J|A|C|S COMMUNICATIONS

Published on Web 08/06/2010

Chiral Brønsted Acid-Catalyzed Allylboration of Aldehydes

Pankaj Jain and Jon C. Antilla*

Department of Chemistry, University of South Florida, 4202 East Fowler Avenue, Tampa, Florida 33620

Received June 7, 2010; E-mail: jantilla@usf.edu

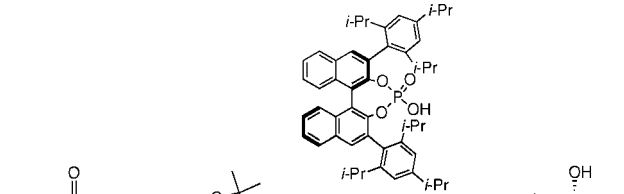
Abstract: The catalytic enantioselective allylation of aldehydes is a long-standing problem of considerable interest to the chemical community. We disclose a new high-yielding and highly enantioselective chiral Brønsted acid-catalyzed allylboration of aldehydes. The reaction is shown to be highly general,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

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 of this reaction was provided by Hoffmann's recognition of the diastereospecificity of the reaction when both (*E*)- and (*Z*)-crotylboronates are used[2a−c] and Brown's highly stereoselective allylborations using pinene-derived chiral reagents.[2d−f] Over the past three decades, additional methodologies that have 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 in part these include work by Yamamoto,[4a] Umani-Ronchi,[4b] Keck,[4c] Denmark,[1b,4d] and others.[4e,f] Also, recent catalytic allylborations by Hall,[5a−g] Miyaura,[5h] Shibasaki,[5i] and Schaus[5j,k] have opened new doors for the synthesis of homoallylic alcohols. However, most stereoselective methods are limited by one or more drawbacks. These include the use of stoichiometric chiral 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 (PAs) 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 as well as 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 reaction time of 1 h (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 the presence of 5 mol % 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.

Table 1. Optimization of the Catalytic Allylboration of Aldehydes[a]



1 2 3a

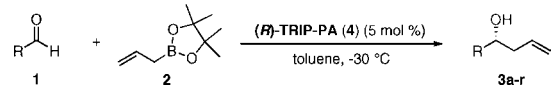
entry	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	ether	16	99	35
2	DCM	16	99	88
3	THF	48	51	6
4	*m*-xylene	48	99	89
5	EtOAc	24	76	29
6	CH_3CN	48	55	33
7	benzene	2	99	92
8	toluene	1	99	93
9	toluene[d]	4	99	96
10	toluene[e]	16	99	98
11	toluene[e,f]	16	99	97
12	toluene[e,g]	16	99	95

[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] Using 2.5 mol % catalyst. [g] Using 1 mol % catalyst.

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 several hindered aldehydes also were effectively allylated (entries 7, 9, and 10). We were particularly pleased to find that heteroaryl (entry 12), α,β-unsaturated (entries 13 and 14), and aliphatic (entries 15 and 16) aldehydes 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).

10.1021/ja104956s

Table 2. Asymmetric Allylboration of Aldehydes[a]

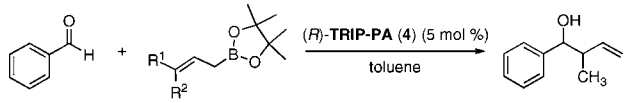


1 2 3a-r

entry	R	product	yield (%)[b]	ee (%)[c]
1	Ph	**3a**	99	98[d]
2	4-ClC_6H_4	**3b**	98	99
3	4-BrC_6H_4	**3c**	99	99
4	4-$NO_2C_6H_4$	**3d**	98	98
5	4-$MeOC_6H_4$	**3e**	95	98
6	3-$MeOC_6H_4$	**3f**	96	97
7	2-MeC_6H_4	**3g**	97	93
8	4-$CO_2MeC_6H_4$	**3h**	96	96
9	1-naphthyl	**3i**	93	98
10	9-anthryl	**3j**	94	91
11	piperonyl	**3k**	98	98
12	2-thienyl	**3l**	91	96[e]
13		**3m**	94	96
14		**3n**	93	93
15	Bn	**3o**	98	90
16	$PhCH_2CH_2$	**3p**	96	87[e]
17	$BnOCH_2$	**3q**	92	79[e]
18	*c*-C_6H_{11}	**3r**	98	73

[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 (*S*) enantiomer of **3a** was also obtained in 98% yield and 97% ee under otherwise identical conditions. [e] In three cases, the opposite (*S*) enantiomer was produced in excess using the (*R*)-**TRIP-PA** catalyst.

Table 3. Asymmetric Crotylboration of Benzaldehyde[a]



1 **5a**: $R^1 = CH_3$, $R^2 = H$ **5b**: $R^1 = H$, $R^2 = CH_3$ **6a** = *syn* **6b** = *anti*

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

[a] Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), 5 mol % (*R*)-**TRIP-PA**. [b] Determined by ^1H NMR analysis. [c] Isolated yield. [d] Determined by chiral HPLC analysis.

We believe these examples represent the first case where a chiral Brønsted acid activates allylboronate 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 enantioselectivity (Table 3). Use of (*E*)-crotylboronate **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 (*Z*)-crotylboronate **5b** was employed, 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 chairlike six-membered cyclic transition state, similar to previous uncatalyzed reactions involving allylboronates.[11] Recent work by Hall[5f,g] and Schaus[5k] suggested that activation by protonation of the boronate oxygen could be involved. Similarly, Lewis acid-promoted boronate activation has also been invoked previously.[5b] As the basis of a working hypothesis, we also propose that activation via protonation of the boronate oxygen by the chiral phosphoric acid catalyst would provide a reasonable explanation for the reactivity (Figure 1).

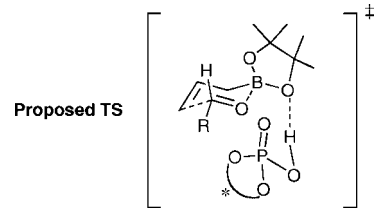


Figure 1. Plausible transition-state assembly for chiral phosphoric acid-catalyzed allylation of aldehydes.

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 to open new vistas for chiral phosphoric acid-catalyzed activation that were not previously evident. Mechanistic investigations and theoretical considerations are in progress and will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (NIH GM-082935) and the National Science Foundation CAREER Program (NSF-0847108) for financial support. We also thank Tao Liang for preparation of the catalyst and Matthew J. Kaplan for helpful suggestions.

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

References

(1) (a) Lachance, H.; Hall, D. G. *Org. React.* **2008**, *73*, 1. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemisry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 10, p 299. (d) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemisry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 403. (e) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (f) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, p 1.

(2) (a) Hoffmann, R. W.; Ladner, W. *Tetrahedron Lett.* **1979**, *20*, 4653. (b) Hoffmann, R. W.; Zeiss, H. J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 306. (c) Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem.* **1981**, *46*, 1309. (d) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (e) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (f) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23.

(3) For selected examples of chirally modified allyl reagents, see: (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14602. (c) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14175. (d) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892. (e) Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (f) Seebach, D.; Beck, A. K.; Imwinkelzied, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954. (g) Riediker, M.; Duthaler, R. O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 494. (h) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594. (i) Kinnaird, I. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (j) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375. (k) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701. (l) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044. (m) Gonzalez, A. Z.; Roman, I. G.; Alicea, E.; Canales, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 1269. (n) Althaus, M.; Mahmood, A.; Suarez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 4025.

(4) (a) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561. (b) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (c) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (d) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488. (e) Malkov, A.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kocovsky, P. *Org. Lett.* **2002**, *4*, 1047. (f) Kim, I. S.; Ngai, M.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891.

(5) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518. (c) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. (d) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426. (e) Hall, D. G. *Synlett* **2007**, 1644. (f) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (g) Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236. (h) Ishiyama, T.; Ahiko, T.-A.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (i) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (j) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (k) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8679.

(6) For reviews, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5173. (c) Terada, M. *Chem. Commun.* **2008**, 4097.

(7) (a) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122. (b) Momiyama, N.; Tabuse, H.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 12882. (c) Sun, F.-L.; Zeng, M.; Gu, Q.; You, S.-L. *Chem.—Eur. J.* **2009**, *15*, 8709.

(8) For selected Brønsted acid activation of carbonyl compounds other than phosphoric acids, see: (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (c) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593. (d) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097.

(9) See the Supporting Information for details on catalyst screening. Both enantiomers of **TRIP-PA** (*R* and *S*) are commercially available or easily prepared from BINOL using a literature procedure (see: Hoffmann, S.; Seayad, A.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424).

(10) The most notable comparison is the work by Hall (ref 5c−g), which used a chiral diol/tin(IV) chloride combination to generate a Lewis acid/Brønsted acid-catalyzed allylboration.

(11) (a) Yang, J. E. *Six-Membered Transition States in Organic Synthesis*; Wiley: Hoboken, NJ, 2008; Chapter 3, pp 97−146. (b) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236.

JA104956S