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Deoxofluorination of Aliphatic Carboxylic Acids: a Route to Trifluoromethyl-Substituted Derivatives

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Supporting Information Placeholder

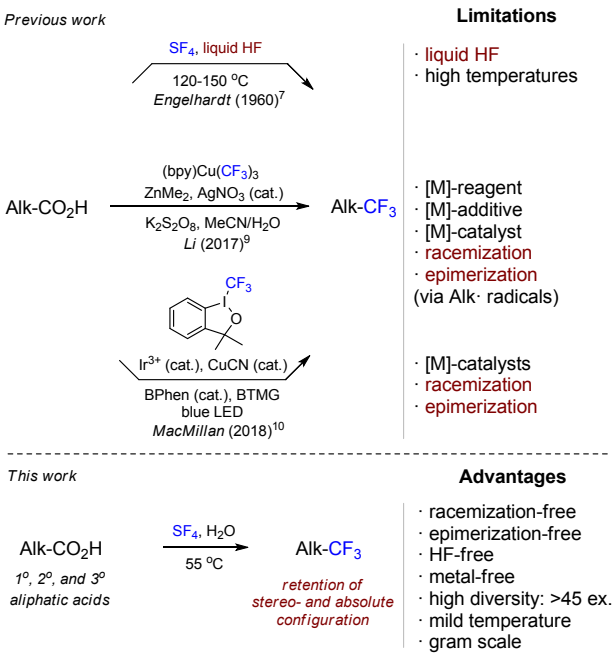
ABSTRACT: Practical method for the synthesis of functionalized aliphatic trifluoromethyl-substituted derivatives from aliphatic acids is developed. The transformation proceeds with sulfur tetrafluoride in the presence of water as a key additive. Compared to previous methods, the reaction gives products with full retention of stereo- and absolute configuration of chiral centers.

INTRODUCTION

More than 20% of all modern pharmaceuticals and up to 30% of agrochemicals contain at least one fluorine atom.[1,2] Among all fluoroalkyl substituents, the trifluoromethyl group is the most prominent - it comprises to a structure of more than seventy approved drugs.[3] On the other hand, in the frame of the recently emerged concept "escape from flatland"[4] medicinal chemists nowadays tend to use more aliphatic compounds in drug discovery projects than in the past. In this context, functionalized trifluoromethyl-substituted aliphatic building blocks look particularly interesting, and elaboration of novel practical methods for their synthesis is important.[5,6]

Aliphatic acids are amongst the most available chemical compound classes, and it would be desirable to have a practical method to converting them into the trifluoromethyl-substituted derivatives. In 1960, Engelhardt performed this transformation by treating aliphatic acids with sulfur tetrafluoride at 150 °C in liquid hydrogen fluoride (Scheme 1).[7] Indeed, the use of liquid hydrogen fluoride at high temperatures prevented a wide application of this method at both academic and industrial institutions.[8] However, in 2017, Li[9] and subsequently MacMillan in 2018[10] independently developed elegant decarboxylative trifluoromethylations of aliphatic carboxylic acids. These transformations proceeded via formation of configurationally unstable alkyl radicals (Alk·), and therefore gave products with erosion of stereo- and absolute stereochemistry of chiral centers. Worth also mentioning a work of Umemoto, who developed Fluolead reagent for the fluorination of hydroxyl and carbonyl groups.[11] In this project, the authors also showed two examples of fluorination of aliphatic acids into trifluoromethyl-substituted derivatives. Unfortunately, the scope of this reaction was not further elaborated.

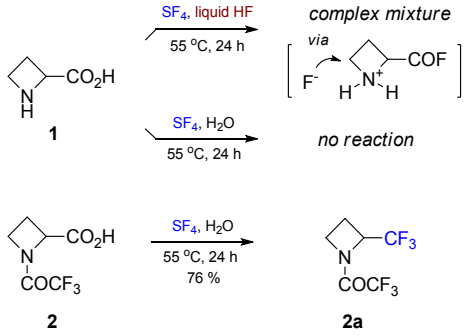
Herein we report on a mild fluorination of aliphatic carboxylic acids with sulfur tetrafluoride in the presence of water as a key additive. In contrast to previous approach of Engelhardt,[7] our method requires no liquid hydrogen fluoride and proceeds at mild temperatures. In contrast to methods of Li[9] and MacMillan,[10] the reaction works with full retention of stereo- and absolute configuration of chiral centers. In addition, our experimental protocol requires no irradiation, no use of metal-containing reagents or additives, and can be performed on a milligram to a gram scale.



Scheme 1. Conversion of aliphatic carboxylic acids into the trifluoromethyl-substituted derivatives.

Within our long-term project on the synthesis of unique fluorinated amines for drug design,[12] we became interested in preparing the previously unknown α-trifluoromethyl-azetidine. First, we tried the original procedure of Engelhardt,[7] and treated azetidine-2-carboxylic acid (**1**) with sulfur tetrafluoride in hydrogen fluoride. Unfortunately, all our attempts to perform this transformation at different temperatures failed, and only formation of complex mixtures was observed. Presumably, an excess of hydrogen fluoride led to ring-opening of the protonated azetidine ring (Scheme 2).

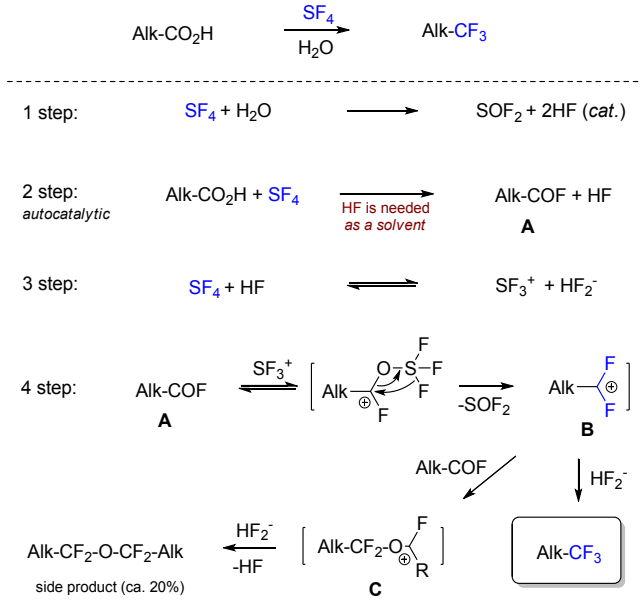
Liquid hydrogen fluoride is used as a solvent in fluorination of amino acids for two reasons:[13-15] a) it protects the amino group by protonation, and b) it activates sulfur tetrafluoride by giving active SF_3^+ intermediate.[15-17] We therefore decided to avoid the use of hydrogen fluoride by protecting nitrogen atom in **1** and adding water to the reaction mixture to initiate the reaction (Scheme 2). We hoped that water would react with sulfur tetrafluoride to give catalytic hydrogen fluoride in a sufficient concentration for the formation of SF_3^+ intermediate. After some experimentation, we found that indeed the reaction proceeded, and only slight heating was required. In fact, heating a mixture of trifluoroacetyl-protected compound **2**,[18] sulfur tetrafluoride and water at 55 °C for one day afforded product **2a** in 76% yield after distillation. Importantly, no cleavage of the azetidine ring was observed. The reaction also produced ca. 20% of the side product RCF_2OCF_2R (**2b**) that remained in the residue after distillation, and we did not isolate it in the pure state.[19]



Scheme 2. Fluorination of acids **1** and **2** with sulfur tetrafluoride.

In our initial optimization attempts, the reaction of crystalline carboxylic acids with sulfur tetrafluoride without any solvent was slow. Even though stochiometrically one equivalent of hydrogen fluoride was to be formed in the reaction, we still needed to add HF at the beginning to initiate the process. Therefore, the use of water as an additive was a key solution. First, sulfur tetrafluoride reacted with water to form the catalytic amount of hydrogen fluoride (Scheme 3, step 1); it acted as a solvent, and initiated the conversion of the carboxylic acid into the acyl fluoride **A** (Scheme 3, step 2). We assume that this step was autocatalytic, producing one equivalent of hydrogen fluoride, that "activated" next sulfur tetrafluoride into an active SF_3^+ intermediate (Scheme 3, step 3). In the final step, SF_3^+ cation reacted with AlkCOF (**A**) to form the difluoromethyl cation (**B**). The latter either reacted with hydrodifluoride anion to give the target Alk-CF_3 product; or with another molecule of AlkCOF to form the side product $AlkCF_2OCF_2Alk$ via the intermediate **C** (Scheme 3, step 4).

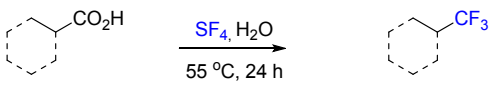
Having realized a high practical potential of this method, we next studied its scope (Scheme 4). Diverse primary (**3**-**17**), secondary (**23**-**31**), tertiary carboxylic acids (**32**-**43**) along with α-bromo (**18**-**20**) and α-amino acids (**2**, **21**, **22**) gave the needed trifluoromethylated products in good yields. Importantly, diverse functional groups, - ester (**24**, **25**, **32**, **35**, **36**, **38**, **41**, **42**), cyclopropyl (**32**-**34**), bromo (**18**-**20**, **26**, **27**), chloro (**28**), protected amino (**2**, **6**-**11**, **21**, **29**-**31**, **39**, **40**), amido (**22**), aryl (**12**-**17**, **33**, **42**), and nitro (**15**-**17**, **23**), - were compatible with the reaction conditions. Among the amino acids used were α- (**2**, **21**), β- (**29**-**31**, **39**, **40**), γ- (**6**-**8**, **11**, **12a**, **13a**) and ω-amino acids (**10**, **1**). Also, various medicinal chemistry relevant rings were compatible with this method: azetidine (**2**, **6**, **9**, **29**), pyrrolidine (**7**, **21**, **22**, **30**, **39**, **40**), piperidine (**8**, **10**, **11**, **31**), cyclopropane (**23**, **32**-**34**), cyclobutane (**27**, **28**, **35**, **37**), spirocyclobutane (**36**), bicyclo[2.2.1]heptane (**42**), and bicyclo[2.2.2]octane (**43**). Structure of products **22a** and **43a** was confirmed by X-Ray analysis.[20]



Scheme 3. Mechanism of fluorination of aliphatic acids with sulfur tetrafluoride/water (additive).

Important to mention, that in contrast to previous methods of Li[9] and MacMillan,[10] ***the current reaction proceeded with full retention of stereo- and absolute configuration of chiral centers***. In fact, from *trans*-acid **23** only *trans*-product **23a** was obtained. Formation of the corresponding *cis*-isomer was not detected. Moreover, three optically pure substrates - α-amino acid (*S*)-**21**, *L*-pyroglutamic acid (*S*)-**22**, and β-amino acid (*S*)-**31** - gave the corresponding optically pure products (*S*)-**21a**, (*S*)-**22a** and (*S*)-**31a** without any detectable level of racemization (>97% *ee*) as determined by chiral HPLC.

During the recent decade, sulfur tetrafluoride has been gaining popularity in the both academic laboratories and industrial institutions.[21] From the practical aspect, the use of Teflon glassware is required. Concerning the reaction scale, we performed all syntheses on 500 mg to 20 g quantity. The pure

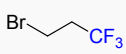


2-43
Aliphatic acid

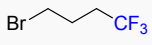
2a-43a
CF_3-product

- racemization-free
- epimerization-free
- HF-free
- metal-free
- >40 examples
- 1°, 2°, and 3° alkyl acids
- gram scale

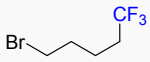
Primary acids



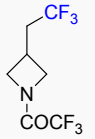
3a (64%)



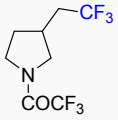
4a (61%)



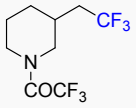
5a (58%)



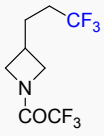
6a (52%)



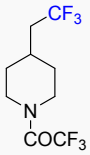
7a (74%)



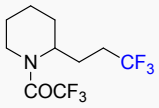
8a (56%)



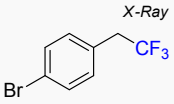
9a (61%)



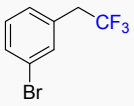
10a (49%)



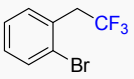
11a (62%)



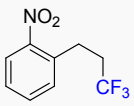
12a (64%)



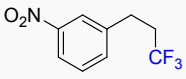
13a (60%)
previously 3 steps (48%)



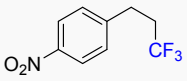
14a (66%)



15a (70%)

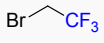


16a (71%)

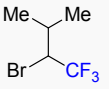


17a (72%)

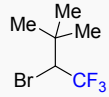
α-Halogeno acids



18a (40%)

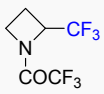


19a (58%)

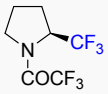


20a (65%)

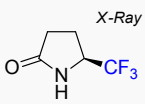
α-Amino acids



2a (76%)

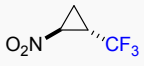


(*S*)-**21a** (51%, >97%ee)
from L-Proline

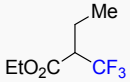


22a (70%, >97%ee)
from L-Pyroglutamic acid

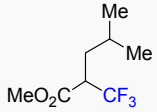
Secondary acids



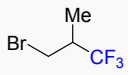
23a (52%)



24a (62%)

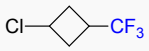


25a (55%)

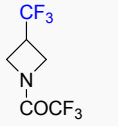


26a (60%)

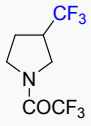
27a (63%)



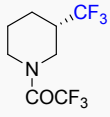
28a (65%)



29a (75%)



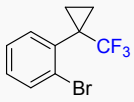
30a (70%)
from β-Proline



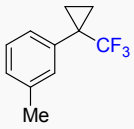
(*S*)-**31a** (57%, >97%ee)
from (S)-nipecotic acid

Tertiary acids

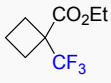
32a (54%)



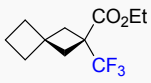
33a (68%)
previously 4 steps (29%)



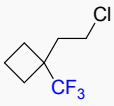
34a (60%)



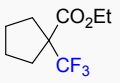
35a (68%)



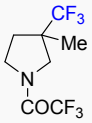
36a (53%)



37a (57%)



38a (69%)



39a (55%)

40a (50%)

41a (53%)

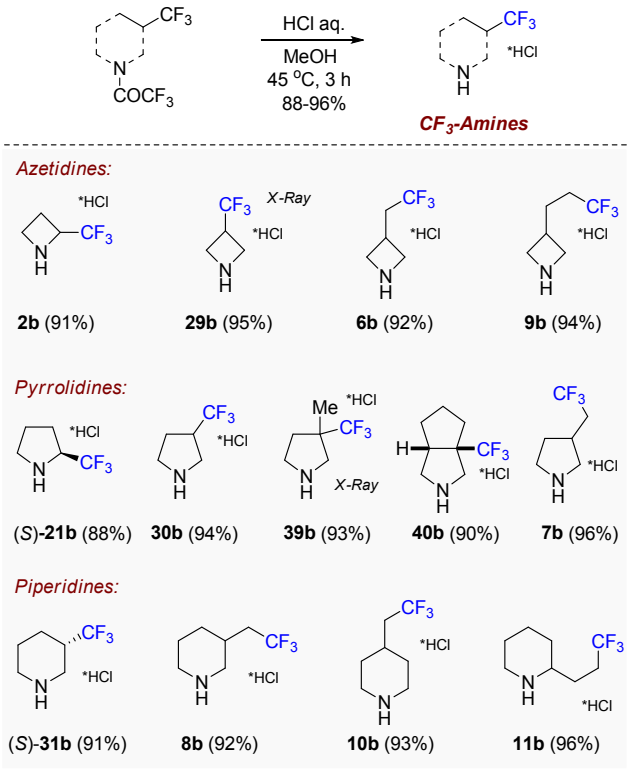
42a (42%)

43a (37%)[a]
previously 10 steps (9%)

Scheme 4. Scope of fluorination of aliphatic acids with sulfur tetrafluoride/water. *Reaction conditions*: (i) aliphatic acid (1.0 equiv), sulfur tetrafluoride (3.0 equiv), water, 55-60 °C, 12 h. (ii) aq. $NaHCO_3$; (a) aq. NaOH was used instead of aq. $NaHCO_3$.

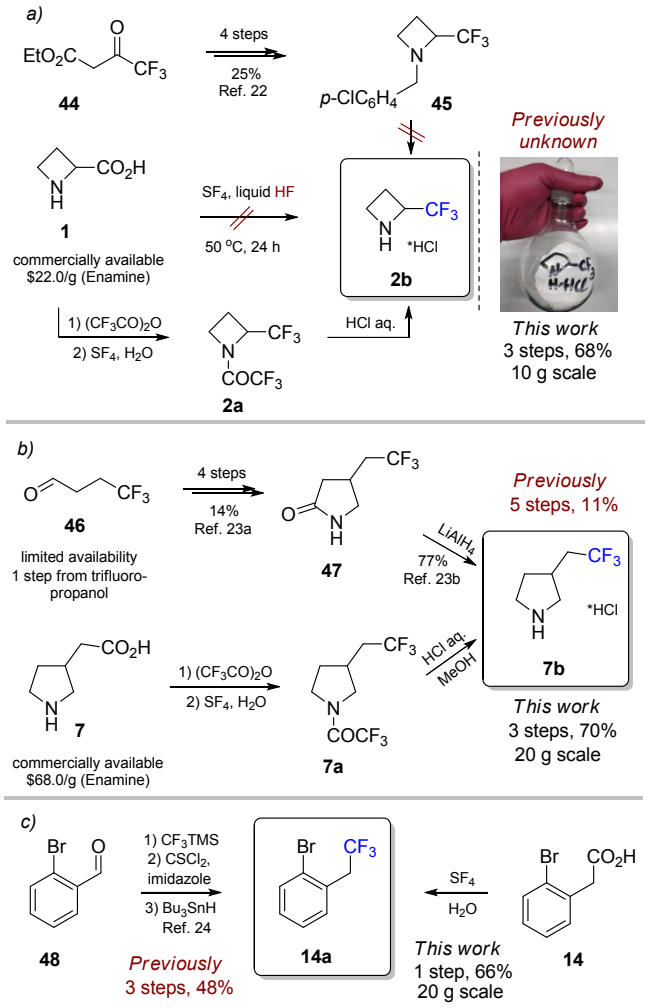
products were isolated from the reaction mixture mostly by simple distillation.

Finally, we also wanted to demonstrate the high practical potential of this method. Azetidines, pyrrolidines and piperidines are amongst the most commonly used amines in medicinal chemistry.[22] Therefore, we synthesized a library of novel or previously hardly accessible trifluoromethyl-substituted azetidines (**2b**, **6b**, **9b**, **29b**), pyrrolidines (**7b**, **21b**, **30b**, **39b**, **40b**) and piperidines (**8b**, **10b**, **11b**, **31b**).[23] The cleavage of *N*-trifluoroacetyl group was performed by heating the compounds at 45 °C for three hours in a dilute solution of aqueous hydrochloric acid in methanol (Scheme 5). The amines were obtained as white crystalline hydrochloride solids stable upon storage. Structure of amine **29b***HCl was confirmed by an X-Ray analysis.[20] Amine **39b***HCl was first converted into a more crystalline **39b***$HClO_4$, and its structure was also proven by X-Ray analysis.[20]



Scheme 5. Synthesis of aliphatic trifluoromethyl-substituted cyclic amines.

Importantly, in spite of a very simple structure, synthesis of azetidine **2b** remained unknown in the literature so far. In 2012, D'hooghe, Van Nguyen, De Kimpe and co-workers reported on a preparation of compound **45** from trifluoroethyl acetoacetic ester (**44**), however, cleavage of *N*-protecting group was not achieved (Scheme 6a).[24] Herein, we performed the synthesis of amine **2b** on 10 g scale in three steps from the commercially available azetidine-carboxylic acid **1**. The synthesis of amine **7b** was previously mentioned in a patent literature in five steps, 11% total yield, from aldehyde **46**.[25] Herein, we prepared amine **7b** in three steps, 68% yield (20 g scale) from the commercially available amino acid **7** (Scheme 6b). Aryl bromide **14a** was recently obtained in three steps from aldehyde **48** employing an organotin reagent.[26] We, in turn, synthesized compound **14a** in one step from acid **14** (Scheme 6c). Trifluoromethyl-cyclopropanes were recently shown to be metabolically stable mimics of the *tert*-butyl group.[27] Hence practical synthetic approaches to them are important.[28] While the known approach to CF_3-cyclopropane **33a** constitutes four chemical steps (Scheme 4),[28b] our method allowed to synthesize compound **33a** (and also **34a**) in only one step in 68% yield. Medicinal chemistry relevant compound **43a** was previously prepared in ten chemical steps.[29] We performed herein a one-step synthesis of **43a** on a gram scale (Scheme 4). Moreover, the cores of bicyclo[2.2.2]octane, bicyclo[2.2.1]heptane were recently proposed to mimic the residues of *meta*- and *para*-disubstituted benzenes.[30] Therefore, we believe that compounds **42a** and **43a** will be become valuable building blocks in modern drug discovery projects.



Scheme 6. Comparison of literature and our approaches to medicinal chemistry-relevant building blocks **2b**, **7b** and **14a**.

As a summary, we developed a practical protocol for the synthesis of functionalized trifluoromethyl-substituted aliphatic derivatives from readily available carboxylic acids. The procedure

included fluorination with sulfur tetrafluoride with an addition of water as a key additive. Importantly, compared to previous methods[9,10] ***the current reaction proceeded with full retention of stereo- and absolute configuration of chiral centers***. The transformation showed wide functional group compatibility. The protocol required no irradiation, and no use of metal-containing reagents or additives. From the practical standpoint, the reaction could be performed on a milligram to multigram scale. To highlight the high practical potential of this transformation, we synthesized (a) a novel or previously scarcely accessible trifluoromethyl-substituted azetidines, pyrrolidines and piperidines (Scheme 5); (b) metabolically stable mimics of the *tert*-butyl group - trifluoromethyl-substituted cyclopropanes **33a**, **34a**; and (c) saturated bioisosteres of the benzene ring - trifluoromethyl-substituted bicyclic scaffolds **42a** and **43a**. Given the high availability of aliphatic carboxylic acids, we believe that our method will soon find a practical wide application in the both academic and industrial research programs.

EXPERIMENTAL SECTION

General Considerations. All chemicals were provided by Enamine Ltd. (www.enamine.net). Autoclaves were provided by UOSLab (en.uoslab.com). All solvents were treated according standard methods. All reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. Product purification was performed using silica gel column chromatography. TLC-characterization was performed with pre-coated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100-200 mesh).^{1}H-NMR, ^{19}F-NMR, ^{13}C-NMR spectra were recorded with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. ^{1}H-NMR spectra were recorded at 400 or 500 MHz (Varian); ^{19}F-NMR spectra were recorded at 376 MHz (Varian) and ^{13}C NMR spectra were recorded at 100 or 126 MHz (Varian). ^{1}H-NMR chemical shifts are reported downfield from $CDCl_3$ (δ = 7.26 ppm), D_2O (δ = 4.79 ppm) or DMSO-d_6 (δ = 2.50 ppm). ^{13}C-NMR chemical shifts for ^{13}C-NMR are reported relative to the central $CDCl_3$ (δ = 77.16 ppm) or DMSO-d_6 (δ = 39.52 ppm). Coupling constants are given in Hz. MS analysis was performed on an LCMS instrument with chemical ionization or GCMS with electrospray ionization. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments.

General procedure for the synthesis of 2a-43a (2a as an example)

Caution! Sulfur tetrafluoride (SF_4) is a toxic gas! Special care must be taken when working with SF_4.[31]

2,2,2-Trifluoro-1-(2-(trifluoromethyl)azetidin-1-yl)ethan-1-one (2a)

Compound **2** (29.55 g, 0.15 mol, 1 equiv) and water (1.5 g, 0.083 mol) were placed in 280 mL autoclave made of Hastelloy nickel alloy. The reaction vessel was cooled down by liquid nitrogen, and SF_4 (48.6 g, 0.45 mol, 3 equiv) was condensed into a reaction vessel. Cooling bath was removed, and the mixture was allowed to warm up to a room temperature. It was then heated at 55-60 °C in oil bath for 24 h. The autoclave was allowed to cool down to a room temperature, and the gaseous products were vented off into a trap with aqueous solution of NaOH (1N). The residue was dissolved in CH_2Cl_2 (300 mL), poured onto ice (500 g) and triturated with saturated aq. $NaHCO_3$ (500 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under a reduced pressure to afford the desired product **2a** (RCF_3) and ca. 20% of the dimer RCF_2OCF_2R. The final product **2a** (RCF_3) was purified by distillation. Yield 25.2 g (0.114 mol, 76%), yellow oil, b.p. 71-72 °C (12 mm Hg). The crude dimeric product remained in the residue after a distillation. ^{1}H NMR (500 MHz, $CDCl_3$, rotamers ~6:1): δ 5.05 – 4.95 (s, 1H), 4.93 – 4.81 (m, 1H), 4.47 (dd, *J* = 16.2, 8.7 Hz, 1H), 4.41 – 4.32 (m, 1H), 4.28 – 4.12 (m, 1H), 2.89 – 2.62 (m, 1H), 2.54 – 2.37 (m, 1H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.2 (q, *J* = 38 Hz), 124.0 (q, *J* = 280 Hz), 115.8 (q, *J* = 288 Hz), 63.2 (q, *J* = 35 Hz), 60.2 (q, *J* = 35 Hz), 51.1 (q, *J* = 2 Hz), 48.9, 18.8, 18.0. ^{19}F NMR (376 MHz, $CDCl_3$, rotamers ~6:1): δ -72.5 (q, *J* = 6.9 Hz), -73.5 (s), -77.2 (s), -78.6 (q, *J* = 6.8 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_6F_6NO$, 222.0354; found 222.0356.

Notes

The reaction on 1 g scale was performed the same, except for: autoclave for 60 mL, 1 drop of water (ca. 50 mg).

The reaction on 3 g scale was performed the same, except for: autoclave for 60 mL, 3 drops of water (ca. 150 mg).

3-Bromo-1,1,1-trifluoropropane (3a)

6.55 g (0.037 mol, 64% yield), colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.44 (t, *J* = 7.8 Hz, 2H), 2.76 – 2.62 (m, 2H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 125.5 (q, *J* = 277.5 Hz), 37.6 (q, *J* = 29.4 Hz), 21.1 (q, *J* = 4.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -66.8 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_3H_5BrF_3$, 176.9527; found 176.9528.

4-Bromo-1,1,1-trifluorobutane (4a)

7.8 g (0.04 mol, 61% yield), colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (t, *J* = 6.3 Hz, 2H), 2.38 – 2.21 (m, 2H), 2.20 – 2.07 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 126.9 (q, *J* = 276.3 Hz), 32.6 (q, *J* = 29.2 Hz), 31.6, 25.4 (q, *J* = 3.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.5 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_4H_7BrF_3$, 190.9683; found 190.9686.

5-Bromo-1,1,1-trifluoropentane (5a)

14.35 g (0.070 mol, 58% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (t, *J* = 6.5 Hz, 2H), 2.22 – 2.04 (m, 2H), 2.01 – 1.88 (m, 2H), 1.79 – 1.68 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 127.0 (q, *J* = 276.4 Hz), 33.0 (q, *J* = 28.8 Hz), 32.6, 31.5, 20.8 (q, *J* = 2.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -66.8 (s). GCMS: *m/z* = 205 (M^+). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_5H_9BrF_3$, 204.9840; found 204.9840.

2,2,2-Trifluoro-1-(3-(2,2,2-trifluoroethyl)azetidin-1-yl)ethan-1-one (6a)

12.34 g (0.0525 mol, 52% yield), white solid, m.p. 29-30 °C, b.p. 97-100 °C (20 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.54 (t, *J* = 9.2 Hz, 1H), 4.29 (t, *J* = 9.8 Hz, 1H), 4.13 (dd, *J* = 8, 6.6 Hz 1H), 3.86 (dd, *J* = 10.7, 6.2 Hz, 1H), 3.15 – 2.99 (m, 1H), 2.52 – 2.33 (m, 1H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.3 (q, *J* = 38 Hz), 126.0 (q, *J* = 277 Hz), 116.1 (q, *J* = 288 Hz), 56.6, 53.5, 37.5 (q, *J* = 29 Hz), 24.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -66.5 (t, *J* = 10.3 Hz), -73.4 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_8F_6NO$, 236.0510; found 236.0515.

2,2,2-Trifluoro-1-(3-(2,2,2-trifluoroethyl)pyrrolidin-1-yl)ethan-1-one (7a)

24.65 g (0.099 mol, 74% yield), yellow oil, b.p. 81-82 °C (7 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$, rotamers ~1:1): δ 3.95 – 3.85 (m, 1H), 3.82 (t, *J* = 8.9 Hz, 1H), 3.73 (t, *J* = 10.4 Hz, 1H), 3.56 (dd, *J* = 17.2, 8.3 Hz, 1H), 3.46 (dd, *J* = 18.5, 9.2 Hz, 1H), 3.23 (t, *J* = 9.7 Hz, 1H), 3.13 (t, *J* = 10.6 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.50 – 2.41 (m, 1H), 2.32 – 2.14 (m, 3H), 1.81 – 1.65 (m, 1H), 1.70 – 1.56 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 156.0 (m), 126.7 (q, *J* = 276 Hz), 126.3 (q, *J* = 276 Hz), 116.3 (q, *J* = 287 Hz), 116.3 (q, *J* = 287 Hz), 52.1, 51.2, 46.8, 46.0 (d, *J* = 3 Hz), 36.9 (m), 33.7, 32.1, 31.0 (m), 29.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -65.7 (s), -65.8 (s), -73.2 (s), -73.3 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_8H_{10}F_6NO$, 250.0667; found 250.0669.

2,2,2-Trifluoro-1-(3-(2,2,2-trifluoroethyl)piperidin-1-yl)ethan-1-one (8a)

18.41 g (0.07 mol, 56% yield), b.p. 52-53 °C (0.1 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$, rotamers ~1:1): δ 4.37 (d, *J* = 13.2 Hz, 1H), 3.95 (dd, *J* = 68.2, 13.4 Hz, 1H), 3.21 – 2.63 (m, 2H), 2.16 – 1.89 (m, 4H), 1.84 – 1.71 (m, 1H), 1.64 – 1.52 (m, 1H), 1.43 – 1.28 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$, rotamers ~1:1): δ 155.7 (q, *J* = 36 Hz), 155.5 (q, *J* = 36 Hz), 126.6 (q, *J* = 277 Hz), 126.5 (q, *J* = 277 Hz), 116.6 (q, *J* = 288 Hz), 50.8, 48.5, 46.3 (q, *J* = 3 Hz), 44.1, 37.4 (q, *J* = 28 Hz), 31.6 (d, *J* = 2 Hz), 30.9, 30.6 (d, *J* = 2 Hz), 30.4, 25.2, 24.3. ^{19}F NMR (376 MHz, $CDCl_3$, rotamers ~1:1): δ -64.0 (s), -64.3 (s), -69.5 (s), -69.6 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_9H_{12}F_6NO$, 264.0823; found 264.0827.

2,2,2-Trifluoro-1-(3-(3,3,3-trifluoropropyl)azetidin-1-yl)ethan-1-one (9a)

18.92 g (0.076 mol, 61% yield), yellow oil, b.p. 83-84 °C (10 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.48 (t, *J* = 8.7 Hz, 1H), 4.22 (t, *J* = 9.5 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.74 (dd, *J* = 10.4, 5.7 Hz, 1H), 2.85 – 2.70 (m, 1H), 2.12 – 1.99 (m, 2H), 1.90 (dd, *J* = 15.0, 7.6 Hz, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 156.4 (q, *J* = 37 Hz), 126.7 (q, *J* = 276 Hz), 116.2 (q, *J* = 288 Hz), 56.8, 53.8, 31.3 (q, *J* = 29.3 Hz), 28.9, 26.5 (d, *J* = 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -66.8, -73.4. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_8H_{10}F_6NO$, 250.0667; found 250.0666.

2,2,2-Trifluoro-1-(4-(2,2,2-trifluoroethyl)piperidin-1-yl)ethan-1-one (10a)

5.78 g (0.022 mol, 49% yield), yellow oil, b.p. 67-68 °C (0.15 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.53 (d, *J* = 13.4, 1H), 4.01 (d, *J* = 13.9 Hz, 1H), 3.13 (t, *J* =13.3 Hz, 1H), 2.77 (t, *J* = 13.0 Hz, 1H), 2.14 – 1.96 (m, 3H), 1.96 – 1.87 (m, 2H), 1.39 – 1.24 (m, 2H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 126.7 (q, *J* = 277 Hz), 116.6 (q, *J* = 288 Hz), 45.7 (q, *J* = 3 Hz), 43.5, 39.8 (q, *J* = 28 Hz), 32.4, 31.5, 30.5 (q, *J* = 2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -64.0 (s), -69.5 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_9H_{12}F_6NO$, 264.0823; found 264.0824.

2,2,2-Trifluoro-1-(2-(3,3,3-trifluoropropyl)piperidin-1-yl)ethan-1-one (11a)

4.7 g (0.017 mol, 62% yield), yellow oil, b.p. 73-74 °C (0.3 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.48 (t, *J* = 8.7 Hz, 1H), 4.22 (t, *J* = 9.5 Hz, 1H), 4.08 – 3.95 (m, 1H), 3.82 – 3.70 (m, 1H), 2.83 – 2.72 (m, 1H), 2.12 – 2.00 (m, 2H), 1.96 – 1.87 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 156.4 (q, *J* = 37 Hz), 126.7 (q, *J* = 276 Hz), 116.2 (q, *J* = 288 Hz), 56.8, 53.8, 31.3 (q, *J* = 29 Hz), 28.9, 26.5 (d, *J* = 3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -66.8 (s), -73.4 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{10}H_{14}F_6NO$, 278.0980; found 278.0987.

1-Bromo-4-(2,2,2-trifluoroethyl)benzene (12a)

1.5 g (6.3 mmol, 64% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 3.33 (q, *J* = 10.7 Hz, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 132.0, 132.0, 129.24 (q, *J* = 3.0 Hz), 125.6 (q, *J* = 276.8 Hz), 122.5, 39.9 (q, *J* = 30.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -66.5 (s). GCMS: *m/z* = 239 (M$^+$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_8H_7BrF_3$, 238.9683; found 238.9685.

1-Bromo-3-(2,2,2-trifluoroethyl)benzene (13a)

0.7 g (2.93 mmol, 60% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.43 (m, 2H), 7.26 – 7.18 (m, 2H), 3.34 (q, *J* = 10.6 Hz, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 133.3, 132.4 (q, *J* = 3.0 Hz), 131.5, 130.4, 128.9 (d, *J* = 8.7 Hz), 125.6 (q, *J* = 276.9 Hz), 122.8, 40.0 (q, *J* = 30.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -66.3 (s). GCMS: *m/z* = 239 (M$^+$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_8H_7BrF_3$, 238.9683; found 238.9687.

1-Bromo-2-(2,2,2-trifluoroethyl)benzene (14a)

20.1 g (84.1 mmol, 66% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 3.64 (q, *J* = 10.5 Hz, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 133.4, 132.1, 130.4 (q, *J* = 2.9 Hz), 129.9, 127.8, 125.7, 123.5 (q, *J* = 277.6 Hz), 39.7 (q, *J* = 30.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -65.6 (s). GCMS: *m/z* = 239 (M$^+$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_8H_7BrF_3$, 238.9683; found 238.9684.

1-Nitro-2-(3,3,3-trifluoropropyl)benzene (15a)

10.28 g (0.043 mol, 70% yield), yellow oil; b.p. 80-81 °C / 0.1 mm Hg. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46-2.56 (m, 2H), 3.15 (t, $^3J_{HH}$ = 8.1 Hz, 2H), 7.4 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 7.44 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 7.6 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 7.99 (d, $^3J_{HH}$ = 7.9 Hz, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 26.1 (q, $^3J_{CF}$ = 3.3 Hz), 34.5 (q, $^2J_{CF}$ = 28.7 Hz), 125.0, 126.4 (q, $^1J_{CF}$ = 276.7 Hz), 128.0, 132.1, 133.4, 134.0, 148.9. ^{19}F NMR (188 MHz, $CDCl_3$): δ - 67.0 (s). GCMS: *m/z* = 219 (M$^+$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_9H_9F_3NO_2$, 220.0585; found 220.0587.

1-Nitro-3-(3,3,3-trifluoropropyl)benzene (16a)

1.36 g (6.2 mmol, 71% yield), yellow oil; b.p. 95-97 °C /0.15 mm Hg. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 – 8.05 (m, 2H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 3.01 (t, *J* = 7.9 Hz, 2H), 2.53 – 2.38 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 148.6, 141.0, 134.7, 129.8, 126.5 (q, *J* = 276.8 Hz), 123.2, 122.0, 35.2 (q, *J* = 28.9 Hz), 28.0 (q, *J* = 3.2 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ - 67.0 (s). GCMS: *m/z* = 219 (M$^+$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_9H_9F_3NO_2$, 220.0585; found 220.0586.

1-Nitro-4-(3,3,3-trifluoropropyl)benzene (17a)

0.56 g (2.56 mmol, 72% yield), white solid, m.p. 32-33 °C; b.p. 101-103 °C /0.15 mm Hg. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42-2.51 (m, 2H), 3.01 (t, $^3J_{HH}$ = 8.3 Hz, 2H), 7.40 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 8.19 (d, $^3J_{HH}$ = 8.7 Hz, 2H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 28.0 (q, $^3J_{CF}$ = 3.3 Hz), 34.8 (q, $^2J_{CF}$ = 29 Hz), 123.8, 126.2 (q, $^1J_{CF}$ = 276.7 Hz), 129.0, 146.3, 146.8. ^{19}F NMR (188 MHz, $CDCl_3$): δ -67.0 (s). GCMS: *m/z* = 219 (M$^+$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_9H_9F_3NO_2$, 220.0585; found 220.0587.

2-Bromo-1,1,1-trifluoroethane (18a)

8.15 g (0.050 mol, 40% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (q, *J* = 8.8 Hz, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 123.2 (q, *J* = 274.6 Hz), 26.1 (q, *J* = 38.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -69.3 (s). Anal. calcd. for $C_2H_2BrF_3$: C, 14.74; H, 1.24. Found: C, 14.50; H, 1.11.

2-Bromo-1,1,1-trifluoro-3-methylbutane (19a)

12.30 g (0.060 mol, 58% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 – 4.06 (m, 1H), 2.31 – 2.17 (m, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 124.2 (q, *J* = 278.5 Hz), 55.6 (q, *J* = 30.5 Hz), 29.1, 21.6, 17.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ -69.1 (s). Anal. calcd. for $C_5H_8BrF_3$: C, 29.29; H, 3.93. Found: C, 29.42; H, 3.79.

2-Bromo-1,1,1-trifluoro-3,3-dimethylbutane (20a)

5.48 g (0.025 mol, 65% yield), pink oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (q, *J* = 8.1 Hz, 1H), 1.20 (s, 9H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 124.6 (q, *J* = 280.0 Hz), 59.4 (q, *J* = 29.2 Hz), 35.0, 28.3 (d, *J* = 1.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -64.1 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_6H_{11}BrF_3$, 218.9996; found 218.9998.

(*S*)-2,2,2-trifluoro-1-(2-(trifluoromethyl)pyrrolidin-1-yl)ethan-1-one (21a)

15.04 g (0.064 mol, 51% yield), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.96 – 4.75 (m, 1H), 3.94 – 3.63 (m, 2H), 2.36 – 1.95 (m, 4H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.0 (q, *J* = 37 Hz), 125.4 (q, *J* = 283 Hz), 116.2 (q, *J* = 288 Hz), 58.4 (q, *J* = 32 Hz), 47.1 (d, *J* = 4 Hz), 24.5, 24.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.0 (s), -74.6 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_8F_6NO$, 236.0510; found 236.0513.

(*S*)-5-(Trifluoromethyl)pyrrolidin-2-one (22a)

0.54 g (3.5 mmol, 70% yield), yellow solid, m.p. 107-108 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (br s, 1H), 4.13 – 4.01 (m, 1H), 2.56 – 2.42 (m, 1H), 2.40 – 2.28 (m, 2H), 2.29 – 2.16 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 179.0, 125.3 (q, *J* = 280.5 Hz), 55.2 (q, *J* = 32.6 Hz), 28.6, 20.7 (d, *J* = 1.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -79.3 (s). GCMS: *m/z* = 153 (M$^+$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_5H_7F_3NO$, 154.0480; found 154.0482.

1-Nitro-2-(trifluoromethyl)cyclopropane (23a)

1.86 g (0.012 mol, 52% yield), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.67 – 4.40 (m, 1H), 2.92 – 2.64 (m, 1H), 2.17 – 1.91 (m, 1H), 1.63 (q, *J* = 7.4 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 123.3 (q, *J* = 272.0 Hz), 55.1, 24.6 (q, *J* = 39.1 Hz), 13.0 (d, *J* = 2.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -67.2 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_4H_5F_3NO_2$, 156.0272; found 156.0274.

Ethyl 2-(trifluoromethyl)butanoate (24a)

4.05 g (0.022 mol, 62% yield), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (q, *J* = 7.1 Hz, 2H), 3.09 – 2.94 (m, 1H), 1.99 – 1.79 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 167.7 (q, *J* = 3.3 Hz), 124.9 (q, *J* = 279.9 Hz), 61.8, 52.0 (q, *J* = 27.3 Hz), 19.8 (d, *J* = 2.3 Hz), 14.2, 11.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ -68.8 (d, *J* = 8.4 Hz). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_{11}F_3O_2$, 184.0711; found 184.0711.

Methyl 4-methyl-2-(trifluoromethyl)pentanoate (25a)

14.06 g (0.071 mol, 55% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.26 – 3.11 (m, 1H), 1.95 – 1.82 (m, 1H), 1.65 – 1.48 (m, 2H), 0.93 (t, *J* = 6.3 Hz, 6H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.5 (q, *J* = 3.3 Hz), 125.0 (q, *J* = 279.8 Hz), 52.7, 48.7 (q, *J* = 27.5 Hz), 35.0, 25.9, 23.0, 21.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -69.1 (d, *J* = 7.7 Hz). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_8H_{13}F_3O_2$, 198.0868; found 198.0869.

3-Bromo-1,1,1-trifluoro-2-methylpropane (26a)

4 g (0.021 mol, 60% yield), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.60 (dd, *J* = 10.4, 3.7 Hz, 1H), 3.22 (t, *J* = 9.8 Hz, 1H), 2.67 – 2.49 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 126.6 (q, *J* = 280.3 Hz), 41.1 (q, *J* = 26.8 Hz), 29.8 (q, *J* = 3.2 Hz), 12.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ -72.8 (d, *J* = 9.3 Hz).). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_4H_7BrF_3$, 190.9683; found 190.9681.

1-Bromo-3-(trifluoromethyl)cyclobutane (27a)

8.53 g (0.042 mol, 63% yield), yellow oil. Mixture 5:4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 – 4.10 (m, 1H), 3.42 – 2.47 (m, 5H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 127.6 (q, *J* = 275.9 Hz), 125.76 (q, *J* = 275.9 Hz), 39.3, 35.3 (q, *J* = 31.2 Hz), 35.0, 34.7 (q, *J* = 3.1 Hz), 34.38 (q, *J* = 3.0 Hz), 34.35 (q, *J* = 32.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.7 (s), -74.1 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_5H_7BrF_3$, 202.9683; found 202.9686.

1-Chloro-3-(trifluoromethyl)cyclobutane (28a)

9.35 g (0.059 mol, 65% yield), colorless oil. Mixture 5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 – 4.23 (m, 1H), 3.21 – 3.06 (m, 1H), 2.89 – 2.62 (m, 2H), 2.61 – 2.36 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 127.7 (q, *J* = 275.8 Hz), 50.2, 34.3 (q, *J* = 3.1 Hz), 33.92, 33.89. ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.6 (s), -74.0 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_5H_7ClF_3$, 159.0188; found 159.0188.

2,2,2-Trifluoro-1-(3-(trifluoromethyl)azetidin-1-yl)ethan-1-one (29a)

20.99 g (0.095 mol, 75% yield), 76%; yellow oil, b.p. 47-49 °C (10 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (t, *J* = 9.6 Hz, 1H), 4.44 (dd, *J* = 9.8, 5.9 Hz, 1H), 4.30 (t, *J* = 10.1 Hz, 1H), 4.19 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.51 – 3.26 (m, 1H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.3 (q, *J* = 38 Hz), 125.6 (q, *J* = 275 Hz), 115.9 (q, *J* = 288 Hz), 51.4, 48.5 (q, *J* = 4 Hz), 32.8 (q, *J* = 33 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.5 (s), -74.8 (d, *J* = 8.1 Hz). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_6H_6F_6NO$, 222.0354; found 222.0357.

2,2,2-Trifluoro-1-(3-(trifluoromethyl)pyrrolidin-1-yl)ethan-1-one (30a)

4.8 g (0.02 mol, 70% yield), yellow oil, b.p. 80-82 °C (20 mm Hg). ^{1}H NMR (300 MHz, $CDCl_3$, rotamers ~2:3): δ 4.15 – 3.47 (m, 4H), 3.24 – 2.80 (m, 1H), 2.44 – 2.00 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 155.6 (q, *J* = 37 Hz), 155.5 (q, *J* = 37 Hz), 126.6 (q, *J* = 278 Hz), 126.3 (q, *J* = 278 Hz), 116.2 (q, *J* = 287 Hz), 46.7 (m), 45.8 (m), 43.2 (q, *J* = 29 Hz), 40.5 (q, *J* = 29 Hz), 26.1, 23.3 (d, *J* = 2.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -71.9 (s), -73.1 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_8F_6NO$, 236.0510; found 236.0513.

(*S*)-2,2,2-Trifluoro-1-(3-(trifluoromethyl)piperidin-1-yl)ethan-1-one (31a)

5.23 g (0.021 mol, 57% yield), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, N-amide bond rotamers ~3:2): δ 4.57 (d, *J* = 13.1, 1H), 4.41 (d, *J* = 13.2 Hz, 1H), 4.07 (d, *J* = 13.8 Hz, 1H), 3.92 (d, *J* = 14.0 Hz, 1H), 3.13 (d, *J* = 10.9 Hz, 1H), 3.07 (d, *J* = 11.3 Hz, 1H), 2.87 – 2.69 (m, 1H), 2.35 – 2.17 (m, 1H), 2.06 (d, *J* = 12.8 Hz,

1H), 1.87 (d, *J* = 9.9 Hz, 1H), 1.69 – 1.42 (m, 2H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$, rotamers ~1.5:1): δ 155.6 (q, *J* = 36 Hz), 155.4 (q, *J* = 36 Hz), 125.9 (q, *J* = 279 Hz), 125.8 (q, *J* = 279 Hz), 116.3 (q, *J* = 288 Hz), 45.9 (q, *J* = 4 Hz), 44.6 (sept., *J* = 4 Hz), 43.7, 42.2 (q, *J* = 3 Hz), 41.1 (q, *J* = 27 Hz), 39.9 (q, *J* = 27 Hz), 24.2, 23.2 (q, *J* = 2 Hz), 23.1, 23.0 (q, *J* = 2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, rotamers ~1.5:1): δ -69.8 (s), -69.9 (s), -73.2 (s), -73.4 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_8H_{10}F_6NO$, 250.0667; found 250.0668.

Ethyl 1-(trifluoromethyl)cyclopropane-1-carboxylate (32a)

1.8 g (9.89 mmol, 54% yield), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (q, *J* = 7.1 Hz, 2H), 1.44 – 1.39 (m, 2H), 1.33 – 1.30 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.5, 124.7(q, *J* = 272.4 Hz), 61.9, 26.6 (q, *J* = 34.3 Hz), 14.1, 13.17, 13.16. ^{19}F NMR (470 MHz, $CDCl_3$) δ -67.3 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_7H_{10}F_3O_2$, 183.0633; found 183.0635.

1-Bromo-2-(1-(trifluoromethyl)cyclopropyl)benzene (33a)

0.53 g (0.002 mol, 68% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 1.52 (t, *J* = 5.5 Hz, 2H), 1.14 (s, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 135.3, 135.1, 133.7, 130.1, 127.5, 127.1, 126.3 (q, *J* = 274.5 Hz), 28.6 (q, *J* = 34.1 Hz), 12.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.1 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_{10}H_9BrF_3$, 264.9840; found 264.9843.

1-Methyl-3-(1-(trifluoromethyl)cyclopropyl)benzene (34a)

1.2 g (0.006 mol, 60% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.19 (m, 3H), 7.13 (d, *J* = 7.1 Hz, 1H), 2.35 (s, 3H), 1.32 (t, *J* = 5.6 Hz, 2H), 1.01 (s, 2H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 138.1, 136.2, 132.1, 129.2, 128.5, 128.4, 126.6 (q, *J* = 273.5 Hz), 28.3 (q, *J* = 33.2 Hz), 21.5, 9.8 (dd, *J* = 4.7, 2.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -70.6 (s). GCMS: *m/z* = 200 (M$^+$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_{11}H_{12}F_3$, 201.0891; found 201.0891.

Ethyl 1-(trifluoromethyl)cyclobutane-1-carboxylate (35a)

3.14 g (0.016 mol, 69% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (q, *J* = 7.1 Hz, 2H), 2.62 – 2.40 (m, 4H), 2.11 – 1.93 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.1, 126.0 (q, *J* = 279.2 Hz), 61.9, 50.8 (q, *J* = 28.5 Hz), 25.8 (d, *J* = 2.5 Hz), 15.6, 14.1. ^{19}F NMR (470 MHz, $CDCl_3$): δ -74.8 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_8H_{12}F_3O_2$, 197.0789; found 197.0785.

Ethyl 2-(trifluoromethyl)spiro[3.3]heptane-2-carboxylate (36a)

12.27 g (0.052 mol, 53% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22 (q, *J* = 7.1 Hz, 2H), 2.55 (d, *J* = 13.0 Hz, 2H), 2.45 (d, *J* = 13.4 Hz, 2H), 2.02 (t, *J* = 7.4 Hz, 4H), 1.84 – 1.70 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.2 (q, *J* = 2.2 Hz), 125.9 (q, *J* = 278.8 Hz), 61.9, 46.8 (q, *J* = 29.0 Hz), 38.8 (q, *J* = 2.3 Hz), 37.6, 35.7, 35.1, 15.9, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.5. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_{11}H_{16}F_3O_2$, 237.1102; found 237.1106.

1-(2-Chloroethyl)-1-(trifluoromethyl)cyclobutane (37a)

2.23 g (0.012 mol, 57% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57 (t, *J* = 8.1 Hz, 2H), 2.41 – 2.29 (m, 2H), 2.24 (t, *J* = 8.3 Hz, 2H), 2.05 – 1.88 (m, 4H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 128.6 (q, *J* = 279.7 Hz), 44.5 (q, *J* = 27.1 Hz), 39.8 (d, *J* = 2.0 Hz), 38.3 (d, *J* = 1.6 Hz), 26.2 (q, *J* = 3.2 Hz), 15.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -77.1 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_7H_{11}ClF_3$, 187.0501; found 187.0501.

Ethyl 1-(trifluoromethyl)cyclopentane-1-carboxylate (38a)

9.45 g (0.045 mol, 69% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (q, *J* = 7.1 Hz, 2H), 2.32 – 2.14 (m, 2H), 2.11 – 1.93 (m, 2H), 1.77 – 1.64 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.0, 127.0 (q, *J* = 280.6 Hz), 61.9, 58.8 (q, *J* = 25.6 Hz), 32.3, 26.2, 14.1. ^{19}F NMR (470 MHz, $CDCl_3$): δ -71.6 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_9H_{14}F_3O_2$, 211.0946; found 211.0949.

2,2,2-trifluoro-1-(3-methyl-3-(trifluoromethyl)pyrrolidin-1-yl)ethan-1-one (39a)

12.95 g (0.047 mol, 55% yield), yellow oil, b.p. 76-78 °C (13 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$, rotamers ~2:1): δ 3.91 – 3.60 (m, 3H), 3.49 (d, 11.0 Hz, 1H), 3.44 (d, 13.3 Hz, 1 H), 2.39 (t, *J* = 13.3, 7.8 Hz, 1H), 2.28 (dt, *J* = 13.5, 8.3 Hz, 1H), 1.94 (dt, *J* = 13.2, 7.0 Hz, 1H), 1.85 (ddd, *J* = 13.6, 8.2, 5.6 Hz, 1H), 1.33, 1.32 (s, 2×3H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$, rotamers ~1.2:1): δ 155.6 (q, *J* = 37 Hz), 127.9 (q, *J* = 280 Hz), 127.6 (q, *J* = 280 Hz), 116.2 (q, *J* = 287 Hz), 53.6, 52.5, 48.3 (q, *J* = 26 Hz), 46.2, 45.6 (q, *J* = 27 Hz), 45.4 (q, *J* = 4 Hz), 33.1, 30.2, 19.3 (q, *J* = 2 Hz), 19.0 (q, *J* = 2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, rotamers ~1.2:1): δ -73.1 (s), -73.2 (s), -77.62 (s), -77.64 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_8H_{10}F_6NO$, 250.0667; found 250.0665.

2,2,2-Trifluoro-1-(3*a*-(trifluoromethyl)hexahydrocyclopenta[c]pyrrol-2(1*H*)-yl)ethan-1-one (40a)

13.75 g (0.05 mol, 50% yield), yellow oil, b.p. 37-38 °C (0.1 mm Hg). ^{1}H NMR (400 MHz, $CDCl_3$, rotamers ~1.5:1): δ 4.00 (dd, *J* = 16.5, 13.6 Hz, 1H), 3.92 – 3.79 (m, 1H), 3.61 – 3.43 (m, 2H), 2.96 – 2.87 (m, 1H), 2.87 – 2.79 (m, 1H), 2.86 – 2.79 (m, 1H), 2.19 – 1.93 (m, 2H), 1.87 – 1.68 (m, 3H), 1.61 – 1.47 (m, 1H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$, rotamers 1.5:1): δ 155.3 (q, *J* = 37 Hz), 155.0 (q, *J* = 37 Hz), 128.5 (q, *J* = 279 Hz), 128.4 (q, *J* = 279 Hz), 116.2 (q, *J* = 287 Hz), 59.7 (q, *J* = 25 Hz), 56.9 (q, *J* = 26 Hz), 53.7, 52.9, 52.7, 52.2 (q, *J* = 3 Hz), 45.7, 43.0, 34.1 (q, *J* = 1 Hz), 33.7, 32.9, 32.7, 25.4, 25.3. ^{19}F NMR (376 MHz, $CDCl_3$, rotamers 1.5:1): δ -72.48 (s), -72.53 (s), -75.6 (s), -75.7 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_{10}H_{12}F_6NO$, 276.0823; found 276.0821.

Ethyl 1-(trifluoromethyl)cyclohexane-1-carboxylate (41a)

10.3 g (0.046 mol, 53% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26 (q, *J* = 7.1 Hz, 2H), 2.34 (d, *J* = 12.5 Hz, 2H), 1.73 (d, *J* = 13.5 Hz, 2H), 1.66 (d, *J* = 12.0 Hz, 1H), 1.51 (td, *J* = 13.0, 3.3 Hz, 2H), 1.35 – 1.12 (m, 6H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 169.0, 126.1 (q, *J* = 283.5 Hz), 61.9, 53.3 (q, *J* = 24.1 Hz), 27.6, 25.0, 22.5, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ -75.3 (s). GCMS: *m/z* = 224 (M$^+$). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_{10}H_{16}F_3O_2$, 225.1102; found 225.1108.

Methyl-4-(trifluoromethyl)bicyclo[2.2.1]heptane-1-carboxylate (42a)

3.55 g (0.016 mol, 42% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 2.14 – 1.83 (m, 4H), 1.81 (s, 2H), 1.75 – 1.65 (m, 2H), 1.62 – 1.51 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.9, 127.9 (q, *J* = 276.4 Hz), 52.5, 51.9, 51.6 (q, *J* = 28.6 Hz), 41.9 (d, *J* = 1.4 Hz), 32.7, 29.4 (d, *J* = 1.2 Hz). ^{19}F

NMR (376 MHz, $CDCl_3$): δ -73.6 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_{10}H_{14}F_3O_2$, 223.0946; found 223.0948.

4-(Trifluoromethyl)bicyclo[2.2.2]octane-1-carboxylic acid (43a)

4-(Methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid (10 g, 0.047 mol, 1 equiv), SF_4 (20.37 g, 0.188 mol, 4 equiv) and water (1.4 g, 0.078 mol) were placed in 250 mL autoclave made of Hastelloy nickel alloy. The mixture was heated at 55-60 °C in oil bath for 18 h. The autoclave was allowed to cool down to r.t, and the gaseous products were vented off in a good fume-hood. The residue was dissolved in of CH_2Cl_2 (300 mL), poured onto ice (500 g) and triturated with saturated aq. $NaHCO_3$ (500 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under a reduced pressure to afford the desired product, (RCF_3) and ca. 20% of the dimer RCF_2OCF_2R. The residue was dissolved in THF (100 mL) and NaOH (9.89 g, 0.236 mol) in 50 mL of water was added. The mixture was stirred at r.t. overnight and then concentrated under reduced pressure. The final product was recrystallized from $CHCl_3$. Yield (3.9 g, 0.0176 mol, 37%), yellow solid, m.p. 223-225 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (dd, *J* = 10.1, 5.4 Hz, 6H), 1.72 (dd, *J* = 10.2, 5.4 Hz, 6H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 183.3, 129.0 (q, *J* = 279.4 Hz), 38.6, 37.5 (q, *J* = 26.0 Hz), 26.9, 23.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ -79.0. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd $C_{10}H_{14}F_3O_2$, 223.0946; found 223.0949.

General procedure for the deprotection of *N*-TFA protected derivatives (2b as an example)

2-(Trifluoromethyl)azetidine hydrochloride (2b)

To a solution of **2b** (15.54 g, 0.07 mol) in 150 mL of MeOH was added 5M hydrochloric acid in MeOH (100 mL). The reaction mixture was vigorously stirred at 45 ºC in oil bath for 16 h. The mixture was concentrated under reduced pressure, washed with Et_2O (3 × 50 mL), and dried under reduced pressure to give **2b** as a white solid. Yield 10.34 g (0.064 mol, 91% yield), m.p. 87-88 °C. ^{1}H NMR (400 MHz, D_2O): δ 5.26 – 5.08 (m, 1H), 4.28 – 4.06 (m, 2H), 2.92 – 2.68 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, D_2O): δ 122.7 (q, *J* = 277.6 Hz), 57.23 (q, *J* = 36.1 Hz), 44.9, 19.0. ^{19}F NMR (376 MHz, D_2O): δ -77.4 (s). (APCI) *m/z* [M+H]$^+$ calculated for $C_4H_7F_3N$: 126.1; found: 126.2 (M+H). Anal. calcd. for $C_4H_7ClF_3N$: C, 29.74; H, 4.37; N, 8.67. Found: C, 29.93; H, 4.55; N, 8.49.

3-(2,2,2-Trifluoroethyl)azetidine hydrochloride (6b)

4.74 g (0.027 mol, 92% yield), yellow solid, m.p. 78-80 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.74 (br s, 2H), 3.99 (t, *J* = 9.2 Hz, 2H), 3.76 (t, *J* = 8.5 Hz, 2H), 3.02 (dt, *J* = 15.3, 7.6 Hz, 1H), 2.81 – 2.66 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6): δ 126.7 (q, *J* = 277 Hz), 49.4, 35.1 (q, *J* = 28 Hz), 26.0 (d, *J* = 3 Hz).^{19}F NMR (376 MHz, DMSO-d_6): δ -64.9 (s). (APCI) *m/z* [M+H]$^+$ calculated for $C_5H_9F_3N$: 140.1; found: 140.1 (M+H). Anal. calcd. for $C_5H_9ClF_3N$: C, 34.20; H, 5.17; N, 7.98. Found: C, 34.02; H, 5.29; N, 7.78.

3-(2,2,2-Trifluoroethyl)pyrrolidine hydrochloride (7b)

20.12 g (0.11 mol, 96% yield), brown oil. ^{1}H NMR (400 MHz, D_2O): δ 3.69 – 3.57 (m, 1H), 3.55 – 3.41 (m, 1H), 3.31 (dd, *J* = 18.8, 9.4 Hz, 1H), 3.02 (t, *J* = 10.8 Hz, 1H), 2.76 – 2.59 (m, 1H), 2.57 – 2.40 (m, 2H), 2.39 – 2.28 (m, 1H), 1.88 – 1.68 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, D_2O): δ 126.6 (q, *J* = 276 Hz), 49.4, 45.1, 35.1 (q, *J* = 29 Hz), 31.8 (d, *J* = 3 Hz), 29.7. ^{19}F NMR (376 MHz, D_2O): δ -65.6 (s). (APCI) *m/z* [M+H]$^+$ calculated for $C_6H_{11}F_3N$: 154.1; found: 154.2 (M+H). Anal. calcd. for $C_6H_{11}ClF_3N$: C, 38.01; H, 5.85; N, 7.39. Found: C, 38.29; H, 6.03; N, 7.50.

3-(2,2,2-Trifluoroethyl)piperidine hydrochloride (8b)

7.12 g (0.035 mol, 92% yield), yellow solid, m.p. 149-151 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.49 (br s, 1H), 9.38 (br s, 1H), 3.30 – 3.02 (m, 2H), 2.83 – 2.56 (m, 2H), 2.45 – 2.22 (m, 2H), 2.22 – 2.03 (m, 1H), 1.93 – 1.57 (m, 3H), 1.40 – 1.08 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6): δ 127.1 (q, *J* = 277 Hz), 46.6, 42.7, 35.8 (q, *J* = 27 Hz), 27.6 (q, *J* = 13 Hz), 21.1. ^{19}F NMR (376 MHz, DMSO-d_6): δ -62.3 (t, *J* = 12.0 Hz). (APCI) *m/z* [M+H]$^+$ calculated for $C_7H_{13}F_3N$: 168.1; found: 168.1 (M+H). Anal. calcd. for $C_7H_{13}ClF_3N$: C, 41.29; H, 6.44; N, 6.88. Found: C, 41.50; H, 6.70; N, 6.68.

3-(3,3,3-Trifluoropropyl)azetidine hydrochloride (9b)

8.58 g (0.045 mol, 94% yield), white solid, m.p. 90-91 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (br s, 2H), 3.94 (t, *J* = 9.7 Hz, 2H), 3.65 (t, *J* = 7.3 Hz, 1H), 2.87 – 2.71 (m, 1H), 2.32 – 2.10 (m, 2H), 1.81 (q, *J* = 8.0 Hz, 2H). ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6): δ 127.5 (q, *J* = 276 Hz), 49.6, 30.5, 29.8 (q, *J* = 28 Hz), 25.0 (d, *J* = 3 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ -65.2 (s). (APCI) *m/z* [M+H]$^+$ calculated for $C_6H_{11}F_3N$: 154.1; found: 154.2 (M+H). Anal. calcd. for $C_6H_{11}ClF_3N$: C, 38.01; H, 5.85; N, 7.39. Found: C, 38.12; H, 5.78; N, 7.50.

4-(2,2,2-Trifluoroethyl)piperidine hydrochloride (10b)

2.12 g (0.01 mol, 93% yield), yellow solid, m.p. 209-210 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (br s, 1H), 9.15 (br s, 1H), 3.19 (d, *J* = 12.6 Hz, 2H), 2.85 (t, *J* = 12.0 Hz, 2H), 2.27 (qd, *J* = 12.0, 7.0 Hz, 2H), 2.01 – 1.87 (d, *J* = 3.4 Hz, 1H), 1.83 (d, *J* = 13.5 Hz, 2H), 1.53 (dd, *J* = 11.5, 3.0 Hz, 1H), 1.47 (dd, *J* = 10.9, 3.4 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6): δ 127.2 (q, *J* = 277 Hz), 42.3, 37.9 (q, *J* = 27 Hz), 27.8. ^{19}F NMR (376 MHz, DMSO-d_6): δ -62.3 (s). (APCI) *m/z* [M+H]$^+$ calculated for $C_7H_{13}F_3N$: 168.1; found: 168.1 (M+H). Anal. calcd. for $C_7H_{13}ClF_3N$: C, 41.29; H, 6.44; N, 6.88. Found: C, 41.03; H, 6.26; N, 6.99.

2-(3,3,3-Trifluoropropyl)piperidine (11b)

2.52 g (0.011 mol, 96% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (d, *J* = 10.6 Hz, 1H), 2.61 (t, *J* = 10.4 Hz, 1H), 2.55 – 2.42 (m, 1H), 2.29 – 2.01 (m, 2H), 1.90 – 1.72 (m, 1H), 1.69 – 1.46 (m, 4H), 1.45 – 1.27 (m, 2H), 1.21 (br s, 1H), 1.13 – 0.96 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 127.5 (q, *J* = 276 Hz), 55.8, 47.18.2, 32.9, 30.5 (q, *J* = 29 Hz), 29.5, 26.8, 24.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ -67.1 (s). (APCI) *m/z* [M+H]$^+$ calculated for $C_8H_{15}F_3N$: 182.1; found: 182.1 (M+H). Anal. calcd. for $C_8H_{14}F_3N$: C, 53.03; H, 7.79; N, 7.73. Found: C, 53.19; H, 7.96; N, 7.50.

2-(Trifluoromethyl)pyrrolidine (21b)

5.14 g (0.029 mol, 88% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 – 3.55 (m, 1H), 3.00 (t, *J* = 5.7 Hz, 2H), 2.06 – 1.64 (m, 5H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 127.1 (q, *J* = 279 Hz), 58.7 (q, *J* = 30 Hz), 47.2, 26.0, 25.7. ^{19}F NMR (376 MHz, DMSO-d_6): δ -77.4 (s). (APEI) *m/z* [M] calculated for $C_5H_8F_3N$: 139.1. Found: 139 (M). Anal. calcd. for $C_5H_8F_3N$: C, 43.17; H, 5.80; N, 10.07. Found: C, 43.01; H, 5.98; N, 10.25.

3-(Trifluoromethyl)azetidine hydrochloride (29b)

11.48 g (0.071 mol, 95% yield), yellow solid, m.p. 155-157 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 9.97 (br s, 1H), 9.89 (br s, 1H),

4.17 (br s, 2H), 3.98 (br s, 2H), 3.86 (tq, J = 16.0, 7.9 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6): δ 125.8 (q, J = 276 Hz), 43.6 (q, J = 4 Hz), 33.3 (q, J = 32 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -72.5 (s). (APCI) *m/z* $[M+H]^+$ calculated for $C_4H_7F_3N$: 126.1; found: 126.2 (M+H). Anal. calcd. for $C_4H_7ClF_3N$: C, 29.74; H, 4.37; N, 8.67. Found: C, 29.59; H, 4.49; N, 8.38.

3-(Trifluoromethyl)pyrrolidine hydrochloride (30b)

3.15 g (0.017 mol, 94% yield), yellow solid, m.p. 89-90 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.88 (br s, 2H), 3.53 – 3.33 (m, 2H), 3.26 – 3.12 (m, 3H), 2.28 – 2.14 (m, 1H), 2.05 – 1.89 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6): δ 126.8 (q, J = 277.6 Hz), 44.6, 43.2 (q, J = 2.9 Hz), 40.4 (q, J = 28.5 Hz), 24.5. ^{19}F NMR (376 MHz, D_2O): δ -71.8 (s). (APCI) *m/z* $[M+H]^+$ calculated for $C_5H_9F_3N$: 140.1; found: 140.2 (M+H). Anal. calcd. for $C_5H_9ClF_3N$: C, 34.20; H, 5.17; N, 7.98. Found: C, 34.32; H, 5.02; N, 8.13.

(*S*)-3-(Trifluoromethyl)piperidine hydrochloride (31b)

2.85 g (0.015 mol, 91% yield), colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65 (s, 2H), 3.40 – 3.31 (m, 1H), 3.23 (d, J = 12.2 Hz, 1H), 2.99 – 2.76 (m, 3H), 1.94 (d, J = 12.5 Hz, 1H), 1.86 – 1.69 (m, 2H), 1.61 – 1.41 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6): δ 126.2 (q, J = 278.5 Hz), 42.5, 41.0 (q, J = 3.2 Hz), 37.0 (q, J = 27.2 Hz), 20.9, 20.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ -72.2 (s). (APCI) *m/z* $[M+H]^+$ calculated for $C_6H_{11}F_3N$: 154.1; found: 154.1 (M+H). Anal. calcd. for $C_6H_{11}ClF_3N$: C, 38.01; H, 5.85; N, 7.39. Found: C, 38.16; H, 5.98; N, 7.13.

3-Methyl-3-(trifluoromethyl)pyrrolidine hydrochloride (39b)

7.85 g (0.041 mol, 93% yield), beige solid, m.p. 195-197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.84 (br s, 2H), 3.41 – 3.17 (m, 4H), 2.21 (dt, J = 15.2, 7.8 Hz, 1H), 1.92 (dt, J = 13.8, 7.1 Hz, 1H), 1.35 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6): δ 128.0 (q, J = 281 Hz), 49.8, 46.9 (q, J = 26 Hz), 44.3, 31.9, 19.3. ^{19}F NMR (376 MHz, D_2O): δ -75.7 (s). (APCI) *m/z* $[M+H]^+$ calculated for $C_6H_{11}F_3N$: 154.1; found: 154.2 (M+H). Anal. calcd. for $C_6H_{11}ClF_3N$: C, 38.01; H, 5.85; N, 7.39. Found: C, 38.15; H, 5.98; N, 7.19.

rac-(3aR,6aR)-3a-(trifluoromethyl)-octahydrocyclopenta[c]pyrrole hydrochloride (40b)

6.89 g (0.032 mol, 90% yield), yellow solid, m.p. 159-160 °C ^{1}H NMR (400 MHz, D_2O): δ 3.87 (d, J = 13.3 Hz, 1H), 3.68 (dd, J = 14.3, 11.5 Hz, 1H), 3.28 (d, J = 13.3 Hz, 1H), 3.15 – 3.05 (m, 2H), 2.12 – 2.00 (m, 1H), 1.98 – 1.75 (m, 4H), 1.69 (d, J = 7.1 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, D_2O): δ 128.1 (q, J = 278.7 Hz), 58.3 (q, J = 26.4 Hz), 51.6, 50.9, 44.4, 32.8, 30.7, 24.2. ^{19}F NMR (376 MHz, D_2O): δ -73.5 (s). (APCI) *m/z* $[M+H]^+$ calculated for $C_8H_{13}F_3N$: 180.1; found: 180.1 (M+H). Anal. calcd. for $C_8H_{13}ClF_3N$: C, 44.56; H, 6.08; N, 6.50. Found: C, 44.88; H, 6.21; N, 6.29

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra of the obtained compounds, photos of the experimental set-up and X-Ray.

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