Highly Enantioselective Michael Addition of α-Substituted Nitrophosphonates to a Vinyl Sulfone

Guo-Ying Chen, Yixin Lu*

Department of Chemistry & Medicinal Chemistry Program, Life Sciences Institute, National University of Singapore, 3 Science Drive 3, Singapore 117543, Republic of Singapore
Fax +65(6779)1691; E-mail: chmlyx@nus.edu.sg

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Abstract: Organocatalytic asymmetric Michael reaction of α-substituted nitrophosphonates to phenyl vinyl sulfone catalyzed by cinchona alkaloid-derived tertiary amine-thioureas afforded α,α-disubstituted nitrophosphonates in very good yields and excellent enantiomeric excesses.

Key words: thiourea, Michael Addition, cinchona alkaloid, vinyl sulfone, nitrophosphonate

α-Aminophosphonic acids, as structural and functional surrogates of α-amino acids, were first investigated in the 1940s.[1] Subsequently, the biological activities and medicinal applications of α-aminophosphonic acids were revealed, which made them interesting targets in organic synthesis.[2] The catalytic asymmetric synthesis of α-aminophosphonic acids was mainly focused on the C–C, C–N, and C–P bond forming reactions.[3] However, asymmetric synthesis of α-aminophosphonic acids containing a quaternary α-carbon center has been explored to a much less extent.

α-Nitrophosphonates have been used as a precursor of α-aminophosphonic acids in recent years. In particular, use of α-substituted α-nitrophosphonates conveniently leads to the formation of α-aminophosphonic acids with a quaternary α-carbon center. In 2008, Johnston reported highly diastereoselective and enantioselective additions of α-nitrophosphonates to imines catalyzed by a chiral Brønsted acid, which serves as a concise route to α-substituted α,β-diaminophosphonic acids.[4] Very recently, Namboothiri et al. disclosed an enantioselective Michael addition of α-substituted α-nitrophosphonates to enones, and the α-aminophosphonates were prepared for the first time.[5] Shortly after, Mukherjee and co-workers reported an asymmetric Michael reaction of α-substituted nitrophosphonate and nitroolefins, generating chiral α,γ-diaminophosphonic acid precursors with contiguous quaternary and tertiary stereocenters.[6]

Vinyl sulfones are useful acceptors in conjugate additions. They are particularly valuable in organic synthesis due to the powerful electron-withdrawing nature of the sulfone functionality, and a variety of well-established post-synthetic manipulations of the sulfone group.[7] Our research group has recently developed a number of asymmetric organocatalytic conjugate additions by employing vinyl sulfones as Michael acceptors.[8] We envisioned that a conjugate addition of α-substituted α-nitrophosphonates to vinyl sulfones may provide a straightforward method to access α,α-dialkyl-substituted aminophosphonic acids, which are interesting molecules in medicinal chemistry.[2] Herein, we document the first organocatalytic asymmetric Michael addition of α-substituted nitrophosphonates to a vinyl sulfone.

To promote the projected Michael addition of α-nitrophosphonates in an asymmetric manner, chiral bifunctional tertiary amines with a suitable Brønsted acid moiety seem to be excellent choices. The catalysts investigated in this study are illustrated in Figure 1. We chose the conjugate addition of nitrophosphonate **1a** to phenyl vinyl sulfone (**2**) in toluene as a model reaction to evaluate the catalytic effects of different bifunctional tertiary amine catalysts. All cinchona alkaloid derived tertiary amine-thiourea catalysts were found to be effective, affording the desired adducts in excellent yields and very good enantioselectivities (Table 1, entries 1–4). While sulfonamide-containing catalyst **C5** afforded the products in excellent ee and slightly decreased chemical yield (entry 5), catalyst **C6** with a guanidine group[9] turned out to be less efficient (entry 6). Overall, tertiary amine-thiourea catalysts clearly performed best for the Michael reaction investigated. Solvent screening was then carried out (entries 7–11), and toluene remained to be the solvent of choice for the reaction. When the reaction of phosphonate **1a** and phenyl vinyl sulfone (**2**) was performed in toluene in the presence of quinidine-derived **C1**, adduct **3a** was obtained in 98% yield and with 96% ee.

With the optimized conditions in hand, the substrate scope was next explored, and the results are summarized in Table 2. In general, the reaction tolerated well with different α-alkyl-substituted α-nitrophosphonates. The reaction was applicable to the nitrophosphonates with an ethyl, a propyl, and a pentyl group at the α-position, and the adducts were obtained in nearly quantitative yields, and excellent enantiomeric excesses (Table 2, entries 1–4). When the size of the alkyl substituent at the α-position was further increased, the enantioselectivity of the reaction was maintained, and chemical yield of the addition was decreased (entry 5). When α-benzyl-substituted nitrophosphonate was employed, the desired Michael addition product was obtained in moderate yield, and with slightly

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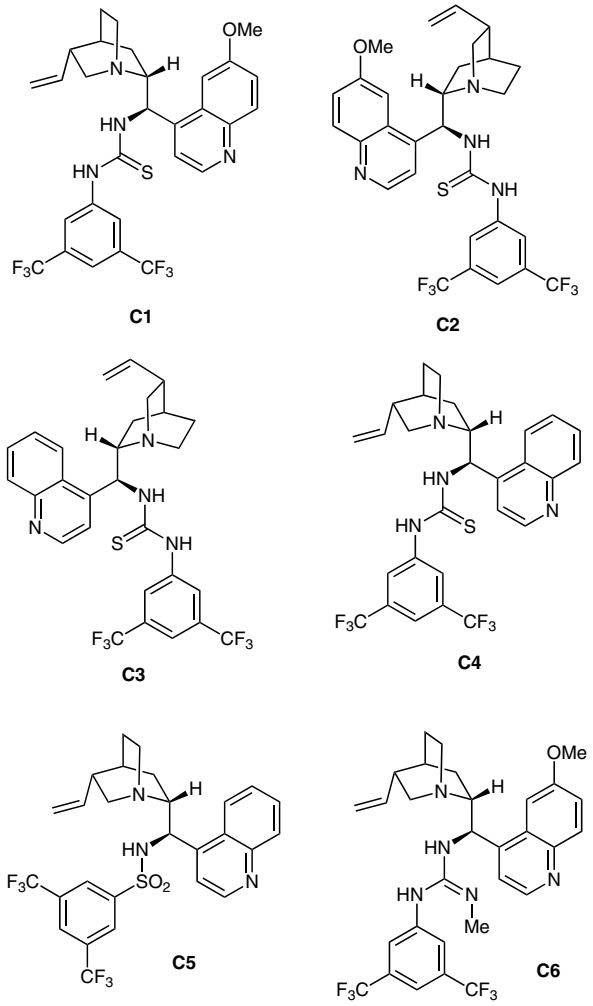
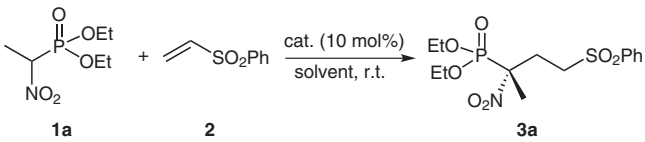


Figure 1 Tertiary amine catalysts derived from cinchona alkaloids

decreased enantiomeric excess (entry 6). When branched alkyl substituent was introduced to the nitrophosphonate, the reaction had to be run at higher temperature for a longer reaction time; the corresponding product could still be obtained in moderate yield and excellent ee (entry 7). However, the *tert*-butyl-substituted nitrophosphonate was unsuitable for the reaction, presumably due to the large steric hindrance introduced by the *tert*-butyl group (entry 8). Equally excellent results were obtained when the reaction was performed at a larger scale (entries 9, 10). The absolute configurations of the products were assigned based on the X-ray crystallographic structure[10] of **3a** (Figure 2).

In conclusion, we have developed the first asymmetric Michael reaction of α-substituted nitrophosphonates to a vinyl sulfone catalyzed by tertiary-amine thiourea catalysts derived from cinchona alkaloids. The desired Michael adducts were prepared in moderate to high chemical yields, and with excellent enantiomeric excesses. The reported method is simple and efficient, representing a promising approach to asymmetric synthesis of α-aminophosphonic acids.

Table 1 Conjugate Addition of Phosphonate **1a** to Phenyl Vinyl Sulfone (**2**) Catalyzed by Bifunctional Tertiary Amines[a]



1a **2** **3a**

Entry	Cat.	Solvent	Yield (%)[b]	ee (%)[c]
1	**C1**	toluene	98	96
2	**C2**	toluene	87	92
3	**C3**	toluene	98	89
4	**C4**	toluene	91	94
5	**C5**	toluene	81	94
6	**C6**	toluene	76	65
7	**C1**	xylenes	98	96
8	**C1**	THF	99	92
9	**C1**	Et_2O	84	92
10	**C1**	CH_2Cl_2	80	94
11	**C1**	$CHCl_3$	91	94

[a] Reactions were performed with nitrophosphonate **1a** (0.025 mmol), phenyl vinyl sulfone (**2**; 0.025 mmol), and the catalyst (0.0025 mmol) in the solvent specified (0.10 mL) at r.t. for 24 h.
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral stationary phase.

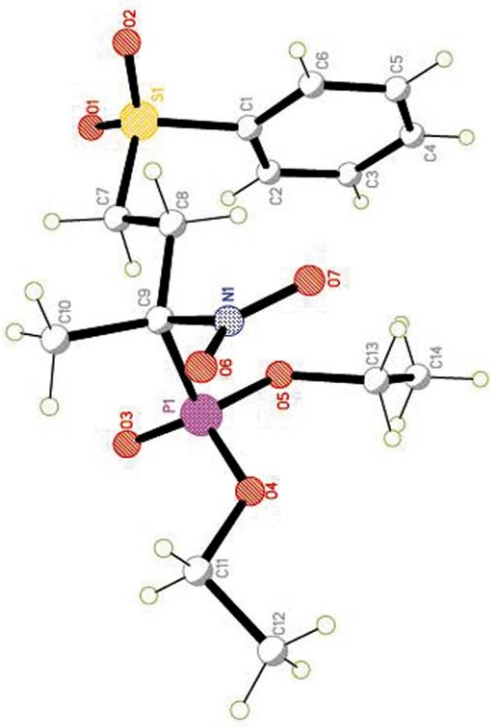
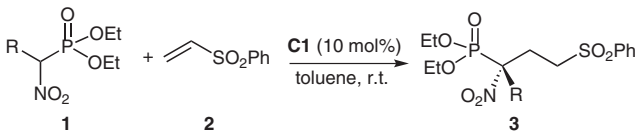


Figure 2 X-ray crystal structure of **3a**

Table 2 The Scope of the Reaction[a]



1 2 3

Entry	Product (R)	Yield (%)[b]	ee (%)[c]
1	**3a** (Me)	98	96
2	**3b** (Et)	98	96
3	**3c** (*n*-Pr)	98	94
4	**3d** (C_5H_{11})	98	94
5	**3e** (C_9H_{19})	65	92
6	**3f** (Bn)	53	86
7[d]	**3g** (*i*-Pr)	50	92
8	**3h** (*t*-Bu)	–[e]	–[e]
9[f]	**3a** (Me)	98	96
10[f]	**3b** (Et)	95	96
11[f]	**3d** (C_5H_{11})	92	94

[a] Reactions were performed with nitrophosphonate **1** (0.025 mmol), phenyl vinyl sulfone (**2**; 0.025 mmol), and **C1** (0.0025 mmol) in toluene (0.10 mL) at r.t. for 24 h.
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] The reaction was performed at 50 °C for 48 h.
[e] No reaction was observed.
[f] Reactions were performed with nitrophosphonate **1** (0.1 mmol), phenyl vinyl sulfone (**2**; 0.1 mmol), and **C1** (0.01 mmol) in toluene (0.2 mL) at r.t. for 24 h.

All the starting materials were obtained from commercial sources and used without further purification, unless otherwise stated. Toluene, THF, and Et_2O were dried and distilled from sodium benzophenone ketyl prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF 300 or AMX 500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton ($CHCl_3$, δ = 7.26), carbon ($CHCl_3$, δ = 77.0). Standard abbreviations for multiplicities were used in the ^1H NMR assignments. Coupling constants were reported in Hertz (Hz). Low-resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in FAB mode. All high-resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For TLC, Merck precoated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Flash chromatographic separations were performed on Merck 60 (0.040–0.063 mm mesh) silica gel. The enantiomeric excesses of products were determined by HPLC analysis on a chiral stationary phase. The nitrophosphonates utilized in the study were synthesized according to the literature procedure,[4] and the thiourea catalysts were also prepared following the literature procedures.[11]

Michael Addition of Nitrophosphonate 1a to Phenyl Vinyl Sulfone (2); Diethyl (*R*)-[2-Nitro-4-(phenylsulfonyl)butan-2-yl]phosphonate (3a); Typical Procedure

To a mixture of nitrophosphonate **1a** (5.3 mg, 0.025 mmol) and phenyl vinyl sulfone **2** (4.2 mg, 0.025 mmol) in toluene (0.1 mL) at r.t. was added the catalyst **C1** (1.5 mg, 0.0025 mmol). The reaction mixture was then stirred for 24 h. The solvent was removed, and the residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 5:1 to 1:1) to afford product **3a** as a colorless solid; yield: 9.3 mg (98%).

HPLC analysis: Daicel Chiralpak IC, *n*-hexane–*i*-PrOH (90:10), 1.0 mL/min, λ = 254 nm, t_R (major) = 47.8 min, t_R (minor) = 72.3 min; 96% ee.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.0 Hz, 6 H), 1.78 (d, *J* = 14.5 Hz, 3 H), 2.51–2.69 (m, 2 H), 3.21–3.31 (m, 2 H), 4.15–4.24 (m, 4 H), 7.58–7.61 (m, 2 H), 7.67–7.71 (m, 1 H), 7.91–7.93 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3, 20.9, 29.0, 51.1, 51.2, 64.5, 64.6, 64.7, 64.8, 87.5, 88.7, 128.1, 129.5, 134.1, 138.5.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{23}NO_7PS$ $[M + H]^+$: 380.0927; found: 380.0933.

Diethyl (*R*)-[3-Nitro-1-(phenylsulfonyl)pentan-3-yl]phosphonate (3b)

Yield: 9.3 mg (98%); colorless oil.

HPLC analysis: Daicel Chiralpak IA, *n*-hexane–*i*-PrOH (90:10), 1.0 mL/min, λ = 254 nm, t_R (major) = 11.1 min, t_R (minor) = 13.0 min; 96% ee.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.0 Hz, 3 H), 1.32–1.34 (m, 6 H), 2.04–2.14 (m, 1 H), 2.32–2.45 (m, 2 H), 2.62–2.73 (m, 1 H), 3.37–3.45 (m, 2 H), 4.10–4.24 (m, 4 H), 7.58–7.61 (m, 2 H), 7.66–7.70 (m, 1 H), 7.93–7.94 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.86, 7.93, 16.3, 26.2, 29.2, 51.6, 64.1, 64.2, 64.7, 64.8, 91.7, 92.9, 128.1, 129.4, 134.0, 138.7.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{25}NO_7PS$ $[M + H]^+$: 394.1084; found: 394.1088.

Diethyl (*R*)-[3-Nitro-1-(phenylsulfonyl)hexan-3-yl]phosphonate (3c)

Yield: 9.9 mg (98%); colorless oil.

HPLC analysis: Daicel Chiralpak IA, *n*-hexane–*i*-PrOH (90:10), 1.0 mL/min, λ = 254 nm, t_R (major) = 10.3 min, t_R (minor) = 12.1 min; 94% ee.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3 H), 1.22–1.43 (m, 8 H), 1.93–2.08 (m, 1 H), 2.20–2.30 (m, 1 H), 2.40–2.45 (m, 1 H), 2.62–2.72 (m, 1 H), 3.40–3.43 (m, 2 H), 4.15–4.22 (m, 4 H), 7.58–7.61 (m, 2 H), 7.67–7.70 (m, 1 H), 7.92–7.93 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 16.3, 16.7, 16.8, 26.6, 37.7, 51.7, 64.2, 64.7, 64.8, 91.3, 92.5, 128.1, 129.4, 134.0, 138.7.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{27}NO_7PS$ $[M + H]^+$: 408.1240; found: 408.1240.

Diethyl (*R*)-[3-Nitro-1-(phenylsulfonyl)octan-3-yl]phosphonate (3d)

Yield: 10.7 mg (98%); colorless oil.

HPLC analysis: Daicel Chiralpak IA, *n*-hexane–*i*-PrOH (90:10), 1.0 mL/min, λ = 254 nm, t_R (major) = 9.2 min, t_R (minor) = 10.7 min; 94% ee.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3 H), 1.13–1.42 (m, 12 H), 1.97–2.05 (m, 1 H), 2.19–2.45 (m, 2 H), 2.63–2.73 (m, 1 H), 3.38–3.45 (m, 2 H), 4.12–4.22 (m, 4 H), 7.58–7.61 (m, 2 H), 7.67–7.70 (m, 1 H), 7.92–7.93 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 16.3, 22.1, 22.8, 26.5, 31.4, 35.6, 51.6, 51.7, 64.2, 64.7, 64.8, 91.3, 92.5, 128.1, 129.4, 134.0, 138.7.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{31}NO_7PS$ [M + H]$^+$: 436.1533; found: 436.1547.

Diethyl (*R*)-[3-Nitro-1-(phenylsulfonyl)dodecan-3-yl]phosphonate (3e)
Yield: 12.0 mg (98%); colorless oil.

HPLC analysis: Daicel Chiralpak IA, *n*-hexane–*i*-PrOH (90:10), 1.0 mL/min, λ = 254 nm, t_R (major) = 9.7 min, t_R (minor) = 11.9 min; 92% ee.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.13–1.41 (m, 20 H), 1.99–2.02 (m, 1 H), 2.25–2.29 (m, 1 H), 2.38–2.43 (m, 1 H), 2.64–2.70 (m, 1 H), 3.40–3.41 (m, 2 H), 4.12–4.22 (m, 4 H), 7.58–7.61 (m, 2 H), 7.67–7.70 (m, 1 H), 7.92–7.93 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 16.3, 22.6, 23.1, 23.2, 26.5, 29.1, 29.3, 31.8, 35.7, 51.6, 64.2, 64.7, 64.8, 91.3, 92.5, 128.1, 129.4, 134.0, 138.6.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{39}NO_7PS$ [M + H]$^+$: 492.2179; found: 492.2183.

Diethyl (*R*)-[2-Nitro-1-phenyl-4-(phenylsulfonyl)butan-2-yl]phosphonate (3f)
Yield: 6.3 mg (53%); colorless oil.

HPLC analysis: Daicel Chiralpak IA, *n*-hexane–*i*-PrOH (90:10), 1.0 mL/min, λ = 254 nm, t_R (major) = 13.6 min, t_R (minor) = 14.6 min; 92% ee.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30–1.34 (m, 6 H), 2.23–2.41 (m, 2 H), 3.16–3.20 (m, 1 H), 3.27–3.34 (m, 1 H), 3.50–3.56 (m, 1 H), 3.72–3.77 (m, 1 H), 4.17–4.27 (m, 4 H), 6.98–6.70 (m, 2 H), 7.23–7.27 (m, 3 H), 7.47–7.50 (m, 2 H), 7.58–7.60 (m, 1 H), 7.78–7.80 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 26.7, 42.5, 51.5, 64.1, 65.0, 92.3, 92.5, 127.9, 128.1, 128.6, 129.1, 129.7, 131.7, 131.8, 133.7, 138.2.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{26}NO_7PS$ + Na [M + Na]$^+$: 478.1060; found: 478.1057.

Diethyl (*S*)-[4-Methyl-3-nitro-1-(phenylsulfonyl)pentan-3-yl]phosphonate (3g)
Yield: 5.1 mg (50%); colorless oil.

HPLC analysis: Daicel Chiralpak IA, *n*-hexane–*i*-PrOH (90:10), 1.0 mL/min, λ = 254 nm, t_R (major) = 17.8 min, t_R (minor) = 21.3 min; 92% ee.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 7.0 Hz, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 1.29–1.35 (m, 6 H), 1.78 (d, *J* = 14.5 Hz, 3 H), 2.28–2.35 (m, 1 H), 2.44–2.56 (m, 1 H), 2.82–2.90 (m, 1 H), 3.41–3.54 (m, 2 H), 4.10–4.27 (m, 4 H), 7.58–7.61 (m, 2 H), 7.67–7.70 (m, 1 H), 7.93–7.95 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3, 17.2, 17.3, 18.2, 36.6, 51.8, 64.2, 64.4, 128.0, 129.4, 133.9.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{27}NO_7PS$ [M + H]$^+$: 408.1240; found: 408.1240.

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