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Enantioselective Synthesis of Quaternary α-Aminophosphonates via Conjugate Addition of α-Nitrophosphonates to Enones§

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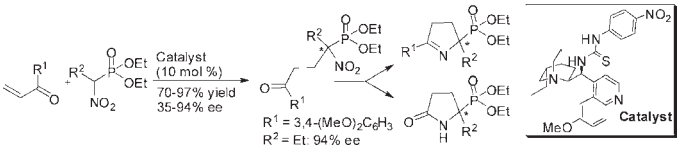
ABSTRACT



Enantioselective Michael addition of α-nitrophosphonates to enones for the synthesis of α-aminophosphonates is reported for the first time. The reaction proceeds in good to high yields and moderate to high selectivity in the presence of a new quinine thiourea catalyst. The quaternary nitrophosphonates were conveniently transformed to cyclic quaternary α-aminophosphonates via in situ reduction–intramolecular cyclization or Baeyer–Villiger oxidation followed by in situ reduction–intramolecular cyclization.

α-Aminophosphonic acids, investigated for the first time by Chavane[1] in the 1940s, are isosteric analogs of α-amino acids due to their ability to mimic the tetrahedral transition states of peptide bond hydrolysis. This property is often exploited in the development of novel protease inhibitors.[2] The antibacterial[3] and antifungal[4] properties of α-aminophosphonic acids as well as their presence in the biologically active natural product K-26[5] also distinguish them as an attractive class of compounds in medicinal chemistry. Among the aminophosphonates,[6] α-aminophosphonates[7] received greater attention as compared to their β-[8] and γ-analogs.[9] Recently, α-aminophosphonates have been employed as organocatalysts in asymmetric aldol and Michael additions.[10]

Since the biological activity of α-aminophosphonates hinges in large measure on the stereochemistry at the

§ Dedicated to Prof. S. N. Balasubrahmanyam on the occasion of his 80th birthday.

(1) Chavane, V. *Bull. Soc. Chim. Fr.* **1948**, *15*, 774.

(2) (a) Kaplan, A. P.; Bartlett, P. A. *Biochemistry* **1991**, *30*, 8165. (b) Beers, S. A.; Schwender, C. F.; Loughney, D. A.; Malloy, E.; Demarest, K.; Jordan, J. *J. Bioorg. Med. Chem.* **1996**, *4*, 1693. For selected reviews: (c) Mucha, A.; Kafarski, P.; Berlicki, Y. *J. Med. Chem.* **2011**, *54*, 5955. (d) Sienczyk, M.; Oleksyszyn, J. *Curr. Med. Chem.* **2009**, *16*, 1673.

(3) (a) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56. (b) Pratt, R. F. *Science* **1989**, *246*, 917.

(4) Maier, L.; Diel, P. J. *Phosphorus Sulfur Silicon* **1991**, *57*, 57.

(5) (a) Yamato, M.; Koguchi, T.; Okachi, R.; Yamada, K.; Nakayama, K.; Kase, H.; Karasawa, A.; Shuto, K. *J. Antibiot.* **1986**, *39*, 44. (b) Ntai, I.; Manier, M. L.; Hachey, D. L.; Bachmann, B. O. *Org. Lett.* **2005**, *7*, 2763. (c) Ntai, I.; Phelan, V. V.; Bachmann, B. O. *Chem. Commun.* **2006**, 4518.

(6) (a) Lejczak, B.; Kafarski, P. *Top. Heterocycl. Chem.* **2009**, *20*, 31. (b) Orsini, F.; Sello, G.; Sisti, M. *Curr. Med. Chem.* **2010**, *17*, 264. (c) Kukhar, V. P.; Hudson, H. R. In *Aminophosphonic and Aminophosphinic Acids*; John Wiley: Chichester, 2000. (d) Kafarski, P.; Lejczak, B. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 301.

(7) For selected recent reviews: (a) Kudzin, Z. H.; Kudzin, M. H.; Drabowicz, J.; Stevens, C. V. *Curr. Org. Chem.* **2011**, *15*, 2015. (b) Liu, B. J.; Cen, C. C.; Wu, M. S.; Kong, D. L. *Asian J. Chem.* **2011**, *23*, 1417. (c) Naydenova, E. D.; Todorov, P. T.; Troev, K. D. *Amino Acids* **2010**, *38*, 23. (d) Sienczyk, M.; Oleksyszyn, J. *Curr. Med. Chem.* **2009**, *16*, 1673. (e) Lewkowski, J. *Focus Organomet. Chem. Res.* **2005**, 167. (f) Syamala, M. *Org. Prep. Proc. Int.* **2005**, *37*, 103. (g) Gröger, H.; Hammer, B. *Chem.—Eur. J.* **2000**, *6*, 943.

(8) For a recent review: (a) Palacios, F.; Alonso, C.; De los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899.

(9) Recent articles: (a) Lyzwa, P.; Mikolajczyk, M. *Heteroat. Chem.* **2011**, *22*, 594. (b) Vicario, J.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2009**, *74*, 452. (c) Ruiz-Gomez, G.; Francesch, A.; Jose Iglesias, M.; Lopez-Ortiz, F.; Cuevas, C.; Serrano-Ruiz, M. *Org. Lett.* **2008**, *10*, 3981. (d) Rai, V.; Mobin, S. M.; Namboothiri, I. N. N. *Tetrahedron: Asymmetry* **2007**, *18*, 2719 and the references cited therein.

(10) Aldol reaction: (a) Diner, P.; Amedjkouh, M. *Org. Biomol. Chem.* **2006**, *4*, 2091. Michael additions: (b) Tao, Q.; Tang, G.; Lin, K.; Zhao, Y.-F. *Chirality* **2008**, *20*, 833. (c) Malmgren, M.; Granander, J.; Amedjkouh, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1934.

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α-carbon, several approaches to enantioenriched α-aminophosphonic acids have been reported, which include resolution and chiral auxiliary based asymmetric synthesis.[11] However, the catalytic asymmetric approaches[12] based on hydrophosphonylation of imines,[13] nucleophilic addition to or hydrogenation of α-iminophosphonates,[14] electrophilic amination of α-phosphonate carbanions,[15] and nucleophilic addition of phosphonate analogues of glycine to electrophiles[16,17] were more appealing. However, to our knowledge, the generation of quaternary α-carbon centers via catalytic asymmetric synthesis of α-amino phosphonic acids remains scarcely explored.[15,17]

As part of our ongoing research program on the stereoselective synthesis of aminophosphonates, we have reported the diastereo- and enantioselective synthesis of γ-nitrophosphonates via Michael addition of α-lithiated phosphonates to nitroalkenes using cinchonine as the chiral catalyst.[18] Enantioenriched β-nitrophosphonates have also been synthesized via Michael addition of dialkyl phosphites to nitroalkenes in the presence of (*S*)-(−)-aluminum lithium bis(binaphthoxide).[19] Herein we report an organocatalyzed enantioselective synthesis of quaternary α-nitrophosphonates via Michael addition of α-nitrophosphonates to enones using a new alkaloid derived thiourea catalyst. Selected transformations of the quaternary α-nitrophosphonates to cyclic quaternary α-aminophosphonates are also reported here.

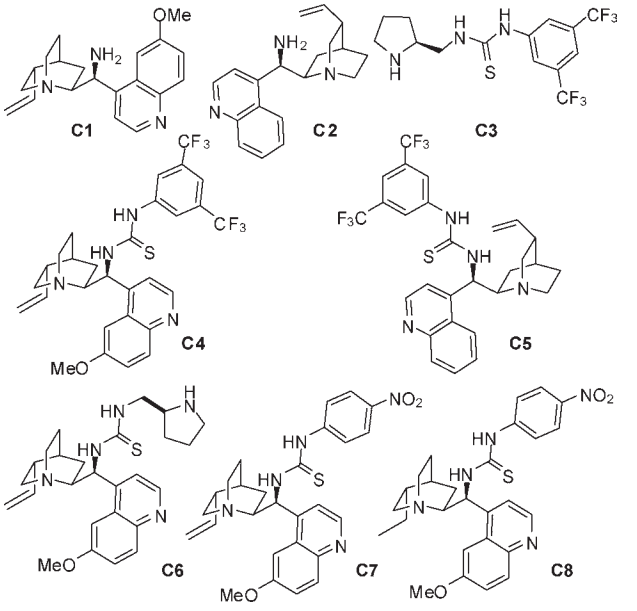


Figure 1. Bifunctional organocatalysts screened.

In order to identify suitable reaction conditions, at the outset, the asymmetric Michael addition of nitrophosphonate **2a**[20] to enone **1a**[21] was carried out in toluene at rt in the presence of 10 mol % of catalysts **C1**−**C8** (Figure 1 and Table 1).[22] The reaction in the presence of primary amines **C1** and **C2** provided quaternary α-nitrophosphonate **3a** in good yield but poor selectivity (Table 1, entries 1−2). The reaction remained incomplete even after 3 days when the L-proline derived thiourea catalyst **C3** was employed (Table 1, entry 3). Subsequently, alkaloid based bifunctional catalysts **C4**−**C8** possessing a strong Lewis basic moiety, such as quinuclidine, to activate the nitrophosphonate **2a**, and a Brønsted acidic moiety, such as thiourea, to activate the Michael acceptor enone **1a**, were screened (Table 1, entries 4−14).

Although the selectivity remained low with **C4**−**C6** (26−31% ee, Table 1, entries 4−6), better selectivity was

(11) For recent reviews: (a) Alfonsov, V. A. *Phosphorus Sulfur Silicon Relat. Elem.* **2008**, *183*, 2637. (b) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279. For recent chiral auxiliary approaches: (c) Kaur, P.; Wever, W.; Rajale, T.; Li, G. *Chem. Biol. Drug. Des.* **2010**, *76*, 314. (d) Palacios, F.; Olszewski, T. K.; Vicario, J. *Org. Biomol. Chem.* **2010**, *8*, 4255.

(12) For reviews: (a) Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17. (b) Ma, J. *Chem. Soc. Rev.* **2006**, *35*, 630. (c) Reference 7g.

(13) (a) For a recent review: Merino, P.; Marques-Lopez, E.; Herrera, R. P. *Adv. Synth. Catal.* **2008**, *350*, 1195. For selected recent articles: (b) Schlemminge, I.; Saida, Y.; Groeger, H.; Maison, W.; Durot, N.; Sasai, H.; Shibasaki, M.; Martens, J. *J. Org. Chem.* **2000**, *65*, 4818 and references therein. (c) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (d) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (e) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978. (f) Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 6269. (g) Zhao, D.; Wang, Y.; Mao, L.; Wang, R. *Chem.—Eur. J.* **2009**, *15*, 10983. (h) Akiyama, T.; Morita, H.; Bachu, P.; Mori, K.; Yamanaka, M.; Hirata, T. *Tetrahedron* **2009**, *65*, 4950. (i) Shi, F.-Q.; Song, B.-A. *Org. Biomol. Chem.* **2009**, *7*, 1292. (j) Nakamura, S.; Nakashima, H.; Yamamura, A.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1209. (k) Alfonsov, V. A.; McKenna, C. E.; Bayandina, E. V.; Kashemirov, B. A.; Yarmieva, L. N.; Punegova, L. N.; Kataeva, O. N. *Heteroatom Chem.* **2008**, *19*, 575. (l) Cheng, X.; Goddard, R.; Buth, G.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5079. (m) Wilt, J. C.; Pink, M.; Johnston, J. N. *Chem. Commun.* **2008**, 4177. (n) Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. *Org. Lett.* **2001**, *3*, 1757.

(14) For selected recent articles: (a) Vicario, J.; Aparicio, D.; Palacios, F. *Phosphorus Sulfur Silicon Relat. Elem.* **2011**, *186*, 638. (b) Goulioukina, N. S.; Bondarenko, G. N.; Lyubimov, S. E.; Davankov, V. A.; Gavrilov, K. N.; Beletskaya, I. P. *Adv. Synth. Catal.* **2008**, *350*, 482. (c) Kobayashi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. *J. Am. Chem. Soc.* **2004**, *126*, 6558. (d) Kiyohara, H.; Matsubara, R.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 5333. (e) Kiyohara, H.; Nakamura, Y.; Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1615. (f) Dodda, R.; Zhao, C.-G. *Tetrahedron Lett.* **2007**, *48*, 4339.

(15) (a) Roeschenthaler, G.-V.; Kukhar, V. P.; Kulik, I. B.; Sorochinsky, A. E.; Soloshonok, V. A. *J. Fluor. Chem.* **2011**, *132*, 834. (b) Bernardi, L.; Zhuang, W.; Jørgensen, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 5772. (c) Kim, M. S.; Hye, R. K.; Kim, Y. D. *Org. Lett.* **2005**, *7*, 2309.

(16) For selected recent articles: (a) Pham, T. S.; Balazs, L.; Petnehazy, I.; Jaszay, Z. *Tetrahedron: Asymmetry* **2010**, *21*, 346. (b) Reddy, M. V. N.; Balakrishna, A.; Kumar, M. A.; Reddy, G. C. S.; Sankar, A. U. R.; Reddy, C. S.; Krishna, T. M. *Chem. Pharm. Bull.* **2009**, *57*, 1391.

(17) (a) Kuwano, R.; Nishio, R.; Ito, Y. *Org. Lett.* **1999**, *1*, 837. (b) Reference 13n.

(18) (a) Reference 9d. (b) Rai, V.; Namboothiri, I. N. N. *Tetrahedron: Asymmetry* **2008**, *19*, 767.

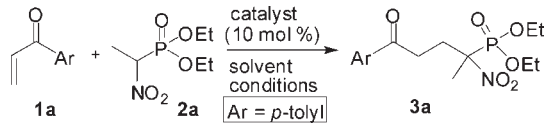
(19) Rai, V.; Namboothiri, I. N. N. *Tetrahedron: Asymmetry* **2008**, *19*, 2335.

(20) For general procedure for the preparation of nitrophosphonates **2**: Zon, J. *Synthesis* **1984**, 661. Also see the Supporting Information.

(21) For general procedure for the preparation of enones **1**: Kundu, N. G.; Dasgupta, S. K.; Chaudhuri, L. N.; Mahanty, J. S.; Shahinian, A. H. *Eur. J. Med. Chem.* **1993**, *28*, 473. Also see the Supporting Information.

(22) (a) **C1**, **C2**, **C4**, and **C5**: Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967. (b) **C3**: Cao, C. L.; Ye, M. C.; Sun, X. L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901. (c) **C6**: Chen, R. J.; Cao, J. Y.; Zou, Q. Y.; Tan, F.; Zhu, Y. X.; Xiao, J. W. *Org. Biomol. Chem.* **2010**, *8*, 1275.

Table 1. Catalyst Screening



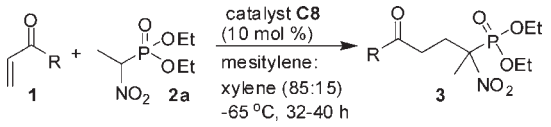
entry	C[a]	solvent	temp (°C)	time (h)	% yield[b]	% ee[c]
1	**C1**	toluene	rt	15	80	00
2	**C2**	toluene	rt	18	82	19[d]
3	**C3**	toluene	rt	72	[e]	[f]
4	**C4**	toluene	rt	17	80	28
5	**C5**	toluene	rt	17	78	26[d]
6	**C6**	toluene	rt	20	78	31
7	**C7**	toluene	rt	15	84	50
8	**C7**	toluene	−65	72	65	62
9	**C8**	toluene	rt	12	82	59
10	**C8**	mesitylene	rt	11	89	62
11	**C8**	xylene	rt	10	87	58
12	**C8**	CH_2Cl_2	rt	10	80	18
13	**C8**	mesitylene	−40	15	90	70
14	**C8**	**mesitylene/ xylene[g]**	**−65**	**34**	**86**	**74**
15	–	mesitylene/ xylene[g]	−65	40	–[h]	–

[a] Catalyst. [b] Isolated yield after silica gel column chromatography. [c] Ee was determined by chiral HPLC. [d] Ent-isomer. [e] Incomplete reaction. [f] Not determined. [g] Ratio 85:15. [h] No reaction.

obtained with 10 mol % of catalysts **C7** and **C8** at rt (50−62% ee, Table 1, entries 7−9). This is attributable to the increase in acidity of the thiourea protons due to the *p*-nitrophenyl moiety. Since 59% ee was obtained at rt with **C8** as the catalyst, further solvent screening was conducted with 10 mol % of **C8** as the catalyst (Table 1, entries 10−14). While there was no appreciable improvement in the selectivity with mesitylene and xylene as solvents (Table 1, entries 10−11), it dropped drastically in CH_2Cl_2 (entry 12). Finally, much higher selectivity was obtained at lower temperature (70% ee, Table 1, entry 13) which was further improved by choosing a mixture of solvents (mesitylene/xylene) and lowering the temperature (74%, entry 14). Any possible background reaction was ruled out by performing the reaction in the absence of any catalyst under the optimized conditions of entry 14 (Table 1, entry 15).

The above optimized conditions were employed to explore the scope of the reaction. Thus, Michael addition of α-nitrophosphonate **2a** to various enones **1a**−**k** was carried out in a mesitylene/xylene solvent system (85:15) in the presence of 10 mol % of catalyst **C8** at −65 °C (Table 2). In general, substituted aromatic enones with the exception of **1h** provided the products in excellent yield and good to high selectivity (Table 2, entries 1, 3−7). For instance, enones **1a** and **1c**, possessing weakly electron-donating substituents, and **1g**, possessing a weakly electron-withdrawing substituent on the aromatic ring, afforded

Table 2. Scope of Enones **1**



entry	R	3	% yield[a]	% ee[b]
1	4-MeC_6H_4	**3a**	86	74
2	Ph	**3b**	81	45
3	3-BrC_6H_4	**3c**	83	70
4	4-$OMeC_6H_4$	**3d**	85	72
5	3,4-$(OMe)_2C_6H_3$	**3e**	86	87
6	3,4,5-$(OMe)_3C_6H_2$	**3f**	84	78
7	4-$CF_3C_6H_4$	**3g**	80	69
8	4-$NO_2C_6H_4$	**3h**	75	35
9	2-furyl	**3i**	78	42
10	2-thienyl	**3j**	82	43
11	*c*-C_6H_{11}	**3k**	70	44

[a] Isolated yield after silica gel column chromatography. [b] Ee was determined by chiral HPLC.

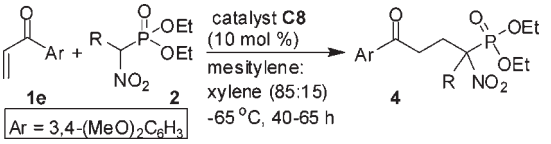
the products **3a**, **3c**, and **3g** in excellent yield and good selectivity (Table 2, entries 1, 3, and 7). Enones **1d**−**f**, possessing strongly electron-donating substituents, were indeed superior in terms of both yield and selectivity (Table 2, entries 4−6). Unsubstituted aromatic enone **1b**, electron-poor aromatic enone **1h**, heteroaromatic enones **1i**−**j**, and aliphatic enone **1k** provided the products **3b** and **3h**−**k**, respectively, in a slightly lower yield and poor selectivity (Table 2, entries 2, 8−11). The poor selectivity in the case of enone **1h** (Table 1, entry 8) is presumably due to the competition between the nitro and carbonyl groups of the enone in H-bonding with the thiourea moiety of **C8**.

Having demonstrated the scope of enones **1** in the Michael addition of nitrophosphonate **2a**, we desired to expand the scope further by employing other nitrophosphonates, viz. **2b**−**i**. Since the best yield and enantioselectivity were obtained with enone **1e** (Table 2, entry 5), additions of nitrophosphonates **2b**−**i** were performed with enone **1e** as the model substrate. It may be noted that, regardless of the nature of the α-substituent in nitrophosphonate **2b**−**i**, the quaternary α-nitrophosphonates **4a**−**h** were formed in good to excellent yield and selectivity. However, as the bulkiness of the α-substituent in nitrophosphonate **2** increases, the rate of the reaction decreases. In the case of α-nitrophosphonates **2g** and **2h**, the reaction was so slow at −65 °C that we had to perform this experiment at −40 °C for 4 days (Table 3, entries 6−7).

The mechanism presumably involves deprotonation of α-nitrophosphonate **2** by the quinuclidine moiety of **C8** and activation of the enone **1** by the thiourea moiety whose acidity is enhanced by the *p*-nitrophenyl group.

The quaternary α-nitrophosphonates **3** and **4** with a keto group at the δ-position were immediate precursors for the enantioselective synthesis of pyrrolidinylphosphonates **5** and **7** (Scheme 1). Thus phosphonate **4a** (94% ee) was

Table 3. Scope of Nitrophosphonates **2**



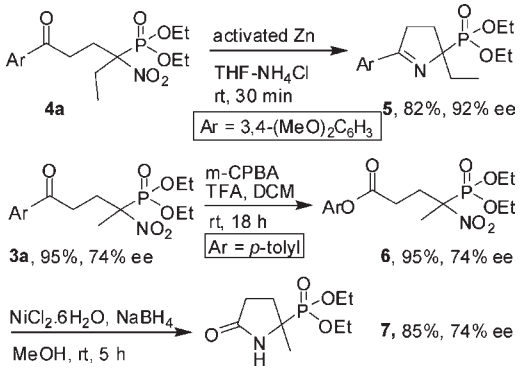
entry	R	2	4	% yield[a]	% ee[b]
1	Et	**2b**	**4a**	89	94
2	*n*-Pr	**2c**	**4b**	95	92
3	*n*-Bu	**2d**	**4c**	97	92
4	*i*-Bu	**2e**	**4d**	88	92
5	*n*-C_5H_{11}	**2f**	**4e**	94	93
6[c]	*c*-C_6H_{11}	**2g**	**4f**	87	87
7[c]	*c*-C_3H_5	**2h**	**4g**	90	87
8	$PhCH_2$	**2i**	**4h**	85	86

[a] Isolated yield after silica gel column chromatography. [b] Ee was determined by chiral HPLC. [c] Reaction performed at −40 °C for 96 h.

subjected to selective reduction of the nitro group using Zn−NH_4Cl to afford dihydropyrrolylphosphonate **5** in 82% yield. In another strategy, Baeyer−Villiger oxidation of phosphonate **3a** (74% ee) afforded nitroester **6** in 95% yield. Selective reduction of the nitro group in **6** using $NiCl_2$−$NaBH_4$ led to the formation of 5-oxopyrrolidinylphosphonate **7** in 85% yield.

In conclusion, a novel approach to cyclic quaternary α-aminophosphonates has been developed via a new quinine thiourea catalyzed enatioselective Michael addition of quaternary α-nitrophosphonates to enones. The scope of enones and nitrophosphonates investigated suggested that electron-rich aryl vinyl ketones are excellent substrates for

Scheme 1. Synthesis of Cyclic Quaternary α-Aminophosphonates



the Michael addition of a variety of tertiary α-nitrophosphonates. Studies on furthering the scope and applications of the products are currently underway in our laboratory and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, and copies of NMR spectra as well as HPLC profiles for all the new/relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.