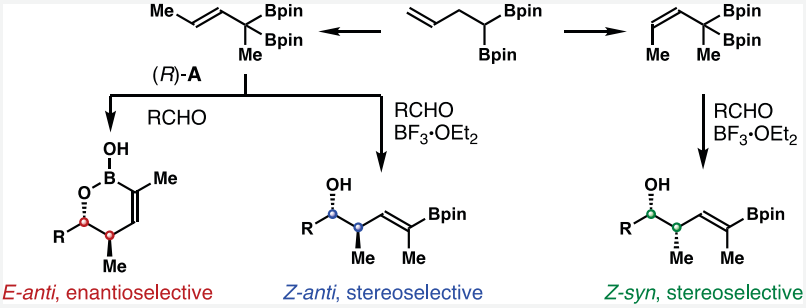
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Article

Development of α,α-Disubstituted Crotylboronate Reagents and Stereoselective Crotylation via Brønsted or Lewis Acid Catalysis

Shang Gao,[§] Meng Duan,[§] Qianzhen Shao, K. N. Houk,* and Ming Chen*

Cite This: J. Am. Chem. Soc. 2020, 142, 18355−18368
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information



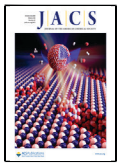
ABSTRACT: The development of α,α-disubstituted crotylboronate reagents is reported. Chiral Brønsted acid-catalyzed asymmetric aldehyde addition with the developed *E*-crotylboron reagent gave (*E*)-*anti*-1,2-oxaborinan-3-enes with excellent enantioselectivities and *E*-selectivities. With BF_3·OEt_2 catalysis, the stereoselectivity is reversed, and (*Z*)-δ-boryl-*anti*-homoallylic alcohols are obtained with excellent *Z*-selectivities from the same *E*-crotylboron reagent. The *Z*-crotylboron reagent also participates in BF_3·OEt_2-catalyzed crotylation to furnish (*Z*)-δ-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_3·OEt_2-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.[1] They have played a significant role in the discovery and development of modern medicines.[2] 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.[3] 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.[4] In parallel, several strategies are known for chemical syntheses of these molecules via a multistep reaction sequence.[5] For example, the Kobayashi group developed a chiral auxiliary-based approach using vinyl ketene silyl *N*,*O*-acetal to access homoallylic alcohol with a trisubstituted alkene.[5a−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.[5g−i] Such structural entities can also be formed via olefin metathesis from the alkene precursors.[5j−l] Reductive coupling of an internal alkyne intermediate is another viable approach to prepare these molecules.[5m−p]

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.[6,7] In principle, asymmetric aldehyde crotylation with α,α-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).[8,9] 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
Published: October 14, 2020



https://dx.doi.org/10.1021/jacs.0c04107

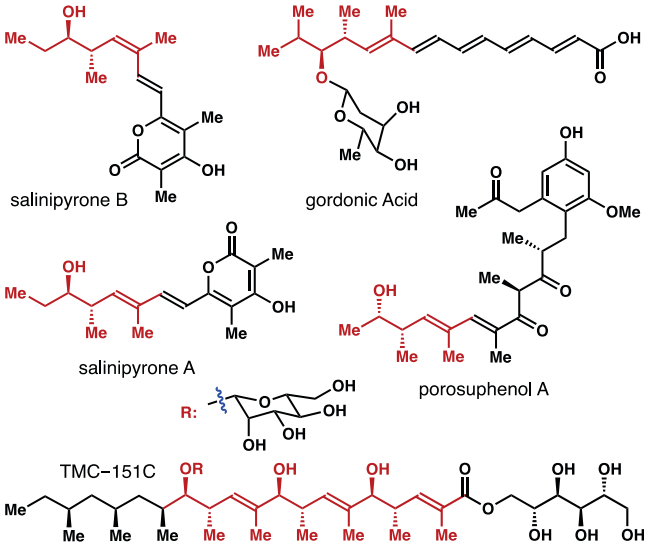
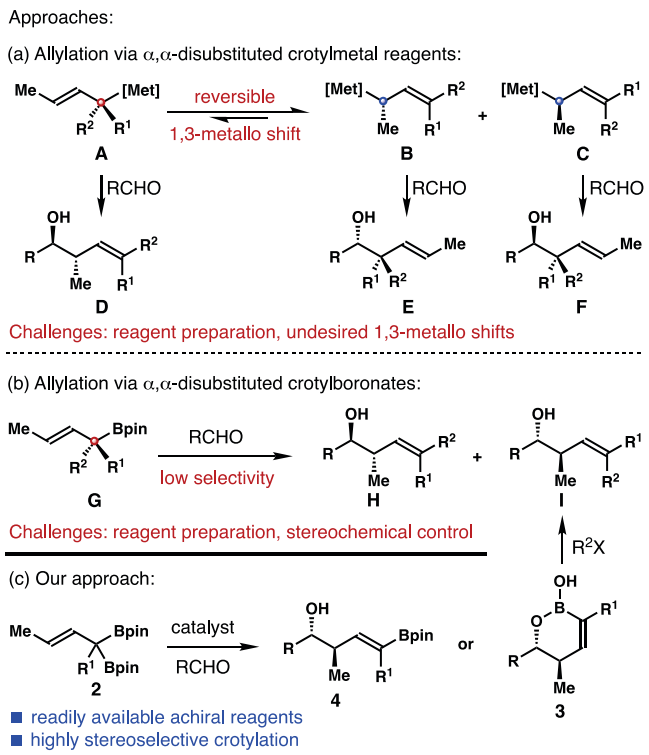


Figure 1. Selected natural products that contain homoallylic alcohols with a trisubstituted alkene group.

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



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 α,α-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^1 and R^2 groups are similar to each other. In addition, enantioselective preparation of such chiral nonracemic α,α-disubstituted crotylboron reagents is synthetically challenging.[10] 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.

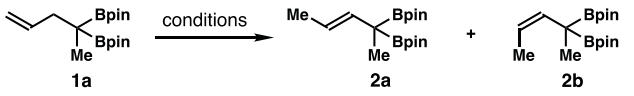
With our continuing efforts to develop novel allylation reagents and catalytic methods for the syntheses of polyketide natural products,[11] we report herein the development of α,α-disubstituted crotylboronate reagents **2** (Scheme 1c). These reagents are achiral and can be conveniently synthesized 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.[12] With precursor **1a** in hand, subsequent transition-metal-catalyzed 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 $RhCl_3{\cdot}3H_2O$.[13] We suspected that the less bulky, ligandless $RhCl_3{\cdot}3H_2O$ 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 $RhCl_3{\cdot}3H_2O$ as the catalyst. In the event, **1a** was treated with 10 mol % of $RhCl_3{\cdot}3H_2O$ 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 ^{t}BuOH also produced boronate **2a** with high *E*-selectivity, 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 (±)-**3a** and *Z*-isomer (±)-**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 α-Bpin group of reagent **2a** has a slight advantage over **TS-2** (α-Bpin in a pseudoequatorial position) owing to less pronounced gauche interactions between the methyl and Bpin groups

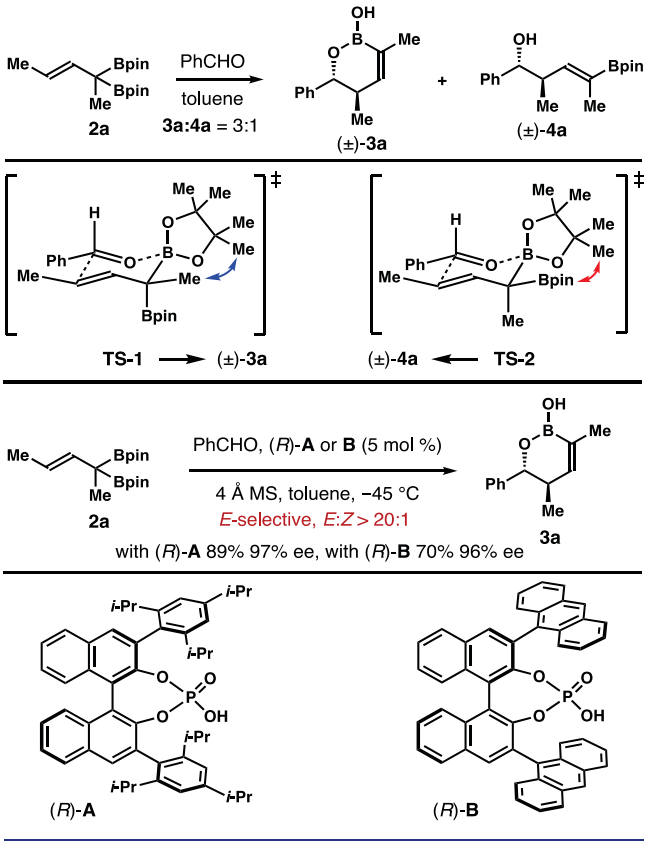
Table 1. Evaluation of Reaction Conditions for *E*-Selective Alkene Transposition of 1a[a]



entry	conditions	2a:2b[b]	yield (%)[c]
1	$RhCl_3{\cdot}3H_2O$ (10 mol %), EtOH, rt	ND	ND
2	$RhCl_3{\cdot}3H_2O$ (10 mol %), EtOH, 40 °C	ND	ND
3	$RhCl_3{\cdot}3H_2O$ (10 mol %), EtOH, 60 °C	>20:1	61
4	$RhCl_3{\cdot}3H_2O$ (10 mol %), ^{t}BuOH, 60 °C	>20:1	49
5[d]	$RhCl_3{\cdot}3H_2O$ (5 mol %), EtOH, 60 °C	>20:1	76
6[e]	$RhCl_3{\cdot}3H_2O$ (5 mol %), EtOH, 60 °C	>20:1	81

[a]Reaction conditions: alkene **1a** (0.2 mmol), $RhCl_3{\cdot}3H_2O$ (5 or 10 mol %), solvent (0.5 mL). [b]The ratios of **2a** and **2b** were determined by ^{1}H NMR analysis of the crude reaction products. [c]Yields of isolated products are listed. [d]The reaction was conducted in a 0.5 mmol scale. [e]The reaction was conducted in a 3 mmol scale.

Scheme 2. Initial Allylation Studies with Reagent 2a

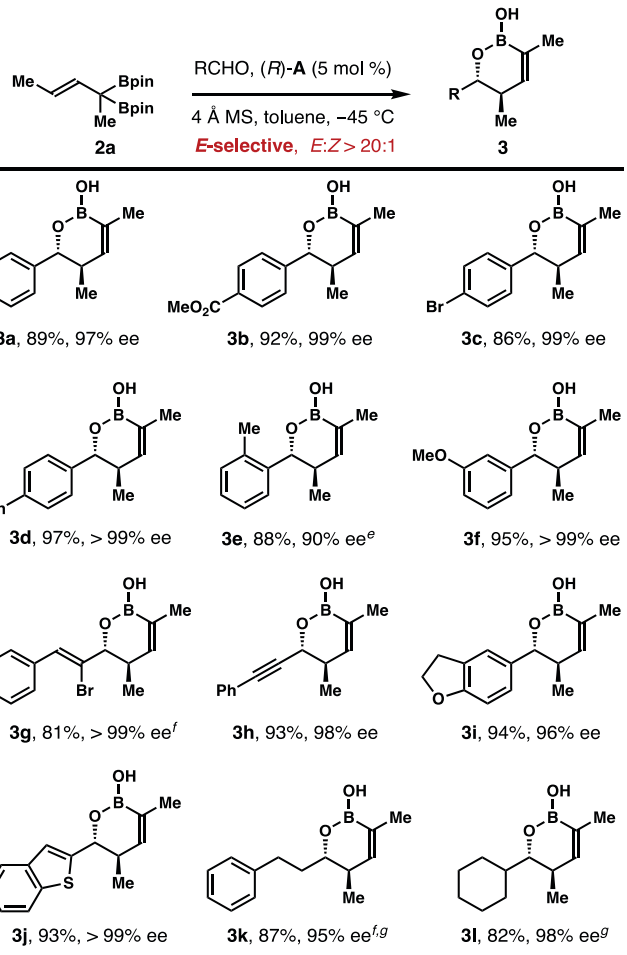


(shown with a blue arrow in **TS-1**) compared to the steric interactions between two Bpin groups (shown with a red arrow, **TS-2**).

Chiral phosphoric acid (*R*)-**A** (Scheme 2) has been reported to catalyze asymmetric allylboration of aldehydes by Antilla and co-workers.[14,15] Following the seminal work, a variety of boron reagents have been shown to undergo chiral phosphoric acid-catalyzed enantioselective addition to aldehydes.[16−18] The origin of enantioselection was elucidated by computational studies from the Houk and Goodman groups.[19] 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 α-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]



[a]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. [b]Yields of isolated products are listed. [c]Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase of the product obtained from cross-coupling with PhI. [d]The *E*/*Z* ratios were determined by ^{1}H NMR analysis of the crude reaction products. [e]10 mol % (*R*)-**A** was used. [f]The ee was determined from the vinyl bromide product obtained from bromination of vinyl Bpin. [g]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. *α,β*-Unsaturated aldehydes also reacted with crotylboronate **2a** to furnish products **3g,h** in 81−93% yields with >20:1 *E*-selectivities and 98−99% ee. Similar results were achieved with aldehydes that contain a heterocycle, and products **3i,j** were isolated in 93−94% yields 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[20−23] 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

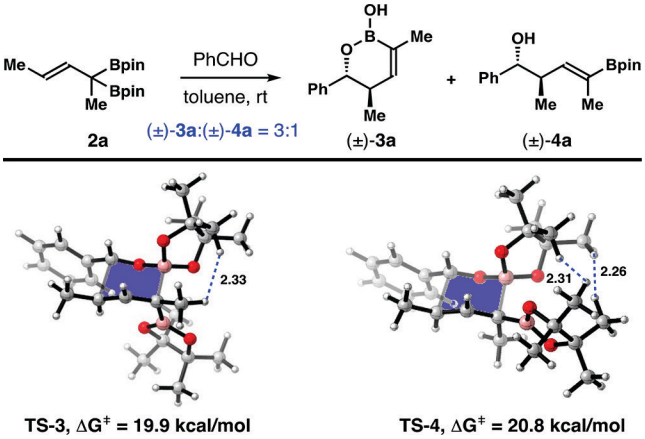


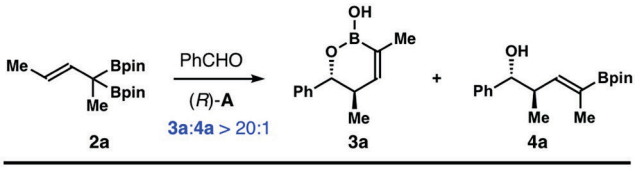
Figure 2. Optimized transition states **TS-3** and **TS-4** of noncatalyzed crotylation of benzaldehyde with crotylboronate **2a**. The bond lengths are in ångstrom.

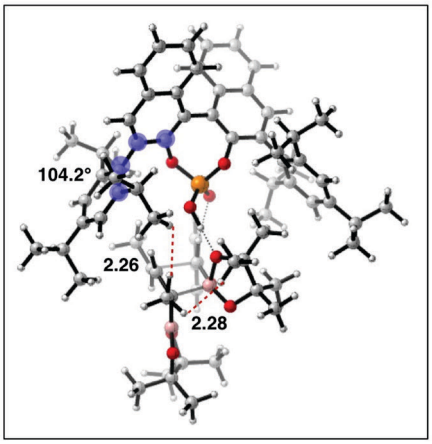
be 0.9 kcal/mol lower in free energy than **TS-4** that delivers (±)-**4a**. This finding is consistent with the experimentally observed selectivity, a 3:1 mixture of (±)-**3a** and (±)-**4a** favoring *E*-isomer **3a**. Examining the optimized geometries indicates that **TS-3** is favored over **TS-4** due to steric factors. In the disfavored transition state **TS-4**, the *α*-Bpin unit of **2a** occupies a pseudoequatorial position; both the H−H nonbonding 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 *α*-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 *α*-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 2,4,6-triisopropylphenyl 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°) by 13°, 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°). We conclude that the unfavorable steric repulsions dictate the *E*-selectivity of chiral phosphoric acid-catalyzed crotylation with reagent **2a**.

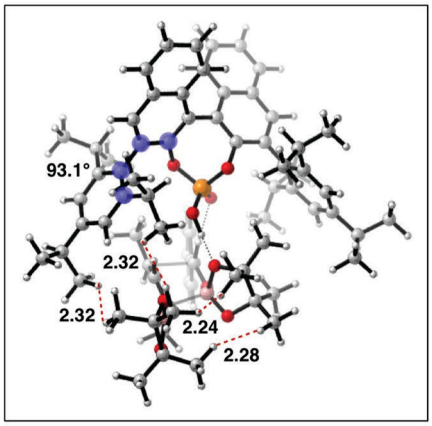
As shown in the studies, chiral phosphoric acid (*R*)-**A** not only defines the stereoselectivity (*E*:*Z* > 20:1) of the crotylation by controlling the orientation of *α*-Bpin group in the transition state but also enables enantioselective addition of **2a** to aldehyde substrates. As shown in Figure 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 *α*-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 *α*-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.[24−28] Scheme 4 shows the proposed model for





TS-5, $\Delta G^{\ddagger}$ = 11.8 kcal/mol



TS-6, $\Delta G^{\ddagger}$ = 13.8 kcal/mol

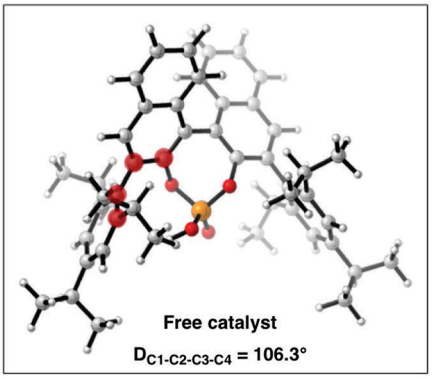


Figure 3. Optimized structures of transition states **TS-5** and **TS-6**. The bond lengths are in ångstrom.

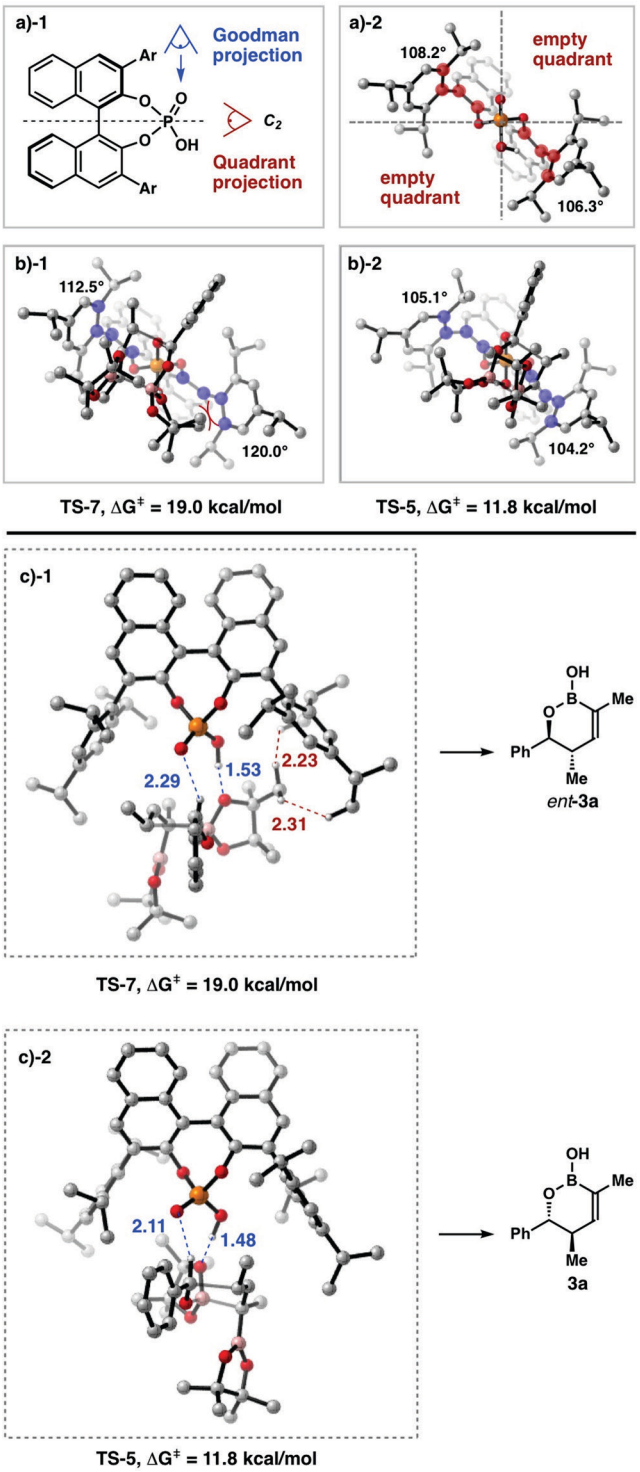
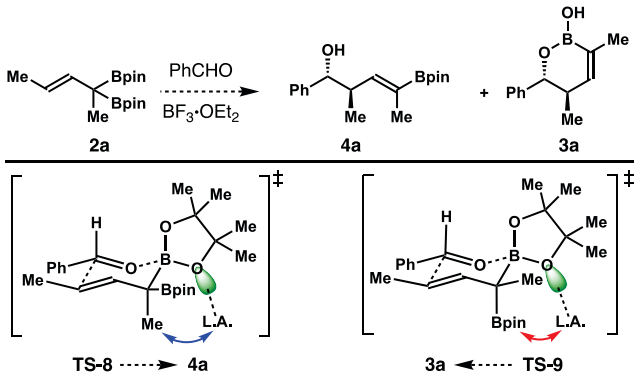


Figure 4. (a) Definition of Goodman and quadrant projections. (b) Quadrant projection of **TS-7**, **TS-5**, and catalyst (*R*)-**A**. (c) Goodman projection of **TS-7** and **TS-5**. The bond lengths are in ångstrom.

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 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 α-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_2Cl_2 in the presence of 20 mol % of a Lewis acid catalyst. As shown in Figure 5, when $BF_3{\cdot}OEt_2$ was utilized, the reaction

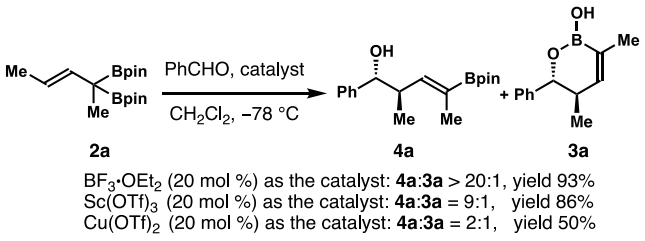
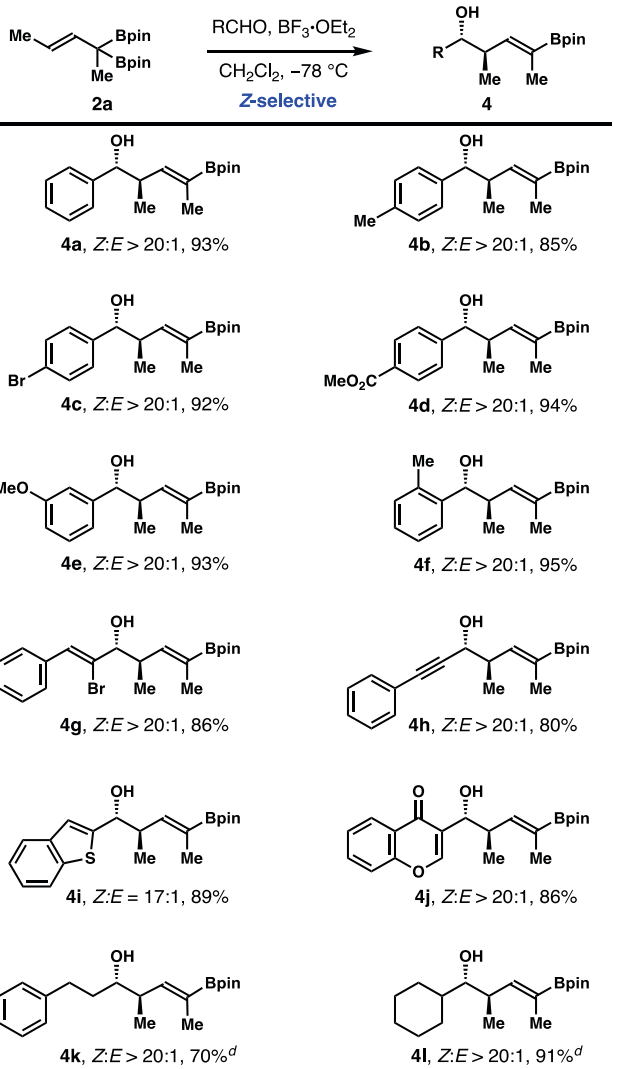


Figure 5. Results of Lewis acid-catalyzed allylation of benzaldehyde with reagent **2a**.

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 $Sc(OTf)_3$ and $Cu(OTf)_2$ 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 $BF_3{\cdot}OEt_2$ 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 $BF_3{\cdot}OEt_2$ 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 $BF_3{\cdot}OEt_2$-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*-selectivity (>20:1) simply by employing an appropriate Lewis acid catalyst.

Substrate Scope for $BF_3{\cdot}OEt_2$-Catalyzed Allylation with *E*-Crotylboron Reagent 2a. The scope of aldehyde that participated in $BF_3{\cdot}OEt_2$-catalyzed allylation with **2a** was explored next. And the results are summarized in Scheme 5.

Scheme 5. Scope of Aldehyde in $BF_3{\cdot}OEt_2$-Catalyzed*Z*-Selective Allylation with Reagent 2a[a−c]



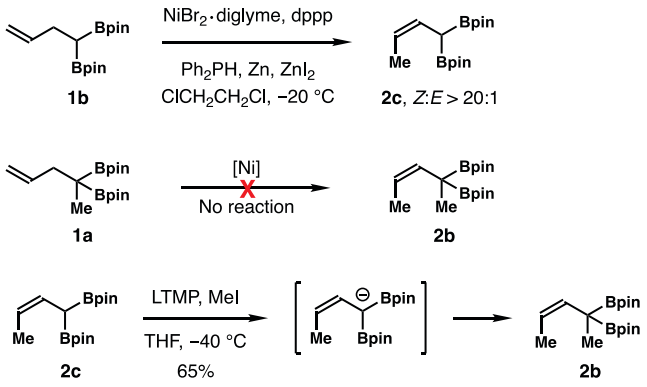
[a]Boronate **2a** (0.13 mmol, 1.3 equiv), aldehyde (0.1 mmol, 1.0 equiv), $BF_3{\cdot}OEt_2$ (20 mol %), CH_2Cl_2, −78 °C. [b]*Z*/*E*-selectivities were determined by ^1H NMR analysis of the crude reaction products. [c]Yields of isolated products are listed. [d]The reactions were conducted at −20 °C.

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 *α*,*β*-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

°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 α-boryl-*Z*-crotylboronate **2c** can be prepared via Ni-catalyzed *Z*-selective olefin transposition from precursor **1b** (Scheme 6).[29]

Scheme 6. Preparation of *Z*-Crotylboron Reagent 2b

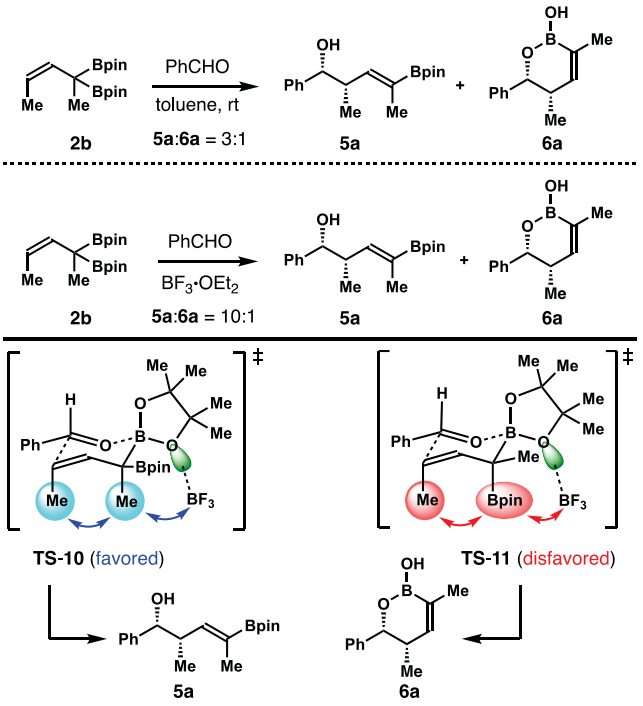


Under identical conditions, however, the reaction with **1a** did not occur. We were not able to generate any *Z*-crotylboron reagent **2b** through this approach even with extensive optimizations. We were pleased to discover that *Z*-reagent **2b** can be conveniently prepared from methylation of crotylboronate **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 α-anion effect).[30]

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_3·OEt_2, 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 $A^{1,3}$ allylic strain[31] between the methyl and α-Bpin groups of reagent **2b** as well as the *syn*-pentane interactions between the BF_3 catalyst and pseudoaxially positioned Bpin group of reagent **2b**. By contrast, $A^{1,3}$ allylic strain between the two methyl groups of **2b** and *syn*-pentane interactions between the BF_3 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 BF_3·OEt_2 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

Scheme 7. Transition State Analyses for Allylation with 2b

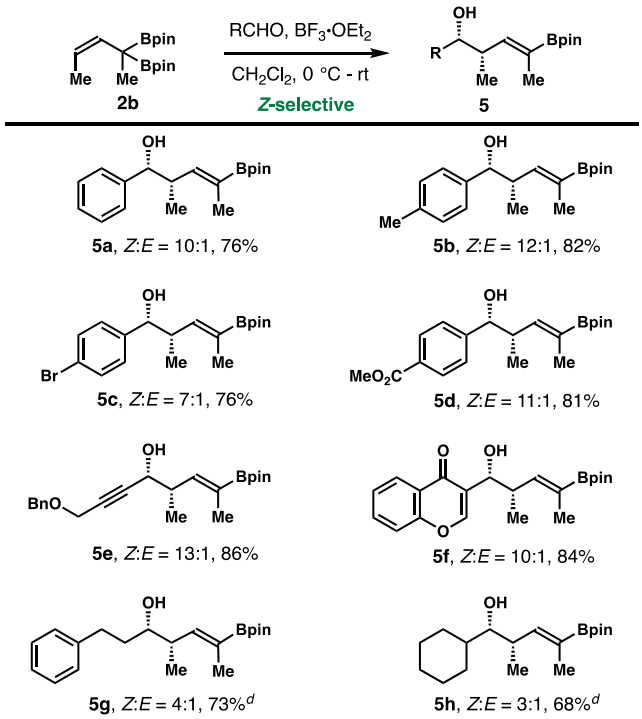


Supporting Information for details). Again, a different reaction mechanism might be operational for the BF_3·OEt_2-catalyzed allylation with *Z*-reagent **2b**.

Substrate Scope for BF_3·OEt_2-Catalyzed *Z*-Selective Allylation with Reagent 2b. Scheme 8 summarizes the scope of aldehyde that reacted with crotylboronate **2b** in the presence of BF_3·OEt_2. The reaction worked reasonably well with several representative aldehyde substrates, including aromatic, α,β-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·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 *Z*-selectivities. In general, the rates of allylation with *Z*-reagent **2b** are slower than the rates with *E*-reagent **2a** likely owing to the additional $A^{1,3}$ 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.[32] 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_2-Catalyzed Allylation with *Z*-Crotylboronate 2b[a–c]



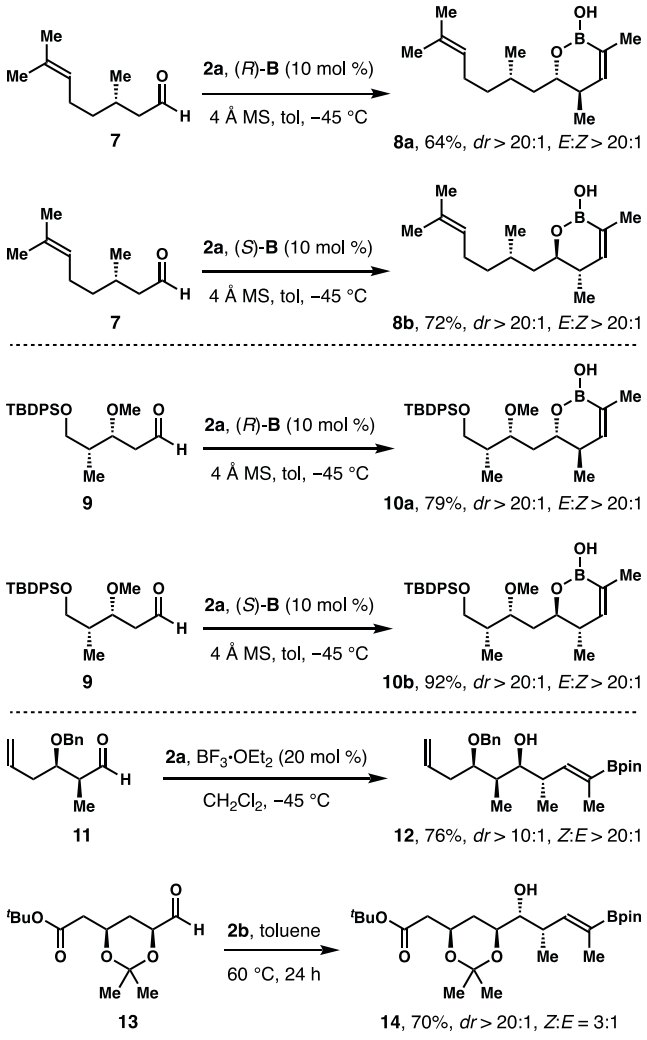
[a]Crotylboronate **2b** (0.13 mmol, 1.3 equiv), aldehyde (0.1 mmol, 1.0 equiv), BF_3·OEt_2 (20 mol %), CH_2Cl_2, 0 °C to rt. [b]Diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction products. [c]Yields of isolated products are listed. [d]The reactions were conducted in toluene at 60 °C without BF_3·OEt_2.

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_3·OEt_2-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_3·OEt_2-catalyzed conditions, presumably due to the ornately functionalized nature of aldehyde **13**. However, the reaction of **13** with boronate **2b** proceeded without BF_3·OEt_2 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, $CuBr_2$-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

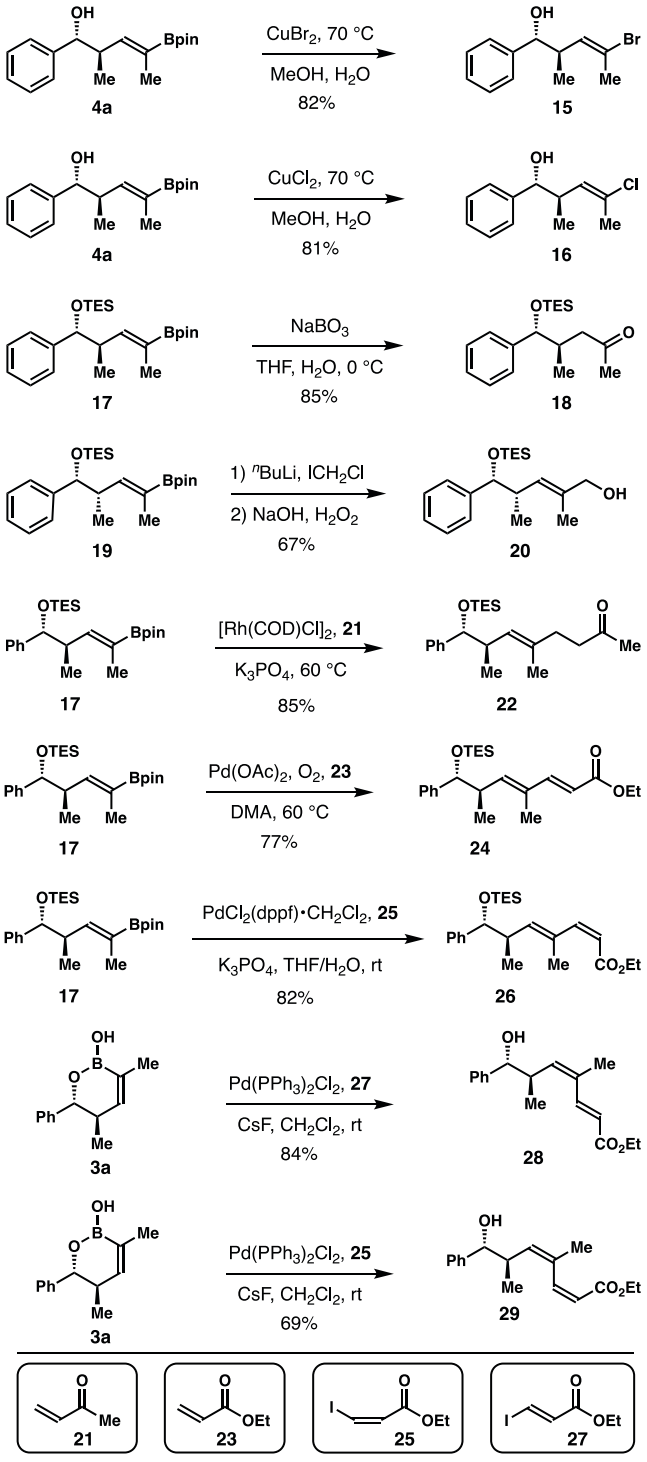
Scheme 9. Brønsted Acid-Catalyzed Double Stereodifferentiation Reactions with Enantioenriched Aldehydes



nucleophiles. Under similar conditions, vinyl chloride **16** was obtained in 81% yield when $CuCl_2$ was used. Oxidation of **17** with $NaBO_3$ gave ketone **18** in 85% yield. Compound **19** underwent a homologation–oxidation sequence to afford alcohol **20** in 67% yield.[33] 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, Rh-catalyzed addition of vinyl boronate **17** to methyl vinyl ketone (**21**) generated ketone **22** in 85% yield.[34] Pd-catalyzed oxidative Heck reaction of **17** with ethyl acrylate (**23**) gave (*E*,*E*)-diene **24** in 77% yield.[35] Pd-catalyzed Suzuki coupling of **17** with (*Z*)-vinyl iodide **25** furnished (*E*,*Z*)-diene **26** in 82% yield.[36] Product **3a** can also be utilized directly for cross-coupling 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.[37] 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

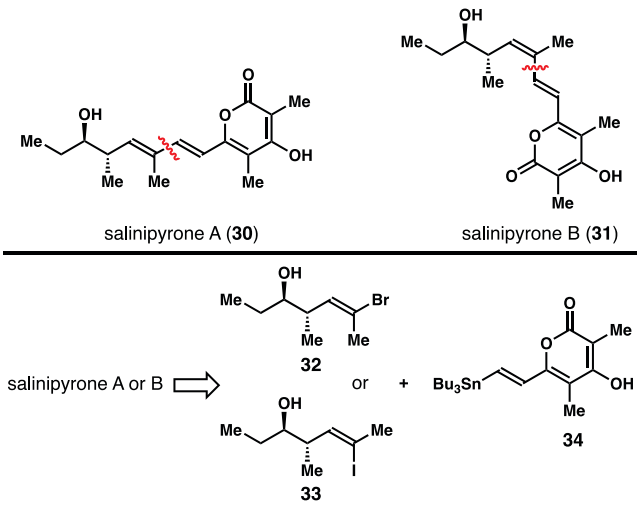
Scheme 10. Derivatization of Reaction Products



of salinipyrones A (**30**) and B(**31**) were pursued.[38] 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 % 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.[39] In parallel, $BF_3{\cdot}OEt_2$-catalyzed allylation of propionaldehyde with reagent **2a** furnished homoallylic alcohol **36** in 68% yield with >20:1 *Z*-selectivity. The vinyl Bpin unit of alcohol **36** was converted into *E*-vinyl bromide under the $CuBr_2$-mediated bromination conditions, affording product **32** in 64% yield. The synthesis of vinyl stannane **34** commenced from aldol reaction of *β*-ketoester **37**[40] and aldehyde **38**.[41] The resulting aldol adduct was subjected to Dess–Martin oxidation[42] 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[43] 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 Pd-catalyzed 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.[38]

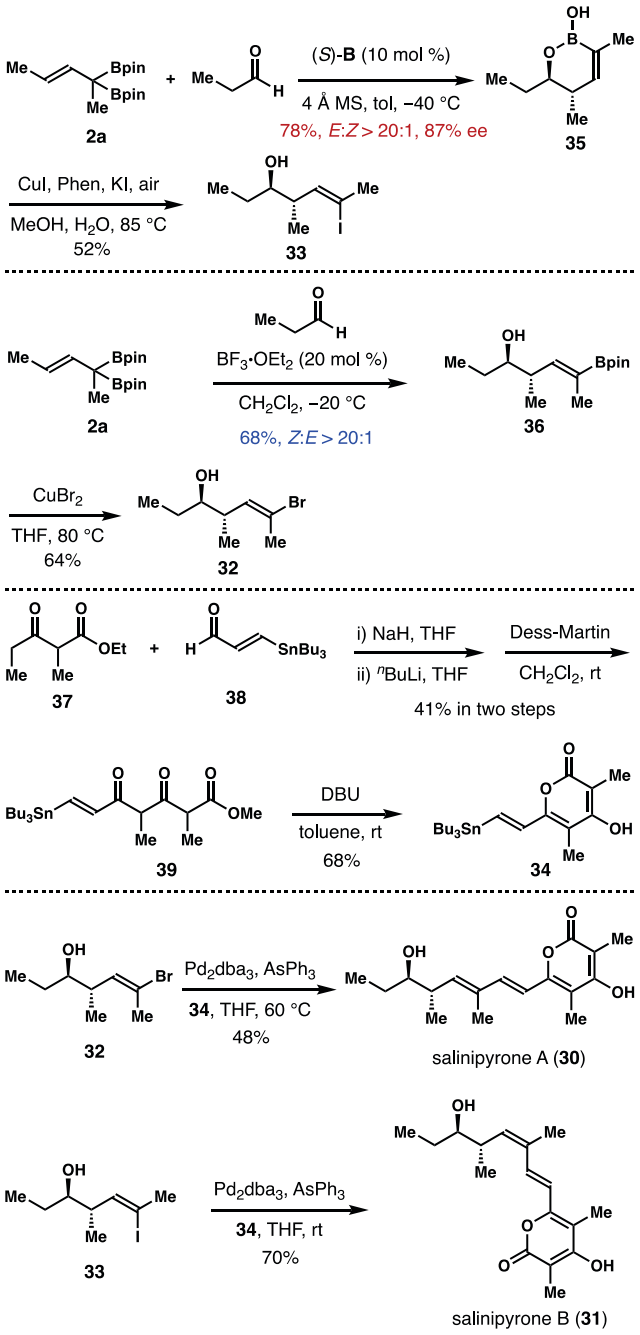
Scheme 11. Retrosynthetic Analysis for the Syntheses of Salinipyrones A and B



CONCLUSIONS

In summary, we developed novel *α,α*-disubstituted *E*- and *Z*-crotylboronate reagents from readily available starting materials. Chiral Brønsted acid-catalyzed asymmetric allylation of aldehydes with *E*-crotylboron reagent **2a** gave (*E*)-*anti*-1,2-oxaborinan-3-enes with excellent enantioselectivities and *E*-selectivities. 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 enantio- and stereoselectivity of chiral Brønsted acid-catalyzed asymmetric allylation. With $BF_3{\cdot}OEt_2$ catalysis, the reactions of aldehydes with **2a** proceeded to give *δ*-boryl-*anti*-homoallylic alcohols with excellent *Z*-selectivities. The inherent *E*-selectivity 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 *δ*-boryl-*syn*-homoallylic 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 $BF_3{\cdot}OEt_2$-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 $BF_3{\cdot}OEt_2$-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

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)

■ AUTHOR INFORMATION

Corresponding Authors

K. N. Houk − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States;* orcid.org/0000-0002-8387-5261; Email: houk@chem.ucla.edu

Ming Chen − *Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama 36849, United States;* orcid.org/0000-0002-9841-8274; Email: mzc0102@auburn.edu

Authors

Shang Gao − *Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama 36849, United States;* orcid.org/0000-0001-8166-5503

Meng Duan − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*

Qianzhen Shao − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c04107

Author Contributions

§S.G. and M.D. contributed equally.

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).

■ REFERENCES

(1) (a) Rohr, J. A New Role for Polyketides. *Angew. Chem., Int. Ed.* **2000**, *39*, 2847. (b) Omura, S., Ed. Macrolide Antibiotics. *Chemistry, Biology, and Practice*, 2nd ed.; Academic Press: New York, 2002. (c) Baerson, S. R., Ed. *Polyketides, Biosynthesis, Biological Activity, and Genetic Engineering*; American Chemical Society: Washington DC, 2006; p 296.

(2) (a) Paterson, I.; Anderson, E. A. The Renaissance of Natural Products as Drug Candidates. *Science* **2005**, *310*, 451. (b) Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs over the Last 25 Years. *J. Nat. Prod.* **2007**, *70*, 461. (c) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. Impact of Natural Products on Developing New Anti-Cancer Agents. *Chem. Rev.* **2009**, *109*, 3012.

(3) (a) Paterson, I.; Cowden, C. J.; Wallace, D. J. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 249. (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p

403. (c) Yeung, K.-S.; Paterson, I. Advances in the Total Synthesis of Biologically Important Marine Macrolides. *Chem. Rev.* **2005**, *105*, 4237. (d) Feng, J.; Kasun, Z. A.; Krische, M. J. Enantioselective alcohol C-H functionalization for polyketide construction: unlocking redox-economy and site-selectivity for ideal chemical synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 5467. (e) Paterson, I.; Lam, N. Y. S. Challenges and discoveries in the total synthesis of complex polyketide natural products. *J. Antibiot.* **2018**, *71*, 215.

(4) (a) Katz, L. Manipulation of Modular Polyketide Synthases. *Chem. Rev.* **1997**, *97*, 2557. (b) Khosla, C. Harnessing the biosynthetic potential of modular polyketide synthases. *Chem. Rev.* **1997**, *97*, 2577. (c) Staunton, J.; Weissman, K. J. Polyketide biosynthesis: A millennium review. *Nat. Prod. Rep.* **2001**, *18*, 380. (d) Khosla, C.; Herschlag, D.; Cane, D. E.; Walsh, C. T. Assembly line polyketide synthases: mechanistic insights and unsolved problems. *Biochemistry* **2014**, *53*, 2875. (e) Weissman, K. J. Genetic engineering of modular PKSs: from combinatorial biosynthesis to synthetic biology. *Nat. Prod. Rep.* **2016**, *33*, 203. (f) Nivina, A.; Yuet, K. P.; Hsu, J.; Khosla, C. Evolution and diversity of assembly-line polyketide synthases. *Chem. Rev.* **2019**, *119*, 12524.

(5) For selected references on the chiral auxiliary approach, see the following: (a) Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. Remote asymmetric induction with vinylketene silyl N,O-acetal. *J. Am. Chem. Soc.* **2004**, *126*, 13604. (b) Hosokawa, S. Remote asymmetric induction reactions using a *E, E*-vinylketene silyl N, O-acetal and the wide range stereocontrol strategy for the synthesis of polypropionates. *Acc. Chem. Res.* **2018**, *51*, 1301. (c) Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. Total synthesis and structure revision of the marine metabolite palmerolide A. *J. Am. Chem. Soc.* **2007**, *129*, 6386. (d) Lipshutz, B. H.; Amorelli, B. Total synthesis of piericidin A1. Application of a modified Negishi carboalumination-nickel-catalyzed cross-coupling. *J. Am. Chem. Soc.* **2009**, *131*, 1396. (e) Fujita, K.; Matsui, R.; Suzuki, T.; Kobayashi, S. Concise total synthesis of (−)-myxalamide A. *Angew. Chem., Int. Ed.* **2012**, *51*, 7271. (f) Symkenberg, G.; Kalesse, M. Structure elucidation and total synthesis of kulkenon. *Angew. Chem., Int. Ed.* **2014**, *53*, 1795. For selected references on the Wittig olefination approach, see the following: (g) Nicolaou, K. C.; Guduru, R.; Sun, Y.-P.; Banerji, B.; Chen, D. Y.-K. Total synthesis of the originally proposed and revised structures of palmerolide A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896. (h) Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. Catalytic asymmetric synthesis of palmerolide A via organoboron methodology. *J. Am. Chem. Soc.* **2009**, *131*, 14216. (i) Ho, S.; Sackett, D. L.; Leighton, J. L. A. Methyl extension strategy for polyketide natural product linker site validation and its application to dictyostatin. *J. Am. Chem. Soc.* **2015**, *137*, 14047. For selected references on the olefin metathesis approach, see the following: (j) Murelli, R. P.; Snapper, M. L. Ruthenium-Catalyzed Tandem Cross-Metathesis/Wittig Olefination: Generation of Conjugated Dienoic Esters from Terminal Olefins. *Org. Lett.* **2007**, *9*, 1749. (k) Ghidu, V. P.; Wang, J.; Wu, B.; Liu, Q.; Jacobs, A.; Marnett, L. J.; Sulikowski, G. A. Synthesis and evaluation of the cytotoxicity of apoptolidinones A and D. *J. Org. Chem.* **2008**, *73*, 4949. (l) Chen, M.; Roush, W. R. Total synthesis of (−)-tirandamycin. C. *Org. Lett.* **2012**, *14*, 426. For selected references on the reductive coupling approach, see the following: (m) Miller, K. M.; Huang, W.-S.; Jamison, T. F. Catalytic asymmetric reductive coupling of alkynes and aldehydes: enantioselective synthesis of allylic alcohols and α-hydroxy ketones. *J. Am. Chem. Soc.* **2003**, *125*, 3442. (n) Komanduri, V.; Krische, M. J. Enantioselective reductive coupling of 1,3-enynes to heterocyclic aromatic aldehydes and ketones via rhodium-catalyzed asymmetric hydrogenation: mechanistic insight into the role of Brønsted acid additives. *J. Am. Chem. Soc.* **2006**, *128*, 16448. (o) Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. New N-heterocyclic carbene ligand and its application in asymmetric nickel-catalyzed aldehyde/alkyne reductive couplings. *J. Am. Chem. Soc.* **2007**, *129*, 9568. (p) Wang, H.; Lu, G.; Sormunen, G. J.; Malik, H. A.; Liu, P.; Montgomery, J. NHC ligands tailored for simultaneous regio- and enantiocontrol in nickel-catalyzed reductive couplings. *J. Am. Chem. Soc.* **2017**, *139*, 9317. For selected reference on the chiral pool approach, see the following: (q) Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. Apoptolidinone A: synthesis of the apoptolidin A aglycone. *Chem. - Eur. J.* **2006**, *12*, 7364.

(6) (a) Yamamoto, Y.; Asao, N. Selective reactions using allylic metals. *Chem. Rev.* **1993**, *93*, 2207. (b) Denmark, S. E.; Fu, J. Catalytic enantioselective addition of allylic organometallic reagents to aldehydes and ketones. *Chem. Rev.* **2003**, *103*, 2763. (c) Lachance, H.; Hall, D. G. Allylboration of carbonyl compounds. *Org. React.* **2009**, *73*, 1. (d) Yus, M.; González-Gómez, J. C.; Foubelo, F. Catalytic enantioselective allylation of carbonyl compounds and imines. *Chem. Rev.* **2011**, *111*, 7774. (e) Yus, M.; González-Gómez, J. C.; Foubelo, F. Diastereoselective allylation of carbonyl compounds and imines: application to the synthesis of natural products. *Chem. Rev.* **2013**, *113*, 5595.

(7) (a) Shibasaki, M.; Kanai, M. Asymmetric synthesis of tertiary alcohols and α-tertiary amines via Cu-Catalyzed C-C bond formation to ketones and ketimines. *Chem. Rev.* **2008**, *108*, 2853. (b) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. Catalytic Carbonyl Addition through Transfer Hydrogenation: A Departure from Preformed Organometallic Reagents. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (c) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. Metal-Catalyzed Reductive Coupling of Olefin-Derived Nucleophiles: Reinventing Carbonyl Addition. *Science* **2016**, *354*, aah5133. (d) Holmes, M.; Schwartz, L. A.; Krische, M. J. Intermolecular metal-catalyzed reductive coupling of dienes, allenes, and enynes with carbonyl compounds and imines. *Chem. Rev.* **2018**, *118*, 6026.

(8) (a) Zimmerman, H. E.; Traxler, M. D. The stereochemistry of the Ivanov and Reformatsky reactions. I. *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) Hoffmann, R. W. Diastereogenic addition of crotylmetal compounds to aldehydes. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.

(9) (a) Diner, C.; Szabó, K. J. Recent advances in the preparation and application of allylboron species in organic synthesis. *J. Am. Chem. Soc.* **2017**, *139*, 2. For selected references on allylation with 1,1-bimetallic reagents, see the following: (b) Shimizu, M.; Kitagawa, H.; Kurahashi, T.; Hiyama, T. 1-Silyl-1-boryl-2-alkenes: reagents for stereodivergent allylation leading to 4-oxy-(*E*)-1-alkenylboronates and 4-oxy-(*Z*)-1-alkenylsilanes. *Angew. Chem., Int. Ed.* **2001**, *40*, 4283. (c) Chen, M.; Ess, D. H.; Roush, W. R. Enantioselective synthesis of (*E*)-δ-stannyl homoallylic alcohols via aldehyde allylboration using s-stannylallylboranes generated by allene hydroboration followed by a highly diastereoselective 1,3-boratropic shift. *J. Am. Chem. Soc.* **2010**, *132*, 7881. (d) Chen, M.; Roush, W. R. Enantioconvergent hydroboration of a racemic allene: Enantioselective synthesis of (*E*)-δ-stannyl-*anti*-homoallylic alcohols via aldehyde crotylboration. *J. Am. Chem. Soc.* **2011**, *133*, 5744. (e) Chen, M.; Roush, W. R. Enantioselective Synthesis of (*E*)-δ-silyl-*anti*-homoallylic alcohols via an enantiodivergent hydroboration-crotylboration reaction of a racemic allenylsilane. *Org. Lett.* **2013**, *15*, 1662. (f) Park, J.; Choi, S.; Lee, Y.; Cho, S. H. Chemo- and stereoselective crotylation of aldehydes and cyclic aldimines with allylic *gem*-diboronate ester. *Org. Lett.* **2017**, *19*, 4054. (g) Wang, M.; Gao, S.; Chen, M. Stereoselective syntheses of (*E*)-γ′,δ-bisboryl-substituted *syn*-homoallylic alcohols via chemoselective aldehyde allylboration. *Org. Lett.* **2019**, *21*, 2151. (h) Gao, S.; Chen, M. α-Silicon effect assisted Curtin-Hammett allylation using allylcopper reagents derived from 1,3-dienylsilanes. *Chem, Sci.* **2019**, *10*, 7554. (i) Gao, S.; Chen, M. Catalytic carboboration of dienylboronate for stereoselective synthesis of (*E*)-γ′,δ-bisboryl-*anti*-homoallylic alcohols. *Chem. Commun.* **2019**, *55*, 11199.

(10) (a) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. Enantiodivergent conversion of chiral secondary alcohols into tertiary alcohols. *Nature* **2008**, *456*, 778. (b) Guzman-Martinez, A.; Hoveyda, A. H. Enantioselective synthesis of allylboronates bearing a tertiary or quaternary B-substituted stereogenic carbon by NHC-Cu-catalyzed substitution reactions. *J. Am. Chem. Soc.* **2010**, *132*, 10634. (c) Hesse, M. J.; Essafi, S.; Watson, C. G.; Harvey, J. N.; Hirst, D.; Willis, C. L.; Aggarwal, V. K. Highly selective allylborations of aldehydes using h

α,α-disubstituted allylic pinacol boronic esters. *Angew. Chem., Int. Ed.* **2014**, *53*, 6145.

(11) (a) Gao, S.; Wang, M.; Chen, M. Syntheses of unsymmetrical 1,4-bifunctional allylboron reagents via Cu-catalyzed highly regio- and stereoselective 1,4-protoboration of dienylboronates and analysis of the origin of chemoselective aldehyde *syn*-(hydroxymethyl)-allylation. *Org. Lett.* **2018**, *20*, 7921. (b) Chen, J.; Gao, S.; Gorden, J. D.; Chen, M. Stereoselective syntheses of γ-boryl substituted *syn*-β-alkoxy- and *syn*-β-amino-homoallylic alcohols via a regio- and stereoselective allene diboration and aldehyde allylboration reaction sequence. *Org. Lett.* **2019**, *21*, 4638. (c) Liu, J.; Gao, S.; Chen, M. Enantioselective syntheses of (*E*)-γ,δ-disubstituted homoallylic alcohols via $BF_3{\cdot}OEt_2$-catalyzed aldehyde allylboration and analysis of the origin of *E*-selectivity: $A^{1,2}$ allylic strain vs. *syn*-pentane interaction. *Tetrahedron* **2019**, *75*, 4110. (d) Chen, J.; Miliordos, E.; Chen, M. Highly diastereo- and enantioselective syntheses of 3,6′-bisboryl-anti-1,2-oxaborinan-3-enes: an entry to chiral homoallylic alcohols with a stereodefined trisubstituted alkene. *Angew. Chem., Int. Ed.* **2020**, DOI: 10.1002/anie.202006420.

(12) Zhang, Z.-Q.; Yang, C.-T.; Liang, L.-J.; Xiao, B.; Lu, X.; Liu, J.-H.; Sun, Y.-Y.; Marder, T. B.; Fu, Y. Copper-catalyzed/promoted cross-coupling of gem-diborylalkanes with nonactivated primary alkyl halides: an alternative route to alkylboronic esters. *Org. Lett.* **2014**, *16*, 6342.

(13) Andrieux, J.; Barton, D. H. R.; Patin, H. Rhodium-catalysed isomerisation of some unsaturated organic substrates. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359.

(14) Jain, P.; Antilla, J. C. Chiral Brønsted acid-catalyzed allylboration of aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 11884.

(15) (a) Akiyama, T.; Itoh, J.; Yokota, D.; Fuchibe, K. Enantioselective Mannich-type reaction catalyzed by a chiral Brønsted acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. Chiral Brønsted acid-catalyzed direct Mannich reactions via electrophilic activation. *J. Am. Chem. Soc.* **2004**, *126*, 5356. For selected reviews, see the following: (c) Akiyama, T. Stronger Brønsted acids. *Chem. Rev.* **2007**, *107*, 5744. (d) Terada, M. Binaphthol-derived phosphoric acid as a versatile catalyst for enantioselective carbon-carbon bond forming reactions. *Chem. Commun.* **2008**, 4097. (e) Akiyama, T.; Mori, K. Stronger Brønsted acids: recent progress. *Chem. Rev.* **2015**, *115*, 9277.

(16) (a) Miura, T.; Nishida, Y.; Morimoto, M.; Murakami, M. Enantioselective synthesis of *anti*-homoallylic alcohols from terminal alkynes and aldehydes based on concomitant use of a cationic iridium complex and a chiral phosphoric acid. *J. Am. Chem. Soc.* **2013**, *135*, 11497. (b) Incerti-Pradillos, C. A.; Kabeshov, M. A.; Malkov, A. V. Highly stereoselective synthesis of *Z*-homoallylic alcohols by kinetic resolution of racemic secondary allyl boronates. *Angew. Chem., Int. Ed.* **2013**, *52*, 5338. (c) Huang, Y.; Yang, X.; Lv, Z.; Cai, C.; Kai, C.; Pei, Y.; Feng, Y. Asymmetric synthesis of 1,3-butadienyl-2-carbinols by the homoallenylboration of aldehydes with a chiral phosphoric acid catalyst. *Angew. Chem., Int. Ed.* **2015**, *54*, 7299. (d) Barrio, P.; Rodriguez, E.; Saito, K.; Fustero, S.; Akiyama, T. γ-Silylboronates in the chiral Brønsted acid-catalysed allylboration of aldehydes. *Chem. Commun.* **2015**, *51*, 5246. (e) Miura, T.; Nakahashi, J.; Murakami, M. Enantioselective synthesis of (*E*)−boryl-substituted *anti*-homoallylic alcohols using palladium and a chiral phosphoric acid. *Angew. Chem., Int. Ed.* **2017**, *56*, 6989. (f) Miura, T.; Nakahashi, J.; Zhou, W.; Shiratori, Y.; Stewart, S. G.; Murakami, M. Enantioselective synthesis of *anti*-1,2-oxaborinan-3-enes from aldehydes and 1,1-di(boryl)alk-3-enes using ruthenium and chiral phosphoric acid catalysts. *J. Am. Chem. Soc.* **2017**, *139*, 10903. (g) Gao, S.; Chen, M. Enantioselective *syn*- and *anti*-alkoxyallylation of aldehydes via Brønsted acid catalysis. *Org. Lett.* **2018**, *20*, 6174. (h) Miura, T.; Oku, N.; Murakami, M. Diastereo- and enantioselective synthesis of (E)-δ-boryl-substituted *anti*-homoallylic alcohols in two steps from terminal alkynes. *Angew. Chem., Int. Ed.* **2019**, *58*, 14620. (i) Gao, S.; Chen, M. Enantioselective syntheses of 1, 4-pentadien-3-yl carbinols via Brønsted Acid catalysis. *Org. Lett.* **2020**, *22*, 400. (j) Gao, S.; Duan, M.; Houk, K. N.; Chen, M. Chiral phosphoric acid dual-function catalysis: asymmetric allylation with α-vinyl allylboron reagents. *Angew. Chem., Int. Ed.* **2020**, *59*, 10540. (k) Chen, J.; Chen, M. Enantioselective syntheses of (*Z*)-6′-boryl-anti-1,2-oxaborinan-3-enes via a dienylboronate protoboration and asymmetric allylation reaction sequence. *Org. Lett.* **2020**, *22*, 7321.

(17) (a) Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. Brønsted acid catalyzed asymmetric propargylation of aldehydes. *Angew. Chem., Int. Ed.* **2012**, *51*, 1391. (b) Reddy, L. R. Chiral Brønsted acid catalyzed enantioselective propargylation of aldehydes with allenylboronate. *Org. Lett.* **2012**, *14*, 1142. (c) Chen, M.; Roush, W. R. Enantioselective synthesis of *anti*- and *syn*-homopropargyl alcohols via chiral Brønsted acid catalyzed asymmetric allenylboration reactions. *J. Am. Chem. Soc.* **2012**, *134*, 10947. (d) Tsai, A. S.; Chen, M.; Roush, W. R. Chiral Brønsted acid catalyzed enantioselective synthesis of *anti*-homopropargyl alcohols via kinetic resolution-aldehyde allenylboration using racemic allenylboronates. *Org. Lett.* **2013**, *15*, 1568. (e) Wang, M.; Khan, S.; Miliordos, E.; Chen, M. Enantioselective syntheses of homopropargylic alcohols via asymmetric allenylboration. *Org. Lett.* **2018**, *20*, 3810.

(18) (a) Reddy, L. R. Chiral Brønsted acid catalyzed enantioselective allenylation of aldehydes. *Chem. Commun.* **2012**, *48*, 9189. (b) Wang, M.; Khan, S.; Miliordos, E.; Chen, M. Enantioselective allenylation of aldehydes via Brønsted acid catalysis. *Adv. Synth. Catal.* **2018**, *360*, 4634.

(19) (a) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. Mechanistic insights into the BINOL-derived phosphoric acid-catalyzed asymmetric allylboration of aldehydes. *J. Am. Chem. Soc.* **2012**, *134*, 2716. (b) Wang, H.; Jain, P.; Antilla, J. C.; Houk, K. N. Origins of stereoselectivities in chiral phosphoric acid catalyzed allylborations and propargylations of aldehydes. *J. Org. Chem.* **2013**, *78*, 1208. (c) Grayson, M. N.; Goodman, J. M. Understanding the mechanism of the asymmetric propargylation of aldehydes promoted by 1,1′-bi-2-naphthol-derived catalysts. *J. Am. Chem. Soc.* **2013**, *135*, 6142. (d) Grayson, M. N.; Yang, Z.; Houk, K. N. Chronology of CH···O hydrogen bonding from molecular dynamics studies of the phosphoric acid-catalyzed allylboration of benzaldehyde. *J. Am. Chem. Soc.* **2017**, *139*, 7717.

(20) Zhao, Y.; Truhlar, D. G. Density functionals with broad applicability in chemistry. *Acc. Chem. Res.* **2008**, *41*, 157.

(21) Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four M06-class functionals and 12 other function. *Theor. Chem. Acc.* **2008**, *120*, 215.

(22) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378.

(23) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A Consistent and Accurate *Ab Initio* Parametrization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H-Pu. *J. Chem. Phys.* **2010**, *132*, 154104.

(24) (a) Kennedy, J. W. J.; Hall, D. G. Dramatic rate enhancement with preservation of stereospecificity in the first metal-catalyzed additions of allylboronates. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Ishiyama, T.; Ahiko, T.; Miyaura, N. Acceleration effect of Lewis acid in allylboration of aldehydes: catalytic, regiospecific, diastereospecific, and enantioselective synthesis of homoallyl alcohols. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (c) Sakata, K.; Fujimoto, H. Quantum chemical study of Lewis acid catalyzed allylboration of aldehydes. *J. Am. Chem. Soc.* **2008**, *130*, 12519.

(25) For selected references of Lewis acid catalyzed allylboration, see the following: (a) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. Scandium-catalyzed allylboration of aldehydes as a practical method for highly diastereo- and enantioselective construction of homoallylic alcohols. *J. Am. Chem. Soc.* **2003**, *125*, 10160. (b) Rauniyar, V.; Hall, D. G. Lewis acids catalyze the addition of allylboronates to aldehydes by electrophilic activation of the dioxaborolane in a closed transition

structure. *J. Am. Chem. Soc.* **2004**, *126*, 4518. (c) Peng, F.; Hall, D. G. Simple, stable, and versatile double-allylation reagents for the stereoselective preparation of skeletally diverse compounds. *J. Am. Chem. Soc.* **2007**, *129*, 3070. (d) Chen, M.; Roush, W. R. Highly (*E*)-selective $BF_3{\cdot}Et_2O$-promoted allylboration of chiral nonracemic α-substituted allylboronates and analysis of the origin of stereocontrol. *Org. Lett.* **2010**, *12*, 2706. (e) Chen, M.; Roush, W. R. Enantioselective synthesis of (*Z*)- and (*E*)-2-methyl-1,5-*anti*-pentenediols via an allene hydroboration-double-allylboration reaction sequence. *J. Am. Chem. Soc.* **2013**, *135*, 9512.

(26) (a) Rauniyar, V.; Hall, D. G. Catalytic enantioselective and catalyst-controlled diastereofacial selective additions of allyl- and crotylboronates to aldehydes using chiral Brønsted acids. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426. (b) Rauniyar, V.; Zhai, H.; Hall, D. G. Catalytic enantioselective allyl- and crotylboration of aldehydes using chiral diol·$SnCl_4$ complexes. Optimization, substrate scope and mechanistic investigations. *J. Am. Chem. Soc.* **2008**, *130*, 8481.

(27) (a) Wu, T. R.; Shen, L.; Chong, J. M. Asymmetric allylboration of aldehydes and ketones using 3,3′-disubstituted binaphthol-modified boronates. *Org. Lett.* **2004**, *6*, 2701. (b) Lou, S.; Moquist, P. N.; Schaus, S. E. Asymmetric allylboration of ketones catalyzed by chiral diols. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (c) Paton, R. S.; Goodman, J. M.; Pellegrinet, S. C. Mechanistic insights into the catalytic asymmetric allylboration of ketones: Brønsted or Lewis acid activation? *Org. Lett.* **2009**, *11*, 37. (d) Alam, R.; Vollgraff, T.; Eriksson, L.; Szabó, K. J. Synthesis of adjacent quaternary stereocenters by catalytic asymmetric allylboration. *J. Am. Chem. Soc.* **2015**, *137*, 11262.

(28) (a) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. Simple organic molecules as catalysts for enantioselective synthesis of amines and alcohols. *Nature* **2013**, *494*, 216. (b) Lee, K.; Silverio, D. L.; Torker, S.; Haeffner, F.; Robbins, D. W.; van der Mei, F. W.; Hoveyda, A. H. Catalytic enantioselective addition of organoboron reagents to fluoroketones controlled by electrostatic interactions. *Nat. Chem.* **2016**, *8*, 768. (c) van der Mei, F. W.; Qin, C.; Morrison, R. J.; Hoveyda, A. H. Practical, broadly applicable, p-selective, *Z*-selective, Diastereoselective, and enantioselective addition of allylboron compounds to mono-, di-, tri-, and polyfluoroalkyl ketones. *J. Am. Chem. Soc.* **2017**, *139*, 9053. (d) Morrison, R. J.; van der Mei, F. W.; Romiti, F.; Hoveyda, A. H. A catalytic approach for enantioselective synthesis of homoallylic alcohols bearing *Z*-alkenyl chloride or trifluoromethyl group. A protecting group-free synthesis of mycothiazole. *J. Am. Chem. Soc.* **2020**, *142*, 436.

(29) (a) Gao, S.; Chen, J.; Chen, M. (*Z*)-α-Boryl-crotylboron reagents via *Z*-selective alkene isomerization and application to stereoselective syntheses of (*E*)-δ-boryl-*syn*-homoallylic alcohols. *Chem. Sci.* **2019**, *10*, 3637. (b) Weber, F.; Schmidt, A.; Röse, P.; Fischer, M.; Burghaus, O.; Hilt, G. Double-Bond Isomerization: Highly reactive nickel catalyst applied in the synthesis of the pheromone (9*Z*,12*Z*)-tetradeca-9,12-dienyl acetate. *Org. Lett.* **2015**, *17*, 2952.

(30) The electronic stabilization provided by the neighboring boron atom may play a role in the equilibrium. (a) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. Copper (I) β-boroalkyls from alkene insertion: isolation and rearrangement. *Organometallics* **2006**, *25*, 2405. (b) Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. DFT Studies of alkene insertions into Cu- B bonds in copper (I) boryl complexes. *Organometallics* **2007**, *26*, 2824. (c) Hong, K.; Liu, X.; Morken, J. P. Simple access to elusive α-boryl carbanions and their alkylation: an umpolung construction for organic synthesis. *J. Am. Chem. Soc.* **2014**, *136*, 10581. (d) Coombs, J. R.; Zhang, L.; Morken, J. P. Enantiomerically enriched tris (boronates): readily accessible conjunctive reagents for asymmetric synthesis. *J. Am. Chem. Soc.* **2014**, *136*, 16140. (e) Wommack, A. J.; Kingsbury, J. S. On the scope of the Pt-catalyzed Srebnik diborylation of diazoalkanes. An efficient approach to chiral tertiary boronic esters and alcohols via B-stabilized carbanions. *Tetrahedron Lett.* **2014**, *55*, 3163. For an overview of boron-stabilized carbanions, see the following: (f) Kliś, T.; Luliński, S.; Serwatowski, J. Formation and Synthetic Applications of metalated organoboranes. *Curr. Org. Chem.* **2010**, *14*, 2549.

(31) (a) Hoffmann, R. W. Allylic 1,3-strain as a controlling factor in stereoselective transformations. *Chem. Rev.* **1989**, *89*, 1841. For recent examples, see the following: (b) Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. Application of the lithiation-borylation reaction to the preparation of enantioenriched allylic boron reagents and subsequent in situ conversion into 1,2,4-trisubstituted homoallylic alcohols with complete control over all elements of stereochemistry. *J. Am. Chem. Soc.* **2010**, *132*, 4025. (c) Han, J.-L.; Chen, M.; Roush, W. R. Diastereo- and enantioselective synthesis of (*E*)-2-methyl-1,2-*syn*- and (*E*)-2-methyl-1,2-*anti*-3-pentenediols via allenylboronate kinetic resolution with $(^dIpc)_2BH$ and aldehyde allylboration. *Org. Lett.* **2012**, *14*, 3028. (d) Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. Nonracemic allylic boronates through enantiotopic-group-selective cross-coupling of geminal bis(boronates) and vinyl halides. *J. Am. Chem. Soc.* **2014**, *136*, 17918.

(32) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. Double asymmetric synthesis and a new strategy for stereochemical control in organic synthesis. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Roush, W. R. Concerning the diastereofacial selectivity of the aldol reactions of.alpha.-methyl chiral aldehydes and lithium and boron propionate enolates. *J. Org. Chem.* **1991**, *56*, 4151. (c) Chen, M.; Roush, W. R. Highly stereoselective synthesis of *anti, anti*-dipropionate stereotriads: a solution to the long-standing problem of challenging mismatched double asymmetric crotylboration reactions. *J. Am. Chem. Soc.* **2012**, *134*, 3925.

(33) Matteson, D. S. α-Halo boronic esters in asymmetric synthesis. *Tetrahedron* **1998**, *54*, 10555.

(34) (a) Hayashi, T.; Yamasaki, K. Rhodium-catalyzed asymmetric 1,4-addition and its related asymmetric reactions. *Chem. Rev.* **2003**, *103*, 2829. (b) Sakai, M.; Hayashi, H.; Miyaura, N. Rhodium-catalyzed conjugate addition of aryl- or 1-alkenylboronic acids to enones. *Organometallics* **1997**, *16*, 4229. (c) Suginome, M.; Ohmori, Y.; Ito, Y. β-Borylallylsilanes as a new tool for convenient synthesis of alkenylboranes. *J. Am. Chem. Soc.* **2001**, *123*, 4601. (d) Ishiyama, T.; Takagi, J.; Kamon, A.; Miyaura, N. Palladium-catalyzed cross-coupling reaction of bis(pinacolato) diboron with vinyl triflates β-substituted by a carbonyl group: efficient synthesis of β-boryl-α, β-unsaturated carbonyl compounds and their synthetic utility. *J. Organomet. Chem.* **2003**, *687*, 284.

(35) Yoo, K. S.; Yoon, C. H.; Jung, K. W. Oxidative palladium (II) catalysis: a highly efficient and chemoselective cross-coupling method for carbon-carbon bond formation under base-free and nitrogenous-ligand conditions. *J. Am. Chem. Soc.* **2006**, *128*, 16384.

(36) Miyaura, N.; Suzuki, A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem. Rev.* **1995**, *95*, 2457.

(37) Krautwald, S.; Carreira, E. M. Stereodivergence in asymmetric catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 5627.

(38) (a) Oh, D.-C.; Gontang, E. A.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. Salinipyrones and pacificanones, mixed-precursor polyketides from the marine actinomycete *Salinispora pacifica*. *J. Nat. Prod.* **2008**, *71*, 570. (b) Ramesh, P.; Meshram, H. M. First total synthesis of salinipyrone A using highly stereoselective vinylogous Mukaiyama aldol reaction. *Tetrahedron* **2012**, *68*, 9289.

(39) (a) Cheng, L.-J.; Mankad, N. P. Copper-catalyzed borocarbonylative coupling of internal alkynes with unactivated alkyl halides: modular synthesis of tetrasubstituted β-borylenones. *Angew. Chem., Int. Ed.* **2018**, *57*, 10328. (b) Partridge, B. M.; Hartwig, J. F. Sterically controlled iodination of arenes via iridium-catalyzed C-H borylation. *Org. Lett.* **2013**, *15*, 140.

(40) Sabitha, G.; Gopal, P.; Yadav, J. S. Total synthesis of the marine polypropionates, siphonarienal, siphonarienone, and pectinatone. *Tetrahedron: Asymmetry* **2009**, *20*, 2205.

(41) (a) Nishimaru, T.; Eto, K.; Komine, K.; Ishihara, J.; Hatakeyama, S. Total synthesis of lajollamycin B. *Chem. - Eur. J.* **2019**, *25*, 7927. (b) Wang, Z.; Moloney, M. G. Synthesis of the middle fragment of oxazolomycin. *Tetrahedron Lett.* **2002**, *43*, 9629.

(42) Dess, D. B.; Martin, J. C. Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *J. Org. Chem.* **1983**, *48*, 4155.
(43) Stille, J. K.; Groh, B. L. Stereospecific cross-coupling of vinyl halides with vinyl tin reagents catalyzed by palladium. *J. Am. Chem. Soc.* **1987**, *109*, 813.