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Additions of functionalized α-substituted allylboronates to aldehydes under the novel Lewis and Brønsted acid catalyzed manifolds

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Abstract—The stereo- and chemoselectivity in the additions of four model α-substituted allylboronates to benzaldehyde was examined under the standard thermal (uncatalyzed) conditions and the novel Lewis and Brønsted acid-catalyzed conditions. With either of Sc(OTf)₃ or triflic acid as catalysts, an α-ethyl allylboronate, **1a**, led to a surprising inversion of stereoselectivity that can be tentatively rationalized through subtle differences in the geometry of the allylboration transition state between uncatalyzed and catalyzed pathways. It was also found that the chemoselectivity of α-silyl reagents (**1c** and **1d**) can be reversed upon use of a catalyst, providing allylsilation products instead of the allylboration product obtained from the thermal uncatalyzed reaction.
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1. Introduction

Since their discovery,[1] uncatalyzed additions of allylboronates to aldehydes have evolved into one of the most popular methods for stereoselective C–C bond formation.[2] Compared to dialkyl allylic boranes, allylic boronic esters are often more advantageous as a class of reagents due to their increased air-stability. Two strategies have been developed for controlling enantiofacial selectivity in the additions of allylic boronates to achiral aldehydes: (1) the use of a chiral diol or a diamine derivative as boron's two non-allylic substituents (B-chiral allylboronates);[3] and (2) the use of optically pure, α-substituted reagents (C-chiral, or α-chiral allylboronates).[4] The recent discovery of Lewis acid catalyzed additions of allylboronates, by our group[5] and others,[6] opened doors to new and highly stereoselective aldehyde allylation methods using B-chiral allylboronates.[7] Whereas the scope of aldehyde substrates in Lewis acid-catalyzed allylboration has been thoroughly investigated, little is known on the scope of functionalized allylboronates. Here, we present an investigation on the scope and stereoselectivity of additions of α-substituted allylboronates promoted by the low-temperature Lewis and Brønsted[8] acid-catalyzed variants. The objec-

tive of this study with racemic α-substituted allylboronates is to provide additional mechanistic insight on the novel catalytic allylboration manifolds, and to help identify the most promising combination of substituents and catalytic conditions in view of using optically pure α-chiral reagents in the future.

The preparation of α-chiral allylboronates **1** and their additions to aldehydes were pioneered by Hoffmann.[4] These reagent-controlled additions proceed with almost perfect transfer of chirality to give two diastereomeric products **4** and **5** (Fig. 1). These Z and E allylic alcohol products are epimeric, and their ratio is highly dependent upon the nature of the α-substituent (R¹) and the nature of the boronic ester.[4] The ratio of **4** and **5** can be explained in terms of steric and dipolar effects on the two competing chairlike transition structures **2** and **3**. With a non-polar alkyl substituent R¹, steric interactions play a dominant role on the relative energies of these putative transition structures. Transition structure **3** is destabilized by a steric interaction between the boronic ester and the pseudo-equatorial α-substituent R¹. On the other hand, transition structure **2** features unfavorable allylic interactions due to the pseudo-axial position of the R¹ substituent. The use of a hindered ester, such as pinacolate, aggravates interactions between R¹ and the pinacol methyls in structure **3**, and tends to favor transition structure **2** leading to the Z-configured product **4**.[9] With a polar R¹ substituent (halogen, alkoxy),

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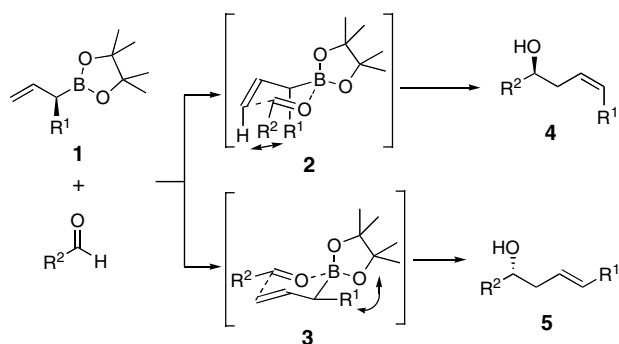* Corresponding author. Tel.: +1 780 492 3141; fax: +1 780 492 8231; e-mail: dennis.hall@ualberta.ca

Figure 1. Postulated competing transition structures in the allylation of aldehydes with α-substituted allylboronates **1**. Note: A stereodefined reagent is shown in order to emphasize the stereochemistry of the reaction and the epimeric relationship between products **4** and **5**.

dipolar effects tend to dominate and further favor transition structure **2** with the pseudo-axial C–R[1] bond *anti* to the axial B–O bond.

2. Results and discussion

Here, a small panel of racemic α-substituted allylboronates of type **1** representing a variety of substituent types (alkyl, silyl, halogen) were prepared. Pinacol allylic boronates were chosen due to their ease of handling and their stability to chromatographic conditions and moisture, and also to help optimize the Z/E ratio of addition products to favor isomer **4**.[9] Thus, α-ethyl, α-bromo, α-trimethylsilyl, and α-dimethylphenylsilyl reagents **1a–d** were prepared using known methods shown in Scheme 1. Reagent **1a**[10] was synthesized through a selective S_N2' addition (or vinylogous Matteson rearrangement) of ethylmagnesium chloride to the known 3-chloropropenylboronate **6**[11] (Eq. 1).[12] α-Bromo reagent **1b** was accessed using a reverse Matteson homologation of dibromomethyl boronate **7** with vinylmagnesium chloride (Eq. 2).[13] Likewise, α-trimethylsilyl reagent **1c** was made using a Matteson homologation on vinylboronate **8** (Eq. 3).[14] Like **1a**, reagent **1d** was synthesized by a
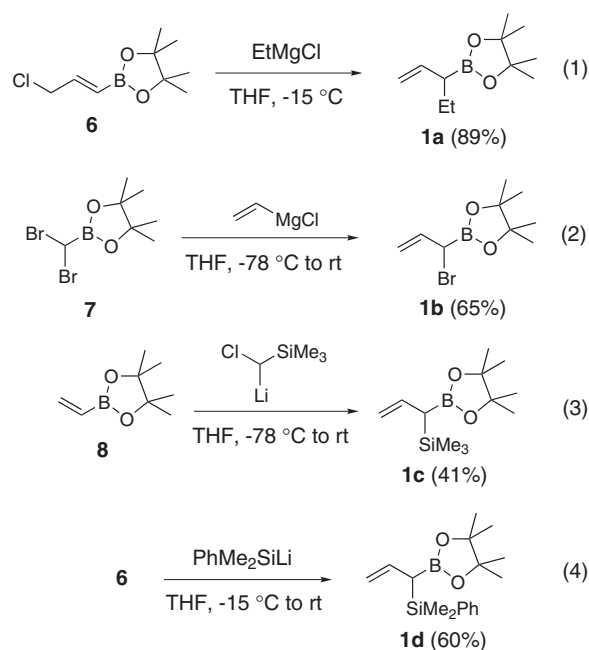
Scheme 1.

selective S_N2' addition on **6**, using dimethylphenylsilyl lithium[15] (Eq. 4).[12]

The allylation of benzaldehyde with α-ethyl reagent **1a** was examined under different conditions (Table 1). The thermal (non-catalyzed) reaction demanded to be performed neat at a temperature of 0 °C to provide a good yield favoring the Z-isomer **4a** over **5a** in a 2:1 ratio (entry 1).[16] In contrast, both Sc(OTf)$_3$-catalyzed[5,7] and TfOH-catalyzed[8] reactions (entries 2 and 3) proceeded at −78 °C to give a comparable ratio favoring E-isomer **5a**. The TfOH-catalyzed reaction is particularly efficient, providing a quantitative yield.[17]

To the best of our knowledge, such an inversion of selectivity is unprecedented and cannot be explained by a temperature effect. It is likely that subtle differences in

Table 1. Allylboration of α-ethyl and α-bromo allylboronates **1a** and **1b** with benzaldehyde[a]

Entry	Boronate	Catalyst	T (°C)	Time (h)	Products	Ratio[b]	Yield (%)[c]
1	**1a** (R = Et)	None	0	15	**4a, 5a**	2:1	75
2	**1a**	Sc(OTf)$_3$	−78	40	**4a, 5a**	1:1.3	63
3	**1a**	TfOH	−78	40	**4a, 5a**	1:1.7	99
4	**1b** (R = Br)	None	0	25	**4b, 5b**	13:1	75
5	**1b**	Sc(OTf)$_3$	−78	40	**4b, 5b**	10:1	50
6	**1b**	TfOH	−78	40	**4b, 5b**	9:1	24

Note: Although racemic **1a/1b** were used, stereodefined reagents are shown in order to emphasize the epimeric relationship between products **4** and **5**.
[a] Typical reaction scale: approx. 0.7–1.0 mmol, 0.2 M in dichloromethane.
[b] Ratio of **4** to **5** as determined by ^{1}H NMR analysis of crude reaction mixtures.
[c] Unoptimized yields of pure products isolated after flash chromatography. m.s. = molecular sieves.
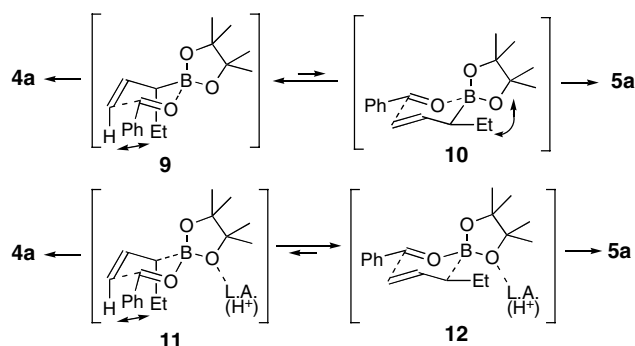
Figure 2. Postulated competing transition structures in the allylation of benzaldehyde with α-ethyl allylboronate (**1a**). L.A. = Lewis acid.

the geometry of the transition structures between the uncatalyzed and catalyzed reaction manifolds are responsible for the inversion of selectivity. Our previous mechanistic study on Lewis acid-catalyzed allylboration supported an electrophilic boronate activation mode through coordination of a boronate oxygen, a process that increases boron's electrophilicity and strengthens the B–O(aldehyde) interaction.[18] In the thermal reaction, the preference for **4a** over **5a** can be explained by the presence of severe non-bonded interactions between the pseudo-equatorial ethyl substituent and the large pinacolate group in transition structure **10** leading to **5a** (Fig. 2).

To explain the inversion of selectivity, we hypothesize that the acid-catalyzed processes feature more advanced transition states with a shorter B–O(aldehyde) bond and a longer B–C bond. Thus, in structure **12** such a longer bond alleviates the non-bonded interactions between the ethyl substituent and the pinacolate, which would become less important than the allylic interaction caused by the pseudo-axial ethyl substituent in structure **11**. Hence, a switch of selectivity from the non-catalyzed reaction occurs and product **5a** becomes predominant. The α-bromo reagent **5b** provided comparable selectivities invariably of conditions employed, thermal, or acid catalyzed (entries 4–6). The yield of product, however, was acceptable only in the uncatalyzed reaction. The

predominance of the Z-isomer **4b** for reactions of α-bromo reagent **1b** can be explained by the particular strength of the dipolar effect described above.

The α-silyl substituted reagents **1c** and **1d** presented further interesting opportunities to gain insight into the mechanism of Lewis and Brønsted acid-catalyzed allylboration. Indeed, as observed by Hiyama and co-workers, addition of these reagents to aldehydes can lead either to alkenylsilane products **13c/13d** via allylboration, or to the common alkenylboronate **14** via allylsilation (Table 2).[19] The nature of products observed would reveal information on the preferred mode of activation by the catalyst, that is, aldehyde activation in the allylsilation versus boronate activation in the allylboration. As can be seen with the modest yields of products, these allylations are difficult (Table 2). However, aside from products, starting materials were recovered with very little degradation. With both reagents **1c** and **1d**, the thermal reaction led to the expected allylboration to give the Z alkenylsilanes **13c** and **13d** as major products (entries 1 and 3).

The predominance of the Z-isomers of **13c/13d** can be explained by the large size of the silyl group, which would aggravate the interactions with the pinacolate group in transition structure **3**. To our initial surprise, both Sc(OTf)$_3$ and TfOH-catalyzed reactions provided the E-alkenylboronate **14** as major product of what appears to be acid-catalyzed allylsilations (entries 2, 3, 5, and 6). No allylboration products were observed. This interesting switch of chemoselectivity can be explained by a preference for an aldehyde activation mode (i.e., transition state assembly **16**) over the electrophilic boronate activation mode (**15**) expected in the absence of an α-silyl substituent (Fig. 3).

3. Conclusion

This study on the allylation of aldehydes using α-substituted allylboronates provides additional insight into the mechanism of Lewis and Brønsted acid-catalyzed allylboration manifolds. Compared to the thermal

Table 2. Allylboration of α-silyl allylboronates **1c** (R = SiMe$_3$) and **1d** (R = SiMe$_2$Ph) with benzaldehyde[a]
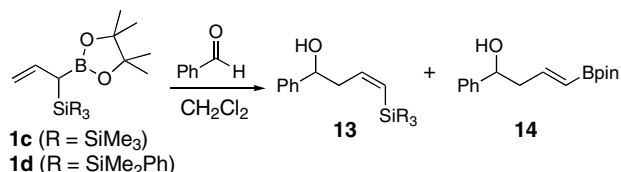
Entry	Boronate	Catalyst	T (°C)	Time (h)	Product	E/Z	Yield (%)[b]
1	1c	None	0	15	13c	1:6.7	46
2	1c	Sc(OTf)$_3$	−78	40	14	4:1	40
3	1c	TfOH	−78	40	14	3:1	43
4	1d	None	0	15	13d	1:6.2	22
5	1d	Sc(OTf)$_3$	−78	40	14	4:1	11
6	1d	TfOH	−78	40	14	4:1	26

[a] Typical reaction scale: approx. 0.3 mmol, 0.2 M in dichloromethane.
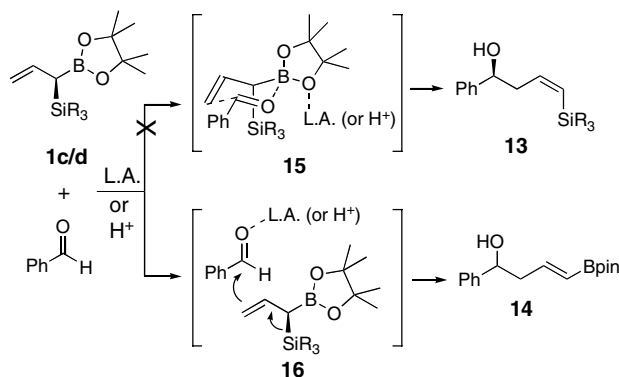[b] Unoptimized yields of pure products isolated after flash chromatography.

Figure 3. Postulated competing mechanisms in the allylation of benzaldehyde with α-silyl allylboronates **1c** and **1d**. Although racemic **1c/1d** were employed, stereodefined reagents are shown in order to emphasize the stereospecificity in the formation of **13**. L.A. = Lewis acid.

uncatalyzed reaction of **1a** the inversion of stereoselectivity in the formation of homoallylic alcohols under acid catalysis is suggestive of a more advanced transition structure with a shorter B–O(aldehyde) bond and a longer B–C bond. The case of α-silyl reagents also led to an interesting switch of selectivity, one of chemoselectivity that provides information on the relative easiness between boronate and aldehyde activation pathways. Overall, our results with reagent **1a** suggest that careful optimization of the nature of the alkyl group and boronate's diol unit in an optically pure α-chiral allylboronate could provide a stereodivergent method to access both enantiomers of homoallylic alcohols by a simple choice of thermal or acid-catalyzed allylboration conditions.

Acknowledgments

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10. Preparation of allylboronate **1a** and spectral data:
Typical procedure to make boronic ester **1a**: In a flame dried flask under inert atmosphere, alkenylboronic ester **6** (630 mg, 3.1 mmol, 1.0 equiv) was charged, diluted with THF (5 mL), and cooled to −15 °C in an ethylene glycol, dry ice bath. A solution of ethylmagnesium chloride 2.0 M in THF (2.0 mL, 4.0 mmol, 1.3 equiv) was added dropwise and the mixture was stirred for 30 min at −15 °C. The reaction mixture was quenched with an aqueous solution of saturated ammonium chloride and brought to room temperature. The phases were then separated, the aqueous phase was extracted three times using dichloromethane. The combined organic phases were washed once with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 562 mg (92% yield) of boronic ester **1a** as a colorless oil (>90% purity). Reagent **1a** was used without further purification.
Characterization for **1a**: IR (dichloromethane cast film) 2978, 1632, 1360, 1319, 1143 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.79 (ddd, 1H, $J = 17.1$ Hz, $J = 10.2$ Hz, $J = 1.2$ Hz), 4.99 (ddd, 1H, $J = 17.1$ Hz, $J = 2.0$ Hz, $J = 1.2$ Hz), 4.94 (ddd, 1H, $J = 10.2$ Hz, $J = 2.0$ Hz, $J = 0.9$ Hz), 1.75 (ddd, 1H, $J = 7.8$ Hz, $J = 7.7$ Hz, $J = 7.6$ Hz), 1.60 (ddq, 1H, $J = 13.3$ Hz, $J = 7.3$ Hz, $J = 7.3$ Hz), 1.46 (ddq, 1H, $J = 13.3$ Hz, $J = 7.4$ Hz, $J = 7.4$ Hz), 1.25 (s, 12H), 0.92 (dd, 3H, $J = 7.4$ Hz, $J = 7.3$ Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 139.5, 113.5, 83.1, 24.7, 24.6, 23.4, 13.5; ^{11}B NMR (CDCl$_3$, 128.3 MHz) δ 33.2; HRMS (EI) m/z calcd for C$_{11}$H$_{21}$BO$_2$: 196.1635. found: 196.1627.
Spectral data for **1b** can be found in Ref. 13.
Spectral data for **1c** can be found in Ref. 14.
Spectral data for **1d** can be found in Ref. 19.
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16. Spectral data for **4a**: Nokami, J.; Nomiyama, K.; Shafi, M. S.; Kataoka, K. *Org. Lett.* **2004**, *6*, 1261–1264; Spectral data for **5a**: Nokami, J.; Nomiyama, K.; Matsuda, S.; Imai, N.; Kataoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1273–1276.
17. Typical procedure for allylboration under triflic acid catalysis: In a flame dried flask, 4 Å molecular sieves

(240 mg) were charged. The flask was purged three times by vacuum–argon exchange. Dichloromethane (4.5 mL) was added followed by triflic acid (8 μL, 0.096 mmol, 10 mol %). The mixture was cooled to −78 °C and freshly distilled benzaldehyde (145 μL, 1.4 mmol, 1.5 equiv) was added. In another flame dried flask, a solution of boronic ester **1a** (188 mg, 0.96 mmol, 1.0 equiv) in 1.3 mL dichloromethane was prepared and added dropwise to the flask containing benzaldehyde at −78 °C. The reaction mixture was stirred at −78 °C for 40 h, then quenched at −78 °C with 1.5 mL of aqueous saturated sodium bicarbonate and brought to room temperature over 3 h. The phases were separated and the aqueous phase was extracted three times

with dichloromethane. The combined organic phases were washed once with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 513 mg of a crude mixture. The ratio of compounds **4a** to **5a** was determined by ^{1}H NMR of the crude mixture. The crude mixture was then purified by flash chromatography on silica gel using 30% hexanes–70% dichloromethane as eluent and afforded 172 mg (quantitative yield) of a mixture of compounds **4a** and **5a** (R_f: 0.26, 100% dichloromethane).

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