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Tri- and tetrafluoropropionamides derived from chiral secondary amines – synthesis and the conformational studies

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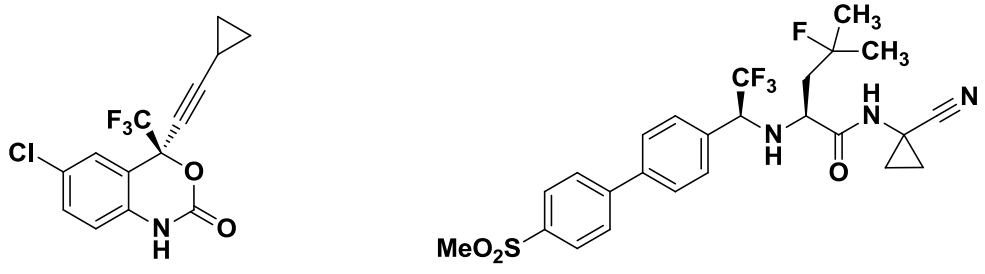
Abstract

A convenient procedure for the preparation of tri- and tetrafluoropropionamides derived from *R*-(+)/*S*-(-)-*N*-methyl-1-phenylethylamine and cyclic pyrrolidine derivative has been described. The X-ray analysis and the theoretical calculations have been used to study conformational analysis of obtained compounds. In contrast to a single *α*-fluorine substituted amides, which preferred *anti* conformation around F-C-C=O bond, for tetrafluorinated amides the additional trifluoromethyl group forces the conformation of the F-C-C=O as nearly *syn*.

Introduction

Amide bond is of key importance for all living organism as the main chemical bond linking amino acids in peptides and proteins. Peptides play a crucial role in most of biological processes, such as enzymatic catalysis, immune protection and others [1, 2]. Fluorinated amides are very interesting species in the design of peptide mimetics, as amino acids derivatives and as traditional fluorine modified drugs [3, 4]. It is well known that the introduction of fluorine or fluorine-containing groups into organic molecules can cause considerable changes in the physical, chemical and biological properties [5-7]. Fluorination can change biological activity, as well as physical properties such as lipophilicity etc. Some examples of new drugs, being trifluoromethylated amido compounds, are Efavirenz (anti-HIV) [8, 9] and Odanacatib (inhibitor of cathepsin K) [10] (Fig. 1). Moreover, *α*-hydroxy-*α*-trifluoromethylated amides arouse interest due to their structural analogy to some of the antiandrogens used in the treatment of prostate cancer in humans [11].



Efavirenz Odanacatib

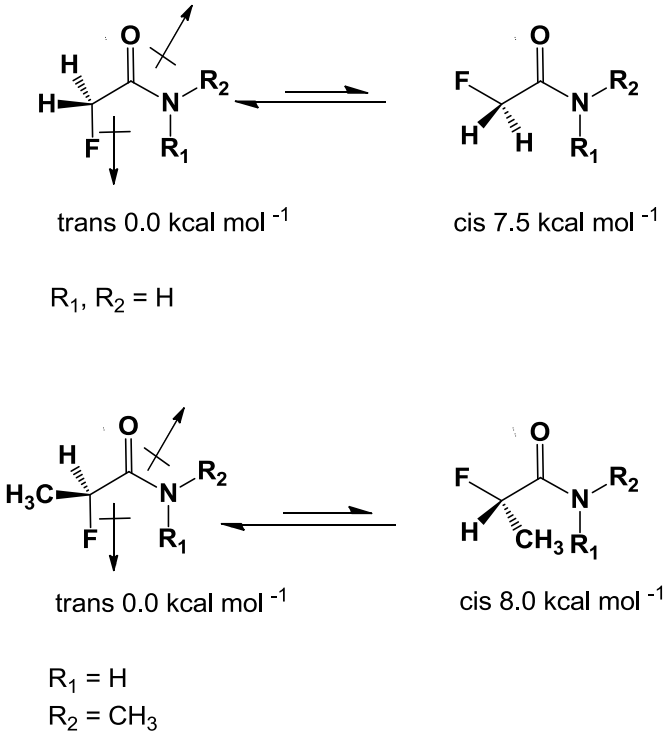
Fig. 1. Examples of biologically active trifluoromethylated amido compounds.

The introduction of a *gem*-difluoromethylene group has been proved to increase the biological activity of many pharmaceuticals containing *β*- and *γ*-lactam groups. For example,

gem-difluoro-*γ*-lactam inhibits *γ*-lactamase, an enzyme responsible for bacterial resistance to *γ*-lactam antibiotics [12]. Moreover *gem*-difluoropropargyl amides are useful as suitable building blocks for the synthesis of fluorinated *δ*-lactams via cycloisomerization [13]. Another example for application the fluorine-containing compounds in synthesis are trifluoroacetamide analogues that serve as an efficient enantioselective nucleophilic trifluoromethylating reagents [14, 15].

Recently, the tri- and tetrafluorinated amides have been studied in our group [16]. As it has been previously reported by Ishikawa [17], it has been shown that the hydrolysis of fluorinated enamines or enamines/amines mixture, has given the corresponding fluorinated amides. Additionally, the formation of the *γ, δ*-unsaturated amides, containing the fluorine atom or the CF_3 group at the *α* position to the carbonyl group, via Claisen rearrangement has been reported [18-20].

Presence of fluorine atom in organic molecules can have a significant influence on the preferred conformation. O'Hagan et al. have shown recently, that this effect is particularly noticeable in a group of fluorinated carbonyl compounds, especially in amides [21, 22]. When fluorine atom is placed in the *α* position to the carbonyl group of an amide it adapts an *anti* conformation with respect to the C=O group and *syn* with respect to the C-N bond. This is a substantial effect of thermodynamic stability estimated to be about 7.5-8.0 kcal mol^{-1} (Scheme 1) [7].



Scheme 1. The energy difference between the *trans* and *cis* conformers of *α*-fluoroamides.

Considering the presence of fluorine atom in *β* position with respect to the nitrogen atom of an amide, the fluorine atom adopts a conformation in which the C-N and C-F bonds are oriented *gauche* to each other, with dihedral angle of approximately 63° (Fig. 2) [23].

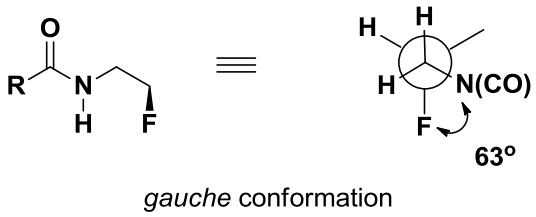
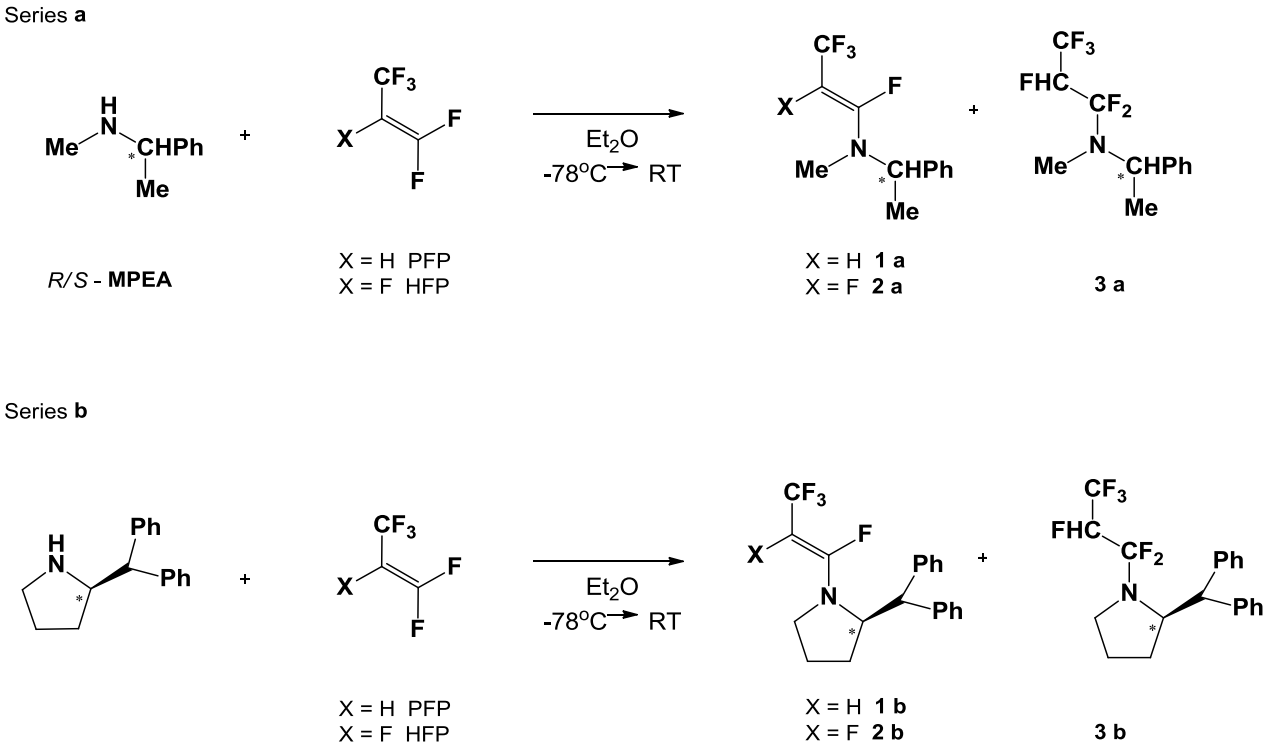


Fig. 2.

In this paper we would like to focus on the synthesis and the conformational analysis of tri- and tetrafluoropropionic acid amides. Addition of hexafluoropropene and 1,1,3,3,3-pentafluoropropene to chiral secondary amines, reaction products distribution, and their usefulness as the new reagents for deoxyfluorination will be published elsewhere.

Results and discussion

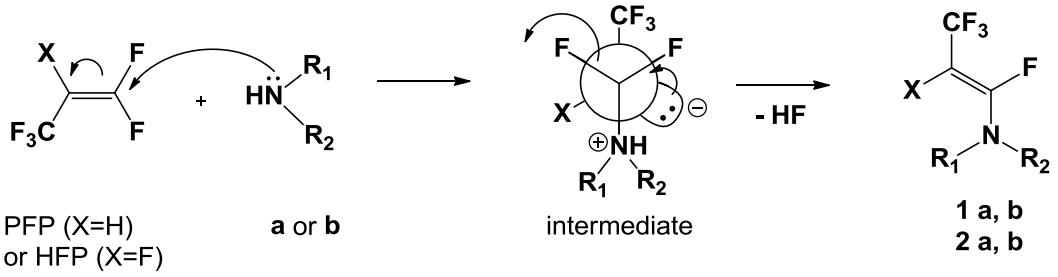
The synthesis of fluorinated amides has been based on the reactions of chiral secondary amines with commercially available 1,1,3,3,3-pentafluoropropene (PFP) or hexafluoropropene (HFP). As the model amines, two enantiomeric *R*-(+)/*S*-(-)-*N*-methyl-1-phenylethylamine (*R*/*S*- MPEA: *Series* **a**), and cyclic pyrrolidine derivative (*Series* **b**) have been chosen. The first step of synthesis, in case of reaction PFP with MPEA, has given the tetrafluorinated enamine **1a** (Scheme 2) with a 73% yield, determined by ^{19}F NMR.



Scheme 2. The synthesis of enamines and mixtures of enamines/amines.

Changing the solvents to THF or DCM, or increasing temperature (reflux) of this reaction had no influence on the yield. Analysis of ^{19}F NMR spectra of **1a** confirmed the enamine

formation, where one signal of the CF_3 group appeared at δ: -52.7 ppm (dd) and the second signal from vinylic fluorine atom at δ: -92.7 ppm (dq). The *Z*-configuration of enamine **1a** was established on the basis on vinylic fluorine and vicinal hydrogen atom coupling constants values. Characteristic coupling constant for *trans* arrangement is $J^3_{F\text{-}H}$ = 30.7 Hz, whereas the second (q) coupling constants was equal 15.2 Hz ($J^4_{F\text{-}CF3}$). Usually for F and H in *trans* arrangement coupling constant *J* varies from 27-32 Hz, while for *cis* geometry of the double bond *J* ranges from 4-6 Hz [24-26]. Exclusive formation of *Z*-isomer of **1a**, could be explained by preferential formation of the most stable zwitterion intermediate, having the CF_3 and NR_1,R_2 groups in antiperiplanar arrangement, followed by *anti* fluoride anion elimination (Scheme 3) [17, 27].



Scheme 3. The formation of *Z*-isomer of **1a**, **b** (**2a**, **b**).

The high stereoselectivity of enamine formation is of striking difference from the previously reported results of the reaction of PFP with some pyrimidine or purine derivatives [27]. Thus, the reactions carried out in DMF (NaH, RT or 60-70°C) yielded high *Z*/*E* ratio of enamines in reaction mixtures. On the other hand, the reactions of PFP with Et_2NH or Me_2NH, led to *Z*-enamines and only traces of corresponding saturated tertiary fluoroalkylamines [16]. Analogous reaction of PFP with cyclic amine-pyrrolidine derivative (*series* **b**) has given *Z*-enamines **1b** as the only product, with a 54% yield, what was determined by ^{19}F NMR. The *Z*-geometry at double bond in enamine **1b** was confirmed by chemical shifts analysis of ^{19}F NMR, i.e. δ: -51.7 ppm (CF_3 group), while vinylic fluoride signal appeared at δ: -87.1 ppm with corresponding coupling constant $J^3_{F\text{-}H}$ = 29.2 Hz (Table 1). These results are in good agreement with previously reported spectral characteristic of PFP-pyrrolidine enamine product [16].

Analogous reaction of appropriate chiral amine (**a** or **b**) with HFP has led to a mixture of enamine and fluorinated tertiary amine **2a/ 3a** with a 79% yield (the ratio of enamine/amine **2a**/**3a** was 1:2), while for **2b/ 3b** yield was 65% and the ratio 1:32 (Scheme 3).

The analysis of ^{19}F NMR spectra of **2a** has indicated the stereochemistry of enamine double bond, similarly to the reaction with PFP, as *E*-geometry. It has been confirmed by higher values of coupling constants ($J^3_{F\text{-}F}$ =118.7 Hz, *trans*) between both vicinal fluorine atoms (δ: -114.5 and δ: -193.5), while signals of CF_3 group have appeared at δ: -65.8 as dd ($J^4_{CF3\text{-}F}$=13.6 Hz, $J^3_{CF3\text{-}F}$=23.1 Hz). Analogous signals for **2b** has appeared at δ: -116.8 and -198.8 with $J^3_{F\text{-}F}$=116.4 Hz (indicating *E*-enamine) and δ: -65.0 (CF_3). Noteworthy, that the reaction of secondary amine with HFP has given mainly Michael type addition products - saturated amines **3a** and **3b**. The fluorine atoms signals of pentafluorinated tertiary amine were located

for **3a** at δ: -74.5 ÷ -74.7 (CF_3) and diastereotopic (-CF_2-) fluorine atoms at δ: -81.5 ÷ -87.5 and δ: -87.7 ÷ -93.3 (multiplets), while for **3b** were situated at δ: -74.8 ÷ -75.0 (CF_3), and at δ: -85.6 ÷ -86.6 (1F) and at δ: -90.4 ÷ -91.5 (1F). High-field shifted fluorine atom signal of CH*F*CF_3 was situated at δ: -207.8 ÷ -208.3 ppm (multiplet) for **3a**, and at δ: -205.5 ÷ -206.0 for **3b** as multiplet, respectively (Table 1).

Table 1. ^{19}F NMR chemical shifts (ppm) and coupling constants for enamines **1a** (**1b**), **2a** (**2b**) and amines **3a** (**3b**)

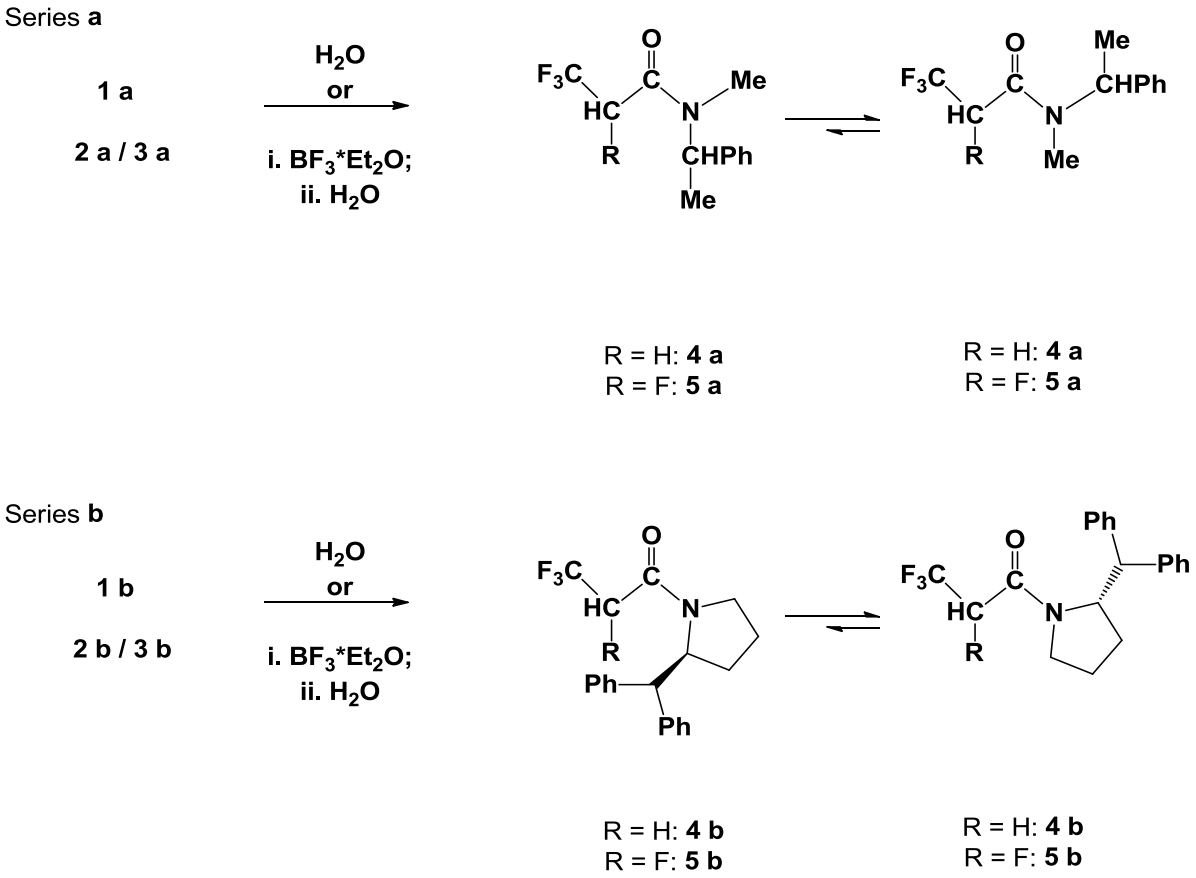
Products		Yield[a] [%]	CF_3	F_α [b]	F_β [b]
Enamines	**1a**	73	-52.7 (dd, J^4=15.2 Hz, J^3=7 Hz)	-92.7 (dq, J^3=30.7 Hz, J^4=15.2 Hz)	n/a
	1b	54	-51.7 (dd, J^4=14.6 Hz, J^3=7.1 Hz)	-87.1 (dq, J^3=29.2 Hz, J^4=14.6 Hz)	n/a
	2a	24	-65.8 (dd, J^4=13.6 Hz, J^3=23.1 Hz)	-193.5 (dq, J^3=118.7 Hz, J^4=13.5 Hz)	-114.5 (dq, J^3=118.8 Hz, J^4=22.6 Hz)
	2b	2	-65.0 (dd, J^4=14.4 Hz, J^3=22.8 Hz)	-198.8 (dq, J^3=118.1 Hz, J^4=13.4 Hz)	-116.8 (dq, J^3=116.4 Hz, J^4=22.8 Hz)
Amines	**3a**	55	-74.5 ÷ -74.7 (m)	-81.5 ÷ -87.5 (m) -87.7 ÷ -93.3 (m)	-207.8 ÷ -208.3 (m)
	3b	63	-74.8 ÷ -75.0 (m)	-85.6 ÷ -86.6 (m) -90.4 ÷ -91.5 (m)	-205.5 ÷ -206.0 (m)

[a] Yield determined by ^{19}F NMR using *m*-fluorotoluene as an internal standard (δ=-114.1(m, 1F)).

[b] Position α and β determined in relation to nitrogen atom.

The formations of major fluoroalkylamines and *E*-enamines, as well as their spectral properties are parallel with analogous results reported by Ishikawa et al. [17]. Thus, reaction of diethylamine, *n*-Bu_2NH or piperidine with HFP yields an enamine/amine mixture with a different ratio depending on substituent bulkiness. In case of piperidine as a starting material the only product is amine, while for Et_2NH as a substrate, the amine/enamine ratio is 1:3. On the other hand, the reaction of uracil, cytidine or guanine derivatives with HFP results in mixtures of *E/Z* isomeric enamines in almost 1:1 ratio, while for adenine analogue the ratio is 2:1 – with a major product being *E*-geometry enamine [27]. Additionally, due to reaction conditions (secondary amine and sodium hydride) fluorinated alkylamine (major product in our case) were not detected in reaction mixture.

Subsequent H_2O addition to **1a, 1b** enamine double bonds has given 3,3,3-trifluoropropionamide **4a, 4b**, while reactions of water with **2a, 2b** has given tetrafluorinated analogues **5a, 5b**. Interestingly, contrarly to prompt hydrolysis of enamines, in case of hydrolysis of fluorinated amines **3a**/**3b** addition of Lewis acid such as BF_3*Et_2O has been necessary (Scheme 4).



Scheme 4. The hydrolysis reaction of **1a**, **1b** (**2a**, **3a**/**2b**, **3b**).

Therefore, as a result of water addition to **1a** and **1b,** the trifluoropropionamide derivatives **4a** and **4b** were isolated from reaction mixtures with a 57% and 38% yield, respectively. Analysis of ^{19}F NMR spectra of **4a** has indicated two triplets at δ: – 62.9 and δ: – 62.8 ($J^{3}_{CF3\text{-}H}$=10.0 Hz) in 71:29 ratio. The phenomenon of existence of two sets of signals in magnetic resonance spectra is well known in case of amides. Thus, due to hindered rotation about partially double amide bond C-N, both *N*-substituent groups are chemically non-equivalent and compounds can exist as two rotamers: *cisoid* and *transoid*, considering the orientation with respect to carbonyl group. Alike, in ^{1}H NMR spectrum of *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMA), both *N*-methyl groups have separate signals [28]. The observed chemical shifts values in ^{1}H NMR spectrum of methyl groups are δ: 2.85 ppm and δ: 2.94 ppm for DMF, while for DMA they appear at δ: 2.93 ppm and δ: 3.03 ppm, respectively. In case of *N*,*N*-dimethyl-3,3,3-trifluoropropionamide, in ^{1}H NMR spectrum signals from H atoms of both *N*-neighboring methyl groups are observed at δ: 3.3 and δ: 3.4 ppm, while in ^{19}F NMR spectra fluorine signal of CF_3 group was located at δ: –63.2 ppm as triplet [16]. Similarly, the compound **4a** can exist as two rotamers (Scheme 4): *transoid* (*trans* **4a**) with larger substituent at nitrogen located in opposite direction to carbonyl group and in the reverse direction as rotamer *cisoid* (*cis* **4a**). The analysis of ^{19}F NMR spectra has shown two signals: the one of major rotamer has been located at δ: –62.9, while for minor rotamer of **4a** it has appeared at δ: – 62.8 (CF_3 group)**.** Considering the ^{1}H NMR spectra of **4a** major and minor rotamer, they indicated that the

signals of *C*-methyl and *N*-methyl groups for major rotamer have been located at δ: 1.42 and δ: 2.60, whereas for minor rotamer have appeared at δ: 1.56 and δ: 2.65. Also methylene protons of trifluoropropionic part for major rotamer have been slightly shifted upfield to δ: 3.18, comparing to δ: 3.26 for the minor one. Interestingly, while the chemical shift of aromatic protons for both rotamers were parallel, the difference of the benzylic protons chemical shift for major and minor rotamers is Δδ =1.03 ppm (δ: 5.99 for major and δ: 4.95 for minor rotamer, respectively).

Table 2. ^{1}H NMR, ^{19}F NMR chemical shifts (ppm) for trifluoropropionamide derivatives and a reference amide IPMA

	Major					**Minor**				
	C*F*$_3$	CF$_3$-C*H*$_2$	N-R$_1$*	N-R$_2$*	C*H*$_3$**	C*F*$_3$	CF$_3$-C*H*$_2$	N-R$_1$*	N-R$_2$*	C*H*$_3$**
IPMA	n/a	n/a	2.83	4.52	1.03	n/a	n/a	2.70	3.92	1.15
4a	-62.9	3.18	2.60	5.99	1.42	-62.8	3.26	2.65	4.95	1.56
4b	-62.7	2.44	3.34	4.43	n/a	-63.3	2.49	3.56 /3.87	3.17	n/a

* **IPMA**: R$_1$ =C*H*$_3$, R$_2$=C*H*(CH$_3$)$_2$; **4a**: R$_1$ = C*H*$_3$, R$_2$ = C*H*CH$_3$Ph; **4b**: R$_1$ = C*H*$_2$CH$_2$, R$_2$ = C*H*CH(Ph)$_2$

** **IPMA**: CH(C*H*$_3$)$_2$; **4a**: CHC*H*$_3$Ph

The relationship of the chemical shift values and *N*-neighboring group arrangement in disubstituted amides has already been reported. In case of *N*-isopropyl-*N*-methyl acetamides (IPMA) the predominant *cis* geometry (*Z*) of the *i*-Pr and the carbonyl C=O groups, has been determined [29]. Thus, the *cis* rotamer signals for *N*-methyl and *N*-C*H*(CH$_3$)$_2$ protons occur at δ: 4.52 and δ: 2.83, whereas for minor *trans* rotamer they occur at δ: 3.92 and δ: 2.70, respectively. The comparison of chemical shifts values of benzylic and *N*-methyl protons for both rotamers of **4a**, and similarity to IPMA relationships have helped to establish the main rotamer of **4a** as having *cis* geometry, while the minor rotamer has been determined as having *trans* geometry.

Similarly, in ^{13}C NMR spectra of *cis* and *trans* isomers of **4a**, both sets of signals are typical and analogous for both isomers, with the exceptions of *N*-neighboring atoms like carbons of C-*C*H$_3$ signal at δ: 15.4 for *cis* **4a** and at δ: 17.9 for *trans* **4a**, whereas *N*-methyl group signal for *cis* **4a** has been located at δ: 30.1 and for *trans* **4a** at δ: 28.4. Simultaneously, similarly to ^{1}H NMR spectra, the largest chemical shift difference has been observed in case of the benzyl carbon atoms signals (*C*-Ph). Thus, signal for major *cis* **4a** has been shifted downfield (δ: 50.8) comparing to *trans* **4a** (δ: 55.7).

As a result of **1b** hydrolysis, the 3,3,3-trifluoropropionamide **4b,** as a mixture of two rotamers with a 53:47 ratio, has been isolated. The comparison of the signals in ^{1}H NMR spectra, due to the larger difference in chemical shifts of protons at chiral carbon, has helped matching the major rotamer with N-C*H*C proton shift δ: 4.43 as *cis* **4b**. The minor rotamer with the analogous proton signal situated at δ: 3.17 has been determined as *trans* **4b**. These data are also in agreement with spectral characterisic of pyrrolidine acetamide [30, 31]. While the chemical shifts of the remaining analogous protons in both **4b** rotamers have been similar, in

^{19}F NMR spectra the *cis* and *trans* **4b** rotamers CF_3 groups signals have appeared at δ: -62.7 and -63.3, respectively.

Next, the hydrolysis reactions of enamine/amine mixture **2a/3a** and **2b/3b** have been performed. The hydrolysis of **2a/3a** mixture has led to formation of **5a** being a mixture of diastereomers (*R,R*)/(*R,S*) **5a** (in 49:51 ratio) with a 78% isolated yield. Separation of both diastereoisomers has given two fractions (after column chromatography) - crystals and the oil - each consisting of two rotameric forms (77:23 ratio).

Table 3. ^{1}H NMR, ^{19}F NMR chemical shifts (ppm) for tetrafluoropropionamide derivatives and a reference amide IPMA

	Major					**Minor**				
	C*F*$_3$	C*F*/C*H*	N-R$_1$*	N-R$_2$*	C*H*$_3$**	CF_3	C*F*/C*H*	N-R$_1$*	N-R$_2$*	C*H*$_3$**
IPMA	n/a	n/a	2.83	4.52	1.03	n/a	n/a	2.70	3.92	1.15
5a (*R,R*)	-75.6	-199.2 / 5.43	2.76	6.05	1.54	-75.5	-196.1 / 5.52	2.72	5.30	1.66
5a (*R,S*)	-75.6	-199.5 / 5.42	2.74	6.02	1.55	-75.5	-197.6 / 5.53	2.71	5.24	1.67
5b (*S,S*)	-75.7	-200.7 /5.11	3.08-3.28	3.74-3.82	n/a	-76.6	-202.7 /5.05	3.08-3.28	3.74-3.82	n/a
5b (*S,R*)	-75.7	-200.6 /4.92	3.40-3.64	4.08-4.17	n/a	-76.6	-203.7 /4.93	3.40-3.64	4.00-4.08	n/a

* **IPMA**: $R_1 = CH_3$, $R_2 = CH(CH_3)_2$; **5a**: $R_1 = CH_3$, $R_2 = CHCH_3Ph$; **5b**: $R_1 = CH_2CH_2$, $R_2 = CHCH(Ph)_2$

** **IPMA**: $CH(CH_3)_2$; **5a**: $CHCH_3Ph$

Similarly to compound **4a** and **4b** the comparison of the ^{1}H NMR spectra and the correlation of protons chemical shifts of *N*-neighboring group in two rotamers with an amide geometry of IPMA and **5a** (with a ratio 77:23) has helped to determine the geometry of major rotamers of both diastereomers of **5a** as *cis* (*Z*) with the *N*-bulky group oriented in the same direction as the carbonyl group. Thus, the signals of benzylic protons for major rotamers *cis* **5a** have been down-field shifted and have been located at δ: 6.02 (*R,S*) and 6.05 (*R,R*) while those of *N*-methyl protons have been situated at δ: 2.74 (*R,S*) and 2.76 (*R,R*). The methylbenzyl C-C*H*$_3$ protons have been recorded at δ: 1.55 (*R,S*) and 1.54 (*R,R*). On the other side, the chemical shift of analogous benzylic (δ: 5.24 and 5.30 for both diastereoisomers) and methylic protons (δ: 2.71/2.72 and 1.67/1.66 for *R,S*/*R,R* diastereoisomers, respectively) in minor rotamers have indicated the *trans* geometry of **5a** (Table 3). These data are consistent with ^{1}H NMR and ^{13}C NMR spectra reported already for *N,N*-dimethylfluoroacetamide (DMFA) and *N,N*-dimethyl-*α*-fluoropropionamide (DMFP), as well as for *N,N*-dimethyl-3,3,3-trifluoroacetamide [32, 17].

Although, the largest difference between chemical shifts of both diastereomers of **5a** has been observed at stereogenic carbon atoms, this notices have not allowed to clearly distinguish the configuration at chiral centre in both diastereomers. While for major rotamers in both

diastereoisomers **5a**, the chemical shifts of appropriate amine moiety protons had been similar ($\Delta\delta \leq 0.3$), the signals derived from tetrafluorinated amide parts have slightly varied i.e. *α*-fluorines (δ: -199.2 and -199.5) with *α*-protons (δ: 5.43 and 5.42) and for trifluoromethyl group (δ: -75.6). On the contrary, for minor rotamers, the signals of *α*-fluorine atoms have been observed at δ: -196.1 and -197.6. The chemical shifts of the rest appropriate protons in whole molecule have been similar.

The comparison of chemical shift values for diastereomeric *α*-methoxy-*α*-(trifluoromethyl)phenyl acetic acid (MPTA) analogues could be applied, as it has already been, in determining of absolute configuration of secondary hydroxyl or amine derivatives [33]. Thus, for the (*R*)-MTPA amide derivatives of the (*R*)-1-phenylethylamine e.g. (*R,R*)-MTPAPEA, the *α*-positioned CF_3 group has been down-field shifted and has been recorded at δ: -70.98, comparing to the analogous signal of (*R,S*) diastereoisomer located at δ: -71.23 in ^{19}F NMR spectra. As a comparison, the signal of *α*-fluorine atom, vicinal to C=O group in crystal of *anti* **5a** has been observed at δ: -196.1 and has resulted in determination of configuration of **5a** diastereoisomer as (*R,R*). Analogously, a signal of *α*-fluorine in ^{19}F NMR spectrum for *anti* **5a** has been placed at δ: -197.6, indicating the configuration (*R,S*) for an oily **5a**.

Analogous hydrolysis reaction of **2b/3b** mixture has given two diastereoisomers **5b**, in 53:47 ratio with 98% isolated yield, each isomer with 77:23 rotamers ratio. The diastereoisomers have been inseparable using column chromatography. As the signals at δ: 4.08-4.17 ppm (m) and δ: 3.40-3.64 ppm (m) corresponding to N-C*H*C and N-CH_2-, respectively, have been matched by integration to major rotamer having *cis* geometry of *N*-bulky group and C=O bond in one diastereomer **5b**, the minor one has had the analogous signals located in range δ: 4.00-4.08 ppm (m) and at δ: 3.40-3.64 ppm (m) (in the same range) indicating *trans* orientation analogous groups in **5b**. Unfortunately, for the major diastereoisomer of **5b**, the signals of hydrogen atoms at chiral carbon, in amine part, were situated in the same range (δ: 3.74-3.82 ppm) as well as slightly shifted signal of *N*-neighboring methylene group (δ: 3.08-3.28 ppm).

Additionally, for both major diastereomers *cis* **5b** the signals derived from tetrafluorinated amide parts have slightly varied i.e. α-fluorines (δ: -200.7 and 200.6), α-protons (δ: 5.11 and 4.92) and trifluoromethyl group (δ: -75.7). On the contrary, for minor *trans* rotamers of both diastereomers **5b**, the signals of *α*-fluorine atoms have been visible at δ: -202.7 and -203.7 ppm, while the chemical shifts of *α*-protons have been observed at δ: 5.05 and δ: 4.93 ppm. The signals of CF_3 groups have been situated at δ: -76.6 ppm. Therefore, aiming to absolute configuration assignment in both diastereomeric **5b** (as a pyrrolidine part has already had *S*-configuration), the correlation of fluorine chemical shift values of CH*F*(CF_3) in minor rotamers of **5b** has been performed. The signal of *α*-fluorine atom, vicinal to C=O group in *trans* **5b** has appeared at δ: -202.7 ppm and could determine **5b** diastereomer as (*S,S*). Analogously, the signal of *α*-fluorine in ^{19}F NMR spectrum for *trans* **5b** has been located at δ: -203.7 ppm, indicating the configuration (*S,R*) **5b**. This assignment is in agreement with the ones performed for (*R,R*)/(*R,S*) **5a** and (*S,S*)/(*S,R*) **5a,** as well as (*R,R*)-MTPAPEA [32].

However, further studies also involving the crystal structure determination would be necessary to the unambiguous assignment of absolute configuration of chiral atoms in fluorinated amide part of both diastereomers **5b.**

Conformational analysis of tetrafluorinated amide - theoretical calculations

While the orientation of the amine part toward carbonyl group is easily detectable based on NMR spectra, the influence of fluorine atoms on steric and electronic effects in molecules and preferable conformation of molecule is the well-known phenomenon. Thus, compound **5a** could exist in a few conformations taking into account only fluorine and CF_3 group orientation with respect to carbonyl group (Fig. 3). The *cis*/*trans* notation deals with the configuration of partially double amide bond C(O)-N, while *syn*/*anti* notation is related to the F-C-C=O torsion angle (*syn* is 0°, *anti* is 180°).

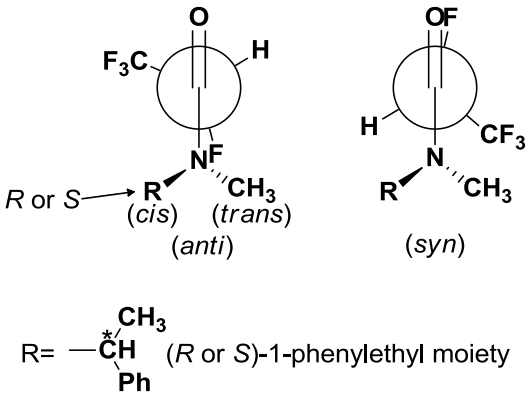


Fig. 3. *Anti* and *syn* conformers of **5a** *R,R cis* (or *R,S cis*).

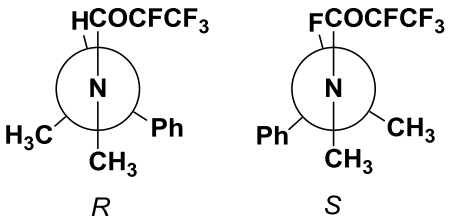


Fig. 4. Most stable conformational arrangement of (*R* or *S*)-1-phenylethyl moiety, which was used during all optimizations at DFT level to quantify the dependence of the conformation on the F-C-C=O torsion angle (Fig. 5).

The most stable conformational arrangement of (*R* or *S*)-1-phenylehtyl moiety has been found (Fig. 4) and used during all optimizations at DFT level in order to quantify the dependence of the conformation on the F-C-C=O torsion angle.

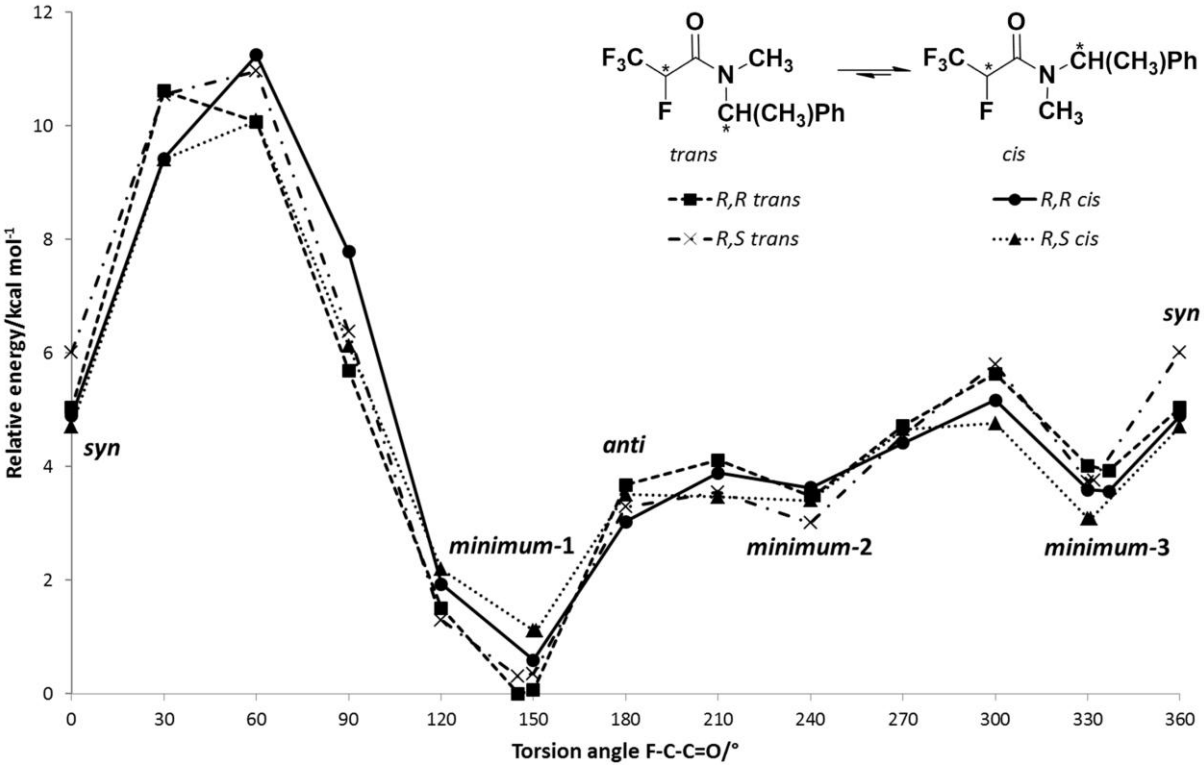


Fig. 5. Potential energy surfaces for **5a:** *R,R trans*, *R,R cis*, *R,S trans* and *R,S cis* at wB97XD/cc-pVDZ level.

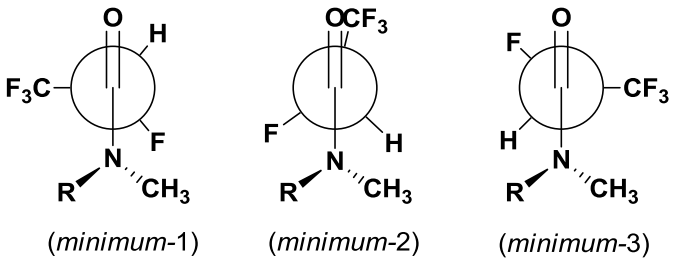


Fig. 6. The geometries of three energy minima on the potential energy surface for **5a** *R,R cis* (or *R,S cis*).

The obtained potential energy surfaces (Fig. 5) for **5a:** *R,R trans*, *R,R cis*, *R,S trans* and *R,S cis* are very similar and all show three energy minima (Fig. 6): *minimum*-1 (deepest minimum at F-C-C=O torsion angle about 150°), *minimum*-2 (very shallow minimum at about 240°) and *minimum*-3 (at about 330°), which result is in agreement with the data obtained by Abraham et al. for *N*,*N*-dimethyl-α-fluoropropionamide (DMFP) [32]. In contrast to *α*-fluorinated *N*-monosubstituted amides, where the most stable conformation is that with the fluorine atom *anti* to the carbonyl group [22], in case of *α*-fluorinated *N*,*N*-disubstituted amides

conformation *anti* is unstable due to the steric congestion (Fig. 5). Two of three potential energy minima obtained for the **5a** are considered to be stable conformers: *minimum*-1 and *minimum*-3 (with F-C-C=O torsion angle about 330° which corresponds to the X-ray structure angle 331.3°) (Fig. 7). There, the X-ray structure is not the global minimum potential energy conformation in the isolated state. Further, the structure of *minimum*-2 seems to be even a shoulder on the potential energy surface and it is considered to be the least stable minimum due to the relatively high potential energy and very low energy barrier of rotation (relaxation) towards the global minimum structure (*minimum*-1). This, on the other hand, is in contrast with the calculation for DMFP, which has CH_3 group instead of CF_3 group [32]. Then, the structure corresponding to the *minimum*-2, having the CH_3 group in *syn* position to the carbonyl C=O, was the most stable one. In our case, the structure of *minimum*-2 have the CF_3 group in *syn* position to carbonyl which seems to be less preferred due to the repulsion between fluorine and oxygen atoms. This observation shows how additional fluorine atom can influence the conformation equilubrium.

These data are in agreement with the crystallographic structure of solid **5a** (Fig. 7) and *R,R* absolute configuration determined from ^{19}F NMR data. The X-ray structure shows that molecule is observed as the *syn* conformer, with the O(1)-C(1)-N(1)-C(4) dihedral angle of 355.6°.

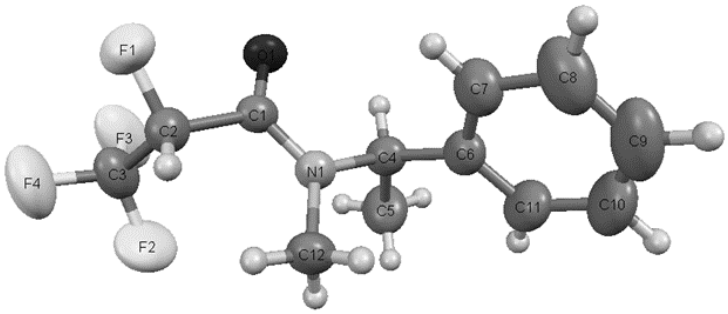


Fig. 7. A perspective drawing and atom labelling of molecule *R,R syn* **5a**. The thermal ellipsoids have been drawn at the 40% probability level. The hydrogen atoms are shown as small spheres of arbitrary diameter.

Analysis of the X-ray structure of amide *R,R* syn **5a** shows that the C-F bond α to the amide carbonyl group is orientated nearly *anti* to the N-C amide bond, with the F(1)-C(2)-C(1)-N(1) dihedral angle of 151.9° and nearly *syn* to the C=O bond, with the F(1)-C(2)-C(1)-O(1) dihedral angle of 331.3° (Table 4).

Table 4. Torsion angles (°) for amide (*R*,*R*)-syn **5a**

Torsion angles (°)	
C(3)-C(2)-C(1)-O(1)	88.2
H(2)A-C(2)-C(1)-O(1)	211.2
F(1)-C(2)-C(1)-O(1)	331.3
F(1)-C(2)-C(1)-N(1)	151.9
C(3)-C(2)-C(1)-N(1)	268.8
H(2)A-C(2)-C(1)-N(1)	31.8
O(1)-C(1)-N(1)-C(12)	176.3
O(1)-C(1)-N(1)-C(4)	355.6

It is deviation from the preferred *anti* conformation of the F-C-C=O for a single fluorine substituent at the α-position with respect to a carbonyl group in α-fluoroamides [21, 22]. Following these observations it has been predicted that the preferred conformation around an amide bond could be caused by the replacement of CH_3 group by trifluoromethyl group in the obtained compounds. Not only the fluorine atom but also trifluoromethyl group dictates the conformation of these amides.

The shortest intermolecular contacts listed in Table 4 show that the strongest interactions can be associated with the proton at C2 in the most electronegative region of fluorine substituents. These and other shortest interactions bind the molecules along crystallographic plane (001) [Fig 8.].

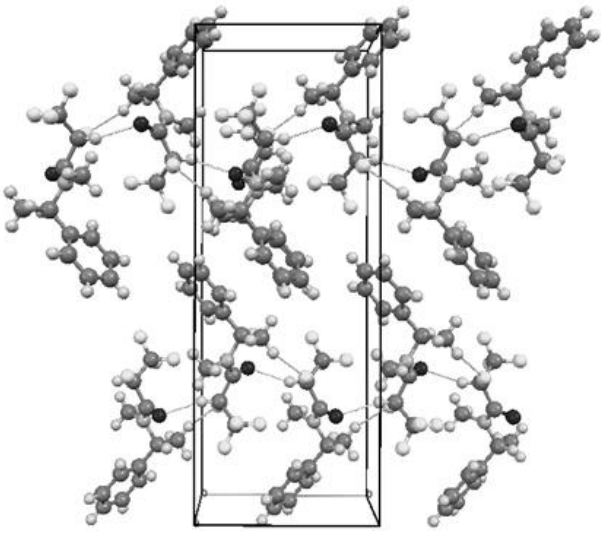


Fig. 8. Autostereographic projection of the crystal structure of *R,R syn* **5a** viewed down [100], with the shortest contacts indicated as the dashed lines [34].

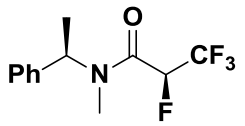
Table 5. The short intermolecular contacts in the crystal of **5a** (Å and °).

D-H···A	D-H	H···A	D···A	<D-H···A	symmetry code
C2-H2a···O1*	0.960	2.296	3.143(5)	144.17	–x, 0.5+y, 1.5-z
C5-H5a···F1*	0.960	2.624	3.470(5)	147.42	–x, y–0.5, 1.5-z
C12-H12c···O1*	0.960	2.703	3.656(5)	171.71	1–x, y, z

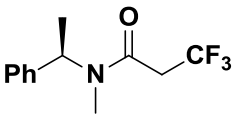
*The H-acceptors transformed according to the symmetry code of the last column.

IR spectra

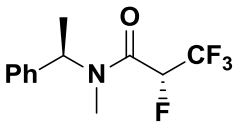
The IR (C=O) wavenumbers in the series **4a**-**5a** have indicated the influence of the C-F bond polarization on the increasing positive charge density on carbon atom, making the C=O bond shorter, due to the electrostatic stability of the C-F bond which is consistent with the results from the quantum mechanical calculations. As a reference point, the amide **4a** with a IR (C=O) ν^{-1} 1659 cm^{-1} has been selected, while for tetrafluorinated (*R,R*) **5a** the wavenumber has equaled to 1655 cm^{-1}. Analogously, for the (*R,S*) diastereomer **5a** the corresponding IR (C=O) ν^{-1} has equaled to 1667 cm^{-1}.



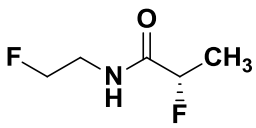
5a (*R, R*)
(C=O) ν^{-1}1655 cm^{-1}



4a (*R*)
(C=O) ν^{-1}1659 cm^{-1}



5a (*R, S*)
(C=O) ν^{-1}1667cm^{-1}



(*S*)-2-fluoro-N-(2-fluoroethyl)-propionamide
(C=O) ν^{-1}1671 cm^{-1}

Fig. 9. IR (C=O) wavenumbers of series **4a**-**5a** in comparison with (*S*)-2-fluoro-*N*-(2-fluoroethyl)-propionamide [21].

Probably, in case of the studied diastereoisomers, the absolute configuration of the carbon atom placed adjacent to amide bond has impact on the general polarization, creating the large difference in C=O stretching frequency between the diastereoisomers (*R,R*) and (*R,S*) of **5a**. These data are parallel with the results obtained for (*S*)-2-fluoro-*N*-(2-fluoroethyl)-propionamide (wavenumber value 1671 cm^{-1}) [21], indicating an "alfa-fluoroamide effect" and adopting a preferred *gauche* conformation of the C-N-(C=O) bonds in α-fluoroamide moiety seen in the crystal structure.

Conclusion

Our experimental results have demonstrated that the hydrolysis reactions of enamines has given 3,3,3-trifluoropropionamides, while an addition of water to enamine/amine mixtures has given tetrafluorinated analogues. The combined spectroscopic, X-ray analyses and theoretical calculations have given us an evidence of the differences in the conformational geometry of the *α*-fluorine substituted amides and new synthesized tri- and tetrafluorinated amides derivatives. According to the latest version of the Cambridge Structural Database, no other structures containing the C(F3)C(HF)C(=O)N- have been determined. In contrast to a single *α*-fluorine substituted amides which preferred *anti* conformation of the F-C-C=O, for the tetrafluorinated amides the additional trifluoromethyl group has enforced that the C-F bond *α* to the amide carbonyl group is orientated nearly *anti* to the N-C amide bond, and nearly *syn* to the C=O bond. These data could be considered in a design of important CF_3-building blocks employed in the synthesis of useful compounds such as peptides analogs.

Experimental section

General procedures

^1H (Me_4Si) NMR spectra were determined with solutions in $CDCl_3$ at 300 MHz, ^{13}C (Me_4Si) at 75 MHz and ^{19}F NMR (CCl_3F) at 282 MHz. The yields of reaction products were conveniently evaluated by ^{19}F NMR in $CDCl_3$ using *m*-fluorotoluene as internal standard. Mass spectra were obtained by electron impact (MS-EI) techniques with ionizing energy 70 eV, unless otherwise noted. Optical rotations were measured at 20 °C in $CHCl_3$ using a 243 B Perkin-Elmer polarimeter. [α] D values were determined at 589 nm. IR spectra were performed using spectrometer FT-IR IFS 66/s from Bruker. Reagent grade chemicals were used and solvents were dried by refluxing with sodium metal-benzophenone (THF), with CaH_2 (CH_2Cl_2), with NaH (Et_2O) and distilled under an argon atmosphere. All moisture sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. Reaction temperatures below 0^oC were obtained using a bath cooling (dry ice/*iso*-propanol). Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60-F_{254} with EtOAc/hexane as developing systems. Visualization of the reactions products was achieved using UV light (254 nm) and a standard procedure (solution of phosphomolybdenic acid or $KMnO_4$). Merck Kieselgel 60 (230-400 mesh) was used for column chromatography. 1,1,3,3,3-pentafluoropropene (PFP) and hexafluoropropene (HFP) were provided to us by SynQuest Laboratories Ltd. *R*-(+)- and (*S*)-(-)-*N*,*α*-dimethylbenzylamine (**a**) and BF_3*Et_2O were supplied by Sigma Aldrich. 2(*S*)-2(diphenylmethyl)pyrrolidine (**b**) was achieved according to known literature method [35-37]. All products of the analogous reactions provided with (*R*) or (*S*) *N*,*α*-dimethylbenzylamine gave the same result with the identical spectral data (with an exeption of [α])- typical for enantiomers.

Teoretical calculations

The quantum mechanical calculations of potential energy in vacuum with the DFT (wB97XD) method have been performed using the *GAUSSIAN03* program [38], in order to systematic search for possible conformations. The long-range corrected hybrid functional wB97XD [39] with the correlation-consistent polarized basis set cc-pVDZ [40] have been used as the necessary compromise between the desired accurancy and the computational time needed.

Crystal structure analysis

The structure of compound *R,R syn* **5a** was determined by single-crystal diffraction. A KuMa KM-4 CCD four-circle diffractometer and MoKα radiation (0.71073 Å) was used. The structure was solved by direct methods with program SHELXS and refined by full-matrix least squares on F^2 by SHELXL [41]. Hydrogen atoms were located from the molecular geometry at idealized positions and assigned isotropic thermal parameters depending on the equivalent displacement parameters of their carriers.

X-ray crystal structure analysis for **5a** (CCDC 989111)‡: formula $C_{12}H_{13}F_4NO$, M = 263.23, colourless crystal 0.30 × 0.10 × 0.10 mm, a = 6.07446(13) Å, b = 8.98778(19) Å, c = 24.2410(6) Å, β = 90°, V = 1323.46(5)Å^3, ρ_{calc} = 1.321g/cm^3, μ = 1.075 mm^{-1}, Z = 4, orthorhombic, space group $P2_12_12_1$, λ = 1.54184 Å, T = 293(2) K, θ scans, reflections collected/unique 21223/2734 [R(int) = 0.0301], 164 refined parameters, R = 0.0441, *w*R2 = 0.1384, goodness-of-fit on F^2 = 1.106, max. residual electron density 0.257 and -0.164e.Å^{-3}.

General procedure for the synthesis of enamines

Chiral secondary amine (1 equiv.) and dried solvent (3 mL) were placed in a glass pressure-vessel. The solution was cooled to -78 °C and the pressure was lowered. Next, the excess of 1,1,3,3,3-pentafluoropropene (PFP) was transferred to the glass tube and the vessel was sealed. The cooling bath was removed and the mixture was brought to the room temperature with stirring overnight. After (approximately) 16-24 hours the crude mixture was used for the next step.

Note: The choice of solvent has depended on a solubility of amines. The elevated temperature of reaction (reflux) has not affected the yield.

***(R,Z)-1,3,3,3-tetrafluoro-N-methyl-N-(1-phenylethyl)prop-1-en-1-amine* 1a**

Reaction of PFP (180 mg, 1.36 mmol) and *R*-(+)-*N*,*α*-dimethylbenzylamine a (0.1 mL, 92 mg, 0.68 mmol) in dried THF, according to the general procedure, gave a mixture of adduct 1a (yield 73%) and traces of an amide 4a.

1a ^{19}F NMR δ: – 52.75 (3F, dd, J_{CF3-F}=15.2 Hz, J_{CF3-H}=7.0 Hz, CF_3), -92.73 (1F, dq, J_{F-H}=30.7 Hz, J_{F-CF3}=15.2 Hz, F).

(S,Z)-2-Benzhydryl-1-(1,3,3,3-tetrafluoroprop-1-enyl)pyrrolidine 1b

Reaction of PFP (112 mg, 0.85 mmol) and 2(*S*)-2(diphenylmethyl)-pyrrolidine (100 mg, 0.42 mmol) in dried CH_2Cl_2, according to the general procedure led to a mixture of adduct **1b** (yield 54%) and traces of amide **4b**.

1b ^{19}F NMR δ: – 51.68 (3F, dd, $J_{CF3\text{-}F}$=14.6 Hz, $J_{CF3\text{-}H}$=7.1 Hz, CF_3), -87.15 (1F, dq, $J_{F\text{-}H}$=29.2 Hz, $J_{F\text{-}CF3}$=14.6 Hz, F).

General procedure for the synthesis of enamine/amine mixtures

Chiral secondary amine (1 equiv.) and dried solvent (3 mL) were placed in a glass pressure-vessel. The solution was cooled to -78 °C and the pressure was lowered. Next, the excess of hexafluoropropene (HFP) was transferred to the glass tube and the vessel was sealed. The cooling bath was removed and the mixture was brought to the room temperature with stirring overnight. After (approximately) 16-24 hours the crude mixture was used for the next step.

Note: The choice of solvent has depended on a solubility of amines. The elevated temperature of reaction (reflux) has not affected the yield.

(R,E)-1,2,3,3,3-pentafluoro-N-methyl-N-(1-phenylethyl)prop-1-en-1-amine 2a

1,2,3,3,3-pentafluoro-N-methyl-N-((R)-1-phenylethyl)propan-1-amine 3a

Reaction of HFP (180 mg, 1.2 mmol) and *R*-(+)-*N*,*α*-dimethylbenzylamine (0.1 mL, 92 mg, 0.68 mmol), according to the general procedure, gave a mixture of the enamine **2a** (yield 24%) and amine **3a** (yield 55%).

2a ^{19}F NMR δ: - 65.79 (3F, dd, $J_{CF3\text{-}F}$=23.1 Hz, $J_{CF3\text{-}F}$=13.6 Hz, CF_3), -114. 48 (1F, dq, $J_{F\text{-}F}$=118.8 Hz, $J_{F\text{-}CF3}$=22.6 Hz, F), -193.51 (1F, dq, $J_{F\text{-}F}$=118.7 Hz, $J_{F\text{-}CF3}$=13.5 Hz, F),

3a ^{19}F NMR δ: -74.50 ÷ -74.69 (3F, m, CF_3), -81.48 ÷ -87.53 (1F, m, F), -87.72 ÷ -93.33 (1F, m, F), -207.82 ÷ -208.26 (1F, m, F).

(2S,E)-(2-benzhydryl)-1-(perfluoroprop-1-enyl)pyrrolidine 2b

(2S)-2-benzhydryl-1-(1,2,3,3,3-pentafluoropropyl)pyrrolidine 3b

Reaction of HFP (126 mg, 0.84 mmol) and 2(*S*)-2(diphenylmethyl)-pyrrolidine (100 mg, 0.42 mmol) according to the general procedure gave a mixture of enamine **2b** (yield 2%) and amine **3b** (yield 63%).

2b ^{19}F NMR δ: – 65.01 (3F, dd, $J_{CF3\text{-}F}$=22.8 Hz, $J_{CF3\text{-}F}$=14.4 Hz, CF_3), -116. 85 (1F, dq, $J_{F\text{-}F}$=116.4 Hz, $J_{F\text{-}CF3}$=22.8 Hz, F), -198.85 (1F, dq, $J_{F\text{-}F}$=118.1 Hz, $J_{F\text{-}CF3}$=13.4 Hz, F),

3b ^{19}F NMR δ: -74.83 ÷ -74.96 (3F, m, CF_3), -85.57 ÷ -86.65 (1F, m, F), -90.42 ÷ -91.51 (1F, m, F), -205.53 ÷ -206.01 (1F, m, F).

General procedure for the synthesis of amide.

Method A: The crude reaction mixture (enamines **1a,b**) obtained in first step was readily hydrolyzed by addition of water (2 equiv.). Next, the reaction mixture was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified on silica gel (AcOEt/hexane) to give an appropriated amide.

Method B: The crude reaction enamines/amines mixture **2a/3a** and **2b/3b** obtained in first step was readily hydrolyzed by addition of boron trifluoride diethyl etherate (2 equiv.) and water (2 equiv.). Next, the reaction mixture was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified on silica gel (AcOEt/hexane) to give an appropriated amide.

3,3,3-Trifluoro-N-methyl-N-((R)-1-phenylethyl)propanamide 4a

An enamine 2a was readily hydrolyzed by addition of water (2 equiv.). The product was purified on a silica gel (10% AcOEt/hexane) to give an amide 4a (two rotamers with 71/29 ratio), as an oil (96 mg, 57%).

[α] *D* 25 + 172° (c 0.4, $CHCl_3$),

IR (KBr/film) ν 3090, 3064, 3032, 2981, 2945, 2882, 1659, 1605, 1586, 1450, 1429, 1406, 1268, 1137, 1114, 1092, 922, 854, 784, 701, 644,

Rotamer *cis* **4a**: ^{1}H NMR δ: 1.42 (3H, d, *J*=7.1 Hz, CH_3), 2.60 (3H, s, NCH_3), 3.18 (2H, q, $J_{H\text{-}CF3}$=10.1 Hz, CH_2), 5.99 (1H, q, *J*=7.1 Hz, $CH(CH_3)$), 7.12-7.33 (m, 5H, Ph); ^{13}C NMR δ: 15.43 (CH_3), 30.08 (NCH_3), 38.64 (q, *J*=28.9 Hz, CH_2), 50.80 (CH), 124.36 (q, *J*=276.6 Hz, CF_3), 127.31 (Ph), 127.63 (Ph), 128.65 (Ph), 139.76 (Ph), 163.41 (q, *J*=3.1 Hz, C=O); ^{19}F NMR δ: – 62.90 (3F, t, $J_{CF3\text{-}H}$=10.0 Hz, CF_3),
Rotamer *trans* **4a**: ^{1}H NMR δ: 1.56 (3H, d, *J*=6.9 Hz, CH_3), 2.65 (3H, s, NCH_3), 3.26 (2H, q, $J_{H\text{-}CF3}$=10.0 Hz, CH_2), 4.95 (1H, q, *J*=6.8 Hz, $CH(CH_3)$), 7.12-7.33 (5H, m, Ph); ^{13}C NMR δ: 17.89 (CH_3), 28.41 (NCH_3), 38.24 (q, *J*=28.8 Hz, CH_2), 55.68 (CH), 124.30 (q, *J*=276.7 Hz, CF_3), 126.33 (Ph), 127.96 (Ph), 129.01 (Ph), 139.38 (Ph), 163.33 (q, *J*=2.8 Hz, C=O); ^{19}F NMR δ: – 62.78 (3F, t, $J_{CF3\text{-}H}$=10.0 Hz, CF_3),

MS *m/z* (rel. int.) 245 $[M]^+$ (50), 230 $[M\text{-}15]^+$ (20), 134 (5), 120 (100), 111 (25), 77 (50), 69 (5).

1-((S)-2-Benzhydrylpyrrolidin-1-yl)-3,3,3-trifluoropropan-1-one 4b

An enamine **1b** was readily hydrolyzed by addition of water (2 equiv.). The product was purified on a silica gel (20% AcOEt/hexane) to give an amide **4b** (two rotamers with 53/47 ratio) as an oil (55 mg, 38%).

[α] *D* 25 ° + 2.3° (c 2.8, $CHCl_3$),

IR (KBr/film) ν 3086, 3061, 3027, 2980, 2889, 1652, 1601, 1582, 1494, 1449, 1440, 1350, 1267, 1252, 1218, 1189, 1113, 1032, 919, 851, 754, 701.

Rotamer *cis* **4b** ^{1}H NMR δ: 1.65-1.80 (1H, m, CH*H*), 1.87-2.10 (3H, m, C*HH*), 2.44 (2H, q, *J*=10.2 Hz, CH_2CF_3), 3.34 (2H, dt, *J*=9.9, 8.1 Hz, C*HH*N), 4.43 (1H, dt, *J*=10.5, 5.9 Hz, NCH), 4.63 (1H, d, *J*=5.5 Hz, $CH(Ph)_2$), 6.97-7.47 (m, 10H, Ph); ^{13}C NMR δ: 23.57 (CH_2), 27.20 (CH_2CH), 39.80 (q, *J*=28.8 Hz, *C*H_2CF_3), 45.04 (CH_2N), 51.66 (*C*$H(Ph)_2$), 60.25 (CH), 124.16 (q, *J*=276.9 Hz, CF_3), 126.27 (Ph), 127.42 (Ph), 128.06 (Ph), 128.72 (Ph), 128.89 (Ph), 140.18 (Ph), 141.50 (Ph), 161.84 (q, *J*=3.3 Hz, C=O); ^{19}F NMR δ: -62.74 (3F, t, J_{CF3-H}=10.2 Hz),

Rotamer *trans* **4b**, ^{1}H NMR δ: 1.65-1.80 (1H, m, CH*H*), 1.87-2.10 (3H, m, C*HH*), 2.49 (2H, q, *J*=10.3 Hz, CH_2CF_3), 3.17 (1H, dt, *J*=9.9, 4.2 Hz, NCH), 3.56 (1H, dt, *J*=12.6, 6.6 Hz, CH*H*N), 3.87 (1H, dt, *J*=12.4, 8.1 Hz, C*H*HN), 4.63 (1H, d, *J*=5.5 Hz, $CH(Ph)_2$), 6.97-7.47 (m, 10H, Ph); ^{13}C NMR δ: 21.08 (CH_2), 30.56 (CH_2CH), 37.63 (q, *J*=28.6 Hz, *C*H_2CF_3), 47.58 (CH_2N), 53.94 (*C*$H(Ph)_2$), 62.99 (CH), 123.98 (q, *J*=276.8 Hz, CF_3), 126.77(Ph), 127.17 (Ph), 128.31 (Ph), 128.84 (Ph), 129.61 (Ph), 141.08 (Ph), 141.76 (Ph), 162.49 (q, *J*=3.3 Hz,C=O); ^{19}F NMR δ: -63.30 (3F, t, J_{CF3-H}=10.3 Hz),
MS *m/z* (rel. int.) 347 $[M]^+$ (3), 264 (3), 180 (65), 165 (27), 70 (100).

(S/R)-2,3,3,3-Tetrafluoro-N-methyl-N-((R)-1-phenylethyl)propanamide 5a

The enamine/amine mixture 2a/ 3a were readily hydrolyzed by addition of water (2 equiv.) and boron trifluoride diethyl etherate (2 equiv.) giving compound 5a (two diastereoisomers with 51/49 ratio). The product was purified on a silica gel (10% AcOEt/hexane) to give an amide (*R*,*S*) 5a as an oil (72 mg, 40%) and an amide (*R*,*R*) 5a as a crystalline solid (68 mg, 38%), each diastereoisomer as the two rotamers with 77/23 ratio.

(*R*,*S*) 5a

[α] *D* 25 + 118° (c 0.2, $CHCl_3$),

IR (KBr/film) ν 3090, 3064, 3032, 2982, 2946, 2883, 1667, 1605, 1585, 1496, 1450, 1420, 1348, 1287, 1266, 1189, 1153, 1128, 1086, 1029, 947, 925, 870, 844, 784, 754, 699, 659.

Rotamer *cis* **(*R*,*S*) 5a** ^{1}H NMR δ: 1.55 (3H, d, *J*=7.1 Hz, CH_3), 2.74 (3H, d, $^5J_{CH3-F}$=2.3 Hz, NCH_3), 5.42 (1H, dq, J_{H-F}=46.4 Hz, J_{H-CF3}=6.2 Hz, CHF), 6.02 (1H, q, *J*=7.0 Hz, $CH(CH_3)$),

7.20-7.44 (m, 5H, Ph), ^{13}C NMR δ: 15.13 (CH_3), 29.25 (NCH_3), 52.13 (CH), 84.54 (dq, *J*=198.7, 34.1 Hz, CHF), 121.30 (dq, *J*=282.4, *J*=26.2 Hz, CF_3), 127.49 (Ph), 127.99 (Ph), 128.84 (Ph), 138.95 (Ph), 161.08 (d, *J*=19.4 Hz, C=O), ^{19}F NMR δ: -75.60 (3F, dd, J_{CF3-F}=12.9 Hz, J_{CF3-H}=6.2 Hz, CF_3), -199.52 (1F, ddq, J_{F-H}=46.4 Hz, J_{F-CF3}=12.8 Hz, $^5J_{F-CH3}$=1.9 Hz, F),
Rotamer *trans* **(*R,S*) 5a** ^{1}H NMR δ: 1.67 (3H, d, *J*=6.8 Hz, CH_3), 2.71 (3H, d, $^5J_{CH3-F}$=0.9 Hz, NCH_3), 5.24 (1H, q, *J*=6.8 Hz, $CH(CH_3)$), 5.53 (1H, dq, J_{H-F}=46.4 Hz, J_{H-CF3}=6.2 Hz, CHF), 7.20-7.44 (m, 5H, Ph), ^{13}C NMR δ 17.68 (CH_3), 29.84 (NCH_3), 54.64 (CH), 85.06 (dq, *J*=199.3, 34.0 Hz, CHF), 121.18 (dq, *J*=282.5 Hz, *J*=26.9 Hz, CF_3), 126.74 (Ph), 128.18 (Ph), 129.05 (Ph), 138.65 (Ph), 160.96 (d, *J*=18.8 Hz, C=O), ^{19}F NMR δ -75.46 (3F, dd, J_{CF3-F}=13.0 Hz, J_{CF3-H}=6.2 Hz, CF_3), -197.58 (1F, ddq, J_{F-H}=46.2 Hz, J_{F-CF3}=13.0 Hz, $^5J_{F-CH3}$=0.7 Hz, F),

(*R,R*) 5a

[α] *D* 25 + 182° (c 0.3, $CHCl_3$),

IR (KBr/film) ν 3088, 3064, 3033, 3000, 2957, 1655, 1606, 1496, 1457, 1425, 1352, 1267, 1189, 1158, 1130, 1089, 1049, 1028, 926, 870, 839, 784, 749, 699, 671, 658,

Rotamer *cis* **(*R,R*) 5a** ^{1}H NMR δ: 1.54 (3H, d, *J*=7.1 Hz, CH_3), 2.76 (3H, d, $^5J_{CH3-F}$=2.6 Hz, NCH_3), 5.43 (1H, dq, J_{H-F}=46.4 Hz, J_{H-CF3}=6.1 Hz, CHF), 6.05 (1H, q, *J*=7.1 Hz, $CH(CH_3)$), 7.12-7.56 (m, 5H, Ph), ^{13}C NMR δ: 15.18 (CH_3), 29.06 (NCH_3), 52.02 (CH), 84.63 (dq, *J*=198.9, 34.0 Hz, CHF), 121.30 (dq, *J*=282.3, *J*=26.3 Hz, CF_3), 127.40 (Ph), 127.92 (Ph), 128.79 (Ph), 138.95 (Ph), 161.09 (d, *J*=19.1 Hz, C=O), ^{19}F NMR δ: -75.58 (3F, dd, J_{CF3-F}=12.8 Hz, J_{CF3-H}=6.2 Hz, CF_3), -199.15 (1F, ddq, J_{F-H}=46.7 Hz, J_{F-CF3}=12.8 Hz, $^5J_{F-CH3}$=2.5 Hz,F),
Rotamer *trans* **(*R,R*) 5a** ^{1}H NMR δ: 1.66 (3H, d, *J*=6.8 Hz, CH_3), 2.72 (3H, d, $^5J_{CH3-F}$=1.0 Hz, NCH_3), 5.30 (1H, q, *J*=6.8 Hz, $CH(CH_3)$), 5.52 (1H, dq, J_{H-F}=46.5 Hz, J_{H-CF3}=6.1 Hz, CHF), 7.12-7.56 (m, 5H, Ph), ^{13}C NMR δ: 17.54 (CH_3), 29.12 (NCH_3), 54.48 (CH), 85.89 (dq, *J*=201.4, 34.0 Hz, CHF), 121.18 (dq, *J*=283.9 Hz, *J*=26.8 Hz, CF_3), 126.74 (Ph), 128.07 (Ph), 128.95 (Ph), 138.83 (Ph), 160.98 (d, *J*=18.0 Hz, C=O), ^{19}F NMR δ: -75.48 (3F, dd, J_{CF3-F}=12.7 Hz, J_{CF3-H}=6.4 Hz, CF_3), -196.08 (1F, ddq, J_{F-H}=46.4 Hz, J_{F-CF3}=12.6 Hz, $^5J_{F-CH3}$=1.0 Hz, F),

MS *m/z* (rel. int.) 263 $[M]^+$ (35), 248 $[M-15]^+$ (15), 186 (5), 162 (15), 142 (50), 129 (5), 105 (100), 101 (18), 77 (40), 69 (5).

1-((S)-2-Benzhydrylpyrrolidin-1-yl)-(R/S)-2,3,3,3-tetrafluoropropan-1-one 5b

The enamine/amine mixture **2b/3b** were readily hydrolyzed by addition of water (2 equiv.) and boron trifluoride diethyl etherate (2 equiv.). The crude product was purified on a silica gel (20% AcOEt/hexane) giving mixture of two diastereoisomers with 53/47 ratio of **5b** as an oil (152 mg, 98%), each diastereoisomer as a mixture of two rotamers with 77/23 ratio.

IR (KBr/film) ν 3086, 3061, 3028, 2983, 2890, 1667, 1600, 1494, 1450, 1285, 1192, 1142, 869, 701,

Rotamer *cis* **5b** (major diastereoisomer) ^{1}H NMR δ: 1.57-1.70 (2H, m, CH_2), 1.87-2.10 (2H, m, CH_2), 3.08-3.28 (2H, m, CH_2N), 3.74-3.82 (1H, m, NCH), 4.37 (1H, d, *J*=6.9 Hz, $CH(Ph)_2$), 5.11 (1H, dq, J_{H-F}=46.5 Hz, J_{H-CF3}=6.3 Hz, CHF), 6.95-7.45 (m, 10H, Ph), ^{13}C NMR δ: 25.72 (CH_2), 39.19 (CH_2), 45.66 (CH_2N), 51.22 ($CH(Ph)_2$), 61.10 (CH), 85.57 (dq, *J*=203.2 Hz, *J*=33.6 Hz, CHF), 120.52 (dq, *J*=282.1 Hz, *J*=25.5 Hz, CF_3), 128.41 (Ph), 128.84 (Ph), 129.56 (Ph), 144.72 (Ph), 159.53 (d, *J*=20.5 Hz, C=O), ^{19}F NMR δ: – 75.72 (3F, dd, J_{CF3-F}=13.3 Hz, J_{CF3-H}=6.6 Hz, CF_3), -200.68 (1F, dq, J_{F-H}=47.5 Hz, J_{F-CF3}=13.4 Hz, F),

Rotamer *trans* **5b** (major diastereoisomer) ^{1}H NMR δ: 1.79-1.92 (2H, m, CH_2), 1.87-2.10 (2H, m, CH_2), 3.08-3.28 (2H, m, CH_2N), 3.74-3.82 (1H, m, NCH), 4.46 (1H, d, *J*=6.3 Hz, $CH(Ph)_2$), 5.05 (1H, dq, J_{H-F}=46.6 Hz, J_{H-CF3}=6.6 Hz, CHF), 6.95-7.45 (m, 10H, Ph), ^{13}C NMR δ: 26.66 (CH_2), 39.34 (CH_2), 46.56 (CH_2N), 53.40 ($CH(Ph)_2$), 61.10 (CH), 85.52 (dq, *J*=199.7 Hz, *J*=33.5 Hz, CHF), 120.94 (dq, *J*=282.8 Hz, *J*=26.3 Hz, CF_3), 128.45 (Ph), 129.24 (Ph), 129.30 (Ph), 145.52 (Ph), 161.18 (d, *J*=22.4 Hz, C=O), ^{19}F NMR δ: – 76.64 (3F, dd, J_{CF3-F}=11.0 Hz, J_{CF3-H}=6.5 Hz, CF_3), -202.67 (1F, dq, J_{F-H}=46.4 Hz, J_{F-CF3}=11.1 Hz, F),

Rotamer *cis* **5b** (minor diastereoisomer) ^{1}H NMR δ: 1.22-1.40 (2H, m, CH_2), 1.79-1.92 (2H, m, CH_2), 3.40-3.64 (2H, m, CH_2N), 4.08-4.17 (1H, m, NCH), 4.57 (1H, d, *J*=5.5 Hz, $CH(Ph)_2$), 4.92 (1H, dq, J_{H-F}=45.4 Hz, J_{H-CF3}=5.5 Hz, CHF), 6.95-7.45 (m, 10H, Ph), ^{13}C NMR δ: 26.90 (CH_2), 35.06 (CH_2), 46.58 (CH_2N), 52.25 ($CH(Ph)_2$), 61.36 (CH), 85.64 (dq, *J*=201.2 Hz, *J*=33.7 Hz, CHF), 121.03 (dq, *J*=282.2 Hz, *J*=26.0 Hz, CF_3), 128.04 (Ph), 128.63 (Ph), 129.57 (Ph), 140.89 (Ph), 159.49 (d, *J*=19.3 Hz, C=O), ^{19}F NMR δ: – 75.74 (3F, dd, J_{CF3-F}=12.6 Hz, J_{CF3-H}=5.9 Hz, CF_3), -200.59 (1F, dq, J_{F-H}=45.7 Hz, J_{F-CF3}=12.4 Hz, F),

Rotamer *trans* **5b** (minor diastereoisomer) ^{1}H NMR δ: 1.22-1.40 (2H, m, CH_2), 1.41-1.55 (2H, m, CH_2), 3.40-3.64 (2H, m, CH_2N), 4.00-4.08 (1H, m, NCH), 4.62 (1H, d, *J*=5.5 Hz, $CH(Ph)_2$), 4.93 (1H, dq, J_{H-F}=44.4 Hz, J_{H-CF3}=6.5 Hz, CHF), 6.95-7.45 (m, 10H, Ph), ^{13}C NMR δ: 27.40 (CH_2), 35.26 (CH_2), 46.28 (CH_2N), 54.25 ($CH(Ph)_2$), 61.26 (CH), 82.21 (dq, *J*=209.3 Hz, *J*=33.7 Hz, CHF), 120.57 (dq, *J*=280.0 Hz, *J*=24.7 Hz, CF_3), 128.44 (Ph), 128.93 (Ph), 130.17 (Ph), 140.93 (Ph), 161.20 (d, *J*=21.2 Hz, C=O), ^{19}F NMR δ: – 76.62 (3F, dd, J_{CF3-F}=14.4 Hz, J_{CF3-H}=6.0 Hz, CF_3), -203.73 (1F, dq, J_{F-H}=45.1 Hz, J_{F-CF3}=14.4 Hz, F),

MS *m/z* (rel. int.) 264 (5), 198 (100), 165 (20), 129 (3), 101 (5), 77 (2), 70 (50).

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