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FULL PAPER

Synthesis of 2-fluoroalkyl 4-substituted azepanes

Guillaume Masson,[a] Sarah Rioton,[a] Domingo Gomez Pardo,*[a] Janine Cossy*[a]

Abstract: Synthesis of di- or tri-substituted fluoroalkylated azepanes was achieved by ring-expansion of pyrrolidines *via* a regioselective attack of nucleophiles on a bicyclic azetidinium intermediate. A broad scope of azepanes, substituted at C4 and bearing a α-trifluoromethyl, α-difluoromethyl or α-perfluorobutyl group, can be synthesized by this method by using a wide variety of nucleophiles.

Introduction

Seven-membered *N*-heterocycles, *e.g.* azepanes, are important scaffolds present in a number of natural products, pharmaceuticals[1] and agrochemicals – Selected examples are depicted in Figure 1. According to the FDA orange book,[2] azepanes are in the top 60 most frequently used ring system in small molecular drugs.[3] It is worth mentioning that the introduction of a fluoroalkylated group in the α position of an amine can modify the physico-chemical properties of a compound, such as its metabolic stability, lipophilicity, pKa,[4] while maintaining the hydrogen bond donor properties. For example, the introduction of trifluoromethyl groups in the α position of amines was used to form bio-isosters of amides, improving in some cases the biological activity of a compound.[5] Another interesting fluoroalkyl group of interest is the difluoromethyl,[6,7] due to its capacity to form hydrogen bonding, for example with a hydroxy or a thiol group present in proteins.[8,9] Furthermore a perfluoroalkyl chain can be of great value to further increase the lipophilicity of a molecule, and some marketed drugs contain either a trifluoromethyl, difluoromethyl or perfluoroalkyl[10] motif.

Due to the importance of azepanes in medicinal chemistry, and the possibility to modulate the properties of these compounds by introducing fluorinated groups,[11], the development of methods to access α-fluoroalkylated azepanes **I** is of interest (Figure 1).

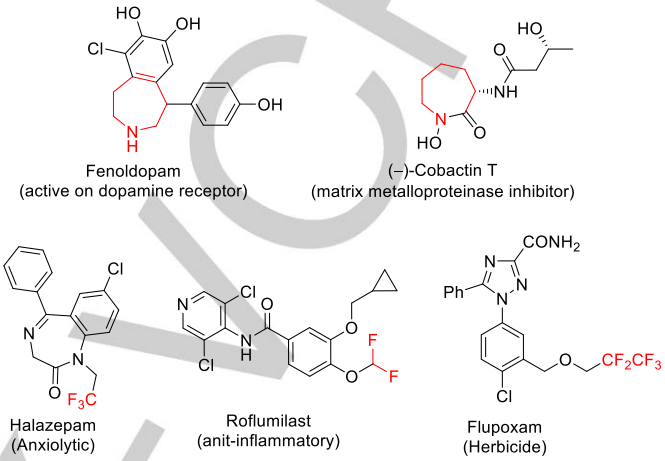
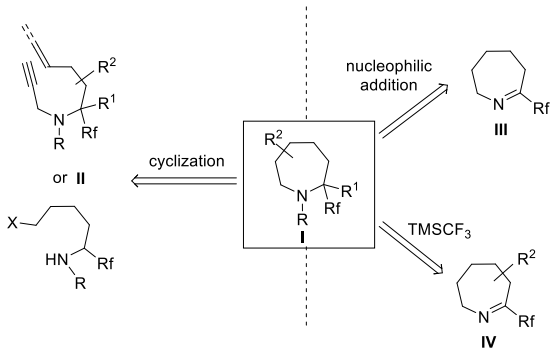


Figure 1. Azepanes in bioactive molecules and drugs containing a trifluoro-, a difluoro- or a perfluoro-alkyl group.

Different methods can be used to produce α-fluoroalkylated azepanes, either by cyclization of linear α-fluoroalkylated amines **II**,[12,13,14] addition of nucleophiles on fluoroalkylated cyclic imines **III**,[15] or addition of trifluoromethyl anions on cyclic imines **IV**.[16] However, in most cases the methods are dealing with the preparation of α-trifluoromethylated azepanes, excluding the other fluoroalkylated groups, and only few examples are reported for the synthesis of highly enantio-enriched fluoroalkylated azepanes (Scheme 1).



Scheme 1. Previous syntheses of fluoroalkylated azepanes.

In the context of our ring-expansion program,[17] we would like to report the synthesis of optically active α-trifluoromethyl-, α-difluoromethyl- and α-perfluoroalkyl- substituted azepanes **A**, which were envisaged by regioselective ring-opening of an

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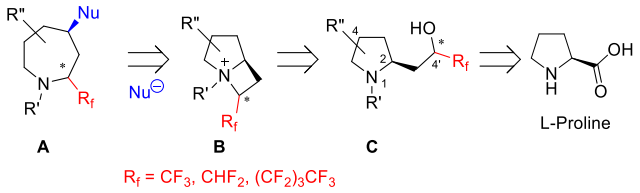
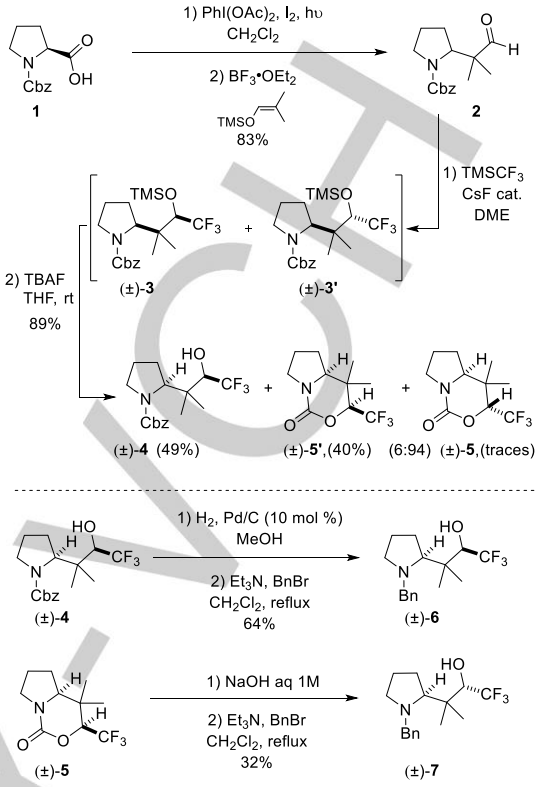
azetidinium intermediates of type **B** issued from pyrrolidines **C**. These latter would be synthesized from L-proline (Scheme 2).



Scheme 2. Strategy to access α-fluoroalkylated azepanes.

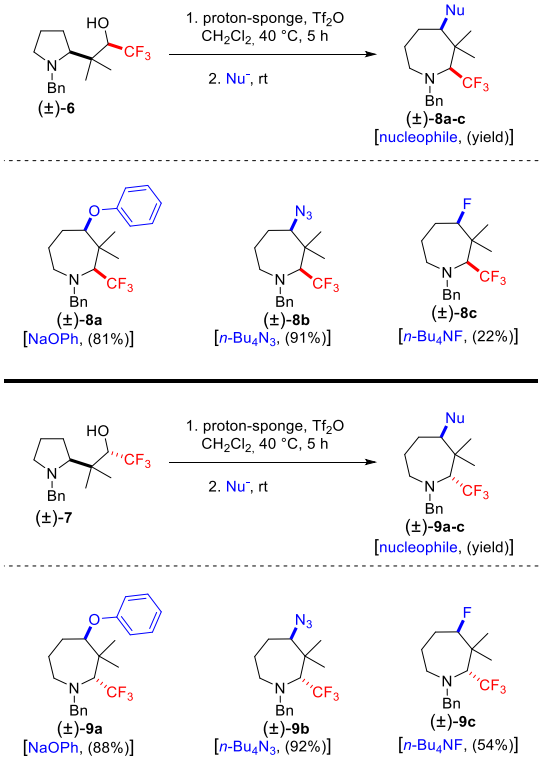
Results and Discussion

At first, the ring-expansion of pyrrolidines (±)-**6** and (±)-**7** was studied Compounds (±)-**6** and (±)-**7** were prepared from *N*-Cbz-L-proline in 4 steps. Thus, the *N*-protected proline **1** underwent an iodo-decarboxylation ($PhI(OAc)_2$, I_2, h*v*) and the resulting iminium intermediate was then treated with 2-methyl-1(trimethylsilyoxy)propene in the presence of a Lewis acid to produce aldehyde **2** (83%).[18] After addition of $TMSCF_3$ (1.6 equiv) on aldehyde **2**, in the presence of CsF (0.4 equiv), the trifluoromethyl trimethylsily ethers were obtained as a mixture of two diastereomers (±)-**3** and (±)-**3'**. After treatment of (±)-**3** and (±)-**3'** with TBAF, three products were isolated: the desired pyrrolidine (±)-**4** (49%) as a unique diastereomer, and two diasteromeric bicyclic compounds (±)-**5** and (±)-**5'**. It seems that the diastereomer (±)-**3'** underwent a cyclization to form the bicylic compound (±)-**5'** (40%), while the other diastereoisomer (±)-**3** almost did not cyclize as only traces of (±)-**5** were detected. Compounds (±)-**4** and (±)-**5** were then transformed to the corresponding *N*-benzyl pyrrolidines (±)-**6** and (±)-**7**. The transformation of *N*-Cbz pyrrolidines to the *N*-benzyl pyrrolidines is of importance as the ring-expansion is achieved via an azetidinium intermediate which is coming from an intramolecular nucleophilic attack of the nitrogen of the pyrrolidine onto the C4' of the side chain. Thus, after a hydrogenolysis/*N*-benzylation sequence, (±)-**4** was transformed to pyrrolidine (±)-**6** in 64% yield. To realize the transformation of (±)-**5** to pyrrolidine (±)-**7**, two steps were necessary. After treatment of (±)-**5** with NaOH, the pyrrolidine was *N*-benzylated (BnBr, Et_3N, CH_2Cl_2) leading to the formation of (±)-**7** (Scheme 3).



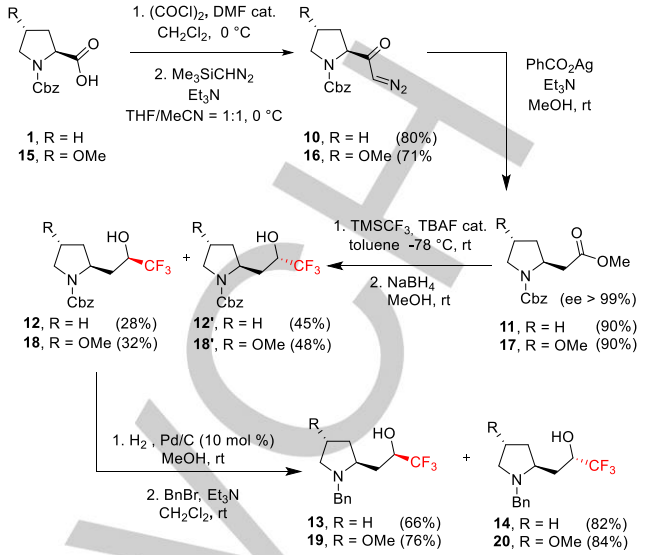
Scheme 3. Synthesis of the racemic trifluoromethyl pyrrolidines (±)-**6** and (±)-**7**.

Having pyrrolidines (±)-**6** and (±)-**7** in hand, these latter were treated under the previously tuned up conditions allowing the ring-expansion of pyrrolidines to piperidines,[17c] e.g. with Tf_2O (1.1 equiv) in the presence of the 1,8-bis-(dimethylamino)naphthalene (proton-sponge) (2.0 equiv), in CH_2Cl_2 followed by the addition of a nucleophile. After optimization of the conditions, the best yield in azepane (±)-**8** was obtained from (±)-**6** when the first step (formation of the azetidinium) was realized in refluxing CH_2Cl_2 for 5 h, and the second step (ring-opening of the azetidinium by a nucleophile) was achieved at room temperature (Scheme 4). By using sodium phenoxide as the nucleophile, (±)-**8a** was isolated with an excellent yield of 81%. *n*-Tetrabutylammonium azide and *n*-tetrabutylammonium fluoride were also used as nucleophiles and led respectively to the corresponding azepanes (±)-**8b** and (±)-**8c** in 91% and 22% yield respectively. It is worth mentioning that pyrrolidine (±)-**7** was also transformed to azepanes (±)-**9a–c** in moderate to excellent yields, by using the same nucleophiles as for the transformation of (±)-**6** to (±)-**8a–c**. In all cases, the azepanes were obtained with diastereoselectivities superior to 95:5 (Scheme 4).



Scheme 4. Ring-expansion of (±)-**6** and (±)-**7** using different nucleophiles.

As the ring-expansion of pyrrolidines (±)-**6** and (±)-**7** was successful in the racemic series, the synthesis of optically active pyrrolidines **C** was considered using an Arndt-Eistert homologation of L-proline[19] *via* a diazoketone. To synthesize diazoketone **10**, *N*-Cbz-proline **1** was treated with oxalyl chloride (1.3 equiv, CH_2Cl_2, DMF cat.), and the resulting acyl chloride was then treated with (trimethylsilyl)diazomethane (2.2 equiv, Et_3N, THF/CH_3CN, 0°C, 5 h) to afford the desired diazoketone in 80% yield. After a Wolff rearrangement, induced by silver benzoate, the ketene intermediate was trapped with methanol to give the corresponding methyl ester **11** (90%, 99% ee).[19] A first attempt to synthesize **13** and **14** from **11** was realized but a racemization was observed, as the ee dropped from 99% to 30% (*cf.* Supporting Information). In order to overcome this racemization, we decided to modify the first sequence of reaction to access pyrrolidines **13** and **14** from the pyrrolidino-ester **11** (ee > 99%). The pyrrolidino-ester **11** was directly treated with $TMSCF_3$/TBAF (toluene, –78°C to rt) and the resulting trifluoromethyl ketone was reduced by $NaBH_4$ (MeOH, rt). The trifluoromethyl alcohols **12** and **12'** were isolated in 28% and 45% respectively. After a hydrogenolysis/*N*-benzylation sequence, the pyrrolidino-alcohols **13** and **14** were isolated in 66% and 82% respectively (dr > 95:5). We were also able to perform the same sequence starting from the *trans*-4-methoxy *N*-Cbz-L-proline **15** to access the corresponding pyrrolidines **19** and **20**, bearing a methoxy group at C4 (Scheme 5).



Scheme 5. Synthesis of enantio-enriched trifluoromethyl pyrrolidines.

Starting from **11**, we were also able to access the difluoromethyl and perfluorobutyl derivatives (Scheme 6). Difluoromethyl pyrrolidines **22** and **22'** were synthetized in 3 steps from **11**. The pyrrolidino-ester **11** was treated with the anion of diethyl(difluoromethyl)phosphonate generated with LDA (THF, –78°C).[20] The resulting difluoro ketophosphonate **21** was obtained in 46% yield. After cleavage of the phosphonate (MeOH, MeONa, 0°C)[20] and reduction ($NaBH_4$, MeOH, rt), the pyrrolidines **22** and **22'** were formed in a 40:60 ratio. After a hydrogenolysis/*N*-benzylation sequence, the *N*-benzyl pyrrolidines **23** and **24** were isolated in 74% and 78% yield respectively from **22** and **22'** (Scheme 6).

Perfluorobutyl pyrrolidines **26** and **27** were synthetized in 4 steps from the pyrrolidino-ester **11** (Scheme 6). At first, the pyrrolidino-ester **11** was reacted with perfluoro butyllithium (perfluorobutyl iodide, MeLi.LiBr, THF, –78 °C) to form a perfluorobutyl ketone intermediate, which is subsequently reduced with $NaBH_4$[21] to form the two diastereomeric perfluorobutyl alcohols **25** and **25'**. After cleavage of the carbamate by hydrogenolysis and *N*-benzylation, the two diastereomes, *N*-benzyl perfluorobutyl pyrrolidines **26** and **27**, were obtained in 62% and 68% yield respectively (Scheme 6).

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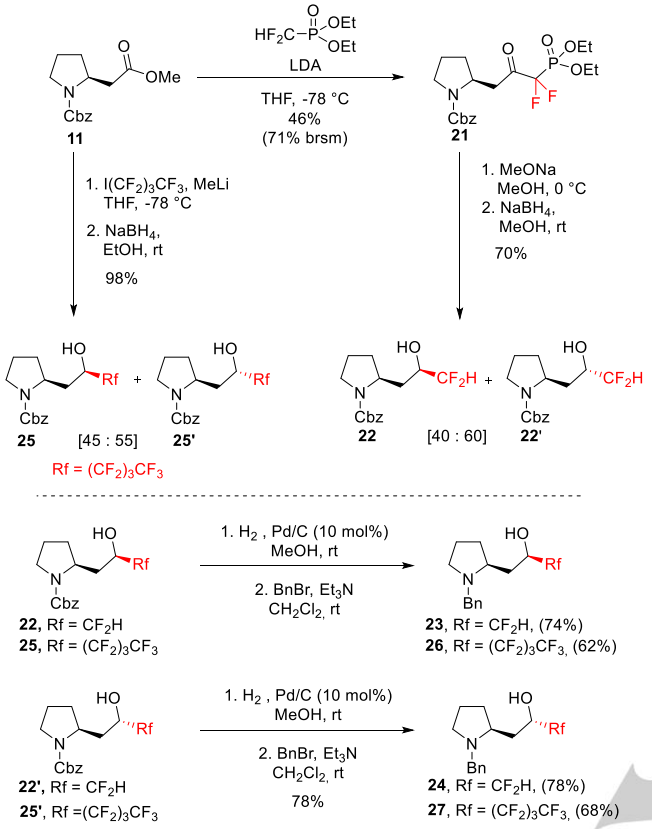
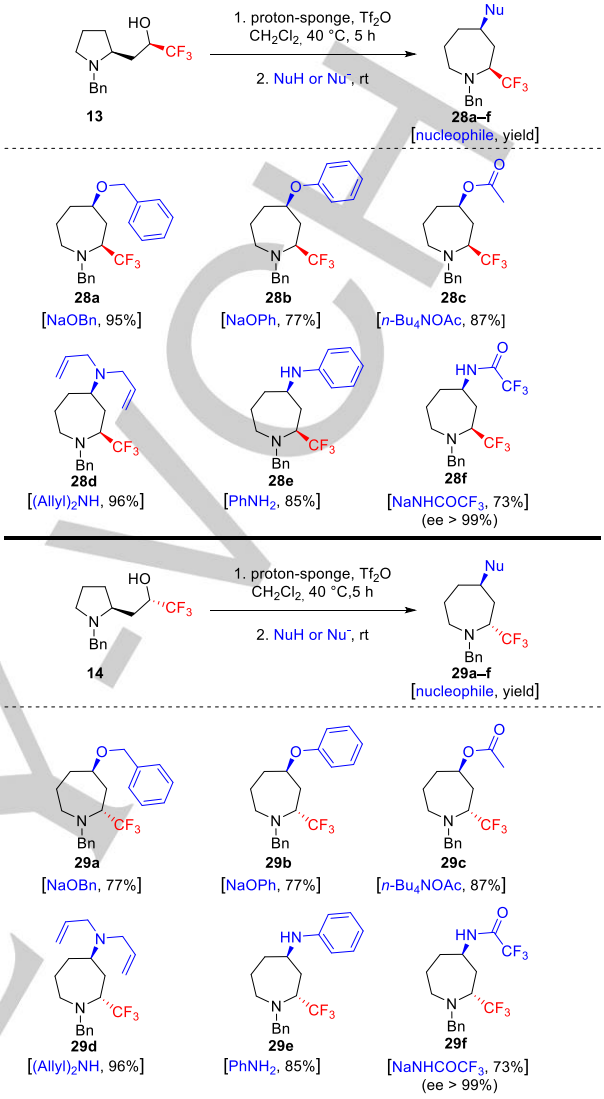


Scheme 6. Synthesis of difluoromethyl and perfluorobutyl pyrrolidines.

The ring-expansion was also performed on **13** and **14**. When **13** and **14** were treated with Tf_2O (1.1 equiv) in the presence of the proton sponge (2.0 equiv) in refluxing CH_2Cl_2, followed by the addition of nucleophiles such as alcoholates, amines, azide, sodium acetimidate, thiol, hydride, cyanide, malonate, cuprate, the corresponding azepanes **28** and **29** were isolated in good yields (52% to 95%).[22] The results are reported in Scheme 7.



Scheme 7. Ring-expansion of **13** and **14** using different nucleophiles.

The enantiomeric excess measured by chiral supercritical fluid chromatography (SFC) for **28f** and **29f**, revealed to be superior to 99%. As expected, a complete transfer of chirality from the starting proline to the newly formed azepanes occured. It is worth mentioning that as **28f** and **29f** were crystalline, an X-ray diffraction (CCDC 1850086 and 1850085) was realized confirming the relative and absolute configuration of the stereogenic centers (Figure 2).

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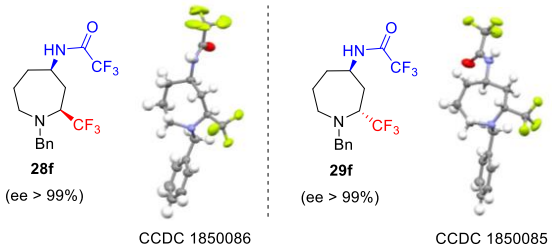
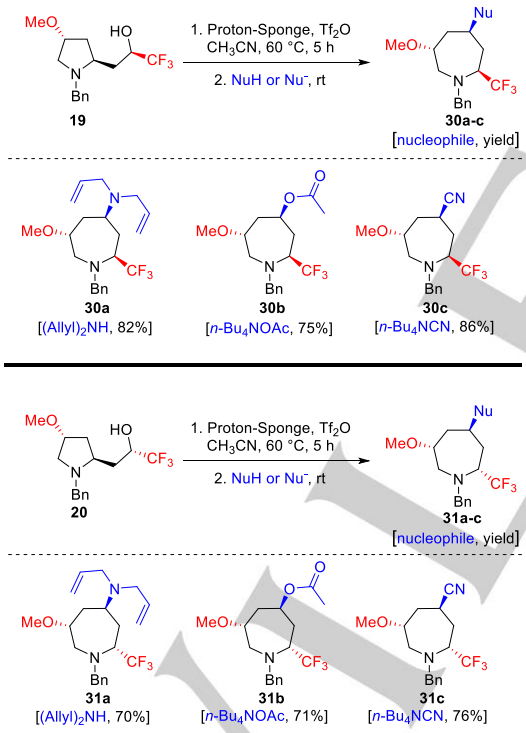


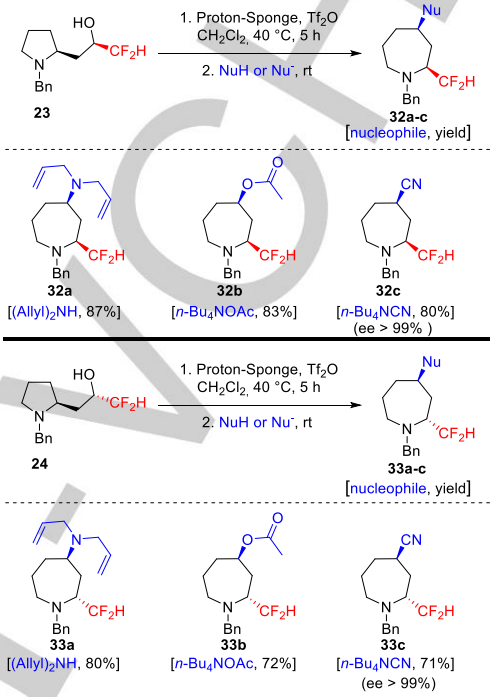
Figure 2. X-ray diffraction of **28f** and **29f**.

Pyrrolidines **19** and **20** synthesized from 3-hydroxyproline were also involved in the ring-expansion. However, by using the initial reaction conditions (proton-sponge, Tf_2O, CH_2Cl_2, 40 °C) we were unable to achieve a complete conversion of **19** to the azetidinium. Fortunately, by switching CH_2Cl_2 to CH_3CN and heating the reaction up to 60 °C, the complete disappearance of the pyrrolidines **19** and **20** was observed by TLC. After addition of a nucleophiles such as an amine, an acetate or a cyanide, the corresponding azepanes were formed with a good overall yield for both diastereomers (Scheme 8).



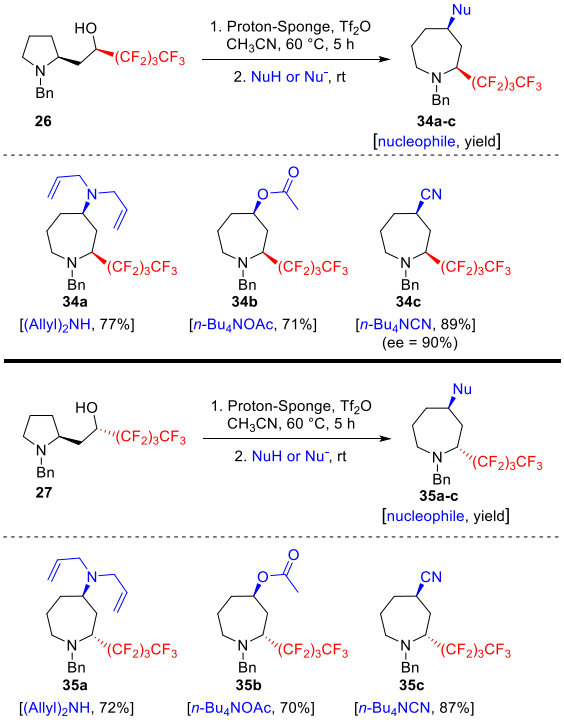
Scheme 8. Ring-expansion of pyrrolidines **19** and **20** using different nucleophiles.

The two diastereomers **23** and **24** bearing a difluoromethyl group were submitted to the ring-expansion conditions using different nucleophiles (Tf_2O, proton-sponge, then addition of a nucleophile). Whatever the nucleophiles, the disubstituted azepanes **32a–c**, **33a–c** were formed in good to excellent yields, and with excellent diastereoselectivity and an excellent enantiomeric excess (Scheme 9).



Scheme 9. Ring-expansion of pyrrolidines **23** and **24** using different nucleophiles.

Perfluorobutyl pyrrolidines **26** and **27** were then involved in the ring-expansion process. It is worth mentioning that the presence of a perfluoroalkyl side chain instead of a CF_3 or a CF_2H group in the pyrrolidino-alcohols does not alter the rearrangement. However, due to the presence of a bulky fluorinated group, the azetidinium intermediate was difficult to form. Thus, acetonitrile was used as the solvent and the reaction was heated at 60 °C ensuring a complete formation of the azetidinium intermediate. After the addition of a nucleophile, the azepanes **34a–c** and **35a–c** were obtained with excellent yields, diastereoselectivity and enantiomeric excess (Scheme 10).



Scheme 10. Ring-expansion of pyrrolidines **26** and **27** using different nucleophiles.

As this ring-expansion allows the access to a wide variety of enantio-enriched azepanes, the access to biologically active α-trifluoromethyl azepanes could be of interest. We choose to synthetize the α-trifluoromethyl analog of azelastine, an antihistaminic and bronchodilator used in the treatment of allergy and asthma (Figure 3).

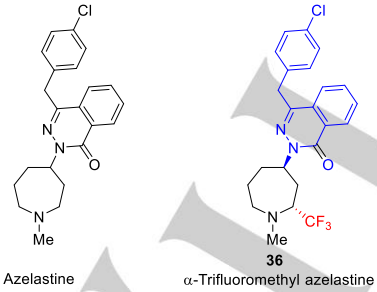
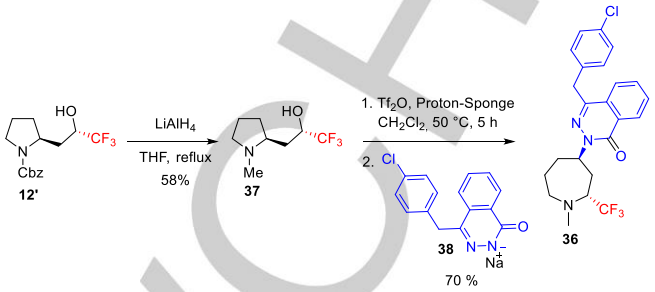


Figure 3. Azelastine and its targeted trifluoromethyl analog.

The synthesis of α-trifluoromethyl azelastine **36** started with the synthesis of *N*-methyl trifluoromethyl pyrrolidine **37** issued from the reduction of the *N*-Cbz pyrrolidine **12'** ($LiAlH_4$, THF, reflux) (Scheme 11). The *N*-methyl pyrrolidine **37** was then submitted to the ring-expansion conditions using **38**[23] as the nucleophile. The desired trifluoromethyl azelastine **36** was formed and isolated with a good yield of 70%. The trifluoromethyl analog of azelastine was obtained in 2 steps from pyrrolidine **12'** with an overall yield of 40.6 % (Scheme 11).



Scheme 11. Synthesis of α-trifluoromethyl azelastine **36**.

Conclusion

The ring-expansion of pyrrolidino-alcohols **C** to azepanes **A** *via* a bicyclic azetidinium intermediate **B** showed an excellent regioselectivity and complete transfer of chirality from L-proline to the corresponding azepanes. This ring-expansion tolerates various fluorinated groups such as a trifluoromethyl, a difluoromethyl as well as a perfluorobutyl group. The 2-fluoroalkyl 4-substituted azepanes were obtained with excellent diastereoselectivity and excellent enantiomeric excesses and should be of interest for medicinal chemists.

Experimental Section

General : All reactions were run under an argon atmosphere in oven-dried glassware unless otherwise specified. All commercially available compounds were purchased from Merck and used as received.Anhydrous solvents, such as tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. The other anhydrous solvents, CH_3CN and DMF, were purchased from Merck and used as received.Analytical thin layer chromatography (TLC) was performed over silica gel plates (Merck 60F254) visualized either with a UV lamp (254 nm) or by using a solution of phosphomolybdic acid in ethanol followed by heating. Flash chromatography was performed over silica gel (230-400 mesh).Infrared spectra (IR) were recorded on a Bruker TENSOR™ 27 (IR-FT) with attenuated total reflectance (ATR) and wavenumbers are indicated in cm^{-1}.^{1}H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz in $CDCl_3$ (unless otherwise specified) and the observed signals are reported as follows: chemical shift in parts per million from tetramethylsilane with TMS as an internal indicator (TMS δ 0 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances), integration. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ (unless otherwise specified) and the observed signals were reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator

($CDCl_3$ δ 77.16 ppm). ^{19}F NMR were recorded at 380 MHz in $CDCl_3$. Coupling constants (*J*) are reported in Hertz (Hz). All NMR spectra were obtained at rt unless otherwise specified. High-resolution mass spectra (HRMS) were performed by "Groupe de Spectrométrie de masse de Sorbonne Université campus Pierre et Marie Curie (Paris)". Optical rotations were determined using a Anton Paar MCP 100 polarimeter. The enantiomeric excesses were determined by supercritical fluid chromatography (SFC) analysis on a chiral stationary phase using a Minigram Berger SFC-Mettler Toledo apparatus.

General procedure for the synthesis of 2-trifluoromethylated-3,3-dimethyl-4-substituted azepanes

To a stirred solution of compound (±)-**6** or (±)-**7** (1 equiv) and proton sponge (2 equiv) in CH_2Cl_2 (0.1 M) was added Tf_2O (1.1 equiv) at rt. The reaction mixture was stirred for 5 h in a sealed tube at 40 °C. After 5 h, the reaction was stirred at rt and the nucleophile (2.5 equiv) was added. After 5 min the reaction was diluted with H_2O, extracted with CH_2Cl_2 and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by flash column chromatography (PE/Et_2O = 95:05) to obtain the azepanes.

(±)-(*2S*,4R)-1-Benzyl-2-(trifluoromethyl)-3,3-dimethyl-4-phenoxy azepane (8a)**

Prepared according to the general procedure from (±)-**6** (29.4 mg, 0.098 mmol, 1 equiv), proton sponge (41.8 mg, 0.195 mmol, 2 equiv), Tf_2O (0.018 mL, 0.107 mmol, 1.1 equiv), sodium phenoxide (41.5 mg, 0.244, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford compound **8a** (30 mg, 0.079 mmol, 81%). **IR (neat)**: 2929, 1598, 1585, 1493, 1454, 1369, 1299, 1240, 1171, 1126, 1089, 1027, 1014, 990, 946, 900 cm^{-1}. **^{1}H NMR ($CDCl_3$, 400 MHz)**:[24] *δ* 7.39–7.24 (m, 7H), 6.92 (tt, *J* = 7.3, 1.0 Hz, 1H), 6.87 (br d, *J* = 8.0 Hz, 2H), 4.25 (m, 1H), 4.11 (d, J_{AB} = 13.6 Hz, 1H), 4.00 (br d, J_{AB} = 12.9 Hz, 1H), 3.21 (q, *J* = 9.8 Hz, 1H), 2.99 (m, 1H), 2.75 (m, 1H), 2.00-1.86 (m, 2H), 1.70 (m, 1H), 1.46 (m, 1H), 1.25 (q, *J* =1.9 Hz, 3H), 1.18 (s, 3H). **^{13}C NMR ($CDCl_3$, 100 MHz)**: *δ* 158.5, 139.8, 129.7 (2C), 129.1 (2C), 128.5 (2C), 127.8 (d_{app}, $^1J_{C\text{-}F}$ = 292.4 Hz), 127.4, 120.6, 115.7 (2C), 82.2, 70.7 (q, $^2J_{C\text{-}F}$ = 23.8 Hz), 48.3 (C_7), 43.1, 30.4, 27.3, 22.0, 20.7. **HRMS**: calcd for $C_{22}H_{27}F_3NO$ ($M+H^+$): 378.2039; Found: 378.2039

(±)-(*2S*,4R)-4-Azido-1-benzyl-2-(trifluoromethyl)-3,3-dimethyl azepane (8b)**

Prepared according to the general procedure from (±)-**6** (52.4 mg, 0.174 mmol, 1.0 equiv), proton sponge (74.5 mg, 0.348 mmol, 2.0 equiv), Tf_2O (0.032 mL, 0.193 mmol, 1.1 equiv), and *n*-Bu_4NN_3(127 mg, 0.445 mmol, 2.6 equiv). The crude product was then purified by flash column chromatography (PE/Et_2O = 95:05) to afford compound **8b** (51.7 mg, 0.158 mmol, 91 %). **IR (neat)**: 2929, 2094, 1454, 1394, 1370, 1339, 1254, 1207, 1125, 1088, 1053, 1028, 981, 934 cm^{-1}. **^{1}H NMR ($CDCl_3$, 400 MHz)**: *δ* 7.43–7.20 (m, 5H), 4.04 (d, J_{AB} = 13.5 Hz, 1H), 3.91 (d, J_{AB} = 13.5 Hz, 1H), 3.60 (dd, *J* = 9.5, 2.3 Hz, 1H), 3.13 (q, *J* = 9.8 Hz, 1H), 2.90 (m, 1H), 2.72 (ddd, *J* = 14.2, 5.4, 5.4 Hz, 1H), 1.99 (m, 1H), 1.87 (m, 1H), 1.66 (m, 1H), 1.54 (m, 1H), 1.17 (s, 3H), 1.11 (q, *J* = 2.0 Hz, 3H). **^{13}C NMR ($CDCl_3$, 100 MHz)**: *δ* 139.3, 129.1 (2C), 128.5 (2C), 127.8 (q, $^1J_{C\text{-}F}$ = 292.1 Hz), 127.5, 70.5 (q, $^2J_{C\text{-}F}$ = 23.7 Hz), 70.1, 61.8, 47.4, 42.7, 31.3, 28.7, 23.3, 20.1 (q, $^4J_{C\text{-}F}$ = 2.3 Hz). **HRMS:** calcd for $C_{16}H_{22}F_3N_4$ ($M+H^+$): 327.1791; Found: 327.1793

(±)-(*2S*,4R)-1-Benzyl-4-fluoro-2-(trifluoromethyl)-3,3-dimethyl azepane (8c)**

Prepared according to the general procedure from (±)-**6** (49.1 mg, 0.163 mmol, 1.0 equiv), proton sponge (69.8 mg, 0.326 mmol, 2.0 equiv), Tf_2O (0.030 mL, 0.181 mmol, 1.1 equiv), and *n*-Bu_4NF (1M in THF, 0.410 mL, 0.410 mmol,2.5 equiv). The crude product was then purified by flash column chromatography (PE/Et_2O = 95:05) to afford compound **8c** (10.9 mg, 0.036 mmol, 22%). **IR (neat):** 2926, 1495, 1470, 1455, 1372, 1258, 1214, 1174, 1126, 1091, 1028, 996, 940, 902 cm^{-1}. **^{1}H NMR ($CDCl_3$, 400 MHz)**: *δ* 7.39–7.23 (m, 5H), 4.48 (dm, *J* = 46.8 Hz, 1H), 4.02 (d, J_{AB} = 13.6 Hz, 1H), 3.91 (d, J_{AB} = 13.6 Hz, 1H), 3.15 (q, *J* = 9.8 Hz, 1H), 2.92 (m, 1H), 2.72 (m, 1H), 2.04–1.85 (m, 2H), 1.75 (m, 1H), 1.47 (m, 1H), 1.17 (br s, 3H), 1.14 (d_{app}, *J* = 3.1 Hz, 3H). **^{13}C NMR ($CDCl_3$, 100 MHz)**: *δ* 139.4, 129.1 (2C), 128.5 (2C), 127.4, 126.2 (s_{app}, CF_3), 97.7 (d, $^1J_{C\text{-}F}$ = 178.7 Hz), 69.9 (qd, *J* = 24.7, 3.6 Hz), 61.6, 48.1, 42.3 (d, $^3J_{C\text{-}F}$ = 20.3 Hz), 29.4 (d, $^4J_{C\text{-}F}$ = 8.0 Hz), 28.7 (d, $^3J_{C\text{-}F}$ = 22.5 Hz), 20.8 (d, $^4J_{C\text{-}F}$ = 10.3 Hz), 20.2. **HRMS**: calcd for $C_{16}H_{22}F_4N$ ($M+H^+$): 304.1683; Found: 304.1684

(±)-(*2S,4S*)-1-Benzyl-2-(trifluoromethyl)-3,3-dimethyl-4-phenoxy azepane (9a)

Prepared according to the general procedure from (±)-**7** (41.4 mg, 0.137 mmol, 1.0 equiv), proton sponge (58.9 mg, 0.275 mmol, 2.0 equiv), Tf_2O (0.025 mL, 0.151 mmol, 1.1 equiv), sodium phenoxide (58.4 mg, 0.344 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/Et_2O = 95:05) to afford compound **9a** (45.8 mg, 0.121 mmol, 88 %). **IR (neat)**: 2930, 1598, 1585, 1493, 1453, 1391, 1361, 1327, 1298, 1237, 1194, 1154, 1132, 1098, 1070, 1028, 1010, 955 cm^{-1}. **^{1}H NMR ($CDCl_3$, 400 MHz**): *δ* 7.34–7.15 (m, 7H), 6.93–6.81 (m, 3H), 4.17 (m, 1H), 4.13 (d, J_{AB} = 14.0 Hz), 3.89 (d, J_{AB} = 13.9 Hz, 1H), 3.22 (q, *J* = 10.1 Hz, 1H), 2.84 (m, 1H), 2.65 (m, 1H), 1.97–1.62 (m, 3H), 1.43 (m, 1H), 1.24 (s, 3H), 1.14 (q, *J* = 1.6 Hz, 3H). **^{13}C NMR ($CDCl_3$, 100 MHz)**:[24] *δ* 158.5, 139.8, 129.8 (2C), 128.8 (2C), 128.4 (2C), 127.2, 120.9, 116.0 (2C), 84.7, 71.6 (d_{app}, $^2J_{C\text{-}F}$ = 29.0 Hz), 42.6, 26.6, 25.1 (C_9), 23.9, 21.3. **HRMS**: calcd for $C_{22}H_{27}F_3NO$ ($M+H^+$): 378.2039; Found: 378.2039

(±)-(*2S*,4S)-4-Azido-1-benzyl-2-(trifluoromethyl)-3,3-dimethyl azepane (9b)**

Prepared according to the general procedure from (±)-**7** (41.0 mg, 0.136 mmol, 1.0 equiv), proton sponge (58.3 mg, 0.272 mmol, 2.0 equiv), Tf_2O (0.025 mL, 0.151 mmol, 1.1 equiv), and *n*-Bu_4NN_3 (98.3 mg, 0.346 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/Et_2O = 95:05) to afford compound **9b** (40.8 mg, 0.125 mmol, 92 %). **IR (neat)**: 2933, 2095, 1470, 1454, 1388, 1366, 1323, 1250, 1192, 1155, 1133, 1099, 1041, 1028, 982, 951, 928 cm^{-1}. **^{1}H NMR ($CDCl_3$, 400 MHz)**: *δ* 7.38–7.22 (m, 5H), 4.05 (br d, J_{AB} = 13.6 Hz, 1H), 3.89 (d, J_{AB} = 13.7 Hz, 1H), 3.49 (m, 1H), 3.14 (q, *J* = 10.3 Hz, 1H), 2.85 (m, 1H), 2.73 (m, 1H), 1.98–1.77 (m, 3H), 1.61 (m, 1H), 1.16 (br s, 3H), 1.12 (br s, 3H). **^{13}C NMR ($CDCl_3$, 100 MHz)**:[24] *δ* 139.4, 129.0 (2C), 128.5 (2C), 128.0 (q, *J* = 291.6 Hz), 127.4, 71.9 (q, *J* = 23.7 Hz), 71.3, 62.9, 48.2, 42.1, 27.7, 24.8, 22.7. **HRMS**: calcd for $C_{16}H_{22}F_3N_4$ ($M+H^+$): 327.1791; Found: 327.1793

(±)-(*2S,4R*)-1-Benzyl-4-fluoro-2-(trifluoromethyl)-3,3-dimethyl azepane (9c)

Prepared according to the general procedure from (±)-**7** (56.3 mg, 0.187 mmol, 1.0 equiv), proton sponge (80.1 mg, 0.374 mmol, 2.0 equiv), Tf_2O (0.034 mL, 0.205 mmol, 1.1 equiv), and *n*-Bu_4NF (1M in THF, 0.467 mL, 0.467 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/Et_2O = 95:05) to afford compound **9c** (30.8 mg, 0.102 mmol, 54%). **IR (neat)**: 2939, 1495, 1479, 1454, 1370, 1355, 1248, 1205, 1155, 1135, 1100, 1076, 1000, 1006, 981, 954, 926 cm^{-1}. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.40–7.20 (m, 5H), 4.47 (dd_{app}, J = 45.5, 10.0, 1H), 4.04 (d, J_{AB} = 13.7 Hz, 1H), 3.87 (d, J_{AB} = 13.8 Hz, 1H), 3.15 (qd, J = 10.4, 2.9 Hz, 1H), 2.83 (m, 1H), 2.69 (m, 1H), 2.05–1.79 (m, 2H), 1.73 (m, 1H), 1.59 (m, 1H), 1.21**–**1.14 (m, 6H). **^{13}C NMR ($CDCl_3$, 100 MHz)**:[24] δ 139.4, 128.9 (2C), 128.5 (2C), 127.9 (d_{app}, $^1J_{C\text{-}F}$ = 289.9 Hz), 127.4, 99.3 (d, $^1J_{C\text{-}F}$ = 173.6 Hz), 70.9, 60.8 (C_{10}), 48.7, 28.6 (d, $^2J_{C\text{-}F}$ = 19.5 Hz), 23.7, 23.2, 20.8 (d, $^3J_{C\text{-}F}$ = 11.9 Hz). **HRMS**: calcd for $C_{16}H_{22}F_4N$ ($M+H^+$): 304.1683; Found: 304.1685

(2*S*,4*S*,6*R*)-4-*N*,*N*-Diallylamine-1-benzyl-6-methoxy-2-(trifluoromethyl)azepan (30a)

Prepared according to the general procedure from **19** (35 mg, 0.115 mmol, 1 equiv), proton sponge (50 mg, 0.29 mmol, 2 equiv), Tf_2O (0.021 mL, 0.13 mmol, 1.1 equiv), and diallylamine (0.035 mL, 0.288 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford **30a** (36 mg, 0.084 mmol, 82%) as a colorless oil. **$[\alpha]_D^{20}$** –12.4 (*c* 2.05, $CHCl_3$) **IR (neat)**: 2932, 1720, 1643, 1603, 1495, 1455, 1365, 1273, 1155, 1114, 1029, 989, 919 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.38 (d, J = 7.2 Hz, 2H), 7.26 (m, 3H), 5.80 (m, 2H), 5.14 (m, 4H), 4.34 (d, J_{AB} = 13.5 Hz, 1H), 3.90 (d, J_{AB} = 13.4 Hz, 1H), 3.33–3.31 (m, 1H), 3.31 (s, 3H), 3.28–3.19 (m, 1H), 3.18–2.97 (m, 7H), 2.24–2.09 (m, 2H), 1.56 (ddd, J = 14.0, 12.0, 9.4 Hz, 1H), 1.41 (ddd, J = 14.0, 11.1, 3.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 139.9, 137.2 (2C), 129.3 (2C), 128.3 (2C), 128.1 (q, $^1J_{C\text{-}F}$ = 291.6 Hz), 127.1, 117.0 (2C), 78.5, 60.5, 58.3 (q, $^2J_{C\text{-}F}$ = 26.5 Hz), 56.5, 53.2 (2C), 51.5, 49.6, 35.9, 32.0. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: δ –73.0 (s, 3F). **HRMS**: calcd for $C_{21}H_{30}F_3N_2O$ ($M+H^+$): 383.2305. Found: 383.2300.

(2*S*,4*S*,6*R*)-4-Acetate-1-benzyl-6-methoxy-2-(trifluoromethyl)azepane (30b)

Prepared according to the general procedure from **19** (35 mg, 0.115 mmol, 1 equiv), proton sponge (50 mg, 0.23 mmol, 2 equiv), Tf_2O (0.021 mL, 0.13 mmol, 1.1 equiv), and tetrabutylammonium acetate (87 mg, 0.29 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford compound **30b** (30 mg, 0.087 mmol, 75%) as a colorless oil.

$[\alpha]_D^{20}$ –12.4 (*c* 2.05, $CHCl_3$) **IR (neat)**: 2930, 1735, 1495, 1454, 1366, 1233, 1163, 1115, 1098, 1076, 1025, 942 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.39 (d, J = 7.22 Hz, 2H), 7.32 (t, J = 7.1 Hz, 2H), 7.25 (m; 1H), 5.15 (tt_{app}, J = 10.1, 2.5 Hz, 1H), 4.37 (d, J_{AB} = 13.7 Hz, 1H), 3.93 (d, J_{AB} = 13.7 Hz, 1H), 3.48–3.38 (m, 1H), 3.38–3.32 (m, 1H), 3.28 (s, 3H), 3.13–3.03 (m, 2H), 2.32–2.19 (m, 2H), 2.04 (s, 3H), 1.89 (m, 1H), 1.68 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 170.2, 139.5, 129.0 (2C), 128.4 (2C), 127.4 (q, $^1J_{C\text{-}F}$ = 289.1 H), 127.3, 77.6, 69.0, 60.2, 57.8 (q, $^2J_{C\text{-}F}$ = 26.9 Hz), 56.6, 48.9, 38.9, 34.3, 21.4. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: δ –73.5 (s, 3F). **HRMS**: calcd for $C_{17}H_{23}F_3NO_3$ ($M+H^+$): 346.1625. Found: 346.1624.

(2*S*,4*S*,6*R*)-1-Benzyl-4-carbonitril-6-methoxy-2-(trifluoromethyl)azepane (30c)

Prepared according to the general procedure from **19** (35 mg, 0.115 mmol, 1 equiv), proton sponge (50 mg, 0.23 mmol, 2 equiv), Tf_2O (0.021 mL, 0.13 mmol, 1.1 equiv), and tetrabutylammonium cyanide (82 mg, 0.29 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford **30c** (31 mg, 0.099, 86%) as a colorless oil. **$[\alpha]_D^{20}$** –3.4 (*c* 0.95, $CHCl_3$) **IR (neat):** 2931, 1684, 1494, 1455, 1382, 1362, 1257, 1205, 1161, 1098, 1072, 1029, 1006, 965, 906 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.41–7.25 (m, 5H), 4.28 (d, J_{AB} = 13.2 Hz, 1H), 3.93 (d, J_{AB} = 13.2 Hz, 1H), 3.40–3.29 (m, 1H), 3.34 (s, 3H), 3.22 (m, 1H), 3.18–3.12 (m, 2H), 3.05 (m, 1H), 2.50–2.35 (m, 2H), 1.87 (m, 1H), 1.69 (ddd, J = 14.9, 11.6, 3.6 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 138.9, 129.3 (2C), 128.6 (2C), 127.6, 127.4 (q, $^1J_{C\text{-}F}$ = 294.9 Hz), 122.8, 77.8, 60.0, 57.4 (q, $^2J_{C\text{-}F}$ = 26.1 Hz), 56.6, 49.3, 38.1, 32.5, 22.7. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: δ –71.9 (s, 3F). **HRMS**: calcd for $C_{16}H_{20}F_3N_2O$ ($M+H^+$): 313.1522. Found: 313.1521.

(2*R*,4*S*,6*R*)-4-*N*,*N*-Diallyl-1-benzyl-6-methoxy-2-(trifluoromethyl)azepane (31a)

Prepared according to the general procedure from **20** (45 mg, 0.148 mmol, 1 equiv), proton sponge (64 mg, 0.296 mmol, 2 equiv), Tf_2O (0.027 mL, 0.163 mmol, 1.1 equiv), and diallylamine (0.046 mL, 0.37 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford **31a** (40 mg, 0.104, 70%) as a colorless oil. **$[\alpha]_D^{20}$** +5 (*c* 0.95, $CHCl_3$) **IR (neat)**: 2931, 1727, 1642, 1454, 1364, 1272, 1154, 1111, 1097, 1053, 1028, 990, 918 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.32–7.15 (m, 5H), 5.81 (m, 2H), 5.28–4.99 (m, 4H), 3.95 (d, J_{AB} = 14.0 Hz, 1H), 3.90 (d, J_{AB} = 14.0 Hz, 1H), 3.44–3.28 (m, 3H), 3.17–3.06 (m, 4H), 3.11 (s, 3H) 2.86 (dd_{app}, J = 15.5, 6.6 Hz, 1H), 2.65 (dd_{app}, J = 15.5, 3.6 Hz, 1H), 2.06–1.86 (m, 3H), 1.76 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 139.8, 136.0 (2C), 128.6 (2C), 128.4 (2C), 127.3 (d_{app}, $^1J_{C\text{-}F}$ = 284.8 Hz) 127.2, 117.4 (2C), 77.0, 61.0 (q, $^2J_{C\text{-}F}$ = 27.0 Hz), 56.9, 56.7, 52.7 (2C), 52.0, 50.4, 34.7, 28.3. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: δ –74.1 (s, 3F). **HRMS**: calcd for $C_{21}H_{30}F_3N_2O$ ($M+H^+$): 383.2305. Found: 383.2302.

(2*R*,4*S*,6*R*)-4-Acetate-1-benzyl-6-methoxy-2-(trifluoromethyl)azepane (31b)

Prepared according to the general procedure from **20** (45 mg, 0.148 mmol, 1 equiv), proton sponge (64 mg, 0.296 mmol, 2 equiv), Tf_2O (0.027 mL, 0.163 mmol, 1.1 equiv), and tetrabutylammonium acetate (112 mg, 0.37 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford **31b** (36 mg, 0.104 mmol, 71%) as a colorless oil. **$[\alpha]_D^{20}$** +5 (*c* 0.95, $CHCl_3$) **IR (neat)**: 2942, 1739, 1495, 1454, 1370, 1275, 1240, 1155, 1115, 1074, 1090, 1026 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.33–7.19 (m, 5H), 5.29 (m, 1H), 4.05 (d, J_{AB} = 13.8 Hz, 1H), 3.87 (d, J_{AB} = 13.8 Hz, 1H), 3.38 (m, 1H), 3.31 (m, 1H), 3.03 (s, 3H), 2.88–2.70 (m, 2H), 2.35 (m, 1H), 2.26 (m, 1H), 2.09 (s, 3H), 1.93 (m, 1H), 1.44 (ddd, J = 14.1, 10.2, 2.9 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 170.1, 139.0, 128.8 (2C), 128.5 (2C), 127.5, 127.3 (q, $^1J_{C\text{-}F}$ = 286.10 Hz), 73.5, 67.5, 60.0 (q, $^2J_{C\text{-}F}$ = 27.67 Hz), 59.1, 56.9, 49.4, 38.6,

29.9, 21.3. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: δ –75.8 (s, 3F). **HRMS**: calcd for $C_{17}H_{23}F_3NO_3$ (M+H$^+$): 346.1625. Found: 346.1623.

(2*R*,4*S*,6*R*)-1-Benzyl-4-carbonitril-6-methoxy-2-(trifluoromethyl)azepane (31c)

Prepared according to the general procedure from **20** (45 mg, 0.148 mmol, 1 equiv), proton sponge (64 mg, 0.296 mmol, 2 equiv), Tf_2O (0.027 mL, 0.163 mmol, 1.1 equiv), and tetrabutylammonium cyanide (105 mg, 0.37 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford compound **31c** (35 mg, 0.112 mmol, 76%) as a colorless oil. **$[\alpha]_D^{20}$** +78 (*c* 0.65, $CHCl_3$) **IR (neat):** 2934, 1496, 1455, 1385, 1363, 1327, 1256, 1234, 1156, 1115, 1040, 1075, 1029, 1016, 986, 965 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.56–7.41 (m, 2H), 7.39–7.24 (m, 3H), 4.17 (d, J_{AB} = 13.4 Hz, 1H), 3.99 (d, J_{AB} = 13.3 Hz, 1H), 3.71 (m, 1H), 3.23 (m, 1H), 3.08 (m, 1H), 2.95–2.86 (m, 1H), 2.92 (s, 3H) 2.75 (m, 1H), 2.46 (m, 1H), 2.35 (m, 1H), 1.92 (dd$_{app}$, J = 14.2, 12.8 Hz, 1H), 1.39 (ddd, J = 13.9, 10.8, 3.9 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 138. 6, 129.7 (2C), 128.5 (2C), 127.9 (q, $^1J_{C\text{-}F}$ = 290.9 Hz) 127.7, 120.4, 76.3, 61.3 (q, $^2J_{C\text{-}F}$ = 26.8 Hz), 59.80, 56.9, 47.7, 37.4, 29.1, 23.8. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: δ –73.1 (s, 3F). **HRMS**: calcd for $C_{16}H_{20}F_3N_2O$ (M+H$^+$): 313.1522. Found: .313.1521

General procedure for the synthesis of difluoromethylated-4-substituted azepanes

To a stirred solution of compound **23** or **24** (1 equiv) and proton sponge (2 equiv) in CH_2Cl_2 (0.1 M) was added Tf_2O (1.1 equiv) at rt. The reaction mixture was stirred for 5 h in a sealed tube at 40 °C. After 5 h, the reaction was cooled to rt and the nucleophile (2.5 equiv) was added. After 5 min the reaction was diluted with H_2O, extracted with CH_2Cl_2 and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to obtain the azepanes.

(2*S*,4*R*)-4-*N*,*N*-diallylamin-1-benzyl-2-(difluoromethyl)azepane (32a)

Prepared according to the general procedure from compound **23** (30 mg, 0.117 mmol, 1 equiv), proton sponge (50.4 mg, 0.235 mmol, 2 equiv), Tf_2O (0.021 mL, 0.130 mmol, 1.1 equiv), and diallylamine (36 µL, 0.29 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford compound **32a** (34 mg, 0.102 mmol, 87%) as a colorless oil. **$[\alpha]_D^{20}$** –6 (*c* 1.9, $CHCl_3$) **IR (neat)**: 2927, 1641, 1494, 1452, 1417, 1374, 1264, 1216, 1170, 1135, 1103, 1042, 993, 917 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.33–7.21 (m, 5H), 5.84 (m, 2H), 5.50 (td$_{app}$, J = 56.9, 3.2 Hz, 1H), 5.22–5.10 (m, 4H), 3.99 (d, J_{AB} = 13.8 Hz, 1H), 3.76 (d, J_{AB} = 13.8 Hz, 1H), 3.13 (dd, J_{AB} = 14.1, 6.1 Hz, 2H), 3.04 (dd, J_{AB} = 14.1, 6.5 Hz, 2H), 2.94–2.81 (m, 4H), 2.07 (br dd, J = 14.1, 3.9 Hz, 1H), 2.00–1.79 (m, 1H), 1.68–1.54 (m, 2H), 1.44–1.32 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 140.2, 137.5 (2C), 128.8 (2C), 128.5 (2C), 127.2, 117.8 (t, $^1J_{C\text{-}F}$ = 246.12 Hz), 116.9 (2C), 62.0 (t, $^2J_{C\text{-}F}$ = 21.57 Hz), 59.7, 57.6, 53.1 (2C), 47.9, 32.2, 29.3, 22.5. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: δ –121.1 (d, J = 274.8 Hz, 1F), –130.1 (d, J = 275.1 Hz, 1F). **HRMS**: calcd for $C_{20}H_{29}F_2N_2$ (M+H$^+$): 335.2293. Found: 335.2285

(2*S*,4*R*)-4-Acetate-1-benzyl-2-(difluoromethyl)azepane (32b)

Prepared according to the general procedure from compound **23** (30 mg, 0.117 mmol, 1 equiv), proton sponge (50.4 mg, 0.235 mmol, 2 equiv), Tf_2O (0.021 mL, 0.130 mmol, 1.1 equiv), and tetrabutylammonium acetate (88.6 mg, 0.29 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford compound **32b** (29 mg, 0.097 mmol, 83%) as a colorless oil. **$[\alpha]_D^{20}$** –11 (*c* 0.6, $CHCl_3$) **IR (neat):** 2937, 1730, 1495, 1453, 1365, 1241, 1169, 1114 1024, 968, 940, 920 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.37–7.21 (m, 5H), 5.56 (td$_{app}$, J = 56.6, 3.2 Hz, 1H), 4.94 (br tt, J = 10.4, 2.8 Hz, 1H), 4.00 (d, J_{AB} = 13.9 Hz, 1H), 3.81 (d, J_{AB} = 13.9 Hz, 1H), 3.11 (m, 1H), 2.96–2.80 (m, 2H), 2.22–1.83 (m, 3H), 2.05 (s, 3H), 1.66 (m, 1H), 1.54 (m, 1H), 1.40 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 170.4, 139.7, 128.7 (2C), 128.5 (2C), 127.4, 117.3 (t, $^1J_{C\text{-}F}$ = 247.67 Hz), 73.4, 60.5 (t, $^2J_{C\text{-}F}$ = 21.19 Hz), 59.2, 47.6, 35.0, 33.0, 21.5, 20.9. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: δ –121.3 (d, J = 277.4 Hz, 1F), –130.0 (d, J = 277.1 Hz, 1F). **HRMS**: calcd for $C_{16}H_{22}F_2NO_2$ (M+H$^+$): 298.1613. Found: 298.1611

(2*S*,4*R*)-1-Benzyl-4-carbonitril-2-(difluoromethyl)azepane (32c)

Prepared according to the general procedure from compound **23** (30 mg, 0.117 mmol, 1 equiv), proton sponge (50.4 mg, 0.235 mmol, 2 equiv), Tf_2O (0.021 mL, 0.130 mmol, 1.1 equiv), and tetrabutylammonium cyanide (78.9 mg, 0.29 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford compound **32c** (25 mg, 0.094, 80%) as a colorless oil. **$[\alpha]_D^{20}$** –21 (*c* 0.8, $CHCl_3$) **IR (neat):** 2936, 2238, 1494, 1467, 1453, 1377, 1335, 1211, 1173, 1134, 1106, 1041, 1030, 971, 916 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.38–7.24 (m, 5H), 5.63 (td$_{app}$, J = 56.1, 3.3 Hz, 1H), 4.02 (d, J_{AB} = 13.8 Hz, 1H), 3.82 (d, J_{AB} = 13.8 Hz, 1H), 3.08 (m, 1H), 2.97–2.76 (m, 3H), 2.40 (dd$_{app}$, J = 15.0, 5.5 Hz, 1H), 2.23 (m, 1H), 1.99 (m, 1H), 1.78–1.45 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 139.3, 128.7 (4C), 127.6, 122.8, 116.8 (t, $^1J_{C\text{-}F}$ = 249.3 Hz), 62.0 (t, $^2J_{C\text{-}F}$ = 20.8 Hz), 59.2, 47.6, 33.7, 30.7 (t, $^2J_{C\text{-}F}$ = 3.1 Hz), 28.0, 25.5. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: δ –121.0 (d, J = 281.4 Hz, 1F), –129.2 (d, J = 281.8 Hz, 1F). **HRMS**: calcd for $C_{15}H_{19}F_2N_2$ (M+H$^+$): 265.1511. Found: 265.1509

(2*R*,4*R*)-4-*N*,*N*-Diallylamin-1-benzyl-2-(difluoromethyl)azepane (33a)

Prepared according to the general procedure from compound **24** (44 mg, 0.17 mmol, 1 equiv), proton sponge (74 mg, 0.34 mmol, 2 equiv), Tf_2O (0.031 mL, 0.190 mmol, 1.1 equiv), and diallylamine (53 µL, 0.43 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford compound **33a** (46 mg, 0.138 mmol, 80%) as a colorless oil. **$[\alpha]_D^{20}$** –10 (*c* 0.95, $CHCl_3$) **IR (neat):** 2929, 2810, 1642, 1574, 1494, 1453, 1417, 1378, 1357, 1277, 1150, 1117, 1057, 1035, 995, 984, 918 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.35–7.20 (m, 5H), 5.85 (m, 2H), 5.68 (td$_{app}$, J = 56.8, 4.7 Hz, 1H), 5.18 (m, 4H), 3.80 (d, J_{AB} = 14.2 Hz, 1H), 3.75 (d, J_{AB} = 14.2 Hz, 1H), 3.26–3.02 (m, 6H), 2.86 (m, 1H), 2.61 (m, 1H), 2.04 (ddd, J = 14.5, 9.4, 4.9 Hz 1H), 1.85–1.73 (m, 2H), 1.70–1.53 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 140.1, 137.1 (2C), 128.5 (2C), 128.4 (2C), 127.1, 118.2 (t, $^1J_{C\text{-}F}$ = 245.31 Hz), 116.9 (2C), 61.5 (t, $^2J_{C\text{-}F}$ = 22.85 Hz), 56.4, 55.6, 52.7 (2C), 51.9, 30.4, 26.8, 25.4. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: δ –120.6 (d, J = 278.5 Hz, 1F), –125.8 (d, J = 278.4 Hz, 1F). **HRMS**: calcd for $C_{20}H_{29}F_2N_2$ (M+H$^+$): 335.2293. Found: 335.2292

(*2R,4R*)-4-Acetate-1-benzyl-2-(difluoromethyl)azepane (33b)

Prepared according to the general procedure from compound **24** (44 mg, 0.172 mmol, 1 equiv), proton sponge (74 mg, 0.34 mmol, 2 equiv), Tf_2O (0.031 mL, 0.190 mmol, 1.1 equiv), and tetrabutylammonium acetate (104 mg, 0.34 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford compound **33b** (37 mg, 0.124 mmol, 72%) as a colorless oil. **$[\alpha]_D^{20}$** +1.9 (*c* 1.1, $CHCl_3$) **IR (neat)**: 2937, 1736, 1495, 1442, 1430, 1371, 1245, 1232, 1166, 1132, 1042, 1026, 990 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: *δ* 7.38–7.22 (m, 5H), 5.59 (td_{app}, *J* = 56.8, 3.6 Hz, 1H), 5.29 (m, 1H), 3.95 (d, J_{AB} = 13.9 Hz, 1H), 3.81 (d, J_{AB} = 13.9 Hz, 1H), 3.12 (m, 1H), 2.87 (m, 2H), 2.23–2.11 (m, 1H), 2.14 (s, 3H), 2.09–2.00 (m, 1H), 2.00–1.91 (m, 1H), 1.91–1.79 (m, 1H), 1.63 (m, 1H), 1.45 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: *δ* 170.3, 139.9, 128.7 (2C), 128.5 (2C), 127.3, 117.8 (t, $^1J_{C\text{-}F}$ = 247.51 Hz), 71.4, 59.8 (t, $^2J_{C\text{-}F}$ = 21.68), 57.6, 49.5, 33.4, 29.6, 21.5, 21.1. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: *δ* –120.9 (d, *J* = 276.0 Hz, 1F), –129.4 (d, *J* = 276.0 Hz, 1F). **HRMS**: calcd for $C_{16}H_{22}F_2NO_2$ ($M+H^+$): 298.1613. Found: 298.1610

(*2R,4R*)-1-Benzyl-4-carbonitril -2-(difluoromethyl)azepane (33c)

Prepared according to the general procedure from compound **24** (44 mg, 0.17 mmol, 1 equiv), proton sponge (74 mg, 0.34 mmol, 2 equiv), Tf_2O (0.031 mL, 0.190 mmol, 1.1 equiv), and tetrabutylammonium cyanide (116 mg, 0.43 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford compound **33c** (32 mg, 0.12 mmol, 71%) as a colorless oil. **$[\alpha]_D^{20}$** +16 (*c* 0.84, $CHCl_3$) **IR (neat)**: 2935, 2237, 1495, 1453, 1377, 1359, 1225, 1159, 1129, 1099, 1050, 1040, 987, 945, 925 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: *δ* 7.42–7.22 (m, 5H), 5.58 (td_{app}, *J* = 56.7 Hz, 2.8 Hz, 1H), 4.12 (d, J_{AB} = 14.1 Hz, 1H), 3.95 (d, J_{AB} = 14.1 Hz, 1H), 3.38–3.22 (m, 2H), 2.96–2.82 (m, 2H), 2.30 (m, 1H), 2.11 (m, 1H), 2.02–1.84 (m, 2H), 1.62–1.45 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)**: *δ* 139.9, 128.8 (2C), 128.5 (2C), 127.3, 121.2, 117.2 (t, $^1J_{C\text{-}F}$ = 247.6 Hz), 61.5 (dd, $^2J_{C\text{-}F}$ = 21.2, 19.8 Hz), 59.0, 47.8, 32.3, 28.3, 28.2, 23.9. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: *δ* –120.9 (d, *J* = 277.4 Hz, 1F), –131.2 (d, *J* = 277.3 Hz, 1F). **HRMS**: calcd for $C_{15}H_{19}F_2N_2$ ($M+H^+$): 265.1511. Found: 265.1510

General procedure for the synthesis of perfluorinated substituted azepanes

To a stirred solution of compound **26** or **27** (1 equiv) and proton sponge (2 equiv) in CH_3CN (0.1 M) was added Tf_2O (1.1 equiv) at rt. The reaction mixture was stirred for 5 h in a sealed tube at 60 °C. After 5 h, the reaction was cooled to rt and the nucleophile (2.5 equiv) was added. After 5 min the reaction was diluted with H_2O, extracted with CH_2Cl_2 and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to obtain the azepanes.

(*2S,4R*)-4-*N,N*-Diallylamine-1-benzyl-2-(perfluorobutyl)azepane (34a)

Prepared according to the general procedure from **26** (35 mg, 0.083 mmol, 1 equiv), proton sponge (35.4 mg, 0.165 mmol, 2 equiv), Tf_2O (0.015 mL, 0.090 mmol, 1.1 equiv), and diallylamine (25 µL, 0.20 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford **34a** (32 mg, 0.064, 77%) as a colorless oil. **$[\alpha]_D^{20}$** +4.5 (*c* 0.65, $CHCl_3$) **IR (neat)**: 3001, 1459, 1425, 1355, 1223, 1165, 1135, 1029 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.33–7.21 (m, 5H), 5.84 (m, 2H), 5.23–5.10 (m, 4H), 4.16 (d, J_{AB} = 13.6 Hz, 1H), 3.87 (d, J_{AB} = 13.6 Hz, 1H), 3.40 (m, 1H), 3.13 (dd, *J* = 14.1, 6.1 Hz, 2H), 3.03 (dd, *J* = 14.1, 6.5 Hz, 2H), 2.91 (t_{app}, *J* = 9.6 Hz, 1H), 2.86–2.70 (m, 2H), 2.20 (m; 1H), 1.91 (m, 1H), 1.78 (m, 1H), 1.67–1.49 (m, 1H), 1.40 (ddd_{app}, *J* = 24.1, 12.6, 4.7 Hz, 1H), 1.22 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**:[25] *δ* 139.0, 137.3 (2C), 128.8 (2C), 128.4 (2C), 127.3, 117.0 (2C), 62.5, 59.7, 56.7, 53.2 (2C), 45.4, 32.2, 31.1, 21.3. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: *δ* –80.84 (dd, *J* = 10.9, 8.4 Hz, 3F), –118.51 (m, 2F), –121.55 (s, 2F), –125.50– –126.60 (m, 2F). **HRMS**: calcd for $C_{23}H_{28}F_9N_2$ ($M+H^+$): 503.2103. Found: 503.2096

(*2S,4R*)-4-Acetate-1-benzyl-2-(perfluorobutyl)azepane (34b)

Prepared according to the general procedure from compound **26** (35 mg, 0.083 mmol, 1 equiv), proton sponge (35.4 mg, 0.165 mmol, 2 equiv), Tf_2O (0.015 mL, 0.090 mmol, 1.1 equiv), and tetrabutylammonium acetate (104 mg, 0.34 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford **34b** (27 mg, 0.058 mmol, 71%) as a colorless oil. **$[\alpha]_D^{20}$** –25.8 (*c* 1.46, $CHCl_3$) **IR (neat)**: 2941, 1735, 1468, 1454, 1365, 1231, 1215, 1199, 1131, 1104, 1026, 995, 940 cm^{-1} **^{1}H NMR (400 MHz, $CDCl_3$)** *δ* 7.35–7.23 (m, 5H), 4.92 (t_{app}, *J* = 14.1, 1H), 4.19 (d, J_{AB} = 13.6 Hz, 1H), 3.93 (d, J_{AB} = 13.6 Hz, 1H), 3.65 (qd_{app}, *J* = 12.9, 5.9 Hz, 1H), 2.94–274 (m, 2H), 2.28–2.10 (m, 2H), 2.06 (s, 3H), 2.05–1.98 (m, 1H), 1.72–1.46 (m, 2H), 1.24 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: *δ* 170.3, 138.6, 128.8 (2C), 128.5 (2C), 127.4, 119.1–115.4 (4C), 72.4, 60.8 (t, $^2J_{C\text{-}F}$ = 21.09 Hz), 59.0, 45.0, 35.1, 34.8, 21.5, 19.7. **{1H}^{19}F NMR (376 MHz, $CDCl_3$)**: *δ* -80.8 (t, 3F), -117.9 (dm, *J* = 281.5 Hz, 1F),-–119.3 (dm, *J* = 286.2 Hz, 1F), –121.5 (m, 2F),–126.1 (t_{app}, 2F). **HRMS**: calcd for $C_{19}H_{21}F_9NO_2$ ($M+H^+$): 466.1423. Found: 466.1418

(*2S,4R*)-1-Benzyl-4-carbonitril-2-(perfluorobutyl)azepane (34c)

Prepared according to the general procedure from **26** (35 mg, 0.083 mmol, 1 equiv), proton sponge (35.4 mg, 0.165 mmol, 2 equiv), Tf_2O (0.015 mL, 0.090 mmol, 1.1 equiv), and tetrabutylammonium cyanide (55.5 mg, 0.206 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford **34c** (32 mg, 0.074 mmol, 89%) as a colorless oil. **$[\alpha]_D^{20}$** –15.0 (*c* 1.33, $CHCl_3$) **IR (neat)**: 2939, 2210, 1468, 1455, 1354, 1229, 1214, 1199, 1131, 1079, 1012 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: *δ* 7.39–7.21 (m, 5H), 4.16 (d, J_{AB} = 13.5 Hz, 1H), 3.95 (d, J_{AB} = 13.5 Hz, 1H), 3.58 (m, 1H), 2.95 (dd_{app}, *J* = 14.8, 10.3 Hz, 1H), 2.86–2.77 (m, 2H), 2.50 (dd_{app}, *J* = 14.8, 6.1 Hz, 1H), 2.24 (m, 1H), 2.15 (m, 1H), 1.72–1.51 (m, 2H), 1.43 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: *δ* 138.2, 128.9 (2C), 128.7 (2C), 127.7, 122.5, 121–108.8 (m, 4C), 61.7 (t, $^2J_{C\text{-}F}$ = 21.0 Hz), 59.4, 45.9, 33.8, 32.1, 27.5, 24.5. **{1H}^{19}F NMR (376 MHz, CDCl3)**: δ –80.85 (m, 3F), –116.95 (dm, *J* = 280.3 Hz, 1F), –118.93 (dm, *J* = 282.1 Hz, 1F), –121.85 (m, 2F), –126.06 (m, 2F). **HRMS**: calcd for $C_{18}H_{18}F_9N_2$ ($M+H^+$): 433.1321. Found: 433.1321

(*2R,4R*)-4-*N,N*-Diallylamin-1-benzyl-2-(perfluorobutyl)azepane (35a)

Prepared according to the general procedure from **27** (40 mg, 0.094 mmol, 1 equiv), proton sponge (40 mg, 0.185 mmol, 2 equiv), Tf_2O (0.017 mL, 0.101 mmol, 1.1 equiv), and diallylamine (29 µL, 0.24 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford **35a** (34 mg, 0.068 mmol, 72%) as a colorless oil. **$[\alpha]_D^{20}$** +6.3 (*c* 1.7, $CHCl_3$) **IR (neat)**: 2932, 1642, 1496, 1454,

1354, 1296, 1231, 1215, 1200, 1185, 1131, 1094, 995, 919 cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 7.40–7.13 (m, 5H), 5.87 (m, 2H), 5.32–5.07 (m, 4H), 4.05 (d, J_{AB} = 13.8 Hz, 1H), 3.76–3.69 (m, 1H), 3.66 (d, J_{AB} = 13.8 Hz, 1H), 3.24 (m, 1H), 3.12 (m, 4H), 2.88 (m, 1H), 2.51 (m, 1H), 2.24 (m, 1H), 1.93 (m, 1H), 1.79 (m, 1H), 1.74–1.42 (m, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)**:[25] δ 138.9, 136.8 (2C), 128.6 (2C), 128.4 (2C), 127.1, 117.1 (2C), 60.5 (dd, $^2J_{C\text{-}F}$ = 24.16, 21.23 Hz), 57.2, 52.8 (2C), 52.2, 51.4, 29.1, 25.9, 24.2. **{1H}^{19}F NMR (376 MHz, CDCl$_3$)**: δ –80.8 (m, 3F), –112.4 (d, J = 294.2 Hz, 1F), –120.2 (d, J = 294.2 Hz, 1F), –120.4 (dm, J = 311.2 Hz, 1F), –122.7 (dm, J = 310.8 Hz, 1F), –125.0 (dm, J = 298.6 Hz, 1F), –127.3 (d, J = 292.1 Hz, 1F) **HRMS**: calcd for $C_{23}H_{28}F_9N_2$ (M+H$^+$): 503.2103. Found: 503.2100

(*2R,4R*)-4-Acetate-1-benzyl-2-(perfluorobutyl)azepane (35b)

Prepared according to the general procedure from **27** (62 mg, 0.15 mmol, 1 equiv), proton sponge (63 mg, 0.2953 mmol, 2 equiv), Tf_2O (0.027 mL, 0.162 mmol, 1.1 equiv), and tetrabutylammonium acetate (111 mg, 0.37 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford **35b** (49 mg, 0.105 mmol, 70%) as a colorless oil. **$[\alpha]_D^{20}$** +15.8 (*c* 0.8, $CHCl_3$) **IR (neat)**: 2943, 1740, 1443, 1430, 1420, 1371, 1354, 1228, 1215, 1200, 1130, 1085, 1059, 1023, 996, 947 cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 7.40–7.19 (m, 5H), 5.33 (m, 1H), 4.21 (d, J_{AB} = 13.7 Hz, 1H), 3.79 (d, J_{AB} = 13.7 Hz, 1H), 3.64 (qd$_{app}$, J = 26.2, 13.7, 4.9 Hz, 1H), 2.84 (ddd, J = 15.4, 9.0, 2.2 Hz, 1H), 2.72 (ddd, J = 15.5, 6.7, 2.6 Hz, 1H), 2.33 (m, 1H), 2.21 (m, 1H), 2.16 (s, 3H), 2.01 (m, 1H), 1.80 (m, 1H), 1.63 (m, 1H), 1.39 (m, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ 170.4, 138.8, 128.8 (2C), 128.5 (2C), 127.2, 121.1–106.1 (m, 4C), 71.3, 60.8 (t, $^2J_{C\text{-}F}$ = 20.5 Hz), 56.3, 47.2, 32.9, 30.1, 21.5, 20.0. **{1H}^{19}F NMR (376 MHz, CDCl$_3$)**: δ –80.8 (m, 3F), –116.9 (brd, J = 293.5 Hz, 1F), –118.4 (brd, J = 273.9 Hz, 1F), –120.7 (dm, J = 298.1 Hz, 1F), –121.9 (dm, J = 295.1 Hz, 1F), –125.6 (dm, J = 292.2 Hz, 1F), –126.7 (dm, J = 295.1 Hz, 1F) **HRMS**: calcd for $C_{19}H_{21}F_9N_1$ (M+H$^+$): 466.1423. Found: 466.1420

(*2R,4R*)-1-Benzyl-4-carbonitril-2-(perfluorobutyl)azepane (35c)

Prepared according to the general procedure from **27** (50 mg, 0.120 mmol, 1 equiv), proton sponge (50 mg, 0.24 mmol, 2 equiv), Tf_2O (0.0216 mL, 0.241 mmol, 1.1 equiv), and tetrabutylammonium cyanide (79 mg, 0.295 mmol, 2.5 equiv). The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford **35c** (45 mg, 0.104 mmol, 87%) as a colorless oil. **$[\alpha]_D^{20}$** +29.0 (*c* 1.0, $CHCl_3$) **IR (neat)**: 2938, 2210, 1684, 1454, 1354, 1214, 1205, 1197, 1130, 1079, 1054, 1025, 1001 980, 923 cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 7.51–7.18 (m, 5H), 4.41 (d, J_{AB} = 14.2 Hz, 1H), 3.95 (d, J_{AB} = 14.2 Hz, 1H), 3.83 (m, 1H), 3.29 (m, 1H), 2.95–2.73 (m, 2H), 2.44 (m, 1H), 2.21–2.00 (m, 2H), 1.88 (m, 1H), 1.57 (m, 1H), 1.38 (m, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)**:[25] δ 138.8, 128.8 (2C), 128.5 (2C), 127.3, 120.7, 63.0 (t, $^2J_{C\text{-}F}$ = 20.4 Hz), 58.8, 45.2, 32.0, 29.8, 28.2, 22.5. **{^{1}H}^{19}F NMR (376 MHz, CDCl$_3$)**: δ –80.84 (m, 3F), –115.7 (dm, J = 287.2 Hz, 1F), –120.4 (dm, J = 279.3 Hz, 1F), –121.2 (dm, J = 300.6 Hz, 1F), –122.1 (dm; J = 300.6 Hz, 1F), –125.6 (dm, J = 292.9 Hz, 1F), –126.6 (dm, J =296.2 Hz, 1F). **HRMS**: calcd for $C_{18}H_{18}F_9N_2$ (M+H$^+$): 433.1321. Found: 433.1319

4-(4-chlorobenzyl)-2-((2*R*,4*R*)-1-methyl-2-(trifluoromethyl)azepan-4-yl)phthalazin-1(2H)-one (36)

Prepared according to the general procedure from **37** (100 mg, 0.51 mmol, 1 equiv), proton sponge (217 mg, 0.1 mmol, 2 equiv), Tf_2O (0.093 mL, 0.56 mmol, 1.1 equiv), and the sodium phtalizinone solution* [*prepared as follow: phtalizinone (550 mg, 2 mmol, 4 equiv) in DMF (1 mL) was added dropwise to the stirred suspension of NaH (61 mg, 1.5 mmol, 23 equiv) in DMF (1 mL) at 0 °C.]. The crude product was then purified by flash column chromatography (PE/EtOAc = 95:05 to 90:10) to afford compound **36** (160 mg, 0.36 mmol, 70%) as a colorless oil. **$[\alpha]_D^{20}$** –10.4 (*c* 1.4, $CHCl_3$) **IR (neat)**: 2937, 1647, 1587, 1490, 1452, 1445, 1380, 1322, 1310, 1263, 1223, 1163, 1150, 1114, 1105, 1031, 1016, 966, 912 cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 8.46 (m, 1H), 7.80–7.66 (m, 3H), 7.30–7.25 (m, 2H), 7.22–7.17 (m, 2H), 5.51 (m, 1H), 4.30 (d, J_{AB} = 15.7 Hz, 1H), 4.26, (d, J_{AB} = 15.7 Hz, 1H), 3.55 (m, 1H), 3.13 (dt$_{app}$, J = 10.1, 4.8 Hz, 1H), 2.86 (m, 1H), 2.56 (s, 3H), 2.48 (ddd$_{app}$, J = 15.2, 11.0, 7.5 Hz, 1H), 2.20 (ddd, J = 15.2, 5.9, 3.7 Hz, 1H), 2.07 (m, 1H), 1.96–1.78 (m, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ 158.4, 145.2, 136.1, 133.1, 132.8, 131.6, 130.2 (2C), 129.0 (2C), 128.8, 128.2, 127.7, 126.8 (d$_{app}$, $^1J_{C\text{-}F}$ = 283.0 Hz), 124.7, 61.4 (q, $^2J_{C\text{-}F}$ = 27.5 Hz), 55.2, 53.5, 39.1, 38.4, 31.6, 29.2, 24.2. **{1H}^{19}F NMR (376 MHz, CDCl$_3$)**: δ –73.94 (s, 3F). **HRMS**: calcd for $C_{23}H_{24}ClF_3N_3O$ (M+H$^+$): 450.1555. Found: 450.1556

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Keywords: azepanes • ring-expansion reaction • azetidinium • regioselective ring-opening • fluoroalkyl group

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[24] Some carbons are not visble on ^{13}C nmr see supporting information for more informations

[25] Perfluoroalkyl chain not visible on ^{13}C

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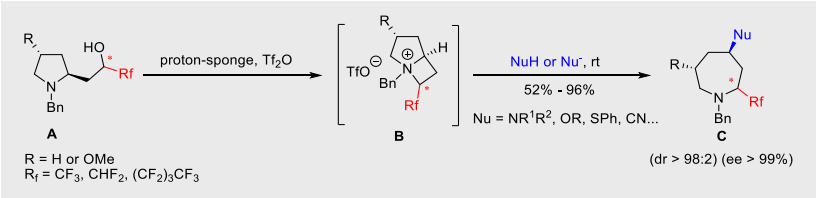

The synthesis of a variety of highly enantio-enriched 2-fluoroalkyl 4-substituted azepanes was achieved using a ring-expansion of pyrrolidines *via* an azetidinium intermediate. This reaction is regioselective and a broad scope of nucleophiles can be used which gives access to a great diversity of substituted azepanes.

Ring-expansion

Guillaume Masson, Sarah Rioton, Domingo Gomez Pardo, Janine Cossy**

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Synthesis of 2-fluoroalkyl 4-substituted azepanes