Supplementary Information

Amide α-C–H Oxidative Coupling Reactions Enabled by Base-Promoted Halogen Transfer

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Table of Contents

1. General Information

General Reagent Information: All reactions were performed under a nitrogen (N_2) atmosphere unless otherwise noted. Benzyl alcohol (TCI catalog # B2378), 2,5-dibromothiophene (Ambeed catalog #A137367), 2-bromothiophene (Oakwood Chemical catalog #001055) and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6, Chem-Impex catalog #03901) were purchased from the indicated vendors and used as received. Potassium hydroxide (KOH for synthesis, Millipore Sigma catalog #814353, acidimetric assay ≥85.0%) was purchased as a powder and used as received. KOH and 18-crown-6 were stored at room temperature (rt) inside a N_2 filled glovebox and used immediately if brought outside the glovebox. 2-Methoxy-*N*-methylaniline (Combi-blocks catalog #HC-2923) was purified *via* silica column chromatography using 15% EtOAc and 85% Hexanes as the eluent before use. Potassium bis(trimethylsilyl)amide (1M solution in THF, KHMDS, TCI catalog #P3032) was used as received and stored in a desiccator. Tetrahydrofuran (THF) was deoxygenated and dried by passage over packed columns of neutral alumina and copper (II) oxide under positive pressure of N_2. All other solvents and reagents were purchased from Millipore Sigma, Combi-Blocks, TCI, Acros Organics, Matrix Scientific, AlfaAesar, or Synthonix and used as received unless otherwise noted. Flash chromatography was performed on 40-63 μm silica gel (SiliaFlash® F60 from Silicycle). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 Å F254 plates (20 x 20 cm, 1000 μm, SiliaPlate from Silicycle, #TLG-R10011B-341) and visualized with UV light (254 nm) or $KMnO_4$ solution.

General Analytical Information: All reported compounds were characterized by ^{1}H, ^{13}C, and ^{19}F (as applicable) NMR spectroscopy, FTIR spectroscopy and mass spectrometry. Melting point analysis was conducted if the compound was solid. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were obtained on a Bruker NEO400, Bruker US400 and Bruker Ascend 400 instruments. ^{1}H NMR data is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR data is reported as follows: chemical shift (δ ppm), multiplicity (if applicable, d = doublet, t = triplet, q = quartet), and coupling constant (Hz). All ^{1}H NMR signals are reported as chemical shifts (δ ppm) relative to residual tetramethylsilane at 0.00 ppm[1] or $CDCl_3$ at 7.26 ppm.[2] ^{19}F NMR signals are reported as chemical shifts relative to added 1,4-difluorobenzene internal standard calibrated to -119.7 ppm.[3,4] High resolution mass spectra (HRMS) were recorded on a 6230 LC-MS B-TOF equipped with a dual ESI source provided by Colorado State University Materials and Molecular Analysis Center. IR spectra were recorded using a Thermo Scientific Nicolet iS-50 FTIR Spectrometer and reported as frequency of absorption (cm^{-1}). Melting point analyses were conducted using a Mel-Temp capillary melting point apparatus. Thin-layer chromatography analysis was performed on silica gel 60 Å F_{254} plates (250 μm, SiliaPlate from Silicycle, #TLG-R10014B- 323) and interpreted using UV light (254 nm).

Nomenclature Note: The names provided for the structures in this document were obtained from ChemDraw Professional 23.1.2.

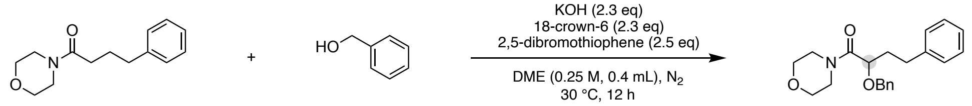
2. Optimization of the α-Functionalization of Amides

(a) Evaluation of changes in base, halogen transfer reagent, solvent, temperature, concentration, reaction time, and additive equivalence for the direct α-etherification of amides

Preliminary experiments varying base and solvent indicated that numerous combinations could promote the α-etherification of 1-morpholino-4-phenylbutan-1-one (**1**) using benzyl alcohol as a model alcohol. The set of conditions provided in Table S1 offer a benchmark for comparison to inform readers of the effect that specific changes of reagents or conditions have on yield. These studies were set up in a N_2 filled glovebox on a 0.10 mmol scale while a Schlenk line protocol for 1.0 mmol scale reactions was used for isolated yields shown in the substrate table.

General procedure for condition variation: 1-Morpholino-4-phenylbutan-1-one (**1**, 23.8 mg, 0.10 mmol, 1.0 eq), benzyl alcohol (**2**, 14.1 mg, 0.13 mmol, 1.3 eq), and 2,5-dibromothiophene (**XTR 1**, 60.5 mg, 0.25 mmol, 2.5 eq) were added to an oven-dried 4 mL vial (Thermo Fisher Scientific, Product #033405P) containing a magnetic stir bar. The vial was brought into a N_2 filled glovebox and anhydrous solvent (0.4 mL, 0.25 M), 18-crown-6 (60.8 mg, 0.23 mmol, 2.3 eq), and KOH (12.9 mg, 0.23 mmol, 2.3 eq) were added in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, Product #03392A) lined with a PTFE septum (Thermo Fisher Scientific, Product #B7995-15), removed from the glovebox, and placed into a 30 °C preheated aluminum reaction block and the reaction mixture was stirred for 12 hours. The reaction solution was cooled to room temperature, then 1,3,5-trimethoxybenzene internal standard was weighed into the vial. For each experiment, the mass of 1,3,5-trimethoxybenzene weighed into the vial was recorded separately. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (**3**). The aromatic C–H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aliphatic C–H signals of **3** at 4.14 ppm (dd, 1H) to determine the yield. The results are summarized in Table S1 below. A representative example ^1H NMR spectrum for the crude reaction solution from entry 1 of Table S1 is shown in Figure S1 to show how the yield was determined.

Standard Conditions



1, 0.10 mmol (1.0 eq) + **2**, 0.13 mmol (1.3 eq) → **3**

Entry	Change from the “standard conditions”	Yield
1	none	89%
2	r.t. instead of 30 °C	69%
3	LiOH used instead of KOH	0%
4	NaOH used instead of KOH	40%
5	KO-*t*-Bu used instead of KOH	25%
6	LDA used instead of KOH	0%
7	1.3 eq of KOH used instead of 2.3 eq	74%
8	1.3 eq of KOH used instead of 2.3 eq and 1.3 eq of 2,5-dibromothiophene used instead of 2.5 eq	67%
9	KOH used from Acros Organics (catalog # 437131) instead of KOH from Millipore Sigma (catalog # 814353)	82%
10	THF used as solvent instead of DME	52%
11	1,4-dioxane used as solvent instead of DME	55%
12	PhMe used as solvent instead of DME	66%
13	0.5 M DME instead of 0.25 M	64%
14	1.0 M DME instead of 0.25 M	80%
15	2 h instead of 12 h	56%
16	6 h instead of 12 h	68%
17	0.5 eq of 18-crown-6 instead of 2.3 eq	85%
18	1.0 eq of 18-crown-6 instead of 2.3 eq	79%
19	no 2,5-dibromothiophene	0%
20	2,5-dibromothiophene from Oakwood Chemical (catalog # 137367) instead of 2,5-dibromothiophene from Ambeed (catalog # 001055)	81%
21	2,5-diiodothiophene instead of 2,5-dibromothiophene	75%
22	2-iodothiophene instead of 2,5-dibromothiophene	49%
23	2-bromothiophene instead of 2,5-dibromothiophene	47%
24	2,3-dibromothiophene instead of 2,5-dibromothiophene	87%
25	*N*-iodosuccinimide used instead of 2,5-dibromothiophene	0%
26	*N*-bromosuccinimide used instead of 2,5-dibromothiophene	0%
27	*N*-chlorosuccinimide used instead of 2,5-dibromothiophene	0%
28	bromine used instead of 2,5-dibromothiophene	0%
29	iodine used instead of 2,5-dibromothiophene	0%
30	CI_4 used instead of 2,5-dibromothiophene	0%
31	CBr_4 used instead of 2,5-dibromothiophene	0%
32	CCl_4 used instead of 2,5-dibromothiophene	0%
33	Reaction run open to air instead of under N_2	52%
34	1.0 eq of H_2O added	38%

Table S1: Condition variation for the α-etherification of 1-morpholino-4-phenylbutan-1-one (**1**).

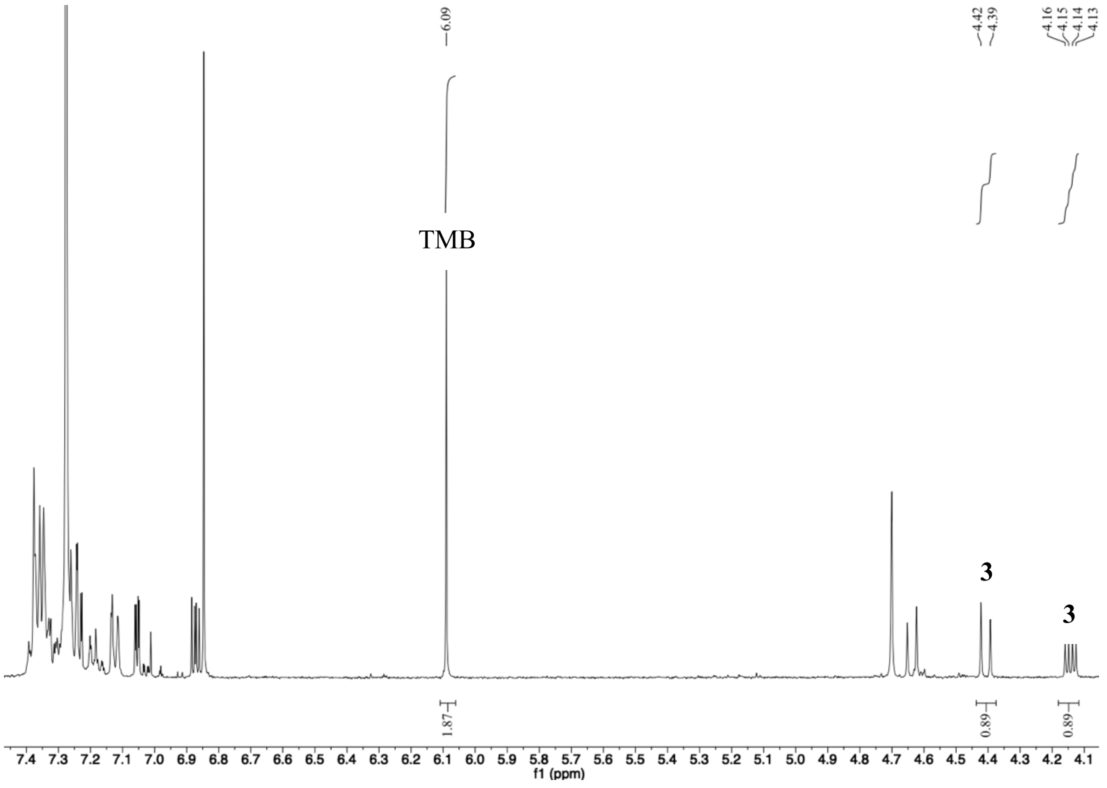


Figure S1: ^{1}H NMR spectral window of the crude reaction solution of Entry 1 from Table S1 above. 1,3,5-Trimethoxybenzene internal standard (10.5 mg, 0.06 mmol, signal at 6.09 ppm calibrated to 1.87 for 0.1 mmol scale reaction) was used to determine the yield of 2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (**3**, 89% yield).

(b) Comparison of 2.3 equivalents and 0.5 equivalents of 18-crown-6 additive for the direct α-functionalization of amides

Purpose: We sought to compare the effect on the yield of the α-coupling reactions of aliphatic alcohols, phenols, thiols, and thiophenols with the model amide 1-morpholino-4-phenylbutan-1-one (**1**) on a 0.1 mmol scale with 2.3 equivalents and 0.5 equivalents 18-crown-6 additive loading.

Procedure: The General procedure for condition variation (Page S3) was followed.

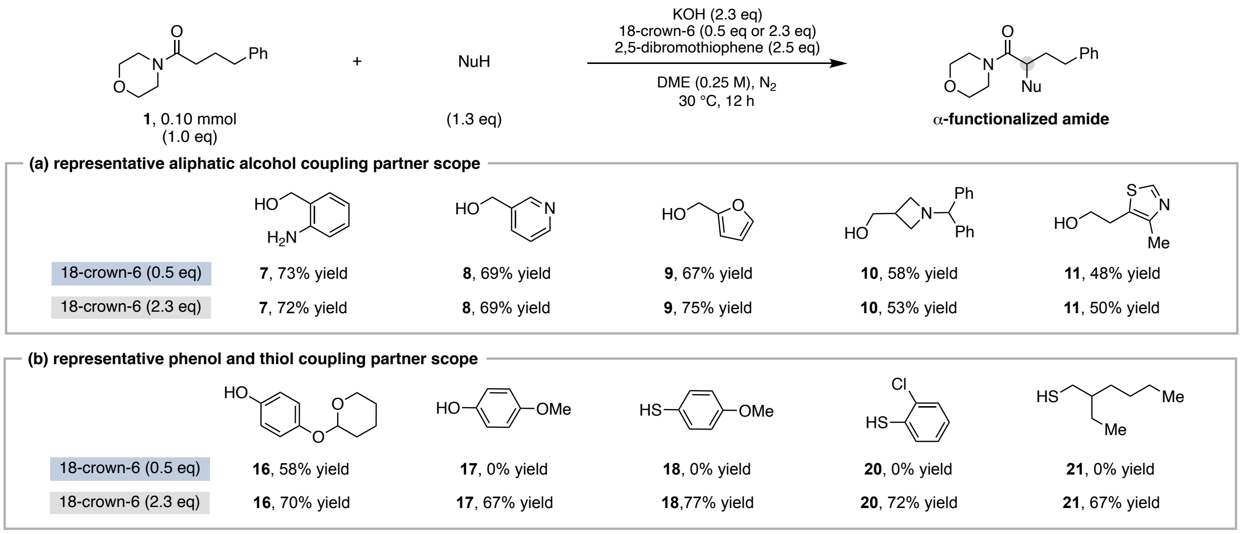


Figure S2: Comparison of the α-functionalization of **1** with various pronucleophiles at 2.3 equivalents and 0.5 equivalents of 18-crown-6 additive loading.

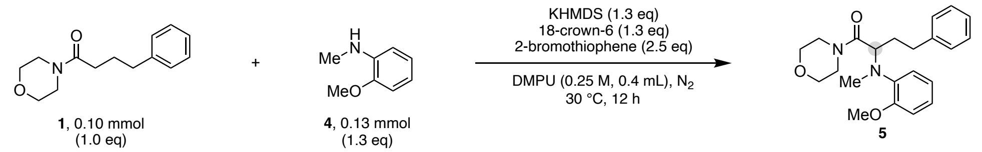
Discussion: Aliphatic alcohols give comparable yields regardless of the equivalents of 18-crown-6 additive used. For phenols, thiols, and thiophenols, the higher 18-crown-6 additive loading is necessary in order to achieve productive yields. For the general development of the substrate scope, 2.3 equivalents of 18-crown-6 was used for overall generality, while the practical reduction to 0.5 equivalents is illustrated on a multigram scale reaction in Figure 4.

(c) Evaluation of changes in optimal base, halogen transfer reagent, solvent, temperature, concentration, reaction time, and additive equivalence for the direct α-amination of amides

Preliminary experiments varying base and solvent indicated that numerous combinations could promote the α-amination of 1-morpholino-4-phenylbutan-1-one (**1**) using 2-methoxy-*N*-methylaniline (**4**) as a model amine. The set of conditions provided in Table S2 offer a benchmark for comparison to inform readers of the effect that specific changes of reagents or conditions have on yield. These studies were set up in a N_2 filled glovebox on a 0.10 mmol scale while a Schlenk line protocol for 1.0 mmol scale reactions was used for isolated yields shown in the substrate table.

General procedure for condition variation: 1-Morpholino-4-phenylbutan-1-one (**1**, 23.3 mg, 0.1 mmol, 1.0 eq), 2-methoxy-*N*-methylaniline (**4**, 17.8 mg, 0.13 mmol, 1.3 eq), and 2-bromothiophene (**XTR 2**, 40.8 mg, 0.25 mmol, 2.5 eq) were added to an oven-dried 4 mL vial (Thermo Fisher Scientific, Product #033405P) containing a magnetic stir bar. The vial was brought into a N_2 filled glovebox and anhydrous solvent (0.4 mL, 0.25 M), 18-crown-6 (34.4 mg, 0.13 mmol, 1.3 eq), and KHMDS (25.9 mg, 0.13 mmol, 1.3 eq) were added in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, Product #03392A) lined with a PTFE septum (Thermo Fisher Scientific, Product #B7995-15), removed from the glovebox, and placed into a 30 °C preheated aluminum reaction block and the reaction mixture was stirred for 12 hours. The reaction solution was cooled to room temperature, then 1,3,5-trimethoxybenzene internal standard was weighed into the vial. For each experiment, the mass of 1,3,5-trimethoxybenzene weighed into the vial was recorded separately. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 2-((2-methoxyphenyl)(methyl)amino)-1-morpholino-4-phenylbutan-1-one (**5**). The aromatic C–H signal of 1,3,5-trimethoxybenzene at 6.09 ppm was integrated against the aliphatic C–H signals of **5** at 4.47 ppm (dd, 1H) to determine the yield. The results are summarized in Table S2 below. A representative example ^{1}H NMR spectrum for the crude reaction solution from entry 1 of Table S2 is shown in Figure S3 to show how the yield was determined.

Standard Conditions



Entry	Change from the "standard conditions"	Yield
1	none	91%
2	r.t. instead of 30 °C	80%
3	KHMDS (1 M in THF) instead of solid KHMDS[a]	91%
4	NaHMDS used instead of KHMDS	69%
5	KO-*t*-Bu used instead of KHMDS	62%
6	KOH used instead of KHMDS	27%
7	2.3 eq of KHMDS used instead of 1.3 eq	84%
8	DME used as solvent instead of DMPU	73%
9	DMF used as solvent instead of DMPU	69%
10	THF used as solvent instead of DMPU	56%
11	PhMe used as solvent instead of DME	81%
12	0.5 M DMPU instead of 0.25 M	84%
13	1.0 M DMPU instead of 0.25 M	61%
14	2 h instead of 12 h	91%
15	0.5 eq of 18-crown-6 instead of 1.3 eq	89%
16	no 2-bromothiophene	0%
17	2-bromothiophene from Oakwood Chemical (catalog #001055) instead of 2-bromothiophene from Matrix Scientific (catalog # 004198)	84%
18	2,5-dibromothiophene instead of 2-bromothiophene	0%
19	2,5-diiodothiophene instead of 2-bromothiophene	43%
20	2-iodothiophene instead of 2-bromothiophene	63%
21	Reaction run open to air instead of under N_2	76%

Table S2: Condition variation for the α-amination of 1-morpholino-4-phenylbutan-1-one (**1**).
[a] reaction run on 1.0 mmol scale, see General Procedure for the α-Amination of Amides.

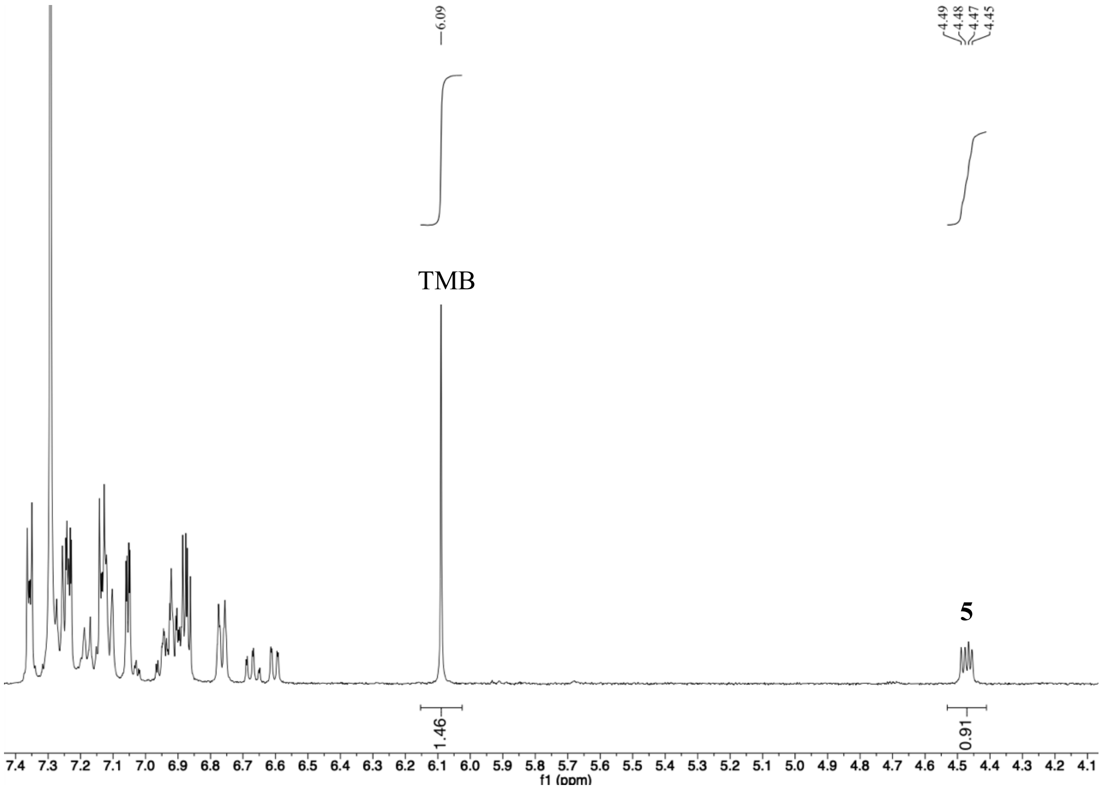
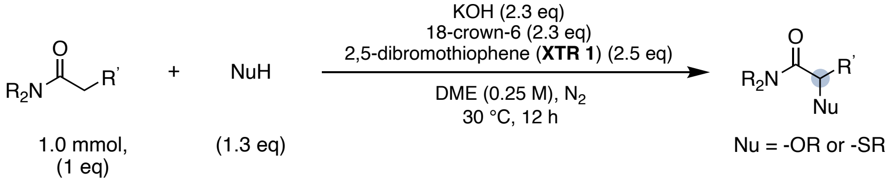


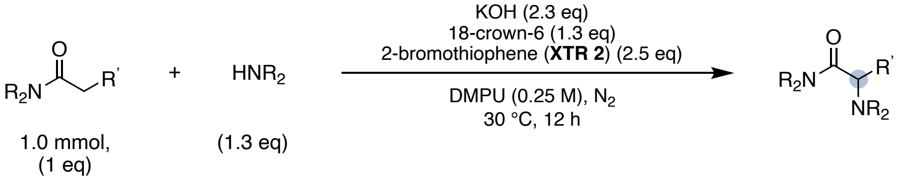
Figure S3. ^{1}H NMR spectral window of the crude reaction solution of Entry 1 from Table S2 above. 1,3,5-Trimethoxybenzene internal standard (8.2 mg, 0.05 mmol, signal at 6.09 ppm calibrated to 1.46 for 0.1 mmol scale reaction) was used to determine the yield of 2-((2-methoxyphenyl)(methyl)amino)-1-morpholino-4-phenylbutan-1-one (**5**, 91% yield).

3. General Procedures for the α-Functionalization of Amides

The reaction optimization studies were conducted inside a N_2 filled glovebox, while the general procedure for 1.0 mmol scale isolation reactions was developed using a standard manifold Schlenk line. The yields determined by ^{1}H NMR spectroscopy of the optimization reactions are comparable to those for the 1.0 mmol scale isolation procedure.



General Procedure for the α-Etherification and α-Thiolation of Amides: The appropriate amide (1.0 mmol, 1.0 eq), pronucleophile (if solid, 1.3 mmol, 1.3 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), and KOH (129.0 mg, 2.3 mmol, 2.3 eq) were added in successive order to an oven-dried 25 mL round bottom flask containing a magnetic stir bar. The flask was sealed with a rubber septum (Thermo Fisher Scientific, Product #CG302206) and subsequently evacuated and backfilled five times with N_2, and left under a positive pressure of N_2 on a manifold Schlenk line using a needle inlet. Anhydrous DME (4 mL, 0.25 M), pronucleophile (if liquid, 1.3 mmol, 1.3 eq), and 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq) were added *via* syringe in successive order. The needle inlet was removed and the septum was wrapped with parafilm and the flask was placed into a preheated 30 °C silicon oil bath with stirring for 12 hours. The reaction solution was allowed to cool to room temperature and was subsequently transferred into separatory funnel containing saturated ammonia chloride (50 mL). The aqueous mixture was extracted with DCM (3 x 50 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography using the conditions given below.



General Procedure for the α-Amination of Amides: The appropriate amide (1.0 mmol, 1.0 eq), pronucleophile (if solid, 1.3 mmol, 1.3 eq), and 18-crown-6 (345.5 mg, 1.3 mmol, 1.3 eq), were added in successive order to an oven-dried 25 mL round bottom flask containing a magnetic stir bar. The flask was sealed with a rubber septum (Thermo Fisher Scientific, Product #CG302206) and subsequently evacuated and backfilled five times with N_2, and left under a positive pressure of N_2 on a manifold Schlenk line using a needle inlet. Anhydrous DMPU (2.7 mL, 0.25 M), pronucleophile (if liquid, 1.3 mmol, 1.3 eq), 2-bromothiophene (0.24 mL, 2.5 mmol, 2.5 eq), and KHMDS (1M solution in THF, 1.3 mL, 1.3 mmol, 1.3 eq) were added *via* syringe in successive order. The needle inlet was removed and the septum was wrapped with parafilm and the flask was placed into a preheated 30 °C silicon oil bath with stirring for 12 h. The reaction solution was allowed to cool to rt and was subsequently transferred into separatory funnel containing saturated ammonia chloride (150 mL). The aqueous mixture was extracted with toluene (3 x 50 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography using the conditions given below.

4. Notes on Pronucleophile and Amide Scope Limitations

(a) Pronucleophile Scope Limitations

Purpose: We sought to identify limitations of the pronucleophile scope for this method with the coupling of the model amide 1-morpholino-4-phenylbutan-1-one (**1**) on a 0.1 mmol scale.

Procedure: The General procedure for condition variation (Page S3) was followed.

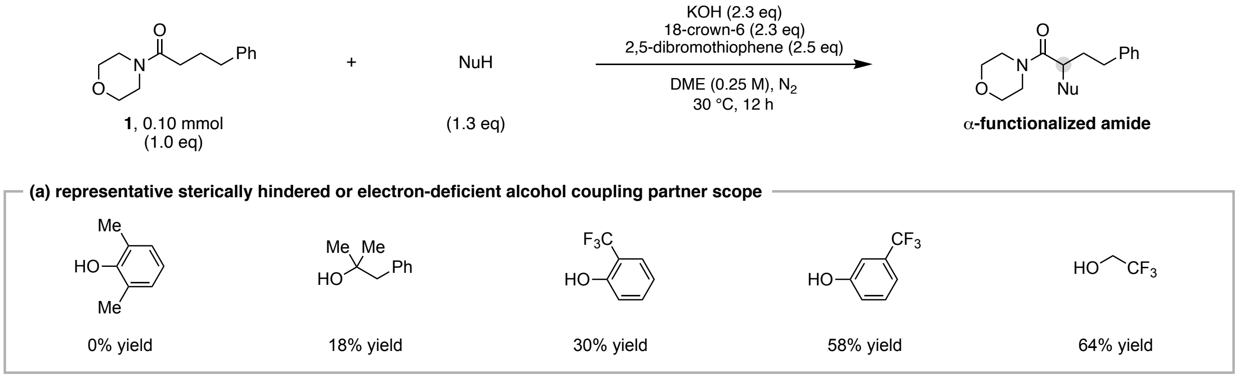


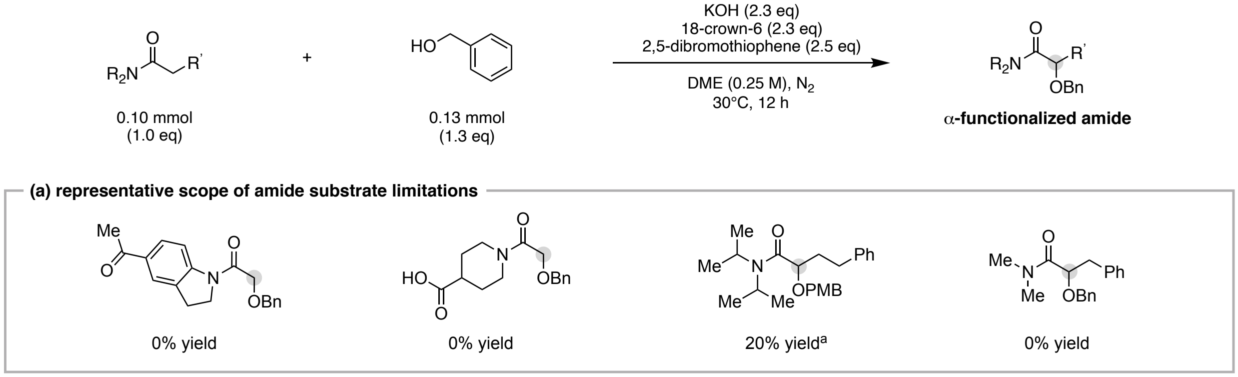
Figure S4: Evaluation of the α-etherification of **1** with various sterically hindered or electron-deficient pronucleophiles.

Discussion: Sterically hindered tertiary alcohols (2-methyl-1-phenylpropan-2-ol) and phenols (1,6-dimethylphenol) give little or no yield, while alcohols and phenols with electron-withdrawing groups give a slight reduction, but still modest, yield. No starting material remains when tertiary alcohols are used, suggesting other base-promoted processes outcompete the desired α-coupling. In contrast, starting material remains with sterically hindered or electron-deficient phenols, suggesting these pronucleophiles interfere with amide deprotonation.

(b) Amide Scope Limitations

Purpose: We sought to demonstrate the amide structural limitations of this method using the coupling of benzyl alcohol (**2**) with a variety of amide substrates.

Procedure: The General procedure for condition variation (Page S3) was followed.



[a] Reaction run at 1.0 mmol scale with 2.3 eq. of nucleophile and 3.3 eq of KOH/18-crown-6

Figure S5: Evaluation of the α-etherification conditions with various amide substrates.

Discussion: Amide substrates containing other acidic positions (*e.g.,* ketone or carboxylic acid) are not tolerated under these conditions. An *N*,*N*-diisopropylamide gives low yield, likely due to steric hinderance and its impact on α-deprotonation. Meanwhile, a phenylalanine derivative gives no yield, perhaps due to competitive benzylic deprotonation or elimination side processes, although such side products were not observed.

(c) Other Carbonyl-containing Substrate Scope Limitations

Purpose: An immediate question regarding this protocol is whether or not it is applicable to other carbonyl-based functional groups. To test this, we examined the coupling of benzyl alcohol (**2**) with representative substrates containing carboxylic acid, ester, and ketone groups.

Procedure: The General procedure for condition variation (Page S3) was followed.

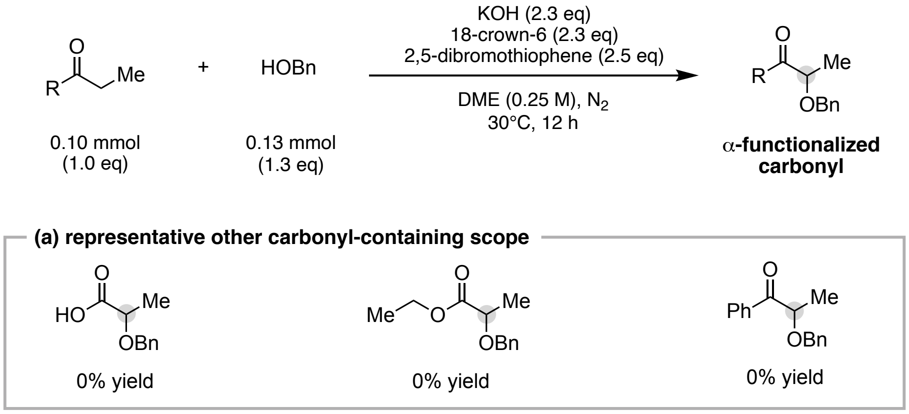


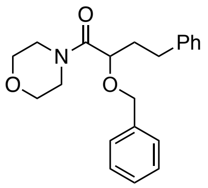
Figure S6: Evaluation of the α-etherification conditions with various carbonyl substrates.

Discussion: The optimized reaction conditions are not effective for α-etherification of carboxylic acids, esters, or ketones. For the acid, complete mass balance is retained, likely due to initial –OH deprotonation and a subsequent lack of reactivity. Mass balance is also retained for the ester, suggesting that α-halogenation is not productive using 2,5-dibromothiophene oxidant. In contrast, the ketone undergoes undesired base-promoted side reactions (*e.g.*, aldol processes). We anticipate that adjustments in the base and oxidant strengths can be used to overcome these considerations.

5. Characterization Data for the α-Functionalization of Amides

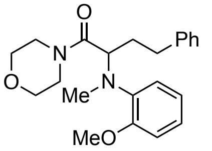
(a) Characterization data for the α-functionalized amide substrates in Table 1

2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (3)



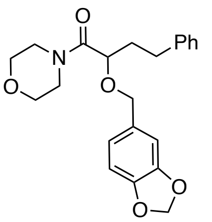
The title product was prepared according to the general procedure for α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (20% EtOAc, 20% diethyl ether, 60% hexanes) afforded the title compound as a clear oil (229.9 mg, 0.68 mmol, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 7.25 (m, 2H), 7.17 (m, 1H), 7.11 (m, 2H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.13 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.70 – 3.37 (m, 8H), 2.84 (m, 1H), 2.76 – 2.60 (m, 1H), 2.19 – 2.06 (m, 1H), 2.06 – 1.85 (m, 1H). **^{13}C NMR** (101 MHz, DMSO) δ 169.1, 141.2, 137.9, 128.4, 128.3, 128.3, 127.9, 127.6, 125.9, 76.5, 70.4, 66.2, 66.1, 45.1, 41.9, 33.4, 31.1. **IR** (neat, cm^{-1}) 2956, 2855, 2359, 1637, 1453, 1112. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{26}NO_3]^+$ =340.1907, 340.1908 found.

2-((2-methoxyphenyl)(methyl)amino)-1-morpholino-4-phenylbutan-1-one (5)



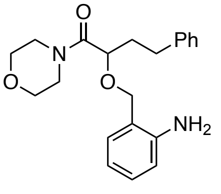
The title product was prepared according to the general procedure for the α-amination using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), 2-methoxy-*N*-methylaniline (178.3 mg, 1.3 mmol, 1.3 eq), 2-bromothiophene (0.24 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (343.5 mg, 1.3 mmol, 1.3 eq), KHMDS (1M solution in THF, 1.3 mL, 1.3 mmol, 1.3 eq) and DMPU (2.7 mL). Silica gel chromatography (25% EtOAc, 75% hexanes) afforded the title compound as a pale-yellow solid (297.9 mg, 0.81 mmol, 81% yield). **Mp**: 93 – 94 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.25 (m, 2H), 7.20 – 7.04 (m, 3H), 7.01 – 6.82 (m, 3H), 6.82 – 6.65 (m, 1H), 4.47 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.85 (m, 1H), 3.62 (m, 4H), 3.56 – 3.10 (m, 5H), 3.01 – 2.87 (m, 1H), 2.78 (m, 4H), 2.54 – 2.38 (m, 2H), 1.99 – 1.84 (m, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 169.3, 152.0, 141.9, 140.1, 128.6, 128.4, 125.9, 122.8, 121.3, 120.6, 111.3, 67.2, 66.8, 57.5, 55.1, 46.0, 42.4, 34.8, 32.6, 29.5. **IR** (neat, cm^{-1}) 2919, 2858, 2360, 1631, 1235, 1111. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{22}$H$_{29}$N$_2$O$_3$]$^+$ = 369.2173, 369.2175 found.

2-(benzo[*d*][1,3]dioxol-5-ylmethoxy)-1-morpholino-4-phenylbutan-1-one (6)



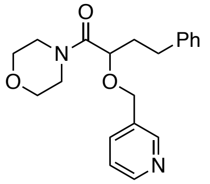
The title product was prepared according to the general procedure for α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), benzo[*d*][1,3]dioxol-5-ylmethanol (197.8 mg, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (20% diethyl ether, 80% toluene) afforded the title compound as a pale-yellow oil (285.1 mg, 0.74 mmol, 74% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.42 – 7.22 (m, 2H), 7.22 – 7.02 (m, 3H), 6.84 (s, 1H), 6.77 (d, *J* = 1.6 Hz, 2H), 5.96 (s, 2H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.29 (d, *J* = 11.3 Hz, 1H), 4.11 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.72 – 3.38 (m, 8H), 2.89 – 2.75 (m, 1H), 2.74 – 2.60 (m, 1H), 2.17 – 2.03 (m, 1H), 2.03 – 1.90 (m, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 170.3, 147.9, 147.5, 141.1, 131.3, 128.6, 128.6, 126.2, 121.9, 108.9, 108.2, 101.2, 78.1, 71.6, 67.2, 66.8, 45.6, 42.6, 34.2, 31.9. **IR** (neat, cm^{-1}) 2856, 1636, 1489, 1441, 1239, 1112, 1032. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{22}$H$_{26}$NO$_5$]$^+$ =384.1805, 384.1809 found.

2-((2-aminobenzyl)oxy)-1-morpholino-4-phenylbutan-1-one (7)



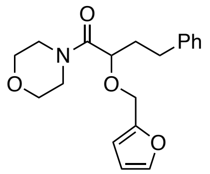
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), (2-aminophenyl)methanol (160.1 mg, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (80% diethyl ether, 20% hexanes) afforded the title compound as an orange oil (263.1 mg, 0.77 mmol, 77% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.31 – 7.11 (m, 6H), 7.06 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.81 – 6.54 (m, 2H), 4.41 (m, 4H), 4.05 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.72 – 3.45 (m, 6H), 3.16 (d, *J* = 3.8 Hz, 2H), 2.94 – 2.78 (m, 1H), 2.78 – 2.63 (m, 1H), 2.21 – 1.99 (m, 1H), 1.95 – 1.74 (m, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 171.0, 147.2, 141.0, 130.5, 129.9, 128.7, 128.6, 126.3, 121.2, 117.3, 115.8, 74.7, 70.9, 67.1, 66.5, 45.4, 42.5, 34.7, 31.7. **IR** (neat, cm^{-1}) 3440, 3350, 2921, 2857, 2360, 1635, 1454, 1110. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{21}$H$_{27}$N$_2$O$_3$]$^+$ =355.2016, 355.2023 found.

1-morpholino-4-phenyl-2-(pyridin-3-ylmethoxy)butan-1-one (8)



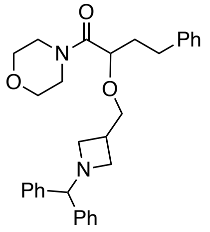
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), pyridin-3-ylmethanol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (4% MeOH, 96% DCM) afforded the title compound as a yellow oil (217.5 mg, 0.64 mmol, 64% yield). **^{1}H NMR** (400 MHz, DMSO) δ 8.56 (d, *J* = 2.9 Hz, 1H), 8.52 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.77 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.40 (dd, *J* = 7.3, 4.3 Hz, 1H), 7.33 – 7.22 (m, 2H), 7.22 – 7.10 (m, 3H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.25 (dd, *J* = 8.1, 4.9 Hz, 1H), 3.60 – 3.41 (m, 8H), 2.78 – 2.55 (m, 2H), 2.05 – 1.83 (m, 2H). **^{13}C NMR** (101 MHz, DMSO) δ 168.9, 149.1, 148.9, 141.2, 135.7, 133.4, 128.4, 128.4, 125.9, 123.5, 76.6, 68.0, 66.2, 66.1, 45.1, 41.9, 33.4, 31.1. **IR** (neat, cm^{-1}) 2919, 2855, 2360, 2341, 1636, 1428, 1111. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{25}N_2O_3]^+$ =341.1860, 341.1863 found.

2-(furan-2-ylmethoxy)-1-morpholino-4-phenylbutan-1-one (9)



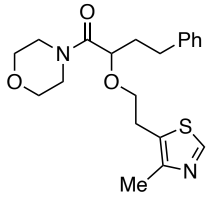
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), furan-2-ylmethanol (0.11 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (5% EtOAc, 20% diethyl ether, 75% hexanes then 30% EtOAc, 20% diethyl ether, 50% hexanes) afforded the title compound as a pale-yellow oil (225.8 mg, 0.69 mmol, 69% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.36 – 7.04 (m, 6H), 6.40 – 6.26 (m, 2H), 4.54 (d, *J* = 12.8 Hz, 1H), 4.40 (d, *J* = 12.9 Hz, 1H), 4.10 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.69 – 3.34 (m, 9H), 2.80 (m, 1H), 2.66 (m, 1H), 2.07 (m, 1H), 2.00 – 1.86 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1, 151.1, 143.1, 141.0, 128.6, 128.5, 126.1, 110.5, 110.2, 77.7, 67.0, 66.7, 63.3, 45.5, 42.5, 34.1, 31.7. **IR** (neat, cm^{-1}) 2920, 2855, 2360, 2342, 1637, 1434, 1112. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{24}NO_4]^+$ =330.1700, 330.1695 found.

2-((1-benzhydrylazetidin-3-yl)methoxy)-1-morpholino-4-phenylbutan-1-one (10)



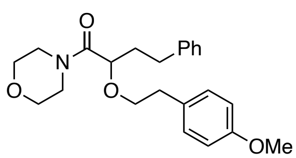
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), (1-benzhydrylazetidin-3-yl)methanol (329.4 mg, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (98% DCM, 2% MeOH) afforded the title compound as a pale-yellow oil (252.4 mg, 0.52 mmol, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.3 Hz, 4H), 7.32 – 7.21 (m, 6H), 7.21 – 7.08 (m, 5H), 4.34 (s, 1H), 4.02 (dd, *J* = 9.1, 4.7 Hz, 1H), 3.79 – 3.42 (m, 10H), 3.27 (q, *J* = 7.4 Hz, 2H), 2.99 – 2.84 (m, 2H), 2.80 (m, 1H), 2.74 – 2.58 (m, 2H), 2.12 – 1.86 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.2, 142.2, 141.0, 128.5, 128.4, 127.5, 127.1, 126.1, 79.5, 77.9, 72.0, 67.0, 66.8, 56.5, 56.3, 45.4, 42.5, 33.9, 31.8, 29.8. **IR** (neat, cm^{-1}) 2953, 2851, 2359, 2341, 1639, 1451, 1112. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{31}H_{37}N_2O_3]^+$ =485.2799, 485.2811 found.

2-(2-(4-methylthiazol-5-yl)ethoxy)-1-morpholino-4-phenylbutan-1-one (11)



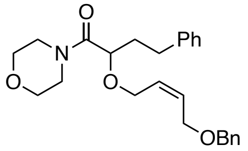
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), 2-(4-methylthiazol-5-yl)ethan-1-ol (0.17 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (3% MeOH, 97% DCM) afforded the title compound as a brown solid (137.0 mg, 0.37 mmol, 37% yield). **Mp**: 46 – 49 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.61 (s, 1H), 7.30 (m, 2H), 7.22 (m, 1H), 7.17 – 7.09 (m, 2H), 4.04 (dd, J = 9.0, 4.6 Hz, 1H), 3.86 – 3.73 (m, 1H), 3.73 – 3.37 (m, 9H), 3.08 (t, J = 6.4 Hz, 2H), 2.82 (m, 1H), 2.76 – 2.62 (m, 1H), 2.44 (s, 3H), 2.15 – 1.91 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 170.1, 149.8, 149.7, 141.1, 128.7, 128.6, 127.9, 126.3, 79.7, 69.7, 67.2, 66.8, 45.5, 42.6, 34.1, 31.9, 27.2, 15.2. **IR** (neat, cm^{-1}) 2915, 2857, 2360, 1647, 1449, 1109. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{20}$H$_{27}$N$_2$O$_3$S]$^+$ =375.1737, 375.1744 found.

2-(4-methoxyphenethoxy)-1-morpholino-4-phenylbutan-1-one (12)



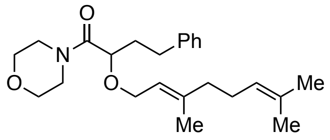
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), 2-(4-methoxyphenyl)ethan-1-ol (197.8 mg, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (15% EtOAc, 85% hexanes to 55% EtOAc, 45% hexanes) afforded the title compound as a clear oil (266.1 mg, 0.69 mmol, 69% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.26 (m, 2H), 7.22 – 7.01 (m, 5H), 6.84 (d, J = 8.8 Hz, 2H), 3.99 (dd, J = 9.1, 4.8 Hz, 1H), 3.77 (m, 4H), 3.67 – 3.34 (m, 9H), 2.90 – 2.58 (m, 4H), 2.10 – 1.87 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 170.5, 158.4, 141.2, 131.1, 130.1, 128.6, 128.6, 126.2, 113.9, 80.0, 71.0, 67.2, 66.9, 55.4, 45.5, 42.6, 35.7, 34.1, 31.9. **IR** (neat, cm^{-1}) 2916, 2855, 2360, 2341, 1636, 1244, 1111, 1028. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{23}$H$_{30}$NO$_4$]$^+$ =384.2169, 384.2178 found.

(*Z*)-2-((4-(benzyloxy)but-2-en-1-yl)oxy)-1-morpholino-4-phenylbutan-1-one (13)



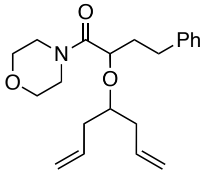
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), (*Z*)-4-(benzyloxy)but-2-en-1-ol (0.22 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (15% EtOAc, 40% diethyl ether, 45% hexanes) afforded the title compound as a pale-yellow oil (269.4 mg, 0.66 mmol, 66% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.43 – 7.23 (m, 7H), 7.19 (t, J = 8.9 Hz, 3H), 5.90 – 5.65 (m, 2H), 4.50 (s, 2H), 4.18 – 3.93 (m, 5H), 3.59 (m, 8H), 2.87 – 2.62 (m, 2H), 2.13 – 1.88 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 170.4, 141.2, 138.1, 129.9, 128.8, 128.7, 128.6, 128.6, 127.9, 127.9, 126.3, 78.8, 72.6, 67.2, 66.9, 65.9, 65.5, 45.6, 42.7, 34.2, 31.9. **IR** (neat, cm^{-1}) 3026, 2852, 2360, 2342, 1639, 1453, 1113. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{25}$H$_{32}$NO$_4$]$^+$ =410.2326, 410.2332 found.

(*E*)-2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-1-morpholino-4-phenylbutan-1-one (14)



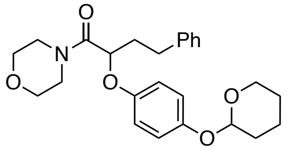
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), (*E*)-3,7-dimethylocta-2,6-dien-1-ol (0.23 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (15% EtOAc, 5% MTBE, 80% hexanes) afforded the title compound as a pale-yellow oil (277.4 mg, 0.72 mmol, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 2H), 7.24 – 7.03 (m, 3H), 5.34 (m, 1H), 5.19 – 4.99 (m, 1H), 4.08 (m, 2H), 3.94 (dd, *J* = 11.9, 7.6 Hz, 1H), 3.72 – 3.49 (m, 8H), 2.89 – 2.76 (m, 1H), 2.75 – 2.63 (m, 1H), 2.17 – 1.88 (m, 6H), 1.69 (s, 3H), 1.66 (s, 3H), 1.61 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7, 141.2, 140.9, 131.8, 128.6, 128.5, 126.1, 123.9, 120.1, 78.4, 67.1, 66.8, 66.0, 45.5, 42.5, 39.6, 34.1, 31.9, 26.4, 25.7, 17.7, 16.5. **IR** (neat, cm^{-1}) 2921, 2852, 2360, 2342, 1639, 1453, 1113. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{24}H_{36}NO_3]^+$ =386.2690, 386.2691 found.

2-(hepta-1,6-dien-4-yloxy)-1-morpholino-4-phenylbutan-1-one (15)



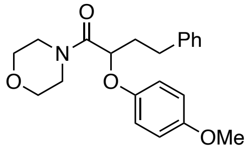
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), hepta-1,6-dien-4-ol (0.17 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (70% EtOAc, 30% hexanes) afforded the title compound as a clear oil (211.5 mg, 0.62 mmol, 62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 2H), 7.24 – 7.12 (m, 3H), 5.92 – 5.67 (m, 2H), 5.08 (ddd, *J* = 13.6, 5.9, 2.1 Hz, 4H), 4.19 (dd, *J* = 8.1, 5.6 Hz, 1H), 3.62 (m, 8H), 3.53 – 3.44 (m, 1H), 2.96 – 2.75 (m, 1H), 2.74 – 2.55 (m, 1H), 2.43 – 2.20 (m, 4H), 2.10 – 1.89 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1, 141.2, 134.2, 128.5, 128.4, 126.2, 117.7, 117.6, 79.5, 78.8, 67.1, 66.8, 45.8, 42.6, 38.5, 37.3, 35.1, 32.1. **IR** (neat, cm^{-1}) 2918, 2854, 2360, 2342, 1637, 1432, 1114. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{30}NO_3]^+$ =344.2220, 344.2222 found.

1-morpholino-4-phenyl-2-(4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenoxy)butan-1-one (16)



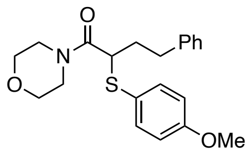
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), 4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenol (0.22 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (20% EtOAc, 40% diethyl ether, 40% hexanes) afforded the title compound as a white, opaque oil (307.4 mg, 0.72 mmol, 72% yield). We note that this compound is likely generated in a 1:1 diastereomeric ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.10 (m, 5H), 6.97 (d, *J* = 9.1 Hz, 2H), 6.80 (d, *J* = 9.1 Hz, 2H), 5.29 (t, *J* = 3.7 Hz, 1H), 4.75 – 4.63 (m, 1H), 4.00 – 3.83 (m, 1H), 3.77 – 3.42 (m, 8H), 3.37 (m, 1H), 2.92 (m, 1H), 2.85 – 2.68 (m, 1H), 2.34 – 2.08 (m, 2H), 2.08 – 1.76 (m, 3H), 1.76 – 1.51 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3, 151.9, 151.7, 140.5, 128.3, 126.0, 117.6, 115.4, 97.0, 78.3, 78.2, 66.7, 66.5, 61.9, 45.4, 42.6, 34.0, 31.6, 30.3, 25.0, 18.7. **IR** (neat, cm^{-1}) 2942, 2852, 1636, 1502, 1214, 1112. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{25}H_{32}NO_5]^+$ = 426.2275, 426.2290 found.

2-(4-methoxyphenoxy)-1-morpholino-4-phenylbutan-1-one (17)



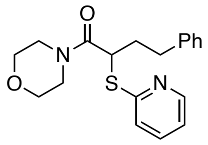
The title product was prepared according to the general procedure for the α-etherification using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), 4-methoxyphenol (161.4 mg, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (20% EtOAc, 20% diethyl ether, 60% hexanes) afforded the title compound as a yellow solid (222.7 mg, 0.63 mmol, 63% yield). **Mp**: 85 – 87 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.24 – 7.12 (m, 3H), 6.82 (s, 4H), 4.69 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.80 – 3.43 (m, 10H), 3.42 – 3.27 (m, 1H), 2.99 – 2.85 (m, 1H), 2.85 – 2.70 (m, 1H), 2.39 – 2.08 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.7, 154.6, 151.6, 140.9, 128.7, 126.4, 115.9, 115.0, 78.8, 67.1, 66.9, 55.8, 45.8, 43.0, 34.4, 32.0. **IR** (neat, cm^{-1}) 2953, 2852, 2360, 1645, 1506, 1226. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{26}NO_4]^+$ =356.1856, 356.1883 found.

2-((4-methoxyphenyl)thio)-1-morpholino-4-phenylbutan-1-one (18)



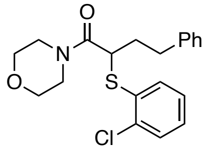
The title product was prepared according to the general procedure for the α-thiolation using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), 4-methoxybenzenethiol (0.16 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (20% EtOAc, 60% hexanes, 20% diethyl ether) afforded the title compound as a yellow oil (213.8 mg, 0.58 mmol, 58% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.9 Hz, 2H), 7.31 – 7.22 (m, 2H), 7.16 (m, 3H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 3.73 – 3.31 (m, 7H), 3.20 (m, 2H), 2.88 – 2.73 (m, 1H), 2.71 – 2.54 (m, 1H), 2.29 (m, 1H), 2.02 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 160.5, 141.1, 137.0, 128.6, 128.6, 126.2, 122.1, 114.6, 67.0, 66.5, 55.4, 46.2, 45.8, 42.4, 33.3, 33.1. **IR** (neat, cm^{-1}) 2920, 2853, 2360, 2343, 1640, 1492, 1244, 1113. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{26}NO_3S]^+$ =372.1628, 372.1642 found.

1-morpholino-4-phenyl-2-(pyridin-2-ylthio)butan-1-one (19)



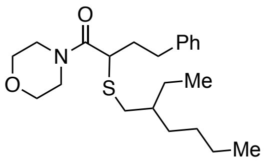
The title product was prepared according to the general procedure for α-thiolation using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), pyridine-2-thiol (144.5 mg, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (50% EtOAc, 30% hexanes, 20% diethyl ether) afforded the title compound as an orange oil (269.2 mg, 0.79 mmol, 79% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 4.0 Hz, 1H), 7.48 (td, *J* = 7.4, 1.9 Hz, 1H), 7.27 (m, 2H), 7.23 – 7.07 (m, 4H), 6.99 (dd, *J* = 8.5, 5.0 Hz, 1H), 5.01 (dd, *J* = 8.0, 6.5 Hz, 1H), 3.82 – 3.48 (m, 7H), 3.41 (m, 1H), 2.74 (m, 2H), 2.43 (m, 1H), 2.24 – 2.10 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.3, 157.0, 149.1, 141.0, 136.2, 128.5, 128.3, 126.0, 122.4, 119.9, 66.8, 66.6, 46.3, 42.6, 41.3, 34.4, 33.3. **IR** (neat, cm^{-1}) 2921, 2853, 2360, 2341, 1641, 1452, 1413, 1113. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{23}N_2O_2S]^+$ =343.1475, 343.1476 found.

2-((2-chlorophenyl)thio)-1-morpholino-4-phenylbutan-1-one (20)



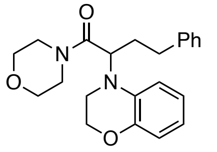
The title product was prepared according to the general procedure for the α-thiolation using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), 2-chlorobenzenethiol (0.15 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (30% EtOAc, 70% hexanes) afforded the title compound as a pale-yellow oil (223.4 mg, 0.59 mmol, 59% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.42 (m, 2H), 7.32 – 7.08 (m, 7H), 3.93 (dd, *J* = 8.9, 5.3 Hz, 1H), 3.76 – 3.58 (m, 2H), 3.58 – 3.39 (m, 3H), 3.28 (m, 1H), 3.16 (m, 2H), 2.86 – 2.75 (m, 1H), 2.69 – 2.59 (m, 1H), 2.42 (m, 1H), 2.07 (m, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 169.1, 140.7, 138.0, 135.5, 131.9, 130.2, 129.8, 128.6, 128.6, 127.4, 126.4, 66.9, 66.5, 46.3, 44.3, 42.6, 33.3, 33.3. **IR** (neat, cm^{-1}) 2920, 2853, 2360, 2342, 1641, 1449, 1430, 1113. **HRMS** (ESI) [M+H]$^+$ calcd. for [$C_{20}H_{23}ClNO_2S$]$^+$ =376.1133, 376.1132 found.

2-((2-ethylhexyl)thio)-1-morpholino-4-phenylbutan-1-one (21)



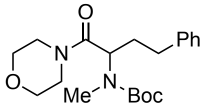
The title product was prepared according to the general procedure for the α-thiolation using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), 2-ethylhexane-1-thiol (0.23 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (100% hexanes to 50% EtOAc, 50% hexanes) afforded the title compound as a yellow oil (255.9 mg, 0.68 mmol, 68% yield). Product **21** is comprised of two sets of signals in the following ^{1}H NMR and ^{13}C NMR data, which may be due to the formation of a 1:1 diastereomeric ratio as racemic thiol was used. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.28 (m, 2H), 7.18 (m, 3H), 3.83 – 3.56 (m, 5H), 3.50 (m, 2H), 3.38 – 3.17 (m, 2H), 2.82 – 2.64 (m, 2H), 2.59 (m, 1H), 2.53 – 2.43 (m, 1H), 2.37 (m, 1H), 2.11 – 1.97 (m, 1H), 1.48 – 1.19 (m, 9H), 0.94 – 0.79 (m, 6H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 169.2, 169.2, 141.3, 128.7, 128.5, 126.1, 67.1, 66.6, 46.3, 42.4, 41.1, 39.3, 39.3, 33.4, 33.0, 32.7, 32.6, 32.4, 32.4, 29.0, 28.9, 25.8, 25.8, 23.0, 14.2, 11.0, 10.9. **IR** (neat, cm^{-1}) 2957, 2922, 2854, 1640, 1429, 1114. **HRMS** (ESI) [M+H]$^+$ calcd. for [$C_{22}H_{36}NO_2S$]$^+$ =378.2461, 378.2459 found.

2-(2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)-1-morpholino-4-phenylbutan-1-one (22)



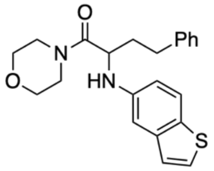
The title product was prepared according to the general procedure for the α-amination using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (0.16 mL, 1.3 mmol, 1.3 eq), 2-bromothiophene (0.24 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (343.5 mg, 1.3 mmol, 1.3 eq), KHMDS (1M solution in THF, 1.3 mL, 1.3 mmol, 1.3 eq) and DMPU (2.7 mL). Silica gel chromatography (25% EtOAc, 75% hexanes) afforded the title compound as a white solid (352.1 mg, 0.96 mmol, 96% yield). **Mp**: 114 – 117 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.31 (m, 2H), 7.20 (m, 4H), 6.79 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.71 (td, *J* = 7.6, 1.7 Hz, 1H), 6.64 (td, *J* = 7.6, 1.6 Hz, 1H), 6.20 (d, *J* = 8.8 Hz, 1H), 4.30 (dd, *J* = 9.4, 4.4 Hz, 1H), 4.25 – 4.04 (m, 2H), 3.74 (m, 2H), 3.68 – 3.51 (m, 3H), 3.51 – 3.15 (m, 5H), 2.89 – 2.72 (m, 1H), 2.64 – 2.49 (m, 1H), 2.49 – 2.34 (m, 1H), 1.95 – 1.78 (m, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 168.8, 144.7, 141.3, 133.3, 128.8, 128.7, 126.4, 121.7, 118.7, 117.2, 111.4, 67.2, 67.0, 64.9, 55.3, 46.0, 42.6, 41.8, 32.7, 28.1. **IR** (neat, cm^{-1}) 2924, 2848, 2359, 2341, 1641, 1502, 1240, 1117. **HRMS** (ESI) [M+H]$^+$ calcd. for [$C_{22}H_{27}N_2O_3$]$^+$ =367.2016, 367.2013 found.

tert-butyl methyl(1-morpholino-1-oxo-4-phenylbutan-2-yl)carbamate (23)



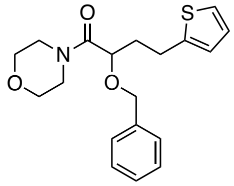
The title product was prepared according to the general procedure for the α-amination using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), *tert*-butyl methylcarbamate (0.18 mL, 1.3 mmol, 1.3 eq), 2-bromothiophene (0.24 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (343.5 mg, 1.3 mmol, 1.3 eq), KHMDS (1M solution in THF, 1.3 mL, 1.3 mmol, 1.3 eq) and DMPU (2.7 mL). Silica gel chromatography (25% EtOAc, 75% hexanes) afforded the title compound as a clear oil (162.5 mg, 0.45 mmol, 45% yield). Product **23** is comprised of rotamers and both rotamers are presented in the following ^{1}H NMR and ^{13}C NMR data. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.11 (m, 5H), 5.01 (m, 0.73 H), 4.69 (m, 0.27 H), 3.83 – 3.29 (m, 8H), 2.80 (overlapped s, 3H), 2.73 – 2.49 (m, 2H), 2.29 – 1.93 (m, 2H), 1.44 (overlapped s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.2, 168.9, 155.6, 154.6, 141.5, 141.1, 128.6, 128.5, 128.4, 126.3, 126.1, 80.7, 80.4, 67.2, 67.1, 66.8, 54.2, 53.5, 46.0, 45.6, 42.7, 42.6, 32.1, 32.0, 30.8, 30.6, 29.4, 29.2, 28.4, 28.4. **IR** (neat, cm^{-1}) 2969, 2853, 1683, 1648, 1444, 1136, 1114. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{31}N_2O_4]^+$ =363.2278, 363.2280 found.

2-(benzo[*b*]thiophen-5-ylamino)-1-morpholino-4-phenylbutan-1-one (24)



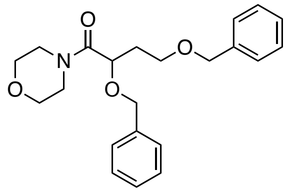
The title product was prepared according to the general procedure for the α-amination using 1-morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq), benzo[*b*]thiophen-5-amine (194.0 mg, 1.3 mmol, 1.3 eq), 2-bromothiophene (0.24 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (343.5 mg, 1.3 mmol, 1.3 eq), KHMDS (1M solution in THF, 1.3 mL, 1.3 mmol, 1.3 eq) and DMPU (2.7 mL). Silica gel chromatography (35% EtOAc, 65% hexanes) afforded the title compound as an orange solid (232.2 mg, 0.61 mmol, 61% yield). **Mp**: 173 – 177 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 5.4 Hz, 1H), 7.31 (m, 2H), 7.27 – 7.15 (m, 3H), 7.12 (d, J = 5.4 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 6.75 (dd, J = 8.7, 2.4 Hz, 1H), 4.51 (s, 1H), 4.27 (dd, J = 7.9, 4.6 Hz, 1H), 3.85 – 3.40 (m, 6H), 3.31 (m, 2H), 2.92 – 2.71 (m, 2H), 2.16 – 1.91 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.9, 144.9, 141.3, 141.0, 130.5, 128.7, 127.2, 126.4, 123.3, 123.2, 115.1, 106.6, 67.1, 66.7, 53.1, 45.8, 42.6, 34.7, 31.7. **IR** (neat, cm^{-1}) 3297, 2922, 2858, 2360, 2341, 1633, 1603, 1229, 1113. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{22}H_{25}N_2O_2S]^+$ =381.1626, 381.1633 found.

2-(benzyloxy)-1-morpholino-4-(thiophen-2-yl)butan-1-one (25)



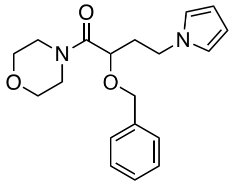
The title product was prepared according to the general procedure for the α-etherification and thiolation using 1-morpholino-4-(thiophen-2-yl)butan-1-one (239.3 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (35% EtOAc, 65% hexanes) afforded the title compound as a pale-yellow oil (225.4 mg, 0.65 mmol, 65% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 7.11 (dd, J = 5.2, 1.2 Hz, 1H), 6.89 (dd, J = 5.1, 3.4 Hz, 1H), 6.72 (t, J = 1.1 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 11.5 Hz, 1H), 4.20 (dd, J = 9.3, 4.3 Hz, 1H), 3.74 – 3.41 (m, 8H), 3.10 – 2.88 (m, 2H), 2.25 – 2.10 (m, 1H), 2.09 – 1.94 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.2, 143.7, 137.4, 128.6, 128.2, 128.1, 127.0, 124.9, 123.5, 77.8, 71.8, 67.1, 66.8, 45.6, 42.6, 34.5, 26.0. **IR** (neat, cm^{-1}) 2853, 2918, 2853, 1638, 1434, 1112. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{24}NO_3S]^+$ =346.1471, 346.1470 found.

2,4-bis(benzyloxy)-1-morpholinobutan-1-one (26)



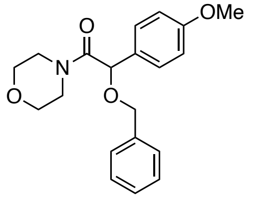
The title product was prepared according to the general procedure for the α-etherification and thiolation using 4-(benzyloxy)-1-morpholinobutan-1-one (263.3 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (gradient column using 15% EtOAc, 75% hexanes, 10% diethyl ether to 40% EtOAc, 50% hexanes, 10% diethyl ether) afforded the title compound as a pale-yellow oil (188.8 mg, 0.51 mmol, 51% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.39 – 7.20 (m, 10H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.50 – 4.34 (m, 4H), 3.73 – 3.40 (m, 10H), 2.10 – 1.96 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 170.3, 138.4, 137.6, 128.5, 128.5, 128.2, 128.0, 127.7, 127.7, 75.1, 73.1, 71.6, 67.1, 66.8, 66.3, 45.6, 42.5, 33.0. **IR** (neat, cm^{-1}) 2959, 2855, 2360, 2341, 1640, 1453, 1111. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{22}$H$_{28}$NO$_4$]$^+$ =370.2013, 370.2017 found.

2-(benzyloxy)-1-morpholino-4-(1*H*-pyrrol-1-yl)butan-1-one (27)



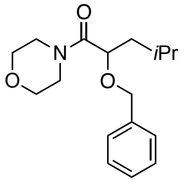
The title product was prepared according to the general procedure for the α-etherification and thiolation using 1-morpholino-4-(1*H*-pyrrol-1-yl)butan-1-one (222.3 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (40% EtOAc, 60% hexanes) afforded the title compound as an orange oil (175.6 mg, 0.53 mmol, 53% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.41 – 7.28 (m, 5H), 6.49 (t, *J* = 2.1 Hz, 2H), 6.09 (t, *J* = 2.1 Hz, 2H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 4.10 – 3.92 (m, 3H), 3.88 – 3.52 (m, 4H), 3.48 (t, *J* = 5.1 Hz, 2H), 3.31 – 3.15 (m, 2H), 2.28 – 2.11 (m, 1H), 2.11 – 1.98 (m, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 169.7, 137.2, 128.7, 128.5, 128.3, 120.7, 108.6, 74.4, 71.6, 67.1, 66.8, 45.7, 45.4, 42.5, 34.8. **IR** (neat, cm^{-1}) 2959, 2855, 2359, 1639, 1436, 1271, 1111. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{19}$H$_{25}$N$_2$O$_3$]$^+$ =329.1860, 329.1870 found.

2-(benzyloxy)-2-(4-methoxyphenyl)-1-morpholinoethan-1-one (28)



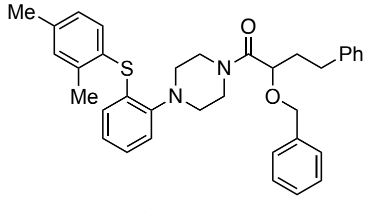
The title product was prepared according to the general procedure for the α-etherification and thiolation using 2-(4-methoxyphenyl)-1-morpholinoethan-1-one (235.3 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (264.3 mg, 1.0 mmol, 1.0 eq), KOH (56.1 mg, 1.0 mmol, 1.0 eq) and DME (4.0 mL). Silica gel chromatography (25% EtOAc, 75% hexanes) afforded the title compound as a opaque, white oil (154.4 mg, 0.45 mmol, 45% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.43 – 7.28 (m, 7H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.18 (s, 1H), 4.66 (d, *J* = 2.9 Hz, 2H), 3.80 (s, 3H), 3.62 (s, 4H), 3.52 – 3.16 (m, 4H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 169.2, 159.6, 137.5, 128.7, 128.6, 128.1, 128.1, 127.8, 114.2, 81.0, 71.8, 67.0, 66.5, 55.4, 45.9, 42.8. **IR** (neat, cm^{-1}) 2959, 2854, 1640, 1510, 1245, 1111. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{20}$H$_{24}$NO$_4$]$^+$ =342.1700, 342.1696 found.

2-(benzyloxy)-4-methyl-1-morpholinopentan-1-one (29)



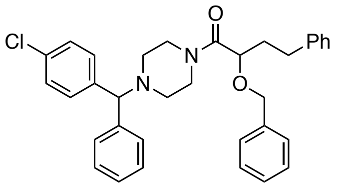
The title product was prepared according to the general procedure for the α-etherification and thiolation using 4-methyl-1-morpholinopentan-1-one (185.3 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (10% EtOAc, 90% hexanes) afforded the title compound as a clear oil (150.5 mg, 0.52 mmol, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.21 (m, 5H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.23 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.78 – 3.55 (m, 8H), 1.91 – 1.71 (m, 2H), 1.50 – 1.41 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.9, 137.5, 128.6, 128.1, 128.0, 78.9, 71.9, 67.2, 66.9, 45.7, 42.6, 41.5, 24.9, 23.3, 21.8. **IR** (neat, cm^{-1}) 2955, 2865, 2359, 2340, 1637, 1453, 1113. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{17}H_{26}NO_3]^+$ = 292.1908, 292.1908 found.

2-(benzyloxy)-1-(4-(2-((2,4-dimethylphenyl)thio)phenyl)piperazin-1-yl)-4-phenylbutan-1-one (30)



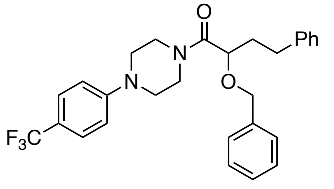
The title product was prepared according to the general procedure for the α-etherification and thiolation using 1-(4-(2-((2,4-dimethylphenyl)thio)phenyl)piperazin-1-yl)-4-phenylbutan-1-one (444.6 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (10% diethyl ether, 90% hexanes to 30% diethyl ether, 70% hexanes) afforded the title compound as a pale-yellow oil (396.0 mg, 0.72 mmol, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 6.82 (m, 16H), 6.52 (d, *J* = 7.9 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.21 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.87 – 3.54 (m, 4H), 3.05 – 2.83 (m, 5H), 2.75 – 2.65 (m, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 2.23 – 1.97 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4, 148.6, 142.5, 141.4, 139.5, 137.7, 136.3, 134.8, 131.9, 128.7, 128.7, 128.6, 128.4, 128.1, 128.0, 127.8, 126.5, 126.2, 125.7, 125.0, 120.0, 78.6, 71.8, 52.2, 51.8, 45.5, 42.8, 34.5, 32.1, 21.3, 20.7. **IR** (neat, cm^{-1}) 2924, 2847, 2359, 2342, 1639, 1440, 1024. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{35}H_{39}N_2O_2S]^+$ =551.2727, 551.2729 found.

2-(benzyloxy)-1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-4-phenylbutan-1-one (31)



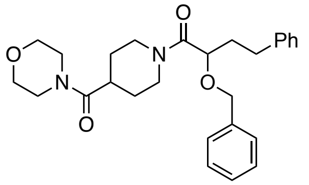
The title product was prepared according to the general procedure for the α-etherification and thiolation using 1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-4-phenylbutan-1-one (433.0 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (20% EtOAc, 60% hexanes, 20% diethyl ether) afforded the title compound as a pale-yellow oil (388.3 mg, 0.72 mmol, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.13 (m, 17H), 7.10 (d, *J* = 6.9 Hz, 2H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.18 (s, 1H), 4.12 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.57 (m, 4H), 2.81 (m, 1H), 2.71 – 2.58 (m, 1H), 2.34 (m, 2H), 2.25 (m, 2H), 2.15 – 2.02 (m, 1H), 2.02 – 1.85 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1, 141.6, 141.5, 141.3, 140.8, 137.7, 132.9, 129.2, 128.9, 128.8, 128.6, 128.5, 128.5, 128.1, 128.1, 128.0, 127.9, 127.5, 126.1, 78.6, 75.3, 71.6, 52.2, 51.8, 45.0, 42.4, 34.3, 31.9. **IR** (neat, cm^{-1}) 2359, 2342, 1637, 1487, 1452, 1088. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{34}H_{36}ClN_2O_2]^+$ =539.2460, 539.2456 found.

2-(benzyloxy)-4-phenyl-1-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)butan-1-one (32)



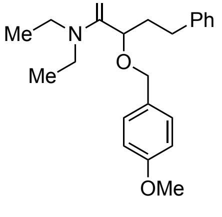
The title product was prepared according to the general procedure for the α-etherification and thiolation using 4-phenyl-1-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)butan-1-one (433.0 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (20% EtOAc, 20% diethyl ether, 60% hexanes) afforded the title compound as a white solid (414.2 mg, 0.86 mmol, 86% yield). **Mp**: 84 – 86 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.4 Hz, 2H), 7.41 – 7.22 (m, 7H), 7.17 (m, 3H), 6.88 (d, J = 9.1 Hz, 2H), 4.65 (d, J = 11.6 Hz, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.19 (dd, J = 9.1, 4.5 Hz, 1H), 3.71 (m, 4H), 3.23 (t, 2H), 3.11 (m, 2H), 2.92 – 2.81 (m, 1H), 2.75 – 2.65 (m, 1H), 2.23 – 2.08 (m, 1H), 2.08 – 1.96 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.2, 152.9, 141.1, 137.4, 128.5, 128.5, 128.5, 128.2, 128.0, 126.5 (q, J = 3.8 Hz), 126.1, 124.7 (q, J = 270.8 Hz), 121.2 (q, J = 32.7 Hz), 115.0, 78.4, 71.7, 48.4, 48.1, 44.3, 41.8, 34.3, 31.8. **^{19}F NMR** (376 MHz, $CDCl_3$) δ 61.48. **IR** (neat, cm^{-1}) 2925, 2360, 2342, 1640, 1613, 1334, 1098. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{28}H_{30}F_3N_2O_2]^+$ =483.2254, 483.2268 found.

2-(benzyloxy)-1-(4-(morpholine-4-carbonyl)piperidin-1-yl)-4-phenylbutan-1-one (33)



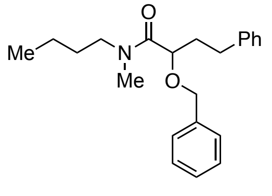
The title product was prepared according to the general procedure for the α-etherification and thiolation using 1-(4-(morpholine-4-carbonyl)piperidin-1-yl)-4-phenylbutan-1-one (344.5 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (97% DCM and 3% MeOH) afforded the title compound as a pale-yellow oil (198.1 mg, 0.53 mmol, 53% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 – 6.86 (m, 10H), 4.74 – 4.50 (m, 2H), 4.35 (t, J = 10.5 Hz, 1H), 4.14 (d, J = 8.4 Hz, 1H), 4.01 (d, J = 13.8 Hz, 1H), 3.71 – 3.38 (m, 8H), 3.03 – 2.77 (m, 2H), 2.77 – 2.58 (m, 3H), 2.20 – 2.03 (m, 1H), 2.03 – 1.87 (m, 1H), 1.82 – 1.51 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 172.4, 170.0, 169.8, 141.0, 140.9, 137.4, 137.4, 128.4, 128.3, 128.3, 128.1, 128.0, 127.8, 125.9, 77.7, 77.6, 71.5, 71.4, 66.7, 66.6, 45.8, 43.9, 43.8, 41.9, 41.6, 41.4, 37.8, 37.7, 34.1, 31.7, 31.7, 28.7, 28.5, 28.3, 28.3. **IR** (neat, cm^{-1}) 2923, 2857, 1625, 1436, 1112, 1011. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{27}H_{35}N_2O_4]^+$ =451.2591, 451.2595 found.

***N*,*N*-diethyl-2-((4-methoxybenzyl)oxy)-4-phenylbutanamide (34)**



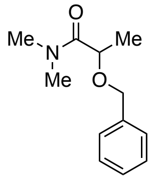
The title product was prepared according to the general procedure for the α-etherification and thiolation using *N*,*N*-diethyl-4-phenylbutanamide (219.3 mg, 1.0 mmol, 1.0 eq), (4-methoxyphenyl)methanol (0.29 mL, 2.3 mmol, 2.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (872.3 mg, 3.3 mmol, 3.3 eq), KOH (185.1 mg, 3.3 mmol, 3.3 eq) and DME (4.0 mL). Silica gel chromatography (15% EtOAc, 85% hexanes) afforded the title compound as a clear oil (197.6 mg, 0.56 mmol, 56% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.40 – 7.02 (m, 7H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.28 (d, *J* = 11.4 Hz, 1H), 4.08 (dd, *J* = 9.1, 4.0 Hz, 1H), 3.80 (s, 3H), 3.49 – 3.08 (m, 4H), 2.83 (m, 1H), 2.73 – 2.58 (m, 1H), 2.13 (m, 1H), 1.97 – 1.83 (m, 1H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 170.9, 159.4, 141.5, 130.0, 129.8, 128.6, 128.4, 126.1, 113.9, 76.1, 70.8, 55.3, 40.8, 40.2, 34.4, 31.9, 14.4, 13.0. **IR** (neat, cm^{-1}) 2916, 2848, 2360, 2341, 1636, 1612, 1247. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{22}$H$_{30}$NO$_3$]$^+$ = 356.2220, 356.2210 found.

2-(benzyloxy)-*N*-butyl-*N*-methyl-4-phenylbutanamide (35)



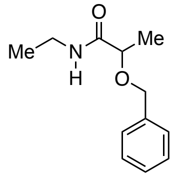
The title product was prepared according to the general procedure for the α-etherification and thiolation using *N*-butyl-*N*-methyl-4-phenylbutanamide (233.3 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.24 mL, 2.3 mmol, 2.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (872.3 mg, 3.3 mmol, 3.3 eq), KOH (185.1 mg, 3.3 mmol, 3.3 eq) and DME (4.0 mL). Silica gel chromatography (10% diethyl ether, 10% EtOAc, 80% hexanes) afforded the title compound as a clear oil (153.4 mg, 0.45 mmol, 45% yield). Product **35** is comprised of rotamers and both rotamers are presented in the following ^{13}C NMR data. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.48 – 6.97 (m, 10H), 4.65 (dd, *J* = 13.9, 11.7 Hz, 1H), 4.33 (dd, *J* = 11.7, 9.6 Hz, 1H), 4.13 (td, *J* = 9.3, 4.1 Hz, 1H), 3.42 – 3.30 (m, 1H), 3.13 – 2.96 (m, 1H), 2.94 – 2.80 (m, 4H), 2.76 – 2.64 (m, 1H), 2.25 – 2.06 (m, 1H), 2.02 – 1.86 (m, 1H), 1.64 – 1.15 (m, 4H), 1.07 (m, 1H), 0.93 (t, *J* = 7.3 Hz, 1H), 0.79 (t, *J* = 7.3 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 171.6, 171.2, 141.5, 141.5, 138.0, 137.9, 128.7, 128.9, 128.6, 128.6, 128.5, 128.5, 128.5, 128.2, 128.2, 127.9, 127.9, 126.1, 126.1, 77.4, 75.8, 71.3, 71.2, 48.9, 48.2, 34.5, 34.4, 33.9, 33.8, 31.9, 31.8, 30.8, 29.3, 20.2, 19.9, 14.0, 13.8. **IR** (neat, cm^{-1}) 2955, 2861, 2359, 2341, 1640, 1453, 1101. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{22}$H$_{30}$NO$_2$]$^+$ = 340.2272, 340.2276 found.

2-(benzyloxy)-*N*,*N*-dimethylpropanamide (36)



The title product was prepared according to the general procedure for the α-etherification and thiolation using *N*,*N*-dimethylpropionamide (101.1 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel chromatography (35% EtOAc, 65% hexanes) afforded the title compound as a brown oil (175.1 mg, 0.84 mmol, 84% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.38 – 7.23 (m, 5H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.35 (q, *J* = 6.7 Hz, 1H), 3.05 (s, 3H), 2.96 (s, 3H), 1.43 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 172.0, 137.8, 128.5, 128.0, 127.9, 74.4, 71.0, 36.6, 36.1, 17.7. **IR** (neat, cm^{-1}) 2981, 2932, 2359, 2341,1641, 1496, 1101. **HRMS** (ESI) [M+H]$^+$ calcd. for [C$_{12}$H$_{18}$NO$_2$]$^+$ = 208.1333, 208.1330 found.

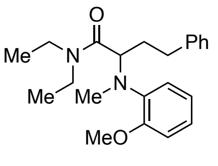
2-(benzyloxy)-*N*-ethylpropanamide (37)



The title product was prepared according to the general procedure for the α-etherification and thiolation using *N*-ethylpropionamide (101.1 mg, 1.0 mmol, 1.0 eq), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (872.3 mg, 3.3 mmol, 3.3 eq), KOH (185.1 mg, 3.3 mmol, 3.3 eq) and DME (4.0 mL). Silica gel chromatography (20% EtOAc, 80% hexanes) afforded the title compound as an orange oil (43.2 mg, 0.21 mmol, 21% yield). **^{1}H NMR**

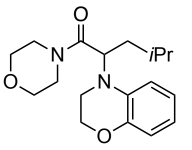
(400 MHz, $CDCl_3$) δ 7.35 (q, J = 7.1 Hz, 5H), 4.59 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 11.6 Hz, 1H), 3.96 (q, J = 6.8 Hz, 1H), 3.38 – 3.23 (m, 2H), 1.42 (d, J = 6.8 Hz, 3H), 1.14 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.1, 137.5, 128.8, 128.2, 128.0, 76.4, 72.1, 33.9, 18.8, 15.0. **IR** (neat, cm^{-1}) 3308, 2975, 2931, 2360, 2340,1653, 1525, 1103. **HRMS** (ESI) [M+H]$^+$ calcd. for $[C_{12}H_{18}NO_2]^+$ = 208.1333, 208.1330 found.

***N*,*N*-diethyl-2-((2-methoxyphenyl)(methyl)amino)-4-phenylbutanamide (38)**



The title product was prepared according to the general procedure for α-amination using *N*,*N*-diethyl-4-phenylbutanamide (219.3 mg, 1.0 mmol, 1.0 eq), 2-methoxy-*N*-methylaniline (178.3 mg, 1.3 mmol, 1.3 eq), 2-bromothiophene (0.24 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (343.5 mg, 1.3 mmol, 1.3 eq), KHMDS (1M solution in THF, 1.3 mL, 1.3 mmol, 1.3 eq) and DMPU (2.7 mL). Silica gel chromatography (10% EtOAc, 90% hexanes) afforded the title compound as a pale-yellow oil (237.1 mg, 0.67 mmol, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.03 (m, 5H), 6.97 – 6.83 (m, 3H), 6.78 (d, J = 8.0 Hz, 1H), 4.49 (dd, J = 9.2, 4.8 Hz, 1H), 3.66 (s, 3H), 3.63 – 3.53 (m, 2H), 3.14 (m, 1H), 2.99 (m, 1H), 2.79 (s, 3H), 2.74 – 2.63 (m, 1H), 2.54 – 2.32 (m, 2H), 1.85 – 1.74 (m, 1H), 1.10 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1, 152.2, 142.2, 140.2, 128.6, 128.3, 125.8, 122.5, 121.1, 120.9, 111.2, 58.4, 55.19, 41.1, 40.2, 35.1, 32.7, 28.9, 14.6, 13.1. **IR** (neat, cm^{-1}) 2961, 2931, 2360, 2341, 1635, 1498, 1236. **HRMS** (ESI) [M+H]$^+$ calcd. for $[C_{22}H_{31}N_2O_2]^+$ = 355.2381, 355.2381 found.

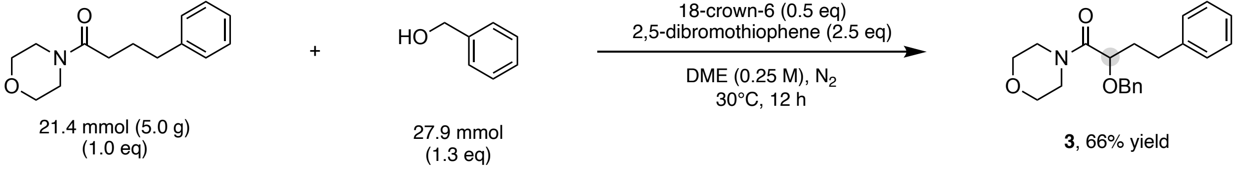
2-(2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)-4-methyl-1-morpholinopentan-1-one (39)



The title product was prepared according to the general procedure for the α-amination using 4-methyl-1-morpholinopentan-1-one (185.3 mg, 1.0 mmol, 1.0 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (0.16 mL, 1.3 mmol, 1.3 eq), 2-bromothiophene (0.24 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (343.5 mg, 1.3 mmol, 1.3 eq), KHMDS (1M solution in THF, 1.3 mL, 1.3 mmol, 1.3 eq) and DMPU (2.7 mL). Silica gel chromatography (20% EtOAc, 80% hexanes) afforded the title compound as a yellow oil (272.5 mg, 0.86 mmol, 86% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.83 (m, 2H), 6.73 – 6.59 (m, 2H), 4.51 (dd, J = 9.0, 5.3 Hz, 1H), 4.24 – 4.08 (m, 2H), 3.88 – 3.33 (m, 8H), 3.33 – 3.20 (m, 2H), 2.06 – 1.93 (m, 1H), 1.69 – 1.55 (m, 1H), 1.48 – 1.37 (m, 1H), 1.02 – 0.89 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3, 144.8, 133.6, 121.7, 118.6, 117.2, 111.3, 67.2, 67.1, 65.0, 54.6, 46.2, 42.6, 41.7, 35.7, 25.2, 23.4, 22.4. **IR** (neat, cm^{-1}) 2955, 2866, 2360, 2341, 1647, 1498, 1238, 1113. **HRMS** (ESI) [M+H]$^+$ calcd. for $[C_{18}H_{27}N_2O_3]^+$ =319.2017, 319.2011 found.

6. Multigram Scale Synthesis of 3 with Lower 18-Crown-6 Additive Loading

Purpose: We sought to demonstrate the scalability of this method through the coupling reaction of benzyl alcohol with the model amide 1-morpholino-4-phenylbutan-1-one (**1**) on a 5-gram scale (21.4 mmol) with a lower 18-crown-6 additive loading (0.5 equivalence).



Procedure: To an oven-dried 250 mL round bottom flask charged with a magnetic stir bar, 1-morpholino-4-phenylbutan-1-one (5.00 g, 21.4 mmol, 1.0 eq), 18-crown-6 (2.83 g, 10.7 mmol, 0.5 eq), and KOH (2.77 g, 49.3 mmol, 2.3 eq) were added in successive order. The flask was sealed with a rubber septum (Thermo Fisher Scientific, Product #NC9683109) and subsequently evacuated and backfilled five times with N_2, and left under a positive pressure of N_2 on a manifold Schlenk line using a needle inlet. Anhydrous DME (85.7 mL, 0.25 M), benzyl alcohol (2.9 mL, 27.86 mmol, 1.3 eq), and 2,5-dibromothiophene (6.54 mL, 53.6 mmol, 2.5 eq) were added *via* syringe in successive order. The needle inlet was removed and the septum was wrapped with parafilm and the flask was placed into a preheated 30 °C silicon oil bath with stirring for 12 hours. The reaction solution was allowed to cool to room temperature and was subsequently transferred into separatory funnel containing saturated ammonia chloride (500 mL). The aqueous mixture was extracted with DCM (3 x 250 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (15% EtOAc, 20% diethyl ether, 65% hexanes) to afford the title compound as a clear oil (4.83 g, 14.2 mmol, 66% yield). The characterization data of the isolated material matches that of product **3** described on page S8 from the 1 mmol scale reaction.

7. Mechanistic Experiments

a) Reaction profile analysis of the α-etherification of 1-morpholino-4-phenylbutan-1-one (1)

Purpose and Discussion: A reaction profile was compiled to monitor the formation of 2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (**3**) product and 2-bromothiophene byproduct in the oxidative coupling of 1-morpholino-4-phenylbutan-1-one (**1**) with benzyl alcohol. As shown below, we observe the conversion of **1** into **3** with concomitant formation of 2-bromothiophene byproduct from **XTR 1** over a 10-hour period. This observation is consistent with the *in situ* formation of the α-brominated amide intermediate, although we note that we do not observe the α-brominated amide intermediate during the course of the reaction.

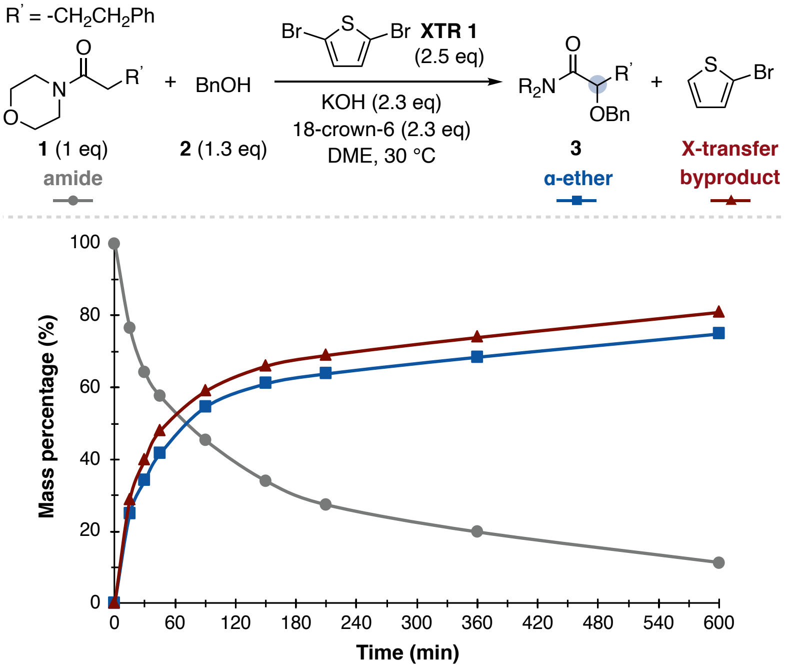


Figure S7: Reaction profile analysis of **1** with **XTR 1**, benzyl alcohol, KOH, and 18-crown-6 ether.

Procedure: 1-Morpholino-4-phenylbutan-1-one (466.6 mg, 2.0 mmol, 1.0 eq), 18-crown-6 (1.22 g, 4.6 mmol, 2.3 eq), KOH (258.1 mg, 4.6 mmol, 2.3 eq), and the internal standard, 1,3,5-trimethoxybenzene (120.0 mg, 2.14 mmol) were added in to an oven-dried 25 mL round bottom flask containing a magnetic stir bar. The flask was sealed with a rubber septum (Thermo Fisher Scientific, Product # CG302206) and subsequently evacuated and backfilled five times with N$_2$, and left under a positive pressure of N$_2$ on a manifold Schlenk line using a needle inlet. Anhydrous DME (8.0 mL, 0.25 M), benzyl alcohol (0.27 mL, 2.6 mmol, 1.3 eq), and 2,5-dibromothiophene (0.56 mL, 5.0 mmol, 2.5 eq) were added *via* syringe in successive order. The septum was wrapped with parafilm and placed into a preheated 30 °C silicon oil bath with stirring. After the time indicated, an aliquot was removed *via* syringe from the flask and quenched with 0.2 mL of CDCl$_3$. The aliquot was analyzed by ^{1}H NMR spectroscopy using the 1,3,5-trimethoxybenzene as the internal standard (singlet at 6.09 ppm) to determine the yields of 2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (**3**, 4.15 ppm, dd, 1H), 1-morpholino-4-phenylbutan-1-one (**1**, 2.33 ppm, t, 2H), and 2-bromothiophene (7.06 ppm, dd, 1H). The data points are presented in the table below. The starting material and product were normalized in reference to the starting material mass percentage at 0 minutes. No other discernable side products were observed in the ^{1}H NMR spectra. The ^{1}H NMR spectrum for the crude reaction solution from entry 8 of Table S3 is shown in Figure S8 to show how the yield was determined.

Entry	Time (min)	Starting Material (1)	Product (3)	2-Bromothiophene
1	0	100%	0%	0%
2	15	76%	25%	29%
3	30	64%	34%	40%
4	45	58%	42%	48%
5	90	45%	55%	59%
6	150	34%	61%	66%
7	210	27%	64%	69%
8	360	20%	69%	74%
9	600	11%	75%	81%

Table S3. Time point yields for the reaction profile analysis of **3**.

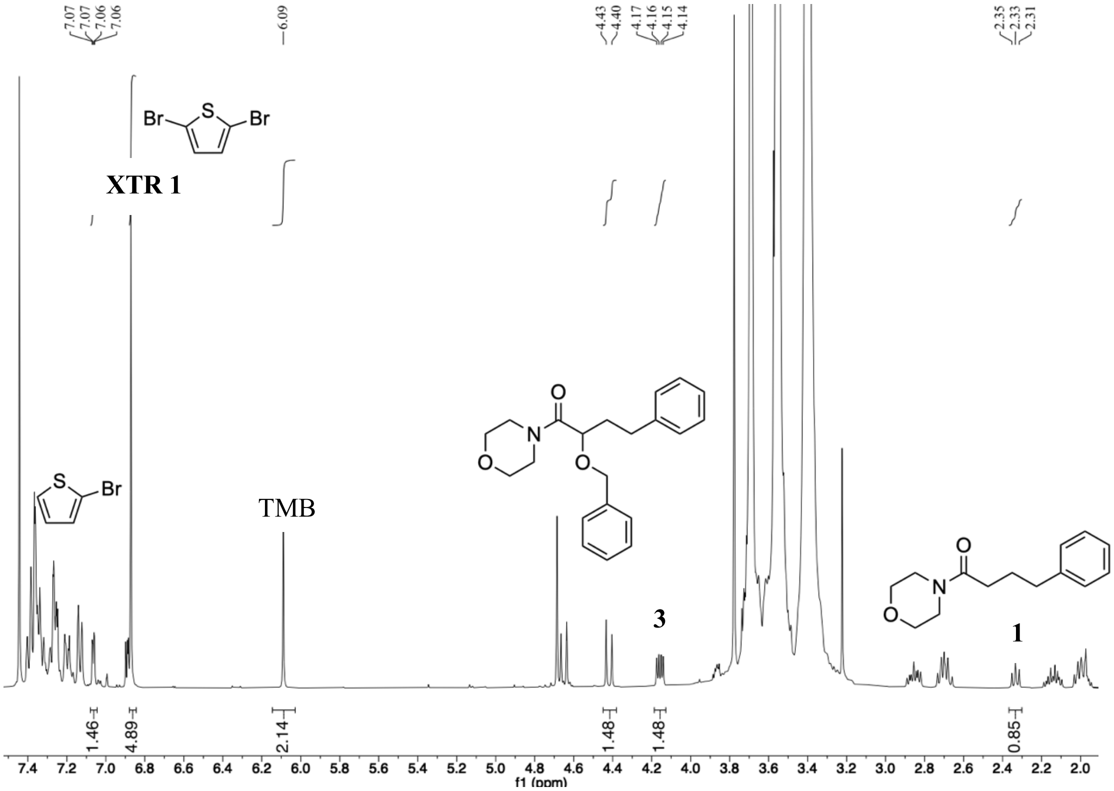
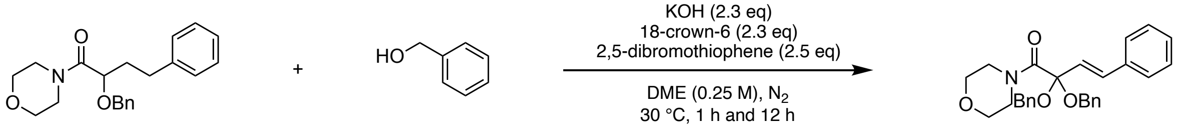


Figure S8. ^{1}H NMR spectral window of the crude reaction solution from the 360 min time point from the reaction profile analysis study of **3**. 1,3,5-Trimethoxybenzene internal standard (120.0 mg, 2.14 mmol, signal at 6.09 ppm) was used to determine the yield of 2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (**3**, 69% yield), 2-bromothiophene (74% yield), and the amount of remaining 1-morpholino-4-phenylbutan-1-one benzene (**1**, 20% yield).

b) Resubjection of 2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (3) to reaction conditions

Purpose: To probe the propensity for the product to undergo further oxidation, we resubjected 2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (**3**) to the α-etherification reaction conditions to study any oxidation products within 1-hour and 12-hour reaction times.



1.0 mmol, **3**
(1.0 eq)

1.3 mmol
(1.3 eq)

40

1 h = 5% yield of **40**, 94% of **3** remains
12 h = 14% yield of **40**, 85% of **3** remains

Procedure: 2-(Benzyloxy)-1-morpholino-4-phenylbutan-1-one (**3**, 339.4 mg, 1.0 mmol, 1.0 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq), and the internal standard, 1,3,5-trimethoxybenzene (64.1 mg, 1.14 mmol) were added in to an oven-dried 25 mL round bottom flask containing a magnetic stir bar. The flask was sealed with a rubber septum (Thermo Fisher Scientific, Product # CG302206) and subsequently evacuated and backfilled five times with N_2, and left under a positive pressure of N_2 on a manifold Schlenk line using a needle inlet. Anhydrous DME (4.0 mL, 0.25 M), benzyl alcohol (0.13 mL, 1.3 mmol, 1.3 eq), and 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq) were added *via* syringe in that order. The septum was wrapped with parafilm and placed into a preheated 30 °C silicon oil bath with stirring. After the time indicated, an aliquot was removed *via* syringe from the flask and subsequently quenched with 0.2 mL of $CDCl_3$. The aliquot was analyzed by ^1H NMR spectroscopy using the 1,3,5-trimethoxybenzene as the internal standard (singlet at 6.09 ppm) to assess the yields of 2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (**3**, 4.15 ppm, dd, 1H) and (*E*)-2,2-bis(benzyloxy)-1-morpholino-4-phenylbut-3-en-1-one (**40**, 6.32 ppm, d, 1H). The starting material and product were normalized in reference to the starting material mass percentage at 0 minutes. No other significant side products were observed in the ^1H NMR spectra. For the 12-hour reaction, a separate reaction was performed using the above procedure with 1,3,5-trimethoxybenzene (65.6 mg, 1.17 mmol) as the internal standard added post-reaction for analysis.

Entry	Time (min)	Starting Material (3)	Product (40)
1	0	100%	0%
2	15	100%	0%
3	30	99%	1%
4	45	98%	2%
5	60	94%	5%

Table S4. Numerical results for the overoxidation of **3** during a 1-hour time period.

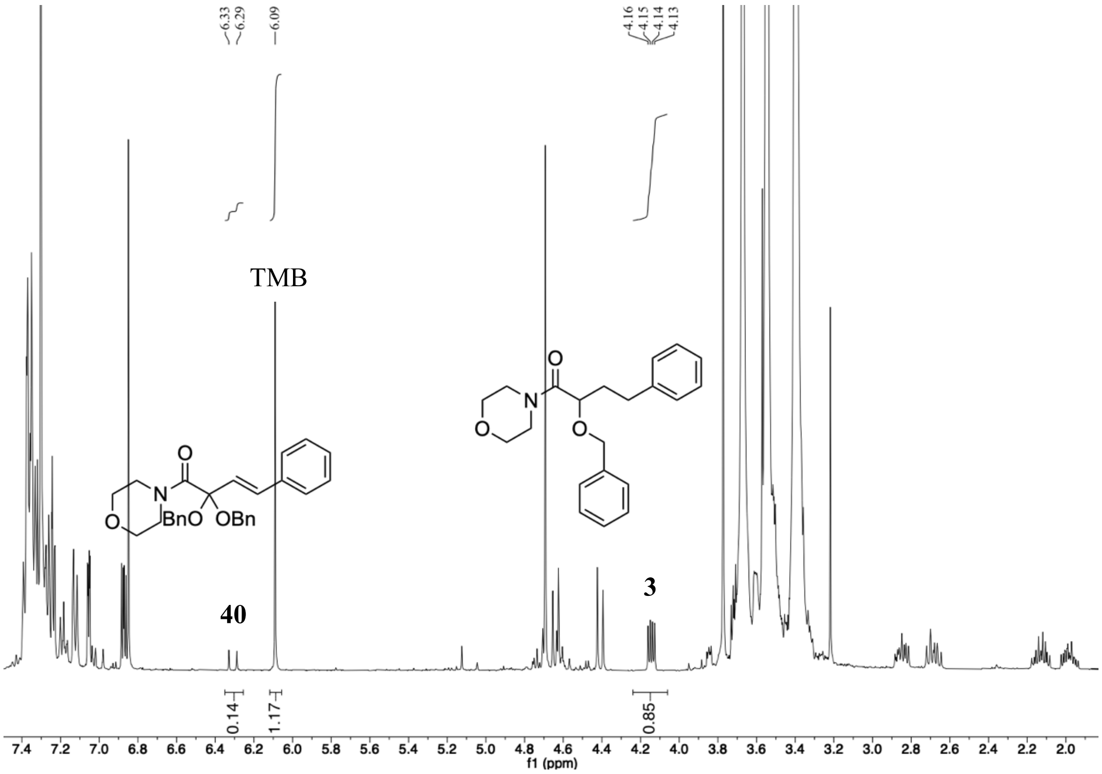
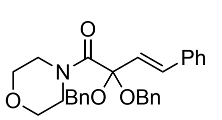


Figure S9. ^{1}H NMR spectral window of the crude reaction solution at 12 hours. 1,3,5-Trimethoxybenzene internal standard (65.6 mg, 1.17 mmol, signal at 6.09 ppm) was used to determine the yield of (*E*)-2,2-bis(benzyloxy)-1-morpholino-4-phenylbut-3-en-1-one (**40**, 14% yield) and the amount of remaining 2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (**3**, 85% yield).

Discussion: The over-oxidized product (**40**) was produced slowly over the course of the reaction. At 1 hour, 5% of **40** was produced while 94% of **3** remained and at 12 hours 14% of **40** formed with 85% of **3** remaining. This shows that over-oxidation is a relatively much slower process than the initial α-etherification reaction and explains why mono-oxidation selectivity is observed.

(*E*)-2,2-bis(benzyloxy)-1-morpholino-4-phenylbut-3-en-1-one (40)



The title product was prepared according to the procedures above using 2-(benzyloxy)-1-morpholino-4-phenylbutan-1-one (339.4 mg, 1.0 mmol, 1.0 eq), 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq), 18-crown-6 (607.8 mg, 2.3 mmol, 2.3 eq), KOH (129.0 mg, 2.3 mmol, 2.3 eq) and DME (4.0 mL). Silica gel preparatory plate chromatography (25% EtOAc, 10% diethyl ether, 65% hexanes) afforded the title compound as a clear oil (22.2 mg, 0.05 mmol, 5% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (m, 15H), 7.00 (d, *J* = 16.4 Hz, 1H), 6.31 (d, *J* = 16.3 Hz, 1H), 4.72 (d, *J* = 11.8 Hz, 2H), 4.62 (d, *J* = 11.8 Hz, 2H), 3.83 – 3.41 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5, 137.8, 135.5, 134.8, 128.9, 128.9, 128.6, 127.8, 127.8, 127.0, 125.4, 101.0, 67.2, 66.8, 65.2, 47.3, 43.7. **IR** (neat, cm^{-1}) 2917, 2851, 2359, 1656, 1114, 1026. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{28}H_{30}NO_4]^+$ = 444.2170, 444.2174 found.

c) Subjection of 1-morpholino-4-phenylbutan-1-one (1) to lithium amide bases and common electrophilic brominating reagents

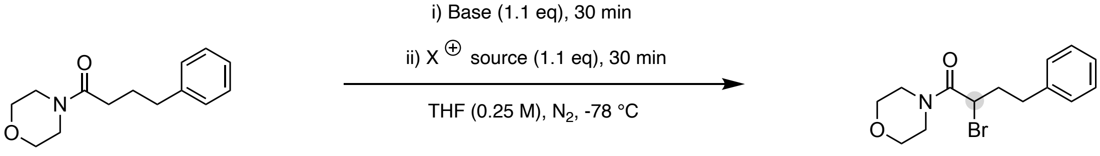
Purpose: Control reactions were conducted on the model amide 1-morpholino-4-phenylbutan-1-one (**1**) using common, lithium amide bases (*i.e.,* lithium diisopropylamide (LDA), lithium 2,2,6,6-tetramethylpiperidine (LiTMP)) in sequence with electrophilic brominating reagents (*i.e.,* Br_2, CBr_4, and NBS). The results illustrate that a traditional, sequential deprotonation-halogenation sequence is not applicable to unactivated amides with low yields of 2-bromo-1-morpholino-4-phenylbutan-1-one (**41**) formed and other carbonyl-containing side products present.

Procedure for base generation used for 1 mmol scale α-deprotonative halogenation studies of 1-morpholino-4-phenylbutan-1-one (1): An oven-dried 25 mL round bottom flask charged with a magnetic stir bar was sealed with a rubber septum (Thermo Fisher Scientific, Product # CG302206) and cooled to 0 °C *via* an ice bath. The flask was evacuated and backfilled five times with N_2, and left under a positive pressure of N_2 on a manifold Schlenk line using a needle inlet. Dissolved in 1.15 mL of anhydrous THF, 1.1 mmol of the protonated amine base (for LiTMP, 2,2,6,6-tetramethylpiperidine (155.4 mg, 1.1 eq), for LDA, diisopropylamine (111.3 mg, 1.1 eq)) was added to the flask and allowed to stir. Then, 1.1 mmol of freshly titrated *n*-BuLi (1.6 M in hexanes, Millipore Sigma, catalog #186171) was added to the flask *via* syringe and allowed to stir for 30 minutes before immediate use.

Procedure for 1 mmol scale α-deprotonation and α-bromination of model amide, 1-morpholino-4-phenylbutan-1-one (1):

If using freshly generated lithium amide base solution: The round bottom flask containing the base solution was transferred to a -78 °C bath (acetone and dry ice) and allowed to stir for 15 minutes. 1-Morpholino-4-phenylbutan-1-one (**1**, 233.3 mg, 1.0 mmol, 1.0 eq) dissolved in anhydrous THF (1.0 mL) was added slowly to the flask and allowed to stir for 30 minutes. Then, the bromine source (1.1 mmol, 1.1 eq) dissolved in anhydrous THF (1.0 mL) was slowly added to the flask *via* syringe and allowed to stir for 30 minutes. The reaction mixture was quenched with aqueous ammonia chloride (5 mL) and then extracted three times with DCM (5 mL). The organic layer was dried over sodium sulfate and concentrated *via* rotary evaporation. The organic material was reconstituted in $CDCl_3$ and 1,3,5-trimethoxybenzene internal standard (signal at 6.09 ppm) was used to determine the yield of 2-bromo-1-morpholino-4-phenylbutan-1-one (**41**, 4.23 ppm, t, 1H)[5] and the amount of remaining of 1-morpholino-4-phenylbutan-1-one (**1**, 2.31 ppm, t, 2 H).

If using commercial LDA solution: An oven-dried 25 mL round bottom flask charged with a magnetic stir bar was sealed with a rubber septum (Thermo Fisher Scientific, Product # CG302206) and cooled to -78 °C bath (acetone and dry ice). The flask was evacuated and backfilled five times with N_2, and left under a positive pressure of N_2 on a manifold Schlenk line using a needle inlet. LDA (1.1 mL of 1 M in THF, Millipore Sigma catalog # 774766, 1.0 mmol, 1.1 eq) was added to the flask *via* syringe and was allowed to stir for 15 minutes. 1-Morpholino-4-phenylbutan-1-one (233.3 mg, 1.0 mmol, 1.0 eq) dissolved in anhydrous THF (1.45 mL) was added slowly to the flask *via* syringe and allowed to stir for 30 minutes. Then, the bromine source (1.1 mmol, 1.1 eq) dissolved in anhydrous THF (1.45 mL) was slowly added to the flask *via* syringe and allowed to stir for 30 minutes. The reaction mixture was quenched with aqueous ammonia chloride (5 mL) and then extracted three times with DCM (5 mL). The organic layer was dried over sodium sulfate and concentrated *via* rotary evaporation. The organic material was reconstituted in $CDCl_3$ and 1,3,5-trimethoxybenzene internal standard (signal at 6.09 ppm) was used to determine the yield of 2-bromo-1-morpholino-4-phenylbutan-1-one (**41**, 4.23 ppm, t, 1H) and the amount of remaining of 1-morpholino-4-phenylbutan-1-one (**1**, 2.31 ppm, t, 2 H). ^{1}H NMR spectrum for the crude reaction solution from entry 2 of Table S5 is shown in Figure S10 to show how the yield was determined. ^{1}H NMR and ^{13}C NMR spectra for the crude reaction solution from entry 3 of Table S5 is shown in Figure S11 and S12 respectively to show the formation of other carbonyl-containing side products formed.



1.0 mmol, **1**
(1.0 eq)

41

Entry	Base Used	X$^\oplus$ Source Used	Starting Material (1)	Product (41)
1	Commercial LDA	Br_2	45%	18%
2	Commercial LDA	NBS	87%	0%
3	Commercial LDA	CBr_4	66%	2%
4	Generated LDA	Br_2	57%	5%
5	Generated LiTMP	Br_2	28%	2%

Table S5. Results for the deprotonative bromination of **1** using lithium amide bases.

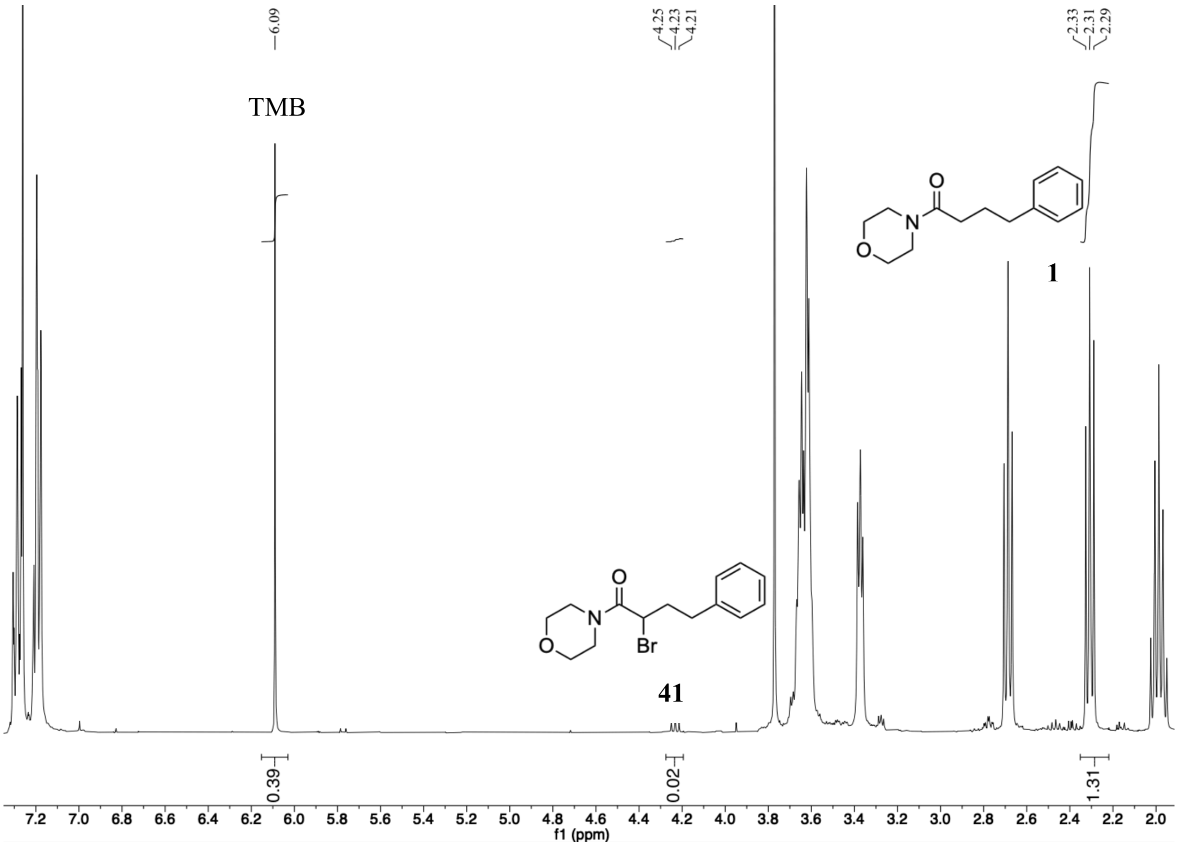


Figure S10. ^{1}H NMR spectral window of Entry 3 from Table S5. 1,3,5-Trimethoxybenzene internal standard (22.0 mg, 0.39 mmol, signal at 6.09 ppm) was used to determine the yield of 2-bromo-1-morpholino-4-phenylbutan-1-one (**41**, 2% yield) and the amount of remaining 1-morpholino-4-phenylbutan-1-one (**1**, 66% yield).

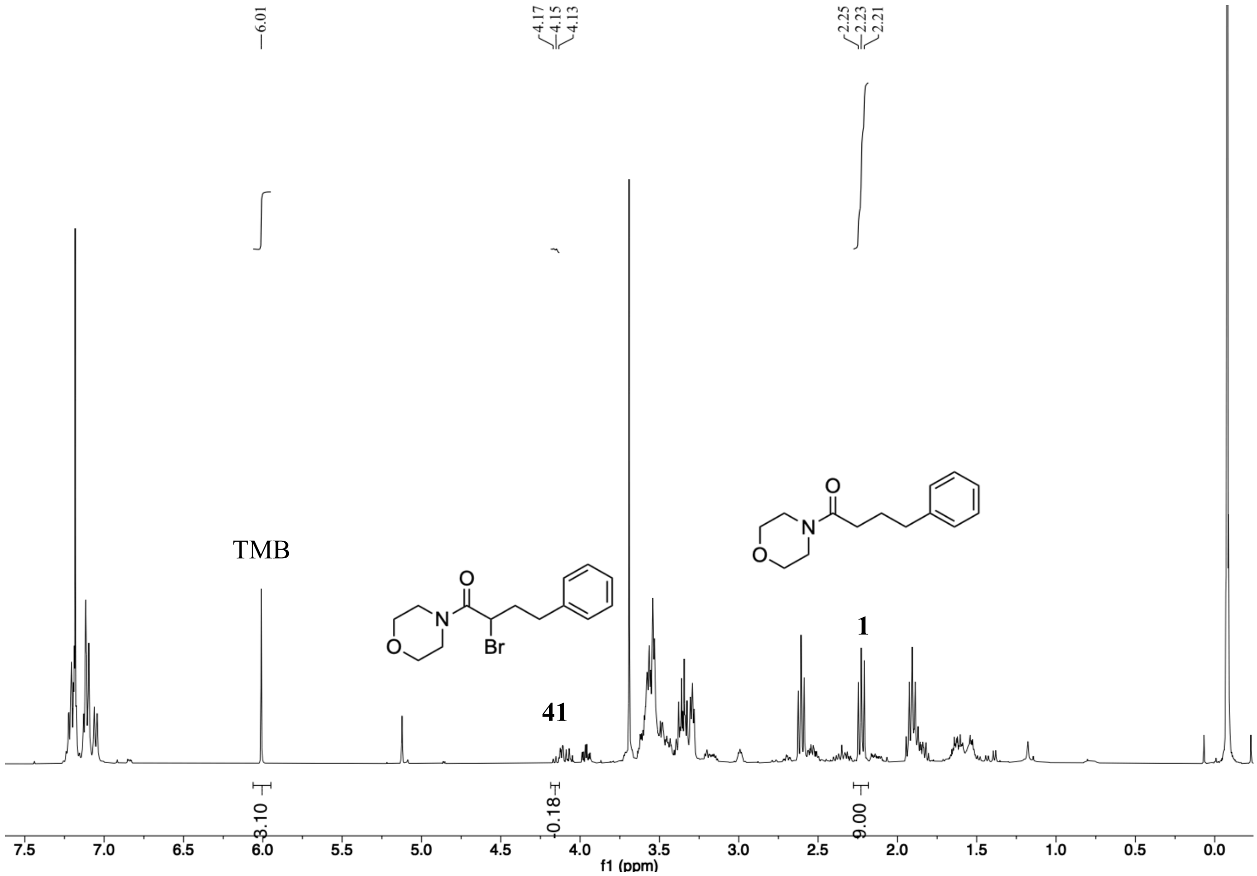


Figure S11. ^{1}H NMR spectral window of Entry 4 from Table S5. 1,3,5-Trimethoxybenzene internal standard (17.4 mg, 0.31 mmol, signal at 6.09 ppm) was used to determine the yield of 2-bromo-1-morpholino-4-phenylbutan-1-one (**41**, 18% yield) and the amount of remaining 1-morpholino-4-phenylbutan-1-one (**1**, 45% yield). Other peaks present in the 3.90-4.30 ppm range indicates other products formed.

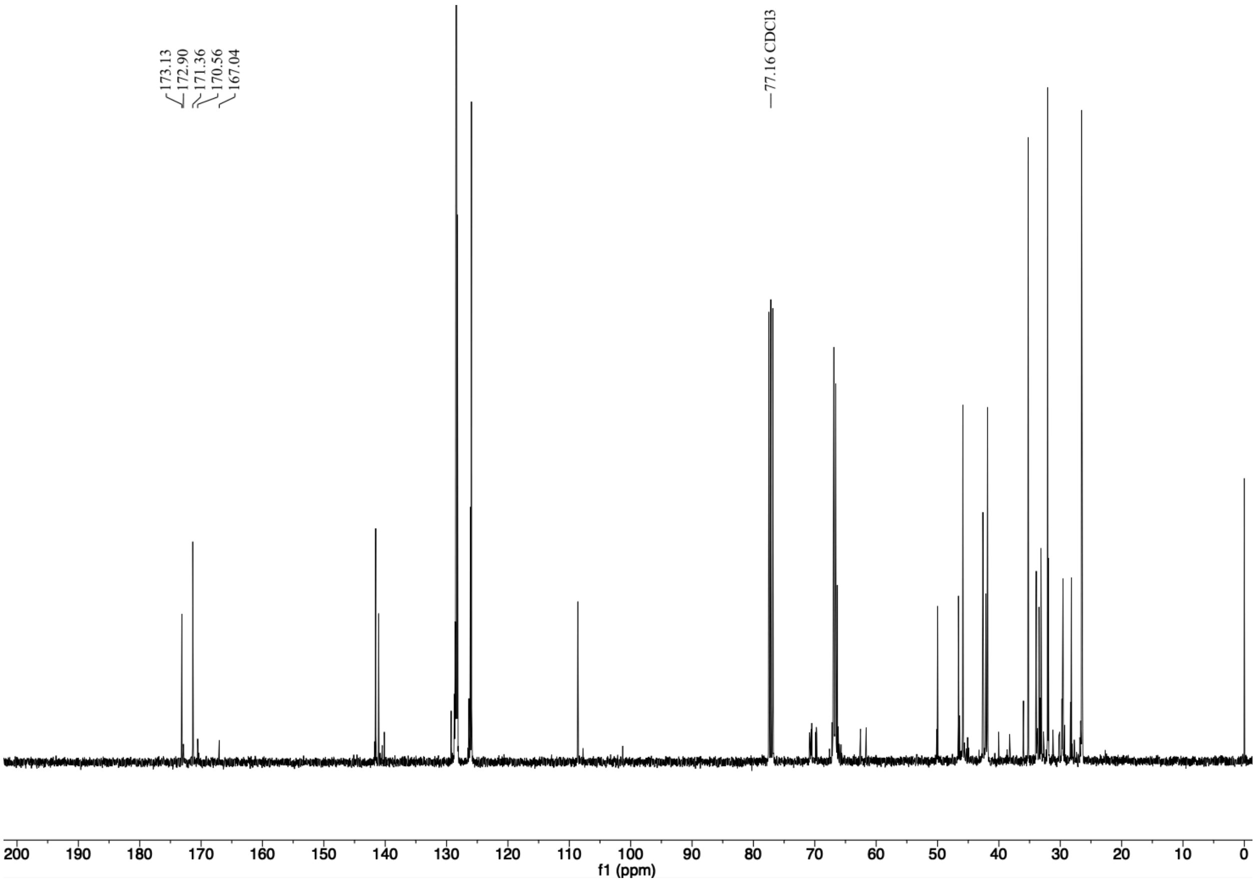
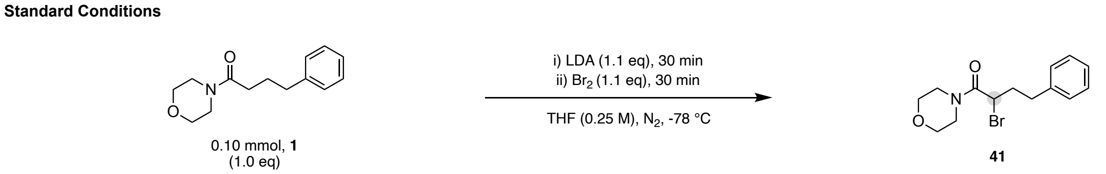


Figure S12. ^{13}C NMR spectral window of Entry 4 from Table S5. Peaks present in the carbonylic range (167-173 ppm) indicate that other carbonyl-containing side products were produced.

Discussion: Traditional enolate formation and bromination protocols proved ineffective with low amounts of 2-bromo-1-morpholino-4-phenylbutan-1-one (**41**) formed and significant remaining 1-morpholino-4-phenylbutan-1-one (**1**) present. Additional reaction conditions were also investigated to determine if higher yields of 2-bromo-1-morpholino-4-phenylbutan-1-one (**41**) could be formed but were not successful. As summarized below, change in reaction conditions did not give an increase in brominated product further illustrating the difficultly of this approach towards the α-halogenation of amides.

General procedure for condition variation of 0.1 mmol scale α-deprotonation and α-bromination of model amide 1-morpholino-4-phenylbutan-1-one (1): Inside an N_2 filled glovebox, LDA (110 μL 1 M in THF, 1.0 mmol, 1.1 eq) was added to an oven-dried 4 mL vial (Thermo Fisher Scientific, Product #033405P) charged with a magnetic stir bar and was subsequently sealed with a screw cap (Thermo Fisher Scientific, Product #03392A) lined with a PTFE septum (Thermo Fisher Scientific, Product #B7995-15). In a separate oven-dried 4 mL vial, 1-morpholino-4-phenylbutan-1-one (23.3 mg, 0.10 mmol, 1.0 eq) and anhydrous solvent (200 μL) were added and the vial was sealed with a screw cap lined with a PTFE septum. In another separate oven-dried 4 mL vial, bromine and anhydrous solvent (90 μL) were added and sealed with a screw cap lined with a PTFE septum. All vials were removed from the glovebox and the vial containing

LDA was placed into a -78 °C dry ice/acetone bath and the solution was stirred for 15 minutes. The amide solution was then transferred to the LDA vial *via* syringe and allowed to stir for 30 minutes. The bromine solution was then added *via* syringe and allowed to stir for 30 minutes. The reaction mixture was quenched with a saturated ammonium chloride solution, then 1,3,5-trimethoxybenzene internal standard was weighed into the vial. For each experiment, the mass of 1,3,5-trimethoxybenzene weighed into the vial was recorded separately. A small aliquot was removed and injected into an NMR tube and constituted in ($CDCl_3$). ^1H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 2-bromo-1-morpholino-4-phenylbutan-1-one (**35**). The aromatic C–H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aliphatic C–H signals of **41** at 4.23 ppm (t, 1H) to determine the yield. The results are summarized in Table S6 below.

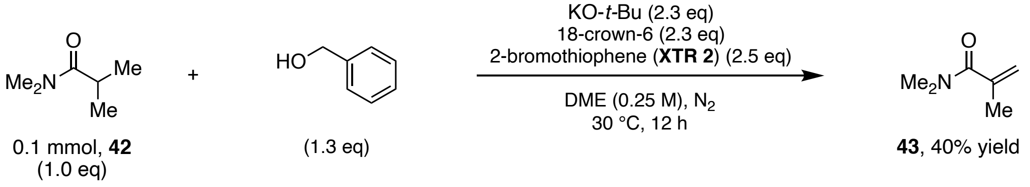


Entry	Change from the "standard conditions"	Yield
1	none	12%
2	0 °C used instead of -78 °C	9%
3	1 M HCl quench used instead of sat. ammonium chloride	12%
4	MeOH quench used instead of sat. ammonium chloride	11%
5	$CDCl_3$ quench used instead of sat. ammonium chloride	5%

Table S6. Condition variation for the α-bromination of 1-morpholino-4-phenylbutan-1-one (**1**).

d) Subjection of *N*,*N*-dimethylisobutyramide (42) to the α-etherification reaction conditions

Purpose: As an indirect probe the formation of an α-brominated intermediate, *N*,*N*-dimethylisobutyramide (**42**) was subjected to slightly altered α-etherification reaction conditions. In this case, we hypothesized that if an α-bromo intermediate is generated, elimination would be more likely than substitution and would provide indirect support for an operable X-transfer mechanism. Because this substrate is structurally distinct from the model amides of the substrate scope, we found that a different 2-bromothiophene (**XTR 2**) X-transfer reagent was required for reactivity. The original α-etherification reaction conditions using KOH and 2,5-dibromothiophene gave full retention of *N*,*N*-dimethylisobutyramide with no observable products formed; however, the more basic KO-*t*-Bu and **XTR 2** led to observable reactivity.



Procedures: *N*,*N*-Dimethylisobutyramide (11.5 mg, 0.10 mmol, 1.0 eq), benzyl alcohol (14.1 mg, 0.13 mmol, 1.3 eq), and 2-bromothiophene (40.8 mg, 0.25 mmol, 2.5 eq) were added to an oven-dried 4 mL vial (Thermo Fisher Scientific, Product #033405P) charged with a magnetic stir bar and the vial was sealed with a screw cap (Thermo Fisher Scientific, Product #03392A) lined with a PTFE septum (Thermo Fisher Scientific, Product #B7995-15)**.** Inside an N_2 filled glovebox, anhydrous DME (0.4 mL, 0.25 M), 18-crown-6 (60.8 mg, 0.23 mmol, 2.3 eq), and KO-*t*Bu (14.5 mg, 0.23 mmol, 2.3 eq) were added in successive order to the vial and consequently sealed. The vial was removed from the glovebox, and placed into a 60 °C preheated aluminum reaction block and the reaction mixture was stirred for 12 hours. The reaction solution was cooled to room temperature, then 1,3,5-trimethoxybenzene internal standard was weighed into the vial. For each experiment, the mass of 1,3,5-trimethoxybenzene weighed into the vial was recorded separately. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of *N*,*N*-dimethylmethacrylamide (**43**). The aromatic C–H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the vinylic C–H signals of **43** at 5.19 ppm (quintet, 1H) to determine a 40% yield. The ^{1}H NMR spectrum for the crude reaction solution is shown in Figure S13 to show how the yield was determined. Product formation was confirmed through spiking commercial *N*,*N*-dimethylmethacrylamide into the crude NMR sample.

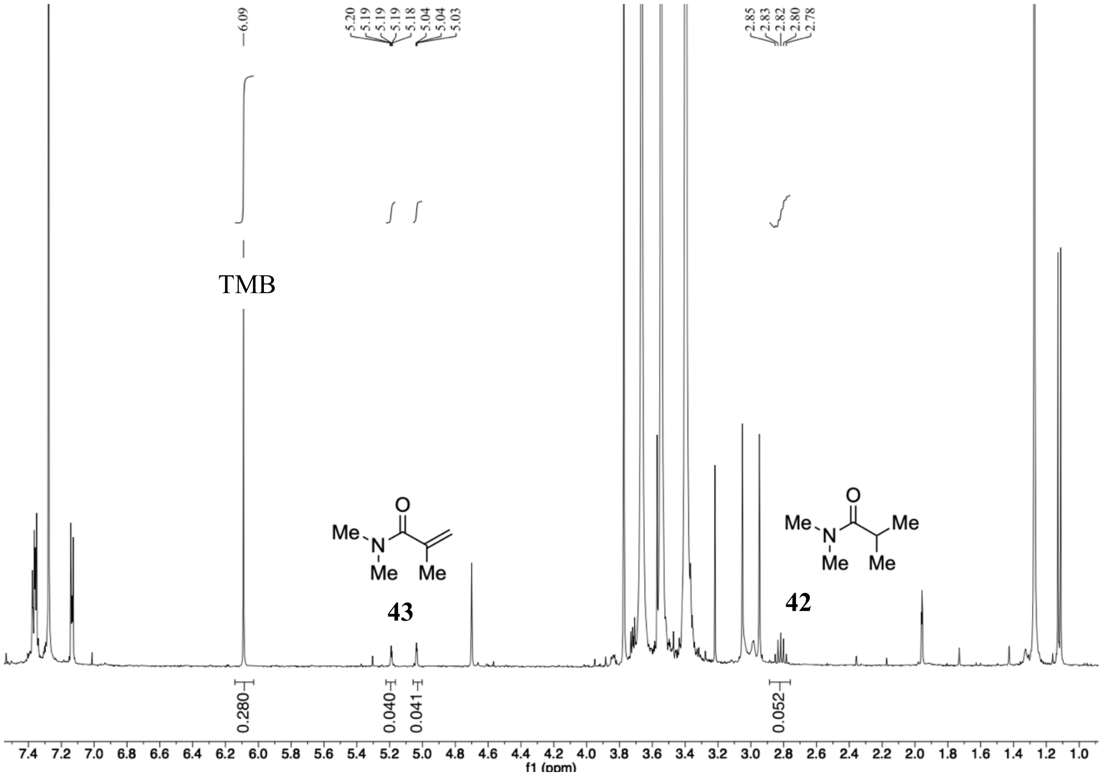
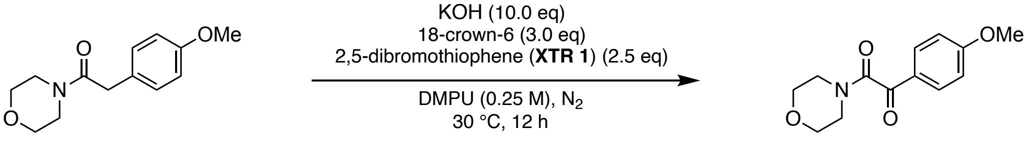


Figure S13. ^{1}H NMR spectral window of the subjection of *N*,*N*-dimethylisobutyramide (**42**) to altered α-etherification reaction conditions. 1,3,5-Trimethoxybenzene internal standard (15.6 mg, 0.28 mmol, signal at 6.09 ppm) was used to determine the yield of *N*,*N*-dimethylmethacrylamide (**43**, 40% yield).

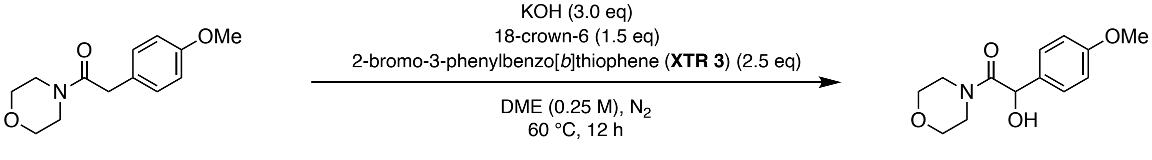
8. General Procedure for the Selective Oxidation of Amide 45



1.0 mmol, **45**
(1.0 eq)

46

Procedure for the α-Oxidation of Amide 45: 2-(4-Methoxyphenyl)-1-morpholinoethan-1-one (235.3 mg, 1.0 mmol, 1.0 eq) was added to an oven-dried 25 mL round bottom flask. The flask was sealed with a rubber septum (Thermo Fisher Scientific, Product #CG302206) and subsequently evacuated and backfilled five times with N_2, and left under a positive pressure of N_2 on a manifold Schlenk line using a needle inlet. 18-crown-6 (792.8 mg, 3.0 mmol, 3.0 eq) and KOH (561.1 mg, 10.0 mmol, 10.0 eq) were added to a separate oven-dried 25 mL round bottom flask containing a magnetic stir bar and was sealed with a rubber septum. The flask was subsequently evacuated and backfilled five times with N_2, and left under a positive pressure of N_2 on a manifold Schlenk line using a needle inlet. Anhydrous DME (4 mL, 0.25 M) was added portion-wise to the flask containing 2-(4-Methoxyphenyl)-1-morpholinoethan-1-one. The amide solution and 2,5-dibromothiophene (0.28 mL, 2.5 mmol, 2.5 eq) were transferred *via* syringe to the flask containing the KOH and 18-crown-6. The needle inlet was removed and the septum was wrapped with parafilm and placed into a preheated 60 °C silicon oil bath with stirring for 12 h. The reaction solution was allowed to cool to rt and was subsequently transferred into separatory funnel containing saturated ammonia chloride (50 mL). The aqueous mixture was extracted with DCM (3 x 50 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (2% MeOH, 25% diethyl ether, 73% DCM). The fractions containing 1-(4-methoxyphenyl)-2-morpholinoethane-1,2-dione (**46**) was concentrated under reduced pressure, reconstituted in hexanes (25 mL) and was subsequently transferred into separatory funnel containing water (200 mL). The organic layer was extracted with water (3 x 200 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure to afford 1-(4-methoxyphenyl)-2-morpholinoethane-1,2-dione (**46**) as a light brown solid (178.9 mg, 0.72 mmol, 72% yield). Spectroscopic characterization of this compound is consistent with a previous literature report.[6] **^{1}H NMR** (401 MHz, $CDCl_3$) δ 7.60 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 3.83 (s, 3H), 3.74 – 3.01 (m, 7H), 2.81 (m, 1H).



1.0 mmol, **45**
(1.0 eq)

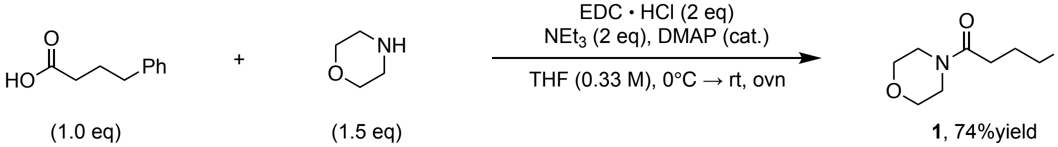
47

Procedure for the α-Hydroxylation of Amide 45: 2-(4-Methoxyphenyl)-1-morpholinoethan-1-one (235.3 mg, 1.0 mmol, 1.0 eq), 2-bromo-3-phenylbenzo[*b*]thiophene[7] (719.9 mg, 2.5 mmol, 2.5 eq), 18-crown-6 (396.4 mg, 1.5 mmol, 1.5 eq), and KOH (168.3 mg, 3.0 mmol, 3.0 eq) were added in successive order to an oven-dried 25 mL round bottom containing a magnetic stir bar. The flask was sealed with a rubber septum (Thermo Fisher Scientific, Product #CG302206) and subsequently evacuated and backfilled five times with N_2, and left under a positive pressure of N_2 on a manifold Schlenk line using a needle inlet. Anhydrous DMPU (4 mL, 0.25 M) was added *via* syringe and the needle inlet was removed and the septum was wrapped with parafilm and placed into a preheated 30 °C silicon oil bath with stirring for 12 h. The reaction solution was allowed to cool to rt and was subsequently transferred into separatory funnel containing 5% LiCl aqueous solution (50 mL). The aqueous mixture was extracted with DCM (3 x 50 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography using a gradient from 60% diethyl ether and 40% EtOAc to 100% EtOAc and then to 10% MeOH and 90% EtOAc. The fractions containing 2-hydroxy-2-(4-methoxyphenyl)-1-morpholinoethan-1-one (**47**) was concentrated under reduced pressure, reconstituted in hexanes (25 mL) and was subsequently transferred into separatory funnel containing water (200 mL). The organic layer was extracted with water (3 x 200 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure to afford 2-hydroxy-2-(4-methoxyphenyl)-1-morpholinoethan-1-one (**47**) the title compound as a white solid (202.9 mg, 0.81 mmol, 81% yield). **Mp**: 190 °C – 192 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 2H), 4.35 (s, 1H), 3.73 (m, 5H), 3.63 – 3.21 (m, 5H), 3.00 (ddd, *J* = 10.6, 7.5, 3.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.8, 158.6, 129.7, 128.9, 113.9, 66.8, 66.4, 55.2, 52.6, 46.2, 42.7. **IR** (neat, cm^{-1}) 3300, 2956, 2850, 1628, 1512, 1280, 1030. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{24}H_{36}NO_3]^+$ = 252.1231, 252.1225 found.

9. Starting Material Synthesis and Characterization

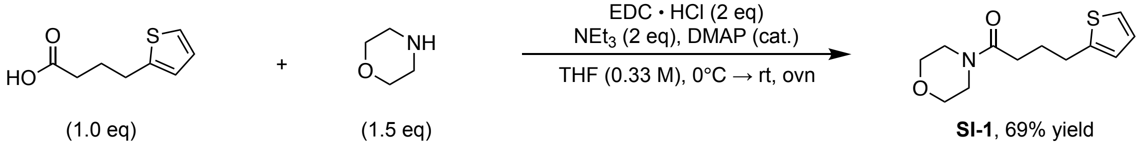
Non-commercial substrates and reagents used are described below; all other materials were purchased from commercial suppliers and used as received.

1-morpholino-4-phenylbutan-1-one (1)



Procedure: In a 500 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (180 mL, 0.33 M), 4-phenylbutanoic acid (4.93 g, 30.0 mmol, 1.0 eq), triethylamine (8.33 mL, 60.0 mmol, 2.0 eq), and morpholine (3.92 mL, 45.0 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 11.50 g, 60.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~60 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (300 mL). The organic layer was extracted once with water (150 mL) and then with 1 M HCl (2 x 150 mL). The combined aqueous layers were back-extracted with ethyl acetate (300 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (25%EtOAc, 75%hexanes) to provide a clear solid (5.15 g, 22.2 mmol, 74% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.13 (m, 3H), 3.63 (dt, *J* = 13.4, 4.5 Hz, 6H), 3.36 (t, *J* = 4.9 Hz, 2H), 2.68 (t, *J* = 7.4 Hz, 2H), 2.35 – 2.26 (t, *J* = 6.9 Hz 2H), 1.98 (m, *J* = 7.4 Hz, 2H). Spectroscopic characterization of this compound is consistent with a previous literature report.[8]

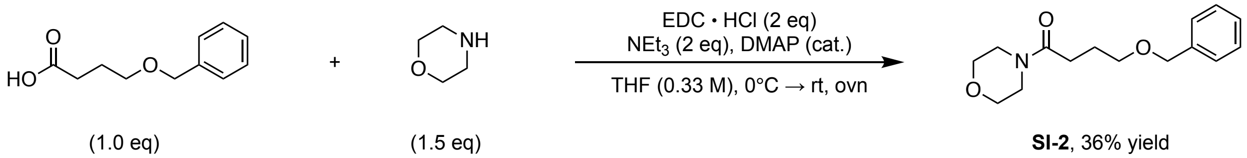
1-morpholino-4-(thiophen-2-yl)butan-1-one (SI-1)



SI-1, 69% yield

Procedure: In a 500 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (180 mL, 0.33 M), 4-(thiophen-2-yl)butanoic acid (5.11 g, 30.0 mmol, 1.0 eq), triethylamine (8.33 mL, 60.0 mmol, 2.0 eq), and morpholine (3.92 mL, 45 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 11.50 g, 60.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~60 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (300 mL). The organic layer was extracted once with water (150 mL) and then with 1 M HCl (2 x 150 mL). The combined aqueous layers were back-extracted with ethyl acetate (300 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (75% EtOAc,25% hexanes) to provide a pale, yellow oil (4.97 g, 20.8 mmol, 69% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.89 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.80 – 6.74 (m, 1H), 3.61 (dd, *J* = 9.9, 5.1 Hz, 3H), 3.36 (t, *J* = 4.9 Hz, 2H), 2.88 (t, *J* = 7.8 Hz, 2H), 2.36 – 2.28 (m, 2H), 2.01 (p, *J* = 7.4 Hz, 2H). Spectroscopic characterization of this compound is consistent with a previous literature report.[9]

4-(benzyloxy)-1-morpholinobutan-1-one (SI-2)

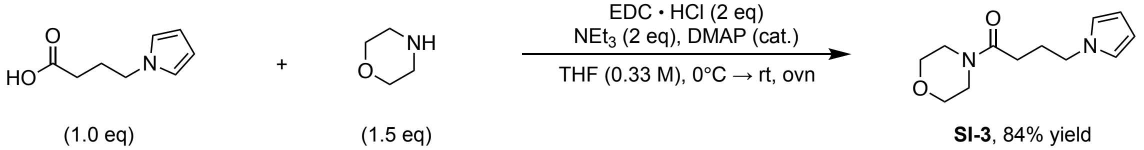


SI-2, 36% yield

Procedure: In a 250 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (60 mL, 0.33 M), 4-(benzyloxy)butanoic acid (1.94 g, 10.0 mmol, 1.0 eq), triethylamine (2.33 mL, 15.0 mmol, 2.0 eq), and morpholine (1.31 mL, 15.0 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 3.83 g, 20.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~20 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (100 mL). The organic layer was extracted once with water (50 mL) and then with 1 M HCl (2 x 50 mL). The combined aqueous layers were back-extracted with ethyl acetate (100 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (35% EtOAc/ 65% hexanes) to provide a clear oil

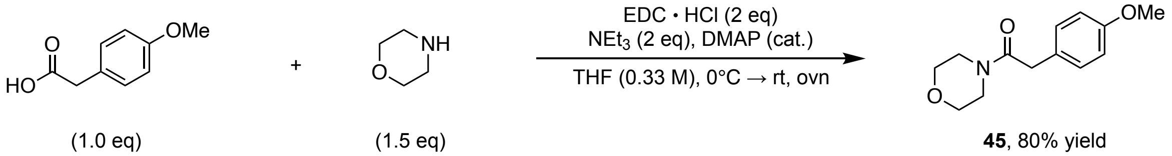
(956.4 mg, 3.63 mmol, 36% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 5H), 4.48 (s, 2H), 3.66 – 3.55 (m, 6H), 3.53 (t, *J* = 6.0 Hz, 2H), 3.48 – 3.32 (m, 2H), 2.41 (t, *J* = 7.1 Hz, 2H), 2.00 – 1.84 (m, *J* = 6.3 Hz 2H). Spectroscopic characterization of this compound is consistent with a previous literature report.[10]

1-morpholino-4-(1*H*-pyrrol-1-yl)butan-1-one (SI-3)



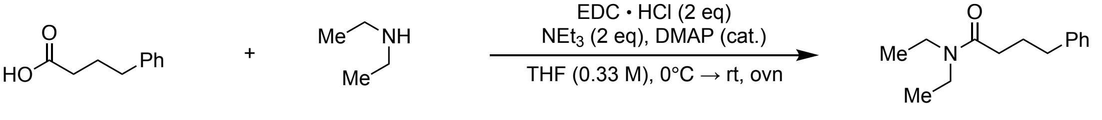
Procedure: In a 250 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (60 mL, 0.33 M), 4-(1*H*-pyrrol-1-yl)butanoic acid (1.53 g, 10.0 mmol, 1.0 eq), triethylamine (2.78 mL, 20.0 mmol, 2.0 eq), and morpholine (1.31 mL, 15.0 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 3.83 g, 20.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~20 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (100 mL). The organic layer was extracted once with water (50 mL) and then with 1 M HCl (2 x 50 mL). The combined aqueous layers were back-extracted with ethyl acetate (100 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (100% EtOAc) to provide an orange oil (1.8592 g, 8.4 mmol, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.62 (t, *J* = 2.1 Hz, 2H), 6.13 (t, *J* = 1.7 Hz, 2H), 3.96 (t, *J* = 7.0 Hz, 2H), 3.61 (m, 6H), 3.39 – 3.23 (m, 2H), 2.23 – 2.14 (m, 2H), 2.09 (p, *J* = 6.2 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 120.5, 108.1, 66.8, 66.5, 48.5, 45.7, 41.9, 29.0, 26.6. **IR** (neat, cm^{-1}) 2961, 2855, 2360, 1637, 1233, 1112, 725. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{12}H_{19}N_2O_2]^+$=223.1442, 223.1441 found.

2-(4-methoxyphenyl)-1-morpholinoethan-1-one (45)



Procedure: In a 250 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (60.0 mL, 0.33 M), 2-(4-methoxyphenyl)acetic acid (1.66 g, 10.0 mmol, 1.0 eq), triethylamine (2.78 mL, 20.0 mmol, 2.0 eq), and morpholine (1.31 mL, 15.0 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 3.83 g, 20.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~20 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (100 mL). The organic layer was extracted once with water (50 mL) and then with 1 M HCl (2 x 50 mL). The combined aqueous layers were back-extracted with ethyl acetate (100 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (50% EtOAC/ 50% hexanes) to provide a white solid (1.88 g, 8.0 mmol, 80% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.21 – 7.08 (m, 2H), 6.91 – 6.79 (m, 2H), 3.80 (s, 3H), 3.65 (m, 6H), 3.55 – 3.33 (m, 4H). Spectroscopic characterization of this compound is consistent with a previous literature report.[11]

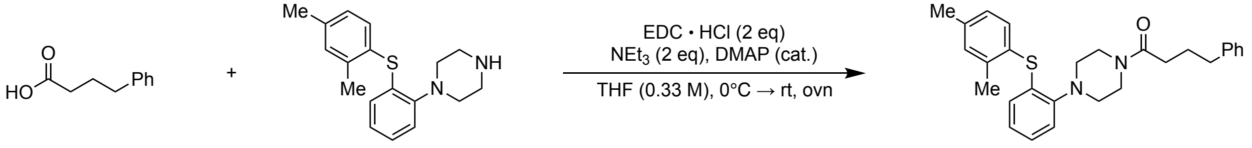
***N*,*N*-diethyl-4-phenylbutanamide (SI-4)**



(1.0 eq) (1.5 eq) **SI-4**, 65% yield

Procedure: In a 250 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (180.0 mL, 0.33 M), 4-phenylbutanoic acid (4.93 g, 30.0 mmol, 1.0 eq), triethylamine (8.34 mL, 60.0 mmol, 2.0 eq), and *N,N*-diethylamine (4.65 mL, 45.0 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 11.50 g, 60.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~20 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (300 mL). The organic layer was extracted once with water (150 mL) and then with 1 M HCl (2 x 150 mL). The combined aqueous layers were back-extracted with ethyl acetate (300 mL). The organic layer was dried over Na$_2$SO$_4$. The Na$_2$SO$_4$ was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (25% EtOAc/ 75% hexanes) to provide a clear oil (4.30 g, 19.6 mmol, 65% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.24 (m, 2H), 7.14 (m, 3H), 3.33 (q, J = 7.1 Hz, 2H), 3.17 (q, J = 7.1 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 2.37 – 2.15 (t, J = 7.3 Hz, 2H), 1.96 (p, J = 7.4 Hz, 2H), 1.26 – 0.84 (m, 6H). Spectroscopic characterization of this compound is consistent with a previous literature report.[12]

1-(4-(2-((2,4-dimethylphenyl)thio)phenyl)piperazin-1-yl)-4-phenylbutan-1-one (SI-5)

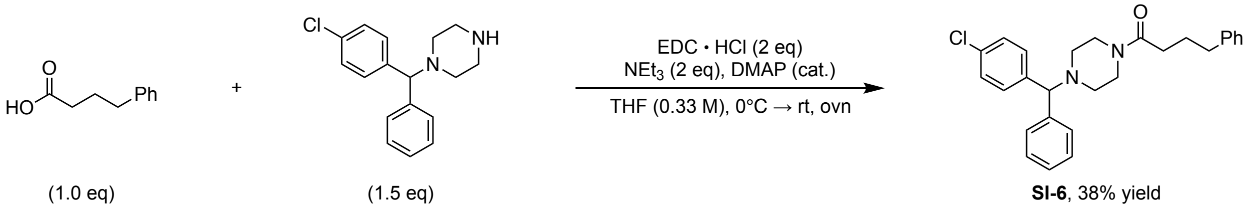


(1.0 eq) (1.5 eq) **SI-5**, 86% yield

Procedure: In a 50 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (10 mL, 0.33 M), 4-phenylbutanoic acid (328.4 mg, 2.0 mmol, 1.0 eq), triethylamine (0.56 mL, 4.0 mmol, 2.0 eq), and 1-(2-((2,4-dimethylphenyl)thio)phenyl)piperazine (895.4 mg, 3.0 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 766.8 mg, 4.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~4 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (20 mL). The organic layer was extracted once with water (10 mL) and then with 1 M HCl (2 x 10 mL). The combined aqueous layers were back-extracted with ethyl acetate (20 mL). The organic layer was dried over Na$_2$SO$_4$. The Na$_2$SO$_4$ was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (25% EtOAc/ 75% hexanes) to provide an orange oil (767.4 mg, 1.72 mmol, 86% yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.36 (d, J = 7.8 Hz, 1H), 7.31 – 7.11 (m, 6H), 7.11 – 6.93 (m, 3H), 6.92 –

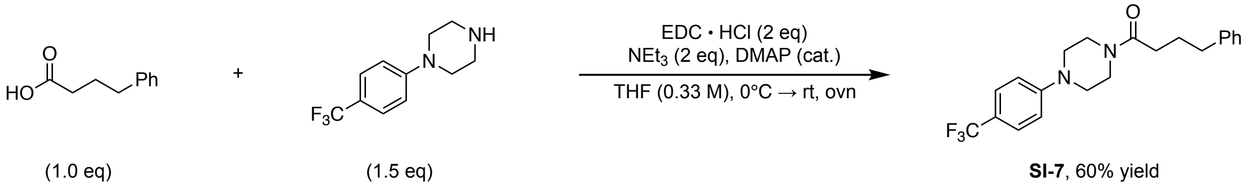
6.81 (m, 1H), 6.53 (dd, J = 7.9, 1.6 Hz, 1H), 3.94 – 3.68 (m, 2H), 3.63 – 3.48 (m, 2H), 3.01 (t, J = 5.1 Hz, 4H), 2.70 (t, J = 7.6 Hz, 2H), 2.41 – 2.29 (m, 8H), 2.01 (m, J = 7.5 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.5, 148.6, 142.4, 141.8, 139.4, 136.3, 134.7, 131.8, 128.6, 128.5, 127.9, 127.8, 126.6, 126.0, 125.7, 124.9, 120.0, 52.1, 51.5, 46.1, 42.1, 35.5, 32.5, 26.9, 21.3, 20.7. **IR** (neat, cm^{-1}) 2917, 2360, 2341, 1640, 1469, 1438, 1223, 1024. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{28}H_{33}N_2OS]^+$ = 445.2308, 445.2316 found.

1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-4-phenylbutan-1-one (SI-6)



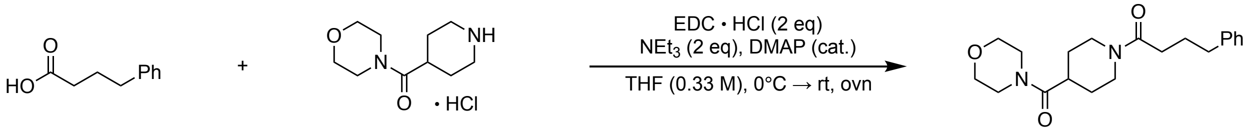
Procedure: In a 500 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (180 mL, 0.33 M), 4-phenylbutanoic acid (4.93 g, 30.0 mmol, 1.0 eq), triethylamine (8.4 mL, 60.0 mmol, 2.0 eq), and 1-((4-chlorophenyl)(phenyl)methyl)piperazine (12.91 g, 45.0 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 11.50 g, 60.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~60 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (300 mL). The organic layer was extracted once with water (150 mL) and then with 1 M HCl (2 x 150 mL). The combined aqueous layers were back-extracted with ethyl acetate (300 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (100% EtOAc) to provide a pale yellow solid (4.91 g, 11.3 mmol, 38% yield). **Mp**: 96 °C – 98 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 4H), 7.31 – 7.23 (m, 2H), 7.23 – 7.13 (m, 3H), 4.20 (s, 1H), 3.71 – 3.51 (m, 2H), 3.38 (dd, J = 6.0, 4.1 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.41 – 2.22 (m, 6H), 2.03 – 1.87 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.4, 153.0, 141.6, 128.6, 128.5, 126.57 (q, J = 3.8 Hz), 126.1, 124.70 (q, J = 270.8 Hz), 121.28 (q, J = 32.8 Hz), 115.0, 48.4, 48.1, 45.1, 41.2, 35.3, 32.3, 26.7. **IR** (neat, cm^{-1}) 2849, 2827, 2359, 2342, 1641, 1435, 1230. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{27}H_{30}ClN_2O]^+$ =433.2041, 433.2041 found.

4-phenyl-1-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)butan-1-one (SI-7)



Procedure: In a 250 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (66 mL, 0.33 M), 4-phenylbutanoic acid (1.81 g, 11.0 mmol, 1.0 eq), triethylamine (3.07 mL, 22.0 mmol, 2.0 eq), and 1-(4-(trifluoromethyl)phenyl)piperazine (3.84 g, 17.0 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 4.22 g, 22.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~20 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (100 mL). The organic layer was extracted once with water (50 mL) and then with 1 M HCl (2 x 50 mL). The combined aqueous layers were back-extracted with ethyl acetate (100 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (75% EtOAc, 25% hexanes) to provide a white solid (2.50 g, 6.6 mmol, 60% yield). **Mp**: 94–96 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.1 Hz, 2H), 7.35 – 7.24 (m, 2H), 7.20 (m, 3H), 6.90 (d, *J* = 8.5 Hz, 2H), 3.77 (m, 2H), 3.54 (m, 2H), 3.23 (m, 4H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.44 – 2.25 (t, *J* = 7.5 Hz, 2H), 2.01 (p, *J* = 7.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.4, 153.0, 141.6, 128.6, 128.5, 126.6 (q, *J* = 3.8 Hz), 126.1, 124.7 (q, *J* = 270.8 Hz), 121.3 (q, *J* = 32.8 Hz), 115.0, 48.4, 48.1, 45.1, 41.2, 35.3, 32.3, 26.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.43. **IR** (neat, cm^{-1}) 2922, 2831, 2360, 1646, 1610, 1189, 1099. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{21}H_{24}F_3N_2O]^+$ =377.1835, 377.1834 found.

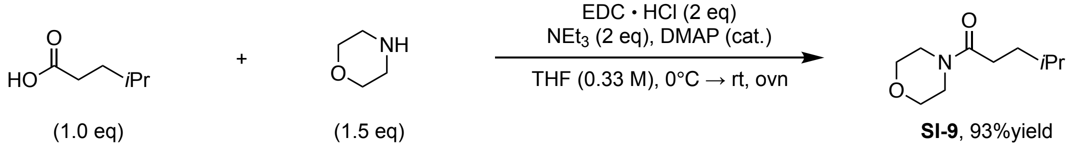
1-(4-(morpholine-4-carbonyl)piperidin-1-yl)-4-phenylbutan-1-one (SI-8)



(1.0 eq) (1.5 eq) **SI-8**, 26% yield

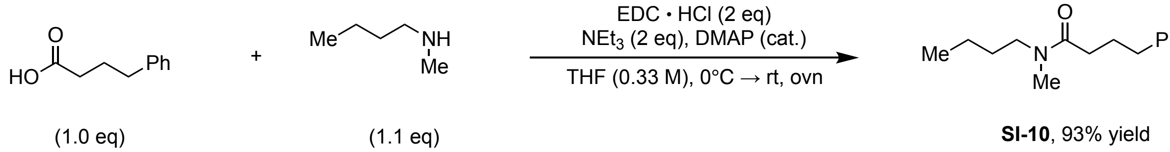
Procedure: In a 250 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (150 mL, 0.33 M), 4-phenylbutanoic acid (4.93 g, 30.0 mmol, 1.0 eq), triethylamine (7.88 mL, 60.0 mmol, 2.0 eq), and morpholino(piperidin-4-yl)methanone hydrochloride (10.56 g, 45.0 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 11.50 g, 60.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~60 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (300 mL). The organic layer was extracted once with water (150 mL) and then with 1 M HCl (2 x 150 mL). The combined aqueous layers were back-extracted with ethyl acetate (300 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (100% EtOAc) to provide a white solid (2.71 g, 7.9 mmol, 26% yield). **Mp**: 83–84 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.18 (m, 3H), 4.59 (d, *J* = 13.4 Hz, 1H), 3.80 (d, *J* = 13.6 Hz, 1H), 3.74 – 3.34 (m, 8H), 3.10 – 2.89 (m, 1H), 2.67 (m, 4H), 2.32 (td, *J* = 7.4, 3.6 Hz, 2H), 1.95 (p, *J* = 7.6 Hz, 2H), 1.88 – 1.53 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 170.8, 141.5, 128.3, 128.1, 125.7, 66.6, 66.5, 45.7, 44.6, 41.8, 40.8, 37.8, 35.1, 32.1, 28.5, 28.1, 26.5. **IR** (neat, cm^{-1}) 2862, 2360, 1634, 1432, 1185, 1119. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{29}N_2O_3]^+$ =345.2173, 345.2179 found.

4-methyl-1-morpholinopentan-1-one (SI-9)



Procedure: In a 100 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (60 mL, 0.33 M), 4-methylpentanoic acid (1.16 g, 10.0 mmol, 1.0 eq), triethylamine (2.78 mL, 20.0 mmol, 2.0 eq), and morpholine (1.31 mL, 15.0 mmol, 1.5 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 3.83 g, 20.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~20 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (100 mL). The organic layer was extracted once with water (50 mL) and then with 1 M HCl (2 x 50 mL). The combined aqueous layers were back-extracted with ethyl acetate (100 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (75% EtOAc, 25% hexanes) to provide a clear oil (1.71 g, 9.3 mmol, 93% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.73 – 3.55 (m, 6H), 3.47 (t, *J* = 4.9 Hz, 2H), 2.39 – 2.25 (m, 2H), 1.67 – 1.45 (m, 3H), 0.92 (overlapped s, 6H). Spectroscopic characterization of this compound is consistent with a previous literature report.[13]

N-butyl-*N*-methyl-4-phenylbutanamide (SI-10)



Procedure: In a 100 mL round bottom flask charged with a magnetic stir bar, anhydrous THF (60 mL, 0.33 M), 4-phenylbutanoic acid (1.64 g, 10.0 mmol, 1.0 eq), triethylamine (2.78 mL, 20.0 mmol, 2.0 eq), and *N*-methylbutan-1-amine (1.26 mL, 11.0 mmol, 1.1 eq) were added in that order. The flask was cooled to 0 °C in an ice bath and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 3.83 g, 20.0 mmol, 2.0 eq) was added portion-wise and then a catalytic amount of dimethylaminopyridine (DMAP, ~20 mg) was added. The mixture was stirred overnight at room temperature. The reaction solution was subsequently transferred into separatory funnel and diluted with ethyl acetate (100 mL). The organic layer was extracted once with water (50 mL) and then with 1 M HCl (2 x 50 mL). The combined aqueous layers were back-extracted with ethyl acetate (100 mL). The organic layer was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated under reduced pressure. The resulting crude material was purified using flash silica gel chromatography (25% EtOAc, 75% hexanes) to provide a clear oil (2.16 g, 9.3 mmol, 93% yield). This compound is comprised of rotamers and both rotamers are presented in the following NMR data. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (m, 5H), 3.35 (t, *J* = 7.5 Hz, 1H), 3.23 – 3.08 (t, *J* = 7.5 Hz, 1H), 2.89 (d, *J* = 3.0 Hz, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.37 – 2.22 (m, 2H), 2.04 – 1.88 (m, 2H), 1.56 – 1.39 (m, 2H), 1.38 – 1.17 (m, 2H), 0.91 (q, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.5, 172.4, 142.0, 141.9, 128.6, 128.4, 125.9, 125.9, 49.7, 47.5, 35.4, 35.3, 33.4, 32.8, 32.1, 30.6, 29.5, 26.9, 26.6, 20.1, 20.0, 13.9, 13.9. **IR** (neat, cm^{-1})

2955, 2861, 2359, 1640, 1453, 1133. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{15}H_{24}NO]^+$ = 234.1853, 234.1856 found.

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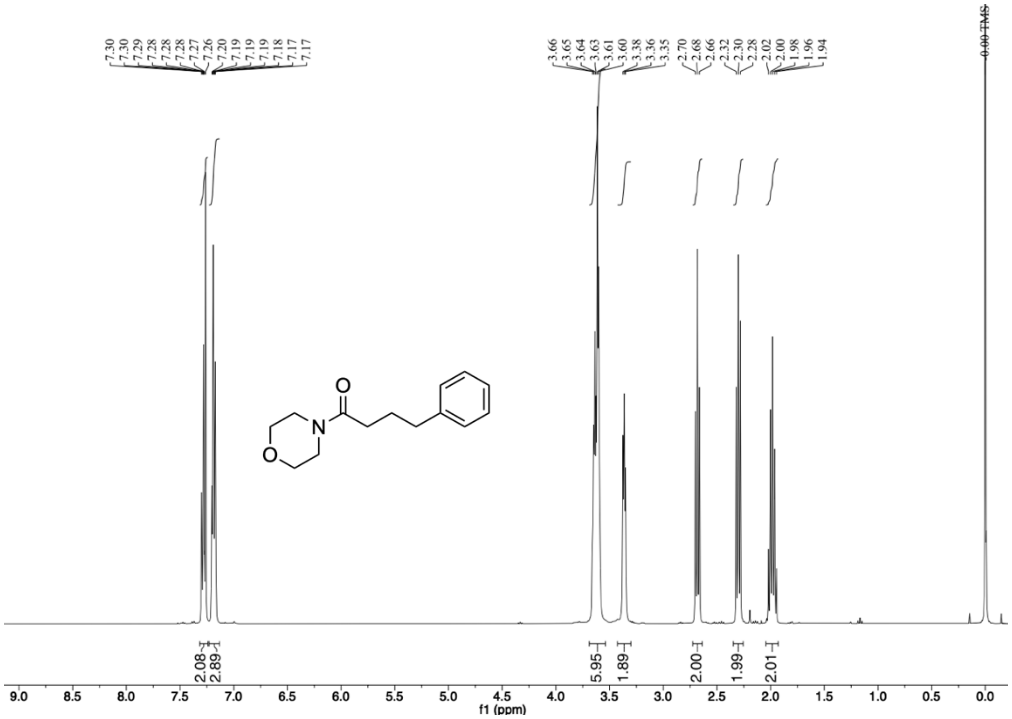
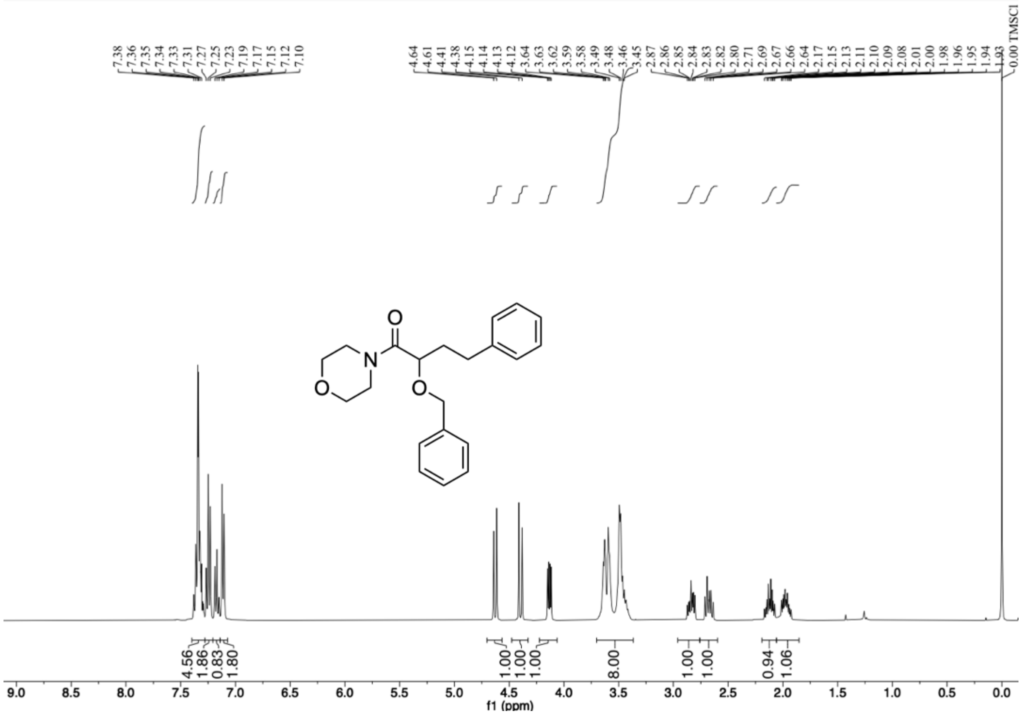
11. NMR Spectra



^{1}H NMR spectrum of **1** (400 MHz, CDCl$_3$)



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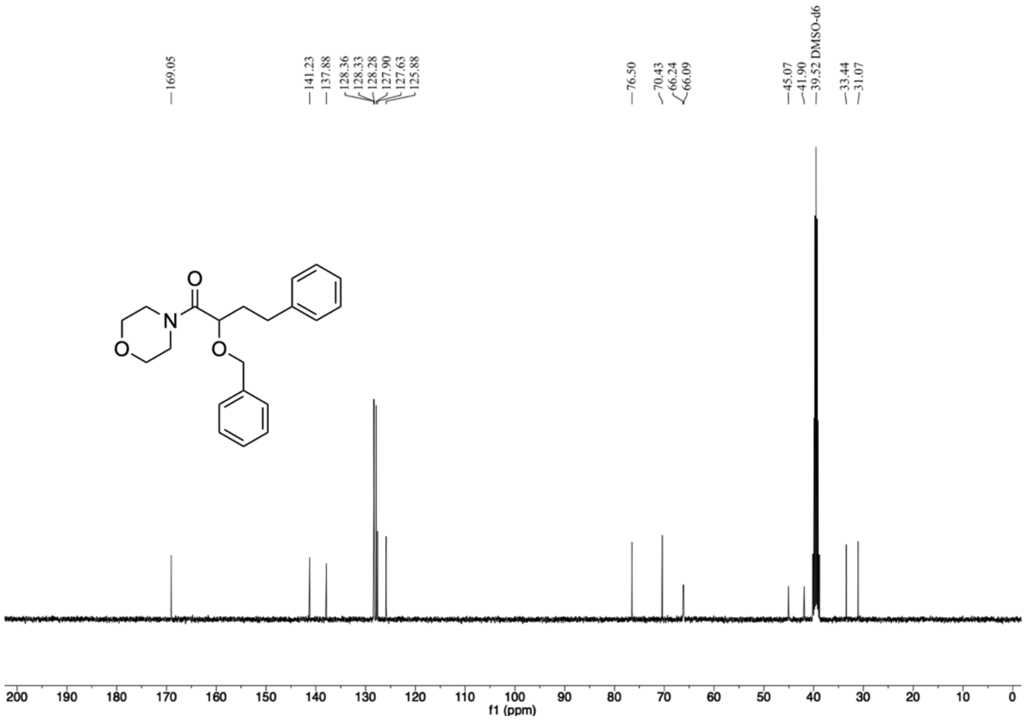
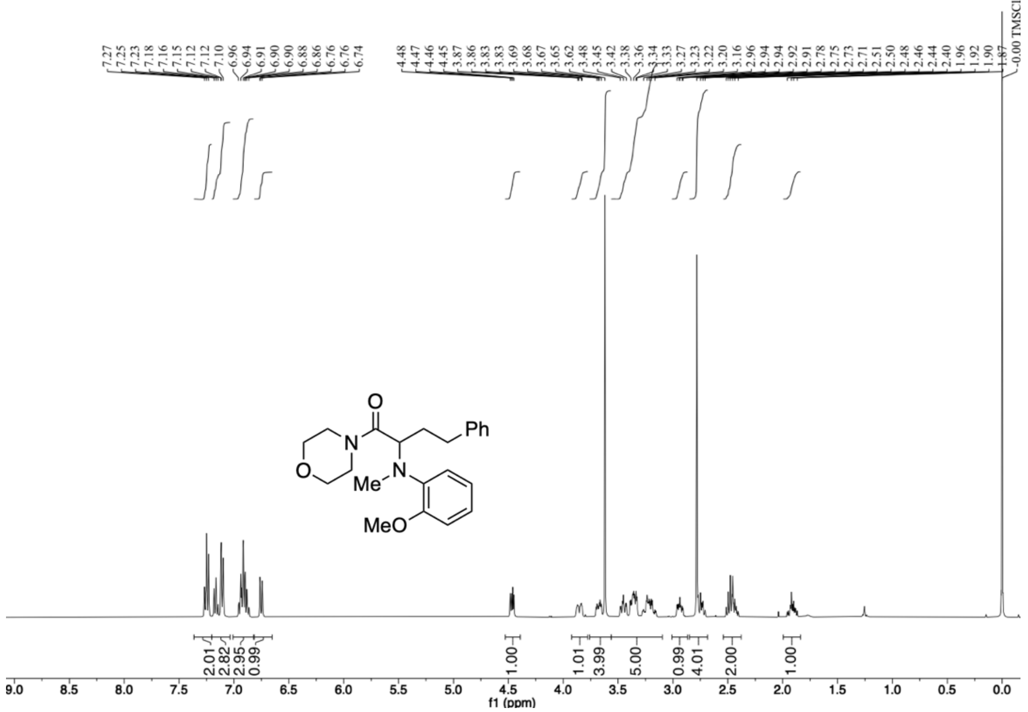
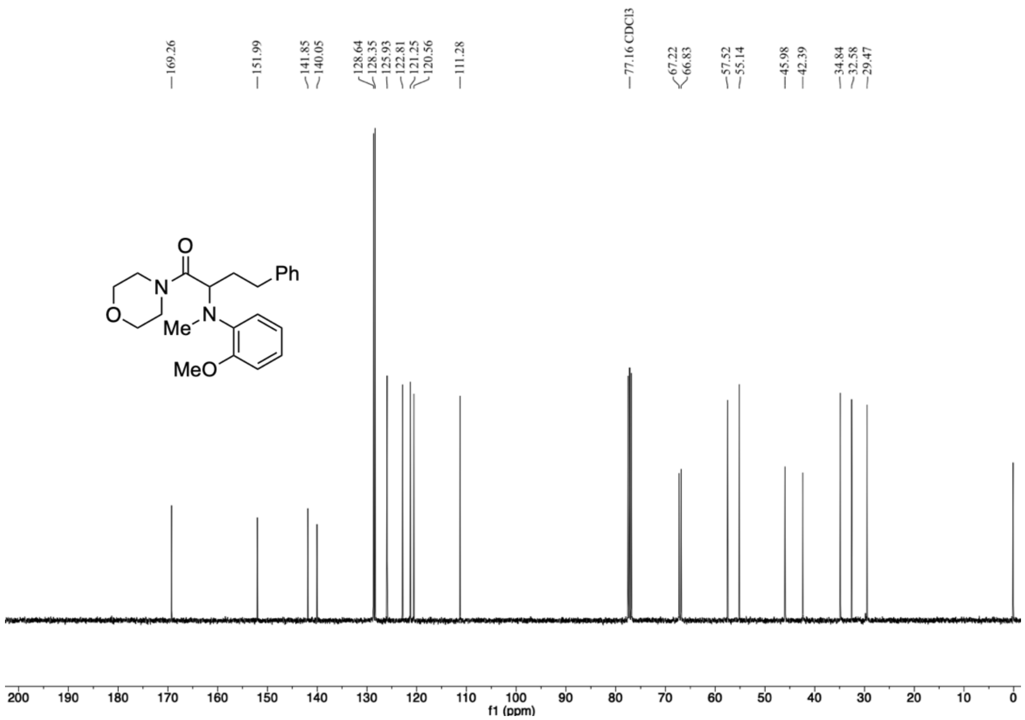


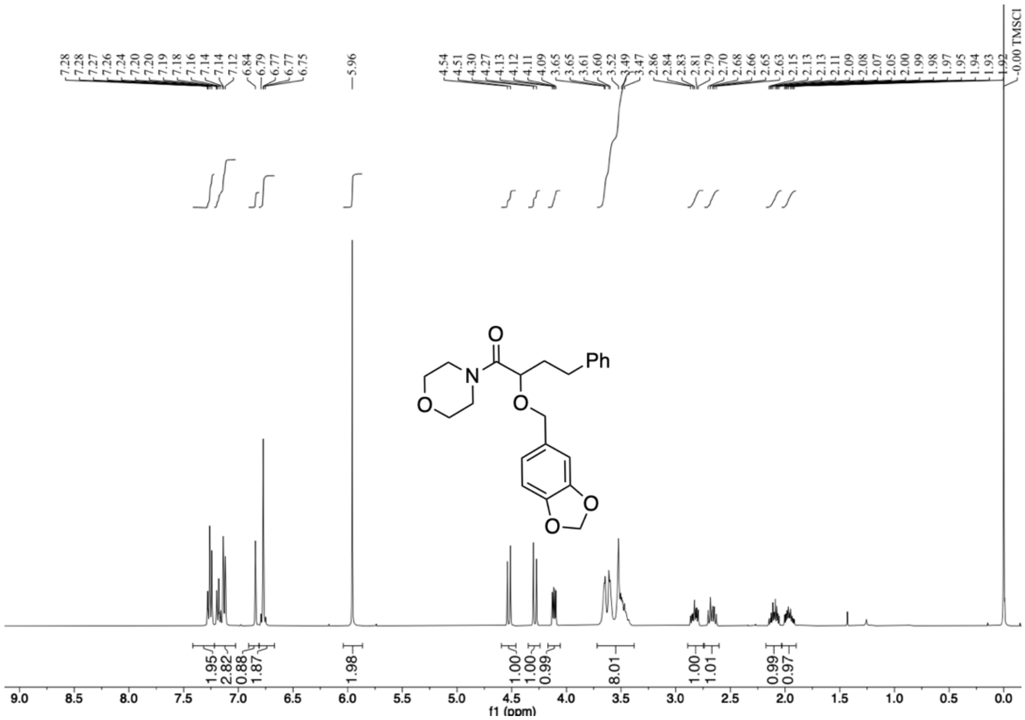
^{13}**C NMR** spectrum of **3** (101 MHz, CDCl$_3$)



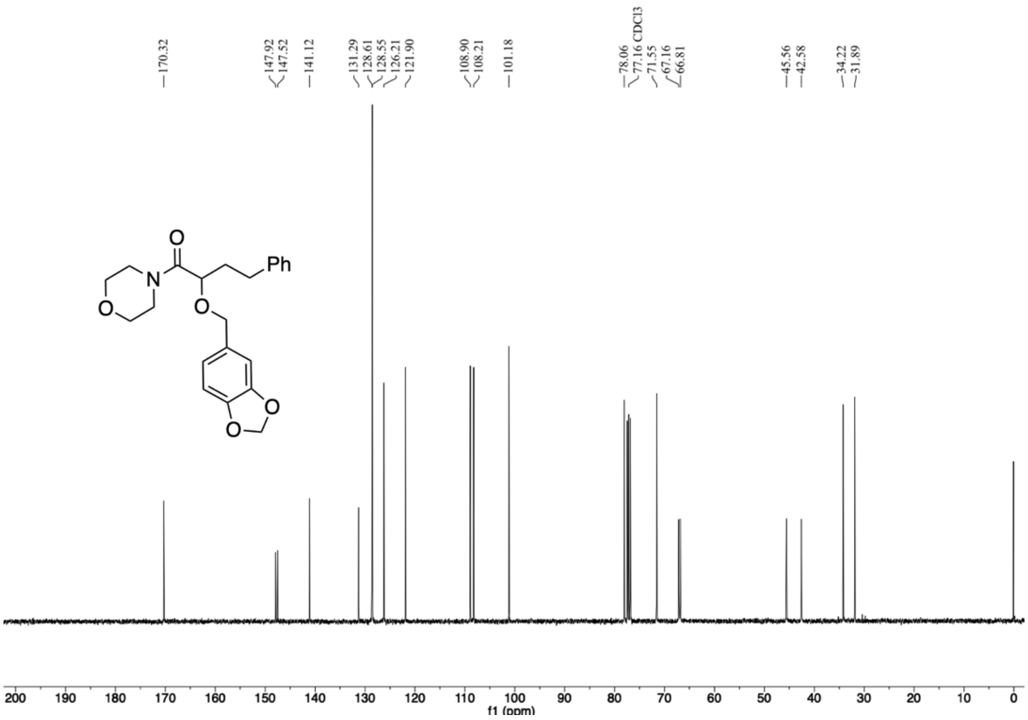
^{1}**H NMR** spectrum of **5** (400 MHz, CDCl$_3$)



^{13}C NMR spectrum of **5** (101 MHz, CDCl$_3$)



^{1}H NMR spectrum of **6** (400 MHz, CDCl$_3$)



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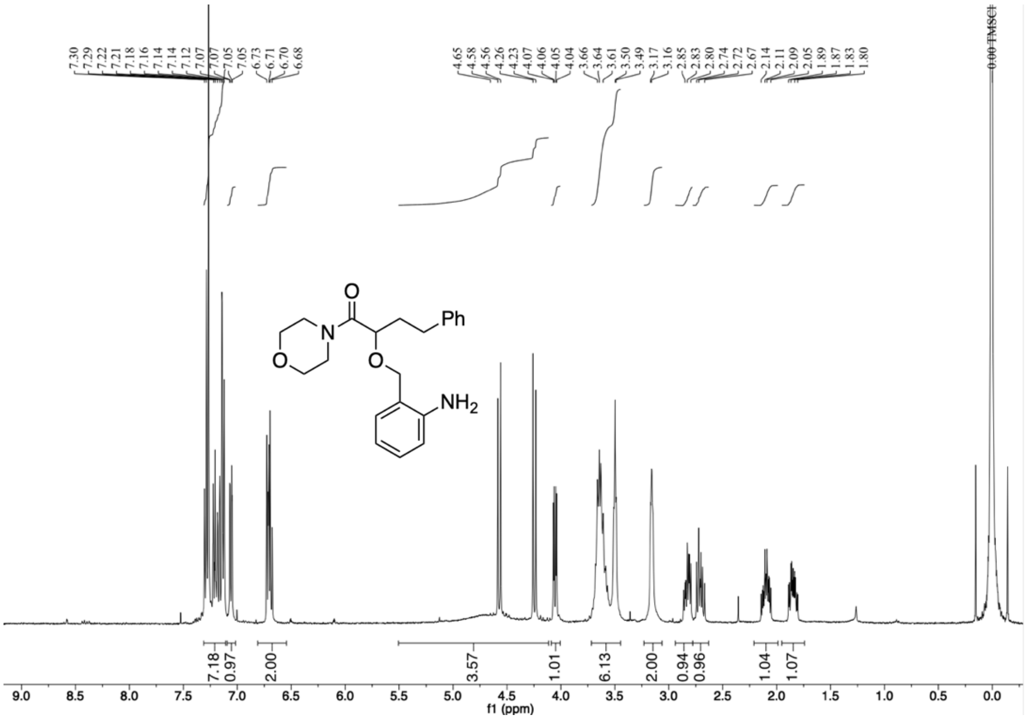
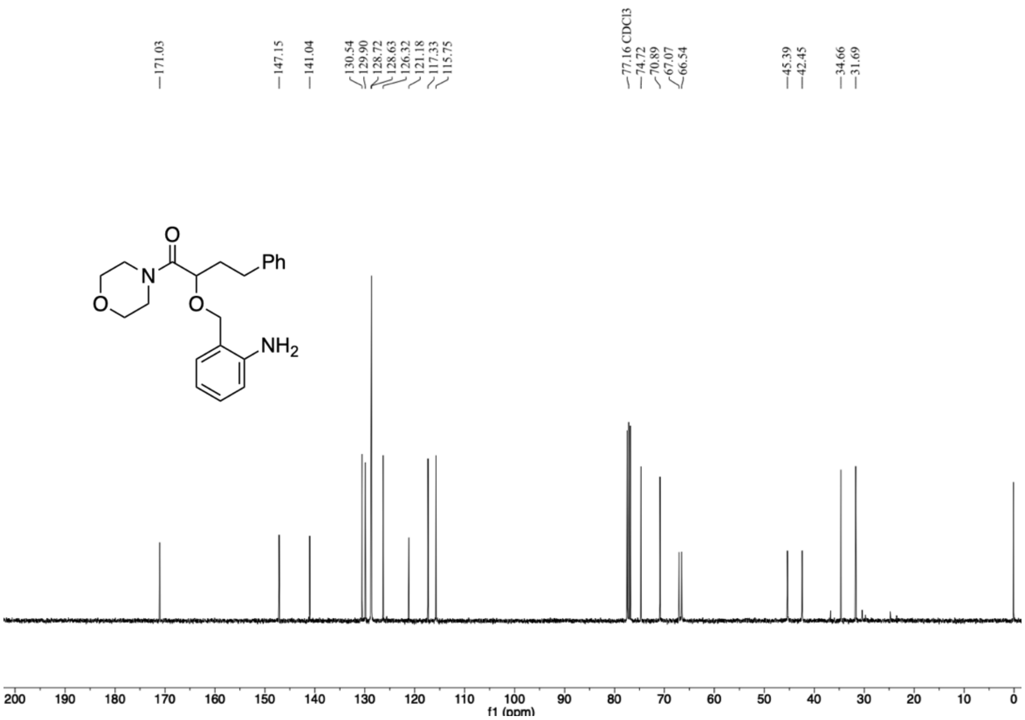
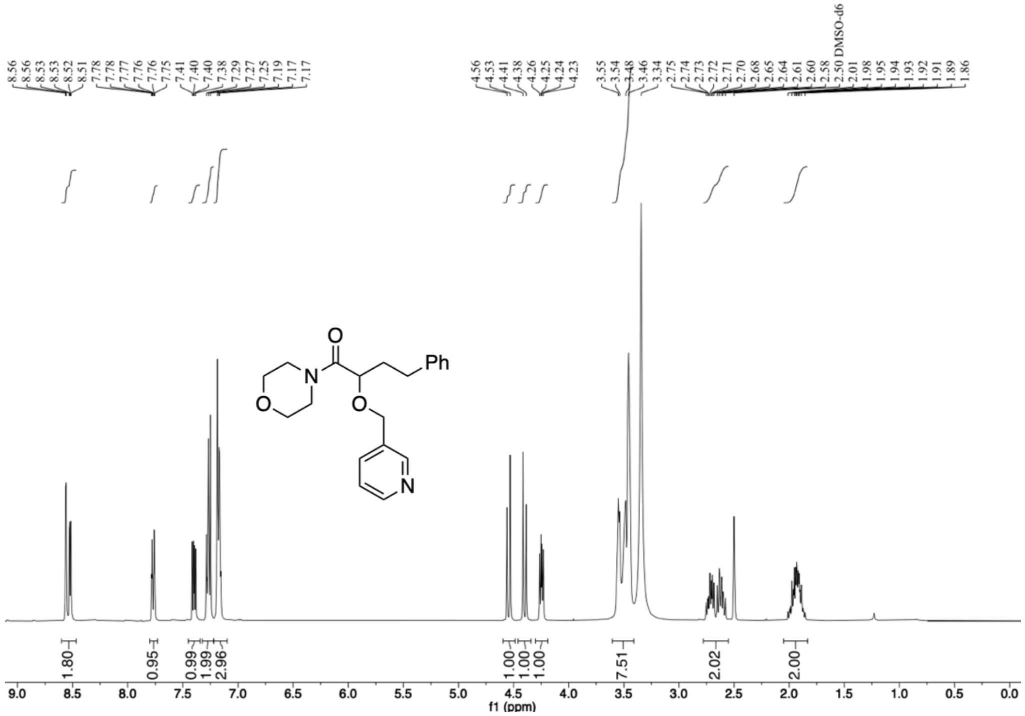


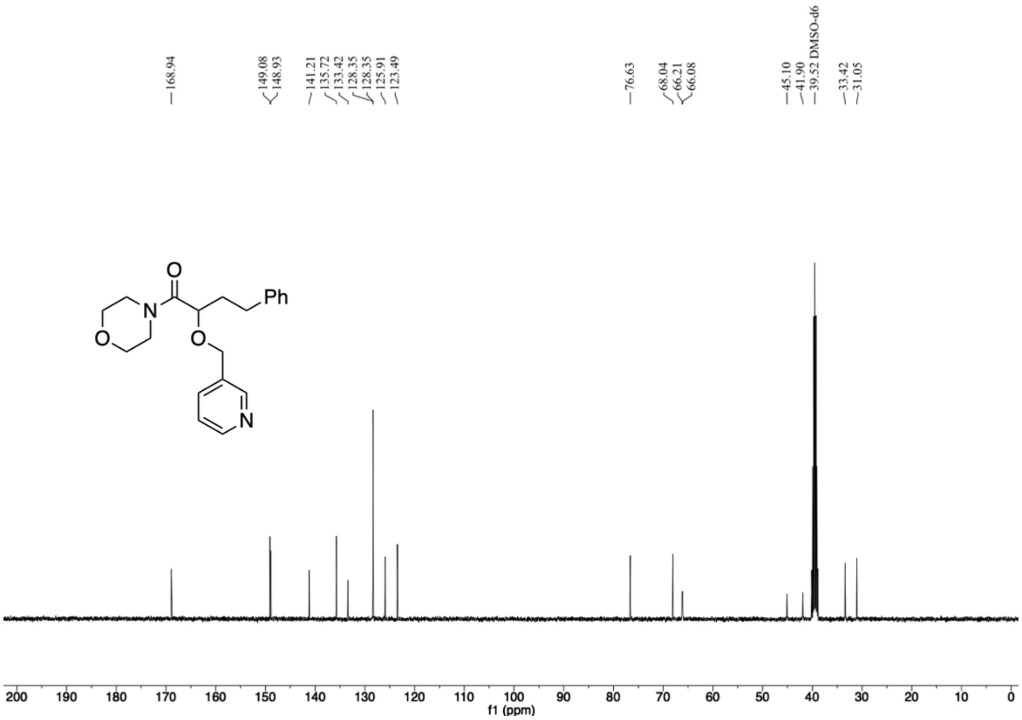
^{1}H NMR spectrum of **7** (400 MHz, $CDCl_3$)



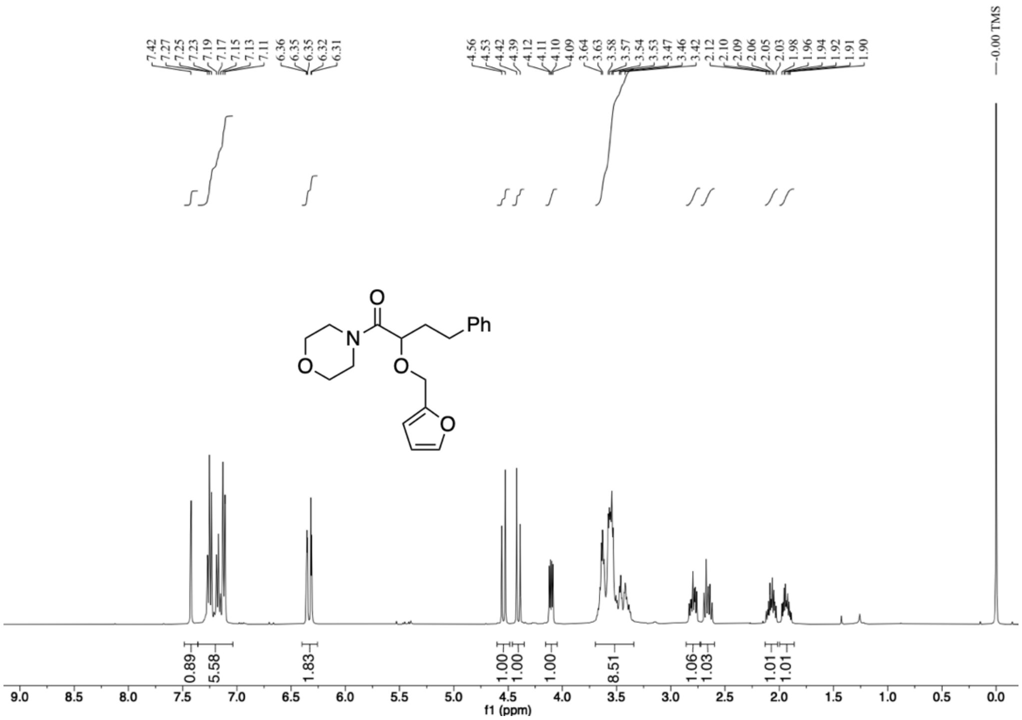
^{13}C NMR spectrum of **7** (101 MHz, CDCl$_3$)



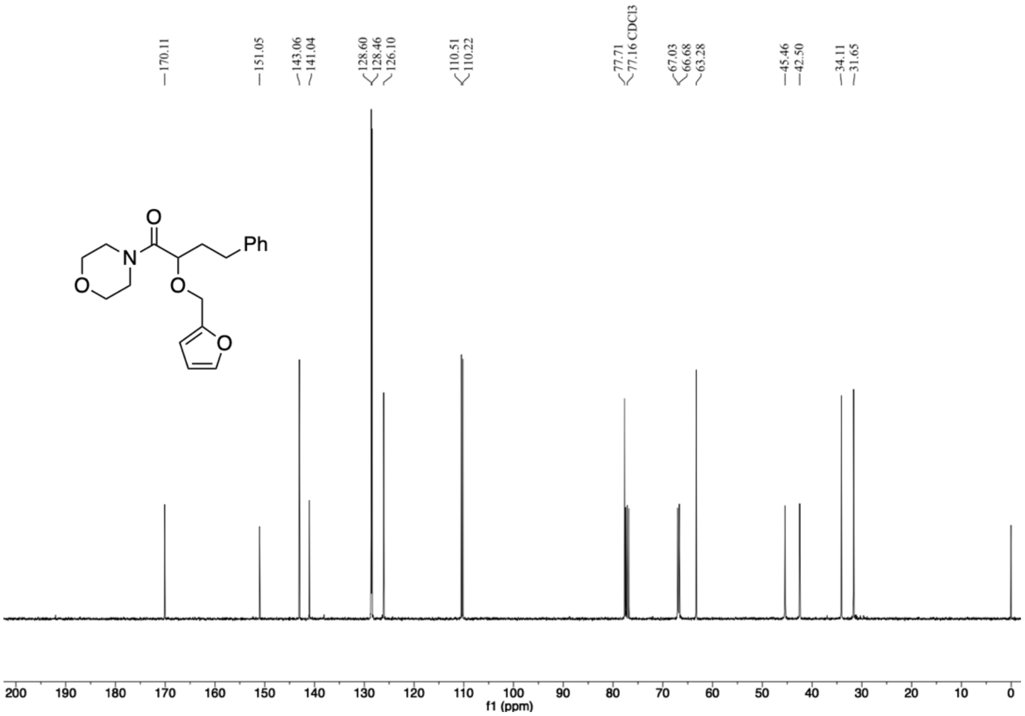
^{1}H NMR spectrum of **8** (400 MHz, DMSO-d_6)



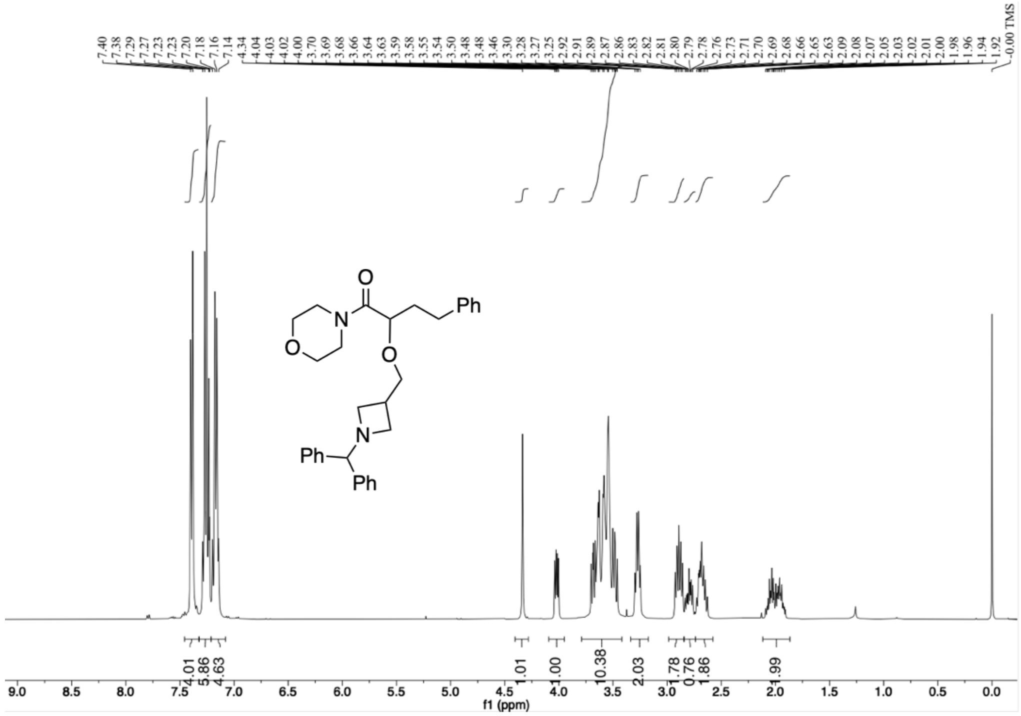
^{13}**C NMR** spectrum of **8** (101 MHz, DMSO-d_6)



^{1}**H NMR** spectrum of **9** (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of **9** (101 MHz, CDCl$_3$)



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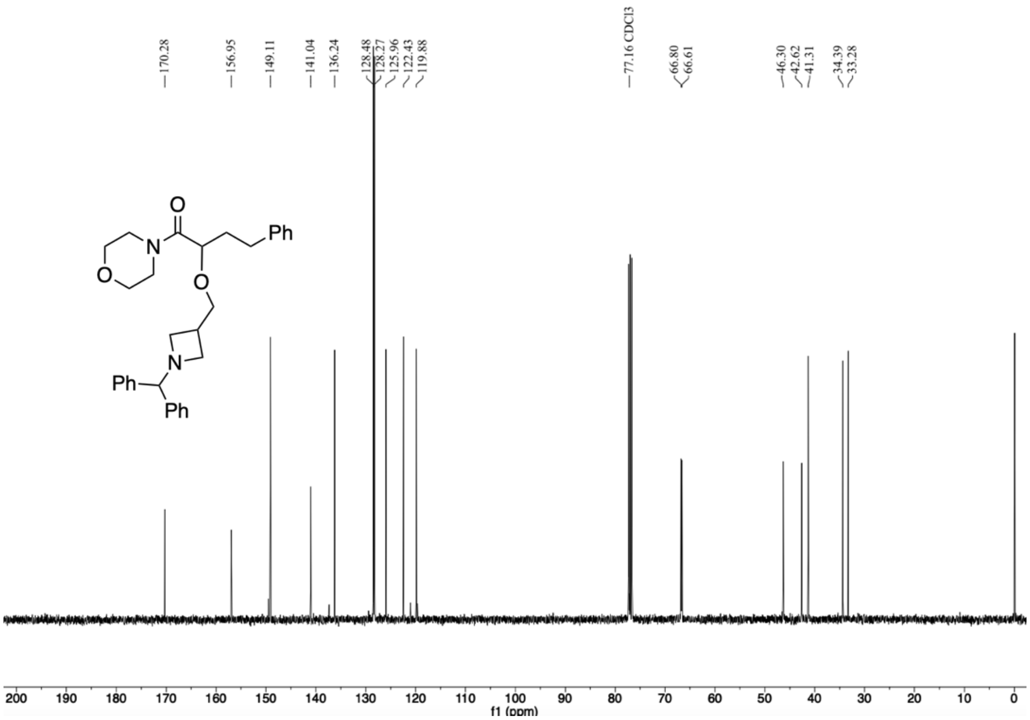

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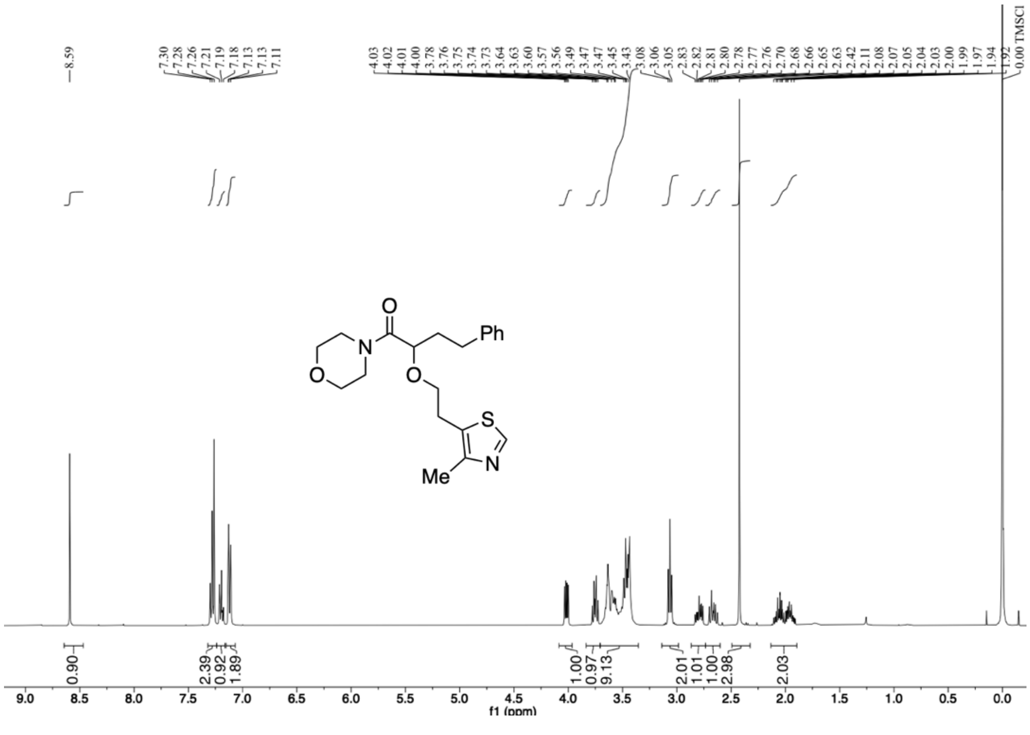

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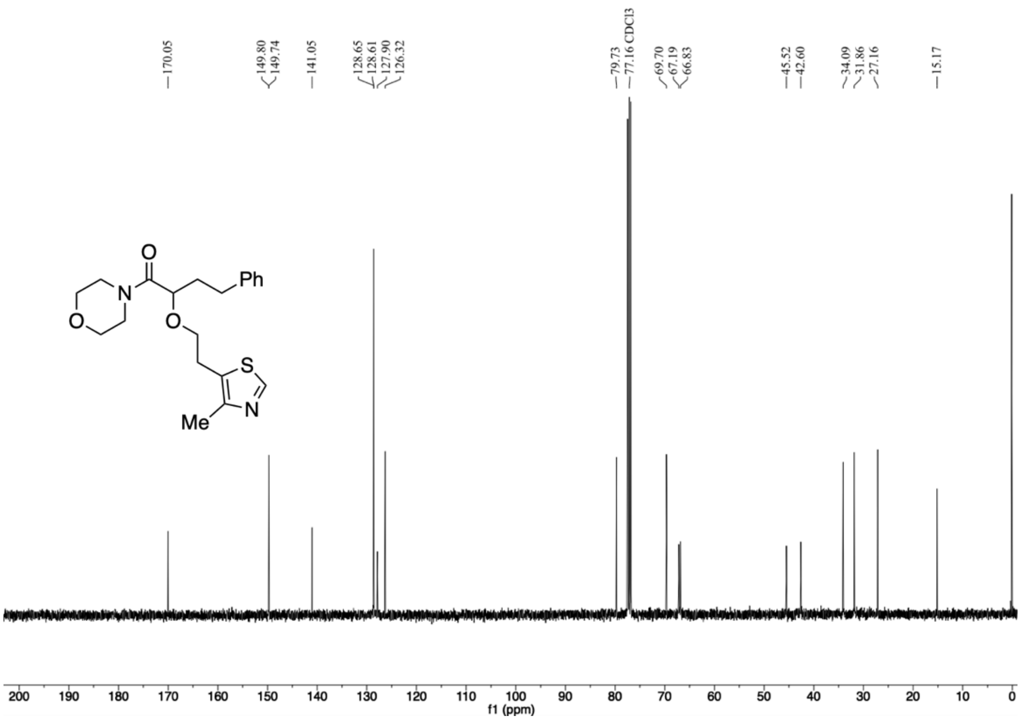

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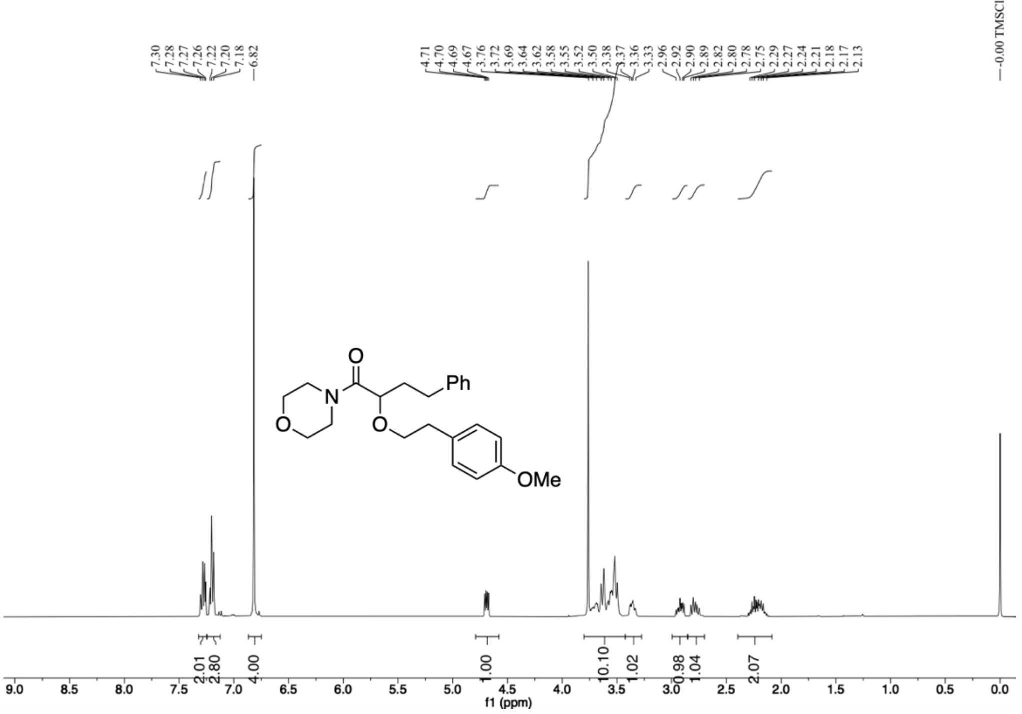

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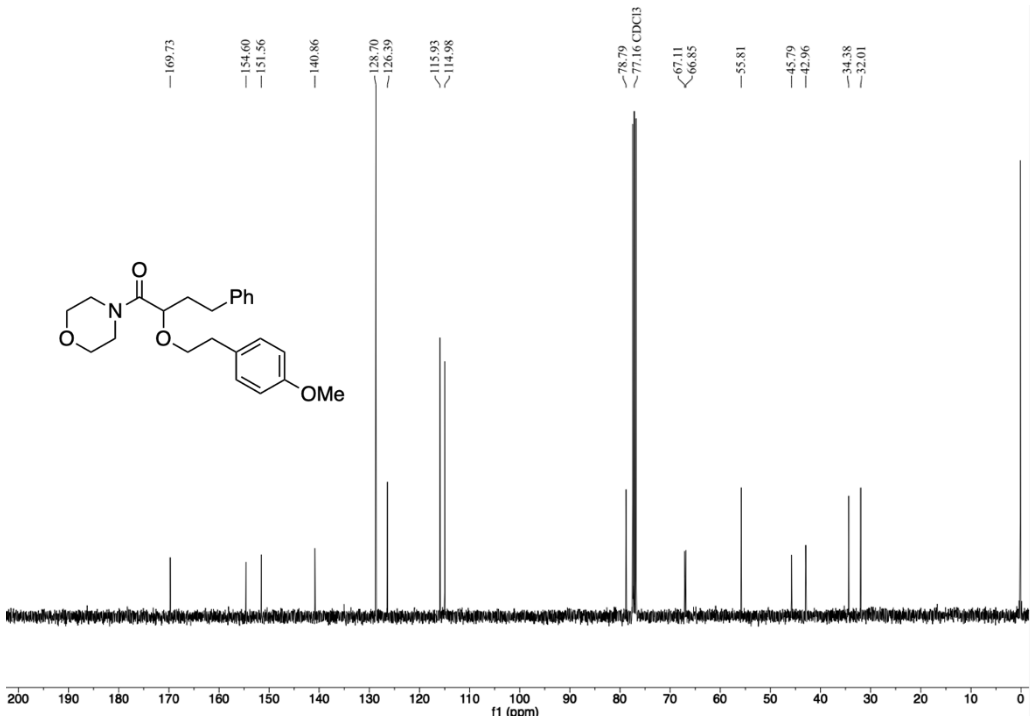

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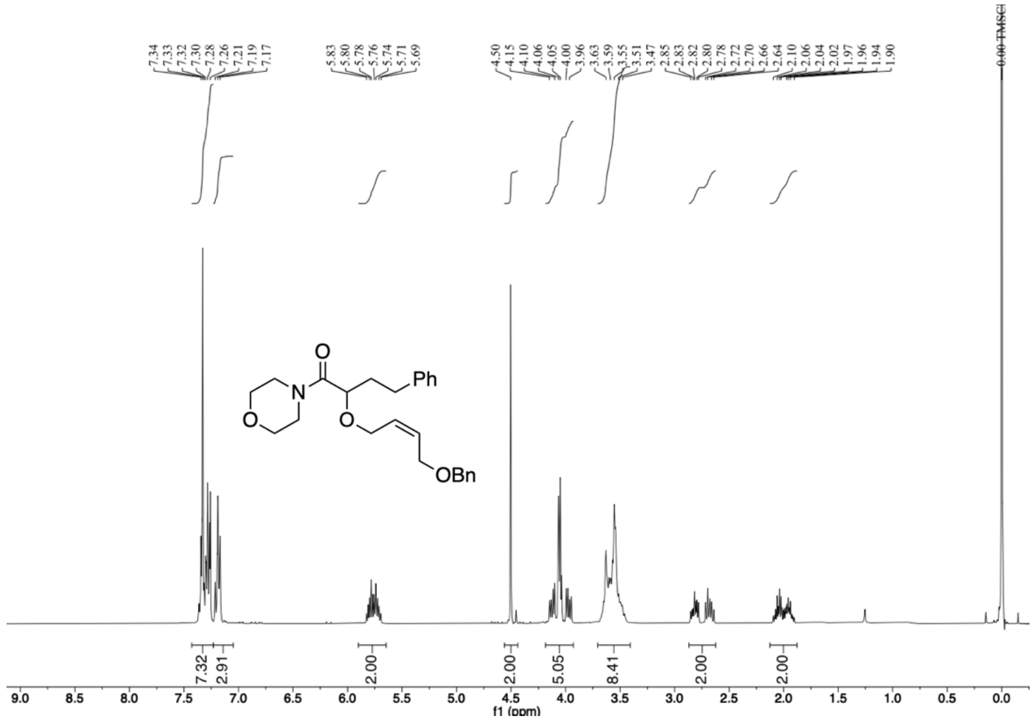

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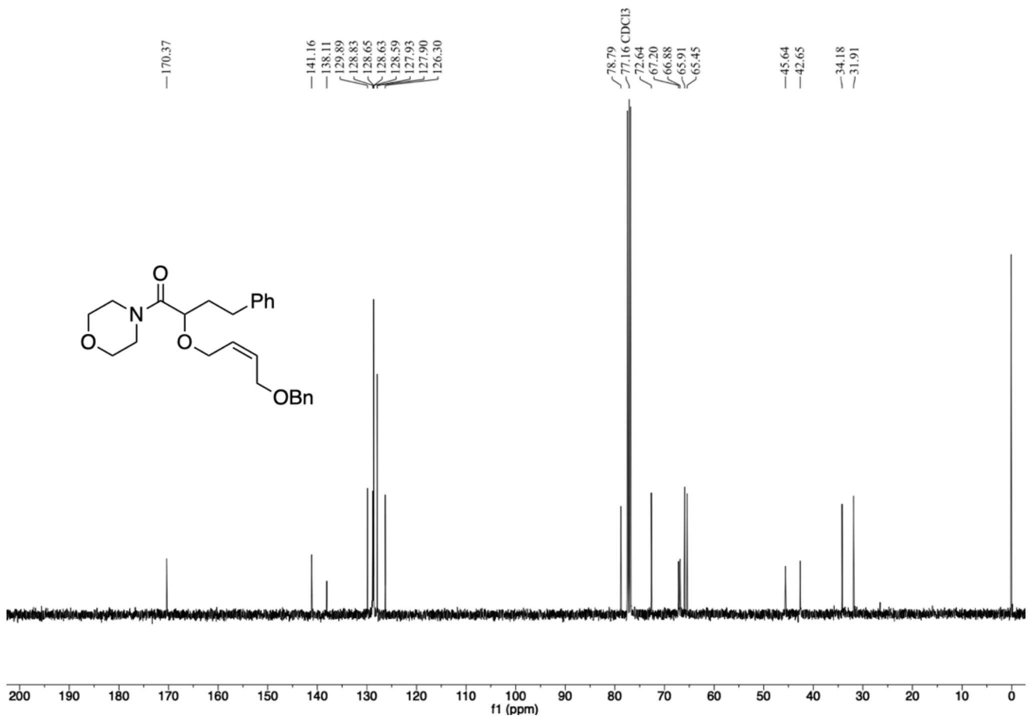
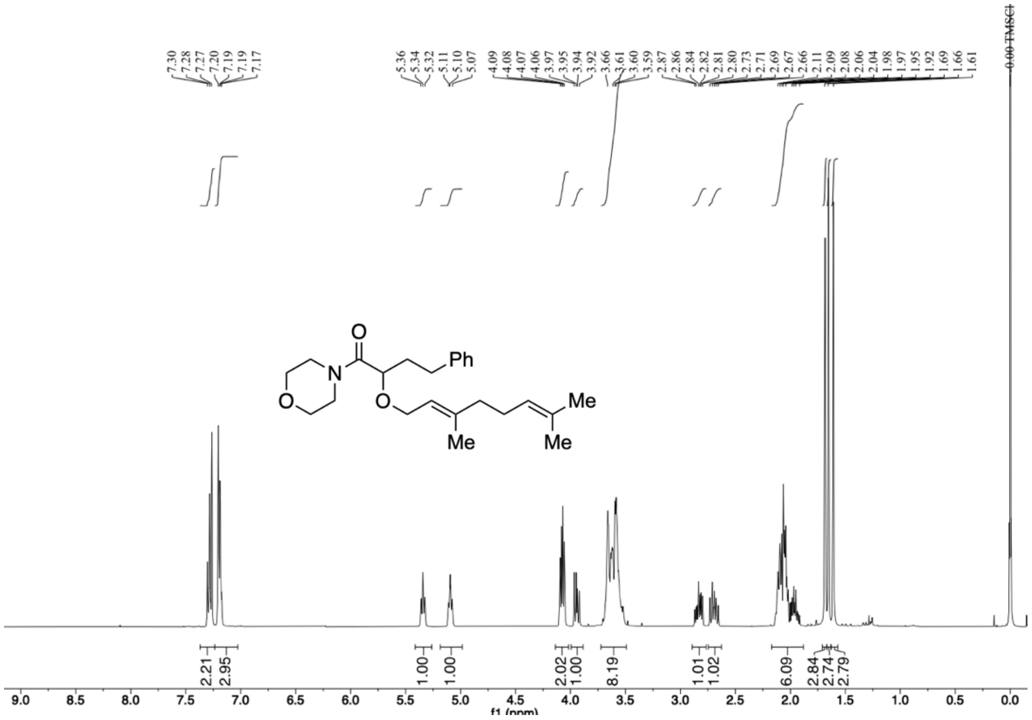


^{13}C NMR spectrum of **13** (101 MHz, CDCl$_3$)



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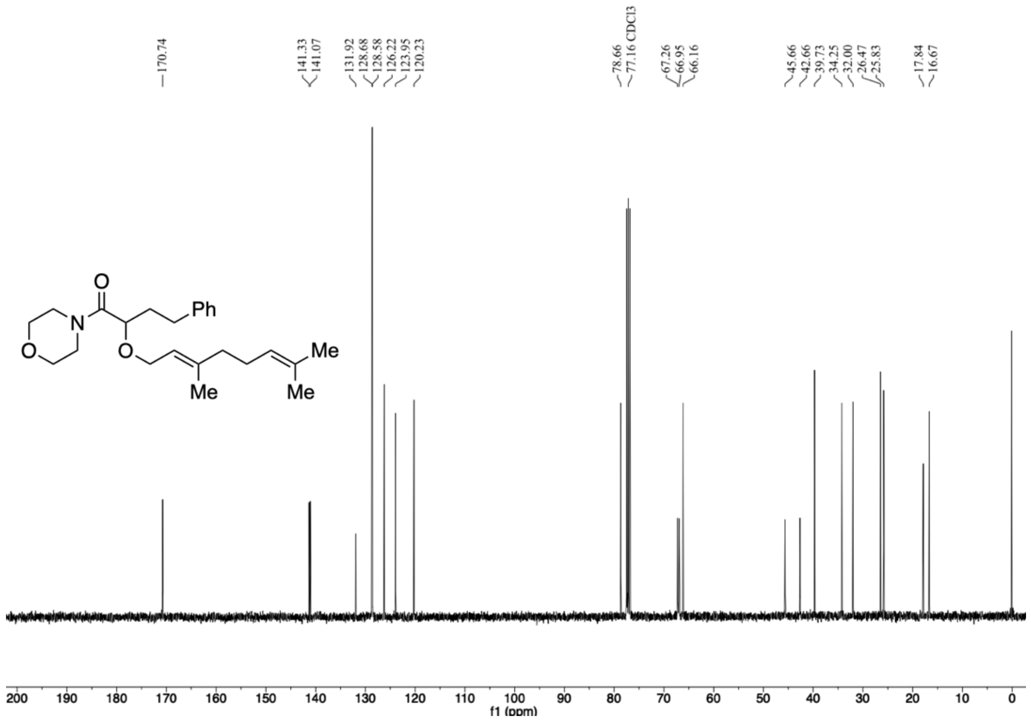
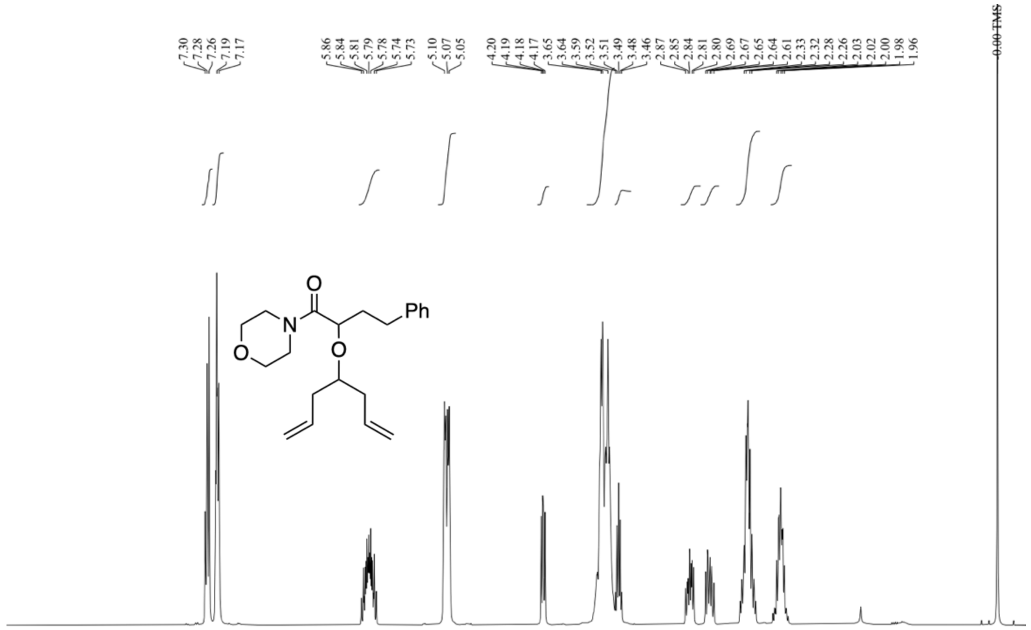
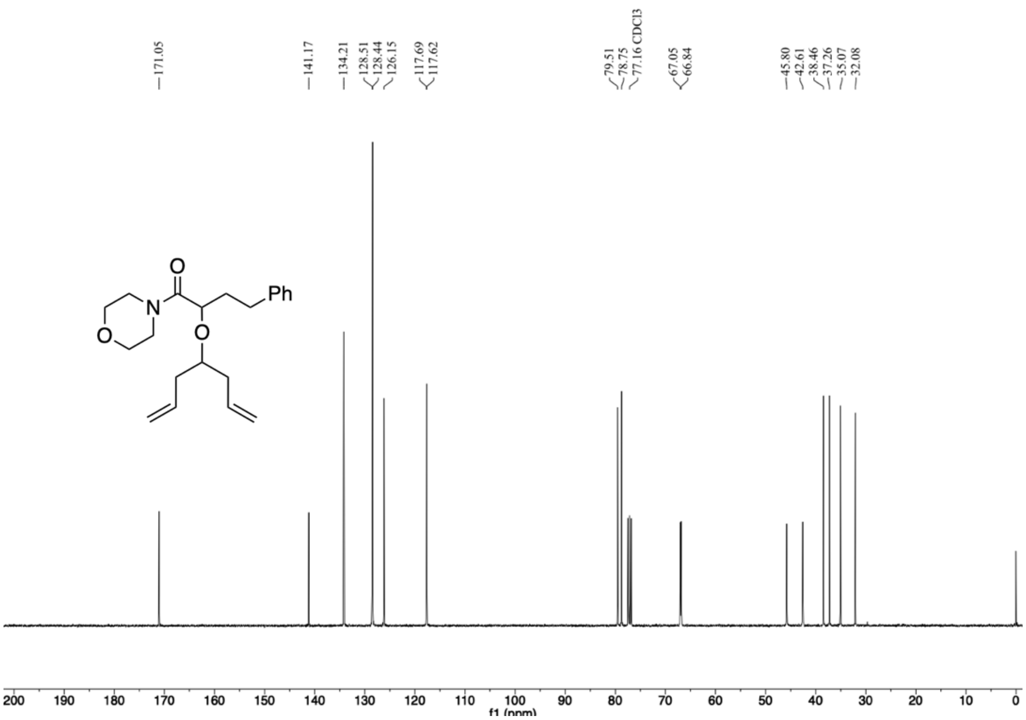


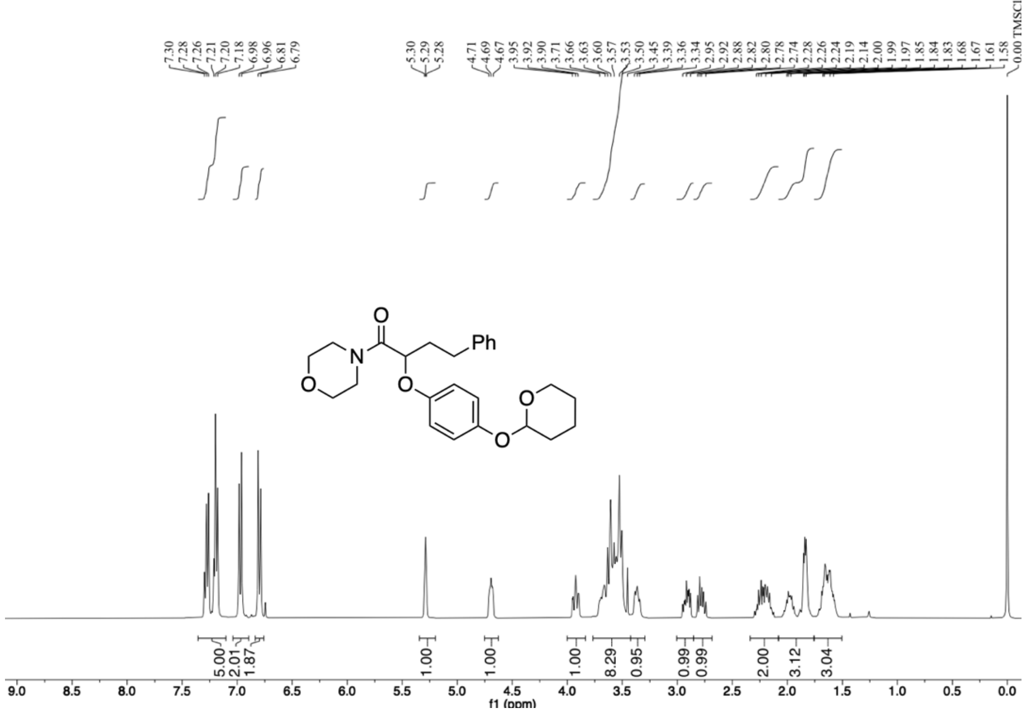
^{13}C NMR spectrum of **14** (101 MHz, CDCl$_3$)



^{1}H NMR spectrum of **15** (400 MHz, CDCl$_3$)

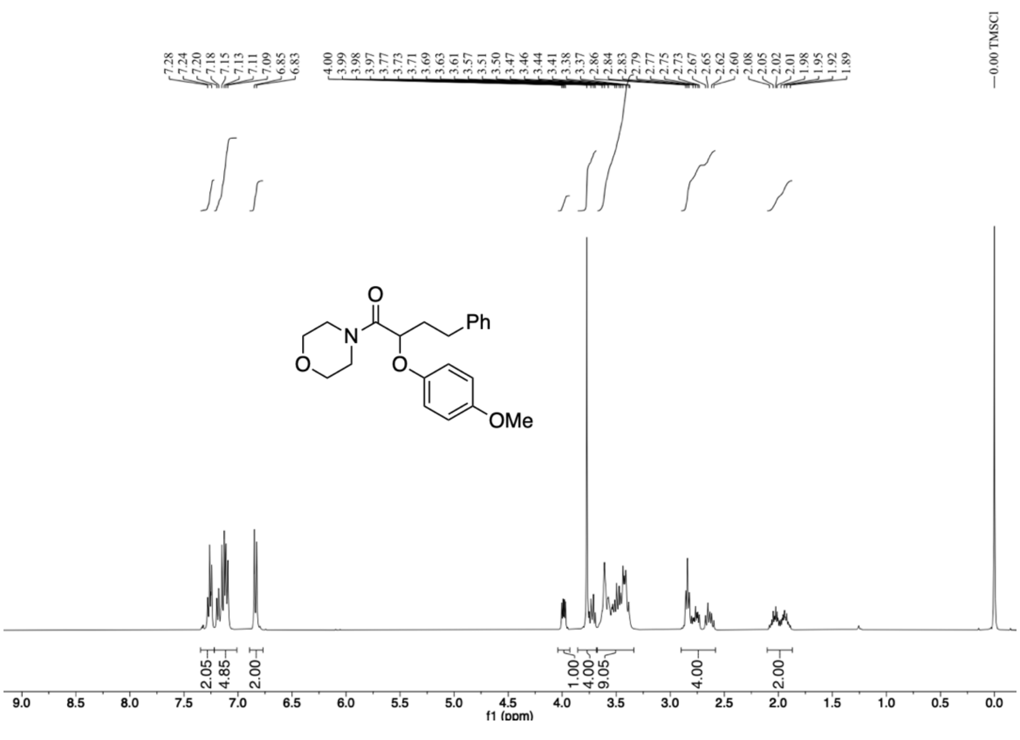


^{13}**C NMR** spectrum of **15** (101 MHz, $CDCl_3$)

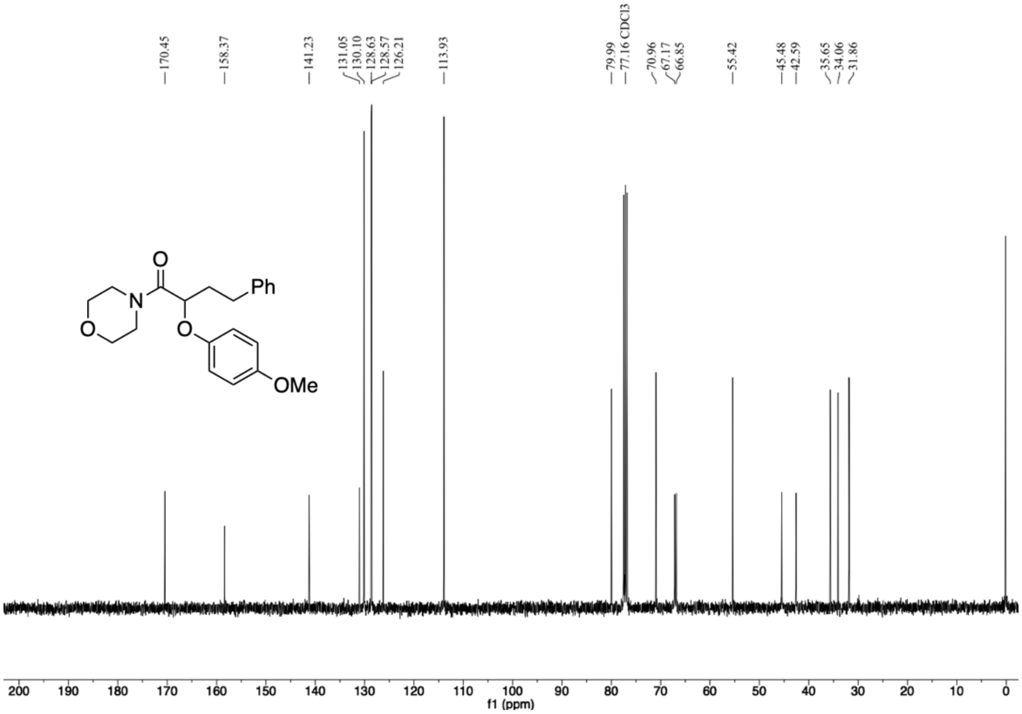


^{1}**H NMR** spectrum of **16** (400 MHz, $CDCl_3$)

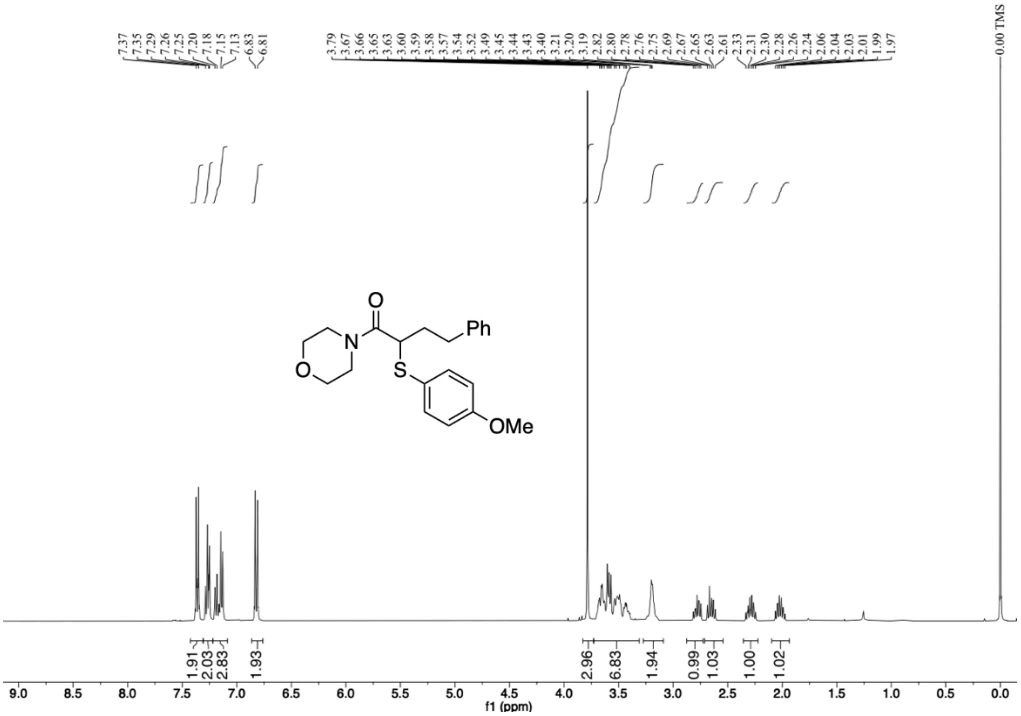
^{13}C NMR spectrum of **16** (101 MHz, CDCl$_3$)



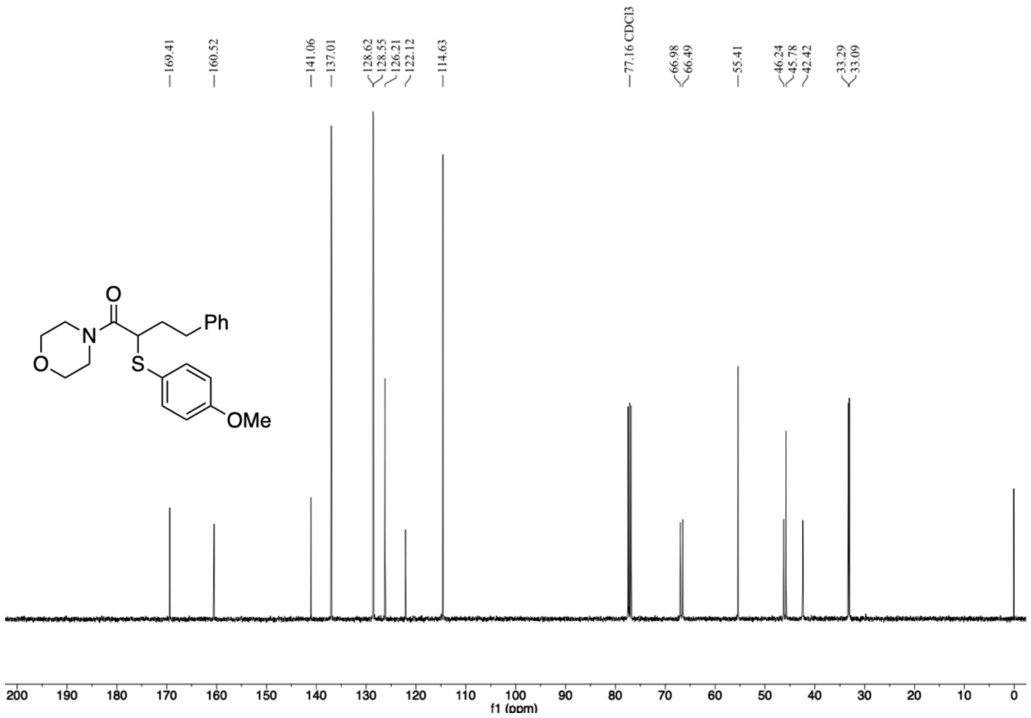
^{1}H NMR spectrum of **17** (400 MHz, CDCl$_3$)



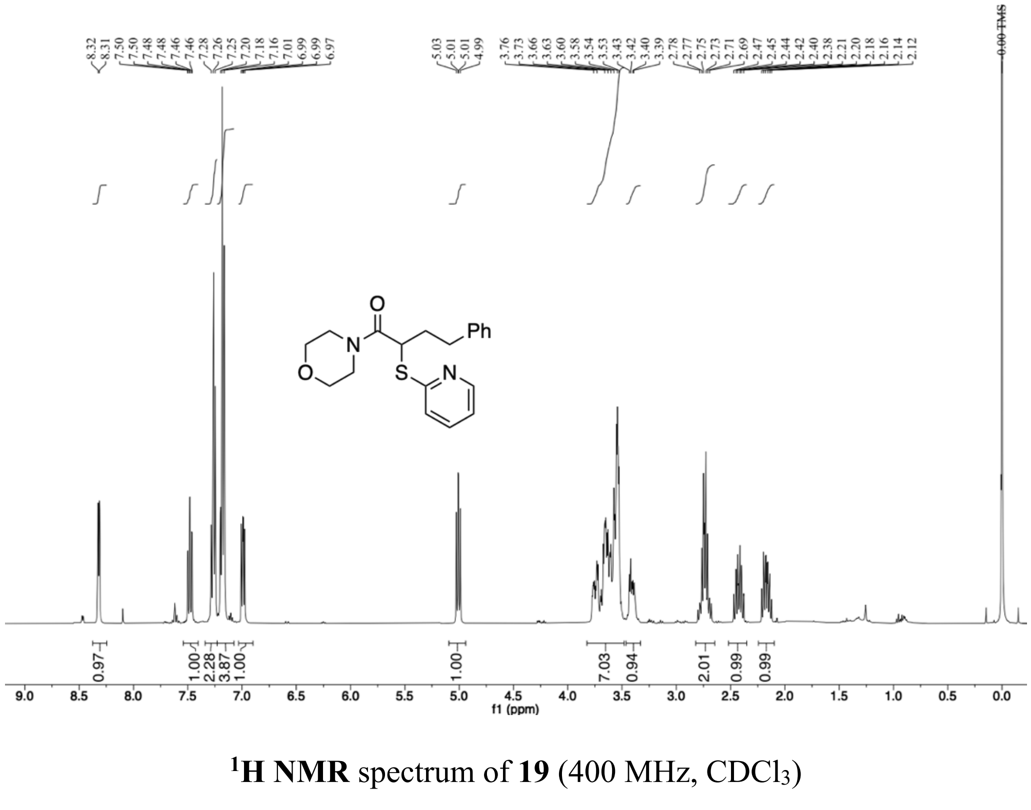
^{13}C **NMR** spectrum of **17** (101 MHz, CDCl$_3$)



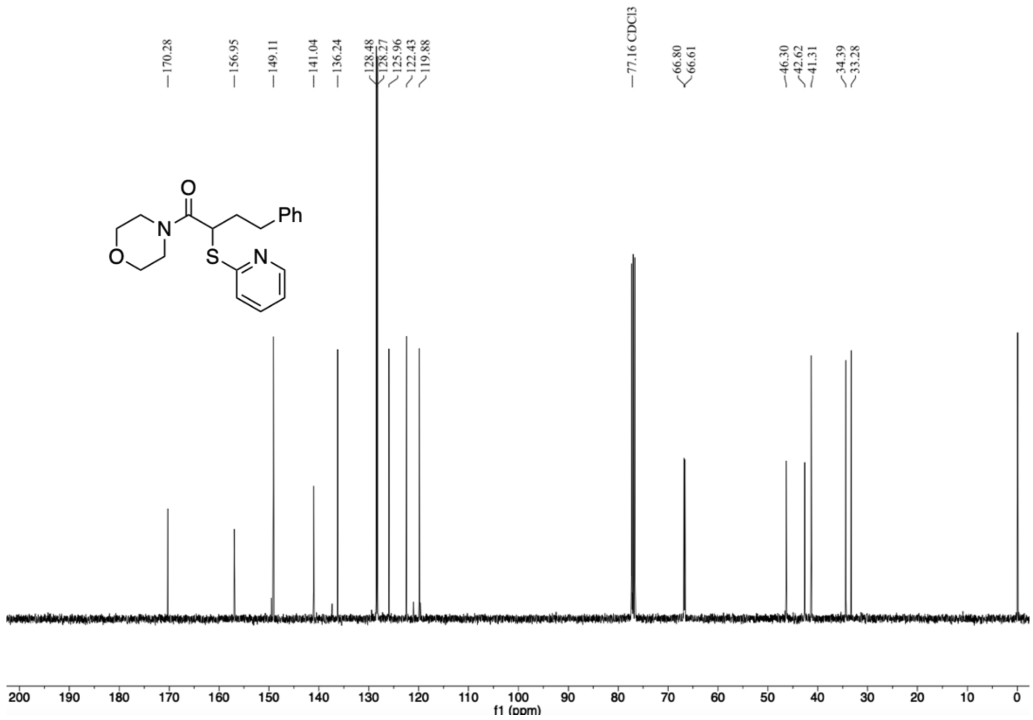
^{1}H **NMR** spectrum of **18** (400 MHz, CDCl$_3$)



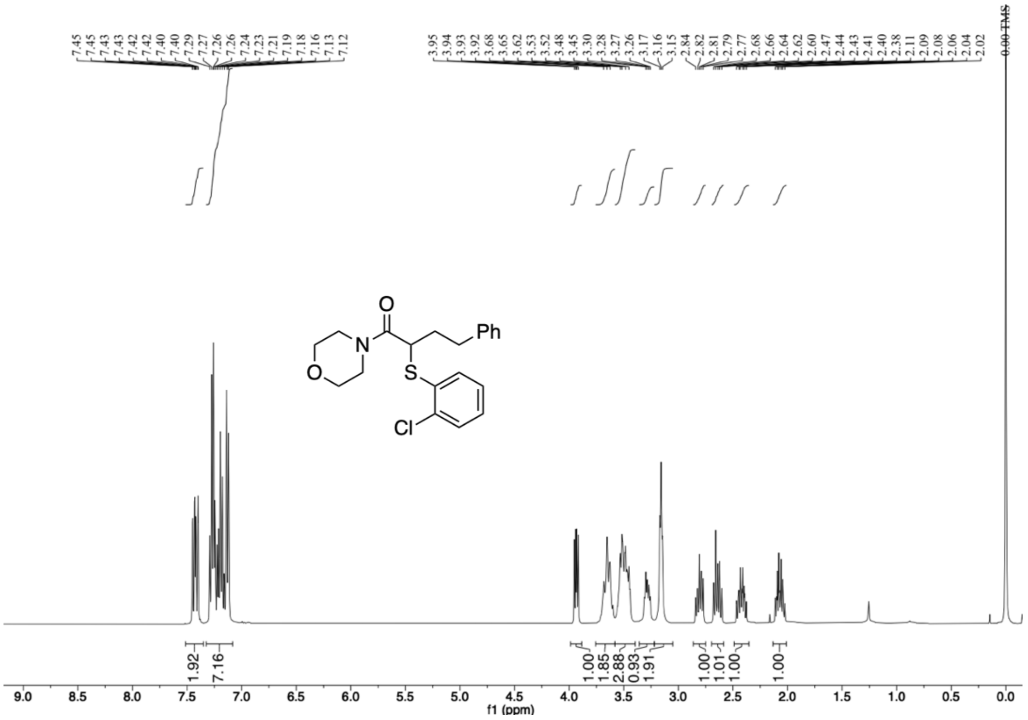
^{13}C NMR spectrum of **18** (101 MHz, $CDCl_3$)



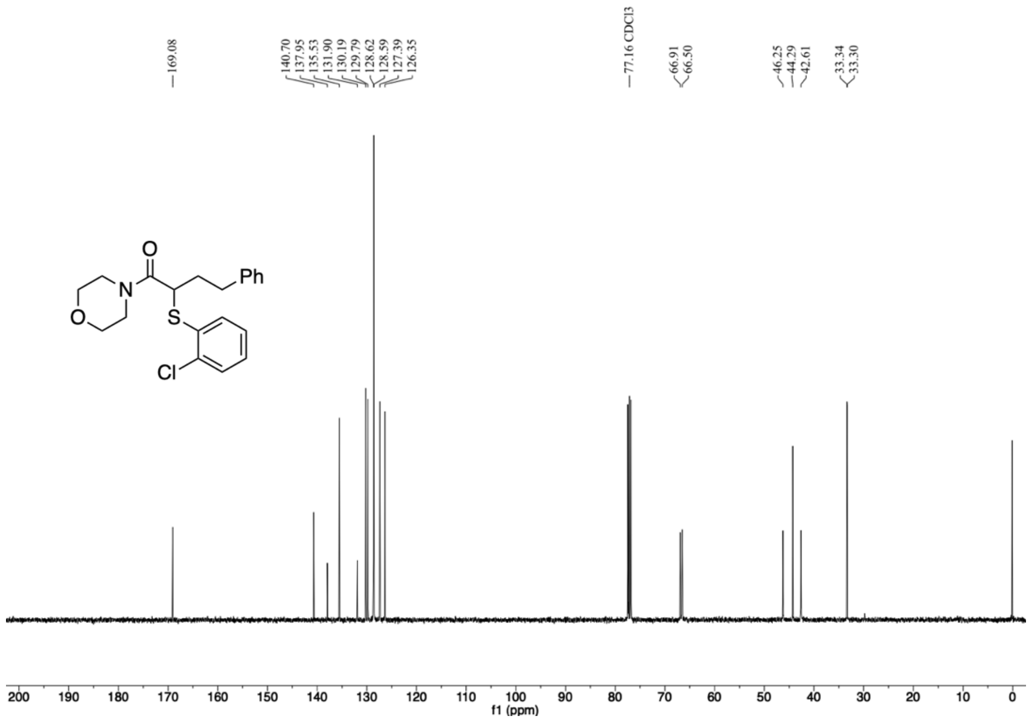
^{1}H NMR spectrum of **19** (400 MHz, $CDCl_3$)



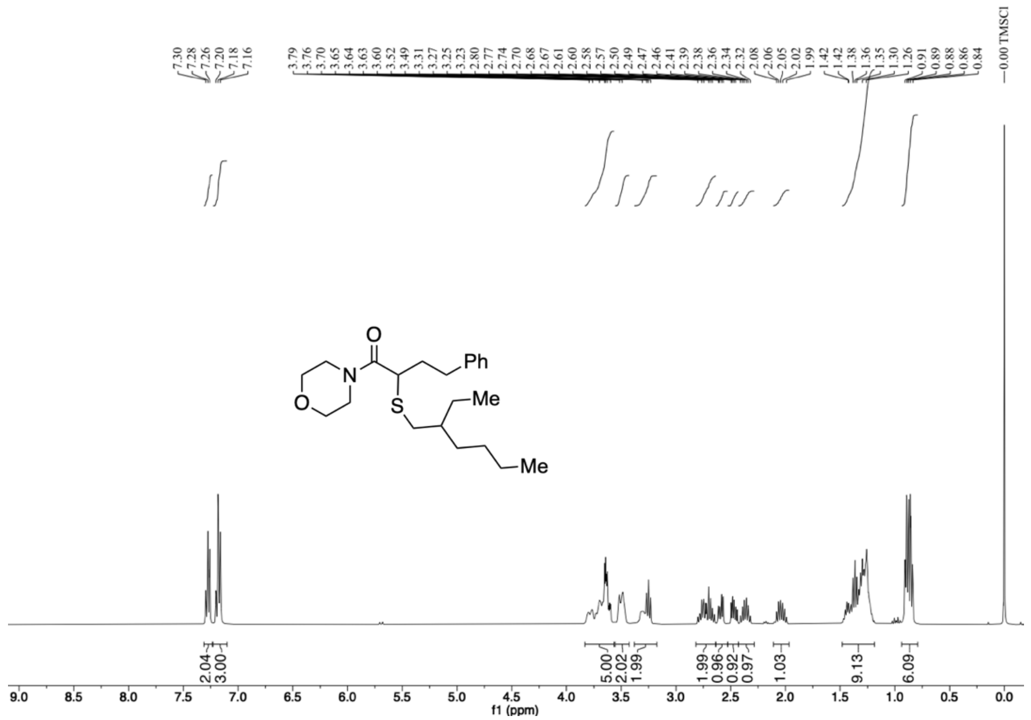
^{13}C NMR spectrum of **19** (101 MHz, CDCl$_3$)



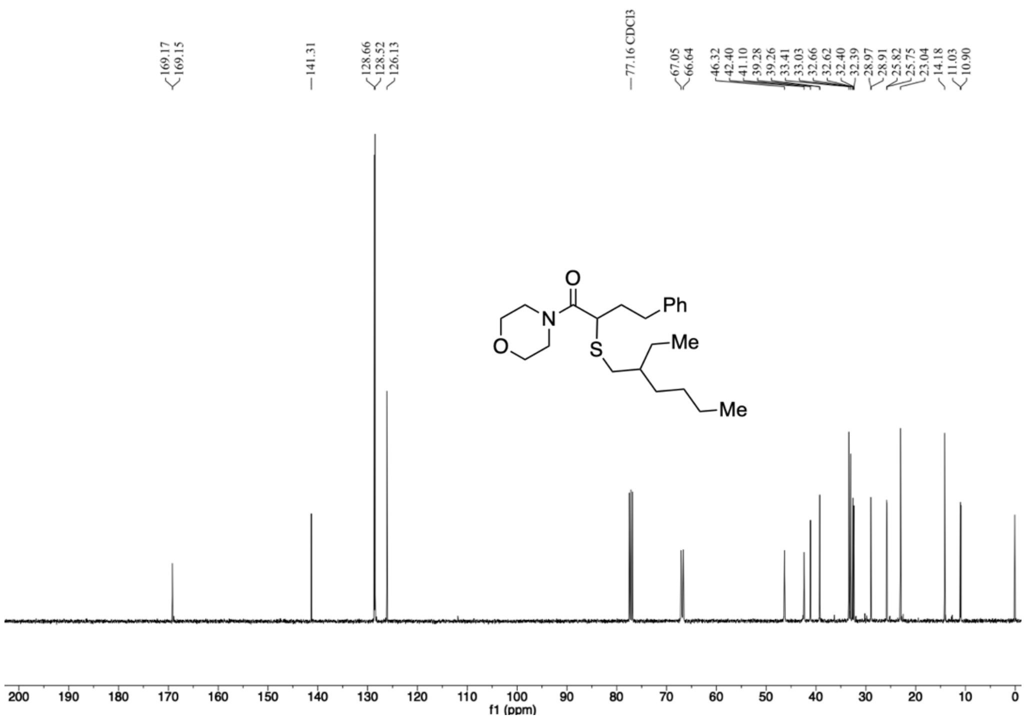
^{1}H NMR spectrum of **20** (400 MHz, CDCl$_3$)



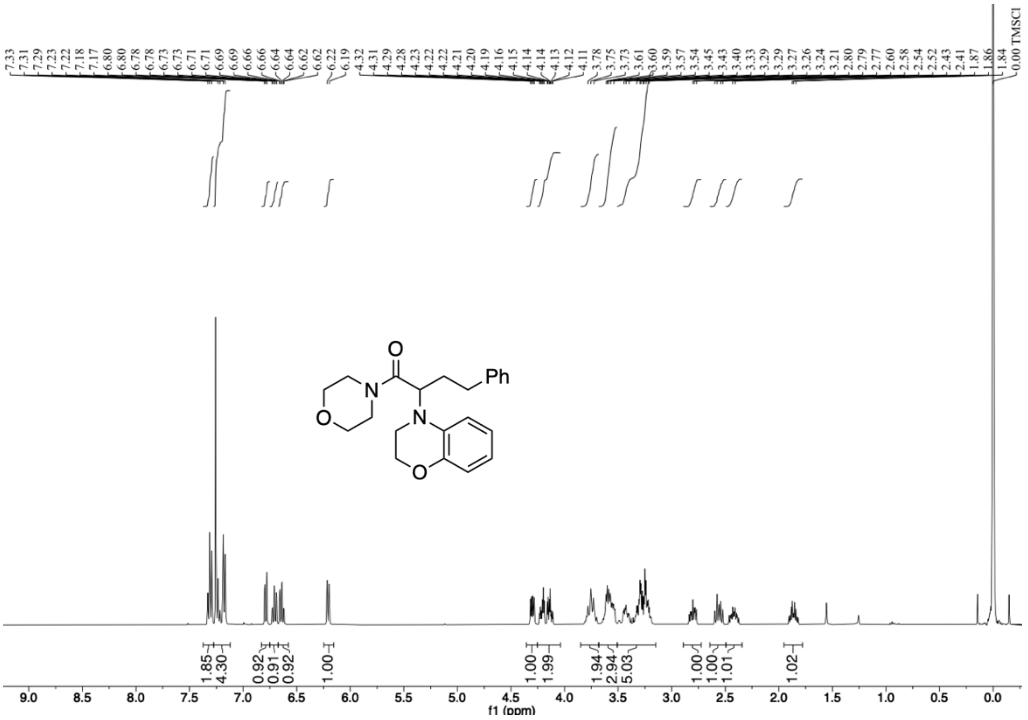
^{13}C NMR spectrum of **20** (101 MHz, CDCl$_3$)



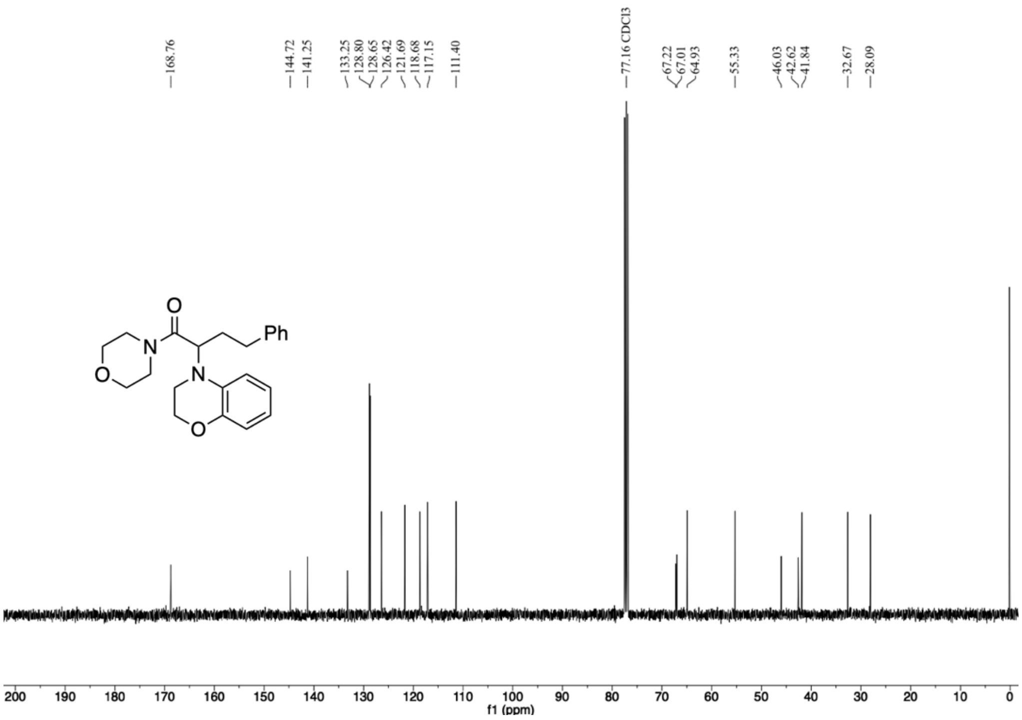
^{1}H NMR spectrum of **21** (400 MHz, CDCl$_3$)



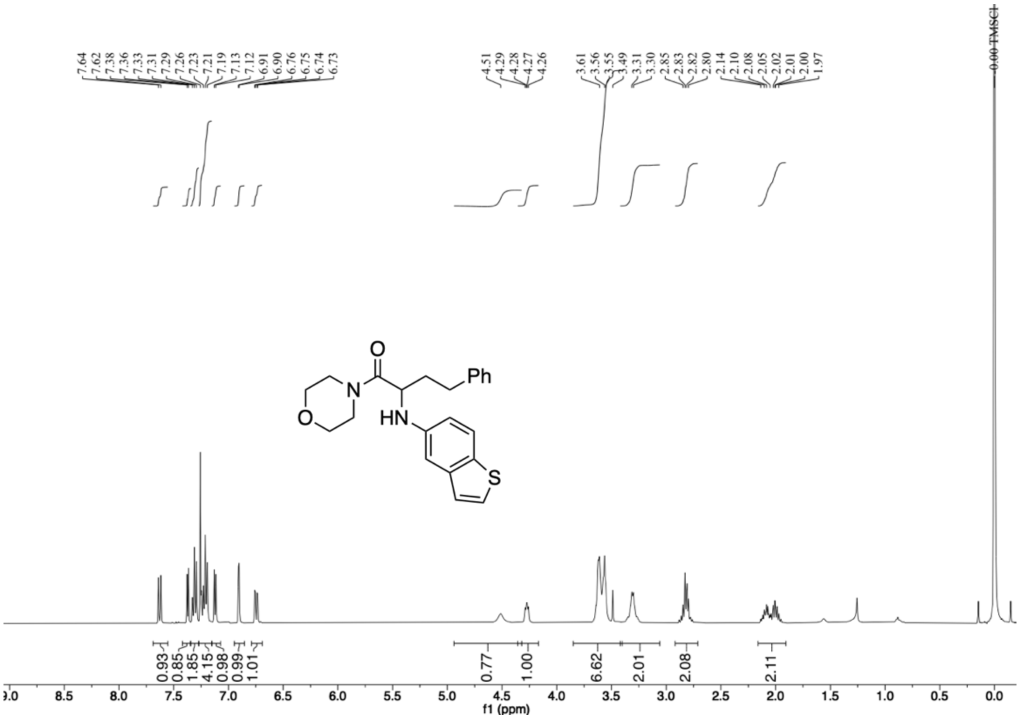
^{13}C NMR spectrum of **21** (101 MHz, CDCl$_3$)



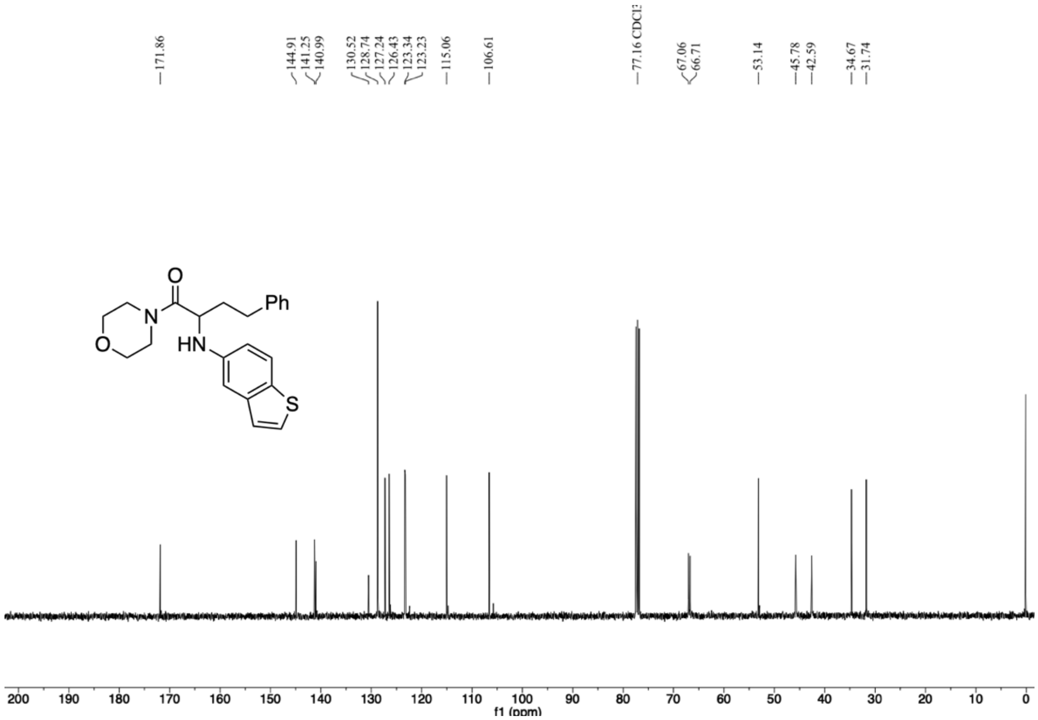
^{1}H NMR spectrum of **22** (400 MHz, CDCl$_3$)



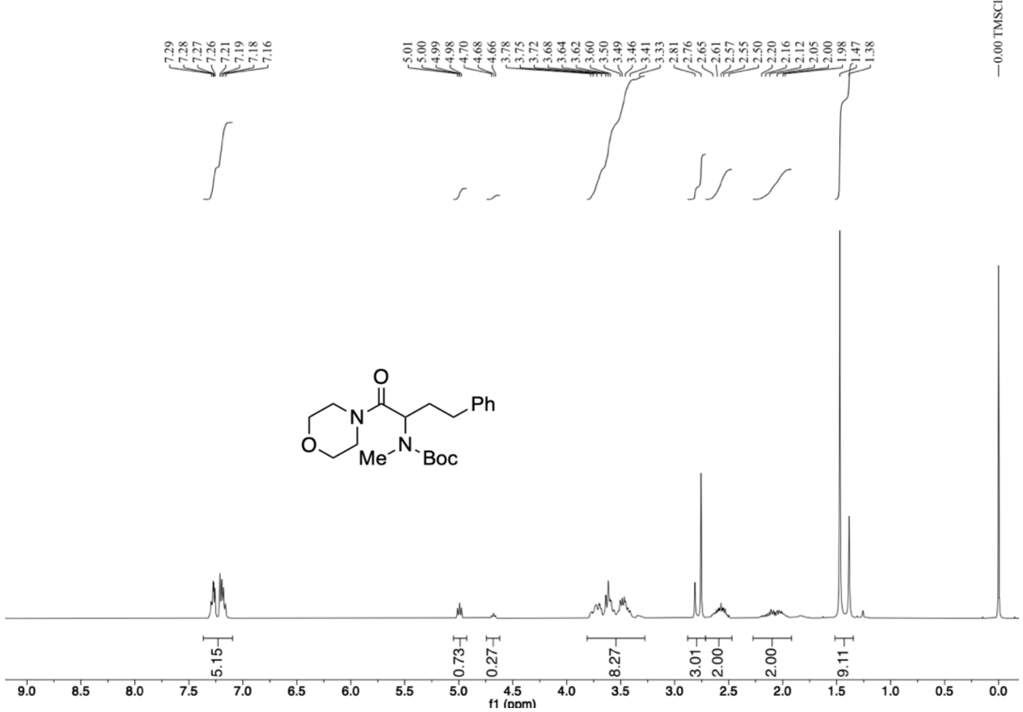
^{13}C NMR spectrum of **22** (101 MHz, CDCl$_3$)



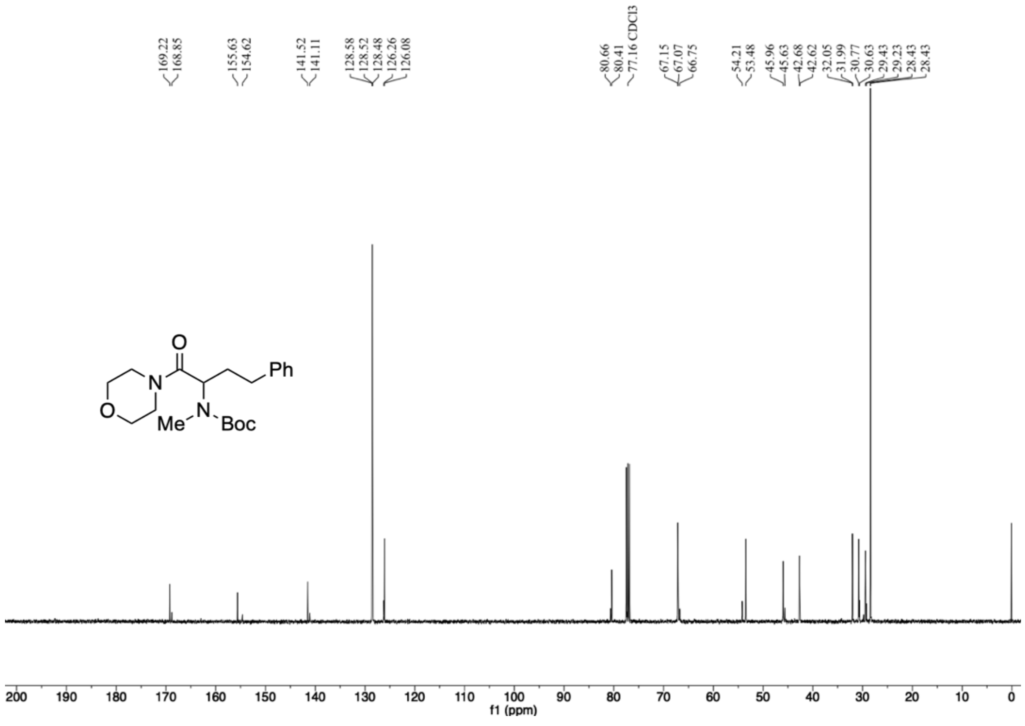
^{1}H NMR spectrum of **23** (400 MHz, CDCl$_3$)



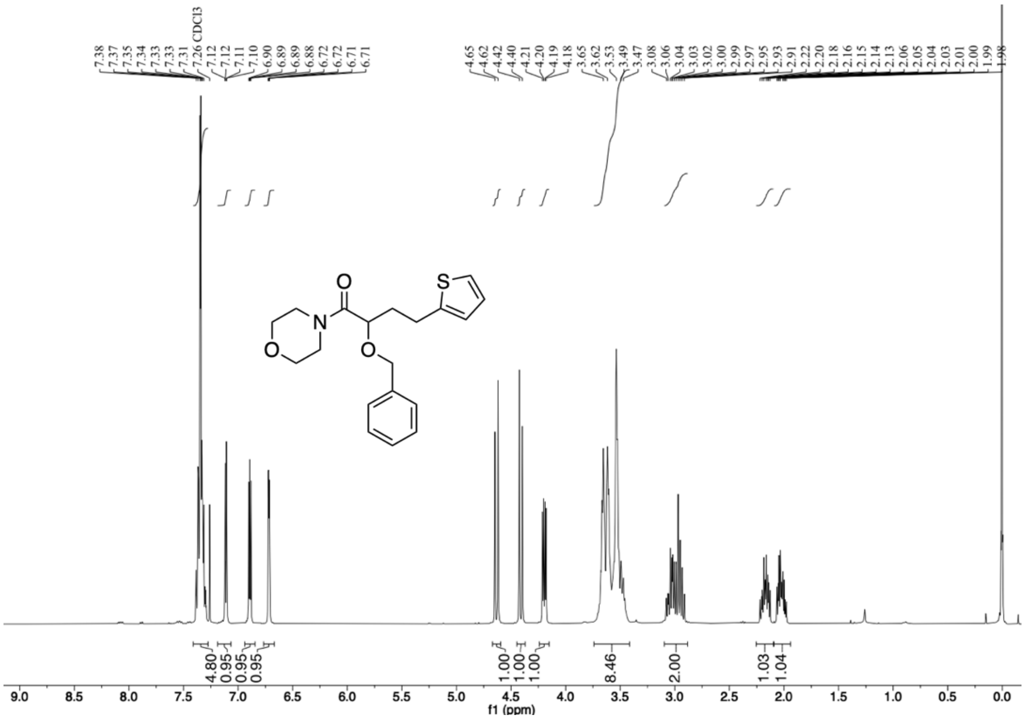
^{13}C NMR spectrum of **23** (101 MHz, CDCl$_3$)



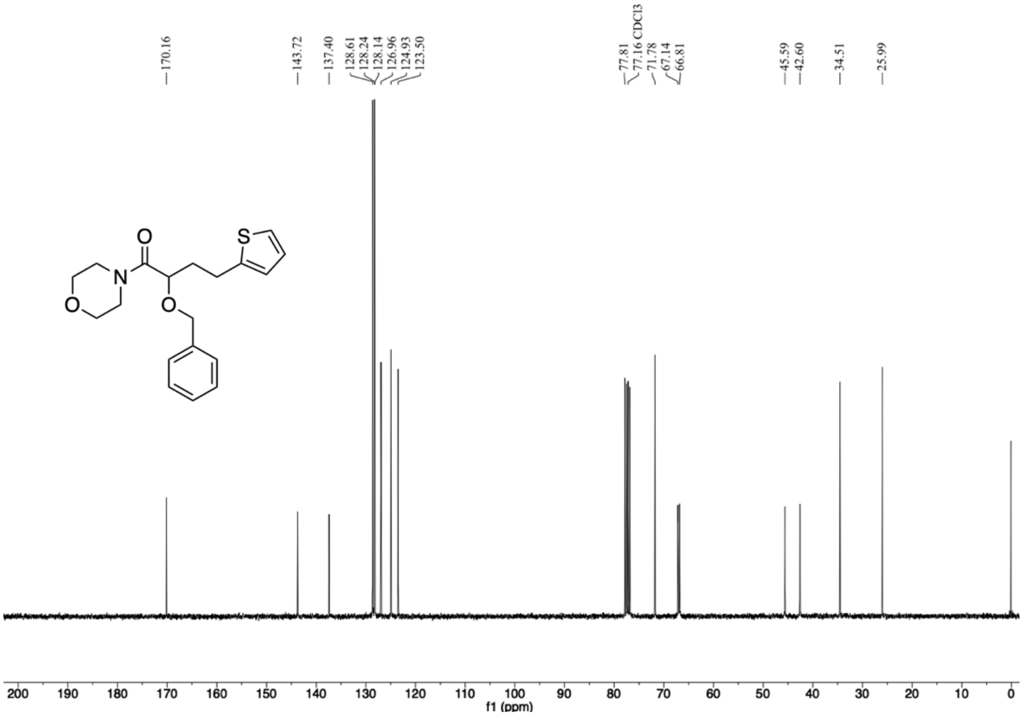
^{1}H NMR spectrum of **24** (400 MHz, CDCl$_3$)



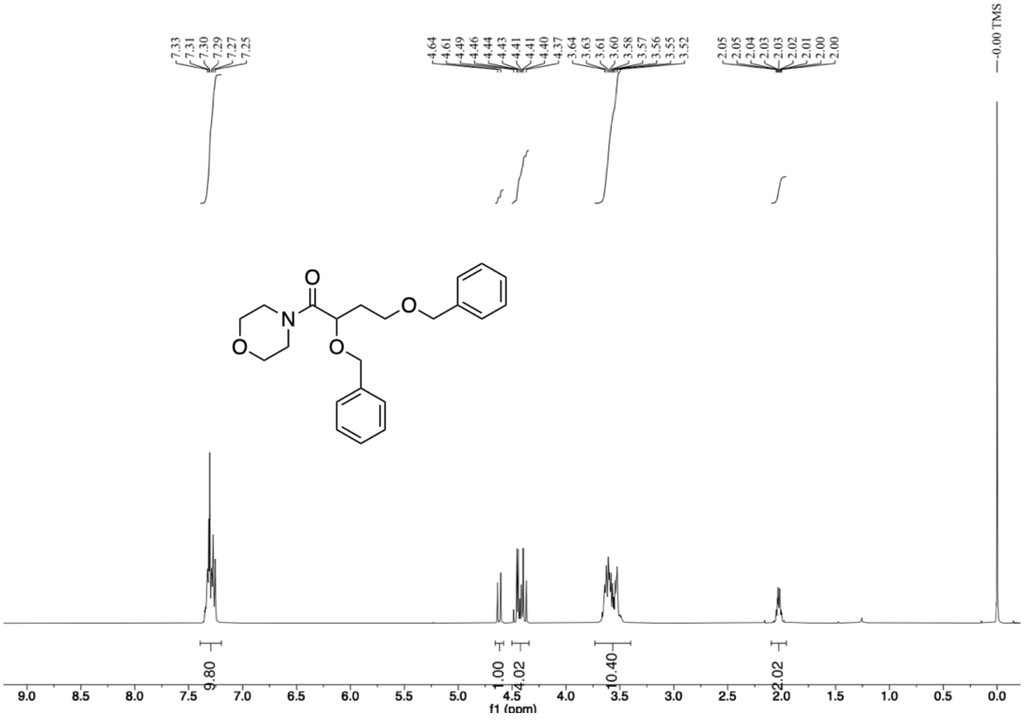
^{13}C NMR spectrum of **24** (101 MHz, CDCl$_3$)



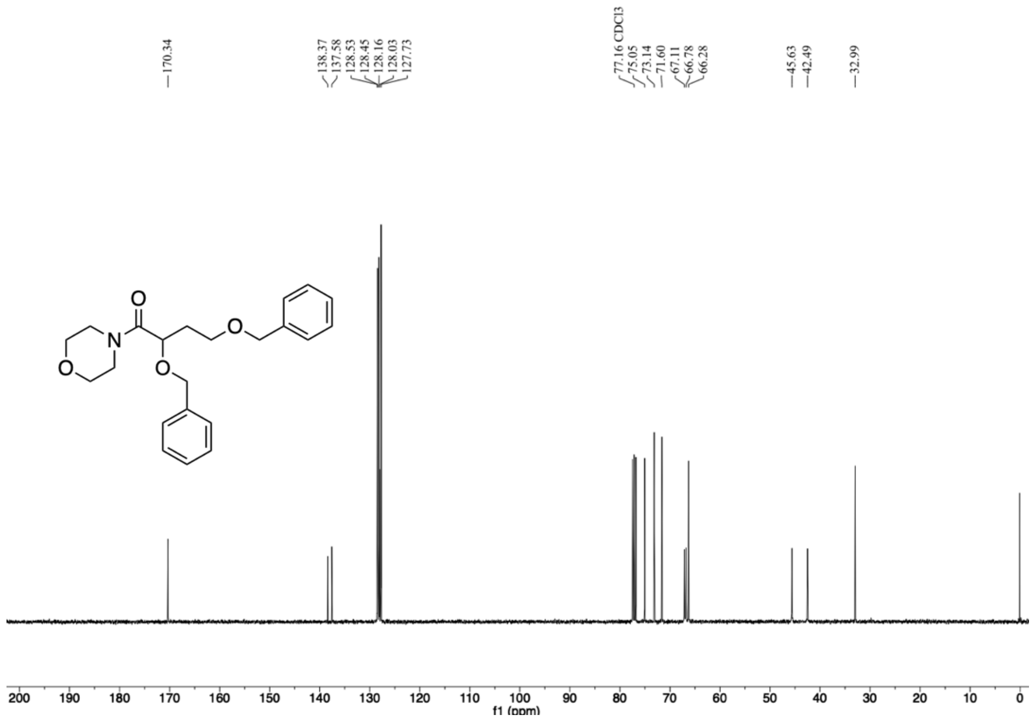
^{1}H NMR spectrum of **25** (400 MHz, CDCl$_3$)



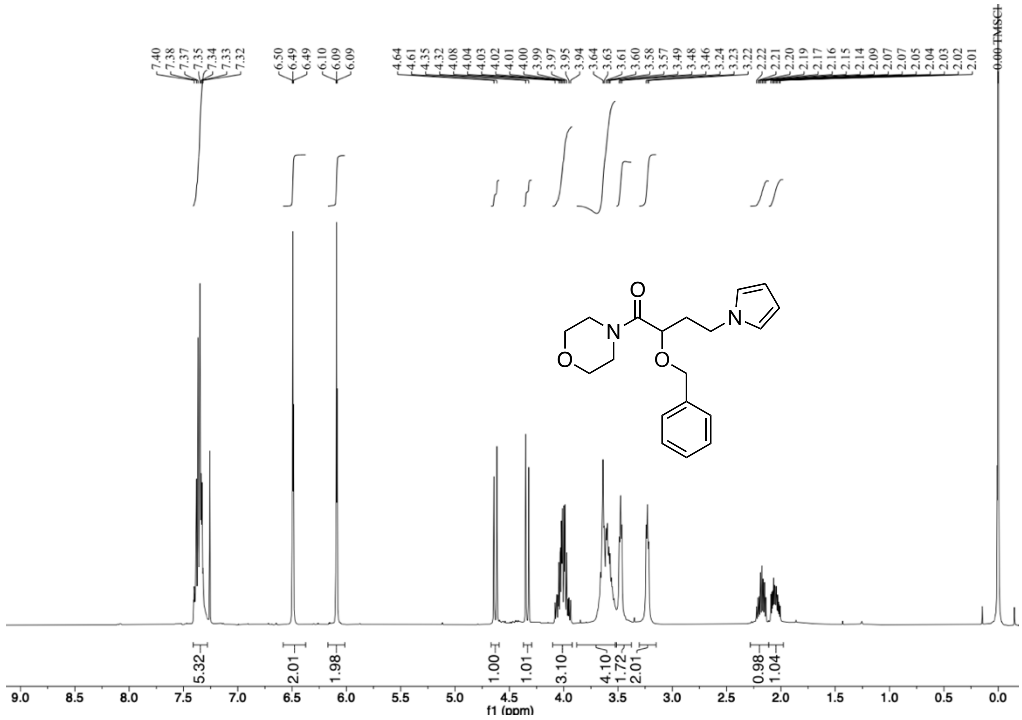
^{13}**C NMR** spectrum of **25** (101 MHz, CDCl$_3$)



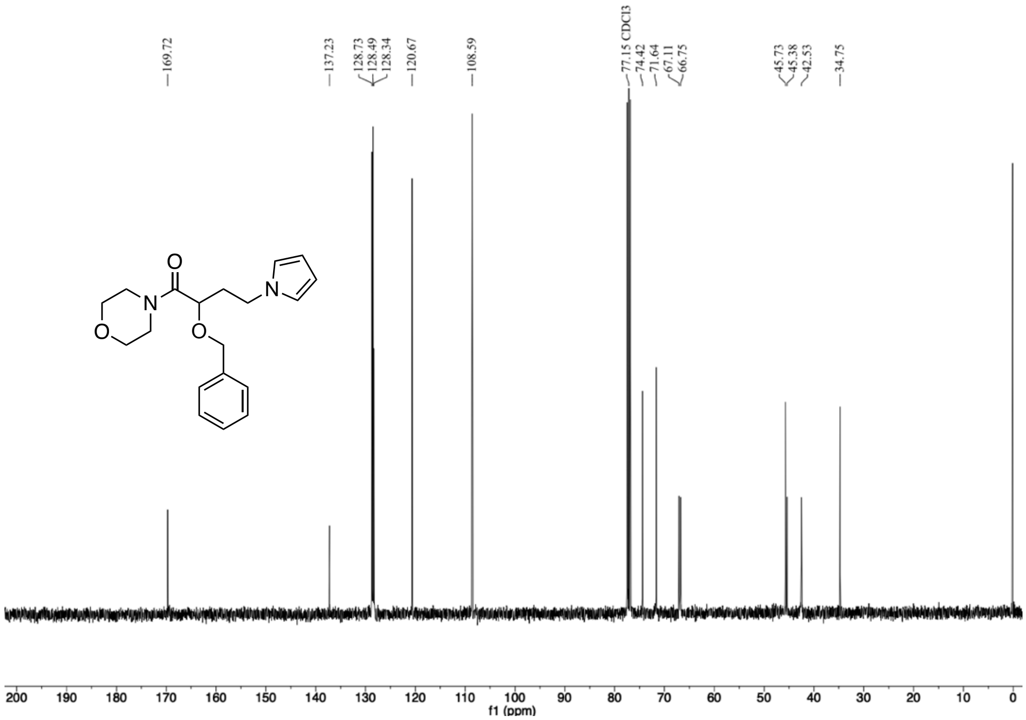
^{1}**H NMR** spectrum of **26** (400 MHz, CDCl$_3$)



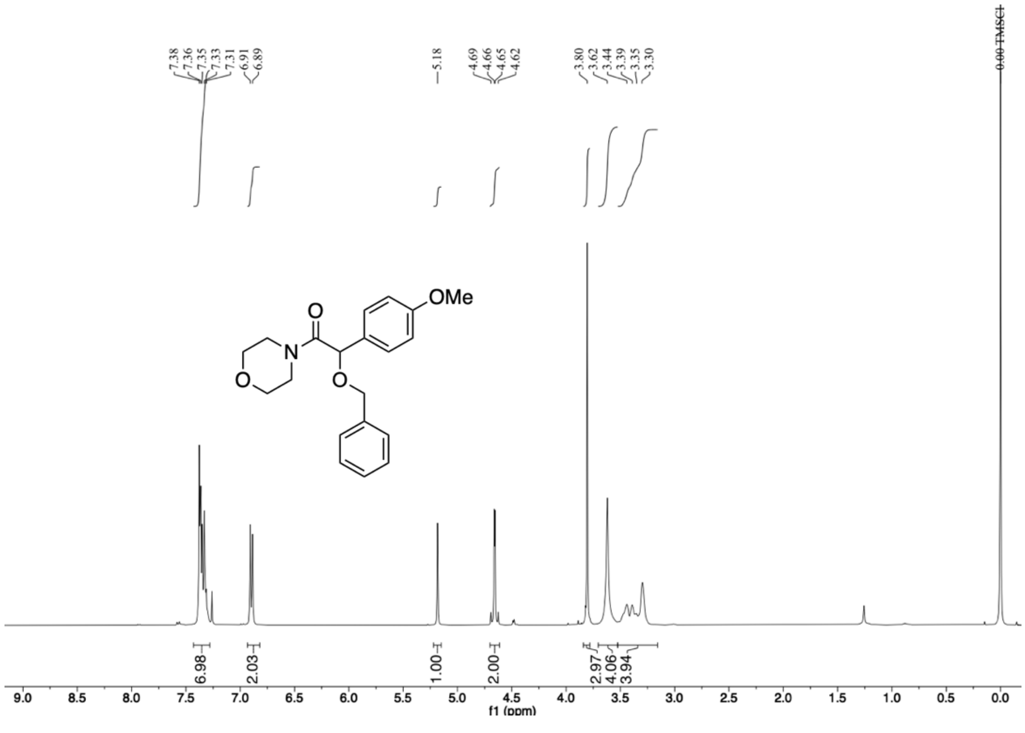
^{13}C NMR spectrum of **26** (101 MHz, $CDCl_3$)



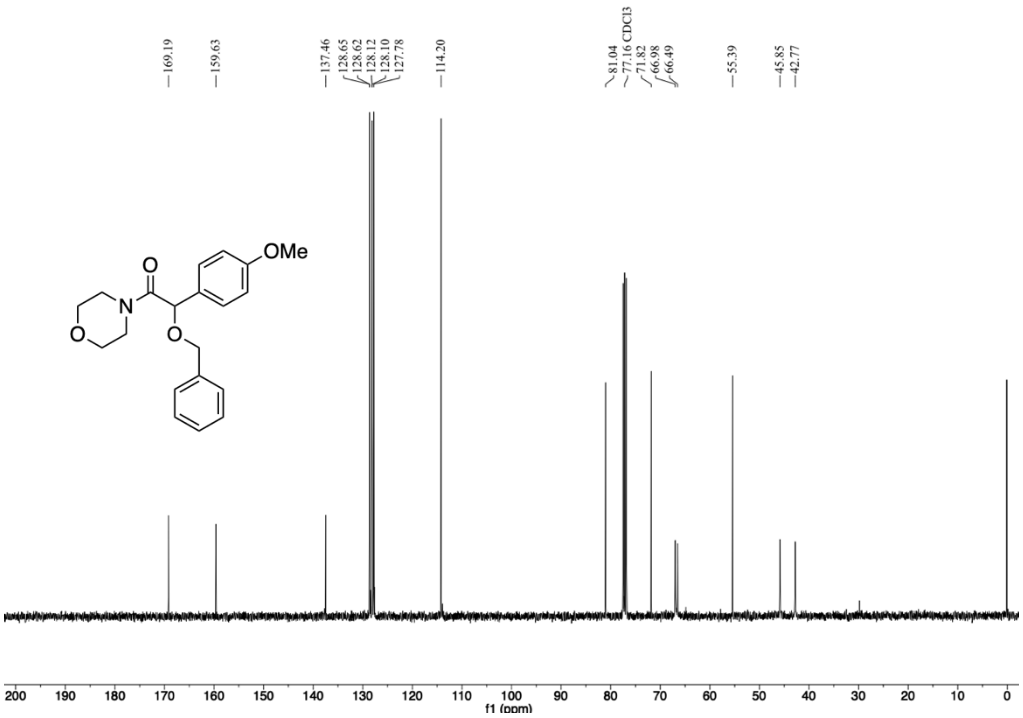
^{1}H NMR spectrum of **27** (400 MHz, $CDCl_3$)



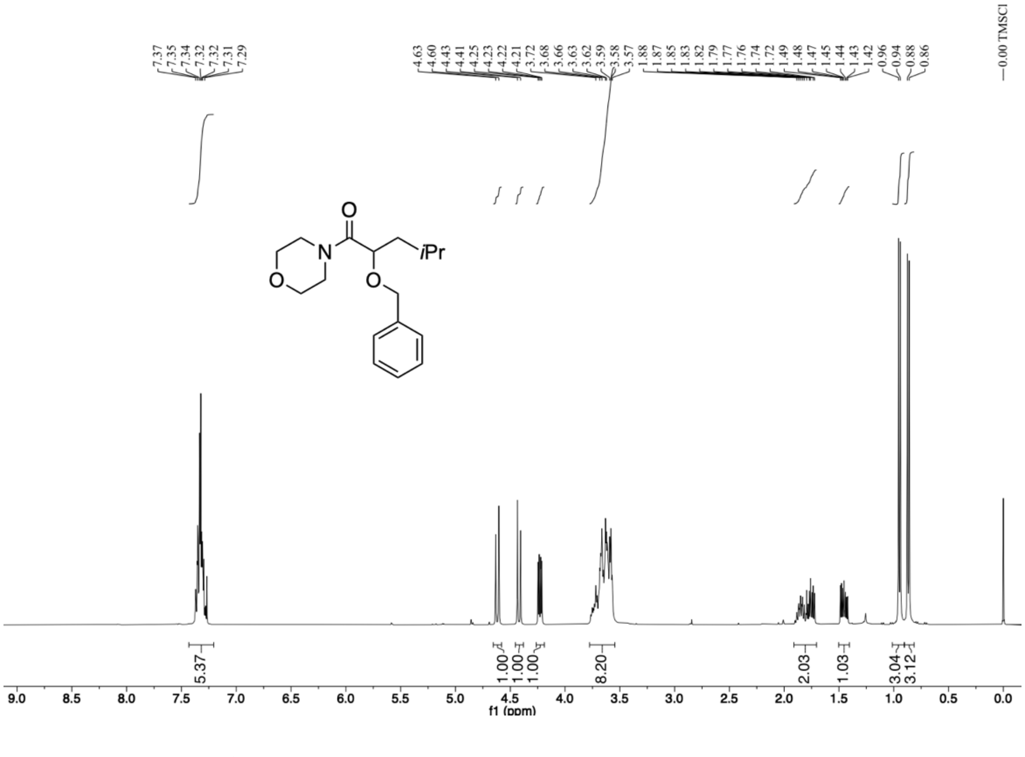
^{13}C NMR spectrum of **27** (101 MHz, CDCl$_3$)



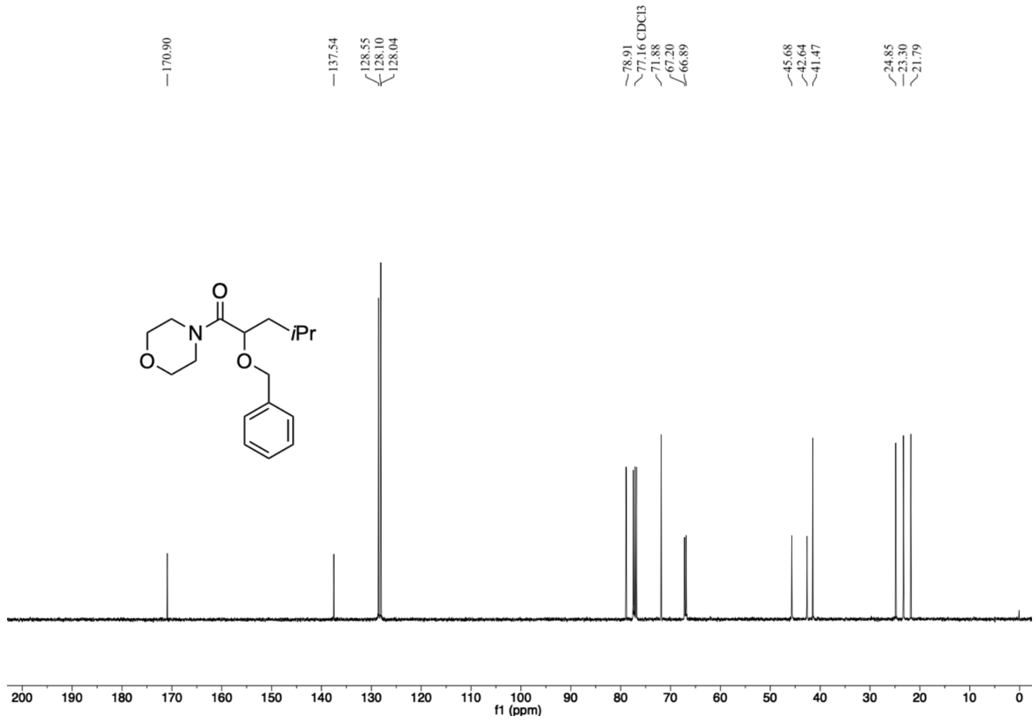
^{1}H NMR spectrum of **28** (400 MHz, CDCl$_3$)



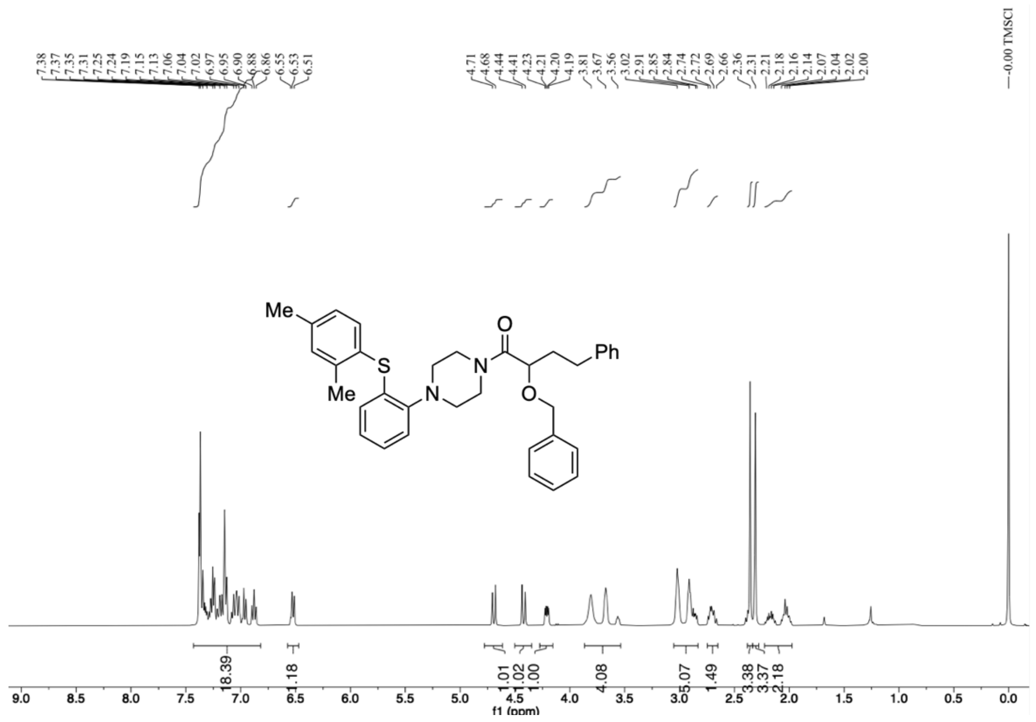
^{13}**C NMR** spectrum of **28** (101 MHz, CDCl$_3$)



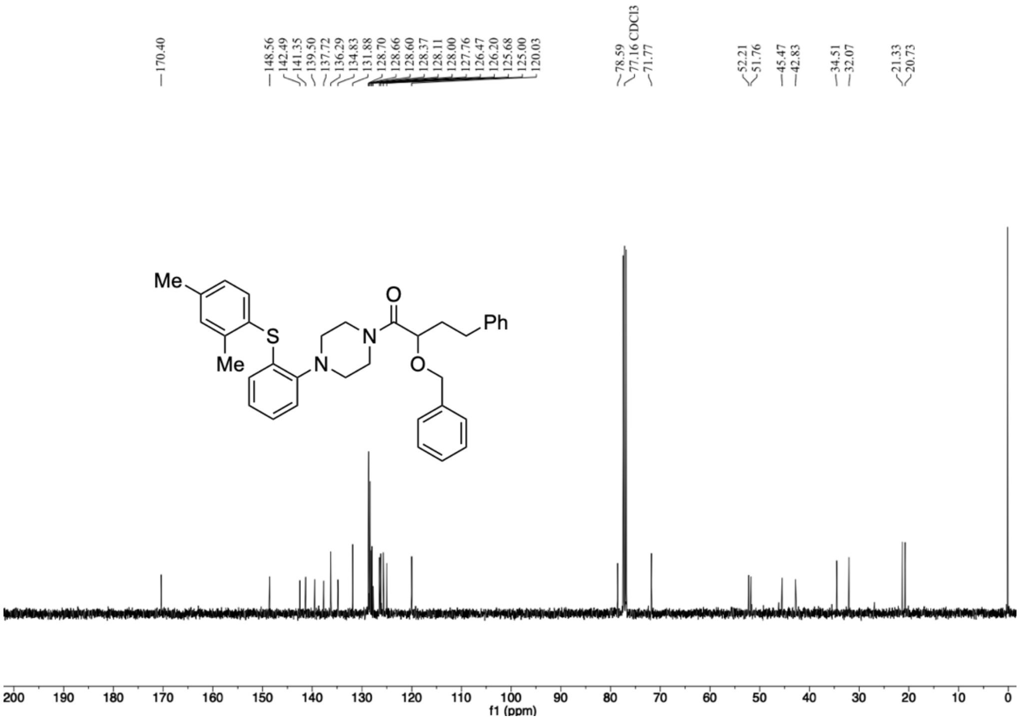
^{1}**H NMR** spectrum of **29** (400 MHz, CDCl$_3$)



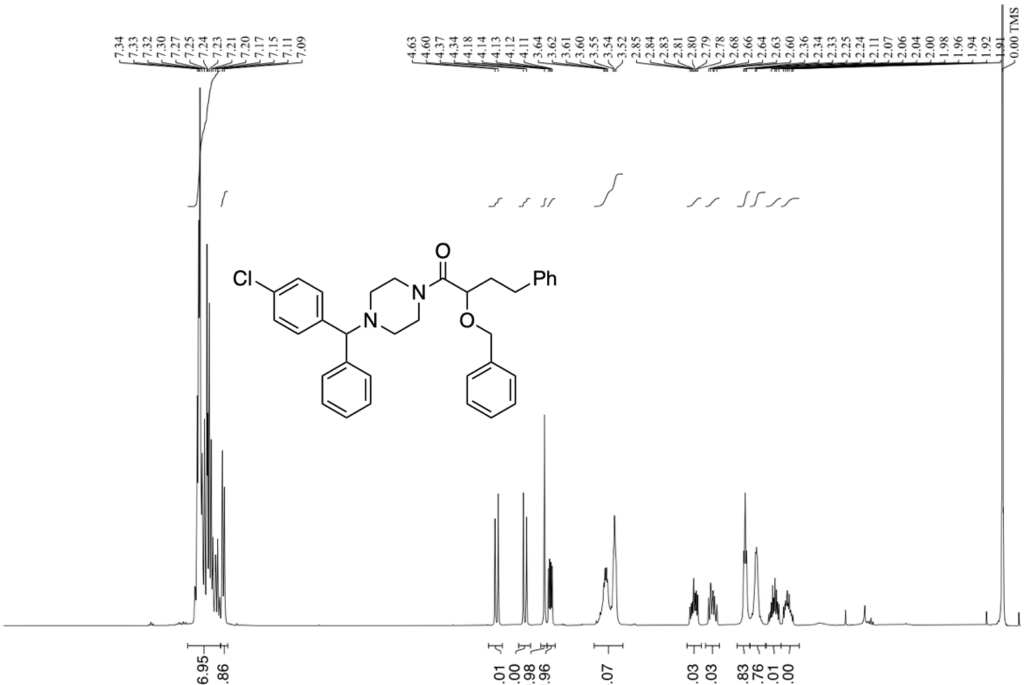
^{13}C NMR spectrum of **29** (101 MHz, $CDCl_3$)



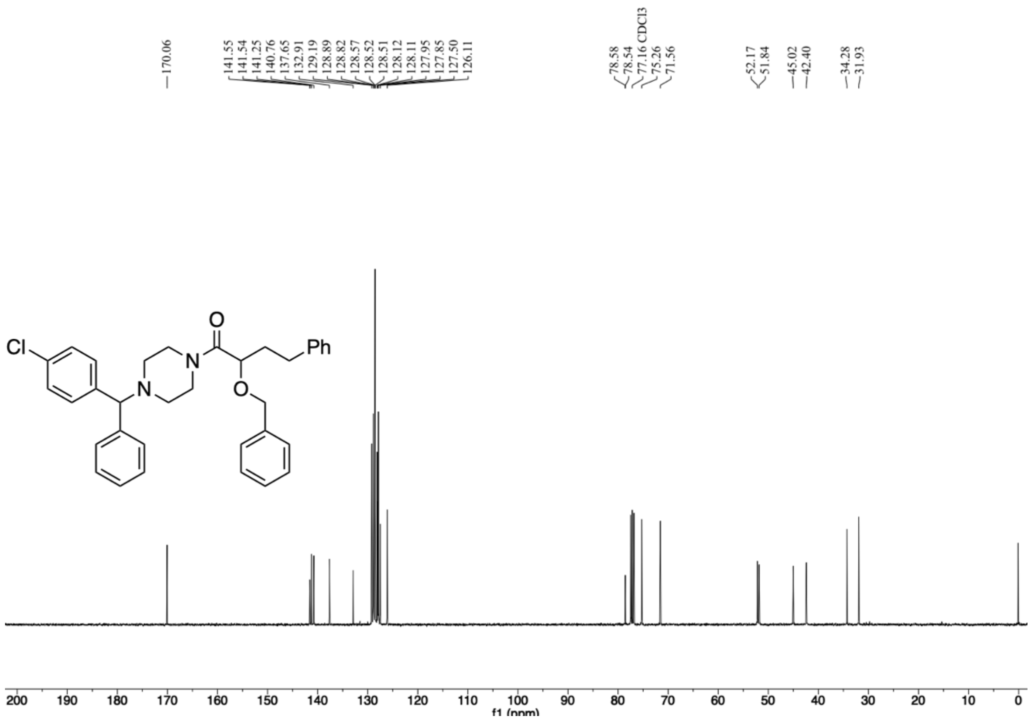
^{1}H NMR spectrum of **30** (400 MHz, $CDCl_3$)



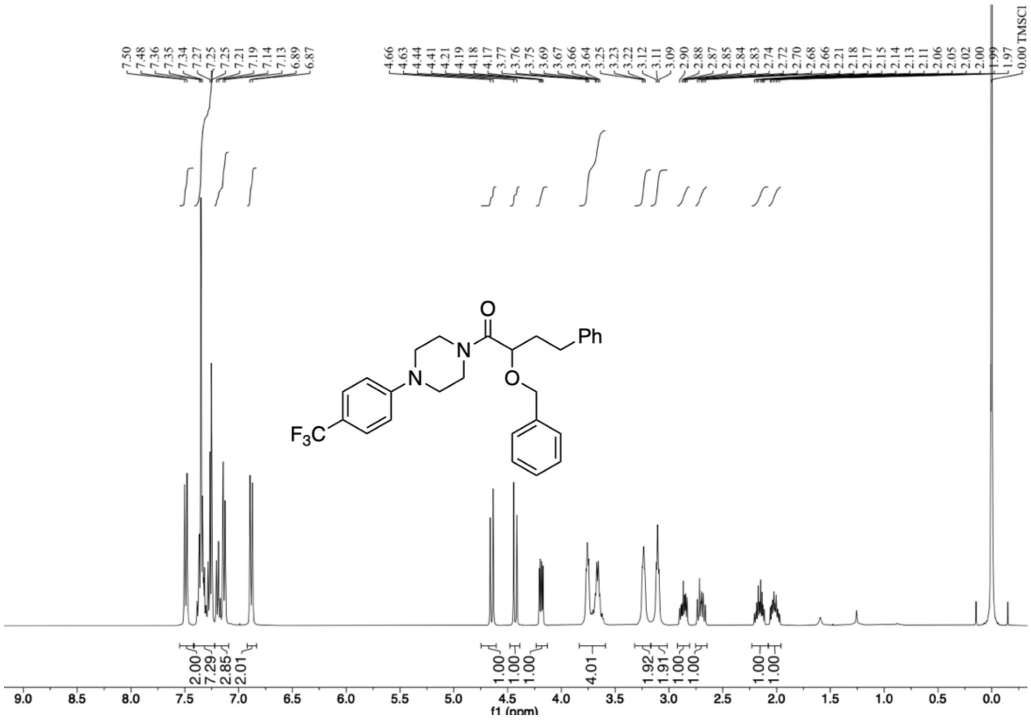
^{13}C NMR spectrum of **30** (101 MHz, CDCl$_3$)



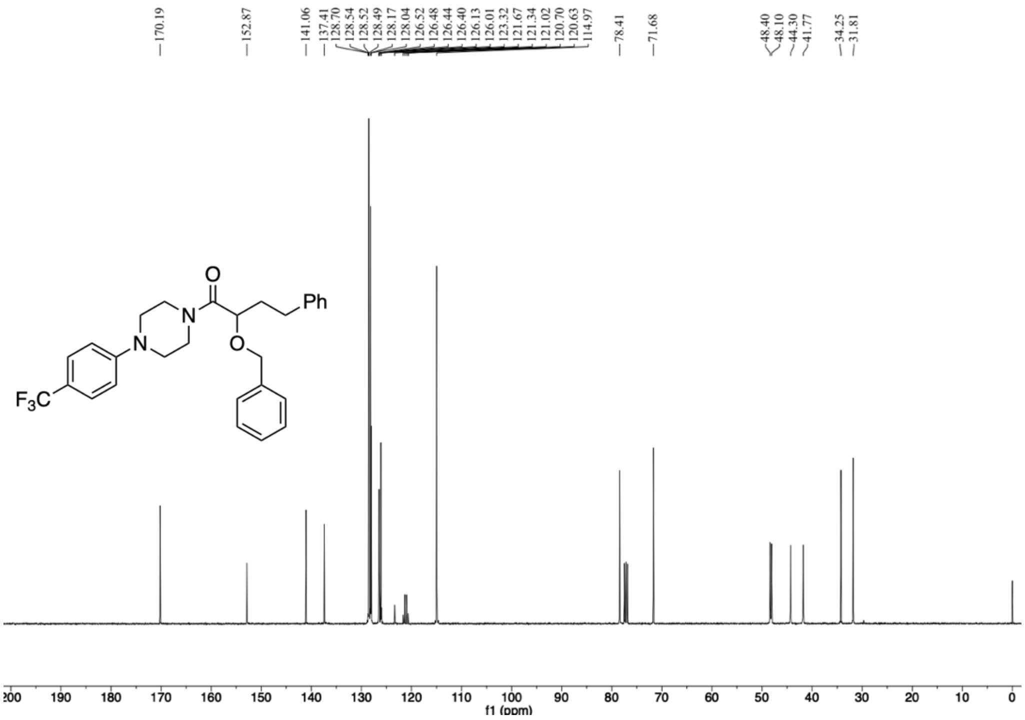
^{1}H NMR spectrum of **31** (400 MHz, CDCl$_3$)



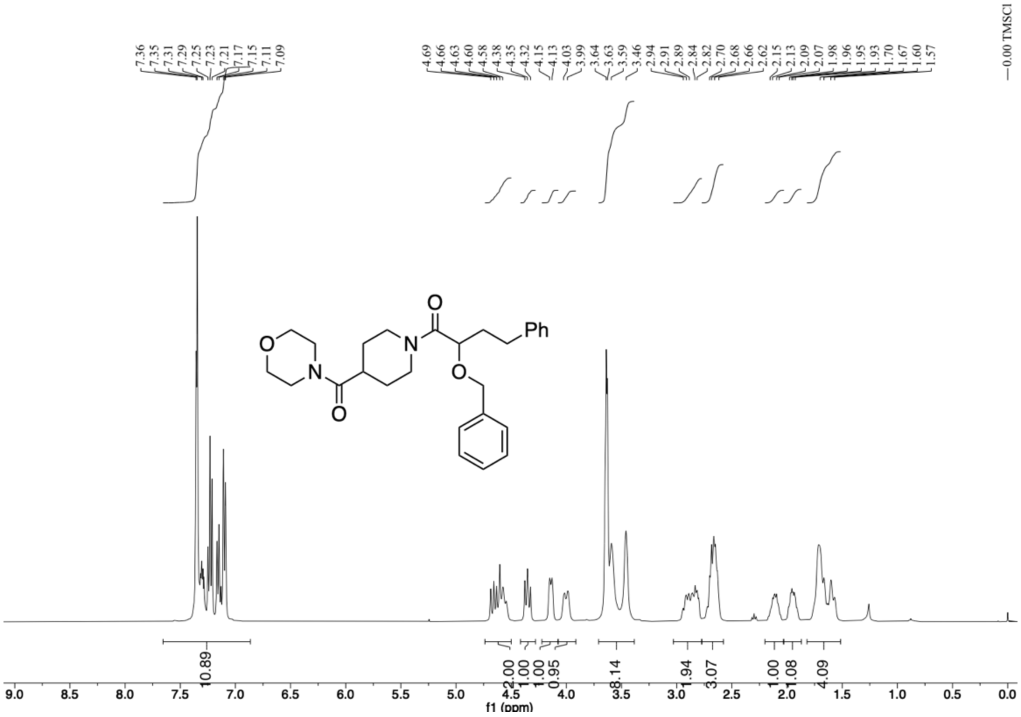
^{13}**C NMR** spectrum of **31** (101 MHz, $CDCl_3$)



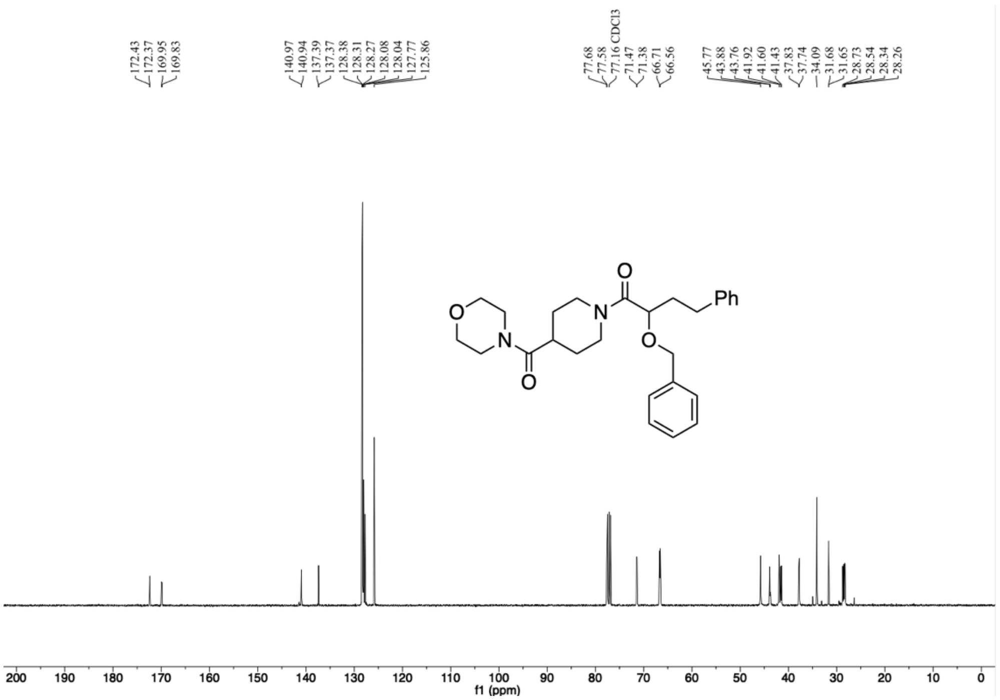
^{1}**H NMR** spectrum of **32** (400 MHz, $CDCl_3$)



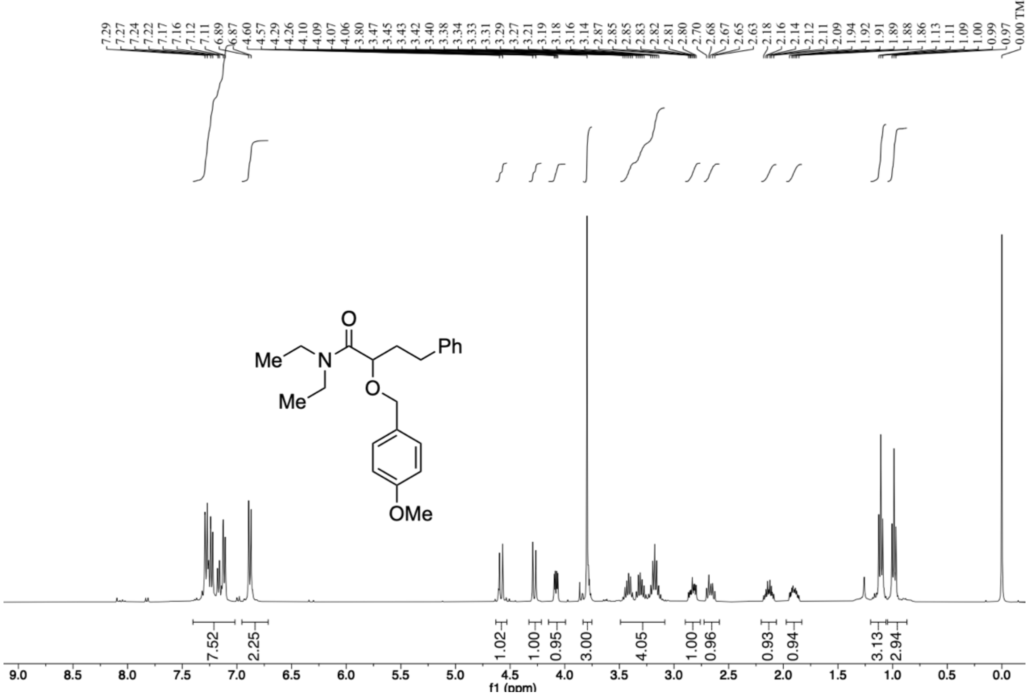
^{13}**C NMR** spectrum of **32** (101 MHz, CDCl$_3$)



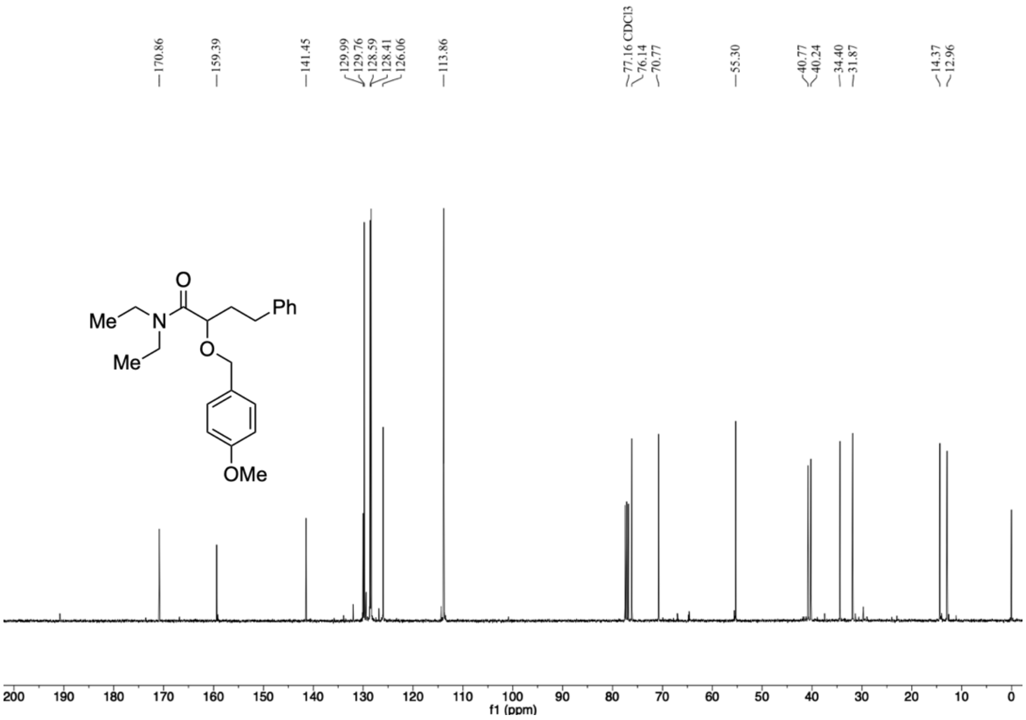
^{1}**H NMR** spectrum of **33** (400 MHz, CDCl$_3$)



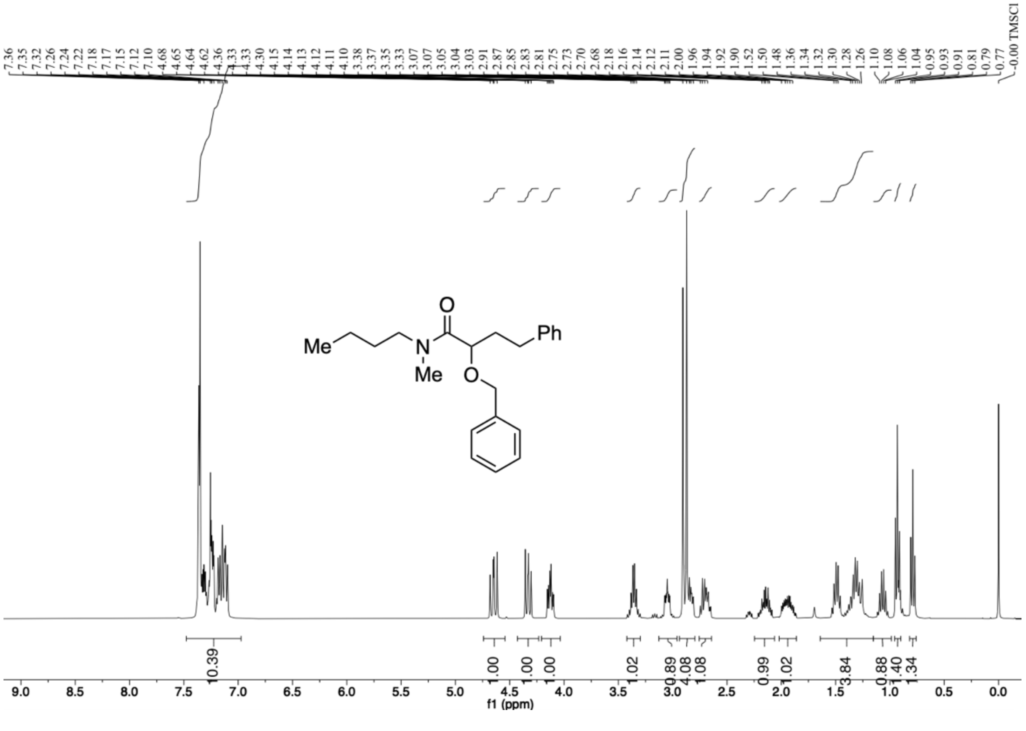
^{13}C NMR spectrum of **33** (101 MHz, CDCl$_3$)



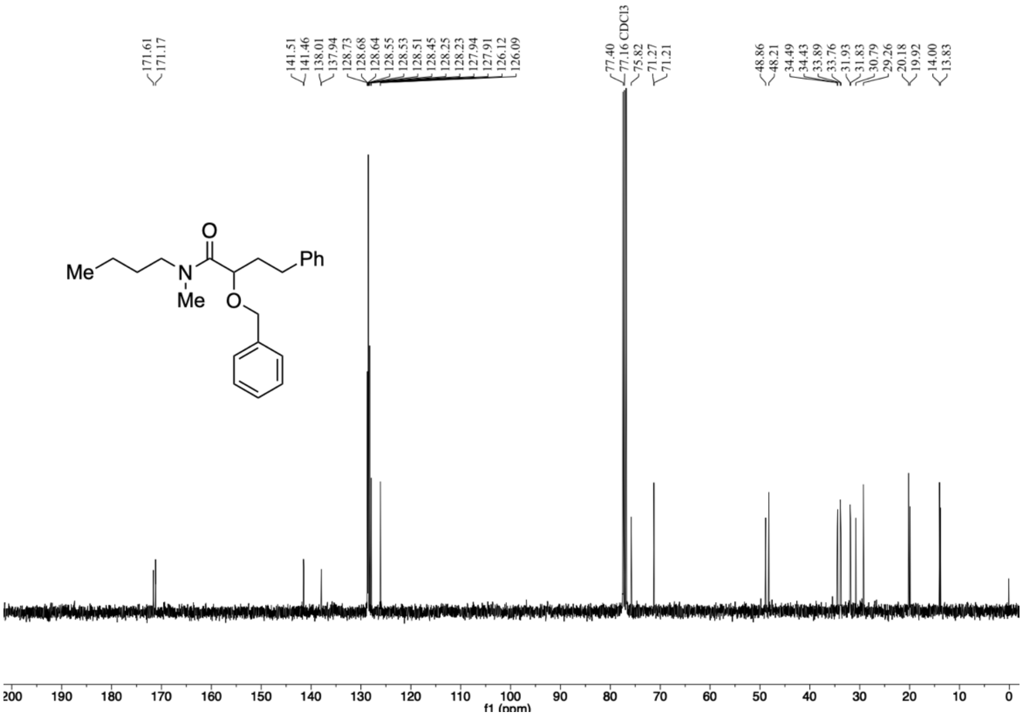
^{1}H NMR spectrum of **34** (400 MHz, CDCl$_3$)



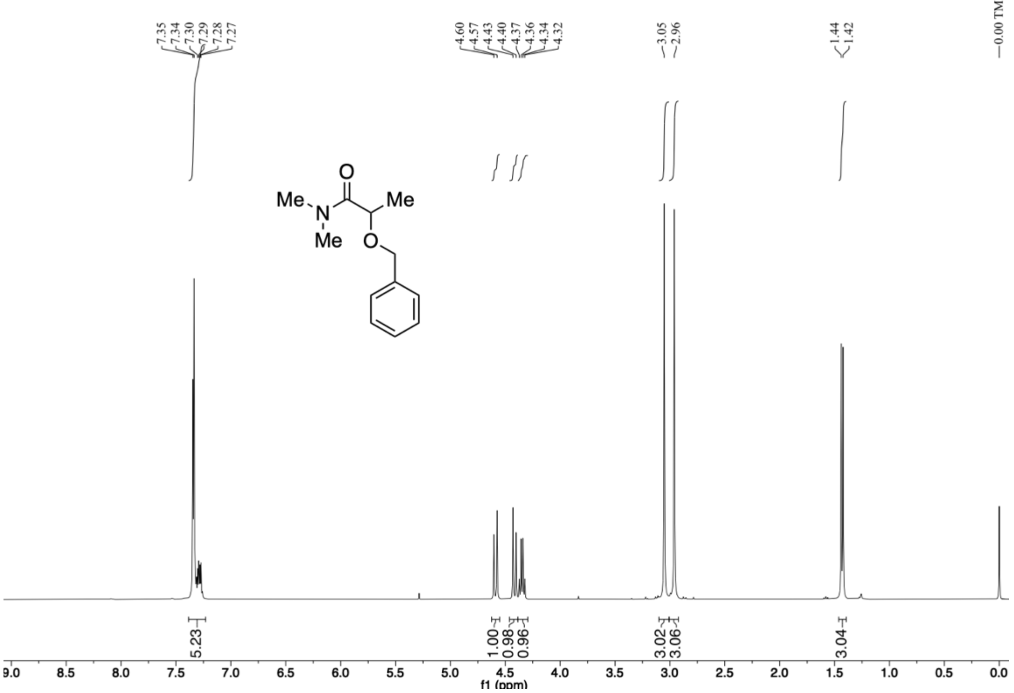
^{13}**C NMR** spectrum of **34** (101 MHz, CDCl$_3$)



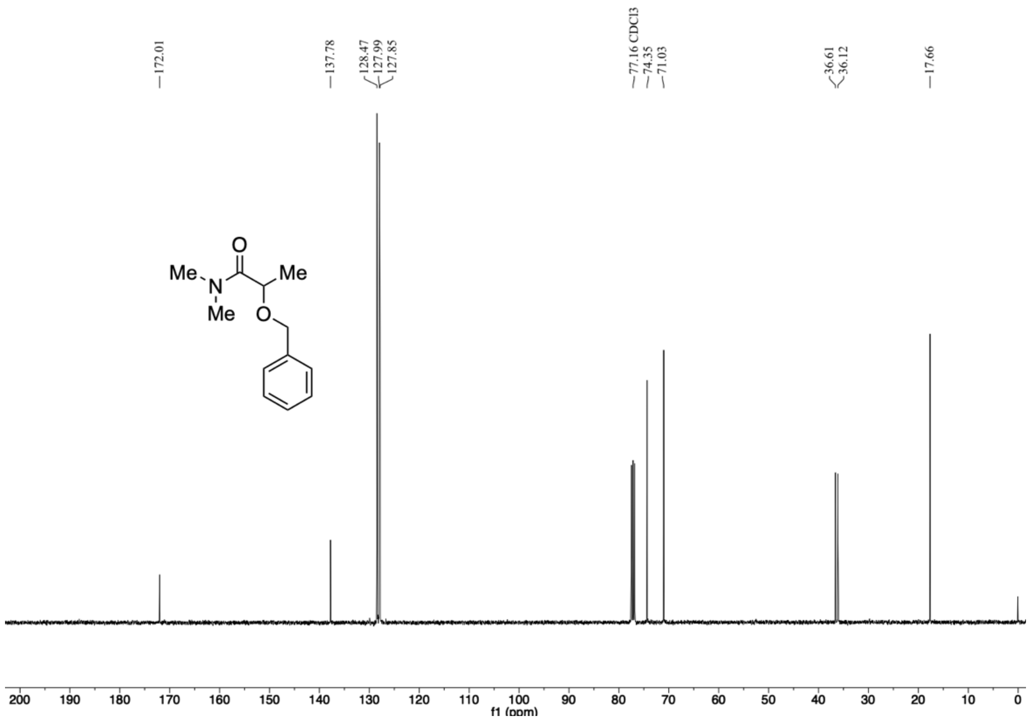
^{1}**H NMR** spectrum of **35** (400 MHz, CDCl$_3$)



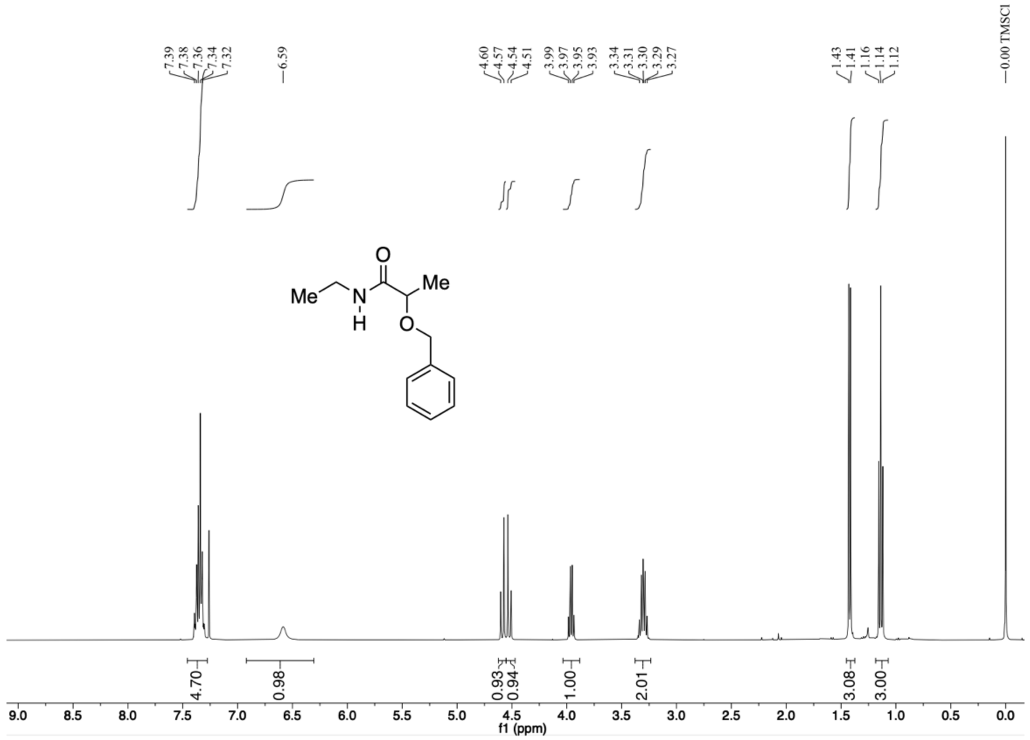
^{13}**C NMR** spectrum of **35** (101 MHz, CDCl$_3$)



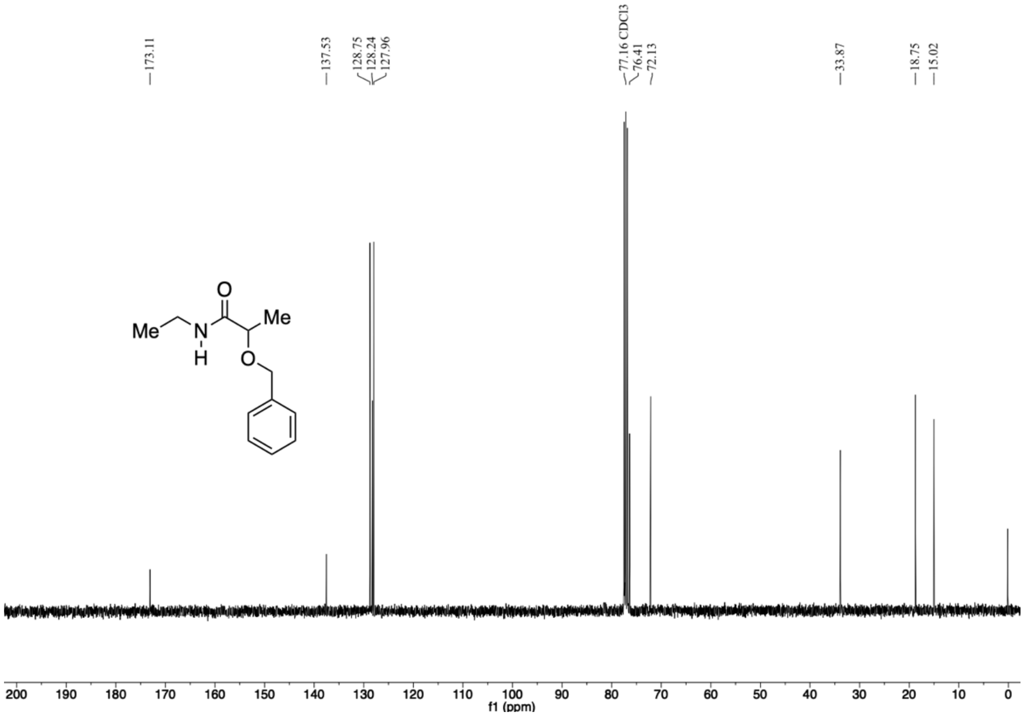
^{1}**H NMR** spectrum of **36** (400 MHz, CDCl$_3$)



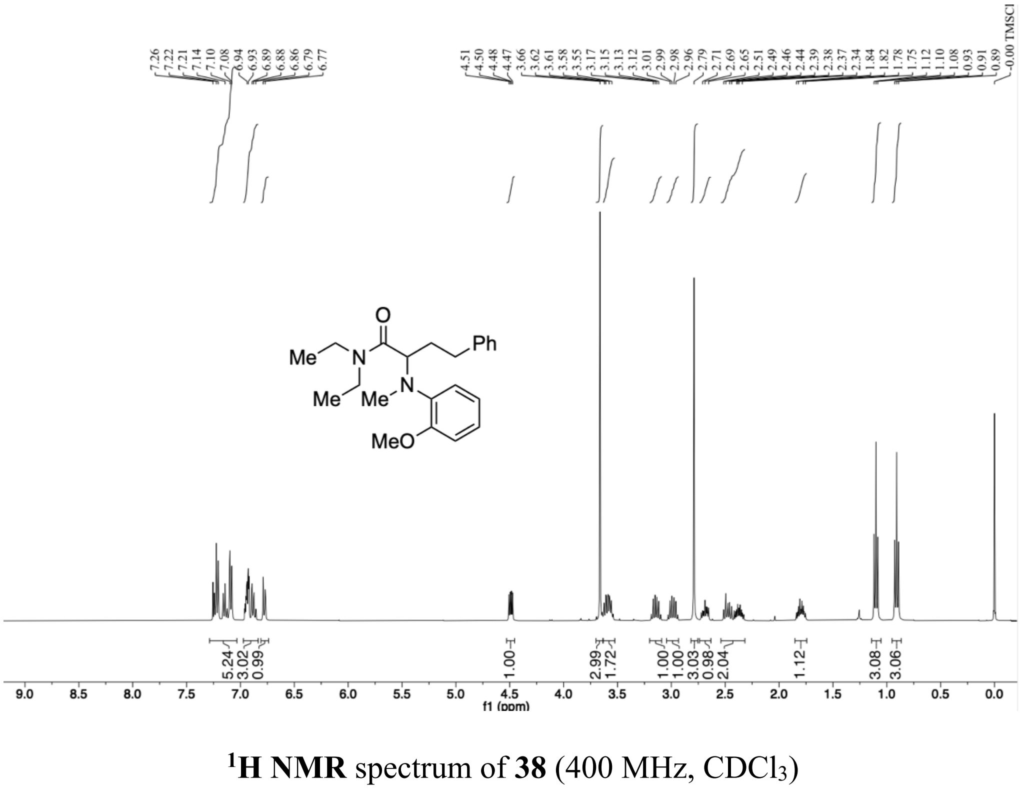
^{13}C NMR spectrum of **36** (101 MHz, CDCl$_3$)



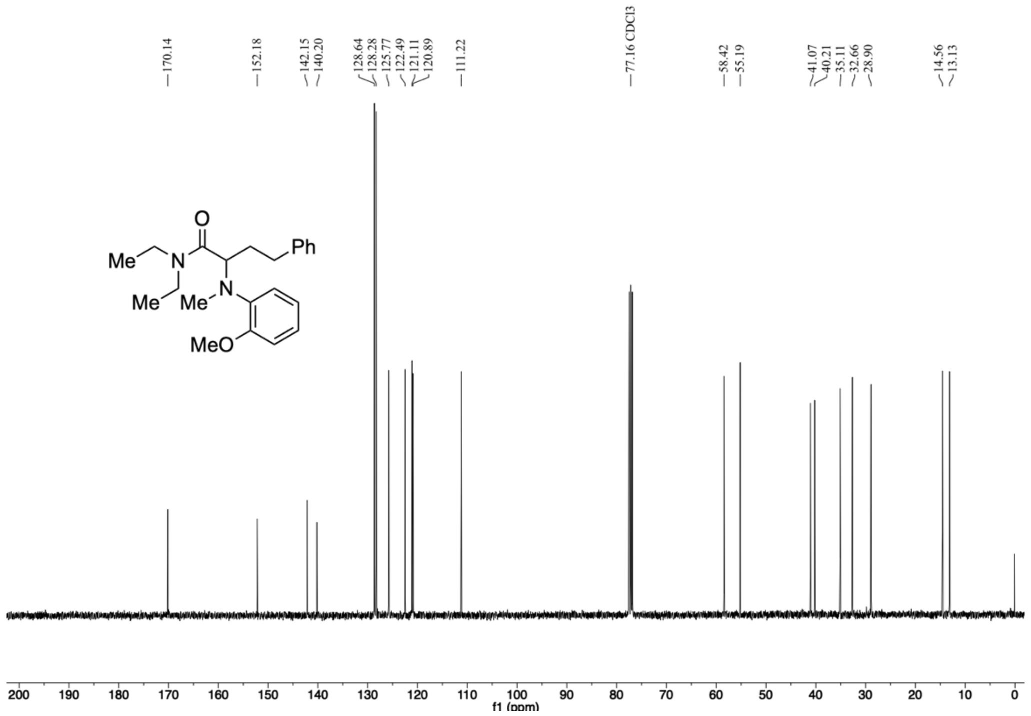
^{1}H NMR spectrum of **37** (400 MHz, CDCl$_3$)



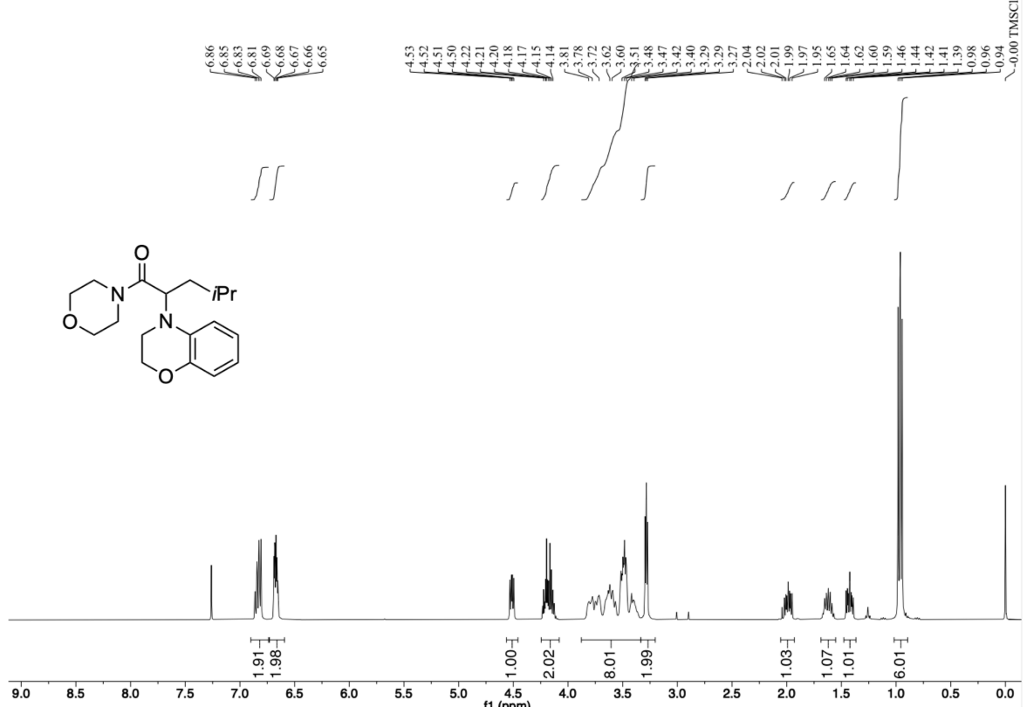
^{13}C NMR spectrum of **37** (101 MHz, $CDCl_3$)



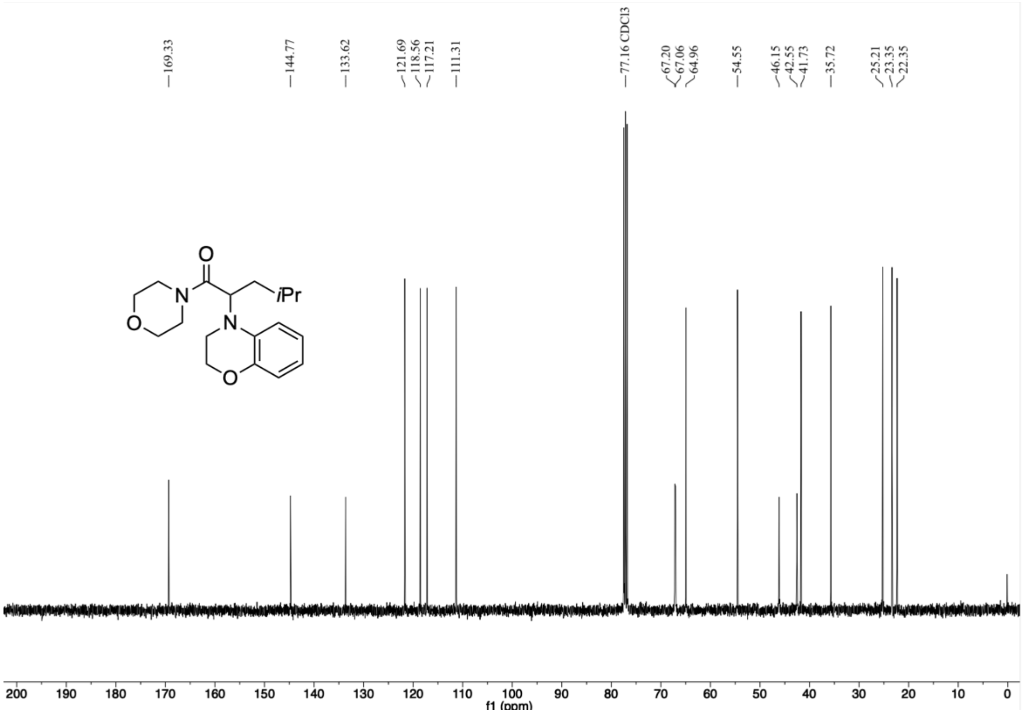
^{1}H NMR spectrum of **38** (400 MHz, $CDCl_3$)



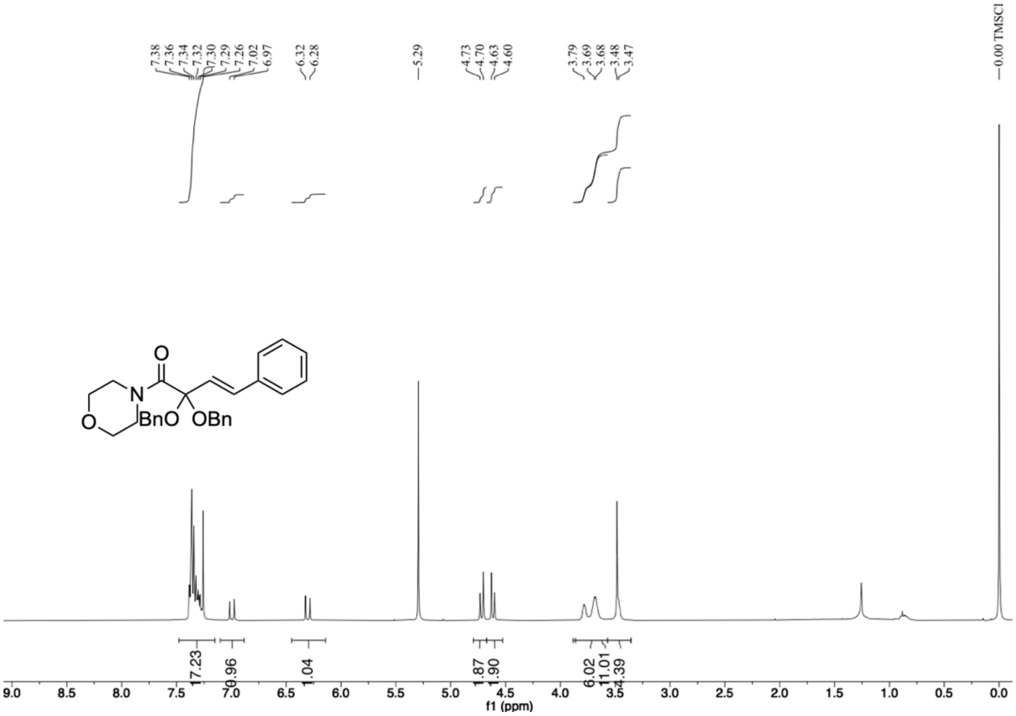
^{13}C NMR spectrum of **38** (101 MHz, CDCl$_3$)



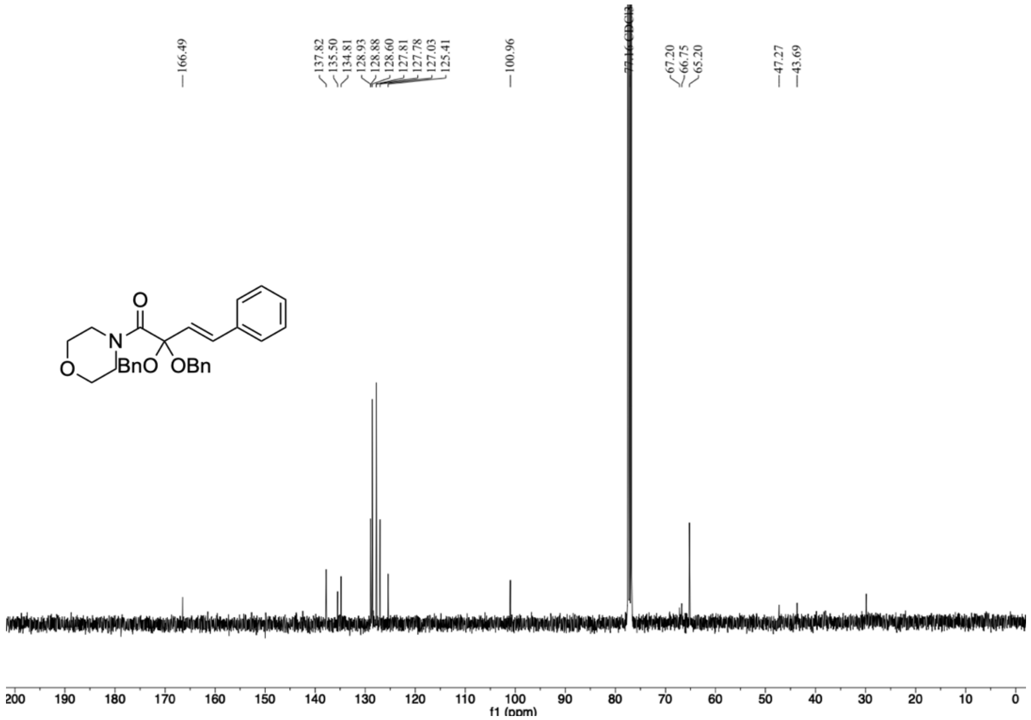
^{1}H NMR spectrum of **39** (400 MHz, CDCl$_3$)



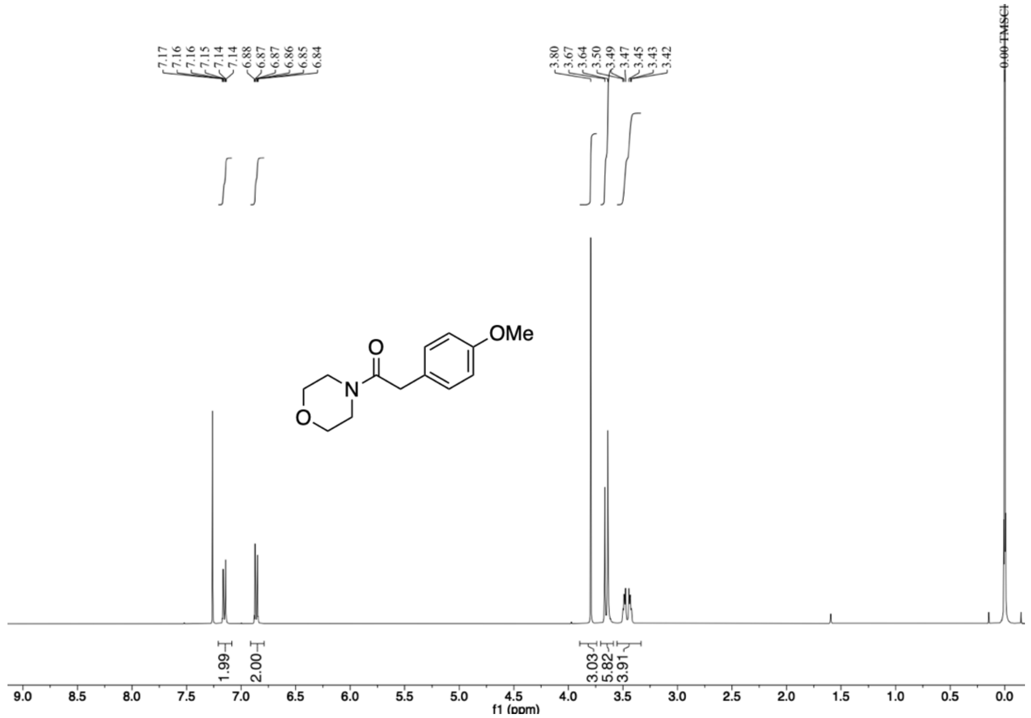
^{13}C NMR spectrum of **39** (101 MHz, CDCl$_3$)



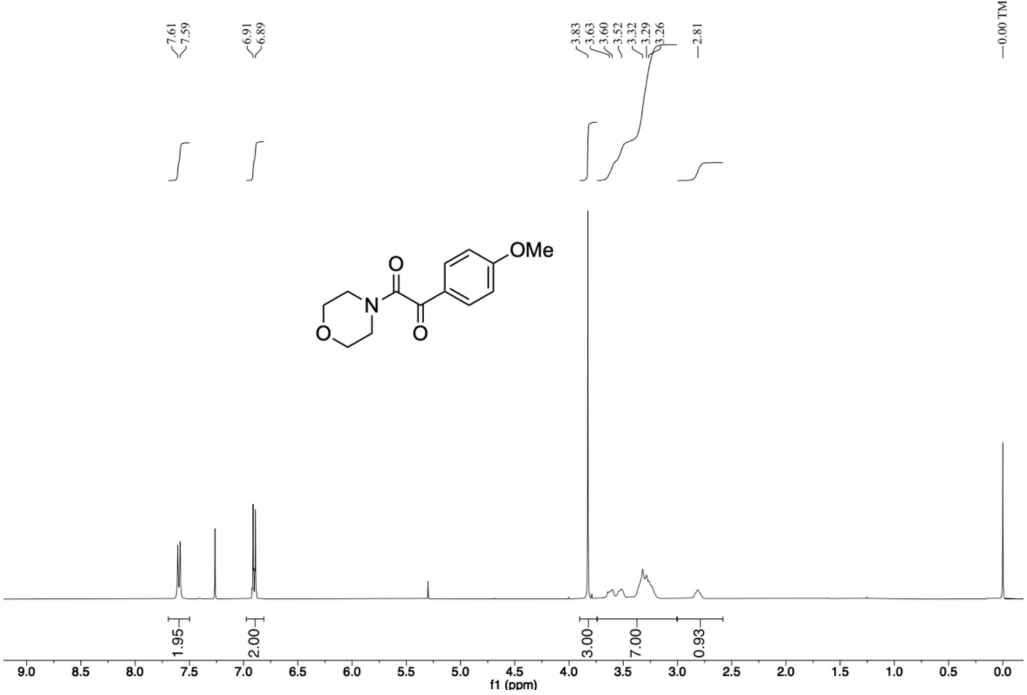
^{1}H NMR spectrum of **40** (400 MHz, CDCl$_3$)



^{13}**C NMR** spectrum of **40** (101 MHz, CDCl$_3$)

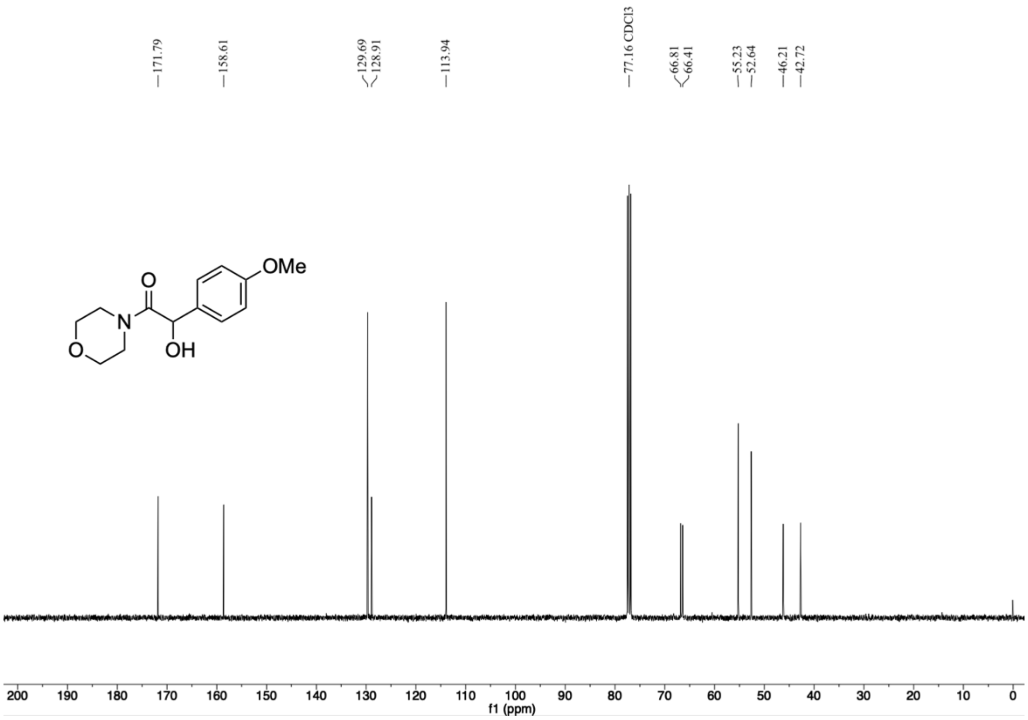


^{1}**H NMR** spectrum of **45** (400 MHz, CDCl$_3$)

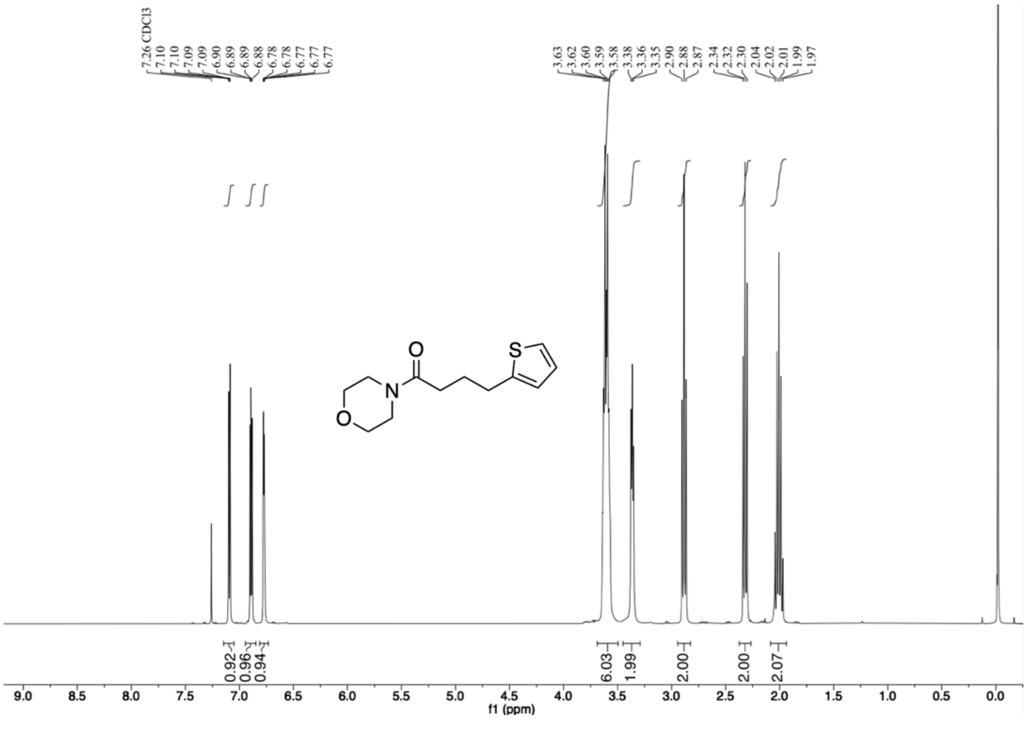


^{1}**H NMR** spectrum of **46** (400 MHz, CDCl$_3$)

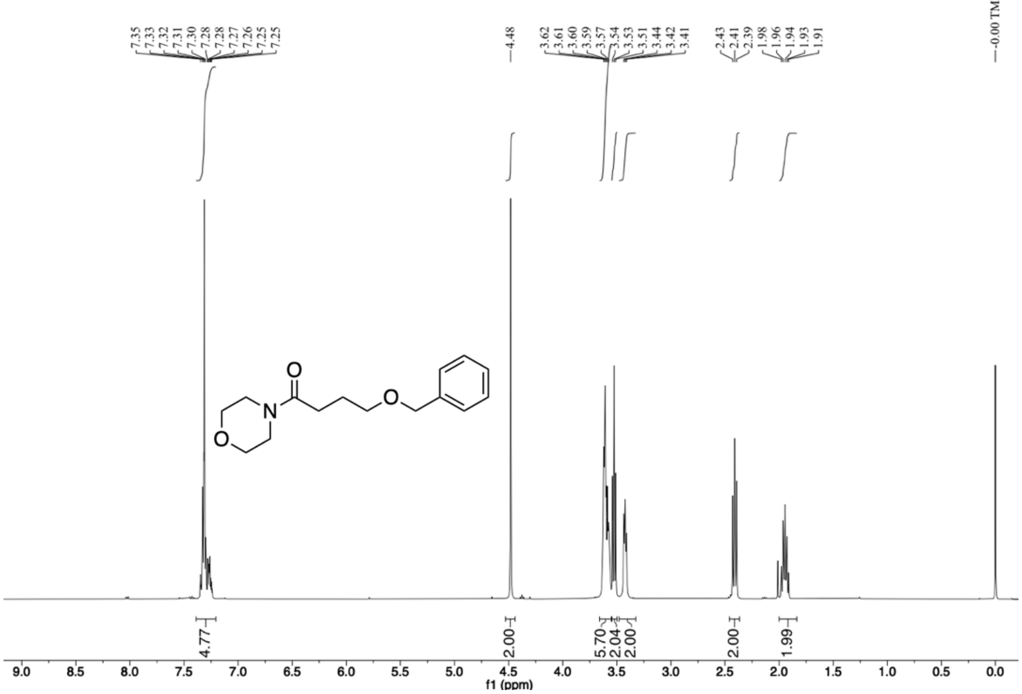
^{1}**H NMR** spectrum of **47** (400 MHz, CDCl$_3$)



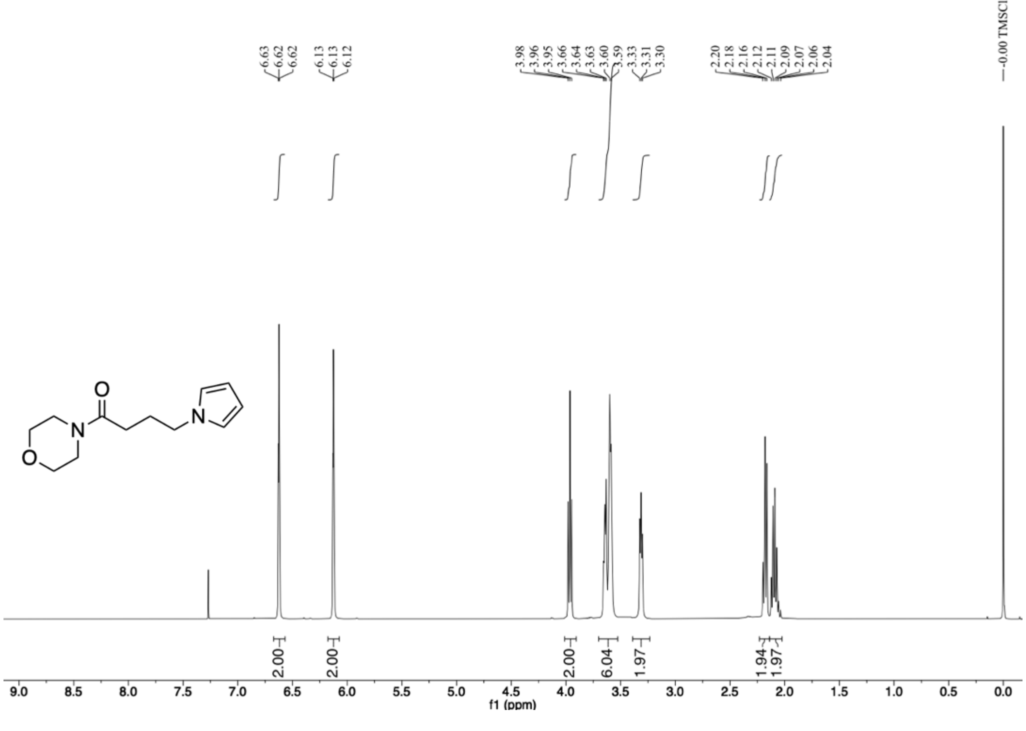
^{13}**C NMR** spectrum of **47** (101 MHz, CDCl$_3$)



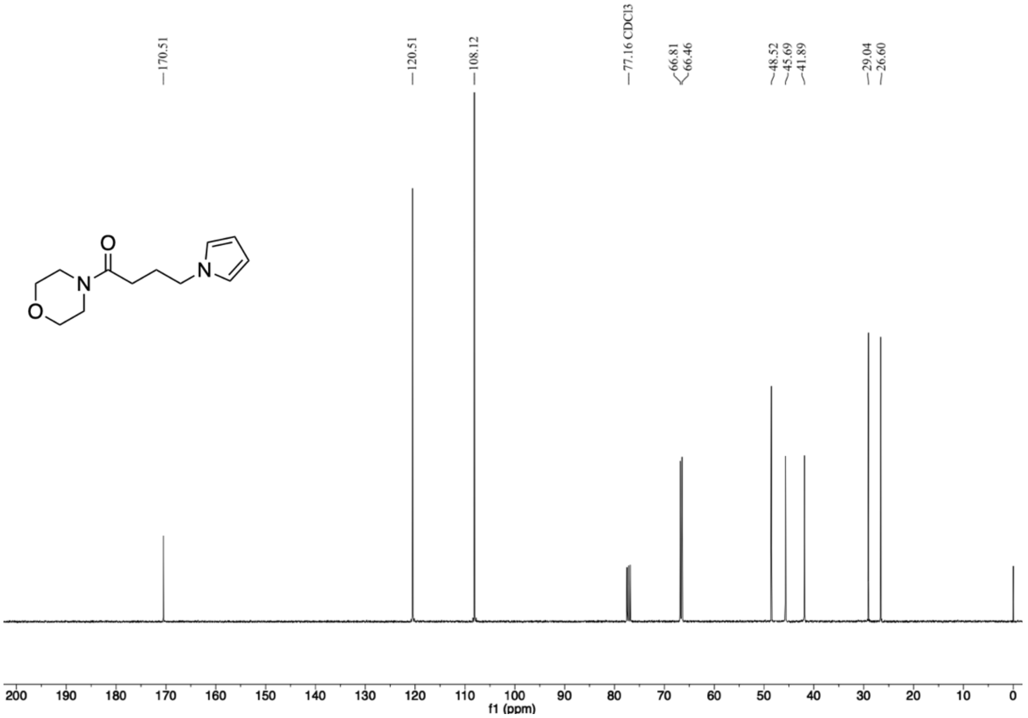
^{1}**H NMR** spectrum of **SI-1** (400 MHz, CDCl$_3$)



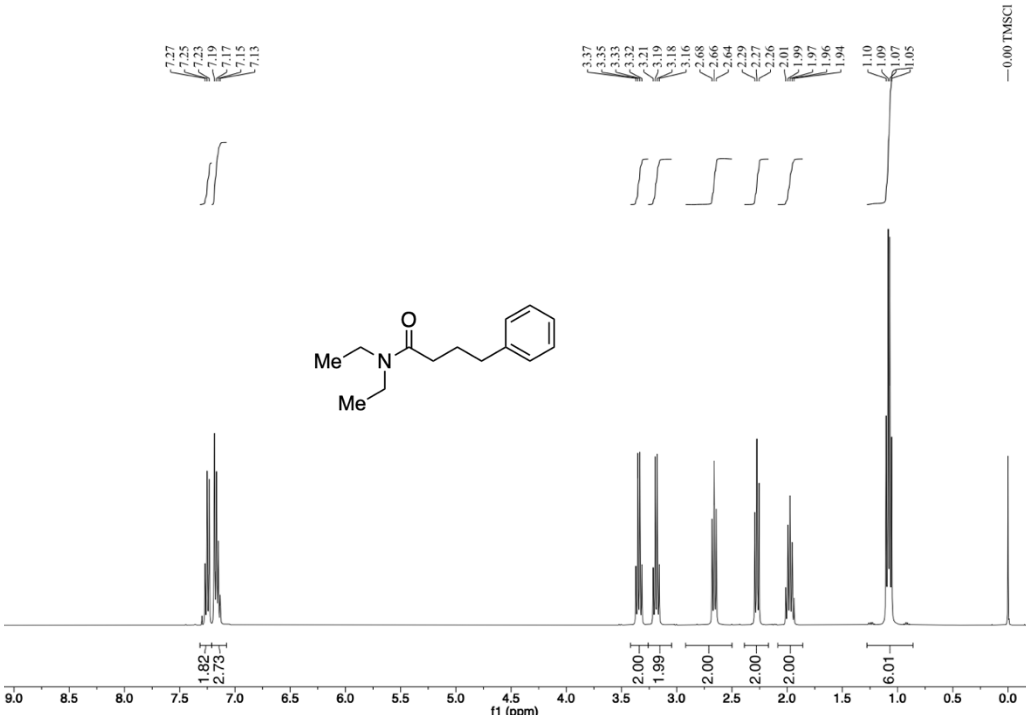
^{1}H NMR spectrum of **SI-2** (400 MHz, $CDCl_3$)



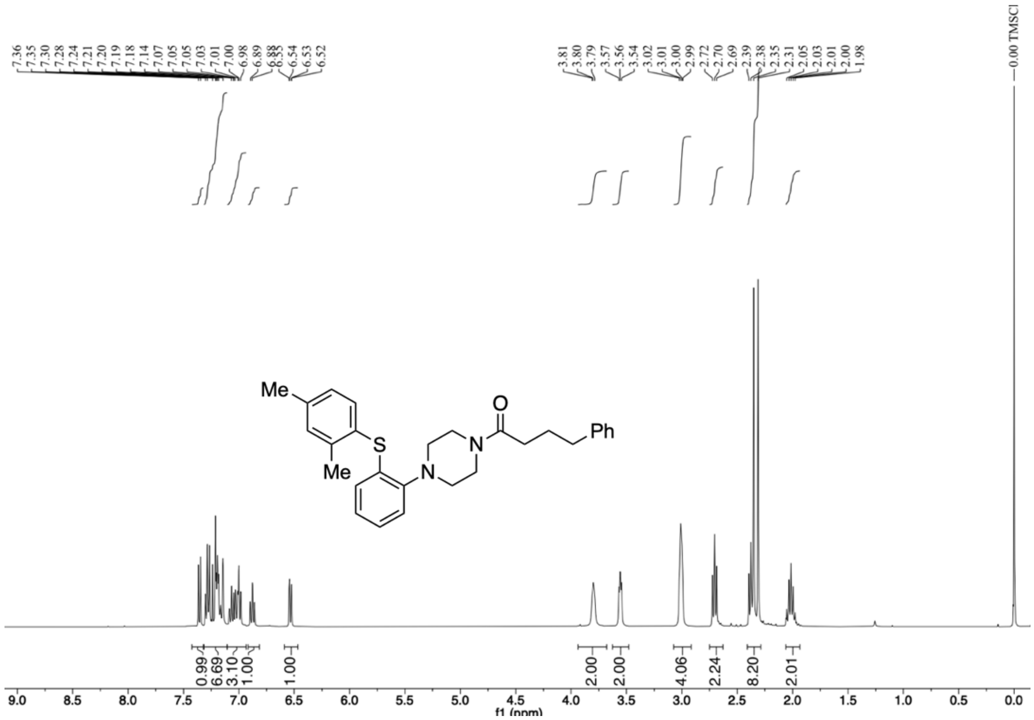
^{1}H NMR spectrum of **SI-3** (400 MHz, $CDCl_3$)



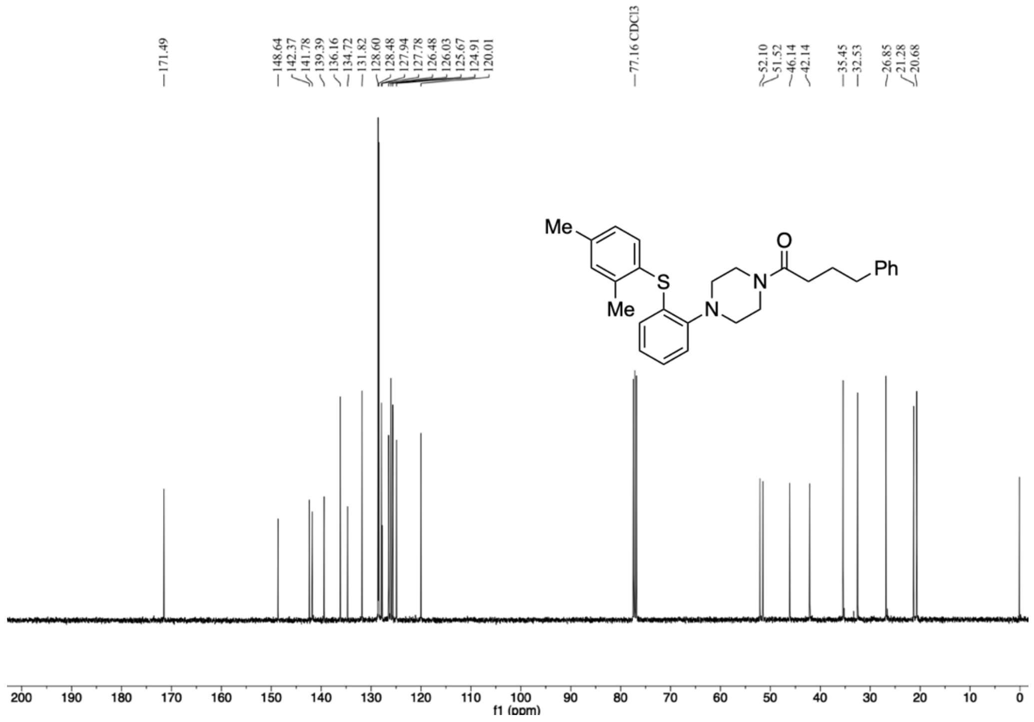
^{13}**C NMR** spectrum of **SI-3** (101 MHz, CDCl$_3$)



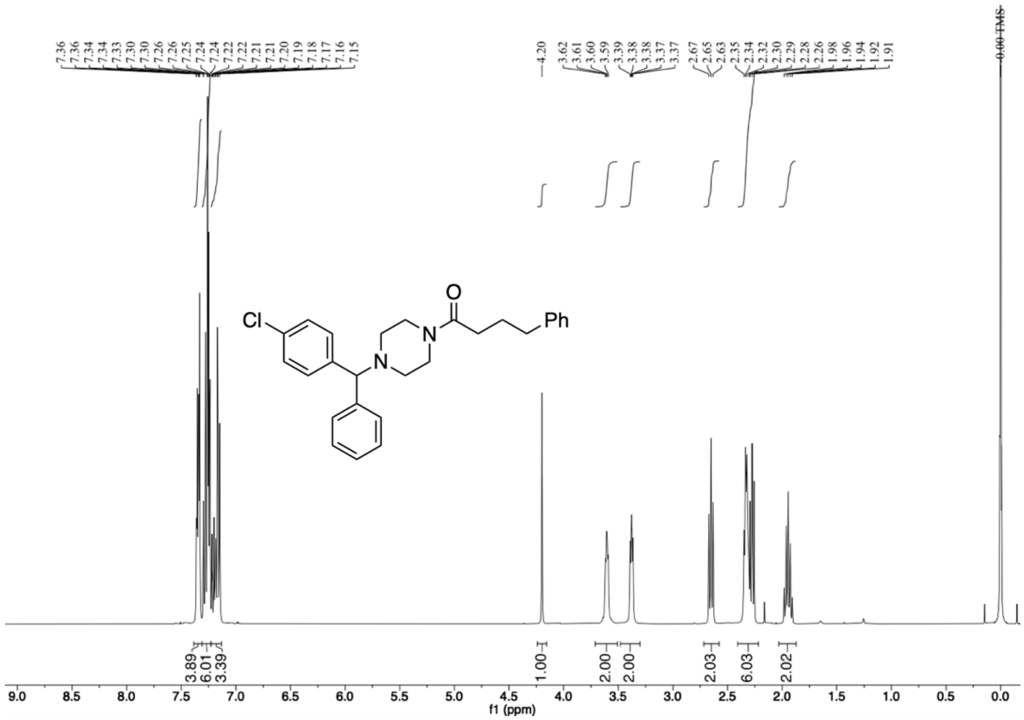
^{1}**H NMR** spectrum of **SI-4** (400 MHz, CDCl$_3$)



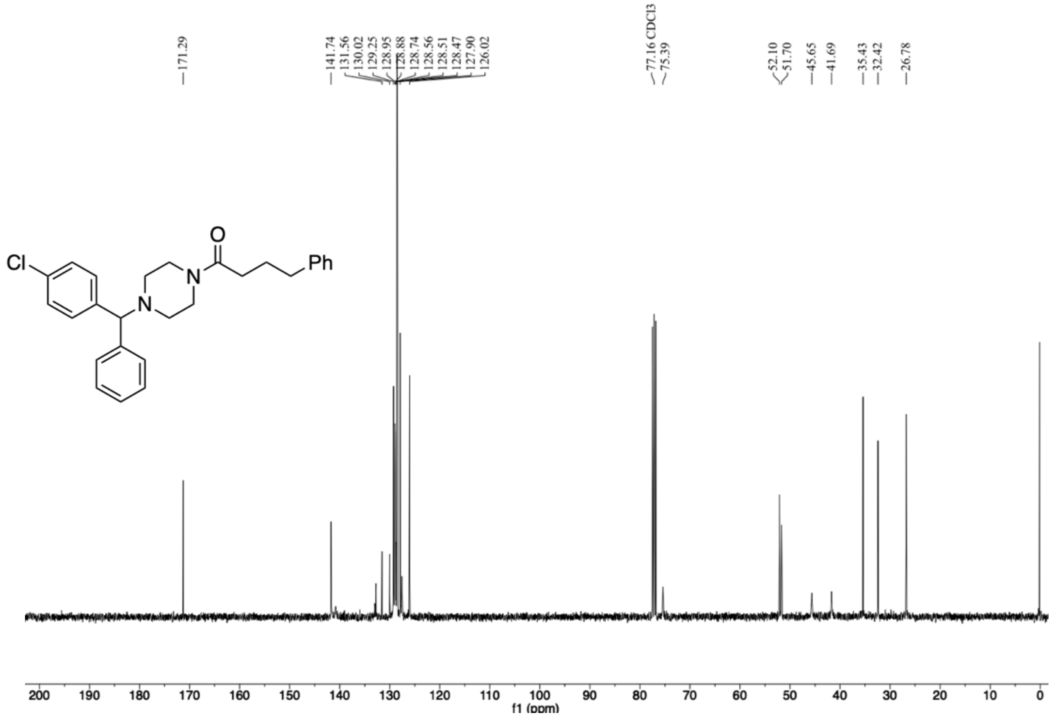
^{1}H NMR spectrum of **SI-5** (400 MHz, CDCl$_3$)



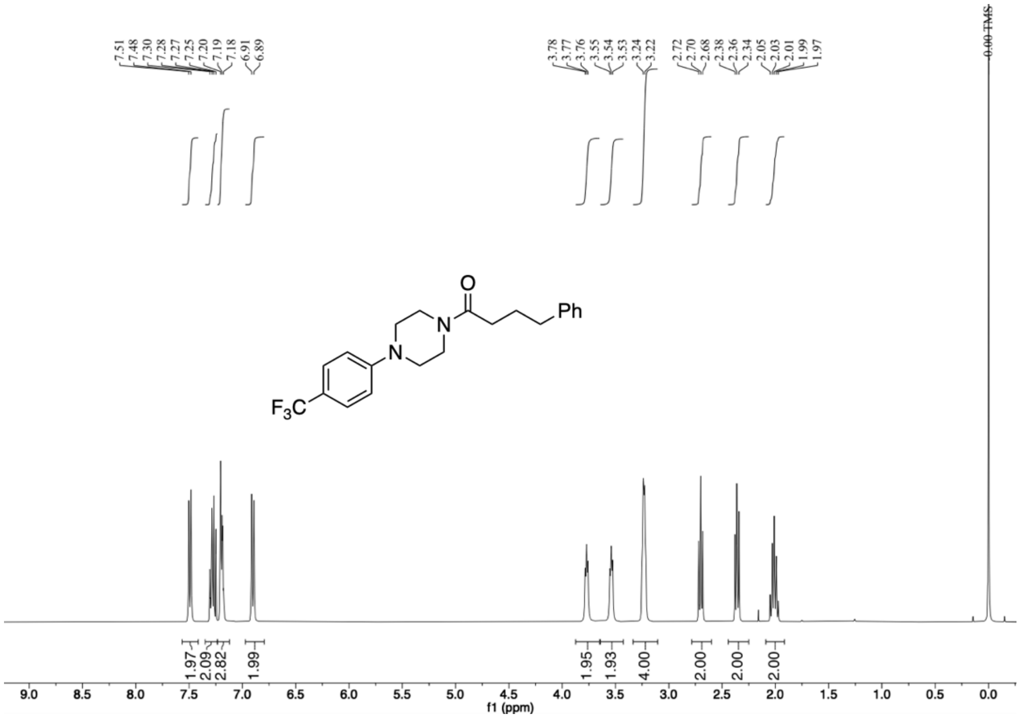
^{13}C NMR spectrum of **SI-5** (101 MHz, CDCl$_3$)



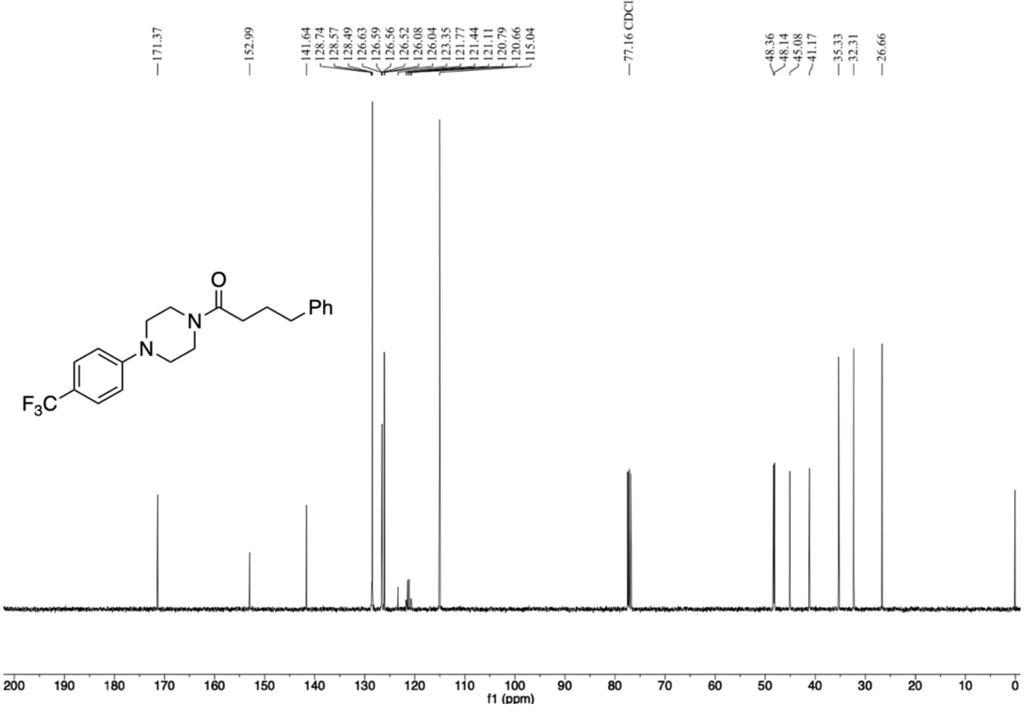
^{1}**H NMR** spectrum of **SI-6** (400 MHz, $CDCl_3$)



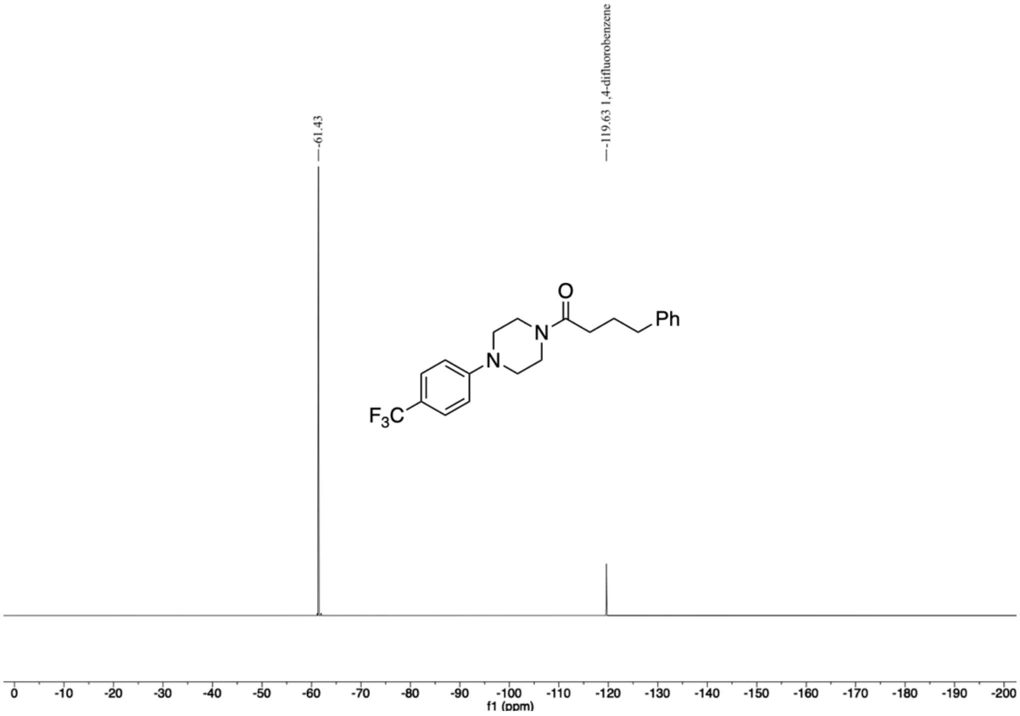
^{13}**C NMR** spectrum of **SI-6** (101 MHz, $CDCl_3$)



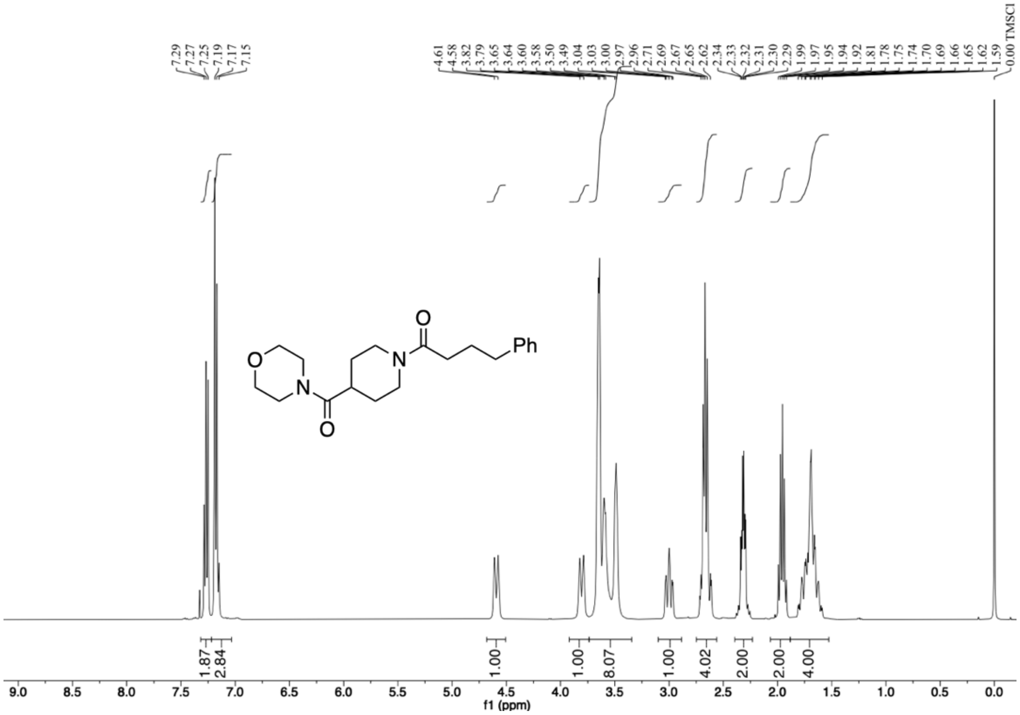
^{1}H NMR spectrum of **SI-7** (400 MHz, $CDCl_3$)



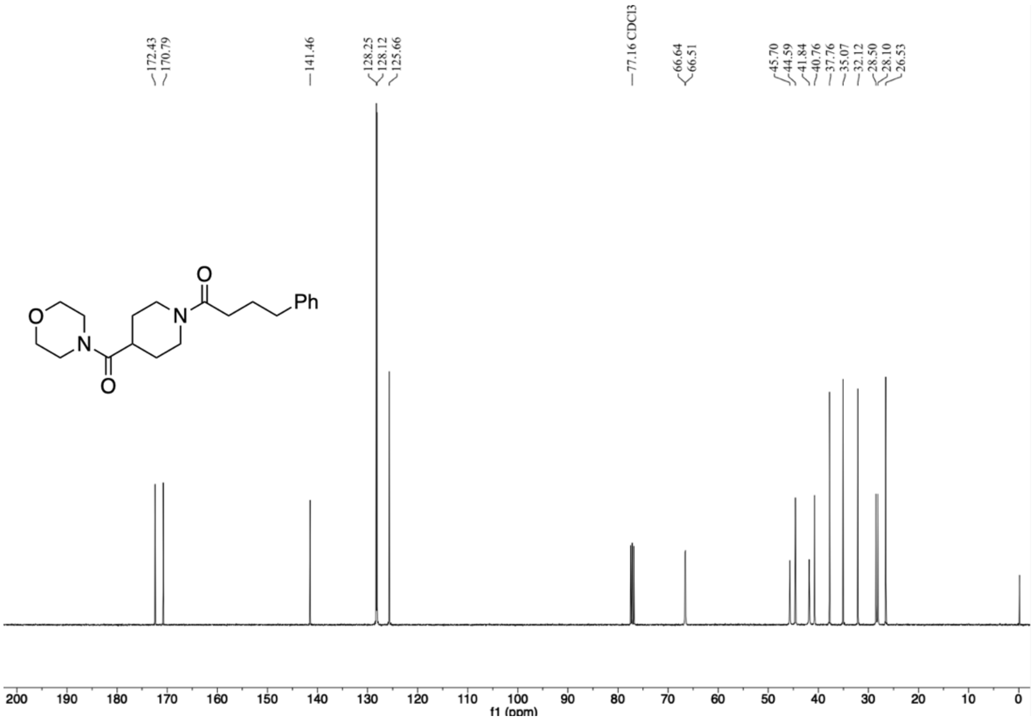
^{13}C NMR spectrum of **SI-7** (101 MHz, $CDCl_3$)



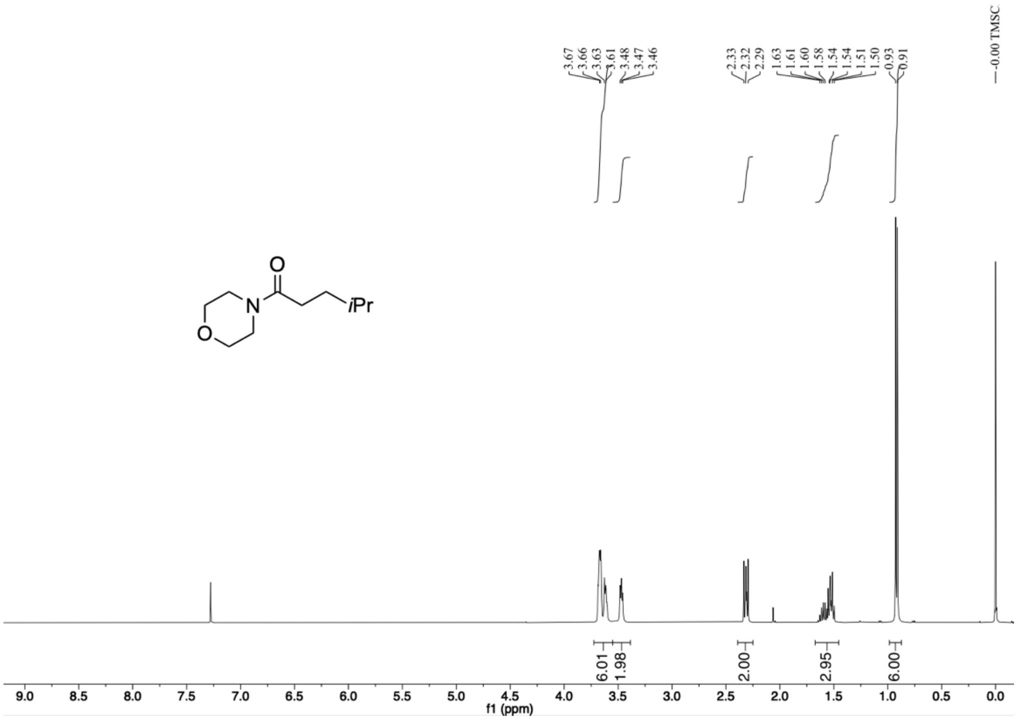
^{19}F NMR spectrum of **SI-7** (376 MHz, $CDCl_3$)



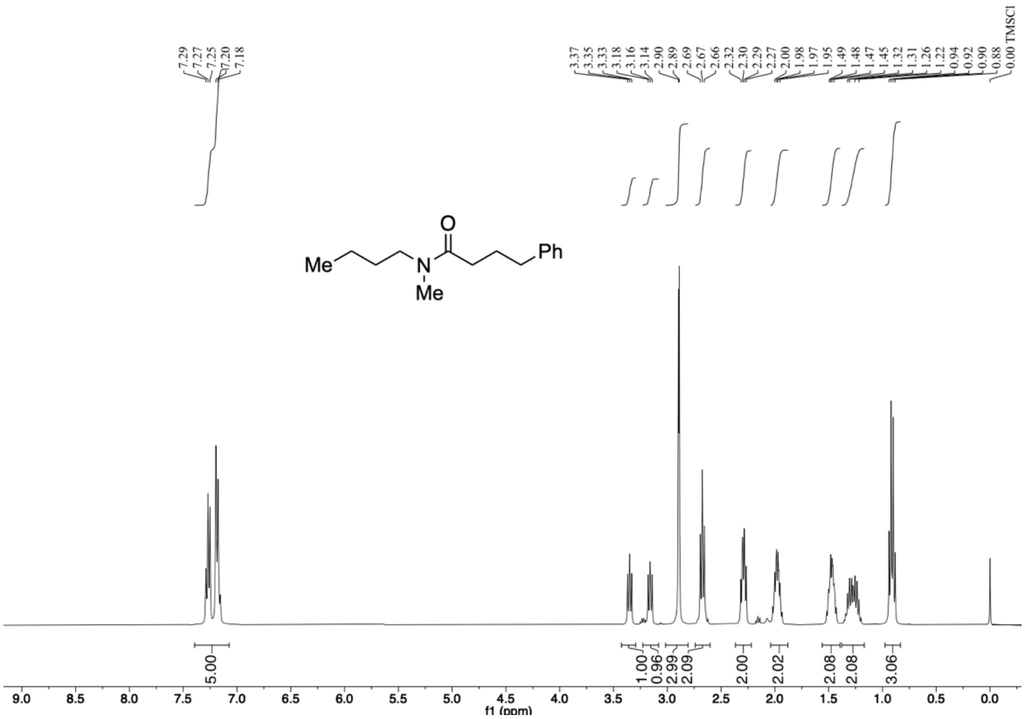
^{1}H NMR spectrum of **SI-8** (400 MHz, $CDCl_3$)



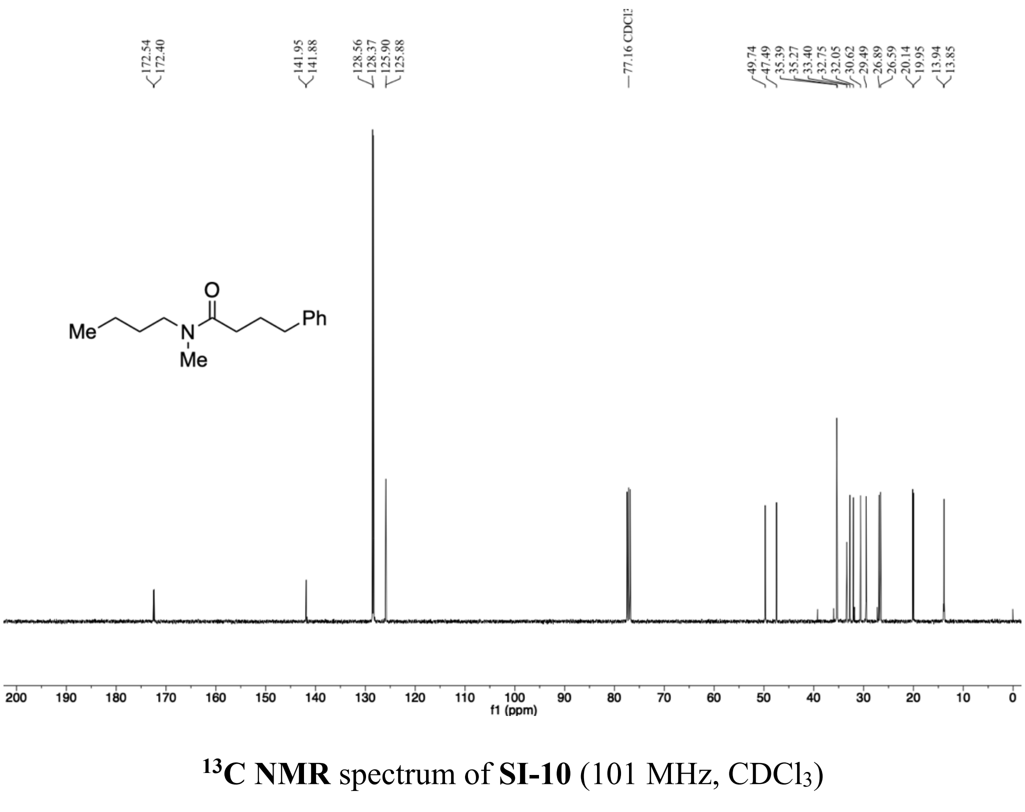
^{13}C NMR spectrum of **SI-8** (101 MHz, CDCl$_3$)



^{1}H NMR spectrum of **SI-9** (400 MHz, CDCl$_3$)



^{1}**H NMR** spectrum of **SI-10** (400 MHz, $CDCl_3$)



^{13}**C NMR** spectrum of **SI-10** (101 MHz, $CDCl_3$)