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PAPER

Click-chemistry approach to isoxazole-containing α-CF_3-substituted α-aminocarboxylates and α-aminophosphonates

Daria V. Vorobyeva,*[a] Natalya M. Karimova,[a] Irina L. Odinets,[a] Gerd-Volker Röschenthaler*[b] and Sergey N. Osipov[a]

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A convenient strategy for the synthesis of isoxazole-containing α-CF_3-substituted α-aminocarboxylates and α-aminophosphonates have been developed. The method is based on copper-catalyzed 1,3-dipolar cycloaddition of different aromatic nitrile oxides to functionalized acetylenes.

Introduction

The development of new methods for the synthesis of five membered heterocyclic compounds is an ever-expanding area in bioorganic and medicinal chemistry. Specifically, those containing the isoxazole ring have been widely used as key building blocks for drugs. Its derivatives are endowed with a broad spectrum of pharmacological properties, for example, hypoglycemic, analgesic, anti-inflammatory, antibacterial, anti-HIV, and anticancer activity.[1] In addition, they also can be used as agrochemicals with herbicidal and soil fungicidal activity.[2] Recently, isoxazoles bearing carboxamide moieties demonstrated to have significant pharmacological applications. For examples, the cyclooxygenase-2 (COX-2) selective inhibitor valdecoxib **A** is currently prescribed for the treatment of arthritis and inflammatory diseases.[3] This compound exhibit anti-inflammatory activity with reduced gastrointestinal side effects. Oxacillin and its derivatives **B** are useful compounds because of their narrow spectrum antibiotic properties.[4] The isoxazoles **C** containing trifluoromethyl and aryl groups were also shown to be potent *in vivo* antithrombotic efficacy[5] (Fig. 1).

Many synthetic approaches have been reported for the formation of the isoxazole core, including reactions of hydroxylamine with 1,3-dicarbonyl compounds, α,β-unsaturated carbonyl compounds, and α,β-unsaturated nitriles as well as (3 + 2)-cycloadditions of nitrile oxides to alkynes.[6] Although, these strategies are highly convergent, in many cases either strong bases or strong mineral acids are required, or prolonged heating at elevated temperatures is necessary. In addition, the observed regioselectivities of the heterocyclization are often poor. Recently, Fokin and co-workers have described an elegant approach to 3,5- and 3,4-disubstituted isoxazoles based on "click" methodology.[7] The method includes transition-metal-catalyzed regioselective 1,3-dipolar cycloaddition of highly energetic nitrile oxides to alkynes.

On the other hand, fluorinated α-aminocarboxylic and α-aminophosphonic acids derivatives, which can function as selective inhibitors of variety biologically active enzymes, have been attracting considerable interest.[8] Moreover, it is known, that the incorporation of α-trifluoromethyl-α-amino acids (α-CF_3-AA) and their phosphate analogues into strategically important positions of peptides retards proteolytic degradation, induces a secondary structure motif, and improves the lipophilicity[9] enhancing *in vivo* absorption, thus improving permeability through certain body barriers. Therefore, the combination of the isoxazole and α-amino acid (or α-amino phosphonic acid) pharmacophores within the same molecule appears to be an attractive challenge for diversity-oriented synthesis of potent drugs.

[a]*A.N. Nesmeyanov Institute of Organoelement compounds, Russian Academy of Sciences, 119991, Moscow, Russia. Vavilov str. 28, Russia. E-mail: vorobyeva-daria@yandex.ru; Fax: +7 495 135 5085*
[b]*Jacobs University Bremen gGmbH, P.O. Box 750 561, D-28725, Bremen, Germany. E-mail: g.roeschenthaler@jacobs-university.de*

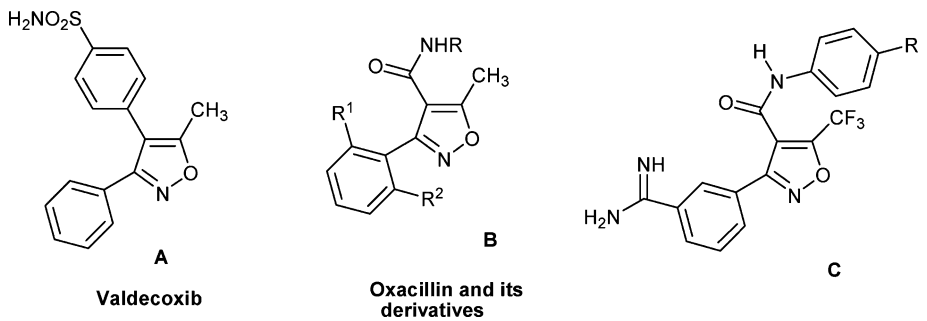
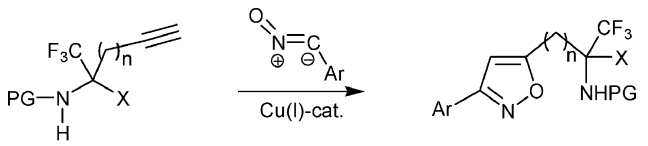


Fig. 1

Herein, we report an efficient synthetic approach to novel isoxazole-containing α-CF_3-α-aminocarboxylates and α-aminophosphonates (Fig. 2).



n = 0,1 X = CO_2Me, P(O)$(OEt)_2$

PG = Cbz, Boc;

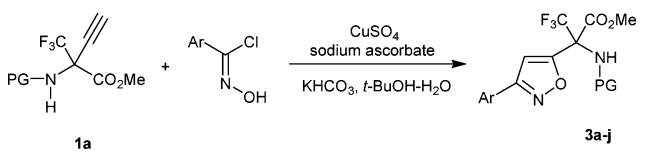
Fig. 2

Results and discussion

The highly reactive nitrile oxides were generated *in situ* in order to avoid dimerization from the corresponding hydroxymoyl chlorides derived by a two step procedure from different commercially available aromatic aldehydes.[7a] The synthesis of the starting α-alkynyl-α-CF_3-α-aminocarboxylates **1a** (n = 0), **1b** (n = 1) and α-alkynyl-α-CF_3-α-aminophosphonates **2a** (n = 0), **2b** (n = 1) was accomplished according to earlier methodology reported based on the addition of C-nucleophiles to electrophilic imines.[10,11]

The 1,3-dipolar cycloaddition of highly energetic nitrile oxides to alkynes **1** and **2** have been investigated using *in situ* generation of Cu(I) moiety from $CuSO_4$ pentahydrate (5 mol%) and sodium ascorbate (30 mol%) in a mixture of *tert*-butanol/water in a ratio of 1 : 1.[7a,12]

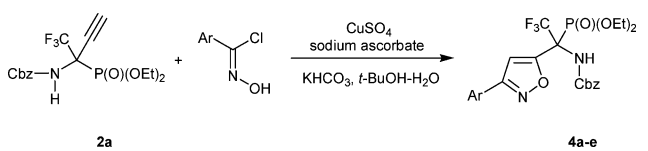
Thus, we found that ethynyl-substituted aminocarboxylates **1a** with different protecting groups on the amino group easily reacted with the corresponding nitrile oxides at room temperature to afford 3,5-disubstituted isoxazoles **3a–j** in good yields, the reaction goes to completion within 1–2 h (Entries 1–10, Table 1, Scheme 1). The small excess of nitrile oxides (1.1 equiv.) provides the best conversion of the starting acetylenes.



1a **3a-j**

Scheme 1

It turned out that ethynyl-substituted aminophosphonate **2a** demonstrates comparable reactivity towards different nitrile oxides under the above-mentioned conditions yielding the corresponding isoxazole-containing α-trifluoromethyl-α-aminophosphonate derivatives in good yield (Entries 1–5, Scheme 2, Table 2). It should be noted, that the variation of substituents (Ar) in the starting hydroxymoyl chlorides did not

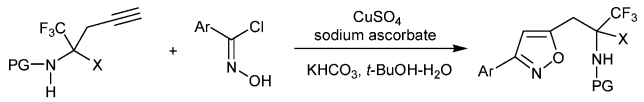


2a **4a-e**

Scheme 2

essentially affect the yield of the products; in all cases isoxazole-containing derivatives **4a–e** were isolated in good yields. However, the usage of too much excess of nitrile oxides may cause side reactions leading to a decrease in yields of the desired products. In all cases, the purification of the final isoxazoles has been achieved by column chromatography on silica gel or recrystallization.

The cycloadditions of propargyl-containing aminocarboxylates **1b** and aminophosphonate **2b** to organic nitrile oxides have been investigated under similar conditions. As it turned out the reactions of **1b** and **2b** with the highly reactive nitrile oxides (*e.g.* *p*-CH_3O–C_6H_4-, C_6H_5-, *p*-F–C_6H_4-derivatives) unexpectedly led to formation of a mixture of two possible 3,5- and 3,4-substituted regioisomers in a ~5 : 1 ratio, respectively (NMR-analysis), which could not be separated chromatographically. At the same time, in the case of electron-deficient nitrile oxides derived from *p*-NO_2- and *p*-CF_3-benzaldehydes the reaction occurs regioselectively to yield the desired 3,5-disubstituted isoxazoles **5a–f** (Entries 1–6, Scheme 3, Table 3).



1b, 2b **5a-f**

Scheme 3

One possible further synthetic application of the obtained compounds has been also demonstrated. Thus, we have elaborated the methods for the selective removal of protecting groups from the amino group for **3e**, **3f** and **5e**. As a result it was found that the Boc-group can be easily removed by treatment of **3f** or **5e** with trifluoroacetic acid in CH_2Cl_2 at room temperature to furnish the corresponding aminoesters **6** and **7**. However, attempting to obtain the aminoester **6** from **3e** using the classical palladium-catalyzed hydrogenation in methanol the simultaneous cleavage of the labile N–O bond of the isoxazole-ring[13] occurs to give the corresponding iminoenol **8** in excellent yield (Scheme 4).

Conclusion

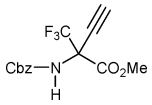
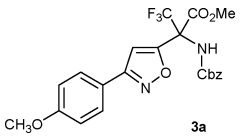
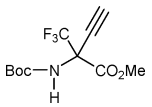
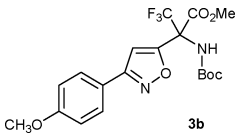
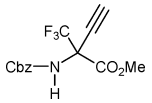
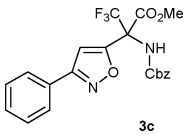
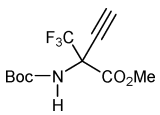
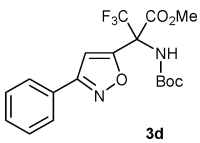
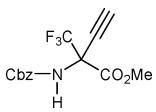
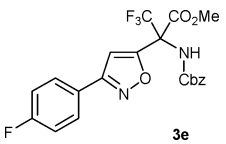
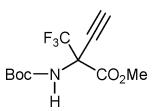
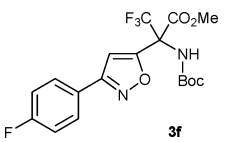
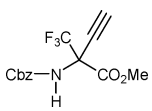
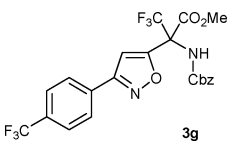
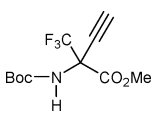
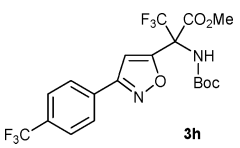
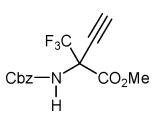
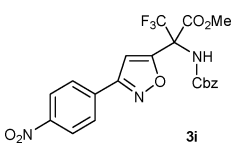
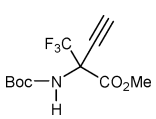
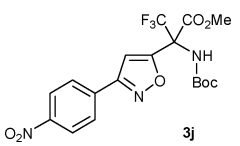
In summary, we have developed an effective procedure for the synthesis of novel α-CF_3-substituted α-aminocarboxylic and α-aminophosphonic acid derivatives bearing the isoxazole pharmacophore. The method is based on copper-catalyzed 1,3-dipolar cycloaddition of different aromatic nitrile oxides to functionalized acetylenes. The compounds obtained can be regarded as promising drug candidates. Their biological activity is under current investigation and will be published somewhere in due course.

Experimental

General information

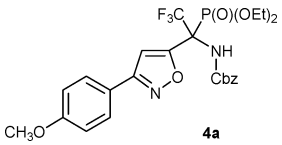
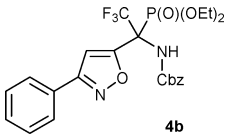
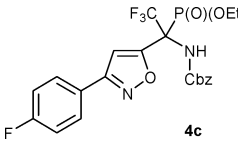
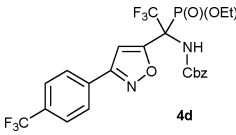
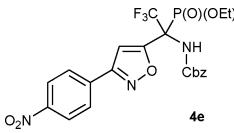
All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light or spraying by $Ce(SO_4)_2$, solution in 5% H_2SO_4. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM) and ethyl acetate/hexanes as eluent. NMR

Table 1 Synthesis of isoxazole-containing α-CF_3-α-aminocarboxylates

Entry	Alkyne	Ar	Product	Yield (%)[a]
1		4-CH_3O-C_6H_4	 **3a**	60
2		4-CH_3O-C_6H_4	 **3b**	77
3		C_6H_5	 **3c**	70
4		C_6H_5	 **3d**	68
5		4-F-C_6H_4	 **3e**	89
6		4-F-C_6H_4	 **3f**	62
7		4-CF_3-C_6H_4	 **3g**	78
8		4-CF_3-C_6H_4	 **3h**	77
9		4-NO_2-C_6H_4	 **3i**	67
10		4-NO_2-C_6H_4	 **3j**	70

[a] Isolated yields after purification by column chromatography or recrystallization.

Table 2 Synthesis of isoxazole-containing α-CF_3-α-aminophosphonates

Entry	Ar	Product	Yield (%)[a]
1	4-CH_3O-C_6H_4	 **4a**	55
2	C_6H_5	 **4b**	65
3	4-F-C_6H_4	 **4c**	58
4	4-CF_3-C_6H_4	 **4d**	80
5	4-NO_2-C_6H_4	 **4e**	68

[a] Isolated yields after purification by column chromatography or recrystallization.

spectra were obtained on a Bruker AV-300, AV-600 and on a Jeol ECX-400 spectrometers operating at 300 MHz, 400 MHz and 600 MHz respectively (TMS) for ^1H; 100 MHz and 151 MHz for ^{13}C; 282 MHz and 376.2 MHz for ^{19}F (CF_3COOH); 121 MHz and 161 MHz for ^{31}P (H_3PO_4). High resolution mass spectra (HRMS) were recorded using a Bruker Daltonics (MicroTOF-Q). Electrospray ionization (ESI) mass spectra (MS) were obtained from methanol solution.

General procedure for the synthesis of isoxazoles

To a solution of the corresponding acetylene **1** or **2** (1.0 mmol) in *t*-BuOH–H_2O (1 : 1 ratio) (5 ml) was added the corresponding hydroxymoyl chloride (1.1 mmol), sodium ascorbate (0.3 mmol) and 0.5 M copper sulfate pentahydrate (0.05 mmol), $KHCO_3$ (4 mmol), sequentially. The reaction mixture was stirred at room temperature for 1.5–2 h until the completion of the reaction monitored by TLC. After evaporation of the mixed solvent under reduced pressure, water (5 ml) was added to a residue and the aqueous mixture was extracted with ethyl acetate (2 × 10 ml). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash chromatography on silica gel eluting by ethyl acetate–hexanes (1 : 8) or by recrystallization.

Methyl *N*-[(benzyloxy)carbonyl]-3,3,3-trifluoro-2-[3-(4-methoxyphenyl)isoxazol-5-yl] alaninate (3a). Yield: 60% as colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 6H, $2OCH_3$), 5.12 (br s, 2H, CH_2), 6.32 (br s, 1H, NH), 6.86 (s, 1H, CH), 6.99 (d, J = 8.8 Hz, 2H, CH_{Ar}), 7.35 (br s, 5H, Ph), 7.75 (d, J = 8.8 Hz, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ 2.31 (s, 3F, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 54.8, 55.4, 64.1 (q, J = 31.0 Hz, $>C<$), 68.0, 103.8, 114.4, 120.6, 122.6 (q, J = 283.0 Hz, CF_3), 128.4, 128.5, 128.6, 128.7, 135.4, 153.9, 161.4, 161.6, 162.6, 163.9; Calcd for $C_{22}H_{19}N_2F_3O_6$ (464.39): C, 56.90; H, 4.12; N, 6.03; found: C, 56.87; H, 3.99; N, 5.94.

Methyl *N*-(*tert*-butoxycarbonyl)-3,3,3-trifluoro-2-[3-(4-methoxyphenyl)isoxazol-5-yl]alaninate (3b). Yield 77% as a white solid; M.p. 133–135 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H, $3CH_3$), 3.92 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.99 (s, 1H, NH), 6.91 (s, 1H, CH), 7.04 (d, J = 8.7 Hz, 2H, CH_{Ar}), 7.82 (d, J = 8.7 Hz, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ 4.39 (s, 3F, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.9, 54.5, 55.3, 64.1 (q, J = 31.2 Hz, $>C<$), 82.1, 103.4, 114.4, 120.6, 122.3 (q, J = 288.6 Hz, CF_3), 128.3, 153.1, 161.3, 161.9, 162.5, 163.7; Calcd for $C_{19}H_{21}N_2F_3O_6$ (430.37): C, 53.02; H, 4.92; N, 6.51; found: C, 53.10; H, 4.99; N, 6.39.

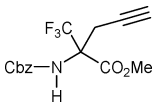
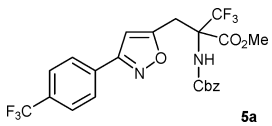
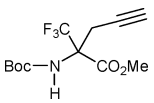
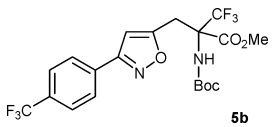
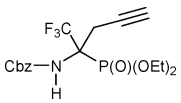
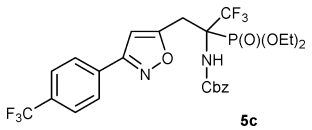
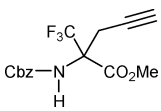
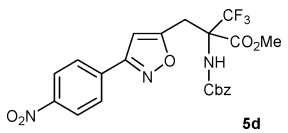
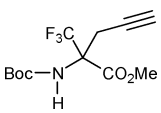
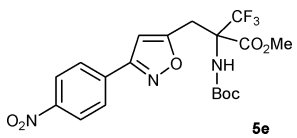
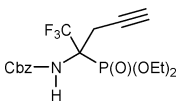
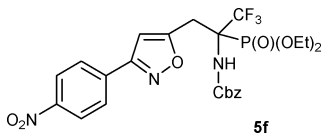
Methyl *N*-[(benzyloxy)carbonyl]-3,3,3-trifluoro-2-(3-phenylisoxazol-5-yl)alaninate (3c). Yield: 70% as white solid; M.p. 86–88 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (3H, OCH_3), 4.99–5.07 (m, 2H, CH_2), 6.17 (br s, 1H, NH), 6.84 (s, 1H, CH), 7.27 (br s, 5H, Ph), 7.39–7.41 (3H, CH_{Ar}), 7.74–7.75 (m, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ 4.64 (s, 3F, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 54.6, 63.9 (q, J = 31.2 Hz, $>C<$), 67.8, 103.8, 122.1 (q, J = 287.6 Hz, CF_3), 126.7, 127.9, 128.1, 128.3, 128.4, 128.8, 130.3, 135.1, 153.6, 161.6, 162.7, 163.2; Calcd for $C_{21}H_{17}N_2F_3O_5$ (434.36): C, 58.07; H, 3.94; N, 6.45; found: C, 58.11; H, 3.95; N, 6.52.

Methyl *N*-(*tert*-butoxycarbonyl)-3,3,3-trifluoro-2-(3-phenylisoxazol-5-yl)alaninate (3d). Yield 68% as a white solid; M.p. 115–116 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H, $3CH_3$), 3.96 (s, 3H, OCH_3), 5.99 (s, 1H, NH), 6.98 (s, 1H, CH), 7.51–7.54 (m, 3H, CH_{Ar}), 7.86–7.90 (m, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ 4.43 (s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 54.5, 64.1 (q, J = 28.7 Hz, $>C<$), 82.1, 103.8, 122.3 (q, J = 287.8 Hz, CF_3), 126.9, 128.2, 128.9, 130.4, 153.1, 162.3, 162.8, 163.6; Calcd for $C_{18}H_{19}N_2F_3O_5$ (400.34): C, 54.00; H, 4.78; N, 7.00; found: C, 53.94; H, 4.77; N, 7.01.

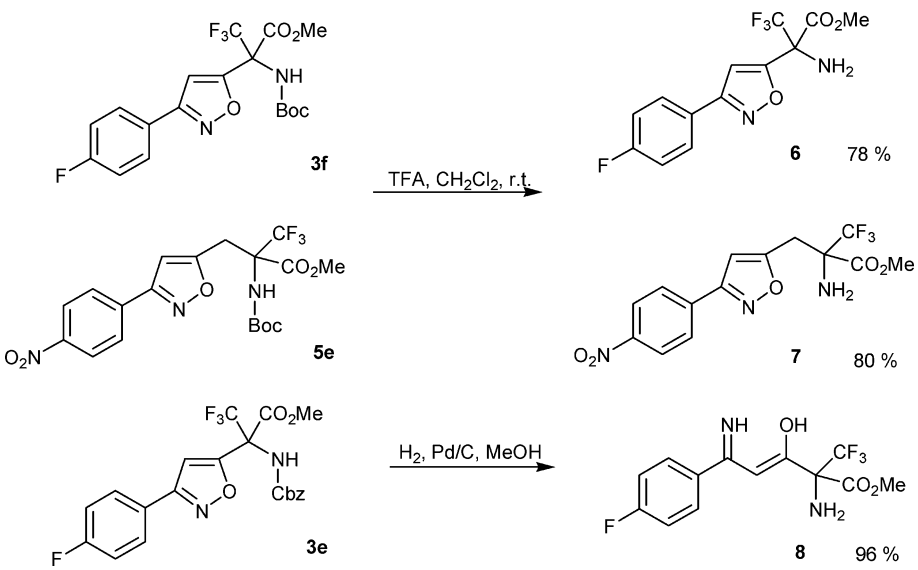
Methyl *N*-[(benzyloxy)carbonyl]-3,3,3-trifluoro-2-[3-(4-fluorophenyl)isoxazol-5-yl] alaninate (3e). Yield: 89% as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (3H, OCH_3), 5.16 (br s, 2H, CH_2), 6.32 (br s, 1H, NH), 6.95 (s, 1H, CH), 7.22 (t, J = 8.5 Hz, 2H, CH_{Ar}), 7.41 (br s, 5H, Ph), 7.86 (t, J = 7.1 Hz, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ −31.96, 4.65 (s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.9, 64.1 (q, J = 31.2 Hz, $>C<$), 68.0, 103.9, 116.1 (d, J = 21.6 Hz, $C_{Ar\text{-}m}$), 122.2 (q, J = 288.1 Hz, CF_3), 124.3, 128.4, 128.5, 128.6, 128.9 (d, J = 8.8 Hz, $C_{Ar\text{-}o}$), 135.3, 153.8, 161.9, 162.0, 163.3, 164.1 (d, J = 250.7 Hz, $C_{Ar\text{-}p}$); Calcd for $C_{21}H_{16}N_2F_4O_5$ (452.35): C, 55.75; H, 3.54; N, 6.19; found: C, 56.02; H, 3.73; N, 5.88.

Methyl *N*-(*tert*-butoxycarbonyl)-3,3,3-trifluoro-2-[3-(4-fluorophenyl)isoxazol-5-yl] alaninate (3f). Yield 62% as a white solid; M.p. 119–121 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H, $3CH_3$), 3.96 (s, 3H, OCH_3), 5.99 (s, 1H, NH), 6.96 (s, 1H,

Table 3 Isoxazole-containing α-CF_3-α-aminocarboxylates and α-CF_3-α-aminophosphonates

Entry	Alkyne	Ar	Product	Yield (%)[a]
1		4-CF_3-C_6H_4	 **5a**	62
2		4-CF_3-C_6H_4	 **5b**	64
3		4-CF_3-C_6H_4	 **5c**	58
4		4-NO_2-C_6H_4	 **5d**	68
5		4-NO_2-C_6H_4	 **5e**	72
6		4-NO_2-C_6H_4	 **5f**	65

[a] Isolated yields after purification by column chromatography or recrystallization.



Scheme 4

CH), 7.16 (t, J = 8.6 Hz, 2H, CH_{Ar}), 7.85–7.90 (m, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ –32.08, 4.45 (s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 54.6, 64.1 (q, J = 30.2 Hz, $>C<$), 82.2, 103.7, 116.1 (d, J = 21.6 Hz, $C_{Ar\text{-}m}$), 122.2 (q, J = 287.5 Hz, CF_3), 124.4, 128.9 (d, J = 8.8 Hz, $C_{Ar\text{-}o}$), 153.1, 161.9, 162.6, 163.6, 164.0 (d, J = 250.7 Hz, $C_{Ar\text{-}p}$); Calcd for $C_{18}H_{18}N_2F_4O_5$ (418.34): C, 51.67; H, 4.31; N, 6.70; found: C, 51.59; H, 4.37; N, 6.54.

Methyl *N*-[(benzyloxy)carbonyl]-3,3,3-trifluoro-2-{3-[4-(trifluoromethyl)phenyl]isoxazol-5-yl}alaninate (3g). Yield: 78% as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, OCH_3), 5.10 (br s, 2H, CH_2), 6.34 (br s, 1H, NH), 6.98 (s, 1H, CH), 7.34 (br s, 5H, Ph), 7.72 (d, J = 8.0 Hz, 2H, CH_{Ar}), 7.92 (d, J = 4.0 Hz, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ 3.66 and 13.74 (both s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.9, 64.2 (q, J = 31.3 Hz, $>C<$), 68.0, 104.1, 122.2 (q, J = 287.5 Hz, CF_3), 123.8 (q, J = 272.4 Hz, CF_3), 125.9, 127.3, 128.1, 128.2, 128.5, 131.6, 132.2 (q, J = 32.8 Hz, $C_{Ar\text{-}p}$), 135.3, 153.8, 161.7, 162.6, 163.2; Calcd for $C_{22}H_{16}N_2F_6O_5$ (502.36): C, 52.60; H, 3.21; N, 5.58; found: C, 52.88; H, 3.20; N, 5.27.

Methyl *N*-(*tert*-butoxycarbonyl)-3,3,3-trifluoro-2-{3-[4-(trifluoromethyl)phenyl]isoxazol-5-yl}alaninate (3h). Yield 77% as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H, $3CH_3$), 3.90 (s, 3H, OCH_3), 6.00 (br s, 1H, NH), 6.99 (s, 1H, CH), 7.72 (d, J = 8.0 Hz, 2H, CH_{Ar}), 7.94 (d, J = 8.0 Hz, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ 3.66 and 13.74 (both s, 3F, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.9, 54.6, 64.2 (q, J = 31.7 Hz, $>C<$), 82.2, 103.9, 122.2 (q, J = 287.8 Hz, CF_3), 123.8 (q, J = 272.4 Hz, CF_3), 125.9, 127.3, 131.7, 132.2 (q, J = 32.8 Hz, $C_{Ar\text{-}p}$), 153.1, 161.7, 163.1, 163.5; Calcd for $C_{19}H_{18}N_2F_6O_5$ (468.34): C, 48.73; H, 3.87; N, 5.98; found: C, 48.59; H, 3.41; N, 5.67.

Methyl *N*-[(benzyloxy)carbonyl]-3,3,3-trifluoro-2-[3-(4-nitrophenyl)isoxazol-5-yl] alaninate (3i). Yield 67% as a white solid; M.p. 116–118 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H, OCH_3), 5.03 (br s, 2H, CH_2), 6.22 (br s, 1H, NH), 6.96 (s, 1H, CH), 7.27 (br s, 5H, Ph), 7.94 (d, J = 7.2 Hz, 2H, CH_{Ar}), 8.26 (d, J = 7.2 Hz, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ 4.76 (s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.1, 63.7 (q, J = 30.0 Hz, $>C<$), 68.1, 104.3, 122.4 (q, J = 289.4 Hz, CF_3), 124.3, 127.9, 128.3, 128.6, 128.7, 134.2, 135.2, 148.9, 153.7, 161.0, 163.1, 163.2; Calcd for $C_{21}H_{16}N_3F_3O_7$ (479.36): C, 52.61; H, 3.34; N, 8.77; found: C, 52.68; H, 3.32; N, 8.51.

Methyl *N*-(*tert*-butoxycarbonyl)-3,3,3-trifluoro-2-[3-(4-nitrophenyl)isoxazol-5-yl]alaninate (3j). Yield 70% as a white solid; M.p. 142–144 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H, $3CH_3$), 3.98 (s, 3H, OCH_3), 5.99 (br s, 1H, NH), 7.11 (s, 1H, CH), 8.09 (d, J = 8.8 Hz, 2H, CH_{Ar}), 8.40 (d, J = 8.6 Hz, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ 4.57 (s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 54.6, 64.2 (q, J = 30.1 Hz, $>C<$), 82.3, 104.1, 122.1 (q, J = 289.7 Hz, CF_3), 124.2, 127.8, 134.3, 148.9, 153.2, 161.0, 163.4, 163.7; Calcd for $C_{18}H_{18}N_3F_3O_7$ (445.35): C, 48.54; H, 4.07; N, 9.44; found: C, 48.39; H, 4.02; N, 9.61.

Diethyl {1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-[3-(4-methoxyphenyl)isoxazol-5-yl]ethyl}phosphonate (4a). Yield: 55% as white solid; M.p. 103–104 °C;^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 6H, $2CH_3$), 3.86 (s, 3H, OCH_3), 4.09–4.29 (m, 4H, $2OCH_2$), 5.05 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 5.1 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 5.99 (d, J = 8.0 Hz, 1H, NH), 6.74 (s, 1H, CH), 6.98 (d, J = 8.3 Hz, 2H, CH_{Ar}), 7.33 (br s, 5H, Ph), 7.76 (d, J = 8.3 Hz, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ 8.31 (s, 3F, CF_3); ^{31}P NMR (161 MHz, $CDCl_3$) δ 11.55; ^{13}C NMR (151 MHz, $CDCl_3$) δ 16.3, 55.4, 61.8 (dq, J = 141.5, 32.4 Hz, $>C<$), 65.8 (d, J = 6.6 Hz, OCH_2-), 65.9 (d, J = 6.6 Hz, OCH_2-), 67.9, 103.1, 114.3, 120.8, 123.3 (q, J = 287.8 Hz, CF_3), 128.3, 128.4, 128.6, 135.4, 153.6, 161.1, 161.2, 162.2; Calcd for $C_{24}H_{26}N_2F_3O_7P$ (542.44): C, 53.15; H, 4.83; N, 5.16; found: C, 53.19; H, 4.75; N, 5.21.

Diethyl [1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-(3-phenylisoxazol-5-yl)ethyl] phosphonate diethyl {1-{[(benzyloxy)-carbonyl]amino}-2,2,2-trifluoro-1-[3-(4-methoxyphenyl)isoxazol-5-yl]ethyl}phosphonate (4b). Yield: 65% as white solid; M.p. 95–97 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 6H, $2CH_3$), 4.00–4.24 (m, 4H, $2OCH_2$), 4.98 (d_{AB}, J_{AB} = 12.1 Hz, 1H, CH_2), 5.04 (d_{AB}, J_{AB} = 12.1 Hz, 1H, CH_2), 5.96 (d, J = 10.3 Hz, 1H, NH), 6.75 (s, 1H, CH), 7.25 (br s, 5H, Ph), 7.37–7.40 (m, 3H, CH_{Ar}), 7.72–7.75 (m, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ 9.28 (s, 3F, CF_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 10.28; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J = 4.3 Hz, $2CH_3$-), 61.6 (dq, J = 142.2, 31.9 Hz, $>C<$), 65.7 (t, J = 7.9 Hz, $2OCH_2$-), 67.7, 103.1, 123.1 (q, J = 288.7 Hz, CF_3), 126.7, 128.1, 128.2, 128.3, 128.4, 128.7, 130.1, 135.2, 153.3, 161.2, 162.4; Calcd for $C_{23}H_{24}N_2F_3O_6P$ (512.41): C, 53.91; H, 4.72; N, 5.47; found: C, 53.69; H, 4.73; N, 5.17.

Diethyl {1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-[3-(4-fluorophenyl)isoxazol-5-yl]ethyl}phosphonate (4c). Yield: 58% as white solid; M.p. 105–107 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 8.0 Hz, 6H, $2CH_3$), 4.11–4.30 (m, 4H, $2OCH_2$), 5.05 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 5.10 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 6.02 (d, J = 8.0 Hz, 1H, NH), 6.77 (s, 1H, CH), 7.15 (t, J = 8.0 Hz, 2H, CH_{Ar}), 7.32 (br s, 5H, Ph), 7.78 (br s, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ –33.35, 8.26 (s, 3F, CF_3); ^{31}P NMR (161 MHz, $CDCl_3$) δ 10.28 (d, J = 3.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (d, J = 2.0 Hz, CH_3-), 16.4 (d, J = 2.0 Hz, CH_3-), 61.8 (dq, J = 142.0, 30.0 Hz, $>C<$), 65.9 (d, J = 7.0 Hz, OCH_2-), 66.1 (d, J = 8.0 Hz, OCH_2-), 68.0, 103.3, 116.1 (d, J = 22.0 Hz, $C_{Ar\text{-}m}$), 123.3 (q, J = 287.0 Hz, CF_3), 124.6, 128.4, 128.5, 128.7, 128.9 (d, J = 8.0 Hz, $C_{Ar\text{-}o}$), 135.4, 153.6, 161.7, 161.8, 164.0 (d, J = 249.0 Hz, $C_{Ar\text{-}p}$); Calcd for $C_{23}H_{23}N_2F_4O_6P$ (530.41): C, 52.08; H, 4.37; N, 5.84; found: C, 52.19; H, 4.34; N, 5.19.

Diethyl (1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-{3-[4-(trifluoromethyl)phenyl] isoxazol-5- yl}ethyl)phosphonate (4d). Yield: 80% as white solid; M.p. 132–134 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 8.0 Hz, 6H, $2CH_3$), 4.12–4.30 (m, 4H, $2OCH_2$), 5.05 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 5.10 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 6.03 (d, J = 8.0 Hz, 1H, NH), 6.84 (s, 1H, CH), 7.32 (br s, 5H, Ph), 7.72 (d, J = 8.0 Hz, 2H, CH_{Ar}), 7.93 (d, J = 8.0 Hz, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ 8.28 and 13.76 (both s, 3F, CF_3); ^{31}P NMR (161 MHz, $CDCl_3$) δ 10.73; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (d, J = 2.0 Hz, CH_3-), 16.4 (d, J = 2.0 Hz, CH_3-), 61.8 (dq, J = 140.0, 30.0 Hz, $>C<$), 65.9 (d, J = 7.0 Hz, OCH_2-), 66.1 (d, J = 8.0 Hz, OCH_2-), 68.1, 103.4, 123.3 (q, J = 287.0 Hz, CF_3), 123.9 (q, J = 270.0 Hz, CF_3), 125.9, 127.3, 128.4, 128.5, 128.7, 131.9, 132.2 (q, J = 33.0 Hz, $C_{Ar\text{-}p}$),

135.4, 153.6, 161.5, 162.3; Calcd for $C_{24}H_{23}N_2F_6O_6P$ (580.41): C, 49.66; H, 3.99; N, 4.83; found: C, 49.58; H, 3.95; N, 4.77.

Diethyl {1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-[3-(4-nitrophenyl)isoxazol-5-yl] ethyl}phosphonate (4e). Yield: 68% as white solid; M.p. 145–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, J = 6.7 Hz, 6H, $2CH_3$), 4.15–4.39 (m, 4H, $2OCH_2$), 5.12 (d_{AB}, J_{AB} = 11.9 Hz, 1H, CH_2), 5.17 (d_{AB}, J_{AB} = 11.9 Hz, 1H, CH_2), 6.1 (d, J = 8.8 Hz, 1H, NH), 6.94 (s, 1H, CH), 7.39 (br s, 5H, Ph), 8.06 (d, J = 8.5 Hz, 2H, CH_{Ar}), 8.39 (d, J = 8.2 Hz, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ 9.22 (d, J = 3.0 Hz, 3F, CF_3); ^{31}P NMR (161 MHz, $CDCl_3$) δ 10.09 (d, J = 3.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 61.7 (dq, J = 142.6, 30.9 Hz, $>C<$), 65.9 (d, J = 6.6 Hz, OCH_2-), 66.1 (d, J = 6.6 Hz, OCH_2-), 68.0, 103.4, 123.2 (q, J = 288.9 Hz, CF_3), 124.2, 127.8, 128.4, 128.6, 134.4, 135.3, 148.8, 153.6, 160.8, 162.8; Calcd for $C_{23}H_{23}N_3F_3O_8P$ (557.41): C, 49.56; H, 4.16; N, 7.54; found: C, 49.58; H, 4.19; N, 7.54.

Methyl 2-{[(benzyloxy)carbonyl]amino}-3,3,3-trifluoro-2-({3-[4-(trifluoromethyl)phenyl] isoxazol-5-yl}methyl)propanoate (5a). Yield 62% as a white solid; M.p. 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 3.99 (s, 3H, OCH_3), 4.60 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 5.01 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 5.21 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 6.02 (br s, 1H, NH), 6.30 (s, 1H, CH), 7.24–7.36 (m, 5H, Ph), 7.69 (d, J = 8.0 Hz, 2H, CH_{Ar}), 7.74 (d, J = 8.0 Hz, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ 2.17 and 13.79 (both s, 3F, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.4, 55.9, 64.6 (q, J = 29.8 Hz, $>C<$), 62.2, 102.9, 123.3 (q, J = 288.2 Hz, CF_3), 123.9 (q, J = 272.4 Hz, CF_3), 124.1, 127.7, 128.2, 128.4, 128.6, 134.6, 135.8, 148.6, 153.8, 160.6, 165.8, 167.2; Calcd for $C_{23}H_{18}N_2F_6O_5$ (516.39): C, 53.05; H, 3.51; N, 5.42; found: C, 53.56; H, 3.58; N, 4.98.

Methyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-({3-[4-(trifluoromethyl)phenyl] isoxazol-5-yl}methyl)propanoate (5b). Yield 64% as a white solid; M.p. 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H, $3CH_3$), 3.73 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 3.98 (s, 3H, OCH_3), 4.54 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 5.73 (br s, 1H, NH), 6.51 (s, 1H, CH), 7.71 (d, J = 8.0 Hz, 2H, CH_{Ar}), 7.86 (d, J = 8.0 Hz, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ 2.14 and 13.73 (both s, 3F, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.6, 28.1, 54.7, 64.7 (q, J = 29.4 Hz, $>C<$), 81.1, 103.1, 123.5 (q, J = 287.7 Hz, CF_3), 123.8 (q, J = 272.5 Hz, CF_3), 126.0, 127.0, 132.1 (q, J = 31.1 Hz, $C_{Ar\text{-}p}$), 132.2, 153.3, 161.3, 166.3, 167.3; Calcd for $C_{20}H_{20}N_2F_6O_5$ (482.37): C, 49.80; H, 4.18; N, 5.81; found: C, 49.66; H, 4.14; N, 5.62.

Diethyl [1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-({3-[4-(trifluoromethyl)phenyl] isoxazol-5-yl}methyl)ethyl]phosphonate (5c). Yield: 58% as white solid; M.p. 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.27 (m, 6H, $2CH_3$), 3.81–3.89 (m, 1H, CH_2), 4.02–4.29 (m, 4H, $2OCH_2$, 1H, CH_2), 5.11 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 5.23 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 5.61 (d, J = 8.0 Hz, 1H, NH), 6.38 (s, 1H, CH), 7.32–7.47 (br s, 5H, Ph), 7.67 (d, J = 8.0 Hz, 2H, CH_{Ar}), 7.76 (d, J = 8.0 Hz, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ 7.38 (3F, CF_3); ^{31}P NMR (161 MHz, $CDCl_3$) δ 14.78; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 26.5, 61.7 (dq, J = 142.4, 30.2 Hz, $>C<$), 66.1, 68.0, 103.4, 123.1 (q, J = 288.5 Hz, CF_3), 123.7 (q, J = 272.4 Hz, CF_3), 126.1, 127.3, 128.3, 128.5, 128.6, 132.1 (q, J = 31.2 Hz, $C_{Ar\text{-}p}$), 134.3, 135.3, 153.6, 161.3, 162.7; Calcd for $C_{25}H_{25}N_2F_6O_6P$ (594.44): C, 50.51; H, 4.24; N, 4.71; found: C, 50.37; H, 4.28; N, 4.44.

Methyl 2-{[(benzyloxy)carbonyl]amino}-3,3,3-trifluoro-2-{[3-(4-nitrophenyl)isoxazol-5-yl]methyl}propanoate (5d). Yield 68% as a white solid; M.p. 125–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (d_{AB}, J_{AB} = 14.3 Hz, 1H, CH_2), 3.93 (s, 3H, OCH_3), 4.55 (d_{AB}, J_{AB} = 15.3 Hz, 1H, CH_2), 4.95 (d_{AB}, J_{AB} = 11.3 Hz, 1H, CH_2), 5.16 (d_{AB}, J_{AB} = 12.1 Hz, 1H, CH_2), 5.95 (br s, 1H, NH), 6.25 (s, 1H, CH), 7.19–7.26 (m, 5H, Ph), 7.72 (d, J = 8.5 Hz, 2H, CH_{Ar}), 8.23 (d, J = 9.1 Hz, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ 3.19 (s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 55.9, 64.7 (q, J = 29.8 Hz, $>C<$), 62.2, 102.9, 123.3 (q, J = 288.6 Hz, CF_3), 124.1, 127.7, 128.2, 128.4, 128.6, 134.7, 135.8, 148.7, 153.9, 160.7, 165.9, 167.2; Calcd for $C_{22}H_{18}N_3F_3O_7$ (493.37): C, 53.56; H, 3.68; N, 8.52; found: C, 53.56; H, 3.47; N, 8.41.

Methyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-{[3-(4-nitrophenyl)isoxazol-5-yl] methyl}propanoate (5e). Yield 72% as a white solid; M.p. 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H, $3CH_3$), 3.73 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 3.97 (s, 3H, OCH_3), 4.54 (d_{AB}, J_{AB} = 12.0 Hz, 1H, CH_2), 5.71 (s, 1H, NH), 6.53 (s, 1H, CH), 7.91 (d, J = 8.5 Hz, 2H, CH_{Ar}), 8.30 (d, J = 8.5 Hz, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ 2.12 (s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 28.0, 54.9, 64.7 (q, J = 29.0 Hz, $>C<$), 81.2, 103.1, 123.5 (q, J = 288.0 Hz, CF_3), 124.3, 127.6, 134.9, 148.8, 153.3, 160.7, 166.3, 167.9; Calcd for $C_{19}H_{20}N_3F_3O_7$ (459.37): C, 49.68; H, 4.39; N, 9.15; found: C, 49.74; H, 4.34; N, 9.16.

Diethyl (1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-{[3-(4-nitrophenyl)isoxazol-5-yl]methyl}ethyl)phosphonate (5f). Yield: 65% as white solid; M.p. 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22–1.31 (m, 6H, $2CH_3$), 3.82–3.90 (m, 1H, CH_2), 4.15–4.27 (m, 4H, $2OCH_2$, 1H, CH_2), 5.12 (d_{AB}, J_{AB} = 11.7 Hz, 1H, CH_2), 5.23 (d_{AB}, J_{AB} = 12.3 Hz, 1H, CH_2), 5.59 (d, J = 7.9 Hz, 1H, NH), 6.39 (s, 1H, CH), 7.37 (br s, 5H, Ph), 7.81 (d, J = 7.3 Hz, 2H, CH_{Ar}), 8.27 (d, J = 8.1 Hz, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ 7.38 (3F, CF_3); ^{31}P NMR (161 MHz, $CDCl_3$) δ 14.78; ^{13}C NMR (151 MHz, $CDCl_3$) δ 16.2, 25.8, 61.6 (dq, J = 152.5, 29.1 Hz, $>C<$), 64.6 (d, J = 6.6 Hz, OCH_2-), 64.8 (d, J = 5.5 Hz, OCH_2-), 67.5, 102.6, 124.2 (q, J = 287.8 Hz, CF_3), 124.1, 127.6, 128.4, 128.5, 128.7, 135.1, 135.8, 148.6, 154.5, 160.6, 167.9; Calcd for $C_{24}H_{25}N_3F_3O_8P$ (571.44): C, 50.44; H, 4.41; N, 7.35; found: C, 49.77; H, 4.31; N, 7.14.

General procedure for the removing of the Boc-protecting group

A solution of **3f** and **5e** (1 mmol) in a biphasic mixture of trifluoroacetic acid/dichlormethane (2 ml/5 ml) was stirred at room temperature for 50 min. After evaporation of solvents under reduced pressure, water (5 ml) was added to the residue and the resulting water solution was neutralized with saturated solution of sodium bicarbonate until pH 7. Then the mixture was extracted with diethyl ether (3 × 10 ml). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting by ethyl acetate–hexanes (1 : 8) or by recrystallization.

Methyl 3,3,3-trifluoro-2-[3-(4-fluorophenyl)isoxazol-5-yl]-alaninate (6). Yield 78% as a colorless oil; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 2.52 (br s, 2H, NH_2), 3.91 (s, 3H, OCH_3), 6.77 (s, 1H, CH), 7.16 (t, J = 8.0 Hz, 2H, CH_{Ar}), 7.78–7.82 (m, 2H, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ −33.02, 0.84 (s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.5, 64.2 (q, J = 30.0 Hz, $>C<$), 102.6, 116.2 (d, J = 21.9 Hz, $C_{Ar\text{-}m}$), 123.1 (q, J = 285.0 Hz, CF_3), 124.5, 128.9 (d, J = 8.6 Hz, $C_{Ar\text{-}o}$), 161.9, 165.4, 164.1 (d, J = 229.0 Hz, $C_{Ar\text{-}p}$), 165.7; Calcd for $C_{11}H_8N_2F_4O_3$ (318.22): C, 49.07; H, 3.17; N, 8.80; found: C, 49.05; H, 3.17; N, 8.79.

Methyl 2-amino-3,3,3-trifluoro-2-{[3-(4-nitrophenyl)isoxazol-5-yl]methyl}propanoate (7). Yield 80% as white solid; M.p. 88–90 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.94 (br s, 2H, NH_2), 3.27 (d_{AB}, J_{AB} = 16.0 Hz, 1H, CH_2), 3.70 (d_{AB}, J_{AB} = 16.0 Hz, 1H, CH_2), 3.87 (s, 3H, OCH_3), 6.59 (s, 1H, CH), 7.96 (d, J = 8.0 Hz, 2H, CH_{Ar}), 8.31 (d, J = 12.0 Hz, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −1.43 (s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 53.9, 64.1 (q, J = 28.0 Hz, $>C<$), 102.5, 124.4 (q, J = 287.2 Hz, CF_3), 124.2, 127.7, 134.9, 148.7, 160.9, 168.0; Calcd for $C_{14}H_{12}N_3F_3O_5$ (359.26): C, 46.80; H, 3.37; N, 11.70; found: C, 46.68; H, 3.29; N, 11.58.

Methyl 3-[2-(4-fluorophenyl)-2-iminoethylidene]-2-(trifluoromethyl)serinate (8). To a solution of Cbz-protected aminoester **3e** (1.5 mmol) in methanol (20 ml) 10% Pd/C (5%- mol) was added and a slow stream of hydrogen was bubbled through the mixture at room temperature. When TLC indicated no starting material (about 2 h), the mixture was filtered and the solvent was evaporated to dryness. Yield 96% as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (br s, 2H, NH_2), 3.85 (s, 3H, OCH_3), 5.72 (s, 1H, CH), 5.77 (br s, 1H, NH), 7.15 (dt, J = 8.0, 1.0 Hz, 2H, CH_{Ar}), 7.52–7.56 (m, 2H, CH_{Ar}); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −31.19, 3.82 (s, 3F, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.8, 71.1 (q, J = 27.0 Hz, $>C<$), 90.0, 116.2 (d, J = 21.9 Hz, $C_{Ar\text{-}m}$), 123.6 (q, J = 282.1 Hz, CF_3), 128.8 (d, J = 8.9 Hz, $C_{Ar\text{-}o}$), 132.1, 164.5, 164.6 (d, J = 250.8 Hz, $C_{Ar\text{-}p}$), 167.8, 183.4; MS(ESI) calcd for $C_{13}H_{12}N_2F_4O_3$ $[M+Na]^+$ 343.2294, found 343.2287.

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