Supporting Information

Discovery of Clinical Candidate *N*-((1*S*)-1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethyl)-7-methoxy-2-oxo-2,3-dihydropyrido[2,3-*b*]pyrazine-4(1*H*)-carboxamide (TAK-915): A Highly Potent, Selective, and Brain-Penetrating Phosphodiesterase 2A Inhibitor for the Treatment of Cognitive Disorders

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■ Abbreviations

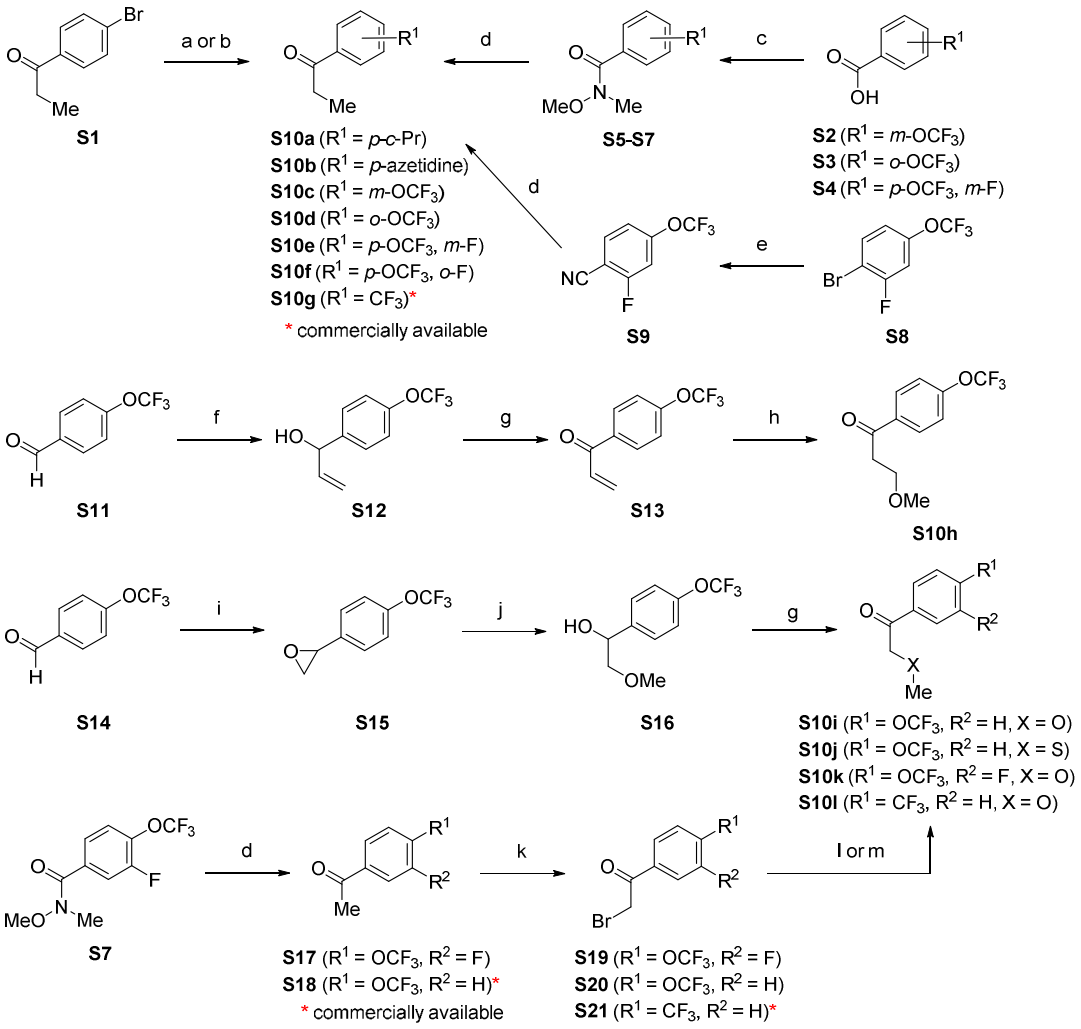
CCDC, Cambridge Crystallographic Data Centre; dppf, 1,1′-bis(diphenylphosphino)ferrocene; DIEA, *N*,*N*-diisopropylethylamine; DMF, *N*,*N*-dimethylformamide; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBt, 1-hydroxybenzotriazole; MFS, molecular formula strings; PDB, Protein Data Bank; RHS, right-hand side; rt, room temperature; TLC, thin layer chromatography

■ Synthetic Section

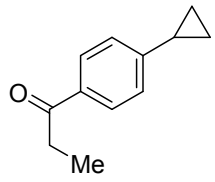
General Chemistry Information. All solvents and reagents were obtained from commercial sources and were used as received. Microwave-assisted reactions were carried out in a single-mode reactor, Biotage Initiator 2.0 or 2.5 microwave synthesizer. Yields were not optimized. All reactions were monitored by thin layer chromatography (TLC) analysis on Merck Kieselgel 60 F254 plates or Fuji Silysia NH plates, or LC–MS (liquid chromatography–mass spectrometry) analysis. LC–MS analysis was performed on a Shimadzu liquid chromatography–mass spectrometer system operating in APCI (+ or −) or ESI (+ or −) ionization mode. Analytes were eluted using a linear gradient with a mobile phase of water/acetonitrile containing 0.05% TFA or 5 mM ammonium acetate and detected at 220 nm. Column chromatography was carried out on silica gel ((Merck Kieselgel 60, 70–230 mesh, Merck) or (Chromatorex NH-DM 1020, 100–200 mesh, Fuji Silysia Chemical, Ltd.)), or on prepacked Purif-Pack columns (SI or NH, particle size: 60 µm, Fuji Silysia Chemical, Ltd.). Analytical HPLC was performed using a Corona Charged Aerosol Detector or photo diode array detector with a Capcell Pak C18AQ (3.0 mm ID × 50 mm L, Shiseido, Japan) or L-column2 ODS (2.0 mm ID × 30 mm L, CERI, Japan) column at a temperature of 50 °C and a flow rate of 0.5 mL/min. Mobile phases A and B under neutral conditions were a mixture of 50 mmol/L ammonium acetate, water, and acetonitrile (1:8:1, v/v/v) and a mixture of 50 mmol/L ammonium acetate and acetonitrile (1:9, v/v), respectively. The ratio of mobile phase B was increased linearly from 5% to 95% over 3 min, and then maintained at 95% over the next 1 min. Mobile phases A and B under acidic conditions were a mixture of 0.2% formic acid in 10 mmol/L ammonium formate and 0.2% formic acid in acetonitrile, respectively. The ratio of mobile phase B was increased linearly from 14% to 86% over 3 min, and then maintained at 86% over the next 1 min. All final test compounds were purified to >95% chemical purity as measured by analytical HPLC. Elemental analyses were carried out by Takeda Analytical Laboratories, and all results were within ±0.4% of the theoretical values. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Mercury-300 (300 MHz), Varian (400 MHz), Bruker DPX300 (300 MHz), or Bruker Avance III (400 MHz) instrument. All ^{1}H NMR spectra were consistent with the proposed structures. All

proton shifts are given in parts per million (ppm) downfield from tetramethysilane (δ) as the internal standard in deuterated solvent, and coupling constants (*J*) are in hertz (Hz). NMR data are reported as follows: chemical shift, integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; dd, doublet of doublets; td, triplet of doublets; ddd, doublet of doublet of doublets; and brs, broad singlet), and coupling constants. Very broad peaks for protons of, for example, hydroxyl and amino groups are not always indicated.

Scheme 1. Synthesis of Common Ketone Intermediates **S10** for RHS Benzylamine Moieties[a]

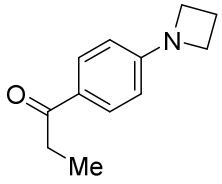


[a] Reagents and conditions: (a) cyclopropylboronic acid, $PdCl_2$(dppf), K_3PO_4, DME, H_2O, 85 °C, 20 h, 78% (for **S10a**); (b) azetidine, $Pd_2(dba)_3$, Xantphos, NaO*tert*-Bu, toluene, 85 °C, 20 h, 73% (for **S10b**); (c) *N*,*O*-dimethylhydroxylamine hydrochloride, EDCI or EDCI·HCl, HOBt or HOBt·H_2O, Et_3N, DMF, 0 °C–rt, 16 h, 86–96%; (d) EtMgBr, Et_2O, THF, 0 °C to rt, 16 h–3 days, 69–96%; (e) $ZnCN_2$, $Pd_2(dba)_3$, dppf, DMF, 100 °C, overnight, 43%; (f) vinylmagnesium bromide, THF, 0 °C, 2 h, 60%; (g) 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (Dess–Martin periodinane), CH_3CN, 0 °C or rt, 1–1.5 h, 67–97%; (h) $PdCl_2(CH_3CN)_2$, MeOH, CH_2Cl_2, 0 °C to rt, 50%; (i) $(CH_3)_3SOI$, NaH, DMSO, THF, rt, 1 h, 45%; (j) NaOMe, DMF, 60 °C, 2 h, 65%; (k) Br_2, AcOH, 50 °C, 1 or 3 h, 82%; (l) MeOH, Ag_2CO_3, $BF_3{\cdot}OEt_2$, 50–60 °C, 2.5 h–overnight, 80–90%; (m) NaSMe, THF, 0 °C to rt, 2 h, 86%.



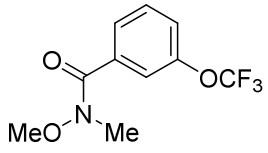
S10a

1-(4-Cyclopropylphenyl)propan-1-one (S10a). A mixture of 1-(4-bromophenyl)propan-1-one (**S1**) (1.07 g, 5.00 mmol), cyclopropylboronic acid (558 mg, 6.50 mmol, $PdCl_2$(dppf) (183 mg, 0.25 mmol) and K_3PO_4 (2.12 g, 10.0 mmol) in DME (15 mL) and water (5 mL) was stirred at 85 °C for 20 h under N_2. The mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 9:1 to 7:3) to give **S10a** (679 mg, 3.90 mmol, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73–0.82 (2H, m), 1.01–1.10 (2H, m), 1.21 (3H, t, *J* = 7.2 Hz), 1.94 (1H, tt, *J* = 8.3, 5.0 Hz), 2.97 (2H, q, *J* = 7.2 Hz), 7.08–7.16 (2H, m), 7.82–7.90 (2H, m). MS (ESI/APCI) *m*/*z* 174.89 $[M + H]^+$.



S10b

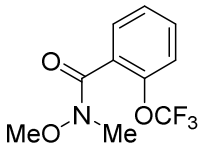
1-(4-(Azetidin-1-yl)phenyl)propan-1-one (S10b). A mixture of 1-(4-bromophenyl)propan-1-one (**S1**) (639 mg, 3.00 mmol), azetidine (303 μL, 4.50 mmol), $Pd_2(dba)_3$ (137 mg, 0.15 mmol), xantphos (174 mg, 0.30 mmol) and sodium *tert*-butoxide (432 mg, 4.50 mmol) in toluene (15 mL) was stirred under N_2 at 85 °C for 20 h.The mixture was quenched with water at rt and extracted with EtOAc. The organic layer was separated, washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 19:1 to 4:1) to give **S10b** (414 mg, 2.19 mmol, 73%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, t, *J* = 7.3 Hz), 2.42 (2H, quin, *J* = 7.3 Hz), 2.90 (2H, q, *J* = 7.2 Hz), 3.99 (4H, t, *J* = 7.3 Hz), 6.32–6.39 (2H, m), 7.82–7.90 (2H, m).



S5

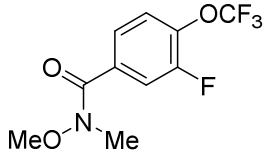
N-Methoxy-N-methyl-3-(trifluoromethoxy)benzamide (S5). To a mixture of 3-(trifluoromethoxy)benzoic acid (**S2**) (5.00 g, 24.3 mmol), EDCI (7.03 g, 36.6 mmol) and HOBt (4.94 g, 36.6 mmol) in DMF (50 mL) were added *N*,*O*-dimethylhydroxylamine hydrochloride (2.63 g, 26.7 mmol) and Et_3N (7.36 g, 72.9 mmol). The mixture was stirred at 10 °C for 16 h, and then

poured into water (100 mL). The mixture was extracted with EtOAc (150 mL × 3), washed with saturated aqueous NaCl (400 mL × 3), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford **S5** (5.31 g, 21.3 mmol, 88%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (3H, s), 3.55 (3H, s), 7.28–7.34 (1H, m), 7.45 (1H, t, *J* = 8.0 Hz), 7.57 (1H, s), 7.64 (1H, d, *J* = 8.0 Hz).



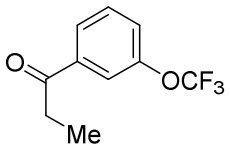
S6

***N*-Methoxy-*N*-methyl-2-(trifluoromethoxy)benzamide (S6).** To a mixture of 2-(trifluoromethoxy)benzoic acid (**S3**) (5.00 g, 24.3 mmol), EDCI (7.03 g, 36.6 mmol) and HOBt (4.94 g, 36.6 mmol) in DMF (50 mL) were added *N*,*O*-dimethylhydroxylamine hydrochloride (2.63 g, 26.7 mmol) and Et_3N (7.36 g, 72.9 mmol). The mixture was stirred at 10 °C for 16 h, and then poured into water (100 mL). The mixture was extracted with EtOAc (150 mL × 3), washed with saturated aqueous NaCl (300 mL × 3), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford **S6** (5.21 g, 20.9 mmol, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (3H, s),3.45 (3H, s), 7.27–7.37 (2H, m), 7.39–7.50 (2H, m).



S7

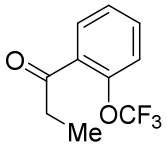
***3*-Fluoro-*N*-methoxy-*N*-methyl-4-(trifluoromethoxy)benzamide (S7).** A mixture of 3-fluoro-4-(trifluoromethoxy)benzoic acid (**S4**) (15.0 g, 66.9 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (7.18 g, 73.6 mmol), EDCI·HCl (16.7 g, 87.0 mmol), HOBt·H_2O (13.3 g, 87.0 mmol) and Et_3N (12.1 mL, 87.0 mmol) in DMF (200 mL) was stirred at rt for 64 h. The mixture was quenched with water and extracted with EtOAc. The organic layer was separated, washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 19:1 to 4:1) to give **S7** (17.6 g, 65.7 mmol, 98%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (3H, s), 3.56 (3H, s), 7.30–7.39 (1H, m), 7.52–7.64 (2H, m). MS (ESI/APCI) *m*/*z* 268.0 $[M + H]^+$.



S10c

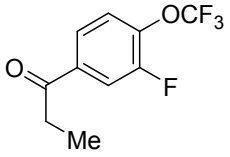
***1*-(3-(Trifluoromethoxy)phenyl)propan-1-one (S10c).** To a solution of *N*-methoxy-*N*-methyl-3-(trifluoromethoxy)benzamide (**S5**) (5.31 g, 21.3 mmol) in THF (50 mL) was added dropwise 3 M EtMgBr solution in Et_2O (14.2 mL, 42.6 mmol) at 0 °C under N_2. The

mixture was stirred at 12 °C for 16 h and then poured into saturated aqueous NH_4Cl (50 mL). The mixture was extracted with EtOAc (80 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 10:1) to afford **S10c** (3.23 g, 14.8 mmol, 69%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t, *J* = 7.2 Hz), 3.01 (2H, q, *J* = 7.2 Hz), 7.34–7.44 (1H, m), 7.51 (1H, t, *J* = 8.0 Hz), 7.81 (1H, s), 7.85–7.92 (1H, m).



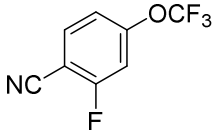
S10d

1-(2-(Trifluoromethoxy)phenyl)propan-1-one (S10d). To a solution of *N*-methoxy-*N*-methyl-2-(trifluoromethoxy)benzamide (**S6**) (5.21 g, 20.9 mmol) in THF (30 mL) was added dropwise 3 M EtMgBr solution in Et_2O (13.9 mL, 41.7 mmol) at 0 °C under N_2. The mixture was stirred at 10 °C for 16 h and then poured into saturated aqueous NH_4Cl (50 mL). The mixture was extracted with EtOAc (100 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 10:1) to afford **S10d** (3.23 g, yield: 71%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, t, *J* = 7.2 Hz), 2.95 (2H, q, *J* = 7.2 Hz), 7.28–7.33 (1H, m), 7.34–7.41 (1H, m), 7.48–7.55 (1H, m), 7.70 (1H, dd, *J* = 7.6, 2.0 Hz).



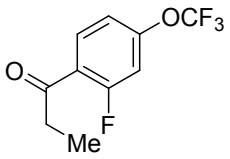
S10e

1-(3-Fluoro-4-(trifluoromethoxy)phenyl)propan-1-one (S10e). To a solution of 3-fluoro-*N*-methoxy-*N*-methyl-4-(trifluoromethoxy)benzamide (**S7**) (5.00 g, 18.7 mmol) in THF (200 mL) at 0 °C was added dropwise 3 M ethylmagnesium bromide solution in Et_2O (7.49 mL, 22.5 mmol). The mixture was stirred at rt for 3 days. The mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 49:1 to 7:3) to give **S10e** (2.60 g, 11.0 mmol, 59%) as a pale yellow. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, *J* = 7.2 Hz), 2.98 (2H, q, *J* = 7.3 Hz), 7.34–7.49 (1H, m), 7.71–7.88 (2H, m).



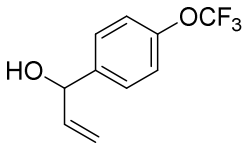
S9

2-Fluoro-4-(trifluoromethoxy)benzonitrile (S9). A mixture of dicyanozinc (4.53 g, 38.6 mmol), 1-bromo-2-fluoro-4-(trifluoromethoxy)benzene (**S8**) (10.0 g, 38.6 mmol), $Pd_2(dba)_3$ (1.77 g, 1.93 mmol) and dppf (2.14 g, 3.86 mmol) in DMF (150 mL) was stirred at 100 °C overnight under N_2. The mixture was partitioned between EtOAc and saturated aqueous NaCl. The mixture was filtered through a cake of celite and the filtrate was extracted with EtOAc. The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (basic silica gel, hexane/ethyl acetate, 49:1 to 1:1), followed by a second column chromatography purification (silica gel, hexane/ethyl acetate, 49:1 to 7:3) to give **S9** (3.39 g, 16.5 mmol, 43%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07–7.18 (2H, m), 7.65–7.76 (1H, m).



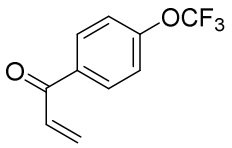
S10f

1-(2-Fluoro-4-(trifluoromethoxy)phenyl)propan-1-one (S10f). To a solution of 2-fluoro-4-(trifluoromethoxy)benzonitrile (**S9**) (3.79 g, 18.5 mmol) in THF (50 mL) at 0 °C was added dropwise 3 M ethylmagnesium bromide solution in Et_2O (7.39 mL, 22.2 mmol). The mixture was stirred at 0 °C for 1 h under N_2. The mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 49:1 to 1:1) to give **S10f** (1.12 g, 4.75 mmol, 26%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14–1.24 (3H, m), 3.00 (2H, qd, J = 7.2, 3.2 Hz), 6.95–7.05 (1H, m), 7.05–7.13 (1H, m), 7.96 (1H, t, J = 8.5 Hz).



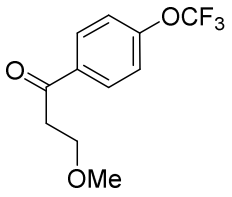
S12

1-(4-(Trifluoromethoxy)phenyl)prop-2-en-1-ol (S12). To a solution of 4-(trifluoromethoxy)benzaldehyde (**S11**) (21.0 g, 110 mmol) in THF (316 mL) at 0 °C was added dropwise 1 M vinylmagnesium bromide solution in THF (133 mL, 133 mmol). The mixture was stirred at 0 °C for 2 h under Ar. The mixture was quenched with saturated aqueous NH_4Cl at 0 °C and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 100:0 to 4:1) to give **S12** (14.4 g, 66.0 mmol, 60%) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.00–5.15 (2H, m), 5.63 (1H, d, J = 4.5 Hz), 5.85–6.03 (1H, m), 7.31 (2H, d, J = 8.5 Hz), 7.42–7.48 (2H, m). MS (ESI/APCI) m/z 201.0 $[M + H - H_2O]^+$.



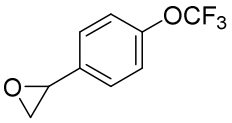
S13

1-(4-(Trifluoromethoxy)phenyl)prop-2-en-1-one (S13). To a solution of 1-(4-(trifluoromethoxy)phenyl)prop-2-en-1-ol (**S12**) (9.8 g, 44.9 mmol) in CH_3CN (150 mL) was added Dess–Martin periodinane (21.0 g, 49.4 mmol) at rt. The mixture was stirred at rt for 1 h. The mixture was evaporated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 100:0 to 17:3) to give **S13** (6.47 g, 29.9 mmol, 67%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (1H, dd, *J* = 10.5, 1.5 Hz), 6.46 (1H, dd, *J* = 17.1, 1.7 Hz), 7.13 (1H, dd, *J* = 17.0, 10.5 Hz), 7.31 (2H, d, *J* = 7.9 Hz), 7.98–8.04 (2H, m). MS (ESI/APCI) *m*/*z* 217.0 $[M + H]^+$.



S10h

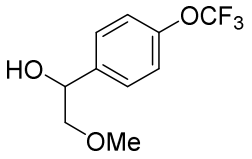
3-Methoxy-1-(4-(trifluoromethoxy)phenyl)propan-1-one (S10h). To a solution of 1-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one (**S13**) (7.92 g, 36.6 mmol) in CH_2Cl_2 (92 mL) was added methanol (1.48 mL, 36.6 mmol) and $PdCl_2(CH_3CN)_2$ (0.951 g, 3.66 mmol) at 0 °C. The mixture was stirred at rt overnight under Ar and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 100:0 to 17:3) to give **S10h** (4.55 g, 18.3 mmol, 50%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22 (2H, t, *J* = 6.4 Hz), 3.38 (3H, s), 3.82 (2H, t, *J* = 6.4 Hz), 7.22–7.36 (2H, m), 7.97–8.07 (2H, m). MS (ESI/APCI) *m*/*z* 249.0 $[M + H]^+$.



S15

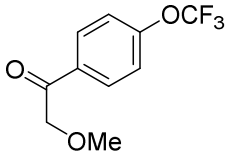
2-(4-(Trifluoromethoxy)phenyl)oxirane (S15). To a suspension of 4-(trifluoromethoxy)benzaldehyde (**S14**) (5.00 g, 26.3 mmol) in DMSO (35 mL) was added portionwise trimethylsulfoxonium iodide (8.10 g, 36.8 mmol) over 5 min. After H_2 gas evolution ceased, the cloudy solution was treated with a solution of 4-(trifluoromethoxy)benzaldehyde (5.00 g, 26.3 mmol) in THF (35 mL) over 15 min. After 1 h of stirring, ethanol (1 mL) was slowly added, then the THF and ethanol were removed under reduced pressure. The DMSO solution was poured into water (100 mL) and then extracted with extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The

residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 100:0 to 7:3) to give **S15** (2.44 g, 12.0 mmol, 45%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76 (1H, dd, *J* = 5.3, 2.7 Hz), 3.16 (1H, dd, *J* = 5.7, 4.2 Hz), 3.87 (1H, dd, *J* = 3.8, 2.7 Hz), 7.14–7.24 (2H, m), 7.27–7.36 (2H, m).



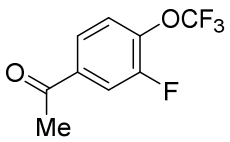
S16

2-Methoxy-1-(4-(trifluoromethoxy)phenyl)ethanol (S16). To a solution of 2-(4-(trifluoromethoxy)phenyl)oxirane (**S15**) (1.00 g, 4.90 mmol) in DMF (5 mL) was added NaOMe (1.32 g, 24.5 mmol) at rt. After being stirred at 60 °C for 2 h, the mixture was partitioned between EtOAc and water, the organic layer was washed with saturated aqueous NaCl, dried over with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 19:1 to 1:9) to give **S16** (0.752 g, 3.18 mmol, 65%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (1H, br. s.), 3.40 (1H, dd, *J* = 9.8, 8.7 Hz), 3.43 (3H, s), 3.54 (1H, dd, *J* = 9.8, 3.7 Hz), 4.90 (1H, dd, *J* = 8.7, 3.0 Hz), 7.12–7.24 (2H, m), 7.34–7.46 (2H, m).



S10i

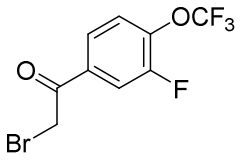
2-Methoxy-1-(4-(trifluoromethoxy)phenyl)ethanone (S10i). To a solution of 2-methoxy-1-(4-(trifluoromethoxy)phenyl)ethanol (**S16**) (930 mg, 3.94 mmol) in CH_3CN (20 mL) at 0 °C was added portionwise Dess–Martin periodinane (2.51 g, 5.91 mmol). The mixture was stirred at rt for 1.5 h. $NaHCO_3$ aqueous solution and $Na_2S_2O_3$ aqueous solution were sequentially added. After stirring for 15 min, the mixture was extracted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 19:1 to 3:2) to afford **S10i** (898 mg, 3.83 mmol, 97%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.36 (3H, s), 4.80 (2H, s), 7.48–7.57 (2H, m), 8.01–8.10 (2H, m).



S17

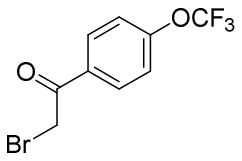
1-(3-Fluoro-4-(trifluoromethoxy)phenyl)ethanone (S17). To a solution of 3-fluoro-*N*-methoxy-*N*-methyl-4-(trifluoromethoxy)benzamide (**S7**) (13.3 g, 49.7 mmol) in THF

(250 mL) was added 3 M MeMgBr solution in Et_2O (21.5 mL, 64.6 mmol) at 0 °C. After being stirred at rt for 4 h, the mixture was quenched with 1 M HCl aqueous solution and extracted with EtOAc. The organic layer was separated, washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 19:1 to 4:1) to give **S17** (10.2 g, 45.9 mmol, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (3H, s), 7.36–7.46 (1H, m), 7.74–7.84 (2H, m).



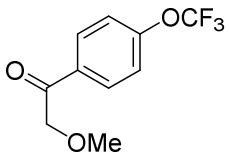
S19

2-Bromo-1-(3-fluoro-4-(trifluoromethoxy)phenyl)ethanone (S19). To a stirred solution of 1-(3-fluoro-4-(trifluoromethoxy)phenyl)ethanone (**S17**) (4.41 g, 19.9 mmol) in AcOH (176 mL) was added Br_2 (1.04 mL, 19.9 mmol). The mixture was stirred at 50 °C for 3 h and then concentrated in vacuo. The mixture was partitioned between EtOAc and $NaHCO_3$ aqueous solution. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 99:1 to 91:9) to give **S19** (4.91 g, 16.3 mmol, 82%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (2H, s), 7.36–7.51 (1H, m), 7.77–7.91 (2H, m). MS (ESI/APCI) *m*/*z* 300.9 $[M - H]^-$.



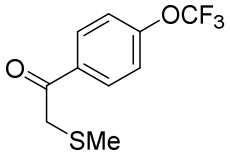
S20

2-Bromo-1-(4-(trifluoromethoxy)phenyl)ethanone (S20). To a solution of 4'-(trifluoromethoxy)acetophenone (**S18**) (10.0 g, 49.0 mmol) in AcOH (100 mL) was added a solution of Br_2 (2.64 mL, 51.5 mmol) in AcOH (10 mL) at rt. The mixture was stirred at 50 °C for 1 h. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo to give **S20** (11.3 g, 39.9 mmol, 82%). This was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (2H, s), 7.33 (2H, d, J = 7.9 Hz), 8.00–8.11 (2H, m).



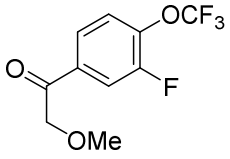
S10i

2-Methoxy-1-(4-(trifluoromethoxy)phenyl)ethanone (S10i). To a solution of 2-bromo-1-(4-(trifluoromethoxy)phenyl)ethanone (**S20**) (9.91 g, 35.0 mmol) in MeOH (250 mL) was added Ag_2CO_3 (12.6 g, 45.5 mmol) and $BF_3{\cdot}OEt_2$ (5.96 g, 42.0 mmol) at rt. After being stirred at 50°C overnight, the mixture was filtered, and the filtrate was concentrated in vacuo. The mixture was diluted with water and extracted with EtOAc. The organic layer was separated, washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 100:0 to 4:1) to give **S10i** (6.85 g, 29.3 mmol, 84%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (3H, s), 4.67 (2H, s), 7.27–7.35 (2H, m), 7.94–8.07 (2H, m).



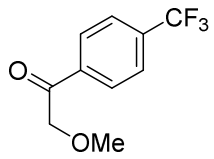
S10j

2-(Methylsulfanyl)-1-(4-(trifluoromethoxy)phenyl)ethanone (S10j). Sodium methanethiolate (1.24 g, 17.7 mmol) was added to a solution of 2-bromo-1-(4-(trifluoromethoxy)phenyl)ethanone (**S20**) (5.00 g, 17.7 mmol) in THF (150 mL) at 0 °C. The mixture was stirred at rt for 1 h, and then passed through a cake of basic silica gel pad (hexane/ethyl acetate, 10:1). The appropriate fractions were concentrated in vacuo to give **S10j** (4.23 g, 16.9 mmol, 96%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (3H, s), 3.74 (2H, s), 7.27–7.36 (2H, m), 7.99–8.10 (2H, m).



S10k

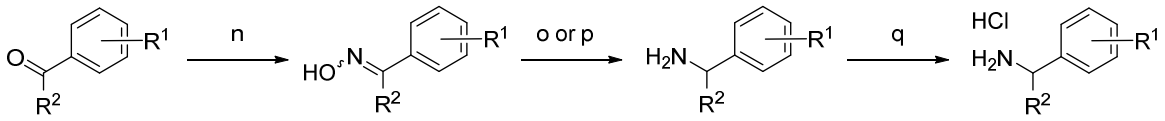
1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethanone (S10k). To a solution of 2-bromo-1-(3-fluoro-4-(trifluoromethoxy)phenyl)ethanone (**S19**) (4.91 g, 16.3 mmol) in MeOH (150 mL) was added Ag_2CO_3 (5.85 g, 21.2 mmol) at rt. $BF_3{\cdot}OEt_2$ (2.48 mL, 19.6 mmol) was added dropwise to the mixture, which was stirred at 60 °C for 2.5 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 19:1 to 4:1) to give **S10k** (3.28 g, 13.0 mmol, 80%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (3H, s), 4.63 (2H, s), 7.38–7.46 (1H, m), 7.75–7.87 (2H, m).



S10l

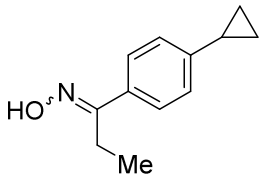
2-Methoxy-1-(4-(trifluoromethyl)phenyl)ethanone (S10l). To a solution of 2-bromo-1-(4-(trifluoromethyl)phenyl)ethanone (**S21**) (2.50 g, 9.36 mmol) in MeOH (50 mL) were added Ag_2CO_3 (2.99 g, 12.2 mmol) and $BF_3{\cdot}OEt_2$ (1.42 mL, 11.2 mmol) at rt. After being stirred at 50 °C for overnight, the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was quenched with water and extracted with EtOAc. The organic layer was separated, washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 19:1 to 4:1) to give **S10l** (1.84 g, 8.43 mmol, 90%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (3H, s), 4.70 (2H, s), 7.75 (2H, d, J = 8.3 Hz), 8.06 (2H, d, J = 7.9 Hz).

Scheme 2. Synthesis of RHS Benzylamine Moieties **S23** and **S24** from Ketones **S10**[a]



S10a-l **S22a-l** **S23a-l** **S24c-f**, **S24h**, **S24l**

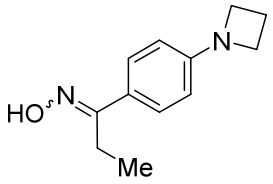
[a] Reagents and conditions: (n) hydroxylammonium chloride, Et_3N, EtOH, rt–80 °C, 3–72 h, (taken on crude); (o) H_2, 10% Pd/C or Raney Ni or 20% $Pd(OH)_2$/C, EtOH or MeOH, rt, 4 h–overnight, (taken on crude); (p) $BH_3{\cdot}THF$, reflux, 20 h or overnight, (taken on crude); (q) HCl, EtOAc, rt.



S22a

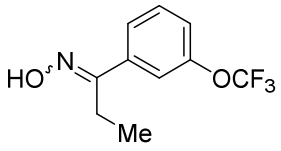
1-(4-Cyclopropylphenyl)-N-hydroxypropan-1-imine (S22a). To a solution of 1-(4-cyclopropylphenyl)propan-1-one (**S10a**) (679 mg, 3.90 mmol) and hydroxylammonium chloride (542 mg, 7.79 mmol) in EtOH (40 mL) was added Et_3N (1.09 mL, 7.79 mmol) at rt. After being stirred for 72 h, the mixture was concentrated in vacuo, quenched with water, and extracted with EtOAc. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford **S22a** (738 mg, 3.90 mmol, quantitative yield). This was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$)

δ 0.66–0.76 (2H, m), 0.93–1.03 (2H, m), 1.05–1.21 (3H, m), 1.84–1.97 (1H, m), 2.49–2.85 (2H, m), 7.07 (2H, d, *J* = 8.3 Hz), 7.44–7.56 (2H, m), 7.80 (1H, brs). MS (ESI/APCI) *m*/*z* 190.2 $[M + H]^+$.



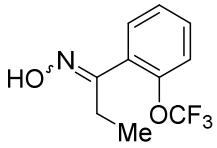
S22b

1-(4-(Azetidin-1-yl)phenyl)-N-hydroxypropan-1-imine (S22b). To a solution of 1-(4-(azetidin-1-yl)phenyl)propan-1-one (**S10b**) (410 mg, 2.17 mmol) in EtOH (30 mL) were added hydroxylammonium chloride (602 mg, 8.67 mmol) and Et_3N (1.21 mL, 8.67 mmol) at rt. After being stirred for 20 h, the mixture was concentrated in vacuo, quenched with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford **S22b** (443 mg, 2.17 mmol, quantitative yield). This was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04–1.22 (3H, m), 2.38 (2H, quin, *J* = 7.3 Hz), 2.49–2.82 (2H, m), 3.91 (4H, t, *J* = 7.2 Hz), 6.38–6.47 (2H, m), 7.29–7.53 (3H, m). MS (ESI/APCI) *m*/*z* 205.1 $[M + H]^+$.



S22c

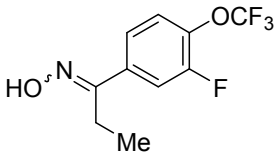
1-(3-(Trifluoromethoxy)phenyl)propan-1-one oxime (S22c). To a solution of 1-(3-(trifluoromethoxy)phenyl)propan-1-one (**S10c**) (3.23 g, 14.8 mmol) in EtOH (20 mL) were added hydroxylammonium chloride (1.23 g, 17.8 mmol) and Et_3N (1.80 g, 17.8 mmol). The mixture was stirred at reflux for 16 h. After cooling to rt, the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and H_2O (50 mL). The aqueous phase was extracted with EtOAc (50 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford **S22c** (3.04 g, 13.0 mmol, 88%) as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.18 (3H, t, *J* = 7.6 Hz), 2.81 (2H, q, *J* = 7.6 Hz), 7.18–7.25 (1H, m), 7.42 (1H, t, *J* = 8.0 Hz), 7.49 (1H, s), 7.51–7.58 (1H, m), 8.44 (1H, brs).



S22d

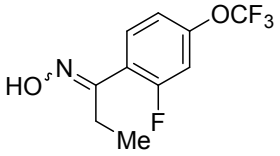
1-(2-(Trifluoromethoxy)phenyl)propan-1-one oxime (S22d). To a solution of 1-(2-(trifluoromethoxy)phenyl)propan-1-one (**S10d**) (3.23 g, 14.8 mmol) in EtOH (25 mL) were added hydroxylammonium chloride (1.12 g, 16.3 mmol) and Et_3N (1.65 g, 16.3 mmol). The mixture

was stirred at reflux for 16 h. After cooling to rt, the mixture was concentrated under reduced pressure to remove EtOH. The residue was partitioned between EtOAc (30 mL) and water (30 mL). The aqueous phase was extracted with EtOAc (30 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford **S22d** (2.31 g, 9.91 mmol, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, t, *J* = 7.6 Hz), 2.77 (2H, q, *J* = 7.6 Hz), 7.27–7.35 (2H, m), 7.36–7.44 (2H, m), 8.28 (1H, s).



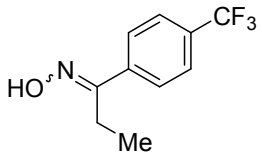
S22e

1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-N-hydroxypropan-1-imine (S22e). To a solution of 1-(3-fluoro-4-(trifluoromethoxy)phenyl)propan-1-one (**S10e**) (2.51 g, 10.6 mmol) in EtOH (35.4 mL) was added hydroxylammonium chloride (0.89 g, 12.8 mmol) and Et_3N (1.78 mL, 12.8 mmol) at rt. The mixture was stirred at rt overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give **S22e** (2.69 g, 10.7 mmol, quantitative yeild) as a pale yellow oil. This was used in the next reaction without further purification.



S22f

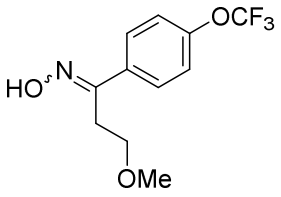
1-(2-Fluoro-4-(trifluoromethoxy)phenyl)-N-hydroxypropan-1-imine (S22f). A mixture of 1-(2-fluoro-4-(trifluoromethoxy)phenyl)propan-1-one (**S10f**) (1.12 g, 4.74 mmol), hydroxylammonium chloride (0.395 g, 5.69 mmol) and Et_3N (0.793 mL, 5.69 mmol) in EtOH (30 mL) was stirred at 80 °C for 3 h. The mixture was poured into saturated aqueous NaCl and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo to give **S22f** (1.27 g, 5.06 mmol, quantitative yeild) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, t, *J* = 7.7 Hz), 2.48–2.85 (1H, m), 6.93–7.14 (2H, m), 7.19–7.53 (1H, m), 7.83–8.53 (1H, m).



S22g

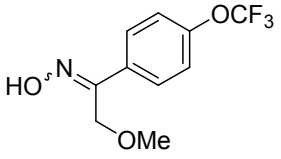
N-Hydroxy-1-(4-(trifluoromethyl)phenyl)propan-1-imine (S22g). To a solution of 1-(4-(trifluoromethyl)phenyl)propan-1-one (**S10g**) (2.00 g, 9.89 mmol) in EtOH (100 mL) were added hydroxylammonium chloride (1.38 g, 19.8 mmol) and Et_3N (2.76 mL, 19.8 mmol) at rt. After

being stirred for 20 h, the mixture was quenched with water and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford **S22g** (2.15 g, 9.90 mmol, quantitative yield). The residue was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06–1.23 (3H, m), 2.54–2.90 (2H, m), 7.47–7.78 (4H, m), 8.14–8.53 (1H, m).



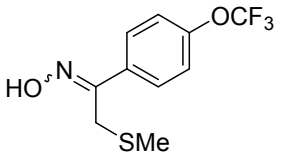
S22h

N-Hydroxy-3-methoxy-1-(4-(trifluoromethoxy)phenyl)propan-1-imine (S22h). To a solution of 3-methoxy-1-(4-(trifluoromethoxy)phenyl)propan-1-one (**S10h**) (4.55 g, 18.3 mmol) in EtOH (92 mL) was added hydroxylammonium chloride (1.53 g, 22.0 mmol) and Et_3N (3.07 mL, 22.0 mmol) at rt. The mixture was stirred at 70 °C overnight. The mixture was poured into water at rt and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo to give **S22h** (4.70 g, 17.9 mmol, 97%) as a yellow oil. This was used in the next reaction without further purification.



S22i

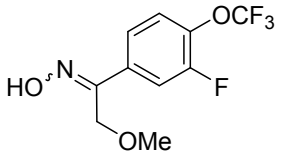
N-Hydroxy-2-methoxy-1-(4-(trifluoromethoxy)phenyl)ethanimine (S22i). To a solution of 2-methoxy-1-(4-(trifluoromethoxy)phenyl)ethanone (**S10i**) (898 mg, 3.83 mmol) in EtOH (20 mL) were added hydroxylammonium chloride (320 mg, 4.60 mmol) and Et_3N (0.641 mL, 4.60 mmol). The mixture was stirred at 80 °C for 4 h and then evaporated under reduced pressure to remove EtOH. The residue was partitioned between EtOAc and water. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford **S22i** (949 mg, 3.81 mmol, 99%) as a colorless oil. This was used in the next reaction without furthur purification. MS (ESI/APCI) *m*/*z* 250.1 $[M + H]^+$.



S22j

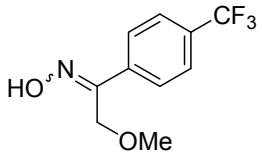
N-Hydroxy-2-(methylsulfanyl)-1-(4-(trifluoromethoxy)phenyl)ethanimine (S22j). A mixture of 2-(methylthio)-1-(4-(trifluoromethoxy)phenyl)ethanone (**S10j**) (3.85 g, 15.4 mmol), triethylamine (3.11 g, 30.8 mmol) and hydroxylammonium chloride (1.39 g, 20.0 mmol) in EtOH (100 mL) was

stirred at 80 °C for 16 h. The mixture was poured into saturated aqueous NaCl and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo to give **S22j** (3.78 g, 14.3 mmol, 93%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (3H, s), 3.83 (2H, s), 7.15–7.39 (2H, m), 7.62–7.87 (2H, m), 8.22 (1H, brs). MS (ESI/APCI) *m*/*z* 266.0 $[M + H]^+$.



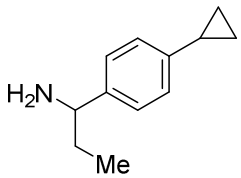
S22k

1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-N-hydroxy-2-methoxyethanimine (S22k). To a solution of 1-(3-fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethanone (**S10k**) (3.28 g, 13.0 mmol) and hydroxylammonium chloride (1.81 g, 26.0 mmol) in EtOH (150 mL) was added Et_3N (3.63 mL, 26.0 mmol) at rt. After being stirred for 60 h (over weekend), the mixture was concentrated in vacuo, quenched with iced water, and extracted with EtOAc. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford **S22k** (3.26 g, 12.2 mmol, 94%). This was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33–3.42 (3H, m), 4.25–4.68 (2H, m), 7.27–7.63 (3H, m), 7.68 (1H, s). MS (ESI/APCI) *m*/*z* 268.1 $[M + H]^+$.



S22l

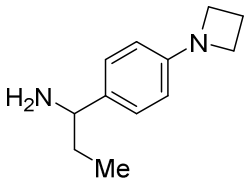
N-Hydroxy-2-methoxy-1-(4-(trifluoromethyl)phenyl)ethanimine (S22l). To a solution of 2-methoxy-1-(4-(trifluoromethyl)phenyl)ethanone (**S10l**) (1.84 g, 8.43 mmol) in EtOH (100 mL) were added hydroxylammonium chloride (1.17 g, 16.9 mmol) and Et_3N (2.35 mL, 16.9 mmol) at rt. After being stirred for 4.5 h, the mixture was concentrated, quenched with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford **S22l** (1.97 g, 8.43 mmol, quantitative yield). This was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33–3.40 (3H, m), 4.29–4.72 (2H, m), 7.58–7.83 (4H, m), 8.01–8.39 (1H, m). MS (ESI/APCI) *m*/*z* 234.1 $[M + H]^+$.



S23a

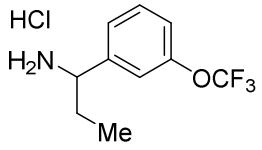
1-(4-Cyclopropylphenyl)propan-1-amine (S23a). To a solution of

1-(4-cyclopropylphenyl)propan-1-one oxime (**S22a**) (738 mg, 3.90 mmol) in THF (40 mL) was added 1 M BH_3·THF solution in THF (7.09 mL, 7.80 mmol) at rt. After being refluxed for 20 h, the mixture was quenched with 1 M HCl aqueous solution at rt and extracted with EtOAc. The organic layer was separated, washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford **S23a** (630 mg, 3.60 mmol, 92%). This was used in the next reaction without further purification.



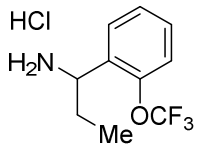
S23b

1-(4-(Azetidin-1-yl)phenyl)propan-1-amine (23b). A mixture of 1-(4-(azetidin-1-yl)phenyl)propan-1-one oxime (**S22b**) (443 mg, 2.17 mmol) and 10% Pd/C (containing 50% water, 45 mg) in MeOH (15 mL) was hydrogenated under balloon pressure at rt for 20 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give **S23b** (410 mg, 2.15 mmol, 99%) as a colorless oil. This was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.3 Hz), 1.61–1.72 (2H, m), 2.28–2.41 (2H, m), 3.70 (1H, t, J = 7.0 Hz), 3.86 (4H, t, J = 7.2 Hz), 6.38–6.46 (2H, m), 7.11–7.19 (2H, m).



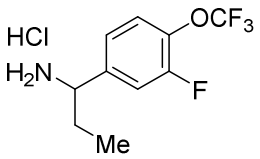
S24c

1-(3-(Trifluoromethoxy)phenyl)propan-1-amine Hydrochloride (24c). A mixture of 1-(3-(trifluoromethoxy)phenyl)propan-1-one oxime (**S22c**) (1.03 g, 4.21 mmol) and Raney Ni (300 mg) in MeOH (100 mL) was hydrogenated under 50 psi at 50 °C for 4 h. The suspension was filtered through a pad of Celite and the filter cake was washed with MeOH (50 mL × 3). The combined filtrate was concentrated to afford the crude product. The residue was purified by preparative HPLC (column: YMC-pack ODS-A 4.6 mm ID × 150 mm L; mobile phase A: 0.05% HCl in water; mobile phase B: 0.05% HCl in acetonitrile; flow rate: 1.5 mL/min). After most of the solvent was removed under reduced pressure, the residue was lyophilized to afford **S24c** (330 mg, 1.29 mmol, 31%) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 0.75 (3H, t, J = 7.2 Hz), 1.71–1.85 (1H, m), 1.92–2.05 (1H, m), 4.17–4.28 (1H, m), 7.34–7.42 (1H, m), 7.51–7.61(3H, m), 8.66 (3H, brs).



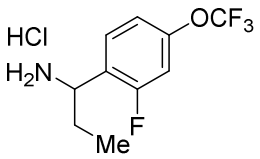
S24d

1-(2-(Trifluoromethoxy)phenyl)propan-1-amine Hydrochloride (S24d). A mixture of 1-(2-(trifluoromethoxy)phenyl)propan-1-one oxime (**S22d**) (2.31 g, 9.91 mmol) and Raney Ni (1.00 g) in MeOH (100 mL) was hydrogenated under 50 psi at 50 °C for 4 h. The suspension was filtered through a pad of Celite and the filter cake was washed with MeOH (50 mL × 2). The combined filtrate was concentrated to afford the crude product as a white wax-like solid. The residue was dissolved in EtOAc (70 mL) and MeOH (10 mL). 4 M HCl solution in EtOAc (40 mL, 160 mmol) was added to the above mixture. The mixture was stirred at 15 ℃ for 2 h and the solvent was removed under reduced pressure. The resulting solid was triturated with MTBE, collected by filtration, rinsed with MTBE (50 mL × 3), and dried to afford **S24d** (1.36 g, 5.32 mmol, 54%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.78 (3H, t, J = 7.2 Hz), 1.76–1.89 (1H, m), 1.96–2.10 (1H, m), 4.31–4.41 (1H, m), 7.39–7.48 (1H, m), 7.49–7.59 (2H, m), 7.84 (1H, dd, J = 6.8, 2.4 Hz), 8.69 (3H, brs). MS (ESI/APCI) m/z 219.9 $[M + H]^+$.



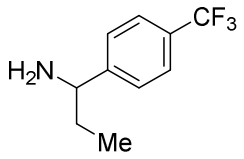
S24e

1-(3-Fluoro-4-(trifluoromethoxy)phenyl)propan-1-amine Hydrochloride (S24e). A mixture of 1-(3-fluoro-4-(trifluoromethoxy)phenyl)propan-1-one oxime (**S22e**) (2.69 g, 10.71 mmol) and 10% Pd/C (containing 50% water, 540 mg) in EtOH (36 mL) was hydrogenated under balloon pressure at rt overnight. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 7:3 to 0:100). The desired fractions were collected and evaporated. To a solution of the residue in EtOAc (10 mL) was added 4 M HCl solution in EtOAc (10 mL, 40 mmol). The mixture was concentrated in vacuo. The resulting solid was triturated with diisopropyl ether, collected by filtration, rinsed with diisopropyl ether, and dried to give **S24e** (1.85 g, 6.76 mmol, 63%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 (3H, t, J = 7.5 Hz), 1.74–1.92 (1H, m), 1.92–2.12 (1H, m), 4.24 (1H, dd, J = 9.0, 5.8 Hz), 7.50 (1H, d, J = 8.5 Hz), 7.67 (1H, td, J = 8.3, 0.9 Hz), 7.80 (1H, dd, J = 11.6, 2.0 Hz), 8.76 (3H, brs).



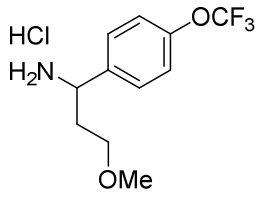
S24f

1-(2-Fluoro-4-(trifluoromethoxy)phenyl)propan-1-amine Hydrochloride (S24f). A mixture of 1-(2-fluoro-4-(trifluoromethoxy)phenyl)propan-1-one oxime (**S22f**) (1.27 g, 5.06 mmol) and 10% Pd/C (containing 50% water, 150 mg) in MeOH (30 mL) was hydrogenated under balloon pressure at rt for 2 days. LC–MS showed no reaction. After the Pd/C was filtered off, Raney nickel (100 mg, 0.85 mmol) was then added to the mixture. The mixture was hydrogenated under balloon pressure at rt for 2 days. LC–MS showed the reaction was slow with most of the starting material remained. After the Raney nickel was filtered off, 20% $Pd(OH)_2/C$ (containing 50% water, 100 mg, 0.71 mmol) was added to the mixture, which was hydrogenated under balloon pressure at rt overnight. The mixture was passed through a cake of celite, and the filtrate was concentrated in vacuo. To the residue was added 4 M HCl solution in EtOAc (5 mL, 20 mmol). The resulting solid was triturated with diisopropyl ether at 0 °C, collected by filtration, rinsed with diisopropyl ether at 0 °C, and dried to give **S24f** (647 mg, 2.36 mmol, 47%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.79 (3H, t, J = 7.3 Hz), 1.73–1.92 (1H, m), 1.93–2.10 (1H, m), 4.32–4.50 (1H, m), 7.41 (1H, d, J = 8.7 Hz), 7.52 (1H, dd, J = 10.5, 1.5 Hz), 7.80 (1H, t, J = 8.5 Hz), 8.56 (2H, brs). MS (ESI/APCI) m/z 221.0 $[M + H]^+$.



S23g

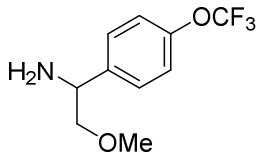
1-(4-(Trifluoromethyl)phenyl)propan-1-amine (S23g). A mixture of crude 1-(4-(trifluoromethyl)phenyl)propan-1-one oxime (**S22g**) (2.15 g, 9.90 mmol) and 20% $Pd(OH)_2/C$ (containing 50% water, 200 mg) in EtOH (100 mL) was hydrogenated under balloon pressure at rt for 5 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo and purified by column chromatography (basic silica gel, hexane/ethyl acetate, 9:1 to 1:1) to give **S23g** (988 mg, 4.86 mmol, 49%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.3 Hz), 1.62–1.77 (2H, m), 3.89 (1H, t, J = 6.8 Hz), 7.44 (2H, d, J = 7.9 Hz), 7.58 (2H, d, J = 7.9 Hz). NH_2 peak was not observed. MS (ESI/APCI) m/z 204.1 $[M + H]^+$.



S24h

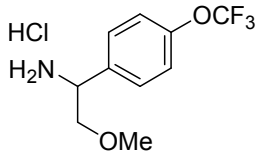
3-Methoxy-1-(4-(trifluoromethoxy)phenyl)propan-1-amine Hydrochloride (S24h). A mixture of 3-methoxy-1-(4-(trifluoromethoxy)phenyl)propan-1-one oxime (**S22h**) (4.70 g, 17.9 mmol) and 20% $Pd(OH)_2/C$ (containing 50% water, 300 mg) in MeOH (89 mL) was hydrogenated under balloon pressure at rt overnight. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel,

hexane/ethyl acetate/methanol, 1:1:0 to 0:100:0 to 0:3:2). The desired fractions were collected and evaporated. To the residue was added 4 M HCl solution in EtOAc (15 mL, 60 mmol) at rt. The mixture was stirred at rt for 10 min and concentrated in vacuo. The residue was triturated with hexane/diisopropyl ether, collected by filtration, rinsed with hexane/diisopropyl ether, and dried to give **S24h** (2.40 g, 8.40 mmol, 47%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.92–2.08 (1H, m), 2.26 (1H, d, J = 5.3 Hz), 3.05–3.16 (1H, m), 3.18 (3H, s), 3.25–3.36 (1H, m), 4.36 (1H, brs), 7.46 (2H, d, J = 8.1 Hz), 7.60–7.72 (2H, m), 8.62 (3H, brs).



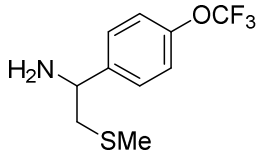
S23i

2-Methoxy-1-(4-(trifluoromethoxy)phenyl)ethanamine (S23i). A mixture of 2-methoxy-1-(4-(trifluoromethoxy)phenyl)ethanone oxime (**S22i**) (948.6 mg, 3.81 mmol) and 10% Pd/C (containing 50% water, 300 mg) in MeOH (20 mL) was hydrogenated under balloon pressure at rt overnight. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give **S23i** (854 mg, 3.63 mmol, 95%) as a white wax-like solid. This was used in the next reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (3H, s), 3.29–3.38 (2H, m), 3.98–4.15 (1H, m), 7.25–7.34 (2H, m), 7.47–7.54 (2H, m). MS (ESI/APCI) m/z 236.1 $[M + H]^+$.



S24i

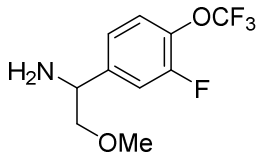
2-Methoxy-1-(4-(trifluoromethoxy)phenyl)ethanamine Hydrochloride (S24i). To a 4 M HCl solution in EtOAc (100 mL, 400 mmol) was added a solution of 2-methoxy-1-(4-(trifluoromethoxy)phenyl)ethanamine (**S23i**) (4.80 g, 20.4 mmol) in EtOAc (10 mL) at rt. After being stirred for 2 h, the mixture was concentrated in vacuo. The resulting solid was triturated with diisopropyl ether, collected by filtration, rinsed with diisopropyl ether, and dried to afford **S24i** (4.20 g, 15.5 mmol, 76%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.34 (3H, s), 3.58–3.74 (2H, m), 4.58 (1H, dd, J = 6.6, 5.5 Hz), 7.46 (2H, d, J = 8.7 Hz), 7.65 (2H, d, J = 8.3 Hz), 8.57 (3H, brs). MS (ESI/APCI) m/z 236.1 $[M + H]^+$.



S23j

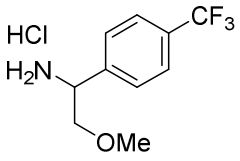
2-(Methylsulfanyl)-1-(4-(trifluoromethoxy)phenyl)ethanamine (S23j). A mixture of 1.1 M BH_3·THF solution in THF (5.14 mL, 5.65 mmol) and

2-(methylthio)-1-(4-(trifluoromethoxy)phenyl)ethanone oxime (**S22j**) (500 mg, 1.88 mmol) in THF (50 mL) was stirred at reflux under N_2 overnight and then 1 M HCl aqueous solution was added. After being stirred at rt for 15 min, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give **S23j** (515 mg, 2.05 mmol, quantitative yeild) as a colorless oil. This was used to the next reaction without further purification. MS (ESI/APCI) *m*/*z* 235.0 $[M + 1 - NH_3]^+$.



S23k

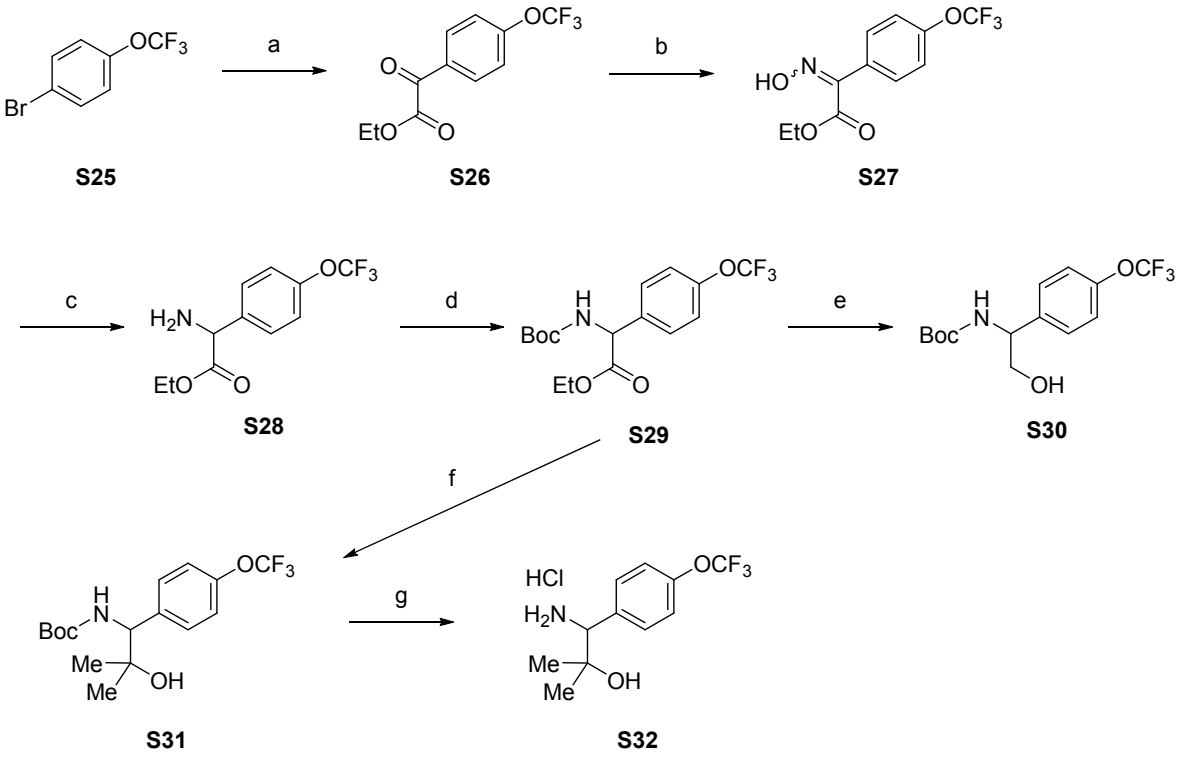
1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethanamine (S23k). A solution of 1-(3-fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethanone oxime (**S22k**) (3.26 g, 12.2 mmol) in EtOH (60 mL) was treated with 20% $Pd(OH)_2/C$ (containing 50% water, 1 g) under H_2 for 5 h. The catalyst was filtered off and the filtrate was concentrated in vacuo to afford **S23k** (2.87 g, 11.3 mmol, 93%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32–3.44 (4H, m), 3.43–3.54 (1H, m), 3.56–3.99 (2H, m), 4.19 (1H, brs), 6.99–7.48 (3H, m). MS (ESI/APCI) *m*/*z* 254.1 $[M + H]^+$.



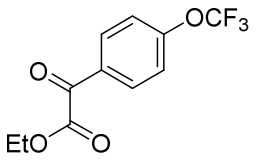
S24l

2-Methoxy-1-(4-(trifluoromethyl)phenyl)ethanamine Hydrochloride (S24l). A mixture of 2-methoxy-1-(4-(trifluoromethyl)phenyl)ethanone oxime (**S22l**) (1.97 g, 8.43 mmol) and 10% Pd/C (containing 50% water, 200 mg) in EtOH (100 mL) was hydrogenated under balloon pressure at rt overnight. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. To a stirred 4 M HCl solution in EtOAc (20 mL, 80 mmol) was added a solution of crude 2-methoxy-1-(4-(trifluoromethyl)phenyl)ethanamine obtained above (1.85 g, 8.43 mmol) in EtOAc (5 mL) at rt. After being stirred for 30 min, the mixture was concentrated in vacuo. The residue was triturated with ethyl acetate, collected by filtration, rinsed with ethyl acetate, and dried to afford **S24l** (1.81 g, 7.08 mmol, 84%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26–3.41 (3H, m), 3.59–3.78 (2H, m), 4.58–4.73 (1H, m), 7.66–7.91 (4H, m), 8.69 (3H, brs). MS (ESI/APCI) *m*/*z* 220.1 $[M + H]^+$.

Scheme 3. Synthesis of RHS Benzylamine Moiety **S32**[a]

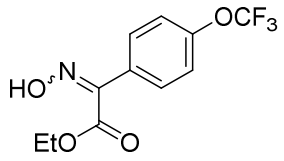


[a] Reagents and conditions: (a) *n*-BuLi, THF, –78 °C, 50 min, then ethyl 2-chloro-2-oxoacetate, –78 °C to rt, overnight, 23%; (b) hydroxylammonium chloride, Et_3N, EtOH, 80 °C, overnight, 27%; (c) H_2, 10% Pd/C, EtOH, rt, overnight, 86%; (d) Boc_2O, THF, rt, 2 days, (taken on crude); (e) LAH, THF, 0 °C, 30 min, 62%; (f) MeMgBr, THF, 0 °C, 2 h, 41%; (g) HCl, EtOAc, rt, 84%.



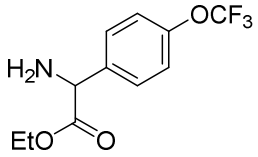
S26

Ethyl Oxo(4-(trifluoromethoxy)phenyl)acetate (S26). To a solution of 1-bromo-4-(trifluoromethoxy)benzene (**S25**) (10.0 g, 41.5 mmol) in THF (200 mL) at –78 °C was added dropwise 1.6 M butyllithium solution in hexane (31.1 mL, 49.8 mmol). The mixture was stirred at –78 °C for 50 min under N_2. Then, ethyl 2-chloro-2-oxoacetate (6.23 g, 45.6 mmol) was added to the mixture at –78 °C. The mixture was gradually warmed to rt and stirred at the same temperature overnight. The mixture was poured into 1 M HCl aqueous solution at 0 °C and extracted with EtOAc. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 49:1 to 1:1) to give **S26** (2.50 g, 9.54 mmol, 23%) as an orange oil, which contained some impurities. This was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41–1.47 (3H, m), 4.41–4.51 (2H, m), 7.30–7.40 (2H, m), 8.04–8.19 (2H, m).



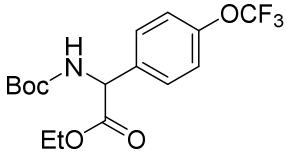
S27

Ethyl 2-(Hydroxyimino)-2-(4-(trifluoromethoxy)phenyl)acetate (S27). A mixture of Et_3N (1.60 mL, 11.4 mmol), ethyl 2-oxo-2-(4-(trifluoromethoxy)phenyl)acetate (**S26**) (2.50 g, 9.54 mmol) and hydroxylammonium chloride (0.795 g, 11.4 mmol) in EtOH (100 mL) was stirred at 80 °C overnight. The mixture was poured into saturated aqueous NaCl and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 49:1 to 1:1) to give **S27** (725 mg, 2.62 mmol, 27%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (2H, t, J = 7.0 Hz), 1.40 (3H, t, J = 7.2 Hz), 4.36 (2H, q, J = 7.2 Hz), 4.46 (2H, q, J = 7.2 Hz), 7.19–7.33 (4H, m), 7.53–7.64 (4H, m), 8.65 (1H, brs), 9.22 (1H, brs).



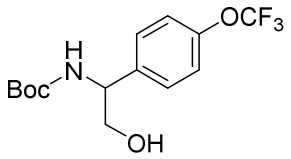
S28

Ethyl Amino(4-(trifluoromethoxy)phenyl)acetate (S28). A mixture of ethyl 2-(hydroxyimino)-2-(4-(trifluoromethoxy)phenyl)acetate (**S27**) (720 mg, 2.60 mmol) and 10% Pd/C (containing 50% water, 140 mg) in EtOH (15 mL) was hydrogenated under balloon pressure at rt overnight. The mixture was filtered and the filtrate was concentrated in vacuo to give **S28** (590 mg, 2.24 mmol, 86%) as a pale orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18–1.28 (3H, m), 2.09 (2H, brs), 3.97–4.37 (2H, m), 4.63 (1H, s), 7.13–7.25 (2H, m), 7.43 (2H, d, J = 8.7 Hz). MS (ESI/APCI) m/z 264.1 $[M + H]^+$.



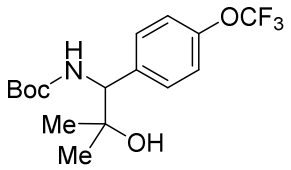
S29

Ethyl ((tert-Butoxycarbonyl)amino)(4-(trifluoromethoxy)phenyl)acetate (S29). A mixture of ethyl amino(4-(trifluoromethoxy)phenyl)acetate (**S28**) (590 mg, 2.24 mmol) and Boc_2O (430 mg, 2.47 mmol) in THF (20 mL) was stirred at rt for 2 days. The mixture was concentrated in vacuo to give crude **S29** (952 mg, 2.62 mmol, quantitative yeild) as a yellow oil. This was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, t, J = 7.2 Hz), 1.53 (9H, s), 3.99–4.33 (2H, m), 5.32 (1H, d, J = 6.8 Hz), 5.63 (1H, brs), 7.19 (2H, d, J = 7.9 Hz), 7.41 (2H, d, J = 8.7 Hz).



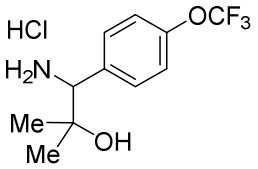
S30

tert-Butyl (2-Hydroxy-1-(4-(trifluoromethoxy)phenyl)ethyl)carbamate (S30). To a suspension of LAH (41.8 mg, 1.10 mmol) in THF (5 mL) at 0 °C was added ethyl ((*tert*-butoxycarbonyl)amino)(4-(trifluoromethoxy)phenyl)acetate (**S29**) (100 mg, 0.28 mmol). The mixture was stirred at the same temperature for 30 min and then $MgSO_4$ and a small amount of H_2O were sequentially added, followed by EtOAc. The mixture was filtered through celite pad and the filtrate was concentrated in vacuo to give **S30** (54.8 mg, 0.171 mmol, 62%) as a colorless gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (9H, s), 3.71 (1H, brs), 3.86 (2H, brs), 4.79 (1H, brs), 5.28 (1H, brs), 7.11–7.24 (2H, m), 7.29–7.41 (2H, m). MS (ESI/APCI) *m*/*z* 320.1 $[M - H]^-$.



S31

tert-Butyl (2-Hydroxy-2-methyl-1-(4-(trifluoromethoxy)phenyl)propyl)carbamate (S31). To a solution of methylmagnesium bromide (1 M THF solution, 2.20 mL, 2.20 mmol) in THF (5 mL) at 0 °C was added *tert*-butyl (2-hydroxy-1-(4-(trifluoromethoxy)phenyl)ethyl)carbamate (**S30**) (200 mg, 0.55 mmol). The mixture was stirred at 0 °C for 2 h. The mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 9:1 to 1:4) to give **S31** (78 mg, 0.224 mmol, 41%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, s), 1.36 (3H, s), 1.40 (9H, brs), 1.49 (1H, brs), 4.50 (1H, d, *J* = 5.3 Hz), 5.52 (1H, d, *J* = 5.7 Hz), 7.14–7.23 (2H, m), 7.29–7.38 (2H, m).

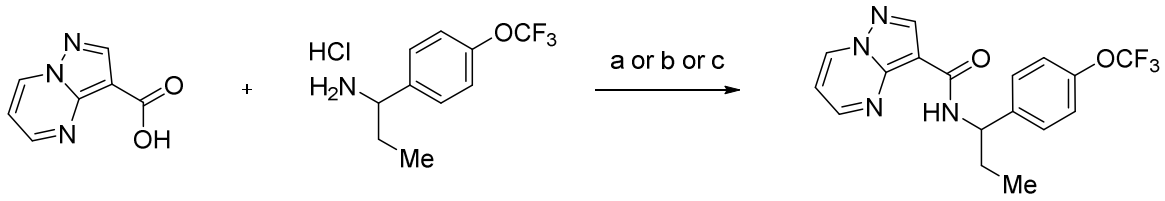


S32

1-Amino-2-methyl-1-(4-(trifluoromethoxy)phenyl)propan-2-ol Hydrochloride (S32). A mixture of *tert*-butyl (2-hydroxy-2-methyl-1-(4-(trifluoromethoxy)phenyl)propyl)carbamate (**S31**) (78 mg, 0.22 mmol) and 4 M HCl solution in EtOA (5 mL, 20 mmol) was stirred at rt for 1 h. The mixture was concentrated in vacuo to give **S32** (53.3 mg, 0.187 mmol, 84%) as a pale yellow solid. ^{1}H

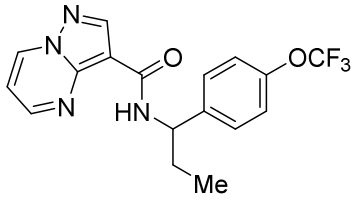
NMR (300 MHz, DMSO-d_6) δ 0.97 (3H, s), 1.23 (3H, s), 4.23 (1H, s), 5.39 (1H, s), 7.38–7.52 (2H, m), 7.55–7.71 (2H, m), 8.37 (3H, brs). MS (ESI/APCI) *m*/*z* 250.1 $[M + H]^+$.

Scheme 4. Synthesis of Pyrazolo[1,5-*a*]pyrimidine Derivative **5**[a]



S33 **45** **5**

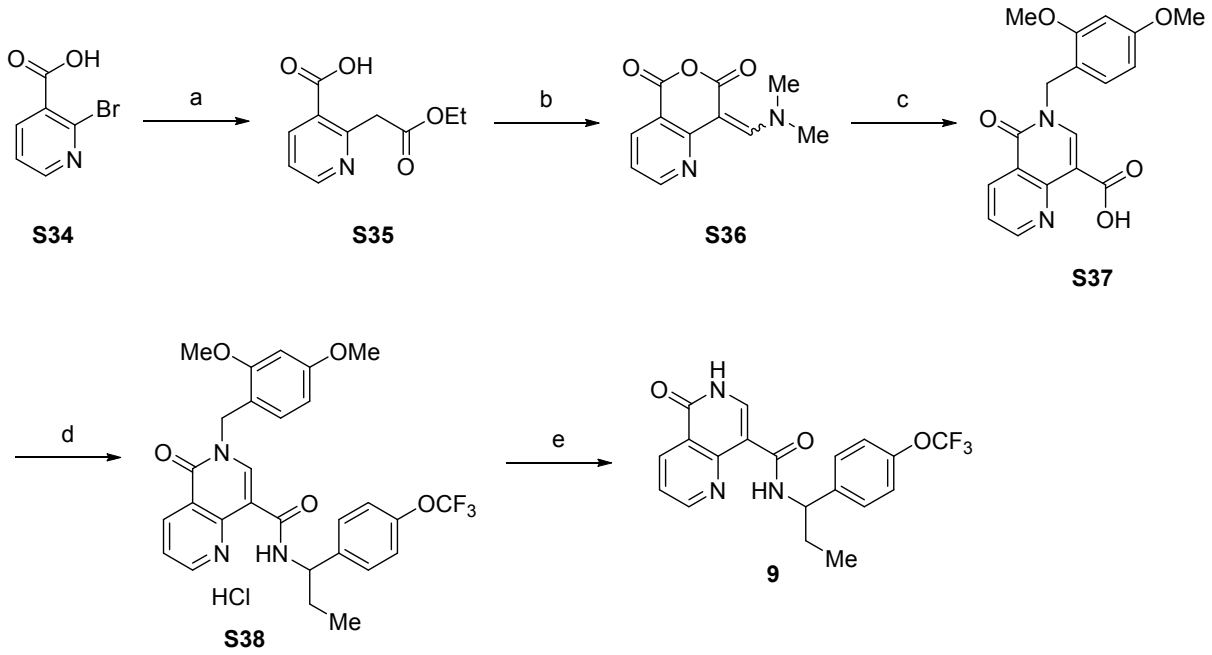
[a] Reagents and conditions: (a) EDCI·HCl, HOBt·H_2O, Et_3N, DMF, rt, overnight, 83%.



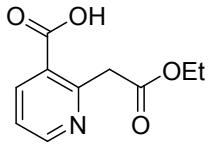
5

N-(1-(4-(Trifluoromethoxy)phenyl)propyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (5). A mixture of pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (**S33**) (26.7 mg, 0.16 mmol), 1-(4-(trifluoromethoxy)phenyl)propan-1-amine hydrochloride (**45**) (46.0 mg, 0.18 mmol), EDCI·HCl (37.6 mg, 0.20 mmol), HOBt·H_2O (30.1 mg, 0.20 mmol), and Et_3N (0.027 mL, 0.20 mmol) in DMF (1.5 mL) was stirred at rt overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 4:1 to 0:100). The desired fractions were collected and concentrated in vacuo. The resulting solid was triturated with diisopropyl ether, collected by filtration, rinsed with diisopropyl ether, and dried to give **5** (49.2 mg, 0.135 mmol, 83%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (3H, t, J = 7.4 Hz), 1.81–1.96 (2H, m), 5.05 (1H, q, J = 7.2 Hz), 7.25–7.37 (3H, m), 7.47–7.56 (2H, m), 8.32 (1H, d, J = 8.0 Hz), 8.56 (1H, s), 8.86 (1H, dd, J = 4.2, 1.9 Hz), 9.29–9.37 (1H, m). MS (ESI/APCI) *m*/*z* 365.2 $[M + H]^+$. HPLC purity: 100%.

Scheme 5. Synthesis of 5,6-Dihydro-1,6-naphthyridine Derivative **9**[a]

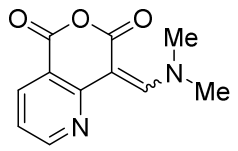


[a] Reagents and conditions: (a) ethyl acetoacetate, Na, EtOH, $Cu(OAc)_2$, reflux, 16 h, 54%; (b) $POCl_3$, DMF, 0 °C to 5 °C, 2 h, (taken on crude); (c) 2,4-dimethoxybenzylamine, Et_3N, DMF, 5 °C, 16 h, 26% (2 steps from **S35**); (d) amine **45**, EDCI, HOBt, Et_3N, DMF, 5 °C to 40 °C, 32 h; (e) TFA, reflux, 16 h, 12% in 2 steps from **S37**.



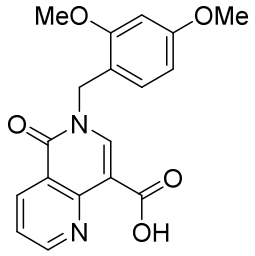
S35

2-(2-Ethoxy-2-oxoethyl)nicotinic Acid (S35). Na (2.85 g, 124 mmol) was dissolved in absolute EtOH (100 mL) and the solution was cooled to rt. To the resulting solution were added ethyl acetoacetate (9.66 g, 74.3 mmol), 2-bromonicotinic acid (**S34**) (10.0 g, 49.5 mmol), and $Cu(OAc)_2$ (360 mg, 1.98 mmol). The mixture was stirred at reflux for 16 h. After cooling to rt, the mixture was acidified with AcOH (80 mL) and concentrated in vacuo. The residue was diluted with water (50 mL) and the mixture was extracted with CH_2Cl_2 (50 mL × 5). The extract was concentrated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2/methanol, 100:0 to 10:1) to afford **S35** (5.60 g, 26.8 mmol, 54%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 (3H, t, J = 7.2 Hz), 4.06 (2H, q, J = 7.2 Hz), 4.17 (2H, s), 7.46 (1H, dd, J = 8.0, 4.8 Hz), 8.27 (1H, dd, J = 8.0, 2.0 Hz), 8.66 (1H, dd, J = 4.8, 2.0 Hz), 13.35 (1H, brs).



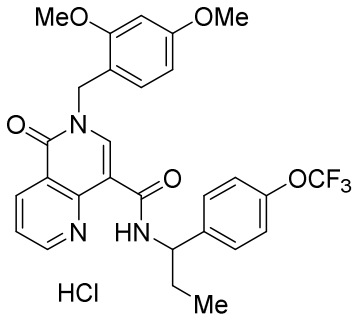
S36

(8E or 8Z)-8-((Dimethylamino)methylene)-5H-pyrano[4,3-b]pyridine-5,7(8H)-dione (S36). To a stirred solution of 2-(2-ethoxy-2-oxoethyl)nicotinic acid (**S35**) (700 mg, 3.35 mmol) in DMF (5 mL) was added $POCl_3$ (0.70 mL, 7.5 mmol) dropwise at 0 °C. The mixture was stirred at 5 °C for 2 h, and then poured into ice/water (20 mL). The mixture was extracted with CH_2Cl_2 (20 mL × 3). The extract was concentrated in vacuo to afford crude **S36** (400 mg) as a yellow solid. This was used in the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (3H, s), 3.55 (3H, s), 7.12 (1H, dd, *J* = 8.0, 4.8 Hz), 8.39 (1H, d, *J* = 7.2 Hz), 8.57 (1H, dd, *J* = 4.8, 1.6 Hz), 8.79 (1H, s).



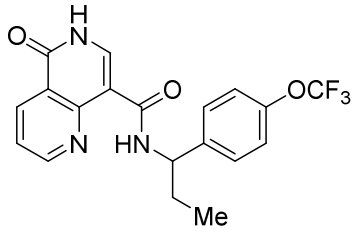
S37

6-(2,4-Dimethoxybenzyl)-5-oxo-5,6-dihydro-1,6-naphthyridine-8-carboxylic Acid (S37). To a suspension of crude (8*E* or 8*Z*)-8-((dimethylamino)methylene)-5*H*-pyrano[4,3-*b*]pyridine-5,7(8*H*)-dione (**S36**) (400 mg) in DMF (8 mL) were added Et_3N (740 mg, 7.32 mmol) and 2,4-dimethoxybenzylamine (919 mg, 5.50 mmol), and the mixture was stirred at 5 °C for 16 h. The mixture was poured into ice/water (30 mL) and then acidified with 1 M HCl aqueous solution to pH ~ 1. The precipitate was collected by filtration, washed with water (5 mL), and dried to afford **S37** (300 mg, 0.881 mmol, 26% in 2 steps from **S35**) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.75 (3H, s), 3.78 (3H, s), 5.16 (2H, s), 6.52 (1H, dd, *J* = 8.4, 2.4 Hz), 6.59 (1H, d, *J* = 2.4 Hz), 7.24 (1H, d, *J* = 8.4 Hz), 7.74 (1H, dd, *J* = 8.0, 4.8 Hz), 8.67 (1H, s), 8.73 (1H, dd, *J* = 8.0, 2.0 Hz), 9.06 (1H, dd, *J* = 4.8, 2.0 Hz).



S38

6-(2,4-Dimethoxybenzyl)-5-oxo-N-(1-(4-(trifluoromethoxy)phenyl)propyl)-5,6-dihydro-1,6-napht hyridine-8-carboxamide (S38). A mixture of 6-(2,4-dimethoxybenzyl)-5-oxo-5,6-dihydro-1,6-naphthyridine-8-carboxylic acid (**S37**) (300 mg, 0.882 mmol), 1-(4-(trifluoromethoxy)phenyl)propan-1-amine hydrochloride (**45**) (226 mg, 0.882 mmol), EDCI (253 mg, 1.32 mmol), HOBt (178 mg, 1.32 mmol) and Et_3N (268 mg, 2.65 mmol) in DMF (5 mL) was stirred at 5 °C for 16 h and then at 40 °C for 16 h. After cooling to rt, the mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (15 mL × 2). The extract was concentrated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 5:1 to 2:1) to afford impure **S38** (500 mg, 93% LC–MS purity). 100 mg of impure **S38** was further purified by preparative HPLC (column: YMC-pack ODS-A 4.6 mm ID × 150 mm L; mobile phase A: 0.05% HCl in water; mobile phase B: 0.05% HCl in acetonitrile; flow rate: 1.5 mL/min). After most of the solvent was removed under reduced pressure, the residue was lyophilized to afford **S38** (27 mg, 0.0467 mmol, 26%) as a yellow solid. The remaining impure **S38** (370 mg, 93% LC–MS purity) was used in the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (3H, t, J = 7.2 Hz), 1.82–1.91 (2H, m), 3.74 (3H, s), 3.76 (3H, s), 5.05 (1H, q, J = 7.2 Hz), 5.06–5.17 (2H, m), 6.50 (1H, dd, J = 8.4, 2.4 Hz), 6.58 (1H, d, J = 2.4 Hz), 7.18 (1H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.49 (2H, d, J = 8.8 Hz), 7.67 (1H, dd, J = 8.0, 4.8 Hz), 8.52 (1H, s), 8.69 (1H, dd, J = 8.0, 2.0 Hz), 9.09 (1H, dd, J = 4.8, 2.0 Hz), 10.99 (1H, d, J = 7.6 Hz). MS (ESI/APCI) m/z 542.1 $[M + H]^+$.

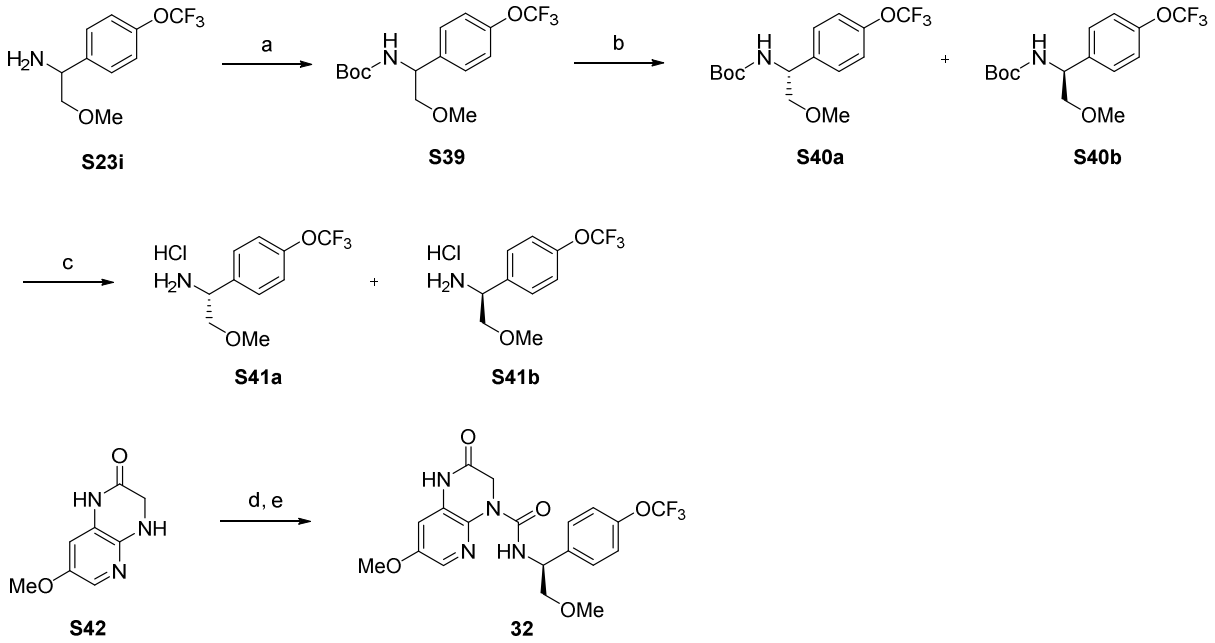


9

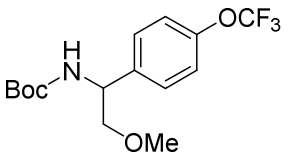
5-Oxo-N-(1-(4-(trifluoromethoxy)phenyl)propyl)-5,6-dihydro-1,6-naphthyridine-8-carboxamide (9). A solution of impure 6-(2,4-dimethoxybenzyl)-5-oxo-N-(1-(4-(trifluoromethoxy)phenyl)propyl)-5,6-dihydro-1,6-naphthy ridine-8-carboxamide (**S38**) (370 mg, 93% LC–MS purity) in TFA (3 mL) was stirred at reflux for

16 h. After cooling to rt, the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and the solution was washed with saturated $NaHCO_3$ (20 mL). The organic layer was concentrated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 2:1 to 0:100), followed by preparative TLC (EtOAc) to afford **9** (30 mg, 0.0767 mmol, 12% in 2 steps from **S37**) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (3H, t, J = 7.2 Hz), 1.81–1.94 (2H, m), 5.06 (1H, q, J = 7.2 Hz), 7.33 (2H, d, J = 8.0 Hz), 7.50 (2H, d, J = 8.8 Hz), 7.66 (1H, dd, J = 8.0, 4.8 Hz), 8.20 (1H, s), 8.66 (1H, dd, J = 8.0, 2.0 Hz), 9.09 (1H, dd, J = 4.8, 2.0 Hz), 11.01 (1H, d, J = 7.6 Hz), 12.17 (1H, brs). MS (ESI/APCI) m/z 392.0 [M + H]$^+$. mp 185 °C.

Scheme 6. Alternative Synthetic Route for **32**[a]



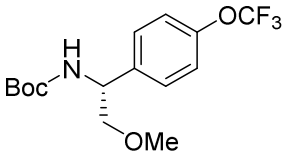
[a] Reagents and conditions: (a) Boc_2O, Et_3N, THF, rt, 20 h, 82%; (b) Chiralpak IC, hexane/EtOH, = 930:70; (c) HCl, EtOAc, rt, 1 h, 96%; (d) 4-nitrophenyl chloroformate, DIEA, THF, rt, 24 h, (taken on crude); (e) amine **S41b**, Et_3N, DMF, rt, 24 h, 52% (2 steps from **S42**).



S39

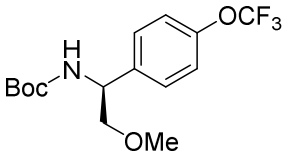
tert-Butyl (2-Methoxy-1-(4-(trifluoromethoxy)phenyl)ethyl)carbamate (S39). To a solution of 2-methoxy-1-(4-(trifluoromethoxy)phenyl)ethanamine (**S23i**) (10.8 g, 45.9 mmol) in THF (250 mL) were added Boc_2O (11.7 mL, 50.5 mmol) and Et_3N (7.68 mL, 55.1 mmol) at rt. After being stirred

for 20 h, the mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 19:1 to 4:1) to give **S39** (12.7 g, 37.8 mmol, 82%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (9H, brs), 3.35 (3H, s), 3.46–3.67 (2H, m), 4.80 (1H, brs), 5.29 (1H, brs), 7.13–7.21 (2H, m), 7.30–7.39 (2H, m).



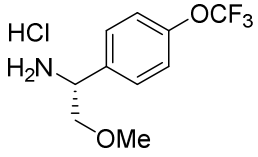
S40a

tert-Butyl ((1R)-2-Methoxy-1-(4-(trifluoromethoxy)phenyl)ethyl)carbamate (S40a). Resolution of the enantiomers of **S39** was carried out chromatographically using a Chiralpak IC 50 mm ID × 500 mm L column (hexane/ethanol, 930:70) at 85 mL/min. Resolution of **S39** (12.7 g, 37.8 mmol) provided **S40a** as a white solid (5.84 g, 17.4 mmol, 46%, 92% theoretical) as the first eluting enantiomer. Analytical HPLC analysis carried out on a 4.6 mm ID × 250 mm L Chiralpak IC column (hexane/ethanol, 90:10) at a flow rate of 1.0 mL/min indicated that **S40a** was of 99.4% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (9H, brs), 3.35 (3H, s), 3.49–3.67 (2H, m), 4.80 (1H, brs), 5.29 (1H, brs), 7.13–7.21 (2H, m), 7.30–7.38 (2H, m).



S40b

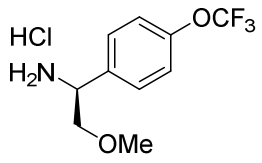
tert-Butyl ((1S)-2-Methoxy-1-(4-(trifluoromethoxy)phenyl)ethyl)carbamate (S40b). Resolution of the enantiomers of **S39** was carried out chromatographically using a Chiralpak IC 50 mm ID × 500 mm L column (hexane/ethanol, 930:70) at 85 mL/min. Resolution of **S39** (12.7 g, 37.8 mmol) provided **S40b** as a white solid (5.95 g, 17.7 mmol, 47%, 94% theoretical) as the second eluting enantiomer. Analytical HPLC analysis carried out on a 4.6 mm ID × 250 mm L Chiralpak IC column (hexane/ethanol, 90:10) at a flow rate of 1.0 mL/min indicated that **S40b** was of 99.8% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (9H, brs), 3.35 (3H, s), 3.49-3.66 (2H, m), 4.81 (1H, brs), 5.29 (1H, brs), 7.13–7.21 (2H, m), 7.30–7.39 (2H, m)..



S41a

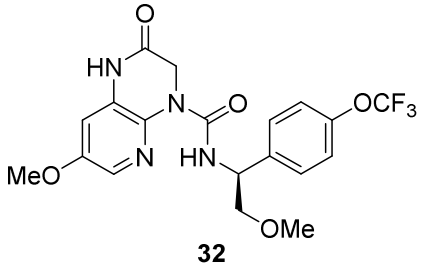
(1R)-2-Methoxy-1-(4-(trifluoromethoxy)phenyl)ethanamine Hydrochloride (S41a). A mixture of

tert-butyl ((1*R*)-2-methoxy-1-(4-(trifluoromethoxy)phenyl)ethyl)carbamate (**S40a**) (5.84 g, 17.4 mmol) and 4 M HCl solution in EtOAc (30 mL, 120 mmol) was stirred at rt for 1 h. The mixture was concentrated in vacuo, and the residue was triturated with diisopropyl ether, collected by filtration, rinsed with diisopropyl ether, and dried to give **S41a** (4.52 g, 16.6 mmol, 96%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.33 (3H, s), 3.60–3.77 (2H, m), 4.52–4.61 (1H, m), 7.46 (2H, d, J = 8.3 Hz), 7.68 (2H, d, J = 8.7 Hz), 8.67 (3H, brs). MS (ESI/APCI) m/z 219.0 [M + H – (NH_3)]$^+$.



S41b

(1S)-2-Methoxy-1-(4-(trifluoromethoxy)phenyl)ethanamine Hydrochloride (S41b). A mixture of *tert*-butyl ((1*S*)-2-methoxy-1-(4-(trifluoromethoxy)phenyl)ethyl)carbamate (**S40b**) (5.95 g, 17.7 mmol) and 4 M HCl solution in EtOAc (30 mL, 120 mmol) was stirred at rt for 1 h. The mixture was concentrated in vacuo, and the residue was triturated with diisopropyl ether, collected by filtration, rinsed with diisopropyl ether, and dried to give **S41b** (4.30 g, 15.8 mmol, 89%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ3.33 (3H, s), 3.60–3.77 (2H, m), 4.52–4.61 (1H, m), 7.46 (2H, d, J = 8.3 Hz), 7.68 (2H, d, J = 8.7 Hz), 8.67 (3H, brs). MS (ESI/APCI) m/z 219.1 [M + H – (NH_3)]$^+$.

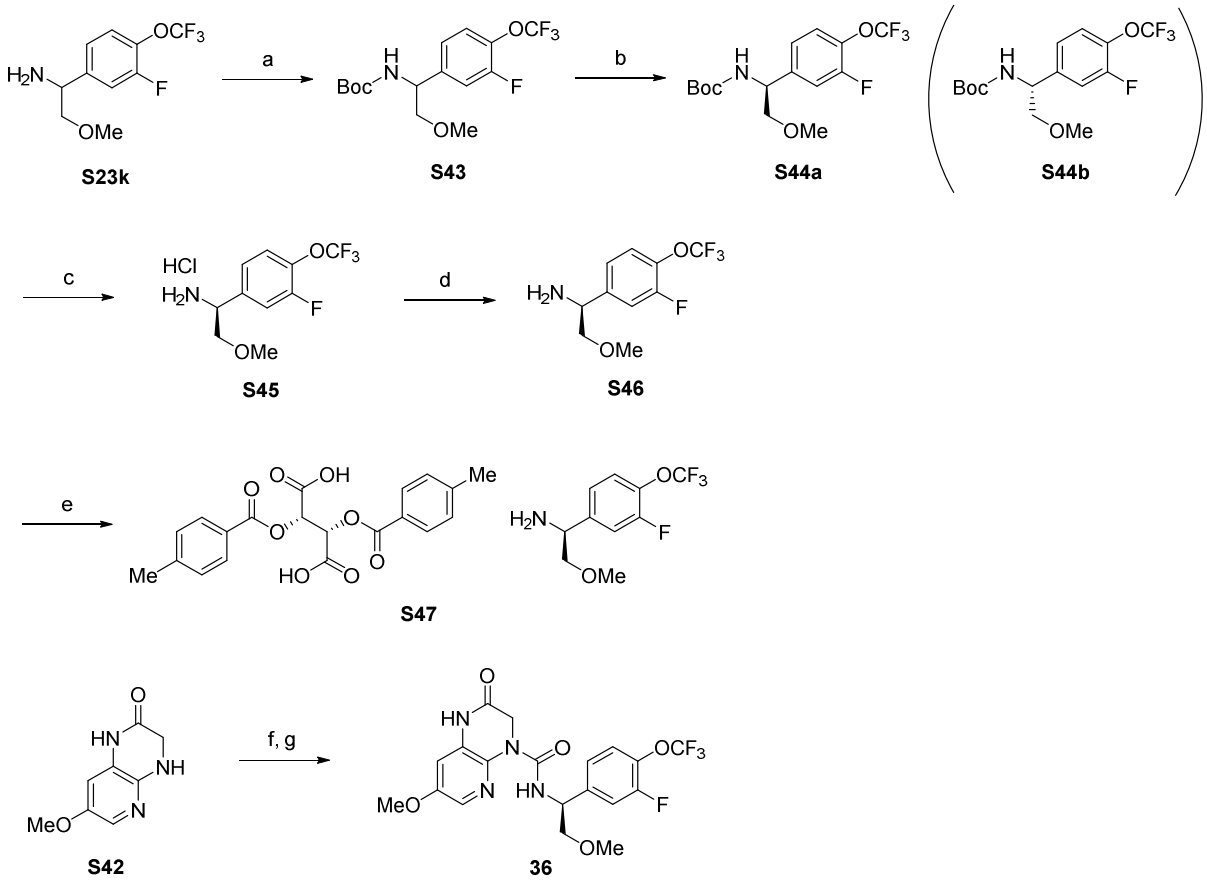


32

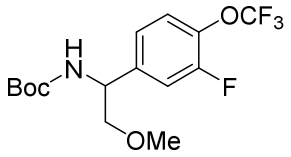
7-Methoxy-N-((1S)-2-methoxy-1-(4-(trifluoromethoxy)phenyl)ethyl)-2-oxo-2,3-dihydropyrido[2,3-b]pyrazine-4(1H)-carboxamide (32). To a solution of 7-methoxy-3,4-dihydropyrido[2,3-*b*]pyrazin-2(1*H*)-one (**S42**)[1] (179 mg, 1.00 mmol) and 4-nitrophenyl carbonochloridate (242 mg, 1.20 mmol) in THF (10 mL) was added DIEA (262 μL, 1.50 mmol) at rt. After being stirred at rt for 24 h, the mixture was concentrated in vacuo. To a solution of the residue and (1*S*)-2-methoxy-1-(4-(trifluoromethoxy)phenyl)ethanamine hydrochloride (**S41b**) (299 mg, 1.10 mmol) in DMF (10 mL) was added Et_3N (418 μL, 3.00 mmol) at rt. After being stirred at rt for 24 h, the mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 4:1 to 1:4) to give **32** (227 mg, 0.515 mmol, 52%) as a white solid after recrystallization from heptane/acetone. Analytical HPLC analysis carried out on a 4.6 mm ID × 150

mm L Chiralpak IA column (CO_2/methanol, 820:180) at a flow rate of 4.0 mL/min indicated that **32** was of >99.9% ee as the first eluting enantiomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (3H, s), 3.68 (2H, d, J = 4.9 Hz), 3.87 (3H, s), 4.65 (2H, s), 5.12–5.22 (1H, m), 6.80 (1H, d, J = 2.6 Hz), 7.13–7.21 (2H, m), 7.37–7.44 (2H, m), 7.71 (1H, d, J = 2.6 Hz), 8.90 (1H, s), 10.17 (1H, d, J = 7.2 Hz). MS (ESI/APCI) m/z 441.1 $[M + H]^+$. Anal. Calcd for $C_{19}H_{19}N_4O_5F_3$: C, 51.82; H, 4.35; N, 12.72. Found: C, 51.65; H, 4.41; N, 12.62.

Scheme 7. Alternative Synthetic Route for **36** and Synthesis of (+)-Di-(p-toluoyl)-$_D$-tartaric Acid Salt **S47** Suitable for X-ray Crystallography[a]

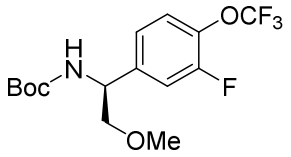


[a] Reagents and conditions: (a) Boc_2O, Et_3N, THF, rt, 16 h, 79%; (b) Chiralpak AD, hexane/EtOH, = 950:50; (c) HCl, EtOAc, rt, 3 h, 95%; (d) $NaHCO_3$, H_2O, quant.; (e) (2*S*,3*S*)-(+)-di-(p-toluoyl)-$_D$-tartaric acid, EtOH, H_2O, 50 °C, overnight; (f) 4-nitrophenyl chloroformate, DIEA, THF, rt, 3 h, 88%; (g) amine **S45**, DIEA, DMF, rt, 16 h, 63%.



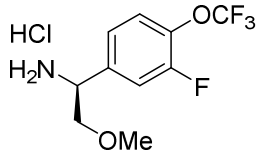
S43

tert-Butyl (1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethyl)carbamate (S43). To a solution of 1-(3-fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethanamine (**S23k**) (7.47 g, 29.5 mmol) in THF (200 mL) were added Boc_2O (7.53 mL, 32.5 mmol) and Et_3N (6.17 mL, 44.3 mmol) at rt. After being stirred at rt for 16 h, the mixture was quenched with water and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 19:1 to 4:1) to give **S43** (8.25 g, 23.4 mmol, 79%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H, brs), 3.35 (3H, s), 3.49–3.67 (2H, m), 4.78 (1H, brs), 5.34 (1H, brs), 7.08–7.29 (3H, m). MS (ESI/APCI) *m*/*z* 254.0 $[M + H - (Boc)]^+$.



S44a

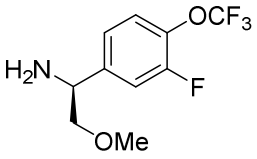
tert-Butyl ((1S)-1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethyl)carbamate (S44a). Resolution of the enantiomers of **S43** was carried out chromatographically using a Chiralpak AD 50 mm ID × 500 mm L column (hexane/ethanol, 950:50) at 80 mL/min. Resolution of **S43** (12.5 g, 35.5 mmol) provided **S44a** as a white solid (5.73 g, 16.2 mmol, 46%, 92% theoretical) as the first eluting enantiomer. Analytical HPLC analysis carried out on a 4.6 mm ID × 250 mm L Chiralpak AD column (hexane/ethanol, 950:50) at a flow rate of 1.0 mL/min indicated that **S44a** was of >99.9% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H, brs), 3.35 (3H, s), 3.49–3.66 (2H, m), 4.77 (1H, brs), 5.34 (1H, brs), 7.07–7.30 (3H, m). MS (ESI/APCI) *m*/*z* 254.0 $[M + H - (Boc)]^+$.



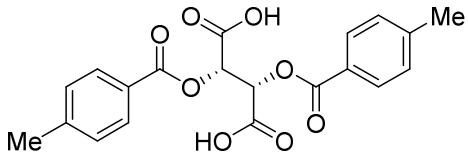
S45

(1S)-1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethanamine hydrochloride (S45). A mixture of *tert*-butyl ((1*S*)-1-(3-fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethyl)carbamate (**S44a**) (5.73 g, 16.2 mmol) and 4 M HCl solution in EtOAc (100 mL, 400 mmol) was stirred at rt for 3 h. The mixture was concentrated in vacuo, and the resulting solid was triturated with diisopropyl ether, collected by filtration, rinsed with diisopropyl ether, and dried to give **S45** (4.45 g, 15.4 mmol, 95%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.33 (3H, s), 3.61–3.78 (2H, m), 4.55–4.64 (1H, m), 7.47–7.56 (1H, m), 7.64–7.83 (2H, m), 8.74 (3H, brs). MS (ESI/APCI) *m*/*z*

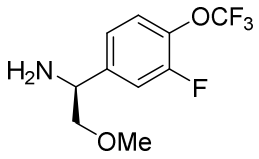
254.0 $[M + H]^+$.



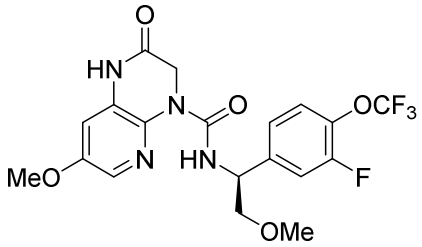
S46



S47



(+)-Di-(p-toluoyl)-$_D$-tartaric acid salt of S46 (S47). (1*S*)-1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethanamine hydrochloride (**S45**) (2.00 g, 6.90 mmol) was suspended in EtOAc and neutralized with saturated aqueous $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford (1*S*)-1-(3-fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethanamine (**S46**) (1.74 g, 6.87 mmol, quantitative yeild) as a colorless oil. **S46** (127 mg, 0.500 mmol) and (2*S*,3*S*)-(+)-di-(*p*-toluoyl)-$_D$-tartaric acid (193 mg, 0.500 mmol) were dissolved in EtOH (200 µl) and water (200 µl) at rt. The mixture was heated to 50 °C and standed overnight to give (2*S*,3*S*)-2,3-bis((4-methylbenzoyl)oxy)butanedioic acid - (1*S*)-1-(3-fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethanamine (1:1) (**S47**) suitable for X-ray crystallography.

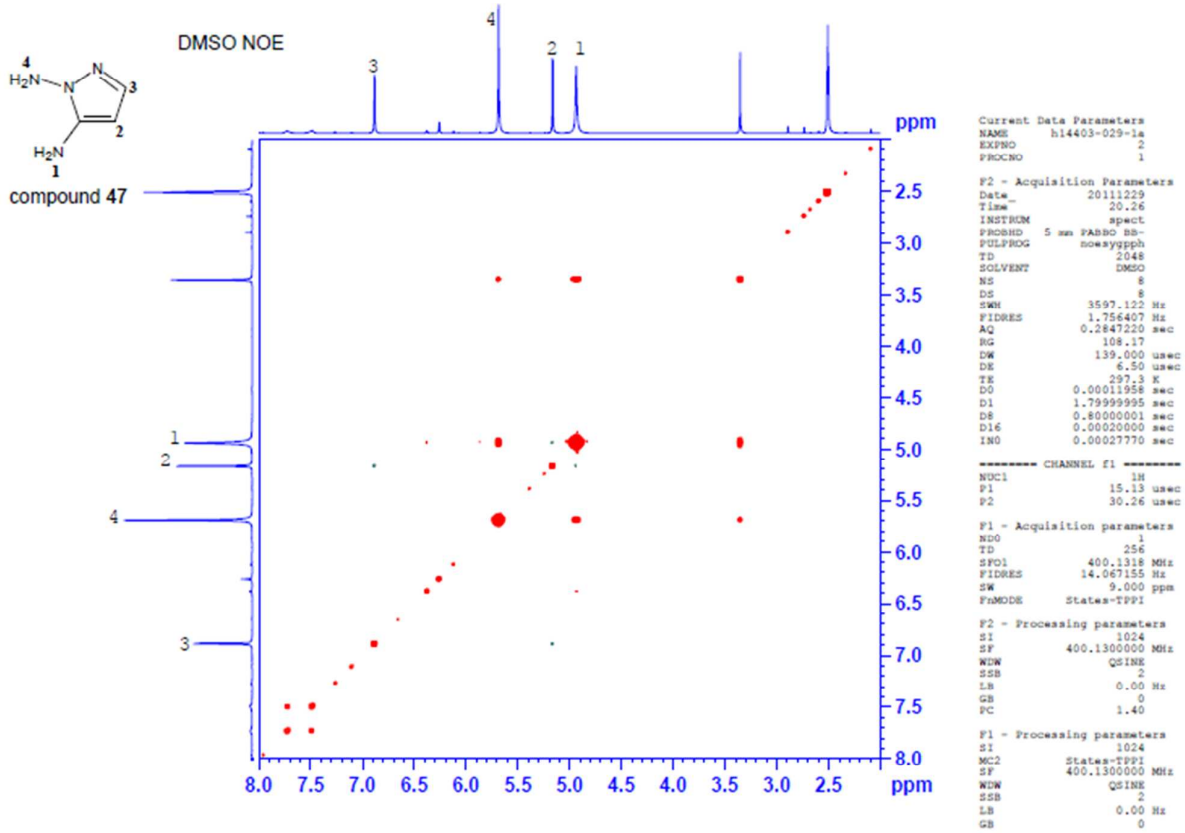


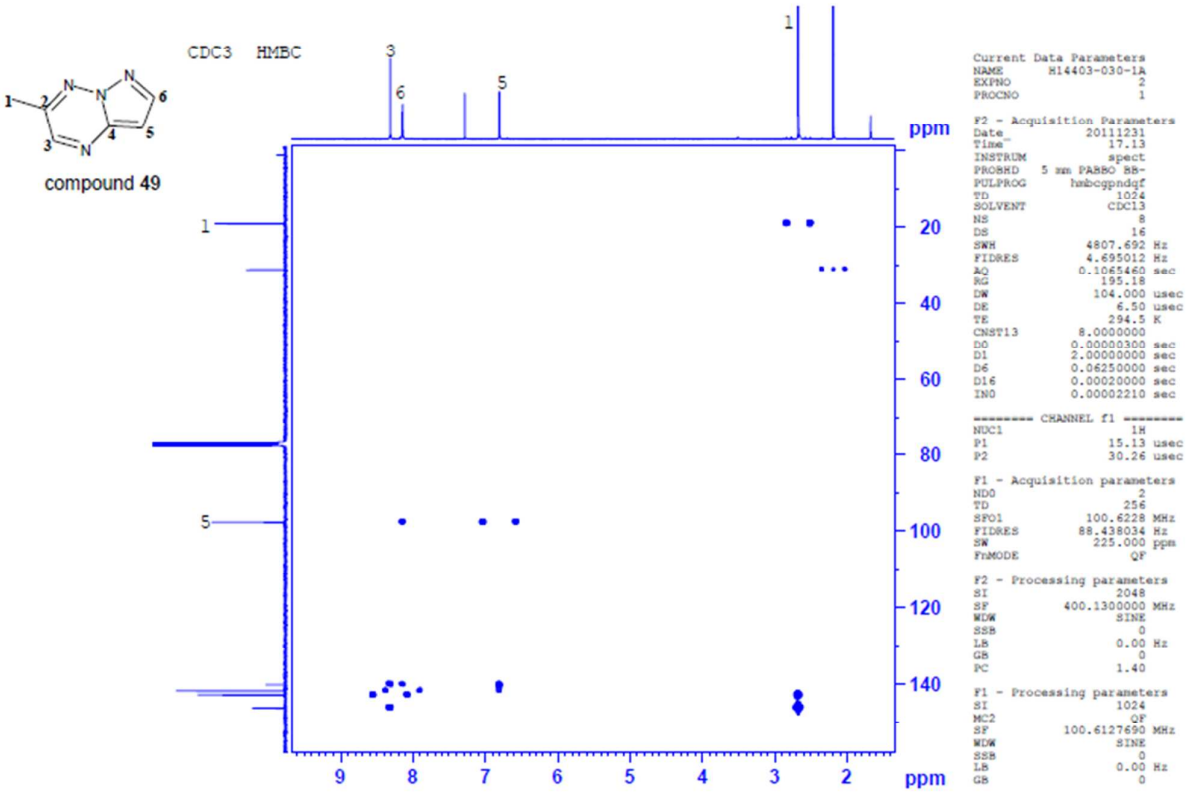
36

N-((1S)-1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-2-methoxyethyl)-7-methoxy-2-oxo-2,3-dihydro pyrido[2,3-b]pyrazine-4(1H)-carboxamide (36). To a suspension of 7-methoxy-3,4-dihydropyrido[2,3-*b*]pyrazin-2(1*H*)-one **S42**[1] (2.49 g, 13.90 mmol) and DIEA (7.13 mL, 41.7 mmol) in THF (120 mL) was added portionwise 4-nitrophenyl chloroformate (3.64 g, 18.1 mmol) at 0 °C. The mixture was stirred at rt under N_2 for 3 h and then concentrated in vacuo. To the residue were added *i*-Pr_2O (200 mL) and saturated aqueous NaCl (150 mL) and the mixture was srirred at rt for 20 min. The resulting precipitate was filtered, washed with water and then diisopropyl ether, and dried to give 4-nitrophenyl 7-methoxy-2-oxo-2,3-dihydropyrido[2,3-*b*]pyrazine-4(1*H*)-carboxylate (4.20 g, 12.2 mmol, 88%) as a gray solid. A mixture of 4-nitrophenyl 7-methoxy-2-oxo-2,3-dihydropyrido[2,3-*b*]pyrazine-4(1*H*)-carboxylate obtained above (4.20 g, 12.2 mmol), DIEA (11.9 mL, 69.5 mmol), **S45** (4.43 g, 15.3 mmol) and DMF (130 mL) was stirred at rt for 16 h and concentrated in vacuo. To the residue were added EtOAc (200 mL), THF (100 mL), and $NaHCO_3$ aqueous solution (200 mL). The phases were separated and the aqueous phase was extracted with EtOAc/THF (2:1). The phases were washed with saturated aqueous NaCl, dried

over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (basic silica gel (200 g), hexane/ethyl acetate, 3:17) to give **36** (5.01 g, 10.9 mmol, 79%) as a pale yellow solid. To a solution of **36** (5.00 g, 10.9 mmol) in EtOH (200 mL) was added activated carbon (10 g). After the mixture was stirred at rt for 30 min, the insoluble material was removed by filtration and washed with acetone several times. The filtrate was concentrated in vacuo. To a solution of the obtained compound (4.17g) in acetone (35 mL) was added dropwise heptane (70 mL) at 52 °C (precipitate occurred) and the mixture was stirred at 52 °C for 1 h. Additional heptane (35 mL) was added dropwise at 52 °C and then gradually cooled to rt. The mixture was stirred overnight, and then stirred at 5 °C for 1 h. The precipitate was collected by filtration, rinsed with acetone/heptane (7:21) to give **36** (3.15 g, 6.87 mmol, 63%) as a white solid. Analytical HPLC analysis carried out on a 4.6 mm ID × 150 mm L Chiralpak ADH column (hexane/ethanol, 650:350) at a flow rate of 1.0 mL/min indicated that **36** was of >99.9% ee as the first eluting enantiomer. ^{1}H NMR (300 MHz, DMSO-d_6) d 3.29 (3H, s), 3.56–3.70 (2H, m), 3.83 (3H, s), 4.30–4.52 (2H, m), 4.95–5.16 (1H, m), 6.96 (1H, d, J = 2.6 Hz), 7.29 (1H, d, J = 8.3 Hz), 7.43–7.57 (2H, m), 7.75 (1H, d, J = 3.0 Hz), 10.02 (1H, d, J = 7.2 Hz), 10.78 (1H, brs). MS (ESI/APCI) m/z 459.2 $[M + H]^+$. HPLC purity: 99.9%.

■ NOE Data for 47 and HMBC Data for 49





■ Determination of the Absolute Stereochemistry of Amine S41a

The absolute configuration of **S41a** was determined by X-ray crystallography.

Crystal data for **S41a**: $C_{10}H_{13}F_3NO_2^+ \cdot Cl^- \cdot 0.25C_7H_8$, MW = 294.70; crystal size, 0.20 × 0.09 × 0.06 mm; colorless, block; triclinic, space group *P*1, a = 7.2413(3) Å, b = 14.4003(6) Å, c = 14.4361(6) Å, α = 105.170(8)°, β = 103.917(8)°, γ = 92.350(7)°, V = 1401.53(12) Å^3, Z = 4, Dx = 1.397 g/cm^3, T = 100 K, μ = 2.736 mm^{-1}, λ = 1.54187 Å, R_1 = 0.051, wR_2 = 0.133, Flack Parameter[2] = 0.036(13).

All measurements were made on a Rigaku R-AXIS RAPID-191R diffractometer using graphite monochromated Cu-Kα radiation. The structure was solved by direct methods with SHELXS-97[3] and was refined using full-matrix least-squares on F^2 with SHELXL-97.[3] All non-H atoms were refined with anisotropic displacement parameters.

CCDC 1548480 for compound **S41a** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx?.

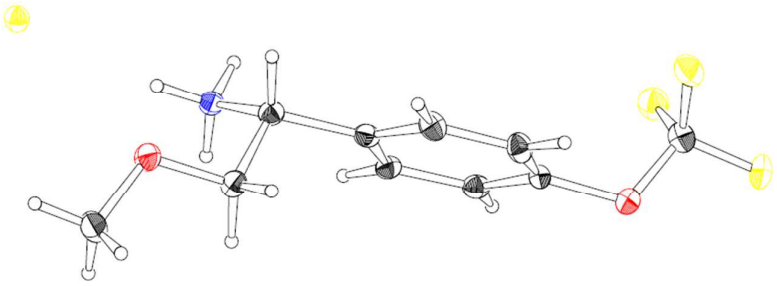


Figure 1. ORTEP of **S41a**, thermal ellipsoids are drawn at 20% probability.

■ Determination of the Absolute Stereochemistry of Amine S46

The absolute configuration of **S46** was determined by X-ray crystallography of its (+)-di-(*p*-toluoyl)-$_D$-tartaric acid salt **S47**.

Crystal data for **S47**: $C_{10}H_{12}F_4NO_2^+ \cdot C_{20}H_{17}O_8^-$, MW = 639.55; crystal size, 0.20 × 0.11 × 0.09 mm; colorless, block; monoclinic, space group $P2_1$, a = 7.88545(14) Å, b = 25.3299(5) Å, c = 15.2262(3) Å, $\alpha = \gamma$ = 90°, β = 90.330(7)°, V = 3041.20(10) Å^3, Z = 4, Dx = 1.397 g/cm^3, T = 100 K, μ = 1.044 mm^{-1}, λ = 1.54187 Å, R_1 = 0.060, wR_2 = 0.160, Flack Parameter[2] = 0.01(15).

All measurements were made on a Rigaku R-AXIS RAPID-191R diffractometer using graphite monochromated Cu-Kα radiation. The structure was solved by direct methods with SIR92[4] and was

refined using full-matrix least-squares on F^2 with SHELXL-97.[3] All non-H atoms were refined with anisotropic displacement parameters.

CCDC 1548479 for compound **S47** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx?.

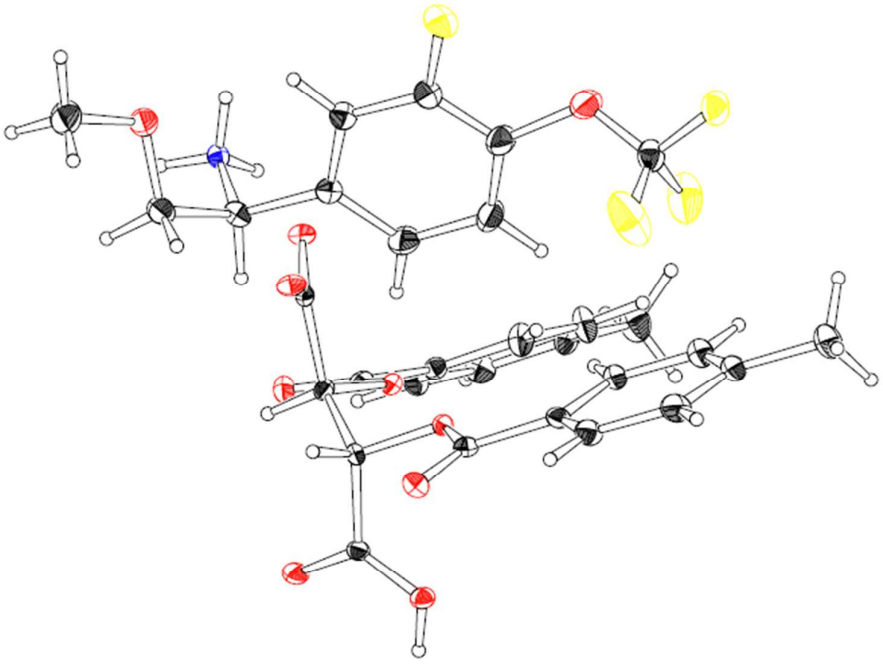


Figure 2. ORTEP of **S47**, thermal ellipsoids are drawn at 20% probability.

■ Molecular Formula Strings (MFS)

Table 1. Molecular Formula Strings of Molecules in the Manuscript

compd	SMILES	PDE2A IC_{50} (nM)
3	CCC(NC(=O)c1cnn2cccnc12)c1ccc(OC)cc1	3800
4a	CCC(NC(=O)c1cnn2cc(C)cnc12)c1ccc(OC(F)(F)F)cc1	53
4b	CCC(NC(=O)c1cnn2cc(C)cnc12)c1ccc(OC(F)(F)F)cc1	24
5	CCC(NC(=O)c1cnn2cccnc12)c1ccc(OC(F)(F)F)cc1	480
6	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)cc1	78

7	CCC(NC(=O)c1cc(=O)[nH]c2cccnc12)c1ccc(OC(F)(F)F)cc1	21
8	CCC(NC(=O)c1cnn2nc(C)cnc12)c1ccc(OC(F)(F)F)cc1	6500
9	CCC(NC(=O)c1c[nH]c(=O)c2cccnc12)c1ccc(OC(F)(F)F)cc1	19000
10	CCC(NC(=O)N1CC(=O)Nc2ccccc12)c1ccc(OC(F)(F)F)cc1	70000
6a	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)cc1	66
6b	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)cc1	>100000
11	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC)cc1	610
12	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(cc1)C(F)(F)F	72
13	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(cc1)C1CC1	80
14	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(cc1)N1CCC1	500
15	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1cccc(OC(F)(F)F)c1	4100
16	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccccc1OC(F)(F)F	8100
17	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)c(F)c1	42
18	CCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)cc1F	210
19	COCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)cc1	19
20	COCCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)cc1	62
21	CCCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)cc1	250
22	OCC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)cc1	65
23	CC(C)(O)C(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)cc1	24
24	CS(=O)(=O)CC(NC(=O)N1CC(=O)Nc2cccnc12)c1ccc(OC(F)(F)F)cc1	29
25	COCC(NC(=O)N1CC(=O)Nc2ccc(C)nc12)c1ccc(OC(F)(F)F)cc1	40
26	COCC(NC(=O)N1CC(=O)Nc2cc(C)cnc12)c1ccc(OC(F)(F)F)cc1	8.7
27	COCC(NC(=O)N1CC(=O)Nc2c(C)ccnc12)c1ccc(OC(F)(F)F)cc1	85
28	COCC(NC(=O)N1CC(=O)Nc2cc(cnc12)C1CC1)c1ccc(OC(F)(F)F)cc1	3.5

29	COCC(NC(=O)N1CC(=O)Nc2cc(Cl)cnc12)c1ccc(OC(F)(F)F)cc1	33
30	COCC(NC(=O)N1CC(=O)Nc2cc(OC)cnc12)c1ccc(OC(F)(F)F)cc1	2.8
31	COCC(NC(=O)N1CC(=O)Nc2cc(OC(C)C)cnc12)c1ccc(OC(F)(F)F)cc1	77
32	COCC(NC(=O)N1CC(=O)Nc2cc(OC)cnc12)c1ccc(OC(F)(F)F)cc1	1.6
33	COCC(NC(=O)N1CC(=O)Nc2cc(OC)cnc12)c1ccc(OC(F)(F)F)cc1	39000
34	COCC(NC(=O)N1CC(=O)Nc2cc(OC)cnc12)c1ccc(cc1)C(F)(F)F	7.2
35	COCC(NC(=O)N1CC(=O)Nc2cc(OC)cnc12)c1ccc(cc1)C(F)(F)F	21000
36	COCC(NC(=O)N1CC(=O)Nc2cc(OC)cnc12)c1ccc(OC(F)(F)F)c(F)c1	0.61
37	COCC(NC(=O)N1CC(=O)Nc2cc(OC)cnc12)c1ccc(OC(F)(F)F)c(F)c1	910

References

(1) Mikami, S.; Nakamura, S.; Ashizawa, T.; Sasaki, S.; Taniguchi, T.; Nomura, I.; Kawasaki, M. Nitrogenated Heterocyclic Compound. WO 2013161913, October 31, 2013.

(2) Flack, H. D. *Acta Cryst. A* **1983**, *39*, 876–881.

(3) Sheldrick, G. M. *Acta Cryst. A* **2008**, *64*, 112–122.

(4) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M.; Polidori, G.; Camalli, M. *J. Appl. Cryst.* **1994**, *27*, 435–436.