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Highly (*E*)-Selective $BF_3 \cdot Et_2O$-Promoted Allylboration of Chiral Nonracemic α-Substituted Allylboronates and Analysis of the Origin of Stereocontrol

Ming Chen and William R. Roush*

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458

roush@scripps.edu

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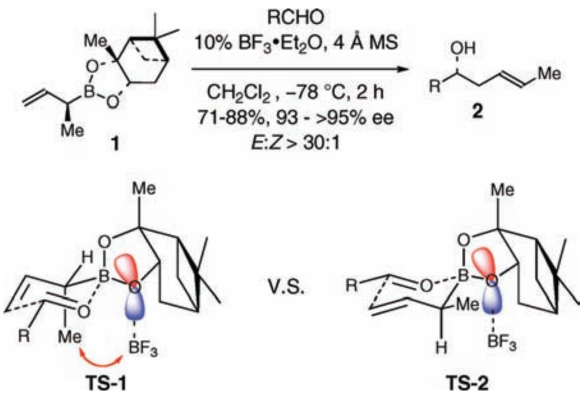
ABSTRACT



δ-Methyl-substituted homoallylic alcohols 2 were prepared in 71−88% yield, *E*:*Z* >30:1 and 93% to >95% ee via $BF_3 \cdot Et_2O$-promoted allylboration with α-Me-allylboronate 1. The origin of high (*E*)-selectivity is proposed.

The asymmetric carbonyl allylboration reaction is a valuable method for C−C bond formation. In the vast majority of cases that have been described, the asymmetric induction derives from the use of chiral auxiliaries attached to boron.[1,2] Although not as widely adopted in the literature, the addition of enantioenriched α-substituted allylboronates to carbonyl compounds is a useful alternative.[3−5] Pioneered by Hoffmann et al., carbonyl addition reactions of enantioenriched α-substituted allylboronates **3** proceed with near perfect chirality transfer.[3,4] A mixture of (*Z*)- and (*E*)-homoallylic alcohols **4** and **5** can be generated from two competing transition states **TS-3** and **TS-4** (Figure 1). The ratio of the two homoallylic alcohols depends in part on the electronic property of the

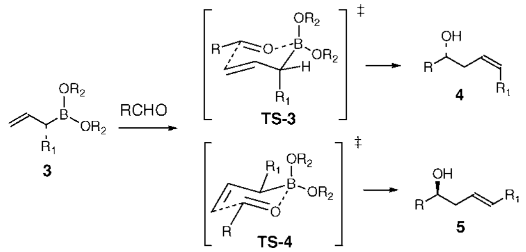


Figure 1. Competing transition states for carbonyl addition reaction of α-substituted allylboronates **3**.

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group at the α-position. When the α-substituent is a polar group,[3] such as an alkoxy group or halogen atom, allylboration proceeds predominately via **TS-3** to give (*Z*)-homoallylic alcohol **4**. Although the exact origin of the high (*Z*)-selectivity remains unclear, several factors, including steric effects, dipolar effects, and stereoelectronic minimization of $\pi-\sigma^*$ delocalization in the transition states, have been proposed[3l] and supported by computational studies.[4s] However, when the α-substitution is a nonpolar alkyl group,[4,5] a mixture of (*Z*)- and (*E*)-homoallylic alcohols **4** and **5** is often obtained. Until recently,[5l−n,9] synthetically useful selectivity has proven challenging to achieve with enantioenriched α-alkyl-substituted allyl- or (*E*)-crotylboronates.

Lewis or Brønsted acid promoted allylboration with allylboronate reagents is an important emerging topic in carbonyl allylation chemistry.[6,7] As demonstrated by Hall and coworkers, allylboration in the presence of a catalytic amount of a chiral, nonracemic Lewis or Brønsted acid provides homoallylic alcohols in high yields and excellent enantioselectivities.[8] However, Lewis or Brønsted acid promoted allylboration with enantioenriched, α-substituted allylboronates largely remains underdeveloped.[9] Recently, Hall reported the enantioselective synthesis and Lewis acid promoted allylborations of α-$TMSCH_2$-substituted allylboronates that generate (*E*)-*δ*-$TMSCH_2$-substituted homoallylic alcohols with excellent selectivities.[9c]

In connection with an ongoing problem in natural product synthesis, we had occasion to explore Lewis acid promoted allylborations of enantioenriched α-substituted allylboronates. We found and report herein that (*E*)-*δ*-methyl-homoallylic alcohols **2** are obtained in good yields and excellent enantioselectivities from $BF_3{\cdot}Et_2O$-promoted allylboration reactions of **1**.[10] In addition, we have found that *δ*-chloro-substituted homoallylic alcohols **14** can also be obtained in good yield and 3−6:1 (*E*)-selectivity from $BF_3{\cdot}Et_2O$-promoted allylboration reactions of **13**. The origin of (*E*)-selectivity in these reactions is proposed.

α-Methyl-substituted allylboronate **8** was prepared from methyl boronate **6**,[11] by using the Matteson homologation (Scheme 1).[12] Allylboration reactions of hydrocinnamaldehyde with **8** are summarized in Table 1. The noncatalyzed reaction provided a 1:1.4 mixture of ***ent*-2a** and **9** (entry 1). Similar results were obtained when the reaction was performed in the presence of 10% $Sc(OTf)_3$ (entry 2). When the reaction was

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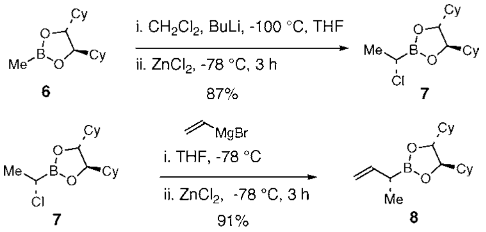
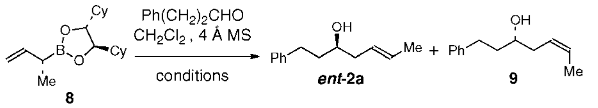
Scheme 1. Synthesis of Allylboronate **8**



carried out in the presence of either 10% or stoichiometric $BF_3\cdot Et_2O$, a 3:1 mixture of ***ent*-2a** and **9** was obtained (entries 3 and 4). Despite additional attempts to optimize this reaction, we were unable to achieve synthetically useful selectivity in allylboration reactions of **8**.

Table 1. Optimization for Allylboration Reactions with **8**

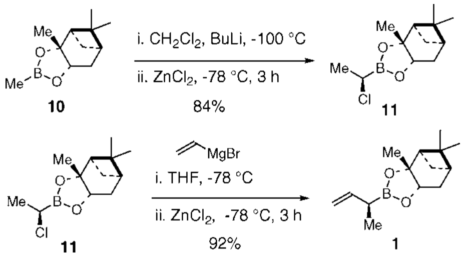


entry	conditions	***ent*-2a**:**9**[a]	yield (%)[b]
1	no catalyst, −78 °C to rt, 8 h	1:1.4	67
2	10% $Sc(OTf)_3$, −78 °C to rt, 8 h	1:1.5	63
3	10% $BF_3\cdot Et_2O$, −78 °C, 2 h	3:1	78
4	100% $BF_3\cdot Et_2O$, −78 °C, 2 h	3:1	71

[a] Based on ^1H NMR analysis of the crude reaction mixture. [b] Yield of isolated mixture of products.

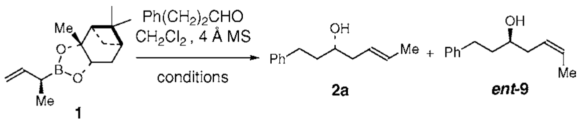
Pinanediol is a useful chiral director for the Matteson homologation.[13] We hoped that allylboronate **1** would provide access to the desired (*E*)-homoallylic alcohols with excellent selectivity based on Hall's work.[9c] Accordingly, allylboronate **1** was prepared with high diastereoselectivity from **10** (Scheme 2).[14]

Scheme 2. Synthesis of Allylboronate **1**



Results of allylboration of hydrocinnamaldehyde with reagent **1** are presented in Table 2. The reaction in the absence of Lewis acid gave a 1.5:1 mixture of alcohols **2a** and ***ent*-9** (entry 1). With the addition of 10% $Sc(OTf)_3$, a 3:1 mixture of **2a** and ***ent*-9** was obtained (entry 2).

Table 2. Optimization for Allylboration Reactions with **1**

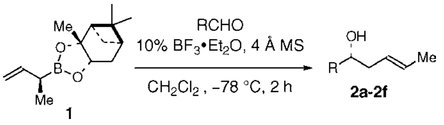


entry	conditions	**2a**:***ent*-9**[a]	yield (%)[b]
1	no catalyst, −78 °C to rt, 8 h	1.5:1	71
2	10% $Sc(OTf)_3$, −78 °C to rt, 8 h	3:1	64
3	10% $BF_3\cdot Et_2O$, −78 °C, 2 h	>30:1	79
4	100% $BF_3\cdot Et_2O$, −78 °C, 2 h	>30:1	68

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

Gratifyingly, when the reaction was carried out in the presence of 10% $BF_3\cdot Et_2O$, (*E*)-homoallylic alcohol **2a** was obtained as the only product ($E:Z > 30:1$) in 94% ee and 79% yield (entry 3).

Table 3. Preparation of (*E*)-*δ*-Me-Homoallylic Alcohols **2a**−**2f**



entry	RCHO	product	yield (%)[a]	ee (%)[b]
1	$Ph(CH_2)_2CHO$	**2a**	79	>95
2	$PhCH_2CHO$	**2b**	88	>95
3	PhCHO	**2c**	75	94
4	CyCHO	**2d**	71	>95
5	$BnO(CH_2)_2CHO$	**2e**	84	93
6	$BnOCH_2CHO$	**2f**	73	95

[a] Yield of isolated (*E*)-homoallylic alcohols. [b] Enantiomeric purity and absolute stereochemistry of **2a**−**2f** were determined by using the Mosher ester analysis.[15]

As summarized in Table 3, BF_3-mediated allylboration of a variety of aldehydes using **1** proceeded with near perfect chirality transfer. (*E*)-*δ*-Methyl-substituted homoallylic alcohols **2a**−**2f** were obtained in 93% to >95% ee and 71−88% yield. The correspoding (*Z*)-isomers were not detected in any of these experiments.

We suspect the high (*E*)-selectivity in these reactions originates from minimization of 1,3-*syn*-pentane interactions in the competing transition states.[16] As shown in Figure 2, it is conceivable that BF_3 will coordinate to the lower lone pair of electrons (in blue) of the oxygen atom distal to the angular methyl group to minimize steric interactions.[17] If so, **TS-1** is disfavored due to a 1,3-*syn*-pentane interaction

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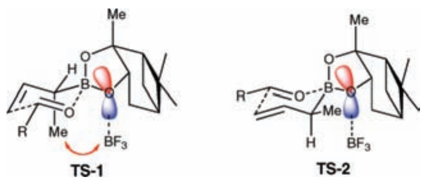


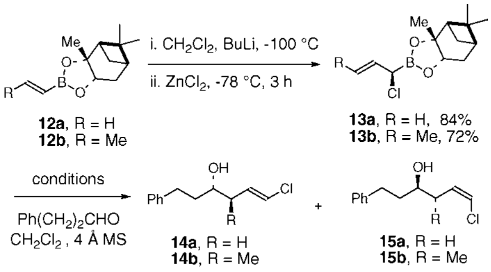
Figure 2. Competing transition states for BF$_3$-catalyzed aldehyde allylboration with α-methyl allylboronate **1**.

between the pseudoaxial methyl group and the BF$_3$ ligand; this interaction is absent in **TS-2**. Accordingly, product formation proceeds via **TS-2** and homoallylic alcohols with (*E*)-olefin geometry are obtained with excellent selectivity.

We were intrigued by the possibility that BF$_3$·Et$_2$O-promoted aldehyde allylboration could be used to induce (*E*)-selectivity with reagents that have much higher intrinsic preference for positioning of the α-substituent in a pseudoaxial position in the allylboration transition state. α-Chloro-substituted allylboronates, such as **13**, are known to give (*Z*)-*δ*-chloro-substituted homoallylic alcohols, e.g., **15**, with high (*Z*)-selectivity in allylboration reactions.[3]

The sensitive α-chloro-substituted allylboronates **13a** and **13b** were synthesized, and their allylboration reactions were explored (Table 4). The reaction of hydrocinnamaldehyde with **13a** in the absence of BF$_3$·Et$_2$O provided (*Z*)-*δ*-chloro-homoallylic alcohol **15a** in 72% yield.[18] Similarly, crotylboration with **13b** gave alcohol **15b** in 70% yield.[18] In both cases, high (*Z*)-selectivity (≥10:1) was observed, consistent with Hoffmann's report.[3] However, when these reactions were performed in the presence of 10% BF$_3$·Et$_2$O, reagent **13a** provided a 6:1 mixture of *δ*-chloro-homoallylic alcohols **14a** and **15a**,[18] and reagent **13b** provided a 3:1 mixture of alcohols **14b** and **15b**.[18]

Table 4. Allylboration with α-Cl-Allylboronates **13**



12a, R = H
12b, R = Me

13a, R = H, 84%
13b, R = Me, 72%

14a, R = H
14b, R = Me

15a, R = H
15b, R = Me

entry	substrate	conditions	**14:15**[a]	yield (%)[b]
1	**13a**	No catalyst, −78 °C to rt, 24 h	1:12	72
2	**13b**	No catalyst, −78 °C to rt, 24 h	1:10	70
3	**13a**	10% BF$_3$·Et$_2$O, −78 °C, 24 h	6:1	63
4	**13b**	10% BF$_3$·Et$_2$O, −78 °C, 24 h	3:1	52

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

These data indicate that the strong preference of reagents **13** to react with aldehydes via a transition state analogous to **TS-5** (but lacking the BF$_3$ ligand) can be overridden in the presence of BF$_3$·Et$_2$O. As shown in Figure 3, **TS-5** is disfavored owing to the 1,3-*syn*-pentane interaction. In the competing (and now favored) transition state **TS-6**, the α-Cl substitution is positioned in a pseudoequatorial arrangement to minimize interactions with the chlorine substituent. Ultimately, these reactions lead to the formation of (*E*)-homoallylic alcohols **14** with 3−6:1 (*E*)-selectivity.

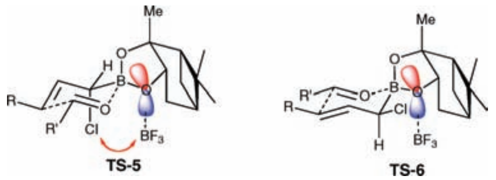


Figure 3. Competing transition states for BF$_3$-catalyzed aldehyde allylboration with α-chloro allylboronates **13**.

In summary, we have demonstrated the highly (*E*)-selective allylboration of aldehydes with reagent **1** in the presence of a catalytic amount of BF$_3$·Et$_2$O. (*E*)-*δ*-Methyl-substituted homoallylic alcohols **2** were prepared in 71−88% yield and excellent enantioselectivities. (*E*)-*δ*-Chloro-substituted homoallylic alcohols **14** were also obtained in good yields and 3−6:1 (*E*)-selectivity from reagents **13a**,**b**. We postulate that minimization of 1,3-*syn*-pentane interactions in the transition states is responsible for the (*E*)-selectivity of these reactions.

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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.

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[17] Coordination to the non-bonded electron pair (indicated in red) is disfavored owing to a 1,3-interaction with the angular methyl group. Coordination to the distal oxygen atom is disfavored for steric reasons.

[18] The enantiomeric purity of homoallylic alcohols **14** and **15** was ca.15−30% ee, presumably due to epimerization of the α-chloro center during preperations of reagents **13a** and **13b**. Matteson, D. S.; Erdik, E. *Organmetallics* **1983**, *2*, 1083.