Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Phosphoric Acid Bearing an (*S*)-Biphenol Backbone

Takahiko Akiyama,*[a] Takuya Katoh,[a] Keiji Mori,[a] Kazuaki Kanno[b]

[a] Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588, Japan
Fax +81(3)59921029; E-mail: takahiko.akiyama@gakushuin.ac.jp

[b] Mitsubishi Chemical Group Science and Technology Research Center, Inc., 1000 Kamoshida-cho, Aoba-ku, Yokohama 227-8502, Japan

Received 23 January 2009

Abstract: A novel chiral phosphoric acid bearing a biphenol backbone was synthesized and its catalytic activity was investigated in the enantioselective Mannich-type reaction of ketene silyl acetals with aldimines.

Key words: asymmetric synthesis, chiral Brønsted acid, Mannich-type reaction, biphenol, phosphoric acid

The development of efficient chiral catalysts continues to be one of the most challenging topics in synthetic organic chemistry.[1] A number of organocatalysts[2] as well as metal-based catalysts have been reported. We focused on stronger Brønsted acid catalysts and synthesized a cyclic phosphoric acid **1**, using (*R*)-BINOL as the starting material. Phosphoric acid **1a** (Ar = 4-$O_2NC_6H_4$) exhibited excellent catalytic activity as a chiral Brønsted acid catalyst for the Mannich-type reaction of silyl enolate with aldimines,[3] which is a useful method for the preparation of β-amino carbonyl compounds.[4] We also demonstrated that phosphoric acid **1** worked as a bifunctional chiral catalyst bearing a Lewis basic site and a Brønsted acidic site (Figure 1).[5] Recently, chiral phosphoric acid has drawn much attention as an efficient chiral catalyst.[6–8] A number of phosphoric acids have been synthesized from BINOL and their catalytic activities investigated. In contrast, other backbones for chiral phosphoric acid have been little studied. For example, we synthesized a phosphoric acid bearing a TADDOL scaffold and investigated its catalytic activity in the Mannich-type reaction.[9] Antilla and coworkers developed a phosphoric acid starting from VAPOL, bearing the biphenyl framework.[10] We report herein the preparation of a novel phosphoric acid bearing the biphenol backbone and its application as a chiral Brønsted acid in the Mannich-type reaction of silyl enolate with aldimines.

We selected chiral (*S*)-biphenol derivative **3** as the chiral scaffold[11] and synthesized novel phosphoric acid **2a**, bearing the (*S*)-biphenol backbone in six steps. (Scheme 1) These steps involved Lewis acid promoted dealkylation, followed by protection of the OH group with MOM ether, *o*-lithiation and introduction of boronic ester, and subsequent Suzuki–Miyaura coupling to install *p*-nitrophenyl

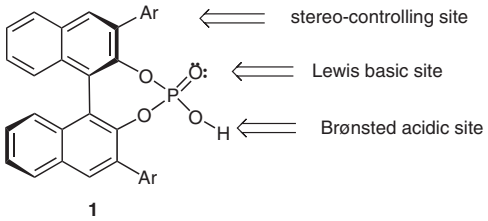


Figure 1 Functional chiral catalyst

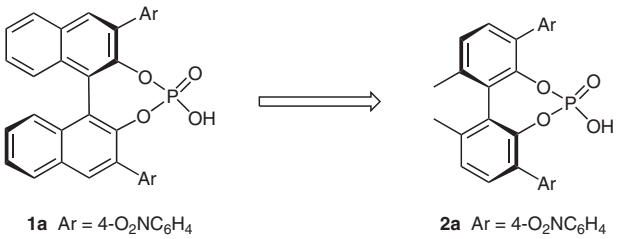


Figure 2 Design of a novel chiral Brønsted acid catalyst

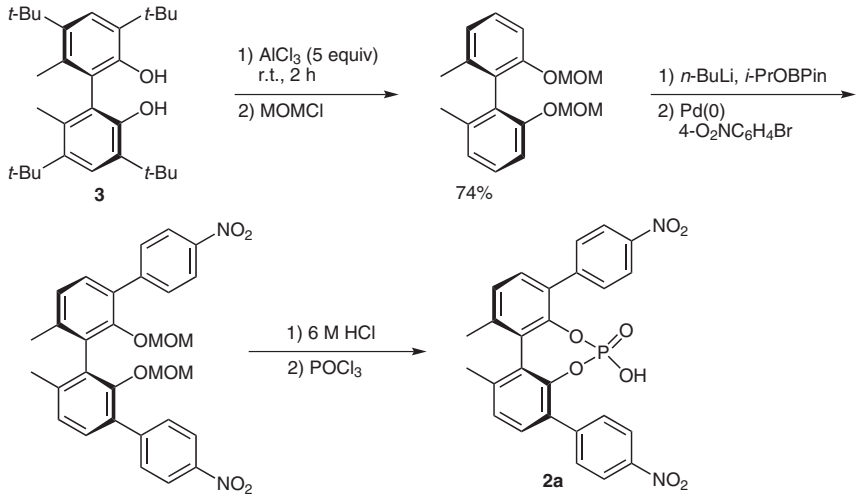
group at 3,3′-position. Acid-promoted cleavage of the MOM group followed by phosphorylation gave **2a** (Figure 2).[12]

At the outset, the Mannich-type reaction of aldimines with a ketene silyl acetal, derived from ethyl isobutyrate, was studied by means of 10 mol% of **2a**, and the results are shown in Table 1. Corresponding β-amino esters were obtained in excellent chemical yields with high enantioselectivities.[13] It was found that **2a** exhibited comparable catalytic activity to **1a** bearing the binaphthyl backbone.[14]

Next, the Mannich-type reaction of aldimines with a silyl enolate that was derived from ethyl propionate was investigated and the results are shown in Table 2. Aldimines derived from substituted benzaldehyde and cinnamaldehyde gave corresponding β-amino-2-methylpropionates with high *syn* selectivity and high to excellent enantioselectivities: the enantioselectivity of the *syn* isomer was as high as 93% (entry 5). It was found that **2a** exhibited higher enantioselectivities than **1a** in entries 2, 4, and 5.[15]

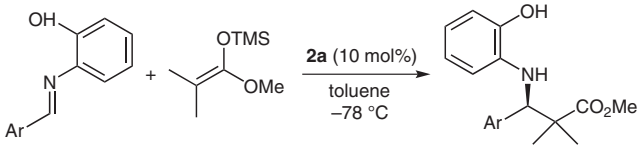
The present Mannich-type reaction is considered to proceed via a nine-membered transition state, as shown in Figure 3. Phosphoric acid **1** played two roles: (1) phosphoric acid hydrogen activated aldimine by acting as a Brønsted acid, and (2) phosphoryl oxygen formed a hydrogen bond with *o*-hydroxy group by acting as a Lewis base, thereby fixing the transition state. Hence, the phos-

SYNLETT 2009, No. 10, pp 1664–1666
Advanced online publication: 02.06.2009
DOI: 10.1055/s-0029-1217330; Art ID: Y00209ST



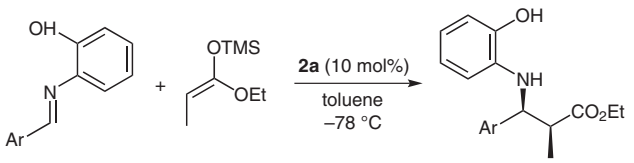
Scheme 1 Preparation of a phosphoric acid **2a**

Table 1 Results of the Mannich-Type Reactions



Entry	Ar	Time (h)	Yield (%)	ee (%)
1	Ph	13	100	87
2	4-MeC_6H_4	47	90	86
3	4-FC_6H_4	13	86	77

Table 2 Results of the Mannich-Type Reactions



Entry	Ar	Yield (%)	*syn*/*anti*	ee (%)[b]
1	Ph	100	86:14	90
2	4-MeC_6H_4	87	81:19	87
3	4-$MeOC_6H_4$	100	87:13	82
4	4-FC_6H_4	93	86:14	90
5	PhCH=CH	94	94:6	93

[a] Ketene silyl acetal *E*/*Z* = 91:9.
[b] Of the *syn*-isomer.

phoric acid **1** worked as a bifunctional catalyst[16] bearing both Brønsted acidic and Lewis basic sites.

In summary, we have synthesized a novel phosphoric acid bearing the (*S*)-biphenol backbone and demonstrated its catalytic activity in the Mannich-type reaction of ketene silyl acetal with aldimines. The corresponding β-amino esters were obtained with high to excellent enantioselectivities.

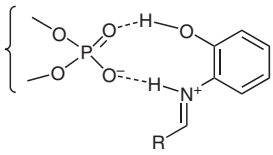


Figure 3 Proposed transition state

Typical Experimental Procedure for the Mannich-Type Reaction

Ketene silyl acetal was added dropwise over 1 min to a soln of aldimine (0.15 mmol) and phosphoric acid (0.015 mmol) in toluene (1 mL) at –78 °C. The reaction was stirred at this temperature. The mixture was quenched by the addition of sat. $NaHCO_3$ and KF at –78 °C. After filtration over Celite, the filtrate was extracted with EtOAc. The conbined organic layers were washed successively washed with 10% aq HCl and brine, dried over anhyd Na_2SO_4, and concentrated to dryness. The remaining solid was purified by TLC (SiO_2, hexane–EtOAc = 3:1) to give β-amino ester in high yield. The ee was determined on a Daicel Chiralpak AS-H, AD-H or IA column.

References and Notes

(1) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**.
(2) (a) *Asymmetric Organocatalysis*; Berkessel, A.; Gröger, H., Eds.; Wiley-VCH: Weinheim, **2005**. (b) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2007**.
(3) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (b) Itoh, J.; Fuchibe, K.; Akiyama, T. *Synthesis* **2008**, 1319.
(4) For reviews of Mannich reactions, see: (a) Friestad, G. K.; Mathiesa, A. K. *Tetrahedron* **2007**, *63*, 2541. (b) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797.
(5) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756.
(6) For selected examples, see: (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Uraguchi, D.;

Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (c) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360. (d) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (e) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424. (f) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2254. (g) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (h) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (i) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802. (j) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292. (k) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484. (l) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790. (m) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5565. (n) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2007**, 1441. (o) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Koeckritz, A.; Pews-Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065. (p) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 6798. (q) Terada, M.; Tanaka, H.; Sorimachi, K. *Synlett* **2008**, 1661. (r) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 2840. (s) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4122. (t) Rueping, M.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 5836.

(7) For reviews, see: (a) Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3909. (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Akiyama, T. In *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H.; Ishihara, K., Eds.; Wiley-VCH: Weinheim, **2008**, 62. (e) Terada, M. *Chem. Commun.* **2008**, 4097.

(8) For our reports, see: (a) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141. (b) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am Chem. Soc.* **2006**, *128*, 13070. (c) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796. (d) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 4016. (e) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399.

(9) For a chiral phosphoric acid derived from TADDOL, see: Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.* **2005**, *347*, 1523.

(10) For use of phosphoric acid derived from biphenol derivative, see: (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (b) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830. (c) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084. (d) See also: Moreau, J.; Duboc, A.; Hubert, C.; Hurvois, J.-P.; Renaud, J.-L. *Tetrahedron Lett.* **2007**, *48*, 8647.

(11) (a) Takai, M.; Urata, T.; Takahashi, T. JP 2004189696, **2004**. See also: (b) Hua, Z.; Vassar, V. C.; Ojima, I. *Org. Lett.* **2003**, *5*, 3831. (c) Ojima, I.; Takai, M.; Takahashi, T.; Urata, H. WO 2004076464, **2004**.

(12) **(*S*)-6,6′-Dimethyl-3,3′-bis(4-nitrophenyl)-1,1′-biphenyl-2,2′-yl Phosphate (2a)**
$[\alpha]_D^{21}$ +365 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.04 (m, 4 H), 7.55–7.53 (m, 4 H), 7.39–7.37 (m, 4 H), 2.58 (s, 1 H), 2.35 (s, 6 H). ^{31}P NMR(400 MHz, $CDCl_3$): δ = 0.74. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9, 144.7, 143.1, 140.3, 130.2, 130.0, 129.7, 128.4, 127.7, 123.3, 20.0. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.74. Anal. Calcd (%) for $C_{26}H_{19}O_8P$: C, 60.24; H, 3.69; N, 5.40. Found: C, 60.13; H, 3.66; N, 5.45%.

(13) **(*R*)-Methyl 3-(*N*-2-Hydroxyphenylamino)-2,2-dimethyl-3-phenylpropionate**
$[\alpha]_D^{21}$ +1.4 (*c* 0.45, $CHCl_3$; 87% ee); R_f = 0.4 (hexane–EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.19 (m, 5 H), 6.69 (1 H, dd, *J* = 7.7, 1.5 Hz), 6.61 (1 H, ddd, *J* = 7.7, 7.7, 1.5 Hz), 6.53 (1 H, ddd, *J* = 7.7, 7.7, 1.5 Hz), 6.38 (1 H, dd, *J* = 7.7, 1.5 Hz), 5.80 (br s, 1 H), 4.55 (br s, 1 H), 4.55 (s, 1 H), 3.69 (s, 3 H), 1.24 (s, 3 H), 1.22 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.7, 144.3, 139.0, 135.5, 128.3, 127.9, 127.41, 121.0, 117.9, 114.4, 113.9, 64.6, 52.2, 47.4, 24.4, 20.0.

(14) When **1a** was employed in the reaction with the aldimine derived from benzaldehyde, the corresponding adduct was obtained in 87% ee.[3]

(15) The enantioselectivities obtained with **1a**: 96% (Ar = Ph), 81% (Ar = 4-MeC_6H_4), 88% (Ar = 4-$MeOC_6H_4$), 84% (Ar = 4-FC_6H_4), 90% (Ar = $PhCH{=}CHC_6H_4$).[3]

(16) For bifunctional Lewis acids, see: Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989.