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The reaction of cyclic imines with the Ruppert–Prakash reagent. Facile approach to α-trifluoromethylated nornicotine, anabazine, and homoanabazine

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ABSTRACT

We have demonstrated that the Ruppert–Prakash reagent is able to react with a number of cyclic imines under acidic condition to afford the corresponding α-trifluoromethyl derivatives of nitrogen heterocycles. 5–7-Membered cyclic imines bearing various alkyl, aryl or heterocyclic group were successfully involved in this transformation. Novel trifluoromethylated analogues of nicotine, anabasine, and homoanabasine alkaloids were synthesized.

1. Introduction

Piperidine and pyrrolidine moieties are common to many naturally occurring and synthetic alkaloids, medications, and potent drug candidates.[1] The combination of these saturated heterocycles with the pyridine ring gives rise to the well-known *tobacco* alkaloids, such as nicotine, nornicotine, and anabasine. In the last two decades much attention has been paid to the synthesis of novel analogues of nicotine and anabasine and toward study of their biological activities.[2] The goal of these investigations is to develop drugs that have medical benefit for the effective treatment of central nervous system (CNS) disorders without the unfavorable side-effects of nicotine and anabasine.[3] Many of these natural alkaloid analogues possess remarkable potential as therapeutic agents for CNS neurodegenerative disorder due to their affinity to neuronal acetylcholine receptors (nAChRs). In particular, they have beneficial effects in the treatment of Alzheimer's and Parkinson's disease, schizophrenia, Tourette's syndrome, etc.[4] (for example, the anti-Parkinson's drug SIB-1508Y[5]).

The synthesis of nicotine and anabasine derivatives bearing an α-trifluoromethyl (α-Tfm) group at the pyrroline or piperidine rings has not yet been described so far,[6] despite the possible interest in fluorinated analogues.[7] In this paper, we have focused our interest on direct trifluoromethylation of 5–7-membered cyclic imines. This transformation can open an easy access to derivatives of α-Tfm pyrrolidines, α-Tfm piperidines, and α-Tfm azepanes, which are not only valuable fluorinated building blocks that can be converted into other nitrogen Tfm-containing heterocycles, but also are potential bioactive substrates. Particularly, this approach gives a great opportunity to synthesize α-Tfm substituted nornicotine, anabazine, and homoanabasine in one-step starting from the appropriate cyclic imines with the pyridine moiety.

2. Results and discussion

According to available literature, cyclic imines can be synthesized by several approaches.[8] Our experience in this area has demonstrated that the most convenient are the following two methods: (a) Claisen condensation of *N*-protected cyclic amides with esters followed by simultaneous deprotection and decarboxylation in acidic media; (b) reaction of *N*-protected amides with readily available organolithium reagents followed by deprotection (Scheme 1).[9] These approaches utilize cheap and easily available starting compounds and allow the preparation of a broad variety of 2-substituted cyclic imines. This is very promising from a synthetic point of view.[10] To investigate the possibility of direct trifluoromethylation of cyclic imines, many 2-substituted

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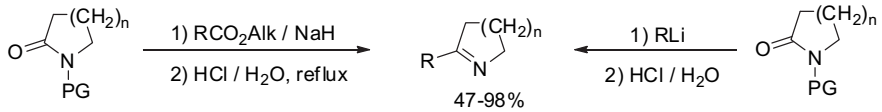


1a-q (n = 1); **2a-e** (n = 2); **3a-e** (n = 3)

PG = vinyl, $(EtO)_2CH$, TMS

R = Alk, Ar,Het

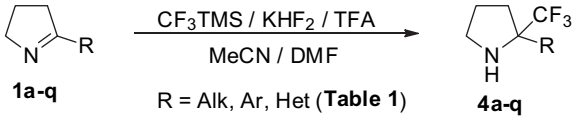
Scheme 1. Synthesis of cyclic imines.

pyrrolines **1a**–**q** and their six- and seven-membered homologs **2a**–**e** and **3a**–**e** were synthesized (Scheme 1).

Among the currently available reagents for nucleophilic trifluoromethylation we have chosen $TMSCF_3$, known as the Ruppert–Prakash reagent, as the most efficient, general and widely used.[11] Under standard Ruppert's reaction conditions, only activated imines, such as azirines,[12] imines of perfluorinated ketones,[13] *N*-sulfonylated aldimines,[14] and nitrones[15] react with $TMSCF_3$. To involve non-activated imines into this transformation several improvements have been reported. Namely, using up to one equimolar amount of highly lipophilic tetraalkylammonium fluoride,[16] initial generation of an iminium boron complex,[17] using highly basic phosphines as initiators,[18] addition of TMS-imidazole,[19] and carrying out the reaction under acidic conditions with KHF_2 as initiator.[20] Only the last two approaches are applicable for non-activated ketimines—the class of imines to which the 2-substituted cyclic imines **1**–**3** belong.

We have chosen 2-methylpyrroline **1a** as a model substrate and examined its reaction with $TMSCF_3$ in the presence of TMS-imidazole or with KHF_2 as initiator. According to the ^{19}F NMR data, treatment of the imine **1a** with $TMSCF_3$, cesium fluoride, and TMS-imidazole in THF did not lead to the desired α-Tfm pyrrolidine, despite the authors[19] having reported the synthesis of Tfm amines from acyclic imines under these conditions.

It was rewarding to find that pyrroline **1a** reacted with $TMSCF_3$ in the presence of an equimolar amount of trifluoroacetic acid and potassium hydrofluoride in acetonitrile, giving rise to the 2-Tfm-2-methylpyrrolidine **4a** in 37% yield. It was also found that using DMF as co-solvent not only accelerates the reaction, but increases the yield of **4a** up to 49%. Under these conditions a variety of pyrrolines **1a**–**q** were introduced into the reaction to afford products of trifluoromethylation **4a**–**q** in moderate to good yields (Scheme 2, Table 1).



Scheme 2. Reaction of Puppert–Prakash reagent with pyrrolines.

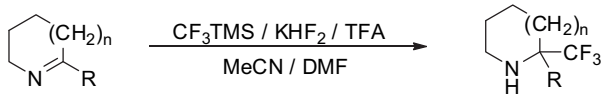
It is worthy to note that all pyrrolines studied give very similar yields of the reaction products regardless of the nature of the substituent at the pyrroline ring. The presence of a bulky *tert*-butyl **1d** and adamantyl **1e** group, the electron withdrawing pyridine ring **1q** or electron releasing thienyl substituent **1n** did not lead to reduced yield of the trifluoromethylated products. Moreover, this approach was found to be applicable for acid sensitive furyl imine **1p** giving rise to 2-furyl-2-Tfm-pyrrolidine **4p**. The imine **4p** can be conveniently transformed to α-Tfm-proline by oxidative cleavage of the furyl group to the carboxylic moiety. Earlier we have performed such oxidations with $RuCl_3/NaIO_4$ or ozone for the synthesis of 2-pentafluoroethyl-2-furyl pyrroline.[21] α-Tfm-proline is a prospective candidate for synthetic modification of biologically active peptides due to the ability of proline to determine the conformation of the peptide backbone.[22]

Table 1
Synthesis of 2-trifluoromethyl pyrrolidines with the Ruppert–Prakash reagent

Entry	Imine	Product	R	Yield (%)
1	**1a**	**4a**	CH_3–	49
2	**1b**	**4b**	*n*-C_4H_9–	57
3	**1c**	**4c**	*cyclo*-C_6H_{11}–	68
4	**1d**	**4d**	*tert*-C_4H_9–	71
5	**1e**	**4e**	1-Adamantyl	79
6	**1f**	**4f**	CH_3SCH_2–	75
7	**1g**	**4g**	4-$CH_3C_6H_4$–	48
8	**1h**	**4h**	3,4-$(CH_3)_2C_6H_3$–	62
9	**1i**	**4i**	3,5-$(CH_3)_2C_6H_3$–	65
10	**1j**	**4j**	4-BrC_6H_4–	61
11	**1k**	**4k**	4-FC_6H_4–	53
12	**1l**	**4l**	4-$CH_3OC_6H_4$–	49
13	**1m**	**4m**	3-$CF_3C_6H_4$–	64
14	**1n**	**4n**	2-Thienyl–	71
15	**1o**	**4o**	5-CH_3–2-thienyl	52
16	**1p**	**4p**	2-Furyl–	60
17	**1q**	**4q**	3-Pyridyl–	68

Trifluoromethylation of the pyridine imine **1q** leads selectively to target α-Tfm-nornicotine **4q** in 68% isolated yield. Earlier we have shown that pentafluoroethylation of analogous imine 2-(4-pyridine)pyrroline with C_2F_5Li was directed to the pyridine ring to form the dihydropyridine derivative, and therefore cannot be applied for preparation of perfluoroalkyl derivatives of nicotine.[21]

To investigate the scope and limitation of the reaction several tetrahydropyridines **2a**–**e** and dehydroazepanes **3a**–**e** were also tested. Six- and seven-membered cyclic imines **2a**–**e** and **3a**–**e** react with the $TMSCF_3$ similarly to afford the 2-trifluoromethyl substituted piperidines **5a**–**e** and azepanes **6a**–**e** in moderate to good yields (Scheme 3, Table 2). In such way, the target α-Tfm anabasine **5e** and α-Tfm homoanabasine **6e** were synthesized in 67% and 56% isolated yield, respectively. It is also notable that the reaction is general and the five-, six- and seven-membered cyclic imines give similar results.



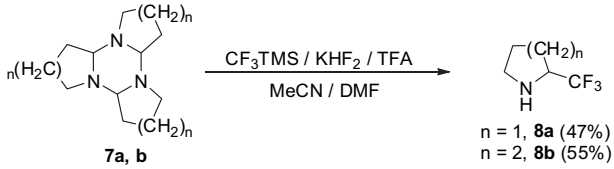
Scheme 3. Reaction of the Ruppert–Prakash reagent with six- and seven-membered cyclic imines.

Our interest in further investigations of cyclic imines toward the reaction with the Ruppert–Prakash reagent led us to study unsubstituted pyrroline and tetrahydropyridine, which are useful building blocks for a large variety of biologically important organic molecules.[23] These highly reactive imines oligomerize easily form mainly trimers **7a**,**b**, which are not active under the basic conditions usually required for the Ruppert–Prakash reaction. Carrying

Table 2
Synthesis of 2-trifluoromethyl piperidines and azepanes with the Ruppert–Prakash reagent

Entry	Imine	Product	R	Yield (%)
1	**2a**	**5a**	*tert*-C_4H_9–	56
2	**2b**	**5b**	*cyclo*-C_6H_{11}–	53
3	**2c**	**5c**	C_6H_5–	49
4	**2d**	**5d**	2-Furyl–	65
5	**2e**	**5e**	3-Pyridinyl–	67
6	**3a**	**6a**	*tert*-C_4H_9–	56
7	**3b**	**6b**	4-CH_3Bn–	71
8	**3c**	**6c**	C_6H_5–	44
9	**3d**	**6d**	2-Furyl–	56
10	**3e**	**6e**	3-Pyridinyl–	56

out such a reaction with KHF_2/TFA gave us the opportunity to synthesize 2-trifluoromethyl substituted pyrroline **8a** and piperidine **8b** (Scheme 4).



Scheme 4. Reaction of the unsubstituted cyclic imines with Ruppert–Prakash reagent.

3. Conclusion

Thus we have found that the Ruppert–Prakash reagent is able to react with a number of cyclic imines under acidic conditions to afford the corresponding α-trifluoromethylated nitrogen heterocycles. Cyclic imines bearing various alkyl, aryl or heterocyclic groups can be successfully involved in these transformations. Novel trifluoromethylated analogues of nicotine, anabasine, and homoanabasine alkaloids as well as simplest α-trifluoromethyl piperidine and pyrrolidine alkaloids have been synthesized.

4. Experimental

4.1. General information

NMR spectra were obtained on a Jeol ECX-400 (399.8 MHz for ^{1}H; 376.2 MHz for ^{19}F; 100.5 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); chemical shifts for ^{19}F NMR data are referenced to $CFCl_3$ (0.0). High resolution mass spectra (HRMS) were recorded using a Bruker Daltonics (MicroTOF-Q). Electrospray ionization (ESI) mass spectra (MS) were obtained from methanol solution. Melting points are uncorrected. TLC was carried out on precoated silica plates (Merck $60F_{254}$) with UV light visualization. Flash chromatography was performed using MP Silica 60 (320–630 mesh) with the indicated solvents. All reactions were conducted in flame-dried or oven dried glassware under a nitrogen atmosphere. Acetonitrile was distilled from CaH_2 prior to use. All reagents were purchased from Aldrich unless otherwise stated. The starting imines **1a**–**j**, **1q**, **2a**–**c**, **2e**, **3a**, **3c**, and **3e** were prepared by the reaction of ethyl ester of the appropriate carboxylic acids with *N*-vinylpyrrolidin-2-one, *N*-vinylcaprolactam or *N*-(diethoxymethyl)piperidin-2-one according to the described procedure.[9b,24] Cyclic imines **1k**–**p**, **2d**, **3b**, and **3d** were obtained by the reaction of corresponding lithium compounds with *N*-vinylpyrrolidin-2-one, 1-(trimethylsilyl)caprolactam or 1-(trimethylsilyl) piperidin-2-one.[25] Trimers of unsubstituted 3,4-dihydro-2*H*-pyrrole (pyrroline) **7a** and 2,3,4,5-tetrahydropyridine **7b** were prepared according to the procedure of Claxton et al.,[26] starting from the *N*-chloropyrrolidine and *N*-chloropiperidine, respectively, which were synthesized from piperidine and pyrrolidine by chlorination with *N*-chlorosuccinimide.[27]

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

Keeping the temperature at about 0 °C, trifluoroacetic acid (0.95 mL, 12.5 mmol), KHF_2 (585 mg, 7.5 mmol), and trifluoromethyltrimethylsilane (1.9 mL, 12.5 mmol) were successively added to a solution of the corresponding imine **1**, **2** or **3** (10 mmol) in dry acetonitrile (50 mL). After stirring for 12 h at rt, the solvent was gently evaporated under reduced pressure, the residue was quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with ether (3×10 mL). The combined extract was dried over Na_2SO_4, the solvent was evaporated at reduced pressure and the residue was purified by column chromatography on silica gel eluting with a 20/1 mixture of hexane/ethyl acetate. This afforded the tagged amine. In the case of volatile amines **4a**, **4d**, **5a**, **6a**, **8a**, and **8b** the combined extract was mixed with hydrochloric acid (1.5 mL), evaporated to dryness, and the residue was washed with pentane. In this way the amines **4a**, **4d**, **5a**, **6a** were isolated as hydrochloride. For comparison to the reported data, the hydrochloride of 2-Tfm-pyrrolidine **8a** and 2-Tfm-piperidine **8b** were again treated with aqueous $NaHCO_3$ and were analyzed as free bases.

*4.2.1. 2-Methyl-2-(trifluoromethyl)pyrrolidine hydrochloride (**4a**).* Colorless crystals (49%), mp 117–118 °C; ν_{max} (Nujol) 1157, 2897, 3431 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (3H, s, CH_3), 1.93–2.01 (1H, m), 2.13–2.19 (1H, m), 2.34–2.39 (2H, m), 3.54–3.56 (2H, m), 10.43 and 10.78 (2H, br s, H_2N^+). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 23.2, 33.1, 46.8, 67.5 (q, $^2J_{CF}$=29.7 Hz, *C*–CF_3), 124.9 (q, $^1J_{CF}$=282.8 Hz, CF_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.9 (CF_3). ESIMS *m*/*z* (rel int.): 154 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_6H_{11}F_3N$ (M+H) 154.0838, found 154.0840.

*4.2.2. 2-Butyl-2-(trifluoromethyl)-pyrrolidine (**4b**).* Colorless liquid (57%); ν_{max} (Nujol) 1144, 3444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (3H, t, *J*=5.5 Hz, CH_3), 1.28–1.35 (4H, m), 1.5–1.64 (3H, m), 1.68–1.76 (2H, m, incl. 1.74 (br s, NH)), 1.85–1.87 (1H, m), 1.97–2.02 (1H, m), 2.94–3.05 (2H, m, CH_2–N). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 23.2, 25.6, 26.4, 31.2, 35.0, 47.7 (CH_2–NH), 66.8 (q, J_{CF}=24.9 Hz, *C*–CF_3), 128.6 (q, J_{CF}=283.7 Hz, CF_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ −78.4 (CF_3). ESIMS *m*/*z* (rel int.): 196 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_9H_{17}F_3N$ (M+H) 196.1313, found 196.1306.

*4.2.3. 2-Cyclohexyl-2-(trifluoromethyl)-pyrrolidine (**4c**).* Colorless liquid (68%); ν_{max} (Nujol) 1139, 2931, 3391 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05–1.25 (5H, m), 1.47–1.53 (1H, m), 1.64–1.68 (3H, m), 1.73–1.95 (7H, m), 2.94–3.00 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 26.4, 26.8, 26.9, 27.9, 28.0, 30.0, 44.8, 47.6 (CH_2–NH), 69.6 (q, J_{CF}=24.0 Hz, *C*–CF_3), 129.0 (q, J_{CF}=286.6 Hz, CF_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.1 (CF_3). ESIMS *m*/*z* (rel int.): 222 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{11}H_{19}F_3N$ (M+H) 222.1464, found 222.1469.

*4.2.4. 2-tert-Butyl-2-(trifluoromethyl)pyrrolidine hydrochloride (**4d**).* Colorless crystals (71%), mp 149–150 °C; ν_{max} (Nujol) 1158, 2977 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$): δ 1.27 (9H, br s, $(CH_3)_3C$), 2.00–2.04 (1H, m), 2.10–2.15 (1H, m), 2.19–2.26 (2H, m), 3.47–3.49 and 3.65–3.68 (2H, m, CH_2–N), 9.58 and 11.02 (2H, br s, H_2N^+). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4 (1C, $(CH_3)_3C$), 26.3 (3C, $(CH_3)_3C$),

30.2, 36.8, 48.4 (CH_2–NH), 76.4 (q, J_{CF}=25.9 Hz, CF_3–*C*), 125.8 (q, J_{CF}=287.5 Hz, CF_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.2 (CF_3). HRMS (ESI): calcd for $C_9H_{17}F_3N$ (M−Cl) 196.1308, found 196.1292.

*4.2.5. 2-(1-Adamantyl)-2-(trifluoromethyl)pyrrolidine (**4e**).* Yellow crystals (68%), mp 35 °C; ν_{max} (Nujol) 1160, 2929, 3274 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.61–1.72 (m, 14H), 1.76–1.83 (m, 2H), 1.92–1.99 (m, 4H), 2.91–2.95 (m, 1H), 3.00–3.04 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 28.2, 28.6 (s, 3C, C_{Ad}), 36.9 (s, 6C, C_{Ad}), 39.0 (1C_q, C_{Ad}), 47.9 (CH_2–NH), 72.2 (q, J_{CF}=22.2 Hz, CF_3–*C*), 129.7 (q, J_{CF}=289.0 Hz, CF_3). ^{19}F NMR ($CDCl_3$): δ −77.5 (CF_3). MS (ESI) *m*/*z* (%): 274 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{15}H_{23}F_3N$ (M+H) 274.1777, found 274.1777.

*4.2.6. 2-[(Methylthio)methyl]-2-(trifluoromethyl)-pyrrolidine (**4f**).* Colorless liquid (75%); ν_{max} (Nujol) 1165, 2922, 3346 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.80–1.94 (3H, m), 1.98–2.07 (2H, m, incl. 2.00 (br s, NH)), 2.17 (3H, s, CH_3–S), 2.82, 2.90 (2H, AB-system, *J*=13.3 Hz, C**H**$_2$–SMe), 2.96–3.02 (1H, m), 3.11–3.14 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4, 26.4, 31.4, 40.2 (*C*H_2–S), 48.0 (CH_2–N), 67.0 (q, J_{CF}=25.9 Hz, *C*–CF_3), 127.8 (q, J_{CF}=283.7 Hz, CF_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ 78.7 (CF_3). ESIMS *m*/*z* (rel int.): 200 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_7H_{13}F_3NS$ 200.0715 (M+H), found 200.0726.

*4.2.7. 2-(4-Methylphenyl)-2-(trifluoromethyl)-pyrrolidine (**4g**).* Colorless liquid (48%); ν_{max} (Nujol) 1152, 2977, 3380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.77–1.86 (1H, m), 1.95–2.05 (1H, m), 2.20–2.27 (2H, m), 2.35 (3H, s, CH_3–Ar), 2.51–2.58 (1H, m), 3.07–3.13 (1H, m), 3.17–3.22 (1H, m), 7.18 (2H, d, *J*=7.8 Hz, Ar–H), 7.40 (2H, d, *J*=7.8 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1 (*C*H_3–Ar), 25.4, 34.4, 47.0 (CH_2–N), 69.7 (q, J_{CF}=25.9 Hz, *C*–CF_3), 127.3 (2C, Ar), 127.6 (q, $^1J_{CF}$=283.7 Hz, CF_3), 129.0 (2C, Ar), 137.1 (C_q, Ar), 137.9 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.6 (CF_3). ESIMS *m*/*z* (rel int.): 230 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{12}H_{15}F_3N$ (M+H) 230.1146, found 230.1151.

*4.2.8. 2-(3,4-Dimethylphenyl)-2-(trifluoromethyl)-pyrrolidine (**4h**).* Colorless liquid (62%); ν_{max} (Nujol) 1151, 2972, 3381 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.79–1.85 (1H, m), 1.97–2.05 (1H, m), 2.21–2.25 (1H, m), 2.24 (1H, br s, NH), 2.26 (3H, s, Ar–CH_3), 2.30 (3H, s, Ar–CH_3), 2.51–2.58 (1H, m), 3.10–3.17 (1H, m), 3.18–3.23 (1H, m), 7.13–7.15 (1H, m, Ar–H), 7.23–7.25 (1H, m, Ar–H), 7.29 (1H, br s, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4 (Ar–*C*H_3), 20.0 (Ar–*C*H_3), 25.5, 34.4, 47.0 (CH_2–N), 69.9 (q, J_{CF}=25.9 Hz, *C*–CF_3), 124.8 (Ar), 127.6 (q, J_{CF}=284.7 Hz, CF_3), 128.6 (Ar), 129.6 (Ar), 136.5 (C_q, Ar), 136.6 (C_q, Ar), 137.5 (C_q, Ar). ^{19}F NMR (376 MHz, CDCl3): δ −76.6 (CF_3). ESIMS *m*/*z* (rel int.): 244 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{13}H_{17}F_3N$ (M+H) 244.1285, found 244.1308.

*4.2.9. 2-(3,5-Dimethylphenyl)-2-(trifluoromethyl)-pyrrolidine (**4i**).* Colorless crystals (65%), mp 44–46 °C; ν_{max} (Nujol) 1161, 2976, 3395 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.78–1.84 (1H, m), 1.96–2.03 (1H, m), 2.17–2.27 (2H, m), 2.35 (6H, s, 2CH_3–Ar), 2.49–2.57 (1H, m), 3.07–3.13 (1H, m), 3.16–3.22 (1H, m), 6.96 (1H, s, Ar–H), 7.11 (2H, s, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5 (2C, s, 2*C*H_3–Ar), 25.4, 34.4, 47.0 (CH_2–N), 69.8 (q, J_{CF}=26.8 Hz, *C*–CF_3), 125.2 (2C, s, Ar), 127.5 (q, J_{CF}=284.7 Hz, CF_3), 129.8 (Ar), 137.8 (2C_q, s, Ar), 140.0 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.5 (CF_3). ESIMS *m*/*z* (rel int.): 244 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{13}H_{17}F_3N$ (M+H) 244.1308, found 244.1301.

*4.2.10. 2-(4-Bromophenyl)-2-(trifluoromethyl)-pyrrolidine (**4j**).* Colorless liquid (61%); ν_{max} (Nujol) 1158, 2979, 3380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.72–1.80 (1H, m), 1.93–2.03 (1H, m), 2.13–2.18 (1H, m), 2.25 (br s, 1H, NH), 2.49–2.51 (1H, m), 3.08–3.21 (2H, m, CH_2–N), 7.46 (2H, d, *J*=8.7 Hz, Ar–H), 7.47 (2H, d, *J*=8.7 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 34.6, 46.9 (CH_2–N), 69.6 (q, J_{CF}=26.8 Hz, *C*–CF_3), 122.3 (C_q, Ar), 127.2 (q, J_{CF}=284.7 Hz, CF_3), 129.3 (2C, Ar), 131.3 (2C, Ar), 139.3 (Cq, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.4 (CF_3). HRMS (ESI): calcd for $C_{10}H_{12}BrFN$ (M−CF_2) 244.0132, found 244.0330.

*4.2.11. 2-(4-Fluorophenyl)-2-(trifluoromethyl)-pyrrolidine (**4k**).* Colorless liquid (53%); ν_{max} (Nujol) 1160, 2981, 3387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.75–1.86 (1H, m), 1.94–2.04 (1H, m), 2.16–2.21 (1H, m), 2.23 (1H, br s, NH), 2.50–2.57 (1H, m), 3.06–3.12 (1H, m), 3.18–3.24 (1H, m), 7.00–7.08 (2H, m, Ar), 7.49 (2H, dd, *J*=8.8 and 5.6 Hz. Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 34.7, 46.9 (CH_2–N), 69.8 (q, J_{CF}=26.8 Hz, *C*–CF_3), 115.1 (2C, d, J_{CF}=22.0 Hz, Ar), 127.3 (q, J_{CF}=284.7 Hz, CF_3), 129.3 (2C, d, J_{CF}=7.7 Hz, Ar), 137.1 (C_q, Ar), 162.5 (C_q, d, J_{CF}=247.2 Hz, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.6 (3F, s, CF_3), −114.5 (1F, br s, Ar–F). ESIMS *m*/*z* (rel int.): 244 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{11}H_{12}F_4N$ (M+H) 234.0900, found 234.0889.

*4.2.12. 2-(4-Methoxyphenyl)-2-(trifluoromethyl)-pyrrolidine (**4l**).* Reddish liquid (49%); ν_{max} (Nujol) 1150, 2961, 3375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.77–1.84 (1H, m), 1.96–2.02 (1H, m), 2.18–2.23 (1H, m), 2.25 (1H, br s, NH), 2.48–2.55 (1H, m), 3.06–3.12 (1H, m), 3.16–3.22 (1H, m), 3.80 (3H, s, CH_3-OAr), 6.88 (2H, d, *J*=8.9 Hz, Ar–H), 7.42 (2H, d, *J*=8.9 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.4, 34.4, 47.0 (CH_2–N), 55.2 (CH_3O), 69.6 (q, $^2J_{CF}$=26.8 Hz, *C*–CF_3), 113.6 (2C, Ar), 127.6 (q, $^1J_{CF}$=284.7, CF_3), 128.6 (2C, Ar), 132.0 (C_q, Ar),159.4 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.7 (CF_3). ESIMS *m*/*z* (rel int.): 246 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{12}H_{15}F_3NO$ (M+H) 246.1089, found 246.1100.

*4.2.13. 2-(Trifluoromethyl)-2-[3-(trifluoromethyl)phenyl]pyrrolidine (**4m**).* Colorless liquid (64%); ν_{max} (Nujol) 1159, 2983, 3388 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.79–1.85 (1H, m), 1.98–2.04 (1H, m), 2.19–2.26 (1H, m), 2.32 (1H, br s, NH), 2.57–2.64 (1H, m), 3.09–3.15 (1H, m), 3.23–3.29 (1H, m), 7.49 (1H, t, *J*=7.8 Hz, Ar–H), 7.60 (1H, d, *J*=7.8 Hz, Ar–H), 7.76 (1H, d, *J*=7.8 Hz, Ar–H), 7.89 (1H, s, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 34.8, 46.9 (CH_2–N), 69.8 (q, J_{CF}=26.9 Hz, CF_3–*C*), 124.1 (q, J_{CF}=273.2 Hz, CF_3–Ar), 124.4 (q, J_{CF}=285.6 Hz, CF_3), 124.4 (q, J_{CF}=2.8 Hz, Ar), 124.9 (q, J_{CF}=3.8 Hz, Ar), 128.7 (Ar), 130.6 (q, J_{CF}=31.6 Hz, Ar), 131.0 (Ar), 141.5 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.4 (3F, s, CF_3–C_q), −62.6 (3F, s, CF_3–Ar). HRMS (ESI): calcd for $C_{12}H_{12}F_6N$ (M+H) 284.0868, found 284.0874.

*4.2.14. 2-(2-Thienyl)-2-(trifluoromethyl)-pyrrolidine (**4n**).* Colorless liquid (71%); ν_{max} (Nujol) 1161, 2980, 3377 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.85–1.92 (1H, m), 1.93–2.02 (1H, m), 2.21–2.28 (1H, m), 2.31 (1H, br s, NH), 2.47 (1H, dt, *J*=13.2 and 8.1 Hz), 3.12–3.21 (2H, m), 7.01 (1H, dd, *J*=3.7 and 5.1 Hz, Ar–H), 7.08 (1H, d, *J*=3.7 Hz, Ar–H), 7.25 (1H, d, *J*=5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 36.1, 47.2 (CH_2–N), 68.2 (q, J_{CF}=27.8 Hz, CF_3–*C*), 125.3 (2C, Ar), 126.9 (q, J_{CF}=283.7 Hz, CF_3), 127.5 (Ar), 145.7 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.2 (CF_3). ESIMS *m*/*z* (rel int.): 222 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_9H_{11}F_3NS$ (M+H) 222.0559, found 222.0559.

*4.2.15. 2-(5-Methylthien-2-yl)-2-(trifluoromethyl)-pyrrolidine (**4o**).* Colorless liquid (52%); ν_{max} (Nujol) 1165, 2977, 3373 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.82–2.01 (2H, m), 2.23–2.28 (2H, m), 2.38–2.42 (1H, m), 2.43 (3H, s, CH_3–Ar), 3.14–3.17 (2H, m, CH_2–NH), 6.64 (1H, d, *J*=3.7 Hz, Ar–H), 6.85 (1H, d, *J*=3.7 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 25.6, 35.8, 47.2 (CH_2–N), 68.3 (q, J_{CF}=27.8 Hz, *C*–CF_3), 125.2 (Ar), 125.5 (Ar), 125.7 (q, $^1J_{CF}$=283.7 Hz, CF_3), 139.8 (C_q, Ar), 142.6 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.2 (CF_3). ESIMS *m*/*z* (rel int.): 236 $[M+H]^+$ (100), 166

[M−CF_3] (80). HRMS (ESI): calcd for $C_{10}H_{13}F_3NS$ (M+H) 236.0715, found 236.0718.

*4.2.16. 2-(2-Furanyl)-2-(trifluoromethyl)-pyrrolidine (**4p**).* Colorless liquid (60%); ν_{max} (Nujol) 1168, 2977, 3386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.80–1.86 (1H, m), 1.91–1.95 (1H, m), 2.24–2.30 (3H, m), 3.07–3.11 (2H, m, CH_2–N), 6.33 (2H, br s, 2Ar–H), 7.38 (1H, br s, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.4, 32.5, 47.0 (CH_2–N), 66.6 (q, J_{CF}=28.8 Hz, *C*–CF_3), 107.8 (Ar), 110.6 (Ar), 126.4 (q, J_{CF}=282.8 Hz, CF_3), 142.5 (Ar), 152.6 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.5 (CF_3). ESIMS *m*/*z* (rel int.): 206 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_9H_{11}F_3NO$ (M+H) 206.0787, found 206.0786.

*4.2.17. 2-(3-Pyridinyl)-2-(trifluoromethyl)-pyrrolidine (α-trifluoromethylnornicotine) (**4q**).* Colorless liquid (68%); ν_{max} (Nujol) 1161, 2979, 3297 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.69–1.76 (1H, m), 1.88–1.95 (1H, m), 2.09–2.16 (1H, m), 2.34 (1H, br s, NH), 2.46–2.53 (1H, m), 2.99–3.04 (1H, m), 3.12–3.18 (1H, m), 7.21 (1H, dd, *J*=8.2 and 4.4 Hz, Ar–H), 7.79 (1H, d, *J*=8.2 Hz, Ar–H), 8.47 (1H, d, *J*=4.4 Hz, Ar–H), 8.71 (s, 1H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 34.4, 46.7 (CH_2–N), 68.7 (q, J_{CF}=25.9 Hz, CF_3–*C*), 122.9 (Ar), 127.1 (q, J_{CF}=284.7 Hz, CF_3), 135.2 (Ar), 135.8 (C_q, Ar), 149.0 (Ar), 149.2 (Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.6 (CF_3). ESIMS *m*/*z* (rel int.): 217 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{10}H_{12}F_3N_2$ (M+H) 217.0948, found 217.0947.

*4.2.18. 2-tert-Butyl-2-(trifluoromethyl)piperidine hydrochloride (**5a**).* Colorless crystals (56%), mp 161–162 °C; ν_{max} (Nujol) 1152, 2921, 3436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 9H), 1.77–1.82 (2H, m), 1.90–1.99 (1H, m), 1.86 (br s, 1H), 2.03–2.11 (2H, m), 3.15–3.19 (1H, m), 3.70–3.74 (1H, m), 8.72 and 10.33 (2H, br s, H_2N^+). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4 (1C, $(CH_3)_3C$), 26.5, 27.5 (3C, $((CH_3)_3C)$), 29.7, 39.6, 48.5 (CH_2–N), 71.7 (q, J_{CF}=23.0 Hz, *C*–CF_3), 126.3 (q, J_{CF}=290.4 Hz, CF_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.7 (CF_3). ESIMS *m*/*z* (rel int.): 224 $[M-Cl]^+$ (100). HRMS (ESI): calcd for $C_{10}H_{19}F_3N$ (M−Cl) 209.1464, found 209.1466.

*4.2.19. 2-Cyclohexyl-2-(trifluoromethyl)piperidine (**5b**).* Colorless liquid (53%); ν_{max} (Nujol) 1157, 2933, 3386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.10–1.23 (m, 5H), 1.50–1.54 (m, 3H), 1.63–1.74 (m, 6H), 1.76–1.81 (m, 4H), 2.76–2.80 (1H, m), 2.89–2.92 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 25.1, 26.6 (2C, s), 26.8, 27.5, 27.6, 27.7, 40.8, 42.5 (CH_2–N), 59.6 (q, J_{CF}=23.0 Hz, *C*–CF_3), 128.8 (q, J_{CF}=290.4 Hz, CF_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.4 (CF_3). ESIMS *m*/*z* (rel int.): 236 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{12}H_{21}F_3N$ (M+H) 236.1621, found 236.1620.

*4.2.20. 2-Phenyl-2-(trifluoromethyl)piperidine (**5c**).* Colorless liquid (49%); ν_{max} (Nujol) 1153, 2943, 3363 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30–1.36 (1H, m), 1.46–1.52 (2H, m), 1.73 (1H, m), 1.98 (1H, dt, *J*=13.3 and 3.7 Hz), 2.11 (1H, br s, NH), 2.50 (1H, dt, *J*=13.7 and 3.2 Hz), 2.59–2.66 (1H, m), 2.90–2.97 (1H, m), 7.31–7.38 (1H, m, Ar–H), 7.40–7.46 (m, 2H, Ar–H), 7.54 (2H, d, *J*=7.8 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 26.1, 28.3, 41.1 (CH_2–N), 62.5 (q, J_{CF}=25.9 Hz, CF_3–*C*), 126.3 (q, J_{CF}=282.7 Hz, CF_3), 128.1 (Ar),128.8 (2C, Ar), 129.1 (2C, Ar), 135.0 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.0 (s, 3F). ESIMS *m*/*z* (rel int.): 230 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{12}H_{15}F_3N$ (M+H): 230.1163, found 230.1151.

*4.2.21. 2-(2-Furanyl)-2-(trifluoromethyl)-piperidine (**5d**).* Colorless liquid (65%); ν_{max} (Nujol) 1166, 2975, 3382 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33–1.40 (1H, m), 1.46–1.52 (2H, m), 1.70–1.74 (1H, m), 1.89 (1H, dt, *J*=12.8 and 4.1 Hz), 2.20–2.27 (1H, m), 2.36 (1H, br s, NH), 2.53–2.60 (1H, m), 2.90–2.96 (1H, m), 6.37–6.38 (1H, m), 6.40 (1H, dd, *J*=3.2 and 1.8 Hz), 7.44–7.45 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 24.8, 26.9, 41.8 (CH_2–N), 60.4 (q, J_{CF}=26.8 Hz, CF_3–*C*), 110.6 (Ar), 110.7 (Ar), 125.5 (q, J_{CF}=283.7 Hz, CF_3), 142.9 (Ar), 150.2 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.5 (s, 3F). ESIMS *m*/*z* (rel int.): 220 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{10}H_{13}F_3NO$ (M+H) 220.0944, found 220.0944.

*4.2.22. 2-(3-Pyridinyl)-2-(trifluoromethyl)-piperidine (α-trifluoromethylanabasine) (**5e**).* Colorless liquid (68%); ν_{max} (Nujol) 1157, 2944, 3291 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.31–1.36 (1H, m), 1.48–1.54 (2H, m), 1.76–1.81 (1H, m), 1.97–2.05 (2H, m), 2.47–2.60 (2H, m), 2.94–3.00 (1H, m), 7.38 (1H, dd, *J*=8.7 and 5.1 Hz, Ar–H), 7.90 (1H, d, *J*=8.7 Hz, Ar–H), 8.61 (1H, d, *J*=5.1 Hz, Ar–H), 8.80 (s, 1H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.63, 26.11, 28.06, 41.0 (CH_2–N), 61.8 (q, J_{CF}=25.9 Hz, CF_3–*C*), 123.5 (Ar), 125.5 (q, J_{CF}=283.7 Hz, CF_3), 130.9 (C_q, Ar), 136.8 (Ar), 149.4 (Ar), 150.4 (Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.0 (CF_3). HRMS (ESI): calcd for $C_{11}H_{14}F_3N_2$ (M+H) 231.1104, found 231.1104.

*4.2.23. 2-tert-Butyl-2-(trifluoromethyl)-azepane hydrochloride (**6a**).* Colorless crystals (55%), mp 157–159 °C; ν_{max} (Nujol) 1143, 2963, 3426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (9H, s, $(CH_3)_3C$), 1.48–1.53 (1H, m), 1.73–2.12 (6H, m), 2.35–2.41(1H, m), 3.51–3.55 (1H, m), 3.69–3.72 (1H, m), 9.15 and 10.31 (2H, br s, H_2N^+). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4 ($(CH_3)_3C$), 26.5, 27.5 (3C, $(CH_3)_3C$), 29.7, 30.1, 39.6, 48.5 (CH_2–N), 71.7 (q, J_{CF}=23.0 Hz, *C*–CF_3), 126.3 (q, J_{CF}=290.4 Hz, CF_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.7 (CF_3). ESIMS *m*/*z* (rel int.): 224 $[M-Cl]^+$ (100). HRMS (ESI): calcd for $C_{11}H_{21}F_3N$ 224.1628, found 224.1626.

*4.2.24. 2-(4-Methylbenzyl)-2-(trifluoromethyl)azepane (**6b**).* Colorless liquid (71%); ν_{max} (Nujol) 1144, 2957, 3431 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.37–1.64 (3H, m), 1.64–1.80 (4H, m, incl. 2.23 (br s, NH)), 1.87–1.95 (2H, m), 2.35 (3H, s, CH_3–Ar), 2.79–2.94 (4H, m, incl. 2.82 (s, (CH_2–Ar))), 7.10–7.15 (4H, m, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 23.0, 30.9, 32.7, 33.9, 41.4 (CH_2–Ar), 43.4 (CH_2–N), 62.8 (q, J_{CF}=22.0 Hz, *C*–CF_3), 128.8 (2C, Ar), 128.7 (q, J_{CF}=290.4 Hz, CF_3), 130.9 (2C, Ar), 132.8 (C_q, Ar), 136.4 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.3 (CF_3). HRMS (ESI): calcd for $C_{15}H_{21}F_3N$ (M+H) 272.1626, found 272.1621.

*4.2.25. 2-Phenyl-2-(trifluoromethyl)-azepane (**6c**).* Yellowish liquid (44%); ν_{max} (Nujol) 1155, 2928, 3393 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.38–1.52 (2H, m), 1.53–1.57 (2H, m), 1.69–1.78 (2H, m), 2.00 (1H, br s, NH), 2.27–2.43 (2H, m), 2.78–2.84 (1H, m), 3.07–3.13 (1H, m), 7.30–7.45 (3H, m, Ar–H), 7.60–7.66 (2H, m, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 30.1, 33.4, 34.0, 43.7 (CH_2–N), 65.7 (q, J_{CF}=24.0 Hz, *C*–CF_3), 127.8 (q, J_{CF}=286.6 Hz, CF_3), 127.9 (2C, Ar), 128.3 (Ar), 129.3 (2C, Ar), 140.1 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.2 (CF_3). ESIMS *m*/*z* (rel int.): 244 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{13}H_{17}F_3N$ (M+H) 244.1301, found 244.1308.

*4.2.26. 2-(2-Furanyl)-2-(trifluoromethyl)-azepane (**6d**).* Yellow liquid (56%); ν_{max} (Nujol) 1146, 2929, 3415 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.37–1.48 (3H, m), 1.60–1.65 (1H, m), 1.69–1.75 (1H, m), 1.77–1.82 (1H, m), 2.13–2.19 (1H, m), 2.23 (1H, br s, NH), 2.18–2.32 (1H, m), 2.82–2.88 (1H, m), 2.91–2.97 (1H, m), 6.32–6.39 (2H, m, Ar–H), 7.41 (1H, s, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 30.1, 32.1, 33.3, 43.5 (CH_2–N), 63.7 (q, J_{CF}=25.9 Hz, *C*–CF_3), 108.8 (Ar), 110.4 (Ar), 126.9 (q, J_{CF}=287.5 Hz, CF_3), 142.6 (Ar), 153.1 (C_q, Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ 78.3 (CF_3). ESIMS *m*/*z* (rel int.): 234 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{11}H_{15}F_3NO$ (M+H) 234.1100, found 234.1100.

*4.2.27. 2-Pyridin-3-yl-2-(trifluoromethyl)azepane (α-trifluoromethylhomoanabasine) (**6e**).* Colorless liquid (56%); ν_{max} (Nujol) 1160, 2929, 3274 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24–1.34 (1H, m), 1.40–1.55 (3H, m), 1.60–1.78 (2H, m), 2.00 (1H, br s, NH),

2.16–2.28 (1H, m, 1H), 2.30–2.40 (1H, m), 2.72–2.80 (1H, m), 3.05–3.14 (1H, m), 7.26 (1H, dd, J=8.4 and 4.6 Hz, Ar–H), 7.90 (1H, d, J=8.4 Hz, Ar–H), 8.52 (1H, d, J=4.6 Hz, Ar–H), 8.84 (1H, br s, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 29.8, 33.0, 33.7, 43.4 (CH_2–N), 64.7 (q, J_{CF}=24.9 Hz, C–CF_3), 122.9 (Ar), 127.5 (q, J_{CF}=287.5 Hz, CF_3), 135.4 (Ar), 135.6 (C_q, Ar), 149.0 (Ar), 149.4 (Ar). ^{19}F NMR (376 MHz, $CDCl_3$): δ −77.4 (CF_3). ESIMS m/z (rel int.): 245 $[M+H]^+$ (100). HRMS (ESI): calcd for $C_{12}H_{16}F_3N_2$ (M+H) 245.1262, found 245.1266.

*4.2.28. 2-(Trifluoromethyl)pyrrolidine (**8a**).* Compound **8a** was synthesized analogously to the *General procedure for the reaction of cyclic imines with trifluoromethyltrimethylsilane*. Before the addition of trifluoromethyltrimethylsilane the reaction mixture was stirred for 20 min. Colorless liquid (47%); ^{1}H, ^{13}C, and ^{19}F NMR data of free base were identical with the reported ones.[28,29]

*4.2.29. 2-(Trifluoromethyl)piperidine (**8b**).* Compound **8b** was synthesized analogously to the *General procedure for the reaction of cyclic imines with trifluoromethyltrimethylsilane*. Before the addition of trifluoromethyltrimethylsilane the reaction mixture was stirred for 20 min. Colorless liquid (55%); ^{1}H, ^{13}C, and ^{19}F NMR data of free base were identical with the reported ones.[30,29]

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.11.032.

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