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Enantioselective Synthesis of *anti*- and *syn*-Homopropargyl Alcohols via Chiral Brønsted Acid Catalyzed Asymmetric Allenylboration Reactions

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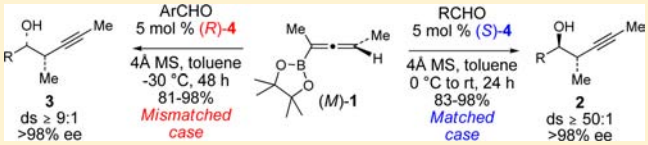
Supporting Information

ABSTRACT: Chiral Brønsted acid catalyzed asymmetric allenylboration reactions are described. Under optimized conditions, *anti*-homopropargyl alcohols **2** are obtained in high yields with excellent diastereo- and enantioselectivities from stereochemically matched aldehyde allenylboration reactions with (*M*)-**1** catalyzed by the chiral phosphoric acid (*S*)-**4**. The *syn*-isomers **3** can also be obtained in good diastereoselectivities and excellent enantioselectivities from the mismatched allenylboration reactions of aromatic aldehydes using (*M*)-**1** in the presence of the enantiomeric phosphoric acid (*R*)-**4**. The stereochemistry of the methyl group introduced into **2** and **3** is controlled by the chirality of the allenylboronate (*M*)-**1**, whereas the configuration of the new hydroxyl stereocenter is controlled by the enantioselectivity of the chiral phosphoric acid catalyst used in these reactions. The synthetic utility of this methodology was further demonstrated in highly diastereoselective syntheses of a variety of *anti*, *anti*-stereotriads, the direct synthesis of which has constituted a significant challenge using previous generations of aldol and crotylmetal reagents.



INTRODUCTION

Asymmetric carbonyl allylation is an important transformation in organic synthesis.[1] These reactions, together with the asymmetric aldol reaction, represent some of the most widely adopted methods for the synthesis of acyclic molecules with contiguous stereocenters. As a useful extension of allylation chemistry, the asymmetric carbonyl propargylation reaction has attracted the attention of the community, and substantial advances have been achieved recently using several allenylmetal reagents.[2−8] However, compared to the exceptionally well-developed asymmetric crotylation reactions, the analogous propargylation reactions of carbonyl compounds using allenylmetal reagents remain largely underdeveloped. One significant advance in this area is the asymmetric carbonyl propargylation reactions developed by Marshall and co-workers using enantioenriched allenylstannanes, allenylsilanes or chiral allenyl zinc, and indium reagents generated in situ from propargyl mesylate intermediates.[5a−c] Depending on the transition states involved in these transformations, either *syn*- or *anti*-homopropargyl alcohols can be synthesized.[9] The synthetic utility of these methods has been demonstrated in the context of several polyketide natural product syntheses.[10,11] However, the diastereoselectivity of aldehyde propargylation reactions, in many occasions, is only moderate, in particular, in reactions with aldehydes lacking α-branches or advanced aldehyde intermediates.[11] Furthermore, the requirement of strong Lewis acids to attain *syn*-selectivity is often incompatible with ornately functionalized aldehyde substrates. Moreover, highly diastereoselective syntheses of the *anti*-homopropargyl alcohol stereoisomers via these procedures are generally lacking. Therefore, the development of a mild, highly diastereo- and enantioselective carbonyl propargylation reaction remains an important objective.

In connection with an ongoing problem in natural product synthesis, we became interested in asymmetric propargylation of aldehydes with allenylboronate reagents. Accordingly, we have developed and report herein highly diastereo- and enantioselective syntheses of *anti*- and *syn*-homopropargyl alcohols via chiral, nonracemic Brønsted acid catalyzed propargylation reactions of aldehydes with allenylboronates **1** (Scheme 1). Key to the success of this procedure is the use of a chiral phosphoric acid catalyst, (*R*)- or (*S*)-**4**, to control the stereochemistry of the hydroxyl groups in **2** and **3** and to achieve levels of diastereomeric control not possible by using the chiral allenylboronate (*M*)-**1** alone.

It is well documented that the reactions of 3-substituted allenylboronates (c.f., **1**) with aldehydes often give mixtures of the *anti*- and *syn*-homopropargylic product diastereomers (analogous to **2** and **3**).[3d,e,i,12] Significantly, in view of the well-established cyclic transition states involved in carbonyl addition reactions using allenylboron reagents,[2−4,8] the reactions of a single enantiomer allenylboronate such as (*M*)-**1**[12] proceed with essentially perfect chirality transfer of the axial chirality of the allene into the propargyl center of the products (e.g., the methyl-bearing carbons of **2** and **3**). However, the reactions suffer from lack of diastereochemical control. The *anti*-isomer **2** is typically favored from reactions of allenylboronates with aliphatic aldehydes, while the *syn*-isomer **3** generally is predominate in the allenylboration reactions of

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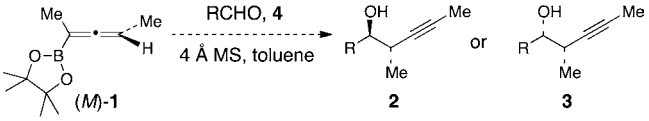
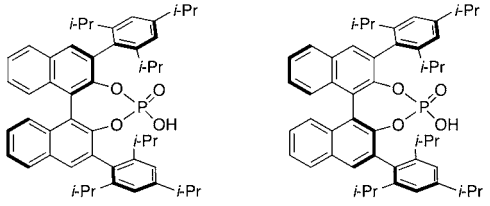
Scheme 1





aromatic aldehyde substrates.[3i] We envisioned that a potential solution to this problem would be to decouple the elements of stereochemical control for the propargyl vs homopropargyl centers via the use of complementary sources of asymmetric induction. By proper selection of a second, external source of chirality for control of the configuration of the hydroxyl group, enantioselective addition of (*M*)-**1** to aldehydes would, in principle, allow independent stereoselective access to either of the *anti*- or *syn*-homopropargyl alcohol isomers, **2** and **3**. Inspired by the recent work of Antilla and Reddy[8] and related work on Brønsted acid-catalyzed allylboration reactions,[13l−o] we anticipated that this plan could be reduced to practice by using the appropriate enantiomer of the chiral, nonracemic Brønsted acid catalyst[13] (*R*)-**4** or (*S*)-**4** to control the enantiotopic face of the aldehyde that participates in the reaction with the allenylboronate (*M*)-**1**.[14]

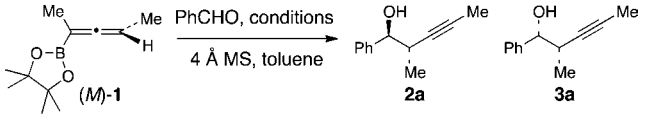
RESULTS AND DISCUSSION

In initial experiments, treatment of benzaldehyde with allenylboronate (*M*)-**1**[12] (1.2 equiv) in toluene at −20 °C for 48 h provided a 1:1.2 mixture of the *anti*-homopropargyl alcohols **2a** and the *syn*-isomer **3a** in 55% combined yield; both **2a** and **3a** were obtained with 95% ee (Table 1, entry 1). The absolute stereochemistry of the secondary hydroxyl groups of **2a** and **3a** was assigned by using the modified Mosher ester analysis.[15] The *anti* vs *syn* stereochemistry of **2a** and **3a** was assigned by ^{1}H NMR studies of the acetonide derivatives obtained following oxidative cleavage of the alkyne unit (see Supporting Information). Gratifyingly, when this reaction was performed in toluene in the presence of 20 mol % of (*S*)-**4**[16] at −30 °C for 48 h, the *anti*-homopropargyl alcohol **2a** was obtained in 94% yield with >50:1 diastereoselectivity and >98% ee (Table 1, entry 2). Similar results were obtained when the reaction was carried out at −20 °C for 48 h (Table 1, entry 3). When 10 mol % of catalyst (*S*)-**4** was used at either −20 or 0 °C, alcohol **2a** was obtained in 95−98% yield, again with outstanding diastereo- and enantioselectivity (Table 1, entries 4 and 5). Finally, when the reaction was performed at 0 °C in the presence of 5 mol % of acid (*S*)-**4** followed by stirring the reaction mixture to ambient temperature for 24 h, alcohol **2a** was again obtained in 98% yield with >50:1 diastereoselectivity and >98% ee (Table 1, entry 6).

The optimized conditions developed for the synthesis of **2a** were then applied to the allenylboration of a variety of aldehydes (Scheme 2). In all cases, *anti*-homopropargyl alcohols **2b−i** were obtained in 83−98% yield with >50:1 diastereoselectivity and >98% ee. The absolute stereochemistry of the secondary hydroxyl groups of **2b−i** was assigned by using the modified Mosher ester analysis.[15]

As indicated in the Introduction Section, we were interested in determining if the diastereomeric *syn*-homopropargyl alcohols **3** could be accessed from allenylboration reactions of aldehydes with (*M*)-**1** by using the enantiomeric chiral acid catalyst (*R*)-**4**.[16] Because these transformations are double

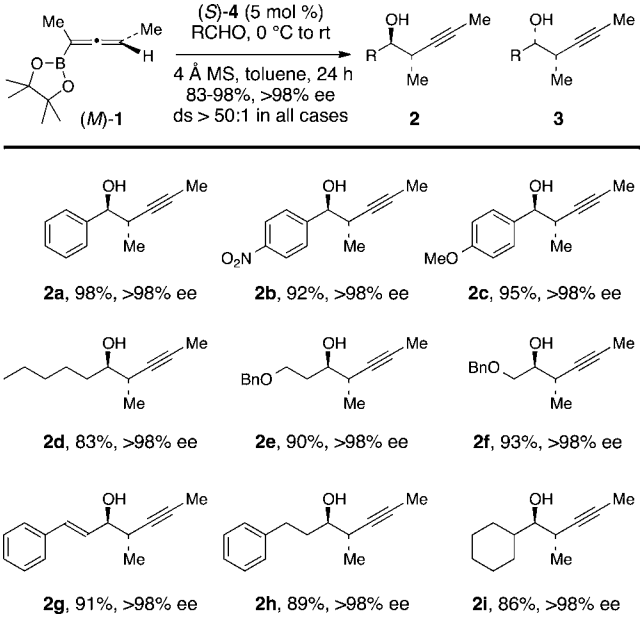
Table 1. Optimization of Matched Allenylboration Reactions Using Allenylboronate (*M*)-1 and Chiral Acid (*S*)-4[a]



entry	conditions	ds (**2a**:**3a**)[b]	yield (**2a** + **3a**)[c]	ee[d]
1	no acid catalyst, −20 °C, 48 h	1:1.2	55%	95%[e]
2	(*S*)-**4**, 20 mol %, −30 °C, 48 h	>50:1	94%	>98%
3	(*S*)-**4**, 20 mol %, −20 °C, 48 h	>50:1	96%	>98%
4	(*S*)-**4**, 10 mol %, −20 °C, 48 h	>50:1	95%	>98%
5	(*S*)-**4**, 10 mol %, 0 °C, 24 h	>50:1	98%	>98%
6	(*S*)-**4**, 5 mol %, 0 °C to rt, 24 h	>50:1	98%	>98%

[a]All reactions were performed using 0.2 mmol of (*M*)-**1**. [b]Based on ^{1}H NMR analysis of the crude reaction mixture. [c]Yield of isolated mixture of products. [d]Determined by Mosher ester analysis.[15] [e]Both **2a** and **3a** were obtained with 95% ee.[15]

Scheme 2. Matched Double Asymmetric Allenylboration Reactions of Aldehydes with Allenylboronate (*M*)-1.[a]



[a]All reactions were run on 0.2 mmol scale. Diastereoselectivities of these reactions were determined by ^{1}H NMR analysis of the crude reaction mixtures. Enantioselectivities for the *anti*-isomer **2** were determined by Mosher ester analysis.[15] Control experiments performed in the absence of any catalyst demonstrated that the reaction of hydrocinnamaldehyde with (*M*)-**1** in toluene provided a 3.5:1 mixture of **2h** and **3h**, while the diastereoselectivity of the allenylboration of cyclohexanecarboxaldehyde favored formation of **2i** (over **3i**) with 6.5:1 selectivity.

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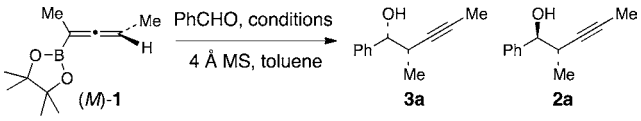
asymmetric reactions,[17] the interplay between the chiral reagent and the chiral phosphoric acid catalyst will determine the diastereoselectivity of these reactions. As shown in Table 2,

Table 2. Optimization of Mismatched Allenylboration Reactions Using Allenylboronate (*M*)-1 and acid (*R*)-4[a]



entry	conditions	ds (3a:2a)[b]	yield (3a + 2a)[c]	ee[d]
1	no acid catalyst, −20 °C, 48 h	1.2:1	55%	95%[e]
2	(*R*)-**4**, 20 mol %, 0 °C, 48 h	5:1	94%	>98%
3	(*R*)-**4**, 20 mol %, −20 °C, 48 h	8:1	96%	>98%
4	(*R*)-**4**, 10 mol %, −20 °C, 48 h	8:1	95%	>98%
5	(*R*)-**4**, 20 mol %, −30 °C, 48 h	10:1	98%	>98%
6	(*R*)-**4**, 10 mol %, −30 °C, 48 h	10:1	98%	>98%
7	(*R*)-**4**, 5 mol %, −30 °C, 48 h	10:1	98%	>98%

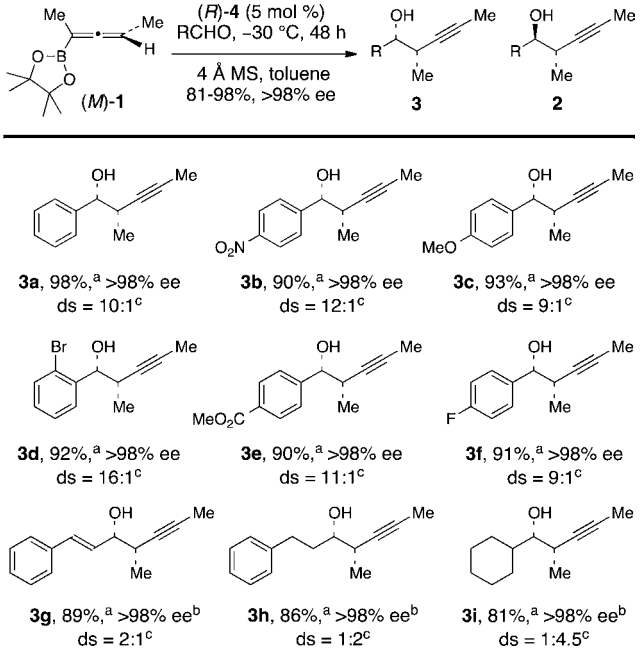
[a]All reactions were performed using 0.2 mmol of (*M*)-**1**. [b]Based on ^{1}H NMR analysis of the crude reaction mixture. [c]Combined yield of **2a** and **3a**. [d]Determined by Mosher ester analysis for alcohol **3a**.[15] [e]Both **2a** and **3a** were obtained with 95% ee.[15]

treatment of benzaldehyde with (*M*)-**1** (1.2 equiv) at 0 °C for 48 h in the presence of 20 mol % of catalyst (*R*)-**4** provided a 5:1 mixture of the *syn*-homopropargyl alcohol **3a** and the *anti*-isomer **2a** in 94% combined yield and >98% ee (for **3a**) (Table 2, entry 2). When the reaction was performed at −20 °C with the same catalyst loading, an 8:1 mixture of **3a** and **2a** was obtained (Table 2, entry 3). Similar results were obtained when the reaction was performed by using 10 mol % of catalyst (*R*)-**4** at −20 °C (Table 2, entry 4). When the reaction was carried out at −30 °C in the presence of as little as 5 mol % of catalyst (*R*)-**4**, a 10:1 mixture of **3a** (>98% ee) and **2a**, was obtained in excellent yield (Table 2, entries 5−7).

The conditions developed for the synthesis of **3a** (Table 2, entry 7) were then applied to a variety of other aldehydes (Scheme 3). *Syn*-homopropargyl alcohols **3b−f** were obtained from aromatic aldehyde precursors in 90−98% yield with ≥9:1 diastereoselectivity and >98% ee (Scheme 3). The absolute stereochemistry of the secondary hydroxyl groups of **3a−f** was assigned by using the modified Mosher ester analysis.[15] The *syn* stereochemistry of **3a** was assigned by ^{1}H NMR studies of an acetonide derivative synthesized after oxidative manipulation of the alkyne unit (see Supporting Information). However, a limitation to the *syn*-selective aldehyde allenylboration reaction is that only aromatic aldehydes are good substrates. As the data for **3g−i** indicate, unsaturated or aliphatic aldehydes, such as cinnamaldehyde or hydrocinnamaldehyde, only gave a 2:1 or 1:2 mixtures of the *syn*- and *anti*-isomers. When cyclohexanecarboxaldehyde was used as the substrate, a 1:4.5 mixture was obtained, favoring the *anti*-isomer **2i**.

The results summarized above suggest that propargylation reactions of aldehydes with allenylboronate (*M*)-**1** and catalyst (*S*)-**4** (Scheme 2) are matched double asymmetric reactions, whereas the reactions with (*M*)-**1** and catalyst (*R*)-**4** (Scheme 3) are likely stereochemically mismatched.[17] These conclusions follow from the fact that the *anti*-homopropargyl alcohols **2** are favored in reactions of allenylboronate **1** with achiral aldehydes (e.g., see footnote a in Scheme 2).[3i,12] Evidently, the chiral

Scheme 3. Mismatched Double Asymmetric Allenylboration Reactions of Aldehydes with Allenylboronate (*M*)-1[d]



[a]Combined yield of **2** and **3**. [b]ee % of the *syn*-isomers **3g−i** were determined by Mosher ester analysis.[15] [c]Reaction diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixtures. [d]All reactions were run on 0.2 mmol scale.

phosphoric acid catalyst (*R*)-**4** is incapable of overriding the intrinsic 3.5−6.5:1 *anti* preference of aliphatic aldehydes in the attempted mismatched double asymmetric reactions summarized in Scheme 3 for the allenylboration of hydrocinnamaldehyde (leading to **3h**) and cyclohexanecarboxaldehyde (leading to **3i**).

Based on the transition-state model presented by Antilla and Houk[8a] (see also refs 3i and 9h and especially ref 13p for an alternative transition-state proposal), we propose that the stereochemically matched allenylboration reactions of aldehydes with allenylboronate (*M*)-**1** and catalyst (*S*)-**4** provides *anti*-homopropargyl alcohol **2** through the boat-like transition state **TS-1**. The mismatched reactions of allenylboronate (*M*)-**1** with the enantiomeric catalyst (*R*)-**4** presumably proceed through transition state **TS-2** to give the *syn*-isomer **3**. As depicted in Scheme 4, it is readily apparent that the terminal methyl group of allenylboronate (*M*)-**1** and the R group of the aldehyde are eclipsed in **TS-2**. When the aldehyde R group is less demanding sterically (i.e., a flat aromatic ring), the enantioselectivity of the chiral catalyst is capable of overriding this interaction, such that the mismatched double asymmetric reactions provide the *syn*-isomer **3** with synthetically useful diastereoselectivity (≥9:1). However, when the aldehyde R group is bulky (e.g., a cyclohexyl group), the eclipsing interaction between the terminal methyl group of the allene (*M*)-**1** and the R group of the aldehyde is sufficiently large that the chiral acid (*R*)-**4** is unable to overcome this interaction. By comparison, in transition state **TS-1** that leads to the formation of the *anti*-isomer **2**, the terminal methyl group of allene (*M*)-**1**, and the aldehyde R group are aligned in such a way that serious steric repulsion is not apparent in the transition state. Therefore, the stereochemically matched double asymmetric

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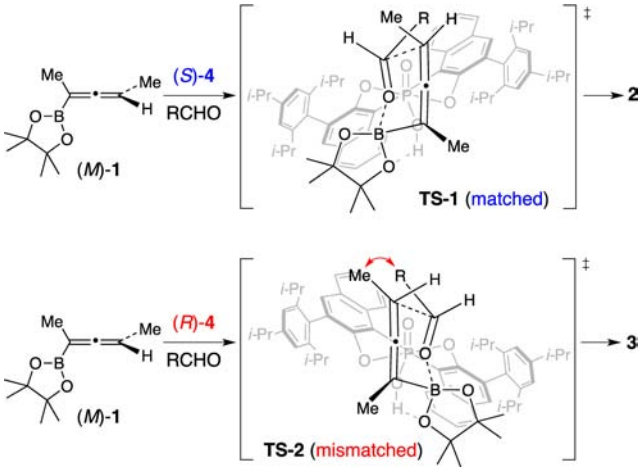
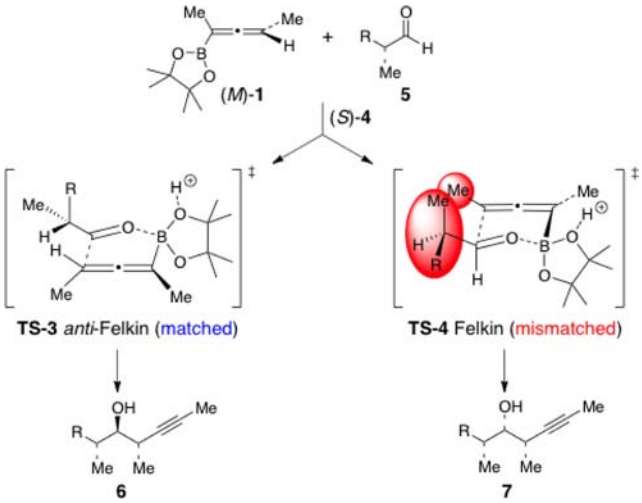
Scheme 4. Transition-State Analysis of the Double Asymmetric Allenylboration Reactions



reactions provide *anti*-adducts with exceptional diastereo- and enantioselectivity.

The synthesis of the *anti*, *anti*-stereotriad unit present in homopropargyl alcohol **6** by using aldol or crotylmetal chemistry represents a notoriously challenging problem in organic synthesis.[18] Because, unlike crotylmetal reagents, only one face of allenylboronate (*M*)-**1** is accessible to the aldehyde substrate and because the transition-state analysis presented in Scheme 4 suggests that the interactions between the aldehyde R group and the terminal methyl group of allenylboronate (*M*)-**1** are negligible in **TS-1**, we anticipated that the *anti*-propargylation reaction of chiral aldehydes **5** using (*M*)-**1** in combination with the chiral phosphoric acid catalyst (*S*)-**4** (see Scheme 5) might constitute an exceedingly simple and direct

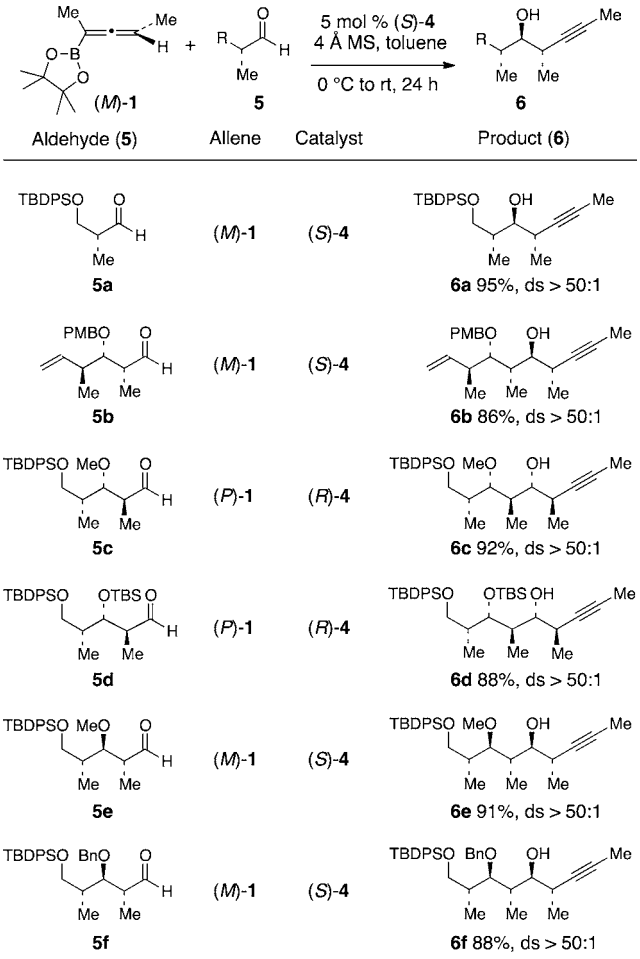
Scheme 5. Transition-State Analysis[a]



[a]The chiral phosphoric acid counter ion is omitted for clarity.

solution to this problem. Toward this end, a variety of chiral aldehydes **5a**–**f** (most of which are exceptionally challenging substrates for mismatched crotylboration reactions)[18f–h] were subjected to propargylation reactions with the appropriate enantiomers of allenylboronate **1** and chiral acid **4**. The results of these experiments are summarized in Table 3. In all cases, the *anti*, *anti*-stereotriads **6a**–**f** were obtained in 86–95% yield

Table 3. Diastereoselective Syntheses of *anti, anti*-Stereotriads 6 via Triple Asymmetric Allenylboration Reactions



with ≥50:1 diastereoselectivity. The absolute stereochemistry of the secondary hydroxyl groups of **6a**–**f** was assigned by using the modified Mosher ester analysis.[15] The *anti* stereochemistry of the newly formed stereocenters in **6a** and **6e** was assigned by ^{1}H NMR studies of acetonide derivatives synthesized following manipulation of the alkyne unit (see Supporting Information).

This methodology can also be utilized to synthesize the *anti*, *syn*-stereotriads **8**. As shown in Scheme 6, treatment of aldehyde **5a** with the enantiomeric allenylboronate (*P*)-**1** in the presence of 5 mol % of chiral acid catalyst (*R*)-**4** provided the *anti*, *syn*-stereotriad **8a** in 93% yield and with >50:1 diastereoselectivity. When the same conditions were applied to the allenylboration of aldehyde **5b**, the *anti*, *syn*-adduct **8b** was obtained in 91% yield, also with >50:1 diastereoselectivity. These reactions proceed with the favored boat-like transition state **TS-5**.

CONCLUSIONS

In summary, we developed highly diastereo- and enantioselective syntheses of *anti*- and *syn*-homopropargyl alcohols **2** and **3** via allenylboration reactions of achiral aldehydes using the chiral, nonracemic allenylboronate (*M*)-**1** in combination with the appropriate enantiomer of the chiral phosphoric acid catalyst **4**. Under optimized conditions, the *anti*-homopropargyl alcohols **2** are obtained in excellent yield and with >50:1 diastereoselectivity via double asymmetric allenylboration

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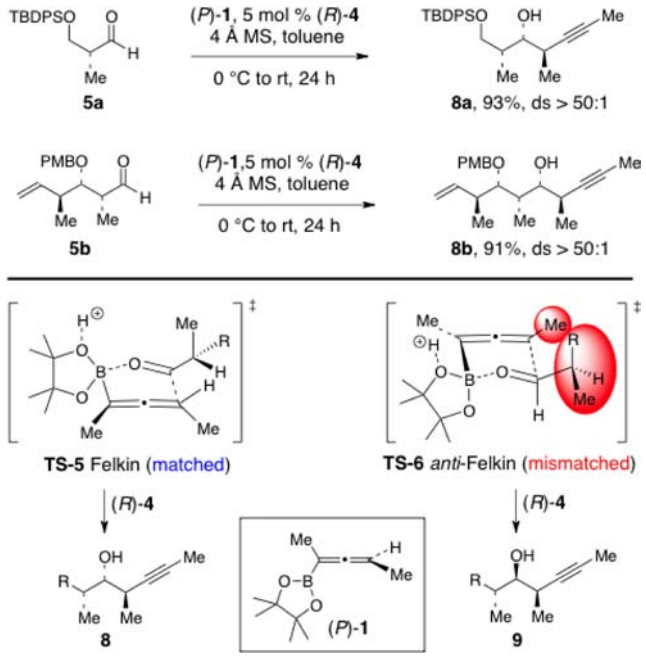
Scheme 6. Diastereoselective Syntheses of *anti, syn*-Stereotriads 8 via Allenylboration Reactions using (*P*)-1 and Acid Catalyst (*R*)-4



reactions in which the stereochemical preferences of allenylboronate (*M*)-**1** and chiral acid catalyst (*S*)-**4** are matched (Scheme 2). The *syn*-isomers **3** can also be synthesized with good diastereoselectivity (≥9:1) with aromatic aldehydes in reactions in which the stereochemical preferences of (*M*)-**1** and the enantiomeric chiral acid catalyst (*R*)-**4** are mismatched (Scheme 3).

Key to the success of these reactions is the use of the chiral phosphoric acid catalysts, (*S*)- and (*R*)-**4**, to control the stereochemistry of the hydroxyl groups in **2** and **3**, respectively. The stereochemistry of the methyl group introduced into **2** and **3** is controlled by the chirality of the allenylboronate (*M*)-**1**, but use of the appropriate enantiomer of the chiral phosphoric acid catalyst is required in order to achieve synthetically useful diastereochemical control of these reactions. This study represents a striking case of a growing number of examples[4d,13l,14] in which the diastereoselectivity of an inherently nondiastereoselective but highly enantioselective transformation (e.g., Table 1, entry 1) is rectified by using a chiral catalyst to alter the relative energetics of the competing transition states in order to control the stereochemistry of the center (e.g., the hydroxyl group in **2** and **3**) that is not controlled by using the primary chiral reagent alone (the allenylboronate (*M*)-**1**, for the work described here). The reactions we describe here differ fundamentally from traditional examples of double asymmetric synthesis, which involve the use of a chiral substrate in combination with the appropriate enantiomer of a chiral reagent.[17] In contrast, we use a chiral reagent in combination with the appropriate enantiomer of a chiral catalyst in order to achieve high diastereochemical control in an inherently highly enantioselective transformation.

The utility of this methodology was further demonstrated in syntheses of a variety of compounds **6** containing the historically challenging *anti, anti*-stereotriad configuration, the synthesis of which has proven to be difficult to accomplish via mismatched double asymmetric aldol and crotylmetal reactions of α-methyl branched aldehydes.[18,20] In addition, it has been amply documented that the alkyne unit in homopropargyl alcohols, like **2** or **6**, can be transformed into many other functional groups, such as (*Z*)- or (*E*)-olefins,[21a−c] vinyl iodides,[10e,11d−f,21d] and many other units that can be derived therefrom. The homopropargyl unit can also be engaged in many C−C forming reactions, such as alkyne ring-closing metathesis[21f] and cross coupling reactions.[11g,h,21g,h,22] Synthetic applications of this method will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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