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Chiral Brønsted Acid-Catalyzed Allylboration of Aldehydes

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Abstract

The catalytic enantioselective allylation of aldehydes is a long-standing problem with considerable interest to the chemical community. We wish to disclose a new high yielding and highly enantioselective chiral Brønsted acid-catalyzed allylboration of aldehydes. The reaction is shown to be highly general, with broad substrate scope that covers aryl, heteroaryl, α,β -unsaturated, and aliphatic aldehydes. The reaction conditions were also shown to be effective for the catalytic enantioselective crotylation of aldehydes. We believe that the high reactivity of the allyl boronate is due to protonation of the boronate oxygen by the chiral phosphoric acid catalyst.

The asymmetric allylboration of aldehydes has been an invaluable tool for the formation of carbon-carbon bonds with control over relative and absolute stereochemistry.¹ The foundation to this reaction was provided by Hoffmann's recognition of the diastereospecificity of the reaction when using both E- and Z- crotylboronates^{2a-c} and Brown's highly stereoselective allylboration using pinene-derived chiral reagents.^{2d-f} Over the past three decades additional methodology that has relied upon stoichiometric chiral reagents or mediators have included work by Roush,^{3a-c} Masamune,^{3d} Corey,^{3e} Seebach,^{3f} Duthaler,^{3g} Panek,^{3h} Leighton,^{3i-j} Chong,^{3k} Soderquist,^{3l,m} and Aggarwal.³ⁿ Catalytic methods have also emerged, and these include, in part, work by Yamamoto,^{4a} Umani-Ronchi,^{4b} Keck,^{4c} Denmark^{1b,4d} and others.^{4e-f} Also, recent catalytic allylboration by Hall,^{5a-g} Miyaura,^{5h} Shibasaki⁵ⁱ and Schaus^{5j-k} have opened new doors for the synthesis of homoallyl alcohols. However, most stereoselective methods are limited by one or more drawbacks. These include the use of stoichiometric chiral

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

inductors, allylation reagents that are difficult to prepare or are air/moisture sensitive, the use of undesirable metal-based catalysts such as tin, or substrates leading to toxic byproducts. Hence, the search continues for a competent, catalytic, and practical solution for the direct enantioselective synthesis of homoallylic alcohols; an important class of versatile intermediates used in the synthesis of pharmaceuticals and natural products.^{1a}

Binaphthyl derived chiral phosphoric acids (PA) have been shown to be versatile and efficient catalysts that promote a variety of enantioselective transformations. Chiral PA catalysts have found success in a large number of carbon-carbon and carbon-heteroatom bond forming processes along with a variety of oxidation and reduction reactions.⁶ Although chiral PA-catalyzed reactions involving aldehydes are very rare,^{7,8} we investigated the enantioselective synthesis of homoallylic alcohols by reacting aldehydes with allylboronic acid pinacol ester **2** using chiral acid-catalyzed conditions. Boronate **2** is a relatively stable, nontoxic, commercially available reagent so it was an ideal choice for our evaluation of the chemistry.

During the initial investigations leading to a catalytic reaction between benzaldehyde and **2**, (*R*)-**TRIP-PA** (**4**) was found to be a very effective promoter.⁹ Upon solvent screening we found that toluene, *m*-xylene, benzene and methylene chloride were effective for the asymmetric synthesis of alcohol **3a** (Table 1). It was determined that toluene was the most suitable solvent, allowing for a 93% ee of **3a** at room temperature in a 1 hour reaction time (entry 8). The enantioselectivity was further improved by reducing the temperature to 0 °C (96% ee, entry 9) and -30 °C (98% ee, entry 10) in presence of 5 mol % of the catalyst. It was fascinating to find that lowering the catalyst loading to 2.5 mol % allowed for a 97% ee (entry 11) and further lowering to 1 mol % (entry 12) still allowed for an impressive 95% enantioselectivity.

The optimized reaction conditions were effective in promoting the asymmetric allylboration of a wide range of aldehydes, allowing for an extremely efficient reaction (Table 2). The substrate scope extended to electron-rich and electron-poor aromatic aldehydes (entries 1–11). An ester functional group was tolerated in the chemistry (entry 8) and also several hindered aldehydes were effectively allylated (entries 7, 9 and 10). We were particularly pleased to find that heteroaryl (entry 12), α,β -unsaturated aldehydes (entries 13 and 14) and aliphatic aldehydes (entries 15 and 16) were found to be allylated efficiently with high enantioselectivity. The only limits on enantioselectivity were found upon further evaluation of aliphatic aldehydes (entries 17 and 18).

We believe these examples represent the first case where a chiral Brønsted acid activates allyl boronate esters, in the absence of a Lewis acid, in a highly enantioselective catalytic process.¹⁰

We were very pleased to find that (*R*)-**TRIP-PA** also promoted the crotylboration of benzaldehyde with high diastereo- and enantioselectivities (Table 3). Use of (*E*)-crotyl boronate **5a** provided the *anti*-isomer **6a** exclusively with 96% ee at room temperature (entry 1) and >99% ee at 0 °C (entry 2) using the general reaction conditions. When employing the (*Z*)-crotyl boronate **5b** the *syn*-isomer **6b** was obtained exclusively with 94% ee at -30 °C.

Although the reaction mechanism for this interesting activation has yet to be investigated by our laboratory, the observed diastereoselectivity in the crotylation strongly suggests that the allylboration proceeds via a type I mechanism involving a chair-like six-membered cyclic transition state similar to previous uncatalyzed reactions involving allyl boronates.¹¹ Recent work by Hall^{5f–g} and Schaus,^{5k} suggest that activation by protonation of the boronate oxygen could be involved. Similarly, Lewis acid promoted boronate activation has also been previously invoked.^{5b} As the basis to a working hypothesis, we also propose that activation via protonation of the boronate oxygen by the chiral phosphoric catalyst would provide a reasonable explanation for the reactivity (Figure 1).

In conclusion we have developed a simple and highly efficient chiral phosphoric acid catalyzed allylboration of aldehydes. The protocol provides a highly enantioselective method for the synthesis of homoallylic alcohols from simple starting materials. The usefulness of this organocatalytic reaction is highlighted by the stability and commercial availability of the substrates and the catalyst. This work also has the potential of opening new vistas for chiral phosphoric acid-catalyzed activation that was not previously evident. Mechanistic investigations and theoretical considerations are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Proposed TS

Figure 1.

A plausible transition state assembly for chiral phosphoric-acid allylation of aldehydes.

Table 1Optimization of the catalytic allylboration of aldehydes^a

entry	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	ether	16	99	35
2	DCM	16	99	88
3	THF	48	51	6
4	<i>m</i> -xylene	48	99	89
5	EtOAc	24	76	29
6	CH ₃ CN	48	55	33
7	benzene	2	99	92
8	toluene	1	99	93
9	toluene ^d	4	99	96
10	toluene ^e	16	99	98
11	toluene ^{e,f}	16	99	97
12	toluene ^{e,g}	16	99	95

^a Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), 5 mol % **(R)-TRIP-PA**, unless otherwise specified.^b Isolated yield.^c Determined by chiral HPLC analysis.^d Reaction conducted at 0 °C.^e Reaction conducted at −30 °C.^f 2.5 mol % catalyst used.^g 1 mol % of catalyst used.

Table 2Asymmetric allylboration of aldehydes^a

entry	R	product	yield (%) ^b
1	Ph	3a	99
2	4-ClC ₆ H ₄	3b	98
3	4-BrC ₆ H ₄	3c	99
4	4-NO ₂ C ₆ H ₄	3d	98
5	4-MeOC ₆ H ₄	3e	95
6	3-MeOC ₆ H ₄	3f	96
7	2-MeC ₆ H ₄	3g	97
8	4-CO ₂ MeC ₆ H ₄	3h	96
9	1-naphthyl	3i	93
10	9-anthryl	3j	94
11	piperonyl	3k	98
12	2-thienyl	3l	91
13		3m	94

entry	R	product	yield (%) ^b
14		3n	93
15	Bn	3o	98
16	PhCH ₂ CH ₂	3p	96
17	BnOCH ₂	3q	92
18	<i>c</i> -C ₆ H ₁₁	3r	98

^a Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), 5 mol % (R) -TRIP-PA.

^b Isolated yield.

^c The products were determined to be (R) by chiral HPLC analysis and optical rotation data in the literature.

^d With (S) -TRIP-PA the opposite enantiomer (S) of **3a** was also obtained in 98% yield and 97% ee under otherwise identical conditions.

^e In three cases the opposite (S) enantiomer was in excess using the (R) -TRIP-PA catalyst.

Table 3

Asymmetric crotylboration of benzaldehyde^a

entry	R ¹	R ²	temp	6a : 6b ^b	yield (%) ^c	ee (%) ^d
1	CH ₃	H	rt	2 : 98	96	96
2	CH ₃	H	0 °C	2 : 98	96	99
3	H	CH ₃	-30 °C	98 : 2	95	94

^aReaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), 5 mol % *(R)*-TRIP-PA.^bDetermined by ¹H NMR.^cIsolated yield.^dDetermined by chiral HPLC analysis.