FLUORINE—CONTAINING AMINO ACIDS SYNTHESIS & PROPERTIES

PT. 2

Fluorine-containing Amino Acids

Synthesis and Properties

Edited by

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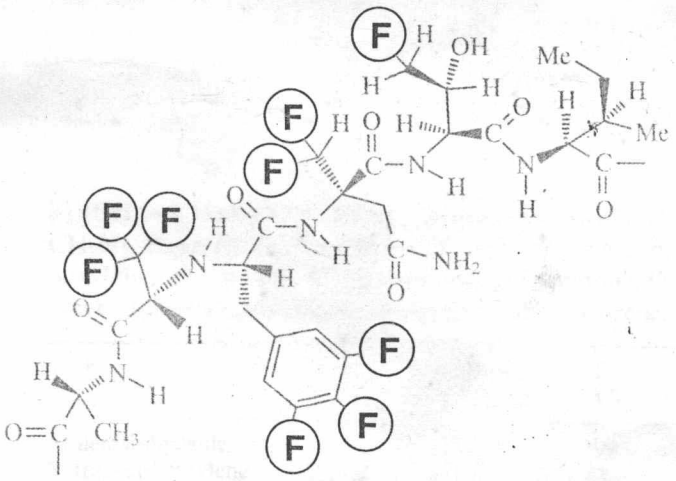

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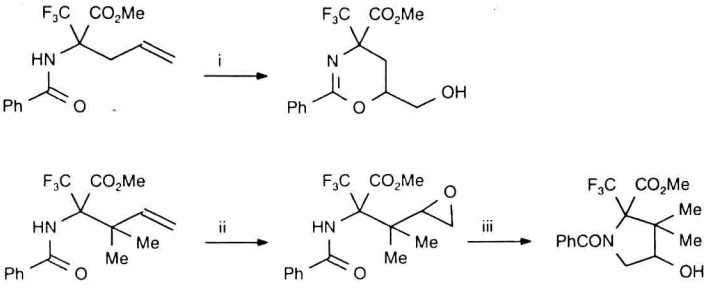
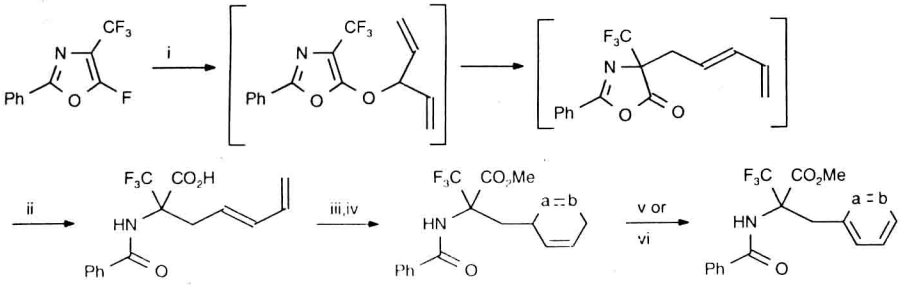


(i) *m*CPBA, $CHCl_3$, 0 °C → r.t. (72%, 50% d.e.); (ii) *m*CPBA, $CHCl_3$, 0 °C → r.t. (61%); (iii) $HClO_4$, H_2O, Et_2O, r.t. (60%)

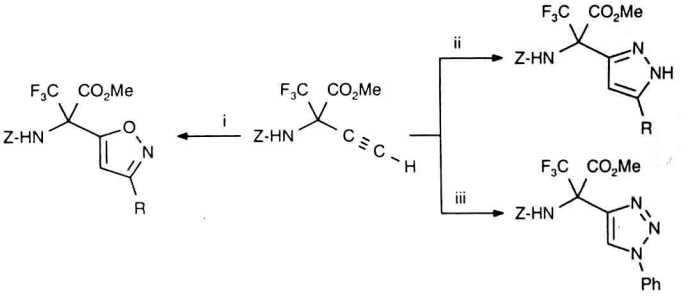
The reaction of 3-hydroxypenta-1,4-dienes with 5-fluoro-4-(trifluoromethyl)oxazoles provides access to 3,3,3-trifluoroalanine derivatives with a diene substructure. *Inter alia*, the large synthetic repertoire of [4 + 2] and [4 + 1] cycloaddition reactions [213] can be applied in order to introduce carbocyclic and heterocyclic ring systems into the side-chain of 2-trifluoromethylamino acids. The alkyne cycloadduct (a ≡ b: dimethylacetylene dicarboxylate) and the naphthoquinone cycloadduct (a = b: naphthoquinone) aromatize on oxidation [181, 182].



(i) $(CH_2{=}CH)_2CHOH$, KOH, dioxane, r.t.; (ii) H_2O, r.t. (89% for i, ii); (iii) CH_2N_2, Et_2O, r.t. (92%); (iv) a = b, see table; or a ≡ b, dimethylacetylene dicarboxylate, toluene, 100 °C; (v) a=b, naphthoquinone, O_2, r.t. (53% for iv, v); (vi) a≡b, dimethylacetylene dicarboxylate, DDQ, benzene, 80 °C (69% for iv, vi)

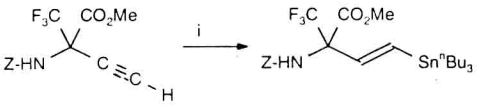
a=b	Solvent	*T* (°C)	Yield (iv) (%)	d.e. (%)	Ref.
Maleic anhydride	toluene	100	56	40	182
Tetracyanoethylene	toluene	r.t.	87	20	182
Azodicarboximide	CH_2Cl_2	r.t.	72	40	182
Diethyl azodicarboxylate	CH_2Cl_2	r.t.	65	50	182
Phthalazine-1,4-dione	CH_2Cl_2	0	65	90	182
Benzo[g]phthalazin-1,4-dione	CH_2Cl_2	0	60	90	182
Nitrosobenzene	CH_2Cl_2	r.t.	60	20	182

α-Trifluoromethylamino acids with a triple bond in the side-chain react with 1,3-dipoles (nitrile oxides, diazoalkanes, phenyl azide) in a regioselective manner to give derivatives of α-trifluoromethylamino acids with heterocyclic side-chains [214].



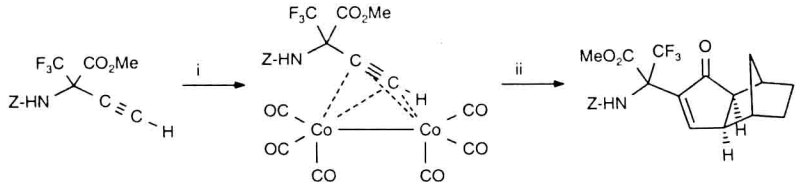
(i) RCX=NOH, NEt_3, Et_2O or $NaHCO_3$, EtOAc (R = Ph, X = Cl, 48%; R = *p*-ClC_6H_4, X = Cl, 39%; R = *p*-FC_6H_4, X = Cl, 56%; R = X = Br, 41%); (ii) $RCHN_2$, (R = H, Et_2O, r.t., 50%; R = CO_2Et, $CHCl_3$, 50 °C, 89%); (iii) PhN_3, THF, cat. DMF, reflux (79%)

Hydrostannation of the alkyne moiety gives (*E*)-vinylstannanes, which undergo palladium-catalyzed cross-coupling with acid chlorides according to the Stille protocol [188, 215]. Iododestannation with I_2 gives (*E*)-vinyl iodides.



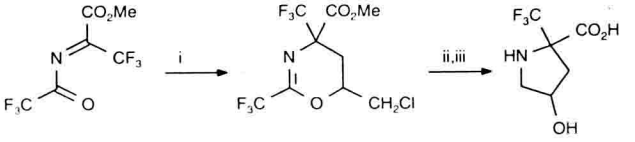
(i) $Bu^n{}_3SnH$, cat. AIBN, benzene, 60 °C (47%)

The alkyne group reacts with dicobalt octacarbonyl to give the stable alkyne–dicobalt complex. Complexes of this type are well known as preparatively valuable building blocks for the regio- and stereoselective synthesis of cyclopentenones. Application of the Pauson–Khand protocol [216] to the cobalt complex of the racemic α-trifluoromethylamino acid gives exclusively a diastereoisomeric mixture of a cyclopentenone-substituted α-trifluoromethylamino acid derivative [188].



(i) $Co_2(CO)_8$, hexanes, r.t.; (ii) norbornene, CO, toluene, 100 °C (54% for i, ii)

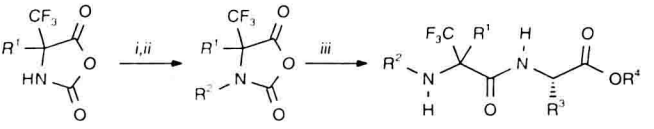
Methyl 6-chloromethyl-5,6-dihydro-2,4-bis(trifluoromethyl)-1,3-oxazin-4-carboxylate, readily obtained via [4 + 2] cycloaddition of allyl chloride to methyl 2-(trifluoroacetylimino)-3,3,3-trifluoropropionate, undergoes ring contraction on methanolysis in the presence of acid. The overall reaction represents an elegant route to α-trifluoromethyl-4-hydroxyproline [217].



(i) $CH_2{=}CHCH_2Cl$, sealed tube, 90 °C; (ii) MeOH, cat. HCl/H_2O, r.t.; (iii) NaOH, H_2O (68% for ii, iii)

N-*Alkylation of α-trifluoromethylamino acids*

A preparatively efficient route to *N*-alkylated α-trifluoromethylamino acids is available via *N*-alkylation of the corresponding *N*-carboxy anhydrides (NCA, Leuchs anhydrides). They are obtained on treatment of a Z-protected α-trifluoromethylamino acid with thionyl chloride and represent *N*-protected, carboxylic group-activated derivatives of α-trifluoromethylamino acids. Deprotonation with sodium hydride and *N*-alkylation with alkyl halides offer a preparatively simple route to *N*-alkyl-α-trifluoromethylamino acids. The carboxylic group can be derivatized subsequently on reaction with nucleophiles [218].



(i) NaH, DMF, r.t.; (ii) R^2I, DMF, r.t.; (iii) H-Xaa-OR^4, r.t.

R^1	R^2	R^3	R^4	Yield (i, ii) (%)	Yield (iii) (%)	Yield (i–iii) (%)	Ref.
Bzl	Me	Me	Bu^t			63	218
Bzl	Me	Bzl	Bu^t	56	71		218
Ph	Me	H	Me			49	218
Ph	Me	Me	Bu^t	42	87		218
Ph	CH_2CO_2Et	H	Bzl	49	77		218
Bu^i	Me	Bzl	Bu^t	47	95		218

4.3.4 PEPTIDE SYNTHESIS WITH α-TRIFLUOROMETHYLAMINO ACIDS

4.3.4.1 Protective group strategy

The first peptides containing α-trifluoromethylamino acids (e.g. with 3,3,3-trifluoroalanine, TFMGly) were described by Weygand *et al.* [90]. α-Trifluoromethylamino acids with orthogonal protective groups (Boc/Z and OMe) are obtained using *N*-(carbamoylimino)-3,3,3-trifluoropropionate as an electrophilic synthon (see Section 4.3.3.4). Alkaline hydrolysis with 1M KOH/methanol (1:1, v/v) gives the free carboxylic acids Boc-TFMXaa-OH or Z-TFMXaa-OH. Hydrogenolytic or acidolytic cleavage of the Z or the Boc group yields H-TFMXaa-OMe. However, the presence of the electron-withdrawing CF_3 substituent in the α-position exerts considerable electronic (pK_a) and steric effects on the reactivity of both the carboxylic and the amino groups. The low basicity of the amino group prevents the formation of dioxopiperazines; esters of α-trifluoromethylamino acids can even be distilled without oligomerization or decomposition [219].

Table 4.1. pK_a values of α-trifluoromethylamino acids compared with the natural amino acids [220]

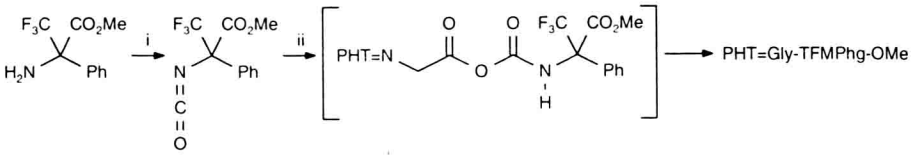
	TFMXaa pK_a (CO_2H)	TFMXaa pK_a (NH_2)	Xaa pK_a (CO_2H)	Xaa pK_a (NH_2)
TFMGly	1.22	5.37	2.35	9.78
TFMAla	1.98	5.91	2.34	9.87
TFMVal	1.90	5.76	2.32	9.62
TFMPhe	1.90	5.25	2.58	9.24
TFMAsp	1.77	6.65	2.09	9.92

4.3.4.2 Amino group activation

Therefore, the activation of the amino group of α-trifluoromethylamino acids is very difficult to achieve. So far, satisfactory results have only been obtained with methyl α-(trifluoromethyl)alaninate (H-TFMAla-OMe, with mixed anhydrides or Fmoc-Yaa-Cl). For the bulkier α-trifluoromethylamino acids, all classical methods fail or result in substantial epimerization of the non-fluorinated amino acid. Peptide bond formation under drastic reaction conditions is useful only with substrates where epimerization is not possible [185].

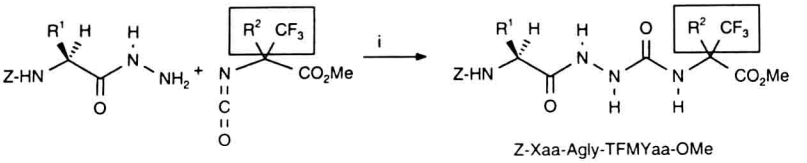
(i) CH_2Cl_2, NEt_3, r.t (49%)

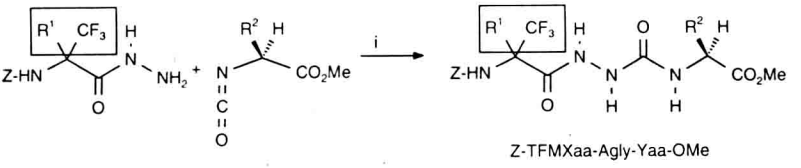
In some cases, dipeptides with *C*-terminal α-trifluoromethylamino acids can be obtained on reaction of PHT=Yaa—OH with isocyanates derived from α-trifluoromethylamino acids [218, 219].



(i) CCl_3OCOCl, dioxane, 70 °C; (ii) PHT=Yaa—OH, toluene, pyridine, reflux (33%)

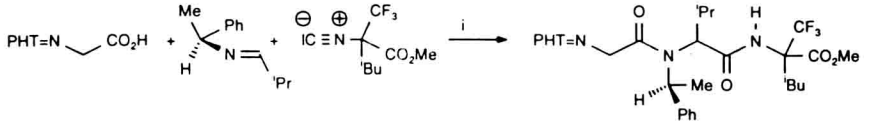
Isocyanates derived from amino acids [219] are valuable components for the synthesis of azapeptides, which are obtained in good yields on reaction of the isocyanate with amino acid hydrazides. Azatripeptides with α-trifluoromethylamino acids in *N*-terminal (H-TFMXaa-Agly-Yaa-OR), *C*-terminal (Z-Xaa-Agly-TFMYaa-OMe) or in both positions (H-TFMXaa-Agly-TFMYaa-OMe) can be synthesized [221].





(i) $CHCl_3$, or Et_2O, 0 °C → r.t.

Similarly, α-trifluoromethylamino acids can subsequently be *N*-formylated and dehydrated to give the corresponding isonitriles [222], which can be used for the synthesis of tripeptides with *C*-terminal α-trifluoromethylamino acids via the Ugi reaction [93].

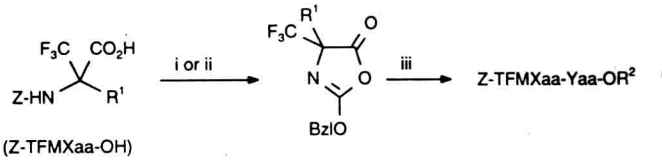


(i) MeOH, r.t.

4.3.4.3 Carboxylic group activation

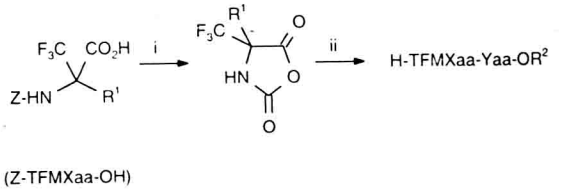
Carboxylic group activation is achieved via the formation of mixed anhydrides with alkyl chloroformates [19] or of Leuchs anhydrides (*N*-carboxy anhydrides, NCA) [223]. The mixed anhydrides formed primarily cyclize

spontaneously to the surprisingly stable oxazolones, which are also formed on treatment of Z-TFMXaa-OH with DCCI, even in the presence of HOBt. Epimerization at the stage of the oxazolone, however, is not a problem with α,α-disubstituted amino acids, as there is no α-proton. Formation of dipeptides Z-TFMXaa-Yaa-OR occurs on ring opening of the oxazolones with amino acid esters H-Yaa-OR [19].



(i) EtO_2CCl, base; CH_2Cl_2, r.t.; (ii) DCCI, HOBt, CH_2Cl_2, r.t.; (iii) H-Yaa-OR^2, CH_2Cl_2, r.t.

The NCA derivatives of α-trifluoromethylamino acids are obtained in very good yields on heating Z-TFMXaa-OH with PCl_5, diphosgene or thionyl chloride [223].



(i) $SOCl_2$, reflux; (ii) H-Yaa-OR^2, CH_2Cl_2, r.t.

The major disadvantage of the NCA method in classical peptide chemistry is the high tendency towards oligomerization, because the amino group of the peptide formed during the reaction can compete with the amino acid ester component. This problem does not arise on ring opening of NCAs derived from α-trifluoromethylamino acids owing to the low pK_a of the newly formed amino function [11].

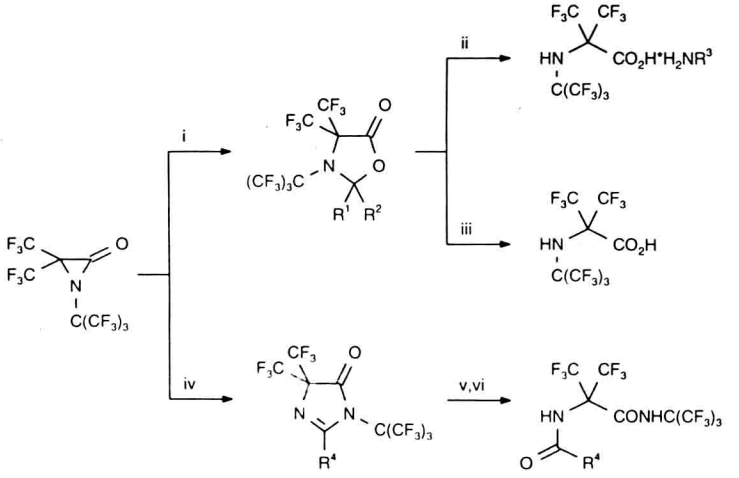
4.3.4.4 Hydrolytic and proteolytic stablility of Z-TFMXaa-OMe - protease-catalyzed peptide synthesis with α-trifluoromethylamino acids

Z-TFMGly-OMe (methyl *N*-benzyloxycarbonyl-3,3,3-trifluoroalaninate) is very unstable at pH > 6. The presence of an α-proton severely destabilizes the CF_3 group and leads to sequential base-catalyzed elimination of hydrogen fluoride. All other α-trifluoromethylamino acids are lacking an α-proton and

are therefore stable towards base. Their rate of alkaline ester hydrolysis (pH 9) is decreased considerably. After 20 min at pH 9, only 4% of Z-TFMPhe-OMe is hydrolyzed to the acid, whereas Z-Phe-OMe is hydrolyzed completely after 5 min under the same conditions. This shows that chemical hydrolysis is slowed by a factor of ca 12 on introduction of a CF_3 group in the α-position. Proteases such as subtilisin, α-chymotrypsin or papain accept α-trifluoromethylamino acids only to a very limited extent. Both the hydrolysis rate and the turnover decrease in the order Z-TFMGly-OMe > Z-TFMAla-OMe > Z-TFMPhe-OMe. The last amino acid is not turned over at all. These data exclude the application of enzyme catalyzed peptide synthesis to α-trifluoromethylamino acids. However, some dipeptide esters with *N*-terminal α-trifluoromethylamino acids are accepted as substrates by proteolytic enzymes. H-TFMPhg-Phe-OMe is converted by α-chymotrypsin or subtilisin within 20 min into the tripeptide H-TFMPhg-Phe-Leu-NH_2 in the presence of H-Leu-NH_2 [19].

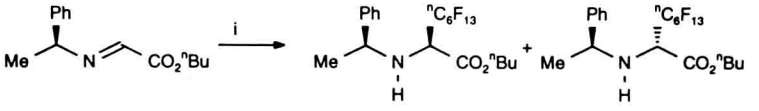
4.3.5 MISCELLANEOUS

Ring expansion of perfluorinated α-lactams with carbonyl compounds or nitriles gives polyfluorinated imidazolinones or imidazolones, respectively. Acid-catalyzed ring opening yields derivatives of 2-amino-3,3,3,3′,3′,3′-hexafluoroisobutyrate [224].



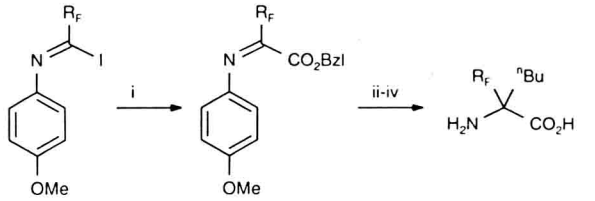
(i) R^1COR^2, 100 °C, sealed tube (R^1 = Ph, R^2 = H, 86%; R^1 = *p*-$MeOC_6H_4$, R^2 = H, 70%; R^1 = Me, R^2 = Me, 63%); (ii) R^3NH_2, 100 °C, sealed tube (R^1 = Ph, R^2 = H, R^3 = Ph, 59%; R^1 = *p*-$MeOC_6H_4$, R^2 = H, R^3 = Ph, 42%); (iii) NaOH, MeOH, 120 °C, sealed tube (53%); (iv) R^4CN, 100 °C, sealed tube (R^4 = Me, 96%; R^4 = Ph, 64%); (v) conc. H_2SO_4, r.t.; (vi) H_2O (R^4 = Me, 55% for v, vi)

A derivative of 2-amino-2*H*-perfluorooctanoic acid is described as a product of the boron trifluoride-catalyzed perfluorohexylation of a glyoxaldimine with perfluorohexyllithium, generated *in situ* from perfluorohexyl iodide and methyllithium/lithium bromide [225].



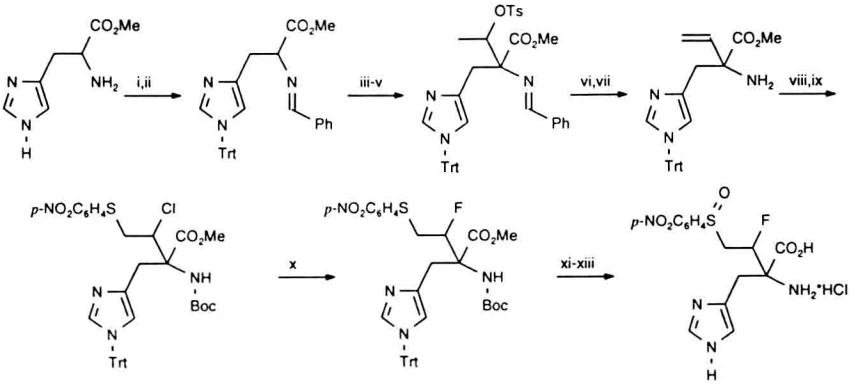
(i) n-$C_6F_{13}I$, BF_3*OEt_2, MeLi, LiBr, Et_2O, −78 °C (53%, 54% d.e.)

Benzyl 2-aryliminoperfluoroalkanoates are formed on palladium-catalyzed carbonylation of *N*-arylperfluoroimidoyl iodides in benzyl alcohol. Subsequent reductive alkylation with organolithium compounds provides a general access to 2-perfluoroalkylamino acids. Deblocking of the amino group is accomplished via ammonium cerium (IV) nitrate oxidation; the carboxylic group can be deprotected hydrogenolytically [119].



(i) $PhCH_2OH$, CO, cat. $Pd_2(dba)_3$*$CHCl_3$, K_2CO_2, toluene, ($R_F = C_2F_5$, 94%, $R_F = C_7F_{15}$, 95%);
(ii) Bu″Li, THF;
(iii) ammonium cerium(IV) nitrate, H_2O, CH_3CN;
(iv) H_2, Pd/C ($R_F = C_2F_5$, 79%; $R_F = C_7F_{15}$, 43% for ii, iii)

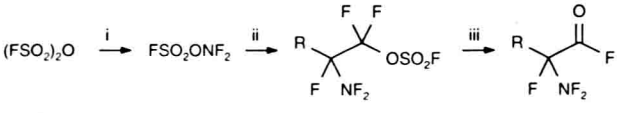
α-Fluoroalkyl derivatives of histidine are obtained via chlorine–fluorine exchange with silver fluoride [226].



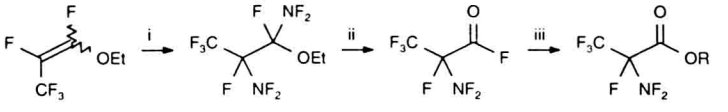
(i) PhCHO; (ii) tritylation; (iii) PhLi; (iv) CH_3CHO; (v) *p*TsCl, base; (vi) DBN; (vii) *p*TsOH, $NaHCO_3$; (viii) $(Boc)_2O$; (ix) *p*-$NO_2C_6H_4SCl$; (x) AgF; (xi) *m*CPBA; (xii) saponification; (xiii) deprotection

4.4 PERFLUORINATED AMINO ACIDS

Perfluoroglycyl fluoride, perfluoroalanyl fluoride, perfluoroaminoisobutyryl fluoride or their derivatives are obtained from terminal perfluoroalkenes [227–230] or bis(trifluoromethyl)ketene [231] with *N*-fluorinated hydrazine or hydroxylamine derivatives.

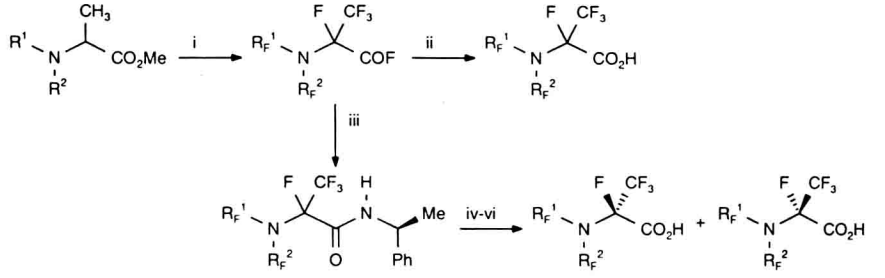


(i) N_2F_2; (ii) $RCF{=}CF_2$ (R = F, CF_3); (iii) KF



(i) N_2F_4 (80%); (ii) SbF_5 (72%); (iii) ROH (100%)

Electrochemical fluorination of *N,N*-disubstituted alanine derivatives affords among other products the corresponding perfluorinated amino acid fluorides [232]. In contrast to the electrofluorination of *N,N*-dimethyl derivatives [233], no cyclized byproducts are observed. Aminolysis of the acid fluorides with (−)-phenylethylamine allows the resolution of the diastereoisomers and optically active perfluoro derivatives of alanine are obtained on cleavage of the amide with sodium hydroxide [234].



(i) electrofluorination; (ii) H_2O; (iii) (−)-PhCH(Me)NH_2, NEt_3, MeCN, r.t.; (iv) chromatographic resolution; (v) H_2SO_4, r.t.; (vi) 6M NaOH, reflux

R_F^1	R_F^2	Yield (i) (%)	Ref.
—$(CF_2)_4$—		20	232
—$(CF_2)_2O(CF_2)_2$—		14	232
—$(CF_2)_5$—		14	232
—$(CF_2)_6$—		21	232
—$(CF_2)_2(NCF_3)(CF_2)_2$—		3	232

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