

Enantioselective Synthesis of 2-Methyl-1,2-*syn*- and 2-Methyl-1,2-*anti*-3-butenediols via Allene Hydroboration–Aldehyde Allylboration Reaction Sequences

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2-Methyl-1,2-*syn*- and 1,2-*anti*-diols are common structural motifs in natural products.¹ Stereocontrolled syntheses of these units mainly rely on the Sharpless asymmetric dihydroxylation reaction.² However, when the substrate contains multiple olefins, a highly regioselective dihydroxylation can be challenging owing to the influence of the substitution pattern, steric and electronic effects of the individual double bonds.³ Consequently, a tactic frequently used in the synthesis of molecules which contain 1,2-diol units and potentially conflicting olefin functionalities is to install the diol before introduction of the olefin.^{4–6} Alternatively, diastereoselective 1,2-addition of a methyl group to α -hydroxy- α',β' -unsaturated ketones or addition of a vinyl metal species to α -alkoxyl methyl ketones also provides access to these 1,2-diol subunits.^{7,8} In connection with an ongoing problem in natural product synthesis, we have developed and report herein a direct, one-step, highly diastereo- and enantioselective synthesis of 2-methyl-1,2-*syn*- and 2-methyl-1,2-*anti*-3-butenediols via allene hydroboration–aldehyde allylboration reaction sequences.

In 1995, Brown reported the diastereo- and enantioselective synthesis of *anti*-1,2-diols **4** by a sequence involving the hydroboration of allenylboronate **1** with diisopinocampheylborane [(*l*-Ipc)₂BH] (Figure 1).⁹ It is believed that hydroboration of allenylboronate **1** with (*d*-Ipc)₂BH initially forms γ -boryl-(*Z*)-allylborane **2-Z** as the kinetic product, which isomerizes rapidly through reversible 1,3-borotropic shifts to give γ -boryl-(*E*)-allylborane **2-E**.^{10–14} We subsequently adopted this procedure for the synthesis of 1,5-*anti*- and 1,5-*syn*-diols **5** and **6** by using the intermediate β -alkoxyallylboronate **3** in a second allylboration reaction.¹⁵ The stereochemical course of the second allylboration event depends on the structure of the boronate unit.¹⁵ The double allylboration methodology has been applied in several synthetic studies targeting natural products.^{16–20}

By analogy to the results in Figure 1, we anticipated that the hydroboration of 1-methyl-allenylboronate **7**²¹ with diisopinocampheylborane [(*d*-Ipc)₂BH] followed by (single) aldehyde allylboration and oxidative workup would provide a flexible, general synthesis of 1,2-*anti*-diols **9**, bearing a quaternary center. In initial experiments, treatment of allenylboronate **7** with (*d*-Ipc)₂BH in toluene at 0 °C for 2 h followed by addition of hydrocinnamaldehyde at –78 °C (4 h) and then standard oxidative workup provided, surprisingly, the *syn*-1,2-diol **8a** in 72% yield and 92% e.e. (Scheme 1). The absolute stereochemistry of the secondary hydroxyl group of **8a** was assigned by using the modified Mosher ester analysis.²² The *syn* stereochemistry of **8a** (and subsequently also of **8e**) was assigned by ¹H NOE studies of the corresponding acetone derivatives (see Supporting Information (SI)). The conditions developed for the synthesis of **8a** were then applied to a variety of aldehydes. 1,2-*syn*-Diols **8a–g** were obtained in 56–82% yield with >20:1 diastereoselectivity and 85–92% e.e. (Scheme 1).

Assuming that the allylboration reaction proceeds by way of the usual chairlike transition state,^{23,24} the results in Scheme 1 indicate that the intermediate produced in the hydroboration of **7** is the

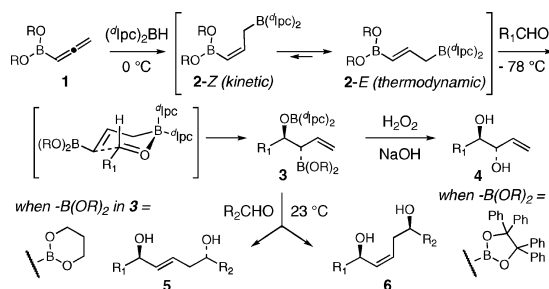
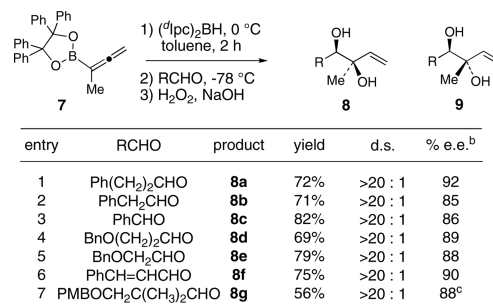


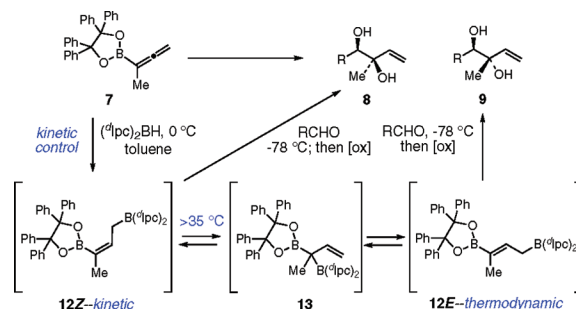
Figure 1. Hydroboration–allylboration of allenylboronate **1**.

Scheme 1. Synthesis of *syn*-1,2-Diols **8** via Kinetic Hydroboration of **7**^a



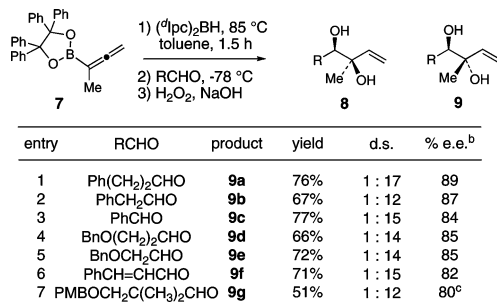
^a Reactions were performed by treating **7** with (*d*-Ipc)₂BH (1.0 equiv) in toluene at 0 °C followed by the addition of RCHO (1 equiv) at –78 °C. The mixture was then allowed to stir at –78 °C for 4 h. The reactions were subjected to standard oxidative workup (NaOH, H₂O₂) at 0 °C before product isolation. ^b Determined by Mosher ester analysis, unless noted otherwise. ^c See SI for enantiomeric purity determination.

Scheme 2. Kinetic Hydroboration of **7** and Thermodynamically Controlled Allylboration Isomerization

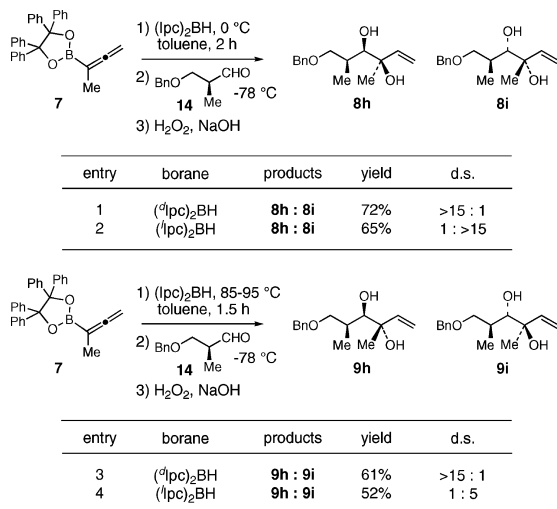


γ -boryl-(*Z*)-allylic borane **12Z** (Scheme 2). In contrast to the elusive intermediate **2-Z** in the hydroboration of allenylboronate **1**, the kinetic hydroboration product **12Z** does not isomerize to the thermodynamically more stable **12E** at 0 °C.

We were intrigued by the possibility that the diastereomeric *anti*-diols **9** could also be accessed if **12Z** could be induced to isomerize

Scheme 3. Synthesis of *anti*-1,2-Diols **9** via Hydroboration of **7** and Thermodynamically Controlled Allylborane Isomerization^a

^a Reactions were performed by treating **7** with (*d*)Ipc₂BH (1.0 equiv) in toluene at 85–95 °C for 1.5 h followed by the addition of RCHO (1 equiv) at –78 °C. The mixture was then allowed to stir at –78 °C for 4 h. The reactions were subjected to standard oxidative workup (NaOH, H₂O₂) at 0 °C before product isolation. ^b Determined by Mosher ester analysis, unless indicated otherwise. ^c See SI for % e.e. determination for **9g**.

Scheme 4. Double Asymmetric Allylboration Reactions with Aldehyde **14**

to the γ -boryl-(*E*)-allylborane **12E**. Indeed, when the hydroboration of allenylboronate **7** was performed at 35 °C for 16 h followed by treatment of the allylborane product with hydrocinnamaldehyde at –78 °C, a 3:1 mixture of diols **9a** and **8a** was obtained. Hydroboration of **7** at 65 °C for 5 h led to a 5:1 mixture of **9a** and **8a**. Prolonged heating of the hydroboration reaction at 65 °C (16 h), however, only led to decomposition. When the hydroboration of **7** was performed at 85 °C in toluene for 1.5 h, followed by addition of hydrocinnamaldehyde at –78 °C, *anti*-diol **9a** was obtained with 17:1 d.r. (**9a**:**8a**) in 76% yield and 89% e.e. (Scheme 3). The stereochemistry of *anti*-diol **9a** (and subsequently also of **9e**) was assigned by ¹H NOE studies of the corresponding acetone derivatives (see SI). The hydroboration–isomerization–allylboration sequence was then applied to a variety of aldehydes (Scheme 3). In all cases, 1,2-*anti*-diols **9a–g** were obtained in good yield with $\geq$ 12:1 diastereoselectivity and 80–89% e.e.

Finally, double asymmetric allylboration reactions of **12Z** and **12E** with chiral aldehyde **14** are summarized in Scheme 4. Kinetic controlled hydroboration of allenylboronate **7** with either (*d*)Ipc₂BH or (*l*)Ipc₂BH and treatment with aldehyde **14** provided *syn*-diols **8h** or **8i** with excellent diastereoselectivity (>15:1) in 72% and 65% yield, respectively (entries 1 and 2). Alternatively, when the

hydroboration of **7** was performed at 85–95 °C for 1.5 h with (*d*)Ipc₂BH [to give the thermodynamic allylborane **12E**] followed by addition of **14** at –78 °C, *anti*-diol **9h** was obtained with excellent diastereoselectivity (>15:1) (entry 3). Similarly, a 5:1 mixture of *anti*-diols **9i** and **9h** was obtained in 52% yield from **12E** generated by the hydroboration of **7** with (*l*)Ipc₂BH (entry 4). The latter reaction is stereochemically mismatched.²⁵

The data presented herein indicate that the hydroboration of **7** with (Ipc)₂BH proceeds under kinetic control at 0 °C and provides **12Z** with excellent selectivity. Evidently, the normally facile 1,3-isomerization that has been documented for other allylboranes^{10–14} is slow in the case of **12Z** owing to steric hindrance in the transition state leading to the 1,1-diboryl species **13**. However, isomerization is readily achieved at higher temperatures, and a $\geq$ 12:1 mixture of **12E** and **12Z** is obtained at 85 °C. Thus, synthetically useful selectivity for synthesis of either the 1,2-*syn* or 1,2-*anti* diol diastereomers **8** and **9** can be achieved by appropriate control of the hydroboration conditions. Applications of this method in the synthesis of natural products will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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