.6H₂O, Zinc phthalocyanine and methylene blue trihydrate did not facilitate this reaction but slightly descreased the reaction efficiency (Figure S2, see the supporting information). On basis of these results and previous references,¹⁶ it could be inferred that the amines may promote the generation of superoxide radical anion $(O_2^{\bullet-})$. Inspired by previous work¹⁷ which demonstrated that *p*-cresol was an efficient superoxide generator, we reckoned that in situ generated phenols also could contribute as a catalyst to the generation of O2*-. This inference was supported by the fact that the replacement of Et₃N with 2,6-dimethyl phenol led to excellent reaction efficiency (Figure S3, see the supporting information). The O2*- intermediate was detected by nitro-blue tetrazolium (NBT),18 judged from the color change of the reaction solution from light brown to deep purple during the reaction (Figure 1). Additionally, the existence of O2.-intermediate was further confirmed by the control experiment in which PhB(OH)₂ reacted with in situ generated NaO₂ under dark condition (Scheme 1b).¹⁹ When triethylamine was replaced by N,N-dicyclohexylmethylamine, the co-proyduct dicyclohexylamine was detected by GC-MS (Scheme 1c).



Figure 1. The color change of the reaction solution during the reaction in the presence of NBT.

According to these results and relevant literature,^{14, 15c, 15f} a possible mechanism for the photocatalytic oxidative hydroxylation of boronic acids is described in Scheme 2. At the beginning, Et₃N can serve as photosensitizer and afford singlet oxygen ($^{1}O_{2}$) under UV irradiation. Next, the $^{1}O_{2}$ obtains an electron from Et₃N (or phenols), producing a $O_{2}^{\bullet-}$ along with a radical cation (Et₃N⁺⁺). The resulting $O_{2}^{\bullet-}$ can add to the vacant porbital of boron to afford intermediate **A** which undergoes single electron transfer (SET) with Et₃N⁺⁺ to give intermediate **B** undergoes 1,2-aryl shift, followed by hydrolysis to provide the final product.



Scheme 2. A plausible mechanism

Conclusions

In conclusion, we have disclosed a the photocatalytic aerobic hydroxylation of boronic acids using O_2 as the oxidant, providing a green entry to a variety of functionalized phenols and aliphatic alcohols in a highly concise fashion. This new protocol features photocatalyst-free conditions, wide substrate scope and excellent functional group compatibility. In particular, the advantages including the mild reaction conditions and good functional group tolerance enabled late stage modification of complex molecules. Furthermore, the photocatalyst-free and metal-free conditions wouldn't only significantly decrease the costs, but also allow for easy separation of products, thus offering the approach an opportunity to find some applications in synthetic chemistry.

Conflicts of interest

There are no conflicts to declare.

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$$R^{B(OH)_{2}} \xrightarrow{V} (1 \text{ atm}) \xrightarrow{UV (15 \text{ W}), \text{ Et}_{3}\text{N}} R^{OH}$$

R = Aryl, alkyl

✓ metal-free and photocatalyst-free

mild conditions

🔸 wide substrate scope

excellent functional group compatibility

We disclose a photoinduced aerobic hydroxylation of boronic acids under photocatalyst-free conditions, providing a green entry to phenols and alcohols.