Published in final edited form as:

Org Lett. 2012 June 15; 14(12): 3028–3031. doi:10.1021/ol3010968.

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*₅IpC)₂BH and Aldehyde Allylboration

Jeng-Liang Han, Ming Chen, and William R. Roush*

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458

Abstract

Enantioselective hydroboration of racemic allenylboronate (*±*)-1 with 0.48 equiv of (*d*₅IpC)₂BH 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 (*±*)-1⁴ with (*d*₅IpC)₂BH.

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,

roush@scripps.edu.

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>.

highly enantioselective and enantioconvergent hydroboration of racemic 1-stannyl-1,2-butadiene by using $(\text{Ipc})_2\text{BH}$.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 $(^d\text{Ipc})_2\text{BH}$ (1 equiv) at $-25\text{ }^\circ\text{C}$ followed by addition of hydrocinnamaldehyde at $-78\text{ }^\circ\text{C}$ 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 $(^l\text{Ipc})_2\text{BH}$ (1 equiv) at $-25\text{ }^\circ\text{C}$ 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).

It is apparent from the data in Scheme 1 that the hydroboration of enantioenriched allene (*M*)-**1** with $(^d\text{Ipc})_2\text{BH}$ is most probably a matched double asymmetric reaction, while the hydroboration of (*M*)-**1** with $(^l\text{Ipc})_2\text{BH}$ is likely a mismatched case.⁷ It is also apparent that the rates of the hydroboration reactions of allenylboronate (*M*)-**1** with $(^d\text{Ipc})_2\text{BH}$ and $(^l\text{Ipc})_2\text{BH}$ are quite different. These data suggested that it might be possible to effect the enantioselective hydroboration of racemic allenylboronate ($\pm$)-**1** in a kinetic resolution manifold to access enantioenriched 1,2-*syn*-diols **2**. Gratifyingly, treatment of allene ($\pm$)-**1** (2.1 equiv) with $(^d\text{Ipc})_2\text{BH}$ (1 equiv) at $-25\text{ }^\circ\text{C}$ for 5 h followed by the addition of hydrocinnamaldehyde (0.8 equiv) at $-78\text{ }^\circ\text{C}$ 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 $(^d\text{Ipc})_2\text{BH}$. 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 SI).

Consistent with our previous studies of allene hydroboration,^{6,11} the results in Table 1 suggest that hydroboration of allenylboronate (*M*)-**1** with $(^d\text{Ipc})_2\text{BH}$ at $-25\text{ }^\circ\text{C}$ proceeds via **TS-1** to produce the γ -boryl-(*Z*)-allylborane (*R*)-**Z-4** (Scheme 2). Allylboration of aldehydes with (*R*)-**Z-4** at $-78\text{ }^\circ\text{C}$ then provides boronate intermediate **5** via the chair-like transition state **TS-2**.⁹ Compared to dialkylallylborane (*R*)-**Z-4**, the remaining allenylboronate (*P*)-**1** 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**.

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-borotropic 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 ($\pm$)-**1** with $(^d\text{Ipc})_2\text{BH}$ was performed at $-25\text{ }^\circ\text{C}$ for 5 h followed by heating the solution of (*S*)-**E-7** at $95\text{ }^\circ\text{C}$ for 1.5 h and treatment of the resulting allylborane with hydrocinnamaldehyde at $-78\text{ }^\circ\text{C}$, 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 ¹H nOe studies of the derived acetone 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 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 chair-like 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 (*S*)-**E-7** in the competing transition state **TS-4** is consistent with asymmetric induction derived from the (*d*Ipc)₂B- unit;¹² however, significant A^{1,3} interactions¹³ 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)₂B- auxiliary.

The mismatched hydroboration reaction of allenylboronate (*M*)-**1** with (*t*Ipc)₂BH (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 pathways involved in these reactions are either mismatched with the known enantioselectivity of (*t*Ipc)₂BH (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 (*t*Ipc)₂BH at –25 °C is slow. This then enables kinetic resolution to occur in the enantioselective hydroboration of the racemic allenylboronate (±)-**1** using (*d*Ipc)₂BH 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, the enantiomeric excess of the remaining allenylboronate (*P*)-**1** was 55% ee (Scheme 5b). The enantiomeric purity of the remaining allene (*P*)-**1** in these experiments was determined by the reaction of this species with hydrocinnamaldehyde, as described in the Supporting Information. 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)₂BH.

In summary, we demonstrate that efficient kinetic resolution of racemic allenylboronate (±)-**1** with 0.48 equiv of (*d*Ipc)₂BH 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support provided by the National Institutes of Health (GM038436) is gratefully acknowledged. We thank Eli Lilly for a predoctoral fellowship to M. Chen and the National Science Council, Taiwan for providing a postdoctoral fellowship to J. L. Han (NSC98-2917-I-564-141).

References

1. (a) Jacobsen, EN.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*. Vol. I–III. Springer; Berlin: 1999. (b) Ojima, I. *Catalytic Asymmetric Synthesis*. 2. Wiley/VCH; New York: 2000.
2. For selected reviews on kinetic resolution: Kagan HB, Fiaud JC, Allinger AL, Eliel E. *Topics in Stereochemistry*. Wiley New York 1988; 18:249. Vedejs E, Jure M. *Angew Chem, Int Ed*. 2005; 44:3974.
3. (a) Flamme EM, Roush WR. *J Am Chem Soc*. 2002; 124:13644. [PubMed: 12431072] (b) Kister J, DeBaillie AC, Lira R, Roush WR. *J Am Chem Soc*. 2009; 131:14174. [PubMed: 19775159] (c) Kister J, Nuhant P, Lira R, Sorg A, Roush WR. *Org Lett*. 2011; 13:1868. [PubMed: 21375316] (d) Nuhant P, Kister J, Lira R, Sorg A, Roush WR. *Tetrahedron*. 2011; 67:6497. Corrigendum: *Tetrahedron* 2012, 68, 774. [PubMed: 21857752]
4. Allenylboronates ($\pm$)-**1**, (P)-**1** and (M)-**1** were prepared according to the procedure reported by Sawamura and coworkers: Ito H, Sasaki Y, Sawamura M. *J Am Chem Soc*. 2008; 130:15774. [PubMed: 18973297] Chen M, Roush WR. manuscript submitted.
5. (a) Waters WL, Caserio MC. *Tetrahedron Lett*. 1968:5233. (b) Moore WR, Anderson HW, Clark SD. *J Am Chem Soc*. 1973; 95:835.
6. Chen M, Roush WR. *J Am Chem Soc*. 2011; 133:5744. For recent synthetic applications see: Sun H, Abbott JR, Roush WR. *Org Lett*. 2011; 13:2734. [PubMed: 21510632] Yin M, Roush WR. *Tetrahedron*. 2011; 67:10274. [PubMed: 22711935] Chen M, Roush WR. *Org Lett*. 2012; 14:426. [PubMed: 22148850] Chen M, Roush WR. *Org Lett*. 2012; 14:1880. [PubMed: 22409510]
7. Masamune S, Choy W, Petersen JS, Sita LR. *Angew Chem, Int Ed Engl*. 1985; 24:1.
8. (a) Dale JA, Mosher HS. *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, WR. *Comprehensive Organic Synthesis*. Trost, BM., editor. Vol. 2. Pergamon Press; Oxford: 1991. p. 1 (b) Yamamoto Y, Asao N. *Chem Rev*. 1993; 93:2207. (c) Denmark, SE.; Almstead, NG. *Modern Carbonyl Chemistry*. Otera, J., editor. Wiley-VCH; Weinheim: 2000. p. 299 (d) Denmark SE, Fu J. *Chem Rev*. 2003; 103:2763. [PubMed: 12914480] (e) Lachance H, Hall DG. *Org React*. 2008; 73:1. (f) Yus M, González-Gómez JC, Foubelo F. *Chem Rev*. 2011; 111:7774. [PubMed: 21923136]
10. (a) Hancock KG, Kramer JD. *J Am Chem Soc*. 1973; 95:6463. (b) Kramer GW, Brown HC. *J Organomet Chem*. 1977; 132:9. (c) Henriksen U, Snyder JP, Halgren TA. *J Org Chem*. 1981; 46:3767. (d) Fang GY, Aggarwal VK. *Angew Chem, Int Ed*. 2007; 46:359. (e) Canales E, González AZ, Soderquist JA. *Angew Chem, Int Ed*. 2007; 46:397. (f) Gonzalez AZ, Roman JG, Alicea E, Canales E, Soderquist JA. *J Am Chem Soc*. 2009; 131:1269. [PubMed: 19117388]
11. For recent studies from our group, see ref. 6 and: Chen M, Handa M, Roush WR. *J Am Chem Soc*. 2009; 131:14602. [PubMed: 19778012] Ess DH, Kister J, Chen M, Roush WR. *Org Lett*. 2009; 11:5538. [PubMed: 19899749] Chen M, Ess DH, Roush WR. *J Am Chem Soc*. 2010; 132:7881. [PubMed: 20496899] Stewart P, Chen M, Roush WR, Ess D. *Org Lett*. 2011; 13:1478. [PubMed: 21323387] Chen M, Roush WR. *Org Lett*. 2011; 13:1992. [PubMed: 21410173]

12. (a) Brown HC, Jadhav PK. J Am Chem Soc. 1983; 105:2092.(b) Brown HC, Bhat KS. J Am Chem Soc. 1986; 108:293.
13. Hoffman RW. Chem Rev. 1989; 89:1841.
14. (a) Brown HC, Zweifel G. J Am Chem Soc. 1961; 83:486.(b) Zweifel G, Brown HC. J Am Chem Soc. 1964; 86:397.

Scheme 1.
Initial Hydroboration-Allylboration Studies.

Scheme 2.

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

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

Scheme 4.
Mismatched Hydroboration of $(M)\text{-1}$ with $(\text{lpc})_2\text{BH}$

Scheme 5.

Evidence in Support of a Kinetic Resolution of ($\pm$)-**1** with (d Ipc) $_2$ BH. The enantiomeric purity and absolute configuration of (*P*)-**1** was determined following its reaction with hydrocinnamaldehyde, as described in the Supporting Information.

Table 1

Synthesis of 2-Methyl-1,2-*syn*-diols **2** via Kinetically Controlled Hydroboration of ($\pm$)-**1**^a

entry	RCHO	product	yield	ds	% ee ^b
1	Ph(CH ₂) ₂ CHO	2a	75%	> 20:1	90
2	Ph(CH ₂) ₂ CHO ^c	<i>ent</i> - 2a	82%	> 20:1	90
3	BnO(CH ₂) ₂ CHO	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

^aReactions were performed by treating ($\pm$)-**1** (0.87mmol, 2.1 equiv) with (*d*₁pc)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, H₂O₂) at 0 °C prior to product isolation.

^bDetermined by Mosher ester analysis.⁸

^c(*d*₁pc)₂BH was used.

Table 2

Synthesis of 2-Methyl-1,2-*anti*-diols **3** via Thermodynamically Controlled Hydroboration of ($\pm$)-**1**^a

entry	RCHO	product	yield ^b	ds	% ee ^c
1	Ph(CH ₂) ₂ CHO	3a	89%	1:7	87
2	BnO ₂ C ₆ H ₄ CHO	3b	52%	1:7	90
3	BnO(C ₆ H ₄) ₂ CHO	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

^aReactions were performed by treating ($\pm$)-**1** (0.44 mmol, 2.1 equiv) with (*d*₁pc)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, H₂O₂) at 0 °C prior to product isolation.

^bcombined yield of **2** and **3**

^cDetermined by Mosher ester analysis.⁸