Supporting Information
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Asymmetric Synthesis of cis-(S,R)-3-Amino-4-fluoro-1-methylpyrrolidine

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Supporting Information
EXPERIMENTAL SECTION

General. All chemicals were used as purchased unless otherwise noted. The solvents were reagent grade, reactions were run under a positive pressure of nitrogen unless otherwise noted. Chromatographic separations were performed by flash column chromatography on silica gel. TLC analyses were performed on silica gel plate. Visualization was achieved by UV (254 nm), and staining with iodine, phosphomolybdic acid and heating. Compounds are characterized by $^1$H NMR (400 MHz, Bruker), $^{13}$C NMR (100 MHz, Bruker) and $^{19}$F NMR (376 MHz, Bruker). $^1$H NMR data are reported relative to residual solvent signals, and are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The high-resolution mass spectra (HRMS) were recorded on Agilent 1260-6530 Q-TOF spectrometer (ESI).

Preparation of cis isomer

![1a](image)

1-(2,5-Dihydro-1H-pyrrol-1-yl)-2,2,2-trifluoroethanone (1a). Trifluoroacetic acid (TFA) (22.3 g, 15 mL, 5.2 equiv) was added dropwise to a solution of tert-butyl 2,5-dihydro-1H-pyrrole-1-carboxylate (5 g, 29.6 mmol, 1 equiv). The mixture was stirred for 2 hours until TLC indicates the disappearance of the starting material. TFA was evaporated, and the residue was rinsed with dichloromethane (2 × 20 mL), evaporated to dryness and used in the next step without further purification. The residue was dissolved in anhydrous dichloromethane (40 mL) and cooled to 0 °C. Pyridine (6 g, 82.8 mmol, 2.8 equiv) and 4-dimethylaminopyridine (DMAP) (0.2 g, 1.5 mmol, 0.05 equiv) were added to the solution. After stirring for 5 min, Trifluoroacetic anhydride (TFAA) (7.6 g, 32.5 mmol, 1.1 equiv) was added to the above solution at 0 °C. The mixture was stirred at 25 °C for 16 hours until TLC showed the complete of the reaction.
The reaction mixture was diluted with DCM (30 mL), and successively washed with 1 M H$_2$SO$_4$ (3 × 20 mL), brine (20 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated to give a light brown oil (4.45 g, 92% yield). The product 1a was used without further purification ($^{19}$F NMR indicates that the crude material may contain residue TFAA/TFA). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.84-5.80 (m, 2H), 4.42 (s, 2H), 4.31 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.6 (q, $J$ = 36 Hz), 124.8 (dd, $J$ = 23, 1 Hz), 116.3 (q, $J$ = 285 Hz), 53.2 (dd, $J$ = 161, 4 Hz). $^{19}$F NMR (376 MHz CDCl$_3$) δ -73.49 ppm.

\[ \text{1b} \]

1-(6-Oxa-3-azabicyclo[3.1.0]hexan-3-yl)-2,2,2-trifluoroethanone (1b). To a solution of 1a (5 g, 30.3 mmol, 1 equiv) in 150 mL dichloromethane was added m-CPBA (10.45 g, 60.6 mmol, 2 equiv, 70%). The reaction mixture was stirred at room temperature for 4 days, until the HPLC showed no further conversion of the starting material 1a. The mixture was filtered and the precipitate was washed with dichloromethane (100 mL). The combined organic layer was washed with NaHCO$_3$ (50 mL × 3) and brine (100 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by silica column chromatography to give 1b as a yellow oil (3.84 g, 70% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.98-3.93 (m, 2H), 3.78-3.77 (m, 2H), 3.64 (d, $J$ = 12.8 Hz, 1H), 3.43 (d, $J$ = 14.0 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 156.4 (q, $J$ = 37 Hz), 115.9 (q, $J$ = 286 Hz), 54.3 (dd, $J$ = 192, 2 Hz) 47.8 (dd, $J$ = 63, 4 Hz). $^{19}$F NMR (376 MHz CDCl$_3$) δ -72.6 ppm. HR-MS (HPLC/MS ESI) calcd for C$_6$H$_7$F$_3$NO$_2$ 182.0423 [M + H]$^+$, found 182.0416.

\[ \text{1c} \]

1-((3S,4S)-3-Azido-4-((trimethylsilyl)oxy)pyrrolidin-1-yl)-2,2,2-trifluoroethanone
A 100 mL flask equipped with a stirring bar was charged with 632 mg of (R, R)-Jacobsen ring-opening catalyst (1.00 mmol, 0.02 equiv), flushed with N₂, and sealed. Epoxide 1b (9.05 g, 50.0 mmol, 1 equiv) and TMSN₃ (6.05 g, 52.5 mmol, 1.05 equiv) were added sequentially at 25 °C. The reaction mixture was allowed to stir for 12 h, at which time the excess TMSN₃ was removed under reduced pressure, and the product 1c was isolated by silica column chromatography. The product was obtained as a light brown liquid (12.5 g, 85% yield, 95.3% ee). ¹H NMR (400 MHz, CDCl₃) δ 4.23-4.17 (m, 1H), 3.96-3.43 (m, 5H), 0.11 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 155.6 (dq, J = 14, 36 Hz), 116.0 (q, J = 285 Hz), 73.1 (d, J = 228 Hz), 52.8 (dd, J = 83, 3 Hz), 52.8 (dd, J = 83, 3 Hz), 0.45. ¹⁹F NMR (376 MHz CDCl₃) δ -72.6 ppm. HR-MS (HPLC/MS ESI) calcd for C₉H₁₅F₃N₄O₂Si 297.0989 [M + H]⁺, found 297.1014.

1-(3S,4S)-3-Azido-4-hydroxypyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (3) A 250 mL flask equipped with a stirring bar was charged with 1c (2.5 g, 8.44 mmol, 1 equiv), MeOH (30 mL), and trifluoroacetic acid (1 drop). The mixture was allowed to stir at 25 °C for 1 hour. MeOH was evaporated under reduced pressure, and the residue was purified by silica column chromatography to afford 3 as a light yellow liquid (1.82 g, 95% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.36-4.32 (m, 1H), 4.12-3.62 (m, 6H). ¹³C NMR (100 MHz, CDCl₃): δ = 156.5 (q, J = 37 Hz), 116.1 (q, J = 286 Hz), 72.5 (d, J = 251 Hz), 64.4 (d, J = 238 Hz), 52.7 (dd, J = 89, 3 Hz), 52.7 (dd, J = 81, 3 Hz). ¹⁹F NMR (376 MHz CDCl₃) δ -72.5 ppm. HR-MS (HPLC/MS ESI) calcd for C₆H₈F₃N₄O₂Na 247.0413 [M + Na]⁺, found 247.0430.

Method: Fluorination by Diethylaminosulfur trifluoride (DAST)
A solution of 3 (0.5 g, 2.23 mmol, 1 equiv) in 15 mL of anhydrous DCM under N₂ atmosphere, was cooled to -60 °C by a dry ice/ethanol bath. Diethylaminosulfur trifluoride (DAST) (0.98 mL, 10 mmol, 4.5 equiv) was added to the above solution. The reaction mixture was slowly warmed up to room temperature and stirred at room temperature for 16 hours. TLC was used to monitor the reaction. Once the starting material was consumed, the mixture was carefully quenched by adding saturated NaHCO₃ (10 mL), and extracted with EA (3 × 10 mL). The organic layers were combined and washed with water (10 mL), dried over anhydrous MgSO₄, and concentrated in vacuo to give the crude product. Further column chromatography provides the trans-9 in 66% isolated yield.

1-((3S,4R)-3-Azido-4-fluoropyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (10)

Method A: Fluorination by NMe₄(2, 6-DimethylC₆H₅OH)/SO₂F₂

Tetramethyl ammonium 2, 6-dimethylphenoxide (prepared from 2, 6-Dimethylphenoxide and tetramethylammonium hydroxide ) (3.2 g, 16.4 mmol, 4 equiv) in 20 mL anhydrous DMF was stirred at 25 °C under the atmosphere of sulfuryl fluoride balloon (1 atm) for 1 hour. A solution of 3 (0.94 g, 4.1 mmol, 1 equiv) in anhydrous DMF (10 mL) was added to the above solution. The resulting solution was stirred at 25 °C for 24 h. The reaction mixture was then diluted with ethyl acetate (100 mL), and the organic layer was washed with water (3 × 10 mL), dried over anhydrous MgSO₄, and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography on silica gel. The product 10 was obtained as a yellow oil (0.68 g, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.14-4.98 (m, 1H), 3.98-3.70 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 155.7 (dq, J = 8, 37 Hz), 116.0 (q, J = 287 Hz), 92.0 (dd, J = 238, 185 Hz), 62.1 (dd, J = 27, 256 Hz), 50.6 (m), 49.5 (m). ¹⁹F NMR (376 MHz CDCl₃) δ -72.8, -181.5 ppm. HR-MS (HPLC/MS ESI) calcd for C₆H₅F₄N₄O₂ 227.0551 [M + H]⁺,
found 227.0542.

**Method B: Fluorination by Diethylaminosulfur trifluoride (DAST)/pyridine**

A solution of 3 (0.22 g, 0.96 mmol, 1 equiv) in 15 mL anhydrous DCM under N₂ atmosphere, was cooled to -30 °C by a dry ice/ethanol bath. Excess Pyridine (1 mL, 12 mmol, 12 equiv) and DAST (0.46 mL, 4.5 mmol, 4.5 equiv) were added to the above solution successively, and the reaction mixture was slowly warmed up to room temperature and stirred for 16 hours. TLC was used to monitor the reaction. Once the starting material was consumed, the mixture was carefully quenched in a vent hood by adding saturated NaHCO₃, and extracted with EA (3 × 10 mL). The organic layer was washed with water (3 × 10 mL), dried over anhydrous MgSO₄, and concentrated in vacuo to give the crude product (0.16 g, ~70% yield). The ratio of the cis 10 (-197 ppm) and trans 9 (-181 ppm) isomer (cis:trans = 11:1) was measured by ¹⁹F NMR.

![11](image)

**tert-Butyl (3S,4R)-4-fluoro-1-(2,2,2-trifluoroacetyl)pyrrolidin-3-yl)carbamate (11).** A solution of 10 (0.46 g, 2 mmol, 1 equiv) in MeOH (20 mL) was treated with solid PtO₂ (22.7 mg, 0.1 mmol, 0.05 equiv) and (Boc)₂O (0.52 g, 2.4 mmol, 1.2 equiv) under a H₂ atmosphere (balloon pressure) and stirred at 25 °C for 40 h. The reaction mixture was filtered, washed with MeOH (20 mL), and concentrated in vacuo. The residue was purified by silica column chromatography. The product 11 was obtained as an off-white solid (0.54 g, 88% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.28-5.22 (m, 1H), 5.17-4.99 (m, 1H), 4.46-4.34 (m, 1H), 4.11-3.63 (m, 3H), 3.40-3.24 (m, 1H), 1.40 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 155.5 (m), 116.0 (q, J = 286 Hz), 90.4 (dd, J = 183, 183 Hz), 80.5 (d, J = 10 Hz), 60.0, 51.5 (m), 47.5 (d, J = 61 Hz), 28.1. ¹⁹F NMR (376 MHz CDCl₃) δ -72.5, -196.2 ppm. HR-MS (HPLC/MS ESI) calcd for C₁₁H₁₆F₄N₂O₃Na 323.0989 [M + H]⁺, found 323.0996.
tert-Butyl ((3S, 4R)-4-fluoro-1-methylpyrrolidin-3-yl)carbamate (13). A 250 mL flask equipped with a stirring bar was charged with 11 (0.61 g, 2 mmol, 1 equiv) and 20 mL of MeOH, and then treated with solid K$_2$CO$_3$ (0.33 g, 2.4 mmol, 1.2 equiv). The mixture was allowed to stir at 25 °C for 5 h. TLC indicates the disappearance of the starting material. Formalin (37%) (1.30 g, 16 mmol, 8 equiv) was added to the solution and stirred at 25 °C for 1 hour. The reaction mixture was cooled to 0-5 °C by an ice bath. NaBH$_4$ (6.05 g, 16 mmol, 8 equiv) was added to the above mixture portion wise, and the reaction mixture was stirred at 25 °C for 16 hours. The reaction was quenched with saturated NaHCO$_3$ (20 mL), extracted with ethyl acetate (3 × 50 mL), washed with brine (30 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by silica column chromatography. The pure product 13 was obtained as a white solid (0.32 g, 73% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.50-4.91 (m, 2H), 4.29-4.21 (m, 1H), 3.06-2.93 (m, 2H), 2.90-2.69 (m, 1H), 2.35 (s, 3H), 1.44 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.4, 92.1 (d, $J = 180$ Hz), 79.6, 60.9 (d, $J = 22$ Hz), 58.9, 52.4 (d, $J = 16$ Hz), 42.1, 28.2. $^{19}$F NMR (376 MHz CDCl$_3$) δ -189.5 ppm. HR-MS (HPLC/MS ESI) calcd for C$_{10}$H$_{20}$FN$_2$O$_2$ 219.1503 [M + H]$^+$, found 219.1524.

(3S, 4R)-4-Fluoro-1-methylpyrrolidin-3-amine dihydrochloride (1). A 50 mL flask equipped with a stirring bar was charged with 13 (120 mg, 0.55 mmol, 1 equiv) and treated with HCl in MeOH (4 M) (1 mL, 4 mmol, 7 equiv). The reaction mixture was stirred at 25 °C for 2 hours, and evaporated to dryness. The resulting white solid was recrystallized from MeOH/iPrOH. The product was obtained as a white solid (99 mg, 94%). $^1$H NMR (400 MHz, D$_2$O) δ 5.55 (dt, $J = 51.7$, 3.5 Hz, 1H), 4.36 (dtd, $J = 23.4$, 3.5 Hz, 1H), 2.95-2.85 (m, 2H), 1.55-1.25 (m, 9H). $^{13}$C NMR (100 MHz, D$_2$O) δ 155.1, 128.1 (d, $J = 180$ Hz), 79.6, 60.9 (d, $J = 22$ Hz), 58.9, 52.4 (d, $J = 16$ Hz), 42.1, 28.2. $^{19}$F NMR (376 MHz D$_2$O) δ -189.5 ppm. HR-MS (HPLC/MS ESI) calcd for C$_{10}$H$_{20}$FN$_2$O$_2$ 219.1503 [M + H]$^+$, found 219.1524.
8.9, 3.5 Hz, 1H), 4.01 (m, 1H), 3.88 (m, 1H), 3.82 – 3.52 (m, 2H), 3.00 (s, 3H).\(^{13}\)C NMR (101 MHz, D\(_2\)O) \(\delta 90.4\) (d, \(J = 183.82\) Hz), \(59.6\) (d, \(J = 21.21\) Hz), \(54.4\), \(50.3\) (d, \(J = 17.17\) Hz), \(42.6\). \(^{19}\)F NMR (376 MHz, D\(_2\)O) \(\delta -196.7\) ppm, and \(^{19}\)F NMR (376 MHz, CD\(_3\)OD) \(\delta -198.1\) ppm. HRMS (ESI) calcd for C\(_{5}\)H\(_{12}\)Cl\(_2\)FN\(_2\) [M+H]\(^+\) 119.0979, found 119.0978. Melting point: 264 °C-266 °C

Preparation of \textit{trans} isomers

\[ \text{BnHN} \]
\[ \text{HO}^- \]
\[ \text{NBoc} \]

\[ (\pm)-2 \]

\( (\pm)-1\text{-}\textit{tert}-\text{Butoxycarbonyl-trans-3-benzylamino-4-hydroxypyrrolidine} \) \( (2) \) \textit{tert-Butyl 2, 5-dihydro-1H-pyrrole-1-carboxylate} (20 g, 118.3 mmol) was dissolved in 100 mL of newly distilled CH\(_2\)Cl\(_2\), and the solution was cooled to 0-5 °C. \( m\)-CPBA (27.6 g, 120 mmol, purity of 75%, 1.01 equiv) was added over 3 h. After stirring at room temperature for 2 days, the white precipitate that formed was filtered off and the filtrate was successively washed with saturated NaHSO\(_3\) (150 mL), 5% K\(_2\)CO\(_3\) (150 mL) and saturated NaCl (50 mL), dried over anhydrous Na\(_2\)SO\(_4\) and then concentrated in vacuo. The residue was dissolved in water (200 mL) and then benzylamine (30.4 g, 304 mol, 2.4 eq) was added at room temperature. After stirring at room temperature for 2 h, the reaction mixture was stirred at 65 °C for 3 h. Water (250 mL) was added and the mixture was extracted with EtOAc (100 mL \(\times\) 3). The organic layer was washed with water and then concentrated in vacuo. The residue was triturated with \( i\)-Pr\(_2\)O to give \( (\pm)-2 \) as white crystals. The product was used for resolution directly.

\[ \text{BnHN} \]
\[ \text{HO}^- \]
\[ \text{NBoc} \]

\[ 2 \]

\( (3S, 4S)-1\text{-}\textit{tert}-\text{Butoxycarbonyl-trans-3-benzylamino-4-hydroxypyrrolidine} \) \( (2) \) A mixture of \( (\pm)-2 \) (4.0 g, 13.7 mmol) and \(+\)-mandelic acid (2.29 g, 13.7 mmol) in
CH₃CN (75 mL) and water (6 mL) was heated at 70 °C for 30 min, and cooled to room temperature over 4 h. The resulting crystalline precipitates were collected by filtration, washed with CH₃CN and recrystallized from CH₃CN–H₂O (20:1), giving 4.39 g of (3S,4S)-2·(+)-mandelic acid. The crystals were treated with 3% K₂CO₃ (30 mL) and the liberated amine was extracted three times with EtOAc. The combined organic layer was washed with saturated NaCl and dried over Na₂SO₄. Evaporation of the solvent under reduced pressure led to a residual oil, which was crystallized from i-Pr₂O. The resulting crystals were collected by filtration, washed with i-Pr₂O and dried to give (3S, 4S)-2 as white crystals (24% overall yield from tert-Butyl 2, 5-dihydro-1H-pyrrole-1-carboxylate). ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.25 (m, 5H), 4.72-4.48 (m, 3H), 4.33 (brs, 1H), 4.06-3.63 (m, 5H), 2.14-2.05 (m, 3H), 1.42-1.39 (m, 9H). HR-MS (HPLC/MS ESI) calcd for C₁₈H₂₆N₂O₄Na 357.1785 [M + Na]⁺, found 357.1812.

(3S, 4S)-tert-Butyl 3-(N-benzylacetamido)-4-hydroxy-1-pyrrolidine-1-carboxylate (4) 2 (5.0 g, 17.1 mmol) and K₂CO₃ (5.9 g, 34.2 mmol, 2 equiv) were suspended in 50 mL of DCM and 50 mL of H₂O. Ac₂O (2.5 g, 24.6 mmol, 1.45 equiv) was added dropwise to the above solution. The mixture was stirred at room temperature for 18 h. The organic layer was separated, washed with brine and dried over Na₂SO₄. Evaporation of the solvent under reduced pressure provided 4, which was used in the next step without further purification (5.64 g, 98% yield, 97.9% purity). ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.25 (m, 5H), 4.72-4.48 (m, 3H), 4.33 (brs, 1H), 4.06-3.63 (m, 5H), 2.14-2.05 (m, 3H), 1.42-1.39 (m, 9H). HR-MS (HPLC/MS ESI) calcd for C₁₈H₂₆N₂O₄Na 357.1785 [M + Na]⁺, found 357.1812.

tert-Butyl 6-benzyl-3,6-diazabicyclo[3.1.0]hexane-3-carboxylate (5) 4 (0.5 g, 1.5
mmol) was dissolved in 10 mL of THF, and the solution was cooled to -70°C under a dry ice bath. DAST (0.73 g, 4.5 mmol, 3 equiv) was added dropwise, and the mixture was stirred from -70 °C to 25 °C for 18 h, quenched with saturated NaCl solution, extracted with EtOAc, concentrated and then purified by silica column chromatography to afford 5 (0.31 g, 75% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.25 (m, 5H), 3.68-3.48 (m, 4H), 3.29 (dt, J = 2.4, 12.4 Hz, 2H), 2.42-2.38 (m, 2H), 1.42 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 154.5, 138.2, 128.4, 127.6, 127.1, 79.3, 61.0, 48.2, 47.9, 43.5, 42.9, 28.4. HR-MS (HPLC/MS ESI) calcd for C₁₆H₂₆N₃O₂ 293.2020 [M + NH₄]⁺, found 293.1854.

Note: 5 could be synthesized from 2 and SO₂F₂ and Et₃N directly.

(±)-trans-tert-Butyl 3-(benzylamino)-4-fluoropyrrolidin-1-carboxylate (6) 5 (2.0 g, 7.3 mmol) was treated with 20 mL of HF-Et₃N at 80 °C for 24 h. The mixture was washed with saturated NaHCO₃ solution, dried over Na₂SO₄, and then concentrated in vacuo. The crude was purified by silica column chromatography. 6 was obtained as a white solid (1.39 g, 65%). ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.28 (m, 5H), 4.91 (d, J = 51.6 Hz, 1H), 4.18-3.29 (m, 8H), 1.48 (s, 9H). HR-MS (HPLC/MS ESI) calcd for C₁₆H₂₄FN₂O₂ 295.1816 [M + H]⁺, found 295.1818.

(±)-(3S, 4S)-N-Benzyl-4-fluoro-1-methylpyrrolidin-3-amine (7) 6 (10.0 g, 34 mmol) was dissolved in 100 mL of DCM, and cooled to 0-5 °C with an ice bath. TFA (31 g, 272 mmol, 8 equiv) was added dropwise to the above solution. The mixture was stirred at room temperature for 16 h, washed with saturation NaHCO₃ solution, dried over Na₂SO₄, and then concentrated in vacuo. The crude material was used without
further purification. The residue was dissolved in 80 mL of DMF. NaHCO$_3$ (1.2 eq) and CH$_3$I (1.0 eq) were added. The mixture was stirred for 16 h, diluted with saturated 50 mL of saturated NH$_4$Cl, extracted with EtOAc, washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The product 7 was obtained as a white solid (4.9 g, 44% overall yield from 6). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32-7.24 (m, 5H), 4.87 (ddd, $J$ = 53.6, 3.6, 1.6 Hz, 1H), 3.80 (dd, $J$ = 12, 20.8 Hz, 2H), 3.45 (dt, $J$ = 25.6, 6.4 Hz, 1H), 3.11 (dd, $J$ = 9.2, 6.8 Hz, 1H), 2.91 (dd, $J$ = 23.6, 11.6 Hz, 1H), 2.72 (ddd, $J$ = 30, 11.6, 5.6 Hz, 1H), 2.34 (s, 3H), 2.31-2.14 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.5, 128.3, 128.1, 127.0, 98.0 (d, $J$ = 180 Hz), 64.3 (d, $J$ = 25 Hz), 61.4 (d, $J$ = 2 Hz), 61.1 (d, $J$ = 23 Hz), 52.1, 41.9. $^{19}$F NMR (376 MHz CDCl$_3$) $\delta$ -172.4 ppm. HR-MS (HPLC/MS ESI) calcd for C$_{12}$H$_{18}$FN$_2$ 209.1449 [M + H]$^+$, found 209.1447.

(±)-(3S, 4S)-4-Fluoro-1-methylpyrrolidin-3-amine dihydrochloride (8). 7 (0.50 g, 1.52 mmol) was treated with Pd/C (5 wt%, 100 mg) in 80 mL of EtOH. 0.5 mL of HCl in EtOH (2 M) was added to the mixture, and hydrogenated under 5 atm pressure for 16 h. the residue was concentrated and purified by column chromatography, leading to the product as dihydrochloride salt (0.27 g, 92%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 5.62 (dd, $J$ = 46.4 Hz, 1H), 4.29-3.54 (m, 5H), 3.12 (s, 3H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 92.5 (d, $J$ = 183 Hz), 59.4, 56.0, 54.6, 54.3. $^{19}$F NMR (376 MHz CD$_3$OD) $\delta$ -176.6 ppm. HR-MS (HPLC/MS ESI) calcd for C$_5$H$_{12}$FN$_2$ 119.0979 [M + H]$^+$, found 119.0978.

NMR Spectra
1H NMR (376 MHz, CD3OD) δ -19.1 ppm
Chiral purity determination of 1c

rac-1c

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- **Data Store Operator:** wenlong.wang
- **Data Store Path:** /HZ-MS-HPLC-05/EDRDATA/201802/HRC-THF/THF 2018-02-02 14-34-59 SC.SS.zip
- **Data Store Version:** 2.0

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**Area Percent Report**

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Do not use Multiplier & Dilution Factor with ISIDS

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entio-enriched 1c (95.3% ee)

Chiral purity determination of 1

$ee$ was determined on the Cbz derivative of compound 1

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ee of 1 after 2nd recrystallization (100% ee)