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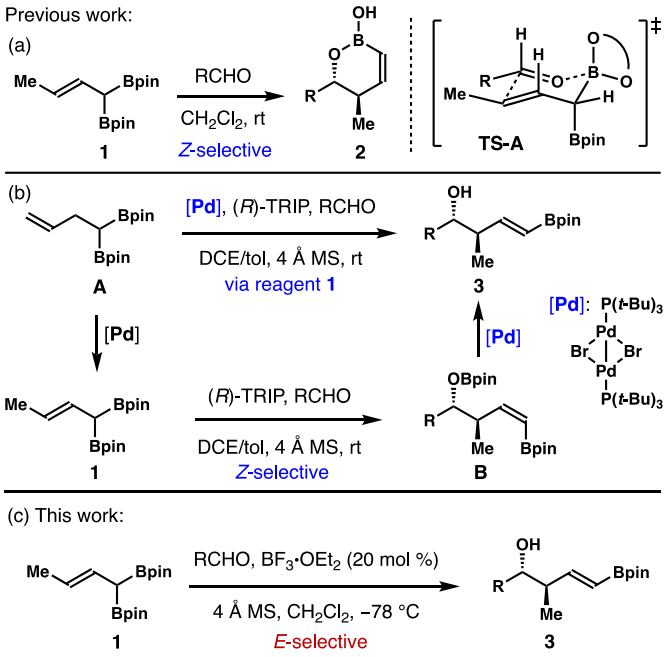
Abstract: Highly stereoselective synthesis of (*E*)-δ-boryl-*anti*-homoallylic alcohols is developed. In the presence of a Lewis acid, aldehyde allylation with α-boryl-(*E*)-crotylboronate gave δ-boryl-*anti*-homoallylic alcohols in good yields with excellent *E*-selectivity. The *E*-vinylboronate group in the products provides a useful handle for cross-coupling reactions as illustrated in the fragment synthesis of chaxamycins.

An emerging topic in the allylation chemistry is carbonyl addition with 1,1-bismetallic allylation reagents.[1,2] In particular, allylation with (*E*)-α-boryl-crotylboronate **1** has recently attracted significant attention.[1] As shown in Scheme 1a, the reaction of reagent **1** with aldehydes proceeds via transition state **TS-A** to give *anti*-1,2-oxaborinan-3-enes **2** with high *Z*-selectivities.[1b,c] It is proposed that the α-Bpin group of **1** is oriented in a pseudo axial position in **TS-A** to minimize steric interactions. The Murakami group disclosed that enantioenriched δ-boryl-substituted *anti*-homoallylic alcohols **3** can be generated from boronate **A** via a one-pot reaction sequence (Scheme 1b).[1a] Pd-catalyzed olefin transposition of **A** generates reagent **1** *in situ*, which undergoes chiral phosphoric acid-catalyzed asymmetric allylation to give the *Z*-adduct **B**. The same Pd complex then catalyzes isomerization of the *Z*-alkene unit of intermediate **B** to form δ-boryl-*anti*-homoallylic alcohols **3**. As part of our program on allylation chemistry,[3] we are interested in developing alternative approaches to access *E*-isomer **3** from reagent **1**. As shown in Scheme 1c, we discovered that, in the presence of Lewis acid BF_3•OEt_2,[4-7] addition of reagent **1** to aldehydes provides δ-boryl-*anti*-homoallylic alcohols **3** with excellent *E*-selectivities.[8-11] The inherent *Z*-selectivity (c.f. **2**) of aldehyde addition with boronate **1** can be inverted by using the BF_3•OEt_2 catalyst. Moreover, the reaction forms alcohols **3** with a functionalized alkene group, which can directly engage in a C□C bond-forming event.

We initiated our studies by identifying a proper Lewis acid catalyst for *E*-selective allylation of benzaldehyde with α-boryl-(*E*)-crotylboronate **1**. As shown in Table 1, the reaction without any



Scheme 1. Allylboration with α-boryl-(*E*)-crotylboronate **1**

catalyst gave a 1:10 mixture of **3a** and **2a** in a combined 96% yield, with *Z*-isomer **2a** as the major product (entry 1). The data confirm the strong inherent pseudo axial preference of the α-Bpin group of reagent **1** in allylation transition state (**TS-A**, Scheme 1).[1b,c] When 10 mol % $Sc(OTf)_3$ was utilized as the catalyst, a 2:1 mixture of **3a** and **2a** was obtained in 78% yield with *E*-isomer **3a** as the major one (entry 2). The reaction between benzaldehyde and boronate **1** with 10 mol % $Cu(OTf)_2$ as the catalyst provided a 1:2 mixture of **3a** and **2a**, slightly favoring *Z*-isomer **2a** (entry 3). The *E*-selectivity was improved to 10:1 when the reaction was conducted in the presence of 10 mol % BF_3•OEt_2 (entry 4). However, the yield was only moderate (57%). Double the loading of BF_3•OEt_2 catalyst (20 mol %) significantly improved the yield (90%), again with high *E*-selectivity (10:1, entry 5). Finally, further enhancement of the *E*-selectivity was achieved by adding 4 Å molecular sieves. The reaction between benzaldehyde and reagent **1** with 20 mol % BF_3•OEt_2 at –78 °C provided *E*-*anti*-adduct **3a** as a single isomer in 97% yield (*E*:*Z* > 20:1, entry 6).

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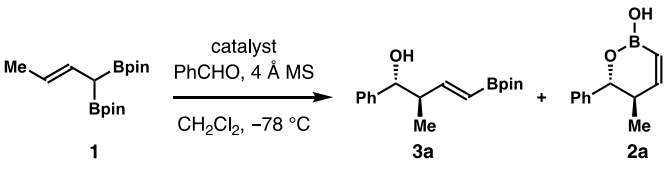
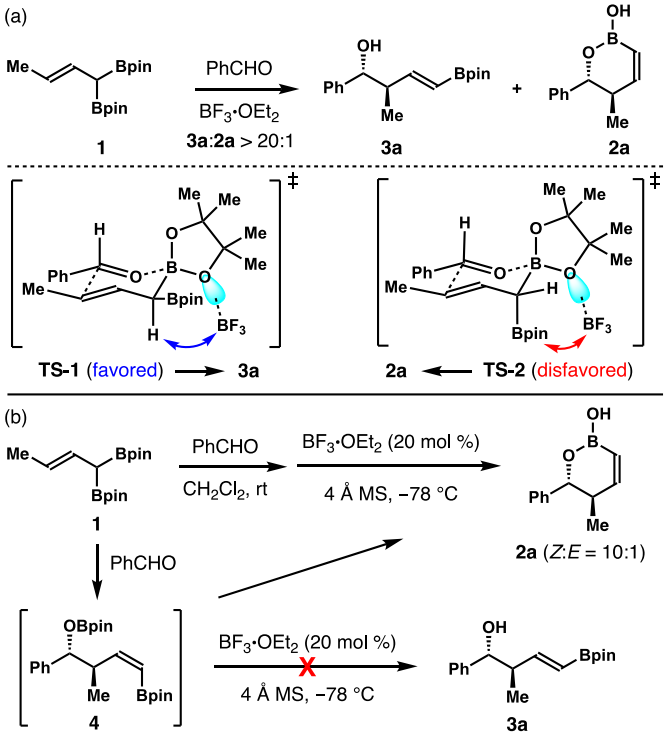
Table 1. Evaluation of the reaction conditions [a]



Entry	Catalyst	3a:2a[b]	Yield (%)[c]
1	no catalyst, rt[d,e]	1:10	96
2	$Sc(OTf)_3$ (10 mol %)[e]	2:1	78
3	$Cu(OTf)_2$ (10 mol %)[e]	1:2	42
4	BF_3•OEt_2 (10 mol %)[e]	10:1	57
5	BF_3•OEt_2 (20 mol %)[e]	10:1	90
6	BF_3•OEt_2 (20 mol %)	>20:1	97

[a] Reaction conditions: boronate **1** (0.13 mmol, 1.3 equiv), catalyst (10 or 20 mol %), PhCHO (0.1 mmol), CH_2Cl_2 (1 mL), −78 °C, 12 h. [b] The ratios of **3a** and **2a** were determined by ^{1}H NMR analysis of the crude reaction products. [c] Yields of isolated products are listed. [d] The reaction was conducted at ambient temperature. [e] The reactions were conducted without 4 Å molecular sieves.

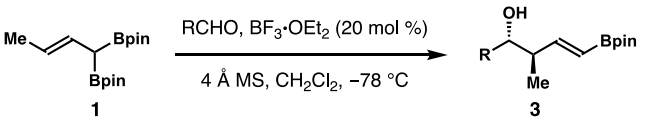


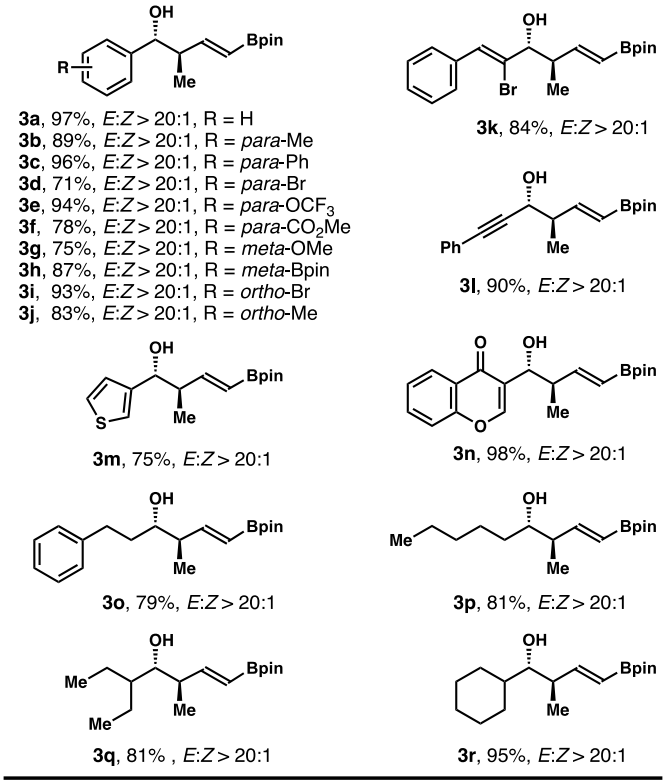
Scheme 2. Analyses of the origin of *E*-selectivity

The rationale of observed *E*-selectivity is outlined in Scheme 2. **TS-1** and **TS-2** are the two competing transition states with BF_3 catalyst coordinating to the most accessible lone pair of electrons of the oxygen atoms (shown in light blue in Scheme 2a). In **TS-2** that leads to **2a**, 1,3-*syn*-pentane interactions are developed between the pseudo axially positioned Bpin group and the BF_3 catalyst (shown with a red arrow in **TS-2**). By contrast, such 1,3-*syn*-pentane interactions in **TS-1** are substantially minimized because only a small hydrogen atom occupies the pseudo axial position (shown with a blue arrow in **TS-1**). Although gauche interactions between two Bpin groups of reagent **1** are present in **TS-1**, such gauche interactions are much weaker compared to the 1,3-*syn*-pentane interactions in **TS-2**.[12] Consequently, BF_3•OEt_2-catalyzed allylation with boronate **1** proceeds via the favored transition state **TS-1**, delivering alcohol **3a** with high *E*-selectivity.

We also considered whether the *E*-selectivity originates from BF_3-catalyzed alkene isomerization of the initial allylation *Z*-adduct **4** (Scheme 2b). To rule out this potential pathway, the reaction of boronate **1** with benzaldehyde was conducted in the absence of the BF_3•OEt_2 catalyst. When benzaldehyde was fully consumed, 20 mol % of BF_3•OEt_2 was added to the reaction mixture. After stirring at −78 °C for 12 h, a 10:1 mixture was obtained with *Z*-isomer **2a** as the major product. The selectivity is identical to the one from the uncatalyzed reaction (entry 1, Table 1). Therefore, it is evident that the reaction does not involve a BF_3-catalyzed *Z*-alkene isomerization pathway to generate *E*-isomer **3**.

Table 2. Scope of BF_3•OEt_2-catalyzed *E*-selective allylation [a-c]

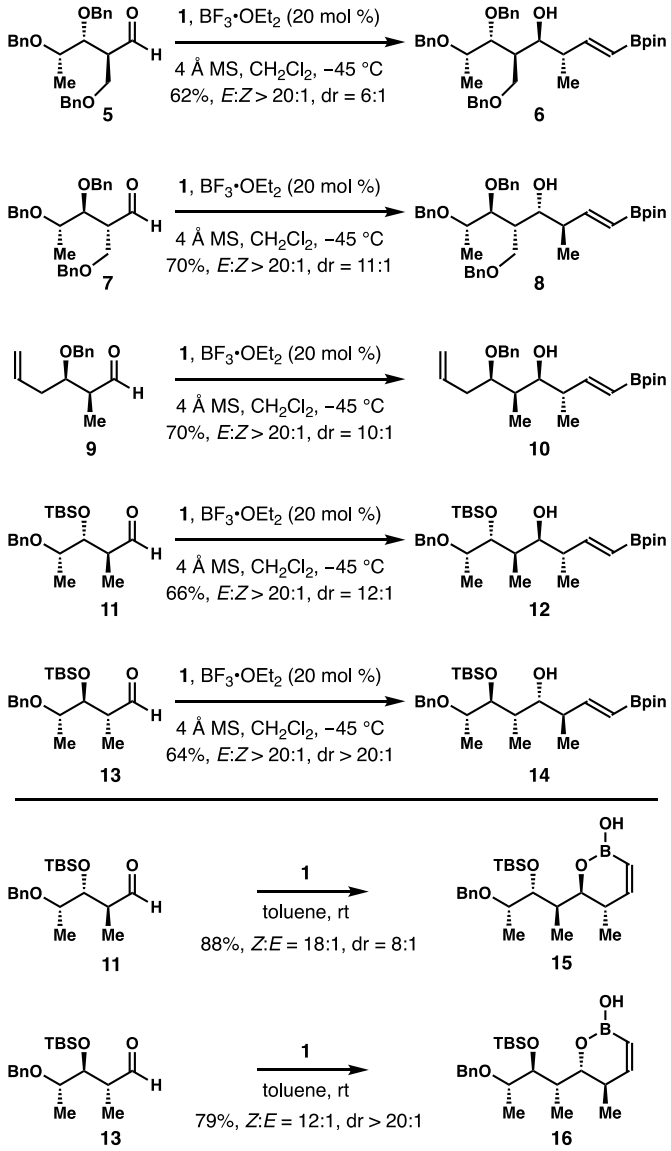




(a) Reagent **1** (0.13 mmol, 1.3 equiv), aldehyde (0.1 mmol, 1.0 equiv), BF_3•OEt_2 (20 mol %), 4 Å molecular sieves (50 mg), CH_2Cl_2 (1 mL), −78 °C. (b) *E*/*Z*-selectivities were determined by ^{1}H NMR analysis of crude reaction products. (c) Yields of isolated products are listed.

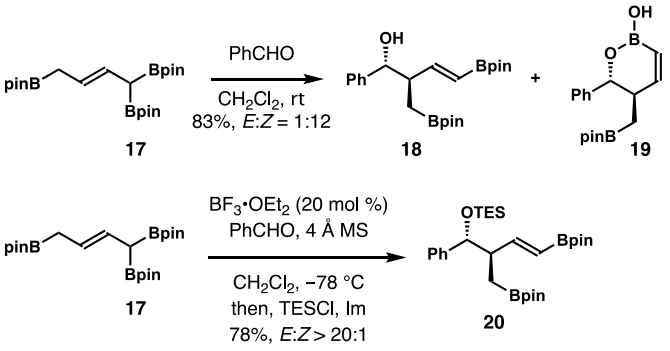
The reaction scope was explored next and the results are summarized in Table 2. Under the developed conditions, a wide variety of aldehydes participated in the reaction to give (*E*)-δ-boryl-*anti*-homoallylic alcohols **3** in good yields with excellent *E*-selectivities. Aromatic aldehydes with an alkyl or aryl group at the *para*-position reacted with boronate **1** to afford products **3b**,**c** in 89-96% yields with >20:1 *E*-selectivities. Aldehydes with a Br atom, an OCF_3 group or an electron-withdrawing CO_2Me group at the *para*-position are suitable substrates for the reaction. Alcohols **3d**-**f** were obtained in 71-94% yields with excellent *E*-selectivities. Reactions of aromatic aldehydes with diverse substituents at the *meta*- or *ortho*-position proceeded smoothly to form alcohols **3g**-**j**

in 75-93% yields with >20:1 *E*-selectivities. The reaction tolerates α,β-unsaturated aldehydes and substrates that contain a heterocycle, forming alcohols **3k**-**n** in 75-98% yields with >20:1 *E*-selectivities. Notably, BF_3•OEt_2-catalyzed reactions of several aliphatic aldehydes with boronate **1** delivered products **3o**-**r** in 79-95% yields with excellent *E*-selectivities (>20:1).



Scheme 3. Allylation with enantioenriched aldehydes

To explore whether the *E*-selective allylation can be used in reactions with chiral, nonracemic aldehydes to generate allylated products diastereoselectively, we synthesized a collection of enantioenriched aldehydes and conducted BF_3•OEt_2-catalyzed allylation studies with reagent **1**. As shown in Scheme 3, the reaction of aldehyde **5** with reagent **1** was slow at −78 °C. However, upon elevating the reaction temperature to −45 °C, product **6** was formed in 62% yield with >20:1 *E*-selectivity and 6:1 diastereoselectivity. Formation of any product with *Z*-olefin geometry was not detected. The reaction of aldehyde **7** under the same conditions gave product **8** in 70% yield with >20:1 *E*-selectivity and 11:1 dr. Similar results were obtained from aldehyde **9**; adduct **10** was afforded in 70% yield with >20:1 *E*-selectivity and 10:1 dr. Excellent *E*-selectivities were also achieved in reactions with chiral aldehydes **11** and **13**. Allylated products **12** and **14** were obtained in 66% and 64% yield with 12:1 and >20:1 dr, respectively. The diastereoselectivities in these reactions are governed by the inherent Felkin-Anh preference of the aldehydes,[13] while BF_3•OEt_2 catalyst dictates the *E*-selectivity of the reactions. It is worth noting that the reactions of chiral aldehydes **11** and **13** with boronate **1** in the absence of the BF_3•OEt_2 catalyst produced *Z*-isomers **15** and **16** with 18:1 and 12:1 *Z*-selectivity, respectively. The inherent *Z* preferences were overridden in reactions of **11** and **13** with the BF_3•OEt_2 catalyst, affording alcohols **12** and **14** with excellent *E*-selectivities.



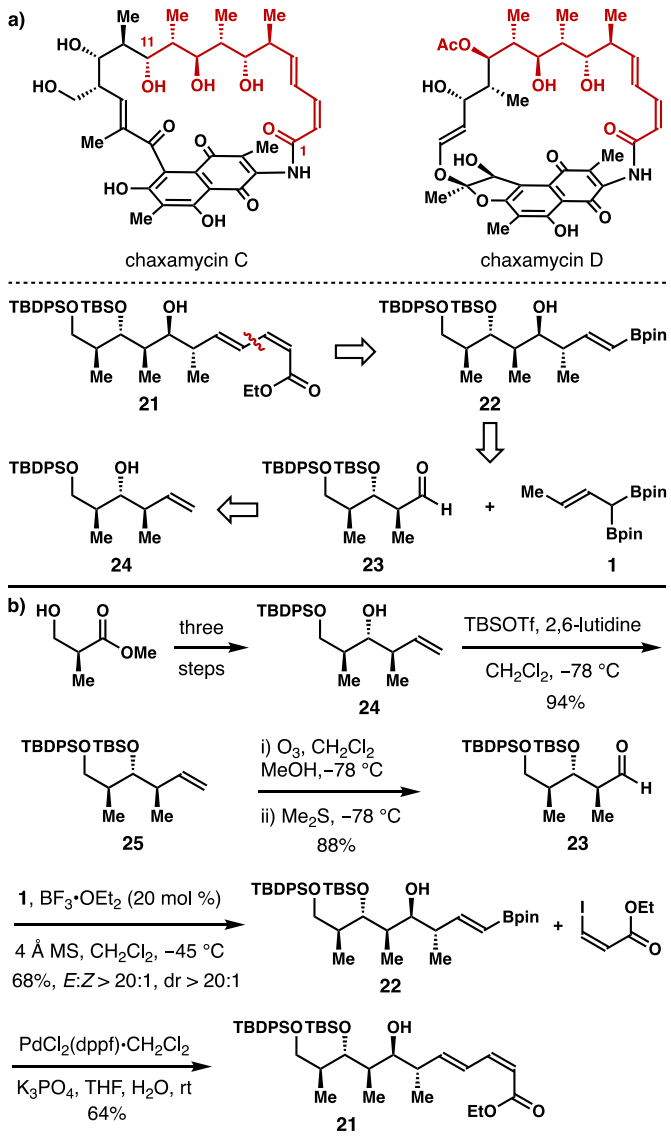
Scheme 4. *E*-Selective allylation with boronate reagent **17**

In addition to boronate **1**, the protocol was also applied to reagent **17**.[14] As shown in Scheme 4, the reaction of boronate **17** with benzaldehyde in the absence of any catalyst formed a 1:12 mixture of two products **18** and **19**, with *Z*-isomer **19** as the major component of the mixture. By contrast, in the presence of the BF_3•OEt_2 catalyst, the reaction with reagent **17** generated *E*-product **20** as the only isomer upon *in situ* protection.

To highlight the synthetic utility of the developed *E*-selective allylation, stereoselective synthesis of a fragment of chaxamycins C and D was pursued.[15] As shown in Scheme 5a, the C(1)-C(11) fragment (**21**) of chaxamycins can be assembled via a Suzuki coupling between vinylboronate **22** and ethyl *Z*-iodo-acrylate. Boronate **22** can be obtained via *E*-selective allylation of aldehyde **23**, which can be synthesized from known compound **24**.[16]

Synthesis of the C(1)-C(11) fragment of chaxamycins C and D is shown in Scheme 5b. Known alcohol **24** was synthesized from Roche ester in three steps.[16] Alcohol silylation of **24** formed TBS-ether **25** in 94% yield. Ozonolysis of **25** under standard conditions gave aldehyde **23** in 88% yield. BF_3•OEt_2-catalyzed allylation of aldehyde **23** with reagent **1** afforded alcohol **22** in 68% yield with >20:1 *E*-selectivity and diastereoselectivity. Pd-catalyzed Suzuki coupling of **22** with ethyl *Z*-iodo-acrylate furnished diene **21**, which represents the C(1)-C(11) fragment of chaxamycins C and D.

In summary, we developed a BF_3•OEt_2-catalyzed highly *E*-selective allylation with α-boryl-(*E*)-crotylboronate to give δ-boryl-*anti*-homoallylic alcohols. The reactions with a collection of enantioenriched aldehydes gave allylated products with excellent *E*-selectivities and high diastereoselectivities, which highlight the synthetic utility of the method in assembling stereochemically rich intermediates that are valuable for complex molecule synthesis. Moreover, the *E*-vinylboronate group in the products provides a handle for transition metal-catalyzed cross-coupling reactions as illustrated in the fragment synthesis of chaxamycins C and D.



Scheme 5. Synthesis of the C(1)-C(11) fragment of chaxamycins

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