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Chiral Brønsted Acid Catalyzed Enantioselective Synthesis of *anti*-Homopropargyl Alcohols via Kinetic Resolution—Aldehyde Allenylboration Using Racemic Allenylboronates

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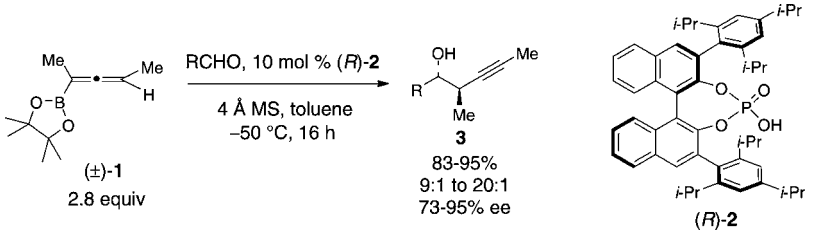
ABSTRACT



A chiral phosphoric acid catalyzed kinetic resolution/allenylboration of racemic allenylboronates with aldehydes is described. Allenylboration of aldehydes with 2.8 equiv of allenylboronate (±)-1 in the presence of 10 mol % of catalyst (*R*)-2 provided *anti*-homopropargyl alcohols 3 in 83—95% yield with 9:1 to 20:1 diastereoselectivity and 73—95% ee. The catalyst enables the kinetic resolution of the racemic allenylboronate (±)-1 to set the methyl stereocenter and biases the facial attack of the aldehyde to set the stereochemistry of the hydroxyl group in 3.

Asymmetric crotylation of aldehydes with crotylboron reagents is a well established method to generate stereodefined acyclic molecules bearing an olefinic handle.[1] Similarly, allenylboration of 3-substituted allenylboron reagents provides homopropargyl alcohols with an alkyne moiety which are equally valuable in polyketide natural product syntheses.[2,3] Due to the closed transition states involved in allenylboration reactions, the axial chirality of 3-substituted allenylboron reagents is directly transferred to the stereochemistry of the propargylic position in the product (e.g., the position that bears the methyl group in **3** and **4**, Scheme 1).[3,4] The stereochemistry of the hydroxyl group in the homopropargyl products is controlled by the facial approach of the allenylboronate to the aldehyde.

As shown in Scheme 1, allenylboration of an aldehyde with (*M*)-**1** can provide either *anti*-homopropargyl alcohol *ent*-**3** or the *syn* adduct **4** via the two competing transition states **TS-1** and **TS-2**. These two transition states, arising from opposing diastereofacial approches of the reagent to

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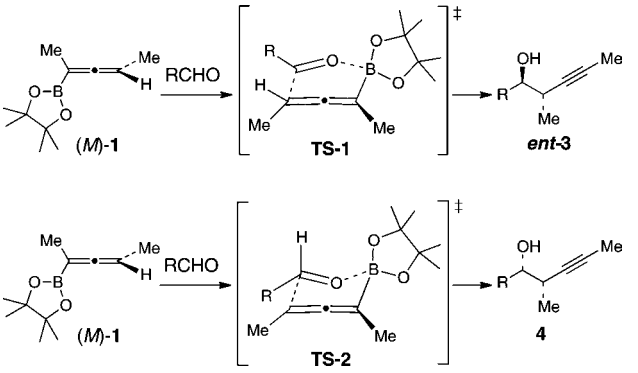
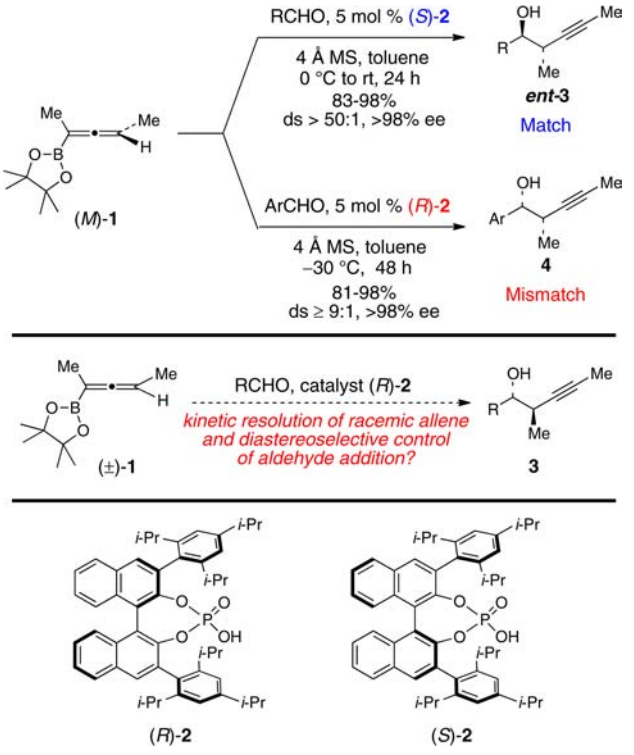
the aldehyde substrates, often have similar energy and poor *anti*/*syn* diastereoselectivity is generally observed.[3b,c,h,4] Consequently, in order to obtain homopropargyl alcohol products with high diastereo- and enantioselectivity, single enantiomer 3-substituted allenylboron reagents are required as well as a means to control the diastereofacial selectivity of the addition of the reagent to the aldehyde substrate.

Scheme 1. Aldehyde Allenylboration Reactions with Allenylboronate (*M*)-**1**



We recently demonstrated that the chiral, nonracemic phosphoric acid catalyst **2**[5] can bias the two competing transition states (e.g., **TS-1** and **TS-2**) such that either *syn*- or *anti*- products can be obtained with good to excellent diastereoselctivity and with very high enantioselectivity.[6] As illustrated in Scheme 2, allenylboration of aldehydes with (*M*)-**1** in the presence of 5 mol % of catalyst (*S*)-**2** gave *anti*-homopropargyl alcohols *ent*-**3** in 83−98% yield and excellent diastereo- (> 50:1 ds) and enantioselectivity (> 98% ee). We infer that this transformation is stereochemically matched. On the other hand, mismatched allenylborations of aldehydes with (*M*)-**1** in the presence of the enantiomeric catalyst (*R*)-**2** provided the *syn*-adducts **4** with ≥9:1 ds and > 98% ee. Importantly, the reaction of (*M*)-**1** and aldehydes in the presence of (*S*)-**2** proceeded at a faster rate than the reaction with the (*M*)-**1**/(*R*)-**2** pairing.[6] These differing rates form the basis of a possible kinetic resolution of a racemic allenylboronate, such as (±)-**1**,[7] in reactions catalyzed by chiral phophoric acids such as **2** and would eliminate the need to synthesize enantioenriched allenylboron reagents for use in aldehyde allenylboration reactions.[2b,8] Thus, a single enantiomer phosphoric acid catalyst might be able *both* to select the more reactive allenylboronate enantiomer from a racemic mixture *and* to direct its addition to the aldehyde with high facial diastereoselectivity. Accordingly, we are pleased to report that the chiral, nonracemic Brønsted acid (*R*)-**2** catalyzes the allenylboration of aldehydes with racemic allene (±)-**1** with kinetic resolution to obtain *anti*-homopropargyl alcohols **3** with high diastereo- and enantioselectivity.

Scheme 2. Proposed Kinetic Resolution/Aldehyde Allenylboration with Racemic Allenylboronate (±)-**1**



Initial studies of the chiral phosphoric acid catalyzed kinetic resolution−allenylboration reactions of (±)-**1** were performed with hydrocinnamaldehyde as the substrate (Table 1). Treatment of hydrocinnamaldehyde with 2.1 equiv of allenylboronate (±)-**1** and 5 mol % of catalyst (*R*)-**2** at ambient temperature provided enantiomerically enriched (71% ee) *anti*-homopropargyl alcohol **3a** in 92% yield with 10:1 diastereoselectivity (Table 1, entry 2). The enantiomeric excess of **3a** was determined by using the Mosher ester

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(4) Sasaki, Y.; Sawamura, M.; Ito, H. *Chem. Lett.* **2011**, *40*, 1044.

(5) For recent reviews of Brønsted acid catalysts, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (c) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 6706. (d) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406.

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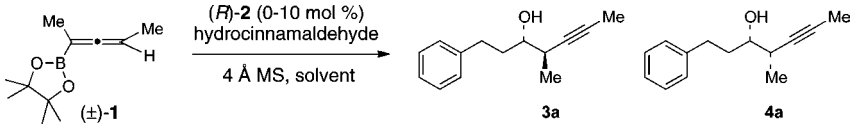
(7) For a recent study of kinetic resolution in the enantioselective hydroboration of racemic allenylboronate (±)-**1** with diisopinocampheylborane, see: Han, J.-L.; Chen, M.; Roush, W. R. *Org. Lett.* **2012**, *14*, 3028.

(8) The synthesis of these reagents have generally been derived from the S_N2' substitution of enantioenriched propargyl alcohol derivatives or enantioselective hydrometalation of enynes amongst other methods; see refs 2a and 3.

Table 1. Kinetic Resolution/Allenylboration Reactions of Hydrocinnamaldehyde Using Racemic Allenylboronate (±)-**1** and Chiral Acid (*R*)-**2**[a]



entry	solvent	temp (°C)	time (h)	(*R*)-**2** (mol %)	(±)-**1** (equiv)	ds[b]	yield[c]	% ee[d]
1	toluene	55	24	0%	1.1	3.5:1	90%	–
2	toluene	23	24	5%	2.1	10:1	92%	71
3	toluene	−30	24	5%	2.1	20:1	92%	78
4	CH_2Cl_2	−30	24	5%	2.1	11:1	89%	80
5	Et_2O	−30	38	5%	2.1	6:1	63%	49
6	toluene	−30	24	5%	2.8	20:1	89%	84
7	toluene	−50	16	10%	2.8	20:1	93%	90

[a] Reactions were performed with 0.15 mmol of aldehyde at a concentration of 0.2 M. [b] Product diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Combined isolated yield of both diastereomers. [d] Enantioselectivity of the major product was determined by Mosher ester analysis.[9]

analysis.[9] To confirm that the reaction indeed proceeded via the kinetic resolution pathway, the remaining allenylboronate was isolated and subjected to the uncatalyzed allenylboration with hydrocinnamaldehyde. The homopropargyl alcohol product obtained from the reaction is a 3.5:1 mixture of *anti*- and *syn*-diastereomers *ent*-**3a** and *ent*-**4a**. The enantiomeric excess of both diastereomers obtained from this experiment was 60% ee.

When the allenylboration reaction of (±)-**1** and hydrocinnamaldehyde was performed in toluene at −30 °C in the presence of 5 mol % of catalyst (*R*)-**2**, *anti*-homopropargyl alcohol **3a** was obtained with 20:1 diastereoselectivity and 78% ee (entry 3). A solvent screen showed that while dichloromethane was a competent solvent (entry 4), reactions performed in toluene provided better diastereoselectivity with nearly equivalent enantioselectivity. Coordinating solvents, such as diethyl ether, were detrimental (entry 5). Increasing the equivalents of allenylboronate (±)-**1** used in the reaction to 2.8 equiv resulted in improved enantioselectivity (84% ee; entry 6). Finally, by increasing the catalyst loading to 10 mol % and by performing the reaction in toluene at −50 °C for 16 h, the allenylboration reaction provided homopropargyl alcohol **3a** in 93% yield with 20:1 diastereoselectivity and 90% ee (entry 7).

The conditions developed for the kinetic resolution–allenylboration of hydrocinnamaldehyde were then applied to the reactions of a variety of representative achiral aldehydes; the results of these experiments are summarized in Figure 1. Unhindered aliphatic and α,β-unsaturated aldehydes provided homopropargyl alcohols **3a**–**c** with excellent diastereo- and enantioselectivities. The homopropargyl alcohols derived from a range of substituted aromatic aldehydes were obtained in 86–93% yield with

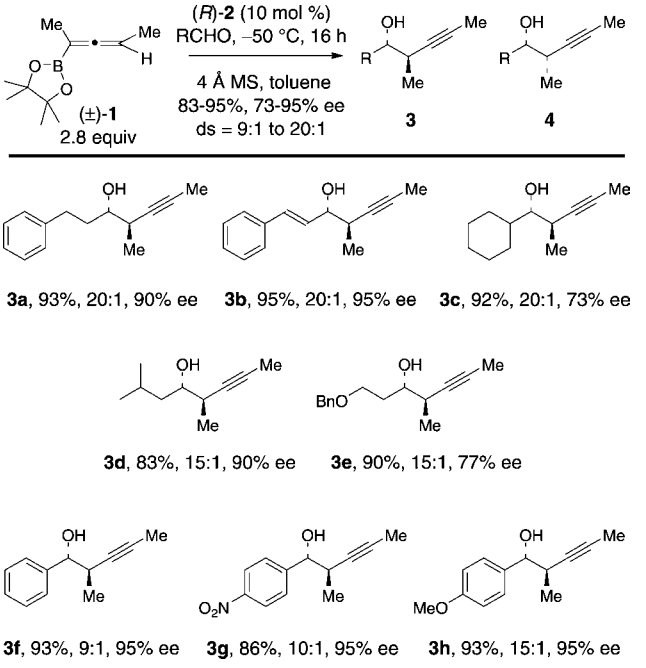


Figure 1. Kinetic resolution/allenylboration reactions of representative aldehydes with allenylboronate (±)-**1**. Reactions were performed with 0.2 mmol of aldehyde at a concentration of 0.2 M. Product diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction products. The combined isolated yield of both diastereomers is provided. The enantiomeric purity of the major product was determined by Mosher ester analysis.[9]

9–15:1 diastereoselectivities and 95% ee (**3f**–**h**). High diastereoselectivities were obtained for the reactions leading to **3d** and **3e**; however, the enantioselectivities were only moderate in these cases (73–77% ee).

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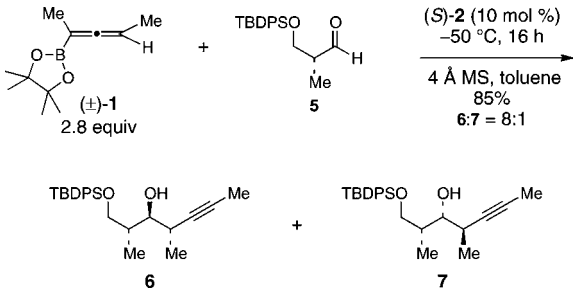
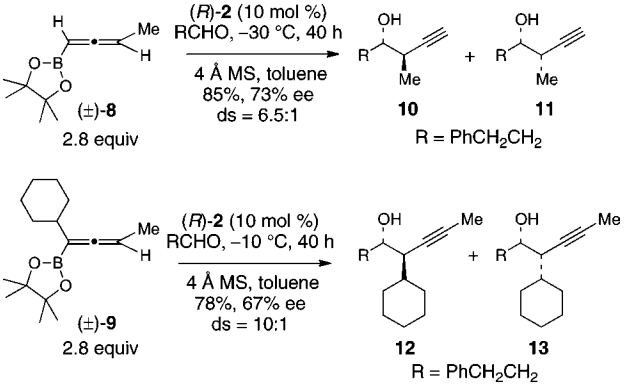
To further evaluate the synthetic utility of this kinetic resolution–allenylboration procedure, the allenylboration reaction with the chiral, nonracemic aldehyde **5** was explored (Scheme 3). When the allenylboration of aldehyde **5** with 2.8 equiv of racemic **1** was performed in the presence of 10 mol % of acid catalyst (*S*)-**2**, an 8:1 mixture of homopropargyl alcohols **6** and **7** was obtained, favoring the *anti*,*anti*-homopropargyl alcohol **6**. This result demonstates an exceedingly simple means to generate the *anti*, *anti*-stereotriad from the racemic allenylboronate (±)-**1**.[10]

Scheme 3. Allenylboration of Chiral Aldehyde **5**



Finally, racemic allenylboronates (±)-**8** and (±)-**9** were tested in this kinetic resolution–allenylboration reaction sequence (Scheme 4). By using the conditions determined to be optimal in our studies of the kinetic resolution–allenylboration reactions of (±)-**1**, the allenylboration of hydrocinnamaldehyde with allene (±)-**8** provided a 6.5:1 mixture of homopropargyl alcohols **10** and **11** with a terminal alkyne unit in 85% yield and 73% ee. Similarly, the allenylboration of hydrocinnamaldehyde with allene (±)-**9** (2.8 equiv) and 10 mol % of catalyst (*R*)-**2** at −10 °C afforded homopropargyl alcohols **12** and **13** in 78% yield with 10:1 diastereoselectivity and 67% ee. These results suggest that further optimization may be required in order to achieve high diastereo- and enantioselectivity in the kinetic resolution–allenylboration reactions of substrates such as (±)-**8** and (±)-**9**.

Scheme 4. Kinetic Resolution/Allenylboration Reactions with Racemic Allenylboronates **8** and **9**



In summary, we developed a chiral Brønsted acid catalyzed kinetic resolution–allenylboration reaction of racemic allenylboronate (±)-**1**. When performed in the presence of 10 mol % of acid (*R*)-**2**, the kinetic resolution–aldehyde allenylboration reaction of (±)-**1** provided *anti*-homopropargyl alcohols **3** in 83–95% yield with 9:1 to 20:1 diastereoselectivity and 73–95% ee. The kinetic resolution of racemic allene (±)-**1** and its controlled diastereofacial addition to a chiral aldehyde was exemplified by the chiral Brønsted acid catalyzed allenylboratin of **5**, which provided the *anti*,*anti*-homopropargyl alcohol **6** with 8:1 selectivity. Synthetic applications of this methodology will be reported in due course.

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Supporting Information Available. 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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The authors declare no competing financial interest.