ORGANIC LETTERS

2012
Vol. 14, No. 8
2126–2129

Highly Efficient Asymmetric Mannich Reaction of Dialkyl α-Diazomethylphosphonates with *N*-Carbamoyl Imines Catalyzed by Chiral Brønsted Acids

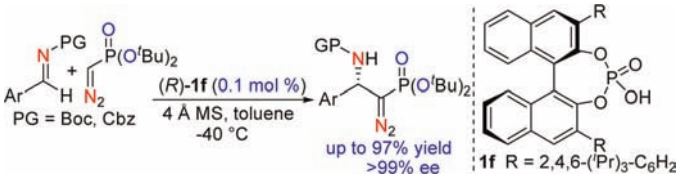
Hui Zhang, Xiaojing Wen, Lihua Gan, and Yungui Peng*

School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, P. R. China

pengyungui@hotmail.com

Received March 15, 2012

ABSTRACT



An efficient method involving the first use of chiral phosphoric acids as catalysts in the asymmetric Mannich reaction of dialkyl diazomethylphosphonates and *N*-carbamoyl imines is developed. With only 0.1 mol % catalyst 1f, the reaction proceeded smoothly and produced the corresponding β-amino-α-diazophosphonate with up to 97% yield and >99% *ee*.

α-Diazocarbonyl compounds are valuable synthons, and they have been investigated as nucleophiles in asymmetric transformations,[1] such as addition reactions with carbonyl compounds[2] and imines.[3] Recent advances in the asymmetric reactions of diazoacetates and imines catalyzed by chiral Brønsted acids[3a−e,4] or chiral Lewis acids[3h,5] have produced the corresponding enantiopure α-amino-β-diazo carbonyl compounds or developed aziridine derivatives. These derivatives can be further transformed into β-amino acid, β-amino-α-hydroxy acid, and other common synthetic intermediates.[6] Surprisingly, α-diazomethylphosphonates as isosteric analogs of their

(1) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (c) Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001**, *617–618*, 98. (d) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (e) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797. (f) Padwa, A. *J. Organomet. Chem.* **2001**, *617–618*, 3. (g) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617–618*, 47. (h) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50. (i) Zhao, Y. H.; Wang, J. B. *Synlett.* **2005**, 2886. (j) Johnston, J. N.; Muchalski, H.; Troyer, T. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2290.

(2) (a) Hashimoto, T.; Miyamoto, H.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 11280. (b) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 6614. (c) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 2434. (d) Trost, B. M.; Malhotra, S.; Koschker, P.; Ellerbrock, P. *J. Am. Chem. Soc.* **2012**, *134*, 2075.

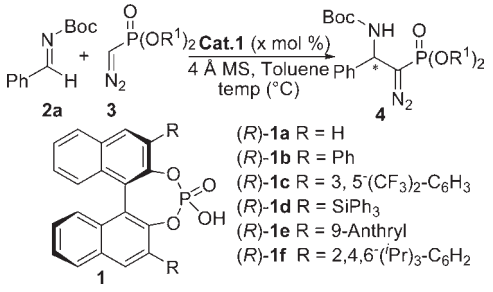
(3) (a) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. (b) Hashimoto, T.; Kimura, H.; Nakatsu, H.; Maruoka, K. *J. Org. Chem.* **2011**, *76*, 6030. (c) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011**, *3*, 642. (d) Akiyama, T.; Suzuki, T.; Mori, K. *Org. Lett.* **2009**, *11*, 2445. (e) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360. (f) Zhao, Y. H.; Jiang, N.; Wang, J. B. *Tetrahedron Lett.* **2003**, *44*, 8339. (g) Qian, Y.; Xu, X. F.; Jiang, L. Q.; Prajapati, D.; Hu, W. H. *J. Org. Chem.* **2010**, *75*, 7483. (h) Lu, Z. J.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185. (i) Hashimoto, T.; Uchiyama, N.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 14380. (j) Huang, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 8892. (k) Hashimoto, T.; Nakatsu, H.; Yamamoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 9730. (l) Jiang, J.; Xu, H. D.; Xi, J. B.; Ren, B. Y.; Lv, F. P.; Guo, X.; Jiang, L. Q.; Zhang, Z. Y.; Hu, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 8428. (m) Zeng, X. F.; Zeng, X.; Xu, Z. J.; Lu, M.; Zhong, G. F. *Org. Lett.* **2009**, *11*, 3036. (n) Hashimoto, T.; Nakatsu, H.; Watanabe, S.; Maruoka, K. *Org. Lett.* **2010**, *12*, 1668. (o) Hashimoto, T.; Nakatsu, H.; Yamamoto, K.; Watanabe, S.; Maruoka, K. *Chem.—Asian J.* **2011**, *6*, 607.

(4) (a) Hu, G.; Huang, L.; Huang, R. H.; Wulff, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 15615. (b) Desai, A. A.; Ren, H.; Mukherjee, M.; Wulff, W. D. *Org. Process Res. Dev.* **2011**, *15*, 1108. (c) Troyer, T. L.; Muchalski, H.; Hong, K. B.; Johnston, J. N. *Org. Lett.* **2011**, *13*, 1790. (d) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612.

10.1021/ol300664d
Published on Web 03/30/2012

α-diazoacetate counterparts have seldom been used as nucleophiles in the asymmetric Mannich reaction with imines[3a−c,f] to give the corresponding β-amino-α-diazophosphonate products. These products could be easily transformed to a variety of β-amino phosphoric acid[7] and β-amino-α-hydroxyphosphoric acid[8] derivatives via simple reduction or oxidation of the diazo moiety alternatively. The β-amino phosphoric acid derivatives are interesting and potentially useful in the synthesis of inhibitors of human renin, calpain I, and anti-HIV agents.[6c] Most of the reported methods for the synthesis of optically pure β-amino phosphoric acid derivatives start from chiral sources, such as proteinogenic amino acids or amino aldehydes thereof.[7c,e] There are only a few methods available for catalytic asymmetric hydrogenation or aminohydroxylation.[7f−i,8a] β-Amino-α-diazophosphonate could provide an alternative facile access to important β-amino phosphoric acid derivatives that cannot be obtained by derivatization of proteinogenic amino acids. Although enantiopure β-amino-α-diazophosphonates are important in organic synthesis, there are few reports on the asymmetric Mannich reaction of α-diazomethylphosphonate with imines. This is presumably because of the bulky and tetrahedral phosphonate moiety, which will lower the reactivity. To date, only one group has investigated the catalysis of the asymmetric transformation by axially chiral dicarboxylic acid. They have resulted in the β-amino-α-diazophosphonate derivatives with good *ee*, but the studies used a 5% catalyst loading, and the catalytic efficiency and applicability of the imine substrates require improvement.[3a,b]

Table 1. Optimization of Catalysts and Reaction Conditions[a]



entry	cat.(%)	R_1	temp (°C)	*t*	yield(%) [b]	*ee* (%) [c]
1	**1a** (10)	Me	0	3.3 h	62	0
2	**1b** (10)	Me	0	36 h	31	38 (*S*)
3	**1c** (10)	Me	0	40 min	65	-11 (*R*)
4	**1d** (10)	Me	0	36 h	39	27 (*S*)
5	**1e** (10)	Me	0	55 min	68	43 (*S*)
6	**1f** (10)	Me	0	15 min	73	94 (*S*)
7	**1f** (5)	Me	0	1 h	73	94 (*S*)
8	**1f** (2)	Me	0	2 h	70	94 (*S*)
9	**1f** (2)	Me	-20	2.5 h	70	97 (*S*)
10	**1f** (2)	Me	-40	10 h	73	97 (*S*)
11	**1f** (2)	Et	-40	2 h	81	98 (*S*)
12	**1f** (2)	^{i}Pr	-40	2 h	82	98 (*S*)
13	**1f** (2)	Bn	-40	100 min	94	97 (*S*)
14	**1f** (2)	^{t}Bu	-40	10 min	91	>99 (*S*)
15	**1f** (2)	^{t}Bu	-20	5 min	91	98 (*S*)
16	**1f** (2)	^{t}Bu	-60	20 min	91	>99 (*S*)
17	**1f** (1)	^{t}Bu	-40	30 min	91	>99 (*S*)
18	**1f** (0.5)	^{t}Bu	-40	1 h	90	>99 (*S*)
19	**1f** (0.2)	^{t}Bu	-40	2.5 h	91	>99 (*S*)
20	**1f** (0.1)	^{t}Bu	-40	4 h	91	>99 (*S*)
21	**1f** (0.05)	^{t}Bu	-40	22 h	93	>99 (*S*)

[a] Reactions were performed with benzaldehyde *N*-Boc imine (0.15 mmol) and α-diazomethylphosphonate (0.10 mmol) in the presence of phosphoric acid **1** and 4 Å MS (50 mg) in toluene (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Binaphthylphosphates have been extensively used as chiral catalysts in a wide range of asymmetric organic transformations.[9] For example, pioneering work by Terada and co-workers demonstrated that chiral phosphoric acid could catalyze the asymmetric Mannich reaction of *N*-acylimines and *tert*-butyl diazoacetate with high efficiency and excellent enantioselectivity.[3e] The chiral phosphoric acids performed well in those asymmetric transformations prompted us to investigate their use in the reaction of *N*-carbamoyl imines with α-diazomethylphosphonate. Our aim was to develop an efficient catalytic methodology for the synthesis of β-amino-α-diazophosphonate with

(5) (a) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099. (b) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518. (c) Loncaric, C.; Wulff, W. D. *Org. Lett.* **2001**, *3*, 3675. (d) Zhang, Y.; Lu, Z. J.; Desai, A.; Wulff, W. D. *Org. Lett.* **2008**, *10*, 5429. (e) Mukherjee, M.; Gupta, A. K.; Lu, Z. J.; Zhang, Y.; Wulff, W. D. *J. Org. Chem.* **2010**, *75*, 5643. (f) Desai, A. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 13100. (g) Gupta, A. K.; Mukherjee, M.; Wulff, W. D. *Org. Lett.* **2011**, *13*, 5866.

(6) (a) Zhao, Y. H.; Ma, Z. H.; Zhang, X. M.; Zou, Y. P.; Jin, X. L.; Wang, J. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 5977. (b) Zhao, Y. H.; Jiang, N.; Chen, S. F.; Peng, C.; Zhang, X. M.; Zou, Y. P.; Zhang, S. W.; Wang, J. B. *Tetrahedron* **2005**, *61*, 6546. (c) Park, H.; Cho, C. W.; Krische, M. J. *J. Org. Chem.* **2006**, *71*, 7892.

(7) (a) Palacios, F.; Alonso, C.; De Los Santos, J. M. *Enantioselective Synthesis of β-amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2005. (b) Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899. (c) Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J.; Wieczorek, M. W.; Blaszcyk, J. *Chem. Commun.* **1996**, 1503. (d) Xu, C. F.; Yuan, C. Y. *Eur. J. Org. Chem.* **2004**, 4410. (e) Zhang, D. H.; Yuan, C. Y. *Chem.—Eur. J.* **2009**, *15*, 4088. (f) Zhang, J. Z.; Li, Y.; Wang, Z.; Ding, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 11743. (g) Ryglowski, A.; Kafarski, P. *Tetrahedron* **1996**, *52*, 10685. (h) Kadyrov, R.; Holz, J.; Schäffner, B.; Zayas, O.; Almena, J.; Börner, A. *Tetrahedron: Asymmetry* **2008**, *19*, 1189. (i) Doherty, S.; Knight, J. G.; Bell, A. L.; El-Menabawey, S.; Vogels, C. M.; Decken, A.; Westcott, S. A. *Tetrahedron: Asymmetry* **2009**, *20*, 1437. (j) Wang, J.; Heikkinen, L. D.; Li, H.; Zu, L. S.; Jiang, W.; Xie, H.-X.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1052.

(8) (a) Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379. (b) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Rogers, W. L.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, E. W. Jr. *J. Med. Chem.* **1995**, *38*, 4557. (c) Zygmunt, J.; Gancarz, R.; Lejczak, B.; Wieczorek, P.; Kafarski, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2989. (d) Piotrowska, D. G.; Wróblewski, A. E. *Tetrahedron* **2009**, *65*, 4310. (e) Wróblewski, A. E.; Piotrowska, D. G. *Tetrahedron: Asymmetry* **2000**, *11*, 2615. (f) Cravotto, G.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron: Asymmetry* **1998**, *9*, 745. (g) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1401. (h) Barco, A.; Benetti, S.; Bergamini, P.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1999**, *40*, 7705. (i) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587.

(9) (a) Cheon, C. H.; Yamamoto, H. *Chem. Commun.* **2011**, 3043. (b) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (f) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909. (g) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31. (h) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. (i) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395.

high enantioselectivity and broad substrate scope. Herein, we described that binapthylphosphates are capable of an even higher *ee* and excellent yield and can operate at a 0.1% catalyst loading in the asymmetric Mannich reaction.

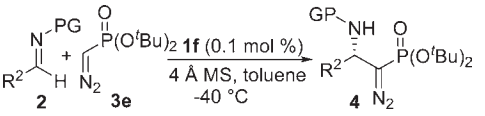
The reaction of benzaldehyde *N*-Boc imine **2a** with dimethyl α-diazomethylphosphonate **3a** was investigated first as a model reaction. Chiral phosphoric acids **1a**−**1f** were used as catalysts. Molecular sieves (4 Å) were used to scavenge water. With a 10 mol % catalyst load in toluene at 0 °C the reaction proceeded smoothly, with moderate yields (31−73%) and low to good enantioselectivities (−11% *ee* to 94% *ee*) (Table 1, entries 1−6). When the reaction was catalyzed by chiral phosphoric acid **1a**, the product was racemic (Table 1, entry 1). Introduction of phenyl groups to the structure of catalyst **1a** at the 3- and 3′-positions (catalyst **1b**) decreased the reactivity (31% yield, 36 h) and increased the enantioselectivity to 38% *ee* (Table 1, entry 2). With electron-deficient aryl groups at the 3- and 3′-positions (catalyst **1c**), the product with the opposite configuration was obtained with a low *ee* (Table 1, entry 3). Further changes of the substituents at the 3- and 3′-positions to $-SiPh_3$ (catalyst **1d**), 9-anthyl (catalyst **1e**), and 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$ (catalyst **1f**) were investigated. Among these, **1f** showed good catalytic efficiency and stereocontrol, with a reaction yield of 73% and 94% *ee* in 15 min (Table 1, entry 6).

Using **1f** as the catalyst, we investigated decreasing the catalyst loads from 10% to 5% and then 2%. To maintain the yield and enantioselectivity, the reaction time had to be increased to 1 h (5% catalyst load, 73% yield, 94% *ee*) and 2 h (2% catalyst load, 70% yield, 94% *ee*) (Table 1, entries 6−8). Lowering the reaction temperature to −20 or −40 °C increased the enantioselectivity to 97% *ee* (Table 1, entries 9 and 10). Under these reaction conditions (2% catalyst load, −40 °C, toluene), we investigated changing R^1 from Me (**3a**) to Et (**3b**), ^{i}Pr (**3c**), and ^{t}Bu (**3e**). With these changes, a large increase in the reactivity was observed as the steric hindrance of R^1 increased (Table 1, entries 10−14). This could be attributed to the change in the negative charge of the α-carbon in α-diazomethylphosphonate caused by variation of R^1, which would alter the nucleophilicity to the phenyl *N*-Boc imine. With di-*tert*-butyl α-diazomethylphosphonate as the nucleophile, and a decreased reaction temperature (−60 °C), the reaction was complete within 20 min with excellent yield (91%) and enantioselectivity (>99% *ee*) (Table 1, entry 16). At −40 °C, further reductions in the catalyst load to 1%, 0.5%, 0.2%, and 0.1% were investigated. With these loadings, the reaction time had to be increased to 30 min (1%), 1 h (0.5%), 2.5 h (0.2%), and 4 h (0.1%), but the yield (91%) and enantioselectivity (>99% *ee*) remained the same (Table 1, entries 17−20). Even with reduction of the catalyst load to 0.05%, the reaction could be performed in 22 h with 93% yield and >99% *ee* (Table 1, entry 21). Various solvents, including DCM, $CHCl_3$, THF, Et_2O, CH_3CN, *m*-xylene, and toluene, were screened for the reaction, and toluene performed the best.

After establishing the optimized reaction conditions, the scope of the asymmetric Mannich reaction of di-*tert*-butyl diazomethylphosphonates and *N*-carbamoyl imines was investigated (Table 2). The reaction had a broad substrate scope, with good yields and excellent enantioselectivities achieved irrespective of the presence of electronic donating or withdrawing substituents on the aromatic ring of the imine (Table 2, entries 2−9, 11−13, and 15−16).

The substituent pattern influenced the reactivity, with *ortho* substitution decreasing the reactivity dramatically (Table 2, entries 2, 6, 10, 12, and 14). This was particularly apparent with electronic withdrawing substituents Cl and NO_2 at the *ortho* position. In these cases, even with a 5% catalyst load, only moderate yields (55% and 52%) were obtained with excellent enantioselectivity (>97% *ee*) (Table 2, entries 10 and 14). Imines substituted with naphthalene and heteroaromatics were also tested, and these were suitable for the asymmetric Mannich reactions (Table 2, entries 17−19). The furyl imine showed slightly lower reactivity, and a 1% catalyst load was required to promote the reaction (Table 2, entry 18). Benzyloxycarbonyl (Cbz) is a useful orthogonal *N*-protecting group in organic synthesis, and we investigated *N*-Cbz imines instead of *N*-Boc imines in the reaction under the same conditions. These reactions gave the desired asymmetric Mannich products in good yields and enantioselectivities (Table 2, entries 20−22). The reactivities of the *N*-Cbz

Table 2. Catalytic Asymmetric Mannich Reactions of *N*-Carbamoyl Imines with Di-*tert*-butyl α-Diazomethylphosphonate[a]



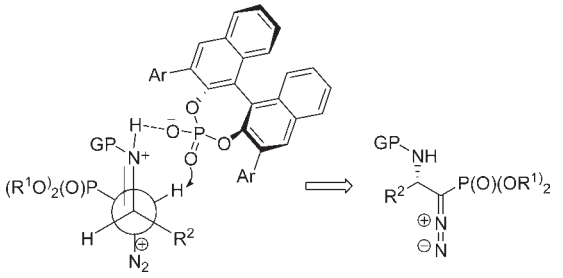
entry	R_2/PG	*t* (h)	yield (%)[b]	*ee* (%)[c]
1	Ph/Boc	4	91	>99 (*S*)
2	2-MeOC$_6$H$_4$/Boc	24	84	>99 (*S*)
3	3-MeOC$_6$H$_4$/Boc	6	90	96 (*S*)
4	4-MeOC$_6$H$_4$/Boc	1.5	87	>99 (*S*)
5	3,4-(OCH$_2$O)C$_6$H$_3$/Boc	5	87	99 (*S*)
6[d]	2-MeC$_6$H$_4$/Boc	6	97	95 (*S*)
7	3-MeC$_6$H$_4$/Boc	5	91	97 (*S*)
8	4-MeC$_6$H$_4$/Boc	2	95	>99 (*S*)
9	4-FC$_6$H$_4$/Boc	4.5	94	>99 (*S*)
10[e]	2-ClC$_6$H$_4$/Boc	48	55	98 (*S*)
11	4-ClC$_6$H$_4$/Boc	5	93	>99 (*S*)
12[e]	2-BrC$_6$H$_4$/Boc	24	81	98 (*S*)
13	4-BrC$_6$H$_4$/Boc	2	95	>99 (*S*)
14[e]	2-NO$_2$C$_6$H$_4$/Boc	48	52	97 (*S*)
15	3-NO$_2$C$_6$H$_4$/Boc	5	91	>99 (*S*)
16	4-NO$_2$C$_6$H$_4$/Boc	24	85	>99 (*S*)
17	2-Np/Boc	24	82	99 (*S*)
18[d]	2-Furyl/Boc	3	84	>99 (*S*)
19	2-Thienyl/Boc	8	94	>99 (*S*)
20	Ph/Cbz	48	87	92 (*S*)
21	4-MeOC$_6$H$_4$/Cbz	20	92	95 (*S*)
22	4-FC$_6$H$_4$/Cbz	6	86	98 (*S*)
23[f]	Ph/Boc	2	93	99 (*R*)
24[f]	4-MeOC$_6$H$_4$/Boc	2	87	>99 (*R*)
25[f]	4-NO$_2$C$_6$H$_4$/Boc	12	95	>99 (*R*)

[a] Reactions were performed with arylaldehyde *N*-carbamoyl imine (0.15 mmol) and di-*tert*-butyl α-diazomethylphosphonate (0.10 mmol) in the presence of (*R*)-**1f** (0.1%) and 4 Å MS (50 mg) in toluene (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] With 1% catalyst load. [e] With 5% catalyst load. [f] With 0.1% (*S*)-**1f** as the catalyst.

imines were lower than those of the corresponding *N*-Boc imines, and the reaction times needed to be increased (Table 2, entries 1, 4, and 9 vs 20−22). When (*S*)-**1f** was used as the catalyst, enantiomeric products were produced with excellent yields and enantioselectivities (Table 2, entries 23−25).

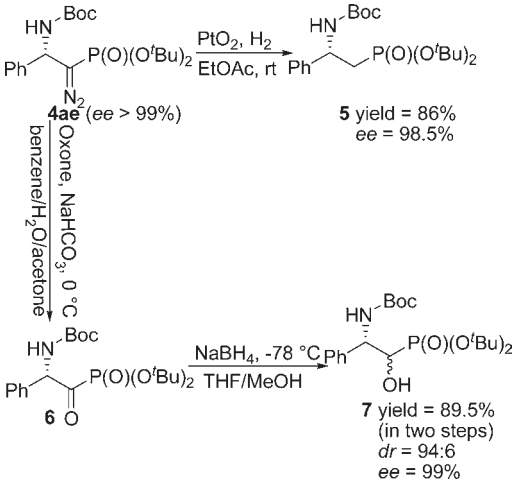
The absolute configuration of *N*-Boc-protected **4aa** was determined to be ***S*** by comparison of its HPLC retention time and optical rotation with literature data reported.[3a,b] To account for the observed outcome, the mechanism is supposed to be similar to that of the enantioselective α-substitution reaction of diazoacetate with imine catalyzed by chiral phosphoric acid proposed by Terada.[9h] A transition state model is proposed as Scheme 1. The phosphoric acid acts as a dual function catalyst with both Brønsted acid and Brønsted basic sites, the acid proton captures the nitrogen of imine through hydrogen-bonding interactions to activate it, and then the negative carbon of diazomethylphosphonate nucleophile attacks from the *Si*-face of imine; subsequently, the phosphoryl oxygen would function as a Brønsted basic site for deprotonation *via* intracomplex and give the Mannich product.

Scheme 1. Proposed a Transition State Model



To demonstrate the potential utility of β-amino-α-diazophosphonate products in organic synthesis (Scheme 2), the diazo moiety of adduct **4ae** was subjected to hydrogenation catalysis by PtO_2 under a hydrogen atmosphere. The β-*N*-Boc amino di-*tert*-butyl phosphonate ester was obtained almost without loss of enantiomeric excess. Additional deprotection of the Boc and di-*tert*-butyl ester under mildly acidic conditions gave the β-amino phosphoric acid.[7] The oxidation of the diazo moiety by oxone, and subsequent diastereoselective reduction of the carbonyl with $NaBH_4$ to hydroxyl, produced the β-*N*-Boc amino-α-hydroxyl di-*tert*-butyl phosphonate ester with good yield, diastereoselectivity, and enantioselectivity.[6a,b] This methodology provides an efficient alternative route to β-amino phosphoric acid derivatives with high optical purity and is especially important for those that cannot be derived from proteinogenic amino acids.

Scheme 2. Synthetic Utility of β-Amino-α-diazophosphonate



In conclusion, we demonstrated that chiral phosphoric acids can be used in the catalysis of the asymmetric Mannich reaction of *N*-carbamoyl imines with dialkyl diazomethylphosphonates. A highly efficient method for the synthesis of various chiral β-amino-α-diazophosphonates and their derivatives was established. Further use of these β-amino phosphoric acid derivatives in peptide mimetics is underway.

Acknowledgment. We are grateful for financial support from the National Science Foundation of China (Grant Nos. 20872120 and 21172180) and the Municipal Science Foundation of Chongqing City (Grant No. 2009BB5110).

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

The authors declare no competing financial interest.