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Blacklight-Induced Hydroxylation of Arylboronic Acids Leading to Hydroxyarenes Using Molecular Oxygen and Tetrabutylammonium Borohydride

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Dedicated to Prof. E. Peter Kündig on the occasion of his 75th birthday

A new simple protocol for the conversion of arylboronic acids to hydroxyarenes was achieved using molecular oxygen in the presence of tetrabutylammonium borohydride under blacklight irradiation (360 nm). A radical chain mechanism in which a superoxide ion $(O_2^{-\bullet})$ plays a key role is proposed.

Keywords: arylboronic acids, borohydrides, hydroxyarenes, photo-irradiation, radical reactions, superoxide ion, synthetic methods.

Introduction

Oxidation of arylboronic acids to phenols by hydrogen peroxide has a long history.^[1-6] Recently, hydroxylation of arylboronic acids with other oxidants such as $NaClO_2$,^[7] *N*-oxide,^[8] or hydroxylamine have been developed.^[9] The use of molecular oxygen as the stoichiometric oxidant is ideal because it is readily available and soluble in common organic solvents.^[10] Transition-metal-catalyzed hydroxylation of arylboronic acids using molecular oxygen is emerging as a valuable alternative to traditional hydroxylation.^[11-14] Electrochemical hydroxylation of arylboronic acids was investigated by both the Fuchigami group^[15] and the Jørgensen group,^[16] and these researchers found that a superoxide ion (O2-•) likely plays a key role. The reaction proceeds through the generation of superoxide from oxygen at the cathode. Recent reports have shown that visible light uses molecular oxygen as an oxidant to initiate the aerobic oxidative hydroxylation of arylboronic acids with $Ru(II)(bpy)_{3,}^{[17]}$ methylene blue,^[18] rose bengal,^[19,20] and Et_3N .^[21]

Tetrahydroborate anion (BH_4^{\bullet}) is well known to promote hydride addition to carbonyl compounds, but it also participates in free radical reactions involving hydrogen atom transfer (HAT).^[22–24] We are fascinated by the capability of borohydride derivatives as HATtype radical mediators and previously reported carbon-carbon bond-forming reactions^[25–31] using alkyl halides with electron-deficient olefin, CO, and formaldehyde. In this work, we report that the hydroxylation of arylboronic acids is aided by a simple protocol using tetrabutylammonium borohydride, Bu_4NBH_4 , and molecular oxygen under blacklight irradiation.

Results and Discussion

In the initial study, 4-methoxyphenylboronic acid (**1a**) was chosen as a model substrate to explain the occurrence of the conversion to 4-methoxyphenol (**2a**; *Table 1*). When the reaction of **1a** with Bu₄NBH₄ was irradiated by a blacklight (360 nm) using a *Pyrex* tube

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B(OH) ₂		B–H (1 equiv.) blacklight (15W, <i>Pyrex</i>)		Мео	
MeO		MeCN (2 mL), r.t., 15 h			
0	1a			2a	
Entry	B–H	Air or O ₂	Light	Yield [%] ^[a]	
1	Bu ₄ NBH ₄	air	(+)	72	
2	Bu ₄ NBH ₄	air	(—)	0	
3	(—)	air	(+)	1	
4	NaBH ₄	air	(+)	34	
5	Bu ₄ NBH ₄	O ₂	(+)	77	
6 ^[b]	Bu ₄ NBH ₄	0 ₂	(+)	79	
7 ^[b,c]	Bu_4NBH_4	O ₂	(—)	32	

Table 1. Hydroxylation of 4-methoxyphenylboronic acid (1a).

^[a] Yields of isolated product after column chromatography on SiO_2 . ^[b] Reaction time: 4 h. ^[c] AIBN (0.2 equiv., instead of blacklight), 80 °C.

under air, the desired hydroxylation proceeded to give the product **2a** in a 72% yield after acid workup (*Entry 1*). For efficient conversion, both irradiation and borohydride are required (*Entries 2* and 3). The reaction using NaBH₄ also gave **2a**, albeit in a 34% yield presumably due to the lower solubility of NaBH₄ in acetonitrile (*Entry 4*). Under an oxygen atmosphere, a shorter reaction time (4 h) sufficed to complete the reaction to give a 79% yield of **2a** (*Entry 6*). The reaction using AIBN under thermal conditions proceeded to give **2a**, albeit in a low 32% yield (*Entry 7*).

Encouraged by the results shown in Table 1, we then applied the reaction conditions to the hydroxylation of a variety of arylboronic acids 1 (Table 2). 4-Methylphenylboronic acid (1b) and 4-biphenylboronic acid (1c) gave the corresponding phenols 2b and 2c in good yields (Entries 2 and 3). Then, 4-bromophenylboronic acid (1d) gave 4-bromophenol (2d) in a 60% yield and reduced phenol in a 5% yield (Entry 4). The reaction of 3-methoxyphenylboronic acid (1e) gave 3methoxyphenol (2e) in an 88% yield (Entry 5). 3-Methylphenylboronic acid (**1f**) and 2-methylphenylboronic (**1g**) gave the corresponding phenols 2f and 2g in 61 and 63% yield, respectively (Entries 6 and 7). The reactions of α - and β -naphthylboronic acids also proceeded to give 1-naphthol (2h) and 2naphthol (21) in 73 and 71% yield, respectively (Entries 8 and 9). The reaction of dibenzofuran-4boronic acid (1j) gave 2j in a 49% yield (*Entry 10*). Alkyl boronic acid such as octylboronic acid also worked but with less efficiency (Entry 11). Although we tried the reaction of aryl boronic acids having ester or amide group, the hydroxylation products were obtained in

Table 2.	Hydroxylation of Arylboronic Acids. ^[a]	
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$\frac{Bu_4}{blac}$ Ar - B(OH) ₂ 1 $\frac{Bu_4}{O_2}$		NBH ₄ :klight (15 W, <i>Pyrex</i>) MeCN, r.t.		Ar—OH 2	
Entry 1		Rea time	action 2 e [h]		Yield [%] ^[b]
1 MeO	i(OH) ₂ 1a	4	MeO	⊣ 2a	78%
2 ^[c]	ЭН) ₂ 1b	20	И	2b	80% ^[d]
3 Ph)2 1c	4	Ph	2c	65%
4 ^[c] Br	^{0H)} 2 1d	20	Br	2d	60% ^{[d][e]}
5 ^[c] B(OH) ₂	1e	20	OH	2e	88%
6 ^[c] B(OH) ₂	1f	20	OH	2f	61%
7 ^[c] B(OH) ₂ Me	1g	20	OH	2g	63%
8 B(OH) ₂	1h	4	OH	2h	73%
9 B	(OH) ₂ 1i	4	OF	2i	71%
	1ј В(ОН) ₂	4		2j ∺	49%
11 B(OH) ₂	1k	4	ОН	2k	27% ^[d]

^[a] Conditions: **1** (0.5 mmol), Bu₄NBH₄ (0.5 mmol), MeCN (2 mL), 4 or 20 h. ^[b] Isolated yields after column chromatography on SiO₂. ^[C] Bu₄NBH₄ (1.0 mmol) was used. ^[d] Determined by ¹H-NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. ^[e] 5% of phenol was also obtained.

low yields. We conducted the reaction of 4-methoxyphenylboronic acid in the presence of 1-dodecene. The hydroxylation product was obtained in 88% (NMR) and 1-dodecene was recovered. Thus, alkene is compatible in this reaction.



To gather further insights into the radical mechanism for the borohydride-mediated hydroxylation of arylboronic acids, the reaction of **1a** in the presence of radical scavengers such as TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) and 1,4-dinitrobenzene was carried out (*Scheme 1*). In both cases, the reaction was terminated, which resulted in a very low yield of pmethoxyphenol **2a** and suggested an intervention by radical intermediates.

Based on control experiments and the results of previous studies on the use of Bu_4NBH_4 in radical reactions, we proposed a radical chain mechanism (*Scheme 2*). In this mechanism, borane radical anion **A** reacts with molecular oxygen to give a superoxide anion **B**. The generated superoxide adds to an arylboronic acid to afford radical anion **C**, which then abstracts a hydrogen from borohydride to afford intermediate **D** along with borane radical anion **A**. The formation of the hydroxylated product occurs by a 1,2-aryl shift of **D** into **E** followed by hydrolysis. Despite



Scheme 1. Control Experiments.



Scheme 2. Plausible mechanism.

lower efficiency, AIBN can initiate the present reaction (Table 1, Entry 7). Presumably, the cyanopropyl radical abstracts hydrogen from BH_4^- to generate **A**. It has been proposed that the electrochemically generated superoxide **B** undergoes a conversion of arylboronic acids to phenols similar to that of intermediate C, in which the reaction proceeds without following the photo-irradiation protocol.^[15,16] On the other hand, treatment of borohydride with molecular oxygen did not cause any significant charge transition band in the UV-vis spectrum. Consequently, we theorized that blacklight irradiation would facilitate the initiation step between arylboronic acids and borohydride.^[32] The new weak absorption was observed in the mixture of 4-methoxyphenylboronic acid and Bu₄NBH₄. Please see the Supporting Information in detail. An alternative mechanism involves oxidation of arylboronic acids by in situ-formed H₂O₂, which is generated from oxygen and borohydride by light irradiation.

Conclusions

In summary, we have developed a novel protocol for hydroxylation of arylboronic acids using molecular oxygen and Bu_4NBH_4 under blacklight irradiation. We theorized that a single electron transfer from a borane radical anion to molecular oxygen would generate a superoxide ion, which could play a key role in the hydroxylation of arylboronic acids.

Experimental Section

General Information

Thin-layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F254, Art. 5715, 0.25 mm) and was visualized through either fluorescence quenching under UV light or by staining with either *p*-anisaldehyde/AcOH/H₂SO₄/EtOH or $12MoO_3 \cdot H_3PO_4$ /EtOH. The products were purified by flash chromatography on silica gel (Kanto Chem. Co. Silica Gel 60 N (spherical, neutral, 40–50 mm)). ¹H-NMR spectra were recorded with a JEOL JMN-ECS400 (400 MHz) spectrometer and referenced to the solvent peak at 7.26 ppm. ¹³C-NMR spectra were recorded with a JEOL JMN-ECS400 (100 MHz) spectrometer and referenced to the solvent peak at 77.0 ppm.





General Procedure

Arylboronic acid (0.5 mmol), Bu_4NBH_4 (0.5 mmol), and MeCN (2 mL) were placed in a *Pyrex* test tube and the mixture was irradiated by blacklight (15 W) with stirring for 4 h (or 20 h) under an atmosphere of oxygen. The reaction was quenched carefully using an aqueous solution of HCl (1 N, 5 mL), and the resultant mixture was extracted with ether (3×10 mL). The combined organic layers were washed with brine (10 mL) and dried over MgSO₄. After removal of the solvent in a vacuum, the residue was purified through flash column chromatography on silica gel (hexane/ ether) to give the desired hydroxyarenes.

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Author Contribution Statement

T. K. performed the experiments and analyzed the data. *T. K.* and *I. R.* designed and wrote the paper.

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