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Diastereoselective synthesis of cyclic 1,3-aminoalcohols bearing $CF_3(CCl_3)$-groups

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ABSTRACT

An aldol-type reaction of cyclic imines and cyclic lactims with carbonyl compounds activated by electron withdrawing trifluoromethyl or trichloromethyl groups proceeded without any catalyst under mild condition. β-Hydroxymethyl substituted cyclic imines or imidates are formed as a result of the reaction. The reduction of the prepared imines leads stereoselectively to the cyclic 1,3-aminoalcohols. Application of methyl trifluoropyruvate in this transformation opens an opportunity for the synthesis of γ-aminoacids derivatives which contain pyrrolidine moiety.

1. Introduction

There is a significant importance of the substances containing in their structures fluorinated moiety especially a trifluoromethyl group due to their potent usefulness for medicinal chemistry and material science [1]. The numerous successful strategies for syntheses of such compounds have been previously described [2]. However, the development of new methods that allow facile introduction of fluorinated fragments into organic molecules is still a topical task of modern organic synthesis.

In the recent years studies of the aldol reaction involving fluorine-containing carbonyl compounds have received a significant attention, especially the diastereo- and enantio-selective version of such transformations [3]. However, to the best of our knowledge, this methodology has never been applied to the reaction of fluorinated ketones with imines where C=N bound is incorporated in a ring. These imines are very promising building blocks from the synthetic point of view and some examples of their transformations have been recently published [4]. The pyrrolidine and piperidine fragment is an especially important structural unit of many natural compounds, for example, proline, pipecolinic acid and some alkaloids. We have previously reported that acyclic imines react smoothly with some trifluoromethylketones to give β-hydroxy-β-trifluoromethyl imines in good yields [5]. In this study we investigated the reactions of cyclic aliphatic imines and lactim ethers with hexafluoroacetone, methyl trifluoropyruvate, chloral and demonstrated that this approach provides a convenient and efficient synthesis of nitrogen heterocycles bearing a trihalomethylcarbinol moiety.

2. Results and discussion

In the framework of our ongoing study of the synthetic potential of cyclic imines we propose that the using of these imines in aldol-type condensation with certain halogenated carbonyl compounds opens the opportunity for a facile incorporation of trihalomethylcarbinol fragments at the β-position of nitrogen heterocycles. To examine this hypothesis, different starting 2-substituted pyrrolines **1** have been obtained accordingly to two main strategies (Scheme 1) which are usually applied for this purpose in the literature [6,7]. The variability of the synthetic approach to these imines together with accessibility and cheapness of starting *N*-vinyl pyrrolidone permit to synthesize a wide variety of requested imines **1a–g**.

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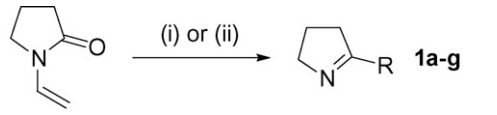
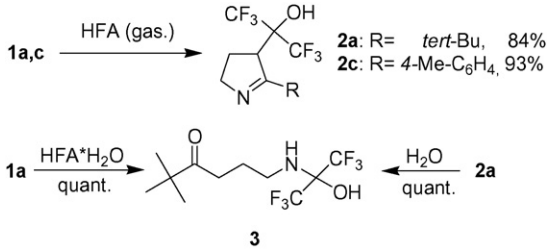


R= *tert*-Bu(**1a**), Ph(**1b**), 4-MeC$_6$H$_4$(**1c**), 4-MeOC$_6$H$_4$(**1d**), 4-FC$_6$H$_4$(**1e**), 2-Furyl(**1f**), 4-Py(**1g**)

Scheme 1. Synthesis of the starting imines **1**: (i) RCO_2Et and NaH, then HCl (aq.) (**1a**, **1b**, **1g**); (ii) RLi, then HCl (aq.) (**1b**–**f**).



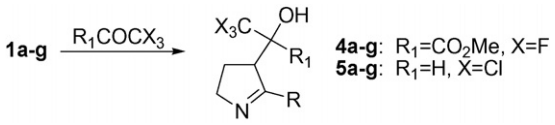
Scheme 2. Reactions of imines **1a**, **c** with HFA.

In the beginning of our investigation hexafluoroacetone (HFA) was allowed to react with model imines **1a** and **1c** in order to check their reactivity. It has been found that the reaction of both alkyl **1a** and aryl **1c** pyrrolines starts at low temperature (below −30 °C) and gives iminoalcohols **2a**, **c** in good yields during 6 h at ambient temperature (Scheme 2). Consequently, the reaction proceeds under extremely mild conditions without any catalyst in contrast to literature examples of aldol-type reaction of imines with carbonyl compounds. Usually such transformation demands acids or bases to complete the reaction [8]. The nature of solvents plays not significant role in this transformation, therefore, THF, DCM and toluene can be used, however, the usage of diethyl ether as a solvent permits to obtain products as crystalline solids directly from reaction mixtures. It should be noted that the crystalline products **2a** and **2c** are stable at air but they absorb water quickly in solution which results in destruction of the imine ring in spite of the fact that cyclic imines **1a**, **c** itself are stable even in water solution [9]. Indeed, treatment of the sterically hindered adduct **2a** with water led to the acyclic hemi-aminal **3** in 1/2 h which can be alternatively obtained by direct interaction between **1a** and hexafluoroacetone hydrate. These transformations illustrate the reversibility of the HFA addition to imine **1a** what is well known for classical aldol reaction under certain condition [10]. The formation of **3** using hexafluoroacetone hydrate opens the possibility of mild protection of the amino-group.

Besides NMR and MS data the molecular structure of adduct **2a** was established by the X-ray analysis (Fig. 1) [11]. Interestingly, the OH group forms no intramolecular hydrogen bridge towards the imino nitrogen whereas the 1,3-iminoalkohols often exhibits a strong intramolecular hydrogen bond between hydroxyl-group and nitrogen atom, inducing an almost planar six-membered ring [5]. Also normal C=N bond length 128 pm were observed [12].

Then we try to involve in the reaction with cyclic imines **1** other activated carbonyl compounds such as chloral and methyl trifluoropyruvate. The reaction of methyl trifluoropyruvate can open a very interesting possibility to construct the derivatives of γ-aminoacids which may be interesting from biochemical point of view. On the other hand the reaction with trichloroacetaldehyde can led to the trichloromethylcarbinols which are very remarkable and diverse synthetic building blocks [13].

Similar to the reaction of HFA, cyclic imines **1** react with methyl trifluoropyruvate and chloral at room temperature in an aldol-type



Scheme 3. Reactions of cyclic imines **1a**–**g** with methyl trifluoropyruvate and trichloroacetaldehyde.

reaction to afford the substituted β-hydroxyimines (Scheme 3) in high yield and good diastereoselectivity (up to 97% de) (Table 1). The diastereomeric excesses of iminoalcohols **4a**–**g** and **5a**–**g** were measured by ^{19}F for fluorine-contained compound and by ^{1}H together with ^{13}C NMR spectroscopy for others.

To establish the relative configuration of predominate diastereomer X-ray structural study was performed. Accordingly to the X-ray structural data [14] the configuration of the major diastereoisomer of **4e** is *syn* (*erythro*) (Figs. 2 and 3) [15]. Analogous to the molecular structure of iminoalcohol **2a** there is no intramolecular hydrogen bond between OH group and nitrogen atom in the structure of *syn* **4e**. Another structural feature of iminoalcohol **4e** is almost planar pyrroline ring and normal lengths of C=N double bond. As it may be concluded based on similarity of NMR spectral data for main stereoisomers of iminoalcohols **4** the configuration of all major diastereomers in these series are *syn* and several assumptions can be made to rationalize the observed stereoselectivity.

The control of the stereochemistry of the classical aldol reaction in diastereoselective manner has a subject of intensive researches especially over the last two decades [16], but a little is known about stereochemical behavior of cyclic imines in aldol reaction. Following the Zimmerman–Traxler rule, valid for the kinetically

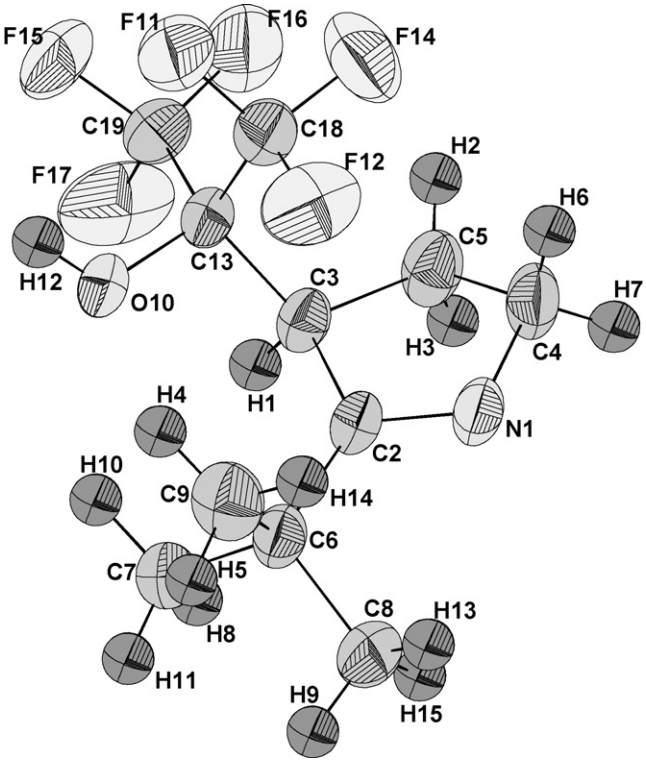


Fig. 1. The molecular structure of **2a** (thermal ellipsoids with 50% probability). Selected bond lengths (pm) and bond angels [11]: N(1)–C(2) 128.1(2), N(1)–C(4) 147.0(3), C(3)–C(13) 155.8(3), O(10)–C(13) 138.8(2); C(2)–N(1)–C(4) 110.81(2), N(1)–C(2)–C(6) 120.57(2), N(1)–C(2)–C(3) 113.01(2), C(5)–C(3)–C(13) 116.81(2), C(2)–C(3)–C(13) 116.66(2), O(10)–C(13)–C(18) 108.40(2), O(10)–C(13)–C(19) 108.26(2), O(10)–C(13)–C(3) 106.91(2).

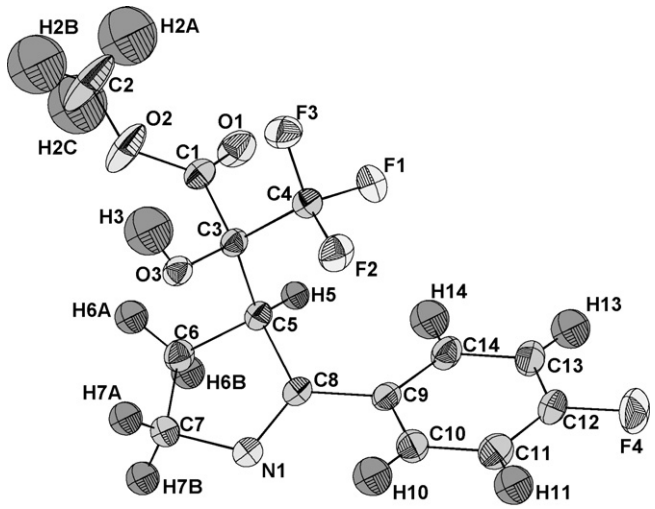


Fig. 2. The molecular structure of major diastereoisomer **4e** (thermal ellipsoids with 50% probability). Selected bond lengths (pm) and bond angels [14]: O(1)–C(1) 119.9(1), C(6)–C(7) 153.1(4), C(7)–N(1) 147.5(7), C(1)–C(3) 154.7(5), N(1)–C(8) 127.8(0), O(2)–C(2) 145.7(6), C(8)–C(9) 148.2(1), C(3)–O(3) 139.3(7); O(1)–C(1)–O(2) 124.96(1), N(1)–C(7)–C(6) 105.32(1), C(8)–N(1)–C(7) 109.84(1), O(3)–C(3)–C(4) 107.53(1), O(3)–C(3)–C(1) 114.53(1), C(4)–C(3)–C(1) 105.77(1), O(3)–C(3)–C(5) 109.27(1), C(4)–C(3)–C(5) 114.32(1), C(1)–C(3)–C(5) 105.57(1).

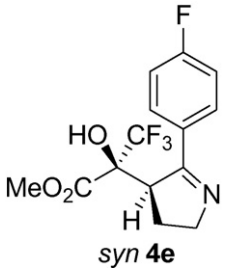
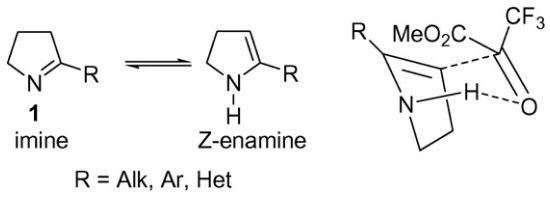


Fig. 3. Visualization of the molecular structure of *syn* **4e** in an extended manner (*zig-zag*).

controlled product, the stereochemistry of aldol product is determined by the configuration of the enolate or, in our case, by the configuration of the enamine. Incorporation of the enamine double bond to five-membered cycle makes possible generation only *Z*-enamine which should preferably gives the *syn* iminoalcohol (Scheme 4). This prediction coincides with the observed stereoselectivity.

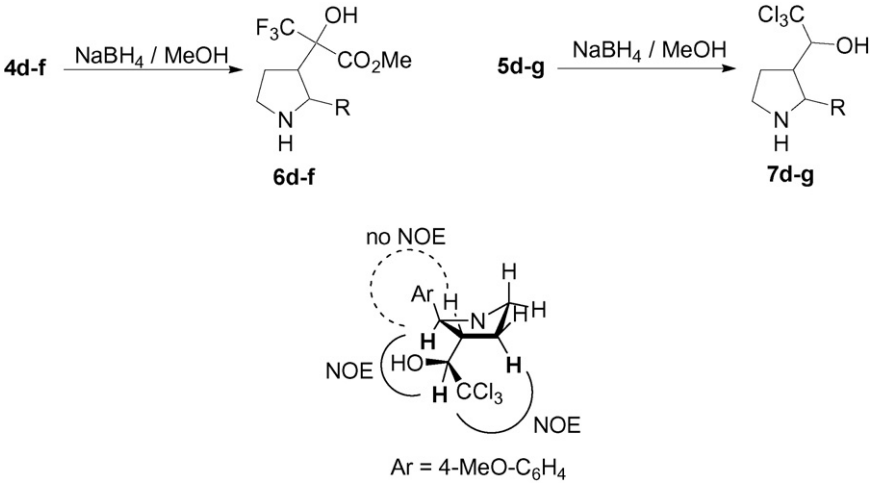


Scheme 4. The imine–enamine equilibrium and Zimmerman–Traxler transition state.

Table 1
Results of the reactions *via* Scheme 3

Entry	R	Product	Yield (%)	de (%)
1	*tert*-Bu	**4a**	71	94
2	C_6H_5	**4b**	81	89
3	4-Me–C_6H_4	**4c**	90	90
4	4-MeO–C_6H_4	**4d**	89	93
5	4-F–C_6H_4	**4e**	92	74
6	2-Furyl	**4f**	78	94
7	4-Py	**4g**	91	88
8	*tert*-Bu	**5a**	69	96
9	C_6H_5	**5b**	87	92
10	4-Me–C_6H_4	**5c**	85	94
11	4-MeO–C_6H_4	**5d**	85	95
12	4-F–C_6H_4	**5e**	84	80
13	2-Furyl	**5f**	75	97
14	4-Py	**5g**	90	90

However, we suggest that *syn*-adducts **4** are thermodynamically controlled products. Although some details of the reaction deserve further study, the reversibility of the aldol reaction of cyclic imines **1** as it was pointed out above for iminoalcohol **2a** may confirms our assumption. Moreover, realization of the Zimmerman–Traxler six-membered chairlike transition state in case of rigid cyclic imines **1** should be difficult for sterical reasons. For the same reasons an intramolecular hydrogen bond between OH group and nitrogen atom in the structure of iminoalcohols **4e** and **2a** is not observed whereas analogous linear β-iminoalcohols exhibits a strong intramolecular hydrogen bond inducing a six-membered ring [5]. The observed configuration of main diastereoisomers corresponds obviously to the most favorable isomers since the more sterically bulky group CO_2Me and C(R)=N fragment of the pyrroline cycle are the most distant from each other (Figs. 2 and 3).



Scheme 5. Reduction of **4** and **5** with $NaBH_4$ and NOESY data for **7d**.

Table 2
Results of the reduction *via* Scheme 4

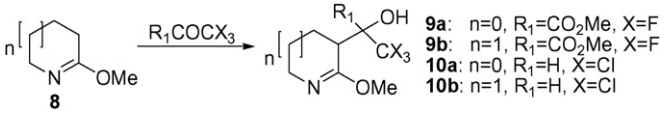
Entry	R	Product	Yield (%)	*trans* (%)
1	4-MeO–C_6H_4	**6d**	82	57
2	4-F–C_6H_4	**6e**	87	82
3	2-Furyl	**6f**	80	78
4	4-MeO–C_6H_4	**7d**	89	71
5	4-F–C_6H_4	**7e**	91	70
6	2-Furyl	**7f**	89	72
7	4-Py	**7g**	67	88

The prepared imines **4** and **5** are very favorable precursors for the preparation of substituted pyrrolidines bearing trihalomethylcarbinol fragment. We found that simple reduction of the imine double bond of the iminoalcohol **4** and **5** with sodium borohydride in methanol is appreciable (Scheme 5). As a result one diastereomer is formed preferentially. Moreover, the carrying out of the reaction under low temperature permits to achieve the moderate diastereoselectivity. It is clear from Table 2 that the nature of the substituent at position 2 of pyrroline ring does not significantly influence on the selectivity of the reduction.

The vicinal H–H constants between the protons at C-2 and C-3 carbon atoms of pyrrolidine ring are equal 7.3 Hz in both series of main stereoisomers of cyclic amines **6** and **7**. However, to prove the geometry of relative position of substituents at pyrrolidine cycle 2D NOE experiment for aminoalcohol **7d** was performed. As it is clear from the obtained results (Scheme 5) the aryl group and trichloromethylcarbinol fragment are placed in relative *trans*-location of pyrrolidine ring to minimize steric interactions between these bulky groups. It is notable that pyrrolidine alcohols **6** and **7** may be isolated as single diastereomers with 95+% purity just by double or in cases of **7d**–**f** single recrystallization of crude products from ethylacetate/hexane mixture.

Our interest in further investigation of cyclic imines led us to study cyclic lactim ethers. Cyclic lactim ethers are useful building blocks for large variety of practically important organics [17]. It has been shown that acyclic lactim ethers are very active in aldol reaction with chloral and bromal and low stereoselectivity is observed in this reaction [18].

We found that cyclic lactims **8** react with electron-deficient methyl trifluoropyruvate and chloral at room temperature to afford the substituted β-hydroxylactims in good yield (Scheme 6, Table 3). As one would expect the five-membered lactim ethers react with methyl trifluoropyruvate and chloral with lower diastereoselectivity compared to the reaction with cyclic imines **1** (Table 3 entries 1 and 3). Surprisingly, the diastereomeric excess of products **9b** and **10b** is very good (94 and 88% correspondingly)



Scheme 6. Reactions of cyclic lactims **8** with methyl trifluoropyruvate and chloral.

Table 3
Results of the reaction *via* Scheme 6

Entry	Product	Yield (%)	Main diastereomer (%)
1	**9a**	91	56
2	**9b**	84	97
3	**10a**	97	65
4	**10b**	89	94

and, probably now, it is impossible to make well-founded assumption to explain this fact.

3. Conclusion

In summary, we have studied the interactions of some cyclic imines and lactims with carbonyl compounds activated by electron withdrawing trifluoromethyl or trichloromethyl groups in an aldol-type reaction at mild condition and the absence of a catalyst. The products of the reaction are corresponding β-hydroxy imines which can be simply reduced to the 1,3-aminoalcohols. The using of methyl trifluoropyruvate in analogous transformation permits to obtain γ-aminoacids with moderate diastereoselectivity.

4. Experimental

4.1. General experimental procedures

NMR spectra were obtained on a Bruker DPX-200 (200.1 MHz for ^{1}H; 188.3 MHz for ^{19}F; 50.32 MHz for ^{13}C) or a Bruker AM-360 (360.1 MHz for ^{1}H; 90.5 MHz for ^{13}C) spectrometers, chemical shifts for ^{1}H NMR data are referenced internally to tetramethylsilane (0.0); chemical shifts for ^{13}C NMR data are referenced to corresponding $CDCl_3$ (77.2), $(CD_3)_2SO$ (39.5); chemical shifts for ^{19}F NMR data are referenced to $CFCl_3$ (0.0) or $PhCF_3$ (−63.90). High-resolution mass spectra (HRMS) and mass spectra (MS) were recorded using a Varian MAT CH7A instrument at 70 eV. Chemical ionization mass spectra (CIMS) were obtained on the same equipment with ammonia or isobutane as the reagent gas. The X-ray structural study was carried out on a Siemens P4 diffractometer using graphite monochromated Mo Kα radiation (λ = 71.073 pm). The structures were solved by *direct method* and anisotropically refined based on F^2 using the SHELX-97 program package [19]. The C–H hydrogen atoms were placed in calculated position, assigned common isotropic thermal parameters and allowed to ride on their parent atoms. Melting points are uncorrected. Ether was distilled from sodium/benzophenone prior to use. All other commercially available reagents and solvents were employed without further purification. The starting imines **1a**, **1b** and **1g** were prepared by the reaction of ethyl ester of the appropriate carboxylic acids with *N*-vinylpyrrolidin-2-one according to the described procedure [7,20]. Cyclic imines **1c**–**f** were obtained by the reaction of corresponding lithium compounds with *N*-vinylpyrrolidin-2-one [6]. The requested lactim ethers were synthesized from the corresponding lactams by the reaction with dimethyl sulphate [21].

4.2. General procedure for the reaction of cyclic imines with hexafluoroacetone

A solution of corresponding cyclic imine (10 mmol) in 30 ml of ether was placed into pressure-suitable ampoule, cooled to −190 °C and pumped off *in vacuo*. Then measured amount of gaseous hexafluoroacetone (12 mmol) was placed to the ampoule, the mixture warmed up to the ambient temperature and was stirred for 6 h. The crystal solid was filtered and dried in dry box at room temperature.

1,1,1,3,3,3-Hexafluoro-2-[5-(4-methylphenyl)-3,4-dihydro-2H-pyrrol-4-yl]propan-2-ol (**2c**), white crystals, mp 148–149 °C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.17–2.52 (5H, m, incl. 2.35 (3H, s, Ar–CH_3)), 3.82–4.23 (4H, m), 7.10–7.17 (2H, m, Ar–H), 7.52–7.59 (2H, m, Ar–H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9 (Ar–**C**H_3), 25.0, 49.8, 60.7 (CH_2N), 78.6 (sp, $^2J_{CF}$ = 28.5 Hz, $(CF_3)_2$**C**), 123.0 (q, $^1J_{CF}$ = 289.0 Hz, CF_3), 123.4 (q, $^1J_{CF}$ = 288.4 Hz, CF_3), 128.6 (Ar), 129.7 (Ar), 133.3 (Ar), 141.4 (Ar), 171.2 (C=N). ^{19}F NMR (188 MHz,

$CDCl_3$): δ −75.2 (3F, q, $^4J_{FF}$ = 8.6 Hz, CF_3), −74.1 (3F, q, $^4J_{FF}$ = 8.6 Hz, CF_3). EIMS 70 eV, *m/z* (rel. int.): 325 $[M]^+$ (25), 306 $[M–F]^+$ (5), 256 $[M–CF_3]^+$ (6), 131 $[M–194]^+$ (100). HRMS (EI): calcd. for $C_{14}H_{13}F_6NO$ (M) 325.0901; found 325.0891.

2-(5-tert-Butyl-3,4-dihydro-2H-pyrrol-4-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**2a**), white crystals, mp 192–193 °C (dec.), ^1H NMR (200 MHz, CD_3CN): δ 1.28 (9H, s, $C(CH_3)_3$), 2.03–2.30 (2H, m), 3.52–3.97 (3H, m), 5.68 (1H, bs, OH). ^{13}C NMR (50 MHz, CD_3CN): δ 26.4, 30.9 (($\mathbf{C}H_3)_3C$), 38.5(($CH_3)_3\mathbf{C}$, 49.8 (CH_2), 59.9 (CH_2N), 78.2 (sp, $^2J_{CF}$ = 27.3 Hz, $(CF_3)_2\mathbf{C}$), 124.6 (q, $^1J_{CF}$ = 289.5 Hz, CF_3), 124.8 (q, $^1J_{CF}$ = 290.3 Hz, CF_3), 182.1 (C=N). ^{19}F NMR (188 MHz, CD_3CN): δ −75.6 (3F, q, $^4J_{FF}$ = 9.1 Hz, CF_3), −73.7 (3F, q, $^4J_{FF}$ = 9.1 Hz, CF_3). EIMS 70 eV, *m/z* (rel. int.): 291 $[M]^+$ (10), 276 $[M–CH_3]^+$ (100), 222 $[M–CF_3]^+$ (4), 206 $[M-119]^+$ (15). HRMS (EI): calcd. for $C_{11}H_{15}F_6NO$ (M) 291.1058; found 291.1049.

2,2-Dimethyl-6-{[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]amino}hexan-3-one (**3**). The hexafluoroacetone hydrate (12 mmol) was added to a stirred solution of imine **1a** (10 mmol) in 25 ml of THF under cooling in ice-bath. After addition the cooling bath was removed and mixture was stirred at room temperature for 1 h. Then the solvent was removed under vacuum, the residue was carefully washed with dry ether and dried in dry box at room temperature. The product was obtained as white crystals, mp 79–81 °C, ^1H NMR (200 MHz, $(CD_3)_2CO$): δ 1.09 (9H, s, $C(CH_3)_3$), 1.73–1.78 (2H, m, CH_2), 2.47–2.52 (2H, m, CH_2–CO), 3.63–3.67 (2H, m, CH_2–N), 8.80 (2H, bs, OH and NH). ^{13}C NMR (50 MHz, $(CD_3)_2CO$): δ 22.5, 27.9 (($\mathbf{C}H_3)_3C$), 32.7 ($\mathbf{C}H_2$–CO), 35.4 (($CH_3)_3\mathbf{C}$), 59.7 (CH_2N), 90.2 (sp, $^2J_{CF}$ = 32.3 Hz, $(CF_3)_2\mathbf{C}$), 121.3 (q, $^1J_{CF}$ = 290.3 Hz, $2CF_3$), 185.1 (C=O). ^{19}F NMR (188 MHz, $(CD_3)_2CO$): δ −81.8 (s, $2CF_3$). Anal. Calcd. for $C_{11}H_{17}F_6NO_2{\cdot}2H_2O$: C, 38.3; H, 6.1. Found: C, 38.5; H, 6.0.

4.3. General procedure for the reaction of cyclic imines with methyl trifluoropyruvate

A solution of methyl trifluoropyruvate (10 mmol) in 5 ml of ether was added dropwise to a stirred solution of corresponding cyclic imine (10 mmol) in 25 ml of appropriate solvent (ether for **4a**, 1/1 mixture of hexane and ether for **4b–f**, and 1/1 mixture of ether and dichloromethane for **4g**) at 0 °C under dry atmosphere. The cooling bath was removed and mixture was stirred at room temperature for 12 h. Then the reaction mixture was cooled again to 0 °C, the crystal solid was filtered and dried in dry box at room temperature.

Methyl 2-(5-tert-butyl-3,4-dihydro-2H-pyrrol-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate (**4a**), white crystals, mp 147–148 °C, ^1H NMR (200 MHz, $CDCl_3$): δ 1.22 (9H, s, $C(CH_3)_3$), 1.91–2.12 (1H, m), 2.36–2.46 (1H, m), 3.47–3.55 (1H, m), 3.68–4.04 (5H, m, incl. 3.83 (3H, s, OCH_3)). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.0, 29.2 ($C(\mathbf{C}H_3)_3$), 37.1 ($\mathbf{C}(CH_3)_3$), 50.6, 54.2 (OCH_3), 59.1 (CH_2N), 79.5 (q, $^2J_{CF}$ = 28.4 Hz, $CF_3\mathbf{C}$), 118.8 (q, $^1J_{CF}$ = 288.2 Hz, CF_3), 159.0 ($\mathbf{C}O_2CH_3$), 162.6 (C=N). ^{19}F NMR (188 MHz, $CDCl_3$): δ −75.6 (s, CF_3). EIMS 70 eV, *m/z* (rel. int.): 281 $[M]^+$ (17), 266 $[M–CH_3]^+$ (100), 222 $[M–CO_2CH_3]^+$ (14). HRMS (EI): calcd. for $C_{12}H_{18}F_3NO_3$ (M) 281.1239; found 281.1244.

Methyl 3,3,3-trifluoro-2-hydroxy-2-(5-phenyl-3,4-dihydro-2H-pyrrol-4-yl)propanoate (**4b**), white crystals, mp 156–158 °C, ^1H NMR (200 MHz, $CDCl_3$): δ 2.07–2.38 (2H, m), 3.85 (3H, s, OCH_3), 3.90–4.16 (3H, m), 7.35–7.45 (3H, m, Ar–H), 7.66–7.71 (2H, m, Ar–H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.9, 49.8, 54.4 (OCH_3), 60.4 (CH_2N), 79.7 (q, $^2J_{CF}$ = 29.7 Hz, $CF_3\mathbf{C}$), 123.2 (q, $^1J_{CF}$ = 288.4 Hz, CF_3), 127.9 (Ar), 128.0 (Ar), 130.0 (Ar), 169.6 ($\mathbf{C}O_2CH_3$), 171.4 (C=N). ^{19}F NMR (188 MHz, $CDCl_3$): δ −74.3 (s, CF_3). EIMS 70 eV, *m/z* (rel. int.): 301 $[M]^+$ (8), 242 $[M–CO_2CH_3]^+$ (9), 144 $[M–F_3CC(OH)CO_2CH_3]^+$ (64), 117 $[M-184]^+$ (100). HRMS (EI): calcd. for $C_{14}H_{14}F_3NO_3$ (M) 301.0926; found 301.0918.

Methyl 3,3,3-trifluoro-2-hydroxy-2-[5-(4-methylphenyl)-3,4-dihydro-2H-pyrrol-4-yl]propanoate (**4c**), white crystals, mp 148–150 °C, ^1H NMR (200 MHz, $CDCl_3$): δ 2.03–2.31 (2H, m), 2.36 (3H, s, Ar–CH_3), 3.85 (3H, s, OCH_3), 3.95–4.08 (3H, m), 7.13–7.21 (2H, m, Ar–H), 7.54–7.62 (2H, m, Ar–H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.36 (Ar–$\mathbf{C}H_3$), 26.0, 50.4, 53.7 (OCH_3), 61.2 (CH_2N), 79.4 (q, $^2J_{CF}$ = 28.5 Hz, $CF_3\mathbf{C}$), 123.7 (q, $^1J_{CF}$ = 287.9 Hz, CF_3), 127.8 (Ar), 128.8 (Ar), 131.8 (Ar), 140.2 (Ar), 169.1 ($\mathbf{C}O_2CH_3$), 170.9 (C=N). ^{19}F NMR (188 MHz, $CDCl_3$): δ −74.4 (s, CF_3). EIMS 70 eV, *m/z* (rel. int.): 315 $[M]^+$ (11), 256 $[M–CO_2CH_3]^+$ (11), 158 $[M–F_3CC(OH)CO_2CH_3]^+$ (58), 131 $[M-184]^+$ (100). HRMS (EI): calcd. for $C_{15}H_{16}F_3NO_3$ (M) 315.1082; found 315.1076.

Methyl 3,3,3-trifluoro-2-hydroxy-2-[5-(4-methoxyphenyl)-3,4-dihydro-2H-pyrrol-4-yl]propanoate (**4d**), white crystals, mp 157–158 °C (dec.), ^1H NMR (200 MHz, $(CD_3)_2SO$): δ 1.93–2.20 (2H, m), 3.69 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.84–4.05 (3H, m), 6.89–6.93 (2H, m, Ar–H), 7.58–7.62 (2H, m, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): 28.8, 51.1, 54.5 (OCH_3), 56.4 (OCH_3), 60.5 (CH_2N), 80.7 (q, $^2J_{CF}$ = 26.5 Hz, $CF_3\mathbf{C}$), 114.3 (Ar), 125.0 (q, $^1J_{CF}$ = 288.6 Hz, CF_3), 129.8 (Ar), 130.7 (Ar), 161.6 (Ar), 169.9 ($\mathbf{C}O_2CH_3$), 171.5 (C=N). ^{19}F NMR (188 MHz, $(CD_3)_2SO$): δ −72.9 (s, CF_3). Anal. Calcd. for $C_{15}H_{16}F_3NO_4$: C, 54.4; H, 4.9. Found: C, 54.4; H, 4.9.

Methyl 3,3,3-trifluoro-2-hydroxy-2-[5-(4-fluorophenyl)-3,4-dihydro-2H-pyrrol-4-yl]propanoate (**4e**), white crystals, mp 146–147 °C (dec.), ^1H NMR (200 MHz, $CDCl_3$): δ 1.97–2.28 (2H, m), 3.70 (3H, s, OCH_3), 3.80–3.95 (3H, m), 6.93–7.02 (2H, m, Ar–H), 7.58–7.66 (2H, m, Ar–H). ^{13}C NMR (50 MHz, $CDCl_3$): 25.4, 50.5, 52.3 (OCH_3), 60.5 (CH_2N), 78.5 (q, $^2J_{CF}$ = 27.6 Hz, $CF_3\mathbf{C}$), 114.5 (Ar), 124.2 (q, $^1J_{CF}$ = 288.6 Hz, CF_3), 129.6 (Ar), 130.8 (Ar), 166.4 (d, $^1J_{CF}$ = 248.8 Hz, C_{Ar}–F), 167.9 ($\mathbf{C}O_2CH_3$), 170.0 (C=N). ^{19}F NMR (188 MHz, $CDCl_3$): δ −107.0 (1F, bs, Ar–F), −72.9 (3F, s, CF_3). Anal. Calcd. for $C_{14}H_{13}F_4NO_3$: C, 52.7; H, 4.1. Found: C, 52.5; H, 4.2.

Methyl 3,3,3-trifluoro-2-hydroxy-2-[5-(2-furyl)-3,4-dihydro-2H-pyrrol-4-yl]propanoate (**4f**), white crystals, mp 134–135 °C, ^1H NMR (200 MHz, $(CD_3)_2SO$): δ 1.94–2.10 (1H, m), 2.15–2.34 (1H, m), 3.59 (3H, s, OCH_3), 3.77–3.98 (3H, m), 6.57 (1H, dd, $^3J_{HH}$ = 3.4 Hz, $^3J_{HH}$ = 1.6 Hz, Ar–H), 6.81 (1H, d, $^3J_{HH}$ = 3.4 Hz, Ar–H), 7.09 (1H, bs, OH), 6.81 (1H, d, $^3J_{HH}$ = 1.6 Hz, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 25.6, 50.9, 53.5 (OCH_3), 60.2 (CH_2N), 79.2 (q, $^2J_{CF}$ = 29.5 Hz, $CF_3\mathbf{C}$), 111.8 (Ar), 112.4 (Ar), 124.2 (q, $^1J_{CF}$ = 288.6 Hz, CF_3), 144.7 (Ar), 149.3 (Ar), 160.7 (C=N), 168.3 ($\mathbf{C}O_2CH_3$). ^{19}F NMR (188 MHz, $(CD_3)_2SO$): δ −72.2 (s, CF_3). EIMS 70 eV, *m/z* (rel. int.): 291 $[M]^+$ (21), 232 $[M–CO_2CH_3]^+$ (5), 134 $[M-157]^+$ (100). HRMS (EI): calcd. for $C_{12}H_{12}F_3NO_4$ (M) 291.0718; found 291.0718.

Methyl 3,3,3-trifluoro-2-hydroxy-2-[5-(4-pyridyl)-3,4-dihydro-2H-pyrrol-4-yl]propanoate (**4g**), yellowish crystals, mp 138–139 °C, ^1H NMR (200 MHz, $(CD_3)_2SO$): δ 1.93–2.27 (2H, m), 3.73 (3H, s, OCH_3), 3.78–3.95 (2H, m, CH_2N), 4.12 (1H, d, $^3J_{HH}$ = 10.2 Hz, CH–C=N), 7.25 (1H, bs, OH), 7.60 (2H, d, $^3J_{HH}$ = 6.1 Hz, Ar–H), 8.61 (2H, d, $^3J_{HH}$ = 6.1 Hz, Ar–H). ^{13}C NMR (90 MHz, $(CD_3)_2SO$): δ 28.3, 51.2, 54.6 (OCH_3), 61.6 (CH_2N), 80.4 (q, $^2J_{CF}$ = 27.3 Hz, $CF_3\mathbf{C}$), 123.5 (2C, Ar), 124.9 (q, $^1J_{CF}$ = 287.8 Hz, CF_3), 144.7 (Ar), 150.7 (Ar), 169.5 ($\mathbf{C}O_2CH_3$), 171.3 (C=N). ^{19}F NMR (188 MHz, $(CD_3)_2SO$): δ −73.3 (s, CF_3). Anal. Calcd. for $C_{13}H_{13}F_3N_2O_3$: C, 51.6; H, 4.3. Found: C, 51.0; H, 4.3.

4.4. General procedure for the reaction of cyclic imines with trichloroacetaldehyde

A solution of trichloroacetaldehyde (10 mmol) in 5 ml of ether was added dropwise to a stirred solution of corresponding cyclic imine (10 mmol) in 25 ml of ether at 0 °C under dry atmosphere. The cooling bath was removed and mixture was stirred at room temperature for 12 h. Then the reaction mixture was cooled again

to 0 °C, the crystal solid was filtered and dried in dry box at room temperature.

1-(5-tert-Butyl-3,4-dihydro-2H-pyrrol-4-yl)-2,2,2-trichloroethanol (**5a**), white crystals, mp 169–170 °C, ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.20 (9H, s, $C(CH_3)_3$), 1.64–1.84 (1H, m), 2.46–2.65 (1H, m), 3.54–3.72 (3H, m), 4.52 (1H, d, $^3J_{HH}$ = 6.4 Hz, HO–C**H**)), 6.66 (1H, d, $^3J_{HH}$ = 6.4 Hz, **H**O–CH). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 24.9, 30.3 (C(**C**$H_3)_3$), 36.9, 50.2, 60.8 (NCH_2), 81.1 (CCl_3**C**), 105.2 (CCl_3), 183.1 (C=N). EIMS 70 eV, *m*/*z* (rel. int.): 256 [M–CH_3]$^+$ (7), 236 [M–Cl]$^+$ (34), 154 [M–CCl_3]$^+$ (14), 71 [M-200]$^+$ (100). HRMS (EI): calcd. for $C_{10}H_{16}{}^{35}Cl_2NO$ (M–Cl) 236.0616; found 236.0609.

2,2,2-Trichloro-1-(5-phenyl-3,4-dihydro-2H-pyrrol-4-yl)ethanol (**5b**), white crystals, mp 203–204 °C (dec.), ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.92–2.11 (1H, m), 2.54–2.66 (1H, m), 3.84–4.04 (2H, m), 4.16–4.21 (1H, m), 4.26 (1H, d, $^3J_{HH}$ = 6.4 Hz, HO–C**H**), 6.90 (1H, d, $^3J_{HH}$ = 6.4 Hz, **H**O–CH), 7.47–7.51 (3H, m, Ar–H), 7.80–7.85 (2H, m, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 23.6, 49.8, 61.8 (NCH_2), 80.6 (CCl_3**C**), 105.0 (CCl_3), 128.5 (Ar), 129.3 (Ar), 130.9 (Ar), 133.9 (Ar), 172.9 (C=N). EIMS 70 eV, *m*/*z* (rel. int.): 291 [M]$^+$ (10), 174 [M–CCl_3]$^+$ (26), 144 [M–Cl_3CCHOH]$^+$ (10), 71 [M-220]$^+$ (100). HRMS (EI): calcd. for $C_{12}H_{12}Cl_3NO$ (M) 290.9985; found 290.9995.

2,2,2-Trichloro-1-[5-(4-methylphenyl)-3,4-dihydro-2H-pyrrol-4-yl]ethanol (**5c**), white crystals, mp 197–198 °C (dec.), ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.88–2.08 (1H, m), 2.23 (3H, s, Ar–CH_3), 2.54–2.69 (1H, m), 3.84–3.95 (2H, m), 4.07–4.12 (1H, m), 4.26 (1H, d, $^3J_{HH}$ = 6.4 Hz, HO–C**H**)), 6.74 (1H, d, $^3J_{HH}$ = 6.4 Hz, **H**O–CH), 7.22 (2H, d, $^3J_{HH}$ = 7.8 Hz, Ar–H), 7.69 (2H, d, $^3J_{HH}$ = 7.8 Hz, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 20.9 (CH_3–Ar), 22.9, 49.0, 60.9 (NCH_2), 80.0 (CCl_3**C**), 104.3 (CCl_3), 127.8 (Ar), 129.2 (Ar), 130.4 (Ar), 140.1 (Ar), 172.1 (C=N). EIMS 70 eV, *m*/*z* (rel. int.): 305 [M]$^+$ (12), 188 [M–CCl_3]$^+$ (28), 131 [M-174]$^+$ (54), 118 [M-187]$^+$ (100). HRMS (EI): calcd. for $C_{13}H_{14}{}^{35}Cl_2NO$ (M–Cl) 305.0141; found 305.0142.

2,2,2-Trichloro-1-[5-(4-methoxyphenyl)-3,4-dihydro-2H-pyrrol-4-yl]ethanol (**5d**), white crystals, mp 183–184 °C (dec.), ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.86–2.06 (1H, m), 2.42–2.61 (1H, m), 3.79 (3H, s, OCH_3), 3.84–3.91 (2H, m), 4.08–4.12 (1H, m), 4.25 (1H, d, $^3J_{HH}$ = 6.5 Hz, HO–C**H**), 6.88 (1H, d, $^3J_{HH}$ = 6.5 Hz, **H**O–CH), 7.02 (2H, d, $^3J_{HH}$ = 8.3 Hz, Ar–H), 7.77 (2H, d, $^3J_{HH}$ = 8.3 Hz, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 24.4, 50.3, 56.6 (OCH_3), 62.3 (NCH_2), 81.5 (CCl_3**C**), 105.8 (CCl_3), 115.4 (Ar), 127.0 (Ar), 130.8 (Ar), 162.1 (Ar), 172.6 (C=N). EIMS 70 eV, *m*/*z* (rel. int.): 321 [M]$^+$ (34), 204 [M–CCl_3]$^+$ (28), 131 [M-174]$^+$ (52), 134 [M-187]$^+$ (100). HRMS (EI): calcd. for $C_{13}H_{14}{}^{35}Cl_3NO_2$ (M) 321.0090; found 321.0093.

2,2,2-Trichloro-1-[5-(4-fluorophenyl)-3,4-dihydro-2H-pyrrol-4-yl]ethanol (**5e**), white crystals, mp 181–182 °C (dec.), ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.89–2.09 (1H, m), 2.52–2.64 (1H, m), 3.82–4.02 (2H, m), 4.11–4.22 (2H, m, incl. 4.20 (1H, d, $^3J_{HH}$ = 6.8 Hz, HO–C**H**)), 6.91 (1H, d, $^3J_{HH}$ = 6.8 Hz, **H**O–CH), 7.27–7.37 (2H, m, Ar–H), 7.82–7.89 (2H, m, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 22.9, 49.0, 61.0 (NCH_2), 79.7 (CCl_3**C**), 104.0 (CCl_3), 115.5 (d, $^2J_{CF}$ = 22.0 Hz, C-5 and C-3 Ar), 129.7 (Ar), 130.0 (d, $^2J_{CF}$ = 8.8 Hz, C-2 and C-6 Ar), 163.0 (d, $^1J_{CF}$ = 248.1 Hz, C_{Ar}–F), 170.9 (C=N). ^{19}F NMR (188 MHz, CD_3CN): δ −110.99 (m, Ar–F). EIMS 70 eV, *m*/*z* (rel. int.): 309 [M]$^+$ (28), 192 [M–CCl_3]$^+$ (79), 135 [M-174]$^+$ (100). HRMS (EI): calcd. for $C_{12}H_{11}{}^{35}Cl_3NO$ (M) 308.9890; found 308.9887.

2,2,2-Trichloro-1-[5-(2-furyl)-3,4-dihydro-2H-pyrrol-4-yl]ethanol (**5f**), white crystals, mp 172–173 °C (dec.), ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.87–1.96 (1H, m), 2.45–2.60 (1H, m), 3.84–3.94 (3H, m), 4.47 (1H, d, $^3J_{HH}$ = 6.3 Hz, HO–C**H**), 6.62–6.65 (1H, m, Ar–H), 6.94–6.98 (2H, m, 1Ar–H and **H**O–CH), 7.85 (1H, bs, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 22.6, 49.9, 61.4 (NCH_2), 80.3 (CCl_3**C**), 104.1 (CCl_3), 111.9 (Ar), 112.9 (Ar), 145.1 (Ar), 148.9 (Ar) 162.7 (C=N). EIMS 70 eV, *m*/*z* (rel. int.): 281 [M]$^+$ (22), 164 [M–CCl_3]$^+$ (51), 107 [M-174]$^+$ (45), 71 [M-288]$^+$ (100). HRMS (EI): calcd. for $C_{10}H_{10}{}^{35}Cl_2{}^{37}ClNO_2$ (M) 282.9748; found 282.9751.

2,2,2-Trichloro-1-(5-pyridin-4-yl-3,4-dihydro-2H-pyrrol-4-yl)ethanol (**5g**), white crystals, mp 192–194 °C (dec.), ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.94–2.13 (1H, m), 2.53–2.64 (1H, m), 3.96–4.01 (2H, m), 4.15–4.22 (2H, m, incl. 4.18 (1H, d, $^3J_{HH}$ = 6.4 Hz, HO–C**H**)), 6.94 (1H, d, $^3J_{HH}$ = 6.4 Hz, **H**O–CH), 7.71 (2H, d, $^3J_{HH}$ = 5.9 Hz, Ar–H), 8.72 (2H, d, $^3J_{HH}$ = 5.9 Hz, Ar–H). ^{13}C NMR (90 MHz, $(CD_3)_2SO$): δ 24.3, 50.6, 63.0 (NCH_2), 80.9 (CCl_3**C**), 105.3 (CCl_3), 123.3 (Ar), 141.8 (Ar), 151.7 (Ar), 172.4 (C=N). EIMS 70 eV, *m*/*z* (rel. int.): 292 [M]$^+$ (13), 257 [M–Cl]$^+$ (12), 175 [M–CCl_3]$^+$ (40), 71 [M-221]$^+$ (100). HRMS (EI): calcd. for $C_{11}H_{11}{}^{35}Cl_3N_2O$ (M) 291.9937; found 291.9931.

4.5. General procedure for the reduction of compounds 4d–f and 5d–g

Sodium borohydride (0.5 g, 13 mmol) was portion wise added to a stirred solution of corresponding adducts **4** or **5** (5 mmol) in 15 ml of methanol at −25 °C under nitrogen atmosphere. After stirring for 3 h at this temperature the cooling bath was removed and mixture was stirred for additional 3 h at room temperature. Then methanol was removed in vacuum, the residue was quenched with saturated $NaHCO_3$ and extracted with ethylacetate. The extract was dried under Na_2SO_4, solvent was removed and residual solid was dried in vacuum.

Methyl 3,3,3-trifluoro-2-hydroxy-2-[2-(4-methoxyphenyl)-pyrroidinel-3-yl]propanoate (**6d**), white crystals, mp 137–138 °C, ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.80–1.90 and (1H, m), 1.24–2.41 (1H, m), 2.64–2.77 (1H, m), 2.88–3.02 (1H, m), 3.20 (3H, s, Ar–OCH_3), 3.70 (3H, s, OCH_3), 3.22–3.28 (1H, m, CH-3), 4.32 (1H, d, $^3J_{HH}$ = 7.3 Hz, CH-2), 6.72–6.76 (2H, m, Ar–H), 7.08–7.13 (2H, m, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): 25.4, 45.2, 48.1, 52.4 (CO_2**C**H_3), 54.9 (Ar–OCH_3), 61.1 (CH_2N), 77.5 (q, $^2J_{CF}$ = 26.9 Hz, CF_3**C**), 112.4 (Ar), 125.1 (q, $^1J_{CF}$ = 289.6 Hz, CF_3), 130.2 (Ar), 134.7 (Ar), 134.7 (Ar), 167.2 (**C**O_2CH_3). ^{19}F NMR (188 MHz, $(CD_3)_2SO$): δ −76.0 (s, CF_3). EIMS 70 eV, *m*/*z* (rel. int.): 333 [M]$^+$ (31), 274 [M–CO_2CH_3]$^+$ (94), 264 [M–CF_3]$^+$ (30), 148 [M-185]$^+$ (100). HRMS (EI): calcd. for $C_{15}H_{18}F_3NO_4$ (M) 333.1188; found 315.1172.

Methyl 3,3,3-trifluoro-2-[2-(4-fluorophenyl)-pyrrolidin-3-yl]-2-hydroxypropanoate (**6e**), white crystals, mp 117–118 °C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.82–1.91 (1H, m), 2.23–2.53 (1H, m), 2.74–3.04 (3H, m), 3.24 (3H, s, OCH_3), 4.33 (1H, d, $^3J_{HH}$ = 7.3 Hz, CH-2), 6.95–7.03 (2H, m, Ar–H), 7.19–7.26 (2H, m, Ar–H). ^{13}C NMR (50 MHz, $CDCl_3$): 25.8, 45.2, 48.0, 52.4 (OCH_3), 60.8 (CH_2N), 77.5 (q, $^2J_{CF}$ = 26.8 Hz, CF_3**C**), 113.5 (d, $^2J_{CF}$ = 21.2 Hz, C-3 and C-5 Ar), 124.3 (q, $^1J_{CF}$ = 289.7 Hz, CF_3), 130.5 (d, $^2J_{CF}$ = 7.1 Hz, C-2 and C-6 Ar), 139.2 (Ar), 161.0 (d, $^1J_{CF}$ = 243.0 Hz, C_{Ar}–F), 167.9 (**C**O_2CH_3). ^{19}F NMR (188 MHz, $CDCl_3$): δ −117.2 (1F, bs, Ar–F), −75.9 (3F, s, CF_3). EIMS 70 eV, *m*/*z* (rel. int.): 321 [M]$^+$ (8), 262 [M–CO_2CH_3]$^+$ (36), 252 [M–CF_3]$^+$ (9), 135 [M-186]$^+$ (100). HRMS (EI): calcd. for $C_{14}H_{15}F_4NO_3$ (M) 321.0988; found 321.0967.

Methyl 3,3,3-trifluoro-2-[2-(2-furyl)-pyrrolidin-3-yl]-2-hydroxypropanoate (**6f**), white crystals, mp 117–118 °C, ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.85–1.87 (1H, m), 2.03–2.18 (1H, m), 2.83–2.90 (2H, m), 3.11–3.15 (1H, m, CH-3), 3.68 (3H, s, OCH_3), 4.21 (1H, d, $^3J_{HH}$ = 7.4 Hz, CH-2), 6.08 (1H, d, $^3J_{HH}$ = 3.4 Hz, Ar–H), 6.28 (1H, dd, $^3J_{HH}$ = 3.4 Hz, $^3J_{HH}$ = 1.6 Hz, Ar–H), 7.45 (1H, d, $^3J_{HH}$ = 1.6 Hz, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 25.4, 45.0, 45.4, 53.5 (OCH_3), 57.0 (CH_2N), 77.7 (q, $^2J_{CF}$ = 27.3 Hz, CF_3**C**), 108.0 (Ar), 110.4 (Ar), 124.6 (q, $^1J_{CF}$ = 289.7 Hz, CF_3), 142.0 (Ar), 154.9 (Ar), 168.8 (**C**O_2CH_3). ^{19}F NMR (188 MHz, $(CD_3)_2SO$): δ −75.6 (s, CF_3). EIMS 70 eV, *m*/*z* (rel. int.): 293 [M]$^+$ (17), 234 [M–CO_2CH_3]$^+$ (33), 224 [M–CF_3]$^+$ (9), 115 [M-178]$^+$ (100). HRMS (EI): calcd. for $C_{12}H_{14}F_3NO_4$ (M) 293.0875; found 293.0874.

2,2,2-Trichloro-1-[2-(4-methoxyphenyl)-pyrrolidin-3-yl]ethanol (**7d**), white crystals, mp 147–148 °C, ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.79–1.93 (1H, m), 2.22–2.33 (1H, m), 2.73–2.85 (2H, m), 3.04–

3.14 (1H, m, CH-3), 3.56 (1H, bs, HOC**H**), 3.74 (3H, s, OCH_3), 4.15 (1H, d, $^3J_{HH}$ = 7.3 Hz, CH-2), 6.37 (1H, bs, OH), 6.89 (2H, d, $^3J_{HH}$ = 8.3 Hz, Ar–H), 7.75 (2H, d, $^3J_{HH}$ = 8.3 Hz, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 25.8, 43.9, 45.3, 54.9 (OCH_3), 65.3 (NCH_2), 79.5 (**C**CCl_3), 105.5 (CCl_3), 113.4 (Ar), 128.7 (Ar), 133.0 (Ar), 158.0 (Ar–OMe). EIMS 70 eV, *m*/*z* (rel. int.): 323 $[M]^+$ (4), 206 $[M + H–CCl_3]^+$ (100). HRMS (EI): calcd. for $C_{13}H_{16}{}^{35}Cl_3NO_2$ (M) 323.0247; found 321.0249.

2,2,2-Trichloro-1-[2-(4-fluorophenyl)-pyrrolidin-3-yl]ethanol (**7e**), white crystals, mp 136–137 °C (dec.), ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.79–1.95 (1H, m), 2.23–2.39 (1H, m), 2.75–2.88 (2H, m), 3.01–3.15 (1H, m, CH-3), 3.51 (1H, d, $^3J_{HH}$ = 0.9 Hz, HOC**H**), 4.23 (1H, d, $^3J_{HH}$ = 7.3 Hz, CH-2), 7.10–7.19 (2H, m, Ar–H), 7.32–7.40 (2H, m, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 25.8, 43.9, 45.3, 65.0 (NCH_2), 79.3 (CCl_3**C**), 105.4 (CCl_3), 114.7 (d, $^2J_{CF}$ = 21.2 Hz, C-5 and C-3 Ar), 129.5 (d, $^2J_{CF}$ = 7.1 Hz, C-2 and C-6 Ar), 137.6 (Ar), 161.0 (d, $^1J_{CF}$ = 241.6 Hz, Ar–F). ^{19}F NMR (188 MHz, CD_3CN): δ −116.7 (m, Ar–F). EIMS 70 eV, *m*/*z* (rel. int.): 311 $[M]^+$ (3), 194 $[M–CCl_3]^+$ (100), 136 $[M-175]^+$ (42). HRMS (EI): calcd. for $C_{12}H_{13}{}^{35}Cl^{37}Cl_2FNO$ (M) 314.9988; found 314.9977.

2,2,2-Trichloro-1-[2-(2-furyl)-pyrrolidin-3-yl]ethanol (**7f**), white crystals, mp 162–163 °C (dec.), ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.79–1.93 (1H, m), 2.07–2.26 (1H, m), 2.61–2.86 (3H, m), 2.91–3.07 (1H, m, CH-3), 3.69 (1H, d, $^3J_{HH}$ = 2.8 Hz, HOC**H**), 4.26 (1H, d, $^3J_{HH}$ = 7.3 Hz, CH-2), 6.25–6.26 (1H, m, Ar–H), 6.54 (1H, bs, OH), 6.39 (1H, m, Ar–H), 7.57 (1H, bs, Ar–H). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 27.2, 45.5, 45.9, 60.2 (NCH_2), 80.9 (CCl_3**C**), 106.2 (CCl_3), 107.9 (Ar), 111.0 (Ar), 142.8 (Ar), 156.5 (Ar). EIMS 70 eV, *m*/*z* (rel. int.): 283 $[M]^+$ (19), 165 $[M–CCl_3]^+$ (40), 107 $[M-176]^+$ (45), 71 $[M-212]^+$ (100). HRMS (EI): calcd. for $C_{10}H_{12}{}^{35}Cl^{37}Cl_2NO_2$ (M) 286.9875; found 286.9871.

2,2,2-Trichloro-1-(2-pyridin-4-ylpyrrolidin-3-yl)ethanol (**7g**), white crystals, mp 193–194 °C (dec.), ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.87–1.95 (1H, m), 2.23–2.32 (1H, m), 2.78–2.91 (3H, m), 3.08–3.14 (1H, m, CH-3), 3.49 (1H, bs, HOC**H**), 4.25 (1H, d, $^3J_{HH}$ = 7.3 Hz, CH-2), 6.44 (1H, bs, OH), 7.77 (2H, d, $^3J_{HH}$ = 5.0 Hz, Ar–H), 8.5 (2H, d, $^3J_{HH}$ = 5.0 Hz, Ar–H). ^{13}C NMR (90 MHz, $(CD_3)_2SO$): δ 25.8, 43.9, 45.5, 64.5 (NCH_2), 79.3 (CCl_3**C**), 105.3 (CCl_3), 123.2 (Ar), 149.3 (Ar), 150.7 (Ar). EIMS 70 eV, *m*/*z* (rel. int.): 294 $[M]^+$ (4), 259 $[M–Cl]^+$ (2), 177 $[M–CCl_3]^+$ (100), 120 $[M-174]^+$ (30). HRMS (EI): calcd. for $C_{11}H_{13}{}^{35}Cl_3N_2O$ (M) 294.0094; found 294.0083.

4.6. General procedure for the reaction of cyclic imidates with methyl trifluoropyruvate and trichloroacetaldehyde

A solution of methyl trifluoropyruvate or chloral (10 mmol) in 5 ml of ether was added dropwise to a stirred solution of corresponding cyclic lactim ether **8** (10 mmol) in 25 ml of ether at 0 °C under dry atmosphere. The cooling bath was removed and mixture was stirred at room temperature for 12 h. Then the reaction mixture was cooled again to 0 °C, the crystal solid was filtered and dried in dry box at room temperature.

Methyl 3,3,3-trifluoro-2-hydroxy-2-(5-methoxy-3,4-dihydro-2H-pyrrol-4-yl)propanoate (**9a**), white crystals, mp 124–125 °C, ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.80–1.93 (1H, m), 2.03–2.24 (1H, m), 3.26–3.54 (2H, m), 3.63 (major) and 3.66 (minor) (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 25.9 (major) and 27.9 (minor), 48.2, 53.4 (bs, OCH_3), 54.5 (bs, OCH_3), 56.5 (major) and 56.9 (minor) (CH_2N), 78.0 (q, $^2J_{CF}$ = 27.3 Hz, CF_3**C**), 125.0 (q, $^1J_{CF}$ = 288.2Hz, CF_3), 169.4 (**C**O_2CH_3), 170.3 (C=N). ^{19}F NMR (188 MHz, $(CD_3)_2SO$): δ −74.5 (major) and 72.5 (minor) (s, CF_3). Anal. Calcd. for $C_9H_{12}F_3NO_4$: C, 44.6; H, 5.2. Found: C, 44.6; H, 5.3.

Methyl 3,3,3-trifluoro-2-hydroxy-2-(2-methoxy-3,4,5,6-tetrahydropyridin-3-yl)propanoate (**9b**), white crystals, mp 104–105 °C, ^{1}H NMR (200 MHz, CD_3CN): δ 1.40–1.60 (1H, m), 1.69–1.92 (3H, m), 3.18–3.37 (2H, m), 3.42–3.55 (4H, m, incl. 3.47 (3H, s, CO_2CH_3)), 3.84 (3H, s, OCH_3), 4.66 (1H, s, OH). ^{13}C NMR (50 MHz, CD_3CN): δ 22.6, 22.8, 42.3, 46.1 (OCH_3), 52.5 (OCH_3), 54.4 (CH_2N), 79.4 (q, $^2J_{CF}$ = 27.9 Hz, CF_3**C**), 124.7 (q, $^1J_{CF}$ = 288.1 Hz, CF_3), 158.3 (**C**O_2CH_3), 170.7 (C=N). ^{19}F NMR (188 MHz, CD_3CN): δ −74.1 (s, CF_3). EIMS 70 eV, *m*/*z* (rel. int.): 269 $[M]^+$ (34), 210 $[M–CO_2CH_3]^+$ (100), 196 $[M-73]^+$ (52). HRMS (EI): calcd. for $C_{10}H_{14}F_3NO_4$ (M) 269.0875; found 269.0871.

2,2,2-Trichloro-1-(5-methoxy-3,4-dihydro-2H-pyrrol-4-yl)ethanol (**10a**), white crystals, mp 183–184 °C (dec.), ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05–2.20 (1H, m), 2.46–2.65 (1H, m), 3.47–3.75 (3H, m), 3.81 (3H, s, OCH_3), 4.59 (1H, bs), 5.34 (1H, bs, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.3, 45.7, 53.7 (OCH_3), 56.0 (NCH_2), 79.7 (CCl_3**C**), 103.2 (CCl_3), 171.7 (C=N). EIMS 70 eV, *m*/*z* (rel. int.): 245 $[M]^+$ (1), 210 $[M–Cl]^+$ (100), 128 $[M–CCl_3]^+$ (37). HRMS (EI): calcd. for $C_7H_{10}{}^{35}Cl_2NO_2$ (M–Cl) 210.0089; found 210.0092.

2,2,2-Trichloro-1-(2-methoxy-3,4,5,6-tetrahydropyridin-3-yl)ethanol (**10b**), white crystals, mp 191–192 °C (dec.), ^{1}H NMR (200 MHz, $(CD_3)_2SO$): δ 1.28–1.47 (1H, m), 1.59–2.12 (3H, m), 3.00–3.08 (1H, m), 3.18–3.43 (2H, m), 3.53 (3H, s, OCH_3), 4.66 (1H, dd, $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 1.5 Hz, HO–C**H**), 6.92 (1H, d, $^3J_{HH}$ = 6.9 Hz, **H**O–CH). ^{13}C NMR (50 MHz, $(CD_3)_2SO$): δ 20.2, 21.5, 39.3, 45.6 (NCH_2), 52.0 (OCH_3), 80.2 (CCl_3**C**), 103.9 (CCl_3), 160.0 (C=N). EIMS 70 eV, *m*/*z* (rel. int.): 224 $[M–Cl]^+$ (100), 142 $[M–CCl_3]^+$ (6). HRMS (EI): calcd. for $C_8H_{12}{}^{35}Cl_2NO_2$ (M–Cl) 224.0245; found 224.0248.

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