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Diastereo- and Enantioselective Synthesis of (*E*)-2-Methyl-1,2-*syn*- and (*E*)-2-Methyl-1,2-*anti*-3-pentenediols via Allenylboronate Kinetic Resolution with (^{d}Ipc)$_2$BH and Aldehyde Allylboration

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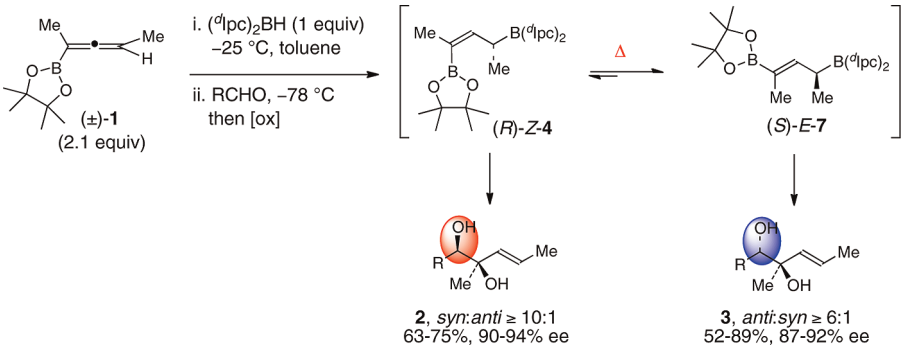
ABSTRACT



Enantioselective hydroboration of racemic allenylboronate (±)-1 with 0.48 equiv of (^{d}Ipc)$_2$BH at −25 °C proceeds with efficient kinetic resolution and provides allylborane (*R*)-*Z*-4. When heated to 95 °C, allylborane (*R*)-*Z*-4 isomerizes to the thermodynamically more stable allylborane isomer (*S*)-*E*-7. Subsequent allylboration of aldehydes with (*R*)-*Z*-4 or (*S*)-*E*-7 at −78 °C followed by oxidative workup provides 1,2-*syn*- or 1,2-*anti*-diols, 2 or 3, respectively, in 87−94% ee.

Asymmetric synthesis of chiral, nonracemic molecules is a major objective of current research in organic chemistry.[1] Because it is generally easier and more cost-effective to synthesize racemic compounds rather than to perform an enantioselective synthesis, resolution of racemates remains a valuable tool to access highly enantiomerically enriched compounds, especially for the synthesis of ligands or reagents needed for enantioselective synthetic methods. Among many available resolution strategies, kinetic resolution of a racemic starting material is a well-established approach.[2] By taking advantage of the different rates of reaction of each enantiomer of a racemate with a chiral, nonracemic reagent or catalyst, kinetic resolution enables partial or complete separation of the racemate and allows access to a variety of highly enantiomerically enriched molecules. As part of ongoing studies to expand the scope of the double allylboration chemistry developed in our laboratory,[3] we describe here the diastereo- and enantioselective synthesis of (*E*)-2-methyl-1,2-*syn*- and (*E*)-2-methyl-1,2-*anti*-3-pentenediols via the efficient kinetic resolution of racemic allenylboronate (±)-**1**[4] with (^{d}Ipc)$_2$BH.

(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) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644. (b) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14174. (c) Kister, J.; Nuhant, P.; Lira, R.; Sorg, A.; Roush, W. R. *Org. Lett.* **2011**, *13*, 1868. (d) Nuhant, P.; Kister, J.; Lira, R.; Sorg, A.; Roush, W. R. *Tetrahedron* **2011**, *67*, 6497. Corrigendum: *Tetrahedron* **2012**, *68*, 774.

(4) Allenylboronates (±)-**1**, (*P*)-**1**, and (*M*)-**1** were prepared according to the procedure reported by Sawamura and co-workers: (a) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774. (b) Chen, M.; Roush, W. R. Manuscript submitted.

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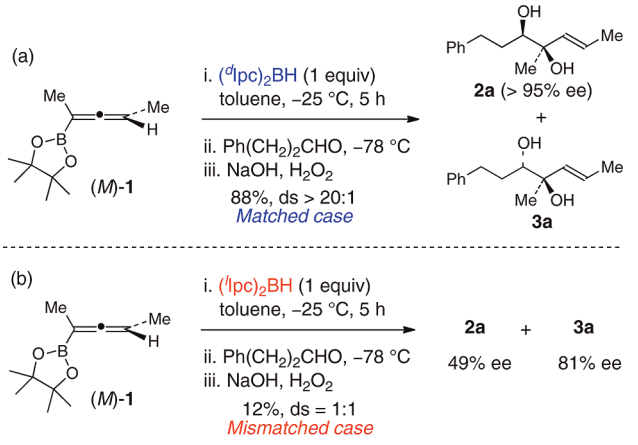
The enantioselective hydroboration of allenes has received remarkably little attention until recently.[5,6] Caserio and Moore documented low levels of enantioselectivity in attempts to accomplish the kinetic resolution of 2,3-pentadiene via hydroboration with diisopinocampheylborane [$(Ipc)_2BH$].[5] More recently, we demonstrated the remarkable, highly enantioselective and enantioconvergent hydroboration of racemic 1-stannyl-1,2-butadiene by using $(^dIpc)_2BH$.[6] The latter study prompted us to explore more broadly the enantioselective hydroboration of racemic allenes.

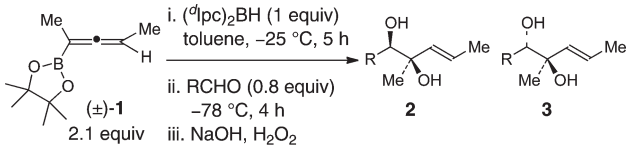
In an initial experiment (Scheme 1a), the enantiomerically enriched allenylboronate (*M*)-**1**[4] (1 equiv, 95% ee) was treated with $(^dIpc)_2BH$ (1 equiv) at −25 °C followed by addition of hydrocinnamaldehyde at −78 °C and subsequent oxidative workup. This reaction provided the 1,2-*syn*-diol **2a** in 88% yield with >20:1 diastereoselectivity and >95% ee. In contrast, when (*M*)-**1** was treated with $(^lIpc)_2BH$ (1 equiv) at −25 °C under otherwise identical conditions, a 1:1 mixture of 1,2-*syn*-diol **2a** (49% ee) and 1,2-*anti*-diol **3a** (81% ee) was obtained in 12% combined yield (Scheme 1b).

Scheme 1. Initial Hydroboration−Allylboration Studies



It is apparent from the data in Scheme 1 that the hydroboration of enantioenriched allene (*M*)-**1** with $(^dIpc)_2BH$ is most probably a matched double asymmetric reaction, while the hydroboration of (*M*)-**1** with $(^lIpc)_2BH$ is likely a mismatched case.[7] It is also apparent that the rates of the hydroboration reactions of allenylboronate (*M*)-**1** with $(^dIpc)_2BH$ and $(^lIpc)_2BH$ are quite different. These data suggested that it might be possible to effect the enantioselective hydroboration of racemic allenylboronate (±)-**1** in a kinetic resolution manifold to access enantioenriched 1,2-*syn*-diols **2**. Gratifyingly, treatment of allene (±)-**1** (2.1 equiv) with $(^dIpc)_2BH$ (1 equiv) at −25 °C for 5 h followed by the addition of hydrocinnamaldehyde (0.8 equiv) at −78 °C provided the 1,2-*syn*-diol **2a** in 75% yield with >20:1 diastereoselectivity and 90% ee after oxidation (entry 1, Table 1). Compared to the results in Scheme 1a, the erosion of the enantioselectivity (90% vs >95% ee) is likely due to involvement of minor amounts of allylboranes deriving from the mismatched hydroboration of allene (*P*)-**1** with $(^dIpc)_2BH$. The conditions developed for the synthesis of **2a** were then applied to a variety of aldehydes; 1,2-*syn*-diols **2b**−**e** were obtained in 63−75% yield with ≥10:1 diastereoselectivity and 90−94% ee (entries 3−6, Table 1). The absolute stereochemistry of the secondary hydroxyl groups of **2a**−**e** was assigned by using the modified Mosher ester analysis.[8] The *syn* stereochemistry of **2a** was assigned by the ^1H NOE studies of a derived acetonide derivative (see Supporting Information (SI)).

Table 1. Synthesis of 2-Methyl-1,2-*syn*-diols **2** via Kinetically Controlled Hydroboration of (±)-**1**[a]



entry	RCHO	product	yield	ds	% ee[b]
1	$Ph(CH_2)_2CHO$	**2a**	75%	>20:1	90
2	$Ph(CH_2)_2CHO$[c]	*ent*-**2a**	82%	>20:1	90
3	$BnO(CH_2)_2CHO$	**2b**	72%	>20:1	90
4	PhCHO	**2c**	63%	>20:1	93
5	CyCHO	**2d**	73%	>20:1	94
6	PhCH=CHCHO	**2e**	74%	10:1	92

[a] Reactions were performed by treating (±)-**1** (0.87 mmol, 2.1 equiv) with $(^dIpc)_2BH$ (1.0 equiv) in toluene at −25 °C for 5 h, followed by addition of RCHO (0.8 equiv) at −78 °C. The mixture was then allowed to stir at −78 °C for 4 h. The reactions were subjected to a standard workup (NaOH, H_2O_2) at 0 °C prior to product isolation. [b] Determined by Mosher ester analysis.[8] [c] $(^lIpc)_2BH$ was used.

Consistent with our previous studies of allene hydroboration,[6,11] the results in Table 1 suggest that hydroboration of allenylboronate (*M*)-**1** with $(^dIpc)_2BH$ at −25 °C proceeds via **TS-1** to produce the γ-boryl-(*Z*)-allylborane (*R*)-*Z*-**4** (Scheme 2). Allylboration of aldehydes with (*R*)-*Z*-**4** at −78 °C then provides boronate intermediate **5** via the chairlike transition state **TS-2**.[9] Compared to dialkylallylborane (*R*)-*Z*-**4**, the remaining allenylboronate (*P*)-**1**

(5) (a) Waters, W. L.; Caserio, M. C. *Tetrahedron Lett.* **1968**, 5233. (b) Moore, W. R.; Anderson, H. W.; Clark, S. D. *J. Am. Chem. Soc.* **1973**, *95*, 835.

(6) (a) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2011**, *133*, 5744. For recent synthetic applications 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.

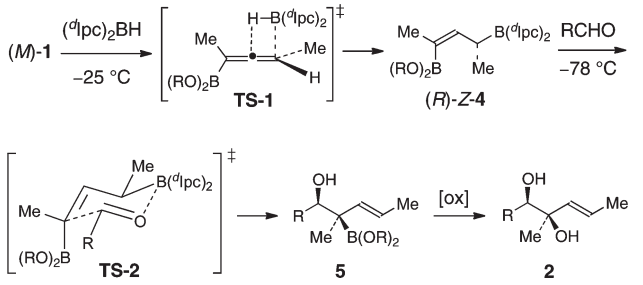
(7) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(8) (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.

(9) (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed. Pergamon Press: Oxford, 1991; Vol. 2, p 1. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; p 299. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (e) Lachance, H.; Hall, D. G. *Org. React.* **2008**, *73*, 1. (f) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774.

and boronate intermediate **5** are much less reactive toward aldehyde addition. Therefore, products deriving from reactions of these intermediates with aldehydes were not observed. Subsequent oxidation of **5** under standard conditions gives the isolated 1,2-*syn*-diols **2**.

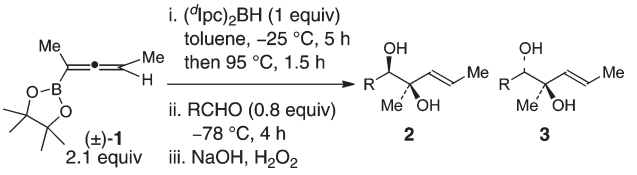
Scheme 2. Proposed Kinetic Hydroboration of (*M*)-**1** and Allylboration of (*R*)-*Z*-**4** with Aldehydes



It has been demonstrated[11a] that the kinetically generated γ-boryl-(*Z*)-allylboranes isomerize to the thermodynamically more stable γ-boryl-(*E*)-allylboranes via reversible 1,3-boratropic shifts.[10,11] Accordingly, we anticipated that allylborane (*S*)-*E*-**7** could be obtained from (*R*)-*Z*-**4** under thermodynamically controlled isomerization conditions, which would permit access to 1,2-*anti*-diols **3**. Indeed, when the hydroboration of allenylboronate (±)-**1** with $(^{d}Ipc)_2BH$ was performed at −25 °C for 5 h followed by heating the solution of (*R*)-*Z*-**4** at 95 °C for 1.5 h and treatment of the resulting allylborane with hydrocinnamaldehyde at −78 °C, a 1:7 mixture of 1,2-*syn*-diol **2a** and 1,2-*anti*-diol **3a** (87% ee) was obtained in 89% combined yield after oxidative workup. Similar results were obtained when the isomerization was carried out at higher temperatures. The hydroboration−isomerization−allylboration reaction sequence was applied to a variety of aldehydes (Table 2); 1,2-*anti*-diols **3b**−**f** were obtained in 52−87% yield with synthetically useful diastereoselectivity (ds ≥ 6:1) and 87−92% ee. The absolute stereochemistry of the secondary hydroxyl group of **3a**−**f** was assigned by using the modified Mosher ester analysis.[8] The *anti* stereochemistry of **3a** was assigned by ^{1}H NOE studies of the derived acetonide derivative (see SI).

As illustrated in Scheme 3, we postulate that kinetic hydroboration of allenylboronate (*M*)-**1** with $(^{d}Ipc)_2BH$ at −25 °C initially generates allylborane (*R*)-*Z*-**4**, which

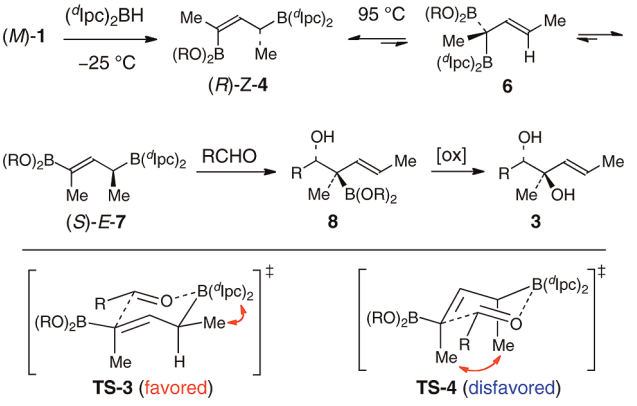
Table 2. Synthesis of 2-Methyl-1,2-*anti*-diols **3** via Thermodynamically Controlled Hydroboration of (±)-**1**[a]



entry	RCHO	product	yield[b]	ds	% ee[c]
1	$Ph(CH_2)_2CHO$	**3a**	89%	1:7	87
2	$BnOCH_2CHO$	**3b**	52%	1:7	90
3	$BnO(CH_2)_2CHO$	**3c**	84%	1:10	92
4	PhCHO	**3d**	80%	1:10	88
5	CyCHO	**3e**	87%	1:6	90
6	PhCH=CHCHO	**3f**	86%	1:15	87

[a] Reactions were performed by treating (±)-**1** (0.44 mmol, 2.1 equiv) with $(^{d}Ipc)_2BH$ (1.0 equiv) in toluene at −25 °C for 5 h and heating at 95 °C for 1.5 h, followed by the addition of RCHO (0.8 equiv) at −78 °C. The mixture was then allowed to stir at −78 °C for 4 h. The reactions were subjected to a standard workup (NaOH, H_2O_2) at 0 °C prior to product isolation. [b] Combined yield of **2** and **3**. [c] Determined by Mosher ester analysis.[8]

Scheme 3. Proposed Thermodynamically Controlled Isomerization and Allylboration of (*S*)-*E*-**7** with Aldehydes



isomerizes at 95 °C to the thermodynamically more stable allylborane (*S*)-*E*-**7** via the intermediacy of the 1,1-diboryl species **6**. Allylboration of aldehydes with (*S*)-*E*-**7** at −78 °C proceeds via the chairlike transition state **TS-3** to give the boronate **8**. Subsequent oxidation of **8** gives 1,2-*anti*-diols **3**. Based on these considerations, it is readily apparent that the absolute configuration of the secondary alcohol of **3** is controlled by the α-boryl stereocenter of (*S*)-*E*-**7**, since the *re*-face addition to the aldehyde in **TS-3** is opposite to that expected based on the known enantioselectivity of the $(^{d}Ipc)_2B$- unit.[12] By comparison, the relative disposition of the aldehyde and the crotyl unit of

(10) (a) Hancock, K. G.; Kramer, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 6463. (b) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9. (c) Henriksen, U.; Snyder, J. P.; Halgren, T. A. *J. Org. Chem.* **1981**, *46*, 3767. (d) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 359. (e) Canales, E.; González, A. Z.; Soderquist, J. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 397. (f) Gonzalez, A. Z.; Roman, J. G.; Alicea, E.; Canales, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 1269.

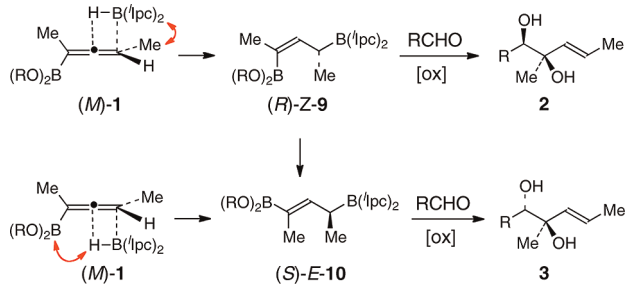
(11) For recent studies from our group, see ref 6 and: (a) Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14602. (b) Ess, D. H.; Kister, J.; Chen, M.; Roush, W. R. *Org. Lett.* **2009**, *11*, 5538. (c) Chen, M.; Ess, D. H.; Roush, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 7881. (d) Stewart, P.; Chen, M.; Roush, W. R.; Ess, D. *Org. Lett.* **2011**, *13*, 1478. (e) Chen, M.; Roush, W. R. *Org. Lett.* **2011**, *13*, 1992.

(12) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

(*S*)-*E*-**7** in the competing transition state **TS-4** is consistent with asymmetric induction derived from the (^{d}Ipc)$_2$B- unit;[12] however, significant A^{1,3} interactions[13] develop between the two methyl groups of the crotyl unit (shown in red in **TS-4**). We conclude that the unfavorable A^{1,3} interaction in **TS-4** is sufficiently large to override the enantioselectivity of the (^{d}Ipc)$_2$B- auxiliary.

The mismatched hydroboration reaction of allenylboronate (*M*)-**1** with (^{l}Ipc)$_2$BH (Scheme 1b) must generate two diastereomeric allylboranes (*R*)-*Z*-**9** and (*S*)-*E*-**10**, in order to explain the formation of a mixture of alcohols **2** and **3** in 12% yield (Scheme 4). The low efficiency is presumably due to the fact that the hydroboration path-

Scheme 4. Mismatched Hydroboration of (*M*)-**1** with (^{l}Ipc)$_2$BH

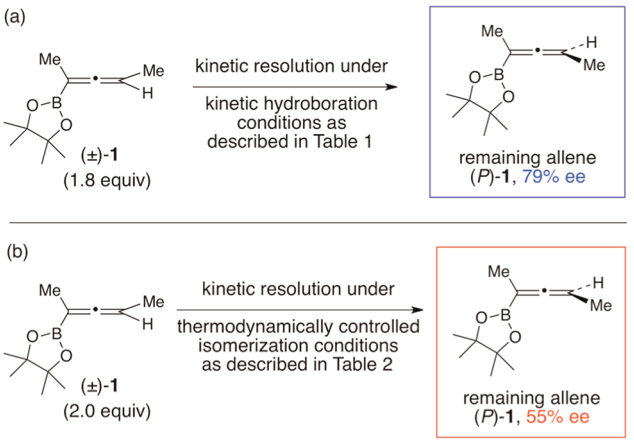


ways involved in these reactions are either mismatched with the known enantioselectivity of (^{l}Ipc)$_2$BH (as inferred from the hydroboration of (*Z*)-olefins)[14] or mismatched with respect to the preference of allene hydroboration to occur *anti* to bulky substituents at the distal position.[10f,11] These stereochemical mismatches provide the basis to rationalize that the rate of mismatched hydroboration of (*M*)-**1** with (^{l}Ipc)$_2$BH at −25 °C is slow. This then enables kinetic resolution to occur in the enantioselective hydroboration of the racemic allenylboronate (±)-**1** using (^{d}Ipc)$_2$BH at this temperature.

To obtain further evidence that a kinetic resolution process is indeed involved in this reaction sequence, additional studies to determine the enantiomeric excess of the remaining allenylboronate (*P*)-**1** were carried out as summarized in Scheme 5. Under kinetic hydroboration conditions using 1.8 equiv of racemic **1** under conditions described in Table 1, the enantiomeric excess of the remaining allenylboronate (*P*)-**1** was determined to be 79% ee (Scheme 5a). When the hydroboration was performed with 2.0 equiv of racemic **1** under the thermodynamically controlled isomerization conditions as described in Table 2 using 2.0 equiv of racemic **1**, the enantiomeric excess of the remaining allenylboronate (*P*)-**1** was 55% ee

(13) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(14) (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.

Scheme 5. Evidence in Support of a Kinetic Resolution of (±)-**1** with (^{d}Ipc)$_2$BH[a]



[a] The enantiomeric purity and absolute configuration (*P*)-**1** was determined following its reaction with hydrocinnamaldehyde, as described in the SI.

(Scheme 5b). The enantiomeric purity of the remaining allene (*P*)-**1** in these experiments was determined by the reaction of this species with hydrocinnamldehyde, as described in the SI. The results presented in Scheme 5, together with the data presented in Tables 1 and 2, support our conclusion that an efficient kinetic resolution indeed occurs when racemic allenylboronate **1** is treated with 0.45−0.55 equiv of (^{d}Ipc)$_2$BH.

In summary, we demonstrate that efficient kinetic resolution of racemic allenylboronate (±)-**1** with 0.48 equiv of (^{d}Ipc)$_2$BH at −25 °C provides the allylborane (*R*)-*Z*-**4**. Subsequent allylboration of aldehydes with (*R*)-*Z*-**4** at −78 °C followed by oxidation gives 1,2-*syn*-diols **2** in 63−82% yield with ≥10:1 diastereoselectivity and 90−94% ee. Allylborane (*R*)-*Z*-**4** isomerizes to the thermodynamically more stable allylborane (*S*)-*E*-**7** when heated to 95 °C. Allylboration of aldehydes with (*S*)-*E*-**7** provides 1,2-*anti*-diols **3** in 52−89% yield with synthetically useful diastereoselectivity (ds ≥6:1) and 87−92% ee. 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.