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ORIGINAL ARTICLE

Trifluoromethyl-modified dipeptides by $ZrCl_4$-promoted aza-Henry reactions

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Abstract Chiral (*R*)-1-phenylethylamine was successfully employed in a tandem aza-Henry addition–reduction reaction to give chiral β-nitro α-trifluoromethyl amines. A subsequent coupling reaction with *N*-Boc-protected amino acids leads to obtain optically pure CF_3-modified dipeptides carrying two different *N*-protecting groups. These peptidomimetic units are characterized by the presence of the [$CH(CF_3)NH$] group as mimetic of the natural [CONH] peptidic bond and can be used for the synthesis of more complex CF_3-modified peptides after selective deprotection of one of the two amine functions. 2D NMR spectral analyses were employed to determine the absolute configurations of all newly synthesized chiral compounds.

Keywords Amino acids · NMR techniques · Organo-fluorine chemistry · Peptidomimetics

Introduction

The special nature of fluorine imparts a variety of properties to certain molecules making them potential drug candidates, including enhanced-binding interactions, metabolic stability, changes in physical properties, and selective reactivity (Cahard and Bizet 2014; O'Hagan 2013; Zhang et al. 2012; Filler and Saha 2009; Couve-Bonnaire et al. 2007; Müller et al. 2007). Selective incorporation of fluorinated residues into proteins is actually considered a powerful strategy to modulate the properties of those peptides which show great potential as highly active pharmaceuticals (Salwiczek et al. 2012; March et al. 2012; Merkel and Budisa 2012; Buer and Marsh 2012; Mikami et al. 2011; Qiu and Qing 2011; Acena et al. 2010; Kukhar et al. 2009). The success of substitution with fluorine stems from its unique properties: small size, very low polarizability and strong inductive effect. As a consequence, the presence of fluorine within a peptide often favorably modifies the biophysical, biological and chemical properties such as hydrophobicity, acidity/basicity, reactivity and conformation. Numerous examples can be found where fluorine has effectively replaced either hydrogen or oxygen in compounds that have retained comparable activities, albeit with different properties (Buer et al. 2012; McKinney and Urban 2010; Fustero et al. 2009; Molteni et al. 2004). An important modification consists in the incorporation of a [$CH(CF_3)NH$] unit as a surrogate of the natural [CONH] peptidic bond, due to the fact that the trifluoromethyl group is an effective xenobiotic function for the peptide backbone modification (Cho et al. 2013; Jagodzinska et al. 2009; Zanda 2004; Sani et al. 2003; Molteni et al. 2003; Volonterio et al. 2002) (Fig. 1).

Unfortunately, the synthetic accessibility of fluorinated peptides is limited by the availability of appropriate building blocks both for the liquid and for the solid-phase synthesis.

(*E*)-Trifluoromethyl aldimines (Bégué et al. 2005), can be easily synthesized through a solvent-free reaction starting from commercial trifluoroacetaldehyde ethyl hemiacetal (Gong and Kato 2004) and several primary

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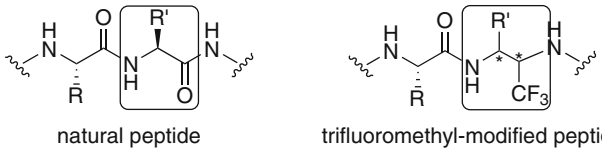


Fig. 1 [CH(CF_3)NH] unit as mimetic of natural [CONH] peptidic bond

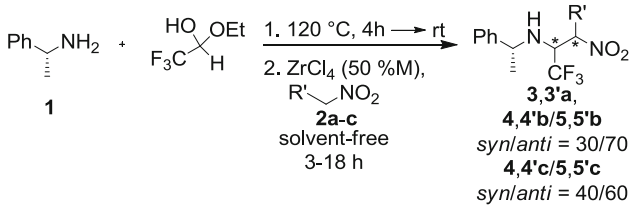
amines (Carroccia et al. 2010, 2011) and can be considered interesting precursors for the construction of small fluorinated peptides, already containing both the CF_3 group and the nitrogen atom. Then, starting from our recent studies on the $ZrCl_4$-catalyzed aza-Henry addition of different nitro alkanes on (*E*)-trifluoromethyl aldimines (Fioravanti et al. 2012), the synthesis of *N*,*N*′-diprotected CF_3-modified dipeptides by a short procedure was considered (Scheme 1).

Results and discussion

Chiral (*R*)-1-phenylethylamine (**1**) is considered as a suitable starting primary amine due to the presence of the benzylic group that can be easily removed under mild hydrogenolytic conditions. Considering that the imine synthesis was performed under solvent-free conditions as well as the aza-Henry addition, a one-pot reaction was attempted. So, to the commercial amine **1** trifluoroacetaldehyde ethyl hemiacetal in equimolar ratio was added, heating to 120 °C and the reaction was followed by ^{19}F NMR spectroscopy (4 h) (Carroccia et al. 2010). After bringing the reaction to room temperature, $ZrCl_4$ (50 % M) and the appropriate nitro alkane **2** (5 eq) were added directly in the same vessel (Scheme 2).

The aza-Henry reactions were followed by ^{19}F NMR spectroscopy and the results are reported in Table 1.

In all cases, complete disappearance of the CF_3 signal of the non-isolated intermediate imine was observed by ^{19}F NMR spectra and the expected β-nitro α-trifluoromethyl amines were obtained in satisfactory yields after flash chromatography on silica gel. In hope of enhancing the stereoselective outcome, the reactions were repeated by varying the temperature (0 and −20 °C), but no significant changes in the diastereomeric ratios (dr) were determined by the ^{19}F NMR analysis performed on the crude mixtures. As reported in Table 1, when using nitromethane **2a** a



Scheme 2 One-pot synthesis of β-nitro α-trifluoromethyl amines under solvent-free conditions

Table 1 Results of the tandem Zr-catalyzed aza-Henry addition

Entry	**2**	R′	*T* (h)	Products	Yield (%)[a]	Dr[b]
1	**a**	H	3	**3,3′a**	80	80:20
2	**b**	Me	18	*syn*-**4,4′b**	24	72:28
				anti-**5,5′b**	52	72:28
3	**c**	Et	18	*syn*-**4,4′c**	24	67:33
				anti-**5,5′c**	48	67:33

[a] After flash chromatography on silica gel

[b] Diastereomeric ratios by ^{19}F NMR spectra performed on the crude mixtures

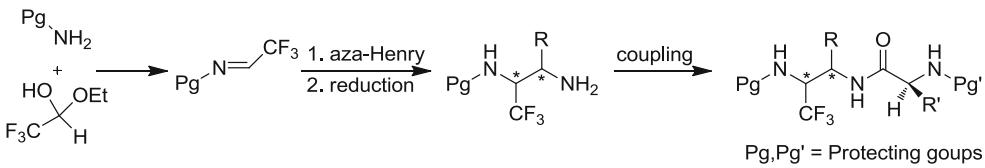
moderate diastereomeric ratio was observed (entry 1) and, when the aza-Henry reactions were performed using nitro alkanes **2b** or **2c** (entries 2 and 3), all the four possible diastereomers were obtained, although in different ratios (Fig. 2).

Nevertheless, we underline that complete stereoselectivity can paradoxically result in a limitation in the strategic synthesis of CF_3-modified dipeptides. In fact, it is important to access each of the new diastereomeric products, because of the possible drastic difference of reactivity in biological matrices among stereoisomers. Fortunately, the diastereomers from the reaction mixture could be easily separated by column chromatography to obtain diastereomerically pure compounds.

To univocally assign the chirality of the newly formed stereocenters, 2D NOESY ^1H NMR spectra (Fig. 3) were acquired on the purified **3a** (**a**) and **3′a** (**b**).

These experiments permit to determine interproton distances through the measure of cross-peak volumes and thus determine molecular geometry (Aliev et al. 2012; Falk et al. 2001; Silvi et al. 2013; Carroccia et al. 2012; Aresu et al. 2013b, c). In fact, as reported (Jeener et al. 1979) starting from a reference cross peak whose interproton

Scheme 1 Procedure for the synthesis of *N*,*N*′-diprotected CF_3-modified dipeptides



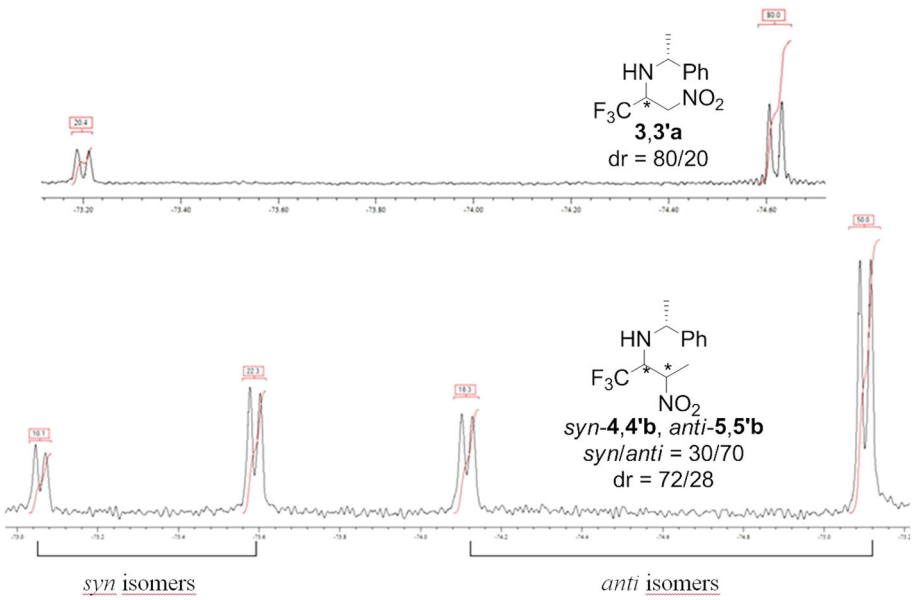


Fig. 2 ^{19}F NMR spectra performed on the crude mixtures of **3**,**3′a** and *syn*-**4**,**4′b** and *anti*-**5**,**5′b**

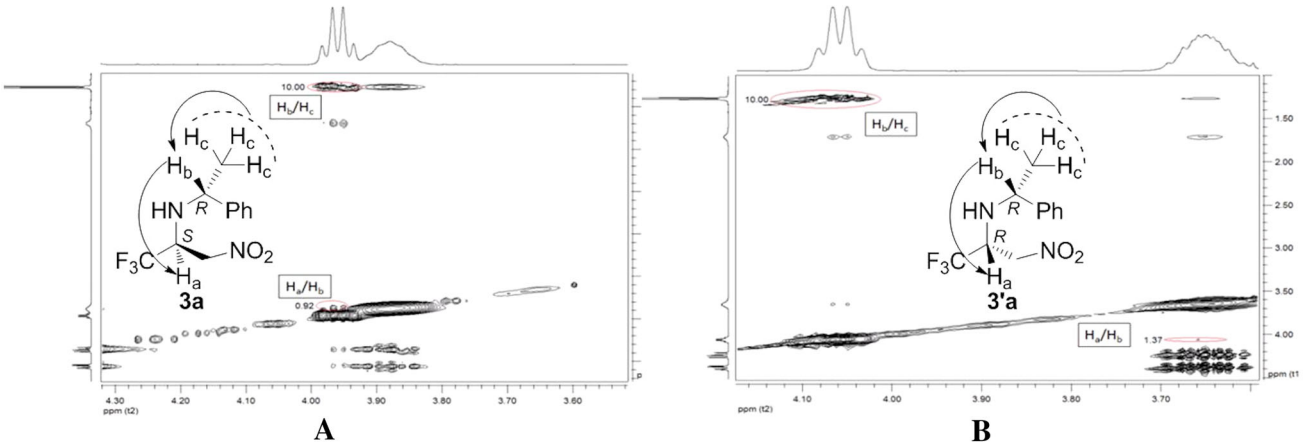


Fig. 3 2D NOESY of **3a** (**a**) and **3′a** (**b**). In both spectra the cross peaks corresponding to the interproton correlations H_a/H_b and H_b/H_c are evidenced

distance is known, it is possible to calculate the distances between other protons according to the following equation:

$$\frac{V_X}{V_R} = \left(\frac{d_R}{d_X}\right)^6,$$

in which V_R is the volume of the reference cross peak, d_R is the corresponding interproton distance and V_X is the volume relative to the unknown distance d_X.

Considering that the chiral center on the amine residue is always in *R* configuration, the interproton distance between H_b and the protons H_c in both **3** and **3′a** can be considered as a fixed value and employed as a ruler to determine the distance between H_a and H_b. On the basis of the optimized geometries of both diastereomers, 2.66 Å was found as the medium value of the interproton distance (d_R) between H_b and the protons H_c and the corresponding volume V_R was set at 10 arbitrary units (au). Therefore, the volumes relative to the cross peaks between H_a and H_b (V_X) were found to be 0.92 au for **3a** and 1.37 au for **3′a**, and the corresponding interproton distances (3.96 and 3.70 Å, respectively, with a confidence level of ∼3 %) (Jones et al. 2011) were calculated. Thus, comparing the collected data (Fig. 4), the absolute configurations of the new chiral centers, *S* for **3a** and *R* for **3′a**, were univocally assigned.

The results showed that the nucleophilic attack takes place preferentially on the less hindered *Si* face of the intermediate non-isolated (*E*,*R*)-trifluoromethyl imine **I**, probably following the mechanism reported in Scheme 3 for the synthesis of the major isomer (*R*,*S*)-**3a**, that involves the formation of the chiral metallic intermediate **II**.

Finally, 2D NOESY ^{1}H NMR spectra were performed also on *syn*-**4**,**4′b**,**c** *anti*-**5**,**5′b**,**c**, and the absolute

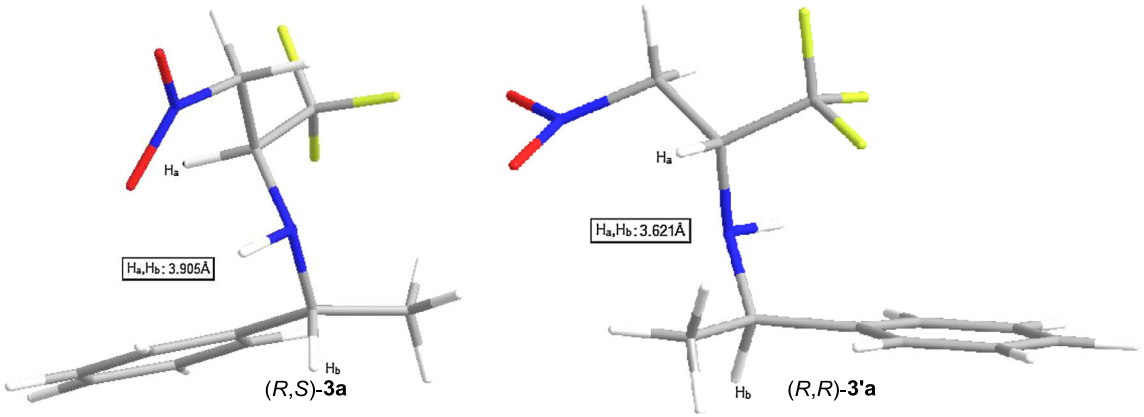
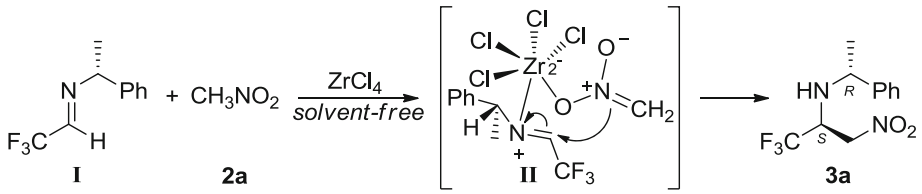
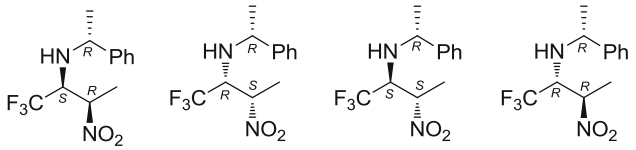


Fig. 4 Optimized geometries of (*R*,*S*)-**3a** and (*R*,*R*)-**3′a**

Scheme 3 Proposed pathway for the synthesis of the major isomer (*R*,*S*)-**3a**





syn/*anti* = 3/7; **4b**/**4b'**/**5b**/**5b'** = 2/1/5/2

Fig. 5 Absolute configurations of *syn*-**4**,**4′b** and *anti*-**5**,**5′b**

configurations of all new chiral centers of diastereomerically pure β-nitro α-trifluoromethyl amines were assigned (Fig. 5).

The obtained chiral β-nitro amines were considered in a selective reduction reaction of the nitro group to form the corresponding chiral β-diamines whose primary amine group may give a coupling reaction with *N*-protected α-amino acids under classical reaction conditions.

To test the procedure, the racemic mono-benzyl 1,2-diamine **7**, obtained from the corresponding β-nitro α-trifluoromethyl amine **6** (Fioravanti et al. 2012), was considered in a coupling reaction with *N*-Boc-Gly or *N*-Boc-l-Val performed in the presence of *N*,*N*′–dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) (Scheme 4).

The use of *N*-Boc-l-Val leads to diastereomers (*S*,*S*)-**9** and (*R*,*S*)-**9′** (Grishina et al. 2005) that were obtained as optically pure CF_3-modified dipeptides by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). The absolute configurations were assigned on the basis of NOESY analyses, following the above reported methodology and choosing like distance ruler the one between the proton of NH Boc-protected and the proton on the L-Valine chiral center. Due to the presence of two different *N*-protecting groups on the synthesized compounds, on the basis of the planned synthetic strategy it is possible to choose the further site of growth and molecular diversification. In fact, a hydrogenolysis reaction permits to remove the benzyl group, while an acidic hydrolysis leads to remove the Boc group.

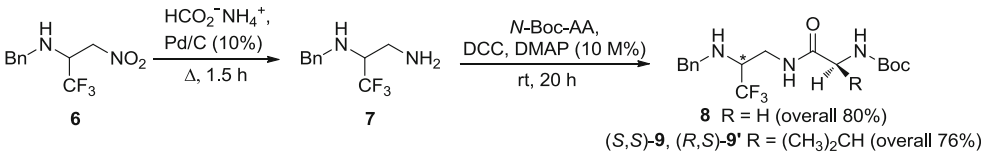
Then, the complete synthetic procedure was successfully performed starting from the optically pure β-nitro α-trifluoromethyl amines **3a** and **3′a** to obtain directly optically pure (*R*,*S*)-**11** and (*R*,*R*)-**11′a** (Scheme 5).

A subsequent hydrogenolysis reaction (Grishina et al. 2005) leads to the corresponding (*S*)-**12** and (*R*)-**12′a**, as chiral CF_3-modified dipeptides, in which the presence of a primary amine function can allow a further molecular growth.

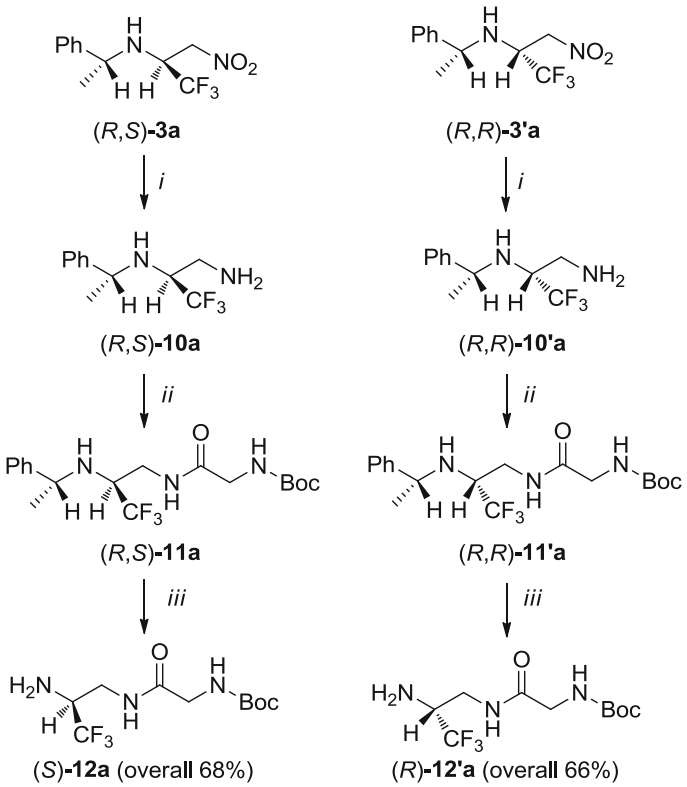
Conclusion

In conclusion, the synthesis of optically pure trifluoromethyl-modified dipeptides has been reported here. The process involves a tandem Zr-catalyzed aza-Henry addition–reduction reaction aiming to replace the natural [CONH] peptidic bond with the [$CH(CF_3)NH$] mimetic unit. Starting from the commercially cheap (*R*)-1-

Scheme 4 Coupling reaction with *N*-Boc-Gly or *N*-Boc-l-Val



Scheme 5 Synthetic procedure for *N*-Boc-protected optically pure CF_3-modified dipeptides



Reagents and conditions: *i:* HCO_2-NH_4^+ (5 eq), Pd/C (10 %M), CH_3OH, at reflux, 1.5 h; *ii: N*-Boc-Gly, DCC, DMAP (10 %M), CH_2Cl_2, rt, 24 h; *iii:* H_2, Pd/C (10 %M), anhydrous MeOH, rt, 24 h

phenylethylamine, a chiral metal complex was proposed as an intermediate to explain the stereoselective reaction outcome. The synthesis can be considered a green procedure, the one-pot key step taking place under solvent-free conditions. Moreover, the obtained compounds are suitable for potential combinatorial applications and for industrial use as building blocks for drug discovery, such as other different peptidomimetic structures reported by us (Fioravanti et al. 2010a, b; Aresu et al. 2013a).

Experimental

IR spectra were recorded on a Perkin-Elmer 1600 FT/IR spectrophotometer in $CHCl_3$ as the solvent. ^1H NMR and ^{13}C NMR spectra were recorded on a VARIAN XL-300 spectrometer at 300 and 75 MHz or by a Bruker Avance III at 400 and 101 MHz, respectively, at room temperature. $CDCl_3$ was used as the solvent and $CHCl_3$ and $CDCl_3$ as the internal standard for ^1H and ^{13}C, respectively. ^{19}F NMR spectra were recorded on a VARIAN XL-300 spectrometer at 282.2 MHz, using $CDCl_3$ as the solvent and C_6F_6 as the internal standard. The NOESY experiments were performed by a Bruker Avance III at 400 MHz using $CDCl_3$ as the solvent and $CHCl_3$ as the internal standard and used to assist in structure elucidation (Claridge 2009). HR-MS analyses were performed using a Micromass Q-TOF Micro quadrupole-time of flight (TOF) mass spectrometer equipped with an ESI source and a syringe pump. The experiments were conducted in the positive ion mode. Optical rotation was determined at 25 °C with a JASCD DIP-370 polarimeter at a wavelength of 589 nm, using a quartz cell of 1 cm length.

One-pot synthesis of β-nitro α-trifluoromethyl amines under solvent-free conditions: general procedure

A stirred equimolar solution (1 mmol) of trifluoroacetaldehyde ethyl hemiacetal (90 % aq. solution, 160 mg) and (*R*)-1-phenylethylamine (122 mg) was heated at 120 °C

under solvent-free conditions in a flask fitted with a calcium chloride tube. After 4 h, the reaction mixture was cooled to room temperature and $ZrCl_4$ (0.5 mmol, 116 mg) and nitro compound **2** (5 mmol) were added under stirring. The reactions were followed by ^1H and ^{19}F NMR (3–18 h, see Table 1). Then, after addition of water (5 mL), the crude mixtures were extracted three times with Et_2O. The collected organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The crude mixtures were purified by flash chromatography on silica gel.

Synthesis of **3** and **3′a**. Yield: 80 % (210 mg). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 9:1).

*(2S)-1,1,1-Trifluoro-3-nitro-N-[(1R)-1-phenylethyl]propan-2-amine (**3a**)*

Yellow pale oil (64 %, 168 mg). IR: 3,328, 1,570 cm^{-1}. $[\alpha]_D^{25}$ −79.0 (c = 4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J = 6.4 Hz, 3H), 1.79 (br, 1H), 3.91–4.02 (m, 1H), 4.05 (q, J = 6.4 Hz, 1H), 4.45 (dd, J = 12.8, 7.8 Hz, 1H), 4.65 (dd, J = 12.8, 4.6 Hz, 1H), 7.27–7.39 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.22, 55.5, 56.03 (q, J = 28.6 Hz), 73.9, 124.9 (q, J = 283.4 Hz), 126.6 (2C), 127.7, 128.6 (2C), 143.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.3 (d, J = 7.0 Hz). HR-MS (ESI/Q-TOF) *m/z* calcd for $C_{11}H_{14}F_3N_2O_2$ $[M + H]^+$ 263.1007, found 263.1011; *m/z* calcd for $C_{11}H_{13}F_3N_2NaO_2$ $[M + Na]^+$ 285.0827, found 285.0834.

*(2R)-1,1,1-Trifluoro-3-nitro-N-[(1R)-1-phenylethyl]propan-2-amine (**3′a**)*

Yellow pale oil (16 %, 42 mg). $[\alpha]_D^{25}$ −15.3 (c = 3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.5, 3H), 1.77 (br, 1H), 3.59–3.80 (m, 1H), 4.11 (q, J = 6.4, 1H), 4.29 (dd, J = 12.6, 9.3, 1H), 4.44 (dd, J = 12.6, 4.3, 1H), 7.15–7.38 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.8, 55.2 (q, J = 28.8 Hz), 55.9, 74.7, 125.3 (q, J = 286.2 Hz), 127.0 (2C), 127.9, 128.7 (2C), 142.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.9 (d, J = 6.6 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{11}H_{14}F_3N_2O_2$ $[M + H]^+$: 263.1007, found 263.1002; (*m/z*) calcd for $C_{11}H_{13}F_3N_2NaO_2$ $[M + Na]^+$: 285.0827, found 285.0821.

Synthesis of *syn*-**4,4′b** and *anti*-**5,5′b.** Yield: 76 % (210 mg). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 92:8). IR: 3,990, 1,550 cm^{-1}.

*(2S,3R)-1,1,1-Trifluoro-3-nitro-N-[(1R)-1-phenylethyl]butan-2-amine (syn-**4b**)*

Yellow oil (17 %, 46 mg). $[\alpha]_D^{25}$ −8.8 (c = 3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3H), 1.45 (d, J = 6.8 Hz, 3H), 1.74 (br, 1H), 3.65–3.78 (m, 1H), 3.89 (q, J = 6.3 Hz, 1H), 4.55–4.45 (m, 1H), 7.16–7.28 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.5, 22.7, 55.9, 58.4 (q, J = 27.6 Hz), 80.4, 124.3 (q, J = 284.9 Hz), 127.1 (2C), 127.7, 128.6 (2C), 142.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.6 (d, J = 6.9 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{12}H_{16}F_3N_2O_2$ $[M + H]^+$: 277.1164, found 277.1159; (*m/z*) calcd for $C_{12}H_{15}F_3N_2NaO_2$ $[M + Na]^+$: 299.0983, found 299.0978.

*(2R,3S)-1,1,1-Trifluoro-3-nitro-N-[(1R)-1-phenylethyl]butan-2-amine (syn-**4′b**)*

Yellow oil (7 %, 21 mg). $[\alpha]_D^{25}$ −16.4 (c = 3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J = 6.7 Hz, 3H), 1.42 (d, J = 7.7 Hz, 3H), 1.57 (br, 1H), 3.11–3.26 (m, 1H), 3.89 (q, J = 6.4 Hz, 1H), 4.50–4.59 (m, 1H), 7.08–7.17 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1, 22.7, 56.1, 59.6 (q, J = 28.5 Hz), 82.2, 124.3 (q, J = 284.9 Hz), 126.5, 127.3 (2C), 127.8 (2C), 142.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.1 (d, J = 6.7 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{12}H_{16}F_3N_2O_2$ $[M + H]^+$: 277.1164, found 277.1171; (*m/z*) calcd for $C_{12}H_{15}F_3N_2NaO_2$ $[M + Na]^+$: 299.0983, found 299.0986.

*(2S,3S)-1,1,1-Trifluoro-3-nitro-N-[(1R)-1-phenylethyl]butan-2-amine (anti-**5b**)*

Yellow oil (37 %, 105 mg). $[\alpha]_D^{25}$ −7.8 (c = 3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.4 Hz, 3H), 1.52 (d, J = 6.8 Hz, 3H), 1.89 (br, 1H), 3.90 (q, J = 6.3 Hz, 1H), 4.12–4.01 (m, 1H), 4.58–4.67 (m, 1H), 7.17–7.28 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.4, 22.8, 55.8, 58.7 (q, J = 28.3 Hz), 80.6, 124.8 (q, J = 284.1 Hz), 126.7, 127.7 (2C), 128.6 (2C), 144.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.10 (d, J = 7.4 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{12}H_{16}F_3N_2O_2$ $[M + H]^+$: 277.1164, found 277.1168; (*m/z*) calcd for $C_{12}H_{15}F_3N_2NaO_2$ $[M + Na]^+$: 299.0983, found 299.0977.

*(2R,3R)-1,1,1-Trifluoro-3-nitro-N-[(1R)-1-phenylethyl]butan-2-amine (anti-**5′b**)*

Yellow oil (15 %, 38 mg). $[\alpha]_D^{25}$ −8.0 (c = 3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 6.5 Hz, 3H), 1.60 (d, J = 8.0 Hz, 3H), 1.75 (br, 1H), 4.67–4.58 (m, 1H), 3.98 (q, J = 6.4 Hz, 1H), 4.63–4.74 (m, 1H), 7.14–7.30 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1, 22.7, 56.1, 59.3 (q, J = 28.4 Hz), 82.9, 124.6 (q, J = 284.5 Hz), 126.7 (2C), 127.7, 128.6 (2C), 144.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.1 (d, J = 7.1 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{12}H_{16}F_3N_2O_2$ $[M + H]^+$: 277.1164, found 277.1165; (*m/z*) calcd for $C_{12}H_{15}F_3N_2NaO_2$ $[M + Na]^+$: 299.0983, found 299.0984.

Synthesis of *syn*-**4**,**4′c** and *anti*-**5**,**5′c**. Yield: 72 % (210 mg). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 92:8). IR: 3,350, 1,560 cm^{-1}.

*(2S,3R)-1,1,1-Trifluoro-3-nitro-N-[(1R)-1-phenylethyl]pentan-2-amine (syn-**4c**)*

Yellow oil (16 %, 44 mg). $[\alpha]_D^{25}$ −14.5 (c = 3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 1.37 (d, J = 6.5, 3H), 1.56 (br, 1H), 1.95–2.07 (m, 2H), 3.56–3.62 (m, 1H), 4.05 (q, J = 6.4, 1H), 4.38–4.43 (m, 1H), 7.29–7.37 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.2, 24.2, 24.6, 55.9, 58.6 (q, J = 28.4 Hz), 88.5, 124.3 (q, J = 284.7 Hz), 126.5, 127.2 (2C), 128.7 (2C), 142.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.7 (d, J = 7.4 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{13}H_{18}F_3N_2O_2$ $[M + H]^+$: 291.1132, found 291.1137.

*(2R,3S)-1,1,1-Trifluoro-3-nitro-N-[(1R)-1-phenylethyl]pentan-2-amine (syn-**4′c**)*

Yellow oil (8 %, 25 mg). $[\alpha]_D^{25}$ +17.1 (c = 4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (t, J = 7.4 Hz, 3H), 1.30 (d, J = 6.5 Hz, 3H), 1.48 (br, 1H), 1.57–1.67 (m, 2H), 3.05–3.15 (m, 1H), 4.05 (q, J = 6.4 Hz, 1H), 4.40 (m, 1H), 7.18–7.30 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.2, 24.2, 24.7, 55.8, 58.0 (q, J = 27.8 Hz), 88.5, 124.3 (q, J = 284.6 Hz), 127.5 (2C), 127.8, 128.6 (2C), 142.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.6 (d, J = 6.9 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{13}H_{18}F_3N_2O_2$ $[M + H]^+$: 291.1132, found 291.1128.

*(2S,3S)-1,1,1-Trifluoro-3-nitro-N-[(1R)-1-phenylethyl]pentan-2-amine (anti-**5c**)*

Yellow oil (32 %, 90 mg). $[\alpha]_D^{25}$ −9.8 (c = 4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, J = 7.3 Hz, 3H), 1.34 (d, J = 6.5, 3H), 1.69 (br, 1H), 1.92–2.05 (m, 2H), 3.79–3.89 (m, 1H), 4.05 (q, J = 6.4, 1H), 4.52–4.57 (m, 1H), 7.27–7.35 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.5, 22.8, 23.0, 56.1, 59.0 (q, J = 28.2 Hz), 88.0, 124.5 (q, J = 284.4 Hz), 126.8 (2C), 127.7, 128.7 (2C), 143.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.7 (d, J = 7.4 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{13}H_{18}F_3N_2O_2$ $[M + H]^+$: 291.1132, found 291.1125.

*(2R,3R)-1,1,1-Trifluoro-3-nitro-N-[(1R)-1-phenylethyl]pentan-2-amine (anti-**5′c**)*

Yellow oil (16 %, 50 mg). $[\alpha]_D^{25}$ −13.6 (c = 4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, J = 7.4 Hz, 3H), 1.32 (d, J = 6.6, 3H), 1.70 (br, 1H), 2.12–2.25 (m, 2H), 3.56–3.64 (m, 1H), 4.10 (q, J = 6.4, 1H), 4.57–4.62 (m, 1H), 7.31–7.37 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.5, 21.8, 22.0, 56.3, 59.4 (q, J = 28.6 Hz), 90.1, 124.9 (q, J = 284.2 Hz), 126.8 (2C), 127.8, 128.3 (2C), 144.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.7 (d, J = 6.8 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{13}H_{18}F_3N_2O_2$ $[M + H]^+$: 291.1132, found 291.1139.

Reduction reactions: synthesis of (*R*,*S*)-**10a** and (*R*,*R*)-**10′a**

To a solution of **3a** or **3′a** (262 mg, 1 mmol) in anhydrous MeOH, under an inert atmosphere (Ar), anhydrous ammonium formate (310 mg, 5 mmol) and Pd/C 10 % (95 mg) were added. The reaction mixture was kept at reflux for 1.5 h and then filtered off to remove the catalyst. The solvent was evaporated under vacuum and 5 mL of water was added; the mixture was extracted three times with Et_2O. The collected organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum.

*(2S)-3,3,3-Trifluoro-N^2-[(1R)-1-phenylethyl]propane-1,2-diamine [(R,S)-**10a**]*

Yellow oil. Yield: 81 % (188 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). $[\alpha]_D^{25}$ +12.7 (c = 5, $CHCl_3$). IR: 3,488, 3,395 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 6.4 Hz, 3H), 1.89 (br, 3H), 2.76 (dd, J = 13.4, 5.7 Hz, 1H), 2.87–3.03 (m, 2H), 3.97 (q, J = 6.4 Hz, 1H), 7.17–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 39.4, 55.2, 57.9 (q, J = 26.1 Hz), 126.2 (q, J = 284.3 Hz), 126.7 (2C), 127.3, 128.5 (2C), 144.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.4 (d, J = 7.7 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{11}H_{16}F_3N_2$ $[M + H]^+$: 233.1266, found 233.1272.

*(2R)-3,3,3-Trifluoro-N^2-[(1R)-1-phenylethyl]propane-1,2-diamine [(R,R)-**10′a**]*

Yellow oil. Yield: 80 % (186 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). $[\alpha]_D^{25}$ +14.2 (c = 4.5, $CHCl_3$). $\underline{\nu}_{max}$ 3,488, 3,395 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, J = 6.5 Hz, 3H), 1.57 (br, 3H), 2.59 (dd, J = 12.3, 7.5 Hz, 1H), 2.68–2.85 (m, 2H), 4.09 (q, J = 6.3 Hz, 1H), 7.35–7.20 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 40.9, 56.2, 58.2 (q, J = 25.7 Hz), 126.4 (q, J = 284.6 Hz), 127.0 (2C), 127.4, 128.5 (2C), 144.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.1 (d, J = 6.5 Hz). HR-MS (ESI/Q-TOF) (*m/z*) calcd for $C_{11}H_{16}F_3N_2$ $[M + H]^+$: 233.1266, found 233.1258.

Coupling reactions: general procedure

To a solution of **7** (33 Fioravanti et al. 2012), (*R*,*S*)-**10a** or (*R*,*R*)-**10′a** (0.5 mmol) in 10 mL of CH_2Cl_2 equimolar amounts of α-amino acid *N*-Boc-protected, *N*,*N*′-dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4-dimethylaminopyridine (DMAP, 10 % M) were added. After 24 h of stirring at room temperature, the crude mixture was filtered off to remove the formed *N*,*N*′-dicyclohexylurea (DCU) and the solvent was evaporated under vacuum.

*tert-Butyl (2-{[2-(benzylamino)-3,3,3-trifluoropropyl]amino}-2-oxoethyl)carbamate (**8**)*

White viscous oil. Yield: 90 % (202 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 85:25). ν_{max} 3,450, 3,342, 1,718, 1,677 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.67 (br, 1H), 3.07–3.31 (m, 2H), 3.57–4.12 (m, 5H), 5.06 (br, 1H), 6.48 (br, 1H), 7.15–7.44 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 28.1 (3C), 44.2, 51.5, 57.7 (q, J = 27.0 Hz), 80.2, 125.9 (q, J = 283.8 Hz) 127.3 (2C), 128.2, 128.4 (2C), 139.1, 156.0, 170.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.8 (d, J = 5.9 Hz). HR-MS (ESI/Q-TOF) (*m*/*z*) calcd for $C_{17}H_{25}F_3N_3O_3$ $[M + H]^+$: 376.1770, found 376.1778; (*m*/*z*) calcd for $C_{17}H_{24}F_3N_3NaO_3$ $[M + Na]^+$: 398.1667, found 398.1659.

*tert-Butyl [(2S)-1-{[(2S)-2-(benzylamino)-3,3,3-trifluoropropyl]amino}-3-methyl-1-oxobutan-2-yl]carbamate (S,S-**9**)*

Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). White viscous oil. Yield: 42 % (105 mg). $[\alpha]_D^{25}$ −14.1 (c = 3, $CHCl_3$). ν_{max} 3,440, 3,342, 1,708, 1,670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H), 1.36 (s, 9H), 2.01 (br, 1H), 3.04–3.18 (m, 1H), 3.63–4.00 (m, 6H), 4.96 (br, 1H), 6.29 (br, 1H), 7.15–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (2C), 28.2 (3C), 30.6, 37.5, 51.5, 57.1–59.0 (q, J = 26.7 Hz), 60.1, 82.3, 125.6 (q, J = 284.1 Hz), 127.4, 128.2 (2C), 128.6 (2C), 139.1, 172.0, 179.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.6 (d, J = 5.0 Hz). HR-MS (ESI/Q-TOF) (*m*/*z*) calcd for $C_{20}H_{31}F_3N_3O_3$ $[M + H]^+$: 418.2239, found 418.2243; (*m*/*z*) calcd for $C_{20}H_{30}F_3N_3NaO_3$ $[M + Na]^+$: 440.2137, found 440.2129.

*tert-Butyl [(2S)-1-{[(2R)-2-(benzylamino)-3,3,3-trifluoropropyl]amino}-3-methyl-1-oxobutan-2-yl]carbamate (R,S-**9′**)*

Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). White viscous oil. Yield: 44 % (110 mg). $[\alpha]_D^{25}$ −10.5 (c = 4, $CHCl_3$). ν_{max} 3,440, 3,343, 1,710, 1,671 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H), 1.38 (s, 9H), 2.13 (br, 1H), 3.02–3.19 (m, 1H), 3.64–3.98 (m, 6H), 4.89 (br, 1H), 6.31 (br, 1H), 7.15–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (2C), 28.3 (3C), 30.4, 37.6, 51.4, 57.7 (q, J = 26.9 Hz), 60.0, 80.1, 125.8 (q, J = 284.3 Hz), 127.5, 128.4 (2C), 128.6 (2C), 139.1, 155.8, 171.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.7 (d, J = 5.3 Hz). HR-MS (ESI/Q-TOF) (*m*/*z*) calcd for $C_{20}H_{31}F_3N_3O_3$ $[M + H]^+$: 418.2239, found 418.2242; (*m*/*z*) calcd for $C_{20}H_{30}F_3N_3NaO_3$ $[M + Na]^+$: 440.2137, found 440.2131.

*tert-Butyl (2-oxo-2-{(2S)-3,3,3-trifluoro-2-[(1R)-1-phenylethylamino]propylamino}ethyl) carbamate [(R,S)-**11a**]*

Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). White viscous oil. Yield: 91 % (212 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). $[\alpha]_D^{25}$ +10.4 (c = 3, $CHCl_3$). ν_{max} 3,450, 3,342, 1,708, 1,667 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3H), 1.85 (s, 9H), 1.86 (br, 1H), 3.66–3.86 (m, 4H), 3.96–4.02 (m, 2H), 5.29 (br, 1H), 6.64 (br, 1H), 7.18–7.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 24.7, 28.2 (3C), 44.5, 55.3, 56.0 (q, J = 26.8 Hz), 80.4, 126.5 (q, J = 284.6 Hz), 126.8 (2C), 127.3, 128.5 (2C), 144.4, 156.1, 169.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.0 (d, J = 7.8 Hz). HR-MS (ESI/Q-TOF) (*m*/*z*) calcd for $C_{18}H_{27}F_3N_3O_3$ $[M + H]^+$ 390.2005, found 390.1997; (*m*/*z*) calcd for $C_{18}H_{26}F_3N_3NaO_3$ $[M + Na]^+$: 412.1824, found 412.1831.

*tert-Butyl (2-oxo-2-{(2R)-3,3,3-trifluoro-2-[(1R)-1-phenylethylamino]propylamino}ethyl) carbamate [(R,R)-**11′a**]*

Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). White viscous oil. Yield: 89 % (208 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). $[\alpha]_D^{25}$ +8.9 (c = 3, $CHCl_3$). ν_{max} 3,457, 3,352, 1,728, 1,668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J = 6.5 Hz, 3H), 1.45 (s, 9H), 1.89 (br, 1H), 3.50–3.77 (m, 4H), 3.96–4.12 (m, 2H), 5.13 (br, 1H), 6.46 (br, 1H), 7.41–7.17 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 24.9, 28.2 (3C), 44.2, 56.4 (q, J = 26.9 Hz), 60.3, 80.3, 126.8 (q, J = 284.5 Hz), 126.9 (2C), 127.6, 128.7 (2C), 144.1, 156.0, 169.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.2 (d, J = 5.6 Hz). HR-MS (ESI/Q-TOF) (*m*/*z*) calcd for $C_{18}H_{27}F_3N_3O_3$ $[M + H]^+$: 390.2005, found 390.1999; (*m*/*z*) calcd for $C_{18}H_{26}F_3N_3NaO_3$ $[M + Na]^+$: 412.1824, found 412.1819.

Synthesis of *N*-Boc-protected CF_3-modified dipeptides (*S*)-**12** and (*R*)-**12′a**

In a two-neck flask trifluoromethyl dipeptides (*R*,*S*)-**11** and (*R*,*R*)-**11′a** (0.4 mmol) were dissolved in 5 mL of anhydrous MeOH and 60 mg of 10 % Pd/C were added. The reaction mixtures were hydrogenated under atmospheric pressure at room temperature for 24 h after which the crude mixtures were filtered off to remove the catalyst and the solvent was removed by evaporation at reduced pressure.

*tert-Butyl (2-{[(2S)-2-amino-3,3,3-trifluoropropyl]amino}-2-oxoethyl)carbamate [(S)-**12a**]*

Yellow pale oil. Yield: 95 % (150 mg). $[\alpha]_D^{25}$ –5.5 ($c = 3.5$, $CHCl_3$). IR: 3,390, 3,342, 1,708, 1,667 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.75–3.85 (m, 4H), 4.05–4.30 (m, 1H), 5.13 (br, 2H), 6.60 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1 (3C), 33.6, 41.0, 53.6 (q, $J = 27$ Hz), 80.3, 124.8 (q, $J = 283.7$ Hz), 156.8, 162.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.3 (d, $J = 3.9$ Hz). HR-MS (ESI/Q-TOF) (*m*/*z*) calcd for $C_{10}H_{18}F_3N_3O_3$ $[M + H]^+$: 286.1300, found 286.1305; (*m*/*z*) calcd for $C_{10}H_{18}F_3N_3NaO_3$ $[M + Na]^+$: 308.1198, found 308.1205.

*tert-Butyl (2-{[(2R)-2-amino-3,3,3-trifluoropropyl]amino}-2-oxoethyl) carbamate [(R)-**12′a**]*

Yellow pale oil. Yield: 93 % (141 mg). $[\alpha]_D^{25}$ +5.5 ($c = 3$, $CHCl_3$).

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