Enantioselective Syntheses of 1,4-Pentadien-3-yl Carbinols via Brønsted Acid Catalysis

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Supporting Information



ABSTRACT: An asymmetric addition of substituted 1,3-pentadienylboronates to aldehydes via Brønsted acid catalysis is reported. Under the developed conditions, a variety of synthetically useful 1,4-pentadien-3-yl carbinols were obtained in good yields with high enantioselectivities in the presence of a catalytic amount of a chiral phosphoric acid.

E nantioenriched 1,4-pentadien-3-yl carbinols (e.g., A and 2 in Scheme 1) are important building blocks in organic





synthesis.¹⁻⁴ They are valuable intermediates not only in natural product synthesis¹ but also in the preparation of small-molecule probes for biological evaluations.² For instance, compound **A**, which contains a 1,4-pentadien-3-yl carbinol moiety, underwent a highly diastereoselective intramolecular Pauson–Khand reaction to give ketone **B** (Scheme 1a).^{1a} Ketone **B** was a key intermediate in the total synthesis of natural product penostatin B.^{1a} Additionally, 1,4-pentadien-3-yl carbinols can serve as precursors to generate cross-

conjugated trienes, which readily participate in sequential Diels–Alder reactions to generate polycyclic structures.²

Several methods are available for the syntheses of racemic 1,4-pentadien-3-yl carbinols (2).³ Shibasaki reported a pentadienylchromium complex-mediated coupling of pentadienyl esters with carbonyl compounds to give racemic 1,4pentadien-3-yl carbinols 2 with high γ -selectivity.^{3a} Nishigaichi developed a $ZnCl_2$ -promoted γ -selective addition of 1,3pentadienyl stannanes to aldehydes to generate racemic carbinols 2.3b The Araki and Fallis groups showed that racemic carbinols 2 can also be synthesized via regioselective aldehyde allylation with pentadienyl indium reagents generated from bromo-pentadienes and indium metal.^{2a,3c} A Ti-mediated carbonyl addition with pentadienyl titanium reagents was disclosed by the Sato and Schlosser groups independently.^{3d,e} By contrast, very few methods are known to produce enantioenriched 1,4-pentadien-3-yl carbinols 2, in particular the catalytic asymmetric variants. Yamamoto and co-workers reported a BINAP·Ag(I) complex-catalyzed asymmetric γ selective addition to aldehydes with pentadienyl stannanes, and carbinols 2 were obtained with moderate to high enantioselectivities (58-90% ee). However, the toxicity of organotin reagents poses a severe limit on their synthetic utilities on a practical scale. Therefore, the development of nontoxic reagents and practical methods to synthesize enantioenriched 1,4-pentadien-3-yl carbinols is highly desirable in chemical synthesis.

In connection with an ongoing synthesis project, we became interested in developing catalytic asymmetric methods to generate enantioenriched 1,4-pentadien-3-yl carbinols.⁵ We

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envisioned that these structural entities should be readily available from the addition of 1,3-pentadienylboronate [e.g., **1a** (Scheme 1b)] to aldehydes. Given the well-established Zimmerman–Traxler transition states in allylboration chemistry,⁶ such additions should be highly γ -selective to generate 1,4-pentadien-3-yl carbinols. An external chiral catalyst should be able to control the absolute configuration of the secondary alcohol group. Inspired by prior work on chiral phosphoric acid-catalyzed asymmetric carbonyl addition with unsaturated organoboron compounds,^{7–10} we report herein our studies of enantioselective syntheses of 1,4-pentadien-3-yl carbinols via chiral phosphoric acid-catalyzed asymmetric allylboration.

Scheme 2 shows the prepared 1,3-pentadienylboronate reagents with different substitution patterns. Reagent 1b was





synthesized by adopting the reported literature methods.¹¹ Reagents **1a**, **1c**, and **1d** were obtained via a Matteson homologation approach¹² from the corresponding 1,3-dienyl boronates (see the Supporting Information for details).^{13,14}

With several 1,3-pentadienylboronate reagents in hand, subsequent chiral phosphoric acid-catalyzed allyl addition to aldehydes was conducted. In initial experiments, treatment of benzaldehyde (1 equiv) with 1,3-pentadienylboronate 1a (1.3 equiv) in the presence of 5 mol % phosphoric acid (R)-A (Scheme 1) and 4 Å molecular sieves at -45 °C in toluene for 48 h provided 1,4-pentadien-3-yl carbinol 2a in 75% yield with 97% ee.

$$1a \xrightarrow{Me}_{B_{-0}} \xrightarrow{Me}_{Me} + \underbrace{0}_{H} \xrightarrow{(R)-A (5 \text{ mol }\%)}_{75\%, 97\% \text{ ee}} \xrightarrow{OH}_{1}$$

We next explored the scope of aldehyde that underwent asymmetric allyl addition with 1,3-pentadienylboronate 1a, and the results are summarized in Scheme 3. Under the developed reaction conditions, a variety of aldehydes with diverse electronic properties participated in reactions with 1a to give alcohols 2 in good yields with high enantioselectivities. Aromatic aldehydes with an electron-donating group at the para position reacted with 1a to deliver products 2b and 2c in 93-98% yields with 99% ee. Reactions of aromatic aldehydes with an electron-withdrawing group at the para position proceeded smoothly to give carbinol products 2d-f in 92-96% yields with 94-95% ee. Halogen-substituted aldehydes also reacted with boronate 1a to afford products 2g-i in 90-96% yields with 91–95% ee. α_{β} -Unsaturated aldehydes and aldehydes containing a heterocycle were tolerated under the reaction conditions, and carbinol products 2j-l were generated



Scheme 3. Scope of Aldehydes for Asymmetric Allylation

^aReaction conditions: allyl boronate 1a (0.13 mmol, 1.3 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, 48 h. ^bEnantioselectivities were determined by HPLC analysis using a chiral stationary phase. ^cYields of the isolated product.

in 92–96% yields with 93–98% ee. Finally, reaction of 1a with an aliphatic aldehyde substrate, hydrocinnamaldehyde, also worked well to produce 2m in 88% yield with 91% ee. The absolute configuration of the secondary hydroxyl group in alcohols 2 was determined by modified Mosher ester analyses.¹⁵

Reactions of reagent **1b** with a variety of aldehydes were conducted under the standard reaction conditions, and the results are summarized in Scheme 4. Reagent **1b** readily added to aromatic aldehydes in the presence of 5 mol % phosphoric acid (*R*)-A at -45 °C to form products **3a**-**i** in 84–97% yields with 93–99% ee. α,β -Unsaturated aldehydes and heterocycle-containing aldehydes were suitable substrates for asymmetric allylation with **1b**, and secondary alcohols **3j**–**l** were isolated in 71–96% yields with 95–99% ee. Hydrocinnamaldehyde also reacted with **1b** to afford carbinol **3m** in 84% yield with 94% ee (Scheme 4).

The results of aldehyde allylation with reagent 1c in the presence of 5 mol % phosphoric acid (*R*)-A are summarized in Scheme 5. Reactions of 1c with various aldehydes, including aromatic, α,β -unsaturated, heteroaromatic, and aliphatic aldehydes, occurred to deliver carbinol products 4a-m in 84–97% yields with 92–99% ee and >20:1 dr (Scheme 5).¹⁶

Asymmetric allylboration of aldehydes with reagent 1d was also conducted. As summarized in Scheme 6, the reactions worked well with several representative aldehydes under Scheme 4. Scope of Aldehydes for Asymmetric Allylation with 1,3-Pentadienylboronate $1b^{a-c}$



^{*a*}Reaction conditions: allyl boronate **1b** (0.13 mmol, 1.3 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, 48 h. ^{*b*}Enantioselectivities were determined by HPLC analysis using a chiral stationary phase. ^cYields of isolated product.

standard reaction conditions, and carbinols 5a-f bearing two different alkene groups were obtained in 77–95% yields with 93–99% ee and excellent diastereoselectivities (Scheme 6). Again, the absolute configuration of the secondary hydroxyl group in alcohols 3–5 was determined by modified Mosher ester analyses.¹⁵

The 1,4-pentadien-3-yl carbinol products 4 and 5 obtained from allylboron reagents 1c and 1d contain two different alkene units, which underwent several transformations with excellent chemoselectivity. As depicted in Scheme 7, hydroboration of 6 with $({}^{d}Ipc)_{2}BH$ occurred at the monosubstituted alkene unit. Oxidation of the borane intermediate followed by deprotection of the TES group with TBAF gave diol 7 in 56% yield. Ir-catalyzed hydroboration of 8 with HBpin also occurred at the terminal alkene unit to produce boronate 9 in 72% yield.¹⁷ By contrast, the more electron-rich, internal alkene group of alcohol 4e participated in an iodoetherification reaction to form tetrahydrofuran derivative 10a in 61% yield with 3:1 diastereoselectivity (see the Supporting Information for the assignment of the relative configuration of 10 with NOE studies). Pt-catalyzed asymmetric alkene diboration of 6 occurred at the monosubstituted alkene group to furnish diboronate 11 in 76% yield with excellent diastereoselectivity.¹⁸ A detectable amount of product generated from diboration of the 1,1-substituted alkene group in 6 was not formed.

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"Reaction conditions: allyl boronate 1c (0.13 mmol, 1.3 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, 48 h. ^bEnantioselectivities were determined by HPLC analysis using a chiral stationary phase. 'Yields of isolated product.

Scheme 6. Scope of Aldehydes for Asymmetric Allylation with 1,3-Pentadienylboronate $1d^{a-c}$



"Reaction conditions: allyl boronate 1d (0.13 mmol, 1.3 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, 48 h. ^bEnantioselectivities were determined by HPLC analysis using a chiral stationary phase. 'Yields of isolated product.



Alcohol products **2** and **3** obtained from reagents **1a** and **1b**, respectively, contain two terminal alkene units that are diastereotopic. It is conceivable that one of the two alkene groups should participate in subsequent transformations with high diastereoselectivity. For instance, Pt-catalyzed asymmetric diboration¹⁸ of **12** with (*S*,*S*)-L as the ligand gave diboronate **13** in 90% yield with >10:1 diastereoselectivity (Scheme 7). In the presence of the enantiomeric ligand (*R*,*R*)-L, asymmetric diboration¹⁸ of **12** also proceeded smoothly to afford diboronate **15** in 84% yield with >10:1 diastereoselectivity. When enantioenriched ligand L was replaced with an achiral

ligand PCy₃, the Pt-catalyzed diboration generated a mixture of four diastereomers with low selectivity. Therefore, the asymmetric alkene diborations with Pt(dba)₃/L as the catalyst system are completely catalyst-controlled reactions. The absolute configuration of the secondary alcohol in 12 did not impact the stereochemical outcomes of asymmetric diboration. The relative configuration of 13 and 15 was assigned by NOE, ¹H NMR, and ¹³C NMR studies of the corresponding acetonide derivatives 14 and 16 (see the Supporting Information for the details of structural assignment).¹⁹ It is worth noting that the asymmetric diboration reaction not only sets one stereogenic center at the terminal alkene group but also generates a stereocenter α to the alkene group (highlighted in 13 and 15).

In summary, asymmetric syntheses of a variety of 1,4pentadien-3-yl carbinols via Brønsted acid catalysis were developed. In the presence of a catalytic amount of phosphoric acid (R)-A, allylboration of a broad range of aldehydes with reagents 1 bearing different substitution patterns occurred to give various 1,4-pentadien-3-yl carbinols in good yields with high enantioselectivities. Subsequent alkene functionalization of the TES ethers of 1,4-pentadien-3-yl carbinols 2 proceeded with high diastereoselectivities. Functionalization of the derivatives of carbinols 4 and 5 occurred with excellent chemoselectivities to generate synthetically useful intermediates. Synthetic application of this method is currently ongoing.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04089.

Experimental procedures and spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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reagent 1c (\sim 3%). The diastereoselectivities of compounds 4 are >20:1 in all cases.

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