Supporting Information

Electrophilic Zinc Homoenolates: Synthesis of Cyclopropylamines from Cyclopropanols and Amines

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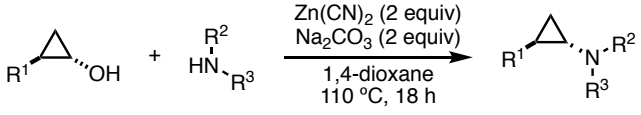
A. General information

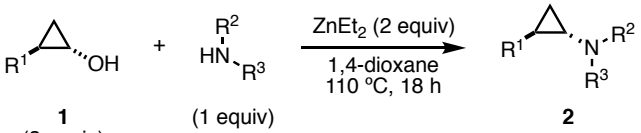
Unless otherwise noted, all reactions were set up on benchtop and run under argon or nitrogen using flame-dried glassware and anhydrous solvents. Anhydrous solvents were purchased from Sigma–Aldrich in Sure/Seal bottles and were used as received. Compounds were purified by flash column chromatography using SiliCycle SilicaFlash P60. Commercial amines were purchased from Acros, Alfa Aesar, Fisher, and Sigma–Aldrich; if liquid the amine was filtered through a plug of alumina (Acros, 50–200 μm, 60A) before use. Diethylzinc was purchased from Sigma–Aldrich as a 1.0 M solution THF and was titrated according to Knochel's protocol.[1] Zinc chloride was purchased from Sigma–Aldrich; before use it was dried at 150 ºC for 4 h under vacuum and after cooling to r.t. was made into a 1.0 M solution in THF. Bis(iodozinco)methane was prepared according to the procedure reported by Nomura et al.[2] Dess–Martin periodinane (DMP) was prepared according to literature procedures.[3,4] *N*-chlorosuccinimide (NCS) was purchased from Acros and was recrystallized from AcOH before use. Commercial aldehydes were distilled before use. All other commercial compounds and reagents were used as received. Cyclopropylamine synthesis reactions were performed in 16-mL Fisherbrand threaded tubes (manufacturer no. FB7375016125; Fisher catalog no. 14-959-35A) whose ends were sealed with size-19 rubber septa and electrical tape. Synthesized amines, cyclopropanols, and cyclopropylamines were stored at –20 ºC; however, cyclopropanols and cyclopropylamines without aryl substituents at the 2 position were generally bench-stable for several months, as were most tertiary cyclopropylamine products.

^{1}H and ^{13}C NMR spectra were recorded on Varian MercuryPlus 400 MHz or Bruker AvanceIII 400 MHz spectrometers. IR spectra were obtained on a Perkin-Elmer Spectrum 100 instrument equipped with a single-bounce diamond/ZnSe ATR accessory as solids or thin films. Melting points were obtained on a Fisher-Johns Melting Point Apparatus. High-resolution mass spectra (HRMS) were recorded on a JEOL AccuTOF JMS-T1000LV mass spectrometer equipped with a Direct Analysis in Real Time (DART) ion source. SFC-HPLC cyclopropanol resolution was performed at Merck & Co., Inc. (2000 Galloping Hill Road, Kenilworth, NJ, USA 07033) using a Diacel Chiralpak column (AD). Chiral HPLC analyses were performed on a Shimadzu 20A series system using a Daicel Chiralpak column (IA or IG).

B. Procedures for the synthesis of cyclopropylamines

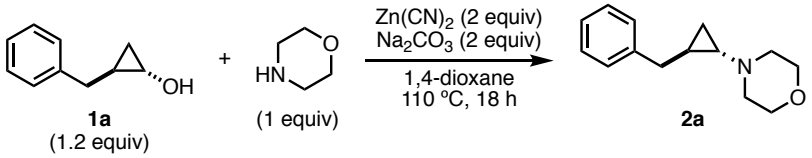


General procedure A: Cyclopropylamine synthesis using zinc cyanide *Caution: When using zinc cyanide care was taken to ensure reaction mixtures were kept basic to avoid formation of toxic HCN gas.* To a 16-mL threaded tube containing a stir bar was added zinc cyanide (47 mg, 0.40 mmol, 2.0 equiv), sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv), and amine (if a solid) (0.20 mmol, 1.0 equiv). The tube was sealed with a septum and electrical tape and was evacuated and backfilled with nitrogen (×3). If the amine was an oil, the amine was then added, followed by a solution of cyclopropanol in 1,4-dioxane (2.0 mL of a 0.12 M solution in dioxane, 0.24 mmol, 1.2 equiv). The reaction mixture was stirred in a 110 ºC oil bath. After 18 h the reaction was removed, opened to air, and quenched with sat. aq. $NaHCO_3$. The solution was extracted with EtOAc (×3). The organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated. The *trans*/*cis* d.r. was determined by ^{1}H NMR of the crude residue or by GC-MS peak areas in cases where diastereomeric proton signals could not be easily distinguished. The crude residue was purified by flash column chromatography to isolate the *trans* product.

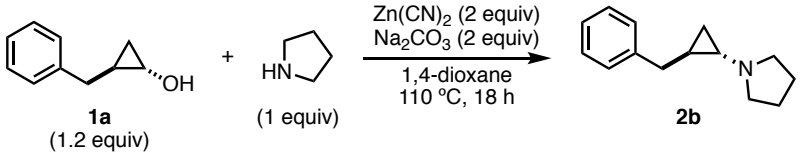


General procedure B: Cyclopropylamine synthesis using diethylzinc To a 12-mL threaded tube was added amine (if a solid) (0.20 mmol, 1.0 equiv). The tube was sealed with a septum and electrical tape and was evacuated and backfilled with nitrogen (×3). If the amine was an oil, the amine was then added, followed by a solution of cyclopropanol in 1,4-dioxane (2.0 mL of a 0.20 M solution in dioxane, 0.40 mmol, 2.0 equiv). Diethylzinc was added (0.40 mL of a 1.0 M solution in hexanes, 0.40 mmol, 2.0 equiv) and the reaction mixture was stirred in a 110 ºC oil bath. After 18 h the reaction was removed, opened to air, and quenched with sat. aq. $NaHCO_3$. The solution was extracted with EtOAc (×3). The organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated. The *trans*/*cis* d.r. was determined by ^{1}H NMR of the crude residue or by GC-MS peak areas in cases where diastereomeric proton signals could not be easily distinguished. The crude residue was purified by flash column chromatography to isolate the *trans* product.

Procedures for racemic scope

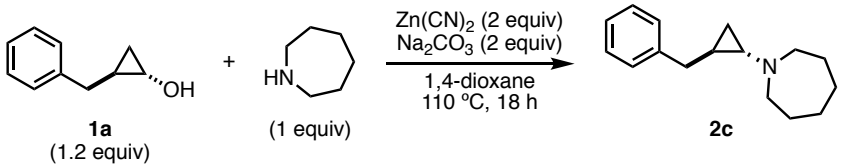


4-(*trans*-2-Benzylcyclopropyl)morpholine (2a): According to general procedure A, cyclopropylamine **2a** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.12 M solution in 1,4-dioxane, 0.24 mmol, 1.2 equiv), morpholine (17 μL, 0.20 mmol, 1.0 equiv), zinc cyanide (47 mg, 0.40 mmol, 2.0 equiv), and sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (20/1/79 EtOAc/NEt_3/hexanes) to yield **2a** as a colourless oil. Trial 1: 38 mg isolated (0.175 mmol, 88%; >20:1 d.r.); trial 2: 36 mg isolated (0.166 mmol, 83%; >20:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.34–7.16 (m, 5H), 3.65–3.56 (m, 4H), 2.64 (dd, J = 14.5, 6.4 Hz, 1H), 2.57–2.37 (m, 5H), 1.55 (ddd, J = 6.8, 3.4, 3.4 Hz, 1H), 1.16–1.05 (m, 1H), 0.75–0.65 (m, 1H), 0.49–0.41 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.5, 128.33, 128.28 125.9, 66.9, 53.4, 45.9, 38.5, 21.0, 13.0 ppm; **IR** (neat): 3027, 2957, 2917, 2853, 2806, 1604, 1496, 1450, 1264, 1204, 1116, 1069, 1038, 918, 895, 855, 771, 741, 698 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{14}H_{20}NO$ (M+H) 218.15449; found 218.15505.



1a (1.2 equiv) (1 equiv) **2b**

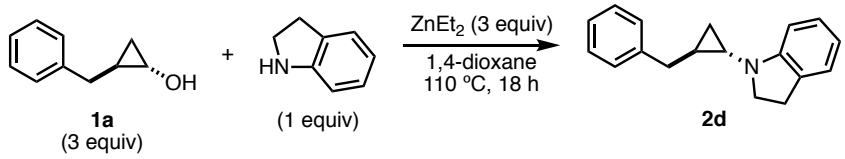
1-(*trans*-2-Benzylcyclopropyl)pyrrolidine (2b): According to general procedure A cyclopropylamine **2b** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.12 M solution in 1,4-dioxane, 0.24 mmol, 1.2 equiv), pyrrolidine (17 μL, 0.20 mmol, 1.0 equiv), zinc cyanide (47 mg, 0.40 mmol, 2.0 equiv), and sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (5/95 NEt_3/hexanes) to yield cyclopropylamine **2b** as a colourless oil. Trial 1: 35 mg isolated (0.174 mmol, 87%; 5.9:1 d.r.); trial 2: 30 mg isolated (0.149 mmol, 75%; 4.8:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.36–7.12 (m, 5H), 2.69–2.40 (m, 6H), 1.79–1.67 (m, 4H), 1.52 (ddd, J = 6.8, 3.4, 3.4 Hz, 1H), 1.21–1.09 (m, 1H), 0.77–0.70 (m, 1H), 0.47–0.40 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.7, 128.3, 128.2, 125.8, 53.8, 43.0, 38.5, 23.5, 20.4, 13.2 ppm; **IR** (neat): 3027, 2964, 2926, 2909, 2876, 2785, 1496, 1454, 1202, 1145, 920, 740, 697 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{14}H_{20}N$ (M+H) 202.15957; found 202.15986.



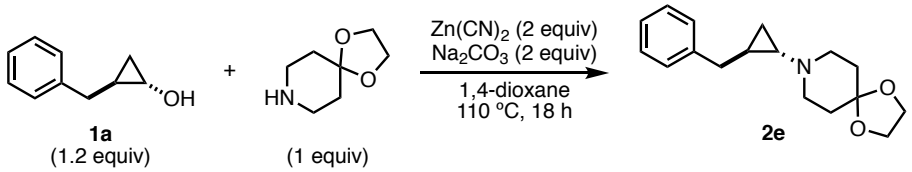
1a (1.2 equiv) (1 equiv) **2c**

1-(*trans*-2-Benzylcyclopropyl)azepane (2c): According to general procedure A cyclopropylamine **2c** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.12 M solution in 1,4-dioxane, 0.24 mmol, 1.2 equiv), azepane (23 μL, 0.20 mmol, 1.0 equiv), zinc cyanide (47 mg, 0.40 mmol, 2.0 equiv), and sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv). The product was purified by flash column chromatography (10/1/89 EtOAc/NEt_3/hexanes) to yield cyclopropylamine **2c** as a colourless oil. Trial 1: 36 mg isolated (0.157 mmol, 79%; >20:1 d.r.); trial 2: 28 mg isolated (0.115 mmol, 58%; >20:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.34–7.15 (m, 5H), 2.74–2.44 (m, 6H), 1.78 (ddd, J = 6.7, 3.4 Hz, 1H), 1.66–1.49 (m, 8H), 1.16–1.05 (m, 1H), 0.73–0.63 (m, 1H), 0.46–0.39 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.8, 128.4, 128.2, 125.8, 55.5, 45.2, 38.6, 27.6, 27.1,

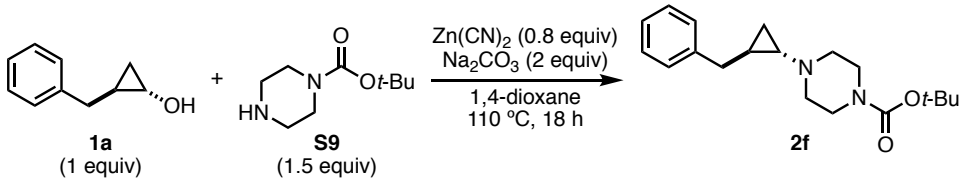
22.3, 14.7 ppm; **IR** (neat): 3027, 2919, 2852, 2806, 1496, 1453, 1384, 1281, 1238, 1164, 1000, 740, 696 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{16}H_{24}N$ (M+H) 230.19087; found 230.19055.



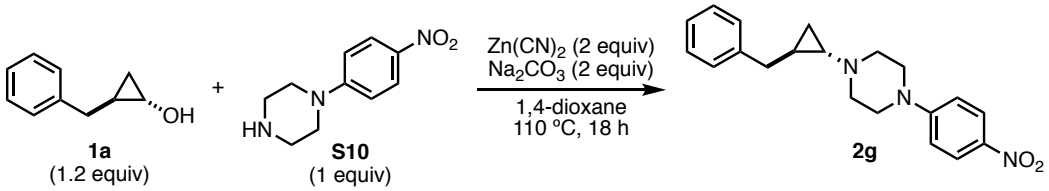
1-(*trans*-2-Benzylcyclopropyl)indoline (2d): According to general procedure B cyclopropylamine **2d** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.30 M solution in 1,4-dioxane, 0.60 mmol, 3.0 equiv), indoline (22 μL, 0.20 mmol, 1.0 equiv), and diethylzinc (0.60 mL of a 1.0 M solution in hexanes, 0.60 mmol, 3.0 equiv). The product was purified by flash column chromatography (gradient of 2/1/97 to 3/1/96 EtOAc/NEt_3/hexanes) to yield cyclopropylamine **2d** as a colourless oil. Trial 1: 37 mg isolated (0.148 mmol, 74%; >20:1 d.r.); trial 2: 36 mg isolated (0.144 mmol, 72%; >20:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.38–7.20 (m, 5H), 7.08–7.02 (m, 1H), 7.02–6.94 (m, 1H), 6.71–6.64 (m, 1H), 6.54–6.47 (m, 1H), 3.32–3.18 (m, 2H), 2.90–2.82 (m, 2H), 2.76-2.61 (m, 2H), 2.02 (ddd, *J* = 6.6, 3.2, 3.2 Hz, 1H), 1.38–1.24 (m, 1H), 0.96–0.86 (m, 1H) 0.72–0.64 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 152.9, 141.1, 130.4, 128.6, 128.4, 127.1, 126.1, 124.4, 118.3, 108.4, 54.0, 38.4, 37.0, 28.5, 20.6, 13.4 ppm; **IR** (neat): 3062, 3051, 3027, 2955, 2922, 2849, 1729, 1606, 1486, 1453, 1395, 1374, 1335, 1264, 1214, 1172, 1156, 1072, 1029, 1018, 908, 868, 737, 697 cm^{-1}; **HRMS** *m/z* (DART): calcd $C_{18}H_{20}N$ (M+H) 250.15957; found 250.15904**.**



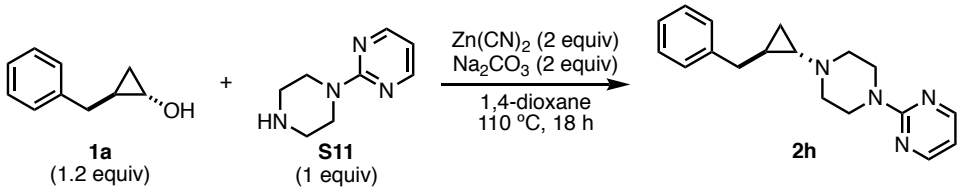
8-(*trans*-2-Benzylcyclopropyl)-1,4-dioxa-8-azaspiro[4.5]decane (2e): According to general procedure A cyclopropylamine **2e** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.12 M solution in 1,4-dioxane, 0.24 mmol, 1.2 equiv), 4-piperidone ethylene ketal (27 μL, 0.20 mmol, 1.0 equiv), zinc cyanide (47 mg, 0.40 mmol, 2.0 equiv), and sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (40/1/59 EtOAc/NEt_3/hexanes) to yield **2e** as a colourless oil. Trial 1: 45 mg isolated (0.165 mmol, 83%; >20:1 d.r.); trial 2: 51 mg isolated (0.187 mmol, 94%; >20:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.31–7.15 (m, 5H), 3.93 (s, 4H), 2.69–2.47 (m, 5H), 2.39 (dd, *J* = 14.4, 7.9 Hz, 1H), 1.69–1.60 (m, 4H), 1.55 (ddd, *J* = 6.9, 3.4, 3.4 Hz, 1H), 1.13–1.04 (m, 1H), 0.72–0.65 (m, 1H), 0.48–0.42 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.6, 128.4, 128.2, 125.9, 107.3, 64.2, 51.2, 45.2, 38.6, 34.7, 21.5, 13.7 ppm; **IR** (neat): 3027, 2999, 2951, 2928, 2884, 2809, 1603, 1496, 1454, 1228, 1142, 1109, 1078, 1039, 945, 918, 741, 698 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{17}H_{24}NO_2$ (M+H) 274.18070; found 274.18079.



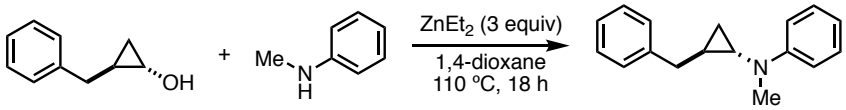
***tert*-Butyl 4-(*trans*-2-benzylcyclopropyl)piperazine-1-carboxylate (2f):** According to general procedure A, cyclopropylamine **2f** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.10 M solution in 1,4-dioxane, 0.20 mmol, 1.0 equiv), amine **S9** (56 mg, 0.30 mmol, 1.5 equiv), zinc cyanide (19 mg, 0.16 mmol, 0.80 equiv), and sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (gradient of 20/79/1 to 30/69/1 EtOAc/hexanes/NEt_3) to yield **2g** as a viscous colourless oil. Trial 1: 40 mg isolated (0.126 mmol, 63% yield; >20:1 d.r.); trial 2: 44 mg isolated (0.139 mmol, 70% yield; >20:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.34–7.24 (m, 2H), 7.23–7.17 (m, 3H), 3.39–3.24 (m, 4H), 2.64 (dd, J = 14.5, 6.4 Hz, 1H), 2.53–2.28 (m, 5H), 1.55–1.40 (m, 10H), 1.17–1.04 (m, 1H), 0.74–0.65 (m, 1H), 0.52-0.41 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 154.7, 141.5, 128.4, 128.3, 126.0, 79.5, 52.8, 45.6, 38.6, 28.45, 28.43, 21.3, 13.4 ppm; **IR** (neat): 3003, 2976, 2917, 2861, 2807, 1694, 1454, 1418, 1365, 1248, 1166, 1158, 1124, 1004, 740, 698 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{19}H_{29}N_2O_2$ (M+H) 317.22290; found 317.22162.



1-(*trans*-2-Benzylcyclopropyl)-2-(4-nitrophenyl)piperazine (2g): According to general procedure A cyclopropylamine **2g** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.12 M solution in 1,4-dioxane, 0.24 mmol, 1.2 equiv), amine **S10** (41 mg, 0.20 mmol, 1.0 equiv), zinc cyanide (47 mg, 0.40 mmol, 2.0 equiv), and sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (gradient of 24/1/75 to 34/1/65 EtOAc/NEt_3/hexanes) to yield **2g** as an orange-yellow solid. Trial 1: 42 mg isolated (0.124 mmol, 62%; >20:1 d.r.); trial 2: 40 mg isolated (0.119 mmol, 60%; 19:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 8.14–8.07 (m, 2H), 7.35–7.17 (m, 5H), 6.82–6.74 (m, 2H), 3.38–3.26 (m, 4H), 2.75–2.51 (m, 5H), 2.39 (dd, J = 14.5, 8.1 Hz, 1H), 1.57 (ddd, J = 6.8, 3.4, 3.4 Hz, 1H), 1.21–1.08 (m, 1H), 0.78–0.71 (m, 1H), 0.56–0.48 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): 154.9, 141.5, 138.3, 128.4, 126.0, 125.9, 112.6, 52.4, 47.0, 45.3, 38.5, 21.5, 13.4 ppm; **IR** (neat): 3059, 2998, 2949, 2902, 2886, 2849, 2821, 1587, 1487, 1446, 1315, 1241, 1233, 1153, 1106, 1028, 932, 828, 753, 733, 690 cm^{-1}; **m.p.**: 134–135 °C; **HRMS** *m/z* (DART): calcd for $C_{20}H_{24}N_3O_2$ (M+H) 338.18685; found 338.18709.

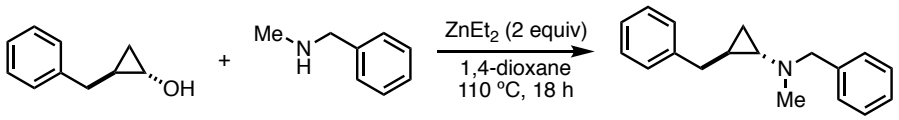


2-(4-(*trans*-2-Benzylcyclopropyl)piperazin-1-yl)pyrimidine (2h): According to general procedure A, cyclopropylamine **2h** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.12 M solution in 1,4-dioxane, 0.24 mmol, 1.2 equiv), amine **S11** (33 mg, 0.20 mmol, 1.0 equiv), zinc cyanide (47 mg, 0.40 mmol, 2.0 equiv), and sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (gradient of 40/1/59 to 50/1/49 EtOAc/NEt_3/hexanes) to yield **2h** as a colourless oil (sample contained a small amount (<5%) of *cis* isomer). Trial 1: 39 mg isolated (0.132 mmol, 66%; 15:1 d.r.); trial 2: 42 mg isolated (0.143 mmol, 72%; 15:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 8.28 (d, J = 4.7, 2H), 7.34–7.15 (m, 5H), 6.45 (t, J = 4.7 Hz, 1H), 3.78–3.69 (m, 4H), 2.70–2.38 (m, 6H), 1.54 (ddd, J = 6.8, 3.4, 3.4 Hz, 1H), 1.23–1.08 (m, 1H), 0.79–0.72 (m, 1H), 0.51–0.45 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_H 161.6, 157.7, 141.5, 128.4, 128.3, 125.9, 109.6, 52.9, 45.6, 43.5, 38.6, 21.2, 13.4 ppm; **IR** (neat): 3065, 3027, 2999, 2036, 2909, 2852, 2806, 1583, 1546, 1494, 1445, 1392, 1356, 1306, 1256, 982, 962, 796, 741, 698 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{18}H_{23}N_4$ (M+H) 295.19227; found 295.19243.



1a (3 equiv) + (1 equiv) → **2i**

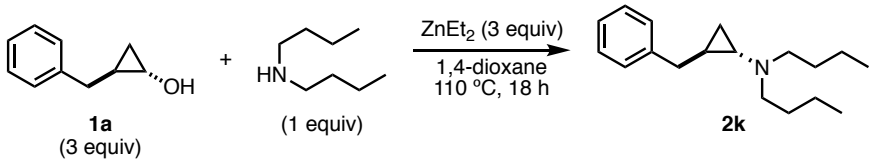
***N*-(*trans*-2-benzylcyclopropyl)-*N*-methylaniline (2i):** According to general procedure B, cyclopropylamine **2i** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.30 M solution in 1,4-dioxane, 0.60 mmol, 3.0 equiv), *N*-methylaniline (22 µL, 0.20 mmol, 1.0 equiv), and diethylzinc (0.60 mL of a 1.0 M solution in hexanes, 0.60 mmol, 3.0 equiv). The crude residue was purified by flash column chromatography (4/95/1 EtOAc/hexanes/NEt_3) to yield **2i** as a colourless oil. Trial 1: 40 mg isolated (0.169 mmol, 85% yield; >20:1 d.r.); trial 2: 34 mg isolated (0.143 mmol, 72%; >20:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.38–7.15 (m, 7H), 6.92–6.83 (m, 2H), 6.78–6.70 (m, 1H), 2.90–2.78 (m, 4H), 2.65 (dd, J = 14.5, 7.4 Hz, 1H), 2.31–2.24 (m, 1H), 1.35–1.24 (m, 1H), 0.94–0.75 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 150.5, 140.9, 128.8, 128.6, 128.5, 126.2, 117.3, 113.7, 40.1, 38.8, 38.4, 23.6, 16.3 ppm; **IR** (neat): 3063, 3026, 3001, 2921, 2854, 1600, 1576, 1497, 1472, 1453, 1392, 1340, 1331, 1301, 1233, 1188, 1115, 1031, 990, 749, 691 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{17}H_{20}N$ (M+H) 238.15957; found 238.15904.



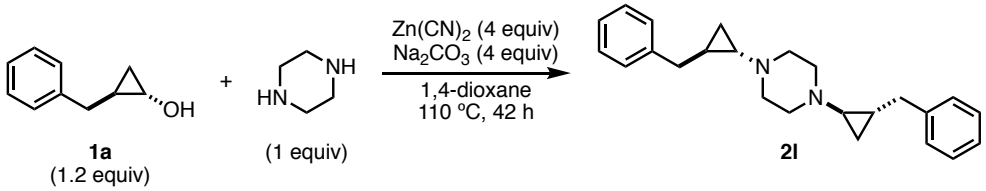
1a (2 equiv) + (1 equiv) → **2j**

***N*-(*trans*-2-benzylcyclopropyl)-*N*-methylbenzylamine (2j):** According to general procedure B, cyclopropylamine **2j** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.20 M solution in 1,4-dioxane, 0.40 mmol, 2.0 equiv), *N*-methylbenzylamine (26 µL, 0.20 mmol, 1.0 equiv), and diethylzinc (0.40 mL of a 1.0 M solution in hexanes, 0.40 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (10:89:1 EtOAc/hexanes/NEt_3) to yield **2j** as a yellow oil. Trial 1: 37 mg isolated (0.147 mmol, 74% yield; 14:1 d.r.); trial 2: 36 mg isolated (0.143 mmol, 72%; 13:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.38-7.11 (m, 10H), 3.64–3.51 (m, 2H), 2.51 (d, J = 7.2 Hz, 2H), 2.16 (s, 3H), 1.64–1.58 (m, 1H), 1.17–1.07 (m, 1H), 0.74–0.67 (m, 1H), 0.50–0.43 (m, 1H) ppm; **^{13}C NMR** (100 MHz,

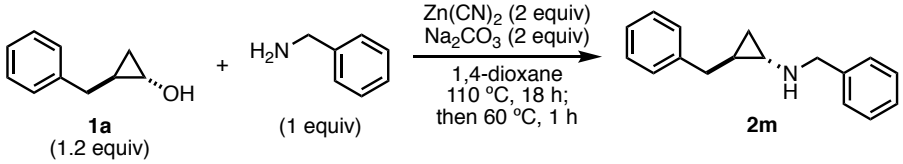
$CDCl_3$, 298 K) δ_H 141.6, 138.5, 129.3, 128.4, 128.2, 128.0, 126.8, 125.9, 60.1, 45.6, 41.8, 38.5, 22.4, 14.5 ppm; **IR** (neat): 3064, 3027, 3001, 2977, 2917, 2884, 2837, 2782, 1603, 1495, 1452, 1363, 1227, 1075, 1049, 1029, 928, 734, 696 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{18}H_{22}N$ (M+H) 252.17522; found 252.17525.



***trans*-2-Benzyl-*N*,*N*-dibutylcyclopropan-1-amine (2k):** According to general procedure B, cyclopropylamine **2k** was prepared using the following amounts of reagent: cyclopropanol **1a** (2.0 mL of a 0.30 M solution in 1,4-dioxane, 0.60 mmol, 3.0 equiv), dibutylamine (34 µL, 0.20 mmol, 1.0 equiv), and diethylzinc (0.60 mL of a 1.0 M solution in hexanes, 0.60 mmol, 3.0 equiv). The crude residue was purified by flash column chromatography (5/95 NEt_3/hexanes) to yield **2l** as a yellow oil. This sample contained some *cis* isomer (ca. 10%). Trial 1: 25 mg isolated (0.0964 mmol, 48%; 10:1 d.r.); trial 2: 31 mg isolated (0.119 mmol, 60%; 12:1 d.r.). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.35–7.15 (m, 5H), 2.63–2.36 (m, 5H), 1.59 (ddd, J = 6.9, 3.5, 3.5 Hz, 1H), 1.42–1.01 (m, 10H), 0.85 (t, J = 7.3 Hz, 6H), 0.71–0.63 (m, 1H), 0.48–0.40 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 100 MHz): δ_C 141.6, 128.4, 128.2, 125.8, 54.9, 43.6, 38.7, 28.7, 21.8, 20.8, 14.3, 14.0 ppm; **IR** (neat): 3028, 2956, 2928, 2871, 2860, 2806, 1605, 1496, 1465, 1454, 1377, 1173, 1094, 1078, 1030, 740, 697 cm^{-1}; **HRMS** m/z (DART): calcd for $C_{18}H_{30}N$ (M+H) 260.23782; found 260.23752.

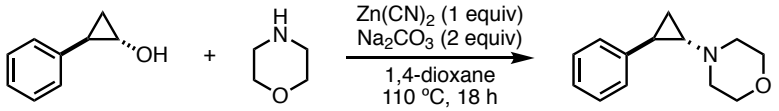


1,4-Bis(*trans*-2-benzylcyclopropyl)piperazine (2l): Cyclopropylamine **2l** was prepared according to general procedure A with the modification that the reaction was stopped after 42 h. The following amounts of reagent were used: cyclopropanol **1a** (2.0 mL of a 0.22 M solution in 1,4-dioxane, 0.44 mmol, 2.2 equiv), piperazine (17 mg, 0.20 mmol, 1.0 equiv), zinc cyanide (94 mg, 0.80 mmol, 4.0 equiv), and sodium carbonate (85 mg, 0.80 mmol, 4.0 equiv). The crude residue was purified by flash column chromatography (5/95 NEt_3/hexanes) to yield the mixture of *trans*,*trans*-**2l** and *cis*,*trans*-**2l** as a colourless oil. Trial 1: 30 mg isolated (0.087 mmol, 44%; d.r. = 95:4:<1 *trans,trans*/*cis,trans*/*cis,cis*); trial 2: 30 mg isolated (0.087 mmol, 44%; 95:4:<1 *trans,trans*/*cis,trans*/*cis,cis*). The isolated mixture could be further subjected to flash column chromatography (20/1/79 EtOAc/NEt_3/hexanes) to partially separate the major diastereomer *trans*,*trans*-**2l** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.34–7.15 (m, 10H), 2.66–2.15 (m, 12H), 1.52–1.44 (m, 2H), 1.14–1.02 (m, 2H), 0.72–0.62 (m, 2H), 0.47–0.38 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.6, 128.3, 128.2, 125.9, 52.9, 45.6, 38.6, 21.0, 13.2 ppm; **IR** (neat): 3026, 3000, 2936, 2900, 2883, 2805, 1495, 1451, 1372, 1270, 1211, 1143, 1032, 926, 738, 696 cm^{-1}; **m.p.**: 49–51 ºC; **HRMS** *m/z* (DART): calcd for $C_{24}H_{31}N_2$ (M+H) 347.24872; found 347.24786.



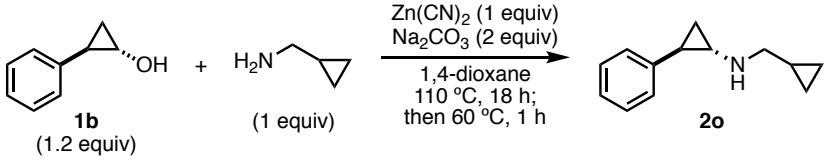
1a (1.2 equiv) (1 equiv) **2m**

***trans*-*N*,2-Dibenzylcyclopropan-1-amine (2m):** Cyclopropylamine **2m** was prepared according to general procedure A with the modification that after 18 h at 110 ºC the reaction was stirred for an additional 1 h at 60 ºC to push the cyclopropylamine/imine equilibrium towards cyclopropylamine product. The following amounts of reagent were used: cyclopropanol **1a** (2.0 mL of a 0.12 M solution in 1,4-dioxane, 0.24 mmol, 1.2 equiv), benzylamine (22 μL, 0.20 mmol, 1.0 equiv), zinc cyanide (47 mg, 0.40 mmol, 2.0 equiv), and sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (gradient of 8/2 to 7/3 hexanes/EtOAc) to yield **2m** as a yellow oil. Trial 1: 26 mg isolated (0.110 mmol, 55%; 4.9:1 d.r.); trial 2: 21 mg isolated (0.088 mmol, 44%; 5.1:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.34–7.17 (m, 10H), 3.75 (s, 2H), 2.60–2.44 (m, 2H), 2.05 (ddd, J = 6.8, 3.4, 3.4 Hz, 1H), 1.82 (br s, 1H), 1.14–1.04 (m, 1H), 0.70–0.64 (m, 1H), 0.47–0.40 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.7, 128.3, 128.3, 128.3, 128.2, 126.8, 125.9, 53.6, 38.4, 37.2, 21.5, 13.8 ppm; **IR** (neat): 3085, 3063, 3027, 3000, 2919, 2848, 1648, 1603, 1495, 1453, 1393, 1158, 1074, 1029, 731, 695 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{17}H_{20}N$ (M+H) 238.15957; found 238.15966.



1b (1.2 equiv) (1 equiv) **2n**

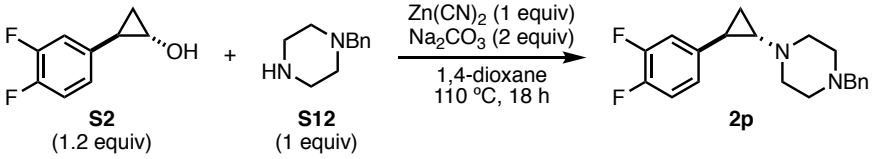
4-(*trans*-2-Phenylcyclopropyl)morpholine (2n): According to general procedure A, cyclopropylamine **2n** was prepared using the following amounts of reagent: cyclopropanol **1b** (32 mg, 0.24 mmol, 1.2 equiv), morpholine (17.5 μL, 0.20 mmol, 1.0 equiv), zinc cyanide (23 mg, 0.20 mmol, 1.0 equiv), sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv), and 1,4-dioxane (1.0 mL, 0.10 M). The crude residue was purified by flash column chromatography (6/4 hexanes/EtOAc) to yield cyclopropylamine **2n** as a colourless oil. Trial 1: 25 mg isolated (0.123 mmol, 62%; 7.2:1 d.r.); trial 2: 27 mg isolated (0.133 mmol, 67%; 7.2:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.29–7.22 (m, 2H), 7.19–7.13 (m, 1H), 7.09–7.04 (m, 2H), 3.75–3.63 (m, 4H), 2.71–2.60 (m, 4H), 2.04–1.96 (m, 1H), 1.93–1.87 (m, 1H), 1.15–1.08 (m, 1H), 1.00–0.93 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.9, 128.3, 126.0, 125.7, 66.9, 53.4, 49.0, 24.2, 16.1 ppm; **IR** (neat): 2957, 2934, 2901, 2853, 2807, 1605, 1498, 1450, 1440, 1372, 1263, 1205, 1115, 1070, 959, 883, 872, 781, 748, 696 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{13}H_{18}NO$ (M+H) 204.13884; found 204.13886.



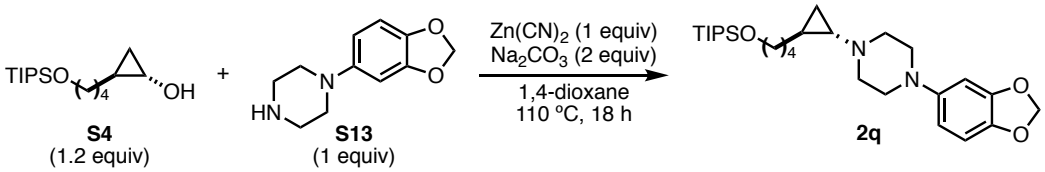
1b (1.2 equiv) (1 equiv) **2o**

***trans*-*N*-(Cyclopropylmethyl)-2-phenylcyclopropan-1-amine (2o):** Cyclopropylamine **2o** was prepared according to general procedure A with the modification that after 18 h at 110 ºC the reaction was stirred for 1 h at 60 ºC to push the cyclopropylamine/imine equilibrium towards

cyclopropylamine product. The following amounts of reagent were used: cyclopropanol **1b** (32 mg, 0.24 mmol, 1.2 equiv), cyclopropanemethylamine (17 μL, 0.20 mmol, 1.0 equiv), zinc cyanide (23 mg, 0.20 mmol, 1.0 equiv), sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv), and 1,4-dioxane (2.0 mL, 0.10 M). The crude residue was purified by flash column chromatography (60/1/39 EtOAc/NEt_3/hexanes) to yield cyclopropylamine **2o** as a colourless oil. Trial 1: 20 mg isolated (0.107 mmol, 54%; 10:1 d.r.); trial 2: 15 mg isolated (0.080 mmol, 40%; 10:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.29–7.21 (m, 2H), 7.17–7.11 (m, 1H), 7.07–7.01 (m, 2H), 2.65–2.52 (m, 2H), 2.39 (ddd, J = 7.3, 4.4, 3.1 Hz, 1H), 1.96–1.80 (m, 2H), 1.13–1.05 (m, 1H), 1.01–0.93 (m, 1H), 0.51–0.43 (m, 2H), 0.14–0.08 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 100 MHz): δ_C 142.4, 128.2, 125.8, 125.4, 54.6, 41.4, 25.2, 17.1, 11.3, 3.4, 3.4 ppm; **IR** (neat): 3078, 3026, 3002, 2925, 2854, 2816, 1674, 1650, 1604, 1497, 1459, 1430, 1381, 1216, 1075, 1016, 827, 745, 695 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{13}H_{18}N$ (M+H) 188.14392; found 188.14365.

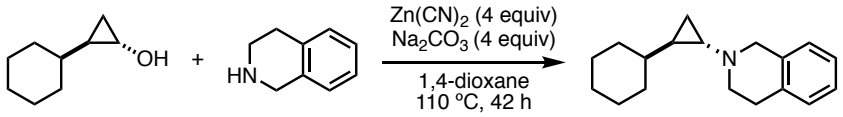


1-Benzyl-4-(*trans*-2-(3,4-difluorophenyl)cyclopropyl)piperazine (2p): According to general procedure A cyclopropylamine **2p** was prepared using the following amounts of reagent: cyclopropanol **S2** (2.0 mL of a 0.12 M solution in 1,4-dioxane, 0.24 mmol, 1.2 equiv), amine **S12** (35 mg, 0.20 mmol, 1.0 equiv), zinc cyanide (23 mg, 0.20 mmol, 1.0 equiv), and sodium carbonate (42 mg, 0.40 mmol, 1.0 equiv). The crude residue was purified by flash column chromatography (10/1/89 AcMe/NEt_3/hexanes) to yield **2p** as a colourless oil. Trial 1: 29 mg isolated (0.088 mmol, 44%; 10:1 d.r.); trial 2: 34 mg isolated (0.104 mmol, 52%; 8.2:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.36–7.18 (m, 5H), 7.06–6.95 (m, 1H), 6.86–6.73 (m, 2H), 3.57–3.46 (m, 2H), 2.75–2.24 (m, 8H), 1.92 (ddd, J = 9.2, 5.8, 3.2 Hz, 1H), 1.80 (ddd, J = 7.3, 4.4, 3.2 Hz, 1H), 1.14–1.05 (m, 1H), 0.92–0.83 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 150.4 (dd, J = 245.8, 12.7 Hz), 148.6 (dd, J = 243.9, 12.6 Hz), 139.2 (dd, J = 5.9, 3.6 Hz), 137.9, 129.2, 128.2, 127.1, 122.0 (dd, J = 5.9, 3.3 Hz), 116.9 (d, J = 16.9 Hz), 114.9 (d, J = 17.4 Hz), 63.0, 52.89, 52.87, 48.8, 23.8 (d, J = 1.5 Hz), 16.5 ppm; **IR** (neat): 3065, 3028, 2937, 2909, 2991, 2809, 2766, 1678, 1606, 1520, 1454, 1424, 1350, 1275, 1268, 1209, 1140, 1118, 1011, 928, 866, 814, 771, 736, 697 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{20}H_{23}F_2N_2$ (M+H) 329.18293; found 329.18231.



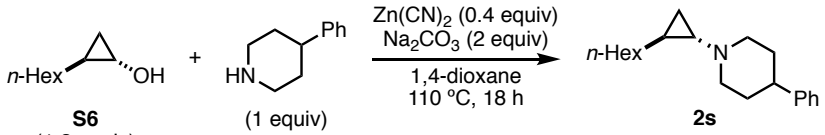
1-(Benzo[1,3]dioxol-5-yl)-4-(*trans*-2-(4-((triisopropylsilyl)oxy)butyl)cyclopropyl)-piperazine (2q): According to general procedure A, cyclopropylamine **2q** was prepared using the following amounts of reagent: cyclopropanol **S4** (2.0 mL of a 0.12 M solution in 1,4-dioxane, 0.24 mmol, 1.2 equiv), amine **S13** (41 mg, 0.20 mmol, 1.0 equiv), zinc cyanide (47 mg, 0.40 mmol, 2.0 equiv), and sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (5/95 NEt_3/hexanes) to yield **2q** as a colourless oil. Trial 1: 64 mg isolated (0.135 mmol, 68%); trial 2: 72 mg isolated (0.152 mmol, 76%; >20:1 d.r.). **^{1}H NMR**

(400 MHz, $CDCl_3$, 298 K): δ_H 6.72–6.67 (m, 1H), 6.56–6.53 (m, 1H), 6.37–6.32 (m, 1H), 5.88 (s, 2H), 3.67 (t, J = 6.3 Hz, 2H), 3.04–2.98 (m, 4H), 2.75–2.69 (m, 4H), 1.63–0.73 (m, 29H), 0.63–0.55 (m, 1H), 0.33–0.25 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 148.1, 147.6, 141.4, 109.0, 108.1, 100.8, 99.9, 63.4, 53.2, 50.8, 45.7, 32.8, 32.5, 25.7, 19.9, 18.0, 13.0, 12.0 ppm; **IR** (neat): 2939, 2890, 2864, 2815, 1632, 1616, 1505, 1490, 1462, 1452, 1380, 1242, 1211, 1041, 958, 937, 882, 794, 733, 680 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{27}H_{47}N_2O_3Si$ (M+H) 475.33559; found 475.33493.



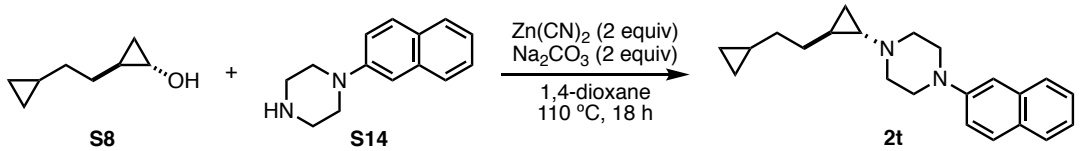
S5 (1.2 equiv) (1 equiv) **2r**

2-(*trans*-2-Cyclohexylcyclopropyl)-1,2,3,4-tetrahydroisoquinoline (2r): Cyclopropylamine **2r** was prepared according to general procedure A with the modification that the reaction was stirred for 42 h. The following amounts of reagent were used: cyclopropanol **S5** (2.0 mL of a 0.12 M solution in 1,4-dioxane, 0.24 mmol, 1.2 equiv), 1,2,3,4-tetrahydroisoquinoline (25 μL, 0.20 mmol, 1.0 equiv), zinc cyanide (94 mg, 0.80 mmol, 4.0 equiv), and sodium carbonate (85 mg, 0.80 mmol, 4.0 equiv). The product was purified by flash column chromatography (4:1:95 EtOAc/NEt_3/hexanes) to yield **2r** as a colourless oil. Trial 1: 34 mg isolated (0.151 mmol, 76%; >20:1 d.r.); trial 2: 33 mg isolated (0.146 mmol, 73%; >20:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.18–7.00 (m, 4H), 3.90–3.62 (m, 2H), 2.99–2.80 (m, 4H), 1.91–1.58 (m, 5H), 1.54 (ddd, J = 6.8, 3.4, 3.4 Hz, 1H), 1.36–0.81 (m, 6H), 0.78–0.51 (m, 2H), 0.42–0.34 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 134.3, 128.7, 126.6, 126.6, 126.0, 125.6, 55.9, 50.9, 44.3, 41.0, 33.0, 32.6, 28.9, 26.9, 26.5, 26.2, 12.1 ppm; **IR** (neat): 2920, 2849, 2789, 2737, 1498, 1448, 1382, 1279, 1240, 1150, 940, 935, 880, 861, 738 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{18}H_{26}N$ (M+H) 256.20652; found 256.20646.



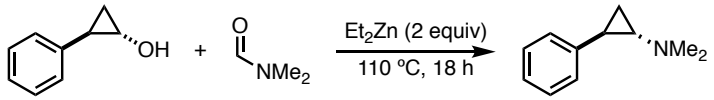
S6 (1.2 equiv) (1 equiv) **2s**

1-(*trans*-2-Hexylcyclopropyl)-4-phenylpiperidine (2s): According to general procedure A, cyclopropylamine **2s** was prepared using the following amounts of reagent: cyclopropanol **S6** (4.0 mL of a 0.12 M solution in 1,4-dioxane, 0.48 mmol, 1.2 equiv), 4-phenylpiperidine (65 mg, 0.40 mmol, 1.0 equiv), zinc cyanide (19 mg, 0.16 mmol, 0.40 equiv), and sodium carbonate (85 mg, 0.80 mmol, 2.0 equiv). The crude residue was adsorbed onto silica and purified by flash column chromatography (5/1/94 EtOAc/NEt_3/hexanes) to yield **2s** as a colourless oil (80 mg, 0.280 mmol, 70%; >20:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.34–7.14 (m, 5H), 3.21–3.07 (m, 2H), 2.57–2.44 (m, 1H), 2.34–2.16 (m, 2H), 1.88–1.63 (m, 3H), 1.45–0.98 (m, 12H), 0.95–0.75 (m, 4H), 0.66–0.55 (m, 1H), 0.33–0.23 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 146.6, 128.4, 126.9, 126.1, 54.7, 54.2, 46.3, 42.9, 33.4, 32.9, 31.9, 29.7, 29.4, 29.2, 22.7, 20.0, 14.1, 13.2 ppm; **IR** (neat): 2955, 2921, 2853, 2790, 1494, 1455, 1380, 1254, 1024, 755, 697 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{20}H_{32}N$ (M+H) 286.25348; found 286.25412.



S8 (1.2 equiv) **S14** (1 equiv) **2t**

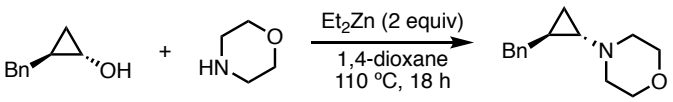
1-(*trans*-2-(2-Cyclopropylethyl)cyclopropyl)-4-(naphthalen-2-yl)piperazine (2t): According to general procedure A, cyclopropylamine **2t** was prepared using the following amounts of reagent: cyclopropanol **S8** (1.0 mL of a 0.12 M solution in 1,4-dioxane, 0.12 mmol, 1.2 equiv), amine **S14** (21 mg, 0.10 mmol, 1.0 equiv), zinc cyanide (23 mg, 0.20 mmol, 2.0 equiv), and sodium carbonate (21 mg, 0.20 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (5/95 NEt_3/hexanes) to yield **2t** as a white solid. Trial 1: 16 mg isolated (0.050 mmol, 50%; 4.6:1 d.r.); trial 2: 23 mg isolated (0.072 mmol, 72%; 6.7:1 d.r.). **^{1}H NMR** ($CDCl_3$, 400 MHz, 298 K): δ_H 7.75–7.65 (m, 3H), 7.42–7.35 (m, 1H), 7.32–7.23 (m, 2H), 7.13–7.09 (m, 1H), 3.31–3.20 (m, 4H), 2.85–2.72 (m, 4H) 1.45–1.18 (m, 5H), 0.94–0.83 (m, 1H), 0.76–0.60 (m, 2H), 0.46–0.29 (m, 3H), 0.06–0.02 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 149.2, 134.6, 128.6, 128.4, 127.4, 126.7, 126.2, 123.3, 119.4, 110.2, 53.1, 49.5, 45.9, 34.5, 32.7, 19.8, 13.1, 10.7, 4.5, 4.5 ppm; **IR** (neat): 3074, 2998, 2918, 2849, 2825, 1626, 1597, 1508, 1448, 1384, 1272, 1255, 1223, 1199, 1149, 1014, 963, 826, 805, 742 cm^{-1}; **m.p.**: 50–52 ºC; **HRMS** *m/z* (DART): calcd for $C_{22}H_{29}N_2$ (M+H) 321.23307; found 321.23266.



1c (1 equiv) (0.1 M) **2u**

***trans*-*N*,*N*-Dimethyl-2-phenylcyclopropan-1-amine (2u):** Cyclopropylamine **2u** was prepared according to general procedure B with the modification that DMF was used both as solvent and amine source. The following amounts of reagent were used: cyclopropanol **1c** (81 mg, 0.60 mmol, 1.0 equiv), DMF (3.0 mL, 0.20 M), and diethylzinc (1.2 mL of a 1.0 M solution in hexanes, 1.2 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (Et_2O) to yield **2u** as a colourless oil. Due to the volatility of the product, the yield was determined by ^{1}H NMR of the crude residue using dodecane as internal standard (0.34 mmol, 57%; 8.4:1 d.r.). The analytical data is consistent with literature reports:[5] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.49–7.05 (m, 5H), 2.42 (s, 6H), 2.01 (ddd, J = 9.2, 5.8, 3.3 Hz, 1H), 1.83 (ddd, J = 7.2, 4.5, 3.4 Hz, 1H), 1.18–1.08 (m, 1H), 1.03–0.95 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 142.1, 128.2, 126.1, 125.6, 53.4, 50.2, 45.0, 25.2, 17.2 ppm.

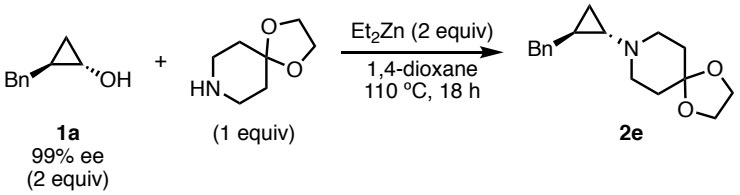
Procedures for making enantioenriched cyclopropylamines



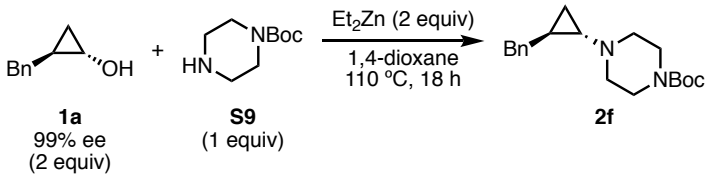
1a 99% ee (2 equiv) (1 equiv) **2a**

4-(*trans*-2-Benzylcyclopropyl)morpholine (2a): According to general procedure B, enantioenrichd cyclopropylamine **2a** was prepared using the following amounts of reagent: cyclopropanol **1a** (99% ee; 0.50 mL of a 0.20 M solution in 1,4-dioxane, 0.10 mmol, 2.0 equiv),

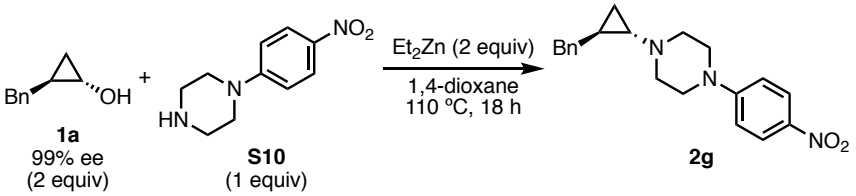
morpholine (4.4 μL, 0.050 mmol, 1.0 equiv), and diethylzinc (0.10 mL of a 1.0 M solution in hexanes, 0.10 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (20/1/79 EtOAc/NEt_3/hexanes) to yield **2a**. The yield was determined by GC-MS analysis of the crude residue using dodecane as internal standard (0.047 mmol, 93%, >20:1 d.r.). **Chiral HPLC** (Chiralpak IA, 98/2 hexanes/IPA, 0.7 mL/min, λ = 215 nm): t_R (major): 7.42 min; t_R (minor): 7.19 min; 89% ee, 90% es.



8-(*trans*-2-Benzylcyclopropyl)-1,4-dioxa-8-azaspiro[4.5]decane (2e): According to general procedure B, enantioenriched cyclopropylamine **2e** was prepared using the following amounts of reagent: cyclopropanol **1a** (99% ee; 0.50 mL of a 0.20 M solution in 1,4-dioxane, 0.10 mmol, 2.0 equiv), 4-piperidone ethylene ketal (6.4 μL, 0.050 mmol, 1.0 equiv), and diethylzinc (0.10 mL of a 1.0 M solution in hexanes, 0.10 mmol, 2.0 equiv). The crude residue was purified by flash column chromatography (40/1/59 EtOAc/NEt_3/hexanes) to yield **2e**. The yield was determined by ^{1}H NMR analysis of the crude residue using dodecane as internal standard (0.050 mmol, >99%, >20:1 d.r.). **Chiral HPLC** (Chiralpak IA, 99/1 hexanes/IPA, 0.7 mL/min, λ = 207 nm): t_R (major): 13.13 min; t_R (minor): 14.08 min; 88% ee, 89% es.

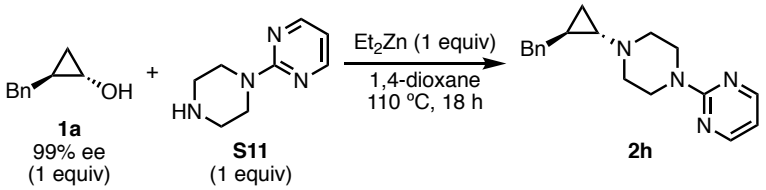


***tert*-Butyl 4-(*trans*-2-benzylcyclopropyl)piperazine-1-carboxylate (2f):** According to general procedure B, enantioenriched cyclopropylamine **2f** was prepared using the following amounts of reagent: cyclopropanol **1a** (99% ee; 0.40 mL of a 0.20 M solution in 1,4-dioxane, 0.080 mmol, 2.0 equiv), amine **S9** (7.5 mg, 0.040 mmol, 1.0 equiv), and diethylzinc (0.080 mL of a 1.0 M solution in hexanes, 0.080 mmol, 2.0 equiv). The yield was determined by ^{1}H NMR analysis of the crude residue using dodecane as internal standard (0.036 mmol, 91%, >20:1 d.r.). **Chiral HPLC** (Chiralpak IG, 98/2 hexanes/THF, 0.7 mL/min, λ = 217 nm): t_R (major): 23.43 min; t_R (minor): 22.46 min; 90% ee, 91% es.

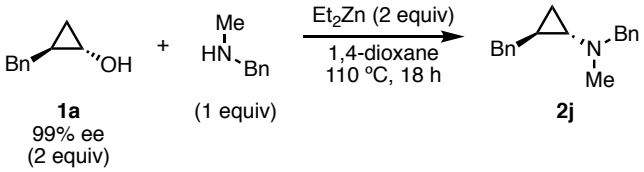


1-(*trans*-2-Benzylcyclopropyl)-2-(4-nitrophenyl)piperazine (2g): According to general procedure B, enantioenriched cyclopropylamine 2g was prepared using the following amounts of reagent: cyclopropanol 1a (99% ee, 0.40 mL of a 0.20 M solution in 1,4-dioxane, 0.080 mmol, 2.0 equiv), amine **S10** (8.3 mg, 0.040 mmol, 1.0 equiv), and diethylzinc (0.080 mL of a 1.0 M solution in hexanes, 0.080 mmol, 2.0 equiv). The yield was determined by ^{1}H NMR analysis of

the crude residue using dodecane as internal standard (0.018 mmol, 45%, >20:1 d.r.). Chiral HPLC (Chiralpak IG, 90/10 hexanes/IPA, 0.7 mL/min, λ = 354 nm): t_R (major): 32.73 min; t_R (minor): 31.71 min; 92% ee, 93% es.

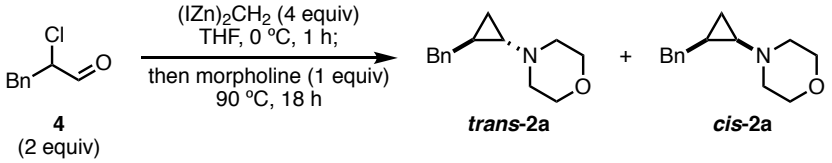


2-(4-(*trans*-2-Benzylcyclopropyl)piperazin-1-yl)pyrimidine (2h): According to general procedure B, enantioenriched cyclopropylamine **2h** was prepared using the following amounts of reagent: cyclopropanol **1a** (99% ee; 0.50 mL of a 0.20 M solution in 1,4-dioxane, 0.10 mmol, 1.0 equiv), amine **S11** (16 mg, 0.10 mmol, 1.0 equiv), and diethylzinc (0.10 mL of a 1.0 M solution in hexanes, 0.10 mmol, 1.0 equiv). The crude residue was purified by flash column chromatograph (40/1/59 EtOAc/NEt_3/hexanes) to yield **2h**. The yield was determined by ^{1}H NMR analysis of the crude residue using dodecane as internal standard (0.087 mmol, 87%, >20:1 d.r.). **Chiral HPLC** (Chiralpak IA, 98.9/1/0.1 hexanes/IPA/diethylamine, 0.7 mL/min, λ = 251 nm): t_R (major): 12.56 min; t_R (minor): 12.18 min; 91% ee, 92% es.



***N*-(*trans*-2-benzylcyclopropyl)-*N*-methylbenzylamine (2j):** According to general procedure B, enantioenriched cyclopropylamine **2j** was prepared using the following amounts of reagent: cyclopropanol **1a** (99% ee; 0.40 mL of a 0.20 M solution in 1,4-dioxane, 0.080 mmol, 2.0 equiv), *N*-benzylmethylamine (5.2 μL, 0.040 mmol, 1.0 equiv), and diethylzinc (0.080 mL of a 1.0 M solution in hexanes, 0.080 mmol, 2.0 equiv). The yield was determined by ^{1}H NMR analysis of the crude residue using dodecane as internal standard (0.040 mmol, >99%, >20:1 d.r.). **Chiral HPLC** (Chiralpak IG, 98/2 hexanes/THF, 0.7 mL/min, λ = 190 nm): t_R (major): 6.30 min; t_R (minor): 6.83 min; 88% ee, 89% es.

Procedures for one-pot cyclopropanol synthesis from α-chloroaldehydes

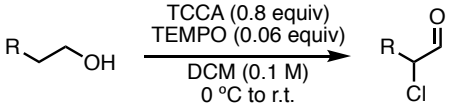


4-(*trans*-2-Benzylcyclopropyl)morpholine (2a): To a flame-dried 1-dram reaction vial was added α-chloroaldehyde **4** (34 mg, 0.20 mmol, 2.0 equiv). The vial was closed with a septum-cap and was rigorously sealed with electrical tape. The vial was evacuated and backfilled with nitrogen (×3) and cooled to 0 ºC. Bis(iodozinco)methane (2.1 mL of a 0.19 M solution in THF, 0.40 mmol, 4.0 equiv) was added and the reaction was stirred at 0 ºC for 1 h. Then, morpholine (8.7 μL, 0.10 mmol, 1.0 equiv) was added and the reaction was stirred at 90 ºC for 18 h. The

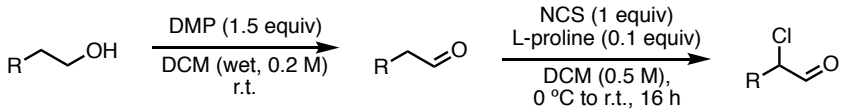
reaction was cooled to r.t., opened to air, and quenched with sat. aq. NH_4Cl. The solution was extracted with EtOAc (×3), and the organic fractions were combined, washed with sat. aq. $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (24/1/75 EtOAc/NEt_3/hexanes) to yield **2a** (17 mg, 0.78 mmol, 78%; d.r. before purification = 4.7:1).

4-(*cis*-2-Benzylcyclopropyl)morpholine (*cis*-2a): To a flame-dried 100-mL Schlenk flask was added α-chloroaldehyde **4** (0.67 g, 4.0 mmol, 2.0 equiv). The flask was sealed with a septum and was evacuated and backfilled with nitrogen (×3). The septum was rigorously sealed with electrical tape. Bis(iodozinco)methane (35 mL of a 0.23 M solution in THF, 8.0 mmol, 4.0 equiv) was added and the reaction was stirred for 1 h at 0 ºC. Morpholine (0.17 mL, 2.0 mmol, 1.0 equiv) was added and the reaction was stirred at 90 ºC for 18 h. The solution was extracted with EtOAc (×3), and the organic fractions were combined, washed with sat. aq. $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (10/1/89 EtOAc/NEt_3/hexanes) to yield ***cis*-2a** as a colourless oil (33 mg, 0.15 mmol, 8%; d.r. before purification = 5.1:1 *trans*/*cis*). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.37–7.07 (m, 5H), 3.75–3.59 (m, 4H), 2.94 (dd, J = 15.0, 5.9 Hz, 1H), 2.74 (dd, J = 15.0, 8.4 Hz, 1H), 2.61–2.45 (m, 4H), 1.80–1.74 (m, 1H), 1.18–1.06 (m, 1H), 0.74–0.66 (m, 1H), 0.26–0.19 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): 142.8, 128.3, 128.2, 125.6, 67.1, 54.0, 43.1, 33.0, 19.0, 11.0 ppm.

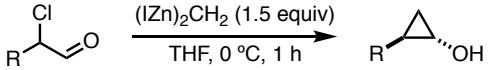
C. Preparation of cyclopropanol starting materials



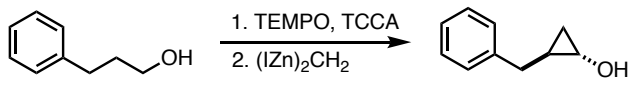
General procedure C: α-Chloroaldehyde synthesis from alcohols using TEMPO and TCCA. The procedure follows that reported by Jing et al.[6] To a flask were added TEMPO (0.060 equiv) and DCM (reagent grade, 0.10 M). The solution was cooled to 0 ºC and alcohol (1.0 equiv) was added. Trichloroisocyanuric acid (TCCA) was added in three portions over 10 min (0.80 equiv). After addition, the reaction was warmed to r.t. and stirred open to air until conversion to α-chloroaldehyde was complete. The solution was diluted with pentane, filtered, and concentrated under vacuum to yield crude α-chloroaldehyde. These materials could be stored neat at –20 ºC for ca. 1 week before degradation was apparent.



General procedure D: Two-step α-chloroaldehyde synthesis from alcohols using DMP then NCS and L-proline. To a flask were added DCM (reagent grade, 0.20 M), alcohol (1.0 equiv), and DMP (1.5 equiv). The reaction was stirred open to air until full conversion of alcohol was observed. Then, the solution was washed with 10% aq. $Na_2S_2O_3$ (×2), sat. aq. $NaHCO_3$ (×2), H_2O (×1), and brine (×1). The solution was dried over $MgSO_4$, filtered, and concentrated under vacuum. Conversion of aldehyde to α-chloroaldehyde was performed according to the procedure reported by Halland et al.[7] The crude aldehyde material was transferred to a flame-dried flask. The flask was evacuated and backfilled with nitrogen (×3) and DCM (0.50 M) was added. The solution was cooled to 0 ºC and both NCS (1.0 equiv) and L-proline (0.10 equiv) were added at once. The reaction was stirred under nitrogen for 16 h while the ice bath was allowed to slowly warm to r.t. The solution was diluted with pentane, filtered, and concentrated under vacuum to yield crude α-chloroaldehyde.

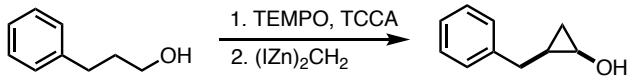


General procedure E: Conversion of α-chloroaldehydes to cyclopropanols using bis(iodozinco)methane. The procedure used follows that reported by Cheng et al.[8] The crude α-chloroaldehyde material (1.0 equiv) was transferred to a flame-dried flask. The flask was evacuated and backfilled with nitrogen (×3) and put into a 0 ºC ice bath. Bis(iodozinco)methane was added in 10 mL portions over 10 min (1.5 equiv). The reaction was stirred under nitrogen for 1 h at 0 ºC. The reaction was opened to air and quenched at 0 ºC with sat. aq. NH_4Cl. The solution was extracted with Et_2O (×3). The organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated under vacuum. Cyclopropanol was purified by flash column chromatography to yield the *trans* isomer; d.r. of the reaction was determined by ^1H NMR analysis of the crude reaction mixture.



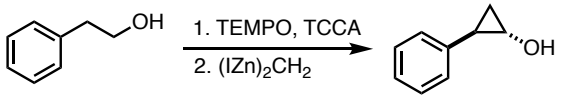
1a

***trans*-2-Benzylcyclopropanol (1a):** According to general procedures C and E, cyclopropanol **1a** was prepared with the following details: Step 1: 3-Phenyl-1-propanol (3.5 mL, 26 mmol, 1.0 equiv), TEMPO (0.24 g, 1.6 mmol, 0.060 equiv), TCCA (4.8 g, 21 mmol, 0.80 equiv), and DCM (260 mL, 0.10 M). The reaction was run in a 500-mL flask and was stopped after 3 h. The organic filtrate was further washed with sat. aq. $NaHCO_3$ (×2), H_2O (×1), and brine (×2). Step 2: Bis(iodozinco)methane (200 mL of a 0.17 M solution in THF, 34 mmol, 1.3 equiv). The reaction was run in a 500-mL flask. The crude residue was purified by flash column chromatography (gradient of 8/2 to 7/3 hexanes/EtOAc) to yield **1a** as a light yellow oil (1.8 g, 12 mmol, 46% over 2 steps; d.r. before purification = 9.4:1 *trans*/*cis*). **1a** was resolved by SFC-HPLC (Chiralpak AD, 30×250 mm, 5% 2:1 MeOH/MeCN, 70 mL/min, 25 mg/mL in MeOH). **1a** was bench-stable over several months. The analytical data is consistent with literature reports.[8] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.37–7.18 (m, 5H), 3.35 (ddd, J = 6.3, 5.3, 2.7 Hz, 1H), 2.62–2.45 (m, 2H), 1.98 (br s, 1H), 1.31–1.19 (m, 1H), 0.81 (ddd, J = 9.9, 5.8, 3.0 Hz, 1H), 0.50 (ddd, J = 12.2, 6.0, 6.0 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 141.1, 128.4, 128.3, 126.0, 52.6, 37.3, 21.5, 14.6 ppm; **Chiral HPLC** (Chiralpak IG, 99/1 hexanes/IPA, 1.0 mL/min, λ = 215 nm): t_R (major): 40.41 min; t_R (minor): 39.19 min; 99% ee.



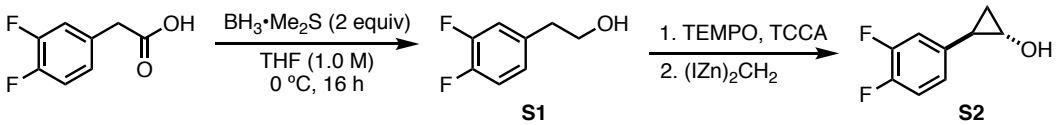
***cis*-1a**

***cis*-2-Benzylcyclopropanol (*cis*-1a)**: According to general procedures C and E, cyclopropanol ***cis*-1a** was prepared with the following details: Step 1: 3-Phenyl-1-propanol (27 mL, 200 mmol, 1.0 equiv), TEMPO (1.9 g, 12 mmol, 0.060 equiv), TCCA (37 g, 160 mmol, 0.80 equiv), and DCM (2.0 L, 0.10 M). The reaction was run in a 10-L flask and was stopped after 3 h. Step 2: Bis(iodozinco)methane (1.0 L of a 0.22 M solution in THF, 220 mmol, 1.1 equiv). The reaction was run in a 2-L flask and was stopped after 1 h. ***cis*-1a** was purified from the crude residue over 3 consecutive rounds of flash column chromatography (gradient of 9/1 to 7/3 hexanes/EtOAc) to yield ***cis*-1a** as a colourless oil (32 mg, 0.22 mmol, 0.11%; d.r. before purification = 3.4:1 *trans*/*cis*). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.46–7.11 (m, 5H), 3.63 (ddd, J = 6.5, 6.5, 4.0 Hz, 1H), 2.91–2.77 (m, 2H), 1.10–0.97 (m, 1H), 0.85–0.76 (m, 1H), 0.44–0.37 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 142.2, 128.4, 128.2, 125.8, 50.1, 32.6, 18.6, 13.3 ppm.



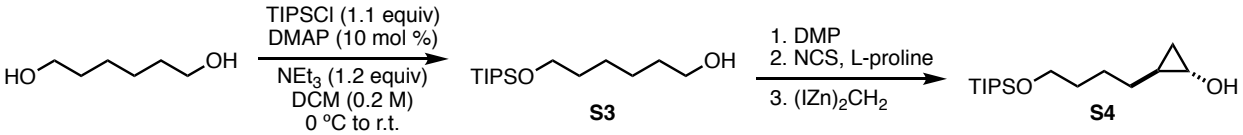
1b

***trans*-2-Phenylcyclopropanol (1b):** According to general procedures C and E, cyclopropanol **1b** was prepared with the following details. Step 1: 2-Phenylethanol (3.6 mL, 30 mmol, 1.0 equiv), TEMPO (0.28 g, 1.8 mmol, 0.060 equiv), trichloroisocyauric acid (5.6 g, 24 mmol, 0.80 equiv), and DCM (300 mL, 0.10 M). The reaction was performed in a 1-L flask and was stopped after 75 min. Step 2: Bis(iodozinco)methane (120 mL of a ca. 0.50 M solution in THF, 60 mmol, 2.0 equiv). The reaction was performed in a 250-mL flask. The crude residue was purified by flash column chromatography (gradient of 8/2 to 7/3 hexanes/EtOAc) to yield **1b** as a yellow solid (2.2 g, 16 mmol, 53% over 2 steps; d.r. before purification = 4.4:1 *trans*/*cis*). The analytical data is consistent with literature reports:[9] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.31–7.98 (m, 5H), 3.66–3.59 (m, 1H), 2.29–2.02 (m, 2H), 1.34–1.22 (m, 1H), 1.10–0.99 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.1, 128.3, 125.8, 125.7, 55.4, 25.5, 17.8 ppm.



2-(3,4-Difluorophenyl)ethanol (S1): To a flame-dried 100-mL flask was added 3,4-difluorophenylacetic acid (3.4 g, 20 mmol, 1.0 equiv). The flask was evacuated and backfilled with nitrogen (×3) and THF (20 mL, 1.0 M) was added. The solution was cooled to 0 ºC and borane dimethylsulfide complex (20 mL of a 2.0 M solution in THF, 40 mmol, 2.0 equiv) was added. The reaction was stirred for 16 h under nitrogen. The reaction was quenched with sat. aq. $NaHCO_3$ and the mixture was extracted with DCM (×3). The organic fractions were combined, washed with brine, dried over $MgSO_4$, and concentrated to yield **S1** as a colourless oil (2.8 g, 18 mmol, 90%). This compound is commercially available (286440-92-4). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.13–7.01 (m, 2H), 6.97–6.90 (m, 1H), 3.84 (t, J = 6.5 Hz, 2H), 2.82 (t, J = 6.4 Hz, 2H), 1.62–1.44 (br s, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): 150.2 (dd, J = 246.4, 12.6 Hz), 149.2 (dd, J = 244.7, 12.6 Hz), 135.7 (dd, J = 5.6, 3.9 Hz), 124.8 (dd, J = 5.9, 3.4 Hz), 117.7 (d, J = 16.7 Hz), 117.2 (d, J = 17.2 Hz), 63.3, 38.3 (d, J = 1.3 Hz) ppm.

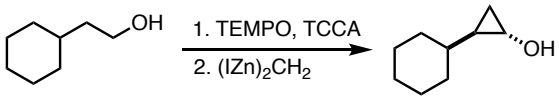
***trans*-2-(3,4-Difluorophenyl)cyclopropanol (S2):** According to general procedures C and E, cyclopropanol **S2** was prepared with the following details: Step 1: Alcohol **S1** (2.2 g, 14 mmol, 1.0 equiv), TEMPO (0.14 g, 0.85 mmol, 0.060 equiv), TCCA (2.6 g, 11 mmol, 0.80 equiv), and DCM (140 mL, 0.10 M). The reaction was performed in a 500-mL flask and was stopped after 80 min. Step 2: Bis(iodozinco)methane (50 mL of a 0.38 M solution in THF, 19 mmol, 1.4 equiv). The reaction was performed in a 100-mL flask and was stopped after 80 min. The crude residue was purified by flash column chromatography (7/3 hexanes/EtOAc) to yield **S2** as a colourless oil (0.62 g, 3.6 mmol, 24% over 2 steps; d.r. before purification = >20:1 *trans*/*cis*). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.08–6.98 (m, 1H), 6.84–6.70 (m, 2H), 3.62–3.51 (m, 1H), 2.23–2.01 (m, 2H), 1.35–1.23 (m, 1H), 1.04–0.94 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 150.2 (dd, J = 246.0, 12.6 Hz), 148.7 (dd, J = 244.0, 12.5 Hz), 138.2 (dd, J = 5.8, 3.6 Hz), 121.8 (dd, J = 5.9, 3.4 Hz), 117.0 (d, J = 16.7 Hz), 114.6 (d, J = 17.4 Hz), 55.2, 24.7 (d, J = 1.5 Hz), 17.9 ppm; **IR** (neat): 3377 (br), 1715, 1609, 1519, 1429, 1277, 1208, 1161, 1115, 1076, 887, 819, 771 cm^{-1}.



6-((Triisopropylsilyl)oxy)hexan-1-ol (S3): To a flame-dried 50-mL flask was added 1,6-hexanediol (0.59 g, 5.0 mmol, 1.0 equiv) and DMAP (56 mg, 0.50 mmol, 0.10 equiv). The flask was sealed with a septum and evacuated and backfilled three times with nitrogen. DCM (25 mL, 0.20 M) was added and the solution was cooled to 0 ºC. Chlorotriisopropylsilane (1.1 mL, 5.5 mmol, 1.1 equiv) was added followed by triethylamine (0.84 mL, 6.0 mmol, 1.2 equiv). The reaction was removed from the ice bath and stirred at r.t. for 18 h under nitrogen. The solution was concentrated and the crude residue was purified by flash column chromatography (gradient of 100% hexanes to 1:1 hexanes/EtOAc) to yield **S3** as a colourless oil (0.66 g, 2.4 mmol, 47%). The analytical data is consistent with literature reports:[10] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 3.71–3.61 (m, 4H), 1.63–1.50 (m, 4H), 1.45–1.33 (m, 4H), 1.28–1.18 (m, 1H), 1.14–0.97 (m,

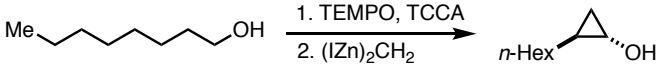
21H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 63.3, 63.0, 32.9, 32.8, 25.63, 25.56, 18.0, 12.0 ppm.

***trans*-2-(4-((Triisopropylsilyl)oxy)butyl)cyclopropanol (S4):** According to general procedures D and E, cyclopropanol **S5** was prepared with the following details. Step 1: Alcohol **S3** (0.66 g, 2.4 mmol, 1.0 equiv), DMP (1.5 g, 3.6 mmol, 1.5 equiv), and DCM (reagent grade, 12 mL, 0.20 M). The reaction was performed in a 50-mL flask and was stopped after 1 h. Step 2: NCS (0.32 g, 2.4 mmol, 1.0 equiv), L-proline (28 mg, 0.24 mmol, 0.10 equiv), and DCM (4.8 mL, 0.50 M). The reaction was performed in a 25-mL flask and was stopped after 16 h. Step 3: Bis(iodozinco)-methane (11 mL of a 0.33 M solution in THF, 3.6 mmol, 1.5 equiv). The reaction was performed in a 50 mL flask and was stopped after 1 h. The crude residue was purified by flash column chromatography (9/1 hexanes/EtOAc) to yield **S4** as a colourless oil (0.38 g, 1.3 mmol, 55% over 3 steps; d.r. before purification >20:1 *trans*/*cis*). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): 3.71–3.63 (m, 2H), 3.22–3.18 (m, 1H), 1.88–1.69 (br m, 1H), 1.61–0.86 (m, 28H), 0.72–0.64 (m, 1H), 0.35–0.27 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 63.3, 52.8, 32.7, 31.4, 25.2, 20.9, 18.0, 14.5, 12.0 ppm; **IR** (neat): 3305 (br), 2941, 2892, 2865, 1462, 1383, 1255, 1203, 1103, 1070, 1013, 996, 917, 881, 788, 679 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{16}H_{35}O_2Si$ (M+H) 287.24063; found 287.24010.



S5

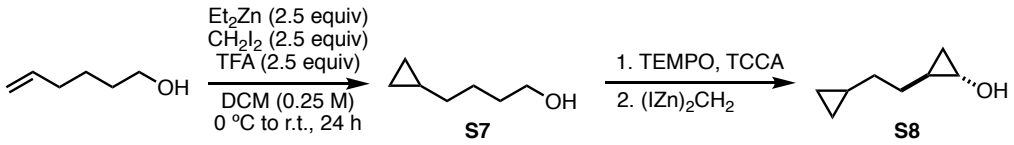
***trans*-2-Cyclohexylcyclopropanol (S5):** According to general procedures C and E, **S5** was prepared with the following details. Step 1: 2-Cyclohexylethanol (2.8 mL, 20 mmol, 1.0 equiv), trichloroisocyanuric acid (3.7 g, 16 mmol, 0.80 equiv), TEMPO (0.19 g, 1.2 mmol, 0.060 equiv), DCM (200 mL, 0.10 M). The reaction was performed in a 500-mL flask and was stopped after 2.5 h at r.t. Step 2: Bis(iodozinco)methane (90 mL of a 0.19 M solution in THF, 17 mmol, 0.85 equiv). The reaction was performed in a 250-mL flask. The crude residue was purified by flash column chromatography (8:2 hexanes/EtOAc) to yield **S5** as a colourless oil (0.97 g, 6.9 mmol, 35% over 2 steps; d.r. before purification >20:1 *trans*/*cis*). The analytical data is consistent with literature reports.[8] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 3.24 (ddd, J = 6.4, 5.3, 2.7 Hz, 1H), 1.86–1.55 (m, 6H), 1.23–0.93 (m, 5H), 0.81–0.72 (m, 1H), 0.67–0.60 (m, 1H), 0.58–0.47 (m, 1H), 0.38–0.31 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 51.6, 40.2, 32.8, 31.9, 27.6, 26.4, 26.2, 26.2, 13.3 ppm.



S6

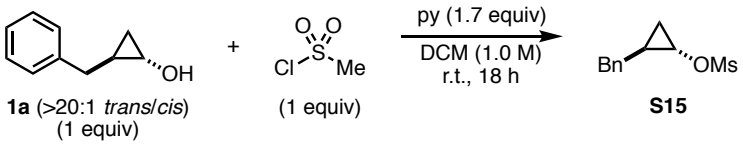
trans-2-Hexylcyclopropanol (S6): According to general procedures C and E, cyclopropanol **S6** was prepared with the following details: Step 1: 1-Octanol (2.4 mL, 15 mmol, 1.0 equiv), TEMPO (0.17 g, 0.90 mmol, 0.06 equiv), TCCA (2.8 g, 12 mmol, 0.80 equiv), and DCM (150 mL, 0.10 M). The reaction was performed in a 500-mL flask and was stopped after 2 h. Step 2: Bis(iodozinco)methane (56 mL of a 0.38 M solution in THF, 21 mmol, 1.4 equiv). The reaction was performed in a 100-mL flask and was stopped after 80 min. The crude residue was purified by flash column chromatography (75/25 hexanes/EtOAc) to yield **S6** as a colourless oil (0.64 g, 4.5 mmol, 30% over 2 steps; d.r. before purification = 18:1 *trans*/*cis*). The analytical data is

consistent with literature reports:[8] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 3.22–3.17 (m, 1H), 1.44–1.01 (m, 11H), 0.97–0.80 (m, 4H), 0.71–0.63 (m, 1H), 0.34–0.26 (m, 1H) ppm.



4-Cyclopropylbutanol (S7): To a flame-dried 100-mL flask was added DCM (40 mL, 0.25 M), hex-5-en-1-ol (1.2 mL, 10 mmol, 1.0 equiv), and diiodomethane (1.2 mL, 25 mmol, 2.5 equiv). The solution was cooled to 0 ºC and diethylzinc (25 mL of a 1.0 M solution in hexanes, 25 mmol, 2.5 equiv) was added dropwise over 10 min. Trifluoroacetic acid (1.9 mL, 25 mmol, 2.5 equiv) was added dropwise over 10 min. The reaction was stirred for 24 h under nitrogen while the ice bath was allowed to slowly warm to r.t. The reaction was opened to air and quenched with sat. aq. NH_4Cl. The solution was extracted with DCM (×3). The organic fractions were combined and washed with brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was then added to a 50-mL flask with DCM (20 mL, 0.50 M), and *m*-CPBA (0.49 g of a 70% w/w suspension in H_2O, 2.0 mmol, 0.20 equiv) was added. The solution was stirred for 2 h open to air and then quenched with sat. aq. NH_4Cl. The mixture was extracted with DCM (×3), and the organic fractions were combined, washed with sat. aq. $NaHCO_3$ (×1) and brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (8/2 hexanes/EtOAc) to yield **S7** as a colourless, fruity-smelling oil (0.51 g, 4.5 mmol, 45%). This sample still contained a small amount (<10%) of unreacted alkene material. The analytical data is consistent with literature reports:[11] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 3.62 (t, J = 6.6 Hz, 2H), 1.63–1.53 (m, 3H), 1.49–1.39 (m, 2H), 1.24–1.17 (m, 2H), 0.70–0.58 (m, 1H), 0.45–0.31 (m, 2H), 0.04––0.08 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 63.0, 34.5, 32.6, 25.8, 10.8, 4.3 ppm.

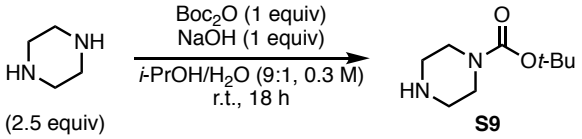
***trans*-2-(2-Cyclopropylethyl)cyclopropanol (S8)**: According to general procedures C and E, cyclopropanol **S8** was prepared with the following details: Step 1: Alcohol **S7** (0.44 g, 3.9 mmol, 1.0 equiv), TEMPO (36 mg, 0.23 mmol, 0.06 equiv), TCCA (0.72 g, 3.1 mmol, 0.80 equiv), and DCM (39 mL, 0.10 M). The reaction was performed in a 100-mL flask and was stopped after 180 min. Step 2: Bis(iodozinco)methane (35 mL of a 0.17 M solution in THF, 5.9 mmol, 1.5 equiv). The reaction was performed in a 100-mL flask and was stopped after 45 min. The crude residue was purified by flash column chromatography (9/1 hexanes/EtOAc) to yield **S8** as a colourless oil (0.17 g, 1.3 mmol, 33% over 2 steps; d.r. before purification = >20:1). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 3.23–3.18 (m, 1H), 2.01–1.47 (br m, 1H), 1.38–1.11 (m, 4H), 1.00–0.89 (m, 1H), 0.73–0.60 (m, 2H), 0.47–0.25 (m, 3H), 0.08––0.07 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 52.8, 34.0, 31.7, 20.8, 14.5, 10.6, 4.5, 4.4 ppm; **IR** (neat): 3327 (br), 3076, 2999, 2915, 2852, 1712, 1455, 1428, 1297, 1201, 1152, 1068, 1043, 1014, 923, 820 cm^{-1}.



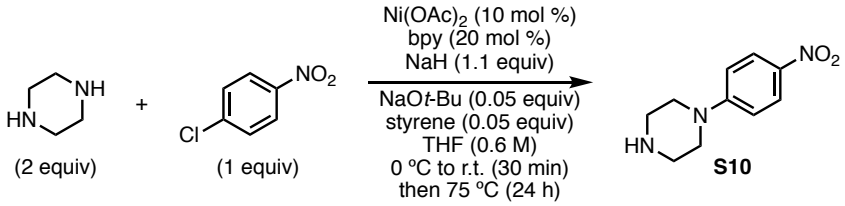
***trans*-2-Benzylcyclopropylmethanesulfonate (S15):** To an oven-dried 1-dram vial was transferred **1a** (74 mg, 0.50 mmol, 1.0 equiv; >20:1 *trans*/*cis*). The vial was sealed with a septum and evacuated and backfilled with nitrogen (×3). To the vial was added DCM (0.50 mL, 1.0 M),

methanesulfonylchloride (0.04 mL, 0.50 mmol, 1.0 equiv), and pyridine (0.07 mL, 0.85 mmol, 1.7 equiv). The reaction was stirred at r.t. overnight. The reaction was quenched with sat. aq. NH_4Cl. The solution was extracted with DCM (×3) and the organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (7/3 hexanes/EtOAc) to yield **S15** as a colourless oil (75 mg, 0.33 mmol, 66%; >20:1 d.r.). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.38–7.18 (m, 5H), 4.01 (ddd, *J* = 5.4, 2.3, 2.3 Hz, 1H), 2.82 (s, 3H), 2.71–2.53 (m, 2H), 2.64–1.53 (m, 1H), 1.23–1.16 (m, 1H), 0.84–0.76 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 139.4, 128.6, 128.4, 126.5, 58.5, 37.3, 36.5, 19.6, 11.9 ppm; **IR** (neat): 3086, 3063, 3029, 2939, 2918, 2855, 1604, 1584, 1497, 1455, 1356, 1132, 1047, 1017, 967, 885, 861, 819, 727, 699 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{11}H_{15}O_3S$ (M+H) 227.07419; found 227.07507.

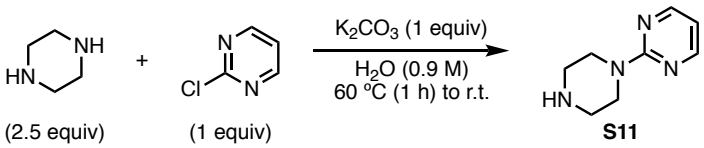
D. Preparation of amine starting materials



***tert*-Butyl piperazine-1-carbozylate (S9): S9** was prepared according to a procedure reported by Biannic et al.[12] To a 50-mL flask was added piperazine (0.86 g, 10 mmol, 2.5 equiv), sodium hydroxide (0.16 g, 4.0 mmol, 1.0 equiv), isopropanol (12 mL) and water (1.3 mL). Boc anhydride (0.92 mL, 4.0 mmol, 1.0 equiv) was added and the reaction was stirred at room temperature for 18 h. The solution was concentrated to remove isopropanol. The mixture was diluted with water, filtered through a fritted funnel to remove diboc-piperazine, and the filtrate was extracted with DCM (×3). The combined organic fractions were dried over $MgSO_4$ and concentrated to yield **S9** as a white crystalline solid (0.53 g, 2.8 mmol, 70%). Analytical data matches that reported in the literature.[13] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 3.43–3.34 (m, 4H), 2.85–2.76 (m, 4H), 1.46 (s, 9H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 154.8, 79.5, 45.9, 28.41, 28.39 ppm.

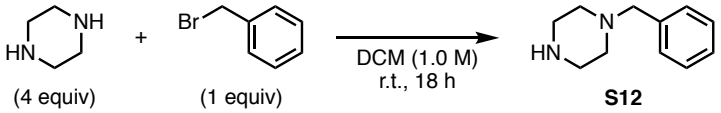


1-(4-Nitrophenyl)piperazine (S10): Amine **S10** was prepared following the protocol reported by Brenner et al.[14] To a flame-dried 50-mL flask was added piperazine (1.7 g, 20 mmol, 2.0 equiv), 4-nitrochlorobenzene (1.6 g, 10 mmol, 1.0 equiv), anhydrous nickel acetate (0.18 g, 1.0 mmol, 10 mol %), 2,2'-bipyridine (0.31 g, 2.0 mmol, 20 mol %), and sodium *tert*-butoxide (48 mg, 0.50 mmol, 0.050 equiv). The flask was sealed with a septum and evacuated and backfilled with nitrogen (×3). The flask was put into a 0 ºC ice bath and THF (17 mL, 0.60 M) was added. Styrene (0.060 mL, 0.50 mmol, 0.050 equiv) was added and the mixture was stirred for 30 min under nitrogen, allowing the mixture to slowly warm to r.t. The reaction was then heated to 75 ºC and stirred at that temperature under nitrogen. After 24 h, the reaction was cooled to r.t., opened to air, and quenched with isopropanol. The mixture was diluted with DCM, filtered over Celite, and the filtrate was concentrated. The crude residue was purified by flash column chromatography (40/1/59 MeOH/NEt_3/EtOAc) to yield **S10** as a yellow-brown solid (0.43 g, 2.1 mmol, 21%). The analytical data is consistent with literature reports:[15] **^{1}H NMR** (400 MHz, $CDCl_3$, 298K): δ_H 8.22–8.08 (m, 2H), 6.91–6.77 (m, 2H), 3.49–3.35 (m, 4H), 3.12–2.98 (m, 4H), 2.03 (br s, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): 155.2, 138.4, 125.9, 112.6, 48.1, 45.7 ppm.

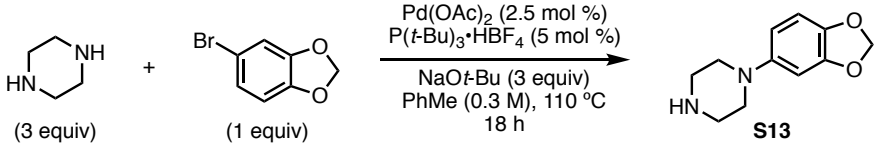


2-(Piperazin-1-yl)pyrimidine (S11): Amine **S11** was prepared according to a procedure reported by Wang et al.[16] To a 25-mL flask was added piperazine (0.54 g, 6.3 mmol, 2.5 equiv), potassium carbonate (0.35 g, 2.5 mmol, 1.0 equiv), and water (2.8 mL, 0.90 M). The solution was heated to 60 ºC and 2-chloropyrimidine (0.29 g, 2.5 mmol, 1.0 equiv) was added in small portions over 10

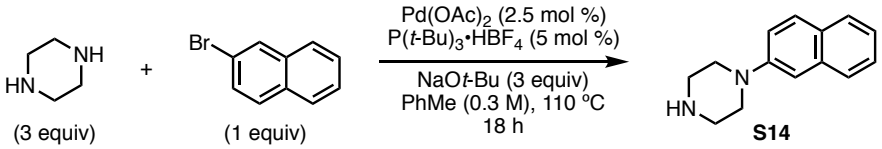
min. The reaction was stirred open to air for another 1 h at 60 ºC then cooled to r.t. The solution was filtered through a fritted funnel and the aqueous filtrate was extracted with $CHCl_3$ (×3). The organic phases were combined, dried over $MgSO_4$, and concentrated under vacuum to yield **S11** as a yellow solid (0.35 g, 2.1 mmol, 84%). **S11** was fairly hygroscopic so exposure to air was minimized. The analytical data is consistent with literature reports:[15] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 8.30 (d, J = 4.7 Hz, 2H), 6.46 (dd, J = 4.7, 4.7 Hz, 1H), 3.83–3.75 (m, 4H), 2.97–2.88 (m, 4H), 1.85–1.76 (br m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 157.6, 138.0, 109.7, 46.0, 44.9 ppm.



Benzylpiperazine (S12): Amine **S12** was prepared according to a procedure reported by Zhou et al.[17] To a flame-dried 25-mL flask was added piperazine (0.86 g, 10 mmol, 4.0 equiv). The flask was evacuated and backfilled with nitrogen (×3) and DCM (2.5 mL, 1.0 M) was added, followed by benzyl bromide (0.30 mL, 2.5 mmol). The reaction was stirred for 18 h under nitrogen. The reaction was opened to air and the solution was washed with sat. aq. $NaHCO_3$ (×1), H_2O (×1), brine (×1). The organic layer was dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (85/14/1 $CHCl_3$/MeOH/NEt_3) to yield **S12** as a waxy yellow solid (0.22 g, 1.25 mmol, 50%). The analytical data is consistent with literature reports:[17] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.31–7.15 (m, 5H), 5.55 (br s, 1H), 3.46 (s, 2H), 3.03–2.94 (m, 4H), 2.61–2.30 (m, 4H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 137.5, 129.1, 128.4, 127.3, 63.1, 52.0, 44.8 ppm.

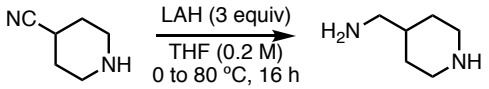


1-(Benzo[1,3]dioxol-5-yl)piperazine (S13): The Buchwald–Hartwig amination conditions used to make **S13** were based on those reported by Nishiyama et al.[18] To a flame-dried 25-mL Schlenk flask was added piperazine (0.78 g, 9.0 mmol, 3.0 equiv), palladium acetate (17 mg, 0.075 mmol, 2.5 mol %), tri-*tert*-butylphosphonium tetrafluoroborate (44 mg, 0.15 mmol, 5.0 mol %), and sodium *tert*-butoxide (0.86 g, 9.0 mmol, 3.0 equiv). The flask was sealed with a septum and electrical tape, evacuated and backfilled with nitrogen (×3), and toluene (10 mL, 0.30 M) was added, followed by 5-bromobenzo[1,3]dioxole (0.36 mL, 3.0 mmol, 1.0 equiv). The reaction was stirred at 110 ºC. After 18 h the reaction was cooled to r.t., opened to air, and quenched with water. The mixture was extracted with EtOAc (×3), and the organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (85/14/1 $CHCl_3$/MeOH/NEt_3) to yield **S13** as a tan solid (0.52 g, 2.5 mmol, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 6.76–6.68 (m, 1H), 6.59–6.53 (m, 1H), 6.41–6.32 (m, 1H), 5.89 (s, 2H), 3.03 (m, 8H), 2.42 (br s, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 148.2, 147.9, 141.6, 109.1, 108.1, 100.8, 100.0, 52.0, 46.1 ppm.



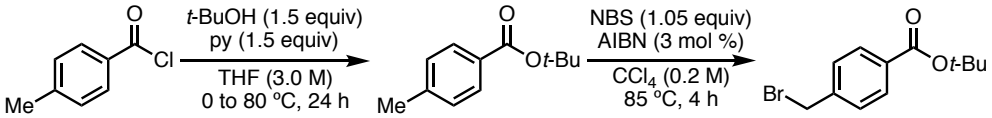
1-(Naphthalen-2-yl)piperazine (S14): The Buchwald–Hartwig amination conditions used to prepare **S14** were based on those reported by Nishiyama et al.[18] To a flame-dried 25-mL Schlenk flask was added piperazine (0.78 g, 9.0 mmol, 3.0 equiv), 2-bromonaphthalene (0.62 g, 3.0 mmol, 1.0 equiv), palladium acetate (17 mg, 0.075 mmol, 2.5 mol %), tri-*tert*-butylphosphonium tetrafluoroborate (44 mg, 0.15 mmol, 5.0 mol %), and sodium *tert*-butoxide (0.86 g, 9.0 mmol, 3.0 equiv). The flask was sealed with a septum and electrical tape, evacuated and backfilled with nitrogen (×3), and toluene (10 mL, 0.30 M) was added. The reaction was stirred at 110 ºC. After 18 h the reaction was cooled to r.t., opened to air, and quenched with water. The mixture was extracted with EtOAc (×3), and the organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (14/1/85 MeOH/NEt_3/$CHCl_3$) to yield **S14** as a tan solid (0.45 g, 2.1 mmol, 70%). The analytical data is consistent with literature reports.[19] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): 7.77–7.67 (m, 3H), 7.44–7.36 (m, 1H), 7.33–7.23 (m, 2H), 7.15–7.09 (m, 1H), 3.30–3.22 (m, 4H), 3.14–3.06 (m, 4H), 2.09 (br s, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): 149.6, 134.6, 128.7, 128.6, 127.4, 126.8, 126.2, 123.4, 119.5, 110.3, 50.8, 46.1 ppm.

E. Synthesis of (±)-GSK2879552



S16

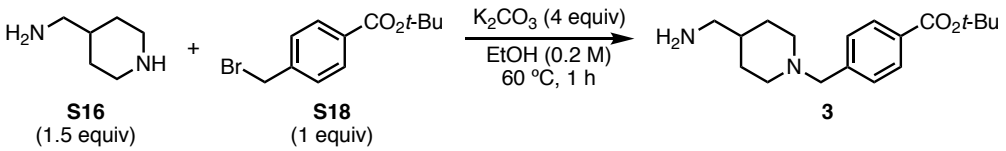
Piperidin-4-ylmethanamine (S16): To a flame-dried flask with reflux condenser was added lithium aluminum hydride (0.91 g, 24 mmol, 3.0 equiv). The flask was sealed and evacuated and backfilled with nitrogen (×3), and THF (40 mL, 0.20 M) was added. The solution was cooled to 0 ºC and piperidine-4-carbonitrile (0.89 mL, 8.0 mmol, 1.0 equiv) was added dropwise. The reaction was refluxed at 80 ºC under nitrogen for 16 h. The reaction was cooled to 0 ºC. To the solution was added H_2O (2.3 mL), 15% NaOH (2.3 mL), and H_2O (2.3 mL). The solution was filtered and the sticky filter cake was vigorously extracted with EtOAc (×3). The organic fractions were combined and concentrated. The concentrate was dissolved in $CHCl_3$, dried over $MgSO_4$, and concentrated under vacuum to yield crude **S16** as a chunky orange-yellow oil (0.89 g, 7.8 mmol, 98%). **S16** was used in the next step without further purification or characterization.



S17 **S18**

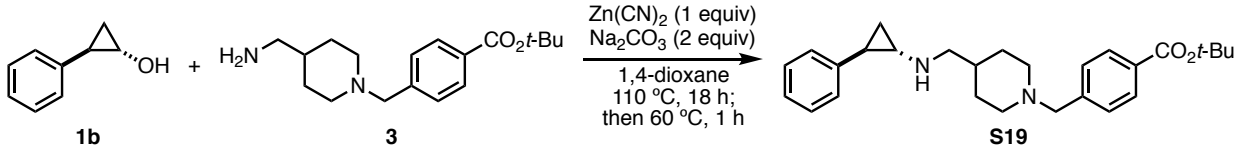
***tert*-Butyl-4-methylbenzoate (S17):** A flame-dried 50-mL two-neck flask was equipped with a reflux condenser. The flask was evacuated and backfilled with nitrogen (×3), THF (17 mL, 3.0 mL) was added, and the solution was cooled to 0 ºC. To the flask was added 4-toluoyl chloride (6.6 mL, 50 mmol, 1.0 equiv), *tert*-butanol (7.2 mL, 75 mmol, 1.5 equiv), and pyridine (6.1 mL, 75 mmol, 1.5 equiv). The reaction was refluxed at 80 ºC for 24 h under nitrogen. The reaction was quenched with H_2O and the solution was extracted with Et_2O (×3). The organic phases were combined, washed with 10% H_2SO_4 (×1), 10% NaOH (×1), H_2O (×2), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash column chromatography (gradient of 100% hexanes to 5/95 EtOAc/hexanes) to yield **S17** as a colourless oil (7.7 g, 40 mmol, 80%). The analytical data is consistent with literature reports:[20] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.91–7.83 (m, 2H), 7.23–7.16 (m, 2H), 2.39 (s, 3H), 1.58 (s, 9H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 165.9, 142.9, 129.4, 129.3, 128.8, 80.6, 28.2, 21.6 ppm.

***tert*-Butyl-4-(bromomethyl)benzoate (S18):** Benzyl bromide **S18** was prepared according to a procedure reported by Acharya et al.[21] To a flame-dried 100-mL flask with reflux condenser was added **S17** (1.9 g, 10 mmol, 1.0 equiv) and the flask was evacuated and backfilled with nitrogen (×3). Carbon tetrachloride (40 mL, 0.25 M) was added, followed by *N*-bromosuccinimide (1.87 g, 10.5 mmol, 1.05 equiv) and 2,2'-azobis(2-methylpropionitrile) (49 mg, 0.30 mmol, 0.03 equiv). The reaction was refluxed at 85 ºC for 4 h under nitrogen. The solution was diluted with pentane (50 mL), filtered, and concentrated under vacuum. The crude residue was purified by flash column chromatography (gradient of 0/100 to 2/98 EtOAc/hexanes). **S18** was obtained as a white solid containing an inseparable mixture of un-, mono-, and dibrominated products (2.5 g, 0.12:1:0.16 un-/mono-/dibrominated; 2.1 g monobrominated, 7.4 mmol, 74%). The analytical data for **S18** is consistent with literature reports:[22] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.98–7.93 (m, 2H), 7.47–7.38 (m, 2H), 4.49 (s, 2H), 1.59 (s, 9H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 165.1, 142.0, 132.0, 129.9, 128.8, 81.2, 32.3, 28.2 ppm.



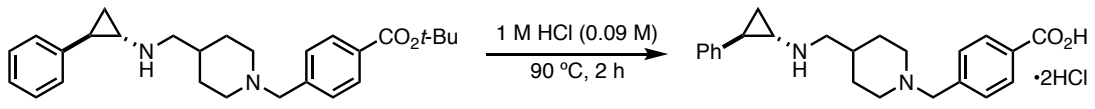
S16 (1.5 equiv) **S18** (1 equiv) **3**

***tert*-Butyl 4-((4-(aminomethyl)piperidin-1-yl)methyl)benzoate (3):** To a flame-dried 50-mL flask was added benzyl bromide **S18** (0.69 g of a 79% w/w mixture of un-, mono-, and dibrominated) and potassium carbonate (1.1 g, 8.0 mmol, 4.0 equiv). The flask was sealed and evacuated and backfilled with nitrogen (×3). Ethanol (10 mL, 0.20 M) was added, followed by amine **S16** (0.38 mL, 3.0 mmol, 1.5 equiv). The reaction was stirred at 60 ºC under nitrogen and was monitored by ^{1}H NMR. After 1 h the reaction was cooled to r.t., opened to air, and concentrated under vacuum. The concentrate was purified by flash column chromatography (15/1/84 MeOH/NEt_3/$CHCl_3$) to yield **3** as an off-white solid (0.44 g, 1.45 mmol, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.98–7.88 (m, 2H), 7.41–7.32 (m, 2H), 3.52 (s, 2H), 3.12 (br m, 3H), 2.91–2.82 (m, 2H), 2.66 (d, J = 6.6 Hz, 2H), 1.97 (dt, J = 11.8, 2.5 Hz, 2H), 1.77–1.68 (m, 2H), 1.58 (s, 9H), 1.51–1.36 (m, 1H), 1.27 (dq, J = 12.2, 3.8 Hz, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 165.7, 143.3, 130.8, 129.4, 128.8, 80.8, 63.0, 53.4, 47.3, 37.8, 29.9, 28.2 ppm; **IR** (neat): 3230 (br), 2983, 2943, 2932, 2908, 2846, 2801, 2760, 1706, 1609, 1576, 1450, 1415, 1366, 1393, 1291, 1256, 1163, 1115, 1099, 1017, 999, 979, 968, 850, 812, 755, 697 cm^{-1}; **m.p.**: 92–93 ºC; **HRMS** *m/z* (DART): calcd for $C_{18}H_{29}N_2O_2$ (M+H) 305.22290; found 305.22367.



1b (1.2 equiv) **3** (1 equiv) **S19**

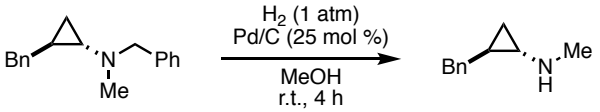
***tert*-Butyl 4-((4-(((*trans*-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoate (S19):** Cyclopropylamine **S19** was prepared according to general procedure A with the modification that after 18 h at 110 ºC the reaction was stirred for an additional 1 h at 60 ºC to push the cyclopropylamine/imine equilibrium towards cyclopropylamine. The following amounts of reagent were used: cyclopropanol **1b** (32 mg, 0.24 mmol, 1.2 equiv), amine **3** (61 mg, 0.20 mmol, 1.0 equiv), zinc cyanide (23 mg, 0.20 mmol, 1.0 equiv), sodium carbonate (42 mg, 0.40 mmol, 2.0 equiv), and 1,4-dioxane (1.0 mL, 0.20 M). The crude residue was purified by flash column chromatography (gradient of 5/0/95 to 7/1/94 MeOH/NEt_3/$CHCl_3$) to yield **S19** as a yellow oil (46 mg, 0.109 mmol, 55%). The analytical data is consistent with that reported in the patented synthesis of **(±)-GSK2879552**:[23] **^{1}H NMR** (400 MHz, CD_3OD, 298 K): δ_H 7.99–7.87 (m, 2H), 7.48–7.36 (m, 2H), 7.29–7.00 (m, 5H), 4.88 (br s, 2H), 3.68–3.48 (m, 2H), 2.99–2.82 (m, 2H), 2.67–2.54 (m, 2H), 2.31 (ddd, J = 7.5, 4.5, 3.6 Hz, 1H), 2.12–1.97 (m, 2H), 1.92 (ddd, J = 9.3, 5.9, 3.3 Hz, 1H), 1.82–1.68 (br m, 2H), 1.66–1.42 (m, 11H), 1.35–1.18 (m, 2H), 1.12–0.96 (m, 2H) ppm; **^{13}C NMR** (100 MHz, CD_3OD, 298 K): δ_C 167.2, 143.9, 143.4, 132.2, 130.6, 130.3, 129.3, 126.8, 126.6, 82.2, 63.8, 56.2, 54.6, 42.6, 36.6, 31.3, 28.5, 25.2, 16.7 ppm.



S19 **(±)-GSK2879552**

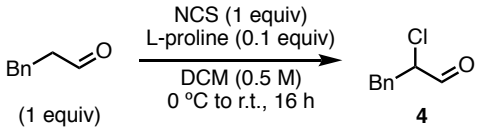
4-((4-(((*trans*-2-Phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)benzoic acid dihydrochloride ((±)-GSK2879552): Cyclopropylamine **(±)-GSK2879552** was prepared according to the procedure reported by Johnson et al.:[23] To a 1-dram reaction vial was added cyclopropylamine **S19** (19 mg, 0.045 mmol, 1.0 equiv) and 1 M aq. HCl (0.54 mL, 0.09 M, 12 equiv). The vial was sealed and stirred at 90 ºC for 2 h. The solution was cooled to r.t. and concentrated under a stream of compressed air to yield **(±)-GSK2879552** as an off-white solid (18 mg, 0.041 mmol, 91%). The analytical data matches the patented report:[23] **^{1}H NMR** (400 MHz, CD_3OD, 298 K): δ_H 8.14 (d, J = 7.9 Hz, 2H), 7.74 (d, J = 7.8 Hz, 2H), 7.60–6.99 (m, 5H), 4.45 (br s, 2H), 3.70–2.88 (m, 8H), 2.64 (dd, J = 10.3, 6.6, 3.6 Hz, 1H), 2.30–1.94 (m, 3H), 1.81–1.53 (m, 3H), 1.47–1.28 (m, 1H) ppm; **^{13}C NMR** (100 MHz, CD_3OD, 298 K): 168.8, 139.4, 134.9, 133.7, 132.8, 131.5, 129.8, 128.0, 127.5, 61.1, 53.5, 53.03, 52.97, 39.8, 32.3, 28.2, 27.9, 22.5, 13.5 ppm.

F. Deprotection of N-*benzylcyclopropylamine 2j*



***trans*-2-Benzyl-*N*-methylcyclopropan-1-amine (S20):** To a flame-dried 1-dram reaction vial was added palladium on carbon (27 mg of a 10% w/w mixture, 0.025 mmol, 25 mol %). The vial was evacuated and backfilled with nitrogen (×2), then hydrogen (×2). MeOH (0.50 mL) was added. To this mixture was added **2j** (0.50 mL of a 0.20 M solution in MeOH, 0.10 mmol, 1.0 equiv). The reaction was stirred at r.t. for 10 min while hydrogen was bubbled through the solution, then the reaction was stirred at r.t. for 4 h under a balloon of hydrogen. The reaction was opened to air, diluted with MeOH, filtered over Celite, and concentrated to yield crude **S20** as a colourless oil. The yield was determined by ^{1}H NMR analysis of the crude reaction mixture using dodecane as internal standard (0.10 mmol, >99%; >20:1 d.r.). **S20** was characterized without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): 7.34–7.13 (m, 5H), 2.65–2.45 (m, 2H), 2.39 (s, 3H), 2.05–1.95 (m, 2H), 1.10–0.98 (m, 1H), 0.66–0.60 (m, 1H), 0.46–0.40 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 128.3, 128.2, 125.8, 110.0, 39.6, 38.4, 35.8, 21.1, 13.6 ppm.

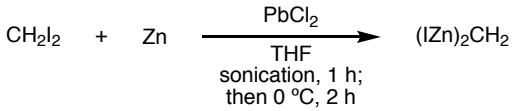
G. Preparation of α-chloroaldehyde starting materials



2-Chloro-3-phenylpropanal (4): α-Chloroaldehyde **4** was prepared according to the procedure reported by Halland et al.[7] To a flame-dried 25-mL flask was added NCS (0.40 g, 3.0 mmol, 1.0 equiv) and L-proline (35 mg, 0.30 mmol, 0.10 equiv). The flask was evacuated and backfilled with nitrogen (×3) and DCM (6.0 mL, 0.50 M) was added. The solution was cooled to 0 ºC and hydrocinnamaldehyde (0.40 mL, 3.0 mmol, 1.0 equiv) was added. The reaction was stirred under nitrogen for 16 h, during which time the cooling bath was slowly allowed to warm to r.t. The reaction was diluted with pentane, filtered, and concentrated to yield **4** as a colourless oil. The analytical data is consistent with literature reports:[7] **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 9.54 (d, J = 2.2 Hz, 1H), 7.37–7.21 (m, 5H), 4.41–4.36 (m, 1H), 3.38 (dd, J = 14.5, 5.7 Hz, 1H), (dd, J = 14.5, 8.3 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 194.4, 135.4, 129.4, 128.7, 127.4, 63.9, 38.3 ppm.

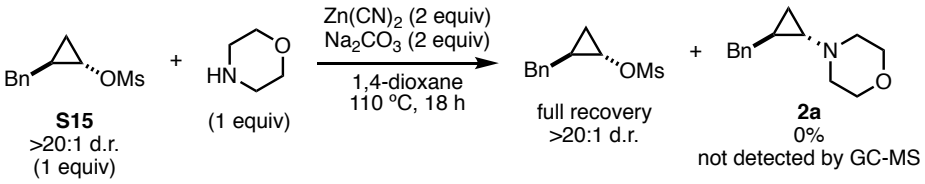
H. Preparation of reagents and miscellaneous compounds

Zinc dust was activated according to the procedure reported by Fieser and Fieser.[24] Zinc was stirred for 2 min in 10% aq. HCl and the solution was filtered through a fritted funnel. Zinc chunks were broken up and washed with H_2O until the pH of the filtrate turned neutral (×3), then with acetone (×3). Zinc dust was dried under vacuum for 8 h before use.



Bis(iodozinco)methane was prepared according to the procedure reported by Nomura et al.[2] To a flame-dried 250-mL flask equipped with stir bar were added activated zinc dust (9.8 g, 150 mmol, 2.3 equiv) and lead chloride (0.017 g, 0.060 mmol). The flask was sealed with a septum and evacuated and backfilled with nitrogen (×3). THF (12 mL) was added followed by diiodomethane (0.48 mL, 6.0 mmol). The solution was sonicated for 1 h under nitrogen. THF was added (120 mL) and the solution was cooled to 0 ºC. While stirring, diiodomethane (4.8 mL, 60 mmol) was added dropwise over 15 min at 0 ºC. The reaction was stirred for an additional 2 h at 0 ºC under nitrogen and then was left to settle for 12 h before use. Solutions were stored sealed at r.t. under an atmosphere of nitrogen. The reagent was titrated using Knochel's protocol[1] and was generally found to be 0.18–0.19 M; this concentration could be increased by adding less THF in step 2 without affecting the efficacy of the reagent.

I. Mechanistic experiments



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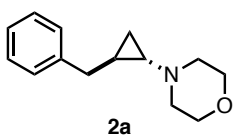
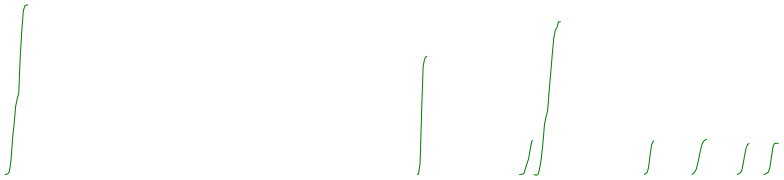
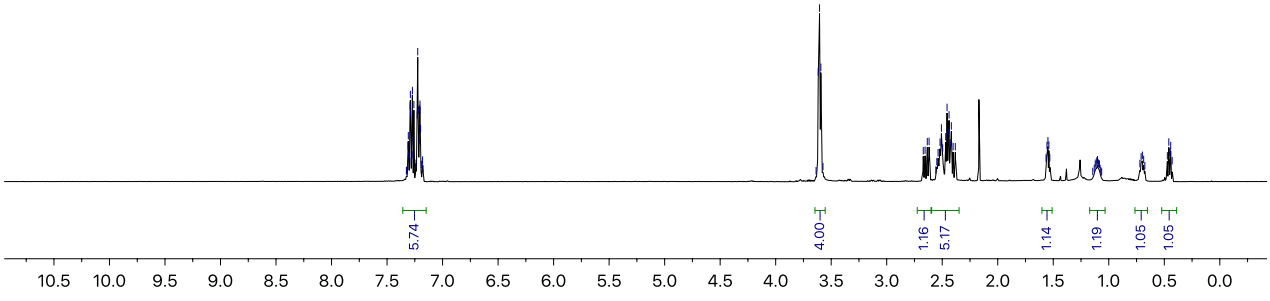
K. ^{1}H and ^{13}C NMR spectra

400 MHz, $CDCl_3$

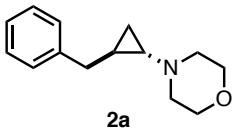


2a





100 MHz, $CDCl_3$



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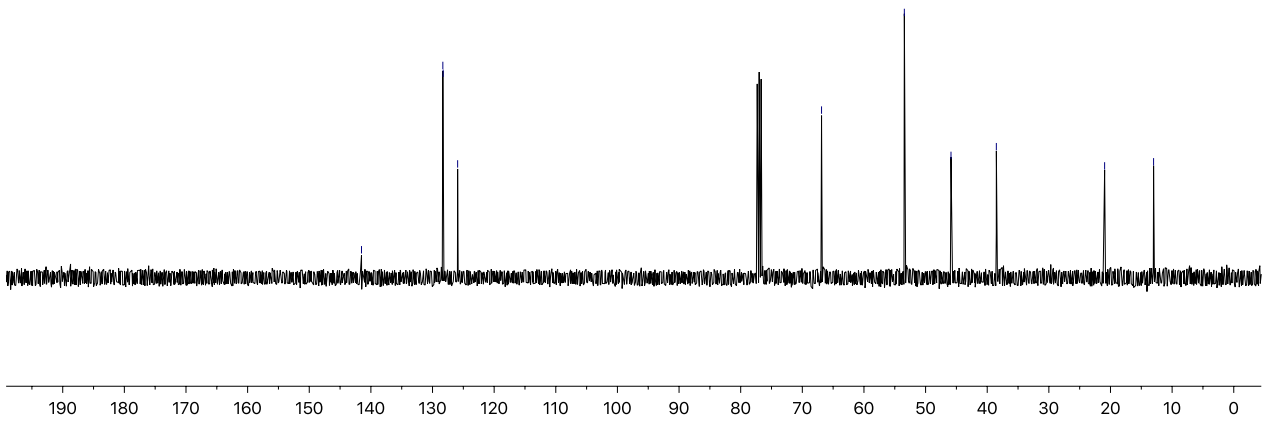
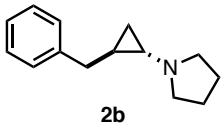
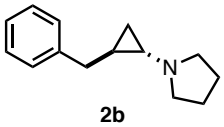


400 MHz, $CDCl_3$



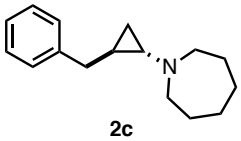
2b

100 MHz, $CDCl_3$



2b

400 MHz, $CDCl_3$



2c

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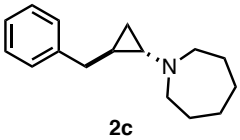

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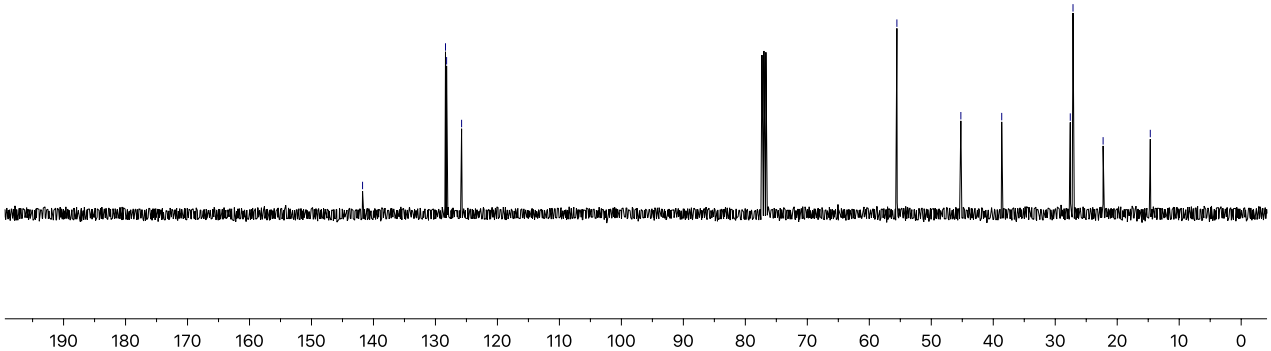
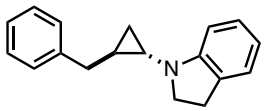


400 MHz, $CDCl_3$



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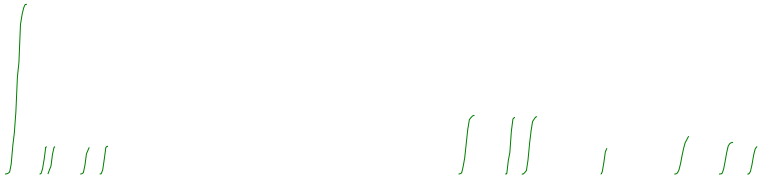
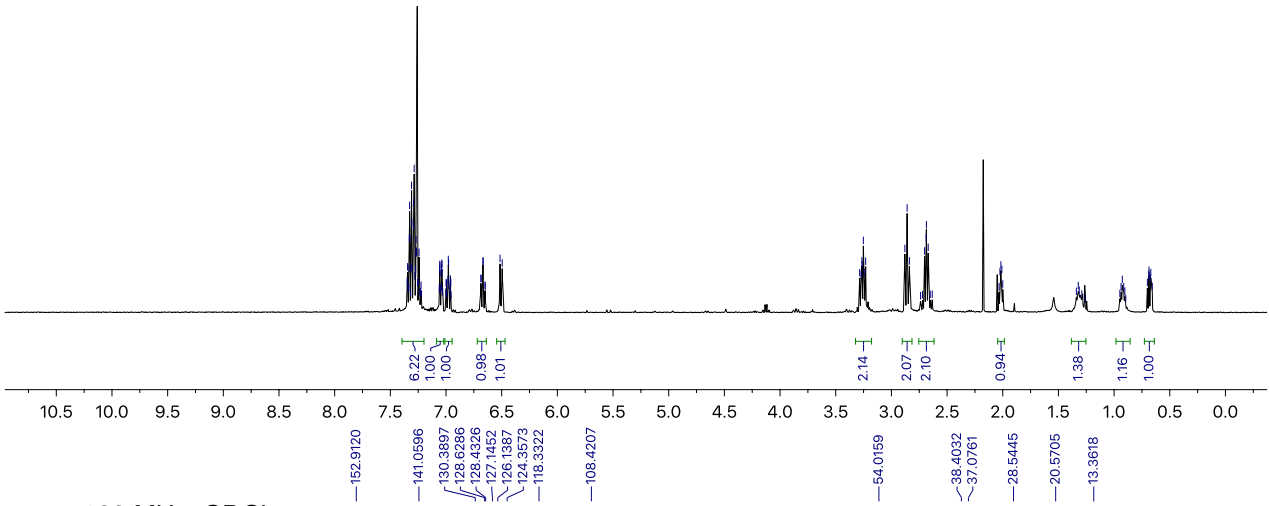
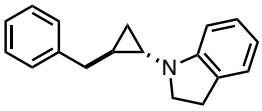
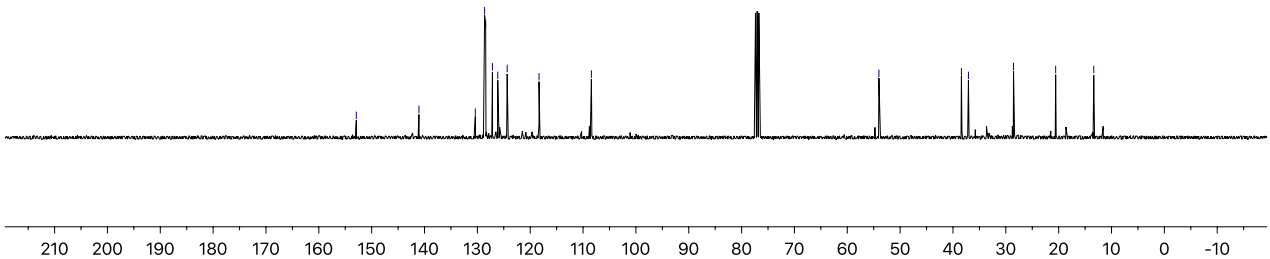




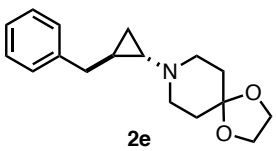
100 MHz, $CDCl_3$



2d



400 MHz, $CDCl_3$



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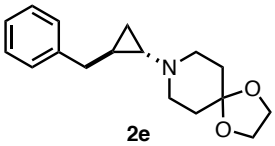
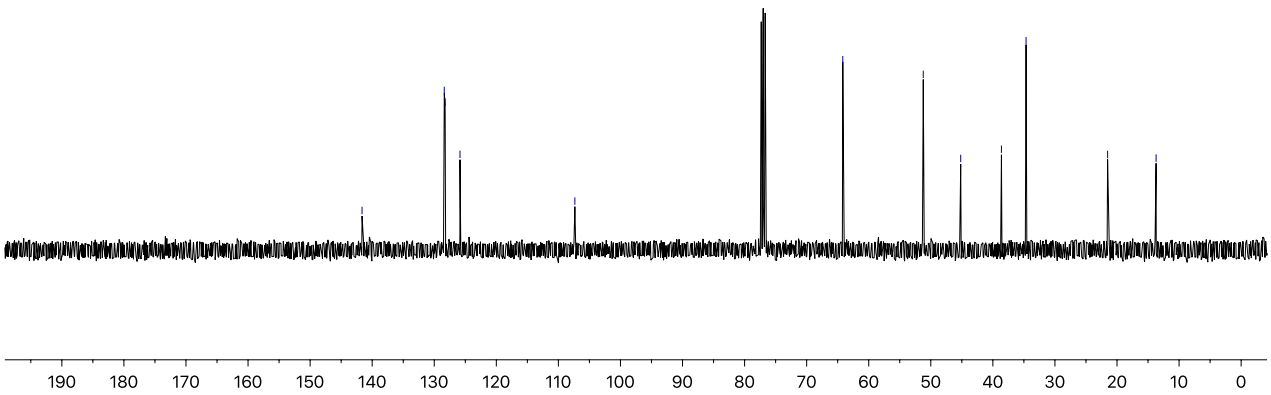
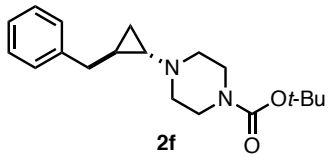


2e

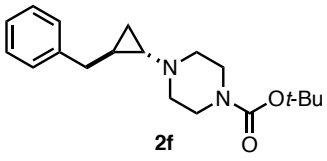


400 MHz, $CDCl_3$



2f

100 MHz, $CDCl_3$



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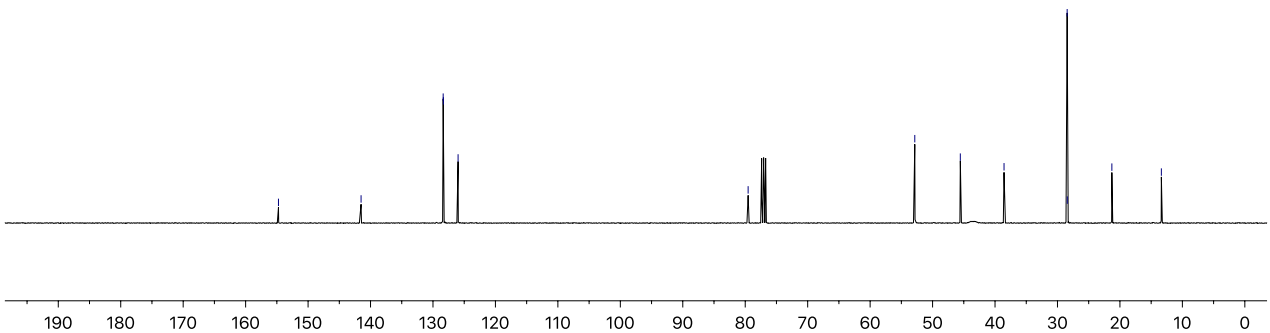
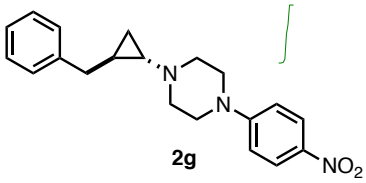
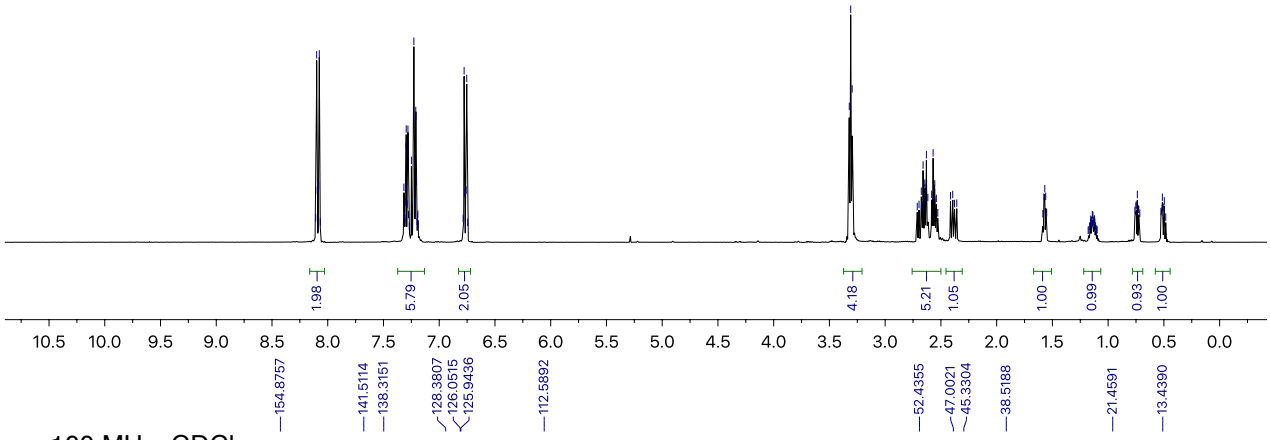


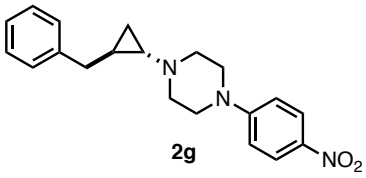
400 MHz, $CDCl_3$



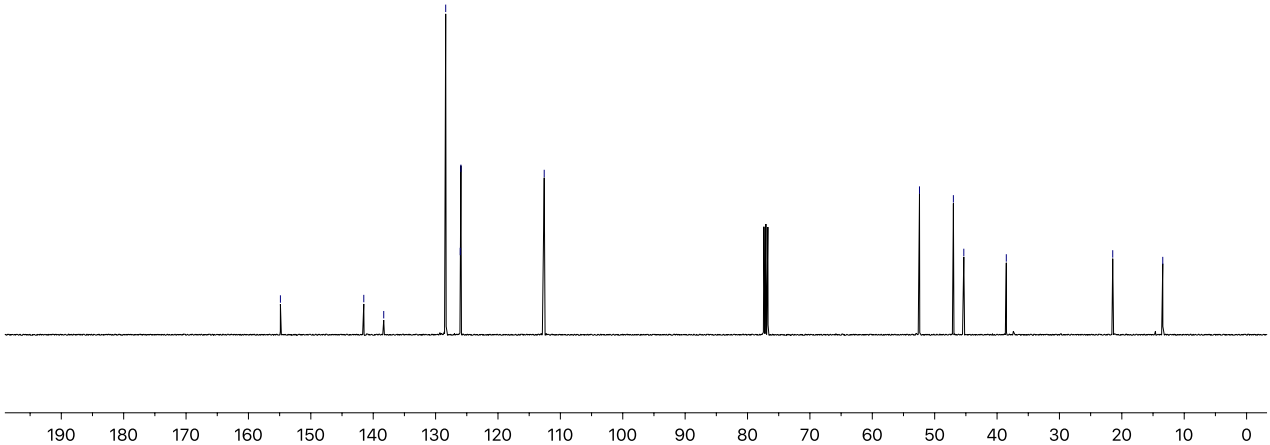
2g



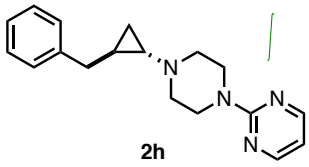
100 MHz, $CDCl_3$



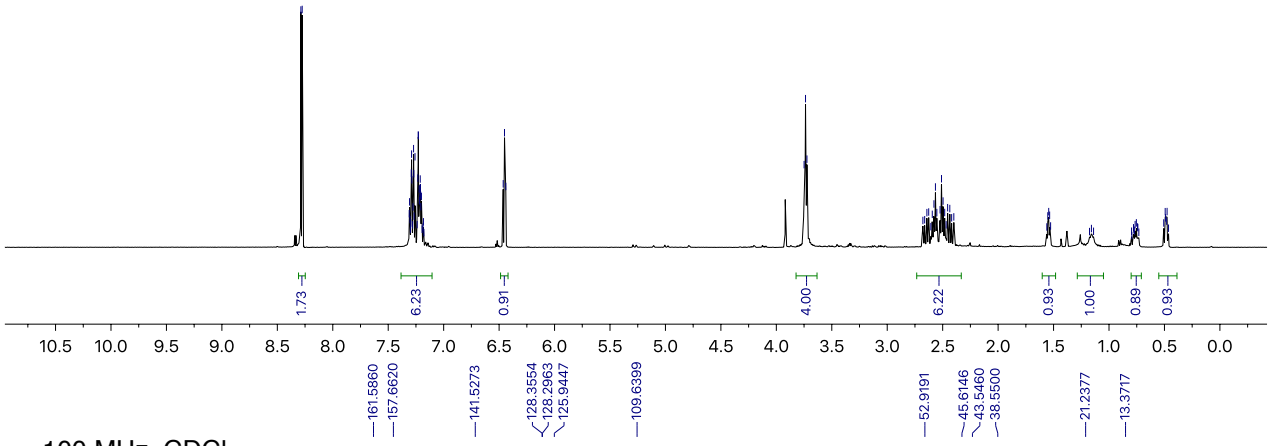
2g



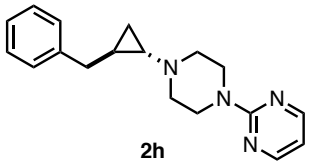
400 MHz, $CDCl_3$



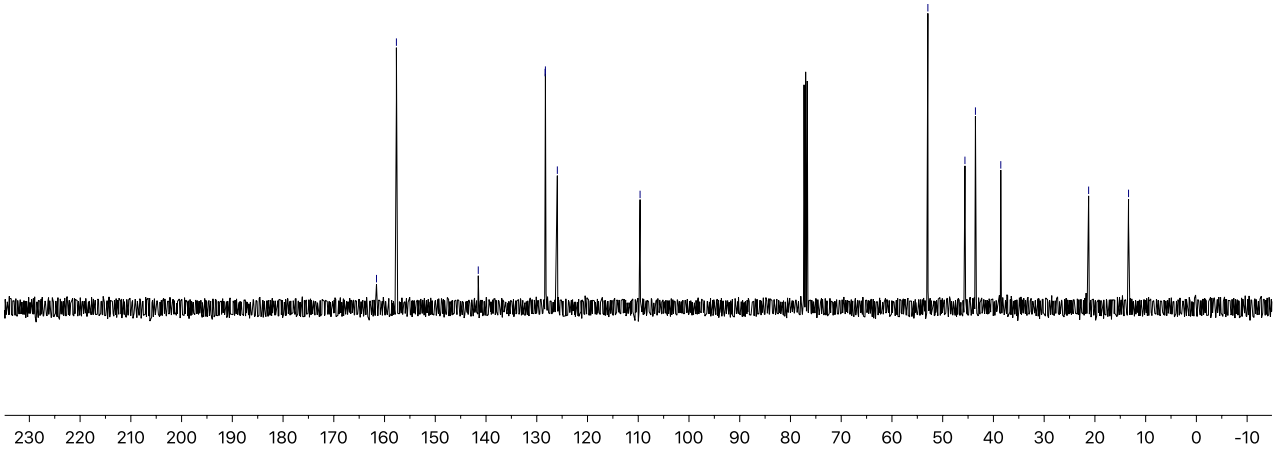
2h

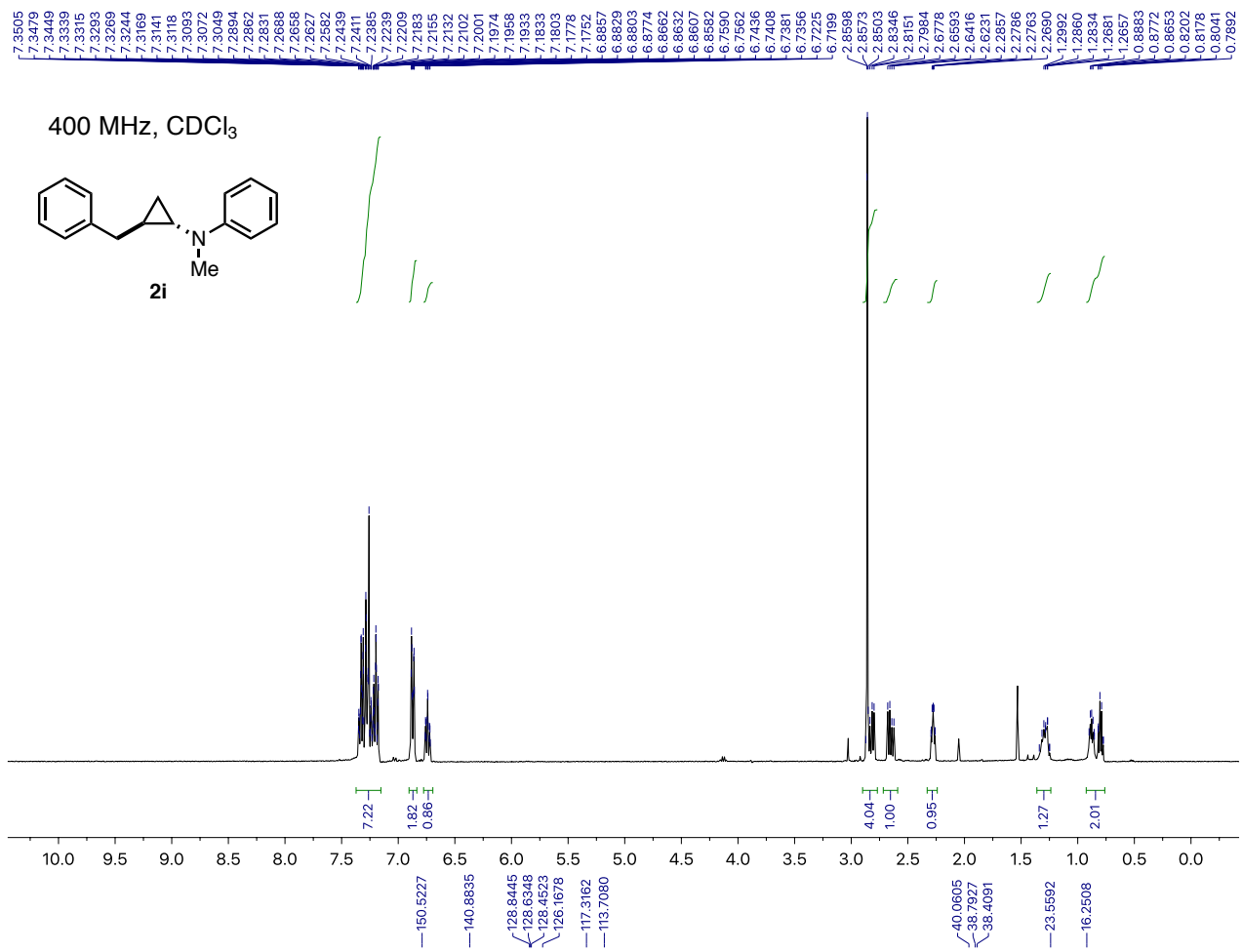


100 MHz, $CDCl_3$



2h




400 MHz, CDCl3
N
Me
2i
7.22
1.82
0.86
4.04
1.00
0.95
1.27
2.01
150.5227
140.8835
128.8445
128.6348
128.4523
126.1678
117.3162
113.7080
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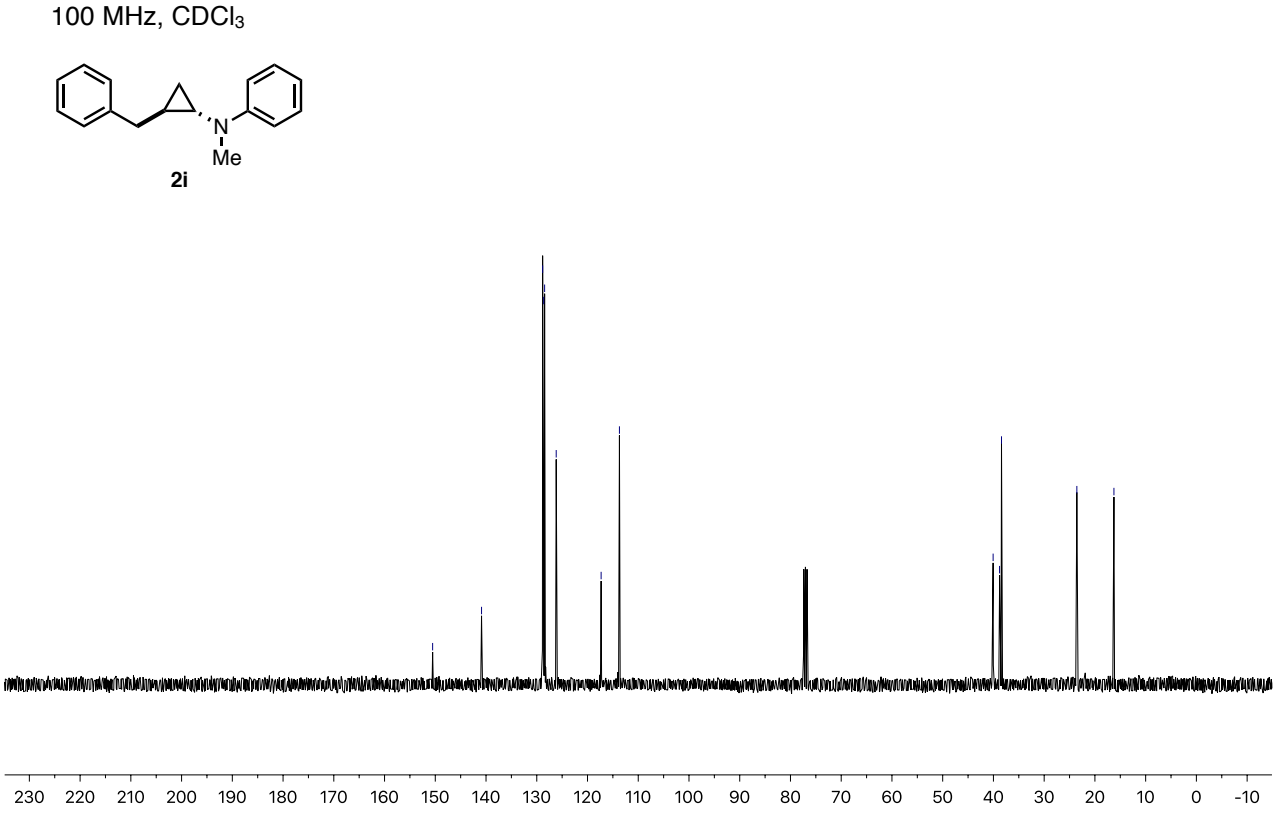
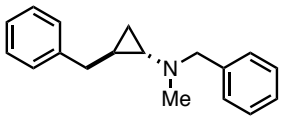
38.7927
38.4091
23.5592
16.2508

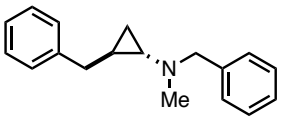

100 MHz, CDCl3
N
Me
2i

400 MHz, $CDCl_3$

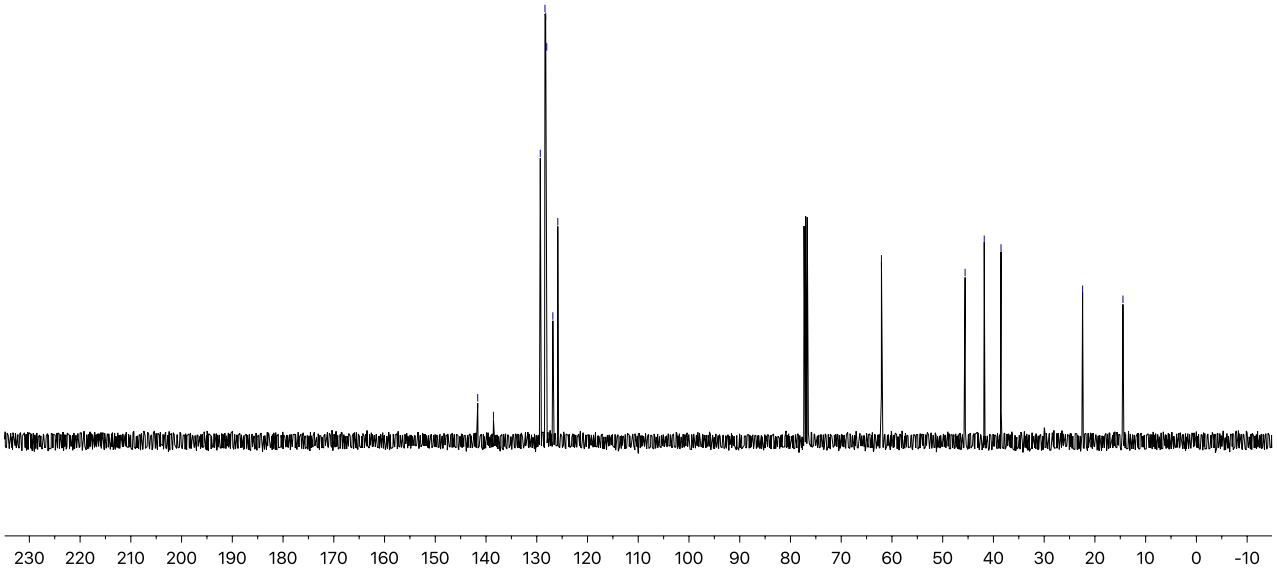


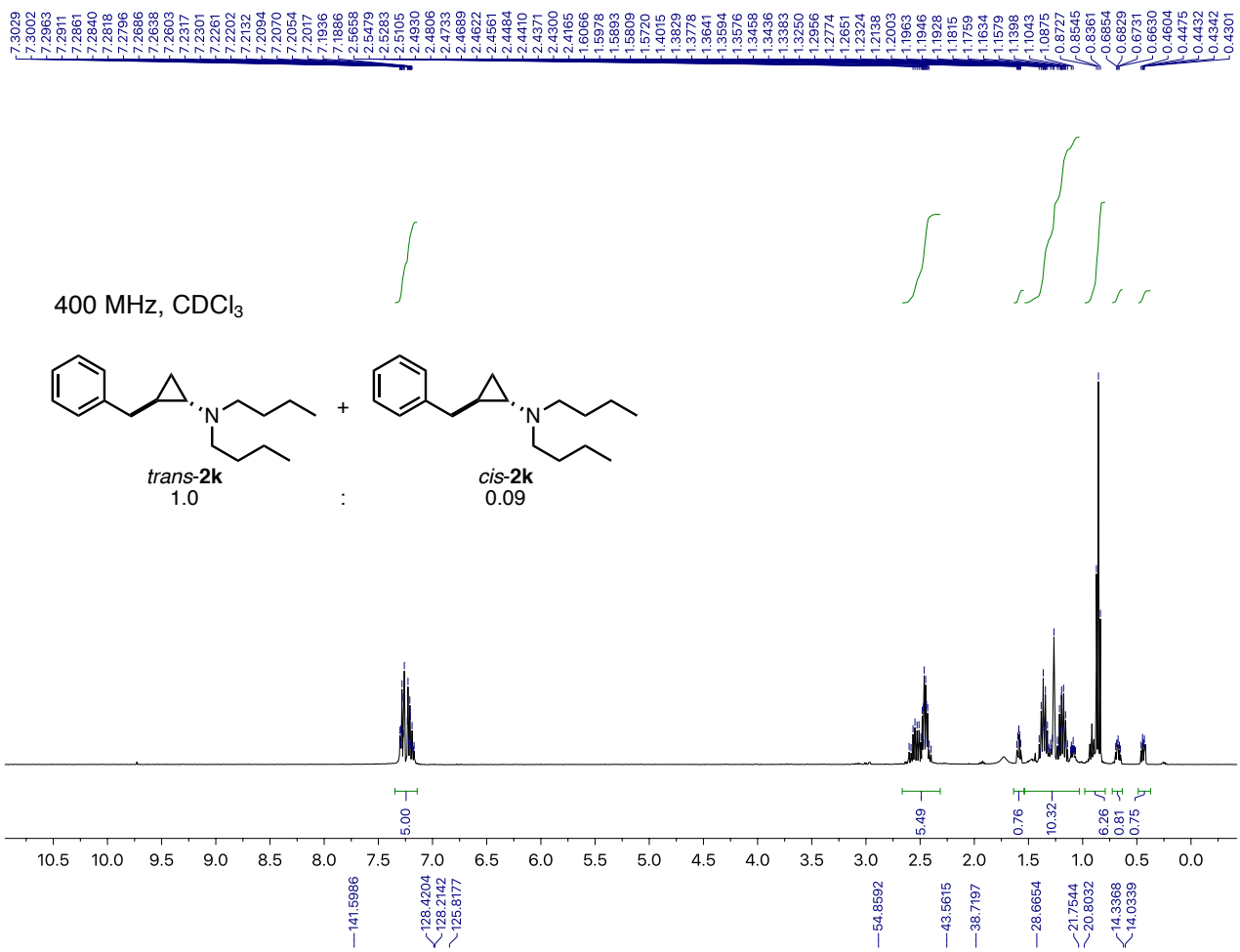
2j

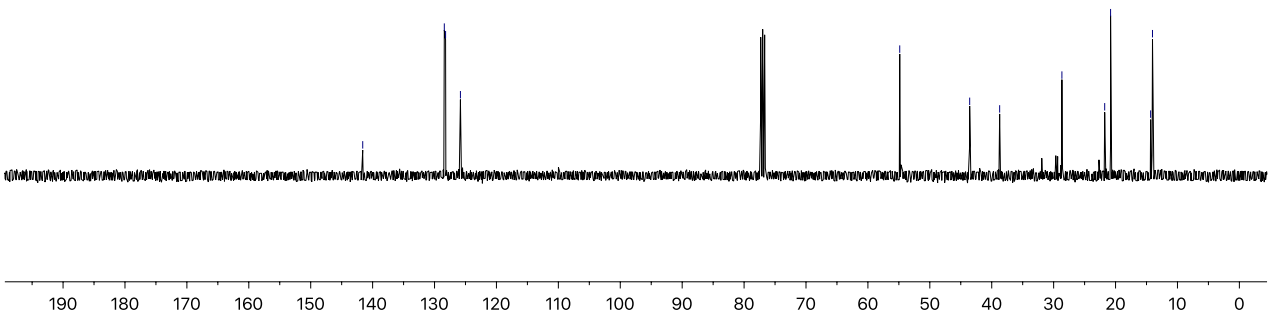
100 MHz, $CDCl_3$

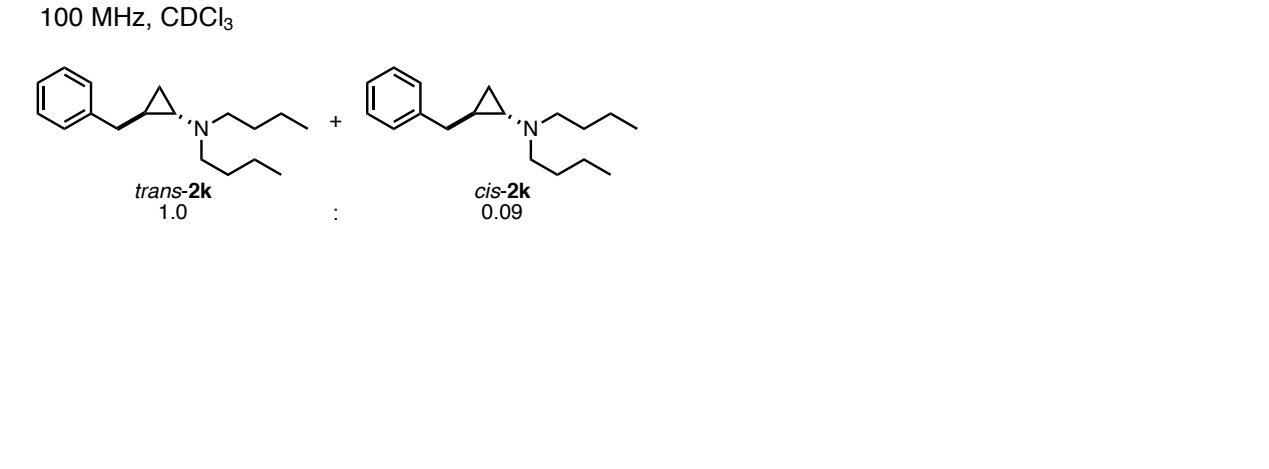


2j

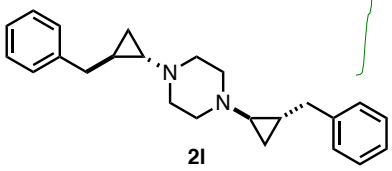



400 MHz, CDCl3
trans-2k
1.0
:
cis-2k
0.09

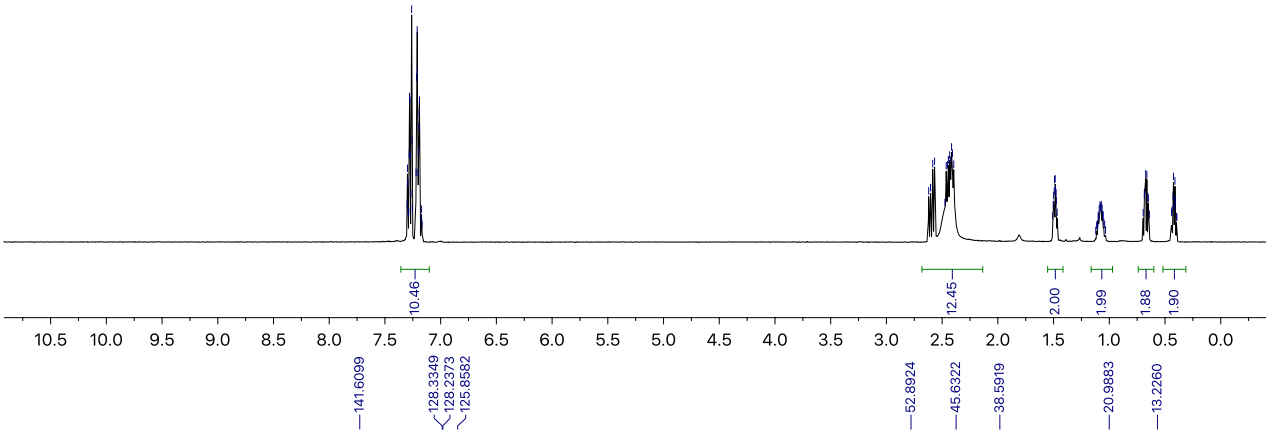



100 MHz, CDCl3
trans-2k
1.0
:
cis-2k
0.09

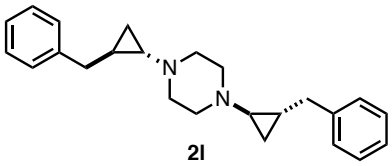
400 MHz, $CDCl_3$



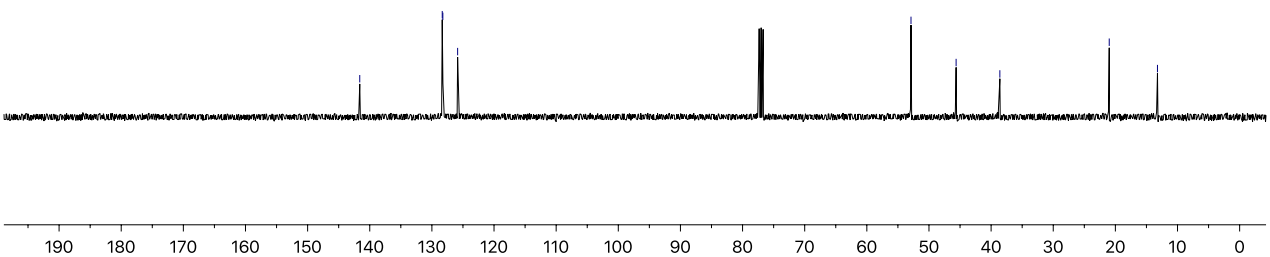
2l



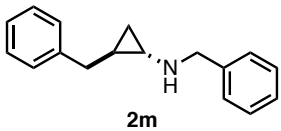
100 MHz, $CDCl_3$



2l

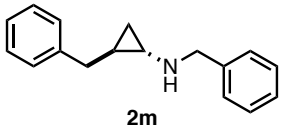


400 MHz, $CDCl_3$

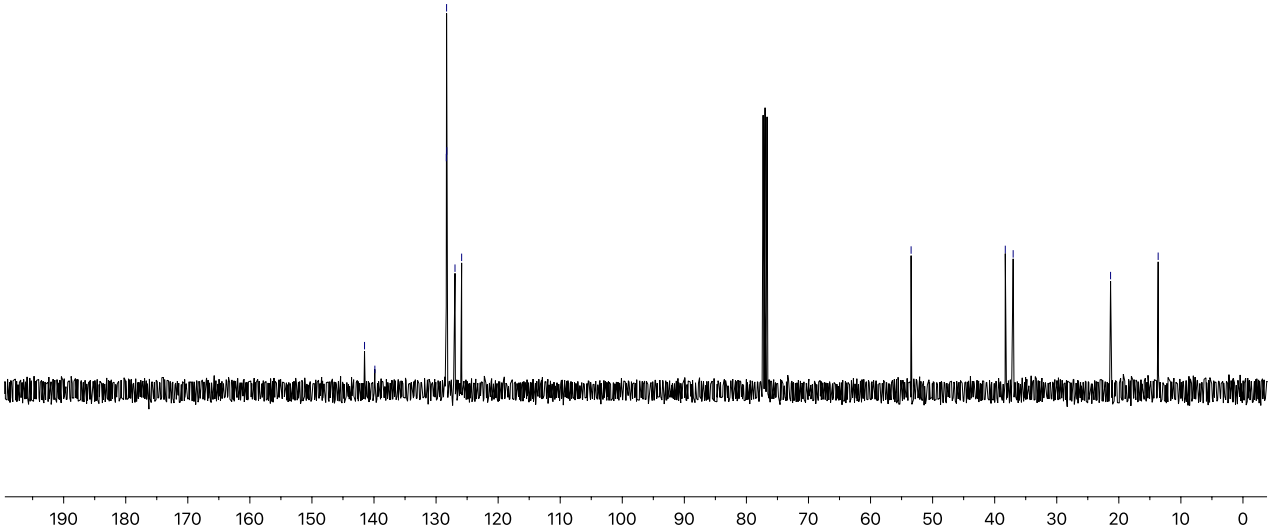


2m

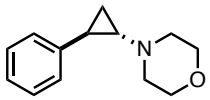
100 MHz, $CDCl_3$



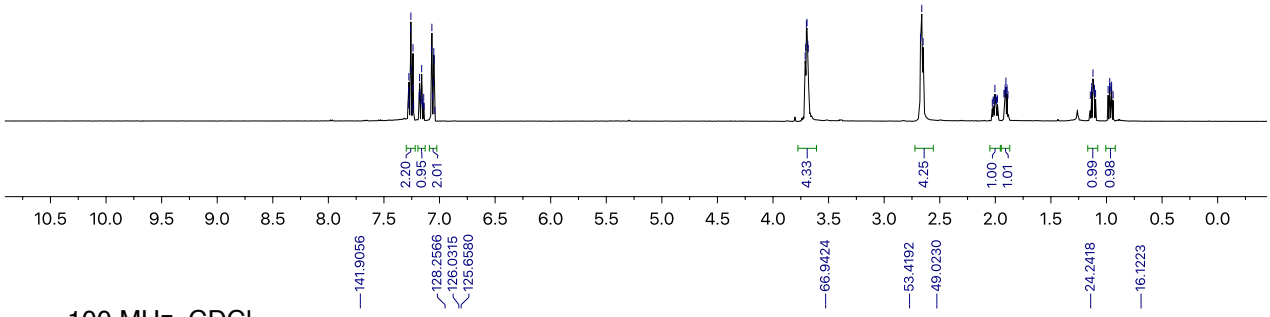
2m



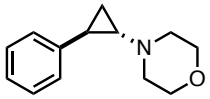
400 MHz, $CDCl_3$



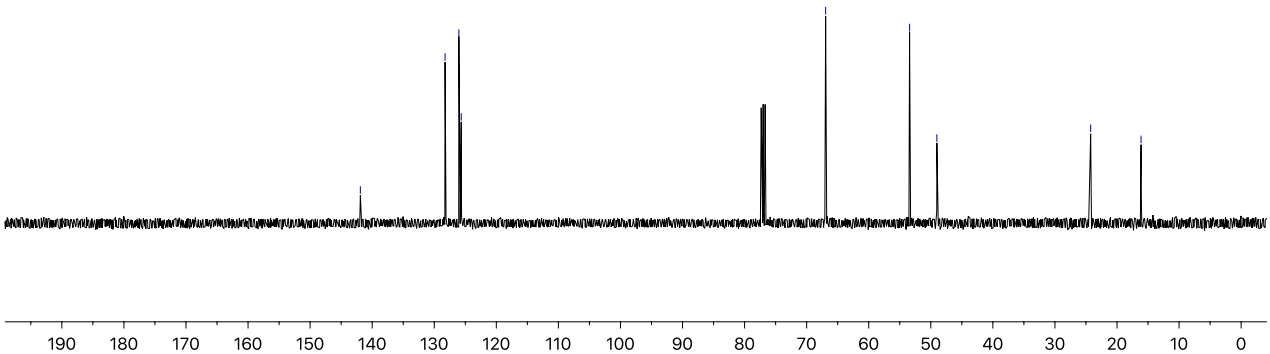
2n



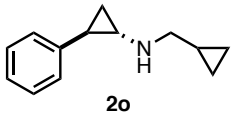
100 MHz, $CDCl_3$



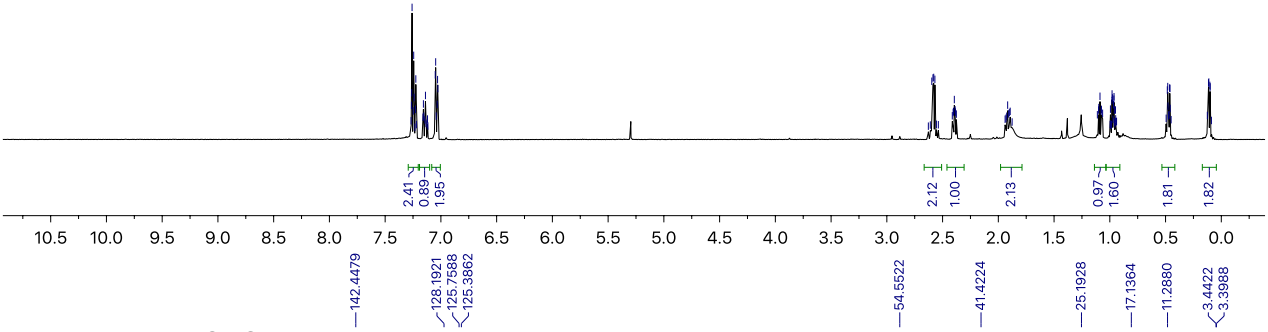
2n



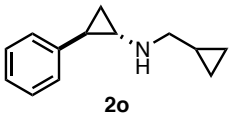
400 MHz, $CDCl_3$



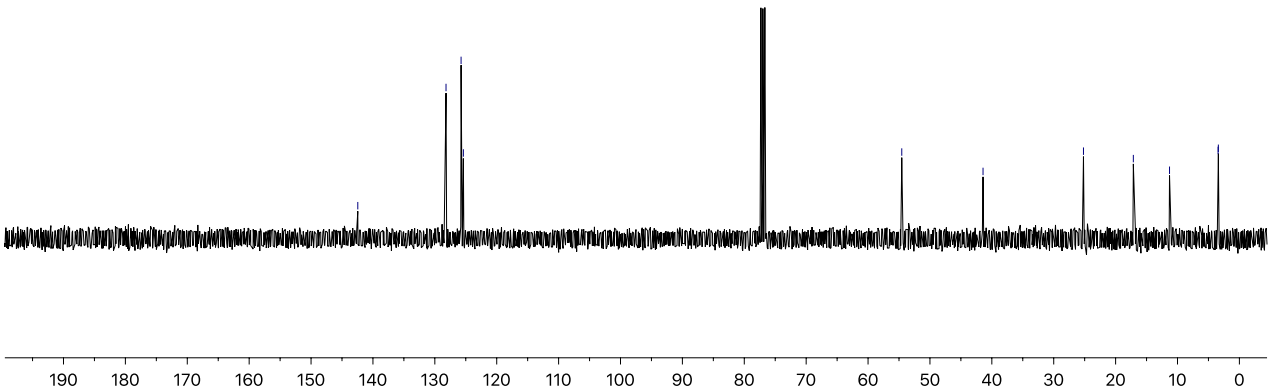
2o



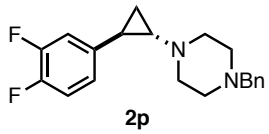
100 MHz, $CDCl_3$



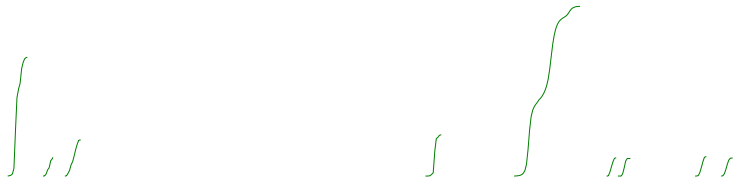
2o

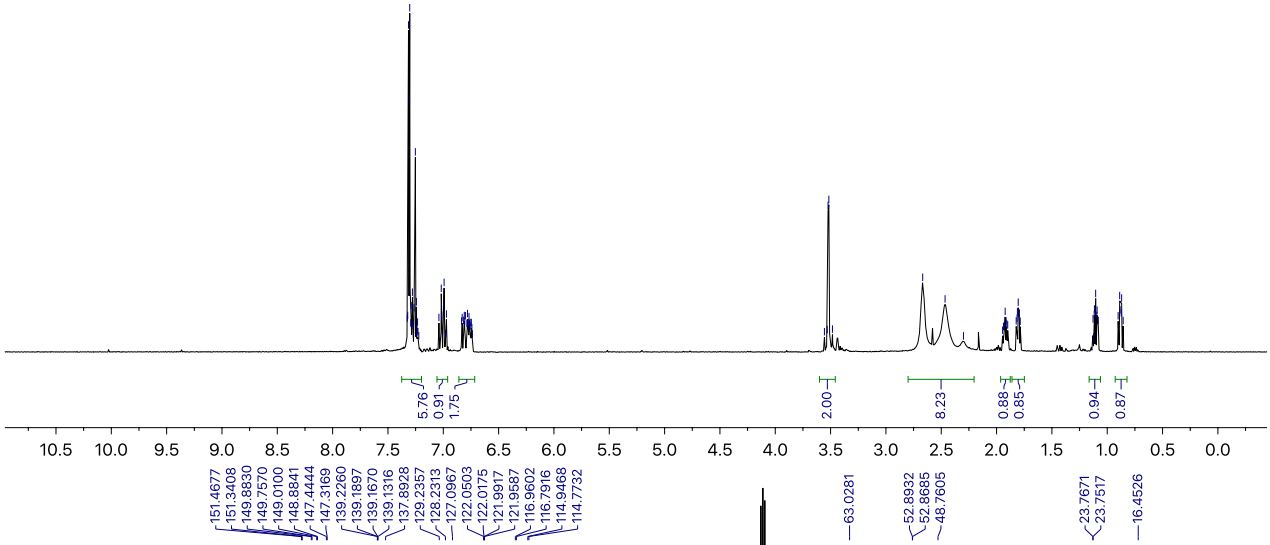


400 MHz, $CDCl_3$

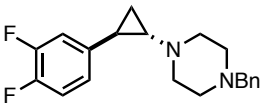


2p

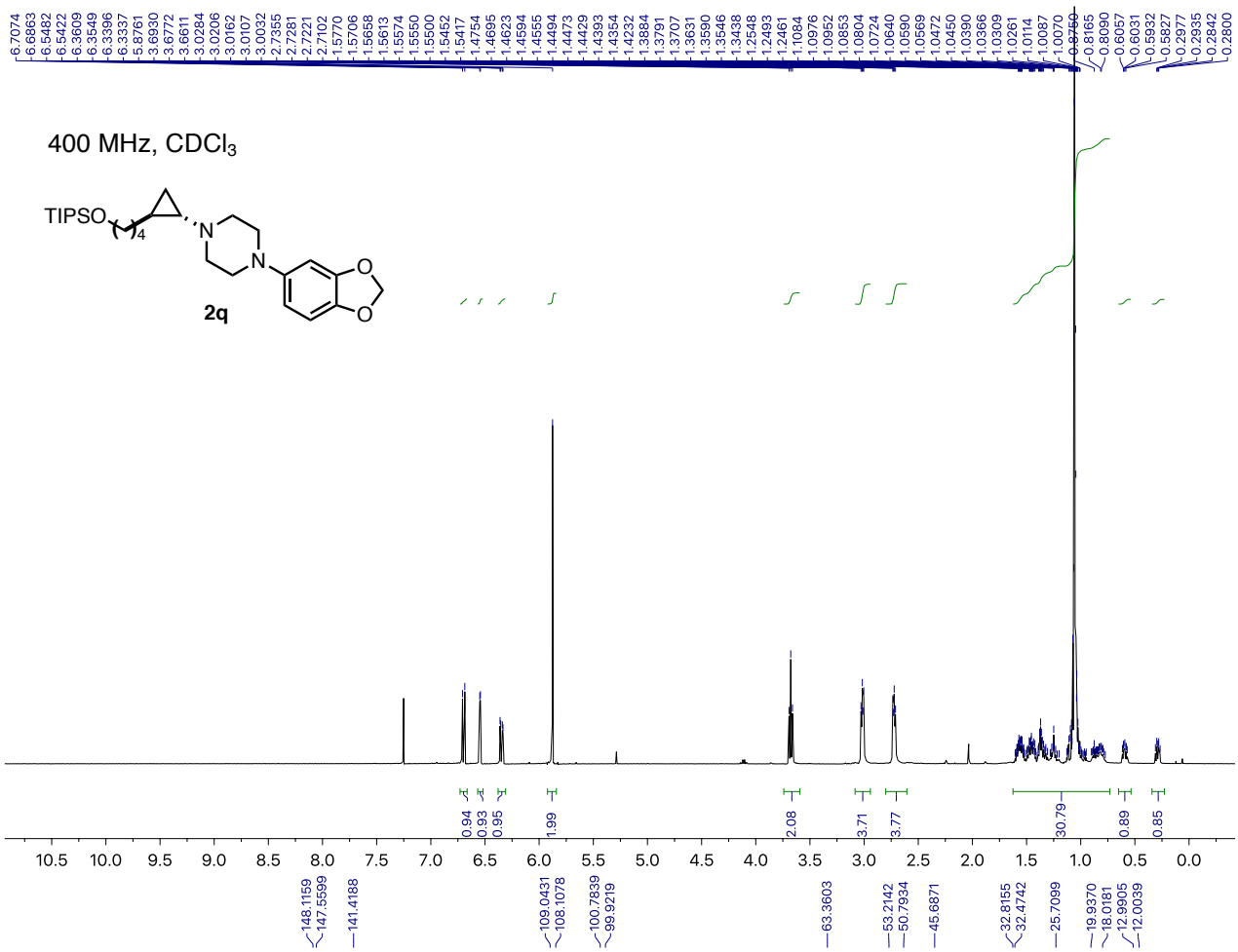


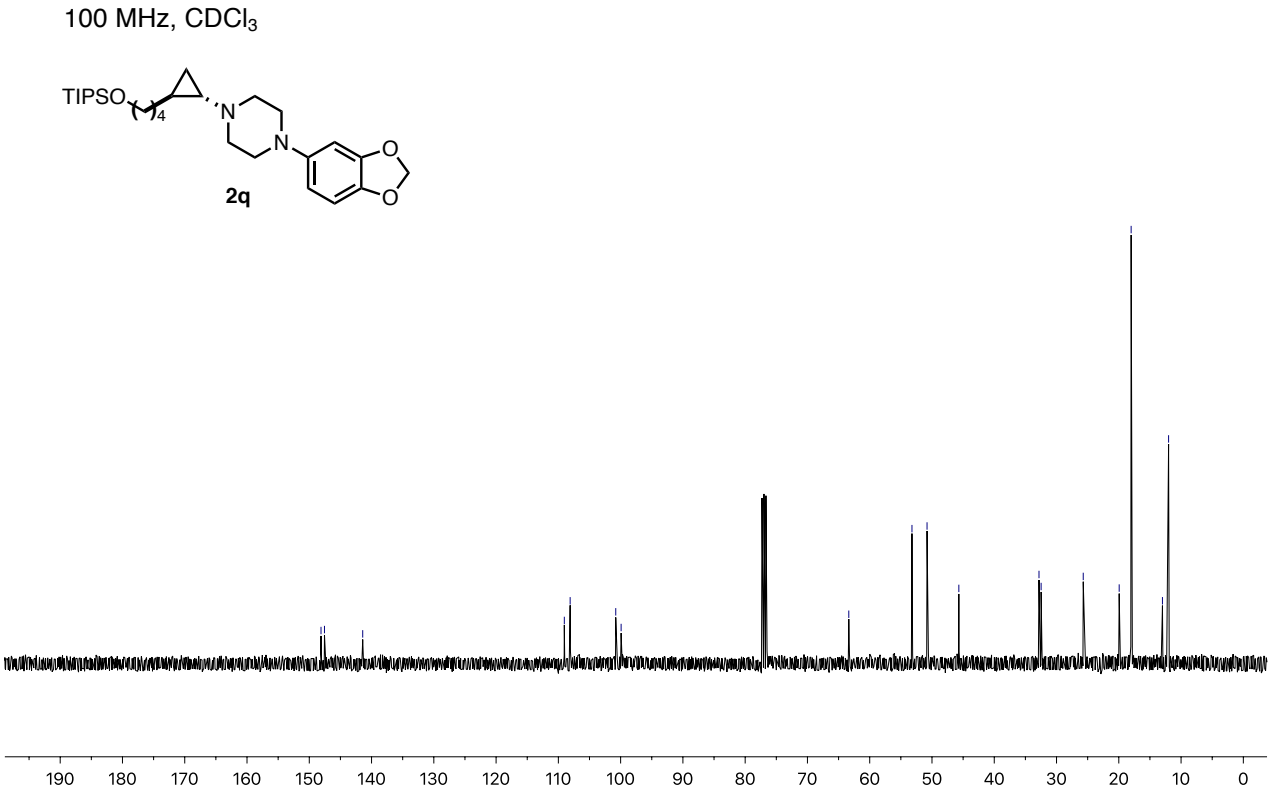


100 MHz, $CDCl_3$

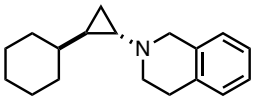


2p


400 MHz, CDCl3
TIPSO
4
N
N
O
O
2q

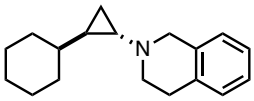

100 MHz, CDCl3
TIPSO
4
N
N
O
O
2q

400 MHz, $CDCl_3$



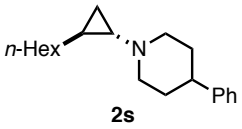
2r

100 MHz, $CDCl_3$

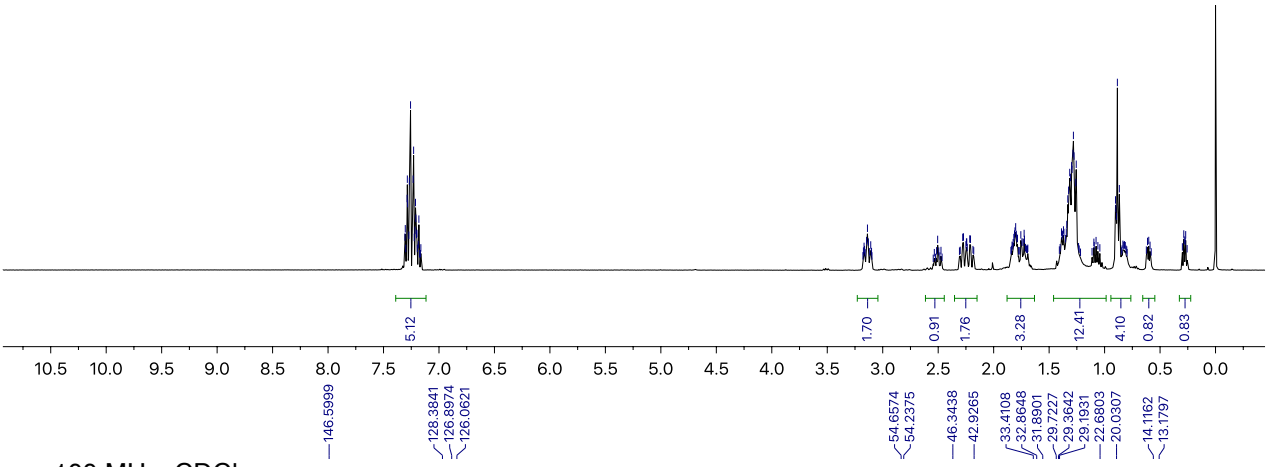


2r

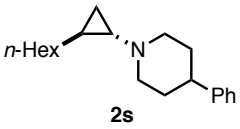
400 MHz, $CDCl_3$



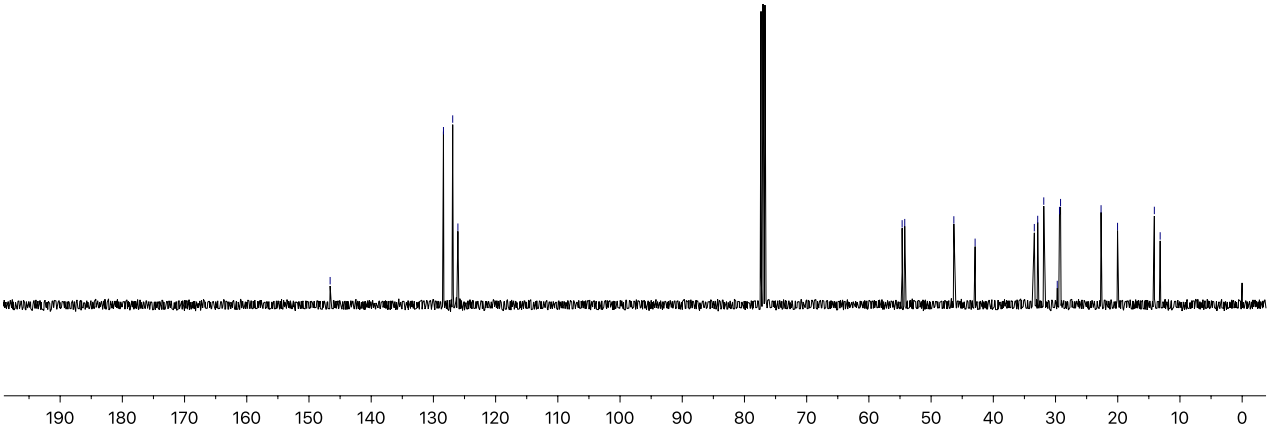
2s



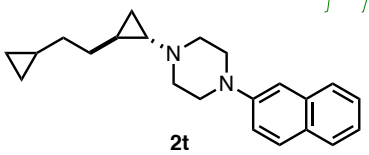
100 MHz, $CDCl_3$



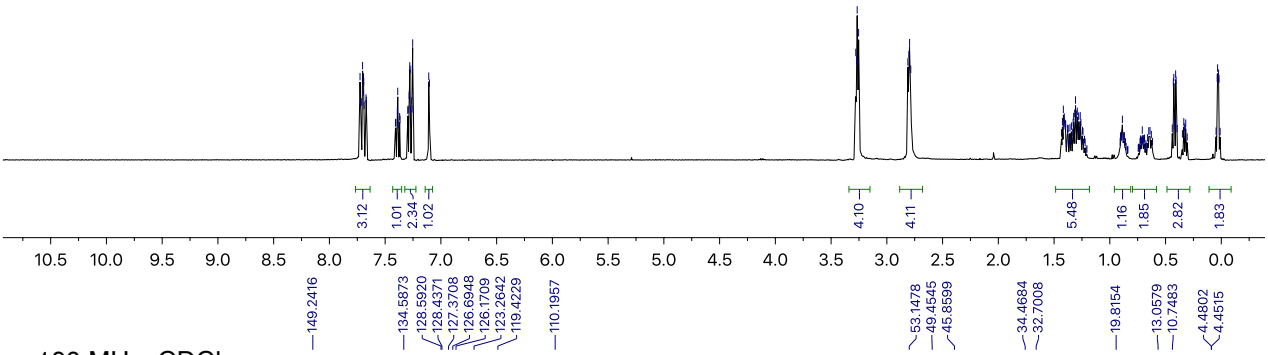
2s



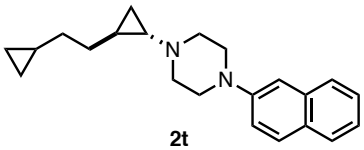
400 MHz, $CDCl_3$



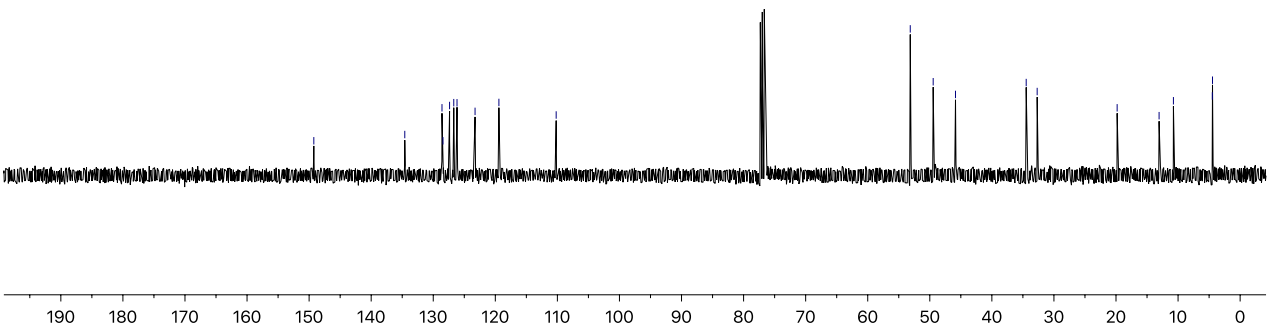
2t



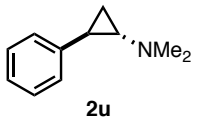
100 MHz, $CDCl_3$



2t

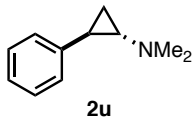


400 MHz, $CDCl_3$

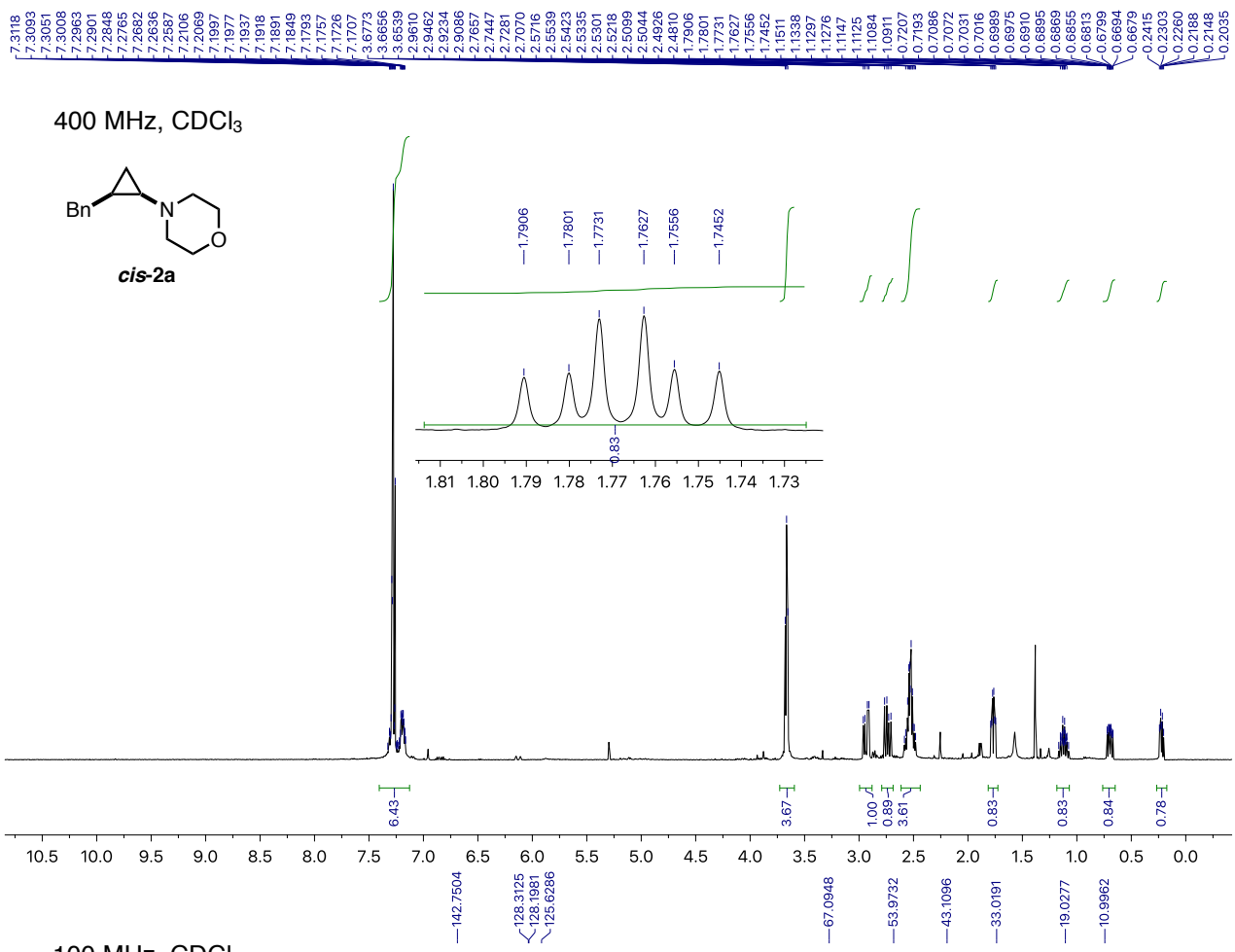


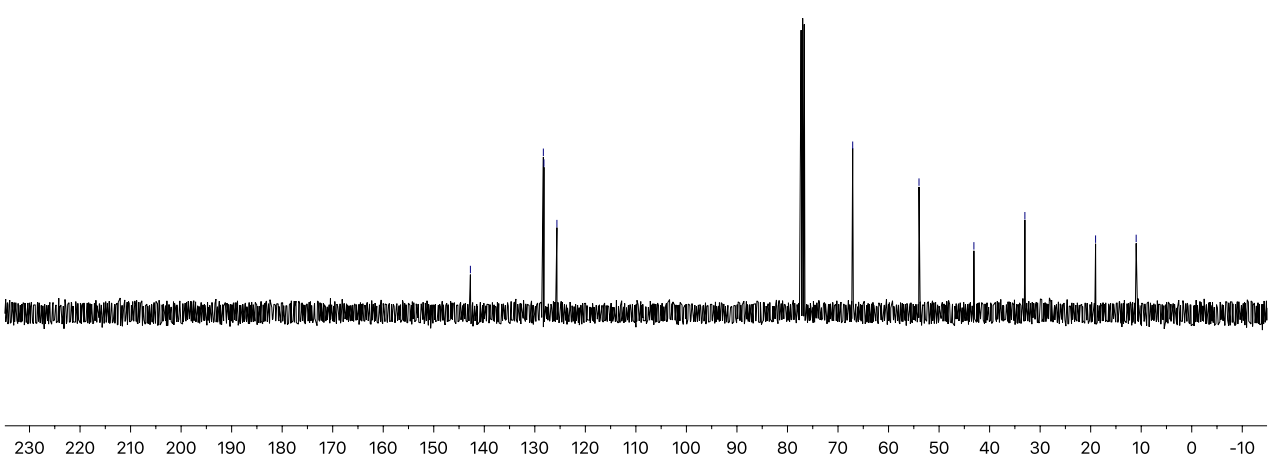
2u

100 MHz, $CDCl_3$

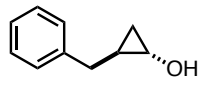


2u


400 MHz, CDCl3
Bn
N
O
cis-2a
7.3118
7.3093
7.3051
7.3008
7.2963
7.2901
7.2848
7.2765
7.2682
7.2636
7.2587
7.2106
7.2069
7.1997
7.1977
7.1937
7.1918
7.1891
7.1849
7.1793
7.1757
7.1726
7.1707
3.6773
3.6656
3.6539
2.9610
2.9462
2.9234
2.9086
2.7657
2.7447
2.7281
2.7070
2.5716
2.5539
2.5423
2.5335
2.5301
2.5218
2.5099
2.5044
2.4926
2.4810
1.7906
1.7801
1.7731
1.7627
1.7556
1.7452
1.1511
1.1338
1.1297
1.1276
1.1147
1.1125
1.1084
1.0911
0.7207
0.7193
0.7086
0.7072
0.7031
0.7016
0.6989
0.6975
0.6910
0.6895
0.6869
0.6855
0.6813
0.6799
0.6694
0.6679
0.2415
0.2303
0.2260
0.2188
0.2148
0.2035
1.7906
1.7801
1.7731
1.7627
1.7556
1.7452
0.83
1.81 1.80 1.79 1.78 1.77 1.76 1.75 1.74 1.73
6.43
3.67
1.00
0.89
3.61
0.83
0.83
0.84
0.78
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

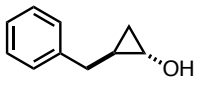

100 MHz, CDCl3
Bn
N
O
cis-2a
142.7504
128.3125
128.1981
125.6286
67.0948
53.9732
43.1096
33.0191
19.0277
10.9962
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

400 MHz, $CDCl_3$

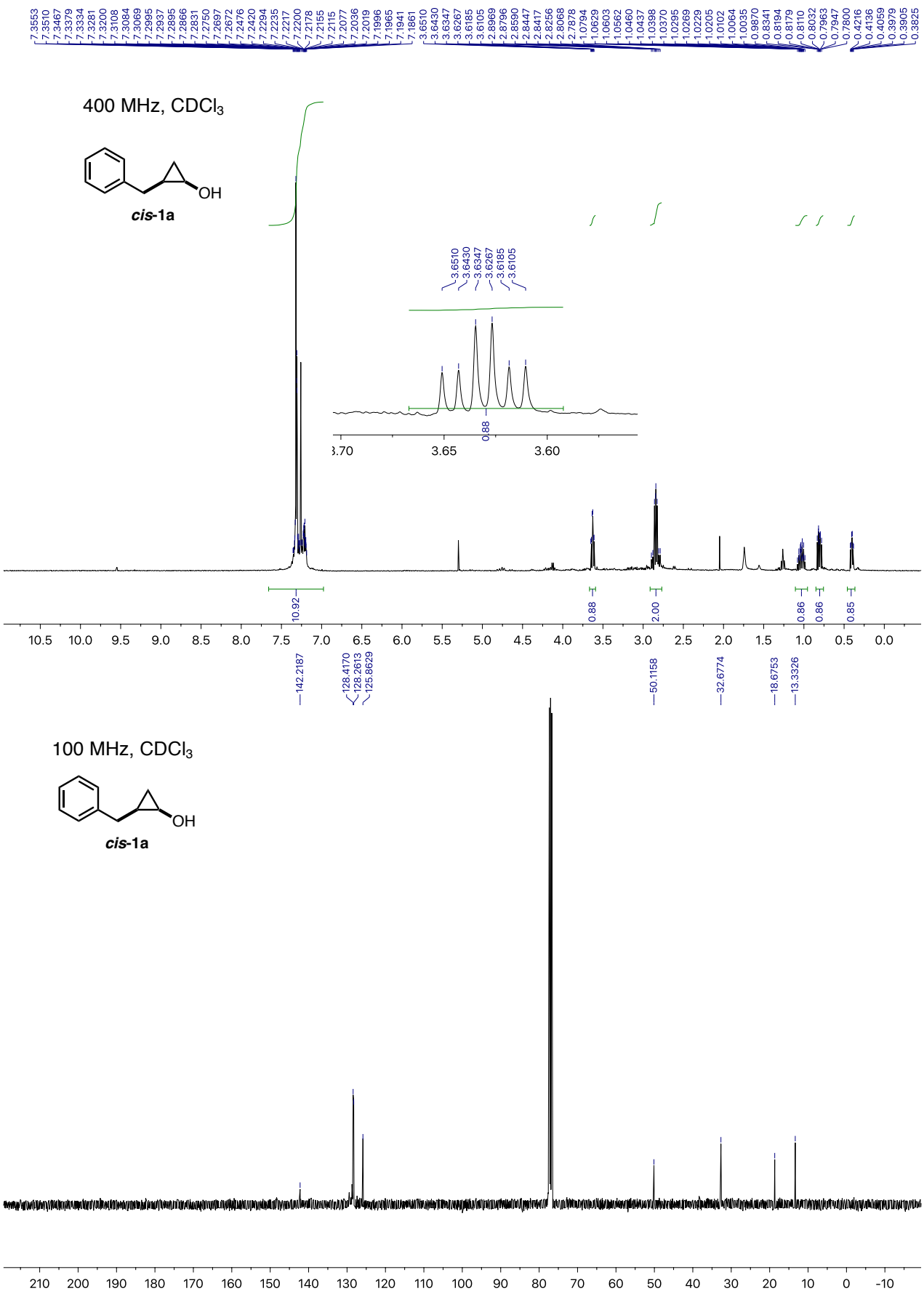


1a

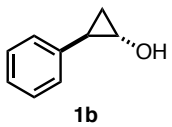
100 MHz, $CDCl_3$



1a

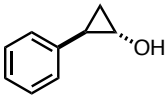

400 MHz, CDCl3
OH
cis-1a
100 MHz, CDCl3
OH
cis-1a

400 MHz, $CDCl_3$

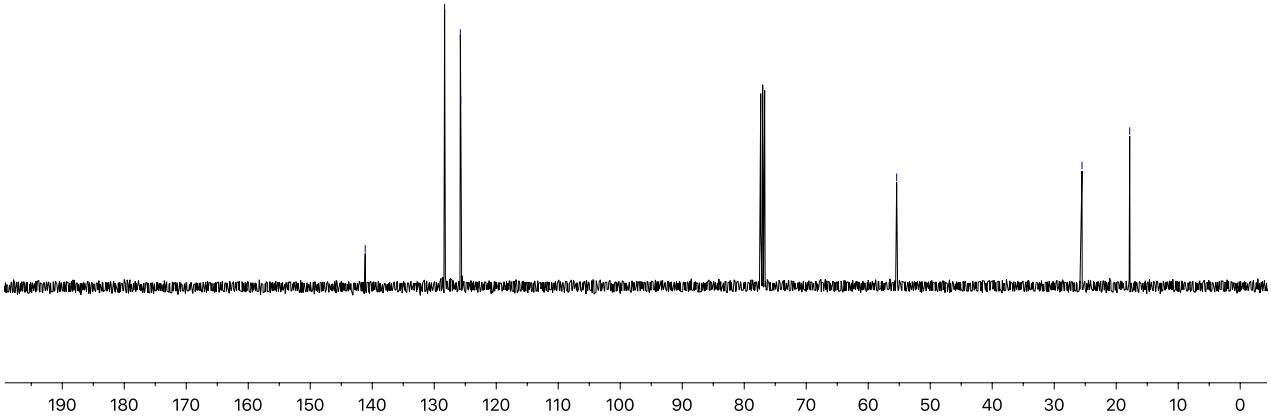


1b

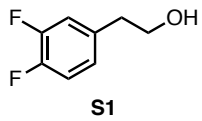
100 MHz, $CDCl_3$



1b

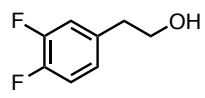


400 MHz, $CDCl_3$

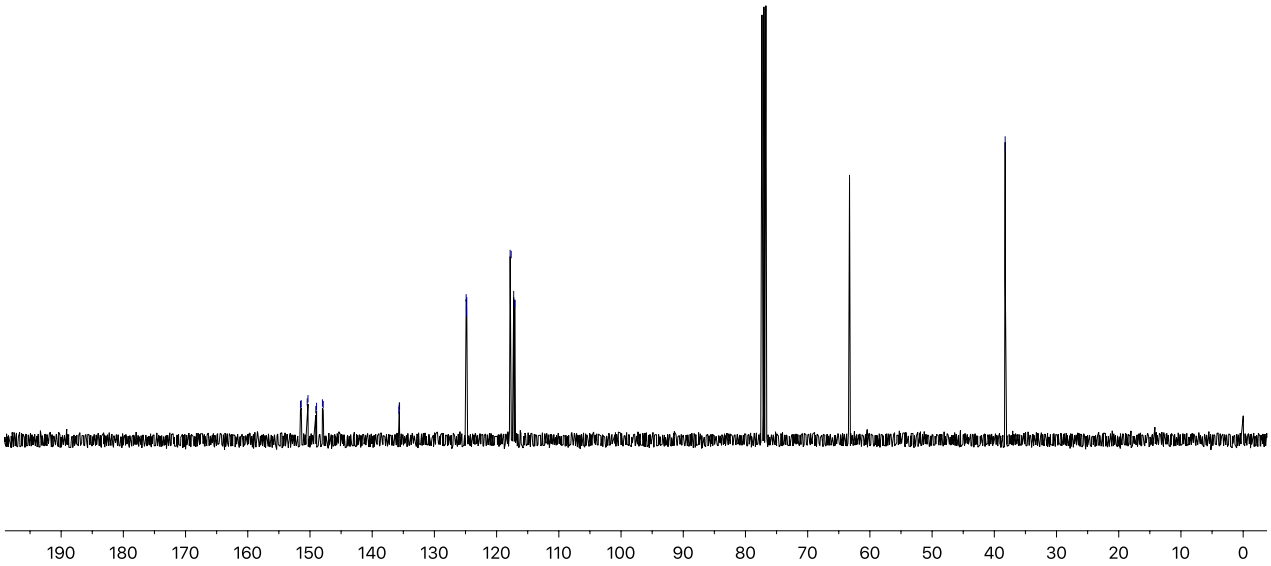


S1

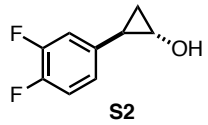
100 MHz, $CDCl_3$



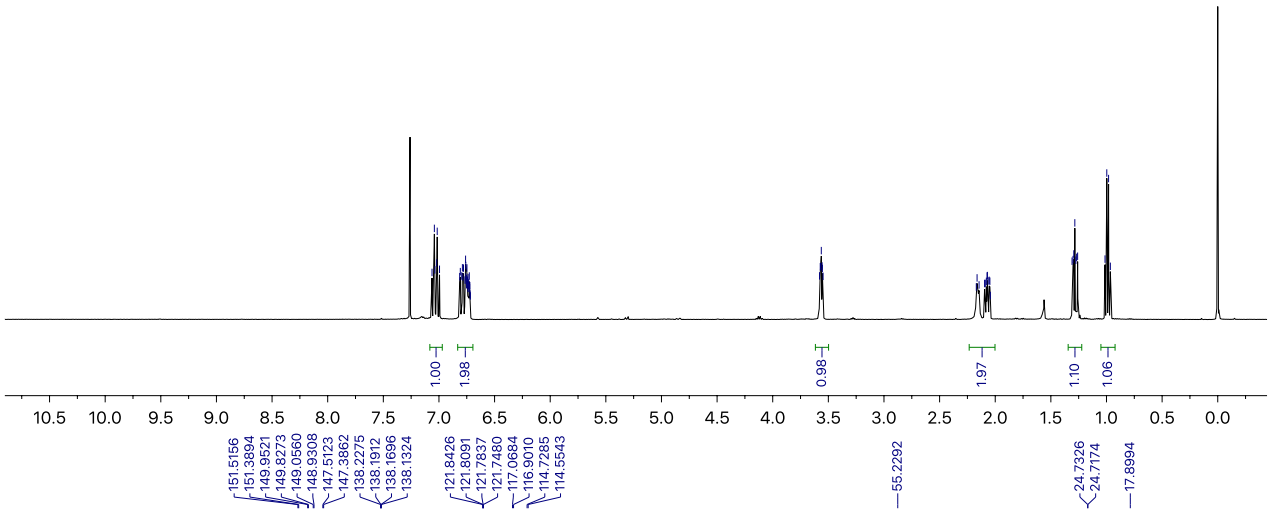
S1



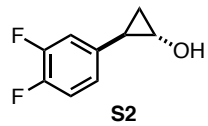
400 MHz, $CDCl_3$



S2

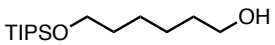


100 MHz, $CDCl_3$



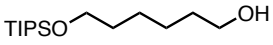
S2

400 MHz, $CDCl_3$

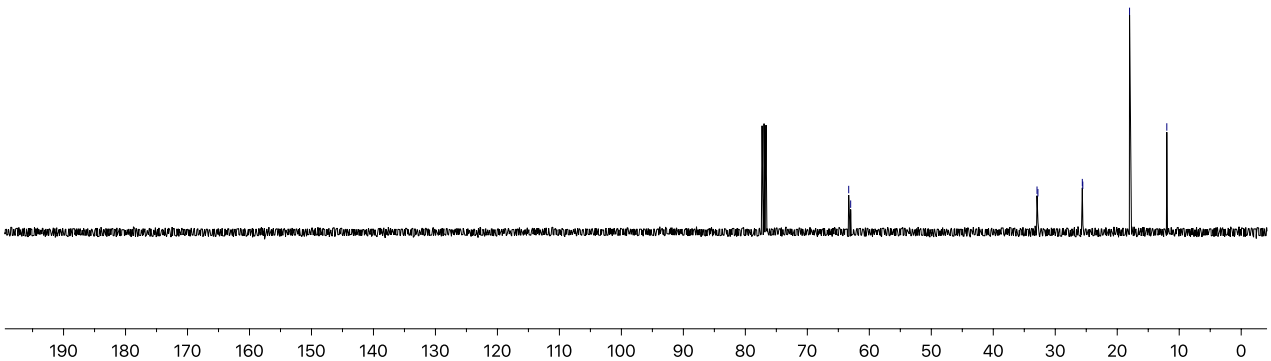


S3

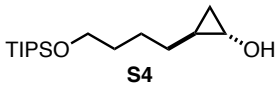
100 MHz, $CDCl_3$



S3

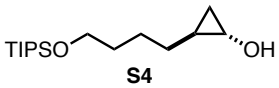


400 MHz, $CDCl_3$

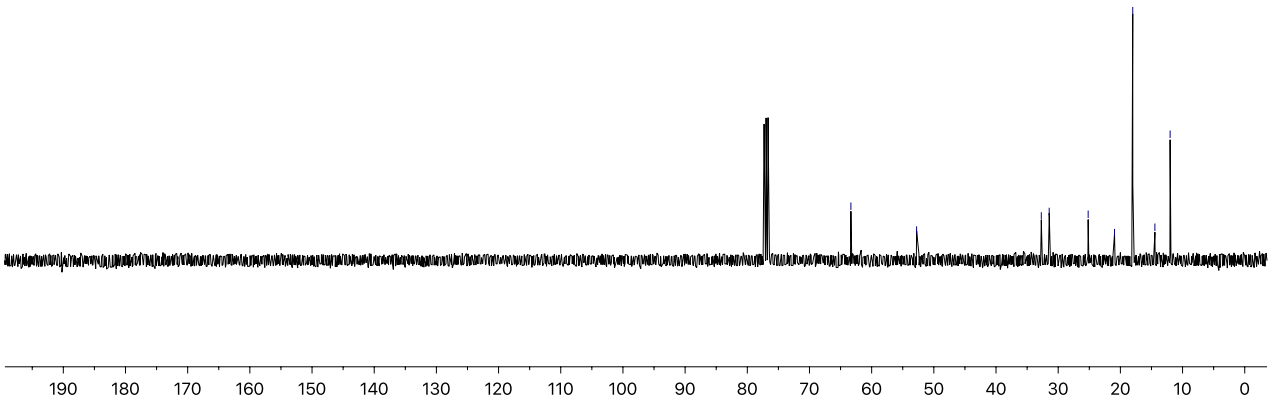


S4

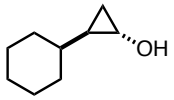
100 MHz, $CDCl_3$



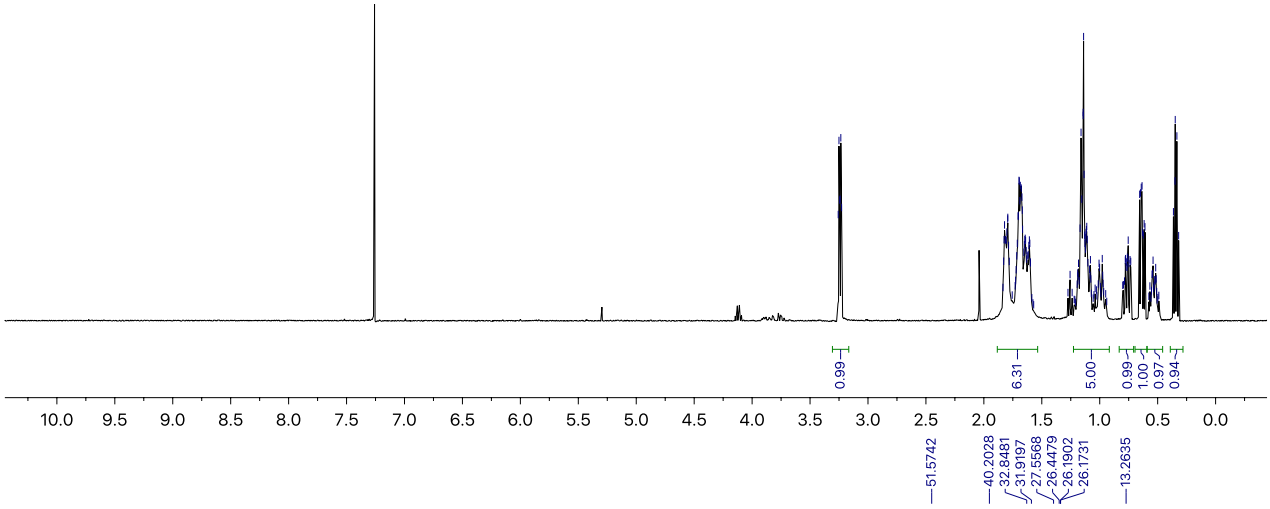
S4



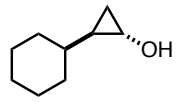
400 MHz, $CDCl_3$



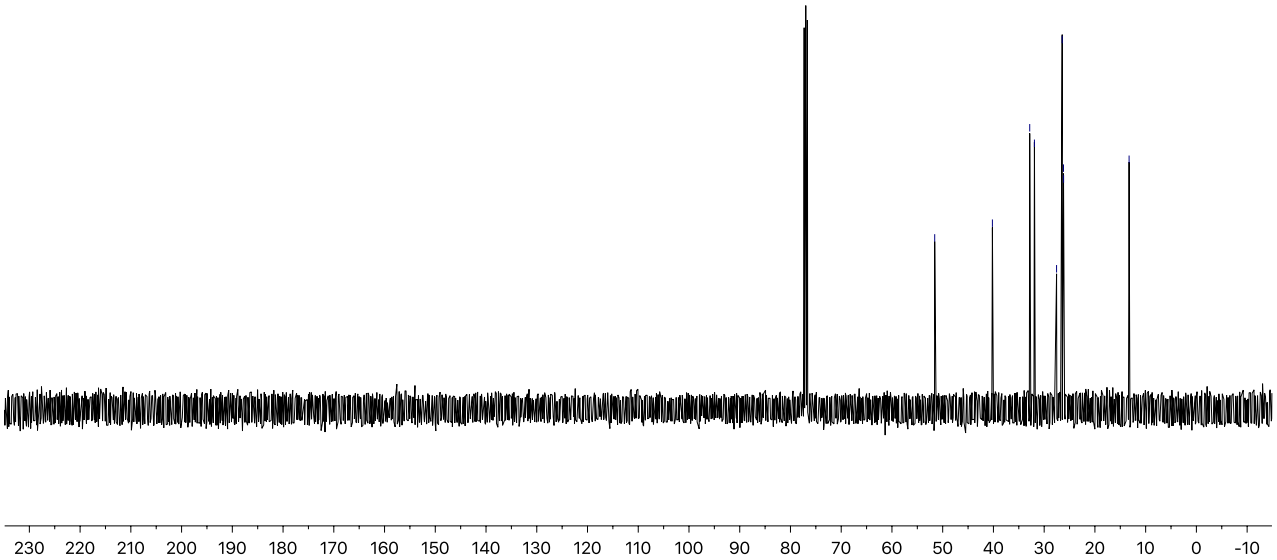
S5



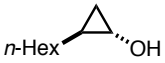
100 MHz, $CDCl_3$



S5

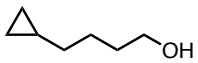


400 MHz, $CDCl_3$

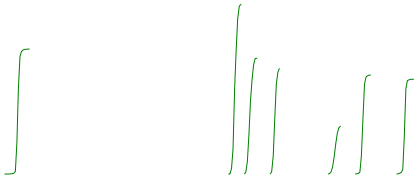


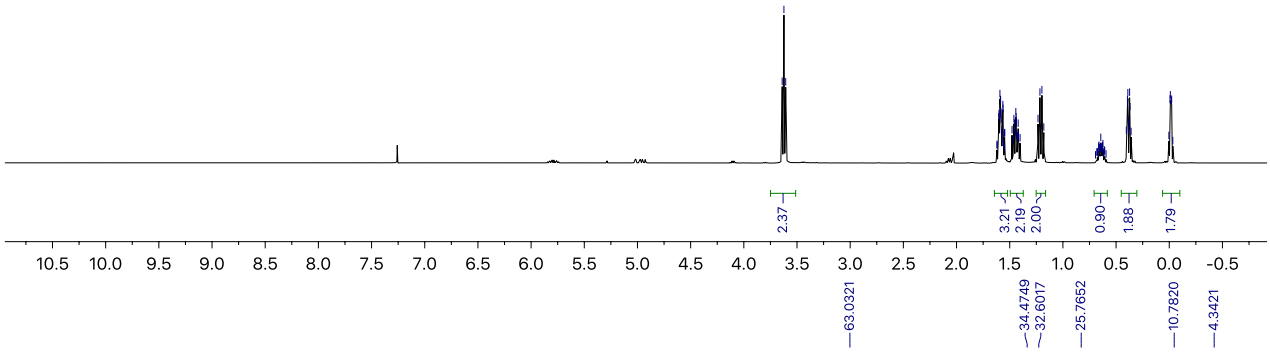
S6

400 MHz, $CDCl_3$

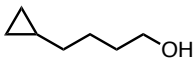


S7

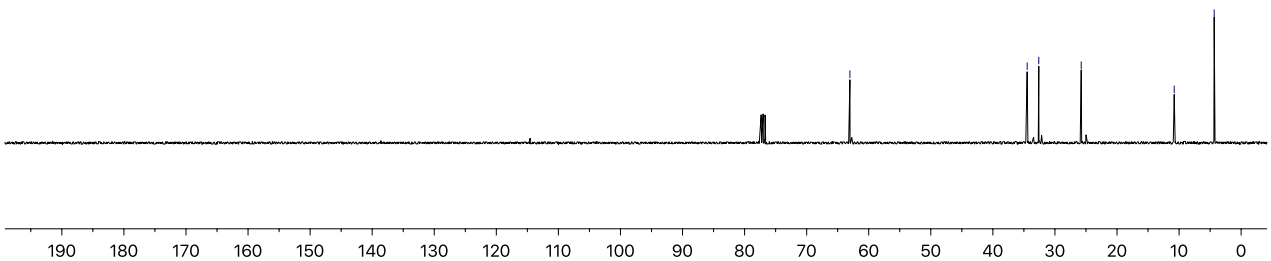




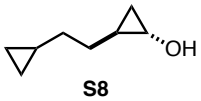
100 MHz, $CDCl_3$



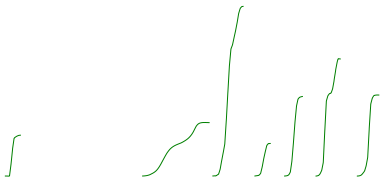
S7

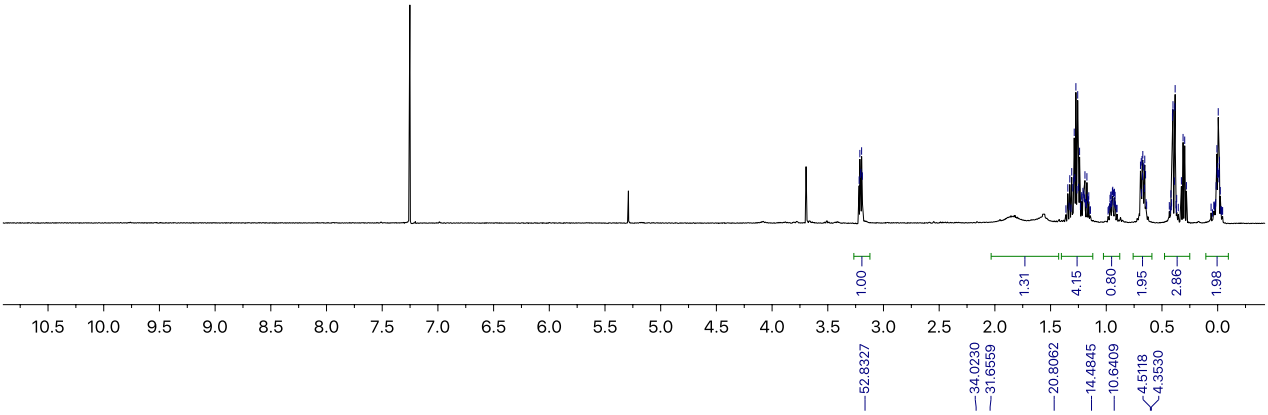


400 MHz, $CDCl_3$

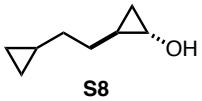


S8

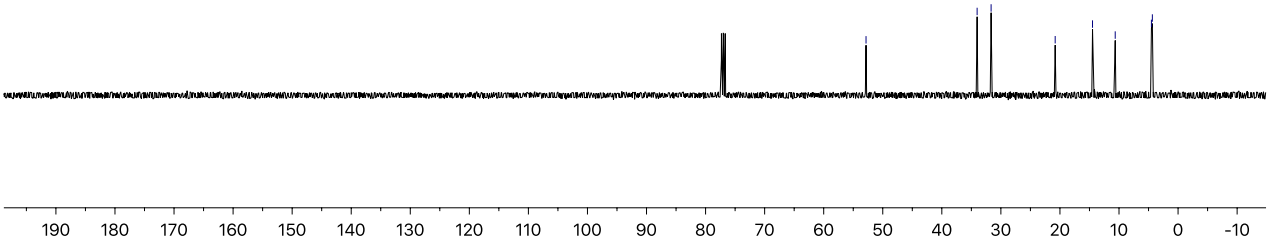




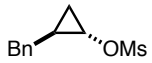
100 MHz, $CDCl_3$



S8

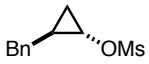


400 MHz, $CDCl_3$

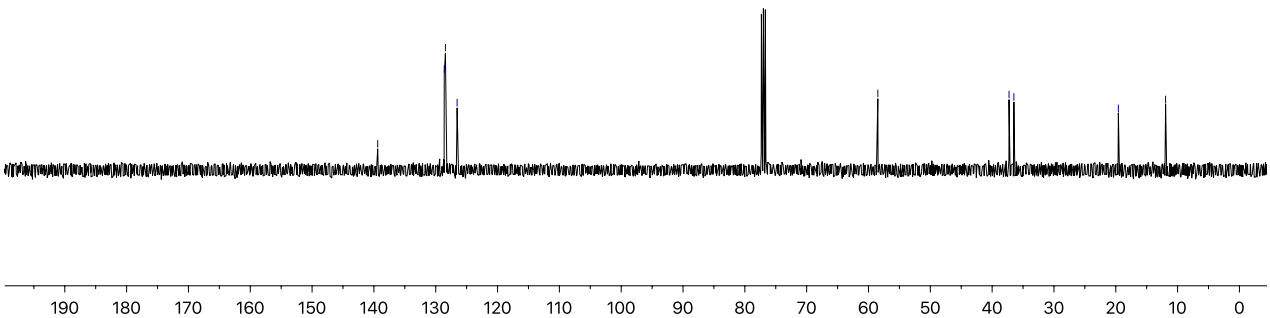


S15

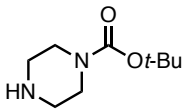
100 MHz, $CDCl_3$



S15

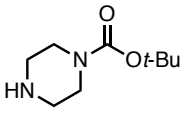


400 MHz, $CDCl_3$



S9

100 MHz, $CDCl_3$

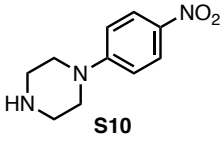


S9

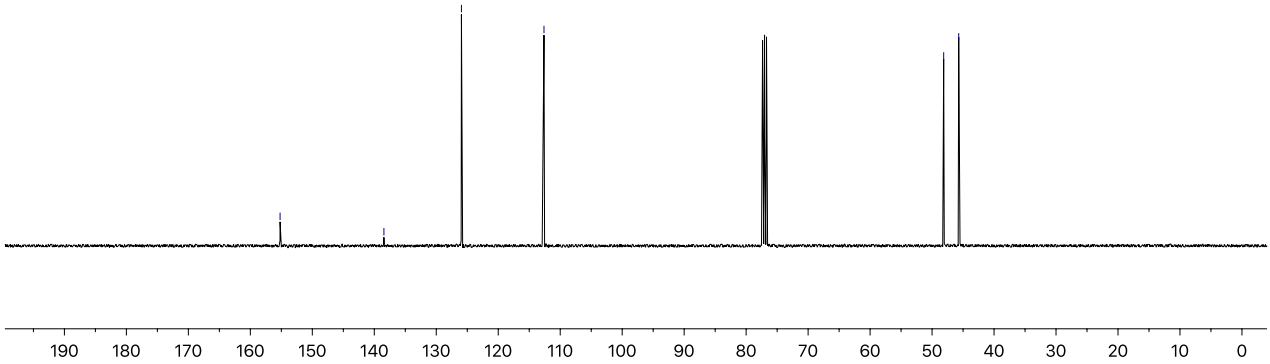
400 MHz, $CDCl_3$

S10

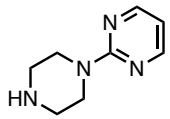
100 MHz, $CDCl_3$



S10

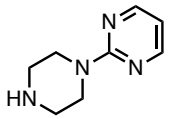


400 MHz, $CDCl_3$

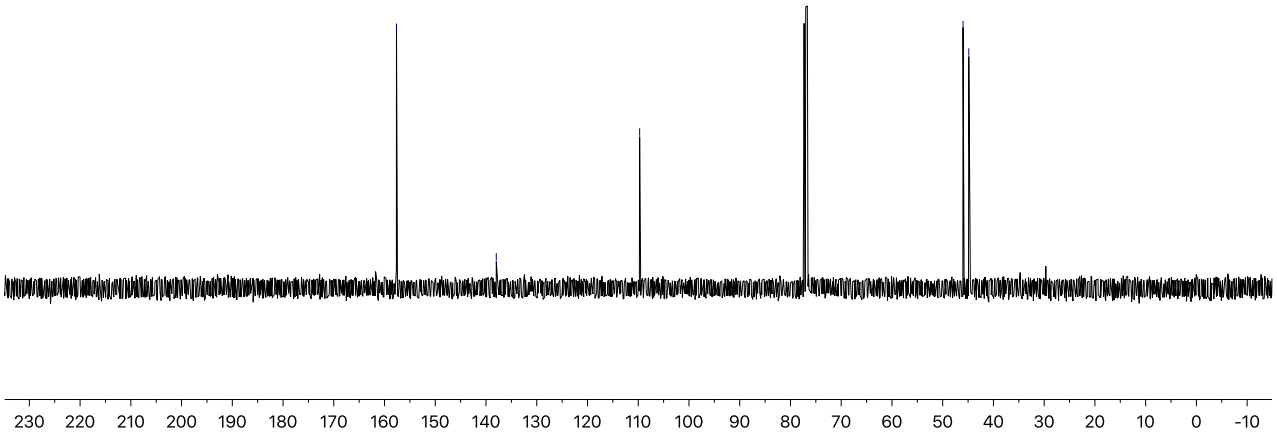


S11

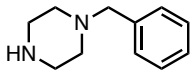
100 MHz, $CDCl_3$



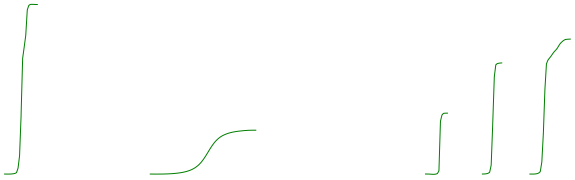
S11

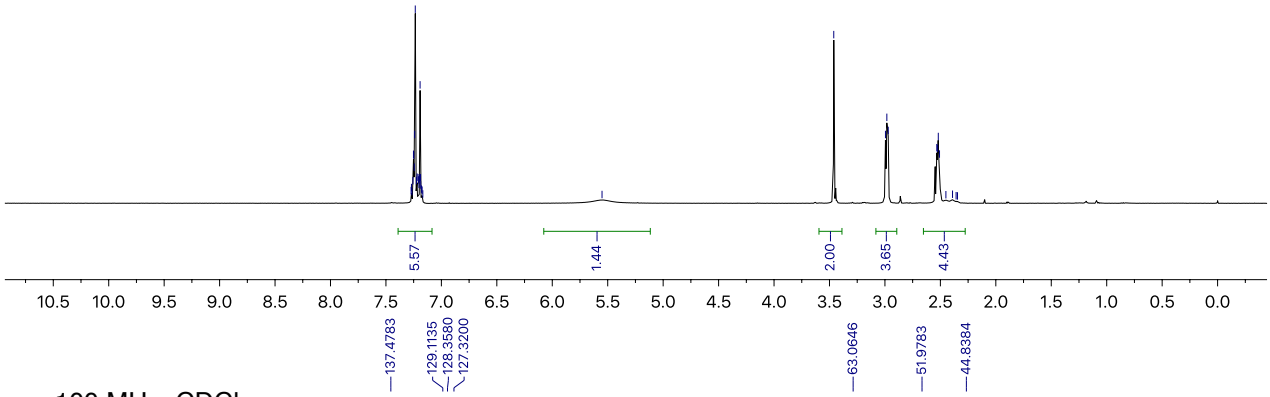


400 MHz, $CDCl_3$

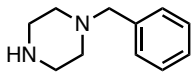


S12

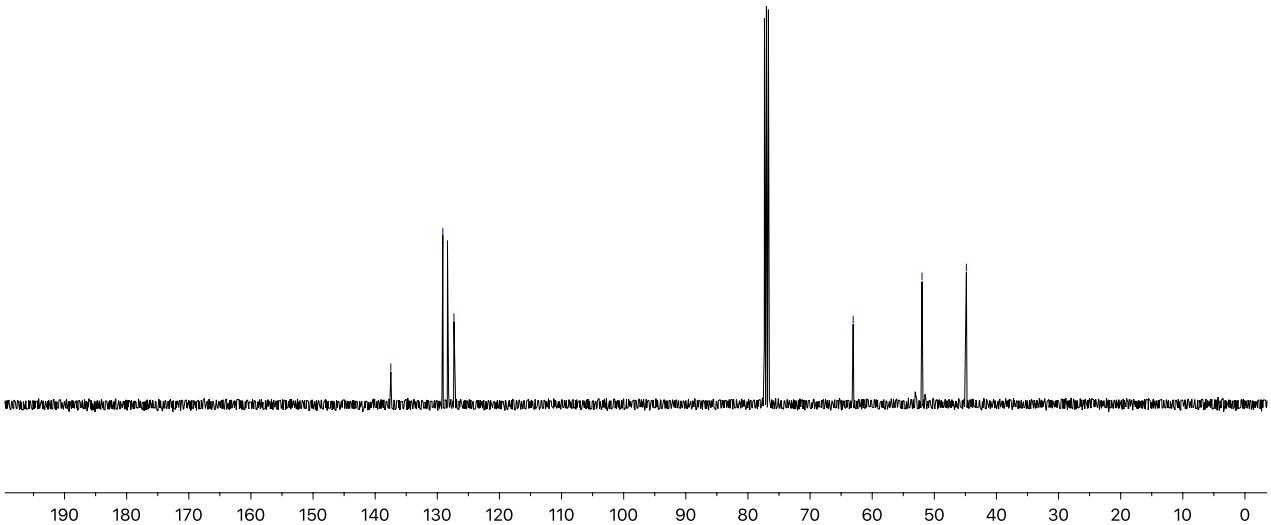




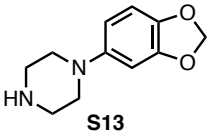
100 MHz, $CDCl_3$



S12



400 MHz, $CDCl_3$

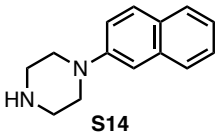


S13

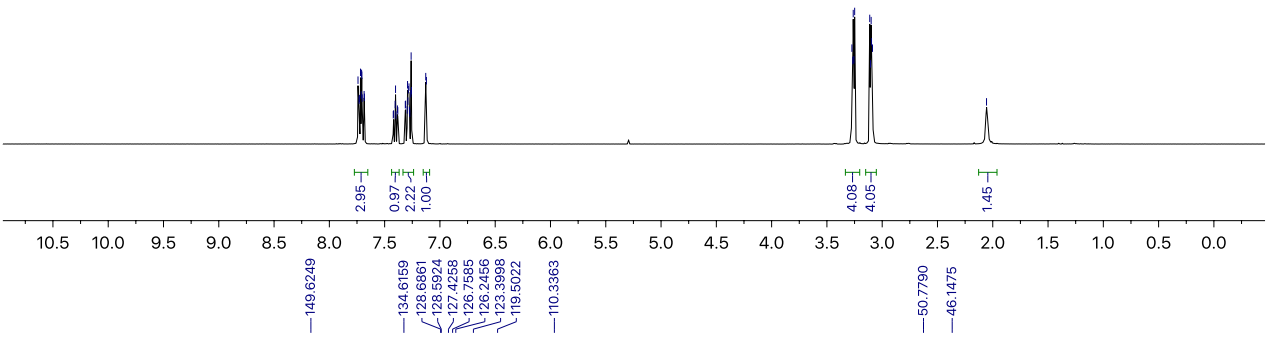
100 MHz, $CDCl_3$

S13

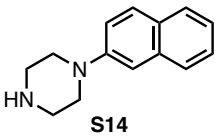
400 MHz, $CDCl_3$



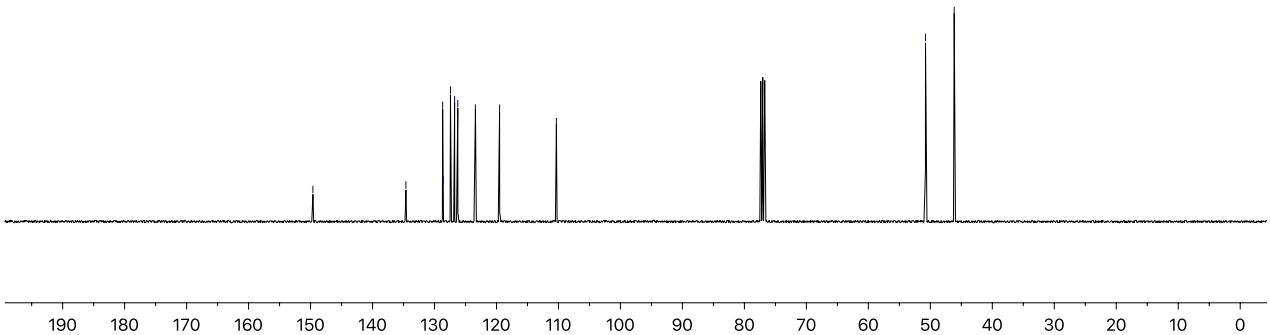
S14



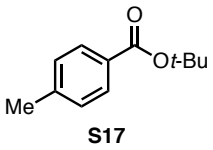
100 MHz, $CDCl_3$



S14

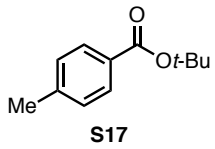


400 MHz, $CDCl_3$

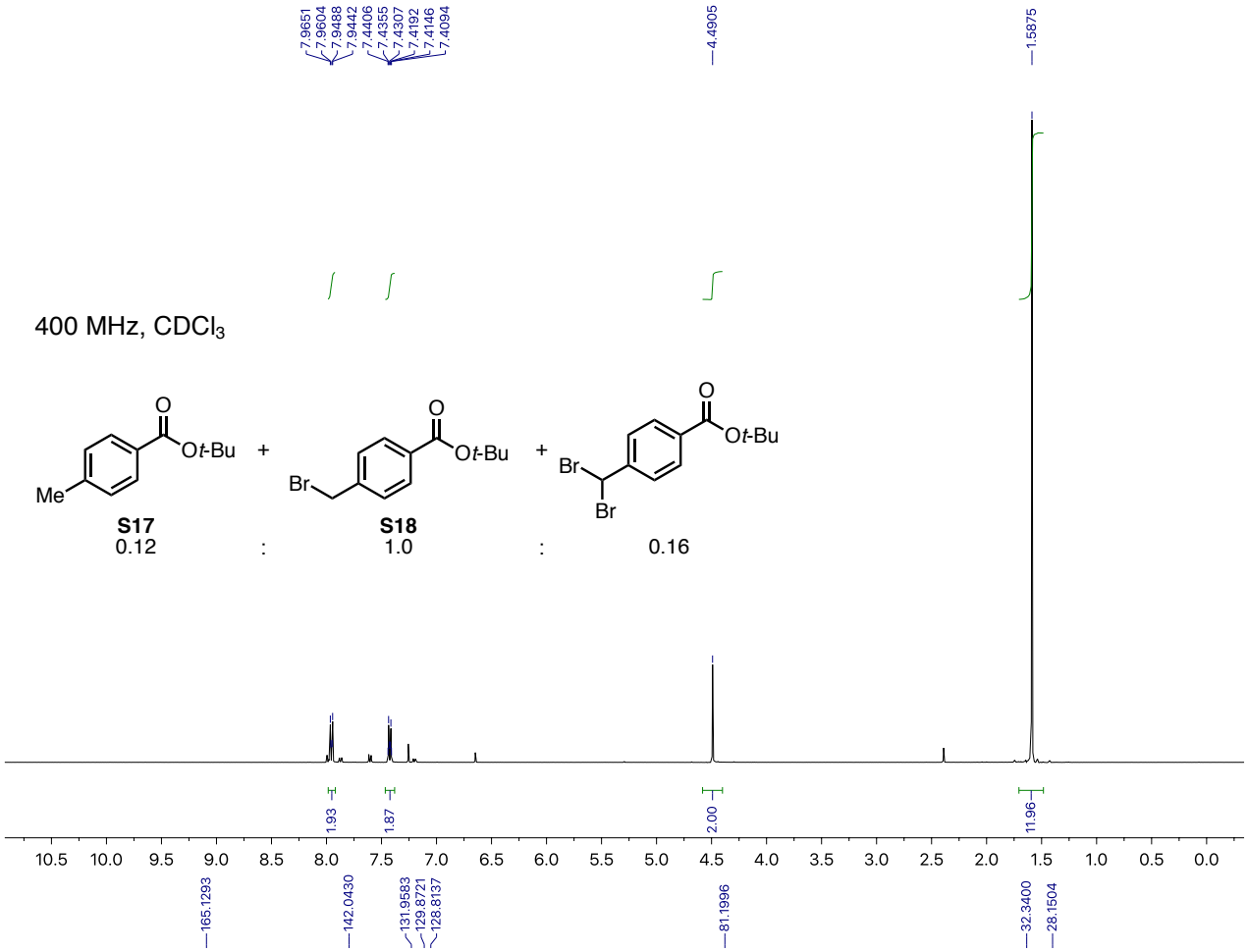


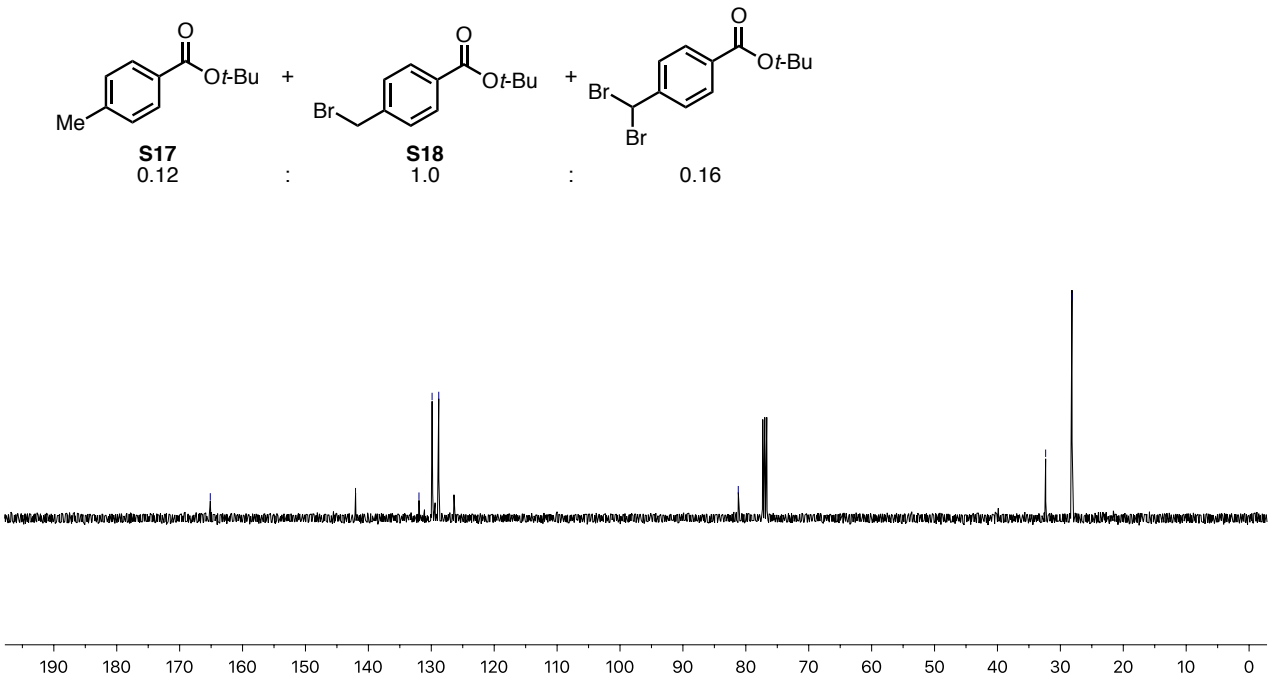
S17

100 MHz, $CDCl_3$

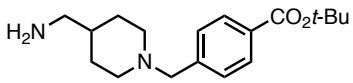


S17


7.9651
7.9604
7.9488
7.9442
7.4406
7.4355
7.4307
7.4192
7.4146
7.4094
4.4905
1.5875
400 MHz, CDCl3
Me
Ot-Bu
Br
Br
S17
0.12
:
S18
1.0
:
0.16
1.93
1.87
2.00
11.96
165.1293
142.0430
131.9583
129.8721
128.8137
81.1996
32.3400
28.1504

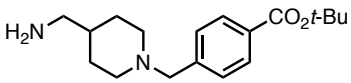

100 MHz, CDCl3
Me
Ot-Bu
Br
Br
S17
0.12
:
S18
1.0
:
0.16

400 MHz, $CDCl_3$

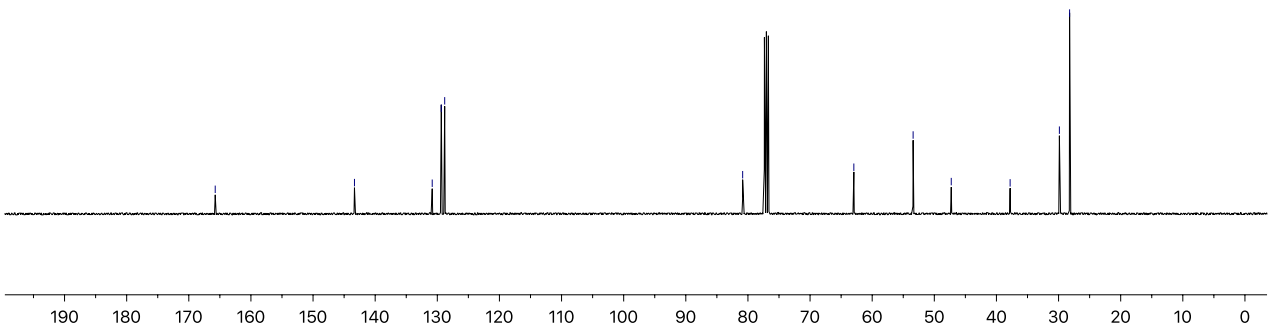


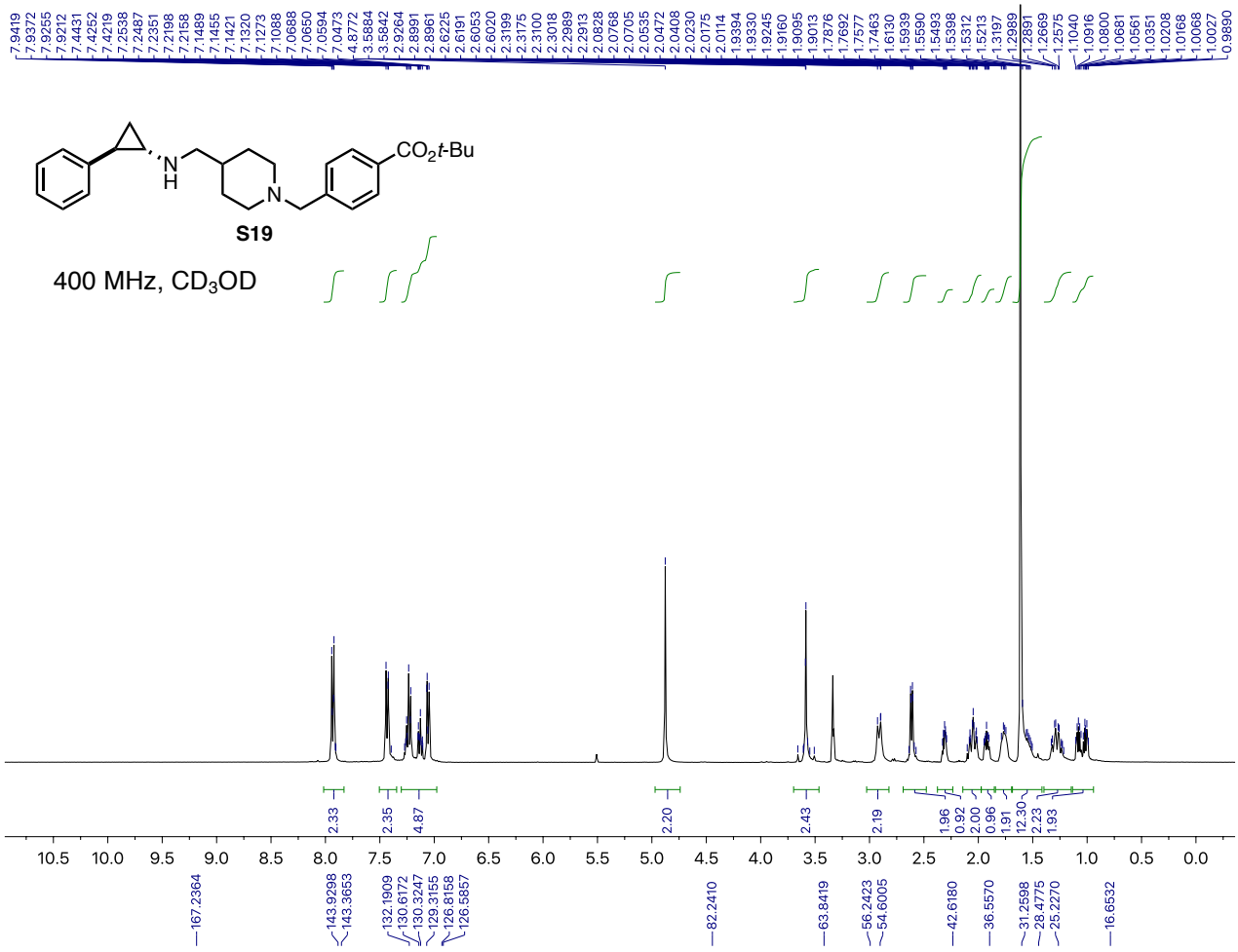
3

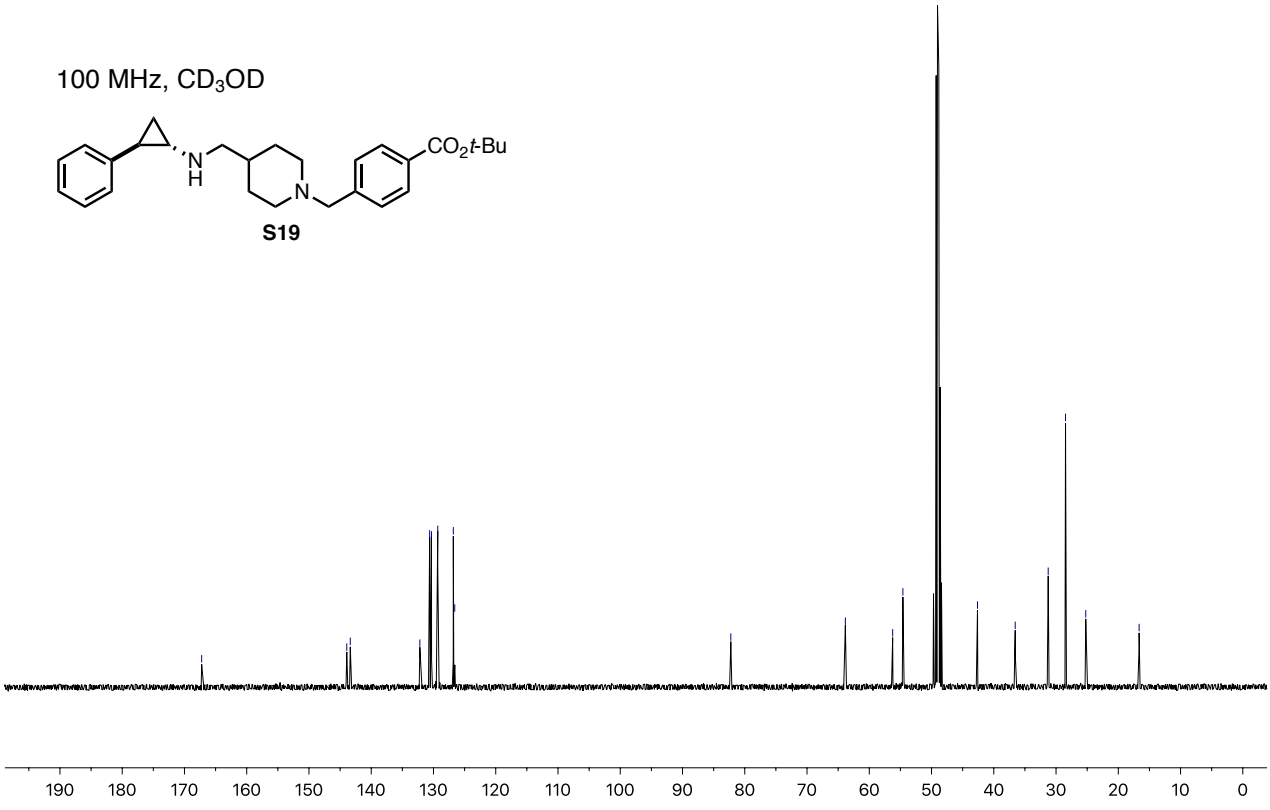
100 MHz, $CDCl_3$

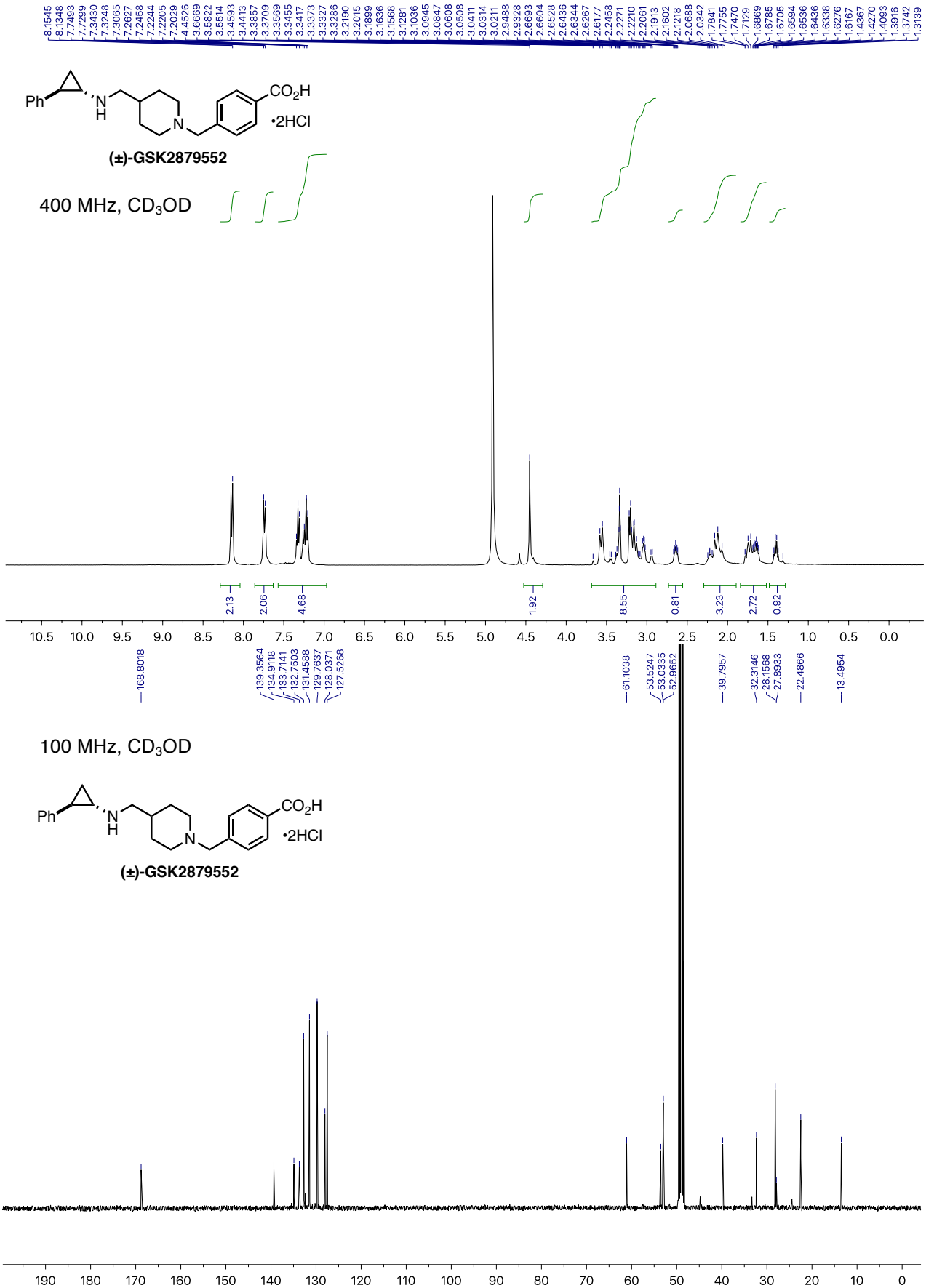


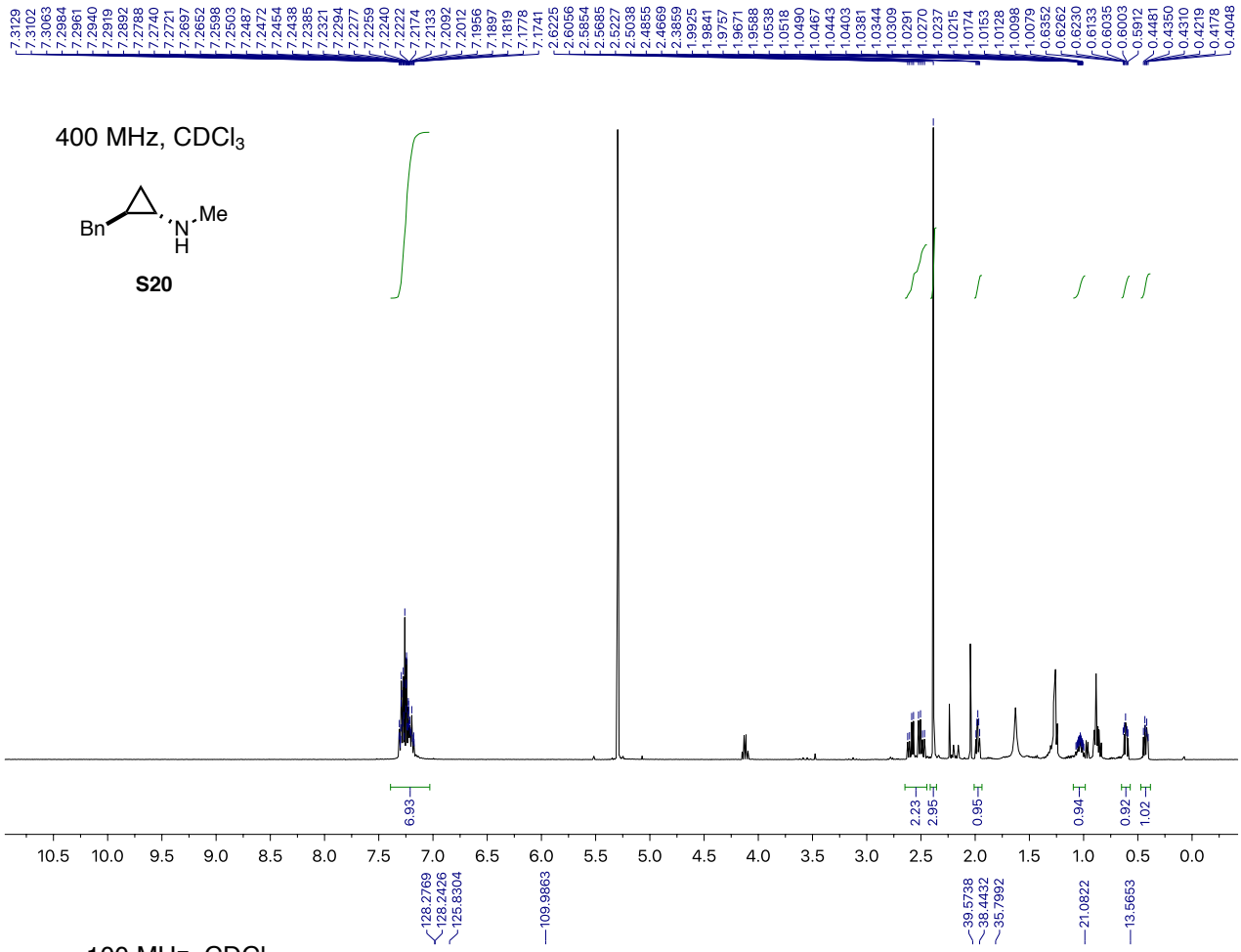
3

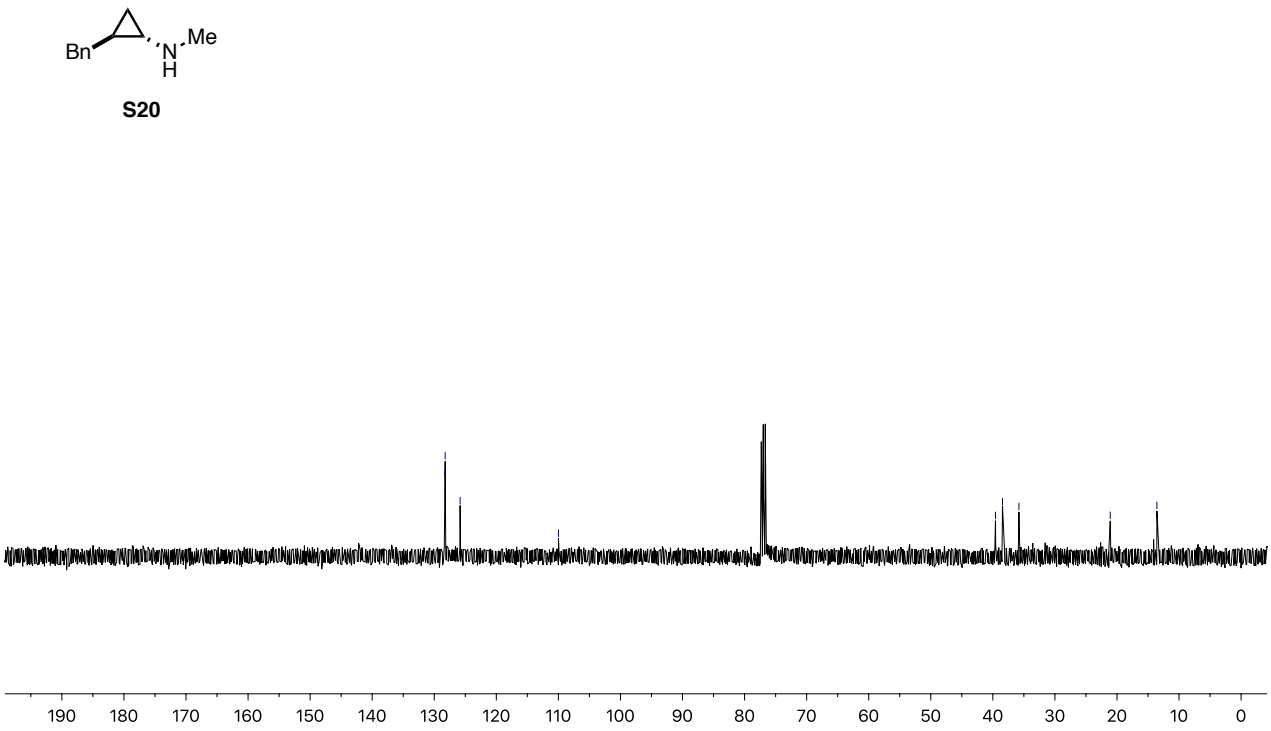



CO2t-Bu
N
H
N
S19
400 MHz, CD3OD

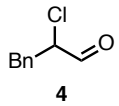

CO2t-Bu
N
H
N
S19
100 MHz, CD3OD


Ph
N
H
N
CO2H
•2HCl
(±)-GSK2879552
400 MHz, CD3OD
100 MHz, CD3OD

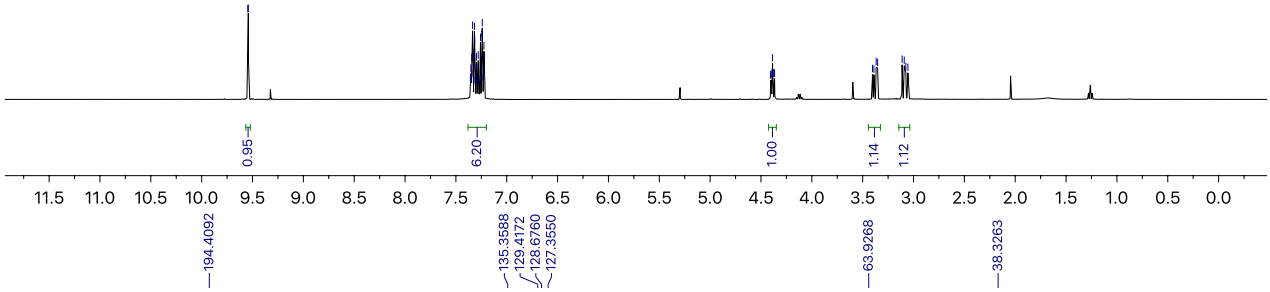

400 MHz, CDCl3
Bn
N
H
Me
S20


100 MHz, CDCl3
Bn
N
H
Me
S20

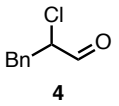
400 MHz, $CDCl_3$



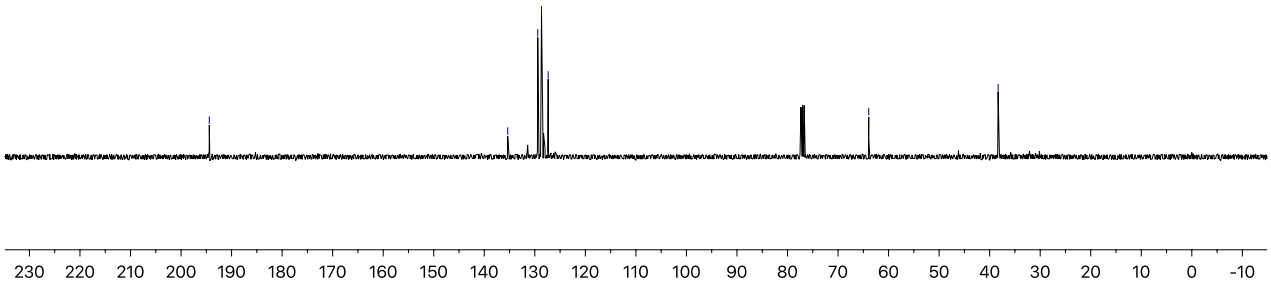
4



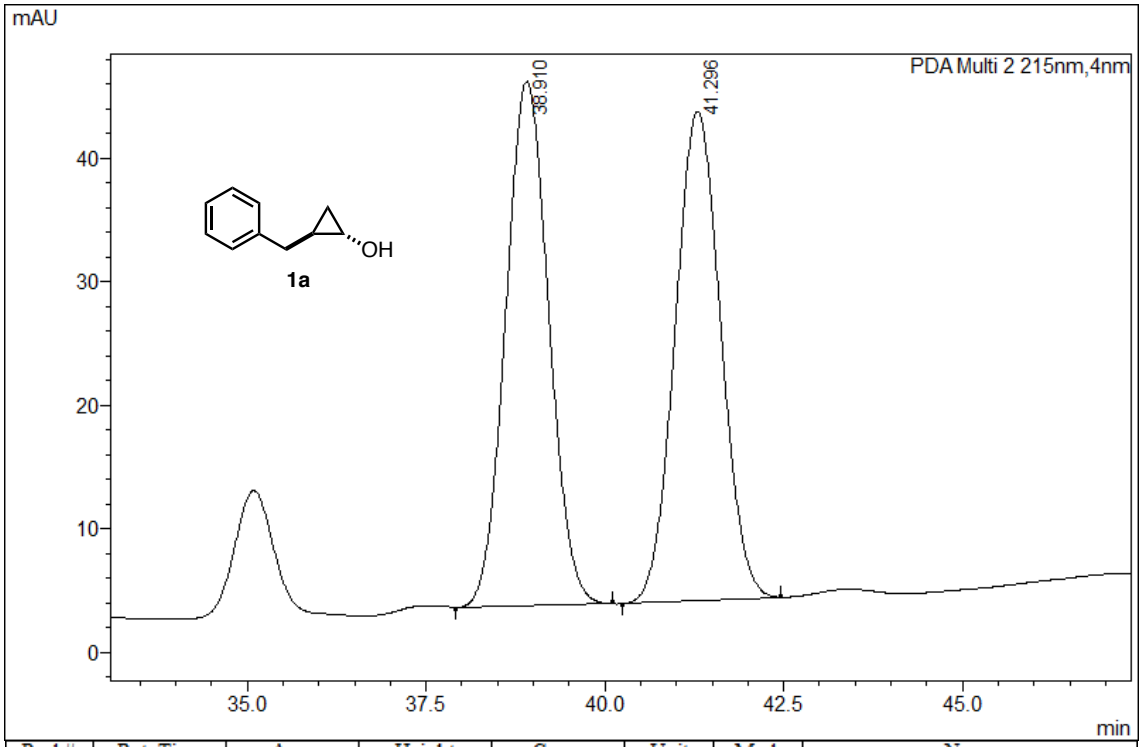
100 MHz, $CDCl_3$



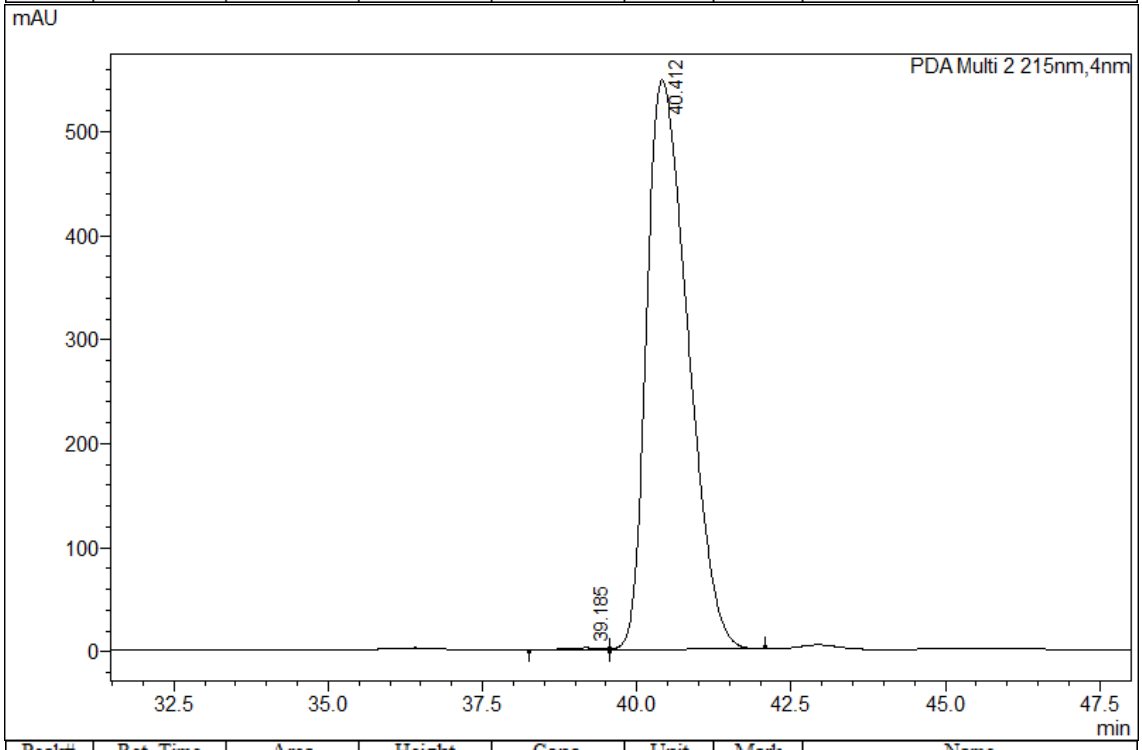
4



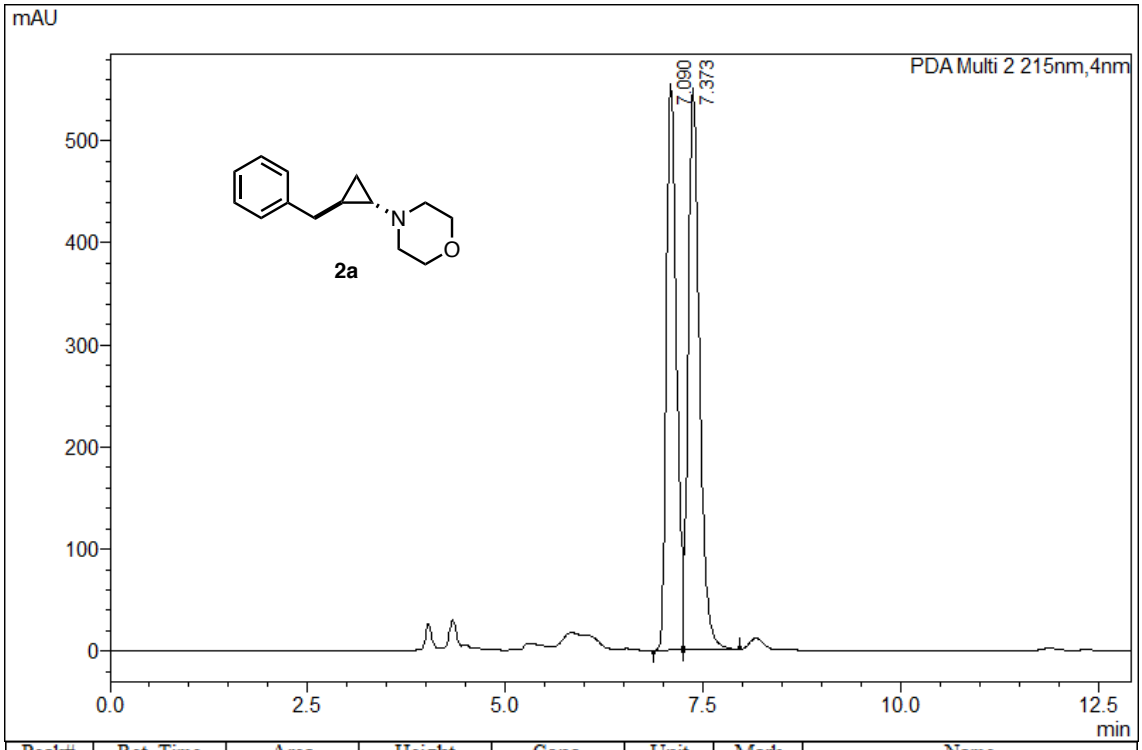
L. HPLC traces



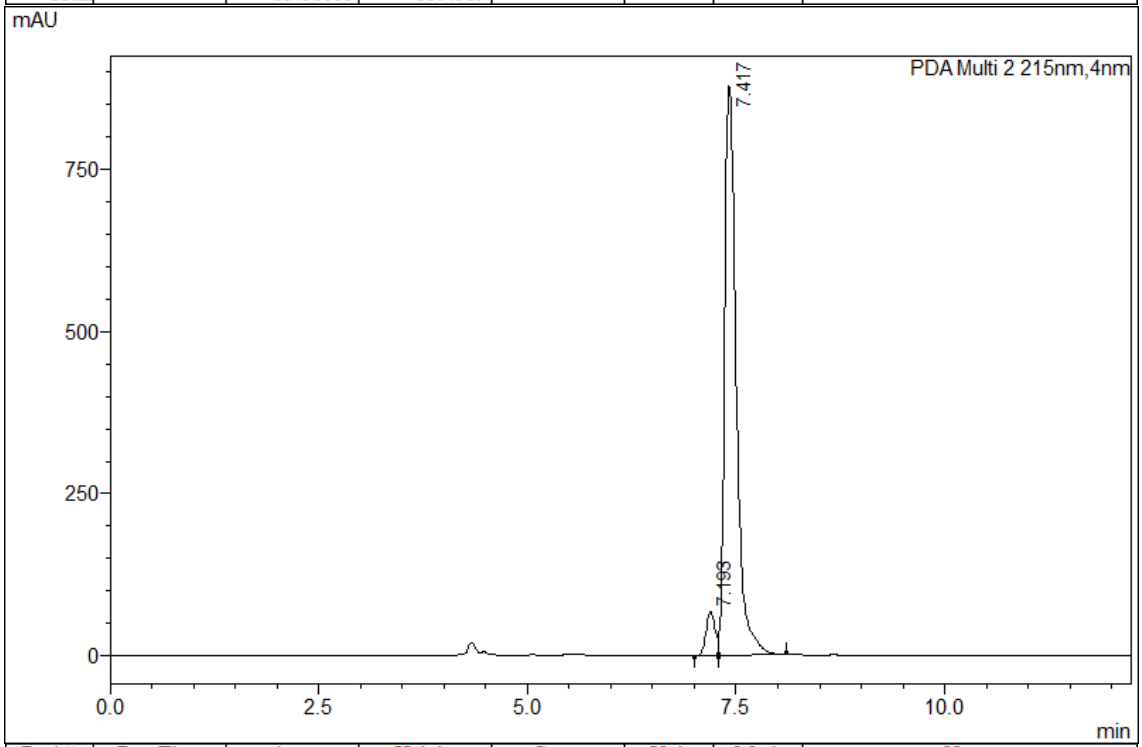
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	38.910	1784347	42443	0.000			
2	41.296	1760079	39591	0.000			
Total		3544425	82034				



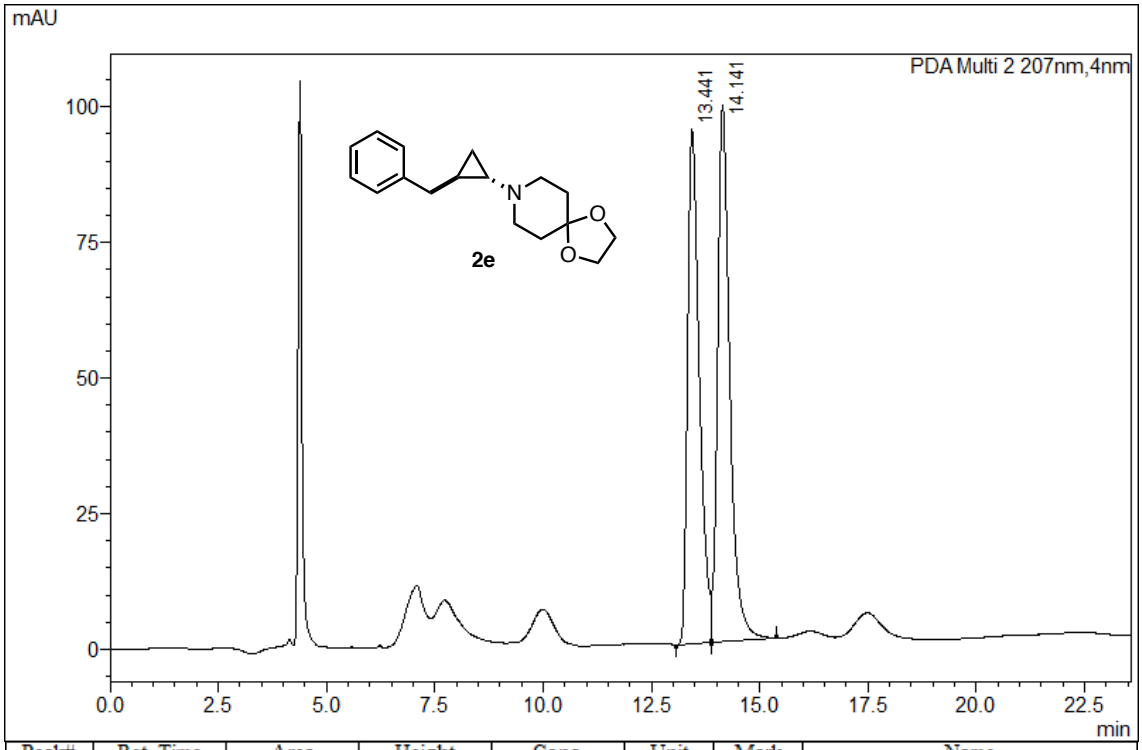
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	39.185	76110	1842	0.000		M	
2	40.412	25528135	547285	0.000		V	
Total		25604246	549127				



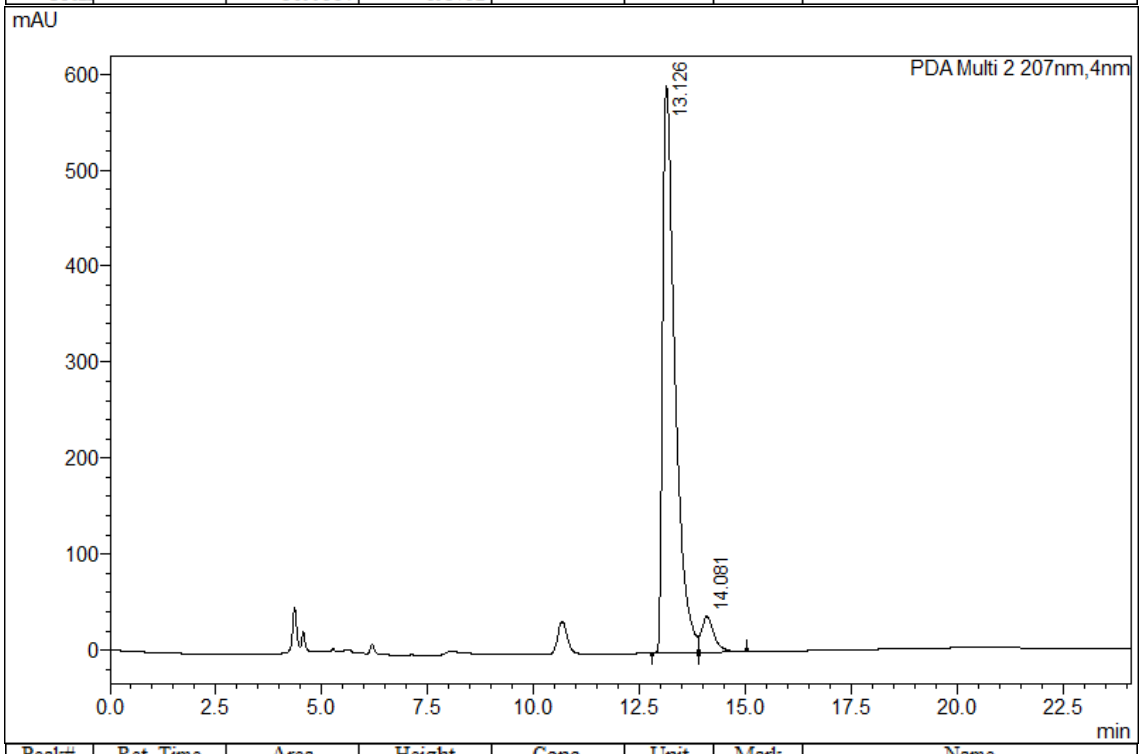
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	7.090	5052393	555234	0.000			
2	7.373	5443608	549755	0.000		V	
Total		10496001	1104989				



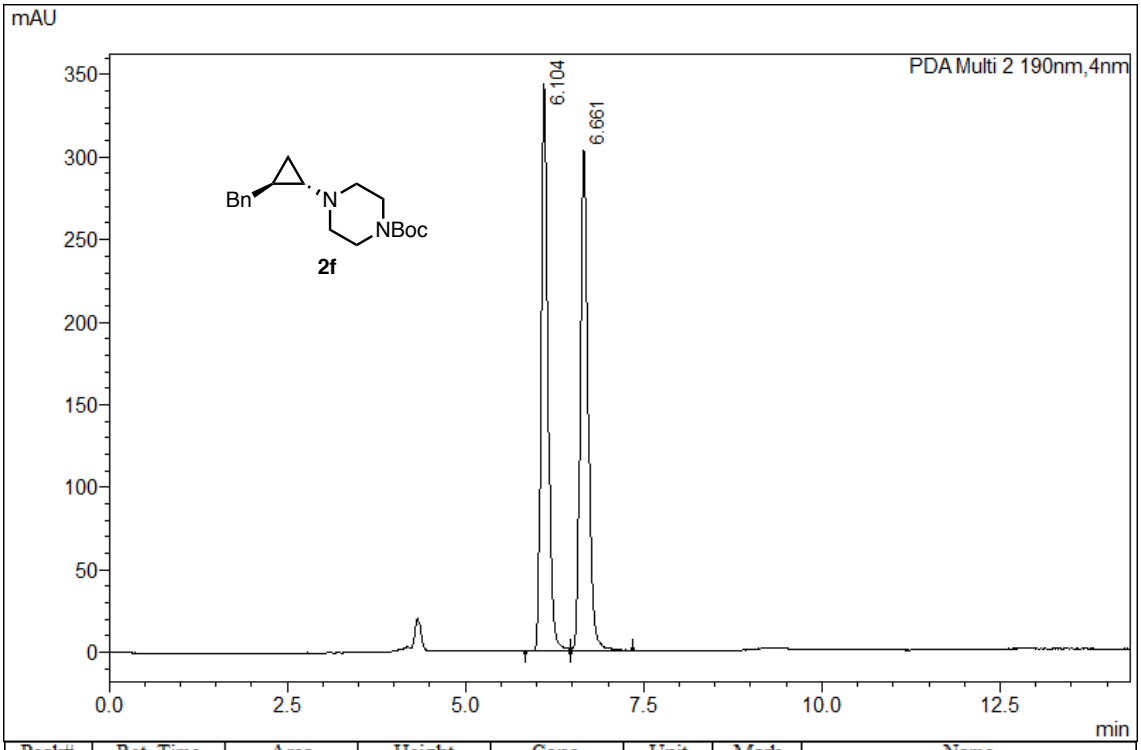
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	7.193	504303	67702	0.000			
2	7.417	8482342	878728	0.000		V M	
Total		8986645	946429				



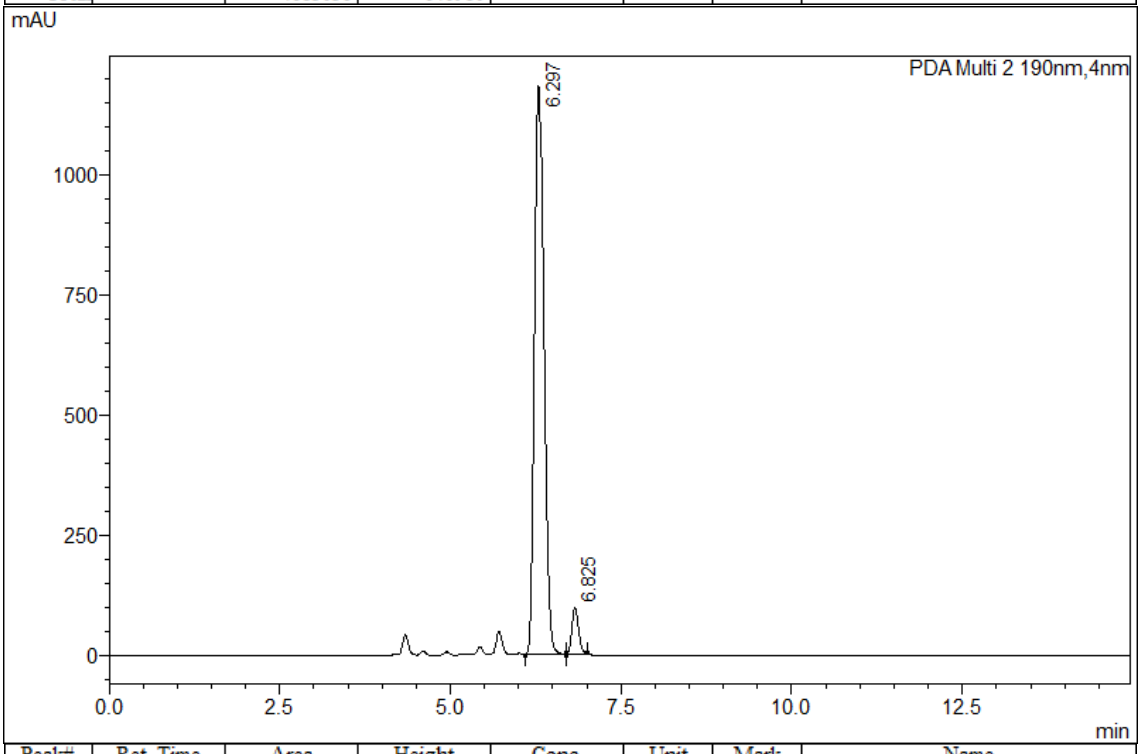
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	13.441	1771508	94799	0.000			
2	14.141	1928077	98953	0.000		V	
Total		3699584	193752				



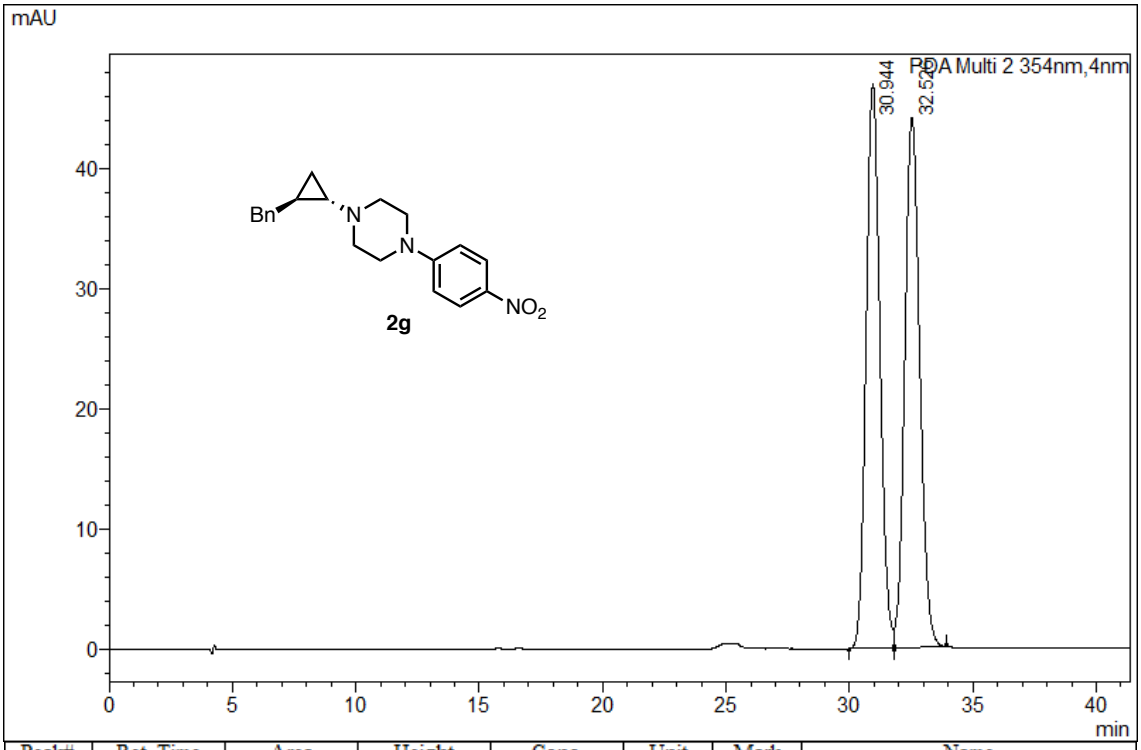
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	13.126	12008028	591140	0.000		M	
2	14.081	768793	37262	0.000		V M	
Total		12776821	628403				



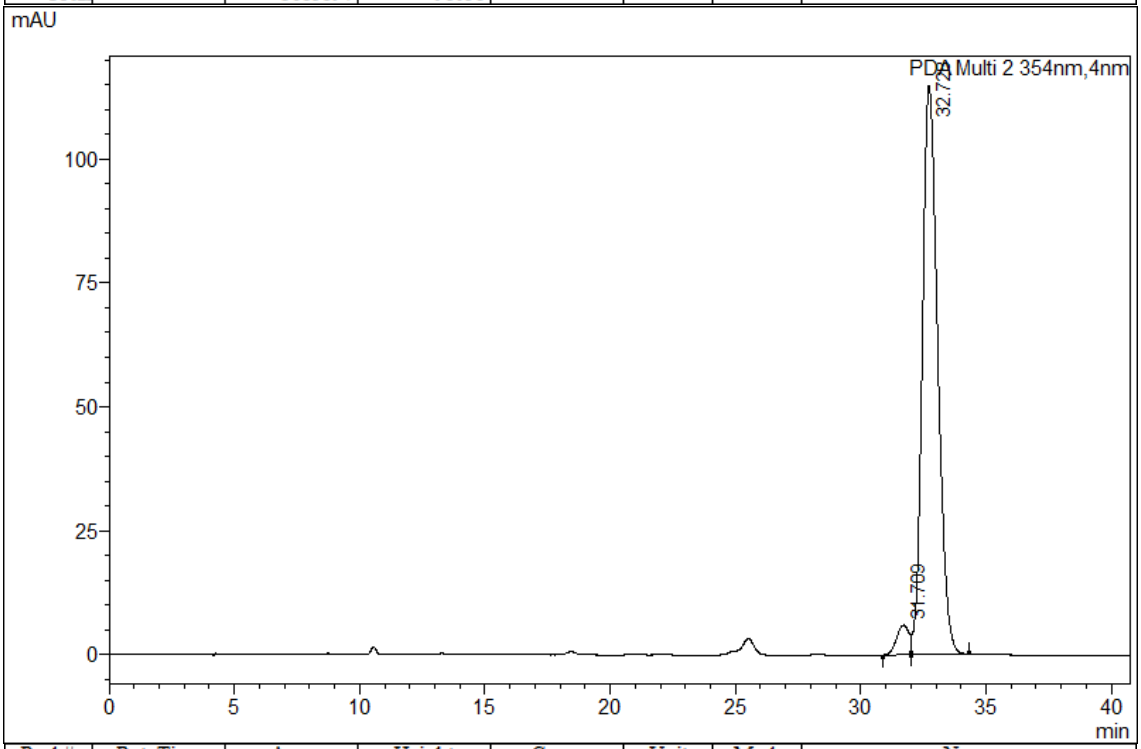
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	6.104	2329076	343708	0.000		M	
2	6.661	2353961	303272	0.000		V M	
Total		4683036	646980				



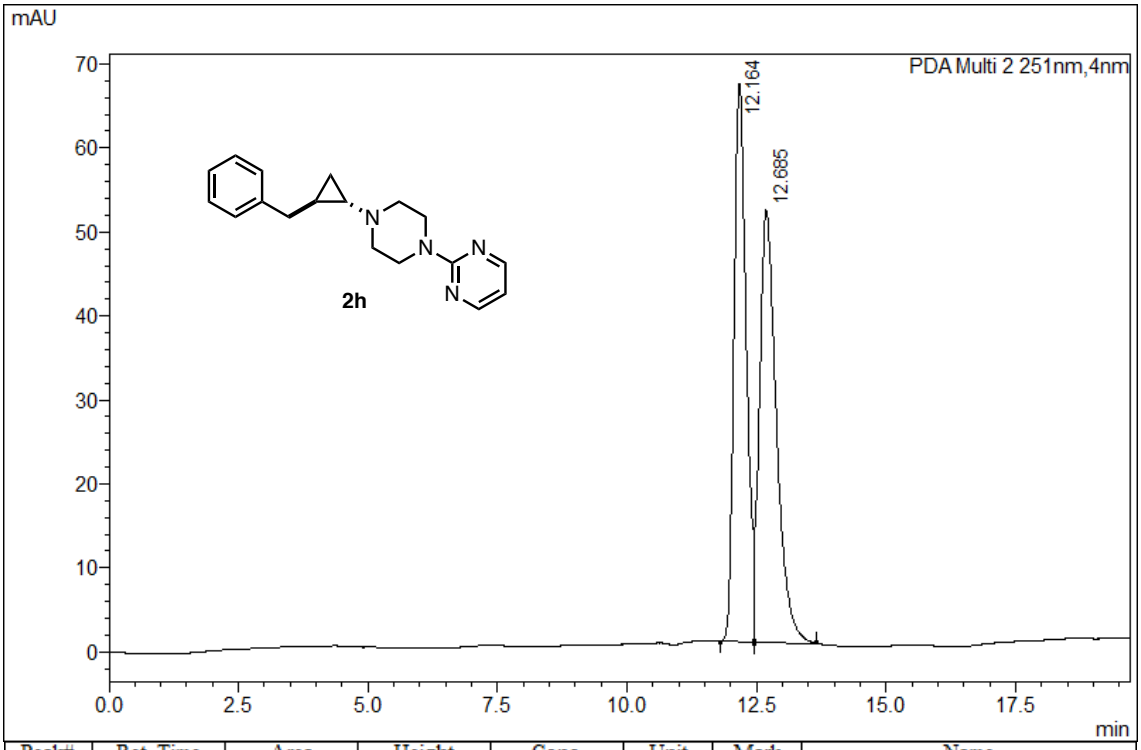
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	6.297	11216732	1184626	0.000		M	
2	6.825	688377	97345	0.000		M	
Total		11905109	1281970				



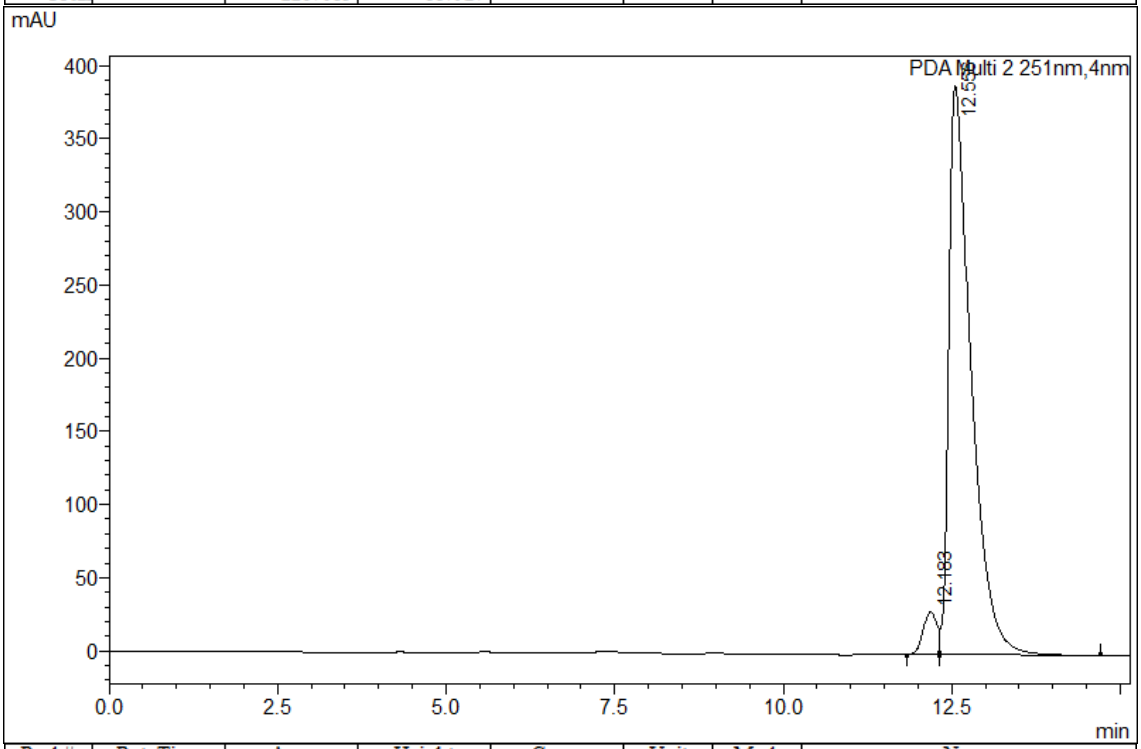
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	30.944	1830287	46978	0.000			
2	32.526	1855607	44073	0.000		V	
Total		3685894	91051				



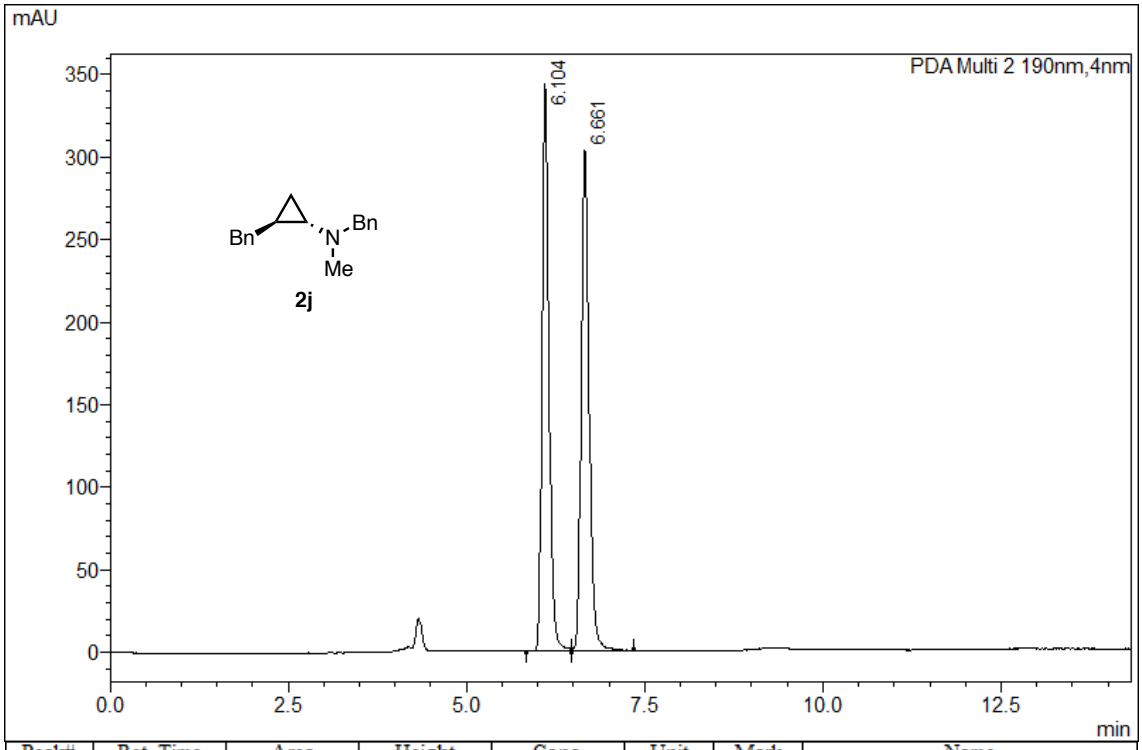
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	31.709	209501	5983	0.000		M	
2	32.728	4899925	114875	0.000		SV M	
Total		5109426	120858				



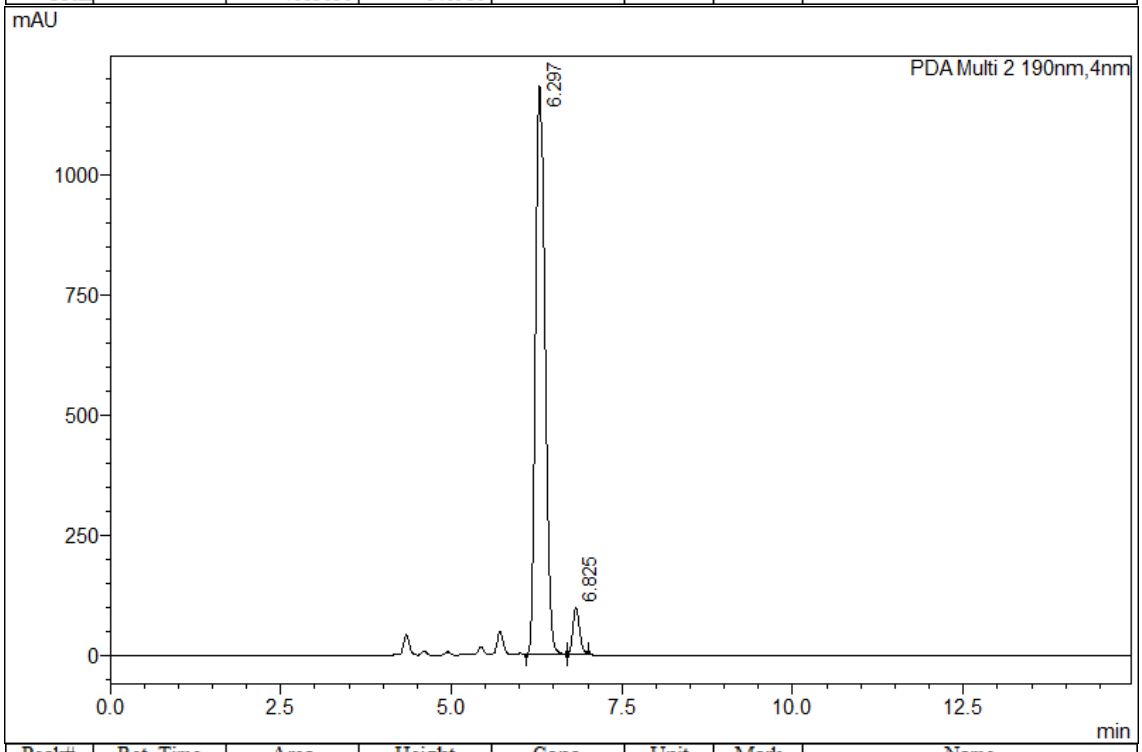
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	12.164	1098052	66457	0.000			
2	12.685	1168962	51470	0.000		V M	
Total		2267015	117927				



Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	12.183	402791	28752	0.000			
2	12.556	8915842	388799	0.000		V	
Total		9318632	417551				



Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	6.104	2329076	343708	0.000		M	
2	6.661	2353961	303272	0.000		V M	
Total		4683036	646980				



Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	6.297	11216732	1184626	0.000		M	
2	6.825	688377	97345	0.000		M	
Total		11905109	1281970				