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Enantio- and Diastereoselective Synthesis of *syn*-β-Hydroxyallylsilanes via a Chiral (*Z*)-γ-Silylallylboronate

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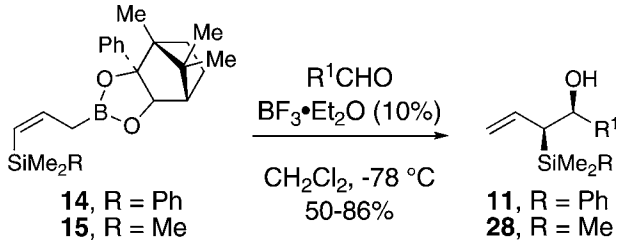
ABSTRACT



***syn*-β-Hydroxyallylsilanes of general structure 11 and 28 are prepared in 50–86% yield and 91–95% ee (for aliphatic aldehydes; 50% ee for benzaldehyde) via the BF_3·Et_2O-promoted γ-silylallylboration reactions, using reagents 14 and 15.**

The Lewis acid-promoted [3+2]-annulation reaction of chiral allylsilanes and carbonyl electrophiles is an important method for the synthesis of substituted tetrahydrofurans.[1−7] Previous studies in our laboratory have demonstrated that β-alkoxyallylsilanes **1** undergo highly diastereoselective [3+2]-annulation reactions with aldehydes and certain highly activated ketones, with the stereochemical outcome depending on the nature of the Lewis acid−carbonyl electrophile combination (Figure 1). Under nonchelate controlled conditions (BF_3·OEt_2 catalysis), the 2,5-*cis*-tetrahydrofurans **4** are obtained with ≥20:1 selectivity, whereas when a chelating Lewis acid such as $SnCl_4$ is employed (in concert with a carbonyl electrophile that is capable of supporting a chelate with the Lewis acid), the 2,5-*trans*-tetrahydrofurans **5** are obtained, also with ≥20:1 selectivity.[3] We have employed this technology in the total syntheses of asimicin,[8] bullaticin,[9] and amphidinolide E,[10−12] as well as in approaches to the synthesis of pectenotoxin-2,[13] amphidinolides C and F,[14] and angelmicin B.[15]

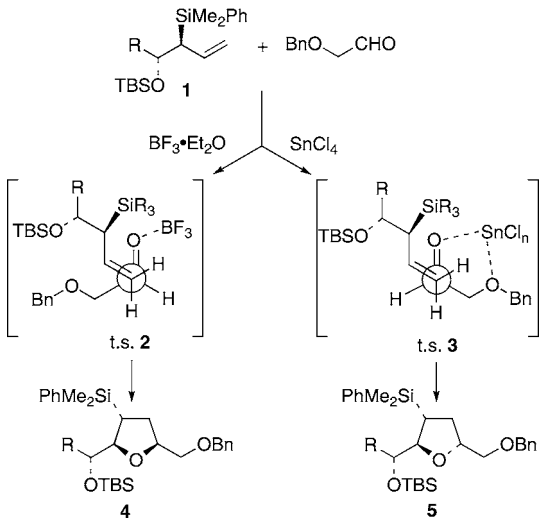


Figure 1. [3+2]-Annulation reactions of *anti*-β-alkoxyallylsilanes.

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anti-β-Alkoxyallylsilanes **1** are synthesized with 80−92% ee via the asymmetric allylboration reactions of aldehydes with chiral allylboronate **6** or allylboronate **7**.[16,17] However, attempts to extend this methodology to the enantioselective synthesis of the *syn*-β-alkoxyallylsilanes **11**, needed for the enantioselective synthesis of substituted tetrahydrofurans **12** and **13**, have proven to be unexpectedly challenging. The reactions of aldehydes with the tartrate ester modifed (*Z*)-γ-silylallylboronate **8** proceed with only 50−60% ee,[9] and attempts to generate **9** via hydroboration of silylallene **10** with $(Ipc)_2BH$ at low temperature give the (*E*)-γ-silylallylborane **7** with excellent selectivity, presumably via thermodynamically controlled isomerization of the kinetically formed (*Z*)-γ-silylallylborane.[18,19]

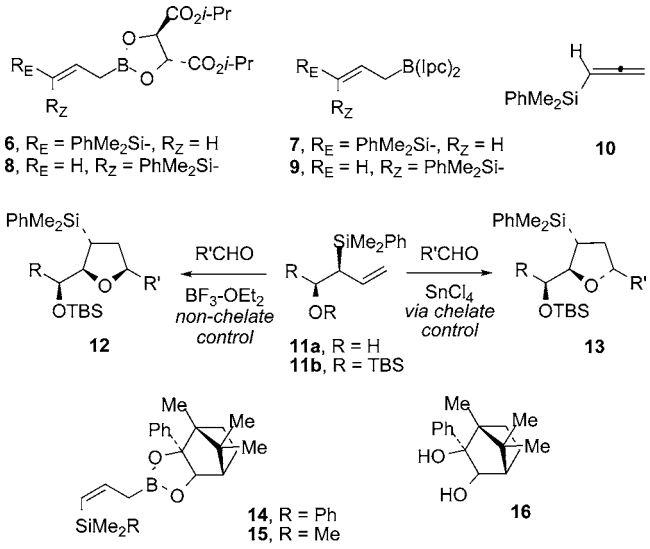

Figure 2. (*Z*)-γ-Silylallylborating agents for the enantioselective synthesis of *syn*-β-alkoxyallylsilanes **11**.

We report herein the synthesis and allylborations of the chiral (*Z*)-γ-silylallylboronates **14** and **15**, which undergo Lewis acid accelerated reactions with aldehydes at −78 °C and give the targeted *syn*-β-hydroxyallylsilanes **11a** with excellent enantioselectivity (typically >90% ee). This solution to the problem posed by the synthesis of **11a** was stimulated by recent reports by Ishiyama[20] and Hall[21] that use of catalytic amounts of Lewis acid greatly enhances the rates of reactions of allylboronates and aldehydes. Hall also demonstrated that under Lewis acid-promoted reaction conditions, crotylborations of aliphatic aldehydes using reagents incorporating Hoffmann's chiral auxiliary **16**[22] proceed with excellent enantioselectivity.[23]

(*Z*)-γ-Silylallylboronates **14** and **15** seemed ideally suited for synthesis via Matteson's α-halomethylboronate alkylation chemistry.[24,25] Thus, transesterification of the iodomethylboronic ester **17** with diol **16**[22,26] provided the chiral iodomethylboronic ester **18** (Figure 3). However, in spite of

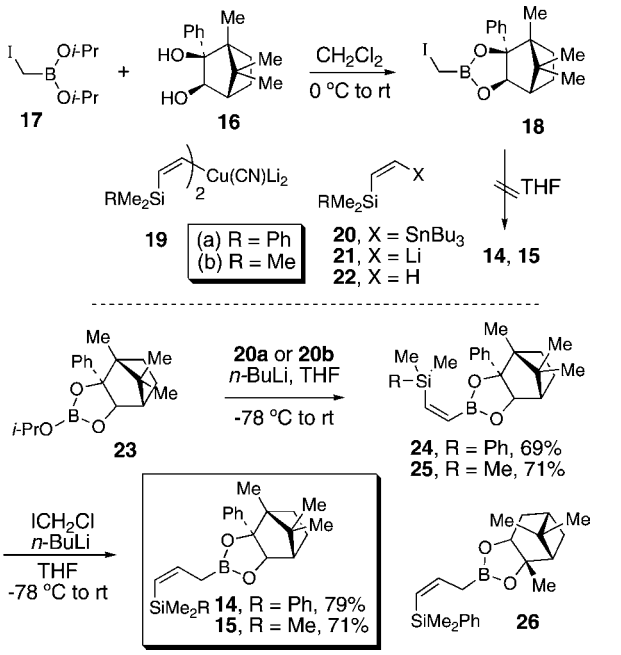

Figure 3. Synthesis of (*Z*)-γ-silylallylborates **14**, **15**, and **26**.

considerable experimentation, treatment of **18** with the cyanocuprate **19a** (which we previously employed in the synthesis of **8**)[9] or with the (*Z*)-silylvinyllithium **21** (generated by treatment of vinylstannane **20**[27] with BuLi in THF at −78 °C) did not provide the targeted silylallylboronates **14** or **15**; only vinylsilane **22** resulting from protonation of **19a** or **21** was obtained.

Successful syntheses of **14** and **15** were ultimately achieved by addition of chloromethyllithium[28] to vinylboronates **24** and **25**.[29] The (*Z*)-silylvinylbororonates **24** and **25** were prepared in 69−71% yields by treatment of boronate

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(26) Diol **16** was synthesized by a four-step sequence recently developed by Hall: Lachance, H.; St-Onge, M.; Hall, D. G. *J. Org. Chem.* **2005**, *70*, 4180.
(27) Marakami, M.; Matsuda, T.; Itami, K.; Ashida, S.; Terayama, M. *Synthesis* **2004**, *9*, 1522.
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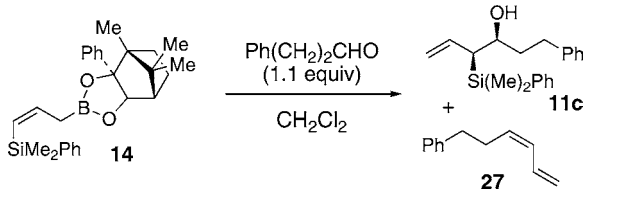
23 with the vinyllithiums **21a** or **21b** (which were generated by treatment of vinylstannanes **20a** and **20b**, respectively, with *n*-BuLi in THF at −78 °C). Dropwise addition of 1.1 equiv of *n*-BuLi to a −78 °C mixture of 1.5 equiv of chloroiodomethane and the corresponding vinyl boronate ester (**24** or **25**) in THF provided the targeted (*Z*)-γ-silylallylboronates **14** and **15** in 71−79% yield after chromatographic purification. Reagents **14** and **15** are stable to chromatography and could be stored at −20 °C for long periods of time without any apparent decomposition.[30] An analogous sequence was employed for the synthesis of the related pinanediol-derived (*Z*)-γ-silylallylboronate **26**.

Table 1. Optimization of Conditions for Allylboration Reactions of **14**



entry	reaction conditions	product(s) (%)[a]
1	$Sc(OTf)_3$ (10 mol %), 32 h, −78 °C	no reaction[b]
2	$Sc(OTf)_3$ (10 mol %), 48 h, −50 °C	no reaction[b]
3	BF_3•OEt_2 (100 mol %), 14 h, −78 °C	**27** (63%)
4	BF_3•OEt_2 (100 mol %), 1 h, −78 °C	**27** (20%) + **11c** (30%)
5	BF_3•OEt_2 (10 mol %), 3 h, −78 °C	**11c** (85%)

[a] Yield of isolated product(s). [b] Based on ^{1}H NMR analysis of the crude reaction mixture.

Table 1 summarizes the definition of conditions for the Lewis acid-promoted allylboration reactions of the (*Z*)-γ-silylallylboronate **14**. At the outset, we were concerned that the product allylsilane **11c** might be unstable with respect to Lewis acid-promoted Peterson elimination under the reaction conditions,[31] or that **11c** might react further with a second equivalent of aldehyde to give dihydropyran products.[32,33] While the latter pathway was not observed, the Petersen elimination of **11c** was a serious problem under certain conditions, especially when BF_3•OEt_2 was used to promote the allylboration reaction (Table 1). No reaction was observed when a mixture of **14** and hydrocinnamaldehyde (1.1 equiv) were treated with 10 mol % of $Sc(OTf)_3$ even up to −50 °C for extended time periods (entries 1 and 2). When the reaction was performed with stoichiometric BF_3•OEt_2 for 14 h, the only isolated product was diene **27** (63% yield, entry 3). However, at shorter reaction times (entry 4), and especially when 10 mol % of BF_3•OEt_2 was used as catalyst, the Petersen elimination pathway was suppressed and the *syn*-β-hydroxyallylsilane **11c** was obtained in 85% yield (entry 5). Also noteworthy is that **11c** was obtained with 95% ee as judged by Mosher esters analysis,[34] and the diastereomeric *anti*-β-hydroxyallylsilane was not detected (≥98:2 dr).

Results of the BF_3•OEt_2-promoted allylborations of representative aldehydes are summarized in Figure 4. The

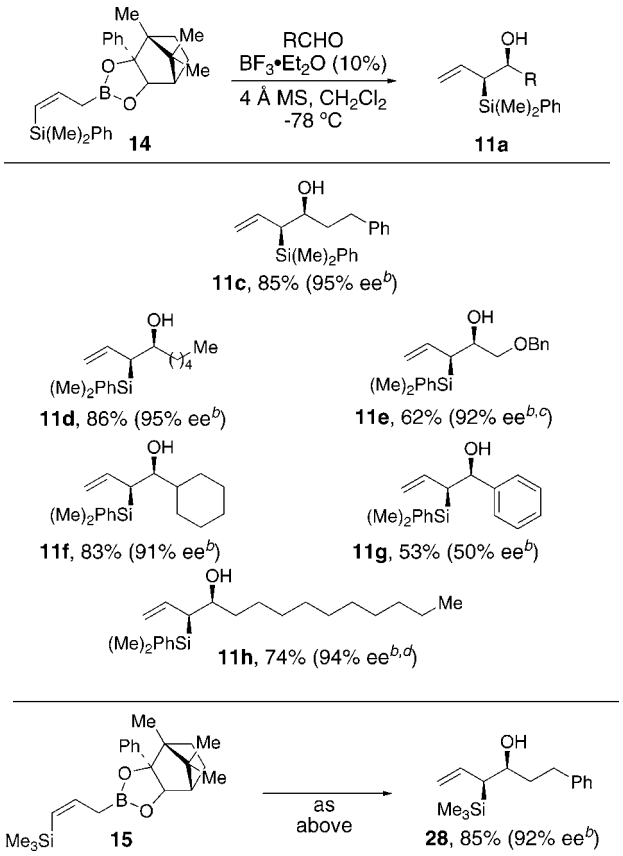


Figure 4. Enantio- and diastereosynthesis of *syn*-β-hydroxyallylsilanes via BF_3•OEt_2[a] catalyzed allylboration of aldehydes with (*Z*)-γ-silylallylboronates **14** and **15**. Footnotes: (*a*) 10 mol % BF_3•OEt_2 was employed unless otherwise indicated; (*b*) determined by Mosher esters analysis; (c) 15% of **14** was also recovered; (*d*) 20 mol % of BF_3•OEt_2 was employed.

reactions with aliphatic aldehydes consistently provided the *syn*-β-hydroxyallylsilane products **11c**, **11d**, **11e**, **11f**, and **11h** with 91−95% ee (Mosher ester analysis).[34] Similar results were obtained in the synthesis of **28** (92% ee) from the trimethylsilyl-substituted allylboronate **15**. We previously had been able to achieve only 50−64% ee for the γ-silylallylboration of aldehydes by using reagent **8**.[9] The only outlier from the trend of superior enantioselectivity for the BF_3•OEt_2-promoted allylborations with **14** (and **15**) is the allylboration of benzaldehyde, which provided **11g** with only 50% ee. All attempts to improve this result by variation of

(29) While our work was in progress Hall reported the synthesis of a type (III) bis-metal allyl reagent by a similar homologation process: Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070.

(30) ^{1}H NMR analysis of samples of **14** and **15** stored at −20 °C for 8 weeks showed no signs of decomposition and/or olefin isomerization.

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reaction conditions were unsuccessful. Hall has also found that aromatic aldehydes were poor substrates for the Lewis acid-promoted crotylboration reaction.[23]

Surprisingly, however, attempts to use the pinanediol derived reagent **26** in Lewis acid-promoted allylboration reactions were completely unsuccessful, with no reaction being observed under a variety of conditions (Figure 5).

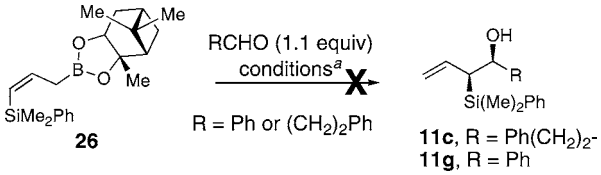

Figure 5. Attempted allylboration reactions with pinanediol derived reagent **26**. Footnote: (*a*) conditions employed in Table 1 failed to provide any of the allylboration product as judged by ^{1}H NMR analysis of the crude reaction mixtures.

Finally, double asymmetric γ-silylallylboration reactions of **29** and *ent*-**29** with **14** are summarized in Figure 6. These reactions were much slower than those summarized in Figure 4, and required 2 to 4 days with 30% $BF_3{\cdot}OEt_2$ at -55 °C. That the diastereoselectivity of these two transformations was only 6−7:1, and given the very long reaction times, suggests that some racemization of **29** (or *ent*-**29**) may have occurred under the reaction conditions, thereby limiting the overall reaction diastereoselectivity.

In summary, we have developed a convenient method for synthesis of *syn*-β-hydroxyallylsilanes of general structure

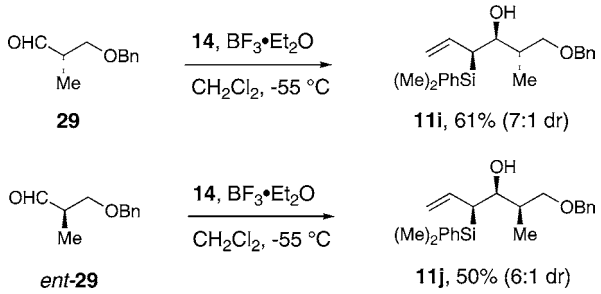

Figure 6. Double asymmetric *syn*-γ-silylallylboration reactions of **14**.

11 and **28** via the $BF_3{\cdot}OEt_2$-promoted γ-silylallylborations of aliphatic aldehydes with reagents **14** and **15**. Aliphatic aldehydes undergo the γ-silylallylboration reaction with 91−95% ee, whereas the selectivity with benzaldehyde is much lower (50% ee). Utilization of this technology in several ongoing synthesis projects will be reported in due course.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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