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# Development of $\alpha$ , $\alpha$ -Disubstituted Crotylboronate Reagents and Stereoselective Crotylation via Brønsted or Lewis Acid Catalysis

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**ABSTRACT:** The development of  $\alpha, \alpha$ -disubstituted crotylboronate reagents is reported. Chiral Brønsted acid-catalyzed asymmetric aldehyde addition with the developed *E*-crotylboron reagent gave (*E*)-anti-1,2-oxaborinan-3-enes with excellent enantioselectivities and *E*-selectivities. With BF<sub>3</sub>·OEt<sub>2</sub> catalysis, the stereoselectivity is reversed, and (*Z*)- $\delta$ -boryl-anti-homoallylic alcohols are obtained with excellent *Z*-selectivities from the same *E*-crotylboron reagent. The *Z*-crotylboron reagent also participates in BF<sub>3</sub>·OEt<sub>2</sub>-catalyzed crotylation to furnish (*Z*)- $\delta$ -boryl-syn-homoallylic alcohols with good *Z*-selectivities. DFT computations establish the origins of observed enantio- and stereoselectivities of chiral Brønsted acid-catalyzed asymmetric allylation. Stereochemical models for BF<sub>3</sub>·OEt<sub>2</sub>-catalyzed reactions are proposed to rationalize the *Z*-selective allyl additions. These reactions generate highly valuable homoallylic alcohol products with a stereodefined trisubstituted alkene unit. The synthetic utility is further demonstrated by the total syntheses of salinipyrones A and B.

#### INTRODUCTION

Polyketides are structurally complex secondary metabolites that often display a variety of biological activities.<sup>1</sup> They have played a significant role in the discovery and development of modern medicines.<sup>2</sup> Over the past several decades, polyketides have attracted significant attention from synthetic organic and chemical biology communities due to their structural complexity and medicinal relevance.<sup>3</sup> As illustrated in Figure 1, one structural feature of numerous polyketides is the homoallylic alcohol unit with a stereodefined trisubstituted alkene embedded in the carbon skeleton of these natural products (highlighted in red in Figure 1). Biosynthetically, such structural motifs are assembled via a series of transformations by collaborative efforts of several domains of the polyketide synthase, including ketosynthase, ketoreductase, and dehydratase.<sup>4</sup> In parallel, several strategies are known for chemical syntheses of these molecules via a multistep reaction sequence.<sup>5</sup> For example, the Kobayashi group developed a chiral auxiliary-based approach using vinyl ketene silyl N,Oacetal to access homoallylic alcohol with a trisubstituted alkene.  $S^{a-f}$  Alternatively, these molecules can be assembled by constructing the trisubstituted alkene from appropriate intermediates with the requisite stereocenters. For instance, the classic Wittig olefination of an aldehyde intermediate is one

method of choice to synthesize trisubstituted alkenes.<sup>5g-i</sup> Such structural entities can also be formed via olefin metathesis from the alkene precursors.<sup>5j-1</sup> Reductive coupling of an internal alkyne intermediate is another viable approach to prepare these molecules.<sup>5m-p</sup>

As one of the most adopted methods to synthesize acyclic molecules with contiguous stereocenters, asymmetric carbonyl addition with crotylmetal reagents has been extensively utilized to synthesize polyketide natural products.<sup>6,7</sup> In principle, asymmetric aldehyde crotylation with  $\alpha,\alpha$ -disubstituted crotylmetal reagents **A** (Scheme 1a) could provide a direct access to homoallylic alcohols with a stereodefined trisubstituted alkene unit (e.g., **D**, Scheme 1a).<sup>8,9</sup> However, to date there is no report on enantioselective synthesis of tertiary allylic organometallics such as **A**. Moreover, crotylmetal reagents **A** are prone to undergo reversible 1,3-metallo shifts

Received: April 15, 2020





**Figure 1.** Selected natural products that contain homoallylic alcohols with a trisubstituted alkene group.

## Scheme 1. Approaches to Enantioenriched Homoallylic Alcohols with a Stereodefined Trisubstituted Alkene

Approaches:

(a) Allylation via  $\alpha, \alpha$ -disubstituted crotylmetal reagents:



to form thermodynamically more stable secondary organometallics **B** or **C** (or a mixture of **A**, **B**, and **C**). It is conceivable that subsequent allylation event is unlikely to be selective, and a mixture of products **D**, **E**, and **F** will be generated from the process (approach a, Scheme 1). By contrast, crotylboronates are known to be configurationally stable and will not participate in reversible 1,3-metallo shifts at ambient temperature. Therefore, asymmetric allylation of aldehydes with  $\alpha$ , $\alpha$ disubstituted crotylboronate **G** could in theory produce the requisite homoallylic alcohols with a stereodefined trisubstituted alkene unit (approach b, Scheme 1). However, this reaction often generates a mixture of two products **H** and **I**. And stereoselectivity is low when the sizes of R<sup>1</sup> and R<sup>2</sup> groups are similar to each other. In addition, enantioselective preparation of such chiral nonracemic  $\alpha, \alpha$ -disubstituted crotylboron reagents is synthetically challenging.<sup>10</sup> To our knowledge, highly stereoselective generation of homoallylic alcohols with a stereodefined trisubstituted alkene unit through allylation is an unsolved problem. Therefore, we set a goal to develop catalytic methods to address this challenge.

With our continuing efforts to develop novel allylation reagents and catalytic methods for the syntheses of polyketide natural products,<sup>11</sup> we report herein the development of  $\alpha, \alpha$ -disubstituted crotylboronate reagents **2** (Scheme 1c). These reagents are achiral and can be conveniently synthesized from 1,1-diborylalkanes. In the presence of a proper catalyst, crotylation of aldehydes with reagents **2** generates products **3** or **4** with excellent selectivities (approach c, Scheme 1). This approach provides a general solution to access homoallylic alcohols with a stereodefined trisubstituted alkene unit. Moreover, products **3** and **4** are highly versatile intermediates that can undergo a variety of subsequent transformations. In particular, cross-coupling reactions with electrophiles will produce homoallylic alcohols with a trisubstituted olefin (e.g., H and I, Scheme 1b).

#### RESULTS AND DISCUSSION

Reagent Development. To implement the strategy outlined in Scheme 1c, we prepared 1,1-diborylalkane precursor 1a via sequential alkylation of 1,1-diborylmethane.<sup>17</sup> With precursor 1a in hand, subsequent transition-metalcatalyzed olefin transposition was conducted. Initial experiments with Ru- or Ir-catalyzed olefin transposition of 1a did not proceed. Presumably the steric bulk of nearby tetrasubstituted carbon atom prevents coordination of the alkene group of 1a to the ligand-bound catalyst. Barton and coworkers showed that transposition of a sterically congested alkene of ergosterol can be achieved with RhCl<sub>3</sub>·3H<sub>2</sub>O.<sup>13</sup> We suspected that the less bulky, ligandless RhCl<sub>3</sub>·3H<sub>2</sub>O catalyst should be more accessible to bind the alkene unit of 1a compared to a bulky ligand-bound catalyst. To test the hypothesis, isomerization of 1a was conducted with RhCl<sub>3</sub>.  $3H_2O$  as the catalyst. In the event, 1a was treated with 10 mol % of RhCl<sub>2</sub>·3H<sub>2</sub>O in ethanol. No reaction occurred at ambient temperature or 40 °C even with prolonged time (24 h) (entries 1 and 2, Table 1). However, alkene transposition of 1a proceeded smoothly at elevated temperature (60 °C), and the desired product 2a was isolated in 61% yield (entry 3, Table 1). Formation of Z-isomer **2b** was not detected. Switching the solvent to <sup>t</sup>BuOH also produced boronate 2a with high Eselectivity, albeit with a slightly lower yield (entry 4, Table 1). In larger scale reactions, the catalyst loading can be reduced to 5 mol %, and product 2a was isolated in 76-81% yields with >20:1 E-selectivity (entries 5 and 6, Table 1).

**Development of** *E*-Selective Crotylation with Reagent 2a. With a robust approach to access reagent 2a, we carried out subsequent aldehyde allylation studies with 2a. As shown in Scheme 2, addition of 2a to benzaldehyde in the absence of any catalyst produced a 3:1 mixture of *E*-isomer  $(\pm)$ -3a and *Z*-isomer  $(\pm)$ -4a. These data suggest that the two competing transition states TS-1 and TS-2 have similar energies. TS-1 with pseudoaxial placement of the  $\alpha$ -Bpin group of reagent 2a has a slight advantage over TS-2 ( $\alpha$ -Bpin in a pseudoequatorial position) owing to less pronounced gauche interactions between the methyl and Bpin groups

Table 1. Evaluation of Reaction Conditions for *E*-Selective Alkene Transposition of  $1a^{a}$ 

$\checkmark$	Bpin conditions Me Bpin Me 1a	Bpin Bpin + Me 2a	Me Me Bpin 2b
entry	conditions	2a:2b	yield (%) <sup>c</sup>
1	RhCl <sub>3</sub> ·3H <sub>2</sub> O (10 mol %), EtOH, rt	ND	ND
2	RhCl <sub>3</sub> ·3H <sub>2</sub> O (10 mol %), EtOH, 40	0°C ND	ND
3	RhCl <sub>3</sub> ·3H <sub>2</sub> O (10 mol %), EtOH, 60	0 °C >20:1	61
4	$RhCl_3 \cdot 3H_2O$ (10 mol %), <sup>t</sup> BuOH, 6	60 °C >20:1	49
5 <sup>d</sup>	RhCl <sub>3</sub> ·3H <sub>2</sub> O (5 mol %), EtOH, 60	°C >20:1	76
6 <sup>e</sup>	RhCl <sub>3</sub> ·3H <sub>2</sub> O (5 mol %), EtOH, 60	°C >20:1	81

<sup>*a*</sup>Reaction conditions: alkene **1a** (0.2 mmol), RhCl<sub>3</sub>·3H<sub>2</sub>O (5 or 10 mol %), solvent (0.5 mL). <sup>*b*</sup>The ratios of **2a** and **2b** were determined by <sup>1</sup>H NMR analysis of the crude reaction products. <sup>*c*</sup>Yields of isolated products are listed. <sup>*d*</sup>The reaction was conducted in a 0.5 mmol scale. <sup>*e*</sup>The reaction was conducted in a 3 mmol scale.





(shown with a blue arrow in TS-1) compared to the steric interactions between two Bpin groups (shown with a red arrow, TS-2).

Chiral phosphoric acid (R)-A (Scheme 2) has been reported to catalyze asymmetric allylboration of aldehydes by Antilla and co-workers.<sup>14,15</sup> Following the seminal work, a variety of boron reagents have been shown to undergo chiral phosphoric acid-catalyzed enantioselective addition to aldehydes.<sup>16–18</sup> The origin of enantioselection was elucidated by computational studies from the Houk and Goodman groups.<sup>19</sup> We were intrigued whether the addition of phosphoric acid (R)-A to the reaction of benzaldehyde and reagent 2a could enhance stereoselectivity while maintaining a high level of enantioselection. In the event, 5 mol % of phosphoric acid (*R*)-**A** was added to the reaction of **2a** with benzaldehyde at -45 °C in toluene. Gratifyingly, product **3a** was obtained in 89% yield with 97% ee and excellent *E*-selectivity (>20:1). A similar level of stereoselectivity and enantioselectivity was also achieved when phosphoric acid (*R*)-**B** was utilized as the catalyst under otherwise identical conditions (Scheme 2). These data indicate that the acid catalyst (*R*)-**A** or (*R*)-**B** enables highly face selective addition to benzaldehyde. More importantly, it also controls the stereoselectivity by positioning the more bulky  $\alpha$ -Bpin group of **2a** in a pseudoaxial orientation in the transition state and the less sterically demanding methyl group in a pseudoequatorial orientation (cf. **TS-1** with the acid catalyst).

Substrate Scope for Phosphoric Acid-Catalyzed Crotylation with *E*-Crotylboronate 2a. The scope of aldehyde that undergoes enantioselective crotylation with boronate 2a was explored next. As summarized in Scheme 3,

Scheme 3. Scope of Aldehyde in Chiral Phosphoric Acid-Catalyzed E-Selective Allylation with Reagent  $2a^{a-d}$ 



<sup>*a*</sup>Allylboronate **2a** (0.13 mmol, 1.3 equiv), aldehyde (0.1 mmol, 1.0 equiv), (R)-**A** (5 mol %) toluene (0.3 mL), -45 °C. <sup>*b*</sup>Yields of isolated products are listed. <sup>*c*</sup>Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase of the product obtained from cross-coupling with PhI. <sup>*d*</sup>The *E/Z* ratios were determined by <sup>1</sup>H NMR analysis of the crude reaction products. <sup>*e*</sup>10 mol % (*R*)-**A** was used. <sup>*f*</sup>The ee was determined from the vinyl bromide product obtained from bromination of vinyl Bpin. <sup>*g*</sup>10 mol % catalyst (*R*)-**B** was used as the catalyst.

in the presence of 5 mol % of catalyst (R)-A, the reaction worked well with a broad scope of aldehydes. Allylation products 3 were obtained with excellent E-selectivities and enantiomeric excess. For instance, reactions of aromatic aldehydes with a substituent at the para-position provided products 3b-d in 86-97% yields with >20:1 E-selectivity and 99% ee. The conversion was low for ortho-substituted aldehydes under standard conditions. The reaction rate was significantly enhanced by increasing the catalyst loading to 10 mol %, affording product 3e in 88% yield with diminished enantioselectivity (90% ee). The reaction of meta-substituted aldehyde with 2a proceeded smoothly to give product 3f in 95% yield with >20:1 E-selectivity and 99% ee.  $\alpha_{\beta}$ -Unsaturated aldehydes also reacted with crotylboronate 2a to furnish products 3g,h in 81-93% yields with >20:1 Eselectivities and 98-99% ee. Similar results were achieved with aldehydes that contain a heterocycle, and products 3i,j were isolated in 93-94% vields with >20:1 *E*-selectivities and 96–99% ee. The reactions of aliphatic aldehydes with acid (R)-A as the catalyst gave products with moderate enantioselectivities (~85% ee). However, when phosphoric acid (R)-B was employed as the catalyst, allylated products were obtained with excellent enantioselectivities. In the presence of 10 mol % acid (R)-B, reactions of several representative aliphatic aldehydes with reagent 2a furnished products 3k,l in 82-87% yields with >20:1 E-selectivities and 95-98% ee.

**Computational Studies.** To gain further insights into the origins of observed *E*-selectivity and enantioselectivity of the chiral phosphoric acid-catalyzed crotylation with reagent **2a**, we applied density functional theory (DFT) calculations at the M06-2X/6-311+G(d,p)-SMD(toluene)//B3LYP-D3/6-31G(d) level of theory<sup>20-23</sup> using Gaussian 09 with the ultrafine grid. The uncatalyzed allylboration of benzaldehyde with crotylboronate **2a** was studied first. As illustrated in Figure 2, transition state **TS-3** leading to (±)-**3a** was found to



**Figure 2.** Optimized transition states **TS-3** and **TS-4** of noncatalyzed crotylation of benzaldehyde with crotylboronate **2a**. The bond lengths are in ångstrom.

be 0.9 kcal/mol lower in free energy than TS-4 that delivers  $(\pm)$ -4a. This finding is consistent with the experimentally observed selectivity, a 3:1 mixture of  $(\pm)$ -3a and  $(\pm)$ -4a favoring *E*-isomer 3a. Examining the optimized geometries indicates that TS-3 is favored over TS-4 due to steric factors. In the disfavored transition state TS-4, the  $\alpha$ -Bpin unit of 2a occupies a pseudoequatorial position; both the H–H non-

bonding distances (2.31 and 2.26 Å) are shorter than those in TS-3 (2.33 Å), which indicates a larger repulsion between the two Bpin groups of reagent 2a in TS-4 than that in TS-3. The energetics are in reasonable agreement with the experimentally obtained stereoselectivity.

Next, we explored chiral phosphoric acid (R)-A catalyzed asymmetric allylation of benzaldehyde with crotylboronate 2a. As shown in Figure 3, transition state TS-6 has a pseudoequatorial placement of the Bpin group of reagent 2a and gives alcohol 4a. The competing transition state TS-5 that leads to product 3a has a pseudoaxial placement of the  $\alpha$ -Bpin group. DFT computations showed that the calculated free energy of TS-5 is 2.0 kcal/mol lower than that of TS-6. DFT calculations also indicate that, besides the repulsion between two Bpin groups of reagent 2a in TS-6, the steric repulsion between the Bpin unit and the isopropyl groups of the acid catalyst (R)-A further destabilizes transition state TS-6. The nonbonding H-H distances are 2.32 and 2.32 Å (TS-6 in Figure 3). By contrast, with pseudoaxial orientation of the  $\alpha$ -Bpin group, transition state TS-5 does not have such repulsive interactions. Further investigations revealed that to avoid significant steric clashes, the dihedral angle between 2,4,6triisopropylphenyl group and the BINOL backbone of the catalyst is 93.1° in TS-6, which differs from the dihedral angle in the free catalyst  $(106.3^{\circ})$  by  $13^{\circ}$ , resulting in unfavorable catalyst distortion. In contrast, this dihedral angle in TS-5 is 104.2°, which is close to the one in the free catalyst  $(106.3^{\circ})$ . We conclude that the unfavorable steric repulsions dictate the E-selectivity of chiral phosphoric acid-catalyzed crotylation with reagent 2a.

As shown in the studies, chiral phosphoric acid (R)-A not only defines the stereoselectivity (E:Z > 20:1) of the crotylation by controlling the orientation of  $\alpha$ -Bpin group in the transition state but also enables enantioselective addition of 2a to aldehyde substrates. As shown in Figure 4, the calculated re-face attack in transition state TS-5 is more favorable energetically than si-face attack in TS-7 by 7.2 kcal/mol. The results explain the 97% ee observed experimentally. To better identify the factors that impact the enantioselectivity, optimized geometries of transition states TS-5 and TS-7 were compared. On the basis of the quadrant projection, the  $\alpha$ -Bpin group is positioned in the narrow quadrant in TS-7, forcing the dihedral angle between 2,4,6-triisopropylphenyl group and the BINOL backbone of the catalyst to a significant distortion (120.0°) compared to optimized free catalyst (106.3°). By contrast, the  $\alpha$ -Bpin group of **2a** occupies an empty quadrant in more favorable transition state TS-5. In addition, the steric repulsion between the 2,4,6-triisopropylphenyl substituent of acid catalyst (R)-A and the Bpin group of 2a leads to a longer H-bond distance in TS-7 (1.53 and 2.29 Å) than those in TS-5 (1.48 and 2.11 Å) (Figure 4c). The shorter H-bond length results in a more compact transition state TS-5 compared to TS-7. Therefore, both the catalyst distortion and weaker H-bond interaction destabilize transition state TS-7, which leads to the exceptional enantioselectivity of the chiral phosphoric acid (R)-A catalyzed allylation with reagent 2a.

**Development of** *Z***-Selective Crotylation with Reagent 2a.** While the phosphoric acid-catalyzed aldehyde addition with reagent **2a** gave products with excellent *E*-selectivity, we were intrigued whether it is possible to achieve *Z*-selective allylation with **2a** in the presence of an appropriate Lewis acid.<sup>24-28</sup> Scheme **4** shows the proposed model for

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Figure 3. Optimized structures of transition states TS-5 and TS-6. The bond lengths are in ångstrom.

Lewis acid-catalyzed allylation with reagent 2a that may provide products with different stereochemical outcomes. There are two competing transition states TS-8 and TS-9 that lead to the formation of products 4a and 3a, respectively, when a Lewis acid coordinates to the lone pair of electrons of the oxygen atom shown in green. In TS-8, 1,3-syn-pentane interactions (shown with a blue arrow in TS-8) are developed

projection of TS-7 and TS-5. The bond lengths are in angstrom.

between the pseudoaxially positioned methyl group and the Lewis acid catalyst. In the competing transition state TS-9, similar 1,3-syn-pentane interactions also exist between the pseudoaxially oriented  $\alpha$ -Bpin group and the Lewis acid (shown with a red arrow in TS-9). It is apparent that steric interactions in the latter case are much more severe. However, gauche interactions between the pinacol moiety on boron and the pseudoequatorially oriented substituent (the Bpin group in

Scheme 4. Transition State Analyses for Proposed Lewis Acid-Catalyzed Allylation with Reagent 2a



**TS-8** or the methyl group in **TS-9**) should also be taken into account. Although the overall balance of *syn*-pentane and gauche interactions will ultimately determine the E/Z-selectivity of the reaction, we postulate that the *syn*-pentane interactions should be the dominant factor and **TS-8** should be more favorable to give alcohol **4a** as the major product.

Next, allylation studies of benzaldehyde with reagent 2a in the presence of a Lewis acid catalyst were conducted to probe whether product 3a or 4a will be formed preferentially. Benzaldehyde was treated with reagent 2a at -78 °C in CH<sub>2</sub>Cl<sub>2</sub> in the presence of 20 mol % of a Lewis acid catalyst. As shown in Figure 5, when BF<sub>3</sub>·OEt<sub>2</sub> was utilized, the reaction



Figure 5. Results of Lewis acid-catalyzed allylation of benzaldehyde with reagent 2a.

provided alcohol 4a in 93% yield with >20:1 Z-selectivity. The formation of E-isomer 3a was not detected. Other Lewis acid catalysts such as Sc(OTf)<sub>3</sub> and Cu(OTf)<sub>2</sub> gave inferior results. To evaluate whether the origin of observed Z-selectivity is consistent with the proposed stereochemical model in Scheme 4, density functional theory (DFT) calculations at the M06-2X/6-311+G(d,p)-SMD(dichloromethane)//B3LYP-D3/6-31G(d) level of theory using Gaussian 09 with the ultrafine grid were conducted. However, the results from extensive computational studies with BF<sub>3</sub>·OEt<sub>2</sub> catalyst coordinating to an oxygen atom of the BPin group cannot explain the observed Z-selectivity (see Supporting Information for details). We also considered the option that the BF3. OEt2 catalyst coordinates to the oxygen atom of the carbonyl group of benzaldehyde. Again, the computational results are not consistent with the experimental data (see Supporting Information for details). Therefore, the BF<sub>3</sub>·OEt<sub>2</sub>-catalyzed aldehyde allylation with reagent 2a likely proceeds via a much more complicated mechanism. This will be the subject for future studies. Nevertheless, it is remarkable that the inherent E-selectivity (3:1,Scheme 2) of the reaction can be reversed to excellent Z-

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selectivity (>20:1) simply by employing an appropriate Lewis acid catalyst.

Substrate Scope for  $BF_3$ ·OEt<sub>2</sub>-Catalyzed Allylation with *E*-Crotylboron Reagent 2a. The scope of aldehyde that participated in  $BF_3$ ·OEt<sub>2</sub>-catalyzed allylation with 2a was explored next. And the results are summarized in Scheme 5.

Scheme 5. Scope of Aldehyde in  $BF_3$ ·OEt<sub>2</sub>-CatalyzedZ-Selective Allylation with Reagent 2a<sup>a-c</sup>



<sup>*a*</sup>Boronate **2a** (0.13 mmol, 1.3 equiv), aldehyde (0.1 mmol, 1.0 equiv), BF<sub>3</sub>·OEt<sub>2</sub> (20 mol %), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C. <sup>*b*</sup>Z/*E*-selectivities were determined by <sup>1</sup>H NMR analysis of the crude reaction products. <sup>*c*</sup>Yields of isolated products are listed. <sup>*d*</sup>The reactions were conducted at -20 °C.

Overall, the reaction worked well with a broad scope of aldehyde substrates. Aromatic aldehydes with different substitution patterns reacted with reagent **2a** to provide homoallylic alcohols **4a**-**f** in 85–95% yields with >20:1 *Z*-selectivities. The reactions of  $\alpha,\beta$ -unsaturated aldehydes with boronate **2a** occurred to give products **4g,h** in 80–86% yields with >20:1 *Z*-selectivities. Aldehydes that contain a heterocycle are also suitable substrates for the reaction, furnishing products **4i,j** in 86–89% yields with 17:1 to >20:1 stereoselectivities. The reaction rates of aliphatic aldehydes with **2a** at -78 °C were slow. Upon elevation of the reaction temperature to -20

 $^{\circ}$ C, the reaction was complete within 12 h, and alcohols 4k,l were obtained in 70–91% yields with >20:1 Z-selectivities.

**Development of Z-Crotylboronate 2b and Z-Selective Allylation with Reagent 2b.** We recently showed that  $\alpha$ boryl-Z-crotylboronate 2c can be prepared via Ni-catalyzed Zselective olefin transposition from precursor 1b (Scheme 6).<sup>29</sup>



Under identical conditions, however, the reaction with 1a did not occur. We were not able to generate any Z-crotylboron reagent 2b through this approach even with extensive optimizations. We were pleased to discover that Z-reagent 2b can be conveniently prepared from methylation of crotylboronate 2c that was obtained via olefin transposition from 1b (Scheme 6). Treatment of 2c with LiTMP and MeI at -40 °C gave Z-crotylboron reagent 2b in 65% isolated yield. It is worth noting that the Z-olefin geometry is conserved during the process. Erosion of the Z-olefin was not detected; presumably the anion generated from deprotonation is localized at the carbon atom due to electronic stabilization provided by the neighboring two boron atoms (the boron  $\alpha$ anion effect).<sup>30</sup>

After securing of reagent 2b, allylation studies of aldehydes with 2b were carried out. As shown in Scheme 7, the reaction of reagent 2b with benzaldehyde in the absence of any catalyst provided a 3:1 mixture of products 5a and 6a, favoring the *Z*-isomer 5a. In the presence of 20 mol % BF<sub>3</sub>·OEt<sub>2</sub>, the *Z*-selectivity was improved to 10:1, and *Z*-isomer 5a was isolated in 76% yield (Scheme 7).

The proposed stereochemical model to explain the observed Z-selectivity of this reaction is shown in Scheme 7. Between the two competing transition states TS-10 and TS-11 that lead to the formation of 5a and 6a, TS-11 suffers A<sup>1,3</sup> allylic strain<sup>31</sup> between the methyl and  $\alpha$ -Bpin groups of reagent **2b** as well as the syn-pentane interactions between the BF3 catalyst and pseudoaxially positioned Bpin group of reagent 2b. By contrast, A<sup>1,3</sup> allylic strain between the two methyl groups of 2b and syn-pentane interactions between the BF<sub>3</sub> catalyst and axially positioned methyl group of 2b are developed in transition state TS-10. The overall steric repulsion in TS-10 is considerably less severe than that in TS-11 because of the larger pseudoaxially positioned Bin group in TS-11. Therefore, the reaction of benzaldehyde with reagent 2b in the presence of BF3·OEt2 produced the major Z-isomer 5a that is derived from the favored transition state TS-10. DFT computational studies on  $BF_3$ -catalyzed crotylation with reagent 2b were also conducted. However, similar to the case of 2a, the computational results cannot explain experimental data (see the



Supporting Information for details). Again, a different reaction mechanism might be operational for the  $BF_3 \cdot OEt_2$ -catalyzed allylation with Z-reagent 2b.

Substrate Scope for BF<sub>3</sub>·OEt<sub>2</sub>-Catalyzed Z-Selective Allylation with Reagent 2b. Scheme 8 summarizes the scope of aldehyde that reacted with crotylboronate 2b in the presence of BF<sub>3</sub>·OEt<sub>2</sub>. The reaction worked reasonably well with several representative aldehyde substrates, including aromatic,  $\alpha,\beta$ -unsaturated aldehydes, and aldehydes that contain a heterocycle. Products 5a-f were isolated in 76-86% yields with (7-13):1 Z-selectivities. Reaction with aliphatic aldehydes did not proceed under the developed conditions. In the absence of  $BF_3 \cdot OEt_2$ , however, the reactions of aliphatic aldehydes with 2b did occur at 60 °C, and alcohols 5g,h were obtained in 68-73% yields with moderate Zselectivities. In general, the rates of allylation with Z-reagent 2b are slower than the rates with E-reagent 2a likely owing to the additional A<sup>1,3</sup> allylic strain between the two methyl groups involved in TS-10 (Scheme 7). We also attempted catalytic asymmetric allylation reactions of benzaldehyde with reagent **2b** with either acid (*R*)-A or (*R*)-B as the catalyst. However, the reactions did not proceed to give any desired product. Currently we are evaluating other catalysts for enantioselective aldehyde addition with reagent 2b.

**Stereodifferentiation Reactions with Enantioenriched Aldehydes.** Double stereodifferentiation reaction is an important approach to generate diastereomeric products from enantioenriched starting materials.<sup>32</sup> To probe whether the developed catalytic conditions could be used to selectively form diastereomeric products by using two enantiomeric catalysts, reactions of enantioenriched aldehydes with boronate **2a** were examined. As shown in Scheme 9, the reaction of (*S*)citronellal (7) with **2a** in the presence of 10 mol % of phosphoric acid catalyst (*R*)-**B** afforded product **8a** in 64% yield with >20:1 diastereoselectivity and *E*-selectivity. A similar diastereoselectivity and *E*-selectivity (>20:1) were observed

### Scheme 8. Scope of Aldehyde in $BF_3$ ·OEt<sub>2</sub>-Catalyzed Allylation with Z-Crotylboronate $2b^{a-c}$



<sup>*a*</sup>Crotylboronate **2b** (0.13 mmol, 1.3 equiv), aldehyde (0.1 mmol, 1.0 equiv), BF<sub>3</sub>·OEt<sub>2</sub> (20 mol %), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt. <sup>*b*</sup>Diastereose-lectivities were determined by <sup>1</sup>H NMR analysis of the crude reaction products. <sup>*c*</sup>Yields of isolated products are listed. <sup>*d*</sup>The reactions were conducted in toluene at 60 °C without BF<sub>3</sub>·OEt<sub>2</sub>.

when acid catalyst (S)-B was used, and product **8b** was isolated in 72% yield. Studies with structurally more elaborated aldehyde **9** were also conducted. The reaction between **9** and boronate **2a** with (R)-B as the catalyst gave product **10a** in 79% yield. When the enantiomeric catalyst (S)-B was used, the reaction of **9** with reagent **2a** furnished product **10b** in 92% yield. In both cases, the reactions proceeded with >20:1 diastereoselectivities and *E*-selectivities. It is apparent that these double stereodifferentiation reactions proceeded under complete catalyst control to give products with high diastereoselectivities and *E*-selectivities.

In addition, diastereoselective reactions of enantioenriched aldehydes with reagents **2a** and **2b** were conducted. As shown in Scheme 9, BF<sub>3</sub>·OEt<sub>2</sub>-catalyzed allylation of aldehyde **11** with reagent **2a** gave product **12** in 76% yield with >20:1 *Z*-selectivity and high diastereoselectivity. The reaction of aldehyde **13** with reagent **2b** gave a complex mixture under the BF<sub>3</sub>·OEt<sub>2</sub>-catalyzed conditions, presumably due to the ornately functionalized nature of aldehyde **13**. However, the reaction of **13** with boronate **2b** proceeded without BF<sub>3</sub>·OEt<sub>2</sub> at 60 °C to give product **14** in 70% yield with >20:1 diastereoselectivity and a synthetically useful *Z*-selectivity (3:1).

**Product Derivatization.** The reactions of reagents 2 with aldehyde substrates produce homoallylic alcohol products bearing a vinyl Bpin group that can participate in a variety of subsequent transformations (Scheme 10). For instance, CuBr<sub>2</sub>-mediated bromination of 4a provided vinyl bromide 15 in 82% yield. Vinyl bromide 15 should undergo transition-metal-catalyzed cross-coupling reactions with various aryl or vinyl

Scheme 9. Brønsted Acid-Catalyzed Double Stereodifferentiation Reactions with Enantioenriched Aldehydes



nucleophiles. Under similar conditions, vinyl chloride 16 was obtained in 81% yield when CuCl<sub>2</sub> was used. Oxidation of 17 with NaBO3 gave ketone 18 in 85% yield. Compound 19 underwent a homologation-oxidation sequence to afford alcohol 20 in 67% yield.<sup>33</sup> On the other hand, the vinyl Bpin group in the products can be used directly for cross-coupling reactions to form a carbon-carbon bond. For example, Rhcatalyzed addition of vinyl boronate 17 to methyl vinyl ketone (21) generated ketone 22 in 85% yield.<sup>34</sup> Pd-catalyzed oxidative Heck reaction of 17 with ethyl acrylate (23) gave (E,E)-diene 24 in 77% yield.<sup>35</sup> Pd-catalyzed Suzuki coupling of 17 with (Z)-vinyl iodide 25 furnished (E,Z)-diene 26 in 82% yield.<sup>36</sup> Product 3a can also be utilized directly for crosscoupling reactions. Suzuki coupling of 3a with (E)-vinyl iodide 27 gave (Z,E)-diene 28 in 84% yield. Under similar conditions, (Z,Z)-diene 29 was obtained in 69% yield from the coupling reaction with (Z)-vinyl iodide 25. Therefore, all four isomers of dienes were generated in high yields by employing different cross-coupling partners.<sup>37</sup> These studies highlight the versatile reactivities of allylation products (3, 4, and 5) to produce homoallylic alcohols with a stereodefined trisubstituted alkene.

**Total Synthesis of Salinipyrones A and B.** To further demonstrate the synthetic utility of the method, total syntheses

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of salinipyrones A (30) and B(31) were pursued.<sup>38</sup> As shown in Scheme 11, we envisioned that salinipyrone A could be assembled via a Stille coupling of vinyl bromide 32 with vinyl stannane 34. A similar reaction between vinyl iodide 33 and vinyl stannane 34 should provide salinipyrone B. Vinyl halide 32 or 33 should be readily available via bromination or iodination of the corresponding vinyl boron precursor that can be obtained from allylation with crotylboronate 2a.

Syntheses of salinipyrones A (30) and B(31) using this strategy are shown in Scheme 12. Asymmetric allylation of propionaldehyde with reagent 2a in the presence of 10 mol %

Scheme 11. Retrosynthetic Analysis for the Syntheses of Salinipyrones A and B



of chiral phosphoric acid (S)-B gave product 35 in 78% yield with 87% ee and >20:1 E-selectivity. CuI-mediated iodination of 35 provided Z-vinyl iodide 33 in 52% yield.<sup>39</sup> In parallel, BF<sub>3</sub>·OEt<sub>2</sub>-catalyzed allylation of propionaldehyde with reagent 2a furnished homoallylic alcohol 36 in 68% yield with >20:1 Zselectivity. The vinyl Bpin unit of alcohol 36 was converted into E-vinyl bromide under the CuBr2-mediated bromination conditions, affording product 32 in 64% yield. The synthesis of vinyl stannane 34 commenced from aldol reaction of  $\beta$ -ketoester 37<sup>40</sup> and aldehyde 38.<sup>41</sup> The resulting aldol adduct was subjected to Dess-Martin oxidation<sup>42</sup> to deliver product 39 in 41% yield over two steps. Treatment of 39 with DBU in toluene generated vinyl stannane 34 in 68% yield. Pd-catalyzed Stille coupling<sup>43</sup> of vinyl stannane 34 with vinyl bromide 32 at 60 °C gave salinipyrone A (30) in 48% yield. Similarly, salinipyrone B (31) was obtained in 70% yield from the Pdcatalyzed cross-coupling of vinyl iodide 33 and vinyl stannane 34 at ambient temperature. The spectroscopic data of synthetic salinipyrones A and B were in excellent agreement with the data previously reported for the two natural products.<sup>38</sup>

#### CONCLUSIONS

In summary, we developed novel  $\alpha, \alpha$ -disubstituted E- and Zcrotylboronate reagents from readily available starting materials. Chiral Brønsted acid-catalyzed asymmetric allylation of aldehydes with E-crotylboron reagent 2a gave (E)-anti-1,2oxaborinan-3-enes with excellent enantioselectivities and Eselectivities. The results demonstrate the dual-function of the chiral Brønsted acid catalysts: enhance the diastereochemical control while maintaining high enantioselectivity. DFT computation studies establish the origins of observed enantioand stereoselectivity of chiral Brønsted acid-catalyzed asymmetric allylation. With BF3 OEt2 catalysis, the reactions of aldehydes with 2a proceeded to give  $\delta$ -boryl-anti-homoallylic alcohols with excellent Z-selectivities. The inherent Eselectivity in the noncatalyzed reaction with 2a is reversed by simply employing  $BF_3 \cdot OEt_2$  as the catalyst.  $BF_3 \cdot OEt_2$ -catalyzed allyl addition with Z-crotylboron reagent 2b gave  $\delta$ -boryl-synhomoallylic alcohols with good Z-selectivities. The presence of  $BF_3 \cdot OEt_2$  catalyst enhances the Z-selectivities in these reactions. Stereochemical models for both BF<sub>3</sub>·OEt<sub>2</sub>-catalyzed allylations with reagents 2a and 2b are proposed to rationalize

#### Scheme 12. Total Synthesis of Salinipyrones A and B



the observed Z-selectivities. DFT calculations of BF<sub>3</sub>·OEt<sub>2</sub>catalyzed allylations were also conducted, although the prediction is different from the experimental results. Such discrepancy suggests a much more complex scenario is involved in these processes. This approach provides a general solution to access homoallylic alcohols with a stereodefined trisubstituted alkene unit. Such structural entities are challenging to synthesize with prior allylation chemistry. Moreover, the reaction products contain a vinyl boron unit that can undergo a variety of transformations to form intermediates that are highly valuable for the syntheses of polyketide natural products. The synthetic utility is further demonstrated by total syntheses of salinipyrones A and B. Other synthetic applications will be reported in due course.

#### ASSOCIATED CONTENT

#### **③** Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c04107.

Experimental procedures and spectra for all new compounds (PDF)

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#### Notes

The authors declare no competing financial interest.

#### ACKNOWLEDGMENTS

Financial support provided by Auburn University (to M.C.) is gratefully acknowledged. We are grateful to the National Science Foundation (Grant CHE-1764328 to K.N.H) for financial support of this work. Calculations were performed on the Hoffman2 cluster at UCLA and the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the National Science Foundation (Grant OCI-1053575).

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