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Enantioconvergent Hydroboration of a Racemic Allene: Enantioselective Synthesis of (*E*)- δ -Stannyl-*anti*-Homoallylic Alcohols via Aldehyde Crotylboration

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Abstract

The enantioconvergent hydroboration of racemic allenylstannane ($\pm$)-**1** with (d^4 IpC)₂BH converts both enantiomers of ($\pm$)-**1** into the enantioenriched crotylborane (*S*)-**E-3**. Subsequent crotylboration of aldehydes with (*S*)-**E-3** provides (*E*)- δ -stannyl-homoallylic alcohols **5** in good yields and with excellent enantioselectivity.

Asymmetric synthesis of chiral, nonracemic molecules is a major objective in organic chemistry. A wide variety of highly enantiomerically enriched molecules can be generated with excellent selectivity owing to the many classes of highly enantioselective chiral reagents, auxiliaries and catalysts that have been developed over the past several decades.¹

The prevailing approach in asymmetric synthesis focuses on introducing chirality in reactions of prochiral substrates using chiral reagents or chiral catalysts. Other strategies, however, are available for the synthesis of highly enantiomerically enriched compounds. Because it is often easier and more cost effective to synthesize racemates, resolution remains a valuable tool to access highly enantiomerically enriched molecules (especially in the pharmaceutical industry). Kinetic resolution is a well-established approach that enables partial or complete separation of a racemate based on the different rates of reaction of each enantiomer with a chiral, nonracemic reagent or catalyst.² However, even in an ideal case, the overall efficiency of kinetic resolution is limited to a theoretical maximum yield of 50%. The other 50% of enantiomeric material is discarded or recycled. Additional strategies, such as dynamic kinetic resolution (DKR),³ address this limitation when applicable. DKR involves rapid racemization of substrates or symmetrization of reaction intermediates, with product formation occurring under Curtin–Hammett control via a rate-determining enantioselective transition state. In this way, both enantiomers of the substrate are converted into a single enantiomerically enriched product with 100% theoretical yield.

We describe here a remarkable example of the enantioconvergent reaction of a racemic allene to give an enantiomerically enriched product.⁴ Unlike dynamic kinetic resolution, the enantioconvergent reaction process does not involve racemization of the substrate or the symmetrization of a reaction intermediate prior to the enantioselective step. Rather, both enantiomers of the racemate are converted into different enantiomerically enriched intermediates by chemically distinct, kinetically controlled pathways. Subsequent transformations of the non-racemic intermediates provide the same enantiomer of a single reaction product with high enantiomeric excess.

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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>.

As part of ongoing studies to expand the utility of the double allylboration chemistry developed in our laboratory,⁵ we studied the hydroboration of racemic 3-methyl-allenylstannane ($\pm$)-**1** with *d*-diisopinocampheylborane [$(^d\text{Ipc})_2\text{BH}$]. As depicted in Figure 1, this reaction could lead either to reagent **2** or **3**, which when treated with aldehydes should react to provide **4** or **5**, respectively.⁶ The homoallylic alcohol products **4** and **5** are properly functionalized for use in subsequent C–C bond forming reactions.⁷ However, because allenylstannane ($\pm$)-**1** is racemic, we assumed at the outset that the enantioselective hydroboration would need to be performed in the kinetic resolution manifold.⁸

In the event, treatment of ($\pm$)-**1** with 1.0 equiv of $(^d\text{Ipc})_2\text{BH}$ at 0°C in diethyl ether followed by addition of 1.0 equiv of hydrocinnamaldehyde at –78 °C provided (*E*)- δ -stannyl-*anti*-homoallylic alcohol **5a** in 71% yield. *Significantly, the reaction proved to be highly enantioselective, as homoallylic alcohol 5a was obtained with 92% ee from racemic allene ($\pm$)-1.* Several other aldehyde substrates were also examined in this hydroboration-allylboration sequence (Table 1). In all cases, (*E*)- δ -stannyl-*anti*-homoallylic alcohols **5** were obtained in 56–73% yields with high enantioselectivities (88–94% ee⁹); however, the yields of **5** are 81–89% when RCHO is the limiting reagent (0.7 equiv) (Table 1). Each reaction also provided 3–5% of the (*E*)- δ -stannyl-*syn*-homoallylic alcohol isomer **6** (20–30% e.e.).

Assuming that the crotylboration proceeds through a chair-like transition state,⁶ the results in Table 1 indicate that the intermediate produced in the hydroboration of racemic allene ($\pm$)-**1** with $(^d\text{Ipc})_2\text{BH}$ is (*S*)- α -tributylstannyl-(*E*)-crotylboration [(*S*)-*E*-**3**] (Figure 2). The Bu₃Sn group is positioned α to the boron atom in (*S*)-*E*-**3** presumably due to the ability of the C–Sn bond to interact with the empty p orbital on boron.^{10,11} Subsequent crotylboration of aldehydes with (*S*)-*E*-**3** via the chair-like **TS-1** (with equatorial placement of the α -Bu₃Sn group) provides **5**.

Based on the data in Table 1, it was immediately apparent that these reactions do not involve the kinetic resolution of racemic allene ($\pm$)-**1** with $(^d\text{Ipc})_2\text{BH}$, as the maximum yield of the kinetic resolution would be only 50%. Rather, the efficiency and enantioselectivity of this process led to the supposition that hydroboration of racemic allene ($\pm$)-**1** with $(^d\text{Ipc})_2\text{BH}$ converted both allene enantiomers, (*P*)-**1** and (*M*)-**1**, into the same non-racemic intermediate (*S*)-*E*-**3**.

Direct evidence in support of this deduction was obtained by performing the hydroboration of the two enantiomerically enriched allenes, (*P*)-**1** and (*M*)-**1**, with $(^d\text{Ipc})_2\text{BH}$ (Figure 2).¹² Hydroboration of allene (*P*)-**1** ($\geq 95\%$ ee)¹² with 1 equiv of $(^d\text{Ipc})_2\text{BH}$ at 0°C, followed by addition of hydrocinnamaldehyde at –78 °C provided alcohol (*R,S*)-**5a** in 81–88% yield and $>95\%$ ee. Monitoring of this hydroboration reaction by ¹H-NMR spectroscopy revealed that (*S*)-*E*-**3** is the major allylboration species present (see Supporting Information). Notably, when the enantiomeric allene (*M*)-**1** ($\geq 95\%$ ee)¹² was treated under identical conditions with 1 equiv of $(^d\text{Ipc})_2\text{BH}$ and then 1 equiv of hydrocinnamaldehyde, the identical alcohol (*R,S*)-**5a** was isolated, albeit in reduced yield (42%) and diminished enantioselectivity (82% ee). Here again, (*S*)-*E*-**3** was observed when the hydroboration of (*M*)-**1** with $(^d\text{Ipc})_2\text{BH}$ was monitored by ¹H-NMR spectroscopy (data not shown). Based on the mechanism discussed subsequently, the hydroboration of allene (*P*)-**1** with $(^d\text{Ipc})_2\text{BH}$ likely is a matched double asymmetric reaction, while hydroboration of allene (*M*)-**1** with $(^d\text{Ipc})_2\text{BH}$ is presumed to be the mismatched pair.¹³ The minor *syn* diastereomer **6a** and *ent*-**6a** from these two experiments are enantiomeric; thus, an enantioconvergent process is not dominant in the pathway(s) leading to the minor *syn* diastereomers **6a/ent-6a**. The diminished chemical efficiency of the mismatched hydroboration of (*M*)-**1** is likely due to competitive addition of boron to the central allene carbon in this series.^{8b,c} The overall chemical efficiency and

enantioselectivity of the reactions of the racemic allene **1** summarized in Table 1 are thus approximated by the weighted average of the efficiencies (yield and enantioselectivity) of the matched and mismatched double asymmetric hydroboration reactions of (*P*)-**1** and (*M*)-**1**, respectively.

We considered the possibility that if (*P*)-**1** and (*M*)-**1** equilibrate (i.e., racemize) under the hydroboration conditions, the results in Table 1 and Figure 2 could be explained by a dynamic kinetic resolution.^{4b} If so, (*M*)-**1** could be funneled to (*P*)-**1** under Curtin–Hammett conditions while the matched hydroboration with (*d*Ipc)₂BH funnels (*P*)-**1** selectively to intermediate (*S*)-**E-3**. However, this possibility was eliminated by experiments in which single enantiomer allene (*P*)-**1** (≥95% ee) was treated separately with 0.5 equiv of (*d*Ipc)₂BH or (*l*Ipc)₂BH under standard conditions. In all cases the recovered allene (≥95% ee) showed no detectable sign of racemization even when the hydroboration reactions were extended to 12 h at 0°C (see Table S1 in Supporting Information). Therefore, the enantioconvergent hydroboration reaction of racemic **1** does not involve a dynamic kinetic resolution process.

As depicted in Figure 3, we propose that the hydroboration of allene (*P*)-**1** with (*d*Ipc)₂BH occurs on the *re*-face (bottom face, as drawn) of the methyl substituted olefin unit of (*P*)-**1**, *anti* to the Bu₃Sn group to give intermediate (*R*)^{*d*}-**Z-7**. The face selectivity of this step is consistent with the known enantioselectivity of hydroboration of (*Z*)-olefins by (*d*Ipc)₂BH,^{8b,14} as well as by the preference of allene hydroboration to occur *anti* to bulky substituents at the distal position.^{5, 15h, 15i} The hydroboration of (*P*)-**1** by (*d*Ipc)₂BH is thus stereochemically matched. The resulting allylborane (*R*)^{*d*}-**Z-7** can undergo a stereochemically controlled, stereospecific, suprafacial 1,3-borotropic shift,¹⁵ to give (*S*)^{*d*}-**E-3**. As noted in the second equation of Figure 3, hydroboration of (*P*)-**1** on the olefin adjacent to the Bu₃Sn-group inexorably leads, via sigma bond rotations and the indicated stereospecific 1,3-borotropic shifts, to the diastereomeric reagent (*R*)^{*d*}-**E-3** (which will undergo crotylboration of aldehydes to give *ent*-**5**).¹⁶ Thus, the regiochemistry of the enantioselective hydroboration (e.g., right-hand vs. left-hand allenyl double bond) determines the absolute stereochemistry of the 1,1-boryl stannyl stereocenter in intermediate **3**. In order to explain the enantioconvergent hydroboration process, we propose that hydroboration of the enantiomeric allene (*M*)-**1** with (*d*Ipc)₂BH occurs (preferentially) on the *si*-face (top face, as drawn in the third equation of Fig. 3) of the Bu₃Sn-substituted olefin of (*M*)-**1**, *syn* to the methyl group, to provide, directly, reagent (*S*)^{*d*}-**E-3**—the same intermediate as obtained from (*P*)-**1** in the first equation. The sense of hydroboration in the conversion of (*M*)-**1** to (*S*)-**E-3** is again consistent with the enantioselectivity of hydroboration of (*Z*)-olefins by (*d*Ipc)₂BH^{8b,14} but is mismatched in that the hydroboration occurs on the sterically disfavored olefin face *syn* to the distal methyl substituent. A second possible pathway that permits (*S*)-**E-3** to be generated from (*M*)-**1** is shown in the fourth equation of Figure 3. In this case, hydroboration of (*M*)-**1** by (*d*Ipc)₂BH on the Bu₃Sn-substituted olefin *anti* to the distal methyl group, requires that (*d*Ipc)₂BH interact with the allene in a manner opposite to that previously documented^{8b,14} for hydroborations of (*Z*)-alkenes by this reagent (hence, this pathway is stereochemically disfavored on the part of (*d*Ipc)₂BH)). The resulting product, (*R*)^{*d*}-**Z-8** can isomerize to (*S*)-**E-3** by way of (*S*)^{*d*}-**E-9** via two successive sigma bond rotations and suprafacial 1,3-borotropic shifts.¹⁵ These insights indicate that the “top” vs. “bottom” sense of allene hydroboration does not influence the enantiomeric purity of the 1,1-boryl stannyl stereocenter in **3**. However, as is the case with (*P*)-**1**, hydroboration of (*M*)-**1** at the opposite end of the allene, in this case on the methyl-substituted allenyl double bond as shown in the 5th equation of Fig. 3, inevitably produces the diastereomeric reagent, (*R*)^{*d*}-**E-3**. The latter pathway presumably contributes to the reduced enantioselectivity of the crotylboration reactions of the reagent generated from (*M*)-**1** and (*d*Ipc)₂BH.¹⁶

This analysis also provides the basis to rationalize that the dominant pathways that give rise to the minor *syn*-homoallylic alcohols **6** (Table 1) are not enantioconvergent (Fig. 2): **6a** [from (*P*)-**1**] derives from (*S*)^d-**Z-8**, whereas *ent*-**6a** [from (*M*)-**1**] derives at least in part from (*R*)^d-**Z-8**.

The 1,3-borotropic shifts presented in Figure 3 are concerted, stereospecific suprafacial sigmatropic rearrangements that involve the transfer of chirality from one center (in the precursor) to a new center in the product. As such, the stereochemistry at the new center established in the product of each borotropic shift [e.g., the α -boryl- α -stannyl center in (*S*)-**E-3**] is determined by the configuration and enantiomeric purity of the stereocenter in the 1,3-transposed precursor [e.g., (*R*)-**Z-7** in the hydroboration of (*P*)-**1**].^{15f,g} Thus, the success of this method for generation of (*S*)-**E-3** translates directly to the enantioselectivity of the allene hydroboration step using (*d*Ipc)₂BH. This is in contrast to our recent report on the hydroboration of the parent mono-substituted allenylstannane,^{15k} in which the stereochemistry and enantiomeric purity of the α -boryl- α -stannyl center is induced by the diisopinocampheylborane unit during the 1,3-borotropic shift.

To gain further insight into the stereochemistry and mechanism of these allene hydroboration reactions, the hydroboration-crotylation sequence with allenylstannane (*P*)-**1** was conducted using dicyclohexylborane (Cy₂BH). As shown in Figure 4, hydroboration of (*P*)-**1** with Cy₂BH at 0 °C, followed by addition of hydrocinnamaldehyde at -78 °C provided alcohol **5a** in 61% yield and 68% ee along with the *syn*-isomer **6a** in 10% yield and 72% ee. When the hydroboration was carried out at ambient temperature, a ca. 2:1 mixture of **5a** and **6a** was obtained with much lower enantiomeric purity (41% and 46% ee, respectively).

These data indicate that the regioselectivity of the hydroboration of (*P*)-**1** with the achiral borane Cy₂BH is only moderately selective—the enantioselectivity data for the experiment performed at 0 °C suggests that the reaction occurs 80–85% of the time on the right-hand olefin unit of the allene and 15–20% of the time on the left-hand olefin unit—analogous to the first two equations of Fig. 3. The regioselectivity is ca. 70:30 when the hydroboration is performed at ambient temperature. The significant amounts of *syn*-**6a** produced in these experiments suggest that pathway analogous to the 2nd or 4th equations of Figure 3 becomes increasingly accessible especially at higher hydroboration reaction temperatures. (The latter pathway is not stereochemically disfavored because Cy₂B is achiral). Overall, these results reinforce our analysis of the reactions summarized in Figure 3, and demonstrate that the enantiofacial selectivity of the enantiomerically pure borane (*d*Ipc)₂BH plays a crucial role in determining the stereochemical outcome of the enantioselective hydroborations of allenes (*P*)-**1** and (*M*)-**1**.

Other racemic allenes are also substrates for the enantioconvergent hydroboration reaction. As illustrated in Table 2, subjection of racemic allene ($\pm$)-**10** to the standard hydroboration-crotylboration conditions using one equivalent of (*d*Ipc)₂BH and one equivalent of aldehyde provides the (*E*)- δ -stannyl-*anti*-homoallylic alcohols **12a** and **12b** in 71–76% yields with excellent diastereo- and enantioselectivities (>25:1 dr, and 94% ee). Similarly, homoallylic alcohols **12c** and **12d** were obtained in 59–61% yields and 95–97% ee, along with approximately 10% of (*E*)- δ -stannyl-*syn*-homoallylic alcohols **13c** and **13d** from racemic allene ($\pm$)-**11**.¹⁷ The stoichiometries, chemical efficiencies and enantioselectivity of these reactions, as for those in Table 1, are consistent with both enantiomers of racemic allenes ($\pm$)-**10** and ($\pm$)-**11** undergoing enantioconvergent hydroboration reactions with (*d*Ipc)₂BH.

In conclusion, we have documented a remarkable enantioconvergent and highly enantioselective allene hydroboration reaction of the readily available racemic

allenylstannanes ($\pm$)-**1**. The data presented here demonstrate that hydroboration of ($\pm$)-**1** with (d Ipc)₂BH converts both enantiomers, (*P*)-**1** and (*M*)-**1**, into the same intermediate, (*S*)-**E-3**. Subsequent crotylboration of (*S*)-**E-3** with a variety of aldehydes provides (*E*)- δ -stannyl-*anti*-homoallylic alcohols **5** in good yields and high enantioselectivities.

There are a few points worth noting. First, the studies presented here constitute the first examples of the highly enantioselective hydroborations of chiral allenes.⁸ The sense of asymmetric induction is dictated by the enantioselectivity of the chiral, nonracemic borane, (d Ipc)₂BH, which parallels the enantioselectivity of the hydroboration of (*Z*)-alkenes with this reagent.¹⁴ Second, the hydroboration of the two enantiomers of racemic allene **1** proceed with different modes of allene addition (Figure 3), a regiochemical divergence also noted by Bergman.^{4a} The crotylboration reagent (*S*)-**E-3** is then obtained from the initial hydroboration intermediates, (*R*)-**Z-7** and/or (*R*)-**Z-8**, via reversible but stereospecific 1,3-borotropic shifts.¹⁵ *The ability of both allene enantiomers to converge to a single, highly enantioselective reagent (S)-E-3 via this hydroboration sequence represents a remarkable example of the enantioconvergent reaction of the two enantiomers of a racemate.* Therefore, synthesis of enantiomerically pure allenylstannanes (*P*)-**1** or (*M*)-**1** is not necessary to obtain homoallylic alcohols **5** with high enantiomeric excess, nor is it necessary to utilize a kinetic resolution in the hydroboration step. Finally, these studies also represent an important advance in crotylboration chemistry. A problem associated with the vast majority of allyl- and crotylmallation reagents is that the terminal vinyl group in the product often needs to be manipulated by one or more steps to set up additional C–C bond-forming events.^{15k} The highly diastereo- and enantioselective stannyl-crotylboration reaction described here, however, provides *anti*-3-alkyl-homoallylic alcohol products with an (*E*)-vinylstannane that can be used directly in a variety of subsequent C–C bond forming reactions.⁷ Illustrations of this methodology and further application in natural product synthesis will be described in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. The preference for the α -stannyl group to occupy an equatorial position in the transition state overrides the enantioselectivity of the $(\text{Ipc})_2\text{B}$ -unit, as shown in ref. 15k. Thus, the reactions of (*S*)^d-**E-3** and (*R*)^d-**E-3** with aldehydes will lead to enantiomeric homoallylic alcohols **5a** and *ent*-**5a**.
17. The decreased diastereoselectivity with **11** may be due to decreased *si*-face hydroboration of the (*M*) enantiomer of **11**.

Figure 1.
Proposed enantioselective hydroboration of racemic allenylstannane (±)-**1** and subsequent crotylboration reactions.

Figure 2. Proposed reaction pathway and hydroboration-allylboration of single enantiomeric allenes **(P)-1** and **(M)-1**.

Figure 3.

Proposed hydroboration pathways for the two enantiomers of allenylstannane ($\pm$)-**1**. The (*R*)- or (*S*)-descriptor defines the configuration of the allylic borane stereocenter in each intermediate, *E* and *Z* denote the double bond configuration, and the “d” superscript denotes the absolute configuration of the Ipc_2B —unit. Thus, (*S*)^d-*E*-**3** and (*R*)^d-*E*-**3** are diastereomers and not enantiomers.

temperature	% yield	ratio (5a:6a)	% ee (5a)	% ee (6a)
0 °C	71	5:1	68	72
23 °C	77	2:1	41	46

Figure 4.

Hydroboration-allylboration of allenylstannane (*P*)-**1** with Cy_2BH .

Table 1Synthesis of δ -stannyl homoallylic alcohols **5** from $(\pm)$ -**1**^a

entry	RCHO	product ^b	% yield (5) ^{b,c}	% e.e. (5) ^d
1	Ph(CH ₂) ₂ CHO	5a	71	92
2	Ph(CH ₂) ₂ CHO ^d	<i>ent</i> - 5a	67 (84)	88
3	PhCH ₂ CHO	5b	69	92
4	PhCHO	5c	67 (89)	89
5	BnO(CH ₂) ₂ CHO	5d	73	94
6	BnOCH ₂ CHO	5e	70	90
7	PhCH=CHCHO	5f	71 (87)	92
8	CyCHO	5g	64 (81)	93
9	<i>t</i> -Bu ^f	5h	56	90 ^g

^aThe reactions were performed by treating $(\pm)$ -**1** in Et₂O (0.1 M) with (^dIpc)₂BH (1.0 equiv.) at 0 °C followed by addition of RCHO (1.0 equiv.) at −78 °C. The mixture was stirred at −78 °C for 8 h. The reactions were terminated by addition of NaHCO₃ and H₂O₂ at 0 °C prior to product isolation.

^b Isolated yield of **5**. In addition, small amounts of *syn*-homoallylic alcohols **6** (20–30% e.e.) were also obtained in each experiment (3–5%). The diastereoselectivity of these reactions was typically ≥15:1 (ratio of **5** to **6**).

^cYields in parentheses are based on RCHO (0.7 equiv) used as the limiting reagent.

^dDetermined by Mosher ester analysis.

^e(^dIpc)₂BH was used.

^fReaction was warmed to ambient temperature after the addition of *t*-BuCHO.

^gDetermined by Mosher ester analysis of the diol obtained after ozonolysis of **5h**.

Table 2

Enantioconvergent hydroboration and allylboration reactions of racemic allenes ($\pm$)-**10** and ($\pm$)-**11**^a

$\text{Bu}_3\text{Sn}-\text{CH}=\text{CH}-\text{R}'$
 $\text{R}' = \text{Ph}, (\pm)\text{-10}$
 $\text{R}' = \text{Et}, (\pm)\text{-11}$

1) 1 equiv. $(\text{dpc})_2\text{BH}$, 0°C
 2) RCHO , -78°C

Products: **12** and **13**

entry	allene	RCHO	ratio (12:13)	% yield ^b	% ee (12) ^c
1	10	Ph(CH ₂) ₂ CHO	>25:1	71 (12a)	94
2	10	PhCHO	>25:1	76 (12b)	94
3	11	Ph(CH ₂) ₂ CHO	5:1	59 (12c) + 10 (13c)	95
4	11	PhCHO	6:1	61 (12d) + 11 (13d)	97

^aThe reactions were performed by treating ($\pm$)-**10** or ($\pm$)-**11** in Et₂O (0.1 M) with (*d*₁pc)₂BH (1.0 equiv.) at 0°C for 5 h followed by addition of RCHO (1.0 equiv.) at -78°C . The mixture was stirred at -78°C for 8 h. The reactions were terminated by addition of NaHCO₃ and H₂O₂ at 0°C prior to product isolation.

^b Isolated yield of the indicated products (listed in parentheses).

^c Determined by Mosher ester analysis.