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Chiral Brønsted Acid Catalyzed Enantioselective Propargylation of Aldehydes with Allenylboronate

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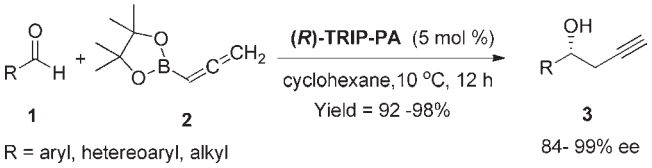
ABSTRACT



A highly enantioselective chiral Brønsted acid catalyzed propargylation of aldehydes with allenylboronate is described. The reaction is shown to be practical and quite general with a broad substrate scope covering aryl, polyaryl, heteroaryl, α,β-unsaturated, and aliphatic aldehydes.

Organocatalysis, the use of small, chiral organic molecules as enantioselective catalysts, has been a fruitful area of research for the past decade.[1] In 2004, Akiyama[2] and Terada[3] independently reported the utility of binaphthyl-derived chiral phosphoric acids (PAs) as enantioselective catalysts. Thereafter, these chiral PAs became an important alternative to metal catalysts for carbon−carbon and carbon−heteroatom bond-forming processes as well as a variety of oxidation and reduction reactions.[4] However, only a limited number of chiral PA-catalyzed reactions involving aldehydes had been reported.[5]

Chiral homopropargylic alcohols are valuable synthons as the alkyne moiety[6] present in these molecules makes them synthetically versatile. These building blocks are routinely utilized for the synthesis of a wide variety of bioactive natural products and compounds of pharmaceutical interest.[8]

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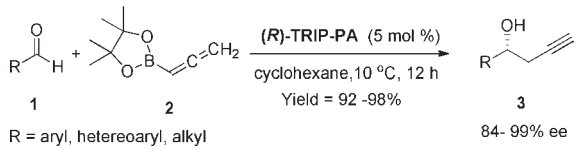
Scheme 1. Asymmetric Synthesis of Homopropargylic Alcohols

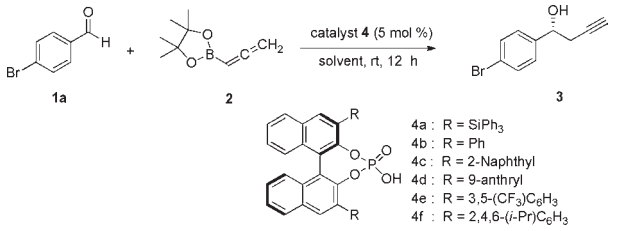


An asymmetric propargylation of aldehydes provides direct access to this class compounds.[7] Significant progress has been made over the past three decades, including work by Yamamoto,[9] Keck,[10] Denmark,[11] Nozaki–Hiyama,[12] Sigman,[13] Fandrick,[14] Trost,[15] and Shibasaki.[16] However, since there are disadvantages to most stereoselective methods such as the use of stoichiometric chiral inductors, difficult to prepare and/or sensitive propargylation reagents, and the possibility of toxic byproducts from the use of metal catalysts, the need remains for a practical method for the enantioselective synthesis of homopropargylic alcohols not using metal catalysts (Scheme 1).

In this light, we reasoned that chiral Brønsted acid catalyzed enantioselective propargylation of aldehydes with allenylboronate would be ideal because allenylboronate is a relatively stable, nontoxic, and commercially available reagent. Such a reaction as the chiral Brønsted acid mediated enantioselective propargylation of aldehydes with allenylboronate has not been described to our knowledge.[4,5] Herein, we report our synthetic efforts in this direction.[17]

We began our investigation by studying the reaction of 4-bromobenzaldehyde **1a** with allenylboronic acid pinacol ester **2** in the presence of a chiral phosphoric acid catalyst in benzene (Table 1). The reaction proceeded at 23 °C and was completed in 12 h. Catalysts with various substitution patterns on the 3,3′ position of the binaphthyl scaffold were examined (Table 1, entries 1–6), and the 2,4,6-triisopropylphenyl substituted catalyst ((***R*)-TRIP-PA**, Table 1, entry 6) was found to be the best in terms of conversion and enantioselectivity.

Table 1. Catalyst Screening for the Propargylation of Aldehydes[a]



entry	catalyst	conversion (%)[b]	ee[c]
1	**4a**	82	16
2	**4b**	100	2
3	**4c**	100	10
4	**4d**	100	20
5	**4e**	100	6
6	**4f**	100	80

[a] Reaction conditions: **1a** (1.0 mmol), **2** (2.0 mmol), 5 mmol % catalyst in benzene (5.0 mL), unless otherwise specified. [b] Conversion was determined by HPLC analysis. [c] Determined by chiral HPLC analysis.

We began our investigation by studying the reaction of 4-bromobenzaldehyde **1a** with allenylboronic acid pinacol ester **2** in the presence of a chiral phosphoric acid catalyst in benzene (Table 1). The reaction proceeded at 23 °C and was completed in 12 h. Catalysts with various substitution patterns on the 3,3′ position of the binaphthyl scaffold were examined (Table 1, entries 1–6), and the 2,4,6-triisopropylphenyl substituted catalyst ((***R*)-TRIP-PA**, Table 1, entry 6) was found to be the best in terms of conversion and enantioselectivity.

Further studies concentrated on the optimization of other reaction parameters such as solvent, temperature, and catalyst loading. Upon solvent screening we found that nonpolar solvents such as benzene, heptane, hexane, pentane, and cyclohexane were effective in making homoproparglic alcohol **3a** (Table 2). It was determined that cyclohexane was a most suitable solvent, yielding an 84% ee at room temperature with a reaction time of 12 h (Table 2, entry 7). The enantioselectivity was further improved by reducing the temperature to 10 °C (88% ee, Table 2, entry 8). It was interesting to see the addition of freshly dried molecular sieves (5 Å)[18] increased the ee to >99% (Table 1, entry 11). The role of molecular sieves can be explained as a water scavenger by entry 9, where the addition of 0.1% water to the reaction mixture dropped the ee to 22%. The structure and absolute configuration of

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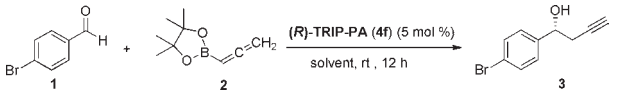
(18) Molecular sieve (5 Å) powder was purchased from Aldrich and was dried at 120 °C under vacuum over 24 h before use.

Table 2. Optimization of the Catalytic Propargylation of Aldehydes[a]



entry	solvent	yield (%)[b]	ee[c]
1	benzene	96	80
2	toluene	95	44
3	CH_2Cl_2	96	20
4	heptane	94	64
5	hexane	95	52
6	pentane	91	62
7	cyclohexane	98	84
8	cyclohexane[d]	96	88
9	cyclohexane[e]	90	22
10	cyclohexane[f]	98	94
11	cyclohexane[g]	98	>99
12	cyclohexane[h]	95	96

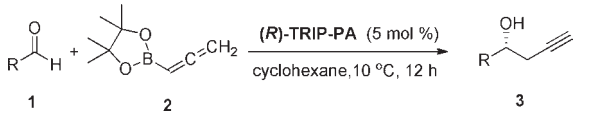
[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), 5 mmol % (***R*)-TRIP-PA**, unless otherwise specified. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Reaction conducted at 10 °C. [e] Using 0.1% water. [f] Using 5 Å M.S. [g] Using 5 Å M.S.; reaction conducted at 10 °C. [h] Using 2.5 mmol % catalyst, 5 Å M.S.; reaction conducted at 10 °C.

(*R*)-**3a** were determined by comparing the ^1H, ^{13}C NMR and specific rotation with literature data.[15]

Encouraged by these results, we turned our attention to other substituted aromatic aldehydes. Interestingly, a large number of electron-rich and -poor substituted aromatic aldehydes, such as *m*-bromo, *p*-chloro, *p*-fluoro, *p*-trifluoro, *p*-methoxy, and *p*-methyl substituted aldehydes, reacted cleanly with **2** in the presence of an **(*R*)-TRIP-PA** (5 mol %) at 10 °C in cyclohexane for 12 h, leading to the corresponding homopropargylic alcohol **3b**–**h** (Table 3, entries 2–8) in excellent yields (92–98%) and with high enantioselectivities (90→99% ee).

Similarly, 2-naphthyl aldehyde **1i** and 1-pyrenecarboxaldehyde **1j** smoothly reacted with **2** under optimal conditions, affording the corresponding homopropargylic alcohols **3i** and **3j** (Table 3, entries 9–10) in 90% and >99% ee, respectively, in excellent yields (95%). We were particularly pleased to find that α,β-unsaturated (Table 3, entry 11) and heteroaryl (Table 3, entries 12 and 13) aldehydes were found to be propargylated efficiently with high enantioselectivity (90- >99% ee). In the same way, an aliphatic aldehyde (Table 3, entry 14) was also competently propargylated with **2** in excellent enantioselectivity (>99%). The only limit on enantioselectivity was found in the case of hydrocinnamaldehyde (Table 3, entry 15), where the enantioselectivity is only 84%.

Table 3. Asymmetric Synthesis of Homopropargylic Alcohols[a]



entry	substrate	product	yield (%)[b]	ee[c]
1	**1a**	**3a**	98	>99
2	**1b**	**3b**	96	92
3	**1c**	**3c**	98	>99
4	**1d**	**3d**	95	90
5	**1e**	**3e**	94	>99
6	**1f**	**3f**	92	91
7	**1g**	**3g**	96	91
8	**1h**	**3h**	92	>99
9	**1i**	**3i**	95	95
10	**1j**	**3j**	95	>99
11	**1k**	**3k**	94	90
12	**1l**	**3l**	96	91
13	**1m**	**3m**	95	91
14	**1n**	**3n**	94	>99
15	**1o**	**3o**	98	84[d]

[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), 5 mmol % (***R*)-TRIP-PA**, and 5 Å M.S. (500 mg) in cyclohexane (5.0 mL), unless otherwise specified. [b] Isolated yield. [c] The products were determined to be *R* by chiral HPLC analysis and optical data in literature. [d] In this case, the opposite (*S*) enantiomer was formed.

Based on recent work by Yamamoto and Terada,[5b,9a,19] a possible stereochemical model to explain the achieved stereoselectivity (*R*-**3**) is shown in Figure 1. This involves a

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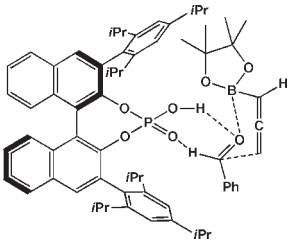

Figure 1. Possible stereochemical model for chiral phosphoric acid catalyzed propargylation of aldehydes.

boat-like cyclic transition state where the aldehyde is oriented to a position where the more sterically demanding substituent is kept away from the catalyst, exposing the *Re* face for the propargylation (Figure 1).

In conclusion, we have developed a simple and practical chiral phosphoric acid catalyzed asymmetric propargylation of a wide range of aldehydes employing allenylboronate with high enantioselectivities and excellent yields. The simple reaction protocol and the ready availability of the chiral phosphoric acid catalysts make this new asymmetric propargylation an attractive alternative to currently existing methods.

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Note Added after ASAP Publication. The authors regret that the version of this paper published ASAP on January 24, 2012, omitted the following reference: Jain, P.; Antilla, J.C. *J. Am. Chem. Soc.* **2010**, *132*, 11884−11886 (DOI: http://dx.doi.org/10.1021/ja104956s). The last sentence of the second paragraph has been rephrased since the original text used sentences from the Antilla paper. The paper was reposted ASAP on February 7, 2012.

Supporting Information Available. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.