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# Synthesis of Fluoroalkylated β-Aminophosphonates and Pyridines from Primary β-Enaminophosphonates

Francisco Palacios,* Ana M. Ochoa de Retana, Julen Oyarzabal, Sergio Pascual, and Guillermo Fernández de Trocóniz

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

*francisco.palacios@ehu.es*

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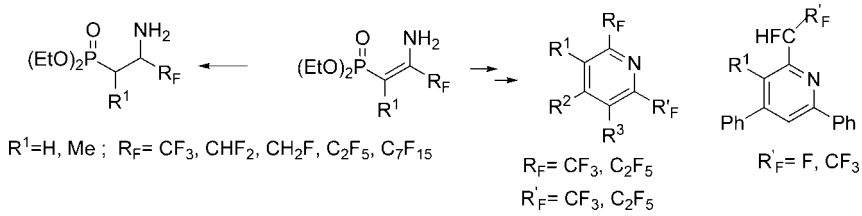


A simple and efficient stereoselective synthesis of fluorine containing β-aminophosphonates by reduction of β-enaminophosphonates is described. Reduction with sodium cyanborohydride in the presence of zinc chloride and the catalytic hydrogenation of β-enaminophosphonates gives β-aminophosphonates. β-Enaminophosphonates are also used as intermediates for the regioselective synthesis of fluoroalkyl-substituted pyridines.

## Introduction

Organophosphorus compounds are important substrates in the study of biochemical processes, and β-aminophosphonates, being isosteres of β-amino acids, play an important role and reveal interesting biological and biochemical properties as enzyme inhibitors, agrochemicals or pharmaceuticals.[1] At the same time, in the field of bioactive molecules, fluoroorganic compounds have received a great deal of attention since the incorporation of a fluorine-containing group into an organic molecule dramatically alters its physical, chemical, and biological properties.[2] These changes in properties make them suitable for diverse applications in synthetic, agricultural, and medicinal chemistry as well as in material science.[3] Special interest has been focused on developing synthetic methods for the preparation of fluorinated building blocks because they can be used for the efficient and/or selective preparation of fluorine-containing molecules with biological activity and commercial applications.[4] In this context, selective fluorination of amino acids and preparation of fluorinated analogues of amino acids has recently been used to stabilize proteins for their application in protein-based biotechnologies such as protein therapeutics and biosensors.[5] For these reasons, the development of new methods for the preparation of fluorine-substituted aminophosphonates[6] is an interesting goal in synthetic organic chemistry, not only because of their use in medicinal chemistry as inhibitors

(1) For reviews see: (a) Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899–931. (b) Palacios, F.; Alonso, C.; de los Santos, J. M. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley: New York, 2005; pp 277−317.

(2) (a) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004. (b) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; Wiley: New York, 1991. (c) *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington, DC, 1991.

(3) (a) Chambers, R. D. *Fluorine in Organic Chemistry*, 2nd ed.; Blackwell: London, 2004. (b) *Organofluorine Compounds: Chemistry and Applications*; Hiyama, T., Ed.; Springer: Berlin, 2000.

(4) (a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets*; Soloshonok, V. A., Ed.; Wiley: New York, 1999. (b) *Fluorine-Containing Amino Acids: Synthesis and Applications*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: New York, 1995.

(5) For recent contributions, see: (a) Meng, H.; Kumar, K. *J. Am. Chem. Soc.* **2007**, *129*, 15615–15622. (b) Chiu, H. P.; Suzuki, Y.; Gullickson, D.; Ahmad, R.; Kokona, B.; Fairman, R.; Cheng, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 15556–15557. (c) Lee, H. Y.; Lee, K. H.; Al-Hashimi, H. M.; Marsh, E. N. G. *J. Am. Chem. Soc.* **2006**, *128*, 337–343.

(6) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868–3935.

(7) For recent contributions, see: (a) Jakeman, D. L.; Ivory, A. J.; Blackburn, G. M.; Wiliamson, M. P. *J. Biol. Chem.* **2003**, *278*, 10957–1962. (b) Boyle, N. A.; Rajwanshi, V. K.; Prhavc, M.; Wang, G.; Fagan, P.; Chen, F.; Ewing, G. J.; Brooks, J. L.; Hard, T.; Leeds, J. M.; Bruice, T. W.; Cook, P. D. *J. Med. Chem.* **2005**, *48*, 2695–2700. (c) Dufresne, C.; Roy, P.; Wang, Z.; Asante-Appiah, E.; Cromlish, W.; Boie, Y.; Forghani, F.; Desmarais, Q.; Wang, K.; Skorey, K.; Waddleton, D.; Ramachadran, C.; Kennedy, B. P.; Xu, L.; Gordon, R.; Chan, C. C.; Leblanc, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1030–1042. (d) Higashimoto, Y.; Saito, S.; Tong, X. H.; Hong, A.; Sakaguchi, K.; Appella, E.; Anderson, C. W. *J. Biol. Chem.* **2000**, *275*, 23199–23203. (e) Herczegh, P.; Buxton, T. B.; McPherson, J. C.; Kovács-Kulyassa, A.; Brewer, P. D.; Sztaricskai, F.; Stroebel, G. G.; Plowman, K. M.; Farcasiu, D.; Hartmann, J. F. *J. Med. Chem.* **2002**, *45*, 2338–2341.



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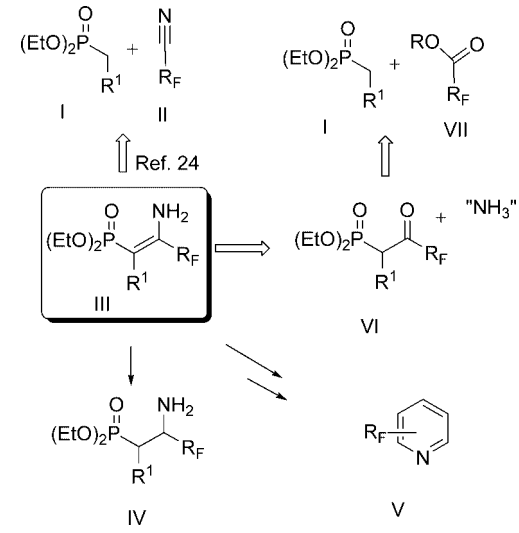
of enzymes ligands for phosphoglycerate kinase,[7a–c] catalytic antibodies, [7d] or antibacterials[7e] but also for the preparation of fluorinated peptidomimetics.[8] However, only the addition of amines[7e] or ammonia[9] to unsaturated phosphonates, the addition of fluorinated phosphonate carbanions to *N*-protected α-haloamines[10a] or imines,[10b–e] or the ring opening of fluorinated aziridines[11] for the synthesis of fluorine-substituted aminophosphonates have been described.

Moreover, enamines have attracted a great deal of attention in recent years because of their range of applications,[12,13] and especially metaloenamines,[14] carbanions derived from enamines or enolizable imines, are useful substrates for the regio- and stereoselective carbon−carbon bond formation reaction with electrophilic reagents.[15,16] However, primary enamines, despite their potential interest as synthons in organic synthesis for the preparation of acyclic and cyclic derivatives, have been less studied, given that they are unstable unless conjugated with an electron-withdrawing group on the $\beta$-carbon atom.[17] In connection with our interest in the preparation of three-,[18] five-,[19] and six-membered[20] phosphorus-substituted nitrogen heterocycles, we described the synthesis of stable primary enamines derived from phosphonates[21a] and carboxylates[21b] as well as their synthetic use for the preparation of functionalized acyclic compounds,[22a] aminophosphonate derivatives,[22b] and phosphorus-containing heterocycles.[23] In this context, we reported the first synthesis of fluorinated primary enamine phosphonates by reaction of alkylphosphonates **I** with fluoroalkyl nitriles **II** (see Scheme 1)[24] and the synthetic application of these intermediates as starting material for the preparation of acyclic fluoroalkyl nitrogenated derivatives.[25] However, for preparative purposes, the use of perfluoroalkylated nitriles has two drawbacks for the preparation of enamines **III** in a multigram scale: the price (availability) of the nitriles and the fact that the low members (C2, C3) are gases with problems for the control of the stoichiometry of the reaction.

**SCHEME 1. Synthetic Strategy for Preparation of β-Aminophosphonates and Pyridines from β-Enaminophosphonates**




Phosphorus substituents could regulate important biological functions and increase biological activity, in a way similar to that reported for pharmaceuticals.[26] Therefore, continuing with our interest in the chemistry of amino phosphorus derivatives[1] and in the design of new phosphorus scaffolds, in this case also containing fluoroalkyl substituents, we report here new alternatives for the selective synthesis of primary $\beta$-enaminophosphonates containing fluoroalkyl substituents in the $\beta$ position **III** (Scheme 1) from easily available starting materials, as well as

(8) (a) Binkert, C.; Frigerio, M.; Jones, A.; Meyer, S.; Pesenti, C.; Prade, L.; Viani, F.; Zanda, M. *ChemBioChem* **2006**, *7*, 181–186. (b) Lazzaro, F.; Crucianelli, M.; De Angelis, F.; Frigerio, M.; Malpezzi, L.; Volonterio, A.; Zanda, M. *Tetrahedron: Asymmetry* **2004**, *15*, 889–893. (c) Volonterio, A.; Bellosta, S.; Bravin, F.; Bellucci, M. C.; Bruche, L.; Colombo, G.; Malpezzi, L.; Mazzini, S.; Meille, S. V.; Meli, M.; Ramirez de Arellano, C.; Zanda, M. *Chem. Eur. J.* **2003**, *9*, 4510–4522. (d) Molteni, M.; Volonterio, A.; Zanda, M. *Org. Lett.* **2003**, *5*, 3887–3890.

(9) Cen, W.; Shen, Y. *J. Fluorine Chem.* **1995**, *72*, 107–110.

(10) (a) Jakeman, D. L.; Wiliamson, M. P.; Blackburn, G. M. *J. Med. Chem.* **1998**, *41*, 4439–4452. (b) Röschenthaler, G. V.; Kukhar, V.; Barten, N.; Gvozdovska, N.; Belik, M.; Sorochinsky, A. *Tetrahedron Lett.* **2004**, *45*, 6665–6667. (c) Sergeeva, N. N.; Golubev, A. S.; Henning, L.; Burger, K. *Synthesis* **2003**, 915–919. (d) Nieschalk, J.; Batsanov, A. S.; O'Hagan, D.; Howard, J. *Tetrahedron* **1996**, *52*, 165–176. (e) Xiao, J.; Yuan, C. *Heteroat. Chem.* **2000**, *11*, 541–545.

(11) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2006**, *71*, 6141–6148.

(12) For an excellent review see: Rappoport, Z. *The Chemistry of Enamines. The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds.; J. Wiley: Chichester, 1994.

(13) For recent reviews, see: (a) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433–2480. (b) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975–978. (c) Elassar, A. Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463–8480.

(14) For reviews see: (a) Shatzmiller, S.; Lidor, R. In reference 12, Part 2, 1994, pp 1507−1533. (b) Martin S. F. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 475.

(15) (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283. (b) Stork, G. *Med. Res. Rev.* **1999**, *19*, 370–387. (c) Cuvigny, T.; Normant, H. *Synthesis* **1977**, 198–200. (d) Stork, G.; Brizzolarra, A.; Landesman, H.; Szmuszkovicz, J.; Terrele, R. *J. Am. Chem. Soc.* **1963**, *85*, 207–222.

(16) (a) Palacios, F.; Aparicio, D.; García, J.; Rodríguez, E.; Fernández, A. *Tetrahedron* **2001**, *57*, 3131–3141. (b) Palacios, F.; Aparicio, D.; García, J.; Vicario, J.; Ezpeleta, J. M. *Eur. J. Org. Chem.* **2001**, 3357–3365. (c) Palacios, F.; Aparicio, D.; García, J.; Rodríguez, E. *Eur. J. Org. Chem.* **1998**, 1413–1423. (d) Palacios, F.; Aparicio, D.; García, J. *Tetrahedron* **1996**, *52*, 9609–9628.

(17) (a) Novak, B. M.; Cafmayer, J. *J. Am. Chem. Soc.* **2001**, *123*, 11083–11084. (b) Erker, G.; Riedel, M.; Koch, S.; Jöedicke, T.; Würthwein, E. U. *J. Org. Chem.* **1995**, *60*, 5284–5290.

(18) (a) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2005**, *70*, 8895–8901. (b) 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. (c) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; Lopez de Munain, R. *J. Org. Chem.* **2002**, *67*, 7283–7288. (d) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Ezpeleta, J. M. *J. Org. Chem.* **2000**, *65*, 3213–3217.

(19) (a) de los Santos, J. M.; Aparicio, D.; López, Y.; Palacios, F. *J. Org. Chem.* **2008**, *73*, 550–557. (b) Palacios, F.; Aparicio, D.; López, Y.; de los Santos, J. M.; Ezpeleta, J. M. *Tetrahedron* **2006**, *62*, 1095–1101. (c) Palacios, F.; Aparicio, D.; Vicario, J. *Eur. J. Org. Chem.* **2005**, 2843–2850. (d) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Alonso, J. M. *Tetrahedron* **2004**, *60*, 8937–8947.

(20) (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.; Aparicio, D.; López, Y.; de los Santos, J. M.; Alonso, C. *Eur. J. Org. Chem.* **2005**, 1142–1147. (c) Palacios, F.; Herran, E.; Rubiales, G.; Ezpeleta, J. M. *J. Org. Chem.* **2002**, *67*, 2131. (d) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Lopez de Munain, R. *Org. Lett.* **2002**, *4*, 2405–2508. (e) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J. *Tetrahedron* **1999**, *55*, 5947–5964.

(21) (a) Palacios, F.; Oyarzabal, J.; Ochoa de Retana, A. M. *Tetrahedron Lett.* **1996**, *37*, 4577–4580. (b) Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690–7696.

(22) (a) Palacios, F.; Vicario, J. *Org. Lett.* **2006**, *8*, 5405–5408. (b) Palacios, F.; Vicario, J.; Maliszewska, A.; Aparicio, D. *J. Org. Chem.* **2007**, *72*, 2682–2685.

(23) (a) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Lopez de Munain, R.; Oyarzabal, J.; Ezpeleta, J. M. *Tetrahedron* **2005**, *61*, 1087–1094. (b) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Lopez de Munain, R. *Tetrahedron Lett.* **2002**, *43*, 5917–5919. (c) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J. *Tetrahedron* **1999**, *55*, 3091–3104.

(24) Palacios, F.; Pascual, S.; Oyarzabal, J.; Ochoa de Retana, A. M. *Org. Lett.* **2002**, *4*, 769–772.

(25) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004**, *69*, 8767–8774.

(26) (a) Toy, A. D. F.; Walsh, E. N. *Phosphorus Chemistry in Everyday Living*; American Chemical Society: Washington, DC, 1987. (b) *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; M. Dekker: New York, 1992.

**SCHEME 2. Synthesis of Ketones 3 and Enamines 6**

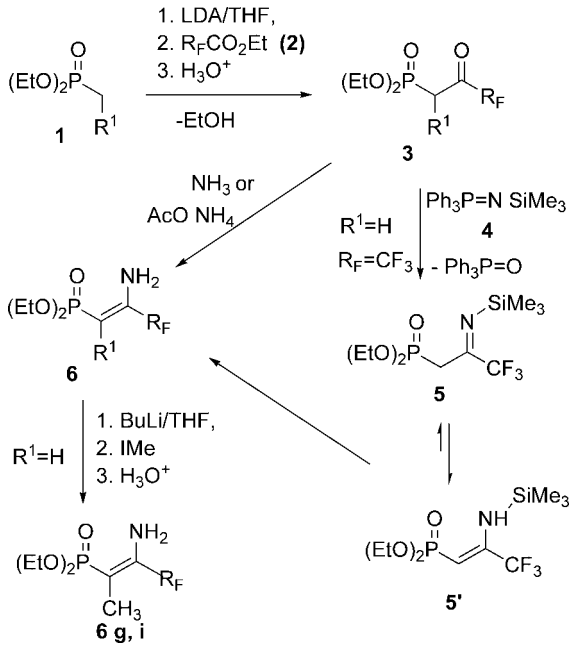



**TABLE 1. β-Keto Phosphonates 3**

| entry | compound | $R^1$ | $R_F$ | yield (%)[a] |
|---|---|---|---|---|
| 1 | **3a**[b] | H | $CF_3$ | 78 |
| 2 | **3b**[b] | H | $C_2F_5$ | 75 |
| 3 | **3c** | H | $C_7F_{15}$ | 91 |
| 4 | **3d** | H | $CHF_2$ | 82 |
| 5 | **3e** | H | $CH_2F$ | 94 |
| 6 | **3f**[b] | $CH_3$ | $CF_3$ | 73 |
| 7 | **3g** | $CH_3$ | $C_2F_5$ | 90 |
| 8 | **3h** | $CH_3$ | $CHF_2$ | 90 |
| 9 | **3i** | $CH_3$ | $CH_2F$ | 90 |

[a] Yield of isolated purified compounds. [b] Reference.[11]

their use as versatile tools for the formation of fluoro-containing β-aminophosphonates **IV** and substituted pyridines **V**. Retrosynthetically, we envisaged obtaining primary enamines **III** by condensation reaction with ammonia or its synthetic equivalent ("$NH_3$", Scheme 1) of β-keto phosphonates **VI**, and these phosphonates **VI** can be easily prepared by simple addition of fluoroalkyl esters **VII** to metallated alkyl phosphonates **I**.[11]

## Results and Discussion

**Synthesis of (*Z*)-Primary β-Enaminophosphonates 6.** The β-keto phosphonates required were prepared by reaction of diethyl methylphosphonates **1** ($R^1 = H, CH_3$) with perfluoroalkyl carboxylates **2** ($R_F = CF_3, C_2F_5, C_7F_{15}$), ethyl 2,2-difluoromethyl acetate **2** ($R_F = CHF_2$), or ethyl 2-fluoromethyl acetate **2** ($R_F = CH_2F$) in the presence of LDA or BuLi in an inert atmosphere, which after workup gave fluorine-substituted β-keto phosphonates **3a**−**3i** in a good yield (Scheme 2, Table 1, entries 1−9).[27] Therefore, the scope of the process was not restricted to perfluoroalkyl carboxylates, given that α′,α′-difluoro- or α′-monofluoro β-keto phosphonates **3** can also be prepared.

The synthesis of enamines by aza-Wittig reaction[28] of *N*-trimethylsilyl phosphazene **4** with β-keto phosphonates **3** was also explored, since this process represents one of the best alternatives for the selective construction of carbon−nitrogen bonds and has been used for the preparation of 1-[22] and 2-azadienes.[20c] Treatment of β-keto phosphonate **3a** with *N*-trimethylsilyl phosphazene **4** gave silylated enamine **5′a**. However, this compound is unstable, and after distillation or chromatography enamine **6a** ($R^1 = H, R_F = CF_3$) was obtained. The process can be explained by initial construction of the C=N double bond with formation of imine **5**, followed by prototropic tautomerie and C−Si bond cleavage of enamine **5′a** in the reaction conditions.

**TABLE 2. β-Enaminophosphonates 6 Obtained**

| entry | compound | $R^1$ | $R_F$ | yield (%)[a] |
|---|---|---|---|---|
| 1 | **6a** | H | $CF_3$ | 74 |
| 2 | **6b** | H | $C_2F_5$ | 71(70)[b] |
| 3 | **6c** | H | $C_7F_{15}$ | 49 |
| 4 | **6d** | H | $CHF_2$ | 72 |
| 5 | **6e** | H | $CH_2F$ | 61(77)[b] |
| 6 | **6f** | $CH_3$ | $CF_3$ | 70 |
| 7 | **6g**[c] | $CH_3$ | $CHF_2$ | 67(51)[d] |
| 8 | **6h**[e] | $CH_3$ | $CH_2F$ | 67 |
| 9 | **6i** | $CH_3$ | $C_2F_5$ | 72[f] |

[a] Yield of isolated purified compounds from ketones **3** and $AcONH_4$. [b] Yield of isolated purified compounds from ketones **3** and $NH_3$. [c] Obtained as a mixture of *Z*/*E* isomers (75:25) and determined by $^{31}P$ NMR. [d] Yield obtained from **6d**. [e] Obtained as a mixture of *Z*/*E* isomers (57:43) and determined by $^{31}P$ NMR. [f] Yield obtained from **6b**.

Next we accomplished the synthesis of β-enaminophosphonates or β-dehydroaminophosphonates **6** by condensation of ammonia gas with β-keto phosphonates **3**. Ammonia was bubbled through a solution of 1 mmol of β-keto phosphonates **3b** ($R^1 = H, R_F = C_2F_5$) and **3e** ($R^1 = H, R_F = CH_2F$) in toluene, and after 7−8 h this led to the formation of enamines **6b** and **6e** (Scheme 2, Table 2, entries 2 and 5). However, when the reaction was extended to a multigram scale, the reaction times were very long and a large amount of starting material did not react. This disadvantage was overcome by using ammonium acetate[29] instead of ammonia. Heating ammonium acetate at 80 °C with β-keto phosphonates **3** (scale 25 mmol) in the absence of solvent gave *Z*-enamines **6** in moderate or good yields (Scheme 2, Table 2, entries 1−6). However, when β-keto phosphonates **3d,e** ($R^1 = CH_3, R_F = CHF_2, CH_2F$) were used, mixtures of *Z*- and *E*-enamines **6g,h** are obtained in good yields with a higher proportion of the *Z* isomer (Scheme 2, Table 2, entries 7 and 8). $^{13}C-^{31}P$ coupling constant ($^3J_{PC}$) in the range of 4−10 Hz showing that the fluoro-substituted alkyl group ($R_F$) and the phosphorus atom in enamines **6** are *cis* related, and values in the range of 24−35 Hz are *trans* related.[30]

This process cannot be used for the synthesis of β-enaminophosphonate **6i** ($R^1 = CH_3, R_F = C_2F_5$) by condensation of β-keto phosphonate **3f** ($R^1 = CH_3, R_F = C_2F_5$) either with ammonia or with ammonium acetate; the starting keto phosphonate **3f** was recovered. Therefore, an alternative strategy was developed for the preparation of α-methyl-substituted enamines **6** ($R^1 = Me$) by methylation reaction of metallated enamines **6** ($R^1 = H$). The reaction of enamines **6b,d** ($R^1 = H$) with methyl

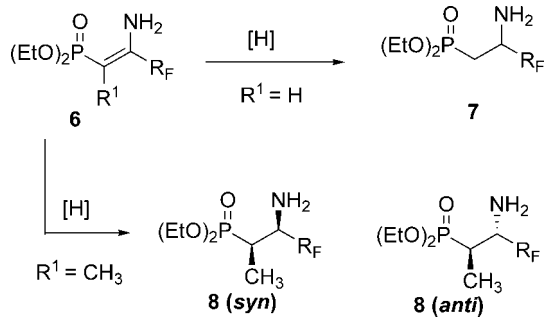
(27) Fluorinated β-keto phosphonates **3**, initially formed, can undergo addition of water to provide the hydrate form. The use of high vacuum allows one to dehydrate the *gem*-diol to recover β-keto phosphonates **3**.[11]

(28) For reviews see: (a) Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. *Tetrahedron* **2007**, *3*, 523–575. (b) Fresneda, M. P.; Molina, P. *Synlett* **2004**, 1–17. (c) Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991**, *23*, 1–59.

(29) (a) Pévet, I.; Meyer, C.; Cossy, J. *Synlett* **2003**, 663–666. (b) Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 902–905.

(30) (a) Palacios, F.; Aparicio, D.; de los Santos, J. M. *Tetrahedron* **1994**, *50*, 12727. (b) Duncan, M.; Gallager, M. J. *Org. Magn. Reson.* **1981**, *15*, 37.

**SCHEME 3. Preparation of Fluorinated β-Aminophosphonates 7 and 8**




iodide in the presence of BuLi gave fluorine-substituted α-methyl enamines **6g,i** ($R^1 = CH_3$) after workup (Scheme 2, Table 2, entries 7 and 9).

**Reduction of β-Enaminophosphonates or β-Dehydroaminophosphonates 6. Synthesis of Fluoroalkylated β-Aminophosphonates.** Aminophosphorus derivatives[31] in general, even those containing fluorine substituents,[6] and β-amino compounds in particular[1,32] have acquired increased interest in recent years because of their application in organic and medicinal chemistry. For this reason we tried to study the use of phosphorylated enamines containing fluoroalkyl substituents for the preparation of fluorinated β-aminophosphorus derivatives. Reduction of α- and β-dehydroamino acid derivatives is an excellent tool for the stereoselective preparation of α-[22a,33] and β-amino acids.[34] Therefore, we explored whether the reduction of isosteric β-dehydroaminophosphonates **6** obtained here (vide supra) could be used to obtain fluoroalkyl-substituted β-aminophosphonates.

For this objective, we thought that the use of hydrides for the reduction of enaminophosphonates **6** could be appropriate. Initially, $NaBH_4$ in THF/$H_2O$ was used, but the starting material was recovered. Other reagents such as $LiAlH_4$, $NaBH[OC(O)CF_3]$, Na/iPrOH, and $BH_3$-pyridine were not effective for the reduction of enamines **6**. However, when the reduction of enamine **6a** ($R^1 = H$, $R_F = CF_3$) was performed using $ZnCl_2$ and $NaBH_3CN$ in refluxing MeOH (Procedure A) the corresponding trifluoromethyl-substituted β-aminophosphonate **7a** (Scheme 3, Table 3, Entry 1) was obtained. The reaction was extended to difluoromethyl ($R^1 = H$, $R_F = CHF_2$), monofluoromethyl ($R^1 = H$, $R_F = CH_2F$), and pentafluoroethyl ($R^1 = H$, $R_F = C_2F_5$) enamines **6**, and the corresponding fluorinated β-aminophosphonate **7b−d** (Scheme 3, Table 3, entries 2−4) were prepared. Spectroscopic data are in agreement with the proposed structure for compounds **7**.

This reduction reaction was extended to α-methyl-substituted enamines **6** ($R^1$ = Me), and when these enamines **6** were treated with $ZnCl_2$ and $NaBH_3CN$ in refluxing MeOH (Procedure A), the corresponding trifluoromethyl **8a** ($R_F = CF_3$), difluoromethyl **8b** ($R_F = CHF_2$), monofluoromethyl **8c** ($R_F = CH_2F$), and pentafluoroethyl **8d** ($R_F = C_2F_5$) β-aminophosphonates were obtained as a mixture of two diastereoisomers, with a higher proportion of the *anti* isomer (Scheme 3, Table 4, entries 1, 3, 5, 6). Very small vicinal coupling constants ($^3J_{HH}$) between 0−5 Hz are characteristic of the *syn* isomers, and higher values (7−12 Hz) for the *anti* isomers.[35]

The stereochemical outcome to the higher proportion of *anti* isomers in this reduction reaction of α-methyl-substituted enamines **6** ($R^1$ = Me) can be explained by the Felkin−Anh approach,[36] in which the $ZnCl_2$ coordinates to the nitrogen imino group (Figure 1).[37] The hydride then attacks the imino double bond from the face opposite to the phosphonate group.

**TABLE 3. β-Aminophosphonates 7 Obtained by Reduction of β-Enaminophosphonates 6 ($R^1 = H$)**

| entry | compound | $R_F$ | yield (%)[a] | |
|---|---|---|---|---|
| 1 | **7a**[b] | $CF_3$ | 67[c] | 79[d] |
| 2 | **7b** | $CHF_2$ | 68[c] | 76[d] |
| 3 | **7c** | $CH_2F$ | 61[c] | |
| 4 | **7d**[b] | $C_2F_5$ | 64[c] | 75[d] |
| 5 | **7e** | $C_7F_{15}$ | | 87[d] |

[a] Yield of isolated purified compounds from enamines **6**. [b] References 9 and 11. [c] Procedure A ($ZnCl_2$−$NaBH_3CN$/MeOH) [d] Procedure B ($H_2$ (80 psi)) and Pd/C, MeOH).

**TABLE 4. β-Aminophosphonates 8 Obtained by Reduction of β-Enaminophosphonates 6 ($R^1 = CH_3$)**

| entry | compound | $R_F$ | *syn*/*anti* **8** ratio[a] | procedure | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **8a** | $CF_3$ | 35/65 | A[c] | 62 |
| 2 | **8a** | $CF_3$ | 100/0 | B[d] | 75 |
| 3 | **8b** | $CHF_2$ | 15/85 | A[c] | 65 |
| 4 | **8b** | $CHF_2$ | 70/30 | B[d] | 69 |
| 5 | **8c** | $CH_2F$ | 22/78 | A[c] | 65 |
| 6 | **8d** | $C_2F_5$ | 25/75 | A[c] | 59 |
| 7 | **8d** | $C_2F_5$ | 90/10 | B[d] | 71 |

[a] Determined by $^{31}P$ NMR. [b] Yield of isolated purified compounds from enamines. [c] Procedure A ($ZnCl_2$−$NaBH_3CN$/MeOH). [d] Procedure B ($H_2$ (80 psi) and Pd/C, MeOH).

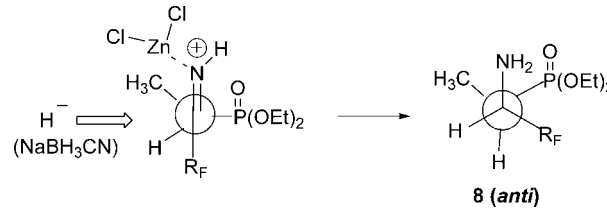



**FIGURE 1.** Felkin−Anh approach. Preferred addition of hydride to enamines **6**.

(31) For reviews, see: (a) Berrlicki, L.; Kafarski, P. *Curr. Org. Chem.* **2005**, *9*, 1829–1850. (b) Kafarski, P.; Lejczak, B. *Curr. Med. Chem. Anti-Cancer Agents* **2001**, *1*, 301–312. (c) *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; Wiley: Chichester, 2000.

(32) For a review of β-phosphapeptidomimetics, see:(a) Palacios, F.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2004**, *8*, 1491–1496.

(33) For recent contributions to hydrogenation of α-dehydroamino acid derivatives, see: (a) Giacomina, F.; Meetsma, A.; Panella, L.; Lefort, L.; de Vries, A. H. M.; de Vries, J. C. *Angew- Chem. Int. Ed.* **2007**, *46*, 1497–1500. (b) Zhang, W.; Zhang, X. *J. Org. Chem.* **2007**, *72*, 31020–1030. (c) Zheng, Q. H.; Hu, X. P.; Duan, Z. C.; Liang, X. M.; Zheng, Z. *J. Org. Chem.* **2006**, *71*, 393–396.

(34) For recent contributions to reduction of β-dehydroamino acid derivatives, see: (a) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267–1267. (b) Ikemoto, N.; Tellers, D. M.; Dreher, S. D.; Liu, J.; Huang, A.; Rivera, N. R.; Njolito, E.; Hsiao, Y.; McWillams, J. C.; Williams, J. M.; Armstrong, J. D.; Sun, Y.; Mathre, D. J.; Grabowski, E. J. J.; Tllyer, R. D. *J. Am. Chem. Soc.* **2004**, *126*, 3048–3049. (c) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553. (d) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Haviari, G.; Célerier; J. P.; Llommet, G.; Gramain, J. C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122–3131.

(35) (a) Gaudemar, A.; Golfrer, M.; Mandelbaum, A.; Parthasarathy, R. *Determination of Configutration by Spectroscopic Methods*; Kaganv H, B., Ed.; G. Thieme: Stuttgart, 1977; Vol. 1, p 39. (b) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.

(36) (a) Chérest, M.; Felfin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199–2204. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–162.

(37) The more favorable conformation involves the phosphonate group being placed in a perpendicular position to the imino group while the bulky group, in our case the methyl group, occupies the remote position from the fluorine susbstituted group.

To test whether the minor isomer (*syn*) could be obtained in a selective fashion, we explored the catalytic hydrogenation of these substrates **6**. Better yields were obtained when the reduction of enamines **6** was accomplished by catalytic hydrogenation with palladium. Catalytic hydrogenation of enamines **6** ($R^1$ = H) with hydrogen (80 psi) and palladium on carbon in methanol (Procedure B) gave β-aminophosphonates **7** (Scheme 3, Table 3, entries 1, 2, 4, 5). This reduction reaction was also extended to α-methyl-substituted enamines **6** ($R^1$ = Me). When enamine **6a** ($R_F$ = $CF_3$) was treated with hydrogen (80 psi) and palladium on carbon in methanol (Procedure B), only the corresponding *syn*-trifluoromethyl β-aminophosphonates **8a** ($R_F$ = $CF_3$) was obtained (Scheme 3, Table 4, entry 2). However, in these reaction conditions (Procedure B) a small proportion of *anti* isomer (*syn*/*anti* ratio 90/10) of pentafluoroethyl β-aminophosphonate **8d** ($R_F$ = $C_2F_5$) was obtained (Scheme 3, Table 4, entry 7), whereas when a mixture of *Z*/*E* (75/25) enamine **6g** ($R_F$ = $CHF_2$) was used, the corresponding α-difluoromethyl β-aminophosphonate **8b** ($R_F$ = $CHF_2$) was obtained (Scheme 3, Table 4, entry 4), as a mixture of two diastereoisomers (*syn*/*anti* ratio 70/30).

The suprafacial (*syn*) addition of hydrogen is the most accepted mechanism for metal-catalyzed hydrogenations, in which the reaction occurs between species that are adsorbed onto the surface (Langmuir—Hinshelwood mechanism).[38] However, the presence of a small proportion of the *anti* isomer can be explained by means of a carbon−carbon double bond isomerization due to the interaction of the metal (Pd) in an addition−elimination sequence.[39,34d] The preparation of some perfluoroalkyl-substituted β-aminophosphonate derivatives such as **7a** and **7b** has been reported.[9,10e,11] However, as far as we know, this strategy reports the first synthesis of β-trifluoromethyl- (**8a**), β-difluoromethyl- (**7b**, **8b**), β-monofluoromethyl- (**7c**, **8c**), perfluoroethyl- (**8d**), and perfluorohepthyl (**7e**)-substituted β-aminophosphonate derivatives. These new fluorinated aminophosphonates could be very interesting starting materials for the preparation of new phosphapeptides containing fluorine atoms.

**Reaction of Enamines with α,β-Unsaturated Ketones. Synthesis of Fluorinated Pyridines.** Fluorine-containing heterocycles in general[4a] and pyridines in particular have acquired increased interest in chemistry.[40] For this reason we tried to explore if phosphorylated enamines containing fluoroalkyl substituents **6** could be used for the preparation of fluorinated pyridine derivatives. Heating fluorine-containing enamines **6** (R = H, $CH_3$, $R_F$ = $CF_3$, $C_2F_5$) with fluorinated α,β-unsaturated ketones[25] **9** ($R_F$ = $CF_3$, $C_2F_5$) at high temperature (100−130 °C) and in the absence of solvent gave only one isomer of polysubstituted pyridines **10** containing two fluoroalkyl groups in position 2 and 6 in a regioselective fashion and moderate yields (Scheme 4, Table 5, entries 1−8). The formation of these pyridines **10** could be explained through a Michael addition of enamine phosphonate **6** to the unsaturated ketones **9** (1,4-addition) followed by cyclization of adduct **11** and aromatization of cyclic compound **12**.

**SCHEME 4. Synthesis of Fluorine-Containing Pyridine Derivatives 10**

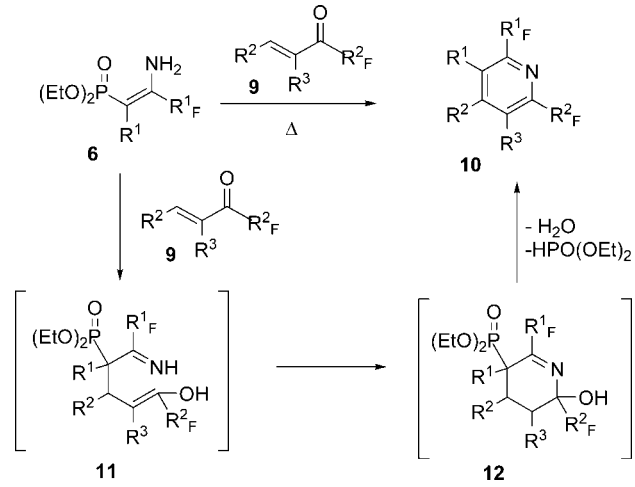



**TABLE 5. β-Fluorinated Pyridines 10 Obtained**

| entry | compound | $R^1$ | $R^1_F$ | $R^3_F$ | $R^2$ | $R^3$ | $R^2_F$ | yield (%)[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | **10a** | H | $CF_3$ | | p-$CH_3$-$C_6H_4$ | H | $CF_3$ | 53 |
| 2 | **10b** | H | $CF_3$ | |  | H | $CF_3$ | 47 |
| 3 | **10c** | H | $C_2F_5$ | | p-$CH_3$-$C_6H_4$ | H | $CF_3$ | 45 |
| 4 | **10d** | H | $CF_3$ | |  | H | $C_2F_5$ | 44 |
| 5 | **10e** | H | $CF_3$ | |  | $CH_3$ | $CF_3$ | 42 |
| 6 | **10f** | $CH_3$ | $CF_3$ | | p-$CH_3$-$C_6H_4$ | H | $CF_3$ | 40 |
| 7 | **10g** | $CH_3$ | $CF_3$ | | p-F-$C_6H_4$ | H | $CF_3$ | 44 |
| 8 | **10h** | $CH_3$ | $CF_3$ | |  | H | $C_2F_5$ | 48 |
| 9 | **14a** | H | | F | | | | 74 |
| 10 | **14b** | H | | $CF_3$ | | | | 31 |
| 11 | **14c** | $CH_3$ | | F | | | | 52 |

[a] Yield of isolated purified compounds from enamines.

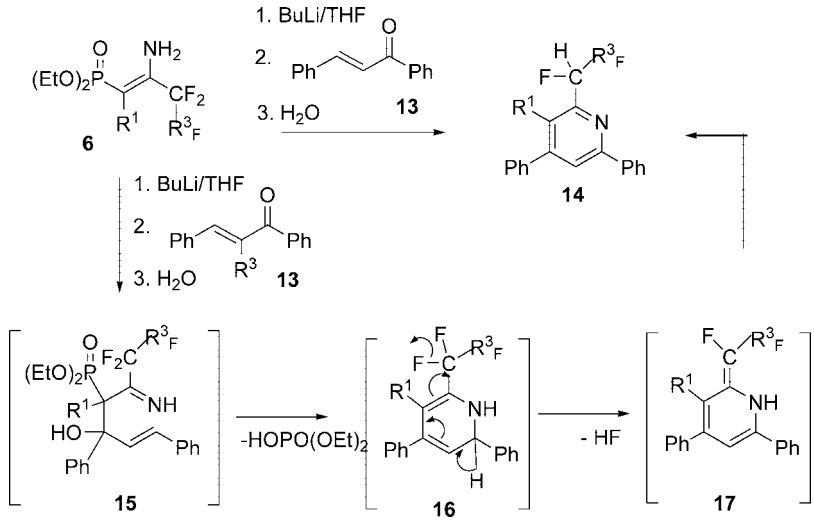
Finally, we explored the reaction of metalo-enamines derived from fluorinated enamines **6** with 1,3-diphenyl-2-propen-1-one **13**, in order to test if the increase of the nucleophilic character of enamine could modify the reactivity toward unsaturated ketones. Reaction of primary enamines **6** with butyllithium, followed by the addition of 1,3-diphenyl-2-propen-1-one **13**, gave fluorine-substituted pyridines **14** in a regioselective fashion (Scheme 5, Table 5, entries 9−11). It is noteworthy that, on the basis of spectroscopic data, the loss of a fluorine atom seems to take place during the formation of these pyridines **14**. The regioselective synthesis of these pyridines **14** could be explained through an addition of metallated enamine phosphonate to the unsaturated ketone **13** (1,2-addition) followed by cyclization, elimination of HF from heterocycles **16** with formation of **17**, followed by prototropic rearrangement to give pyridines **14**. Some methods of synthesis of fluorinated pyridines has been reported.[41] However, as far as we know, this strategy reports

(38) Smith, G. V.; Notheisz, F. *Heterogeneous Catalysis in Organic Chemistry*; Academic Press: New York, 1999.

(39) Siegel, S. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 8, p 417.

(40) For reviews, see: (a) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029. (b) Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Sttahl, M. *ChemBioChem.* **2004**, *5*, 637–643. (c) Jeschke, P. *ChemBioChem* **2004**, *5*, 570–589.

**SCHEME 5. Preparation of Pyridines 14**




the first synthesis of polysubstituted pyridines containing two fluoroalkyl groups **10** and fluorinated pyridines **14**.

## Conclusion

In conclusion, this account describes a simple, mild, and convenient strategy for the preparation of β-trifluoromethyl-, β-difluoromethyl-, β-monofluoromethyl-, perfluoroethyl-, and perfluorohepthyl-substituted β-aminophosphonate derivatives by reduction of β-dehydroaminophosphonates. Reduction with sodium cyanborohydride in the presence of zinc chloride of Cα-methyl-substituted enamines gives *anti* β-aminophosphonates as major products, whereas the catalytic hydrogenation leads mainly to the formation of *syn* β-aminophosphonates. These new fluorinated aminophosphonates could be very interesting starting materials for the preparation of new phosphapeptides containing fluorine atoms, in which the fluoroalkyl substituents could stabilize the corresponding biologically active peptides or proteins.[5] Likewise, the regioselective synthesis of fluorine-containing pyridines from enaminophosphonates and unsaturated ketones is also described. Substituted fluorinated pyridines[40] as well as β-amino phosphonate derivatives[1,32] are important building blocks in organic synthesis and in the preparation of biologically active compounds of interest in medicinal chemistry.

## Experimental Section

**General Procedure for the Synthesis of β-Keto Phosphonates 3.** To a solution of LDA (6 mmol) in THF (25 mL) was added a solution of alkylphosphonate **1** (5 mmol) in THF (15 mL) cooled at −78 °C under nitrogen atmosphere. The mixture was stirred for 1 h at −78 °C, a solution of the corresponding ester was added (6 mmol) in THF (12 mL) at the same temperature, and the mixture was stirred for 1 h and then allowed to warm at 0 °C. After the reaction was complete, the solvent was evaporated under vacuum. The crude residue was treated with HCl to 10% (5 mL) during 30 min. The crude reaction was extracted three times with $CH_2Cl_2$ (3 × 15 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent was evaporated under vacuum. The crude product was purified by vacuum distillation or by chromatography using silica gel eluting with 2:1 hexane/ethyl acetate to afford β-keto phosphonates **3**.

**Diethyl 3,3-Difluoro-2-oxopropylphosphonate 3d.** Obtained as a colorless oil as described in the general procedure (9.43 g, 82%): bp 70−72 °C ($10^{-1}$ Torr); IR (NaCl) $\nu_{max}$ 1751, 1216, 1052 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) δ 1.14 (m, 6H), 3.13 (d, $^2J_{PH}$ = 22.6 Hz, 2H), 3.97 (m, 4H), 5.71 (t, $^2J_{FH}$ = 53.7 Hz, 1H) ppm; $^{13}C$ NMR ($CD_3OD$) δ 14.8, 35.5 (d, $^1J_{PC}$ = 130.4 Hz), 61.7, 108.2 (t, $^1J_{FC}$ = 250.3 Hz), 190.6 (dt, $^2J_{PC}$ = 7.0 Hz, $^2J_{FC}$ = 26.2 Hz) ppm; $^{31}P$ NMR ($CDCl_3$) δ 17,4 ppm ; $^{19}F$ NMR ($CD_3OD$) δ −129.5 (d, $^2J_{FH}$ = 53.4 Hz) ppm; MS (EI) *m/z* 230 ($M^+$, 7). Anal. Calcd for $C_7H_{13}F_2O_4P$: C, 36.53; H, 5.69. Found: C, 36.70; H, 5.55.

**Aza-Wittig Reaction of β-Keto Phosphonate 3a with *N*-Trimethylsilyl Phosphazene 4.** To a solution of *N*-trimethylsilyl phosphazene **4** (1.74 g, 5mmol) in THF (15 mL) was added a solution of β-keto phosphonate **3a** (1.24 g, 5 mmol) in THF (10 mL) at room temperature under nitrogen atmosphere. The mixture was stirred for 3 h at the same temperature. After the reaction was completed, the solvent was evaporated under vacuum to afford the silylated enamine **5′a**. However, this compound was unstable and by distillation or by chromatography enamine **6a** was obtained. Mp 63−65 °C. For spectroscopic data see ref 25.

**General Procedure for the Synthesis of Fluorinated Primary β-Enaminophosphonates 6. General Procedure A.** Ammonia was bubbled through a solution of corresponding β-keto phosphonate **3** (1 mmol) in toluene (10 mL) at 100 °C until TLC showed the disappearance of ketone **3** (4−8 h). Then, the solvent was evaporated under vacuum, and the crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

**General Procedure B.** Ammonium acetate (75 mmol) was heated at 80 °C under vacuum, and the corresponding β-phosphorylated ketone **3** (25 mmol) was added. The mixture was stirred at 100 °C, under vacuum, and in the absence of solvent until TLC showed the disappearance of the β-phosphorilated ketone **3** (1−2 h). Then, a saturated solution of $NaCO_3$ (50 mL) was added, and the organic layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

**General Procedure C.** Butyllithium (1.6 M in hexanes) (25 mmol) was added to a solution of α-unsubstituted fluorinated enaminophosphonate **6** ($R^1$ = H) (25 mmol) in THF (75 mL) at 0 °C and under $N_2$ atmosphere. The mixture was stirred for 1 h at the same temperature. Then, methyl iodide (1.6 mL, 25 mmol) was added, and the reaction was stirred at room temperature until TLC

(41) For recent contributions, see: (a) Sosnovskikh, V. Y.; Irgashev, R. A.; Khalymbadzha, I. A.; Slepukhin, P. A. *Tetrahedron Lett.* **2007**, *48*, 6297–6300. (b) Nenajdenko, V. G.; Druzhinin, S. V.; Belenkova, E. S. *J. Fluorine Chem.* **2006**, *127*, 865–873. (c) Palacios, F.; Alonso, C.; Rodriguez, M.; Martinez de Marigorta, E.; Rubiales, G. *Eur. J. Org. Chem.* **2005**, 1795–1804. (d) Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 327–330.

showed the disappearance of the enaminophosphonate **6**. A saturated solution of ammonium chloride (50 mL) was added, the organic layer was extracted with $CH_2Cl_2$ (3 × 50 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

**(*Z*)-Diethyl 2-Amino-3,3-difluoro-1-propenylphosphonate 6d.** Obtained as a red solid as described in the general procedure B from diethyl 3,3-difluoro-2-oxopropylphosphonate **3d** and ammonium acetate (4.12 g, 72%): mp 70−71 °C; IR (KBr) $\nu_{max}$ 3409, 3316, 1653, 1224, 1049 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.27 (m, 6H), 4.00 (m, 4H), 4.11 (d, $^2J_{PH}$ = 10.1 Hz, 1H), 5.69 (sa, 2H), 5.94 (t, $^2J_{FH}$ = 55.2 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 15.6, 60.9, 74.7 (d, $^1J_{PC}$ = 193.9 Hz), 111.6 (dt, $^3J_{PC}$ = 27.7 Hz, $^1J_{FC}$ = 216.0 Hz), 154.0 (t, $^2J_{FC}$ = 22.1 Hz); $^{31}P$ NMR ($CDCl_3$) $\delta$ 23.0; $^{19}F$ NMR ($CDCl_3$) $\delta$ −122.0 (d, $^2J_{FH}$ = 54.9 Hz); MS (EI) *m*/*z* 229 ($M^+$, 20). Anal. Calcd for $C_7H_{14}F_2NO_3P$: C, 36.69; H, 6.16; N, 6.11. Found: C, 36.55; H, 6.25; N, 6.00.

**General Procedure for the Synthesis of Fluoroalkylated *β*-Aminophosphonates 7 and 8. General Procedure A.** To a solution of $ZnCl_2$ (1 mmol) and $NaBH_3CN$ (2 mmol) in anhydrous methanol (3 mL) was added a solution of the corresponding fluorinated enaminophosphonate **6** (1 mmol) in anhydrous methanol (3 mL) at room temperature under nitrogen atmosphere. The mixture was heated at methanol reflux until TLC showed the disappearance of the fluorinated enaminophosphonate **6** and then was allowed at room temperature. A solution of NaOH 1 M (10 mL) was added, the organic layer was extracted with $Et_2O$ (3 × 15 mL), washed with saturated solution of NaCl, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (ethyl acetate).

**General Procedure B.** To a solution of fluorinated enaminophosphonate **6** (1 mmol) and Pd/C (0.1 mmol) in anhydrous methanol was applied 80 psi of hydrogen, and the reaction was stirred until TLC showed the disappearance of the enamine **6** (48−72 h). Then the reaction was filtrated through celite, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (ethyl acetate).

**Diethyl 2-Amino-3-fluoropropylphosphonate 7c.** Obtained as a pale yellow oil as described in the general procedure A (130 mg, 61%): $R_f$ 0.20 (ethyl acetate/ methanol, 8/2); IR (NaCl) $\nu_{max}$ 3400, 1607, 1442, 1391, 1225, 1025 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.34 (t, $^3J_{HH}$ = 7.1 Hz, 6H), 1.82 (ddd, $^2J_{HH}$ = 15.3 Hz, $^2J_{PH}$ = 17.5 Hz, $^3J_{HH}$ = 8.9 Hz, 1H), 1.98 (m, 1H), 2.01 (sa, 2H), 3.47 (m, 1H), 4.13 (m, 4H), 4.34 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 16.7, 29.9 (dd, $^1J_{PC}$ = 141.5 Hz, $^3J_{FC}$ = 5.7 Hz), 47.1 (dd, $^2J_{FC}$ = 20.7 Hz, $^2J_{PC}$ = 4.1 Hz), 62.1, 87.7 (dd, $^1J_{FC}$ = 172.7 Hz, $^3J_{PC}$ = 18.1 Hz); $^{31}P$ NMR ($CDCl_3$) $\delta$ 29.3 (d, $^4J_{PF}$ = 3.2 Hz); $^{19}F$ NMR ($CDCl_3$) $\delta$ −226.1 (ddt, $^2J_{FH}$ = 47.3 Hz, $^3J_{FH}$ = 16.8 Hz, $^4J_{PF}$ = 3.0 Hz); HRMS ($EI^+$) calcd for $C_7H_{17}FNO_3P$ [$M^+$] 213.0930, found $M^+$ 213.0925.

***syn*/*anti*-Diethyl 2-Amino-3,3,3-trifluoro-1-methylpropylphosphonate 8a.** Obtained as a mixture of *syn*/*anti* isomers (35:65) as a pale yellow oil as described in the general procedure A (163 mg, 62%) or obtained as a mixture of *syn*/*anti* isomers (100:0) as a pale yellow oil as described in the general procedure B (197 mg, 75%). Both isomers can be separated by chromatography using silica gel. ***syn*-8a**: $R_f$ 0.1 (ethyl acetate); IR (NaCl) $\nu_{max}$ 3378, 3317, 1117, 1031 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.11 (dd, $^3J_{PH}$ = 18.8 Hz, $^3J_{HH}$ = 7.3 Hz, 3H), 1.20 (m, 6H), 1.57 (sa, 2H), 2.28 (ddq, $^2J_{PH}$ = 23.6 Hz, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 1.8 Hz, 1H), 3.77 (ddq, $^3J_{PH}$ = 11.9 Hz, $^3J_{FH}$ = 8.2 Hz, $^3J_{HH}$ = 1.8 Hz, 1H), 4.11 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 6.6, 16.1, 31.1 (d, $^1J_{PC}$ = 144.0 Hz), 51.8 (q, $^2J_{FC}$ = 29.0 Hz), 62.0, 126.0 (dq, $^1J_{FC}$ = 282.0 Hz, $^3J_{PC}$ = 25.7 Hz); $^{31}P$ NMR ($CDCl_3$) $\delta$ 30.7 ; $^{19}F$ NMR ($CDCl_3$) $\delta$ −76.1(d, $^3J_{FH}$ = 3.63 Hz). ***anti*-8a**: $R_f$ 0.15 (ethyl acetate); IR (NaCl) $\nu_{max}$ 3390, 2959, 1732, 1454, 1116 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.22 (d, $^3J_{HH}$ = 7.6 Hz, 3H), 1.27 (m, 6H), 1.78 (sa, 2H), 2.10 (m, 1H), 3.29 (m, 1H), 4.11 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 12,2, 16.2, 33.2 (d, $^1J_{PC}$ = 143.0 Hz), 55.2(q, $^2J_{FC}$ = 28.7 Hz), 62.0, 125.9 (dq, $^1J_{FC}$ = 282.5 Hz, $^3J_{PC}$ = 16.6 Hz); $^{31}P$ NMR ($CDCl_3$) $\delta$ 29.9 ; $^{19}F$ NMR ($CDCl_3$) $\delta$ −74.6(d, $^3J_{FH}$ = 7.63 Hz); MS (EI) *m*/*z* 264 ($M^+$ + 1, 2). Anal. Calcd for $C_8H_{17}F_3NO_3P$:C, 36.51; H, 6.51; N, 5.32. Found: C, 36.76; H, 6.42; N, 5.46.

**General Procedure for the Synthesis of Fluorinated Pyridines 10.** A mixture of the corresponding fluorinated enaminophosphonate **6** (2 mmol) and fluorinated α,*β*-unsaturated ketones[25] **9** (2 mmol) in the absence of solvent was stirred at 100−130 °C under nitrogen atmosphere, until TLC showed the disappearance of fluorinated enaminophosphonate **6**. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

**2-*p*-Tolyl-2,6-bis(trifluoromethyl)pyridine 10a.** Obtained as a white solid as described in the general procedure (323 mg, 53%): $R_f$ 0.61 (hexane/ethyl acetate, 15/1); mp 56−57 °C; IR (KBr) $\nu_{max}$ 3431, 1390, 1197, 1141 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.37 (s, 3H), 7.29 (d, $^3J_{HH}$ = 7.9 Hz, 2H), 7.52 (d, $^3J_{HH}$ = 7.9 Hz, 2H), 8.01 (s, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 21.2, 121.0 (q, $^1J_{FC}$ = 275.0 Hz), 120.5, 127.0, 130.4, 132.6, 141.3, 149.3 (q, $^2J_{FC}$ = 35.2 Hz), 152.4; $^{19}F$ NMR ($CDCl_3$) $\delta$ −68.6; MS (EI) *m*/*z* 305 ($M^+$, 100). Anal. Calcd for $C_{14}H_9F_6N$: C, 55.09; H, 2.97; N, 4.59. Found: C, 54.80; H, 2.93; N, 4.55.

**General Procedure for the Synthesis of Fluorinated Pyridines 14.** Butyllithium (1.6 M in hexanes) (1.25 mL, 2 mmol) was added to a solution of fluorinated enaminophosphonate **6** (2 mmol) in anhydrous THF (6 mL) at 0 °C and under $N_2$ atmosphere. The mixture was stirred for 1 h at the same temperature. Then, a solution of 1, 3-diphenyl-2-propen-1-one **13** (2 mmol) in anhydrous THF (6 mL) was added. The reaction was stirred at room temperature or was heated at reflux until TLC showed the disappearance of the fluorinated enaminophosphonate **6**. Then, a saturated solution of ammonium chloride (15 mL) was added, the organic layer was extracted with $Et_2O$ (3 × 15 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

**4,6-Diphenyl-2-difluoromethylpyridine 14a.** Obtained as a colorless oil as described in the general procedure (416 mg, 74%): $R_f$ 0.96 (ethyl acetate); IR (NaCl) $\nu_{max}$ 3038, 2957, 1605, 1126 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.78 (t, $^2J_{FH}$ = 55.6 Hz, 1H), 7.43−8.17 (m, 12H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 114.4 (t, $^1J_{FC}$ = 241.2 Hz), 116.3 (d, $^3J_{FC}$ = 2.5 Hz), 119.9, 128.8−129.7, 137.7, 138.4, 150.7, 153.3 (t, $^2J_{FC}$ = 25.7 Hz), 157.8; $^{19}F$ NMR ($CDCl_3$) $\delta$ −115.6; MS (EI) *m*/*z* 281 ($M^+$, 100). Anal. Calcd for $C_{18}H_{11}F_2N$: C, 76.87; H, 4.63; N, 4.98. Found: C, 76.94; H, 4.55; N, 4.90.

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**Supporting Information Available:** Experimental procedures and characterization data ($^1H$ NMR, $^{13}C$ NMR, $^{31}P$ NMR, IR, and elemental analysis) for compounds **3c−e,g−i**, **6d,g−i**, **7b,c,e**, **8a−d**, **10a−h**, and **14a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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