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Efficient synthesis of fluorinated α- and β-amino nitriles from fluoroalkylated α,β-unsaturated imines

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ABSTRACT

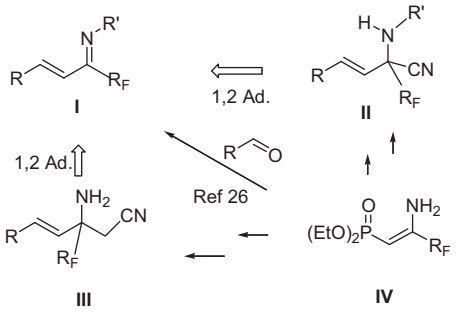
A simple and efficient synthesis of fluoroalkylated α-amino nitrile (**4**) derivatives by regioselective 1,2-addition of trimethylsilyl cyanide to fluoroalkylated α,β-unsaturated imines (**1**) is described. Fluoroalkylated β-amino nitriles (**7**) are also prepared by regioselective 1,2-addition of α-carbanions derived from acetonitrile to fluoroalkylated α,β-unsaturated imines (**1**). Fluoroalkylated α-(**4**) and β-amino nitriles (**7**) are also prepared through an 'one pot' procedure by reaction of enaminophosphonate **2** with BuLi, addition of aldehydes and subsequent addition of either trimethylsilyl cyanide or α-carbanion derived from acetonitrile. Basic hydrolysis of α-(**4**) and β-amino nitriles (**7**) gives fluoroalkylated α-(**5**) and β-amino acids (**8**).

1. Introduction

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.[1] Special interest has been focused on developing synthetic methods for the preparation of fluorinated building blocks as they can be used for the efficient and/or selective preparation of fluorine-containing molecules with commercial applications[2] and interest in medicinal chemistry.[3] The preparation of fluorinated analogues of amino acids has recently been used to stabilize proteins for their application in protein-based biotechnologies,[4] and to the preparation of fluorinated peptidomimetics.[5]

Furthermore, there is a growing need in organic synthesis for efficient methodologies for the construction of quaternary carbon centers[6] and α- and β-amino nitriles possess a wide variety of biological activities in search of new therapeutic agents,[7] and are versatile compounds for generating molecular diversity and amino acid derivatives.[8] The Strecker reaction,[9] has been widely applied to aldimines, however few examples were reported with ketimines.[10] Specifically in the case of fluorinated imines, only the asymmetric Strecker reaction of *N*-sulfinyl ketimines[11a] has been described and four examples for the addition of trimethylsilyl cyanide to fluorinated *N*-substituted ketimines in the presence of palladium acetate,[11b] gallium triflate,[11c] Lewis acids,[11d] or an acid polymer[11e] have been reported.

In this context, α,β-unsaturated imines (**I**, Scheme 1) also called 1-azadienes are a versatile family of compounds with a wide range of applications in preparative organic chemistry.[12] Besides the well known aza-Diels–Alder reaction[13] for the preparation of six membered heterocycles and [4+1] cycloadditions for the



Scheme 1. Fluorinated α,β-unsaturated imines (I). Templates for the preparation of α- and β-amino nitriles.

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synthesis of pyrroles,[14] unsaturated imines have been extensively used in the synthesis of several natural products.[15] Moreover, owing to their ambident electrophilic character, α,β-unsaturated imines can either undergo (1,2)[16] or conjugate (1,4)[17] nucleophilic addition processes. However, generally, the control on the regioselectivity, is difficult and very often the double nucleophilic addition products are obtained.[18]

The simplest method for the synthesis of α,β-unsaturated imines implies condensation of α,β-unsaturated carbonyl compounds (1,2-addition) with primary amines.[19] This method is often complicated by Michael addition reaction (1,4-addition), especially in the case of α,β-unsaturated ketones, but can be avoided by using the Aza–Wittig reaction[20,21] of phosphazenes and has been recently applied for the construction of α,β-unsaturated imines derived from α-aminoesters[22a] and α-aminophosphonates.[22b] Likewise, an olefination reaction of α-phosphonylated imines or enamines with aldehydes to generate the conjugated C=C bond of 1-azadienes is usually a good alternative.[23]

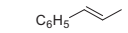
In this context, we described the preparation of fluorine-substituted aminophosphonates from fluorinated aziridines[24] and from enamines[25] and we applied this strategy for the preparation of first stable *N*-unsubstituted α,β-unsaturated imines[26] **I** (R=H) from primary enaminophosphonates[27] **IV**. Here, we report our own results concerning the preparation of fluorinated α- **II** and β-amino-nitriles derivatives **III** (see Scheme 1).

2. Results and discussion

2.1. Synthesis of fluoroalkylated α-amino nitriles 4

Unsaturated imines **1** were prepared by deprotonation of primary enamines **2** with butyllithium, followed by the addition of aldehydes in a stereoselective fashion and in good yields.[26] For synthetic purposes imines **1** can be used without isolation. Trimethylsilyl cyanide **3** in methanol was added over the fluorinated imines **1** (R_F=CF_3, CHF_2, C_2F_5), and the reaction mixture was heated at methanol reflux (24–36 h, see Experimental section) to give only fluoroalkylated α-amino nitriles **4** in good yields keeping the *trans*-configuration of the C–C double bond (Scheme 2, procedure A, Table 1, entries 1–11). The scope of the process is very wide, because the variation of the aldehyde (R^2) proved to be possible (aromatic-, heteroaromatic- or cinnamaldehyde) and the fluoroalkyl group (R_F) was not restricted to trifluoromethyl (R_F=CF_3, Table 1, entries 1–6) or perfluoroethyl (R_F=C_2F_5, Table 1, entries 10, 11) given that difluoromethyl-substituted derivatives (R_F=CHF_2, Table 1, entries 7–9) can also be prepared. Formation of fluoroalkylated α-amino nitriles **4** involves a regioselective 1,2-addition of cyanide **3** to α,β-unsaturated imines **1** (see Scheme 2). Conjugate addition (1,4-addition) of trimethylsilyl cyanide **3** was not detected.

Table 1
Fluoroalkylated α-amino nitriles **4**

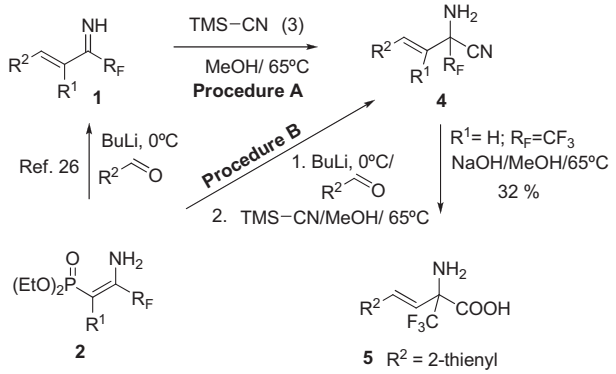
Entry	Compound	R^1	R^2	R_F	Yield(%)[a]
1	**4a**	H	*p*-Me–C_6H_4	CF_3	81 (85)[b]
2	**4b**	H		CF_3	78 (83)[b]
3	**4c**	H		CF_3	68
4	**4d**	H		CF_3	84
5	**4e**	Me	*p*-Me–C_6H_4	CF_3	69
6	**4f**	Me	*p*-NO_2–C_6H_4	CF_3	65 (70)[b]
7	**4g**	H	*p*-Me–C_6H_4	CHF_2	78 (83)[b]
8	**4h**	H	*p*-F–C_6H_4	CHF_2	82(86)[b]
9	**4i**	Me	*p*-Me–C_6H_4	CHF_2	58 (62)[b]
10	**4j**	H	*p*-Me–C_6H_4	C_2F_5	62 (66)[b]
11	**4k**	Me	*p*-NO_2–C_6H_4	C_2F_5	58

[a] Yield of isolated purified compounds obtained from **1** (procedure A).
[b] Yield obtained from **2** (procedure B).

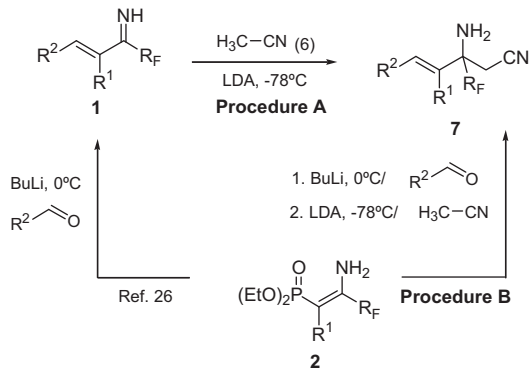
These α-amino nitriles **4** can also be prepared through treatment of enaminophosphonates[28] **2** with BuLi, addition of aldehydes **2** and subsequent addition of the cyanide **3** (Scheme 2, Procedure B, Table 1, entries 1, 2, 6–10). Nitrile hydrolysis was first tried with hydrochloride acid (4 M), and a very complex reaction mixture was obtained. However, basic hydrolysis of α-amino nitrile **4c** (R^1=H; R^2=2-thienyl; R_F=CF_3) with NaOH in refluxing methanol gave α-amino acid **5** in low yield (32%). As far as we know, *N*-unsubstituted fluoroalkylated α-amino nitriles **4** were described and obtained by the first time.

2.2. Synthesis of fluoroalkylated β-amino nitriles 7

The versatility of α,β-unsaturated imines as starting materials for the preparation of acyclic compounds being known, the synthetic applications of these substrates α,β-unsaturated imines **1** as intermediates in the preparation of β-amino nitriles was also explored. Addition of the C-α carbanion derived from acetonitrile **6** at −78 °C over azadienes **1**, and after the reaction mixture was allowed to warm to room temperature, gave trifluoromethylated β-amino nitrile **7** (Scheme 3, Procedure A, Table 2, entries 1–5) in a regioselective fashion. The formation of this functionalized nitrile **7** involves a selective 1,2-addition of the C-α carbanion derived from acetonitrile **6** to the C=N imine moiety of α,β-unsaturated imine **1** with the formation of adducts **7**. Fluorinated β-amino nitriles **7** may also be prepared from enaminophosphonate[28] **2** with BuLi, addition of aldehydes and subsequent addition of the C-α carbanion derived from acetonitrile **6** (Scheme 3, Procedure B, Table 2, entries 1–4). The scope of this process for the preparation of amino nitriles **7** is wide, because variation of aldehyde (R^1) proved to be aromatic or heteroaromatic, and trifluoromethyl-



Scheme 2. Synthesis of fluoroalkylated α-amino nitriles **4** and α-amino acid **5**.



Scheme 3. Synthesis of fluoroalkylated β-amino nitriles **7**.

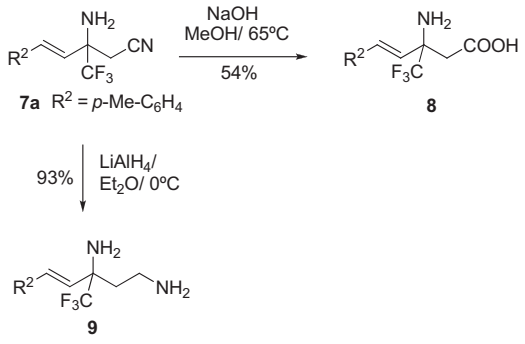
Table 2
Fluoroalkylated β-amino nitriles **7**

Entry	Compound	R^1	R^2	R_F	Yield(%)[a]
1	**7a**	H	*p*-Me–C_6H_4	CF_3	56 (60)[b]
2	**7b**	H	*p*-NO_2–C_6H_4	CF_3	52 (55)[b]
3	**7c**	CH_3	*p*-Me–C_6H_4	CF_3	53 (57)[b]
4	**7d**	H	*p*-F–C_6H_4	CHF_2	50 (53)[b]
5	**7e**	H		C_2F_5	25

[a] Yield of isolated purified compounds obtained from **1** (procedure A).
[b] Yield obtained from **2** (procedure B).

(R_F=CF_3) difluoromethyl- (R_F=CHF_2) and pentafluoroethyl-substituted compounds (R_F=C_2F_5) can also be prepared.

Amino nitriles are excellent intermediates in preparative organic synthesis for generating molecular diversity and amino-acid derivatives, and we used fluorinated β-amino nitrile **7a** for the synthesis of fluorinated β-amino acid and fluorinated diamine. Basic hydrolysis of β-amino nitrile **7a** (R^1=H, R^2=*p*-Me–C_6H_4; R_F=CF_3) with NaOH (25%) in refluxing methanol gave β-amino acid **8** in moderate yield (54%), while the selective nitrile reduction of β-amino nitrile **7a** with $LiAlH_4$ in ether led to the formation of functionalized fluoromethylated diamine **9** in excellent yield (93%). In both compounds **8** and **9** the *trans*-configuration of the C–C double bond is retained (Scheme 4).



7a R^2 = *p*-Me-C_6H_4 **8** **9**

Scheme 4. Synthesis of trifluoromethylated β-amino acid **8** and diamine **9**.

3. Conclusion

In conclusion, this account describes a very simple, mild and convenient strategy for the preparation of β-trifluoromethyl-, β-difluoromethyl- and perfluoroethyl- substituted α- and β-amino nitrile derivatives by simple regioselective 1,2-addition of trimethylsilyl cyanide or metallated acetonitrile to fluoroalkylated α,β-unsaturated imines **1**. These new fluorinated amino nitriles could be very interesting starting materials for the preparation of new fluorinated diamines, fluoroalkylated amino acids and fluorine containing peptidomimetics, in which the fluoroalkyl substituents could stabilize the corresponding biologically active peptides or proteins.[3,5] Fluoroalkylated α- and β-amino nitrile can also be prepared by olefination reaction of enaminophosphonate **2** with base (BuLi), addition of aldehydes and subsequent addition of trimethylsilyl cyanide or metallated acetonitrile. High chemical diversity can be achieved because the variation of the aldehyde (R^1), fluoroalkyl group (R_F) proved to be possible. Additional diversity can be introduced with the nitrile reagent, given that by means of trimethylsilyl cyanide α-amino nitriles can be prepared, whereas with the use of metallated acetonitrile β-amino nitriles can be obtained. Amino nitrile derivatives (α, β)[7,8] are important building blocks in organic synthesis and in the preparation of biologically active compounds of interest in medicinal chemistry.

4. Experimental section

4.1. General methods

Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Melting points are uncorrected. FT-IR spectra were obtained as solids in KBr or as neat oils in NaCl. Mass spectra (MS) were made by electron impact (EI) at an ionizing voltage of 70 eV or by chemical ionization (CI).^{1}H (300, 400 MHz), ^{13}C (75, 100 MHz) and ^{31}P NMR (120,160 MHz) spectra were recorded on a 300 MHz or 400 MHz spectrometers, respectively, in $CDCl_3$, as specified below. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. All coupling constants (J) values are given in hertz. Chemical shifts (δ_C) are reported in parts per million (ppm), relative to $CDCl_3$, as internal standard in a broad band decoupled mode. The abbreviations used are as follows: s, singlet; d, doublet; dd, double–doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are reported in Hertz. All the NH and NH_2 exchanged with D_2O. Flash-column chromatography was carried out using commercial grades of silica-gel finer than 230 mesh. Analytical thin layer chromatography (TLC) was performed on precoated silica-gel 60 F_{254} plates, and spot visualization was accomplished by UV light (254 nm) or $KMnO_4$ solution. Unsaturated imines **1** were prepared according to literature procedure.[26]

4.2. General procedure for the synthesis of fluoroalkylated αamino nitriles 4

General procedure A: TMSCN (0.27 mL, 2 mmol) was added to a solution of fluoroalkyated α,β-unsubstituted imine **1** (1 mmol) in anhydrous methanol (15 mL). The mixture was heated at methanol reflux until TLC showed the disappearance of the fluorinated α,β-unsaturated imine **1** (24–30 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: Butyllithium (1.6 M in hexanes) (0.65 mL, 1 mmol) was added to a solution of corresponding β-enamine phosphonate **2** (1 mmol) in anhydrous THF (6 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred for 1 h at the same temperature. Then, a solution of corresponding aldehyde (1 mmol) in THF (6 mL) was added and the reaction was stirred at room temperature until TLC showed the disappearance of **2** (7–8 h). Then, the solvent was evaporated under vacuum and the crude residue was solved with anhydrous methanol (15 mL). TMSCN (0.27 mL, 2 mmol) was added and the mixture was heated at methanol reflux until TLC showed the disappearance of fluorinated α,β-unsubstituted imine **1** (24–30 h). Then, the solvent was evaporated under vacuum and the crude product was purified by chromatography using silica-gel (hexane/ethyl acetate).

*4.2.1. 2-Amino-4-p-tolyl-2-(trifluoromethyl)but-3-enenitrile (**4a**).* Compound **4a** was obtained as a white solid (195 mg, 81%) from imine **1**, from enaminophosphonate **2** (204 mg, 85%) as described in the general procedure. Mp 51–52 °C. R_f 0.47 (hexane/ethyl acetate, 7/3). IR (KBr)ν_{max} 3394, 3332, 2921, 2219, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 2H, NH_2), 2.36 (s, 3H, CH_3), 6.06 (d, $^3J_{HH}$=15.9 Hz, 1H,=CH), 7.15 (d, $^3J_{HH}$=15.9 Hz, 1H,=CH), 7.17 (d, $^3J_{HH}$=7.9 Hz, 2H, Har), 7.33 (d, $^3J_{HH}$=7.9 Hz, 2H, Har) ppm; ^{13}C NMR ($CDCl_3$) δ 21.3, 59.4 (q, $^2J_{FC}$=31.7 Hz), 116.4, 117.3, 122.6 (q, $^1J_{FC}$=284.5 Hz), 127.2, 129.6, 131.3, 137.7, 139.8 ppm; ^{19}F NMR

($CDCl_3$) δ −79.4 ppm; MS (EI): m/z 240 (M^+, 19); Anal. Calcd for $C_{12}H_{11}F_3N_2$: C, 60.00; H, 4.62; N, 11.66. Found: C, 60.23; H, 4.70; N, 11.79.

4.3. Synthesis of 2-amino-4-(thiophen-2-yl)-2-(trifluoromethyl)but-3-enoic acid (5)

A solution of α-aminonitrile **4c** (0.252 g, 1 mmol) in methanol (8 mL) and NaOH 25% (22 mL) was heated at reflux during 1.5 h until TLC showed the disappearance of α-amino nitrile **4c**. After the reaction was completed, the solvent was evaporated under vacuum. The crude residue was treated with HCl 2 M (5 mL) during 30 min. The crude reaction was extracted with CH_2Cl_2 (3×100 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under vacuum. The product **5** was obtained as a white solid (80 mg, 32%). Mp 178–180 °C. R_f 0.25 (hexane/ethyl acetate, 7/3). IR (KBr)ν_{max} 3392, 3025, 1642, 1451 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02 (s, 2H, NH_2), 6.02 (d, $^3J_{HH}$=15.6 Hz, 1H,=CH), 7.06 (m, 1H, Har), 7.28 (d, $^3J_{HH}$=3.2 Hz, 1H, Har), 7.40 (d, $^3J_{HH}$=5.0 Hz, 1H, Har) ppm, 7.83 (d, $^3J_{HH}$=15.6 Hz, 1H,=CH); ^{13}C NMR ($CDCl_3$)δ 49.6 (q, $^2J_{FC}$=21.7 Hz), 116.1, 125.2 (q, $^1J_{FC}$=260.2 Hz), 128.1, 129.5, 131.8, 139.6, 141.4, 170.3 ppm; ^{19}F NMR ($CDCl_3$) δ −78.1 ppm; HRMS (EI^+) calcd for $C_9H_8F_3NO_2S$ [M^+] 251.0228, found M^+251.0223.

4.4. Synthesis of fluoroalkylated β-amino nitriles 7

General procedure A: LDA (1.2 mmol) was added to a solution of acetonitrile **6** (1 mmol) in anhydrous THF (6 mL) at −78 °C under nitrogen atmosphere. Then, a solution of fluorinated azadiene **1** (0.214 g, 1 mmol) in dry THF was added to the solution of metallated acetonitrile and the mixture was stirred at −78 °C until TLC showed the disappearance of **1** (48–72 h). Then, the reaction was allowed to reach room temperature and a saturated solution of NH_4Cl (10 mL) was added and the organic layer was extracted with CH_2Cl_2 (3×25 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under vacuum and the crude product was purified by chromatography using silica-gel (hexane/ethyl acetate).

General procedure B: Butyllithium (1.6 M in hexanes) (0.65 mL, 1 mmol) was added to a solution of corresponding β-enamine phosphonate **2** (1 mmol) in anhydrous THF (6 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred for 1 h at the same temperature. Then, a solution of corresponding aldehyde (1 mmol) in THF (6 mL) was added and the reaction was stirred at room temperature until TLC showed the disappearance of **2** (7–8 h). Then, the mixture was added to a solution of metallated acetonitrile **6** with LDA at −78 °C in THF during 1 h and the reaction was stirred at −78 °C until TLC showed the disappearance of **1** (48–72 h). Then, the reaction was allowed to reach room temperature and a saturated solution of NH_4Cl (10 mL) was added and the organic layer was extracted with CH_2Cl_2 (3×25 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under vacuum and the crude product was purified by chromatography using silica-gel (hexane/ethyl acetate).

*4.4.1. 3-Amino-5-p-tolyl-3-(trifluoromethyl)pent-4-enenitrile (**7a**).* Compound **7a** was obtained as a pale brown oil from imine **1** (142 mg, 56%), from enaminophosphonate **2** (152 mg, 60%) as described in the general procedure. R_f 0.36 (hexane/ethyl acetate, 7/3). IR (KBr)ν_{max} 3397, 3335, 2257, 1177 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H, CH_3), 2.95 (d, $^2J_{HH}$=16.9 Hz, 1H, CH_2), 3.03 (d, $^2J_{HH}$=16.9 Hz, 1H, CH_2), 6.22 (d, $^3J_{HH}$=16.0 Hz, 1H,=CH), 6.97 (d, $^3J_{HH}$=16.0 Hz, 1H,=CH), 7.13 (d, $^3J_{HH}$=7.8 Hz, 2H, Har), 7.33 (d, $^3J_{HH}$=7.8 Hz, 2H, Har) ppm; ^{13}C NMR ($CDCl_3$) δ 21.2, 26.4, 60.0 (q, $^2J_{FC}$=27.7 Hz), 117.1, 123.5, 127.5 (q, $^1J_{FC}$=285.5 Hz), 127.9, 130.4, 134.2, 135.6, 139.8 ppm; ^{19}F NMR ($CDCl_3$) δ −81.0 ppm; MS (EI): m/z 254 (M^+, 37); Anal. Calcd for $C_{13}H_{13}F_3N_2$: C, 61.41; H, 5.15; N, 11.02. Found: C, 61.57; H, 5.19; N, 11.10.

4.5. Synthesis of 3-amino-5-*p*-tolyl-3-(trifluoromethyl)pent-4-enoic acid (8)

A solution of β-aminonitrile **7a** (0.254 g, 1 mmol) in methanol (8 mL) and NaOH 25% (22 mL) was heated at reflux during 2 h until TLC showed the disappearance of the β-aminonitrile **7a**. After the reaction was completed, the solvent was evaporated under vacuum. The crude residue was treated with HCl 2 M (5 mL) during 30 min. The crude reaction was extracted with CH_2Cl_2 (3×100 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel (ethyl acetate) and gave the corresponding β-amino acid **8**: obtained as a white solid (147 mg, 54%). Mp:106–107 °C. R_f 0.37 (ethyl acetate). IR (KBr)ν_{max} 3371, 3351, 3302, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H, CH_3), 2.63 (s, 2H, CH_2), 6.20 (d, $^3J_{HH}$=16.0 Hz, 1H,=CH), 6.79 (d, $^3J_{HH}$=16.0 Hz, 1H,=CH), 7.09 (d, $^3J_{HH}$=7.8 Hz, 2H, Har), 7.27 (d, $^3J_{HH}$=7.8 Hz, 2H, Har) ppm; ^{13}C NMR ($CDCl_3$)δ 21.2, 40.2, 61.0 (q, $^1J_{FC}$=25.5 Hz), 125.3, 127.7 (q, $^1J_{FC}$=284.5 Hz), 127.8, 130.3, 134.3, 134.6, 139.3, 174.0 ppm; ^{19}F NMR ($CDCl_3$) δ −81.3 ppm; MS (EI): m/z 273 (M^+, 29); Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.29; H, 5.22; N, 5.25.

4.6. Synthesis of 5-*p*-tolyl-3-(trifluoromethyl)pent-4-ene-1,3-diamine (9)

A solution of β-amino nitrile **7a** (0.254 g, 1 mmol) in anhydrous ethyl ether (3 mL) was added to $LiAlH_4$ (2.5 mmol) in anhydrous ethyl ether (6 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred for 1 h at the same temperature until TLC showed the disappearance of fluorinated β-amino nitrile **7a**. Then, H_2O was added dropwise to the suspension, next NaOH was added and again H_2O. The mixture was filtered through Celite and concentrated under vacuum afforded 240 mg (93%) of diamine **9,** obtained as a colorless oil. R_f 0.41 (ethyl acetate). IR (KBr)ν_{max} 3370, 3330, 3296, 2926, 1112 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (m, 2H, NH_2), 2.13 (s, 4H, 2 CH_2), 2.22 (s, 3H, CH_3), 2.70–2.73 (m, 2H, NH_2),6.01 (d, $^3J_{HH}$=16.0 Hz, 1H,=CH), 6.69 (d, $^3J_{HH}$=16.0 Hz, 1H,=CH), 7.02 (d, $^3J_{HH}$=7.6 Hz, 2H, Har), 7.19 (d, $^3J_{HH}$=7.6 Hz, 2H, Har) ppm; ^{13}C NMR ($CDCl_3$) δ 20.9, 36.0, 36.4, 60.2 (q, $^1J_{FC}$=26.1 Hz), 124.5, 126.3, 127.7 (q, $^1J_{FC}$=284.5 Hz), 129.1, 132.0, 132.9, 137.8 ppm; ^{19}F NMR ($CDCl_3$) δ −82.5 ppm; MS (EI): m/z 258 (M^+, 36); Anal. Calcd for $C_{13}H_{17}F_3N_2$: C, 60.45; H, 6.63; N, 10.85. Found: C, 60.24; H, 6.69; N, 10.99.

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Supplementary data

Experimental procedures and characterization data (^1H NMR, ^{13}C NMR, ^{31}P NMR, ^{19}F NMR, IR and elemental analysis) for compounds **4b**–**4k**, **7b**–**7e**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.12.046.

References and notes

1. *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; Wiley: New York, NY, 1991.
2. (a) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; J. Wiley: Chischester, UK, 2009; (b) Chambers, R. D. *Fluorine in Organic Chemistry*, 2nd ed.; Blackwell: London, 2004; (c) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004; (d) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets*; Soloshonok, V. A., Ed.; Wiley: New York, NY, 1999; (e) *Fluorine Containing Amino Acids, Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: New York, NY, 1995.
3. For recent reviews see: (a) Federsel, H. J. *Acc. Chem. Res.* **2009**, *42*, 671–680; (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330; (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369; (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886; (e) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029.
4. For recent contributions see: (a) Chiu, H. P.; Kokona, B.; Fairman, R.; Cheng, R. P. *J. Am. Chem. Soc.* **2009**, *131*, 13192–13343; (b) Salwiczek, M.; Samsonov, S.; Vagt, T.; Nyakutura, E.; Fleige, E.; Numata, J.; Coelten, H.; Pisabarro, M. T.; Koksch, B. *Chem.—Eur. J.* **2009**, *15*, 7628–7636; (c) Meng, H.; Kumar, K. *J. Am. Chem. Soc.* **2007**, *129*, 15615–15622.
5. (a) Buer, B. C.; de la Salud-Bea, R.; Al Hashimi, H. M.; Marsh, E.; Neil, G. *Biochemistry* **2009**, *48*, 10810–10817; (b) Meng, H.; Krishnaji, S. T.; Beinborn, M.; Kumar, K. *J. Med. Chem.* **2008**, *151*, 7303–7307; (c) Binkert, C.; Frigerio, M.; Jones, A.; Meyer, S.; Pesenti, C.; Prade, L.; Viani, F.; Zanda, M. *ChemBioChem* **2006**, *7*, 181–186.
6. For recent eviews see: (a) Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2010**, *2*, 192–196; (b) Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2010**, *43*, 440–454; (c) Koester, D. C.; Werz, D. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 7971–7973.
7. Undavia, N. K.; Patwa, B. S.; Navadiya, H. D.; Jivani, A. R.; Dave, P. N. *Int. J. Chem. Sci.* **2009**, *7*, 1019–1026.
8. For recent reviews see (a) Wang, M. X. *Chimia* **2009**, *63*, 331–333; (b) Gonzalez-Vera, J. A.; Garcia-Lopez, M. T.; Herranz, R. *Mini-Rev. Org. Chem.* **2008**, *5*, 209–221.
9. Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27–45.
10. (a) Connon, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1176–1178; (b) Vilaivan, T.; Bhanthumunavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315–1392; (c) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795–2827.
11. (a) Wang, H.; Zhao, X.; Li, Y.; Lu, L. *Org. Lett.* **2006**, *8*, 1379–1381; (b) Yamasaki, Y.; Maekawa, T.; Ishihara, T.; Ando, T. *Chem. Lett.* **1985**, 1387–1390; (c) Prakash, G. K. S.; Mathew, T.; Panja, C.; Alconcel, S.; Vaghoo, H.; Do, C.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 3703–3706; (d) Huguenot, F.; Brigaud, T. *J. Org. Chem.* **2006**, *71*, 7075–7078; (e) Prakash, G. K. S.; Thomas, T. E.; Bychinskaya, I.; Prakash, A. G.; Panja, C. H.; Vaghoo, H.; Olah, G. A. *Green Chem.* **2008**, *10*, 1105–1110.
12. For reviews of 1-azadienes see (a) Groenendal, B.; Ruijer, E.; Orru, R. V. A. *Chem. Commun.* **2008**, 5474–5489; (b) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379–471; (c) Buonora, P.; Olsen, J. C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138.
13. For recent contributions see: (a) Singh, L.; Ishar, M. P. S.; Elango, M.; Subramaniam, V.; Gupta, V.; Kanwal, P. *J. Org. Chem.* **2008**, *73*, 2224–2233; (b) Lu, J. Y.; Arndt, H. D. *J. Org. Chem.* **2007**, *72*, 4205–4212; (c) Esquivias, J.; Gomez Arrayas, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 1480–1481.
14. For recent contributions see: (a) Mizuno, A.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 8318–8320; (b) Lu, Y.; Arndtsen, B. A. *Org. Lett.* **2009**, *11*, 1369–1372.
15. (a) Atobe, M.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2005**, *46*, 2669–2673; (b) Schnermann, M. J.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 15704–15705.
16. Contributions to selective 1,2 addition to α,β-unsaturated imines: (a) Groenendaal, B.; Vugts, D. J.; Schmitz, R. F.; de Kanter, F. J. J.; Ruijer, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2008**, *73*, 719–722; (b) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847–2850; (c) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875–5878.
17. Recent contributions to selective conjugate addition to α,β-unsaturated imines: (a) Vicario, J.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2009**, *74*, 452–455; (b) Palacios, F.; Vicario, J. *Org. Lett.* **2006**, *8*, 5405–5408; (c) Shimizu, M.; Takahashi, A.; Kawai, S. *Org. Lett.* **2006**, *8*, 3585–3587.
18. Contributions to double addition to α,β-unsaturated imines: (a) Van Meenen, E.; Moonen, K.; Verwée, A.; Stevens, C. V. *J. Org. Chem.* **2006**, *71*, 7903–7906; (b) Moonen, K.; Van Meenen, E.; Verwée, A.; Stevens, C. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7407–7411; (c) Shimizu, M.; Kamiya, M.; Hachiya, I. *Chem. Lett.* **2005**, *34*, 1456–1457.
19. (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; (c) Brady, W. T.; Shieh, C. H. *J. Org. Chem.* **1983**, *48*, 2499–2502.
20. For reviews see: (a) Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2009**, *13*, 810–828; (b) Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. *Tetrahedron* **2006**, *63*, 523–575.
21. For contributions of creation of the C=N bouble bond by means of this process see: (a) Palacios, F.; Herrán, E.; Rubiales, G.; Alonso, C. *Tetrahedron* **2007**, *63*, 5669–5676; (b) Palacios, F.; Herrán, E.; Alonso, C.; Rubiales, G.; Lecea, B.; Ayerbe, M.; Cossío, F. P. *J. Org. Chem.* **2006**, *71*, 6020–6030; (c) Cossío, F. P.; Alonso, C.; Lecea, B.; Ayerbe, M.; Rubiales, G.; Palacios, F. *J. Org. Chem.* **2006**, *71*, 2839–2847; (d) Palacios, F.; Alonso, C.; Rubiales, G.; Villegas, M. *Tetrahedron* **2005**, *61*, 2779–2794.
22. (a) Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690–7696; (b) Palacios, F.; Vicario, J.; Maliszewska, A. *J. Org. Chem.* **2007**, *72*, 2682–2685.
23. (a) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Oyarzabal, J. *Org. Lett.* **2002**, *4*, 769–772; (b) Palacios, F.; Aparicio, D.; Vicario, J. *Eur. J. Org. Chem.* **2002**, 4131–4136; (c) Palacios, F.; Aparicio, D.; García, J.; Rodríguez, E.; Fernández-Acebes, A. *Tetrahedron* **2001**, *57*, 3131–3141.
24. Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2006**, *71*, 6141–6148.
25. Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J.; Pascual, S.; Fernandez de Troconiz, G. *J. Org. Chem.* **2008**, *73*, 4568–4574.
26. Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004**, *69*, 8767–8774.
27. For a review of β-aminophosphonates see: Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899–931.
28. These primary enamines are stable and can be easily prepared from commercially available starting materials.[26]