Hydroxyl-Directed Stereoselective Diboration of Alkenes

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S *Supporting Information*

ABSTRACT: An alkoxide-catalyzed directed diboration of alkenyl alcohols is described. This reaction occurs in a stereoselective fashion and is demonstrated with cyclic and acyclic homoallylic and bishomoallylic alcohol substrates. After oxidation, the reaction generates 1,2-diols such that the process represents a method for the stereoselective directed dihydroxylation of alkenes.

The olefin diboration reaction is a useful strategy for the conversion of alkenes into a range of important building blocks.[1] In this connection, we[2] and others[3] have developed strategies for the catalytic enantioselective addition of diboron reagents to prochiral isolated alkenes. While these reactions occur selectively with monosubstituted, *trans*-1,2-disubstituted, and trisubstituted alkenes, the minimally biased prochiral π-faces of *cis*-1,2-disubstituted and 1,1-disubstituted alkenes render selective reactions of these substrate classes much more difficult to engineer. As one strategy to address this issue, we considered that a directing group located proximal to the reacting olefin might provide an additional organizational element and enable a solution to these more challenging substrate classes.[4,5] Herein, we describe highly efficient and selective directed diboration of cyclic and acyclic homoallylic and bishomoallylic alcohols.[6] In addition to providing a stereoselective route to synthetically versatile 1,2-bis-(pinacolboronates), this process provides an alternative to directed OsO4-promoted dihydroxylations that typically require stoichiometric amounts of osmium and that do not reliably extend to homoallylic alcohol substrates.[7]

In lieu of transition-metal catalysts, Lewis bases have been shown to activate diboron reagents for addition to unsaturated substrates. While N-heterocyclic carbenes[8] and phosphines[9] have been shown to catalyze the addition of $B_2(pin)_2$ to activated olefins,[10] metal alkoxides[11] used in conjunction with alcohols have been shown to promote the addition of $B_2(pin)_2$ to isolated unactivated alkenes. While computational studies performed by Fernandez suggest that the mechanism of the alkoxide-catalyzed reaction occurs by alkoxide-induced transfer of a boryl anion to the alkene providing a transient three-membered boracycle, mechanistic experiments have not detailed precise features of the reaction. None the less, development of a directed process that involves association of an alkoxide to $B_2(pin)_2$, followed by delivery of the diboron reagent to a tethered alkene, appeared plausible. Issues central to a selective directed reaction include (a) whether the geometry required for addition of the diboron to the alkene could be maintained concurrently with intramolecular alkoxide-diboron association; (b) whether the directed process could compete with high background reaction rates; (c) whether the directed reaction could indeed enable the selective reaction of challenging hindered substrate classes.

To begin probing the ability of alcohol functional groups, or their derived alkoxides to promote selective diboration of adjacent alkenes, substrate **1** was examined under a range of reaction conditions. As depicted in Table 1 entry 1, homoallylic alcohol **1** was first heated with $B_2(pin)_2$ in the absence of base and was found to be unreactive. When the derived sodium alkoxide of substrate **1** was employed (entry 2) the substrate was also left unchanged. Inclusion of 5 equiv of methanol in the reaction of the alkoxide resulted in a significant improvement

Table 1. Catalytic Enantioselective Diboration of 1[a]

entry	base (equiv)	B$_2$(pin)$_2$ (equiv)	additive (equiv)	conv (%)	dr
1	none	1.05	0	<5	na
2	NaH (1.0)	1.05	0	<5	na
3	NaH (1.0)	1.05	CH$_3$OH (5)	87	12.5:1
4	NaO*t*Bu (0.15)	1.05	CH$_3$OH (5)	83	7.7:1
5	Na$_2$CO$_3$ (0.15)	1.05	CH$_3$OH (5)	68	7.9:1
6	KO*t*Bu (0.15)	1.05	CH$_3$OH (5)	90	12.3:1
7	Cs$_2$CO$_3$ (0.15)	1.05	CH$_3$OH (5)	87	12.5:1
8	Cs$_2$CO$_3$ (0.15)	1.05	*i*PrOH (5)	64	7.4:1
3	Cs$_2$CO$_3$ (0.15)	1.05	*t*BuOH (5)	42	9.5:1
4	Cs$_2$CO$_3$ (0.15)	1.05	H$_2$O (5)	9	3.8:1
5	Cs$_2$CO$_3$ (0.15)	1.05	PhOH (5)	51	13.2:1
6	Cs$_2$CO$_3$ (0.15)	1.05	CF$_3$CH$_2$OH (5)	45	5.6:1
9	Cs$_2$CO$_3$ (0.3)	2.0	CH$_3$OH (5)	>95	9.9:1
10[b]	Cs$_2$CO$_3$ (0.3)	2.0	CH$_3$OH (17)	>95	12.9:1
11	Cs$_2$CO$_3$ (0.3)	2.0	CH$_3$OH (25)	>95	12.1:1
12	Cs$_2$CO$_3$ (0.3)	2.0	CH$_3$OH (50)	>95	9.5:1
13	Cs$_2$CO$_3$ (0.3)	2.0	CH$_3$OH (solvent)	>95	5.7:1

[a]Percent conversion determined by ^{1}H NMR analysis, stereoselectivity (dr) determined by SFC. [b]Reaction time is 1 h.
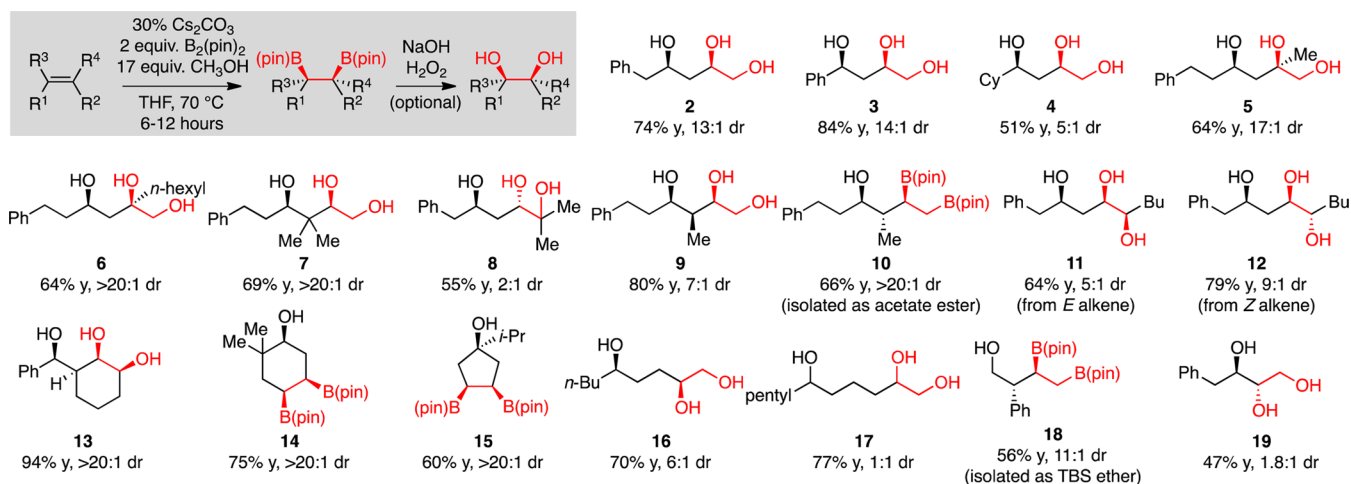
**Figure 1.** Directed diboration of alkenyl alcohols.

providing the product in 87% conversion and 12.5:1 diastereomer ratio favoring the *syn* isomer of product. Reasoning that the substrate alkoxide likely participates in reversible acid–base equilibrium with methanol, a catalytic amount of NaO*t*Bu in the presence of methanol was examined and found to provide the product in good yields and moderate stereoselection. Examination of other bases in the presence of methanol showed that KO*t*Bu and Cs_2CO_3 provided higher levels of selectivity and also very good conversion to product. In an effort to achieve complete conversion and shorter reaction times, the amounts of Cs_2CO_3 and $B_2(pin)_2$ were increased. While the stereoselection was slightly diminished with 30 mol % Cs_2CO_3 and 5 equiv of methanol, use of 17 equiv of methanol restored the selectivity to a high level and provided complete conversion in 1 h (entry 10). That the selectivity improves with added methanol, and is high even with 50 equiv (entry 12), is remarkable for a reaction that appears to occur by an alkoxide directing effect; indeed, even when the reaction is run in methanol as solvent, a medium that should favor the generation of methoxide at the expense of substrate alkoxide, good levels of stereocontrol are still observed in the reaction (entry 13).

The scope of the directed diboration reaction was examined with a panel of substrates. Unless otherwise noted, the alkenyl alcohol was subjected to $B_2(pin)_2$ in the presence of cesium carbonate and methanol and subjected to oxidative work up with basic hydrogen peroxide (see Supporting Information (SI) for details). Under these conditions, the probe substrate in Table 1 was converted to the derived diol **2** in 74% isolated yield (Figure 1). In addition to terminal alkene substrates, the reaction extends to 1,1-disubstituted alcohols (products **5** and **6**) and also applies to prenyl- and *anti*- and *syn*-crotyl-derived substrates as well (products **7–10**). That the reaction occurs by stereospecific directed *syn* addition could be ascertained by observing selective diboration of both *trans*- and *cis*-olefin substrates (products **11** and **12**).[12] Also of note, cyclic alkenes participate (products **13–15**) and are converted to the *syn* diboration product in useful yields. Reaction product **13** is particularly notable as the corresponding OsO$_4$-catalyzed dihydroxylation strongly favors the opposite stereoisomer of reaction product (see the SI). The hydroxyl group could be moved one carbon further away from the alkene and still have significant impact on the reaction selectivity as exemplified by product **16**; however, with a trishomoallylic alcohol the reaction

was nonselective. Lastly, an allylic alcohol was found to participate (**19**) but with low selectivity under the present conditions, and a tetra-substituted alkene was found to be unreactive (data not shown).

The observations in Table 1 demonstrate the importance of an alcohol additive as well as the requirement of a Bronsted base in the reaction. To gain insight into the manner in which the resident alcohol functional group influences the stereoselective diborations in Figure 1, several other experiments were undertaken. To probe the role of the hydroxyl functional group, the derived methyl ether was examined in the diboration reaction. As depicted in Scheme 1, diboration of **20** did indeed occur; however, an equal mixture of diastereomers **21** was produced. This observation suggests that the hydroxyl group

Scheme 1
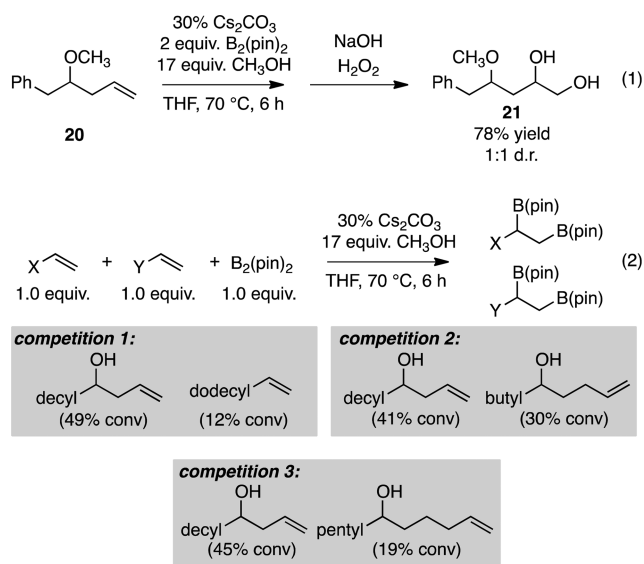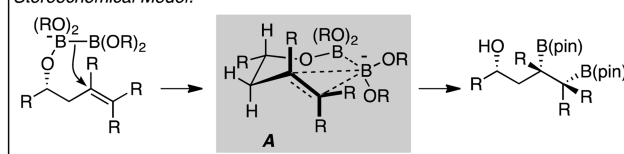
does not function as a neutral Lewis basic chelating group but either participates in hydrogen bonding or participates as the derived alkoxide. If one of these modes applies and results in delivery of the diboron reagent to the adjacent alkene, then a rate acceleration is anticipated for the directed versus the nondirected process. To probe this detail, an equimolar mixture of a homoallylic alcohol and 1-tetradecene was subjected to diboration with a deficiency of $B_2(pin)_2$. After 6 h of reaction, it was found that the homoallylic alcohol had been consumed to a greater extent (49% conversion, see Scheme 1, eq 2, competition 1) than tetradecene (12% conversion). This experiment establishes a lower limit for the reaction rate ratio of $>\sim 4$. In line with observed selectivity, a similar experiment showed that a bishomoallylic alcohol reacts at a rate comparable to the homoallylic alcohol (competition 2), whereas a trishomoallylic alcohol reacts slower (Scheme 1, competition 3).

Combined, the experiments in Scheme 1 are highly suggestive of a directed process involving association between the substrate and the diboron reagent. While more detailed investigation is clearly warranted, the observation that the reaction is stereoselective even when run in methanol solvent, suggests that hydrogen bonding between the substrate alcohol and $B_2(pin)_2$ may not be the dominant effect and that coordination of the substrate alkoxide with the diboron reagent is more likely a critical feature. Although the precise mechanism and a role for methanol still remain to be determined, structure **A** that involves alkoxide-$B_2(pin)_2$ association rationalizes the stereochemical outcome of most reactions in Figure 1 and is in line with the mechanistic features delineated by Fernandez.

To probe the utility of the directed diboration in preparative organic synthesis, a larger scale reaction was conducted with an aim on evaluating practical aspects. In this experiment, the diboration of **1** was conducted on 5.1 g scale, and all reagents were handled in the open atmosphere (Scheme 2). Moreover,

Scheme 2
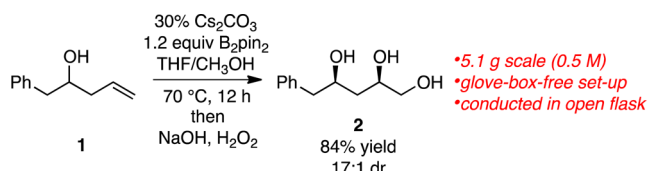
the reaction was conducted in a typical round-bottom flask fitted with a reflux condenser but was exposed to the open atmosphere and without a drying tube attached. To minimize the amount of $B_2(pin)_2$ employed but still obtain complete conversion in a reasonable time frame, the reaction was run at a increased substrate concentration (0.5 M). After 12 h at 70 °C, followed by oxidative workup, triol **2** was obtained in 84% yield and as a 17:1 mixture of *syn:anti* diastereomers.

Also in connection to synthesis utility, the ability to address more complex targets with directed diboration was examined. In this regard, vicinal bis(boronates) participate in effective cross-coupling reactions that can provide a number of useful functional group arrays.[13] When these cross-couplings are applied to directed diboration products, they may provide new strategies for constructing important and challenging structural motifs. To examine this possibility in the context of directed diboration, we targeted the C6–C13 portion of spongistatin,[14] a subunit that has been prepared previously through carbonyl

allylation methods.[15] As depicted in Scheme 3, TBDPS protected 3-buten-1-ol (**22**) was subjected to cascade

Scheme 3
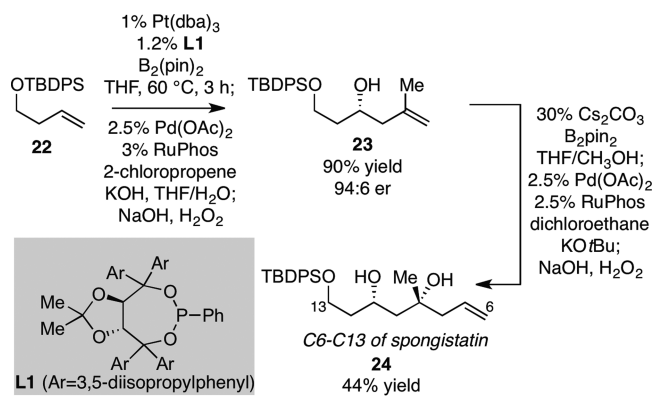
asymmetric diboration/cross-coupling to furnish substituted homoallylic alcohol **23**. Directed diboration was followed by catalytic cross-coupling and oxidation to provide **24** with moderate yield but in excellent levels of stereocontrol.

In conclusion, the diboration of alkenyl alcohols benefits from substrate directing effects to control the product configuration. Examination of other substitution patterns and directing groups should further expand these processes, and such studies are in progress as is a critical analysis of operative mechanisms.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures, characterization, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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