

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

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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 temperature 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*- β -nitrostyrene **2a** took place to form adduct **3a** more rapidly (5 min)

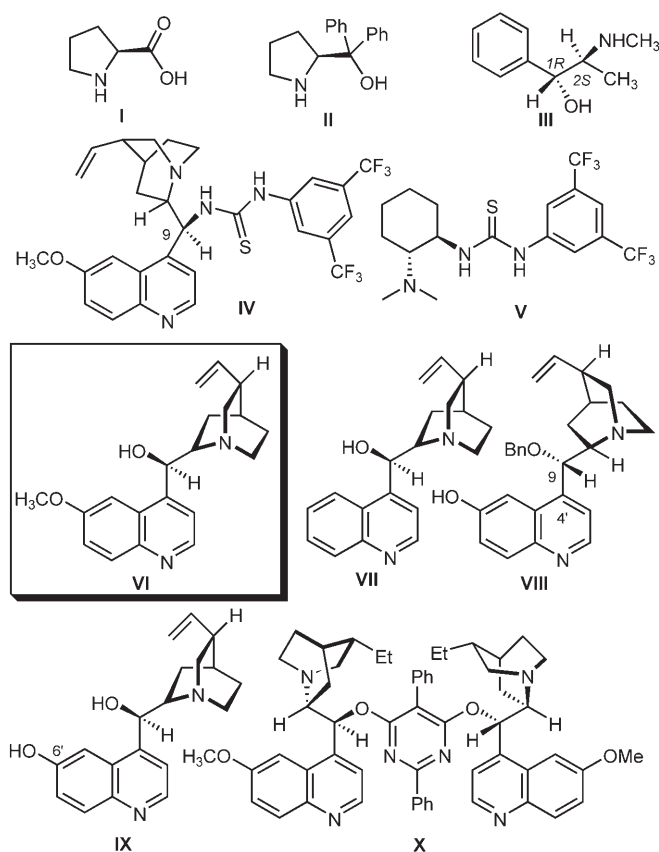


Figure 1. Structures of chiral organocatalysts.

Table 1. Results of exploratory studies of catalytic asymmetric Michael addition reaction of diphenyl phosphite (**1a**) with *trans*- β -nitrostyrene (**2a**).^[a]

Entry	Catalyst	<i>t</i>	Yield [%] ^[b]	% <i>ee</i> ^[c]
1	I	24 h	29	−13
2	II	1 h	93	−18
3	III	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]

Entry	R	<i>t</i>	Yield [%] ^[b]	% <i>ee</i> ^[c]
1	Ph, 1a	5 min	88	23
2	2-Cl-C ₆ H ₄ , 1b	48 h	37	19
3	2-Me-C ₆ H ₄ , 1c	48 h	<5	n.d. ^[d]
4	3,5-Me ₂ -C ₆ H ₃ , 1d	48 h	<5	n.d. ^[d]
5	Et, 1e	48 h	<5	n.d. ^[d]

^[a] Unless specified, see Experimental Section.

^[b] Isolated yields.

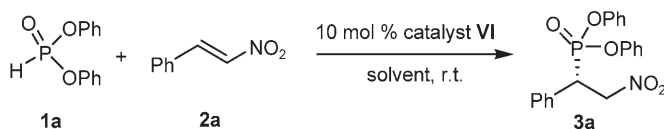
^[c] Determined by chiral HPLC analysis (Chiralpak AS-H).

^[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 **VI**-catalyzed 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 3,5-positions 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

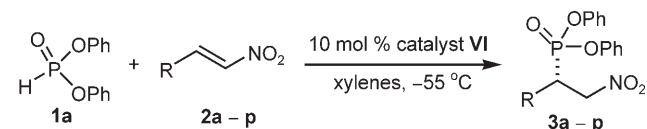
Table 3. Solvent effect on **VI**-catalyzed asymmetric Michael addition of diphenyl phosphite (**1a**) with *trans*- β -nitrostyrene (**2a**).^[a]

Entry	Solvent	<i>t</i>	Yield [%] ^[b]	% <i>ee</i> ^[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	CH ₂ Cl ₂	30 min	82	30
8	CH ₃ NO 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.

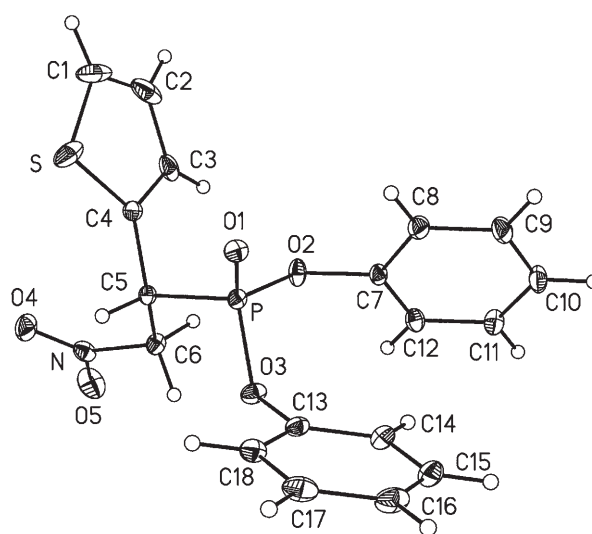
To demonstrate the generality of the **VI**-catalyzed Michael addition processes, reactions of a variety of nitroalkenes **2** with diphenyl phosphite **1a** in xylenes were explored (Table 4). As the data show, the processes took place smoothly to give adducts **3** in moderate to good yields (60–85% 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]

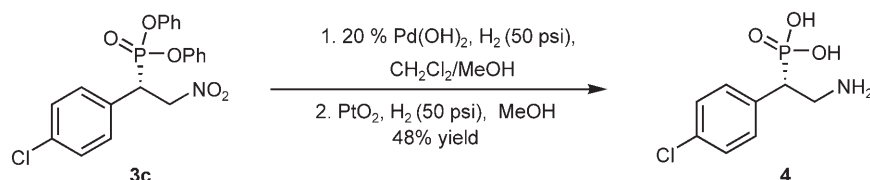
Table 4. The scope of **VI**-catalyzed asymmetric Michael addition of diphenyl phosphite (**1a**) to *trans*- β -nitrostyrene (**2a**).^[a]

Entry	R	<i>t</i> [days]	Yield [%] ^[b]	% <i>ee</i> ^[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-C ₆ H ₄ , 3e	6.5	83	80
6	4-MeO-C ₆ H ₄ , 3f	7	78	75
7 ^[d]	2-MeO-C ₆ H ₄ , 3g	7	77	64
8 ^[d]	2,4-(MeO) ₂ -C ₆ H 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 , 3j	5	78	81
11	2-thiophene, 3k	7	79	88
12 ^[d]	2-furan, 3l	6	67	72
13 ^[d]	Me ₂ CHCH ₂ , 3m	4	77	45
14 ^[d]	PhCH ₂ CH ₂ , 3n	4	68	63
15 ^[d]	<i>n</i> -C ₅ H ₁₁ , 3o	5	62	60
16 ^[d]	<i>n</i> -C ₆ H ₁₃ , 3p	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 two-step transformation (Scheme 1).

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



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

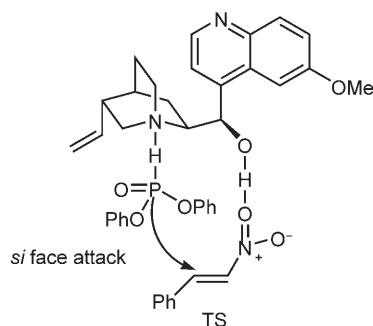


Figure 3. Proposed a transition state model.

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} , $\lambda = 254 \text{ nm}$: $t_{\text{minor}} = 12.6 \text{ min}$, $t_{\text{major}} = 17.2 \text{ min}$, *ee* = 70%; $[\alpha]_{\text{D}}^{25}$ (major): -9.7 (*c* 1.0 in CHCl_3).

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- [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.