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Chemoselective trifluoromethylation of the C=N group of α-iminoketones derived from arylglyoxals

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ABSTRACT

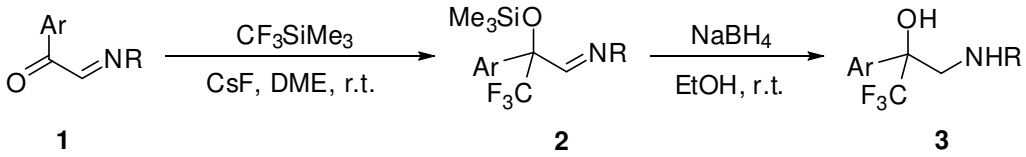
Chemoselective addition of (trifluoromethyl)trimethylsilane to the C=N group of *N*-(*tert*-butyl)-α-iminoketones in the presence of a fluoride ion as a catalyst was achieved under acidic conditions. Subsequent diastereoselective reductions of the obtained α-amino-α-(trifluoromethyl)ketones led to β-amino-β-(trifluoromethyl) alcohols in very good yields and high diastereoselectivities. Different reducing agents were tested; the reduction performed with $LiAlH_4$ and Raney-Ni, respectively, afforded the desired diastereoisomers in a reversed ratio.

1. Introduction

Synthesis of organofluorine compounds is of current interest in synthetic organic chemistry, both in academic laboratories and in industry. Especially, derivatives containing trifluoromethyl substituents are recognized as attractive building blocks and target molecules due to their potential applications in pharmacy, medicinal chemistry, crop-protection, and the advanced materials industry [1]. On the other hand, β-amino alcohols represent very useful substrates in organic synthesis and are also known as versatile chiral auxiliaries or catalysts in asymmetric synthesis [2]. Their derivatives with a CF_3 group combine unique physical, chemical and biological properties resulting from the presence of the trifluoromethyl substituent [3]. Methods applied for the preparation of β-amino-α-(trifluoromethyl) alcohols are summarized in a recent review [3c]. Similarly, protocols used for the synthesis of β-amino-β-(trifluoromethyl) alcohols are presented in an earlier review [3a]. In the case of the latter derivatives, no nucleophilic trifluoromethylation protocols have been applied to synthesize them on a preparative scale.

Several methods for the preparation of β-amino-β-(trifluoromethyl) alcohols in racemic and enantiomerically pure form are available. The oldest one consists of two steps, i.e. condensation of a respective carbonyl compound with a nitroalkane followed by the reduction of the obtained β-nitroalcohol [4a,b]. In an alterative, synthetically useful approach, 1,3-oxazolidines derived from (trifluoromethyl)carbonyl compounds or trifluoropyruvate were explored as key starting materials in multistep syntheses [4c-e]. Another, relevant method involves ring opening of *N*-alkyl-2-(trifluoromethyl)aziridines under acidic conditions [4f-h]. Some other reported multistep procedures require the use of *N*,*S*-ketals of trifluoropyruvaldehydes, which in general are rather difficult to obtain [4i-j]. However, (trifluoromethyl)trimethylsilane ('Ruppert-Prakash Reagent', RPR) was not used in any of these procedures. (Trifluoromethyl)trimethylsilane is presently recognized as the most convenient reagent for the introduction of the CF_3 group into electrophilic substrates [5].

In our previous studies, chemoselective additions of CF_3SiMe_3 to the C=O group of α-iminoketones **1** led to silyl ethers **2** as sole products [6] (Scheme 1). Further, simultaneous reduction of the C=N function and desilylation gave the desired β-amino α-(trifluoromethyl) alcohols **3** in high yields.

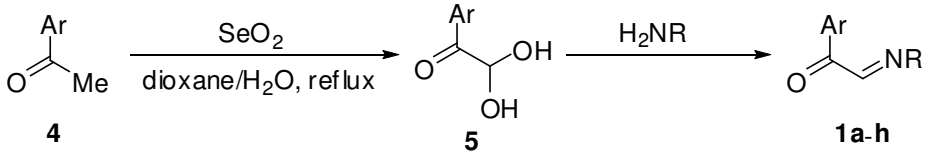


Scheme 1. Synthesis of β-amino α-(trifluoromethyl) alcohols.

The goal of the presented study was to develop a protocol for the chemoselective addition of the Ruppert-Prakash reagent to the C=N group in α-iminoketones of type **1**. Typical ald- and ketimines do not undergo nucleophilic trifluoromethylation under standard conditions [5]. However, nucleophilic additions of RPR onto diversely activated imines are known, and selected examples are described in publications collected in ref. [7]. For example, in protocols presented in [7a,b], imines were converted in situ into highly reactive iminium cations by addition of trifluoroacetic (TFA) or triflic acid (TfOH). The addition of CF_3SiMe_3 occurred in the presence of fluoride or HF_2^- ions. Importantly, under these conditions, the C=O group of a ketone did not react with the trifluoromethylating agent. On the other hand, under 'classical' conditions, the same substrates gave exclusively products of the addition onto the C=O bond [6].

2. Results and discussion

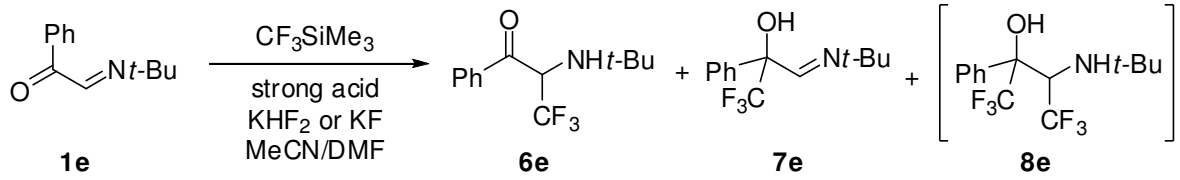
α-Iminoketones of type **1** derived from arylglyoxals were selected as key substrates in the present study. They were prepared according to a known protocol via a two-step procedure [6,8]. In the first step, oxidation of appropriate methyl ketones **4** led to 2,2-dihydroxyethanones **5**, which were converted into α-iminoketones **1** by treatment with the corresponding primary amines (Scheme 2).



Scheme 2. Two-step preparation of α-iminoketones **1a**–**h**.

Substrates **1** bearing a *t*-Bu substituent on the *N*-atom are significantly more stable than those containing an *i*-Pr or MeO group. Therefore α-iminoketone **1e** was chosen as a model

compound for optimization of the reaction conditions. Addition of CF_3SiMe_3 was carried out under conditions described for the nucleophilic addition of RPR to the acid-activated C=N bonds [7a-b] (Scheme 3, Table 1).



1e **6e** **7e** **8e**

Scheme 3. Reaction of α-iminoketone **1e** with Ruppert-Prakash reagent in the presence of a strong acid and a F^- source.

Table 1

Optimization of the reaction conditions for the synthesis of β-amino-β-(trifluoromethyl) ketone **6e**.

Entry	Salt [mmol]		Acid [mmol]		RPR [mmol]	t	T [ºC]	Conversion [%]	**6/7** ratio
	KF	KHF_2	TFA	TfOH					
1	1.5	–	2.00	–	1.50	16 h	~20	39	69 : 31
2	–	0.75	1.25	–	1.50	16 h	~20	52	74 : 26
3	–	0.75	–	1.6	1.50	16 h	~20	0	–
4	–	0.75	1.25	–	1.50	24 h	–15	10	55 : 45
5	–	2.00	3.00	–	2.00	48 h	–15	25	90 : 10
6	–	1.00	–	1.6	3.25	48 h	–15	0	–
7	4.0	–	6.00	–	2.00	48 h	–15	40	4 : 96
8	–	1.00	1.50	–	2.00	72 h	–15	52	50 : 50
9	–	2.50	3.75	–	2.50	72 h	~20	69	51 : 49
10	–	2.50	3.75	–	2.50	30 d	–15	82	90 : 10

Next, a series of experiments was performed under various conditions in order to optimize the formation of α-amino-α-trifluoromethyl ketone **6e**. The progress of the reaction was monitored by ^{1}H-NMR spectroscopy. The most intensive signals at 1.0–1.5 ppm were attributed to the *tert*-butyl group, and the quartet localized at 4.8 ppm ($^3J_{H,F}$ = 7.2 Hz) evidenced the presence of the desired **6e**. The presence of the α-hydroxy-α-(trifluoromethyl) imine **7e**, formed in a competitive CF_3 addition to the C=O group of **1e**, was indicated by another *t*-Bu singlet shifted down-field compared with the corresponding signal of **6e** (Fig. 1).

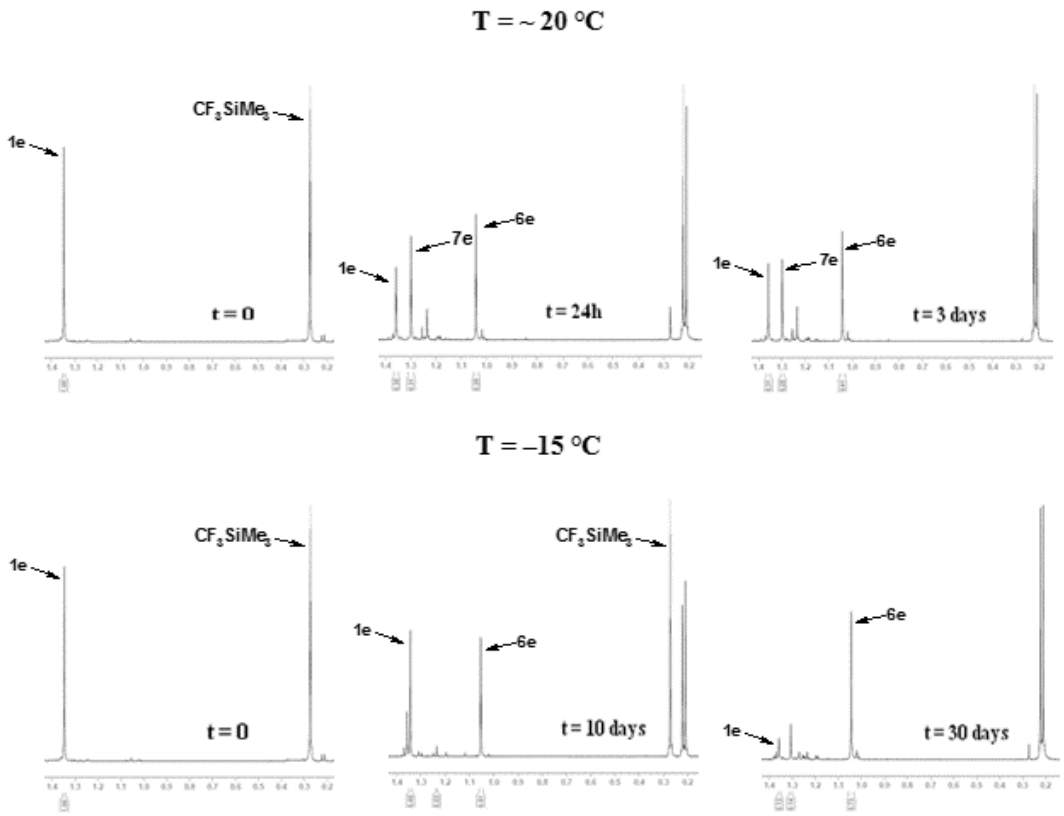
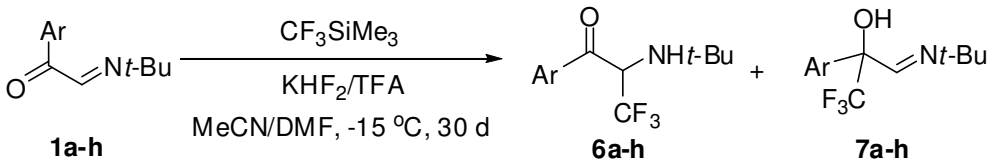


Figure 1. Nucleophilic addition of CF_3SiMe_3 to **1e** in the presence of TFA at 25 and –15 °C, respectively.

Subsequently, experiments were performed in CD_3CN as a solvent of choice using different amounts of KF or KHF_2, TFA or TfOH, and various temperatures as well as reaction times (Table 1). The best results were achieved using **1e**, KHF_2, TFA, and CF_3SiMe_3 in a ratio of 1:2.50:3.75:2.50 at –15 °C after 30 days. Thus, compared with analogous addition of RPR to the C=O group in **1e** under neutral conditions (DME, CsF, r.t.), the reaction is very slow [6]. After this time, CF_3SiMe_3 completely disappeared from the mixture. However, small amounts of **1e** remained unchanged (ca. 82% conversion). The ratio of **6e** and **7e** was established as ca. 9:1. It is worth mentioning that the 2:1 adduct **8e** was not formed, despite the fact that CF_3SiMe_3 was used in a two-fold excess. Experiments in CD_3CN showed that under acidic conditions at room temperature fast decomposition of CF_3SiMe_3 occurred. This process was slow at –15ºC, but unfortunately the addition of CF_3SiMe_3 was also very sluggish. It seems that α-iminoketones are less reactive towards Ruppert-Prakash reagent under acidic conditions than 'simple' aldimines, the reactions of which are described in ref. [7].

The preferred trifluoromethylation of the C=N group can be explained based on the mechanism proposed in ref. [7a]. It is plausible that in analogy to imines, α-imino ketone **1e** is protonated under the reaction conditions, and the iminium salt formed thereby is more reactive than the keto group towards CF_3SiMe_3.

Next, using the optimized conditions, a series of reactions with diverse α-iminoketones **1** was carried out (Scheme 4). The results presented in Table 2 show that the best yields of products **6** were obtained with imino ketones **1** bearing electron-rich aryl groups. The presence of electron withdrawing substituents at the aryl moiety results in significantly lower yields, and the products formed could not be isolated in pure form. In almost all cases, the desired compound **6** was formed as the major product (Table 2).



Scheme 4. Trifluoromethylation of α-iminoketones **1a-h** under acidic conditions

Table 2. Trifluoromethylation of α-iminoketones **1a-h** with CF_3SiMe_3 in MeCN solution in the presence of KHF_2 and TFA at –15 °C for 30 days

Entry	**1**	Ar	Conversion [%]	**6/7** ratio	Yield of **6** [%][a)]
1	**a**	3,4-$(OCH_2O)C_6H_3$	95	95 : 5	47
2	**b**	3,4-$(MeO)_2C_6H_3$	97	96 : 4	53
3	**c**	4-$MeOC_6H_4$	93	98 : 2	70
4	**d**	7-Et-Benzofur-2-yl	92	88 : 12	40
5	**e**	Ph	95	89 : 11	54
6	**f**	4-BrC_6H_4	65	93 : 7	19
7	**g**	4-$CF_3C_6H_4$	51	90 : 10	-[b)]
8	**h**	4-$NO_2C_6H_4$	40	50 : 50	-[b)]

[a)] Yield of isolated product.

[b)] Product was not isolated in a pure form.

The structure of **6a** was established by X-ray crystallography (Fig. 2). Since the space group is centrosymmetric, the compound in the crystal is racemic. There are two symmetry-

independent molecules in the asymmetric unit. The molecules have very similar conformations, with an r.m.s. fit of the non-hydrogen atoms of 0.389 Å. The amine group of each independent molecule forms an intramolecular hydrogen bond with the adjacent carbonyl O-atom to give a 5-membered loop with a graph set motif [9] of S(5). Remarkably, the amine group NH(*t*-Bu) is not involved in any intermolecular interactions.

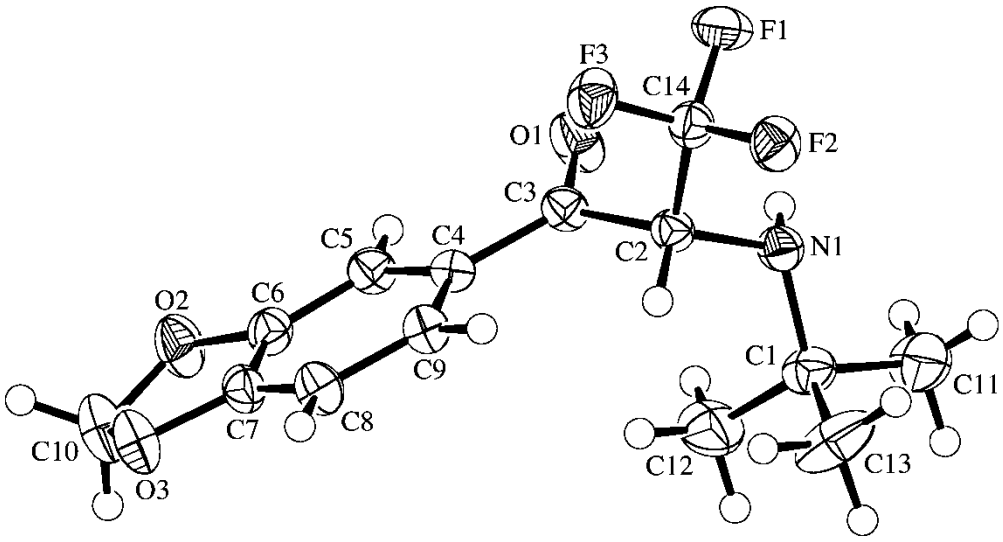
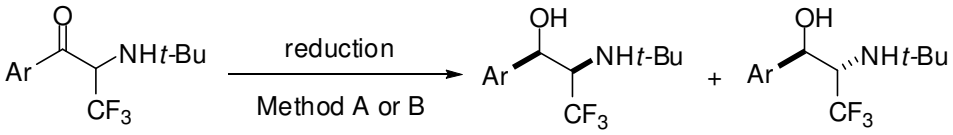


Fig. 2. ORTEP plot [8] of the molecular structure of one of the symmetry-independent molecules of **6a** (50% probability ellipsoids; arbitrary numbering of the atoms)

After chromatographic workup, α-amino-α-(trifluormethyl) ketones **6** were used as substrates for the preparation of β-amino-β-(trifluoromethyl) alcohols **9a–e** (Scheme 5). Various reducing agents and reaction conditions were tested ($NaBH_4$/EtOH; $NaBH_4$, $ZnCl_2$/EtOH; $LiBH_4$/EtOH; BH_3/THF; $LiAlH_4$/THF; Raney-Ni/MeOH) and the best chemical yields and stereoselectivities were achieved when the reduction was performed with $LiAlH_4$ in THF (Table 3). The ^{1}H NMR analysis of the crude reaction mixtures showed that the products **9** were formed as ca. 95:5 mixtures of diastereoisomers. However, by using Raney-Ni as the reducing reagent in the reaction with **6e** performed in MeOH, the ratio of diastereoisomers was changed to 24:76 in favor of the opposite isomer.



6a-e *threo*-**9a-e** *erythro*-**9a-e**

Method A: $LiAlH_4$, THF, 0 °C to r.t., 12 h
Method B: Raney-Ni, MeOH, reflux, 3 h

Scheme 5. Syntheses of β-amino-β-(trifluoromethyl) alcohols **9a–e** via reductions of α-amino-α-(trifluormethyl) ketones **6a–e**

Table 3. Diastereoselective reductions of α-amino-α-(trifluormethyl) ketones **6**

Entry	**6**	Ar	Reduction method	*dr*	Yield [%][a]		
					total	*fast*-**9'**[b]	*slow*-**9**[b]
1	**a**	3,4-$(OCH_2O)C_6H_3$	A	95 : 5	71	–	50
2	**b**	3,4-$(MeO)_2C_6H_3$	A	95 : 5	84	–	30
3	**c**	4-$MeOC_6H_4$	A	95 : 5	84	–	67
4	**d**	7-Et-Benzofur-2-yl	A	90 : 10	74	–	56
5	**e**	Ph	A	96 : 4	68	–	57
6	**e'**	Ph	B	24 : 76	57	39	–

[a] Yields of isolated products.

[b] Notations *fast* and *slow* relate to the polarity of the products, i.e., less polar and more polar, respectively.

The major components were isolated chromatographically, and their structures were confirmed by spectroscopic methods. For example, in the ^{13}C NMR spectrum of *slow*-**9e**, the signals of CHNH and CHOH were found as quartets with $^2J_{C,F}$ = 25.9 and $^3J_{C,F}$ = 1.5 Hz, respectively, at 59.2 and 71.8 ppm. In the case of *fast*-**9e**, the corresponding signals appeared at 60.3 and 68.9 ppm with $^2J_{C,F}$ = 26.91 and $^3J_{C,F}$ = 2.0 Hz, respectively. The structure of the major diastereoisomer obtained via $LiAlH_4$ reduction (*slow*-**9**) can be tentatively assigned as the *threo*-isomer based on the results of analogous reductions reported for other α-amino ketones [10]. Similarly, reductions of α-amino ketones with Raney-Ni occur diastereoselectively in favor of the *erythro*-isomer [11]. Thus, the *erythro*-configuration is attributed to the less polar product **9e'** (Table 3).

3. Conclusions

For the first time, the chemoselective trifluoromethylation of the C=N group of α-iminoketones derived from arylglyoxals was achieved using CF_3SiMe_3 (Ruppert-Prakash reagent, RPR). The change of the chemoselectivity of the CF_3-addition from the C=O to the C=N group originates from the in situ conversion of the imine into an iminium salt. The trifluoromethylated α-imino ketones obtained thereby were used for the preparation of β-amino-β-(trifluoromethyl) alcohols. Efficient highly diastereoselective reductions were performed with $LiAlH_4$ in THF. On the other hand, the procedure using Raney-Ni as the reducing agent in MeOH solution, led to the opposite diastereoisomer as the major product. The elaborated methods open a straightforward access to the preparation of a new type of β-amino-β-(trifluoromethyl) alcohols, which potentially are attractive substrates for the synthesis of more complex fluorinated products, e.g. heterocycles, of practical importance.

4. Experimental

4.1. General information

Melting points were determined on a Melt-Temp II apparatus (Aldrich) in capillaries, and they are uncorrected. The ^{1}H, $^{13}C\{^{1}H\}$ and ^{19}F NMR spectra were recorded on a Bruker Avance III 600 spectrometer using thesolvent signal as reference. Assignments of signals in ^{13}C NMR spectra were achieved using HMQC and HMBC techniques. IR spectra were measured using a NEXUS FT-IR spectrophotometer. The ESI-MS spectra were obtained using a Varian 500 MS LS Ion Trap spectrometer.

4.2. Materials

All solvents were used as commercial products. (Trifluoromethyl)trimethylsilane (RPR) was purchased from Fluorochem. Acetonitrile (MeCN) and trifluoroacetic acid (TFA) were dried over phosphorus pentoxide (P_2O_5) and freshly distilled prior to use. Tetrahydrofuran (THF) was dried over sodium in the presence of benzophenone and freshly distilled from the violet-coloured solution prior to use. Anhydrous dimethylformamide (DMF) was purchased from Sigma-Aldrich. 2,2-Dihydroxyethanones **5** [12a,b] and α-imino ketones **1** [6a,13] were prepared according to the known protocols.

*4.3. Reaction of α-imino ketones **1** with (trifluoromethyl)trimethylsilane (RPR) under the C=N activation conditions – general procedure*

Potassium hydrogenfluoride (KHF_2; 316mg, 2.5 mmol), anhydrous *N*,*N*-dimethylformamide (DMF) (0.25 ml), and the corresponding α-imino ketone **1** (1.0 mmol) dissolved in dry MeCN (1.5 ml) were placed in a dry two-neck flask, equipped with a septum and a balloon filled with argon. Next, trifluoroacetic acid (TFA; 428 mg, 3.75 mmol) dissolved in 0.5 ml of dry MeCN was added at –10 °C (ice bath). After 5 min, CF_3SiMe_3 (355 mg, 2.5 mmol) was added dropwise. The mixture was left at –15 °C (freezer) for 30 days. After this time, a saturated aqueous solution of K_2CO_3 was added and then the mixture was extracted with CH_2Cl_2 (4 x 5 ml). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration, the solvents were removed under reduced pressure. α-(Trifluoromethyl)-α-amino ketones were purified by column chromatography (SiO_2, hexane/Et_2O 85:15).

*2-(*tert-*Butylamino)-1-[(3',4'-methylendioxo)phenyl]-3,3,3-trifluoropropan-1-one* (**6a**). Yield: 141 mg (47%), colorless crystals, m.p. 72–75 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.08 (s, 9H, $(CH_3)_3C$), 2.68 (br. s, 1H, NH), 4.71 (q, $^3J_{H,F}$ = 7.9 Hz, 1H, CH), 6.11 (s, 2H, CH_2), 6.94□6.96 (m, 1 arom. CH), 7.50□7.51 (m, 1 arom. CH), 7.64□7.66 (m, 1 arom. CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.5 ($(\mathbf{C}H_3)_3C$), 50.8 ($(CH_3)_3\mathbf{C}$), 56.9 (q, $^2J_{C,F}$ = 28.2 Hz, CH), 102.2, 108.2, 108.4 (3 arom. CH), 123.8 (q, $^1J_{C,F}$ = 270.0 Hz, CF_3), 125.7 (CH_2), 130.1, 148.6, 150.0 (3 arom. C), 194.2 (C=O). ^{19}F NMR (565 MHz, $CDCl_3$): δ □71.3 (d, $^3J_{H,F}$ = 7.9 Hz, 3F, CF_3). IR (KBr): *ν* 3326*w* (NH), 2964*m*, 2907*w,* 1661*s* (C=O), 1602*s*, 1441*s*, 1253*vs,* 1164*vs*, 1115*s*. ESI-MS: 304 (75, $[M+1]^+$), 326 (100, $[M+23]^+$). Anal. calcd for $C_{14}H_{16}F_3NO_3$: C, 55.45; H, 5.32; found: C, 55.84; H, 5.10.

*2-(*tert-*Butylamino)-1-(3',4'dimethoxyphenyl)-3,3,3-trifluoropropan-1-one* (**6b**). Yield: 168 mg (53%), colorless crystals, m.p. 82–84 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.05 (s, 9H, $(CH_3)_3C$), 2.68 (br. s, 1H, NH), 3.95, 3.97 (2s, 6H, 2 CH_3O), 4.75 (q, $^3J_{H,F}$ = 7.9 Hz, 1H, CH), 6.94□6.96 (m, 1 arom. CH), 7.56□7.57 (m, 1 arom. CH), 7.63□7.64 (m, 1 arom. CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.6 ($(\mathbf{C}H_3)_3C$), 50.8 ($(CH_3)_3\mathbf{C}$), 55.1, 55.2 (2 CH_3O), 56.6 (q, $^2J_{C,F}$ = 28.5 Hz, CH), 110.2, 110.8, 124.0 (3 arom. CH), 123.9 (q, $^1J_{C,F}$ = 280.0 Hz, CF_3), 128.5, 149.5, 154.6 (3 arom. C), 194.6 (C=O). ^{19}F NMR (565 MHz, $CDCl_3$): δ □71.3 (d, $^3J_{H,F}$ = 7.9 Hz, 3F, CF_3). IR (KBr): *ν* 3296*m* (NH), 2984*m*, 2970*m*, 1674*s* (C=O),

1592*s*, 1513*s*, 1266*vs,* 1240*vs*, 1168*vs*, 1151*vs*. ESI-MS: 320 (100, $[M+1]^+$), 342 (35, $[M+23]^+$). Anal. calcd for $C_{15}H_{20}F_3NO_2$: C, 56.42; H, 6.31; found: C, 56.61; H, 6.47.

*2-(*tert-*Butylamino)-1-(4'-methoxyphenyl)-3,3,3-trifluoropropan-1-one* (**6c**).

Yield: 202 mg (70%), colorless crystals, m.p. 71–73 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.05 (s, 9H, $(CH_3)_3C$), 2.70 (br. s, 1H, NH), 3.90 (s, 3H, CH_3O), 4.74 (q, $^3J_{H,F}$ = 7.9 Hz, 1H, CH), 6.99□7.00 (m, 2 arom. CH), 7.99□8.00 (m, 2 arom. CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.5 (($\mathbf{C}H_3)_3C$), 50.8 ($(CH_3)_3\mathbf{C}$), 55.6 (CH_3O), 56.8 (q, $^2J_{C,F}$ = 28.1 Hz, CH), 114.2, 131.4 (4 arom. CH), 123.9 (q, $^1J_{C,F}$ = 279.5 Hz, CF_3), 128.3, 164.6, (2 arom. C), 194.4 (C=O). ^{19}F-NMR (565 MHz, $CDCl_3$): δ □71.3 (d, $^3J_{H,F}$ = 7.9 Hz, 3F, CF_3). IR (KBr): *ν* 3333*w* (NH), 2973*w*, 1661*s* (C=O), 1598*s*, 1569*s*, 1253*s,* 1224*s*, 1184*s*. ESI-MS: 290 (65, $[M+1]^+$), 312 (100, $[M+23]^+$). Anal. calcd for $C_{14}H_{18}F_3NO_2$: C, 58.12; H, 6.27; found: C, 58.38; H, 5.89.

*2-(*tert-*Butylamino)-1-(7'-ethylbenzofur-2'-yl)-3,3,3-trifluoropropan-1-one* (**6d**).

Yield: 131 mg (40%), colorless crystals, m.p. 75–79 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.10 (s, 9H, $(C\mathbf{H}_3)_3C$), 1.41 (t, $^3J_{H,H}$ = 7.6 Hz, 3H, CH_3), 2.62 (s, 1H, NH), 3.03 (q, $^3J_{H,H}$ = 7.6 Hz, 2H, CH_2), 4.81 (q, $^3J_{H,F}$ = 7.4 Hz, 1H, CH), 7.26□7.30 (m, 1 arom. CH), 7.36□7.38 (m, 1 arom. CH), 7.58–7.60 (m, 1 arom. CH), 7.70 (s, 1H, CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.8 (CH_3), 22.9 (CH_2), 29.6 (($\mathbf{C}H_3)_3C$), 50.8 ($(CH_3)_3\mathbf{C}$), 58.3 (q, $^2J_{C,F}$ = 29.0 Hz, CH), 115.5, 121.1, 124.6, 128.2 (4 arom. CH), 123.8 (q, $^1J_{C,F}$ = 280.2 Hz, CF_3), 126.7, 129.2, 150.9, 155.0 (4 arom. C), 187.0 (C=O). ^{19}F-NMR (565 MHz, $CDCl_3$): δ □71.7 (d, $^3J_{H,F}$ = 7.4 Hz, 3F, CF_3). IR (KBr): *ν* 3322*w* (NH), 2970*m*, 2911*w,* 1634*s* (C=O), 155s, 1259*s,* 1171*s*, 1154*s*, 1125*s*. ESI-MS: 328 (100 $[M+1]^+$). Anal. calcd for $C_{17}H_{20}F_3NO_2$: C, 62.38; H, 6.16; found: C, 62.56; H, 6.20.

*2-(*tert-*Butylamino)-1-phenyl-3,3,3-trifluoropropan-1-one* (**6e**).

Yield: 140 mg (54%), colorless crystals, m.p. 76–78 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.06 (s, 9H, $(C\mathbf{H}_3)_3C$), 2.68 (br. s, 1H, NH), 4.80 (q, $^3J_{H,F}$ = 7.2 Hz, 1H, CH), 7.53□7.55 (m, 2 arom. CH), 7.64□7.67 (m, 1 arom. CH), 8.00□8.01 (m, 2 arom. CH). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 29.6 (($\mathbf{C}H_3)_3C$), 50.8 ($(CH_3)_3\mathbf{C}$), 57.1 (q, $^2J_{C,F}$ = 28.2 Hz, CH), 123.8 (q, $^1J_{C,F}$ = 280.1 Hz, CF_3), 128.9, 129.0, 134.3 (5 arom. CH), 135.3 (1 arom. C), 196.5 (C=O) ppm. ^{19}F NMR (565 MHz, $CDCl_3$): δ □71.1 (d, $^3J_{H,F}$ = 7.2 Hz, 3F, CF_3). IR (KBr): *ν* 3332*w* (NH), 2970*w*, 2865*w*, 1677*s* (C=O), 1595*w*, 1444*w*, 1375*m,* 1217*s*, 1164*s*, 1118*s*. ESI-MS: 260 (100, $[M+1]^+$), 282 (25, $[M+23]^+$). Anal. calcd for $C_{13}H_{16}F_3NO$: C, 60.22; H, 6.22; found: C, 60.13; H, 6.23.

*2-(*tert-*Butylamino)-1-(4'-bromophenyl)-3,3,3-trifluoropropan-1-one* (**6f**).

Yield: 64 mg (19%), colorless solid, m.p. 77–79 °C (hexane). ^{1}H NMR (600 MHz, DMSO-d6): δ 1.03 (s, 9H, (C**H**$_3$)$_3$C), 2.53 (s, 1H, NH), 4.98 (q, $^{3}J_{H,F}$ = 7.2 Hz, 1H, CH), 7.74□7.77 (m, 2 arom. CH), 8.00□8.03 (m, 2 arom. CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 34.1 ((**C**H$_3$)$_3$C), 56.0 ((CH$_3$)$_3$**C**), 62.4 (q, $^{2}J_{C,F}$ = 27.9 Hz, CH), 122.5 (4 arom. CH), 129.5 (q, $^{1}J_{C,F}$ = 279.5 Hz, CF_3), 134.7, 139.4 (2 arom. C), 201.5 (C=O). ^{19}F NMR (565 MHz, $CDCl_3$): δ □71.8 (d, $^{3}J_{H,F}$ = 7.9 Hz, 3F, CF_3). IR (KBr): *ν* 3322*m* (NH), 2970*m*, 1681*vs* (C=O), 1586*vs*, 1563*m*, 1247*vs,* 1210*vs*, 1178*vs*. HR-ESI-MS: 338.03649 (338.03619 calcd. for $C_{13}H_{16}BrF_3NO$, $[M+1]^+$).

4.4. Reduction of α-(trifluoromethyl)-α-amino ketones **6**

Method A–general procedure: α-(Trifluoromethyl)-α-amino ketone **6** (1.0 mmol) was placed in a dry flask and dissolved in dry THF (~ 2 ml). Then, $LiAlH_4$ (1.0 ml, 2 M solution in THF, 2 mmol) was added at –10°C (ice bath), the solution was stirred magnetically and left to reach room temperature (12h). After this time, the reaction was subsequently quenched with water (~ 2 ml) and saturated NaOH and extracted with Et_2O (5 x 5 ml). The organic layers were combined, dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. The obtained β-(trifluoromethyl)-β-amino alcohols **9**, obtained as a mixture of diastereoisomers, were purified using column chromatography (SiO_2, hexanes/Et_2O 85:15).

*2-(*tert*-Butylamino)-1-[(3',4'-methylendioxy)phenyl]-3,3,3-trifluoropropan-1-ol* (**9a**). Total yield *slow*-**9a** + *fast*-**9'a**: 215 mg (71%). Yield of *slow*-**9a**: 152 mg (50%), colorless crystals, m.p. 73–75 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.14 (s, 9H, (C**H**$_3$)$_3$C), 1.25 (br. s, 1H, NH), 3.26* (d, $^{3}J_{H,H}$ = 6.0 Hz, 1H, OH), 3.58 (dq, $^{3}J_{H,H}$ = 6.0 Hz, $^{3}J_{H,F}$ = 7.3 Hz, 1H, C**H**NH), 4.82* (*pseudo*-t, $^{3}J_{H,H}$ = 6.0 Hz, 1H, C**H**OH), 5.98 (s, 2H, CH_2), 6.79□6.82 (m, 2 arom. CH), 6.87□6.88 (m, 1 arom. CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 30.2 ((**C**H$_3$)$_3$C), 51.0 ((CH$_3$)$_3$**C**), 59.1 (q, $^{2}J_{C,F}$ = 25.8 Hz, CHNH), 71.4 (q, $^{4}J_{C,F}$ = 1.5 Hz, 1H, CHOH), 101.0 (CH_2), 107.3, 107.9, 120.4 (3 arom. CH), 125.5 (q, $^{1}J_{C,F}$ = 282.2 Hz, CF_3), 133.6, 147.3, 147.6 (3 arom. C). ^{19}F NMR (565 MHz, $CDCl_3$): δ □69.1 (d, $^{3}J_{H,F}$ = 7.3 Hz, 3F, CF_3). IR (KBr): *ν* 3332*m* (NH), 3207*br.s* (OH), 2970*s*, 2918*m*, 1503*vs*, 1484*vs*, 1154*vs*, 1138*vs*, 1108*vs*. HR-ESI-MS: 306.13111 (306.13115 calcd. for $C_{14}H_{19}F_3NO_3$, $[M+1]^+$), 328.11284 (328.11310 calcd. for $C_{14}H_{18}F_3NNaO_3$, $[M+23]^+$).

*2-(*tert*-Butylamino)-1-(3',4'-dimethoxyphenyl)-3,3,3-trifluoropropan-1-ol* (**9b**).

Total yield: *slow*-**9b** + *fast*-**9'b**: 268 mg (84%). Yield of *slow*-**9b**: 96 mg (30%), colorless crystals, m.p. 115–117 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.12 (s, 9H, $(CH_3)_3C$), 1.21 (s, 1H, NH), 3.18* (d, $^3J_{H,H}$ = 6.2 Hz, 1H, OH), 3.58 (dq, $^3J_{H,H}$ = 6.2 Hz, $^3J_{H,F}$ = 7.9 Hz, 1H, C**H**NH), 3.90, 3.91 (2s, 6H, 2 CH_3O), 4.85* (*pseudo*-t, $^3J_{H,H}$ = 6.2 Hz, 1H, C**H**OH), 6.85□6.90 (m, 2 arom. CH), 6.92□6.93 (m, 1 arom. CH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 30.2 ((**C**$H_3)_3$C), 50.9 ($(CH_3)_3$**C**), 55.90, 55.91 (2 CH_3O), 59.2 (q, $^2J_{C,F}$ = 25.8 Hz, CHNH), 71.6 (q, $^3J_{C,F}$ = 1.5 Hz, 1H, CHOH), 110.3, 110.8, 119.3 (3 arom. CH), 125.6 (q, $^1J_{C,F}$ = 282.3 Hz, CF_3), 132.1, 148.8, 148.9, (3 arom. C) ppm. ^{19}F NMR (565 MHz, $CDCl_3$): δ □69.2 (d, $^3J_{H,F}$ = 7.9 Hz, 3F, CF_3) ppm. IR (KBr): *v* 3319*m* (NH), 3220*br.m* (OH), 2970*m*, 2954*m*, 1510*m*, 1365*w*, 1270*s,* 1224*s*, 1151*vs*, 1125*s*, 1026*m*. ESI-MS: *m/z* 322 (100, $[M+1]^+$), 344 (20, $[M+23]^+$). Anal. calcd for $C_{15}H_{22}F_3NO_3$: C, 56.07; H, 6.90; found: C, 56.22; H, 6.94.

*2-(*tert-*Butylamino)-1-(4'-methoxyphenyl)-3,3,3-trifluoropropan-1-ol* (**9c**).

Total yield *slow*-**9c** + *fast*-**9'c**: 244 mg (84%). Yield of *slow*-**9c**: 195 mg (67%), colorless solid, m.p. 71–73 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.13 (s, 9H, $(CH_3)_3C$), 1.29 (br. s, 1H, NH), 3.19 (s, 1H, OH), 3.60 (dq, $^3J_{H,H}$ = 4.2 Hz, $^2J_{H,F}$ = 7.9 Hz, 1H, C**H**NH), 3.83 (s, 3H, CH_3O), 4.87 (d, $^3J_{H,H}$ = 4.2 Hz, 1H, C**H**OH), 6.89□6.91 (m, 2 arom. CH), 7.27□7.29 (m, 2 arom. CH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 30.2 ((**C**$H_3)_3$C), 50.9 ($(CH_3)_3$**C**), 55.2 (CH_3O), 59.2 (q, $^2J_{C,F}$ = 25.8 Hz, CHNH), 71.3 (q, $^3J_{C,F}$ = 1.5 Hz, 1H, CHOH), 113.6, 128.0 (4 arom. CH), 125.6 (q, $^1J_{C,F}$ = 282.3 Hz, CF_3), 131.7, 159.4 (2 arom. C). ^{19}F NMR (565 MHz, $CDCl_3$): δ □69.2 (d, $^3J_{H,F}$ = 7.9 Hz, 3F, CF_3). IR (KBr): *v* 3332*br.m* (NH, OH)**, 2974*m*, 1661*s*, 1602*s*, 1572*s,* 1250*vs*, 1217*s*, 1184*vs*. ESI-MS: 292 (100, $[M+1]^+$). Anal. calcd for $C_{14}H_{20}F_3NO_2$: C, 57.72; H, 6.92; found: C, 57.77; H, 7.01.

*2-(*tert-*Butylamino)-1-(7'-ethylbenzofur-2'-yl)-3,3,3-trifluoropropan-1-ol* (**9d**).

Total yield of *slow*-**9d** + *fast*-**9'd**: 243 mg (74%). Yield of *slow*-**9d**: 184 mg (56%), colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18 (s, 9H, $(CH_3)_3C$), 1.41 (t, $^3J_{H,H}$ = 7.8 Hz, 3H, CH_3), 1.63 (s, 1H, NH), 2.88□2.98 (m, 2H, CH_2), 3.78 (dq, $^3J_{H,H}$ = 4.2 Hz, $^3J_{H,F}$ = 7.4 Hz 1H, C**H**NH), 3.63 (s, 1H, OH), 4.99 (d, $^3J_{H,H}$ = 4.2 Hz, 1H, C**H**OH), 6.67 (s, 1H, CH),7.10□7.11 (m, 1 arom. CH), 7.14□7.17 (m, 1 arom. CH), 7.37□7.39 (m, 1 arom. CH). ^{13}CNMR (150 MHz, $CDCl_3$): δ 13.8 (CH_3), 22.9 (CH_2), 29.6 ((**C**$H_3)_3$C), 50.8 ($(CH_3)_3$**C**), 58.4 (q, $^2J_{C,F}$ = 27.0 Hz, **C**HNH), 65.8 (q, $^3J_{C,F}$= 2.1 Hz, **C**HOH), 105.0, 118.7, 123.0, 123.6 (4 arom. CH), 125.2 (q, $^1J_{C,F}$ = 282.3 Hz, CF_3), 127.4, 124.7, 153.5, 154.9 (4 arom. C). ^{19}F NMR (565 MHz,

* In contrast to amino alcohols **9c-e**, for compounds **9a**,**b** signals attributed to the H-atoms of OH and CH groups in the ^{1}H NMR spectra were observed as d and *pseudo*-t, respectively.

** For derivatives **9c,d,e'** absorption bands attributed to the OH and NH groups appeared as broad bands and it was not possible to identify separate absorption for OH and NH groups.

$CDCl_3$): δ −70.3 (d, $^3J_{H,F}$ = 7.4 Hz, 3F, CF_3). IR (KBr): *v* 3401*br.s* (NH, OH)**, 2970*vs*, 2927*s*, 1602*m*, 1421*s,* 1371*vs*, 1246*vs*, 1161*vs*. HR-ESI-MS: 330.16745 (330.16754 calcd. for $C_{17}H_{23}F_3NO_2$, $[M+1]^+$).

*2-(*tert-*Butylamino)-1-phenyl-3,3,3-trifluoropropan-1-ol* (**9e**).

Total yield: *slow*-**9e** + *fast*-**9'e**: 177 mg (68%). Yield of *slow*-**9e**: 149 mg (57%), colorless crystals, m.p. 83–85 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.11 (s, 9H, $(CH_3)_3C$), 1.27 (s, 1H, NH), 3.27 (s, 1H, OH), 3.61 (dq, $^3J_{H,F}$ = 7.9 Hz, $^3J_{H,H}$ = 4.2 Hz, 1H, C**H**NH), 4.88 (d, $^3J_{H,H}$ = 4.2 Hz, 1H, C**H**OH), 7.29−7.32 (m, 1 arom. CH), 7.33−7.35 (m, 4 arom. CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 30.1 ((**C**$H_3)_3$C), 51.0 ($(CH_3)_3$**C**), 59.2(q, $^2J_{C,F}$ = 25.9 Hz, CHNH), 71.8 (q, $^3J_{C,F}$ = 1.5 Hz, CHOH), 125.6 (q, $^1J_{C,F}$ = 282.3 Hz, CF_3), 126.8, 127.9, 128.1 (5 arom. CH), 139.6 (1 arom. C). ^{19}F NMR (565 MHz, $CDCl_3$): δ −69.0 (d, $^3J_{H,F}$ = 7.9 Hz, 3F, CF_3). IR (KBr): *v* 3315*m* (NH), 3207*br.m* (OH), 2967*m*, 1612*m*, 1519*s*, 1246*vs*, 1161*vs,* 1125*vs,* 1026*m*. ESI-MS: 262 (65, $[M+1]^+$), 284 (100, $[M+23]^+$). Anal. calcd for $C_{13}H_{18}F_3NO$: C, 59.76; H, 6.94; found: C, 59.75; H, 6.93.

Method B: To a solution of α-(trifluoromethyl)-α-amino ketone **6e** in MeOH, a portion of a freshly prepared suspension of Raney-Nickel in MeOH (~ 2 ml) was added. The mixture was heated to reflux for 4 h (the progress of the reaction should be controlled by TLC analysis because the reaction time strongly depends from the quality of Raney-Ni). Then, Raney-Nickel was removed by filtration through a Cellite pad, and the solvent was removed in vacuo. Analytically pure product was obtained after purification using column chromatography.

*2-(*tert-*Butylamino)-1-phenyl-3,3,3-trifluoropropan-1-ol* (**9e'**).

Total yield of *slow*-**9e** + *fast*-**9'e**: 149 mg (57%). Yield of *fast*-**9'e**: 102 mg (39%), colorless crystals, m.p. 32–34 °C (hexane). ^{1}H NMR (600 MHz, $CDCl_3$):*** δ 1.00 (s, 9H, (C**H**$_3)_3$C), 3.38 (dq, $^3J_{H,F}$ = 8.2 Hz, $^3J_{H,H}$ = 4.2 Hz, 1H, C**H**NH), 4.78 (d, $^3J_{H,H}$ = 4.2 Hz, 1H, C**H**OH), 7.29−7.32 (m, 1 arom. CH), 7.37−7.41 (m, 4 arom. CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.9 ((**C**$H_3)_3$C), 50.9 ($(CH_3)_3$**C**), 60.3 (q, $^2J_{C,F}$ = 26.1 Hz, **C**HNH), 68.9 (q, ^3J = 2.0 Hz, **C**HOH), 126.1 (q, $^1J_{C,F}$ = 281.0 Hz, CF_3), 126.2, 127.7, 128.3 (5 arom. CH), 142.4 (1 arom. C). ^{19}F NMR (565 MHz, $CDCl_3$): δ −72.2 (d, $^3J_{H,F}$ = 8.2 Hz, 3F, CF_3). IR (KBr): *v* 3368*br.s* (NH, OH)**, 3063*s*, 2970*s*, 2924*s*, 1500*m*, 1447*s*, 1368*s*, 1121*s*. ESI-MS: 262 (100 $[M+1]^+$, 284 (20, $[M+23]^+$). Anal. calcd for $C_{13}H_{18}F_3NO$: C, 59.76; H, 6.94; found: C, 59.82; H, 6.88.

*** Absorption signals of NH and OH groups could not be found in the registered spectrum.

4.6. X-ray crystal-structure determination of **6e**

All measurements were made on an Agilent Technologies Super Nova area detector diffractometer [14] using Cu K_α radiation (λ 1.54184 Å) from a micro-focus X-ray source and an Oxford Instruments Cryojet XL cooler. The data collection and refinement parameters are given below [15] and a view of the molecule is shown in Fig. 2. Data reduction was performed with CrysAlisPro [14]. The intensities were corrected for Lorentz and polarization effects, and an empirical absorption correction using spherical harmoics [14] was applied. Equivalent reflections were merged. The structure was solved by direct methods using SHELXS-2013 [16], which revealed the positions of all non-hydrogen atoms. There are two symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program *PLATON* [17], but none could be found. The non-hydrogen atoms were refined anisotropically. The amine H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). The refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Neutral atom scattering factors for non-hydrogen atoms were taken from ref. [18], and the scattering factors for H-atoms were taken from ref. [19]. Anomalous dispersion effects were included in F_c [20]; the values for f' and f'' were those of ref. [21]. The values of the mass attenuation coefficients are those of ref. [22]. The SHELXL-2013 program [16] was used for all calculations.

Crystal data for **6e**: $C_{14}H_{16}F_3NO_3$, M = 303.28, crystallized from Et_2O/*i*Pr_2O/*i*PrOH/EtOH/MeOH/CH_2Cl_2, colorless, prism, crystal dimensions 0.17× 0.18× 0.20 mm, triclinic, space group $P\bar{1}$, Z = 4, reflections for cell determination 7874, 2θ range for cell determination 4 – 153°, a = 10.6646(3) Å, b = 10.7270(4) Å, c = 14.4117(4) Å, α = 84.120(3)°, β = 79.985(3)°, γ = 62.748(3)°, V = 1442.86(9) Å^3, T = 160(1) K, D_X = 1.396 g·cm^{-3}, μ(Cu$K\alpha$) = 1.069 mm^{-1}, scan type ω, $2\theta_{(max)}$ = 153.3°, transmission factors (min; max) 0.714; 1.000, total reflections measured 12947, symmetry independent reflections 5967,

reflections with $I > 2\sigma(I)$ 5525, reflections used in refinement 5967, parameters refined 394, $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0351, $wR(F^2)$ [all data] = 0.0950 ($w = [\sigma^2(F_o^2)+(0.0463P)^2+0.3636P]^{-1}$, where $P = (F_o^2+2F_c^2)/3$), goodness of fit 1.057, secondary extinction coefficient 0.0022(4), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) = 0.29; –0.24 e Å^{-3}.

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6. References

[1] a) P. Kirsch, Modern Fluoroorganic Chemistry, Wiley-VCH, Weinheim, Germany, 2004; b) J.-P. Bégué, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine, Wiley, Hoboken, New Jersey, 2008;c) K. Müller, C. Faeh, F. Diedrich, Science 317 (2007) 1881–1886; d) V. Nenajdenko (Ed.), Fluorine in Heterocyclic Chemistry, Springer Verlag, Berlin, 2013; e) J. Wang, M. Sanchez-Rosello, J.L. Aceña, C. del Pozo, A.E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, Chem. Rev. 114 (2014) 2432–2506.

[2] a) K. Soai, S. Niwa, Chem. Rev. 92 (1992) 833–856; b) D.J. Ager, I. Prakash, D.R. Schaad, Chem. Rev. 96 (1996), 835–875; c) E.J. Corey, C.J. Helal, Angew. Chem. Int. Ed. 37 (1998) 1986–2012; d) J. Franzén, M. Marigo, D. Fielenbach, T.C. Wabnitz, A. Kjærsgaard, K.A. Jørgensen, J. Am. Chem. Soc. 127 (2005) 18296–18304.

[3] a) P. Bravo, M. Crucianelli, T. Ono, M. Zanda, J. Fluorine Chem. 97 (1999) 27–49; b) Y. Fujwara, T. Katagiri, K. Uneyama, Tetrahedron Lett. 44 (2003) 6161–6165; c) G. Mlostoń, E. Obijalska, H. Heimgartner, J. Fluorine Chem. 131 (2010) 829–843.

[4] a) R. E. Marti, J. Heinzer, D. Seebach, Liebigs Ann. Chem. (1995) 1193–1215; b) A.K. Beck, D. Seebach, Chem. Ber. 124 (1991), 2897–2911; c) J. Pytkowicz, O. Stephany, S. Marinkovic, Org. Biol. Chem. 8 (2010) 4540–4542; d) J. Simon, E. Chelain, T. Brigaud, Org. Lett. 14 (2012) 604–607; e) F. Huguenot, T. Brigaud, J. Org. Chem. 71 (2006) 7075–7078; f) N.M. Karimova, Yu.L. Teplenicheva, A.F. Kolomiets, A.V. Fokin, *Russ. Chem. Bull* .46 (1997) 1136–1139; g) T. Katagiri, H. Ihara, M. Takahashi, Tetrahedron: Asymmetry 8 (1997) 2933–2937; h) F. Grellpois, J. Nonnenmacher, F. Lachaud, Org. Biol. Chem. 9 (2011) 1160–1168; i) A. Arnone, P. Bravo, S. Capelli, G. Fronza, S.V. Meille, M. Zanda, G. Cavicchio, M. Crucianelli, J. Org. Chem. 61 (1996) 3375–3378; j)

S. Fustero, A. Navaro, B. Pina, A. Asensio, P. Bravo, M. Crucianelli, A. Volonterio, M. Zanda, J. Org. Chem. 63 (1998) 6210–6219.

[5] a) R.P. Singh, J.M. Shreeve, Tetrahedron 56 (2000) 7613–7632; b) J.-A. Ma, D. Cahard, J. Fluorine Chem. 128 (2007) 975–996; c) G. Rubiales, C. Alonso, E.M. DeMarigorta, F. Palacios, Arkivoc (2014) ii, 362–405.

[6] a) G. Mloston, E. Obijalska, A. Linden, H. Heimgartner, Tetrahedron: Asymmetry 19 (2008) 1676–1683; b) G.Mlostoń, E. Obijalska, A. Tafelska-Kaczmarek, M. Zaidlewicz, J. Fluorine Chem. 131 (2010) 1289–1296; c) G. Mlostoń, E. Obijalska, H. Heimgartner, J. Fluorine Chem. 132 (2011) 951–955.

[7] a) V.V. Levin, A.D. Dilman, P.A. Belyakov, M.I. Struchkova, V.A. Tartakovsky, Eur. J. Org. Chem.(2008), 5226–5230; b) R.T. Gritsenko, V.V. Levin, A.D. Dilman, P.A. Belyakov, M.I. Struchkova, V.A. Tartakovsky, Tetrahedron Lett. 50 (2009) 2994–2997; c) G.K.S. Prakash, R. Mogi, G.A. Olah, Org. Lett. 8 (2006) 3589–3592; d) G.K.S. Prakash, M. Mandal, G.A. Olah, Angew. Chem. Int. Ed. 40 (2001) 589–590; e) V.A. Petrov, Tetrahedron Lett. 41 (2000) 6959–6963.

[8] C.K. Johnson, ORTEP II: Report ORNL-5138, OakRidge National Laboratories, Oak Ridge, TN, 1976.

[9] J. Bernstein, R.E. Davis, L. Shimoni, N.-L. Chang, Angew. Chem. Int. Ed. Engl. 34 (1995) 1555–1573.

[10] a) D.T. Collin, D. Hartley, D. Jack, L.H.C. Lunts, J.C. Press, A.C. Ritchie, P. Toon, J. Med. Chem. 13 (1970) 674-680; b) D.L. Musso, N.B. Mehta, F.E. Soroko, Bioorg. Med. Chem. Lett. 7 (1997) 1–6.

[11] a) H. Schulz, Pharmazie 22 (1967) 19–22; b) L. Villa, F. Taddei, L. Schenett, V. Ferri, Farmaco-Edizione Scientifica 29 (1974) 159–166; c) M.A. Dumpis, N.I. Kudryashova, N.V. Khromov-Borisov, J. Org. Chem. USSR 21 (1985) 1939–1944.

[12] a) G. Fodor, Ö. Kovács, J. Am. Chem. Soc. 71 (1949) 1045–1048; b) C. Rioux-Lacoste, C. Viel, Bull. Soc. Chim. Fr. (1974) 2463–2470.

[13] B. Alcaide, G. Escobar, R. Pérez-Ossorio, J. Plumet, D. Sanz, J. Chem. Res. Mini Print (1984) 1464–1472.

[14] CrysAlisPro, Version 1.171.37.31d, Agilent Technologies, Yarnton, Oxfordshire, England, 2014.

[15] CCDC-1009447contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, via www.ccdc.cam.ac.uk/data_request/cif.

[16] G.M. Sheldrick, Acta Crystallogr. A 64 (2008) 112–122.

[17] A.L. Spek, Acta Crystallogr. D 65 (2009) 148–155.

[18] E.N. Maslen, A.G. Fox, M.A. O'Keefe, in 'International Tables for Crystallography', Ed. A.J.C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, pp. 477–486.

[19] R.F. Stewart, E.R. Davidson, W.T. Simpson, J. Chem. Phys. 42 (1965) 3175–3187.

[20] J.A. Ibers, W.C. Hamilton, Acta Crystallogr. 17 (1964) 781–782.

[21] D.C. Creagh, W.J. McAuley, in 'International Tables for Crystallography', Ed. A.J.C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.6.8, pp. 219–222.

[22] D.C. Creagh, J.H. Hubbell, in 'International Tables for Crystallography', Ed. A.J.C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.4.3, pp. 200–206.