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

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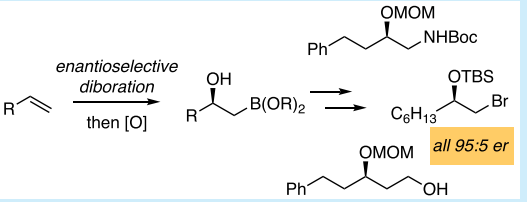
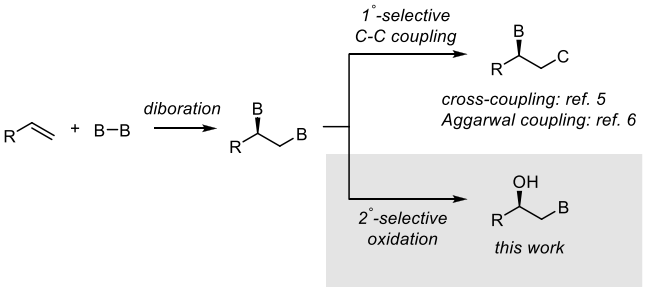
Supporting Information

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 2-hydro-1-boronic esters which are shown to be versatile intermediates in the synthesis of chiral building blocks.



Catalytic enantioselective diboration is a valuable tool for transforming inexpensive, abundant alkenes into a variety of functionalized chiral products.[1] Over the past several years, our group has introduced efficient and stereoselective alkene diboration reactions that are catalyzed by chiral rhodium[1a,b] or platinum[1c,d] complexes and most recently has developed a carbohydrate-catalyzed asymmetric process.[1f,g] In addition to these reports, Nishiyama[2] has advanced a Rh(phebox)-catalyzed enantioselective process, and Hoveyda[3] 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 monofunctionalization of 1,2-bis(boronates) can be conducted (Scheme 1): the

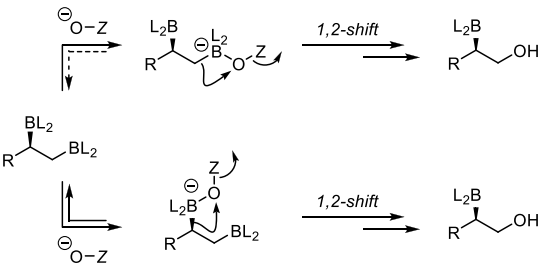
Scheme 1. Site-Selective Functionalization of 1,2-Bis(boronates)



organoboron motif 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 nonfunctionalized[4] 1,2-bis(boronates) have been developed, one involving regioselective Suzuki−Miyaura coupling[5] 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 (Scheme 2, eq 1).

Scheme 2. Prospective Selectivity Paradigms in Vicinal Diboronate Oxidation Reactions



Alternatively, if 1,2-boronate rearrangement is the rate-limiting step and coordination of the oxidant to boron is reversible, then the more substituted electron-rich carbon may migrate preferentially, providing selectivity as depicted in eq 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-bis(boronic) **1** (Table 1) was treated with a 1:1 mixture of potassium hydride and *tert*-butyl hydroperoxide for 1 h and analyzed by ^{1}H NMR. This reaction proceeded to 65% conversion, providing mono-oxidation

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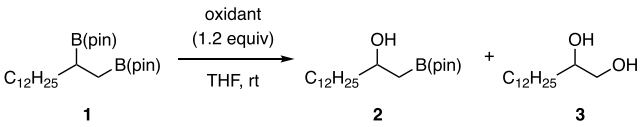
Table 1. Survey of Oxidants in Selective Oxidation of 1,2-Bis(boronates)



1 2 3

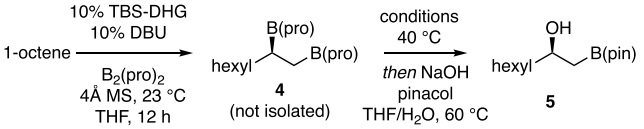
entry	oxidant	% conv[a]	2[b] (%)	3[b] (%)
1	KH/*t*BuOOH	65	10	52
2	mCPBA	62	<5	43
3	$(t\text{-BuO})_2$	<5		
4	$(BzO)_2$	<5		
5	pyridine *N*-oxide	<5		
6	Me_3NO	65	42	23

[a]Conversion determined by ^{1}H NMR versus an internal standard. [b]Percent yield determined after purification by silica gel chromatography.

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. *m*-Chloroperbenzoic acid afforded overoxidized product **3** exclusively (entry 2). The neutral peroxides di-*tert*-butyl peroxide and dibenzoyl peroxide 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 to be 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 of TMANO was increased, the extent of reaction increased from 65% (Table 1, entry 6) to 72%; however, the isolated yield of mono-oxidation product remained the same (Table 2, entry 1). The presence of significant amounts of overoxidation product suggested that the mono-oxidation product **5** (or its derived borate ester) may be more reactive toward 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 overoxidation was less problematic. With 1-butanol as solvent, other amine *N*-oxides

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



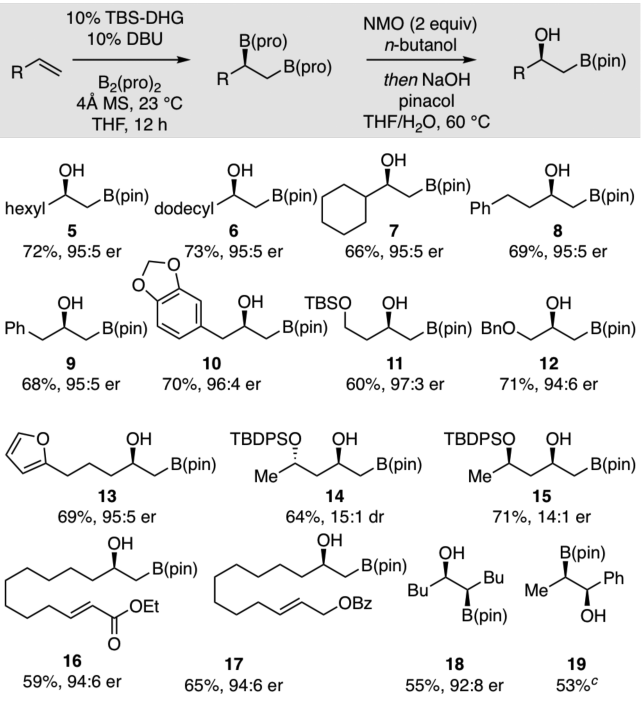
entry	oxidant	equiv	solvent	conv[a] (%)	5[b] (%)
1	TMANO	1.5	THF	72	41
2	TMANO	1.5	DMF	80	36
3	TMANO	1.5	$CHCl_3$	68	40
4	TMANO	1.5	toluene	67	32
5	TMANO	1.5	*n*-BuOH	65	44
6	TBANO	1.5	*n*-BuOH	49	42
7	TBANO	2.0	*n*-BuOH	82	64
8	NMO	1.5	*n*-BuOH	54	46
9	NMO	2.0	*n*-BuOH	92	70

[a]Conversion determined by ^{1}H NMR versus an internal standard. [b]Percent yield determined after purification by silica gel chromatography.

and reaction conditions were then examined, with 2 equiv 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

Table 3. Substrate Survey in Tandem Diboration/Mono-Oxidation



[a]Conversion determined by ^{1}H NMR versus an internal standard. [b]Percent yield determined after purification by silica gel chromatography. [c]This experiment employed Cs_2CO_3 catalysis in place of TBS-DHG/DBU, and therefore, the product is racemic.

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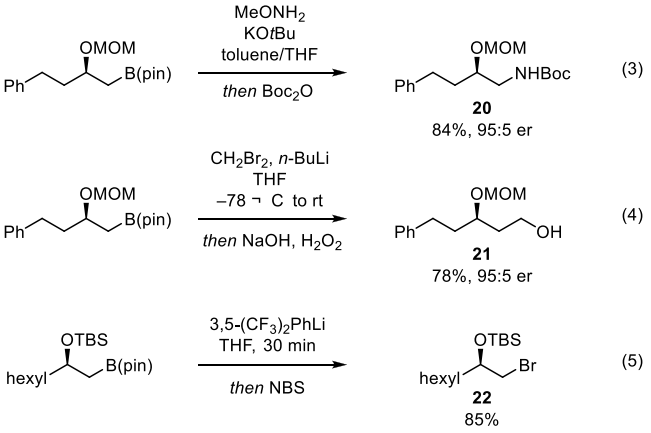
also underwent smooth transformation to the β-hydroxyboronate (compounds **9**, **10**), as did compounds with a protected hydroxyl groups (entries **11**, **12**, **14**, and **15**). Of consequence with respect to synthetic utility, alkenes bearing adjacent preexisting stereogenic centers underwent 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 a preparatively useful scale with only minor modification (see the 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 eq 3, after hydroxyl protection the primary boronic ester can be transformed into a Boc-protected amine (**20**) using a method developed in our laboratory.[9] Conversion of terminal alkenes to enantiomerically enriched 1,2-amino alcohols 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 4).[10] Lastly, by employing an approach developed by Aggarwal (eq 5), the pinacol boronate can be replaced with a bromine atom.[11]



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 β-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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01204.

Procedures, characterization, and spectral and chromatographic data (PDF)

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Notes

The authors declare no competing financial interest.

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