DOI: 10.1002/adsc.200600429

Quinine-Catalyzed Enantioselective Michael Addition of Diphenyl Phosphite to Nitroolefins: Synthesis of Chiral Precursors of α-Substituted β-Aminophosphonates

Jian Wang,^a Lora D. Heikkinen,^a Hao Li,^a Liansuo Zu,^a Wei Jiang,^a Hexin Xie,^a and Wei Wang^{a,*}

^a Department of Chemistry, University of New Mexico, MSC03 2060, Albuquerque, NM 87131-0001, USA Fax: (+1)-505-277-2609; e-mail: wwang@unm.edu

Received: August 22, 2006

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A quinine-promoted, enantioselective Michael addition reaction of diphenyl phosphite with nitroalkenes has been developed. This methodology affords a facile access to enantiomerically enriched β -nitrophosphates, precursors for the preparation of synthetically and biologically useful β -aminophosphonates.

Keywords: amino acids; asymmetric catalysis; Michael addition; organic catalysis

In the recent past, the enantioselective synthesis of α and β -aminophosphonic acids has received considerable attention as a result of their increasing applications in peptide and medicinal chemistry.^[1,2] They serve as the surrogates of α - and β -amino acids in peptides and peptidomimetics with significantly improved bioactivities and stabilities and as therapeutic agents with a broad spectrum of biological activities.^[1,2] A great deal of effort has been directed toward the development of asymmetric methods for synthesis of α -aminophosphonic acids.^[1,3] In contrast, the approaches for enantioselective synthesis of β aminophosphonic acids are sparse.^[2] Among the small number of non-racemic strategies described thus far are those relying on the use of chiral precursors^[4] or auxiliaries,^[5] and enzymatic resolutions.^[6] To our knowledge, only one single enantioselective, catalytic method has been disclosed using the Sharpless asymmetric aminohydroxylation of α , β -unsaturated phosphonates.^[7] Herein, we report a new organocatalytic, enantioselective Michael addition reactions of phosphites with nitroolefins to afford β -nitrophosphonates. The Michael adducts can be conveniently transformed to chiral α -substituted β -aminophosphonic acids.

The Michael addition of phosphorus compounds to nitroolefins is a convenient method for synthesis of β -nitrophosphonates, precursors for preparation of β -aminophosphonic acids. The non-asymmetric conjugation addition processes were first reported by Pudovik et al.^[8] Yoshimura described an improved procedure for the Michael addition reaction by employing dialkyl phosphites as Michael donors.^[9] The asymmetric version of the process was recently disclosed by Enders and co-workers using TADDOL as chiral auxiliary for stereocontrol.^[10] However, a catalytic, enantioselective approach for the process has not yet been reported. The study we present here showed that it was possible to develop such a process in the presence of an organocatalyst.^[11,12]

In the exploratory study, 10 bifunctional organocatalysts, including L-proline I,^[13] L-pyrrolidinol II, (1R,2S)-ephedrine III, amine thioureas $IV^{[14]}$ and $V^{[15]}$ Cinchona alkaloids VI-X,^[16] were screened for their catalytic ability to promote the Michael addition reaction of diphenyl phosphite **1a** with *trans*-β-nitrostyrene 2a (Figure 1 and Table 1) since they had been demonstrated for the activation of nitroolefins in organocatalysis. The initial reactions were performed by using 10 mol% of the catalyst at room tmperature in Et₂O. Examination of the results revealed that their catalytic activities varied significantly (Table 1). For example, processes promoted by L-pyrrolidinol II and (1R,2S)-ephedrine III exhibited good activity (1 h and 1.5 h, respectively), but with low enantioselectivities (18% and 0% ee, respectively, Table 1, entries 2 and 3). Under the same reaction conditions, poor results were obtained for L-proline I and amine thioureas IV and V (entries 1, 4 and 5). A promising result came from the study of natural product Cinchona alkaloid quinine VI (entry 6). By using catalyst VI, reaction of diphenyl phosphite 1a with trans-\beta-nitrostyrene 2a took place to form adduct **3a** more rapidly (5 min)





Figure 1. Structures of chiral organocatalysts.

Tal	ole 1. Res	ults of exp	ploratory	stu	dies of	cata	alytic asyr	nmet-
ric	Michael	addition	reaction	of	dipher	nyl	phosphite	(1a)
wit	with <i>trans</i> - β -nitrostyrene (2a). ^[a]							

O, OPr H ^P OPr 1a	+ Ph 2a	NO ₂ 10 r	nol % catalyst Et₂O, r.t.	
Entry	Catalyst	t	Yield [%]	^[b] % $ee^{[c]}$
1	I	24 h	29	-13
2	П	1 h	93	-18
3	Ш	1.5 h	87	rac. ^[d]
4	IV	24 h	38	11
		24 h	21	-8
6	VI	5 min	88	23
7	VII	5 min	91	16
8	VIII	2 h	86	-17
9	IX	24 h	42	15
10	X	24 h	<5	n.d. ^[e]

^[a] *Reaction conditions:* see Experimental Section.

^[b] Isolated yields.

^[c] Determined by chiral HPLC analysis (Chiralpak AS-H).

^[d] Racemic.

^[e] Not determined.

 Table 2. Optimization of phosphites 1.^[a]

+ Ph NO ₂	10 mol % c	eatalyst VI	
R	t	Yield [%] ^[b]	% ee ^[c]
Ph, 1a	5 min	88	23
2-Cl-C ₆ H ₄ , 1b	48 h	37	19
$2-Me-C_6H_4$, 1c	48 h	< 5	n.d. ^[d]
$3,5-Me_2-C_6H_3$, 1d	48 h	< 5	n.d. ^[d]
Et, 1e	48 h	< 5	n.d. ^[d]
	+ Ph 2a 2a R Ph, 1a 2-Cl-C ₆ H ₄ , 1b 2-Me-C ₆ H ₄ , 1c 3,5-Me ₂ -C ₆ H ₃ , 1d Et, 1e	$\begin{array}{cccc} + & & & & & \\ & & & & \\ & & & & \\ \hline & & & &$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

^[a] Unless specified, see Experimental Section.

^[b] Isolated yields.

^[c] Determined by chiral HPLC analysis (Chiralpak AS-H).

^[d] Not determined.

albeit with poor enantioselectivity (23% ee). The encouraging outcome prompted us to carry out a more detailed investigation aimed at improving the enantioselectivity of the Michael reaction with a focus on the modification of quinine. First, a benzyl group was introduced at the position C-9 in catalyst VIII to restrict the rotation of C-4'/C-9 bond, however, no gain was observed (entry 8). Second, the results turned out to be disappointing when an acidic and a possible additional H-bonding donor C-6'-OH was incorporated into catalyst IX (entry 9), indicating an extra hydrogen bond donor affecting the reaction rate. The observation was further confirmed by cinchonidine VII catalyzed the process (entry 7). Finally, a more structurally rigid Cinchona alkaloid dimer X was surveyed with an unsatisfactory result observed as well (Table 1, entry 10). As a result, the organocatalyst **VI** proved to be of the choice for further investigation.

To further improve the enantioselectivity of the VIcatalyzed Michael reaction, we have studied the effect of nucleophilic phosphites 1 (Table 2). Among the dialkyl and diphenyl phosphites examined, diphenyl phosphite (1a) still afforded the best result (5 min, 88% yield, 23% *ee*, entry 1). If substituents (methyl group or chloride) were introduced to the 2- or 3,5positions on the phenyl rings, the reaction rates significantly decreased (entries 2–4). When the diethyl phosphite (1e) was used, the reaction also proceeded very slowly (48 h, <5% yield, entry 5).

A survey of solvents revealed that the reaction media had a significant effect on this process. For example, the reaction carried out in xylenes gave the highest enantioselectivity (42% *ee*, Table 3, entry 3). Lower enantioselectivities were observed when other solvents were used in the processes (Table 3, entries 1, 2 and 7–10). By lowering the reaction temperature, the *ee* was improved in xylenes (entries 3–6). At –55 °C, the enantioselectivity was increased to 70% *ee* (entry 6). Therefore, xylenes were selected as the

Table 3. Solvent effect on VI-catalyzed asymmetric Michael addition of diphenyl phosphite (1a) with *trans*- β -nitrostyrene (2a).^[a]

ON OPh		10 mol % catalyst VI	o OPh P−OPh
H' OPh	Ph Y	solvent, r.t.	
19	2a		Ph ~

Entry	Solvent	t	Yield [%] ^[b]	% ee ^[c]
1	Et ₂ O	5 min	88	23
2	toluene	5 min	95	30
3	xylenes	5 min	93	42
4 ^[f]	xylenes	45 min	90	52
5 ^{g]}	xylenes	8 h	86	53
6 ^{h]}	xylenes	6 days	82	70
7	$\dot{C}H_2Cl_2$	30 min	82	30
8	CH_3NO_2	8 h	88	22
9	MeOH	36 h	< 5	n.d. ^[d]
10	DMF	5 min	85	rac. ^[e]

^[a] Unless specified, see Experimental Section.

^[b] Isolated yields.

- ^[c] *ee* determined by chiral HPLC analysis (Chiralpak AS-H).
- ^[d] Not determined.

^[e] Racemic mixture.

^[f] Reaction at 0°C.

- ^[g] Reaction at -20 °C.
- ^[h] Reaction at -55 °C.

reaction medium for the processes to probe the scope of the asymmetric processes at -55 °C.

To demonstrate the generality of the VI-catalyzed Michael addition processes, reactions of a variety of nitroalkenes 2 with diphenyl phosphite 1a in xylenes were explored (Table 4). As the data show, the processes took place smoothly to give adducts 3 in moderate to good yields (60-85% yield) with moderate to high ee (45-88% ee). Analysis of these data reveals that the nature of the electronic and substitution pattern of the substituents on the aromatic rings has an impact on enantioselectivity. Reactions of nitroolefins with electron-withdrawing groups at the para-position (entries 2-4) or electron-donating substituents at the ortho-position of the phenyl ring (entries 7 and 8) occurred with relatively lower enantioselectivities (64-77% ee). However, the nitrostyrenes bearing electron-donating groups at the para-positions gave the higher ee (75-88% ee, entries 5, 6, 9 and 10). The reaction is also applicable to heterocyclic nitroolefins (entries 11 and 12) with good yields (67% and 79%, respectively) and good to high enantioselectivities (72% and 88% ee, respectively). Relatively low ee values were also observed for aliphatic nitroalkenes (45-63% ee, entries 13-16). The absolute configuration of 3k prepared under the conditions was determined by X-ray crystallography to be R (Figure 2).^[17] **Table 4.** The scope of **VI**-catalyzed asymmetric Michael addition of diphenyl phosphite (1a) to *trans*- β -nitrostyrene (2a).^[a]

OPh	NO ₂	10 mol % catalyst VI	O OPh P-OPh
H ^P OPh	+ R' ~ -	xylenes, –55 °C	
1a	2a – p		3a – p

Entry	R	t [days]	Yield [%] ^[b]	% ee ^[c]
1	Ph. 3a	6	82	70
2	4-F-C ₆ H ₄ , 3b	6	85	77
3	$4-Cl-C_{6}H_{4}, 3c$	6	82	72
4	$4-Br-C_{6}H_{4}$, 3d	6	83	66
5	4-Me- $\overset{\circ}{C_6H_4}$, 3e	6.5	83	80
6	$4-\text{MeO-C}_6\text{H}_4$, 3f	7	78	75
7 ^[d]	$2-\text{MeO-C}_6\text{H}_4$, 3g	7	77	64
8 ^[d]	$2,4-(MeO)_2-C_6H_3$, 3h	6	78	71
9 ^[d]	3-BnO-4-MeO-C ₆ H ₃ , 3i	5	82	82
$10^{[d]}$	3,4-(OCH ₂ O)-C ₆ H ₃ , 3 j	5	78	81
11	2-thiophene, 3k	7	79	88
12 ^[d]	2-furan, 3 l	6	67	72
13 ^[d]	Me_2CHCH_2 , 3m	4	77	45
14 ^[d]	$PhCH_2CH_2$, 3n	4	68	63
15 ^[d]	$n-C_5H_{11}$, 30	5	62	60
16 ^[d]	<i>n</i> -С ₆ Н ₁₃ , 3р	5	60	55

^[a] Unless specified, see Experimental Section for reaction conditions.

^[b] Isolated yields after flash chromatography.

^[c] Determined by chiral HPLC analysis (Chiralpak AS-H).

^[d] Reaction performed at -20 °C.

In a study, we demonstrated that the chiral β -nitrophosphonate **3c** could be conveniently converted to corresponding β -aminophosphonic acid **4** in a twostep transformation (Scheme 1).



Figure 2. X-ray crystal structure of 3k.

1054 asc.wiley-vch.de



Scheme 1. Synthesis of β -aminophosphonic acid 4 from β -nitrophosphonate 3c.



Figure 3. Proposed a transition state model.

Our preliminary understanding of this enantioselective Michael addition reaction invokes H-bonding interaction between both substrates and the catalyst **VI** (Figure 3). In this proposed simple transition state (TS) model, the *trans*- β -nitrostyrene is activated by the OH group of the catalyst. Meanwhile, the amino moiety *via* the second H-bonding interaction activates and directs the phosphite group for *si* face attack of the *trans*- β -nitrostyrene, which affords the observed (S) product.

In summary, the first small molecule quinine **VI** catalyzed enantioselective conjugate addition of diphenyl phosphite to nitroolefins has been developed. This methodology provides a general and convenient access to a wide range of good to high enantiomerically enriched β -nitrophosphates, precursors for preparation of synthetically and biologically useful β -aminophosphonates. Further investigation of the full scope of the Michael reaction, its mechanism and applications are underway in our laboratory and the results will be reported in due course.

Experimental Section

Typical Procedure (Table 4, entry 1)

Catalyst quinine (VI) (8 mg, 0.025 mmol) was added to a vial containing xylenes (3 mL), diphenyl phosphite (1a) (52.5 μ L, 0.25 mmol) and *trans*- β -nitrostyrene (2a) (38 mg, 0.25 mmol) at -55 °C. After 6 days of stirring, TLC analysis indicated completion of the reaction. The reaction mixture was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ethyl acetate/hexane= 1:15 to 1:4) to afford the adduct **3a** as a white solid; yield: 79 mg (82%) with 70% *ee*, determined by HPLC (Chiralpak

AS-H, 2-propanol/hexane = 40/60, flow rate 0.5 mL min⁻¹, $\lambda = 254$ nm): t_{minor} = 12.6 min, t_{major} = 17.2 min, *ee* = 70 %; [α]_D²⁵ (major): = -9.7 (*c* 1.0 in CHCl₃).

Acknowledgements

The financial support for this research by the Department of Chemistry and the Research Allocation Committee, University of New Mexico, NIH-INBRE (P20 RR016480) and the American Chemical Society-PRF (G1 type) is gratefully acknowledged.

References

- For reviews of syntheses and applications of α-aminophosphonic acids, see: a) S. Hannour, A. Ryglowski, M. L. Roumestant, P. Viallefont, J. Martinez, F. Ouazzani, A. El Hallaoui, *Phosphorus, Sulfur Silicon* 1998, 419; b) I. M. Lefebvre, S. A. Evans, *Phosphorus, Sulfur Silicon* 1999, 397; c) H. Groger, B. Hammer, *Chem. Eur. J.* 2000, 6, 943.
- [2] For reviews of syntheses and applications of β-amino-phosphonic acids, see: a) F. Palacios, C. Alonso, J. M. De Los Santos, in: *Enantioselective Synthesis of β-Amino Acids*, 2nd edn., (Eds.: E. Juaristi, V. A. Soloshonok), John Wiley & Sons, Inc., Hoboken, N. J., 2005, p 277; b) F. Palacios, C. Alonso, J. M. De Los Santos, *Chem. Rev.* 2005, 105, 899.
- [3] For recent selected examples of asymmetic synthesis of α-aminophosphonic acids, see: a) A. B. Smith, III, K. M. Yager, C. M. Taylor, J. Am. Chem. Soc. 1995, 117, 10879; b) F. A. Davis, S. Lee, H. Yan, D. D. Titus, Org. Lett. 2001, 3, 1757; c) G. D. Joly, E. N. Jacobsen, J. Am. Chem. Soc. 2004, 126, 4102; d) S. Kobayashi, H. Kiyohara, Y. Nakamura, R. Matsubara, J. Am. Chem. Soc. 2004, 126, 6558; e) T. Akiyama, H. Morita, J. Itoh, K. Fuchibe, Org. Lett. 2005, 7, 2583.
- [4] a) M. M. Campbell, N. I. Carruthers, S. J. Mickel, *Tetrahedron* 1982, 38, 2513; b) M. E. Duggan, D. S. Karanewsky, *Tetrahedron Lett.* 1983, 43, 2935; c) L. D. Arnold, T. Kalantar, J. D. Vederas, J. Am. Chem. Soc. 1985, 107, 7105; d) T. Yokomatsu, T. Yamagishi, S. Shibuya, *Tetrahedron: Asymmetry* 1993, 4, 1401; e) F. Palacios, A. M. Ochoa de Retana, J. I. Gil, *Tetrahedron Lett.* 2000, 41, 5363; f) C. de Risi, A. Dondoni, D. Perrone, G. P. Pollini, *Tetrahedron Lett.* 2001, 42, 3033; g) F. Palacios, D. Aparicio, A. M. Ochoa de Retana, J. M. De Los Santos, J. I. Gil, R. Lopez de Munain, *Tetrahedron: Asymmetry* 2003, 14, 689.

- [5] a) V. A. Soloshonok, Y. N. Belokon, N. A. Kuzmina, V. I. Maleev, N. Y. Svistunova, V. A. Solodenko, V. P. Kukhar, J. Chem. Soc., Perkin Trans. 1 1992, 1525; b) S. Hanessian, Y. L. Bennani, Y. Hervé, S ynlett 1993, 35; c) F. A. Davis, T. Ramachandarf, Y.-D. Wu, J. Org. Chem. 2003, 68, 6894.
- [6] C. Yuan, C. Xu, Y. Zhang, Tetrahedron 2003, 59, 6095.
- [7] A. A. Thomas, K. B. Sharpless, J. Org. Chem. 1999, 64, 8379.
- [8] A. N. Pudovik, F. N. Siditikova, Dokl. Akad. Nauk. SSSR 1959, 125, 826.
- [9] C. Shin, Y. Yonezawa, K. Katayama, J. Yoshimura, Bull. Chem. Soc. Jpn. 1973, 46, 1727.
- [10] D. Enders, L. Tedeschi, J. W. Bats, Angew. Chem. 2000, 39, 4605; D. Enders, L. Tedeschi, J. W. Bats, Angew. Chem. Int. Ed. 2000, 39, 4605.
- [11] For recent reviews of asymmetric Michael addition reactions, see: a) M. Sibi, S. Manyem, *Tetrahedron* 2001, 56, 8033; b) N. Krause, A. Hoffmann-Röder, *Synthesis* 2001, 171; c) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* 2002, 1877; d) J. Christoffers, A. Baro, *Angew. Chem.* 2003, *115*, 1726; J. Christoffers, A. Baro, *Angew. Chem. Int. Ed.* 2003, *42*, 1688; e) P. I. Dalko, L. Moisan, *Angew. Chem.* 2004, *116*, 5248; P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* 2004, *43*, 5138;.
- [12] For selected examples of organocatalyzed asymmetric Michael addition of nitroolefins, see: a) B. List, P. Pojarliev, H. J. Martin, Org. Lett. 2001, 3, 2423; b) D. Enders, A. Seki, Synlett 2002, 26; c) O. Andrey, A. Alexakis, G. Bernardinelli, Org. Lett. 2003, 5, 2559; d) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas, III, Org. Lett. 2004, 6, 2527; e) J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka, C. F. Barbas, III, Synthesis 2004, 1509; f) T. Ishii, S. Fiujioka, Y. Sekiguchi, H. Kotsuki, J. Am. Chem. Soc. 2004, 126, 9558; g) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, Chem. Commun. 2004, 1808; h) Y. Hayashi, T. Gotoh, T. Hayasji, M. Shoji, Angew. Chem. 2005, 117, 4284; Y. Hayashi, T. Gotoh, T. Hayasji, M. Shoji, Angew. Chem. Int. Ed. 2005, 44, 4212; i) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, Angew. Chem. 2005, 117, 6734; R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, Angew. Chem. Int. Ed. 2005, 44, 6576; j) S. B. Tsogoevam, D. A. Yalalov, M. J. Hateley,

C. Weckbecker, K. Huthmacher, Eur. J. Org. Chem.
2005, 4995; k) S. H. McCooey, S. J. Connon, Angew.
Chem. 2005, 117, 6525; S. H. McCooey, S. J. Connon, Angew. Chem. Int. Ed. 2005, 44, 6367; l) J. Ye, D. J. Dixon, P. S. Hynes, Chem. Commun. 2005, 4481; m) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, Li. Deng, Angew. Chem. 2005, 117, 107; H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, Li. Deng, Angew. Chem. Int. Ed. 2005, 44, 105; n) Y.-M. Xu, W.-B. Zou. H. Sunden, I. Ibrahem, A. Córdova, Adv. Synth. Catal. 2006, 348, 418; o) W. Wang, J. Wang, H. Li, Angew. Chem. Int. Ed. 2005, 44, 1369 and J. Wang, H. Li, B.-S. Lou, L.-S. Zu, H. Guo, W. Wang, Chem. Eur. J. 2006, 12, 4321.

- [13] B. List, Tetrahedron 2002, 58, 5573.
- [14] For recent reviews of thioureas catalyzed reactions, see: a) P. R. Schreiner, *Chem. Soc. Rev.* 2003, 32, 289; b) Y. Takemoto, *Org. Biomol. Chem.* 2005, 3, 4299; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* 2006, 45, 1520; d) B. List, *Chem. Commun.* 2006, 819; e) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* 2006, 348, 999; f) S. J. Connon, *Chem. Eur. J.* 2006, 12, 5418; g) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* 2006, 45, 7496; examples of thioureas catalyzing reactions, see: h) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* 2003, 125, 12672; i) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* 2004, 6, 625.
- [15] a) B. Vakulya, S. Varga, A. Csampai, T. Soós, *Org. Lett.* **2005**, *7*, 1967; b) L. Bernardi, F. Fini, R. P. Herrera, A. Ricci, V. Sgarzani, *Tetrahedron* **2006**, *62*, 375.
- [16] A review of *Cinchona* alkaloids catalyzing reactions, see: a) S.-K. Tian, Y.-G. Chen, J.-F. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* 2004, *37*, 621; recent selected examples of cinchona alkaloids catalyzing reactions, see: b) S. Lou, B. M. Tkoka, M. Ting, S. E. Schaus, *J. Am. Chem. Soc.* 2005, *127*, 11256; c) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* 2006, 1191; d) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* 2006, *128*, 6049.
- [17] CCDC-618770 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk.