Supporting Information

Phosphothreonine (pThr)–Based Multifunctional Peptide Catalysis for Asymmetric Baeyer–Villiger Oxidations of Cyclobutanones

Aaron L. Featherston, Christopher R. Shugrue, Brandon Q. Mercado,

and Scott J. Miller*

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107, United States

*Correspondence to: scott.miller@yale.edu

Table of Contents:

1. General Information

All reactions were carried out under benchtop conditions, without exclusion of air or moisture, unless otherwise stated. Room temperature is considered 20–23 °C. All reagents were obtained from commercial suppliers and used as received, without further purification, unless otherwise stated. THF, CH_2Cl_2, DMF, and PhMe were dried over alumina and dispensed under argon from a Seca Solvent purification system by GlassContour. Triethylamine (Et_3N), *N,N′*-diisopropyl ethylamine (*i*-Pr_2NEt), and *N,N′*-diisopropylamine (*i*-Pr_2NH) were distilled over CaH under a nitrogen atmosphere prior to use. Zinc-copper couple (Zn–Cu) was prepared according to literature procedure or obtained from commercial suppliers. Phosphorous oxytrichloride ($POCl_3$), phosphorous trichloride (PCl_3) and trichloroacetyl chloride (Cl_3CCOCl) were distilled over potassium carbonate under a N_2 atmosphere prior to use. Deionized water was used for reactions, extractions, and RPchromatography. HPLC grade solvents were used for all other chromatography.

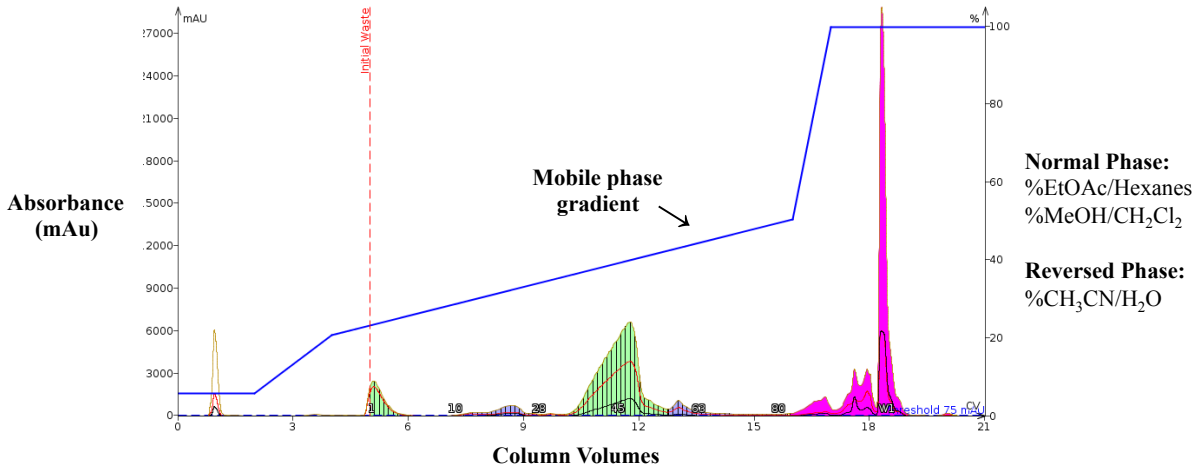
Unless otherwise stated, all NMR data were acquired at ambient temperature. NMR solvents, chloroform-*d* ($CDCl_3$), dimethylsulfoxide-d_6 (DMSO-d_6), acetone-d_6 [$(CD_3)_2O$], and methanol-d_4 (CD_3OD) were purchased from Cambridge Isotopes and used as received. $CDCl_3$ was stored over activated 4Å molecular sieves at ambient temperature, and DMSO-d_6/CD_3OD ampules were used immediately upon opening. NMR spectra were processed with MestReNova v10.0.1-14719 software using the baseline and phasing correction features. Multiplicities and coupling constants were calculated using the multiplet analysis feature with manual intervention as necessary. ^{1}H NMR spectra were obtained on Agilent 400 MHz, 500 MHz or 600 MHz spectrometers. Proton chemical shifts (δ) are reported in ppm and referenced to residual solvent peaks for $CDCl_3$ (δ 7.26 ppm), DMSO-d_6 (δ 2.50 ppm), $(CD_3)_2O$ (δ 2.05 ppm), and CD_3OD (δ 3.31 ppm).[1] Proton data are reported as chemical shift, (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept), multiplet (m), broad singlet (bs), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), doublet of triplets (dt), doublet of triplet of triplets (dtt), etc. and and apparent (app)] coupling constants [Hz], and integrations). ^{13}C NMR spectra were obtained on Agilent 500 (125 MHz) MHz or 600 (150 MHz) MHz spectrometers with full proton decoupling. Carbon chemical shifts (δ) are reported in ppm and referenced to residual solvent peaks for $CDCl_3$ (δ 77.2 ppm), DMSO-d_6 (δ 39.5 ppm), $(CD_3)_2O$ (δ 206.26 ppm), and CD_3OD (δ 49.0 ppm) with multiplicity and coupling constants [Hz] indicated when present. ^{19}F NMR spectra were obtained on Agilent 400 (376 MHz) MHz or 500 (471 MHz) MHz spectrometers without proton decoupling. Fluorine chemical shifts (δ) are referenced to $CFCl_3$ (δ 0.00 ppm) and were calibrated by the spectrometer using the solvent deuterium lock signal. Fluorine data are reported as chemical shift, (multiplicity, coupling constant [Hz], and integrations). ^{31}P NMR spectra were obtained on Agilent 400 (162 MHz) MHz or 500 (202 MHz) MHz spectrometers with full proton decoupling. Phosphorus chemical shifts (δ) are referenced to H_3PO_4 (δ 0.00 ppm) and calibrated by the spectrometer using the solvent deuterium lock signal.

Analytical thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 F_{254} precoated plates (0.25 mm thickness) and developed plates were visualized using a UV lamp and/or potassium permanganate ($KMnO_4$) stain. TLC R_f values are reported. Normal-phase flash-column chromatography was performed using either silica gel 60 Å (32–63 microns) or an automated Biotage Isolera One flash purification system equipped with a 10, 25, or 50 g SNAP Ultra (HP Sphere, 25 μm

silica) cartridge. Reversed-phase flash-column chromatography was performed using an automated Biotage Isolera One flash purification system equipped with a 12, 30, 60 or 120 g SNAP C-18 (HS 50 µm silica) or SNAP Ultra C-18 (HP Sphere, 25 µm silica) cartridge.

Ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters Acquity SQD2 instrument equipped with an Ultra BEH C-18 column (1.7 µm particle size, 2.1 x 50 mm), a dual atmospheric pressure chemical ionization (API)/electrospray ionization (ESI) mass spectrometry detector, and a photodiode array detector. High-resolution mass spectrometry (HRMS) was conducted by the Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign using either electron ionization (EI) or electrospray ionization (ESI). Infrared spectra were recorded on a Nicolet 6700 ATR/FT-ATR spectrometer, and ν_{max} are partially reported in cm^{-1}. Optical rotations were recorded on a Autopol VI Automatic Polarimeter at the sodium D-line (589 nm) using a Type 40T TempTrol^{TM} cell of 0.50 dm path length at 20 °C and reported as follows: $[\alpha]_{\lambda}^{temp}$, concentration (*c* in g/100 mL), and solvent. Analytical normal-phase high-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series instrument equipped with a photodiode array detector (254 nm) and columns (chiral supports, 5 µm particle size, 4.5 x 250 mm) from Daicel Chemical Industries.

Example automated chromatography trace



Abbreviations:

Ac = acetyl; Acpc = 1-aminocyclopropane-1-carboxylic acid; Aib = α-aminoisobutyric acid; Aic = 2-aminoindane-2-carboxylic acid; Aq = aqueous; Boc = *tert*-butoxycarbonyl; Bop = (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; Bn = benzyl; Bz = benzoyl; Cbz = carboxybenzyl; Dap = 2,3-diaminoproprionic acid; DMAP = 4-dimethylaminopyridine; DMF = *N,N′*-dimethylformamide; DMSO = dimethylsulfoxide; EDC•HCl = *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride; ee = enantiomeric excess, er = enantiomer ratio; ESI = electrospray ionization; EtOAc = Ethyl acetate; FCC = Flash-Column Chromatography; Fmoc = 9-Fluorenylmethoxycarbonyl; FT = Fourier transform; HATU = O-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate; HBTU = O-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate; HOBt = 1-Hydroxybenzotriazole; HPLC = high-performance liquid chromatography; HRMS = high-resolution mass spectrometry; IR = infrared; UPLC-MS = Ultra-performance liquid chromatography mass spectrometry; NMM = 4-methylmorpholine; NMR = nuclear magnetic resonance; pPhSer = *β-threo*-phosphophenylserine; pThr = phosphothreonine; pSer = phosphoserine; RP = reversed-phase; rt = room temperature; TFA = trifluoroacetic acid; THF = tetrahydrofuran; TLC = thin-layer chromatography; TOF = time-of-flight.

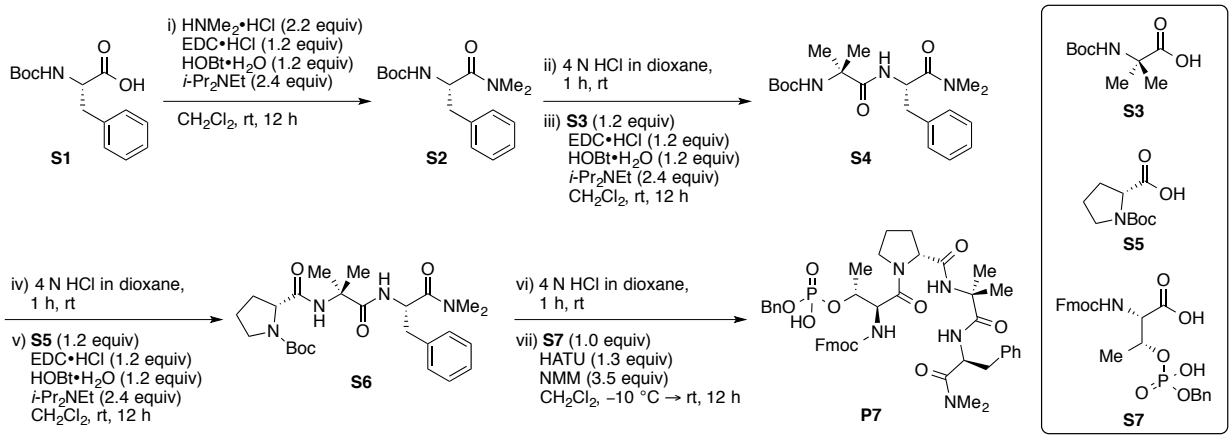
2. Solution phase synthesis of peptide catalysts

General Remarks

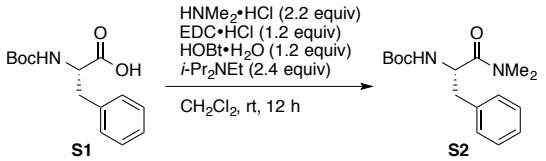
The solution phase synthesis of the peptides were completed using the Boc protecting group strategy unless otherwise stated.[2] All amino acids and coupling reagents were purchased from commercial suppliers unless otherwise noted. Yields are not optimized. Typical coupling times were between 3–24 hours and monitored by UPLC-MS for completion. Increased purity and yields for the coupling of the phosphorylated amino acids were obtained by purifying the peptides prior to this step (*vide infra*). Once synthesized, peptides were stored at –20 °C to prevent any adverse side reactivity. See reference 3 for the preparation and characterization of peptide **P2**. Peptides **P7** and **P12** were previously reported, and the synthetic procedures are reiterated below.[4]

2.1. Representative synthesis and characterization of Peptide Catalyst P7

2.1.1 Scheme



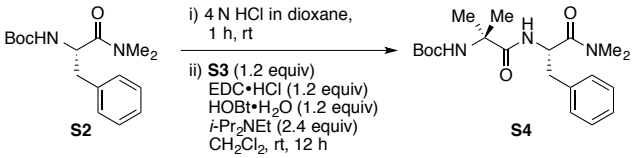
2.1.2 Procedure 1: Installation of *N,N′*-dimethylamide



Boc-^{L}Phe-OH (**S1**, 2.65 g, 10.0 mmol, 1.00 equiv), HOBt•H_2O (1.84 g, 12.0 mmol, 1.2 equiv), EDC•HCl (2.30 g, 12.0 mmol, 1.2 equiv) and *N,N′*-dimethylamine hydrochloride (1.79 g, 22.0 mmol, 2.2 equiv) were suspended in anhydrous CH_2Cl_2 (50 mL, 0.2 M) followed by dropwise addition of *i*-Pr_2NEt (4.18 mL, 24.0 mmol, 2.4 equiv). Gradually, the cloudy suspension became clear, and the resulting solution was stirred at rt. After 14 h, the pale yellow reaction mixture was transferred to a separatory funnel, diluted with CH_2Cl_2 (100 mL), and washed with 10% aqueous (w/v) citric acid (1 x 50 mL). The aqueous layer was back-extracted with CH_2Cl_2 (25 mL) and the combined organics washed sequentially with saturated aqueous $NaHCO_3$ (1 x 50 mL), saturated aqueous NaCl (1 x 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude Boc-Phe-NMe_2 (**S2**) as a clear, pale yellow oil (2.98 g,

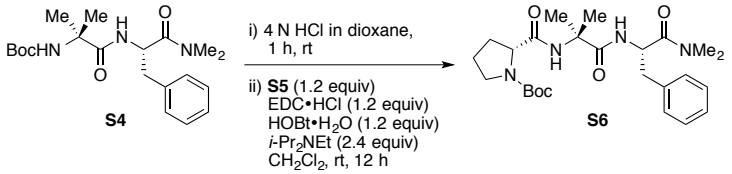
>99% crude yield). The identity of **S2** was confirmed by UPLC-MS. **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{25}N_2O_3$ 293.19, found 293.26.

2.1.3 General Peptide Coupling Protocol (Deprotection and Peptide Coupling)



Boc-Deprotection 1: Crude Boc-Phe-NMe_2 (**S2**, 2.98 g, assumed 10 mmol, 1.0 equiv) was dissolved in 4.0 N HCl in 1,4-dioxane (12.5 mL, 50 mmol, 5 equiv) and stirred vigorously for 1 h. Excess HCl was evaporated by bubbling N_2 through the solution for 1 h, and the remaining solvent was removed *in vacuo* to afford H-Phe-NMe_2•HCl as a white solid, which was dried thoroughly under reduced pressure before proceeding to the next coupling step.

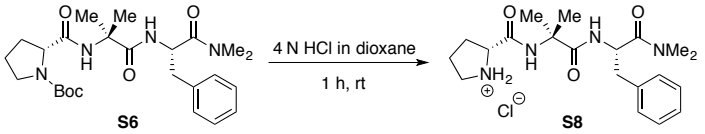
Peptide Coupling 1: To a flask containing HCl•H-Phe-NMe_2 (assumed 10 mmol, 1.0 equiv) was added Boc-Aib-OH (**S3**, 2.44 g, 12.0 mmol, 1.2 equiv), HOBt•H_2O (1.84 g, 12.0 mmol, 1.2 equiv), and EDC•HCl (2.30 g, 12.0 mmol, 1.2 equiv). The solid mixture was suspended in anhydrous CH_2Cl_2 (50 mL) followed by dropwise addition of *i*-Pr_2NEt (4.18 mL, 24.0 mmol, 2.4 equiv). Gradually, the cloudy suspension became clear, and the resulting solution was stirred at rt. After 14 h, the pale yellow reaction mixture was transferred to a separatory funnel, diluted with CH_2Cl_2 (100 mL), and washed with 10% aqueous (w/v) citric acid (1 x 50 mL). The aqueous layer was back extracted with CH_2Cl_2 (50 mL), and the combined organics washed sequentially with saturated aqueous $NaHCO_3$ (1 x 50 mL), saturated aqueous NaCl (1 x 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude Boc-Aib-Phe-NMe_2 (**S4**) as an off-white foam (3.96 g, >99% crude yield). The identity of **S4** was confirmed by UPLC-MS. **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{32}N_3O_4$ 378.24, found 378.24.



Boc-Deprotection 2: The deprotection of Boc-Aib-Phe-NMe_2 (**S4**, 3.96 g, assumed 10.0 mmol, 1.0 equiv) was accomplished in the same manner as described in Boc-deprotection 1 (*vide supra*) to provide H-Aib-Phe-NMe_2•HCl as a white solid.

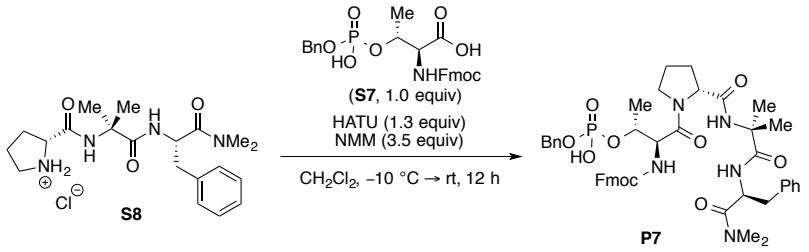
Peptide Coupling 2: To a flask containing H-Aib-Phe-NMe_2•HCl (assumed 10 mmol, 1.0 equiv) was added Boc-D-Pro-OH (**S5**, 2.58 g, 12.0 mmol, 1.2 equiv), HOBt•H_2O (1.84 g, 12.0 mmol, 1.2 equiv), and EDC•HCl (2.30 g, 12.0 mmol, 1.2 equiv). The solid mixture was suspended in anhydrous CH_2Cl_2 (50 mL) followed by dropwise addition of *i*-Pr_2NEt (4.18 mL, 24.0 mmol, 2.20 equiv). Gradually, the cloudy

suspension became clear, and the resulting solution was stirred at rt. After 14 h, the pale yellow reaction mixture was transferred to a separatory funnel, diluted with CH_2Cl_2 (100 mL), and washed with 10% aqueous (w/v) citric acid (50 mL). The aqueous layer was back extracted CH_2Cl_2 (1 x 50 mL), and the combined organics washed sequentially with saturated aqueous $NaHCO_3$ (1 x 50 mL), saturated aqueous NaCl (1 x 50 mL). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude peptide as an off-white foam which was directly purified by automated FCC (SNAP Ultra 100 g, CV = 164 mL, 1% MeOH/CH_2Cl_2 for 1 CV, 1–8% MeOH/CH_2Cl_2 linear gradient over 12 CV, then 8% MeOH/CH_2Cl_2 for 1 CV, 100 mL·min^{-1} flowrate) to afford Boc-D-Pro-Aib-Phe-NMe_2 as a white foam (**S6**, 3.82 g, 80% overall yield from **S1**). UPLC-MS. **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{39}N_4O_5$ 475.29; found 475.38.



Boc-Deprotection 3: The deprotection of Boc-D-Pro-Aib-Phe-NMe_2 (2.09 g, 4.4 mmol, 1.0 equiv) was accomplished in the same manner as described in Boc-deprotection 1 (*vide supra*) with 4 N HCl in dioxane (11 mL, 44 mmol, 10 equiv) to provide H-D-Pro-Aib-Phe-NMe_2•HCl as a white solid. *Note:* It is essential at this point, before coupling to Fmoc-pThr(Bn)-OH (**S7**), to ensure removal of all HCl by extensive drying under vacuum (>12h).

2.1.4. Procedure 2: HATU mediated Fmoc-pThr(Bn)-OH coupling



Peptide Coupling 3 using HATU: To a round bottom flask containing H-D-Pro-Aib-Phe-NMe_2 (assumed 4.4 mmol, 1.1 equiv) was added Fmoc-pThr(Bn)-OH (**S7**, 2.05 g, 4.0 mmol, 1.0 equiv) and suspended in CH_2Cl_2 (20 mL). NMM (1.54 mL, 14 mmol, 3.5 equiv) was added to the mixture, and the resulting clear, colorless solution was cooled to –10 °C (brine/ice bath) followed by addition of HATU (1.98 g, 5.2 mmol, 1.3 equiv) in a single portion. The mixture slowly turned yellow over time and was allowed to warm to rt overnight. After 16 hours, the mixture was diluted with CH_2Cl_2 (30 mL) and washed with 10% aqueous (w/v) citric acid (1 x 40 mL), with saturated aqueous brine as needed to aid in phase separation. The aqueous layer is back extracted thrice with CH_2Cl_2, and the combined organics washed with saturated aqueous NaCl (1 x 40 mL). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude peptide, which was directly purified *via* RP-FCC (SNAP Ultra C18 120 g, CV = 164 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 3 CV, 30–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O

over 3 CV, 80 mL·min^{-1} flowrate). Pure fractions were pooled, concentrated *in vacuo* (35–37 °C, 10 mbar), azeotroped twice with CH_3CN and twice with CH_2Cl_2 to provide **P7** as a white foam.

Yield: 2.46 g, 71% from **S6**

IR (FT-ATR, cm^{-1}, neat): 3303, 2945, 1631, 1523, 1450, 1381, 1239, 998, 738, 697

^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.55 (bs, 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.58 (dd, *J* = 7.6, 3.9 Hz, 2H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.42–7.33 (m, 4H), 7.31–7.24 (m, 5H), 7.24–7.15 (m, 5H), 6.93–6.79 (m, 2H), 5.13 (q, *J* = 6.1 Hz, 1H), 5.05 (d, *J* = 7.2 Hz, 2H), 5.01 (dt, *J* = 9.5, 6.6 Hz, 1H), 4.50 (dd, *J* = 8.3, 3.9 Hz, 1H), 4.39 (qd, *J* = 10.7, 7.1 Hz, 2H), 4.29 (dd, *J* = 7.7, 5.3 Hz, 1H), 4.17 (t, *J* = 7.0 Hz, 1H), 3.74–3.67 (m, 1H), 3.59–3.52 (m, 1H), 3.13 (dd, *J* = 13.2, 9.6 Hz, 1H), 3.07 (dd, *J* = 13.2, 6.1 Hz, 1H), 2.72 (s, 3H), 2.62 (s, 3H), 2.11 (ddd, *J* = 13.6, 8.3, 4.3 Hz, 1H), 2.06–1.96 (m, 2H), 1.85 (td, *J* = 14.6, 12.5, 8.1 Hz, 1H), 1.43 (s, 6H), 1.37 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.4, 172.8, 170.8, 169.9, 156.9, 143.8, 141.4, 136.7, 136.4 (d, *J* = 7.7 Hz), 129.5, 128.6, 128.4, 128.4, 127.9, 127.8, 127.3, 127.0, 125.3 (d, *J* = 4.0 Hz), 120.1, 120.1, 73.4 (d, *J* = 5.6 Hz), 69.0 (d, *J* = 5.5 Hz), 67.3, 62.6, 57.8 (d, *J* = 5.0 Hz), 57.1, 50.9, 48.0, 47.3, 38.5, 37.4, 36.2, 29.0, 25.7, 25.4, 25.3, 19.1 (d, *J* = 3.9 Hz).

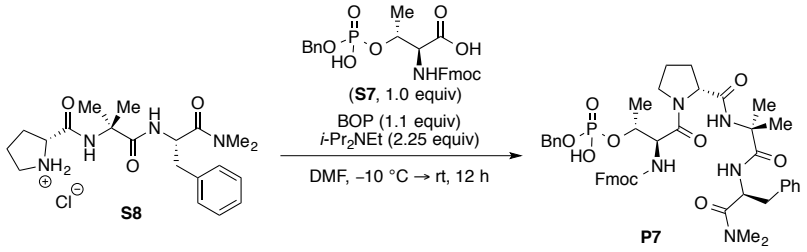
^{31}P NMR (162 MHz, Chloroform-*d*) δ –2.17.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{46}H_{55}N_5O_{10}P$ 868.3687, found 868.3691.

Elemental Analysis: Anal. Calcd for $C_{46}H_{54}N_5O_{10}P$: C, 63.66; H, 6.27; N, 8.07 Found: C, 63.63; H, 6.42; N, 7.96.

$[\alpha]_D^{20}$ +22.5 (*c* = 1.02, $CHCl_3$).

2.1.5. Procedure 3: BOP mediated Fmoc-pThr(Bn)-OH coupling[3]

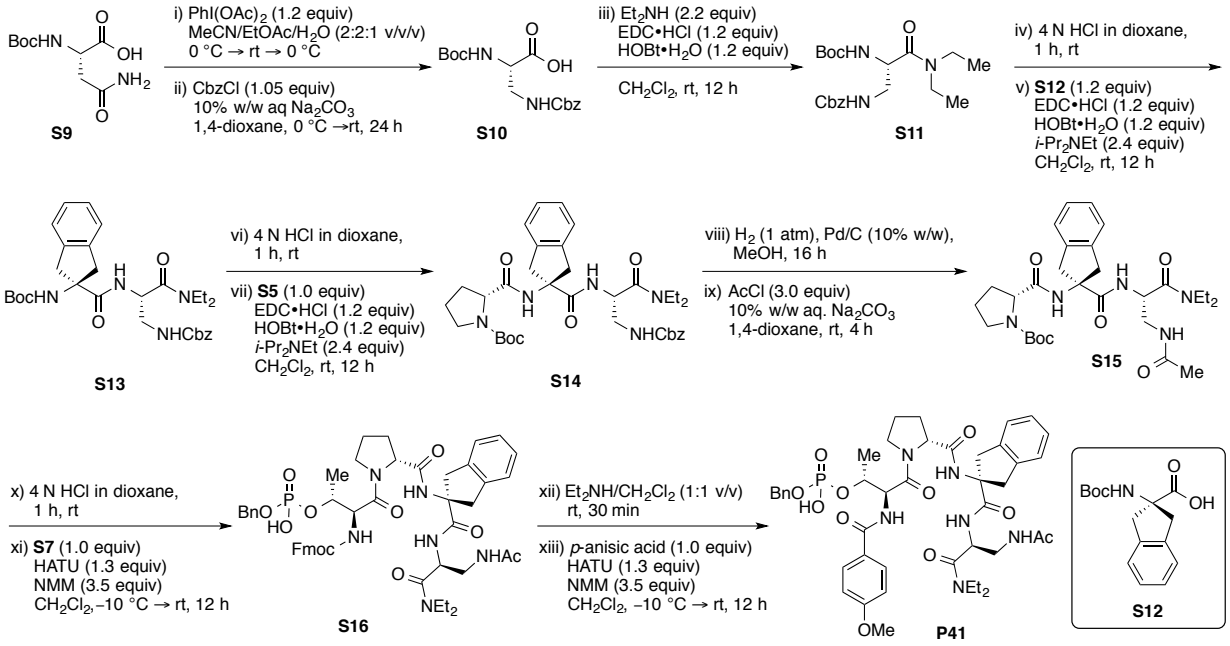


Peptide Coupling 3 using BOP: To a flame-dried round-bottom flask under a N_2 atmosphere was added Fmoc-pThr(Bn)-OH (**S7**, 0.512 g, 1.0 mmol, 1.0 equiv), BOP (0.487 g, 1.1 mmol, 1.1 equiv) and dissolved in DMF (8.0 mL) at –10 ºC. After 30 min, a solution of H-D-Pro-Aib-Phe-NMe_2 (**S8**, assumed 1.1 mmol, 1.1 equiv) in DMF (12 mL) was added *via* syringe, followed by dropwise addition of *i*-Pr_2NEt (0.39 mL, 2.25 mmol, 2.25 equiv). The resulting solution was allowed to slowly warm to rt and stirred overnight. After 16 hours, the mixture was diluted with EtOAc (120 mL) and washed with 80:20 10% w/v citric acid/5% aqueous LiCl (50 mL). The aqueous layer was back extracted with EtOAc and the combined organics washed with 5% aqueous LiCl (2 x 50 mL), saturated aqueous NaCl (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude peptide was purified *via* RP-FCC (SNAP C18 120 g, CV = 132 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–

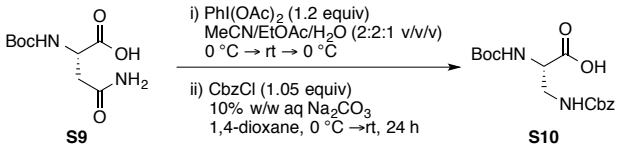
30% CH_3CN/H_2O linear gradient over 3 CV, 30–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 4 CV, 80 mL·min^{-1} flowrate) to provide **P7** as a white foam (545 mg, 63% yield from **S6**). The characterization data were consistent with those detailed above.

2.2 Synthesis and characterization of Peptide Catalyst P41–42.

2.2.1. Scheme



2.2.2. Procedure 4: Synthesis of Boc-^{L}Dap(Cbz)-OH



Step 1: According to the procedure of Zhang *et al.*[5], Boc-Asn-OH (20.0 g, 0.86 mol, 1.0 equiv) was suspended in a solution of 2:2:1 (v/v/v) CH_3CN /EtOAc/H_2O (240 mL). The mixture was cooled to 0 °C (ice bath) followed by portion wise addition of $PhI(OAc)_2$ (33.3 g, 0.10 mol, 1.2 equiv) over ~5 min. The reaction mixture was maintained at 0 °C for 1 hour, and then warmed to rt. Initially the suspension became a clear solution and within an hour a white precipitate began to form. After 5 h, the reaction mixture was cooled to 0 °C for 2 h to facilitate precipitation and the white solid was collected by vacuum filtration through a sintered glass funnel. The filter cake was washed with EtOAc (3 x 200 mL) and the product dried under high vacuum to afford Boc-^{L}Dap-OH as a white powder that was used without further purification.

Yield: 11.86 g, 67%

^{1}H NMR (600 MHz, Methanol-d_4) δ 4.06 (t, J = 6.5 Hz, 1H), 3.18 (dd, J = 12.4, 6.7 Hz, 1H), 3.13 (dd, J = 12.6, 6.2 Hz, 1H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 174.8, 158.0, 80.9, 53.9, 43.1, 28.7.

Step 2: Cbz protection: To a solution of Boc-Dap-OH (5.11 g, 25 mmol, 1.0 equiv) in 1,4-dioxane (40 mL) and 10% w/w aqueous Na_2CO_3 (60 mL, 2.5 equiv) was added benzyl chloroformate (4.48 g, 26.3 mmol, 1.05 equiv) dropwise at 0 °C. The reaction mixture was allowed to slowly warm to rt overnight. After 16 h, the reaction mixture was transferred to a separatory funnel, diluted with EtOAc, and acidified with 1 N HCl. The organic layer was separated, and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics were washed with saturated aqueous NaCl (1 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product that was used without further purification. The characterization data was in agreement with literature values.[6]

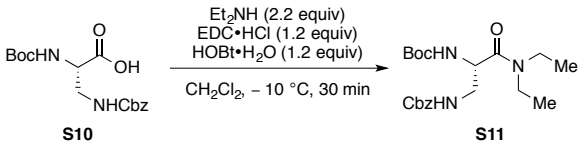
Yield: 7.75 g, 92%

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 7.48–7.16 (m, 6H), 6.94 (d, J = 8.2 Hz, 1H), 5.02 (s, 2H), 4.05 (q, J = 6.9 Hz, 1H), 3.53–3.21 (m, 2H), 1.38 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 172.2, 156.2, 155.3, 137.1, 128.4, 127.8, 127.6, 78.3, 65.4, 53.6, 41.6, 28.2.

MS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{22}N_2O_6Na$ 361.14, found 361.15.

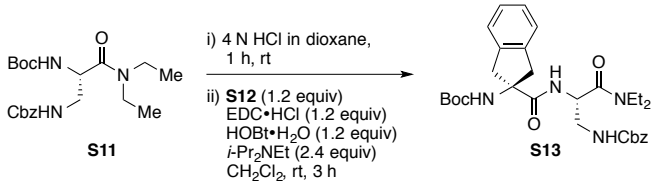
2.2.3. Procedure 5: Installation of *N,N′*-diethylamide



S10 **S11**

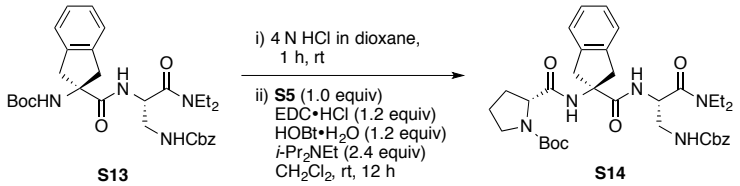
Boc-Dap(Cbz)-OH (**S10**, 3.16 g, 9.34 mmol, 1.00 equiv), HOBt•H_2O (1.72 g, 11.2 mmol, 1.2 equiv), EDC•HCl (2.14 g, 11.2 mmol, 1.2 equiv) were suspended in anhydrous CH_2Cl_2 (47 mL, 0.2 M) followed by dropwise addition of diethylamine (1.93 mL, 18.7 mmol, 2.0 equiv) at –10 °C (brine/ice bath) After 30 min, the reaction mixture was transferred to a separatory funnel, diluted with CH_2Cl_2 (100 mL), and washed with 10% aqueous (w/v) citric acid (1 x 50 mL). The aqueous layer was back extracted with CH_2Cl_2 (25 mL) and the combined organics washed sequentially with saturated aqueous $NaHCO_3$ (1 x 50 mL), saturated aqueous NaCl (1 x 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude Boc-Dap(Cbz)-NEt_2 (**S11**) as a viscous, colorless oil (3.13 g, 85% crude yield). The identity of **S11** was confirmed by UPLC-MS. **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{32}N_3O_5$ 394.23, found 394.42.

2.2.4 General Peptide Coupling Protocol (Deprotection and Peptide Coupling)



Boc-Deprotection 1: Crude Boc-Dap(Cbz)-NEt_2 (**S11**, 3.13 g, assumed 7.95 mmol, 1.0 equiv) was dissolved in 4.0 N HCl in 1,4-dioxane (20 mL, 80 mmol, 10 equiv) and stirred vigorously for 1 h. Excess HCl was evaporated by bubbling N_2 through the solution for 1 h, and the remaining solvent removed *in vacuo* to afford H-Dap(Cbz)-NEt_2•HCl as a white solid, which was dried thoroughly under reduced pressure before proceeding to the next coupling step.

Peptide Coupling 1: To a flask containing H-Dap(Cbz)-NEt_2•HCl (assumed 7.95 mmol, 1.0 equiv) was added Boc-Aic-OH (**S12**, 2.27 g, 8.2 mmol, 1.03 equiv), HOBt•H_2O (1.47 g, 9.6 mmol, 1.2 equiv), and EDC•HCl (1.84 g, 9.6 mmol, 1.2 equiv). The solid mixture was suspended in anhydrous CH_2Cl_2 (40 mL) followed by dropwise addition of *i*-Pr_2NEt (3.3 mL, 19.2 mmol, 2.4 equiv). Gradually, the cloudy suspension became clear, and the resulting solution was stirred at rt. After 3 h, the pale yellow reaction mixture was transferred to a separatory funnel, diluted with CH_2Cl_2 (100 mL), and washed with 10% aqueous (w/v) citric acid (1 x 50 mL). The aqueous layer was back extracted with CH_2Cl_2 (50 mL), and the combined organics washed sequentially with saturated aqueous $NaHCO_3$ (1 x 50 mL), saturated aqueous NaCl (1 x 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude Boc-Aic-Dap(Cbz)-NEt_2 (**S13**) as a white foam (4.45 g, >99% crude yield). The identity of **S13** was confirmed by UPLC-MS. **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{41}N_4O_6$ 553.30, found 553.56.

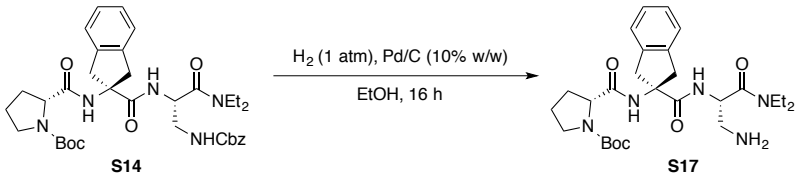


Boc-Deprotection 2: The deprotection of Boc-Aic-Dap(Cbz)-NEt_2 (**S13**, 4.45 g, assumed 7.95 mmol, 1.0 equiv) was accomplished in the same manner as described in Boc-deprotection 1 (*vide supra*) to provide H-Aic-Dap(Cbz)-NEt_2•HCl as a white solid.

Peptide Coupling 2: To a flask containing H-Aic-Dap(Cbz)-NEt_2•HCl (assumed 10 mmol, 1.0 equiv) was added Boc-D-Pro-OH (**S5**, 2.06 g, 9.6 mmol, 1.2 equiv), HOBt•H_2O (1.47 g, 9.6 mmol, 1.2 equiv), and EDC•HCl (1.84 g, 9.6 mmol, 1.2 equiv). The solid mixture was suspended in anhydrous CH_2Cl_2 (40 mL) followed by dropwise addition of *i*-Pr_2NEt (3.3 mL, 19.2 mmol, 2.4 equiv). Gradually, the cloudy suspension became clear, and the resulting solution was stirred at rt. After 14 h, the pale yellow reaction mixture was transferred to a separatory funnel, diluted with CH_2Cl_2 (100 mL), and washed with 10%

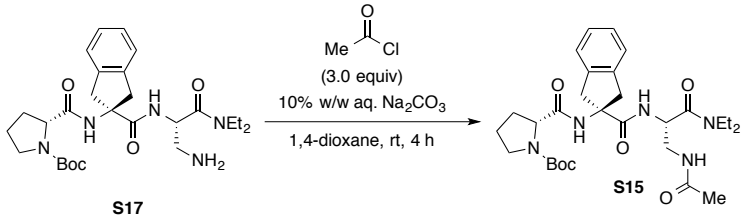
aqueous (w/v) citric acid (1 x 50 mL). The aqueous layer was back extracted CH_2Cl_2 (1 x 50 mL), and the combined organics washed sequentially with saturated aqueous $NaHCO_3$ (1 x 50 mL), saturated aqueous NaCl (1 x 50 mL). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude Boc-D-Pro-Aic-Dap(Cbz)-NEt_2 as a pale yellow foam (**S14**, 5.17 g, >99% yield). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{35}H_{48}N_5O_7$ 650.36; found 650.56.

2.2.5. Procedure 6: Cbz-Hydrogenolysis



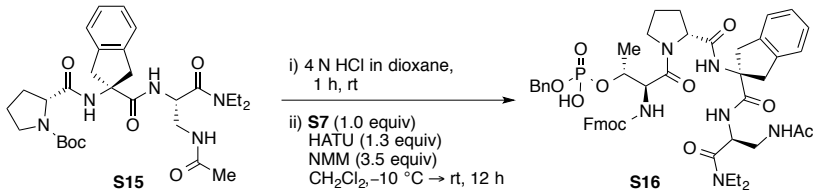
Cbz-Deprotection: To a round bottom flask containing Pd/C (10% w/w, 780 mg, 0.15 equiv) wetted with EtOAc was added a solution of Boc-D-Pro-Aic-Dap(Cbz)-NEt_2 (**S14**, 5.17 g, 7.95 mmol, 1.0 equiv) in EtOH (40 mL, 0.20 M). The flask was fitted with a balloon of H_2, subjected to three cycles of vacuum and H_2 purging, and the resultant mixture stirred vigorously at rt. Reaction completion was monitored by UPLC-MS, and upon complete deprotection (~16 h), the mixture was filtered through a pad of Celite® and the filter pad washed CH_2Cl_2 (3 x 25 mL). The filtrate was concentrated under reduced pressure to afford **S17**, which was used directly without further purification. **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{42}N_5O_5$ 516.32; found 516.64.

2.2.6. Procedure 7: Dap Acetylation



Dap Acetylation: To a solution of **S17** (assumed 7.95 mmol, 1.0 equiv) in 1,4-dioxane (32 mL) and 10% w/w aqueous Na_2CO_3 (23 mL, 24 mmol, 2.5 equiv) was added acetyl chloride (1.7 mL, 24 mmol, 3.0 equiv) dropwise over 3 h at rt. After an additional 1 h, the reaction mixture was transferred to a separatory funnel and diluted with CH_2Cl_2. The aqueous layer was extracted thrice with CH_2Cl_2, and the combined organics were washed with saturated aqueous $NaHCO_3$ (2 x 40 mL), 10% aqueous (w/v) citric acid (1 x 40 mL), and saturated aqueous NaCl (1 x 40 mL). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude trimer, which was directly purified by automated FCC (SNAP Ultra 100 g, CV = 164 mL, 1% MeOH/CH_2Cl_2 for 1 CV, 1–12% MeOH/CH_2Cl_2 linear gradient over 14 CV, 100 mL·min^{-1} flowrate) to afford Boc-D-Pro-Aic-Dap(Ac)-NEt_2 as a white foam (**S15**, 3.026 g, 68% yield from **S14**). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{44}N_5O_6$ 558.33; found 558.66.

2.1.7. HATU mediated Fmoc-pThr(Bn)-OH coupling



Boc-Deprotection 3: The deprotection of Boc-D-Pro-Aic-Dap(Ac)-NEt_2 (2.34 g, 4.2 mmol, 1.0 equiv) was accomplished in the same manner as described in Boc-deprotection 1 (*vide supra*) with 4 N HCl in dioxane (10.5 mL, 42 mmol, 10 equiv) to provide H-D-Pro-Aic-Dap(Ac)-NEt_2•HCl as a white solid. *Note:* It is essential at this point, before coupling to Fmoc-pThr(Bn)-OH (**S7**), to ensure removal of all HCl by extensive drying under vacuum (>12h).

Peptide Coupling 3 using HATU: To a round bottom flask containing H-D-Pro-Aic-Dap(Ac)-NEt_2 (assumed 4.2 mmol, 1.1 equiv) was added Fmoc-pThr(Bn)-OH (**S7**, 1.95 g, 3.82 mmol, 1.0 equiv) and suspended in CH_2Cl_2 (20 mL, 0.2 M). *N*-methylmorpholine (1.47 mL, 13.4 mmol, 3.5 equiv) was added to the mixture, and the resulting clear, colorless solution was cooled to –10 °C (brine/ice bath) followed by addition of HATU (1.89 g, 4.96 mmol, 1.3 equiv) in a single portion. The mixture slowly turned yellow over time and was allowed to warm to rt overnight. After 16 hours, the mixture was diluted with CH_2Cl_2 (30 mL) and washed with 10% aqueous (w/v) citric acid (1 x 40 mL), with saturated aqueous brine as needed to aid in phase separation. The aqueous layer is back extracted thrice with CH_2Cl_2, and the combined organics washed with saturated aqueous NaCl (1 x 40 mL). The organics were dried over Na_2SO_4, filtered through celite, and concentrated *in vacuo* to afford the crude peptide, which was directly purified *via* RP-FCC using (SNAP-Ultra-C18 120 g, CV = 164 mL, 0.1% trifluoroacetic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–30% CH_3CN/H_2O linear gradient over 2 CV, 30–70% CH_3CN/H_2O linear gradient over 12 CV, and held at 100% CH_3CN for 2 CV, 65 $mL \cdot min^{-1}$ flowrate). *In order to remove residual TFA, which is detrimental to catalysis, the purified product was re-subjected to RP-FCC with a formic acid additive* (SNAP Ultra C18 60 g, CV = 90 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, 55–100% CH_3CN/H_2O linear gradient over 2 CV, and held at 100% CH_3CN for 4 CV, 50 $mL \cdot min^{-1}$ flowrate). Pure fractions were pooled, concentrated in vacuo (35–37 °C, 10 mbar), azeotroped twice with CH_3CN and twice with CH_2Cl_2 to provide **S16** as a white foam.

Yield: 1.83 g, 71% from **S15**

IR (FT-ATR, cm^{-1}, neat): 3311, 2977, 1629, 1523, 1449, 1381, 1241, 994, 738, 696

^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.42 (bs, 1H), 7.72 (ddd, *J* = 7.6, 2.0, 0.9 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.42–7.23 (m, 10H), 7.22–7.14 (m, 3H), 7.10 (dtd, *J* = 15.8, 7.1, 1.3 Hz, 2H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.55 (bd, *J* = 8.8 Hz, 1H), 5.21 (q, *J* = 7.7, 7.2 Hz, 1H), 5.10–5.01 (m, 2H), 4.97 (ddd, *J* = 10.6, 7.5, 3.3 Hz, 1H), 4.53 (dd, *J* = 10.7, 6.7 Hz, 1H), 4.46 (dd, *J* = 10.7, 6.6 Hz, 1H), 4.34 (dd, *J* = 8.4, 2.7 Hz, 1H), 4.19 (t, *J* = 6.6 Hz, 1H), 4.16 (t, *J* = 7.5 Hz, 1H), 4.05 (d, *J* = 17.0 Hz, 1H), 3.81 (ddd, *J* = 13.9, 7.9, 3.2 Hz, 1H), 3.66 (dq, *J* = 14.4, 7.1 Hz, 1H), 3.54 (dq, *J* = 14.7, 7.3 Hz, 1H), 3.50–3.39 (m, 4H), 3.33 (ddd, *J* = 14.3, 10.2, 4.4 Hz, 1H), 3.24 (dd, *J* = 17.1, 11.8 Hz, 2H), 3.21–3.14 (m,

1H), 2.26–2.17 (m, 1H), 2.01 (s, 3H), 1.84–1.64 (m, 3H), 1.33 (t, J = 7.2 Hz, 3H), 1.30 (d, J = 6.5 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H).

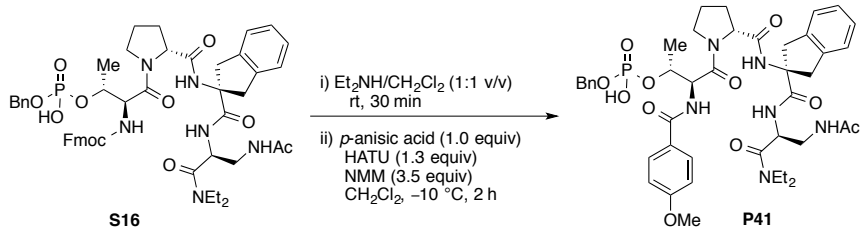
^{13}C NMR (151 MHz, Chloroform-*d*) δ 173.9, 172.2, 171.7, 171.4, 170.9, 156.8, 143.7, 143.6, 141.7, 141.5, 141.4, 139.3, 136.4 (d, J = 7.4 Hz), 128.6, 128.4, 127.9, 127.9, 127.8, 127.2, 126.9, 126.6, 125.1, 125.1, 124.6, 124.4, 120.2, 120.1, 72.8 (d, J = 5.7 Hz), 69.2 (d, J = 5.6 Hz), 67.2, 67.0, 63.9, 58.1 (d, J = 3.3 Hz), 50.5, 48.3, 47.3, 44.3, 43.2, 42.5, 41.7, 40.6, 29.5, 25.5, 23.1, 19.6 (d, J = 5.9 Hz), 14.2.

^{31}P NMR (162 MHz, Chloroform-*d*)) δ –4.01.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{50}H_{60}N_6O_{11}P$ 951.4058, found 951.4067.

Optical: $[\alpha]_D^{20}$ = –39.5° (c = 1.10, $CHCl_3$).

2.2.8. Procedure 8: Fmoc deprotection and Amide Coupling



Fmoc-Deprotection: **S16** (1.14 g, 1.2 mmol, 1.0 equiv) was dissolved in Et_2NH/CH_2Cl_2 (1:1 v/v, 6.0 mL, 0.2 M). The resulting solution was stirred for 30–45 minutes, after which the solvent was removed *in vacuo* to afford H-pThr(Bn)-D-Pro-Aic-Dap(Ac)-NEt_2, which was dried thoroughly under Hi-Vacuum to remove excess Et_2NH before proceeding to the next coupling step. The identity of H-pThr(Bn)-D-Pro-Aic-Dap(Ac)-NEt_2 was confirmed by UPLC-MS. **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{35}H_{50}N_6O_9P$ 729.34; found 729.56.

Installation of N-terminal protecting group: To crude H-pThr(Bn)-D-Pro-Aic-Dap(Ac)-NEt_2 (assumed 1.2 mmol, 1.0 equiv) was added *p*-anisic acid (0.201 g, 1.32 mmol, 1.1 equiv) and suspended in CH_2Cl_2 (6.0 mL). *N*-methylmorpholine (0.46 mL, 4.2 mmol, 3.5 equiv) was added to the mixture and the mixture cooled to –10 °C (brine/ice bath) followed by addition of HATU (0.593 g, 1.56 mmol, 1.3 equiv). The mixture slowly turned yellow over time. After 2 h, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with 10% aqueous (w/v) citric acid (2 x 30 mL) with saturated aqueous NaCl as needed. The aqueous layer was back extracted thrice with CH_2Cl_2, and the combined organics washed with saturated aqueous NaCl (1 x 40 mL). The organics were dried over Na_2SO_4, filtered through celite, and concentrated under reduced pressure to afford the crude peptide which was directly purified *via* RP-FCC (SNAP Ultra C18 120 g, CV = 164 mL, 0.1% formic acid buffer, 5% CH_3CN/H_2O for 2 CV, 5–20% CH_3CN/H_2O linear gradient over 2 CV, 20–50% CH_3CN/H_2O linear gradient over 12 CV, then 50–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 4 CV, 60 mL·min^{-1} flowrate). Pure fractions were pooled, concentrated *in vacuo* (35–37 °C, 10 mbar), azeotroped twice with CH_3CN and twice with CH_2Cl_2 to provide **P41** as a white foam.

Yield: 685 mg, 66% from **S16**

IR (FT-ATR, neat, cm^{-1}): 3310, 2979, 1626, 1537, 1506, 1437, 1301, 1255, 1181, 984, 845, 739

^{1}H NMR (800 MHz, Chloroform-*d,* 5.0 mM) δ 8.54 (bs, 1H), 7.89 (app d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 6.5 Hz, 2H), 7.38 (s, 1H), 7.38–7.34 (m, 2H), 7.34–7.28 (m, 3H), 7.21 (d, *J* = 6.7 Hz, 1H), 7.18–7.11 (m, 4H), 6.92 (app d, *J* = 8.8 Hz, 2H), 5.30 (s, 1H), 5.11 (dd, *J* = 12.0, 7.5 Hz, 1H), 5.05 (dd, *J* = 11.9, 7.3 Hz, 1H), 4.99–4.90 (m, 2H), 4.23 (t, *J* = 8.4 Hz, 1H), 4.10 (d, *J* = 16.8 Hz, 1H), 3.88 (ddd, *J* = 14.0, 8.3, 3.0 Hz, 1H), 3.85 (s, 3H), 3.74–3.46 (m, 6H), 3.33 (ddd, *J* = 14.2, 10.3, 4.3 Hz, 1H), 3.28 (d, *J* = 17.1 Hz, 1H), 3.25–3.15 (m, 2H), 2.37–2.31 (m, 1H), 2.04 (s, 3H), 1.91–1.84 (m, 1H), 1.84–1.77 (m, 1H), 1.73–1.65 (m, 1H), 1.39 (d, *J* = 6.6 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, Chloroform-*d*) δ 174.3, 172.3, 171.8, 171.7, 171.4, 167.3, 162.9, 141.9, 139.3, 136.3 (d, *J* = 7.6 Hz), 129.5, 128.6, 128.4, 127.8, 126.9, 126.5, 125.0, 124.6, 124.3, 114.1, 73.8 (d, *J* = 4.9 Hz), 69.4 (d, *J* = 6.1 Hz), 66.8, 64.1, 56.4, 55.6, 50.6, 48.5, 44.6, 43.2, 42.6, 41.8, 40.5, 29.8, 25.6, 23.2, 19.6 (d, *J* = 5.6 Hz), 14.1, 12.8.

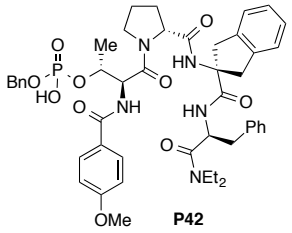
^{31}P NMR (202 MHz, Chloroform-*d*) δ –4.07.

HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{43}H_{56}N_6O_{11}P$ 863.3745, found 863.3726.

Elemental Analysis: Anal. Calcd for $C_{43}H_{55}N_6O_{11}P$: C, 59.85; H, 6.42; N, 9.74 Found: C, 59.97; H, 6.70; N, 9.53.

$[\alpha]_D^{20}$ –52.9 (*c* = 1.32, $CHCl_3$).

2.2.9. Characterization data for P42



P42

P42 was prepared in a similar fashion as **P41** by following Procedure 5 with Boc-Phe-OH (**S1,** 4.0 mmol), General Peptide Coupling Protocol 2.1.3, and Procedures 2 and 8. The crude material was purified *via* RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 5% CH_3CN/H_2O for 2 CV, 5–20% CH_3CN/H_2O linear gradient over 2 CV, 20–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 2 CV, 30 $mL \cdot min^{-1}$ flowrate).

Note: In some instances, the peptides may be contaminated with minor impurities that are inseparable when using a formic acid buffer. In these instances, the peptide is resubjected to RP-FCC using a TFA buffer (SNAP-Ultra-C18 30 g, CV = 45 mL, 0.1% trifluoroacetic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–30% CH_3CN/H_2O linear gradient over 1 CV, 30–100% CH_3CN/H_2O linear gradient over 12 CV, and held at 100% CH_3CN for 2 CV, 30 $mL \cdot min^{-1}$ flowrate). In order to remove residual TFA, which is detrimental to catalysis, the purified product is subjected to a final RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10–20% CH_3CN/H_2O linear gradient over 1 CV, 20–60% CH_3CN/H_2O linear gradient over 10 CV, 60–100% CH_3CN/H_2O linear gradient over 1 CV, and held at 100% CH_3CN for 2 CV, 25 $mL \cdot min^{-1}$ flowrate). Pure fractions were pooled,

concentrated in vacuo (35–37 °C, 10 mbar), azeotroped twice with CH_3CN and twice with CH_2Cl_2 to provide **P42** as a white foam.

Yield: 140 mg, 53% from Fmoc-pThr(Bn)-D-Pro-Aic-Phe-NEt_2.

IR (FT-ATR, neat, cm^{-1}): 3311, 2979, 1625, 1607, 1505, 1454, 1303, 1255, 1179, 986, 740.

^{1}H NMR (800 MHz, Chloroform-*d,* 5.0 mM) δ 8.43 (bd, *J* = 8.5 Hz, 1H), 7.87 (app d, *J* = 8.8 Hz, 2H), 7.80–7.71 (m, 1H), 7.43–7.36 (m, 3H), 7.35–7.28 (m, 3H), 7.26–7.24 (m, 3H), 7.24–7.19 (m, 1H), 7.16–7.09 (m, 5H), 6.91 (app d, *J* = 8.8 Hz, 2H), 5.39 (bs, 1H), 5.14 (dd, *J* = 12.0, 7.7 Hz, 1H), 5.09 (dd, *J* = 12.0, 7.5 Hz, 1H), 4.94–4.88 (m, 2H), 4.33 (t, *J* = 7.9 Hz, 1H), 3.98 (d, *J* = 17.0 Hz, 1H), 3.84 (s, 3H), 3.65–3.52 (m, 3H), 3.41–3.31 (m, 3H), 3.27–3.20 (m, 2H), 3.11 (dq, *J* = 15.3, 7.6 Hz, 1H), 3.07–2.98 (m, 0H), 2.92 (dq, *J* = 14.6, 7.2 Hz, 1H), 2.32–2.25 (m, 1H), 1.88–1.71 (m, 3H), 1.38 (d, *J* = 6.6 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.2 Hz, 3H).

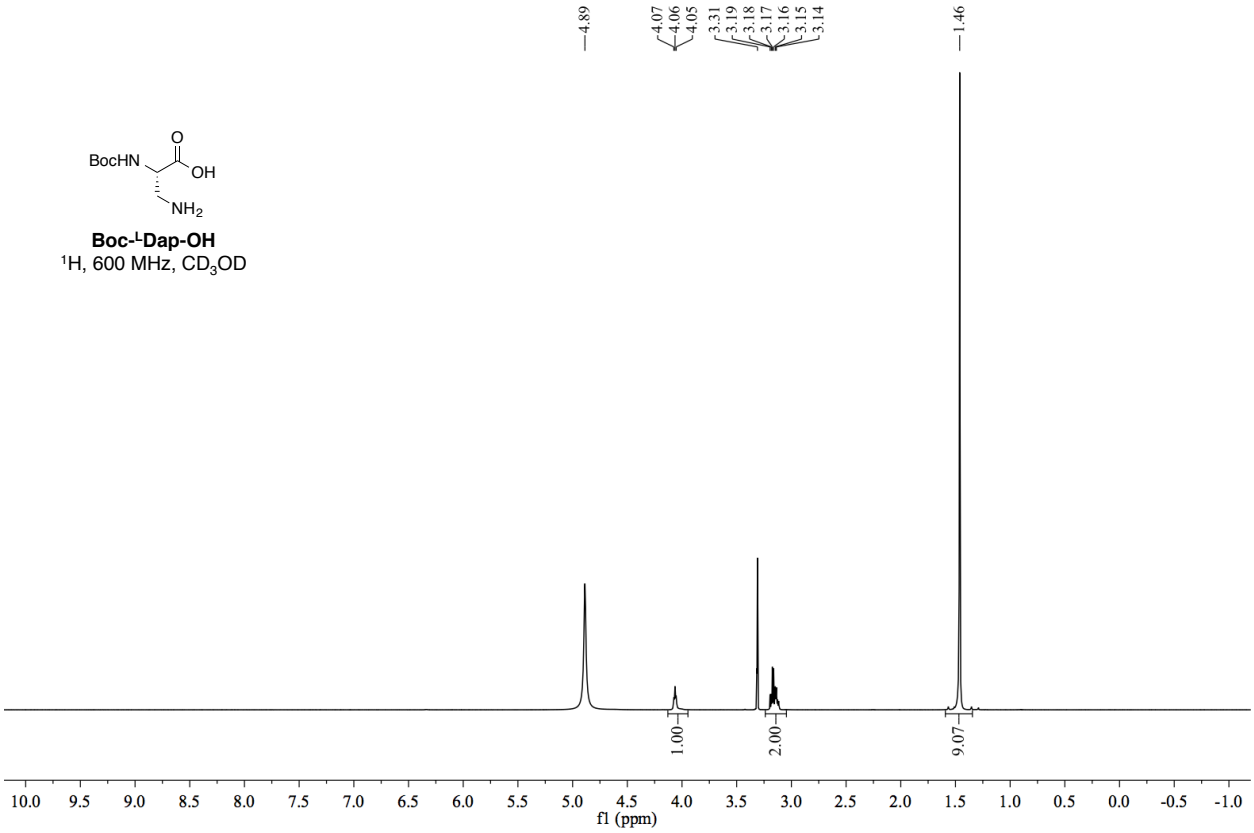
^{13}C NMR (151 MHz, Chloroform-*d*) δ 173.5, 172.0, 171.6, 170.8, 167.8, 163.2, 162.8, 141.4, 139.8, 136.8, 136.3 (d, *J* = 7.1 Hz), 129.8, 129.6, 128.6, 128.5, 128.4, 127.8, 127.0, 126.8, 126.6, 125.2, 124.6, 124.3, 114.0, 73.2 (d, *J* = 5.3 Hz), 69.2 (d, *J* = 5.4 Hz), 66.9, 62.6, 57.5, 55.6, 51.2, 48.3, 44.4, 42.9, 42.5, 41.4, 38.7, 29.5, 25.0, 19.2 (d, *J* = 4.5 Hz), 13.6, 12.5.

^{31}P NMR (202 MHz, Chloroform-*d*) δ –3.14.

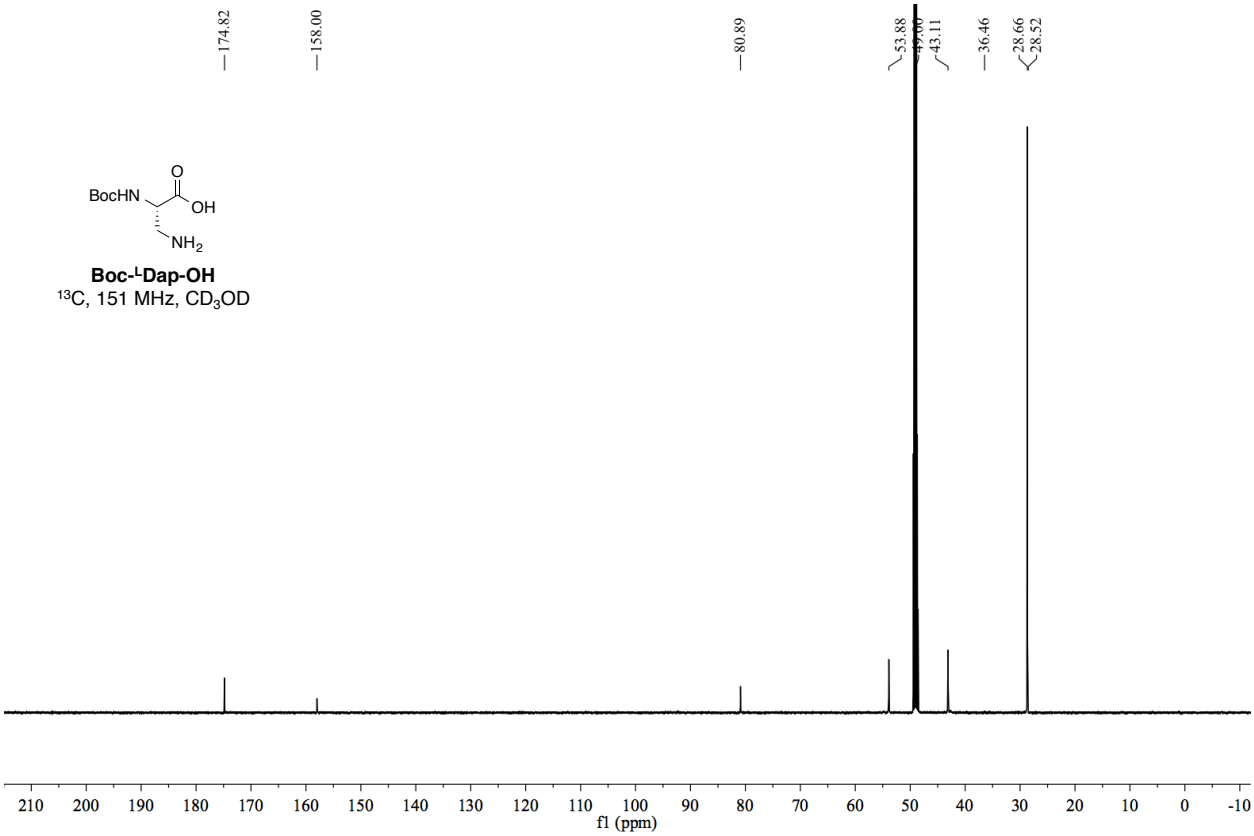
HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{47}H_{57}N_5O_{10}P$ 882.3843, found 882.3862.

$[\alpha]_D^{20}$ –9.6 (*c* = 0.98, $CHCl_3$).

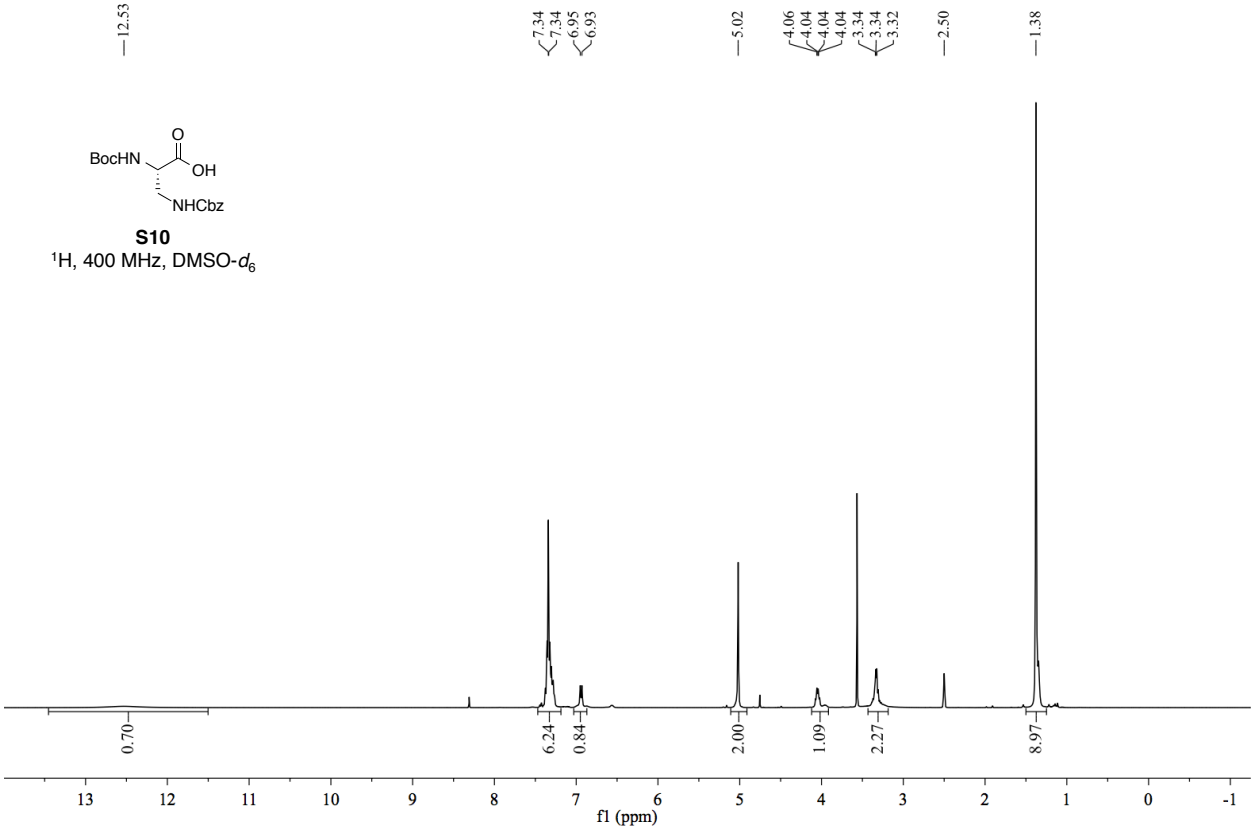
2.3. NMR Spectra of P7, S16, P41–42



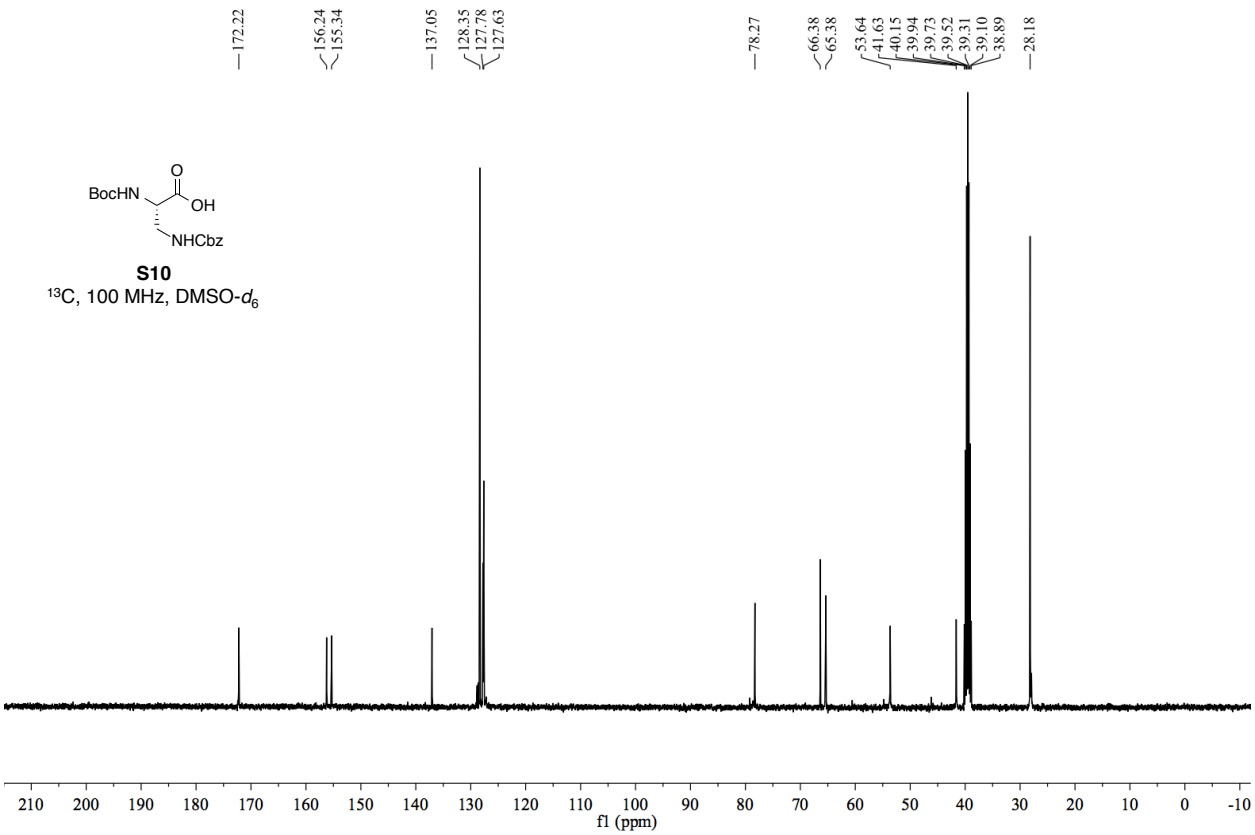
Boc-^{L}Dap-OH
^{1}H, 600 MHz, CD_3OD



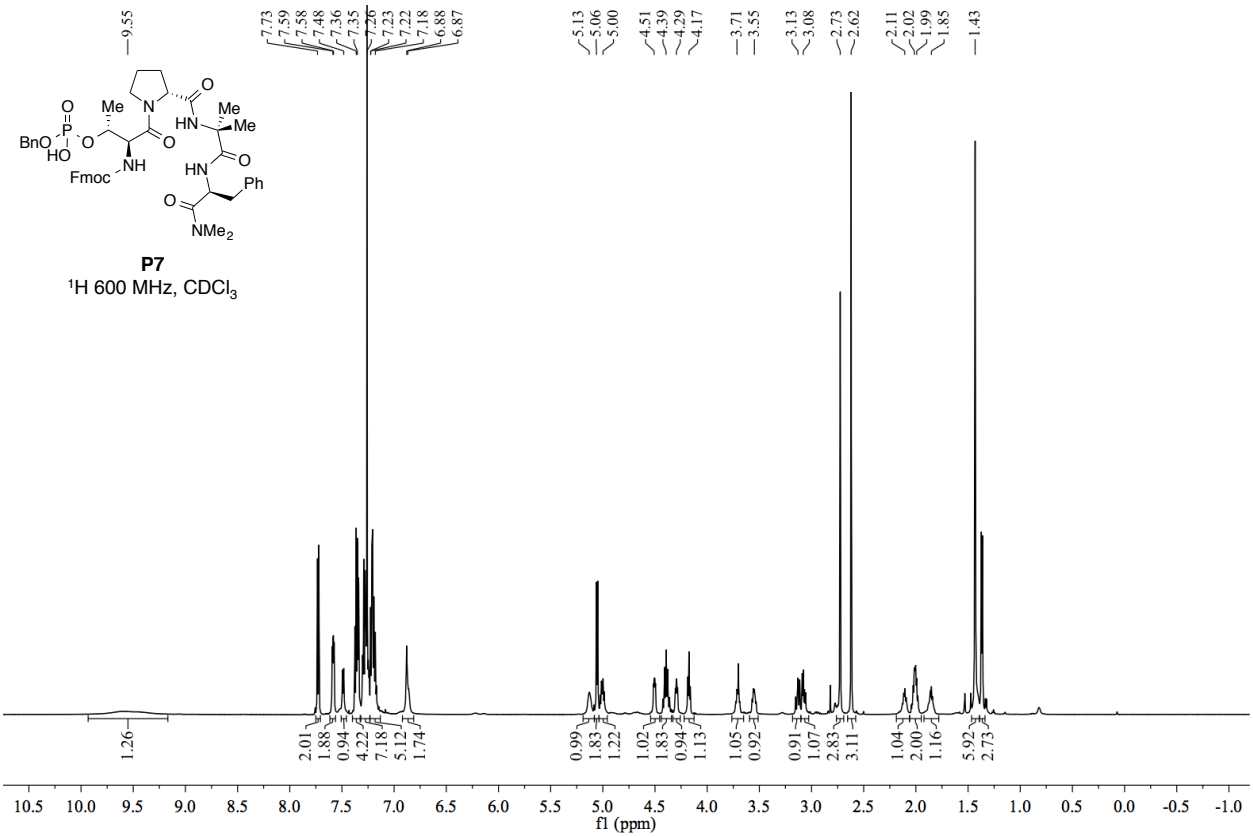
Boc-^{L}Dap-OH
^{13}C, 151 MHz, CD_3OD



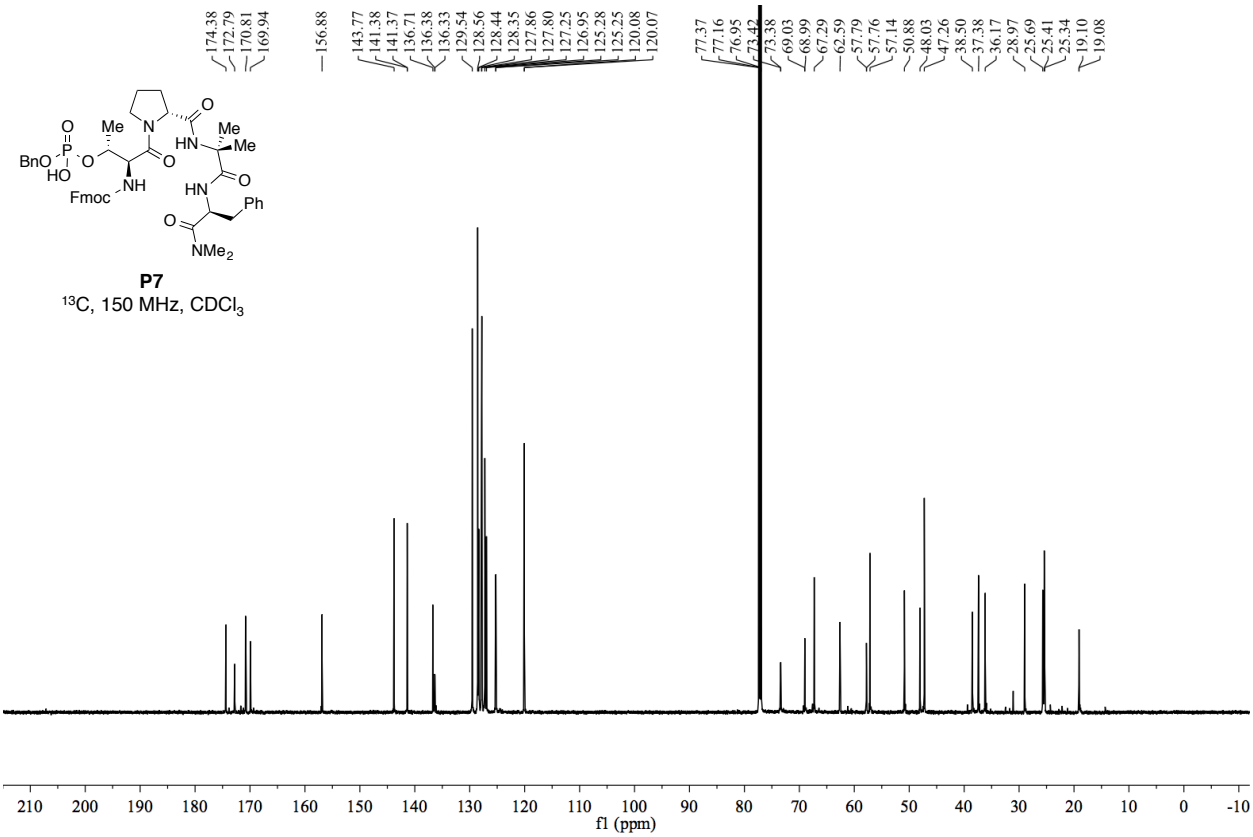
S10
^{1}H, 400 MHz, DMSO-d_6



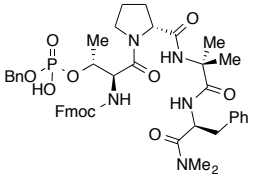
S10
^{13}C, 100 MHz, DMSO-d_6



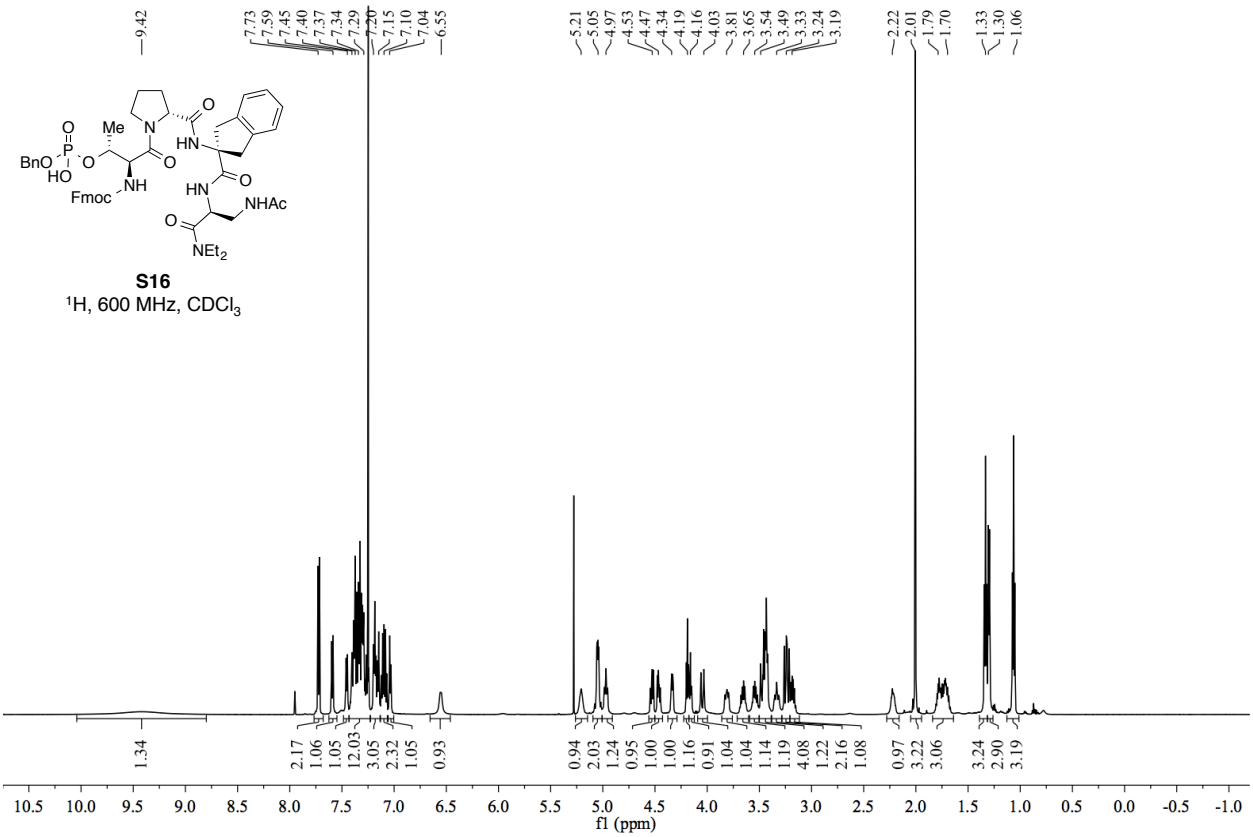
P7
^{1}H 600 MHz, $CDCl_3$

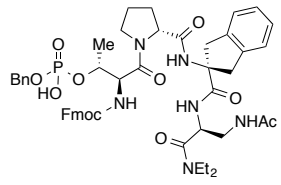


P7
^{13}C, 150 MHz, $CDCl_3$



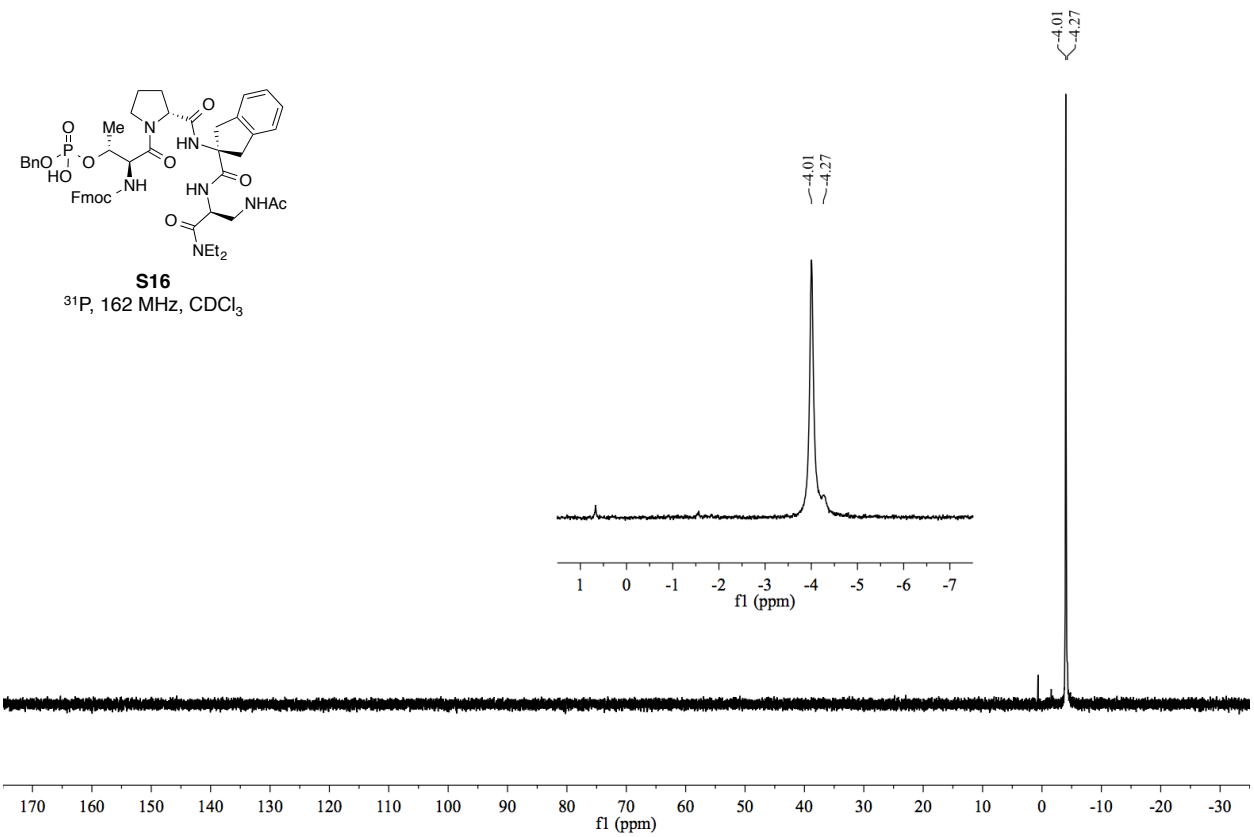
P7
^{31}P, 162 MHz, $CDCl_3$



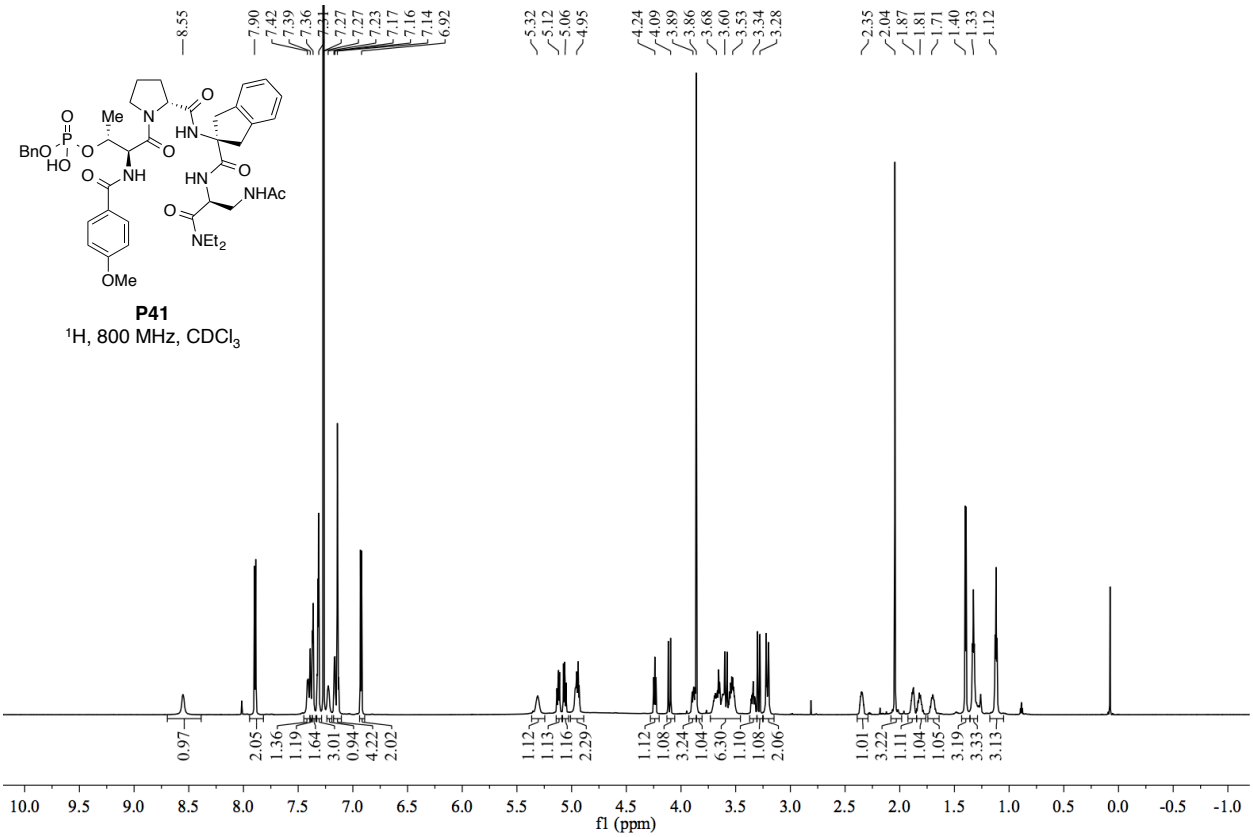


S16
^{1}H, 600 MHz, $CDCl_3$

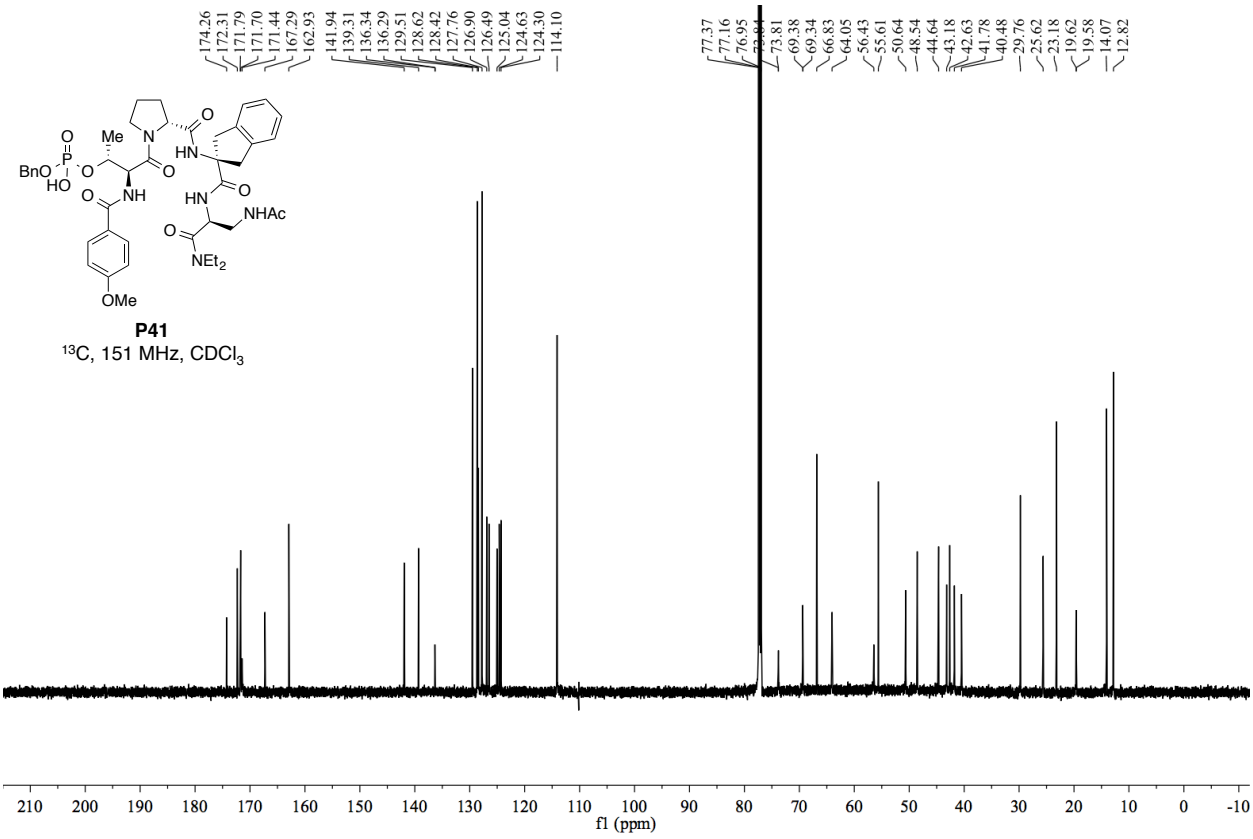
S16
^{13}C, 151 MHz, $CDCl_3$



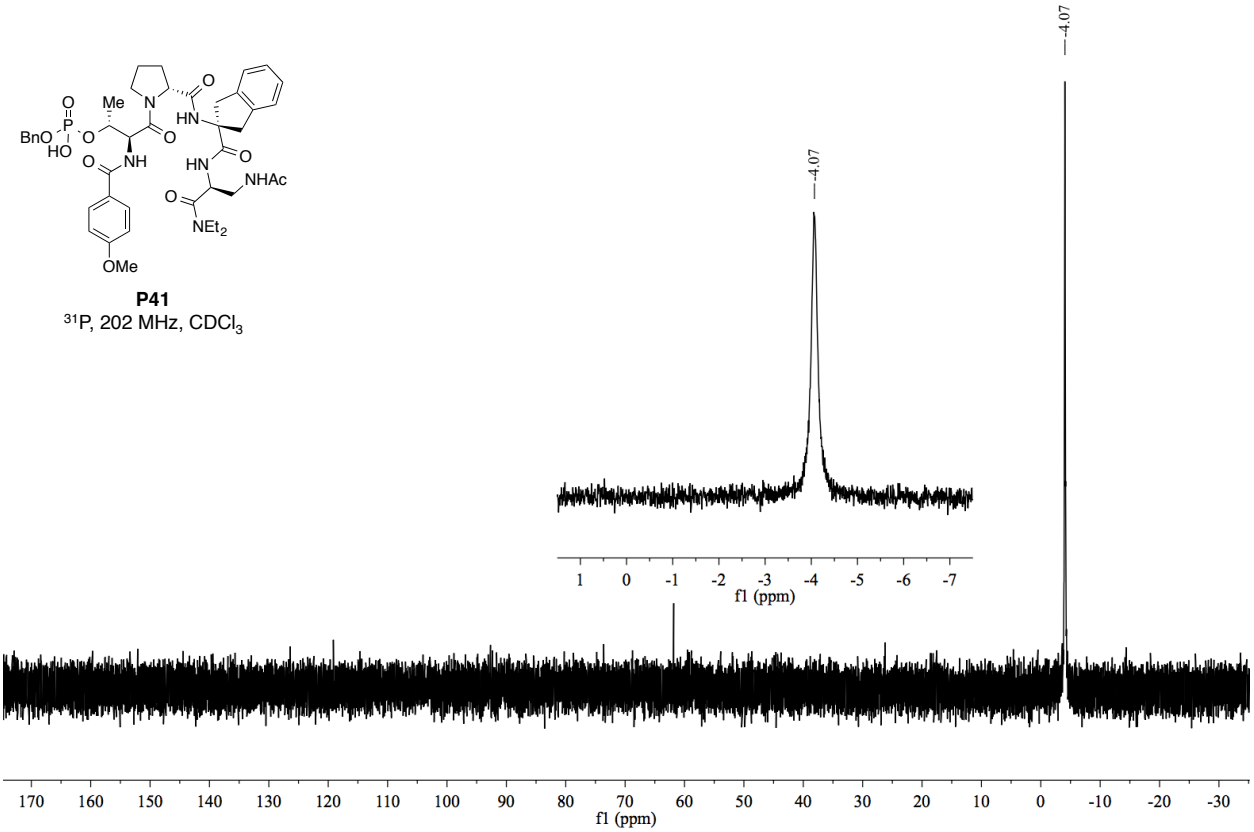
S16
^{31}P, 162 MHz, $CDCl_3$



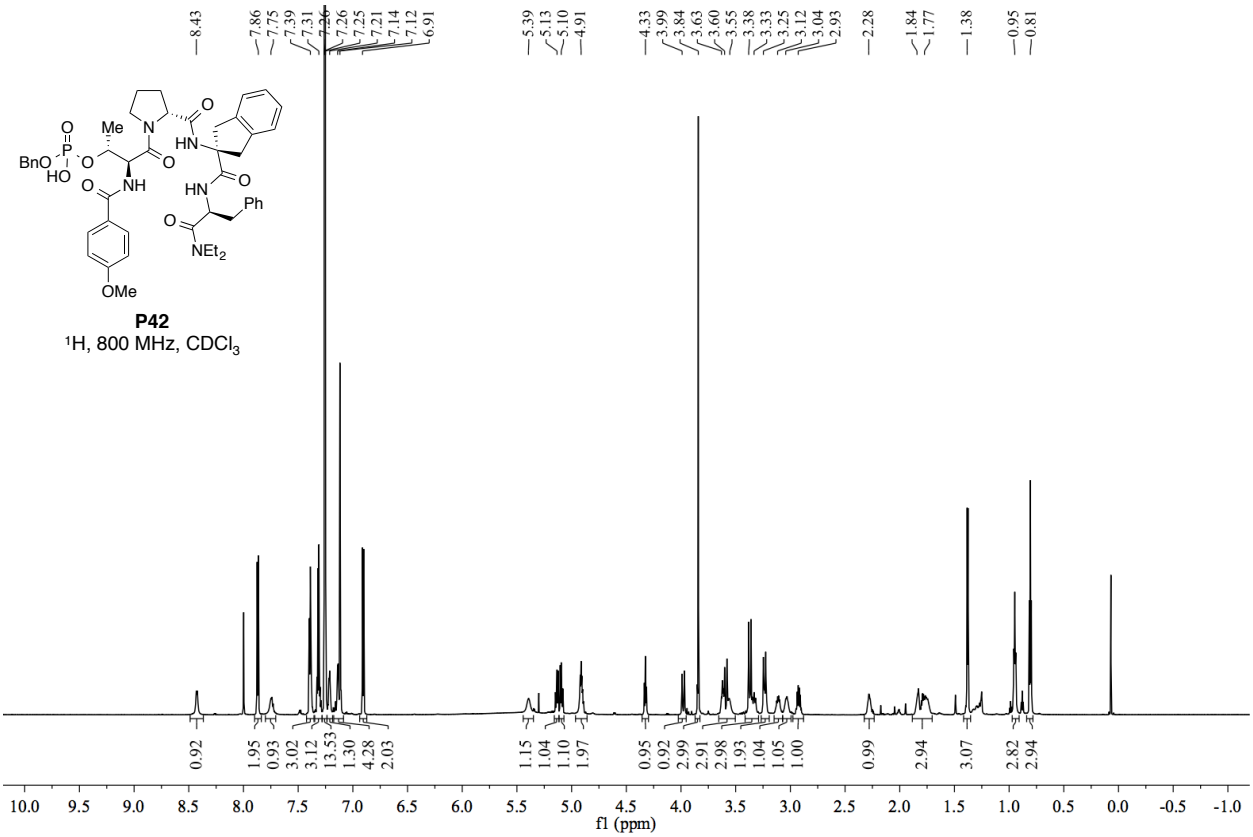
P41
^{1}H, 800 MHz, $CDCl_3$



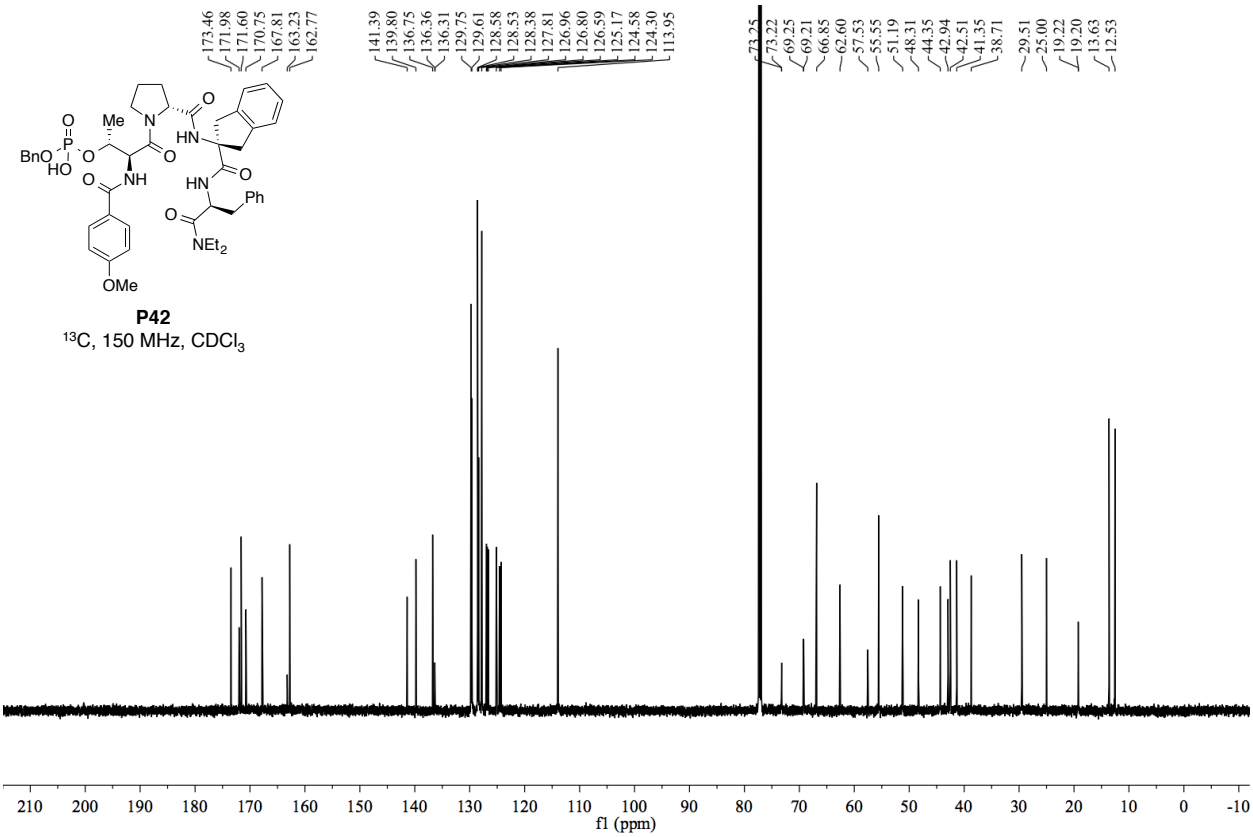
P41
^{13}C, 151 MHz, $CDCl_3$



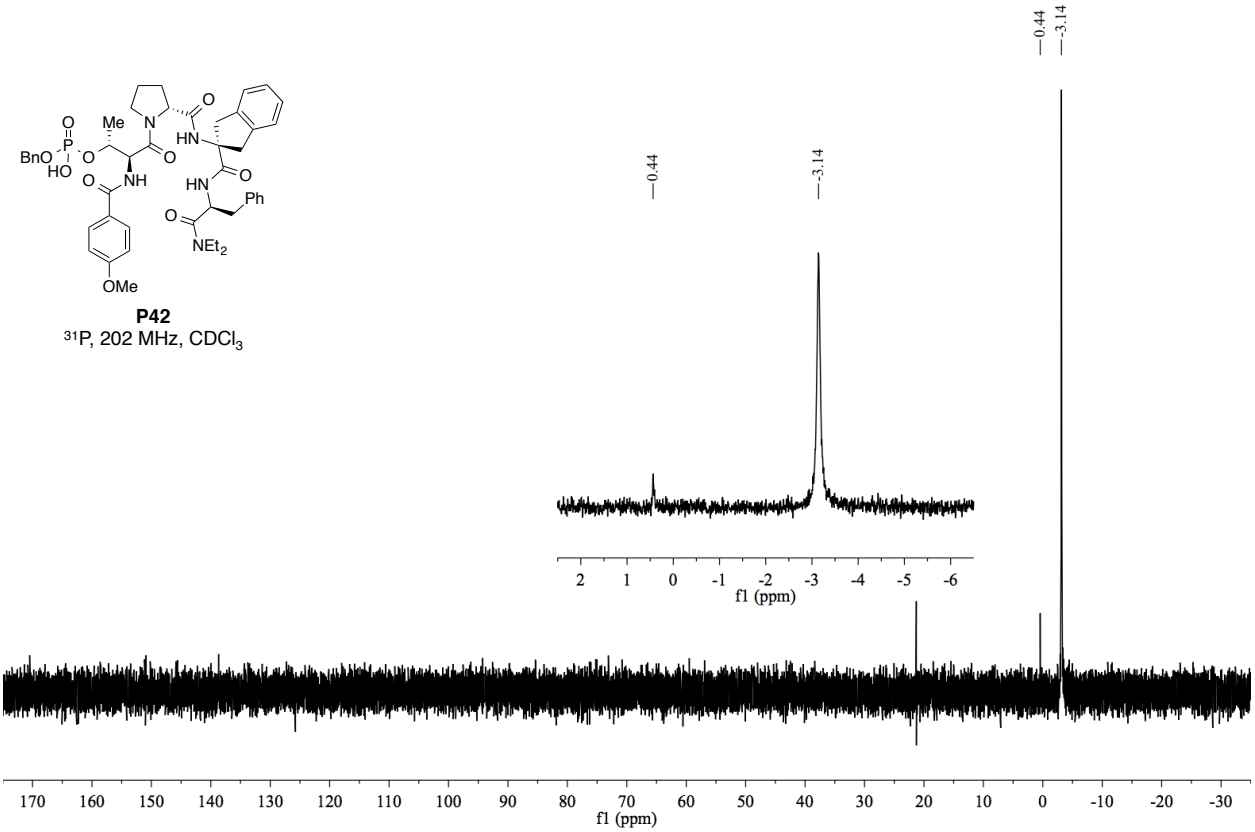
P41
^{31}P, 202 MHz, $CDCl_3$



P42
^{1}H, 800 MHz, $CDCl_3$



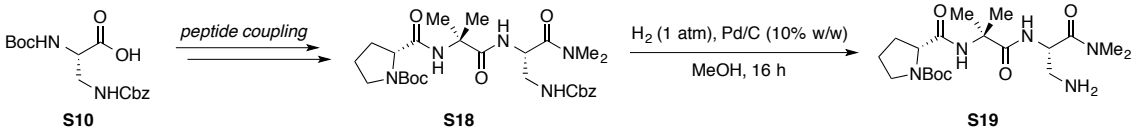
P42
^{13}C, 150 MHz, $CDCl_3$



P42
^{31}P, 202 MHz, $CDCl_3$

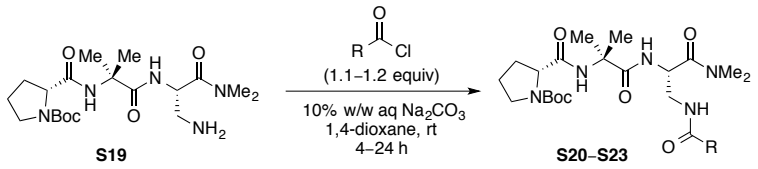
2.4 Additional synthetic methods for preparation of trimer peptide derivatives (S19–S28)

2.4.1 Synthesis of Boc-D-Pro-Aib-Dap-NMe_2 (S19)

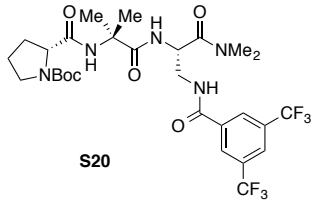


***tert*-butyl (*R*)-2-((1-(((*S*)-3-amino-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S19): S18** was prepared by following Procedure 1 with Boc-Dap(Cbz)-OH (**S10,** 10.0 mmol) and General Peptide Coupling Protocol 2.1.3 to afford **S18** as a white foam (3.48 g, 64% yield from **S10**), which was subjected to hydrogenolysis Procedure 6 using Boc-D-Pro-Aib-Dap(Cbz)-NMe_2 (**S18**, 2.91 g, 5.3 mmol, 1.0 equiv) and Pd/C (10% w/w, 291 mg, 0.10 equiv) in MeOH (50 mL, 0.10 M) to afford the desired peptide as a white foam (**S19**, 2.16 g, 99% yield). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{36}N_5O_5$ 414.27; found 414.21.

2.4.2 Procedure 9: Schotten-Baumann Acylation (Dap-Acylation)

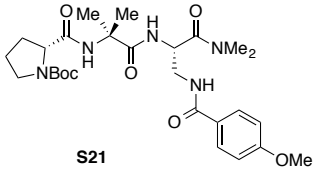


To a solution of amine (**S19**, 1.0 equiv) in 1,4-dioxane (0.25 M wrt **S19**) and 10% w/w aqueous Na_2CO_3 (2.0–2.2 equiv) was added the appropriate acid chloride (1.1–1.2 equiv) dropwise at 0 °C or rt. The reaction mixture was allowed to slowly warm to rt overnight. After 16 h, the reaction mixture was transferred to a separatory funnel and diluted with CH_2Cl_2. The organics were washed sequentially with saturated aqueous $NaHCO_3$, 10% HCl, and saturated aqueous NaCl. The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude peptide as an off-white foam, which was directly purified by automated FCC with an appropriate MeOH/CH_2Cl_2 gradient.



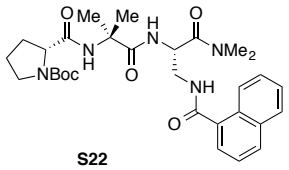
***tert*-butyl (*R*)-2-((1-(((*S*)-3-(3,5-bis(trifluoromethyl)benzamido)-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S20)** was synthesized from **S19** (212 mg, 0.51 mmol, 1.0 equiv) following Procedure 9 with 3,5-bis(trifluoromethyl)benzoyl chloride (158 mg, 0.57 mmol, 1.1 equiv) and 10% w/w aqueous Na_2CO_3 (1.0 mL, 1.1 mmol, 2.2 equiv). The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 1% MeOH/CH_2Cl_2

for 1 CV, 1–12% MeOH/CH_2Cl_2 linear gradient over 14 CV, 65 mL·min^{-1} flowrate) to afford **S20** as a white foam (198 mg, 59%). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{38}F_6N_5O_6$ 654.27; found 654.41.



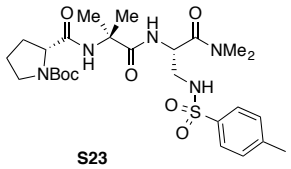
S21

***tert*-butyl (*R*)-2-((1-(((*S*)-1-(dimethylamino)-3-(4-methoxybenzamido)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S21)** was synthesized from **S19** (141 mg, 0.34 mmol, 1.0 equiv) following Procedure 9 with 4-methoxybenzoyl choride (70 mg, 0.41 mmol, 1.2 equiv) and 10% aqueous (w/w) Na_2CO_3 (0.72 mL, 0.75 mmol, 2.2 equiv). The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 1% MeOH/CH_2Cl_2 for 1 CV, 1–12% MeOH/CH_2Cl_2 linear gradient over 14 CV, 65 mL·min^{-1} flowrate) to afford **S21** as a white foam (151 mg, 81%). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{42}N_5O_7$ 548.31; found 548.43.



S22

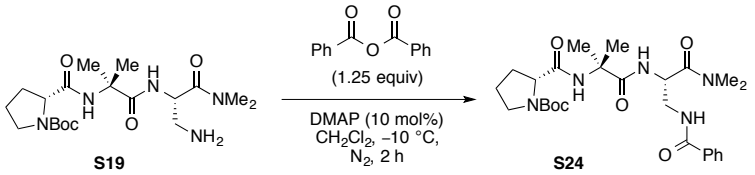
***tert*-butyl (*R*)-2-((1-(((*S*)-3-(1-naphthamido)-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S22)** was synthesized from **S19** (207 mg, 0.50 mmol, 1.0 equiv) following Procedure 9 with 1-napthoyl chloride (114 mg, 0.6 mmol, 1.2 equiv) and 10% w/w aqueous Na_2CO_3 (0.9 mL, 1.0 mmol, 2.0 equiv). The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 1% MeOH/CH_2Cl_2 for 1 CV, 1–12% MeOH/CH_2Cl_2 linear gradient over 14 CV, 65 mL·min^{-1} flowrate) to afford **S22** as a white foam (233 mg, 82%). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{42}N_5O_6$ 568.31; found 568.39.



S23

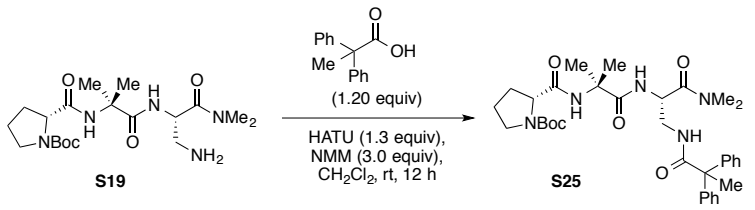
***tert*-butyl (*R*)-2-((1-(((*S*)-1-(dimethylamino)-3-((4-methylphenyl)sulfonamido)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S23)** was synthesized from **S19** (207 mg, 0.51 mmol, 1.0 equiv) following Procedure 9 with *p*-toluenesulfonyl chloride (114 mg, 0.60 mmol, 1.2 equiv) and 10% aqueous (w/w) Na_2CO_3 (0.9 mL, 1.0 mmol, 2.0 equiv). The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 1% MeOH/CH_2Cl_2 for 1 CV, 1–12% MeOH/CH_2Cl_2 linear gradient over 14 CV, 65 mL·min^{-1} flowrate) to afford **S23** as a white foam (198 mg, 59%). **MS** (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{26}H_{41}N_5O_7SNa$ 590.26; found 590.29.

2.4.3 Procedure 10: Acylation of Dap *via* anhydride



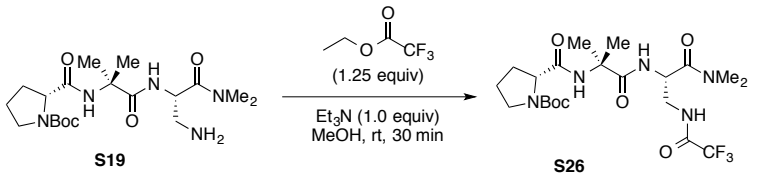
***tert*-butyl (*R*)-2-((1-(((*S*)-3-benzamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S24):** To a solution of amine (**S19**, 207 mg, 0.50 mmol, 1.0 equiv) and *N,N'*-dimethylaminopyridine (6.1 mg, 0.05 mmol, 0.10 equiv) in CH_2Cl_2 (5.0 mL) at –10 °C was added benzoic anhydride (124 mg, 0.55 mmol, 1.1 equiv) under a N_2 atmosphere. After 2 hrs, the reaction was diluted with CH_2Cl_2 (5 mL) and washed sequentially with 10% aqueous (w/v) citric acid (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and saturated aqueous NaCl (10 mL). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude peptide, which was directly purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 1% MeOH/CH_2Cl_2 for 1 CV, 1–12% MeOH/CH_2Cl_2 linear gradient over 14 CV, 65 mL·min^{-1} flowrate) to afford **S24** as a white foam (213 mg, 82%). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{40}N_5O_6$ 518.30; found 519.41.

2.4.4 Procedure 11: HATU mediated amide coupling of Dap



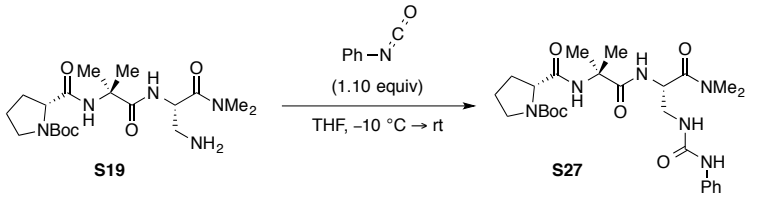
***tert*-butyl (*R*)-2-((1-(((*S*)-1-(dimethylamino)-3-(2,2-diphenylpropanamido)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S25):** To a solution of amine (**S19**, 207 mg, 0.50 mmol, 1.0 equiv) and 2,2-diphenylproprionic acid (136 mg, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (6.0 mL) was added N-methylmorpholine (0.46 mL, 4.2 mmol, 3.5 equiv) followed by HATU (0.593 g, 1.56 mmol, 1.3 equiv). The mixture slowly turned yellow over time. After completion, the mixture was diluted with CH_2Cl_2 washed with 10% aqueous (w/v) citric acid, saturated aqueous $NaHCO_3$ (10 mL), and saturated aqueous NaCl (10 mL). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude peptide, which was directly purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 1% MeOH/CH_2Cl_2 for 1 CV, 1–12% MeOH/CH_2Cl_2 linear gradient over 14 CV, 65 mL·min^{-1} flowrate) to afford **S25** as a white foam (279 mg, 90%). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{48}N_5O_6$ 622.36; found 622.57.

2.4.5 Procedure 12: Triflouroacetylation of Dap



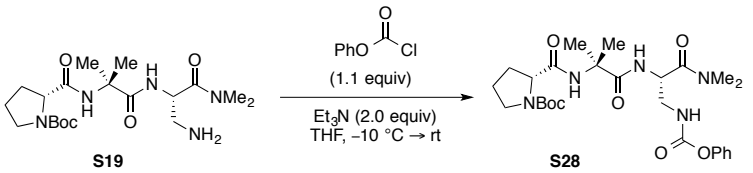
***tert*-butyl (*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-(2,2,2-trifluoroacetamido)propan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S26):** Adapting the procedure of Curphey[7], to a solution of amine (**S19**, 313 mg, 0.75 mmol, 1.0 equiv) in MeOH (1.5 mL) was added Et_3N (105 μL, 0.75 mmol, 1.0 equiv) followed by dropwise addition of ethyl trifluoroacetate (113 μL, 0.95 mmol, 1.25 equiv). The solution was stirred for 30 minutes and the volatiles removed under reduced pressure to afford the crude product, which was directly purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 1% MeOH/CH_2Cl_2 for 1 CV, 1–15% MeOH/CH_2Cl_2 linear gradient over 14 CV, 65 mL·min^{-1} flowrate) to afford **S26** as a white foam (293 mg, 77%). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{35}F_3N_5O_6$ 510.25; found 510.39.

2.4.6 Procedure 13: Installation of urea of Dap



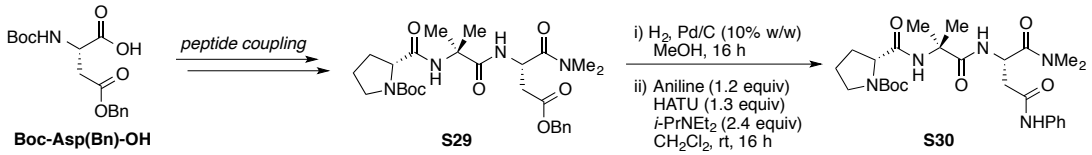
***tert*-butyl (*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-(3-phenylureido)propan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S27)** To a solution of amine S19 (207 mg, 0.5 mmol, 1.0 equiv) in THF (5 mL) at –10 °C was added the phenyl isocyanate (66 mg, 0.55 mmol, 1.1 equiv) dropwise. After completion, as determined by LC/MS, the volatiles removed under reduced pressure to afford the crude product, which was directly purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 1% MeOH/CH_2Cl_2 for 1 CV, 1–12% MeOH/CH_2Cl_2 linear gradient over 14 CV, 65 mL·min^{-1} flowrate) to afford **S27** as a white foam (92.5 mg, 35%). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{41}N_6O_6$ 533.31; found 533.40.

2.4.7 Procedure 14: Carbamoylation of Dap



***tert*-butyl (*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-((phenoxycarbonyl)amino)propan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S28)** To a solution of amine **S19** (207 mg, 0.5 mmol, 1.0 equiv) and Et_3N (140 µL, 1.0 mmol, 2.0 equiv) in THF (5.0 mL) at –10 °C was added phenyl chloroformate (86 mg, 0.55 mmol, 1.1 equiv) dropwise. After completion, as determined by LC/MS, the reaction was quenched by addition of saturated aqueous NH_4Cl. The reaction mixture was transferred to a separatory funnel, and the product extracted thrice with CH_2Cl_2. The combined organics were dried over dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude peptide, which was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 1% MeOH/CH_2Cl_2 for 1 CV, 1–12% MeOH/CH_2Cl_2 linear gradient over 14 CV, 65 mL·min^{-1} flowrate) to afford **S28** as a white foam (197 mg, 74%). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{40}N_5O_7$ 534.29; found 534.55.

2.5 Synthesis of Peptide S30 (Boc-D-Pro-Aib-Asn(Ph)-NMe_2)

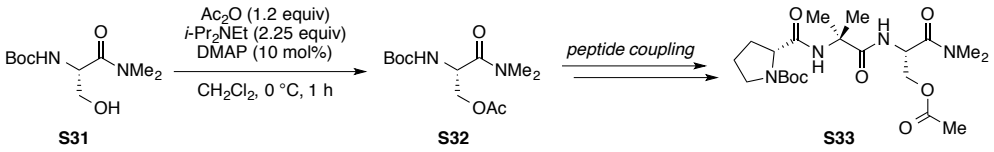


***tert*-butyl (*R*)-2-((1-(((*S*)-1-(dimethylamino)-1,4-dioxo-4-(phenylamino)butan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S30): S29** was prepared by following Procedure 1 with Boc-Asp(Bn)-OH (1.29 g, 4.0 mmol, 1.0 equiv) and General Peptide Coupling Protocol 2.1.3 to afford **S29** as a white foam (1.33 g, 62% yield). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{41}N_4O_7$ 533.30; found 533.45.

Step 1: Benzyl Hydrogenolysis: Modified Procedure 6, to a round bottom flask containing Pd/C (10% w/w, 50 mg) wetted with EtOAc was added a solution of **S29** (0.532 g, 1.0 mmol, 1.0 equiv) in MeOH (10 mL, 0.10 M). The flask was fitted with a balloon of H_2, subjected to three cycles of vacuum and H_2 purging, and the resultant mixture stirred vigorously at rt. After 18 h, the mixture was filtered through a pad of Celite® and the filter pad was washed CH_2Cl_2 (3 x 25 mL). The filtrate was concentrated under reduced pressure to afford crude acid, as a white foam, that was used without further purification (429 mg, 97% yield). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{35}N_4O_7$ 443.25; found 443.30.

Step 2: HATU amide coupling: Modified Procedure 11, to a solution of Boc-D-Pro-Aib-Asp-NMe_2 (**S29**, 221 mg, 0.50 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL) was added aniline (55 µL, 0.60 mmol, 1.2 equiv), *i*-Pr_2NEt (210 µL, 1.2 mmol, 2.4 equiv) and HATU (247 mg, 0.65 mmol, 1.3 equiv). After 14 h, the yellow-orange reaction mixture was transferred to a separatory funnel, diluted with CH_2Cl_2 (20 mL), and washed with 10% aqueous (w/v) citric acid (20 mL). The aqueous layer was back-extracted with CH_2Cl_2 (25 mL), and the combined organics were washed sequentially with saturated aqueous $NaHCO_3$ (20 mL), saturated aqueous NaCl (20 mL). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude trimer, which was directly purified by RP-FCC (SNAP Ultra C18 60 g, CV = 90 mL, 5% CH_3CN/H_2O for 2 CV, 5–85% CH_3CN/H_2O linear gradient over 10 CV, 65 $mL \cdot min^{-1}$ flowrate) **S31** as a white foam (180 mg, 70%). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{40}N_5O_6$ 518.30, found 518.43.

2.6 Synthesis of Peptide S33 (Boc-D-Pro-Aib-Ser(Ac)-NMe_2)



***tert*-butyl (*R*)-2-((1-(((*S*)-3-acetoxy-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (S33): S31** was prepared by following Procedure 1 with Boc-Ser-OH to afford **S31** as a white foam (822 mg, 47% yield). **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{21}N_2O_4$ 233.15; found 233.13.

Acylation: A 100 mL round bottom flask was charged with Boc-Ser-NMe_2 (**S31**, 822 mg, 3.54 mmol, 1.0 equiv.) and CH_2Cl_2 (35 mL). The vessel was capped with a septum, placed under an atmosphere of Argon, and cooled to 0 °C. Acetic anhydride (402 µL, 4.25 mmol, 1.2 equiv.) was added, followed by *i*-Pr_2NEt (740 µL, 4.25 mmol, 1.2 equiv.), and the reaction was stirred at 0 °C for 1 h. Upon completion, the reaction solution was treated with 10% HCl (35 mL) and transferred to a separatory funnel. The organics were separated and washed with saturated aqueous NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield a crude white solid that was used without further purification (**S32**, 762 mg, 78% yield). **MS** (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{22}N_2O_5Na$ 297.14; found 297.20.

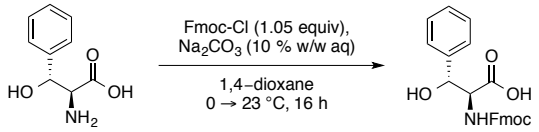
Peptide Coupling: Boc-D-Pro-Aib-Ser(Ac)-NMe_2 (**S33**) was prepared according to General Peptide Coupling Protocol 2.1.3 from Boc-Ser(Ac)-NMe_2 (**S32**, 751 mg, 1.7 mmol) in 57% overall yield. **MS** (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{37}N_4O_7$ 457.27; found 457.42.

3. Synthesis of Phosphorylated Amino acids

3.1 General Remarks

Fmoc-pThr(Bn)-OH (**S7**) and Fmoc-pSer(Bn)-OH (**S34**) were purchased form Chem-Impex and used as received. Fmoc-pPhSer(Bn)-OH (**S35**) and Fmoc-*allo*-pThr(Bn)-OH (**S36**) were prepared from the corresponding *N*-protected amino acid by adapting literature precedent.[8]

3.2 Procedure 15: Fmoc Carbamoylation[9]



S37 **S38**

(2*S*,3*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-hydroxy-3-phenylpropanoic acid (S38): Adapting the procedure of Karunaratne *et al.*[9a] a solution of 9-fluorenylmethoxycarbonyl chloride (749 mg, 2.90 mmol, 1.05 equiv) in 1,4-dioxane (1.0 mL) was added dropwise to a mixture of H-*threo*-β-phenylserine (**S37**, 2.76 mmol, 1.0 equiv) in 1,4-dioxane (3.4 mL) and 10% aqueous (w/w) Na_2CO_3 (7.3 mL) at 0 °C. The mixture was gradually warmed to rt overnight, poured onto ice-cold water and washed with Et_2O (2 x 40 mL). The aqueous layer was acidified by addition of 6 N HCl to pH ~2 and extracted with EtOAc (3 x 50 mL). The organics were combined, dried over Na_2SO_4, filtered and concentrated to afford the desired product **S38** as a white solid that was used without further purification. The characterization data were in close agreement with literature values.[9b]

Yield: 1.108 g, quantitative

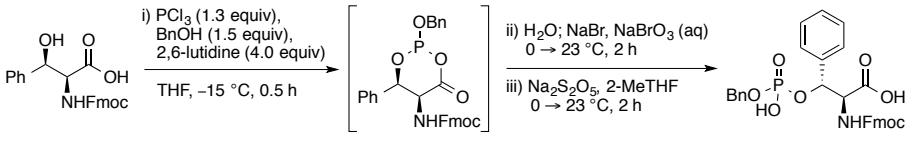
IR (FT-ATR, neat, cm^{-1}): 3393, 3066, 1701, 1518, 1450, 1414, 1333, 1218, 1052, 737

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 7.87 (d, J = 7.6 Hz, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.46–7.36 (m, 4H), 7.35–7.19 (m, 6H), 5.72 (s, 1H), 5.17 (d, J = 3.4 Hz, 1H), 4.31 (dd, J = 9.5, 3.3 Hz, 1H), 4.23–4.01 (m, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 171.9, 156.2, 143.7, 143.7, 142.1, 140.6, 140.6, 127.8, 127.6, 127.1, 126.2, 125.5, 125.3, 120.1, 72.3, 65.9, 60.4, 46.5.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{22}NO_5$ 404.1498, found 404.1505

3.3 Procedure 16: One-pot phosphorylation and benzyl protection



S38 **S39** **S35**

(2*S*,3*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-3-phenylpropanoic acid (S35): Adapting the procedure of Petrillo *et al.,*[8] to a flame-dried 100 mL two-

neck round bottom flask equipped with argon inlet and a digital thermometer fitted through a septum was added freshly distilled PCl_3 (0.23 mL, 2.6 mmol, 1.3 equiv) to anhydrous THF (4.0 mL) and cooled to –15 ºC using a brine/ice bath. Benzyl alcohol (0.31 mL, 3.0 mmol, 1.5 equiv) was then added at a rate that kept the internal temperature below –10 ºC. The solution was then allowed to stir for 15 minutes at –15 ºC (the consumption of PCl_3 was confirmed by ^{31}P NMR analysis in $CDCl_3$). 2,6-Lutidine (>99.5%, 0.93 mL, 6.0 mmol, 3.00 equiv) was then added to the flask at a rate that kept the reaction below –5 ºC, forming a thick-white slurry.

In an oven-dried vial, 2,6-lutidine (>99.5%, 2.0 mmol, 1.0 equiv) was added to a suspension of **S38** (807 mg, 2.0 mmol, 1.00 equiv) in THF (4.0 mL) resulting in a homogeneous solution. This solution was subsequently added to the reaction vessel, at a rate that kept the reaction temperature below –5 ºC, over 45 minutes. Additional THF (0.50 mL) was used to rinse the flask containing the *N*-protected amino acid (**S37**). The reaction progress was monitored by ^{31}P NMR and was judged complete when no change in the ratio of the dichlorophosphite to intermediate phosphite **S39** was observed (~ 2 h).

Upon reaction completion, H_2O (2.5 mL) was added to the flask, maintaining the temperature below 5 ºC. During the addition, a biphasic mixture formed. NaBr (470 mg, 4.6 mmol, 2.3 equiv) was then added in one portion to the biphasic mixture at 0 ºC, followed by 20% w/w aqueous $NaBrO_3$ (151 mg in 0.6 mL H_2O, 1.0 mmol, 0.50 equiv). After the addition was complete the cooling bath was removed and the reaction was allowed to warm to ambient temperature, resulting in the appearance of an orange color. The oxidation of the phosphite was monitored by UPLC-MS and complete consumption of the intermediate phosphite was usually observed in 3–5 h. Next, 10% aqueous (w/w) $Na_2S_2O_5$ (0.38 mL, 0.4 mmol, 0.2 equiv) was added to the flask until a colorless solution persisted. 2-MeTHF (10 mL) was added and the layers were shaken and separated. The organic layer was washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a crude residue, which was directly purified *via* RP-FCC (SNAP Ultra C18 120 g, CV = 164 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 75 $mL \cdot min^{-1}$ flowrate). Pure fractions were pooled, concentrated *in vacuo* (35–37 °C, 10 mbar) to provide the title compound **S35** as a pale pink solid.

Yield: 670 mg, 58%

IR (FT-ATR, neat, cm^{-1}): 3388, 2968, 1729, 1520, 1450, 1227, 1039, 1013, 996, 737.

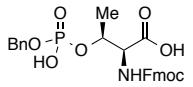
^{1}H NMR (600 MHz, DMSO-d_6) δ 7.95 (d, J = 9.4 Hz, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.73 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.52–7.48 (m, 2H), 7.44–7.37 (m, 2H), 7.36–7.24 (m, 10H), 5.82 (dd, J = 8.5, 4.0 Hz, 1H), 4.92–4.80 (m, 2H), 4.48 (ddd, J = 9.4, 4.1, 1.7 Hz, 1H), 4.17–4.07 (m, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 170.6, 156.3, 143.8, 143.7, 140.67, 140.65, 137.9, 136.8 (d, J = 8.2 Hz), 128.3, 128.0, 127.9, 127.9, 127.7, 127.5, 127.1, 126.9, 125.6, 125.5, 120.1, 77.9 (d, J = 5.1 Hz), 67.4 (d, J = 5.2 Hz), 66.2, 59.9 (d, J = 7.9 Hz), 46.5.

^{31}P NMR (162 MHz, DMSO-d_6) δ –2.18.

HRMS (ESI/Q-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{28}NO_8PNa$ 596.1450, found 596.1429.

$[\alpha]_D^{20}$ –29.2 (c = 1.05, EtOH).



S36

***N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*O*-((benzyloxy)(hydroxy)phosphoryl)-*L*-allothreonine (S36)** was prepared by following Procedure 16 with Fmoc-*allo*-threonine-OH (1.50 g, 4.4 mmol, 1.0 equiv) and benzyl alcohol (>99%, 0.68 mL, 6.6 mmol, 1.5 equiv). The crude material was purified using RP-FCC (SNAP Ultra C18 120 g, CV = 164 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 1 CV, 75 $mL \cdot min^{-1}$ flowrate) to provide the title compound as a white foam. The characterization data were in agreement with literature values.[8]

Yield: 1.43 g, 64%

IR (FT-ATR, neat, cm^{-1}): 1705, 1520, 1450, 1213, 995, 735

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.89 (d, J = 7.6 Hz, 2H), 7.86 (d, J = 9.0 Hz, 1H), 7.75 (dd, J = 7.5, 4.3 Hz, 2H), 7.42 (td, J = 7.4, 1.3 Hz, 2H), 7.39–7.29 (m, 8H), 4.93 (dd, J = 7.1, 1.8 Hz, 2H), 4.77–4.66 (m, 1H), 4.39 (dd, J = 9.0, 4.9 Hz, 1H), 4.31–4.18 (m, 3H), 1.29 (d, J = 6.5 Hz, 3H).

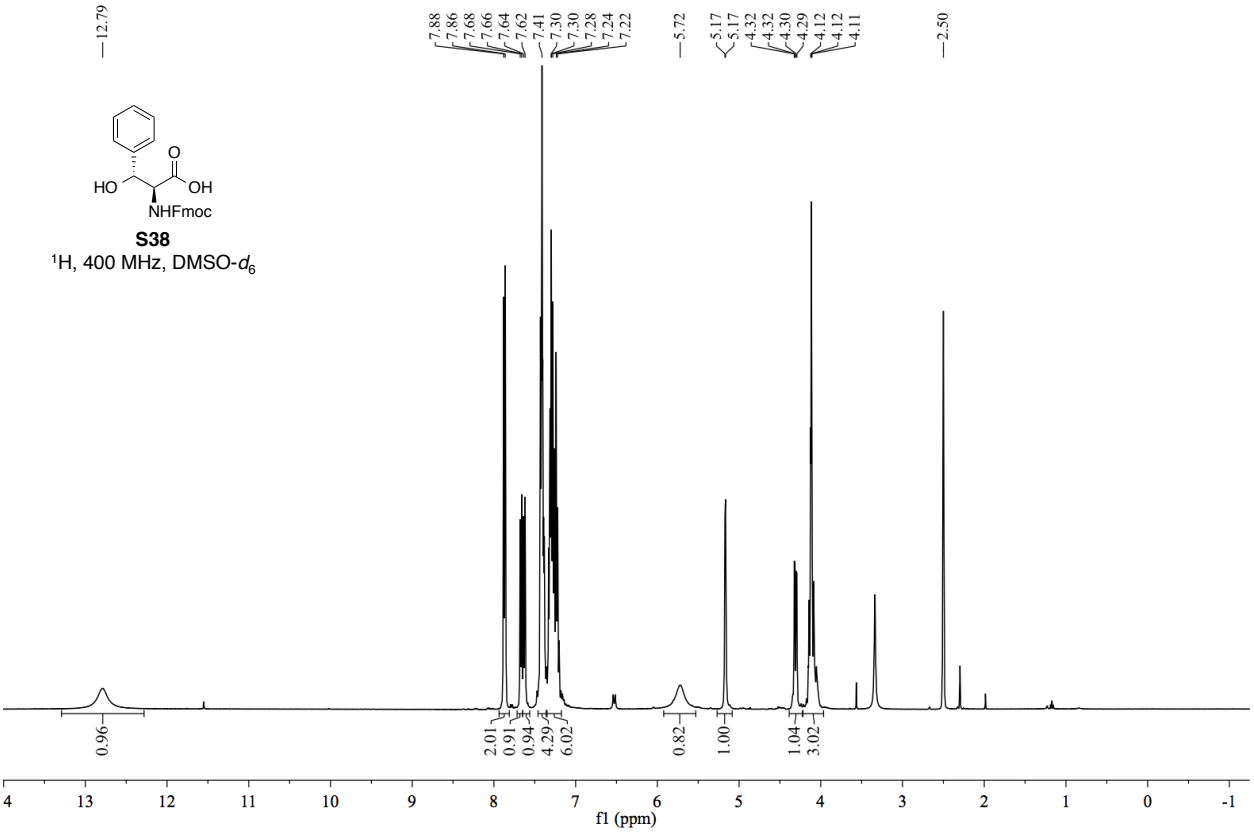
^{13}C NMR (151 MHz, DMSO-d_6) δ 171.0, 156.3, 143.8 (d, J = 7.5 Hz), 140.7 (d, J = 2.0 Hz), 136.8 (d, J = 7.8 Hz), 128.4, 128.0, 127.7, 127.6, 127.1, 127.1, 125.4 (d, J = 6.1 Hz), 120.2, 72.4 (d, J = 5.2 Hz), 67.5 (d, J = 5.2 Hz), 66.0, 58.6 (d, J = 6.3 Hz), 46.6, 17.5 (d, J = 3.2 Hz).

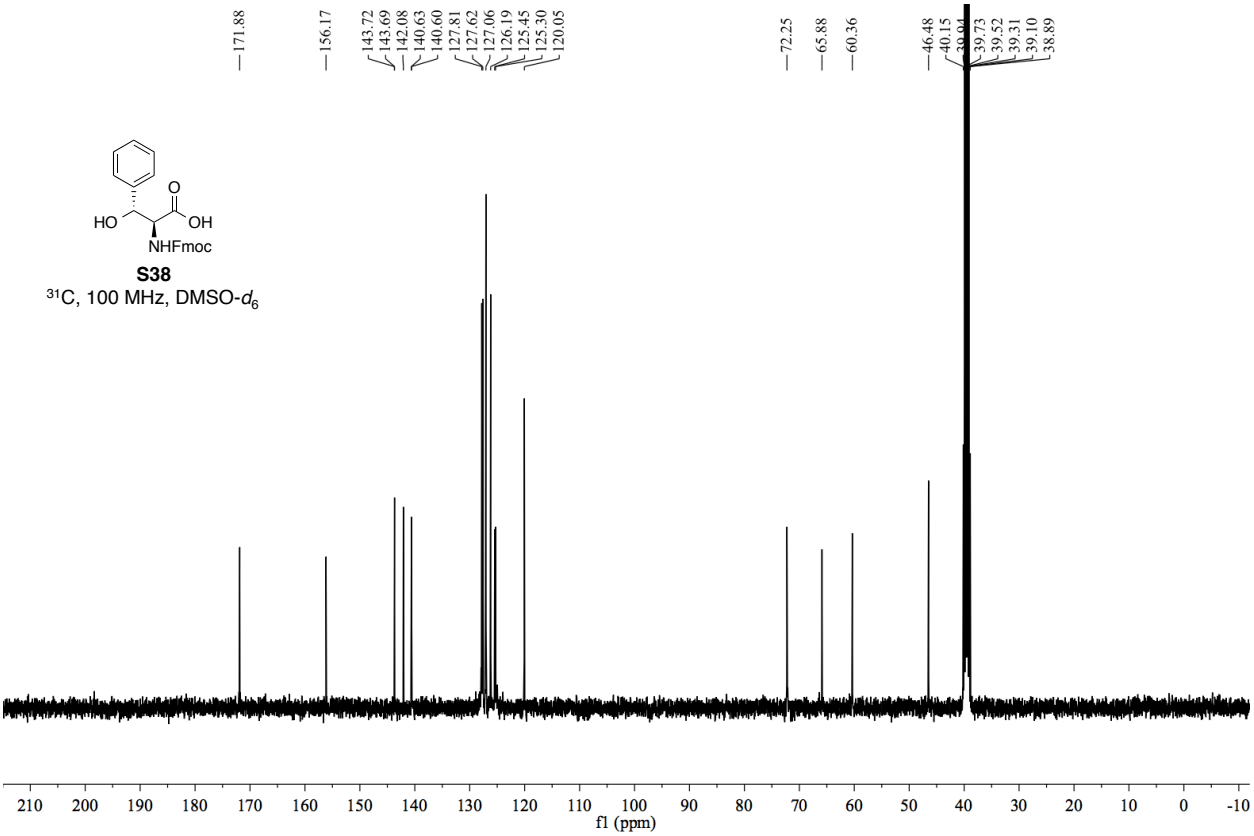
^{31}P NMR (202 MHz, DMSO-d_6) δ –1.91.

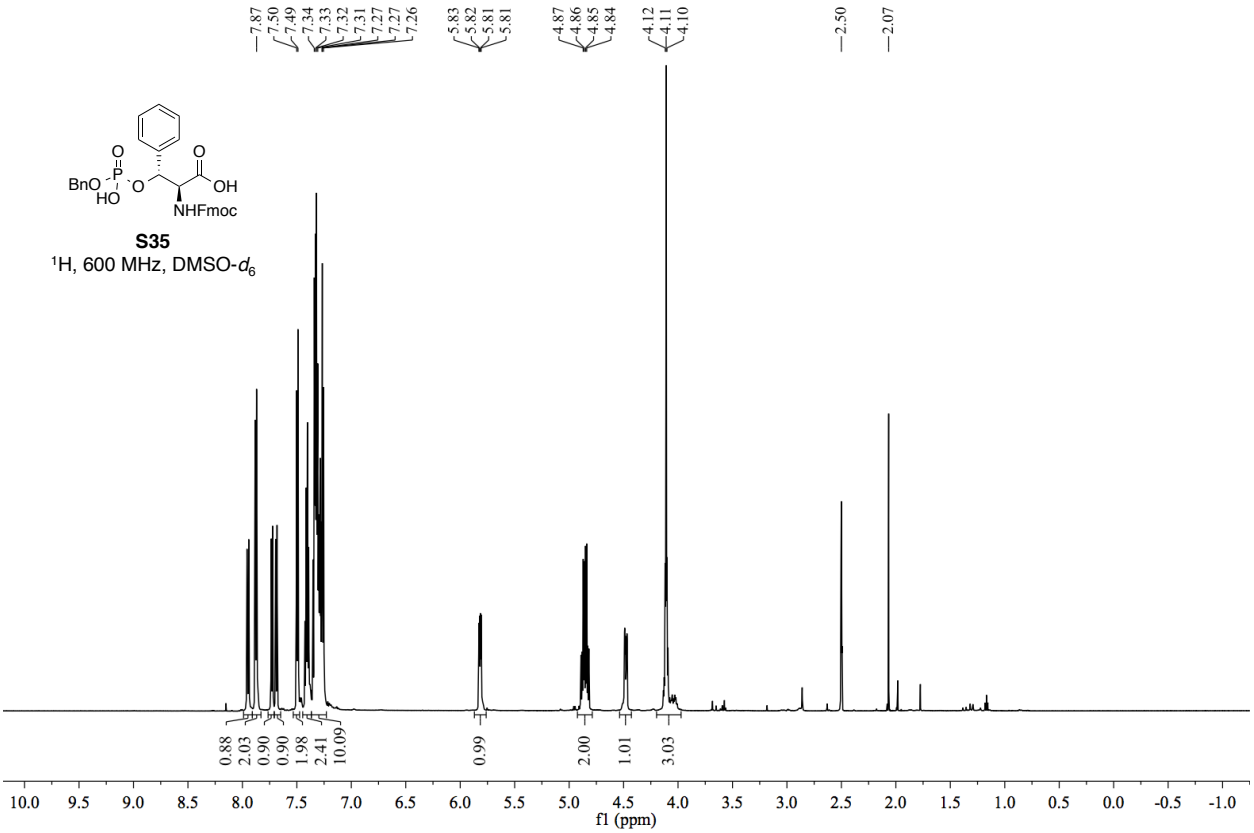
HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{27}NO_8P$ 512.1474, found 512.1494.

$[\alpha]_D^{20}$ +6.48 (c = 1.08, EtOH), –13.4 (c = 2.27, DMF); [Lit.[8]: **$[\alpha]_D^{20}$** –10.8 (c = 5.28, DMF)]

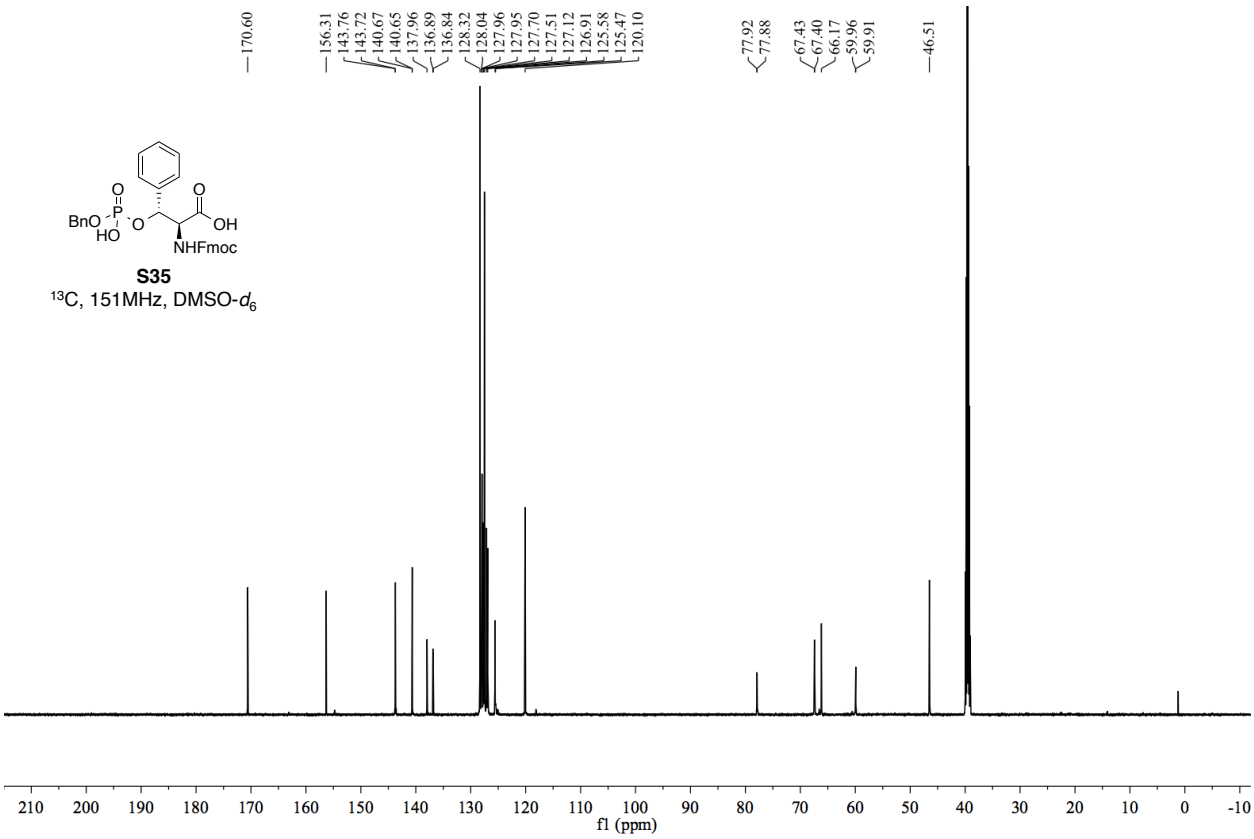
3.4 NMR Spectra of S35–36, S38



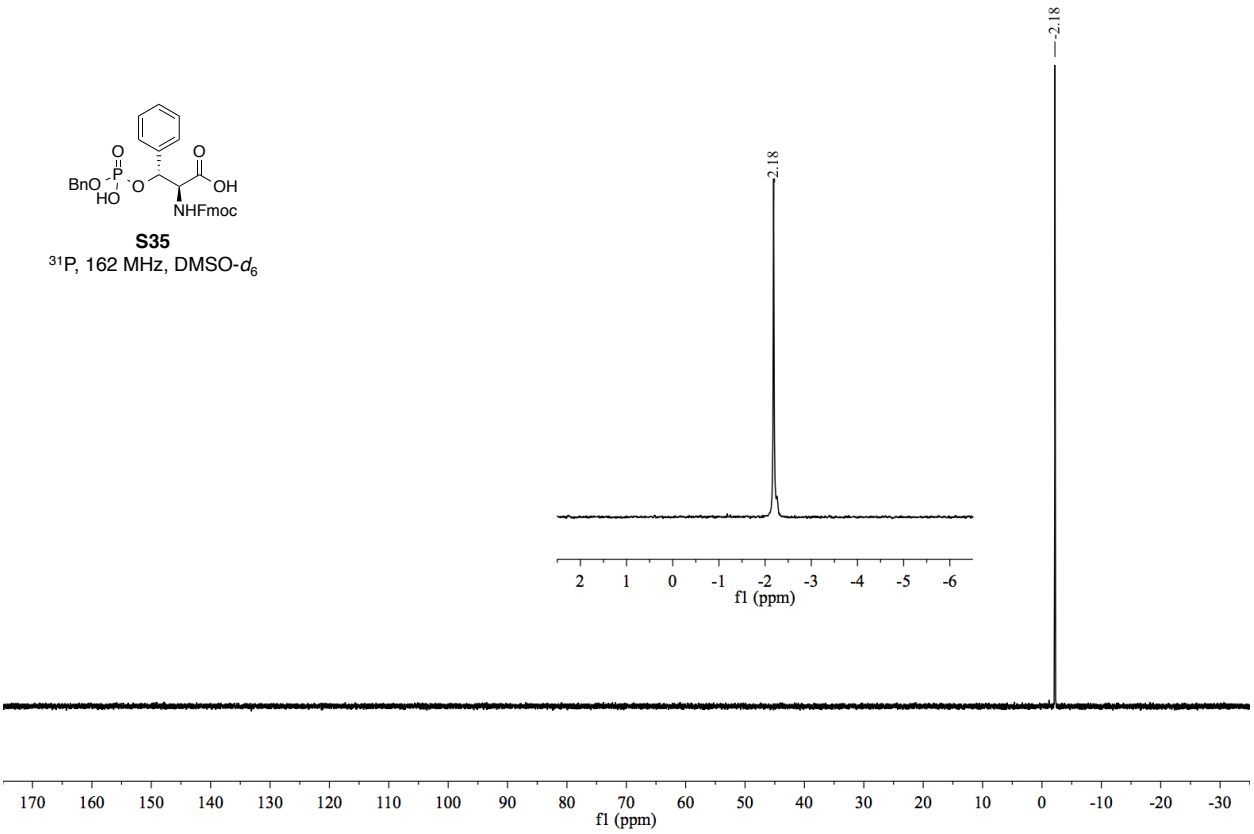




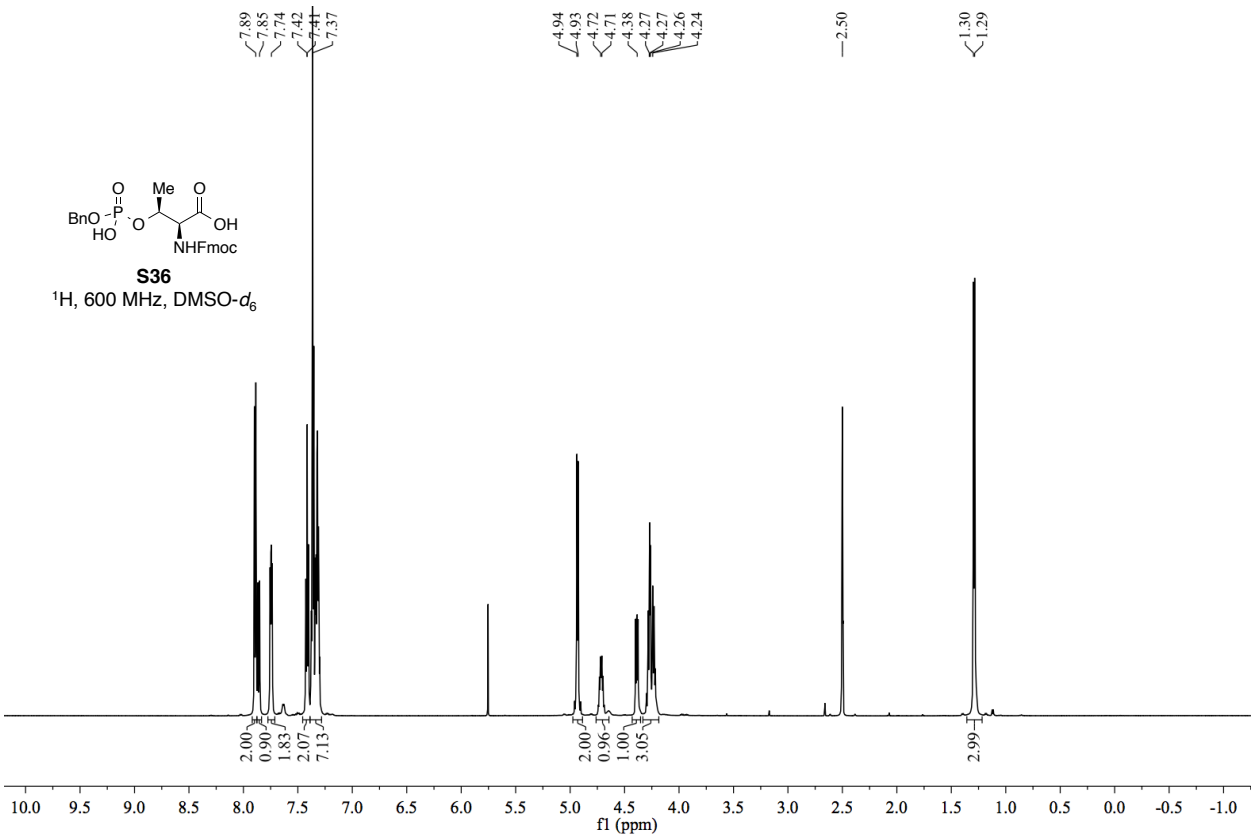
S35
^{1}H, 600 MHz, DMSO-d_6



S35
^{13}C, 151MHz, DMSO-d_6

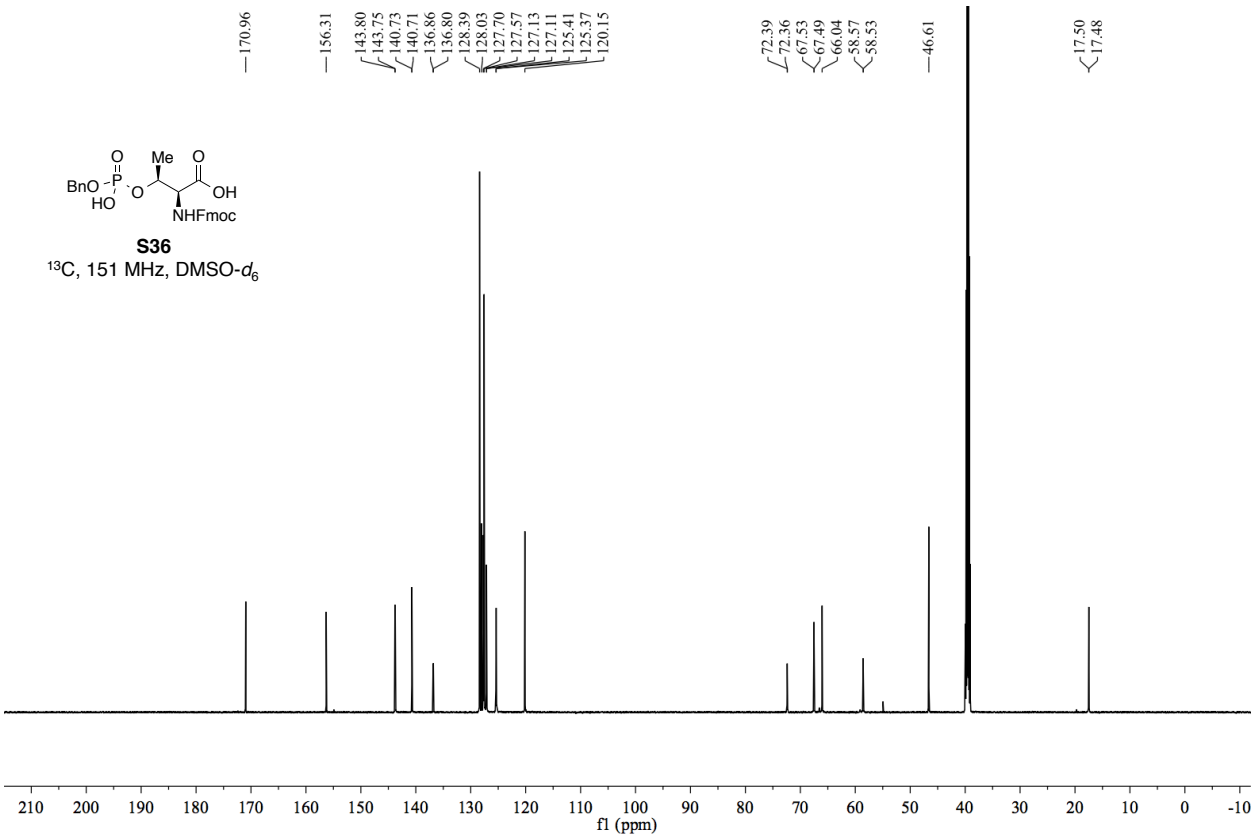


S35
^{31}P, 162 MHz, DMSO-d_6



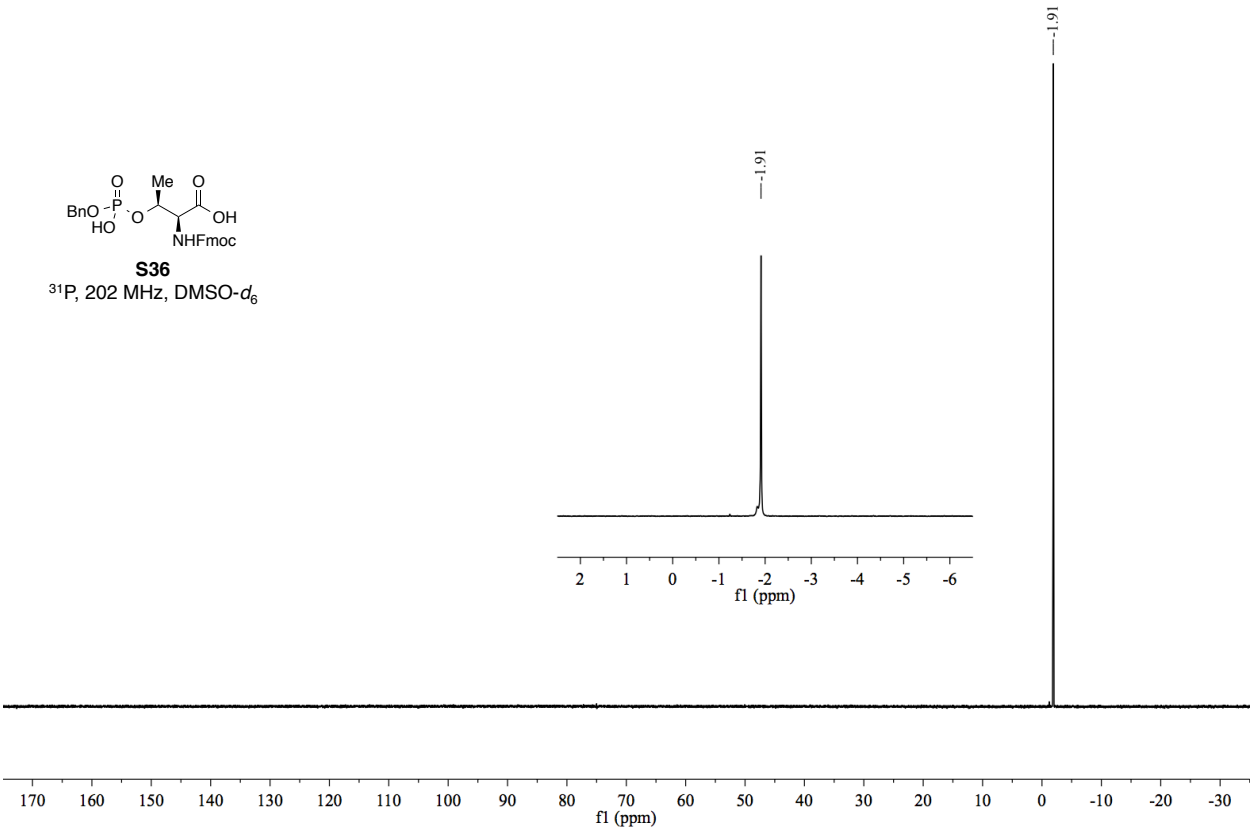
S36

^{1}H, 600 MHz, DMSO-d_6



S36

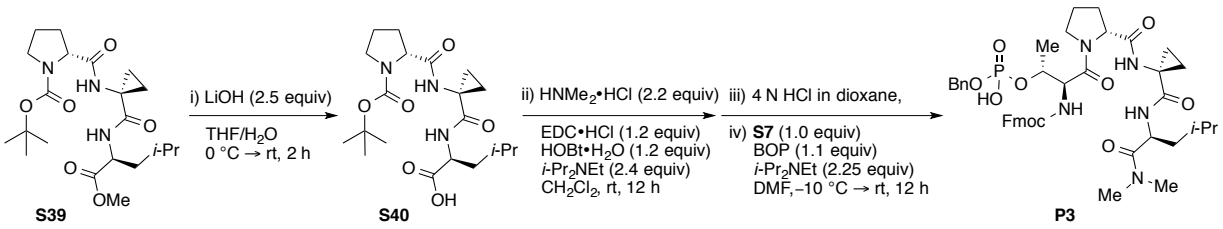
^{13}C, 151 MHz, DMSO-d_6



S36
^{31}P, 202 MHz, DMSO-d_6

4. Characterization and spectra of peptides

4.1 Peptide catalysts P3–6, P8–41, P43, Dmaa-6

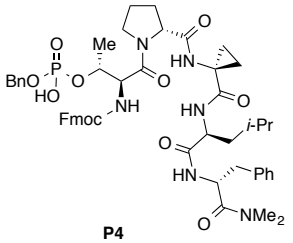


(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-4-methyl-1-oxopentan-2-yl)carbamoyl)cyclopropyl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P3) was synthesized from H-Leu-OMe by following procedure 2.1.3 General Peptide Coupling Protocol to provide Boc-D-Pro-Acpc-Leu-OMe (**S39**). **S39** (2.05 g, 4.8 mmol, 1.0 equiv) was dissolved in THF (50 mL) and cooled to 0 ºC, followed by addition of LiOH (0.273 g, 11.4 mmol, 2.5 equiv) in H_2O (35 mL). The reaction mixture was then allowed to warm to rt. After 2 hours, the reaction mixture was acidified to pH ~ 2 with 1 N HCl. The product was extracted with EtOAc (3 x 100 mL), and the combined organics washed with saturated aqueous NaCl (1 x 100 mL). The organics were dried over Na_2SO_4, filtered and concentrated to afford Boc-D-Pro-Acpc-Leu-OH (**S40**, *quantitative*) that was used without further purification. **S40** was then subjected to Procedure 1 [84% yield after purification (SNAP C18 60 g, CV = 66 mL, 5–100% CH_3CN/H_2O over 12 CV, 65 mL·min^{-1} flowrate)] followed by procedure 3 using Fmoc-pThr(Bn)-OH (**S7**, 388 mg, 0.76 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP C18 60 g, CV = 66 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 3 CV, 30–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 4 CV, and held at 100% CH_3CN for 5 CV, 50 mL·min^{-1} flowrate) to provide **P3** as a white foam.

Yield: 361 mg, 58% from Boc-D-Pro-Acpc-Leu-NMe_2 and **S7**

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –4.16.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{43}H_{55}N_5O_{10}P$ 832.3687, found 832.3721.



(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(((*R*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)cyclopropyl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P4) was synthesized from Boc-D-Pro-Acpc-Leu-OH (**S40)** and Boc-Phe-NMe_2 (**S2**) by following 2.1.3 General Peptide Coupling Protocol, then Procedure 3 using Fmoc-pThr(Bn)-OH (**S7**, 307 mg, 0.60 mmol, 1.0

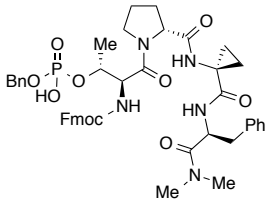
equiv). The crude material was purified by RP-FCC (SNAP C18 60 g, CV = 66 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 3 CV, 30–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 4 CV, and held at 100% CH_3CN for 1 CV, 50 mL·min^{-1} flowrate) to provide **P4** as a white foam.

Single crystals of compound **P4** were grown at rt by dissolving **P4** in a minimal amount of anhydrous 1,4-dioxane. Pentane was slowly added *via* vapor diffusion, which initially resulted in a colorless oil. The mother liquor was removed and suitable crystals of **P4** were observed from slow crystallization of the oil after several days.

Yield: 434 mg, 74% from Boc-D-Pro-Acpc-Leu-D-Phe-NMe_2 and **S7**

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –2.31.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{52}H_{64}N_6O_{11}P$ 979.4371, found 979.4365.



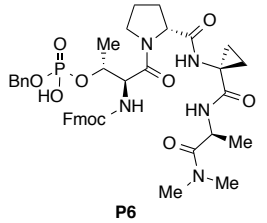
P5

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)cyclopropyl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P5) was synthesized from Boc-Phe-OH by following Procedures 1 and 2.1.3 General Peptide Coupling Protocol, then Procedure 3 using Fmoc-pThr(Bn)-OH (**S7**, 384 mg, 0.75 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP C18 60 g, CV = 66 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 3 CV, 30–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 4 CV, and held at 100% CH_3CN for 1 CV, 50 mL·min^{-1} flowrate) to provide **P5** as a white foam.

Yield: 360 mg, 55% from Boc-D-Pro-Acpc-Phe-NMe_2 and **S7**

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –3.73.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{46}H_{53}N_5O_{10}P$ 866.3530, found 866.3516.



P6

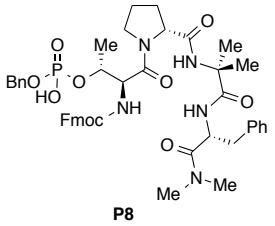
(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxopropan-2-yl)carbamoyl)cyclopropyl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P6) was synthesized from Boc-Ala-OH by following Procedures 1 and 2.1.3 General Peptide Coupling Protocol, then Procedure 3 using Fmoc-pThr(Bn)-OH (**S7**, 281 mg, 0.55 mmol, 1.0

equiv). The crude material was purified by RP-FCC (SNAP C18 60 g, CV = 66 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–20% CH_3CN/H_2O linear gradient over 3 CV, 20–50% CH_3CN/H_2O linear gradient over 12 CV, then 50–100% CH_3CN/H_2O over 4 CV, and held at 100% CH_3CN for 1 CV, 50mL·min^{-1} flowrate) to provide **P6** as a white foam.

Yield: 70 mg, 16% from Boc-D-Pro-Acpc-Ala-NMe_2 and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –3.68.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{40}H_{49}N_5O_{10}P$ 790.3217, found 790.3214.



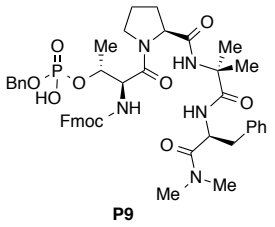
P8

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*R*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P8) was synthesized from Boc-D-Phe-OH by following Procedures 1 and 2.1.3 General Peptide Coupling Protocol, then Procedure 3 using Fmoc-pThr(Bn)-OH (**S7**, 480 mg, 0.94 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP C18 60 g, CV = 66 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 3 CV, 30–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 4 CV, and held at 100% CH_3CN for 1 CV, 50 mL·min^{-1} flowrate) to provide **P8** as a white foam.

Yield: 402 mg, 49% from Boc-D-Pro-Aib-D-Phe-NMe_2 and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –1.35.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{46}H_{55}N_5O_{10}P$ 868.3687, found 868.3650.



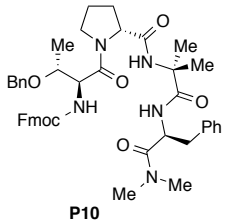
P9

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*S*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P9) was synthesized from Boc-Phe-OH by following Procedures 1 and 2.1.3 General Peptide Coupling Protocol, then Procedure 3 using Fmoc-pThr(Bn)-OH (**S7**, 307 mg, 0.60 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP C18 120 g, CV = 132 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 3 CV, 30–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 4 CV, and held at 100% CH_3CN for 1 CV, 80 mL·min^{-1} flowrate) to provide **P9** as a white foam.

Yield: 282 mg, 54% from Boc-Pro-Aib-Phe-NMe_2 and **S7**

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –1.25.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{46}H_{53}N_5O_{10}P$ 868.3687, found 868.3692.

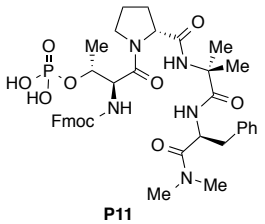


P10

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(benzyloxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P10) was prepared according to *Boc-Deprotection 3* and Procedure 2, using Boc-D-Pro-Aib-Phe-NMe_2 (**S6**, 142 mg, 0.30 mmol, 1.0 equiv), Fmoc-Thr(Bn)-OH (155 mg, 0.36 mmol, 1.2 equiv), HATU (148 mg, 0.39 mmol, 1.3 equiv), and NMM (100 μL, 0.90 mmol, 3.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 10% CH_3CN/H_2O for 1 CV, 10–100% CH_3CN/H_2O linear gradient over 16 CV, and held at 100% CH_3CN for 1 CV, 30 mL·min^{-1} flowrate) to provide **P10** as a white foam.

Yield: 161 mg, 68% from **S6** and Fmoc-Thr(Bn)-OH

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{46}H_{54}N_5O_7$ 788.4023, found 788.4023.



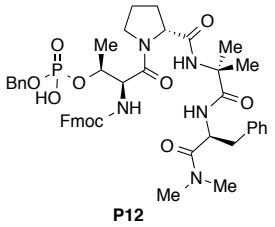
P11

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxo-3-(phosphonooxy)butan-2-yl)carbamate (P11) was prepared according to *Boc-Deprotection 3* and a modification of Procedure 6, using **P7** (63.5 mg, 0.07 mmol, 1.0 equiv), Pd/C (10% w/w, 12.5 mg, 0.20 equiv) in MeOH (1 mL). The crude material was purified by RP-FCC (SNAP Ultra C18 12 g, CV = 17 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–30% CH_3CN/H_2O linear gradient over 2 CV, 30–65% CH_3CN/H_2O linear gradient over 16 CV, then 65–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 4 CV, 12 mL·min^{-1} flowrate) to provide **P11** as a white foam.

Yield: 36.3 mg, 67%

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –0.05.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{39}H_{49}N_5O_{10}P$ 778.3217, found 778.3185.



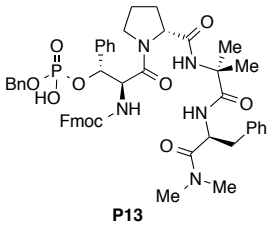
P12

(9*H*-fluoren-9-yl)methyl ((2*S*,3*S*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P12) was prepared according to *Boc-Deprotection 3* and Procedure 2, using Boc-D-Pro-Aib-Phe-NMe_2 (**S6**, 157 mg, 0.33 mmol, 1.1 equiv) and Fmoc-*allo*-pThr(Bn)-OH (**S36**, 153 mg, 0.3 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 25 mL·min^{-1} flowrate) to provide **P12** as a white foam.

Yield: 201 mg, 77% from **S6** and **S36**

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –0.85.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{46}H_{55}N_5O_{10}P$ 868.3687, found 868.3685.



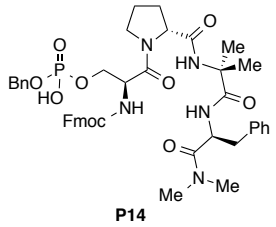
P13

(9*H*-fluoren-9-yl)methyl ((1*R*,2*S*)-1-(((benzyloxy)(hydroxy)phosphoryl)oxy)-3-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-oxo-1-phenylpropan-2-yl)carbamate (P13) was prepared according to *Boc-Deprotection 3* and a modification of Procedure 2, using Boc-D-Pro-Aib-Phe-NMe_2 (**S6**, 114 mg, 0.24 mmol, 1.2 equiv), Fmoc-pPhSer (Bn)-OH (**S35**, 115 mg, 0.2 mmol, 1.0 equiv), HATU (92 mg, 0.24 mmol, 1.2 equiv) and NMM (77 μL, 0.70 mmol, 3.5 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 3 CV, 30–65% CH_3CN/H_2O linear gradient over 13 CV, then 65–100% CH_3CN/H_2O over 3 CV, 50 mL·min^{-1} flowrate) to provide **P13** as a white foam.

Yield: 143 mg, 77% from **S6** and **S35**

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –1.82.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{51}H_{57}N_5O_{10}P$ 930.3843, found 930.3845.



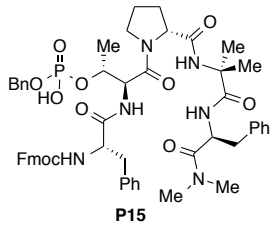
P14

(9*H*-fluoren-9-yl)methyl ((2*S*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxopropan-2-yl)carbamate (P14) was prepared according to *Boc-Deprotection 3* and Procedure 3, using Boc-D-Pro-Aib-Phe-NMe_2 (**S6**, 313 mg, 0.66 mmol, 1.1 equiv) and Fmoc-pSer(Bn)-OH (**S34**, 298 mg, 0.60 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP C18 120 g, CV = 132 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 3 CV, 30–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 4 CV, and held at 100% CH_3CN for 1 CV, 80 $mL \cdot min^{-1}$ flowrate) to provide **P14** as a white foam.

Yield: 273 mg, 53% from **S6** and **S14**

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –0.54.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{45}H_{53}N_5O_{10}P$ 854.3530, found 854.3539.



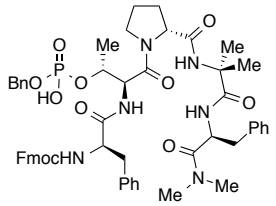
P15

(9*H*-fluoren-9-yl)methyl ((2*S*)-1-(((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (P15) was prepared according to Procedure 8, using **P7** (55 mg, 0.063 mmol, 1.0 equiv), Fmoc-Phe-OH (29 mg, 0.076 mmol, 1.2 equiv), HATU (31 mg, 0.082 mmol, 1.3 equiv), and NMM (18 µL, 0.16 mmol, 2.5 equiv). The crude material was purified by RP-FCC (SNAP C18 12 g, CV = 15 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 2 CV, 30–65% CH_3CN/H_2O linear gradient over 16 CV, then 65–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 6 CV, 18 $mL \cdot min^{-1}$ flowrate) to provide **P15** as a white foam.

Yield: 40 mg, 63% from **P7**

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –1.62.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{55}H_{64}N_6O_{11}P$ 1015.4371, found 1015.4339.



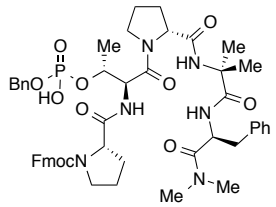
P16

(9*H*-fluoren-9-yl)methyl ((2*R*)-1-(((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (P16) was prepared according to Procedure 8, using **P7** (55 mg, 0.063 mmol, 1.0 equiv), Fmoc-D-Phe-OH (29 mg, 0.076 mmol, 1.2 equiv), HATU (31 mg, 0.082 mmol, 1.3 equiv), and NMM (18 µL, 0.16 mmol, 2.5 equiv). The crude material was purified by RP-FCC (SNAP C18 12 g, CV = 15 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 2 CV, 30–65% CH_3CN/H_2O linear gradient over 16 CV, then 65–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 6 CV, 18 mL·min^{-1} flowrate) to provide **P16** as a white foam.

Yield: 42.8 mg, 67% from **P7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –0.61.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{55}H_{64}N_6O_{11}P$ 1015.4371, found 1015.4364.



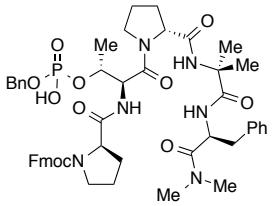
P17

(9*H*-fluoren-9-yl)methyl (2*S*)-2-(((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (P17) was prepared according to Procedure 8, using **P7** (55 mg, 0.063 mmol, 1.0 equiv), Fmoc-Pro-OH (26 mg, 0.076 mmol, 1.2 equiv), HATU (31 mg, 0.082 mmol, 1.3 equiv), and NMM (18 µL, 0.16 mmol, 2.5 equiv). The crude material was purified by RP-FCC (SNAP C18 12 g, CV = 15 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 2 CV, 30–65% CH_3CN/H_2O linear gradient over 16 CV, then 65–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 5 CV, 18 mL·min^{-1} flowrate) to provide **P17** as a white foam.

Yield: 40 mg, 66% from **P7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.04.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{51}H_{62}N_6O_{11}P$ 965.4214, found 965.4211.



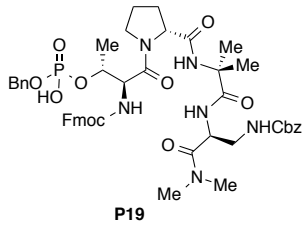
P18

(9*H*-fluoren-9-yl)methyl (2*R*)-2-(((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (P18) was prepared according to Procedure 8, using **P7** (260 mg, 0.30 mmol, 1.0 equiv), Fmoc-D-Pro-OH (29 mg, 0.076 mmol, 1.1 equiv), HATU (148 mg, 0.39 mmol, 1.3 equiv), and NMM (0.12 mL, 1.05 mmol, 3.5 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–30% CH_3CN/H_2O linear gradient over 2 CV, 30–65% CH_3CN/H_2O linear gradient over 16 CV, then 65–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 4 CV, 35 mL·min^{-1} flowrate) to provide **P18** as a white foam.

Yield: 199 mg, 69% from **P7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –1.54.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{51}H_{62}N_6O_{11}P$ 965.4214, found 965.4210.



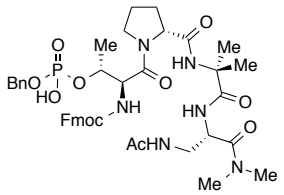
P19

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-3-(((benzyloxy)carbonyl)amino)-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P19) was prepared according to Procedure 2, using **S18** (181 mg, 0.33 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 153 mg, 0.30 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 35 mL·min^{-1} flowrate) to provide **P19** as a white foam.

Yield: 179 mg, 63% from **S18** and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.61.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{48}H_{58}N_6O_{12}P$ 941.3850, found 941.3826.



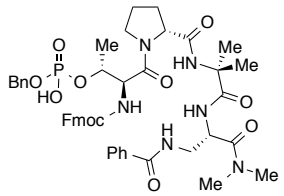
P20

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-1-((*R*)-2-((1-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-oxobutan-2-yl)carbamate (P20) was synthesized from **S18** by following Procedures 6 and 7, and then Procedure 2 using Fmoc-pThr(Bn)-OH (**S7**, 2.05 g, 4.0 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP C18 120 g, CV = 132 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 65 mL·min^{-1} flowrate) to provide **P20** as a white foam.

Yield: 2.48 g, 73% from **S18** and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.23.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{42}H_{54}N_6O_{11}P$ 849.3588, found 849.3603.



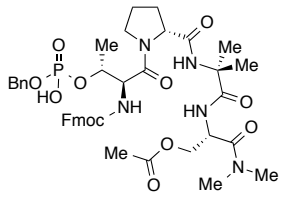
P21

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-1-((*R*)-2-((1-(((*S*)-3-benzamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-oxobutan-2-yl)carbamate (P21) was prepared according to Procedure 2, using **S24** (171 mg, 0.33 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 153 mg, 0.30 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 35 mL·min^{-1} flowrate) to provide **P21** as a white foam.

Yield: 148 mg, 54% from **S24** and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.77.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{47}H_{56}N_6O_{11}P$ 911.3745, found 911.3752.



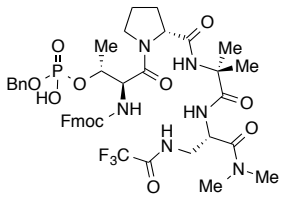
P22

(2*S*)-2-(2-((2*R*)-1-(*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*O*-((benzyloxy)(hydroxy)phosphoryl)-*L*-threonyl)pyrrolidine-2-carboxamido)-2-methylpropanamido)-3-(dimethylamino)-3-oxopropyl acetate (P22) prepared according to Procedure 2, using **S33** (296 mg, 0.67 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 312 mg, 0.61 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 60 g, CV = 90 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–60% CH_3CN/H_2O linear gradient over 12 CV, then 65–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 4 CV, 50 mL·min^{-1} flowrate) to provide **P22** as a white foam.

Yield: 261 mg, 51% from **S33** and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –1.38.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{42}H_{53}N_5O_{12}P$ 850.3428, found 850.3420.



P23

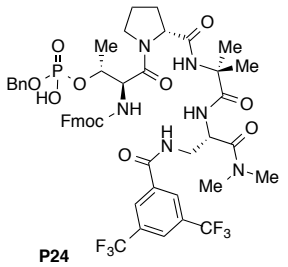
(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-(2,2,2-trifluoroacetamido)propan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P23) was prepared according to Procedure 2, using **S26** (168 mg, 0.33 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 153 mg, 0.30 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 25 mL·min^{-1} flowrate) to provide **P23** as a white foam.

Yield: 112 mg, 41% from **S26** and **S7**

^{19}F NMR: (470 MHz, Chloroform-*d*) δ –75.73.

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –2.05.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{42}H_{51}F_3N_6O_{11}P$ 903.3306, found 903.3279.



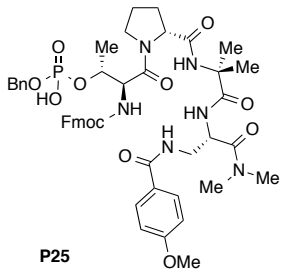
(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-3-(3,5-bis(trifluoromethyl)benzamido)-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P24) was prepared according to Procedure 2, using **S20** (198 mg, 0.30 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 141 mg, 0.28 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 35 mL·min^{-1} flowrate) to provide **P24** as a white foam.

Yield: 203 mg, 65% from **S20** and **S7**

^{19}F NMR: (376 MHz, Acetone-d_6) δ –63.22.

^{31}P NMR: (162 MHz, Acetone-d_6) δ –1.23.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{49}H_{54}F_6N_6O_{11}P$ 1047.3492, found 1047.3489.

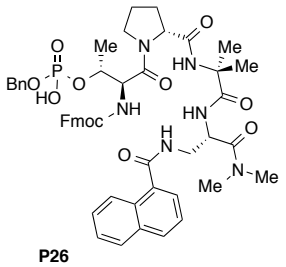


(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-3-(4-methoxybenzamido)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P25) was prepared according to Procedure 2, using **S21** (151 mg, 0.28 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 128 mg, 0.25 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–65% CH_3CN/H_2O linear gradient over 12 CV, then 65–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 4 CV, 30 mL·min^{-1} flowrate) to provide **P25** as a white foam.

Yield: 191 mg, 81% from **S21** and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.52.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{48}H_{58}N_6O_{12}P$ 941.3850, found 941.3852.



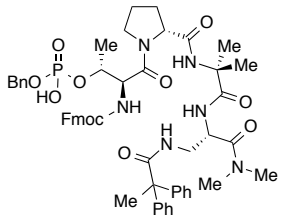
P26

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-1-((*R*)-2-((1-(((*S*)-3-(1-naphthamido)-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-oxobutan-2-yl)carbamate (P26) was prepared according to Procedure 2, using **S22** (233 mg, 0.41 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 191 mg, 0.37 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 4 CV, 30 mL·min^{-1} flowrate) to provide **P26** as a white foam.

Yield: 183 mg, 52% from **S22** and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.26.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{51}H_{58}N_6O_{11}P$ 961.3901, found 961.3896.



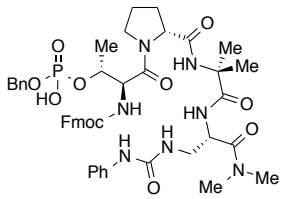
P27

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-3-(2,2-diphenylpropanamido)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P27) was prepared according to Procedure 2, using **S25** (205 mg, 0.33 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 153 mg, 0.30 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 60 g, CV = 90 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 4 CV, 50 mL·min^{-1} flowrate) to provide **P27** as a white foam.

Yield: 200 mg, 66% from **S25** and **S7**

^{31}P NMR: (162 MHz, DMSO-d_6) δ –1.38.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{55}H_{64}N_6O_{11}P$ 1015.4371, found 1015.4359.



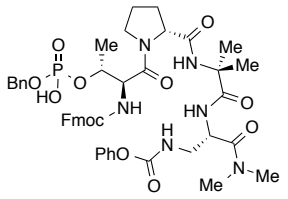
P28

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-(3-phenylureido)propan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P28) was prepared according to Procedure 2, using **S27** (93 mg, 0.17 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 81 mg, 0.16 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 4 CV, 35 mL·min^{-1} flowrate) to provide **P28** as a white foam.

Yield: 97 mg, 66% from **S27** and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.02.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{47}H_{57}N_7O_{11}P$ 926.3854, found 926.3824.



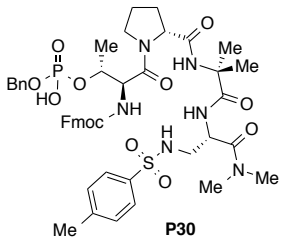
P29

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1-oxo-3-((phenoxycarbonyl)amino)propan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P29) was prepared according to Procedure 2, using **S28** (197 mg, 0.37 mmol, 1.0 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 223 mg, 0.44 mmol, 1.2 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 35 mL·min^{-1} flowrate) to provide **P29** as a white foam.

Yield: 268 mg, 66% from **S28** and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.47.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{47}H_{56}N_6O_{12}P$ 927.3694, found 927.3663.



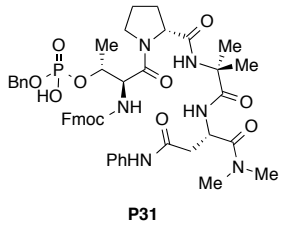
P30

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-3-((4-methylphenyl)sulfonamido)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P30) was prepared according to Procedure 2, using **S23** (213 mg, 0.38 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 174 mg, 0.34 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 4 CV, 30 mL·min^{-1} flowrate) to provide **P30** as a white foam.

Yield: 245 mg, 75% from **S23** and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –1.49.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{47}H_{58}N_6O_{12}PS$ 961.3571, found 961.3568.



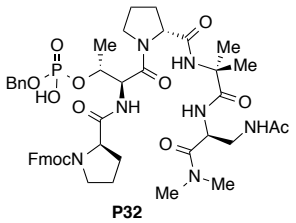
P31

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-((*R*)-2-((1-(((*S*)-1-(dimethylamino)-1,4-dioxo-4-(phenylamino)butan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (P31) was prepared according to Procedure 2, using **S30** (180 mg, 0.35 mmol, 1.1 equiv) and Fmoc-pThr(Bn)-OH (**S7**, 163 mg, 0.32 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–60% CH_3CN/H_2O linear gradient over 12 CV, then 60–100% CH_3CN/H_2O over 1 CV, and held at 100% CH_3CN for 4 CV, 30 mL·min^{-1} flowrate) to provide **P31** as a white foam.

Yield: 130 mg, 45% from **S30** and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –1.20.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{47}H_{56}N_6O_{11}P$ 911.3745, found 911.3745.



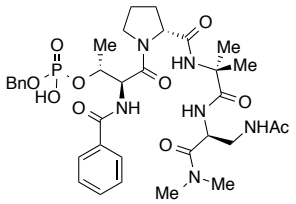
P32

(9*H*-fluoren-9-yl)methyl (2*R*)-2-(((2*S*,3*R*)-1-((*R*)-2-((1-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-oxobutan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (P32) was prepared according to Procedure 8, using **P20** (50 mg, 0.06 mmol, 1.0 equiv), Fmoc-D-Pro-OH (22 mg, 0.066 mmol, 1.1 equiv), HATU (30 mg, 0.078 mmol, 1.3 equiv), and NMM (23 µL, 0.21 mmol, 3.5 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 12 g, CV = 17 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 3 CV, 10–30% CH_3CN/H_2O linear gradient over 2 CV, 30–65% CH_3CN/H_2O linear gradient over 16 CV, then 65–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 18 mL·min^{-1} flowrate) to provide **P32** as a white foam.

Yield: 42 mg, 73% from **P20**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –1.46.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{47}H_{61}N_7O_{12}P$ 946.4116, found 946.4108.



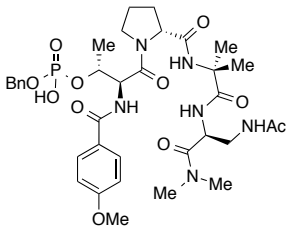
P33

(2*R*,3*S*)-4-((*R*)-2-((1-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-benzamido-4-oxobutan-2-yl benzyl hydrogen phosphate (P33) was prepared according to Procedure 8, using **P20** (50 mg, 0.06 mmol, 1.0 equiv), benzoic acid (8.1 mg, 0.066 mmol, 1.1 equiv), HATU (30 mg, 0.078 mmol, 1.3 equiv), and NMM (23 µL, 0.21 mmol, 3.5 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 12 g, CV = 17 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 1 CV, 10–20% CH_3CN/H_2O linear gradient over 1 CV, 20–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 18 mL·min^{-1} flowrate) to provide **P33** as a white foam.

Yield: 20 mg, 46% from **P20**

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –0.06.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{48}N_6O_{10}P$ 731.3170, found 731.3186.



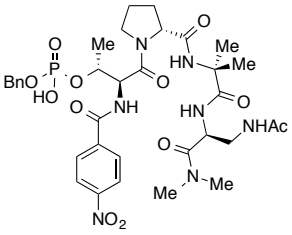
P34

(2*R*,3*S*)-4-((*R*)-2-((1-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(4-methoxybenzamido)-4-oxobutan-2-yl benzyl hydrogen phosphate (P34) was prepared according to Procedure 8, using **P20** (849 mg, 1.0 mmol, 1.0 equiv), 4-methoxybenzoic acid (167 mg, 1.1 mmol, 1.1 equiv), HATU (494 mg, 1.3 mmol, 1.3 equiv), and NMM (0.38 mL, 3.5 mmol, 3.5 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 120 g, CV = 164 mL, 0.1% formic acid buffer, 5% CH_3CN/H_2O for 1 CV, 5–40% CH_3CN/H_2O linear gradient over 15 CV, then 40–100% CH_3CN/H_2O linear gradient over 2 CV, and held at 100% CH_3CN for 2 CV, 65 mL·min^{-1} flowrate) to provide **P34** as a white foam.

Yield: 378 mg, 50% from **P20**

^{31}P NMR: (202 MHz, Chloroform-*d*) δ –0.99.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{35}H_{50}N_6O_{11}P$ 761.3275, found 761.3292.



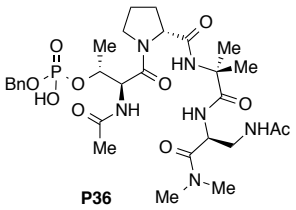
P35

(2*R*,3*S*)-4-((*R*)-2-((1-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(4-nitrobenzamido)-4-oxobutan-2-yl benzyl hydrogen phosphate (P35) was prepared according to Procedure 8, using **P20** (170 mg, 0.20 mmol, 1.0 equiv), 4-nitrobenzoic acid (37 mg, 0.22 mmol, 1.1 equiv), HATU (99 mg, 0.26 mmol, 1.3 equiv), and NMM (77 µL, 0.70 mmol, 3.5 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 5% CH_3CN/H_2O for 1 CV, 5–40% CH_3CN/H_2O linear gradient over 14 CV, then 40–100% CH_3CN/H_2O linear gradient over 2 CV, and held at 100% CH_3CN for 2 CV, 25 mL·min^{-1} flowrate) to provide **P35** as a white foam.

Yield: 72 mg, 46% from **P20**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –1.26.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{47}N_7O_{12}P$ 776.3020, found 776.2997.



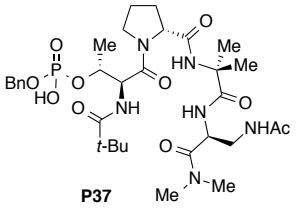
P36

(2*R*,3*S*)-3-acetamido-4-((*R*)-2-((1-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-4-oxobutan-2-yl benzyl hydrogen phosphate (P36): P20 (170 mg, 0.20 mmol, 1.0 equiv) was dissolved in Et_2NH/CH_2Cl_2 (1:1 v/v, 1.0 mL). The resulting solution was stirred for 30 minutes, after which the solvent was removed *in vacuo* and dried under Hi-Vacuum to remove excess Et_2NH. The crude residue was dissolved in CH_2Cl_2 (1.0 mL) and cooled to –10 °C followed by dropwise addition of acetic anhydride (28.4 μL, 0.30 mmol, 1.5 equiv). The reaction mixture was allowed to warm to rt overnight. After 16 h, the volatiles removed were under reduced pressure to afford the crude product, which was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 5% CH_3CN/H_2O for 1 CV, 5–50% CH_3CN/H_2O linear gradient over 16 CV, then 50–100% CH_3CN/H_2O linear gradient over 1 CV, and held at 100% CH_3CN for 4 CV, 25 $mL \cdot min^{-1}$ flowrate) to provide **P36** as a white foam.

Yield: 55.4 mg, 41% from **P20**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –1.49.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{46}N_6O_{10}P$ 669.3013, found 669.3010.



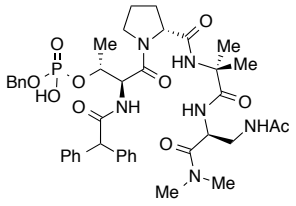
P37

(2*R*,3*S*)-4-((*R*)-2-((1-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-4-oxo-3-pivalamidobutan-2-yl benzyl hydrogen phosphate (P37): P20 (170 mg, 0.20 mmol, 1.0 equiv) was dissolved in Et_2NH/CH_2Cl_2 (1:1 v/v, 1.0 mL). The resulting solution was stirred for 30 minutes, after which the solvent was removed *in vacuo* and dried under Hi-Vacuum to remove excess Et_2NH. The crude residue was dissolved in CH_2Cl_2 (1.0 mL) and cooled to –10 °C followed by dropwise addition of trimethylacetic anhydride (61 μL, 0.30 mmol, 1.5 equiv). The reaction mixture was allowed to warm to rt overnight. After 16 h, the volatiles were removed under reduced pressure to afford the crude product, which was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 5% CH_3CN/H_2O for 1 CV, 5–50% CH_3CN/H_2O linear gradient over 16 CV, then 50–100% CH_3CN/H_2O linear gradient over 1 CV, and held at 100% CH_3CN for 4 CV, 25 $mL \cdot min^{-1}$ flowrate) to provide **P37** as a white foam.

Yield: 76.8 mg, 54% from **P20**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.55.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{52}N_6O_{10}P$ 711.3483, found 711.3459.



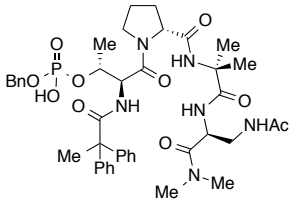
P38

(2*R*,3*S*)-4-((*R*)-2-((1-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(2,2-diphenylacetamido)-4-oxobutan-2-yl benzyl hydrogen phosphate (P38) was prepared according to Procedure 8, using **P20** (170 mg, 0.20 mmol, 1.0 equiv), diphenyl acetic acid (47 mg, 0.22 mmol, 1.1 equiv), HATU (99 mg, 0.26 mmol, 1.3 equiv), and NMM (77 µL, 0.70 mmol, 3.5 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 5% CH_3CN/H_2O for 2 CV, 5–20% CH_3CN/H_2O linear gradient over 2 CV, 20–50% CH_3CN/H_2O linear gradient over 12 CV, then 50–100% CH_3CN/H_2O linear gradient over 1 CV, and held at 100% CH_3CN for 4 CV, 30 mL·min^{-1} flowrate) to provide **P38** as a white foam.

Yield: 82.6 mg, 50% from **P20**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.31.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{41}H_{54}N_6O_{10}P$ 821.3639, found 821.3602.



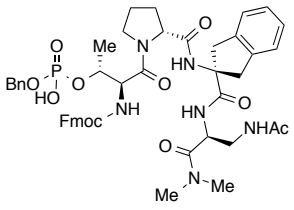
P39

(2*R*,3*S*)-4-((*R*)-2-((1-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(2,2-diphenylpropanamido)-4-oxobutan-2-yl benzyl hydrogen phosphate (P39) was prepared according to Procedure 8, using **P20** (170 mg, 0.20 mmol, 1.0 equiv), 2,2'-diphenyl proprionic acid (50 mg, 0.22 mmol, 1.1 equiv), HATU (99 mg, 0.26 mmol, 1.3 equiv), and NMM (77 µL, 0.70 mmol, 3.5 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 0.1% formic acid buffer, 5% CH_3CN/H_2O for 2 CV, 5–20% CH_3CN/H_2O linear gradient over 2 CV, 20–50% CH_3CN/H_2O linear gradient over 12 CV, then 50–100% CH_3CN/H_2O linear gradient over 1 CV, and held at 100% CH_3CN for 4 CV, 30 mL·min^{-1} flowrate) to provide **P39** as a white foam.

Yield: 87.9 mg, 53% from **P20**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.63.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{42}H_{56}N_6O_{10}P$ 835.3796, found 835.3810.



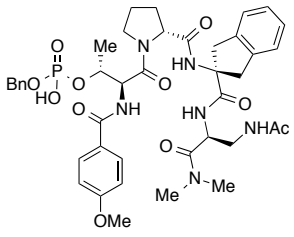
S41

(9*H*-fluoren-9-yl)methyl ((2*S*,3*R*)-1-((*R*)-2-((2-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)carbamoyl)-2,3-dihydro-1*H*-inden-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(((benzyloxy)(hydroxy)phosphoryl)oxy)-1-oxobutan-2-yl)carbamate (S41) was synthesized from Boc-Dap(Cbz)-OH (**S10**) by following Procedures 1 and 2.1.3 General Peptide Coupling Protocol, Procedures 6–7, and lastly Procedure 2 using Fmoc-pThr(Bn)-OH (**S7**, 0.994 g, 1.9 mmol, 1.0 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 60 g, CV = 90 mL, 0.1% formic acid buffer, 10% CH_3CN/H_2O for 2 CV, 10–25% CH_3CN/H_2O linear gradient over 2 CV, 25–55% CH_3CN/H_2O linear gradient over 12 CV, then 55–100% CH_3CN/H_2O over 2 CV, and held at 100% CH_3CN for 4 CV, 50 $mL \cdot min^{-1}$ flowrate) to provide **S41** as a white foam.

Yield: 1.19 g, 68% from Boc-D-Pro-Aic-Dap(Ac)-NMe_2 and **S7**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –3.50.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{48}H_{56}N_6O_{11}P$ 923.3745, found 923.3740.



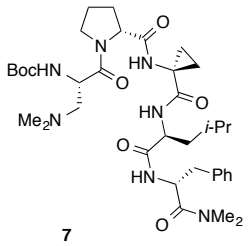
P40

(2*R*,3*S*)-4-((*R*)-2-((2-(((*S*)-3-acetamido-1-(dimethylamino)-1-oxopropan-2-yl)carbamoyl)-2,3-dihydro-1*H*-inden-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(4-methoxybenzamido)-4-oxobutan-2-yl benzyl hydrogen phosphate (P40) was prepared according to Procedure 8, using **S41** (508 mg, 0.55 mmol, 1.0 equiv), 4-methoxybenzoic acid (93 mg, 0.61 mmol, 1.1 equiv), HATU (274 mg, 0.72 mmol, 1.3 equiv), and NMM (0.21 mL, 1.9 mmol, 3.5 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 120 g, CV = 164 mL, 0.1% formic acid buffer, 5% CH_3CN/H_2O for 2 CV, 5–20% CH_3CN/H_2O linear gradient over 2 CV, 20–50% CH_3CN/H_2O linear gradient over 12 CV, then 50–100% CH_3CN/H_2O linear gradient over 1 CV, and held at 100% CH_3CN for 2 CV, 80 $mL \cdot min^{-1}$ flowrate) to provide **P40** as a white foam.

Yield: 219 mg, 48% from **S41**

^{31}P NMR: (162 MHz, Chloroform-*d*) δ –2.56.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{41}H_{52}N_6O_{11}P$ 835.3432, found 835.3425.



7

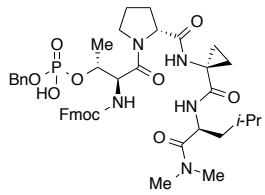
***tert*-butyl ((*S*)-3-(dimethylamino)-1-((*R*)-2-((1-(((*S*)-1-(((*R*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)cyclopropyl)carbamoyl)pyrrolidin-1-yl)-1-oxopropan-2-yl)carbamate (Dmaa-7)** was synthesized according to literature procedure[10] from Boc-D-Pro-Acpc-Leu-D-Phe-NMe_2 (205 mg, 0.35 mmol, 1.0 equiv), Boc-Dmaa-OH (89 mg, 0.39 mmol, 1.1 equiv), HBTU (160 mg, 0.42 mmol, 1.2 equiv), i-Pr_2NEt (0.15 mL, 0.84 mmol, 2.4 equiv) and CH_2Cl_2 (1.75 mL). The crude material was purified by RP-FCC (SNAP C18 30 g, CV = 33 mL, 30% MeOH/H_2O for 1 CV, then 30–100% MeOH/H_2O linear gradient over 18 CV, and held at 100% MeOH for 2 CV, 25 mL·min^{-1} flowrate) to provide **Dmaa-7** as a white foam.

Single crystals of compound **7** were grown at rt by dissolving **7** in a minimal amount of EtOAc then pentane was slowly added *via* vapor diffusion. Single crystals were observed after two days.

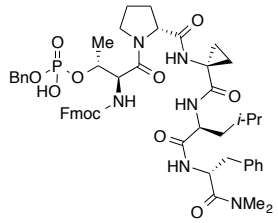
Yield: N/D

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{36}H_{58}N_7O_7$ 700.4398, found 700.4382.

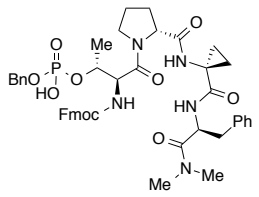
4.1 NMR Spectra of P3–6, P8–41, P43



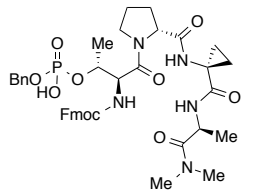
P3
^{31}P, 202 MHz, $CDCl_3$



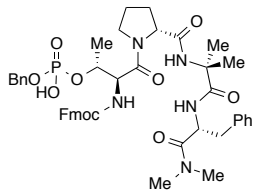
P4
^{31}P, 202 MHz, $CDCl_3$



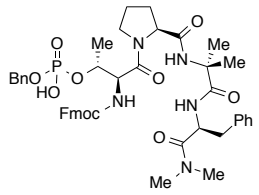
P5
^{31}P, 202 MHz, $CDCl_3$



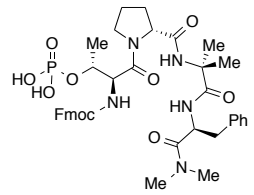
P6
^{31}P, 162 MHz, $CDCl_3$



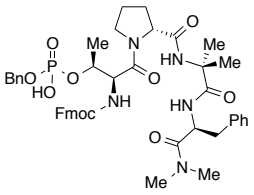
P8
^{31}P, 162 MHz, $CDCl_3$



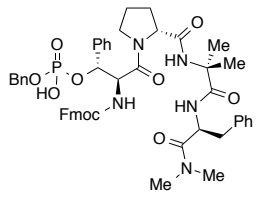
P9
^{31}P, 202 MHz, $CDCl_3$



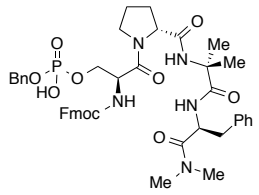
P11
^{31}P, 162 MHz, $CDCl_3$



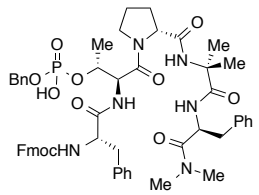
P12
^{31}P, 202 MHz, $CDCl_3$



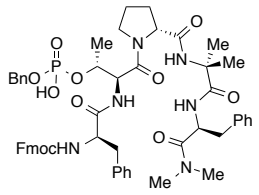
P13
^{31}P, 202 MHz, $CDCl_3$



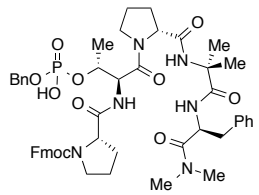
P14
^{31}P, 202 MHz, $CDCl_3$



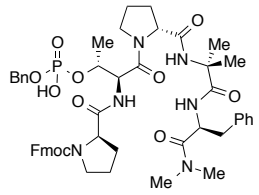
P15
^{31}P, 202 MHz, $CDCl_3$



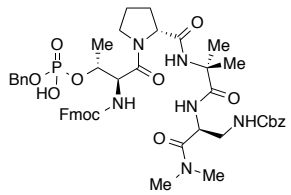
P16
^{31}P, 162 MHz, $CDCl_3$



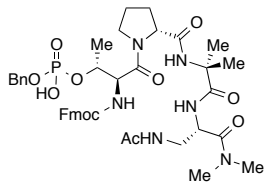
P17
^{31}P, 162 MHz, $CDCl_3$



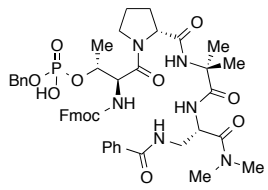
P18
^{31}P, 162 MHz, $CDCl_3$



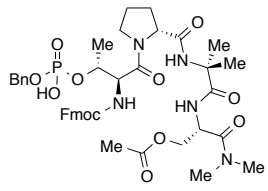
P19
^{31}P, 162 MHz, $CDCl_3$



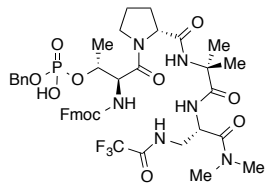
P20
^{31}P, 162 MHz, $CDCl_3$



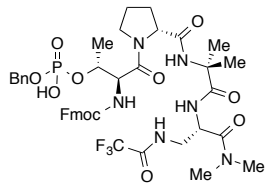
P21
^{31}P, 162 MHz, $CDCl_3$



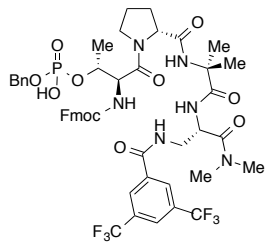
P22
^{31}P, 162 MHz, $CDCl_3$



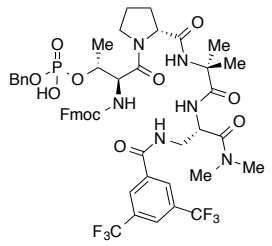
P23
^{19}F, 470 MHz, $CDCl_3$



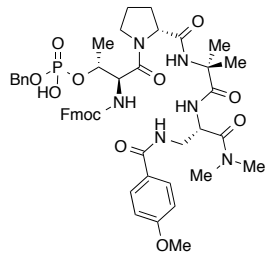
P23
^{31}P, 202 MHz, $CDCl_3$



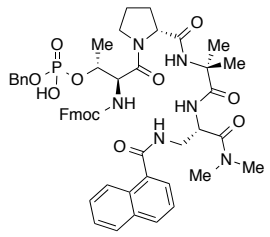
P24
^{19}F, 376 MHz, $(CD_3)_2CO$-d_6



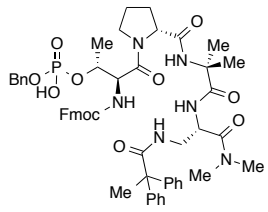
P24
^{31}P, 162 MHz, $(CD_3)_2CO$-d_6



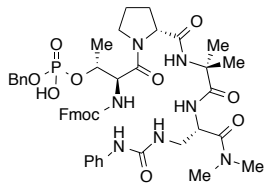
P25
^{31}P, 162 MHz, $CDCl_3$



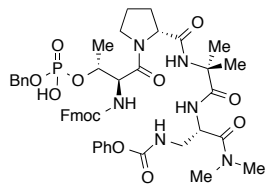
P26
^{31}P, 162 MHz, $CDCl_3$



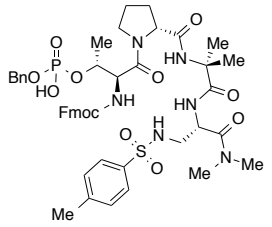
P27
^{31}P, 162 MHz, DMSO-d_6



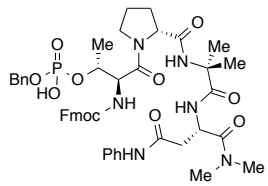
P28
^{31}P, 162 MHz, $CDCl_3$



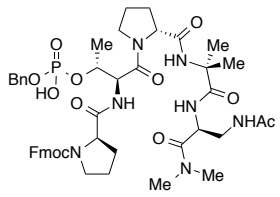
P29
^{31}P, 162 MHz, $CDCl_3$



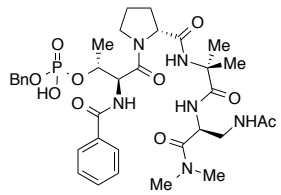
P30
^{31}P, 162 MHz, $CDCl_3$



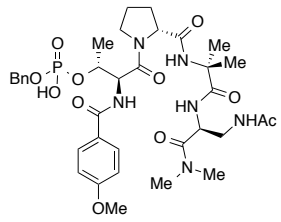
P31
^{31}P, 162 MHz, $CDCl_3$



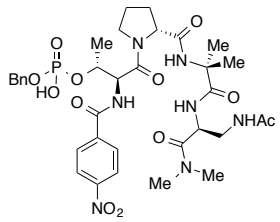
P32
^{31}P, 162 MHz, $CDCl_3$



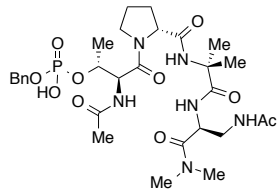
P33
^{31}P, 202 MHz, $CDCl_3$



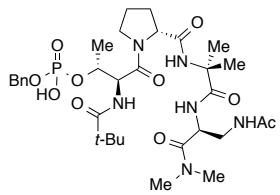
P34
^{31}P, 202 MHz, $CDCl_3$



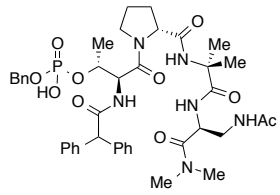
P35
^{31}P, 162 MHz, $CDCl_3$



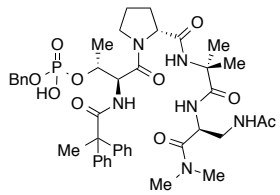
P36
^{31}P, 162 MHz, $CDCl_3$



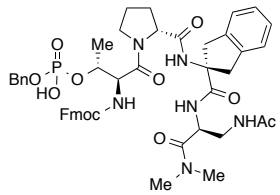
P37
^{31}P, 162 MHz, $CDCl_3$



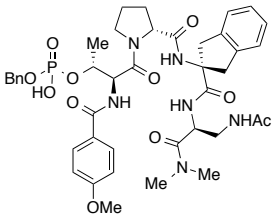
P38
^{31}P, 162 MHz, $CDCl_3$



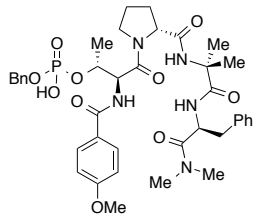
P39
^{31}P, 162 MHz, $CDCl_3$



S41
^{31}P, 162 MHz, $CDCl_3$



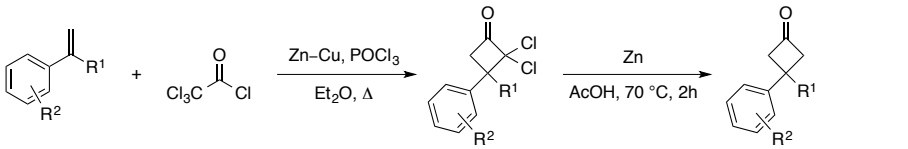
P40
^{31}P, 162 MHz, $CDCl_3$



P43
^{31}P, 162 MHz, $CDCl_3$

5. Synthesis and characterization of cyclobutanone substrates 4a–4t

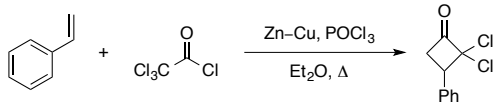
5.1. Synthesis of 4a–b, S42–52



S42: R^1, R^2 = H
S43: R^1 = CH_3, R^2 = H
S44: R^1 = H, R^2 = 2-Br
S45: R^1 = H, R^2 = 3-Br
S46: R^1 = H, R^2 = 4-Br
S47: R^1 = CH_3, R^2 = 2-Br

4a: R^1, R^2 = H
4b: R^1 = CH_3, R^2 = H
S48: R^1 = H, R^2 = 2-Br
S49: R^1 = H, R^2 = 3-Br
S50: R^1 = H, R^2 = 4-Br
S51: R^1 = CH_3, R^2 = 2-Br

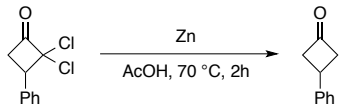
5.1.1 Procedure 17: [2+2] Ketene Cycloaddition[11]



S42

2,2-dichloro-3-phenylcyclobutan-1-one (S42):[11] To a flame dried 250 mL two-neck round bottom flask equipped with reflux condenser and pressure-equalizing addition funnel was added Zn-Cu couple (1.60 g, 25.0 mmol, 2.5 equiv), styrene (1.04 g, 10.0 mmol, 1.0 equiv) and Et_2O (20 mL) under a positive atmosphere of N_2. To the stirred suspension was added a solution of $POCl_3$ (1.90 mL, 20.0 mmol, 2.0 equiv), trichloroacetyl chloride (2.20 mL, 20.0 mmol, 2.0 equiv) and Et_2O (10 mL) over a period of 2 h. After the addition was complete, the reaction was refluxed overnight. The reaction mixture was cooled to rt and filtered through a pad of Celite®. The filter pad washed 3 x Et_2O, and the filtrate was *cautiously* washed water (2x), twice with saturated aqueous $NaHCO_3$ (2x), brine (1x), and dried over $MgSO_4$. The volatiles were removed *in vacuo* and the crude residue was routinely used in the next step without further purification.

5.1.2 Procedure 18: Zinc-Catalyzed Reductive dehalogenation[11]



S42 **4a**

3-phenylcyclobutan-1-one (4a): [11] To a vigorously stirred suspension of zinc dust (2.62 g, 40.0 mmol, 4.0 equiv) in acetic acid (8 mL) was added dropwise a solution of **S42** (2.15 g, 10.0 mmol, 1.0 equiv) in acetic acid (10 mL) at 0 °C. After the addition was complete, the mixture was heated to 70 °C and stirred for 2–4 h. The mixture was cooled to rt and the volume of acetic acid was reduced *in vacuo*. The crude residue was suspended in Et_2O, and filtered through a pad of Celite®. The filter pad was washed with Et_2O and the combined filtrate was wwashed sequentially with water (2 x 20 mL), saturated aqueous

$NaHCO_3$ (2 x 20 mL), and saturated aqueous NaCl (1 x 20 mL). The organics were dried over $MgSO_4$, filtered, concentrated *in vacuo*. The crude residue was purified by FCC (SiO_2, 8:1 hexanes/EtOAc) to afford the title compound as a colorless, clear oil. The characterization data were in agreement with literature values.[11b]

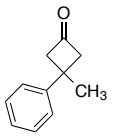
Yield: 572 mg, 39% yield over two steps

TLC: R_f = 0.34 (10% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3028, 2921, 1780, 1602, 1495, 1454, 1379, 1164, 1101, 1078, 757.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42–7.21 (m, 5H), 3.76– 3.61 (m, 1H), 3.57–3.43 (m, 2H), 3.34–3.20 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.9, 143.7, 128.9, 126.8, 126.6, 54.9, 28.6.



4b

3-methyl-3-phenylcyclobutan-1-one (4b): In the first step, Procedure 17 was followed using α-methylstyrene (3.55 g, 30.0 mmol, 1.0 equiv). The product obtained was purified by automated FCC (SNAP Ultra 100 g, CV = 164 mL, 0–8% EtOAc/hexanes linear gradient over 8 CV, 100 $mL \cdot min^{-1}$ flowrate) to afford **S43** as a clear oil (3.16 g, 46% yield). In the second step, procedure 18 was followed using **S43** (3.16 g, 13.8 mmol, 1.0 equiv). The crude material was purified by FCC (SiO_2, 7.5% EtOAc/hexanes, isocratic) to provide the title compound as a colorless, clear oil. The characterization data were in agreement with literature values.[12]

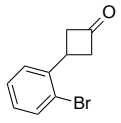
Yield: 1.83 g, 38% yield over two steps

TLC: R_f = 0.42 (10% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 2959, 2920, 1780, 1496, 1445, 1380, 1302, 1185, 1141, 1079, 1028, 763, 700.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42–7.29 (m, 4H), 7.29–7.23 (m, 1H), 3.53–3.42 (m, 2H), 3.17–3.07 (m, 2H), 1.62 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.7, 148.4, 128.7, 126.4, 125.7, 59.4, 34.1, 31.2.



S48

3-(2-bromophenyl)cyclobutan-1-one (S48): In the first step, a modification of Procedure 17 was followed using 2-bromostyrene (3.55 g, 30.0 mmol, 1.0 equiv). After 20 hours, fresh Zn-Cu couple (7.04 g, 110 mmol, 2.5 equiv) was added, followed by a solution of $POCl_3$ (10.3 mL, 110 mmol, 2.0 equiv), trichloroacetyl chloride (12.3 mL, 110 mmol, 2.0 equiv) in Et_2O (60 mL) over a period of 2 h. The reaction was allowed to reflux overnight, after which complete conversion was observed. **S44** was obtained in quantitative yield after work-up and was used without further purification. In the second step,

Procedure 18 was followed using **S44** (16.2 g, 55 mmol, 1.0 equiv) to isolate a **S48** as a pale yellow oil that was used without further purification. The characterization data were in agreement with literature values.[13]

An analytical sample was obtained by FCC (SiO_2, 7.5% EtOAc/hexanes, isocratic) as a colorless oil.

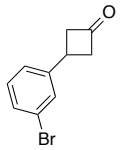
Yield: 10.52 g, 85% yield over two steps

TLC: R_f = 0.34 (10% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3062, 2984, 2928, 1782, 1566, 1471, 1437, 1379, 1331, 1277, 1169, 1100, 1026, 868, 752

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64–7.58 (m, 1H), 7.40–7.29 (m, 2H), 7.19–7.09 (m, 1H), 4.02–3.89 (m, 1H), 3.59–3.47 (m, 2H), 3.28–3.15 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.2, 141.8, 133.3, 128.5, 127.8, 126.6, 124.9, 53.2, 29.1.



S49

3-(3-bromophenyl)cyclobutan-1-one (S49): In the first step, a modification of Procedure 17 was followed using 3-bromostyrene (4.26 g, 23.4 mmol, 1.0 equiv), Zn-Cu couple (4.37 g, 68.3 mmol, 2.9 equiv), $POCl_3$ (5.1 mL, 54.6 mmol, 2.3 equiv), trichloroacetyl chloride (6.11 mL, 54.6 mmol, 2.3 equiv) in Et_2O (80 mL). After 20 hours, fresh Zn-Cu couple (3.74 g, 58.5 mmol, 2.5 equiv) was added, followed by a solution of $POCl_3$ (5.10 mL, 46.8 mmol, 2.0 equiv), trichloroacetyl chloride (5.2 mL, 46.8 mmol, 2.0 equiv) in Et_2O (30 mL) over a period of 2 h. The reaction was allowed to reflux overnight to provide **S45** (~56% conversion) that was taken to the next step. Procedure 18 was followed using **S45** (assumed 23.4 mmol, 1.0 equiv). The crude material was purified by FCC (SiO_2, 5–10% EtOAc/hexanes) to provide the title compound as a colorless, clear oil.

Yield: 1.99 g, 38% yield over two steps

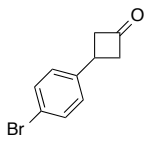
TLC: R_f = 0.31 (10% EtOAc/hexanes; UV/$KMnO_4$)

IR (FT-ATR, neat, cm^{-1}): 3067, 2974, 2929, 1767, 1595, 1563, 1478, 1456, 1415, 1368, 1319, 1301, 1215, 1114, 1071, 876.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 (app s, 1H), 7.41–7.35 (m, 1H), 7.25–7.18 (m, 2H), 3.70–3.59 (m, 1H), 3.56–3.43 (m, 2H), 3.29–3.16 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 205.7, 146.0, 130.4, 129.9, 125.3, 122.9, 54.7, 28.3.

HRMS (EI, 70 eV) *m/z*: $[M]^+$ calcd for $C_{10}H_9BrO$ 223.9837, found 223.9839.



S50

3-(4-bromophenyl)cyclobutan-1-one (S50): In the first step, Procedure 17 was followed using 4-bromostyrene (3.67 g, 20.0 mmol, 1.0 equiv), Zn-Cu couple (3.20 g, 50.0 mmol, 2.5 equiv), $POCl_3$ (3.74 mL, 40.0 mmol, 2.0 equiv), trichloroacetyl chloride (4.50 mL, 40.0 mmol, 2.0 equiv) in Et_2O (60 mL). The reaction was allowed to reflux overnight to provide crude **S46** that was taken to the next step. Procedure 18 was followed using **S46** (assumed 20.0 mmol, 1.0 equiv). The crude material was purified by FCC (SiO_2, 10% EtOAc/hexanes) to provide the title compound as a colorless solid. The characterization data were in agreement with literature values.[11b]

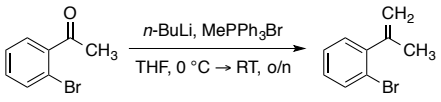
Yield: 1.12 g, 25% yield over two steps

TLC: R_f = 0.33 (10% EtOAc/hexanes; UV/$KMnO_4$)

IR (FT-ATR, neat, cm^{-1}): 1770, 1488, 1396, 1400, 1101, 1074, 1009, 820.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.5 –7.44 (m, 2H), 7.21–7.13 (m, 2H), 3.67–3.60 (m, 1H), 3.57–3.44 (m, 2H), 3.25–3.14 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 206.1, 142.7, 131.9, 128.4, 120.6, 54.8, 28.2.



S52

1-bromo-2-(prop-1-en-2-yl)benzene (S52): To a flame-dried 1 L round bottom flask containing methyltriphenylphosphonium bromide ($MePPh_3Br$) (21.4 g, 60.0 mmol, 1.25 equiv) was added PhMe (150 mL) and the suspension was stirred for 15 minutes. Toluene was then removed *in vacuo* at 45 °C and the salt was dried under vacuum (0.075 mmHg) overnight. The flask was back filled with N_2, fitted with a septum, and the dried $MePPh_3Br$ was suspended in THF (185 mL) followed by dropwise addition of *n*-butyllithium (2.5 M in hexanes, 24.0 mL, 60.0 mmol, 1.25 equiv). After 1 hour, the dark-red solution was cooled to –5 °C, followed by addition of 2'-bromoacetophenone (9.50 g, 48.0 mmol, 1.00 equiv) in THF (15 mL) over a period of 30 minutes. The resulting dark brown solution was allowed to gradually warm to rt and stirred overnight. The reaction was quenched by slow addition of aqueous NH_4Cl (50 mL saturated aqueous NH_4Cl + 50 mL H_2O) and then concentrated under reduced pressure to ½ volume to remove THF. The mixture was transferred to a separatory funnel and extracted with Et_2O (3 x 100 mL). The combined organics were washed with saturated aqueous NaCl (1 x 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a brown semi-solid mixture. To the crude mixture was added 100 mL 5% Et_2O/pentane to precipitate triphenylphosphine oxide, which was passed through a plug of silica. The silica was washed further with 300 mL 5% Et_2O/pentane, and the combined eluent was concentrated *in vacuo* (at 5 °C) resulting in a colorless oil. FCC in isocratic pentane afforded the title compound as a colorless, clear oil. The characterization data were in agreement with literature values.[14]

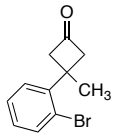
Yield: 7.446 g, 77%

TLC: R_f = 0.70 (100% Pentane)

IR (FT-ATR, neat, cm^{-1}): 3081, 2970, 2914, 1641, 1469, 1432, 1422, 1371, 1305, 1116, 1025, 901, 757, 731, 653.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.27 (td, *J* = 7.4, 1.2 Hz, 1H), 7.20 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.12 (ddd, *J* = 7.9, 7.2, 1.9 Hz, 1H), 5.24 (dq, *J* = 1.9 Hz, 1.6 Hz, 1H), 4.95 (dq, *J* = 1.9, 0.9 Hz, 1H), 2.11 (dd, *J* = 1.6, 0.9 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 145.9, 144.9, 132.9, 129.8, 128.5, 127.4, 121.7, 116.1, 23.7.



S51

3-(2-bromophenyl)-3-methylcyclobutan-1-one (S51): In the first step, a modification of Procedure 17 was followed using **S52** (7.00 g, 36.0 mmol, 1.0 equiv). After 24 hours, fresh Zn-Cu couple (5.70 g, 89.0 mmol, 2.5 equiv) was added, followed by a solution of $POCl_3$ (6.62 mL, 72 mmol, 2.0 equiv), trichloroacetyl chloride (7.93 mL, 72 mmol, 2.0 equiv) in Et_2O (36 mL) over a period of 2 h. The reaction was allowed to reflux overnight to provide **S47** that was taken to the next step. Procedure 18 was followed using **S47** (11.09 g, assumed 36 mmol, 1.0 equiv). The crude material was purified by FCC (SiO_2, 7.5% EtOAc/hexanes, isocratic) to provide the title compound as a colorless, clear oil. The characterization data were in agreement with literature values.[15]

Yield: 3.83 g, 45% (over two steps)

TLC: R_f = 0.37 (10% EtOAc/hexanes; UV/$KMnO_4$)

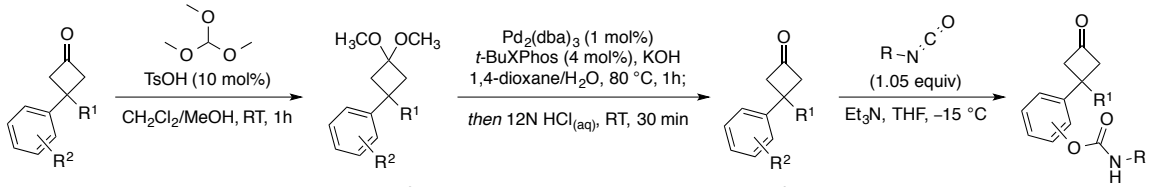
IR (FT-ATR, neat, cm^{-1}): 2965, 2926, 2779, 1471, 1428, 1375, 1258, 1145, 1084, 1024, 752.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61–7.55 (m, 1H), 7.36–7.27 (m, 2H), 7.12 (ddd, *J* = 7.9, 5.9, 3.0 Hz, 1H), 3.58–3.48 (m, 2H), 3.27–3.16 (m, 2H), 1.62 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.6, 145.9, 134.4, 128.4, 128.3, 127.7, 122.3, 59.2, 36.3, 27.8.

5.2. Synthesis of 4c–l, 4r–s

5.2.1 General Scheme for synthesis of carbamate substrates

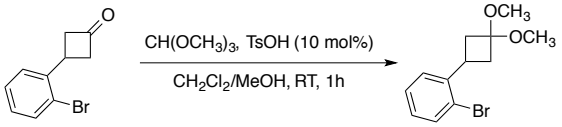


S53: R^1 = H, R^2 = 2-Br
S54: R^1 = H, R^2 = 3-Br
S55: R^1 = H, R^2 = 4-Br
S56: R^1 = CH_3, R^2 = 2-Br

4r: R^1 = H, R^2 = 2-OH
S57: R^1 = H, R^2 = 3-OH
S58: R^1 = H, R^2 = 4-OH
S59: R^1 = CH_3, R^2 = 2-OH

4c–l,4s–t

5.2.2 Procedure 19: Ketalization[16]



S48 **S53**

1-bromo-2-(3,3-dimethoxycyclobutyl)benzene (S53): To a solution of **S48** (9.906 g, 44 mmol, 1.0 equiv) in CH_2Cl_2/MeOH (1:1 v/v, 110 mL) was added trimethyl orthoformate (48 mL, 0.44 mol, 10 equiv) and TsOH (0.836 g, 4.4 mmol, 0.10 equiv) in one portion. After 1 h, the volatiles were removed *in vacuo*, and the resulting oil was diluted with Et_2O (400 mL). The organics were washed with saturated aqueous $NaHCO_3$ (2 x 200 mL), saturated aqueous NaCl (1 x 200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by FCC (SiO_2, 10 % EtOAc/hexanes, isocratic) to obtain the title compound as a colorless oil.

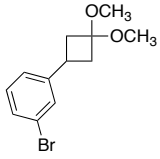
Yield: 10.54 g, 88%

TLC: R_f = 0.45 (10% EtOAc/hexanes; UV/$KMnO_4$)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34–7.27 (m, 2H), 7.07 (ddd, *J* = 8.9, 7.1, 2.2 Hz, 1H), 3.57 (app p, *J* = 8.9 Hz, 1H), 3.26 (s, 3H), 3.19 (s, 3H), 2.79–2.70 (m, 2H), 2.22–2.13 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.4, 132.9, 127.8, 127.5, 127.3, 124.6, 99.9, 49.1, 48.6, 38.3, 30.6.

HRMS (EI, 70 eV) *m/z*: $[M]^+$calcd for $C_{12}H_{15}BrO_2$ 270.0255, found 270.0243.



S54

1-bromo-3-(3,3-dimethoxycyclobutyl)benzene (S54) was prepared according to Procedure 19 using **S49** (562 mg, 2.5 mmol, 1.0 equiv). The crude material was purified by FCC (SiO_2, 10 % EtOAc/hexanes, isocratic) to obtain the title compound as a clear, colorless oil.

Yield: 649 mg, 96%

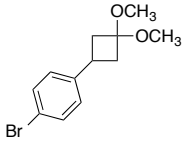
TLC: R_f = 0.45 (10% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 2988, 2943, 2829, 1596, 1565, 1477, 1416, 1272, 1228, 1194, 1147, 1038, 835, 777, 691.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.39 (s, 1H), 7.36–7.29 (m, 1H), 7.20–7.14 (m, 2H), 3.26 (app p, *J* = 8.9 Hz, 1H), 3.23 (s, 3H), 3.18 (s, 3H), 2.69–2.63 (m, 2H), 2.22–2.15 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 147.6, 130.1, 130.0, 129.3, 125.5, 122.7, 100.0, 49.0, 48.6, 39.5, 29.9.

HRMS (EI, 70 eV) *m/z*: $[M]^+$ calcd for $C_{12}H_{15}BrO_2$ 270.0255, found 270.0242.



S55

1-bromo-4-(3,3-dimethoxycyclobutyl)benzene (S55) was prepared according to Procedure 19 using **S50** (450 mg, 2.0 mmol, 1.0 equiv) to afford the crude product as a clear, colorless oil that was used without further purification.

Yield: 539 mg, 99%

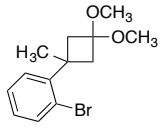
TLC: R_f = 0.46 (10% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 2988, 2941. 2828, 1488, 1271, 1227, 1195, 1148, 1039, 1009, 827.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44–7.39 (m, 2H), 7.15–7.10 (m, 2H), 3.24 (p, *J* = 9.0 Hz, 1H), 3.23 (s, 3H), 3.18 (s, 3H), 2.70–2.63 (m, 2H), 2.20–2.12 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 144.2, 131.5, 128.6, 119.9, 100.0, 49.0, 48.6, 39.6, 29.7.

HRMS (EI, 70 eV) *m/z*: $[M]^+$ calcd for $C_{12}H_{15}BrO_2$ 270.0255, found 270.0244.



S56

1-bromo-2-(3,3-dimethoxy-1-methylcyclobutyl)benzene (S56) was prepared according to Procedure 19 using **S51** (3.01 g, 12.6 mmol, 1.0 equiv). The crude material was purified by FCC (SiO_2, 10 % EtOAc/hexanes, isocratic) to obtain the title compound as a clear, colorless oil.

Yield: 3.59 g, >99%

TLC: R_f = 0.51 (10% EtOAc/hexanes)

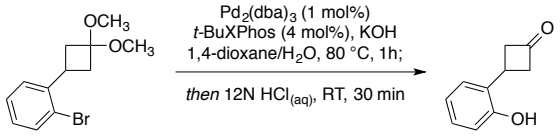
IR (FT-ATR, neat, cm^{-1}): 2940, 2828, 1470, 1434, 1277, 1236, 1132, 1086, 1040, 1021, 887, 753

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.30–7.23 (m, 1H), 7.17 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.03 (td, *J* = 7.5, 1.8 Hz, 1H), 3.25 (s, 3H), 3.13 (s, 3H), 2.61–2.50 (m, 4H), 1.54 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.8, 134.1, 128.0, 127.6, 127.4, 121.6, 98.9, 48.6, 48.5, 44.7, 36.1, 27.9.

HRMS (EI, 70 eV) *m/z*: $[M]^+$calcd for $C_{13}H_{17}BrO_2$ 284.0412, found 284.0399.

5.2.3 Procedure 20: Palladium catalyzed hydroxylation



S53 **4r**

3-(2-hydroxyphenyl)cyclobutan-1-one (4r): Adapting the procedure of Buchwald and co-workers[17], to a flame dried 100 mL two neck flask equipped with magnetic stir bar was added $Pd_2(dba)_3$ (256 mg, 0.28 mmol, 0.01 equiv), *t*-BuXPhos (476 mg, 1.12 mmol, 0.04 equiv), KOH (4.71 g, 84 mmol, 3.0 equiv, powdered) and vacuum-sparged thrice with N_2. Next, a solution of **S53** (7.59 g, 28.0 mmol, 1.0 equiv) in 1,4-dioxane (14 mL) was added followed by degassed H_2O (14 mL). The reaction mixture was heated to 80 °C, and after 1 hour the reaction was complete as judged by LC/MS. The reaction was removed from heat and concentrated HCl (5.9 mL, 12 N) was added in one portion. After 15 min, the reaction mixture was directly purified by FCC (SiO_2, 20% EtOAc/hexanes, isocratic) to afford the title compound as a pale yellow solid. The characterization data were in agreement with literature values.[18]

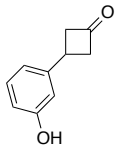
Yield: 4.274 g, 94%

TLC: R_f = 0.28 (20% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3292, 1759, 1744, 1590, 1454, 1368, 1228, 1103, 1044, 1015, 760.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.14 (td, *J* = 7.7, 1.7 Hz, 1H), 6.93 (td, *J* = 7.5, 1.1 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.50 (s, 1H), 3.75 (app p, *J* = 8.3 Hz, 1H), 3.50–3.32 (m, 4H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.5, 154.1, 129.2, 128.1, 120.9, 115.6, 53.1, 25.2 (one sp^2 ^{13}C signal is missing due to overlapping).



S57

3-(3-hydroxyphenyl)cyclobutan-1-one (S57) was prepared according to Procedure 20 using **S54** (488 mg, 1.80 mmol, 1.0 equiv), $Pd_2(dba)_3$ (33 mg, 0.036 mmol, 0.02 equiv), *t*-BuXPhos (61 mg, 0.144 mmol, 0.08 equiv), and KOH (303 mg, 5.4 mmol, 3.0 equiv, powdered). The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 2% EtOAc/hexanes for 1 CV, 2–25% EtOAc/hexanes linear gradient over 16 CV, 60 mL·min^{-1} flowrate) to obtain the title compound as a pale yellow oil.

Yield: 181 mg, 62%

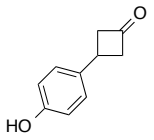
TLC: R_f = 0.32 (20% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3359, 1767, 1587, 1492, 1454, 1375, 1320, 1228, 1161, 1111, 997, 860, 782.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.22 (t, *J* = 7.9 Hz, 1H), 6.90–6.85 (m, 1H), 6.78 (t, *J* = 2.1 Hz, 1H), 6.72 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.76 (s, 1H), 3.64 (app p, *J* = 8.0 Hz, 1H), 3.54–3.42 (m, 2H), 3.29–3.20 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 208.1, 156.2, 145.5, 130.06, 118.9, 113.8, 113.6, 54.6, 28.4.

HRMS (EI, 70 eV) *m/z*: $[M]^+$ calcd for $C_{10}H_{10}O_2$ 162.0681, found 162.0674.



S58

3-(4-hydroxyphenyl)cyclobutan-1-one (S58) was prepared according to Procedure 20 using **S55** (407 mg, 1.50 mmol, 1.0 equiv), $Pd_2(dba)_3$ (18 mg, 0.030 mmol, 0.02 equiv), *t*-BuXPhos (50 mg, 0.12 mmol, 0.08 equiv), and KOH (252 mg, 4.5 mmol, 3.0 equiv, powdered). The crude material was purified by FCC (SiO_2, 20% EtOAc/Hexanes, isocratic) to obtain the title compound as a white solid.

Yield: 100 mg, 41%

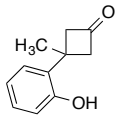
TLC: R_f = 0.29 (20% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3290, 1783, 1748, 1593, 1514, 1373, 1232, 1134, 1105, 832.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.19–7.14 (m, 2H), 6.84–6.81 (m, 2H), 4.91 (s, 1H), 3.67–3.58 (m, 1H), 3.51–3.42 (m, 2H), 3.24–3.15 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 207.5, 154.4, 135.9, 127.9, 115.6, 55.0, 27.9.

HRMS (EI, 70 eV) *m/z*: $[M]^+$ calcd for $C_{10}H_{10}O_2$ 162.0681, found 162.0679.



S59

3-(2-hydroxyphenyl)-3-methylcyclobutan-1-one (S59) was prepared according to a modification of Procedure 20 using **S56** (2.14 g, 7.5 mmol, 1.0 equiv), $Pd_2(dba)_3$ (160 mg, 0.175 mmol, 0.023 equiv), *t*-BuXPhos (293 mg, 0.69 mmol, 0.09 equiv), and KOH (1.26 g, 22.5 mmol, 3.0 equiv, powdered) at 100 °C for 20 h. The crude material was purified by FCC (SiO_2, 15% EtOAc/hexanes, isocratic) followed by RP-FCC (SNAP Ultra C18 60 g, CV = 90 mL, 10% CH_3CN/H_2O for 1 CV, 10–75% CH_3CN/H_2O linear gradient over 14 CV, 75–100% CH_3CN/H_2O linear gradient over 0.5 CV, then 100% CH_3CN/H_2O for 2 CV, 50 $mL \cdot min^{-1}$ flowrate) to provide **S59** as a white crystalline solid, which exists in equilibrium with the corresponding hemiketal (cyclobutanone **A**:hemiketal **B**= 85:15 by ^{1}H NMR).

Yield: 542 mg, 41%

TLC: R_f = 0.35 (20% EtOAc/hexanes)

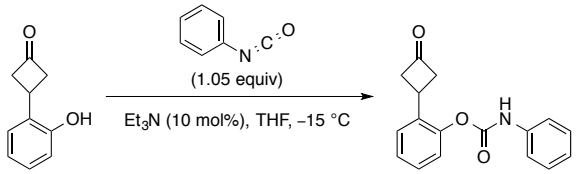
IR (FT-ATR, neat, cm^{-1}): 3348, 3030, 2987, 2964, 1750, 1606, 1590, 1502, 1438, 1368, 1340, 1290, 1208, 1105, 750.

^{1}H NMR (cyclobutanone **A**:hemiketal **B**= 85:15, 600 MHz, Chloroform-*d*) δ 7.20–7.10 (A+B)(m, 2H), 6.94 (A)(td, *J* = 7.5, 1.2 Hz, 1H), 6.91–6.87 (B)(m, 2H), 6.76 (A)(dd, *J* = 7.9, 1.1 Hz, 1H), 5.29 (A)(s, 1H), 3.65 (B)(s, 1H), 3.57–3.49 (A)(m, 2H), 3.16–3.06 (A)(m, 2H), 2.23–2.16 (B)(m, 2H), 1.88–1.80 (B)(m, 2H), 1.59 (A)(s, 3H), 1.57 (B)(s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 209.8, 153.9, 153.6, 135.3, 133.6, 128.1, 127.6, 127.5, 122.2, 120.9, 120.0, 116.1, 114.3, 100.1, 58.9, 43.2, 34.5, 32.4, 28.2, 20.8.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{13}O_2$ 177.0916, found 177.0914.

5.2.4 Procedure 21: Preparation of *N*-carbamates



4r **4c**

2-(3-oxocyclobutyl)phenyl phenylcarbamate (4c): To a solution of **4r** (1.22 g, 7.5 mmol, 1.0 equiv) in THF (1.0 M wrt phenol) at –15 °C was added phenyl isocyanate (938 mg, 7.9 mmol, 1.05 equiv) followed by dropwise addition of catalytic Et_3N (0.10 mL, 0.75 mmol, 0.10 equiv). The reaction mixture was slowly warmed to rt and stirred until completion (usually between 1–24 h). The volatiles were removed under reduced pressure, and the crude residue was directly purified by RP-FCC (SNAP Ultra C18 120 g, CV = 164 mL, 15% CH_3CN/H_2O for 1 CV, 15–70% CH_3CN/H_2O linear gradient over 18 CV, 70–100% CH_3CN/H_2O linear gradient over 0.5 CV, then 100% CH_3CN/H_2O for 2 CV, 65 mL·min^{-1} flowrate).

Yield: 1.87 g, 89%

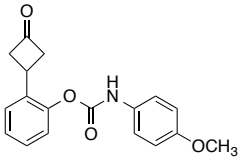
TLC: R_f = 0.44 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3323, 1782, 1709, 1599, 1529, 1492, 1443, 1379, 1315, 1216, 1175, 1092, 1009, 747.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 7.9 Hz, 1H), 7.36–7.30 (m, 3H), 7.28–7.17 (m, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 3.79–3.71 (m, 1H), 3.53–3.41 (m, 1H), 3.31–3.22 (m, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 207.6, 151.3, 148.9, 137.3, 135.2, 129.3, 128.1, 127.7, 126.3, 124.2, 123.1, 118.9, 53.7, 24.7.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3$ 282.1130, found 282.1126.



4d

2-(3-oxocyclobutyl)phenyl (4-methoxyphenyl)carbamate (4d) was synthesized from **4r** (243 mg, 1.5 mmol, 1.0 equiv) following Procedure 21 with 4-methoxyphenyl isocyanate (224 mg, 1.5 mmol, 1.0

equiv). The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 3% EtOAc/hexanes for 1 CV, 3–35% EtOAc/hexanes linear gradient over 16 CV, 60 mL·min^{-1} flowrate) to afford **4d** as a white, crystalline solid.

Yield: 410 mg, 88%

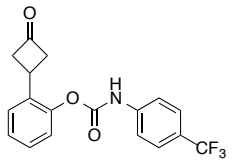
TLC: R_f = 0.29 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3317, 1787, 1723, 1703, 1536, 1509, 1413, 1215, 1175, 1097, 1031, 1007, 823.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42–7.27 (m, 4H), 7.30–7.21 (m, 4H), 6.94–6.82 (m, 3H), 3.80 (s, 3H), 3.84–3.71 (m, 1H), 3.57–3.42 (m, 2H), 3.35–3.22 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.5, 156.5, 151.7, 149.0, 135.3, 130.4, 128.0, 127.7, 126.2, 123.2, 120.9, 114.5, 55.6, 53.8, 24.9.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}NO_4$ 312.1236, found 312.1230.



4e

2-(3-oxocyclobutyl)phenyl (4-(trifluoromethyl)phenyl)carbamate (4e) was synthesized from **4r** (243 mg, 1.5 mmol, 1.0 equiv) following Procedure 21 with 4-trifluoromethylphenyl isocyanate (281 mg, 1.5 mmol, 1.0 equiv). The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 3% EtOAc/hexanes for 1 CV, 3–35% EtOAc/hexanes linear gradient over 16 CV, 60 mL·min^{-1} flowrate) to afford **4e** as a white solid.

Yield: 422 mg, 81%

TLC: R_f = 0.41 (30% EtOAc/hexanes)

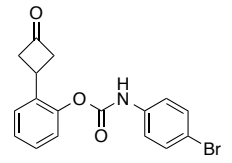
IR (FT-ATR, neat, cm^{-1}): 3333, 1788, 1745, 1720, 1605, 1544, 1492, 1412, 1320, 1217, 1157, 1111, 1067, 1014, 839.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.61–7.55 (m, 4H), 7.38–7.24 (m, 6H), 3.75 (tt, *J* = 9.4, 6.9 Hz, 1H), 3.55–3.47 (m, 2H), 3.31–3.23 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 207.7, 151.1, 148.7, 140.5, 135.1, 128.2, 128.1, 126.6 (q, $^3J_{C–F}$ = 4.0 Hz), 126.6, 126.1 (q, $^2J_{C–F}$ = 32.7 Hz), 124.2 (q, $^1J_{C–F}$ = 271.3 Hz), 123.1, 118.5, 53.9, 25.1.

^{19}F NMR (376 MHz, Chloroform-*d*) δ –62.15.

HRMS (ESI/Q-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{14}F_3NO_3Na$ 372.0823, found 372.0825.



4f

2-(3-oxocyclobutyl)phenyl (4-bromophenyl)carbamate (4f) was synthesized from **4r** (243 mg, 1.5 mmol, 1.0 equiv) following Procedure 21 with 4-bromophenyl isocyanate (297 mg, 1.5 mmol, 1.0 equiv).

The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 3% EtOAc/hexanes for 1 CV, 3–35% EtOAc/hexanes linear gradient over 16 CV, 60 mL·min^{-1} flowrate) to afford **4f** as a white, crystalline solid.

Yield: 491 mg, 91%

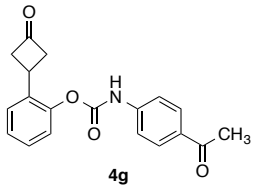
TLC: R_f = 0.41 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3340, 1786, 1708, 1596, 1537, 1489, 1398, 1311, 1215, 1176, 1097, 1006, 826.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47–7.41 (m, 2H), 7.39–7.29 (m, 4H), 7.29–7.22 (m, 3H), 7.11 (s, 1H), 3.74 (tt, *J* = 9.3, 7.0 Hz, 1H), 3.54–3.44 (m, 2H), 3.32–3.19 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.6, 151.2, 148.8, 136.5, 135.1, 132.3, 128.1, 127.9, 126.4, 123.1, 120.5, 116.8, 53.8, 25.0.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}BrNO_3$ 360.0235, found 360.0227.



4g

2-(3-oxocyclobutyl)phenyl (4-acetylphenyl)carbamate (4g) was synthesized from **4r** (79 mg, 0.49 mmol, 1.0 equiv) following Procedure 21 with 4-acetylphenyl isocyanate (79 mg, 0.49 mmol, 1.0 equiv). The crude material was purified by automated FCC (SNAP Ultra 10 g, CV = 17 mL, 10% EtOAc/hexanes for 1 CV, 10–50% EtOAc/hexanes linear gradient over 16 CV, 36 mL·min^{-1} flowrate) to afford **4g** as an off-white, crystalline solid.

Yield: 145 mg, 90%

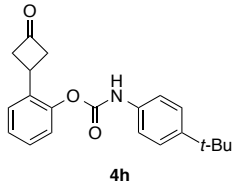
TLC: R_f = 0.36 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3331, 1791, 1723, 1671, 1598, 1536, 1489, 1408, 1357, 1270, 1220, 1171, 1096, 1006, 963, 849.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.98–7.94 (m, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.41 (bs, 1H), 7.38–7.31 (m, 2H), 7.30–7.24 (m, 2H), 3.75 (tt, *J* = 9.4, 6.9 Hz, 1H), 3.54–3.44 (m, 2H), 3.32–3.21 (m, 2H), 2.59 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 207.5, 197.0, 151.0, 148.7, 141.8, 135.1, 132.9, 130.1, 128.2, 128.0, 126.6, 123.0, 118.1, 53.9, 26.6, 25.0.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{18}NO_4$ 324.1236, found 360.0227.



4h

2-(3-oxocyclobutyl)phenyl (4-(*tert*-butyl)phenyl)carbamate (4h) was synthesized from **4r** (122 mg, 0.75 mmol, 1.0 equiv) following Procedure 21 with 4-*tert*-butylphenyl isocyanate (131 mg, 0.75 mmol, 1.0 equiv). The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 3%

EtOAc/hexanes for 1 CV, 3–30% EtOAc/hexanes linear gradient over 16 CV, 50 mL·min^{-1} flowrate) to afford **4h** as a white, crystalline solid.

Yield: 146 mg, 58%

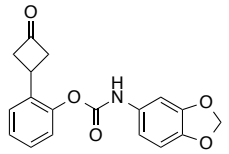
TLC: R_f = 0.50 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3320, 2964, 1782, 1739, 1713, 1597, 1537, 1487, 1319, 1220, 1180, 1100, 1009, 831.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.41–7.29 (m, 6H), 7.28–7.22 (m, 2H), 7.01 (bs, 1H), 3.80–3.70 (m, 1H), 3.53–3.41 (m, 2H), 3.32–3.21 (m, 2H), 1.31 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 207.5, 151.4, 149.0, 147.3, 135.3, 134.7, 128.1, 127.7, 126.3, 126.2, 123.2, 118.7, 53.8, 34.5, 31.5, 24.9.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{24}NO_3$ 338.1756, found 338.1762.



4i

2-(3-oxocyclobutyl)phenyl benzo[*d*][1,3]dioxol-5-ylcarbamate (4i) was synthesized from **4r** (122 mg, 0.75 mmol, 1.0 equiv) following Procedure 21 with 3,4-(methylenedioxy)phenyl isocyanate (122 mg, 0.75 mmol, 1.0 equiv). The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 3% EtOAc/hexanes for 1 CV, 3–20% EtOAc/hexanes linear gradient over 16 CV, and held at 20% EtOAc/hexanes for 4 CV, 60 mL·min^{-1} flowrate) to afford **4i** as a white, crystalline solid.

Yield: 149 mg, 61%

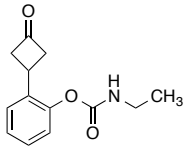
TLC: R_f = 0.16 (20% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3279, 3233, 3059, 2900, 1783, 1775, 1706, 1545, 1526, 1482, 1441, 1345, 1239, 1100, 1034, 929, 751.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.37–7.28 (m, 2H), 7.28–7.20 (m, 2H), 7.13 (s, 1H), 7.00 (s, 1H), 6.80–6.72 (m, 2H), 5.95 (s, 2H), 3.81–3.68 (m, 1H), 3.57–3.39 (m, 2H), 3.33–3.19 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 207.6, 151.5, 148.9, 148.2, 144.4, 135.2, 131.5, 128.1, 127.8, 126.3, 123.1, 112.3, 108.3, 101.9, 101.5, 53.8, 24.9.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{16}NO_5$ 326.1028, found 326.1040.



4j

2-(3-oxocyclobutyl)phenyl ethylcarbamate (4j) was synthesized from **4r** (243 mg, 1.5 mmol, 1.0 equiv) following Procedure 21 with ethyl isocyanate (107 mg, 1.5 mmol, 1.0 equiv). The crude material was

purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 3% EtOAc/hexanes for 1 CV, 3–35% EtOAc/hexanes linear gradient over 16 CV, 70 mL·min^{-1} flowrate) to afford **4j** as a white, crystalline solid.

Yield: 256 mg, 73%

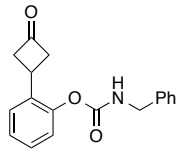
TLC: R_f = 0.18 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3294, 3064, 2981, 2878, 1779, 1701, 1537, 1488, 1451, 1377, 1260, 1205, 1151, 1096, 976, 963, 745.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33–7.13 (m, 5H), 3.78–3.65 (m, 1H), 3.50–3.39 (m, 2H), 3.37–3.20 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.5, 154.1, 149.4, 135.1, 127.9, 127.6, 125.8, 123.1, 53.6, 36.3, 24.9, 15.2.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1127.



4k

2-(3-oxocyclobutyl)phenyl benzylcarbamate (4k) was synthesized from **4r** (243 mg, 1.5 mmol, 1.0 equiv) following Procedure 21 with benzyl isocyanate (199 mg, 1.5 mmol, 1.0 equiv). The crude material was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 3% EtOAc/hexanes for 1 CV, 3–35% EtOAc/hexanes linear gradient over 16 CV, 70 mL·min^{-1} flowrate) to afford **4j** as a white, crystalline solid.

Yield: 365 mg, 82%

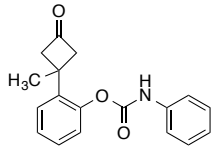
TLC: R_f = 0.30 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3304, 1778, 1737, 1705, 1547, 1528, 1486, 1448, 1263, 1179, 1098, 1019, 743.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43–7.13 (m, 9H), 5.51 (t, *J* = 6.0 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 3.77–3.63 (m, 1H), 3.49–3.35 (m, 2H), 3.30–3.14 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.5, 154.4, 149.3, 138.0, 135.1, 128.9, 127.9, 127.9, 127.8, 127.6, 126.0, 123.1, 53.6, 45.5, 24.8.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}NO_3$ 296.1287, found 296.1300.



4l

2-(1-methyl-3-oxocyclobutyl)phenyl phenylcarbamate (4l) was synthesized from **S59** (211 mg, 1.2 mmol, 1.0 equiv) following Procedure 21 with phenyl isocyanate (143 mg, 1.2 mmol, 1.0 equiv). The

crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 10% CH_3CN/H_2O for 1 CV, 10–100% CH_3CN/H_2O linear gradient over 16 CV, then 100% CH_3CN/H_2O for 2 CV, 25 mL·min^{-1} flowrate) to afford **4l** as a white solid.

Yield: 197 g, 56%

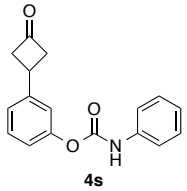
TLC: R_f = 0.42 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3363, 3350, 2967, 1775, 1747, 1603, 1540, 1489, 1441, 1317, 1196, 1169, 1076, 1006, 994.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.47–7.41 (m, 2H), 7.35–7.30 (m, 3H), 7.30–7.24 (m, 3H), 7.21 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 3.56–3.45 (m, 2H), 3.16–3.02 (m, 2H), 1.57 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 207.4, 151.6, 148.3, 139.3, 137.3, 129.3, 128.1, 127.7, 126.2, 124.2, 123.9, 119.0, 58.9, 32.5, 29.2.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}NO_3$ 296.1287, found 296.1299.



4s

3-(3-oxocyclobutyl)phenyl phenylcarbamate (4s) was synthesized from **S57** (162 mg, 1.0 mmol, 1.0 equiv) following Procedure 21 with phenyl isocyanate (119 mg, 1.0 mmol, 1.2 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 10% CH_3CN/H_2O for 1 CV, 10–100% CH_3CN/H_2O linear gradient over 14 CV, then 100% CH_3CN/H_2O for 2 CV, 25 mL·min^{-1} flowrate) to afford **4s** as a white solid.

Yield: 183 mg, 65%

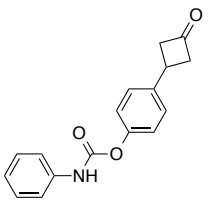
TLC: R_f = 0.36 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3273, 3133, 1770, 1742, 1600, 1545, 1492, 1434, 1377, 1316, 1207, 1151, 1021, 757.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50–7.28 (m, 5H), 7.21–7.05 (m, 5H), 3.68 (app p, *J* = 8.0 Hz, 1H), 3.56–3.40 (m, 2H), 3.33–3.16 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.5, 151.7, 150.9, 145.4, 137.4, 129.8, 129.3, 124.1, 123.9, 120.1, 120.1, 118.9, 54.7, 28.4.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3$ 282.1130, found 282.1132.



4t

4-(3-oxocyclobutyl)phenyl phenylcarbamate (4t) was synthesized from **S58** (89 mg, 0.55 mmol, 1.0 equiv) following Procedure 21 with phenyl isocyanate (69 mg, 0.58 mmol, 1.05 equiv). The crude material was purified by RP-FCC (SNAP Ultra C18 30 g, CV = 45 mL, 10% CH_3CN/H_2O for 1 CV, 10–100% CH_3CN/H_2O linear gradient over 14 CV, then 100% CH_3CN/H_2O for 3 CV, 30 mL·min^{-1} flowrate) to afford **4t** as a white solid.

Yield: 128 mg, 83%

TLC: R_f = 0.42 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3322, 1783, 1714, 1599, 1543, 1507, 1444, 1319, 1221, 1198, 1101, 1012, 844.

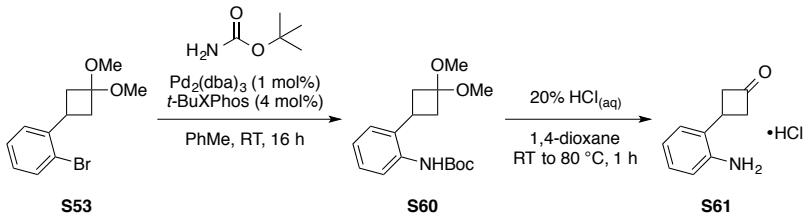
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.38–7.29 (m, 4H), 7.20–7.16 (m, 2H), 7.12 (tt, *J* = 7.4, 1.2 Hz, 1H), 6.99 (s, 1H), 3.74–3.65 (m, 1H), 3.56–3.46 (m, 2H), 3.29–3.21 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 206.6, 151.7, 149.3, 141.2, 137.4, 129.3, 127.7, 124.1, 122.1, 118.8, 55.0, 28.2.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3$ 282.1130, found 282.1125.

5.3. Synthesis and characterization of S57, 4m–4q

5.3.1: Preparation of S57



***tert*-butyl (2-(3,3-dimethoxycyclobutyl)phenyl)carbamate (S60):** Adapting the procedure of Anderson *et al.*[19] to a flame dried 50 mL Schlenk flask equipped with magnetic stir bar was added *tert*-butyl carbamate (0.580 g, 4.95 mmol, 1.1 equiv), NaO*t*-Bu (0.61 g, 6.3 mmol, 1.4 equiv), $Pd_2(dba)_3$ (211 mg, 0.23 mmol, 0.05 equiv), *t*-BuXPhos (289 mg, 0.68 mmol, 0.015 equiv) and vacuum-sparged thrice with N_2. Next, a solution of **S53** (1.22 g, 4.5 mmol, 1.0 equiv) in PhMe (18 mL, 0.25 M). The reaction mixture was stirred at rt overnight. The mixture was then filtered through a pad of SiO_2. The filter pad was washed with 1:1 EtOAc/hexanes, and the combined eluent concentrated under reduced pressure. The crude product was purified by FCC (SiO_2, 20% EtOAc/hexanes, isocratic) to afford **S60** as an orange, crystalline solid.

Yield: 0.95 g, 84% from **S53**

TLC: R_f = 0.45 (20% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3324, 2949, 2826, 1721, 1691, 1586, 1533, 1450, 1301, 1241, 1203, 1147, 1041, 751, 645.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.24–7.17 (m, 2H), 7.08 (td, *J* = 7.5, 1.3 Hz, 1H), 6.22 (s, 1H), 3.31 (app p, *J* = 8.9 Hz, 1H), 3.26 (s, 3H), 3.17 (s, 3H), 2.75–2.64 (m, 2H), 2.28–2.16 (m, 2H), 1.51 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.3, 135.9, 134.2, 127.1, 126.3, 124.1, 122.1, 100.0, 80.6, 49.0, 48.6, 38.0, 28.5, 26.2.

HRMS (ESI/Q-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{25}NO_4Na$ 330.1681, found 330.1697.

3-(2-aminophenyl)cyclobutan-1-one hydrochloride (S61): To a solution of **S60** (614 mg, 2.0 mmol, 1.0 equiv) in 1,4-dioxane (5.0 mL) was added 20% aqueous w/w HCl (5.0 mL) and stirred at rt for 30 min. The reaction mixture was then heated at 80 °C for 30 minutes. The solvent was then removed under reduced pressure to afford the crude product as a tan solid, which was used without further purification. The title compound exists in equilibrium with the corresponding hemiaminal (cyclobutanone:hemiaminal 82:18).

Yield: 400 mg, quantitative from **S60**

IR (FT-ATR, neat, cm^{-1}): 2879, 2736, 2559, 1780, 1491, 1374, 1104, 758

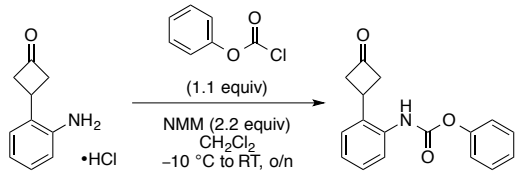
^{1}H NMR (cyclobutanone **A**:hemiaminal **B**= 82:18, 600 MHz, DMSO-d_6) δ 10.50 (A)(bs, 3H), 7.64 (A)(dd, *J* = 7.8, 1.4 Hz, 1H), 7.50 (A)(dt, *J* = 7.8, 1.4 Hz, 1H), 7.42 (A)(td, *J* = 7.6, 1.3 Hz, 1H), (A)7.35 (td, *J* = 7.6, 1.4 Hz, 1H), (B)7.33–7.30 (m, 2H), 7.29–7.22 (B)(m, 2H), 3.92 (A)(app p, *J* = 8.3 Hz, 1H),

3.51–3.42 (A)(m, 2H), 3.31–3.24 (A)(m, 2H), 3.24–3.21 (B)(m, 1H), 2.65–2.57 (B)(m, 2H), 1.93–1.85 (B)(m, 2H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 206.1, 139.8, 137.5, 132.1, 130.6, 128.5, 127.6, 127.2, 127.0, 125.9, 123.7, 122.7, 87.1, 54.3, 40.7, 29.4, 23.2. (one sp^2 ^{13}C signal is missing due to overlapping).

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{12}NO$ 162.0919, found 162.0911.

5.3.2: Synthesis and characterization of 4m–4q



phenyl (2-(3-oxocyclobutyl)phenyl)carbamate (4m): To a solution of crude **S61** (99 mg, 0.50 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL) at –10 °C was added NMM (121 μL, 1.1 mmol, 2.2 equiv) followed by dropwise addition of phenyl chloroformate (86 mg, 0.55 mmol, 1.1 equiv). The reaction mixture was allowed to slowly warm to rt overnight. The reaction was diluted with CH_2Cl_2 and quenched by addition of saturated aqueous NH_4Cl. The product was extracted thrice with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by automated FCC (SNAP Ultra 10 g, CV = 17 mL, 3% EtOAc/hexanes for 1 CV, 3–35% EtOAc/hexanes linear gradient over 16 CV, 30 mL·min^{-1} flowrate) to afford **4m** as a white solid.

Yield: 135 mg, 96% from **S61**

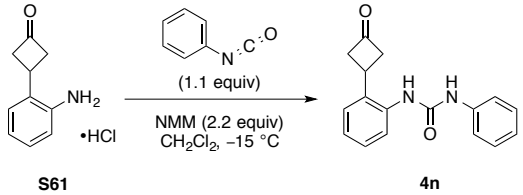
TLC: R_f = 0.33 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3225, 1787, 1723, 1701, 1546, 1494, 1451, 1299, 1233, 1202, 1189, 1017, 748.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.68 (s, 1H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.37 – 7.30 (m, 2H), 7.29 – 7.22 (m, 3H), 7.21 – 7.16 (m, 2H), 6.72 (s, 1H), 3.81 (p, *J* = 8.4 Hz, 1H), 3.58 – 3.49 (m, 2H), 3.34 – 3.25 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 205.6, 152.4, 150.7, 135.2, 135.0, 129.6, 127.9, 126.2, 125.9, 124.1, 121.6, 53.5, 24.7 (one sp^2 ^{13}C signal is missing due to overlapping/peak broadening).

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3$ 282.1130, found 282.1142.



2-(3-oxocyclobutyl)phenyl phenylcarbamate (4n): To a solution of crude **S61** (99 mg, 0.50 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL) at –10 °C was added NMM (121 μL, 1.1 mmol, 2.2 equiv) followed by

dropwise addition of phenyl isocyanate (66 mg, 0.55 mmol, 1.1 equiv). The reaction mixture was allowed to slowly warm to rt overnight. The reaction was diluted with CH_2Cl_2 and quenched by addition of saturated aqueous NH_4Cl. The product was extracted thrice with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was crystallized from hot EtOAc to afford **4n** as a white powder. The mother liquor was concentrated and recrystallized to yield a second batch of **4n**.

Yield: 108 mg, 77% from **S61**

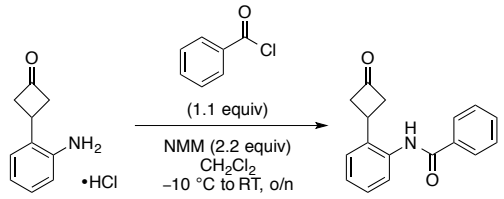
TLC: R_f = 0.57 (50% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3289, 1781, 1633, 1599, 1546, 1490, 1444, 1293, 1234, 1105, 754.

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.94 (s, 1H), 7.89 (s, 1H), 7.70 (dd, J = 8.0, 1.3 Hz, 1H), 7.48–7.44 (m, 2H), 7.41 (dt, J = 7.8, 1.0 Hz, 1H), 7.30–7.26 (m, 2H), 7.23 (td, J = 7.7, 1.6 Hz, 1H), 7.12 (td, J = 7.5, 1.3 Hz, 1H), 6.96 (tt, J = 7.4, 1.2 Hz, 1H), 3.74 (app p, J = 8.3 Hz, 1H), 3.52–3.42 (m, 2H), 3.27–3.18 (m, 2H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 206.4, 152.8, 139.9, 136.9, 134.7, 128.8, 128.8, 126.7, 125.8, 123.8, 123.5, 121.7, 118.1, 52.8, 24.1.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_2$ 281.1290, found 281.1303.



S61 **4o**

***N*-(2-(3-oxocyclobutyl)phenyl)benzamide (4o):** To a solution of crude **S61** (191 mg, 0.96 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL) at –25 °C was added NMM (233 µL, 2.12 mmol, 2.2 equiv) followed by dropwise addition of benzoyl chloride (123 µL, 1.06 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL) over 30 min. The reaction mixture was allowed to slowly warm to rt overnight. The reaction was diluted with CH_2Cl_2 and quenched by addition of saturated aqueous NH_4Cl. The product was extracted thrice with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by FCC (SiO_2, 30–40% EtOAc/hexanes) to afford **4o** as a white, crystalline solid.

Yield: 199 mg, 78% from **S61**

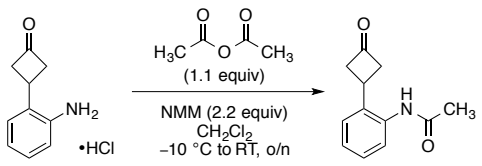
TLC: R_f = 0.21 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3246, 1776, 1647, 1603, 1524, 1488, 1378, 1315, 1274, 1107, 912, 763, 688.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.90–7.84 (m, 2H), 7.73 (s, 1H), 7.59 (ddt, J = 13.3, 6.9, 1.6 Hz, 2H), 7.53–7.48 (m, 2H), 7.38 (ddd, J = 6.4, 2.2, 0.9 Hz, 1H), 7.35–7.28 (m, 2H), 3.84–3.77 (m, 1H), 3.49–3.40 (m, 2H), 3.31–3.24 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 205.9, 166.1, 137.1, 135.4, 134.4, 132.3, 129.1, 127.8, 127.2, 126.9, 126.4, 125.9, 53.5, 25.1.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_2$ 266.1181, found 266.1171.



S61 **4p**

***N*-(2-(3-oxocyclobutyl)phenyl)acetamide (4p):** To a solution of crude **S61** (99 mg, 0.50 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL) at –10 °C was added NMM (121 µL, 1.1 mmol, 2.2 equiv) followed by dropwise addition of acetic anhydride (52 µL, 0.55 mmol, 1.1 equiv). The reaction mixture was allowed to slowly warm to rt overnight. The reaction was diluted with CH_2Cl_2 and quenched by addition of saturated aqueous NH_4Cl. The product was extracted thrice with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by by automated FCC (SNAP Ultra 10 g, CV = 17 mL, 20% EtOAc/hexanes for 1 CV, 20–100% EtOAc/hexanes linear gradient over 16 CV, and held at 100% EtOAc for 8 CV, 30 mL·min^{-1} flowrate) to afford **4p** as a white solid.

Yield: 81 mg, 80% from **S61**

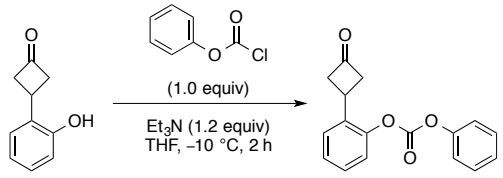
TLC: R_f = 0.60 (75% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3263, 1777, 1651, 1582, 1532, 1453, 1365, 1296, 1270, 1124, 760.

^{1}H NMR (7:1 rotamer ratio [A = major, B = minor], 600 MHz, Chloroform-*d*) δ 7.47–7.36 (A+B)(m, 1H), 7.36–7.30 (A+B)(m, 1H), 7.30–7.24 (A+B)(m, 2H), 7.16 (A+B)(s, 1H), 3.83 (B)(m, 1H), 3.72 (A)(app p, *J* = 8.4 Hz, 1H), 3.57–3.37 (A+B)(m, 2H), 3.32–3.15 (A+B)(m, 2H), 2.18 (A)(s, 3H), 1.88 (B)(s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 206.1, 168.9, 137.3, 135.2, 127.7, 127.0, 126.3, 126.3, 53.6, 24.9, 24.0.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1025.



4r **4q**

2-(3-oxocyclobutyl)phenyl phenyl carbonate (4q): To a solution of **4r** (243 mg, 1.50 mmol, 1.0 equiv) in THF (5.0 mL) at –10 °C was added Et_3N (0.25 mL, 1.8 mmol, 1.2 equiv) followed by dropwise addition of phenyl chloroformate (235 mg, 1.5 mmol, 1.1 equiv). The reaction mixture was allowed to slowly warm to rt overnight. The reaction was diluted with CH_2Cl_2 and quenched by addition of saturated aqueous NH_4Cl. The product was extracted thrice with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure The crude residue was purified by automated FCC (SNAP Ultra 25 g, CV = 45 mL, 1% EtOAc/hexanes for 1 CV, 1–25% EtOAc/hexanes linear gradient over 14 CV, 60 mL·min^{-1} flowrate) to afford **4q** as a white, crystalline solid.

Yield: 300 mg, 71% from **4r**

TLC: R_f = 0.55 (30% EtOAc/hexanes)

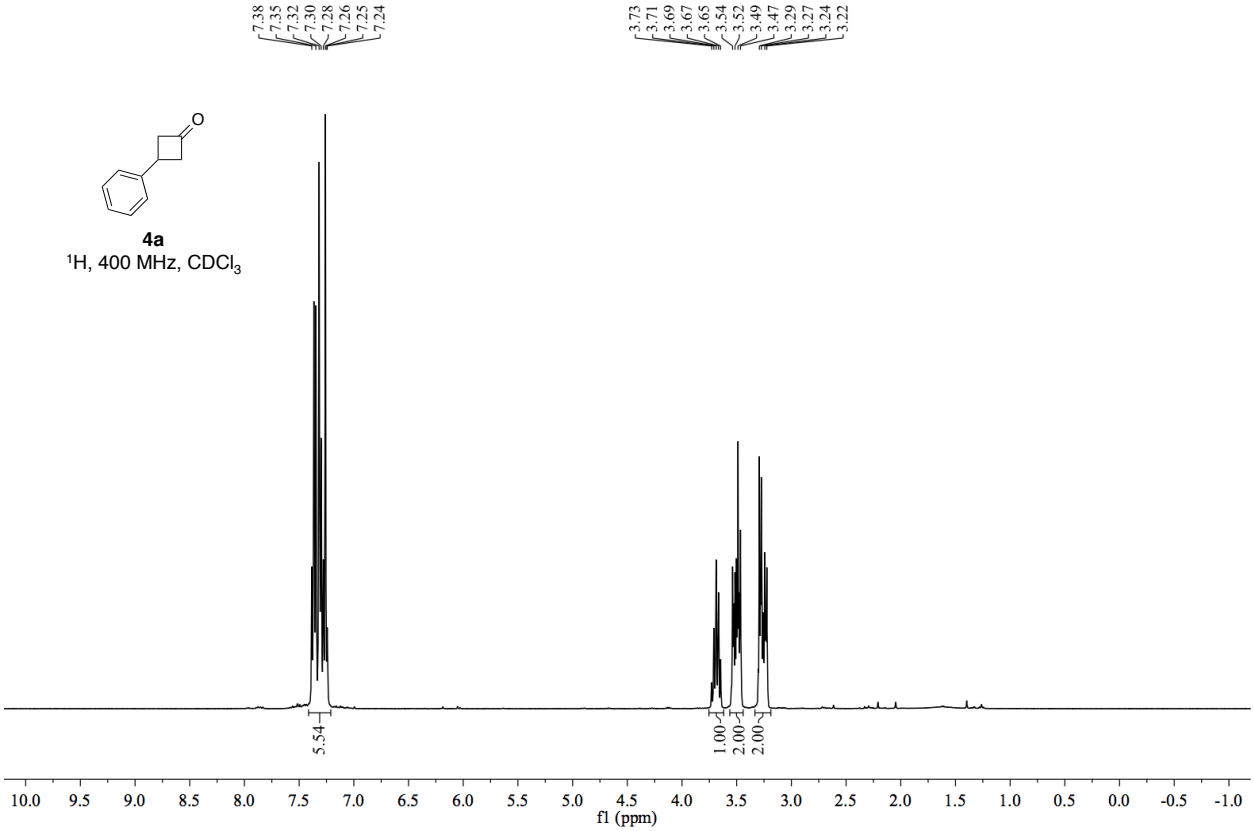
IR (FT-ATR, neat, cm^{-1}): 1784, 1767, 1592, 1488, 1378, 1336, 1245, 1152, 1096, 769.

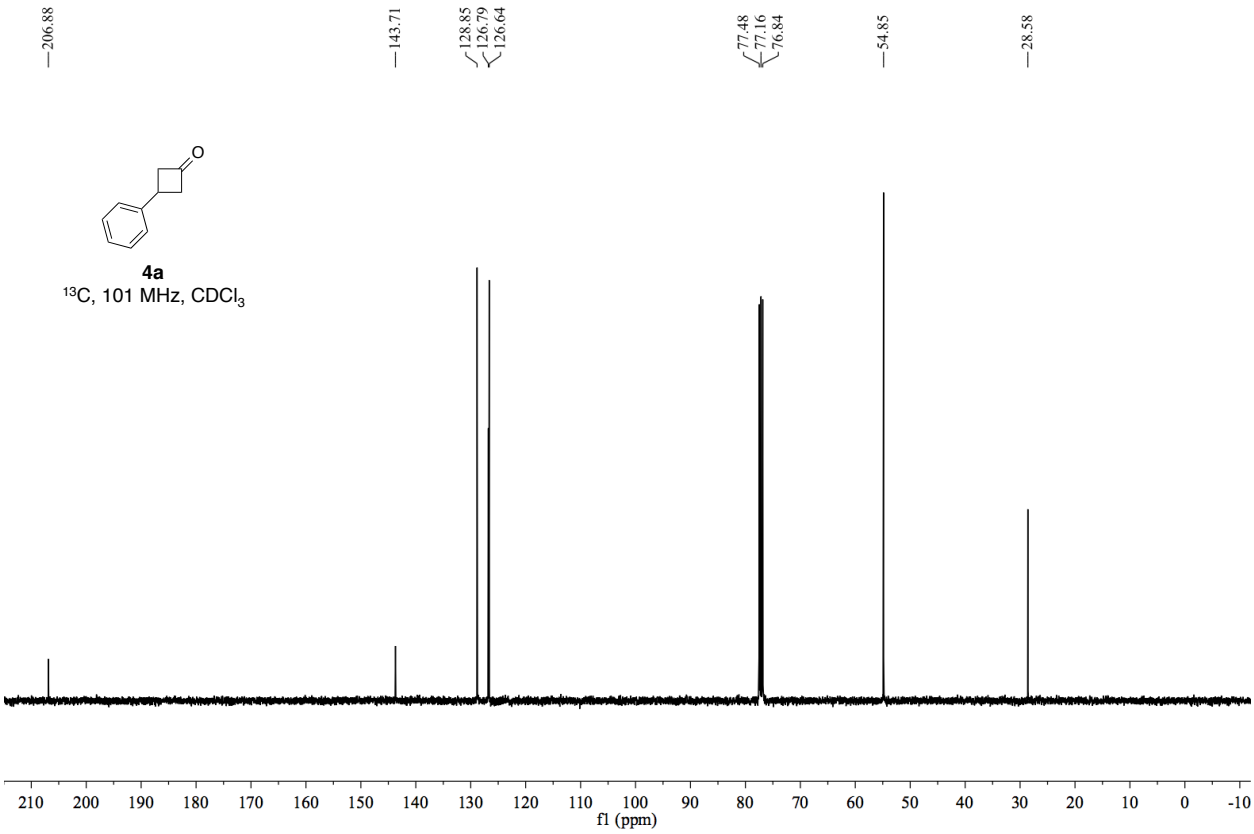
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48–7.23 (m, 9H), 3.91–3.78 (m, 1H), 3.59–3.44 (m, 2H), 3.39–3.25 (m, 2H).

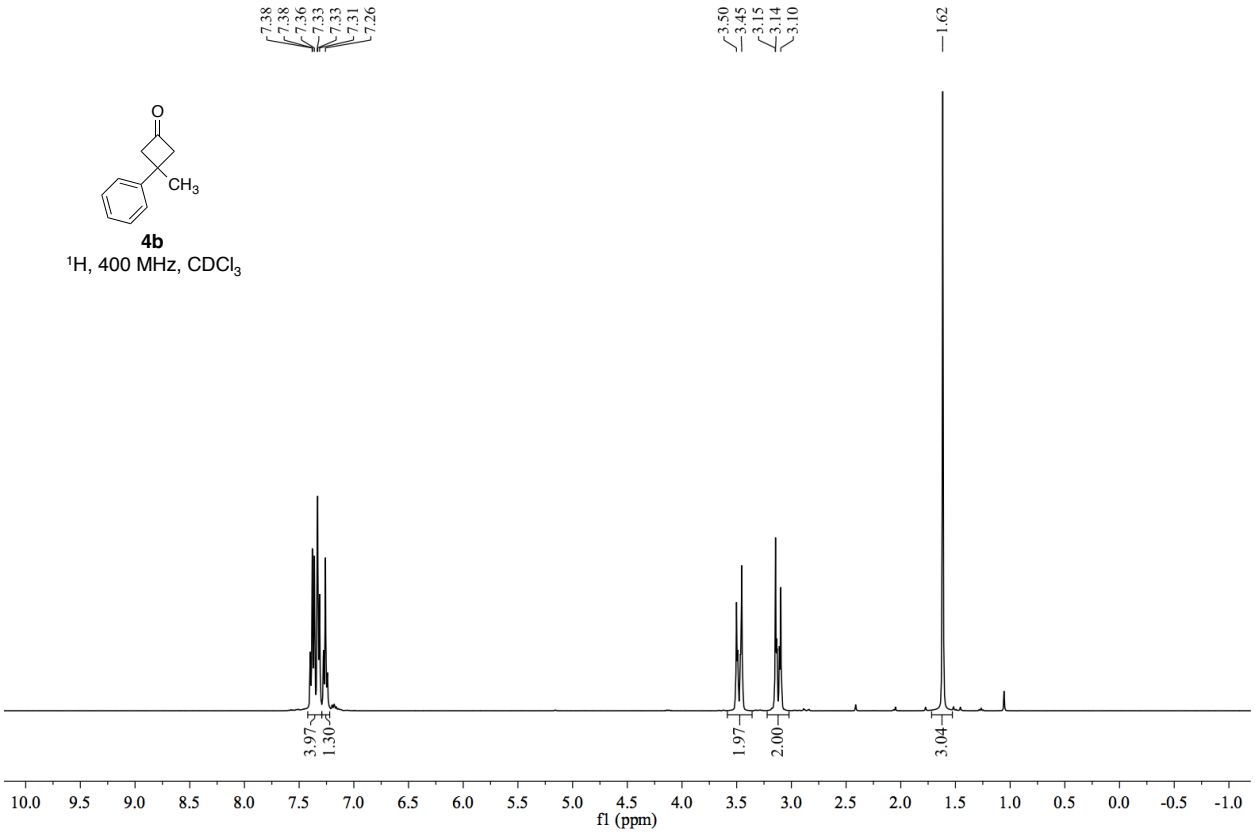
^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.1, 152.0, 151.0, 149.4, 134.8, 129.8, 128.2, 127.3, 127.0, 126.6, 122.2, 120.9, 53.5, 24.0.

HRMS (ESI/Q-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{14}O_4Na$ 305.0790, found 305.0779.

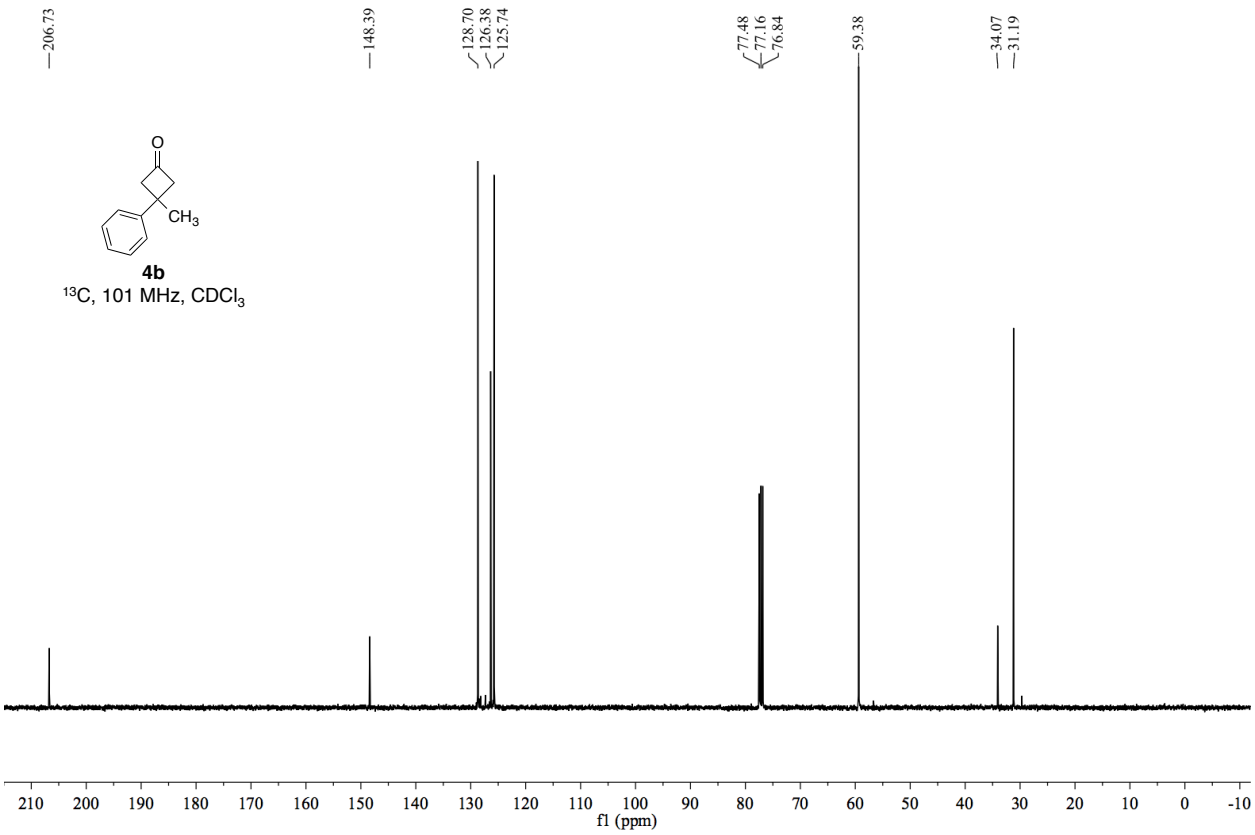
5.4. NMR Spectra



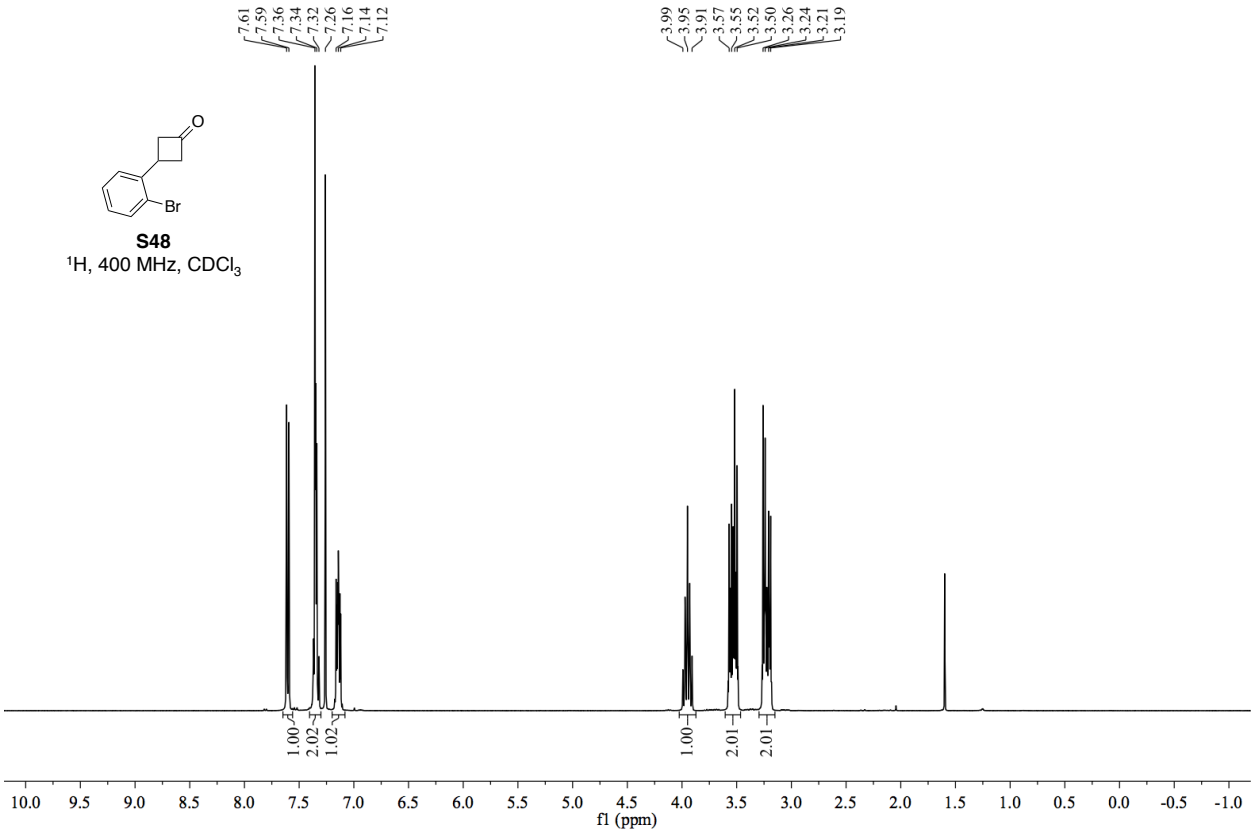




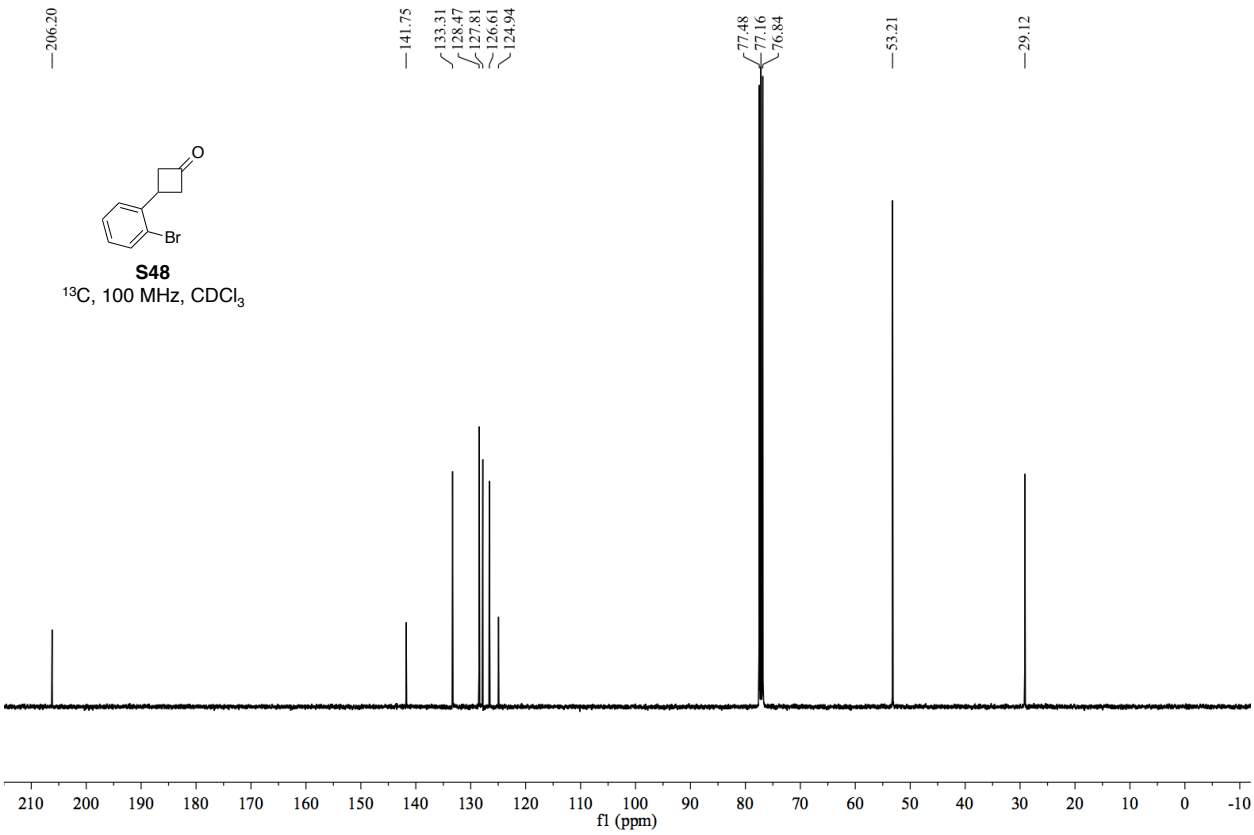
4b
^{1}H, 400 MHz, $CDCl_3$



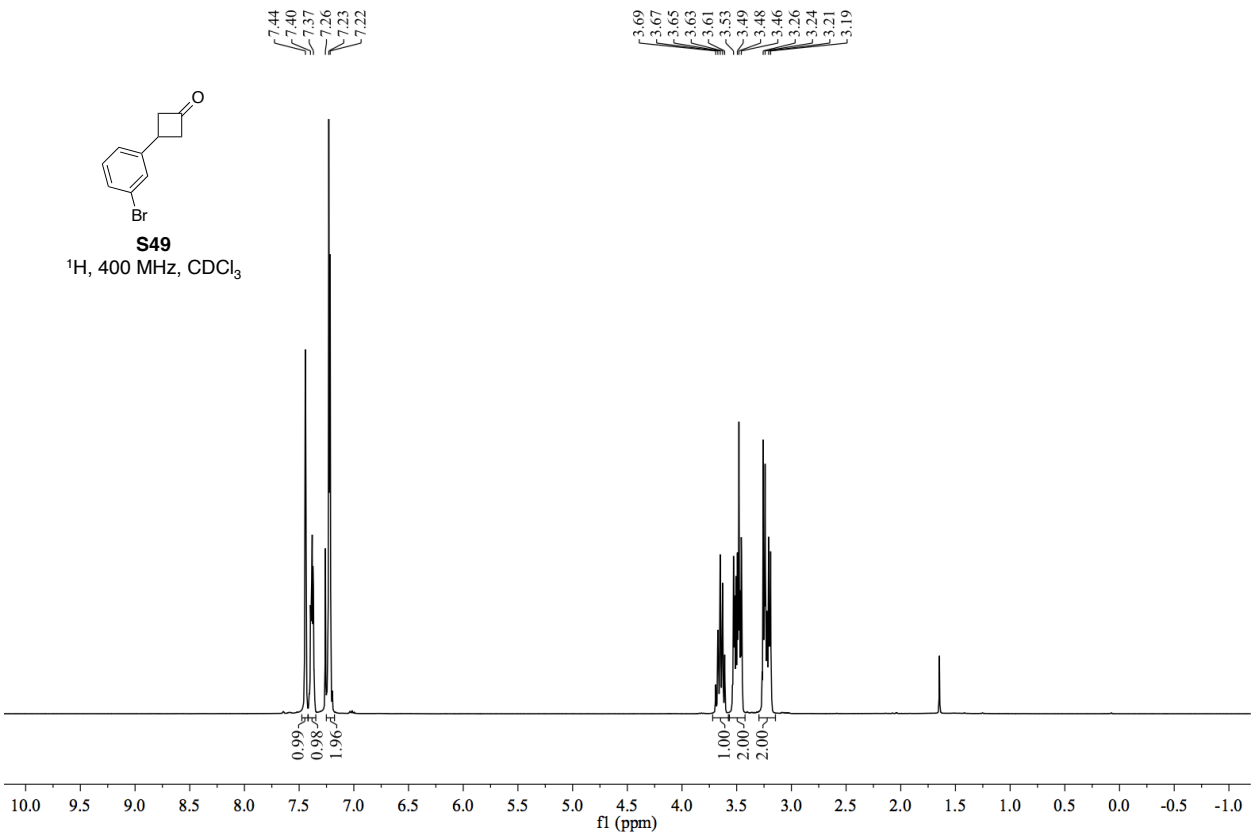
4b
^{13}C, 101 MHz, $CDCl_3$



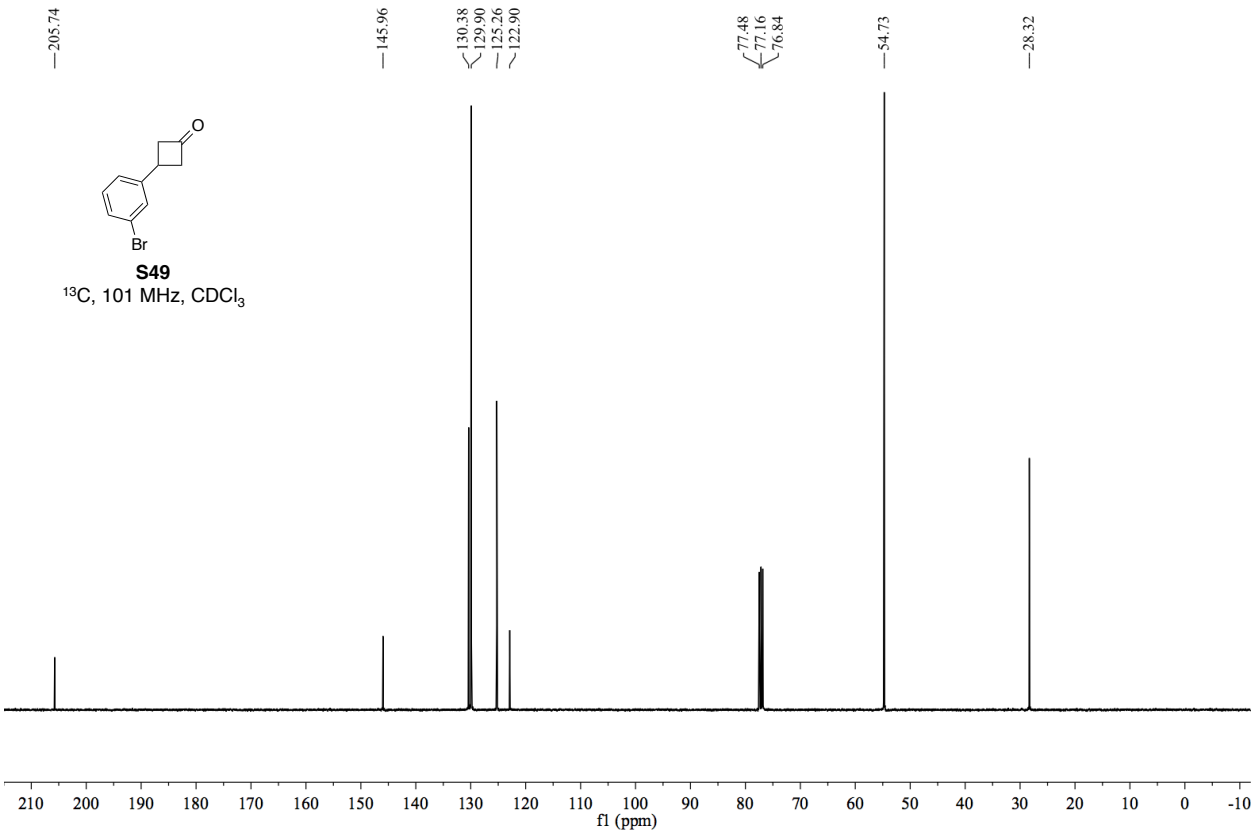
S48
^{1}H, 400 MHz, $CDCl_3$



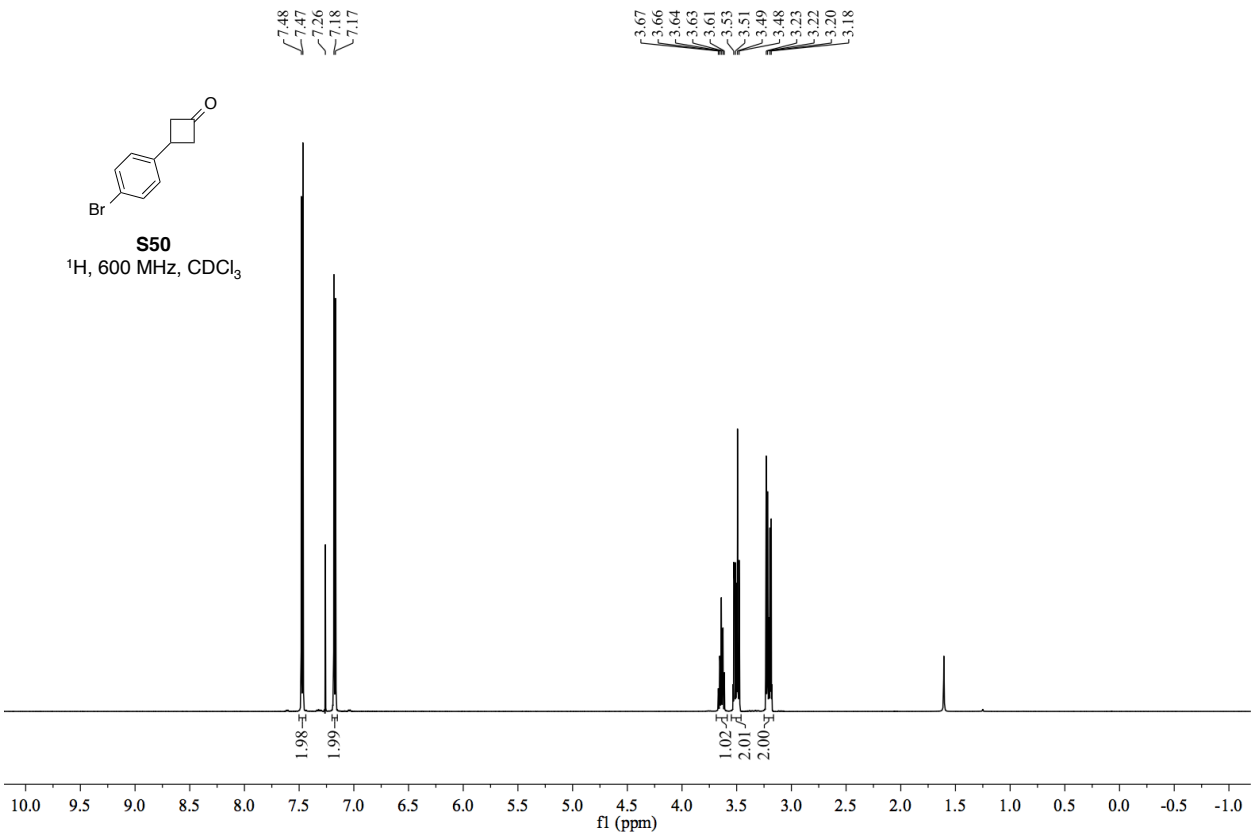
S48
^{13}C, 100 MHz, $CDCl_3$



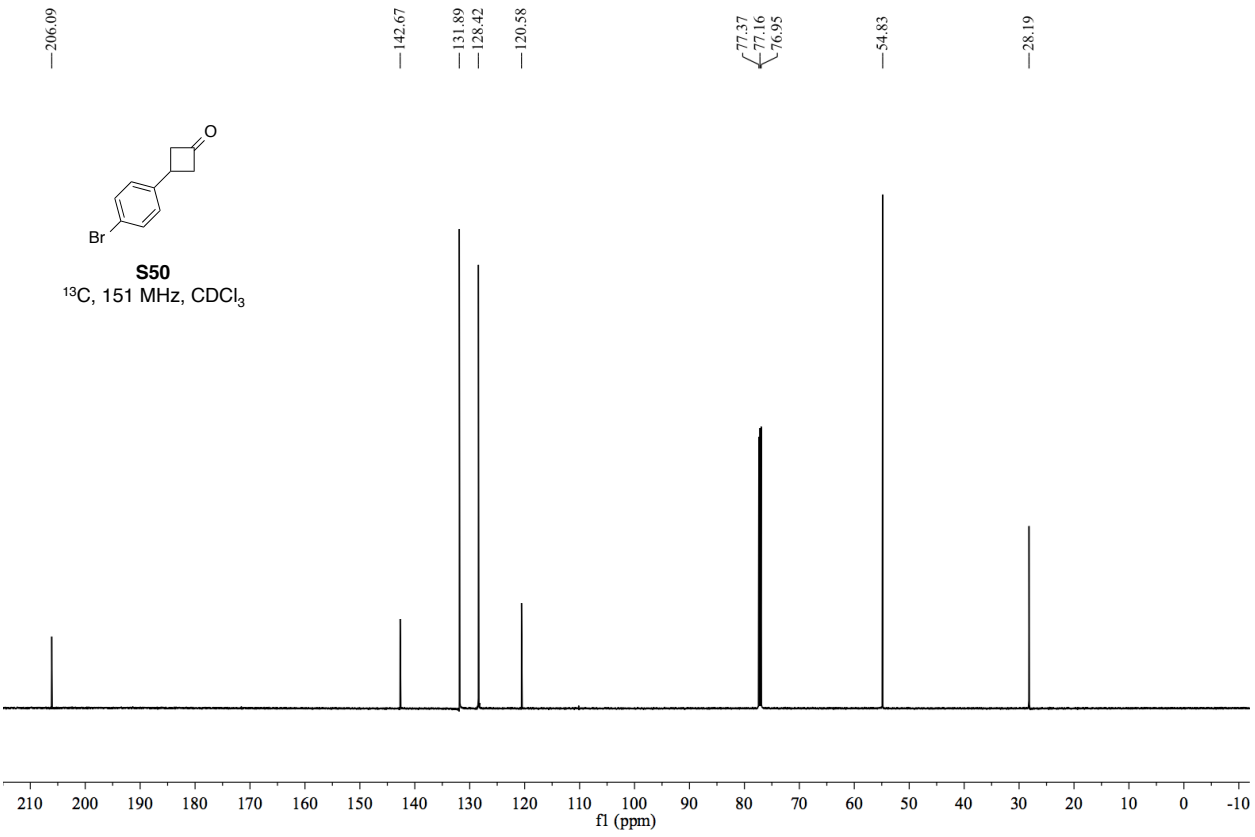
S49
^{1}H, 400 MHz, $CDCl_3$



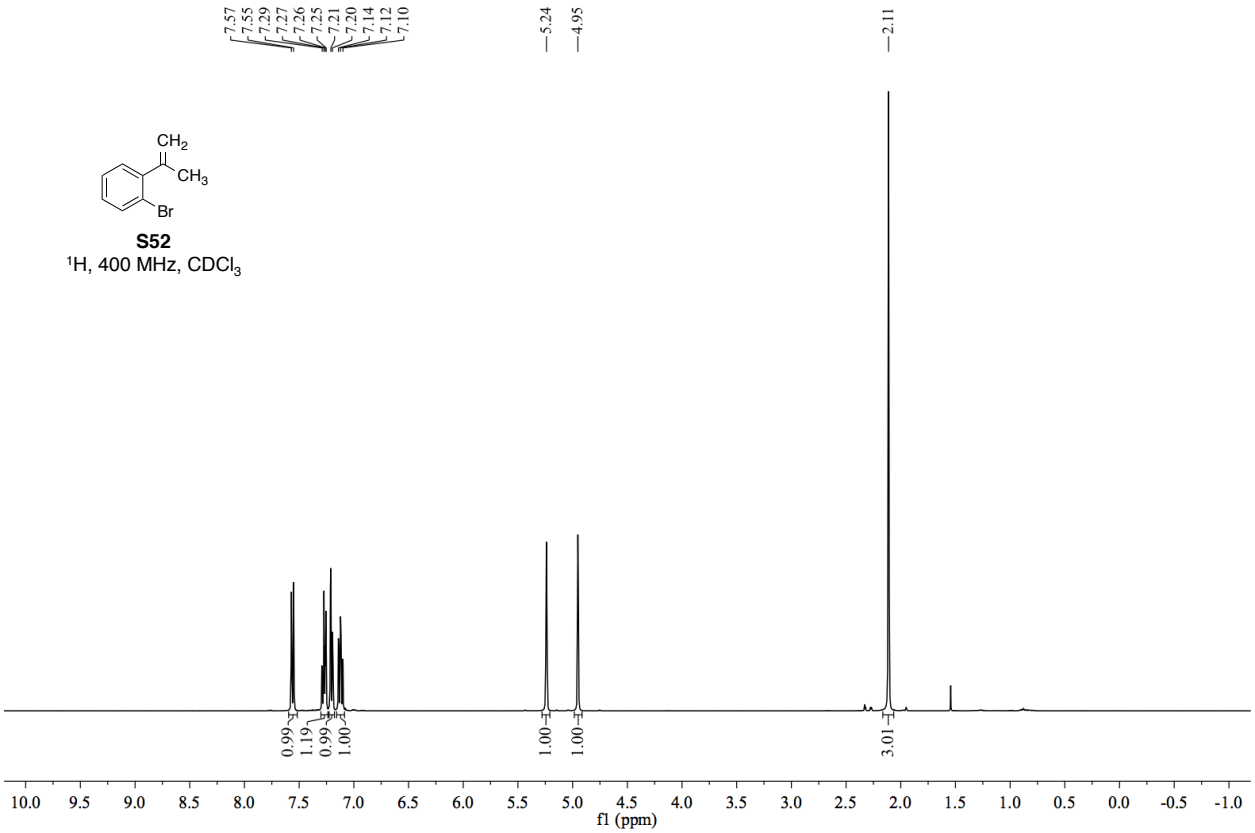
S49
^{13}C, 101 MHz, $CDCl_3$



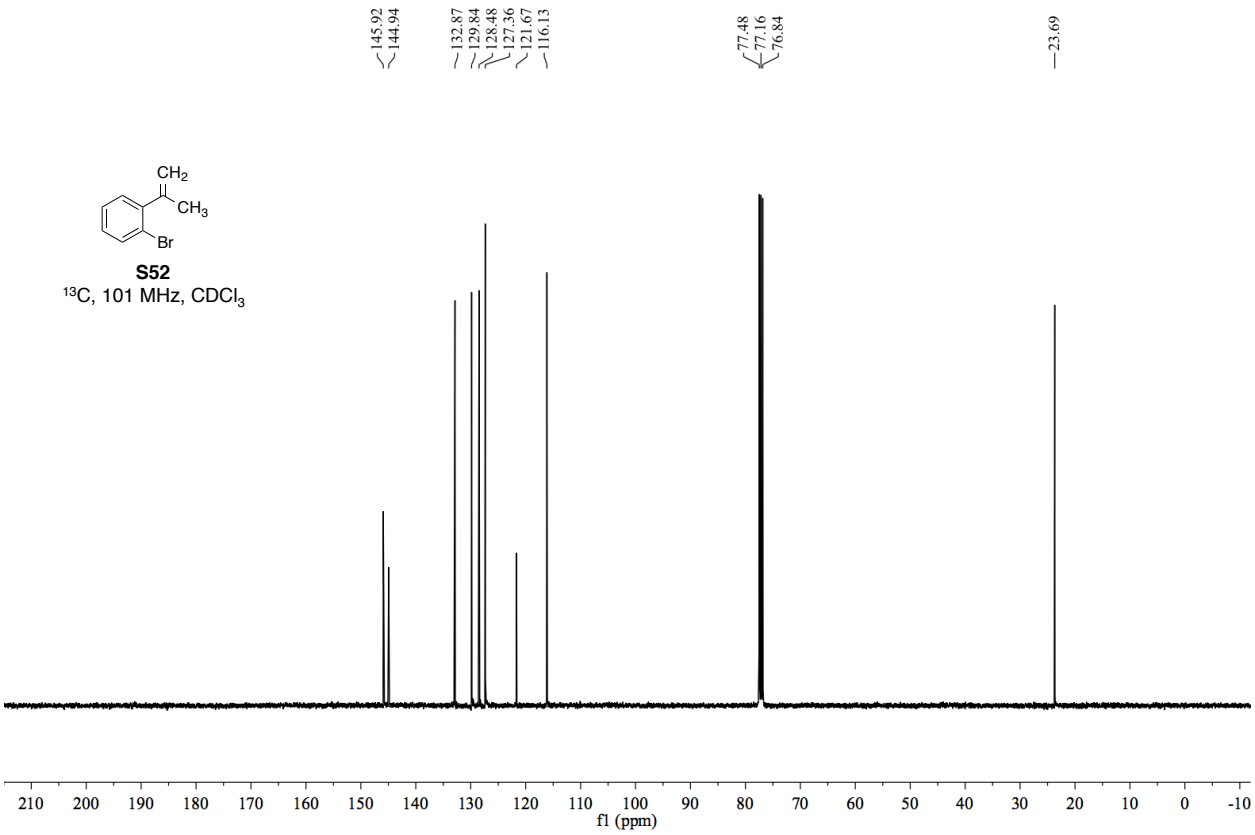
S50
^{1}H, 600 MHz, $CDCl_3$



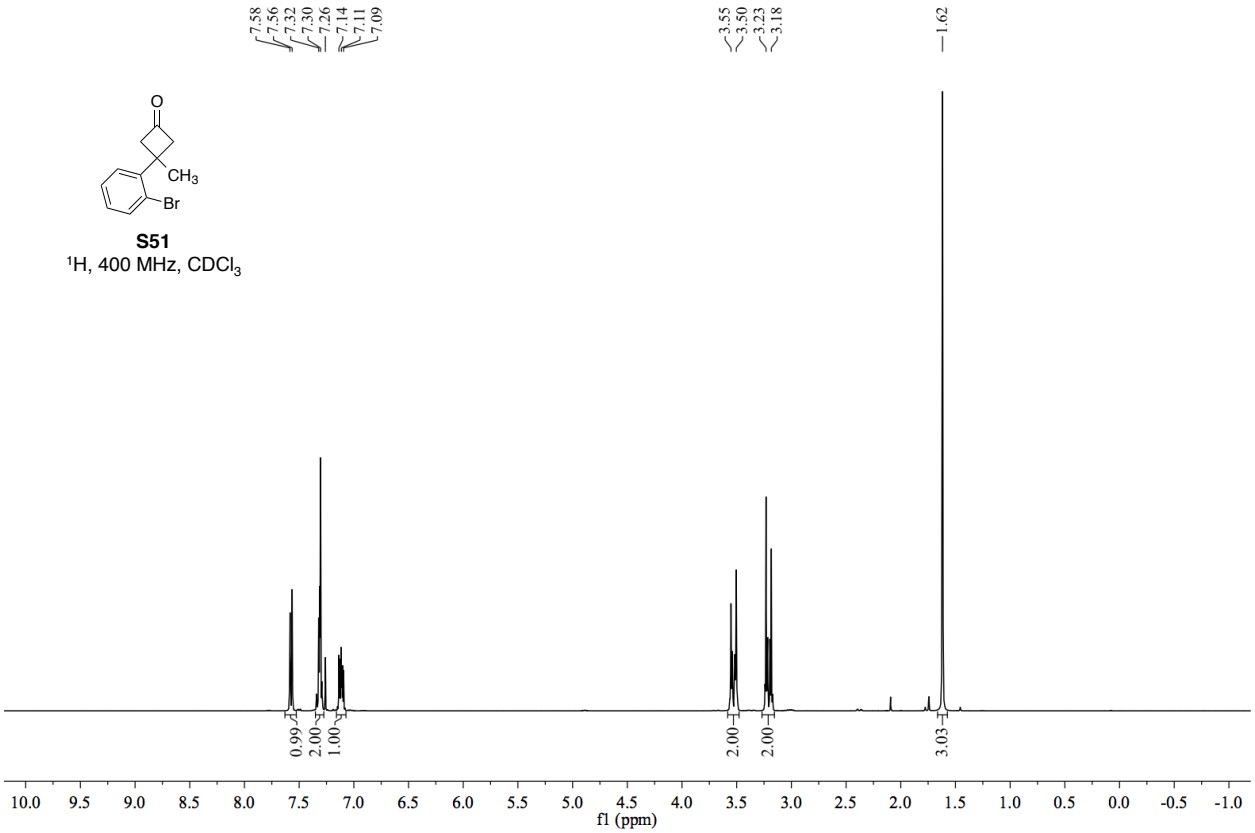
S50
^{13}C, 151 MHz, $CDCl_3$



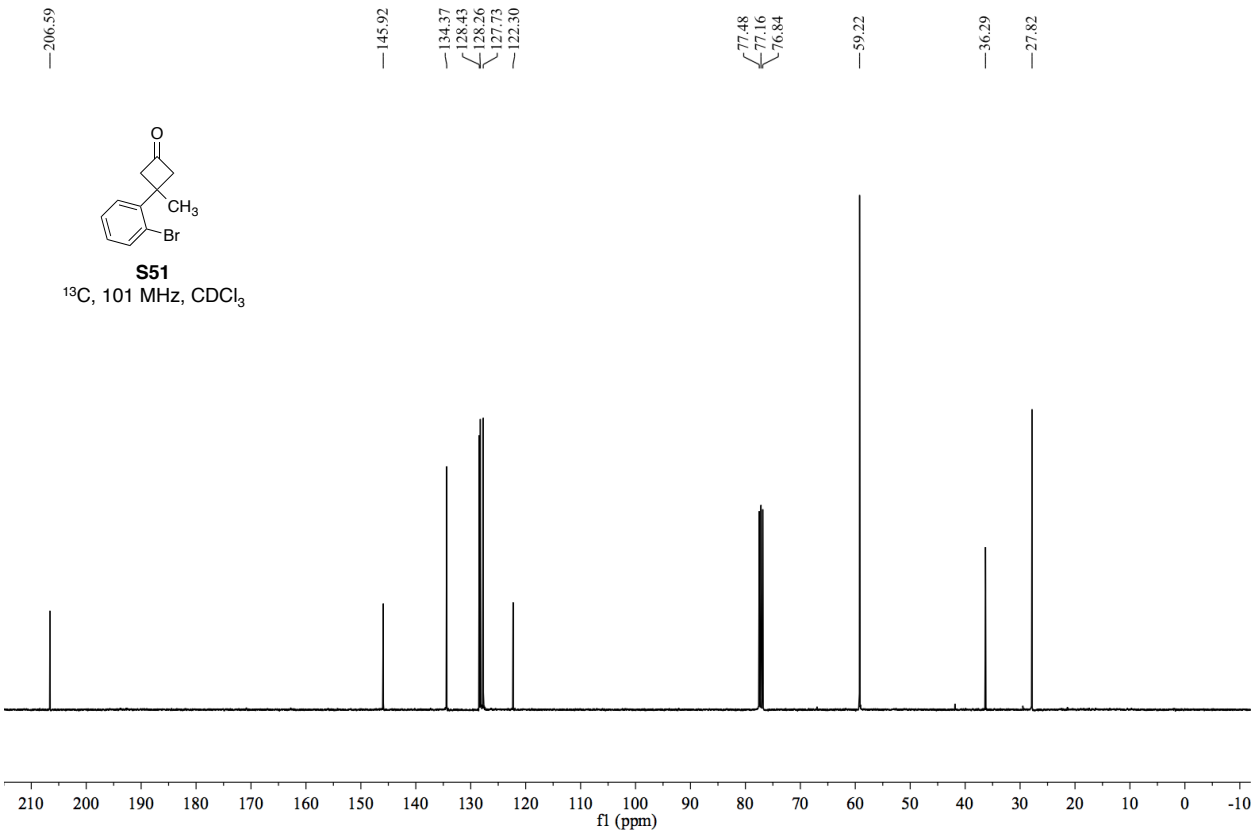
S52
^{1}H, 400 MHz, $CDCl_3$



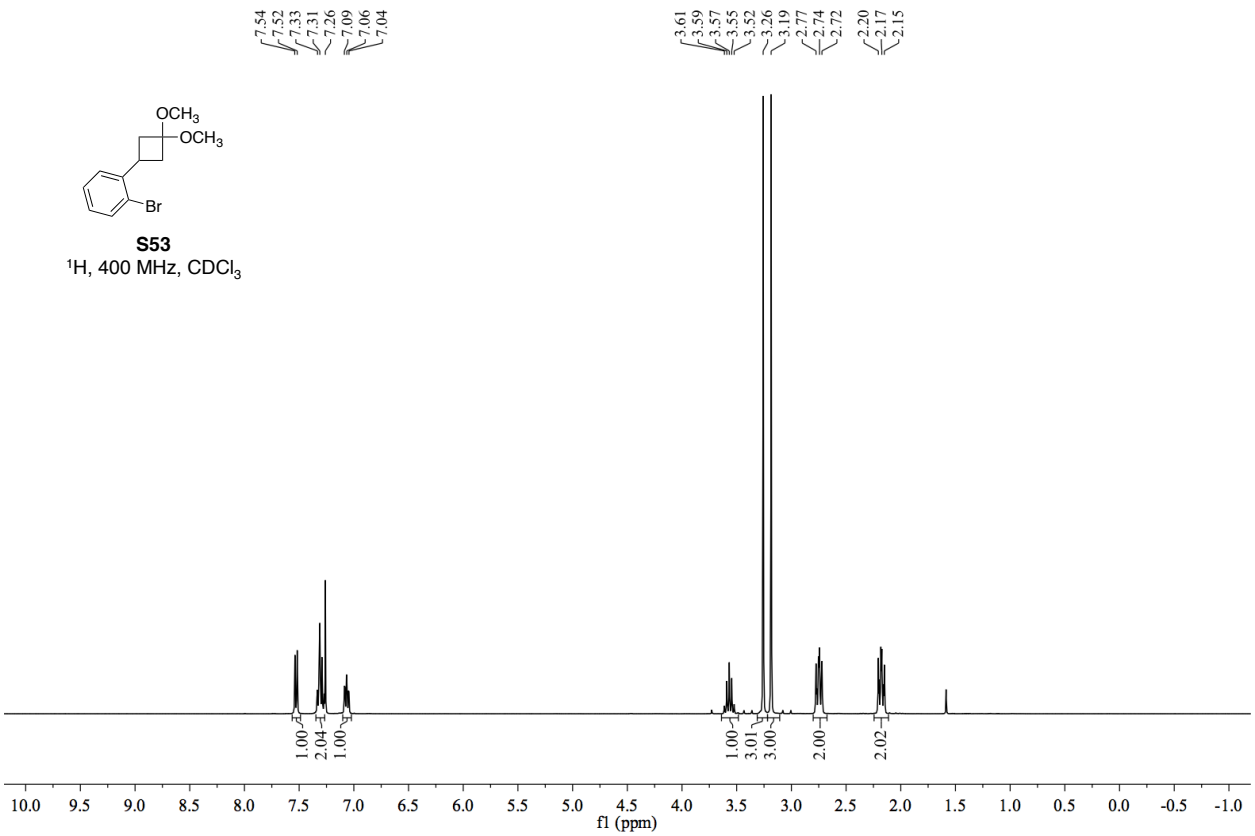
S52
^{13}C, 101 MHz, $CDCl_3$



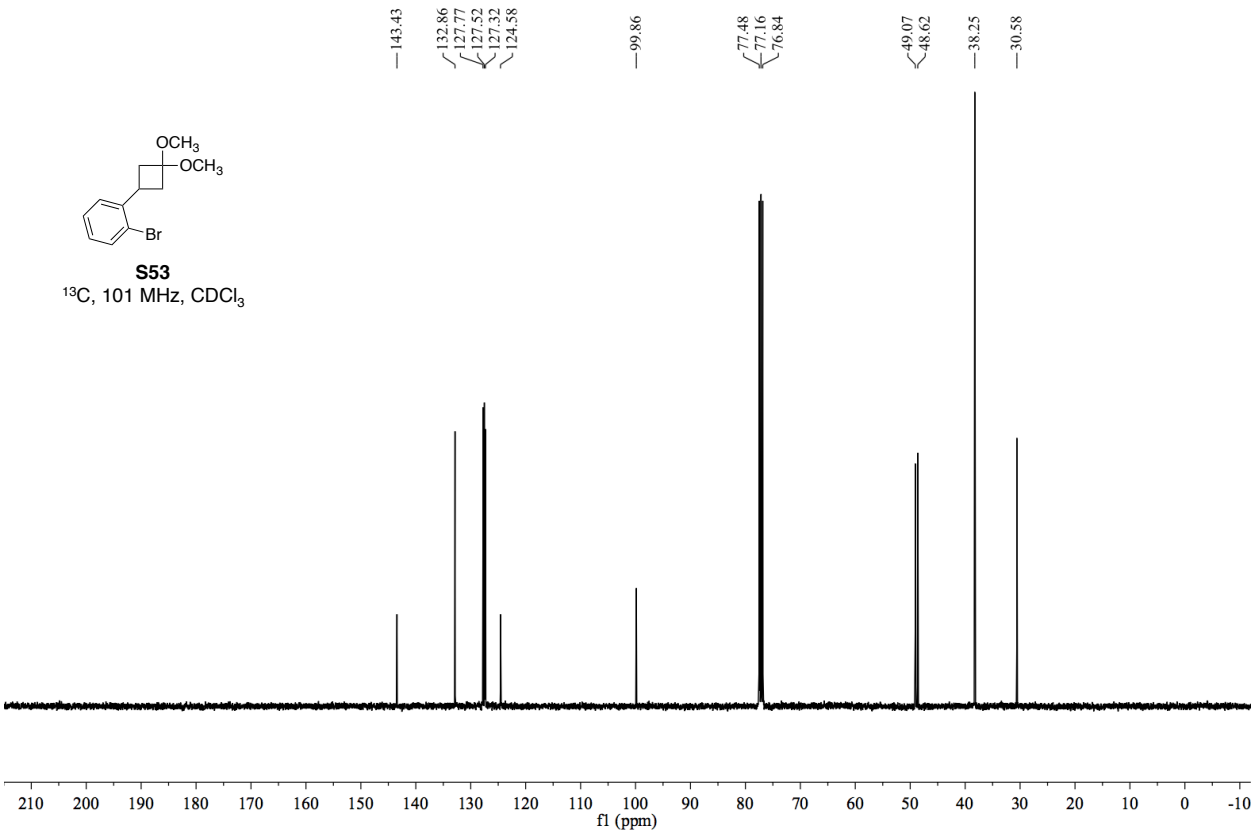
S51
^{1}H, 400 MHz, $CDCl_3$



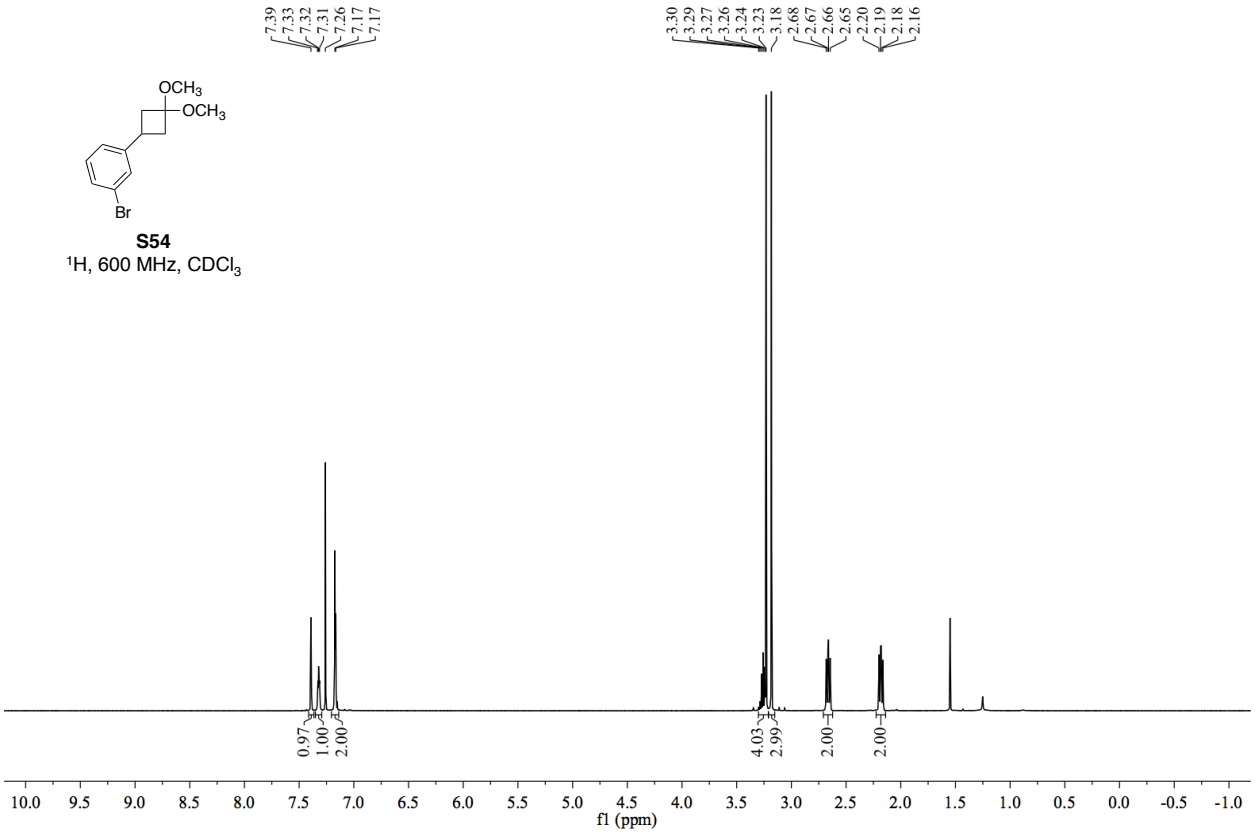
S51
^{13}C, 101 MHz, $CDCl_3$



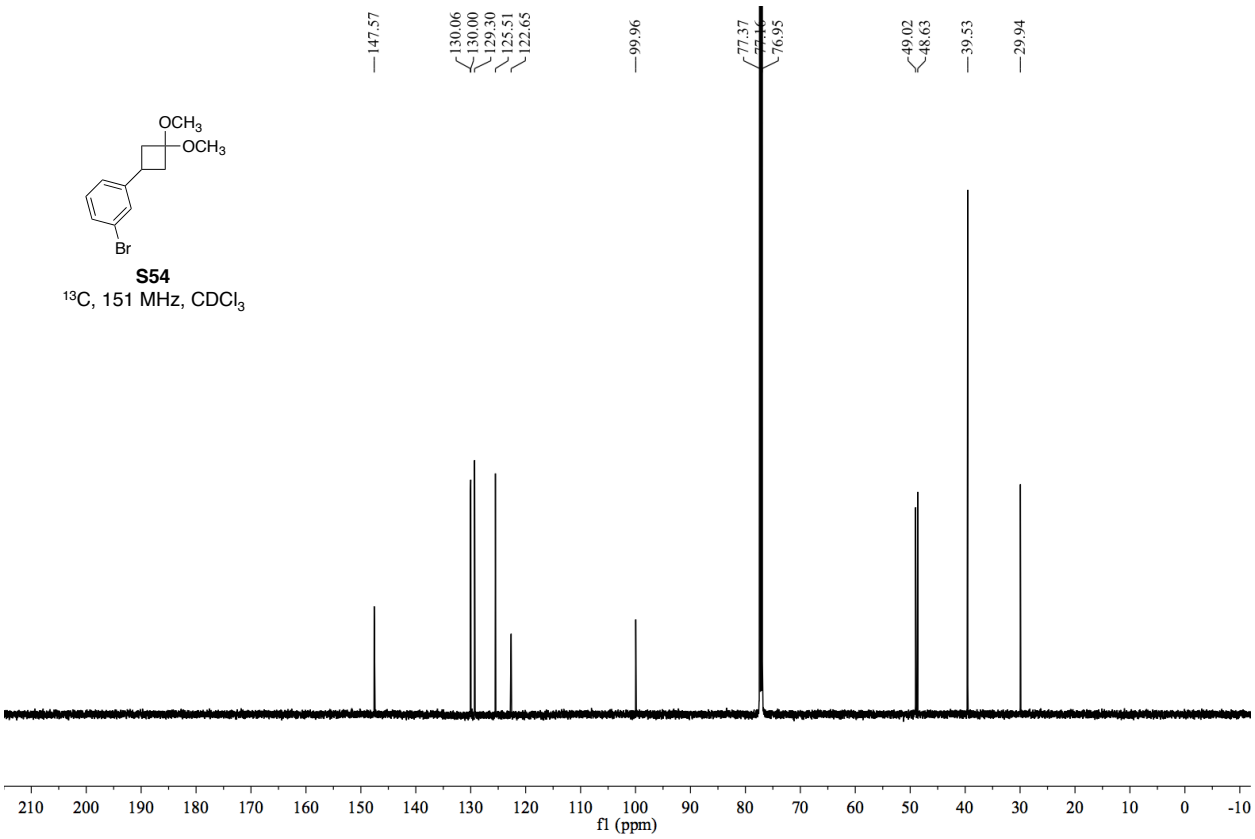
S53
^{1}H, 400 MHz, $CDCl_3$



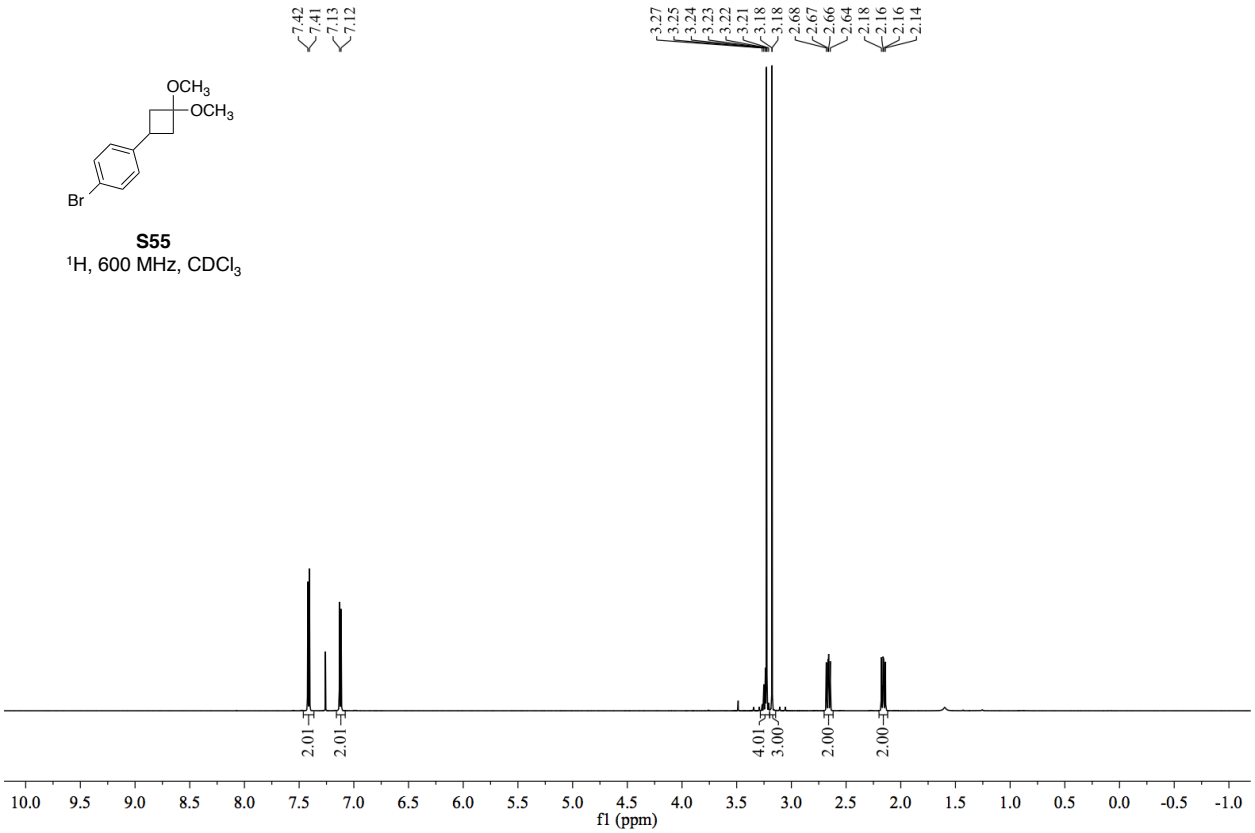
S53
^{13}C, 101 MHz, $CDCl_3$



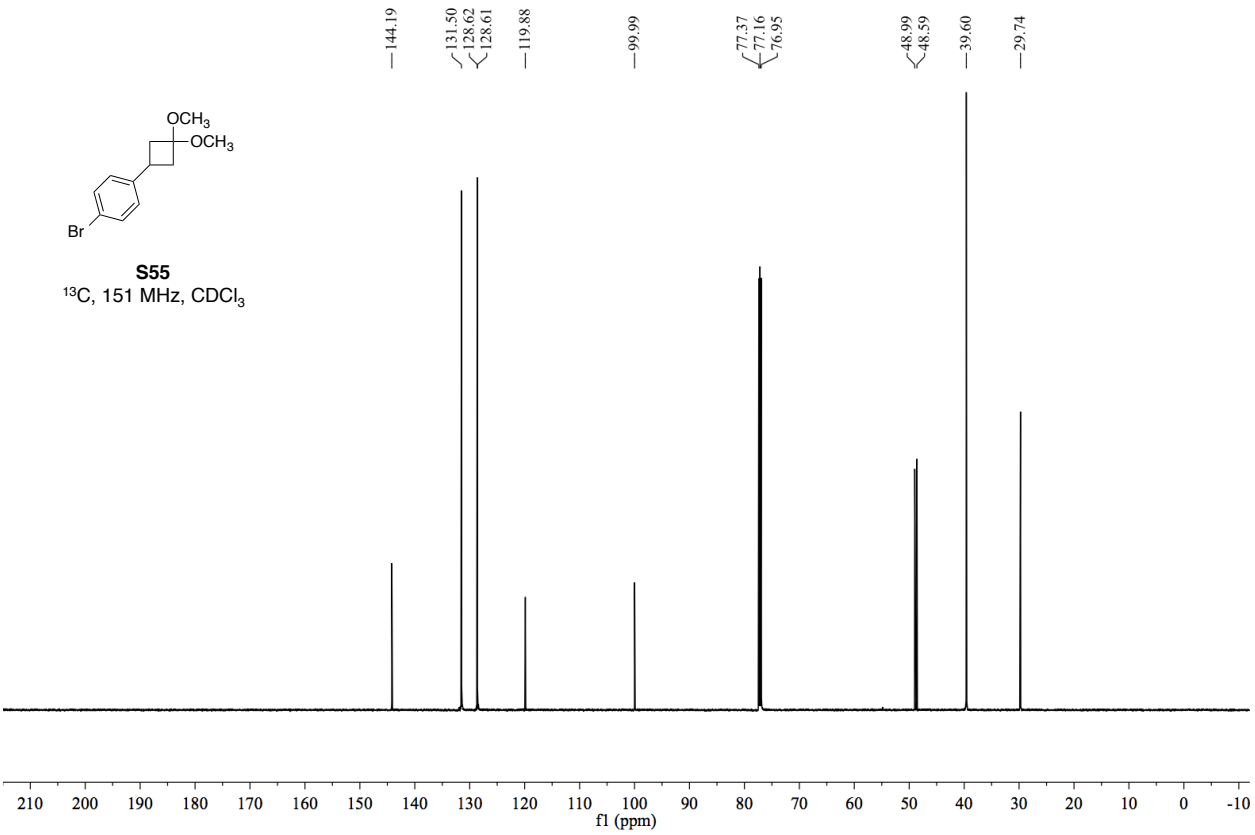
S54
^{1}H, 600 MHz, $CDCl_3$



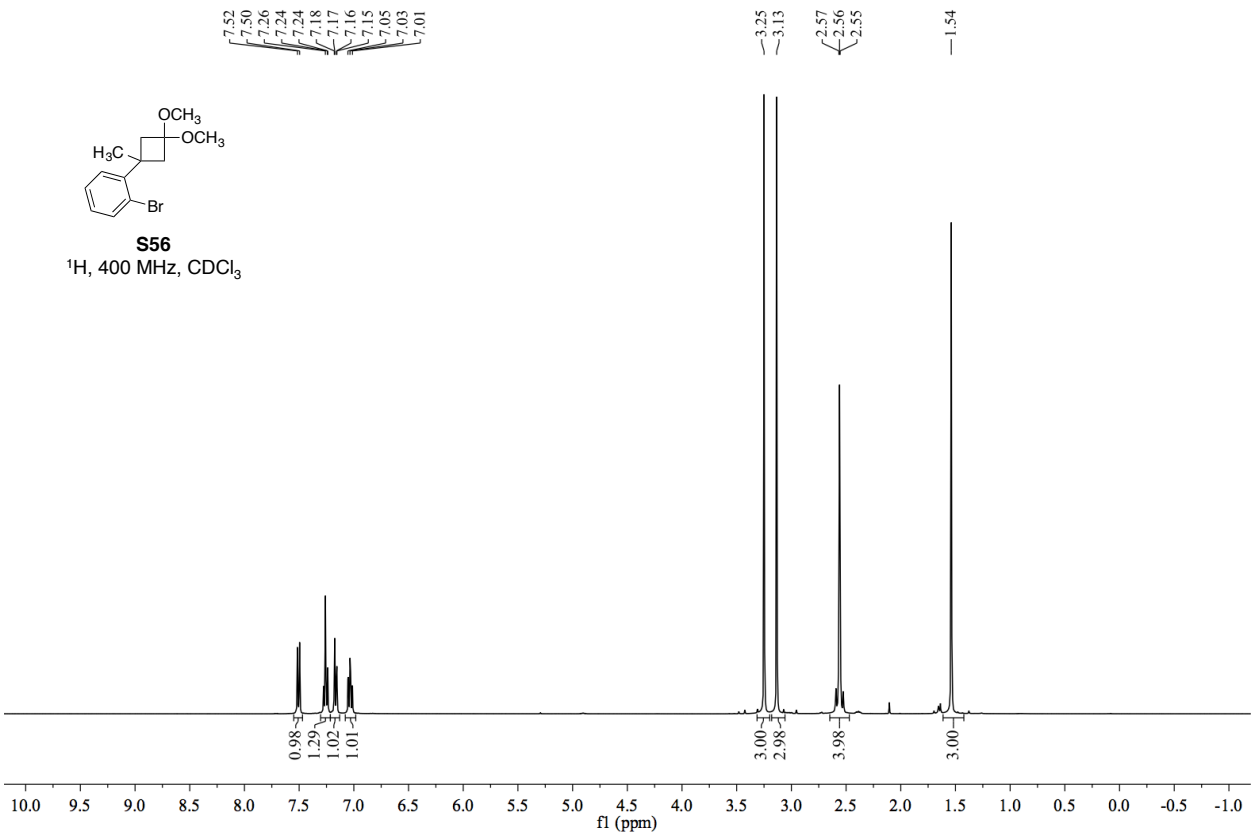
S54
^{13}C, 151 MHz, $CDCl_3$



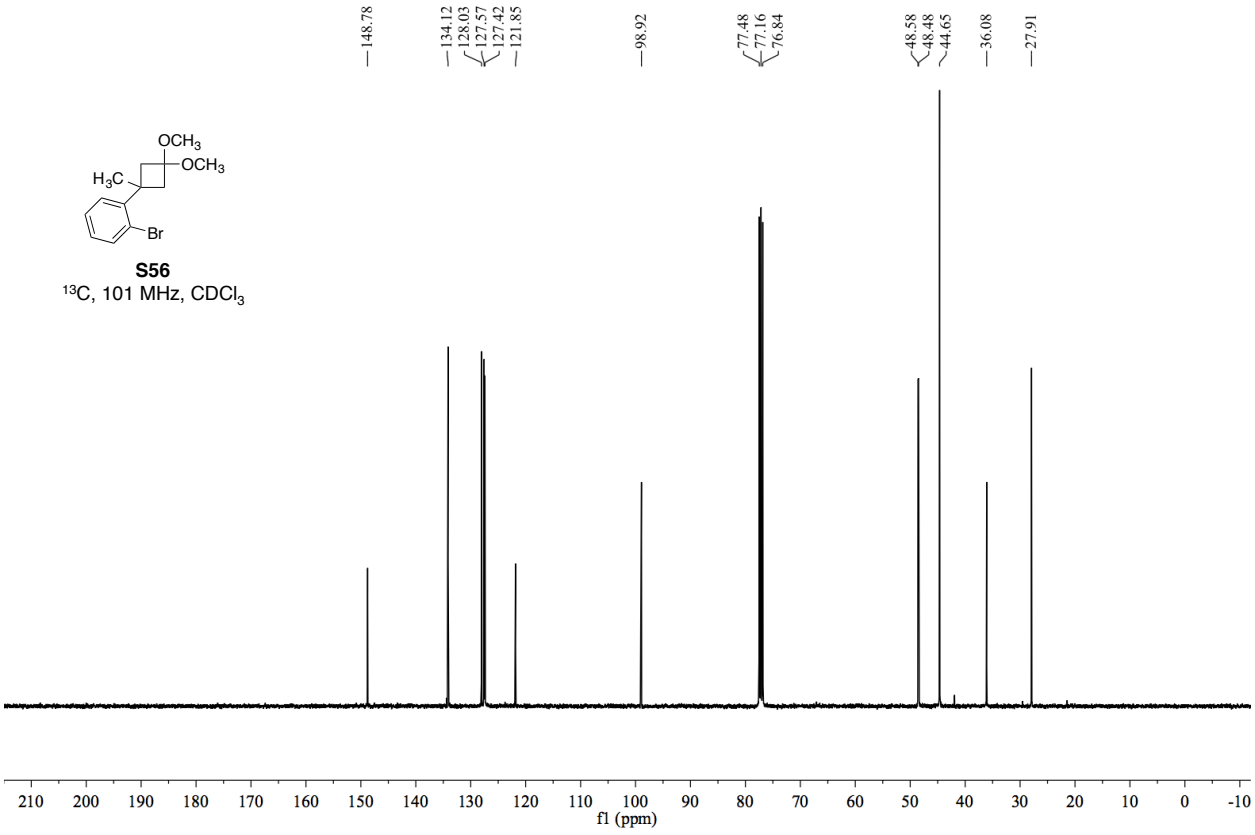
S55
^{1}H, 600 MHz, $CDCl_3$



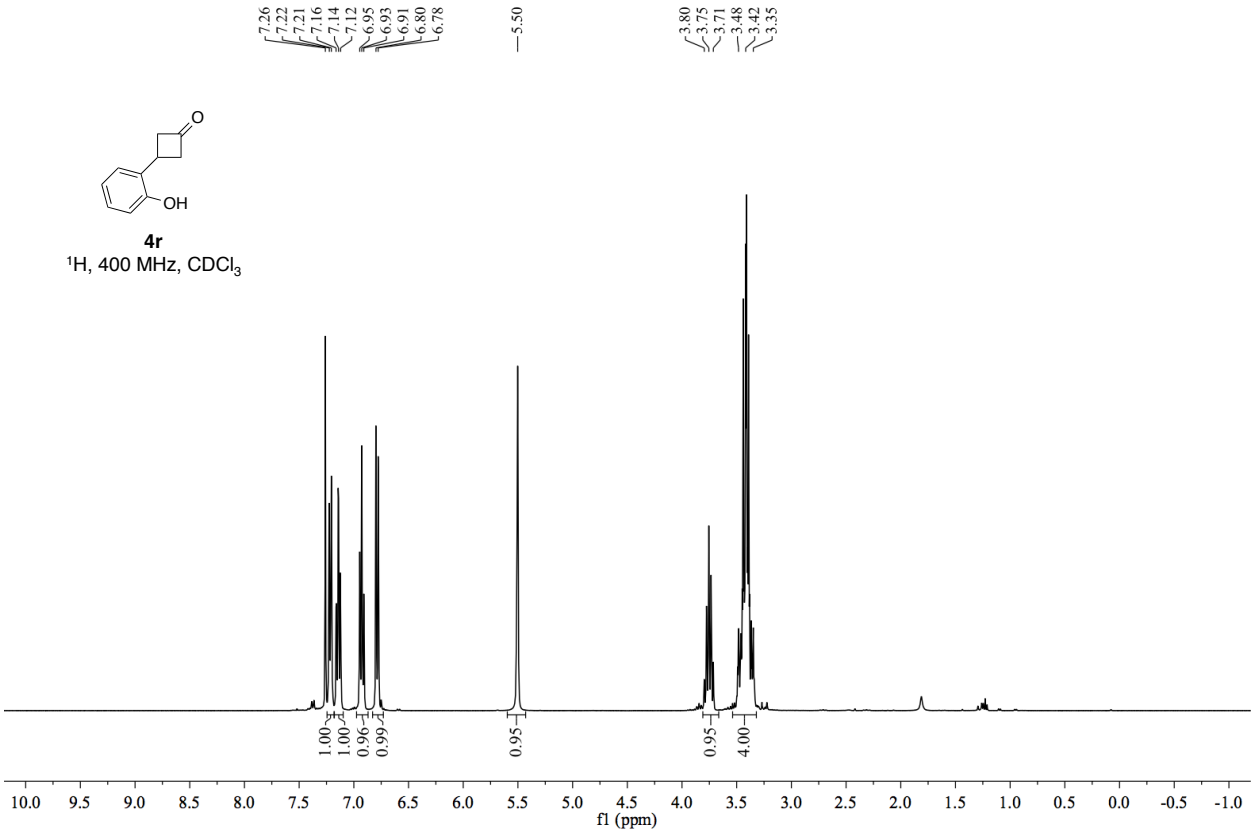
S55
^{13}C, 151 MHz, $CDCl_3$

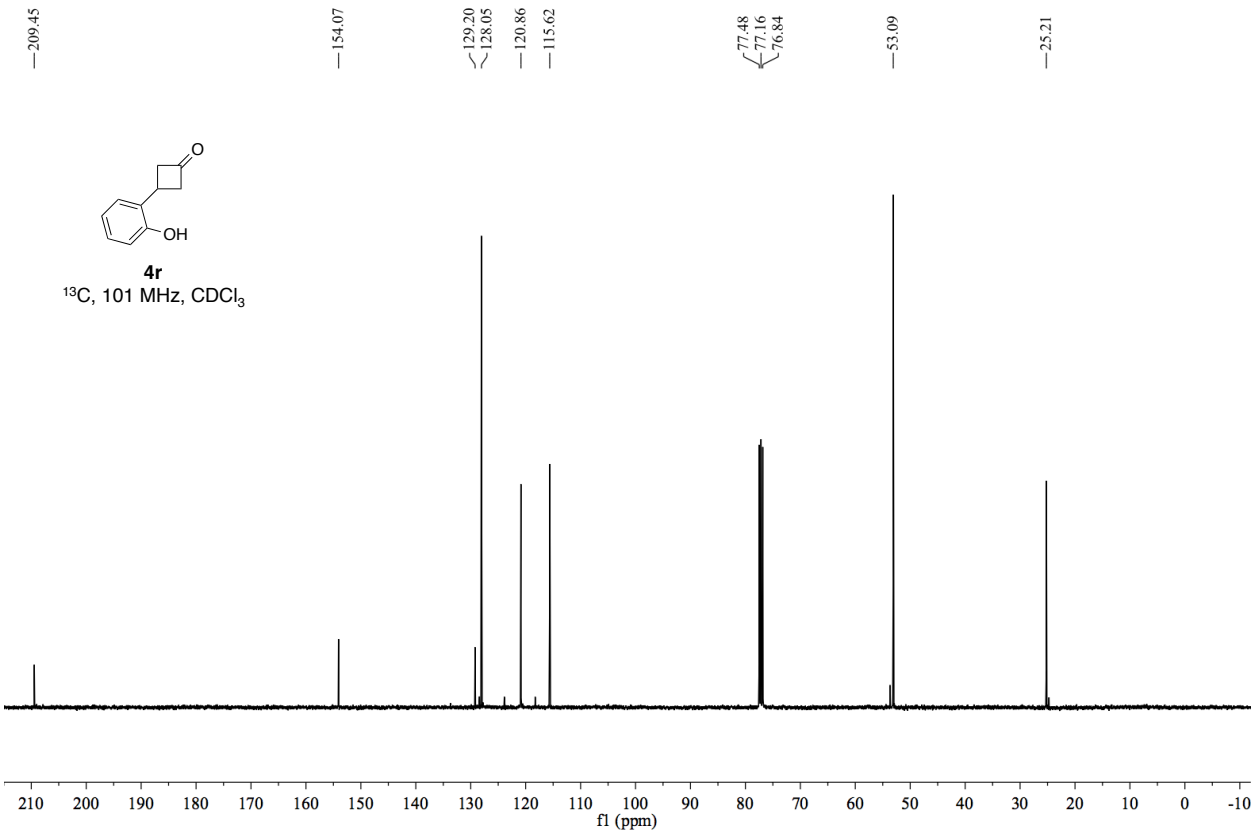


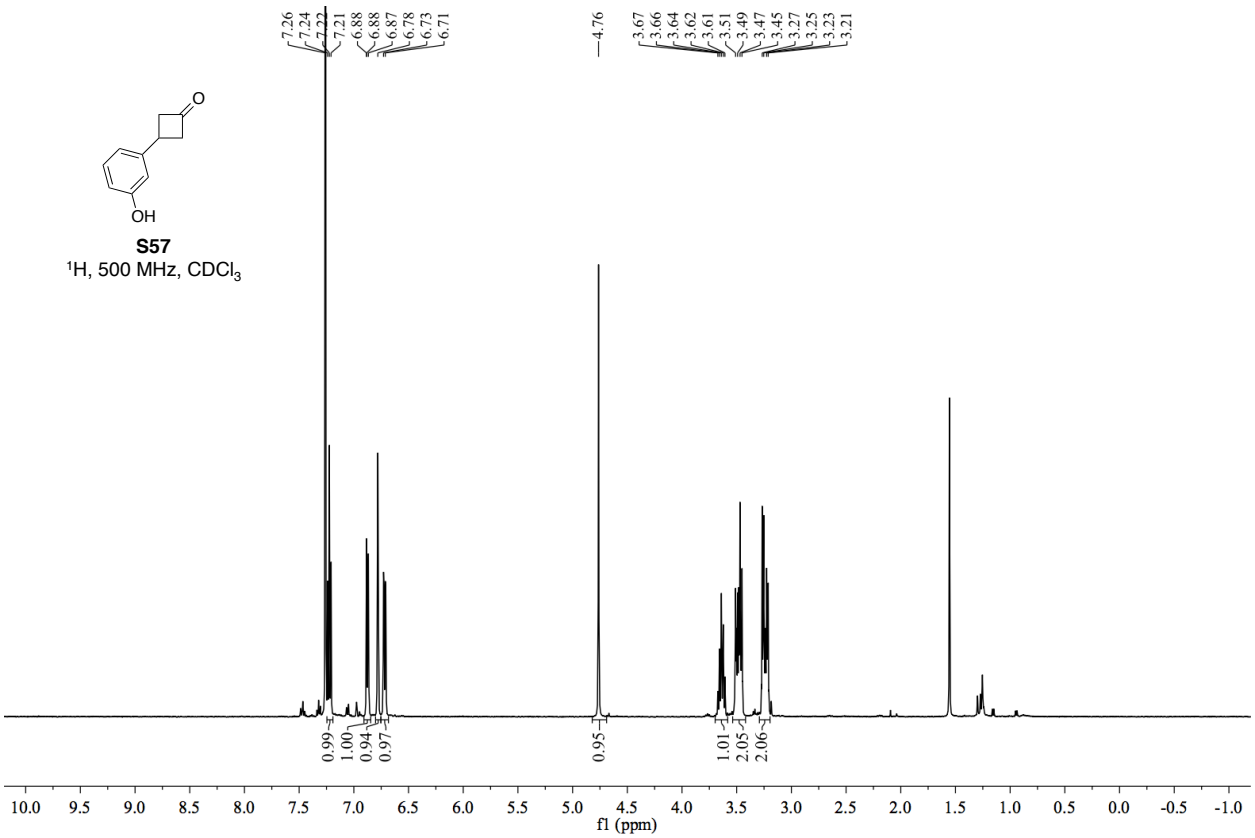
S56
^{1}H, 400 MHz, $CDCl_3$



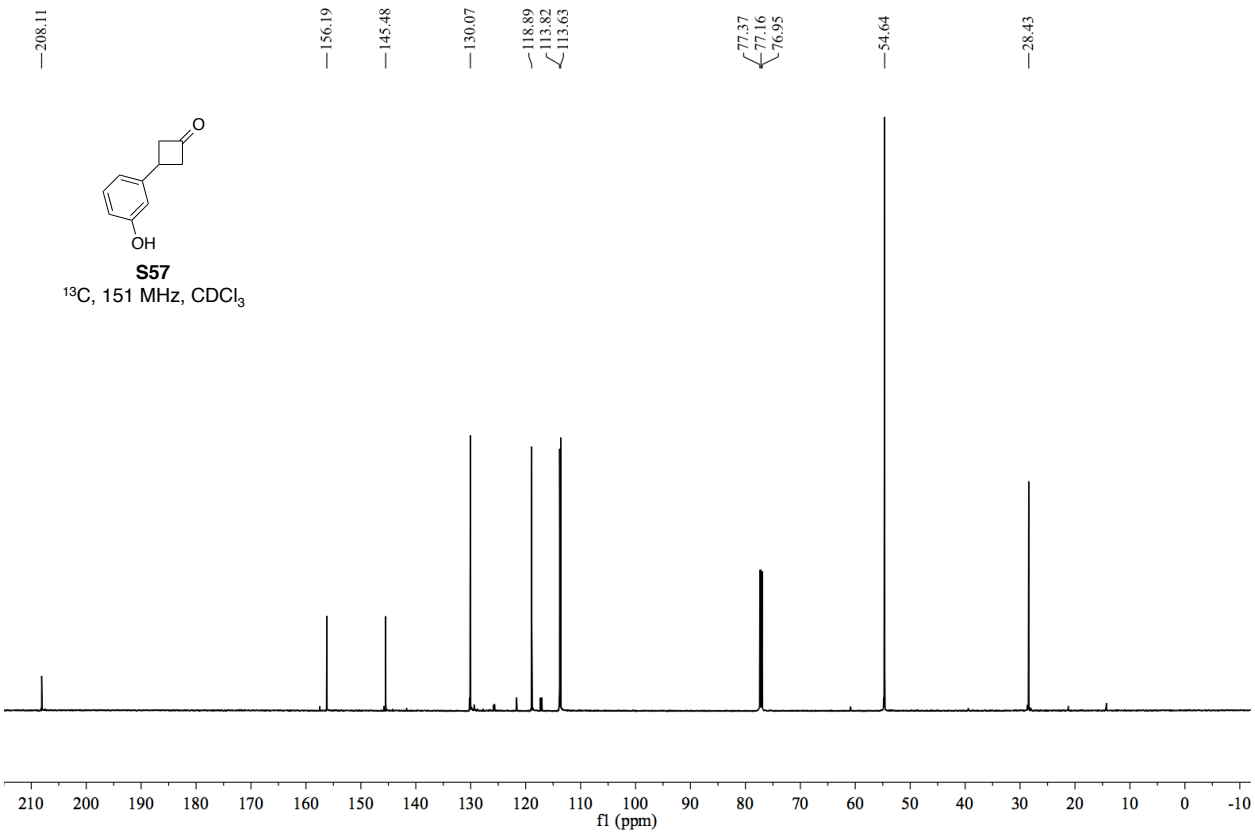
S56
^{13}C, 101 MHz, $CDCl_3$


7.26
7.22
7.21
7.16
7.14
7.12
6.95
6.93
6.91
6.80
6.78
5.50
3.80
3.75
3.71
3.48
3.42
3.35
O
OH
4r
1H, 400 MHz, CDCl3
1.00
1.00
0.96
0.99
0.95
0.95
4.00
f1 (ppm)

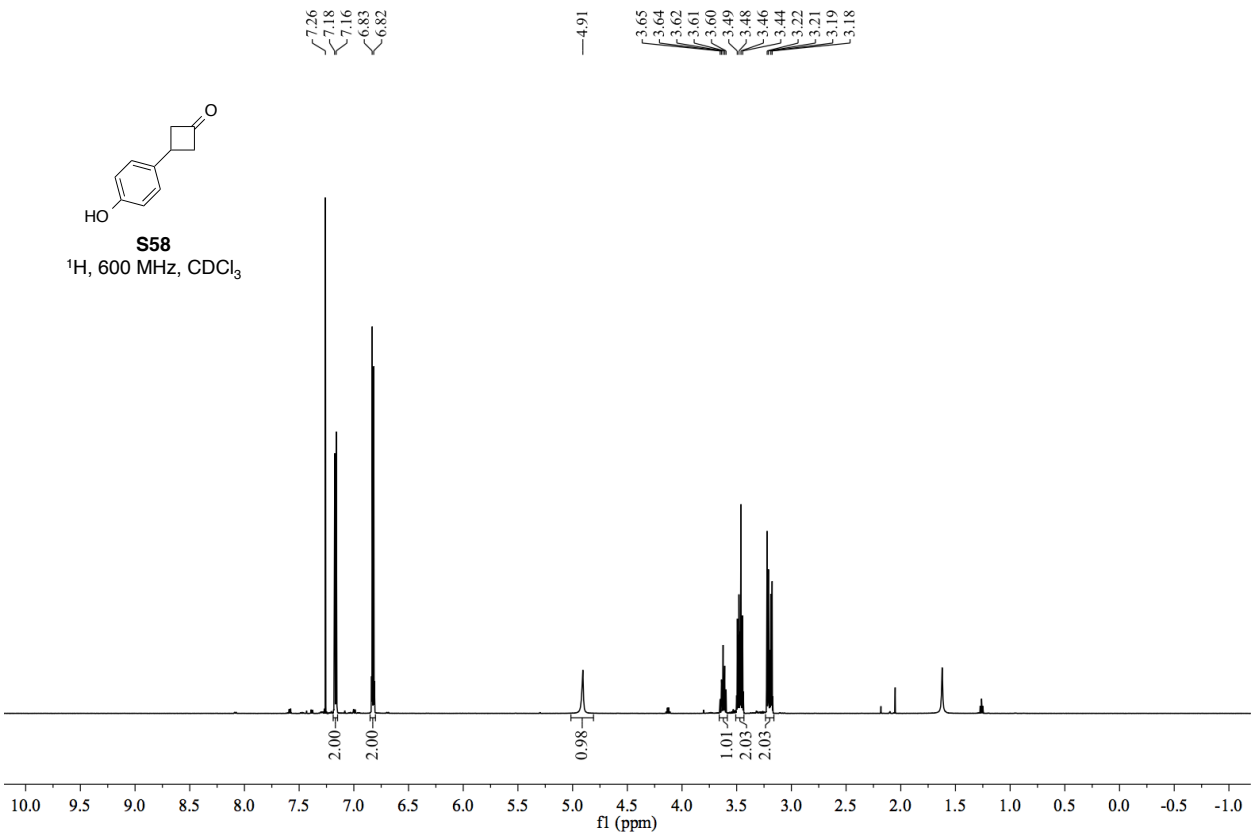

209.45
154.07
129.20
128.05
120.86
115.62
77.48
77.16
76.84
53.09
25.21
O
OH
4r
13C, 101 MHz, CDCl3
f1 (ppm)



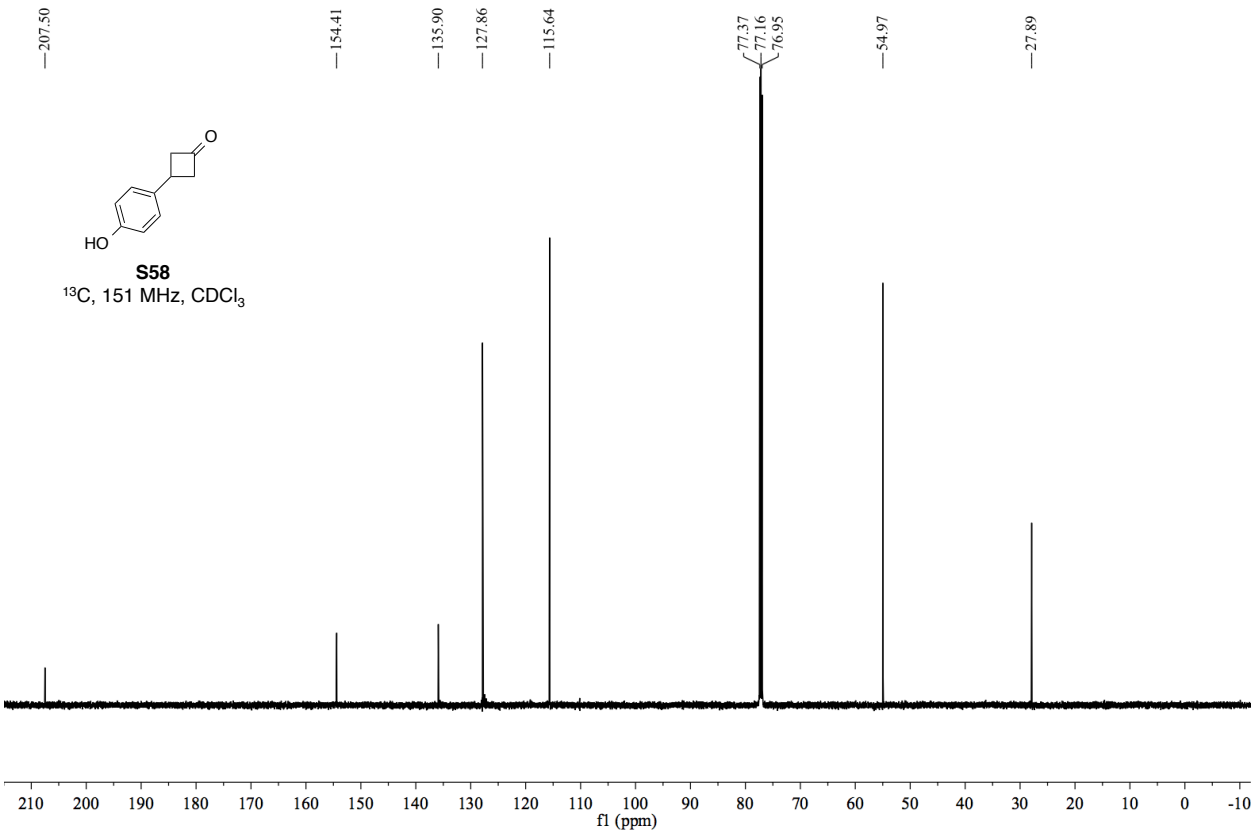
S57
^{1}H, 500 MHz, $CDCl_3$



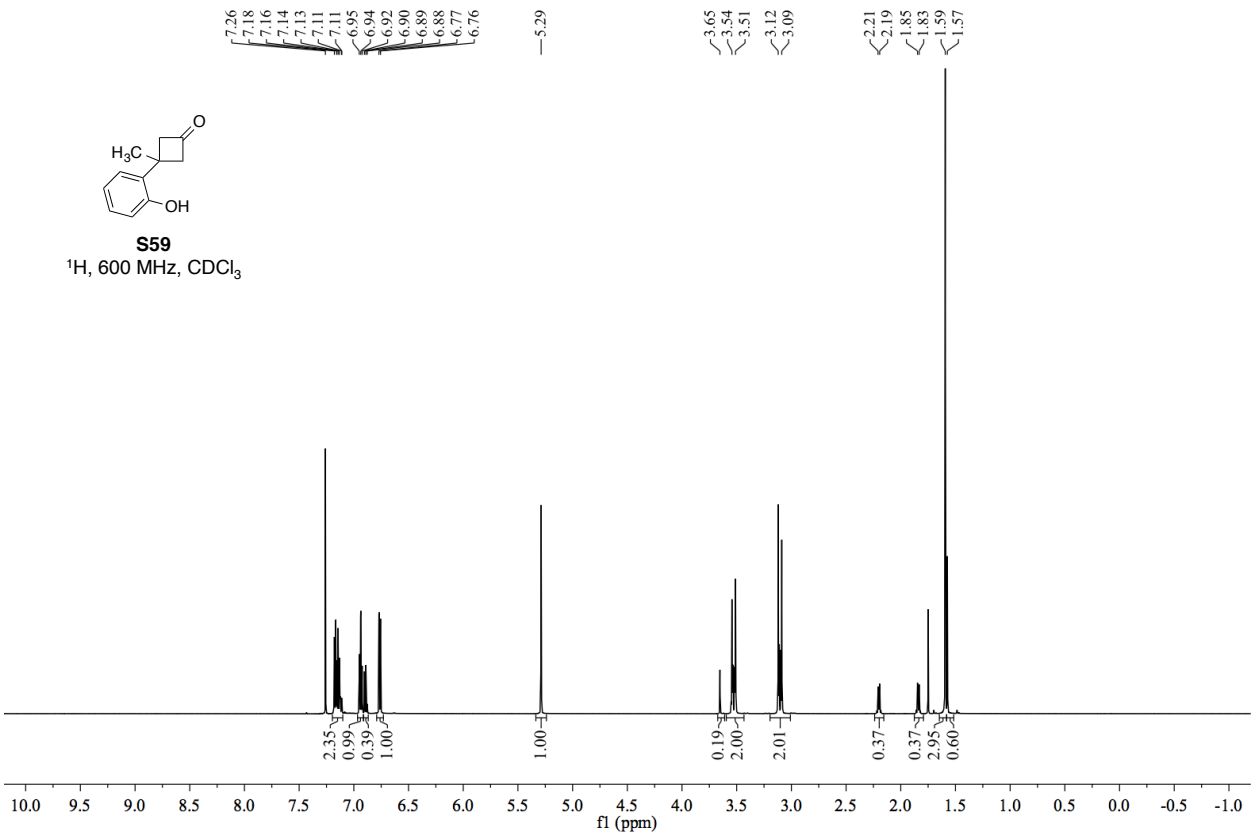
S57
^{13}C, 151 MHz, $CDCl_3$



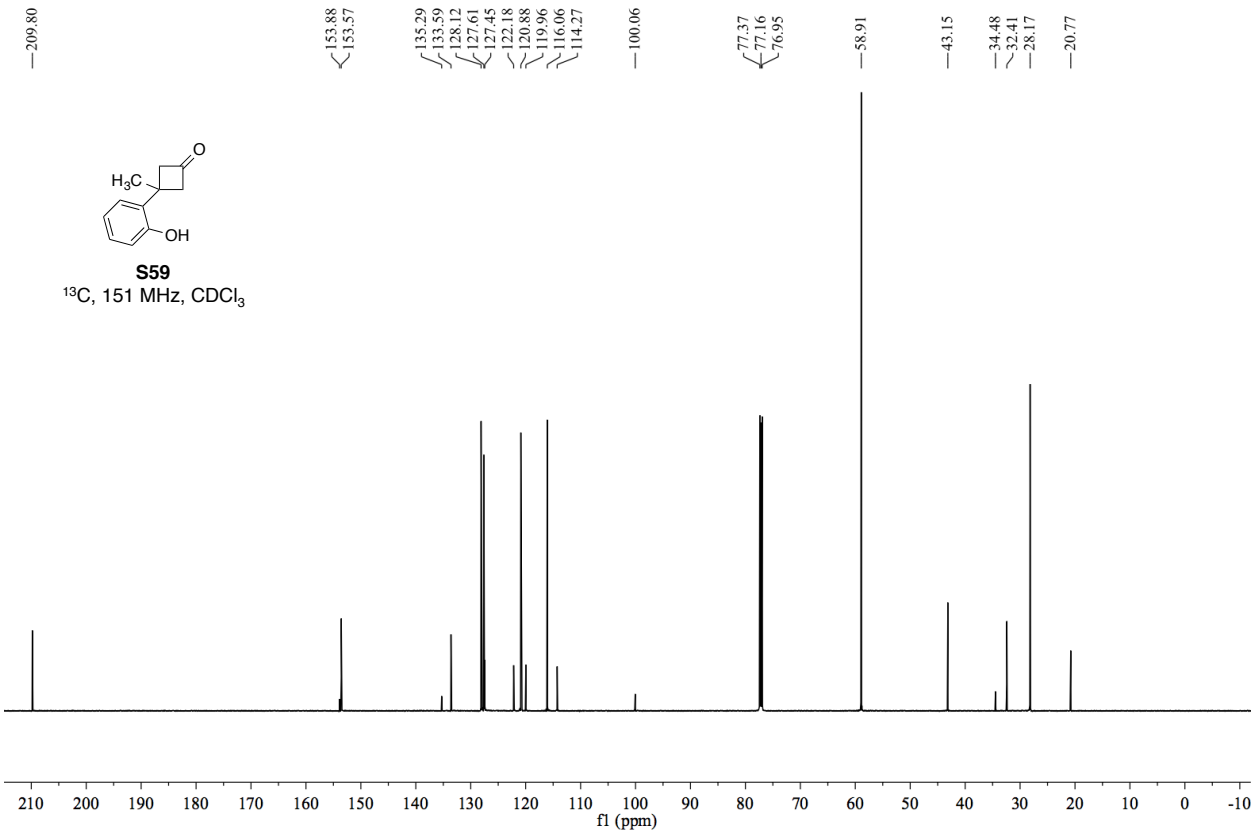
S58
^{1}H, 600 MHz, $CDCl_3$



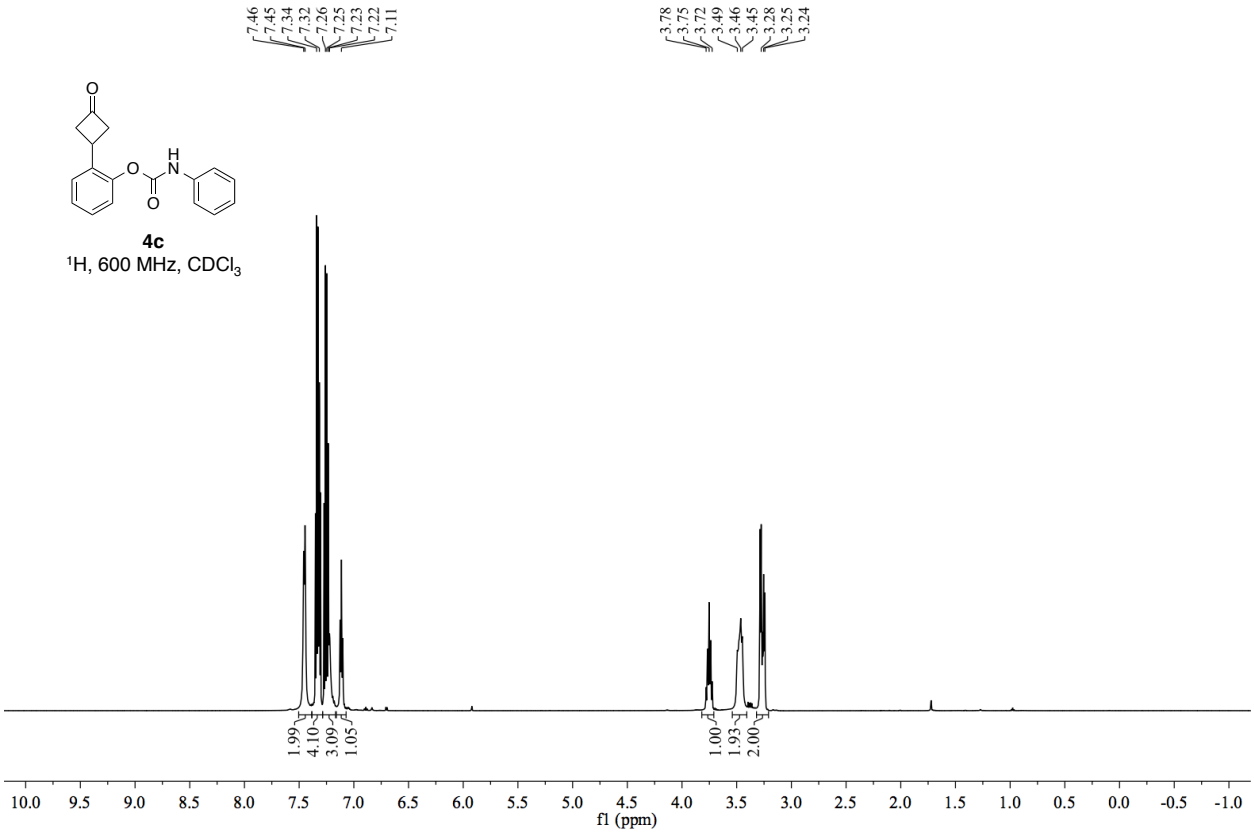
S58
^{13}C, 151 MHz, $CDCl_3$



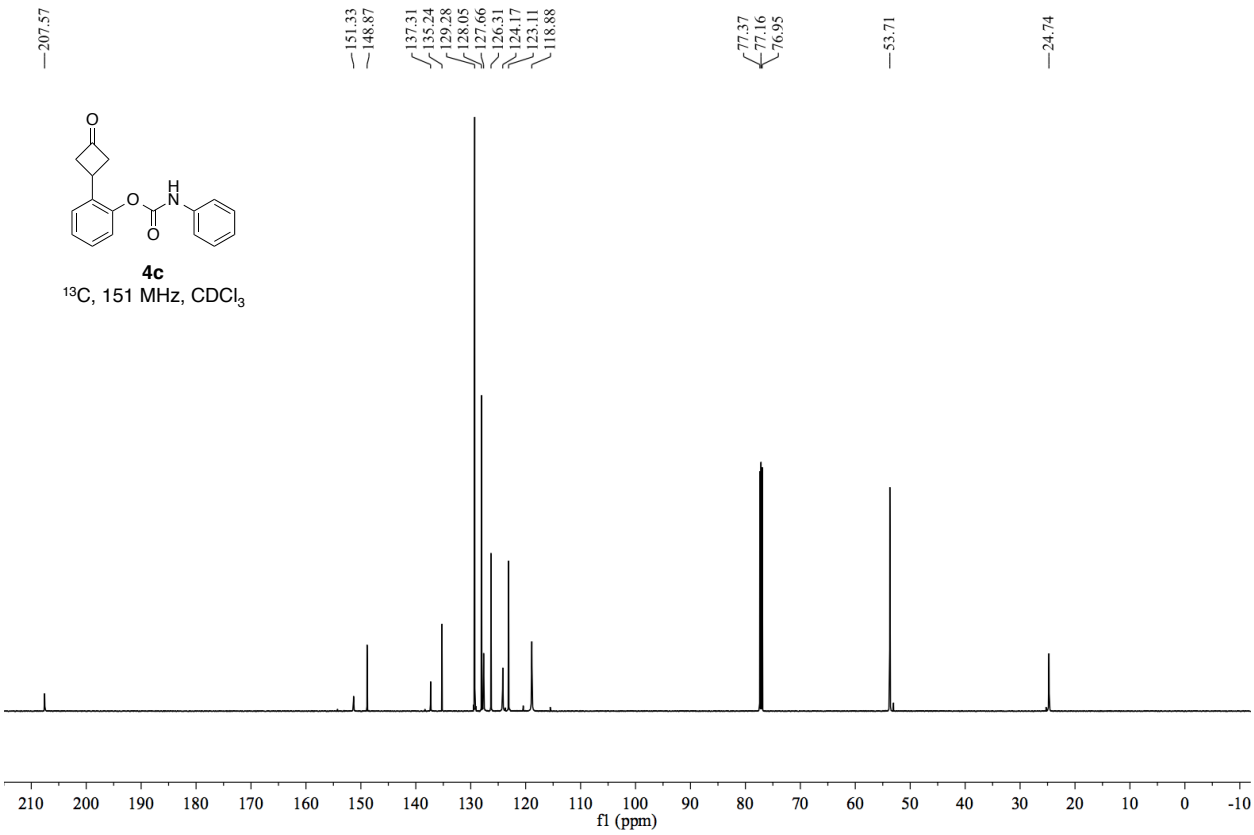
S59
^{1}H, 600 MHz, $CDCl_3$



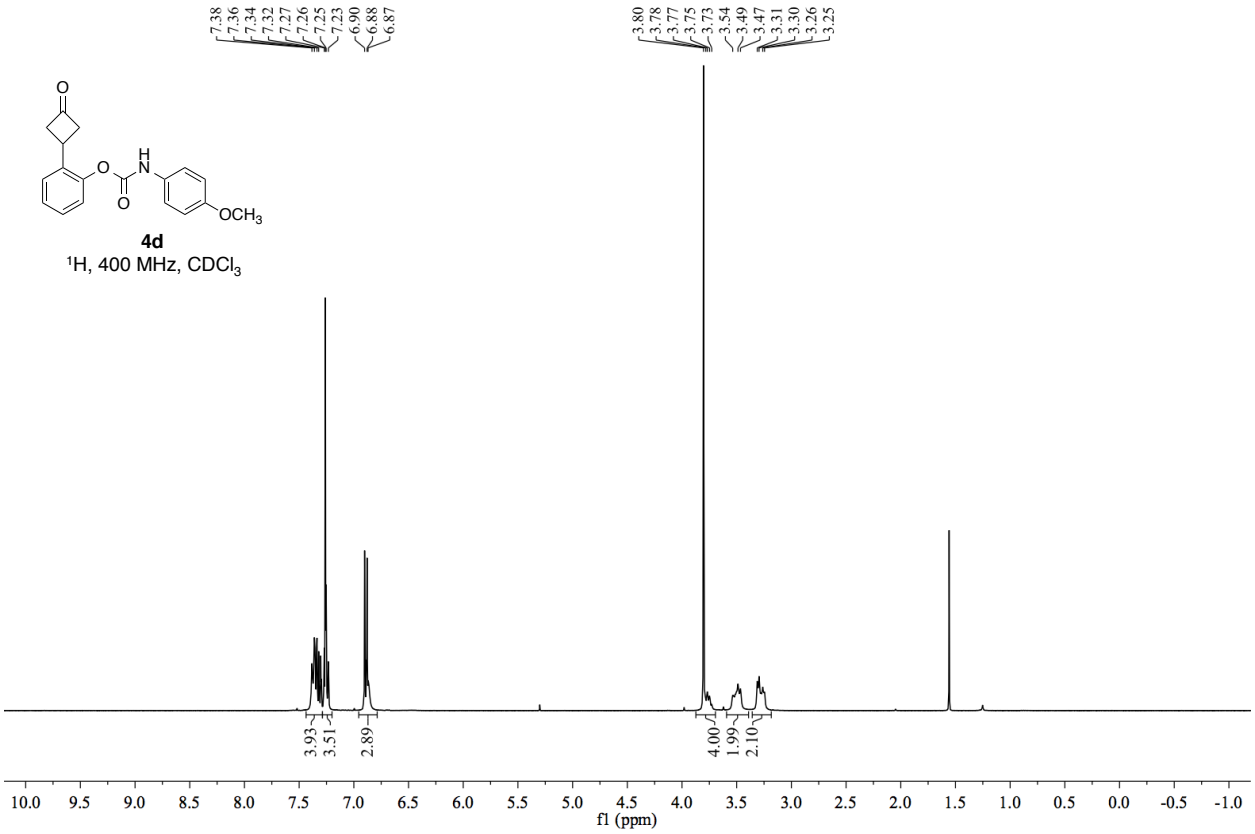
S59
^{13}C, 151 MHz, $CDCl_3$

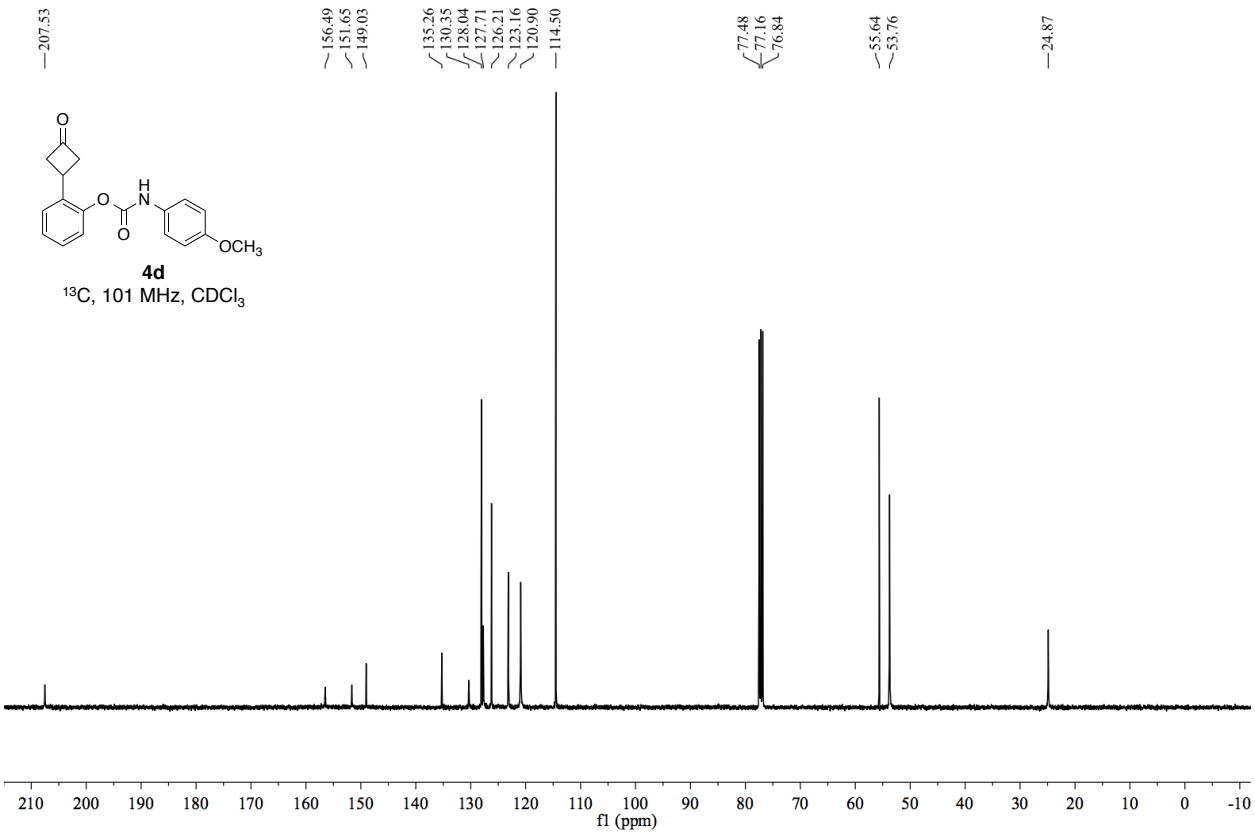


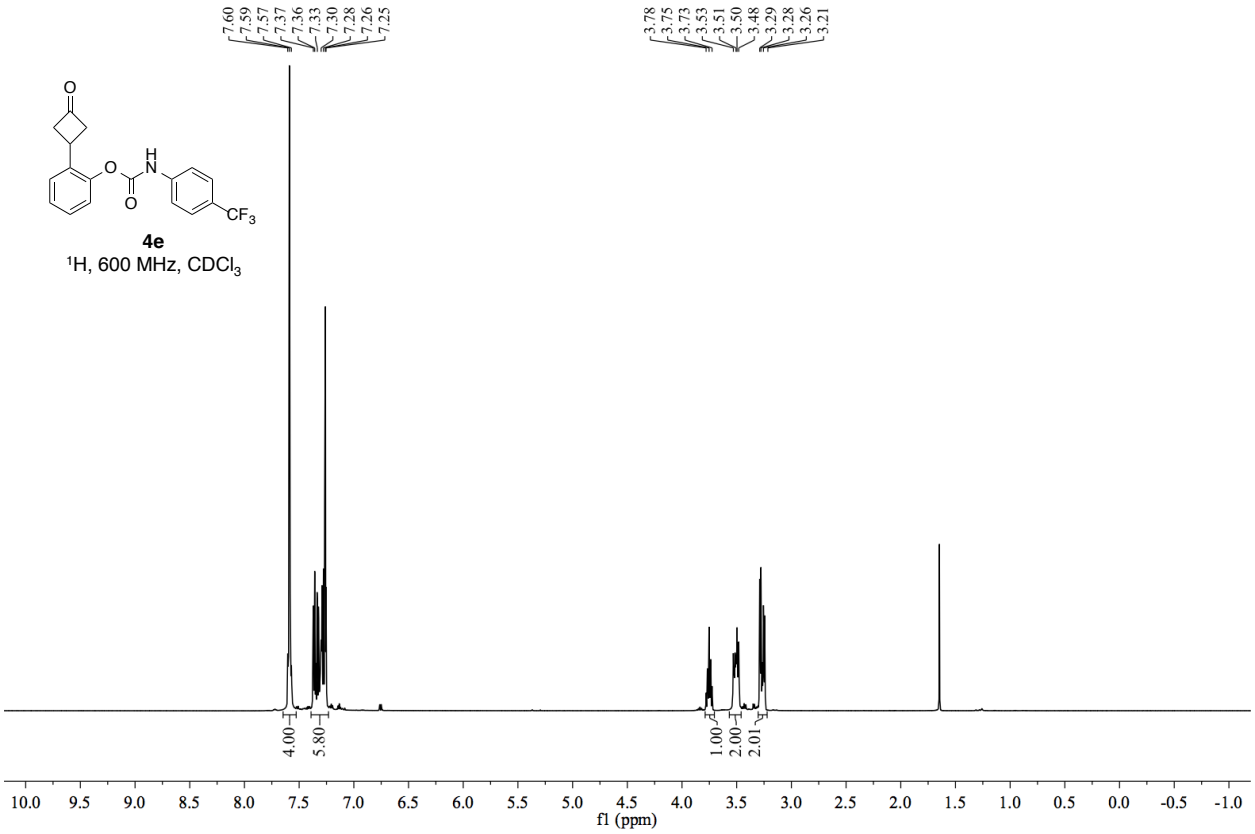
4c
^{1}H, 600 MHz, $CDCl_3$



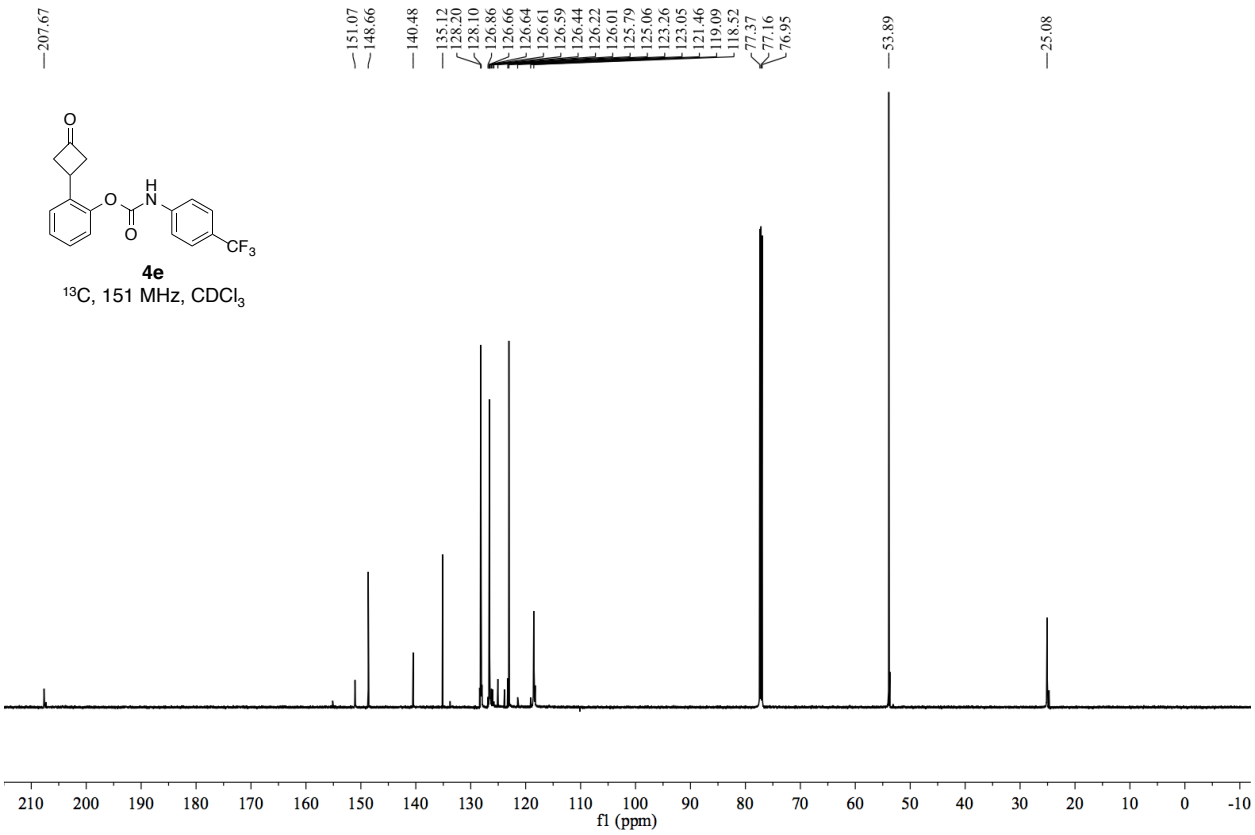
4c
^{13}C, 151 MHz, $CDCl_3$


7.38
7.36
7.34
7.32
7.27
7.26
7.25
7.23
6.90
6.88
6.87
3.80
3.78
3.77
3.75
3.73
3.54
3.49
3.47
3.31
3.30
3.26
3.25
O
O
H
N
O
O
OCH3
4d
1H, 400 MHz, CDCl3
3.93
3.51
2.89
4.00
1.99
2.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

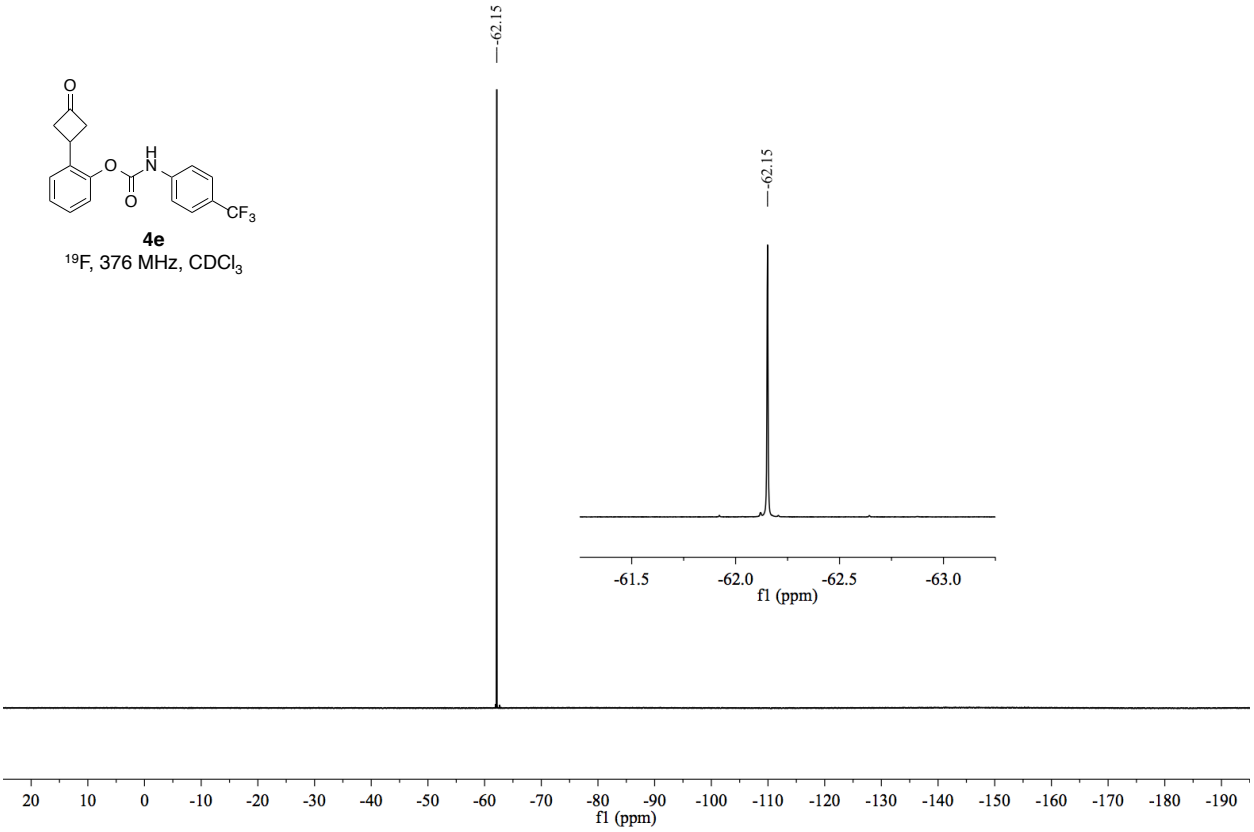

207.53
156.49
151.65
149.03
135.26
130.35
128.04
127.71
126.21
123.16
120.90
114.50
77.48
77.16
76.84
55.64
53.76
24.87
O
O
H
N
O
O
OCH3
4d
13C, 101 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



4e
^{1}H, 600 MHz, $CDCl_3$

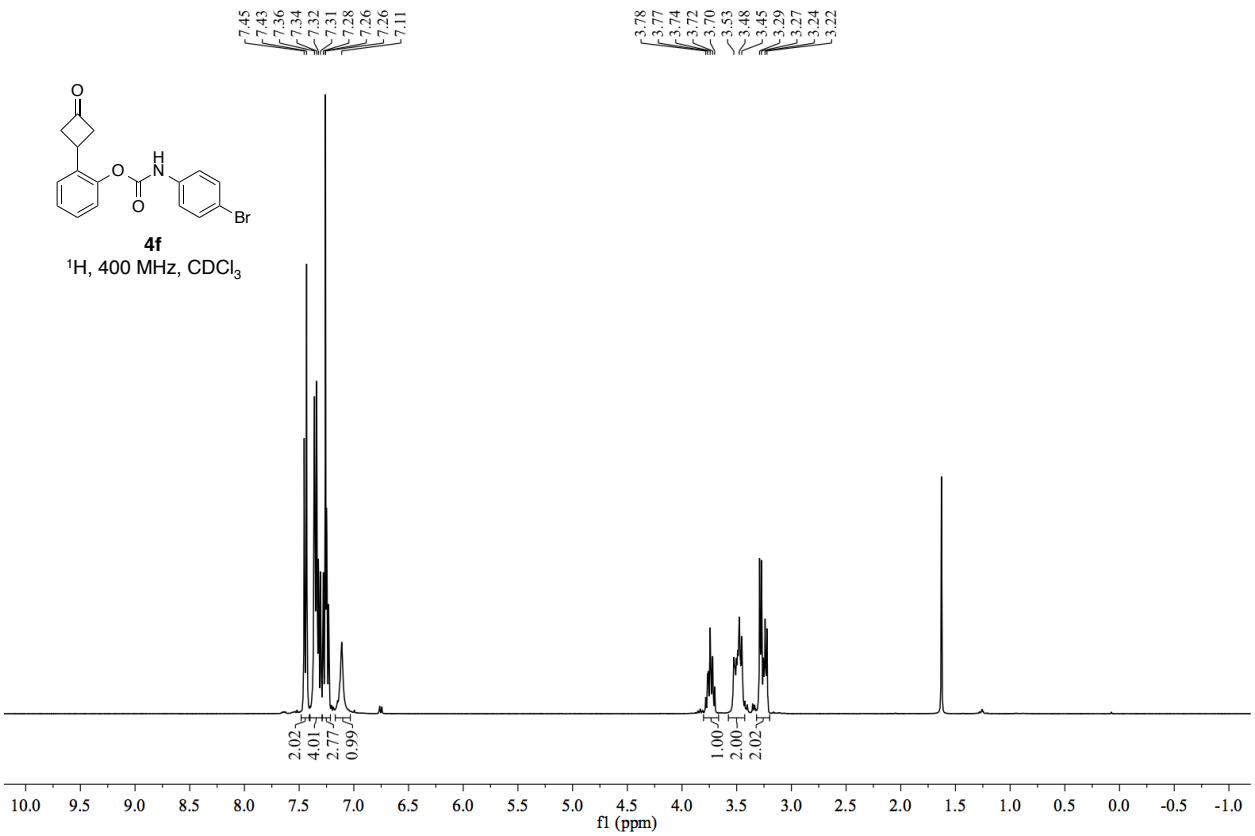


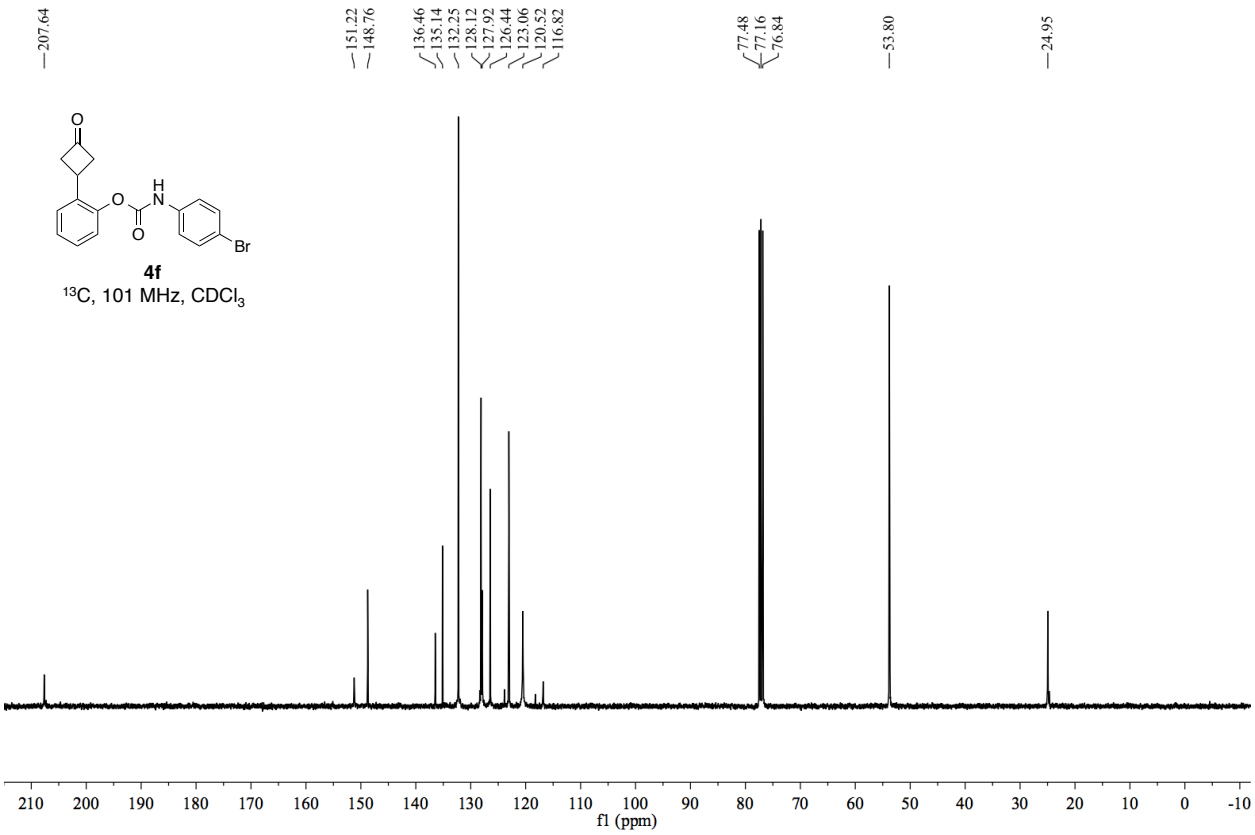
4e
^{13}C, 151 MHz, $CDCl_3$

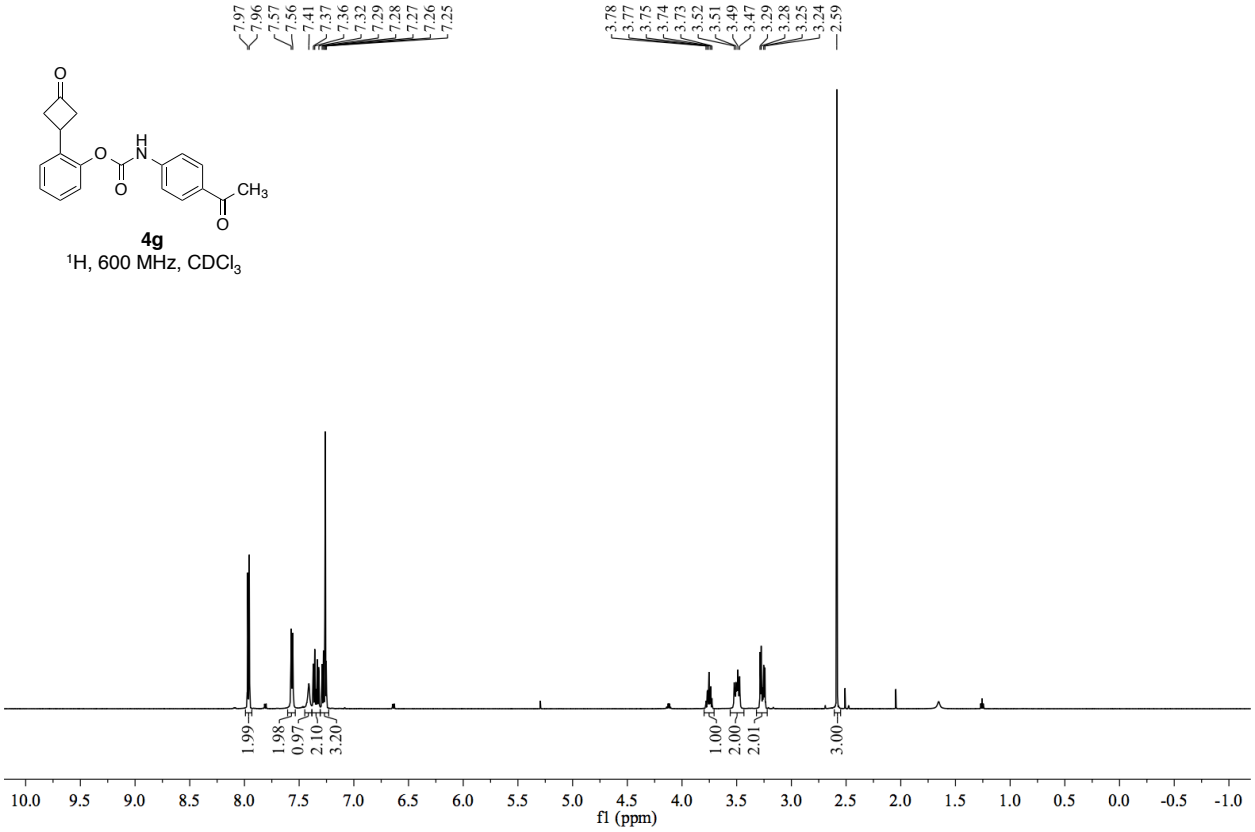


4e

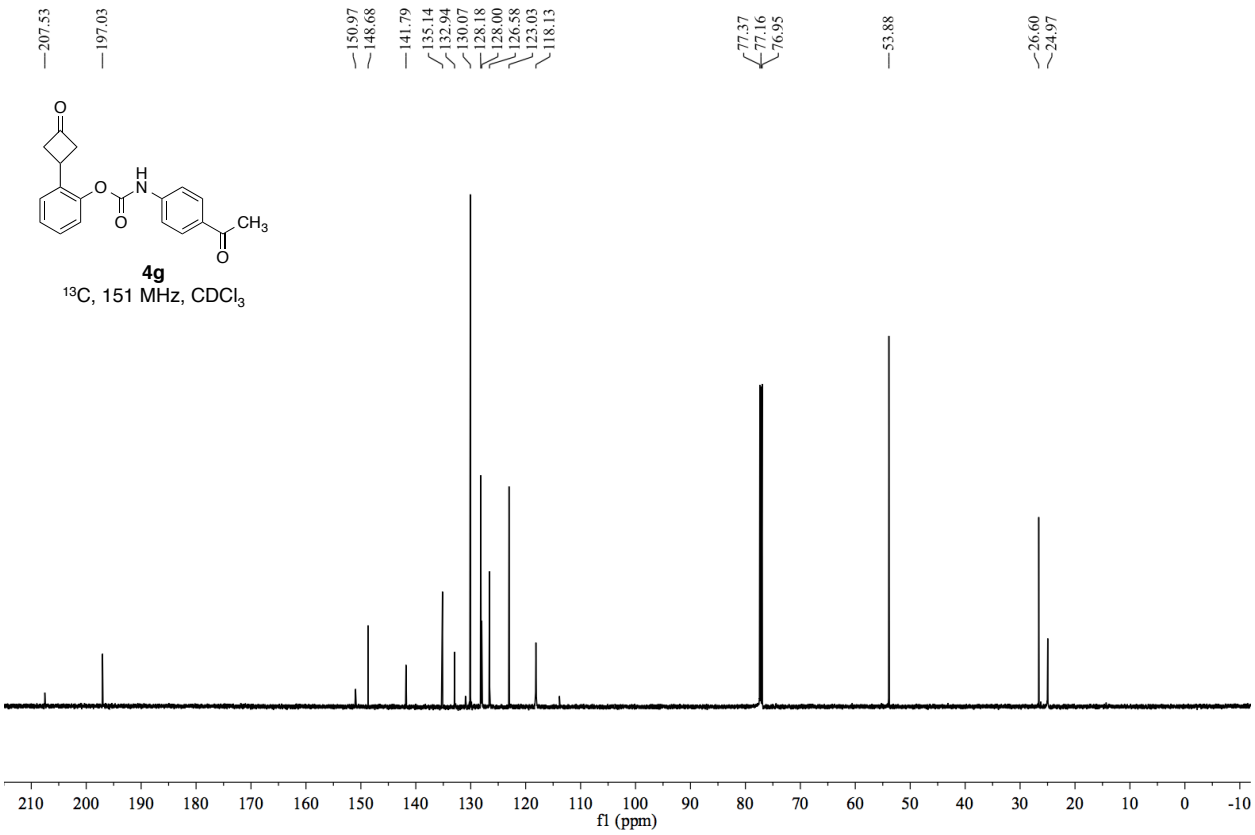
^{19}F, 376 MHz, $CDCl_3$


7.45
7.43
7.36
7.34
7.32
7.31
7.28
7.26
7.26
7.11
3.78
3.77
3.74
3.72
3.70
3.53
3.48
3.45
3.29
3.27
3.24
3.22
O
O
H
N
O
Br
4f
1H, 400 MHz, CDCl3
2.02
4.01
2.77
0.99
1.00
2.00
2.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

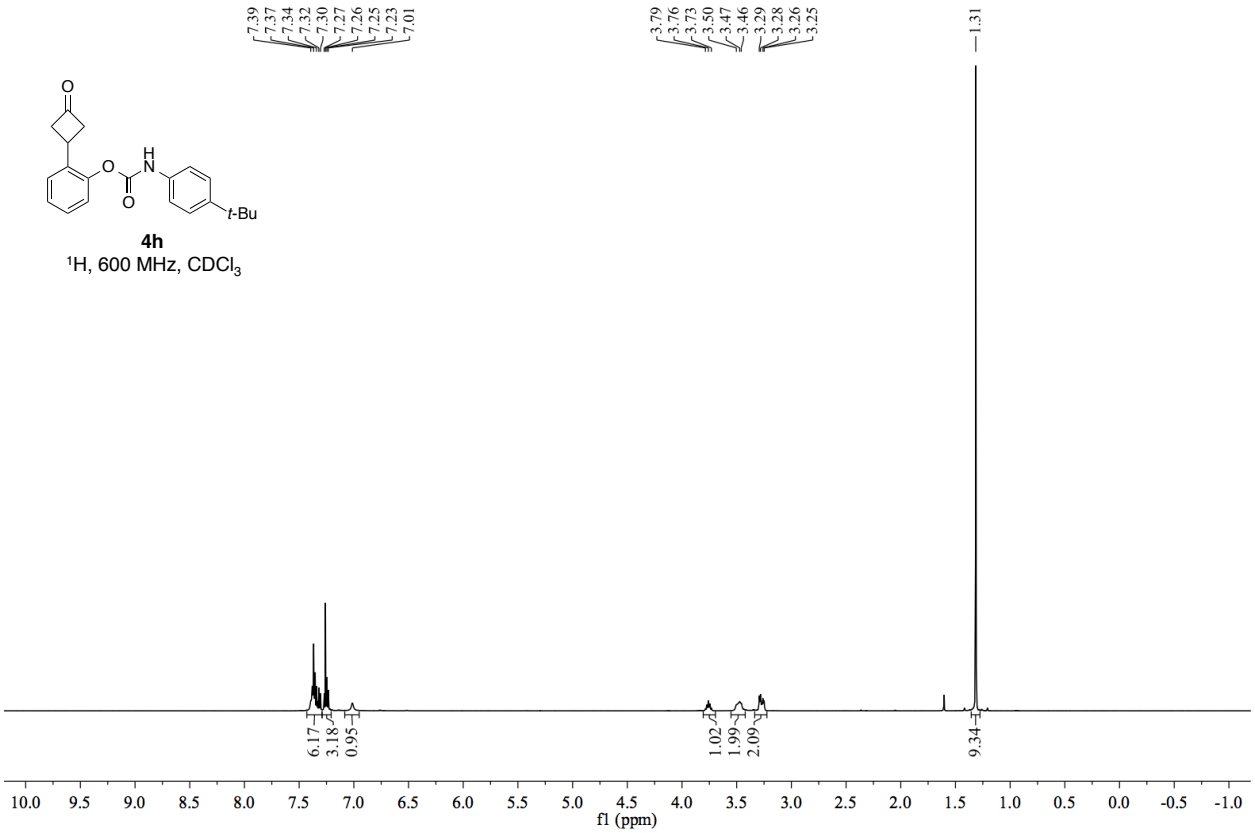

207.64
151.22
148.76
136.46
135.14
132.25
128.12
127.92
126.44
123.06
120.52
116.82
77.48
77.16
76.84
53.80
24.95
O
O
H
N
O
Br
4f
13C, 101 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



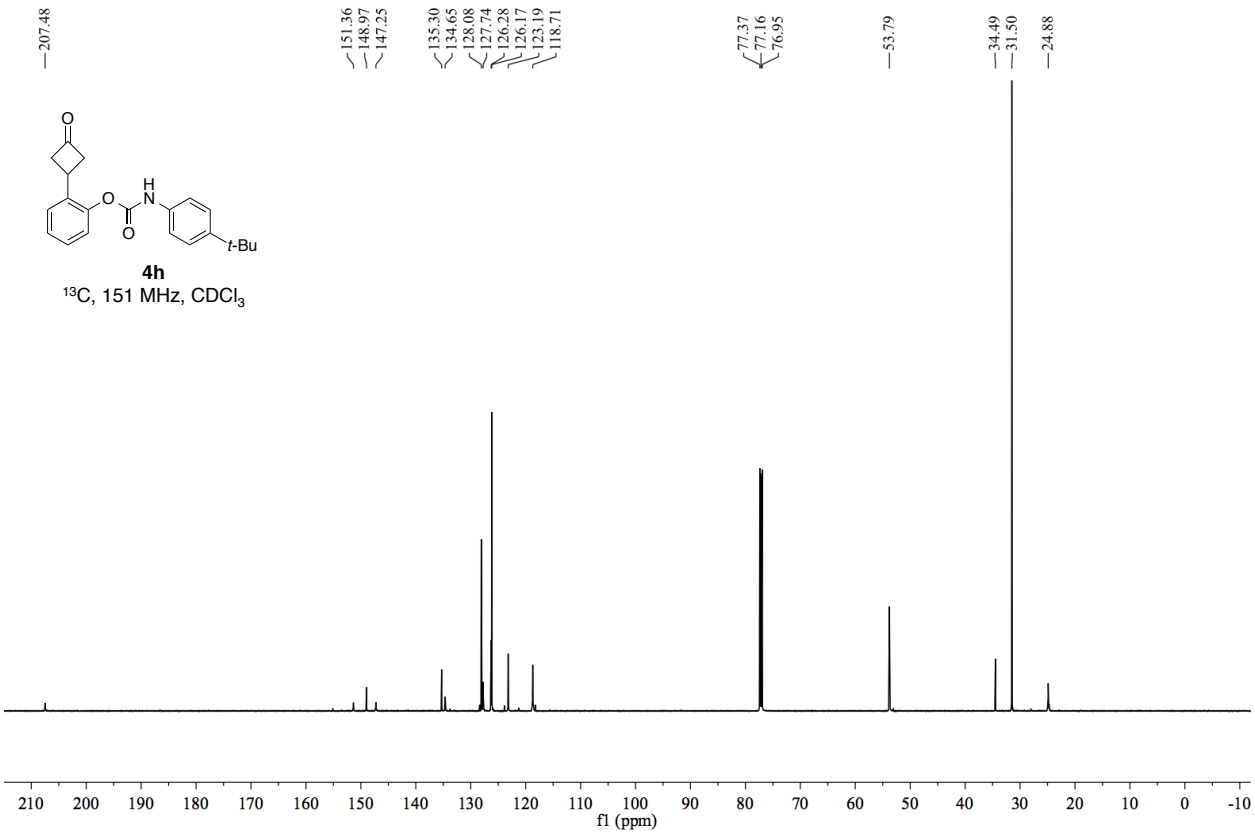
4g
^{1}H, 600 MHz, $CDCl_3$



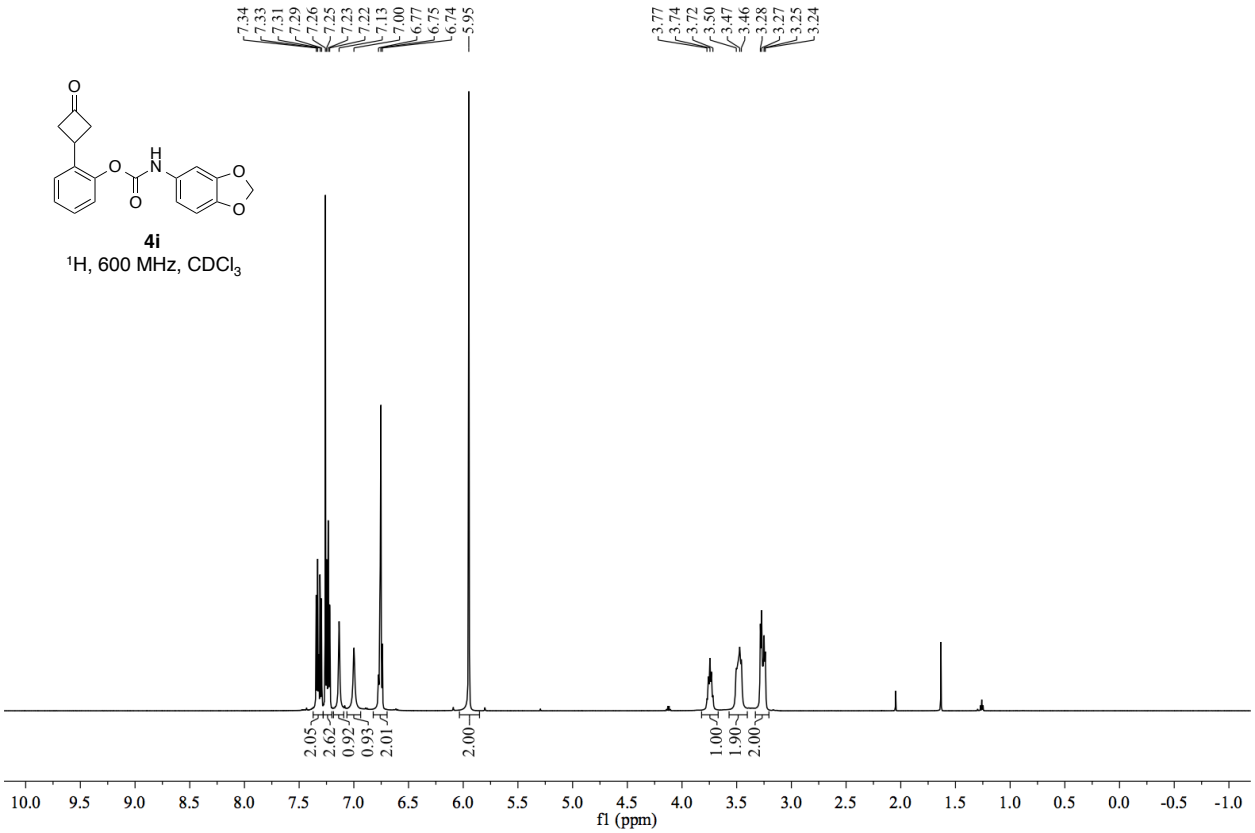
4g
^{13}C, 151 MHz, $CDCl_3$



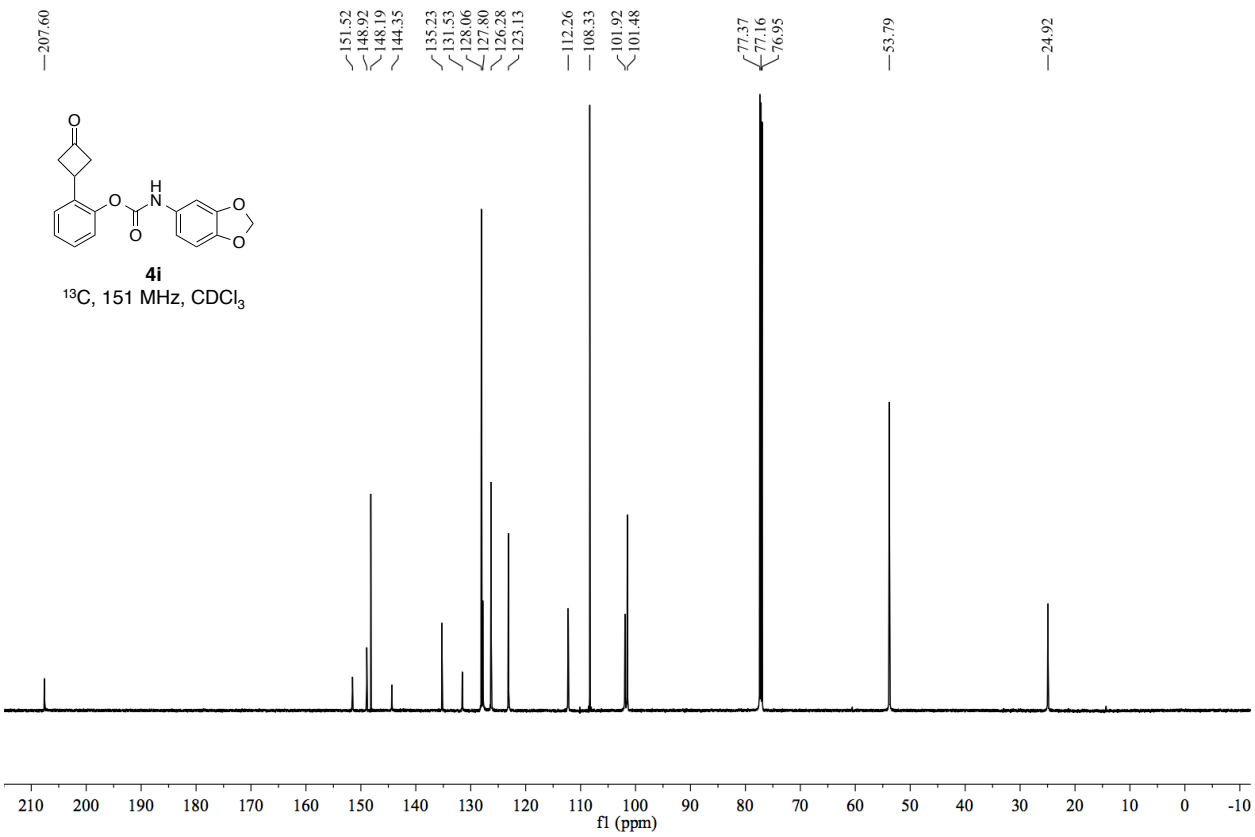
4h
^{1}H, 600 MHz, $CDCl_3$



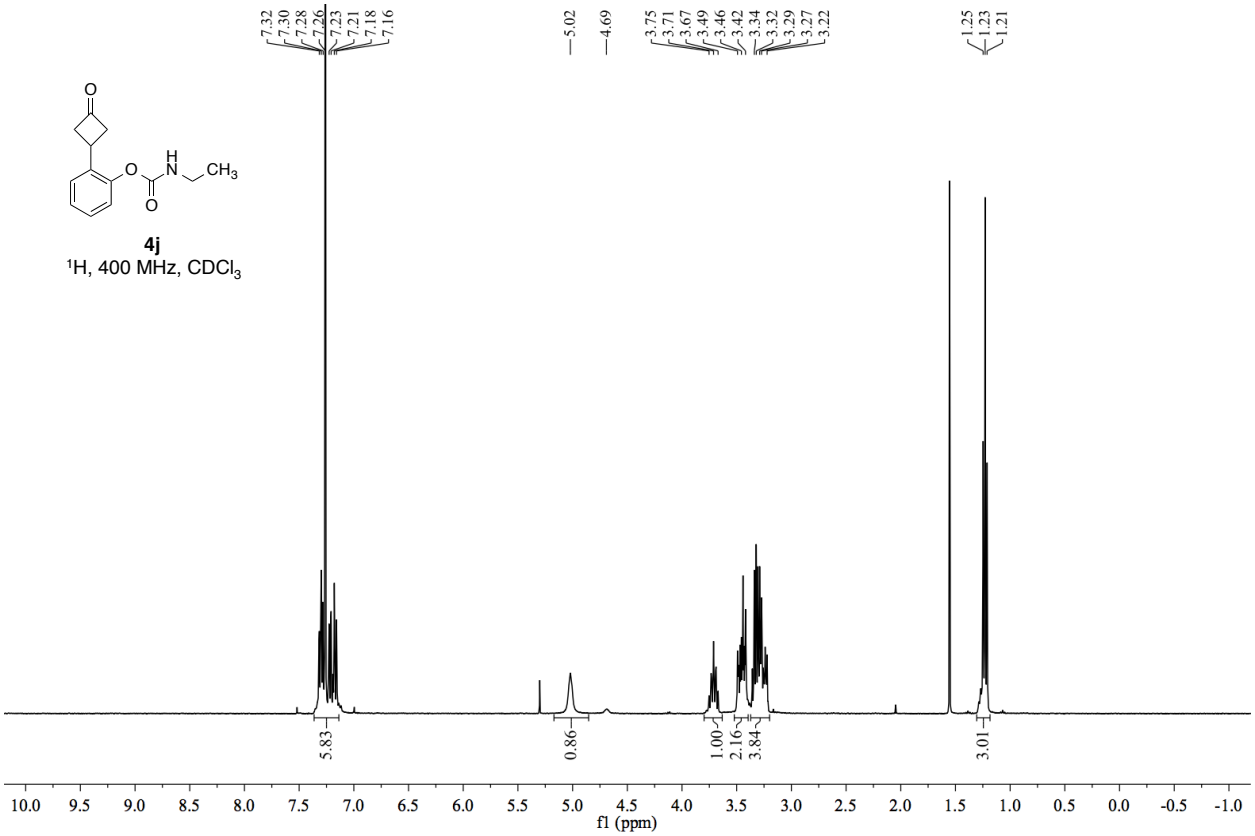
4h
^{13}C, 151 MHz, $CDCl_3$

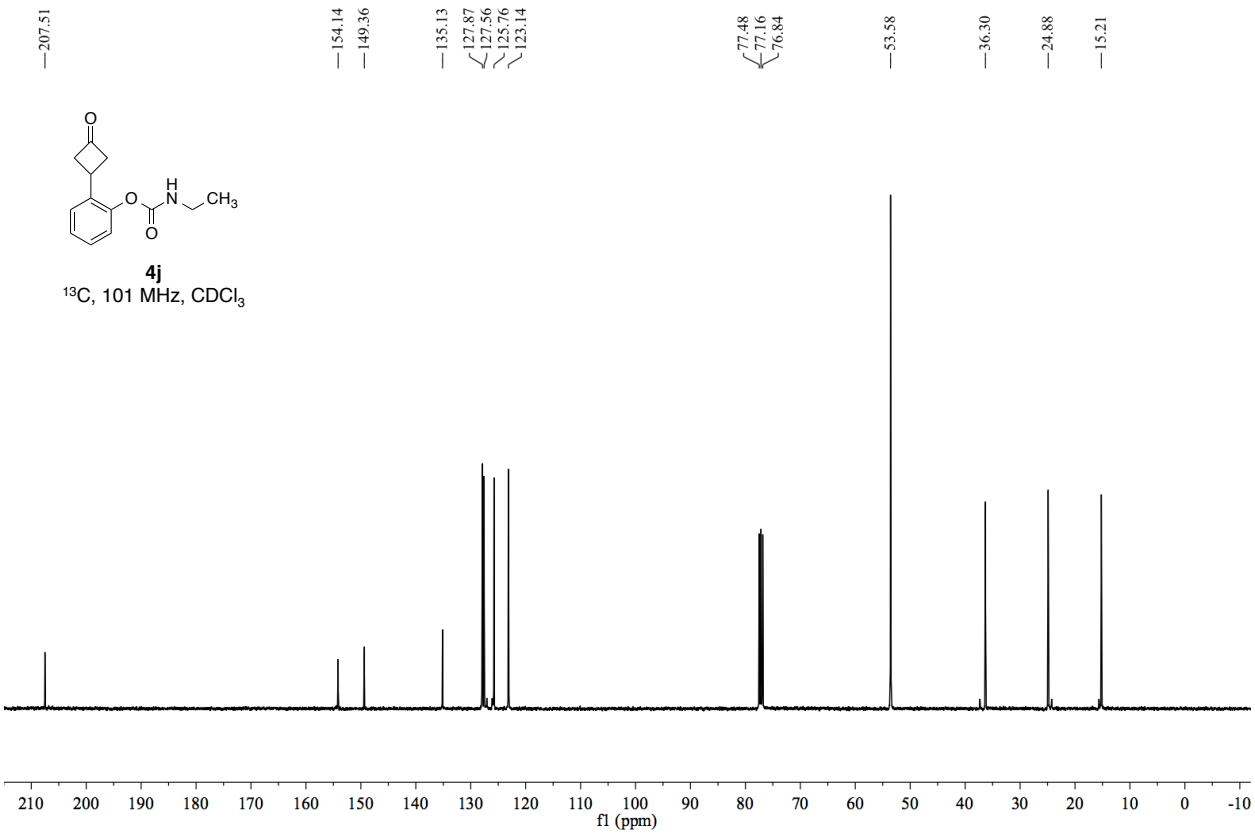


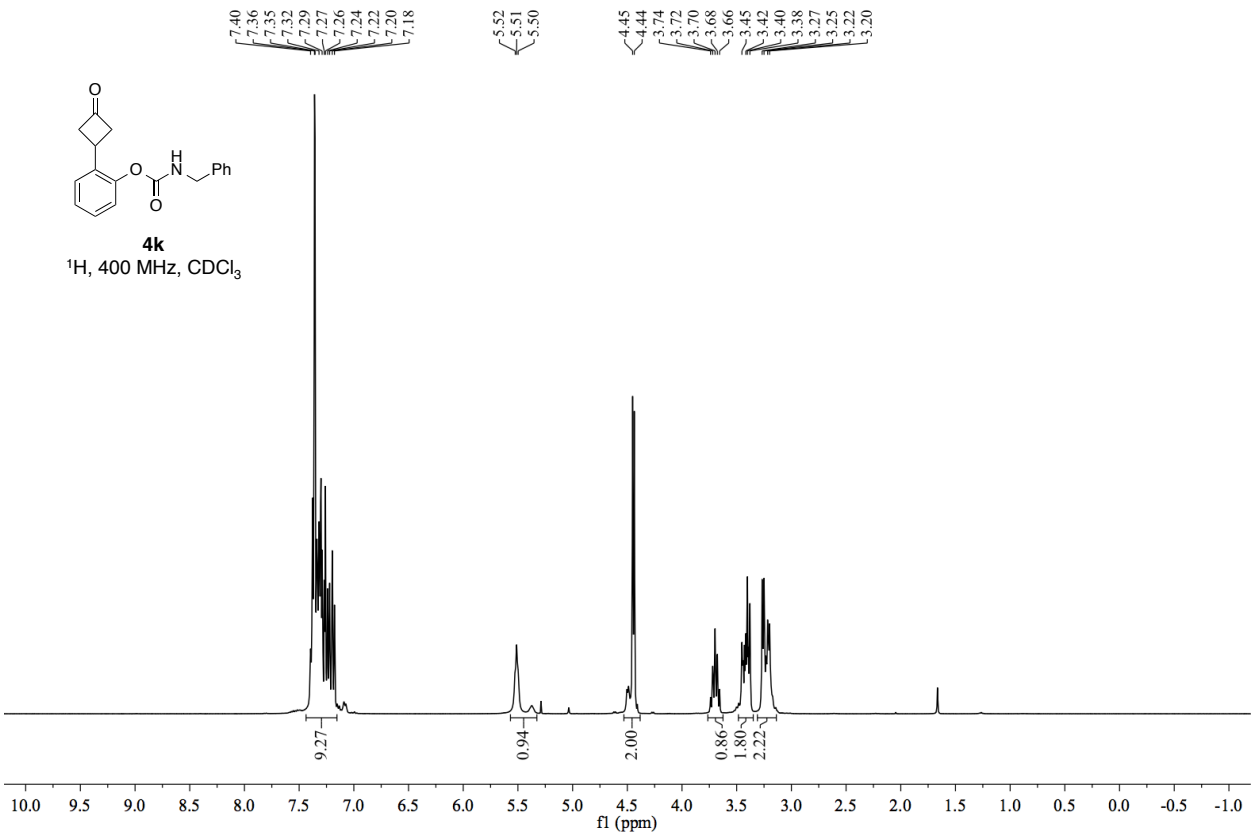
4i
^{1}H, 600 MHz, $CDCl_3$

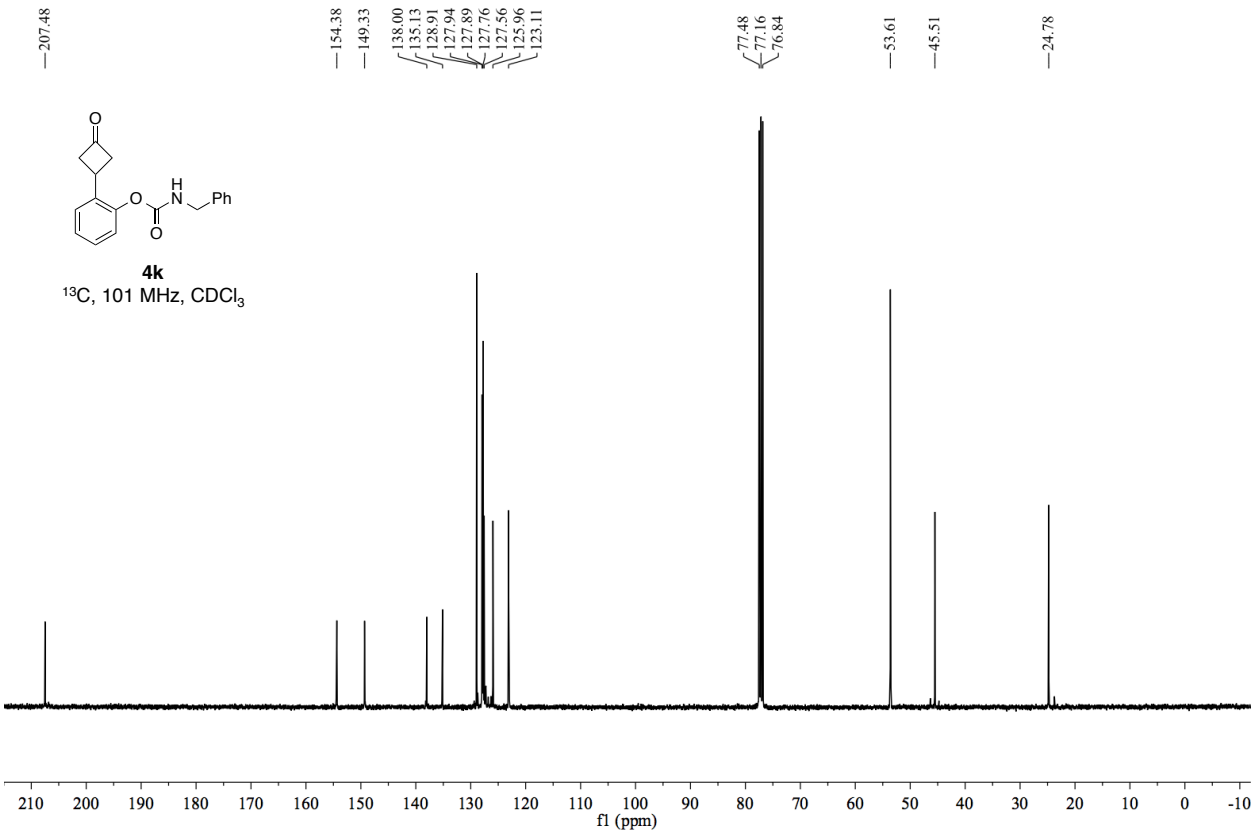


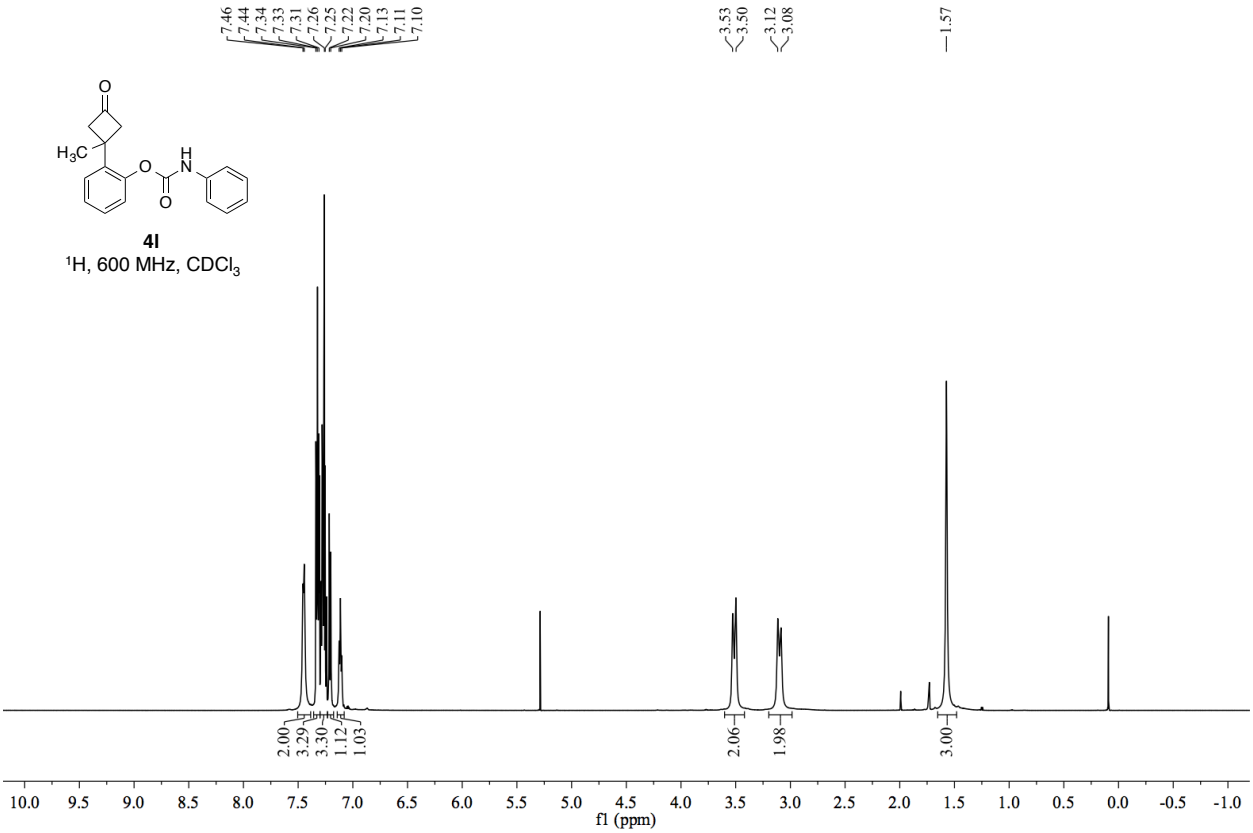
4i
^{13}C, 151 MHz, $CDCl_3$


7.32
7.30
7.28
7.26
7.23
7.21
7.18
7.16
5.02
4.69
3.75
3.71
3.67
3.49
3.46
3.42
3.34
3.32
3.29
3.27
3.22
1.25
1.23
1.21
O
O
H
N
CH3
O
4j
1H, 400 MHz, CDCl3
5.83
0.86
1.00
2.16
3.84
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

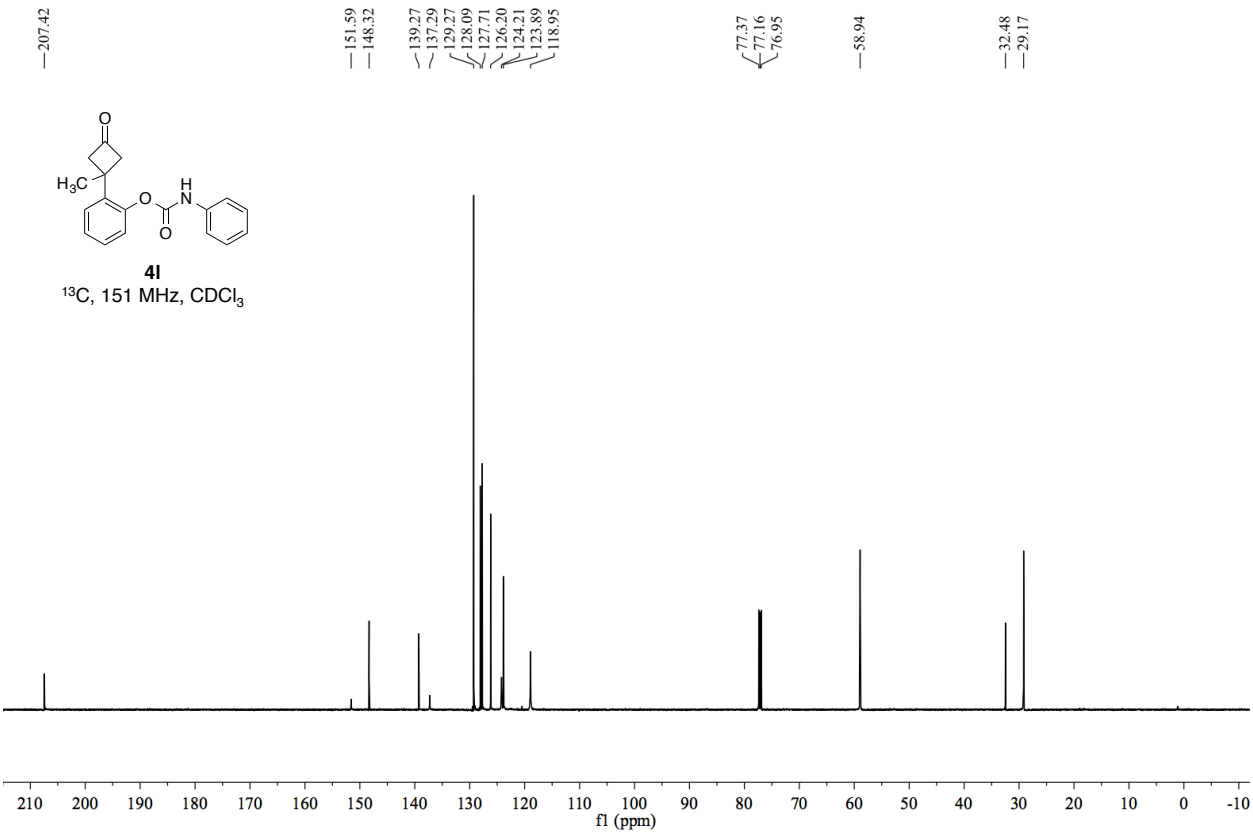

207.51
154.14
149.36
135.13
127.87
127.56
125.76
123.14
77.48
77.16
76.84
53.58
36.30
24.88
15.21
O
O
H
N
CH3
O
4j
13C, 101 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.40
7.36
7.35
7.32
7.29
7.27
7.26
7.24
7.22
7.20
7.18
5.52
5.51
5.50
4.45
4.44
3.74
3.72
3.70
3.68
3.66
3.45
3.42
3.40
3.38
3.27
3.25
3.22
3.20
O
O
H
N
Ph
O
4k
^{1}H, 400 MHz, $CDCl_3$
9.27
0.94
2.00
0.86
1.80
2.22
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

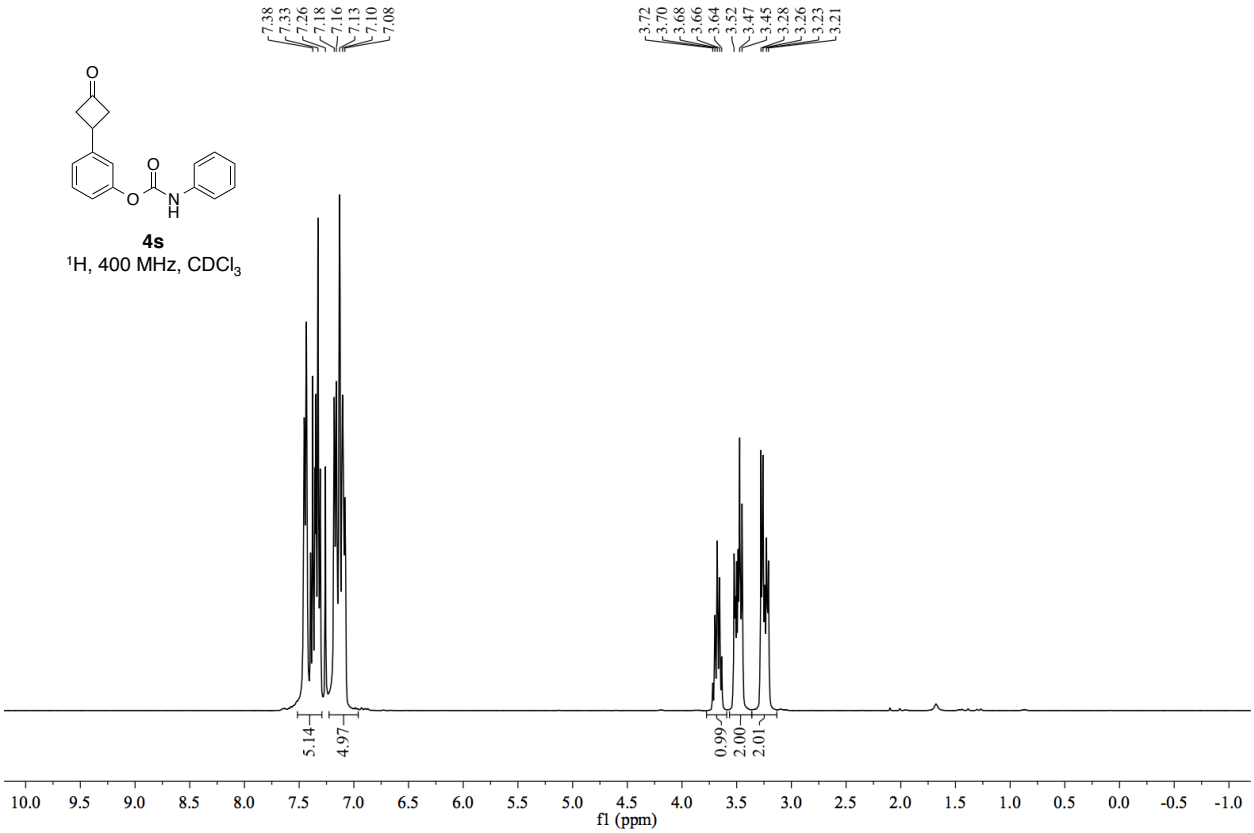

207.48
154.38
149.33
138.00
135.13
128.91
127.94
127.89
127.76
127.56
125.96
123.11
77.48
77.16
76.84
53.61
45.51
24.78
O
O
H
N
Ph
O
4k
^{13}C, 101 MHz, $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

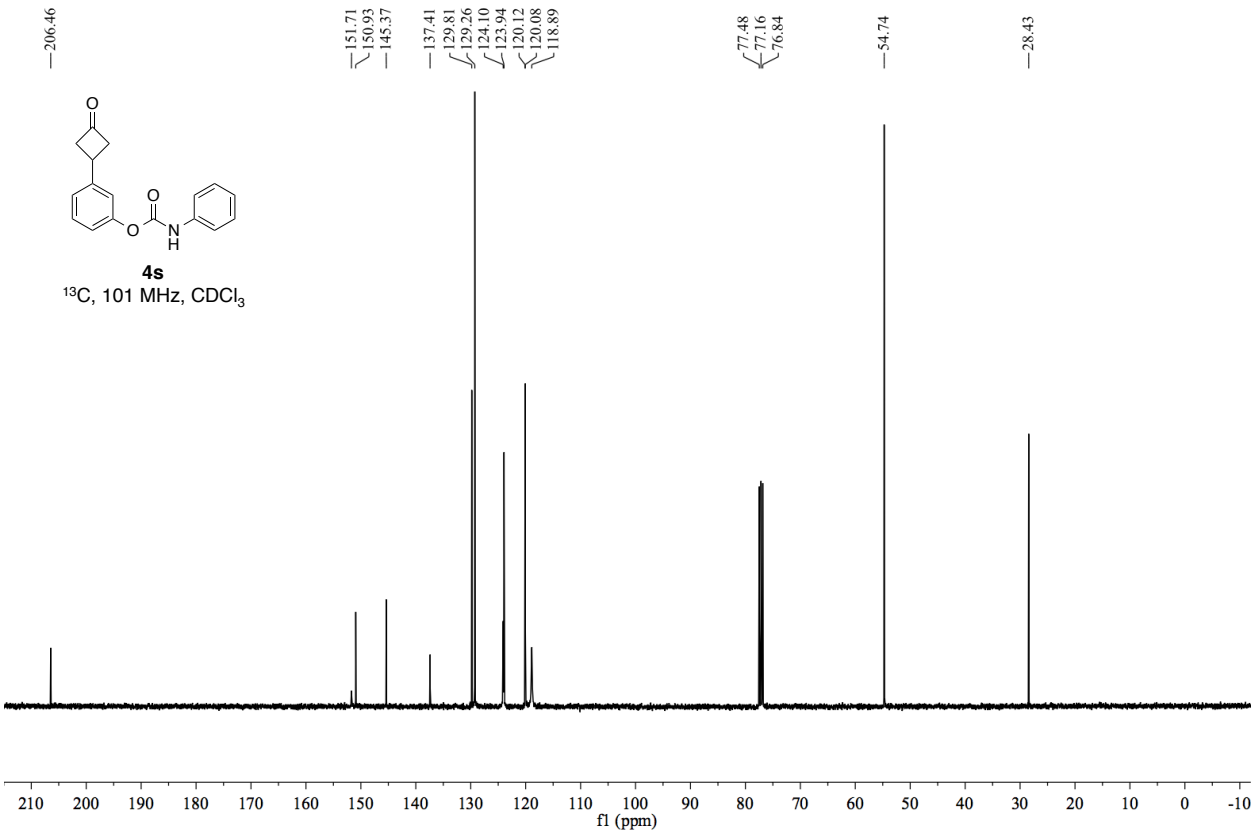


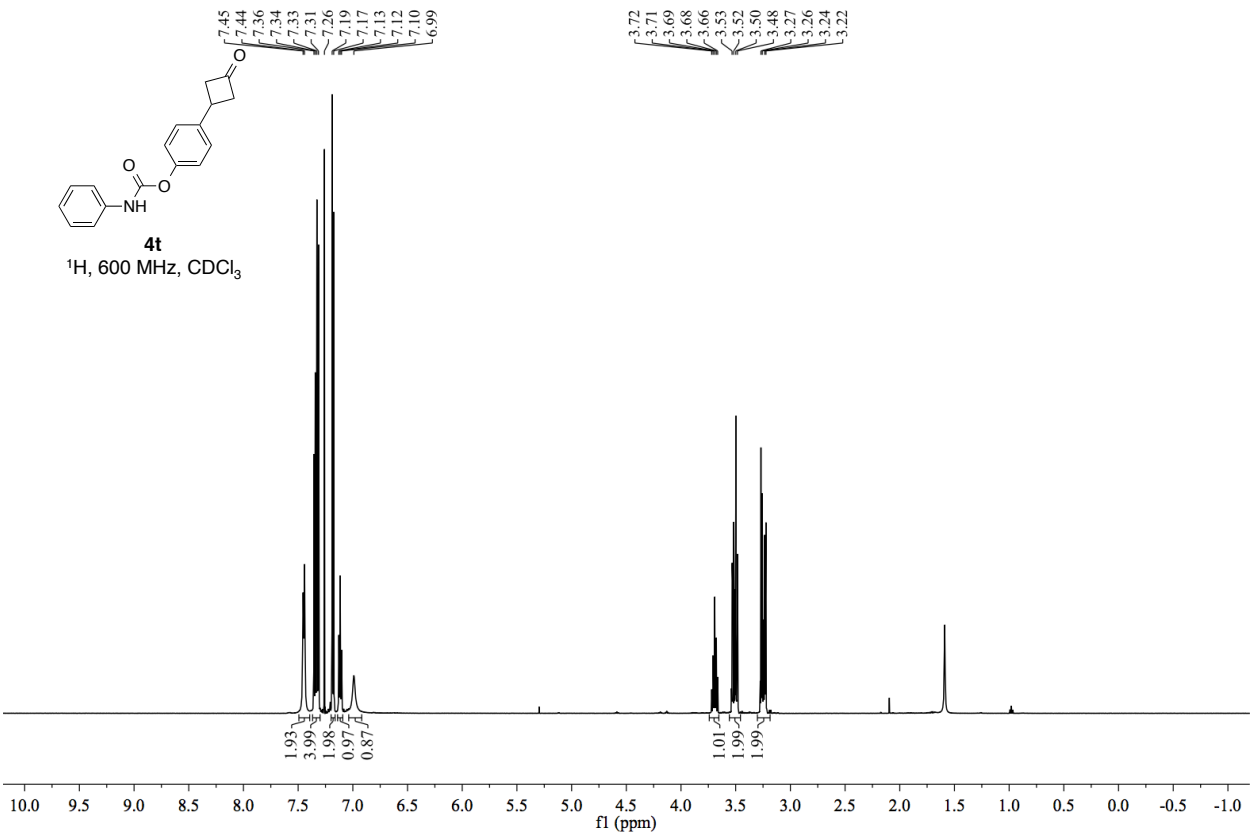
4l
^{1}H, 600 MHz, $CDCl_3$

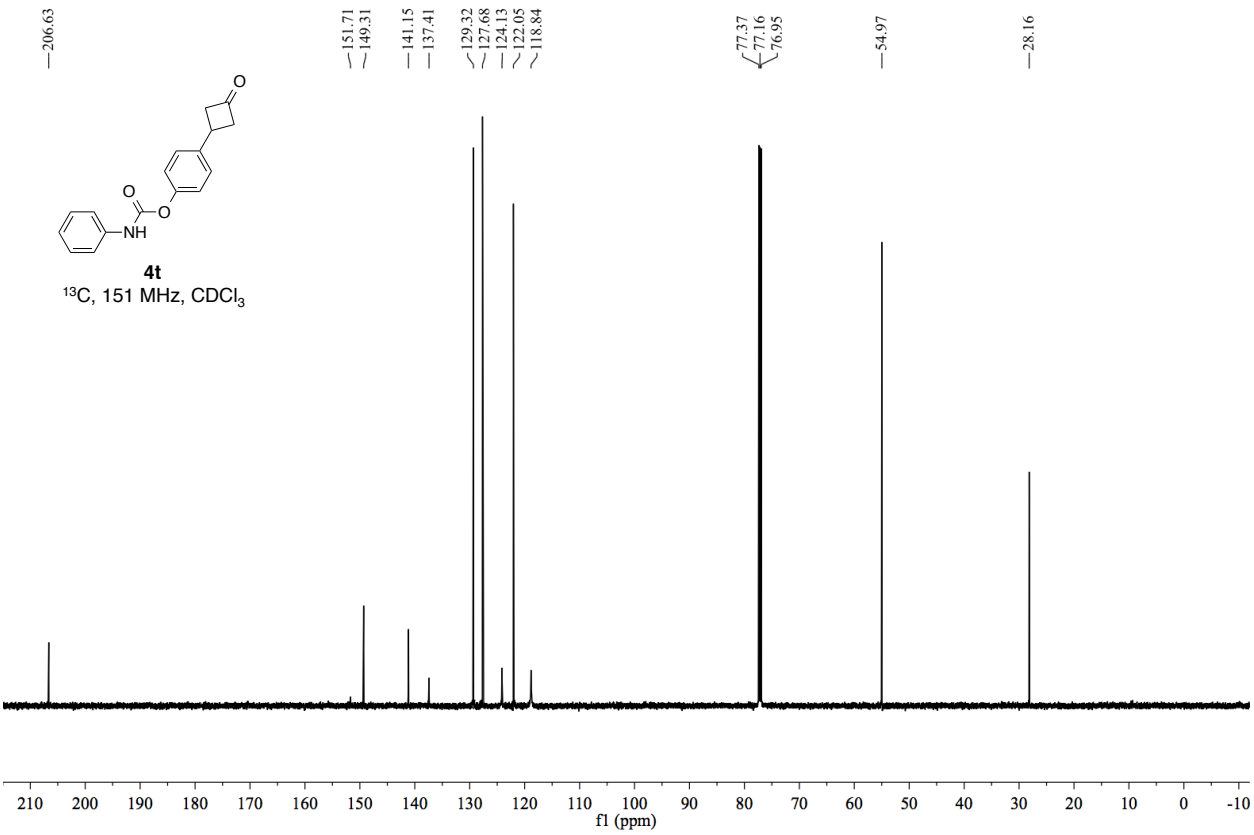


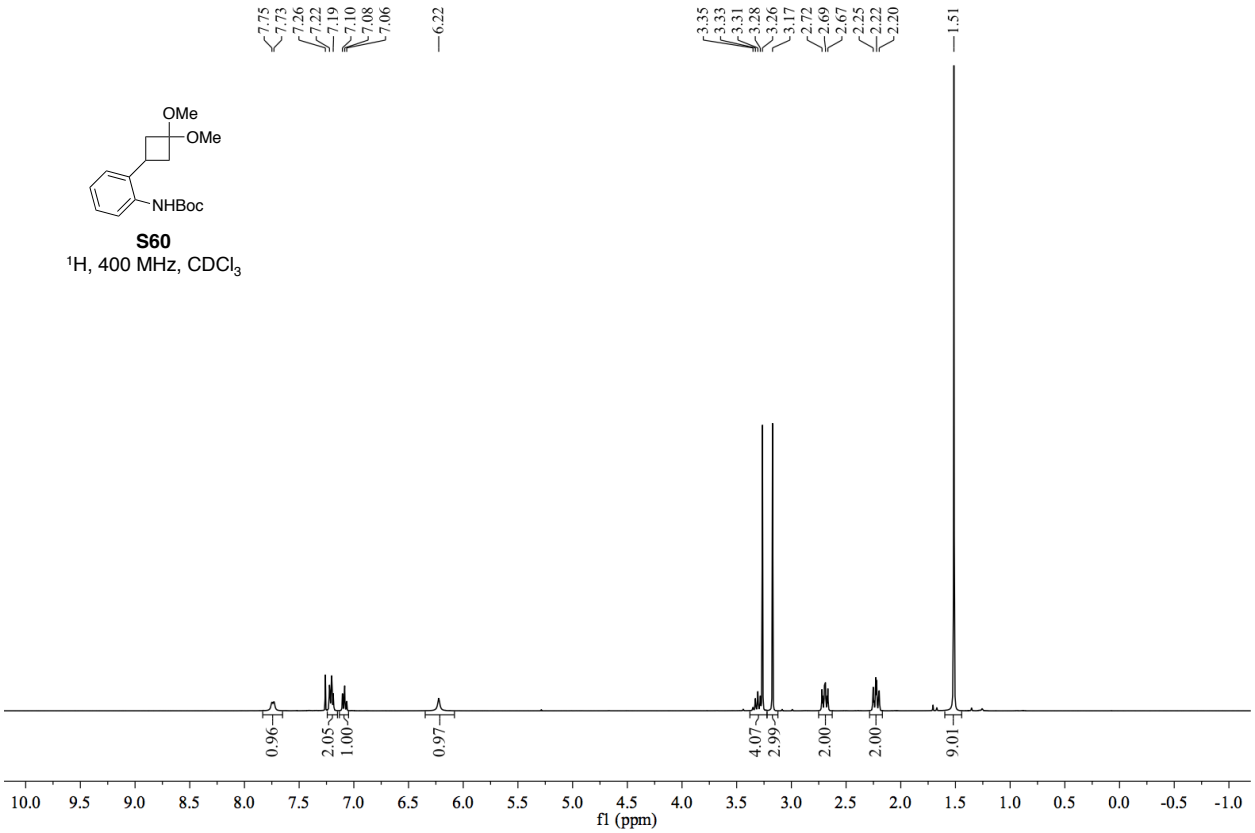
4l
^{13}C, 151 MHz, $CDCl_3$


7.38
7.33
7.26
7.18
7.16
7.13
7.10
7.08
3.72
3.70
3.68
3.66
3.64
3.52
3.47
3.45
3.28
3.26
3.23
3.21
O
O
O
N
H
4s
1H, 400 MHz, CDCl3
5.14
4.97
0.99
2.00
2.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

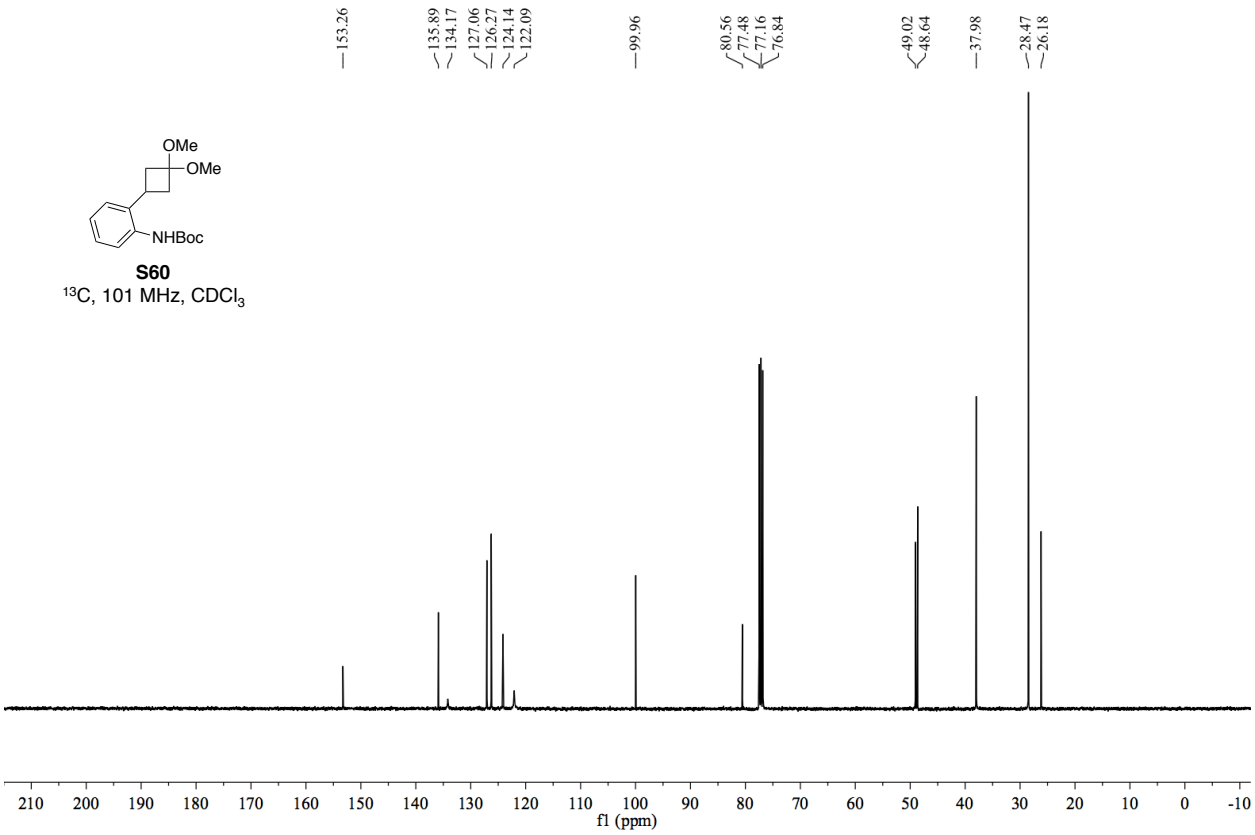

206.46
151.71
150.93
145.37
137.41
129.81
129.26
124.10
123.94
120.12
120.08
118.89
77.48
77.16
76.84
54.74
28.43
O
O
O
N
H
4s
13C, 101 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.45
7.44
7.36
7.34
7.33
7.31
7.26
7.19
7.17
7.13
7.12
7.10
6.99
3.72
3.71
3.69
3.68
3.66
3.53
3.52
3.50
3.48
3.27
3.26
3.24
3.22
O
O
O
NH
4t
1H, 600 MHz, CDCl3
1.93
3.99
1.98
0.97
0.87
1.01
1.99
1.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

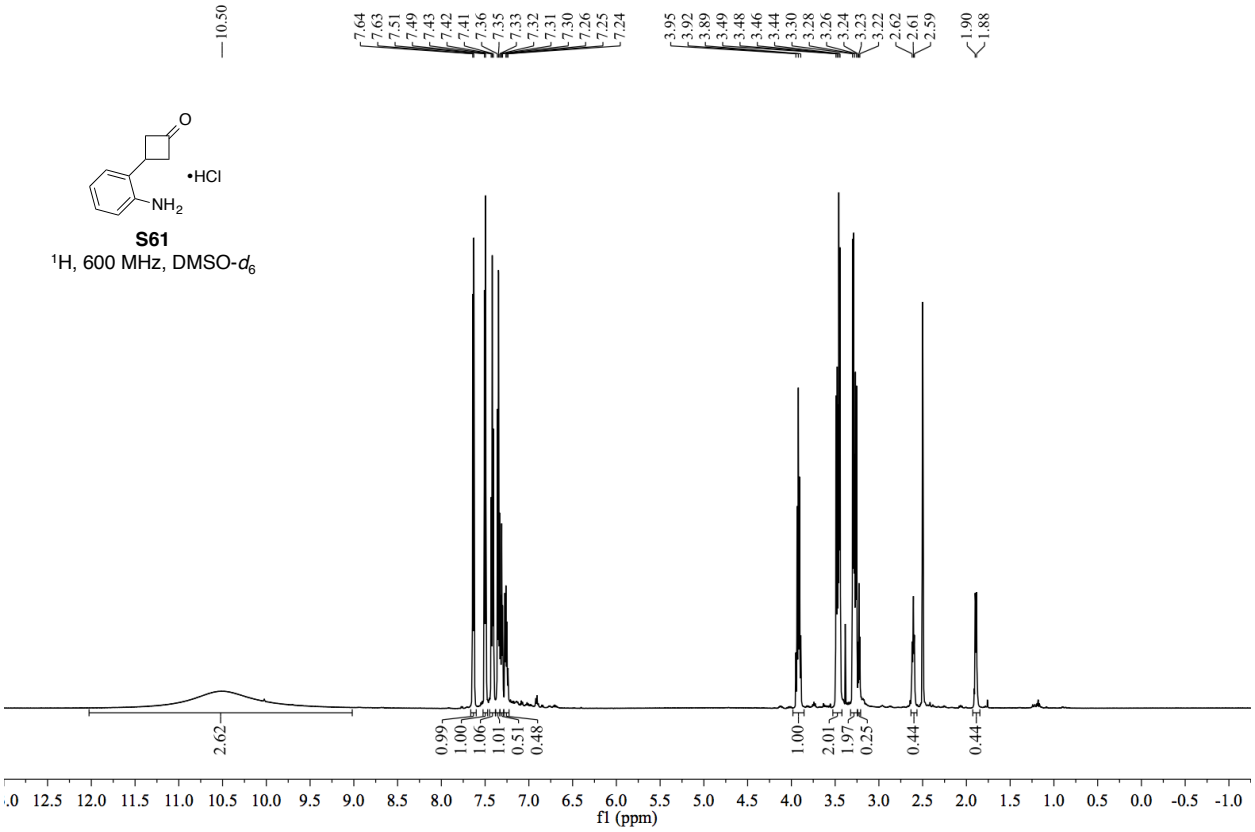

206.63
151.71
149.31
141.15
137.41
129.32
127.68
124.13
122.05
118.84
77.37
77.16
76.95
54.97
28.16
O
O
O
NH
4t
13C, 151 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



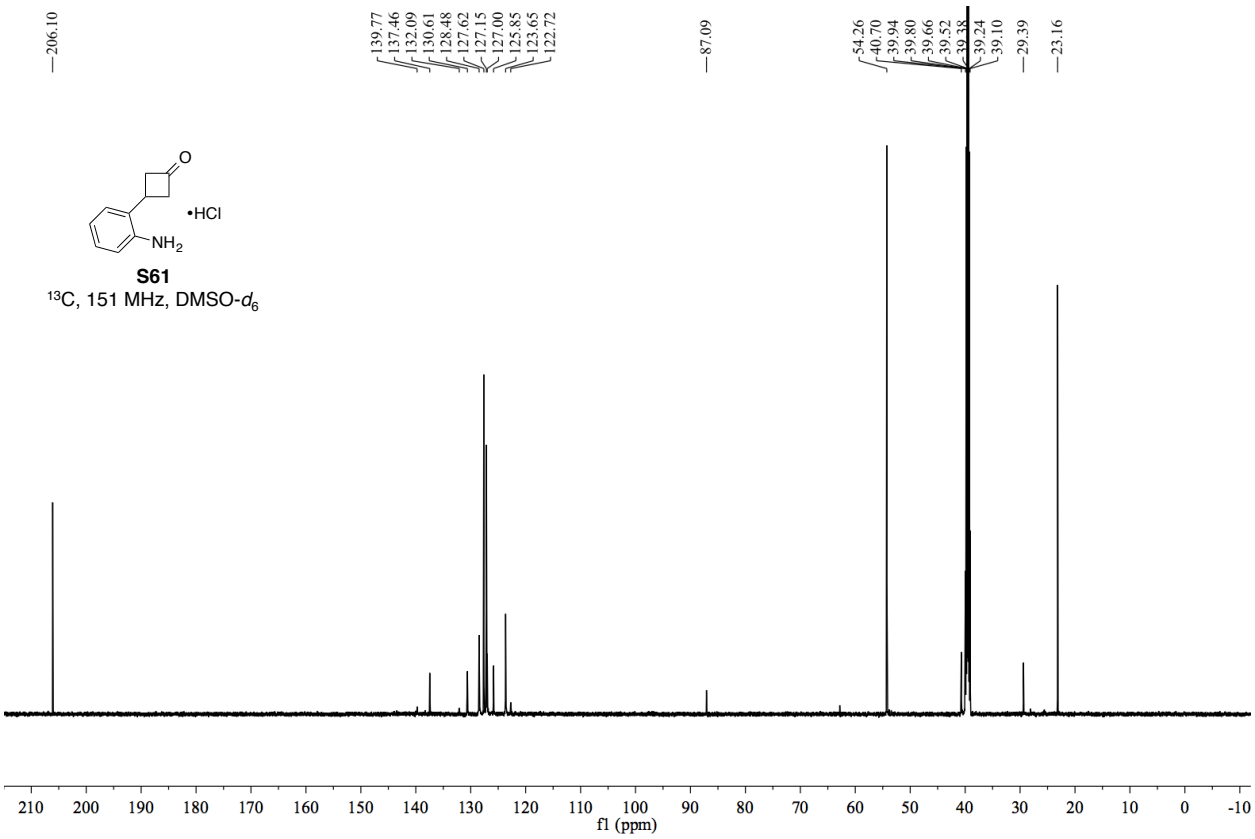
S60
^{1}H, 400 MHz, $CDCl_3$



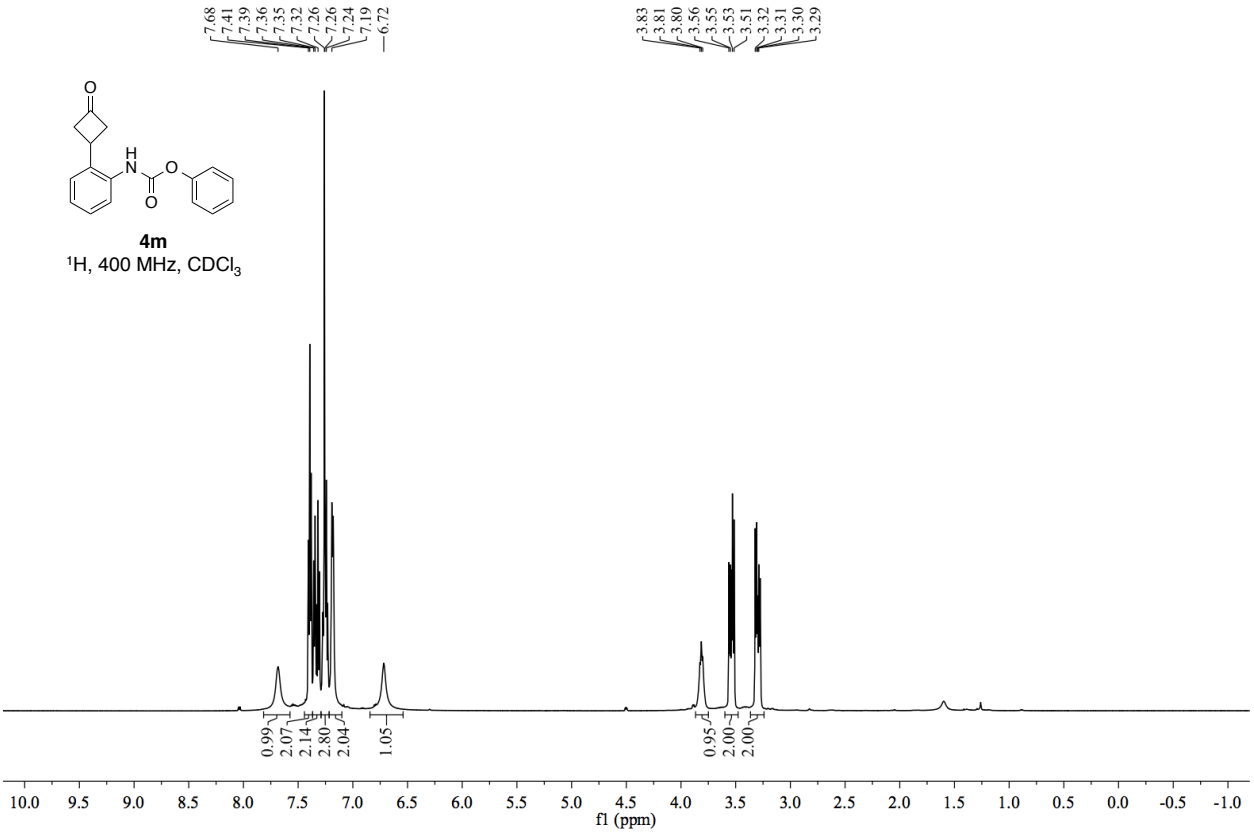
S60
^{13}C, 101 MHz, $CDCl_3$



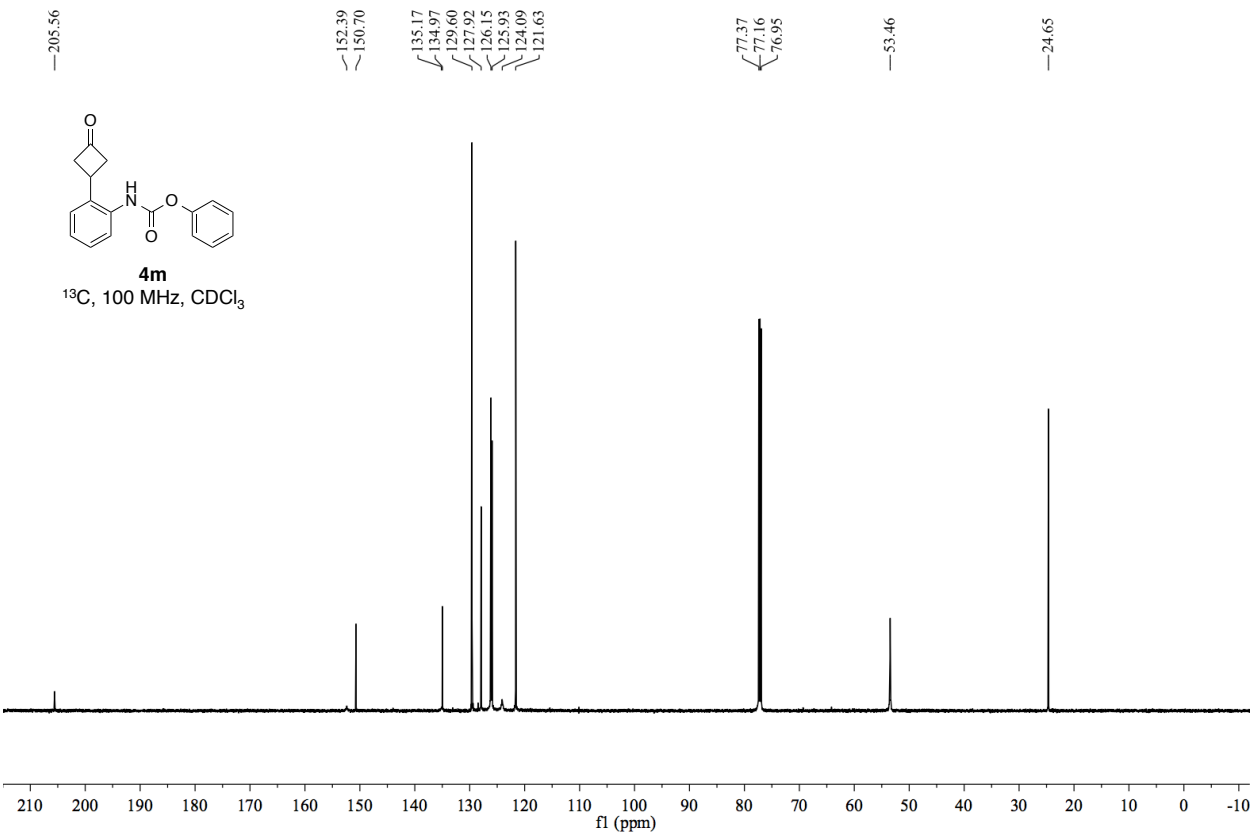
S61
^{1}H, 600 MHz, DMSO-d_6



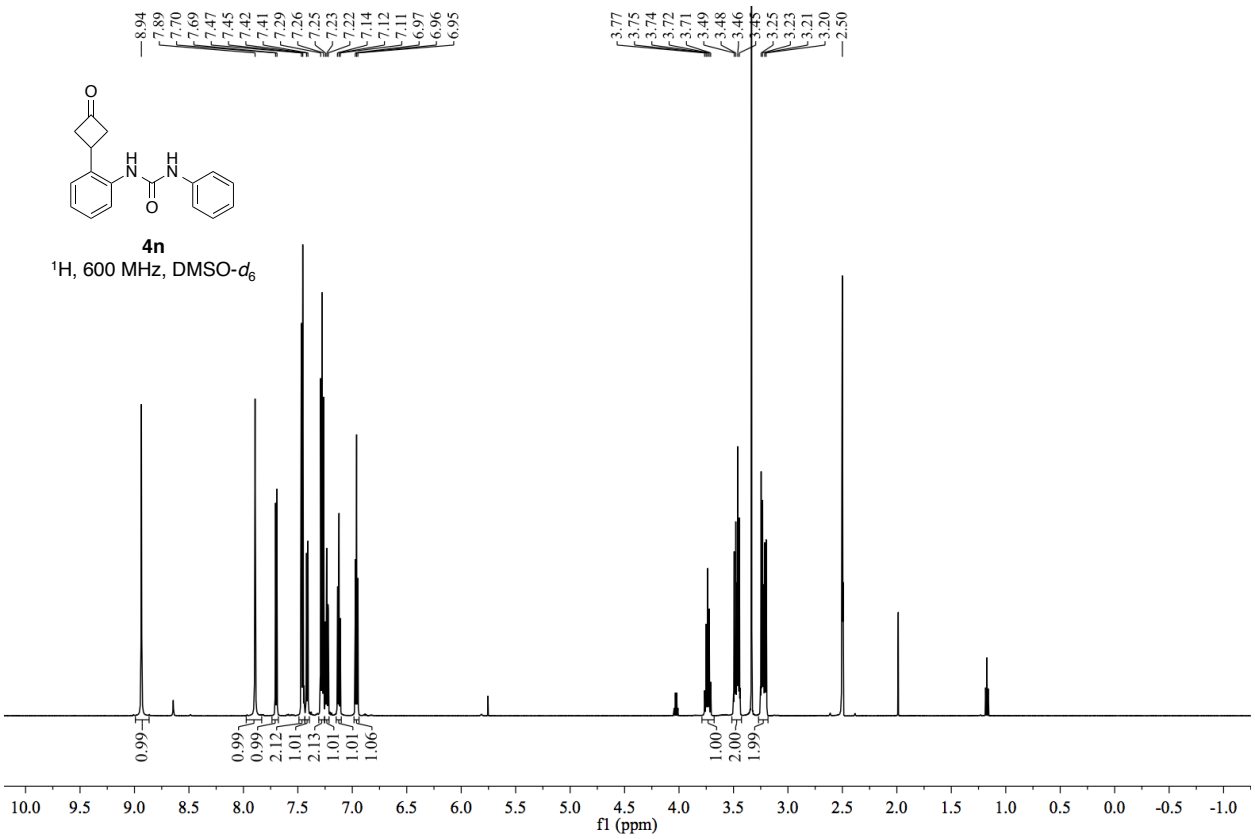
S61
^{13}C, 151 MHz, DMSO-d_6



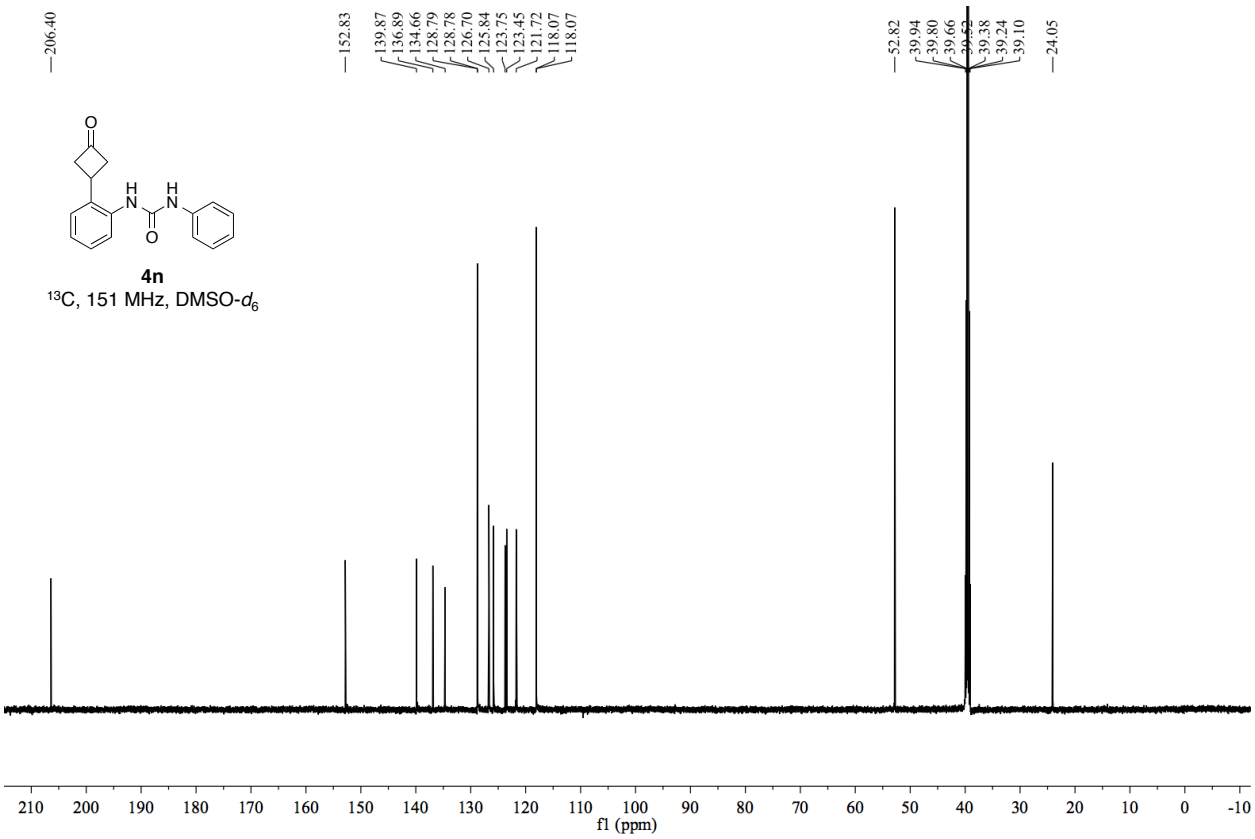
4m
^{1}H, 400 MHz, $CDCl_3$



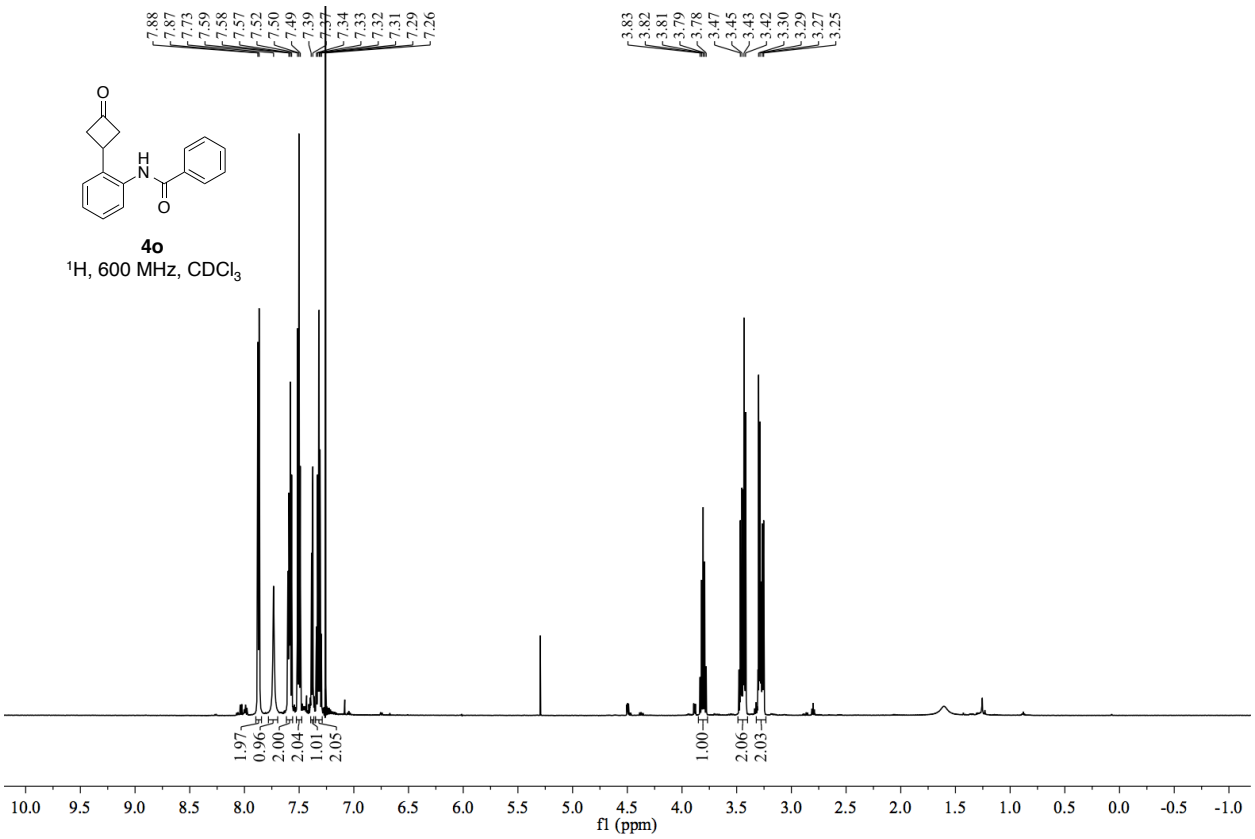
4m
^{13}C, 100 MHz, $CDCl_3$



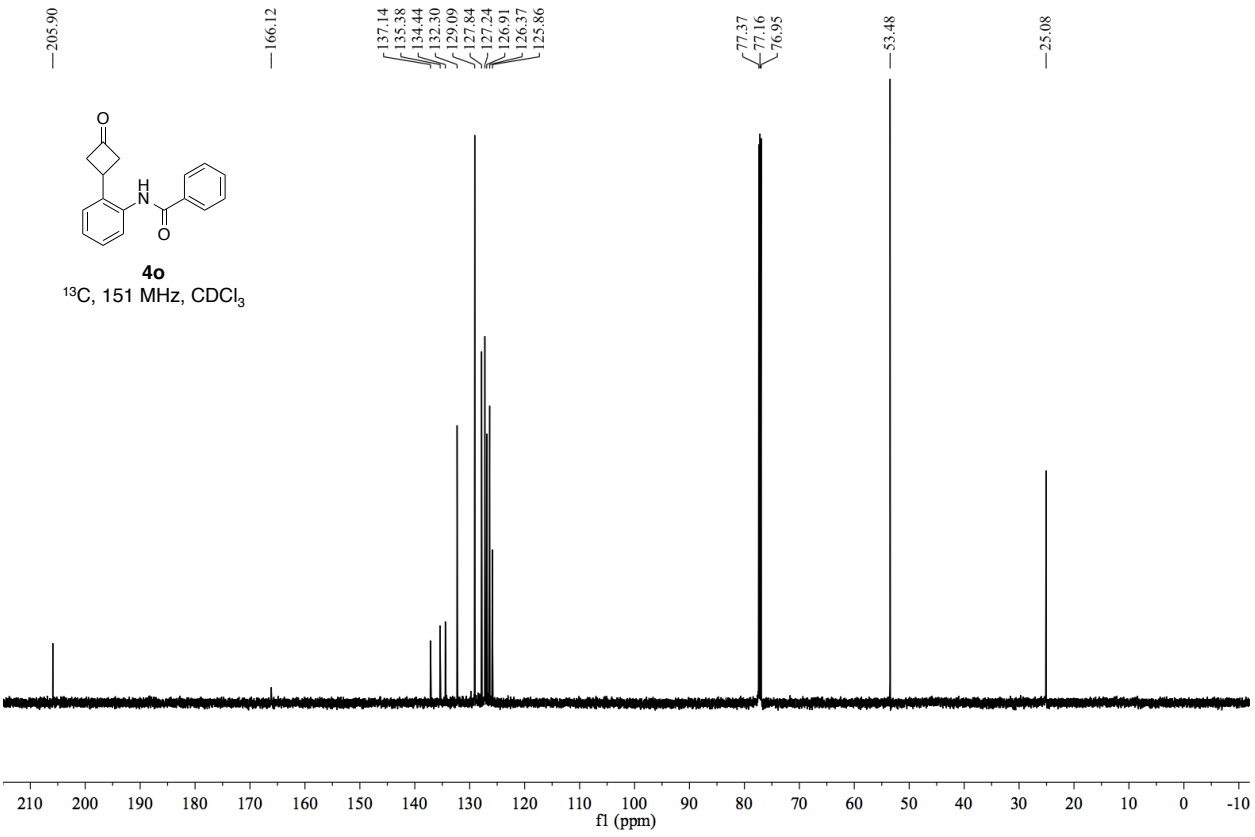
4n
^{1}H, 600 MHz, DMSO-d_6



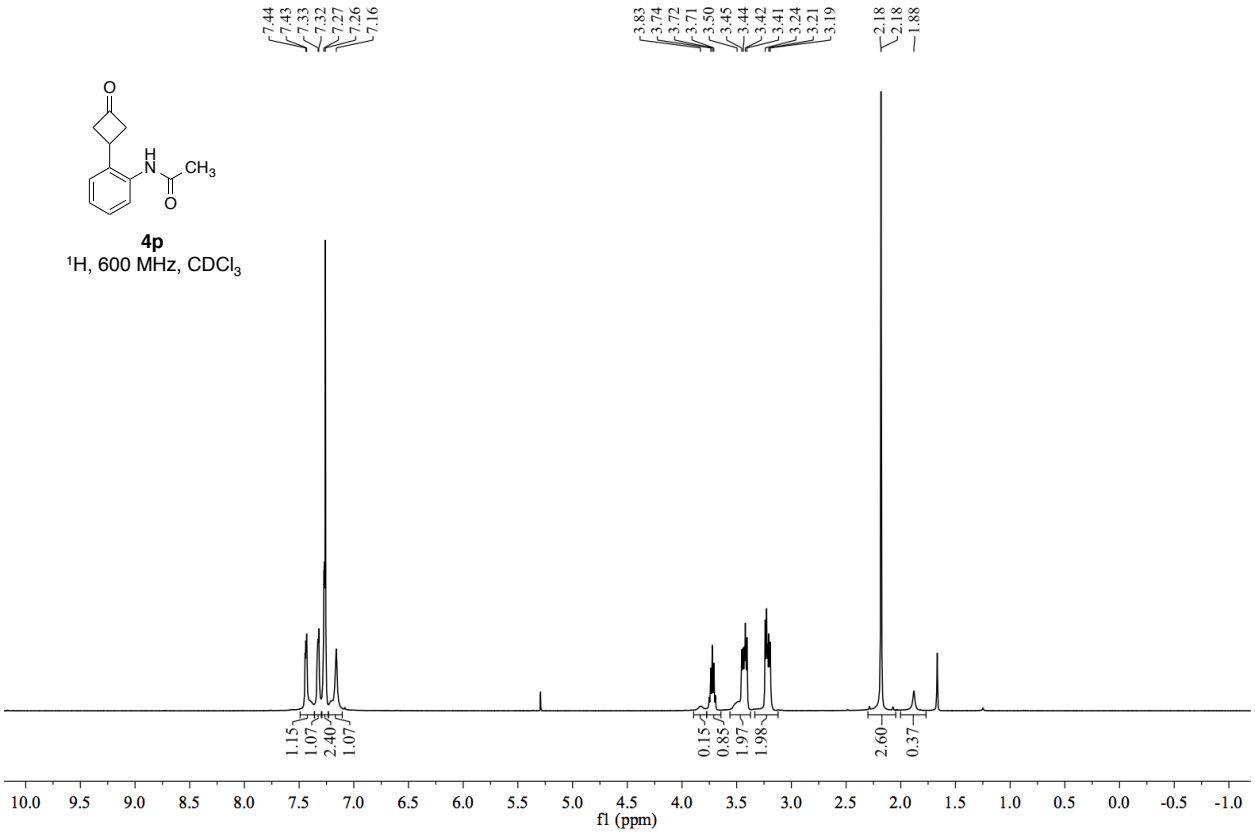
4n
^{13}C, 151 MHz, DMSO-d_6



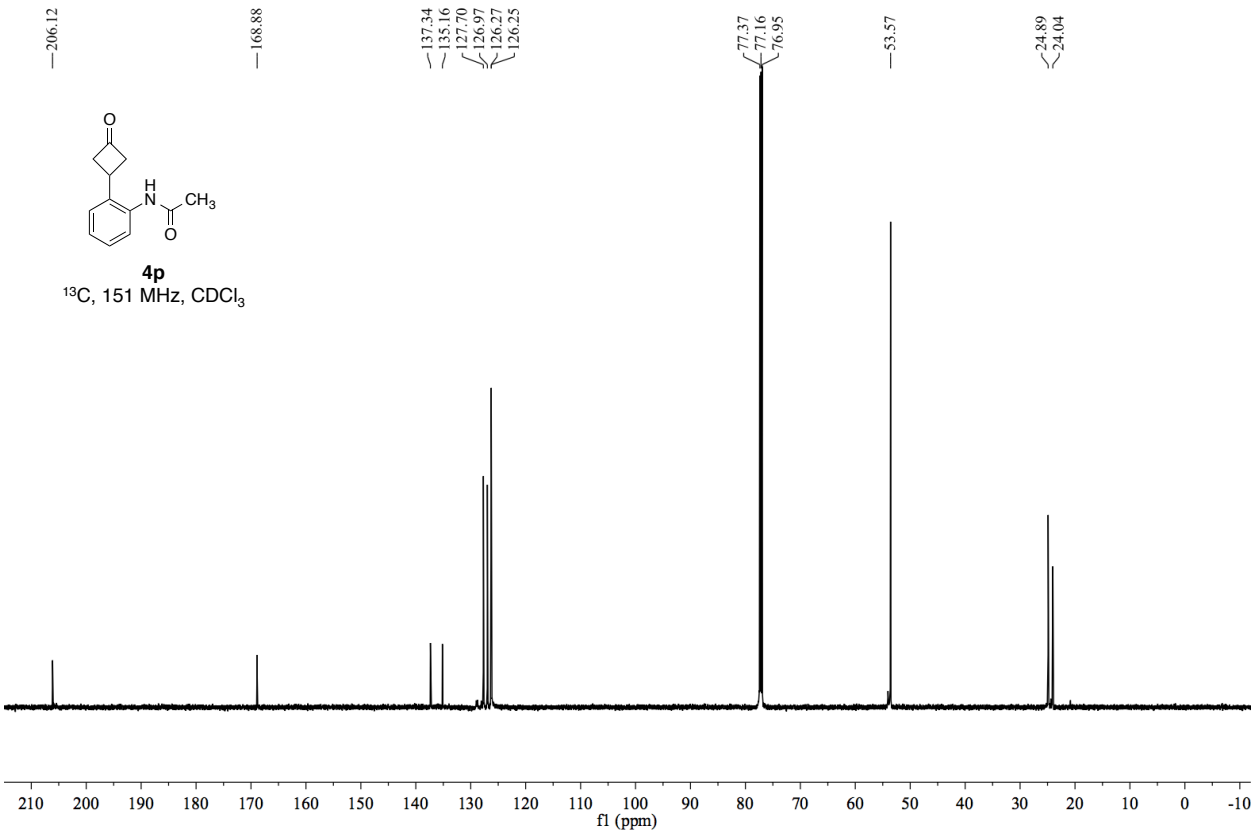
4o
^{1}H, 600 MHz, $CDCl_3$



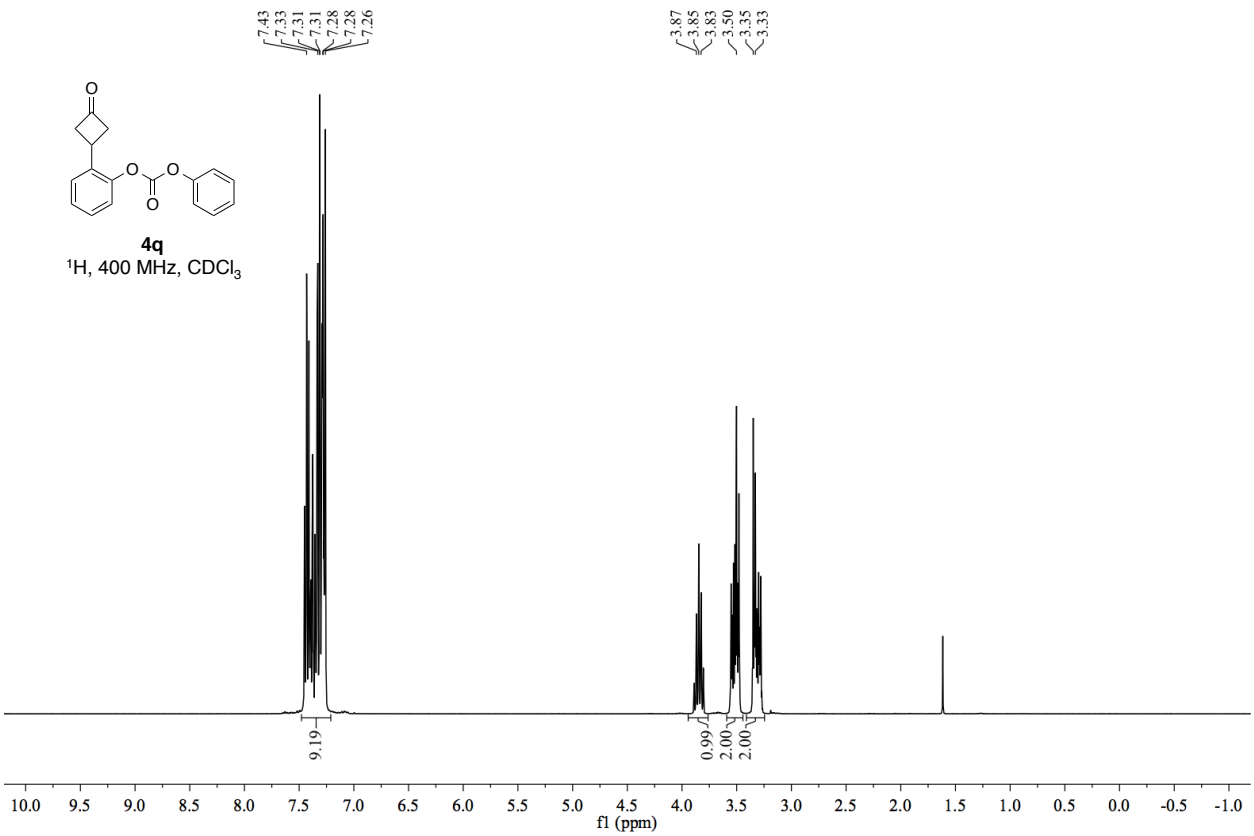
4o
^{13}C, 151 MHz, $CDCl_3$



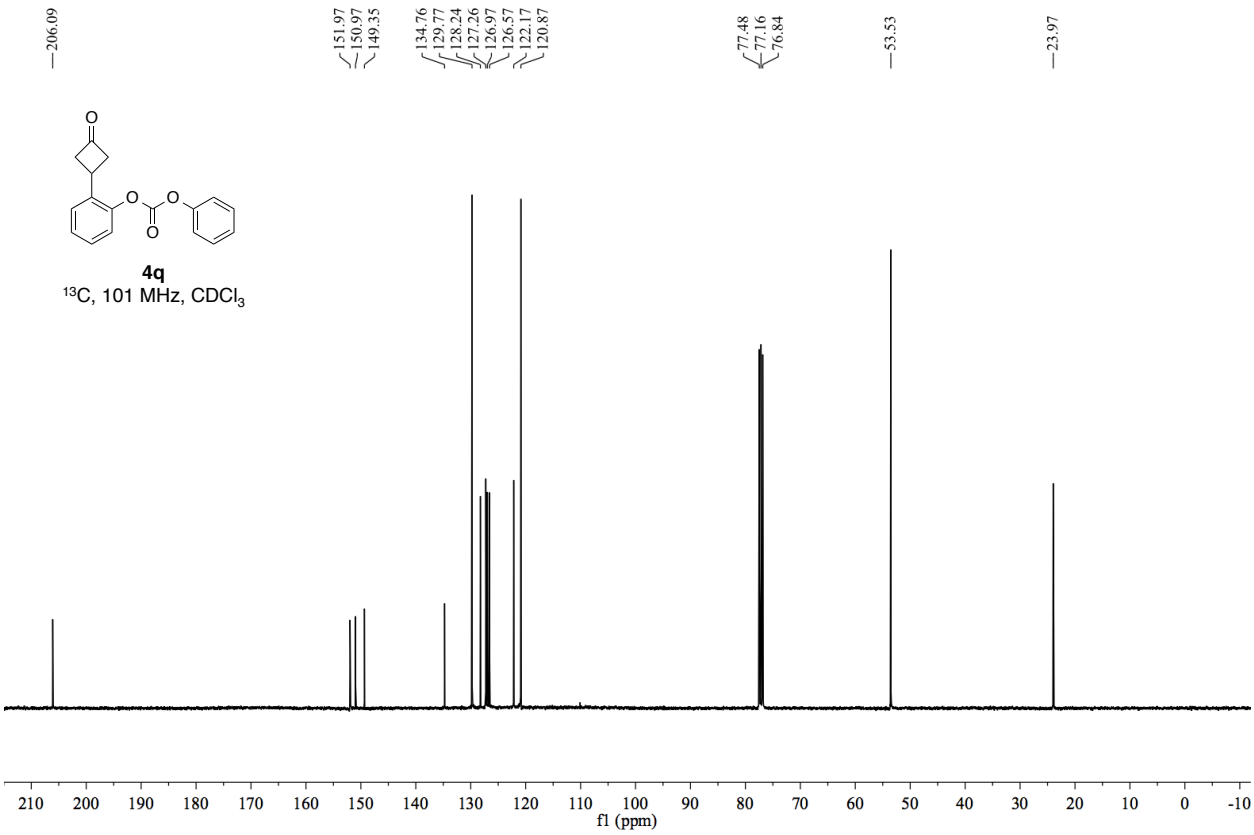
4p
^{1}H, 600 MHz, $CDCl_3$



4p
^{13}C, 151 MHz, $CDCl_3$



4q
^{1}H, 400 MHz, $CDCl_3$



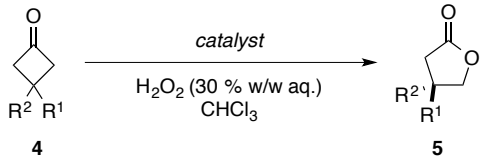
4q
^{13}C, 101 MHz, $CDCl_3$

6. Baeyer–Villiger Oxidation of Cyclobutanones

General Remarks:

Ethanol stabilizer and residual acid were removed by passage of $CHCl_3$ through basic alumina immediately prior to reaction setup. 1,3,5-trimethoxybenzene was purified by sublimation for ^1H NMR yield determination.

6.1 General Procedures A–D



Procedure A: Racemic standard with diphenyl phosphate

To an HPLC vial equipped with Teflon coated stir bar was added **4** (0.0125–0.025 mmol, 1.0 equiv), diphenyl phosphate (0.20 equiv) and dissolved in $CHCl_3$ (0.10 M w.r.t. **4**). Next, 30 % aqueous w/w H_2O_2 (2.0 equiv) was added and the resulting mixture was vigorously stirred 24–48 h. The reaction mixture was then filtered through a SiO_2 (5 cm x 0.5 cm) plug topped with Na_2SO_3, eluting with an appropriate EtOAc/hexanes mixture to afford the racemic *γ*-butyrolactone products (**5**).

Procedure B: Screening procedure for peptide catalysts

To an HPLC vial equipped with Teflon coated stir bar was added **4** (0.025–0.05 mmol, 1.0 equiv), peptide catalyst (0.10–0.20 equiv) and dissolved in $CHCl_3$ (0.10 M w.r.t. **4**). The resulting solution was cooled to 0 °C, followed by addition of 30 % aqueous w/w H_2O_2 (1.5 equiv) the resulting mixture was vigorously stirred overnight at 4 °C (ambient temperature). The reaction mixture was then filtered through a SiO_2 (5 cm x 0.5 cm) plug topped with Na_2SO_3, eluting with an appropriate EtOAc/hexanes mixture. Unreacted starting material (**4**) and lactone products **5** were collected together and concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ and analyzed by ^1H NMR and HPLC.

Procedure C: General protocol for isolated yields experiments

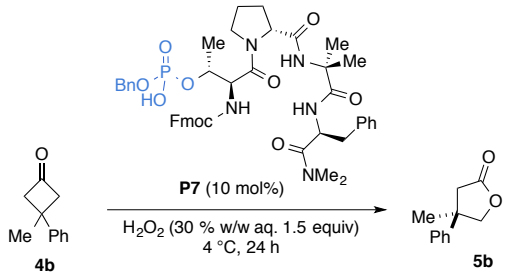
To an oven-dried 10 mL Schlenk tube equipped with Teflon coated stir bar was added **4** (0.10 mmol, 1.0 equiv), peptide catalyst (2.5 mol%) and dissolved in $CHCl_3$ (2.0 mL, 0.05 M w.r.t. **4**). The resulting solution was cooled to –15 °C (maintained by a cryostat, ±3 °C), followed by addition of 30 % aqueous w/w H_2O_2 (15.4 μL, 1.5 equiv) in a single portion, and the resulting mixture was vigorously stirred for 24–96 h. Conversion was monitored by TLC and UPLC-MS for completion. The reaction mixture was then directly purified by FCC (SiO_2, topped with Na_2SO_3) using an appropriate EtOAc/hexanes mixture to afford the enantioenriched *γ*-butyrolactone products (**5**).

Procedure D: General protocol for ^{1}H NMR yields experiments

To an oven-dried 1 dr vial equipped with Teflon coated stir bar was added **4** (0.05 mmol, 1.0 equiv), peptide catalyst (2.5 mol%) and dissolved in $CHCl_3$ (1.0 mL, 0.05 M w.r.t. **4**). The resulting solution was cooled to –15 °C (maintained by a cryostat, ±3 °C), followed by addition of 30 % aqueous w/w H_2O_2 (7.7 µL, 1.5 equiv) in a single portion, and the resulting mixture was vigorously stirred for 24 h. The reaction mixture was then filtered through a SiO_2 (5 cm x 0.5 cm) plug topped with Na_2SO_3 eluting with an appropriate EtOAc/hexanes mixture. Unreacted starting material (**4**) and lactone products **5** were collected together and concentrated *in vacuo*. The crude residue was dissolved in $CDCl_3$ containing an internal standard (1.0 mL; 0.0166 mmol 1,3,5-trimethoxybenzene) and conversion was determined using the ^{1}H signal of the internal standard at δ 6.09 (3H, s) normalized to 1.00.

6.2 Supplementary Screening Tables

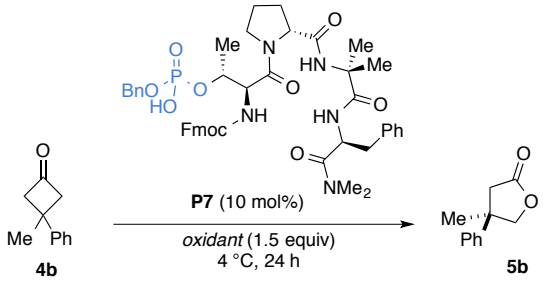
Table S1. Solvent screen. [a]



entry	solvent	conv. (%)[b]	er[c]	observations
1	MeOH	28	50:50	methyl ketal formation
2	EtOH	41	51:49	complex mixtures
3	HFIP	74	53:47	-
4	*i*-PrOH	45	50:50	-
5	Et_2O	24	49:51	**P7** insoluble
6	THF	24	49:51	complex mixture
7	2-MeTHF	22	50:50	complex mixture
8	1,4-dioxane	31	49:51	complex mixture
9	Benzene	97	34:66	-
10	PhMe	87	35:65	-
11	CH_2Cl_2	93	33:67	-
12	$CHCl_3$	92	31:69	-
13[d]	$CHCl_3$	91	31:69	-
14	CCl_4	49	42:58	-
15	EtOAc	38	47:53	complex mixture
16	DMF	-	-	no reaction
17	CH_3CN	31	49:51	complex mixture
18	Acetone	16	50:50	complex mixture
19	t-amylOH	20	51:49	complex mixture

[a] Reactions were performed according to **Procedure B**, and reported results are from a single trial (0.05 mmol). [b] Conversion determined by ^{1}H NMR relative integrations. [c] Enantiomeric ratios were determined by CSP-HPLC analysis (Chiralpak IA, 210 nm). [d] $CHCl_3$ was distilled over K_2CO_3 prior to use.

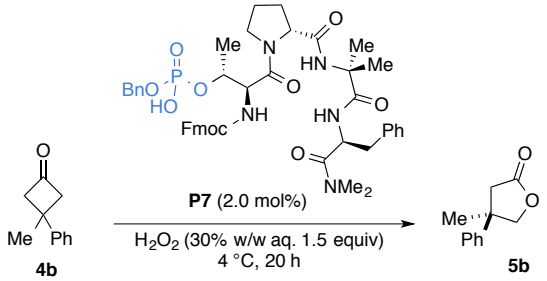
Table S2. Terminal oxidant source. [a]



entry	oxidant	conv. (%)[b]	er[c]
1	50% aq H_2O_2	93	34:66
2	40% aq H_2O_2	89	33:67
3	30% aq H_2O_2	85	33:67
4	20% aq H_2O_2	72	32:68
5	10% aq H_2O_2	53	32:68
6	Urea H_2O_2 complex	15	35:65
7	tBuOOH (70% aq w/w)	14	51:49

[a] Reactions were performed according to **Procedure B**, and reported results are from a single trial (0.05 mmol). [b] Conversion determined by ^{1}H NMR relative integrations. [c] Enantiomeric ratios were determined by CSP-HPLC analysis (Chiralpak IA, 210 nm).

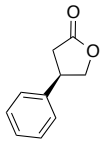
Table S3. Equivalents of H_2O_2. [a]



entry	equivalents oxidant	conv. (%)[b]	er[c]
1	30% aq H_2O_2 (1.5 equiv)	44	32:68
2	30% aq H_2O_2 (2 equiv)	47	32:68
3	30% aq H_2O_2 (3 equiv)	50	32:68
4	30% aq H_2O_2 (5 equiv)	53	32:68

[a] Reactions were performed according to **Procedure B**, and reported results are from a single trial (0.05 mmol). [b] Conversion determined by ^{1}H NMR relative integrations. [c] Enantiomeric ratios were determined by CSP-HPLC analysis (Chiralpak IA, 210 nm).

6.3. Characterization of γ-butyrolactones 5



5a

(*R*)-4-phenyldihydrofuran-2(3*H*)-one (5a)[20a,b] was synthesized from **4a** (7.3 mg, 0.05 mmol, 1.0 equiv) by following **Procedure D** with **P42** (1.1 mg, 1.3 μmol, 0.025 equiv). An analytical sample was obtained by FCC (SiO_2, 15% EtOAc/hexanes) of racemic standard.

Yield: 79% (^{1}H NMR yield, average of 2 trials)

TLC: R_f = 0.34 (20% EtOAc/hexanes)

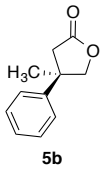
IR (FT-ATR, neat, cm^{-1}): 3068, 3033, 2975, 2906, 1760, 1602, 1496, 1456, 1354, 1156, 1008, 760.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.37 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.33–7.28 (m, 1H), 7.24 (dd, *J* = 7.2, 1.7 Hz, 2H), 4.67 (dd, *J* = 9.1, 7.9 Hz, 1H), 4.27 (dd, *J* = 9.1, 7.9 Hz, 1H), 3.79 (app p, *J* = 8.4 Hz, 1H), 2.93 (dd, *J* = 17.5, 8.7 Hz, 1H), 2.68 (dd, *J* = 17.5, 9.1 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.5, 139.5, 129.3, 127.8, 126.8, 74.2, 41.2, 35.8.

$[\alpha]_D^{20}$ –31.6 (*c* = 0.33, $CHCl_3$), [Lit.[20b] **$[\alpha]_D^{20}$** –67.2 (*c* = 2.0, $CHCl_3$) for **(*R*)-5a**, 99% ee]

Chiral HPLC: Chiralpak IA column, 10% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 220 nm). 80:20 er, t_{ret} = 12.6 min [(*S*) minor], t_{ret} 14.4 = min [(*R*) major].



5b

(*R*)-4-methyl-4-phenyldihydrofuran-2(3*H*)-one (5b)[20a,c] was synthesized from **4b** (7.7 mg, 0.05 mmol, 1.0 equiv) by following **Procedure D** with **P18** (4.8 mg, 5.0 μmol, 0.05 equiv) at –15 °C in $CHCl_3$ (0.5 mL, 0.10 M). An analytical sample was obtained by FCC (SiO_2, 50% EtOAc/hexanes) of racemic standard.

Yield: 73% (^{1}H NMR yield, average of 2 trials)

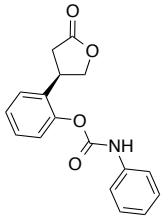
TLC: R_f = 0.41 (20% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 2966, 1772, 1499, 1446, 1302, 1166, 1017, 764, 699.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (t, *J* = 7.7 Hz, 2H), 7.32–7.27 (m, 1H), 7.20–7.17 (m, 2H), 4.45–4.39 (m, 2H), 2.92 (d, *J* = 16.8 Hz, 1H), 2.68 (d, *J* = 16.8 Hz, 1H), 1.53 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.3, 144.4, 129.2, 127.4, 125.3, 78.5, 44.3, 42.1, 28.2.

Chiral HPLC: Chiralpak IA column, 10% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 220 nm. 78:22 e.r., t_{ret} = 12.0 min (minor), t_{ret} = 18.6 min (major).



5c

(*R*)-2-(5-oxotetrahydrofuran-3-yl)phenyl phenylcarbamate (5c) was synthesized from **4c** (28.1 mg, 0.10 mmol, 1.0 equiv) by following **Procedure C** with **P41** (2.2 mg, 2.5 μmol, 0.025 equiv). The crude product was purified by FCC (SiO_2, 30% EtOAc/hexanes) to afford the title compound as a white solid.

*Slow evaporation of **5c** from $CDCl_3$ afforded crystals suitable for x-ray diffraction.*

Yield: 29.3 mg, 99% (Isolated, Average of 2 trials)

TLC: R_f = 0.50 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3314, 1767, 1727, 1705, 1598, 1526, 1499, 1445, 1324, 1213, 1170, 1096, 1029, 754, 688.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 7.9 Hz, 2H), 7.37–7.30 (m, 3H), 7.29–7.22 (m, 4H), 7.11 (t, *J* = 7.4 Hz, 1H), 4.69–4.62 (m, 1H), 4.30 (dd, *J* = 9.3, 6.2 Hz, 1H), 3.96–3.87 (m, 1H), 2.93 (dd, *J* = 17.7, 9.5 Hz, 1H), 2.70 (dd, *J* = 17.7, 7.0 Hz, 1H).

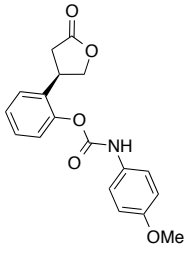
^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.2, 151.2, 148.6, 137.2, 132.7, 129.3, 128.9, 127.8, 126.6, 124.3, 123.5, 119.0, 73.6, 36.2, 35.1.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_4$ 298.1079, found 298.1076.

$[\alpha]_D^{20}$ –22.3 (*c* = 0.68, $CHCl_3$).

Chiral HPLC: *Crude reaction analysis:* Chiralpak IA column, 15% EtOH/hexanes eluent, 1.5 mL·min^{-1} flow rate, 25 °C, 230 nm. t_{ret} = 11.4 min (minor), t_{ret} 15.5 = min (major).

Isolated samples: Chiralpak AD-H column, 20% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm. 94:6 e.r., t_{ret} = 24.1 min (minor), t_{ret} = 37.9 min (major).



5d

(*R*)-2-(5-oxotetrahydrofuran-3-yl)phenyl (4-methoxyphenyl)carbamate (5d) was synthesized from **4d** (31.1 mg, 0.10 mmol, 1.0 equiv) by following **Procedure C** with **P41** (2.2 mg, 2.5 μmol, 0.025 equiv). The crude product was purified by FCC (SiO_2, 25% EtOAc/hexanes) to afford the title compound as a white solid.

Yield: 32.6 mg, 99% (Isolated, Average of 2 trials)

TLC: R_f = 0.39 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3341, 2939, 2842, 1765, 1728, 1708, 1599, 1528, 1511, 1417, 1298, 1212, 1166, 1098, 1015, 830.

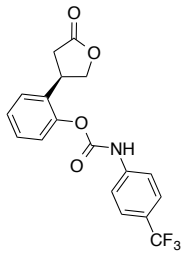
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.39–7.30 (m, 3H), 7.27–7.21 (m, 3H), 7.18 (bs, 1H), 6.86 (app d, *J* = 9.0 Hz, 2H), 4.65 (t, *J* = 8.7 Hz, 1H), 4.29 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.91 (app p, *J* = 7.4 Hz, 1H), 3.78 (s, 3H), 2.92 (dd, *J* = 17.8, 9.5 Hz, 1H), 2.69 (dd, *J* = 17.7, 7.1 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.2, 156.5, 151.6, 148.7, 132.7, 130.3, 128.8, 127.8, 126.5, 123.5, 121.0, 114.5, 73.5, 55.6, 36.2, 35.0.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}NO_5$ 328.1185, found 328.1190.

$[\alpha]_D^{20}$ –14.4 (*c* = 0.77, $CHCl_3$).

Chiral HPLC: Chiralpak AD-H column, 25% EtOH/hexanes eluent, 1.0 $mL \cdot min^{-1}$ flow rate, 25 °C, 230 nm. 93:7 e.r., t_{ret} = 38.8 min (minor), t_{ret} = 50.8 min (major).



5e

(*R*)-2-(5-oxotetrahydrofuran-3-yl)phenyl (4-(trifluoromethyl)phenyl)carbamate (5e) was synthesized from **4e** (34.9 mg, 0.10 mmol, 1.0 equiv) by following **Procedure C** with **P41** (2.2 mg, 2.5 μmol, 0.025 equiv). The crude product was purified by FCC (SiO_2, 30% EtOAc/hexanes) to afford the title compound as a white solid.

*Single crystals were grown by vapor diffusion of pentane into a saturated solution of **5e** (from 92:8 er) in EtOAc*.

Yield: 35.5 mg, 98% (Isolated, Average of 2 trials)

TLC: R_f = 0.47 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3286, 1744, 1606, 1541, 1492, 1412, 1317, 1205, 1162, 1109, 1065, 1003, 840, 749

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.64–7.57 (m, 4H), 7.39–7.34 (m, 2H), 7.33–7.30 (m, 1H), 7.30–7.24 (m, 3H), 4.69 (dd, *J* = 9.4, 8.1 Hz, 1H), 4.33 (dd, *J* = 9.4, 5.5 Hz, 1H), 3.90 (ddt, *J* = 9.7, 8.1, 5.8 Hz, 1H), 2.98 (dd, *J* = 17.8, 9.7 Hz, 1H), 2.72 (dd, *J* = 17.8, 6.1 Hz, 1H).

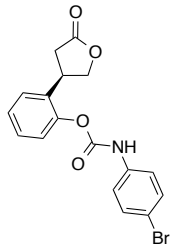
^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.6, 151.0, 148.4, 140.5, 132.6, 129.0, 128.2, 126.7, 126.6 (q, *J* = 3.7 Hz), 126.1 (q, *J* = 32.8 Hz), 124.2 (q, *J* = 271.6 Hz), 123.4, 118.7, 73.6, 36.6, 35.1.

^{19}F NMR (376 MHz, Chloroform-*d*) δ –62.17.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{15}F_3NO_4$ 366.0953, found 366.0969.

$[\alpha]_D^{20}$ –19.0 (*c* = 1.5, $CHCl_3$).

Chiral HPLC: Chiralpak AD-H column, 20% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm. 93:7 e.r., t_{ret} = 17.0 min (minor), t_{ret} = 20.0 min (major),



5f

(*R*)-2-(5-oxotetrahydrofuran-3-yl)phenyl (4-bromophenyl)carbamate (5f) was synthesized from **4f** (36.0 mg, 0.10 mmol, 1.0 equiv) by following **Procedure C** with **P41** (2.2 mg, 2.5 μmol, 0.025 equiv). The crude product was purified by FCC (SiO_2, 30% EtOAc/hexanes) to afford the title compound as a white solid.

*Single crystals were grown by vapor diffusion of pentane into a saturated solution of **5f** (from 92:8 er) in EtOAc*.

Yield: 35.1 mg, 94% (Isolated, average of 2 trials)

TLC: R_f = 0.47 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3315, 1767, 1740, 1595, 1432, 1489, 1397, 1308, 1202, 1174, 1101, 1003, 825.

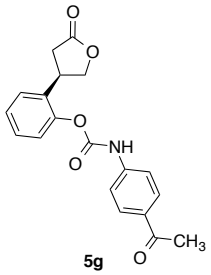
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.46 (s, 1H), 7.41 (app d, *J* = 8.8 Hz, 2H), 7.37–7.31 (m, 3H), 7.28–7.22 (m, 3H), 4.65 (dd, *J* = 9.3, 9.1 Hz, 1H), 4.29 (dd, *J* = 9.3, 6.2 Hz, 1H), 3.89 (tt, *J* = 9.1, 7.0 Hz, 1H), 2.93 (dd, *J* = 17.7, 9.5 Hz, 1H), 2.69 (dd, *J* = 17.7, 7.0 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.4, 151.2, 148.5, 136.5, 132.5, 132.2, 128.9, 128.0, 126.6, 123.4, 120.6, 116.9, 73.5, 36.4, 35.0.

HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}BrNO_4$ 376.0184, found 376.0182.

$[\alpha]_D^{20}$ –14.3 (*c* = 1.5, $CHCl_3$).

Chiral HPLC: Chiralpak AD-H column, 20% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm. 94:6 e.r., t_{ret} = 40.2 min (minor), t_{ret} = 45.0 min (major).



5g

(*R*)-2-(5-oxotetrahydrofuran-3-yl)phenyl (4-acetylphenyl)carbamate (5g) was synthesized from **4g** (32.3 mg, 0.10 mmol, 1.0 equiv) by following **Procedure C** with **P41** (2.2 mg, 2.5 μmol, 0.025 equiv).

The crude product was purified by FCC (SiO_2, 40% EtOAc/hexanes) to afford the title compound as a white solid.

Yield: 32.4 mg, 95% (Isolated, average of 2 trials)

TLC: R_f = 0.21 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3289, 1769, 1744, 1671, 1596, 1533, 1490, 1409, 1359, 1273, 1202, 1169, 1100, 1002, 957.

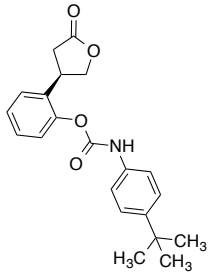
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.73 (bs, 1H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.36 (td, *J* = 7.8, 2.4 Hz, 1H), 7.31–7.23 (m, 3H), 4.67 (dd, *J* = 9.3, 8.0 Hz, 1H), 4.31 (dd, *J* = 9.4, 6.2 Hz, 1H), 3.97–3.86 (m, 1H), 2.95 (dd, *J* = 17.8, 9.5 Hz, 1H), 2.71 (dd, *J* = 17.8, 6.8 Hz, 1H), 2.58 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 197.1, 177.4, 151.0, 148.4, 141.8, 132.9, 132.6, 130.0, 129.0, 128.1, 126.8, 123.4, 118.3, 73.6, 36.4, 35.1, 26.6.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{18}NO_5$ 340.1185, found 340.1174.

$[\alpha]_D^{20}$ –13.8 (*c* = 1.42, $CHCl_3$).

Chiral HPLC: Chiralpak AD-H column, 35% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm). 8:92 er, t_{ret} 21.7 = min (minor), t_{ret}= 37.1 min (major).



5h

(*R*)-2-(5-oxotetrahydrofuran-3-yl)phenyl (4-(*tert*-butyl)phenyl)carbamate (5h) was synthesized from **4h** (33.7 mg, 0.10 mmol, 1.0 equiv) by following **Procedure C** with **P41** (2.2 mg, 2.5 μmol, 0.025 equiv). The crude product was purified by FCC (SiO_2, 25% EtOAc/hexanes) to afford the title compound as a white solid.

Yield: 33.9 mg, 96% (Isolated, average of 2 trials)

TLC: R_f = 0.58 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3313, 2962, 1782, 1743, 1714, 1598, 1538, 1489, 1410, 1321, 1214, 1178, 956.

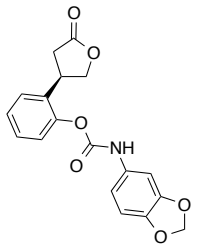
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.43–7.32 (m, 5H), 7.30–7.23 (m, 3H), 7.09 (bs, 1H), 4.67 (t, *J* = 8.4 Hz, 1H), 4.31 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.92 (p, *J* = 7.4 Hz, 1H), 2.94 (dd, *J* = 17.7, 9.5 Hz, 1H), 2.71 (dd, *J* = 17.7, 6.9 Hz, 1H), 1.31 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.1, 151.3, 148.7, 147.4, 134.5, 132.9, 128.9, 127.8, 126.6, 126.2, 123.5, 118.8, 73.6, 36.2, 35.1, 34.5, 31.5.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{24}NO_4$ 354.1705, found 354.1701.

$[\alpha]_D^{20}$ –15.9 (*c* = 0.90, $CHCl_3$).

Chiral HPLC: Chiralpak AD-H column, 20% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm). 94:6 er, t_{ret} 19.9 = min (minor), t_{ret}= 26.7 min (major).



5i

(*R*)-2-(5-oxotetrahydrofuran-3-yl)phenyl benzo[*d*][1,3]dioxol-5-ylcarbamate (5i) was synthesized from **4i** (32.5 mg, 0.10 mmol, 1.0 equiv) by following **Procedure C** with **P41** (2.2 mg, 2.5 μmol, 0.025 equiv). The crude product was purified by FCC (SiO_2, 10% EtOAc/hexanes) to afford the title compound as a white foam.

Yield: 33.1 mg, 97% (Isolated, average of 2 trials)

TLC: R_f = 0.39 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3321, 1771, 1738, 1547, 1488, 1450, 1343, 1242, 1201, 1172, 1101, 1034, 1001, 926.

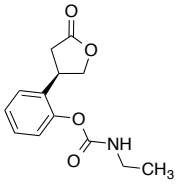
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.34 (ddd, *J* = 8.1, 6.8, 2.1 Hz, 1H), 7.30–7.22 (m, 3H), 7.19–7.09 (m, 2H), 6.83–6.72 (m, 2H), 5.95 (s, 2H), 4.67 (t, *J* = 8.7 Hz, 1H), 4.31 (dd, *J* = 9.3, 6.2 Hz, 1H), 3.91 (p, *J* = 7.4 Hz, 1H), 2.94 (dd, *J* = 17.8, 9.5 Hz, 1H), 2.70 (dd, *J* = 17.8, 6.9 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.3, 151.5, 148.7, 148.2, 144.4, 132.8, 131.4, 128.9, 127.9, 126.5, 123.5, 112.5, 108.4, 102.0, 101.5, 73.6, 36.3, 35.0.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{16}NO_6$ 342.0978, found 342.0975.

$[\alpha]_D^{20}$ –18.6 (*c* = 1.47, $CHCl_3$).

Chiral HPLC: Chiralpak AD-H column, 25% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm). 93:7 er, t_{ret} 35.0 = min (minor), t_{ret}= 45.1 min (major).



5j

(*R*)-2-(5-oxotetrahydrofuran-3-yl)phenyl ethylcarbamate (5j) was synthesized from **4j** (23.3 mg, 0.10 mmol, 1.0 equiv) by following **Procedure C** with **P41** (2.2 mg, 2.5 μmol, 0.025 equiv). The crude product was purified by FCC (SiO_2, 40% EtOAc/hexanes) to afford the title compound as a white solid.

Yield: 23.9 mg, 96% (Isolated, Average of 2 trials)

TLC: R_f = 0.29 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3395, 3321, 1772, 1754, 1726, 1530, 1488, 1446, 1384, 1213, 1183, 1166, 1101, 1019, 980.

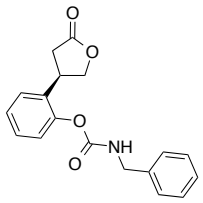
^{1}H NMR (9:1 rotamer ratio [A = major, B = minor], 600 MHz, Chloroform-*d*) δ 7.34–7.15 (A+B)(m, 4H), 5.24 (A)(t, *J* = 6.0 Hz, 1H), 4.90 (B)(s, 1H), 4.68–4.59 (A+B)(m, 1H), 4.27 (A+B)(dd, *J* = 9.2, 6.6 Hz, 1H), 3.95–3.80 (A+B)(m, 1H), 3.42–3.35 (B)(m, 2H), 3.30 (A)(dt, *J* = 13.1, 7.0 Hz, 2H), 2.90 (A+B)(dd, *J* = 17.7, 9.4 Hz, 1H), 2.68 (A+B)(dd, *J* = 17.7, 7.5 Hz, 1H), 1.25 (B)(t, *J* = 7.3 Hz, 3H), 1.22 (A)(t, *J* = 7.3 Hz, 3H).

^{13}C NMR (Major rotamer, 151 MHz, Chloroform-*d*) δ 177.0, 154.0, 149.1, 132.5, 128.7, 127.6, 126.1, 123.4, 73.5, 36.4, 36.2, 34.8, 15.1.

HRMS (ESI/Q-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{15}NO_4Na$ 272.0899, found 272.0894.

$[\alpha]_D^{20}$ –26.4 (*c* = 1.37, $CHCl_3$).

Chiral HPLC: Chiralpak AD-H column, 30% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 220 nm. 85:15 e.r., t_{ret} = 6.3 min (minor), t_{ret} = 7.3 min (major).



5k

(*R*)-2-(5-oxotetrahydrofuran-3-yl)phenyl benzylcarbamate (5k) was synthesized from **4k** (29.5 mg, 0.10 mmol, 1.0 equiv) by following **Procedure C** with **P41** (2.2 mg, 2.5 μmol, 0.025 equiv). The crude product was purified by FCC (SiO_2, 30% EtOAc/hexanes) to afford the title compound as a white solid.

Yield: 29.6 mg, 95% (Isolated, Average of 2 trials)

TLC: R_f = 0.37 (40% EtOAc/hexanes)

IR (FT-ATR, thin film $CHCl_3$, cm^{-1}): 3326, 2025, 2922, 1773, 1717, 1525, 1489, 1454, 1258, 1213, 1178, 1117, 1018, 746.

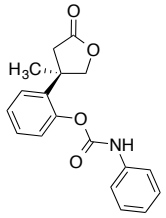
^{1}H NMR (87:13 rotamer ratio [A = major, B = minor], 600 MHz, Chloroform-*d*) δ 7.42–7.06 (A+B)(m, 19H), 5.56 (A)(t, *J* = 6.1 Hz, 1H), 5.40 (B)(bs, 1H), 4.64–4.59 (A)(m, 1H), 4.50 (B)(d, *J* = 6.3 Hz, 2H), 4.46 (A)(d, *J* = 6.0 Hz, 2H), 4.35–4.30 (B)(m, 1H), 4.27 (A)(dd, *J* = 9.3, 6.6 Hz, 1H), 4.13 (B)(t, *J* = 8.2 Hz, 1H), 3.93–3.82 (A)(m, 1H), 3.47 (B)(app p, *J* = 8.1 Hz, 1H), 2.89 (A)(dd, *J* = 17.7, 9.5 Hz, 1H), 2.67 (A)(dd, *J* = 17.7, 7.5 Hz, 1H), 2.61 (B)(dd, *J* = 17.6, 9.0 Hz, 1H), 2.52 (B)(dd, *J* = 17.7, 8.4 Hz, 1H).

^{13}C NMR (Major rotamer, 151 MHz, Chloroform-*d*) δ 177.0, 154.3, 149.1, 137.9, 132.5, 129.0, 128.8, 128.0, 127.8, 127.6, 126.3, 123.4, 73.6, 45.6, 36.1, 34.9.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}NO_4$ 312.1236, found 312.1250.

$[\alpha]_D^{20}$ –19.3 (*c* = 1.66, $CHCl_3$).

Chiral HPLC: Chiralpak AD-H column, 25% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 220 nm. 83:17 e.r., t_{ret} = 12.5 min (minor), t_{ret} = 15.4 min (major).



5l

(*R*)-2-(3-methyl-5-oxotetrahydrofuran-3-yl)phenyl phenylcarbamate (5l) was synthesized from **4l** (29.5 mg, 0.10 mmol, 1.0 equiv) by following **Procedure C** with **P41** (2.2 mg, 2.5 μmol, 0.025 equiv). The crude product was purified by FCC (SiO_2, 25% EtOAc/hexanes) to afford the title compound as a white foam.

Yield: 29.3 mg, 94% (Isolated, Average of 2 trials)

TLC: R_f = 0.53 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3300, 1751, 1724, 1602, 1539, 1490, 1442, 1316, 1187, 1075, 1019, 1003, 745.

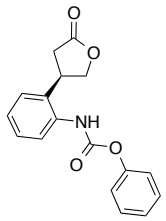
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 7.9 Hz, 2H), 7.40–7.31 (m, 4H), 7.28–7.19 (m, 2H), 7.17–7.09 (m, 2H), 4.58 (d, *J* = 9.1 Hz, 1H), 4.48 (d, *J* = 9.0 Hz, 1H), 2.98 (d, *J* = 16.9 Hz, 1H), 2.80 (d, *J* = 16.9 Hz, 1H), 1.51 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.5, 151.3, 148.1, 137.2, 136.2, 129.3, 128.6, 127.0, 126.5, 124.4, 124.2, 119.1, 78.3, 43.1, 42.1, 27.4.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}NO_4$ 312.1236, found 312.1227.

$[\alpha]_D^{20}$ +8.1 (*c* = 1.10, $CHCl_3$).

Chiral HPLC: Chiralpak AD-H column, 20% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm. 80:20 e.r., t_{ret} = 12.9 min (minor), t_{ret} = 16.9 min (major)



5m

phenyl (*R*)-(2-(5-oxotetrahydrofuran-3-yl)phenyl)carbamate (5m) was synthesized from **4m** (14.0 mg, 0.050 mmol, 1.0 equiv) by following **Procedure D** with **P41** (1.1 mg, 1.3 μmol, 0.025 equiv). An analytical sample was obtained by preparative TLC (SiO_2, 50% EtOAc/hexanes) of racemic standard.

Yield: 81% (^{1}H NMR yield, Average of 2 trials)

TLC: R_f = 0. 42 (40% EtOAc/hexanes)

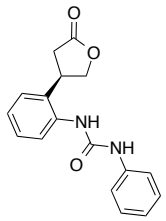
IR (FT-ATR, neat, cm^{-1}): 3291, 1771, 1712, 1589, 1525, 1479, 1456, 1297, 1185, 1161, 1013, 994, 752.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.48–7.42 (m, 1H), 7.42–7.37 (m, 2H), 7.36–7.29 (m, 3H), 7.27–7.23 (m, 1H), 7.22–7.14 (m, 2H), 6.79 (bs, 1H), 4.70 (dd, *J* = 9.3, 7.8 Hz, 1H), 4.31 (dd, *J* = 9.3, 6.7 Hz, 1H), 4.13–3.95 (m, 1H), 2.98 (dd, *J* = 17.7, 9.0 Hz, 1H), 2.65 (dd, *J* = 17.7, 7.7 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.5, 153.3, 150.7, 134.4, 129.6, 128.5, 127.9, 126.5, 126.3, 126.0, 121.6, 73.9, 35.8, 35.7.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_4$ 298.1079, found 298.1065.

Chiral HPLC: Chiralpak AD-H column, 20% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm. 91:9 er, t_{ret} 19.5 = min (major), t_{ret} = 23.2 min (major).



5n

(*R*)-1-(2-(5-oxotetrahydrofuran-3-yl)phenyl)-3-phenylurea (5n) was synthesized from **4n** (14.0 mg, 0.05 mmol, 1.0 equiv) by following **Procedure D** with **P41** (1.1 mg, 1.3 μmol, 0.025 equiv). Due to low solubility in $CHCl_3$, MeOH was added upon work-up. The homogenous solution was then filtered through a SiO_2 column eluting with 100% EtOAc to afford the crude enantioenriched product. An analytical sample was obtained by washing the racemic standard (prepared from the reaction of **4n** with diphenyl phosphate (1.0 equiv) and H_2O_2 (30% w/w aq, 5.0 equiv) in $CHCl_3$ [0.10 M] for 48 hours) with 30% EtOAc/hexanes.

Yield: 32% (^{1}H NMR yield, Average of 2 trials)

TLC: R_f = 0.47 (50% EtOAc/hexanes)

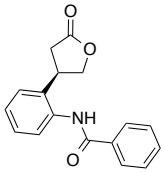
IR (FT-ATR, neat, cm^{-1}): 3329, 3246, 3026, 1772, 1627, 1599, 1550, 1492, 1440, 1313, 1229, 1171, 687

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.09 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.31–7.23 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.3 Hz, 1H), 4.65 (t, *J* = 8.1 Hz, 1H), 4.22 (t, *J* = 8.2 Hz, 1H), 3.99 (p, *J* = 8.1 Hz, 1H), 2.91 (dd, *J* = 17.1, 8.4 Hz, 1H), 2.70 (dd, *J* = 17.1, 8.8 Hz, 1H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 176.6, 153.3, 139.8, 136.7, 132.7, 128.8, 127.3, 126.2, 124.7, 124.7, 121.7, 118.1, 72.9, 35.5, 34.9.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_3$ 297.1239, found 297.1227.

Chiral HPLC: Chiralpak AD-H column, 20% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm). 77:23 er, t_{ret} 29.7 = min (major), $t_{re\ t}$= 37.5 min (minor).



5o

(*R*)-*N*-(2-(5-oxotetrahydrofuran-3-yl)phenyl)benzamide (5o) was synthesized from **4o** (13.3 mg, 0.05 mmol, 1.0 equiv) by following **Procedure D** with **P41** (1.1 mg, 1.3 μmol, 0.025 equiv). An analytical sample was obtained by preparative TLC (SiO_2, 75% EtOAc/hexanes) of racemic standard.

Yield: 74% (^{1}H NMR Yield, Average of 2 trials)

TLC: R_f = 0.26 (40% EtOAc/hexanes)

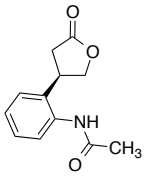
IR (FT-ATR, neat, cm^{-1}): 3272, 1767, 1645, 1603, 1580, 1514, 1480, 1300, 1171, 1017, 752.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.89 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.81 (s, 1H), 7.62–7.56 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.39–7.30 (m, 3H), 7.28 (d, *J* = 7.4 Hz, 1H), 4.67 (dd, *J* = 9.3, 7.8 Hz, 1H), 4.33 (dd, *J* = 9.3, 6.8 Hz, 1H), 3.98 (dtd, *J* = 9.0, 7.8, 6.7 Hz, 1H), 2.92 (dd, *J* = 17.8, 9.0 Hz, 1H), 2.64 (dd, *J* = 17.8, 7.8 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.7, 167.0, 137.1, 134.9, 133.8, 132.5 129.1, 128.4, 128.4, 127.4, 127.3, 126.5, 74.1, 36.0, 35.9.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3$ 282.1130, found 282.1127.

Chiral HPLC: Chiralpak AD-H column, 20% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm). 81:19 er, t_{ret} 34.5 = min (major), t_{ret} = 48.2 min (minor).



5p

(*R*)-*N*-(2-(5-oxotetrahydrofuran-3-yl)phenyl)acetamide (5p) was synthesized from **4p** (10.2 mg, 0.05 mmol, 1.0 equiv) by following **Procedure D** with **P41** (1.1 mg, 1.3 μmol, 0.025 equiv). An analytical sample was obtained by preparative TLC (SiO_2, 100% EtOAc) of racemic standard.

Yield: 62% (^{1}H NMR Yield, Average of 2 trials)

TLC: R_f = 0.47 (100% EtOAc)

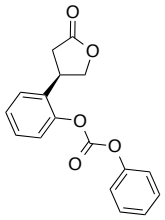
IR (FT-ATR, neat, cm^{-1}): 3248, 1771, 1661, 1585, 1530, 1482, 1447, 1370, 1297, 1273, 1160, 1018, 758.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.36–7.27 (m, 3H), 7.24–7.21 (m, 1H), 7.17 (bs, 1H), 4.66 (dd, *J* = 9.3, 7.8 Hz, 1H), 4.29 (dd, *J* = 9.3, 6.9 Hz, 1H), 3.96–3.86 (m, 1H), 2.92 (dd, *J* = 17.7, 9.1 Hz, 1H), 2.62 (dd, *J* = 17.7, 7.9 Hz, 1H), 2.21 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.8, 169.7, 136.8, 134.7, 128.4, 128.3, 127.4, 126.5, 74.1, 36.1, 35.9, 23.8.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{14}NO_3$ 220.0974, found 220.0974.

Chiral HPLC: Chiralpak AD-H column, 10% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm). 79:21 er, t_{ret} 37.5 = min (major), t_{ret} = 45.9 min (minor).



5q

(*R*)-2-(5-oxotetrahydrofuran-3-yl)phenyl phenyl carbonate (5q) was synthesized from **4q** (14.1 mg, 0.05 mmol, 1.0 equiv) by following **Procedure D** with **P42** (1.1 mg, 1.3 μmol, 0.025 equiv). An analytical sample was obtained by FCC (SiO_2, 50% EtOAc/hexanes) of racemic standard.

Yield: 49% (^{1}H NMR yield, Average of 2 trials)

TLC: R_f = 0.58 (40% EtOAc/hexanes)

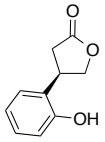
IR (FT-ATR, neat, cm^{-1}): 3300, 3247, 2383, 1770, 1592, 1557, 1493, 1458, 1149, 1220, 1199, 1156, 1022, 755.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44 (t, *J* = 7.8 Hz, 2H), 7.40–7.36 (m, 1H), 7.35–7.26 (m, 6H), 4.70 (dd, *J* = 9.2, 7.9 Hz, 1H), 4.32 (dd, *J* = 9.2, 7.0 Hz, 1H), 4.04 (p, *J* = 8.0 Hz, 1H), 2.96 (dd, *J* = 17.6, 9.1 Hz, 1H), 2.72 (dd, *J* = 17.6, 8.0 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.2, 152.0, 151.0, 149.0, 131.8, 129.84, 129.1, 127.4, 127.3, 126.7, 122.5, 120.9, 73.1, 35.3, 34.8.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}O_5$ 299.0919, found 299.0925.

Chiral HPLC: Chiralpak IA column, 15% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 210 nm. 73:23 er, t_{ret} 14.5 = min (minor), t_{ret}= 17.9 min (major).



5r

(*R*)-4-(2-hydroxyphenyl)dihydrofuran-2(3*H*)-one (5r) was synthesized from **4r** (8.1 mg, 0.05 mmol, 1.0 equiv) by following **Procedure D** with **P42** (1.1 mg, 1.3 μmol, 0.025 equiv). An analytical sample was obtained by preparative TLC (SiO_2, 50% EtOAc/hexanes) of racemic standard.

Yield: 81% (^{1}H NMR Yield, Average of 2 trials)

TLC: R_f = 0.42 (40% EtOAc/hexanes)

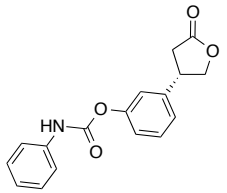
IR (FT-ATR, neat, cm^{-1}): 3340, 1747, 1609, 1594, 1507, 1456, 1343, 1268, 1108, 1011, 752.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.17 (td, *J* = 7.7, 1.6 Hz, 1H), 7.13 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.91 (td, *J* = 7.5, 1.1 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.74 (s, 1H), 4.70 (t, *J* = 8.5 Hz, 1H), 4.40 (dd, *J* = 8.9, 7.6 Hz, 1H), 3.97 (p, *J* = 8.4 Hz, 1H), 2.87 (d, *J* = 9.1 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 178.1, 153.9, 128.9, 128.3, 125.8, 121.1, 115.9, 73.2, 37.0, 34.1.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{11}O_3$ 179.0708, found 179.0712.

Chiral HPLC: Chiralpak AD-H column, 10% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm). 75:25 er, t_{ret} 12.0 = min (minor), t_{ret} = 13.6 min (major).



5s

(*S*)-3-(5-oxotetrahydrofuran-3-yl)phenyl phenylcarbamate (5s) was synthesized from **4s** (14.0 mg, 0.05 mmol, 1.0 equiv) by following **Procedure D** with **P41** (1.1 mg, 1.3 μmol, 0.025 equiv). An analytical sample was obtained by FCC (SiO_2, 50% EtOAc/hexanes) of racemic standard.

*Slow evaporation of **5s** from $CDCl_3$ afforded crystals suitable for x-ray diffraction.*

Yield: 97% (^{1}H NMR Yield, Average of 2 trials)

TLC: R_f = 0.46 (40% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3365, 3307, 1787, 1762, 1601, 1540, 1490, 1327, 1189, 1143, 1011, 766.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.37–7.32 (m, 2H), 7.16–7.10 (m, 3H), 7.08 (t, *J* = 2.1 Hz, 1H), 7.01 (s, 1H), 4.67 (dd, *J* = 9.1, 7.8 Hz, 1H), 4.28 (dd, *J* = 9.1, 7.8 Hz, 1H), 3.80 (p, *J* = 8.3 Hz, 1H), 2.94 (dd, *J* = 17.5, 8.7 Hz, 1H), 2.68 (dd, *J* = 17.5, 9.0 Hz, 1H).

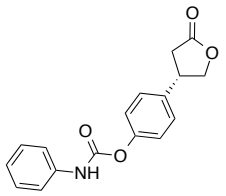
^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.2, 151.5, 151.2, 141.2, 137.3, 130.4, 129.4, 124.3, 124.1, 121.2, 120.4, 118.9, 73.9, 41.0, 35.8.

HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_4$ 298.1079, found 298.1093.

$[\alpha]_D^{20}$ +22.3 (*c* = 0.63, $CHCl_3$, 73% ee) **(*S*)-5s**

$[\alpha]_D^{20}$ –9.77 (*c* = 0.49, $CHCl_3$, 31% ee) **(*R*)-5s**

Chiral HPLC: Chiralpak IA column, 20% EtOH/hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm). 87:13 er, t_{ret} 27.6 = min [(*R*) minor], t_{ret} = 30.0 min [(*S*) major].



5t

(*S*)-4-(5-oxotetrahydrofuran-3-yl)phenyl phenylcarbamate (5t) was synthesized from **4t** (14.0 mg, 0.05 mmol, 1.0 equiv) by following **Procedure D** with **P41** (1.1 mg, 1.3 μmol, 0.025 equiv). An analytical sample was obtained by FCC (SiO_2, 30% EtOAc/hexanes) of racemic standard.

*A sample for specific rotation was obtained from performing **Procedure D** with **P42** (0.025 equiv), which provides the opposite enantiomer than **P41**, to afford **5t** in 21:79 er and 52% isolated yield. The absolute configuration of product **5t** is assigned in analogy to **5s**.*

Yield: 81% (^{1}H NMR Yield, Average of 2 trials)

TLC: R_f = 0.18 (30% EtOAc/hexanes)

IR (FT-ATR, neat, cm^{-1}): 3322, 1780, 1714, 1598, 1542, 1508, 1494, 1445, 1320, 1200, 1159, 1012, 842.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.37–7.31 (m, 2H), 7.28–7.24 (m, 2H), 7.23–7.18 (m, 2H), 7.12 (tt, *J* = 7.5, 1.1 Hz, 1H), 7.01 (s, 1H), 4.66 (dd, *J* = 9.1, 7.8 Hz, 1H), 4.26 (dd, *J* = 9.1, 7.9 Hz, 1H), 3.84–3.76 (m, 1H), 2.93 (dd, *J* = 17.5, 8.8 Hz, 1H), 2.66 (dd, *J* = 17.5, 9.1 Hz, 1H).

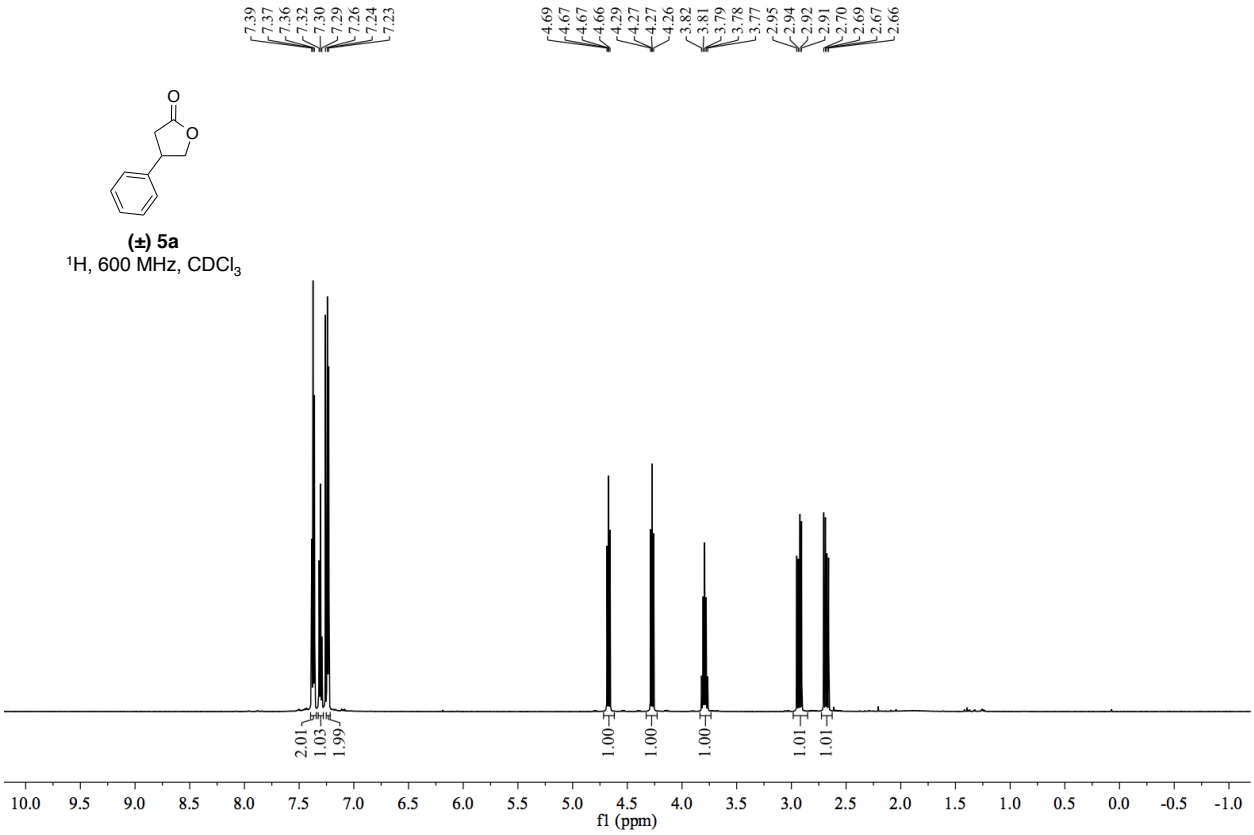
^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.3, 151.5, 150.1, 137.3, 137.0, 129.3, 127.9, 124.2, 122.5, 118.9, 74.1, 40.8, 35.9.

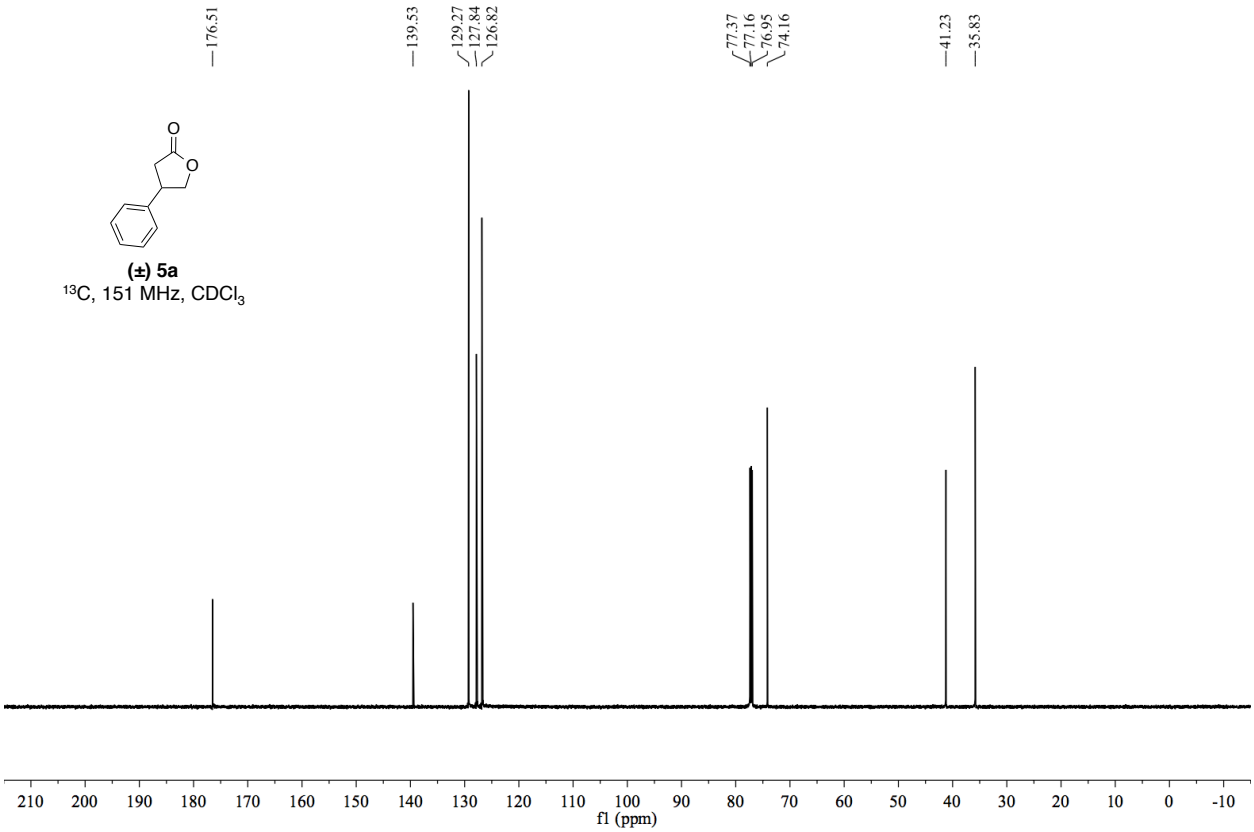
HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_4$ 298.1079, found 298.1077.

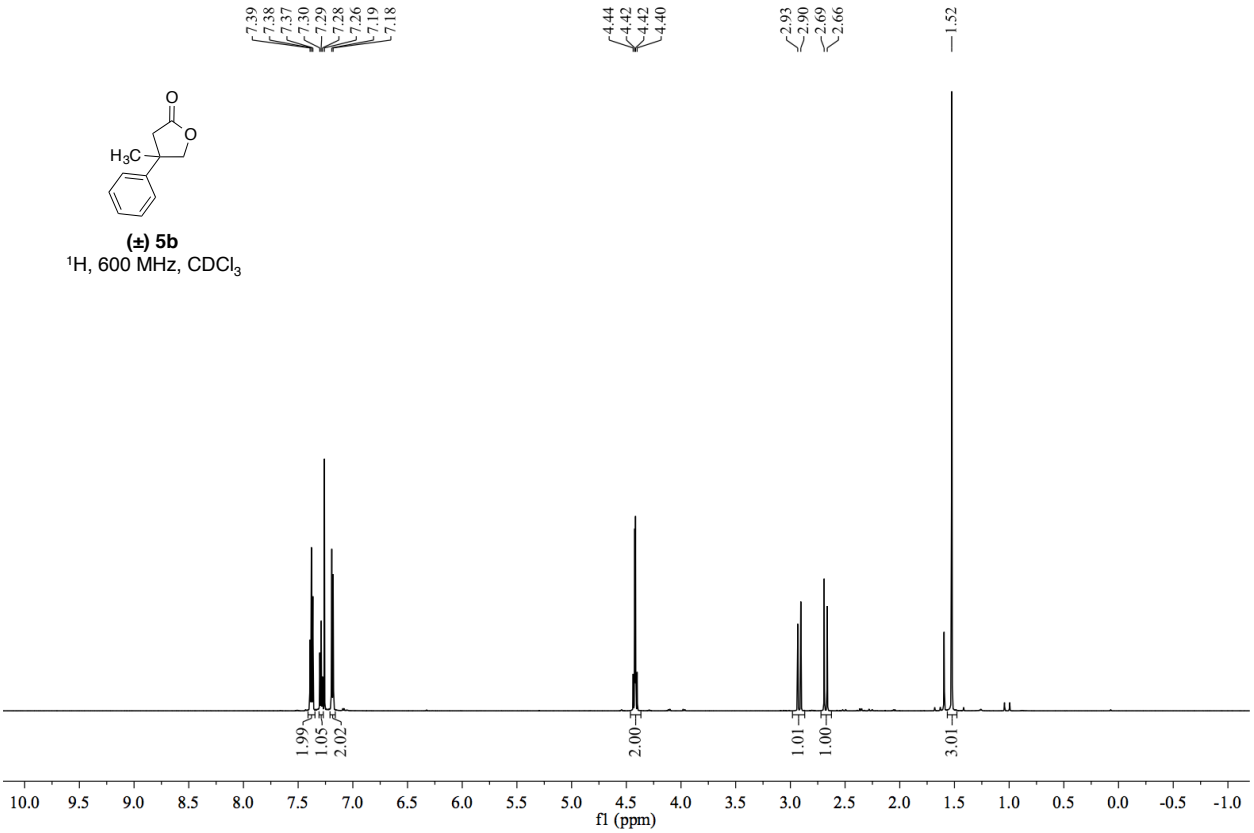
$[\alpha]_D^{20}$ –19.4 (*c* = 0.49, $CHCl_3$, 58% ee) **(*R*)-5t** (*obtained with catalyst P42*)

Chiral HPLC: Chiralpak IA column, 100% EtOH eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm). 61:39 er, t_{ret} 14.6 = min [(*S*) major], t_{ret} = 25.1 min [(*R*) minor].

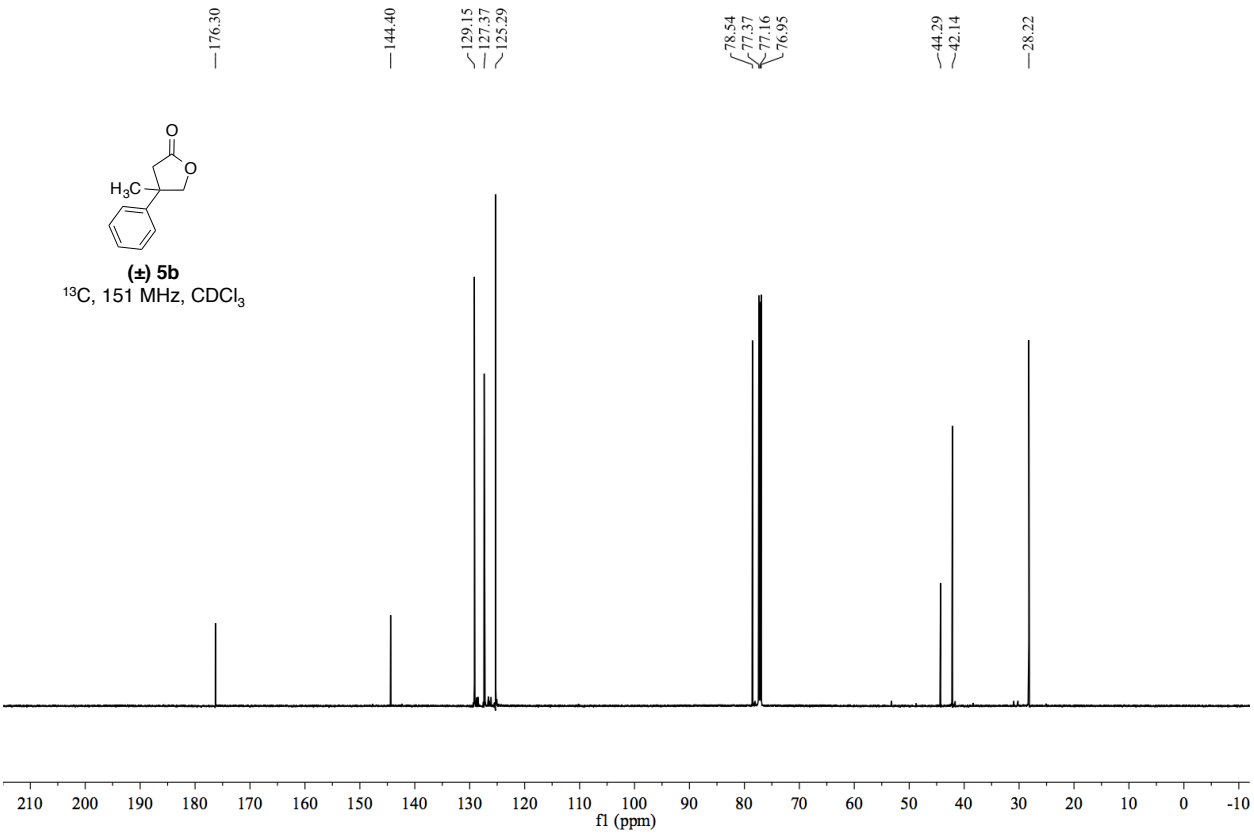
6.4. NMR Spectra of 5



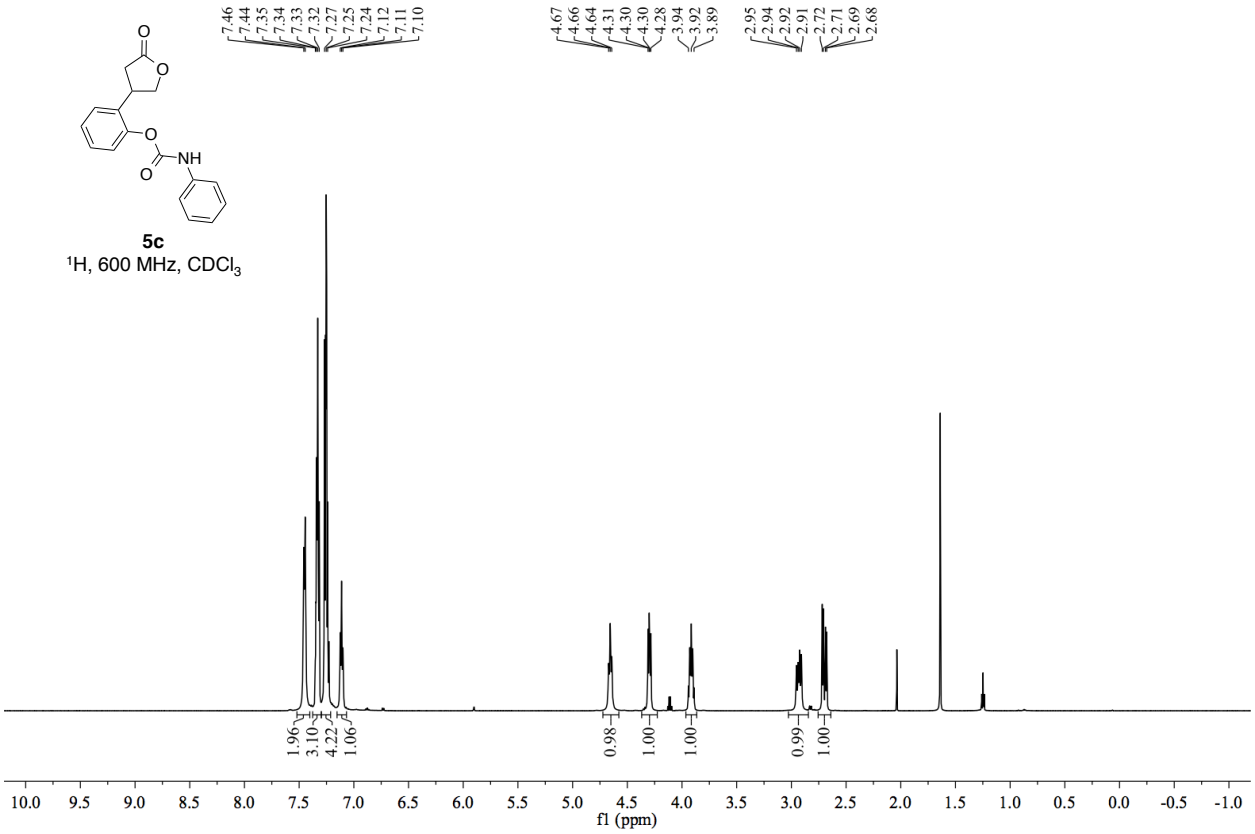




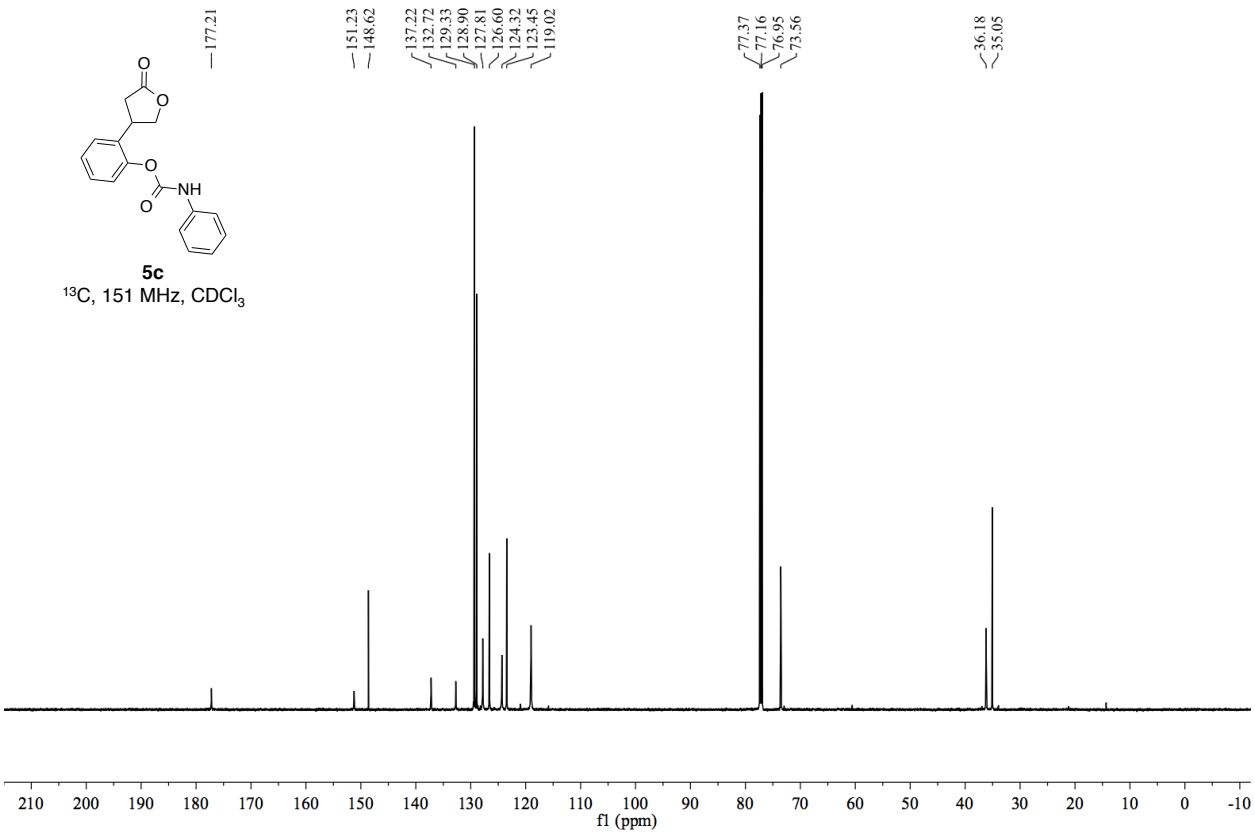
(±) 5b
^{1}H, 600 MHz, $CDCl_3$



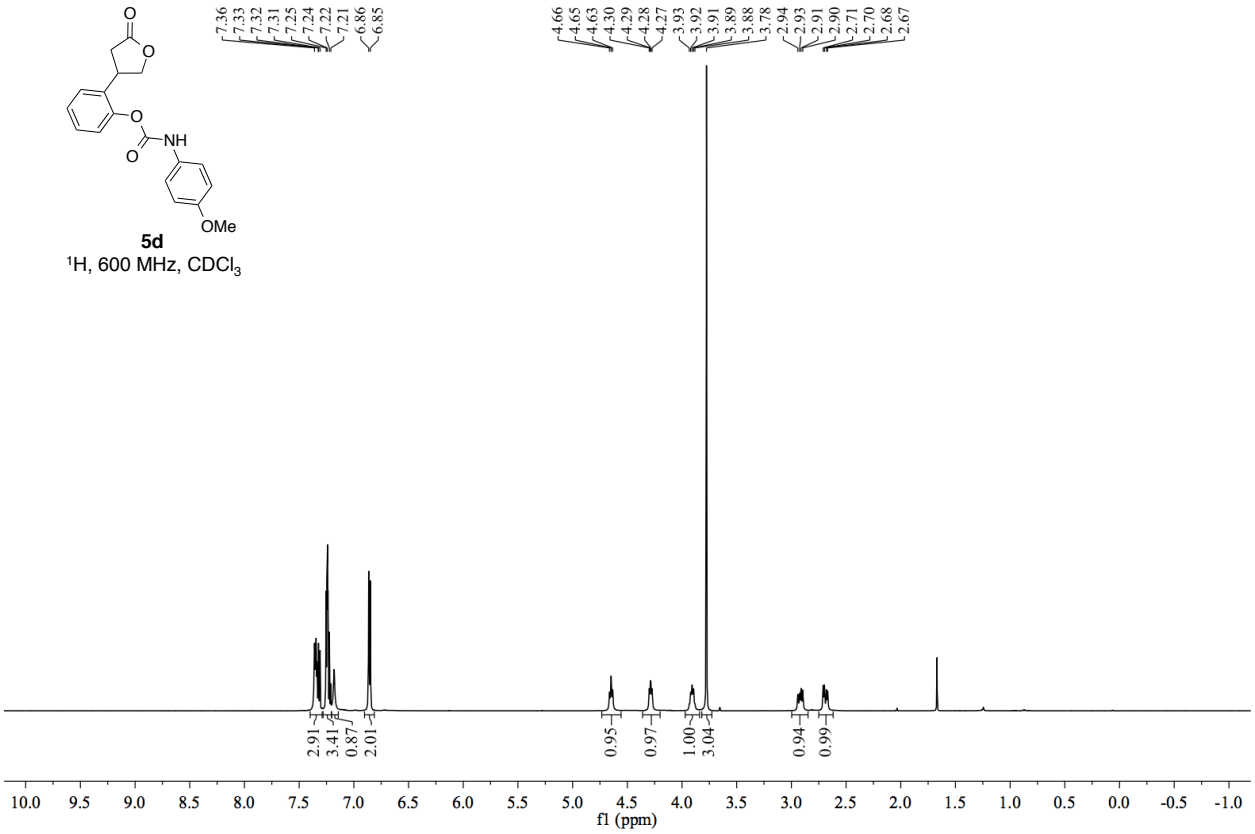
(±) 5b
^{13}C, 151 MHz, $CDCl_3$



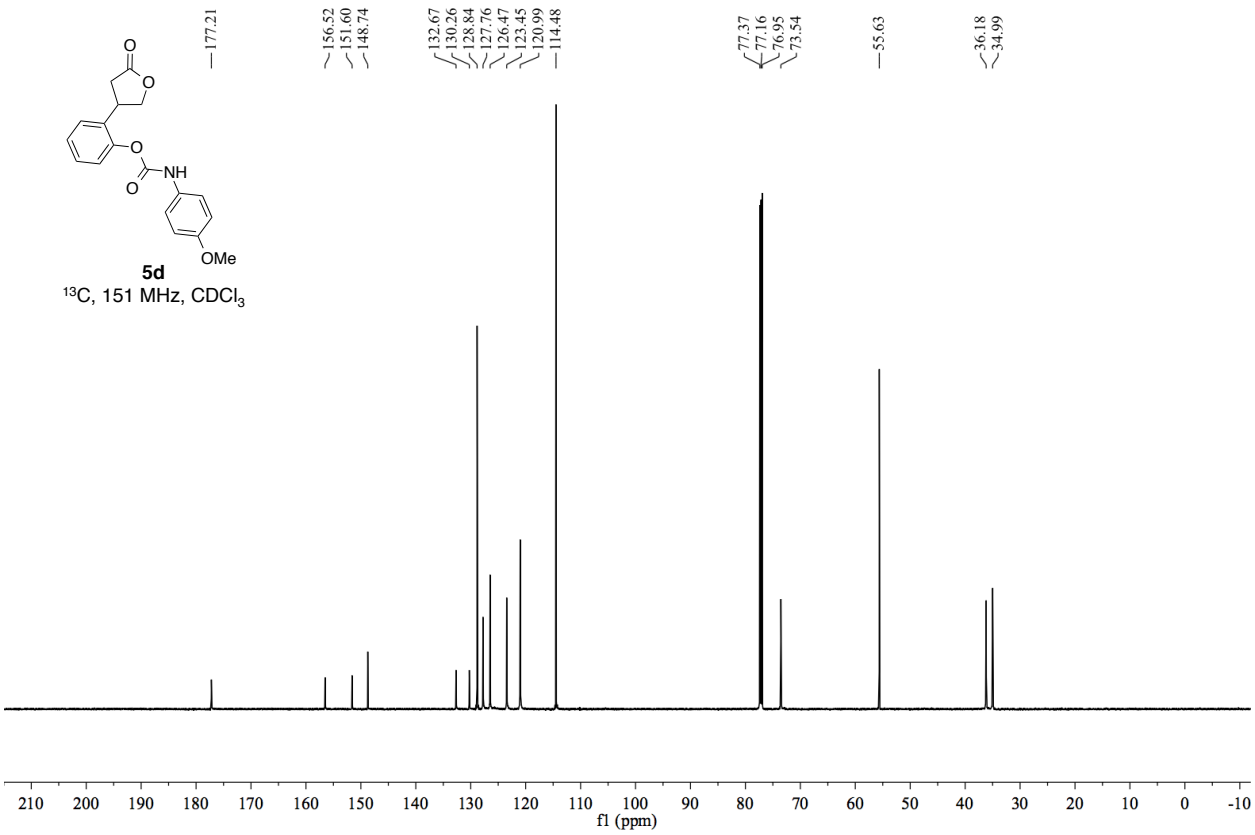
5c
^{1}H, 600 MHz, $CDCl_3$



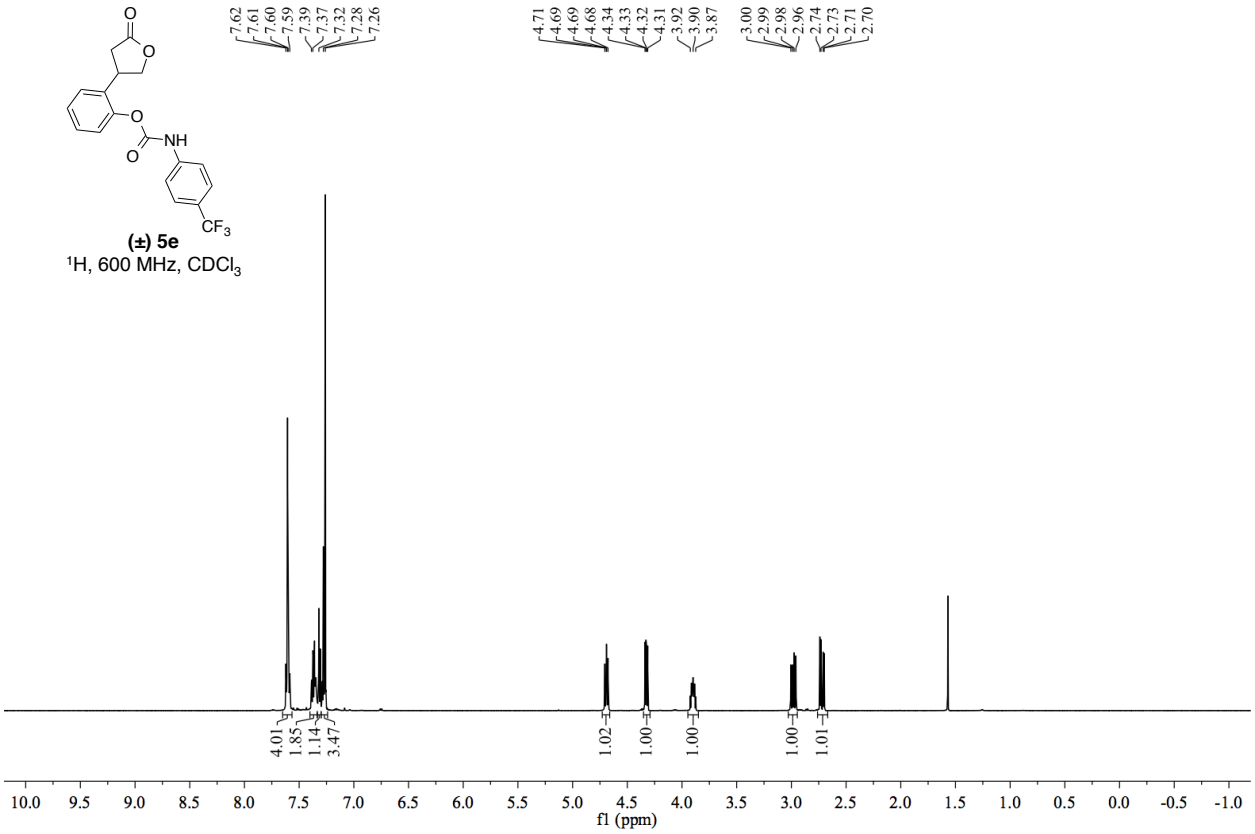
5c
^{13}C, 151 MHz, $CDCl_3$

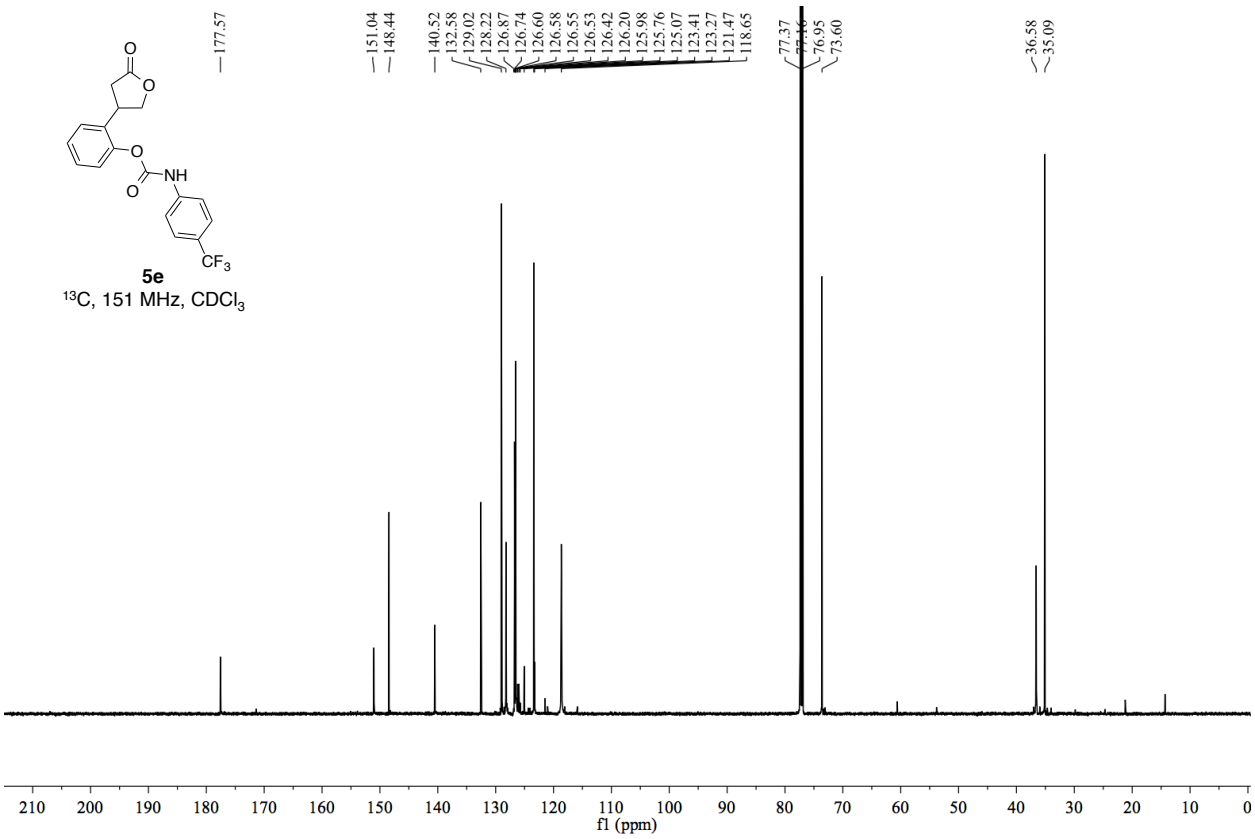


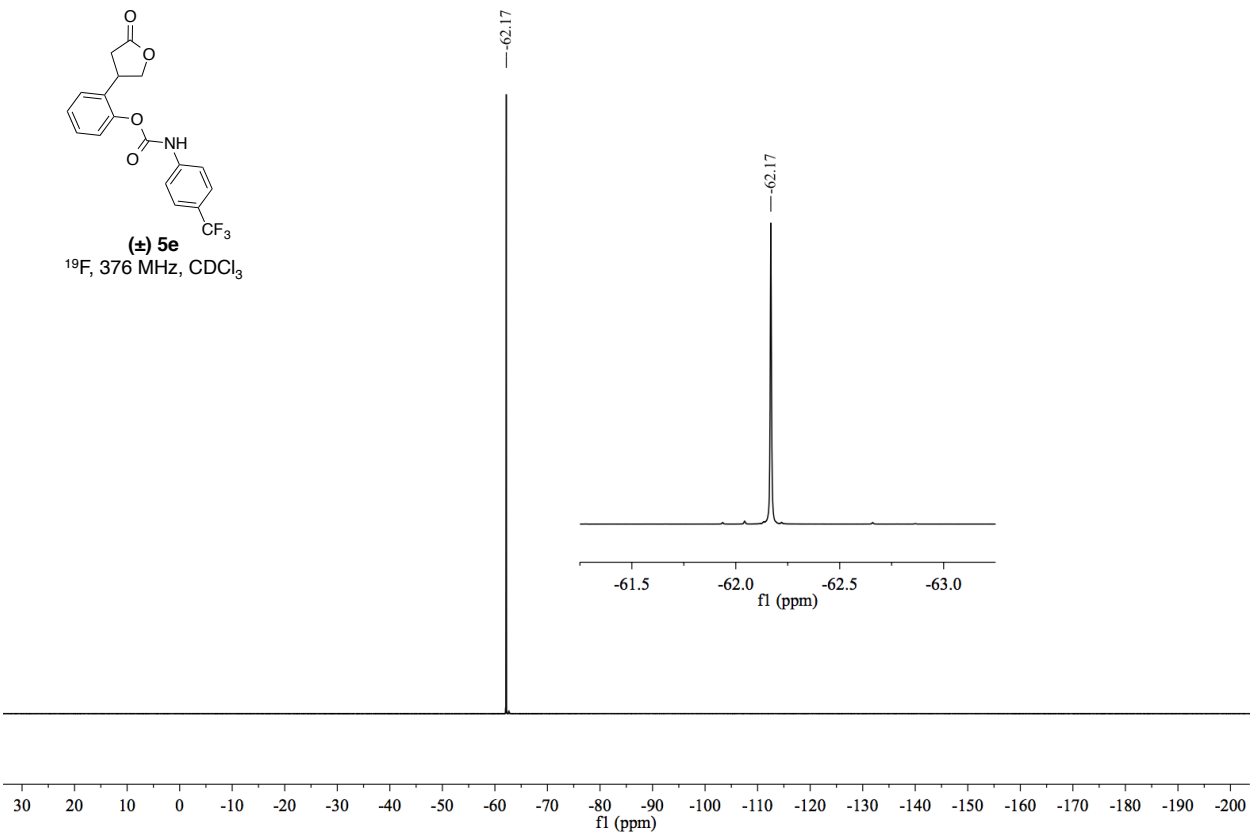
5d
^{1}H, 600 MHz, $CDCl_3$

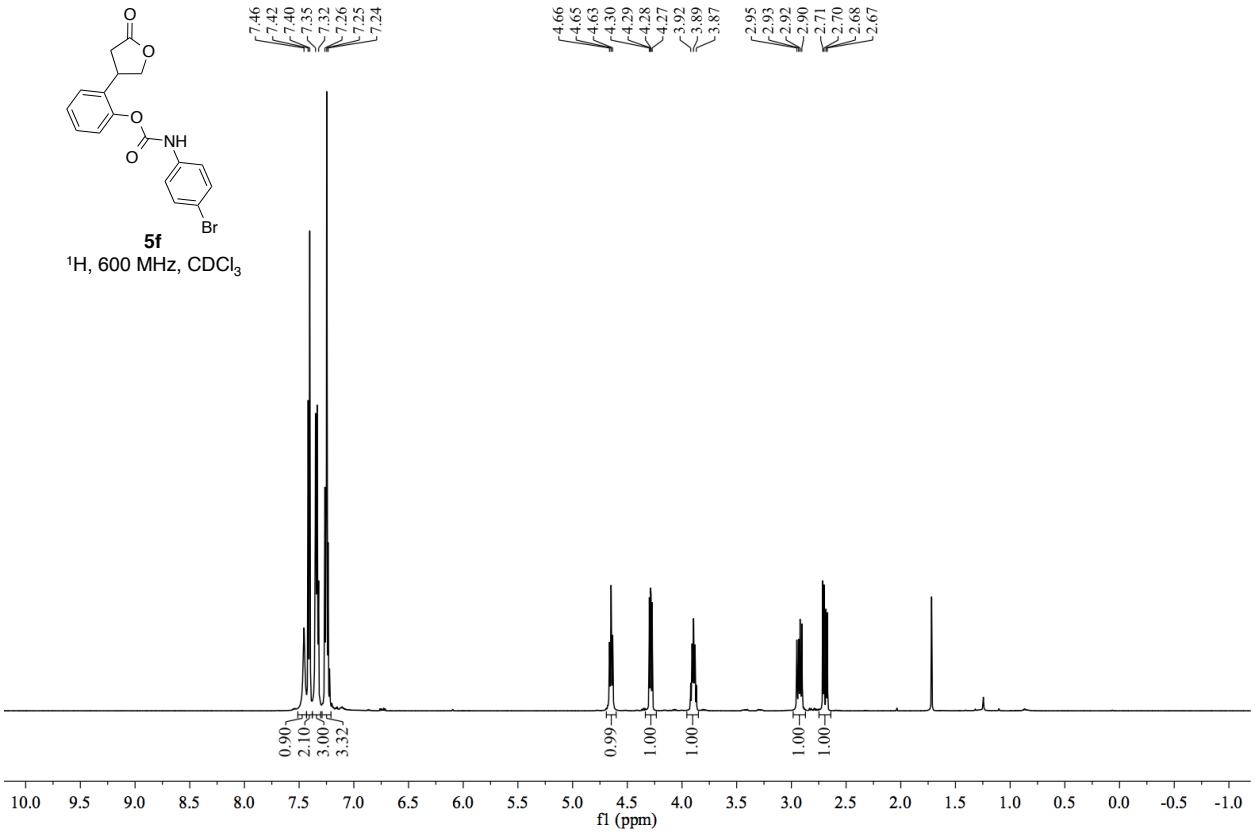


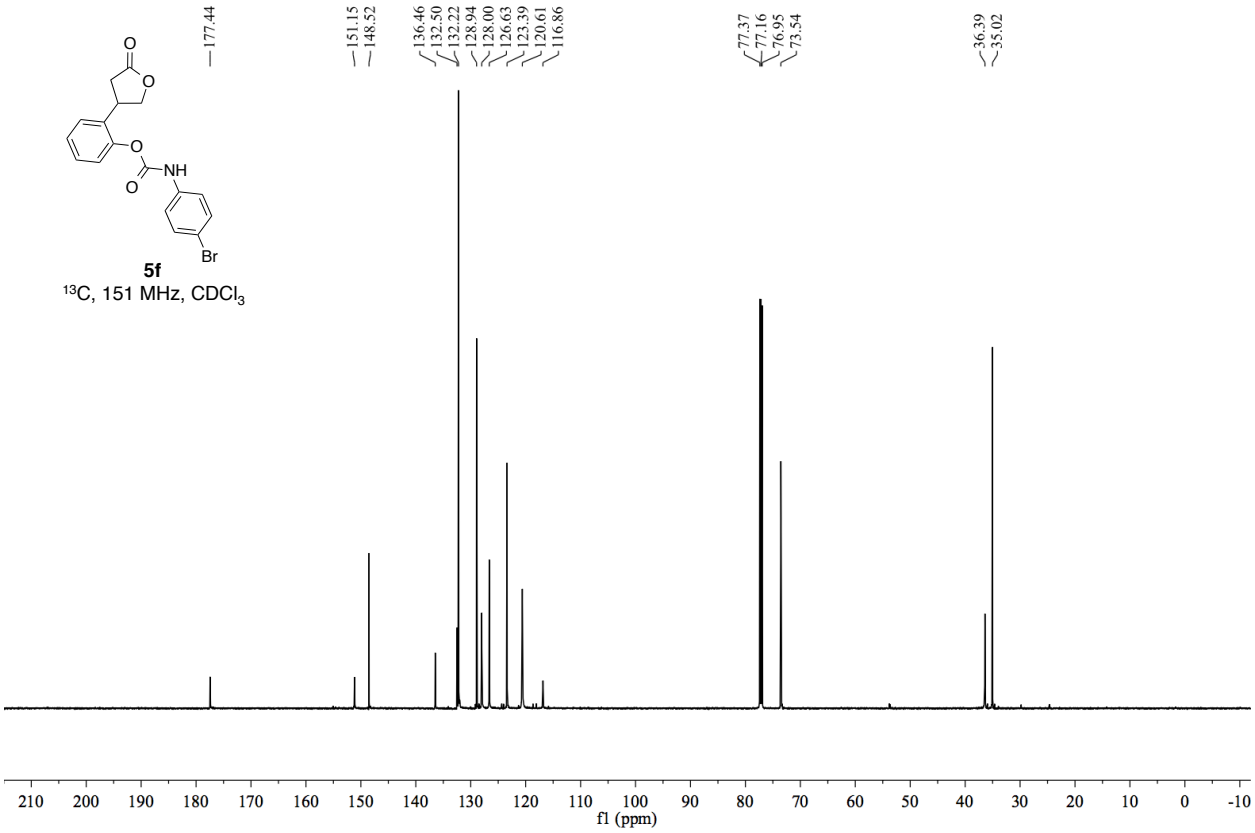
5d
^{13}C, 151 MHz, $CDCl_3$

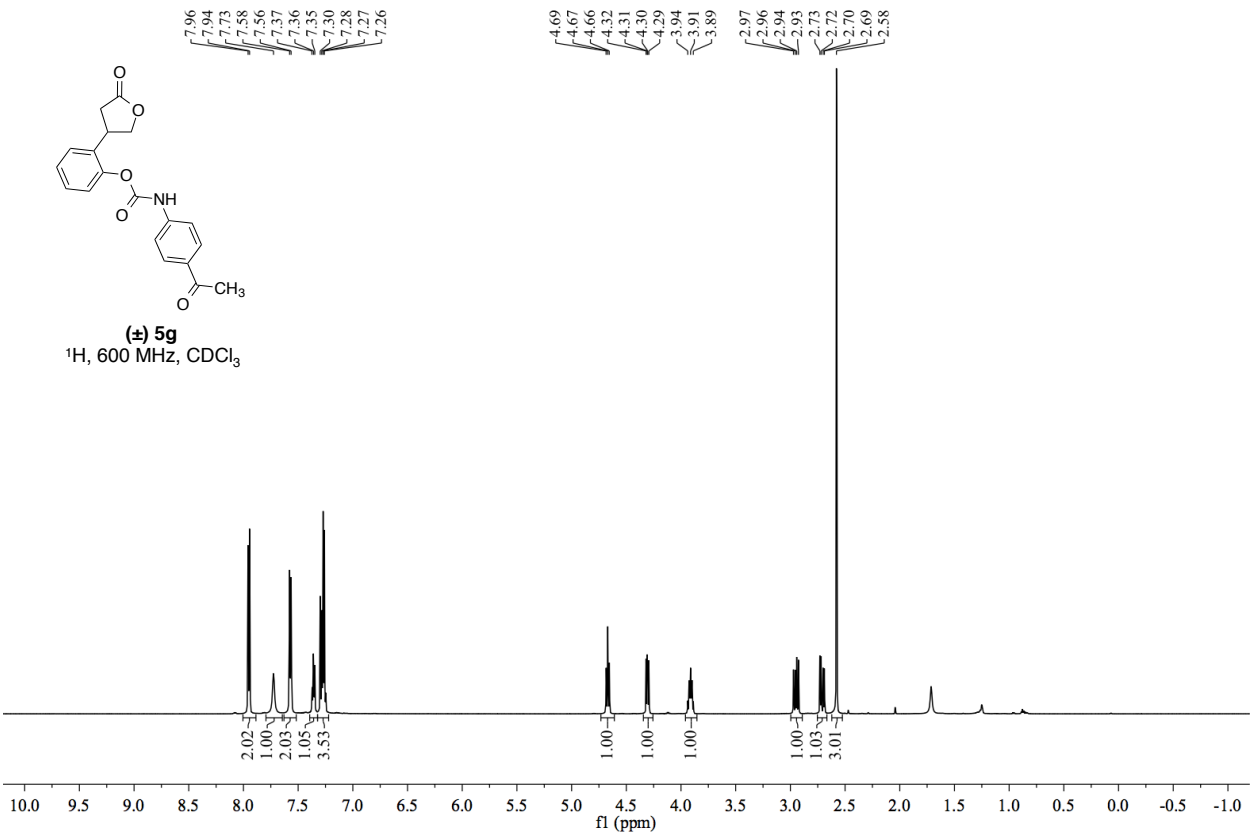

7.62
7.61
7.60
7.59
7.39
7.37
7.32
7.28
7.26
4.71
4.69
4.69
4.68
4.34
4.33
4.32
4.31
3.92
3.90
3.87
3.00
2.99
2.98
2.96
2.74
2.73
2.71
2.70
O
O
O
NH
O
CF3
(±) 5e
1H, 600 MHz, CDCl3
4.01
1.85
1.14
3.47
1.02
1.00
1.00
1.00
1.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


177.57
151.04
148.44
140.52
132.58
129.02
128.22
126.87
126.74
126.60
126.58
126.55
126.53
126.42
126.20
125.98
125.76
125.07
123.41
123.27
121.47
118.65
77.37
77.16
76.95
73.60
36.58
35.09
O
O
O
NH
O
CF3
5e
13C, 151 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

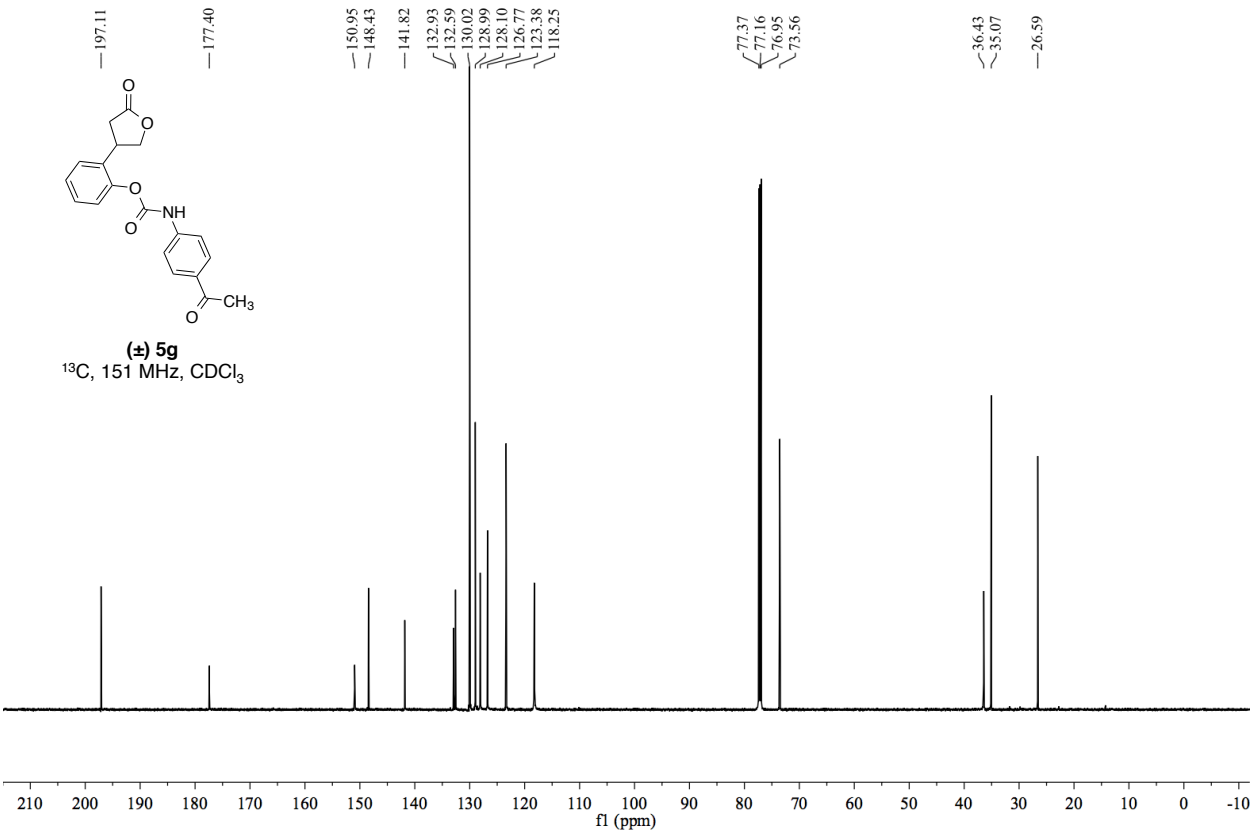

O
O
O
NH
O
CF3
(±) 5e
19F, 376 MHz, CDCl3
-62.17
-62.17
-61.5
-62.0
-62.5
-63.0
f1 (ppm)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


7.46
7.42
7.40
7.35
7.32
7.26
7.25
7.24
4.66
4.65
4.63
4.30
4.29
4.28
4.27
3.92
3.89
3.87
2.95
2.93
2.92
2.90
2.71
2.70
2.68
2.67
0.90
2.10
3.00
3.32
0.99
1.00
1.00
1.00
1.00
f1 (ppm)
5f
^{1}H, 600 MHz, CDCl$_3$

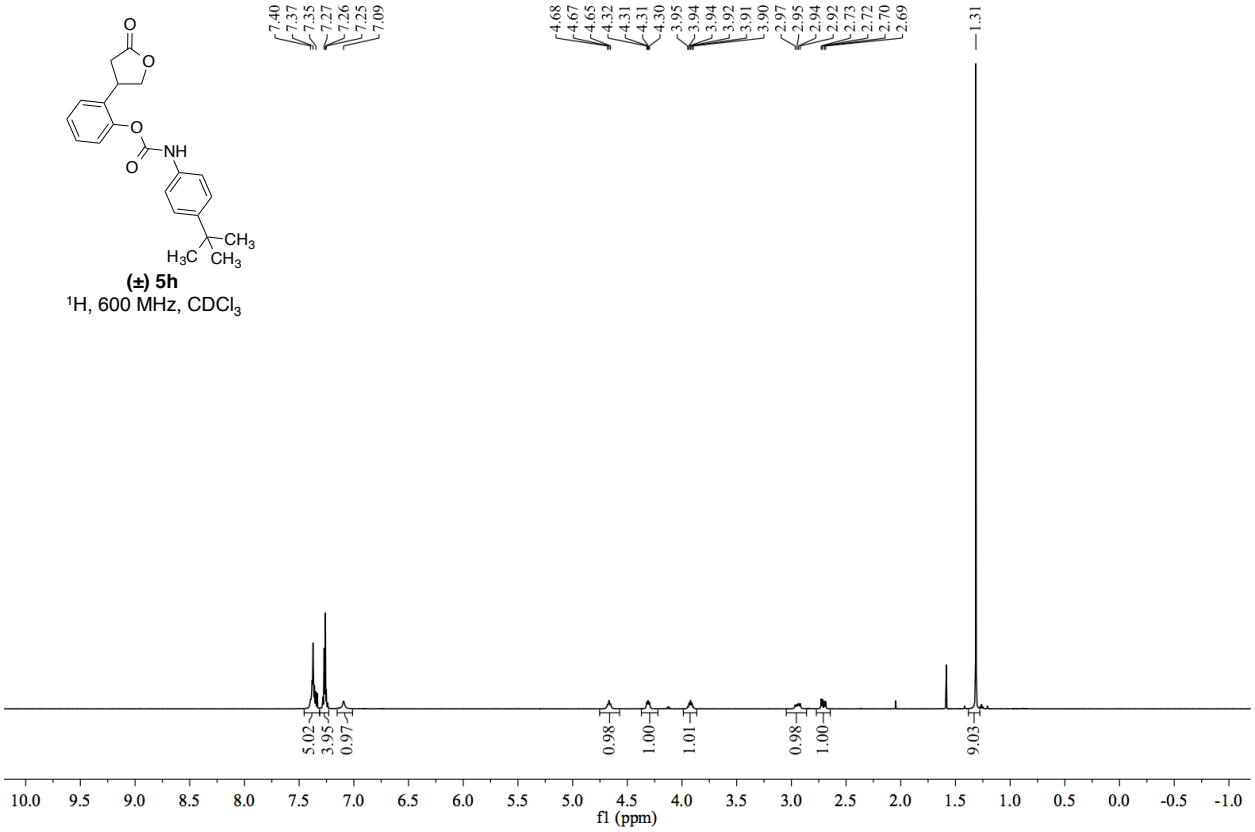

177.44
151.15
148.52
136.46
132.50
132.22
128.94
128.00
126.63
123.39
120.61
116.86
77.37
77.16
76.95
73.54
36.39
35.02
f1 (ppm)
5f
^{13}C, 151 MHz, CDCl$_3$



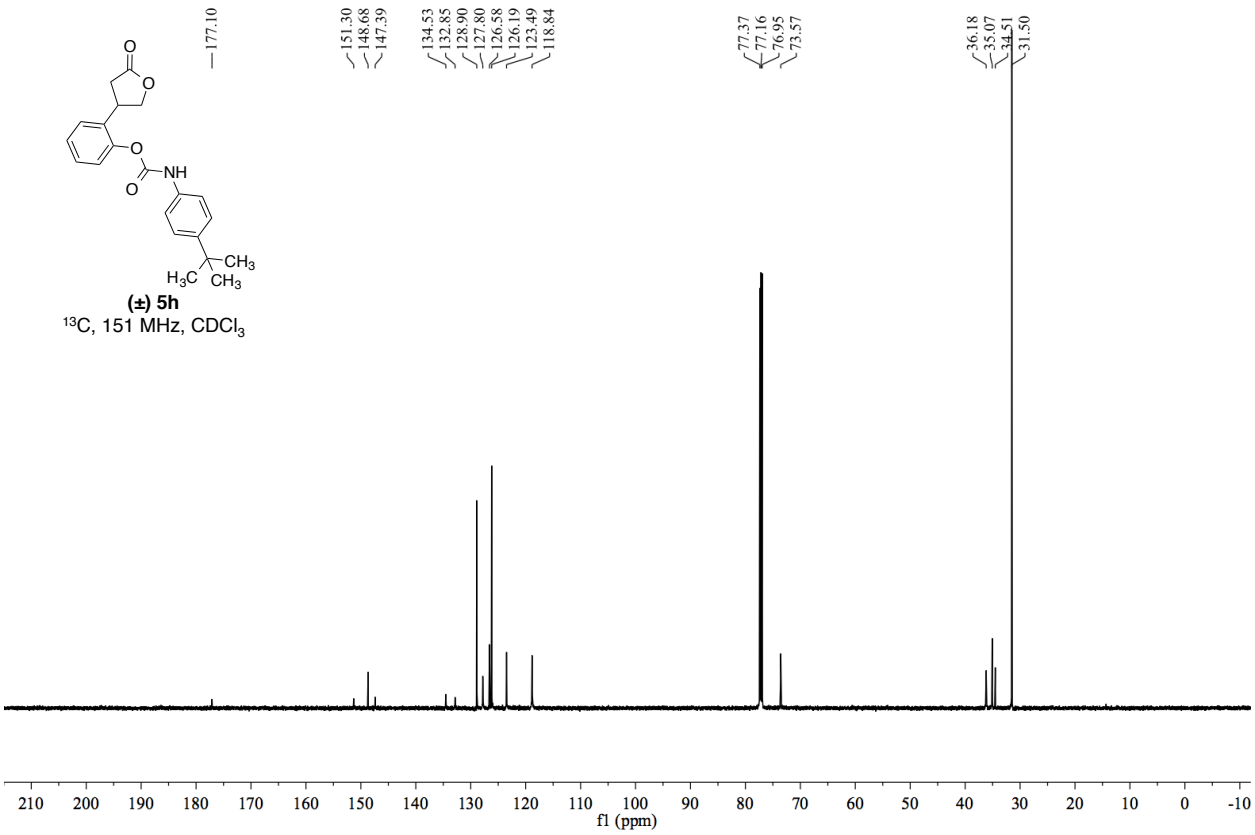
(±) 5g
^{1}H, 600 MHz, $CDCl_3$



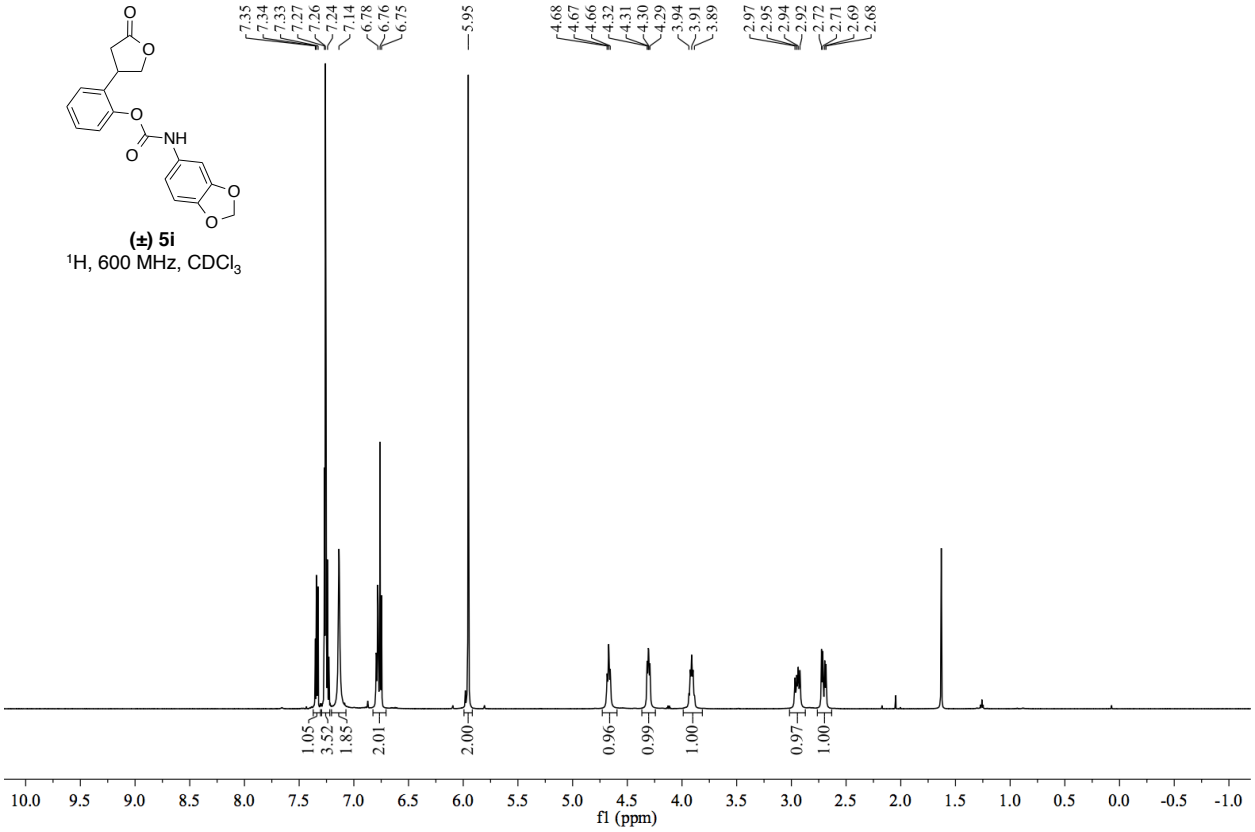
(±) 5g
^{13}C, 151 MHz, $CDCl_3$



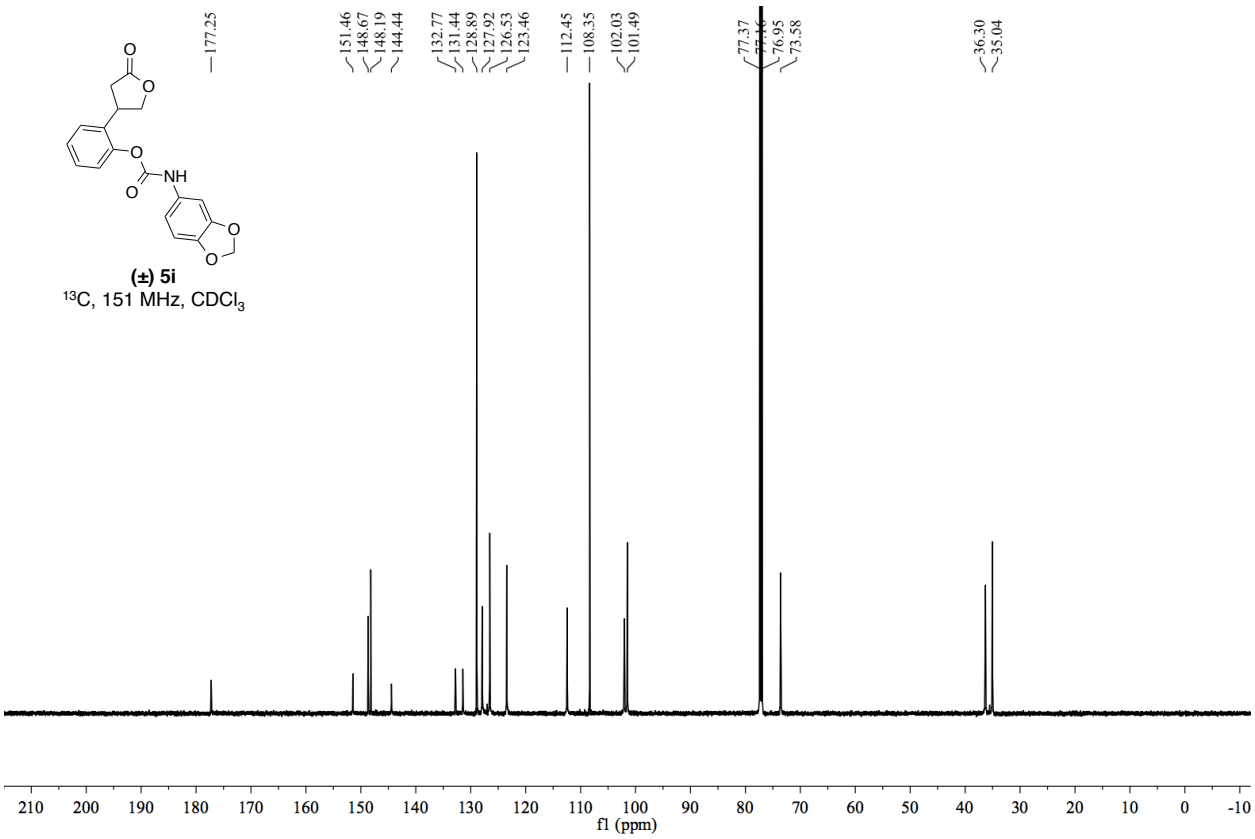
(±) 5h
^{1}H, 600 MHz, $CDCl_3$



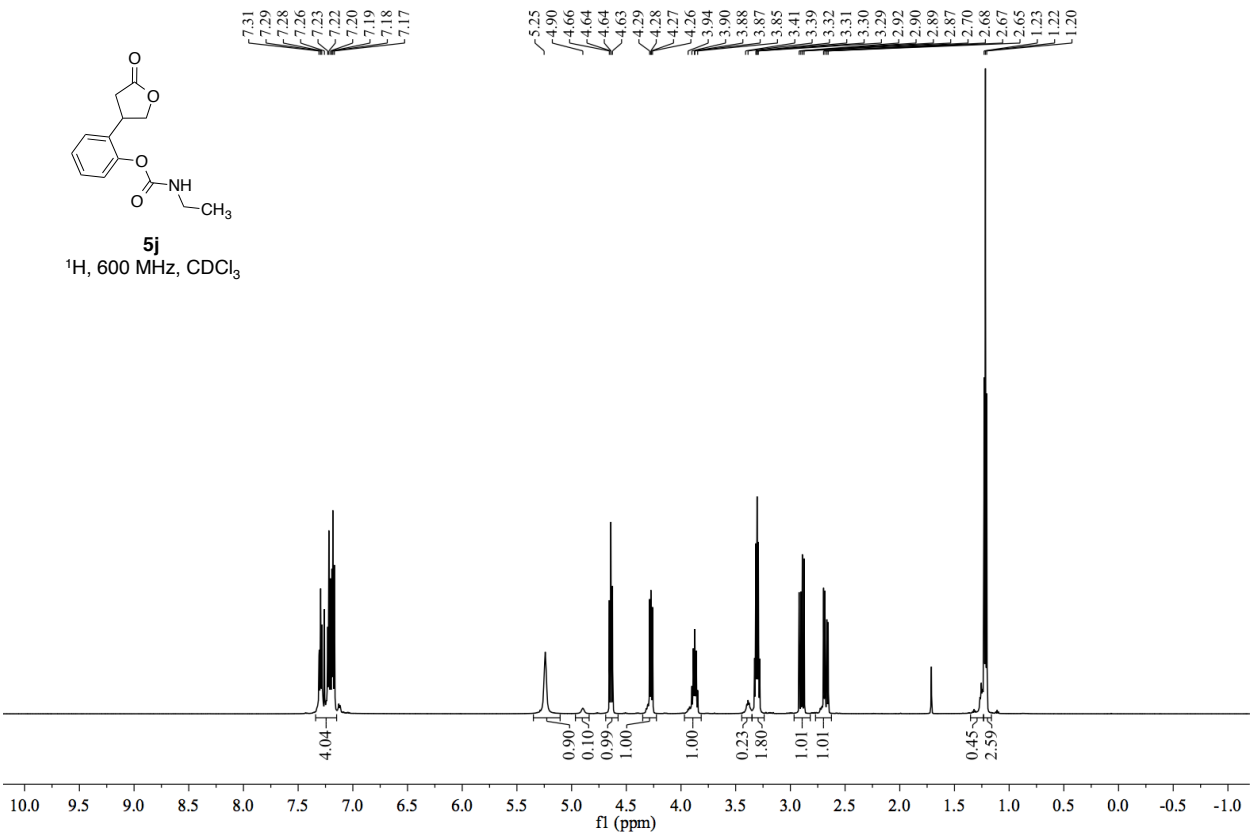
(±) 5h
^{13}C, 151 MHz, $CDCl_3$



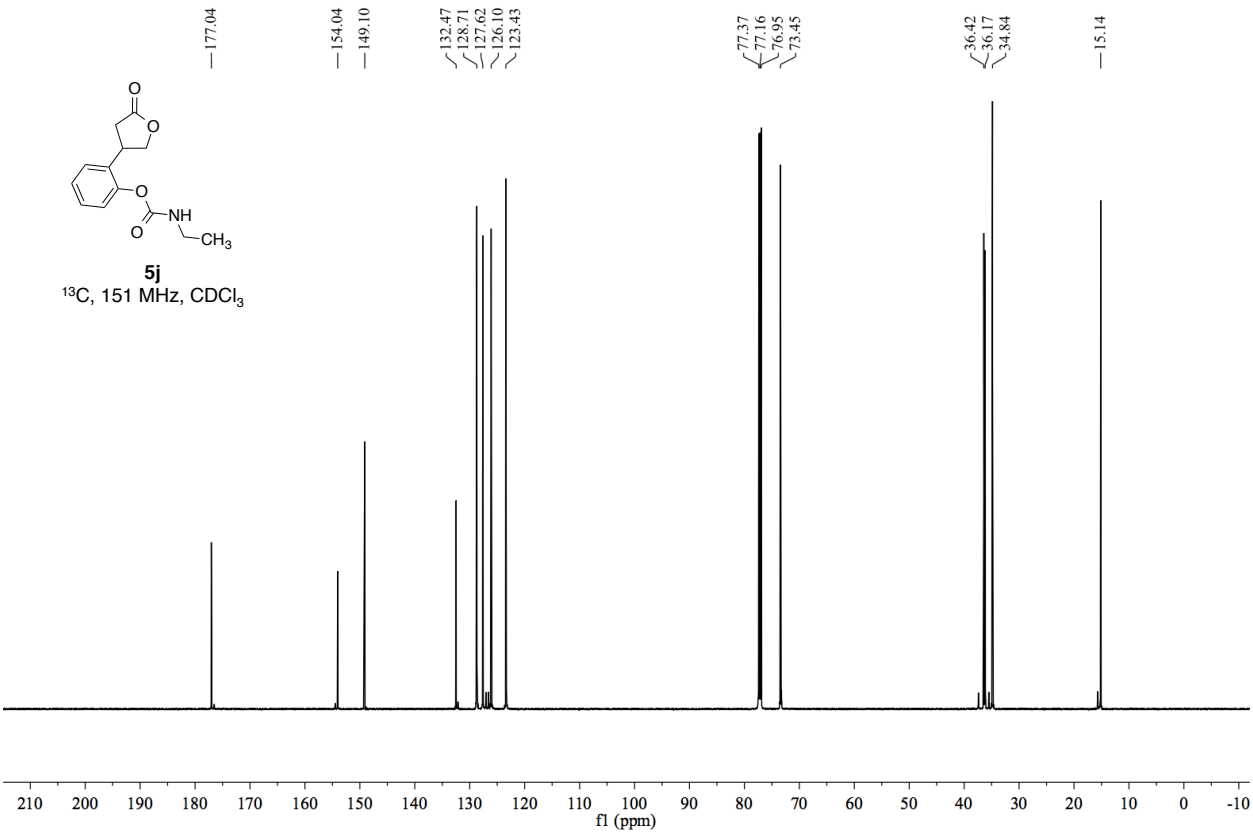
(±) 5i
^{1}H, 600 MHz, $CDCl_3$



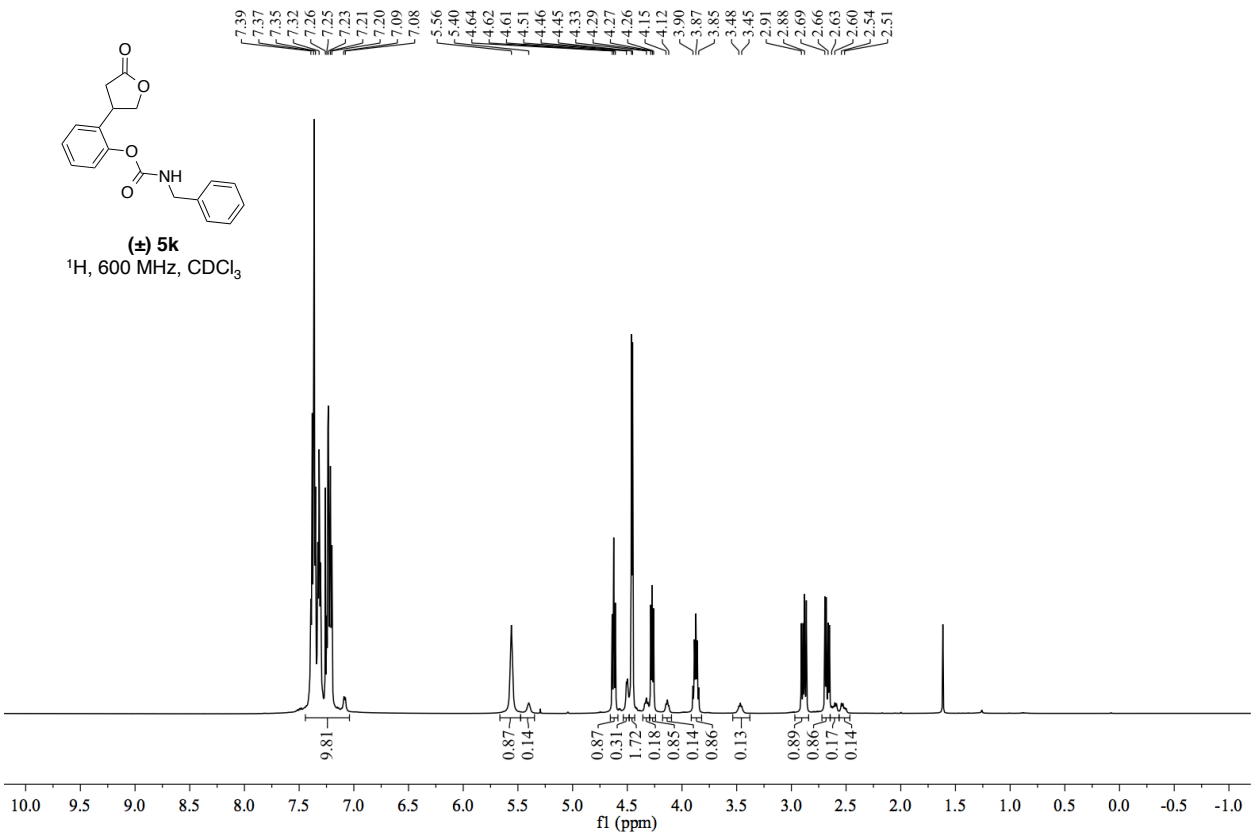
(±) 5i
^{13}C, 151 MHz, $CDCl_3$

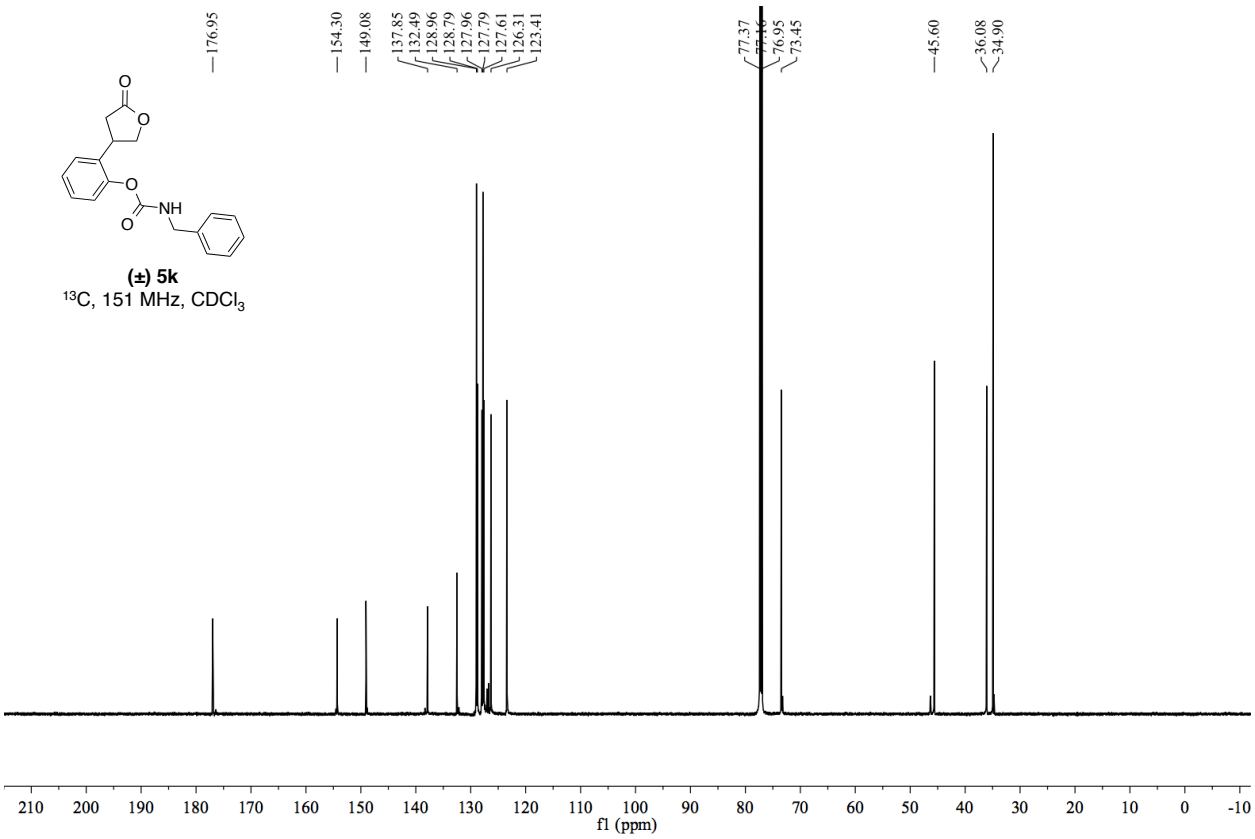


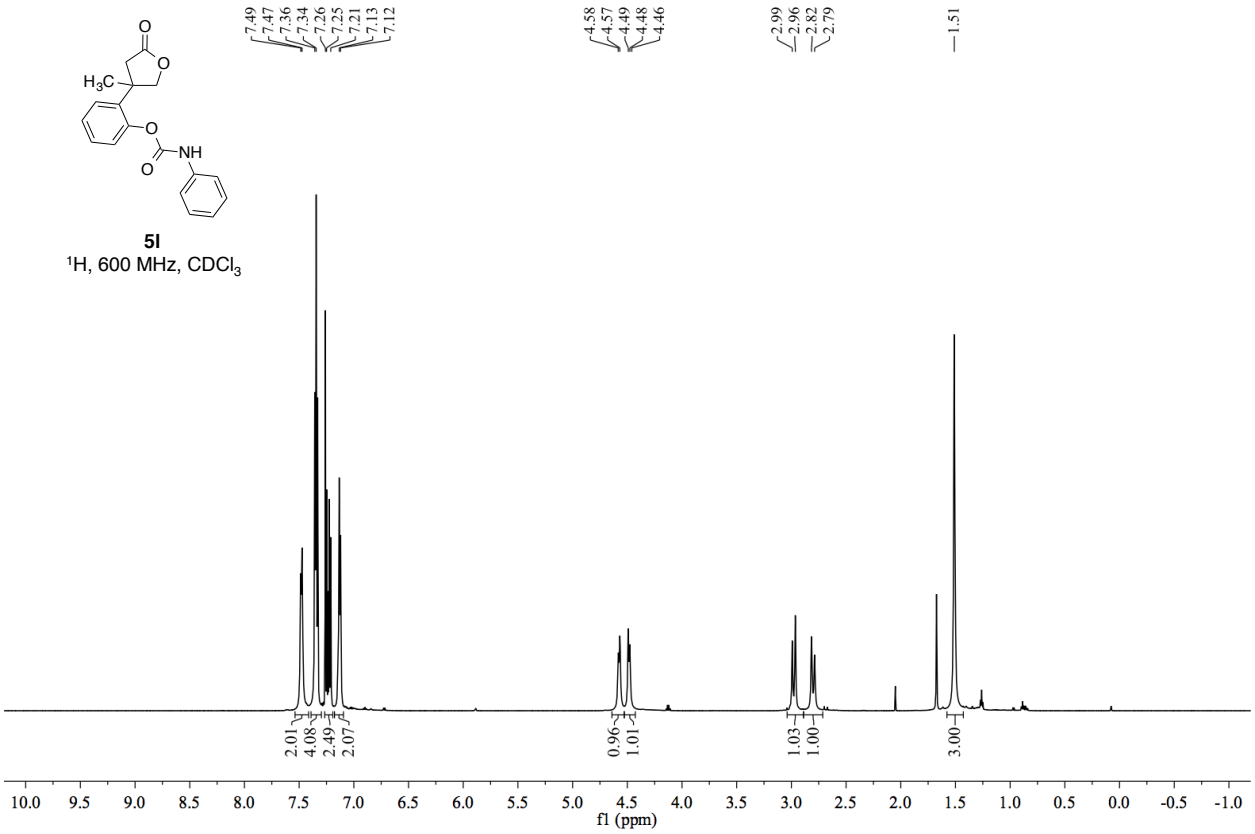
5j
^{1}H, 600 MHz, $CDCl_3$



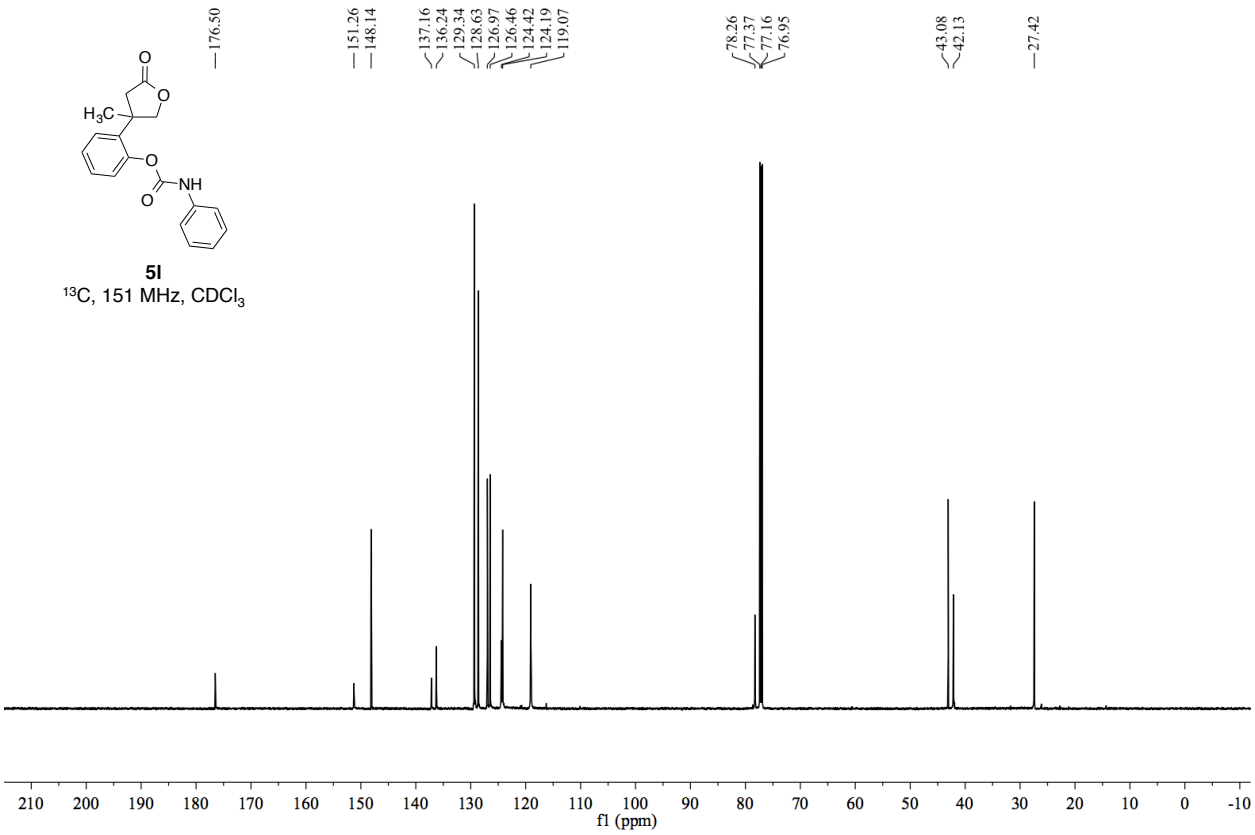
5j
^{13}C, 151 MHz, $CDCl_3$


7.39
7.37
7.35
7.32
7.26
7.25
7.23
7.21
7.20
7.09
7.08
5.56
5.40
4.64
4.62
4.61
4.51
4.46
4.45
4.33
4.29
4.27
4.26
4.15
4.12
3.90
3.87
3.85
3.48
3.45
2.91
2.88
2.69
2.66
2.63
2.60
2.54
2.51
O
O
O
NH
O
(±) 5k
1H, 600 MHz, CDCl3
9.81
0.87
0.14
0.87
0.31
1.72
0.18
0.85
0.14
0.86
0.13
0.89
0.86
0.17
0.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

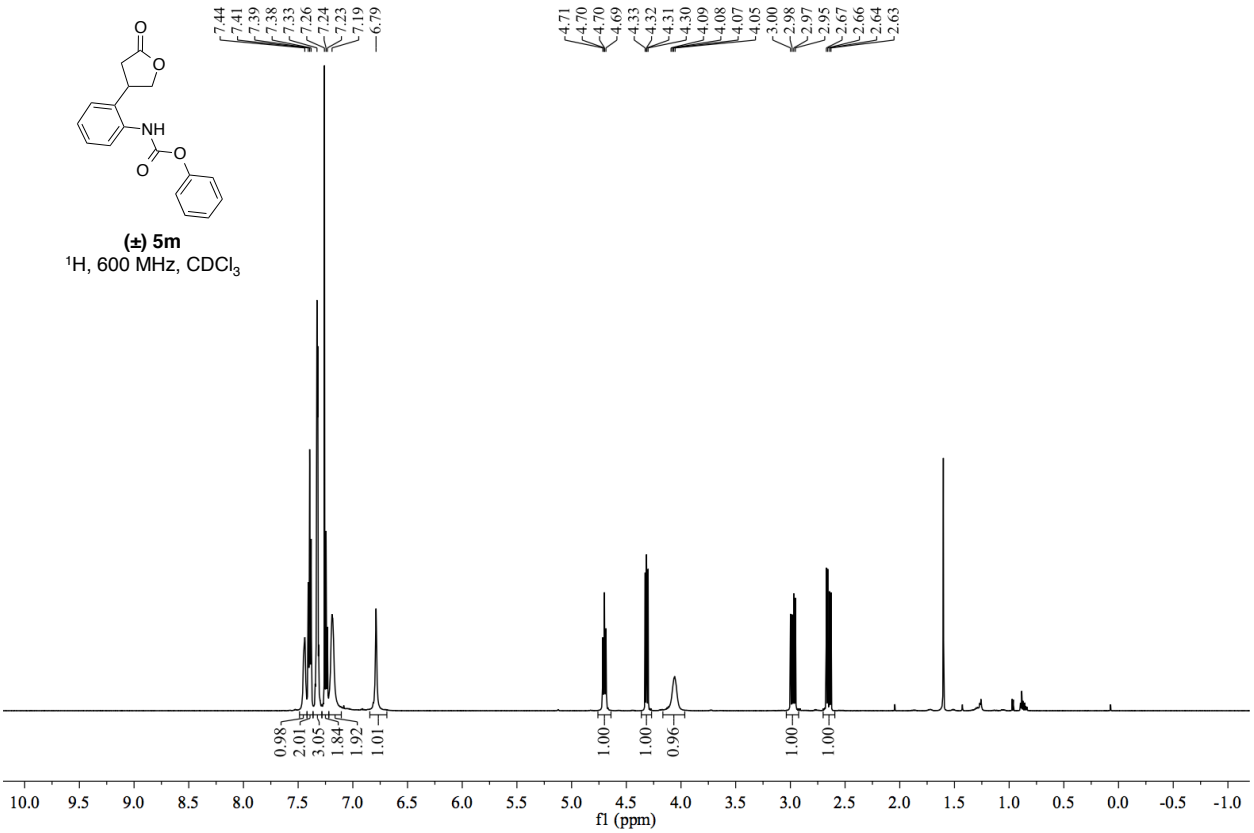

176.95
154.30
149.08
137.85
132.49
128.96
128.79
127.96
127.79
127.61
126.31
123.41
77.37
76.95
73.45
45.60
36.08
34.90
O
O
O
NH
O
(±) 5k
13C, 151 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



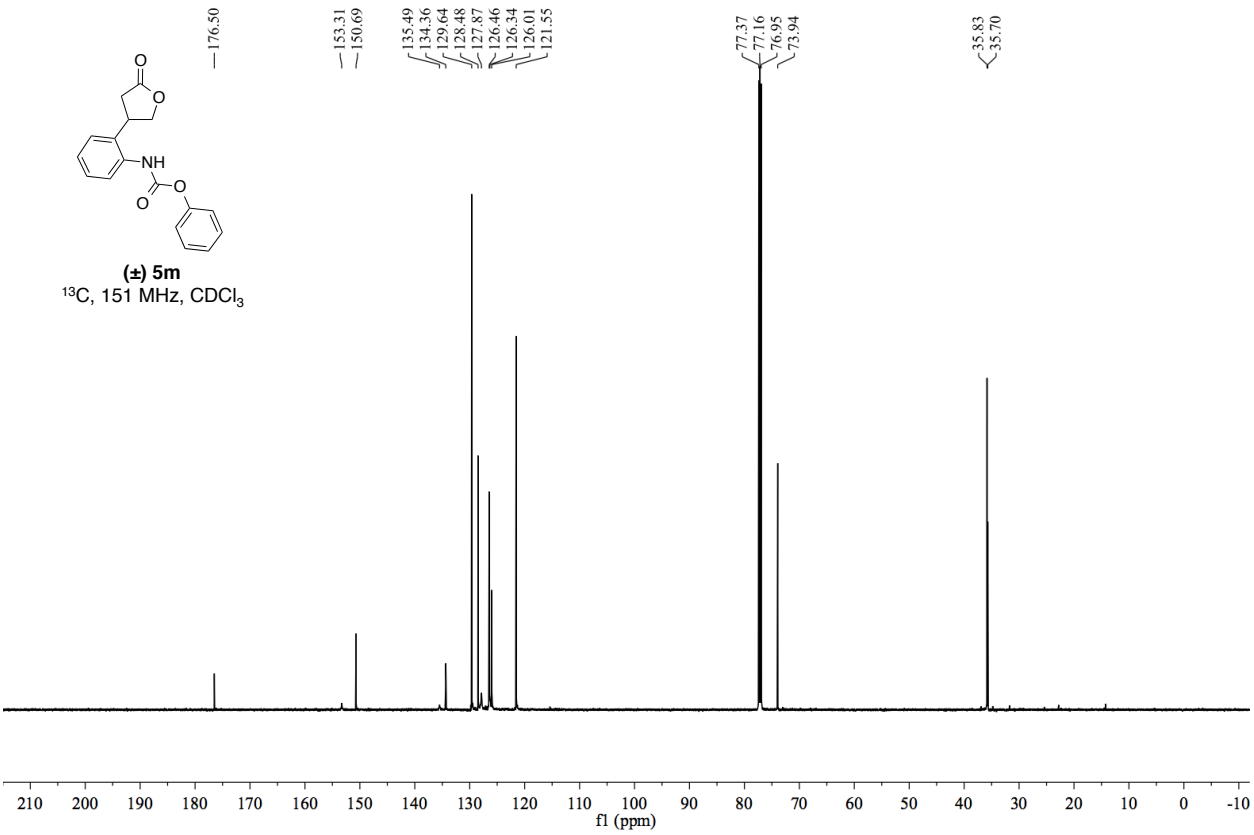
5l
^{1}H, 600 MHz, $CDCl_3$



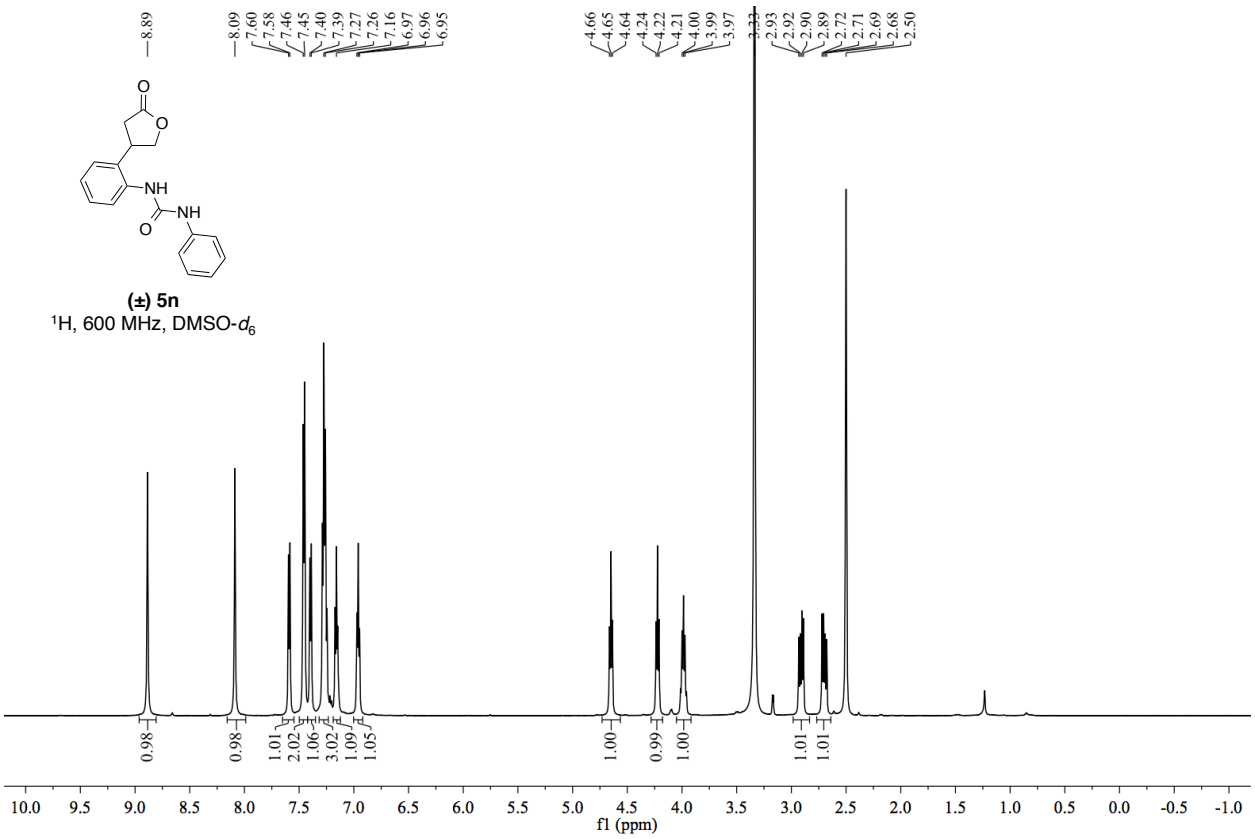
5l
^{13}C, 151 MHz, $CDCl_3$



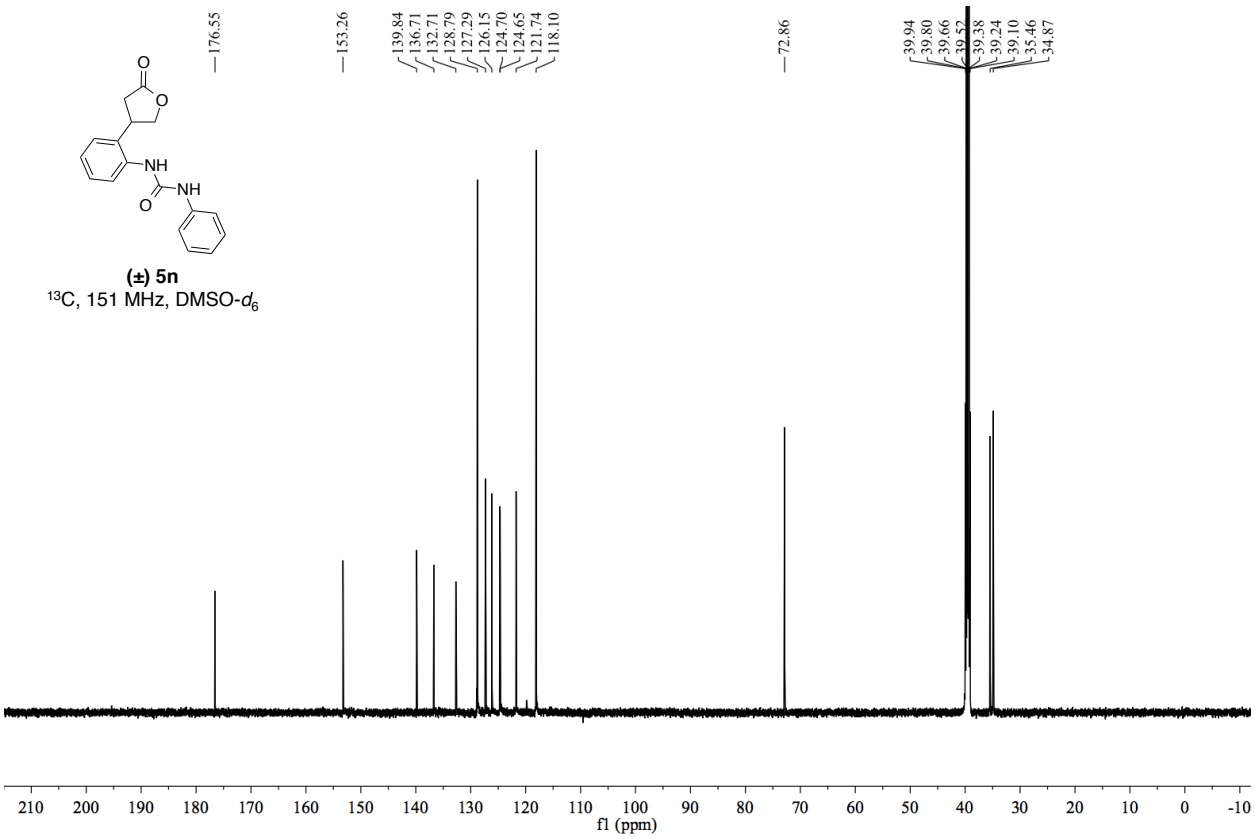
(±) 5m
^{1}H, 600 MHz, $CDCl_3$



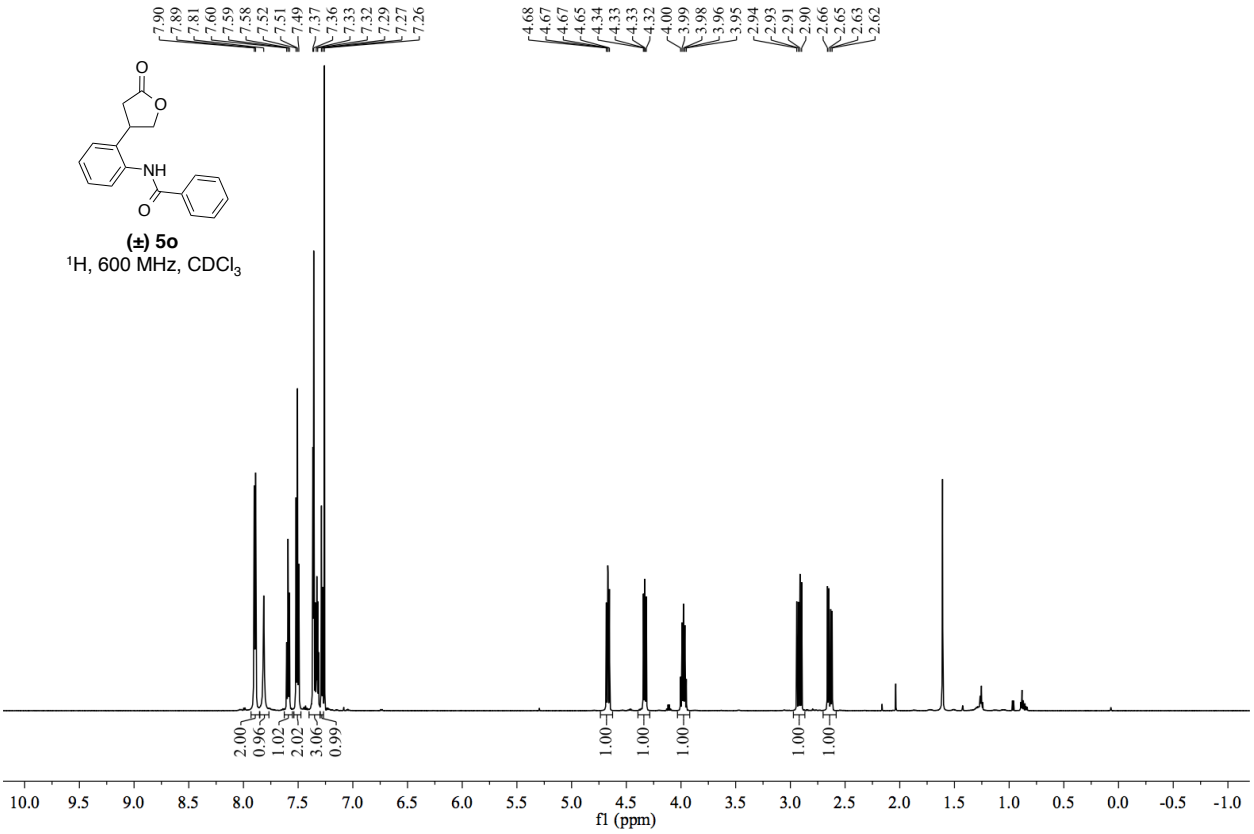
(±) 5m
^{13}C, 151 MHz, $CDCl_3$



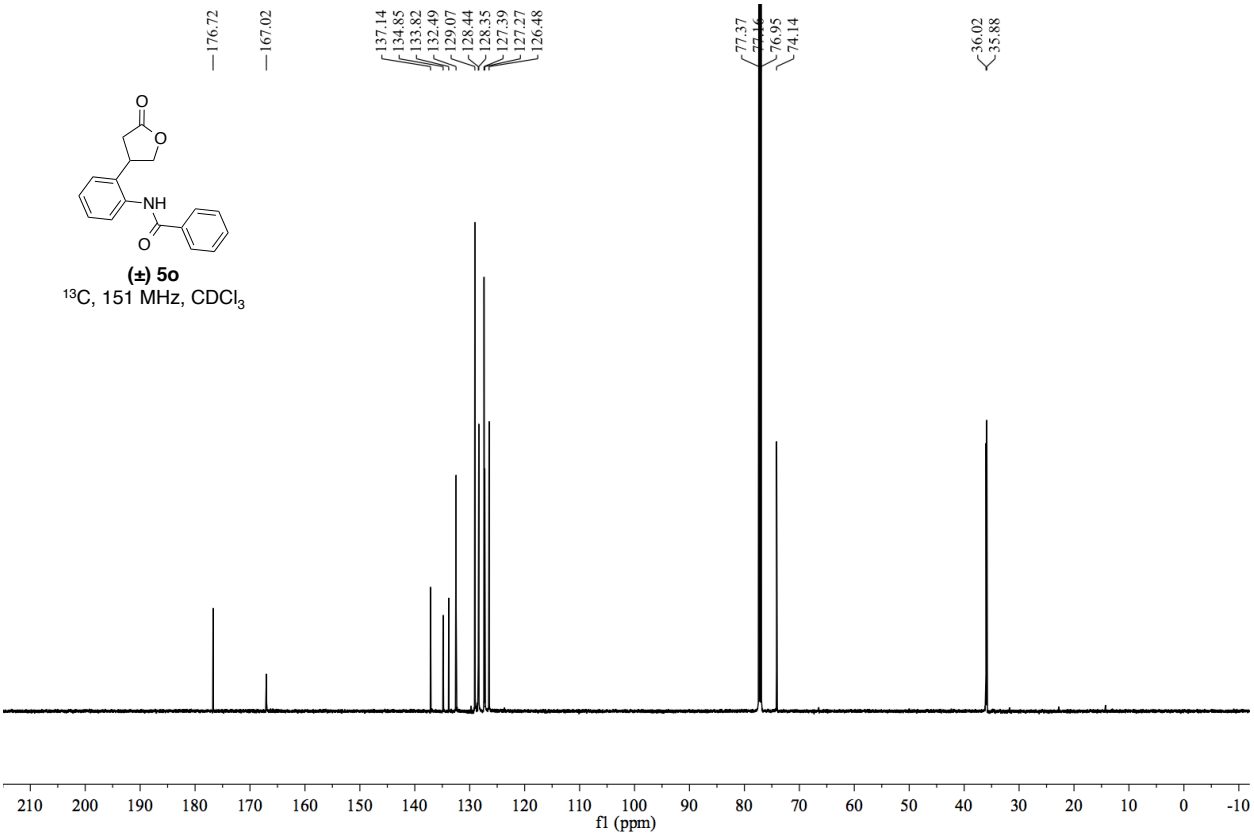
(±) 5n
^{1}H, 600 MHz, DMSO-d_6



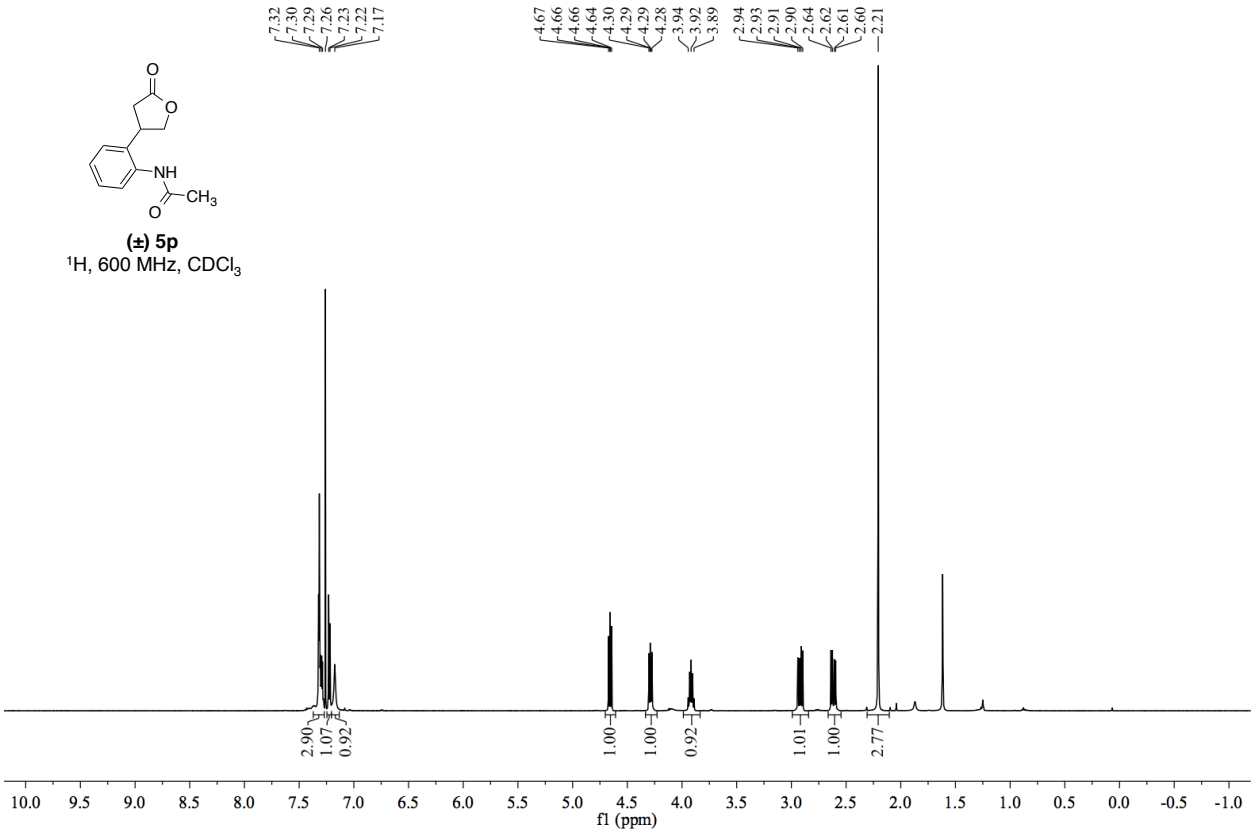
(±) 5n
^{13}C, 151 MHz, DMSO-d_6

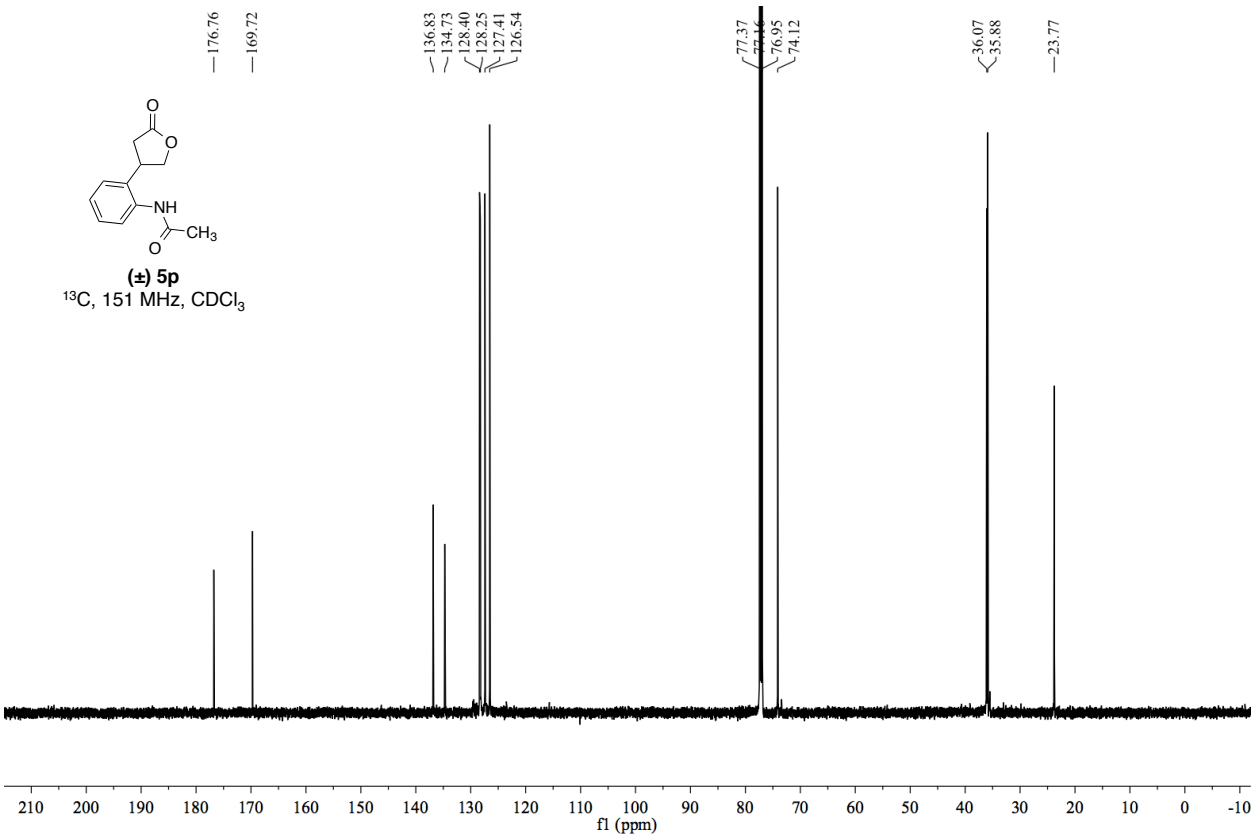


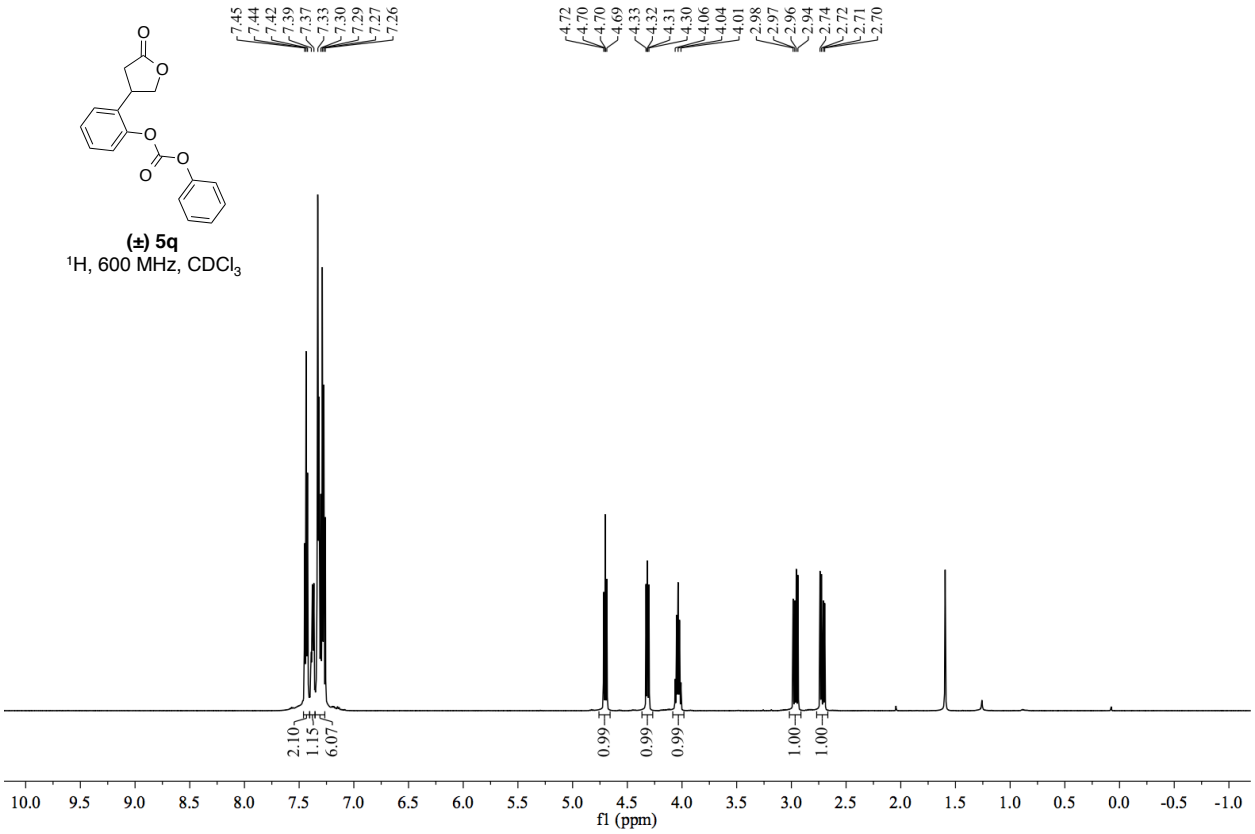
(±) 5o
^{1}H, 600 MHz, $CDCl_3$

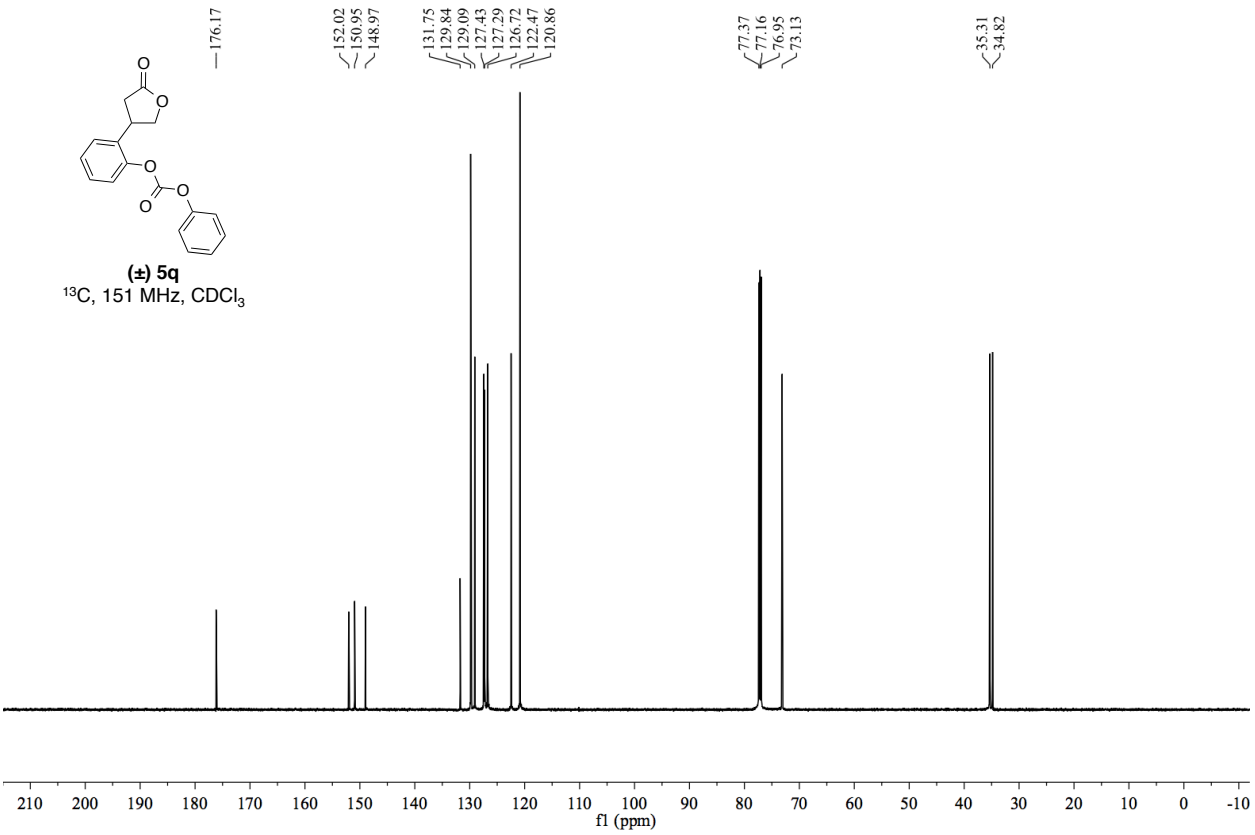


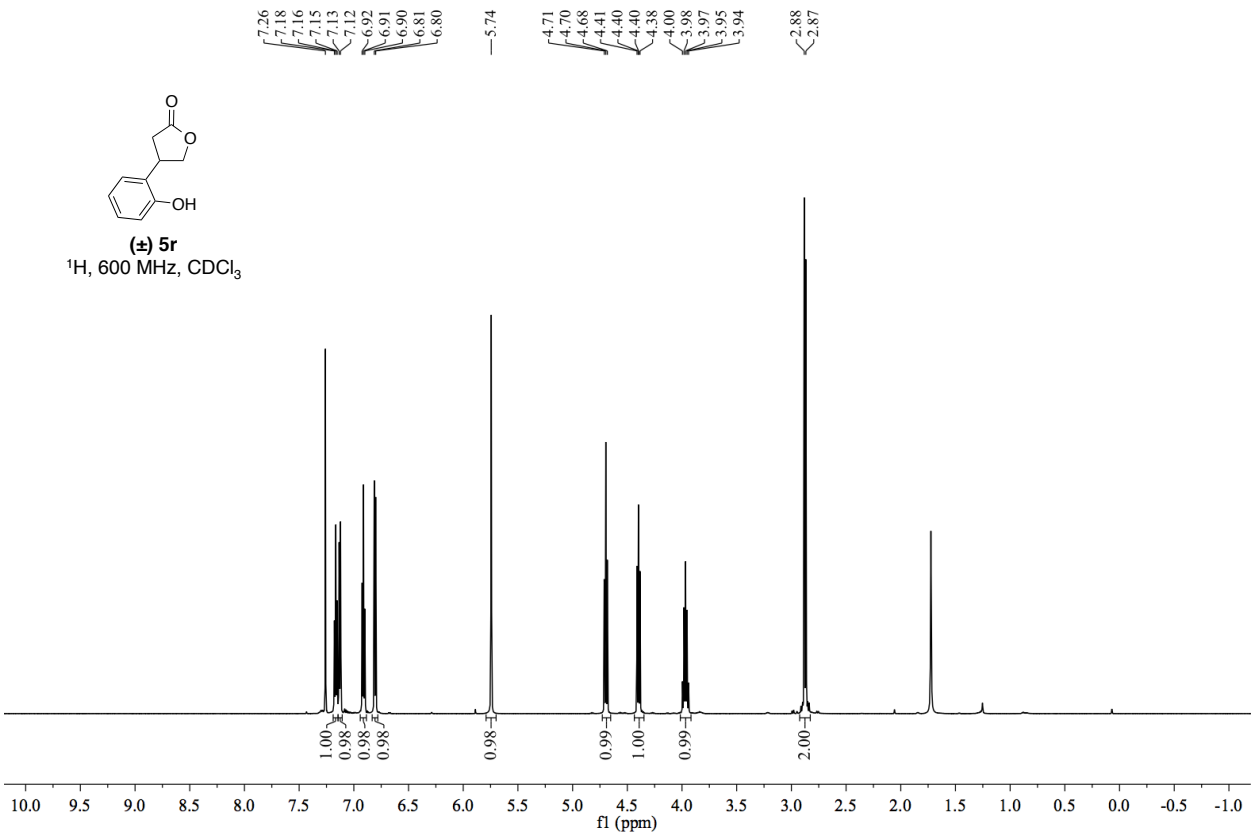
(±) 5o
^{13}C, 151 MHz, $CDCl_3$

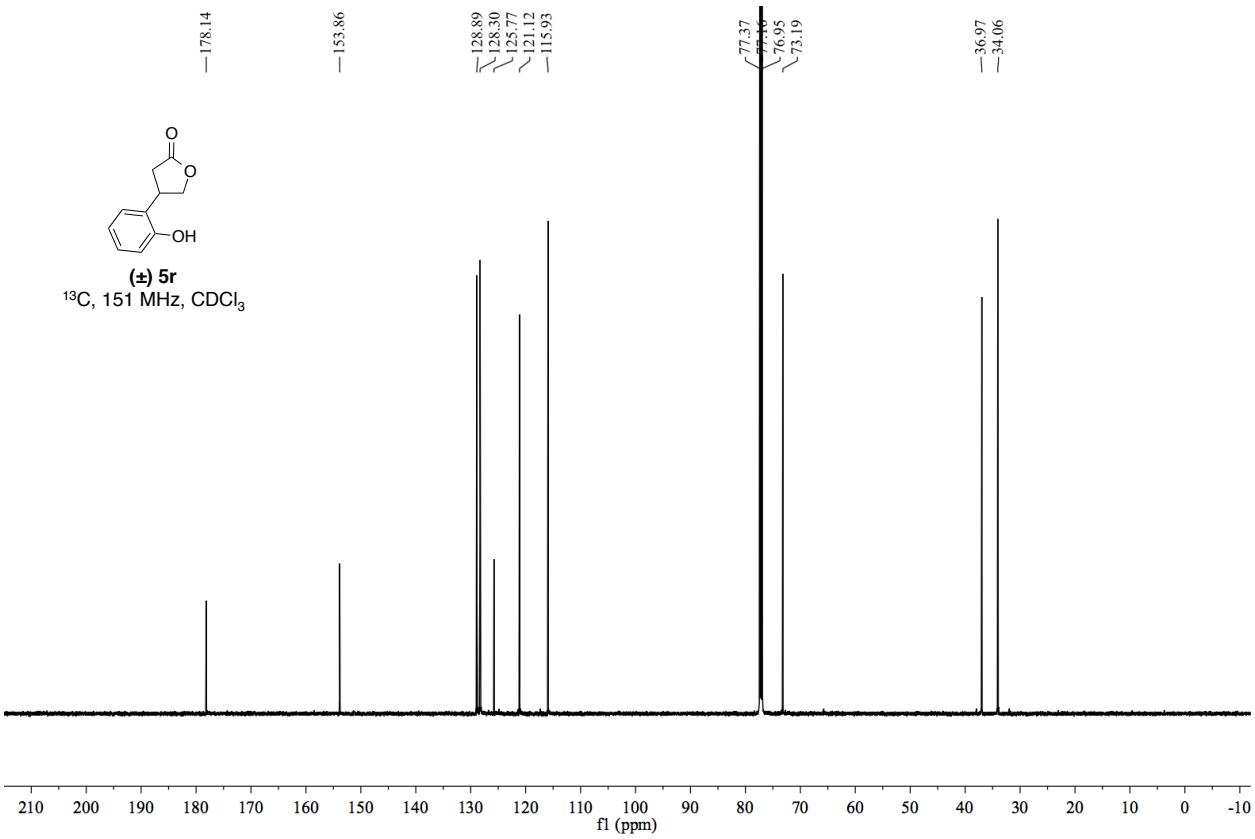

7.32
7.30
7.29
7.26
7.23
7.22
7.17
4.67
4.66
4.66
4.64
4.30
4.29
4.29
4.28
3.94
3.92
3.89
2.94
2.93
2.91
2.90
2.64
2.62
2.61
2.60
2.21
NH
CH3
(±) 5p
1H, 600 MHz, CDCl3
2.90
1.07
0.92
1.00
1.00
0.92
1.01
1.00
2.77
f1 (ppm)

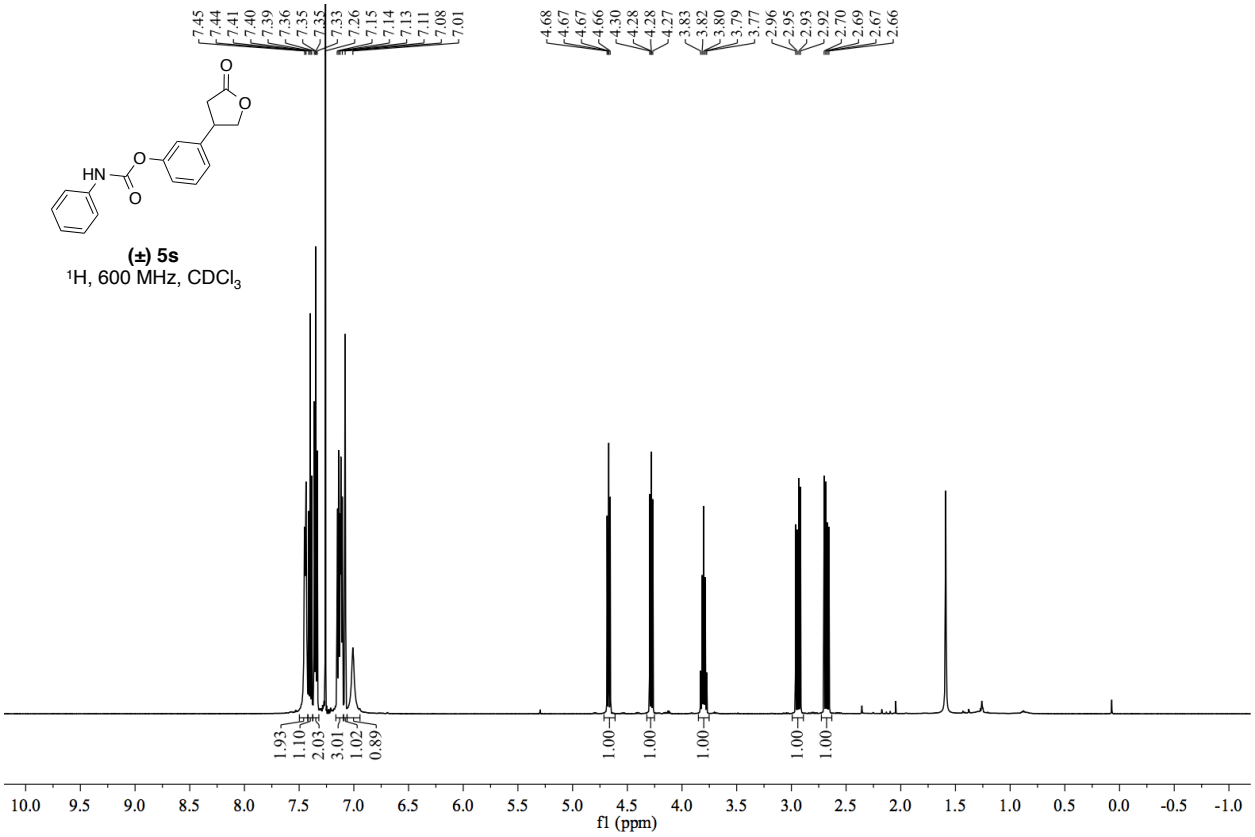

176.76
169.72
136.83
134.73
128.40
128.25
127.41
126.54
77.37
77.16
76.95
74.12
36.07
35.88
23.77
NH
CH3
(±) 5p
13C, 151 MHz, CDCl3
f1 (ppm)

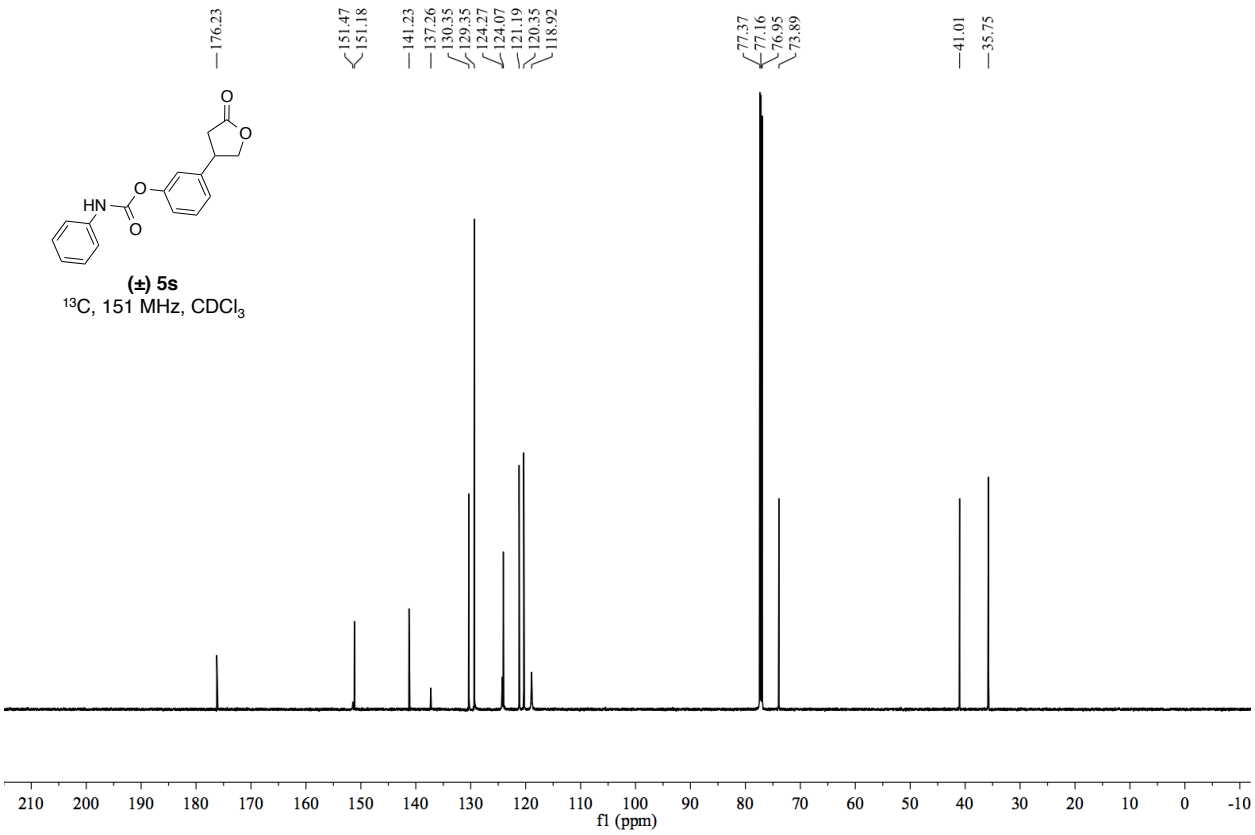

7.45
7.44
7.42
7.39
7.37
7.33
7.30
7.29
7.27
7.26
4.72
4.70
4.70
4.69
4.33
4.32
4.31
4.30
4.06
4.04
4.01
2.98
2.97
2.96
2.94
2.74
2.72
2.71
2.70
(±) 5q
1H, 600 MHz, CDCl3
2.10
1.15
6.07
0.99
0.99
0.99
1.00
1.00
f1 (ppm)

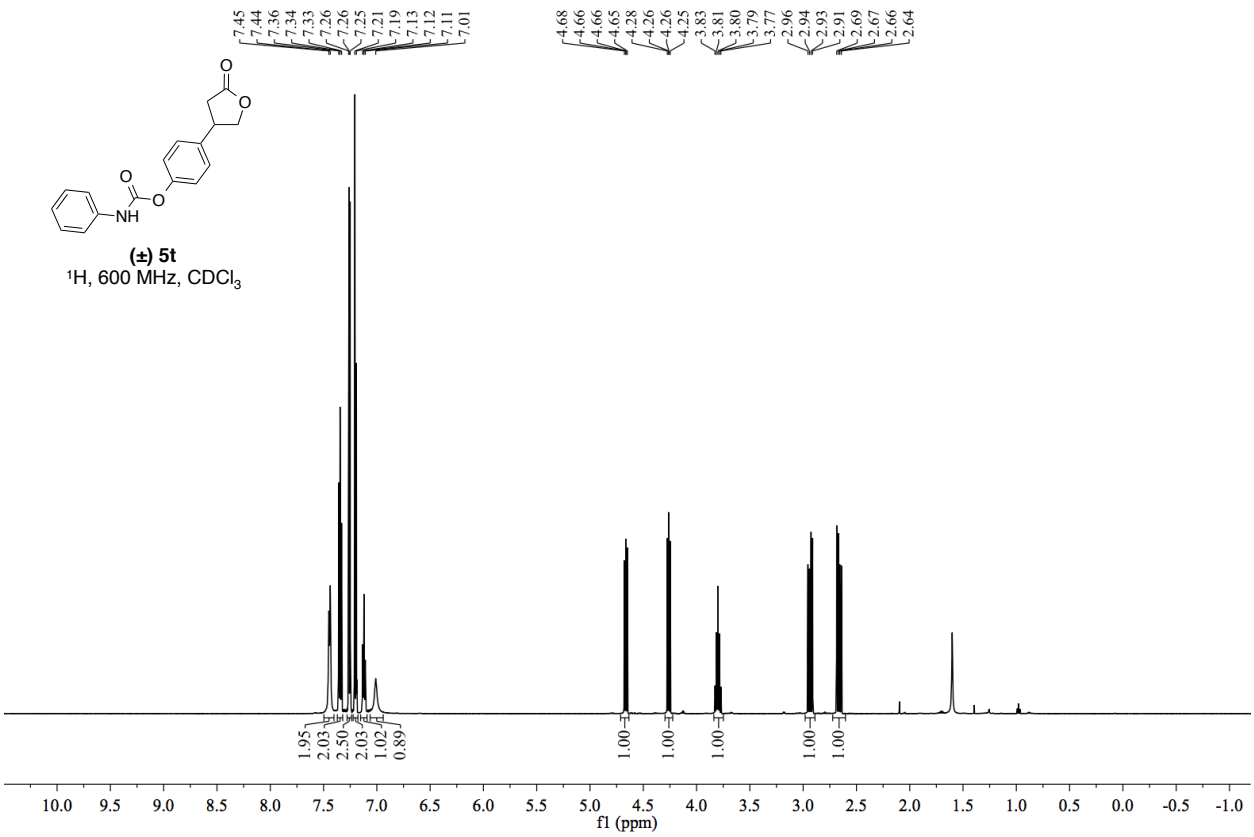

176.17
152.02
150.95
148.97
131.75
129.84
129.09
127.43
127.29
126.72
122.47
120.86
77.37
77.16
76.95
73.13
35.31
34.82
(±) 5q
13C, 151 MHz, CDCl3
f1 (ppm)

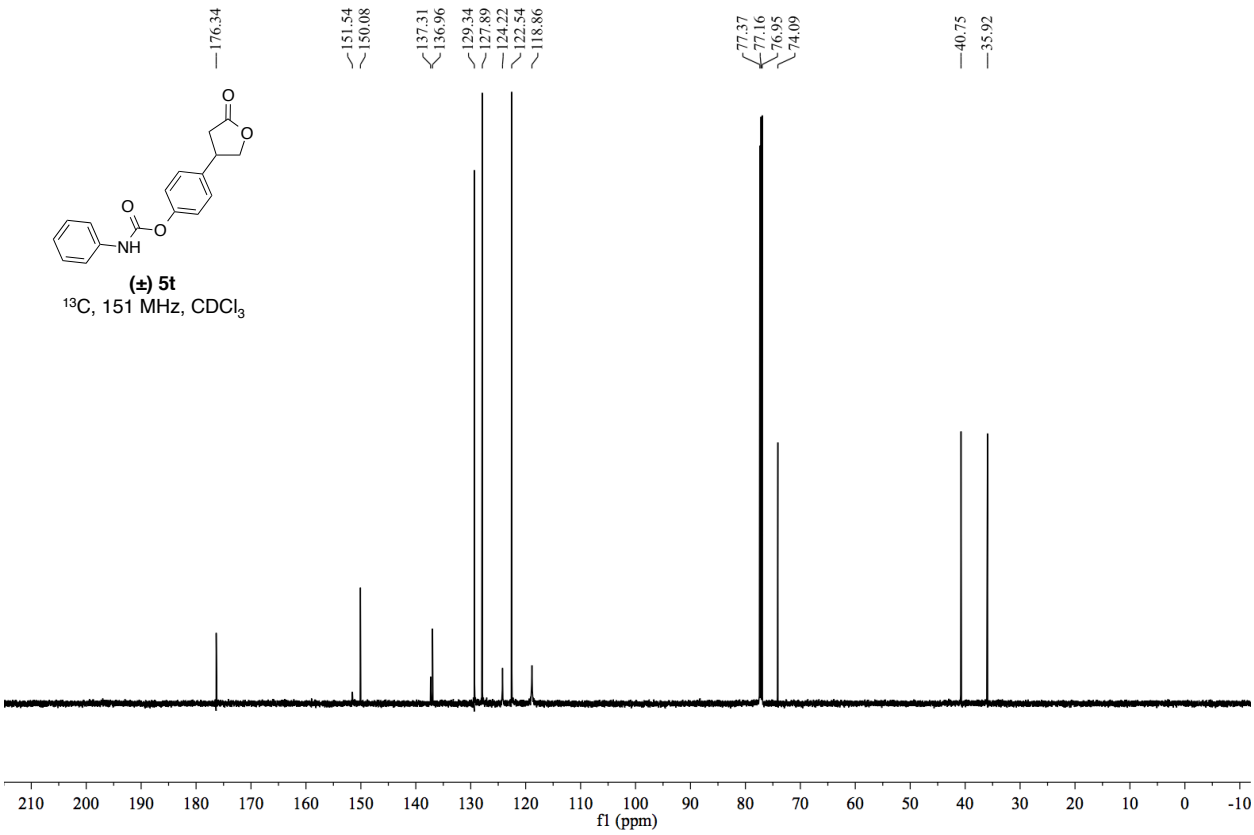

7.26
7.18
7.16
7.15
7.13
7.12
6.92
6.91
6.90
6.81
6.80
5.74
4.71
4.70
4.68
4.41
4.40
4.40
4.38
4.00
3.98
3.97
3.95
3.94
2.88
2.87
O
O
OH
(±) 5r
1H, 600 MHz, CDCl3
1.00
0.98
0.98
0.98
0.98
0.99
1.00
0.99
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


178.14
153.86
128.89
128.30
125.77
121.12
115.93
77.37
76.95
73.19
36.97
34.06
O
O
OH
(±) 5r
13C, 151 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

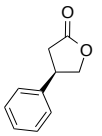

7.45
7.44
7.41
7.40
7.39
7.36
7.35
7.35
7.33
7.26
7.15
7.14
7.13
7.11
7.08
7.01
4.68
4.67
4.67
4.66
4.30
4.28
4.28
4.27
3.83
3.82
3.80
3.79
3.77
2.96
2.95
2.93
2.92
2.70
2.69
2.67
2.66
HN
O
O
O
O
(±) 5s
1H, 600 MHz, CDCl3
1.93
1.10
2.03
3.01
1.02
0.89
1.00
1.00
1.00
1.00
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


176.23
151.47
151.18
141.23
137.26
130.35
129.35
124.27
124.07
121.19
120.35
118.92
77.37
77.16
76.95
73.89
41.01
35.75
HN
O
O
O
O
(±) 5s
13C, 151 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.45
7.44
7.36
7.34
7.33
7.26
7.26
7.25
7.21
7.19
7.13
7.12
7.11
7.01
4.68
4.66
4.66
4.65
4.28
4.26
4.26
4.25
3.83
3.81
3.80
3.79
3.77
2.96
2.94
2.93
2.91
2.69
2.67
2.66
2.64
O
O
O
O
NH
(±) 5t
1H, 600 MHz, CDCl3
1.95
2.03
2.50
2.03
1.02
0.89
1.00
1.00
1.00
1.00
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


176.34
151.54
150.08
137.31
136.96
129.34
127.89
124.22
122.54
118.86
77.37
77.16
76.95
74.09
40.75
35.92
O
O
O
O
NH
(±) 5t
13C, 151 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

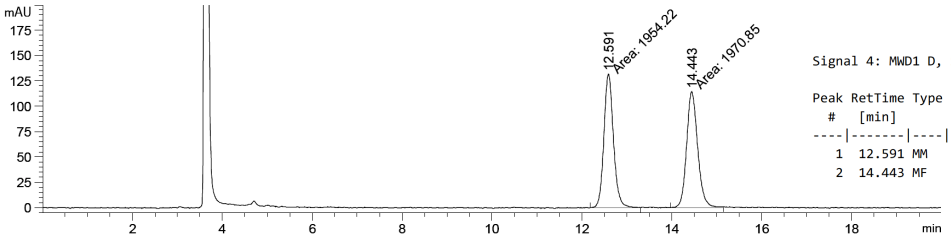
6.5. HPLC Traces of 5



5a

HPLC Conditions:
Chiralpak IA column, 10% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 220 nm

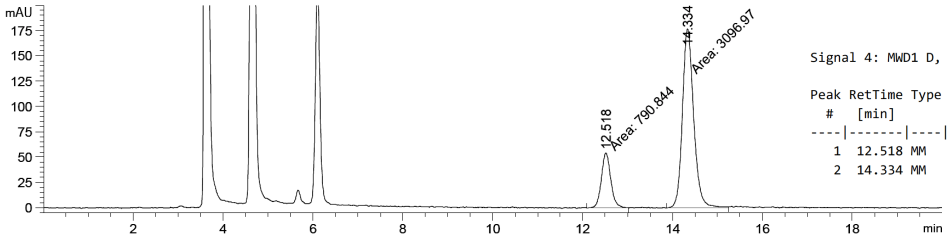
Racemic Standard



Signal 4: MWD1 D, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.591	MM	0.2467	1954.22168	132.03761	49.7881
2	14.443	MF	0.2869	1970.85242	114.48767	50.2119

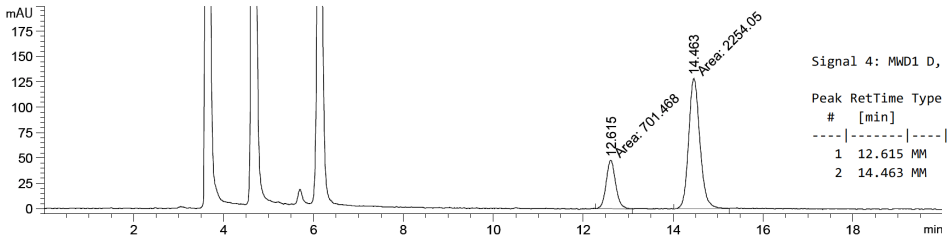
5a with 2.5 mol% **P41**



Signal 4: MWD1 D, Sig=220,4 Ref=360,100

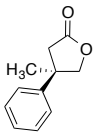
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.518	MM	0.2431	790.84369	54.22167	20.3416
2	14.334	MM	0.2918	3096.96777	176.87714	79.6584

5a with 2.5 mol% **P42**



Signal 4: MWD1 D, Sig=220,4 Ref=360,100

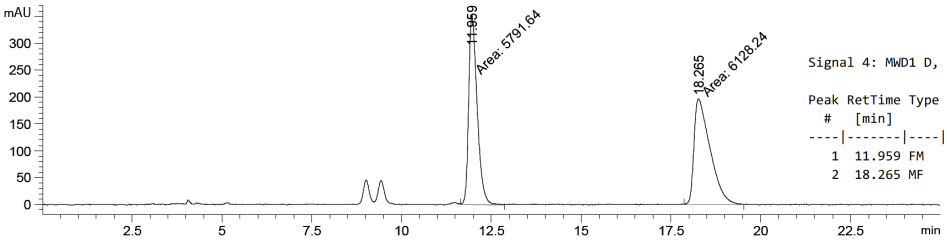
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.615	MM	0.2437	701.46783	47.97670	23.7342
2	14.463	MM	0.2917	2254.04663	128.80429	76.2658



5b

HPLC Conditions:
Chiralpak IA column, 10% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 220 nm

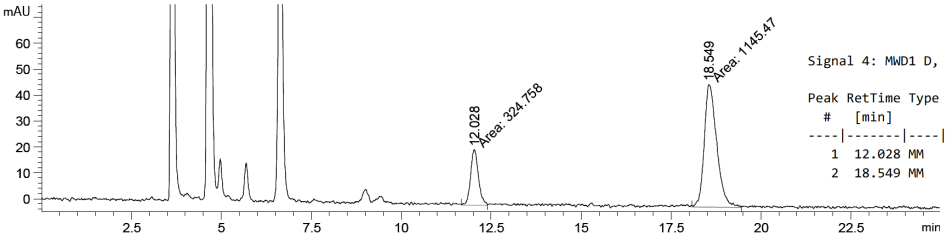
Racemic Standard



Signal 4: MWD1 D, Sig=220,4 Ref=360,100

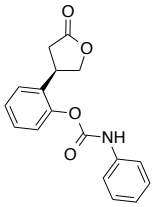
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.959	FM	0.2731	5791.63867	353.41342	48.5881
2	18.265	MF	0.5192	6128.23535	196.70879	51.4119

5b with 10 mol% **P18**



Signal 4: MWD1 D, Sig=220,4 Ref=360,100

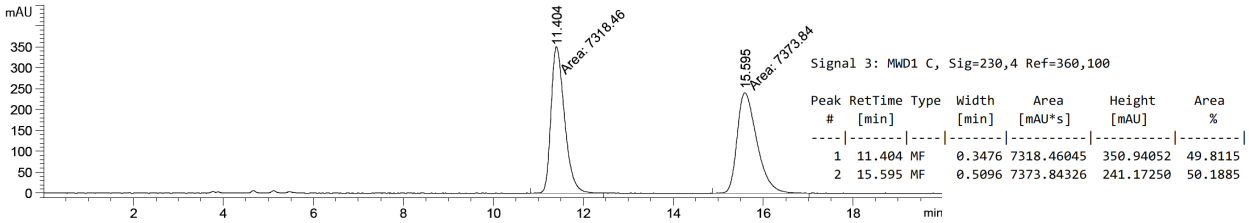
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.028	MM	0.2537	324.75827	21.33115	22.0889
2	18.549	MM	0.4033	1145.47241	47.34128	77.9111



5c

Screening HPLC Conditions:
Chiralpak IA column, 15% EtOH/Hexanes eluent, 1.5 mL·min^{-1} flow rate, 25 °C, 230 nm

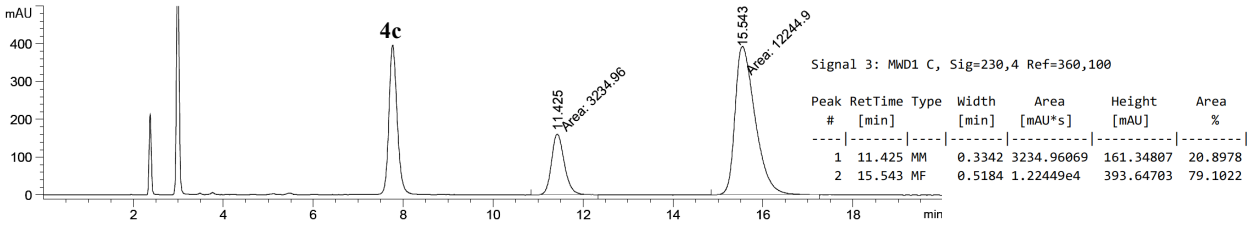
Racemic Standard



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.404	MF	0.3476	7318.46045	350.94052	49.8115
2	15.595	MF	0.5096	7373.84326	241.17250	50.1885

5c with 2.5 mol% **P42**

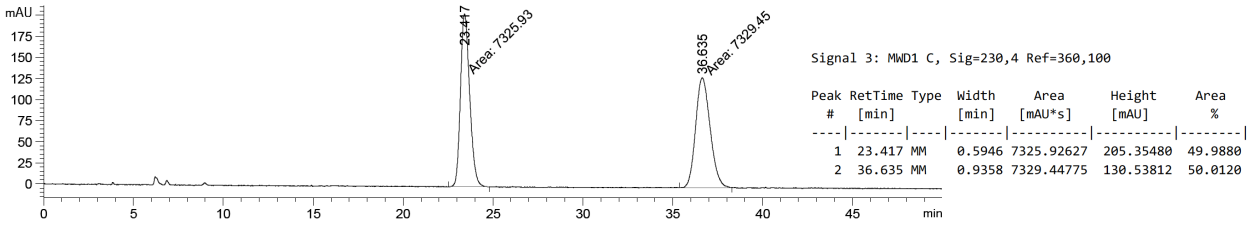


Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.425	MM	0.3342	3234.96069	161.34807	20.8978
2	15.543	MF	0.5184	1.22449e4	393.64703	79.1022

Isolated HPLC Conditions: Chiralpak AD-H column, 20% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm

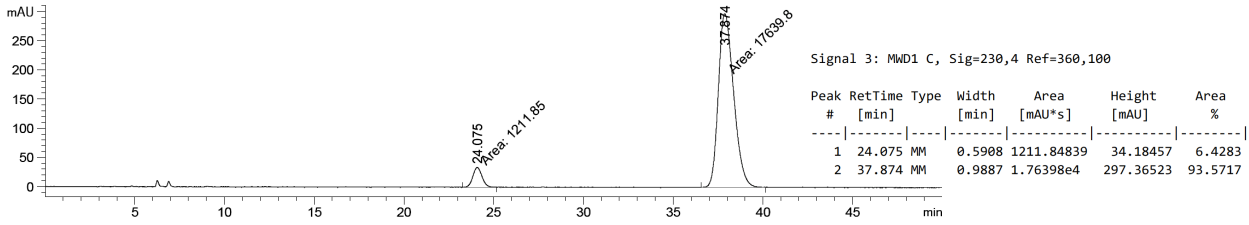
Racemic Standard



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.417	MM	0.5946	7325.92627	205.35480	49.9880
2	36.635	MM	0.9358	7329.44775	130.53812	50.0120

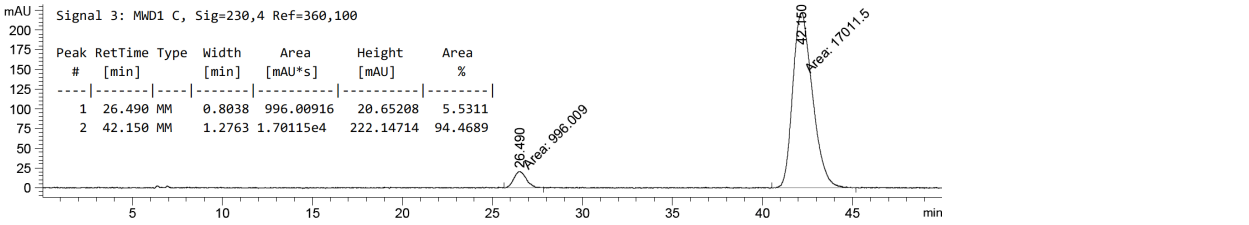
5c with 2.5 mol% **P41**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

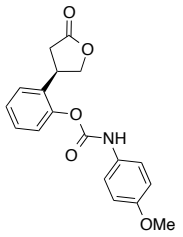
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.075	MM	0.5908	1211.84839	34.18457	6.4283
2	37.874	MM	0.9887	1.76398e4	297.36523	93.5717

5c after crystallization (obtained from 94:6 material with **P41**)



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

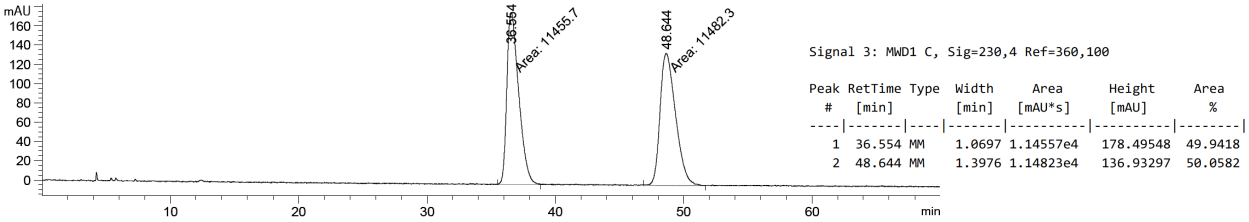
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.490	MM	0.8038	996.00916	20.65208	5.5311
2	42.150	MM	1.2763	1.70115e4	222.14714	94.4689



5d

HPLC Conditions:
Chiralpak AD-H column, 25% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm

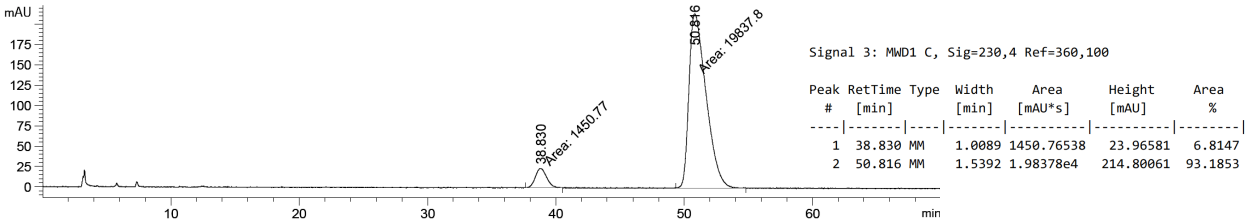
Racemic Standard



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

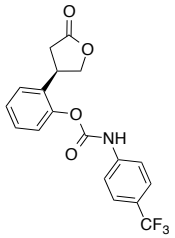
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.554	MM	1.0697	1.14557e4	178.49548	49.9418
2	48.644	MM	1.3976	1.14823e4	136.93297	50.0582

5d



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

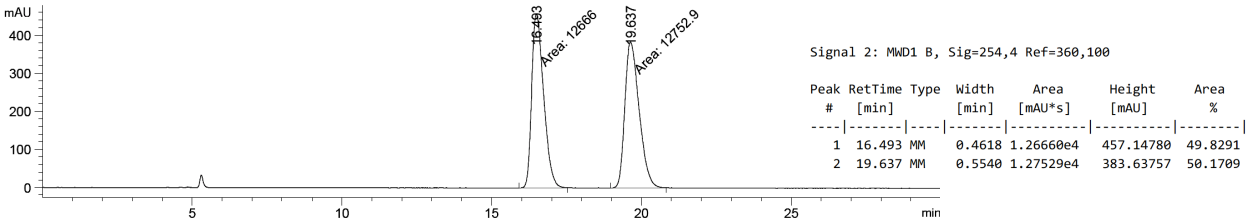
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.830	MM	1.0089	1450.76538	23.96581	6.8147
2	50.816	MM	1.5392	1.98378e4	214.80061	93.1853



5e

HPLC Conditions:
Chiralpak AD-H column, 20% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm

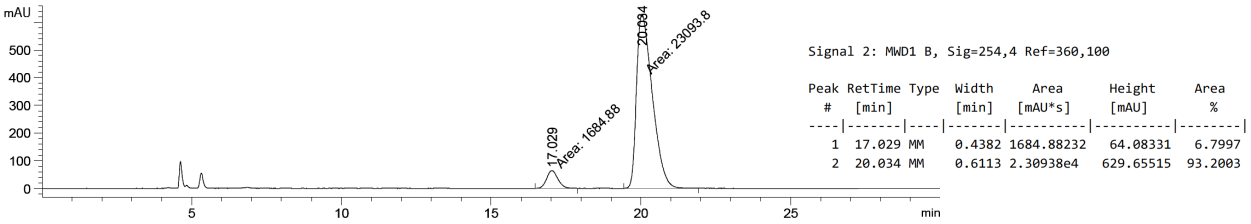
Racemic Standard



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.493	MM	0.4618	1.26660e4	457.14780	49.8291
2	19.637	MM	0.5540	1.27529e4	383.63757	50.1709

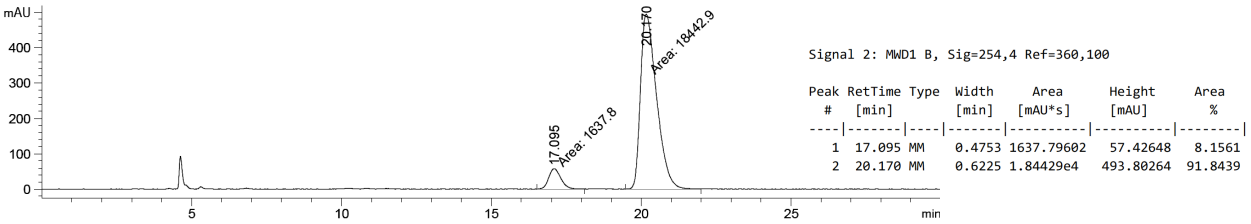
5e



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

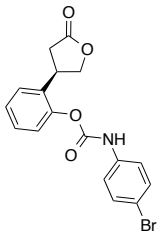
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.029	MM	0.4382	1684.88232	64.08331	6.7997
2	20.034	MM	0.6113	2.30938e4	629.65515	93.2003

5e after crystallization (obtained from 92:8 material with **P40**)



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

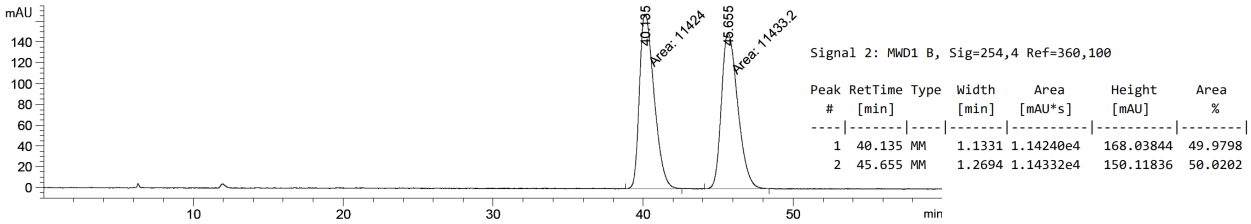
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.095	MM	0.4753	1637.79602	57.42648	8.1561
2	20.170	MM	0.6225	1.84429e4	493.80264	91.8439



5f

HPLC Conditions:
Chiralpak AD-H column, 20% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm

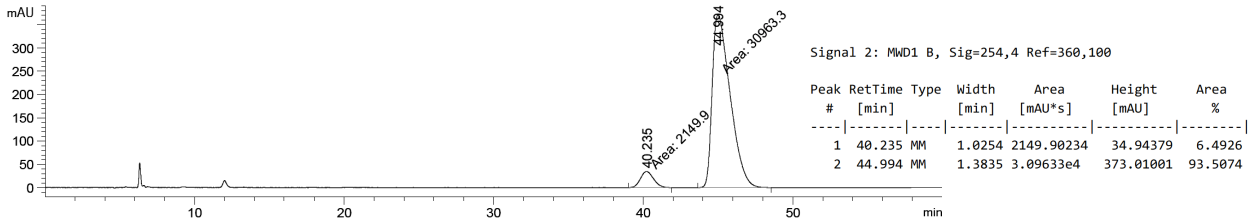
Racemic Standard



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.135	MM	1.1331	1.14240e4	168.03844	49.9798
2	45.655	MM	1.2694	1.14332e4	150.11836	50.0202

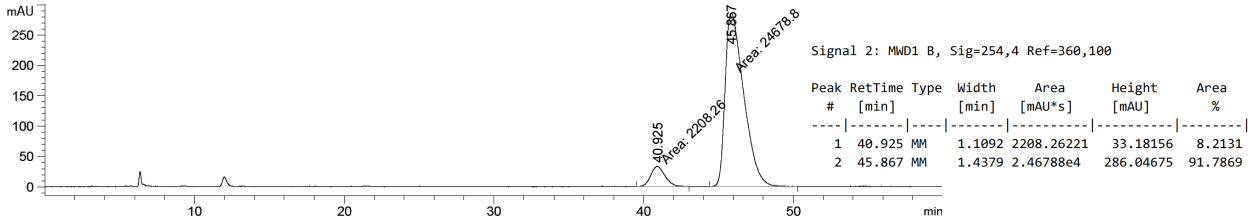
5f



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

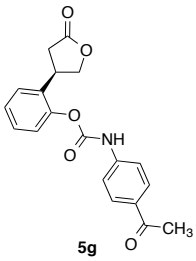
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.235	MM	1.0254	2149.90234	34.94379	6.4926
2	44.994	MM	1.3835	3.09633e4	373.01001	93.5074

5f after crystallization (obtained from 92:8 material with **P40**)



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

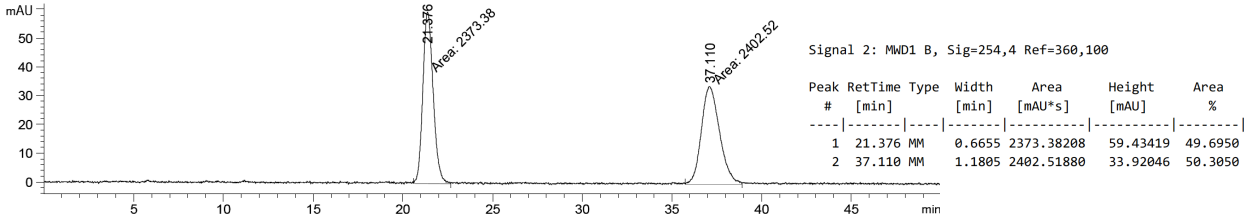
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.925	MM	1.1092	2208.26221	33.18156	8.2131
2	45.867	MM	1.4379	2.46788e4	286.04675	91.7869



5g

HPLC Conditions:
Chiralpak AD-H column, 35% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm

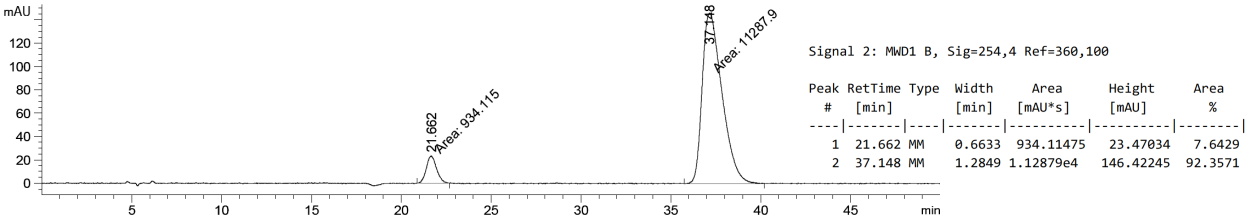
Racemic Standard



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

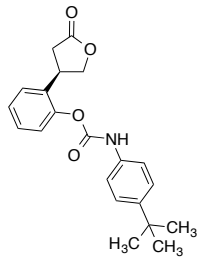
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.376	MM	0.6655	2373.38208	59.43419	49.6950
2	37.110	MM	1.1805	2402.51880	33.92046	50.3050

5g



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

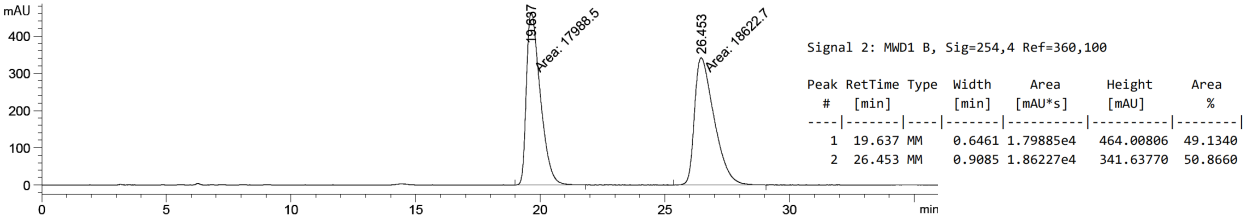
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.662	MM	0.6633	934.11475	23.47034	7.6429
2	37.148	MM	1.2849	1.12879e4	146.42245	92.3571



5h

HPLC Conditions:
Chiralpak AD-H column, 20% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm

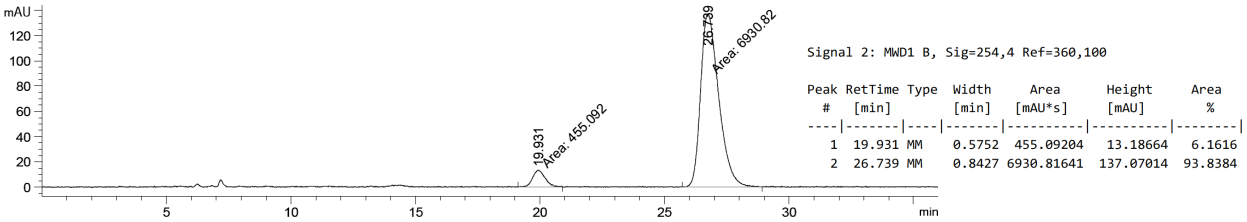
Racemic Standard



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

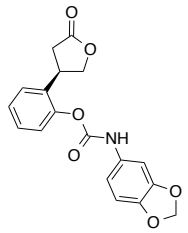
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.637	MM	0.6461	1.79885e4	464.00806	49.1340
2	26.453	MM	0.9085	1.86227e4	341.63770	50.8660

5h



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

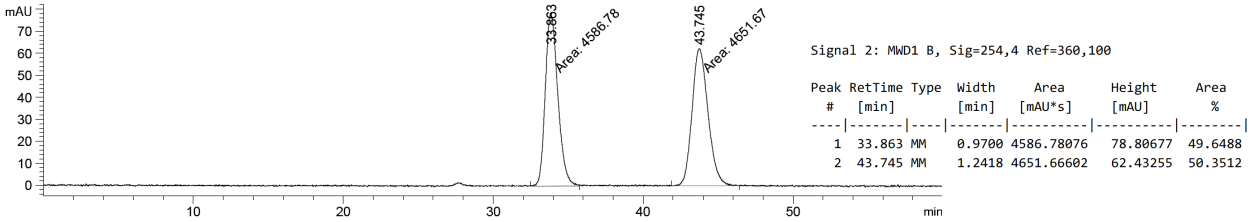
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.931	MM	0.5752	455.09204	13.18664	6.1616
2	26.739	MM	0.8427	6930.81641	137.07014	93.8384



5i

HPLC Conditions:
Chiralpak AD-H column, 25% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm

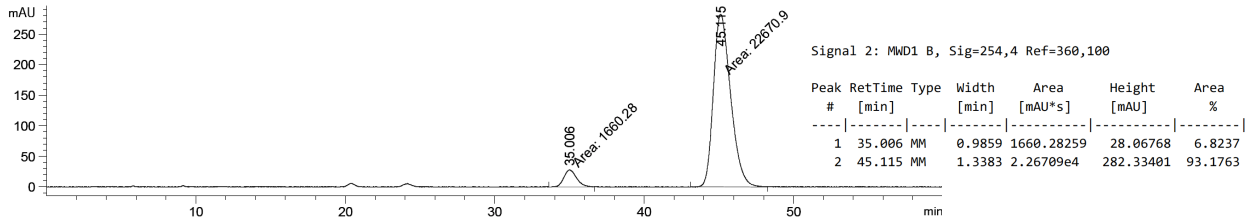
Racemic Standard



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

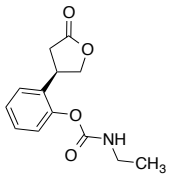
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.863	MM	0.9700	4586.78076	78.80677	49.6488
2	43.745	MM	1.2418	4651.66602	62.43255	50.3512

5i



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

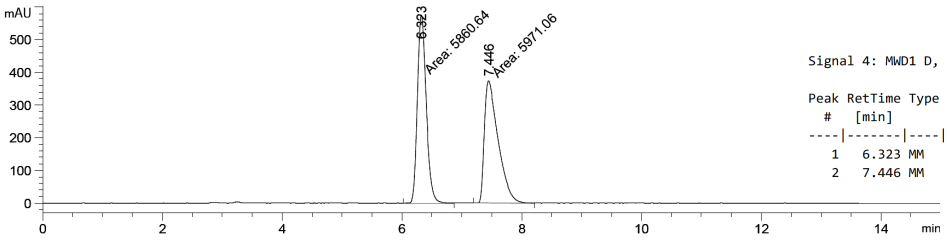
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.006	MM	0.9859	1660.28259	28.06768	6.8237
2	45.115	MM	1.3383	2.26709e4	282.33401	93.1763



5j

HPLC Conditions:
Chiralpak AD-H column, 30% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 220 nm

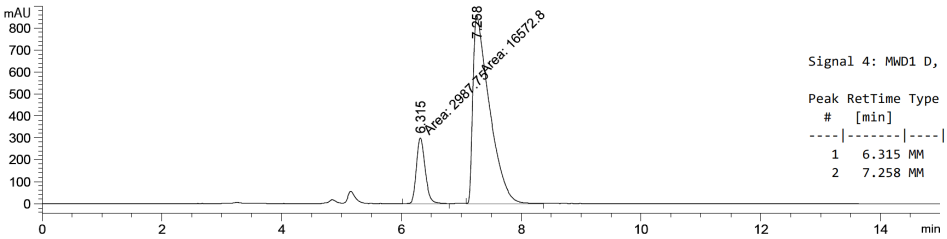
Racemic Standard



Signal 4: MWD1 D, Sig=220,4 Ref=off

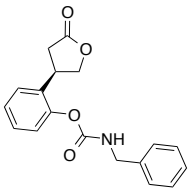
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.323	MM	0.1685	5860.63574	579.66547	49.5334
2	7.446	MM	0.2640	5971.05762	376.93793	50.4666

5j



Signal 4: MWD1 D, Sig=220,4 Ref=off

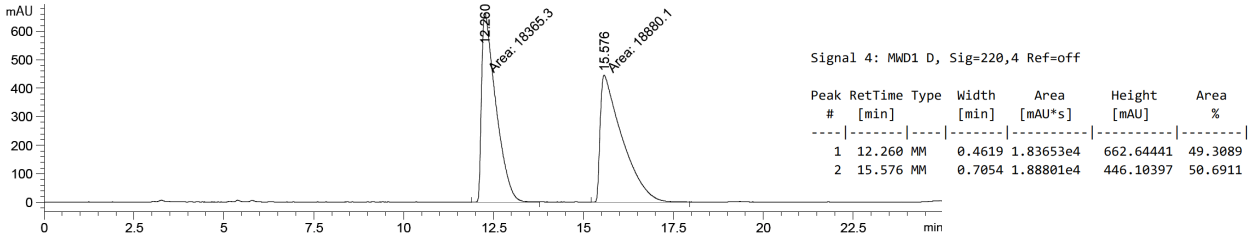
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.315	MM	0.1649	2987.75171	301.92480	15.2744
2	7.258	MM	0.3184	1.65728e4	867.62054	84.7256



5k

HPLC Conditions:
Chiralpak AD-H column, 25% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 220 nm

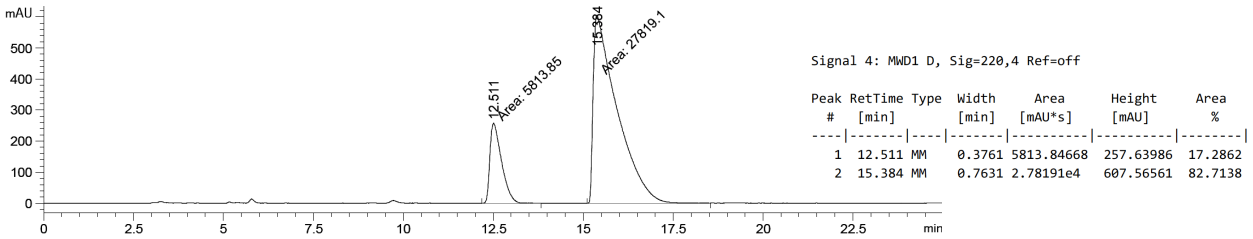
Racemic Standard



Signal 4: MWD1 D, Sig=220,4 Ref=off

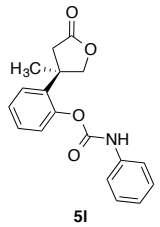
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.260	MM	0.4619	1.83653e4	662.64441	49.3089
2	15.576	MM	0.7054	1.88801e4	446.10397	50.6911

5k



Signal 4: MWD1 D, Sig=220,4 Ref=off

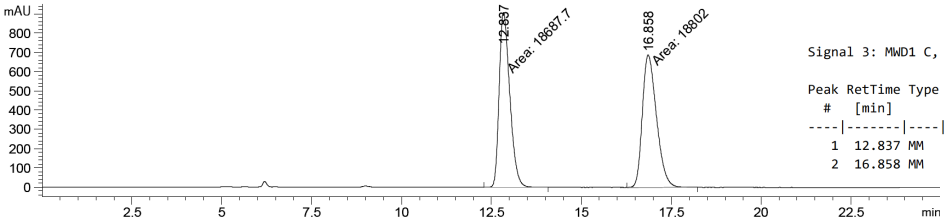
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.511	MM	0.3761	5813.84668	257.63986	17.2862
2	15.384	MM	0.7631	2.78191e4	607.56561	82.7138



5l

HPLC Conditions:
Chiralpak AD-H column, 20% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm

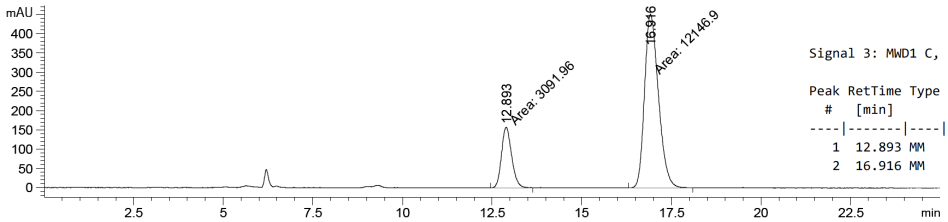
Racemic Standard



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

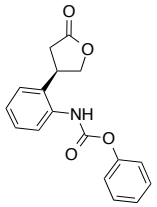
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.837	MM	0.3431	1.86877e4	907.67053	49.8476
2	16.858	MM	0.4551	1.88020e4	688.49689	50.1524

5l



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

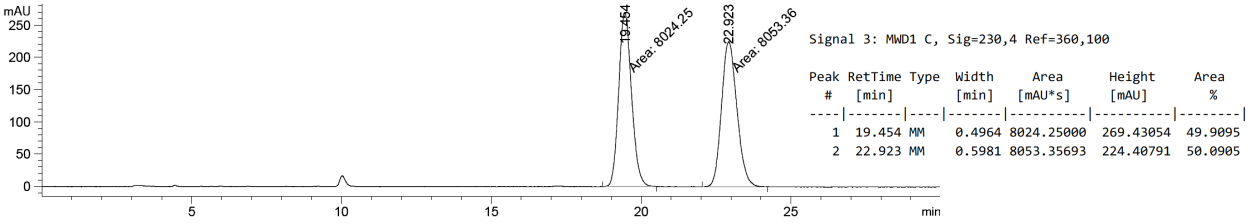
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.893	MM	0.3267	3091.96338	157.71484	20.2900
2	16.916	MM	0.4482	1.21469e4	451.68021	79.7100



5m

HPLC Conditions:
Chiralpak AD-H column, 20% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm

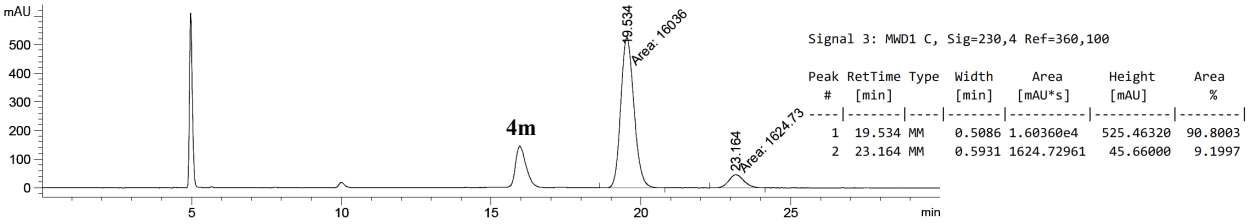
Racemic Standard



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.454	MM	0.4964	8024.25000	269.43054	49.9095
2	22.923	MM	0.5981	8053.35693	224.40791	50.0905

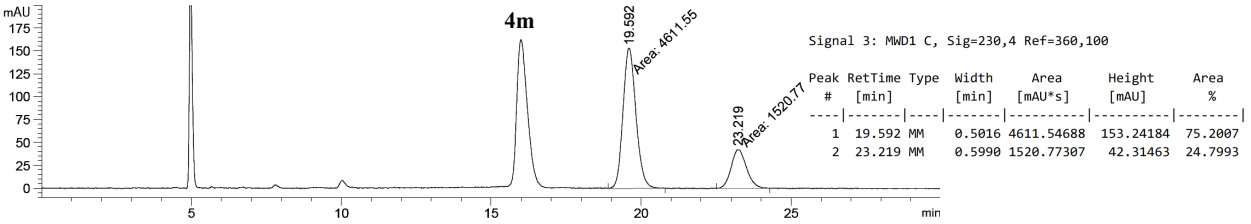
5m from 2.5 mol% **P41**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

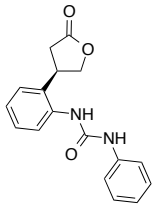
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.534	MM	0.5086	1.60360e4	525.46320	90.8003
2	23.164	MM	0.5931	1624.72961	45.66000	9.1997

5m from 2.5 mol% **P42**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

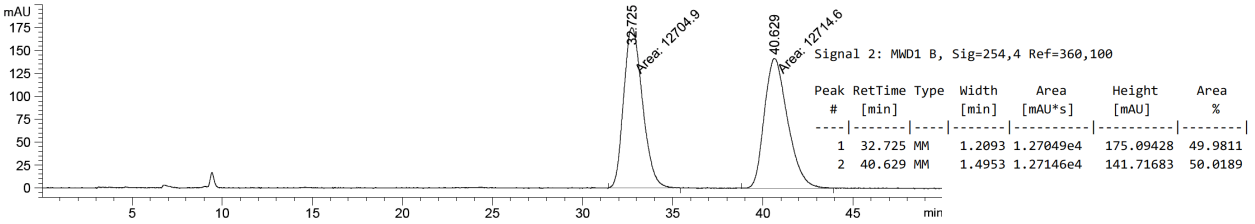
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.592	MM	0.5016	4611.54688	153.24184	75.2007
2	23.219	MM	0.5990	1520.77307	42.31463	24.7993



5n

HPLC Conditions:
Chiralpak AD-H column, 20% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm

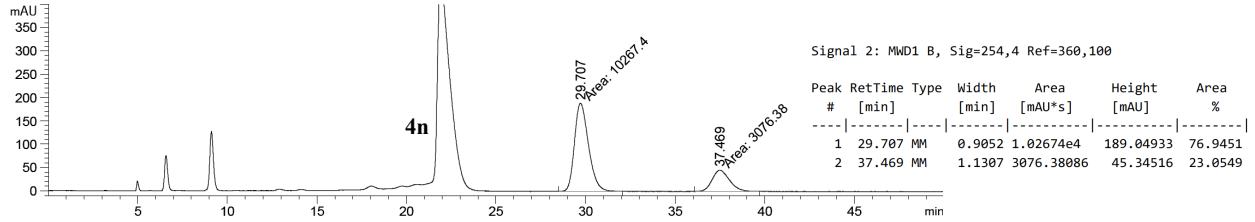
Racemic Standard



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.725	MM	1.2093	1.27049e4	175.09428	49.9811
2	40.629	MM	1.4953	1.27146e4	141.71683	50.0189

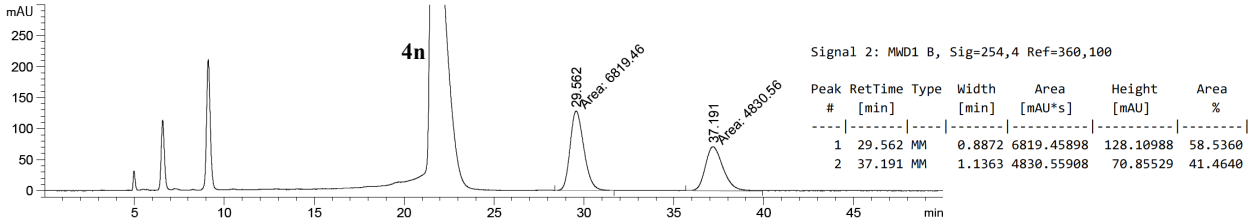
5n from 2.5 mol% **P41**



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

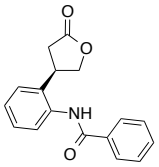
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.707	MM	0.9052	1.02674e4	189.04933	76.9451
2	37.469	MM	1.1307	3076.38086	45.34516	23.0549

5n from 2.5 mol% **P42**



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

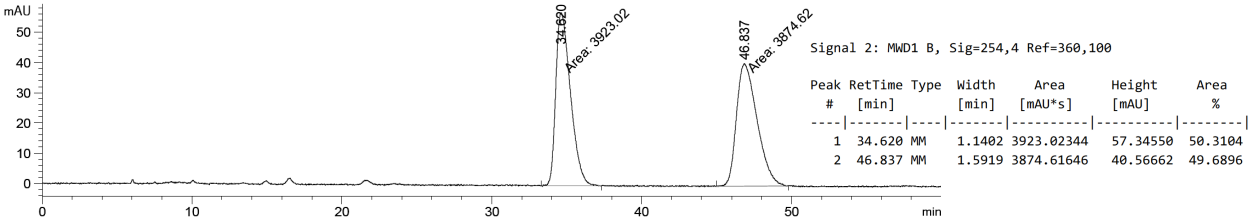
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.562	MM	0.8872	6819.45898	128.10988	58.5360
2	37.191	MM	1.1363	4830.55908	70.85529	41.4640



5o

HPLC Conditions:
Chiralpak AD-H column, 20% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 254 nm

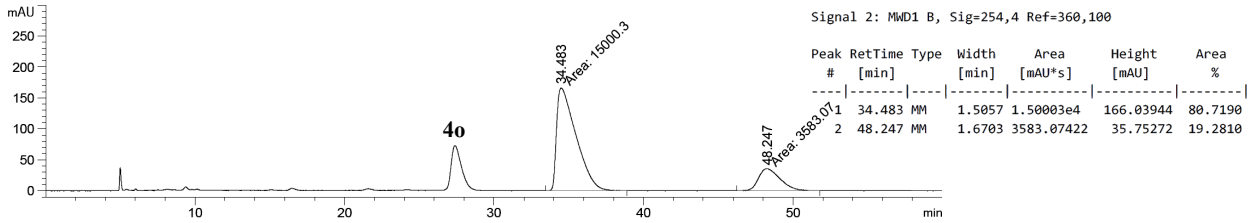
Racemic Standard



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.620	MM	1.1402	3923.02344	57.34550	50.3104
2	46.837	MM	1.5919	3874.61646	40.56662	49.6896

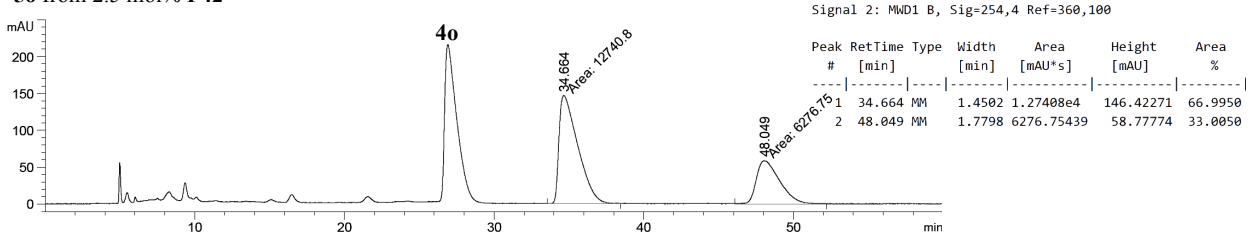
5o from 2.5 mol% **P41**



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

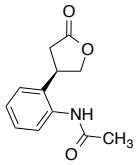
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.483	MM	1.5057	1.50003e4	166.03944	80.7190
2	48.247	MM	1.6703	3583.07422	35.75272	19.2810

5o from 2.5 mol% **P42**



Signal 2: MWD1 B, Sig=254,4 Ref=360,100

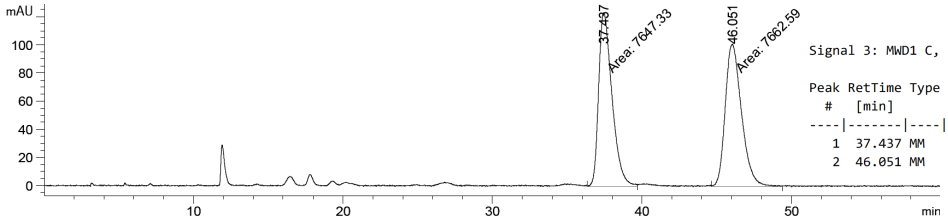
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.664	MM	1.4502	1.27408e4	146.42271	66.9950
2	48.049	MM	1.7798	6276.75439	58.77774	33.0050



5p

HPLC Conditions:
Chiralpak AD-H column, 10% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm

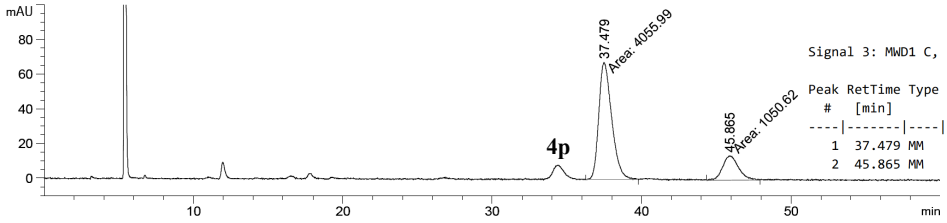
Racemic Standard



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.437	MM	1.0331	7647.32959	123.37562	49.9502
2	46.051	MM	1.2623	7662.59277	101.17049	50.0498

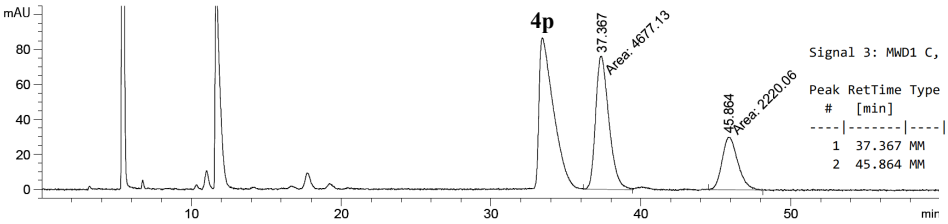
5p from 2.5 mol% **P41**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

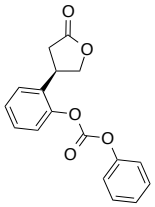
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.479	MM	1.0018	4055.98511	67.48080	79.4263
2	45.865	MM	1.2389	1050.61597	14.13326	20.5737

5p from 2.5 mol% **P42**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

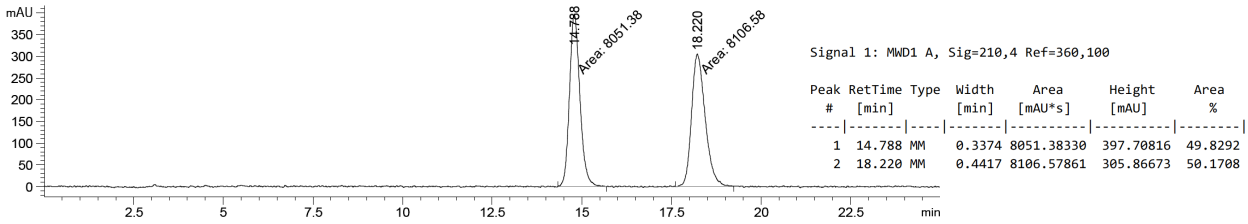
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.367	MM	1.0223	4677.12842	76.25178	67.8121
2	45.864	MM	1.2234	2220.05518	30.24477	32.1879



5q

HPLC Conditions:
Chiralpak IA column, 15% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 210 nm

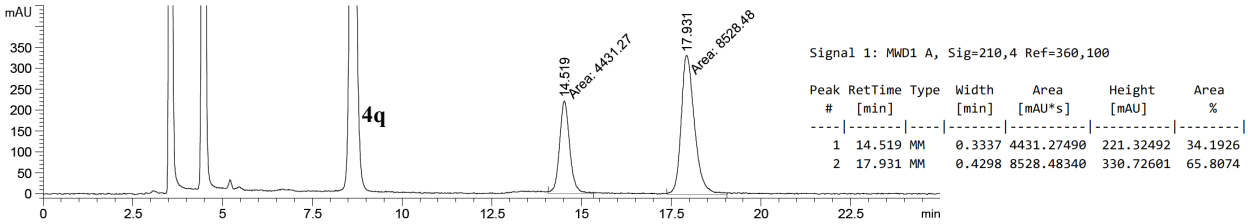
Racemic Standard



Signal 1: MWD1 A, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.788	MM	0.3374	8051.38330	397.70816	49.8292
2	18.220	MM	0.4417	8106.57861	305.86673	50.1708

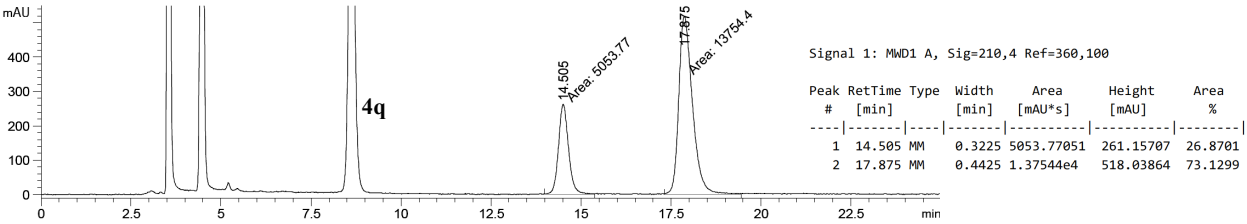
5q from 2.5 mol% **P41**



Signal 1: MWD1 A, Sig=210,4 Ref=360,100

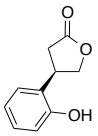
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.519	MM	0.3337	4431.27490	221.32492	34.1926
2	17.931	MM	0.4298	8528.48340	330.72601	65.8074

5q from 2.5 mol% **P42**



Signal 1: MWD1 A, Sig=210,4 Ref=360,100

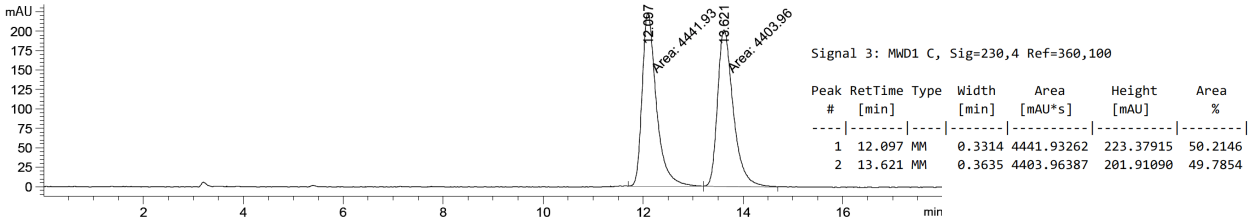
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.505	MM	0.3225	5053.77051	261.15707	26.8701
2	17.875	MM	0.4425	1.37544e4	518.03864	73.1299



5r

HPLC Conditions:
Chiralpak AD-H column, 10% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm

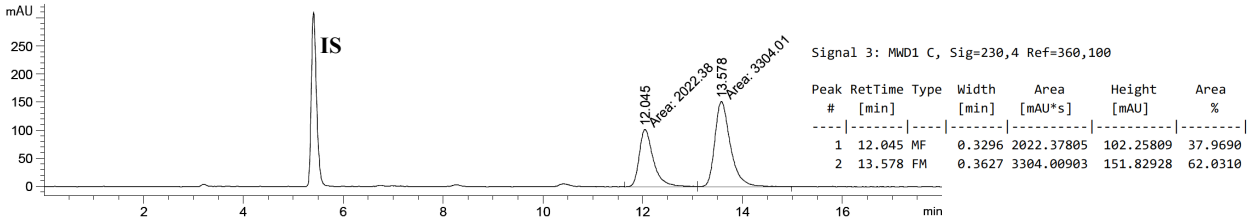
Racemic Standard



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.097	MM	0.3314	4441.93262	223.37915	50.2146
2	13.621	MM	0.3635	4403.96387	201.91090	49.7854

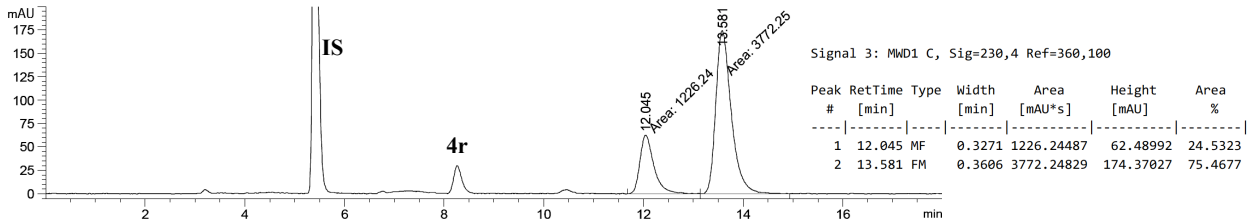
5r from 2.5 mol% **P41**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.045	MF	0.3296	2022.37805	102.25809	37.9690
2	13.578	FM	0.3627	3304.00903	151.82928	62.0310

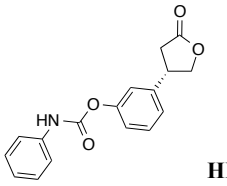
5r from 2.5 mol% **P42**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.045	MF	0.3271	1226.24487	62.48992	24.5323
2	13.581	FM	0.3606	3772.24829	174.37027	75.4677

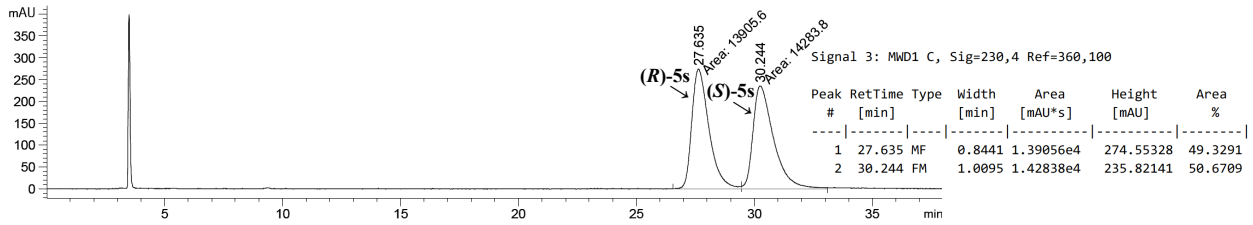
IS, 1,3,5-trimethoxybenzene



5s

HPLC Conditions:
Chiralpak IA column, 20% EtOH/Hexanes eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm

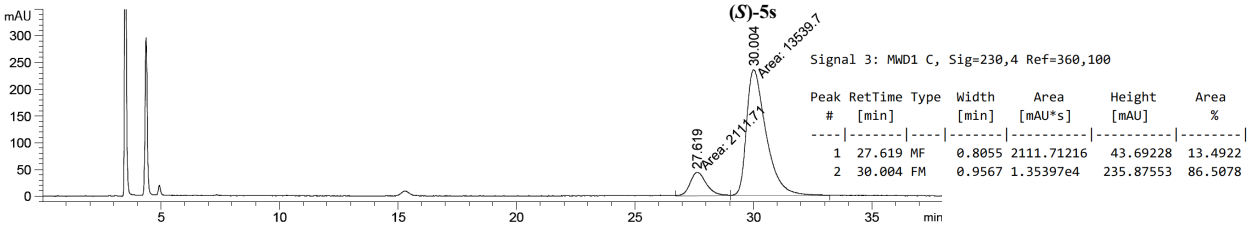
Racemic Standard



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.635	MF	0.8441	1.39056e4	274.55328	49.3291
2	30.244	FM	1.0095	1.42838e4	235.82141	50.6709

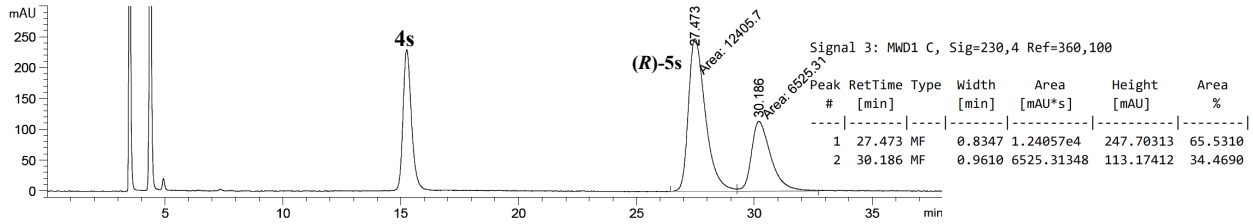
5s from 2.5 mol% **P41**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.619	MF	0.8055	2111.71216	43.69228	13.4922
2	30.004	FM	0.9567	1.35397e4	235.87553	86.5078

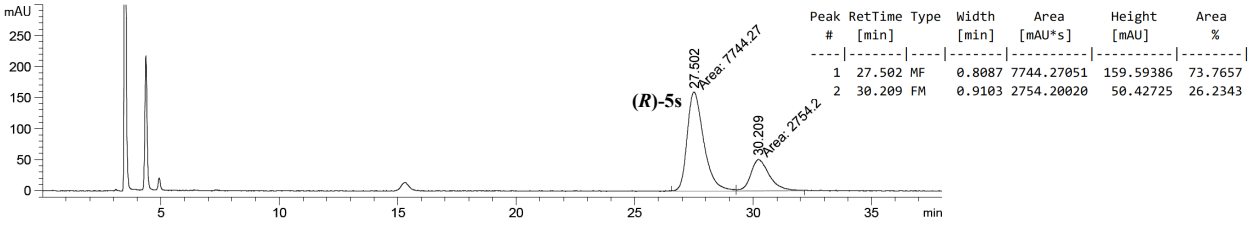
5s from 2.5 mol% **P42**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.473	MF	0.8347	1.24057e4	247.70313	65.5310
2	30.186	MF	0.9610	6525.31348	113.17412	34.4690

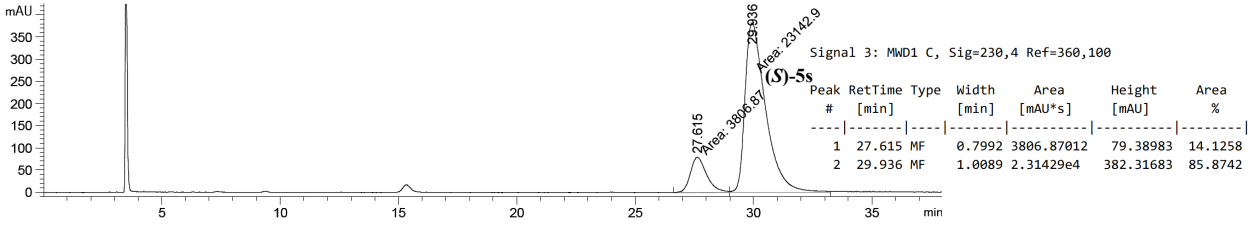
5s from 2.5 mol% **(*R*)-TRIP**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

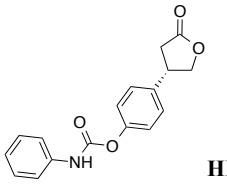
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.502	MF	0.8087	7744.27051	159.59386	73.7657
2	30.209	FM	0.9103	2754.20020	50.42725	26.2343

5s crystallization from slow evaporation of $CHCl_3$



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

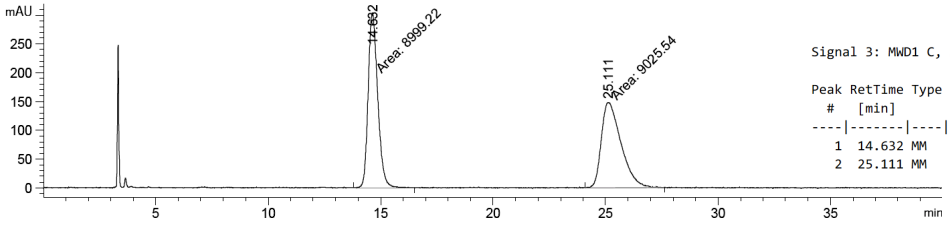
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.615	MF	0.7992	3806.87012	79.38983	14.1258
2	29.936	MF	1.0089	2.31429e4	382.31683	85.8742



5t

HPLC Conditions:
Chiralpak IA column, 100% EtOH eluent, 1.0 mL·min^{-1} flow rate, 25 °C, 230 nm

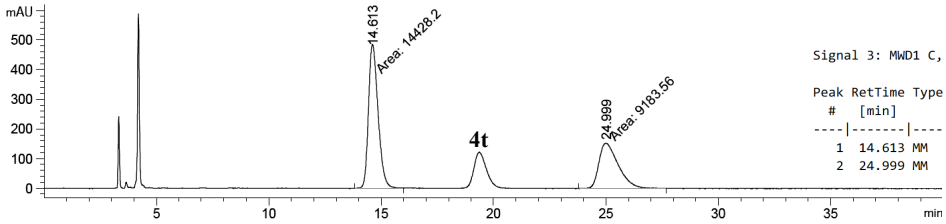
Racemic Standard



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.632	MM	0.4937	8999.21777	303.78833	49.9270
2	25.111	MM	1.0131	9025.53809	148.48137	50.0730

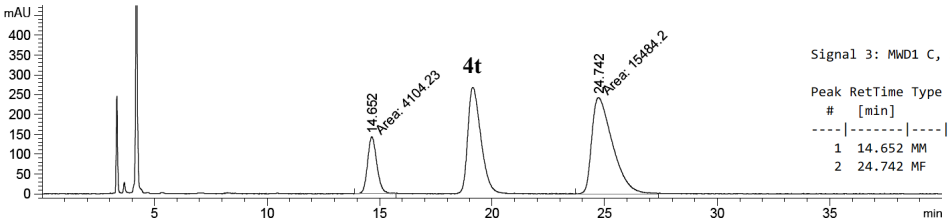
5t from 2.5 mol% **P41**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.613	MM	0.4949	1.44282e4	485.85040	61.1060
2	24.999	MM	0.9998	9183.55762	153.08281	38.8940

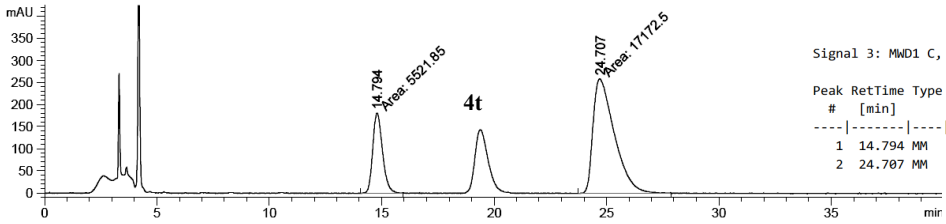
5t from 2.5 mol% **P42**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.652	MM	0.4773	4104.22949	143.32089	20.9524
2	24.742	MF	1.0652	1.54842e4	242.26643	79.0476

5t from 2.5 mol% **(*R*)-TRIP**



Signal 3: MWD1 C, Sig=230,4 Ref=360,100

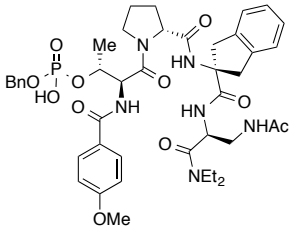
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.794	MM	0.5052	5521.84521	182.16176	24.3314
2	24.707	MM	1.1038	1.71725e4	259.28296	75.6686

7. Structural Studies

7.1 2D ROESY NMR P41 and P42

Spectra were acquired on 500MHz and 800 MHz Agilent spectrometers equipped with an HCN cold probe at ambient temperature. Although the effective catalyst concentrations of the reaction are between 0.25–1.25 mM, NMR samples were prepared at 5.0 mM in $CDCl_3$ in order to obtain reliable ROE correlations, without reaching a concentration where peptide aggregation would become problematic. $CDCl_3$ used for 2D experiments was passed through basic alumina prior to sample preparation. Automatic phasing was performed for ^{1}H, ^{13}C, COSY and HSQC NMR experiments, using manual adjustments as necessary. Manual phasing was performed manually for ROESY. Automatic baseline-correction was also performed using a polynomial fit. Apodization was adjusted to a sine square value of 90.0 ° for both axes. t1 noise reduction was applied to HSQC.

2D NMR Studies of P41



P41

The pulse sequences provided by the manufacturer were used with the following parameters:

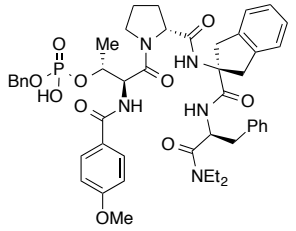
^{1}H NMR: scans = 64, pulse width = 3.75, d1 relaxation delay = 5.0 s.

^{1}H–^{1}H COSY: scans per t1 = 2, t1 increments = 512, pulse width = 8.75, d1 relaxation delay = 5.0 s.

^{1}H–^{13}C HSQC: scans per t1 = 8, t1 increments = 400, pulse width = 7.50, d1 = 4.0.

^{1}H–^{1}H ROESY: scans = 8, t1 increments = 700, pulse width = 7.50, mixing time = 300 ms, d1 = 5.0 s

2D NMR Studies of P42



P42

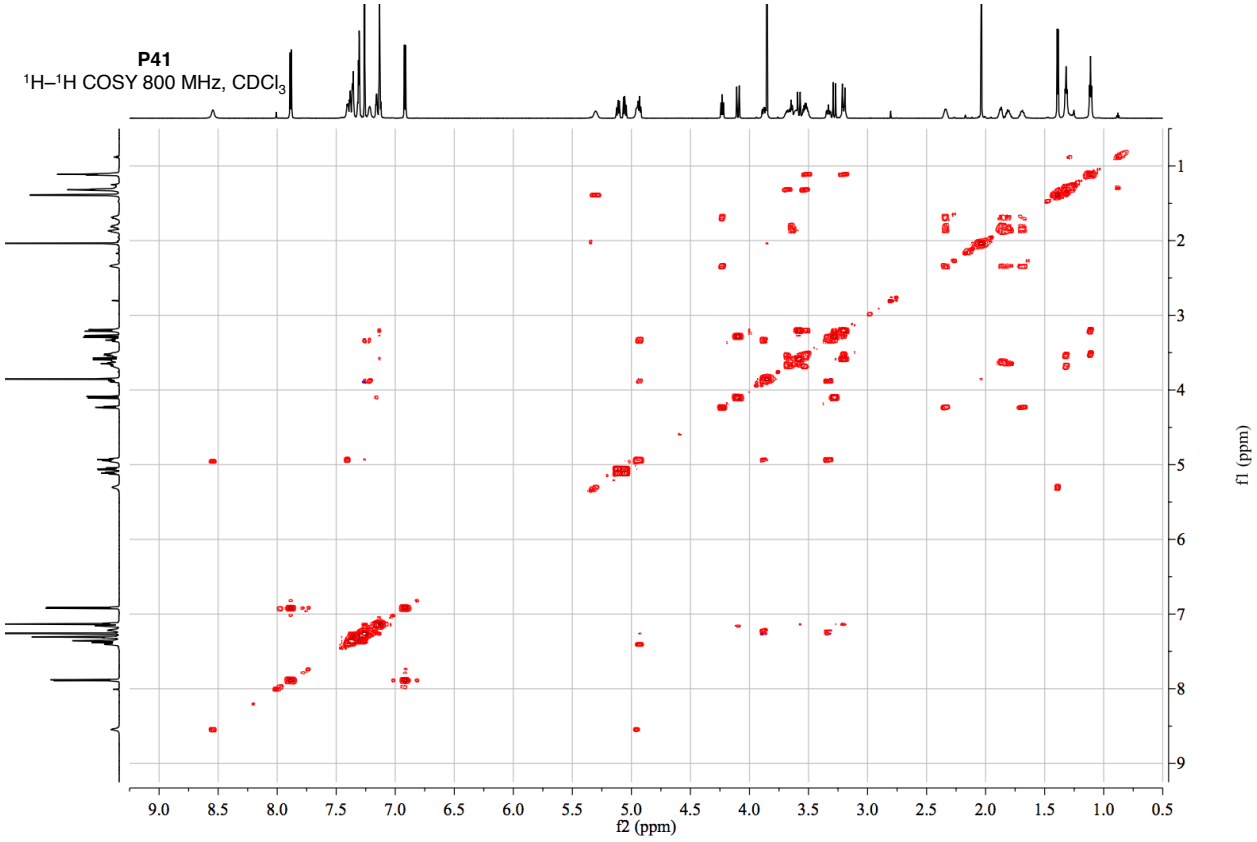
The pulse sequences provided by the manufacturer were used with the following parameters:

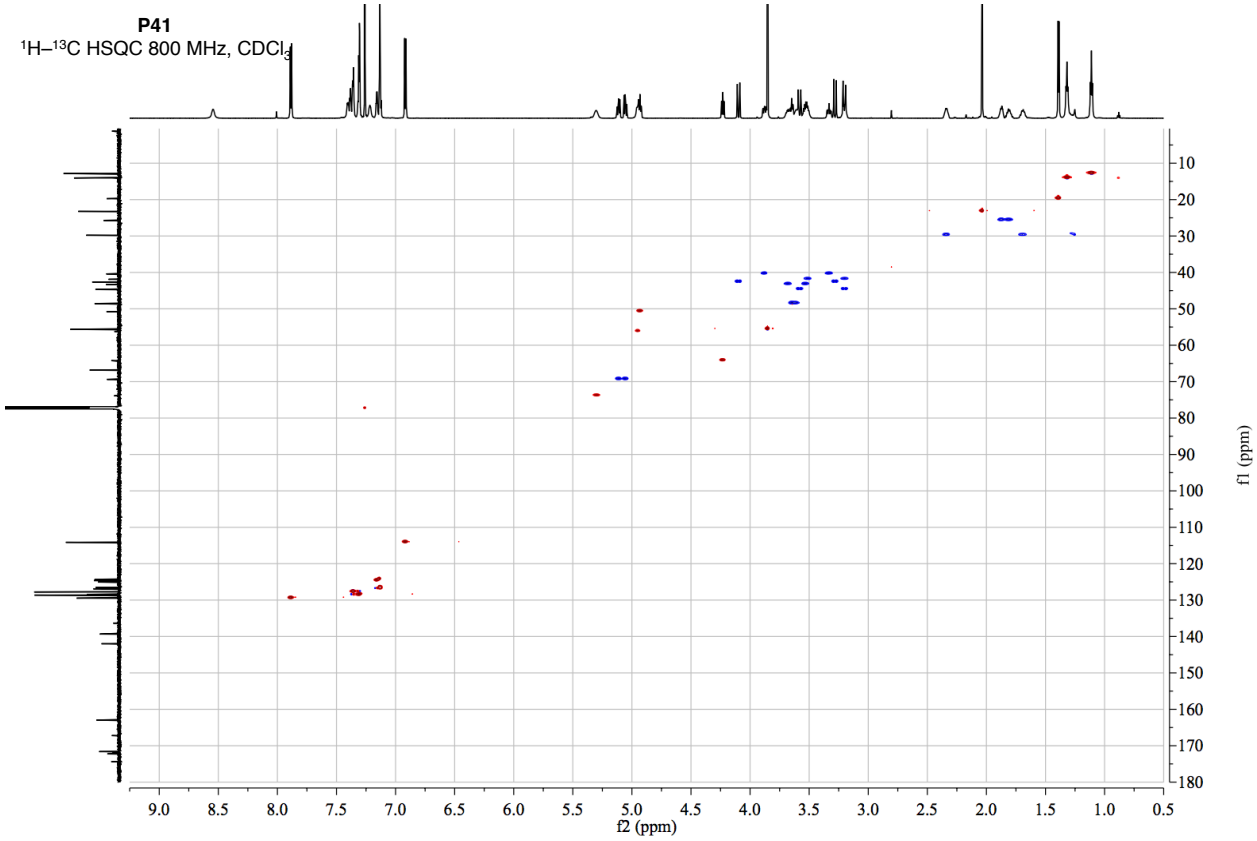
^{1}H NMR: scans = 64, pulse width = 3.75, d1 relaxation delay = 5.0 s.

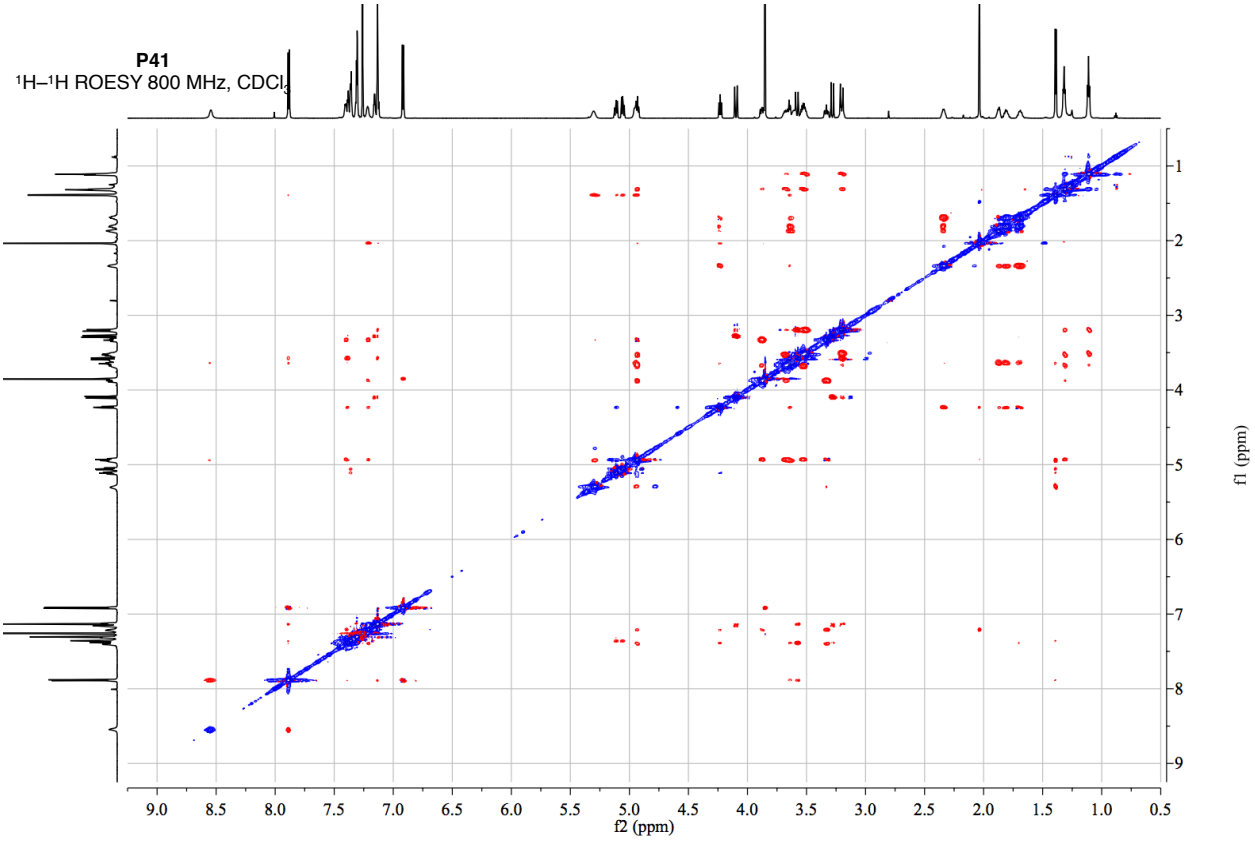
^{1}H–^{1}H COSY: scans per t1 = 2, t1 increments = 512, pulse width = 8.75, d1 relaxation delay = 5.0 s.

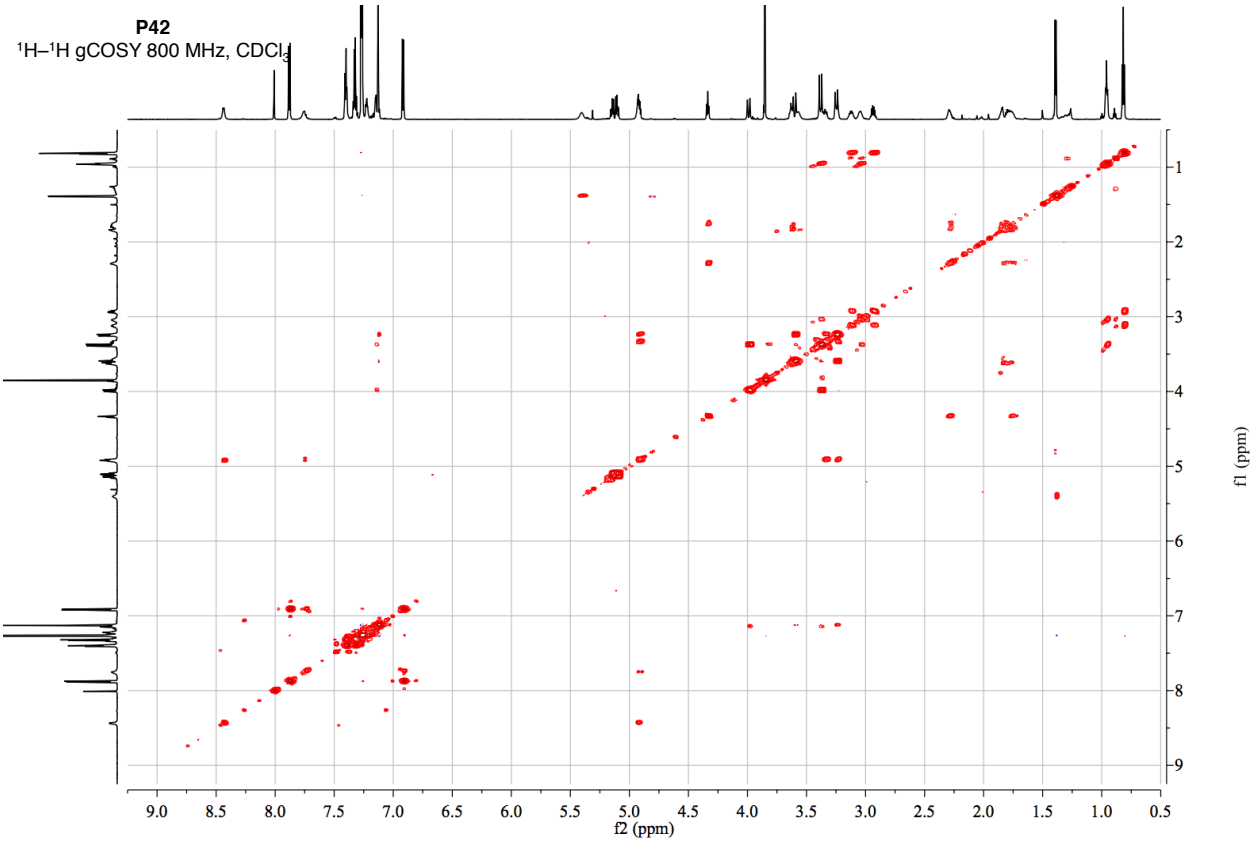
^{1}H–^{13}C HSQC (500 MHz): scans per t1 = 8, t1 increments = 650, pulse width = 7.50, d1 = 4.0.

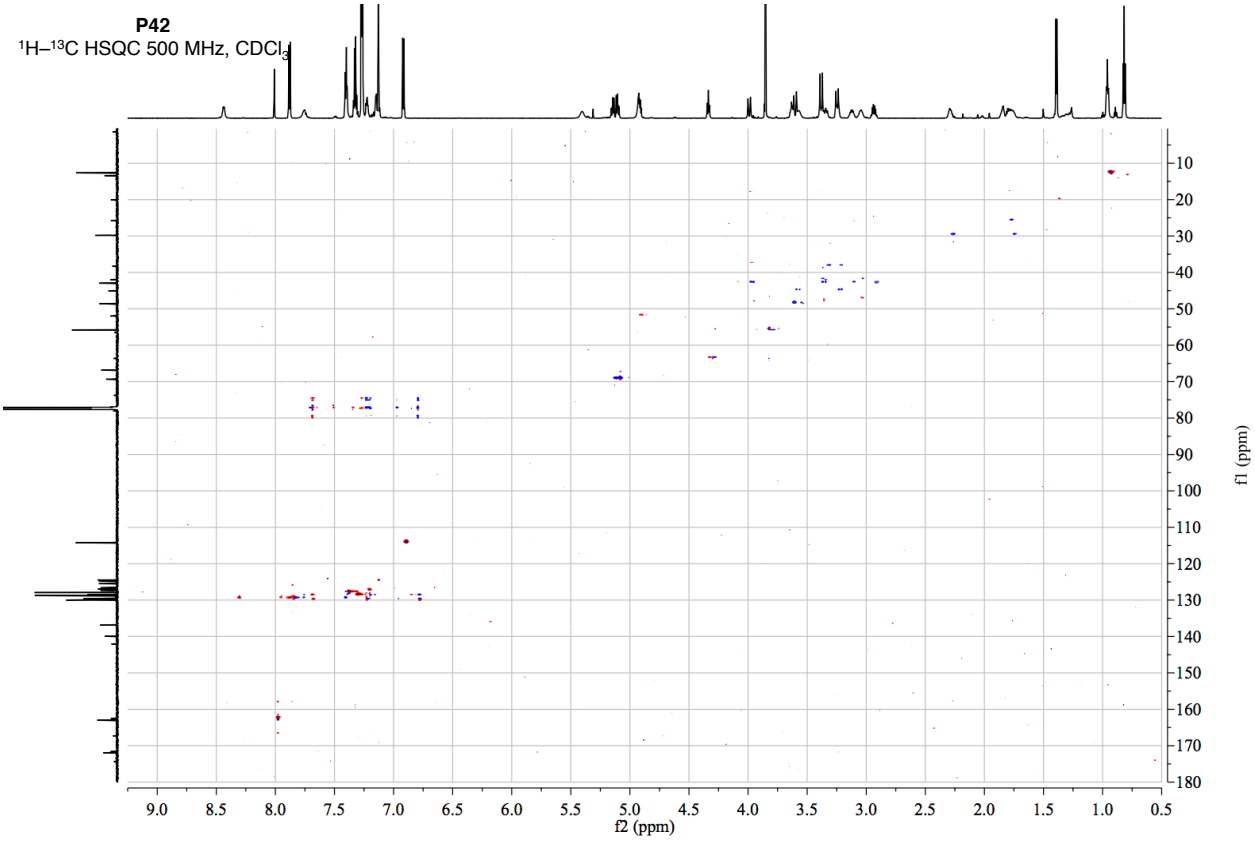
^{1}H–^{1}H ROESY: scans = 8, t1 increments = 800, pulse width = 7.50, mixing time = 300 ms, d1 = 5.0 s

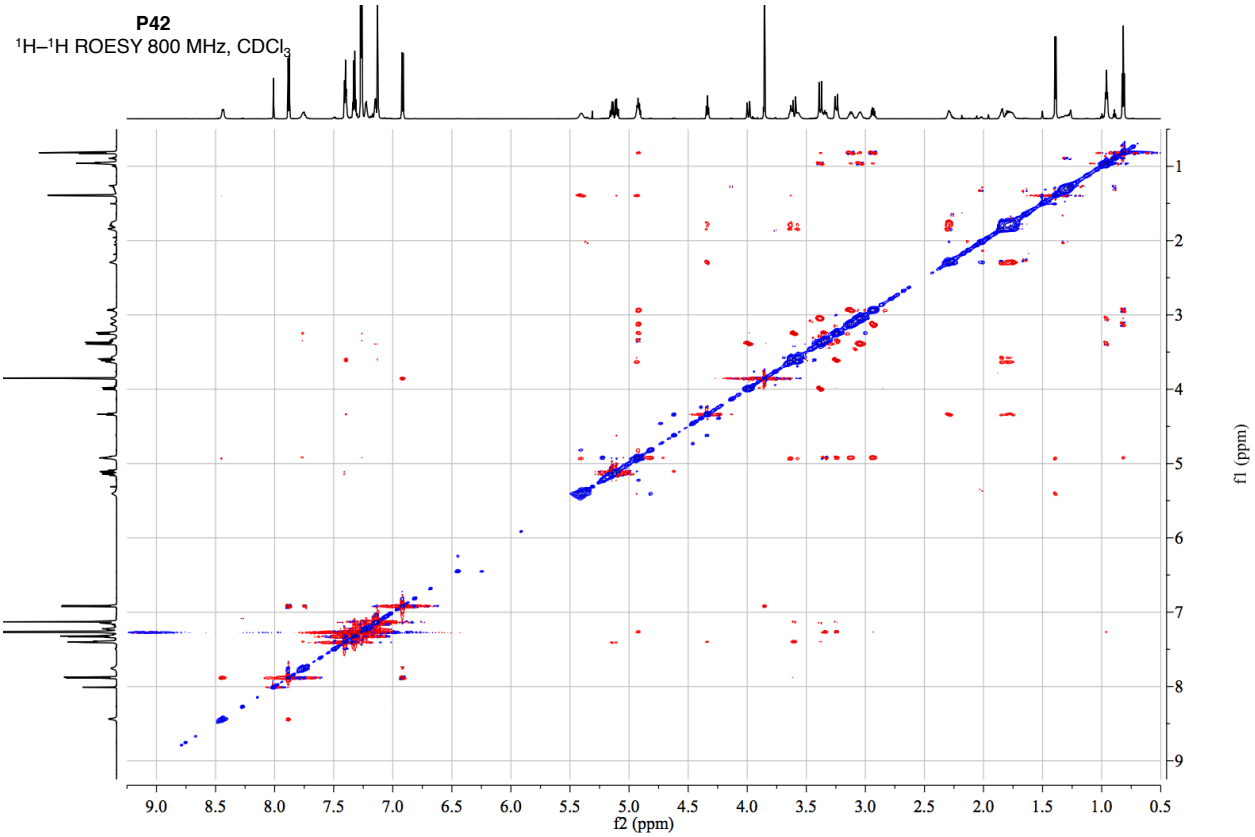

P41
^{1}H–^{1}H COSY 800 MHz, CDCl$_3$
f2 (ppm)
f1 (ppm)


P41
^{1}H–^{13}C HSQC 800 MHz, CDCl$_3$
f2 (ppm)
f1 (ppm)

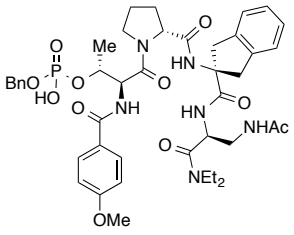

P41
¹H–¹H ROESY 800 MHz, CDCl₃
f2 (ppm)
f1 (ppm)


P42
^{1}H–^{1}H gCOSY 800 MHz, CDCl$_3$
f2 (ppm)
f1 (ppm)


P42
^{1}H–^{13}C HSQC 500 MHz, CDCl$_3$
f2 (ppm)
f1 (ppm)


P42
^{1}H–^{1}H ROESY 800 MHz, CDCl$_3$
f2 (ppm)
f1 (ppm)

7.2 DMSO Titration Studies



P41

Two stock solutions of **P41** (5.0 mM) in $CDCl_3$ and DMSO-d_6 were prepared. The DMSO-d_6 solution was slowly titrated into the $CDCl_3$ solution to yield the reported solvent mixtures. The ^{1}H NMR spectra were referenced to the residual $CHCl_3$ solvent peak (δ 7.26 ppm), and the shifts of each NH were corroborated using ^{1}H–^{1}H COSY.

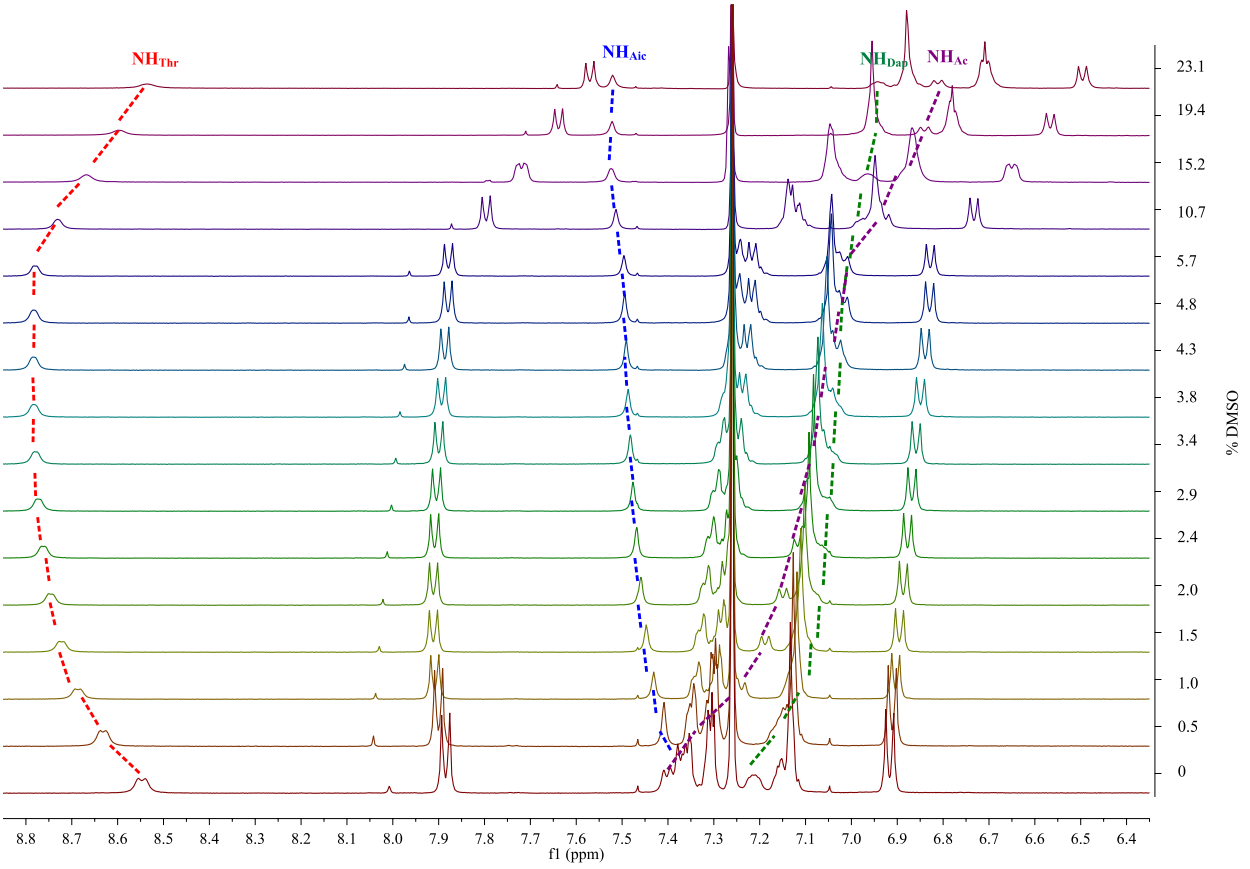
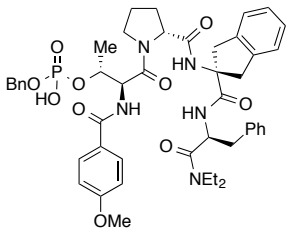


Figure S1. ^{1}H NMR spectra upon titration of DMSO-d_6 for peptide **P41** (5.0 mM concentration in $CDCl_3$ (referenced to 7.26 ppm) at 25 °C).



P42

Two stock solutions of **P42** (5.0 mM) in $CDCl_3$ and DMSO-d_6 were prepared. The DMSO-d_6 solution was slowly titrated into the $CDCl_3$ solution to yield the reported solvent mixtures. The ^{1}H NMR spectra were referenced to the residual $CHCl_3$ solvent peak (δ 7.26 ppm), and the shifts of each NH were corroborated using ^{1}H–^{1}H COSY.

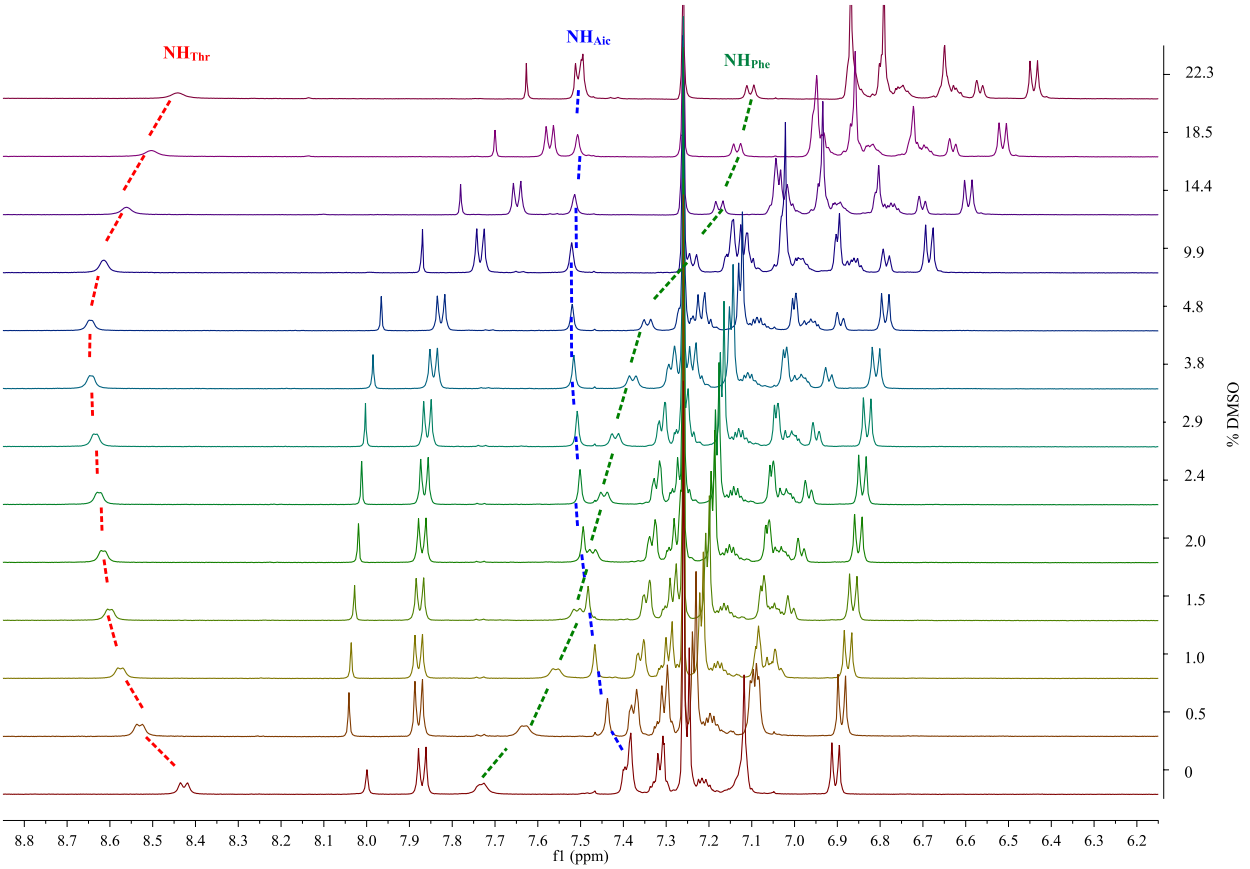


Figure S2. ^{1}H NMR spectra upon titration of DMSO-d_6 for peptide **P42** (5.0 mM concentration in $CDCl_3$ (referenced to 7.26 ppm) at 25 °C).

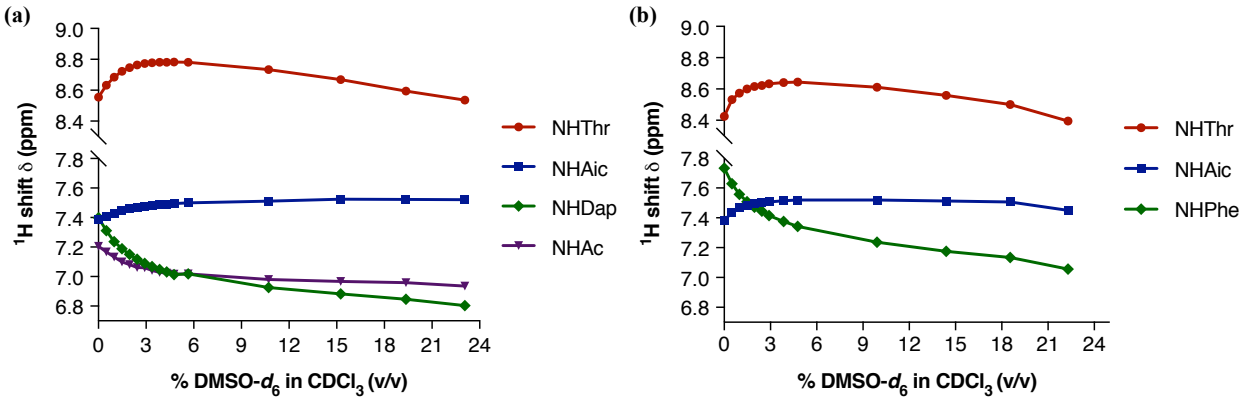


Figure S3. ^{1}H NMR solvent titration curve to identify solvent exposed and hydrogen-bonded amides for peptides (a) **P41** and (b) **P42** (5.0 mM concentration in $CDCl_3$ (referenced to 7.26 ppm) at 25 °C).

8. X-Ray Crystallographic Data

X-Ray Experimental

Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994 CCD detector with Cu Kα (λ = 1.54178 Å) for the structures of **5c**, **5e**, **5f**, **5s**, **P4** and **6**. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software.[21] For structure **4d**, low-temperature diffraction data (ω-scans) were collected at the Advanced Light Source, Lawrence Berkeley National Laboratory on a Bruker D8 goniometer coupled to a PHOTON 200 detector with synchrotron radiation (λ = 0.7749 Å). The data was integrated with the APEX3 software package and absorption corrected with SADABS.[22] All structures were solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL.[23] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). CCDC numbers 1865894 (**4d**), 1867752 (**5c**), 1865895 (**5e**), 1865896 (**5f**), 1865897 (**5s**), 1865899 (**P4**), and 1865898 (**6**), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Details for 4d

Table S4. Crystal data and structure refinement for **4d**.

Identification code	als-17022	
Empirical formula	$C_{18}H_{17}NO_4$	
Formula weight	311.32	
Temperature	93(2) K	
Wavelength	0.7749 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 9.8060(8) Å	α= 89.141(2)°.
	b = 14.9855(12) Å	β= 86.664(2)°.
	c = 21.2136(18) Å	γ = 88.303(2)°.
Volume	3110.4(4) $Å^3$	
Z	8	
Density (calculated)	1.330 Mg/m^3	
Absorption coefficient	0.115 mm^{-1}	
F(000)	1312	
Crystal size	0.080 x 0.020 x 0.020 mm^3	
Crystal color and habit	Colorless Block	
θ range for data collection	1.048 to 27.467°.	
Index ranges	-11<=h<=11, -17<=k<=17, -25<=l<=25	
Reflections collected	28310	
Independent reflections	10983 [R(int) = 0.0534]	
Observed reflections (I > 2σ(I))	7806	
Completeness to θ = 25.027°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7472 and 0.6802	
Data / restraints / parameters	10983 / 0 / 849	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2σ(I)]	$R1$ = 0.0568, w$R2$ = 0.1279	
R indices (all data)	$R1$ = 0.0840, w$R2$ = 0.1411	
Largest diff. peak and hole	0.453 and -0.412 $e.Å^{-3}$	

Refinement details for 4d

All hydrogen atoms were refined as riding atoms; the only exceptions are the hydrogens associated with nitrogen. Those positions were found in the difference map and freely refined. Also, two reflections were recorded improperly and omitted from the least square refinement.

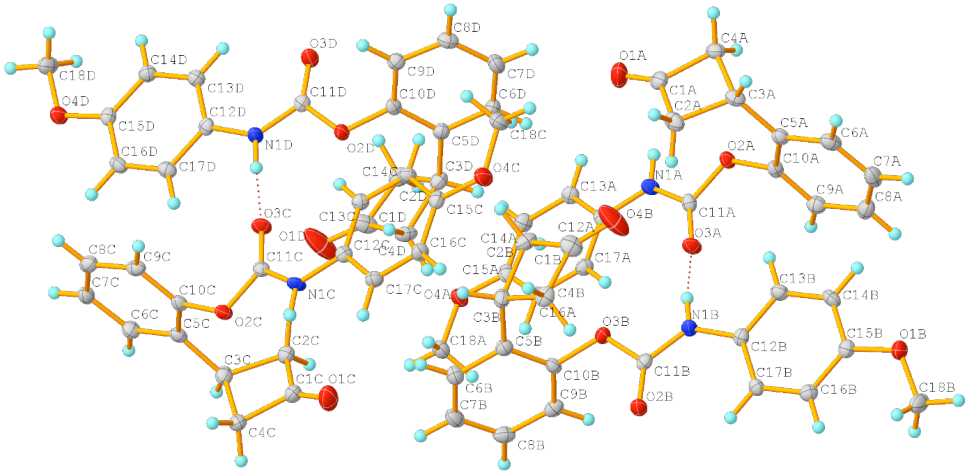


Figure S4. The complete numbering scheme of **4d** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity. Dashed lines highlight hydrogen bonds.

Table S5. Hydrogen bonds for **4d** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1C)-H(1C)...O(3D)#1	0.85(3)	2.17(3)	3.015(3)	170(3)
N(1A)-H(1A)...O(2B)#2	0.87(3)	2.21(3)	3.068(3)	166(3)
N(1B)-H(1B)...O(3A)	0.89(3)	2.14(3)	3.007(3)	162(3)
N(1D)-H(1D)...O(3C)	0.92(3)	2.13(3)	3.026(3)	163(3)

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z #2 x-1,y,z

Crystallographic Details for 5c

Table S6. Crystal data and structure refinement for **5c**.

Identification code	007b-18092	
Empirical formula	$C_{17}H_{15}NO_4$	
Formula weight	297.30	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 13.5517(3) Å	α= 90°.
	b = 9.24610(10) Å	β= 106.796(2)°.
	c = 11.8061(3) Å	γ = 90°.
Volume	1416.20(5) $Å^3$	
Z	4	
Density (calculated)	1.394 Mg/m^3	
Absorption coefficient	0.827 mm^{-1}	
F(000)	624	
Crystal size	0.100 x 0.080 x 0.040 mm^3	
Crystal color and habit	Colorless Plate	
θ range for data collection	3.407 to 66.596°.	
Index ranges	-16<=h<=16, -11<=k<=11, -14<=l<=14	
Reflections collected	48415	
Independent reflections	4979 [R(int) = 0.0583]	
Observed reflections (I > 2σ(I))	4731	
Completeness to θ = 66.596°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.52267	
Data / restraints / parameters	4979 / 1 / 398	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2σ(I)]	R1 = 0.0458, wR2 = 0.1229	
R indices (all data)	R1 = 0.0478, wR2 = 0.1249	
Absolute structure parameter	-0.27(14)	
Extinction coefficient	0.0064(8)	
Largest diff. peak and hole	0.579 and -0.302 e.$Å^{-3}$	

Bayesian statistical analysis of *R*/*S* 5c

The program PLATON[24] was used to calculate statistics on the Bijvoet pairs in the reflection data and the X-ray structure of **5c**. Based on these statistics, it is highly unlikely that a model of **(*S*)-5c** would fit the data collected:

***X-ray structure of (R)*-5c**

Bayesian Statistics	
Student_T υ	13
Select Pairs	2318
θ_Min	5.88
θ_Max	66.59
P2(true)	1.000
P3(true)	1.000
P3(rac-twin)	0.1E-07
P3(false)	0.2E-22
G	1.5904
G (su)	0.2425
Hooft y	-0.30(12)

***X-ray structure of (S)*-5c**

Bayesian Statistics	
Student_T ν	13
Select Pairs	2318
θ_Min	5.88
θ_Max	66.59
P2(true)	0.3E-22
P3(true)	0.3E-22
P3(rac-twin)	0.1E-07
P3(false)	1.000
G	-1.5788
G (su)	0.2424
Hooft y	1.29(12)

Refinement details for 5c

All non-hydrogen atoms were refined anisotropically; the only exceptions are the protons associated with N1 and N2. These sites were found in the difference map and freely refined. The Flack parameter was not determined with a high confidence level. However, it is unlikely that the enantiomer would fit the reflection data appended here. Refinement of the inverse model generates a Flack parameter near unity [1.293(312)]. An inversion twin generates a BASF of 0.3(3).

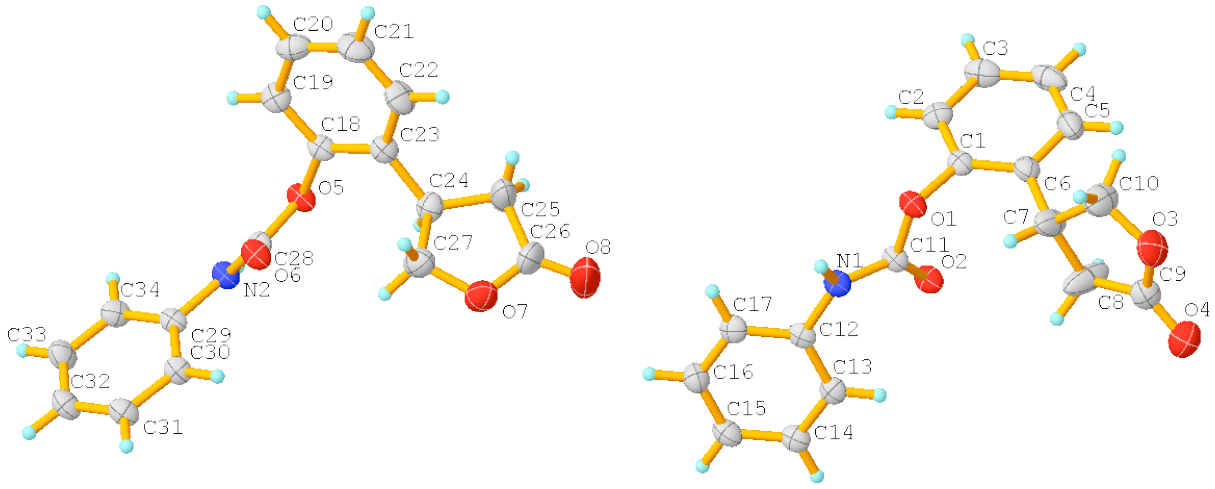


Figure S5. The complete numbering scheme of **5c** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Table S7. Hydrogen bonds for **5c** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(2)#1	0.88	2.02	2.848(4)	155.7
N(2)-H(2A)...O(6)#2	0.88	1.96	2.796(4)	158.1

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y+1/2,-z+1 #2 -x,y-1/2,-z

Crystallographic Details for 5e

Table S8. Crystal data and structure refinement for **5e**.

Identification code	007a-17134	
Empirical formula	$C_{18}H_{14}F_3NO_4$	
Formula weight	365.30	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 11.84980(10) Å	α= 90°.
	b = 9.59060(10) Å	β= 96.0080(10)°.
	c = 14.7080(2) Å	γ = 90°.
Volume	1662.33(3) $Å^3$	
Z	4	
Density (calculated)	1.460 Mg/m^3	
Absorption coefficient	1.085 mm^{-1}	
F(000)	752	
Crystal size	0.200 x 0.200 x 0.030 mm^3	
Crystal color and habit	Colorless Plate	
θ range for data collection	3.021 to 68.316°.	
Index ranges	-14<=h<=14, -11<=k<=11, -17<=l<=17	
Reflections collected	62938	
Independent reflections	6014 [R(int) = 0.0390]	
Observed reflections (I > 2σI))	5597	
Completeness to θ = 67.684°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.89474	
Data / restraints / parameters	6014 / 107 / 523	
Goodness-of-fit on F^2	1.064	
Final R indices [I>2σ(I)]	R1 = 0.0408, wR2 = 0.1144	
R indices (all data)	R1 = 0.0441, wR2 = 0.1176	
Absolute structure parameter	-0.07(4)	
Largest diff. peak and hole	0.365 and -0.201 e.$Å^{-3}$	

Refinement details for 5e

All hydrogen atoms were refined as riding atoms; the only exceptions are H1 and H2, which were found in the difference map and semi-freely refined with distance restraints of 0.88(2) Å. One of the two lactones is disordered over two positions. The thermal parameters were restrained to be similar with similar directions. This is reasonable considering the two models are chemically identical. The site occupies were freely refined and converged at values of 0.55(1)/0.45(1).

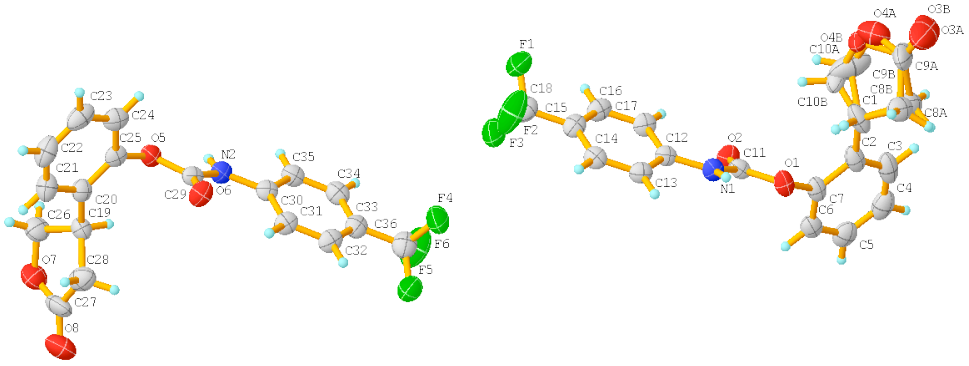


Figure S6. The complete numbering scheme of **5e** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Table S9. Hydrogen bonds for **5e** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2)...O(6)#1	0.89(2)	2.08(3)	2.933(4)	161(3)
N(1)-H(1)...O(2)#2	0.85(3)	2.06(3)	2.895(4)	169(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x,y+1/2,-z+1 #2 -x+2,y-1/2,-z

Crystallographic Details for 5f

Table S10. Crystal data and structure refinement for **5f**.

Identification code	007b-18036	
Empirical formula	$C_{17}H_{14}BrNO_4$	
Formula weight	376.20	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	*I*2	
Unit cell dimensions	*a* = 22.7393(8) Å	α= 90°.
	b = 5.21210(10) Å	β= 93.045(3)°.
	c = 14.2943(4) Å	γ = 90°.
Volume	1691.76(8) $Å^3$	
Z	4	
Density (calculated)	1.477 Mg/m^3	
Absorption coefficient	3.482 mm^{-1}	
F(000)	760	
Crystal size	0.080 x 0.080 x 0.020 mm^3	
Crystal color and habit	Colorless Plate	
θ range for data collection	3.569 to 66.592°.	
Index ranges	-27<=h<=27, -6<=k<=6, -17<=l<=16	
Reflections collected	28915	
Independent reflections	2985 [*R*(int) = 0.0765]	
Observed reflections (I > 2σ(I))	2858	
Completeness to θ = 66.592°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.65505	
Data / restraints / parameters	2985 / 1 / 208	
Goodness-of-fit on F^2	1.040	
Final *R* indices [I>2σ(I)]	*R*1 = 0.0375, w*R*2 = 0.0952	
R indices (all data)	*R*1 = 0.0393, w*R*2 = 0.0969	
Absolute structure parameter	-0.125(16)	
Largest diff. peak and hole	0.939 and -0.944 e.$Å^{-3}$	

Refinement details for 5f

All hydrogen atoms were refined as riding atoms; the proton on N1 was observed in the difference map, but due to its chemically unreadable N-H distance, the hydrogen atom was refined as a riding atom. The program SQUEEZE[24] was used to compensate for the contribution of disordered solvents contained in voids within the crystal lattice from the diffraction intensities. This procedure was applied to the data file and the submitted model is based on the solvent removed data. Based on the total electron density found in the voids (45 e-/Å^3), it is likely that ~1 pentane molecules is present in the unit cell. See "_platon_squeeze_details" in the .cif for more information.

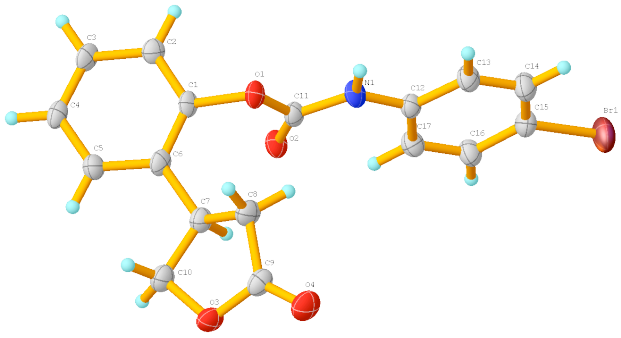


Figure S7. The complete numbering scheme of **5f** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Table S11. Hydrogen bonds for **5f** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(4)#1	0.88	2.11	2.984(6)	173.7

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1,-z+1

Crystallographic Details for 5s

Table S12. Crystal data and structure refinement for **5s**.

Identification code	007b-18082	
Empirical formula	$C_{17}H_{15}NO_4$	
Formula weight	297.30	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.8042(2) Å	α= 90°.
	b = 8.49630(10) Å	β= 103.232(2)°.
	c = 15.8250(3) Å	γ = 90°.
Volume	1414.10(4) $Å^3$	
Z	4	
Density (calculated)	1.396 Mg/m^3	
Absorption coefficient	0.828 mm^{-1}	
F(000)	624	
Crystal size	0.200 x 0.200 x 0.020 mm^3	
Crystal color and habit	Colorless Plate	
θ range for data collection	2.869 to 66.583°.	
Index ranges	-12<=h<=12, -10<=k<=10, -18<=l<=18	
Reflections collected	49823	
Independent reflections	4994 [R(int) = 0.0438]	
Observed reflections (I > 2σ(I))	4909	
Completeness to θ = 66.583°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.49356	
Data / restraints / parameters	4994 / 61 / 452	
Goodness-of-fit on F^2	1.107	
Final R indices [I>2σ(I)]	R1 = 0.0294, wR2 = 0.0723	
R indices (all data)	R1 = 0.0301, wR2 = 0.0728	
Absolute structure parameter	0.09(7)	
Extinction coefficient	0.0088(5)	
Largest diff. peak and hole	0.184 and -0.190 e.$Å^{-3}$	

Bayesian statistical analysis of *R*/*S* 5s

The program PLATON[24] was used to calculate statistics on the Bijvoet pairs in the reflection data and the X-ray structure of **5s**. Based on these statistics, it is highly unlikely that a model of **(*R*)-5s** would fit the data collected:

X-ray structure of (*S)-5s

Bayesian Statistics	
Student_T ν	26
Select Pairs	2313
θ_Min ..	5.95
θ_Max ..	66.58
P2(true)....	1.000
P3(true)....	1.000
P3(rac-twin)	0.9E-10
P3(false) ..	0.1E-50
G	0.8159
G (su)	0.1165
Hooft y	0.09(6)

X-ray structure of (R)-5s

Bayesian Statistics	
Student_T ν	26
Select Pairs	2313
θ_Min ..	5.95
θ_Max ..	66.58
P2(true)....	0.4E-50
P3(true)....	0.4E-50
P3(rac-twin)	0.2E-09
P3(false) ..	1.000
G	-0.8082
G (su)	0.1166
Hooft y	0.90(6)

Refinement details for 5s

All hydrogen atoms were refined as riding atoms; the only exceptions are the protons associated with N1 and N2. These sites were found in the difference map and freely refined. One lactone and one aryl group were modeled as disordered. The site occupancies were freely refined to converged values of 0.832(4) and 0.168(4). These two chemically and crystallographically distinct groups disordered in complementary sets. The equivalent C-C, C-O, and C-N distances were restrained to be similar. Many of the thermal parameters in the minor component were constrained to the same values as their chemically equivalent counterpart. The minor aryl group was constrained to have an ideal geometry. All disordered hydrogen atoms were generated in ideal positions. The Flack parameter was not determined with a high confidence level. However, it is unlikely that the enantiomer would fit the reflection data appended here. Refinement of the inverse model generates a Flack parameter near unity [0.90(7)]. An inversion twin generates a BASF of 0.1(2).

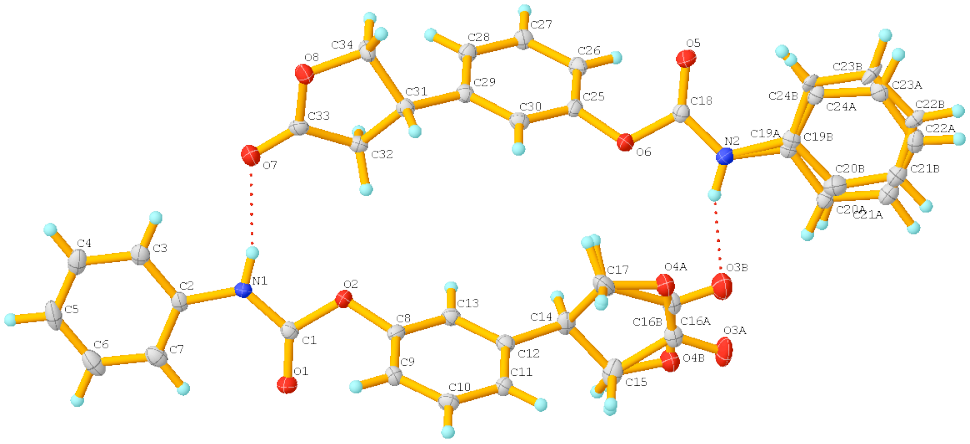


Figure S8. The complete numbering scheme of **5s** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity. Dashed lines highlight hydrogen bond interactions.

Table S13. Hydrogen bonds for **5s** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(7)	0.83(3)	2.12(3)	2.925(3)	164(3)
N(2)-H(2)...O(3B)	0.86(3)	2.01(4)	2.835(12)	159(3)
N(2)-H(2)...O(4A)	0.86(3)	2.28(3)	3.104(3)	159(3)

Crystallographic Details for P4

Table S14. Crystal data and structure refinement for **P4**.

Identification code	007-16171	
Empirical formula	$C_{60}H_{79}N_6O_{15}P$	
Formula weight	1155.26	
Temperature	93(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.8665(7) Å	α= 90°.
	b = 19.0145(13) Å	β= 90°.
	c = 31.360(2) Å	γ = 90°.
Volume	5883.4(7) $Å^3$	
Z	4	
Density (calculated)	1.304 Mg/m^3	
Absorption coefficient	1.015 mm^{-1}	
F(000)	2464	
Crystal size	0.200 x 0.040 x 0.020 mm^3	
Crystal color and habit	Colorless Needle	
θ range for data collection	2.718 to 67.942°.	
Index ranges	-11<=h<=11, -22<=k<=22, -37<=l<=37	
Reflections collected	201514	
Independent reflections	10660 [R(int) = 0.0828]	
Completeness to θ = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.887	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10660 / 41 / 764	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2σ(I)]	$R1$ = 0.0476, w$R2$ = 0.1271	
R indices (all data)	$R1$ = 0.0565, w$R2$ = 0.1348	
Absolute structure parameter	0.028(7)	
Largest diff. peak and hole	0.584 and -0.545 e.$Å^{-3}$	

Refinement details for P4

All hydrogen atoms were refined as riding atoms; the only exceptions are H2, H3, H4, H6, and H10 which were found in the difference map and semi-freely refined with the aid of N-H distance restraints of 0.93(2) angstroms. Two reflections were also improperly recorded due to instrument artifacts; these reflections have been omitted from the refinement.

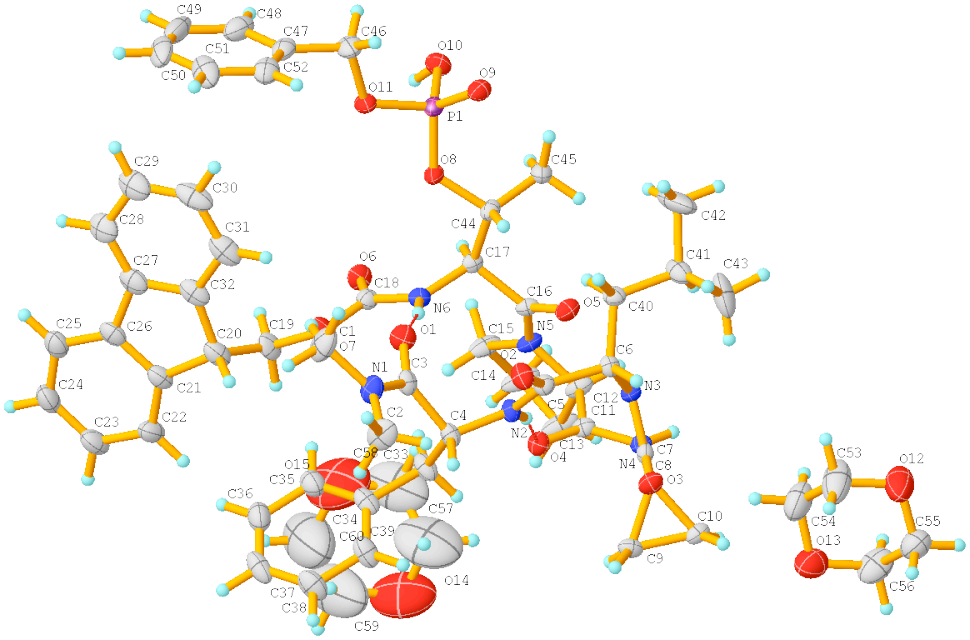


Figure S9. The complete numbering scheme of **P4** with 50% thermal ellipsoid probability levels. The hydrogen atoms have been omitted for clarity.

Table S15. Hydrogen bonds for **P4** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2)...O(4)	0.92(3)	2.07(3)	2.967(4)	166(4)
N(3)-H(3)...O(5)	0.90(3)	2.19(3)	2.998(4)	149(4)
N(3)-H(3)...N(4)	0.90(3)	2.31(4)	2.762(4)	111(3)
N(4)-H(4)...O(9)#1	0.91(3)	1.94(3)	2.846(4)	170(5)
N(6)-H(6)...O(1)	0.89(3)	2.04(3)	2.921(4)	169(4)
O(10)-H(10)...O(2)#2	0.92(3)	1.58(3)	2.488(4)	168(7)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y+1/2,-z+3/2 #2 x-1,y,z

Crystallographic Details for 7

Table S16. Crystal data and structure refinement for **7**.

Identification code	007-16207	
Empirical formula	$C_{36}H_{57}N_7O_7$	
Formula weight	699.88	
Temperature	93(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	*C*2	
Unit cell dimensions	*a* = 26.466(2) Å	α= 90°.
	b = 17.7566(12) Å	β= 124.7890(10)°.
	c = 22.8328(16) Å	γ = 90°.
Volume	8812.2(12) Å^3	
Z	8	
Density (calculated)	1.055 Mg/m^3	
Absorption coefficient	0.600 mm^{-1}	
F(000)	3024	
Crystal size	0.200 x 0.050 x 0.020 mm^3	
Crystal color and habit	Colorless Needle	
θ range for data collection	2.356 to 68.034°.	
Index ranges	-31<=h<=31, -21<=k<=21, -27<=l<=27	
Reflections collected	157433	
Independent reflections	15860 [*R*(int) = 0.0509]	
Completeness to θ = 67.679°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.882	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	15860 / 57 / 988	
Goodness-of-fit on F^2	1.038	
Final *R* indices [I>2σ(I)]	*R*1 = 0.0435, w*R*2 = 0.1200	
R indices (all data)	*R*1 = 0.0492, w*R*2 = 0.1245	
Absolute structure parameter	0.11(4)	
Largest diff. peak and hole	1.437 and -0.387 e.Å^{-3}	

Refinement details for 7

All hydrogen atoms were refined as riding atoms; there are several semi-freely refined hydrogen atoms in this model. The N-H distances were restrained with a target value of 0.95(2), which was similar to N-H distance suggested by the difference map. Atoms C25, C49, C70, and N12 were all modeled as disordered. The C-C and C-N distances were restrained to be similar between the disordered models where appropriate. Additionally, the thermal parameters were restrained to be similar either based on their tensor values or vectors. The site occupancies for the disordered positions were allowed to freely refine to converged values, except for C49; due to the close proximity of the two disordered positions, the occupancies were fixed at 0.70 and 0.30. All disordered positions only consisted of two components and are distinguished by the suffixes "A" and "B". The program SQUEEZE[24] was used to compensate for the contribution of disordered solvents contained in voids within the crystal lattice from the diffraction intensities. This procedure was applied to the data file and the submitted model is based on the solvent removed data. Based on the total electron density found in the voids (295.2 e/Å^3), it is likely that some combination of ethyl acetate, pentane, acetonitrile, water, and/or dichloromethane molecules are present in the unit cell. See "_platon_squeeze_details" in the .cif for more information.

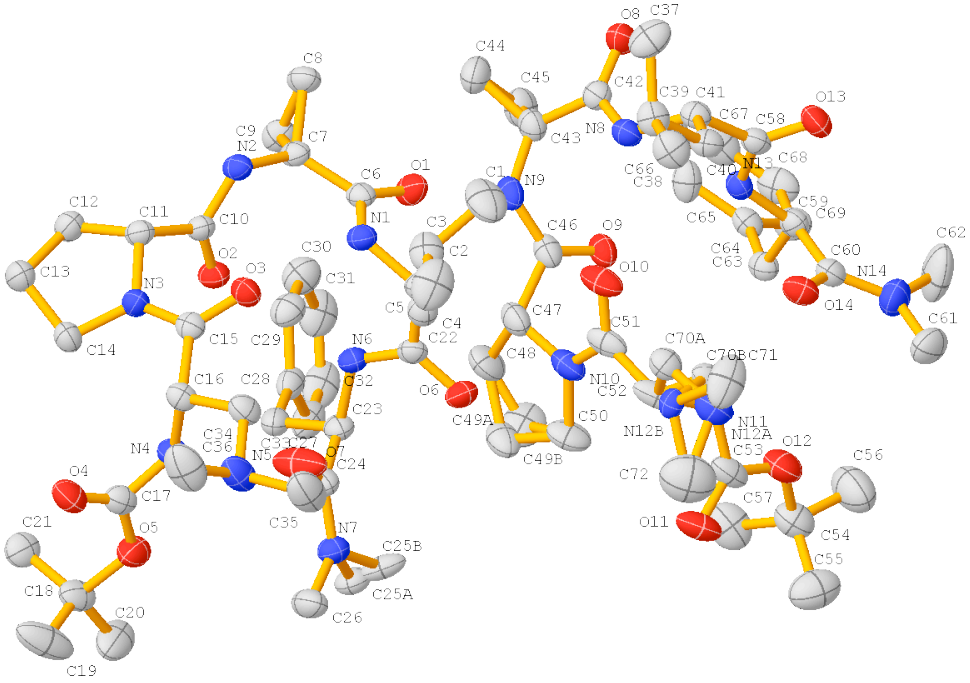


Figure S10. The complete numbering scheme of **7** with 50% thermal ellipsoid probability levels. The hydrogen atoms have been removed for clarity.

Table S17. Hydrogen bonds for **7** [Å and °].

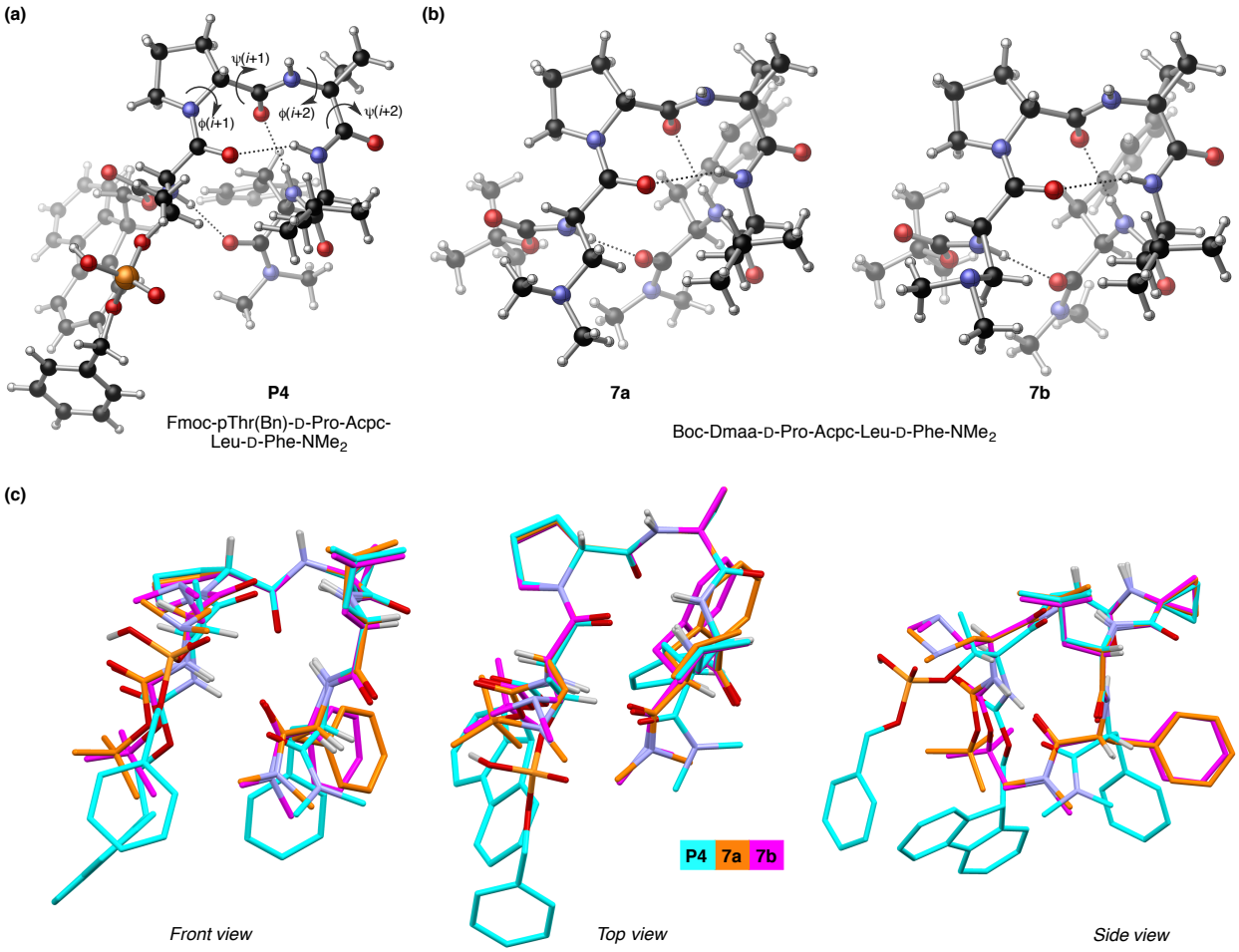
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(4)-H(4)...O(7)	0.94(2)	1.85(2)	2.782(4)	168(3)
N(1)-H(1)...O(3)	0.91(3)	2.27(3)	3.076(3)	147(4)
N(13)-H(13)...O(9)	0.90(3)	2.10(3)	2.961(3)	160(4)
N(6)-H(6)...O(2)	0.92(2)	2.22(3)	3.105(3)	161(3)
N(9)-H(9)...O(1)	0.91(2)	1.86(3)	2.764(3)	175(4)
N(8)-H(8)...O(10)	0.92(2)	2.21(3)	3.060(3)	153(3)
N(11)-H(11)...O(14)	0.91(2)	1.91(3)	2.809(3)	171(4)
N(2)-H(2)...O(8)#1	0.94(2)	1.92(3)	2.821(3)	159(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x-1/2,y-1/2,-z

9. Structural analysis of X-ray crystals P4 and 7

Mercury 3.8[25] was used to calculate structure overlays. To illustrate structure similarities of **P4** and **7** in the solid-state, two types of structure overlays are reported. The loop overlay specifies the N(*i*+1)–Cα(*i*+1)–C'(*i*+1)–N(*i*+2)–Cα(*i*+2)–C'(*i*+2) region and the backbone overlay specifies all backbone and main-chain atoms (excluding those on the *N*-terminal protecting group and *N*,*N*'-dimethyl amide), as the atoms overlaid.[26] Two packing polymorphs of **7** were present in the unit cell with an all-atom overlay RMSD value of 0.43 Å and a loop and backbone RMSD value of 0.02 and 0.08 Å respectively.



Peptide	Loop Dihedrals ϕ(*i*+1)	ψ(*i*+1)	ϕ(*i*+2)	ψ(*i*+2)	Hydrogen Bond Lengths (Å) N(*i*+3)···O(*i*)	N(*i*)···O(*i*+4)	N(*i*+4)···O(*i*+2)	RMSD vs P4 (Å) Loop Region	Backbone
P4	52.3(5)°	–145.0(3)°	–73.7(4)°	–1.4(5)°	2.998(4)	2.921(4)	2.967(4)	n/a	n/a
7a	59.1(4)	–137.3(3)	–72.0(4)	–4.6(4)	3.076(3)	2.782(4)	3.105(4)	0.05	0.21
7b	57.2(4)	–136.7(3)	–68.8(4)	–3.5(4)	3.060(3)	2.809(3)	2.961(3)	0.06	0.21

Figure S11. Structrual analysis of **P4** and **7** in the solid-state.[27] (a) X-ray structure of **P4**. Two 1,4-dioxane solvent molecules omitted for clarity. (b) X-ray structure of **7**. Two distinct packing polymorphs were observed in the unit cell (**7a**, **7b**). **(c)** Structure overlays of **P4**, **7a**, and **7b**.

10. Supplementary References

(1) Fulmer, G.R; Miller, A. J. M.; Sherden, N. H.;Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **2010**, *29*, 2176–2179.

(2) (a) Montalbetti, C. A. G. N.; Falque, V. Amide Bond Formation and Peptide Coupling. *Tetrahedron* **2005**, *61*, 10827–10852. (b) El-Faham, A.; Albericio, F. Peptide Coupling Reagents, More than a Letter Soup. *Chem. Rev.* **2011**, *111*, 6557–6602.

(3) Shugrue, C. R.; Miller, S. J. Phosphothreonine as a Catalytic Residue in Peptide-Mediated Asymmetric Transfer Hydrogenations of 8-Aminoquinolines. *Angew. Chem. Int. Ed.* **2015**, 54, 11173–11176

(4) Kwon, Y.; Chinn, A.; Kim, B.; Miller, S. J. Divergent Control of Point and Axial Stereogenicity: Catalytic Enantioselective C−N Bond-Forming Cross-Coupling and Catalyst-Controlled Atroposelective Cyclodehydration. *Angew. Chem. Int. Ed.* **2018**, *57*, 6251–6255.

(5) Zhang, L.-H.; Kauffman, G. S.; Pesti, J. A.; Yin, J. Rearrangement of Nα-Protected l-Asparagines with Iodosobenzene Diacetate. A Practical Route to β-Amino-l-alanine Derivatives. *J. Org. Chem.* **1997**, *62*, 6918–6920.

(6) (a) Stojković, M. R.; Piotrowski, P.; Schmuck, C.; Piantanida, I. A Short, Rigid Linker Between Pyrene and Guanidiniocarbonyl-Pyrrole Induced a New Set of Spectroscopic Responses to the ds-DNA Secondary Structure. *Org. Biomol. Chem.* **2015**, *13*, 1629–1633. (b) Bernardini, R.; Bernareggi, A.; Cassara, P. G.; D'Arasmo, G.; Menta, E.; Oliva, A. Cephalon, Inc., Frazer, PA. Proteasome Inhibitors and Methods of Using the Same. US2006/0189806 A1, **2006**, pp. 44.

(7) Curphey, T. J. Trifluoroacetylation of Amino Acids and Peptides by Ethyl Trifluoroacetate. *J. Org. Chem.* **1979**, *44,* 2805–2807.

(8) Petrillo, D. E.; Mowrey, D. R.; Allwein, S. P; Bakale, R. P. A General Preparation of Protected Phosphoamino Acids. *Org. Lett.* **2012**, *14*, 1206–1209.

(9) (a) Karunaratne, C. V.; Weldeghiorghis, T. K.; West, C. M.; Taylor, C. M. Conformational Changes Associated with Post-Translational Modifications of Pro^{143} in Skp1 of *Dictyostelium*—A Dipeptide Model System. *J. Am. Chem. Soc*. **2014**, *136*, 15170−15175. (b) Egner, B. J.; Bradley, M. Monitoring the Solid Phase Synthesis of Analogues of Lysobactin and the Katanosins using in situ MALDI-TOF MS. *Tetrahedron* **1997**, *53*, 14021–14030.

(10) Diener, M. E.; Metrano, A. J.; Kusano, S.; Miller, S. J. Enantioselective Synthesis of 3-Arylquinazolin-4(3*H*)-ones via Peptide-Catalyzed Atroposelective Bromination. *J. Am. Chem. Soc.* **2015**, *137*, 12369–12377.

(11) (a) Krepski, L. R.; and Hassner, A. An Improved Procedure for the Addition of Dichloroketene to Unreactive Olefins. *J. Org. Chem*. **1978**, 43, 2879–2882. (b) Trost, B. M.; Xie, J. Palladium-Catalyzed Diastereo- and Enantioselective Wagner−Meerwein Shift: Control of Absolute Stereochemistry in the C−C Bond Migration Event. *J. Am. Chem. Soc*. **2008**, 130, 6231–6242. (c) Zhou, L.; Liu, X.; Ji, J.; Zhang, Y.; Hu, X.; Lin, L.; Feng, X. Enantioselective Baeyer–

Villiger Oxidation: Desymmetrization of Meso Cyclic Ketones and Kinetic Resolution of Racemic 2-Arylcyclohexanones. *J. Am. Chem. Soc.* **2012**, *134*, 17023–17026.

(12) Petersen, K. S.; Stoltz, B. M. Palladium-Catalyzed, Asymmetric Baeyer–Villiger Oxidation of Prochiral Cyclobutanones with PHOX Ligands. *Tetrahedron* **2011**, *67*, 4352–4357.

(13) Malkov, A. V.; Friscourt, F.; Bell, M; Swarbrick, M. E.; Kočovský, P. Enantioselective Baeyer–Villiger Oxidation Catalyzed by Palladium(II) Complexes with Chiral P,N-Ligands. *J. Org. Chem.* **2008**, *73*, 3996–4003.

(14) Maity, S.; Zheng, N. A Visible-Light-Mediated Oxidative C–N Bond Formation/Aromatization Cascade: Photocatalytic Preparation of *N*-Arylindoles. *Angew. Chem. Int. Ed.* **2012**, *51*, 9562–9566.

(15) Zhou, X.; Dong, G. (4+1) vs (4+2): Catalytic Intramolecular Coupling between Cyclobutanones and Trisubstituted Allenes via C–C Activation. *J. Am. Chem. Soc.* **2015**, *137*, 13715–13721.

(16) Jiao, R.; Yang, L. Merck & Co., Inc., Rahway, NJ. Amino Cyclobutylamide Modulators of Chemokine Receptor Activity. U.S. PCT/US2004/007792, **2004**, pp. 78–79.

(17) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. The Selective Reaction of Aryl Halides with KOH: Synthesis of Phenols, Aromatic Ethers, and Benzofurans. *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695.

(18) Matsuda, T.; Shigeno, M.; Murakami, M. Asymmetric Synthesis of 3,4-Dihydrocoumarins by Rhodium-Catalyzed Reaction of 3-(2-Hydroxyphenyl)cyclobutanones. *J. Am. Chem. Soc.*, **2007**, *129*, 12086–12087.

(19) Bhagwanth, S.; Waterson, A. G.; Adjabeng, G. M.; Hornberger, K. R. Room-Temperature Pd-Catalyzed Amidation of Aryl Bromides Using *tert*-Butyl Carbamate. *J. Org. Chem*. **2009**, *74*, 4634–4637.

(20) (a) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. Chiral Brønsted Acid Catalyzed Asymmetric Baeyer–Villiger Reaction of 3-Substituted Cyclobutanones by Using Aqueous H_2O_2. *Angew. Chem. Int. Ed.* **2008**, *47*, 2840–2843. (b) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. Asymmetric 1,4-Hydrosilylations of α,β-Unsaturated Esters. *J. Am. Chem. Soc.* **2004**, *126*, 8352–8353. (c) Toshio, H.; Nobuaki, K.; Masayoshi, T. Chiral Synthesis of 3-Substituted and 3,3-Disubstituted γ-Butyrolactones by Enantioselective Deprotonation Strategy. *Tetrahedron: Asymmetry* **1993**, *4*, 1475–1478.

(21) CrysAlisPro, Rigaku/MSC, The Woodlands, TX, 2015.

(22) APEX3 and SADABS, Bruker AXS Inc., Madison, WI, 2016.

(23) Sheldrick, G. M. A Short History of SHELX. *Acta Cryst.* **2008**, *A64*, 112–122.

(24) Spek, A. L. Structure Validation in Chemical Crystallography. *Acta Cryst.* **2009**, *D65*, 148–155.

(25) Mercury CSD 3.5.1, Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J.; Wood, P. A. *J. Appl. Cryst.,* **2008**, *41*, 466–470.

(26) Metrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Hurtley, A. E.; Miller, S. J. Diversity of Secondary Structure in Catalytic Peptides with β-Turn-Biased Sequences. *J. Am. Chem. Soc.* **2017**, *139*, 492–516.

(27) CYLview was used to render X-ray crystal data: CYLview, 1.0b; Legault, C. Y. L., Universite de Sherbrooke, 2009 (http://www.cylview.org).