Synthesis of Fluorine-Containing Cyclic α-Amino Acid and α-Amino Phosphonate Derivatives by Alkene Metathesis

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The electrophilic imino esters $XF_2CC(=NPG)CO_2Me$ and imino phosphonates $CF_3CC(=NPG)P(O)(OR)_2$ (PG = SO_2Ph, Cbz, Boc) were transformed by nucleophilic and then electrophilic additions into fluorine-containing amino esters and amino phosphonates with two pendent alkene chains $(XF_2C)(CH_2{=}CH(CH_2)_nC(NPG)(Z)(CH_2)_mCH{=}CH_2$ [Z = CO_2Me, $P(O)(OR)_2$]. The ring-closing metathesis was performed on the α-amino ester dienes with $Ru{=}CHPh(Cl)_2(PCy_3)_2$ catalyst and afforded five-, six-, and seven-membered cyclic amino esters, whereas the α-aminophosphonate dienes were transformed with RCM catalyst [Ru=C=C=CPh_2(Cl)(PCy_3)(*p*-cymene)]OTf to give six- and seven-membered cyclic α-amino-α-(trifluoromethyl)phosphonates.

Introduction

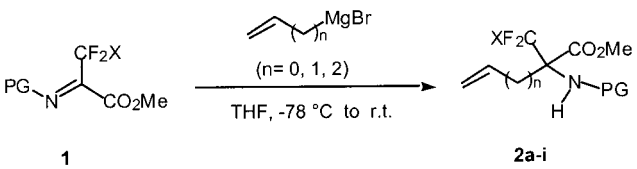
Recently, fluorinated α-amino acids and their derivatives such as α-(fluoromethyl)-substituted α-amino acids, which can function as highly selective inhibitors of pyridoxal phosphate dependent enzymes, have been attracting considerable interest.[1] α-Aminophosphonates, on the other hand, constitute important analogues of α-aminocarboxylic acids, and their syntheses and biological activities have been a focus of attention in medicinal chemistry.[2] These compounds exhibit potential as antibacterial agents[3] and transition-state analogue inhibitors of proteolytic enzymes.[4] In addition, the incorporation of cyclic amino acids of medium ring size into key positions in peptide chains plays an important role, as it constitutes the most prominent pathway to conformationally constrained peptidomimetics, a tool in modern drug discovery.[5] The introduction of a CF_3 group into the α-position of such a cyclic α-amino acid can significantly improve the biological properties of peptides,[6] and this is the motivation for the search for straightforward routes to cyclic α-amino esters and phosphonate analogues containing fluorinated groups blocking the α-positions. A simple route to α-amino α-(difluorohalomethyl) acid esters[7] from electrophilic imines of the $XF_2CC(=NPG)CO_2Me$ type has recently been reported. One possible approach for restricting their flexibility by cyclization is based on intramolecular ring-closing metathesis (RCM). Indeed, since the discovery of efficient and well-defined molybdenum[8] and ruthenium[9] catalysts for alkene metathesis, with high tolerances for a variety of functional groups, this reaction now constitutes a powerful method for the production of carbo-, hetero-, and macrocycles.[10]

We now report a general route to cyclic α-amino α-(fluoromethyl) acid esters and their α-aminophosphonate analogues. It is based on (i) the addition of two hydrocarbon chains, bearing terminal alkene groups, to the electrophilic fluorinated imines $XF_2C(Y){=}NPG$ [Y = CO_2R and $P(O)(OR)_2$; PG = SO_2Ph, Cbz, Boc], followed by (ii) ruthenium-catalyzed ring-closing metathesis. We have already reported the principle of this approach[11] and the first synthesis of fluorinated α-aminophosphonates.[12]

Results

Preparation of Fluorinated α-Amino Acid Esters and Phosphonates Containing Two Terminal Alkene Chains

New fluorine-containing α-amino acid esters with two alkene chains, featuring the 1,6-, 1,7-, and 1,8-diene structures, were first synthesized by addition reactions to the electrophilic fluorinated imines $XF_2CC(CO_2Me){=}NPG$ (**1**)[13] derived from methyl (trifluoro- or chlorodifluoro)pyruvate. The synthetic sequence involves two successive steps. The first step involves the addition of vinyl-, allyl-, and homoallylmagnesium bromides to highly electrophilic *N*-Boc, *N*-Cbz, and *N*-SO_2Ph imines **1**. This reaction takes place at −78 °C in THF or ether to produce the corresponding unsaturated α-amino acid esters **2a**−**i** selectively and in good yields (Scheme 1, Table 1).



1 **2a-i**

Scheme 1

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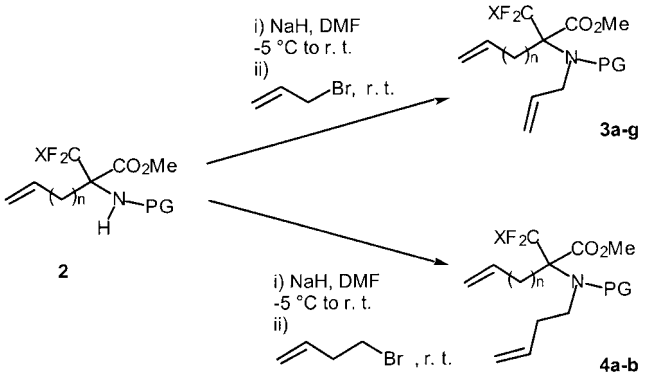
Table 1. Preparation of fluorinated α-amino acid esters **2a**−**i** containing one terminal alkene chain

Entry	Compound	*n*	X	PG	Yield (%)
1	**2a**	0	F	SO_2Ph	57
2	**2b**	0	F	Cbz	61
3	**2c**	0	F	Boc	54
4	**2d**	1	F	SO_2Ph	75
5	**2e**	1	F	Cbz	68
6	**2f**	1	Cl	Boc	65
7	**2g**	2	F	Cbz	77
8	**2h**	2	Cl	Cbz	79
9	**2i**	2	F	Boc	73

The second step involves the deprotonation of compounds **2** with NaH in DMF at 0 °C and subsequent alkylation with allyl bromide to afford the corresponding 1,6-, 1,7-, and 1,8-heterodiene derivatives **3a**−**g** in 55−81% yields (Scheme 2, Table 2). Analogous alkylation with homoallyl bromide affords the 1,8-dienes **4a** and **4b** in 70 and 66% yields, respectively.

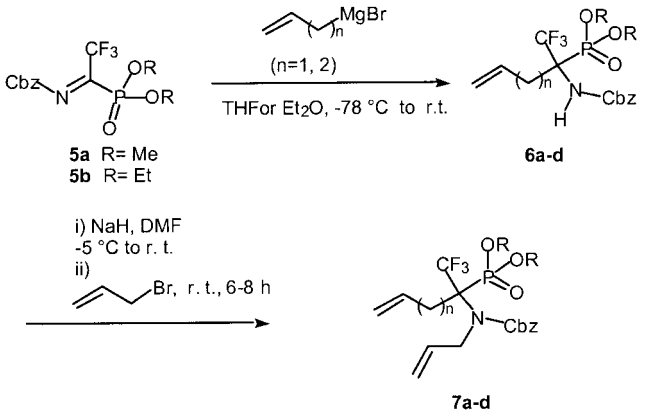


Scheme 2

Table 2. Preparation of dienes **3a**−**g** and **4a**−**b**

Entry	Compound	*n*	X	PG	Yield (%)
1	**3a**	0	F	SO_2Ph	81
2	**3b**	0	F	Cbz	65
3	**3c**	1	F	SO_2Ph	72
4	**3d**	1	F	Boc	55
5	**3e**	2	F	Cbz	67
6	**3f**	2	F	Boc	69
7	**3g**	2	Cl	Cbz	61
8	**4a**	1	F	Cbz	70
9	**4b**	1	Cl	Cbz	66

Under closely related conditions, the iminophosphonates **5a** and **5b**[14] were transformed in two steps, firstly into the fluorinated α-aminophosphonates **6a**−**d** in good yields through addition of allylic and homoallylic Grignard derivatives, and then into the 1,7- and 1,8-dienes **7a**−**d** by deprotonation of **6a**−**d** followed by treatment with allyl bromide (Scheme 3, Table 3).



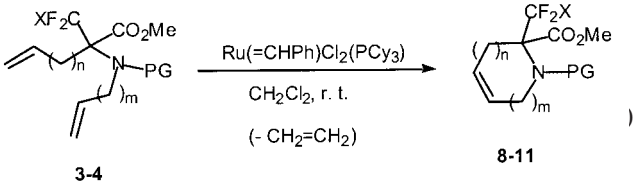
Scheme 3

Table 3. Preparation of the monoenes **6a**−**d** and dienes **7a**−**d**

Entry	*n*	R	**6** (%)	**7** (%)
1	1	Me	**6a** (71)	**7a** (58)
2	1	Et	**6b** (68)	**7b** (69)
3	2	Me	**6c** (66)	**7c** (61)
4	2	Et	**6d** (74)	**7d** (70)

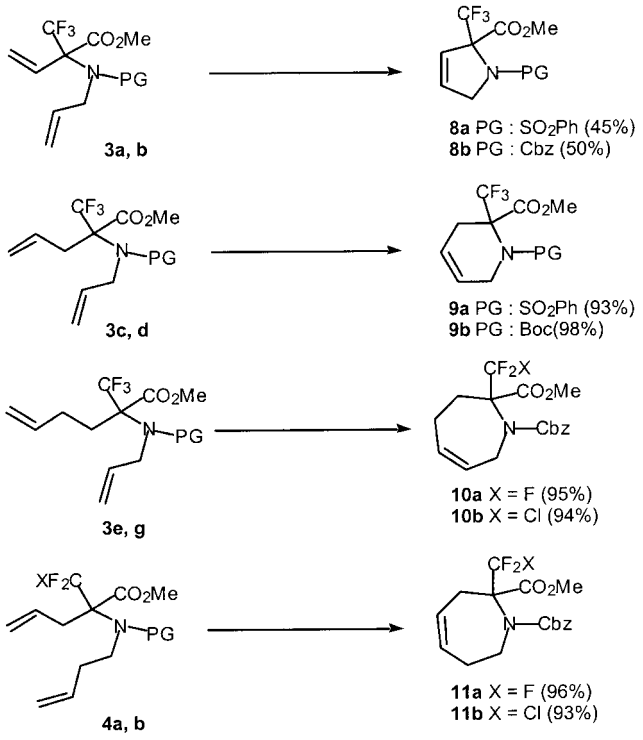
Preparation of Cyclic Fluorinated α-Amino Acid Esters by Ruthenium-Catalyzed Ring-Closing Metathesis

Intramolecular ring-closing metathesis (RCM) of the 1,7- and 1,8-heterodienes **3**−**4** was investigated in an attempt to perform the reaction according to Equation (1), with the help of 5−10 mol-% of a ruthenium catalyst, either $Cl_2(PCy_3)_2Ru{=}CHPh$[9] or (*p*-cymene)$RuCl(PCy_3)(=C{=}C{=}CPh_2)^+X^-$.[15] The neutral precursor $Ru{=}CHPh(Cl)_2(PCy_3)_2$ appeared more efficient with these amino acid ester dienes, as the RCM reaction took place in this case at room temperature whereas the allenylidene precursor required heating in toluene.



Treatment of the 1,7-dienes **3c**−**3d** in dichloromethane in the presence of 10 mol-% of $Ru{=}CHPh(Cl)_2(PCy_3)_2$ catalyst at room temperature for 3−5 h produced the six-membered dehydropipecolinic acid derivatives **9a** and **9b** in excellent yields (Scheme 4). Under similar conditions, the 1,8-dienes **3e** and **3g** afforded the seven-membered cyclic amino acid esters **10a** and **10b**, the tetrahydroazepine-2-carboxylic acid derivatives, whereas the 1,8-dienes **4a** and **4b** selectively yielded their isomers **11a** and **11b** (Scheme 4). These latter reactions thus demonstrate that the position of the double C=C bond of the cyclic amino esters (**10** or **11**) can be

controlled by the length of the respective pendent chains in dienes **3** and **4**.

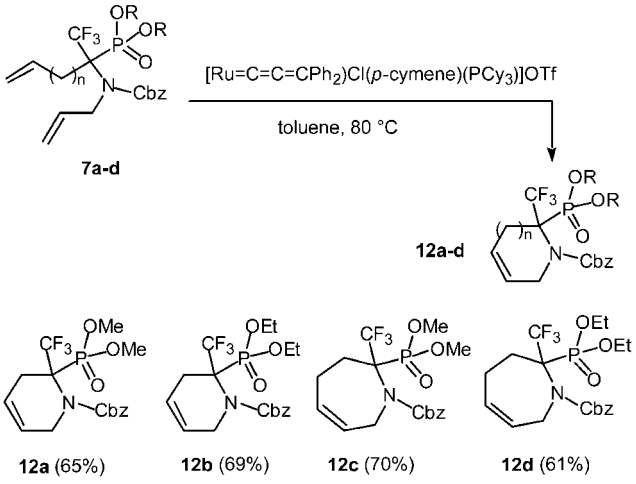


Scheme 4

In contrast, while RCM of the 1,6-dienes **3a** and **3b** also took place under the same conditions to produce the corresponding dehydroprolinates **8a** and **8b**, complete conversion of the starting dienes could not be achieved even after 60 h (conversion ca. 55%). The yields of the products, isolated after column chromatography on silica gel, were only in the 45−50% range.

Preparation of Cyclic Fluorinated α-Aminophosphonates by Ring-Closing Metathesis with the Catalyst [Ru(=C=C=CPh$_2$)Cl(*p*-cymene)(PCy$_3$)]OTf

Ring-closing metathesis of the α-aminophosphonates **7a**−**d** was attempted with the help of both catalyst precursors Ru=CHPh(Cl)$_2$(PCy$_3$)$_2$[9] and [Ru(=C=C=CPh$_2$)Cl(*p*-cymene)(PCy$_3$)]OTf.[15] In this case these complexes were not active at room temperature, but were in toluene at 80 °C, the latter catalyst being more efficient for the transformation of the aminophosphonate substrates. Thus, the transformation of the 1,7- (**7a**, **7b**) and 1,8-heterodienes (**7c**, **7d**) was performed in toluene at 80° C in the presence of 10 mol % of the metathesis catalyst precursor [Ru(=C=C=CPh$_2$)Cl(*p*-cymene)(PCy$_3$)]OTf. This was formed in situ[15b] from [RuCl$_2$(*p*-cymene)]$_2$, by successive addition of PCy$_3$, silver triflate, and then propargylic alcohol HC≡CCPh$_2$OH. Complete conversion of the dienes was achieved within 6 h and the six-membered (**12a**, **12b**) and seven-membered (**12c**, **12d**) heterocycles were obtained in good yields (61−70%) (Scheme 5). Thus, this reaction shows that the presence of fluorinated carbamate and phosphonate groups was tolerated by the allenylidene catalyst. It is noteworthy that ring-closing metathesis had previously been applied to allylic phosphonates to form six- and seven-membered rings but with the phosphorus atom within the cycle.[16]



Scheme 5

Conclusion

The above reactions, resulting in the transformation of reactive electrophilic fluorinated imines into fluorinated *cyclic* α-amino acid esters or α-aminophosphonates, show that the alkene metathesis reaction, performed with ruthenium catalyst precursors, give access not only to a large variety of new fluorinated compounds, but also to useful polyfunctional cyclic derivatives. It also shows that the efficiency of a given ruthenium catalyst, the neutral Ru=CHPh(Cl)$_2$(PCy$_3$)$_2$ or the organometallic salt [Ru=C=C=CPh$_2$(Cl)(PCy$_3$)(*p*-cymene)]OTf, largely depends on the nature of the substrates, as the former is more efficient with amino acid esters and the latter with aminophosphonates.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with Bruker AC 200 and 300 MHz spectrometers; ^{19}F NMR spectra were obtained at 188 MHz with trifluoroacetic acid as external standard. − IR spectra were measured with an IR-20 spectrometer. − Mass data were obtained with an MS-Finnigan MAT ANCOS-50 (70 eV). − Elemental microanalyses were carried out by the microanalytical laboratory at the Institute of Organoelement Compounds RAS, Moscow. − All reactions were routinely monitored by ^{19}F NMR spectroscopy or TLC. − Analytical TLC was performed using Merck precoated 60F-254 silica gel plates (0.25 mm). For flash chromatography, silica gel 60 (30−60 mm) was used with hexane/ethyl acetate eluent mixtures. − Organic solvents were dried and distilled prior to use. For compounds **7b** and **8**, NMR spectra were recorded at 60 °C in [D$_6$]DMSO to avoid the presence of two rotamers resulting from rotation around the amide bonds.

General Procedure for the Preparation of α-Amino Acid Esters 2 and α-Aminophosphonates 6: A Grignard reagent (solution in THF,

10.0 mmol) was added dropwise to a stirred solution of imine **1** or **5** (10.0 mmol) in dry THF (25 mL) at −78 °C. After 1 h at −78 °C, the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched with 1 N HCl and extracted with ether (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried with $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography.

Methyl 2-(Benzenesulfonylamino)-2-(trifluoromethyl)but-3-enoate (2a): Oil. − ^{1}H NMR ($CDCl_3$): δ = 3.86 (s, 3 H, OMe), 5.41 (d, ^3J = 17.0 Hz, 1 H, CH=CH_2), 5.43 (d, ^3J = 10.2 Hz, 1 H, CH=CH_2), 5.75 (s, 1 H, NH), 6.19 (dd, ^3J = 17.0, 10.2 Hz, 1 H, CH=CH_2), 7.37 (s, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 4.8 (s, 3 F, CF_3). − $C_{12}H_{12}F_3NO_4S$ (323.3): calcd. C 44.58, H 3.72, N 4.33; found C 44.39, H 3.71, N 4.55.

Methyl 2-(Benzyloxycarbonylamino)-2-(trifluoromethyl)but-3-enoate (2b): Oil. − ^{1}H NMR ($CDCl_3$): δ = 3.76 (s, 3 H, OMe), 5.15 (s, 2 H, OCH_2), 5.61 (d, ^3J = 17.2 Hz, 1 H, CH=CH_2), 5.63 (d, ^3J = 10.5 Hz, 1 H, CH=CH_2), 5.95 (s, 1 H NH), 6.26 (dd, ^3J = 17.2, 10.5 Hz, 1 H, CH=CH_2), 7.37 (s, 5 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 53.61, 65.99 (q, $^2J_{CF}$ = 29.8 Hz), 67.73, 121.31, 123.50 (q, $^1J_{CF}$ = 286.1 Hz), 128.15, 128.33, 128.45, 128.64, 135.61, 154.47, 164.51. − ^{19}F NMR ($CDCl_3$): δ = 4.2 (s, 3 F, CF_3). − IR (KCl): $\tilde{\nu}$ = 3440, 1770, 1730, 1510 cm^{-1}. − $C_{14}H_{14}F_3NO_4$ (317.3): calcd. C 53.00, H 4.42, N 4.42; Found C 53.19, H 4.71, N 4.45.

Methyl 2-(*tert*-Butoxycarbonylamino)-2-(trifluoromethyl)but-3-enoate (2c): Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 9 H, 3 Me), 3.79 (s, 3 H, OMe), 5.53 (d, ^3J = 17.1 Hz, 1 H, CH=CH_2), 5.55 (d, ^3J = 9.95 Hz, 1 H, CH=CH_2), 5.77 (s, 1 H, NH), 6.29 (dd, ^3J = 17.1, 9.95 Hz, 1 H, CH=CH_2). − ^{19}F NMR ($CDCl_3$): δ = 3.6 (s, 3 F, CF_3). − $C_{11}H_{16}F_3NO_4$ (283.2): calcd. C 46.64, H 5.65, N 4.95; found C 46.49, H 5.71, N 4.85.

Methyl 2-(Benzenesulfonylamino)-2-(trifluoromethyl)pent-4-enoate (2d): Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.87 (dd, J = 5.7, 11.4 Hz, 1 H, CH_2), 3.39 (m, 1 H, CH_2), 3.91 (s, 3 H, OMe), 5.31 (m, 2 H, CH=CH_2), 5.79 (s, 1 H, NH), 5.85 (m, 1 H, CH=CH_2), 7.58 (m, 3 H, Ph), 7.95 (m, 2 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 4.4 (s, 3 F, CF_3). − $C_{13}H_{14}F_3NO_4S$ (337.3): calcd. C 46.29, H 4.15, N 4.15; found C 46.62, H 4.21, N 4.19.

Methyl 2-(Benzyloxycarbonylamino)-2-(trifluoromethyl)pent-4-enoate (2e): Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.91 (m, 2 H, CH_2), 3.76 (s, 3 H, OMe), 5.02 (s, 2 H, OCH_2), 5.11 (s, 1 H, NH), 5.21 (m, 2 H, CH=CH_2), 5.73 (m, 1 H, CH=CH_2), 7.41 (s, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 4.6 (s, 3 F, CF_3). − $C_{15}H_{16}F_3NO_4$ (331.3): calcd. C 54.38, H 4.83, N 4.23; found C 54.75, H 4.91, N 4.45.

Methyl 2-(*tert*-Butoxycarbonylamino)-2-(chlorodifluoromethyl)pent-4-enoate (2f): Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 9 H, 3 Me), 2.79 (dd, J = 8.1, 15.4 Hz, 1 H, CH_2), 3.39 (m, 1 H, CH_2), 3.82 (s, 3 H, OMe), 5.22 (m, 2 H, CH=CH_2), 5.41 (s, 1 H, NH), 5.63 (m, 1 H, CH=CH_2). − ^{13}C NMR ($CDCl_3$): δ = 23.19, 29.74, 54.01, 69.35 (t, $^2J_{CF}$ = 23.8 Hz), 81.56, 121.51, 123.54 (t, $^1J_{CF}$ = 315.3 Hz), 129.87, 154.41, 166.31. − ^{19}F NMR ($CDCl_3$): δ = 21.6 (d_{AB}, $^2J_{FF}$ = 154.6 Hz, 1 F, CF_2Cl), 23.3 (d_{AB}, $^2J_{FF}$ = 154.6 Hz, 1 F, CF_2Cl). − IR (KCl): $\tilde{\nu}$ = 3400, 1770, 1670, 1500 cm^{-1}. − $C_{12}H_{18}ClF_2NO_4$ (313.7): calcd. C 45.93, H 5.74, N 4.46; found C 45.85, H 5.91, N 4.35.

Methyl 2-(Benzyloxycarbonylamino)-2-(trifluoromethyl)hex-5-enoate (2g): Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.26 (m, 4 H, 2 × CH_2), 3.79 (s, 3 H, OMe), 5.00 (m, 2 H, CH=CH_2), 5.09 (s, 2 H, OCH_2), 5.83 (m, 1 H, CH=CH_2), 7.14 (s, 1 H, NH), 7.37 (s, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 4.4 (s, 3 F, CF_3). − $C_{16}H_{18}F_3NO_4$ (345.3): calcd. C 55.65, H 5.22, N 4.05; found C 55.75, H 4.99, N 4.25.

Methyl 2-(Benzyloxycarbonylamino)-2-(chlorodifluoromethyl)hex-5-enoate (2h): Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.36 (m, 4 H, 2 × CH_2), 3.88 (s, 3 H, OMe), 5.05 (s, 2 H, OCH_2), 5.28 (s, 1 H, NH), 5.21 (m, 2 H, CH=CH_2), 5.85 (m, 1 H, CH=CH_2), 7.47 (s, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 22.5 (d_{AB}, $^2J_{FF}$ = 157.1 Hz, 1 F, CF_2Cl), 23.9 (d_{AB}, $^2J_{FF}$ = 157.1 Hz, 1 F, CF_2Cl). − $C_{16}H_{18}ClF_2NO_4$ (361.8): calcd. C 53.11, H 4.98, N 3.87; found C 53.15, H 5.19, N 3.67.

Methyl 2-(*tert*-Butoxycarbonylamino)-2-(trifluoromethyl)hex-5-enoate (2i): Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 9 H, 3 Me), 2.29 (m, 4 H, 2 × CH_2), 3.81 (s, 3 H, OMe), 5.25 (m, 2 H, CH=CH_2), 5.38 (s, 1 H, NH), 5.80 (m, 1 H, CH=CH_2). − ^{13}C NMR ($CDCl_3$): δ = 27.81, 28.25, 28.40, 53.41, 65.59 (q, $^2J_{CF}$ = 28.1 Hz), 80.43, 116.01, 136.34 (q, $^2J_{CF}$ = 288.3 Hz), 141.01, 153.28, 167.48. − ^{19}F NMR ($CDCl_3$): δ = 3.9 (s, 3 F, CF_3). − IR (KCl): 3410, 1770, 1690, 1640, 1500 cm^{-1}.− $C_{13}H_{20}F_3NO_4$ (311.3): calcd. C 50.16, H 6.43, N 4.50; found C 50.26, H 6.79, N 4.29.

2-(Benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)-1,1,1-trifluoropent-4-ene (6a): Oil. − ^{1}H NMR ($CDCl_3$): δ = 3.04 (m, 2 H, CH_2), 3.78 (d, $^3J_{PH}$ = 14.5 Hz, 6 H, 2 × OMe), 5.08 (s, 2 H, OCH_2), 5.25 (m, 2 H, CH=CH_2), 5.40 (d, $^3J_{PH}$ = 4.0 Hz, 1 H, NH), 5.80 (m, 1 H, CH=CH_2), 7.33 (m, 5 H, Ph)., ^{13}C NMR ($CDCl_3$): δ = 53.81, 56.35, 67.89 (dq, $^2J_{CF}$ = 27.5, 27.7 Hz), 71.63, 120.94, 124.53 (q, $^1J_{CF}$ = 287.8 Hz), 128.10, 128.21, 128.43, 129.31, 135.51, 153.15. − ^{19}F NMR ($CDCl_3$): δ = 7.3 (3 F, CF_3). − ^{31}P NMR ($CDCl_3$): δ = 18.7. − IR (KCl): 3420, 1760, 1505, 1270 cm^{-1}. − $C_{15}H_{19}F_3NO_5P$ (381.3): calcd. C 47.24, H 4.98, N 3.67; found C 47.31, H 5.03, N 3.50.

2-(Benzyloxycarbonylamino)-2-(diethoxyphosphoryl)-1,1,1-trifluoropent-4-ene (6b): Oil. − ^{1}H NMR ($CDCl_3$): δ = 0.93 (m, 6 H, 2 × Me), 2.98 (m, 2 H, CH_2), 3.86−4.05 (m, 4 H, 2 × OCH_2), 5.08 (s, 2 H, OCH_2), 5.10 (m, 2 H, CH=CH_2), 5.65 (d, $^3J_{PH}$ = 4.8 Hz, 1 H, NH), 5.81 (m, 1 H, CH=CH_2), 7.27 (m, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 7.0 (3 F, CF_3). − ^{31}P NMR ($CDCl_3$): δ = 18.3. − $C_{17}H_{23}F_3NO_5P$ (409.3): calcd. C 49.88, H 5.62, N 3.42; found C 49.53, H 5.69, N 3.39.

2-(Benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)-1,1,1-trifluorohex-5-ene (6c): Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.35 [m, 4 H, $(CH_2)_2$], 3.82 and 3.84 (d, $^3J_{PH}$ = 14.0 Hz, 6 H, 2 × OMe), 5.05 (m, 2 H, CH=CH_2), 5.10 (s, 2 H, OCH_2), 5.34 (d, $^3J_{PH}$ = 4.8 Hz, 1 H, NH), 5.78 (m, 1 H, CH=CH_2), 7.32 (m, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 7.4 (3 F, CF_3). − ^{31}P NMR ($CDCl_3$): δ = 20.3. − $C_{16}H_{21}F_3NO_4P$ (379.3): calcd. C 48.61, H 5.32, N 3.54; found C 48.42, H 5.48, N 3.67.

2-(Benzyloxycarbonyl)-2-(diethoxyphosphoryl)-1,1,1-trifluorohex-5-ene (6d): Oil. − ^{1}H NMR ($CDCl_3$): δ = 0.90 (m, 6 H, 2 × Me), 2.40−2.80 [m, 4 H, $(CH_2)_2$], 3.75−4.00 (m, 4 H, 2 × OCH_2), 4.95 (s, 2 H, OCH_2), 5.08 (m, 2 H, CH=CH_2), 5.70 (d, $^3J_{PH}$ = 5.0 Hz, 1 H, NH), 5.80 (m, 1 H, CH=CH_2), 7.15 (m, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 6.8 (3 F, CF_3). − ^{31}P NMR (C_6D_6): δ = 17.4. − $C_{18}H_{25}F_3NO_5P$ (423.4): calcd. C 51.06, H 5.91, N 3.31; found C 50.93, H 5.78, N 3.38.

General Procedure for the Preparation of Dienes 3, 4, and 7: A solution of **2** or **6** (1 mmol) in dry THF (3 mL) was added to a suspension of NaH (2 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred at room temperature for 0.5 h and allyl bromide (2 mmol in

2 mL of DMF) was then added. After stirring for an additional 8 h, the mixture was treated with ice/water (10 g of ice, 10 mL of water) and extracted with ether (2 × 30 mL). The combined organic layers were washed with water (10 mL), then with a saturated solution of $NaHCO_3$ (10 mL), and dried with $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (ethyl acetate/petroleum ether).

Methyl 2-[(Benzenesulfonyl)(prop-2-enyl)amino]-2-(trifluoromethyl)-but-3-enoate (3a): Oil. − ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3 H, OMe), 3.95 (m, 2 H, NCH_2), 4.90 (m, 2 H, CH=CH_2), 5.46 (m, 1 H, CH=CH_2), 5.61 (m, 2 H, CH=CH_2), 5.98 (m, 1 H, CH=CH_2), 7.51 (m, 3 H, Ph), 7.97 (m, 2 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 8.1 (s, 3 F, CF_3). − $C_{15}H_{16}F_3NO_4S$ (363.3): calcd. C 49.58, H 4.41, N 3.85; found C 49.62, H 4.71, N 4.11.

Methyl 2-[(Benzyloxycarbonyl)(prop-2-enyl)amino]-2-(trifluoromethyl)but-3-enoate (3b): Oil. − ^{1}H NMR ($CDCl_3$): δ = 3.87 (s, 3 H, OMe), 3.93 (m, 2 H, NCH_2), 4.94 (m, 2 H, CH=CH_2), 5.02 (s, 2 H, OCH_2), 5.49 (m, 1 H, CH=CH_2), 5.71 (m, 2 H, CH=CH_2), 5.88 (m, 1 H, CH=CH_2), 7.50 (s, 5 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 45.31, 53.21, 67.05, 68.81 (q, $^2J_{CF}$ = 29.1 Hz), 120.01, 121.35, 126.44 (q, $^1J_{CF}$ = 289.5 Hz), 128.11, 128.51, 128.60, 128.03, 129.01, 136.10, 154.18, 165.12. − ^{19}F NMR ($CDCl_3$): δ = 6.4 (s, 3 F, CF_3). − IR (KCl): 1750, 1720, 1510, 1490 cm^{-1}. − $C_{17}H_{18}F_3NO_4$ (357.3): calcd. C 57.14, H 5.04, N 3.92; found C 57.12, H 4.91, N 4.01.

Methyl 2-[(Benzenesulfonyl)(prop-2-enyl)amino]-2-(trifluoromethyl)pent-4-enoate (3c): Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.86 (d, J = 5.7 Hz, 2 H, CH_2), 3.81 (s, 3 H, OMe), 3.99 (m, 2 H, NCH_2), 5.09 (m, 4 H, 2 × CH=CH_2), 5.51 (m, 1 H, CH=CH_2), 5.75 (m, 1 H, CH=CH_2), 7.52 (m, 3 H, Ph), 7.98 (m, 2 H,Ph). − ^{19}F NMR ($CDCl_3$): δ = 6.9 (s, 3 F, CF_3). − $C_{16}H_{18}F_3NO_4S$ (377.4): calcd. C 50.93, H 4.77, N 3.71; found C 50.92, H 4.71, N 3.89.

Methyl 2-[(*tert*-Butoxycarbonyl)(prop-2-enyl)amino]-2-(trifluoromethyl)pent-4-enoate (3d): Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.43 (s, 9 H, 3 Me), 2.66 (m, 2 H, CH_2), 3.85 (s, 3 H, OMe), 3.95 (m, 2 H, NCH_2), 5.11 (m, 4 H, 2 × CH=CH_2), 5.65 (m, 2 H, 2 × CH=CH_2). − ^{19}F NMR ($CDCl_3$): δ = 6.2 (s, 3 F, CF_3). − $C_{15}H_{22}F_3NO_4$ (337.3): calcd. C 53.41, H 6.53, N 4.15; found C 53.52, H 6.70, N 4.19.

Methyl 2-[(Benzyloxycarbonyl)(prop-2-enyl)amino]-2-(trifluoromethyl)hex-5-enoate (3e): Oil. − ^{1}H NMR ([D$_6$]acetone): δ = 2.15 (m, 4 H, 2 × CH_2), 3.69 (s, 3 H, OMe), 4.11 (m, 2 H, NCH_2), 5.12 (s, 2 H, OCH_2), 5.19 (m, 4 H, 2 × CH=CH_2), 5.87 (m, 2 H, CH=CH_2), 7.50 (s, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 5.6 (s, 3 F, CF_3). − $C_{19}H_{22}F_3NO_4$ (385.4): calcd. C 59.22, H 5.71, N 3.64; found C 59.32, H 5.91, N 3.51.

Methyl 2-[(*tert*-Butoxycarbonyl)(prop-2-enyl)amino]-2-(trifluoromethyl)hex-5-enoate (3f): Oil. − ^{1}H NMR ([D$_6$]acetone): δ = 1.40 (s, 9 H, 3 Me), 2.21 (m, 4 H, 2 × CH_2), 3.71 (s, 3 H, OMe), 4.18 (m, 2 H, NCH_2), 5.25 (m, 4 H, 2 × CH=CH_2), 5.97 (m, 2 H, CH=CH_2). − ^{19}F NMR ($CDCl_3$): δ = 6.6 (s, 3 F, CF_3). − $C_{16}H_{22}F_3NO_4$ (349.3): calcd. C 54.70, H 6.84, N 3.99; found C 54.52, H 6.81, N 3.99.

Methyl 2-[(Benzyloxycarbonyl)(prop-2-enyl)amino]-2-(chlorodifluoromethyl)hex-5-enoate (3g): Oil. − ^{1}H NMR ([D$_6$]acetone): δ = 1.98 and 2.25 (m, 4 H, 2 × CH_2), 3.68 (s, 3 H, OMe), 4.17 (m, 2 H, NCH_2), 5.13 (s, 2 H, OCH_2), 5.20 (m, 4 H, 2 × CH=CH_2), 5.84 (m, 2 H, CH=CH_2), 7.38 (s, 5 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 27.15, 28.35, 44.81, 53.81, 64.19, 66.51 (t, $^2J_{CF}$ = 23.1 Hz), 118.91, 121.25, 124.15 (t, $^1J_{CF}$ = 318.8 Hz), 128.19, 128.21, 128.37, 128.59, 128.65, 136.01, 153.63, 167.11. − ^{19}F NMR ($CDCl_3$): δ = 23.1 (d_{AB}, $^2J_{FF}$ = 154.6 Hz, 1 F, CF_2Cl), 24.3 (d_{AB}, $^2J_{FF}$ = 154.6 Hz, 1 F, CF_2Cl). − IR (KCl): ṽ = 1790, 1750, 1510−1500 cm^{-1}. − $C_{19}H_{22}ClF_2NO_4$ (401.8): calcd. C 56.78, H 5.48, N 3.48; found C 56.77, H 5.45, N 3.50.

Methyl 2-[(Benzyloxycarbonyl)(but-3-enyl)amino]-2-(trifluoromethyl)pent-4-enoate (4a): Oil. − ^{1}H NMR ([D$_6$]acetone): δ = 2.15 and 2.41 (m, 2 H, CH_2), 3.48 (m, 2 H, CH_2), 3.72 (s, 3 H, OMe), 4.31 (m, 2 H, NCH_2), 5.15 (m, 4 H, 2 × CH=CH_2), 5.19 (s, 2 H, OCH_2), 5.85 (m, 2 H, CH=CH_2), 7.41 (s, 5 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 35.90, 36.15, 45.81, 54.19, 67.31, 70.15 (q, $^2J_{CF}$ = 28.5 Hz), 115.93, 122.73, 124.51 (q, $^1J_{CF}$ = 286.3 Hz), 128.11, 128.21, 128.56, 129.12, 135.81, 136.15, 158.01, 164.39. − ^{19}F NMR ($CDCl_3$): δ = 2.9 (s, 3 F, CF_3). − IR (KCl): 1785, 1760, 1520, 1500 cm^{-1}. − $C_{19}H_{22}F_3NO_4$ (385.4): calcd. C 59.22, H 5.71, N 3.64; found C 59.29, H 5.86, N 3.62.

Methyl 2-[(Benzyloxycarbonyl)(but-3-enyl)amino]-2-(chlorodifluoromethyl)pent-4-enoate (4b): Oil. − ^{1}H NMR ([D$_6$]acetone): δ = 2.19 and 2.38 (m, 2 H, CH_2), 3.41 (m, 2 H, CH_2), 3.75 (s, 3 H, OMe), 4.29 (m, 2 H, NCH_2), 5.17 (m, 4 H, 2 × CH=CH_2), 5.19 (s, 2 H, OCH_2), 5.89 (m, 2 H, CH=CH_2), 7.48 (s, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 24.8 (d_{AB}, $^2J_{FF}$ = 155.5 Hz, 1 F, CF_2Cl), 25.5 (d_{AB}, $^2J_{FF}$ = 155.5 Hz, 1 F, CF_2Cl). − $C_{19}H_{22}ClF_2NO_4$ (401.8): calcd. C 59.22, H 5.71, N 3.64; found C 59.38, H 5.76, N 3.69.

2-[(Benzyloxycarbonyl)(prop-2-enyl)amino]-2-(dimethoxyphosphoryl)-1,1,1-trifluoropent-4-ene (7a): Oil. − ^{1}H NMR ($CDCl_3$): δ = 3.20 (m, 2 H, CH_2), 3.70−3.90 (m, 6 H, 2 × OMe), 4.21 (m, 2 H, NCH_2), 5.15 (s, 2 H, OCH_2), 5.21 (m, 4 H, 2 × CH=CH_2), 5.72−6.01 (m, 2 H, 2 × CH=CH_2), 7.35 (m, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 7.4 (3 F, CF_3). − ^{31}P NMR ($CDCl_3$): δ = 20.1. − $C_{18}H_{23}F_3NO_5P$ (421.4): calcd. C 51.31, H 5.46, N 3.32; found 51.52, H 5.33, N 3.56.

2-[(Benzyloxycarbonyl)(prop-2-enyl)amino]-2-(diethoxyphosphoryl)-1,1,1-trifluoropent-4-ene (7b): Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.08 and 1.11 (t, $^4J_{PH}$ = 4.1 Hz, 6 H, 2 × Me), 2.99 (m, 2 H, CH_2), 3.95−4.19 (m, 4 H, 2 × OCH_2), 4.23 (m, 2 H, NCH_2), 5.08 (m, 4 H, 2 × CH=CH_2), 5.11 (s, 2 H, OCH_2), 5.87 (m, 2 H, 2 × CH=CH_2), 7.23 (m, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 7.9 (3 F, CF_3). − ^{31}P NMR ($CDCl_3$): δ = 18.7. − $C_{20}H_{27}F_3NO_5P$ (449.4): calcd. C 53.45, H 6.01, N 3.12; found C 53.73, H 5.89, N 3.30.

2-[(Benzyloxycarbonyl)(prop-2-enyl)amino]-2-(dimethoxyphosphoryl)-1,1,1-trifluorohex-5-ene (7c): Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.38−2.78 [m, 4 H, $(CH_2)_2$], 3.41 and 3.62 (d, $^3J_{PH}$ = 14.5 Hz, 6 H, 2 × OMe), 4.22 (m, 2 H, NCH_2), 5.07 (m, 4 H, 2 × CH=CH_2), 5.15 (s, 2 H, OCH_2), 5.89 (m, 2 H, 2 × CH=CH_2), 7.24 (m, 5 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 27.44, 29.03, 44.98, 53.08, 56.13, 66.91 (dq, $^2J_{CF}$ = 26.3, 26.5 Hz), 68.15, 117.34, 121.03, 124.81 (q, $^1J_{CF}$ = 286.1 Hz), 128.01, 128.11, 128.31, 128.65, 128.89, 136.10, 153.12. − ^{19}F NMR ($CDCl_3$): δ = 7.7 (3 F, CF_3). − ^{31}P NMR ($CDCl_3$): δ = 19.7. − IR (KCl): 1740, 1510−1500, 1270−1250 cm^{-1}. − $C_{19}H_{25}F_3NO_5P$ (435.4): calcd. C 52.41, H 5.75, N 3.22; found 52.71, H 5.85, N 3.36.

2-[(Benzyloxycarbonyl)(prop-2-enyl)amino]-2-(diethoxyphosphoryl)-1,1,1-trifluorohex-5-ene (7d): Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.01 and 1.08 (t, $^4J_{PH}$ = 4.0 Hz, 6 H, 2 × Me), 2.40−2.80 (m, 4 H, $(CH_2)_2$], 3.90−4.29 (m, 4 H, 2 × OCH_2), 4.25 (m, 2 H, NCH_2), 4.95 (m, 4 H, 2 × CH=CH_2), 5.05 (s, 2 H, OCH_2), 5.90 (m, 2 H, 2 × CH=CH_2), 7.20 (m, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 7.6 (3 F, CF_3). − ^{31}P NMR ($CDCl_3$): δ = 16.9. − $C_{21}H_{29}F_3NO_5P$

(463.4): calcd. C 54.43, H 6.26, N 3.02; found C 54.51, H 6.19, N 3.21.

General Procedure for the Preparation of Cyclic α-Amino Esters 8−12: A mixture of diene **3** (or **4**, or **7**) (1 mmol) and catalyst (10 mol %) was heated at room temperature in dichloromethane (**8**−**11**) or toluene at 80 °C (**12a**−**d**). The solvent was removed in vacuum and the crude product was purified by flash chromatography (ethyl acetate/petroleum ether).

Methyl 1-Benzenesulfonyl-2-trifluoromethyl-3-pyrroline-2-carboxylate (8a): Oil. − ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3 H, OMe), 4.07 (dm, J = 14.0 Hz, 1 H, NCH_2), 4.62 (d, J = 14.0 Hz, 1 H, NCH_2), 5.63 (m, 1 H, =CH), 6.22 (m, 1 H, =CH), 7.51 (m, 3 H, Ph), 7.85 (m, 2 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 6.2 (s, 3 F, CF_3). − $C_{13}H_{12}F_3NO_4S$ (335.3): calcd. C 46.57, H 3.58, N 4.18; found C 46.55, H 3.76, N 4.19.

1-Benzyloxycarbonyl-2-trifluoromethyl-3-pyrroline-2-carboxylate (8b): Oil. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.61 (s, 3 H, OMe), 4.31 (m, 1 H, NCH_2), 4.52 (m, 1 H, NCH_2), 5.08 (s, 2 H, OCH_2), 5.62 and 5.95 (2 m, 1 H, =CH), 6.22 (m, 1 H, =CH), 7.31 (m, 5 H, Ph). − ^{13}C NMR ([D$_6$]DMSO): δ = 55.41, 63.78, 72.17 (q, $^2J_{CF}$ = 29.3 Hz), 68.75, 127.81 (q, $^1J_{CF}$ = 286.1 Hz), 127.98, 128.08, 128.43, 128. 67, 132.76, 136.42, 155.09, 165.67. − ^{19}F NMR ([D$_6$]DMSO): δ = 5.4 (s, 3 F, CF_3). − IR (KCl): $\tilde{\nu}$ = 1775, 1750, 1565 cm^{-1}. − $C_{15}H_{14}F_3NO_{14}$ (489.3): calcd. C 54.71, H 4.25, N 4.25; found C 54.82, H 3.99, N 4.34.

Methyl 1-Benzenesulfonyl-2-trifluoromethyl-4,5-dehydropiperidine-2-carboxylate (9a): Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.71 (dm, J = 18.0 Hz, 1 H, CH_2), 2.92 (dm, J = 18.0 Hz, 1 H, CH_2), 3.65 (dm, J = 16.0 Hz, 1 H, NCH_2), 3.83 (dm, J = 16.0 Hz, 1 H, NCH_2), 3.88 (s, 3 H, OMe), 5.72 (m, 2 H, CH=CH), 7.51 (m, 3 H, Ph), 7.95 (m, 2 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 6.2 (s, 3 F, CF_3). − $C_{14}H_{14}F_3NO_4S$ (349.3): calcd. C 48.14, H 4.01, N 4.01; found C 48.44, H 4.22, N 4.23.

Methyl 1-*tert*-Butoxycarbonyl-2-trifluoromethyl-4,5-dehydropiperidine-2-carboxylate (9b): Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.52 (s, 9 H, 3 Me), 2.77 (m, 2 H, CH_2), 3.82 (m, 1 H, NCH_2), 3.85 (s, 3 H, OMe), 4.25 (m, 1 H, NCH_2), 5.75−6.00 (br. m, 2 H, CH=CH). − ^{13}C NMR ([D$_6$]DMSO): δ = 22.83, 29.35, 40.09, 53.15, 69.31 (q, $^2J_{CF}$ = 27.8 Hz), 80.93, 125.31 (q, $^1J_{CF}$ = 288.3 Hz), 126.03, 129.87, 154.08, 163.85. − ^{19}F NMR ($CDCl_3$): δ = 5.4 (s, 3 F, CF_3). − IR (KCl): $\tilde{\nu}$ = 1770, 1740, 1560 cm^{-1}. − $C_{13}H_{18}F_3NO_4$ (309.3): calcd. C 50.48, H 5.82, N 4.53; found C 50.49, H 5.62, N 4.75.

Methyl 1-Benzyloxycarbonyl-2-trifluoromethyl-1-azacyclohept-5-ene-2-carboxylate (10a): Oil. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.12 (d, J = 5.8 Hz, 1 H, CH_2), 2.37 (d, J = 7.8 Hz, 1 H, CH_2), 2.59 (m, 1 H, CH_2), 2.71 (m, 1 H, CH_2), 3.61 (br. s, 3 H, OMe), 4.08 (d, J = 6.1 Hz, 1 H, NCH_2), 4.31 (m, 1 H, NCH_2), 5.09 (m, 2 H, OCH_2), 5.61 (m, 1 H, =CH), 5.73 (m, 1 H, =CH), 7.34 (m, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 5.0 (s, 3 F, CF_3). − $C_{17}H_{18}F_3NO_4$ (357.3): calcd. C 57.14, H 5.04, N 3.92; found C 57.21, H 4.92, N 4.00.

Methyl 1-Benzyloxycarbonyl-2-chlorodifluoromethyl-1-azacyclohept-5-ene-2-carboxylate (10b): Oil. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.25 (m, 1 H, CH_2), 2.30 (m, 1 H, CH_2), 2.72 (m, 1 H, CH_2), 2.81 (m, 1 H, CH_2), 3.60 (br. s, 3 H, OMe), 4.31 (m, 2 H, NCH_2), 5.12 (br. s, 2 H, OCH_2), 5.69 (m, 2 H, CH=CH), 7.37 (m, 5 H, Ph). − ^{13}C NMR ([D$_6$]DMSO): δ = 26.19, 31.01, 37.54, 53.18, 65.12, 78.21 (t, $^2J_{CF}$ = 27.2 Hz), 123.25, 127.80, 127.83, 127.93, 128.62, 130.03 (t, $^1J_{CF}$ = 312.5 Hz), 137.81, 154.54, 161.31. − ^{19}F NMR ([D$_6$]DMSO): δ = 25.1 (d_{AB}, $^2J_{FF}$ = 161.9 Hz, 1 F, CF_2Cl), 25.9 (d_{AB}, $^2J_{FF}$ = 161.9 Hz, 1F, CF_2Cl). − IR (KCl): $\tilde{\nu}$ = 1755, 1720, 1550 cm^{-1}. − $C_{17}H_{18}ClF_3NO_4$ (392.8): calcd. C 54.62, H 4.82, N 3.75; found C 54.92, H 4.78, N 3.87.

Methyl 1-Benzyloxycarbonyl-2-trifluoromethyl-1-azacyclohept-4-ene-2-carboxylate (11a): M.p. 144−145 °C. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.14 (m, 1 H, CH_2), 2.95 (m, 1 H, CH_2), 3.31 (m, 1 H, CH_2), 3.76 (s, 3 H, OMe), 4.11 (m, 1 H, CH_2), 4.51 (m, 1 H, NCH_2), 4.93 (m, 1 H, NCH_2), 5.11 (m, 2 H, OCH_2), 5.44 (m, 2 H, CH=CH), 7.40 (m, 5 H, Ph). − ^{13}C NMR ([D$_6$]DMSO): δ = 26.25, 28.56, 41.49, 52.15, 67.91, 68.74 (q, $^2J_{CF}$ = 34.1 Hz), 125.11 (q, $^1J_{CF}$ = 288.1 Hz), 125.30, 127.45, 127.84, 128.21, 130.31, 135.91, 155.00, 165.89. − ^{19}F NMR ($CDCl_3$): δ = 4.6 (s, 3 F, CF_3). − MS: *m*/*z* (%) = 357 [M$^+$], 313, 296, 266, 254, 222, 196, 186, 115, 91 (100), 65, 59, 35. − $C_{17}H_{18}F_3NO_4$ (357.3): calcd. C 57.14, H 5.04, N 3.92; found C 57.32, H 5.12, N 4.08.

Methyl 1-Benzyloxycarbonyl-2-chlorodifluoromethyl-1-azacyclohept-4-ene-2-carboxylate (11b): Oil. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.22 (m, 1 H, CH_2), 2.85 (m, 1 H, CH_2), 3.28 (m, 1 H, CH_2), 3.79 (s, 3 H, OMe), 4.09 (m, 1 H, CH_2), 4.43 (m, 1 H, NCH_2), 4.83 (m, 1 H, NCH_2), 5.09 (m, 2 H, OCH_2), 5.64 (m, 2 H, CH=CH), 7.43 (m, 5 H, Ph). − ^{19}F NMR ([D$_6$]DMSO): δ = 20.8 (d_{AB}, $^2J_{FF}$ = 150.9 Hz, 1 F, CF_2Cl), 22.1 (d_{AB}, $^2J_{FF}$ = 150.9 Hz, 1 F, CF_2Cl). − $C_{17}H_{18}ClF_3NO_4$ (392.8): calcd. C 54.62, H 4.82, N 3.75; found C 54.82, H 4.98, N 4.01.

1-Benzyloxycarbonyl-2-dimethoxyphosphoryl-2-trifluoromethyl-4,5-dehydropiperidine (12a): Oil. − ^{1}H NMR ($CDCl_3$): δ = 3.00−2.65 (m, 2 H, CH_2), 3.78 (d, $^3J_{PH}$ 14.4 Hz, 3 H, OMe), 3.86 (d, ^2J = 17.1 Hz, 1 H, NCH_2), 3.95 (d, $^3J_{PH}$ = 14.4 Hz, 3 H, OMe), 4.26 (d, ^2J = 17.1 Hz, 1 H, NCH_2), 5.23 (s, 2 H, OCH_2), 5.78 (m, 2 H, CH=CH), 7.49 (m, 5 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 29.63, 39.13, 53.81, 56.20, 67.32 (dq, $^2J_{CF}$ = 28.3, 28.5 Hz), 72.02, 126.91, 127.83 (q, $^1J_{CF}$ = 279.1 Hz), 128.19, 128.46, 128.71, 129.95, 134.10, 152.89. − ^{19}F NMR ($CDCl_3$): δ = 6.8 (F, CF_3). − ^{31}P NMR ($CDCl_3$): δ = 20.2. − IR (KCl): $\tilde{\nu}$ = 1750, 1560, 1270, 1250 cm^{-1}. − $C_{16}H_{19}F_3NO_5P$ (393.3): calcd. C 48.83, H 4.83, N 3.56; found C 48.92, H 4.98, N 3.67.

1-Benzyloxycarbonyl-2-diethoxyphosphoryl-2-trifluoromethyl-4,5-dehydropiperidine (12b): Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.30 (m, 6 H, 2 CH_3CH_2), 2.75 (m, 2 H, CH_2), 4.15 (m, 4 H, 2 × OCH_2), 4.25 (m, 2 H, NCH_2), 5.20 (s, 2 H, OCH_2), 5.85 (m, 2 H, CH=CH), 7.38 (m, 5 H, Ph). − ^{19}F NMR ($CDCl_3$): δ = 7.5 (3 F, CF_3). − ^{31}P NMR ($CDCl_3$): δ = 16.0. − $C_{18}H_{23}F_3NO_5P$ (421.4): calcd. C 51.31, H 5.46, N 3.33; found C 51.51, H 5.08, N 3.45.

1-Benzyloxycarbonyl-2-dimethoxyphosphoryl-2-trifluoromethyl-1-azacyclohept-5-ene (12c): Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.90−2.4 [m, 4 H, $(CH_2)_2$], 3.73 (d, $^3J_{PH}$ = 11.4 Hz, 3 H, OMe), 3.89 (br. d, $^3J_{PH}$ = 11.4 Hz, 3 H, OMe), 4.06 (d, ^2J = 17.0 Hz, 1 H, NCH_2), 4.39 (d, ^2J = 17.0 Hz, 1 H, NCH_2), 5.19 (m, 2 H, OCH_2), 5.69 (m, 2 H, CH=CH), 7.34 (m, 5 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 27.08, 29.27, 42.37, 53.09, 55.33, 67.97, 68.21 (dq, $^2J_{CF}$ = 27.6, 27.8 Hz), 125.42, 127.99, 128.17, 128.19 (q, $^1J_{CF}$ = 288.3 Hz), 128.41, 131.58, 136.20, 155.53. − ^{19}F NMR ($CDCl_3$): δ = 6.8 s (3 F, CF_3). − ^{31}P NMR ($CDCl_3$): δ = 16.2. − MS: *m*/*z* (%) = 407 [M$^+$], 296, 272, 254, 225, 162, 109, 91 (100), 65, 35. − $C_{17}H_{21}F_3NO_5P$ (407.3): calcd. C 50.12, H 5.16, N 3.43; found C 50.55, H 5.18, N 3.47.

1-Benzyloxycarbonyl-2-diethoxyphosphoryl-2-trifluoromethyl-1-azacyclohept-5-ene (12d): Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.30 (m, 6 H, 2 CH_3CH_2), 3.05−2.35 (m, 4 H, $(CH_2)_2$], 4.15 (m, 4 H, 2 ×

OCH_2), 4.31 (m, 2 H, NCH_2), 5.21 (m, 2 H, OCH_2), 5.71 (m, 2 H, CH=CH), 7.35 (m, 5 H, Ph). – ^{19}F NMR ($CDCl_3$): δ = 7.3 (3 F, CF_3). – ^{31}P NMR ($CDCl_3$): δ = 16.8 (s). – $C_{19}H_{25}F_3NO_5P$ (435.4): calcd. C 52.41, H 5.74, N 3.22; found C 52.62, H 5.62, N 3.12.

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[1] J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, **1991**.
[2] S. C. Field, *Tetrahedron* **1999**, *55*, 12237.
[3] F. R. Atherton, C. M. Massall, R. W. Lambert, *J. Med. Chem.* **1986**, *29*, 29 and references therein.
[4] [4a] P. Kafavski, B. Lejcazk, *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. – [4b] J. Bird, R. C. De Mello, H. P. Harper, D. J. Hunter, E. M. Karran, F. R. Markwell, A. J. Miles-Williams, S. S. Rahman, R. W. Ward, *J. Med. Chem.* **1994**, *37*, 158.
[5] [5a] A. Giannis, T. Kolter, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244. – [5b] J. Gante, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699.
[6] K. Burger, K. Muetze, W. Hollweck, B. Koksch, *Tetrahedron* **1998**, *54*, 5915.
[7] S. N. Osipov, A. S. Golubev, N. Sewald, T. Michel, A. F. Kolomiets, A. V. Fokin, K. Burger, *J. Org. Chem.* **1996**, *61*, 7521.
[8] R. R. Schrock, *Alkene Metathesis in Organic Synthesis* (Ed.: A. Fürstner), Topics in Organometallic Chemistry, Springer **1998**, vol. 1, p. 1–36.
[9] [9a] B. Mohr, D. M. Lynn, R. H. Grubbs, *Organometallics* **1996**, *15*, 4317. – [9b] P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100.
[10] [10a] S. J. Miller, M. E. Blackwell, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 9606. – [10b] A. Fürstner, *J. Org. Chem.* **1996**, *61*, 3942. – [10c] F. P. J. Rutjes, H. E. Schoemaker, *Tetrahedron Lett.* **1997**, *38*, 677. – [10d] M. A. McKenvey, M. Pitarch, *Chem. Commun.* **1996**, 1689.
[11] S. N. Osipov, C. Bruneau, M. Picquet, A. F. Kolomiets, P. H. Dixneuf, *Chem. Commun.* **1998**, 2053.
[12] S. N. Osipov, O. I. Artyushin, A. F. Kolomiets, C. Bruneau, P. H. Dixneuf, *Synlett* **2000**, 1031.
[13] [13a] S. N. Osipov, N. D. Chkanikov, A. F. Kolomiets, A. V. Fokin, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1986**, 1256. – [13b] N. Sewald, K. Burger, in: *Fluorine-containing Amino Acids: Synthesis and Properties* (Eds.: V. P. Kukhar, V. A. Soloshonok), John Wiley and Sons, Chichester, **1995**, p. 139 and references cited therein.
[14] [14a] D. J. Barlow, J. M. Thornton, *J. Mol. Biol.* **1988**, *201*, 601. – [14b] A. M. P. Koskinen, H. Rapoport, *J. Org. Chem.* **1989**, *54*, 1859. – [14c] H. H. Ibrahim, W. D. Lubell, *J. Org. Chem.* **1993**, *58*, 6438.
[15] [15a] A. Fürstner, M. Picquet, C. Bruneau, P. H. Dixneuf, *Chem. Commun.* **1998**, 1315. – [15b] M. Picquet, D. Touchard, C. Bruneau, P. H. Dixneuf, *New J. Chem.* **1999**, 141. – [15c] A. Fürsner, M. Liebl, C. W. Lehmann, M. Picquet, R. Kunz, C. Bruneau, D. Touchard, P. H. Dixneuf, *Chem. Eur. J.* **2000**, *6*, 1847.
[16] P. R. Hanson, D. Stoianova, *Tetrahedron Lett.* **1998**, *39*, 3939.

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