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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 [$(Ipc)_2BH$] (Figure 1).[9] It is believed that hydroboration of allenylboronate **1** with $(^dIpc)_2BH$ 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 [$(^dIpc)_2BH$] 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 $(^dIpc)_2BH$ 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 acetonide 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

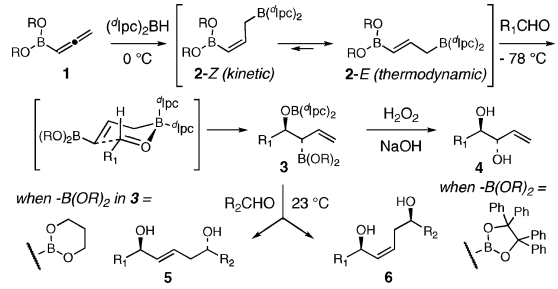
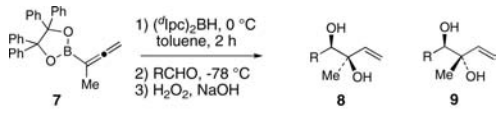


Figure 1. Hydroboration−allylboration of allenylboronate **1**.

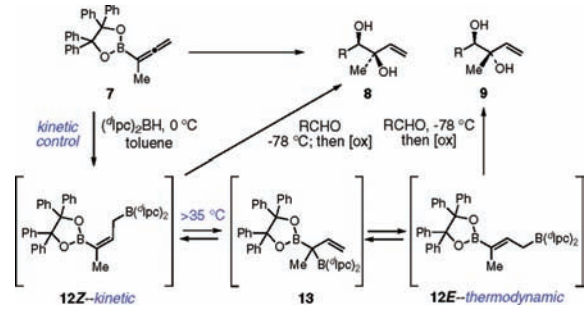
Scheme 1. Synthesis of *syn*-1,2-Diols **8** via Kinetic Hydroboration of **7**[a]



entry	RCHO	product	yield	d.s.	% e.e.[b]
1	$Ph(CH_2)_2CHO$	**8a**	72%	>20 : 1	92
2	$PhCH_2CHO$	**8b**	71%	>20 : 1	85
3	PhCHO	**8c**	82%	>20 : 1	86
4	$BnO(CH_2)_2CHO$	**8d**	69%	>20 : 1	89
5	$BnOCH_2CHO$	**8e**	79%	>20 : 1	88
6	PhCH=CHCHO	**8f**	75%	>20 : 1	90
7	$PMBOCH_2C(CH_3)_2CHO$	**8g**	56%	>20 : 1	88[c]

[a] Reactions were performed by treating **7** with $(^dIpc)_2BH$ (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, H_2O_2) 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 Allylborane Isomerization



γ-boryl-(*Z*)-allylic borane **12*Z*** (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 **12*E*** at 0 °C.

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

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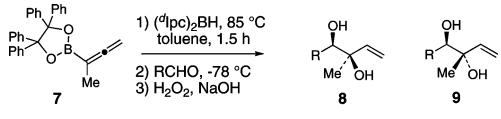
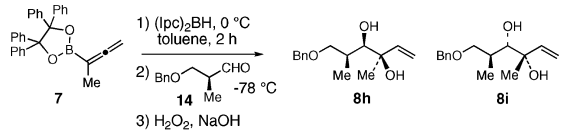
Scheme 3. Synthesis of *anti*-1,2-Diols **9** via Hydroboration of **7** and Thermodynamically Controlled Allylborane Isomerization[a]



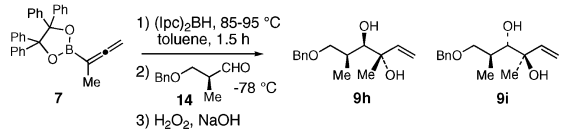
entry	RCHO	product	yield	d.s.	% e.e.[b]
1	$Ph(CH_2)_2CHO$	**9a**	76%	1 : 17	89
2	$PhCH_2CHO$	**9b**	67%	1 : 12	87
3	PhCHO	**9c**	77%	1 : 15	84
4	$BnO(CH_2)_2CHO$	**9d**	66%	1 : 14	85
5	$BnOCH_2CHO$	**9e**	72%	1 : 14	85
6	PhCH=CHCHO	**9f**	71%	1 : 15	82
7	$PMBOCH_2C(CH_3)_2CHO$	**9g**	51%	1 : 12	80[c]

[a] Reactions were performed by treating **7** with (^{d}Ipc)$_2$BH (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, H_2O_2) 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**



entry	borane	products	yield	d.s.
1	(^{d}Ipc)$_2$BH	**8h : 8i**	72%	>15 : 1
2	(^{l}Ipc)$_2$BH	**8h : 8i**	65%	1 : >15



entry	borane	products	yield	d.s.
3	(^{d}Ipc)$_2$BH	**9h : 9i**	61%	>15 : 1
4	(^{l}Ipc)$_2$BH	**9h : 9i**	52%	1 : 5

to the γ-boryl-(*E*)-allylborane **12*E***. 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 ^{1}H NOE studies of the corresponding acetonide 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 ≥12:1 diastereoselectivity and 80−89% e.e.

Finally, double asymmetric allylboration reactions of **12*Z*** and **12*E*** with chiral aldehyde **14** are summarized in Scheme 4. Kinetic controlled hydroboration of allenylboronate **7** with either (^{d}Ipc)$_2$BH or (^{l}Ipc)$_2$BH 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}Ipc)$_2$BH [to give the thermodynamic allylborane **12*E***] 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 **12*E*** generated by the hydroboration of **7** with (^{l}Ipc)$_2$BH (entry 4). The latter reaction is stereochemically mismatched.[25]

The data presented herein indicate that the hydroboration of **7** with (Ipc)$_2$BH proceeds under kinetic control at 0 °C and provides **12*Z*** 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 **12*Z*** 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 ≥12:1 mixture of **12*E*** and **12*Z*** 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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