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Enantioselective Synthesis of (*Z*)-2-Methyl-1,5-*anti*- and (*E*)-2-Methyl-1,5-*anti*-Pentenediols Via an Allene Hydroboration-Double Allylboration Reaction Sequence

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Abstract

Kinetic controlled hydroboration of allenylboronate **5** followed by double allylboration with resulting allylborane (*Z*)-**7** gave (*Z*)-2-methyl-1,5-*anti*-pentenediols **6** in good yield and high enantioselectivity in the presence of 10% BF_3•OEt_2 as the catalyst in the second allylboration step. Under thermodynamically controlled isomerization conditions, (*Z*)-**7** can readily isomerize to (*E*)-**7**. Double allylboration of representative aldehydes with allylborane (*E*)-**7** gave (*E*)-2-methyl-1,5-*anti*-pentenediols **4** in good yield and high enantioselectivity without requiring use of the BF_3•OEt_2 catalyst. Thus, 2-methyl-1,5-*anti*-pentenediols with either olefin geometry can be synthesized from the same allenylboronate precursor **5**. Furthermore, 1,5-pentenediols **4** and **6** can be easily converted to 1,3,5-triols with excellent diastereoselectivity in one step.

Introduction

Enantioselective carbonyl addition using allylmetal reagents is an important transformation in organic synthesis.[1] Compared to the vast majority of conventional carbonyl allylation methods that produce homoallylic alcohols with a terminal olefin unit, allylation with enantioenriched, bifunctional allylboron reagents represents an important advance in allylmetal chemistry.[2–4] Specifically, addition of bifunctional allylboron reagents to aldehydes not only provides stereochemically defined, enantioenriched homoallylic alcohols, but more importantly, the olefin unit in the alcohol products is properly functionalized to enable a variety of subsequent transformations (Figure 1).[5,6] Given the mild conditions typically involved in allylboration reactions, these reagents are particularly attractive for use in late stage convergent fragment assemblies.[6,7] However, enantioselective preparation of such reagents has been challenging and largely remains underdeveloped.[2–4]

Recently, enantioselective allene hydroboration[2n] has emerged as an efficient method to access enantioenriched bifunctional allylboranes. By appropriate selection of the metal species used in the allene precursors, a variety of chiral bifunctional allylboranes have been prepared via hydroboration with diisopinocampheylborane or Soderquist's borane[2c] (10-TMS-9-borabicyclo[3.3.2]decane).[4] Several of these bifunctional allylboranes have been applied in the synthetic studies targeting natural products.[7] In connection with an ongoing problem in natural product synthesis, we have developed and report herein new bifunctional allylboranes which enable enantioselective convergent aldehyde fragment assembly to give

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ASSOCIATED CONTENT Experimental procedures and spectroscopic data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

Dedicated to Professor Larry E. Overman on the occasion of his 70th birthday.

2-methyl-1,5-*anti*-pentenediols with intervening (*Z*)- or (*E*)-olefin units with high selectivity from the same allenylboronate precursor.

In 2002 we reported a diastereo- and enantioselective synthesis of 1,5-pentenediols using a bifunctional allylborane reagent derived from allenylboronate hydroboration.[4a] By analogy, we envisioned that allylborane reagents such as (*Z*)-**2** and (*E*)-**2** might be suitable reagents to prepare methyl substituted 1,5-pentenediols **3** and **4** (Figure 2), respectively. In previous studies of the hydroboration-allylboration reactions of allenylboroante **1a** (wherein the boronate ester is a tetrapheny-lethan-1,2-diol unit) we demonstrated that (*Z*)-**2** and (*E*)-**2** can be obtained with high efficiency via kinetic hydroboration [for (*Z*)-**2**] or by thermal allylborane equilibration of the allylborane intermediates [for (*E*)-**2**].[4b] However, the tetraphenylethan-1,2-diol unit proved to be too bulky, and double allylboration reactions using these first-generation bifunctional allylboranes could not be achieved. After a brief screening of additional boronate ester units, allenylboronate **5** with a 2,2-dimethylpropanediol ester was identified for subsequentdouble allylboration studies. As described herein, use of allenylboronate **5** indeed proved highly useful in the development of a highly diastereo- and enantioselective synthesis of (*E*)-2-methyl-1,5-pentenediols **3** and **4**.

Results and Discussion

In initial experiments, kinetically controlled hydroboration of allenylboronate **5** with $(^{d}\text{Ipc})_2\text{BH}$ (diisopinocampheylborane) was carried out at −30 °C with the solution being allowed to warm slowly to −10 °C to complete the hydroboration. Sequential treatment of resulting allylborane intermediate (not isolated) with hydrocinnamaldehyde (0.7 equiv) at −78 °C for 8 h and then with benzaldehyde (1.5 equiv) provided a 1:1 mixture of (*E*)-*syn*- and (*Z*)-*anti*-1,5-pentenediols **3a** and **6a** in 36% and 39% yield with 93% ee and 95% ee, respectively (Scheme 1).

That two products **3a** and **6a** were obtained in a 1:1 ratio indicates that the two competing transition states for *the second allylboration step* (which lead to the formation of **3a** and **6a**) are very close in energy. In order to improve the diastereoselectivity of the second allylboration step, a number of options, in particular the use of Lewis acid catalyzed allylboration,[8,9] were considered. Because several highly (*E*)-selective, Lewis acid catalyzed allylboration reactions have been reported,[2f,9] we anticipated that application of this strategy to the double allylboration presented in Scheme 1 would give the (*E*)-isomer, **3a**. Intriguingly however, when the second allylboration step was carried out in the presence of 10% BF_3•OEt_2, (*Z*)-*anti*-1,5-pentenediol **6a** was obtained as the only product (ds > 20:1) in 89% yield and with 96% ee (Scheme 2). Application of these conditions to double allylboration reactions of a variety of aldehydes using the allylborane generated from kinetic hydroboration of **5** with $(^{d}\text{Ipc})_2\text{BH}$ gave (*Z*)-*anti*-1,5-pentenediols **6b–e** in 71–89% yield (based on R^1CHO as the limiting reagent) with >20:1 diastereoselectivity and 95–96% ee (Scheme 2). The only example that did not proceed with ≥20:1 diastereoselectivity is the double allylboration reaction leading to **6f**. In this case, a 4:1 mixture was obtained with **6f** (66% yield, 90% ee) as the major product. (When this reaction was performed without BF_3•OEt_2 in the second step, a 1:4 mixture was obtained favoring the (*E*)-*syn*-1,5-diol **3** as the major component). The absolute stereochemistry of the secondary hydroxyl groups of **6** was assigned by using the modified Mosher ester analysis.[10] The *Z* olefin geometry of **6** was assigned by ^{1}H nOe studies (see SI for details).

Because all previous literature examples of Lewis acid catalyzed allylboration of aldehydes with *α*-substituted allylboronates are (*E*)-selective,[2f,9] the formation of (*Z*)-*anti*-1,5-pentenediols **6** presented in Scheme 2 (with BF_3•OEt_2 as the catalyst for the second step) was unexpected and to the best of our knowledge, unprecedented. As shown in Figure 3a,

based on our prior studies,[4b] kinetically controlled hydroboration of allenylboronate **5** provides the bifunctional allylborane intermediate (*Z*)-γ–boryl-allylborane (*Z*)-**7**, which reacts with the first aldehyde to give *syn*-β-alkoxy-allylboronate **8** (The absolute and relative configuration of **8** was derived from corresponding 1,2-diol obtained from oxidative work up of **8** with $NaOH/H_2O_2$).[4b] Assuming that the second allylboration proceeds through a chair-like transition state, the results in Scheme 2 indicate that transition state **TS-2** with pseudo equatorial placement of the methyl group is favored (Figure 3a). We speculate that a six-membered chelate may be responsible for the unexpected (*Z*)-selective allylboration. It has been demonstrated that the addition of a Lewis acid such as BF_3•OEt_2 can accelerate the rate of allylation of aldehydes with allylboronates, owing to the coordination between BF_3 and one of the oxygen atoms in the dioxaborinane unit.[8] As shown in Figure 3b, among the four non-bonded pairs of electrons on the oxygen atoms in the dioxaborinane unit that BF_3 could coordinate to, the two pairs that occupy pseudo axial positions (shown in red in **A**) are likely not accessible owing to the unfavorable 1,3-diaxal steric interactions. Likewise, coordination to the lone pair of electrons which project toward the top of the boron-aldehyde six-membered chelate (shown in black in **B**) is also disfavored. Coordination of BF_3 to the last lone pair of electrons (shown in blue in **C**) apparently suffers from steric interactions with the substituent in the pseudo axial position. However, if disproportionation of BF_3 and intermediate alkoxyborane **8** occurs, a difluoroalkoxyborane substituent would be generated, as indicated in the allylboronate species in **TS-2**.[12] Indeed, NMR studies demonstrated that treatment of Ipc_2BOMe with 1 equiv of BF_3•OEt_2 led to rapid conversion to $Ipc_2BF(OEt_2)$ (B-NMR, 16 ppm)[13a] and $MeOBF_2$ (B-NMR, 0 ppm).[13b] Owing to the Lewis acidity of the difluoroalkoxyborane unit, the boron atom could coordinate to one of the oxygen atoms of the boronate ester (as shown in blue in **TS-2**) to form a six-membered chelate. If so, the second allylboration could proceed via **TS-2** with minimal nonbonding steric interactions to give (*Z*)-*anti*-1,5-pentenediols **6** preferentially. The competing transition state **TS-1** involves an unfavorable 1,3-*syn*-pentane interaction (shown in red),[9e,14] and is therefore disfavored. Moreover all possible internally coordinated complexes corresponding to TS-1 (en route to **3**), by analogy to that depicted in TS-2 for the pathway leading to **6**, suffer from severe non-bonded interactions involving the $–OBF_2$ and an axial methyl group of the 4,4-dimethyl-1,3-dioxa-2-borinane unit in the transition state, and therefore are considered to be disfavored.[15]

As anticipated in Figure 2, the kinetic hydroboration adduct (*Z*)-**2** can undergo reversible 1,3-borotropic shifts[11] at elevated temperatures to give (*E*)-γ–boryl-allylborane (*E*)-**2**.[4b] We were intrigued by the possible stereochemical outcome of double allylboration of aldehydes with bifunctional allylboranes such as (*E*)-**2**. In the event, the hydroboration of allenylboronate **5** with $(^dIpc)_2BH$ was carried out at 0 °C for 2 h followed by heating at 65 °C for 1 h. Treatment of resulting (thermodynamic) allylborane with hydrocinnamaldehyde (0.7 equiv) at −78 °C and then benzaldehyde (1.5 equiv) provided (*E*)-*anti*-1,5-pentenediols **4a** in 87% yield and with > 20:1 diastereoselectivity and 90% ee without the assistance of BF_3•OEt_2. It is worth noting that the addition of a Lewis acid (BF_3•OEt_2) to the second allylboration reaction did not change the stereo-chemical outcome of this reaction. This reaction protocol was then applied to double allylboration reactions with a variety of aldehydes (Scheme 3). In all cases, (*E*)-*anti*-1,5-pentenediols **4b–f** were obtained in 71–92% yield with >20:1 diastereoselectivity and 88–92% ee. The absolute stereochemistry of the secondary hydroxyl groups of **4** was assigned by using the modified Mosher ester analysis.[10] The *E* olefin geometry of **4** was assigned by ^1H nOe studies (see SI for details).

The results in Scheme 3 may be rationalized as follows (Figure 4). Under thermodynamically controlled hydroboration-isomerization conditions, (*E*)-γ–boryl-allylborane (*E*)-**7** was generated from allenylboronate **5**, via the intermediacy of (*Z*)-**7** (see, figure 3, not shown here).[4b] Allylboration of the first aldehyde with (*E*)-**7** gave *anti*-β-

alkoxy-allylboronate **9**. (The absolute and relative configuration of **9** was determined from the derived 1,2-diol obtained from oxidation of **9** with $NaOH/H_2O_2$).[4b] The second allylboration—in the absence of a Lewis acid—proceeds via **TS-3** with pseudo axial placement of the small methyl group to give (*E*)-*anti*-1,5-pentenediols **4** (Figure 4a). The competing transition state **TS-4** with pseudo axial placement of the larger group (shown in red in Figure 4a) is disfavored. If the Lewis acid BF_3•OEt_2 was used, the alkoxydifluroborane **10** could be generated via a disproportionation pathway (Figure 4b). Evidently, however, the second allylation does not proceed via **TS-5** with a six-membered chelate to give 1,5-diol **11**, as the R^1 group is oriented in **TS-5** such that significant non-bonding steric interactions between the R^1 group and the six-membered boronate-aldehyde (R^2CHO) chelate are inevitable (shown in red in Figure 4b). Therefore, **TS-5** is disfavored and the addition of BF_3•OEt_2 does not change the stereochemical outcome of the second allylboration reaction.

While 1,5-diols **4** and **6** are common structural motifs in many natural products,[16] the olefin unit can also be further functionalized. For example, hydroboration reactions of **4e** and **6a** were carried out as summarized in Scheme 4. Hydroboration of diol **6a** with thexylborane[17] followed by oxidative workup provided 1,3,5-triol **12** in 71% yield and > 20:1 diastereoselectivity. The 3,5-*syn*-diol relationship was established by ^{1}H NMR analysis of the acetonide derivative **13** (Scheme 4).[18] Alternatively, hydroboration of diol **4e** with thexylborane followed by oxidative workup provided 1,3,5-triol **14** in 75% yield and > 20:1 diastereoselectivity. Here again, the 1,3-*syn*-diol relationship was established by ^{1}H NMR analysis of the acetonide derivative **15** (Scheme 4). Thus, 1,5-diols **4** and **6** can be transformed into 1,3,5-triols with four stereocenters without any protecting group manipulations. We anticipate that this methodology will be applicable to the synthesis of many polyketide natural products that contain such structural motifs, as illustrated by the highlighted sub-structures of several natural products in Scheme 4.[19]

Conclusions

In summary, we have developed highly diastereo- and enantioselective syntheses of (*Z*)- and (*E*)-2-methyl-*anti*-1,5-pentenediols from allenylboronate **5**. Kinetically controlled hydroboration of **5** followed by double allylboration of the (kinetic) allylborane (*Z*)-**7** gave (*Z*)-2-methyl-1,5-*anti*-pentenediols **6** when 10% of BF_3•OEt_2 was used as the catalyst in the second allylboration step. Key to both transformations is the ability to control the relative placement of ***two*** substituents α- to boron in axial or equatorial positions in the second allylboration transition state. To the best of our knowledge, the results presented here for the double allylboration reactions of (*Z*)-**7** and (*E*)-**7** are the first examples where such control has been achieved.

A six-membered chelate model was proposed to rationalize the unexpected (*Z*)-selective allylboration reaction of **8**, the intermediate produced for the first allylboration reaction of (*Z*)-**7**. When allylborane (*Z*)-**7** was allowed to isomerize at 65 °C, the resulting allylborane (*E*)-**7** underwent double allylboration reactions with two aldehydes to give (*E*)-2-methyl-1,5-*anti*-pentenediols **4** with excellent diastereoselectivity. In this case, use of a Lewis acid was not required in order to achieve diastereoselective allylboration reactions of the derived intermediate **9**. Finally, (*E*)- and (*Z*)-1,5-pentenediols **4** and **6** can be converted to 1,3,5-triols **12** and **14** with excellent stereoselectivity using a hydroboration-oxidation sequence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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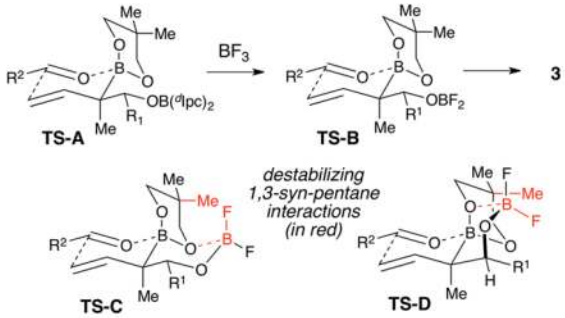
15. Depicted below are potential transition states (A–D) for formation of **3** Transition states A and B are alternatives to TS-1 in Figure 3, and represent non-catalyzed transition structures. Transition states C and D represent internally coordinated transition states, analogous to TS-2 invoked for formation of **6**. It is clear by inspection of TS-C and TS-D that both suffer from severe destabilizing 1,3-syn pentane interactions with the axial methyl group of the boronate ester (highlighted in red).



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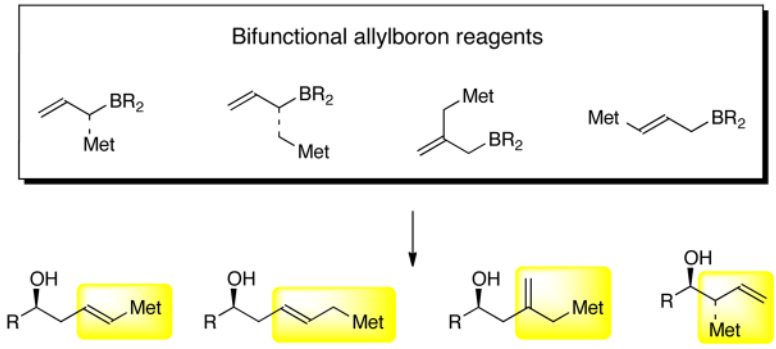


Figure 1.
Representative Allylboration Reactions with Bifunctional Allylboron Reagents

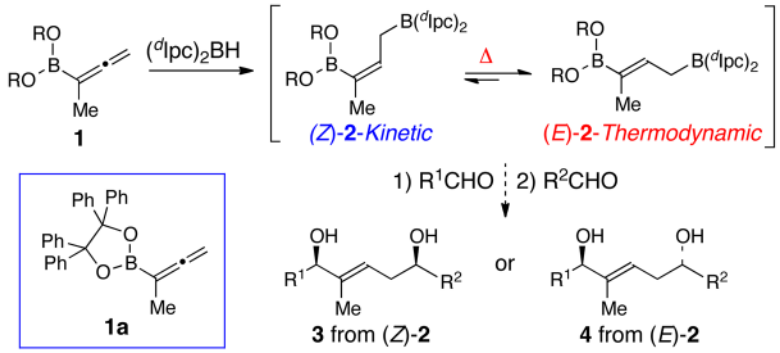


Figure 2.
Proposed Hydroboration-double Allylboration Strategy for the Synthesis of 1,5-Pentenediols **3** and **4**

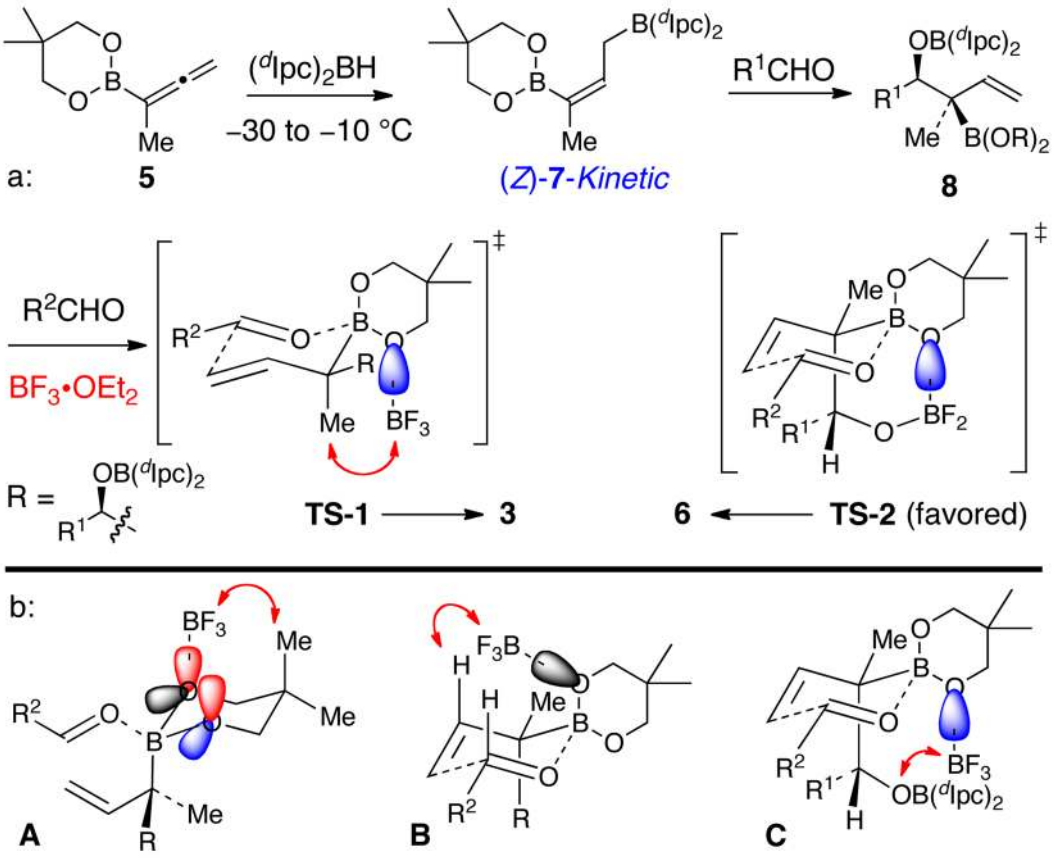


Figure 3.

(a) Analysis of Transition States for Lewis Acid Catalyzed Second Allylboration with Allylboronate **8**. b) Analyses of the Potential Interaction of BF_3 with an Oxygen Atom in the Dioxaborinane Unit.

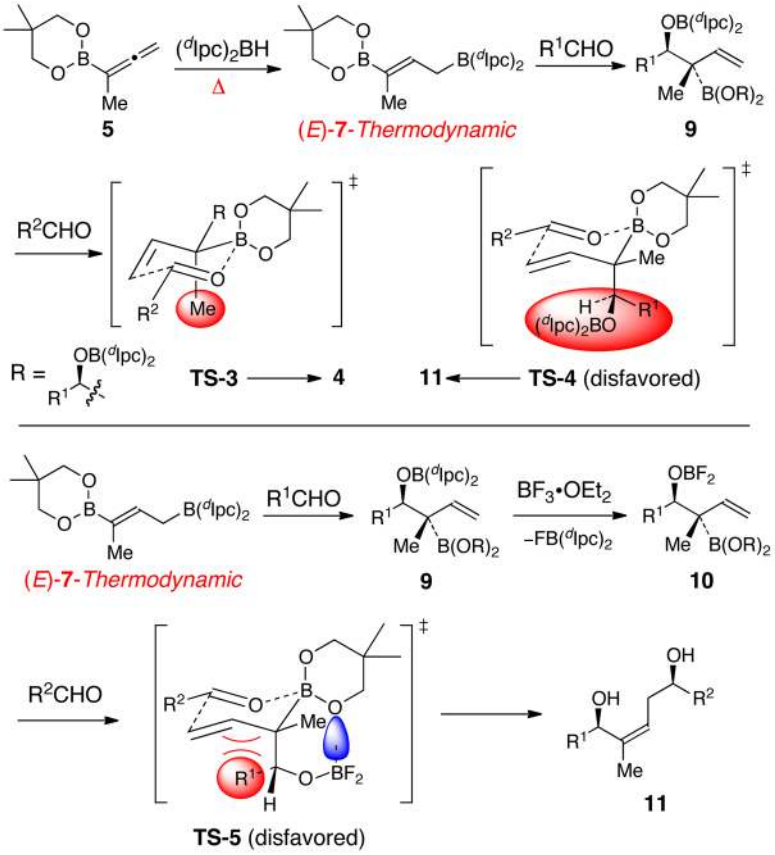
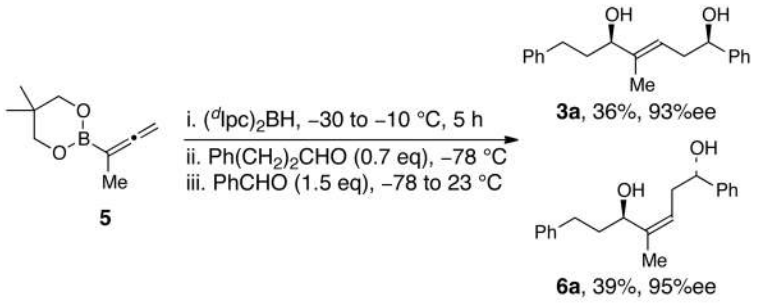
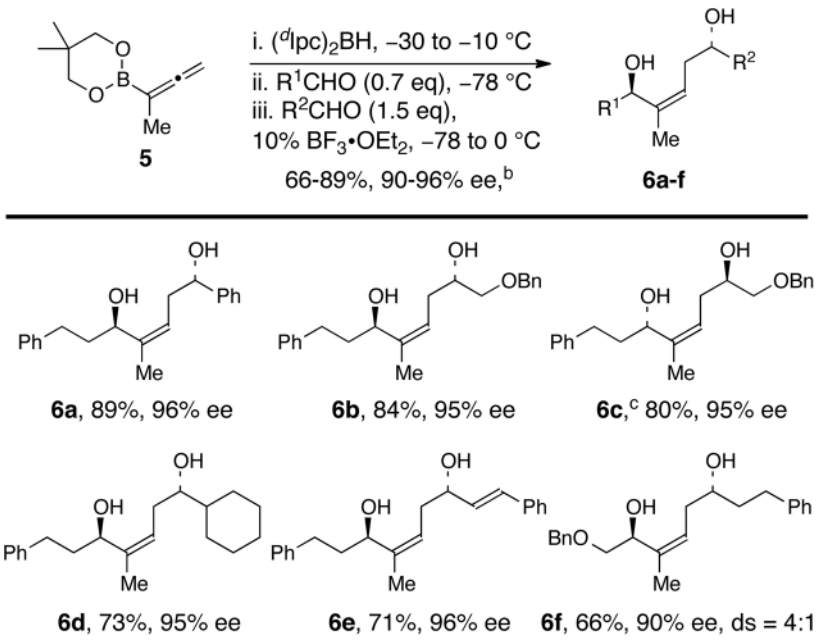


Figure 4.

Transition State Analyses of Second Allylboration with Allylboronate **9**. b) Transition State Analyses of the Lewis Acid BF_3•OEt_2 Catalyzed Second Allylboration with Allylboronate **9**.



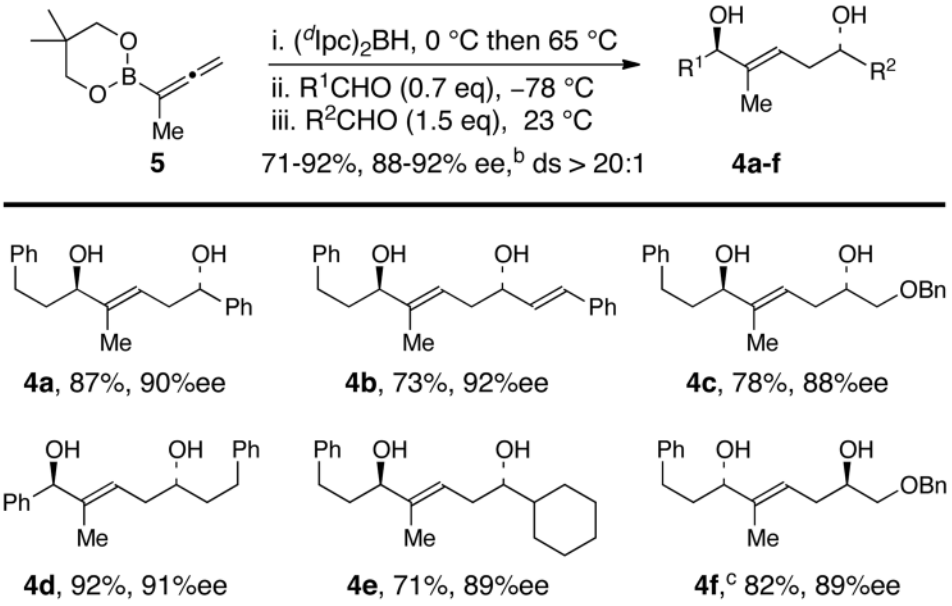
Scheme 1.
Initial Attempts at Hydroboration-Double Allylboration with **5**



Scheme 2.

Synthesis of (*Z*)-1,5-*anti*-Diols **6** via Kinetically Controlled Hydroboration of **5** and the Lewis Acid BF_3•OEt_2 Catalyzed Double Allylboration Reactions of Allylborane (*Z*)-**7**[a]

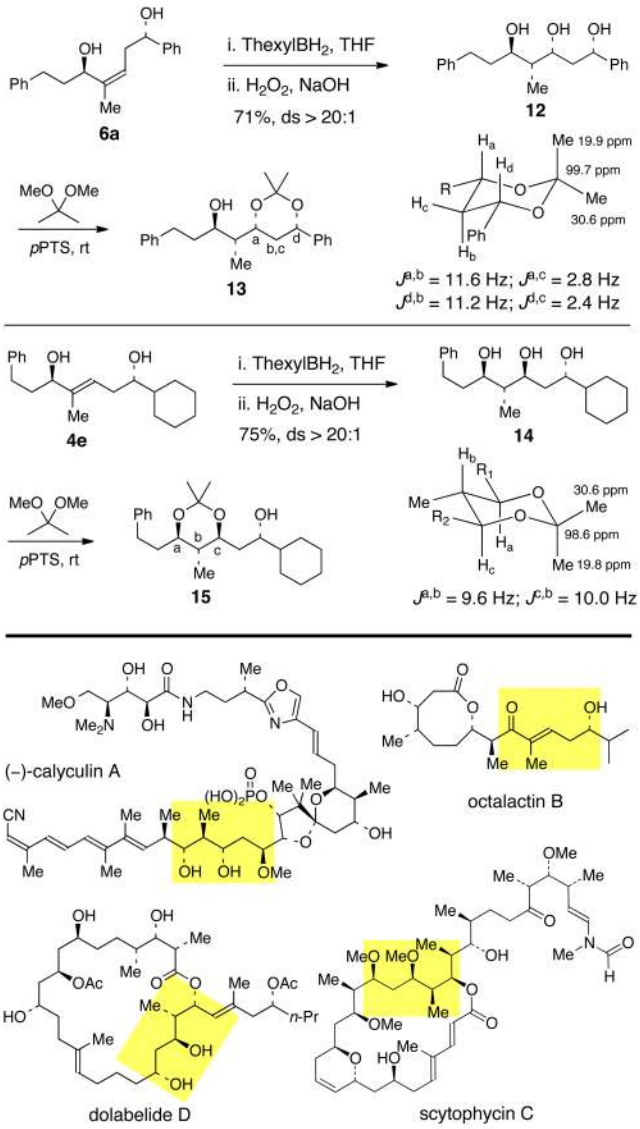
(a) Reactions were performed by treating **5** with (^{d}Ipc)$_2$BH (1 equiv) in toluene at −30 °C and warming to −10 °C over 5 h followed by the addition of R^1CHO (0.7 equiv) at −78 °C. The mixture was then allowed to stir at −78 °C for 8 h, then BF_3•OEt_2 (10%) followed by R^2CHO (1.5 equiv) were added slowly to the reaction mixture, which was kept at −78 °C for 36 h. The reaction mixture was warmed slowly to 0 °C and subjected to a standard workup (NaOH, H_2O_2) at 0 °C prior to product isolation. (b) Determined by Mosher ester analysis.[10] (c) (^{d}Ipc)$_2$BH was used.



Scheme 3.

Synthesis of (*E*)-1,5-*anti*-Diols **4** under Thermodynamically Controlled Allylborane Isomerization Conditions

(a) Reactions were performed by treating **5** with (^{d}Ipc)$_2$BH (1 equiv) in toluene at 0 °C for 2 h followed by heating at 65 °C for 1 h to effect allylborane equilibration via reversible 1,3-boratropic shifts. The solution was cooled to −78 °C, and R^{1}CHO (0.7 equiv) was added at −78 °C. The mixture was stirred at −78 °C for 8 h, then R^{2}CHO (1.5 equiv) was added to the reaction mixture at −78 °C. The reaction mixture was warmed slowly to ambient temperature and stirred for 36 h. The reaction mixtures were then subjected to standard workup (NaOH, H_2O_2, 0 °C) prior to product isolation. (b) Determined by Mosher ester analysis.[10] (c) (^{l}Ipc)$_2$BH was used.



Scheme 4.

(a) Transformation of 1,5-Diols **4e** and **6a** to 1, 3, 5-Triols **12** and **14** via a Hydroboration-oxidation Reaction Sequence (b) Potential Natural Product Targets for this Methodology