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RESEARCH ARTICLE

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Chiral Phosphoric Acid Dual-Function Catalysis: Asymmetric Allylation with α-Vinyl Allylboron Reagents

Shang Gao,[a, #] Meng Duan,[b, #] K. N. Houk,*[b] and Ming Chen*[a]

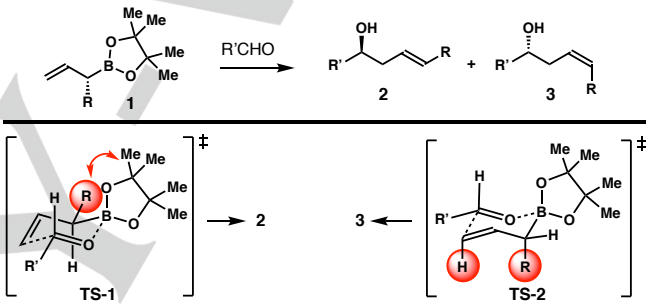
Dedicated to Professor William R. Roush

Abstract: We report a dual function asymmetric catalysis by a chiral phosphoric acid catalyst that controls both enantioselective addition of an achiral α-vinyl allylboronate to aldehydes and pseudo-axial orientation of the α-vinyl group in the transition state. The reaction produces dienyl homoallylic alcohols with high *Z*-selectivities and enantioselectivities. Computational studies revealed that minimization of steric interactions between the alkyl groups of the diol on boron and the chiral phosphoric acid catalyst influences the orientation of α-vinyl substituent of the allylboronate reagent to occupy a pseudo-axial position in the transition state.

Introduction

The asymmetric addition of allylmetal reagents to carbonyl compounds is a widely adopted method for the synthesis of acyclic alcohols with high enantiopurity.[1] Over the past thirty years, many useful allylmetal reagents, including catalytic variants, have been developed.[2-5] Among these available reagents, allylboron compounds are particularly useful.[6] It is well-established that carbonyl addition with allylboron reagents proceeds by way of the cyclic Zimmerman-Traxler transition state to give homoallylic alcohol products,[7] and stereochemical outcomes of these reactions are highly predictable. While chiral, nonracemic allylboranes are valuable for the syntheses of enantioenriched homoallylic alcohols,[8] recent studies have shown that allylboronates are also highly useful reagents for asymmetric allylation because of their low toxicities and remarkable stabilities toward oxygen and moisture.

Several strategies are available for enantioselective carbonyl allylation with allylboronate reagents. Chiral auxiliary based allylboronates are conventional reagents to produce enantioenriched homoallylic alcohols.[9] However, it is inevitable that a stoichiometric amount of chiral auxiliaries are required for these reactions. In comparison, catalytic carbonyl addition with achiral allylboronates, pinacol allylboronate for instance, in the presence of a chiral, nonracemic catalyst represents a significant advance in allylation chemistry. Elegant studies of allylboration using either chiral Lewis or Brønsted acid catalysts have been developed to generate homoallylic alcohols with high enantioselectivities.[10-13] Reactions with enantioenriched, α-substituted allylboronate can also form homoallylic alcohols asymmetrically.[14,15] These reactions typically proceed through chirality transfer, and the enantiopurity of the starting boron reagents will dictate the enantiomeric excess of the alcohol products. Compared to well-developed allylation with reagents that lack the α-substituent, allylation with these α-substituted allylboron reagents, however, has received much less attention.



Scheme 1. Allyl addition to aldehydes with α-substituted allylboronates

The major challenge in asymmetric allylation with α-substituted allylboronates is to control the stereoselectivity of the reactions besides enantioselective preparation of such reagents. Scheme 1 shows the reaction of α-substituted allylboronate reagent **1** with an aldehyde. Two products can be generated from this reaction via two competing transition states, **TS-1** and **TS-2**. In **TS-1**, the α-substituent R occupies a pseudo-equatorial position, which leads to the formation of product **2** with an *E*-olefin unit. This transition state typically suffers a gauche interaction between the pseudo-equatorially oriented R group and the pinacol unit of allylboronate **1**. On the other hand, the α-substituent R was placed in a pseudo-axial position in **TS-2** to form product **3** with *Z*-olefin geometry. In this case, the nonbonding $A^{1,3}$ allylic strain is developed between the H atom and the pseudo-axially oriented R group in **TS-2**. As shown by early studies from the Hoffmann group,[16] when R is not a polar group (R ≠ Cl, Br, OR^1, NR^1R^2), the energies of these two competing transition states are very close to each other. Consequently, the reaction generally provides a mixture of products **2** and **3** with low selectivity (~1:2 in many cases). Therefore, the development of a general approach to proper control the orientation of the α-substituent of reagent **1** in the transition state is an important objective.

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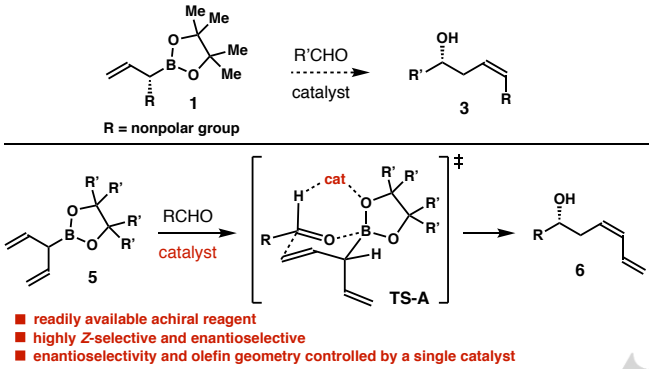
An elegant example of *E*-selective allylation with α-substituted allylboronates was recently disclosed by the Aggarwal group.[17] By using a three-step reaction sequence, homoallylic alcohols **2** were obtained with high *E*-selectivities from reagent **1**. ^{11}B NMR studies showed that the reaction proceeded via the intermediacy of an allylborinate that is substantially more reactive than allylboronates **1**. More importantly, the steric repulsion between the α-substituent (R group) and the pinacol moiety is greatly relieved in the transition state. Consequently, the α-substituent (R group) was positioned in the pseudo-equatorial position to give homoallylic alcohols **2** with high *E*-selectivities.



Scheme 2. Proposed *Z*-selective allylboration with α-substituted allylboronates

In comparison, proper control of the α-substituent (R group) of reagent **1** in the pseudo-axial position in the transition state (e.g., **TS-2**, Scheme 1) will produce *Z*-homoallylic alcohols **3**. While aldehyde allylation with a polar group (R = Cl, Br, OR^1, NR^{1}R^2)[18] substituted allylboronates proceeds with good *Z*-selectivity, the development of highly *Z*-selective allylation is challenging when the α-substituent is a nonpolar group (top panel, Scheme 2).[19-21] In connection with an ongoing synthesis project, we became interested in developing new methods for *Z*-selective allylation with α-substituted allylboronates. We report herein catalytic asymmetric aldehyde allylation with α-vinyl allylboronate **5** that delivers homoallylic alcohols **6** with high *Z*-selectivities and enantioselectivities (bottom panel, Scheme 2). Compared to aldehyde allylation with chiral nonracemic α-substituted allylboron reagents (e.g., **1**) that proceeds via chirality transfer, a salient feature of the reaction we developed is that reagent **5** is achiral and readily available, and the chiral catalyst controls both the enantioselection of allyl addition and more importantly, the axial orientation of the α-vinyl group in the transition state (**TS-A**, Scheme 2). DFT computation studies were conducted to probe the origin of enantioselectivity and *Z*-selectivity of the reaction. In addition, *Z*-dienyl homoallylic alcohol **6** is a common structural motif in many bioactive natural products (Figure 1). The approach we developed offers a straightforward method to access this structural entity from reagent **5** and a corresponding aldehyde substrate.

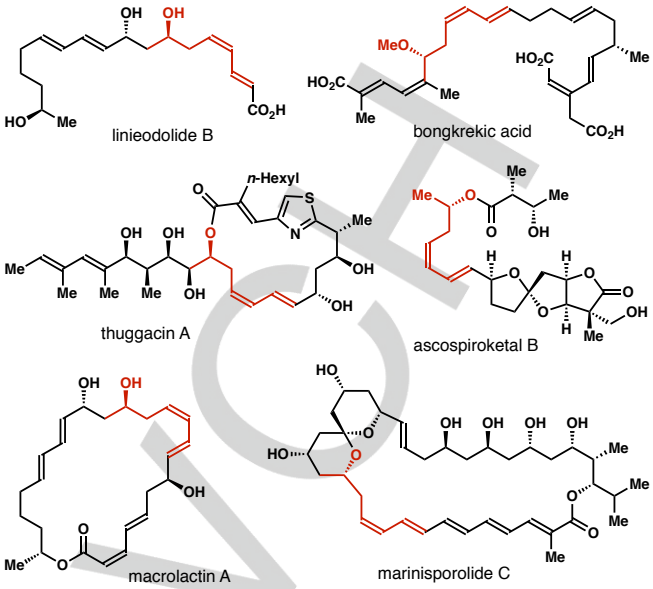
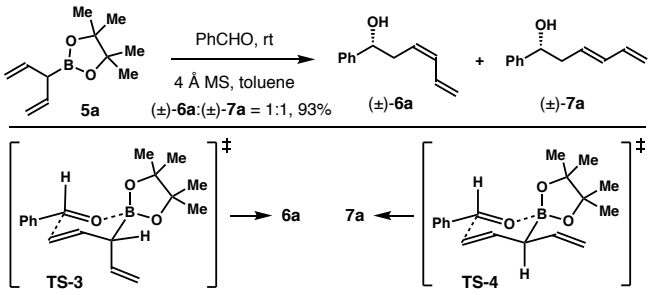


Figure 1. Selected natural products containing a (*Z*)-homoallylic alcohol unit

Results and Discussion

Reaction Development: We began our studies by examining the reaction between allylboronate **5a**[22] and benzaldehyde in the absence of any catalyst. As shown in Scheme 3, the reaction produced a 1:1 mixture of *Z*-isomer (±)-**6a** and *E*-isomer (±)-**7a**. The data suggest that the two competing transition states **TS-3** and **TS-4** have very similar energies. Either pseudo-axial (**TS-3**) or pseudo-equatorial (**TS-4**) placement of the α-vinyl group of reagent **5a** does not have a significant impact on the energy of transition state of the reaction, presumably due to minimal gauche interactions between the small vinyl group and pinacol diol unit on boron.

We were intrigued whether or not the addition of a chiral catalyst can bias the orientation of vinyl group in the transition state. Pioneered by Antilla and coworkers,[12] chiral phosphoric acids such as (*R*)-**A** (Scheme 4)[23] have been shown to catalyze the reaction of aldehydes with a variety of boron reagents.[24-26] The origin of enantioselection was elucidated by computational studies conducted by the Houk and the Goodman groups.[27]



Scheme 3. Allylboration with α-vinyl allylboron **5a** in the absence of a catalyst

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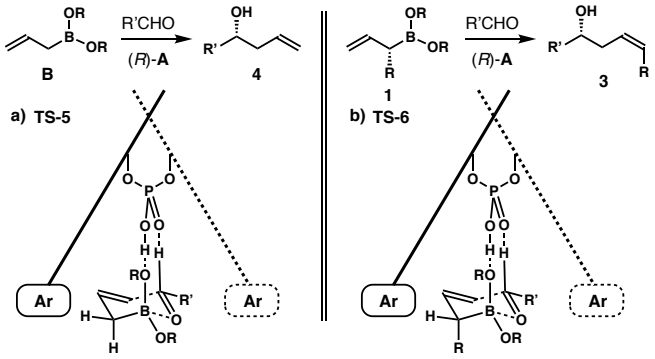
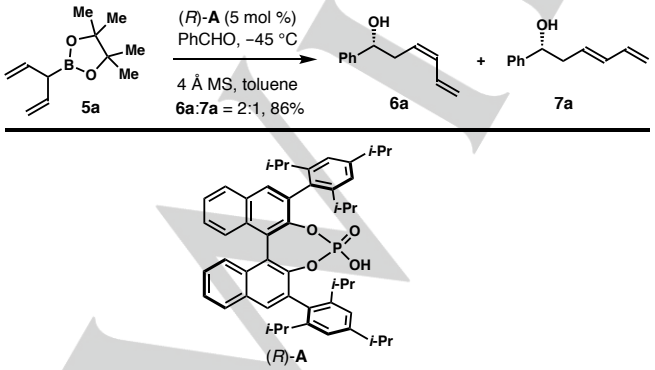


Figure 2. Stereochemical models for chiral phosphoric acid (*R*)-**A** catalyzed allylboration with reagent **B** or **1**

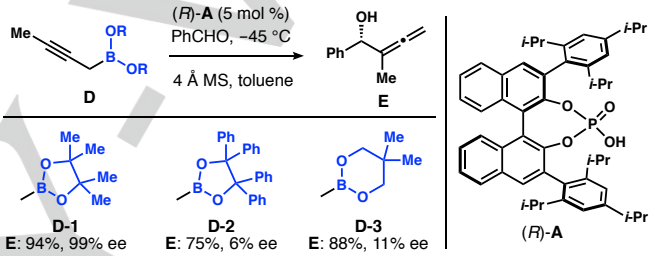
Based on the reported model, Figure 2a shows the favored reaction pathway (**TS-5**) of allylboronate **B** with an aldehyde substrate. By analogy, we speculated that the reaction of α-substituted allylboronate **1** with an aldehyde substrate should proceed through transition state **TS-6** shown in Figure 2b, with pseudo-axial placement of the α-substituent, R group, to give product **3**. The competing transition state leading to the *E*-olefin product would have the R group in the pseudo-equatorial position, and nonbonding steric interaction between the R group of reagent **1** and the Ar group of the catalyst will be developed. Therefore, we decided to choose chiral phosphoric acid (*R*)-**A** as the catalyst for aldehyde addition with boronate **5a**, aiming for *Z*-selective allylboration.

In the event, 5 mol % of phosphoric acid (*R*)-**A** was added to the reaction of **5a** with benzaldehyde at −45 ºC in toluene. Disappointedly, only a 2:1 mixture of **6a** and **7a** was formed, slightly favoring the *Z*-isomer **6a** (Scheme 4). One encouraging aspect of this reaction, however, is that the enantiomeric excess of **6a** is 93% ee.[28] These data indicate that the acid catalyst (*R*)-**A** enables highly face selective allyl addition to benzaldehyde. However, it is not able to control the orientation of the α-vinyl group in the transition state presumably because two competing transition states that led to the formation of **6a** and **7a** have a similar level of energy in the presence of phosphoric acid (*R*)-**A**.



Scheme 4. Chiral phosphoric acid-catalyzed allylation with reagent **5a**

In our recent report on chiral phosphoric acid-catalyzed asymmetric allenylation,[26b] we found that proper choice of the diol unit of propargyl boronate is crucial to the enantioselectivity of the reaction. As shown in Scheme 5, the addition of reagent **D-1** to benzaldehyde produced allenic alcohol **E** in 94 % yield with 99% ee. When the pinacol moiety of **D-1** was replaced with benzopinacol or 2,2-dimethyl-1,3-propanediol (reagent **D-2** or **D-3**), the enantiomeric excess of product **E** decreased to 6% or 11% ee. The significant change in enantiopurity of **E** indicates that the diol unit on boron is essential to the facial selective addition of propargylboron reagent **D** to the aldehyde substrate, presumably due to the interactions between the diol group of **D** and the acid catalyst (*R*)-**A**. Based on these data, we postulated that modifying the diol unit of α-vinyl substituted allylboronate **5** might impact the *E*/*Z* selectivity of the reaction of aldehydes with reagent **5**, while maintaining high level of enantioselection.



Scheme 5. Impact on enantioselectivity of chiral phosphoric acid-catalyzed allenylation with propargylic boronates **D** bearing different diols

To test our hypothesis, allylboronates **5b-h** with different diol units were synthesized.[22] Allylation of benzaldehyde with these boronates in the absence of phosphoric acid catalyst were examined first. In all cases, ~1:1 mixture of racemic alcohol (±)-**6a** and (±)-**7a** was obtained. These data indicate that there is no inherent pseudo-equatorial or pseudo-axial bias of the α-vinyl group of allylboronates **5b-h** in the allylation transition states. Next, asymmetric allylation of benzaldehyde with **5b-h** in the presence of 5 mol % phosphoric acid (*R*)-**A** were examined. As summarized in Table 1, allylation with boronate **5b** bearing an ethyl analog of pinacol group provided a 16:1 mixture of **6a** and **7a** in 92% yield (entry 2) with *Z*-isomer **6a** as the major product. The enantiomeric excess of **6a** was determined to be 94% ee. Encouraged by this initial success, we anticipated that the reaction with boronate **5c**, a propyl analog of pinacol boronate **5a**, should have an even better selectivity. Indeed, excellent *Z*-selectivity was observed in the reaction with allylboronate **5c**. Homoallylic alcohol **6a** was formed as the only product (*Z*:*E* > 30:1) in 86% yield with 95% ee (entry 3). We discovered that further increasing steric bulk of the diol group significantly decreases the rate of allylation. For example, the reaction with boronate **5d** (the *i*-Pr analog of **5a**) proceeded with very low conversion (< 5%, entry 4). Reaction of allylboronate **5e** with cyclopentyl groups gave a 12:1 mixture of **6a** and **7a** in 82% yield with 95% ee for **6a** (entry 5). High *Z*-selectivity was also

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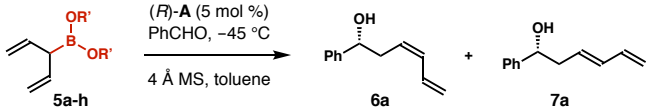
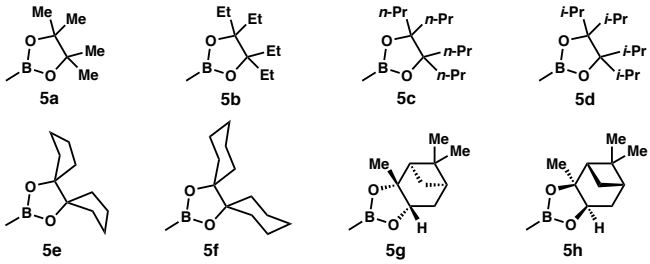
Table 1. Evaluation of *Z*/*E* selectivity in chiral phosphoric acid catalyzed allylboration with reagents **5a-h** bearing different diols



entry	boronate	**6a**:**7a**	% yield (**6a**+**7a**)	% ee (**6a**)
1	**5a**	2:1	86	93
2	**5b**	16:1	92	94
3	**5c**	> 30:1	86	95
4	**5d**	N.D.	< 5	N.D.
5	**5e**	12:1	82	95
6	**5f**	25:1	86	95
7	**5g**	1.5:1	80	N.D.
8	**5h**	2:1	83	N.D.

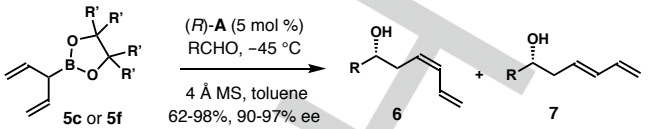


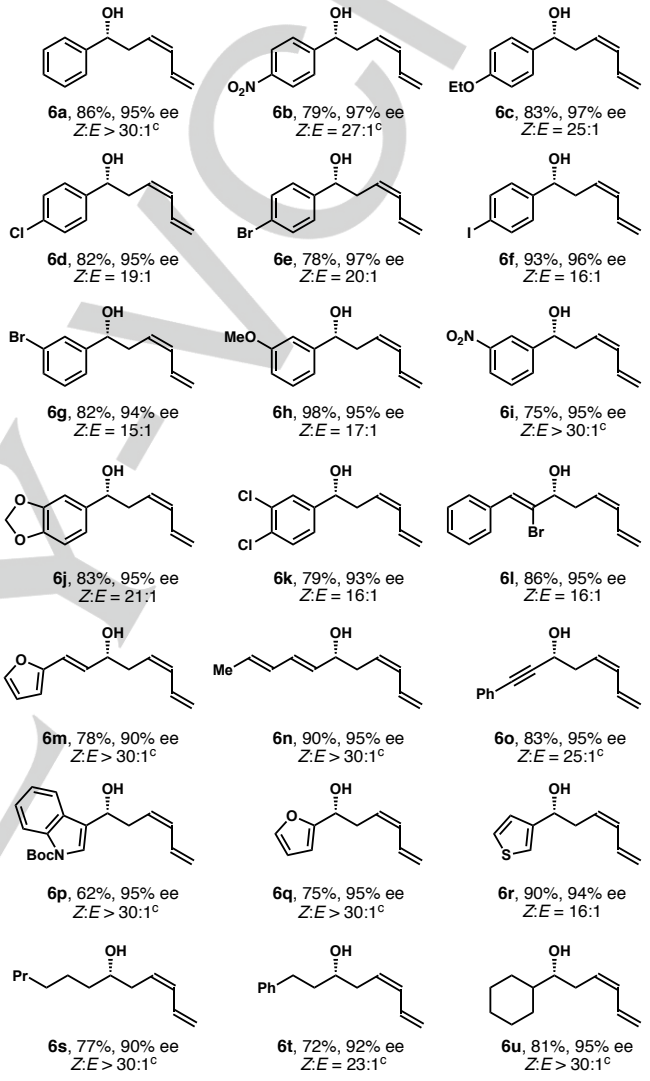
Reaction conditions: allylboronate **5** (0.12 mmol), benzaldehyde (0.1 mmol), phosphoric acid (*R*)-**A** (5 mol %), 4 Å MS, toluene, –45 °C, 48 h. Yields of isolated products are listed. The ratios of **6a** and **7a** were determined by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of **6a** was determined by modified Mosher ester analysis

observed for the reaction with allylboronate **5f** (the cyclohexyl analog), affording **6a** in 86% yield with 25:1 *Z*-selectivity and 95% ee (entry 6). Intriguingly, the enantiomeric excess of the minor product *E*-isomer **7a** is only 50% ee in the reaction with **5f**. Reactions of benzaldehyde with allylboronates **5g**-**h** that have a chiral, nonracemic diol group on boron were also conducted in the presence of acid catalyst (*R*)-**A**. Interestingly, both cases gave very low *Z*/*E* selectivities (entries 7 and 8). Overall, these data showed that the trend for *Z*-selectivities in chiral phosphoric acid-catalyzed reactions with boronates **5** correlates well with respect to the size of diol group on boron: methyl << cyclopentyl < ethyl < cyclohexyl < propyl. However, in the case of boronates with a sterically very demanding diol group, the rate of allylation decreases significantly. Meanwhile, in the absence of the acid catalyst, the 1:1 *Z*/*E* selectivity in these reactions with allylboronates **5a**-**h** indicates that the size of diol unit does not have any apparent impact on orientation of the α-vinyl group in the transition states. Collectively, these data suggest that the observed *Z*/*E* selectivities in chiral phosphoric acid-catalyzed reactions are likely the results of intricate interactions between the acid catalyst and the diol group on boron.

Substrate Scope: With optimal reaction conditions in hand, the scope of aldehyde that underwent enantioselective allylboration with allylboronate **5c** or **5f** was explored.[29] As summarized in Table 2, the reaction worked well with a broad scope of

Table 2. Scope of aldehyde for asymmetric allylboration catalyzed by chiral phosphoric acid (*R*)-**A**[a,b]



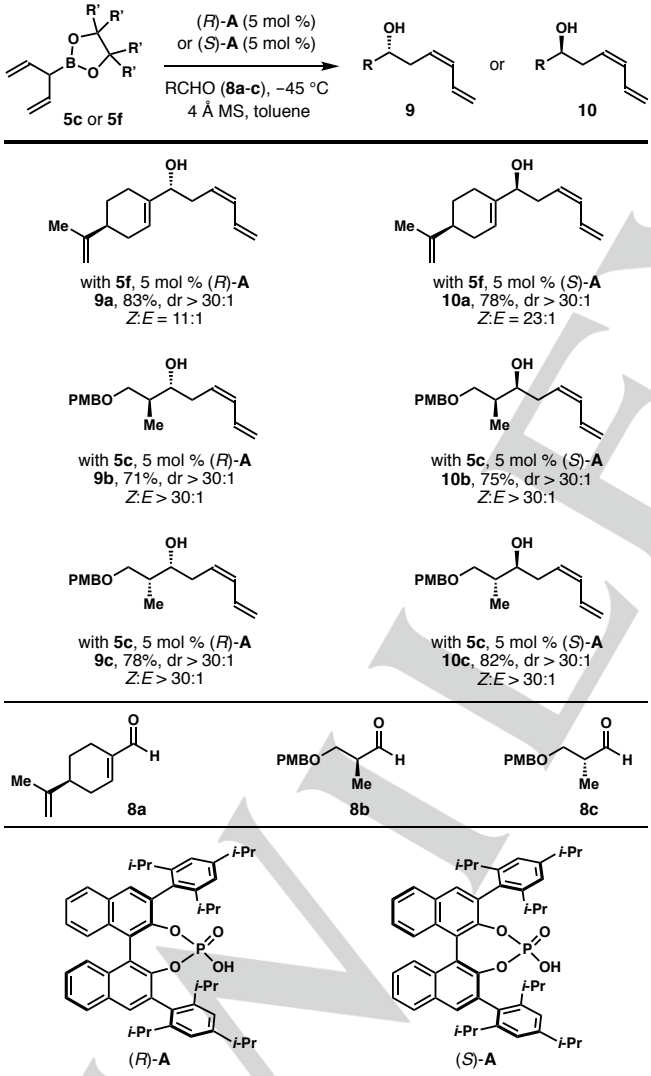


[a] Reaction conditions: allylboronate **5f** (0.12 mmol, 1.2 equiv), aldehyde (0.1 mmol, 1.0 equiv), phosphoric acid (*R*)-**A** (5 mol %), 4 Å molecular sieves (50 mg) toluene (0.3 mL), –45 °C. [b] Yields of isolated products are listed; the *Z*/*E* ratios were determined by ^{1}H NMR analysis of the crude reaction mixture; enantiomeric excesses were determined by modified Mosher ester analysis. [c] Reactions were conducted with **5c**.

aldehydes. Homoallylic alcohol products **6** were obtained in good yields with high *Z*-selectivities and enantiomeric excess. For instance, reactions of aromatic aldehydes with an electron-donating or withdrawing group at the *para*-position provided alcohols **6b**-**c** in 79-83% yields with 25-27:1 *Z*-selectivity and 97% ee. Aromatic aldehydes bearing a halogen atom at *para*-position are suitable substrates for the reaction, and alcohols **6d**-**f** were

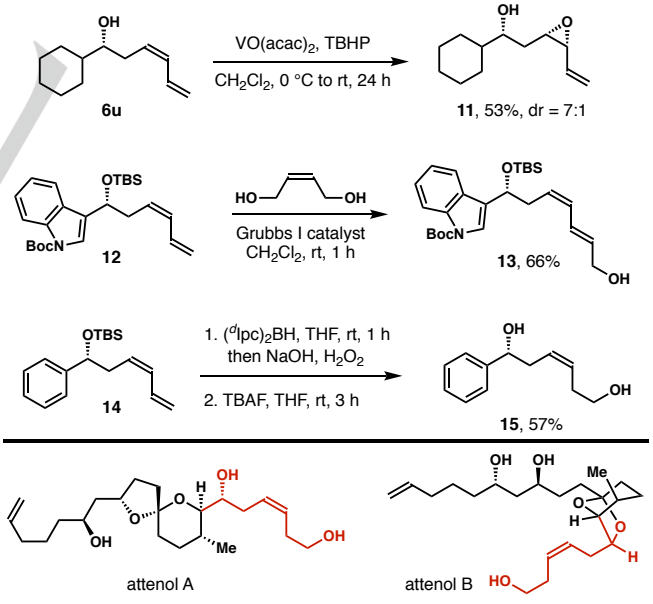
obtained in 78-93% yields with 16-20:1 *Z*-selectivities and 95-97% ee. Similar results were achieved with *meta*-substituted aromatic aldehydes, affording products **6g-i** in 75-98% yields with 15-30:1 *Z*-selectivities and 94-95% ee. Aldehydes with other substitution patterns also reacted with boronate **5** to give alcohols **6j-k** in 79-83% yields with 16-21:1 *Z*-selectivities and 93-95% ee. The reactions of allylboronate **5** with α,β-unsaturated aldehydes proceeded to furnish products **6l-o** in 78-90% yields with 16-30:1 *Z*-selectivities and 90-95% ee. Aldehydes that contain a heterocycle reacted with boronate **5** to give products **6p-r** in 62-90% yields with high *Z*-selectivities and 94-95% ee. Moreover, several representative aliphatic aldehydes also reacted with boronate **5**. Homoallylic alcohol products **6s-u** were isolated in 72-81% yields with 23-30:1 *Z*-selectivities and 90-95% ee.

Table 3. Double stereodifferentiation reactions of enantioenriched aldehydes with reagent **5** catalyzed by chiral phosphoric acids (*R*)-**A** or (*S*)-**A**[a]



[a] Reaction conditions: allylboronate **5f** (0.12 mmol), aldehyde **8** (0.1 mmol), phosphoric acid (*R*)-**A** or (*S*)-**A** (5 mol %), diastereoselectivities and *Z*/*E* ratios were determined by ^{1}H NMR analysis of crude reaction mixtures.

Double Stereodifferentiation Reaction with Enantioenriched Aldehydes: Double stereodifferentiation reaction is a useful strategy to form diastereomeric products with high selectivities from enantioenriched starting materials.[30] Depending on the inherent bias of enantioenriched substrates, these reactions may proceed under catalyst/reagent control or substrate control. To probe whether diastereomeric alcohol products can be obtained selectively by utilizing acid catalyst (*R*)-**A** or (*S*)-**A**, studies on reactions of enantioenriched aldehydes **8a-c** with allylboronate **5c** or **5f** were conducted. As shown in Table 3, in the presence of 5 mol % of catalyst (*R*)-**A**, the reaction of (*S*)-perillaldehyde (**8a**) with **5f** occurred to give product **9a** in 83% yield with 11:1 *Z*-selectivity. When (*S*)-**A** was used as the catalyst, diastereomer **10a** was obtained in 78% with 23:1 *Z*-selectivity. Aldehyde **8b** reacted with allylboronate **5c** in the presence of acid (*R*)-**A** to give product **9b** in 71% yield with > 30:1 *Z*-selectivity and diastereoselectivity. The *Z*-selectivity and diastereoselectivity were equally remarkable (> 30:1) when (*S*)-**A** was employed as the catalyst, affording **10b** in 75% yield. Similar results were achieved in the case of the enantiomeric aldehyde **8c**; alcohol **9c** and **10c** were obtained in 78-82% yields with excellent *Z*-selectivities and diastereoselectivities (> 30:1) by employing acid (*R*)-**A** or (*S*)-**A** separately. Therefore, through the combination of enantiomeric aldehydes and catalysts, all four diastereomeric products (**9b-c**, **10b-c**) were obtained with high *Z*-selectivities and diastereoselectivities.[31] The data suggest that these reactions proceeded under complete catalyst-control in all cases.



Scheme 6. Transformation of reaction products

Product Derivatization: The alcohol products obtained from the reaction contain a conjugated diene unit that can undergo a variety of transformations. As depicted in Scheme 6, hydroxyl directed epoxidation of **6u** using $VO(acac)_2$ gave epoxide **11** in

53% yield with 7:1 dr.[32] Epoxidation of the terminal alkene group was not detected. Cross-metathesis of TBS ether **12** with (*Z*)-2-butene-1,4-diol in the presence Grubbs 1st generation catalyst provided alcohol **13** in 66% yield with high *E*-selectivity.[33] Regioselective hydroboration/oxidation of the terminal alkene in **14** followed by TBS deprotection with TBAF gave diol **15** in 57% yield. This structure entity is an important structural motif of several nature products such as attenols A and B (Scheme 6).[34] To further demonstrate the synthetic utility of the develped method, synthesis of the C1-15 fragment of macrolactin A was also conducted (please see Supporting Information for details).

Computational Studies

To better understand the origins of observed *Z*/*E* selectivity and enantioselectivity of the reaction, density functional theory (DFT) calculations at the M06-2X/6-311+G(d,p)-CPCM(toluene)//B3LYP/6-31G(d) level of theory[35] using Gaussian 09 were performed. The uncatalyzed allylation of benzaldehyde with boronate **5f** was studied first. As shown in Figure 3, the activation free energies of the transition states (**TS-7**, **TS-8**) leading to (±)-**6a** and (±)-**7a** are identical, as found experimentally.

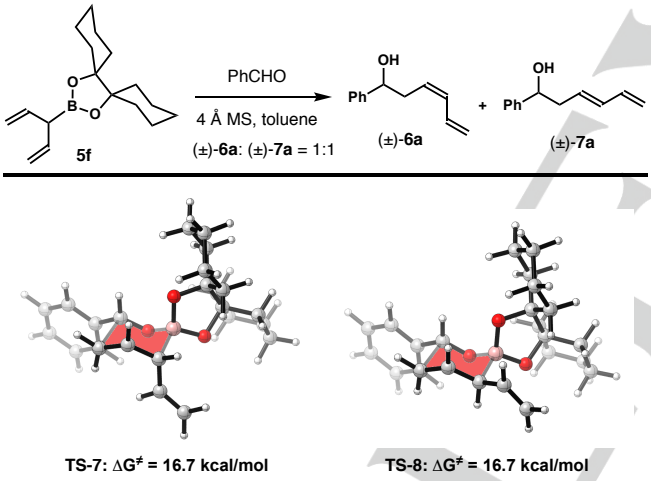


Figure 3. Optimized transition states of uncatalyzed allylation of benzaldehyde with boronate **5f**

Next, we explored enantioselective allylboration of benzaldehyde with boronate **5f** in the presence of phosphoric acid (*R*)-**A** using the model developed by the Goodman and the Houk groups.[27] As shown in Figure 4, the addition of boronate **5f** to benzaldehyde leads to product **6a** via transition state **TS-9** with the vinyl group occupying the pseudo-axial position, while the reaction via transition state **TS-10** with the vinyl group occupying the pseudo-equatorial position produces alcohol **7a**. Energetically, transition state **TS-10** is less favorable than transition state **TS-9** by 0.8 kcal/mol, in reasonable agreement with the observed *Z*-selectivity.[36] Closely examining the

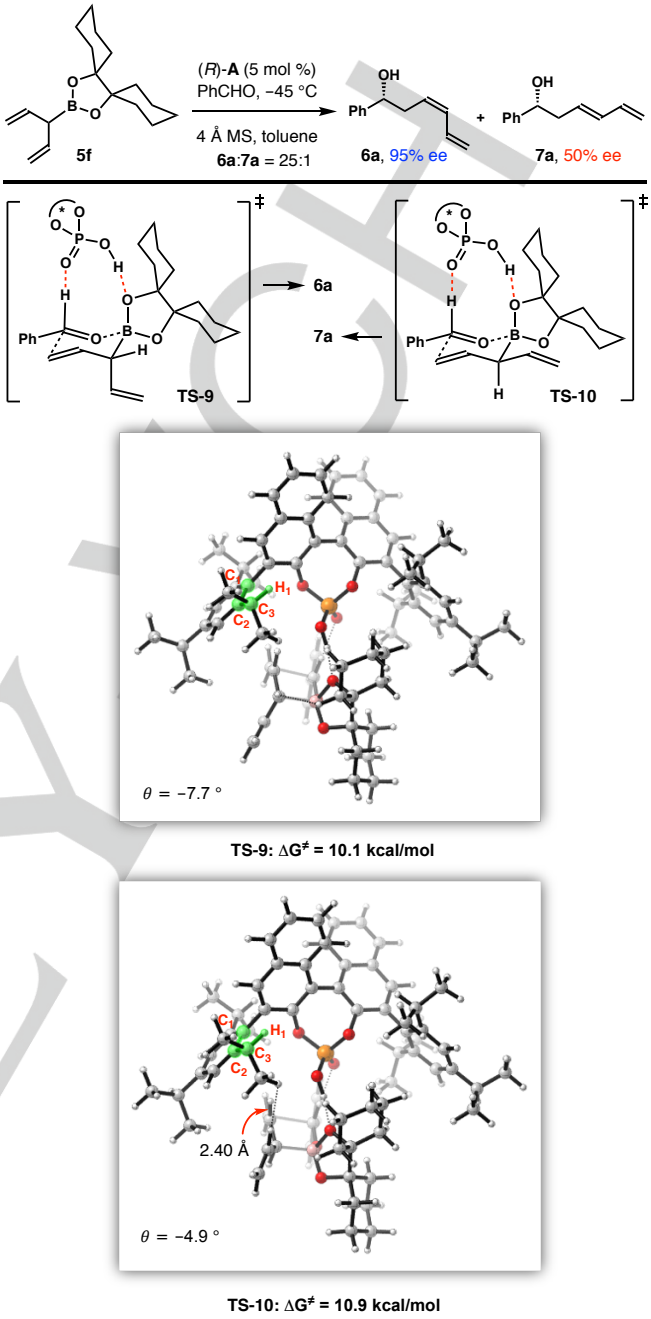


Figure 4. Axial view of transition states **TS-9** and **TS-10**. The bond lengths are in Ångstrom.

geometries of these two transition states **TS-9** and **TS-10** revealed that the vinyl group of allylboronate **5f** in **TS-10** is orientated toward isopropyl groups of the acid catalyst (*R*)-**A**. The shortest H–H non-bonding distance between the isopropyl group and the vinyl group is 2.40 Å (Figure 4), which results in a steric repulsion between these two groups. Such a destabilizing interaction is not present in **TS-9**. Moreover, one of the two isopropyl groups at the *ortho* position of the acid catalyst (*R*)-**A** in **TS-10** rotated with a dihedral angle of –4.9° (C_1-C_2-C_3-H_1, highlighted in green in Figure 4) to minimize steric interactions.

By contrast, the dihedral angle (C_1-C_2-C_3-H_1) is −7.7° in **TS-9**, suggesting the acid catalyst adopts a less favorable conformation in **TS-10**. All these factors contribute to the energy difference between transition states **TS-9** and **TS-10**, which ultimately leads to the observed *Z*-selectivity in these reactions.

The chiral phosphoric acid (*R*)-**A** also dictates the enantioselective addition of boronate **5f** to aldehydes (*re*-face attack to give **6a**). As shown in Figure 5, the energy of optimized transition state **TS-9** is 2.7 kcal/mol lower than that of **TS-11** (*si*-face attack to give *ent*-**6a**), in good agreement with the experimentally observed enantioselectivity (95% ee).

To better elucidate the origin of observed enantioselectivity, we performed a distortion/interaction analysis of the transition states.[37] The structures of **TS-9** and **TS-11** are divided into three fragments: catalyst (*R*)-**A**, benzaldehyde, and the allylboronate (Figure 5). The calculated distortion energy of **TS-11** is 2.1 kcal/mol lower than that of **TS-9**, while the interaction energy of **TS-11** is 4.6 kcal/mol higher than that of **TS-9**. Therefore, the overall energy of **TS-11** is 2.5 kcal/mol higher than **TS-9** based on the distortion/interaction analysis model, indicating transition state **TS-9** is more favorable than **TS-11**.

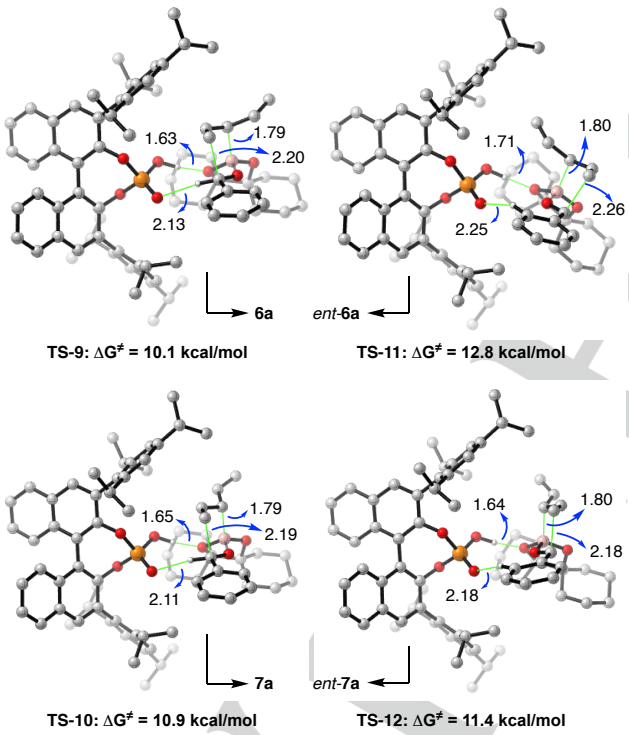


Figure 5. Side view of transition states **TS-9** to **TS-12**. The bond lengths are in Ångstrom.

The origin of different interaction energies can be visualized from optimized geometries of the transition states. As illustrated in Figure 5, the vinyl group is oriented toward the left side in **TS-11**. Such an arrangement results in longer H-bonds (1.71 and 2.25 Å) in the benzaldehyde, allylboronate and catalyst complex in **TS-11** to accommodate the vinyl group. By contrast, these H-bonds are 1.63 and 2.13 Å, respectively, in **TS-9**, which indicates that hydrogen bond strength in **TS-11** is weaker than that in **TS-9**. The different hydrogen bond strengths therefore influence the electrophilicity of the boron atom of allylboronate **5f**. Consequently, this results in longer C−C and C−B bond distances in **TS-11** (2.26 Å and 1.80 Å) compared to those in **TS-9** (2.20 Å and 1.79 Å). Therefore the chiral phosphoric acid catalyzed allylboration reaction proceeds through the more compact and energetically more favored transition state **TS-9** to give alcohol product **6a** with high enantioselectivity.

The reaction also produced a minor product **7a** with *E*-olefin geometry in 50% ee. We also investigated the origin of its formation and enantioselectivity. As shown in Figure 5, the H-bond distances in **TS-10** and **TS-12**, which lead to the formation of **7a** and *ent*-**7a**, respectively, are shorter than those in **TS-11** because of the orientation of the vinyl group in transition state **TS-11**. Therefore, **TS-10** and **TS-12** are energetically more favorable than **TS-11**. The energy difference between **TS-10** and **TS-12**, however, is only 0.5 kcal/mol, which is consistent with the 50% ee of **7a** observed experimentally.

Conclusion

In summary, we developed a highly *Z*-selective and enantioselective aldehyde allylation with achiral α-vinyl allylboronate reagents. Chiral phosphoric acid (*R*)-**A** serves a dual-function catalyst: controlling both enantioselective aldehyde addition and pseudo-axial orientation of the α-vinyl group of the allylboron reagent in the transition state.[38] The origins of observed enantioselectivity and *Z*-selectivity are elucidated by DFT computation studies. Moreover, the results represent a significant advancement of the chemistry of chiral Brønsted acid catalysts by defining their ability to enhance the diastereochemical control (*Z*-selectivity) through reagent development while maintaining high enantioselectivity. Synthetic applications of the method will be reported in due course.

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Keywords: Chiral Phosphoric Acid • α-Vinyl Allylboronate • Dual-Function Catalysis

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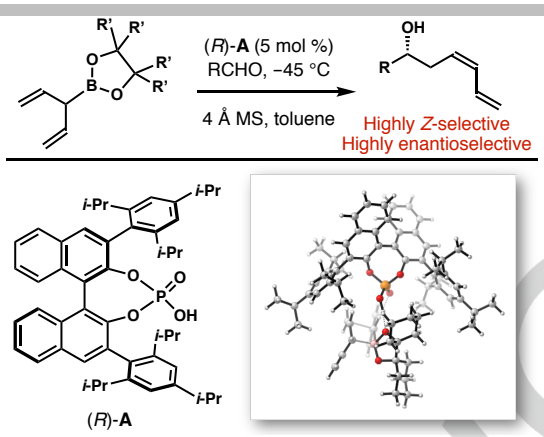
RESEARCH ARTICLE

A dual function asymmetric catalysis by a chiral phosphoric acid catalyst that controls both enantioselective addition of an achiral α-vinyl allylboronate to aldehydes and pseudo-axial orientation of the α-vinyl group in the transition state is developed.



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Chiral Phosphoric Acid Dual-Function Catalysis: Asymmetric Allylation with α-Vinyl Allylboron Reagents