A Convenient Synthesis of CHF_2O-Containing Pyrrolidines and Related Compounds — Prospective Building Blocks for Drug Discovery

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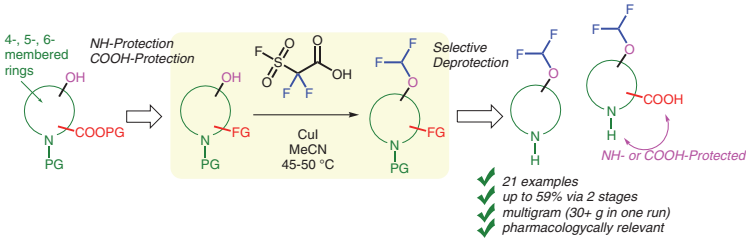

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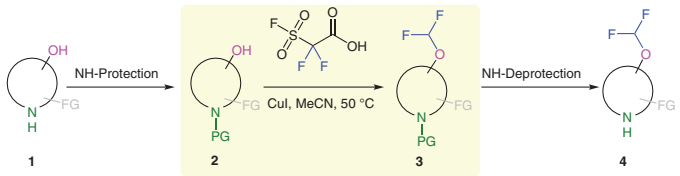
Abstract Fluorine-containing organic molecules, including CHF_2O derivatives, are among the most sought-after in medicinal chemistry. In the current work, a mini-library of 21 compounds with a CHF_2O motif incorporated with azetidine, pyrrolidine (proline), piperidine, 2-azabicyclo[2.2.1]heptane, and 8-azabicyclo[3.2.1]octane cores was synthesized. A multigram scale (10–30 g) procedure for synthesizing the title compounds from commercially available amino alcohols was studied.

Key words fluorine, difluoromethoxy group, azetidine, pyrrolidine, proline, piperidine, building blocks

Fluorinated organic compounds are widely used in life sciences, agrochemicals, and materials science due to the unique properties of fluorine atoms.[1–3] Their strong electronegativity, small size, and capacity to form weak intermolecular bonds offer manifold benefits for customizing vital parameters of the target molecule. Fluorinated fragments are commonly used to adjust a compound's physicochemical properties and enhance its biological properties, such as affinity or metabolic stability.[4–9] Among many other fluorine moieties, the CHF_2O group stands out for its ability to exhibit dynamic lipophilicity. It depends on the chemical environment and can be changed by simply rotating the bonds.[10,11] The CHF_2O functional group possesses a hydrogen atom that can readily form an extra hydrogen bond within the binding site, thereby contributing to its distinct properties.[3] These properties have led to increasing interest in synthesizing compounds containing this group in the last decade.

For aliphatic alcohols, only a few methods are available for their transformation into the CHF_2O group. These include difluoromethylation using 2,2-difluoro-2-(fluorosulfonyl)acetic acid,[12] conversion of formic acid ester,[13] O-difluoromethylation through an S-difluoromethyl sulfonium ylide,[14,15] and desulfurative fluorination.[16,17] The introduction of the CHF_2O group was also achieved using (bromodifluoromethyl)trimethylsilane.[18–20] The first and last methods are preparative and scalable, but the difference in starting material price ($694.6/mol for (bromodifluoromethyl)-trimethylsilane vs. $204.69/mol for 2,2-difluoro-2-(fluorosulfonyl)acetic acid are the current lowest prices at www.emolecules.com) makes the multigram synthesis of CHF_2O derivatives using 2,2-difluoro-2-(fluorosulfonyl)acetic acid more commercially attractive. In this work, we used this approach, the key stage of which was CuI-catalyzed alkylation with the $FSO_2CF_2CO_2H$ N-protected functionalities of 4–6-membered saturated nitrogenous heterocyclic alcohols (Scheme 1). The introduction of the CHF_2O-group via the reaction of $FSO_2CF_2CO_2H$ with aliphatic alcohols was

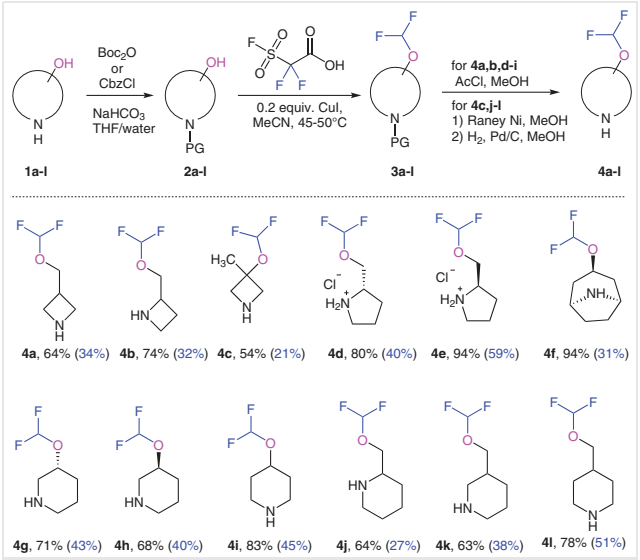


Scheme 1 Proposed synthetic strategy

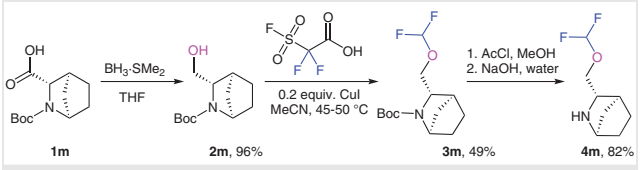
previously studied,[21] but it was only applied in a limited manner to heterocyclic derivatives. In addition, there is limited data on the choice of protecting groups that would tolerate the reaction conditions and be removed without leading to side products. Ways of incorporating additional functional groups, such as carboxyl to the second position of pyrrolidine, were also investigated, which made it possible to obtain derivatives with structures close to those of natural amino acids. Thus, in the current research, a mini-library of 21 compounds was synthesized by using the developed convenient methods.

Initially, commercially available nitrogen *tert*-butyloxycarbonyl (Boc) protected alcohols of saturated heterocycle derivatives (Scheme 2) were tested under the previously elaborated reaction conditions. To compare protecting groups, we synthesized benzyloxycarbonyl (Cbz) protected derivatives. Notably, for several compounds, the replacement of the protecting groups has no significant influence. The reaction yields ranged from 39.6% for **3c** and 41.6% for **3j** to 65% for **3l**. The initial attempt at difluoromethylating the Boc derivative of **2c** yielded a maximum of 15%. Replacing the Boc protecting group with Cbz improved the yield significantly; however, it remained below the average yield for this reaction. It is hypothesized that this is due to steric effects. The final deprotection stage was conducted using acetyl chloride in a methanol solution for Boc derivatives or via catalytic hydrogenation in methanol at atmospheric pressure for Cbz derivatives. It is important to note that evaporation, particularly after the Boc deprotection process, must be carried out without overheating the reaction mass because the CHF_2O group is susceptible to hydrolysis to formate under acidic conditions. The catalytic hydrogenolysis of Cbz derivatives involved a two-step process: first, treatment with Raney nickel, followed by hydrogenolysis on palladium. This process was necessary to eliminate sulfur contamination in the starting material, which persisted even after two chromatographic purifications. The appearance of a distinct odor and slow or non-existent reaction during palladium-catalyzed hydrogenolysis confirmed the need for this step. After the reaction mass was treated with nickel, the reaction proceeded quickly under atmospheric pressure.

Alcohols of type **2a**, **2b**, **2d–f**, and **2j–l** can also be obtained from commercially available amino acids. We demonstrated this approach by synthesizing compound **4m** (Scheme 3). First, the available N-Boc-protected amino acid **1m** was reduced with a borane disulfide complex in high yield. Then, by the reaction of alcohol, **2m** with FSO_2CF_2-CO_2H, a CHF_2O group was introduced in moderate yield. The final step was the Boc deprotection, which resulted in a high yield of **4m** as the hydrochloride.



Scheme 2 Synthesis of compounds **4a–l**. The yields of the last stage and over the two steps of difluoromethylation and deprotection (blue in parentheses) are given.

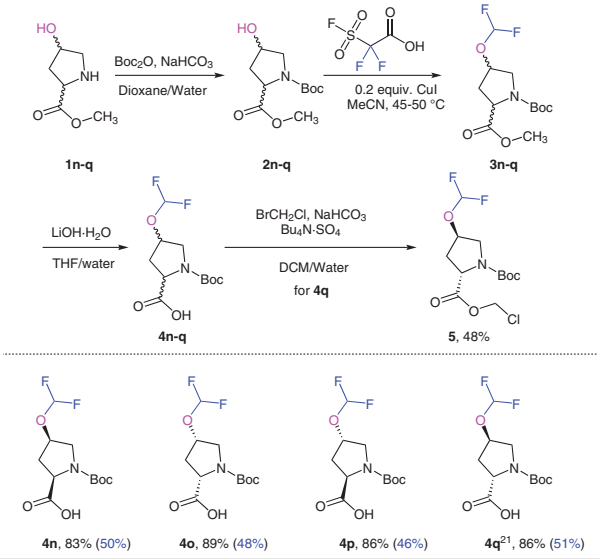


Scheme 3 Synthesis of compounds **4m**

The possibility of designing multifunctional derivatives, such as CHF_2O-containing amino acids, was demonstrated by the preparation of compounds **4n–u**. All possible optical isomers of 1-(*tert*-butoxycarbonyl)-4-(difluoromethoxy)-pyrrolidine-2-carboxylic acid **4n–q** and (2*R*,4*S*)-1-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-4-(difluoromethoxy)pyrrolidine-2-carboxylic acid **4r–u** were obtained starting from commercially available methyl and benzyl esters of the 4-hydroxyproline isomers.

The synthesis of **4n–q** utilized Boc-amino methyl esters **2n–q**, prepared from available methyl ester **1n–q** (Scheme 4). Next, difluoromethylation and saponification steps proceeded in good or excellent yields. Finally, functionalization of the acid group on compound **4q** was performed, producing chloromethyl ester **5** with a moderated yield. Compound **5** is suitable for further modification by nucleophilic substitution reactions.

Likewise to the aforementioned acids **4n–q**, a set of optically pure fluorenylmethoxycarbonyl (Fmoc) protected amino acids **4r–u** was prepared (Scheme 5). It is noteworthy that the difluoromethylation step yields CHF_2O derivatives **3n–q** in a range of 39.4% for **3u** to 43.5% for **3r**. Compared to the Boc and Cbz protecting groups, the Fmoc group was the least tolerant, leading to the lowest yields. The final



Scheme 4 Synthesis of compounds **4n–q**. The yields of the last stage and over the two steps of difluoromethylation and deprotection (blue in parentheses) are given.

step of the hydrogenolysis, as explained earlier, consisted of two stages: initial Raney nickel treatment followed by the hydrogenolysis stage, which gave high yields.

Thus, a mini-library of 21 compounds has been synthesized, comprising primary and secondary alcohol derivatives of azetidine, pyrrolidine (proline), piperidine, 2-azabicyclo[2.2.1]heptane, and 8-azabicyclo[3.2.1]octane. The protocol is suitable for multigram scale synthesis, useful for amino acid modification, and is tolerated by several protecting groups. We expect that the current work will be valuable for the use of CHF_2O cyclic amine derivatives in drug development projects.

Compounds **1j** (CAS 3433-37-2), **1k** (CAS 4606-65-9), **1l** (CAS 6457-49-4), **1m** (CAS 291775-59-2), **1r** (CAS 153461-11-1), **1s** (CAS 2140265-28-5), **1t** (CAS 1864003-48-4), and **1u** (CAS 62147-27-7) are commercially available. Solvents were purified according to standard procedures.

NMR spectra were recorded with Bruker Avance DRX and Varian Unity Plus spectrometers at 25 °C (for ^{1}H at 500 MHz and 400 MHz, for ^{13}C and ^{19}F at 126 MHz and 376 MHz, respectively). Tetramethylsilane (TMS) (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. Mass spectra (ESI-MS) were recorded with Agilent 1290 Infinity II LC and Agilent 1260 Infinity II LC systems. The progress of reactions was monitored using TLC plates (silica gel 60 F254, Merck). Column chromatography was carried out on silica gel 60 (Merck, particle size 0.040–0.063 mm). Elemental analyses are correct within the limits of ±0.3%. Melting points are uncorrected. Compounds **1c**,[30] **1p**,[33] **2a**,[22] **2b**,[23], **2d**,[24] **2e**,[25] **2f**,[26] **2g**,[27] **2h**,[28] **2i**,[29] **2n**,[31] **2o**,[32] and **2q–4q**[21] were previously characterized and obtained according to the procedures communicated elsewhere.

Synthesis of compounds 2c, 2j and 2k; General Procedure for Cbz-Protection

Potassium carbonate (1.5 equiv) was dissolved in water (2 mL/mmol) and a solution of the appropriate alcohol amine in THF (1.7 mL/mmol) was added. The resulting mixture was cooled to 0 °C in an ice bath and a solution of benzyl chloroformate (1.05 equiv) in THF (0.3 mL/mmol) was added dropwise at 0 °C. When the addition was complete, the resulting mixture was allowed to warm to r.t. and stirred overnight.

The reaction mixture was diluted with EtOAc and the organic layer was separated. The aqueous layer was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to obtain Cbz-protected amino alcohol.

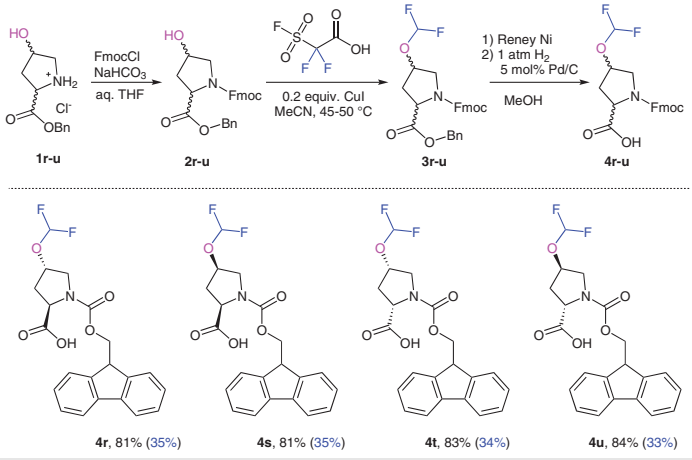
Benzyl 3-Hydroxy-3-methylazetidine-1-carboxylate (2c)

Purified by flash chromatography (hexane/MTBE, 2:1).

Yield: 75.5 g (70.3%); colorless thick oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 4 H), 5.08 (d, *J* = 3.6 Hz, 2 H), 4.01–3.76 (m, 4 H), 2.92 (d, *J* = 3.8 Hz, 1 H), 1.49 (d, *J* = 3.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.18, 135.98, 127.97, 127.56, 127.43, 68.00, 66.32, 62.98, 25.66.



Scheme 5 Synthesis of compounds **4r–u**. The yields of the last stage and over the two steps of difluoromethylation and deprotection (blue in parentheses) are given.

MS (ES-API): *m*/*z* (%) = 178 (100) [M + 1 – CO_2]$^+$, 91 (30) [$C_6H_5CH_2$]$^+$.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.03; H, 6.91; N, 6.37.

Benzyl 2-(Hydroxymethyl)piperidine-1-carboxylate (2j)

Purified by flash chromatography (hexane/MTBE, 2:1).

Yield: 182 g (84.1%); colorless thick oil.

The NMR signal ranges of the compound obtained are in agreement with those previously characterized in the literature.[34]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 4 H), 5.21–5.05 (m, 2 H), 4.35 (dtd, *J* = 8.6, 5.8, 2.3 Hz, 1 H), 4.03 (d, *J* = 13.1 Hz, 1 H), 3.86–3.76 (m, 1 H), 3.61 (dt, *J* = 11.1, 4.8 Hz, 1 H), 2.93 (s, 1 H), 2.39 (s, 1 H), 1.70 (d, *J* = 12.6 Hz, 1 H), 1.65–1.55 (m, 3 H), 1.55–1.35 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.51, 136.23, 127.96, 127.43, 127.26, 66.66, 60.81, 59.88, 52.38, 39.62, 24.69, 19.01, 13.68.

MS (ES-API): *m*/*z* (%) = 250 (15) [M + 1]$^+$, 206 (100) [M + 1 – CO_2]$^+$, 91 (50) [$C_6H_5CH_2$]$^+$.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.35; H, 7.74; N, 5.78.

Benzyl 3-(Hydroxymethyl)piperidine-1-carboxylate (2k)

Purified by flash chromatography (hexane/MTBE, 2:1).

Yield: 179 g (82.7%); colorless thick oil.

The NMR signal ranges of the compound obtained are in agreement with those previously characterized in the literature.[35]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.27 (m, 4 H), 5.11 (d, *J* = 7.8 Hz, 2 H), 4.09–3.70 (m, 2 H), 3.47 (q, *J* = 5.3 Hz, 2 H), 3.17–2.69 (m, 2 H), 2.31 (s, 1 H), 1.84–1.55 (m, 3 H), 1.45 (s, 1 H), 1.24 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.13, 136.33, 127.95, 127.43, 127.25, 66.54, 64.30, 63.92, 46.41, 44.31, 37.65, 26.40, 23.70.

MS (ES-API): *m*/*z* (%) = 250 (40) [M + 1]$^+$, 206 (50%) [M + 1 – CO_2]$^+$, 91 (100) [$C_6H_5CH_2$]$^+$.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.35; H, 7.74; N, 5.78.

Synthesis of *tert*-Butyl (1*R*,3*S*,4*S*)-3-(Hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (2m)

Compound **1m** (80 g, 331.55 mmol) was dissolved in THF (800 mL) and borane dimethyl sulfide complex (62.9 mL, 663.1 mmol, 2 equiv) was added dropwise at 20 °C under an argon atmosphere. After the addition was completed, the resulting mixture was stirred overnight.

Aq. K_2CO_3 solution (247 g in 350 mL of water) was carefully added dropwise to the reaction mixture. When the addition was complete, the resulting mixture was stirred for 30 minutes. The organic layer was separated and the aqueous layer was extracted with MTBE (2 × 600 mL). The combined organic layers were washed with water (600 mL) and brine (500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 2:1) to obtain compound **2m**.

Yield: 72.9 g (95.8%); colorless thick oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.41 (s, 1 H), 4.15–4.01 (m, 1 H), 3.72–3.22 (m, 3 H), 2.36 (d, *J* = 80.9 Hz, 1 H), 1.75–1.62 (m, 2 H), 1.62–1.52 (m, 2 H), 1.44 (s, 9 H), 1.23 (dd, *J* = 8.5, 6.0 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.80, 79.69, 66.71, 66.10, 57.40, 39.18, 35.17, 29.23, 27.95, 27.40, 13.66.

MS (ES-API): *m*/*z* (%) = 172 (100) [M + 1 – 70]$^+$.

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.81; H, 7.79; N, 5.99.

Synthesis of (2*R*,4*S*)-1-*tert*-Butyl 2-Methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (2p)

Compound **1p** (15 g, 82.6 mmol) was suspended in DCM (150 mL) and TEA (24.17 mL, 173.4 mmol, 2.1 equiv) was added. The resulting mixture was stirred for 15 minutes, and a solution of di-*tert*-butyl dicarbonate (18.38 g, 84.2 mmol, 1.02 equiv) in DCM (35 mL) was added dropwise. When the addition was complete, the resulting mixture was stirred overnight.

Water (150 mL) was added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with DCM (50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to obtain compound **2p**.

Yield 18.5 g (91%); colorless thick oil.

The NMR signal ranges of the compound obtained are in agreement with those previously characterized in the literature.[36]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.45–4.38 (m, 1 H), 4.38–4.29 (m, 1 H), 3.67 (d, *J* = 2.9 Hz, 3 H), 3.58–3.28 (m, 3 H), 2.24 (ddd, *J* = 20.6, 11.1, 6.2 Hz, 1 H), 1.98 (ddd, *J* = 13.2, 7.9, 4.8 Hz, 1 H), 1.37 (d, *J* = 25.2 Hz, 10 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.19, 172.97, 158.52, 154.05, 153.49, 79.84, 69.32, 68.59, 57.44, 57.00, 54.16, 54.08, 51.68, 51.49, 38.51, 37.85, 30.58, 27.82, 27.68, 27.17.

MS (ES-API): *m*/*z* (%) = 146 (100) [M + 1 – Boc]$^+$, 146 (100) [M + 1 – *t*-Bu]$^+$.

Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.99; H, 7.75; N, 5.90.

Synthesis of compounds 2r–u; General Procedure for Fmoc Protection

The corresponding compound **1r–u** dissolved in water (3.5 mL/mmol) and sodium bicarbonate (4 equiv) was added. The resulting mixture was stirred for 20 min then THF (3 mL/mmol) was added. The resulting mixture was cooled to 0 °C in an ice bath, and a solution of fluorenylmethyloxycarbonyl chloride (1.15 equiv) in THF (0.5 mL/mmol) was added dropwise at 0 °C. When the addition was complete, the resulting mixture was allowed to warm to r.t. and stirred overnight.

The reaction mixture was extracted twice with EtOAc and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to obtain the appropriate compound.

(2*R*,4*S*)-1-((9*H*-Fluoren-9-yl)methyl) 2-Benzyl 4-Hydroxypyrrolidine-1,2-dicarboxylate (2r)

Purified by flash chromatography (hexane/EtOAc, 2:1).

Yield: 26 g (60%); light-yellow solid; mp 36 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.68 (m, 2 H), 7.63–7.45 (m, 2 H), 7.42–7.15 (m, 9 H), 5.25–4.98 (m, 2 H), 4.64–4.18 (m, 4 H), 3.79–3.43 (m, 2 H), 2.48–2.19 (m, 1 H), 2.09 (dt, *J* = 13.0, 6.2 Hz, 1 H), 1.80 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.34, 171.73, 158.52, 143.61, 143.51, 140.77, 140.74, 134.81, 128.02, 127.88, 127.76, 127.58, 127.17, 127.10, 126.55, 124.67, 124.59, 124.44, 119.44, 119.38, 69.62, 68.80, 67.24, 67.08, 66.49, 66.41, 59.93, 57.54, 57.24, 54.80, 54.13, 46.68, 46.61, 38.82, 37.86.

MS (ES-API): *m*/*z* (100) = 444 [M + 1]$^+$.

Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.05; H, 5.79; N, 3.21.

(2*R*,4*R*)-1-((9*H*-Fluoren-9-yl)methyl) 2-Benzyl 4-hydroxypyrrolidine-1,2-dicarboxylate (2s)

Purified by flash chromatography (hexane/EtOAc, 2:1).

Yield: 42 g (84%); white solid; mp 36 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.88 (dd, *J* = 14.1, 7.6 Hz, 2 H), 7.61 (dd, *J* = 38.3, 7.5 Hz, 2 H), 7.50–7.20 (m, 10 H), 5.22–4.97 (m, 3 H), 4.48–4.06 (m, 5 H), 3.53 (dd, *J* = 11.1, 5.2 Hz, 1 H), 3.23 (td, *J* = 11.4, 3.1 Hz, 1 H), 2.33 (td, *J* = 8.2, 4.2 Hz, 1 H), 1.97–1.88 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.52, 171.31, 170.26, 158.52, 154.02, 153.74, 143.80, 143.75, 143.64, 140.71, 140.69, 140.60, 136.04, 135.91, 128.27, 127.84, 127.79, 127.62, 127.56, 127.53, 127.41, 127.07, 127.03, 126.98, 125.02, 124.95, 120.09, 120.02, 68.48, 67.55, 66.59, 65.82, 65.66, 59.70, 57.67, 57.30, 54.55, 53.99, 46.56, 38.67, 37.64, 20.70, 14.03.

MS (ES-API): *m*/*z* (100) = 444 [M + 1]$^+$.

Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.23; H, 5.51; N, 3.03.

(2*S*,4*S*)-1-((9*H*-Fluoren-9-yl)methyl) 2-Benzyl 4-hydroxypyrrolidine-1,2-dicarboxylate (2t)

Purified by flash chromatography (hexane/EtOAc, 2:1).

Yield: 48.4 g (69%); light-yellow thick oil.

The NMR signal ranges of the compound obtained are in agreement with those previously characterized in the literature.[37]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (t, *J* = 7.2 Hz, 2 H), 7.64–7.45 (m, 2 H), 7.45–7.10 (m, 9 H), 5.33–5.03 (m, 3 H), 4.56–4.19 (m, 5 H), 3.82–3.54 (m, 2 H), 3.45–2.68 (m, 1 H), 2.34 (tdd, *J* = 14.2, 9.7, 4.6 Hz, 1 H), 2.14 (t, *J* = 14.5 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.20, 173.83, 154.96, 154.45, 144.15, 143.97, 143.74, 143.55, 141.34, 141.31, 141.28, 141.21, 135.20, 135.04, 128.60, 128.56, 128.51, 128.42, 128.39, 128.20, 127.76, 127.73, 127.66, 127.11, 127.09, 127.02, 125.13, 125.08, 125.02, 124.90, 120.00, 119.95, 71.10, 70.00, 67.70, 67.67, 67.55, 67.46, 60.41, 58.30, 57.89, 56.06, 55.68, 53.47, 47.17, 47.15, 38.94, 37.82, 21.06, 14.22.

MS (ES-API): *m*/*z* (%) = 444 (100) [M + 1]$^+$.

Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.30; H, 5.75; N, 3.23.

(2*S*,4*R*)-1-((9*H*-Fluoren-9-yl)methyl) 2-Benzyl 4-hydroxypyrrolidine-1,2-dicarboxylate (2u)

Purified by flash chromatography (hexane/EtOAc, 2:1).

Yield: 49.7 g (64%); yellow thick oil.

The NMR signal ranges of the compound obtained are in agreement with those previously characterized in the literature.[37]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85–7.65 (m, 2 H), 7.65–7.47 (m, 2 H), 7.45–7.19 (m, 9 H), 5.25–4.97 (m, 2 H), 4.71–4.38 (m, 3 H), 4.38–4.18 (m, 2 H), 3.80–3.48 (m, 2 H), 2.44–2.26 (m, 1 H), 2.10 (ddd, *J* = 12.4, 7.1, 4.4 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.33, 171.23, 155.01, 154.71, 144.12, 144.02, 143.79, 143.53, 141.31, 141.27, 141.16, 135.52, 135.32, 128.54, 128.52, 128.39, 128.27, 128.09, 127.69, 127.67, 127.61, 127.08, 127.06, 127.03, 125.18, 125.12, 125.10, 124.95, 119.95, 119.90, 119.88, 70.10, 69.27, 67.74, 67.59, 66.98, 66.91, 58.06, 57.75, 55.30, 54.63, 53.43, 47.17, 47.10, 39.31, 38.35.

MS (ES-API): *m*/*z* (%) = 444 (100) [M + 1]$^+$.

Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.30; H, 5.75; N, 3.23.

Synthesis of Compounds 3a–u; General Procedure for Difluoromethylation

Protected amino alcohol was dissolved in MeCN (2.5 mL/mmol), and copper(I) iodide (0.2 equiv) was added. The resulting mixture was heated to 45 °C, and a solution of 2,2-difluoro-2-(fluorosulfonyl)acetic acid in MeCN (1 mL/mmol) was slowly added dropwise, maintaining the internal temperature below 50 °C. When the addition was complete, the reaction mixture was heated at 45 °C for 30 minutes.

The reaction mixture was concentrated in vacuo and the residue was diluted with EtOAc/petroleum ether (1:1). The resulting mixture was filtered through a short SiO_2 pad, and the pad was washed with an additional amount of EtOAc/petroleum ether (1:1). The filtrate was concentrated in vacuo and the residue was purified by flash chromatography.

***tert*-Butyl 3-((Difluoromethoxy)methyl)azetidine-1-carboxylate (3a)**

Purified by flash chromatography (hexane/EtOAc, 5:1).

Yield: 84 g (53%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.19 (td, *J* = 74.1, 2.3 Hz, 1 H), 4.04–3.90 (m, 4 H), 3.66 (ddd, *J* = 8.1, 5.4, 2.1 Hz, 2 H), 2.79 (hept, *J* = 7.0, 6.5 Hz, 1 H), 1.40 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.73 (CO), 117.22, 115.16 (t, $^1J_{C–F}$ = 261.6 Hz, CHF_2), 78.98 (2 × CH_2N), 63.77 (t, $^3J_{C–F}$ = 5.7 Hz, CH_2O), 27.82 (3 × CH_3), 27.40.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –85.01.

MS (ES-API): *m*/*z* (%) = 182 (100) [M + 1 – *t*Bu]$^+$.

Anal. Calcd for $C_{10}H_{17}F_2NO_3$: C, 50.63; H, 7.22; N, 5.90. Found: C, 50.74; H, 7.31; N, 5.99.

***tert*-Butyl 2-((Difluoromethoxy)methyl)azetidine-1-carboxylate (3b)**

Purified by flash chromatography (hexane/EtOAc, 5:1).

Yield: 44 g (43%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.22 (t, *J* = 74.7 Hz, 1 H), 4.32 (q, *J* = 4.3 Hz, 1 H), 4.12 (dd, *J* = 10.9, 4.6 Hz, 1 H), 3.89 (dd, *J* = 10.8, 2.9 Hz, 1 H), 3.78 (ddd, *J* = 9.7, 6.8, 3.1 Hz, 2 H), 2.34–2.00 (m, 2 H), 1.40 (d, *J* = 1.5 Hz, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.93 (CO), 116.08 (t, $^1J_{C–F}$ = 262.8 Hz, CHF_2), 79.63, 63.74, 59.79, 46.54, 28.31 (3 × CH_3), 18.60.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.56.

MS (ES-API): *m*/*z* (%) = 162 (100), 182 (50) [M + 1 – *t*Bu]$^+$.

Anal. Calcd for $C_{10}H_{17}F_2NO_3$: C, 50.63; H, 7.22; N, 5.90. Found: C, 50.59; H, 7.17; N, 5.94.

Benzyl 3-(Difluoromethoxy)-3-methylazetidine-1-carboxylate (3c)

Purified by flash chromatography (hexane/EtOAc, 7:1).

Yield: 39.6 g (40%); light-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 4 H), 6.25 (td, *J* = 74.4, 3.3 Hz, 1 H), 5.11 (d, *J* = 3.0 Hz, 2 H), 4.16 (d, *J* = 9.5 Hz, 2 H), 3.89 (d, *J* = 9.4 Hz, 2 H), 1.66 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.91 (CO), 135.83 (C_{Ar}-1), 128.00 (2 × CH_{Ar}), 127.65 (CH_{Ar}-4), 127.52 (2 × CH_{Ar}), 115.15 (t, $^1J_{C–F}$ = 258.8 Hz, CHF_2), 73.18 (t, $^3J_{C–F}$ = 2.4 Hz, C-O), 66.46 (2 × CH_2N), 60.98 (CH_2O), 23.36 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.28 (d, *J* = 27.3 Hz).

MS (ES-API): *m*/*z* (%) = 228 (100) [M + 1 – 44]$^+$.

Anal. Calcd for $C_{13}H_{15}F_2NO_3$: C, 57.56; H, 5.57; N, 5.16. Found: C, 57.71; H, 5.50; N, 5.21.

(*S*)-*tert*-Butyl 2-((Difluoromethoxy)methyl)pyrrolidine-1-carboxylate (3d)

Purified by flash chromatography (hexane/EtOAc, 5:1).

Yield: 47.1 g (50.3%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.17 (t, *J* = 74.9 Hz, 1 H), 3.94 (d, *J* = 9.8 Hz, 2 H), 3.88 (s, 1 H), 3.32 (s, 2 H), 2.07–1.71 (m, 4 H), 1.44 (s, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.49 and 154.19 (CO), 116.17 (t, $^1J_{C-F}$ = 258.7 Hz) and 115.77 (t, $^1J_{C-F}$ = 260.9 Hz) (CHF_2), 79.59 and 79.34, 63.97 and 63.71, 55.81, 46.85 and 46.43, 28.32 (3xCH_3), 28.54 and 27.70, 23.62 and 22.75.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.60 (d, ^2J = 12.5 Hz), –84.43.

MS (ES-API): *m*/*z* (%) = 252 (100) $[M + 1]^+$.

Anal. Calcd for $C_{11}H_{19}F_2NO_3$: C, 52.58; H, 7.62; N, 5.57. Found: C, 52.50; H, 7.73; N, 5.51.

(*R*)-*tert*-Butyl 2-((Difluoromethoxy)methyl)pyrrolidine-1-carboxylate (3e)

Purified by flash chromatography (hexane/EtOAc, 5:1).

Yield: 47.15 g (63%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (t, *J* = 74.9 Hz, 1 H), 4.03–3.90 (m, 1 H), 3.87 (s, 1 H), 3.44–3.22 (m, 2 H), 2.08–1.71 (m, 4 H), 1.43 (s, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.49 and 154.20, 116.17 (t, *J* = 259.3 Hz) and 115.78 (t, *J* = 261.6 Hz, CHF_2), 79.60 and 79.35, 63.98 and 63.71, 55.81 and 53.33, 46.86 and 46.44, 28.33 (3 × CH_3), 28.55 and 27.70, 23.63 and 22.76.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.63 (d, ^2J = 12.1 Hz), –84.45.

MS (ES-API): *m*/*z* (%) = 252 (100) $[M + 1]^+$.

Anal. Calcd for $C_{11}H_{19}F_2NO_3$: C, 52.58; H, 7.62; N, 5.57. Found: C, 52.47; H, 7.59; N, 5.55.

(1*R*,3*R*,5*S*)-*tert*-Butyl 3-(Difluoromethoxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (3f)

Purified by flash chromatography (hexane/EtOAc, 4:1).

Yield: 63.9 g (46%); white solid; mp 38 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.18 (td, *J* = 75.0, 3.2 Hz, 1 H), 4.43 (t, *J* = 4.7 Hz, 1 H), 4.16 (d, *J* = 42.6 Hz, 2 H), 2.06 (d, *J* = 6.5 Hz, 4 H), 1.92 (d, *J* = 7.2 Hz, 2 H), 1.83 (d, *J* = 14.8 Hz, 2 H), 1.44 (d, *J* = 3.1 Hz, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.76 (CO), 116.04 (t, $^1J_{C-F}$ = 258.0 Hz, CHF_2), 78.77, 69.14 (t, $^3J_{C-F}$ = 4.2 Hz), 52.16, 51.36, 36.00, 35.22, 27.94 (3 × CH_3), 27.47, 26.80.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –82.1.

MS (ES-API): *m*/*z* (%) = 178 (100) $[M + 1 - Boc]^+$, 222 (25) $[M + 1 - t\text{Bu}]^+$.

Anal. Calcd for $C_{13}H_{21}F_2NO_3$: C, 56.31; H, 7.63; N, 5.05. Found: C, 56.21; H, 7.75; N, 5.14.

(*S*)-*tert*-Butyl 3-(Difluoromethoxy)piperidine-1-carboxylate (3g)

Purified by flash chromatography (hexane/EtOAc, 7:1).

Yield: 45.92 g (61.3%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.45–6.01 (m, 1 H), 4.21–4.06 (m, 1 H), 4.03–3.62 (m, 1 H), 3.54 (s, 1 H), 3.15 (s, 2 H), 1.93 (s, 1 H), 1.76 (s, 1 H), 1.70–1.59 (m, 1 H), 1.44 (d, *J* = 1.4 Hz, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.72 (CO), 115.94 (t, $^1J_{C-F}$ = 259.9 Hz, CHF_2), 79.77, 69.04, 49.96–46.85 (m), 44.58–42.67 (m), 30.79, 28.29 (3 × CH_3), 23.17–21.64 (m).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.95, –82.22.

MS (ES-API): *m*/*z* (%) = 84 (100) $[M + 1 - Boc - CHF_2O]^+$, 152 (15) $[M + 1 - Boc]^+$.

Anal. Calcd for $C_{11}H_{19}F_2NO_3$: C, 52.58; H, 7.62; N, 5.57. Found: C, 52.63; H, 7.71; N, 5.55.

(*R*)-*tert*-Butyl 3-(Difluoromethoxy)piperidine-1-carboxylate (3h)

Purified by flash chromatography (hexane/EtOAc, 7:1).

Yield: 52.27 g (59.5%); colorless thick oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.23 (td, *J* = 74.9, 1.5 Hz, 1 H), 4.12 (tt, *J* = 7.8, 3.7 Hz, 1 H), 3.99–3.61 (m, 1 H), 3.52 (s, 1 H), 3.14 (s, 2 H), 1.91 (d, *J* = 11.2 Hz, 1 H), 1.83–1.69 (m, 1 H), 1.64 (d, *J* = 10.2 Hz, 1 H), 1.43 (d, *J* = 1.6 Hz, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.70 (CO), 115.95 (t, $^1J_{C-F}$ = 259.9 Hz, CHF_2), 79.73, 69.04, 49.96–46.85 (m), 44.58–42.67 (m), 30.76, 28.26 (3 × CH_3), 23.17–21.64 (m).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.97, –82.20.

MS (ES-API): *m*/*z* (%) = 84 (100) $[M + 1 - Boc - CHF_2O]^+$, 152 (15) $[M + 1 - Boc]^+$.

Anal. Calcd for $C_{11}H_{19}F_2NO_3$: C, 52.58; H, 7.62; N, 5.57. Found: C, 52.71; H, 7.55; N, 5.48.

***tert*-Butyl 4-(Difluoromethoxy)piperidine-1-carboxylate (3i)**

Purified by flash chromatography (hexane/EtOAc, 7:1).

Yield: 68.42 g (54.8%); light-yellow thick oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.25 (t, *J* = 74.8 Hz, 1 H), 4.34 (dt, *J* = 7.9, 4.0 Hz, 1 H), 3.70 (dq, *J* = 9.8, 3.4, 2.9 Hz, 2 H), 3.23 (ddd, *J* = 13.5, 8.4, 3.7 Hz, 2 H), 1.84 (dq, *J* = 10.3, 3.3 Hz, 2 H), 1.67 (ddt, *J* = 13.0, 8.7, 4.1 Hz, 2 H), 1.45 (s, 10 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.70 (CO), 116.08 (t, $^1J_{C-F}$ = 259.6 Hz, CHF_2), 79.74, 70.60 (t, $^3J_{C-F}$ = 4.2 Hz), 40.63 (2 × CH_2N), 31.82 (2 × CH_2), 28.38 (3 × CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.70.

MS (ES-API): *m*/*z* (%) = 84 (100) $[M + 1 - Boc - CHF_2O]^+$, 152 (50) $[M + 1 - Boc]^+$.

Anal. Calcd for $C_{11}H_{19}F_2NO_3$: C, 52.58; H, 7.62; N, 5.57. Found: C, 52.42; H, 7.48; N, 5.48.

Benzyl 2-((Difluoromethoxy)methyl)piperidine-1-carboxylate (3j)

Purified by flash chromatography (hexane/EtOAc, 8:1).

Yield: 90 g (42%); light-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.28 (m, 6 H), 6.16 (t, *J* = 74.3 Hz, 1 H), 5.14 (q, *J* = 12.5 Hz, 2 H), 4.61–4.44 (m, 1 H), 4.11 (d, *J* = 13.7 Hz, 1 H), 3.99 (dd, *J* = 10.0, 7.6 Hz, 1 H), 3.88 (dd, *J* = 10.0, 7.2 Hz, 1 H), 2.86 (t, *J* = 13.0 Hz, 1 H), 1.76 (d, *J* = 13.5 Hz, 1 H), 1.70–1.58 (m, 3 H), 1.59–1.36 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.66 (CO), 136.77, 128.43 (2 × CH_{Ph}), 127.92, 127.80 (2 × CH_{Ph}), 115.71 (t, $^1J_{C-F}$ = 261.4 Hz, CHF_2), 67.12, 60.64 (t, $^1J_{C-F}$ = 5.0 Hz, CH_2O), 49.27, 39.90, 25.04, 24.99, 19.06.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –85.08.

MS (ES-API): *m*/*z* (%) = 91 (100) $[C_7H_7]^+$, 300 (15) $[M + 1]^+$.

Anal. Calcd for $C_{15}H_{19}F_2NO_3$: C, 60.19; H, 6.40; N, 4.68. Found: C, 60.04; H, 6.29; N, 4.77.

Benzyl 3-((Difluoromethoxy)methyl)piperidine-1-carboxylate (3k)

Purified by flash chromatography (hexane/EtOAc, 6:1).

Yield: 85 g (60.5%); light-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.27 (m, 5 H), 6.18 (t, *J* = 74.6 Hz, 1 H), 5.13 (d, *J* = 3.8 Hz, 2 H), 3.98 (dt, *J* = 13.5, 4.3 Hz, 2 H), 3.71 (tt, *J* = 17.2, 7.8 Hz, 2 H), 3.14–2.55 (m, 2 H), 1.96–1.76 (m, 2 H), 1.76–1.58 (m, 1 H), 1.49 (s, 1 H), 1.35–1.17 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.30 (CO), 136.86, 128.45 (2 × CH_{Ph}), 127.93, 127.81 (2 × CH_{Ph}), 115.84 (t, $^1J_{C–F}$ = 260.7 Hz, CHF_2), 67.03, 65.02, 46.76, 44.50, 35.54, 26.90, 24.22.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –85.03.

MS (ES-API): *m*/*z* (%) = 91 (100) $[C_7H_7]^+$, 236 (92) $[M + 1 – 64]^+$.

Anal. Calcd for $C_{15}H_{19}F_2NO_3$: C, 60.19; H, 6.40; N, 4.68. Found: C, 60.28; H, 6.35; N, 4.54.

Benzyl 4-((Difluoromethoxy)methyl)piperidine-1-carboxylate (3l)

Purified by flash chromatography (hexane/EtOAc, 6:1).

Yield: 75 g (65%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.29 (m, 5 H), 6.19 (t, *J* = 74.7 Hz, 1 H), 5.13 (s, 2 H), 4.22 (s, 2 H), 3.69 (d, *J* = 6.4 Hz, 2 H), 2.79 (s, 2 H), 1.91–1.59 (m, 3 H), 1.21 (q, *J* = 13.6, 12.6 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.21 (CO), 136.84, 128.46 (2 × CH_{Ph}), 127.94, 127.84 (2 × CH_{Ph}), 115.91 (t, $^1J_{C–F}$ = 260.4 Hz, CHF_2), 67.32 (t, *J* = 5.2 Hz, CH_2O), 67.03, 43.64 (2 × CH_2), 35.82 (2 × CH_2), 28.40.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.69.

MS (ES-API): *m*/*z* (%) = 91 (100) $[C_7H_7]^+$, 236 (92) $[M + 1 – 64]^+$.

Anal. Calcd for $C_{15}H_{19}F_2NO_3$: C, 60.19; H, 6.40; N, 4.68. Found: C, 60.09; H, 6.54; N, 4.81.

(1*R*,3*S*,4*S*)-*tert*-Butyl 3-((Difluoromethoxy)methyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (3m)

Purified by flash chromatography (hexane/EtOAc, 5:1).

Yield: 26.52 g (49%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.18 (t, *J* = 74.9 Hz, 1 H), 4.17–3.94 (m, 2 H), 3.54 (t, *J* = 9.5 Hz, 1 H), 3.50–3.40 (m, 1 H), 2.53 (d, *J* = 4.2 Hz, 1 H), 1.79–1.53 (m, 5 H), 1.44 (s, 11 H), 1.39 (dd, *J* = 11.7, 7.1 Hz, 1 H), 1.25 (d, *J* = 10.2 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.14 and 154.48 (CO), 116.07 (t, $^1J_{C–F}$ = 259.6 Hz) and 115.73 (t, $^1J_{C–F}$ = 260.9 Hz) (CHF_2), 79.77 and 79.51, 63.05 and 62.90, 62.44 and 62.21, 57.57 and 56.64, 39.34 and 38.72, 34.56 and 33.79, 30.22 and 29.71, 28.53, 28.45 and 28.37, 27.54, 27.37.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.78, –84.37.

MS (ES-API): *m*/*z* (%) = 154 (100) $[M + 1 – tBu – CHF_2 – OH]^+$, 222 (15) $[M + 1 – tBu]^+$.

Anal. Calcd for $C_{13}H_{21}F_2NO_3$: C, 56.31; H, 7.63; N, 5.05. Found: C, 56.24; H, 7.71; N, 5.19.

(2*R*,4*R*)-1-*tert*-Butyl 2-Methyl 4-(Difluoromethoxy)pyrrolidine-1,2-dicarboxylate (3n)

Purified by flash chromatography (hexane/EtOAc, 3:1).

Yield: 36.6 g (60%); white solid; mp 27 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.18 (t, *J* = 73.3 Hz, 1 H), 4.79 (ddd, *J* = 14.0, 6.5, 3.2 Hz, 1 H), 4.37 (ddd, *J* = 54.9, 9.2, 3.8 Hz, 1 H), 3.72 (s, 4 H), 3.56 (ddd, *J* = 16.0, 11.8, 3.4 Hz, 1 H), 2.46 (dddd, *J* = 26.1, 14.4, 9.2, 5.7 Hz, 1 H), 2.27 (dt, *J* = 13.9, 3.8 Hz, 1 H), 1.43 (d, *J* = 26.2 Hz, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.33 and 172.00, 153.95 and 153.42, 115.45 (t, $^1J_{C–F}$ = 262.1 Hz, CHF_2), 80.43 and 80.38, 71.75 and 70.81, 57.40 and 57.01, 52.41 and 52.26, 52.10 and 51.86, 36.94 and 36.11, 28.32 and 28.19 (3 × CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.19, –83.62, –83.62, –83.80, –83.83, –84.22, –84.26.

MS (ES-API): *m*/*z* (%) = 196 (100) $[M + 1 – Boc]^+$.

Anal. Calcd for $C_{12}H_{19}F_2NO_5$: C, 48.81; H, 6.49; N, 4.74. Found: C, 48.91; H, 6.35; N, 4.82.

(2*S*,4*S*)-1-*tert*-Butyl 2-Methyl 4-(Difluoromethoxy)pyrrolidine-1,2-dicarboxylate (3o)

Purified by flash chromatography (hexane/EtOAc, 3:1).

Yield: 38.5 g (54%); colorless thick oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.18 (t, *J* = 73.3 Hz, 1 H), 4.79 (tt, *J* = 9.6, 4.9 Hz, 1 H), 4.37 (ddd, *J* = 55.2, 9.1, 3.8 Hz, 1 H), 3.72 (s, 4 H), 3.56 (ddd, *J* = 16.1, 12.2, 3.4 Hz, 1 H), 2.46 (dtd, *J* = 26.6, 11.6, 8.9, 5.7 Hz, 1 H), 2.27 (dt, *J* = 13.9, 3.9 Hz, 1 H), 1.42 (d, *J* = 26.2 Hz, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.35 and 172.02, 153.98 and 153.44, 115.47 (t, $^1J_{C–F}$ = 262.3 Hz, CHF_2), 80.46 and 80.41, 71.76 (t, *J* = 5.3 Hz) and 70.81 (t, $^3J_{C–F}$ = 5.2 Hz) (CH_2O), 57.41 and 57.03, 52.44 and 52.29, 52.13 and 51.88, 36.96 and 36.14, 28.33 and 28.21 (3 × CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.18, –83.19, –83.61, –83.62, –83.79, –83.82, –84.21, –84.25.

MS (ES-API): *m*/*z* (%) = 196 (100) $[M + 1 – Boc]^+$.

Anal. Calcd for $C_{12}H_{19}F_2NO_5$: C, 48.81; H, 6.49; N, 4.74. Found: C, 48.99; H, 6.59; N, 4.52.

(2*R*,4*S*)-1-*tert*-Butyl 2-Methyl 4-(Difluoromethoxy)pyrrolidine-1,2-dicarboxylate (3p)

Purified by flash chromatography (hexane/EtOAc 3:1).

Yield: 12 g (53.9%); white solid; mp 68 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.21 (t, *J* = 73.5 Hz, 1 H), 4.83 (p, *J* = 4.8 Hz, 1 H), 4.37 (dt, *J* = 36.4, 7.4 Hz, 1 H), 3.77–3.49 (m, 5 H), 2.50–2.31 (m, 1 H), 2.16 (ddd, *J* = 13.2, 7.0, 5.2 Hz, 1 H), 1.42 (d, *J* = 23.2 Hz, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.06 and 172.88, 153.99 and 153.41, 115.63 (t, $^1J_{C–F}$ = 261.9 Hz, CHF_2), 80.53, 71.78 (t, *J* = 5.1 Hz) and 71.78 (t, *J* = 5.1 Hz) (CH_2O), 57.61 and 57.17, 52.33 and 52.14, 37.23 and 36.24, 28.31 and 28.19 (3 × CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –82.95, –83.37, –83.49, –83.92.

MS (ES-API): *m*/*z* (%) = 196 (100) $[M + 1 – Boc]^+$.

Anal. Calcd for $C_{12}H_{19}F_2NO_5$: C, 48.81; H, 6.49; N, 4.74. Found: C, 48.91; H, 6.35; N, 4.82.

(2*R*,4*S*)-1-((9*H*-Fluoren-9-yl)methyl) 2-Benzyl 4-(Difluoromethoxy)pyrrolidine-1,2-dicarboxylate (3r)

Purified by flash chromatography (hexane/EtOAc, 4:1).

Yield: 12.6 g (43%); light-yellow thick oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (t, *J* = 7.0 Hz, 2 H), 7.65–7.45 (m, 2 H), 7.45–7.17 (m, 8 H), 6.22 (td, *J* = 73.2, 7.1 Hz, 1 H), 5.29–4.98 (m, 2 H), 4.88 (dp, *J* = 17.8, 4.4 Hz, 1 H), 4.54 (dt, *J* = 27.6, 7.5 Hz, 1 H), 4.46–4.20 (m, 2 H), 3.90–3.66 (m, 2 H), 2.69–2.38 (m, 1 H), 2.21 (dq, *J* = 12.9, 6.3 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.27, 158.52, 154.12, 153.70, 143.57, 143.41, 143.22, 143.00, 140.78, 140.69, 134.86, 134.66, 128.07, 127.98, 127.87, 127.81, 127.63, 127.22, 127.20, 127.14, 126.55, 126.52, 124.61, 124.57, 124.54, 124.40, 119.48, 119.42, 115.07 (t, $^1J_{C–F}$ = 262.5 Hz, CHF_2), 71.25 (t, *J* = 5.0 Hz) and 70.43 (t, *J* = 5.5 Hz) (CHO), 67.28, 66.67, 66.61, 57.26, 56.96, 52.91, 52.31, 51.89, 46.60, 36.92, 35.77.

MS (ES-API): *m*/*z* (%) = 494 (100) $[M + 1]^+$.

Anal. Calcd for $C_{28}H_{25}F_2NO_5$: C, 68.15; H, 5.11; N, 2.84. Found: C, 68.19; H, 5.21; N, 2.75.

(2*R*,4*R*)-1-((9*H*-Fluoren-9-yl)methyl) 2-Benzyl 4-(Difluoromethoxy)pyrrolidine-1,2-dicarboxylate (3s)

Purified by flash chromatography (hexane/EtOAc, 4:1).

Yield: 20 g (43%); white solid; mp 42 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (t, *J* = 8.1 Hz, 2 H), 7.66–7.48 (m, 2 H), 7.46–7.20 (m, 9 H), 6.24–5.72 (m, 1 H), 5.32–5.02 (m, 2 H), 4.84 (ddq, *J* = 25.0, 5.6, 2.8 Hz, 1 H), 4.70–4.02 (m, 4 H), 3.91–3.66 (m, 2 H), 2.59–2.33 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.00 and 170.87, 154.54 and 154.20, (144.09, 143.66 and 143.64), (141.34, 141.32, 141.26 and 141.23), (135.58 and 135.41), (128.47, 128.42, 128.34 and 128.25), (127.75, 127.71, 127.65, 127.09, 127.07 and 127.03), (125.14, 125.01, 124.98 and 124.90), 119.99 and 119.94, 115.35 (t, $^1J_{C-F}$ = 263.0 Hz, CHF_2), 71.79 (t, *J* = 5.2 Hz) and 70.86 (t, *J* = 5.3 Hz) (CHO), 67.73 and 67.57, 67.08 and 67.05, 57.74 and 57.48, 52.93 and 52.51, 47.17, 37.36 and 36.27.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.28, –83.70, –83.73, –83.76, –83.83, –84.26.

MS (ES-API): *m*/*z* (%) = 494 (100) $[M + 1]^+$.

Anal. Calcd for $C_{28}H_{25}F_2NO_5$: C, 68.15; H, 5.11; N, 2.84. Found: C, 68.31; H, 5.02; N, 2.71.

(2*S*,4*S*)-1-((9*H*-Fluoren-9-yl)methyl) 2-Benzyl 4-(Difluoromethoxy)pyrrolidine-1,2-dicarboxylate (3t)

Purified by flash chromatography (hexane/EtOAc, 4:1).

Yield: 22 g (40.8%); white solid; mp 83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (t, *J* = 7.5 Hz, 2 H), 7.67–7.45 (m, 2 H), 7.45–7.20 (m, 8 H), 5.97 (td, *J* = 73.0, 17.5 Hz, 1 H), 5.33–4.96 (m, 2 H), 4.92–4.72 (m, 1 H), 4.67–3.97 (m, 4 H), 3.94–3.62 (m, 2 H), 2.41 (td, *J* = 14.2, 9.5 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.02 and 170.89, 154.56 and 154.22, 144.08, 143.65, 141.34, 135.56, 135.40, 128.48, 128.44, 128.37, 128.27, 127.76, 127.72, 127.66, 127.08, 125.15, 125.00, 124.91, 120.00, 119.96, 115.34 (t, $^1J_{C-F}$ = 263.0 Hz, CHF_2), 70.84, 67.74, 67.58, 67.11, 67.07, 57.74, 57.49, 52.95, 52.54, 47.17, 37.39, 36.30.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.30, –83.33, –83.72, –83.75, –83.79, –83.86, –84.21, –84.28.

MS (ES-API): *m*/*z* (%) = 494 (100) $[M + 1]^+$.

Anal. Calcd for $C_{28}H_{25}F_2NO_5$: C, 68.15; H, 5.11; N, 2.84. Found: C, 68.03; H, 5.08; N, 2.96.

(2*S*,4*R*)-1-((9*H*-Fluoren-9-yl)methyl) 2-Benzyl 4-(Difluoromethoxy)pyrrolidine-1,2-dicarboxylate (3u)

Purified by flash chromatography (hexane/EtOAc, 5:1).

Yield: 21.8 g (39%); light-yellow thick oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87–7.66 (m, 2 H), 7.65–7.45 (m, 2 H), 7.45–7.20 (m, 9 H), 6.23 (td, *J* = 73.2, 8.7 Hz, 1 H), 5.35–4.99 (m, 2 H), 4.89 (dt, *J* = 22.6, 4.2 Hz, 1 H), 4.55 (dt, *J* = 35.1, 7.5 Hz, 1 H), 4.45–4.20 (m, 3 H), 3.91–3.64 (m, 2 H), 2.62–2.42 (m, 1 H), 2.31–2.07 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.27, 154.11, 153.68, 143.56, 143.40, 143.21, 142.98, 140.77, 140.69, 134.85, 134.65, 128.06, 127.98, 127.86, 127.81, 127.62, 127.22, 127.20, 127.13, 126.55, 126.51, 124.61, 124.57, 124.53, 124.40, 119.48, 119.41, 115.07 (t, *J* = 262.4 Hz, CHF_2), 71.24, 70.42, 67.28, 67.26, 66.67, 66.60, 57.25, 56.95, 52.31, 51.89, 48.94, 36.92, 35.77.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.03, –83.44, –83.56, –83.98.

MS (ES-API): *m*/*z* (%) = 494 (100) $[M + 1]^+$.

Anal. Calcd for $C_{28}H_{25}F_2NO_5$: C, 68.15; H, 5.11; N, 2.84. Found: C, 68.24; H, 5.27; N, 2.88.

Synthesis of Compounds 4a, 4b, 4d–i, and 4m; General Procedure for Boc Deprotection

Acetyl chloride (2 equiv) was added dropwise to cooled MeOH (3 mL/mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 20 minutes. A solution of the appropriate difluoromethoxy compound in MeOH (0.5 mL/mmol) was then added dropwise to the previous solution at 0 °C. The resulting solution was allowed to warm to r.t. and stirred overnight.

The reaction mixture was concentrated in vacuo at 40 °C, and Et_2O was added to the residue. The resulting suspension was filtered, and the filter cake was washed with Et_2O. The filter cake was dried in vacuo to obtain the target product.

3-((Difluoromethoxy)methyl)azetidine (4a)

The crude product was treated with 20% NaOH and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo.

The crude product was purified by distillation (46 °C, 20 mmHg).

Yield: 31 g (63.8%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.22 (t, *J* = 74.7 Hz, 1 H), 4.00 (d, *J* = 6.5 Hz, 2 H), 3.71 (t, *J* = 8.0 Hz, 2 H), 3.46 (dd, *J* = 8.1, 6.2 Hz, 2 H), 3.00 (p, *J* = 7.1 Hz, 1 H), 2.17 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 115.89 (t, $^1J_{C-F}$ = 260.0 Hz, CHF_2), 65.06 (t, *J* = 5.2 Hz, CH_2O), 49.11 (2 × CH_2), 33.69.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.56.

MS (ES-API): *m*/*z* (%) = 138 (100) $[M + 1]^+$.

Anal. Calcd for $C_5H_9F_2NO$: C, 43.79; H, 6.62; N, 10.21. Found: C, 43.73; H, 6.74; N, 10.12.

2-((Difluoromethoxy)methyl)azetidine (4b)

The crude product was treated with 20% NaOH and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo.

The crude product was purified by distillation (44 °C, 20 mmHg).

Yield: 18.5 g (74.4%); colorless liquid.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 6.65 (t, *J* = 76.5 Hz, 1 H), 3.91 (ddd, *J* = 13.3, 7.4, 5.7 Hz, 1 H), 3.83–3.68 (m, 2 H), 3.44 (td, *J* = 8.2, 6.9 Hz, 1 H), 3.14 (ddd, *J* = 8.8, 6.9, 4.2 Hz, 1 H), 2.16 (dtd, *J* = 10.9, 8.2, 4.3 Hz, 1 H), 1.96 (dq, *J* = 11.0, 8.1 Hz, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 117.59 (t, $^1J_{C-F}$ = 255.9 Hz, CHF_2), 69.59 (t, *J* = 3.8 Hz, CH_2-O), 56.48, 43.29, 23.65.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –82.28.

MS (ES-API): *m*/*z* (%) = 138 (100) $[M + 1]^+$.

Anal. Calcd for $C_5H_9F_2NO$: C, 43.79; H, 6.62; N, 10.21. Found: C, 43.88; H, 6.51; N, 10.34.

(*S*)-2-((Difluoromethoxy)methyl)pyrrolidine (4d)

Yield (HCl salt): 28.17 g (80.1%); yellow powder; mp 85 °C (decomp.); $[\alpha]_D$ +16.84 (MeOH, *c* = 26.7 mmol/L).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.75 (s, 1 H) and 9.32 (s, 1 H), 6.78 (t, *J* = 75.5 Hz, 1 H), 4.23–3.99 (m, 2 H), 3.72 (p, *J* = 7.4 Hz, 1 H), 3.16 (td, *J* = 7.4, 3.5 Hz, 2 H), 2.04 (ddd, *J* = 12.4, 8.1, 4.5 Hz, 1 H), 1.99–1.77 (m, 2 H), 1.62 (dq, *J* = 12.4, 8.3 Hz, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 116.66 (t, $^1J_{C-F}$ = 258.1 Hz, CHF_2), 63.31, 57.51, 44.82, 26.19, 23.02.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –83.36, –83.79, –83.94, –84.37.

MS (ES-API): m/z (%) = 152 (100) $[M + 1]^+$.

Anal. Calcd for $C_6H_{11}F_2NO{\cdot}HCl$: C, 38.41; H, 6.45; N, 7.47. Found: C, 38.27; H, 6.34; N, 7.59.

(*R*)-2-((Difluoromethoxy)methyl)pyrrolidine (4e)

Yield (HCl salt): 33.19 g (94.3%); white powder; mp 84 °C (decomp.); $[\alpha]_D$ –17.76 (MeOH, c = 26.7 mmol/L).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.75 (s, 1 H), 9.30 (s, 1 H), 6.78 (t, J = 75.5 Hz, 1 H), 4.08 (dd, J = 6.2, 3.3 Hz, 2 H), 3.73 (s, 1 H), 3.23–3.05 (m, 2 H), 2.04 (qd, J = 7.8, 3.7 Hz, 1 H), 1.89 (ddd, J = 24.5, 13.5, 5.8 Hz, 2 H), 1.76–1.51 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 116.66 (t, $^1J_{C–F}$ = 258.1 Hz, CHF_2), 63.32 (t, J = 4.6 Hz, CH_2O), 57.49, 44.80, 26.20, 23.02.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –83.36, –83.79, –83.94, –84.37.

MS (ES-API): m/z (%) = 152 (100) $[M + 1]^+$.

Anal. Calcd for $C_6H_{11}F_2NO{\cdot}HCl$: C, 38.41; H, 6.45; N, 7.47. Found: C, 38.35; H, 6.57; N, 7.59.

(1*R*,3*R*,5*S*)-3-(Difluoromethoxy)-8-azabicyclo[3.2.1]octane (4f)

The crude product was treated with 20% NaOH and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo.

The crude product was purified by distillation (50 °C, 0.5 mmHg).

Yield: 28 g (68.6%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.15 (t, J = 75.5 Hz, 1 H), 4.38 (t, J = 5.1 Hz, 1 H), 3.48 (p, J = 3.2 Hz, 2 H), 2.10 (t, J = 7.1 Hz, 2 H), 1.99 (dt, J = 15.1, 4.4 Hz, 2 H), 1.92–1.79 (m, 3 H), 1.79–1.65 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 116.19 (t, $^1J_{C–F}$ = 257.1 Hz, CHF_2), 69.50 (t, $^3J_{C–F}$ = 3.9 Hz, CHO), 52.84 (2 × CHN), 37.63 (2 × CH_2), 28.55 (2 × CH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.81.

MS (ES-API): m/z (%) = 178 (100) $[M + 1]^+$.

Anal. Calcd for $C_8H_{13}F_2NO$: C, 54.23; H, 7.40; N, 7.90. Found: C, 54.31; H, 7.59; N, 7.97.

(*R*)-3-(Difluoromethoxy)piperidine (4g)

The crude product was treated with 20% NaOH and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo.

The crude product was purified by distillation (81 °C, 20 mmHg).

Yield: 22.23 g (70.7%); colorless oil; $[\alpha]_D$ +13.96 (MeOH, c = 33.1 mmol/L).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.26 (t, J = 75.2 Hz, 1 H), 4.16 (tt, J = 7.4, 3.7 Hz, 1 H), 3.09 (dd, J = 12.8, 3.5 Hz, 1 H), 2.91–2.65 (m, 3 H), 2.03–1.86 (m, 3 H), 1.85–1.63 (m, 2 H), 1.51 (ddq, J = 13.1, 8.8, 4.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 115.66 (t, J = 259.1 Hz, CHF_2), 70.17 (t, J = 3.6 Hz, CH-O), 50.81, 45.30, 30.47, 23.45.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.33.

MS (ES-API): m/z (%) = 152 (100) $[M + 1]^+$.

Anal. Calcd for $C_6H_{11}F_2NO$: C, 47.68; H, 7.34; N, 9.27. Found: C, 47.81; H, 7.42; N, 9.21.

(*S*)-3-(Difluoromethoxy)piperidine (4h)

The crude product was treated with 20% NaOH and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo.

The crude product was purified by distillation (80 °C, 20 mmHg).

Yield: 18.66 g (67.5%); colorless oil; $[\alpha]_D$ –13.36 (MeOH, c = 33.1 mmol/L).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.25 (t, J = 75.2 Hz, 1 H), 4.14 (tt, J = 7.5, 3.7 Hz, 1 H), 3.12–3.02 (m, 1 H), 2.90–2.64 (m, 3 H), 1.93 (ddt, J = 12.1, 7.7, 4.0 Hz, 1 H), 1.84 (s, 1 H), 1.77 (dtt, J = 13.8, 7.0, 3.7 Hz, 1 H), 1.68 (dtd, J = 12.7, 8.4, 4.0 Hz, 1 H), 1.48 (dtt, J = 12.7, 8.1, 3.9 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 116.16 (t, J = 258.7 Hz, CHF_2), 70.65 (t, J = 3.3 Hz, CH-O), 51.11, 45.62, 30.83, 23.80.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.33.

MS (ES-API): m/z (%) = 152 (100) $[M + 1]^+$.

Anal. Calcd for $C_6H_{11}F_2NO$: C, 47.68; H, 7.34; N, 9.27. Found: C, 47.74; H, 7.27; N, 9.17.

4-(Difluoromethoxy)piperidine (4i)

The crude product was treated with 20% NaOH and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo.

The crude product was purified by distillation (75 °C, 20 mmHg).

Yield: 34 g (82.6%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.19 (t, J = 75.4 Hz, 1 H), 4.16 (tt, J = 8.9, 4.1 Hz, 1 H), 3.03 (dt, J = 12.8, 4.5 Hz, 2 H), 2.61 (ddd, J = 12.8, 9.9, 3.0 Hz, 2 H), 1.94–1.82 (m, 2 H), 1.56 (tq, J = 9.3, 5.5, 4.7 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 116.16 (t, J = 258.4 Hz, CHF_2), 72.06, 43.92 (2 × CH_2N), 33.53 (2 × CH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.14, –81.18.

MS (ES-API): m/z (%) = 152 (100) $[M + 1]^+$.

Anal. Calcd for $C_6H_{11}F_2NO$: C, 47.68; H, 7.34; N, 9.27. Found: C, 47.57; H, 7.44; N, 9.33.

(1*R*,3*S*,4*S*)-3-((Difluoromethoxy)methyl)-2-azabicyclo[2.2.1]heptane (4m)

Yield (HCl salt): 16.67 g (82.4%); white powder; mp 115 °C (decomp.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.29 (s, 2 H), 6.76 (dd, J = 77.3, 74.8 Hz, 1 H), 4.06–3.78 (m, 3 H), 3.41 (dd, J = 9.0, 5.1 Hz, 1 H), 1.88–1.72 (m, 2 H), 1.72–1.59 (m, 2 H), 1.59–1.35 (m, 2 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 119.02, 117.33, 117.31, 115.61, 64.00, 63.97, 61.52, 58.02, 40.52, 37.67, 35.02, 27.67, 27.54, 25.04.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –83.04, –83.47, –83.89, –84.32.

MS (ES-API): m/z (%) = 178 (100) $[M + 1]^+$.

Anal. Calcd for $C_8H_{13}F_2NO{\cdot}HCl$: C, 44.97; H, 6.61; N, 6.56. Found: C, 44.83; H, 6.49; N, 6.50.

Synthesis of 4c and 4j–l; General Procedure for Cbz Deprotection (D)

Cbz protected compound was added to the suspension of freshly prepared Raney Ni (1 g per 1 g of compound) in MeOH (2 mL/mmol) and the resulting suspension was vigorously stirred overnight.

The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was re-dissolved in MeOH (2 mL/mmol) and 10% Pd/C (5 mol%) was added. The resulting mixture was degassed and backfilled with hydrogen three times and the resulting mixture was hydrogenated at 1 atm (balloon) overnight.

The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in MTBE and the resulting solution was washed with 2N NaOH solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was distilled in vacuo to obtain the appropriate product.

3-(Difluoromethoxy)-3-methylazetidine (4c)

Distilled at 39 °C (20 mmHg).

Yield: 10 g (53.9%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.26 (t, *J* = 75.5 Hz, 1 H), 3.89 (d, *J* = 8.6 Hz, 2 H), 3.50–3.37 (m, 2 H), 1.86 (s, 1 H), 1.68 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 115.57 (t, $^1J_{C-F}$ = 255.3 Hz, CHF_2), 77.81 (t, $^3J_{C-F}$ = 1.9 Hz, C-O), 58.51 (2 × CH_2), 23.45 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –79.31.

MS (ES-API): *m*/*z* (%) = 138 (100) $[M + 1]^+$.

Anal. Calcd for $C_5H_9F_2NO$: C, 43.79; H, 6.62; N, 10.21. Found: C, 43.59; H, 6.73; N, 10.24.

2-((Difluoromethoxy)methyl)piperidine (4j)

Distilled at 35 °C (1 mmHg).

Yield: 31.55 g (63.5%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.19 (t, *J* = 74.9 Hz, 1 H), 3.78 (dd, *J* = 9.7, 3.6 Hz, 1 H), 3.65 (dd, *J* = 9.7, 8.4 Hz, 1 H), 3.07 (ddt, *J* = 11.8, 4.1, 2.1 Hz, 1 H), 2.78 (ddt, *J* = 11.3, 8.3, 3.1 Hz, 1 H), 2.62 (td, *J* = 11.7, 2.8 Hz, 1 H), 1.89 (s, 1 H), 1.86–1.76 (m, 1 H), 1.67–1.51 (m, 2 H), 1.38 (dddd, *J* = 34.7, 16.4, 12.7, 8.9 Hz, 2 H), 1.14 (tdd, *J* = 12.4, 11.0, 3.9 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 116.03 (t, $^1J_{C-F}$ = 260.3 Hz, CHF_2), 68.09 (t, $^3J_{C-F}$ = 4.9 Hz, CH_2O), 55.35, 46.41, 28.40, 26.12, 24.19.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.96, –84.38, –84.54, –84.96.

MS (ES-API): *m*/*z* (%) = 166 (100) $[M + 1]^+$.

Anal. Calcd for $C_7H_{13}F_2NO$: C, 50.90; H, 7.93; N, 8.48. Found: C, 50.73; H, 7.99; N, 8.43.

3-((Difluoromethoxy)methyl)piperidine (4k)

Distilled at 40 °C (1 mmHg).

Yield: 29.73 g (63.4%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (t, *J* = 75.1 Hz, 1 H), 3.73–3.57 (m, 2 H), 3.10 (d, *J* = 11.9 Hz, 1 H), 2.98 (d, *J* = 12.1 Hz, 1 H), 2.54 (td, *J* = 11.7, 3.0 Hz, 1 H), 2.35 (dd, *J* = 12.0, 9.9 Hz, 1 H), 1.78 (q, *J* = 5.4, 4.4 Hz, 2 H), 1.65 (dt, *J* = 13.4, 3.5 Hz, 1 H), 1.57 (s, 1 H), 1.53–1.37 (m, 1 H), 1.20–1.04 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 115.99 (t, $^1J_{C-F}$ = 259.9 Hz, CHF_2), 66.33 (t, $^3J_{C-F}$ = 5.2 Hz, CH_2O), 49.67, 46.86, 36.77, 27.57, 25.80.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.65, –84.66.

MS (ES-API): *m*/*z* (%) = 166 (100) $[M + 1]^+$.

Anal. Calcd for $C_7H_{13}F_2NO$: C, 50.90; H, 7.93; N, 8.48. Found: C, 51.08; H, 8.12; N, 8.54.

4-((Difluoromethoxy)methyl)piperidine (4l)

Distilled at 39 °C (1 mmHg).

Yield: 32.2 g (77.8%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.13 (t, *J* = 75.2 Hz, 1 H), 3.60 (d, *J* = 6.2 Hz, 2 H), 3.03 (dt, *J* = 12.4, 3.1 Hz, 2 H), 2.55 (td, *J* = 12.2, 2.5 Hz, 2 H), 1.67 (ddt, *J* = 15.5, 12.3, 3.0 Hz, 3 H), 1.58 (s, 1 H), 1.22–1.03 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 116.04 (t, $^1J_{C-F}$ = 259.7 Hz, CHF_2), 68.25 (t, $^3J_{C-F}$ = 5.0 Hz, CH_2O), 46.09 (2 × CH_2N), 36.09, 46.09 (CH_2), 29.83, 46.09 (2 × CH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.47.

MS (ES-API): *m*/*z* (%) = 166 (100) $[M + 1]^+$.

Anal. Calcd for $C_7H_{13}F_2NO$: C, 50.90; H, 7.93; N, 8.48. Found: C, 50.84; H, 7.81; N, 8.37.

Synthesis of Compounds 4n–p; General Procedure for LiOH Hydrolysis

The starting compound was dissolved in THF (2 mL/mmol) and the solution of lithium hydroxide monohydrate (1.5 equiv) in water (2 mL/mmol) was added in one portion. The resulting mixture was stirred overnight.

The reaction mixture was diluted with MTBE and the aqueous layer was separated. The organic layer was extracted twice with water and then discarded. The combined aqueous layers were washed with MTBE twice and then acidified with an equimolar amount of sodium hydrosulfate. The resulting mixture was extracted twice with DCM. Combined DCM layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to obtain the appropriate compound.

(2*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(difluoromethoxy)pyrrolidine-2-carboxylic Acid (4n)

Yield: 29 g (83.2%); white powder; mp 72 °C; $[\alpha]_D$ +48.22 (MeOH, *c* = 17.8 mmol/L).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.68–12.38 (m, 1 H), 6.67 (td, *J* = 75.4, 3.5 Hz, 1 H), 4.75 (ddp, *J* = 11.9, 5.8, 2.9 Hz, 1 H), 4.19 (ddd, *J* = 13.2, 9.5, 3.3 Hz, 1 H), 3.64 (ddd, *J* = 15.0, 11.9, 5.7 Hz, 1 H), 3.32 (dd, *J* = 12.0, 3.2 Hz, 1 H), 2.57–2.50 (m, 1 H), 2.06 (tt, *J* = 9.5, 4.1 Hz, 1 H), 1.36 (d, *J* = 25.7 Hz, 9 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 173.34 and 173.01, 153.63 and 153.40, 117.30 (t, $^1J_{C-F}$ = 256.0 Hz, CHF_2), 79.53 and 79.42, 74.31 and 73.30, 57.50 and 57.26, 52.65 and 52.24, 36.57 and 35.81, 28.48 and 28.31 (3 × CH_3).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –81.74 and –81.78.

MS (ES-API): *m*/*z* (%) = 280 (100) $[M - 1]^+$.

Anal. Calcd for $C_{11}H_{17}F_2NO_5$: C, 46.98; H, 6.09; N, 4.98. Found: C, 47.13; H, 6.15; N, 4.90.

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(difluoromethoxy)pyrrolidine-2-carboxylic Acid (4o)

Yield: 21.1 g (88.6%); white solid; mp 71 °C; $[\alpha]_D$ –48.64 (MeOH, *c* = 17.8 mmol/L).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.56 (s, 1 H), 6.68 (td, *J* = 75.4, 3.2 Hz, 1 H), 4.75 (ddt, *J* = 9.0, 5.9, 2.8 Hz, 1 H), 4.19 (ddd, *J* = 13.2, 9.5, 3.3 Hz, 1 H), 3.64 (ddd, *J* = 17.2, 12.0, 5.7 Hz, 1 H), 2.60–2.50 (m, 1 H), 2.05 (tt, *J* = 9.7, 4.4 Hz, 1 H), 1.36 (d, *J* = 26.1 Hz, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.11 and 175.37, 155.14 and 153.68, 115.46 (t, $^1J_{C-F}$ = 262.5 Hz, CHF_2), 81.48 and 80.94, 71.63 and 70.90, 57.27, 53.42, 52.85 and 52.05, 36.89 and 35.46, 28.29 and 28.16 (3 × CH_3).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –81.69 and –81.74.

MS (ES-API): *m*/*z* (%) = 280 (100) $[M - 1]^+$.

Anal. Calcd for $C_{11}H_{17}F_2NO_5$: C, 46.98; H, 6.09; N, 4.98. Found: C, 47.04; H, 6.00; N, 4.75.

(2*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(difluoromethoxy)pyrrolidine-2-carboxylic Acid (4p)

Yield: 9.79 g (85.6%); white powder; mp 87 °C; $[\alpha]_D$ +38.38 (MeOH, *c* = 17.8 mmol/L).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.73 (s, 1 H), 6.74 (t, *J* = 75.4 Hz, 1 H), 4.78 (dt, *J* = 4.6, 2.2 Hz, 1 H), 4.12 (dt, *J* = 10.2, 7.8 Hz, 1 H), 3.63–3.39 (m, 2 H), 2.43–2.28 (m, 1 H), 2.10 (tdd, *J* = 13.8, 7.6, 5.1 Hz, 1 H), 1.35 (d, *J* = 22.1 Hz, 9 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 174.09 and 173.63, 153.88 and 153.40, 117.43 (t, $^{1}J_{C-F}$ = 255.9 Hz, CHF_2), 79.78, 74.37 and 73.78, 57.68 and 57.40, 52.61 and 52.34, 36.68 and 35.88, 28.46 and 28.28 (3 × CH_3).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –81.61 (d, J = 12.2 Hz).

MS (ES-API): m/z (%) = 280 (100) $[M - 1]^+$.

Anal. Calcd for $C_{11}H_{17}F_2NO_5$: C, 46.98; H, 6.09; N, 4.98. Found: C, 46.88; H, 5.94; N, 5.07.

(2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(difluoromethoxy)pyrrolidine-2-carboxylic Acid (4q)[21]

Yield: 9.79 g (86%); white powder; mp 87 °C.

Synthesis of 4r–u; General Procedure for Benzyl Deprotection

The corresponding compound **3r–u** was dissolved in MeOH (15 mL/mmol) and added to the suspension of freshly prepared Raney Ni (1 g per 1 g of compound) in MeOH (5 mL/mmol) and the resulting suspension was vigorously stirred overnight.

The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was re-dissolved in MeOH (15 mL/mmol) and 10% Pd/C (5 mol%) was added. The resulting mixture was degassed and backfilled with hydrogen three times and the resulting mixture was hydrogenated at 1 atm (balloon) overnight.

The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in aq. sodium bicarbonate solution and the resulting solution was washed twice with DCM. The aqueous layer was acidified with an equimolar amount of sodium hydrosulfate. The resulting mixture was extracted twice with DCM. The combined DCM layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to obtain the appropriate compound.

(2*R*,4*S*)-1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-4-(difluoromethoxy)pyrrolidine-2-carboxylic Acid (4r)

Yield: 8.3 g (81%); beige solid; mp 63 °C; $[\alpha]_D$ +39.01 (EtOH, c = 24.8 mmol/L).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (dd, J = 22.8, 7.6 Hz, 2 H), 7.55 (q, J = 11.3, 9.4 Hz, 2 H), 7.40 (q, J = 12.2, 9.8 Hz, 2 H), 7.34 (d, J = 12.0 Hz, 1 H), 6.23 (td, J = 73.0, 15.4 Hz, 1 H), 4.87 (d, J = 21.7 Hz, 1 H), 4.61–4.10 (m, 4 H), 3.71 (qd, J = 11.9, 10.2, 3.8 Hz, 2 H), 2.57–2.18 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.71, 155.17, 153.73, 143.10, 140.79, 127.30, 127.16, 126.60, 124.47, 124.28, 119.53, 119.44, 115.04, 70.96, 67.70, 67.24, 57.19, 56.47, 52.20, 51.93, 46.61, 46.53, 36.79, 35.22.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.47, –83.53, –83.63.

MS (ES-API): m/z (%) = 404 (100) $[M + 1]^+$.

Anal. Calcd for $C_{21}H_{19}F_2NO_5$: C, 62.53; H, 4.75; N, 3.47. Found: C, 62.44; H, 4.73; N, 3.36.

(2*R*,4*R*)-1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-4-(difluoromethoxy)pyrrolidine-2-carboxylic Acid (4s)

Yield: 13.54 g (81%); white solid; mp 74 °C; $[\alpha]_D$ +37.89 (EtOH, c = 12.4 mmol/L).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.75 (s, 1 H), 7.87 (t, J = 7.8 Hz, 2 H), 7.64 (dt, J = 12.1, 4.4 Hz, 2 H), 7.50–7.17 (m, 4 H), 6.71 (t, J = 75.3 Hz, 1 H), 4.82 (d, J = 5.7 Hz, 1 H), 4.69–4.05 (m, 5 H), 3.72 (dt, J = 11.6, 5.7 Hz, 1 H), 3.45 (d, J = 12.0 Hz, 1 H), 2.58 (ddd, J = 14.5, 9.7, 5.6 Hz, 1 H), 2.18 (dd, J = 45.2, 14.0 Hz, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 173.11, 172.71, 154.23, 154.18, 144.25, 144.12, 141.19, 141.17, 141.10, 141.08, 128.14, 127.58, 125.72, 125.63, 125.58, 120.59, 120.56, 120.51, 117.37 (t, $^{1}J_{C-F}$ = 255.9 Hz, CHF_2), 74.53, 73.67, 67.49, 67.23, 57.78, 57.52, 53.16, 52.54, 49.04, 47.11, 47.01, 36.93, 35.84.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –81.63, –81.66.

MS (ES-API): m/z (%) = 404 (100) $[M + 1]^+$.

Anal. Calcd for $C_{21}H_{19}F_2NO_5$: C, 62.53; H, 4.75; N, 3.47. Found: C, 62.71; H, 4.84; N, 3.62.

(2*S*,4*S*)-1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-4-(difluoromethoxy)pyrrolidine-2-carboxylic Acid (4t)

Yield: 15 g (83%); white powder; mp 75 °C; $[\alpha]_D$ –37.32 (EtOH, c = 12.4 mmol/L).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.72 (d, J = 74.2 Hz, 1 H), 7.88 (t, J = 7.9 Hz, 2 H), 7.64 (ddd, J = 15.3, 7.5, 3.5 Hz, 2 H), 7.50–7.20 (m, 5 H), 6.71 (t, J = 75.3 Hz, 1 H), 4.81 (dp, J = 5.7, 2.7 Hz, 1 H), 4.52–4.04 (m, 5 H), 3.71 (dt, J = 11.5, 5.7 Hz, 1 H), 3.43 (d, J = 12.0 Hz, 1 H), 2.58 (s, 1 H), 2.22–2.04 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 176.05, 174.85, 155.35, 143.77, 143.51, 141.30, 127.79, 127.68, 127.10, 126.89, 125.03, 124.94, 123.98, 119.99, 115.38 (t, $^{1}J_{C-F}$ = 262.9 Hz, CHF_2), 71.49, 70.84, 68.03, 67.68, 57.65, 57.01, 52.88, 52.66, 47.13, 37.17, 35.64.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –81.66 (d, J = 10.6 Hz).

MS (ES-API): m/z (%) = 404 (100) $[M + 1]^+$.

Anal. Calcd for $C_{21}H_{19}F_2NO_5$: C, 62.53; H, 4.75; N, 3.47. Found: C, 62.79; H, 4.63; N, 3.39.

(2*S*,4*R*)-1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-4-(difluoromethoxy)pyrrolidine-2-carboxylic Acid (4u)

Yield: 15 g (84%); white powder; mp 65 °C; $[\alpha]_D$ –38.26 (EtOH, c = 24.8 mmol/L).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (dd, J = 24.2, 7.5 Hz, 2 H), 7.55 (q, J = 11.9, 9.8 Hz, 2 H), 7.46–7.28 (m, 4 H), 6.54–6.01 (m, 1 H), 4.87 (dt, J = 23.3, 4.3 Hz, 1 H), 4.63–4.32 (m, 3 H), 4.21 (dt, J = 61.2, 6.8 Hz, 1 H), 3.72 (ddd, J = 16.6, 11.6, 6.2 Hz, 2 H), 2.64–2.14 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.71, 155.17, 153.73, 143.10, 140.79, 127.30, 127.16, 126.60, 124.47, 124.28, 119.53, 119.44, 115.04, 70.96, 67.70, 67.24, 57.19, 56.47, 52.20, 51.93, 46.61, 46.53, 36.79, 35.22.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.47, –83.52, –83.62.

MS (ES-API): m/z (%) = 404 (100) $[M + 1]^+$.

Anal. Calcd for $C_{21}H_{19}F_2NO_5$: C, 62.53; H, 4.75; N, 3.47. Found: C, 62.62; H, 4.81; N, 3.54.

(2*S*,4*R*)-1-*tert*-Butyl 2-(Chloromethyl) 4-(Difluoromethoxy)pyrrolidine-1,2-dicarboxylate (5q)

Sodium bicarbonate (22.2 g, 264.5 mmol, 4 equiv) was suspended in water (150 mL) and tetrabutylammonium sulfate (2.24 g, 6.6 mmol, 0.1 equiv) was added followed by the addition of the solution compound **4q** (18.6 g, 66.1 mmol) in DCM (150 mL). The resulting mixture was stirred for 10 minutes and then cooled to 0 °C in an ice bath. The solution of chloromethyl sulfochloridate (13.1 g, 79.4 mmol, 1.2 equiv) in DCM (10 mL) was added dropwise at 0 °C. When the addition was complete, the reaction mixture was stirred at 0 °C for 30 minutes. Then the bath was removed, and the reaction mixture was stirred at r.t. for 90 minutes.

The organic layer was separated, and the aqueous layer was extracted with DCM (2 × 100 mL). The combined organic layers were washed with water (3 × 150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 19:1) to give compound **5q**.

Yield: 10.57 g (48.5%); colorless oil; $[\alpha]_D$ –72.5 (MeOH, *c* = 15.2 mmol/L).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.23 (t, *J* = 73.2 Hz, 1 H), 5.96–5.53 (m, 2 H), 4.87 (dt, *J* = 8.8, 4.6 Hz, 1 H), 4.45 (dt, *J* = 23.4, 7.7 Hz, 1 H), 3.79–3.54 (m, 2 H), 2.50 (ddd, *J* = 23.9, 11.3, 7.3 Hz, 1 H), 2.20 (ddd, *J* = 13.2, 7.3, 5.3 Hz, 1 H), 1.44 (d, *J* = 17.9 Hz, 8 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.10, 169.89, 158.53, 153.54, 152.70, 117.13, 115.04, 112.95, 80.61, 80.40, 71.16, 70.47, 68.61, 68.43, 56.88, 56.60, 51.96, 51.70, 36.52, 35.37, 27.78, 27.66.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.04, –83.47, –83.62, –84.04.

MS (ES-API): *m*/*z* (%) = 228 (20) $[M – 1 – Boc]^+$, 180 (35) $[M – 1 – Boc – CH_2Cl]^+$.

Anal. Calcd for $C_{12}H_{18}ClF_2NO_5$: C, 43.71; H, 5.50; N, 4.25. Found: C, 43.55; H, 5.70; N, 4.34.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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