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Enantioselective Syntheses of *syn*- and *anti*- β -Hydroxyallylsilanes Via Allene Hydroboration-Aldehyde Allylboration Reactions

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Abstract

The kinetic hydroboration of allenylsilane 5 with $(d^5)Ipc_2BH$ at $-40\text{ }^\circ\text{C}$ provides allylborane 9Z with $\geq 12:1$ selectivity. When the hydroboration is performed at temperatures above $-40\text{ }^\circ\text{C}$, 9Z isomerizes to the thermodynamically more stable allylborane 9E with $>20:1$ selectivity. Subsequent treatment of 9Z or 9E with aldehydes at $-78\text{ }^\circ\text{C}$ provides *syn*- or *anti*- β -hydroxyallylsilanes, 7 or 8, respectively.

Syn- and *anti*- β -hydroxyallylsilanes are versatile and important building blocks in organic synthesis,¹ and have been used in syntheses of a variety of natural products.^{2, 3} Consequently, extensive efforts have been devoted to the stereocontrolled synthesis of β -hydroxyallylsilanes.^{4, 5, 6} Aldehyde allylation using γ -silylallylmetal reagents is the most widely adopted procedure for the synthesis of *anti*- β -hydroxyallylsilanes.^{7, 8} Several enantioselective γ -silylallylboron⁵ and titanium^{6a, 6b} reagents have been developed. More recently, an important advance in the catalytic asymmetric synthesis of *anti*- β -hydroxyallylsilanes has also been achieved.^{6c} However, compared to the methods available to prepare *anti*- β -hydroxyallylsilanes, stereoselective synthesis of the diastereomeric *syn*- β -hydroxyallylsilane isomers, and especially enantioselective syntheses of the *syn* isomers,^{5e, 7f} largely remains an unsolved problem due to the facile isomerization of (*Z*)- and (*E*)- γ -silylallylmetal reagents.^{4, 9, 10} Therefore, development of a stereocontrolled method for synthesis of chiral, nonracemic (*Z*)- γ -silylallylmetal reagents and the corresponding *syn*- β -hydroxyallylsilanes via enantioselective aldehyde allylation remains an important goal. Accordingly, we have developed and report herein a simple, one step, diastereo- and enantioselective synthesis of *syn*- β -hydroxyallylsilanes via a highly stereoselective allene hydroboration-aldehyde allylboration reaction sequence.

We recently reported that hydroboration of allenylstannane 1 with diisopinocampheylborane [$(d^5)Ipc_2BH$] initially forms (*Z*)- γ -stannylallylborane 2 as the kinetic product, and that 2

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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>.

isomerizes rapidly through a highly diastereoselective 1,3-borotropic shift to give the thermodynamically stable α -stannylallylborane **3** (eq. 1, Figure 1).^{11d} Subsequent allylboration of aldehydes with **3** gave (*E*)- δ -stannyl-homoallylic alcohols **4** in good yields and excellent enantioselectivities. With the objective to synthesize the potentially environmentally benign (*E*)- δ -silyl-homoallylic alcohols **6**, we decided to study the hydroboration of allenylsilane **5**¹² (eq. 2, Figure 1).

In initial experiments, treatment of allenylsilane **5** with (*d*Ipc)₂BH in toluene at -40 °C for 5 h followed by addition of hydrocinnamaldehyde at -78 °C provided the β -hydroxyallylsilane **7a** in 76% yield, 87% ee, and 14:1 d.s. and not the originally targeted homoallylic alcohol **6** (entry 1, Table 1). After careful comparison of the ¹H-NMR spectra of the reaction product with the data reported in the literature for **7a**,^{5e, 7f} the major product was determined to be the *syn*- β -hydroxyallylsilane diastereomer (**7a**). The minor product is the *anti*- isomer **8a**. Application of this procedure to the (*Z*)- γ -silylallylboration of a variety of other aldehydes (entries 2–6, Table 1) provided *syn*- β -hydroxyallylsilanes **7b–7f** in 67–80% yields with $\geq 12:1$ diastereoselectivities and 84–87% ee. The absolute stereochemistry of the secondary hydroxyl groups of **7a–7f** were assigned by using the modified Mosher ester analysis.¹³ The regioisomeric (*E*)- δ -silyl-homoallylic alcohols **6** were not observed in these experiments.

The diastereoselectivity of this reaction sequence proved to be highly dependent on experimental conditions. When the hydroboration of **5** was performed at -20 °C followed by addition of hydrocinnamaldehyde at -78 °C, a 2:1 mixture of *syn*- and *anti*- β -hydroxyallylsilanes **7a** and **8a** was obtained in 81% yield. Similarly, when the hydroboration step was carried out at -30 °C, a 3:1 mixture of **7a** and **8a** was obtained in 77% yield. Hydroboration of **5** at -40 °C for 12 h also led to the formation of a 5:1 mixture of **7a** and **8a**. When the hydroboration step was carried out at temperatures below -40 °C (e.g., -50 °C for 5h), the subsequent allylboration of hydrocinnamaldehyde at -78 °C provided **7a** as the only product, albeit in diminished yield (24%), owing to incomplete allene hydroboration.

These results indicate that at temperatures below -40 °C the kinetic hydroboration adduct **9Z**, produced in the reaction of **5** with (*d*Ipc)₂BH, *does not* rapidly isomerize to the thermodynamically more stable allylborane **9E** (Scheme 1). While the 1,3-borotropic shifts of the (*d*Ipc)₂B- group is known to be slow for γ , γ -disubstituted allylboranes,^{11b} this kinetically controlled hydroboration of allenylsilane **5** represents a rare case that a (*Z*)- γ -substituted allylborane can be obtained in good *Z/E* ratio via hydroboration of a mono-substituted allene with dialkylboranes such as (Ipc)₂BH. Most (*Z*)-crotylboranes are configurationally unstable at temperatures above -60 °C.^{9b, 11} Allylboranes incorporating the Soderquist borane (10-TMS-9-borabicyclo[3.3.2]decanyl) auxiliary constitute the only general exception.¹⁰

As shown in Scheme 1, the kinetic adduct **9Z** can isomerize to the more stable allylborane **9E** through a reversible 1,3-borotropic shift⁹ at temperatures above -40 °C, presumably via the intermediacy of **10**. Subsequent allylboration of aldehydes with **9E** should allow access to the diastereomeric *anti*- β -hydroxyallylsilanes **8** (which we have previously demonstrated by an alternative method).^{5d} Indeed, when the hydroboration of allenylsilane **5** was performed at -40 °C with the solution being allowed to warm to 0 °C over 5 h, addition of hydrocinnamaldehyde to the resulting allylborane at -78 °C provided *anti*- β -hydroxyallylsilanes **8a** with >20:1 dr (**8a**:**7a**) in 87% yield and 86% ee (Table 2, entry 1). The hydroboration-isomerization-allylboration sequence was applied to a variety of aldehydes (Table 2). In all cases, *anti*- β -hydroxyallylsilanes **8a–f** were obtained in 80–91% yield and 83–87% ee with >20:1 diastereoselectivity.

To gain insight into the proposed reaction pathways, we carried out ^1H NMR studies of the hydroboration of allenylsilane **5** with $(^d\text{Ipc})_2\text{BH}$ at $-20\text{ }^\circ\text{C}$ and $0\text{ }^\circ\text{C}$.¹⁴ As illustrated in Figure 2, hydroboration of **5** with $(^d\text{Ipc})_2\text{BH}$ at $-20\text{ }^\circ\text{C}$ initially generates (*Z*)- γ -silylallylborane **9Z** ($J = 12.8\text{ Hz}$). Allylborane **9Z** isomerizes at $-20\text{ }^\circ\text{C}$ (monitored over 150 min) to (*E*)- γ -silylallylborane **9E** ($J = 18.4\text{ Hz}$). This isomerization is complete in about 60 min when the reaction mixture is allowed to warm to $0\text{ }^\circ\text{C}$. The fleeting intermediate α -silylallylborane **10** was not observed during these experiments.

Strikingly, while the hydroboration of allenylstannane **1** with $(^d\text{Ipc})_2\text{BH}$ provides α -stannylallylborane **3** as the most stable component of the equilibrating mixture,¹⁵ the resting state of the hydroboration of allenylsilane **5** is (*Z*)- or (*E*)- γ -silylallylboranes, **9Z** or **9E**, depending on the temperature of the hydroboration (Figure 3). Although it is well known that both $\text{R}_3\text{Si}-$ and $\text{R}_3\text{Sn}-$ can stabilize a β -carbocation,¹⁶ the capacity of these two groups to stabilize the β -carbocation is clearly different. For the intermediate α -stannylallylborane **3**, the hyperconjugative interaction between the $\text{Bu}_3\text{Sn}-$ group and the boron atom (isoelectronic to a carbocation) must be strong enough to override the steric repulsion between the $\text{Bu}_3\text{Sn}-$ and the $(^d\text{Ipc})_2\text{B}-$ units.^{11e} The relatively long Sn-C bond ($2.20\text{ \AA}$ in **3**)^{11e} might also be beneficial. On the other hand, for the intermediate α -silylallylborane **10**, it appears that the steric repulsion between the $\text{PhMe}_2\text{Si}-$ group and the $(^d\text{Ipc})_2\text{B}-$ unit overrides the hyperconjugative stabilization.^{11e} The relatively shorter Si-C bond (estimated to be $1.85\text{ \AA}$) and the size of $\text{PhMe}_2\text{Si}-$ group presumably contribute to the steric effect, such that **9Z** or **9E** are much more stable than **10**. These conclusions are supported by a recent computational study.^{11e}

In conclusion, we have developed stereoselective syntheses of (*Z*)- and (*E*)- γ -silylallylboranes **9Z** and **9E** via hydroboration of allenylsilane **5** with $(^d\text{Ipc})_2\text{BH}$. At temperatures below $-40\text{ }^\circ\text{C}$, the hydroboration reaction proceeds under kinetic control to give **9Z** with good selectivity. The normally facile 1,3-borotropic shift⁹ is slow at $-40\text{ }^\circ\text{C}$ in the case of **9Z**. However, isomerization readily occurs at temperatures above $-40\text{ }^\circ\text{C}$, and complete isomerization of **9Z** to **9E** is observed at $0\text{ }^\circ\text{C}$. Thus, by appropriate control of the hydroboration conditions, highly diastereo- and enantioselective syntheses of either *syn*- or *anti*- β -hydroxyallylsilanes, **7** or **8**, can be achieved via aldehyde allylboration reactions of **9Z** and **9E**, respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Fleming I. *Org React*. 1989; 37:57.(b) Masse CE, Panek JS. *Chem Rev*. 1995; 95:1293.(c) Fleming I, Barbero A, Walter D. *Chem Rev*. 1997; 97:2063. [PubMed: 11848898] (d) Chabaud L, James P, Landais Y. *Eur J Org Chem*. 2004:3173.(e) Bates RH, Chen M, Roush WR. *Curr Opin Drug Disc Dev*. 2008; 11:778.
2. (a) Sparks MA, Panek JS. *J Org Chem*. 1991; 56:3431.(b) Panek JS, Yang M. *J Am Chem Soc*. 1991; 113:9868.(c) Huang H, Panek JS. *J Am Chem Soc*. 2000; 122:9836.(d) Wu J, Chen Y, Panek JS. *Org Lett*. 2010; 12:2112. [PubMed: 20387893] For recent applications: (e) Zhang Y, Panek JS. *Org Lett*. 2009; 11:3366. [PubMed: 19719185] (f) Wrona IE, Gozman A, Taldone T, Chiosis G, Panek JS. *J Org Chem*. 2010; 75:2820. [PubMed: 20392070]

3. (a) Roberson CW, Woerpel KA. *J Org Chem*. 1999; 64:1434. [PubMed: 11674199] (b) Smitrovich JH, Woerpel KA. *Synthesis*. 2002:2778.(c) Romero A, Woerpel KA. *Org Lett*. 2006; 8:2127. [PubMed: 16671798] (d) Leonard NM, Woerpel KA. *J Org Chem*. 2009; 74:6915. [PubMed: 19678646]
4. (a) Chan TH, Wang D. *Chem Rev*. 1995; 95:1279.(b) Lombardo M, Trombini C. *Chem Rev*. 2007; 107:3843. [PubMed: 17713958] and references cited therein. (c) Yamamoto Y, Saito Y, Maruyama K. *J Chem Soc, Chem Commun*. 1982:1326.(d) Reetz MT, Wenderoth B. *Tetrahedron Lett*. 1982; 23:5259.(e) Ikeda Y, Yamamoto H. *Bull Chem Soc Jpn*. 1986; 59:657.(f) Landais Y, Mahieux C, Schenk K, Surange SS. *J Org Chem*. 2003; 68:2779. [PubMed: 12662052]
5. For examples of enantioselective synthesis of β -hydroxyallylsilanes using γ -silylallylboron reagents: (a) Roush WR, Grover PT, Lin X. *Tetrahedron Lett*. 1990; 31:7563.(b) Barrett AGM, Malecha JW. *J Org Chem*. 1991; 56:5243.(c) Hunt JA, Roush WR. *Tetrahedron Lett*. 1995; 36:501.(d) Roush WR, Pinchuk AN, Micalizio GC. *Tetrahedron Lett*. 2000; 41:9413.(e) Lira R, Roush WR. *Org Lett*. 2007; 9:4315. [PubMed: 17867698] (f) Kister J, DeBaillie AC, Lira R, Roush WR. *J Am Chem Soc*. 2009; 131:14174. [PubMed: 19775159] (g) Binanzer M, Fang GY, Aggarwal VK. *Angew Chem, Int Ed*. 2010; 49:4264.(h) Robinson A, Aggarwal VK. *Angew Chem, Int Ed*. 2010; 49:6673.
6. For other examples of enantioselective synthesis of β -hydroxyallylsilanes using γ -silylallylmetal reagents, (a) Hafner A, Duthaler RO, Marti R, Rihs G, Rothe-Streit P, Schwarzenbach F. *J Am Chem Soc*. 1992; 114:2321.(b) Adam J-M, Fays L, Laguerre M, Ghosez L. *Tetrahedron*. 2004; 60:7325.(c) Han SB, Gao X, Krische MJ. *J Am Chem Soc*. 2010; 132:9153. [PubMed: 20540509]
7. For selected synthetic applications of β -hydroxyallylsilanes: (a) Micalizio GC, Roush WR. *Org Lett*. 2000; 2:461. [PubMed: 10814351] (b) Roush WR, Dilley GJ. *Synlett*. 2001:955.(c) Heo JN, Micalizio GC, Roush WR. *Org Lett*. 2003; 5:1693. [PubMed: 12735754] (d) Shotwell JB, Roush WR. *Org Lett*. 2004; 6:3865. [PubMed: 15469369] (e) Tinsley JM, Roush WR. *J Am Chem Soc*. 2005; 127:10818. [PubMed: 16076173] (f) Tinsley JM, Mertz E, Chong PY, Rarig RAF, Roush WR. *Org Lett*. 2005; 7:4245. [PubMed: 16146398] (g) Mertz E, Tinsley JM, Roush WR. *J Org Chem*. 2005; 70:8035. [PubMed: 16277325] (h) Va P, Roush WR. *J Am Chem Soc*. 2006; 128:15960. [PubMed: 17165709] (i) Huh CW, Roush WR. *Org Lett*. 2008; 10:3371. [PubMed: 18588305]
8. For other selected applications of β -hydroxyallylsilanes: (a) Paterson I, Findlay AD, Anderson EA. *Angew Chem, Int Ed*. 2007; 46:6699.(b) Kishi N, Maeda T, Mikami K, Nakai T. *Tetrahedron*. 1992; 48:4087.(c) Vincent G, Mansfield DJ, Vors JP, Ciufolini MA. *Org Lett*. 2006; 8:2791. [PubMed: 16774258] (d) Beignet J, Jervis PJ, Cox LR. *J Org Chem*. 2008; 73:5462. [PubMed: 18557649] (e) Peroche S, Remuson R, Gelas-Mialhe Y, Gramain JC. *Tetrahedron Lett*. 2001; 42:4617.(f) Ducray R, Ciufolini MA. *Angew Chem, Int Ed*. 2002; 41:4688.
9. (a) Hancock KG, Kramer JD. *J Am Chem Soc*. 1973; 95:6463.(b) Kramer GW, Brown HC. *J Organomet Chem*. 1977; 132:9.(c) Hoffmann RW, Zeiss HJ. *J Org Chem*. 1981; 46:1309.(d) Henriksen U, Snyder JP, Halgren TA. *J Org Chem*. 1981; 46:3767.(e) Brown HC, Jadhav PK, Bhat KS. *J Am Chem Soc*. 1985; 107:2564.(f) Wang KK, Gu YG, Liu C. *J Am Chem Soc*. 1990; 112:4424.(g) Gu YG, Wang KK. *Tetrahedron Lett*. 1991; 32:3029.(h) Brown HC, Narla G. *J Org Chem*. 1995; 60:4686.(i) Narla G, Brown HC. *Tetrahedron Lett*. 1997; 38:219.(j) Fang GY, Aggarwal VK. *Angew Chem, Int Ed*. 2007; 46:359.(k) Canales E, González AZ, Soderquist JA. *Angew Chem, Int Ed*. 2007; 46:397.(l) González AZ, Román JG, Alicea E, Canales E, Soderquist JA. *J Am Chem Soc*. 2009; 131:1269. [PubMed: 19117388]
10. One notable exception to the rapid isomerization of (*Z*)- and (*E*)-crotylborane isomers has been reported by Soderquist: Burgos CH, Canales E, Matos K, Soderquist JA. *J Am Chem Soc*. 2005; 127:8044. [PubMed: 15926828] . Also see ref 5(f).
11. (a) Flamme EM, Roush WR. *J Am Chem Soc*. 2002; 124:13644. [PubMed: 12431072] (b) Chen M, Handa M, Roush WR. *J Am Chem Soc*. 2009; 131:14602. [PubMed: 19778012] (c) Ess DH, Kister J, Chen M, Roush WR. *Org Lett*. 2009; 11:5538. [PubMed: 19899749] (d) Chen M, Ess DH, Roush WR. *J Am Chem Soc*. 2010; 132:7881. [PubMed: 20496899] (e) Stewart P, Chen M, Roush WR, Ess D. *Org Lett*. 2011; 13 in press (ASAP). (f) Kister J, Nuhant P, Lira R, Sorg A, Roush WR. *Org Lett*. 2011; 13 in press (ASAP).
12. (a) Myers AG, Zheng B. *Org Synth*. 1999; 76:178.(b) Li Z, Yang C, Zheng H, Qiu H, Lai G. *J Organomet Chem*. 2008; 693:3771.(c) Fandrick DR, Reeves JT, Tan Z, Lee H, Song JJ, Yee NK, Senanayake CH. *Org Lett*. 2009; 11:5458. [PubMed: 19877630]

13. (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.
14. We were not able to perform NMR studies at -40°C due to the low solubility of $(^d\text{Ipc})_2\text{BH}$ in d_8 -toluene at this temperature. $(^d\text{Ipc})_2\text{BH}$ is not fully soluble even at -20°C , consequently signal resolution is poor at early stages of the reaction.
15. See SI of ref 11(d) for details.
16. (a) Davis DD, Gray CE. J Org Chem. 1970; 35:1303.(b) Jerkunica JM, Traylor TG. J Am Chem Soc. 1971; 93:6278.(c) Wierschke SG, Chandrasekhar J, Jorgensen WL. J Am Chem Soc. 1985; 107:1496.(d) Lambert JB, Wang GT, Finzel RB. J Am Chem Soc. 1987; 109:7838.(e) Lambert JB, Wang GT, Teramura DH. J Org Chem. 1988; 53:5422.

Figure 1. Hydroboration of allenylstannane **1** and planned hydroboration of allenylsilane **2** with $(^d\text{Ipc})_2\text{BH}$.

Figure 2. ^1H NMR studies of hydroboration of allenylsilane **5** in d_8 -toluene. ^1H resonances in the olefinic region (8–5.5 ppm) are displayed in the partial spectra.

Figure 3.
Comparison of the hydroboration-isomerization pathways for allenylstannane **1** and allenylsilane **5**.

Scheme 1.

Proposed Kinetic Hydroboration of **5** and Thermodynamically Controlled Allylborane Isomerization

Table 1

Synthesis of *syn*- β -Hydroxyallylsilanes **7** via Kinetically Controlled Hydroboration of Allenylsilane **5**^a

entry	RCHO	product	yield	d.s.	% ee ^b
1	Ph(CH ₂) ₂ CHO	7a	76%	14:1	87
2	PhCH ₂ CHO	7b	70%	12:1	87
3	PhCHO	7c	80%	18:1	86
4	CyCHO	7d	67%	20:1	84
5	TBSO(CH ₂) ₂ CHO	7e	71%	15:1	84
6	TBSOCH ₂ CHO	7f	72%	14:1	87

^a Reactions were performed by treating **5** with (d₁Ipc)₂BH (0.9 equiv) in toluene at -40 °C for 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 12 h. The reactions were subjected to a standard workup (NaHCO₃, H₂O₂) at 0 °C prior to product isolation.

^b Determined by Mosher ester analysis.¹³

Table 2

Synthesis of *anti*- β -Hydroxyallylsilanes **8** via Allene Hydroboration and Allylborane Isomerization^a

entry	RCHO	product	yield	d.s.	% ee ^b
1	Ph(CH ₂) ₂ CHO	8a	87%	>20:1	86
2	PhCH ₂ CHO	8b	90%	>20:1	87
3	PhCHO	8c	83%	>20:1	83
4	CyCHO	8d	80%	>20:1	86
5	TBDPSO(CH ₂) ₂ CHO	8e	91%	>20:1	85
6	TBSOCH ₂ CHO	8f	87%	>20:1	84

^a Reactions were performed by treating **5** with (^dIpc)₂BH (0.9 equiv) in toluene at -40 °C and warmed to 0 °C over 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 12 h. The reactions were subjected to a standard workup (NaHCO₃, H₂O₂) at 0 °C prior to product isolation.

^b Determined by Mosher ester analysis.¹³