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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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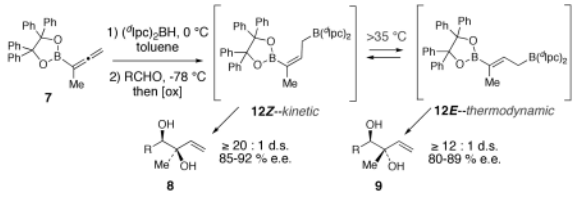
Abstract

The hydroboration of allene **7** with (^{d}Ipc)$_2$BH at 0 °C provides the kinetic allylborane **12*Z*** with ≥20 : 1 selectivity. However, when the hydroboration is performed at 85 °C, the kinetically formed allylborane isomerizes to give the thermodynamic allylborane **12*E*** with ≥12 : 1 selectivity. Subsequent treatment of **12*Z*** or **12*E*** with aldehydes at -78 °C, followed by oxidative workup, provides the 2-methyl-1,2-diols **8** and **9** in good yield and with 80-92% e.e.



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 provide access to these 1,2-diols 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)$_2$BH] (Figure 1).[9] It is believed that hydroboration of allenylboronate **1** with (^{d}Ipc)$_2$BH 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

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

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)$_2$BH] 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)$_2$BH 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% ee (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 ^{1}H nOe studies of the corresponding acetonide derivatives (see Supporting Information). 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% ee (Scheme 1).

Assuming that the allylboration reaction proceeds by way of the usual chair-like transition state,[23,24] the results in Scheme 1 indicate that the intermediate produced in the hydroboration of **7** is the 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 **12*Z*** *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 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 mixture with hydrocinnamaldehyde gave a 3:1 mixture of diols **9a** and **8a**, favoring the *anti*-diol **9a** derived from isomerization of **12*Z*** to the thermodynamically favored allylborane **12*E***. 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% ee (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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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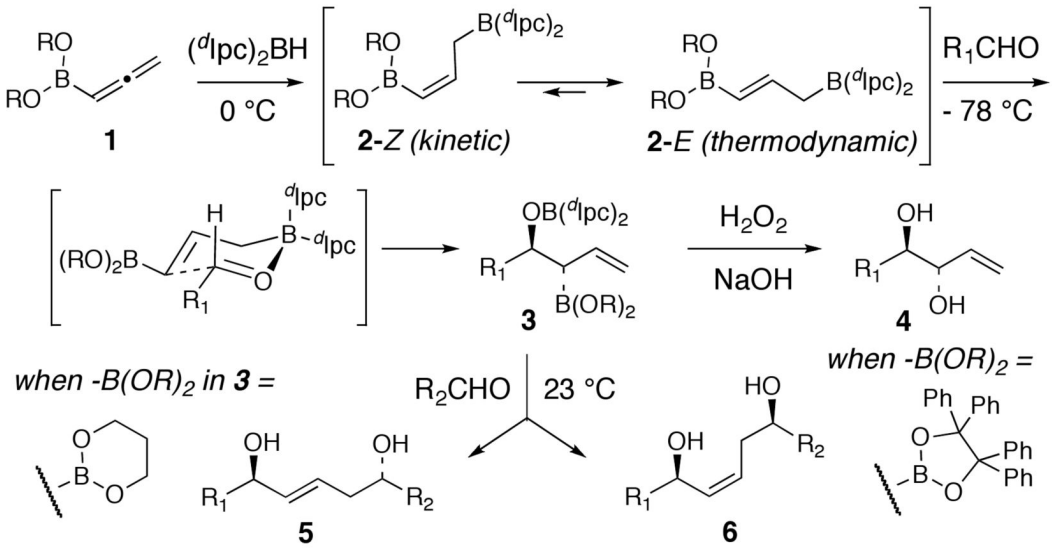
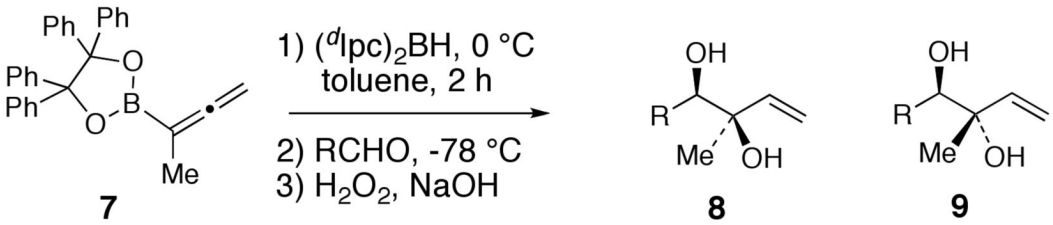


Figure 1.
Hydroboration-Allylboration of Allenylboronate **1**



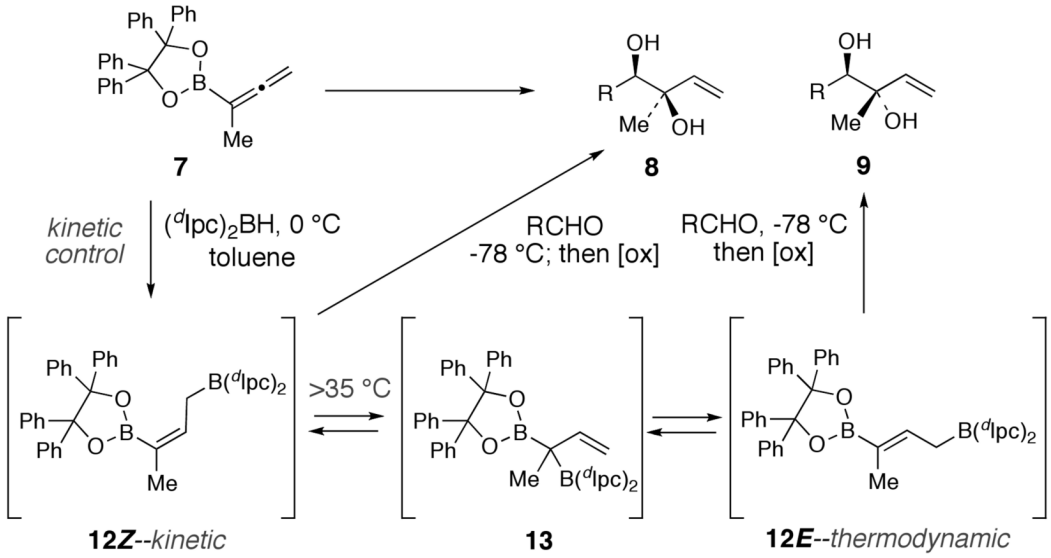
7 8 9

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]

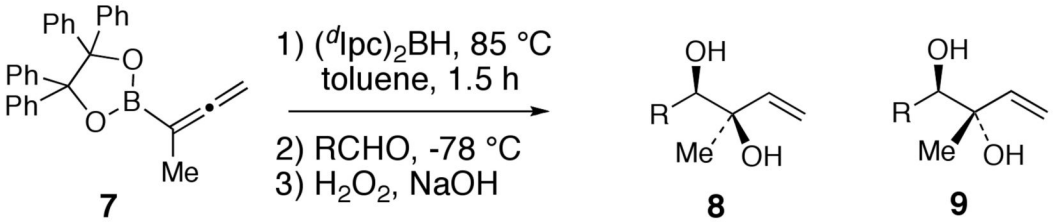
Scheme 1.

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

(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

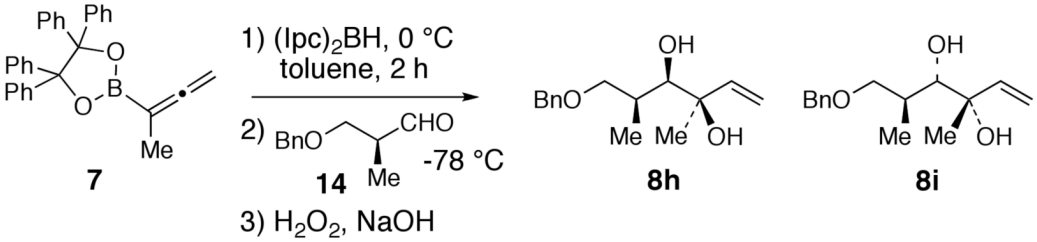


entry	RCHO	product	yield	d.s.	% e.e.[b]
1	$Ph(CH_2)_2CHO$	**9a**	76%	1 : 17	89
2	$PhCH_2CHO$	**9b**	67%	1 : 12	87
3	PhCHO	**9c**	77%	1 : 15	84
4	$BnO(CH_2)_2CHO$	**9d**	66%	1 : 14	85
5	$BnOCH_2CHO$	**9e**	72%	1 : 14	85
6	PhCH=CHCHO	**9f**	71%	1 : 15	82
7	$PMBOCH_2C(CH_3)_2CHO$	**9g**	51%	1 : 12	80[c]

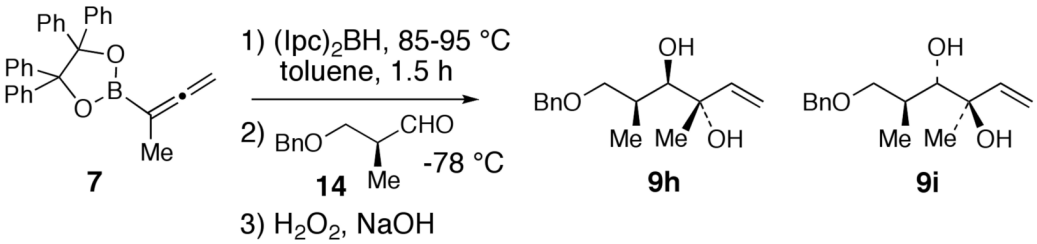
Scheme 3.

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 $(^dIpc)_2BH$ (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**.



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

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