Supplementary Information

Phase-transfer Catalyzed Asymmetric Synthesis of α,β-Unsaturated γ,γ-Disubstituted γ-Lactams

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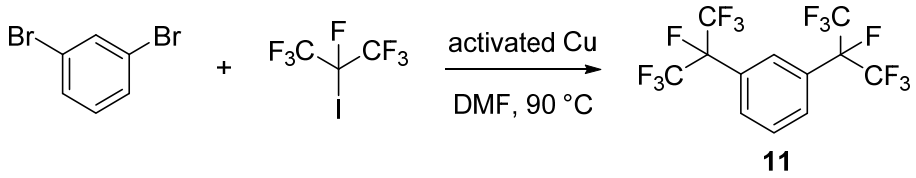
General information

Infrared (IR) spectra were recorded on a ThermoFischer Scientific NICOLET iS5 spectrometer. ^{1}H NMR spectra were measured on JEOL JNM-FX400 (400 MHz) and JNM-ECA500 (500 MHz) spectrometers. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard or from the residual solvent in in $CDCl_3$ or acetone-d_6, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on JEOL JNM-FX400 (100 MHz) and JNM-ECA500 (125 MHz) spectrometers with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments at 210 nm using 4.6 mm x 25 cm Daicel chiral columns. High-resolution mass spectra (HRMS) were performed on Thermo Scientific Exactive Plus Orbitrap LC-MS. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by flash column chromatography silica gel 60 (Merck, 230-400 mesh) or preparative thin layer chromatography silica gel (PLC 60 F_{254}. 0.5 mm).

In experiments requiring dry solvent, CH_2Cl_2, toluene and THF were purchased from Kanto Chemical Co. Inc. as “Dehydrated” and further purified by passing through neutral alumina under nitrogen atmosphere. Commercially obtained reagents were used as received.

Catalyst synthesis

1,3-bis(perfluoropropan-2-yl)benzene[1]

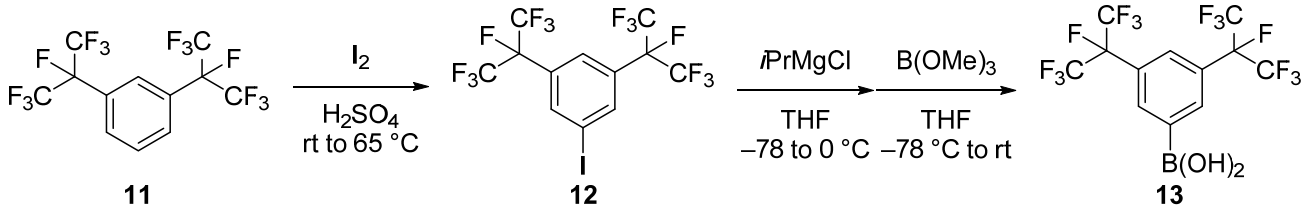


11

Activated copper: Zinc powder (4.3 g, 65.8 mmol) was added in portions to a vigorously stirred solution of $CuSO_4 \cdot 5\ H_2O$ (15.7 g, 62.9 mmol) in water (50 mL). After complete discoloration of the supernatant solution it was decanted and the red residue was stirred with HCl (1 M) until the remaining zinc had been completely oxidized. The precipitated copper was separated by filtration and washed successively with HCl (1 M), water, methanol, ethanol, acetone and Et_2O. The residue was dried in high vacuum to give activated copper (3.72 g, 93%) as a red powder.

Coupling reaction: A suspension of activated copper (12.9 g, 203 mmol) in dehydrated DMF (60 mL) was quickly degassed by evacuating and backfilling the reaction apparatus with argon (3x). To this suspension was added 1,3-dibromobenzene (3.83 mL, 31.7 mmol) and heptafluoro-2-iodopropane (11.7 mL, 82.2 mmol). The mixture was heated to 90 °C and stirred for 49 h. The suspension was filtered through a pad of Celite (washing with Et_2O), and water was added (250 mL). The mixture was extracted with Et_2O and washed successively with aqueous solutions of 1N HCl (100 mL) and NaCl (70 mL). The combined organic layers were dried with Na_2SO_4 and the solvent evaporated under reduced pressure. The obtained residue was purified by passing it through a short column packed with silica gel eluting with pure Et_2O. Removal of the solvent gave the coupling product **11** (11.5 g, 88%) as a red oil.

(3,5-bis(perfluoropropan-2-yl)phenyl)boronic acid[1]



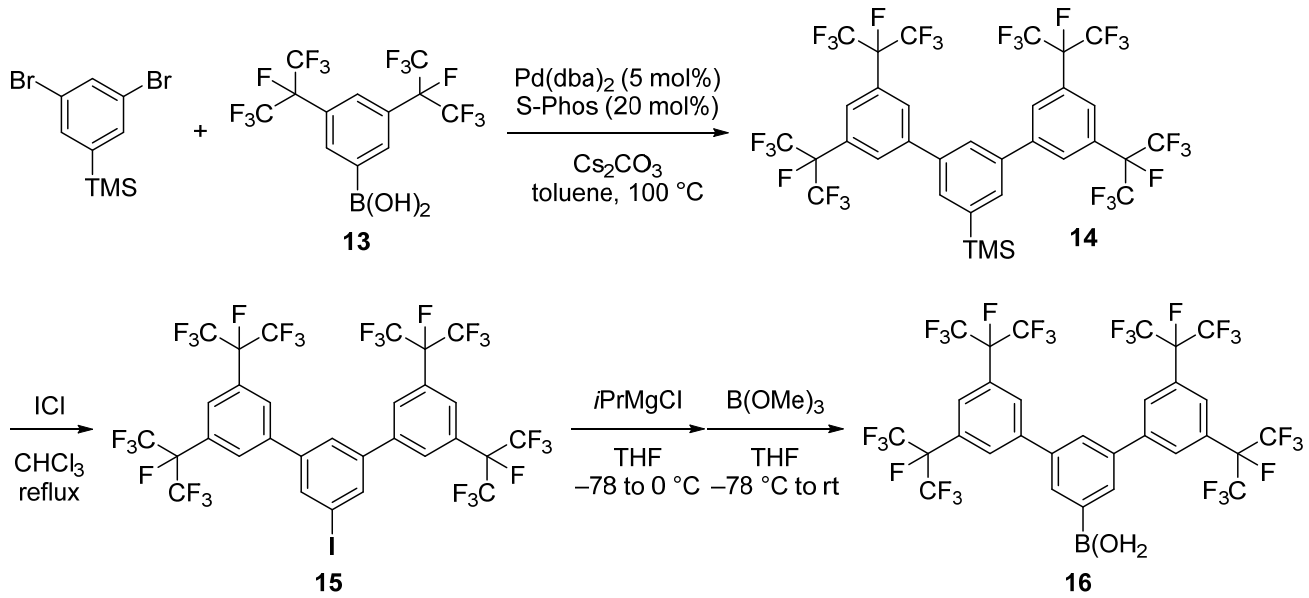
11 **12** **13**

To a mixture of oleum (30%, 36 mL), concentrated H_2SO_4 (17 mL) and iodine (1.94 g, 15.3 mmol) was added 1,3-bis(perfluoropropan-2-yl)benzene **11** (11.5 g, 27.8 mmol) within 1.5 h using a syringe pump. The mixture was stirred for 10 h at room temperature before raising the temperature to 65 °C. After 36 h the reaction mixture was added to crushed ice (200 mL) and extracted with Et_2O. The combined extracts were consecutively washed with a saturated solution of Na_2SO_3, a saturated solution of $NaHCO_3$, water, a saturated solution of NaCl and then dried with Na_2SO_4. The solvents were evaporated under reduced pressure and purified by filtration through a plug of silica eluting

with Et_2O. Removal of the solvent in vacuo gave a mixture (12.07 g) of the iodoarene **12** and the starting material **11** in a ratio of 1.6:1 as a brown oil.

A solution of the product mixture from the first step containing iodoarene **12** (68%, 8.16 g, 15.1 mmol) in THF (80 mL) at -78 °C was treated dropwise with a solution of *i*PrMgCl (2.0 M in THF, 9.5 mL, 19 mmol). After completion of the addition the dry ice bath was replaced by an ice bath and the solution stirred for 2 h 40 min at 0 °C. It was then recooled to -78 °C and a solution of $B(OMe)_3$ (2.3 mL, 21 mmol) in THF (90 mL) was added over 55 min using an addition funnel. The reaction mixture was stirred for 11 h during which time the reaction solution warmed to room temperature. 1N HCl (50 mL) was added and the mixture extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 100:0 to 50:50) to give the boronic acid **13** (5.34 g, 42% over two steps) and a 1:2.6 mixture (2.04 g) of **11** and **12**.

3,5-bis(3,5-bis(perfluoropropan-2-yl)phenyl)phenylboronic acid



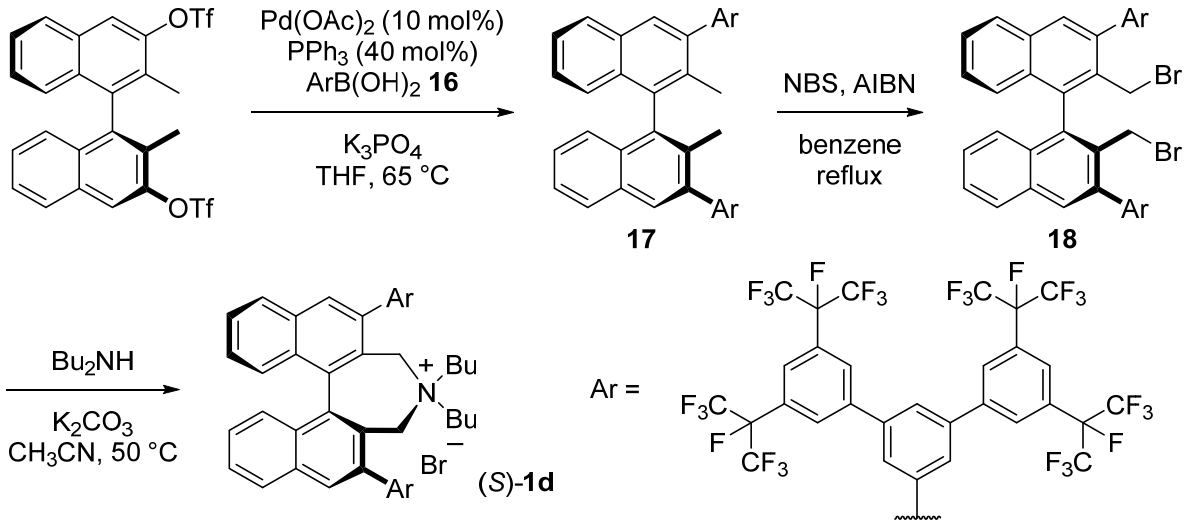
To a Schlenk flask were added boronic acid **13** (835 mg, 1.82 mmol), (3,5-dibromophenyl)trimethylsilane (234 mg, 760 µmol), Cs_2CO_3 (1.36 g, 4.17 mmol), $Pd(dba)_2$ (22.0 mg, 38.3 µmol) and S-Phos (62.3 mg, 152 µmol). The flask was evacuated and backfilled with argon. Degassed toluene (2.3 mL) was added and the septum replaced with a glass stopper. The reaction mixture was heated for 12 h at 100 °C, allowed to cool to room temperature and filtered over a pad of Celite (washing with Et_2O). The solvents were evaporated under reduced pressure and the residue purified by column chromatography on silica gel (eluting with pure hexane). The coupling product **14** (591 mg, 80%) was obtained as a white crystalline solid.

Compound **14** (488 mg, 501 µmol) was dissolved in $CHCl_3$ (10 mL) and a solution of ICl (510 mg, 3.14 mmol) in $CHCl_3$ (1 mL) was added. The reaction mixture was heated to reflux and stirred for 2

h before it was allowed to cool back to room temperature. A saturated solution of $Na_2S_2O_3$ was added and the mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and the solvents were evaporated under reduced pressure yielding the aryl iodide **15** (517 mg, quant.) as a white solid which was found to be pure by ^1H NMR spectroscopy.

A solution of the iodoarene **15** (417 mg, 406 µmol) in THF (5.8 mL) at -78 °C was treated dropwise with a solution of *i*PrMgCl (2.0 M in THF, 0.41 mL, 0.82 mmol). After completion of the addition the dry ice bath was replaced by an ice bath and the solution stirred for 3 h 40 min at 0 °C. This solution was then added dropwise to a solution of $B(OMe)_3$ (136 µL, 1.22 mmol) in THF (5.8 mL) at –40 °C using a syringe. The reaction mixture was stirred for 15 h during which time it was warmed to room temperature. 1N HCl was added and the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and the solvents removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 100:0 → 60:40) to yield the title compound **16** (300 mg, 78%) as a highly viscous oil.

Synthesis of catalyst (*S*)-1d



To a Schlenk flask were added the boronic acid **16** (300 mg, 317 µmol), (*S*)-(2,2'-dimethyl-[1,1'binaphthalene]-3,3'-diylbis(trifluoromethanesulfonate)[2] (76.4 mg, 132 µmol), $K_3PO_4 \cdot xH_2O$ (113 g, 395 µmol), $Pd(OAc)_2$ (3.0 mg, 13 µmol) and PPh_3 (15.2 mg, 58 µmol). The flask was evacuated and backfilled with argon. Degassed THF (1.4 mL) was added and the septum replaced with a glass stopper. The reaction mixture was heated for 15.5 h at 65 °C. After cooling to room temperature, a saturated solution of NH_4Cl was added and the suspension filtered over a pad of Celite (washing with Et_2O). The solvents were evaporated under reduced pressure and the residue purified by column chromatography on silica gel (eluting with hexane). This afforded the pure coupling product and some mixed fractions which were repurified by PLC (eluting with hexane). The coupling product **17** (152 mg, 55% combined yield) was obtained as a white solid.

To **17** (181 mg, 86.9 µmol) was added NBS (31 mg, 0.17 mmol), AIBN (1.4 mg, 8.5 µmol) and benzene (1.75 mL). The flask was equipped with a reflux condenser and the whole apparatus

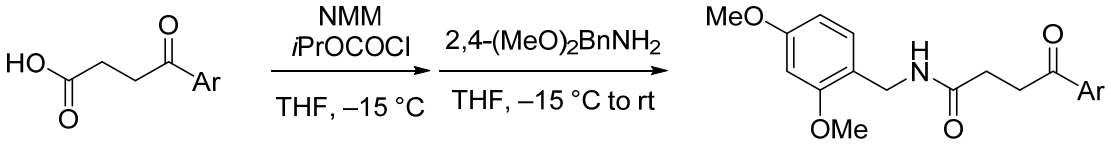
evacuated and backfilled with argon (3x). The reaction mixture was refluxed for 4 h, allowed to cool to room temperature and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with hexane) yield the dibromide **18** (179 mg, 92%) as a white solid.

To the dibromide **18** (179 mg, 79.8 µmol) were added K_2CO_3 (16.8 mg, 122 µmol), CH_3CN (3 mL), THF (2 mL) and di-*n*-butylamine (10.3 mg, 79.7 µmol). The mixture was heated to 50 °C for 19 h. After cooling to room temperature, the mixture was filtered and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 100:0 → 30:1 → 10:1) affording the pure ammonium salt (*S*)-**1d** and a mixed fraction which was repurified by PLC (CH_2Cl_2/MeOH, 10:1). The ammonium salt (*S*)-**1d** (136 mg, 74% combined yield) was obtained as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 2H), 8.12 (m, 10H), 7.98 (s, 2H), 7.92 (s, 2H), 7.84 (s, 2H), 7.81 (s, 2H), 7.69-7.72 (m, 4H), 7.46 (d, *J* = 3.7 Hz, 4H), 5.12 (d, *J* = 13.6 Hz, 2H), 3.98 (d, *J* = 13.6 Hz, 2H), 3.50 (t, *J* = 13.0 Hz, 2H), 2.85 (td, *J* = 13.0, 3.7 Hz, 2H), 1.02-0.67 (m, 8H), 0.47 (t, J = 7.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 141.8, 141.6, 141.0, 140.9, 138.8, 138.7, 134.0, 132.3, 131.3, 123.0, 129.5, 129.3, 129.1, 128.8, 128.6, 128.2, 128.1, 127.8, 127.3, 127.2, 126.9, 123.6, 122.8 (m), 120.4 (dq, $J_{C\text{-}F}$ = 27.6, 289 Hz), 91.2 (sd, $J_{C\text{-}F}$ = 34.8, 204 Hz), 58.2, 24.9, 19.6, 13.1; IR (neat) 1277, 1227, 1191, 1125 cm^{-1}; LRMS (ESI) exact mass calcd. for $C_{90}H_{50}F_{56}N$: *m/z* 2208.30 ($[M - Br]^+$), found: *m/z* 2208.31 ($[M - Br]^+$).

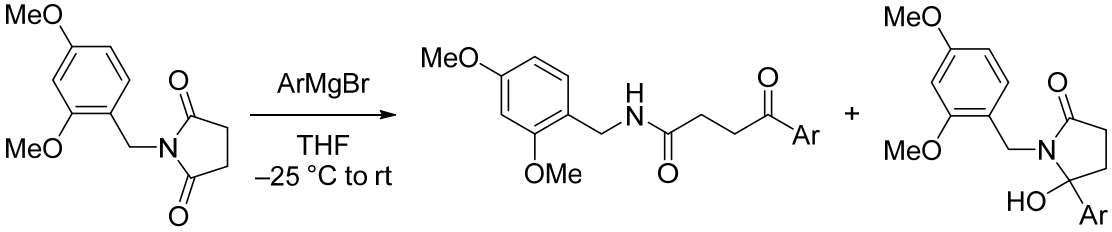
Preparation of substrates

Amide synthesis: General procedure A – via amide bond formation



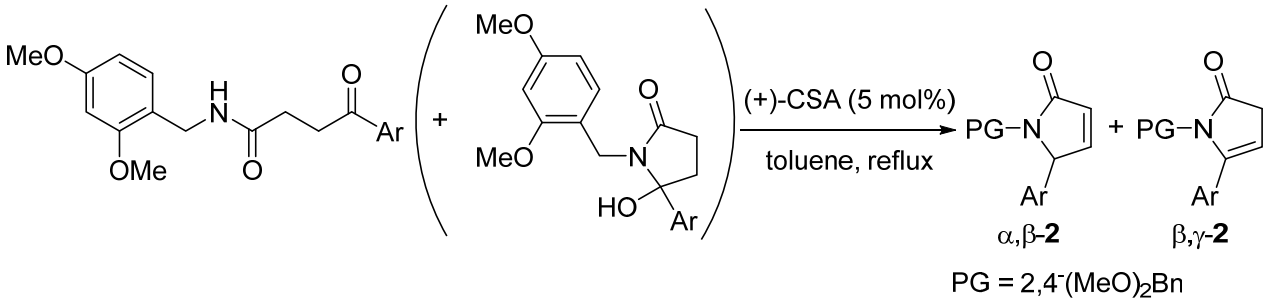
N-Methylmorpholine (1.1 eq) and isobutyl chloroformate (1.1 eq) were sequentially added to a solution of the ketoacid (1.0 eq) in THF (0.5 M) at -15 °C. The reaction mixture was stirred for 3 h at this temperature, 2,4-dimethoxybenzylamine (1.0 eq) was introduced and the flask was allowed to warm to room temperature. After completion of the reaction the suspension was filtered through a pad of Celite (washing with EtOAc) and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give the desired γ-ketoamide.

Amide synthesis: General procedure B – via addition of Grignard reagents to a succinimide[3]



The solution of a Grignard reagent (1.2 – 1.4 eq) was added to a solution of 1-(2,4-dimethoxybenzyl)pyrrolidine-2,5-dione (1.0 eq) in THF (0.3 mL) at -25 °C. The reaction mixture was stirred for 2 to 15 h during which time the ice bath was allowed to gradually warm up. Water was added and the mixture was extracted with EtOAc. The combined organic layers were dried with Na_2SO_4, evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give a mixture of the γ-ketoamide and the corresponding 5-hydroxypyrrolidinone. If the reaction mixture is acidified upon workup using HCl (1 mL) only the γ-ketoamides can be obtained (preferable).

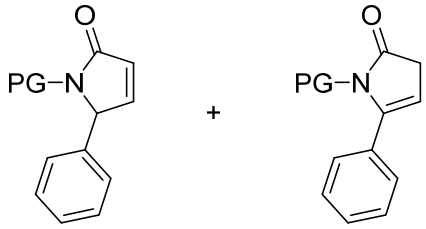
Preparation of unsaturated γ-lactams



To the γ-ketoamide (1.0 eq) was added (+)-camphorsulfonic acid ((+)-CSA) (0.05 eq) and toluene (0.01 M). The flask was equipped with a Dean-Stark apparatus and a reflux condenser. The solution

was purged with nitrogen for 20 min and then heated to reflux under an argon atmosphere. After the completion of the reaction triethylamine (1 eq) was added to the boiling solution and only thereafter it was allowed to cool to room temperature. The reaction mixture was washed with a saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified either by flash column chromatography or by preparative thin layer chromatography (PLC) on silica gel to give the desired unsaturated γ-lactams as a mixture of α,β-**2** and β,γ-**2**.

Compound 2d

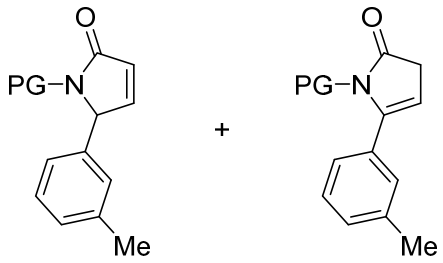


N-(2,4-Dimethoxybenzyl)-4-oxo-4-phenylbutanamide was prepared by the reaction of 3-benzoylpropionic acid (1.0 g, 5.6 mmol) and 2,4-dimethoxybenzylamine (0.84 mL, 5.6 mmol) in THF (12 mL) using *N*-methylmorpholine (0.68 mL, 6.2 mmol) and isobutyl chloroformate (0.81 mL, 6.2 mmol). The reaction mixture was stirred for 30 h at room temperature. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 60:40 → 30:70) to give the title compound as a white solid (1.69 g, 92%).

2d was prepared from this amide (150 mg, 458 μmol) using (+)-CSA (5.3 mg, 23 μmol) in toluene (46 mL). The solution was heated to reflux for 2 h and the acid quenched by the addition of NEt_3 (65 μL, 0.47 mmol). The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 50:50) to give the desired lactams as a yellow oil (113 mg, 80%, α,β-**2d**/β,γ-**2d** = 0.7:1).

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.42 – 7.13 (m, 8.5H), 7.11 (dd, J = 5.8, 1.9 Hz, xH), 7.02 (d, J = 8.3 Hz, 0.7H), 6.91 (d, J = 8.2 Hz, 0.7H), 6.49 (d, J = 2.4 Hz, 0.7H), 6.44 (dd, J = 8.3, 2.4 Hz, 1H), 6.43 – 6.38 (m, 2H), 6.13 (dd, J = 5.9, 1.8 Hz, 0.7H), 5.32 (t, J = 2.6 Hz, 1H), 5.08 (t, J = 1.9 Hz, 0.7H), 4.74 (d, J = 15.0 Hz, 0.7H), 4.57 (s, 2H), 3.86 (d, J = 15.0 Hz, 0.7H), 3.77 (s, 2.1H), 3.74 (s, 3H), 3.72 (s, 2.1H), 3.64 (s, 3H), 3.18 (d, J = 2.7 Hz, 2H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 178.4, 171.6, 161.5, 161.0, 159.2, 158.4, 149.6, 147.5, 136.8, 133.1, 131.3, 129.7, 129.4, 129.1(5), 129.0(5), 128.7, 128.6, 128.1, 126.4, 119.0, 105.3, 105.1, 102.6, 98.9, 98.7, 67.1, 55.6, 55.5, 39.4, 38.4, 37.4; IR (neat) 2938, 2836, 1674, 1613, 1507, 1454, 1291, 1208, 1157, 1126, 1035, 841, 760, 702 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{19}H_{20}NO_3$: *m/z* 310.1438 ($[M + H]^+$), found: *m/z* 310.1441 ($[M + H]^+$).

Compound 2e

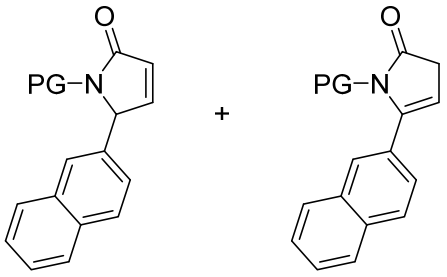


Preparation of N-(2,4-dimethoxybenzyl)-4-oxo-4-(m-tolyl)butanamide: The Grignard reagent was prepared from 3-methylphenyl bromide (0.42 mL, 3.4 mmol) dissolved in THF (3 mL) and Mg turnings (100 mg, 4.11 mmol) suspended in THF (1 mL). The solution of the Grignard reagent (5.2 mL, 3.0 mmol) was added to a solution of 1-(2,4-dimethoxybenzyl)pyrrolidine-2,5-dione (520 mg, 2.09 mmol) in THF (6 mL) and the reaction mixture was stirred for 15 h during which time it warmed to room temperature. Upon work up the reaction mixture was acidified using 1N HCl. The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 50:50 → 40:60) to give the title compound as a yellow solid (495 mg, 69%).

2e was prepared from this amide (145 mg, 425 μmol) using (+)-CSA (5.0 mg, 22 μmol) in toluene (42 mL). The solution was heated to reflux for 1 h 10 min and the acid quenched by the addition of NEt_3 (60 μL, 0.43 mmol). The crude material was purified by flash column chromatography on silica gel (hexane/EtOAc, 50:50) to give the desired lactams as a yellow oil (114 mg, 83%, α,β-**2e**/β,γ-**2e** = 0.7:1).

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.30 – 7.23 (m, 0.7H), 7.22 – 7.18 (m, 1H), 7.17 – 7.13 (m, 1.7H), 7.10 (dd, J = 5.8, 1.9 Hz, 0.7H), 7.07 – 7.00 (m, 2.7H), 6.97 – 6.93 (m, 1.4H), 6.90 (d, J = 8.3 Hz, 1H), 6.50 – 6.38 (m, 3.4 H), 6.12 (dd, J = 5.8, 1.8 Hz, 0.7H), 5.29 (t, J = 2.6 Hz, 1H), 5.04 (t, J = 1.9 Hz, 0.7H), 4.72 (d, J = 14.9 Hz, 0.7H), 4.60 – 4.56 (m, 2H), 3.88 (d, J = 15.0 Hz, 0.7H), 3.77 (s, 2.1H), 3.74 (s, 3H), 3.72 (s, 2.1H), 3.65 (s, 3H), 3.17 (d, J = 2.6 Hz, 2H), 2.32 (s, 2.1H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 178.4, 171.5, 161.4, 161.0, 159.1, 158.4, 149.7, 147.7, 139.3, 138.7, 136.7, 133.0, 131.2, 130.1, 129.7, 129.6, 129.3, 129.0, 128.8, 128.7, 126.4, 125.7, 125.3, 119.1, 119.0, 105.3, 105.1, 102.3, 98.9, 98.7, 67.1, 55.5(9), 55.5(5), 39.4, 38.4, 37.4, 21.4, 21.3; IR (neat) 2971, 2835, 1687, 1611, 1589, 1507, 1207, 1156, 1122, 1034, 790, 724, 702 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{22}NO_3$: *m/z* 324.1600 ($[M + H]^+$), found: *m/z* 324.1601 ($[M + H]^+$).

Compound 2f

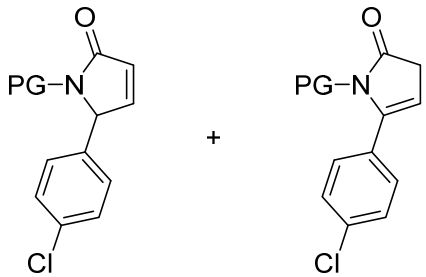


Preparation of N-(2,4-dimethoxybenzyl)-4-(naphthalen-2-yl)-4-oxobutanamide: The Grignard reagent was prepared from 2-bromonaphthalene (745 mg, 3.60 mmol) dissolved in THF (3 mL) and Mg turnings (105 mg, 4.32 mmol) suspended in THF (1 mL). The solution of the Grignard reagent (4.4 mL, 2.6 mmol) was added to a solution of 1-(2,4-dimethoxybenzyl)pyrrolidine-2,5-dione (505 mg, 2.03 mmol) in THF (6.5 mL) and the reaction mixture was stirred for 5 h during which time the temperature rose to 12 °C. The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 50:50 → 30:70) to give a mixture of the title compound and the corresponding 5-hydroxypyrrolidinone in a ratio of 1.35:1 as a white solid (621 mg, 81%).

2f was prepared from this amide (128 mg, 339 μmol) using (+)-CSA (4.2 mg, 18 μmol) in toluene (34 mL). The solution was heated to reflux for 2 h 15 min and the acid quenched by the addition of NEt_3 (50 μL, 0.36 mmol). The crude material was purified by PLC on silica gel (hexane/EtOAc, 40:60) to give the desired lactams as a yellow oil (63 mg, 52%, α,β-**2f**/β,γ-**2f** = 0.7:1).

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.96 – 7.88 (m, 3.4H), 7.85 (d, J = 8.4 Hz, 1H), 7.82 – 7.78 (m, 1.7H), 7.77 – 7.74 (m, 0.7H), 7.57 – 7.48 (m, 3.4H), 7.38 (dd, J = 8.5, 1.7 Hz, 1H), 7.26 – 7.14 (m, 1.4H), 7.08 – 7.03 (m, 0.7H), 6.97 (dt, J = 8.3, 0.9 Hz, 1H), 6.47 – 6.42 (m, 1.7H), 6.40 (dd, J = 8.4, 2.4 Hz, 1H), 6.37 (d, J = 2.4 Hz, 1H), 6.20 (dd, J = 5.9, 1.8 Hz, 0.7H), 5.44 (t, J = 2.6 Hz, 1H), 5.26 (t, J = 1.9 Hz, 0.7H), 4.76 (d, J = 15.0 Hz, 0.7H), 4.68 – 4.65 (m, 2H), 3.91 (d, J = 14.9 Hz, 0.7H), 3.75 (s, 2.1H), 3.72 (s, 3H), 3.67 (s, 2.1H), 3.47 (s, 3H), 3.24 (d, J = 2.7 Hz, 2H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 178.5, 171.6, 161.5, 161.1, 159.2, 158.3, 149.5, 147.5, 134.5, 134.3, 134.1, 134.0, 131.4, 130.5, 129.5, 129.0, 128.9(4), 128.7(5), 128.6(7), 128.6, 128.5, 128.0, 127.9, 127.4, 127.3, 127.2, 127.1, 126.8, 126.3, 125.1, 119.0(4), 118.9(7), 105.4, 105.2, 103.2, 98.9, 98.7, 67.2, 55.6, 55.5, 55.4, 39.5, 38.5, 37.5; IR (neat) 3337, 3003, 1683, 1614, 1507, 1291, 1209, 1036, 820, 751 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{22}NO_3$: *m/z* 360.1594 ($[M + H]^+$), found: *m/z* 360.1592 ($[M + H]^+$).

Compound 2g



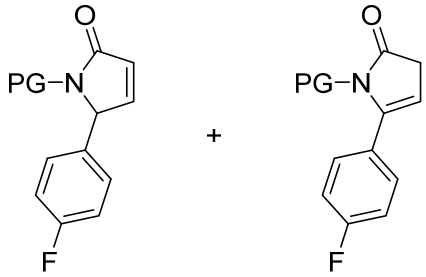
Preparation of 5-(4-chlorophenyl)-1-(2,4-dimethoxybenzyl)-5-hydroxypyrrolidin-2-one: The Grignard reagent was prepared from 4-bromochlorobenzene (1.95 g, 10.2 mmol) dissolved in THF (8 mL) and Mg turnings (296 mg, 12.2 mmol) suspended in THF (2 mL). The solution of the Grignard reagent (3.0 mL, 2.6 mmol) was added to a solution of 1-(2,4-dimethoxybenzyl)pyrrolidine-2,5-dione (527 mg, 2.1 mmol) in THF (10 mL) at -20 °C and the reaction mixture was stirred for 2 h during which time it warmed to 5 °C. Upon work up a

saturated solution of NH_4Cl was added. The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 40:60 to 20:80) to give only the corresponding 5-hydroxypyrrolidinone as a white solid (449 mg, 60%).

2g was prepared from this pyrrolidinone (100 mg, 276 μmol) using (+)-CSA (3.2 mg, 14 μmol) in toluene (28 mL). The solution was heated to reflux for 1.5 h and the acid quenched by the addition of NEt_3 (40 μL, 0.29 mmol). The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 60:40 to 40:60) to give the desired lactams as a purple oil (87 mg, 92%, α,β-**2g**/β,γ-**2g** = 0.7:1).

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.42 – 7.39 (m, 1.4H), 7.38 – 7.34 (m, 2H), 7.29 – 7.25 (m, 2H), 7.19 – 7.15 (m, 1.4H), 7.11 (dd, J = 5.8, 2.0 Hz, 0.7H), 7.03 (d, J = 8.3 Hz, 0.7H), 6.89 (d, J = 8.3 Hz, 1H), 6.47 (d, J = 2.4 Hz, 0.7H), 6.44 (dd, J = 8.3, 2.4 Hz, 0.7H), 6.41 (d, J = 2.4 Hz, 1H), 6.39 (dd, J = 8.3, 2.4 Hz, 1H), 6.14 (dd, J = 5.8, 1.8 Hz, 0.7H), 5.35 (t, J = 2.6 Hz, 1H), 5.10 (t, J = 1.9 Hz, 0.7H), 4.72 (d, J = 14.8 Hz, 0.7H), 4.60 – 4.56 (m, 2H), 3.89 (d, J = 14.9 Hz, 0.7H), 3.77 (s, 2.1H), 3.74 (s, 3H), 3.73 (s, 2.1H), 3.64 (s, 3H), 3.18 (d, J = 2.7 Hz, 2H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 178.3, 171.5, 161.5, 161.1, 159.2, 158.4, 149.3, 146.3, 135.9, 134.9, 134.2, 131.9, 131.5, 130.3, 129.9, 129.7, 129.3, 129.0, 126.7, 118.8, 118.7, 105.4, 105.2, 103.4, 98.9, 98.7, 66.3, 55.6(0), 55.5(7), 39.3, 38.4, 37.4; IR (neat) 3307, 2937, 1673, 1613, 1508, 1208, 1157, 1036, 829, 753 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{19}H_{19}ClNO_3$: *m/z* 344.1048 ($[M + H]^+$), found: *m/z* 344.1044 ($[M + H]^+$).

Compound 2h



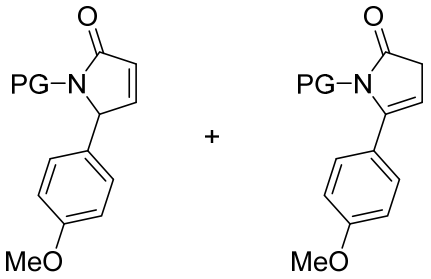
Preparation of N-(2,4-dimethoxybenzyl)-4-(4-fluorophenyl)-4-oxobutanamide: The Grignard reagent was prepared from 4-fluorophenyl bromide (0.40 mL, 3.6 mmol) dissolved in THF (3 mL) and Mg turnings (105 mg, 4.32 mmol) suspended in THF (1 mL). The solution of the Grignard reagent (4.35 mL, 2.6 mmol) was added to a solution of 1-(2,4-dimethoxybenzyl)pyrrolidine-2,5-dione (0.50 g, 2.0 mmol) in THF (6 mL) and the reaction mixture was stirred for 5 h during which time it warmed to 10 °C. The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 50:50 → 30:70) to give a mixture of the title compound and the corresponding 5-hydroxypyrrolidinone in a ratio of 3.7:1 as a white solid (561 mg, 81%).

2h was prepared from this amide (99 mg, 287 μmol) using (+)-CSA (3.4 mg, 15 μmol) in toluene (30 mL). The solution was heated to reflux for 2 h 5 min and the acid quenched by the addition of NEt_3 (40 μL, 0.29 mmol). The crude material was purified by flash column chromatography on silica gel

(hexane/EtOAc, 50:50) to give the desired lactams as a yellow oil (85 mg, 90%, α,β-**2h**/β,γ-**2h** = 0.8:1) containing about 4 mol% of remaining starting material.

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.33 – 7.06 (m, 8H), 7.03 (d, J = 8.3 Hz, 0.8H), 6.89 (d, J = 8.3 Hz, 1H), 6.50 – 6.37 (m, 3.6H), 6.14 (dd, J = 5.9, 1.8 Hz, 0.8H), 5.32 (t, J = 2.6 Hz, 1H), 5.10 (t, J = 1.9 Hz, 0.8H), 4.71 (d, J = 14.8 Hz, 0.8H), 4.59 – 4.55 (m, 2H), 3.87 (d, J = 14.9 Hz, 0.8H), 3.77 (s, 2.4H), 3.74 (s, 3H), 3.74 (s, 2.4H), 3.65 (s, 3H), 3.18 (d, J = 2.7 Hz, 2H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 178.3, 171.5, 163.7 (d, $J_{C\text{-}F}$ = 246 Hz), 163.4 (d, $J_{C\text{-}F}$ = 245 Hz), 161.5, 161.1, 159.2, 158.4, 149.5, 146.4, 132.9 (d, $J_{C\text{-}F}$ = 3 Hz), 131.5, 130.9 (d, $J_{C\text{-}F}$ = 8 Hz), 130.2 (d, $J_{C\text{-}F}$ = 8 Hz), 129.5 (d, $J_{C\text{-}F}$ = 3 Hz), 128.9, 126.6, 118.9, 118.8, 116.4 (d, $J_{C\text{-}F}$ = 22 Hz), 116.0 (d, $J_{C\text{-}F}$ = 22 Hz), 105.4, 105.2, 102.9, 98.9, 98.7, 66.3, 55.6, 55.5, 39.3, 38.3, 37.4; IR (neat) 2939, 1684, 1613, 1590, 1508, 1264, 1209, 1036, 835 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{19}H_{19}FNO_3$: *m/z* 328.1343 ([M + H]$^+$), found: *m/z* 328.1348 ([M + H]$^+$).

Compound 2i



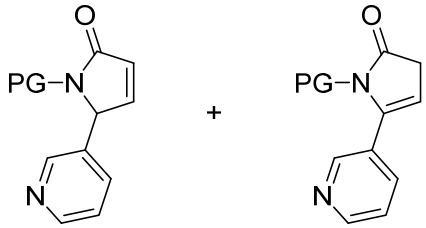
Preparation of N-(2,4-dimethoxybenzyl)-4-(4-methoxyphenyl)-4-oxobutanamide: The Grignard reagent was prepared from 4-methoxyphenyl bromide (0.43 mL, 3.4 mmol) dissolved in THF (3 mL) and Mg turnings (100 mg, 4.11 mmol) suspended in THF (1 mL). The solution of the Grignard reagent (5.0 mL, 2.8 mmol) was added to a solution of 1-(2,4-dimethoxybenzyl)pyrrolidine-2,5-dione (512 mg, 2.05 mmol) in THF (7 mL) and the reaction mixture was stirred for 4.5 h during which time it warmed to 10 °C. Upon work up the reaction mixture was acidified using HCl (1 M). The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 40:60 → 20:80) to give the title compound as a yellow solid (576 mg, 79%).

2i was prepared from this amide (156 mg, 436 μmol) using (+)-CSA (5.0 mg, 22 μmol) in toluene (44 mL). The solution was heated to reflux for 1.5 h and the acid quenched by the addition of NEt_3 (60 μL, 0.43 mmol). The crude material was purified by flash column chromatography on silica gel (hexane/EtOAc, 60:40 → 50:50) to give the desired lactams as a green oil (114 mg, 77%, α,β-**2i**/β,γ-**2i** = 0.7:1). Before concentration of the fractions obtained from column chromatography triethylamine (1 mL/100 mL solvent) was added.

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.24 – 7.14 (m, 2H), 7.11 – 7.04 (m, 2.1H), 7.01 (d, J = 8.3 Hz, 0.7H), 6.97 – 6.83 (m, 4.4H), 6.51 – 6.38 (m, 3.4H), 6.11 (dd, J = 5.9, 1.8 Hz, 0.7H), 5.24 (t, J = 2.7 Hz, 1H), 5.03 (t, J = 1.9 Hz, 0.7H), 4.70 (d, J = 14.9 Hz, 0.7H), 4.60 – 4.53 (m, 2H), 3.84 (d, J =

15.0 Hz, 0.7H), 3.81 (s, 2.1H), 3.79 (s, 3H), 3.77 (s, 2.1H), 3.75 (s, 5.1H), 3.68 (s, 3H), 3.16 (d, *J* = 2.7 Hz, 2H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 178.5, 171.6, 161.6, 161.2, 161.2, 160.9, 159.3, 158.5, 149.8, 147.5, 131.4, 130.2, 129.6, 128.7, 128.5, 126.5, 125.5, 119.3(2), 119.2(8), 115.2, 114.7, 105.5, 105.3, 101.7, 99.1, 98.9, 66.6, 55.7(0), 55.6(7), 55.6, 39.4, 38.3, 37.4; IR (neat) 3001, 1682, 1612, 1589, 1508, 1292, 1250, 1208, 1034, 832, 753 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{22}NO_4$: *m/z* 340.1543 ([M + H]$^+$), found: *m/z* 340.1548 ([M + H]$^+$).

Compound 2j

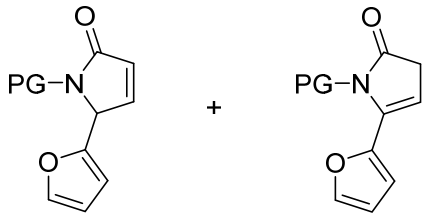


Preparation of N-(2,4-dimethoxybenzyl)-4-oxo-4-(pyridin-3-yl)butanamide: *n*-BuLi (1.56 M in hexanes, 1.54 mL, 2.40 mmol) was added to a solution of 3-bromopyridine (250 µL, 2.59 mmol) in Et_2O (6 mL) at -78 °C and the yellow suspension was stirred for 30 min before a solution of 1-(2,4-dimethoxybenzyl)pyrrolidine-2,5-dione (500 mg, 2.0 mmol) in THF (6 mL) and Et_2O (6 mL) was added. The reaction mixture was stirred for 19 h during which time it was allowed to reach room temperature. Water was added and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and the solvents evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 20/80 → CH_2Cl_2/MeOH, 20/1) to give a mixture of the γ-ketoamide and the corresponding 5-hydroxypyrrolidinone in a ratio of 2:1 as a slightly yellow oil (246 mg, 37%).

2j was prepared from this amide (103 mg, 314 µmol) using (+)-CSA (73 mg, 0.31 mmol, 1.0 eq) in toluene (31 mL). The solution was heated to reflux for 2 h and the acid quenched by the addition of NEt_3 (0.18 mL, 1.29 mmol, 4.1 eq). The crude material was purified by PLC on silica gel (CH_2Cl_2/MeOH, 20:1) to give the desired lactams as a yellow oil (43 mg, 44%, α,β-**2j**/β,γ-**2j** = 1:0.8).

^{1}H NMR (500 MHz, Acetone-d_6) δ 8.60 – 8.50 (m, 1.8H), 8.49 – 8.39 (m, 1.8H), 7.62 (dt, *J* = 7.9, 1.9, 0.8H), 7.46 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.39 – 7.30 (m, 1.8H), 7.17 (dd, *J* = 5.9, 2.0 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 0.8H), 6.48 – 6.42 (m, 2H), 6.41 – 6.37 (m, 1.6H), 6.18 (dd, *J* = 5.9, 1.8 Hz, 1H), 5.44 (t, *J* = 2.6 Hz, 0.8H), 5.15 (t, *J* = 1.9 Hz, 1H), 4.71 (d, *J* = 14.8 Hz, 1H), 4.62 – 4.57 (m, 1.6H), 3.92 (d, *J* = 14.8 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 2.4H), 3.72 (s, 3H), 3.61 (s, 2.4H), 3.22 (d, *J* = 2.7 Hz, 1.6H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 178.1, 171.5, 161.6, 161.2, 159.1, 158.4, 150.5(2), 150.4(9), 150.2, 149.4, 149.1, 144.4, 135.7, 135.2, 132.6, 131.7, 129.2, 129.0, 127.1, 124.6, 123.9, 118.7, 118.5, 105.5, 105.3, 104.4, 98.9, 98.8, 64.8, 55.6(0), 55.5(5), 39.2, 38.5, 37.5; IR (neat) 3398, 1683, 1612, 1508, 1292, 1209, 1159, 1030, 817, 685 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{18}H_{19}N_2O_3$: *m/z* 311.1390 ([M + H]$^+$), found: *m/z* 311.1397 ([M + H]$^+$).

Compound 2k

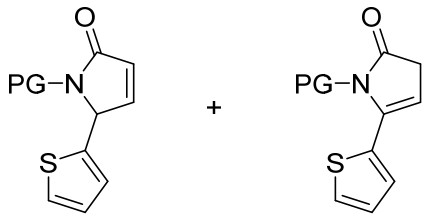


Preparation of N-(2,4-dimethoxybenzyl)-4-(furan-2-yl)-4-oxobutanamide: A solution of 2-furylmagnesium bromide (8.4 mL, 4.1 mmol) prepared according to the literature[4] was added to a solution of 1-(2,4-dimethoxybenzyl)pyrrolidine-2,5-dione (780 mg, 3.13 mmol) in THF (10 mL) at -25 °C. The reaction mixture was stirred 6 h during which time the ice bath gradually warmed to 10 °C. Water was added, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried with Na_2SO_4, evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give the title compound (877 mg, 88%).

2k was prepared from this amide (266 mg, 838 μmol) using (+)-CSA (10.4 mg, 45 μmol) in toluene (82 mL). The solution was heated to reflux for 2 h and the acid quenched by the addition of NEt_3 (0.12 mL, 0.86 mmol). The crude material was purified by flash column chromatography on silica gel (hexane/EtOAc, 50:50 + 1% v/v NEt_3) to give the desired lactams as a green oil (53 mg, 21%, α,β-**2k**/β,γ-**2k** = 0.1:1). Before concentration of solutions containing the product triethylamine (1 mL/100 mL solvent) was added. The NMR data was obtained using $CDCl_3$ that had been passed through a pipette filled with flame dried basic alumina directly before use to remove traces of acid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.36 (m, 1H), 6.88 (dt, *J* = 8.3, 0.9 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 6.36 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.31 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.24 (d, *J* = 3.5 Hz, 1H), 5.59 (t, *J* = 2.9 Hz, 1H), 4.88 – 4.85 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.28 (d, *J* = 2.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 160.0, 157.3, 145.1, 142.6, 136.8, 127.3, 117.8, 111.1, 108.4, 104.0, 101.2, 98.3, 55.3(0), 55.2(7), 39.6, 36.9; IR (neat) 2937, 1705, 1615, 1507, 1209, 1184, 1158, 1122, 1033, 743 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{17}H_{18}NO_4$: *m/z* 300.1230 ($[M + H]^+$), found: *m/z* 300.1222 ($[M + H]^+$).

Compound 2l



Preparation of N-(2,4-dimethoxybenzyl)-4-oxo-4-(thiophen-2-yl)butanamide:[5] Obtained by the reaction of 4-oxo-4-(thiophen-2-yl)butanoic acid containing succinic anhydride from its preparation (60% purity, 0.80 g, 2.6 mmol) and 2,4-dimethoxybenzylamine (0.39 mL, 2.6 mmol) in THF (5 mL)

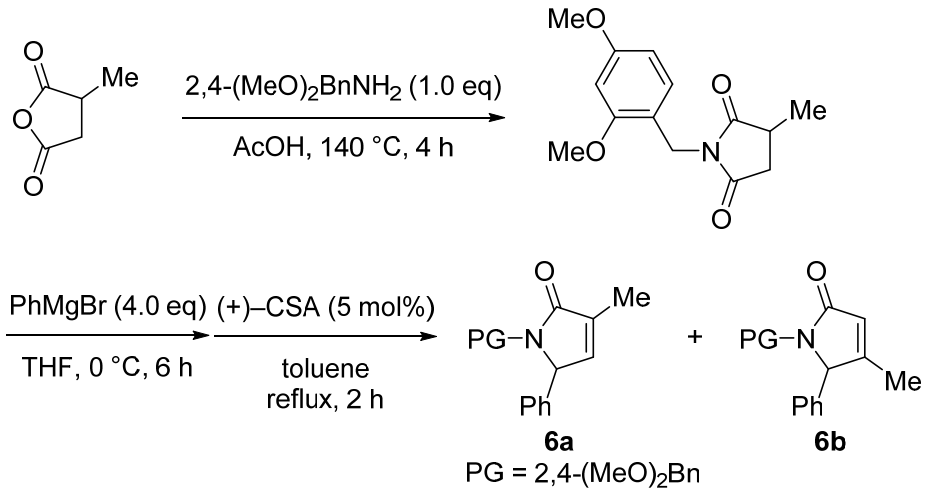
using *N*-methylmorpholine (0.31 mL, 2.8 mmol) and isobutyl chloroformate (0.37 mL, 2.8 mmol). The reaction mixture was stirred for 20 h at room temperature. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 40:60) to give the title compound as a slightly yellow solid (0.56 g, 65%).

2l was prepared from this amide (267 mg, 801 µmol) using (+)-CSA (9.3 mg, 40 µmol) in toluene (80 mL). The solution was heated to reflux for 3 h and the acid quenched by the addition of NEt_3 (0.11 mL, 0.79 mmol). The crude material was purified by flash column chromatography on silica gel (hexane/EtOAc, 60:40 + 1% v/v NEt_3) to give the desired lactams as a green oil (137 mg, 54%, α,β-**2l**/β,γ-**2l** = <0.05:1). Before concentration of solutions containing the product, triethylamine (1 mL/100 mL solvent) was added.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 5.2, 1.1 Hz, 1H), 6.90-6.94 (m, 2H), 6.87 (dd, *J* = 3.6, 1.0 Hz, 1H), 6.38-6.41 (m, 2H), 5.45 (t, *J* = 2.8 Hz, 1H), 4.75 (s, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.27 (d, *J* = 2.7 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.94, 159.99, 157.42, 139.74, 132.40, 127.40, 127.34, 126.55, 126.09, 117.95, 103.94, 103.41, 98.33, 55.32, 55.21, 39.32, 37.30; IR (neat) 2936, 1686, 1614, 1590, 1507, 1288, 1208, 1157, 1122, 1036, 752, 707 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{17}H_{18}NO_3S$: *m/z* 316.1007 ($[M + H]^+$), found: *m/z* 316.1002 ($[M + H]^+$).

Preparation of α- and/or β-substituted unsaturated γ-lactams

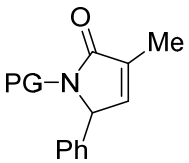
Compound 6a and 6b



Methylsuccinic anhydride (52.5 mg, 0.46 mmol)[6] and 2.4-dimethoxybenzylamine (0.69 mL, 4.6 mmol) were dissolved in AcOH (6 mL). After refluxing for 4 h, AcOH was removed in vacuo. Aqueous $NaHCO_3$ was poured into the residue, and the organic material was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give 1-(2,4-dimethoxybenzyl)-3-methylpyrrolidine-2,5-dione as white solid (1.30 g, 87%).

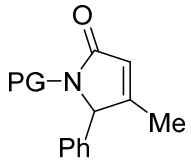
To a solution of PhMgBr (4.7 mmol in 3 mL THF) was added this pyrrolidinone-2,5-dione (670 mg, 2.06 mmol) in THF (10 mL) at 0 ˚C. After stirring for 6 h at rt, NH_4Cl was added to the solution. The organic layer was extracted with EtOAc, dried with Na_2SO_4 and evaporated under reduced pressure. This residue was dissolved in toluene (30 mL) and (+)-CSA (12 mg, 0.05 mmol) was added to this solution. After refluxing for 2 h, the reaction mixture was treated with aqueous $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (hexane/EtOAc = 1:1) to give **6a** as a white solid (88.7 mg, 29%) and **6b** as a white solid (120.1 mg, 39%).

Compound 6a



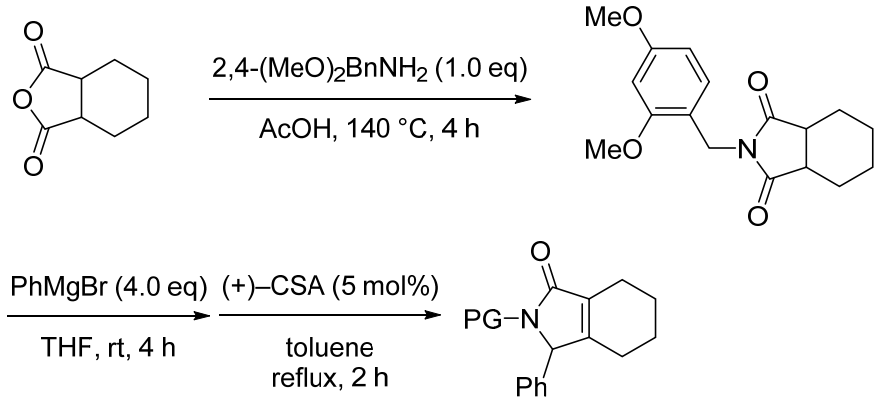
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 3H), 7.06 (m, 3H), 6.56 (s, 1H), 6.38 (m, 2H), 4.86 (d, *J* = 14.7 Hz, 1H), 4.82 (s, 1H), 3.90 (d, *J* = 15.0 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.2, 160.3, 158.3, 141.1, 136.1, 133.8, 131.1, 128.7, 128.1, 127.3, 118.2, 104.0, 98.3, 64.4, 55.3, 55.1, 38.4, 11.1; IR (neat) 1682, 1611, 1588, 1507, 1455, 1438, 1404, 1290, 1263, 1208, 1157, 1119, 1034, 700 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{21}NNaO_3$: *m/z* 346.1414 ($[M + Na]^+$), found: *m/z* 346.1411 ($[M + Na]^+$).

Compound 6b



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 3H), 7.05 (m, 3H), 6.39 (m, 2H), 5.90 (s, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.66 (s, 1H), 3.80 (d, *J* = 17.2 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.7, 160.3, 159.1, 158.3, 135.7, 131.0, 128.7, 128.3, 127.4, 121.7, 118.2, 104.1, 98.3, 69.0, 55.3, 55.1, 38.1, 14.2; IR (neat) 1682, 1611, 1588, 1507, 1455, 1438, 1402, 1293, 1264, 1208, 1157, 1130, 1034, 701, 636 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{22}NO_3$: *m/z* 324.1594 ($[M + H]^+$), found: *m/z* 324.1578 ($[M + H]^+$).

Compound 6c



6c

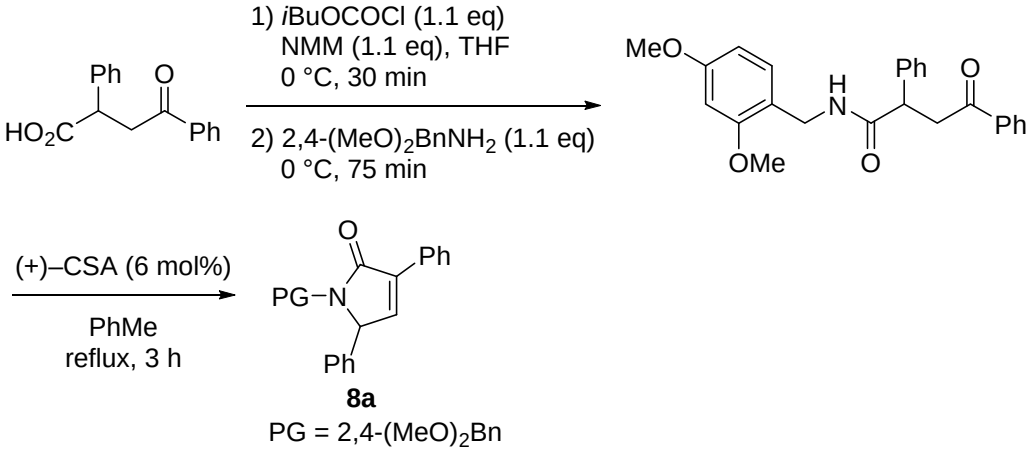
PG = 2,4-$(MeO)_2$Bn

Cyclocyclohexane-1,2-dicarboxylic acid anhydride (200 mg, 1.3 mmol) and 2.4-dimethoxybenzylamine (0.20 ml, 1.3 mmol) were dissolved in AcOH (0.7 ml). After refluxing for 4 h, AcOH was removed in vacuo. Aqueous $NaHCO_3$ was poured into the residue, and the organic material was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give 2-(2,4-dimethoxybenzyl)hexahydro-1H-isoindole-1,3(2H)-dione as a white solid (383 mg, 98%).

To a solution of PhMgBr (5.8 mmol in 12 mL THF) was added this imide (878 mg, 2.9 mmol) in THF (13 mL) at 0 ˚C. After stirring for 4 h at rt, NH_4Cl was added to the solution. The organic layer was extracted with EtOAc, dried with Na_2SO_4 and evaporated under reduced pressure. This residue was dissolved in toluene (70 mL) and (+)-CSA (45.0 mg, 0.145 mmol) was added to this solution. After refluxing for 2 h, the reaction mixture was treated with aqueous $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (hexane/EtOAc = 1:1) to give **6c** as a clear oil (832 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 3H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.04 (dd, *J* = 7.7, 1.5 Hz, 2H), 6.42-6.36 (m, 2H), 4.87 (d, *J* = 15.0 Hz, 1H), 4.65 (s, 1H), 3.88 (d, *J* = 14.7 Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 2.29 (m, 2H), 2.04 (m, 1H), 1.72 (m 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.0, 160.3, 158.3, 154.4, 136.5, 131.2, 130.7, 128.7, 128.0, 127.4, 118.7, 104.2, 98.3, 66.9, 55.3, 55.1, 37.9, 23.0, 22.2, 21.9, 20.3; IR (neat) 1675, 1611, 1588, 1507, 1455, 1436, 1410, 1293, 1264, 1208, 1157, 1143, 1115, 1034, 701 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{25}NNaO_3$: *m/z* 386.1727 ([M + Na]$^+$), found: *m/z* 386.1733 ([M + Na]$^+$).

Compound 8a[7]



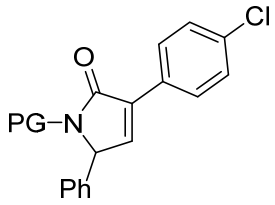
8a

PG = 2,4-$(MeO)_2$Bn

N-Methylmorpholine (31.9 μL, 0.29 mmol) and isobutyl chloroformate (37.7 μL, 0.29 mmol) were added to a solution of 4-oxo-2,4-diphenylbutanoic acid (66.1 mg, 0.26 mmol) in THF (0.78 mL) at 0 ˚C under argon atmosphere. After stirring for 30 min at 0 ˚C, 2,4-dimethoxybenzylamine (43.7 μL, 0.29 mmol) was introduced. The reaction mixture was stirred for 75 min and then poured into 1N HCl. The organic layer was extracted with EtOAc, dried over Na_2SO_4 and evaporated under reduced pressure. This residue was dissolved in toluene (9.0 mL) and (+)-CSA (2.9 mg, 13 μg) was added to this solution. The mixture was heated to reflux for 3 h. The crude material was purified by column chromatography on silica gel (hexane/EtOAc/CH_2Cl_2, 10:1:10) to give **8a** as a white solid (87.5 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.2, 1.2, 2H), 7.41-7.31 (m, 6H), 7.16-7.09 (m, 4H), 6.41 (m, 2H), 6.38 (m, 2H), 4.99 (d, *J* = 2.0, 1H), 4.97 (d, *J* = 15.2 Hz, 1H), 3.96 (d, *J* = 15.2 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.1, 160.4, 158.3, 140.8, 135.7, 134.9, 131.6, 131.3, 128.8, 128.5, 128.3, 127.4, 127.1, 118.0, 104.1, 98.3, 63.9, 55.3, 55.1, 38.5; IR (neat) 1683, 1611, 1588, 1507, 1456, 1399, 1290, 1208, 1156, 1125, 1034, 791, 697 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{25}H_{23}NNaO_3$: *m/z* 408.1570 ([M + Na]$^+$), found: *m/z* 408.1582 ([M + Na]$^+$).

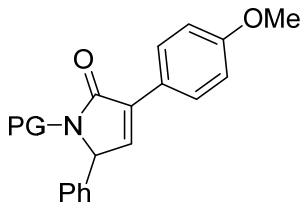
Compound 8b



N-Methylmorpholine (0.22 mL, 2.0 mmol) and isobutyl chloroformate (0.29 mL, 2.2 mmol) were added to a solution of 2-(4-chlorophenyl)-4-oxo-4-phenylbutanoic acid (0.56 g, 2.0 mmol) in THF (10 mL) at 0 ˚C under argon atmosphere. After stirring for 30 min at 0 ˚C, 2,4-dimethoxybenzylamine (0.34 mL, 2.2 mmol) was introduced. The reaction mixture was stirred for 2.5 h and then poured into 1N HCl. The organic layer was extracted with EtOAc, dried over Na_2SO_4 and evaporated under reduced pressure. This residue was dissolved in toluene (40 mL) and (+)-CSA (23 mg, 0.1 mmol) was added to this solution. The mixture was heated to reflux for 4 h. The crude material was purified by column chromatography on silica gel (hexane/EtOAc/CH_2Cl_2 = 10:1:10 then hexane/EtOAc = 3:1) and recrystallization (from hexane and CH_2Cl_2) to give **8b** as a white solid (0.39 g, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.35 (m, 5H), 7.13 (m, 4H), 6.41 (dd, *J* = 10.3 Hz, 2.3 Hz, 1H), 6.40 (s, 1H), 4.99 (d, *J* = 1.9, 1H), 4.95 (d, *J* = 14.7 Hz, 1H), 3.96 (d, *J* = 14.7 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 169.8, 160.5, 158.3, 141.1, 135.4, 134.5, 133.8, 131.4, 130.1, 128.9, 128.6, 128.5, 117.9, 104.1, 98.3, 63.9, 55.4, 55.1, 38.7; IR (neat) 1682, 1612, 1589, 1507, 1490, 1455, 1399, 1289, 1208, 1157, 1125, 1092, 1035, 834, 758, 730, 699 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{25}H_{22}ClNNaO_3$: *m/z* 442.1180 ($[M + Na]^+$), found: *m/z* 442.1187 ($[M + Na]^+$).

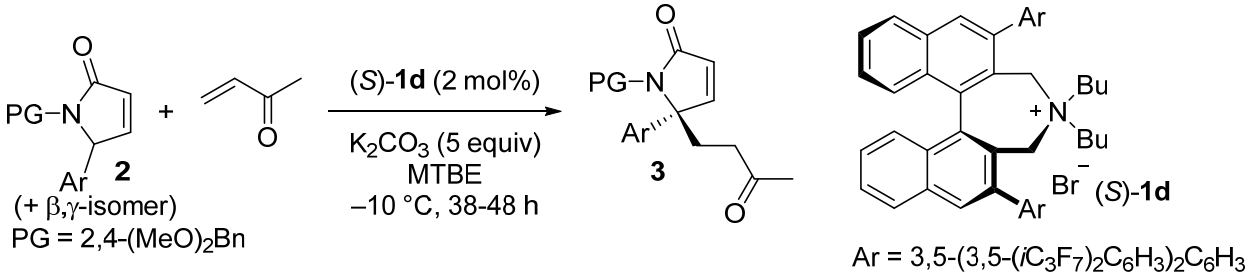
Compound 8c



N-Methylmorpholine (0.22 mL, 2.0 mmol) and isobutyl chloroformate (0.29 mL, 2.2 mmol) were added to a solution of 2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoic acid (0.57 g, 2.0 mmol) in THF (10 mL) at 0 ˚C under argon atmosphere. After stirring for 30 min at 0 ˚C, 2,4-dimethoxybenzylamine (0.34 mL, 2.2 mmol) was introduced. The reaction mixture was stirred for 4 h and then poured into 1N HCl. The organic layer was extracted with EtOAc, dried over Na_2SO_4 and evaporated under reduced pressure. This residue was dissolved in toluene (40 mL) and (+)-CSA (23 mg, 0.1 mmol) was added to this solution. The mixture was heated to reflux for 4 h. The crude material was purified by column chromatography on silica gel (hexane/EtOAc/CH_2Cl_2, 10:1:10) to give **8c** as a brown solid (0.30 g, 34%).

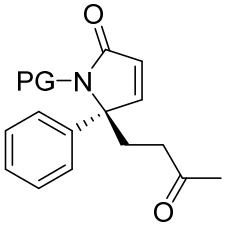
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.9 Hz, 2H), 7.34 (m, 3H), 7.13 (d, *J* = 7.6 Hz, 3H), 7.00 (d, *J* = 2.2 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.40 (dd, *J* = 10.3 Hz, 2.3 Hz, 1H), 6.39 (s, 1H), 4.96 (d, *J* = 2.2, 1H), 4.95 (d, *J* = 14.7 Hz, 1H), 3.95 (d, *J* = 15.0 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.4, 160.4, 159.8, 158.3, 138.8, 136.0, 134.2, 131.3, 128.8, 128.4, 128.3, 127.4, 124.3, 118.1, 113.8, 104.0, 98.3, 63.8, 55.3, 55.2, 55.1, 38.5; IR (neat) 1675, 1609, 1589, 1508, 1455, 1400, 1291, 1251, 1208, 1178, 1157, 1125, 1032, 835, 732, 700 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{26}H_{25}ClNNaO_4$: *m/z* 438.1676 ($[M + Na]^+$), found: *m/z* 438.1682 ($[M + Na]^+$).

Substrate scope (Table 2)



The mixture of unsaturated γ-lactams **2** was dissolved in methyl *tert*-butyl ether (MTBE) to give a stock solution with a concentration of 100 μmol/mL. An aliquot of this solution (1.0 eq) was transferred to a Schlenk tube and the solvent removed under reduced pressure. Catalyst (*S*)-**1d** (2 mol%) was added to the residue, and the flask was evacuated and backfilled with argon. Freshly degassed MTBE (0.1 M) was added through a septum followed by the introduction of the Michael acceptor (2.0 eq). The solution was cooled down to the reaction temperature, the argon inlet closed, the septum removed and finely powdered K_2CO_3 (5.0 eq) was added. After the addition the argon inlet was reopened, the flask purged with argon and then sealed with a greased glass stopper. The reaction mixture was stirred until the complete disappearance of the starting material as confirmed by TLC analysis and mass spectrometry. A saturated aqueous solution of NaCl and water were added and the mixture extracted with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified either by flash column chromatography or by preparative thin layer chromatography (PLC) on silica gel to give **3**.

Compound 3d



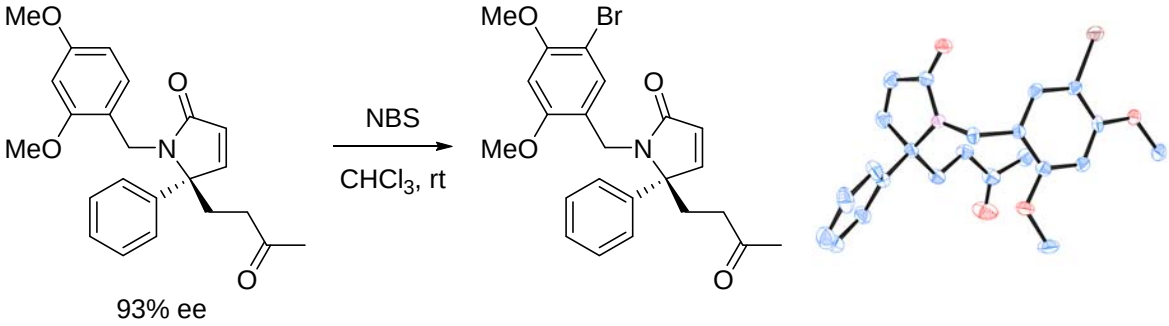
Prepared by the reaction of **2d** (0.10 mmol) with methyl vinyl ketone (16.2 μL, 0.20 mmol) using catalyst (*S*)-**1d** (4.6 mg, 2.0 μmol) and K_2CO_3 (69 mg, 0.50 mmol) in degassed MTBE (1.0 mL). The reaction mixture was stirred for 48 h at -10 °C. The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 40:60 → 20:80) to give **3d** as a colorless oil (33.4 mg, 88%, 93% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.24 (m, 3H), 7.23 – 7.17 (m, 2H), 6.75 (d, *J* = 5.8 Hz, 1H), 6.39 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.22 (d, *J* = 2.4 Hz, 1H), 6.22 (d, *J* = 5.8 Hz, 1H), 4.58 (d, *J* = 14.8 Hz, 1H), 3.99 (d, *J* = 14.8 Hz, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 2.46 (ddd, *J* = 14.2, 9.6, 6.0 Hz, 1H), 2.37 (ddd, *J* = 14.2, 9.5, 4.8 Hz, 1H), 1.99 (ddd, *J* = 18.6, 9.6, 6.0 Hz, 1H), 1.86 (s, 3H), 1.84 (ddd, *J* = 18.4, 9.5, 4.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 172.0, 160.3, 157.7, 152.6, 137.1, 132.5, 128.5, 128.0, 126.4, 125.4, 118.0, 104.5, 97.8, 72.0, 55.3, 54.9,

36.9, 36.1, 29.8, 24.7; IR (neat) 1714, 1683, 1611, 1508, 1291, 1266, 1209, 1159, 1129, 1033 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{26}NO_4$: *m/z* 380.1856 ($[M + H]^+$), found: *m/z* 380.1870 ($[M + H]^+$); $[\alpha]_D^{25}$ = +84.6 (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IB-3, hexane/ethanol = 5:1, flow rate = 0.65 mL/min, retention time: 11.7 min (major) and 16.7 min (minor)).

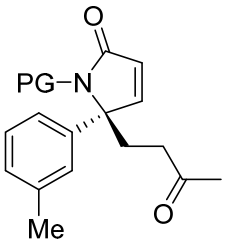
Determination of the absolute configuration of 3d



A solution of compound **3d** (16.4 mg, 43.2 µmol) in $CHCl_3$ (0.5 mL) was added to NBS (7.6 mg, 43 µmol). The solution was stirred for 4 h at room temperature and loaded directly onto a PLC plate (eluted with hexane/EtOAc, 20:80). The obtained product was contaminated with succinimide and was therefore dissolved in CH_2Cl_2. The solution was washed with an aqueous solution of NaOH (15%, 3x), dried with Na_2SO_4, filtered and evaporated under reduced pressure to afford the brominated compound (8.1 mg, 41%) as a white crystalline solid. Crystals suitable for an x-ray analysis were obtained by layering a solution of the product in CH_2Cl_2 with hexane. The x-ray analysis revealed the absolute configuration of the product to be (*R*).

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1531626). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html.

Compound 3e

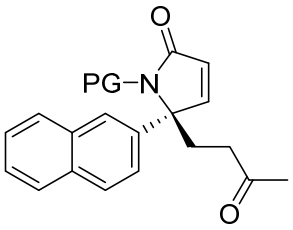


Prepared by the reaction of **2e** (0.10 mmol) with methyl vinyl ketone (16.2 µL, 0.20 mmol) using catalyst (*S*)-**1d** (4.6 mg, 2.0 µmol) and K_2CO_3 (69 mg, 0.50 mmol) in degassed MTBE (1.0 mL). The reaction mixture was stirred for 47 h at -10 °C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 20:80) to give **3e** as a colorless oil (32.7 mg, 83%, 93% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.08 – 7.05 (m, 1H), 7.05 – 7.01 (m, 1H), 6.95 – 6.92 (m, 1H), 6.73 (d, *J* = 5.8 Hz, 1H), 6.39 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.24 – 6.18 (m, 2H), 4.55 (d, *J* = 14.8 Hz, 1H), 4.03 (d, *J* = 14.8 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.44 (ddd, *J* = 14.1, 9.6, 6.0 Hz, 1H), 2.37 (ddd, *J* = 14.2, 9.5, 4.9 Hz, 1H), 2.28 (s, 3H), 1.99 (ddd, *J* = 18.5, 9.6, 6.0 Hz, 1H), 1.87 (s, 3H), 1.85 (ddd, *J* = 18.5, 9.5, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 172.0, 160.3, 157.7, 152.7, 138.2, 136.9, 132.4, 128.7, 128.3, 127.1, 125.3, 123.3, 118.1, 104.4, 97.7, 72.0, 55.3, 54.9, 36.9, 36.0, 29.8, 24.7, 21.4; IR (neat) 1714, 1682, 1610, 1508, 1389, 1291, 1266, 1209, 1158, 1034 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{28}NO_4$: *m/z* 394.2013 ($[M + H]^+$), found: *m/z* 394.2024 ($[M + H]^+$); $[\alpha]_D^{27}$ = +103.1 (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IB-3, hexane/ethanol = 5:1, flow rate = 0.65 mL/min, retention time: 10.6 min (major) and 16.2 min (minor)).

Compound 3f

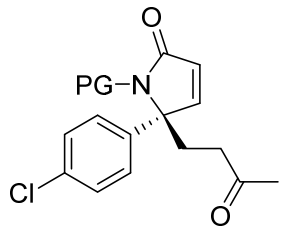


Prepared by the reaction of **2f** (0.10 mmol) with methyl vinyl ketone (16.2 μL, 0.20 mmol) using catalyst (*S*)-**1d** (4.6 mg, 2.0 μmol) and K_2CO_3 (69 mg, 0.50 mmol) in degassed MTBE (1.0 mL). The reaction mixture was stirred for 38 h at -10 °C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 20:80) to give **3f** as a colorless oil (36.0 mg, 84%, 94% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.75 (m, 3H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.04 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.79 (d, *J* = 5.8 Hz, 1H), 6.36 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.29 (d, *J* = 5.8 Hz, 1H), 6.08 (d, *J* = 2.4 Hz, 1H), 4.56 (d, *J* = 14.8 Hz, 1H), 4.05 (d, *J* = 14.8 Hz, 1H), 3.69 (s, 3H), 3.56 (s, 3H), 2.61 (ddd, *J* = 13.9, 9.6, 5.9 Hz, 1H), 2.53 (ddd, *J* = 14.1, 9.6, 4.9 Hz, 1H), 2.07 (ddd, *J* = 18.6, 9.6, 5.9 Hz, 1H), 1.93 (ddd, *J* = 18.3, 9.6, 4.9 Hz, 1H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 207.6, 172.0, 160.3, 157.6, 152.4, 134.4, 133.2, 132.8, 132.5, 128.0(7), 128.0(6), 127.4, 126.5, 126.3, 125.9, 125.7, 124.0, 117.9, 104.6, 97.5, 72.0, 55.3, 54.9, 37.0, 36.1, 29.8, 24.7; IR (neat) 1714, 1682, 1611, 1508, 1389, 1290, 1209, 1159, 1127 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{27}H_{28}NO_4$: *m/z* 430.2013 ($[M + H]^+$), found: *m/z* 430.2029 ($[M + H]^+$); $[\alpha]_D^{31}$ = +165.8 (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IB-3, hexane/ethanol = 5:1, flow rate = 0.65 mL/min, retention time: 12.7 min (major) and 18.2 min (minor)).

Compound 3g

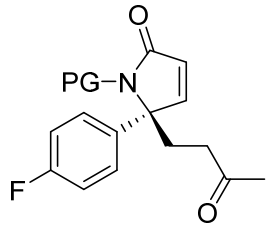


Prepared by the reaction of **3g** (0.10 mmol) with methyl vinyl ketone (16.2 μL, 0.20 mmol) using catalyst (*S*)-**1d** (4.6 mg, 2.0 μmol) and K_2CO_3 (69 mg, 0.50 mmol) in degassed MTBE (1.0 mL). The reaction mixture was stirred for 39 h at -10 °C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 20:80) to give **3g** as a colorless oil (35.7 mg, 86%, 94% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.12 – 7.07 (m, 2H), 6.71 (d, *J* = 5.9 Hz, 1H), 6.39 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.23 (d, *J* = 5.8 Hz, 1H), 6.20 (d, *J* = 2.4 Hz, 1H), 4.50 (d, *J* = 14.8 Hz, 1H), 4.06 (d, *J* = 14.9 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.43 (ddd, *J* = 14.2, 9.3, 6.2 Hz, 1H), 2.37 (ddd, *J* = 14.3, 9.3, 5.2 Hz, 1H), 1.99 (ddd, *J* = 18.5, 9.2, 6.2 Hz, 1H), 1.89 (s, 3H), 1.86 (ddd, *J* = 18.5, 9.1, 5.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 171.7, 160.4, 157.6, 152.2, 135.7, 133.8, 132.4, 128.5, 127.8, 125.7, 117.7, 104.7, 97.6, 71.3, 55.3, 54.9, 36.8, 35.9, 29.8, 24.6; IR (neat) 1714, 1683, 1611, 1508, 1388, 1291, 1265, 1209, 1158, 1129, 1034, 825 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{25}ClNO_4$: *m/z* 414.1467 ($[M + H]^+$), found: *m/z* 414.1470 ($[M + H]^+$); $[\alpha]_D^{31}$ = +128.2 (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IB-3, hexane/ethanol = 5:1, flow rate = 0.65 mL/min, retention time: 12.5 min (major) and 17.9 min (minor)).

Compound 3h



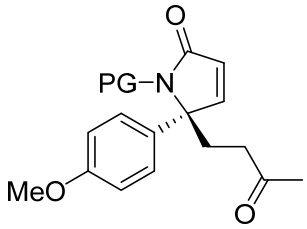
Prepared by the reaction of **2h** (0.10 mmol) with methyl vinyl ketone (16.2 μL, 0.20 mmol) using catalyst (*S*)-**1d** (4.6 mg, 2.0 μmol) and K_2CO_3 (69 mg, 0.50 mmol) in degassed MTBE (1.0 mL). The reaction mixture was stirred for 36 h at -10 °C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 20:80) to give **3h** as a slightly yellow oil (30.3 mg, 76%, 94% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 1H), 7.18 – 7.12 (m, 2H), 6.99 – 6.92 (m, 2H), 6.72 (d, *J* = 5.8 Hz, 1H), 6.39 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.22 (d, *J* = 5.8 Hz, 1H), 6.21 (d, *J* = 2.4 Hz, 1H), 4.52 (d, *J* = 14.9 Hz, 1H), 4.03 (d, *J* = 14.8 Hz, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 2.43 (ddd, *J* = 14.2, 9.3, 6.1 Hz, 1H), 2.37 (ddd, *J* = 14.2, 9.3, 5.2 Hz, 1H), 1.99 (ddd, *J* = 18.6, 9.2, 6.1 Hz, 1H), 1.88 (s, 3H), 1.85 (ddd, *J* = 18.5, 9.2, 5.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.4, 171.8, 162.3 (d, J_{C-F} = 247 Hz), 160.4, 157.6, 152.4, 132.8 (d, J_{C-F} = 2 Hz), 132.4, 128.2 (d, J_{C-F} = 8 Hz),

125.6, 117.8, 115.3 (d, $J_{C\text{-}F}$ = 21 Hz), 104.6, 97.7, 71.4, 55.4, 54.9, 36.9, 35.9, 29.8, 24.8; IR (neat) 1715, 1684, 1611, 1508, 1388, 1291, 1265, 1209, 1160, 1129, 835, 807 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{25}FNO_4$: *m/z* 398.1762 ($[M + H]^+$), found: *m/z* 398.1771 ($[M + H]^+$); $[\alpha]_D^{32} = [\alpha]_D^{32} = +67.9$ (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IB-3, hexane/ethanol = 5:1, flow rate = 0.65 mL/min, retention time: 12.2 min (major) and 17.0 min (minor)).

Compound 3i

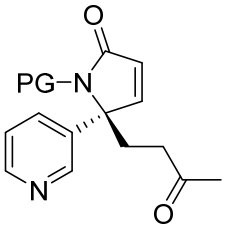


After the aliquotation of the starting material triethylamine was added prior to the removal of the solvent in vacuo. Prepared by the reaction of **2i** (0.10 mmol) with methyl vinyl ketone (16.2 µL, 0.20 mmol) using catalyst (*S*)-**1d** (4.6 mg, 2.0 µmol) and K_2CO_3 (69 mg, 0.50 mmol) in degassed MTBE (1.0 mL). The reaction mixture was stirred for 85 h at -10 °C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 20:80) to give **3i** as a colorless oil (28.3 mg, 69%, 92% ee) that crystallised upon storage at 4 °C.

^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 1H), 7.15 – 7.08 (m, 2H), 6.85 – 6.79 (m, 2H), 6.73 (d, *J* = 5.8 Hz, 1H), 6.39 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.23 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 6.0 Hz, 1H), 4.56 (d, *J* = 14.9 Hz, 1H), 3.96 (d, *J* = 14.9 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 2.40 (ddd, *J* = 14.1, 9.5, 6.0 Hz, 1H), 2.33 (ddd, *J* = 14.2, 9.4, 4.8 Hz, 1H), 1.98 (ddd, *J* = 18.4, 9.4, 6.0 Hz, 1H), 1.85 (s, 3H), 1.82 (ddd, *J* = 18.4, 9.3, 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 171.8, 160.3, 159.2, 157.6, 152.7, 132.4, 128.7, 127.6, 125.2, 118.1, 113.8, 104.5, 97.7, 71.6, 55.3, 55.2, 54.9, 37.0, 35.9, 29.7, 24.9; IR (neat) 1714, 1683, 1611, 1509, 1389, 1291, 1254, 1209, 1183, 1159, 1033, 831 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{28}NO_5$: *m/z* 410.1962 ($[M + H]^+$), found: *m/z* 410.1966 ($[M + H]^+$); $[\alpha]_D^{31} = +119.5$ (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IB-3, hexane/ethanol = 5:1, flow rate = 0.65 mL/min, retention time: 13.3 min (major) and 17.4 min (minor)).

Compound 3j

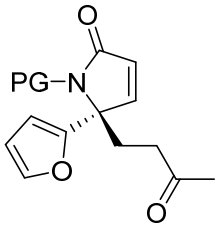


Prepared by the reaction of **2j** (0.10 mmol) with methyl vinyl ketone (16.2 µL, 0.20 mmol) using catalyst (*S*)-**1d** (4.6 mg, 2.0 µmol) and K_2CO_3 (69 mg, 0.50 mmol) in degassed MTBE (1.0 mL). The reaction mixture was stirred for 38 h at -10 °C. The crude material was purified by PLC on silica gel (CH_2Cl_2/MeOH, 20:1) to give **3j** as a slightly yellow oil (34.5 mg, 91%, 94% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 – 8.49 (m, 1H), 8.46 (d, *J* = 4.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.11 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.75 (d, *J* = 5.8 Hz, 1H), 6.37 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.28 (d, *J* = 5.8 Hz, 1H), 6.14 (d, *J* = 2.4 Hz, 1H), 4.44 (d, *J* = 14.8 Hz, 1H), 4.22 (d, *J* = 14.8 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 2.57 – 2.46 (m, 2H), 2.09 – 1.99 (m, 1H), 1.97 – 1.87 (m, 1H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 171.5, 160.5, 157.5, 151.7, 149.2, 147.9, 134.1, 132.8, 132.3, 126.1, 122.9, 117.5, 104.6, 97.7, 70.4, 55.3, 54.9, 36.5, 35.8, 29.8, 24.1; IR (neat) 1714, 1684, 1611, 1508, 1418, 1388, 1291, 1266, 1209, 1159 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{22}H_{25}N_2O_4$: *m/z* 381.1809 ($[M + H]^+$), found: *m/z* 381.1813 ($[M + H]^+$); $[\alpha]_D^{32}$ = +86.1 (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IA-3, hexane/ethanol = 2:1, flow rate = 0.58 mL/min, retention time: 18.7 min (major) and 29.4 min (minor)).

Compound 3k



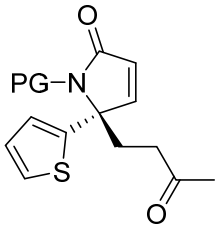
EtOAc was used for the aliquotation of the starting material and triethylamine was added prior to the removal of the solvent in vacuo. Prepared by the reaction of **2k** (0.10 mmol) with methyl vinyl ketone (16.2 µL, 0.20 mmol) using catalyst (*S*)-**1d** (4.6 mg, 2.0 µmol) and K_2CO_3 (69 mg, 0.50 mmol) in degassed MTBE (1.0 mL). The reaction mixture was stirred for 67 h at -30 °C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 80:20) to give **3k** (22.1 mg, 60%, 93% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 1H), 7.26 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.78 (d, *J* = 5.9 Hz, 1H), 6.38 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.31 – 6.29 (m, 2H), 6.28 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.25 (d, *J* = 5.9 Hz, 1H), 4.56 (d, *J* = 15.2 Hz, 1H), 4.14 (d, *J* = 15.2 Hz, 1H), 3.76 (s, 3H), 3.75(7) (s, 3H), 2.38 – 2.29 (m, 2H), 2.04 – 1.95 (m, 1H), 1.90 – 1.82 (m, 1H), 1.88 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 207.2, 171.3, 160.2, 157.6, 150.6, 148.9, 142.6, 131.7, 127.0, 118.0, 110.2, 108.3, 104.4, 97.9, 68.5, 55.3, 55.1, 36.3, 36.2, 29.8, 24.9; IR (neat) 1714, 1687, 1612, 1508, 1392, 1291, 1265, 1209, 1157, 1034 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{24}NO_5$: *m/z* 370.1649 ($[M + H]^+$), found: *m/z* 370.1655 ($[M + H]^+$); $[\alpha]_D^{31} = +56.9$ (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IB-3, hexane/ethanol = 5:1, flow rate = 0.65 mL/min, retention time: 13.0 min (major) and 14.9 min (minor)).

Compound 3l



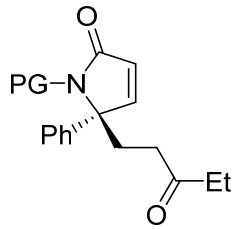
EtOAc was used for the aliquotation of the starting material and triethylamine was added prior to the removal of the solvent in vacuo. Prepared by the reaction of **2l** (0.10 mmol) with methyl vinyl ketone (16.2 μL, 0.20 mmol) using catalyst (*S*)-**1d** (4.6 mg, 2.0 μmol) and K_2CO_3 (69 mg, 0.50 mmol) in degassed MTBE (1.0 mL). The reaction mixture was stirred for 69 h at -30 °C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 80:20) to give **3l** as a slightly brown oil (24.8 mg, 64%, 96% ee).

^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 1H), 7.26 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.03 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.85 (d, *J* = 5.8 Hz, 1H), 6.41 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.30 (d, *J* = 2.4 Hz, 1H), 6.22 (d, *J* = 5.8 Hz, 1H), 4.62 (d, *J* = 15.1 Hz, 1H), 4.11 (d, *J* = 15.0 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.44 (ddd, *J* = 14.6, 9.5, 5.1 Hz, 1H), 2.39 (ddd, *J* = 14.2, 9.3, 6.1 Hz, 1H), 1.96 (ddd, *J* = 18.5, 9.4, 6.1 Hz, 1H), 1.83 (s, 3H), 1.77 (ddd, *J* = 18.5, 9.3, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 171.0, 160.3, 157.7, 151.6, 142.2, 132.4, 126.9, 125.8, 125.7, 125.5, 118.2, 104.6, 97.9, 69.9, 55.3, 55.1, 36.9, 35.8, 29.7, 26.8; IR (neat) 1713, 1686, 1611, 1508, 1389, 1290, 1266, 1209, 1159, 1129, 1033 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{24}NO_4S$: *m/z* 386.1421 ($[M + H]^+$), found: *m/z* 386.1423 ($[M + H]^+$); $[\alpha]_D^{31} = +32.2$ (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IB-3, hexane/ethanol = 5:1, flow rate = 0.65 mL/min, retention time: 13.2 min (major) and 19.8 min (minor)).

Use of other Michael acceptors (Scheme 3)

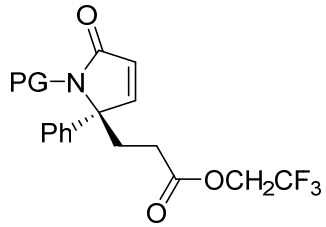
Compound 5a



Prepared by the reaction of **2d** (0.1 mmol) with ethyl vinyl ketone (19.8 μL, 0.2 mmol) using (*S*)-**1d** (4.6 mg, 2.0 μmol) and K_2CO_3 (69.1 mg, 0.5 mmol) in degassed MTBE (1 mL). The reaction mixture was stirred for 48 h at -10 ˚C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 1:1) to give compound **5a** as a colorless oil (32.4 mg, 82%, 86% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, *J* = 8.6 Hz, 1H), 7.26-7.32 (m, 3H), 7.19-7.21 (m, 2H), 6.75 (d, *J* = 5.7 Hz, 1H), 6.39 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.21 (dd, *J* = 4.1, 1.6 Hz, 2H), 4.57 (d, *J* = 14.7 Hz, 1H), 3.99 (d, *J* = 15.0 Hz, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 2.44-2.50 (m, 1H), 2.36-2.42 (m, 1H), 2.01-2.17 (m, 2H), 1.96 (ddd, *J* = 18.2, 9.6, 6.0 Hz, 1H), 1.80 (qd, *J* = 9.4, 4.8 Hz, 1H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 210.31, 172.04, 160.31, 157.68, 152.70, 137.16, 132.46, 128.53, 127.95, 126.38, 125.40, 118.07, 104.50, 97.75, 72.08, 55.29, 54.93, 36.06, 35.77, 35.59, 24.77, 7.70; HRMS (ESI) exact mass calcd. for $C_{24}H_{27}NNaO_4$: *m/z* 416.1832 ([M + Na]$^+$), found: *m/z* 416.1835 ([M + Na]$^+$); $[\alpha]_D^{18}$ = +83.0 (*c* = 0.9, $CHCl_3$).

Compound 5b

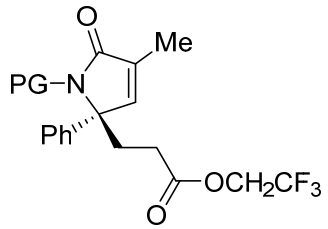


Prepared by the reaction of **2d** (0.1mmol) with 2,2,2-trifluoroethyl acrylate (57.3 μL, 0.45 mmol) using (*S*)-**1d** (4.6 mg, 2.0 μmol) and K_2CO_3 (69.1 mg, 0.5 mmol) in degassed MTBE (1 mL). The reaction mixture was stirred for 84 h at -10 ˚C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 1:1) to give compound **5b** as a colorless oil (30.7 mg, 66%, 86% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.35 (m, 4H), 7.17-7.19 (m, 2H), 6.78 (d, *J* = 5.7 Hz, 1H), 6.38 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.24-6.26 (m, 2H), 4.68 (d, *J* = 14.7 Hz, 1H), 4.28-4.40 (m, 2H), 3.89 (d, *J* = 15.0 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 2.40-2.49 (m, 2H), 1.98-2.05 (m, 1H), 1.87 (ddd, *J* = 17.5, 9.3, 5.7 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 171.76, 171.45, 160.44, 157.73, 151.91, 136.72, 132.37, 128.65, 128.15, 126.31, 126.01, 122.8 (q, J_{C-F} = 246 Hz), 117.55, 104.29, 97.98, 71.73, 60.16 (q, J_{C-F} = 40.8 Hz), 55.23, 54.86, 36.49, 27.17, 26.17; IR (neat) 1682, 1508, 1267, 1209, 1155, 1129, 1033, 813, 765, 735, 696 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{24}NNaO_5F_3$: *m/z* 486.1499 ([M + Na]$^+$), found: *m/z* 486.1497 ([M + Na]$^+$); $[\alpha]_D^{21}$ = $[\alpha]_D^{21}$ = 43.7 (*c* = 1.0, $CHCl_3$).

Substrate scope with α- and/or β-alkylated unsaturated lactams (Table 3)

Compound 7a

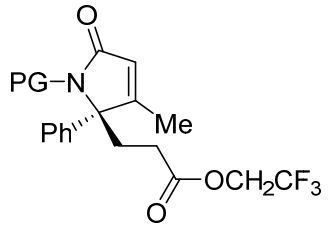


Prepared by the reaction of **6a** (32.3 mg, 0.1mmol) with trifluoroethyl acrylate (24.6 μL, 0.2 mmol) using (*S*)-**1d** (4.6 mg, 2.0 μmol) and Cs_2CO_3 (163 mg, 0.5 mmol) in degassed toluene (1 mL). The reaction mixture was stirred for 82 h at -10 ˚C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 1:1) to give **7a** as a white solid (29.6 mg, 62%, 73% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 4H), 7.16 (dd, *J* = 8.1, 1.6 Hz, 2H), 6.40-6.36 (m, 2H), 6.24 (d, *J* = 2.4 Hz, 1H), 4.65 (d, *J* = 14.7 Hz, 1H), 4.39-4.28 (m, 2H), 3.93 (d, *J* = 15.0 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 2.45-2.41 (m, 2H), 2.05-1.94 (m, 4H), 1.83 (ddd, *J* = 17.3, 8.6, 6.3 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.6, 171.7, 160.4, 157.7, 145.0, 137.9, 134.0, 132.5, 128.6, 127.9, 126.3, 125.1 (q, $J_{C\text{-}F}$ = 279 Hz), 117.9, 104.3, 98.0, 69.5, 60.2 (q, $J_{C\text{-}F}$ = 37.1 Hz), 55.3, 54.9, 36.8, 27.4, 26.5, 11.0 cm^{-1}; IR (neat) 1757, 1683, 1612, 1508, 1396, 1275, 1209, 1158, 1110, 1036, 975, 700 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{25}H_{26}NNaO_5F_3$: *m/z* 500.1655 ([M + Na]$^+$), found: *m/z* 500.1662 ([M + Na]$^+$); $[\alpha]_D^{16}$ = +6.3 (*c* = 0.3, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK AD-3, hexane/ethanol, 10:1, flow rate = 0.50 mL/min, retention time: 13.7 min (minor) and 15.6 min (major)).

Compound 7b



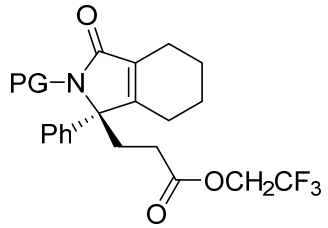
Prepared by the reaction of **6b** (32.3 mg, 0.1mmol) with trifluoroethyl acrylate (24.6 μL, 0.2 mmol) using (*S*)-**1d** (4.6 mg, 2.0 μmol) and Cs_2CO_3 (163 mg, 0.5 mmol) in degassed MTBE (1 mL). The reaction mixture was stirred for 82 h at -10 ˚C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 1:1) to give **7b** as a white solid (39.1 mg, 82%, 67% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ7.35-7.29 (m, 4H), 7.15 (d, J = 6.8 Hz, 2H), 6.37 (dd, J = 8.5, 2.4 Hz, 1H), 6.23 (d, J = 2.4, 1H), 6.01 (d, J = 1.5, 1H), 4.66 (d, J = 14.7 Hz, 1H), 4.33 (ddt, J = 21.6, 9.3, 4.3 Hz, 2H), 3.85 (d, J = 15.0 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.46-2.28 (m, 2H), 1.84 (t, J = 8.2, 2H), 1.62 (d, J = 1.5 Hz, 3H) ; ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.8, 171.4, 161.3, 160.4, 157.7, 137.3, 132.5, 128.6, 128.1, 126.2, 125.1, 123.0, 122.4 (q, $J_{C\text{-}F}$ = 278 Hz), 118.1, 104.3, 98.0, 73.2, 60.2 (q,

$J_{C\text{-}F}$ = 35.9 Hz), 55.2, 54.8, 36.6, 26.9, 25.0, 12.6; IR (neat) 1756, 1682, 1612, 1508, 1392, 1269, 1209, 1158, 1036, 699 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{25}H_{26}NNaO_3F_3$: *m/z* 500.1655 ([M + Na]$^+$), found: *m/z* 500.1663 ([M + Na]$^+$); $[\alpha]_D^{16}$ = +49.6 (*c* = 1.4, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK OD-3, hexane/ethanol, 10:1, flow rate = 0.50 mL/min, retention time: 15.8 min (major) and 17.7 min (minor)).

Compound 7c



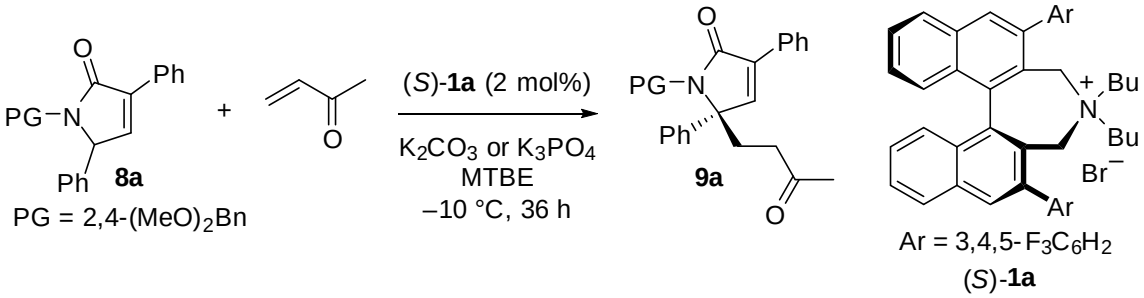
Prepared by the reaction of **6c** (36.3 mg, 0.1mmol) with trifluoroethyl acrylate (24.3 μL, 0.2 mmol) using (*S*)-**1d** (4.6 mg, 2.0 μmol) and Cs_2CO_3 (163 mg, 0.5 mmol) in degassed MTBE (1 mL). The reaction mixture was stirred for 82 h at 0 ˚C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 1:1) to give **7c** as a white solid (25.3 mg, 47%, 56% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 1H), 7.32-7.28 (m, 3H), 7.12 (d, *J* = 7.1 Hz, 2H), 6.37 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.23 (d, *J* = 2.6, 1H), 4.66 (d, *J* = 14.7 Hz, 1H), 4.36-4.28 (m, 2H), 3.89 (d, *J* = 15.0 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.45-2.27 (m, 4H), 1.79 (t, *J* = 8.2, 2H), 1.68-1.60 (m, 6H) ; ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.2, 171.5, 160.3, 157.6, 156.5, 138.1, 132.6, 131.8, 128.5, 127.8, 126.2, 122.8 (q, $J_{C\text{-}F}$ = 304 Hz), 118.5, 104.3, 98.0, 71.1, 60.2 (q, $J_{C\text{-}F}$ = 37.1 Hz), 55.2, 54.8, 36.3, 27.1, 25.2, 22.1, 21.9, 21.3, 20.3; IR (neat) 1757, 1679, 1612, 1508, 1448, 1407, 1279, 1209, 1158, 1102, 1035, 700 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{28}H_{30}NNaO_5F_3$: *m/z* 540.1968 ([M + Na]$^+$), found: *m/z* 540.1979 ([M + Na]$^+$); $[\alpha]_D^{21}$ = -26.7 (*c* = 1.1, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK ID, hexane/isopropanol, 5:1, flow rate = 0.50 mL/min, retention time: 28.5 min (minor) and 33.0 min (major)).

Use of α-aryl unsaturated γ-lactams (Scheme 4)

Compound 9a

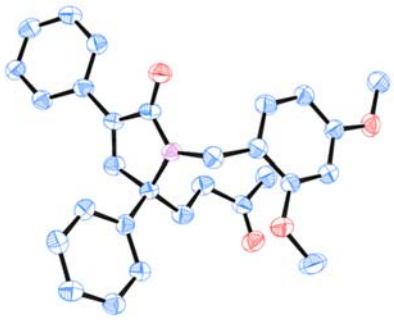


Prepared by the reaction of **8a** (38.5 mg, 0.1mmol) with methyl vinyl ketone (16.3 μL, 0.2 mmol) using (*S*)-**1a** (1.5 mg, 2.0 μmol) and K_2CO_3 (69.1 mg, 0.5 mmol) in degassed MTBE (1 mL). The reaction mixture was stirred for 36 h at -10 ˚C. The crude material was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give compound **9a** as a white solid (27.0 mg, 61%, 91% ee).

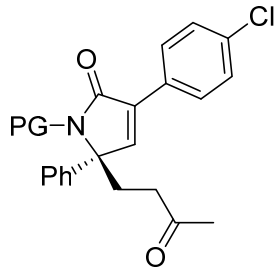
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 6.7 Hz, 1.6 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.25-7.28 (m, 7H), 6.91 (s, 1H), 6.40 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.23 (d, *J* = 2.4, 1H), 4.65 (d, *J* = 14.7 Hz, 1H), 4.09 (d, *J* = 14.7 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 2.60-2.53 (m, 1H), 2.50-2.42 (m, 1H), 2.05-2.02 (m, 1H), 1.90-1.86 (m, 1H), 1.83 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.7, 170.9, 160.4, 157.8, 145.6, 137.9, 132.7, 128.8, 128.6, 128.6, 128.0, 127.2, 126.6, 118.3, 104.7, 97.9, 69.2, 55.4, 55.1, 37.2, 36.5, 30.0, 25.4; IR (neat) 1715, 1676, 1611, 1507, 1392, 1291, 1266, 1209, 1158, 1123, 1034, 731, 696 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{29}H_{29}NNaO_4$: *m/z* 478.1989 ($[M + Na]^+$), found: *m/z* 478.1995 ($[M + Na]^+$); $[\alpha]_D^{20}$ = -13.5 (*c* = 0.3, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK IF, hexane/ethanol = 2:1, flow rate = 0.50 mL/min, retention time: 22.6 min (major) and 33.2 min (minor)).

Crystals suitable for an x-ray analysis were obtained by layering a solution of the product in CH_2Cl_2 with hexane. The x-ray analysis revealed the absolute configuration of the product to be (*R*). The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1531627). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html.



Compound 9b

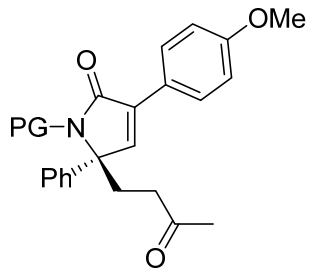


Prepared by the reaction of **8b** (42 mg, 0.1mmol) with methyl vinyl ketone (16.3 μL, 0.2 mmol) using (*S*)-**1a** (1.5 mg, 2.0 μmol) and K_2CO_3 (13.8 mg, 0.1 mmol) in degassed MTBE (1 mL). The reaction mixture was stirred for 156 h at -10 °C. The crude material was purified by PLC on silica gel (hexane/EtOAc = 9:4 then CH_2Cl_2/EtOAc = 10:1) to give **9b** as a white solid (38.7 mg, 79%, 77% ee).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.9 Hz, 2.2 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H) 7.22-7.33 (m, 5H), 6.91 (s, 1H), 6.41 (dd, *J* = 8.5 Hz, 2.4Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 4.64 (d, *J* = 14.7Hz, 1H), 4.08 (d, *J* = 14.7 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 2.41-2.61 (m, 2H), 1.97-2.01 (m, 1H), 1.84-1.91 (m, 1H), 1.83 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.5, 170.5, 160.5, 157.8, 145.8, 137.6, 134.7, 133.0, 132.6, 123.8, 128.7, 128.6, 128.4, 128.0, 126.5, 118.1, 104.7, 97.9, 69.2, 55.3, 55.0, 37.0, 36.6, 29.8, 25.4; IR (neat) 1714, 1676, 1611, 1507, 1491, 1391, 1293, 1266, 1208, 1158, 1122, 1033, 833, 732, 698 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{29}H_{28}ClNNaO_4$: m/z 512.1599 ($[M+Na]^+$), found: 512.1608 ($[M+Na]^+$); $[\alpha]_D^{28}$ = -14.0 (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK ID, hexane/ethanol, 1:1, flow rate = 0.50 mL/min, retention time: 15.0 min (major) and 23.3 min (minor)).

Compound 9c



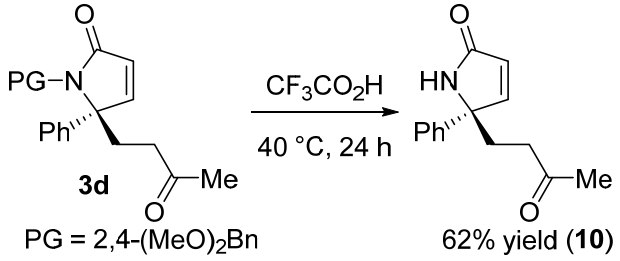
Prepared by the reaction of **8c** (41.5 mg, 0.1mmol) with methyl vinyl ketone (16.3 μL, 0.2 mmol) using (*S*)-**1a** (1.5 mg, 2.0 μmol) and K_3PO_4 (21.3 mg, 0.1 mmol) in degassed MTBE (1 mL) under argon atmosphere. The reaction mixture was stirred for 156 h at -10 °C. The crude material was purified by PLC on silica gel (hexane/EtOAc, 5:4, CH_2Cl_2/EtOAc = 12:1, and hexane/Et_2O = 1:2) to give **9c** as a white solid (23.7 mg, 49%, 90% ee).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 9.4 Hz, 2.4 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.23-7.30

(m, 5H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.79 (s, 1H), 6.40 (dd, *J* = 8.5 Hz, 2.4Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 4.64 (d, *J* = 15Hz, 1H), 4.08 (d, *J* = 15 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H), 2.41-2.58 (m, 2H), 1.84-2.09 (m, 2H), 1.82 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.7, 171.1, 160.4, 160.1, 157.7, 143.5, 138.1, 133.6, 132.6, 128.5, 128.5, 127.8, 126.5, 124.0, 118.3, 113.9, 104.7, 97.9, 69.0, 55.3, 55.3, 55.0, 37.1, 36.5, 29.8, 25.5; IR (neat) 1713, 1608, 1508, 1446, 1392, 1291, 1252, 1208, 1177, 1157, 1122, 1032, 911, 833, 764, 729, 698 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{30}H_{31}NNaO_5$: m/z 508.2094 ($[M+Na]^+$), found: 508.2104 ($[M+Na]^+$); $[\alpha]_D^{29}$ = -21.2 (*c* = 1.0, $CHCl_3$).

The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALPAK ID, hexane/ethanol, 1:1, flow rate = 0.50 mL/min, retention time: 21.7 min (major) and 41.5 min (minor)).

Removal of the 2,4-dimethoxybenzyl moiety (Scheme 5)



3d (0.1mmol) was treated with trifluoroacetic acid (1 mL) for 24 h at 40 ˚C. After removing trifluoroacetic acid in vacuo, the crude material was purified by PLC on silica gel (EtOAc then CH_2Cl_2/MeOH, 10:1) to give compound **10** (14.3 mg, 62%) as white solid.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34-7.40 (m, 4H), 7.28-7.31 (m, 1H), 7.14 (dd, *J* = 5.7, 1.7 Hz, 1H), 6.03 (dd, *J* = 5.7, 1.4 Hz, 1H), 2.30-2.50 (m, 4H), 2.10 (s, 3H); ^{13}C-NMR (125 MHz, CDCL3) δ 207.60, 173.93, 154.48, 139.58, 128.96, 127.86, 125.35, 124.83, 69.15, 37.85, 31.69, 30.16; IR (neat) 1686, 1448, 1361, 1167, 816, 767, 699 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{14}H_{15}NNaO_2$: *m/z* 252.0995 ([M + Na]$^+$), found: *m/z* 252.0996 ([M + Na]$^+$); $[\alpha]_D^{18}$ = +85.9 (*c* = 0.6, $CHCl_3$).

References

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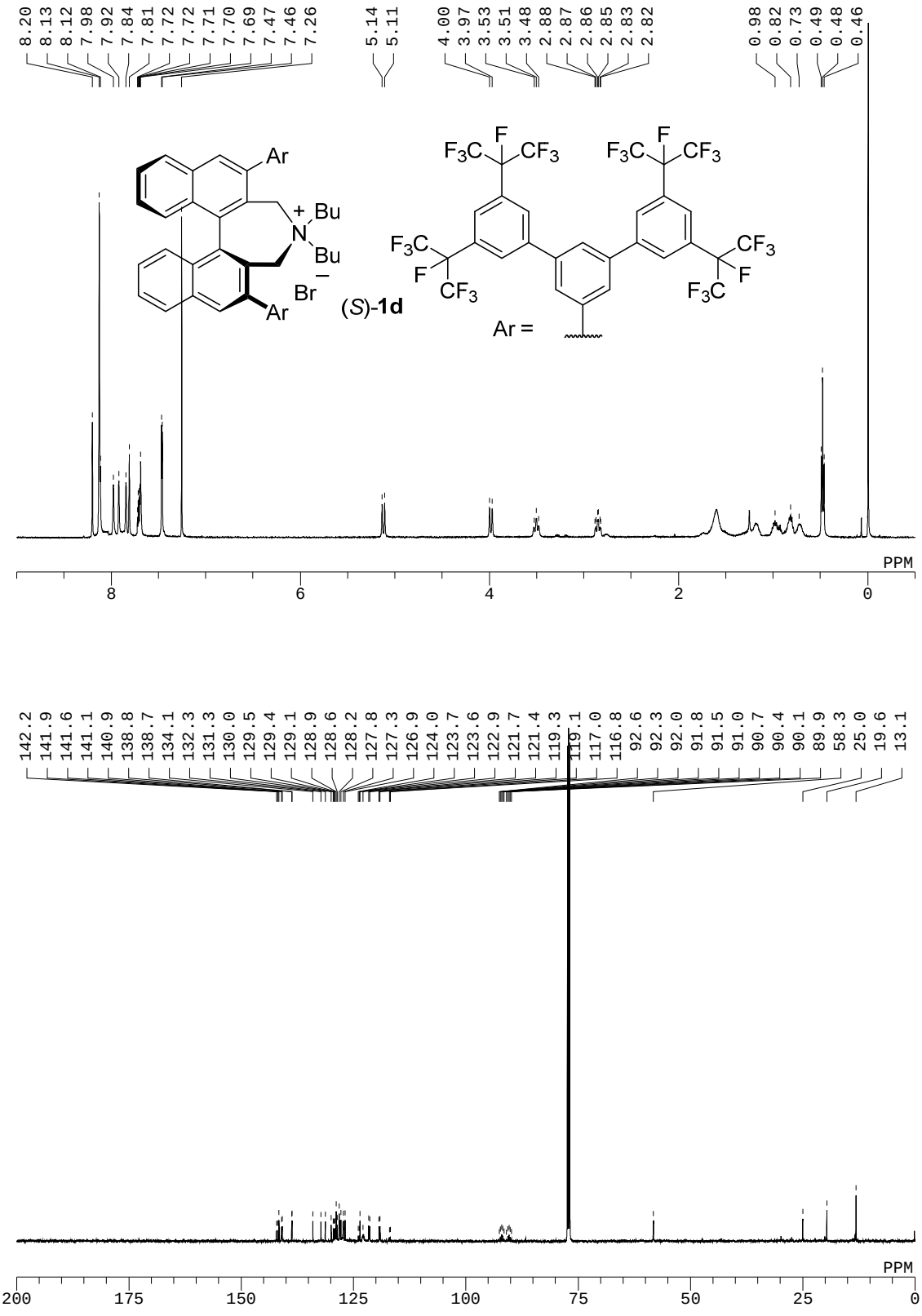
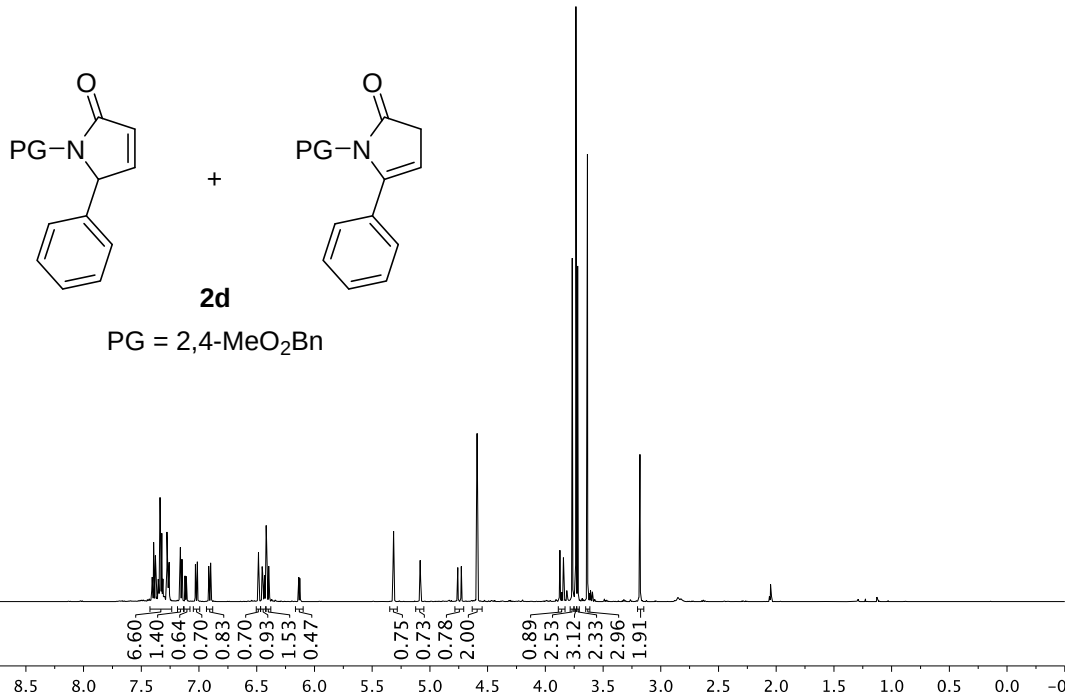
^{1}H and ^{13}C NMR spectra

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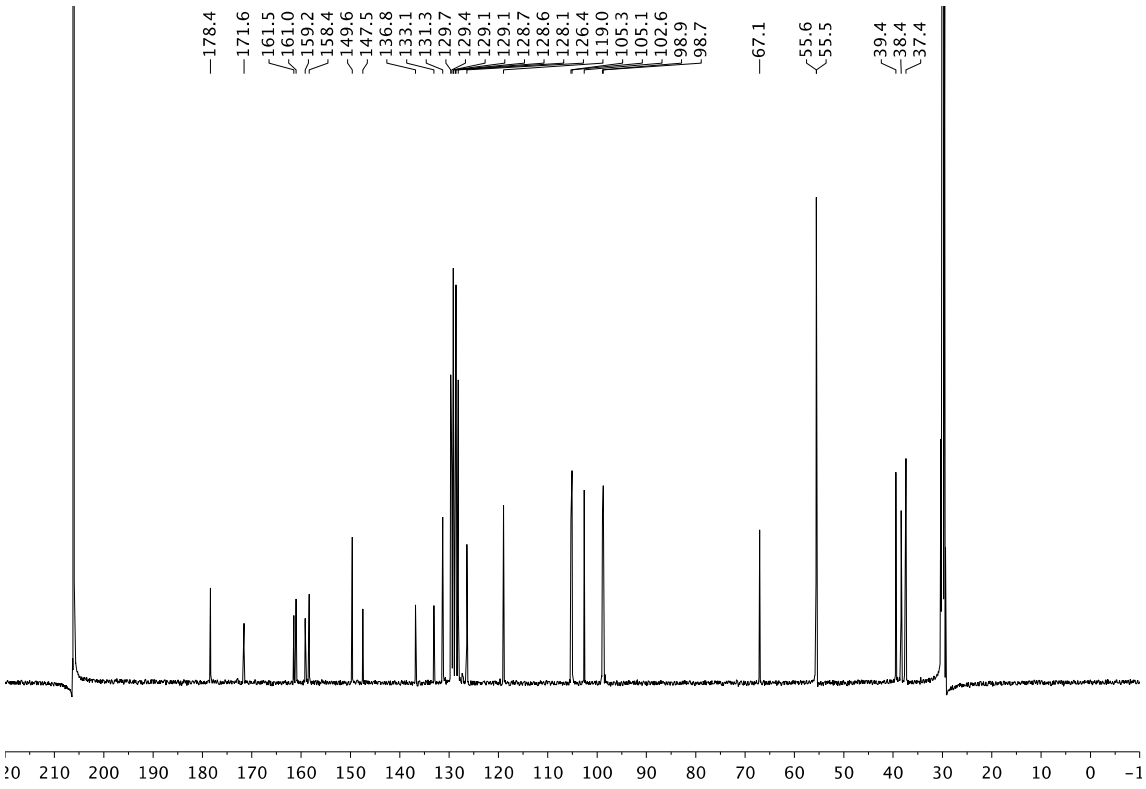
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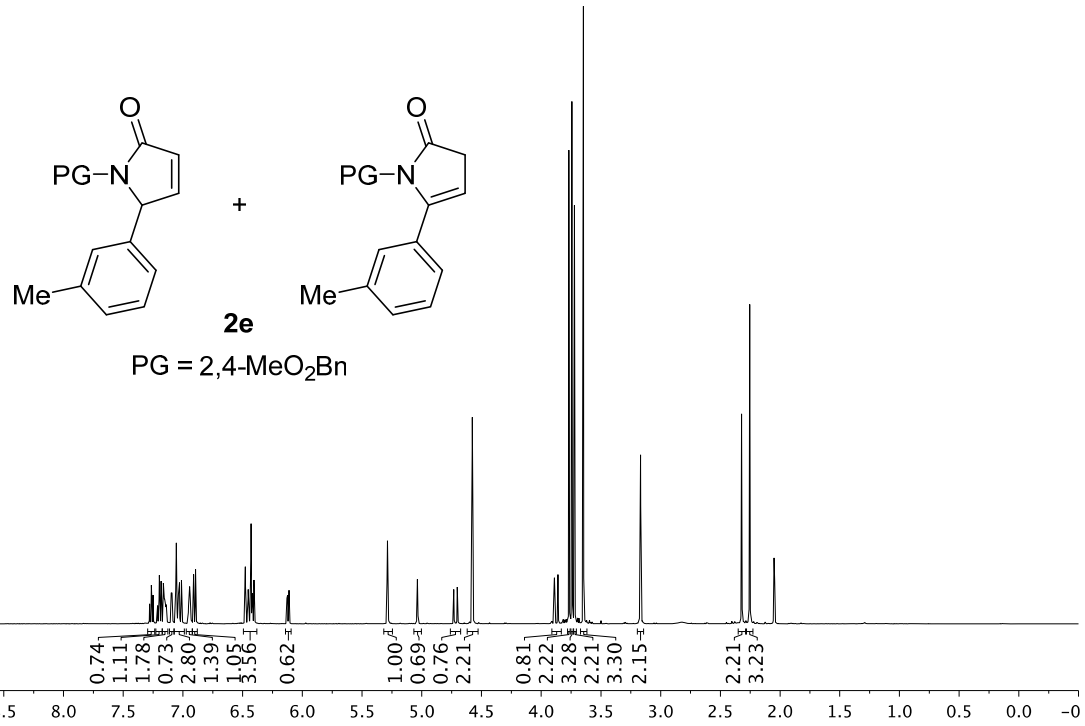
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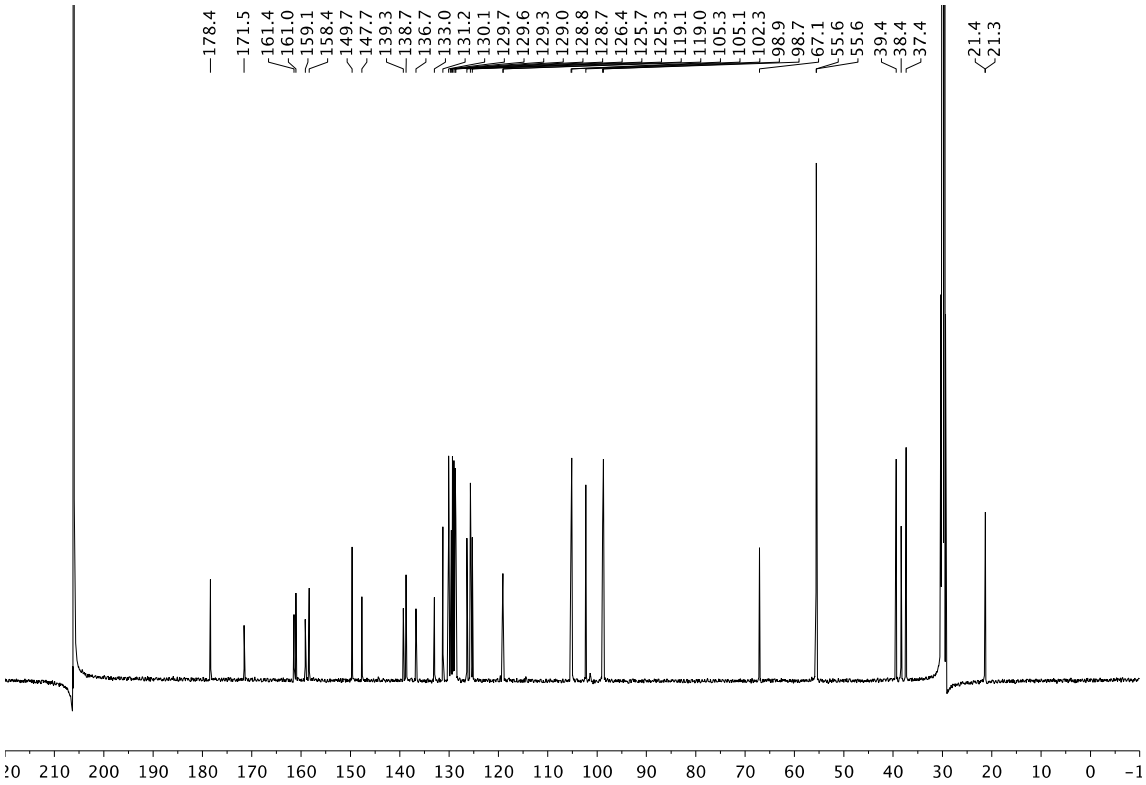
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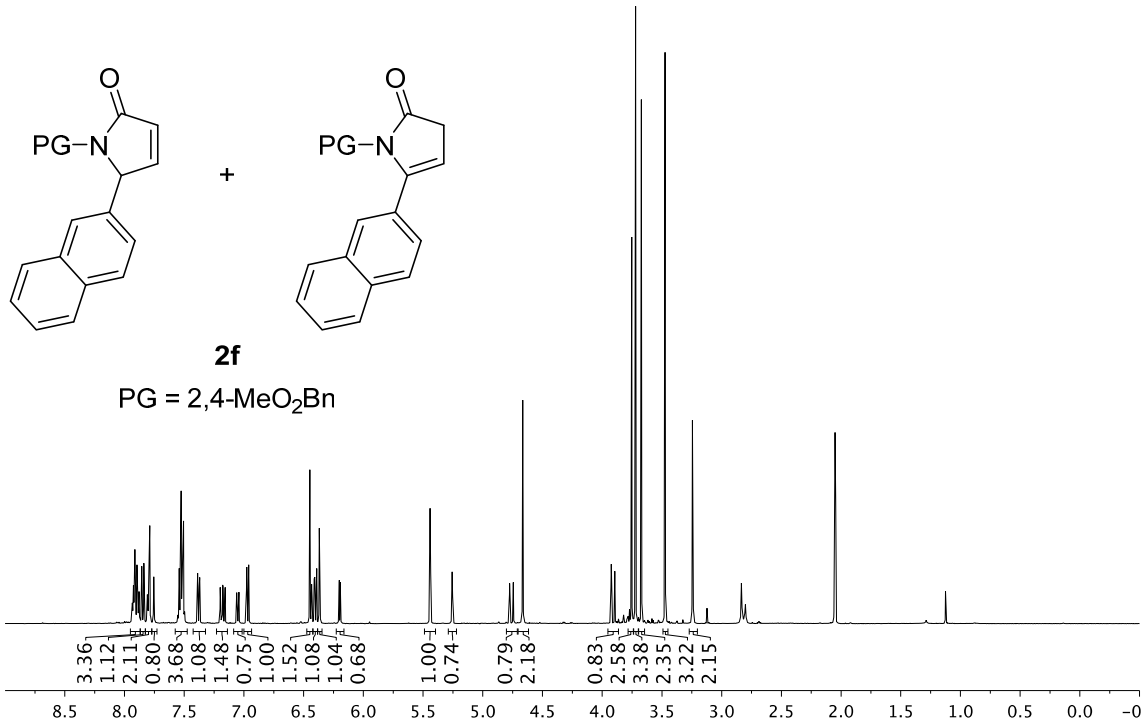

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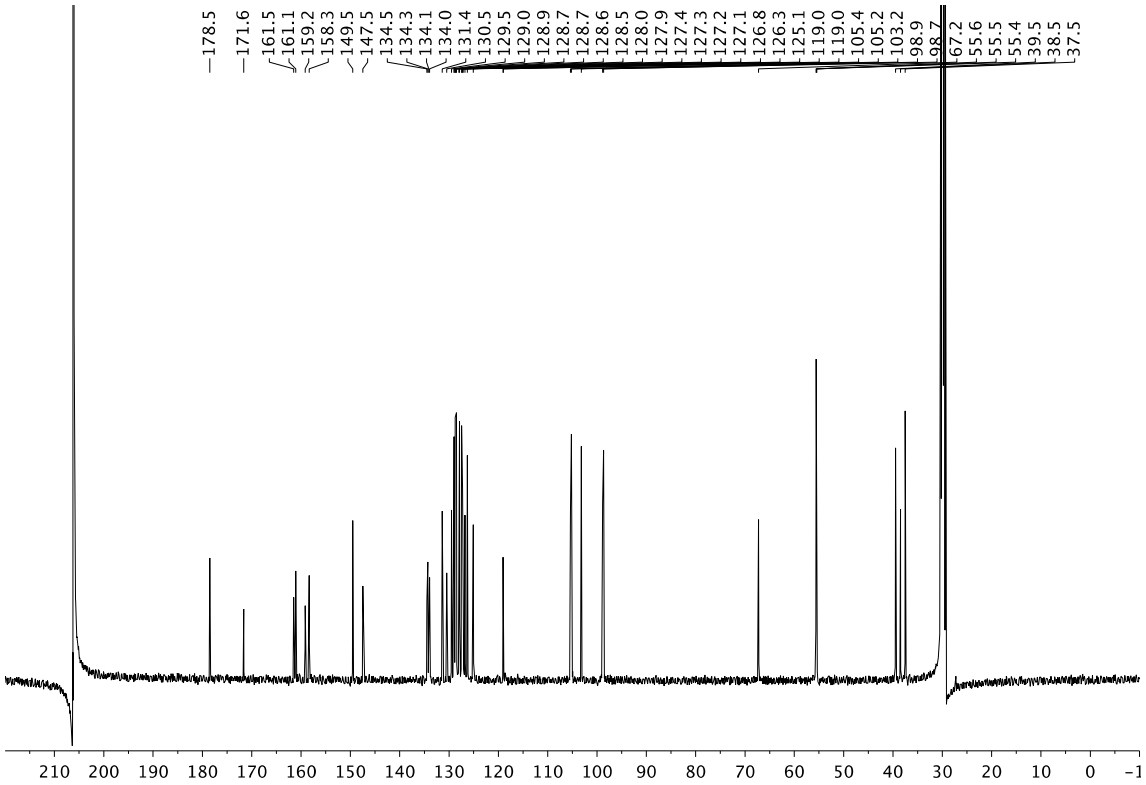

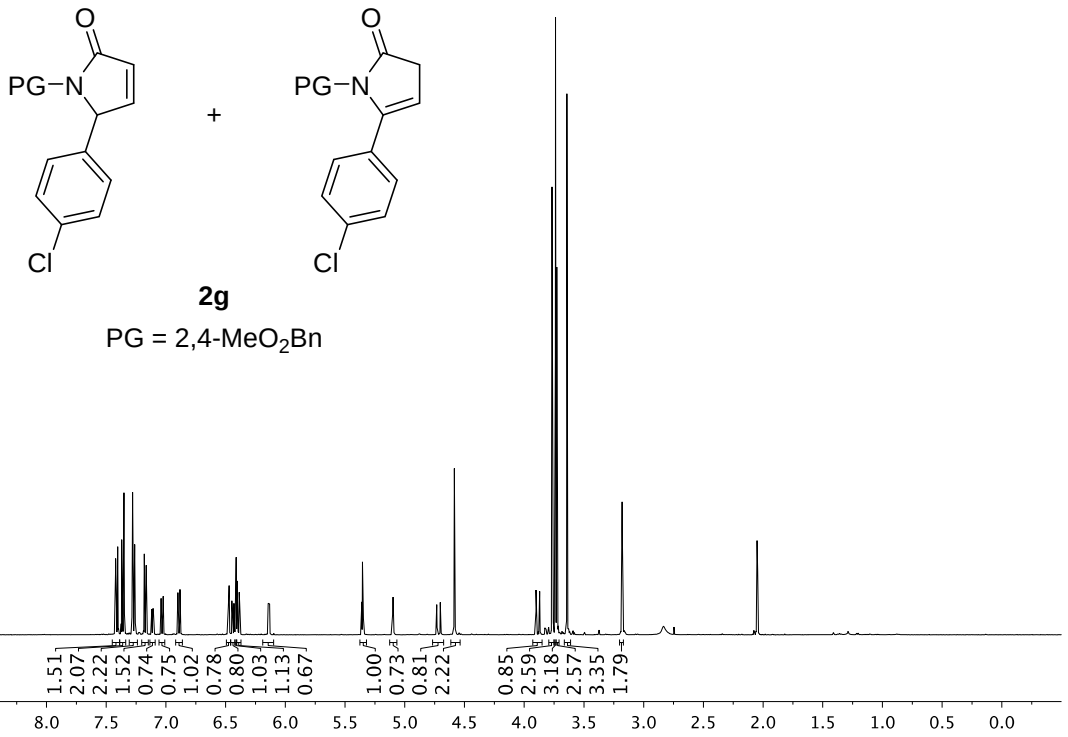

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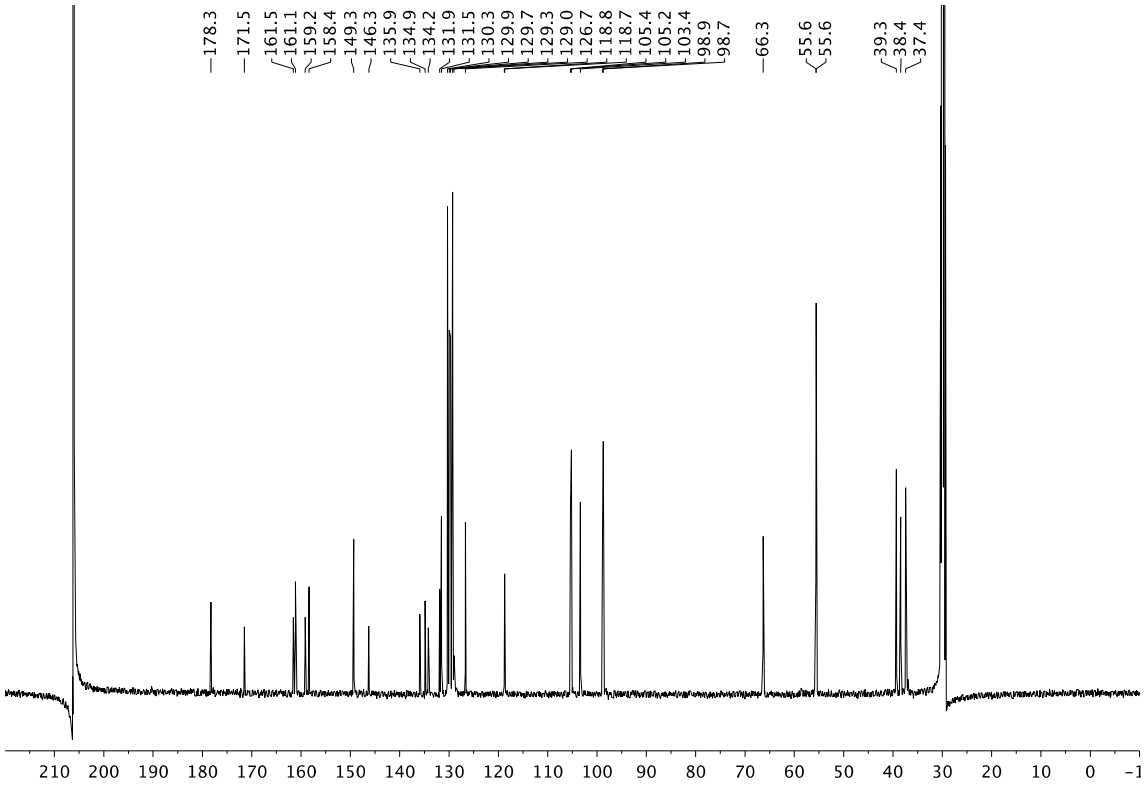

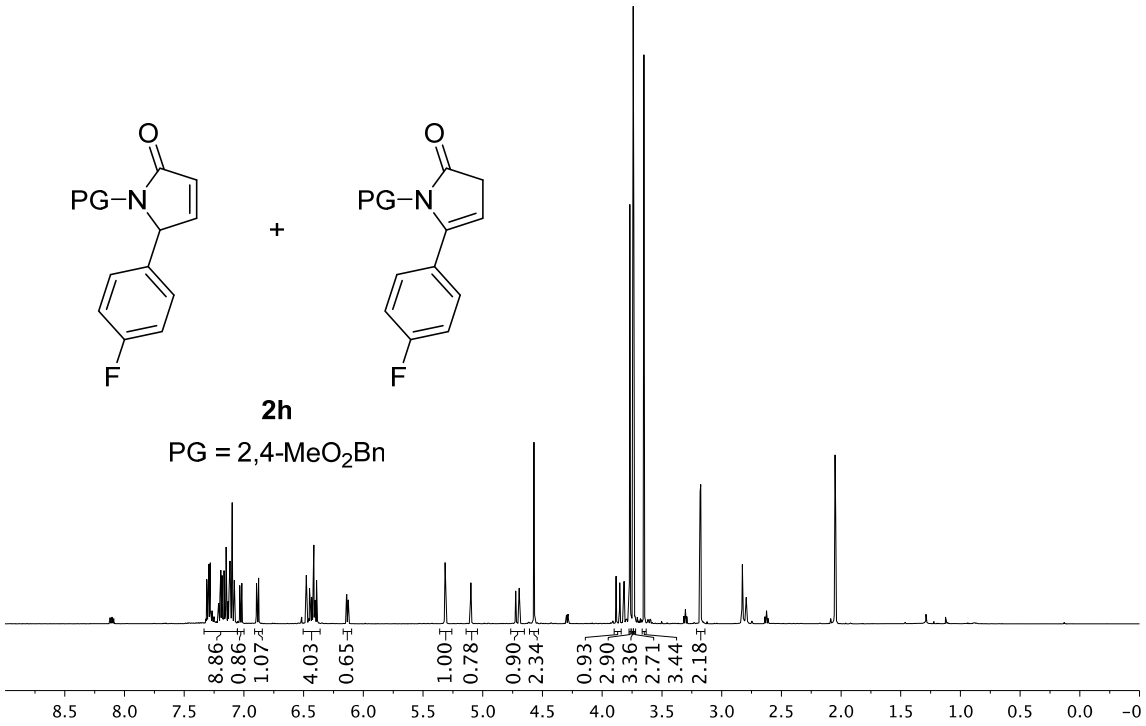
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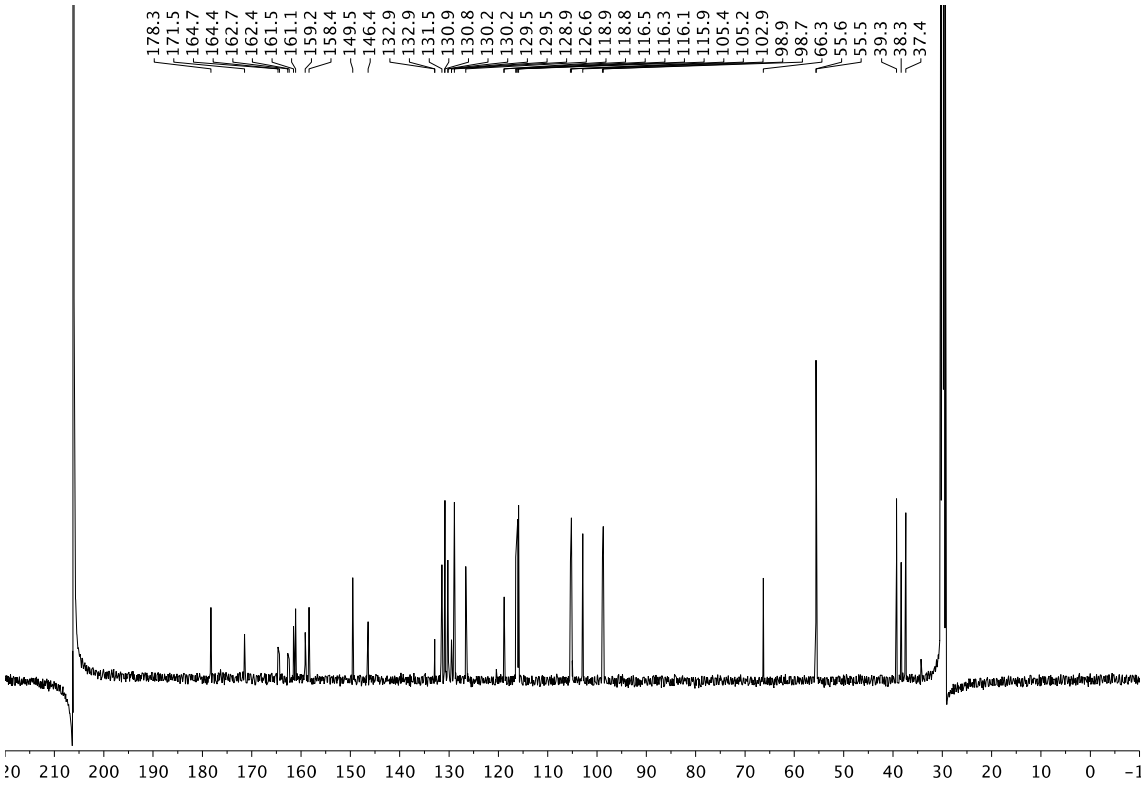
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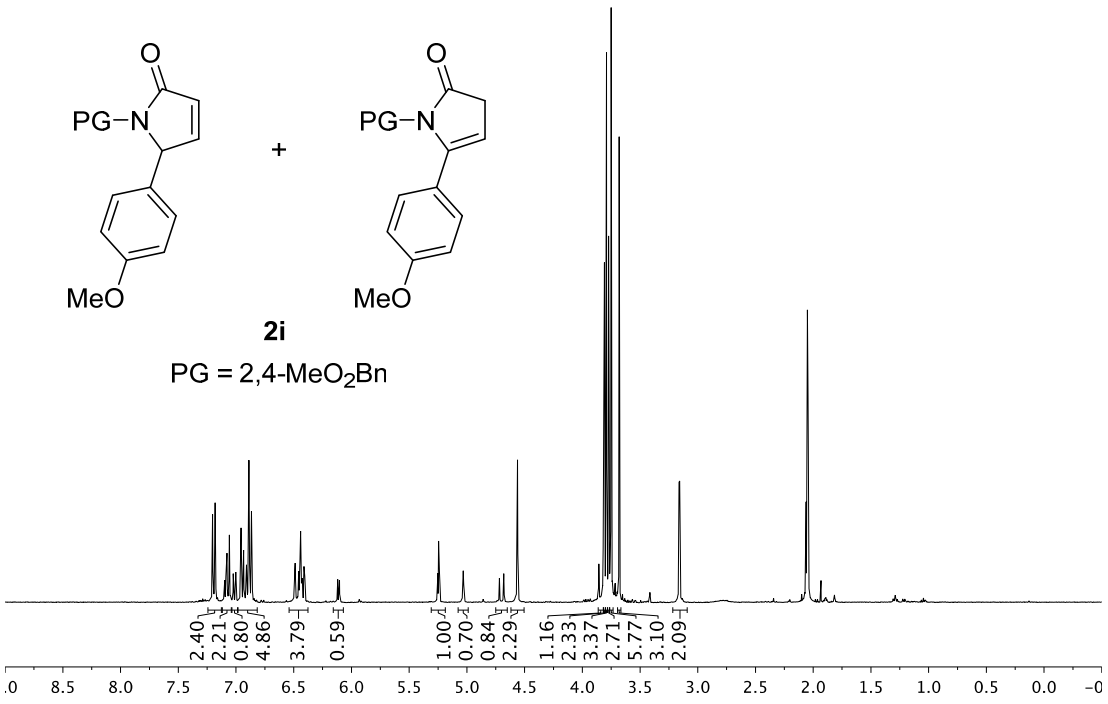
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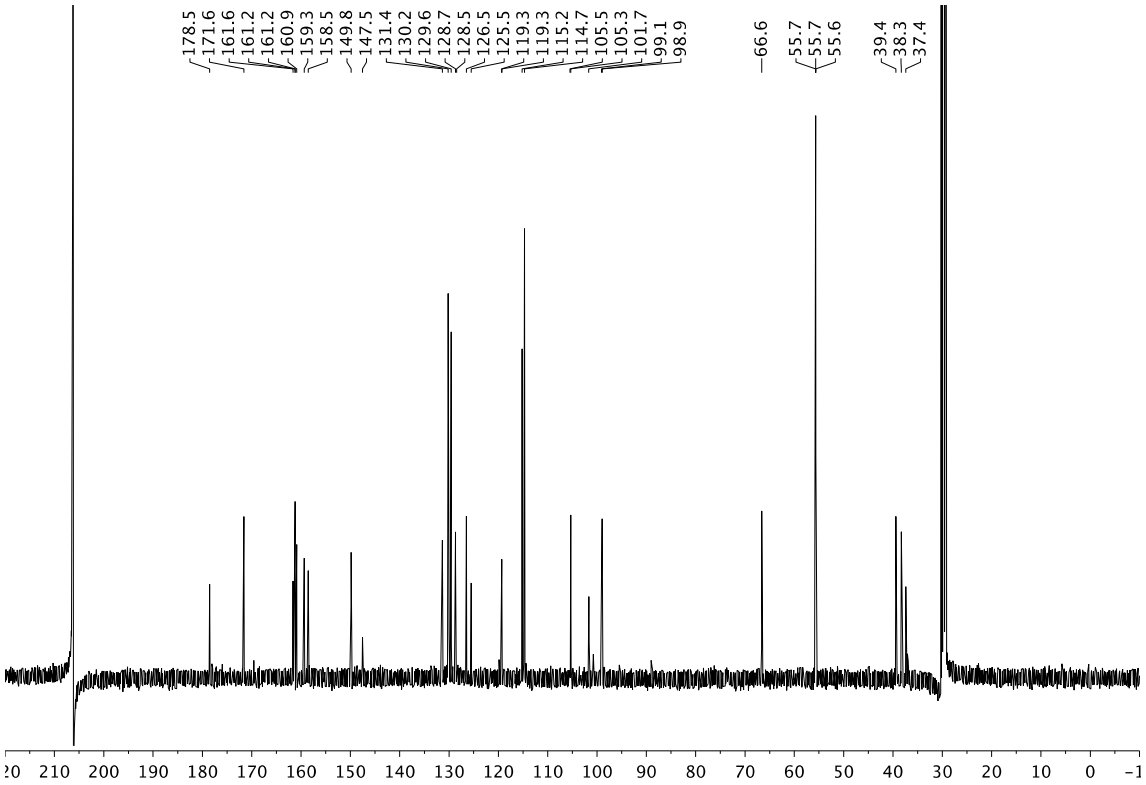
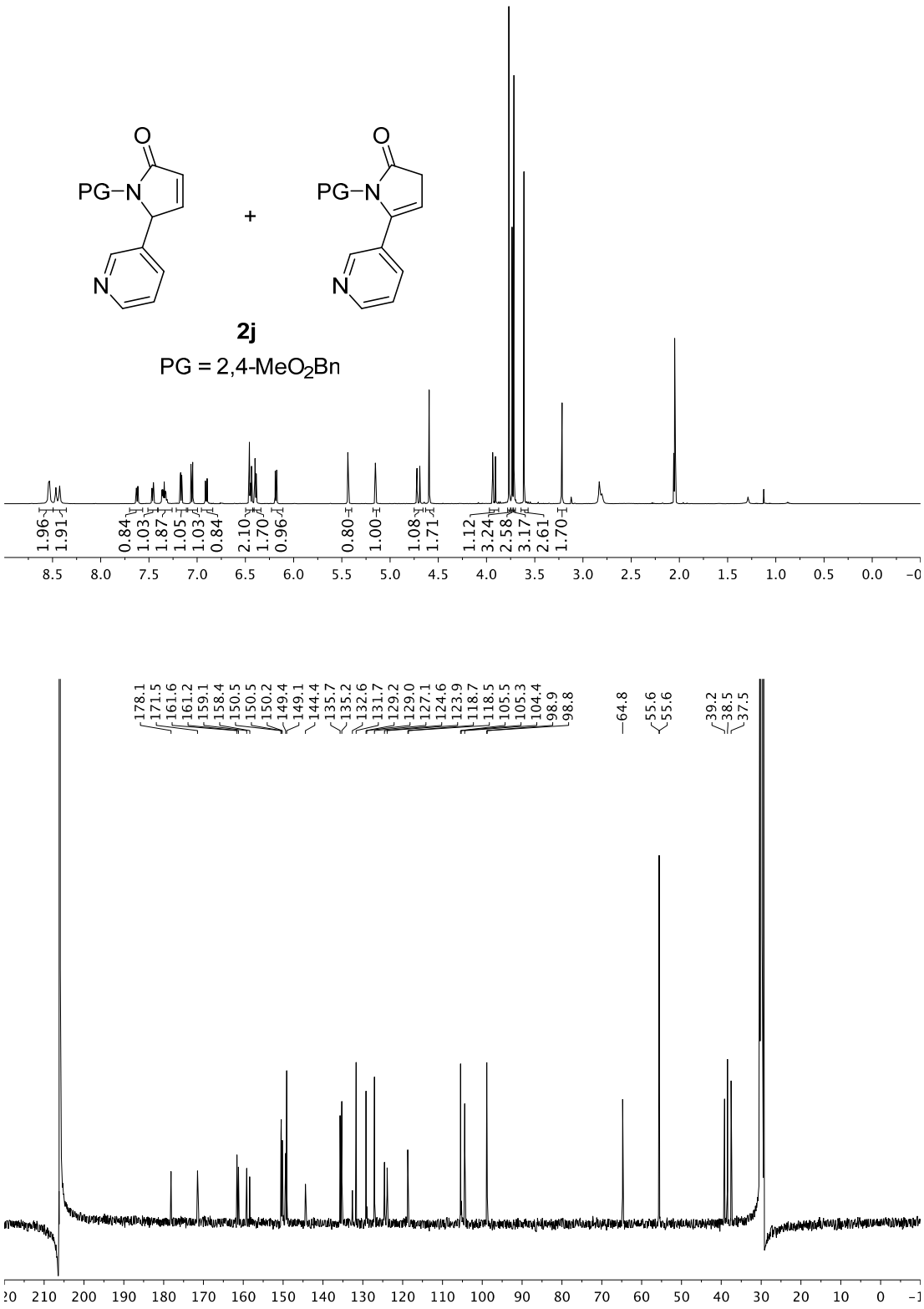
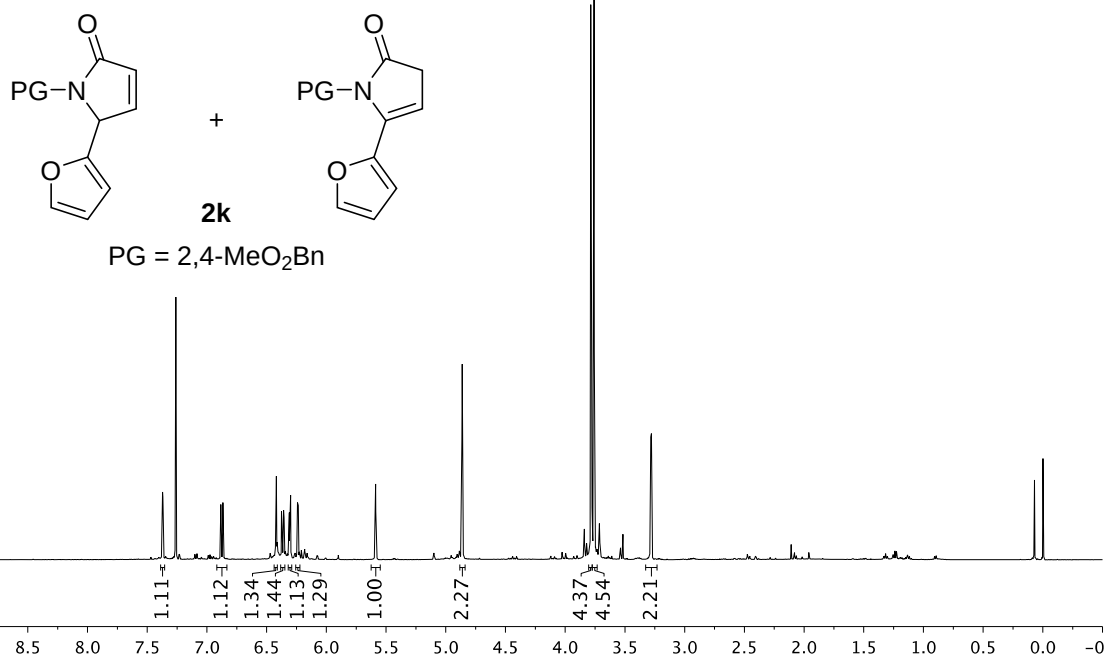
3.10
2.09

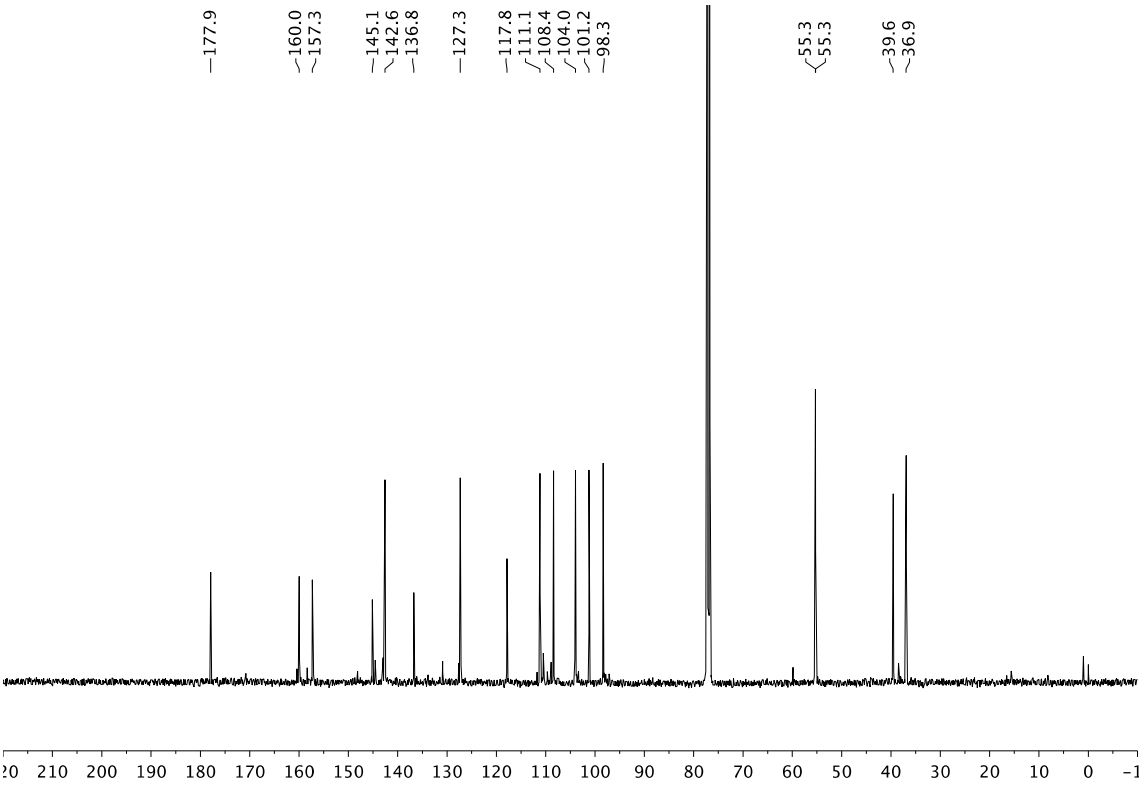

178.5
171.6
161.6
161.2
161.2
160.9
159.3
158.5
149.8
147.5
131.4
130.2
129.6
128.7
128.5
126.5
125.5
119.3
119.3
115.2
114.7
105.5
105.3
101.7
99.1
98.9
66.6
55.7
55.7
55.6
39.4
38.3
37.4

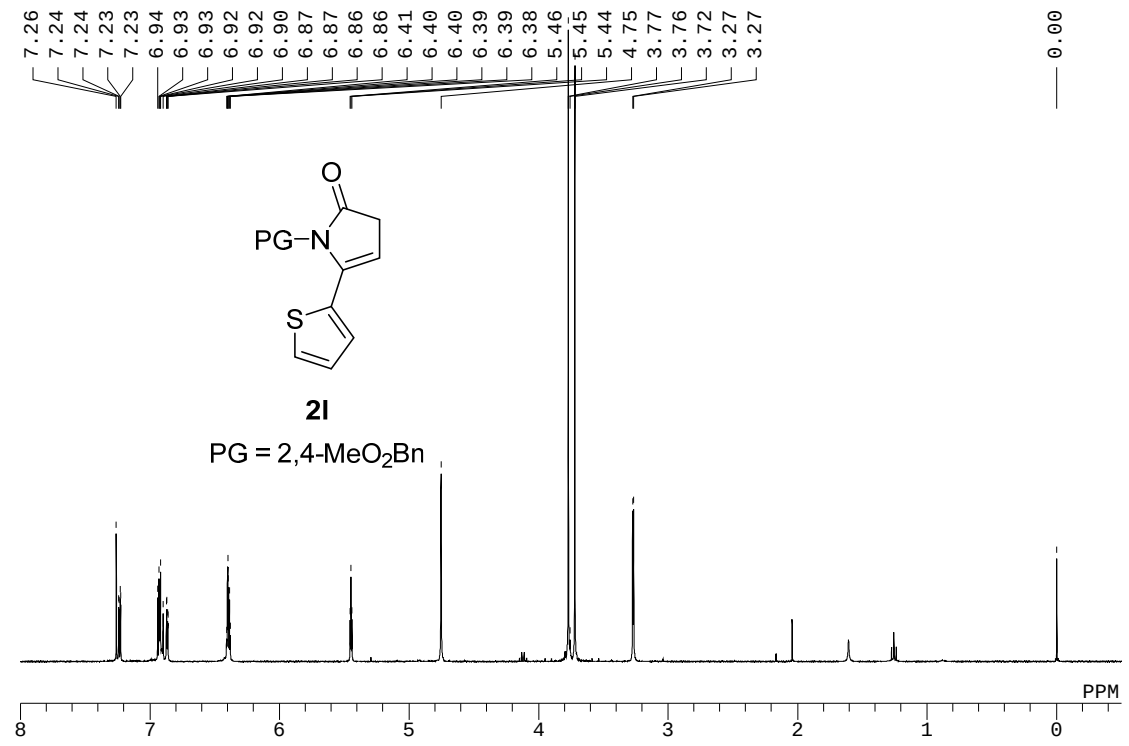

PG–N
O
N
+
PG–N
O
N
2j
PG = 2,4-MeO2Bn
1.96
1.91
0.84
1.03
1.87
1.05
1.03
0.84
2.10
1.70
0.96
0.80
1.00
1.08
1.71
1.12
3.24
2.58
3.17
2.61
1.70
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
178.1
171.5
161.6
161.2
159.1
158.4
150.5
150.5
150.2
149.4
149.1
144.4
135.7
135.2
132.6
131.7
129.2
129.0
127.1
124.6
123.9
118.7
118.5
105.5
105.3
104.4
98.9
98.8
64.8
55.6
55.6
39.2
38.5
37.5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

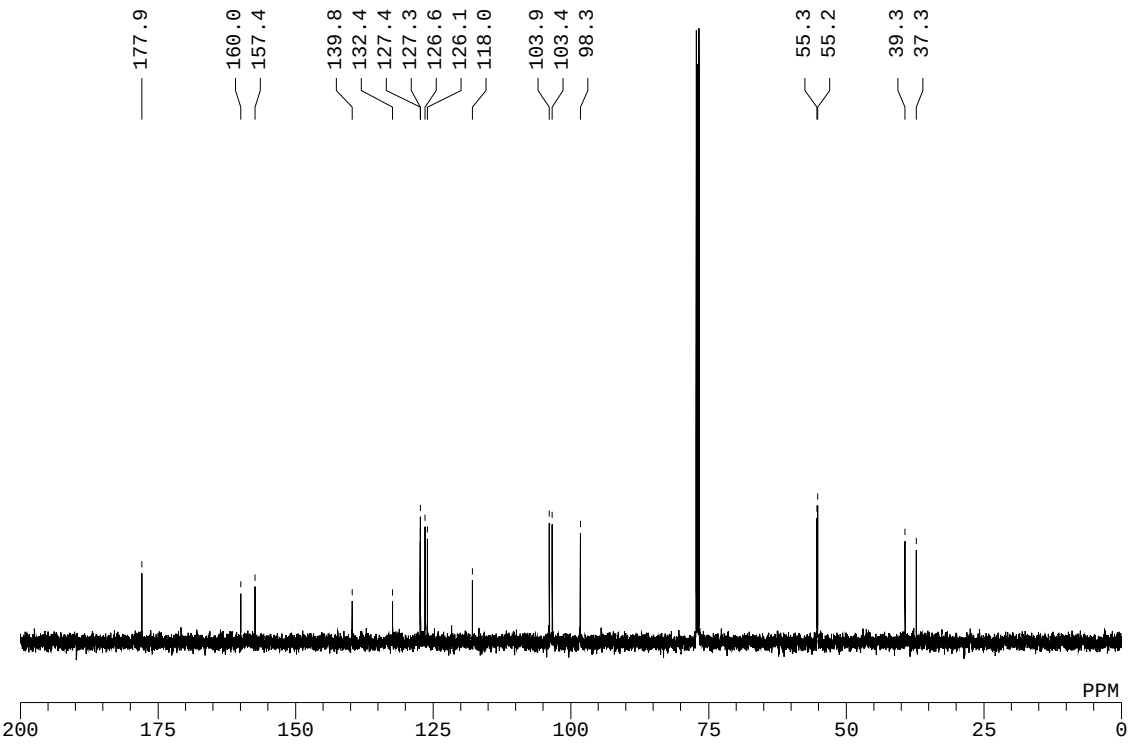


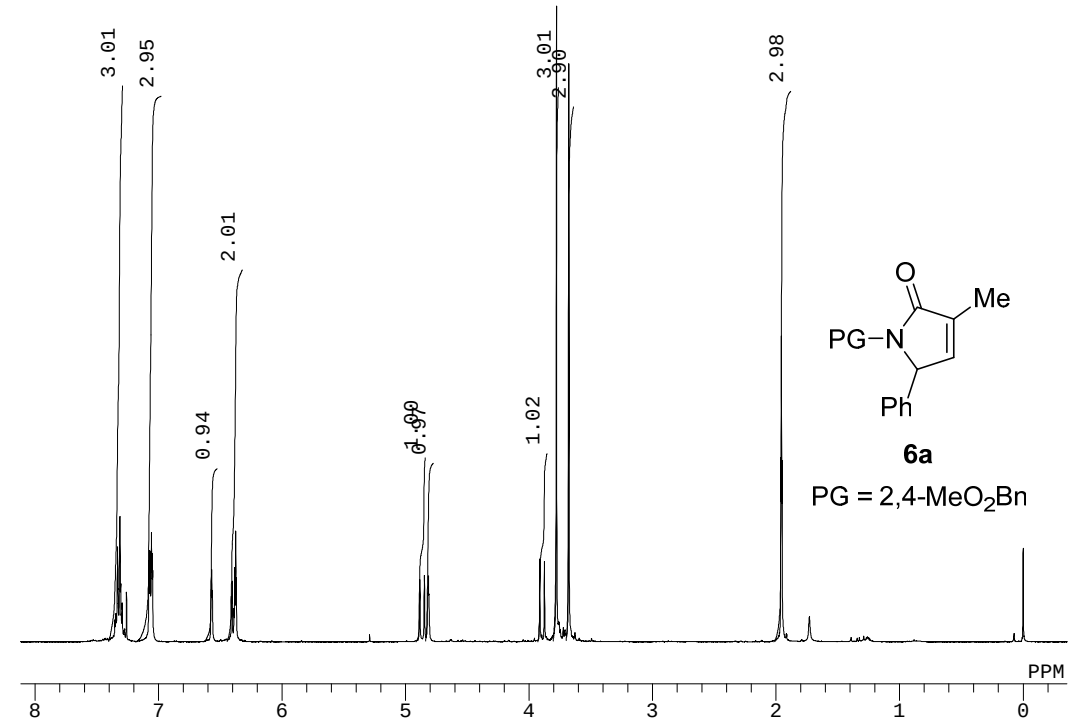
2k

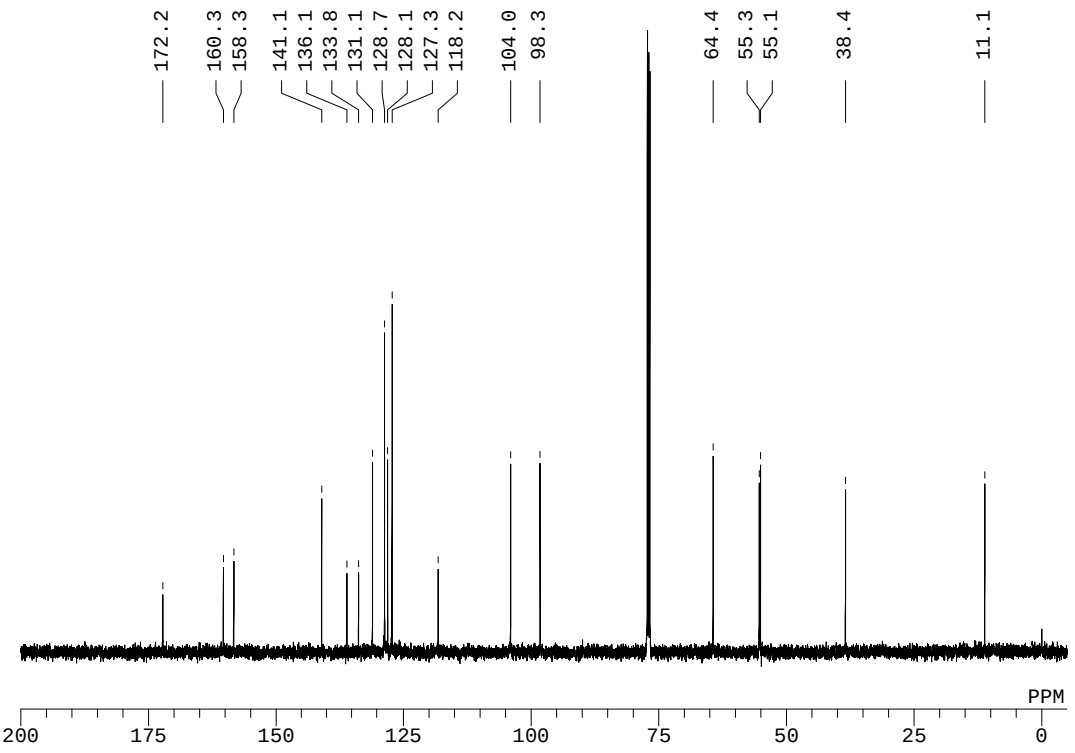
PG = 2,4-MeO_2Bn

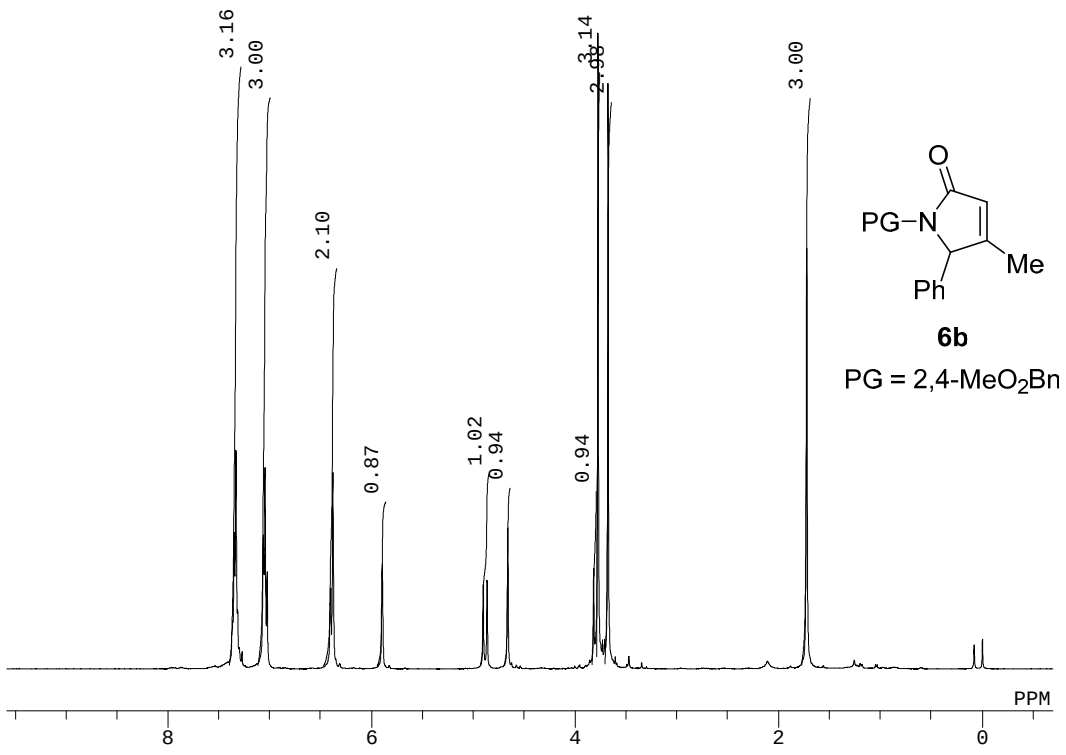


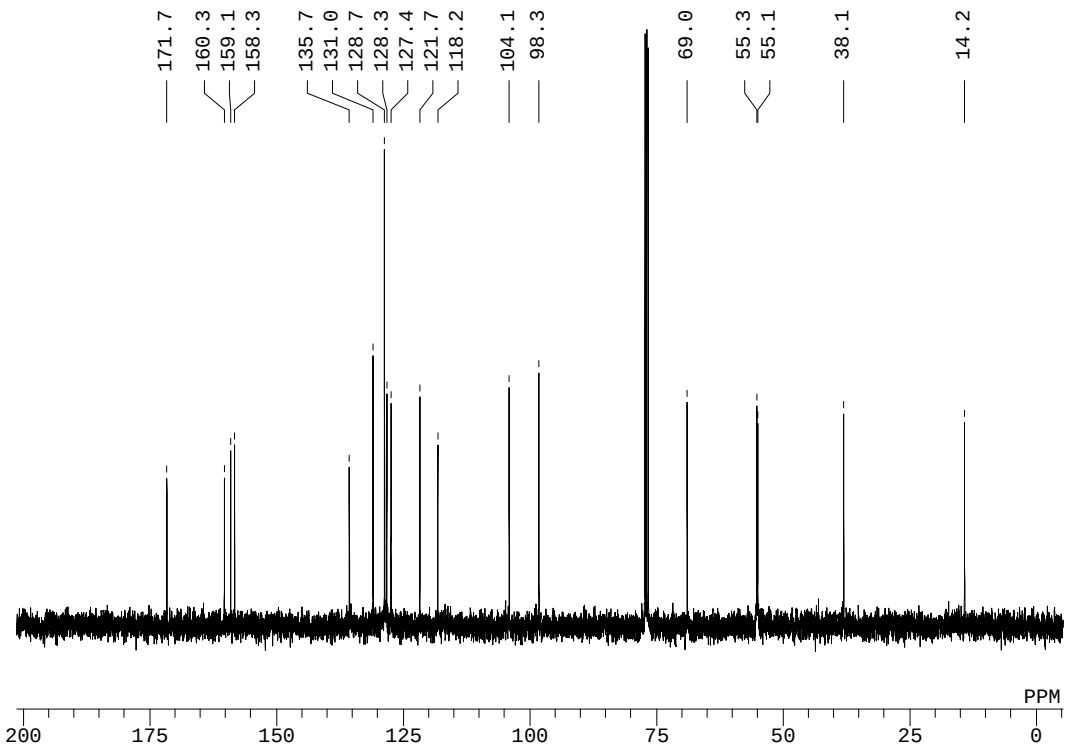

7.26
7.24
7.24
7.23
7.23
6.94
6.93
6.93
6.92
6.92
6.90
6.87
6.87
6.86
6.86
6.41
6.40
6.40
6.39
6.39
6.38
5.46
5.45
5.44
4.75
3.77
3.76
3.72
3.27
3.27
0.00
O
PG–N
S
2l
PG = 2,4-MeO2Bn
PPM
8
7
6
5
4
3
2
1
0

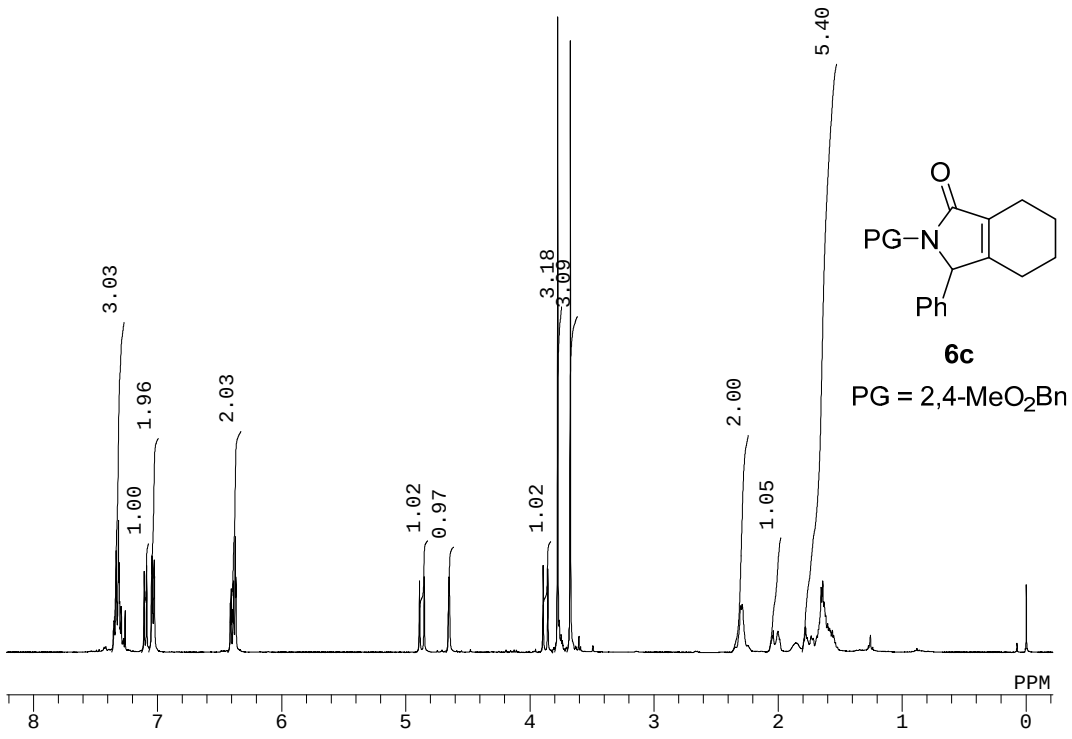

177.9
160.0
157.4
139.8
132.4
127.4
127.3
126.6
126.1
118.0
103.9
103.4
98.3
55.3
55.2
39.3
37.3
PPM
200
175
150
125
100
75
50
25
0

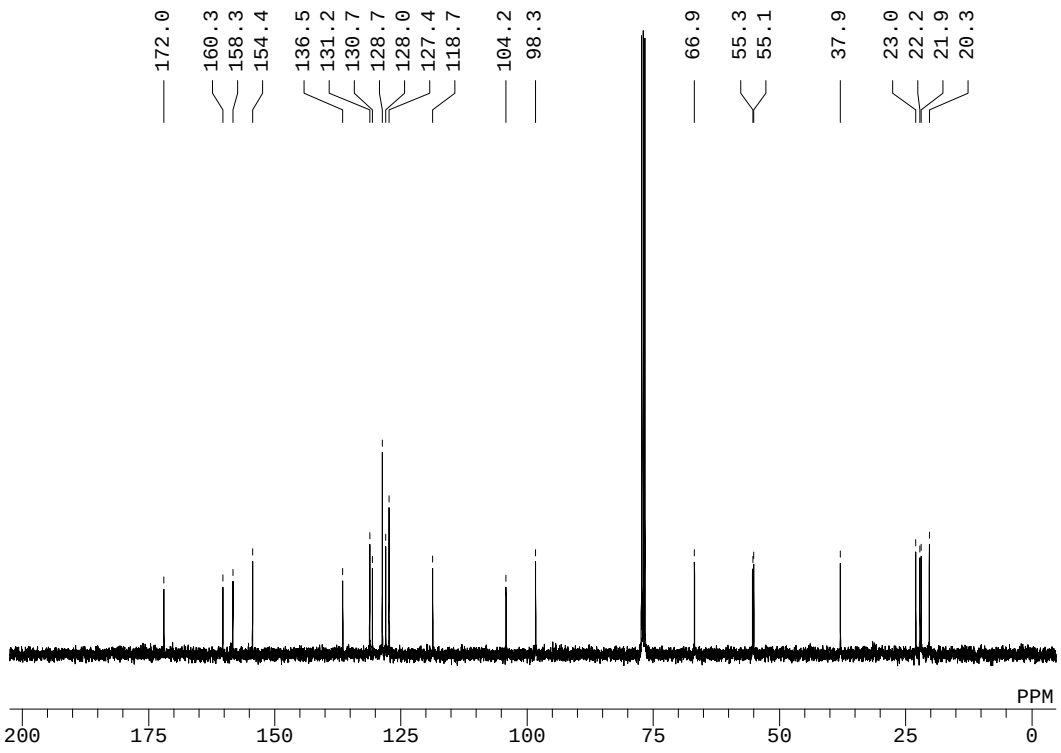

3.01
2.95
2.01
0.94
1.00
0.97
3.01
2.90
1.02
2.98
O
Me
PG–N
Ph
6a
PG = 2,4-MeO2Bn
PPM
8
7
6
5
4
3
2
1
0

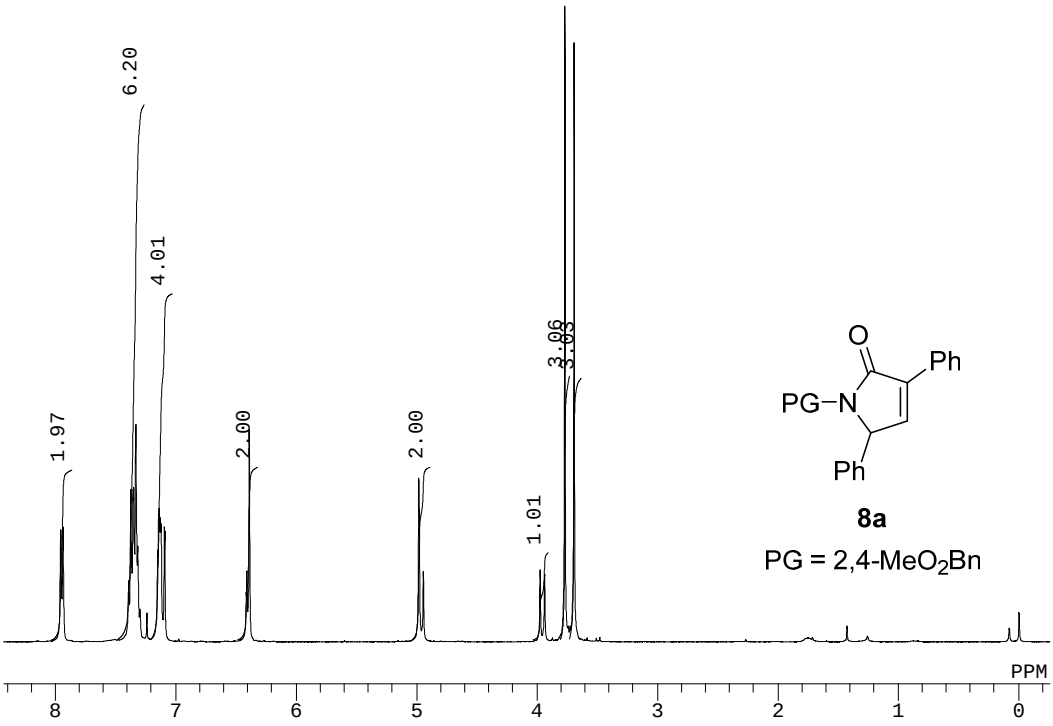

172.2
160.3
158.3
141.1
136.1
133.8
131.1
128.7
128.1
127.3
118.2
104.0
98.3
64.4
55.3
55.1
38.4
11.1
PPM
200
175
150
125
100
75
50
25
0

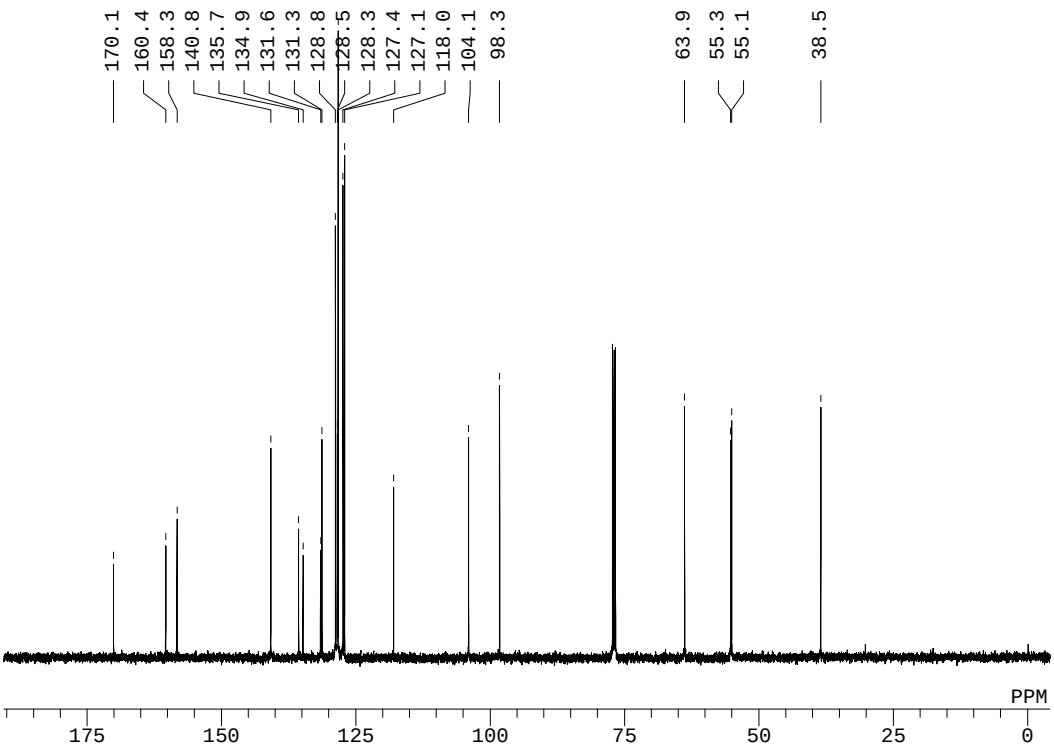

3.16
3.00
2.10
0.87
1.02
0.94
0.94
3.14
2.98
3.00
O
PG–N
Me
Ph
6b
PG = 2,4-MeO2Bn
PPM
8
6
4
2
0

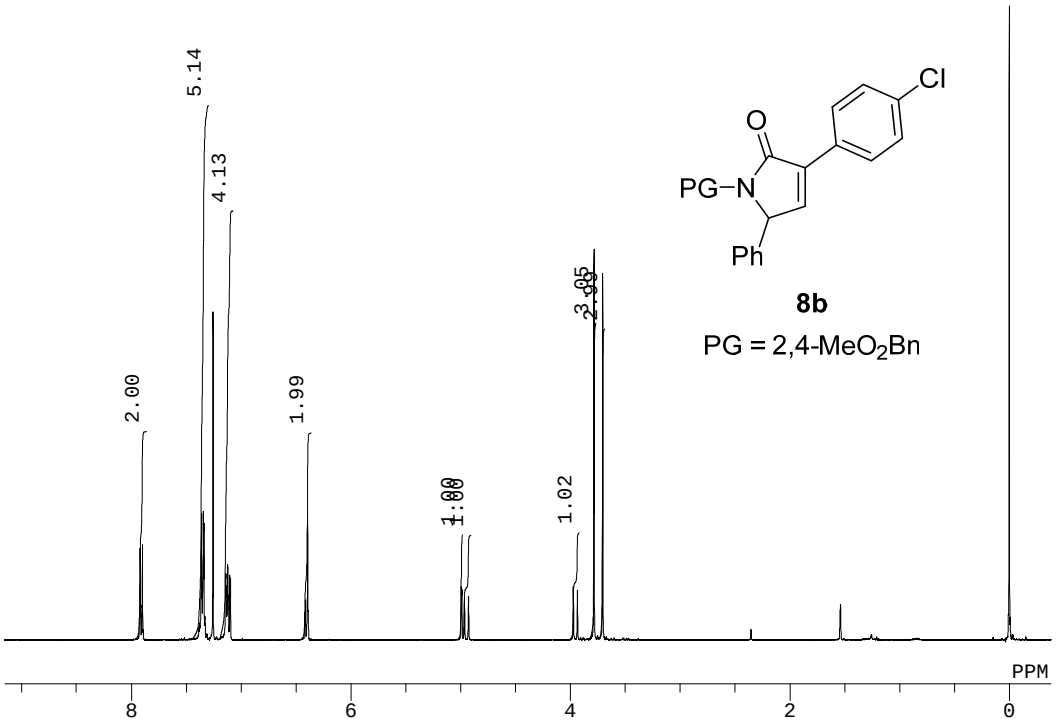

171.7
160.3
159.1
158.3
135.7
131.0
128.7
128.3
127.4
121.7
118.2
104.1
98.3
69.0
55.3
55.1
38.1
14.2
PPM
200
175
150
125
100
75
50
25
0

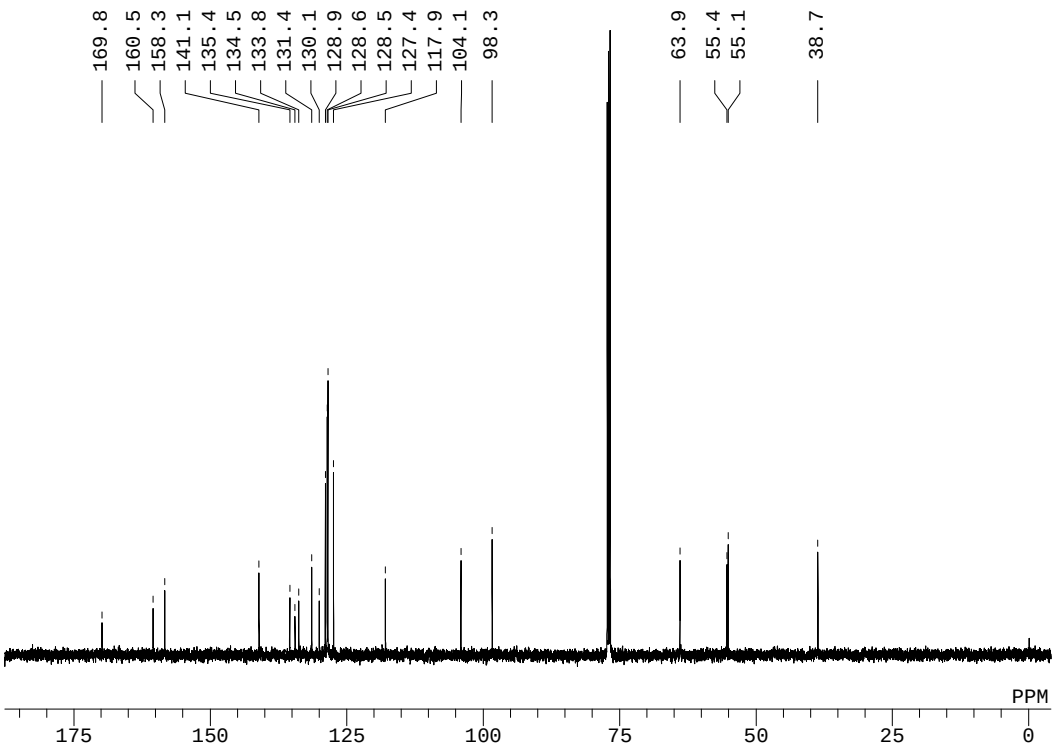

3.03
1.00
1.96
2.03
1.02
0.97
1.02
3.18
3.09
2.00
1.05
5.40
O
PG–N
Ph
6c
PG = 2,4-MeO2Bn
PPM
8
7
6
5
4
3
2
1
0

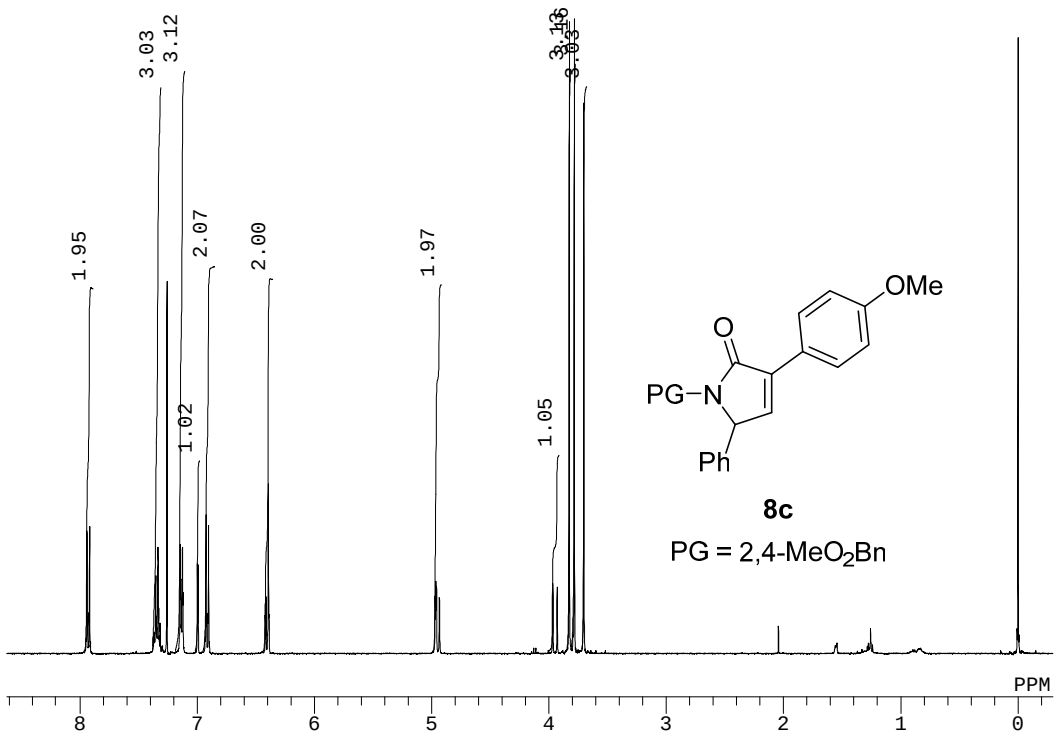

172.0
160.3
158.3
154.4
136.5
131.2
130.7
128.7
128.0
127.4
118.7
104.2
98.3
66.9
55.3
55.1
37.9
23.0
22.2
21.9
20.3
PPM
200
175
150
125
100
75
50
25
0

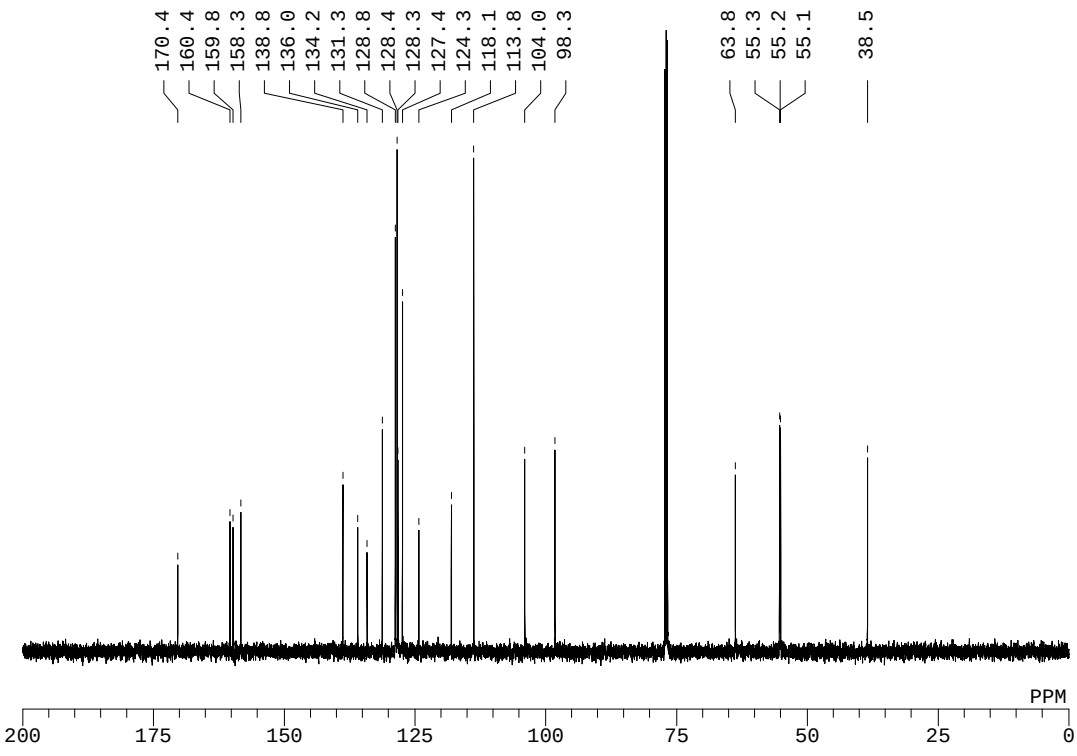

6.20
4.01
1.97
2.00
2.00
3.06
3.03
1.01
O
Ph
PG–N
Ph
8a
PG = 2,4-MeO2Bn
PPM
8
7
6
5
4
3
2
1
0

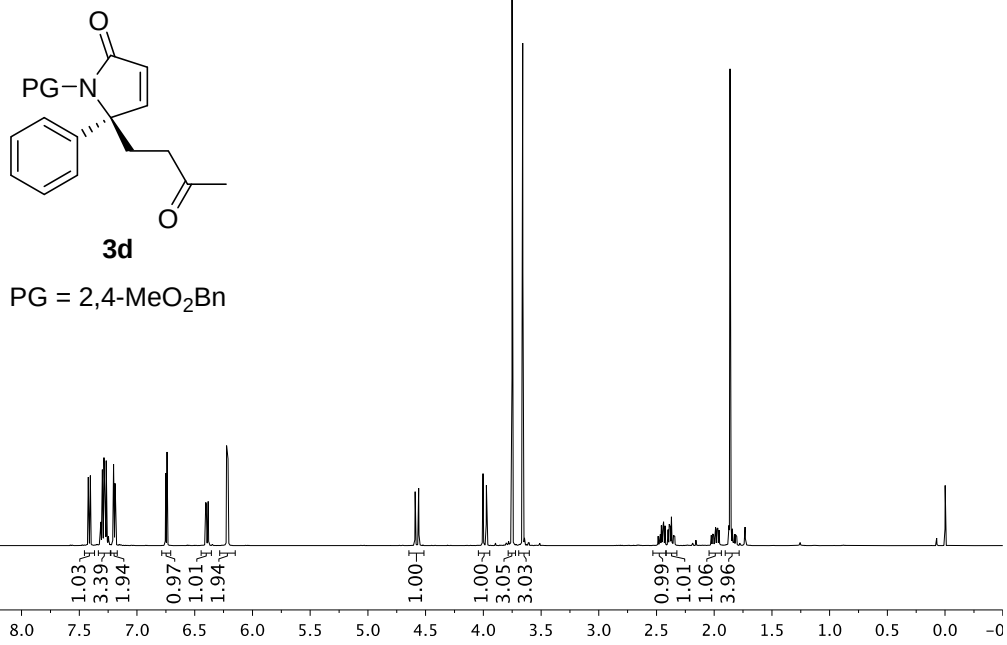

170.1
160.4
158.3
140.8
135.7
134.9
131.6
131.3
128.8
128.5
128.3
127.4
127.1
118.0
104.1
98.3
63.9
55.3
55.1
38.5
PPM
175
150
125
100
75
50
25
0


5.14
4.13
2.00
1.99
1.00
1.00
1.02
3.05
2.99
Cl
O
PG–N
Ph
8b
PG = 2,4-MeO2Bn
PPM
8
6
4
2
0


169.8
160.5
158.3
141.1
135.4
134.5
133.8
131.4
130.1
128.9
128.6
128.5
127.4
117.9
104.1
98.3
63.9
55.4
55.1
38.7
PPM
175
150
125
100
75
50
25
0

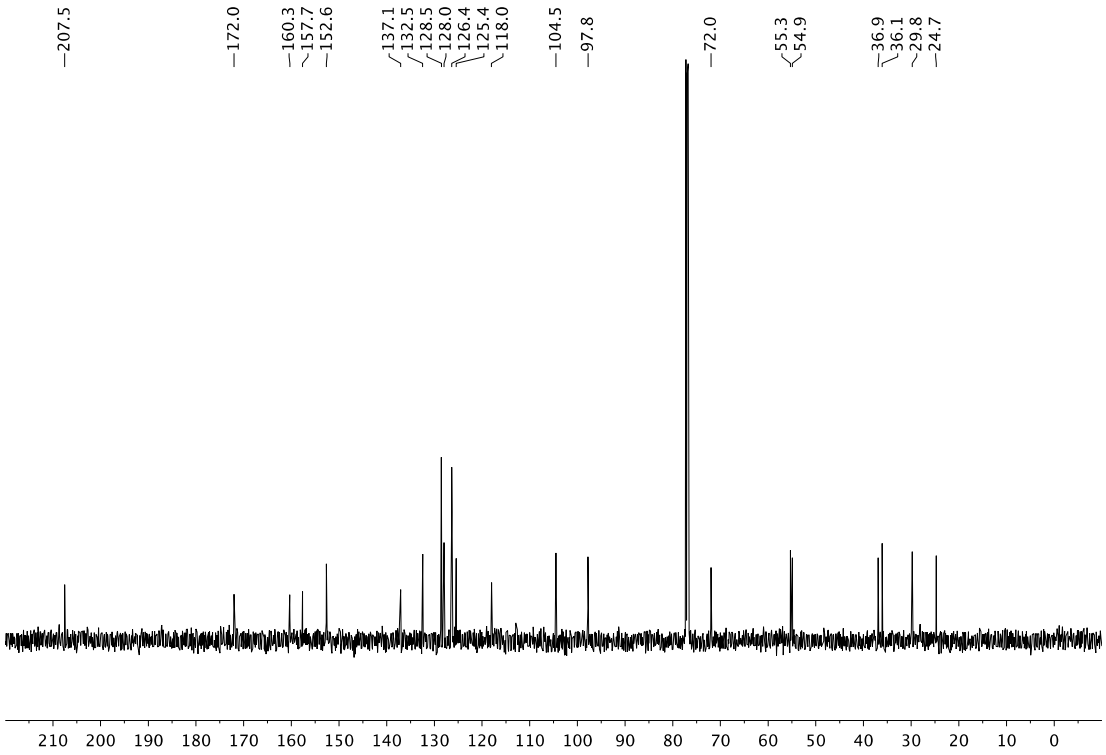

1.95
3.03
3.12
2.07
2.00
1.02
1.97
1.05
OMe
O
PG–N
Ph
8c
PG = 2,4-MeO2Bn
PPM
8
7
6
5
4
3
2
1
0

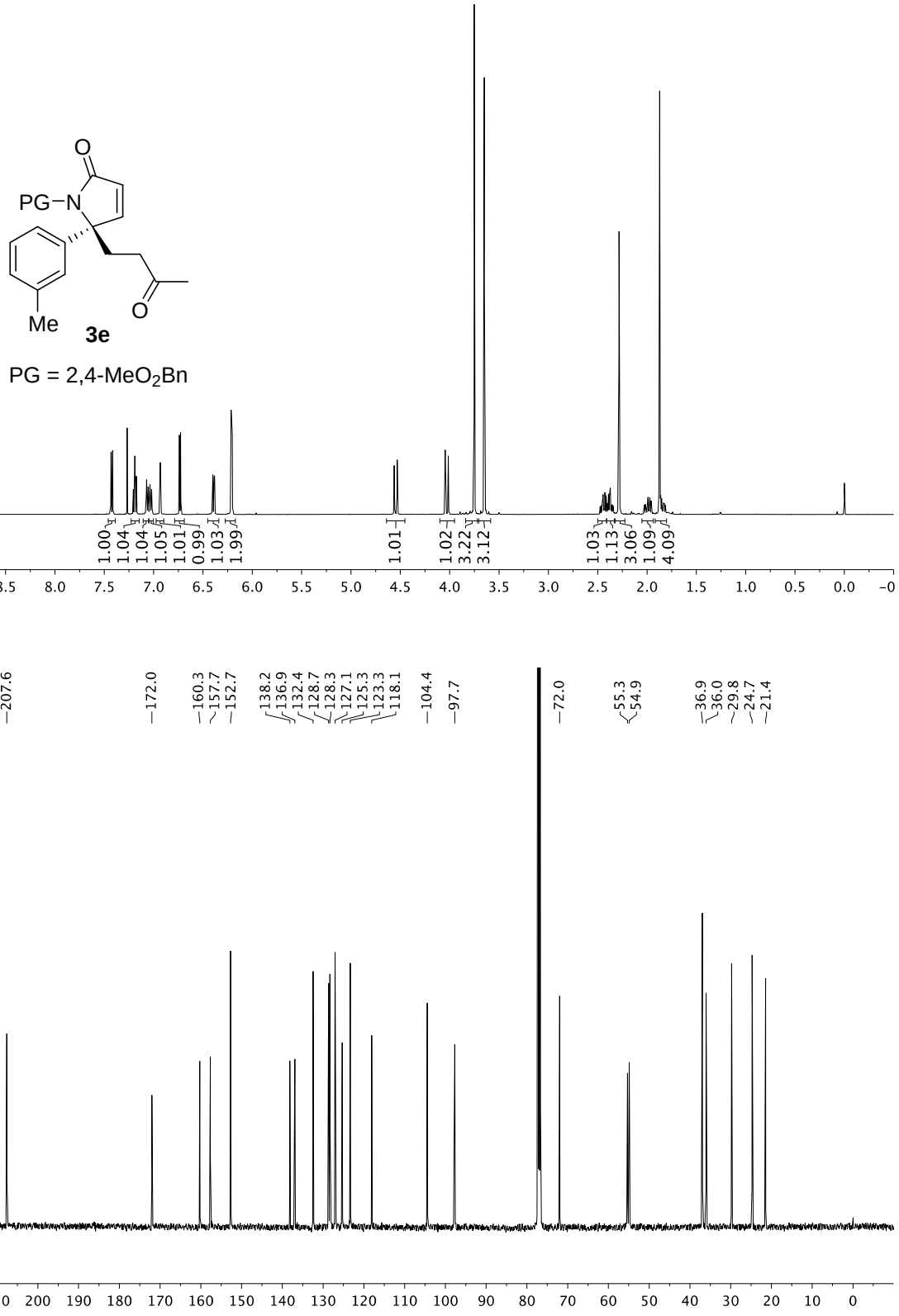

170.4
160.4
159.8
158.3
138.8
136.0
134.2
131.3
128.8
128.4
128.3
127.4
124.3
118.1
113.8
104.0
98.3
63.8
55.3
55.2
55.1
38.5
PPM
200
175
150
125
100
75
50
25
0

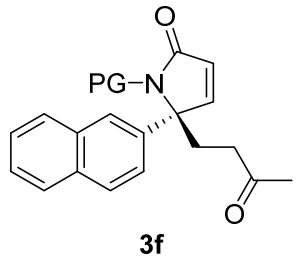


3d

PG = 2,4-MeO_2Bn

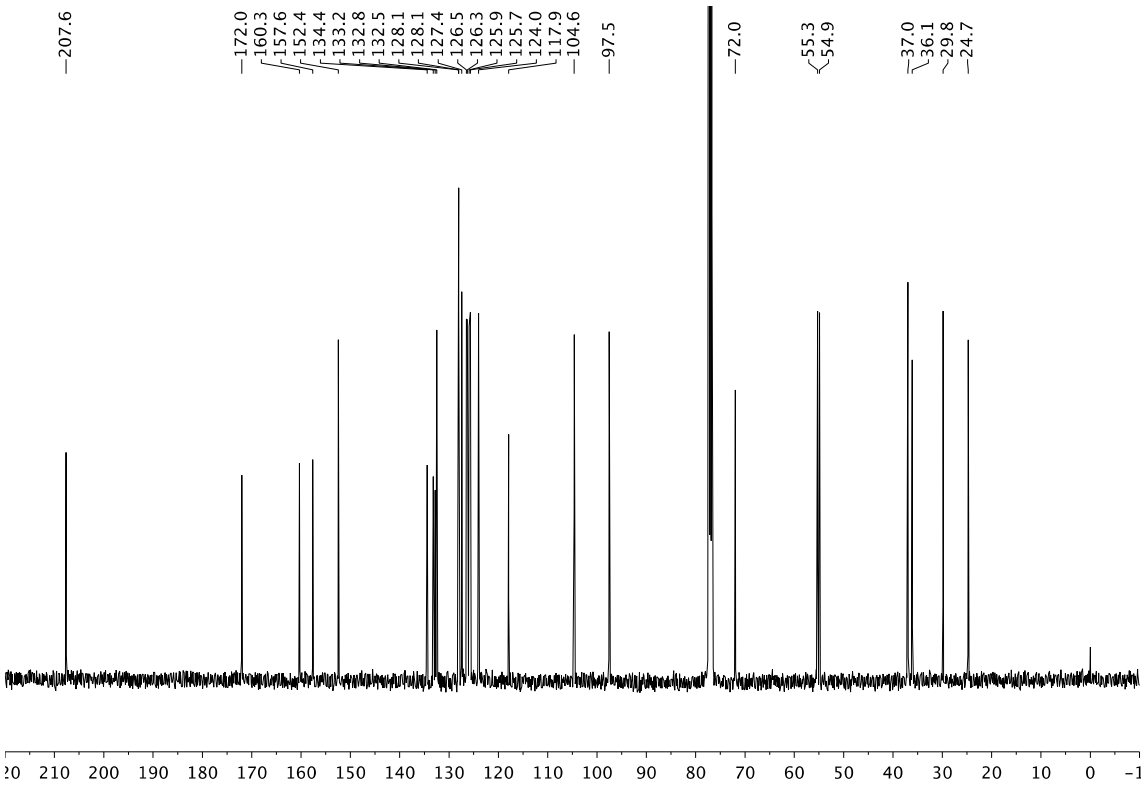


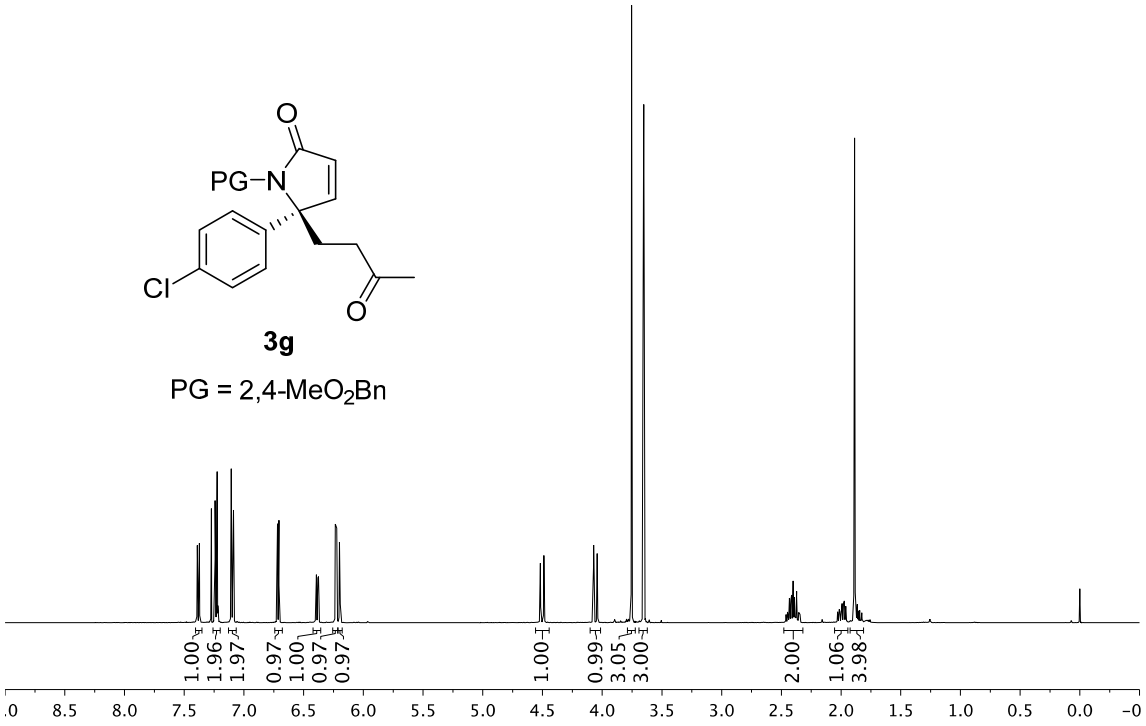

PG−N
O
O
Me
3e
PG = 2,4-MeO2Bn
1.00
1.04
1.04
1.05
1.01
0.99
1.03
1.99
1.01
1.02
3.22
3.12
1.03
1.13
3.06
1.09
4.09
207.6
172.0
160.3
157.7
152.7
138.2
136.9
132.4
128.7
128.3
127.1
125.3
123.3
118.1
104.4
97.7
72.0
55.3
54.9
36.9
36.0
29.8
24.7
21.4

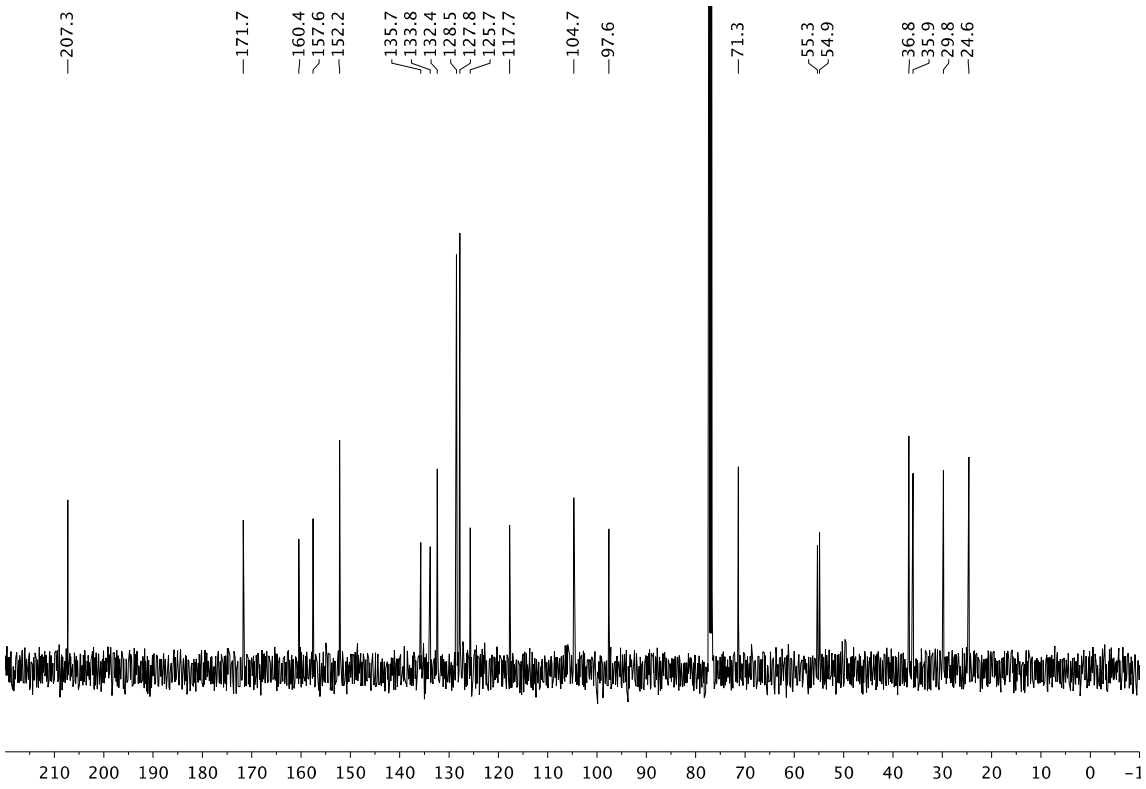


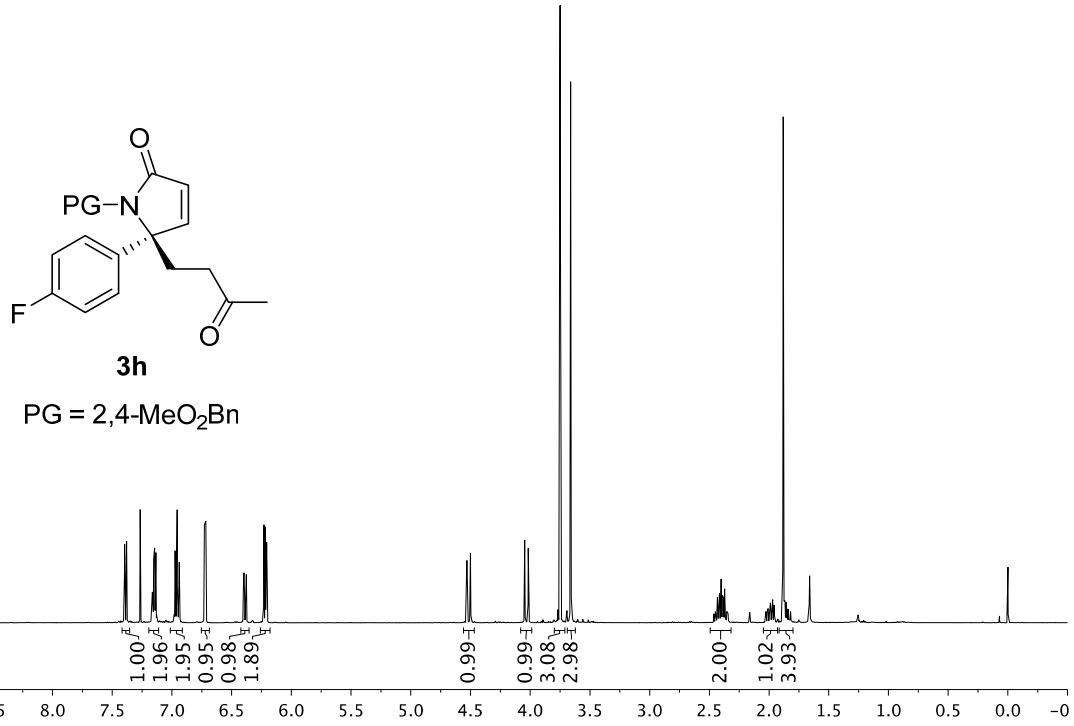
3f

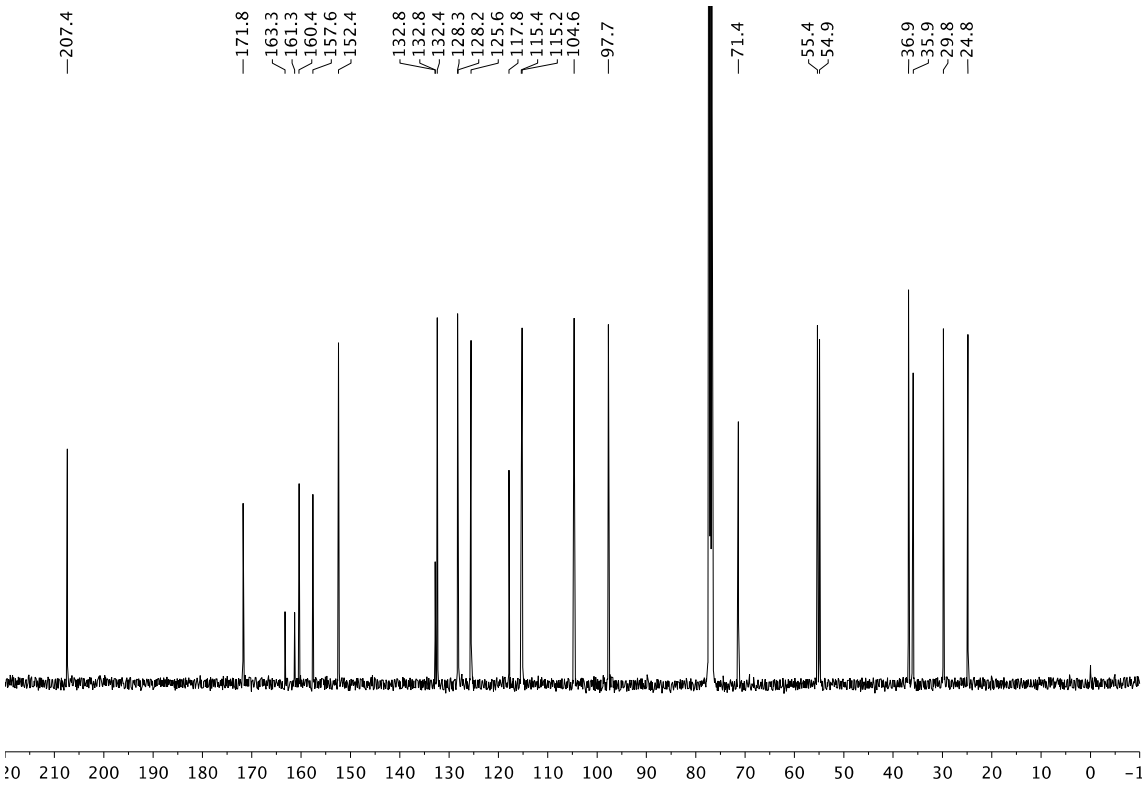
PG = 2,4-MeO_2Bn

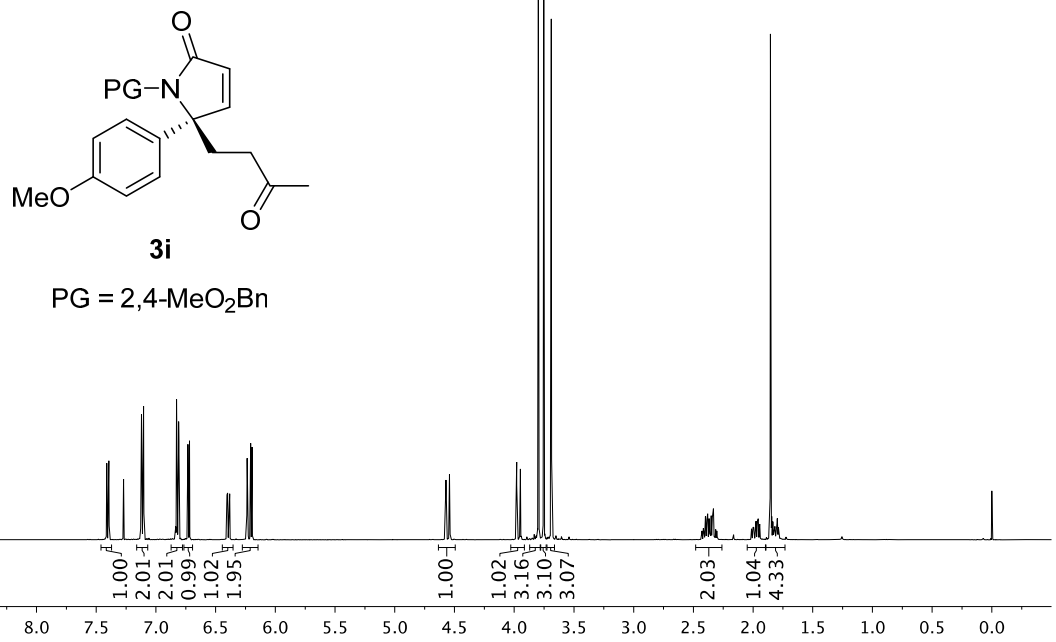



O
PG–N
Cl
O
3g
PG = 2,4-MeO2Bn
1.00
1.96
1.97
0.97
1.00
0.97
0.97
1.00
0.99
3.05
3.00
2.00
1.06
3.98
.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0


207.3
171.7
160.4
157.6
152.2
135.7
133.8
132.4
128.5
127.8
125.7
117.7
104.7
97.6
71.3
55.3
54.9
36.8
35.9
29.8
24.6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1

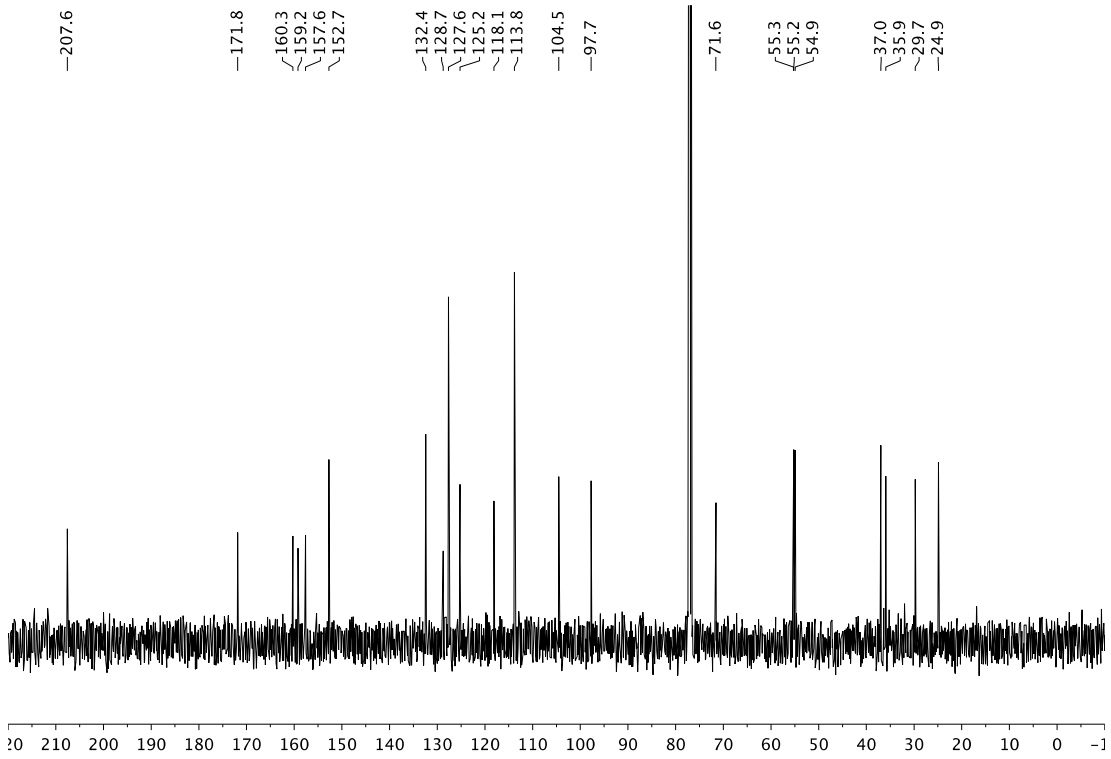

O
PG–N
F
O
3h
PG = 2,4-MeO2Bn
1.00
1.96
1.95
0.95
0.98
1.89
0.99
0.99
3.08
2.98
2.00
1.02
3.93

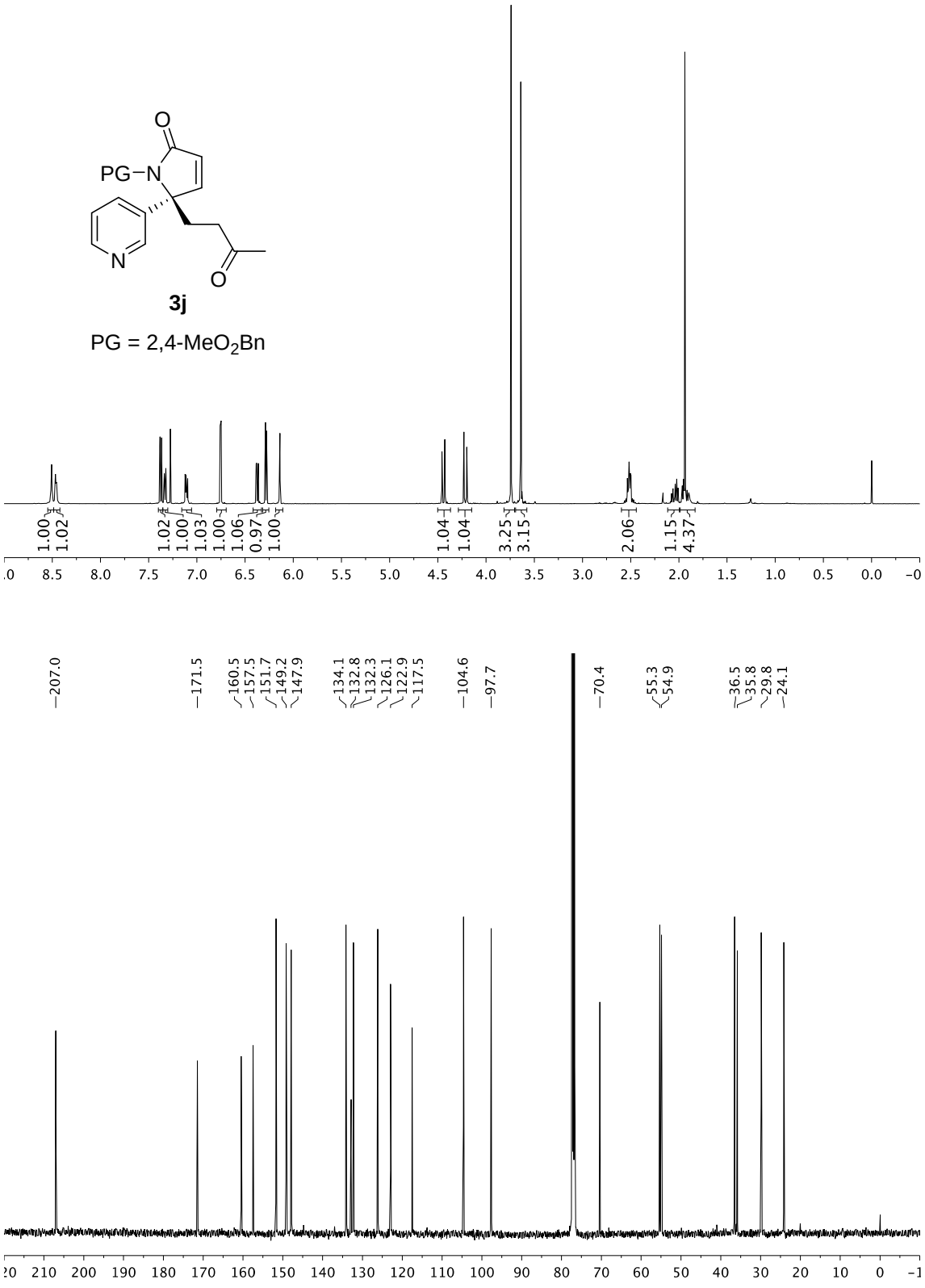

207.4
171.8
163.3
161.3
160.4
157.6
152.4
132.8
132.8
132.4
128.3
128.2
125.6
117.8
115.4
115.2
104.6
97.7
71.4
55.4
54.9
36.9
35.9
29.8
24.8

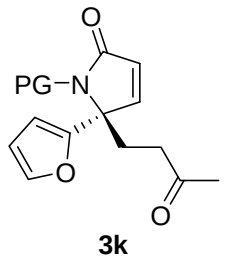


3i

PG = 2,4-MeO_2Bn

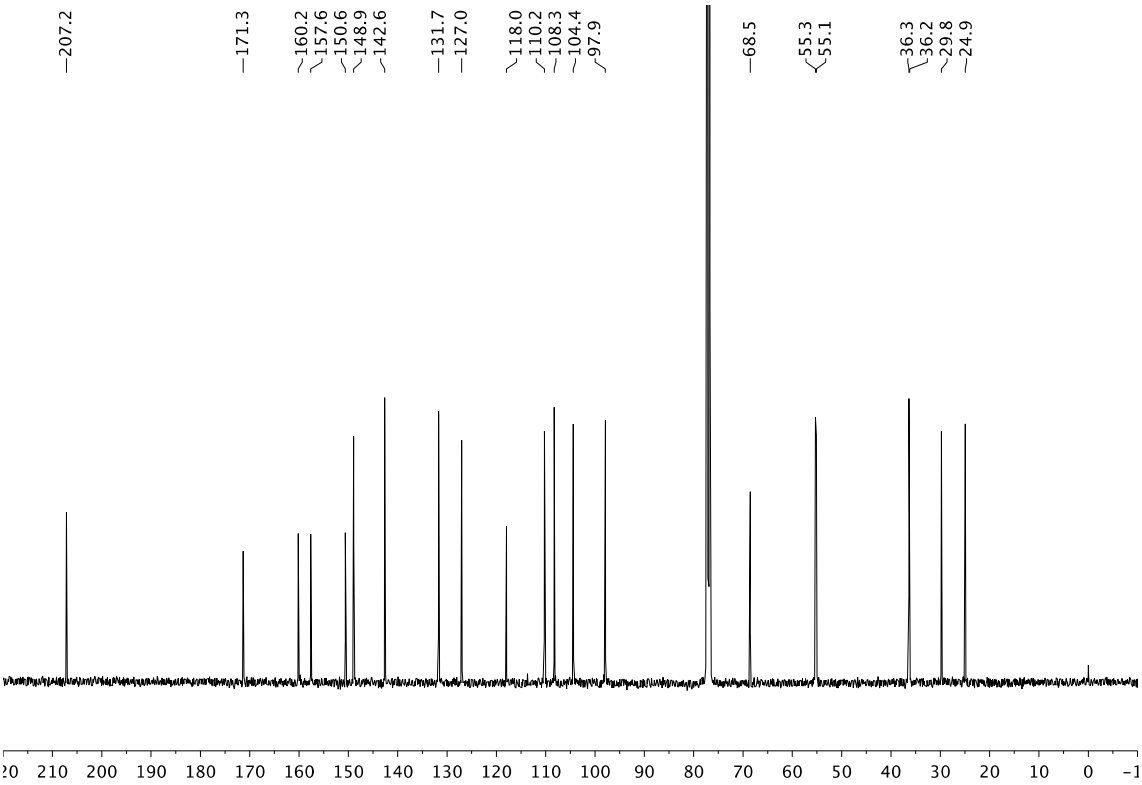


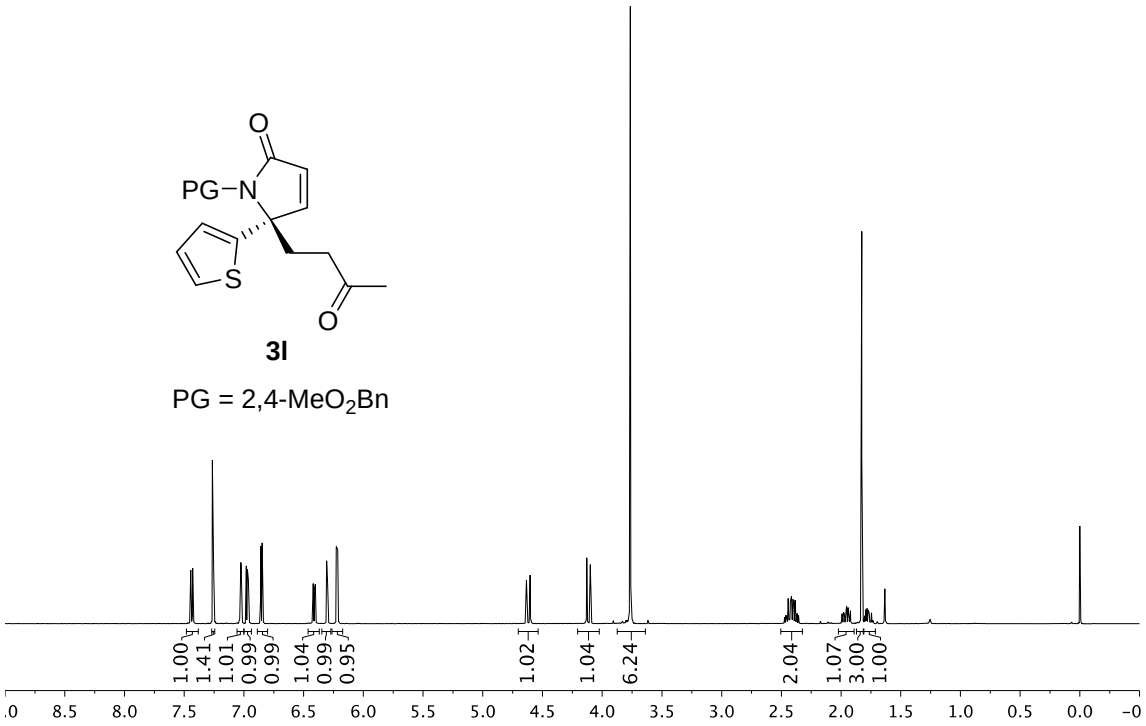

O
PG−N
N
O
3j
PG = 2,4-MeO2Bn
1.00
1.02
1.02
1.00
1.03
1.00
1.06
0.97
1.00
1.04
1.04
3.25
3.15
2.06
1.15
4.37
207.0
171.5
160.5
157.5
151.7
149.2
147.9
134.1
132.8
132.3
126.1
122.9
117.5
104.6
97.7
70.4
55.3
54.9
36.5
35.8
29.8
24.1



3k

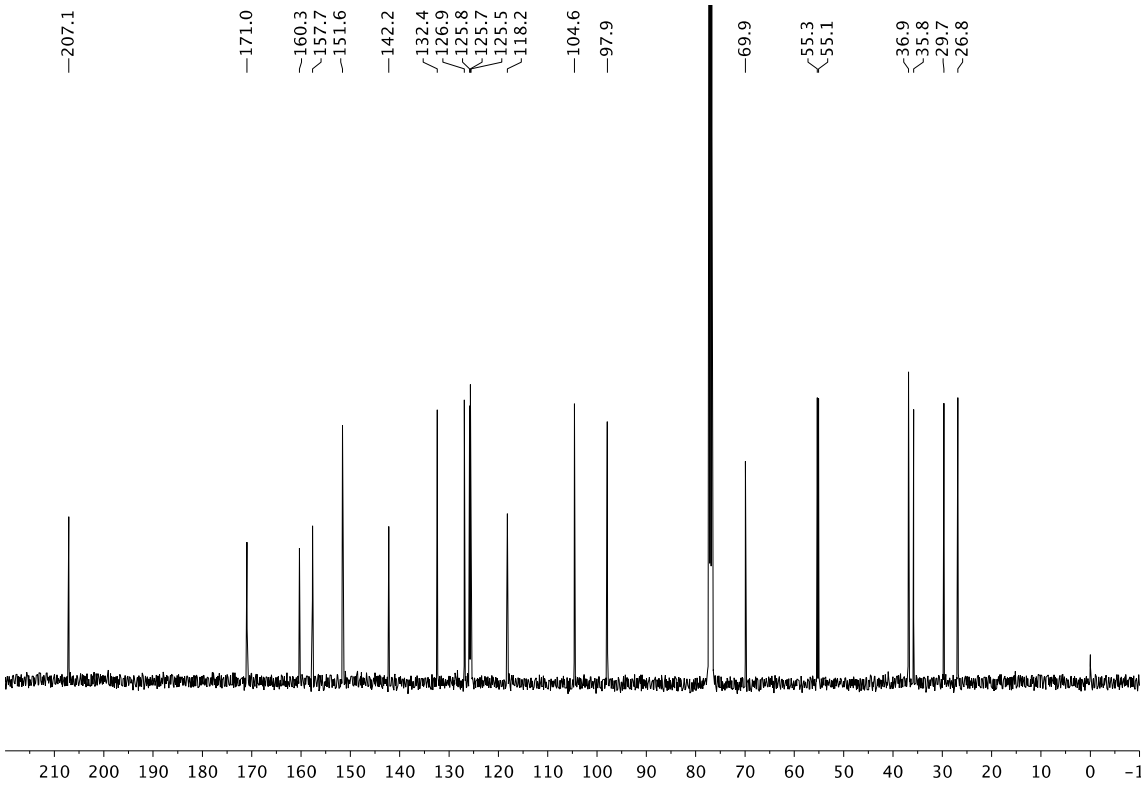
PG = 2,4-MeO_2Bn

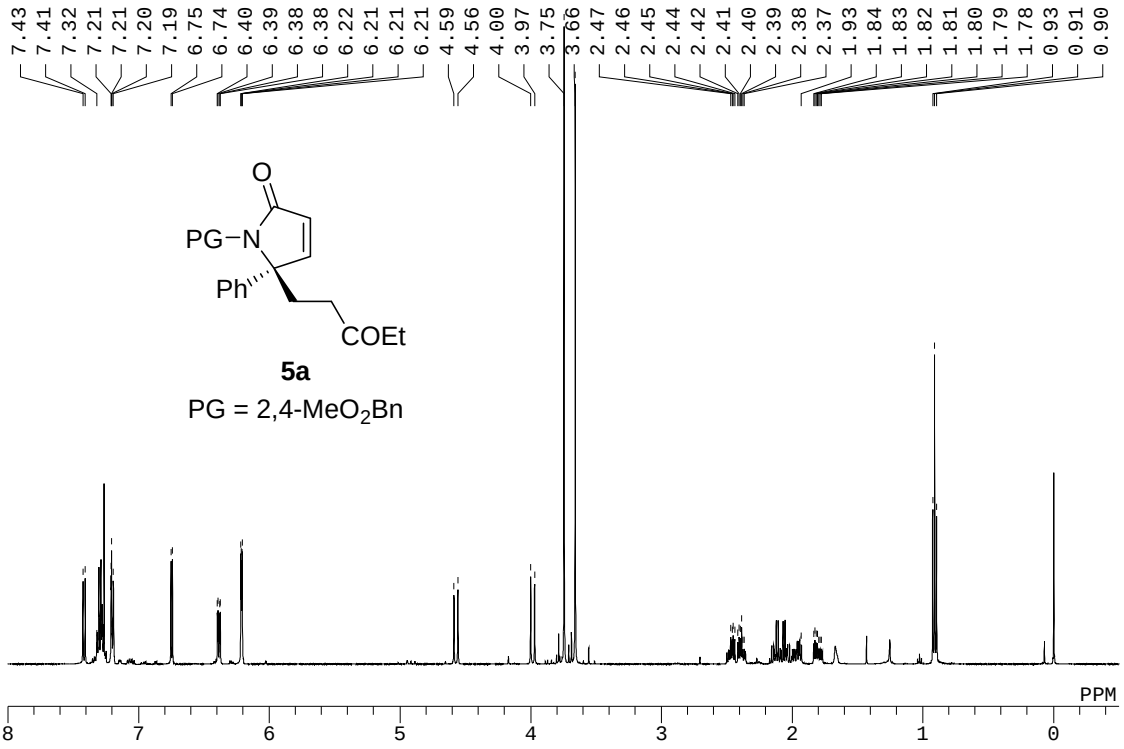




3l

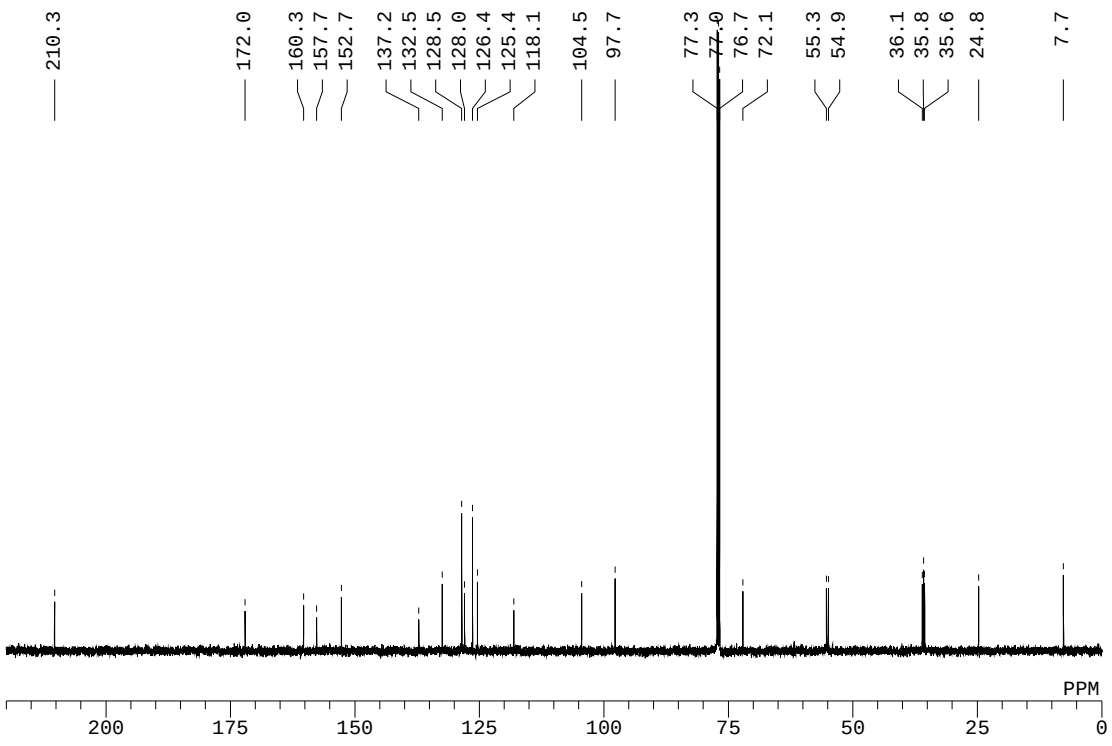
PG = 2,4-MeO_2Bn

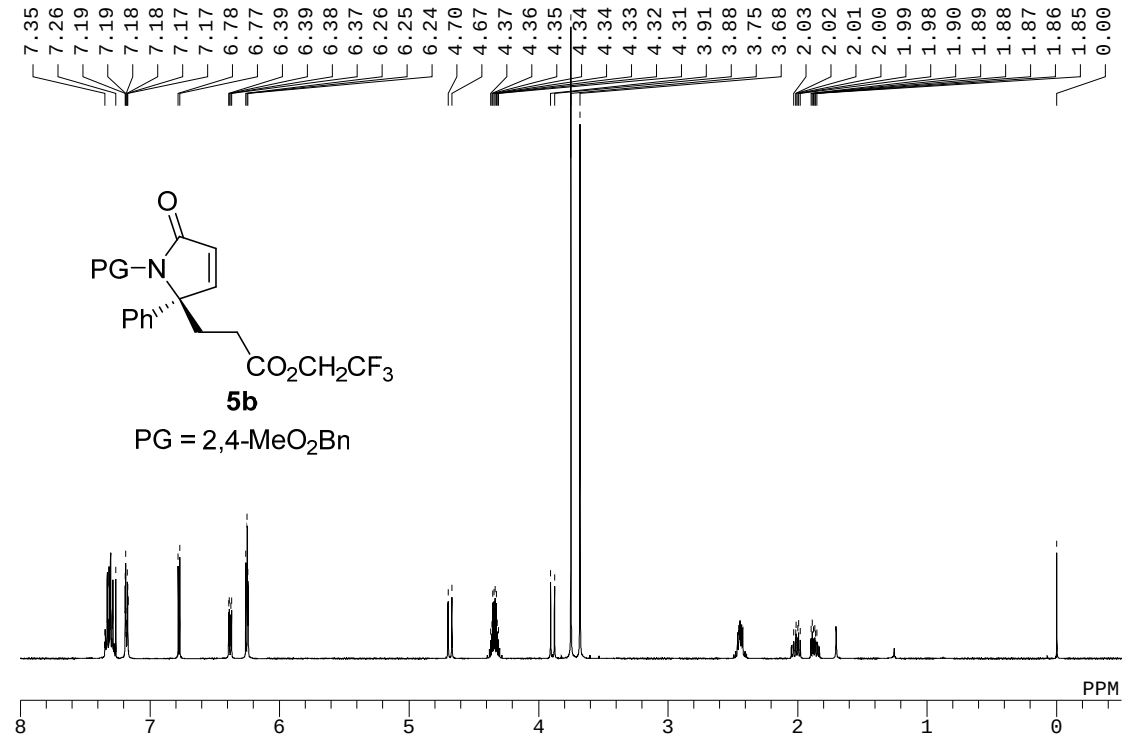


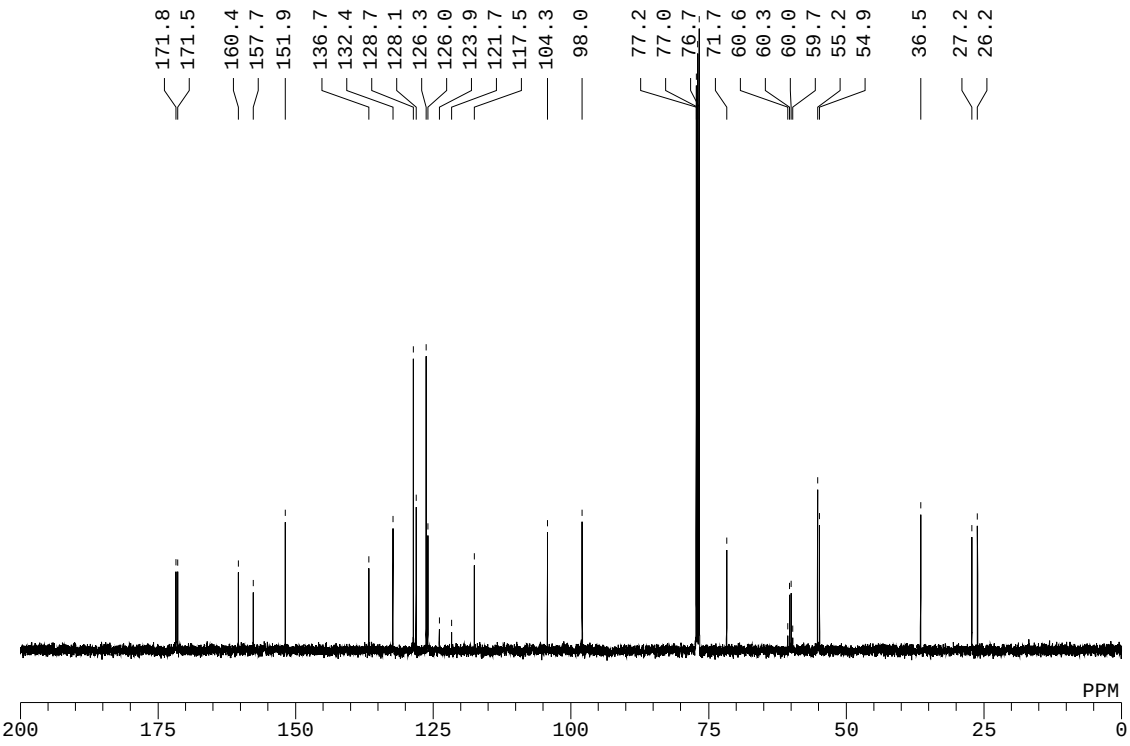


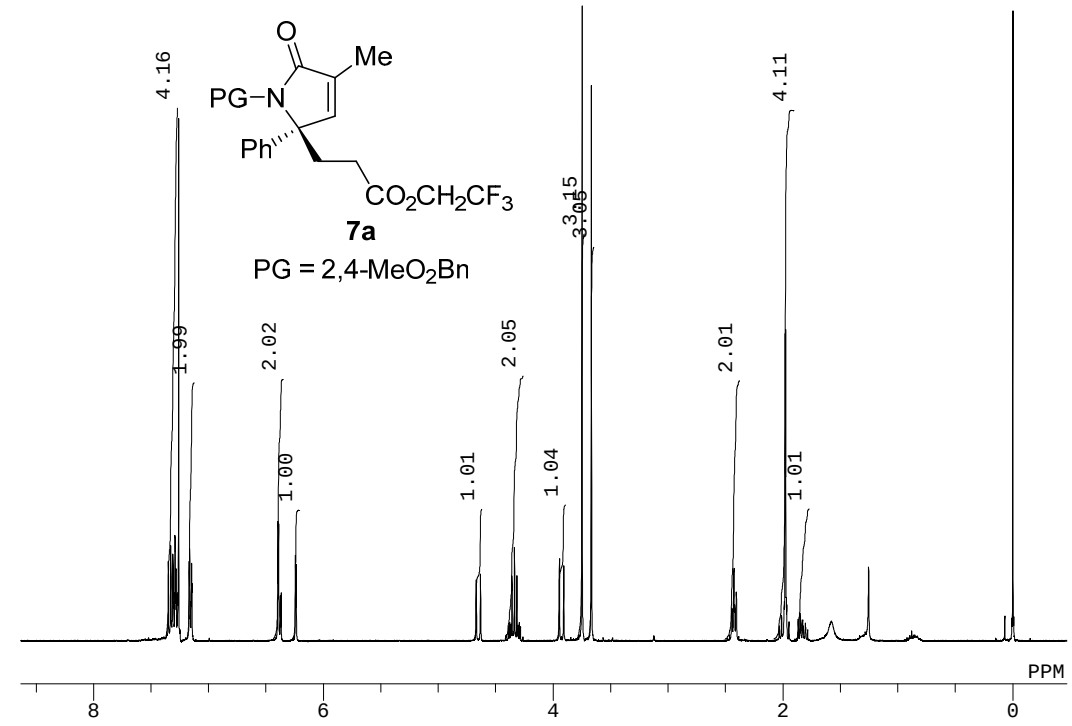
5a

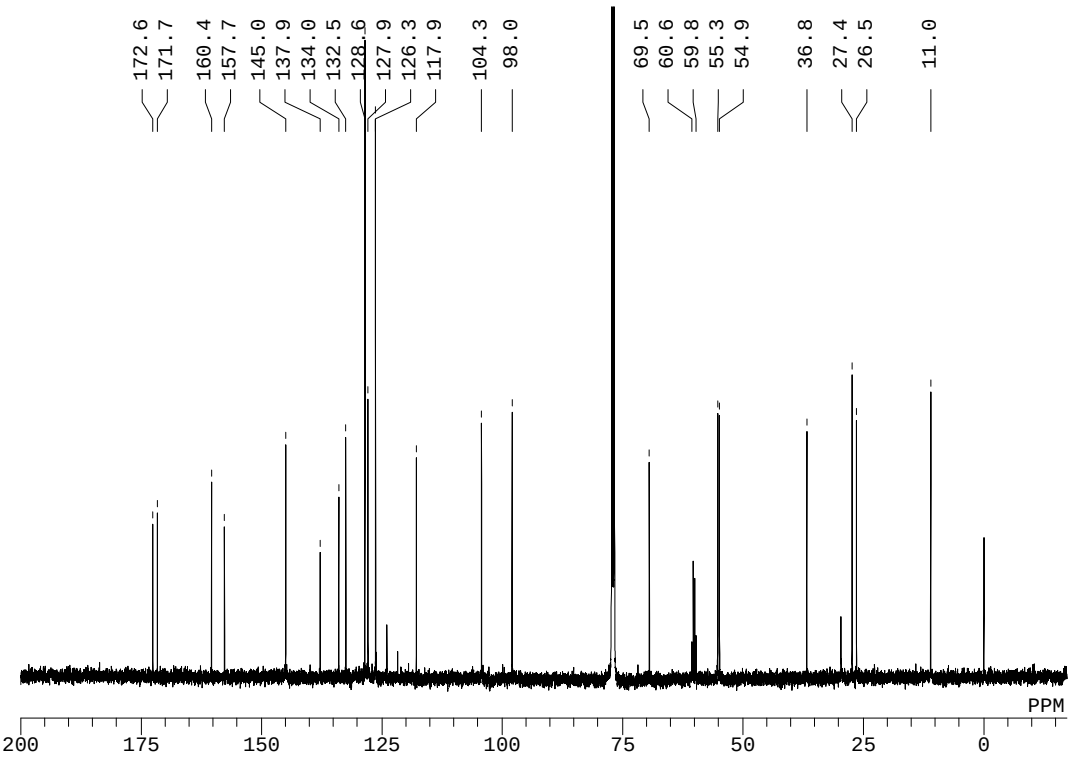
PG = 2,4-MeO_2Bn

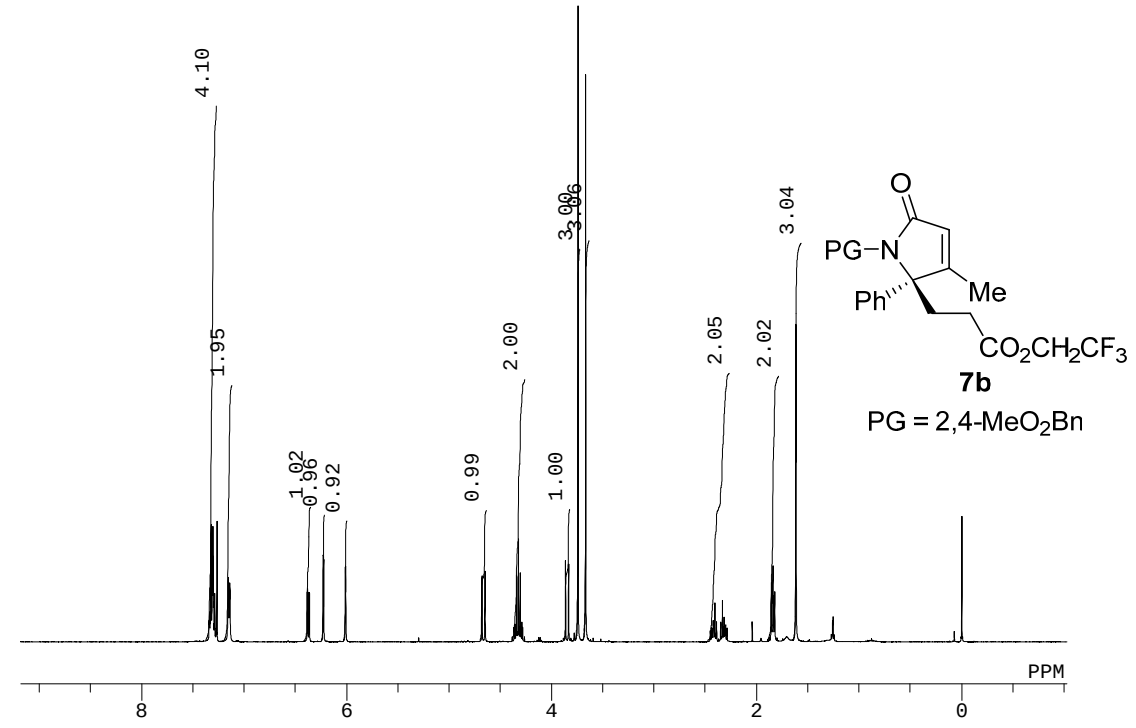



7.35 7.26 7.19 7.19 7.18 7.18 7.17 7.17 6.78 6.77 6.39 6.39 6.38 6.37 6.26 6.25 6.24 4.70 4.67 4.37 4.36 4.35 4.34 4.34 4.33 4.32 4.31 3.91 3.88 3.75 3.68 2.03 2.02 2.01 2.00 1.99 1.98 1.90 1.89 1.88 1.87 1.86 1.85 0.00
O
PG−N
Ph
CO2CH2CF3
5b
PG = 2,4-MeO2Bn
PPM
8 7 6 5 4 3 2 1 0


171.8 171.5 160.4 157.7 151.9 136.7 132.4 128.7 128.1 126.3 126.0 123.9 121.7 117.5 104.3 98.0 77.2 77.0 76.7 71.7 60.6 60.3 60.0 59.7 55.2 54.9 36.5 27.2 26.2
PPM
200 175 150 125 100 75 50 25 0

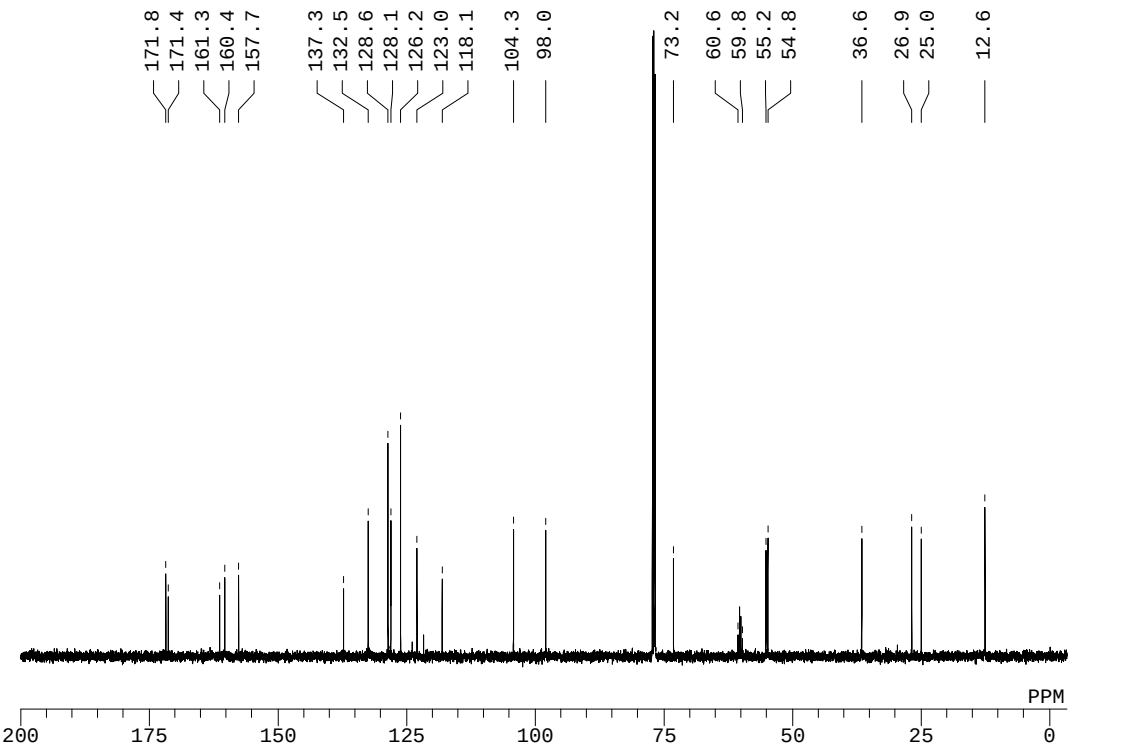

4.16
1.99
2.02
1.00
1.01
2.05
1.04
3.15
3.05
2.01
4.11
1.01
PPM
8
6
4
2
0

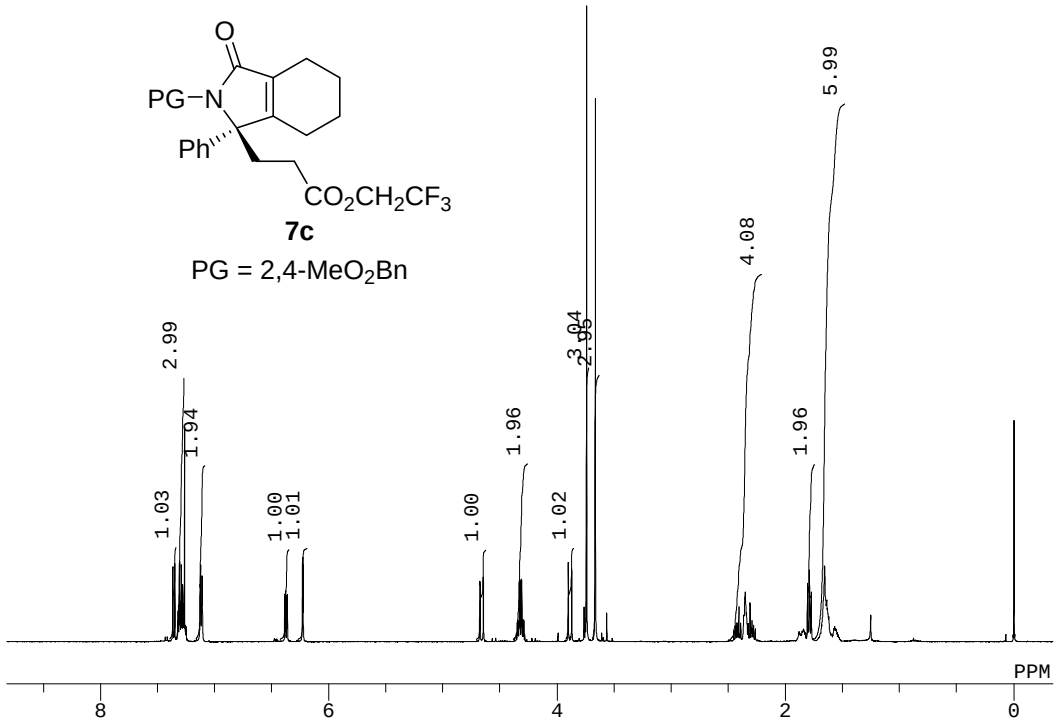

172.6
171.7
160.4
157.7
145.0
137.9
134.0
132.5
128.6
127.9
126.3
117.9
104.3
98.0
69.5
60.6
59.8
55.3
54.9
36.8
27.4
26.5
11.0
PPM
200
175
150
125
100
75
50
25
0

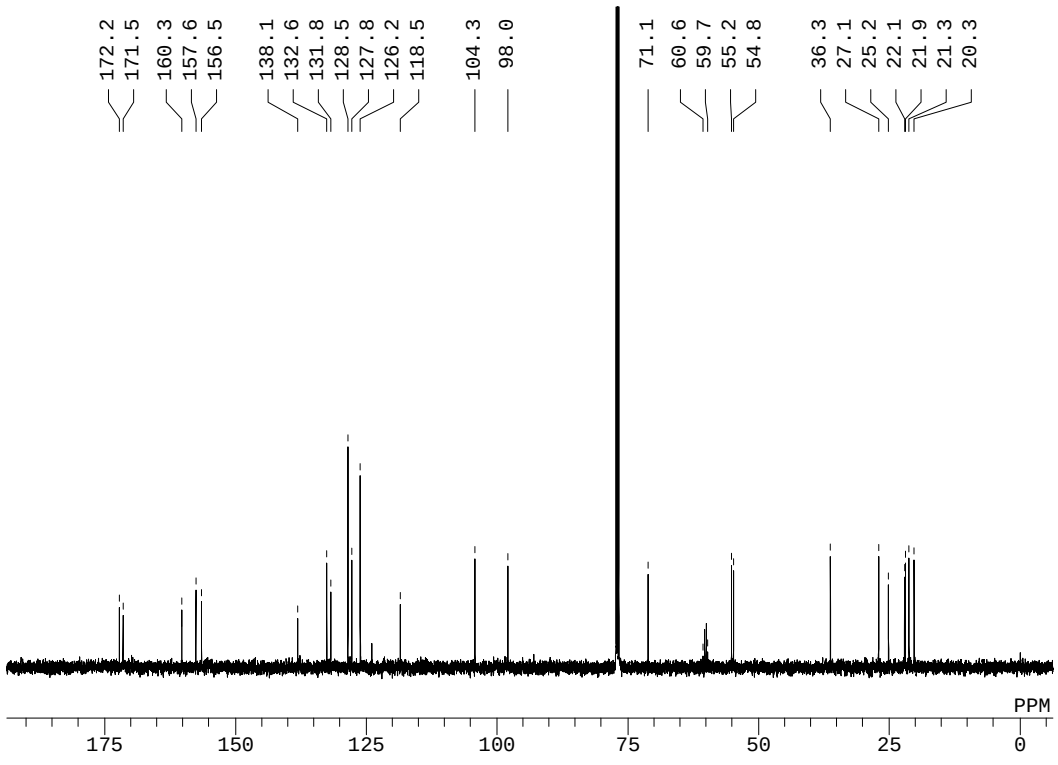


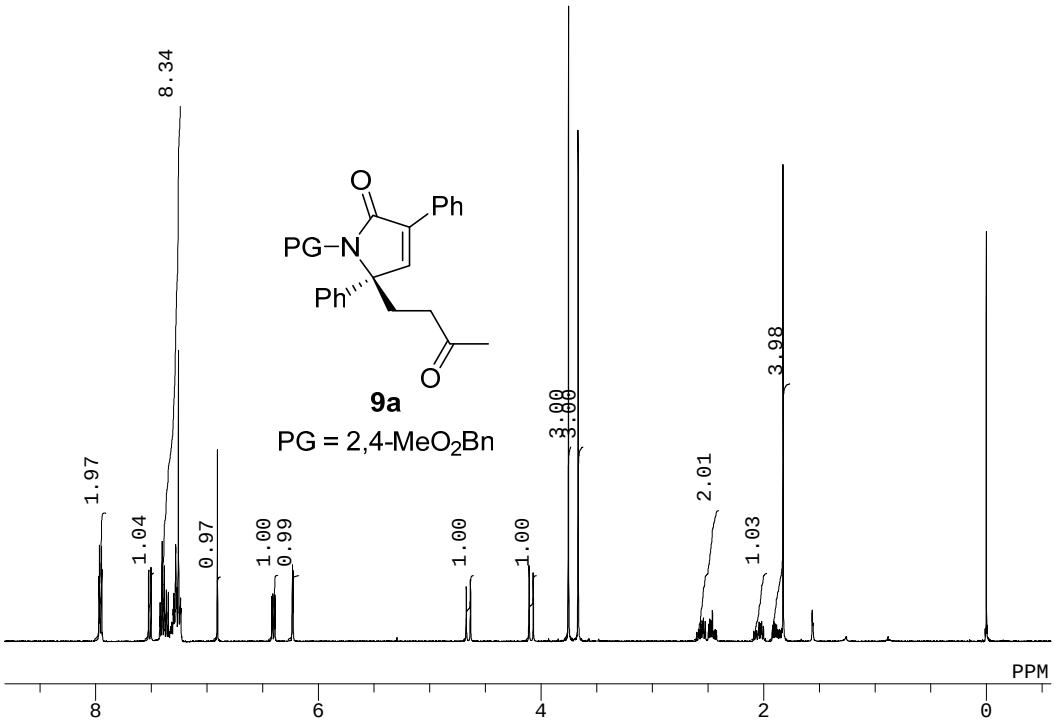
7b

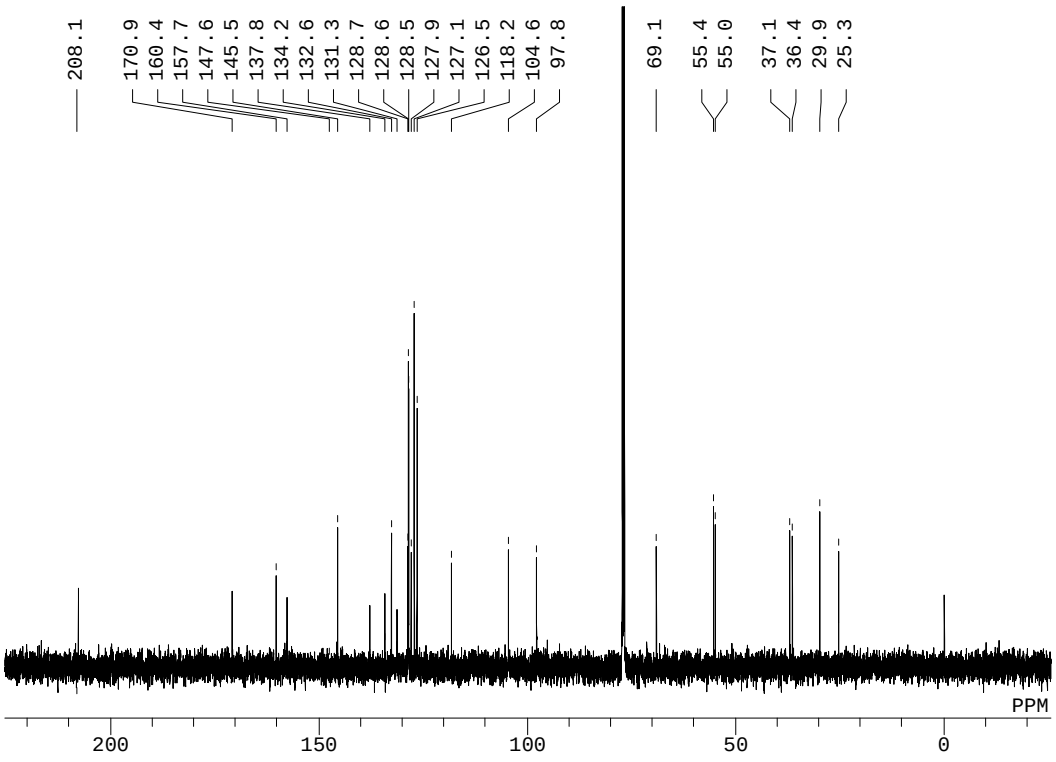
PG = 2,4-MeO_2Bn




O
PG−N
Ph
CO2CH2CF3
7c
PG = 2,4-MeO2Bn
2.99
1.94
1.03
1.00
1.01
1.00
1.96
1.02
3.04
2.95
4.08
1.96
5.99
PPM
8
6
4
2
0

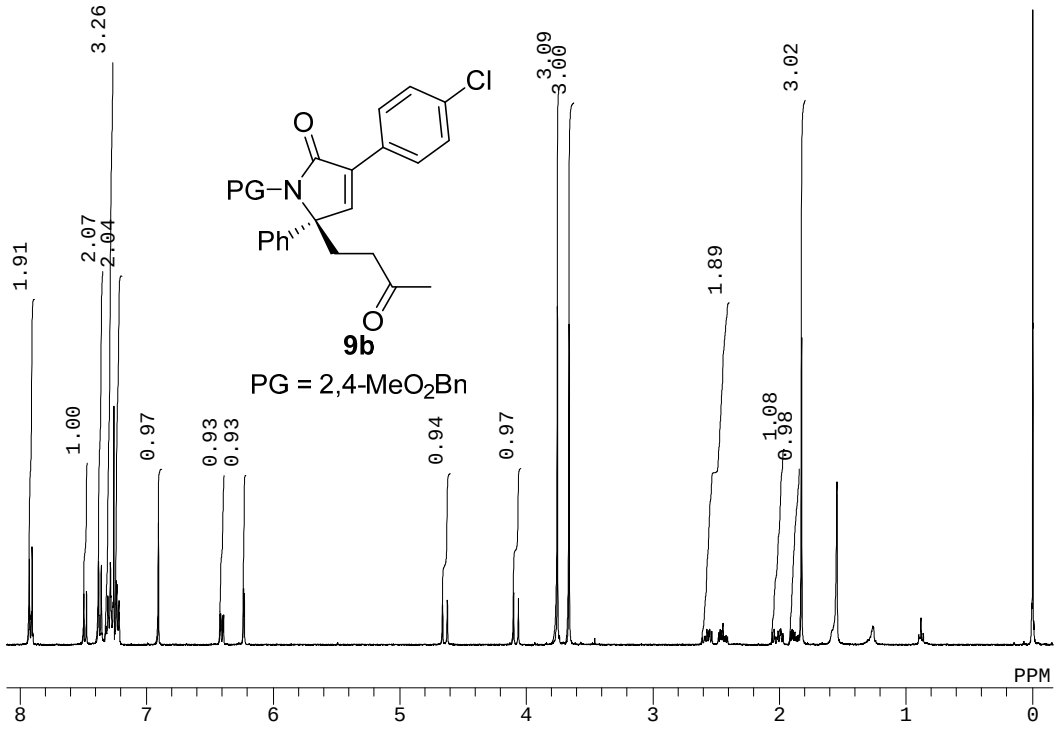

172.2
171.5
160.3
157.6
156.5
138.1
132.6
131.8
128.5
127.8
126.2
118.5
104.3
98.0
71.1
60.6
59.7
55.2
54.8
36.3
27.1
25.2
22.1
21.9
21.3
20.3
PPM
175
150
125
100
75
50
25
0

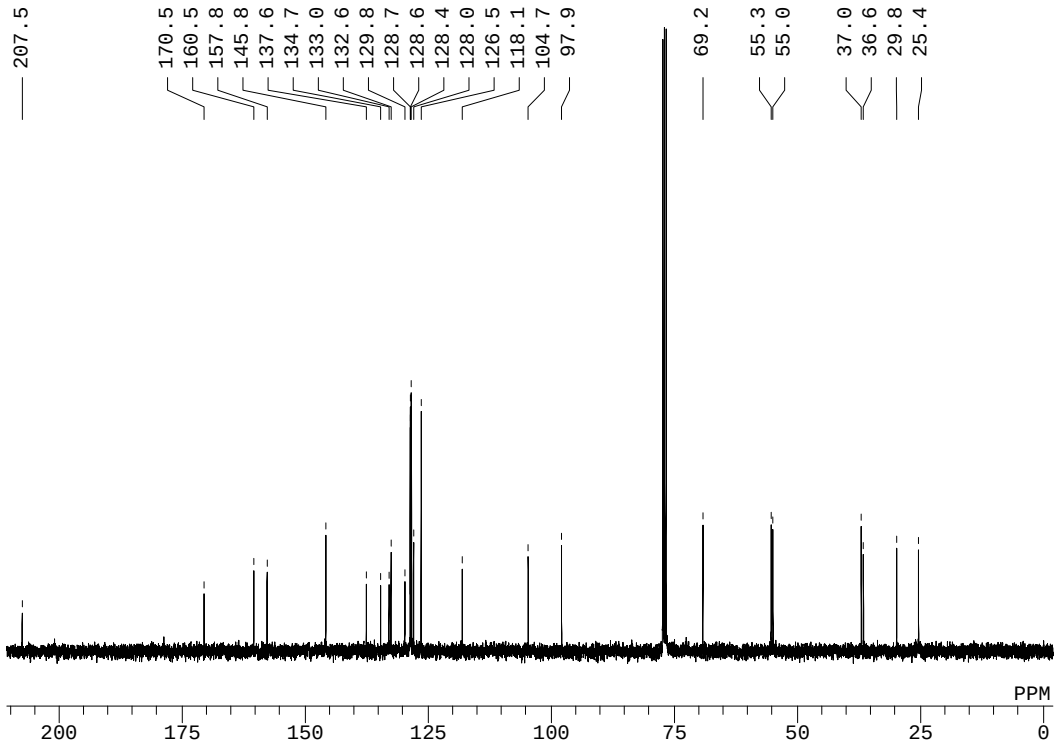


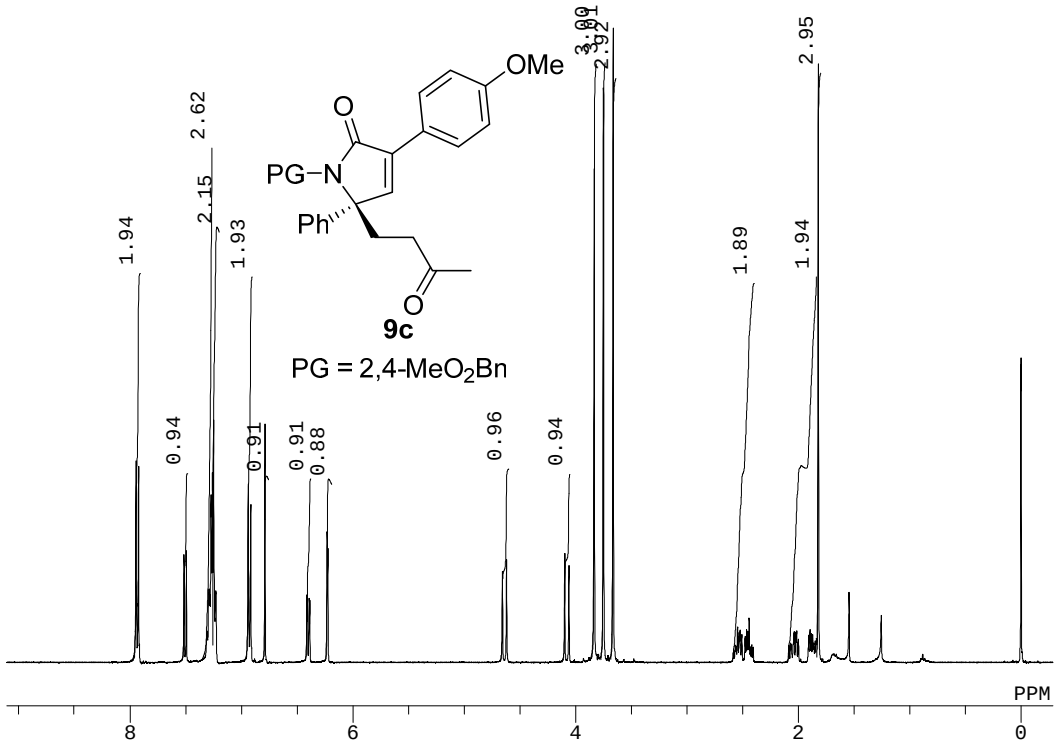


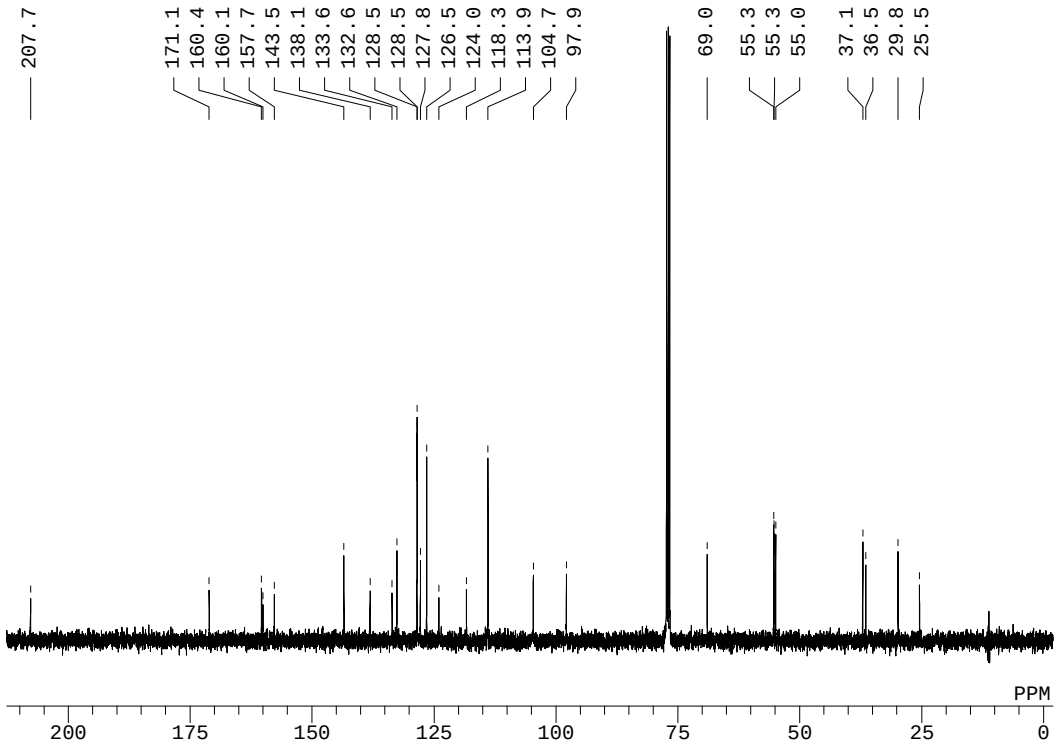
9a

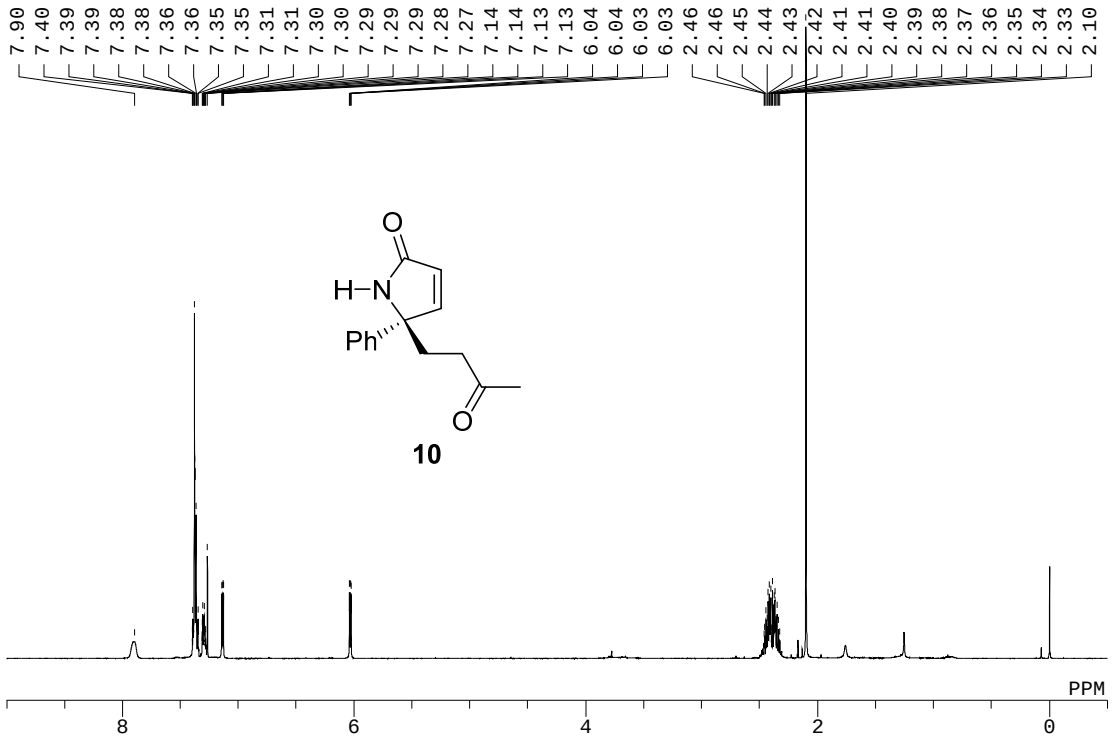
PG = 2,4-MeO_2Bn

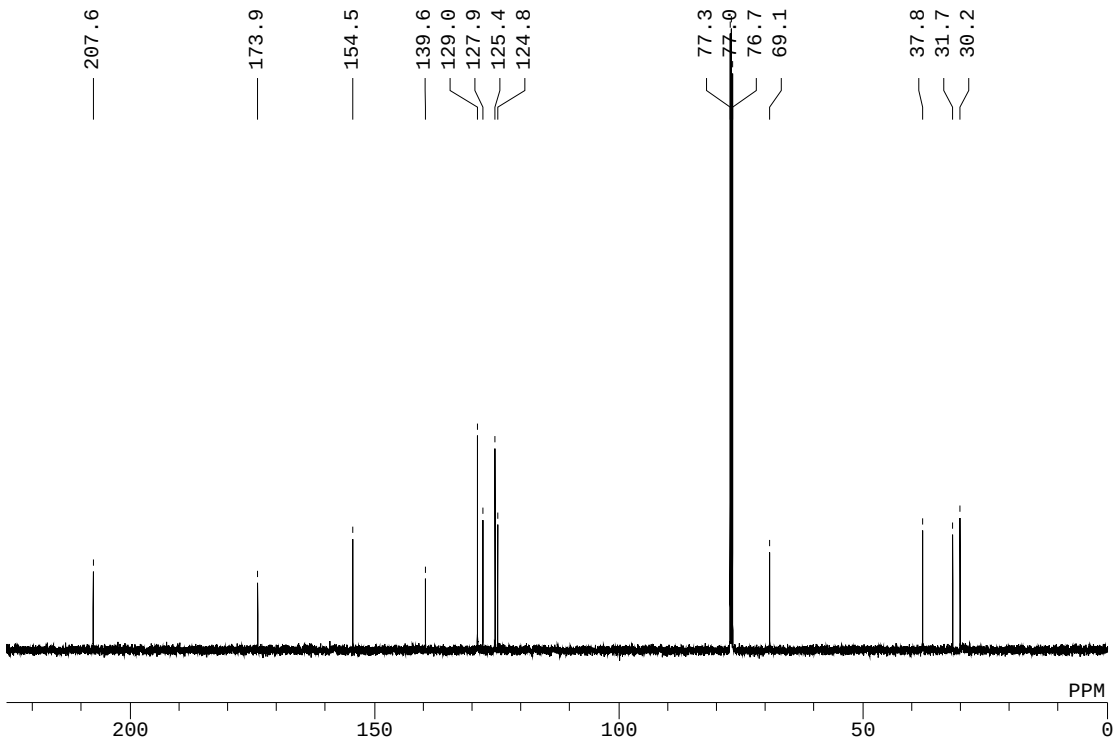

3.26
2.07
2.04
1.91
1.00
0.97
0.93
0.93
0.94
0.97
3.09
3.00
1.89
3.02
1.08
0.98
Cl
O
PG–N
Ph
O
9b
PG = 2,4-MeO2Bn
PPM
8
7
6
5
4
3
2
1
0


207.5
170.5
160.5
157.8
145.8
137.6
134.7
133.0
132.6
129.8
128.7
128.6
128.4
128.0
126.5
118.1
104.7
97.9
69.2
55.3
55.0
37.0
36.6
29.8
25.4
PPM
200
175
150
125
100
75
50
25
0


1.94
2.62
2.15
1.93
0.94
0.91
0.91
0.88
0.96
0.94
3.00
3.01
2.95
1.89
1.94
OMe
O
PG–N
Ph
O
9c
PG = 2,4-MeO2Bn
PPM
8
6
4
2
0


207.7
171.1
160.4
160.1
157.7
143.5
138.1
133.6
132.6
128.5
128.5
127.8
126.5
124.0
118.3
113.9
104.7
97.9
69.0
55.3
55.3
55.0
37.1
36.5
29.8
25.5
PPM
200
175
150
125
100
75
50
25
0


7.90 7.40 7.39 7.39 7.38 7.38 7.36 7.36 7.35 7.35 7.31 7.31 7.30 7.30 7.29 7.29 7.28 7.27 7.14 7.14 7.13 7.13 6.04 6.04 6.03 6.03
2.46 2.46 2.45 2.44 2.43 2.42 2.41 2.41 2.40 2.39 2.38 2.37 2.36 2.35 2.34 2.33 2.10
O
H–N
Ph
O
10
PPM
8
6
4
2
0


207.6
173.9
154.5
139.6 129.0 127.9 125.4 124.8
77.3 77.0 76.7 69.1
37.8 31.7 30.2
PPM
200
150
100
50
0