JOC*Note*

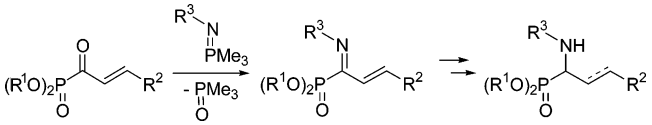
Synthesis of α-Phosphorylated α,β-Unsaturated Imines and Their Selective Reduction to Vinylogous and Saturated α-Aminophosphonates

Francisco Palacios,* Javier Vicario, Agnieszka Maliszewska, and Domitila Aparicio

Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain

francisco.palacios@ehu.es

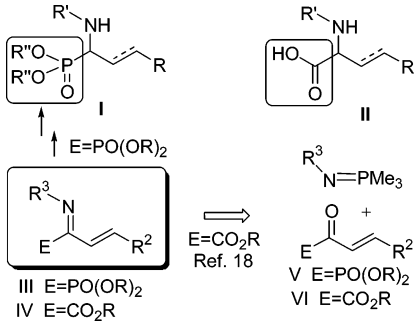
Received December 19, 2006



An efficient synthesis of α,β-unsaturated imines derived from α-aminophosphonates is achieved through aza-Wittig reaction of *P*-trimethyl phosphazenes with β,γ-unsaturated α-ketophosphonates. Selective 1,2-reduction of such 1-azadienes affords β,γ-unsaturated α-aminophosphonates, phosphorylated analogs of vinylglycines, which are hydrogenated to yield saturated α-aminophosphonate derivatives.

α-Aminophosphonates[1] **I** are structurally analogous to α-amino acids **II** (see Scheme 1), obtained by isosteric substitution of the carboxylic acid by a phosphonate moiety. As expected from this analogy the single α-aminophosphonic molecules or their phosphonic esters as well as phosphapeptides containing α-aminophosphonic units show a variety of biological activities[2] such as haptens of catalytic antibodies, peptide mimetics, enzyme inhibitors, and antibacterial or antihypertensive agents. Among this family of compounds, vinylogous α-aminophosphonates **I** are isosters of vinylogous α-aminoacids **II**, also known as α-vinylglycines. Simple α-vinylglycine is a potent inhibitor of several transaminase and decarboxylase enzymes,[3a,b] and there are numerous natural substituted α-vinylglycines such as rhizobitoxin,[3c] radiosumin,[3d] or (L)-*trans*-α-methoxyvinylglycine[3e] that show biological activity. Moreover, it is well-known that molecular modifications involving the introduction of organophosphorus functionalities could increase biological activity[4] or new activity would be expected from the phosphorylated isosters of α-vinylglycines.

SCHEME 1. Strategy for Preparation of α-Aminophosphonate Derivatives



The most common method for the synthesis of α-aminophosphonates involves a variant of the Strecker reaction[5a] consisting of the nucleophilic addition of dialkylphosphites to imines and was described for the first time in the early 1950s.[5b] As part of research on the addition of dialkylphosphites to imines, some regioselective additions to α,β-unsaturated imines derived from cynnamaldehyde[6a] have been reported, in some cases enantioselectively[6b,c] for the preparation of some specific examples of aminophosphonates **I** (mainly, R = Ph, Scheme 1). Likewise, dialkyl trimethylsilylphosphites as mild phosphonylation agents of α,β-unsaturated imines have also been reported,[7] and Stevens et al. recently used this process for an elegant preparation of glutamic acid analogues through a double addition (1,2 and 1,4) of silylphosphite to α,β-unsaturated imines.[8] On the other hand, α,β-unsaturated imines or 1-azadienes are a versatile family of compounds with a wide range of applications in preparative organic chemistry.[9] Besides the well-known aza-Diels−Alder reaction,[10a] 1-azadienes have also been extensively used in the synthesis of several natural products.[10b] Moreover, owing to their ambident electrophilic character, α,β-unsaturated imines can either undergo 1,2[11] or conjugate (1,4)[12] nucleophilic addition processes. However, generally, the control of the regioselectivity is difficult, and very

(1) For an excellent book see: Kukhar, V. P., Hudson, H. R., Eds.; In *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*; J. Wiley: Chichester, 2000.

(2) For reviews, see: (a) Kafarski, P.; Lejczak, B. *Curr. Med. Chem: Anti-Cancer Agents* **2001**, *1*, 301−312. (b) Gambecka, J.; Kafarski, P. *Mini-Rev. Med. Chem.* **2001**, *1*, 133−144. (c) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193 -215.

(3) (a) Griffith, O. W. *J. Biol. Chem.* **1983**, *258*, 1591−1598. (b) Soper, T. S.; Manning, J. M.; Marcotte, P. A.; Walsh, C. T. *J. Biol. Chem.* **1977**, *252*, 1571−1575. (c) Keith, D. D.; de Bernardo, S.; Weigele, M. *Tetrahedron* **1975**, *31*, 2629−2632. (d) Coleman, J. E.; Wright, J. L. C. *J. Nat. Prod.* **2001**, *64*, 668−670. (e) Rando, R. R. *Nature* **1974**, *250*, 586−587.

(4) Toy; A. D. F.; Walsh, E. N. In *Phosphorus Chemistry in Everyday Living*; American Chemical Society: Washington, DC, 1987.

(5) (a) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795−2827. (b) Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528−1531.

(6) (a) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synthesis* **2004**, 2692−2696 and references therein. (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583−2587. (c) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102−4103.

(7) Afarinkia, K.; Cadogan, J. I. G.; Rees, C. W. *Synlett* **1992**, 123−123.

(8) Moonen, K.; van Meenen, E.; Verwée, A.; Stevens, C. V. *Angew. Chem., Int. Ed* **2005**, *44*, 7407−7411.

(9) For reviews, see: (a) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379−471. (b) Buonora, P.; Olsen, J. C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099−6138.

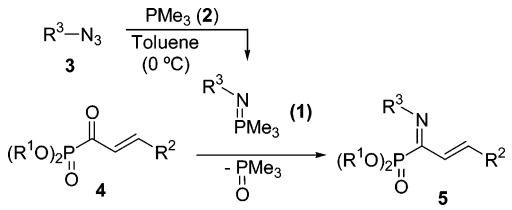
(10) (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418−8420. (b) Schnermann, M. J.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 15704−15705.

(11) Contributions to selective 1,2-addition to α,β-unsaturated imines: (a) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875−5878. (b) Allin, S. M.; Button, M. A. C.; Baird, R. D. *Synlett* **1998**, 1117−1119.

(12) Recent contributions to selective conjugate addition to α,β-unsaturated imines: (a) Palacios, F.; Vicario, J. *Org. Lett.* **2006**, *8*, 5405−5408. (b) Zheng, J.-C.; Liao, W.-W.; Tang, Y.; Sun, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2005**, *127*, 12222−12223.

10.1021/jo062609+ CCC: $37.00
Published on Web 03/01/2007

SCHEME 2. Synthesis of α,β-Unsaturated Imines Derived from α-Aminophosphonate 5



often the double nucleophilic addition products are obtained.[8,13] The simplest method for the synthesis of α,β-unsaturated imines implies condensation of α,β-unsaturated carbonyl compounds with primary amines.[14] This method is often complicated by the Michael addition reaction, especially in the case of α,β-unsaturated ketones.[14,15] However, this preparative drawback can be avoided either by olefination reaction of β-phosphorated imines or enamines with aldehydes to generate the conjugated C═C bond of 1-azadienes[16] or by the aza-Wittig reaction[17,18] of phosphazenes, a strategy recently applied for the construction of 1-azadienes derived from α-aminoester derivatives **IV** (Scheme 1).[19]

In this context, we have used functionalized aminophosphorus derivatives for the preparation of three-,[20] five-,[21] and six-membered[22] phosphorus-substituted nitrogen heterocycles,[23] as well as the synthesis of β-[24] and α-aminophosphonate[25] derivatives. Likewise, we have been involved in the chemistry of azadienes,[16,18] and recently we have reported both an efficient synthesis of α,β-unsaturated imines derived from α-aminoesters,[19] as well as the enantioselective synthesis of α-dehydro-aminoesters.[12a] Continuing with our interest in the chemistry of phosphazenes[19] and functionalized azadienes,[16,18,19] we report here the first synthesis α,β-unsaturated imines derived from α-aminophosphonates **III** (see Scheme 1) by the aza-Wittig approach[19] with the very reactive *P*-trialkyl phosphazenes, as well as their selective 1,2-reduction to vinylogous α-aminophosphonates **I** and their total reduction to obtain saturated α-aminophosphonates **I**.

TABLE 1. Phosphazenes 1 and α,β-Unsaturated Imines Derived from α-Aminophosphonate 5

entry	compd	R^1	R^2	R^3	^{31}P NMR[a] (ppm)	yield[b] (%)
1	**1a**			*p*-Me-C_6H_5	2.5	
2	**1b**			*p*-NO_2-C_6H_5	9.5	
3	**1c**			*p*-MeO-C_6H_5	1.6	
4	**5a**	Me	C_6H_5	*p*-Me-C_6H_5	10.8	89
5	**5b**	Me	2-furyl	*p*-Me-C_6H_5	10.2	89
6	**5c**	Me	OEt	*p*-Me-C_6H_5	10.2	85
7	**5d**	Et	Me	*p*-NO_2-C_6H_5	5.0	
8	**5e**	Et	Me	*p*-MeO-C_6H_5	8.1	

[a] In toluene-d_8. [b] Isolated yield.

P-Trimethyl phosphazenes **1** were readily prepared in situ by addition of trimethylphosphine **2** to azides **3**[26] (Scheme 2; Table 1, entries 1−3). Phosphazenes **1** were used without isolation, and the addition of β,γ-unsaturated α-ketophosphonates **4** gave the phosphorylated *syn*-α,β-unsaturated imines **5** in a regioselective fashion and in high yields (Scheme 2; Table 1, entries 4−8). After consumption of trimethylphosphine **1**, addition of β,γ-unsaturated α-ketophosphonates **4** showed the disappearance of the signal corresponding to the phosphazenes **1** and appearance of the signal corresponding to trimethylphosphine oxide at $\delta = 31.6$ ppm, as well as only one signal corresponding to the phosphorylated (*E*)-α,β-unsaturated imines **5** in the range of $\delta = 5-10$ ppm.

α,β-Unsaturated imines bearing an aromatic (**5a**, $R^2 = C_6H_5$), heteroaromatic (**5b**, R^2 = 2-furyl), or alkoxy (**5c**, R^2 = OEt) substituent in the β position are stable and allowed isolation by the conventional purification techniques, obtaining yields that were good even after chromatography (Table 1, entries 4−6). However, in the case of α,β-unsaturated imines derived from crotonaldehyde (**5d,e**, R^2 = Me), no isolation was possible (Table 1, entries 7 and 8). α,β-Unsaturated imines **5a−c** were fully characterized on the basis of their ^{1}H, ^{13}C, and ^{31}P NMR, IR and MS spectra, whereas only satisfactory ^{31}P NMR for unstable α,β-unsaturated imines **5d,e** was possible due to overlapping of toluene signals in (in situ) ^{1}H or ^{13}C NMR. α,β-Unsaturated imines derived from α-phosphonates **5** were obtained as a single isomer, obvious by the presence of a single signal in ^{31}P NMR. Characteristic signals in the ^{1}H NMR spectrum of **5a** are the doublet corresponding to the CH alkene at $\delta = 7.85$ ppm with a characteristic coupling constant for an *E* configuration[19] ($^3J_{HH} = 16.6$ Hz) and coupled with the double

(13) Shimizu, M.; Kamiya, M.; Hachiya, I. *Chem. Lett.* **2005**, *34*, 1456−1457.

(14) (a) Pearson, W. H.; Jacobs, V. A. *Tetrahedron Lett.* **1994**, *35*, 7001−7004. (b) Teng, M.; Fowler, F. W. *J. Org. Chem.* **1990**, *55*, 5646−5653.

(15) Palacios, F.; Vicario, J.; Aparicio, D. *Eur. J. Org. Chem.* **2006**, 2843−2850.

(16) (a) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004**, *69*, 8767−8774. (b) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Oyarzabal, J. *Org. Lett.* **2002**, *4*, 769−772. (c) Palacios, F.; Aparicio, D.; Vicario, J. *Eur. J. Org. Chem.* **2002**, 4131−4136. (d) Palacios, F.; Aparicio, D.; García, J.; Rodríguez, E.; Fernández-Acebes A. *Tetrahedron* **2001**, *57*, 3131−3141.

(17) For reviews, see: (a) Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso C.; de los Santos J. M. *Tetrahedron* **2007**, *63*, 523−575. (b) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1−17.

(18) For contributions of creation of the C═N double bond by means of this process, see: (a) Palacios, F.; Alonso, C.; Rubiales, G.; Villegas, M. *Tetrahedron* **2005**, *61*, 2779−2794. (b) Palacios, F.; Herrán, E.; Rubiales, G.; Ezpeleta, J. M. *J. Org. Chem.* **2002**, *67*, 2131−2135.

(19) Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690−7696.

(20) (a) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2006**, *71*, 6141−6148. (b) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Ezpeleta, J. M. *J. Org. Chem.* **2000**, *65*, 3213−3217.

(21) (a) Palacios, F.; Aparicio. D.; López, Y.; de los Santos, J. M.; Ezpeleta, J. M. *Tetrahedron* **2006**, *62*, 1095−1101. (b) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Alonso, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 2525−2541. (c) Palacios, F.; Aparicio. D.; de los Santos, J. M. *Tetrahedron* **1996**, *52*, 4123−4132.

(22) (a) Palacios, F.; Herran, E.; Alonso, C.; Rubiales, G.; Lecea, B.; Ayerbe, M.; Cossío, F. P. *J. Org. Chem.* **2006**, *71*, 6020−6030. (b) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Lopez de Munain, R. *Org. Lett.* **2002**, *4*, 2405−2408. (c) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J. *Tetrahedron Lett.* **1996**, *37*, 4577−4580.

(23) For an excellent review of azaheterocyclic phosphonates, see: Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177−6215.

(24) For a recent review, see: Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899−931.

(25) (a) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2005**, *70*, 8895−8901. (b) Palacios, F.; Aparicio. D.; López, Y.; de los Santos, J. M. *Tetrahedron Lett.* **2004**, *45*, 4345−4348. (c) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; Lopez de Munain, R. *Tetrahedron: Asymmetry* **2003**, *14*, 689−700. (d) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; Alonso, J. M. *J. Org. Chem.* **2002**, *67*, 7283−7288.

(26) The formation of the phosphazenes **1** was evident from the visible nitrogen gas formation during the addition of trimethylphosphine and was monitored by ^{31}P NMR using toluene-d_8 as solvent. The spectra showed the disappearance of the signal at $\delta = -61.1$ ppm, corresponding to trimethylphosphine and appearance of a new signal in the range of $\delta = 2-10$ ppm which was attributed to the phosphazenes **1**

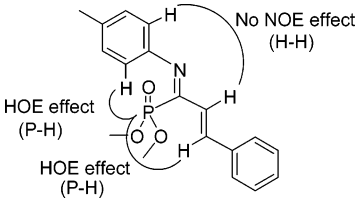
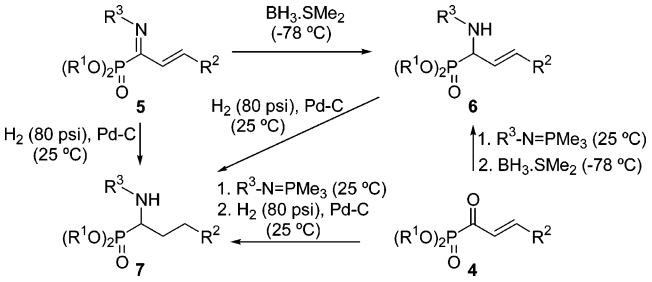


FIGURE 1. NOE and HOE effect observed for α,*β*-unsaturated imine **5a**.

SCHEME 3. Selective 1,2 or Total Reduction of α,*β*-Unsaturated Imines 5



doublet corresponding to the other olefinic CH at $\delta = 6.78$ ppm, which is also coupled with the phosphorus with a coupling constant $^2J_{PH} = 38.4$ Hz. Nuclear Overhauser enhancement spectroscopy (NOESY) and heteronuclear Overhauser enhancement spectroscopy (HOESY) experiments were performed in order to determine the configuration of the imine bond. The NOESY spectrum of α,*β*-unsaturated imine **5a** showed no correlation between olefinic protons and the aromatic protons of the *p*-tolyl group, whereas the HOESY spectrum showed a correlation between the phosphorus signal at $\delta = 10.8$ ppm and the doublet at $\delta = 6.77$ ppm corresponding to the *ortho* protons of the *p*-tolyl substituent (see Figure 1).

These results suggest a *syn* configuration of the imine bond, where phosphonate and aryl substituent are pointing to the same direction. Moreover, the HOESY spectrum showed correlation between the phosphorus signal and the doublet at $\delta = 7.85$ ppm corresponding to the proton in the *β* position of the olefinic bond, which may suggest a *pseudo-trans* conformation in the 1-azadienic system (Figure 1). As far as we known, this strategy leads the first example of 1-azadienes derived from α-aminophosphonates **5**.

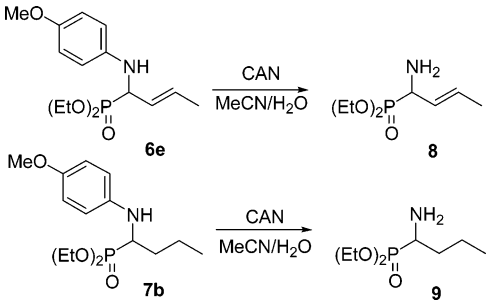
The availability of an efficient method for the synthesis of α,*β*-unsaturated imines **5** derived from α-aminophosphonate raised the possibility of exploring their reactivity toward reduction agents. First, the selective reduction of α,*β*-unsaturated imines **5** was explored. Treatment of α,*β*-unsaturated imines **5** derived from α-aminophosphonates with $BH_3{\cdot}SMe_2$ in toluene at −78 °C afforded only the 1,2-addition adducts, vinylogous α-aminophosphonates **6** with very good yields (Scheme 3; Table 2, entries 1−3), keeping the *E* configuration of the carbon−carbon double bond. It is remarkable that the 1,2-reduction can be also carried out in a one-pot procedure starting from *β*,*γ*-unsaturated α-ketophosphonates **4**. Addition of the *β*,*γ*-unsaturated α-ketophosphonates **4** to the in situ generated phosphazenes **1** (toluene, 25 °C) followed by addition of $BH_3{\cdot}SMe_2$ to the resulting toluene solution at low temperature (−78 °C) also afforded vinylogous α-aminophosphonates **6** with very good yields (Scheme 3; Table 2, entries 1 and 3−5). This last aspect is of special importance due to the unfeasibility of the isolation

TABLE 2. Vinylogous α-Aminophosphonates 6 and Saturated α-Aminophosphonates 7

entry	compd	R^1	R^2	R^3	^{31}P NMR[a] (ppm)	yield[b] (%)
1	**6a**	Me	C_6H_5	*p*-Me-C_6H_5	25.9	84[c], 82[d]
2	**6b**	Me	2-furyl	*p*-Me-C_6H_5		84[c]
3	**6c**	Me	OEt	*p*-Me-C_6H_5	27.2	83[c], 82[d]
4	**6d**	Et	Me	*p*-NO_2-C_6H_5	21.7	88[d]
5	**6e**	Et	Me	*p*-MeO-C_6H_5		87[d]
6	**7a**	Me	C_6H_5	*p*-Me-C_6H_5	29.2	91[e], 88[f]
7	**7b**	Et	Me	*p*-MeO-C_6H_5	33.0	95[e], 84[g]

[a] In $CDCl_3$. [b] Isolated yield. [c] Yield from isolated α,*β*-unsaturated imines **5** using $BH_3.SMe_2$ (toluene, −78 °C). [d] Yield for one-pot procedure from *β*,*γ*-unsaturated α-ketophosphonates **4**. [e] Yield from vinylogous aminophosphonates **6** using H_2, Pd−C (MeOH, 25 °C). [f] Yield from α,*β*-unsaturated imines **5** using H_2, Pd−C (MeOH, 25 °C). [g] Yield from in situ prepared α,*β*-unsaturated imine **5d** using H_2, Pd−C (MeOH, 25 °C).

SCHEME 4. Synthesis of Primary Vinylogous 8 and Saturated α-Aminophosphonates 9



of α,*β*-unsaturated imines **5d,e** containing a methyl group (R^2 = Me) in position 4.

Some specific examples of synthesis of vinylogous α-aminophosphonates **6** (R^2 = Ph) either by nucleophilic addition of dialkylphosphites to α,*β*-unsaturated imines derived from cynnamaldehyde[6,7] or by the addition of trialkylphosphites to unstable α,*β*-unsaturated iminium salts[27] have been reported. However, the new strategy here described can be applied to vinylogous α-aminophosphonates **6** containing not only aromatic (R^2 = Ph) but also heteroaromatic (R^2 = 2-furyl), alkoxi (R^2 = OEt), or alkyl (R^2 = Me) groups.

The synthesis of the saturated α-aminophosphonate **7a** can also be achieved either by hydrogenation of the vinylogous α-aminophosphonate **6a** or by total reduction of the α,*β*-unsaturated imine **5a** (Scheme 3; Table 2, entries 6 and 7). In the case of α,*β*-unsaturated imine **5e** (R^2 = Me), the hydrogenation can be also carried out in a one-pot reaction from *β*,*γ*-unsaturated α-ketophosphonate **4e** to obtain the saturated α-aminophosphonate **7b** in very good yield (Scheme 3; Table 2, entry 7).

Finally, the primary vinylogous α-aminophosphonate **8** (62%) and saturated α-aminophosphonate **9** (65%) were prepared from *p*-methoxyphenyl *N*-substituted compounds by N-deprotection reaction of vinylogous α-aminophosphonate **6e** or saturated α-aminophosphonate **7b** with cerium ammonium nitrate (CAN) (Scheme 4).

The very reactive phosphazene species derived from trimethylphosphine **1** constitute an excellent alternative if selective condensation (1,2-addition) with the carbonyl group of α,*β*-

(27) (a) Atmani, A.; Combret, J.-C.; Malhiac, C.; Kajima Mulkengi, J. *Tetrahedron Lett.* **2000**, *42*, 6045−6048. (b) Stevens, C. V.; Vekemans, W.; Moonen, K.; Rammeloo, T. *Tetrahedron Lett.* **2003**, *44*, 1619−1622.

unsaturated carbonyl compounds **4**, avoiding the undesirable Michael addition (1,4-addition), is required. This methodology applied to β,γ-unsaturated α-ketophosphonates **4** provides access to α,β-unsaturated imines derived from α-aminophosphonates **5**, molecules that are described here for the first time. Moreover, regioselective reduction (1,2-addition) of the imine carbon−nitrogen double bond of α,β-unsaturated imines derived from α-aminophosphonates **5** proves to be a general method for the preparation of vinylogous α-aminophosphonates **6**, whereas total reduction of both double bonds (carbon−nitrogen and carbon−carbon) of α,β-unsaturated imines **5** gives α-aminophosphonates **7**. Likewise primary α-aminophosphonates **8** and **9** can be obtained by selective N-deprotection of the amino group. α-Amino-phosphonate derivatives are important building blocks in organic synthesis[1] and in the preparation of biologically active compounds of interest in medicinal chemistry.[2]

Experimental Section

General Procedure. Synthesis of α,β-Unsaturated Imines 5 Derived from α-Aminophosphonate. To a solution of the corresponding azide **3** (2.0 mmol) in toluene (10 mL) at 0 °C was added a 1.0 M solution of trimethylphosphine in toluene (2 mL). The resulting solution was stirred 30 min until N_2 evolution stopped, which indicates the completion of the reaction and phosphazene **1** formation and can be monitored by ^{31}P NMR. The corresponding neat β,γ-unsaturated α-ketophosphonate **2** (2.0 mmol) was then added, and the reaction was stirred for an additional 30 min at room temperature. α,β-Unsaturated imines **5d,e** were used without any further workup as a toluene solution. For the workup of the reactions corresponding to α,β-unsaturated imines **5a**−**c**, the solution was diluted with CH_2Cl_2 (40 mL), washed with water (3 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford a yellow oily crude that was purified by chromatography (SiO_2, AcOEt/pentane 3:1).

Dimethyl (3-Phenyl-1-*p*-tolylimino-allyl)-phosphonate 5a. Synthesized according to the general procedure with *p*-tolylazide (266 mg, 2 mmol) and diethyl (3-phenyl-acryloyl)-phosphonate (480 mg, 2 mmol), affording 407 mg (89%) of **5a** as a yellow oil. R_f (AcOEt): 0.57. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3 H, CH_3), 3.92 (d, $^3J_{PH}$ = 10.8 Hz, 6 H, 2 × OCH_3), 6.77 (d, $^3J_{HH}$ = 8.1 Hz, 2 H, 2 × CHar), 6.78 (dd, $^3J_{HH}$ = 16.6 Hz, $^3J_{PH}$ = 38.4 Hz, 1 H, CH═), 7.15 (d, $^3J_{HH}$ = 8.1 Hz, 2 H, 2 × CHar), 7.28−7.30 (m, 2H, 2 × CHar), 7.35−7.38 (m, 3 H, 3 × CHar), 7.85 (d, $^3J_{HH}$ = 16.6 Hz, 1 H, CH═). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2 (CH_3), 54.2 (d, $^2J_{PC}$ = 7.1 Hz, 2 × OCH_3), 119.7 (d, $^3J_{PC}$ = 33.2 Hz, CH═), 120.5 (2 × CHar), 128.1 (2 × CHar), 129.0 (2 × CHar), 129.8 (2 × CHar), 130.1 (CHar), 135.3 (Cquat), 135.8 (Cquat), 142.8 (C═H), 147.0 (d, $^3J_{PC}$ = 31.2 Hz, Cquat), 162.9 (d, $^1J_{PC}$ = 214.5 Hz, C═N). ^{31}P NMR (120 MHz, $CDCl_3$): δ 10.8. FTIR (KBr) ν_{max} (cm^{-1}): 1613 (C═N st), 1255 (P═O st). CIMS *m*/*z* (amu): 330 ([M^+ + H], 100), 220 ([M^+] − $PO(OMe)_2$, 78). Anal. Calcd for $C_{18}H_{20}NO_3P$: C 65.65; H 6.12; N 4.25. Found: C 65.71; H 6.05; N 4.27.

General Procedure. Selective Reduction of α,β-Unsaturated Imines 5 with BH_3.SMe_2. Synthesis of Vinylogous α-Aminophosphonates 6. To a solution of α,β-unsaturated imine **5** (1.0 mmol) in toluene (5 mL) at −78 °C was added a 1.0 M solution of BH_3·SMe_2 in CH_2Cl_2 (1.5 mL, 1.5 mmol). The reaction was stirred at −78 °C for 3 h, quenched with a saturated aqueous solution of $NaHCO_3$, and allowed to warm to room temperature. The resulting mixture was diluted in CH_2Cl_2 (20 mL), washed with water (3 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by chromatography (SiO_2, AcOEt/pentane 3:1).

Dimethyl (3-Phenyl-1-*p*-tolylamino-allyl)-phosphonate 6a. Synthesized according to the general procedure with dimethyl (3-phenyl-1-*p*-tolylimino-allyl)-phosphonate **5a** (329 mg, 1.0 mmol), affording 278 mg (84%) of **6a** as a pale yellow oil. R_f (AcOEt): 0.60. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3 H, CH_3), 3.77 (d, $^3J_{PH}$ = 10.7 Hz, 3 H, OCH_3), 3.80 (d, $^3J_{PH}$ = 10.5 Hz, 3 H, OCH_3), 3.89 (broad s, 1H, NH), 4.44 (ddd, $^4J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 6.3 Hz, $^2J_{PH}$ = 25.6 Hz, 1 H, CHN), 6.22 (ddd, $^3J_{PH}$ = 5.2 Hz, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 15.8 Hz, 1 H, CH═), 6.60 (d, $^3J_{HH}$ = 8.5 Hz, 2 H, 2 × CHar), 6.69 (ddd, $^4J_{HH}$ = 1.5 Hz, $^4J_{PH}$ = 4.9 Hz, $^3J_{HH}$ = 15.8 Hz, 1 H, CH═), 6.97 (d, $^3J_{HH}$ = 8.5 Hz, 2 H, 2 × CHar), 7.20−7.35 (m, 5H, 5 × CHar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3 (CH_3), 53.4 (d, $^2J_{PC}$ = 7.6 Hz, OCH_3), 53.9 (d, $^2J_{PC}$ = 7.1 Hz, OCH_3), 54.0 (d, $^1J_{PC}$ = 154.6 Hz, CHN), 113.9 (2 × CHar), 123.3 (d, $^2J_{PC}$ = 4.5 Hz, CH═), 126.6 (2 × CHar), 127.8 (CHar), 127.9 (Cquat), 128.4 (2 × CHar), 129.7 (2 × CHar), 133.3 (d, $^3J_{PC}$ = 10.0 Hz, CH═), 136.1 (d, $^4J_{PC}$ = 4.0 Hz, Cquat), 143.9 (d, $^3J_{PC}$ = 12.6 Hz, Cquat). ^{31}P NMR (120 MHz, $CDCl_3$): δ 25.9. FTIR (KBr) ν_{max} (cm^{-1}): 3310 (N−H st), 1229 (P═O st). CIMS *m*/*z* (amu): 332 ([M^+ + H], 74), 222 ([M^+] − $PO(OMe)_2$, 100). Anal. Calcd for $C_{18}H_{22}NO_3P$: C 65.25; H 6.69; N 4.23. Found: C 65.31; H 6.75; N 4.16.

General Procedure. Synthesis α-Aminophosphonates 7. A solution of α,β-unsaturated imine **5** or vinylogous α-aminophosphonate **6** (0.5 mmol) in EtOH (5 mL) with Pd−C (10%) (32 mg, 0.03 mmol) was stirred for 2 days under H_2 atmosphere at 80 psi. The resulting mixture was filtered through celite and concentrated under reduced pressure. The crude residue was purified by chromatography (SiO_2, AcOEt/pentane 3:1).

Dimethyl (3-Phenyl-1-*p*-tolylamino-propyl)-phosphonate 7a. Synthesized according to the general procedure from dimethyl (3-phenyl-1-*p*-tolylimino-allyl)-phosphonate **5a** (165 mg, 0.5 mmol), affording 258 mg (88%) of **7a** as a colorless oil. Synthesized according to the general procedure from dimethyl (3-phenyl-1-*p*-tolylamino-allyl)-phosphonate **6a** (167 mg, 0.5 mmol), affording 0.241 mg (91%) of **7a** as a colorless oil. R_f (AcOEt): 0.67. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97 (m, 1 H, CH_2), 2.20 (m, 1 H, CH_2), 2.22 (s, 3 H, CH_3), 2.72 (m, 1 H, CH_2), 2.88 (m, 1 H, CH_2), 3.67 (d, $^3J_{PH}$ = 11.0 Hz, 3 H, OCH_3), 3.71 (d, $^3J_{PH}$ = 11.1 Hz, 3 H, OCH_3), 3.80 (m, 1 H, CHN), 6.50 (d, $^3J_{HH}$ = 8.4 Hz, 2 H, 2 × CHar), 6.98 (d, $^3J_{HH}$ = 8.4 Hz, 2 H, 2 × CHar), 7.12−7.16 (m, 2H, 2 × CHar), 7.19−7.30 (m, 3H, 3 × CHar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6 (CH_3), 32.2 (d, $^3J_{PC}$ = 12.1 Hz, CH_2), 32.6 (d, $^2J_{PC}$ = 4.5 Hz, CH_2), 50.5 (d, $^1J_{PC}$ = 155.1 Hz, CHN), 52.8 (d, $^2J_{PC}$ = 7.1 Hz, OCH_3), 53.8 (d, $^2J_{PC}$ = 7.1 Hz, OCH_3), 113.8 (2 × CHar), 126.3 (CHar), 127.7 (Cquat), 128.7 (2 × CHar), 128.9 (2 × CHar), 130.0 (2 × CHar), 141.1 (Cquat), 144.8 (d, $^3J_{PC}$ = 5.0 Hz, Cquat). ^{31}P NMR (120 MHz, $CDCl_3$): δ 29.8. FTIR (KBr) ν_{max} (cm^{-1}): 3297 (N−H st), 1228 (P═O st). CIMS *m*/*z* (amu): 334 ([M^+ + H], 77), 224 ([M^+] − $PO(OMe)_2$, 100). Anal. Calcd for $C_{18}H_{24}NO_3P$: C 64.85; H 7.26; N 4.20. Found: C 64.95; H 7.33; N 4.15.

Acknowledgment. The present work has been supported by the Dirección General de Investigación del Ministerio de Ciencia y Tecnología (MCYT, Madrid DGI, CTQ2006-09323) and by the Universidad del País Vasco (UPV, GIU 06/51). J.V. thanks the Departamento de Educación, Universidades e Investigación del Gobierno Vasco for a postdoctoral fellowship. Drs. J. M. de los Santos and C. Alonso are gratefully acknowledged for their assistance with 2D NMR experiments.

Supporting Information Available: Procedures and full characterization for compounds **5b**−**e**, **6b**−**e**, **7a**−**c**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062609+