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

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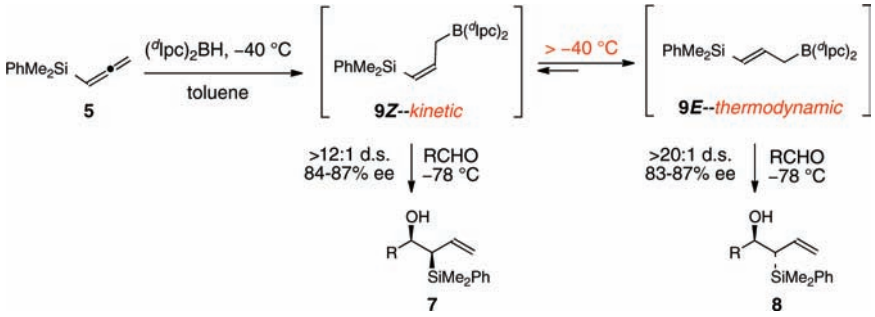
ABSTRACT



The kinetic hydroboration of allenylsilane 5 with $(^d\text{Ipc})_2$BH at −40 °C provides allylborane 9*Z* with ≥12:1 selectivity. When the hydroboration is performed at temperatures above −40 °C, 9*Z* isomerizes to the thermodynamically more stable allylborane 9*E* with >20:1 selectivity. Subsequent treatment of 9*Z* or 9*E* with aldehydes at −78 °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.[4−6] Aldehyde allylation using γ-silylallylmetal reagents is the most widely adopted procedure for the synthesis of *anti*-β-hydroxyallylsilanes.[7,8] Several enantioselective γ-silylallylboron[5] and titanium[6a,b] 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,

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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}Ipc)$_2$BH] initially forms (*Z*)-γ-stannylallylborane **2** as the kinetic product, and that **2** isomerizes rapidly through a highly diastereoselective 1,3-boratropic 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).

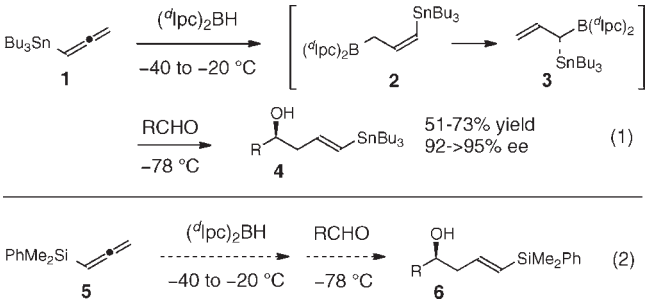

Figure 1. Hydroboration of allenylstannane **1** and planned hydroboration of allenylsilane **2** with (^{d}Ipc)$_2$BH.

In initial experiments, treatment of allenylsilane **5** with (^{d}Ipc)$_2$BH 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 ^{1}H 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 ≥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 5 h), 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 **9*Z***, produced in the reaction of **5** with (^{d}Ipc)$_2$BH, *does not* rapidly isomerize to the thermodynamically more stable allylborane **9*E*** (Scheme 1). While the 1,3-boratropic shifts of the (^{d}Ipc)$_2$B− 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

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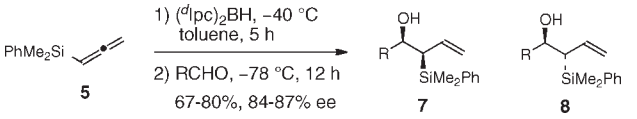
Table 1. Synthesis of *syn*-β-Hydroxyallylsilanes **7** via Kinetically Controlled Hydroboration of Allenylsilane **5**[a]



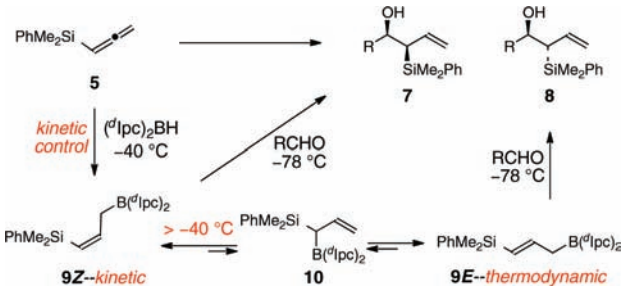
5 7 8

entry	RCHO	product	yield	d.s.	% ee[b]
1	$Ph(CH_2)_2CHO$	**7a**	76%	14:1	87
2	$PhCH_2CHO$	**7b**	70%	12:1	87
3	PhCHO	**7c**	80%	18:1	86
4	CyCHO	**7d**	67%	20:1	84
5	$TBSO(CH_2)_2CHO$	**7e**	71%	15:1	84
6	$TBSOCH_2CHO$	**7f**	72%	14:1	87

[a] Reactions were performed by treating **5** with $(^dIpc)_2BH$ (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 ($NaHCO_3$, H_2O_2) at 0 °C prior to product isolation. [b] Determined by Mosher ester analysis.[13]

can be obtained in good Z/E ratio via hydroboration of a monosubstituted allene with dialkylboranes such as $(Ipc)_2BH$. Most (Z)-crotylboranes are configurationally unstable at temperatures above −60 °C.[9b] Allylboranes incorporating the Soderquist borane (10-TMS-9-borabicyclo[3.3.2]decanyl) auxiliary constitute the only general exception.[10]

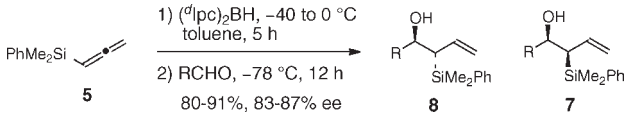
Scheme 1. Proposed Kinetic Hydroboration of **5** and Thermodynamically Controlled Allylborane Isomerization



As shown in Scheme 1, the kinetic adduct **9*Z*** can isomerize to the more stable allylborane **9*E*** through a reversible 1,3-boratropic shift[9,11] 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 $(^dIpc)_2BH$ at −20 and 0 °C.[14] As

Table 2. Synthesis of *anti*-β-Hydroxyallylsilanes **8** via Allene Hydroboration and Allylborane Isomerization[a]



5 8 7

entry	RCHO	product	yield	d.s.	% ee[b]
1	$Ph(CH_2)_2CHO$	**8a**	87%	>20:1	86
2	$PhCH_2CHO$	**8b**	90%	>20:1	87
3	PhCHO	**8c**	83%	>20:1	83
4	CyCHO	**8d**	80%	>20:1	86
5	$TBDPSO(CH_2)_2CHO$	**8e**	91%	>20:1	85
6	$TBSOCH_2CHO$	**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 ($NaHCO_3$, H_2O_2) at 0 °C prior to product isolation. [b] Determined by Mosher ester analysis.[13]

illustrated in Figure 2, hydroboration of **5** with $(^dIpc)_2BH$ at −20 °C initially generates (Z)-γ-silylallylborane **9*Z*** (J = 12.8 Hz). Allylborane **9*Z*** isomerizes at −20 °C (monitored over 150 min) to (E)-γ-silylallylborane **9*E*** (J = 18.4 Hz). This isomerization is complete in about 60 min when the reaction mixture is allowed to warm to 0 °C. The fleeting intermediate α-silylallylborane **10** was not observed during these experiments.

Strikingly, while the hydroboration of allenylstannane **1** with $(^dIpc)_2BH$ 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, **9*Z*** or **9*E***, depending on the temperature of the hydroboration (Figure 3). Although it is well-known that both R_3Si- and R_3Sn- 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 Bu_3Sn- group and the boron

(14) We were not able to perform NMR studies at −40 °C due to the low solubility of $(^dIpc)_2BH$ in d_8-toluene at this temperature. $(^dIpc)_2BH$ is not fully soluble even at −20 °C, consequently signal resolution is poor at early stages of the reaction.

(15) See SI1 of ref 11d for details.

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atom (isoelectronic to a carbocation) must be strong enough to override the steric repulsion between the Bu_3Sn- and the $(^dIpc)_2B-$ units.[11e] The relatively long Sn−C bond (2.20 Å 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 $PhMe_2Si-$ group and the $(^dIpc)_2B-$ unit overrides the hyperconjugative stabilization.[11e] The relatively shorter Si−C bond (estimated to be 1.85 Å) and the size of $PhMe_2Si-$ group presumably contribute to the steric effect, such that **9*Z*** or **9*E*** are much more stable than **10**. These conclusions are supported by a recent computational study.[11e]

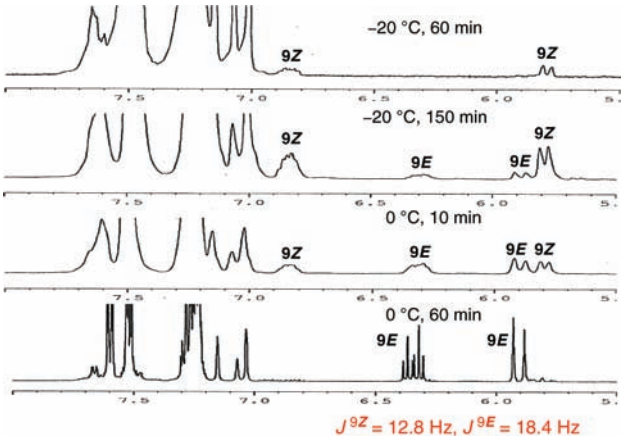

Figure 2. ^1H NMR studies of hydroboration of allenylsilane **5** in d_8-toluene. ^1H resonances in the olefinic region (8−5.5 ppm) are displayed in the partial spectra.

In conclusion, we have developed stereoselective syntheses of (*Z*)- and (*E*)-γ-silylallylboranes **9*Z*** and **9*E*** via hydroboration of allenylsilane **5** with $(^dIpc)_2BH$. At temperatures below −40 °C, the hydroboration reaction proceeds under kinetic control to give **9*Z*** with good selectivity. The normally facile 1,3-boratropic shift[9] is slow at −40 °C in the case of **9*Z***. However, isomerization readily occurs at temperatures above −40 °C, and complete isomerization of **9*Z*** to **9*E*** is observed at 0 °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 reaactions of **9*Z*** and **9*E***, respectively.

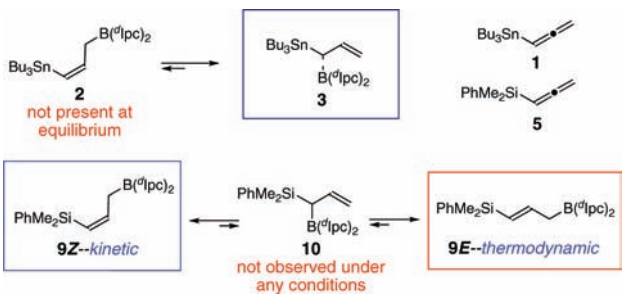

Figure 3. Comparison of the hydroboration-isomerization pathways for allenylstannane **1** and allenylsilane **5**.

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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.