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Novel strategy for the synthesis of fluorinated β-amino acid derivatives from Δ^2-oxazolines

Santos Fustero,* Esther Salavert, Belén Pina, Carmen Ramírez de Arellano† and Amparo Asensio

Departamento de Química Orgánica, Facultad de Farmacia, Avda. Vicente Andrés Estellés s/n, Universidad de Valencia, 46100 Burjassot, Valencia, Spain

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Abstract—Racemic and chiral non-racemic β-fluoroalkyl-β-amino acid derivatives have been prepared in two steps starting from 2-alkyl-Δ^2-oxazolines and fluorinated imidoyl chlorides. Subsequent chemoselective reduction of the C-masked β-enamino acid derivatives initially formed provided the target β-amino acids. The process takes place with total chemoselectivity, high yields and satisfactory diastereoselectivity.

1. Introduction

1,3-Difunctionalised compounds are of considerable importance, both as synthetic intermediates and as potential therapeutic agents. Among all of them, the β-amino acid unit has been recognised as one of the most attractive, as a consequence that it can be transformed to yield a broad spectrum of functionalities, as well as for their increased use as valuable intermediates in the design and construction of novel biologically and medicinally important molecules.[1] In this sense, β-amino acids have shown unique pharmacological properties both as component of natural occurring compounds and in free form.[2] The former is exemplified by the well-known antitumor agent Taxol®, which contains an α-hydroxy β-amino acid side chain.[3] The latter can be exemplified by the antifungal *cis*-pentacine, isolated from bacteria *Streptomices setonii*.[4] β-Amino acids can also form β-peptides, a new class of promising compounds that are able to mimic natural α-peptides showing stronger stability against enzymatic hydrolysis.[5]

Because of their importance considerable research efforts have been devoted in the last two decades, particularly, in the preparation of enantiopure β-amino acids by using different synthetic strategies, such as the chiral pool approach, enzymatic resolutions, diastereoselective reactions with chiral auxiliaries, and catalytic asymmetric synthesis.[1]

Another area of expansion in recent years has to do with recognition of the utility of fluorine-containing molecules, which derives from an awareness of their unique biomedical properties.[6] For this reason, the development of new practical synthetic methods for the preparation of fluorinated chiral synthons and the upgrade of the existing ones are receiving a considerable deal of attention. In particular, fluorinated amino acids and amino alcohols not only exhibit a variety of biological properties, but also are useful and versatile synthetic intermediates in organic synthesis.[7,8]

Despite the above-mentioned general biomedicinal benefits of hydrogen replacement by fluorine, not much is known about the chemistry and biological activity of fluorine containing β-amino acids, very likely due to the lack of methods for their preparation. In fact, there are a limited number of versatile synthetic routes covering the synthesis of fluorinated β-amino acids mostly as racemates.

In general, two main strategies have been used for the synthesis of these derivatives, namely, direct fluorination and the building block approach. One example in the former area was found in 1994 when Davis described the preparation of α-fluoro analogs of the C-13 side chain of taxol®. They were synthesised with poor stereocontrol either by asymmetric electrophilic fluorination of non-fluorinated α-amino esters or, alternatively, by Mannich-type reaction of α-fluoro-enolates with chiral sulfinimines.[9]

Regarding the building block approach, several recent strategies have been developed for the preparation of β-fluoroalkyl-β-amino acids. They include the following reports: (i) Bégué prepared racemic and chiral non-racemic *syn*-(3-fluoroalkyl)isoserinates in good yield but poor diastereoselectivity from (fluoroalkyl)imines via ketene–imine [2+2] cycloaddition.[10] (ii) Uneyama developed a different protocol for synthesising racemic *anti*-(3-fluoroalkyl)isoserinates, involving the diastereoselective reduction

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* Corresponding author. Tel.: +34-96-3864279; fax: +34-96-3864939; e-mail: santos.fustero@uv.es

† Corresponding author regarding X-ray diffraction studies.

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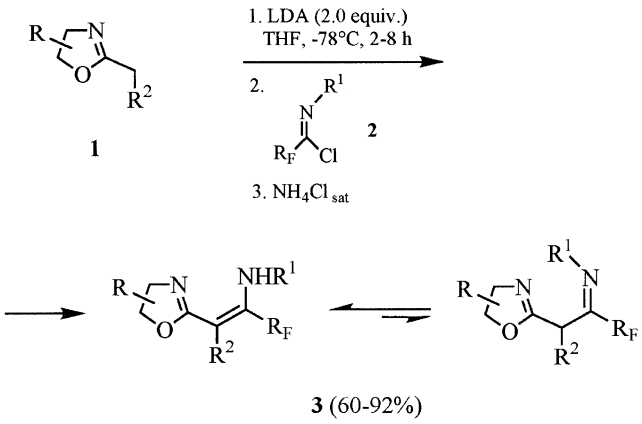


Scheme 1.

of α-hydroxy-β-imino esters, obtained via intramolecular rearrangement of imino ethers.[11] (iii) Previously, Kitazume had described in 1993 the first synthesis of racemic β-(difluoromethyl)-β-amino acid derivatives from difluoroacetaldimine and enol silyl ethers.[12] (iv) Another important route to β-amino acids consists of the asymmetric Michael addition of ammonia or amines to α,β-unsaturated esters. However, only a limited number of α- and β-(trifluoromethyl)-β-alanines have been obtained using this strategy.[13] In this context, Zanda et al. have applied very recently this methodology to the synthesis, both in solution and solid-phase, of novel enantiomerically pure, partially-modified retro and retro-inverso Ψ[NHCH(CF_3)]-peptides.[14] (v) Soloshonok developed a conceptually different methodology for the synthesis of non-racemic β-fluoroalkyl-β-amino acids.[15] The procedure is based on the stereoselective biomimetic transamination of β-fluoroalkyl-β-keto esters and it implies a base-catalysed [1,3]-proton shift reaction followed by hydrolysis and biocatalytic resolution by penicillin acylase. Alternative procedures using chiral bases[15c] and chiral amines[15d] have been also reported.

Finally, an attractive approach to enantiopure β-amino acids involves the chemo- and stereoselective reduction of chiral non-racemic enamines. However, although enamines are well-known intermediates in synthetic organic chemistry, to the best of our knowledge, no examples have been described regarding the preparation of enantiopure fluorinated β-amino acids by using this strategy.[‡] In fact, only three examples related to their synthesis in racemic form have appeared in the literature. In 1995, Shen reported the first two examples of racemic β-fluoroalkyl-β-amino acids obtained by catalytic hydrogenation with Pd/C of *N*-benzyl β-enamino esters.[16] Another method for the preparation of these derivatives is the aforementioned reduction of α-hydroxy-β-imino esters.[11] In this context, we devised very recently an efficient two-step approach for the diastereoselective synthesis of racemic *syn*-α-methyl-β-fluoroalkyl-β-amino esters. The reaction is highly diastereoselective and the approach is based on the chemical reduction of β-fluoroalkyl-β-enamino esters, previously obtained from imidoyl halides and ester enolates.[17]

‡ Although conceptually, the biomimetic transamination is considered to be a reducing agent-free reductive amination, we have not included it in this section.

As a part of our program to study the synthesis and reactivity of fluorinated and non-fluorinated 1,3-difunctionalised derivatives,[18] we have undertaken the development of new and more effective strategies for the preparation of enantiopure fluorinated β-amino acid derivatives. Our synthetic efforts have focused on the carboxylic acid moiety as the site for introducing functionalities that both block this reactive position and can simultaneously act as a chiral auxiliary. Heterocyclic systems such as Δ^2-oxazolines, which have often shown their utility in asymmetric synthesis, fulfil both these requirements.[19]

Our group has previously reported a simple entry to racemic non-fluorinated β-amino acids starting from 2-alkyl-Δ^2-oxazolines.[20] The process, however, appears to be restricted to aromatic systems and in the case of chiral non-racemic derivatives, we observed, in general, poor stereocontrol. Our present goal is to generalise the process to other systems, in particular, to fluorine derivatives. We thus now present an efficient two-step method for the preparation of enantiopure fluorinated β-amino acid derivatives by reduction of masked β-enamino acids **4**, which have been derived from 2-alkyl-Δ^2-oxazolines **1** and imidoyl halides **2**.

2. Results and discussion

Our strategy is based on the reaction of α-metalated 2-alkyl-Δ^2-oxazolines with acylimidoyl species to furnish initially masked β-enamino acid derivatives **3**. Thus, the treatment of 2-methyl (or 2-ethyl)-Δ^2-oxazolines **1** (1.0 equiv.) with 2.0 equiv. of lithium diisopropylamide (LDA) followed by fluorinated imidoyl chlorides **2**[21] (1.1 equiv.) led cleanly to the corresponding C-oxazoline protected β-enamino acids **3**, in overall yield of 69–92%. In general, compounds **3** were isolated as a mixture of imino–enamino tautomers[22] (Scheme 1). Table 1 summarises the obtained results.

In a second step, compounds **3** were reduced to the corresponding protected fluorinated β-amino acid derivatives **4**. The study carried out included, first the search of convenient reducing conditions to produce a chemo- and diastereoselective process and second the effect of the chiral auxiliaries (oxazoline protecting-group and nitrogen substituent) in the diastereoselectivity of the reaction. In one hand, the choice of the reducing agent was crucial because

Table 1. Fluorinated C-oxazoline protected β-enamino acids **3** obtained from 2-alkyl-2-oxazolines **1** and imidoyl chlorides **2**

Entry	1	2		3	Yield (%)[a]	Imino:enamino ratio[b]
		R_F	R^1			
1	**1a**	CF_3	*p*-$MeOC_6H_4$	**3ac**	87	0:100
2	**1a**	CF_2Cl	*p*-$MeOC_6H_4$	**3b**	66	0:100
3	**1a**	CF_3	*c*-C_6H_{11}	**3c**	80	0:100
4	**1a**	CF_2Cl	(*S*)-$C_6H_5(Me)CH$	**3d**	65	0:100
5	**1b**	CF_3	*p*-$MeOC_6H_4$	**3e**[c]	80	0:100
6	**1b**	CF_2CF_3	*p*-$MeOC_6H_4$	**3f**	83	33:66
7	**1c**	CF_2CF_3	*p*-$MeOC_6H_4$	**3g**	70	92:8
8	**1d**	CF_3	*p*-$MeOC_6H_4$	(−)-**3h**	72	0:100
9	**1d**	CF_2Cl	*p*-$MeOC_6H_4$	(−)-**3i**	75	10:90
10	**1e**	CF_3	*p*-$MeOC_6H_4$	(+)-**3j**	92	0:100
11	**1f**	CF_3	*p*-$MeOC_6H_4$	(+)-**3k**	82	25:75
12	**1g**	CF_3	*p*-$MeOC_6H_4$	(−)-**3l**	90	0:100
13	**1g**	CF_2Cl	*p*-$MeOC_6H_4$	(−)-**3m**	70	9:91
14	**1h**	CF_3	*p*-$MeOC_6H_4$	(+)-**3n**	60	0:100

[a] Isolated yield.
[b] Tautomeric ratio estimated by ^1H and/or ^{19}F NMR on the crude reaction mixture.
[c] Lit. Ref. 22a.

our previous results had shown that, with some exception, only dissolving metals were effective with this class of derivatives.[20] Unfortunately, the use of the system Na/*i*-PrOH as reducing agent with compounds **3** afforded a complex reaction mixture instead of the target β-amino acids **4**. On the other hand, to study the diastereoselectivity of the process we focused our attention in the effect of the oxazoline-protecting group as chiral auxiliary; therefore, a series of 2-alkyl-Δ^2-oxazolines **1d**–**h** (Fig. 1) were chosen.[23]

Closely related reductions of fluorinated β-enamino esters had shown that the use of catalytic hydrogenation[16] and borohydride reagents[17] were particularly efficient. Therefore, in a first attempt, we tested the catalytic hydrogenation of achiral derivatives **3** (entries 1–3, 5–7, Table 2). In all these instances the reactions were performed with palladium on carbon (5% Pd) using methanol as solvent and at room temperature for several hours (Method A, Table 2). The process worked well in most of cases regardless of the nature of the substituents in **3** and with total chemoselectivity, furnishing compounds **4** in good yields (Scheme 2 and Table 2).

When two diastereomers were possible as a result of reduction (R^2=Me, entry 7, Table 2) the chemoselective hydrogenation of the enamino moiety using the above-mentioned conditions provided an almost equimolecular and separable mixture of racemic *syn*/*anti* diastereomers in 60% yield. In an attempt to improve the diastereoselectivity, we used the system $ZnI_2/NaBH_4$ in CH_2Cl_2 as solvent (Method B, Table 2), which had been successfully employed in the synthesis of *syn*-α-methyl-β-fluoroalkyl-β-amino esters.[17] After 24 h at room temperature and subsequent work-up, compound **4g** was isolated in good yield. Indeed, the diastereoselectivity was dramatically increased (de 94%) providing the *syn* diastereomer as the major product (Scheme 3).

We next investigated the influence on the diastereoselectivity by employing chiral non-racemic adducts **3**, which locate the chirality either at the nitrogen atom substituent or at the oxazoline portion.

In the first case, compound **3d** [R^1=(*S*)-$C_6H_5(Me)CH$, entry 4, Table 1] was chosen as a simple model. The best reduction conditions found (Method B) were used for this purpose. Thus, compound **4d** (entry 4, Table 2) was obtained in moderate yield, albeit as a 56:44 non-separable mixture of diastereomers (Scheme 3).

This disappointing result turned us to focus on the second approach. Therefore, a number of chiral non-racemic oxazoline derivatives **3h**–**n** (Scheme 2 and Fig. 1) were subjected

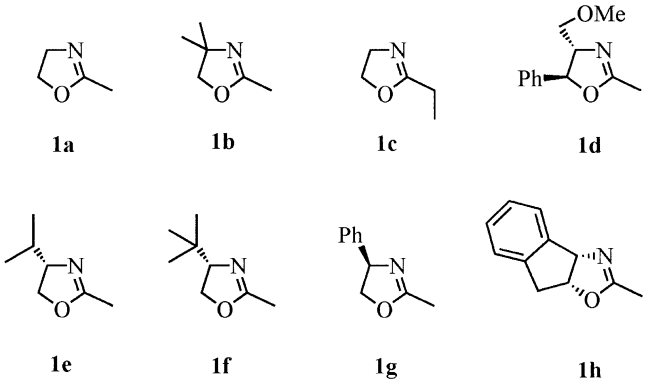
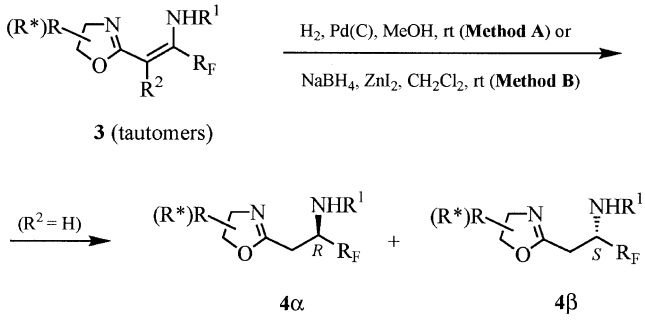


Figure 1.

Table 2. Fluorinated C-oxazoline protected β-amino acid derivatives **4**

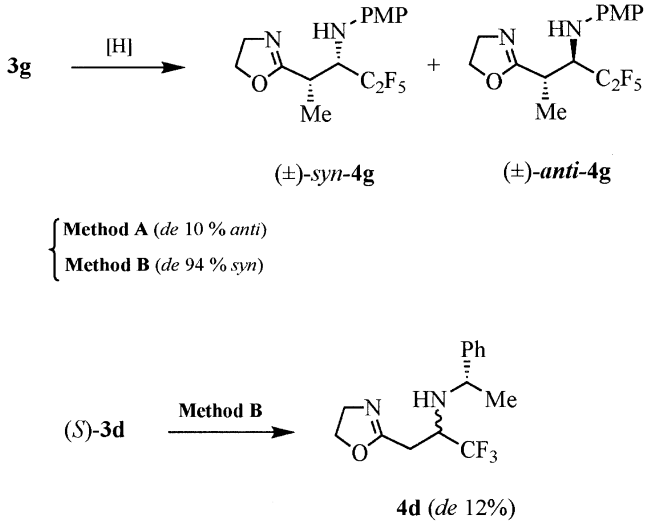
Entry	1	R_F	R^1	4	Yield (%)[a]	Method[b]	Diastereomeric ratio[c]
1	**1a**	CF_3	*p*-$MeOC_6H_4$	**4a**	(72)	**A**	–
2	**1a**	CF_2Cl	*p*-$MeOC_6H_4$	**4b**	(88)90	A,B	–
3	**1a**	CF_3	*c*-C_6H_{11}	**4c**	(85)	A	–
4	**1a**	CF_2Cl	(*S*)-C_6H_5(Me)CH	**4d**	60	B	56:44[d]
5	**1b**	CF_3	*p*-$MeOC_6H_4$	**4e**	(86)	A	–
6	**1b**	CF_2CF_3	*p*-$MeOC_6H_4$	**4f**	(60) 60	A,B	–
7	**1c**	CF_2CF_3	*p*-$MeOC_6H_4$	**4g**	(60) 80	A,B	(45:55) 97:3[e]
8	**1d**	CF_3	*p*-$MeOC_6H_4$	**4h**	(30) 90	A,B	(47:53) 80:20[f]
9	**1d**	CF_2Cl	*p*-$MeOC_6H_4$	**4i**	70	B	78:22[f]
10	**1e**	CF_3	*p*-$MeOC_6H_4$	**4j**	75	B	65:35[f]
11	**1f**	CF_3	*p*-$MeOC_6H_4$	**4k**	65	B	55:45[f]
12	**1g**	CF_3	*p*-$MeOC_6H_4$	**4l**	(20) 80	B	(45:55) 80:20[f]
13	**1g**	CF_2Cl	*p*-$MeOC_6H_4$	**4m**	90	B	70:30[f]
14	**1h**	CF_3	*p*-$MeOC_6H_4$	**4n**	60	B	60:40[f]

[a] Yields of the crude product (not optimised). In parentheses yields corresponding to Method A.
[b] Method A: H_2, Pd(C) 5%, MeOH, rt. Method B: ZnI_2 (3.0 equiv), $NaBH_4$, CH_2Cl_2, rt.
[c] Determined from crude mixture (^{1}H- and ^{19}F NMR).
[d] Diastereomeric ratio for adducts bearing the chirality in the nitrogen atom (see, Scheme 3).
[e] *Syn*/*anti* diastereomeric ratio for (±)-**4g** (Method B) (Scheme 3). In parentheses Method A.
[f] **4**α:**4**β Diastereomeric ratio.



Scheme 2.

to reduction conditions Method B. After work-up, good yields and moderate to good stereocontrol (up to 4:1) were attained only in the case of oxazolines derived of (1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-1-propanol **1d** (entries 8 and 9, Table 2) and (*R*)-2-amino-3-phenyl-1-propanol **1g** (entries 12 and 13, Table 2). For comparison, catalytic hydrogenation of compounds (−)-**3h** and (−)-**3l** was also tested; however, this method provided lower yields of adducts **4h** (30%) and **4l** (20%). In addition, the compounds were obtained with no significant asymmetric



Scheme 3.

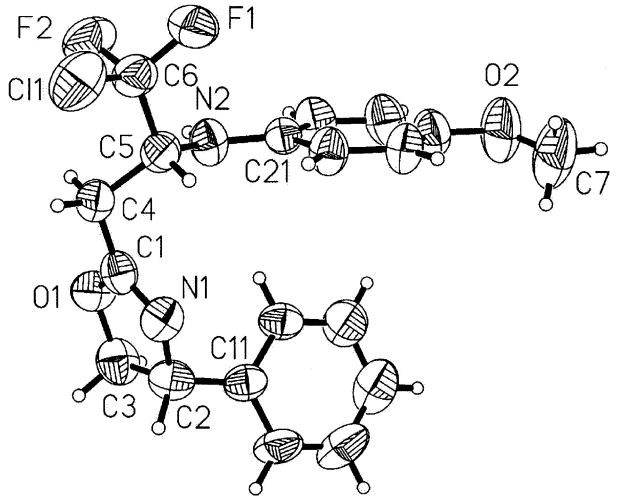


Figure 2. Thermal ellipsoid plot (50% probability level) of **4m**α.

induction as an almost equimolecular mixture of α and β diastereomers.

Surprisingly, when (*S*)-4-isopropyl-2-methyl-Δ^2-oxazoline **1e**, (*S*)-4-*tert*-butyl-2-methyl-Δ^2-oxazoline **1f**, and (1*S*,2*R*)-1-amino-2-indanol derived 2-methyl-Δ^2-oxazoline **1h** (entries 10, 11 and 14 respectively, Table 2 and Fig. 1) were used as chiral substrates, poor asymmetric induction (de 10–30%), lower yields and a non-separable mixture of **4**α and **4**β diastereomers were observed (Scheme 2 and Table 2).

Isomers **4l**α, **4l**β, **4h**α and **4m**α (Table 2) were isolated in the pure form by flash chromatography and purified by crystallisation from hexane or mixtures of hexane/ethanol (see, Section 3). Their structures were ascertained by NMR (^{1}H-, ^{19}F- and ^{13}C) spectroscopy, analyses and/or HRMS. For instance, the ^{1}H NMR spectrum for compound **4l**α displays characteristic signals at δ 2.64 (dd, J=9.6, 14.8 Hz, 1H), 2.83 (dd, J=4.1, 14.8 Hz, 1H) and 4.26 (m, 1H), which correspond to the ABX system of the C*H*$_2$C*H*NH grouping. In the ^{19}F NMR spectrum, the signal of the C*F*$_3$ group appear as a doublet at δ −76.63 (d, J=6.4 Hz, 3F). Further analysis of this product by ^{13}C NMR was in complete agreement with the assigned structure. The most characteristic feature was a quartet centred at δ 55.5 (q, $^2J_{CF}$=30.9 Hz), which corresponds to the *C*HNH carbon atom.

In order to determine the relative configuration of the newly created stereogenic centre at C-2 of the side chain [C(5) in Fig. 2], we carried out an X-ray diffraction analysis with a suitable crystal of the major diastereomer of **4m**.[§] A view of the solid-state structure for **4m**α is depicted in Fig. 2, which shows that the absolute configuration of the new stereogenic centre in **4m**α is *R*, that is, (2′*R*,4*R*)-**4m**.

In the crystal the molecule adopts a U shape with both aromatic rings making a 69.5° dihedral angle. For the C(4)–C(5) bond (Fig. 2), the oxazoline group presents a *gauche* and an *anti* conformation with respect to the *p*-methoxy-phenylamino and the CF_2Cl groups, respectively. The oxazoline ring is planar (mean deviation 0.039 Å) and nearly perpendicular to both *p*-anisyl and phenyl rings (78.2 and 100.3° dihedral angles, respectively). In the crystal, the amino group is hydrogen bonded to the oxazoline nitrogen atom of a different molecule [N(2)–H(2)···N(1)# (#: $x+1$, y, z), N(2)···N(1)# 3.187(7) Å, H(2)···N(1)# 2.33(2) Å, N(2)–H(2)···N(1)# 176(5)°]. The N–H···N intermolecular hydrogen bond forms infinite linear chains (Fig. 3).

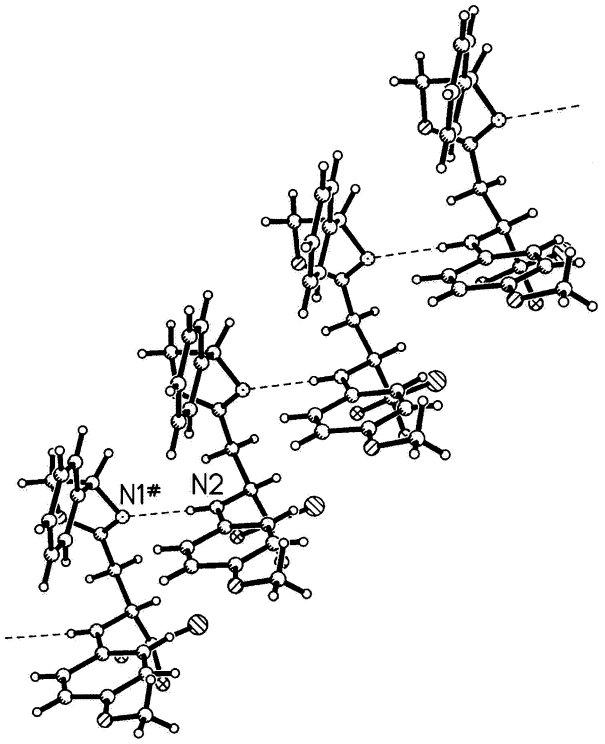


Figure 3. Infinite linear chains of **4m**α formed through N(2)–H(2)···N(1)# (#: $x+1$, y, z) hydrogen bonds.

The stereochemical outcome of the reduction of adducts **3** might be rationalised using a cyclic model as indicated in Fig. 4. It is supposed that ZnI_2 coordinates with both nitrogen atoms in a six-membered metal chelate, much the way the related fluorinated β-imino esters do.[17] The stereodirecting effect of the chiral center at C-4 in the oxazoline ring plays a significant role in the final stereochemical outcome. The hydride preferentially attacks the imino group from the opposite side (*Si* face for **4m**α) of the chiral C-4 substituent. Thus, complexation of adducts **3** by ZnI_2 proved to be useful in 1,5-asymmetric induction, as shown in Fig. 4 and Table 2.

In a last step, enantiopure adducts **4** can be easily transformed into the corresponding N-protected β-amino esters. Thus, the hydrolysis with HCl 1N and subsequent esterification of compound (2′*R*,4*R*)-**4l** gave N-*p*-methoxyphenyl protected methyl and isopropyl β-amino esters (*R*)-**5** with overall yields of 65 and 60%, respectively (Scheme 4).[‖]

[§] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

[‖] Further conversion of **5** into N-unprotected β-amino esters could be carried out by standard procedures. See, for example, Ref. 17.

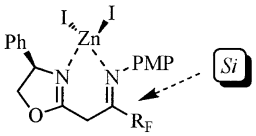


Figure 4.

In an analogous fashion, acid hydrolysis of (2′*R*,4*R*)-**4l**, followed by reduction using $LiAlH_4$ in THF, at room temperature provided the fluorinated γ-amino alcohol derivative (*R*)-**6**, in 70% yield (Scheme 4).

In summary, chiral non-racemic Δ^2-oxazolines have been used as an effective protecting and chiral auxiliary group for the chemo and diastereoselective reduction of β-fluoroalkyl-β-enamino acid derivatives. The approach described herein, which makes use of borohydride reagents, offers a straightforward synthetic pathway to enantiopure β-fluoroalkyl-β-amino acids in good to excellent yield and moderate diastereoselectivity. Alternative procedures for the diastereo- and enantioselective synthesis of these derivatives are in progress and will be reported elsewhere.

3. Experimental

3.1. General

THF was distilled under argon from sodium/benzophenone ketyl as the drying agent. Diisopropylamine, used to generate LDA, was refluxed over KOH_s, distilled, and stored under argon in the presence of 4 Å molecular sieves at 4°C. Solvents used in extractions, recrystallisations, and chromatographic columns were distilled prior to use. All other reagents were commercially available and were used as received. Compounds were visualised on analytical thin layer chromatograms (TLC) by UV light (254 nm). Silica gel (60 Å) for flash chromatography was used for purifying the products.

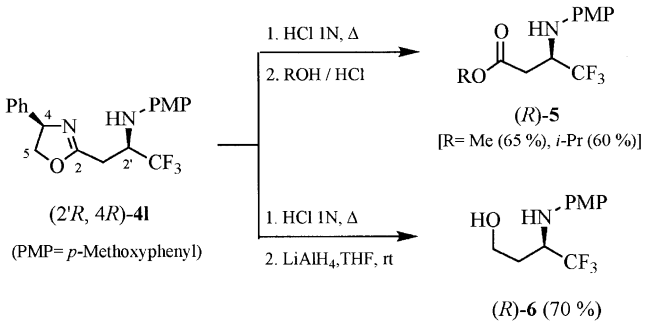
All reactions were conducted under dry nitrogen and the glassware used was oven dried (120°C), evacuated, and purged with argon. Temperatures are reported as bath temperatures. Melting points are reported uncorrected and were measured on a Cambridge Instruments apparatus using open capillary tubes. Nuclear magnetic resonance spectra for ^{1}H-, ^{13}C- and ^{19}F were determined on a Bruker AC-250, 300 and 400 MHz spectrometer, in $CDCl_3$, using tetramethylsilane as an internal standard. Chemical shift values and coupling constants, *J*, are reported in δ ppm and in Hz, respectively. Carbon multiplicities were established by DEPT. High-resolution mass spectral data (HRMS), were obtained at 70 eV by electron impact. Compounds **3a** and **3e** have been previously described.[22a]

3.2. General procedure for the synthesis of *N*-substituted β-enamino-Δ^2-oxazolines 3

To a stirred solution of diisopropylamine (2.6 mL, 20 mmol) in THF (15 mL) at 0°C was added butyllithium (2.5 M in hexane, 8.0 mL, 20 mmol). After stirring for 15 min, the solution was cooled to −78°C and 2-alkyl-Δ^2-oxazoline **1** (10 mmol) in THF (15 mL) was added. The reaction mixture was stirred for 2 h; then, a solution of the desired imidoyl chloride **2** (11 mmol) in THF (15 mL) was slowly added. When TLC analysis showed the disappearance of the starting material, the reaction was quenched by addition of saturated ammonium chloride solution (30 mL). The aqueous layer was extracted with methylene chloride (2×25 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After filtration, the solvents were removed under reduced pressure to furnish the crude product **3**. Purification was carried out as indicated in each case.

3.2.1. (*Z*)-1-Chloro(difluoro)methyl-2-(4,5-dihydro-1,3-oxazol-2-yl)-1-ethenyl(4-methoxyphenyl)amine (3b). White solid, purified by recrystallisation [*n*-hexane–EtOH (10:1)]; mp 85–86°C; ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 10.21 (bs, 1H), 7.15 (d, 2H, *J*=8.7 Hz), 6.83 (d, 2H, *J*=8.7 Hz), 5.29 (s, 1H), 4.25 (t, 2H, *J*=9.0 Hz), 4.00 (t, 2H, *J*=9.0 Hz), 3.75 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −50.92 (s, 2F); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5 (s), 158.0 (s), 157.9 (t, $^2J_{CF}$=25.2 Hz), 131.6 (s), 128.9 (d), 122.1 (t, $^1J_{CF}$=250.8 Hz), 113.6 (d), 83.4 (d), 66.0 (t), 55.3 (q), 54.2 (t); HRMS (EI): Calcd for $C_{13}H_{13}F_2ClN_2O_2$ 302.0633, found 302.0636. Anal. Calcd for $C_{13}H_{13}F_2ClN_2O_2$: C, 51.58; H, 4.33; N, 9.25; found C, 51.25; H, 4.44; N, 9.14.

3.2.2. Cyclohexyl[(*Z*)-2-(4,5-dihydro-1,3-oxazol-2-yl)-1-trifluoromethyl-1-ethenyl]amine (3c). Orange oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (8:1)]; ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 8.61 (d, 1H, *J*=8.52 Hz), 4.93 (s, 1H), 4.07 (t, 2H, *J*=9.1 Hz), 3.86 (t, 2H, *J*=9.1 Hz), 3.29 (m, 1H), 1.06–1.84 (m, 10H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.46 (s, 3F); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.1 (s), 153.4 (q,



Scheme 4.

$^{2}J_{CF}$=30.5 Hz), 120.9 (q, $^{1}J_{CF}$=274.4 Hz), 80.7 (d), 65.6 (t), 54.2 (t), 52.9 (d), 34.8 (t), 25.3 (t), 24.6 (t); HRMS (EI): Calcd for $C_{12}H_{17}F_3N_2O$ 262.1292, found 262.1298.

3.2.3. (*Z*)-[1-(Chloro(difluoro)methyl)-2-(4,5-dihydro-1,3-oxazol-2-yl)-1-ethenyl]-[(1*S*)-1-phenylethyl]amine (3d). Pale yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (3:1)]; $\alpha]^{25}_{D}$=+342.3° (*c* 0.92, $CDCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 9.13 (d, 1H, *J*=9.0 Hz), 7.13–7.26 (m, 5H), 5.02 (s, 1H), 4.83 (m, 1H, *J*=4.5 Hz), 4.12 (t, 2H, *J*=9.0 Hz), 3.94 (t, 2H, *J*=9.0 Hz), 1.46 (d, 3H, *J*=6.5 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −52.59 (d, 1F, *J*=169.3 Hz) −55.61 (d, 1H, *J*=169.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0 (s), 148.2 (t, $^{2}J_{CF}$=26.0 Hz), 145.2 (s), 128.9 (d), 128.6 (t, $^{1}J_{CF}$=245.2 Hz), 127.2 (d), 125.8 (d), 81.7 (t, $^{3}J_{CF}$=8.7 Hz), 66.2 (t), 54.8 (t), 54.1 (d), 25.7 (q); HRMS (EI): Calcd for $C_{14}H_{15}F_2ClN_2O$ 300.0840, found 300.0841.

3.2.4. (*Z*)-2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-(1,1,2,2,2-pentafluoroethyl)-1-ethenyl(4-methoxyphenyl) amine (3f). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (4:1)]; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) (enamino tautomer) δ 9.84 (bs, 1H), 7.00 (d, 2H, *J*=8.6 Hz), 6.73 (d, 2H, *J*=8.6 Hz), 5.23 (s, 1H), 3.80 (s, 2H), 3.70 (s, 3H), 1.19 (s, 3H), 1.16 (s, 3H); (imino tautomer) δ 6.88 (d, 2H, *J*=8.5 Hz), 6.84 (d, 2H, *J*=8.5 Hz), 3.84 (s, 2H), 3.72 (s, 3H), 3.37 (s, 2H), 1.21 (s, 3H), 1.18 (s, 3H); ^{19}F NMR ($CDCl_3$, 235 MHz) (enamino tautomer) δ −83.37 (s, 3F), −111.89 (s, 2F); (imino tautomer) δ −81.72 (s, 3F), −116.72 (s, 2F); ^{13}C NMR ($CDCl_3$, 62.8 MHz) (enamino tautomer) δ 162.4 (s), 157.7 (s), 141.7 (t, $^{2}J_{CF}$=22.3 Hz), 132.9 (s), 128.0 (d), 123.0 (qt, $^{1}J_{CF}$=278.2 Hz and $^{2}J_{CF}$=32.4 Hz), 114.3 (d), 113.6 (tq, $^{1}J_{CF}$=267.2 Hz and $^{2}J_{CF}$=35.4 Hz), 90.4 (t, $^{3}J_{CF}$=6.9 Hz), 77.6 (t), 67.2 (s), 55.2 (q), 28.3 (q); (imino tautomer) δ 162.4 (s), 157.7 (s), 141.7 (t, $^{2}J_{CF}$=22.3 Hz), 132.9 (s), 128.0 (d), 123.0 (qt, $^{1}J_{CF}$=278.2 Hz and $^{2}J_{CF}$=32.4 Hz), 114.3 (d), 113.6 (tq, $^{1}J_{CF}$=267.2 Hz and $^{2}J_{CF}$=35.4 Hz), 90.4 (t, $^{3}J_{CF}$=6.9 Hz), 79.5 (t), 67.5 (s), 55.2 (q), 27.9 (q), 23.8 (t); HRMS (EI): Calcd for $C_{16}H_{17}F_5N_2O_2$ 364.1210, found 364.1192.

3.2.5. (*Z*)-2-(4,5-Dihydro-1,3-oxazol-2-yl)-1-(1,1,2,2,2-pentafluoroethyl)-1-propenyl(4-methoxyphenyl)amine (3g). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (1:1)]; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) (imino tautomer) δ 6.82 (d, 2H, *J*=8.7 Hz), 6.72 (d, 2H, *J*=8.7 Hz), 4.16 (m, 1H), 3.82 (t, 2H, *J*=9.2 Hz), 3.70 (t, 2H, *J*=9.2 Hz), 3.69 (s, 3H), 1.38 (d, 3H, *J*=8.2 Hz); ^{19}F NMR ($CDCl_3$, 235 MHz) (imino tautomer) δ −81.42 (s, 3F), −113.67 (s, 2F); (enamino tautomer) δ −83.03 (s, 3H), −111.12 (s, 2H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) (imino tautomer) δ 165.0 (s), 159.4 (t, $^{2}J_{CF}$=25.7 Hz), 157.3 (s), 139.7 (s), 121.9 (qt, $^{1}J_{CF}$=272.3 Hz and $^{2}J_{CF}$=35.2 Hz), 119.8 (d), 116.0 (tq, $^{1}J_{CF}$=260.0 Hz and $^{2}J_{CF}$=36.8 Hz), 114.1 (d), 67.7 (t), 55.1 (q), 54.1 (t), 34.5 (d), 14.3 (q). HRMS (EI): Calcd for $C_{15}H_{15}F_5N_2O_2$ 350.1053, found 350.1046.

3.2.6. (*Z*)-2-[(4*S*,5*S*)-4-Methoxymethyl-5-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-1-trifluoromethyl-1-ethenyl(4-methoxyphenyl)amine (3h). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (3:1)]; $\alpha]^{25}_{D}$=−98.3° (*c* 0.97, $CDCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 10.12 (bs, 1H), 7.21–7.29 (m, 5H), 7.06 (d, 2H, *J*=8.9 Hz), 6.75 (d, 2H, *J*=8.9 Hz), 5.27 (s, 1H), 5.21 (d, 1H, *J*=6.7 Hz), 4.16 (m, 1H), 3.70 (s, 3H), 3.56 (dd, 1H, *J*=9.5, 4.3 Hz), 3.42 (dd, 1H, *J*=9.6, 6.8 Hz), 3.32 (s, 3H); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −63.35 (s, 3F); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 164.9 (s), 158.0 (s), 144.2 (q, $^{2}J_{CF}$=30.5 Hz), 140.7 (s), 131.5 (s), 128.7 (d), 128.5 (d), 127.3 (d), 125.6 (d), 122.7 (q, $^{1}J_{CF}$=275.0 Hz), 113.8 (d), 83.8 (q, $^{2}J_{CF}$=5.7 Hz), 82.0 (d), 74.2 (t) 63.3 (d), 59.3 (q), 55.3 (q); HRMS (EI): Calcd for $C_{21}H_{21}F_3N_2O_3$ 406.1504, found 406.1501. Anal. Calcd for $C_{21}H_{21}F_3N_2O_3$: C, 62.06; H, 5.21; N, 6.89; found C, 61.70; H, 5.01; N, 6.58.

3.2.7. (*Z*)-1-Chloro(difluoro)methyl-2-[(4*S*,5*S*)-methoxymethyl-5-phenyl-4,5-dihydro-1,3-oxazol-2-yl-1-ethenyl (4-methoxyphenyl)amine (3i). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (3:1)]; $\alpha]^{25}_{D}$=−70.9° (*c* 0.78, $CDCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 10.11 (bs, 1H), 7.12–7.30 (m, 5H), 7.10 (d, 2H, *J*=9.0 Hz), 6.77 (d, 2H, *J*=9.0 Hz), 5.29 (s, 1H), 5.23 (d, 1H, *J*=6.5 Hz), 4.16 (m, 1H), 3.73 (s, 3H), 3.57 (dd, 1H, *J*=9.5, 4.5 Hz), 3.44 (dd, 1H, *J*=9.8, 7.0 Hz), 3.34 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) (enamino tautomer): δ −50.94 (d, 2F, *J*=4.5 Hz); (imino tautomer) δ −59.50 (d, 2F, *J*=17.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0 (s), 158.1 (s), 148.5 (t, $^{2}J_{CF}$=24.7 Hz), 140.7 (s), 131.4 (s), 129.0 (d), 128.0 (d), 128.4 (d), 125.5 (d), 121.1 (t, $^{1}J_{CF}$=231.0 Hz), 113.7 (d), 82.8 (t, $^{3}J_{CF}$=7.7 Hz), 82.1 (d), 74.6 (t) 73.8 (d), 59.3 (q), 55.3 (q); HRMS (EI): Calcd for $C_{21}H_{21}F_2ClN_2O_3$ 422.1208, found 422.1201.

3.2.8. (*Z*)-2-[(4*S*)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-1-trifluoromethyl-1-ethenyl(4-methoxyphenyl)amine (3j). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (4:1)]; $\alpha]^{25}_{D}$=+67.1° (*c* 1.05, $CDCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 10.31 (bs, 1H), 7.05 (d, 2H, *J*=8.7 Hz), 6.76 (d, 2H, *J*=8.7 Hz), 5.17 (s, 1H), 4.17 (m, 1H), 3.77–3.89 (m, 2H), 3.72 (s, 3H), 1.64 (m, 1H), 0.89 (d, 3H, *J*=6.6 Hz), 0.82 (d, 3H, *J*=6.6 Hz); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −63.38 (s, 3F); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 164.2 (s), 157.8 (s), 143.3 (q, $^{2}J_{CF}$=30.5 Hz), 131.8 (s), 127.3 (d), 122.9 (q, $^{1}J_{CF}$=292.0 Hz), 113.9 (d), 84.3 (q, $^{3}J_{CF}$=5.8 Hz), 72.1 (t), 69.0 (d), 55.0 (q), 33.1 (d), 18.9 (q), 18.7 (q); HRMS (EI): Calcd for $C_{16}H_{19}F_3N_2O_2$ 328.1398, found 328.1400.

3.2.9. (*Z*)-2-[(4*S*)-4-(*tert*-Butyl)-4,5-dihydro-1,3-oxazol-2-yl]-1-trifluoromethyl-1-ethenyl(4-methoxyphenyl)amine (3k). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (4:1)]; $\alpha]^{25}_{D}$=+72.2° (*c* 0.83, $CDCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) (enamino tautomer) δ 10.41 (bs, 1H), 7.01 (d, 2H, *J*=8.7 Hz), 6.75 (d, 2H, *J*=8.7 Hz), 5.17 (s, 1H), 4.08 (m, 1H), 3.89–3.96 (m, 2H), 3.71 (s, 3H), 0.85 (s, 9H); ^{19}F NMR ($CDCl_3$, 235 MHz) (enamino tautomer) δ −63.36 (s, 3F); (imino tautomer) δ −71.54 (s, 3F); ^{13}C NMR ($CDCl_3$, 100 MHz) (enamino tautomer) δ 164.2 (s), 159.5 (s), 142.3 (q, $^{2}J_{CF}$=30.2 Hz), 135.4 (s), 127.4 (d), 122.2 (q, $^{1}J_{CF}$=280.2 Hz), 113.9 (d), 84.5 (q, $^{3}J_{CF}$=5.5 Hz), 75.5

(d), 67.2 (t), 55.4 (q), 33.7 (s), 25.7 (q); HRMS (EI): Calcd for $C_{17}H_{21}F_3N_2O_2$ 342.1555, found 342.1571.

3.2.10. 4-Methoxyphenyl{(*Z*)-2[(4*R*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-1-trifluoromethyl-1-ethenyl}lamine (3l). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (4:1)]; $\alpha]^{25}_D=-331.1°$ (*c* 0.99, $CDCl_3$); ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ 10.25 (bs, 1H), 7.18–7.27 (m, 5H), 7.03 (d, 2H, *J*=8.9 Hz), 6.73 (d, 2H, *J*=8.9 Hz), 5.27 (s, 1H), 5.24 (t, 1H, *J*=8.9 Hz), 4.51 (dd, 1H, *J*=8.8, 8.0 Hz), 3.96 (t, 1H, *J*=8.9 Hz), 3.69 (s, 3H); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −63.34 (s, 3F); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7 (s), 158.0 (s), 143.9 (q, $^2J_{CF}$=30.7 Hz), 142.6 (s), 131.6 (s), 128.6 (d), 127.9 (d), 127.5 (d), 126.5 (d), 120.3 (q, $^1J_{CF}$=275.0 Hz), 113.8 (d), 83.8 (q, $^3J_{CF}$=6.2 Hz), 73.3 (t), 69.5 (d), 55.3 (q); HRMS (EI): Calcd for $C_{19}H_{17}F_3N_2O_2$ 362.1242, found 362.1239.

3.2.11. (*Z*)-3-Chloro(difluoro)methyl-2-[(4*R*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-1-ethenyl(4-methoxyphenyl) amine (3m). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (6:1)]; $\alpha]^{25}_D=-98.3°$ (*c* 0.97, $CDCl_3$); ^1H NMR ($CDCl_3$, TMS, 300 MHz) (enamino tautomer) δ 10.26 (bs, 1H), 7.18–7.31 (m, 5H), 7.08 (d, 2H, *J*=8.4 Hz), 6.74 (d, 2H, *J*=8.4 Hz), 5.27 (s, 1H), 5.25 (t, 1H, *J*=8.9 Hz), 4.53 (dd, 1H, *J*=9.0, 8.0 Hz), 3.95 (t, 1H, *J*=8.9 Hz), 3.71 (s, 3H); ^{19}F NMR ($CDCl_3$, 282 MHz) (enamino tautomer) δ −50.65 (d, 1F, *J*=183.5 Hz), −51.30 (d, 1F, *J*=168.0 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 165.6 (s), 157.9 (s), 148.4 (t, $^2J_{CF}$=25.2 Hz), 142.4 (s), 131.3 (s), 128.8 (d), 128.5 (d), 127.4 (d), 126.4 (d), 122.5 (t, $^1J_{CF}$=293.4 Hz), 113.5 (d), 82.8 (q, $^3J_{CF}$=7.6 Hz), 73.2 (t), 69.3 (d), 55.1 (q); HRMS (EI): Calcd for $C_{19}H_{17}F_2ClN_2O_2$ 380.0917, found 380.0936.

3.2.12. (*Z*)-2-[(3a*S*,8b*R*)-4,8b-Dihydro-3a*H*-indeno[2,1-d][1,3]oxazol-2-yl]-1-trifluoromethyl-1-ethenyl (4-methoxyphenyl)amine (3n). Yellow solid, recrystallised with [*n*-hexane–EtOH (10:1)]; mp 114–5°C; $\alpha]^{25}_D=+453.0°$ (*c* 0.70, $CDCl_3$); ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ 10.13 (bs, 1H), 7.19–7.37 (m, 4H), 7.03 (d, 2H, *J*=8.9 Hz), 6.76 (d, 2H, *J*=8.9 Hz), 5.58 (d, 1H, *J*=8.0 Hz), 5.22 (m, 1H, *J*=4.5 Hz), 5.15 (s, 1H), 3.73 (s, 3H), 3.37 (dd, 1H, *J*=17.5, 6.5 Hz), 3.22 (d, 1H, *J*=17.5 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) (enamino tautomer) δ −63.47 (s, 3F); (imino tautomer) δ −71.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7 (s), 158.0 (s), 146.9 (q, $^2J_{CF}$=32.2 Hz), 142.2 (s), 139.7 (s), 131.7 (d), 121.2 (d), 120.7 (q, $^1J_{CF}$=276.9 Hz), 120.8 (d), 120.2 (d), 118.2 (d), 118.0 (d), 113.8 (d), 84.1 (d), 81.5 (d), 76.2 (d), 55.4 (d), 39.5 (t); HRMS (EI): Calcd for $C_{20}H_{17}F_3N_2O_2$ 374.1242, found 374.1235.

3.3. General procedure for the synthesis of *N*-substituted β-amino-Δ^2-oxazolines 4

Method A. A solution of *N*-substituted β-enamino-Δ^2-oxazolines **3** (0.3 g, 0.95 mmol) in 50 mL of MeOH was stirred at room temperature under H_2 atmosphere, in presence of Pd/C (5% Pd) for several hours (2–24 h). The resulting mixture was filtrated through a Celite pad and the solvent removed in vacuo. Purification was carried out as indicated in each case.

Method B. To a solution of *anhydrous* zinc iodide (0.5 g, 1.56 mmol) in dry CH_2Cl_2 (20 mL) at 0°C was added the corresponding *N*-substituted β-enamino-Δ^2-oxazolines **3** (0.52 mmol). After stirring the reaction mixture for 1 h at 0°C, the reducing agent $NaBH_4$ (0.1 g, 2.65 mmol) was added, also at 0°C. Then, the reaction was allowed to reach room temperature, monitored by means of TLC, quenched with saturated ammonium chloride solution (30 mL) and extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure to provide the crude reaction mixture **4**. Purification was carried out as indicated in each case.

3.3.1. 1-(4,5-Dihydro-1,3-oxazol-2-ylmethyl)-2,2,2-trifluoroethyl(4-methoxyphenyl)amine (4a). Brown solid, recrystallised with [*n*-hexane–EtOH (10:1)]; mp 82–4°C; ^1H NMR ($CDCl_3$, TMS, 250 MHz) δ 6.71 (d, 2H, *J*=8.6 Hz), 6.61 (d, 2H, *J*=8.6 Hz), 4.17 (m, 1H), 4.01 (t, 2H, *J*=8.8 Hz), 3.94 (t, 2H, *J*=8.8 Hz), 3.72 (d, 1H, *J*=8.9 Hz), 3.69 (s, 3H), 2.66 (dd, 1H, *J*=14.6, 4.3 Hz), 2.47 (dd, 1H, *J*=14.5, 9.6 Hz); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −45.71 (d, 3F, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 163.9 (s), 153.2 (s), 140.1 (s), 125.5 (q, $^1J_{CF}$=281.4 Hz), 115.8 (d), 114.6 (d), 67.6 (t), 55.6 (s), 54.6 (q, $^2J_{CF}$=29.7 Hz), 54.3 (t), 28.6 (t); HRMS (EI): Calcd for $C_{13}H_{15}F_3N_2O_2$ 288.1085, found 288.1080.

3.3.2. 2-Chloro-1-(4,5-dihydro-1,3-oxazol-2-ylmethyl)-2,2-difluoroethyl(4-methoxyphenyl)amine (4b). Yellow solid, recrystallised with [*n*-hexane–EtOH (10:1)]; mp 71–3°C; ^1H NMR ($CDCl_3$, TMS, 250 MHz) δ 6.77 (d, 2H, *J*=8.7 Hz), 6.69 (d, 2H, *J*=8.7 Hz), 4.36 (m, 1H), 4.22 (t, 2H, *J*=8.7 Hz), 3.99 (t, 2H, *J*=8.7 Hz), 3.85 (d, 1H, *J*=8.8 Hz), 3.74 (s, 3H), 2.85 (dd, 1H, *J*=14.6, 4.1 Hz), 2.74 (dd, 1H, *J*=14.5, 9.6 Hz); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −60.24 (dd, 1F, J_{FF}=166.8 Hz and J_{FH}=7.8 Hz), −61.03 (dd, 1H, J_{FF}=166.8 Hz and J_{FH}=7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.2 (s), 140.1 (s), 130.2 (s), 117.4 (t, $^1J_{CF}$=289.3 Hz), 115.7 (d), 114.8 (d), 67.8 (t), 60.7 (t, $^2J_{CF}$=26.0 Hz), 55.7 (q), 54.1 (t), 29.8 (t); HRMS (EI): Calcd for $C_{13}H_{15}F_2ClN_2O_2$ 304.0790, found 304.0784.

3.3.3. Cyclohexyl[1-(4,5-dihydro-1,3-oxazol-2-ylmethyl)-2,2,2-trifluoroethyl]amine (4c). Colourless oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (2:1)]; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ 4.27–4.31 (m, 2H), 4.25 (t, 2H, *J*=9.0 Hz), 3.51–3.57 (m, 1H), 2.41–2.67 (m, 3H), 1.62–1.84 (m, 5H), 1.60 (bs, 1H), 0.96–1.32 (m, 5H); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −76.70 (d, 3F, *J*=7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1 (s), 126.1 (q, $^1J_{CF}$=281.1 Hz), 67.5 (t), 55.2 (t), 54.4 (q, $^2J_{CF}$=23.2 Hz), 34.0 (d), 33.0 (t), 29.0 (t), 25.8 (t), 24.6 (t). Anal. Calcd for $C_{12}H_{19}F_3N_2O$: C, 54.54; H, 7.25; N, 10.60; found C, 54.28; H, 6.97; N, 10.49.

3.3.4. 2-Chloro-1-(4,5-dihydro-1,3-oxazol-2-ylmethyl)-2,2-difluoroethyl[(1*S*)-1-phenylethyl]amine (4d). Pale yellow oil, obtained as a mixture of diastereomers that were not separated. Data taken from the diastereomeric mixture; ^1H NMR ($CDCl_3$, TMS, 400 MHz) (major diastereomer) δ 7.16–7.25 (m, 5H), 3.68–4.20 (m, 5H), 3.46 (m, 1H), 2.46

(m, 1H), 2.32 (dd, 1H, J=14.5, 10.5 Hz), 2.00 (bs, 1H), 1.25 (d, 3H, J=6.5 Hz); (minor diastereomer) δ 7.16–7.25 (m, 5H), 3.68–4.20 (m, 5H), 3.28 (m, 1H), 2.66 (dd, 1H, J=15.0, 4.4 Hz), 2.46 (m, 1H), 2.00 (bs, 1H), 1.25 (d, 3H, J=6.5 Hz), ^{19}F NMR ($CDCl_3$, 235 MHz) (major diastereomer) δ −58.84 (dd, 1H, J_{FF}=180.2 Hz and J_{FH}=7.2 Hz), −59.62 (dd, 1H, J_{FF}=179.4 Hz and J_{FH}=7.3 Hz); (minor diastereomer) δ −57.32 (dd, 1H, J_{FF}=159.8 Hz and J_{FH}= 4.9 Hz), −58.75 (dd, 1H, J_{FF}=160.4 Hz and J_{FH}=8.5 Hz).

3.3.5. 1-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-ylmethyl)-2,2,2-trifluoroethyl(4-methoxyphenyl)amine (4e). Brown solid, recrystallised with [*n*-hexane–EtOH (10:1)]; mp 65–6°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 6.63 (d, 2H, J=8.7 Hz), 6.55 (d, 2H, J=8.7 Hz), 4.08 (m, 1H), 3.61 (s, 3H), 3.59 (m, 3H), 2.64 (dd, 1H, J=14.5, 4.3 Hz), 2.47 (dd, 1H, J=14.5, 9.6 Hz), 1.05 (s, 3H), 1.05 (s, 3H); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −76.56 (d, 3F, J=6.4 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 161.3 (s), 153.0 (s), 140.0 (s), 125.4 (q, $^1J_{CF}$=281.1 Hz), 115.3 (d), 114.6 (d), 79.1 (t), 67.1 (s), 55.5 (q), 55.2 (q, $^2J_{CF}$=30.1 Hz), 28.7 (q, $^3J_{CF}$=5.7 Hz), 27.9 (q); HRMS (EI): Calcd for $C_{15}H_{19}F_3N_2O_2$ 316.1398, found 316.1397.

3.3.6. 1-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-ylmethyl)-2,2,3,3,3-pentafluoropropyl(4-methoxyphenyl)amine (4f). Yellow solid, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (2:1)]; mp 80–1°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 6.66 (d, 2H, J=8.6 Hz), 6.56 (d, 2H, J=8.6 Hz), 4.32 (m, 1H), 3.66 (d, 1H, J=8.0 Hz), 3.64 (s, 3H), 3.58 (d, 1H, J=10.8 Hz), 3.51 (d, 1H, J=8.0 Hz), 2.70 (dd, 1H, J=14.6, 3.5 Hz), 2.53 (dd, 1H, J=14.5, 9.7 Hz), 1.05 (s, 3H), 1.00 (s, 3H); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −81.49 (s, 3F), −118.91 (dd, 1F, J_{FF}=273.3 Hz and J_{FH}=6.5 Hz), −127.25 (dd, 1F, J_{FF}=272.8 Hz and J_{FH}=18.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.3 (s), 153.1 (s), 139.6 (s), 123.1 (qt, $^1J_{CF}$=281.1 Hz and $^2J_{CF}$=35.7 Hz), 115.2 (d), 113.1 (tq, $^1J_{CF}$=259.6 Hz and $^2J_{CF}$=38.7 Hz), 114.7 (d), 79.1 (t), 67.2 (s), 55.6 (q), 53.6 (t, $^2J_{CF}$=21.2 Hz), 28.0 (q), 28.5 (t, $^3J_{CF}$=5.5 Hz), 27.9 (q); HRMS (EI): Calcd for $C_{16}H_{19}F_5N_2O_2$ 366.1366, found 366.1356.

3.3.7. 1-[1-(4,5-Dihydro-1,3-oxazol-2-yl)ethyl]-2,2,3,3,3-pentafluoropropyl(4-methoxyphenyl)amine (4g). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (3:1)]. Data taken from a diastereomeric mixture, enriched in the major diastereomer (9:1); ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 6.65 (d, 2H, J=8.8 Hz), 6.54 (d, 2H, J=8.8 Hz), 4.56 (m, 1H), 3.96 (t, 2H, J=8.9 Hz), 3.66 (t, 2H, J=8.9 Hz), 3.61 (s, 3H), 3.39 (d, 1H, J=8.8 Hz), 2.92 (m, 1H), 1.23 (d, 3H, J=6.8 Hz); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −82.34 (s, 3F), −118.21 (dd, 1F, J_{FF}=273.3 Hz and J_{FH}=4.2 Hz), −125.92 (dd, 1F, J_{FF}=296.8 Hz and J_{FH}=23.5 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 167.7 (s), 153.0 (s), 139.9 (s), 126.5 (qt, $^1J_{CF}$=281.5 Hz and $^2J_{CF}$=35.0 Hz), 115.6 (d), 114.4 (d), 96.2 (tq, $^1J_{CF}$=260.2 Hz and $^2J_{CF}$=38.9 Hz), 67.3 (t), 55.8 (t, $^2J_{CF}$=27.2 Hz), 55.6 (t), 55.4 (q), 33.3 (d), 11.4 (q); HRMS (EI): Calcd for $C_{15}H_{17}F_5N_2O_2$ 352.1210, found 352.1212.

3.3.8. 4-Methoxyphenyl{(1*R*)-2,2,2-trifluoro-1-[(4*S*,5*S*)-4-methoxymethyl-5-phenyl-4,5-dihydro-1,3-oxazol-2-ylmethyl]ethyl}amine (4hα). Colourless oil; major diastereomer separated by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (2:1)]; $\alpha]^{25}_D$=−44.7° (*c* 0.96, $CDCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.10–7.23 (m, 5H), 6.70 (d, 2H, J=8.4 Hz), 6.57 (d, 2H, J=8.4 Hz), 5.03 (d, 1H, J=7.9 Hz), 4.32 (m, 1H), 4.00 (m, 1H), 3.75 (d, 1H, J=9.2 Hz), 3.66 (s, 3H), 3.37 (dd, 1H, J=9.58, 4.8 Hz), 3.23 (s, 3H), 3.22 (dd, 1H, J=9.6, 6.8 Hz), 2.81 (dd, 1H, J=3.9, 1.5 Hz), 2.66 (dd, 1H, J=14.6, 9.8 Hz); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −76.41 (d, 3F, J=6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7 (s), 153.1 (s), 139.9 (s), 128.7 (d), 128.3 (d), 127.0 (q, $^1J_{CF}$=292.3 Hz), 125.6 (d), 124.0 (s), 115.4 (d), 114.7 (d), 84.1 (d), 74.2 (d), 73.9 (t), 59.1 (q), 55.6 (q), 54.9 (q, $^2J_{CF}$=30.0 Hz), 28.9 (t); HRMS (EI): Calcd for $C_{21}H_{23}F_3N_2O_3$ 408.1660, found 408.1643. Anal. Calcd for $C_{21}H_{23}F_3N_2O_3$: C, 61.76; H, 5.68; N, 6.86; found C, 61.53; H, 5.60; N, 6.93.

3.3.9. 2-Chloro-2,2-difluoro-1-[(4*S*,5*S*)-4-methoxymethyl-5-phenyl-4,5-dihydro-1,3-oxazol-2-ylmethyl]ethyl(4-methoxyphenyl)amine (4i). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (3:1)]. Data taken from a diastereomeric mixture (8:2) enriched in the major diastereomer; ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.130–7.23 (m, 5H), 6.62–6.67 (m, 4H), 5.00 (d, 1H, J=7.9 Hz), 4.38 (m, 1H), 4.16 (m, 1H), 3.76 (d, 1H, J=9.2 Hz), 3.68 (s, 3H), 3.39 (dd, 1H, J=9.5, 4.5 Hz), 3.24 (s, 3H), 3.23 (dd, 1H, J=9.5, 6.9 Hz), 2.93 (dd, 1H, J=3.9, 1.6 Hz), 2.66 (dd, 1H, J=14.6, 9.8 Hz); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −60.54 (m, 3F); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.6 (s), 153.2 (s), 152.8 (s), 139.5 (s), 130.0 (t, $^1J_{CF}$=290.4 Hz), 128.5 (d), 128.1 (d), 125.5 (d), 115.0 (d), 114.48 (d), 83.9 (d), 73.9 (d), 73.8 (t), 59.9 (t, $^2J_{CF}$=30.4 Hz), 58.9 (q), 55.3 (q), 28.9 (t).

3.3.10. 4-Methoxyphenyl{2,2,2-trifluoro-1-(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-ylmethyl]ethyl}amine (4j). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (4:1)]. Data obtained from a diastereomeric mixture (9:1) enriched in the major diastereomer; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 6.70 (d, 2H, J=8.5 Hz), 6.60 (d, 2H, J=8.5 Hz), 4.15 (m, 1H), 3.94 (t, 1H, J=8.4 Hz), 3.78 (t, 1H, J=8.4 Hz), 3.72 (t, 1H, J=8.4 Hz), 3.67 (s, 3H), 2.70 (dd, 1H, J=14.8, 4.2 Hz), 2.54 (dd, 1H, J=14.8, 9.42 Hz), 1.54 (m, 1H, J=6.6 Hz), 0.81 (d, 3H, J=7.2 Hz), 0.72 (d, 3H, J=7.2 Hz); ^{19}F NMR ($CDCl_3$, 235 MHz) (major diastereomer) δ −76.49 (d, 3F, J=6.9 Hz); (minor diastereomer) δ −76.42 (d, 3F, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 162.8 (s), 153.2 (s), 140.2 (s), 127.4 (q, $^1J_{CF}$=279.3 Hz), 115.7 (d), 114.7 (d), 72.2 (d), 70.4 (t), 55.6 (q), 55.3 (q, $^2J_{CF}$=32.3 Hz), 32.5 (t), 28.9 (d), 28.6 (d), 18.5 (q), 18.2 (q); HRMS (EI): Calcd for $C_{16}H_{21}F_3N_2O_2$ 330.1555, found 330.1544.

3.3.11. 1-[(4*S*)-4-(*tert*-Butyl)-4,5-dihydro-1,3-oxazol-2-ylmethyl]-2,2,2-trifluoroethyl(4-methoxyphenyl)amine (4k). Yellow oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (3:1)]. Data obtained from a diastereomeric mixture (3:1) enriched in the major diastereomer; ^{1}H NMR ($CDCl_3$, TMS,

300 MHz) δ 6.5–7.5 (m, 4H), 4.20 (m, 1H), 3.71–3.76 (m, 2H), 3.67 (s, 3H), 3.46 (m, 1H), 3.78 (t, 1H, *J*=8.4 Hz), 2.64 (dd, 1H, *J*=14.3, 4.1 Hz), 2.51 (dd, 1H, *J*=14.8, 8.6 Hz), 0.81 (s, 9H); ^{19}F NMR ($CDCl_3$, 282 MHz) (major diastereomer) δ −75.86 (d, 3F, *J*=7.2 Hz) (minor diastereomer) δ −75.99 (d, 3F, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 162.7 (s), 154.3 (s), 139.2 (s), 121.3 (q, $^1J_{CF}$=280.5 Hz), 116.0 (d), 114.8 (d), 62.9 (d), 61.7 (t), 59.6 (q), 55.1 (q, $^2J_{CF}$=30.5 Hz), 36.2 (s), 30.8 (t), 26.7 (q).

3.3.12. 4-Methoxyphenyl{(1*R*)-2,2,2-trifluoro-1-[(4*R*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-ylmethyl]ethyl}amine (4lα). *Major diastereomer.* White solid, separated by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (4:1)]; $\alpha]^{25}_D$=+11.2° (*c* 0.80, $CDCl_3$); mp 137–8°C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.00–7.18 (m, 5H), 6.71 (d, 2H, *J*=8.8 Hz), 6.63 (d, 2H, *J*=8.8 Hz), 5.04 (t, 1H, *J*=9.2 Hz), 4.40 (dd, 1H, *J*=9.2, 8.0 Hz), 4.26 (m, 1H), 3.96 (t, 1H, *J*=9.2 Hz), 3.72 (d, 1H, *J*=9.2 Hz), 3.68 (s, 3H), 2.83 (dd, 1H, *J*=14.8, 4.1 Hz), 2.64 (dd, 1H, *J*=14.8, 9.6 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −76.63 (d, 3F, *J*=6.4 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 164.3 (s), 153.3 (s), 141.6 (s), 140.0 (s), 128.7 (d), 127.6 (d), 126.4 (d), 120.1 (q, $^1J_{CF}$=290.8 Hz), 115.7 (d), 114.7 (d), 74.9 (t), 69.6 (d), 55.6 (q), 55.5 (q, $^2J_{CF}$=30.9 Hz), 27.7 (t); HRMS (EI): Calcd for $C_{19}H_{19}F_3N_2O_2$ 364.1398, found 364.1447. Anal. Calcd for $C_{19}H_{19}F_3N_2O_2$: C, 62.62; H, 5.26; N, 7.69; found C, 62.57; H, 5.13; N 7.58.

3.3.13. 4-Methoxyphenyl{(1*S*)-2,2,2-trifluoro-1-[(4*R*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-ylmethyl]ethyl}amine (4lβ). *Minor diastereomer.* White solid, separated by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (4:1)]; $\alpha]^{25}_D$=+65.7 (*c* 1.02, $CDCl_3$); mp 94–6°C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.02–7.19 (m, 5H), 6.72 (d, 2H, *J*=8.9 Hz), 6.61 (d, 2H, *J*=8.9 Hz), 5.06 (t, 1H, *J*=9.2 Hz), 4.51 (dd, 1H, *J*=9.3, 8.0 Hz), 4.30 (m, 1H), 3.92 (t, 1H, *J*=9.2 Hz), 3.71 (d, 1H, *J*=9.2 Hz), 3.68 (s, 3H), 2.84 (dd, 1H, *J*=14.8, 4.1 Hz), 2.67 (dd, 1H, *J*=14.8, 9.6 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −76.61 (d, 3F, *J*=6.4 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 164.3 (s), 153.3 (s), 141.6 (s), 140.0 (s), 128.7 (d), 127.6 (d), 126.4 (d), 120.1 (q, $^1J_{CF}$=290.8 Hz), 115.7 (d), 114.7 (d), 74.9 (t), 69.6 (d), 55.6 (q), 55.5 (q, $^2J_{CF}$=30.9 Hz), 27.7 (t); HRMS (EI): Calcd for $C_{19}H_{19}F_3N_2O_2$ 364.1398, found 364.1409.

3.3.14. (1*R*)-2-Chloro-2,2-difluoro-1-[(4*R*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-ylmethyl]ethyl(4-methoxyphenyl) amine (4mα). *Major diastereomer.* Yellow solid; separated by flash chromatography on deactivated (Et_3N 3%) SiO_2 [*n*-hexane–EtOAc (4:1)]; $\alpha]^{25}_D$=+33.3° (*c* 0.93, $CDCl_3$); mp 146–7°C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.97–7.18 (m, 5H), 6.71 (d, 2H, *J*=8.8 Hz), 6.65 (d, 2H, *J*=8.8 Hz), 5.01 (t, 1H, *J*=9.0 Hz), 4.36 (dd, 1H, *J*=9.0, 8.0 Hz), 4.36 (m, 1H), 3.94 (t, 1H, *J*=9.0 Hz), 3.74 (d, 1H, *J*=9.2 Hz), 3.68 (s, 3H), 2.93 (dd, 1H, *J*=14.6, 4.2 Hz), 2.64 (dd, 1H, *J*=14.7, 9.7 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −60.54 (dd, 1F, *J*=167.8, 7.2 Hz), −61.1 (dd, 1F, *J*=160.3, 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 164.2 (s), 153.0 (s), 141.4 (s), 139.8 (s), 132.2 (t, $^1J_{CF}$=298.5 Hz), 128.4 (d), 127.3 (d), 126.2 (d), 115.4 (d), 114.5 (d), 74.7 (t), 69.3 (d), 60.7 (t, $^2J_{CF}$=25.8 Hz), 55.4(q), 29.8 (t); HRMS (EI): Calcd for $C_{19}H_{19}F_2ClN_2O_2$ 380.1103, found 380.1099.

3.3.15. 1-[(3a*S*,8b*R*)-4,8b-Dihydro-3a*H*-indeno[2,1-*d*][1,3]-oxazol-2-ylmethyl]-2,2,2-trifluoromethyl (4-methoxyphenyl)amine (4n). Data obtained from a diastereomeric mixture (3:1) enriched in the major diastereomer; white solid; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.27–7.36 (m, 8H), 4.97–5.58 (m, 2H), 4.10 (m, 1H), 3.66 (s, 3H), 3.65 (m, 1H), 3.24 (dd, 1H, *J*=14.7, 4.1 Hz), 3.09 (dd, 1H, *J*=14.7, 9.6 Hz), 2.62–2.68 (m, 2H); ^{19}F NMR ($CDCl_3$, 376 MHz) (major diastereomer) δ −76.82 (d, 3F, *J*=8.2 Hz); (minor diastereomer) δ −76.95 (d, 3F, *J*=8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.2 (s), 153.0 (s), 140.0 (s), 139.8 (s), 139.3 (s), 132.2 (q, $^1J_{CF}$=298.5 Hz), 128.4 (d), 127.3 (d), 126.2 (d), 115.4 (d), 114.5 (d), 74.7 (t), 69.3 (d), 60.7 (q, $^2J_{CF}$=25.8 Hz), 55.4 (q), 55.3 (d); HRMS (EI): Calcd for $C_{20}H_{19}F_3N_2O_2$ 380.1103, found 380.1099.

3.4. Synthesis of β-aminoesters 5

A suspension of the major diastereoisomer of adduct (+)-**4l**α (0.15 g, 0.41 mmol) in aqueous HCl (1N, 15 mL) was heated at reflux for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in equal parts of concentrated HCl and the corresponding alcohol (10 mL), and the solution was heated to reflux for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution (30 mL) and extracted with dichloromethane (3×20 mL). The organic layers were combined, washed with brine, and dried over sodium sulphate. After filtration, the solvents were removed under reduced pressure to provide the crude reaction mixture **5**. Purification was carried out as indicated in each case.

3.4.1. (*R*)-Methyl 4,4,4-trifluoro-3-(4-methoxy-phenylamino)butanoate (5a). Colourless oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 (*n*-hexane–EtOAc (6:1)); $\alpha]^{25}_D$=+13.5° (*c* 0.42, $CDCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.81 (d, 2H, *J*=9.0 Hz), 6.73 (d, 2H, *J*=9.0 Hz), 4.37 (m, 1H, *J*=7.0 Hz), 3.76 (s, 3H), 3.70 (s, 3H), 2.83 (dd, 1H, *J*=15.6, 4.5 Hz), 2.63 (dd, 1H, *J*=15.6, 8.8 Hz), 2.34 (bs, 1H); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −76.45 (d, 3F, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0 (s), 155.1 (s), 139.5 (s), 125.7 (q, $^1J_{CF}$=290.0 Hz), 116.0 (d), 114.8 (d), 55.8 (q), 54.3 (q, $^2J_{CF}$=28.9 Hz), 52.2 (q), 34.8 (t); HRMS (EI): Calcd for $C_{12}H_{14}F_3NO_3$ 277.0925, found 277.0924.

3.4.2. (*R*)-Isopropyl 4,4,4-trifluoro-3-(4-methoxy-phenylamino)butanoate (5b). Colourless oil, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 (*n*-hexane–EtOAc (7:1)); $\alpha]^{25}_D$=−19.4° (*c* 0.70, $CDCl_3$) obtained from (**4l**); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.71 (d, 2H, *J*=9.0 Hz), 6.62 (d, 2H, *J*=9.0 Hz), 4.87–4.97 (m, 1H, *J*=7.0 Hz), 4.22–4.32 (m, 1H), 3.67 (s, 3H), 3.37 (brd, 1H, *J*=10.0 Hz), 2.70 (dd, 1H, *J*=15.4, 4.4 Hz), 2.48 (dd, 1H, *J*=15.4, 8.9 Hz), 1.13 (d, 3H, *J*=6.2 Hz), 1.07 (d, 3H, *J*=6.2 Hz); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −76.45 (d, 3F, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0 (s), 153.3 (s), 139.7 (s), 125.6 (q, $^1J_{CF}$=289.3 Hz), 115.7 (d), 114.7 (d), 68.9 (d), 55.5 (q), 54.8 (q, $^2J_{CF}$=29.7 Hz), 35.3 (t), 21.6 (q), 21.4 (q); HRMS (EI): Calcd for $C_{14}H_{18}F_3NO_3$ 305.1238, found 305.1250.

3.5. Synthesis of (*R*)-4,4,4-trifluoro-3-(4-methoxy-phenylamino)-butan-1-ol (6)

A suspension of the major diastereoisomer of compound (+)-**4l**α (0.15 g, 0.41 mmol) in aqueous HCl 1N (15 mL) was heated to reflux for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in dry THF (15 mL) and $LiAlH_4$ (0.07 g, 2 mmol) was added to the solution at −78°C. The solution was allowed to reach room temperature and then monitored by means of TLC. The reaction mixture was quenched with methanol (4 mL) and extracted with ethyl acetate (3×20 mL). The organic layers were combined, washed with brine, and dried over sodium sulphate. After filtration, the solvents were removed under reduced pressure to provide the crude reaction mixture **6**. Purification was carried out by flash chromatography using *n*-hexane–EtOAc (3:1)as eluent on silica gel, yielding a white solid (70%).

3.5.1. (*R*)-4,4,4-Trifluoro-3-(4-methoxy-phenylamino)butyl alcohol (6). White solid, purified by flash chromatography on deactivated (Et_3N 3%) SiO_2 (*n*-hexane–EtOAc (4:1)); $\alpha]^{25}_D$=+48.8° (*c* 0.38, $CDCl_3$); mp 97–9°C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.72 (d, 2H, *J*=9.0 Hz), 6.63 (d, 2H, *J*=9.0 Hz), 3.99 (m, 1H), 3.79 (m, 2H), 3.68 (s, 3H), 3.60 (brd, 1H), 2.13 (m, 1H), 1.66 (m, 1H); ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −76.36 (d, 3F, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 153.1 (s), 140.4 (s), 126.2 (q, $^1J_{CF}$=283.4 Hz), 115.4 (d), 114.8 (d), 58.8 (t), 55.6 (q), 54.9 (q, $^2J_{CF}$=28.9 Hz), 31.7 (t); HRMS (EI): Calcd for $C_{11}H_{14}F_3NO_2$ 249.0976, found 249.0987.

3.6. X-Ray structure analysis of 4mα

Colourless lath of 0.73×0.13×0.03 mm size, orthorhombic, $P2_12_12_1$, *a*=5.361(1), *b*=8.605(2), *c*=39.527(8) Å, *V*=1823.5(6) Å^3, *Z*=4, D_c=1.387, *F*(000)=1192 g cm^{-3}, $2\theta_{max}$=61°, diffractometer Nonius CAD4, MoK_α (λ=0.71073 Å), ω-scan, *T*=273 K, 5348 reflections collected of which 3918 were independent (R_{int}=0.056), direct primary solution and refinement on F^2 using SHELX 97 program,[24] 239 refined parameters, amino group hydrogen atom located in a difference Fourier synthesis and refined with a restrained N–H bond length, other hydrogen atoms riding, $R1[I>2\sigma(I)]$=0.0791, *wR*2 (all data)=0.1774, residual electron density 0.214 (−0.228) eÅ^{-3}, absolute structure could not be determined.

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