Supporting Information

Synthesis of *trans*-2-Substituted-Cyclopropylamines from α-Chloroaldehydes

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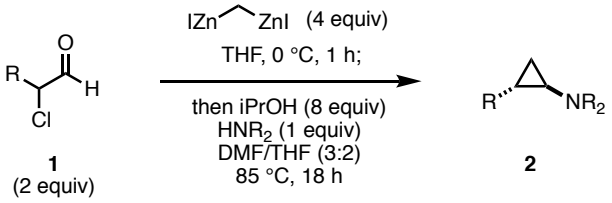
A. General information

Unless otherwise noted, all reactions were set up on the benchtop and run under an atmosphere of argon or nitrogen using flame-dried glassware and anhydrous solvents. Anhydrous tetrahydrofuran (THF) was dried using a PureSolv MD 5 solvent purification system and stored over activated 4Å molecular sieves for three days before use. Anhydrous dimethylformamide (DMF) was purchased from Sigma–Aldrich (Sure/Seal bottle) and was 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. Zinc chloride was purchased from Sigma–Aldrich. Bis(iodozinco)methane was prepared according to the procedure reported by Nomura et al.[1] *N*-Chlorosuccinimide (NCS) was purchased from Acros and was recrystallized from acetic acid (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 8-mL or 16-mL Fisherbrand threaded tubes (manufacturer no. FB7377013100 and FB7375016125; Fisher catalog no. 14-957-76A and 14-959-35A, respectively) 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.

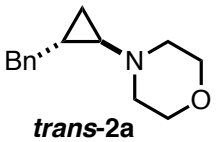
^{1}H and ^{13}C NMR spectra were recorded on Varian MercuryPlus 400 MHz or Bruker AvanceIII 400 MHz spectrometers. IR spectra were obtained on a Perkin-Elmer Spectrum 100 instrument equipped with a single-bounce diamond/ZnSe ATR accessory as solids or thin films. Melting points were obtained on a Fisher-Johns 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.

B. Procedures for the synthesis of cyclopropylamines



General procedure: To a 16-mL threaded tube equipped with a magnetic stir bar was added α-chloroaldehyde (0.40 mmol, 2.0 equiv). The tube was capped with a size-19 rubber septum, sealed rigorously with electrical tape, and was evacuated and backfilled with nitrogen (×3) using Schlenk techniques (the septum was pierced with a needle connected to the Schlenk line with Tygon tubing). The sealed tube was cooled to 0 °C and a solution of bis(iodozincio)methane in THF (typically 0.22–0.25 M, 0.80 mmol, 4.0 equiv) was then added slowly under an inert atmosphere. The solution was allowed to stir for an hour at 0 °C, followed by the addition of anhydrous isopropanol (1.6 mmol, 8.0 equiv) under a balloon of argon or N_2 to relieve pressure. The reaction solution was then warmed to room temperature, followed by the addition of anhydrous DMF (1.5x volume of THF used) and the amine (0.2 mmol, 1.0 equiv). If the amine was a solid, it was added in a minimal amount of anhydrous THF. The top of the septum was sealed with a square of electrical tape, and then the reaction solution was heated in a pre-heated oil bath at 85 °C. After 18 h, the reaction solution was allowed to cool, opened to air, and quenched with sat. aq. NH_4Cl solution. The solution was extracted with EtOAc (×3), the organic fractions combined and washed with sat. aq. NaHCO3 (×1), brine (×5), dried over $MgSO_4$, and concentrated under reduced pressure. The ratio of diastereomers (*trans*:*cis* cyclopropylamines) was determined by ^1H NMR of the crude residue. The crude residue was then purified by flash column chromatography to isolate the *trans*-cyclopropylamine product.

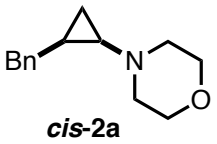
Note: if desired, the cyclopropylamine product can be prepared in low d.r. (~5:1) if no DMF is added to the solution. The *cis*- and *trans*-diastereomers are typically easily separated by column chromatography on silica gel.



***trans*-2a**

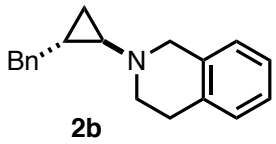
4-(*trans*-2-benzylcyclopropyl)morpholine (*trans*-2a): According to the general procedure, cyclopropylamine ***trans*-2a** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), morpholine (18 μL, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (20/80 EtOAc/hexanes) to yield ***trans*-2a** as a pale yellow oil.
Trial 1: 34 mg isolated (0.158 mmol, 76%; >20:1 d.r.)
Trial 2: 37 mg isolated (0.172 mmol, 83%; >20:1 d.r.)
Average yield: 80%

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.32–7.26 (m, 2H), 7.23–7.20 (m, 3H), 3.62–3.59 (m, 4H), 2.64 (dd, J = 14.5, 6.4 Hz, 1H), 2.56–2.37 (m, 5H), 1.56–1.54 (m, 1H), 1.16–1.05 (m, 1H), 0.72–0.67 (m, 1H), 0.47–0.42 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K) δ_C 141.7, 128.5, 128.4, 126.1, 67.1, 53.6, 46.0, 38.7, 21.1, 13.2 ppm.
NMR data is consistent with a previous literature report.[2]



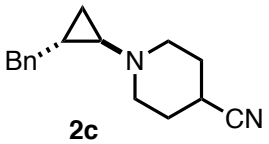
***cis*-2a**

4-(*cis*-2-benzylcyclopropyl)morpholine (*cis*-2a): According to the general procedure, cyclopropylamine ***cis*-2a** was prepared using the following amounts of reagent (7 side-by-side reactions): 2-chloro-3-phenylpropanal (100 mg, 0.59 mmol, 2.0 equiv), bis(iodozincio)methane (5.0 mL of a 0.24 M solution in THF, 1.19 mmol, 4.0 equiv), isopropanol (180 μL, 2.37 mmol, 8.0 equiv), and morpholine (26 μL, 0.30 mmol, 1.0 equiv). The crude residues were combined, extracted and washed as described in the general procedure and purified by flash column chromatography (gradient of 5/95 to 20/80 EtOAc/hexanes) to yield ***cis*-2a** as a pale yellow oil (85 mg, 0.391 mmol, 19%).
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.29–7.26 (m, 2H), 7.21–7.19 (m, 3H), 3.68–3.66 (m, 4H), 2.94 (dd, J = 15.0, 5.9 Hz, 1H), 2.74 (dd, J = 15.0, 8.4 Hz, 1H), 2.56–2.46 (m, 4H), 1.79–1.75 (m, 1H), 1.17–1.06 (m, 1H), 0.72–0.67 (m, 1H), 0.25–0.21 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K) δ_C 142.9, 128.4, 128.3, 125.7, 67.2, 54.1, 43.2, 33.1, 19.1, 11.1 ppm.
NMR data is consistent with a previous literature report.[2]



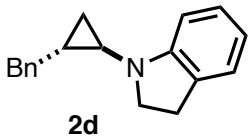
2b

2-(*trans*-2-benzylcyclopropyl)-1,2,3,4-tetrahydroisoquinoline (2b): According to the general procedure, cyclopropylamine **2b** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), 1,2,3,4-tetrahydroisoquinoline (26 μL, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (10/90 EtOAc/hexanes) to yield **2b** as a pale yellow oil.
Trial 1: 32 mg isolated (0.120 mmol, 58%; 10:1 d.r.)
Trial 2: 39 mg isolated (0.148 mmol, 71%, 13:1 d.r.)
Average yield: 65%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.33–7.25 (m, 5H), 7.15–7.03 (m, 3H), 6.97–6.95 (m, 1H), 3.76–3.58 (m, 2H), 2.89–2.76 (m, 4H), 2.75–2.62 (m, 1H), 2.52–2.46 (m, 1H), 1.75–1.72 (m, 1H), 1.27–1.24 (m, 1H), 0.86–0.76 (m, 1H), 0.60–0.50 (m, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K) δ_C 141.7, 134.9, 134.3, 128.8, 128.5, 128.4, 126.7, 126.1, 126.0, 125.6, 55.8, 50.9, 45.2, 38.7, 28.9, 21.5, 13.7 ppm; **IR** (neat): 3063, 3024, 2911, 2787, 2738, 1603, 1584, 1494, 1453, 1428, 1379, 1278, 1239, 1217, 1196, 1172, 1150, 1082, 1029, 1010, 935, 738, 696 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{19}H_{22}N$ (M+H) 264.1747, found 264.1748.



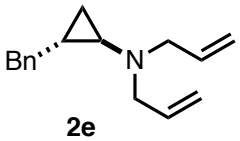
2c

1-(*trans*-2-benzylcyclopropyl)piperidine-4-carbonitrile (2c): According to the general procedure, cyclopropylamine **2c** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 µL, 1.66 mmol, 8.0 equiv), piperidine-4-carbonitrile (23 µL, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (gradient of 5-20% EtOAc/hexanes) to yield **2c** as a pale yellow oil.
Trial 1: 36 mg isolated (0.149 mmol, 72%; >20:1 d.r.)
Trial 2: 35 mg isolated (0.147 mmol, 71%; >20:1 d.r.)
Average yield: 72%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.32–7.27 (m, 2H), 7.23–7.19 (m, 3H), 2.77–2.54 (m, 4H), 2.44–2.29 (m, 3H), 1.87–1.70 (m, 4H), 1.58–1.54 (m, 1H), 1.11–1.03 (m, 1H), 0.71–0.67 (m, 1H), 0.50–0.46 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.6, 128.5, 128.4, 126.1, 121.9, 51.3, 45.7, 38.6, 28.7, 26.2, 21.6, 13.6 ppm; **IR** (neat): 3065, 3029, 2949, 2930, 2854, 2804, 2752, 2672, 2240, 1604, 1496, 1454, 1382, 1290, 1254, 1200, 1177, 1149, 1121,1077, 1040, 1031, 948, 922, 917, 760, 743, 699 cm^{-1} **; HRMS** *m/z* (DART): calcd for $C_{16}H_{21}N_2$ (M+H) 241.1699, found 241.1698.



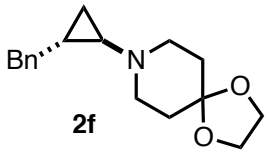
2d

1-(*trans*-2-benzylcyclopropyl)indoline (2d): According to the general procedure, cyclopropylamine **2d** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 µL, 1.66 mmol, 8.0 equiv), indoline (23 µL, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (20/80 EtOAc/hexanes) to yield **2d** as a pale yellow oil.
Trial 1: 36 mg isolated (0.144 mmol, 70%; 20:1 d.r.)
Trial 2: 34 mg isolated (0.136 mmol, 65%; >20:1 d.r.)
Average yield: 68%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.35–7.27 (m, 5H), 7.05–7.00 (m, 1H), 6.98–6.96 (m, 1H), 6.68–6.65 (m, 1H), 6.51–6.49 (m, 1H), 3.30–3.23 (m, 2H), 2.86 (t, J = 8.0 Hz, 2H), 2.70–2.68 (m, 1H), 2.67–2.64 (m, 1H), 2.03–2.00 (m, 1H), 1.33–1.26 (m, 1H), 0.94–0.90 (m, 1H), 0.69–0.66 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K) δ_C 153.0, 141.2, 130.5, 128.8, 128.6, 127.3, 126.3, 124.5, 118.5, 108.6, 54.1, 38.5, 37.2, 28.7, 20.7, 13.5 ppm.
NMR data is consistent with a previous literature report.[2]



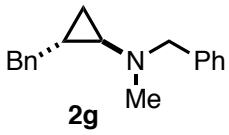
2e

1-(*trans*-2-benzylcyclopropyl)diallylamine (2e): According to the general procedure, cyclopropylamine **2e** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 µL, 1.66 mmol, 8.0 equiv), diallylamine (26 µL, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (10/90 EtOAc/hexanes) to yield **2e** as a pale yellow oil.
Trial 1: 21 mg isolated (0.093 mmol, 45%; 20:1 d.r.)
Trial 2: 20 mg isolated (0.087 mmol, 42%; >20:1 d.r.)
Average yield: 44%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.31–7.26 (m, 2H), 7.24–7.17 (m, 3H), 5.84 (ddt, J = 17.0, 10.2, 6.7 Hz, 2H), 5.14–5.05 (m, 4H), 3.23–3.06 (m, 4H), 2.61 (dd, J = 14.6, 6.6 Hz, 1H) 2.46 (dd, J = 14.6, 7.5 Hz, 1H), 1.72–1.69 (m, 1H), 1.18–1.08 (m, 1H), 0.75–0.72 (m, 1H), 0.51–0.47 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K) δ_C 141.6, 135.3, 128.6, 128.4, 126.0, 117.5, 57.4, 43.1, 38.5, 22.2, 14.6 ppm. **IR** (neat): 3072, 3027, 2920, 2853, 1743, 1641, 1604, 1495, 1454, 1417, 1363, 1223, 1158, 1029, 994, 917, 741, 698 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{16}H_{22}N$ (M+H) 228.1747; found 228.1741;



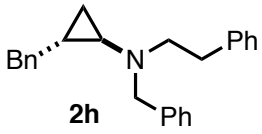
2f

8-(*trans*-2-Benzylcyclopropyl)-1,4-dioxa-8-azaspiro[4.5]decane (2f): According to the general procedure, cyclopropylamine **2f** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 µL, 1.66 mmol, 8.0 equiv), 4-piperidone ethylene ketal (27 µL, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (20/80 EtOAc/hexanes) to yield **2f** as a pale yellow oil.
Trial 1: 23 mg isolated (0.083 mmol, 40%; 20:1 d.r.)
Trial 2: 43 mg isolated (0.158 mmol, 76%, 20:1 d.r.)
Average yield: 58%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.31–7.26 (m, 2H), 7.23–7.16 (m, 3H), 3.93 (s, 4H), 2.67–2.63 (m, 1H), 2.61–2.49 (m, 4H), 2.40 (dd, J = 14.4, 7.9 Hz, 1H), 1.66–1.63 (m, 4H), 1.57–1.54 (m, 1H), 1.15–1.04 (m, 1H), 0.71–0.67 (m, 1H), 0.47–0.43 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K) δ_C 141.7, 128.5, 128.4, 126.0, 107.4, 64.3, 51.3, 45.3, 38.7, 34.7, 21.6, 13.8 ppm.
NMR data is consistent with a previous literature report.[2]



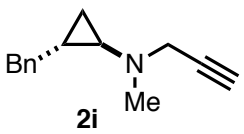
2g

***N*-(*trans*-2-benzylcyclopropyl)-*N*-benzylmethylamine (2g):** According to the general procedure, cyclopropylamine **2g** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), *N*-methylbenzylamine (27 μL, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (20/80 EtOAc/hexanes) to yield **2g** as a pale yellow oil.
Trial 1: 35 mg isolated (0.141 mmol, 68%; 20:1 d.r.)
Trial 2: 40 mg isolated (0.159 mmol, 77%, 14:1 d.r.)
Average yield: 73%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.56–6.97 (m, 10H), 3.66 (d, J = 13.0 Hz, 1H), 3.58 (d, J = 13.0 Hz, 1H), 2.61–2.49 (m, 2H), 2.23–2.16 (s, 3H), 1.70–1.59 (m, 1H), 1.19–1.14 (m, 1H), 0.78–0.73 (m, 1H), 0.53–0.49 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K) δ_C 141.7, 138.7, 129.5, 128.5, 128.4, 128.2, 126.9, 126.0, 62.2, 45.7, 41.9, 38.6, 22.6, 14.6 ppm.
NMR data is consistent with a previous literature report.[2]



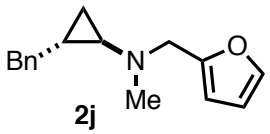
2h

***N*-(*trans*-2-benzylcyclopropyl)-*N*-benzyl-2-phenethylamine (2h):** According to the general procedure, cyclopropylamine **2h** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), *N*-benzyl-2-phenethylamine (44 μL, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (20/80 EtOAc/hexanes) to yield **2h** as a pale yellow oil.
Trial 1: 37 mg isolated (0.108 mmol, 52%; >20:1 d.r.)
Trial 2: 41 mg isolated (0.119 mmol, 57%; >20:1 d.r.)
Average yield: 55%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.37–7.17 (m, 13H), 7.07–7.05 (m, 2H), 3.87–3.82 (m, 1H), 3.77–3.72 (m, 1H), 2.78–2.75 (m, 4H), 2.64–2.54 (m, 2H), 1.87–1.84 (m, 1H), 1.18–1.15 (m, 1H), 0.78–0.70 (m, 1H), 0.61–0.45 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K) δ_C 141.6, 140.9, 139.1, 129.3, 128.8, 128.5, 128.4, 128.3, 128.1, 126.9, 126.0, 125.8, 59.3, 56.2, 43.5, 38.7, 33.2, 22.8, 14.8 ppm; **IR** (neat): 3085, 3062, 3025, 2921, 1604, 1496, 1455, 1132, 1077, 1030, 935, 735, 696 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{25}H_{28}N$ (M+H) found 342.2216; found 342.2218.



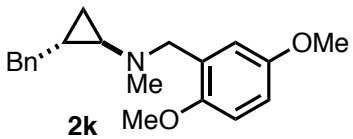
2i

***N*-(*trans*-2-benzylcyclopropyl)-*N*-methylpropargylamine (2i):** According to the general procedure, cyclopropylamine **2i** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), *N*-methylpropargylamine (18 μL, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (20/80 EtOAc/hexanes) to yield **2i** as a pale yellow oil.
Trial 1: 27 mg isolated (0.135 mmol, 65%; >20:1 d.r.)
Trial 2: 24 mg isolated (0.118 mmol, 57%; 20:1 d.r.)
Average yield: 61%
^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ_H 7.31–7.27 (m, 2H), 7.26–7.17 (m, 3H), 3.34 (dd, J =16.8, 2.4 Hz, 1H), 3.29 (dd, J = 16.8, 2.4 Hz, 1H), 2.60 (dd, J = 14.5, 6.6 Hz, 1H), 2.48 (dd, J = 14.5, 7.6 Hz, 1H), 2.33 (s, 3H), 2.23–2.21 (m, 1H), 1.84–1.81 (m, 1H), 1.16–1.05 (m, 1H), 0.71–0.67 (m, 1H), 0.54–0.42 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K) δ_C 141.7, 128.5, 128.4, 126.1, 79.3, 72.9, 45.7, 43.8, 41.3, 38.6, 22.5, 14.3 ppm. **IR** (neat): 2925, 2854, 1738, 1609, 1497, 1454, 1369, 1225, 1220, 1160, 747, 699 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{14}H_{18}N$ (M+H) 200.1434; found 200.1433.



2j

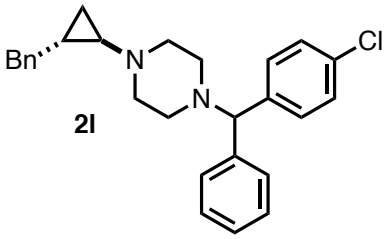
***N*-(*trans*-2-benzylcyclopropyl)-*N*-(furan-2-ylmethyl)methylamine (2j):** According to the general procedure, cyclopropylamine **2j** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal **1a** (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), *N*-methyl-2-furanmethanamine (24 μL, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (20/80 EtOAc/hexanes) to yield **2j** as a pale yellow oil.
Trial 1: 24 mg isolated (0.099 mmol, 50%; 9.6:1 d.r.)
Trial 2: 25 mg isolated (0.105 mmol, 51%; 11:1 d.r.)
Average yield: 51%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.44–7.37 (m, 1H), 7.37–7.18 (m, 5H), 6.38–6.30 (m, 1H), 6.20–6.11 (m, 1H), 3.71–3.57 (m, 2H), 2.55 (d, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.63–1.60 (m, 1H), 1.22–1.07 (m, 1H), 0.75–0.71 (m, 1H), 0.55–0.44 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 152.5, 142.0, 141.7, 128.6, 128.4, 126.0, 110.1, 108.6, 53.7, 45.0, 42.2, 38.6, 22.0, 14.3 ppm; **IR** (neat): 3063, 3027, 2917, 2842, 2777, 1606, 1497, 1455, 1361, 1338, 1221, 1149, 1076, 1013, 917, 806, 728, 699 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{16}H_{20}NO$ (M+H): 242.1539; found 242.1535; **R_f** (9:1 hexanes/EtOAc; $KMnO_4$): 0.21.



2k

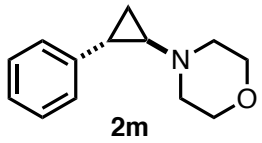
***N*-(*trans*-2-benzylcyclopropyl)-*N*-(2,5-dimethoxybenzyl)methylamine (2k):** According to the general procedure, cyclopropylamine **2k** was prepared using the following amounts of reagent: 2-

chloro-3-phenylpropanal (0.80 mL of a 0.50 M stock solution in THF, 0.40 mmol, 2.0 equiv), bis(iodozincio)methane (2.3 mL of a 0.35 M solution in THF, 0.80 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), 1-(2,5-dimethoxyphenyl)-*N*-methylmethanamine (36 μL, 0.20 mmol, 1.0 equiv), and DMF (4.7 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (gradient of 0 – 30% EtOAc/hexanes) to yield **2k** as a pale yellow oil.
Trial 1: 30 mg isolated (0.096 mmol, 48%; 9.4:1 d.r.)
Trial 2: 34 mg isolated (0.109 mmol, 53%, 9.1:1 d.r.)
Average yield: 51%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.33–7.14 (m, 5H), 6.87–6.71 (m, 3H), 3.76 (s, 6H), 3.64 (d, J = 13.2 Hz, 1H), 3.57 (d, J = 13.3 Hz, 1H), 2.61–2.45 (m, 2H), 2.21 (s, 3H), 1.71–1.63 (m, 1H), 1.21–1.08 (m, 1H), 0.77–0.68 (m, 1H), 0.49–0.40 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 153.5, 152.3, 141.9, 128.5, 128.4, 128.3, 125.9, 117.2, 112.3, 111.7, 56.2, 55.8, 55.8, 46.1, 42.2, 38.6, 22.3, 14.5 ppm; **HRMS** *m/z* (DART): calcd for $C_{20}H_{26}NO_2$ (M+H): 312.1958; found 312.1959; **IR** (neat): 3062, 3027, 2999, 2943, 2908, 2833, 2777, 1604, 1592, 1496, 1463, 1453, 1363, 1272, 1213, 1179, 1156, 1048, 1028, 934, 876, 801, 741, 698 cm^{-1}; **R_f** (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.15.



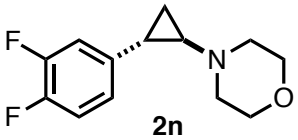
2l

1-(*trans*-2-benzylcyclopropyl)-4-[(4-chlorophenyl)phenylmethyl]piperazine (2l): According to the general procedure, cyclopropylamine **2l** was prepared using the following amounts of reagent: 2-chloro-3-phenylpropanal (70 mg, 0.42 mmol, 2.0 equiv), bis(iodozincio)methane (3.3 mL of a 0.25 M solution in THF, 0.83 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), 1-[(4-chlorophenyl)phenylmethyl]piperazine (60 mg, 0.21 mmol, 1.0 equiv), and DMF (5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (20/80 EtOAc/hexanes) to yield **2l** as a pale yellow oil.
Trial 1: 60 mg isolated (0.145 mmol, 70%; >20:1 d.r.)
Trial 2: 61 mg isolated (0.147 mmol, 71%; 20:1 d.r.)
Average yield: 71%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ_H 7.36–7.30 (m, 4H), 7.30–7.26 (m, 2H), 7.26–7.14 (m, 8H), 4.18 (s, 1H), 2.73–2.28 (m, 10H), 1.60–1.54 (m, 1H), 1.24–1.11 (m, 1H), 0.83–0.71 (m, 1H), 0.49–0.44 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K) δ_C 142.2, 141.5, 141.4, 132.7, 129.3, 129.3, 128.8, 128.8, 128.7, 128.7, 128.5, 128.5, 128.4, 128.0, 128.0, 127.3, 126.1, 126.1, 75.5, 53.4, 51.4, 45.6, 38.6, 20.9, 13.1 ppm. **IR** (neat): 3063, 3028, 2931, 2807, 1746, 1664, 1602, 1587, 1488, 1453, 1379, 1282, 1207, 1139, 1090, 1011, 919, 846, 805, 758, 743, 720, 698, 624 cm^{-1}. **HRMS** *m/z* (DART): calcd for $C_{27}H_{30}ClN_2$ (M+H) 417.2092; found 417.2085.



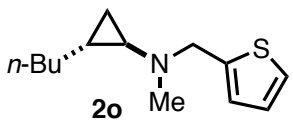
2m

4-(*trans*-2-phenylcyclopropyl)morpholine (2m): According to the general procedure, cyclopropylamine **2m** was prepared using the following amounts of reagent: 2-chloro-2-phenylacetaldehyde (31 mg, 0.20 mmol, 2.0 equiv), bis(iodozincio)methane (2.2 mL of a 0.18 M solution in THF, 0.40 mmol, 4.0 equiv), isopropanol (62 μL, 0.80 mmol, 8.0 equiv), morpholine (8.7 μL, 0.10 mmol, 1.0 equiv), and DMF (3.3 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (40% EtOAc/hexanes) to yield **2m** as a colourless oil.
Trial 1: 12 mg isolated (0.058 mmol, 58%; >20:1 d.r.)
Trial 2: 12 mg isolated (0.060 mmol, 60%, >20:1 d.r.)
Average yield: 59%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.29–7.03 (m, 5H), 3.73–3.66 (m, 4H), 2.67–2.65 (m, 4H), 2.02–1.98 (m, 1H), 1.92–1.89 (m, 1H), 1.14–1.10 (m, 1H), 0.98–0.94 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 142.1, 128.4, 126.2, 125.8, 67.1, 53.6, 49.2, 24.4, 16.3 ppm.
NMR data is consistent with a previous literature report.[2]



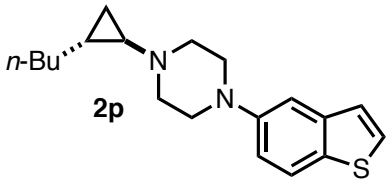
2n

4-(*trans*-2-(3,4-difluorophenyl)cyclopropyl)morpholine (2n): According to the general procedure, cyclopropylamine **2n** was prepared using the following amounts of reagent: 2-chloro-2-(3,4-difluorophenyl)acetaldehyde (38 mg, 0.20 mmol, 2.0 equiv), bis(iodozincio)methane (2.2 mL of a 0.18 M solution in THF, 0.40 mmol, 4.0 equiv), isopropanol (62 μL, 0.80 mmol, 8.0 equiv), morpholine (8.7 μL, 0.10 mmol, 1.0 equiv), and DMF (3.3 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (gradient of 20-40% EtOAc/hexanes) to yield **2n** as a yellow oil.
Trial 1: 8.7 mg isolated (0.036 mmol, 36%; 17:1 d.r.)
Trial 2: 8.8 mg isolated (0.037 mmol, 37%, 12:1 d.r.)
Average yield: 37%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.05–6.98 (m, 1H), 6.84–6.75 (m, 2H), 3.69–3.67 (m, 4H), 2.65–2.63 (m, 4H), 1.96 (ddd, J = 9.4, 5.7, 2.9 Hz, 1H), 1.84 (ddd, J = 7.3, 4.4, 3.2 Hz, 1H), 1.16–1.12 (m, 1H), 0.92–0.88 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 150.3 (dd, J = 247.0, 12.8 Hz), 148.8 (dd, J = 245.9, 12.7 Hz), 139.0, 122.1 (dd, J = 6.0, 3.4 Hz), 117.1 (dd, J = 17.1, 0.8 Hz), 115.0 (d, J = 17.3 Hz), 67.0, 53.5, 49.2, 23.6, 16.3 ppm. **IR** (neat): 2924, 2813, 2857, 1719, 1606, 1516, 1451, 1427, 1275, 1263, 1210, 1182, 1146, 1113, 1069, 1041, 1026, 993, 963, 929, 909, 869, 814, 772, 716, 699, 628 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{13}H_{16}F_2NO$ (M+H) 240.1195; found 240.1196.



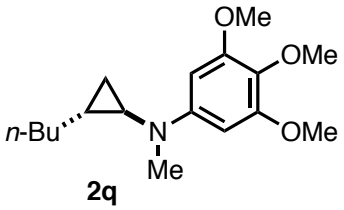
2o

***trans*-2-Butyl-*N*-methyl-*N*-(thiophen-2-ylmethyl)cyclopropan-1-amine (2o):** According to the general procedure, cyclopropylamine **2o** was prepared using the following amounts of reagent: 2-chlorohexanal (0.80 mL of a 0.50 M stock solution in THF, 0.40 mmol, 2.0 equiv), bis(iodozincio)methane (2.3 mL of a 0.35 M solution in THF, 0.80 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), *N*-methyl-1-(thiophen-2-yl)methanamine (24 μL, 0.20 mmol, 1.0 equiv), and DMF (4.7 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (gradient of 0 – 20% EtOAc/hexanes) to yield **2o** as a colourless oil (31 mg isolated, 0.139 mmol, 70%; 16:1 d.r.).
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.23–7.18 (m, 1H), 6.98–6.92 (m, 1H), 6.92–6.86 (m, 1H), 3.88 (s, 2H), 2.30 (s, 3H), 1.48–1.45 (m, 1H), 1.43–1.07 (m, 5H), 0.99–0.77 (m, 5H), 0.66–0.57 (m, 1H), 0.34–0.25 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.4, 126.5, 126.3, 124.8, 55.8, 45.2, 41.6, 32.5, 31.7, 22.7, 21.4, 14.3, 14.2 ppm; **HRMS** *m/z* (DART): calcd for $C_{13}H_{22}NS$ (M+H): 224.1468; found 224.1473; **IR** (neat): 3071, 2956, 2922, 2854, 2780, 1457, 1368, 1341, 1241, 1223, 1170, 1039, 917, 854, 825, 694 cm^{-1}; **R_f** (7:3 hexanes/EtOAc; UV/$KMnO_4$): 0.82.



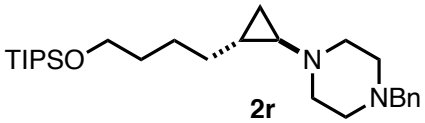
2p

1-(Benzo[b]thiophen-5-yl)-4-(trans-2-butylcyclopropyl)piperazine (2p): According to the general procedure, cyclopropylamine **2p** was prepared using the following amounts of reagent: 2-chlorohexanal (0.80 mL of a 0.50 M stock solution in THF, 0.40 mmol, 2.0 equiv), bis(iodozincio)methane (2.3 mL of a 0.35 M solution in THF, 0.80 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), 1-(benzo[b]thiophen-5-yl)piperazine (44 mg, 0.20 mmol, 1.0 equiv), and DMF (4.7 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (gradient of 0 – 20% EtOAc/hexanes) to yield **2p** as an off-white solid.
Trial 1: 30 mg isolated (0.095 mmol, 48%; >20:1 d.r.)
Trial 2: 44 mg isolated (0.140 mmol, 70%; >20:1 d.r.)
Average yield: 59%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.73 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 5.4 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 5.4 Hz, 1H), 7.09 (dd, J = 8.8, 2.4 Hz, 1H), 3.21–3.16 (m, 4H), 2.81–2.79 (m, 4H), 1.37–1.24 (m, 4H), 1.17–1.05 (m, 1H), 0.99–0.79 (m, 6H), 0.65–0.61 (m, 1H), 0.33–0.29 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 149.5, 140.8, 131.9, 127.0, 123.9, 122.8, 116.9, 109.9, 53.4, 50.4, 45.9, 32.5, 31.8, 22.7, 20.0, 14.2, 13.1 ppm; **HRMS** *m/z* (DART): calcd for $C_{19}H_{27}N_2S$ (M+H) 315.1889; found 315.1888; **IR** (neat): 3067, 2957, 2914, 2881, 2852, 2830, 1597, 1550, 1505, 1448, 1423, 1378, 1352, 1310, 1267, 1238, 1186, 1148, 1109, 1062, 1028, 965, 909, 889, 839, 815, 783, 743, 690, 668 cm^{-1}; **m.p.**: 56–59 ºC; **R_f** (7:3 hexanes/EtOAc; UV): 0.74.



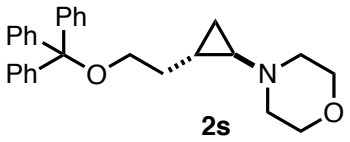
2q

***N*-(trans-2-butylcyclopropyl)-3,4,5-trimethoxy-*N*-methylaniline (2q):** According to the general procedure, cyclopropylamine **2q** was prepared using the following amounts of reagent: 2-chlorohexanal (0.80 mL of a 0.50 M stock solution in THF, 0.40 mmol, 2.0 equiv), bis(iodozincio)methane (2.3 mL of a 0.35 M solution in THF, 0.80 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), 3,4,5-trimethoxy-N-methylaniline (36 μL, 0.20 mmol, 1.0 equiv), and DMF (4.7 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (gradient of 0 – 20% EtOAc/hexanes) to yield **2q** as a colourless oil.
Trial 1: 25 mg isolated (0.085 mmol, 43%; >20:1 d.r.)
Trial 2: 27 mg isolated (0.092 mmol, 46%; >20:1 d.r.)
Average yield: 45%
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ_H 6.17 (s, 2H), 3.86 (s, 6H), 3.78 (s, 3H), 2.94 (s, 3H), 2.09–2.06 (m, 1H), 1.67–1.57 (m, 2H), 1.48–1.32 (m, 3H), 1.20–1.11 (m, 1H), 1.01–0.84 (m, 4H), 0.80–0.73 (m, 1H), 0.64–0.58 (m, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$, 298 K): δ_C 153.6, 147.8, 130.3, 91.7, 61.2, 56.1, 40.7, 39.4, 32.3, 31.3, 22.8, 22.7, 16.2, 14.2 ppm ; **HRMS** *m/z* (DART): calcd for $C_{17}H_{28}NO_3$ 294.2064; found 294.2055; **IR** (neat): 3474 (br), 2955, 2927, 2873, 2858, 1610, 1581, 1511, 1456, 1430, 1262, 1240, 1128, 1011, 802, 763, 732, 641 cm^{-1}; **R_f** (7:3 hexanes/EtOAc; UV): 0.77.



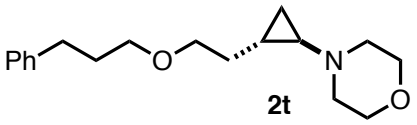
2r

1-Benzyl-4-(*trans*-2-(4-((triisopropylsilyl)oxy)butyl)cyclopropyl)piperazine (2r): According to the general procedure, cyclopropylamine **2r** was prepared using the following amounts of reagent: 2-chloro-6-((triisopropylsilyl)oxy)hexanal (0.80 mL of a 0.50 M stock solution in THF, 0.40 mmol, 2.0 equiv), bis(iodozincio)methane (1.8 mL of a 0.44 M solution in THF, 0.80 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), 1-benzylpiperazine (34 μL, 0.20 mmol, 1.0 equiv), and DMF (3.9 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (gradient of 10 – 40% EtOAc/hexanes) to yield **2r** as a colourless oil.
Trial 1: 54 mg isolated (0.121 mmol, 61%; >20:1 d.r.)
Trial 2: 51 mg isolated (0.115 mmol, 58%, >20:1 d.r.)
Average yield: 60%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.38–7.17 (m, 5H), 3.67–3.64 (m, 2H), 3.50 (s, 2H), 2.74–2.19 (br m, 8H), 1.77–1.22 (m, 7H), 1.17–0.92 (m, 21H), 0.92–0.70 (m, 1H), 0.61–0.50 (m, 1H), 0.29–0.19 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 138.3, 129.4, 128.3, 127.1, 63.6, 63.2, 53.3, 53.1, 45.9, 33.0, 32.7, 25.8, 20.0, 18.2, 13.1, 12.2 ppm; **IR** (neat): 2940, 2893, 2865, 1718, 1463, 1383, 1248, 1102, 1070, 1013, 995, 918, 883, 792, 743, 721, 697, 679, 658, 641 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{27}H_{49}N_2OSi$ (M+H): 445.3609; found 445.3608; **R_f** (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.18.



2s

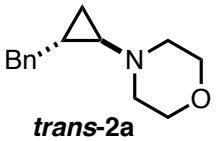
4-(*trans*-2-(2-(trityloxy)ethyl)cyclopropyl)morpholine (2s): According to the general procedure, cyclopropylamine **2s** was prepared using the following amounts of reagent: 2-chloro-4-(trityloxy)butanal (73 mg, 0.20 mmol, 2.0 equiv), bis(iodozincio)methane (2.6 mL of a 0.15 M solution in THF, 0.40 mmol, 4.0 equiv), isopropanol (62 μL, 0.80 mmol, 8.0 equiv), morpholine (8.7 μL, 0.10 mmol, 1.0 equiv), and DMF (3.9 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (gradient of 20-30% EtOAc/hexanes) to yield **2s** as a yellow oil.
Trial 1: 36 mg isolated (0.086 mmol, 86%; >20:1 d.r.)
Trial 2: 34 mg isolated (0.083 mmol, 83%, >20:1 d.r.)
Average yield: 85%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.47–7.41 (m, 6H), 7.32–7.27 (m, 6H), 7.25–7.20 (m, 3H), 3.65–3.55 (m, 4H), 3.21–3.03 (m, 2H), 2.45–2.43 (m, 4H), 1.67–1.58 (m, 1H), 1.42–1.27 (m, 2H), 1.05–0.95 (m, 1H), 0.63–0.59 (m, 1H), 0.32–0.26 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 144.5, 128.9, 127.8, 127.0, 86.6, 67.0, 63.3, 53.6, 46.1, 33.2, 17.2, 12.9 ppm; IR (neat): 3059, 3024, 2922, 2854, 2804, 1597, 1490, 1449, 1265, 1209, 1182, 1154, 1116, 1067, 1034, 1001, 915, 891, 850, 760, 746, 705, 697, 649, 634 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{28}H_{32}NO_2$ (M+H) 414.2428, found 414.2429.



2t

4-(*trans*-2-(2-(3-Phenylpropoxy)ethyl)cyclopropyl)morpholine (2t): According to the general procedure, cyclopropylamine **2t** was prepared using the following amounts of reagent: 2-chloro-4-(3-phenylpropoxy)butanal (1.2 mL of a 0.33 M stock solution in THF, 0.40 mmol, 2.0 equiv), bis(iodozincio)methane (1.8 mL of a 0.44 M solution in THF, 0.80 mmol, 4.0 equiv), isopropanol (127 μL, 1.66 mmol, 8.0 equiv), morpholine (17 μL, 0.20 mmol, 1.0 equiv), and DMF (4.5 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (gradient of 20 – 60% EtOAc/hexanes) to yield **2t** as a colourless oil.
Trial 1: 36 mg isolated (0.124 mmol, 62%; >20:1 d.r.)
Trial 2: 48 mg isolated (0.166 mmol, 83%; >20:1 d.r.)
Average yield: 73%
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ_H 7.44–7.13 (m, 5H), 3.85–3.60 (m, 4H), 3.57–3.40 (m, 4H), 2.82–2.51 (m, 6H), 2.01–1.83 (m, 2H), 1.68–1.54 (m, 1H), 1.50–1.33 (m, 2H), 0.99–0.83 (m, 1H), 0.70–0.59 (m, 1H), 0.40–0.27 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 142.1, 128.5, 128.4, 125.9, 70.6, 70.2, 67.0, 53.7, 45.9, 32.8, 32.5, 31.4, 16.8, 12.6 ppm. **IR** (neat): 3451 (br), 3026, 2932, 2855, 2804, 1604, 1498, 1452, 1372, 1265, 1208, 1185, 1116, 1071, 1045, 912, 890, 849, 746, 700, 612 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{18}H_{28}NO_2$ (M+H): 290.2115; found 290.2107; $\mathbf{R_f}$ (9:1 hexanes/EtOAc; UV/$KMnO_4$): 0.17.

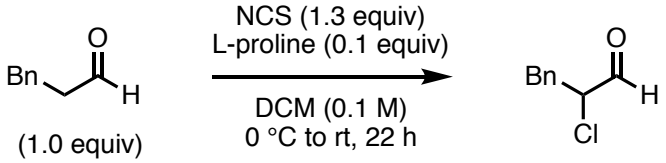
C. Procedure for the synthesis of 2a on 1mmol scale



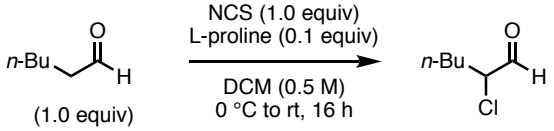
***trans*-2a**

4-(*trans*-2-benzylcyclopropyl)morpholine (*trans*-2a): According to the general procedure, cyclopropylamine ***trans*-2a** was prepared on 1mmol scale using the following amounts of reagent: 2-chloro-3-phenylpropanal (338 mg, 2.00 mmol, 2.0 equiv), bis(iodozincio)methane (16.0 mL of a 0.25 M solution in THF, 4.00 mmol, 4.0 equiv), isopropanol (612 µL, 8.00 mmol, 8.0 equiv), morpholine (87 µL, 1.00 mmol, 1.0 equiv), and DMF (24.0 mL, 1.5x amount of THF used). The crude residue was purified by flash column chromatography (20/80 EtOAc/hexanes) to yield ***trans*-2a** as a pale yellow oil (181 mg isolated, 0.833 mmol, 83%; >20:1 d.r.). NMR data is consistent with the entry above as well as a previous literature report.[2]

D. Preparation of α-chloroaldehydes starting materials

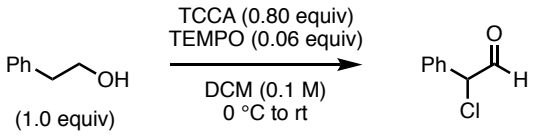


2-Chloro-3-phenylpropanal (1a): To a flame-dried 100-mL flask with a stir bar were added CH_2Cl_2 (44 mL, 0.1 M) and hydrocinnamaldehyde (0.60 mL, 4.6 mmol, 1.0 equiv), and the solution was cooled to 0 °C. At once, *N*-chlorosuccinimide (0.78 g, 5.8 mmol, 1.3 equiv) and L-proline (48 mg, 0.42 mmol, 0.1 equiv) were added. The reaction was stirred at 0 °C for 1 h and at r.t. for an additional 21 h. The reaction was diluted with pentanes (50 mL) and filtered over Celite, and the filtrate was concentrated to yield a colourless oil. The crude product was suspended in pentanes, washed with brine (×1), dried over $MgSO_4$, and concentrated under reduced pressure to yield the product which was used without further purification. **^{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), 3.08 (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.
NMR data is consistent with a previous literature report.[3]

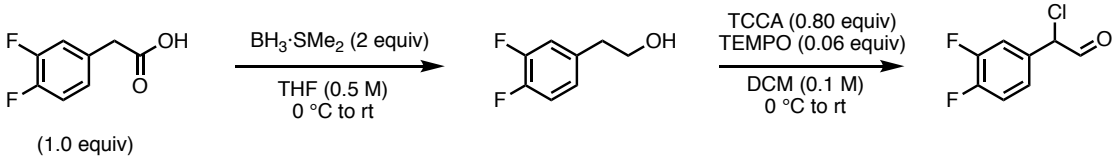


2-Chlorohexanal (S1): To a flame-dried 25-mL flask with a stir bar were added CH_2Cl_2 (12 mL, 0.50 M) and hexanal (0.74 mL, 6.0 mmol, 1.0 equiv), and the solution was cooled to 0 ºC. At once, *N*-chlorosuccinimide (0.80 g, 6.0 mmol, 1.0 equiv) and L-proline (69 mg, 0.60 mmol, 0.10 equiv) were added. The reaction was stirred at 0 ºC for 1 h and at r.t. for an additional 15 h. The reaction was diluted with pentane (20 mL) and filtered over Celite, and the filtrate was concentrated to yield the product as an orange oil (0.71 g, 5.3 mmol, 88%). **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K): δ_H 9.48 (d, J = 2.5, 1H), 4.15 (ddd, J = 8.1, 5.4, 2.5 Hz, 1H), 2.03–1.93 (m, 1H), 1.88–1.78 (m, 1H), 1.55–

1.27 (m, 4H), 0.93–0.90 (m, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$, 298 K): δ_C 195.5, 64.1, 31.9, 27.8, 22.2, 13.9 ppm.
NMR data is consistent with a previous literature report.[4]



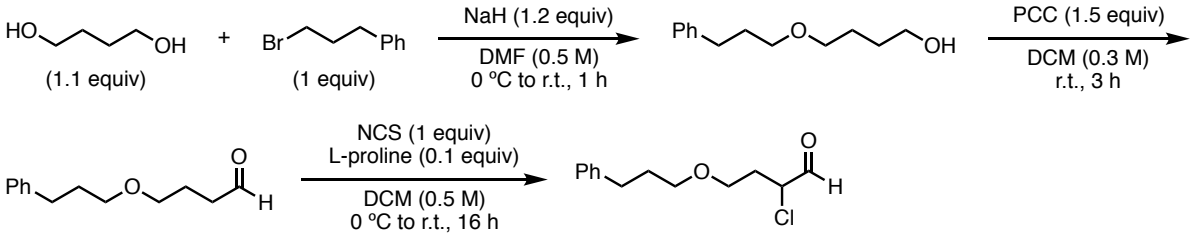
2-Chloro-2-phenylacetaldehyde (S2): To a flame-dried round bottom flask with a stir bar were added 2-phenylethanol (0.48 mL, 4.0 mmol, 1.0 equiv), TEMPO (38 mg, 0.24 mmol, 0.06 equiv), and CH_2Cl_2 (40 mL, 0.1 M), and the solution was cooled to 0 °C. In three portions, trichloroisocyanuric acid (TCCA, 0.74 g, 3.2 mmol, 0.80 equiv) was added over 10 minutes and the reaction mixture was then allowed to warm to room temperature while open to air. After complete consumption of the starting material (as judged by TLC), the solution was diluted with pentanes, filtered, and concentrated under reduced pressure to yield the product as a yellow oil (0.38 g, 2.5 mmol, 61%, 1.00/0.06/0.06 mono-/di-/non-chlorinated product) which was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 9.53 (d, J = 2.8 Hz, 1H), 7.44–7.39 (m, 5H), 5.20 (d, J = 2.8 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 191.4, 133.1, 129.8, 129.4, 128.5, 65.2 ppm.
NMR data is consistent with a previous literature report.[5]



2-(3,4-Difluorophenyl)ethan-1-ol (S3): To a flame-dried round bottom flask with a stir bar were added 3,4-difluorophenylacetic acid (3.0 g, 17 mmol, 1.0 equiv) and anhydrous THF (20 mL, 0.85 M) under an inert atmosphere. The solution was cooled to 0 °C followed by the dropwise addition of $BH_3{\cdot}SMe_2$ (17 mL of a 2.0 M solution in THF, 34 mmol, 2.0 equiv). The reaction was allowed to stir overnight while warming to room temperature, followed by the slow addition of sat. aq. $NaHCO_3$ solution. The organic and aqueous layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (×3). The organic fractions were combined, washed with brine (×2), dried over $MgSO_4$, and concentrated under reduced pressure to yield the product as a colourless oil (2.7 g, 17 mmol, quantitative yield) which was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.13–7.01 (m, 2H), 6.97–6.91 (m, 1H), 3.85 (td, J = 6.4, 5.5 Hz, 2H), 2.82 (t, J = 6.5 Hz, 2H), 1.44 (br s, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 150.2 (dd, J = 247.4, 12.8 Hz), 149.3 (dd, J = 246.7, 12.8 Hz), 135.8 (dd, J = 5.6, 4.0 Hz), 125.0 (dd, J = 6.0, 3.6 Hz), 117.9 (d, J = 17.0 Hz), 117.3 (dd, J = 16.9, 0.7 Hz), 63.4 (d, J = 1.1 Hz), 38.4 (d, J = 1.4 Hz) ppm.
NMR data is consistent with a previous literature report.[2]

2-Chloro-2-(3,4-difluorophenyl)acetaldehyde (S4): To a flame-dried round bottom flask with a stir bar were added 2-(3,4-difluorophenyl)ethan-1-ol (0.60 g, 3.8 mmol, 1.0 equiv), TEMPO (36 mg, 0.23 mmol, 0.06 equiv), and CH_2Cl_2 (38 mL, 0.1 M), and the solution was cooled to 0 °C. In three portions, trichloroisocyanuric acid (TCCA, 0.71 g, 3.0 mmol, 0.80 equiv) was added over 10 minutes and the reaction mixture was then allowed to warm to room temperature while open to air.

After complete consumption of the starting material (as judged by TLC), the solution was diluted with pentanes, filtered, and concentrated under reduced pressure to yield the product as a yellow oil (0.61 g, 3.2 mmol, 85%, 0.98/0.07/0.05 mono-/di-/non-chlorinated product) which was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 9.49 (d, J = 2.4 Hz, 1H), 7.27–7.18 (m, 2H), 7.16–7.11 (m, 1H), 5.17 (d, J = 2.4 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 190.8, 151.1 (dd, J = 245.7, 5.9 Hz), 150.7 (dd, J = 254.0, 15.9 Hz), 130.0 (dd, J = 5.8, 4.0 Hz), 124.8 (dd, J = 6.7, 3.8 Hz), 118.2 (dd, J = 17.8, 1.1 Hz), 117.7 (dd, J = 18.6, 1.3 Hz), 63.7 (d, J = 1.5 Hz) ppm; **IR** (neat) 3078, 2839, 1794, 1734, 1611, 1516, 1433, 1378, 1283, 1210, 1141, 1048, 1030, 964, 946, 877, 818, 770, 678, 635, 614 cm^{-1}**; HRMS** *m/z* (EI+): calcd for $C_8H_5ClF_2O$ (M) 189.9997, found 189.9999.

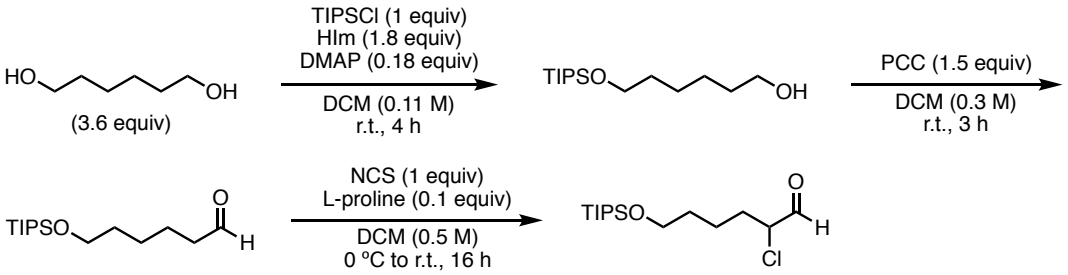


4-(3-Phenylpropoxy)butan-1-ol (S5): To a flame-dried 50-mL flask with a stir bar were added butane-1,4-diol (0.97 mL, 11 mmol, 1.1 equiv) and DMF (20 mL, 0.50 mL), and the solution was cooled to 0 ºC. Sodium hydride (0.48 g of a 60% w/w dispersion in mineral oil, 12 mmol, 1.2 equiv) was added at once and the reaction was stirred at 0 ºC for 15 min. 1-Bromo-3-phenylpropane (1.5 mL, 10 mmol, 1.0 equiv) was added dropwise and the reaction was stirred at r.t. for 1 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (×3). The organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (gradient of 40–60% EtOAc/hexanes) to yield the product as a colourless oil (1.7 g, 8.2 mmol, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.35–7.25 (m, 2H), 7.23–7.14 (m, 3H), 3.69–3.63 (m, 2H), 3.50–3.43 (m, 4H), 2.70–2.49 (m, 2H), 1.97–1.87 (m, 2H), 1.76–1.63 (m, 4H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 142.0, 128.6, 128.4, 125.9, 71.0, 70.2, 62.8, 32.4, 31.3, 30.4, 27.0 ppm; **R_f** (6:4 hexanes/EtOAc; UV/$KMnO_4$): 0.30.
NMR data is consistent with a previous literature report.[6]

4-(3-Phenylpropoxy)butanal (S6): To a 100-mL flask with a stir bar were added 4-(3-phenylpropoxy)butan-1-ol (1.2 g, 6.0 mmol, 1.0 equiv) and CH_2Cl_2 (20 mL, 0.30 M). The solution was cooled to 0 ºC and PCC (1.9 g, 9.0 mmol, 1.5 equiv) was added. The reaction was stirred at r.t. for 3 h. Silica (ca. 2.0 g) and Et_2O (20 mL) were added and the mixture was stirred at r.t. for 1 h. The solution was concentrated and purified by flash column chromatography (gradient of 0–40% EtOAc/hexanes) to yield the product as a colourless oil (0.94 g, 4.6 mmol, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 9.82 (t, J = 1.6 Hz, 1H), 7.36–7.27 (m, 2H), 7.25–7.18 (m, 3H), 3.47–3.44 (m, 4H), 2.75–2.67 (m, 2H), 2.58–2.54 (m, 2H), 2.00–1.86 (m, 4H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 202.4, 142.1, 128.6, 128.4, 125.9, 70.2, 69.7, 41.1, 32.5, 31.4, 22.8 ppm; **IR** (neat): 3027, 2942, 2859, 2723, 1723 (s), 1497, 1456, 1366, 1179, 1112, 1045, 747, 699 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{13}H_{19}O_2$ (M+H): 207.1380; found 207.1373; **R_f** (6:4 hexanes/EtOAc; UV/$KMnO_4$): 0.74.

2-Chloro-4-(3-phenylpropoxy)butanal (S7): To a 25-mL flask with a stir bar were added 4-(3-phenylpropoxy)butanal (0.62 g, 3.0 mmol, 1.0 equiv) and CH_2Cl_2 (6.0 mL, 0.50 M), and the

solution was cooled to 0 ºC. *N*-chlorosuccinimide (0.40 g, 3.0 mmol, 1.0 equiv) and L-proline (35 mg, 0.30 mmol, 0.10 equiv) were added at once and the reaction was stirred at 0 ºC for 1 h and at r.t. for 16 h. The reaction was diluted with pentane and filtered over Celite, and the filtrate was concentrated to yield the product as an orange oil (0.69 g, 2.9 mmol, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 9.58–9.50 (m, 1H), 7.36–7.27 (m, 2H), 7.26–7.16 (m, 3H), 4.48–4.39 (m, 1H), 3.72–3.55 (m, 2H), 3.52–3.36 (m, 2H), 2.76–2.61 (m, 2H), 2.38–2.25 (m, 1H), 2.23–2.08 (m, 1H), 2.01–2.84 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 195.1, 141.9, 128.6, 128.5, 125.9, 70.4, 65.6, 61.7, 33.1, 32.4, 31.3 ppm; **IR** (neat): 3062, 3027, 2935, 2865, 1732 (s), 1603, 1498, 1456, 1369, 1173, 1112, 1043, 818, 746, 699 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{13}H_{18}O_2Cl$ (M+H) 241.0990; found 241.0989.

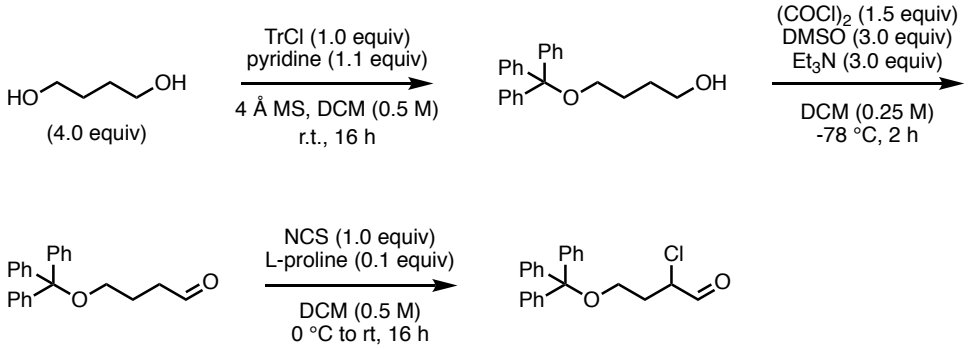


6-((Triisopropylsilyl)oxy)hexan-1-ol (S8): To a 100-mL flask were added hexane-1,6-diol (2.4 g, 20 mmol, 3.6 equiv), imidazole (0.68 g, 10 mmol, 1.8 equiv), DMAP (0.12 g, 1.0 mmol, 0.18 equiv), CH_2Cl_2 (50 mL, 0.11 M), and TIPSCl (1.2 mL, 5.5 mmol, 1.0 equiv). The reaction was stirred at r.t. for 4 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (×3). The organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatograph (gradient of 10–40% EtOAc/hexanes) to yield the product as a colourless oil (1.4 g, 5.1 mmol, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 3.73–3.65 (m, 4H), 1.69–1.52 (m, 4H), 1.50–1.35 (m, 4H), 1.21–1.01 (m, 22H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 63.5, 63.2, 33.1, 33.0, 25.8, 25.7, 18.2, 12.2 ppm; **R_f** (6:4 hexanes/EtOAc; $KMnO_4$): 0.69.
NMR data is consistent with a previous literature report.[2]

6-((Triisopropylsilyl)oxy)hexanal (S9): To a 50-mL flask with stir bar were added 6-((triisopropylsilyl)oxy)hexan-1-ol (1.3 g, 4.7 mmol, 1.0 equiv) and CH_2Cl_2 (16 mL, 0.30 M). The solution was cooled to 0 ºC and PCC (1.5 g, 7.1 mmol, 1.5 equiv) was added. The reaction was stirred at r.t. for 3 h. Silica (ca. 2.0 g) and Et_2O (20 mL) were added and the mixture was stirred at r.t. for 1 h. The solution was concentrated and purified by flash column chromatography (gradient of 0–20% EtOAc/hexanes) to yield the product as a colourless oil (1.1 g, 4.0 mmol, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 9.77 (t, J = 2.0 Hz, 1H), 3.75–3.62 (m, 2H), 2.52–2.32 (m, 2H), 1.74–1.50 (m, 4H), 1.48–1.34 (m, 2H), 1.19–0.95 (m, 21H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 203.0, 63.2, 44.1, 32.8, 25.7, 22.1, 18.2, 12.2 ppm; **R_f** (9:1 hexanes/EtOAc; $KMnO_4$): 0.74.
NMR data is consistent with a previous literature report.[7]

2-Chloro-6-((triisopropylsilyl)oxy)hexanal (S10): To a 25-mL flask with a stir bar were added 6-((triisopropylsilyl)oxy)hexanal (0.82 g, 3.0 mmol, 1.0 equiv) and CH_2Cl_2 (6.0 mL, 0.50 M), and the solution was cooled to 0 ºC. *N*-chlorosuccinimide (0.40 g, 3.0 mmol, 1.0 equiv) and L-proline (35 mg, 0.30 mmol, 0.10 equiv) were added at once and the reaction was stirred at 0 ºC for 1 h and at r.t. for an additional 15 h. The reaction was diluted with pentane (6.0 mL) and was filtered over

a plug of Celite. The filtrate was concentrated to yield the product as a colourless oil (2.7:1 mono/non-chlorinated products), which was used in the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 9.25 (d, J = 2.5 Hz, 1H), 3.78–3.64 (m, 2H), 2.39–2.27 (m, 1H), 1.82–0.93 (m, 28H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 204.5, 64.1, 62.9, 40.6, 32.4, 21.3, 18.2, 12.1 ppm; **IR** (neat) 2941, 2892, 2867, 1711, 1462, 1383, 1247, 1102, 1068, 995, 880, 720, 678 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{15}H_{32}ClO_2Si$ (M+H): 307.1855; found 307.1851.

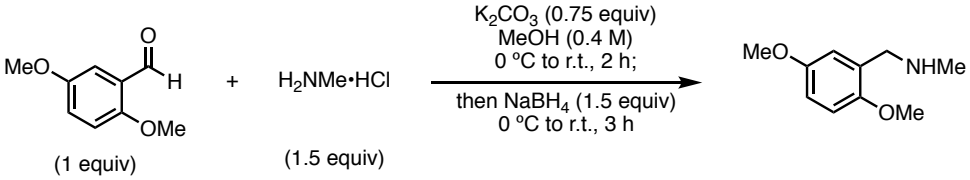


4-(Trityloxy)butan-1-ol (S11): To a flame-dried round bottom flask with stir bar were added 1,4-butanediol (12.6 g, 140 mmol, 4.00 equiv) and anhydrous CH_2Cl_2 (70 mL, 0.5 M) under an inert atmosphere. 4 Å Molecular sieves (25 g), TrCl (9.76 g, 35.0 mmol, 1.00 equiv), and pyridine (3.1 mL, 39 mmol, 1.1 equiv) were then added and the reaction was allowed to stir at room temperature for 16 h. The reaction mixture was then diluted with CH_2Cl_2, filtered over Celite, washed with H_2O (×1), brine (×1), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (gradient of 0–30% EtOAc/hexanes) to afford the product as a white solid (7.40 g, 22.3 mmol, 64%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.46–7.43 (m, 6H), 7.32–7.28 (m, 6H), 7.25–7.21 (m, 3H), 3.63 (t, J = 5.9 Hz, 2H), 3.12 (t, J = 5.9 Hz, 2H), 1.74–1.63 (m, 5H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 144.4, 128.8, 127.9, 127.1, 86.8, 63.6, 63.0, 30.1, 26.7 ppm.
NMR data is consistent with a previous literature report.[8]

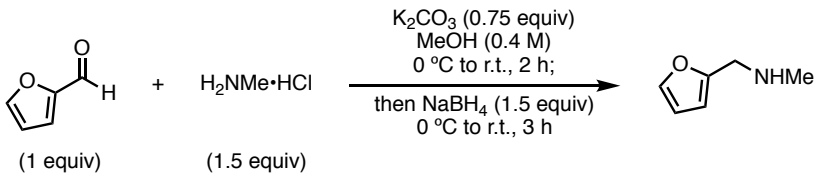
4-(Trityloxy)butanal (S12): To a flame-dried round bottom flask with a stir bar was added oxalyl chloride (0.38 mL, 4.5 mmol, 1.5 equiv) and anhydrous CH_2Cl_2 (6 mL, 0.75 M). The solution was cooled to -78 °C and DMSO (0.64 mL, 9.0 mmol, 3.0 equiv) was added dropwise. After stirring for 10 minutes, 4-(trityloxy)butan-1-ol (1.0 g, 3.0 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added dropwise. After an additional 10 minutes, Et_3N (1.26 mL, 9.0 mmol, 3.0 equiv) was added dropwise to the solution followed by further stirring for 40 minutes, after which the reaction solution was removed from the acetone/dry ice bath and left to stir for an additional 1.5 h while warming. The solution was quenched with H_2O, and the organic and aqueous layers were separated. The aqueous layer was extracted with CH_2Cl_2 (×3) and the organic fractions were combined and washed with brine (×2), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (5% EtOAc/hexanes) to afford the product as a colourless oil (0.56 g, 1.7 mmol, 57%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 9.74 (t, J = 1.6 Hz, 1H), 7.41–7.36 (m, 6H), 7.29–7.23 (m, 6H), 7.22–7.16 (m, 3H), 3.10 (t, J = 6.2 Hz, 2H), 2.49 (td, J = 7.3, 1.7 Hz, 2H), 1.89 (tt, J = 7.3, 6.2 Hz, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 202.5, 144.3, 128.8, 127.9, 127.1, 86.8, 62.7, 41.2, 23.0 ppm.
NMR data is consistent with a previous literature report.[8]

2-Chloro-4-(trityloxy)butanal (S13): To a flame-dried round bottom flask with a stir bar were added CH_2Cl_2 (2 mL, 0.50 M) and 4-(trityloxy)butanal (0.30 g, 0.91 mmol, 1.0 equiv), and the solution was cooled to 0 ºC. At once, NCS (0.12 g, 0.91 mmol, 1.0 equiv) and L-proline (11 mg, 0.09 mmol, 0.10 equiv) were added. The reaction was stirred at 0 ºC for 1 h and at r.t. for an additional 15 h. The reaction was diluted with pentane (20 mL) and filtered over Celite, and the filtrate was concentrated under reduced pressure. The crude residue was suspended in pentanes, washed with brine (×2), dried over $MgSO_4$, and concentrated to afford the product as a colourless oil (0.31 g, 0.85 mmol, 94%, 0.88:0.04 mono/non-chlorinated products) which was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 9.55 (d, J = 2.0 Hz, 1H), 7.45–7.37 (m, 6H), 7.34–7.28 (m, 6H), 7.25–7.22 (m, 3H), 4.51–4.47 (m, 1H), 3.35–3.29 (m, 2H), 2.33–2.23 (m, 1H), 2.08–1.97 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 195.4, 143.9, 128.7, 128.0, 127.3, 87.3, 61.6, 59.0, 33.2 ppm; **IR** (neat): 3059, 3029, 2929, 2883, 1731, 1597, 1490, 1447, 1383, 1318, 1219, 1182, 1155, 1072, 1032, 1002, 900, 851, 762, 747, 702, 647, 632, 604 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{23}H_{21}ClO_2$ (M) 364.1225; found 364.1233.

E. Preparation of amine starting materials

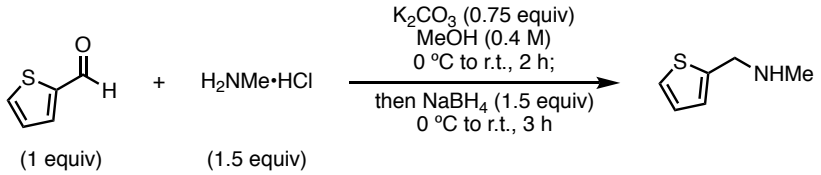


1-(2,5-Dimethoxyphenyl)-*N*-methylmethanamine (S14, CAS: 229486-99-1): To a 50-mL flask with a stir bar were added methylamine hydrochloride (1.0 g, 15 mmol, 1.5 equiv), potassium carbonate (1.0 g, 7.5 mmol, 0.75 equiv), and MeOH (25 mL, 0.40 M), and the reaction was stirred at 0 ºC for 30 min. 2,5-Dimethoxybenzaldehyde (1.2 g, 10 mmol, 1.0 equiv) was added and the reaction was stirred at r.t. for 1 h. The reaction was cooled to 0 ºC and sodium borohydride (0.57 g, 15 mmol, 1.5 equiv) was added. The reaction was stirred at r.t. for 3 h. The reaction was filtered using a fritted funnel, the precipitate was washed with EtOAc (×1), and the filtrate was collected and concentrated. The concentrate was dissolved in EtOAc (50 mL) and the organic layer was washed with H_2O (×1) and brine (×1), dried over $MgSO_4$, and concentrated under reduced pressure to yield the product as a colourless oil (1.1 g, 6.1 mmol, 61%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 6.86–6.83 (m, 1H), 6.80–6.72 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.72 (s, 2H), 2.42 (s, 3H), 1.92 (br s, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 153.5, 152.0, 129.3, 116.2, 112.5, 111.2, 55.9, 55.9, 51.3, 35.9 ppm.
NMR data is consistent with a previous literature report.[9]

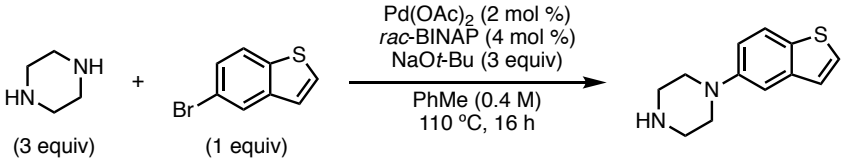


1-(furan-2-yl)-*N*-methylmethanamine (S15): To a 50-mL flask with a stir bar were added methylamine hydrochloride (1.0 g, 15 mmol, 1.5 equiv), potassium carbonate (1.0 g, 7.5 mmol, 0.75 equiv), and MeOH (25 mL, 0.40 M), and the reaction was stirred at 0 ºC for 30 min. Furfural (0.93 mL, 10 mmol, 1.0 equiv) was added and the reaction was stirred at r.t. for 1 h. The reaction was cooled to 0 ºC and sodium borohydride (0.57 g, 15 mmol, 1.5 equiv) was added. The reaction

was stirred at r.t. for 3 h. The reaction was filtered using a fritted funnel, the precipitate was washed with EtOAc (×1), and the filtrate was collected and concentrated. The concentrate was dissolved in EtOAc (50 mL) and the organic layer was washed with H_2O (×1) and brine (×1), dried over $MgSO_4$, and concentrated to yield the product as a colourless oil (0.67 g, 6.0 mmol, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.39–7.33 (m, 1H), 6.33–6.27 (m, 1H), 6.22–6.15 (m, 1H), 3.73 (s, 2H), 2.41 (s, 3H), 1.68 (br s, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 153.8, 141.9, 110.2, 107.1, 48.1, 35.7 ppm; **R_f** (9:1 DCM/MeOH; UV/$KMnO_4$): 0.09. **IR** (neat) 3330, 3120, 2934, 2798, 2850, 1597, 1505, 1447, 1346, 1222, 1149, 1071, 1013, 916, 884, 730 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_6H_{10}NO$ (M+H) 112.0757; found 112.0760.

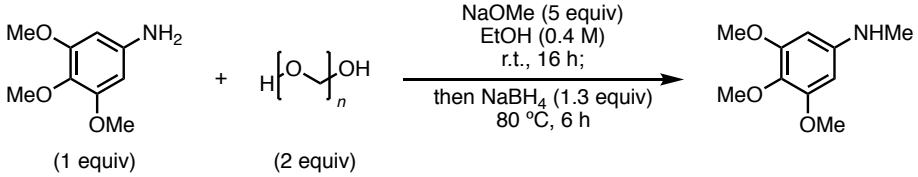


***N*-Methyl-1-(thiophen-2-yl)methanamine (S16):** To a 50-mL flask with a stir bar were added methylamine hydrochloride (1.0 g, 15 mmol, 1.5 equiv), potassium carbonate (1.0 g, 7.5 mmol, 0.75 equiv), and MeOH (25 mL, 0.40 M), and the reaction was stirred at 0 ºC for 30 min. 2-Thiophenecarboxaldehyde (0.93 mL, 10 mmol, 1.0 equiv) was added and the reaction was stirred at r.t. for 1 h. The reaction was cooled to 0 ºC and sodium borohydride (0.57 g, 15 mmol, 1.5 equiv) was added. the reaction was stirred at r.t. for 3 h. The reaction was filtered using a fritted funnel, the precipitate was washed with EtOAc (×1), and the filtrate was collected and concentrated. The concentrate was dissolved in EtOAc (50 mL) and the organic layer was washed with H_2O (×1) and brine (×1), dried over $MgSO_4$, and concentrated to yield the product as a colourless oil (0.99 g, 7.8 mmol, 78%), which was used without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K): δ_H 7.22–7.18 (m, 1H), 6.96–6.89 (m, 2H), 3.94 (s, 2H), 2.47 (s, 3H), 1.76 (s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$, 298 K): δ_C 143.8, 126.7, 125.1, 124.5, 50.4, 35.8 ppm; **R_f** (9:1 DCM/MeOH; UV/*p*-anisaldehyde): 0.14.
NMR data is consistent with a previous literature report.[10]



1-(Benzo[b]thiophen-5-yl)piperazine (S17, CAS: 433303-94-7): To a 25-mL flask with a stir bar were added piperazine (1.0 g, 12 mmol, 3.0 equiv), 5-bromobenzothiophene (0.85 g, 4.0 mmol, 1.0 equiv), palladium(II) acetate (18 mg, 0.080 mmol, 0.020 equiv), *rac*-BINAP (0.10 g, 0.16 mmol, 0.040 equiv), sodium *tert*-butoxide (1.2 g, 12 mmol, 3.0 equiv), and toluene (10 mL, 0.40 M). The reaction was stirred at 110 ºC for 16 h. The reaction was then cooled to r.t., quenched with sat. aq. NH_4Cl, and extracted with EtOAc (×3). The organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (gradient of 100/0/0 to 85/14/1 DCM/MeOH/NEt_3) to yield the product as an off-white solid (0.55 g, 2.5 mmol, 63%). **^{1}H NMR** (500 MHz, $CDCl_3$, (298 K): δ_H 7.73 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 5.2 Hz, 1H), 7.30 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 5.2, 0.7 Hz, 1H), 7.09 (dd, J = 8.5, 2.3 Hz, 1H), 3.20–3.15 (m, 4H), 3.11–3.06 (m, 4H), 2.01 (br s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$, 298 K): δ_C 149.7, 140.7, 131.9, 127.0, 123.7, 122.7, 116.8, 109.8, 51.6, 46.2 ppm; **R_f** (9:1 DCM/MeOH; UV): 0.09. **IR** (neat): 3462, 3415, 2945, 2817, 1670, 1596, 1502, 1472, 1436,

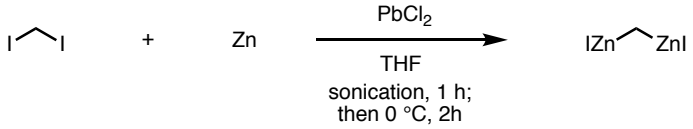
1423, 1342, 1274, 1260, 1230, 1151, 1002, 959, 841, 799, 752, 701, 690, 646 cm^{-1}; **HRMS** *m/z* (DART): calcd for $C_{12}H_{15}N_2S$ (M+H) 219.0951; found 219.0958.



3,4,5-Trimethoxy-N-methylaniline (S18, CAS: 124346-71-0): To a 50-mL flask with a stir bar were added 3,4,5-trimethoxyaniline (0.92 g, 5.0 mmol, 1.0 equiv), paraformaldehyde (0.30 g, 10 mmol, 2.0 equiv), and EtOH (12 mL, 0.40 M), and the solution was stirred at r.t. for 2 min. Sodium methoxide (1.4 g, 25 mmol, 5.0 equiv) was added and the reaction was stirred at r.t. for 16 h. The solution was cooled to 0 ºC and sodium borohydride (0.25 g, 6.5 mmol, 1.3 equiv) was added. The flask was fitted with a reflux condenser and the mixture was stirred at 80 ºC for 6 h. The reaction was cooled to r.t., quenched with sat. aq. $NaHCO_3$, and extracted with EtOAc (×3). The organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (gradient of 40–80% EtOAc/hexanes) to yield the product as a colourless oil (0.80 g, 4.1 mmol, 82%), which was stored under N_2 at −20 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K): δ_H 5.85 (s, 2H), 3.83 (s, 6H), 3.76 (s, 3H), 2.83 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$, 298 K): δ_C 154.1, 146.2, 130.2, 90.1, 61.2, 56.1, 31.3 ppm; **R_f** (6:4 hexanes/EtOAc; UV): 0.18.
NMR data is consistent with a previous literature report.[11]

F. Preparation of reagents and miscellaneous compounds

Zinc dust was activated according to the procedure reported by Fieser and Fieser.[12] Zinc was stirred for 5 minutes in 10% aq. HCl and then filtered through a fritted funnel. Zinc chunks were continuously broken up and washed with H_2O until the pH of the filtrate turned neutral (×3), then with acetone (×3). Zinc dust was then added to a round-bottom flask equipped with a stir bar, and was allowed to stir overnight under high vacuum at 130 °C before use.



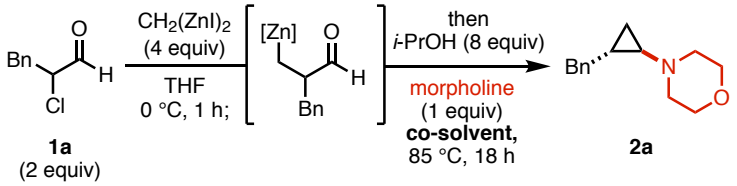
Bis(iodozincio)methane was prepared according to the procedure reported by Nomura et al.[1] To a flame-dried 250-mL flask equipped with a stir bar were added activated zinc dust (9.8 g, 150 mmol, 2.3 equiv) and lead chloride (0.017 g, 0.060 mmol). The flask was sealed with a septum and evacuated and backfilled with nitrogen (×3). THF (10 mL) was added followed by diiodomethane (0.48 mL, 6.0 mmol). The solution was sonicated for 1 h under nitrogen. THF was added (100 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 at r.t. under an atmosphere of nitrogen. The reagent was titrated using Knochel's protocol[13] and was generally found to be 0.20–

0.25 M; this concentration could be increased by adding less THF in step 2 without affecting the efficacy of the reagent.

$ZnCl_2$·TMEDA was prepared according to the procedure reported by Snégaroff et al.[14] To a flame-dried 250-mL flask with stir bar was added $ZnCl_2$ (6.8 g, 50 mmol, 1.0 equiv), THF (120 mL, 0.40 M), and tetramethylethylenediamine (TMEDA) (15 mL, 100 mmol, 2.0 equiv), and the reaction was stirred at room temperature for 2 h. The reaction was then concentrated and the product was recrystallized in THF to afford $ZnCl_2$·TMEDA as a white solid (6.1 g, 26 mmol, 52%).

$ZnCl_2$·2DMF was prepared according to the procedure reported by de Oliveira et al.[15] To a flame-dried 100-mL flask with stir bar was added $ZnCl_2$ (1.4 g, 10 mmol, 1.0 equiv), DMF (25 mL, 0.40 M), and the reaction was stirred at room temperature overnight. The reaction was then concentrated to yield the product as a white solid (2.5 g, 8.7 mmol, 87%).

G. Effect of polar aprotic co-solvent on product d.r.

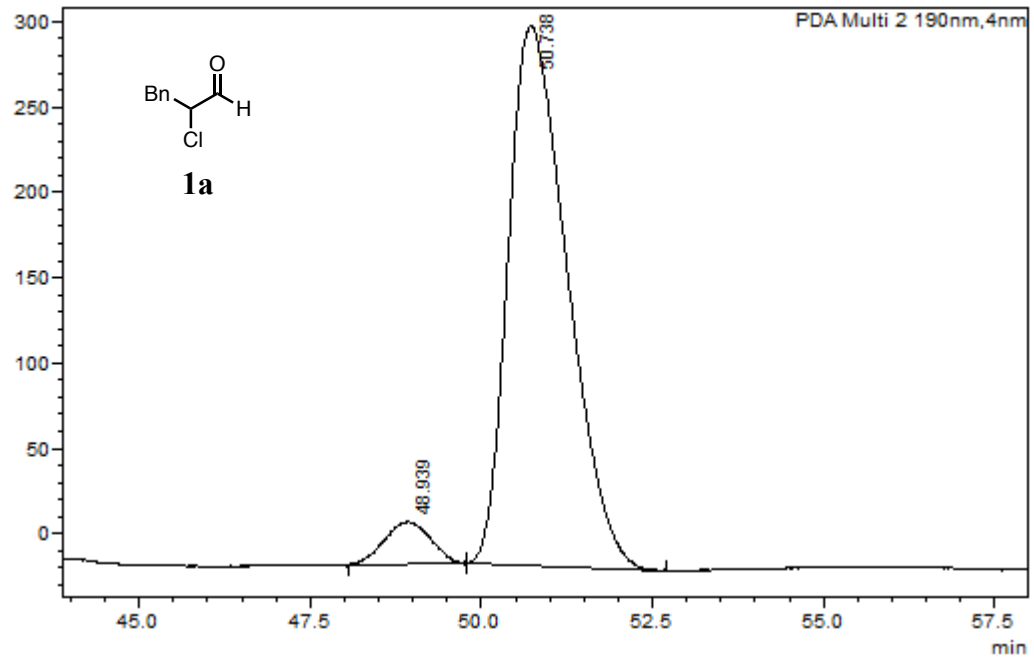


entry	co-solvent	yield[a]	d.r.
1	DMF	76%	>20:1
2	DMA	(61%)	16:1
3	DMSO	(63%)	>20:1
4	DMI[b]	(53%)	16:1

Reactions were performed using α-chloroaldehyde **1a** (0.4 mmol, 2.0 equiv), a solution of $CH_2(ZnI)_2$ in THF (0.8 mmol, 4.0 equiv, typically 0.22–0.25 M), *i*-PrOH (1.6 mmol, 8.0 equiv), morpholine (0.2 mmol, 1.0 equiv), and co-solvent in a 1:1 ratio with THF. [a]Yield in parentheses determined by ^{1}H NMR with dibromomethane as internal standard, otherwise isolated yields; d.r. determined by ^{1}H NMR. [b]1,3-Dimethyl-2-imidazolidinone.

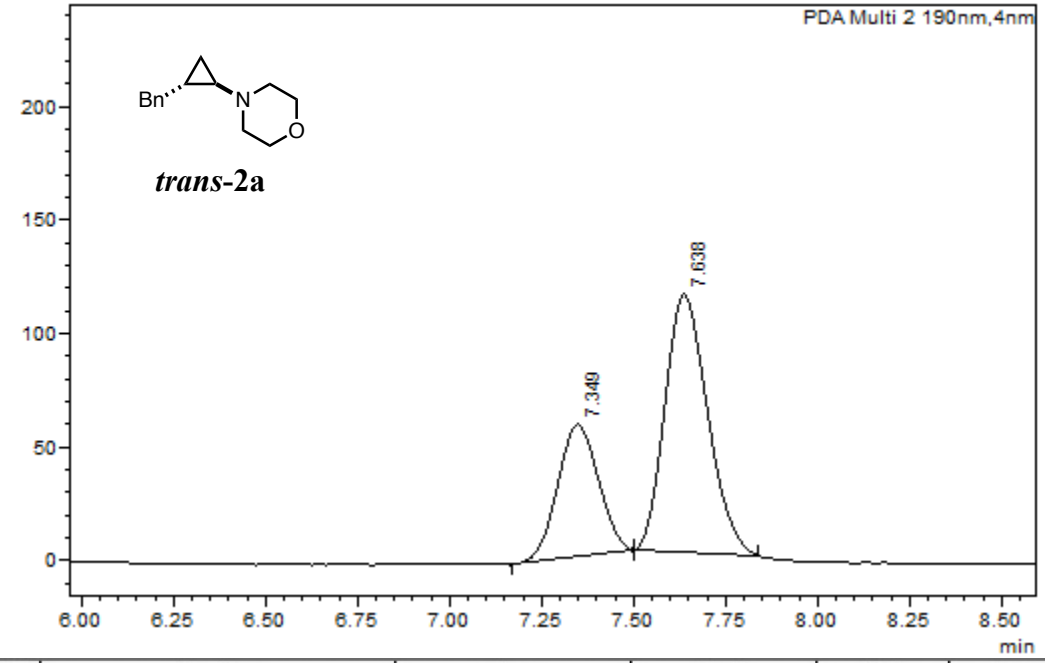
H. HPLC traces

mAU



Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit
1	48.939	1161463	24769	M	0.000	
2	50.738	18964653	315996	M	0.000	
Total		20126116	340765		0.000	

mAU



Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit
1	7.349	438168	58001	M	0.000	
2	7.638	899140	113743	M	0.000	
Total		1337308	171744		0.000	

I. References

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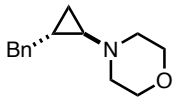
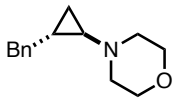
J. ^{1}H and ^{13}C NMR spectra

400 MHz, $CDCl_3$



***trans*-2a**

100 MHz, $CDCl_3$



***trans*-2a**

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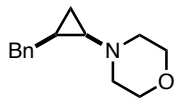
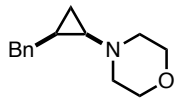
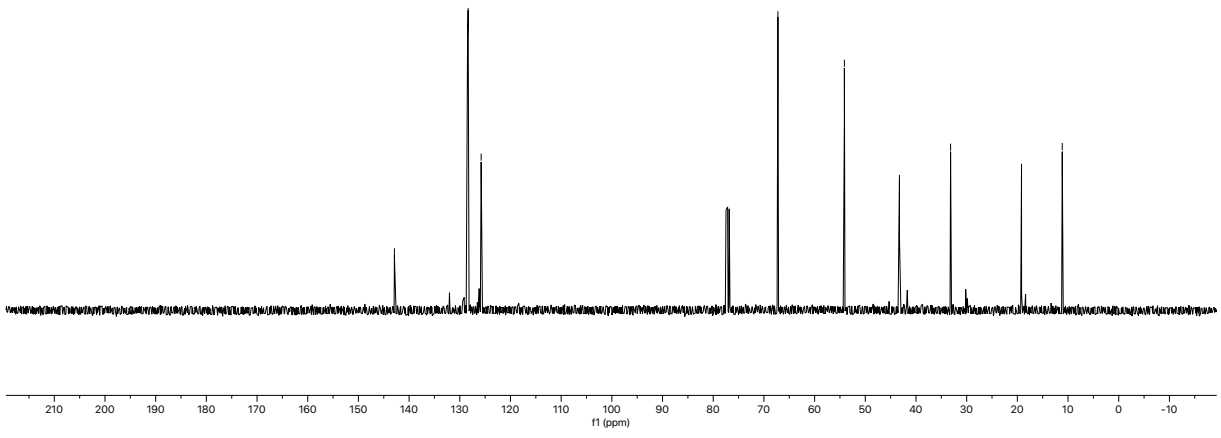


***cis*-2a**

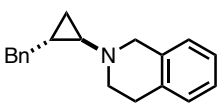
100 MHz, $CDCl_3$



***cis*-2a**

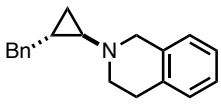


400 MHz, $CDCl_3$

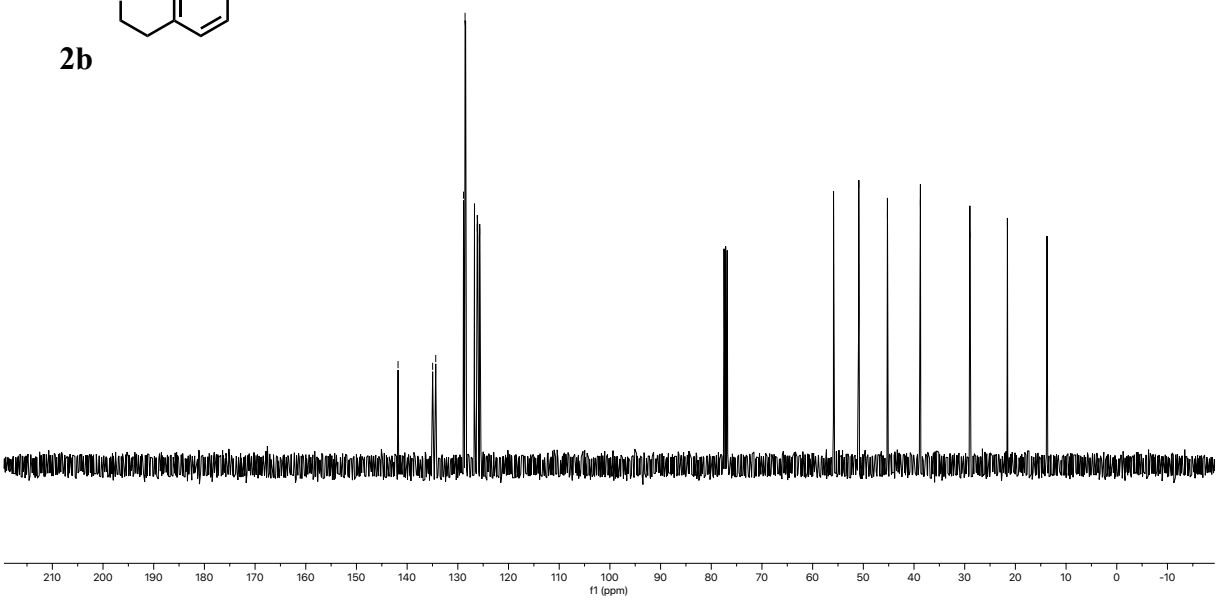


2b

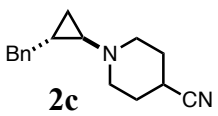
100 MHz, $CDCl_3$



2b

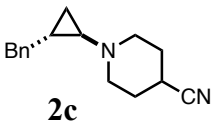


400 MHz, $CDCl_3$



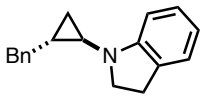
2c

100 MHz, $CDCl_3$



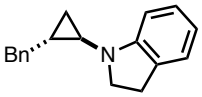
2c

400 MHz, $CDCl_3$

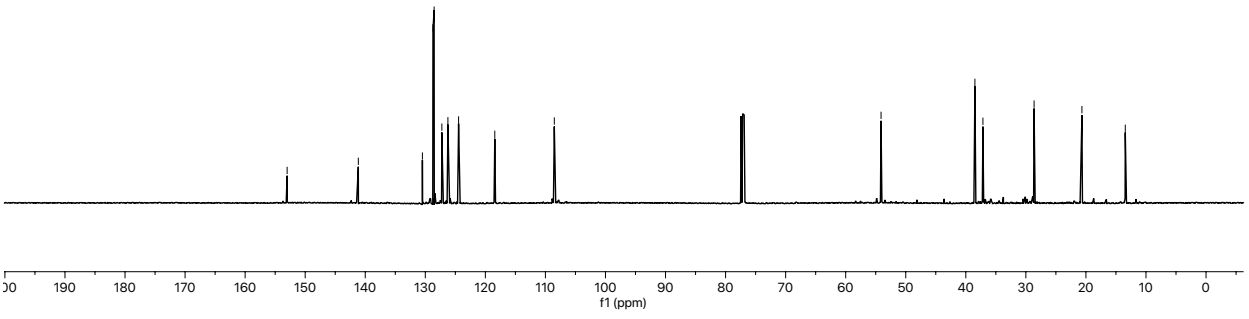


2d

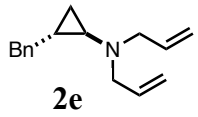
100 MHz, $CDCl_3$



2d

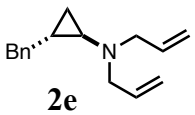


400 MHz, $CDCl_3$



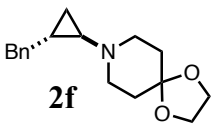
2e

100 MHz, $CDCl_3$



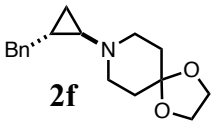
2e

400 MHz, $CDCl_3$



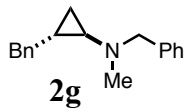
2f

100 MHz, $CDCl_3$



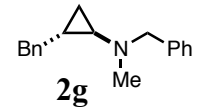
2f

400 MHz, $CDCl_3$



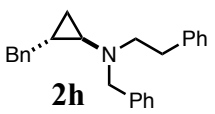
2g

100 MHz, $CDCl_3$



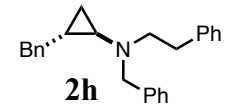
2g

400 MHz, $CDCl_3$

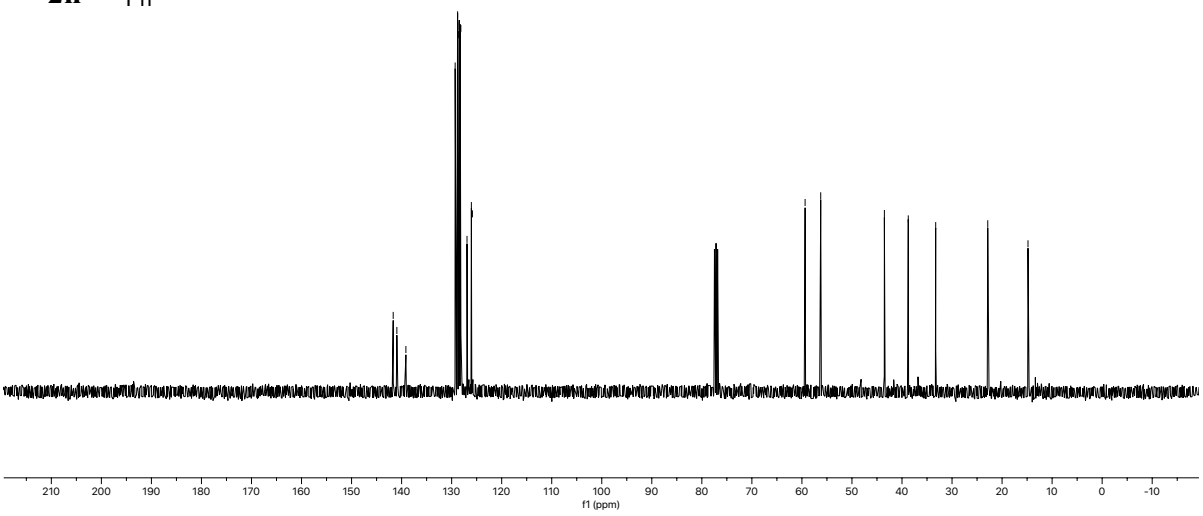


2h

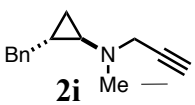
100 MHz, $CDCl_3$



2h

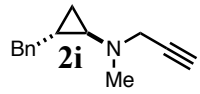


400 MHz, $CDCl_3$



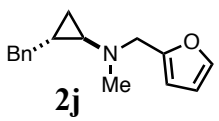
2i

100 MHz, $CDCl_3$



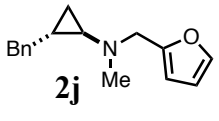
2i

400 MHz, $CDCl_3$

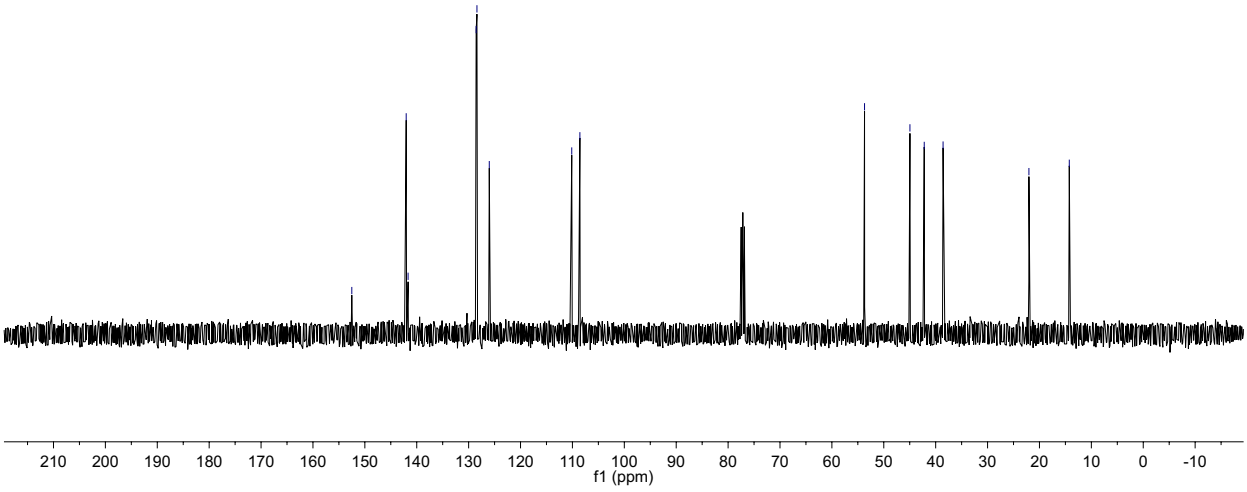


2j

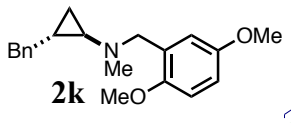
100 MHz, $CDCl_3$



2j

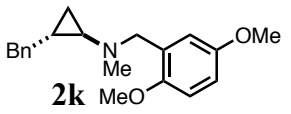


400 MHz, $CDCl_3$

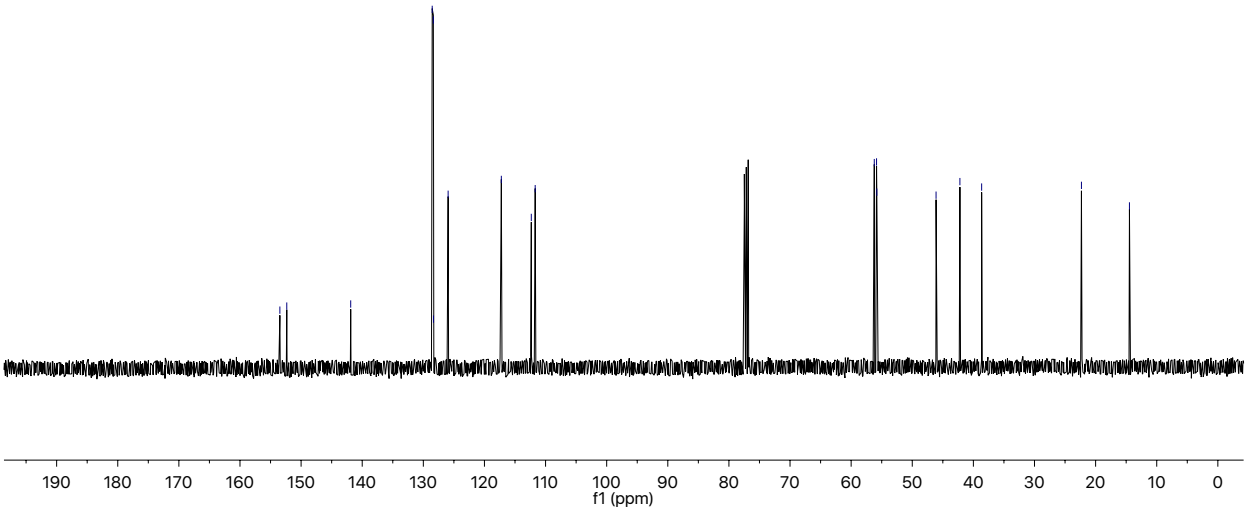


2k

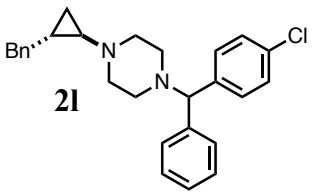
100 MHz, $CDCl_3$



2k

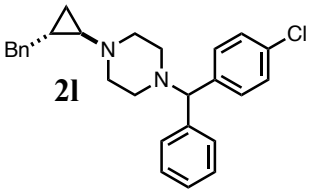


400 MHz, $CDCl_3$

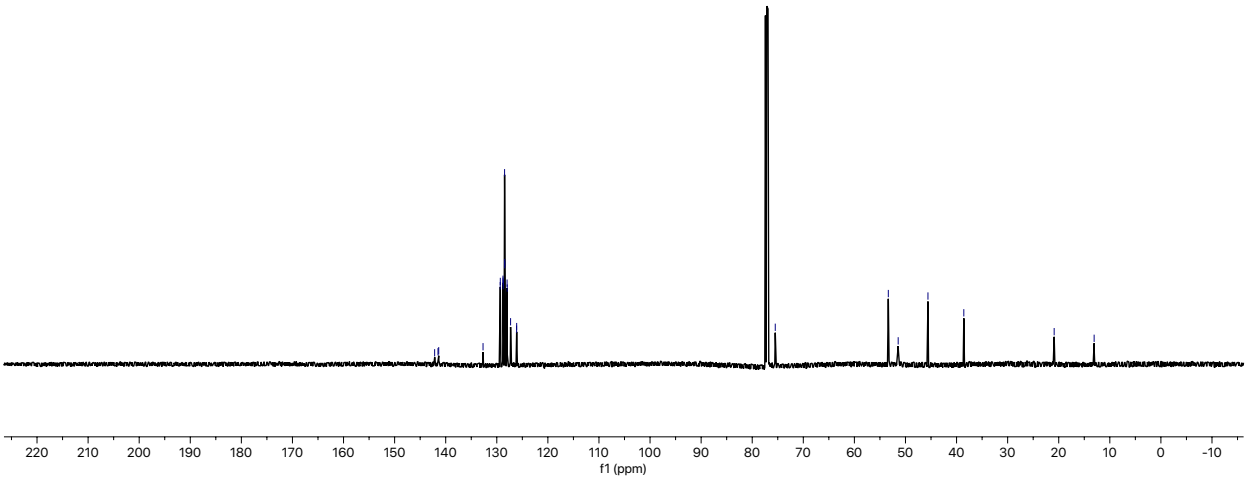


2l

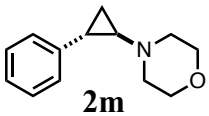
100 MHz, $CDCl_3$



2l

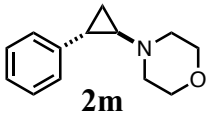


400 MHz, $CDCl_3$



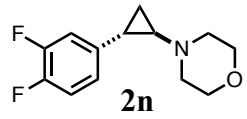
2m

100 MHz, $CDCl_3$



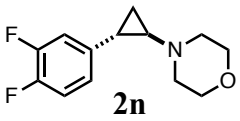
2m

400 MHz, $CDCl_3$



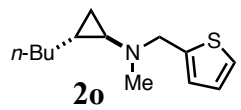
2n

100 MHz, $CDCl_3$



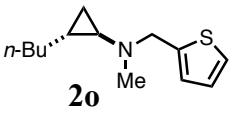
2n

400 MHz, $CDCl_3$

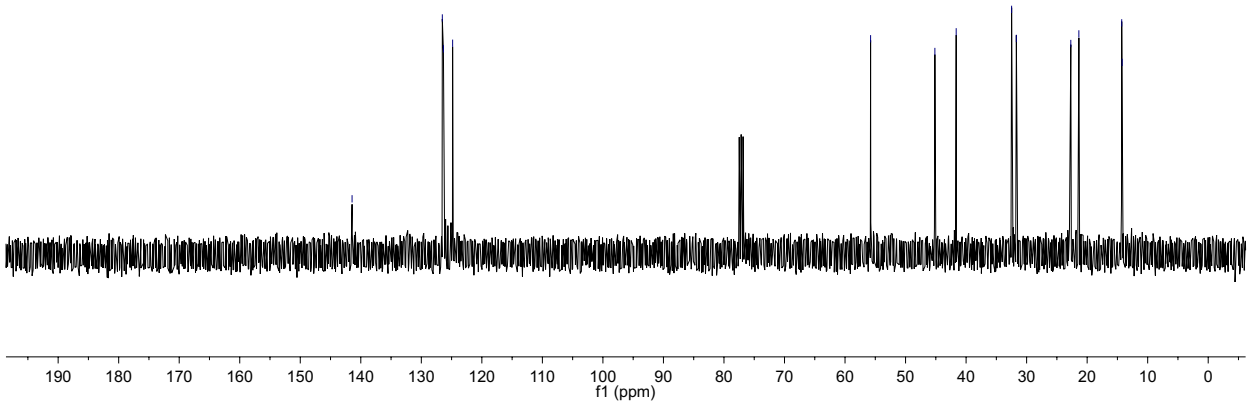


2o

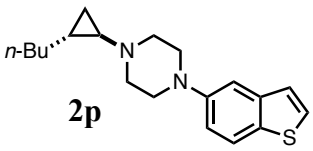
100 MHz, $CDCl_3$



2o

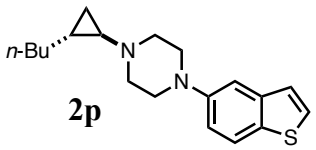


400 MHz, $CDCl_3$

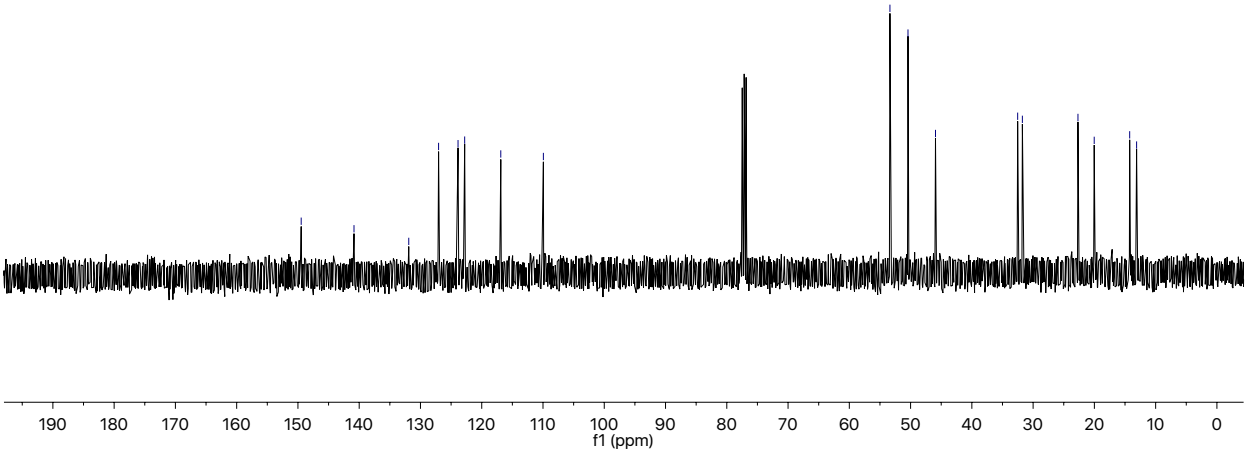


2p

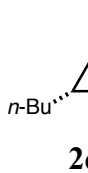
100 MHz, $CDCl_3$



2p

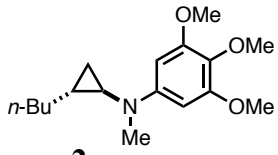


500 MHz, $CDCl_3$



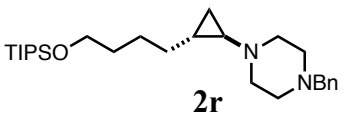
2q

125 MHz, $CDCl_3$



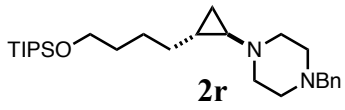
2q

400 MHz, $CDCl_3$

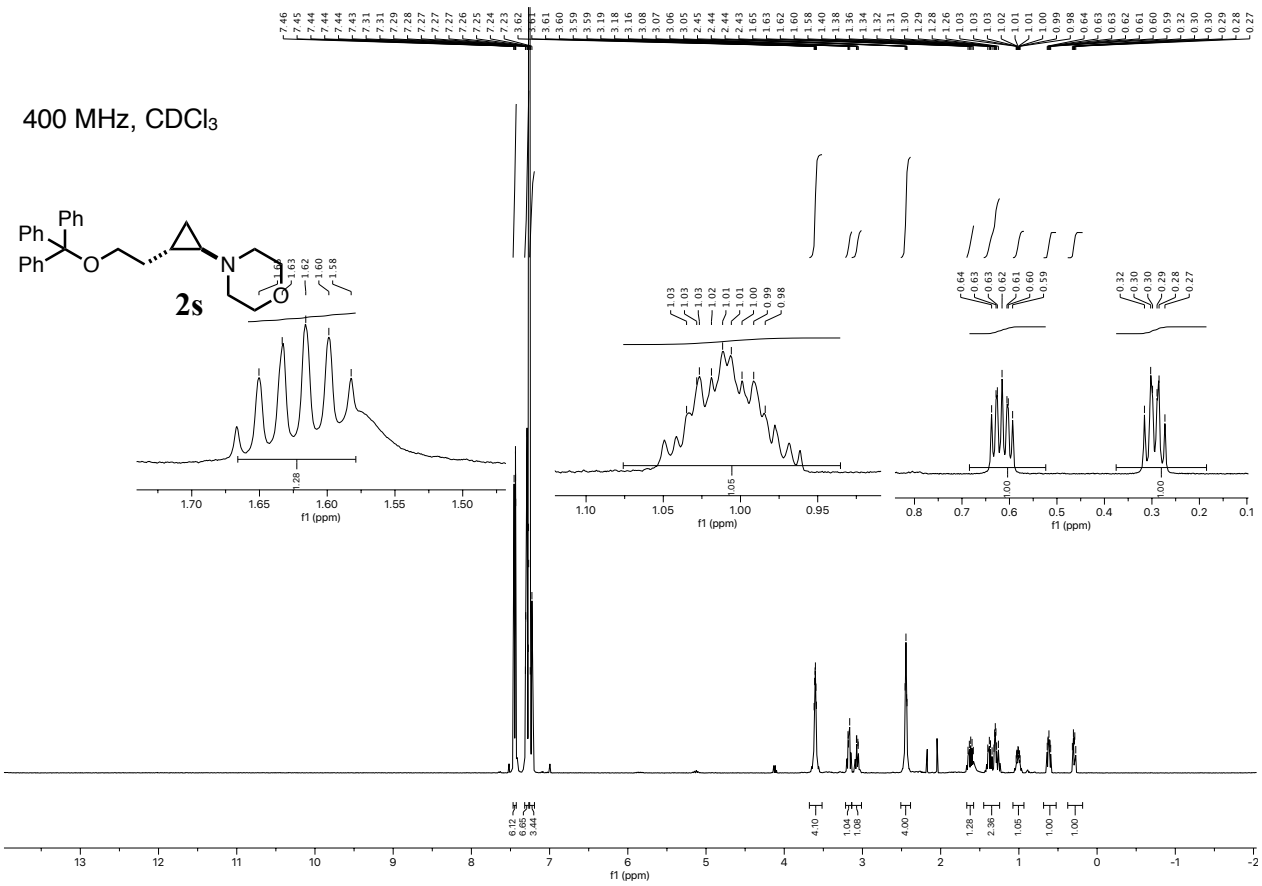


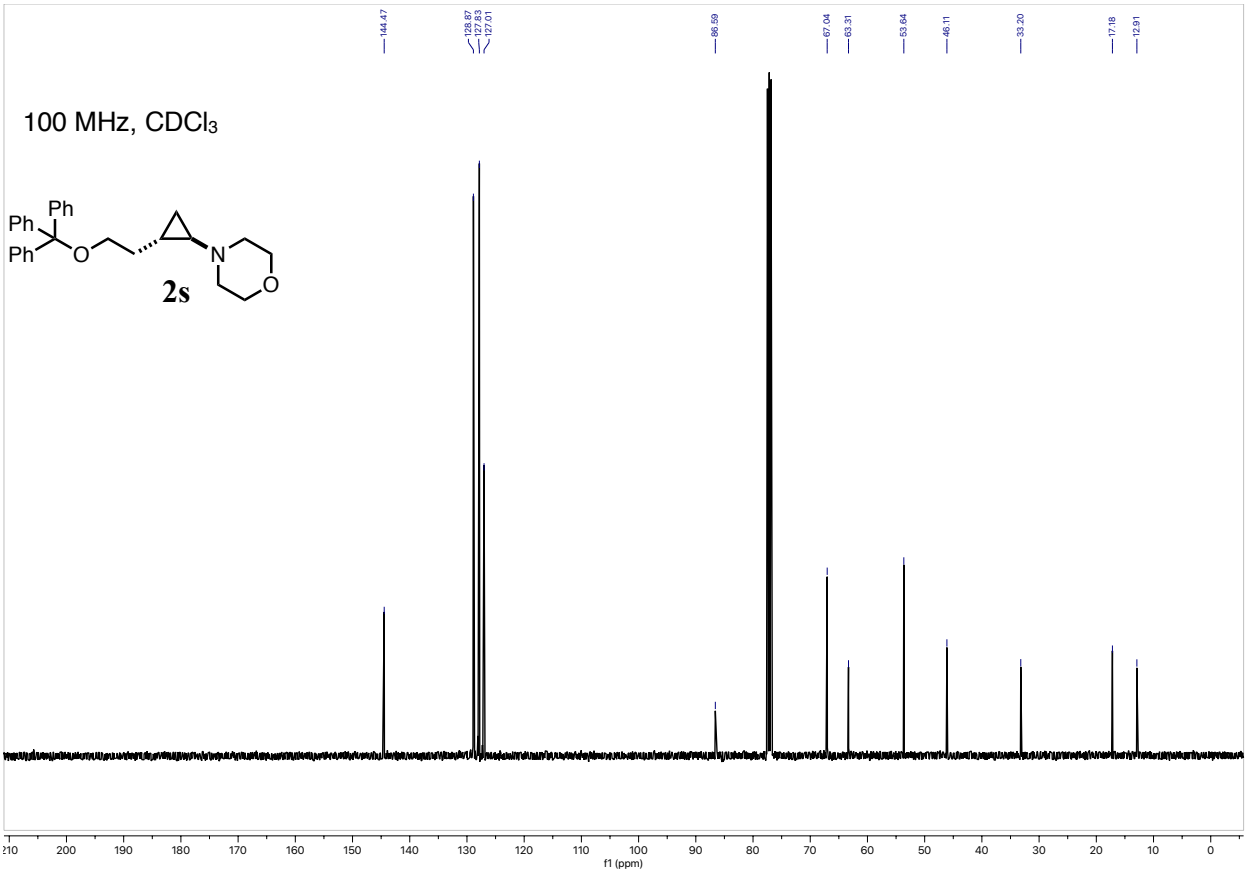
2r

100 MHz, $CDCl_3$

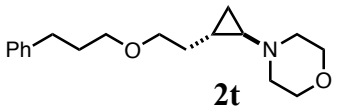


2r


400 MHz, CDCl3
Ph
Ph
O
N
O
2s
f1 (ppm)

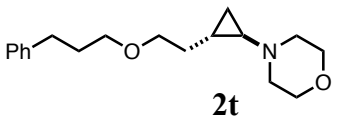

100 MHz, CDCl3
Ph
Ph
O
N
O
2s
f1 (ppm)

400 MHz, $CDCl_3$

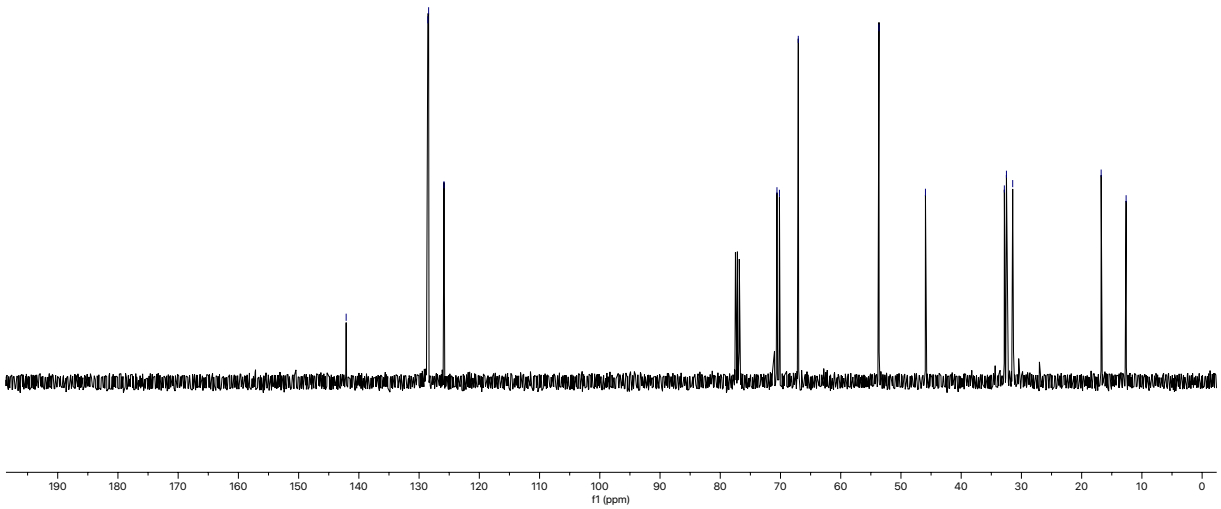


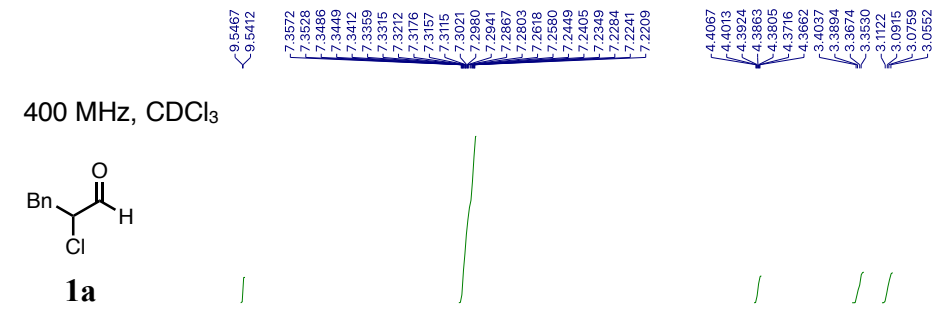
2t

100 MHz, $CDCl_3$



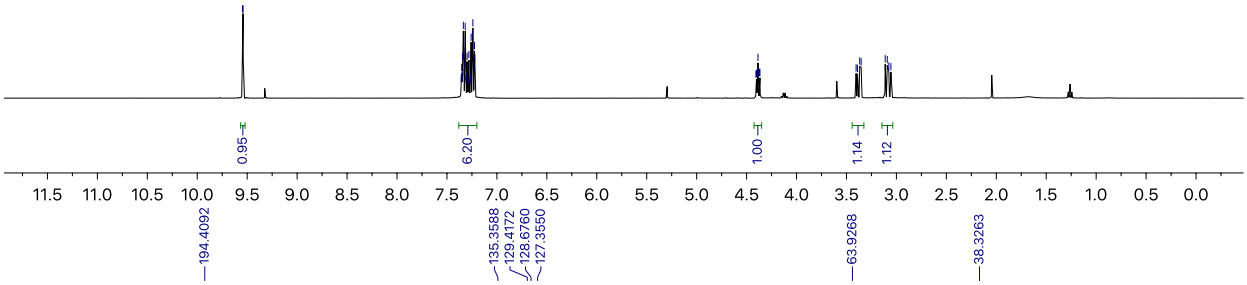
2t



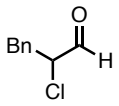


400 MHz, $CDCl_3$

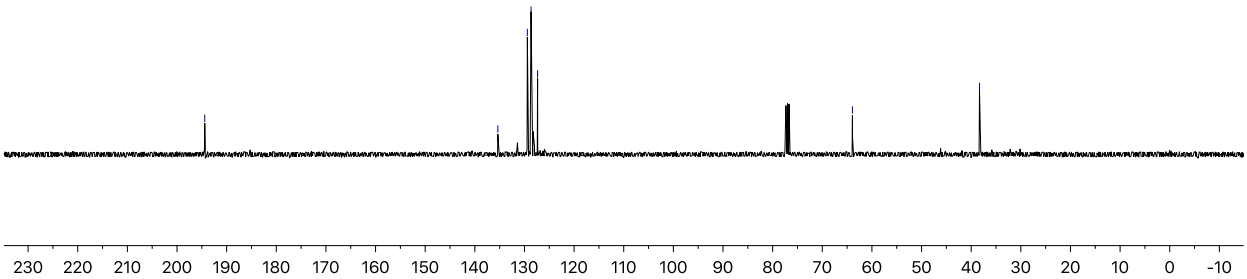
1a



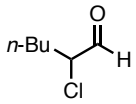
100 MHz, $CDCl_3$



1a

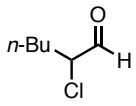


500 MHz, $CDCl_3$

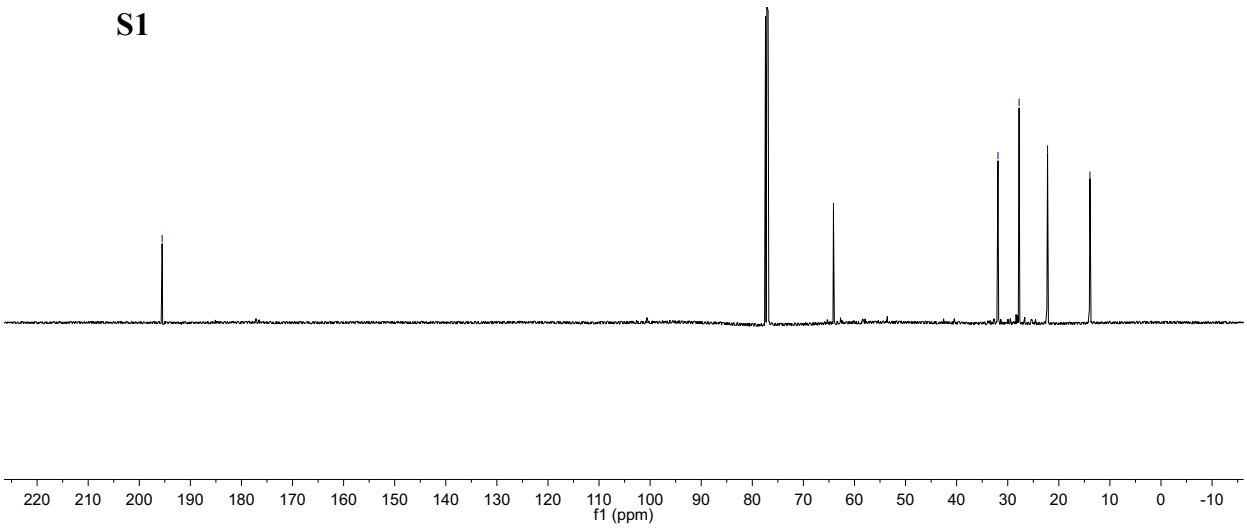


S1

125 MHz, $CDCl_3$

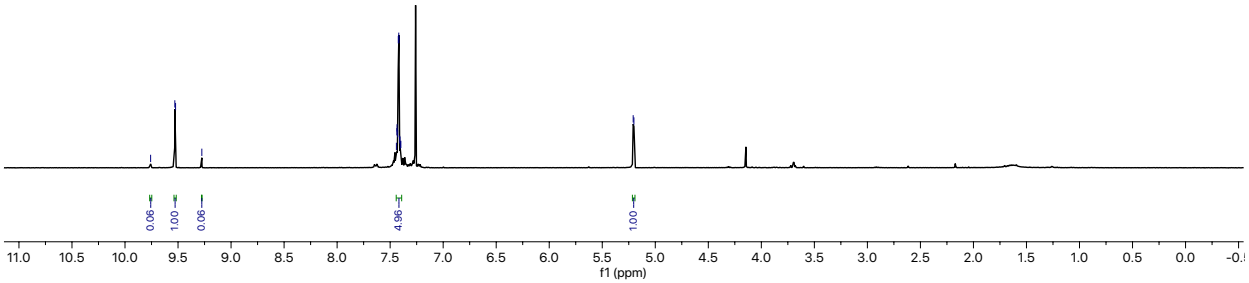


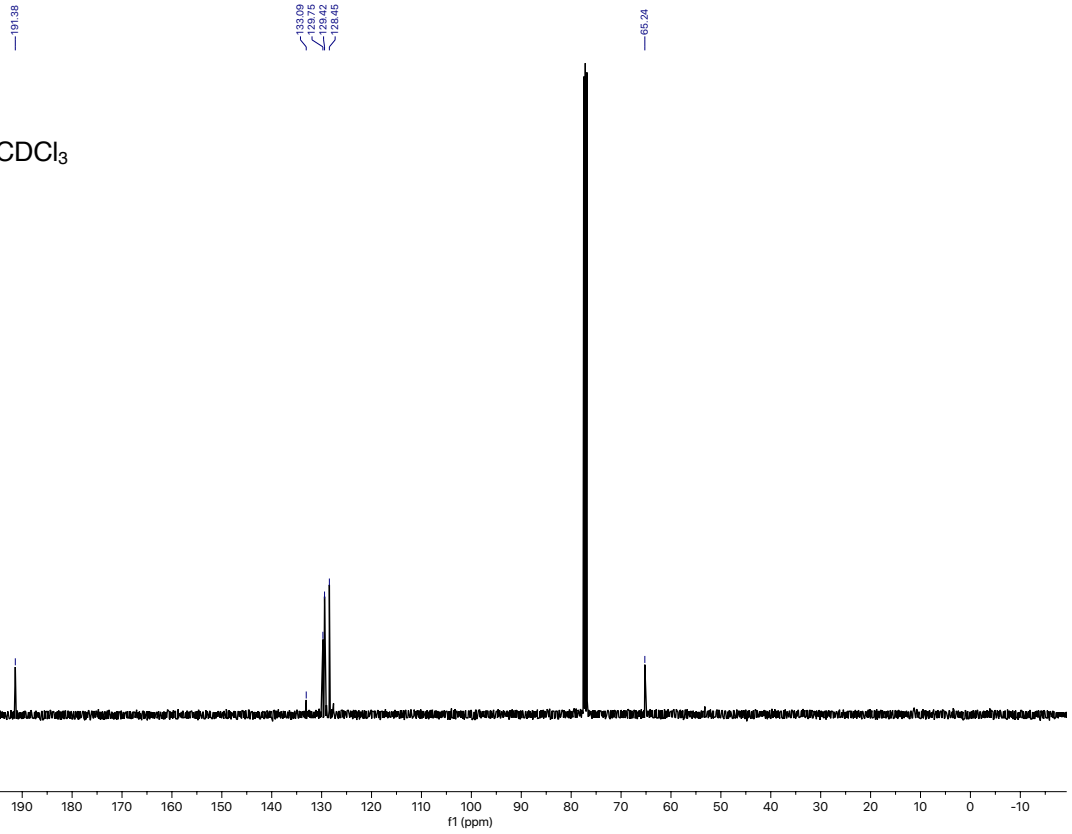
S1



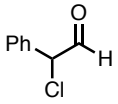
400 MHz, $CDCl_3$

S2



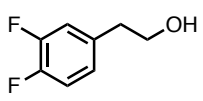


100 MHz, $CDCl_3$



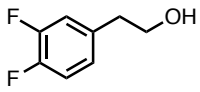
S2

400 MHz, $CDCl_3$

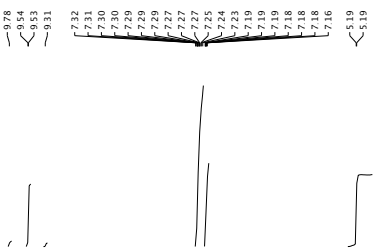


S3

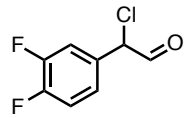
100 MHz, $CDCl_3$



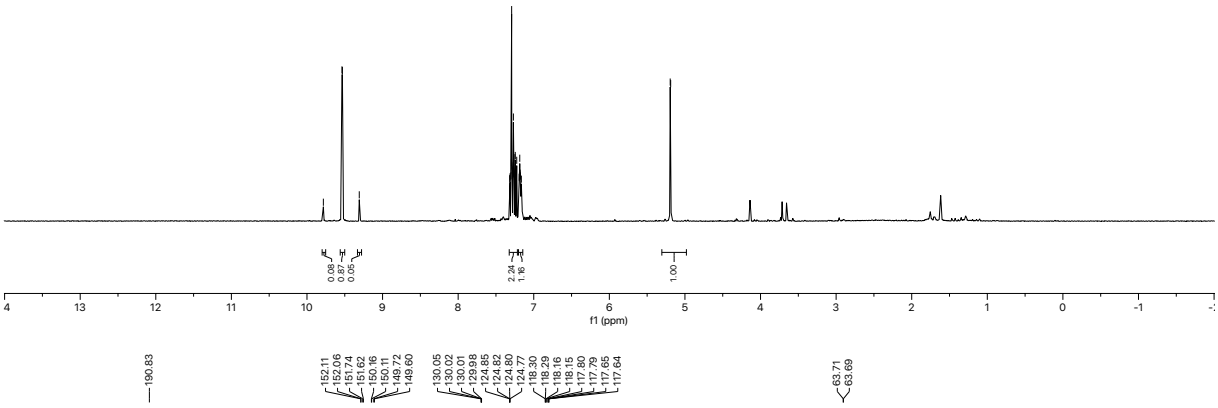
S3



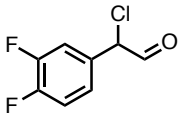
500 MHz, $CDCl_3$



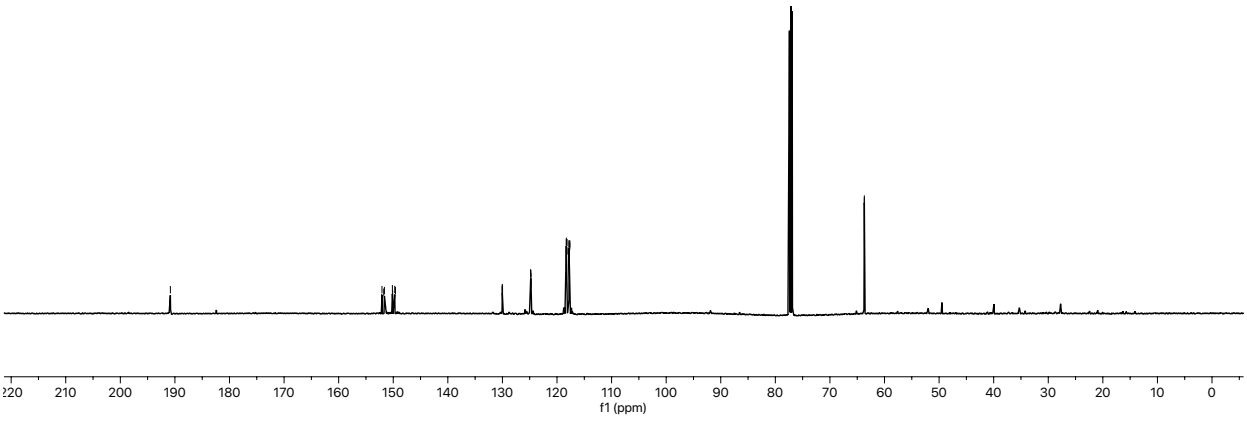
S4



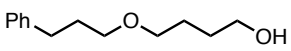
100 MHz, $CDCl_3$



S4

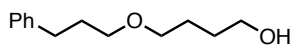


400 MHz, $CDCl_3$



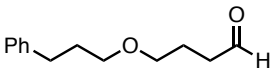
S5

100 MHz, $CDCl_3$

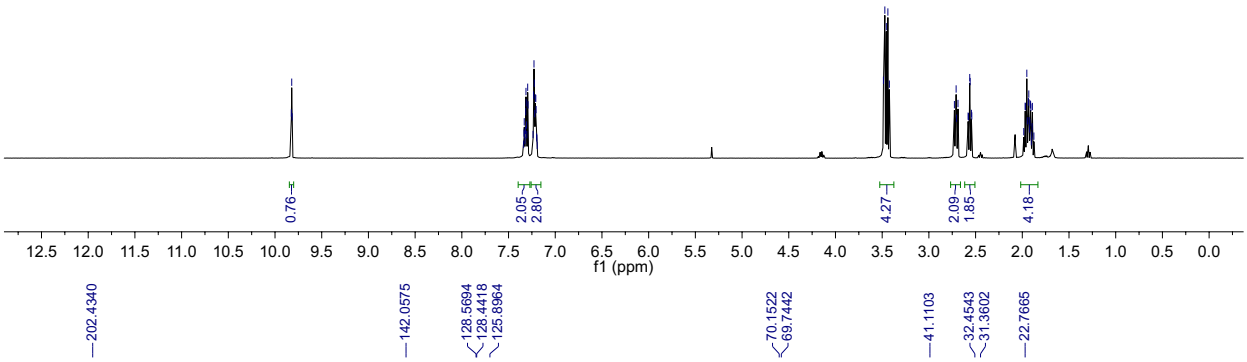


S5

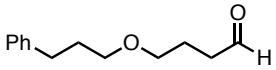
400 MHz, $CDCl_3$



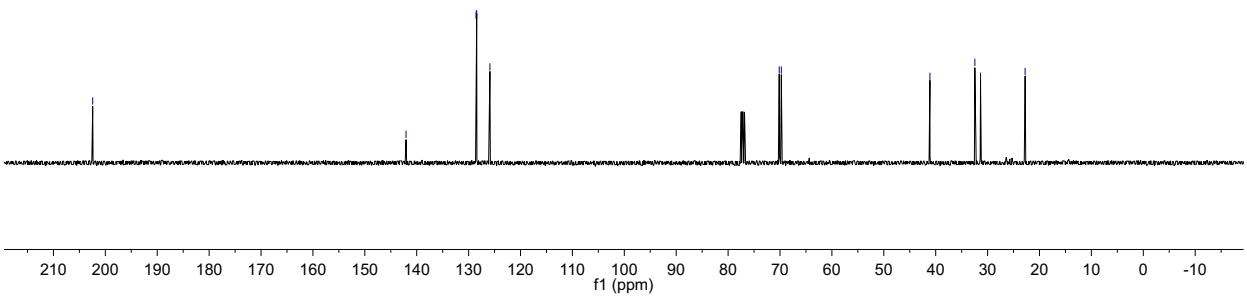
S6



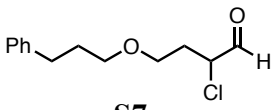
100 MHz, $CDCl_3$



S6

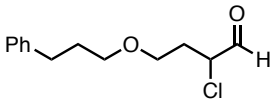


400 MHz, $CDCl_3$

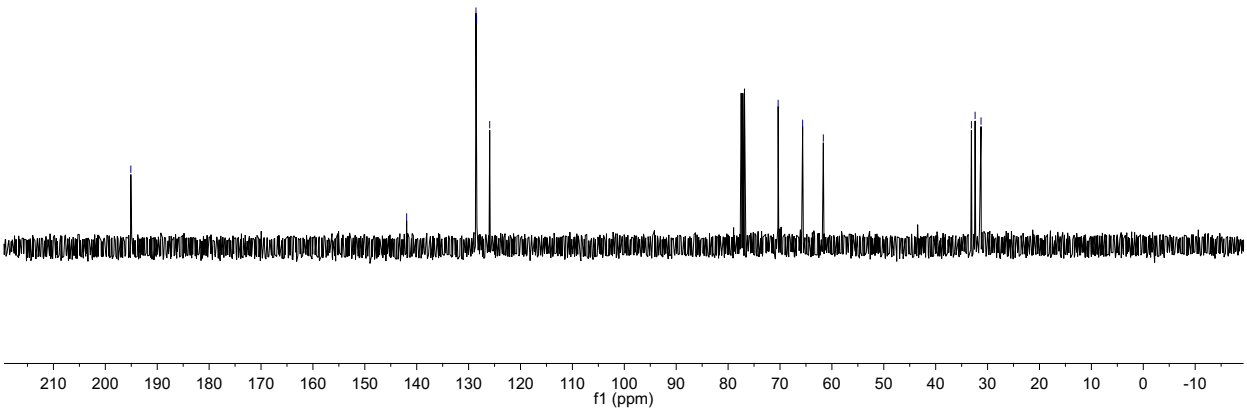


S7

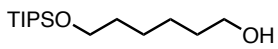
100 MHz, $CDCl_3$



S7

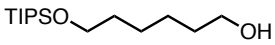


400 MHz, $CDCl_3$



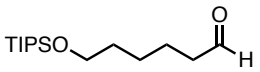
S8

100 MHz, $CDCl_3$



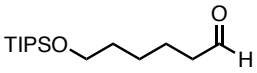
S8

400 MHz, $CDCl_3$



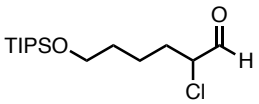
S9

100 MHz, $CDCl_3$



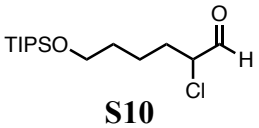
S9

400 MHz, $CDCl_3$

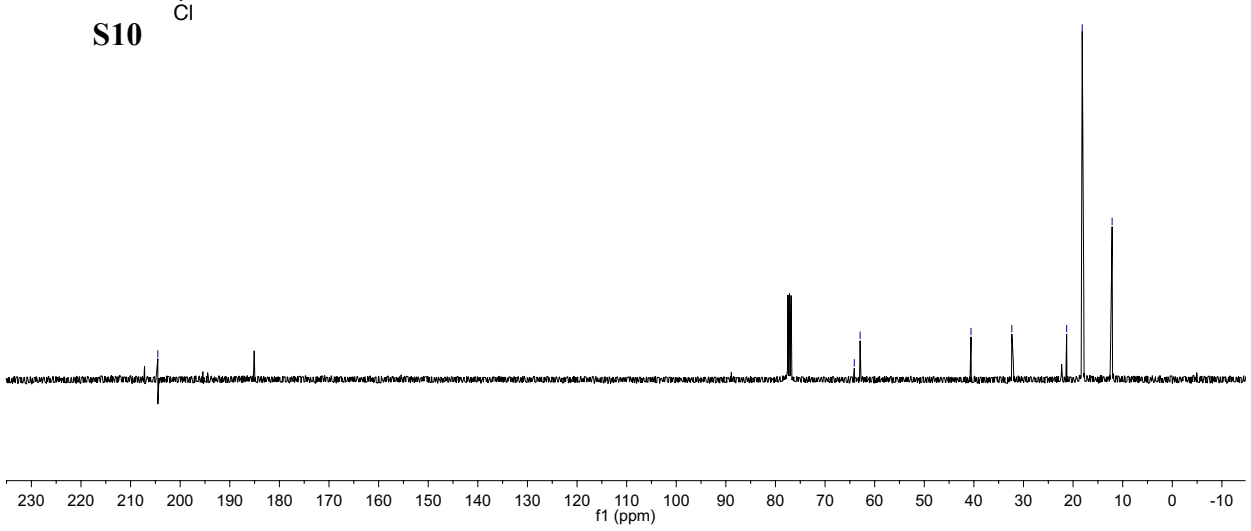


S10

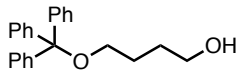
100 MHz, $CDCl_3$



S10

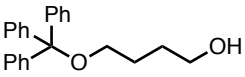


500 MHz, $CDCl_3$



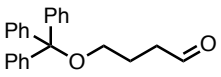
S11

100 MHz, $CDCl_3$



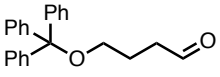
S11

400 MHz, $CDCl_3$



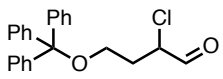
S12

100 MHz, $CDCl_3$



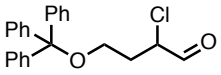
S12

400 MHz, $CDCl_3$



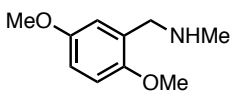
S13

100 MHz, $CDCl_3$



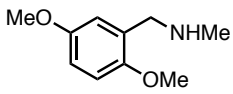
S13

400 MHz, $CDCl_3$

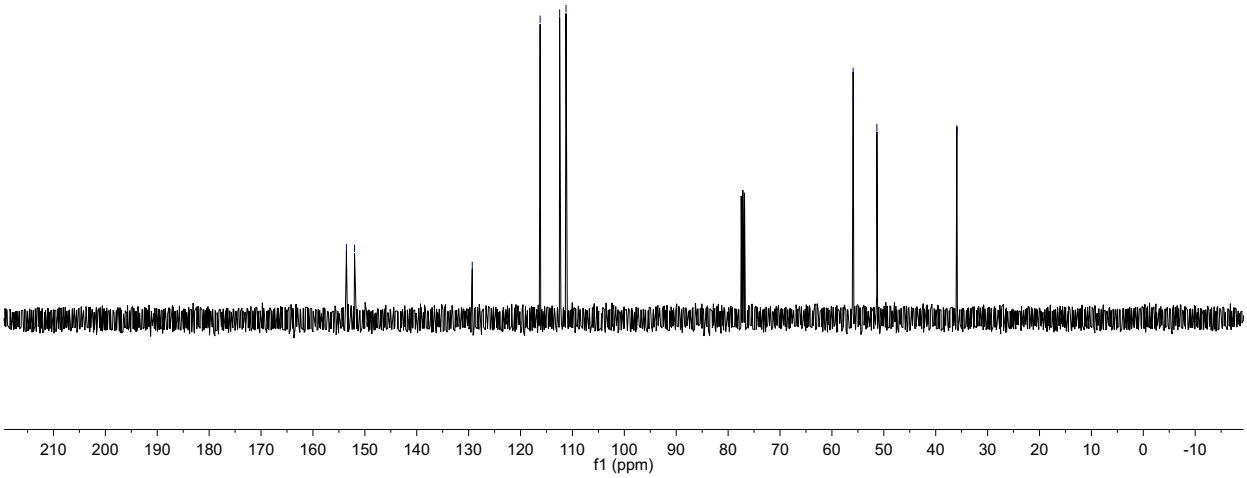


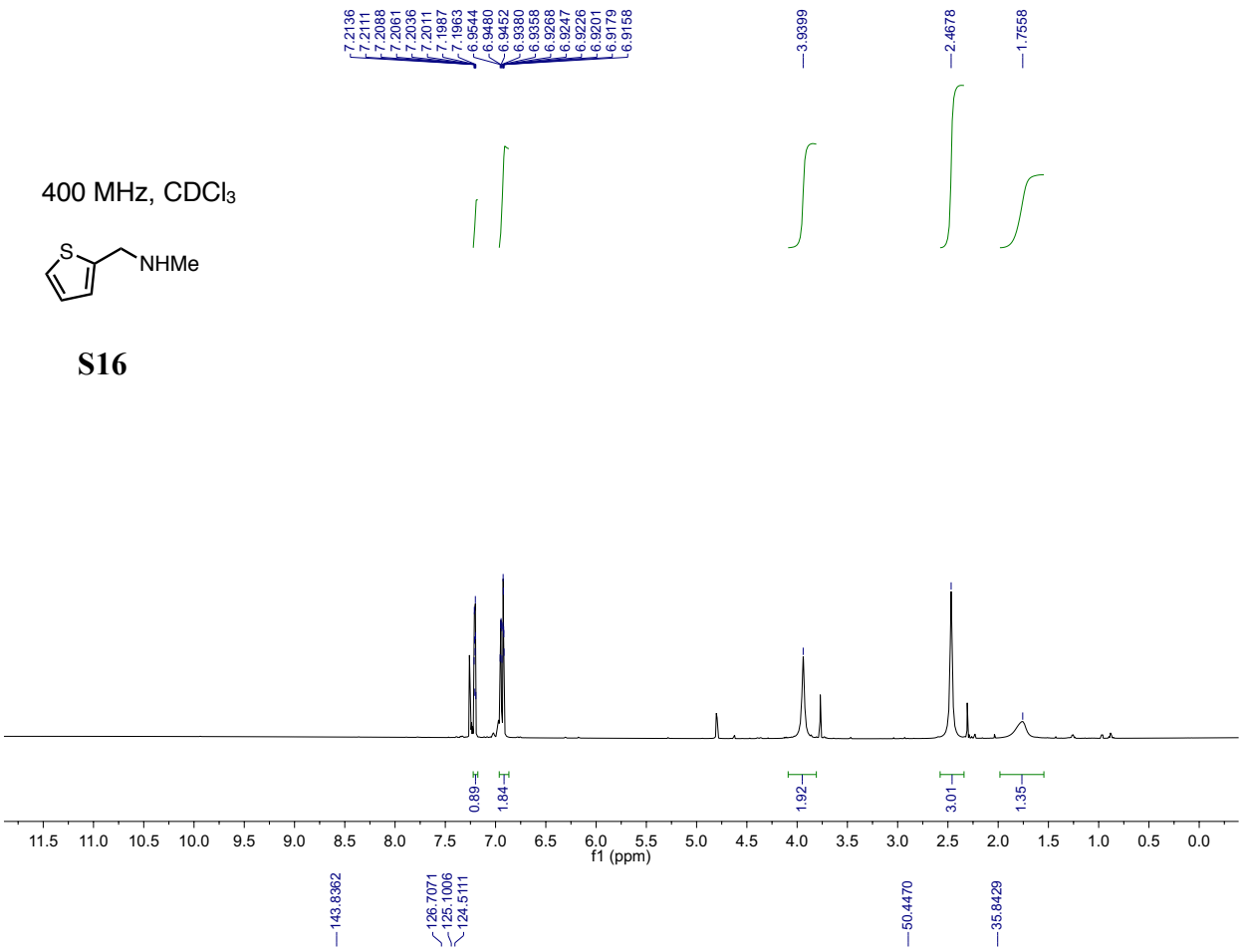
S14

100 MHz, $CDCl_3$



S14

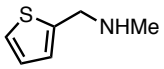




400 MHz, $CDCl_3$

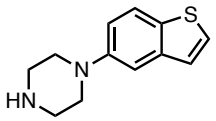
S16

100 MHz, $CDCl_3$



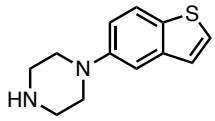
S16

500 MHz, $CDCl_3$



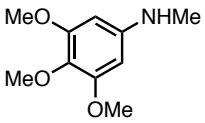
S17

125 MHz, $CDCl_3$



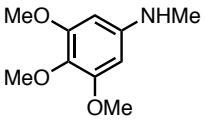
S17

500 MHz, $CDCl_3$



S18

125 MHz, $CDCl_3$



S18