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Site-Selective Mono-Oxidation of 1,2-Bis(boronates)

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Abstract

Site-selective oxidation of vicinal bis(boronates) is accomplished through the use of trimethylamine N-oxide in 1-butanol solvent. The reaction occurs with good efficiency and selectivity across a range of substrates, providing versatile 2-hydroxy-1-boronic esters which are shown to be versatile intermediates in the synthesis of chiral building blocks.

Graphical Abstract

Catalytic enantioselective diboration is a valuable tool for transforming inexpensive, abundant alkenes into a variety of functionalized chiral products.¹¹ Over the past several years, our group has introduced efficient and stereoselective alkene diboration reactions that are catalyzed by chiral rhodium^{1a,1b} or platinum^{1c,1d} complexes, and most recently has developed a carbohydrate-catalyzed asymmetric process.^{1f,1g} In addition to these reports, Nishiyama² has advanced a Rh(phebox) catalyzed enantioselective process, and Hoveyda³ has provided routes to enantiomerically-enriched vicinal bis(boronates) by catalytic alkyne double hydroboration and by a three-component reaction involving vinylboron compounds. While the products of alkene diboration readily undergo stereoretentive oxidation to furnish vicinal diols, particularly useful strategies emerge when site selective mono-functionalization of 1,2-bis(boronates) can be conducted (Scheme 1): the organoboron motif

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Author Contributions

Both authors contributed to the design and conception of the research plan. The manuscript was written through contributions of both authors. All authors have given approval to the final version of the manuscript.

ASSOCIATED CONTENT

Supporting Information

Procedures, characterization, spectral and chromatographic data. The Supporting Information is available free of charge on the ACS Publications website.

that remains after a selective mono-functionalization reaction can be transformed separately, such that the overall process can give rise to a broad array of useful motifs. So far, only two site-selective transformations of non-functionalized⁴ 1,2-bis(boronates) have been developed, one involving regioselective Suzuki-Miyaura coupling⁵ and the other involving homologation with chiral lithiated carbamates.⁶ In this report, we show that with appropriate reaction conditions, oxidation of 1,2-bis(boronates) can be accomplished with excellent site selectivity. Unlike the primary-selective C-C bond-forming reactions mentioned above, the oxidation reaction is secondary-selective and provides a versatile new motif for construction of difunctional molecules.

We considered that selectivity in oxidation of 1,2-bis(boronates) could arise from one of two different manifolds. First, we considered that if coordination of the oxidant to boron was sensitive to steric effects and the subsequent 1,2-boron shift were facile, then selectivity for the primary site might be observed; such an outcome might be expected with a hindered, highly reactive oxidant (eq. 1). Alternatively, if 1,2-boronate rearrangement is the rate limiting step and coordination of the oxidant to boron was reversible, then the more substituted electron-rich carbon may migrate preferentially providing selectivity as depicted in equation 2. With this mechanistic framework as a guiding principle, a series of oxidants and reaction conditions were analyzed for either primary-selective or secondary-selective oxidation.

To gain a baseline understanding of selectivity with peroxyanions,⁷ 1,2-boronic ester **1** (Table 1) was treated with a 1:1 mixture of potassium hydride and *tert*-butylhydroperoxide for one hour and analyzed by ¹H NMR. This reaction proceeded to 65% conversion, providing mono-oxidation product **2** together with the product resulting from over oxidation (**3**); the mono alcohol product arising from oxidation of the primary organoboronic ester was not detected. As depicted in Table 1, other oxidants were examined in the oxidation. *meta*-Chloroperbenzoic acid afforded over-oxidized product **3**, exclusively (entry 2). The neutral peroxides *di-tert*-butylperoxide and dibenzoylperoxide were unreactive even at elevated temperatures. Lastly, amine N-oxides were examined and it was found that whereas pyridine N-oxide is unreactive (entry 5), the more electron-rich reagent trimethylamine N-oxide (TMANO), a compound known to be effective in organoborane oxidations,⁸ provided 75% conversion with the mono-oxidation product being the predominant reaction product (entry 6). Subsequent experiments with TMANO (not shown) revealed that compound **2** was formed with >95% enantiospecificity when enantiomerically-enriched **1** was employed as substrate. For this reason, amine N-oxides were selected as a class of reagents for further study.

To develop reaction sequences that employ alkenes as the substrate for a cascade diboration/mono-oxidation sequence, we investigated direct introduction of amine N-oxides to reaction mixtures obtained from carbohydrate-catalyzed diboration (Table 2). In these experiments, it was found most convenient to treat the crude cascade reaction product with pinacol such that boronic ester exchange would provide a chromatographically-stable pinacolato boronate as the isolable product. As shown in Table 2, when the amount on TMANO was increased, the extent of reaction increased from 65% (Table 1, entry 6) to 72%, however the isolated yield mono-oxidation remained the same (Table 2, entry 1). The presence of significant amounts

of over-oxidation product suggested that the mono-oxidation product **5** (or its derived borate ester) may be more reactive towards TMANO than the bis(boronate) **4**. Reasoning that enhanced reactivity of the mono-oxidation product might be due to intramolecular Lewis acid activation of the remaining boronic ester by the newly formed borate ester motif, we considered other reaction media that might alter such interactions. While DMF, toluene and chloroform - solvents that are not expected to significantly interrupt internal chelation - did not alter the reaction outcome, when 1-butanol was employed as the reaction solvent, the isolated yield became much more reflective of the extent of conversion, suggesting over-oxidation was less problematic. With 1-butanol as solvent, other amine N-oxides and reaction conditions were then examined, with two equivalents of N-methylmorpholine N-oxide (NMO) furnishing the highest overall isolated yield (entry 9, Table 2).

With effective reaction conditions developed, alkenes bearing a number of functional groups were examined in the tandem carbohydrate-catalyzed enantioselective diboration/mono-oxidation sequence. As shown in Table 3, aliphatic alkenes underwent the cascade reaction well, providing good yields and enantioselectivity (compounds **5–8**). Allyl benzenes also underwent smooth transformation to the β -hydroboronate (compounds **9, 10**), as did compounds with a protected hydroxyl groups (entries **11,12,14,15**). Of consequence with respect to synthetic utility, alkenes bearing adjacent pre-existing stereogenic centers underwent the reaction with product stereochemistry arising from near-complete catalyst control (compounds **14, 15**). As shown with compounds **16** and **17**, terminal alkenes can undergo carbohydrate-catalyzed alkene diboration selectively in the presence of internal alkenes. With internal alkenes, mono-oxidation can be accomplished and, as shown by compound **19** the benzylic carbon migrates in preference to a secondary alkyl group. Lastly, it was found that the two-step reaction sequence can be performed on preparatively useful scale with only minor modification (see Supporting Information) and deliver comparable product yield (compound **5**: 65% yield for 1 mmol scale reaction).

To demonstrate the synthetic utility of the β -hydroxyl boronic ester, several tandem enantioselective diboration/mono-oxidation products were subjected to alcohol protection, forming either a silyl ether or a methoxymethyl ether. As shown in equation 1, after hydroxyl protection the primary boronic ester can be transformed into a Boc-protected amine (**20**) using a method developed in our laboratory (eq. 1).⁹ Conversion of terminal alkenes to enantiomerically enriched 1,2-aminoalcohols represents a useful method to synthesize unnatural amino alcohols. It was also found that the boronic ester can undergo homologation when treated with conditions developed by Matteson (for ease of isolation, the boronate was oxidized to alcohol, eq. 2).¹⁰ Lastly, by employing an approach developed by Aggarwal (eq. 3), the pinacol boronate can be replaced with a bromine atom.¹¹

(1)

(2)

(3)

In conclusion, we have developed a secondary-selective mono-oxidation of readily available enantiomerically-enriched 1,2-bis(boronates). Of note, the diboration/oxidation is a simple two-step operation to carry out, only requiring a filtration between the steps, and therefore offers streamlined synthesis of useful b-hydroxyboronic esters. Products generated from the cascade carbohydrate-catalyzed alkene diboration/mono-oxidation sequence can be further transformed into chiral materials bearing other functional groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Site-Selective Functionalization of 1,2-Bis(boronates).

Scheme 2.

Prospective Selectivity Paradigms in Vicinal Diboronate Oxidation Reactions.

Table 1.

Survey of Oxidants in Selective Oxidation of 1,2-Bis(boronates)

Reaction scheme: 1,2-bis(pinacolatoboryl)decane (1) reacts with an oxidant (1.2 equiv) in THF at room temperature to produce 1,2-bis(pinacolatoboryl)decan-1-ol (2) and 1,2-bis(pinacolatoboryl)decan-2-ol (3).

entry	oxidant	% conv ^a	2 (%) ^b	3 (%) ^b
1	KH/ <i>t</i> BuOOH	65	10	52
2	mCPBA	62	<5	43
3	(<i>t</i> -BuO) ₂	<5	-	-
4	(BzO) ₂	<5	-	-
5	pyridine N-oxide	<5	-	-
6	Me ₃ NO	65	42	23

^(a) Conversion determined by ¹H NMR versus an internal standard.^(b) Percent yield determined after purification by silica gel chromatography.

Table 2.

Impact of Solvent and Reaction Conditions on Oxidation of 1,2-Bis(boronates) with Amine Oxides

Reaction scheme: 1-octene $\xrightarrow[4\text{ \AA MS, } 23\text{ }^\circ\text{C, THF, 12 h}]{10\% \text{ TBS-DHG, } 10\% \text{ DBU, } \text{B}_2(\text{pro})_2}$ **4** (not isolated) $\xrightarrow[\text{THF/H}_2\text{O, } 60\text{ }^\circ\text{C}]{\text{conditions } 40\text{ }^\circ\text{C, then NaOH, pinacol}}$ **5**

entry	oxidant	equiv	solvent	conv (%) ^a	5 (%) ^b
1	TMANO	1.5	THF	72	41
2	TMANO	1.5	DMF	80	36
3	TMANO	1.5	CHCl ₃	68	40
4	TMANO	1.5	toluene	67	32
5	TMANO	1.5	<i>n</i> -BuOH	65	44
6	TBANO	1.5	<i>n</i> -BuOH	49	42
7	TBANO	2.0	<i>n</i> -BuOH	82	64
8	NMO	1.5	<i>n</i> -BuOH	54	46
9	NMO	2.0	<i>n</i> -BuOH	92	70

^(a) Conversion determined by ¹H NMR versus an internal standard.^(b) Percent yield determined after purification by silica gel chromatography.

Table 3.

Substrate Survey in Tandem Diboration/Mono-Oxidation

(a) Conversion determined by ¹H NMR versus an internal standard. (b) Percent yield determined after purification by silica gel chromatography. (c) This experiment employed Cs₂CO₃ catalysis in place of TBS-DHG/DBU and therefore the product is racemic.