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Enantioselective Synthesis of (*E*)-δ-Silyl-*anti*-homoallylic Alcohols via an Enantiodivergent Hydroboration-Crotylboration Reaction of a Racemic Allenylsilane

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ABSTRACT

The enantioselective hydroboration of racemic allenylsilane (±)-4 with (^{d}Ipc)$_2$BH proceeds via enantiodivergent pathways to give vinylborane 11 and crotylborane intermediate (*S*)-*E*-5. Subsequent crotylboration of aldehyde substrates with (*S*)-*E*-5 at −78 °C provides (*E*)-δ-silyl-*anti*-homoallylic alcohols in 71−89% yield and with 93−96% ee.

A prevailing approach to the synthesis of chiral, nonracemic molecules focuses on introducing chirality in reactions of prochiral substrates using chiral reagents or chiral catalysts.[1] Resolution of racemates, however, remains a valuable tool to access highly enantioenriched molecules. Among resolution strategies, kinetic resolution[2] and dynamic kinetic resolution[3] have received considerable attention. The enantiodivergent transformation of a racemate, introduced by Kagan,[4] represents another attractive approach to prepare chiral, nonracemic molecules from racemic starting materials. In contrast to kinetic resolution and dynamic kinetic resolution, the enantiodivergent transformation of a racemate involves distinct reactions of each enantiomer of a racemic mixture with a single enantiomer of a chiral reagent or catalyst that proceed at comparable reaction rates ($K_R \approx K_S$) to generate two products that are not enantiomers (Scheme 1). Several elegant transformations utilizing this strategy have been reported.[5] In our continuing efforts to expand the scope of allene hydroboration for the synthesis of functionalized allylboranes,[6] we describe here an enantiodivergent hydroboration of a racemic allenylsilane with the chiral, nonracemic borane reagent, diisopinocampheylborane [(^{d}Ipc)$_2$BH], by which the two enantiomers of the racemic allene react efficiently to give two different, nonequilibrating intermediates. Subsequent reaction of one of the two

(1) (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis I-III*, Springer: Berlin, 1999. (b) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley/VCH: New York, 2000.

(2) For selected reviews on kinetic resolution: (a) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Allinger, A. L., Eliel, E., Eds.; Wiley: New York, 1988; Vol. 18, p 249. (b) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

(3) (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. (b) Huerta, F. F.; Minidis, A. B. E.; Backvall, J.-E. *Chem. Soc. Rev.* **2001**, 321. (c) Trost, B. M.; Fandrick, D. R. *Aldrichim. Acta* **2007**, *40*, 59. (d) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563.

(4) Kagan, H. B. *Tetrahedron* **2001**, *57*, 2449.

(5) For selected examples: (a) Chen, Y.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302. (b) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 930. (c) Davies, H. M. L.; Walji, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1733. (d) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11492. (e) Wu, B.; Parquette, J. R.; RajanBabu, T. V. *Science* **2009**, *326*, 1662.

(6) (a) Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14602. (b) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14174. (c) Ess, D. H.; Kister, J.; Chen, M.; Roush, W. R. *Org. Lett.* **2009**, *11*, 5538. (d) Chen, M.; Ess, D. H.; Roush, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 7881. (e) Stewart, P.; Chen, M.; Roush, W. R.; Ess, D. *Org. Lett.* **2011**, *13*, 1478. (f) Chen, M.; Roush, W. R. *Org. Lett.* **2011**, *13*, 1992. (g) Chen, M.; Roush, W. R. *Org. Lett.* **2012**, *14*, 1556. (h) Kister, J.; Nuhant, P.; Lira, R.; Sorg, A.; Roush, W. R. *Org. Lett.* **2011**, *13*, 1868. (i) Han, J.-L.; Chen, M.; Roush, W. R. *Org. Lett.* **2012**, *14*, 3028.

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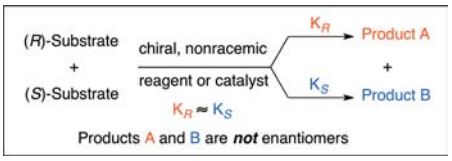
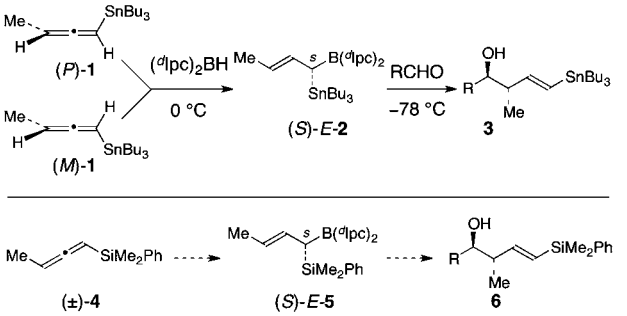
intermediates with aldehydes provides homoallylic alcohols in high yields and with excellent enantioselectivity.

Scheme 1. Enantiodivergent Transformation of a Racemate



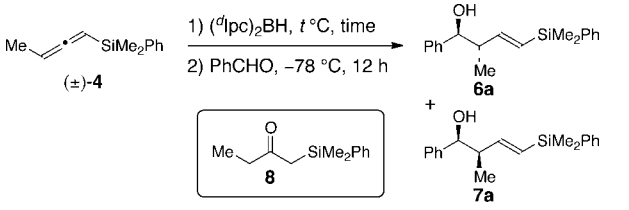
We recently reported an enantioselective synthesis of (*E*)-δ-stannyl-*anti*-homoallylic alcohols from racemic allenylstannane (±)-**1** via an enantioconvergent hydroboration-crotylboration reaction sequence.[7] As illustrated in Scheme 2, hydroboration of racemic allene (±)-**1** with (^{d}Ipc)$_2$BH converted both enantiomers of allenylstannane (±)-**1** into the same crotylborane intermediate, (*S*)-*E*-**2**. Subsequent crotylboration of aldehydes with (*S*)-*E*-**2** gave homoallylic alcohols **3** in good yields and with excellent enantioselectivities. We envisioned that an analogous enantioconvergent reaction sequence might be applicable to an environmentally benign alternative, racemic allenylsilane (±)-**4**,[8] which would then allow the access to highly enantioenriched (*E*)-δ-silyl-*anti*-homoallylic alcohols **6**. The vinylsilane motif of **6** is as useful for many subsequent transformations as is the vinylstannane unit of **3**.

Scheme 2. Proposed Enantioconvergent Reaction of Racemic Allenylsilane (±)-**4**



In initial experiments, treatment of racemic allenylsilane (±)-**4** with (^{d}Ipc)$_2$BH (1 equiv) in toluene at 0 °C for 4 h followed by addition of benzaldehyde (1 equiv) at −78 °C provided a 5:1 mixture of *anti*-homoallylic alcohol **6a** and *syn* isomer **7a** in 41% yield with 76% ee, and 7% yield with 58% ee, respectively (entry 1, Table 1). When the hydroboration was carried out at 40 °C for 2 h and the resulting crotylborane was treated with benzaldehyde at −78 °C, a 2:1 mixture of **6a** (60% ee) and **7a** (50% ee) was obtained in 54% combined yield (entry 2, Table 1). Hydroboration of (±)-**4** at higher temperatures (e.g., 60 °C) followed by crotylboration of benzaldehyde at −78 °C also provided a 2:1 mixture of **6a** and **7a**, but the alcohol products were obtained with much lower enantioselectivity (entry 3, Table 1). When the hydroboration step was performed at −20 °C for 8 h followed by crotylboration of benzaldehyde at −78 °C, a 16:1 mixture of the *anti*-homoallylic alcohol **6a** and *syn* isomer **7a** was obtained in 42% yield and 90% ee (for **6a**, entry 4, Table 1). When the hydroboration of (±)-**4** was carried out at −40 °C for 10 h followed by addition of benzaldehyde at −78 °C, **6a** was obtained as the only product with >95% ee, albeit in diminished yield (31%), owing to incomplete allene hydroboration under these conditions (entry 5, Table 1). Interestingly, a ketone byproduct **8** (*ca.* 40%) was identified from all of these reactions. Additionally, treatment of racemic allenylsilane (±)-**4** with 0.5 equiv of (^{d}Ipc)$_2$BH in toluene at −20 °C for 8 h followed by addition of benzaldehyde (0.45 equiv) at −78 °C provided alcohol **6a** with 92% ee in 58% yield (based on 0.45 equiv aldehyde) (entry 6, Table 1). Once again, ketone **8** was detected. The recovered allene **4** was nearly racemic (< 10% ee).

Table 1. Initial Studies of the Hydroboration-Crotylboration of Racemic Allenylsilane (±)-**4**[a]



entry	t(°C)	time (h)	ds	yield (**6a**)	% ee[b]	yield (**7a**)	% ee[b]
1	0	4	5:1	41%	76	7%	58
2	40	2	2:1	38%	60	16%	50
3	60	2	2:1	36%	28	16%	24
4	−20	8	16:1	42%	90	2%	ND
5	−40	10	>20:1	31%	>95	<1%	ND
6[c]	−20	8	16:1	58%	92	<1%	ND

[a] Reactions were performed by treating (±)-**4** with (^{d}Ipc)$_2$BH (1 equiv, except for entry 6) in toluene followed by the addition of PhCHO (1 equiv) at −78 °C. The mixture was then allowed to stir at −78 °C for 12 h. The reactions were subjected to a standard workup ($NaHCO_3$, H_2O_2) at 0 °C prior to product isolation. [b] Determined by Mosher ester analysis.[9] [c] 0.5 equiv of (^{d}Ipc)$_2$BH was used for the hydroboration and 0.45 equiv of PhCHO was used for the crotylboration. The enantiomeric purity of recovered allene (±)-**4** is less than 10% ee.

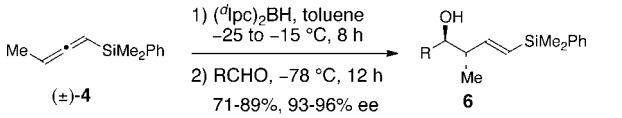
Gratifyingly, when the hydroboration of racemic allene (±)-**4** was performed using (^{d}Ipc)$_2$BH (1 equiv) in toluene at −25 °C with warming of the solution to −15 °C, followed by treatment of the resulting crotylborane (not isolated) with

(7) (a) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2011**, *133*, 5744. For recent synthetic applications of reagent (*S*)-*E*-**2**, see: (b) Sun, H.; Abbott, J. R.; Roush, W. R. *Org. Lett.* **2011**, *13*, 2734. (c) Yin, M.; Roush, W. R. *Tetrahedron* **2011**, *67*, 10274. (d) Chen, M.; Roush, W. R. *Org. Lett.* **2012**, *14*, 426. (e) Chen, M.; Roush, W. R. *Org. Lett.* **2012**, *14*, 1880. (f) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2012**, *134*, 3925. (g) Chen, M.; Roush, W. R. *J. Org. Chem.* **2013**, *78*, 3.

(8) (a) Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630. (b) Fleming, I.; Waterson, D. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1809. (c) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.

benzaldehyde (0.45 equiv) at −78 °C, homoallylic alcohol **6a** was obtained in 85% yield and 95% ee (entry 1, Table 2). Application of this procedure to a variety of other representative achiral aldehydes (entries 3−7, Table 2) provided homoallylic alcohols **6b**−**f** in 71−89% yields (based on the amounts of the aldehydes used in the crotylboration reactions) and with 93−96% ee. The absolute stereochemistry of the secondary hydroxyl groups of alcohols **6a**−**f** was assigned by using the modified Mosher ester analysis.[9] The olefin geometry of homoallylic alcohols **6a**−**f** was assigned as *E* based on ^{1}H NMR analysis (J^E = 18.8−19.2 Hz).

Table 2. Syntheses of (*E*)-δ-Silyl-*anti*-homoallylic Alcohols **6**[a]



entry	RCHO	product	yield[b]	% ee[c]
1	PhCHO	**6a**	85%	95
2[d]	PhCHO	*ent*-**6a**	82%	94
3	PhCH=CHCHO	**6b**	78%	95
4	$Ph(CH_2)_2CHO$	**6c**	89%	93
5	CyCHO	**6d**	71%	94
6	$TBSO(CH_2)_2CHO$	**6e**	72%	95
7	$BnOCH_2CHO$	**6f**	75%	96

[a] Reactions were performed by treating (±)-**4** with $(^d\text{Ipc})_2$BH (1 equiv) in toluene at −25 °C and warming to −15 °C over 8 h followed by the addition of RCHO (0.45 equiv) at −78 °C. The mixture was then allowed to stir at −78 °C for 12 h. The reactions were subjected to a standard workup ($NaHCO_3$, H_2O_2) at 0 °C prior to product isolation. [b] Based on the amount of the aldehydes used in the crotylboration reaction. [c] Determined by Mosher ester analysis.[9] [d] $(^l\text{Ipc})_2$BH was used for the hydroboration reaction.

These results indicate that the hydroboration of the two enantiomers of racemic allenylsilane (±)-**4** with $(^d\text{Ipc})_2$BH follows different pathways compared to those for the racemic allenylstannane (±)-**1**. Based on the efficiency of the reactions of (±)-**4** and the observed formation of ketone **8** (Table 1), we speculated that hydroboration of racemic allenylsilane (±)-**4** with $(^d\text{Ipc})_2$BH proceeds in an enantiodivergent manner. As illustrated in Scheme 3, by analogy to the hydroboration of allenylstannane (±)-**1**,[7a] hydroboration of the (*P*)-enantiomer of allenylsilane **4** with $(^d\text{Ipc})_2$BH is presumed to be a matched case. Hydroboration of (*P*)-**4** with $(^d\text{Ipc})_2$BH should occur on the *re*-face (bottom face, as drawn in the first equation of Scheme 3) of the methyl substituted allene carbon of (*P*)-**4**, *anti* to the $PhMe_2Si$− group to give intermediate (*R*)-*Z*-**9**, which can isomerize to crotylborane (*S*)-*E*-**5** via a reversible boratropic shift. The face selectivity of this hydroboration step is consistent with the known enantioselectivity of hydroboration of (*Z*)-olefins by $(^d\text{Ipc})_2$BH.[7a,10] Hydroboration of (*P*)-**4** on the allenyl unit adjacent to the $PhMe_2Si$-group leads to the diastereomeric reagent (*S*)-*Z*-**10** (bottom face hydroboration, as drawn in the second equation of Scheme 3). Crotylboration of benzaldehyde with (*S*)-*Z*-**10** would give *syn*-homoallylic alcohol **7a**. However, (*S*)-*Z*-**10** can undergo a sequence of reversible 1,3-boratropic shifts to give the diastereomeric reagent (*R*)-*E*-**5**. Crotylboration of benzaldehyde with (*R*)-*E*-**5** would give the enantiomeric alcohol product, *ent*-**6a**. The hydroboration pathway illustrated in the second equation of Scheme 3 is suppressed when the hydroboration is performed at low temperature (e.g., < −20 °C). However, it becomes much more operational at higher hydroboration temperatures, which corresponds to the reduced diastereoselectivity and reduced enantioselectivity of the reactions summarized in entries 1−3 of Table 1.

On the other hand, hydroboration of the other allene enantiomer, (*M*)-**4**, with $(^d\text{Ipc})_2$BH is likely stereochemically mismatched.[7a] The three hydroboration pathways illustrated in the fifth line of Scheme 3 are either mismatched with respect to the enantiofacial selectivity of $(^d\text{Ipc})_2$BH [as determined by the hydroboration of (*Z*)-olefins[7a,10]] or mismatched in that hydroboration occurs on the sterically disfavored face of the allene, *syn* to the $PhMe_2Si$− group. Alternatively, the hydroboration could proceed with opposite regioselectivity, with boron adding to the central allenyl carbon atom of (*M*)-**4**, *anti* to the $PhMe_2Si$ group to give vinylborane **11**, the precursor of ketone **8** (as drawn in the fourth line of Scheme 3). The sense of hydroboration in the conversion of (*M*)-**4** to **11** is consistent with the known enantioselectivity of hydroboration of (*Z*)-olefins by $(^d\text{Ipc})_2$BH,[7a,10] and is also favored in that the hydroboration occurs on the less hindered side of the allene, *anti* to the distal $PhMe_2Si$− group. It appears that the rates of hydroboration of the two enantiomers of the racemic allenylsilane (±)-**4** with $(^d\text{Ipc})_2$BH are comparable (1st and fourth lines of Scheme 3), but also that the hydroboration proceeds with different modes of addition to produce two structurally distinct intermediates, (*S*)-*E*-**5** and **11**, respectively.

To gain support for this analysis, enantiomerically enriched (≥95% ee) allenylsilanes (*P*)-**4** and (*M*)-**4** were prepared for use in hydroboration-crotylboration studies.[8]

(9) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

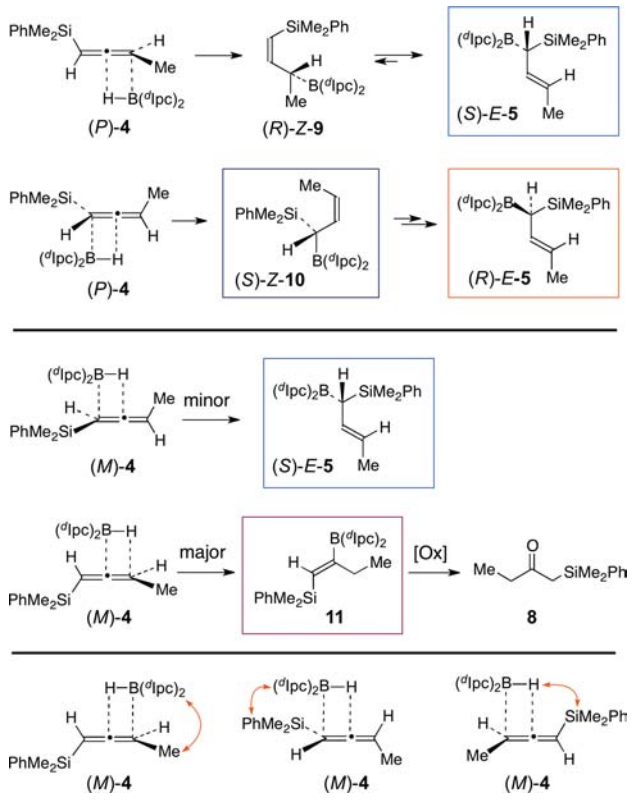
(10) (a) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486. (b) Zweifel, G.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 397.

(11) For early reports on the syntheses of racemic δ-silyl-homoallylic alcohols: (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 3229. (b) Sato, F.; Uchiyama, H.; Iida, K.; Kobayashi, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1983**, 921. (c) Tsai, D. J.; Matteson, D. S. *Organometallics* **1983**, *2*, 236. (d) Fugami, K.; Nakatsukasa, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Chem. Lett.* **1986**, 869. (e) Hodgson, D. M.; Wells, C. *Tetrahedron Lett.* **1992**, *33*, 4761. (f) Shimizu, M.; Kitagawa, H.; Kurahashi, T.; Hiyama, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 4283. (g) Takeda, T.; Wasa, H.; Tsubouchi, A. *Tetrahedron Lett.* **2011**, *52*, 4575.

(12) (a) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857. (b) Fleming, I. *Org. React.* **1989**, *37*, 57. (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

(13) For select reviews of Hiyama coupling: (a) Denmark, S. E.; Liu, J. H.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2978. (b) Denmark, S. E.; Sweis, R. F. In *Metal Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 4. (c) Hiyama, T. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 10 and references cited therein.

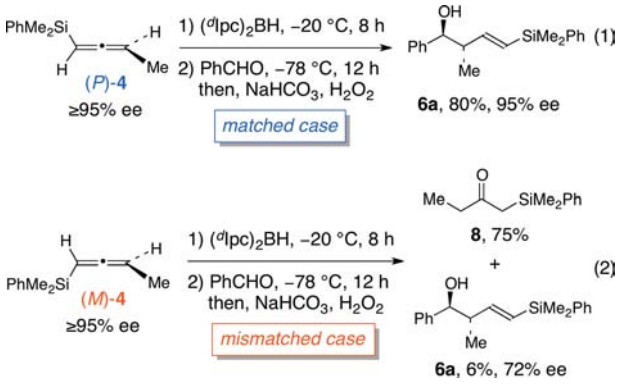
Scheme 3. Proposed Enantioselective and Enantiodivergent Hydroboration-isomerization of the Two Enantiomers of the Racemic Allenylsilane (±)-**4** with (^{d}Ipc)$_2$BH



As illustrated in Scheme 4, hydroboration of (*P*)-**4** with (^{d}Ipc)$_2$BH at −20 °C for 8 h followed by addition of benzaldehyde at −78 °C provided homoallylic alcohol **6a** in 80% yield and 95% ee (eq 1). In contrast, when the identical reaction conditions were used for the hydroboration of the enantiomeric allene (*M*)-**4** with (^{d}Ipc)$_2$BH, ketone **8** was obtained in 75% yield along with 6% of alcohol **6a**, obtained with 72% ee (eq 2). Thus, the enantioconvergent hydroboration process that is dominant in the enantioselective hydroboration of racemic allenylstannane (±)-**1** is only a minor pathway for the enantioselective hydroboration of allenylsilane (*M*)-**4** with (^{d}Ipc)$_2$BH that produces crotylborane (*S*)-*E*-**5** (as drawn in the third line of Scheme 3); the latter reaction is dominated by the enantiodivergent hydroboration pathway that leads to vinylborane **11** (the fourth line of Scheme 3).

Other evidence in support of this analysis was obtained from ^{1}H NMR studies of the hydroboration reactions of (*P*)-**4** or (*M*)-**4** with (^{d}Ipc)$_2$BH. Hydroboration of (*P*)-**4** with (^{d}Ipc)$_2$BH in d_8-toluene produced a major product with two sets of olefinic signals (δ 5.83 ppm, ddq, J = 14.8, 11.2, 1.6 Hz; δ 5.20 ppm, dq, J = 15.2, 6.4 Hz), corresponding to the two (*E*)-olefinic protons of (*S*)-*E*-**5**. Hydroboration of (*M*)-**4** with (^{d}Ipc)$_2$BH, however, produced a major product with a singlet at 5.68 ppm, corresponding to the olefinic proton of vinylborane **11**. Weak olefinic

Scheme 4. Hydroboration-Crotylboration Studies of Single Enantiomeric Allenylsilanes (*P*)-**4** and (*M*)-**4**



signals (< 10%) at 5.83 and 5.20 ppm were also observed. In both experiments, ^{1}H NMR signals corresponding to (*R*)-*Z*-**9** or (*S*)-*Z*-**10** (Scheme 3) were not observed. These data clearly indicate that the enantioselective hydroboration of the two enantiomers of the racemic allenylsilane (±)-**4** proceed with distinct regioselectivities to give different intermediates from each allene enantiomer (*P*)-**4** and (*M*)-**4**. These results are fully consistent with the proposed enantiodivergent hydroboration pathways for racemic allenylsilane (±)-**4** depicted in Scheme 3. Additionally, the efficiency of the reaction as summarized in Table 1 and the enantiomeric purity (< 10% ee) of the recovered allene (entry 6, Table 1) suggest that the rates of the two hydroboration pathways (eqs 1 and 4, Scheme 3) are comparable.

In summary, we have developed an enantioselective synthesis of (*E*)-δ-silyl-*anti*-homoallylic alcohols **6** via an enantiodivergent hydroboration-crotylboration reaction sequence that originates with the hydroboration of racemic allenylsilane (±)-**4** with (^{d}Ipc)$_2$BH. Under optimized conditions, homoallylic alcohols **6**[11] were obtained in high yields and with excellent enantioselectivities from racemic allenylsilane (±)-**4**. Thus, the preparation of enantioenriched allenylsilane is not required to produce highly enantioenriched homoallylic alcohols. In addition, the silyl substituted olefin unit embedded in the homoallylic alcohol products is suitable for use in a variety of subsequent transformations.[12,13] Synthetic applications of this methodology 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.

The authors declare no competing financial interest.