Enantioselective synthesis of α-perfluoroalkylated prolines, their 6,7-membered homologues and derivatives


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General method

$^1$D NMR ($^1$H, $^{19}$F, and $^{13}$C) spectra were obtained with Bruker AV-400, and Agilent 400-MR spectrometers. Chemical shifts for $^1$H NMR spectroscopic data were referenced to internal tetramethylsilane ($\delta = 0.0$ ppm); chemical shifts for $^{13}$C NMR spectroscopic data were referenced to CDCl$_3$ ($\delta = 77.0$ ppm); chemical shifts for $^{19}$F NMR spectroscopic data were referenced to PhCF$_3$ ($\delta = -63.90$ ppm). Enantiomeric excess ($ee$) were determined by HPLC («Stayer» by Akvilon). TLC was carried out on precoated silica plates (Silufol UV-254), which were visualized with UV light and/or staining with ninhydrine solution or aqueous Ce(SO$_4$)$_2$ solution with phosphomolybdic and sulfuric acids. Flash chromatography was carried out using MP Silica 60 (320–630 mesh) with the solvents indicated. Starting cyclic imines were synthesized according to the following procedure$^1$. 1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1R,2R)-(-)-2-9dimethylamino)cyclohexyl thiourea (Takemoto catalyst) was purchased from abcr.

Reaction optimization

The model reactions in several protic (i-PrOH, MeOH), polar aprotic (CH$_2$Cl$_2$, C$_2$H$_4$Cl$_2$, Et$_2$O, DMF, DMSO, CH$_3$CN, THF) and nonpolar (benzene, xylene, toluene, hexane) solvents were investigated. It was found out that the reaction in protic solvents resulted in racemic 3a and proceeded more rapidly (4 days for i-PrOH and 1 day for MeOH). Low conversion (10-12% accordingly $^{19}$F NMR monitoring) after two months was observed in DMF, DMSO, THF and Et$_2$O. Others solvents (CH$_2$Cl$_2$, C$_2$H$_4$Cl$_2$, CH$_3$CN, benzene, xylene, toluene, hexane) demonstrated up to 99% ee, however the reaction in C$_2$H$_4$Cl$_2$ proceeded in reasonable time (4 days) to give after hydrolysis of 2a amide 3a in the highest yield (88%).

Table 1. Solvent optimization

<table>
<thead>
<tr>
<th>Solvent</th>
<th>1st step time</th>
<th>1st step yield</th>
<th>2nd step</th>
<th>$[\alpha]_D^{20}$</th>
<th>ee, %</th>
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<tr>
<td>i-PrOH</td>
<td>4 days</td>
<td>88%</td>
<td></td>
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<tr>
<td>MeOH</td>
<td>1 day</td>
<td>88%</td>
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<tr>
<td>CH$_2$Cl$_2$</td>
<td>4 days</td>
<td>88%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_2$H$_4$Cl$_2$</td>
<td>4 days</td>
<td>88%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>4 days</td>
<td>88%</td>
<td></td>
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<tr>
<td>CH$_3$CN</td>
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<td>Xylene</td>
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<td>88%</td>
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<tr>
<td>Toluene</td>
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<td>88%</td>
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<tr>
<td>Hexane</td>
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<td>88%</td>
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<tr>
<td>Additive</td>
<td>Reaction days</td>
<td>(19F NMR spectra), %</td>
<td>Yield, %</td>
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<td></td>
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<tr>
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<tr>
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<td>98</td>
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<td>-82.2</td>
<td>&gt;99</td>
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<td>94</td>
<td>82</td>
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<tr>
<td>CHCl\textsubscript{3}</td>
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<td>97</td>
<td>68</td>
<td>-81.2</td>
<td>&gt;99</td>
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<tr>
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<td>69</td>
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<td>4</td>
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<td>-</td>
<td>-</td>
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<td>THF</td>
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<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DMF</td>
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<td>7</td>
<td>-</td>
<td>-</td>
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<td>DMSO</td>
<td>30</td>
<td>80</td>
<td>-</td>
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Also to finding an optimal reaction condition different addictive (CF\textsubscript{3}CH(OH)CF\textsubscript{3}, CF\textsubscript{3}CH\textsubscript{2}OH, i-PrOH) for producing HCN were investigated. However use of addictive other than methanol lead to decrease of reaction enantioselectivity.

**Table 2. Additives optimization**
After finding the optimal conditions for obtaining pure enantiomer 2-trifluoromethyl-pyrrolidyne carboxyamide (3a) (99% ee) those were applied for others imines b-e. The reaction was very sensitive to the ring size and substituent at α-position of starting imine. Pentafluoroethyl-substituted imines (1b, 1d) reacted very slowly (about two months) with low enantioselectivity (42% ee for 1b and 11% ee for 1d). The most difficult situation was observed in the case of 6-membered imine 1d bearing pentafluoroethyl group. We believe that these results can be explained by much higher steric bulkiness of C₂F₅ group over CF₃ moiety as well as significant difference in geometry of starting imines. In cases of hydrocyanation of trifluoromethylated imines 1c and 1e reasonably high enantioselectivity was achieved - 79 and 80% ee correspondingly.

**Table 3. Influence of substituent and ring size on reaction enantioselectivity**
To improve enantioselectivity of the reaction with imines 1c and 1e hydrocyanation under decreased temperature was studied. Imines with pentafluoroethyl substituents (1b, 1d) were not used for temperature optimization due to long reaction time. The enantiomeric excess for amide 3c obtained from imine 1c reached 90% ee at -20°C. In the case of amide 3e the improvement of enantioselectivity was lower than expected (from 80% ee to 83% ee at 0°C and 81% ee at -20°C).

**Table 4.** Temperature optimization for imines 1c and 1e
Increasing the amount of Takemoto catalyst (15 mol %) resolved this problem and enantioselectivity of Strecker reaction was improved significantly to provide 95-96% ee for both imines 1c and 1e. Using 20% of catalyst the reaction with 1b also gave appropriate 90% ee for amide 3b in 85% isolated yield (Table 5).

**Table 5.** Optimal condition for enantioselective Strecker reaction with cyclic imines 1a-e

<table>
<thead>
<tr>
<th>Imine</th>
<th>n</th>
<th>R_f</th>
<th>Cat, mol%</th>
<th>T, °C</th>
<th>1st step reaction time, days</th>
<th>Yield of 3, (%)</th>
<th>ee, %</th>
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</thead>
<tbody>
<tr>
<td>1a</td>
<td>1</td>
<td>CF_3</td>
<td>5</td>
<td>rt</td>
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<tr>
<td>1b</td>
<td>1</td>
<td>C_2F_5</td>
<td>20</td>
<td>rt</td>
<td>90</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>1c</td>
<td>2</td>
<td>CF_3</td>
<td>15</td>
<td>-20</td>
<td>6</td>
<td>97</td>
<td>96</td>
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<tr>
<td>1d</td>
<td>2</td>
<td>C_2F_5</td>
<td>5</td>
<td>rt</td>
<td>90</td>
<td>89</td>
<td>11</td>
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<tr>
<td>1e</td>
<td>3</td>
<td>CF_3</td>
<td>15</td>
<td>0</td>
<td>6</td>
<td>98</td>
<td>95</td>
</tr>
</tbody>
</table>
Synthesis

Procedure for synthesis of cyclic nitriles 2a-e

A. For racemic products

In a screw-capped vial cyclic imine (1mmol) and TMSCN (1.5 mmol, 0.215mL) was added. Reaction mixture was dissolved by MeOH (about 5mL) as solvent and stay for a night. After reaction complete, the solvent was carefully removed under vacuum (volatile product) and crude products were let into the next transformation without purification.

B. For asymmetric products

In a screw-capped vial cyclic imine (1mmol) was dissolved in dichloroethane (2mL). To the solution cat Takemoto (0.05mmol for 1a, 0.15 mmol for 1c,e, 0.2mmol for 1b), TMSCN (1.5 mmol, 0.215mL), MeOH (1.5 mmol, 0.05mL) were added. Reaction was monitoring by $^{19}$F spectra. After reaction complete, the solvent was carefully removed under vacuum (volatile product) and the residue was purified by silica gel chromatography (CH$_2$Cl$_2$).

(R)-2-(trifluoromethyl)pyrrolidine-2-carbonitrile (2a), According to NMR $^{19}$F - 100 %, after evaporation – 97%, colorless volatile liquid, $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.87-2.04 (2H, m), 2.24-2.36 (2H, m), 2.53 (1H, bs, NH), 3.13-3.16 (2H, m). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 24.0, 33.0 (CH$_2$-C$_q$), 46.3 (CH$_2$-N), 62.1 (q, $J_{CF}$ = 33.1 Hz, C-CF$_3$), 117.7 (CN), 123.3 (q, $J_{CF}$ = 281.2 Hz, CF$_3$). $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -79.1 (3F, s, CF$_3$). IR(KBr): 3465 (bs), 3273 (bs), 1309, 1189, 1057, 953 cm$^{-1}$. HRMS (ESI): calcd. for C$_6$H$_8$F$_3$N$_2$ [M+H]$^+$ 165.0640, found 165.0636.

Optical rotation $[\alpha]^20_D$ = +12.0 (c = 0.5, MeOH).

2-(Pentafluoroethyl)pyrrolidine-2-carbonitrile (2b), According to NMR $^{19}$F - 100 %, after evaporation – 99%, colorless volatile liquid, $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.98-2.10 (2H, m), 2.26 (1H, bs, NH), 2.36-2.45 (2H, m, CH$_2$), 3.24-3.27 (2H, m). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 23.9, 33.4 (CH$_2$-C$_q$), 46.3 (CH$_2$-N), 61.7 (t, $J_{CF}$ = 26.5 Hz, C-CF$_2$), 112.2 (tq, $J_{CF}$ = 260.6 Hz, $J_{CF}$ = 36.1 Hz, CF$_2$),
117.7 (CN), 118.9 (qt, \( J_{CF} = 287.9 \text{ Hz}, J_{CF} = 35.8 \text{ Hz}, \text{CF}_3 \)). \(^{19}\text{F NMR (280 MHz, CDCl}_3\)): \( \delta -79.1 \) (3F, s, CF\(_3\)), -119.8 (1F, d, \( J_{FF} = 271.3 \text{ Hz}, \text{CF}_2 \)), -123.8 (1F, d, \( J_{FF} = 271.3 \text{ Hz}, \text{CF}_2 \)). IR(KBr): 3361 (bs), 2237, 1346, 1209, 1169, 1111, 1049, 742 cm\(^{-1}\). HRMS (ESI): calcd. for \( \text{C}_7\text{H}_8\text{F}_5\text{N}_2 [\text{M+H}]^+ \) 215.0608, found 215.0606.

Optical rotation \([\alpha]_{20}^D = +7.6 \) (c = 0.5, MeOH).

\[
\text{2-(trifluoromethyl)piperidine-2-carbonitrile (2c), According to NMR \(^{19}\text{F - 100 \%}, after evaporation –73 \%, colorless volatile liquid, \(^1\text{H NMR (400 MHz, CDCl}_3\)): \( \delta 1.47-1.54 \) (1H, m), 1.64-1.82 (3H, m), 1.89-1.91 (1H, m), 2.00-2.03 (1H, m), 2.15 (1H, bs, NH), 2.92-2.97 (1H, m, N-CH\(_2\)), 3.12-3.14 (1H, m, N-CH\(_2\)). \(^{13}\text{C NMR (100 MHz, CDCl}_3\)): \( \delta 20.1, 23.8, 28.3 \) (CH\(_2\)-C\(_q\)), 42.6 (CH\(_2\)-N), 60.7 (q, \( J_{CF} = 30.2 \text{ Hz}, \text{C-CF}_3 \)), 115.3 (CN), 122.8 (q, \( J_{CF} = 282.0 \text{ Hz}, \text{CF}_3 \)). \(^{19}\text{F NMR (280 MHz, CDCl}_3\)): \( \delta -80.2 \) (3F, s, CF\(_3\)). IR(KBr): 3334 (bs), 1311, 1203, 1194, 1176, 1128 cm\(^{-1}\). HRMS (ESI): calcd. for \( \text{C}_7\text{H}_9\text{F}_5\text{N}_2 [\text{M+H}]^+ \) 179.0796, found 179.0801.

Optical rotation \([\alpha]_{20}^D = +40.8 \) (c = 0.5, CH\(_2\)Cl\(_2\)).

\[
\text{2-(Perfluoroethyl)piperidine-2-carbonitrile (2d), According to NMR \(^{19}\text{F - 100 \%}, after evaporation –63 \%, colorless volatile liquid, \(^1\text{H NMR (400 MHz, CDCl}_3\)): \( \delta 1.42-1.54 \) (1H, m), 1.63-1.75 (2H, m), 1.81-1.92 (2H, m), 1.99-2.03 (1H, m), 2.10 (1H, bs, NH), 2.93-2.99 (1H, m, N-CH\(_2\)), 3.11-3.14 (1H, m, N-CH\(_2\)). \(^{13}\text{C NMR (100 MHz, CDCl}_3\)): \( \delta 20.3, 23.8, 28.2 \) (CH\(_2\)-C\(_q\)), 42.7 (CH\(_2\)-N), 61.1 (t, \( J_{CF} = 23.4 \text{ Hz}, \text{C-CF}_2 \)), 112.2 (tq, \( J_{CF} = 262.1 \text{ Hz}, J_{CF} = 36.5 \text{ Hz}, \text{CF}_2 \)), 114.8 (CN), 118.7 (tq, \( J_{CF} = 287.9 \text{ Hz}, J_{CF} = 35.4 \text{ Hz}, \text{CF}_3 \)). \(^{19}\text{F NMR (280 MHz, CDCl}_3\)): \( \delta -78.2 \) (3F, s, CF\(_3\)), -121.9 (1F, d, \( J_{FF} = 278.3 \text{ Hz}, \text{CF}_2 \)), -122.8 (1F, d, \( J_{FF} = 278.3 \text{ Hz}, \text{CF}_2 \)). IR(KBr): 3461 (bs), 3257 (bs), 1338, 1310, 1216, 1058 cm\(^{-1}\). HRMS (ESI): calcd. for \( \text{C}_8\text{H}_{10}\text{F}_5\text{N}_2 [\text{M+H}]^+ \) 229.0764, found 229.0762.
2-(trifluoromethyl)azepane-2-carbonitrile (2e), According to NMR $^{19}$F - 100 %, after evaporation –95 %, colorless volatile liquid. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.56-1.69 (4H, m), 1.70-1.80 (1H, m), 1.84-1.93 (1H, m), 2.09-2.17 (2H, m), 2.28 (1H, bs, NH), 2.90-3.03 (2H, m, N-CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 22.4, 28.5, 30.6, 32.3 (CH$_2$-C$_q$), 43.5 (CH$_2$-N), 62.5 (q, $J_{CF} = 28.8$ Hz, C-CF$_3$), 117.3 (CN), 123.4 (q, $J_{CF} = 284.9$ Hz, CF$_3$). $^{19}$F NMR (280 MHz, CDCl$_3$): δ -79.2 (3F, s, CF$_3$). IR(KBr): 3356 (bs), 1269, 1194, 1180, 1119 cm$^{-1}$. HRMS (ESI): calcd. for C$_7$H$_{11}$F$_3$N [M – CN]$^+$ 166.0844, found 166.0846.

Optical rotation [$\alpha$]$^{20}_D = +32.1$ (c = 1.83, MeOH).

Procedure for synthesis of amides 3a-e

To a solution of aminonitrile 2 (1mmol) in MeOH (3mL) LiOH*H$_2$O (0.21 g, 3.5 mmol), H$_2$O (1 mL), H$_2$O$_2$ 30% (0.5 mL) were added and mixture was stirred at rt for 1.5-2 hours. After that, water was added and solution was extracted with EtOAc. Organic lay was dried on Na$_2$SO$_4$ and concentrated under reduced pressure to obtain crude amide, which was purified by silica gel chromatography (EtOAc/Hex = 2/1).

(R)-2-(trifluoromethyl)pyrrolidine-2-carboxamide (3a), 88 %, 99 % ee, white solid, mp 108-110ºC $^1$H NMR (400 MHz, CDCl$_3$): δ 1.71-1.87 (2H, m), 2.18-2.22 (2H, m), 3.04-3.07 (2H, m), 6.83 (1H, bs, NH$_2$CO), 7.31 (1H, bs, NH$_2$CO). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 25.3, 32.2 (CH$_2$-C$_q$), 47.5 (CH$_2$-N), 70.7 (q, $J_{CF} = 26.2$ Hz, C-CF$_3$), 125.9 (q, $J_{CF} = 283.4$ Hz, CF$_3$), 173.0 (CONH$_2$). $^{19}$F NMR (280 MHz, DMSO): δ -74.1 (3F, s, CF$_3$). IR(KBr): 1703, 1171 cm$^{-1}$. HRMS (ESI): calcd. for C$_6$H$_9$F$_3$N$_2$O [M+H]$^+$ 183.0740, found 183.0747.

Optical rotation [$\alpha$]$^{20}_D = -88.2$ (c = 0.5, MeOH).

HPLC condition: Chiral column Chiracel OJ (250×4.6 mm), heptane/i-PrOH = 9/1, flow rate = 1 mL/min, wavelength = 206 nm. $t_{r_{\text{minor}}} = 8.983$ min (0.455), $t_{r_{\text{major}}} = 10.122$ min (99.545)
2-(pentafluoroethyl)prolinamide (3b), 85 %, 90 % ee, white solid, mp 41-43°C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.68-1.91 (2H, m), 2.23-2.38 (2H, m, CH$_2$-C$_q$), 2.62 (1H, bs, NH), 3.03-3.05 (2H, m, CH$_2$-N), 6.77 (1H, bs, NH$_2$CO), 7.14 (1H, bs, NH$_2$CO).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 25.1, 32.6 (CH$_2$-C$_q$), 47.8 (CH$_2$-N), 70.7 (t, $J_{CF} = 21.6$ Hz, C-CF$_2$), 114.7 (tq, $J_{CF} = 262.4$ Hz, $J_{CF} = 35.8$ Hz, CF$_2$), 119.0 (qt, $J_{CF} = 287.9$ Hz, $J_{CF} = 36.5$ Hz, CF$_3$), 172.7 (d, $J_{CF} = 4.8$ Hz, CONH$_2$).

$^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -79.4 (3F, s, CF$_3$), -115.6 (1F, d, $J_{FF} = 276.6$ Hz, CF$_2$), -120.8 (1F, d, $J_{FF} = 276.8$ Hz, CF$_2$). IR(KBr): 1691, 1213 cm$^{-1}$. HRMS (ESI): calcd. for C$_7$H$_9$F$_5$N$_2$O $[M+H]^+$ 233.0708, found 233.0714.

Optical rotation $[\alpha]_{20}^D = -33.2$ (c = 1, MeOH).

HPLC condition: Chiral column CHIRALPAK AS-H (250×4.6 mm), heptane/i-PrOH = 9/1, flow rate = 1 mL/min, wavelength = 206 nm. $t_r$ minor = 8.338 min (4.858), $t_r$ major = 10.085 min (95.142).
2-(trifluoromethyl)piperidine-2-carboxamide (3c), 97 %, 96% ee, white solid, mp 128-130ºC.  

1H NMR (400 MHz, CDCl₃): δ 1.24-1.60 (4H, m), 1.74-1.82 (2H, m), 2.40-2.44 (1H, m), 2.68-2.75 (1H, m, CH₂-Cq), 3.02-3.05 (1H, m, CH₂-Cq), 6.05 (1H, bs, CONH₂), 7.18 (1H, bs, CONH₂).  

13C NMR (100 MHz, CDCl₃): δ 20.3, 25.3, 26.3 (CH₂-Cq), 42.4 (CH₂-N), 64.7 (q, JCF = 24.7 Hz, C-CF₃), 124.7 (q, JCF = 284.2 Hz, CF₃), 169.6 (CONH₂).  

19F NMR (280 MHz, CDCl₃): δ -76.8 (3F, s, CF₃).  

IR(KBr): 3396 (NH), 3307 (NH), 3217 (NH), 1697 (CO), 1674 (CO), 1184 cm⁻¹.  

HRMS (ESI): calcd. for C₇H₁₁F₃N₂O [M+H]⁺ 197.0896, found 197.0892.  

Optical rotation [α]D₂₀ = +3.2 (c = 0.5, MeOH).  

HPLC condition: Chiral column CHIRALPAK AS-H (250×4.6 mm), heptane/i-PrOH = 9/1, flow rate = 1 mL/min, wavelength = 206 nm.  

$t_r$ minor = 10.937 min (2.241), $t_r$ major = 12.628 min (97.759)
2-(Perfluoroethyl)piperidine-2-carboxamide (3d), 89 %, 11 % ee, white solid, mp 72-74ºC ¹H NMR (400 MHz, CDCl₃): δ 1.22-1.64 (4H, m), 1.78-1.81 (1H, m, CH₂-Cₗ), 2.39-2.43 (1H, m, CH₂-Cₗ), 2.68-2.76 (1H, m, CH₂-NH), 2.98-3.02 (1H, m, CH₂-NH), 6.69 (1H, bs, CONH₂), 7.15 (1H, bs, CONH₂). ¹³C NMR (100 MHz, CDCl₃): δ 20.4, 25.2, 26.2 (CH₂-Cₗ), 42.4 (CH₂-N), 65.2 (t, J_CF = 20.1 Hz, C-CF₂), 114.0 (tq, J_CF = 262.4 Hz, J_CF = 36.5 Hz, CF₂), 119.1 (qt, J_CF = 287.9 Hz, J_CF = 36.7 Hz, CF₃), 169.6 (CONH₂). ¹⁹F NMR (280 MHz, CDCl₃): δ -78.8 (3F, s, CF₃), -121.6 (1F, d, J_FF = 278.8 Hz, CF₂), -122.5 (1F, d, J_FF = 278.8 Hz, CF₂). IR(KBr): 1693, 1678, 1119, 1099, 1059 cm⁻¹. HRMS (ESI): calcd. for C₈H₁₁F₅N₂O [M+H]⁺ 247.0864, found 247.0870.

HPLC condition: Chiral column CHIRALPAK AS-H (250×4.6 mm), heptane/i-PrOH = 9/1, flow rate = 1 mL/min, wavelength = 206 nm. tᵣ_minor = 7.128 min (44.367), tᵣ_major = 7.852 min (55.633)
2-(Trifluoromethyl)azepane-2-carboxamide (3e), 99 %, 96 % ee, white solid, mp 72-73°C. 

**1H NMR (400 MHz, DMSO):**

δ 1.13-1.40 (3H, m), 1.69-1.71 (3H, m), 1.79-1.85 (1H, m), 2.27-2.33 (1H, m), 2.82-2.92 (2H, m, CH₂-N), 7.02 (1H, bs, NH₂CO), 7.62 (1H, bs, NH₂CO).

**13C NMR (100 MHz, DMSO):**

δ 22.7, 29.6, 30.3, 33.0 (CH₂-C₄), 43.7 (CH₂-N), 68.1 (q, J₀CF = 24.0 Hz, C-CF₃), 126.4 (q, J₀CF = 288.2 Hz, CF₃), 173.5 (CONH₂).

**19F NMR (280 MHz, DMSO):**

δ -75.1 (3F, s, CF₃).

**IR(KBr):** 3421 (NH), 3361 (NH), 3250 (bs, NH), 3192 (bs, NH), 1693 (CO), 1171 cm⁻¹.

**HRMS (ESI):** calcd. for C₈H₁₃F₃N₂O [M+H]⁺ 211.1053, found 211.1053.

**Optical rotation [α]²⁰₀ = -21.2 (c = 0.5, MeOH).**

**HPLC condition:** Chiral column 3-AmyCoat (150×4.6 mm), heptane/i-PrOH = 98/2, flow rate = 1 mL/min, wavelength = 206 nm. tᵣ minor = 14.712 min (2.002), tᵣ major = 17.863 min (97.998)
Procedure for synthesis of amino acids 4a-e
Amide 2 (1 mmol) was dissolved in HBr (HI) (4 mL) and was heated to reflux. Reaction was monitoring by NMR $^{19}\text{F}$ spectra. After reaction complete solution concentrated under reduced pressure. Residue was recrystallized with methanol and concentrated to obtain salt of aminoacid.

2-(trifluoromethyl)pyrrolidine-2-carboxylic acid hydrobromide (4a) 99 %, white solid, degradation over 200°C. $^1\text{H}$ NMR (400 MHz, D$_2$O): $\delta$ 1.82-2.08 (2H, m), 2.27-2.39 (2H, m), 2.92-2.98 (1H, m), 3.25-3.31 (1H, m). $^{13}\text{C}$ NMR (100 MHz, D$_2$O): $\delta$ 25.9, 32.1, 47.4 (CH$_2$-N), 71.9 (q, $J_{CF} = 25.0$ Hz, C-CF$_3$), 126.5 (q, $J_{CF} = 281.6$ Hz, CF$_3$), 175.3 (COOH). $^{19}\text{F}$ NMR (280 MHz, D$_2$O): $\delta$ -73.1 (3F, s, CF$_3$). IR(KBr): 3389 cm$^{-1}$ (OH), 2970 cm$^{-1}$ (NH$^+$), 1712 cm$^{-1}$ (CO), 1185 cm$^{-1}$ (CF). HRMS (ESI): calcd. for C$_6$H$_9$F$_3$NO$_2$ [M+H]$^+$ 184.0585, found 184.0576.

Optical rotation $[\alpha]^{20}_D = -21.2$ (c = 0.5, MeOH).

2-(perfluoroethyl)pyrrolidine-2-carboxylic acid hydrobromide (4b), 98 %, white solid, degradation over 200°C. $^1\text{H}$ NMR (400 MHz, D$_2$O): $\delta$ 1.7-1.99 (2H, m), 2.32-2.50 (2H, m), 3.27-3.37 (2H, m). $^{13}\text{C}$ NMR (100 MHz, D$_2$O): $\delta$ 22.0, 30.3, 47.4, 72.2 (t, $J_{CF} = 29.4$ Hz, C-CF$_3$), 111.6 (tq, $J_{CF} = 262.1$ Hz, $J_{CF} = 39.1$ Hz, CF$_2$), 117.5 (qt, $J_{CF} = 281.6$ Hz, $J_{CF} = 35.4$ Hz, CF$_3$), 166.1 (COOH). $^{19}\text{F}$ NMR (280 MHz, D$_2$O): $\delta$ -80.97 (s, CF$_3$), -117.78 (q, $J_{CF} = 285.4$ Hz, CF$_2$). IR(KBr): 2870 cm$^{-1}$ (OH), 2750 cm$^{-1}$ (NH$^+$), 1760 cm$^{-1}$ (CO), 1220 cm$^{-1}$ (CF), 1110 cm$^{-1}$ (CF). HRMS (ESI): calcd. for C$_7$H$_9$F$_5$NO$_2$ [M+H]$^+$ 234.0548 found 234.0548.

Optical rotation $[\alpha]^{20}_D = -18.4$ (c = 0.5, MeOH).

2-(trifluoromethyl)piperidine-2-carboxylic acid hydrobromide (4c), 98 %, brown solid, 255-257°C. $^1\text{H}$ NMR (400 MHz, D$_2$O): $\delta$ 1.20-1.31 (1H, m), 1.43-1.53 (1H, m), 1.67-1.77 (3H, m), 2.32 (1H, d, $J = 14.5$ Hz), 3.09 (1H, dt, $J_{H,H} = 13.0$ Hz, $J_{H,H} = 3.1$ Hz),
3.28 (1H, d, J = 12.8 Hz). $^{13}$C NMR (100 MHz, D$_2$O): δ 17.7, 20.1, 42.9, 66.0 (q, $J_{CF} = 28.4$ Hz, C-CF$_3$), 121.9 (q, $J_{CF} = 284.9$ Hz, CF$_3$), 164.5 (COOH). $^{19}$F NMR (280 MHz, D$_2$O): δ -75.8 (s, CF$_3$). IR(KBr): 3096 cm$^{-1}$ (OH), 2830 cm$^{-1}$ (NH$^+$), 1751 cm$^{-1}$ (CO), 1215 cm$^{-1}$ (CF), 1146 cm$^{-1}$ (CF). HRMS (ESI): calcd. for C$_7$H$_{11}$F$_5$NO$_2$ [M+H]$^+$ 198.0737 found 198.0737.

Optical rotation $[\alpha]_{D}^{20} = +5.9$ (c = 1, MeOH).

$^{1}$H NMR (400 MHz, CDCl$_3$): δ 1.18-1.38 (5H, m), 1.44-1.73 (5H, m), 1.80-1.96 (2H, m), 2.63 (1H, dd, $J_1 = 0.8$ Hz, $J_2 = 13.3$ Hz), 2.89-3.04 (3H, m). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 25.9, 30.0, 44.9 (CH$_2$-C$_q$), 47.3 (CH$_2$-N), 67.2 (q, $J_{CF} = 24.7$ Hz, C-CF$_3$), 128.3 (q, $J_{CF} = 284.5$ Hz, CF$_3$). $^{19}$F NMR (280 MHz, CDCl$_3$): δ -78.2 (3F, s, CF$_3$). IR(KBr): 3299 (bs, NH), 3414 (bs, NH), 1167 (C-F), 1151 (C-F) cm$^{-1}$. HRMS (ESI): calcd. for C$_6$H$_{11}$F$_3$N$_2$ [M+H]$^+$ 169.0947, found 169.0954.

Optical rotation $[\alpha]_{D}^{20} = -1.9$ (c = 0.73, MeOH).

### Procedure for synthesis of diamines 5a-e

To a stirred solution of cyclic nitrile 2a-c,e (2 mmol) in MeOH (5 mL) NH$_3$ aq (3 mL), Ni-Ra were added and reaction was vacuumed and carried out in H$_2$ atmosphere. Mixture was stirred during two days after that, filtered over celite, rinsed by water and concentrated to half volume. Residue extracted with Et$_2$O, organic lay dried over Na$_2$SO$_4$ and concentrated under reduced pressure to obtain pure product.

(2-(Trifluoromethyl)pyrrolidin-2-yl)methanamine (5a), 90 %, yellowish oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.54-1.73 (5H, m), 1.80-1.96 (2H, m), 2.63 (1H, dd, $J_1 = 0.8$ Hz, $J_2 = 13.3$ Hz), 2.89-3.04 (3H, m). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 25.9, 30.0, 44.9 (CH$_2$-C$_q$), 47.3 (CH$_2$-N), 67.2 (q, $J_{CF} = 24.7$ Hz, C-CF$_3$), 128.3 (q, $J_{CF} = 284.5$ Hz, CF$_3$). $^{19}$F NMR (280 MHz, CDCl$_3$): δ -78.2 (3F, s, CF$_3$). IR(KBr): 3299 (bs, NH), 3414 (bs, NH), 1167 (C-F), 1151 (C-F) cm$^{-1}$. HRMS (ESI): calcd. for C$_6$H$_{11}$F$_3$N$_2$ [M+H]$^+$ 169.0947, found 169.0954.
Optical rotation $[\alpha]_{20}^D = -5.2$ (c = 0.5, MeOH).

1-[2-(Pentafluoroethyl)pyrrolidin-2-yl]methanamine (5b), 78 %, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.56-1.81 (6H, m), 1.96-2.04 (1H, m), 2.57 (1H, d, $J = 13.5$ Hz, CH$_2$-NH$_2$), 2.84-2.91 (2H, m including 2.86, d, $J = 13.5$ Hz, CH$_2$-NH$_2$), 2.95-3.00 (1H, m).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 25.6, 30.2, 45.2, 47.1, 67.6 (t, $J_{CF} = 19.2$ Hz, C-C$_2$F$_5$), 116.9 (tq, $J_1 = 257.3$ Hz, $J_2 = 35.0$ Hz, CF$_2$), 119.5 (qt, $J_1 = 287.5$ Hz, $J_2 = 37.2$ Hz, CF$_3$). $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -119.6 (2F, CF$_2$), -79.2 (3F, s, CF$_3$). IR (ATR, ZnSe): 3322 (bs), 2960, 1336, 1191, 1159, 1043, 736 cm$^{-1}$. HRMS (ESI): calcd. for C$_7$H$_{12}$F$_5$N$_2$ [M+H]$^+$ 219.0915, found 219.0925.

Optical rotation $[\alpha]_{20}^D = +2.4$ (c = 0.5, CH$_2$Cl$_2$).

(2-(Trifluoromethyl)piperidin-2-yl)methanamine (5c), 82 %, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.39-1.62 (9H, m), 2.63-2.66 (1H, m, CH$_2$-NH), 2.70 (2H, s, CH$_2$-NH$_2$), 2.79-2.80 (1H, m, CH$_2$-NH). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 19.5, 24.5, 25.4 (CH$_2$-C$_q$), 40.7 (CH$_2$-N), 42.8 (CH$_2$-N), 58.0 (q, $J_{CF} = 22.8$ Hz, C-CF$_3$), 128.1 (q, $J_{CF} = 288.6$ Hz, CF$_3$). $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -75.8 (3F, s, CF$_3$). IR (KBr): 3305 (bs, NH), 1156 (C-F), 1130 (C-F) cm$^{-1}$. HRMS (ESI): calcd. for C$_7$H$_{13}$F$_3$N$_2$ [M+H]$^+$ 183.1104, found 187.1108.

Optical rotation $[\alpha]_{20}^D = -0.8$ (c = 1, CH$_2$Cl$_2$).

1-[2-(Trifluoromethyl)azepan-2-yl]methanamine (5e), 79 %, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.23-1.47 (5H, m), 1.59-1.76 (5H, m), 2.57-2.61 (1H, m), 2.76-2.82 (3H, m). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 22.6, 30.5, 30.9, 33.6, 43.1, 46.3, 61.5 (q, $J_{CF} = 22.1$ Hz, C-CF$_3$), 128.9 (q, $J_{CF} = 290.4$ Hz, CF$_3$). $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -76.9 (3F, s, CF$_3$). IR (neat): 3350 (bs), 1160 cm$^{-1}$. HRMS (ESI): calcd. for C$_8$H$_{18}$F$_3$N$_2$ [M+H]$^+$ 197.1260, found 197.1262.

Optical rotation $[\alpha]_{20}^D = -6.4$ (c = 0.5, CH$_2$Cl$_2$).
Procedure for synthesis of Boc-protected diamines 6a-e

To a solution of diamines 4 (1 mmol) in CH₂Cl₂ Boc₂O (1.1 mmol) and Et₃N (1.5 mmol) were added. Mixture was stirred overnight. After that, reaction was concentrated under reduced pressure and purified with silica gel chromatography (CH₂Cl₂/MeOH = 100/1).

**tert-butyl ((2-(trifluoromethyl)pyrrolidin-2-yl)methyl)carbamate (6a), 99 %, 98% ee, white solid, mp 90-92°C.**

$^1$H NMR (400 MHz, CDCl₃): δ 1.43 (9H, s), 1.68-1.80 (2H, m), 1.84-1.90 (1H, m), 1.95-1.99 (1H, m), 2.10 (1H, bs, NH), 2.96-3.05 (2H, m), 3.28-3.40 (2H, m), 4.97 (1H, bs, NH). $^{13}$C NMR (100 MHz, CDCl₃): δ 25.7, 28.2, 29.9, 43.6, 47.2, 66.9 (q, JCF = 24.7 Hz, C-CF₃), 79.8, 127.9 (q, JCF = 284.5 Hz), 156.7. $^{19}$F NMR (280 MHz, CDCl₃): δ -78.0 (s, CF₃). IR(KBr): 3230 (bs), 2987, 1698, 1554, 1369, 1282, 1164, 946 cm⁻¹.


Optical rotation $[\alpha]^{20}_D = -4.0$ (c = 0.5, MeOH).

HPLC condition: Chiral column CHIRALCEL OD (250×4.6 mm), heptane/i-PrOH = 99.5/0.5, flow rate = 1 mL/min, wavelength = 206 nm.

$\tau_{\text{r minor}} = 20.008$ min (0.7716), $\tau_{\text{r major}} = 17.075$ min (99.228).
tert-butyl ((2-(perfluoroethyl)pyrrolidin-2-yl)methyl)carbamate (6b), 99 %, 97% ee, colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.42 (9H, s), 1.71-1.87 (3H, m), 2.07-2.13 (2H, m), 2.93-3.09 (2H, m), 3.26-3.40 (2H, m), 5.00 (1H, bs, NH). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 25.6, 28.2, 30.0, 43.8, 47.3, 67.5 (t, $J_{CF} = 19.9$ Hz, C-CF$_2$), 79.8, 116.5 (tq, $J_1$ = 222.2 Hz, $J_2$ = 35.0 Hz, CF$_2$), 119.5 (qt, $J_1$ = 287.5 Hz, $J_2$ = 37.0 Hz, CF$_3$). 19F NMR (280 MHz, CDCl$_3$): δ -120.5 (2F, s, CF$_2$), -78.9 (3F, s, CF$_3$). IR(KBr): 3282, 2979, 1698, 1558, 1371, 1172, 950, 728 cm$^{-1}$. HRMS (ESI): calcd. for C$_{12}$H$_{20}$F$_5$N$_2$O$_2$ [M+H]$^+$ 319.1440, found 319.1440.

Optical rotation $[\alpha]_{D}^{20} = +2.4$ (c = 0.5, CH$_2$Cl$_2$).

HPLC condition: Chiral column 3-AmyCoat (150×4.6 mm), heptane/i-PrOH = 98/, flow rate = 1 mL/min, wavelength = 206 nm. $t_r$ minor = 4.832 min (1.404), $t_r$ major = 5.173 min (98.596).
tert-butyl ((2-(trifluoromethyl)piperidin-2-yl)methyl)carbamate (6e), 99%, 95% ee, colorless oil. \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.39 (9H, s), 1.44-1.72 (7H, m), 2.78-2.87 (2H, m), 3.10 (1H, dd, \( J_1 = 4.3 \) Hz, \( J_2 = 14.5 \) Hz), 3.53-3.59 (1H, m), 4.88 (1H, bs, NH). \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 19.4, 24.5, 25.3, 28.2, 40.8, 41.1, 58.0 (q, \( J_{CF} = 23.6 \) Hz, C-CF\(_3\)), 79.5, 127.7 (q, \( J_{CF} = 287.5 \) Hz), 156.0. \( ^{19}F \) NMR (280 MHz, CDCl\(_3\)): \( \delta \) -77.2 (s, CF\(_3\)). IR(KBr): 33230 (bs), 2952, 1716, 1544, 1265, 1172, 744, 651 cm\(^{-1}\). HRMS (ESI): calcd. for C\(_{12}\)H\(_{22}\)F\(_3\)N\(_2\)O\(_2\) [M+H]\(^+\) 283.1628, found 283.1628.

Optical rotation [\( \alpha \)]\(^{20}\)_D = -2.2 (c = 2.1, MeOH).

HPLC condition: Chiral column 3-AmyCoat (150×4.6 mm), heptane/i-PrOH = 98/2, flow rate = 1 mL/min, wavelength = 206 nm. \( t_r \)\(_{\text{minor}} \) = 12.522 min (2.383), \( t_r \)\(_{\text{major}} \) = 14.905 min (97.617).
tert-butyl ((2-(trifluoromethyl)azepan-2-yl)methyl)carbamate (6e), 99%, >99% ee, white solid, mp 82-84°C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.29-1.34 (2H, m), 1.40 (9H, s), 1.55-1.81 (7H, m), 2.77-2.87 (2H, m), 3.16-3.21 (1H, m), 3.30-3.36 (1H, m), 4.82 (1H, bs, NH). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 22.7, 28.2, 30.5, 30.9, 33.6, 43.4, 44.2, 61.7 (q, \(J_{\text{CF}} = 22.2 \text{ Hz}, \text{C-CF}_3\)), 79.6, 128.4 (q, \(J_{\text{CF}} = 289.0 \text{ Hz}\)), 156.2. \(^19\)F NMR (280 MHz, CDCl\(_3\)): \(\delta\)-77.9 (s, CF\(_3\)). IR(KBr): 3268 (bs), 2953, 1687, 1367, 1255, 1162, 1058, 781 cm\(^{-1}\). HRMS (ESI): calcd. for C\(_{12}\)H\(_{22}\)F\(_3\)N\(_2\)O\(_2\) [M+H]\(^+\) 297.1785, found 297.1785.

Optical rotation \([\alpha]^{20}_D = -1.4\) (c = 1, CH\(_2\)Cl\(_2\)).

HPLC condition: Chiral column Kromasil-3-AmyCoat (150x4.6 mm), heptane/i-PrOH = 95.5/0.5, flow rate = 1 mL/min, wavelength = 206 nm. \(t_r_{\text{minor}} = 12.238\) min (0.148), \(t_r_{\text{major}} = 8.512\) min (99.852)
$^1$H NMR (400 MHz, CDCl$_3$) for compound 2a
$^1$H NMR (400 MHz, CDCl$_3$) for compound 2a aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 2a
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 2a
$^1$H NMR (400 MHz, CDCl$_3$) for compound 2b
$^1$H NMR (400 MHz, CDCl$_3$) for compound 2b aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 2b
\(^{19}\text{F} \text{NMR (280 MHz, CDCl}_3\text{)}\) for compound 2b
$^1$H NMR (400 MHz, CDCl$_3$) for compound 2c
$^1$H NMR (400 MHz, CDCl$_3$) for compound 2c aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 2c
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 2c
$^1$H NMR (400 MHz, CDCl$_3$) for compound 2d
$^1$H NMR (400 MHz, CDCl$_3$) for compound 2d aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 2d
\(^{19}\text{F NMR (280 MHz, CDCl}_3\text{)}\) for compound \(2d\)
\(^1\)H NMR (400 MHz, CDCl\(_3\)) for compound 2e
$^1$H NMR (400 MHz, CDCl$_3$) for compound 2e aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 2e
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 2e
$^1$H NMR (400 MHz, CDCl$_3$) for compound 3a
\[^1\text{H}\text{ NMR (400 MHz, CDCl}_3\text{)}\text{ for compound 3a aliphatic region}\]
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 3a
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 3a
$^1$H NMR (400 MHz, CDCl$_3$) for compound 3b
$^1$H NMR (400 MHz, CDCl$_3$) for compound 3b aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 3b
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 3b
$^1$H NMR (400 MHz, CDCl$_3$) for compound 3c
$^1$H NMR (400 MHz, CDCl$_3$) for compound 3c aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 3c
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 3c
$^1$H NMR (400 MHz, CDCl$_3$) for compound 3d
$^1$H NMR (400 MHz, CDCl$_3$) for compound 3d aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 3d
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 3d
$^1$H NMR (400 MHz, CDCl$_3$) for compound 3e
$^1$H NMR (400 MHz, CDCl$_3$) for compound 3e aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 3e
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 3e
$^1$H NMR (400 MHz, D$_2$O) for compound 4a
$^1$H NMR (400 MHz, D$_2$O) for compound 4a aliphatic region
$^{13}$C NMR (100 MHz, D$_2$O) for compound 4a
$^{19}$F NMR (280 MHz, D$_2$O) for compound 4a
$^1$H NMR (400 MHz, D$_2$O) for compound 4b
$^1$H NMR (400 MHz, D$_2$O) for compound 4b aliphatic region
\(^{13}\)C NMR (100 MHz, D\(_2\)O) for compound 4b
$^{19}$F NMR (280 MHz, D$_2$O) for compound 4b
$^{1}$H NMR (400 MHz, D$_2$O) for compound 4c
$^1$H NMR (400 MHz, D$_2$O) for compound 4c aliphatic region
$^{13}$C NMR (100 MHz, D$_2$O) for compound 4c
^{19}F NMR (280 MHz, D_{2}O) for compound 4c
$^1$H NMR (400 MHz, D$_2$O) for compound 4e
$^1$H NMR (400 MHz, D$_2$O) for compound 4e aliphatic region
$^{13}$C NMR (100 MHz, D$_2$O) for compound 4e
$^{19}$F NMR (280 MHz, D$_2$O) for compound 4e
$^1$H NMR (400 MHz, CDCl$_3$) for compound 4a
$^1$H NMR (400 MHz, CDCl$_3$) for compound 5a aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 5a
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 5a
$^1$H NMR (400 MHz, CDCl$_3$) for compound 5b
$^1$H NMR (400 MHz, CDCl$_3$) for compound 5b aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 5b
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 5b
$^{1}$H NMR (400 MHz, CDCl$_3$) for compound 5c
$^1$H NMR (400 MHz, CDCl$_3$) for compound 5c aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 5c
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 5c
$^1$H NMR (400 MHz, CDCl$_3$) for compound 5e
$^1$H NMR (400 MHz, CDCl$_3$) for compound 5e aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 5e
\[ {\textsuperscript{19}}F \text{ NMR (280 MHz, CDCl}_3\text{)} \text{ for compound 5e} \]
$^1$H NMR (400 MHz, CDCl$_3$) for compound 6a
$^1$H NMR (400 MHz, CDCl$_3$) for compound 6a aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 6a
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 6a
$^1$H NMR (400 MHz, CDCl$_3$) for compound 6b
\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] for compound 6b aliphatic region}
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 6b
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 6b
$^{1}$H NMR (400 MHz, CDCl$_3$) for compound 6c
$^1$H NMR (400 MHz, CDCl$_3$) for compound 6c aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 6c
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 6c
$^1$H NMR (400 MHz, CDCl$_3$) for compound 6e
$^1$H NMR (400 MHz, CDCl$_3$) for compound 6e aliphatic region
$^{13}$C NMR (100 MHz, CDCl$_3$) for compound 6e
$^{19}$F NMR (280 MHz, CDCl$_3$) for compound 6e
References