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Supplementary Materials for

Light-Driven Deracemization Enabled by Excited-State Electron Transfer

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This PDF file includes:

Materials and Methods

General Information

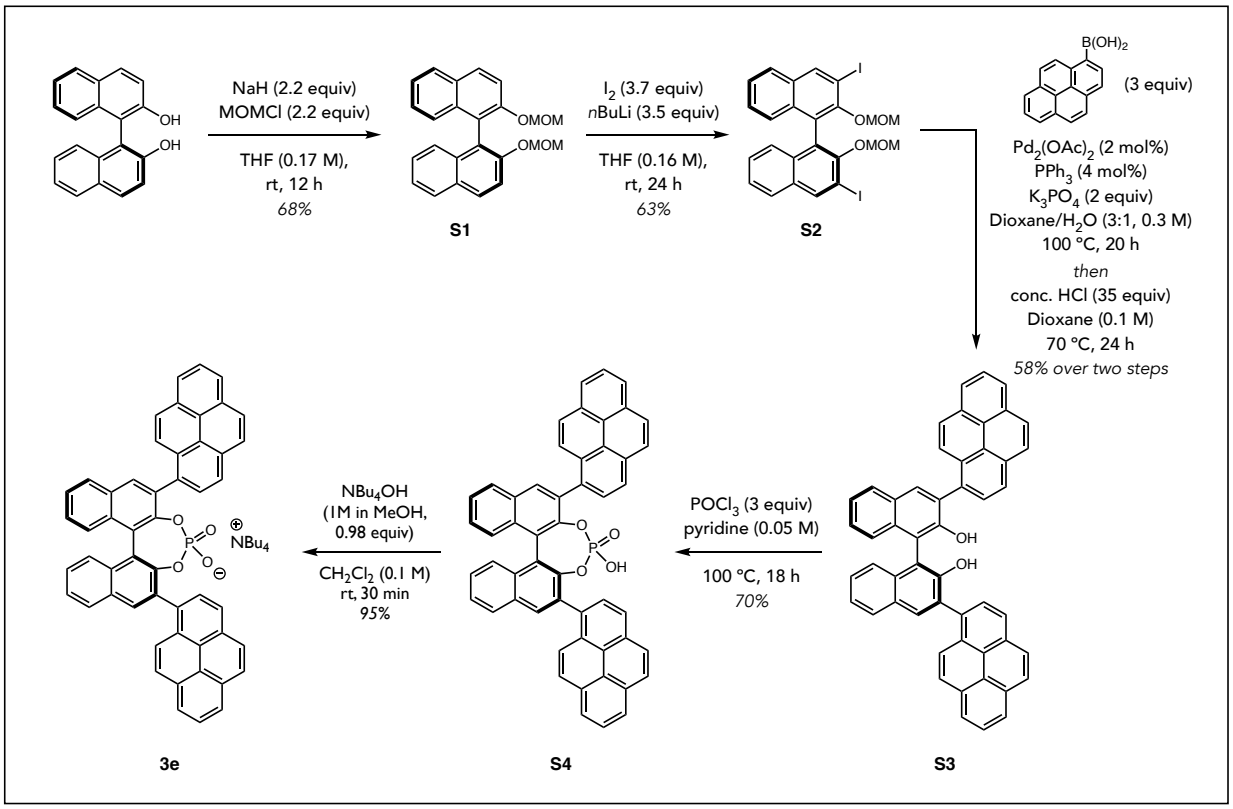
Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego (*30*). Molecular sieves used in reaction development were purchased from Sigma Aldrich (sodium Y zeolite powder) and activated under vacuum at 200 ºC for 48 hours prior to use. All solvents were purified according to the method of Grubbs (*31*). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Thin-layer chromatography (TLC) was performed on Silicycle 250 μm silica gel plates. Visualization of the developed chromatogram was performed by irradiation with UV light, Seebach's stain, and potassium permanganate stain. Normal-phase flash chromatography was performed using a Biotage Isolera One purification system equipped with a 10, 25, 50, or 100 g SNAP Ultra (HP Sphere, 25 μm silica) cartridge and an appropriate linear gradient in the mobile phase. Reverse-phase column chromatography was performed using a Biotage Isolera One purification system equipped with a 30, 60, or 120 g SNAP-C18 column and an appropriate MeOH/H_2O or MeCN/H_2O linear gradient in the mobile phase. Yields refer to purified compounds unless otherwise noted.

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker 500 (500, 126 and 203 MHz) instrument. Some ^{1}H and ^{13}C spectra were recorded on an Agilent 600 (600 and 151 MHz) spectrometer. The chemical shifts are calibrated by internal standard tetramethylsilane (TMS) or residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, hept = septet, m = multiplet, brs = broad singlet), coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift, and no special nomenclature is used for equivalent carbons. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at Princeton University mass spectrometry facilities using an Agilent 6210 TOF LC/MS. Some samples for high-resolution mass spectrometry were submitted to the Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign, where the data was acquired on Waters Synapt G2-Si instrument equipped with an ESI detector. The enantiomeric ratio (er) was determined by High-Performance Liquid Chromatography (HPLC) performed on an Agilent 1260 Infinity Series LC using commercial ChiralPak/ChiralCel columns from Daicel Chemical Industries, notably ChiralPak AD-H (5 μm particle size, 4.6 mm vs. 250 mm), ChiralCel OZ-H (5 μm particle size, 4.6 mm vs. 250 mm), ChiralCel OD-H (5 μm particle size, 4.6 mm vs. 250 mm), and ChiralPak ID (5 μm particle size, 4.6 mm vs. 250 mm). Optical rotations were measured on a Jasco P-1010 polarimeter at the sodium D-line (589 nm) using a cell of 50 mm path length. The concentration values (c) are reported in g/100 mL. Cyclic voltammograms were acquired on a CH Instruments 600E potentiostat. Stern–Volmer experiments were conducted on an Agilent Cary Eclipse Fluorescence Spectrophotometer. Time-correlated single photon counting experiments were conducted on a Horiba DeltaFlex system. UV-Vis spectra were acquired on an Agilent 8453 UV-Visible spectrophotometer.

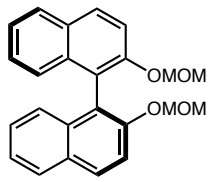
Abbreviation

Acpc	1-Aminocyclopropane-1-carboxylic acid
Aib	α-Aminoisobutyric acid
Boc	*t*-Butoxycarbonyl
$CDCl_3$	Chloroform-*d*
DCM	Dichloromethane
EDC	*N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide
EtOAc	Ethyl acetate
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
Hex	Hexanes
HOBt	1-Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
IPA	Isopropyl alcohol
LCMS	Liquid chromatography mass spectrometry
rt	Room temperature
TFA	Trifluoroacetic acid, trifluoroacetate
THF	Tetrahydrofuran
TLC	Thin-layer chromatography

Synthesis of Chiral Phosphate



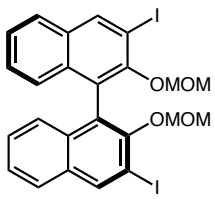
(*S*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (S1):



S1

Sodium hydride (4.61 g, 115 mmol, 2.2 equiv) was added to a 1 L round bottom flask charged with dry THF (240 mL) under argon atmosphere. After cooling to 0 °C, a solution of (*S*)-[1,1'-binaphthalene]-2,2'-diol (15.0 g, 52.4 mmol, 1.0 equiv) in THF (80 mL) was added slowly. The reaction was stirred for 1 hour at 0 °C. Chloromethyl methyl ether (MOMCl) (8.75 mL, 115 mmol, 2.2 equiv) was added slowly. The reaction mixture was let warm to room temperature and react overnight for 12 hours. The reaction was then quenched with sat. NH_4Cl (aq), concentrated, and diluted with CH_2Cl_2 and water. The aqueous layer was then extracted with CH_2Cl_2 three times. The organic layers were combined, washed with brine, dried with Na_2SO_4, and concentrated. The crude solid was dissolved in minimal volume of CH_2Cl_2 and diethyl ether (~100 mL) then ~ 50 mL of hexanes was added. The mixture was allowed to sit at room temperature for 12 hours until colorless crystals formed. The solid was collected by vacuum filtration. Another round of recrystallization gave (*S*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**S1**, 13.3 g, 35.5 mmol, 68% yield) as a white crystalline solid. The spectral data is consistent with the reported literature values (*32*).

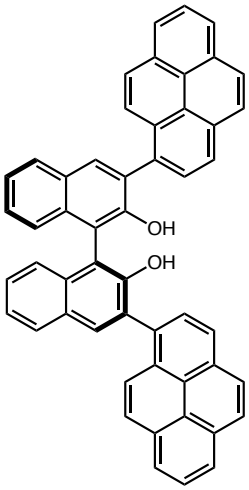
(*S*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (S2):



S2

To an oven dried 500 mL round bottom flask was added (*S*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (6.69 g, 17.9 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with argon three times. Then, THF (200 mL) was added. The solution was cooled to –78 °C, and *n*-butyllithium (2.5 M in hexanes, 25.0 mL, 62.5 mmol, 3.5 equiv) was added dropwise. The reaction was then stirred for 8 hours at 0 °C. The reaction was then cooled to –78 °C, and a solution of iodine (16.8 g, 66.1 mmol, 3.7 equiv) in THF (100 mL) was added *via* cannula under argon atmosphere. The reaction was allowed to warm to rt and stirred for 24 hours. The reaction was quenched with sat. $Na_2S_2O_3$ (aq.), extracted with EtOAc three times, washed with brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by silica gel flash column chromatography (0–5% EtOAc in hexanes) to afford (*S*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**S2**, 7.07 g, 11.3 mmol, 63% yield) as a pale yellow crystalline solid. The spectral data is consistent with reported literature values (*32*).

(*S*)-3,3'-di(pyren-1-yl)-[1,1'-binaphthalene]-2,2'-diol (S3):

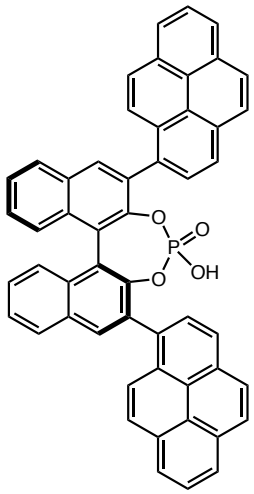


S3

To a 25 mL round bottom flask were added (*S*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (1.00 g, 1.60 mmol, 1.0 equiv), pyren-1-ylboronic acid (1.18 g, 4.79 mmol, 3.0 equiv), triphenylphosphine (0.017 g, 0.064 mmol, 4 mol%), palladium(II) acetate (7.2 mg, 0.032 mmol, 2 mol%), and potassium phosphate (0.678 g, 3.19 mmol, 2.0 equiv). The reaction vessel was evacuated and backfilled with argon three times. Degassed dioxane (4 mL) and water (1.3 mL) were added, and the reaction mixture was stirred at 100 °C for 20 hours. The reaction was filtered over a pad of silica and diluted with water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by silica gel flash column chromatography (0–40% CH_2Cl_2 in hexanes) to afford (*S*)-1,1'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)dipyrene (991 mg) as a pale yellow foamy solid with impurities. The material was carried to the next step without further purification.

To a 50 mL round bottom flask were added crude (*S*)-1,1'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)dipyrene (0.991 g, ~ 1.23 mmol, 1.0 equiv), concentrated hydrochloric acid (1.36 ml, 44.8 mmol, 35 equiv), and dioxane (12.8 ml). The reaction mixture was stirred at 70 °C for 24 hours. The reaction was then diluted with water and extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by silica gel flash column chromatography (10–40% CH_2Cl_2 in hexanes) to afford (*S*)-3,3'-di(pyren-1-yl)-[1,1'-binaphthalene]-2,2'-diol (**S3**, 639 mg, 0.930 mmol, 58% yield over two steps) as a pale yellow foamy solid. The spectral data is consistent with reported literature value (*33*).

(*S*)-4-hydroxy-2,6-di(pyren-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (S4):



S4

To a 50 mL round bottom flask were added (*S*)-3,3'-di(pyren-1-yl)-[1,1'-binaphthalene]-2,2'-diol (**S3**, 0.639 g, 0.930 mmol, 1.0 equiv) and phosphorus oxychloride (0.260 ml, 2.79 mmol, 3.0 equiv) in pyridine (18.6 ml). The reaction was stirred at 100 °C for 18 hours, which was then cooled to rt followed by addition of 20 mL of water. The reaction was stirred at 105 °C for four additional hours, cooled to rt, and acidified with 3*N* HCl (aq). The reaction mixture was diluted with CH_2Cl_2 and washed with 3*N* HCl (aq) three times. The organic layer was dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel flash column chromatography (0–5% MeOH in CH_2Cl_2). Appropriate fractions were combined, concentrated, washed with 3*N* HCl (aq) three times, dried over Na_2SO_4, and concentrated to afford (*S*)-4-hydroxy-2,6-di(pyren-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (**S4**, 490 mg, 0.654 mmol, 70% yield) as a pale yellow foamy solid.

^{1}H NMR (500 MHz, Acetone-d_6) δ 8.62–7.34 (m, 28H), 4.77 (s, 1H).

^{13}C NMR (126 MHz, Acetone-d_6) δ 134.49, 134.25, 133.86, 133.47, 133.40, 132.65, 132.26, 132.07, 131.80, 130.24, 130.15, 130.03, 129.87, 129.70, 128.53, 128.47, 128.30, 128.22, 128.04, 127.98, 127.77, 127.20, 127.07, 126.62, 126.26, 126.23, 126.06, 126.03, 125.89, 125.47, 125.40, 125.33, 125.08, 124.95.

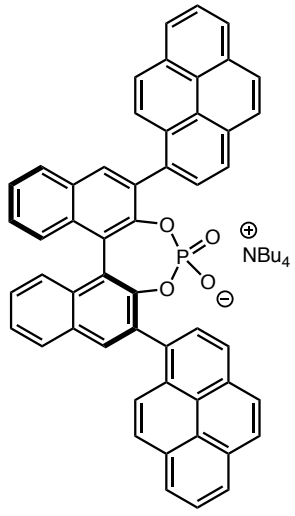
^{31}P NMR (203 MHz, Acetone-d_6) δ 0.42, 0.40, 0.03.

IR (FT-ATR, cm^{-1}) ν_{max} 3041, 2923, 1584, 1494, 1412, 1263, 1245, 1202, 1186, 1151, 1101, 1016, 998, 958, 892, 866, 843, 828, 818, 805, 775, 749, 718, 702, 683, 664.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{52}H_{30}O_4P^+$ requires 749.18762, observed 749.18761, difference 0.01 ppm.

$[\alpha]_D^{21}$ = +418.9° (*c* = 0.12, CH_2Cl_2)

tetrabutylammonium (S)-2,6-di(pyren-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-olate 4-oxide (3e):



3e

To a 2-dram vial was added (*S*)-4-hydroxy-2,6-di(pyren-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (**S4**, 740 mg, 0.989 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL). Tetrabutylammonium hydroxide (1M in MeOH, 969 µL, 0.969 mmol, 0.98 equiv) was added, and the reaction was stirred for 30 min at rt. The reaction solution was then concentrated and purified by reversed-phase column chromatography (C18, 0–100% MeOH/H_2O) to afford tetrabutylammonium (*S*)-2,6-di(pyren-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-olate 4-oxide (**3e**, 930 mg, 0.939 mmol, 95 % yield) as a pale yellow foamy solid.

^{1}H NMR (500 MHz, Acetone-d_6) δ 9.08–7.07 (m, 28H), 3.11–3.03 (m, 8H), 1.50–1.39 (m, 8H), 1.16–1.07 (m, 8H), 0.75 (t, J = 7.4 Hz, 12H).

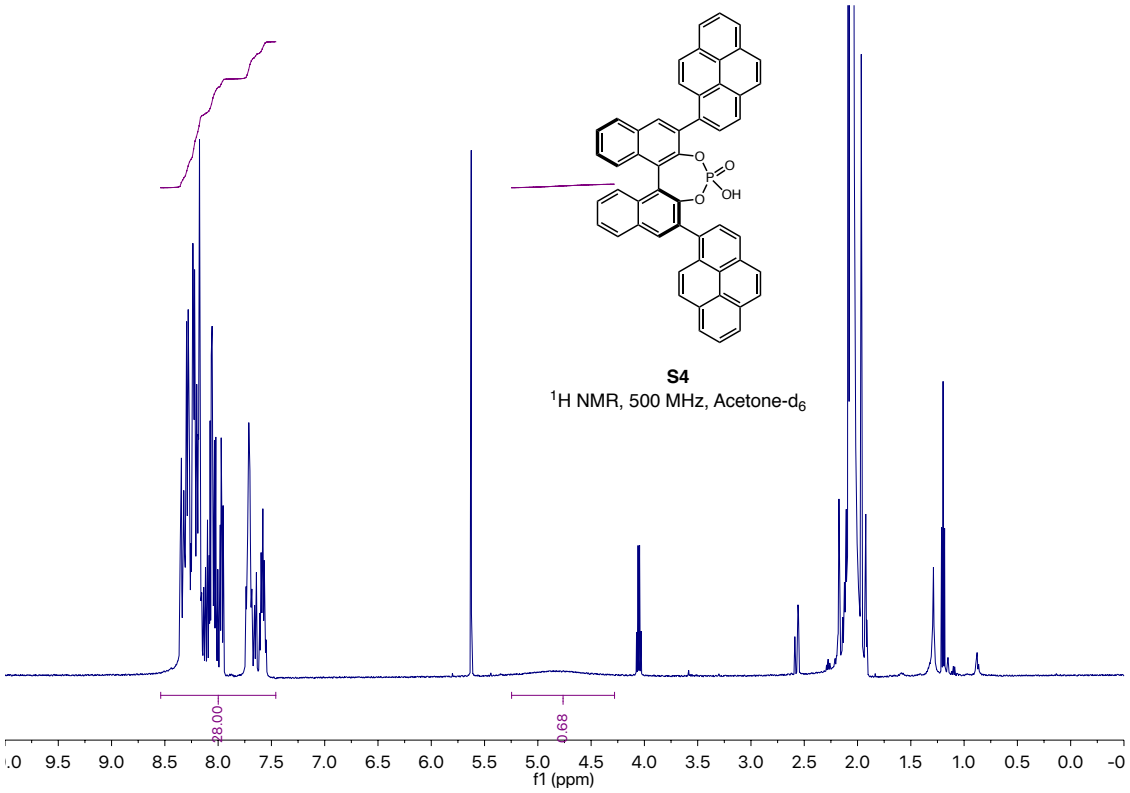
^{13}C NMR (126 MHz, Acetone-d_6) δ 135.72, 133.93, 132.74, 132.32, 131.88, 131.80, 131.38, 130.34, 129.75, 129.21, 129.03, 128.51, 127.86, 127.77, 127.63, 126.79, 126.69, 126.66, 125.76, 125.54, 125.31, 125.14, 58.89, 24.17, 20.13, 13.75.

^{31}P NMR (203 MHz, Acetone-d_6) δ 3.41.

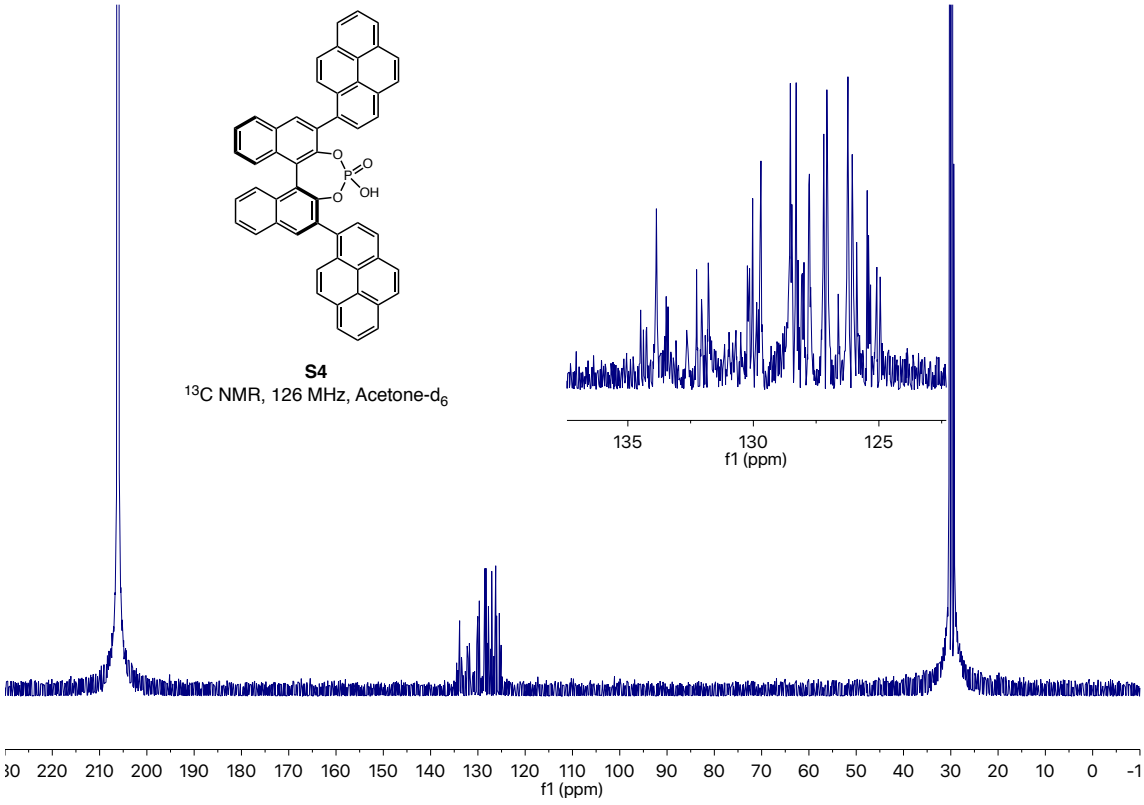
IR (FT-ATR, cm^{-1}) ν_{max} 3042, 2961, 2872, 1701, 1602, 1584, 1487, 1456, 1415, 1382, 1359, 1281, 1208, 1189, 1152, 1097, 1080, 1027, 1001, 980, 964, 892, 871, 846, 834, 818, 804, 774, 749, 696, 685, 663.

HRMS (ESI) (*m/z*) for $[Anion+2H]^+$ $C_{52}H_{30}O_4P^+$ requires 749.18762, observed 749.18890, difference 1.70 ppm. (*m/z*) for $[Cation]^+$ $C_{16}H_{36}N^+$ requires 242.28423, observed 242.28431, difference 0.33 ppm.

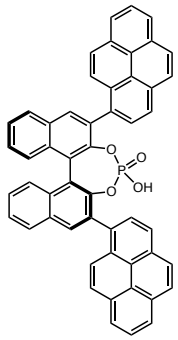
$[\alpha]_D^{21}$ = +199.0° (c = 0.28, CH_2Cl_2)



S4
^{1}H NMR, 500 MHz, Acetone-d_6

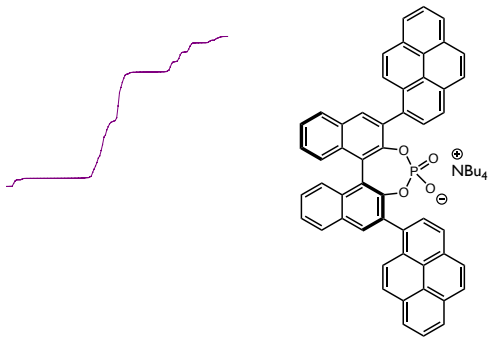


S4
^{13}C NMR, 126 MHz, Acetone-d_6



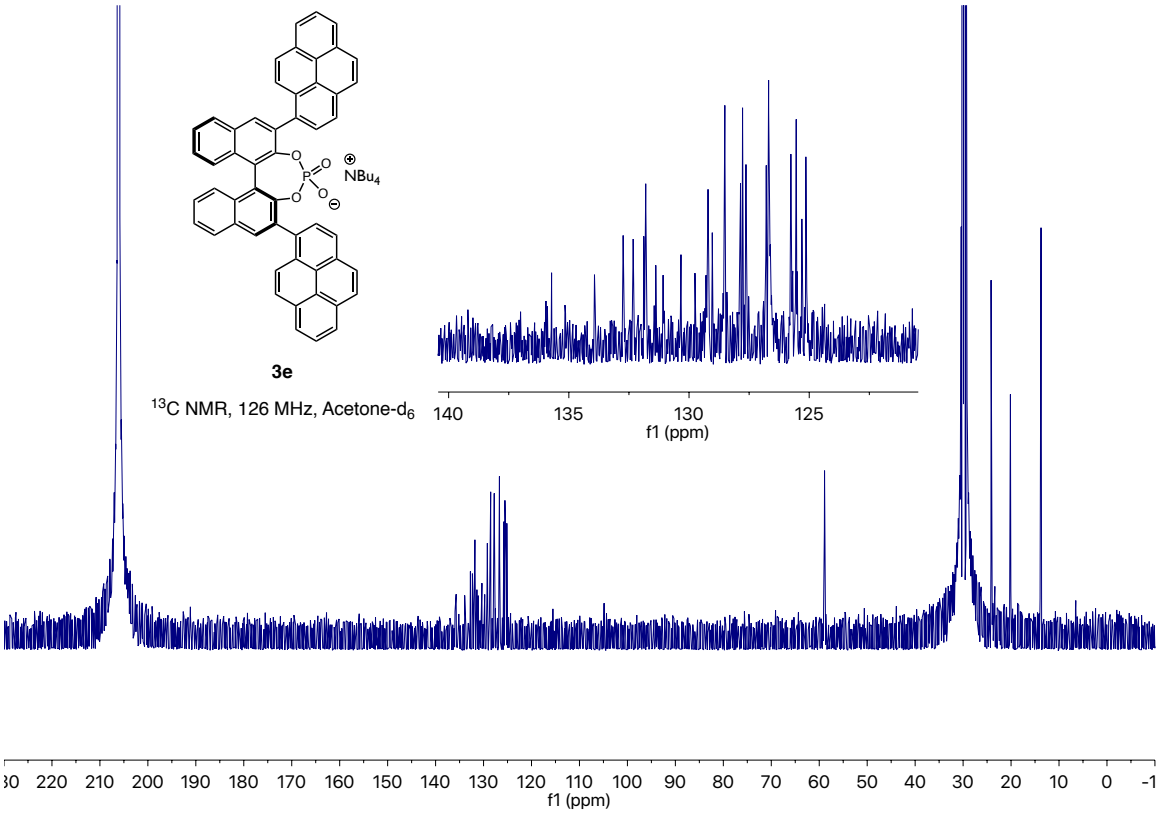
S4

^{31}P NMR, 203 MHz, Acetone-d_6



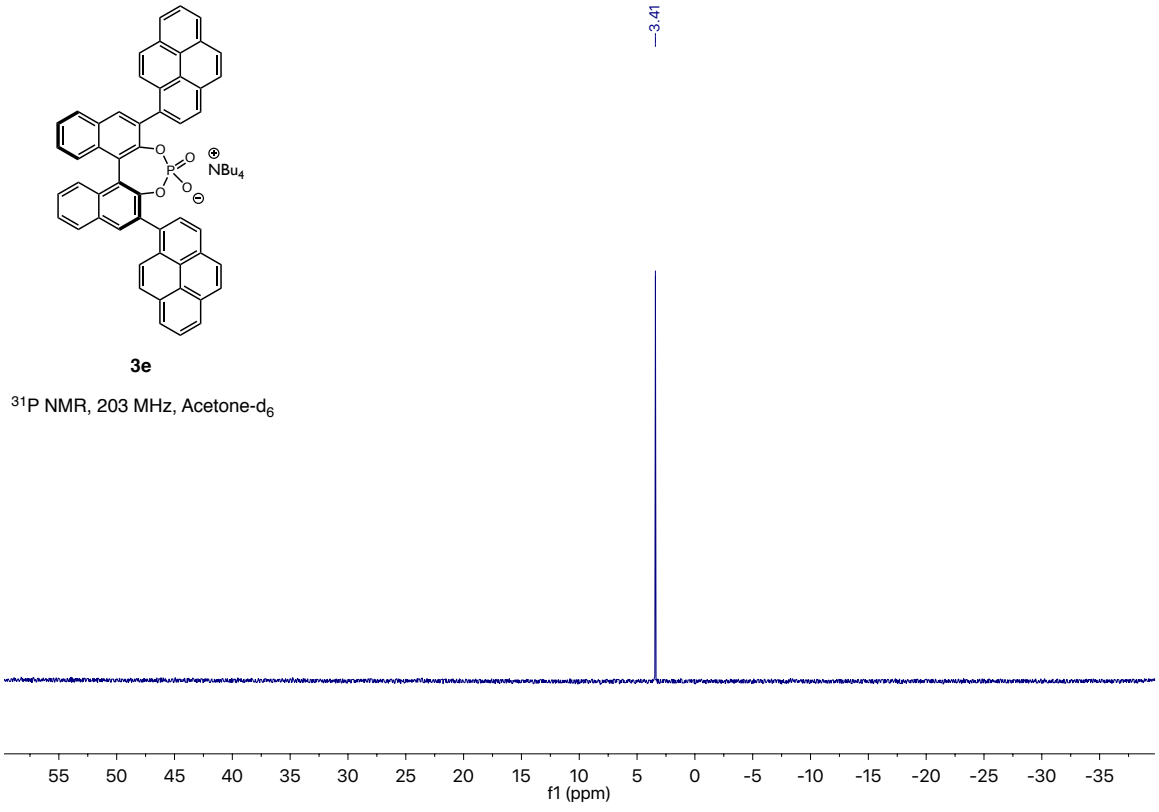
3e

^{1}H NMR, 500 MHz, Acetone-d_6



3e

^{13}C NMR, 126 MHz, Acetone-d_6

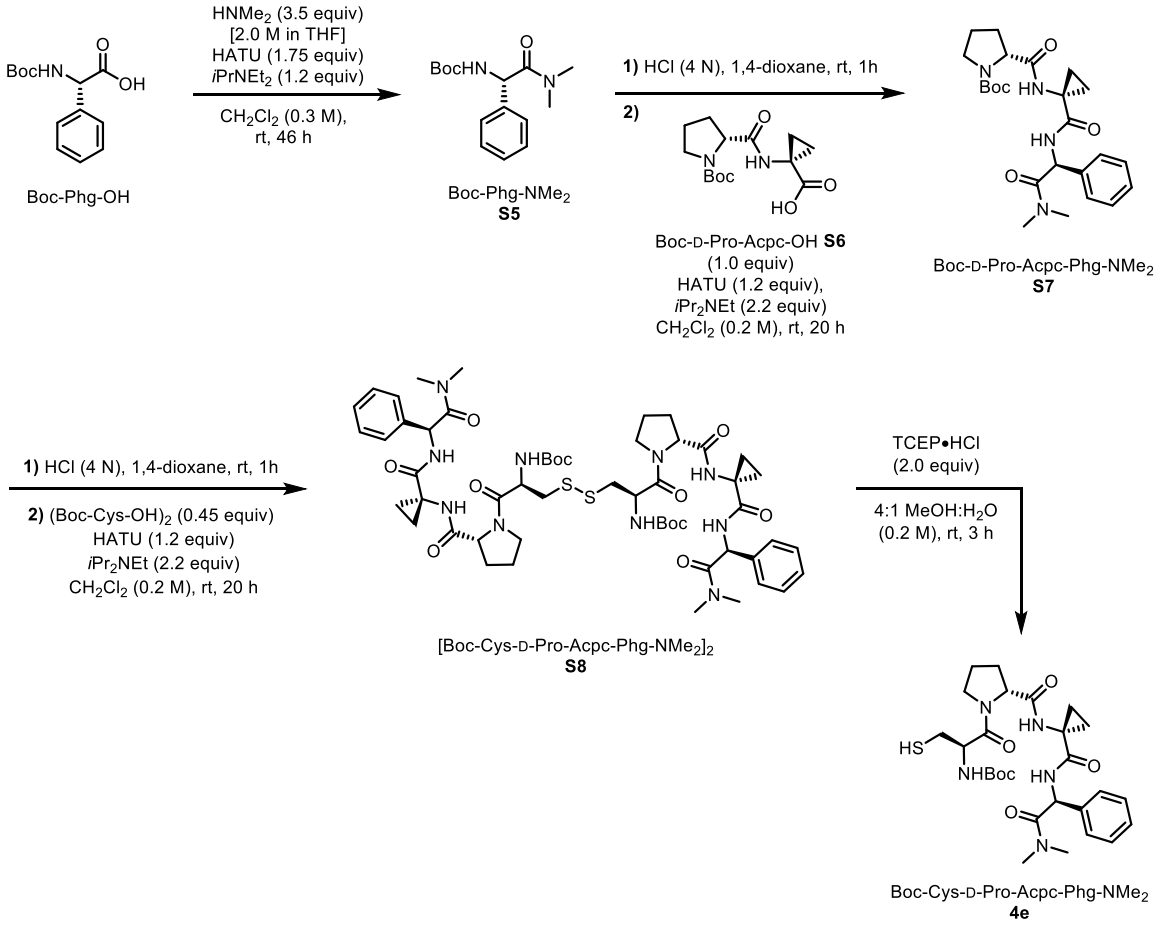


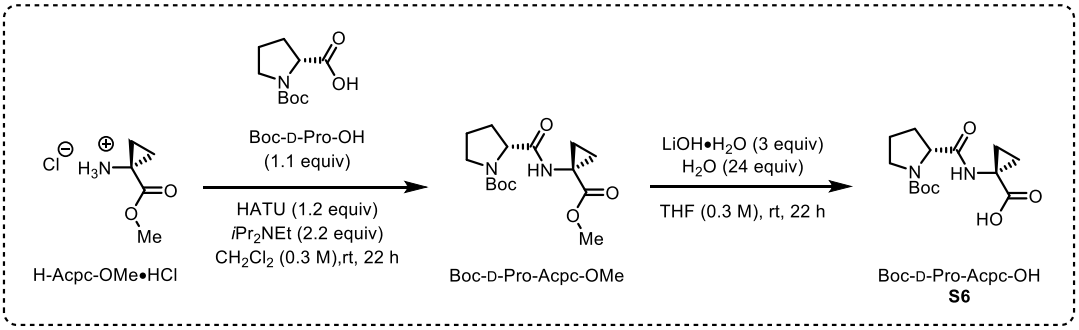
3e

^{31}P NMR, 203 MHz, Acetone-d_6

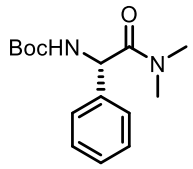
Solution Phase Peptide Synthesis

A. Synthesis and characterization of catalyst 4e





Synthesis of Boc-Phg-NMe$_2$ (S5):



Boc-Phg-NMe$_2$
S5

In a 250 mL round-bottomed flask equipped with a stir bar, Boc-Phg-OH (5.04 g, 20.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (37 mL, 0.3 M) and *i*Pr_2NEt (4.20 mL, 24.0 mmol, 1.2 equiv) was added. *N,N'*-dimethylamine solution (2.0 M in THF, 30.0 mL, 60.0 mmol, 3.0 equiv) was added, followed immediately by HATU (11.42 g, 30.0 mmol, 1.5 equiv). The flask was then sealed with a septum. The reaction mixture was allowed to stir at rt overnight. After 17 h, the reaction completion was assessed by LCMS, indicating 97% conversion. After 22 h, additional *N,N'*-dimethylamine solution (2.0 M in THF, 5 mL, 10.0 mmol, 0.5 equiv) was added, followed immediately by additional HATU (1.90 g, 5.0 mmol, 0.25 equiv). The reaction mixture was allowed to stir at rt overnight. After 24 h, the reaction mixture was concentrated partially *in vacuo* to ~30 mL, then transferred to a separatory funnel, diluted with EtOAc (200 mL), and washed with 10% (w/v) aqueous citric acid (3 x 200 mL), saturated aqueous $NaHCO_3$ (1 x 200 mL) and brine (1 x 200 mL). The organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale pink solid. The crude product was passed through a silica plug to remove polar impurities, eluting with 1:1 EtOAc/hexanes, then recrystallized from hot MTBE [dissolved in ~50 mL hot MTBE, cooled to rt, then slowly removed solvent *in vacuo* until crystallization began (~10 mL removed), then placed in a –20 °C freezer overnight]. The solids were filtered and washed with pentane to provide Boc-Phg-NMe$_2$ (**S5**) as a white powder (4.72 g, 85% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 6.03 (d, *J* = 7.9 Hz, 1H), 5.55 (d, *J* = 7.8 Hz, 1H), 2.98 (s, 3H), 2.89 (s, 3H), 1.41 (s, 9H).

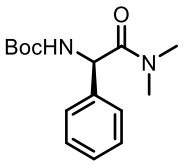
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 155.2, 138.1, 129.1, 128.3, 127.9, 79.8, 55.3, 37.0, 36.1, 28.5.

IR (FT-ATR, cm^{-1}) ν_{max} 3407, 2974, 1704, 1643, 1482, 1401, 1366, 1246, 1164, 1047, 1023, 968, 883, 842, 784, 763, 737, 714, 701, 628, 558, 495.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{15}H_{23}N_2O_3^+$ requires 279.1709, observed 279.1712.

$[\alpha]_D^{20}$ = +148.1° (*c* = 1.00, MeOH)

Synthesis of Boc-D-Phg-NMe$_2$ (*ent*-S5):



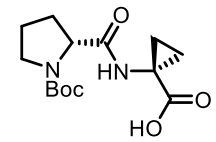
Boc-D-Phg-NMe$_2$
***ent*-S5**

Boc-D-Phg-NMe$_2$ (***ent*-S5**) was synthesized utilizing the same procedure as Boc-Phg-NMe$_2$ (**S5**). The crude product was recrystallized from acetone/hexanes [dissolved in ~100 mL hot acetone/hexanes ~1:5, cooled to rt, then slowly removed acetone *in vacuo* until crystallization began, then placed in a –20 °C freezer overnight]. The crystals were filtered and washed with pentane to provide Boc-D-Phg-NMe$_2$ (***ent*-S5**) as colorless needles (3.96 g, 71% yield). ^{1}H and ^{13}C NMR spectral data were in accordance with Phg-NMe$_2$ (**S5**).

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{15}H_{23}N_2O_3^+$ requires 279.1709, observed 279.1715.

$[\alpha]_D^{20}$ = –149.7° (*c* = 1.00, MeOH)

Synthesis of Boc-D-Pro-Acpc-OH (S6):



Boc-D-Pro-Acpc-OH
S6

Coupling: In a 250 mL round-bottomed flask equipped with a stir bar, Boc-H-Acpc-OMe•HCl (1.52 g, 10.0 mmol, 1.0 equiv), Boc-D-Pro-OH (2.37 g, 11.0 mmol, 1.1 equiv) were dissolved in CH_2Cl_2 (33 mL, 0.3 M), followed by addition of *i*Pr_2NEt (3.90 mL, 22.0 mmol, 2.2 equiv). HATU (4.56 g, 12.0 mmol, 1.2 equiv) was added and the reaction mixture was stirred at rt for 22 h. The reaction mixture was then transferred to a separatory funnel, diluted with EtOAc (200 mL), and washed with 10% (w/v) aqueous citric acid (2 x 150 mL), saturated aqueous $NaHCO_3$ (1 x 150 mL) and brine (1 x 150 mL). The organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford an oily, white solid. The crude product was purified by reversed-phase column chromatography (SNAP Ultra C18 120 g column; gradient = ramp 0–80% MeCN/H_2O over 15 CV, then 3 CV 80% MeCN; 60 mL/min flow rate; monitored λ = 210, 245 nm; 16 x 150 mm test tubes with 20 mL fractions). Fractions containing product were pooled and concentrated *in vacuo* to provide semi-pure Boc-D-Pro-Acpc-OMe as a foamy white solid, which was carried forward without additional purification.

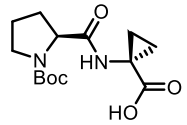
Hydrolysis: In a 250 mL round-bottomed flask equipped with a stir bar, Boc-D-Pro-Acpc-OMe was dissolved in THF (33 mL, 0.3 M) then LiOH•H_2O (1.26 g, 30.0 mmol, 3.0 equiv) and H_2O (4.30 mL, 240.0 mmol, 24 equiv) were added. The flask was capped with a septum and purged with N_2. The reaction mixture was stirred at rt under N_2 for 22 h. The reaction mixture was then transferred to a separatory funnel, diluted with 3:1 $CHCl_3$:*i*PrOH (200 mL), and acidified with 1*N* HCl (200 mL). The layers were mixed, separated, then the aqueous layer was further extracted with 3:1 $CHCl_3$/*i*PrOH (2 x 100 mL). The organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a foamy white solid. The crude product was purified by reversed-phase column chromatography (split into 2 x columns: SNAP Ultra C18 120 g column; gradient = 3 CV 0% MeCN/H_2O with 0.1% formic acid, ramp 0–70% MeCN/H_2O with 0.1% formic acid over 15 CV, then 3 CV 70% MeCN with 0.1% formic acid; 60 mL/min flow rate; monitored λ = 210, 245 nm; 16 x 150 mm test tubes with 20 mL fractions). Fractions containing product were pooled and concentrated *in vacuo* to provide Boc-D-Pro-Acpc-OH (**S6**) as a foamy white solid (1.35 g, 45% yield over 2 steps).

^{1}H NMR (600 MHz, methanol-d_4) (mixture of rotamers ~2:1, asterisks denote minor rotamer peaks) δ 4.17–4.09 (m, 1H), 3.57–3.49 (m, 1H), 3.42–3.35 (m, 1H), 2.30–2.12 (m, 1H), 2.12–1.91 (m, 2H), 1.91–1.79 (m, 1H), 1.58–1.47 (m, 2H), 1.45* (s, 3H), 1.41 (s, 6H), 1.19–1.03 (m, 2H).

^{13}C NMR (151 MHz, methanol-d_4) (mixture of rotamers) δ 177.0, 176.6, 175.9, 175.6, 156.4, 156.0, 81.4, 81.2, 61.7, 61.4, 48.3, 47.9, 34.0, 33.9, 32.2, 31.2, 28.7, 28.6, 25.2, 24.5, 18.0, 17.9, 17.5, 17.4.

IR (FT-ATR, cm^{-1}) ν_{max} 3286, 2978, 1666, 1529, 1394, 1366, 1257, 1159, 1123, 1091, 1037, 1002, 922, 883, 852, 770, 546, 519.
HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{14}H_{23}N_2O_5^+$ requires 299.1607, observed 299.1618.
$[\alpha]_D^{20}$ = +49.2° (*c* = 1.00, MeOH)

Synthesis of Boc-L-Pro-Acpc-OH (*ent*-S6):



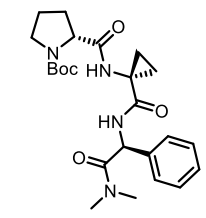
Boc-L-Pro-Acpc-OH
***ent*-S6**

Boc-L-Pro-Acpc-OH (***ent*-S6**) was synthesized utilizing the same procedure as Boc-D-Pro-Acpc-OH (**S6**) (1.58 g, 53% yield over 2 steps). ^{1}H and ^{13}C NMR spectral data were in accordance with Boc-D-Pro-Acpc-OH (**S6)**.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{14}H_{23}N_2O_5^+$ requires 299.1607, observed 299.1608.

$[\alpha]_D^{20}$ = –53.9° (*c* = 1.00, MeOH)

Synthesis of Boc-D-Pro-Acpc-Phg-NMe$_2$ (S7):



Boc-D-Pro-Acpc-Phg-NMe$_2$
S7

<u>Deprotection:</u> In a 250 mL round-bottomed flask equipped with a stir bar, Boc-Phg-NMe$_2$ (**S5**, 1.45 g, 5.2 mmol, 1.0 equiv) was treated with HCl (4*N* in 1,4-dioxane, 13.0 mL, 10.0 equiv) and the reaction mixture was stirred for 1 h at rt. The excess HCl was removed under a stream of N_2 and the reaction mixture was concentrated *in vacuo* to give a white powder.

<u>Coupling:</u> The residue was dissolved in CH_2Cl_2 (26.0 mL, 0.2 M) and *i*Pr_2NEt (2.00 mL, 11.4 mmol, 2.2 equiv) was added. Boc-D-Pro-Acpc-OH (**S6**), 1.56 g, 5.2 mmol, 1.0 equiv) was added, followed by HATU (2.38 g, 6.2 mmol, 1.2 equiv), and the reaction mixture was stirred at rt for 20 h. The reaction mixture was then transferred to a separatory funnel, diluted with EtOAc (200 mL), and washed with 10% (w/v) aqueous citric acid (2 x 200 mL), saturated aqueous $NaHCO_3$ (1 x 200 mL) and brine (1 x 200 mL). The organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a foamy white solid. The crude product was purified by reversed-phase column chromatography (split into 2 x columns: SNAP Ultra C18 120 g column; gradient = ramp 0–80% MeCN/H_2O over 15 CV, then 3 CV 80% MeCN; 60 mL/min flow rate; monitored λ = 210, 245 nm; 16 x 150 mm test tubes with 20 mL fractions). Fractions containing product were pooled and concentrated *in vacuo* to provide Boc-D-Pro-Acpc-Phg-NMe$_2$ (**S7**) as a foamy white solid (1.69 g, 71% yield).

^{1}H NMR (600 MHz, methanol-d_4) (mixture of rotamers ~1:1) δ 8.03 (d, *J* = 6.7 Hz, 0.5H), 7.88 (d, *J* = 6.7 Hz, 0.5H), 7.43–7.27 (m, 5H), 5.79–5.73 (m, 1H), 4.14 (dd, *J* = 8.9, 3.9 Hz, 0.5H), 4.04 (dd, *J* = 8.5, 4.7 Hz, 0.5H), 3.57–3.47 (m, 1H), 3.44–3.36 (m, 1H), 2.98–2.92 (m, 6H), 2.38–2.29 (m, 0.5H), 2.27–2.12 (m, 1H), 2.05–1.83 (m, 2.5H), 1.52–1.44 (m, 1H), 1.42 (s, 4.5H), 1.37 (s, 4.5H), 1.13–1.07 (m, 0.5H), 1.03–0.95 (m, 1.5H).

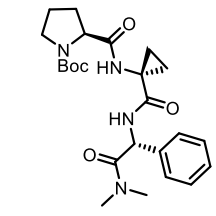
^{13}C NMR (151 MHz, methanol-d_4) (mixture of rotamers) δ 177.2, 176.9, 173.3, 173.2, 172.4, 172.3, 171.6, 171.5, 171.2, 171.2, 156.5, 155.8, 138.3, 137.6, 130.0, 129.9, 129.5, 129.4, 129.3, 129.0, 81.4, 62.0, 61.7, 56.4, 56.3, 55.8, 55.7, 48.2, 47.9, 37.3, 37.3, 36.3, 36.3, 35.5, 35.5, 35.4, 35.4, 32.6, 31.4, 28.7, 28.6, 25.5, 24.7, 17.7, 17.5, 17.3, 16.9.

IR (FT-ATR, cm^{-1}) ν_{max} 3285, 2975, 1642, 1494, 1454, 1396, 1365, 1305, 1257, 1160, 1120, 1090, 1033, 997, 949, 920, 852, 763, 698, 615, 536.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{24}H_{35}N_4O_5^+$ requires 459.2607, observed 459.2594.

$[\alpha]_D^{20}$ = +173.1° (*c* = 1.00, $CHCl_3$)

Synthesis of Boc-L-Pro-Acpc-D-Phg-NMe_2 (*ent*-S7):



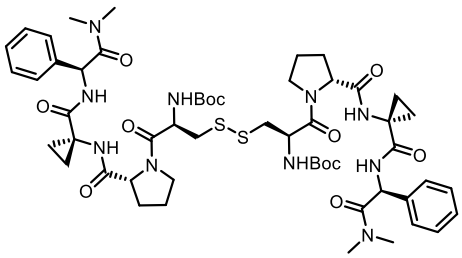
Boc-L-Pro-Acpc-D-Phg-NMe_2
***ent*-S7**

Boc-L-Pro-Acpc-D-Phg-NMe_2 (***ent*-S7**) was synthesized utilizing the same procedure as Boc-D-Pro-Acpc-Phg-NMe_2 (**S7**) (1.10 g, 66% yield). ^{1}H and ^{13}C NMR spectral data were in accordance with Boc-D-Pro-Acpc-Phg-NMe_2 (**S7**).

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{24}H_{35}N_4O_5^+$ requires 459.2607, observed 459.2603.

$[\alpha]_D^{20}$ = –164.0° (*c* = 1.00, $CHCl_3$)

Synthesis of (Boc-Cys-D-Pro-Acpc-Phg-NMe_2)$_2$ (S8):



[Boc-Cys-D-Pro-Acpc-Phg-NMe_2]$_2$
S8

<u>Deprotection:</u> In a 250 mL round-bottomed flask equipped with a stir bar, Boc-D-Pro-Acpc-Phg-NMe_2 (**S7**, 1.08 g, 2.36 mmol, 1.0 equiv) was treated with HCl (4*N* in 1,4-dioxane, 6.0 mL, 10.0 equiv) and the reaction mixture was stirred for 1 h at rt. The excess HCl was removed under a stream of N_2 and the reaction mixture was concentrated *in vacuo* to give a foamy white solid.

<u>Coupling:</u> The residue was dissolved in CH_2Cl_2 (12.0 mL, 0.2 M) and *i*Pr_2NEt (0.90 mL, 5.2 mmol, 2.2 equiv) was added. (Boc-Cys-OH)$_2$ (0.47 g, 1.06 mmol, 0.45 equiv) was added, followed by HATU (1.08 g, 2.8 mmol, 1.2 equiv), and the reaction mixture was stirred at rt for 20 h. The reaction mixture was transferred to a separatory funnel, diluted with EtOAc (200 mL), and washed with 10% (w/v) aqueous citric acid (2 x 200 mL), saturated aqueous $NaHCO_3$ (1 x 200 mL) and brine (1 x 200 mL). The organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a foamy white solid. The crude product was purified by reversed-phase column chromatography (split into 2 x columns: SNAP Ultra C18 120 g column; gradient = ramp 20–100% MeCN/H_2O with 0.1% formic acid over 15 CV, then 3 CV 100% MeCN with 0.1% formic acid; 60 mL/min flow rate; monitored λ = 210, 245 nm; 16 x 150 mm test tubes with 20 mL fractions). Fractions containing product were pooled and concentrated *in vacuo* to provide (Boc-Cys-D-Pro-Acpc-Phg-NMe_2)$_2$ (**S8**) as a foamy white solid (0.933 g, 78% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.8 Hz, 1H), 7.49–7.41 (m, 2H), 7.36–7.23 (m, 4H), 7.16 (s, 1H), 5.90 (d, *J* = 7.8 Hz, 1H), 4.78 (td, *J* = 8.8, 5.1 Hz, 1H), 4.30 (dd, *J* = 8.3, 4.1 Hz, 1H), 3.71 (app. t, *J* = 6.6 Hz, 2H), 3.28 (dd, *J* = 13.3, 8.8 Hz, 1H), 2.97 (dd, *J* = 13.3, 4.9 Hz, 1H), 2.93 (s, 6H), 2.24–2.13 (m, 2H), 2.05–1.96 (m, 1H), 1.96–1.87 (m, 1H), 1.66 (ddd, *J* = 10.0, 7.7, 4.6 Hz, 1H), 1.39 (s, 9H), 1.34 (ddd, *J* = 10.0, 7.7, 4.2 Hz, 1H), 1.02 (ddd, *J* = 10.0, 7.7, 4.6 Hz, 1H), 0.88 (ddd, *J* = 10.0, 7.7, 4.2 Hz, 1H).

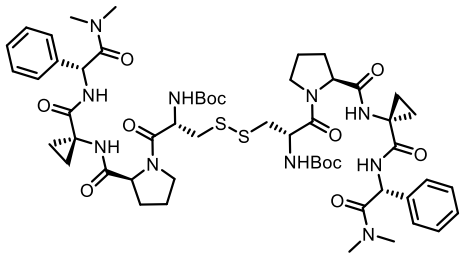
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.3, 170.5, 170.3, 169.8, 155.8, 137.7, 129.0, 128.2, 128.1, 79.8, 61.1, 54.0, 52.6, 47.6, 40.6, 37.2, 36.4, 34.8, 28.5, 28.3, 25.5, 17.5, 17.4.

IR (FT-ATR, cm^{-1}) ν_{max} 3293, 2976, 1633, 1496, 1441, 1408, 1366, 1303, 1248, 1161, 1044, 1018, 869, 698, 616, 540.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{54}H_{77}N_{10}O_{12}S_2^+$ requires 1121.5164, observed 1121.5209.

$[\alpha]_D^{20}$ = +80.4° (*c* = 1.00, $CHCl_3$)

Synthesis of (Boc-D-Cys-L-Pro-Acpc-D-Phg-NMe$_2$)$_2$ (*ent*-S8):



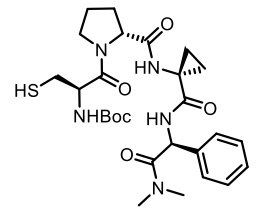
[Boc-D-Cys-L-Pro-Acpc-D-Phg-NMe$_2$]$_2$
***ent*-S8**

(Boc-D-Cys-L-Pro-Acpc-D-Phg-NMe$_2$)$_2$ (***ent*-S8**) was synthesized utilizing the same procedure as (Boc-Cys-D-Pro-Acpc-Phg-NMe$_2$)$_2$ (**S8**) (851 mg, 85% yield). ^{1}H and ^{13}C NMR spectral data were in accordance with (Boc-Cys-D-Pro-Acpc-Phg-NMe$_2$)$_2$ (**S8**).

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{54}H_{77}N_{10}O_{12}S_2^+$ requires 1121.5164, observed 1121.5175.

$[\alpha]_D^{20}$ = –76.8° (*c* = 1.00, $CHCl_3$)

Synthesis of Boc-Cys-D-Pro-Acpc-Phg-NMe$_2$ (4e):



Boc-Cys-D-Pro-Acpc-Phg-NMe$_2$
4e

In a 20 mL scintillation vial equipped with a stir bar, (Boc-Cys-D-Pro-Acpc-Phg-NMe$_2$)$_2$ (**S8**, 685 mg, 0.61 mmol, 1.0 equiv) and tris(2-carboxyethyl)phosphine hydrochloride (TCEP•HCl, 350 mg, 1.2 mmol, 2.0 equiv) were added, then dissolved in 4:1 (v/v) MeOH:H_2O (3.0 mL, 0.2 M). The reaction mixture was stirred at rt for 3 h, then concentrated partially in vacuo to ~1 mL, which was then purified directly by reversed-phase column chromatography (SNAP Ultra C18 120 g column; gradient = ramp 20–100% MeCN/H_2O with 0.1% formic acid over 15 CV, then 3 CV 100% MeCN with 0.1% formic acid; 60 mL/min flow rate; monitored λ = 210, 245 nm; 16 x 150 mm test tubes with 20 mL fractions). Fractions containing product were pooled and concentrated *in vacuo* to provide Boc-Cys-D-Pro-Acpc-Phg-NMe$_2$ (**4e**) as a foamy white solid (600 mg, 87% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.9 Hz, 1H), 7.53–7.43 (m, 3H), 7.37–7.31 (m, 2H), 7.31–7.26 (m, 1H), 7.06 (s, 1H), 5.91 (d, *J* = 7.9 Hz, 1H), 4.57 (td, *J* = 9.3, 4.8 Hz, 1H), 4.29 (dd, *J* = 8.0, 4.4 Hz, 1H), 3.70 (app. t, *J* = 6.6 Hz, 2H), 3.06 (dt, *J* = 13.3, 8.7 Hz, 1H), 2.94 (s, 6H), 2.68 (ddd, *J* = 13.3, 9.6, 4.8 Hz, 1H), 2.31–2.19 (m, 2H), 2.06–1.91 (m, 2H), 1.73–1.64 (m, 2H), 1.42 (s, 9H), 1.34 (ddd, *J* = 10.1, 7.8, 4.3 Hz, 1H), 1.05 (ddd, *J* = 10.1, 7.8, 4.7 Hz, 1H), 0.88 (ddd, *J* = 10.1, 7.7, 4.3 Hz, 1H).

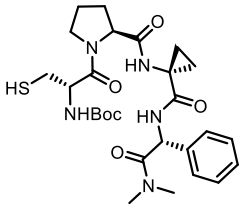
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.2, 170.5, 170.1, 169.8, 156.0, 137.7, 129.0, 128.2, 128.0, 79.8, 60.9, 55.5, 53.9, 47.5, 37.2, 36.4, 34.8, 28.5, 28.0, 26.1, 25.6, 17.6, 17.4.

IR (FT-ATR, cm^{-1}) ν_{max} 3290, 2975, 1633, 1498, 1443, 1410, 1366, 1305, 1250, 1161, 1046, 1003, 868, 699, 616, 540.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{27}H_{40}N_5O_6S^+$ requires 562.2699, observed 562.2683.

$[\alpha]_D^{20}$ = +36.5° (*c* = 1.00, MeOH)

Synthesis of Boc-D-Cys-L-Pro-Acpc-D-Phg-NMe$_2$ (*ent*-4e):



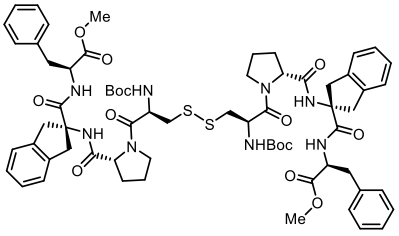
Boc-D-Cys-L-Pro-Acpc-D-Phg-NMe$_2$
***ent*-4e**

Boc-D-Cys-L-Pro-Acpc-D-Phg-NMe$_2$ (***ent*-4e**) was synthesized utilizing the same procedure as Boc-Cys-D-Pro-Acpc-Phg-NMe$_2$ (**4e**) (525 mg, 83% yield). ^{1}H and ^{13}C NMR spectral data were in accordance with Boc-Cys-D-Pro-Acpc-Phg-NMe$_2$ (**4e**).

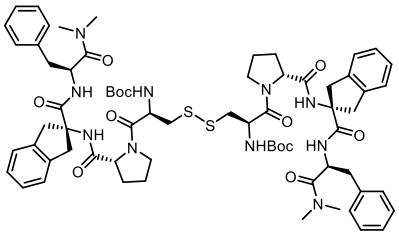
HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{27}H_{40}N_5O_6S^+$ requires 562.2699, observed 562.2700.

$[\alpha]_D^{20}$ = –36.4° (*c* = 1.00, MeOH)

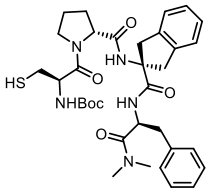
B. HRMS Analysis of Peptide Catalysts 4a–4d and P1–P21



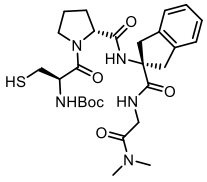
4a
HRMS: (m/z) for $[M+H]^+$ ($C_{66}H_{83}N_8O_{14}S_2$)
requires 1275.5470, observed 1275.5447



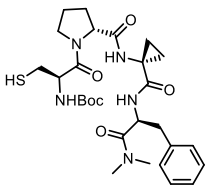
4b
HRMS: (m/z) for $[M+H]^+$ ($C_{68}H_{89}N_{10}O_{12}S_2$)
requires 1301.60974, observed 1301.61018



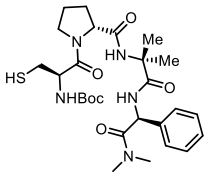
4c
HRMS: (m/z) for $[M+H]^+$ ($C_{34}H_{46}N_5O_6S$)
requires 652.3169, observed 652.3141



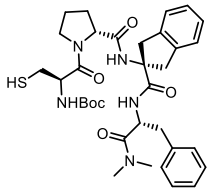
4d
HRMS: (m/z) for $[M+H]^+$ ($C_{27}H_{40}N_5O_6S$)
requires 562.26902, observed 562.26902



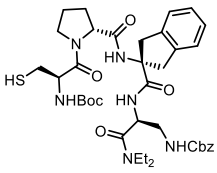
P1
HRMS: (m/z) for $[M+H]^+$ ($C_{28}H_{42}N_5O_6S$)
requires 576.2856, observed 576.2842



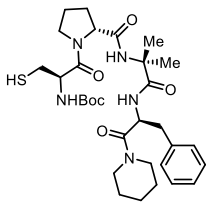
P2
HRMS: (m/z) for $[M+H]^+$ ($C_{27}H_{42}N_5O_6S$)
requires 564.2856, observed 564.2834



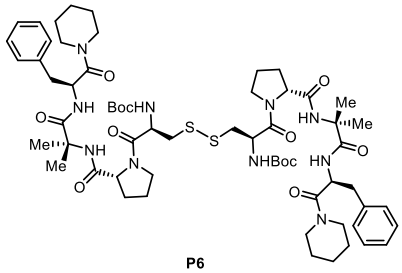
P3
HRMS: (m/z) for $[M+H]^+$ ($C_{34}H_{46}N_5O_6S$)
requires 652.3169, observed 652.3141



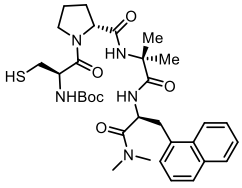
P4
HRMS: (m/z) for $[M+H]^+$ ($C_{38}H_{53}N_6O_8S$)
requires 753.3646, observed 753.3646



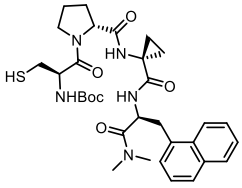
P5
HRMS: (m/z) for $[M+H]^+$ ($C_{31}H_{48}N_5O_6S$)
requires 618.3325, observed 618.3297



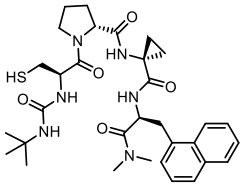
P6
HRMS: (m/z) for $[M+H]^+$ ($C_{62}H_{93}N_{10}O_{12}S_2$)
requires 1233.6416, observed 1233.6383



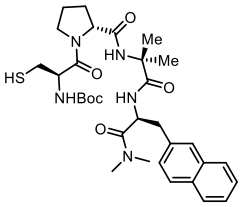
P7
HRMS: (m/z) for $[M+H]^+$ ($C_{32}H_{46}N_5O_6S$) requires 628.3169, observed 628.3158



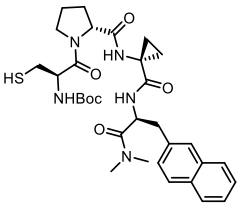
P8
HRMS: (m/z) for $[M+H]^+$ ($C_{32}H_{44}N_5O_6S$) requires 626.3012, observed 626.3008



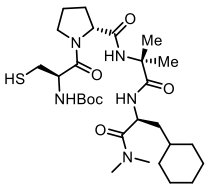
P9
HRMS: (m/z) for $[M+H]^+$ ($C_{32}H_{45}N_6O_5S$) requires 625.3172, observed 625.3159



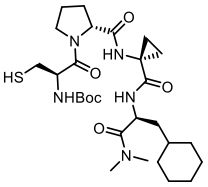
P10
HRMS: (m/z) for $[M+H]^+$ ($C_{32}H_{46}N_5O_6S$) requires 628.31633, observed 628.31546



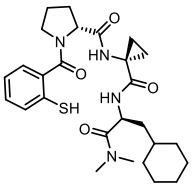
P11
HRMS: (m/z) for $[M+H]^+$ ($C_{32}H_{44}N_5O_6S$) requires 626.30068, observed 626.30098



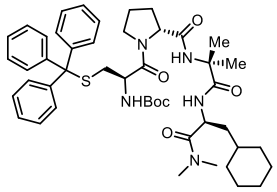
P12
HRMS: (m/z) for $[M+H]^+$ ($C_{28}H_{50}N_5O_6S$) requires 584.34763, observed 584.34676



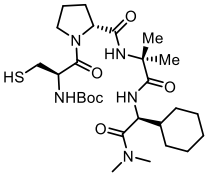
P13
HRMS: (m/z) for $[M+H]^+$ ($C_{28}H_{48}N_5O_6S$) requires 582.33198, observed 582.33200



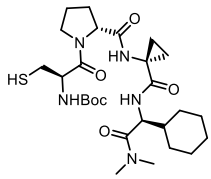
P14
HRMS: (m/z) for $[M+H]^+$ ($C_{27}H_{39}N_4O_4S$) requires 515.26865, observed 515.26871



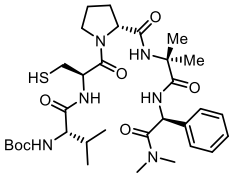
P15
HRMS: (m/z) for $[M+H]^+$ ($C_{47}H_{64}N_5O_6S$) requires 826.4577, observed 826.4578



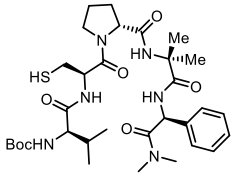
P16
HRMS: (m/z) for $[M+H]^+$ ($C_{27}H_{48}N_5O_6S$) requires 570.3325, observed 570.3308



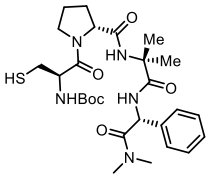
P17
HRMS: (m/z) for $[M+H]^+$ ($C_{27}H_{46}N_5O_6S$) requires 568.3169, observed 568.3170



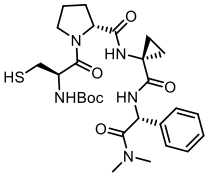
P18
HRMS: (m/z) for $[M+H]^+$ ($C_{32}H_{51}N_6O_7S$) requires 663.3540, observed 663.3530



P19
HRMS: (m/z) for $[M+H]^+$ ($C_{32}H_{51}N_6O_7S$) requires 663.3540, observed 663.3525

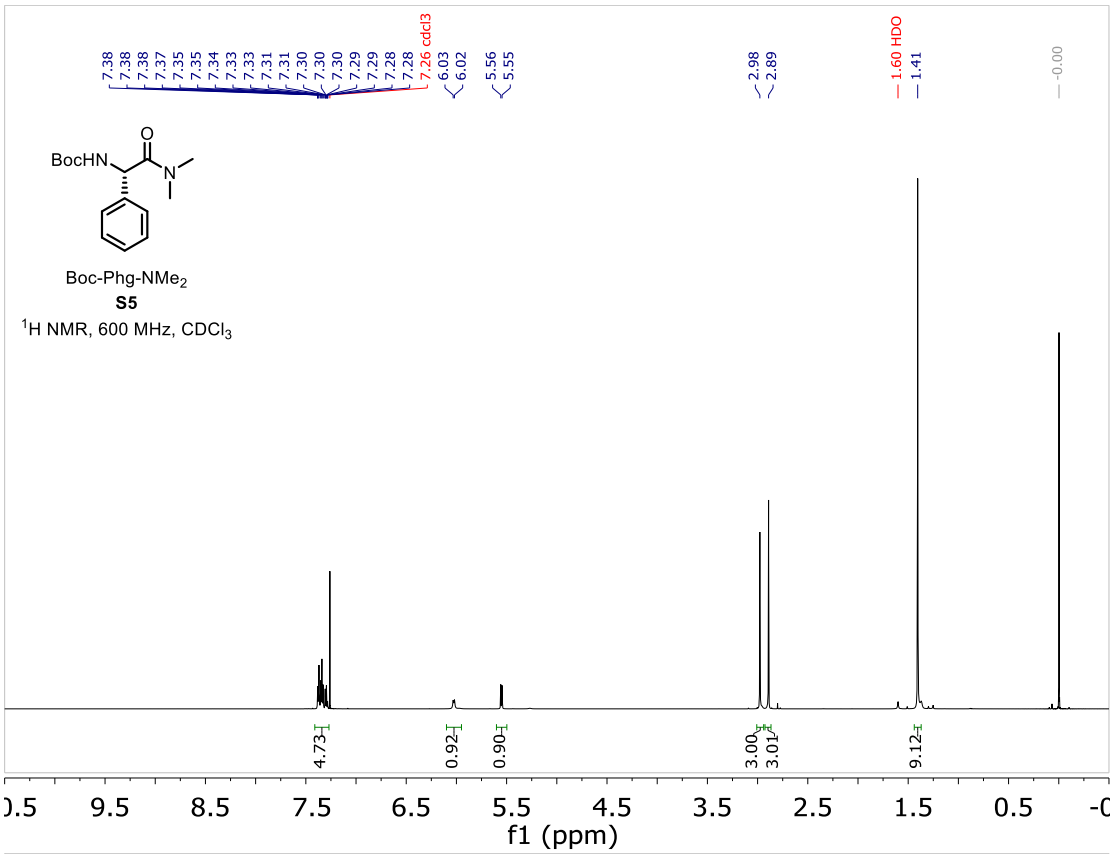


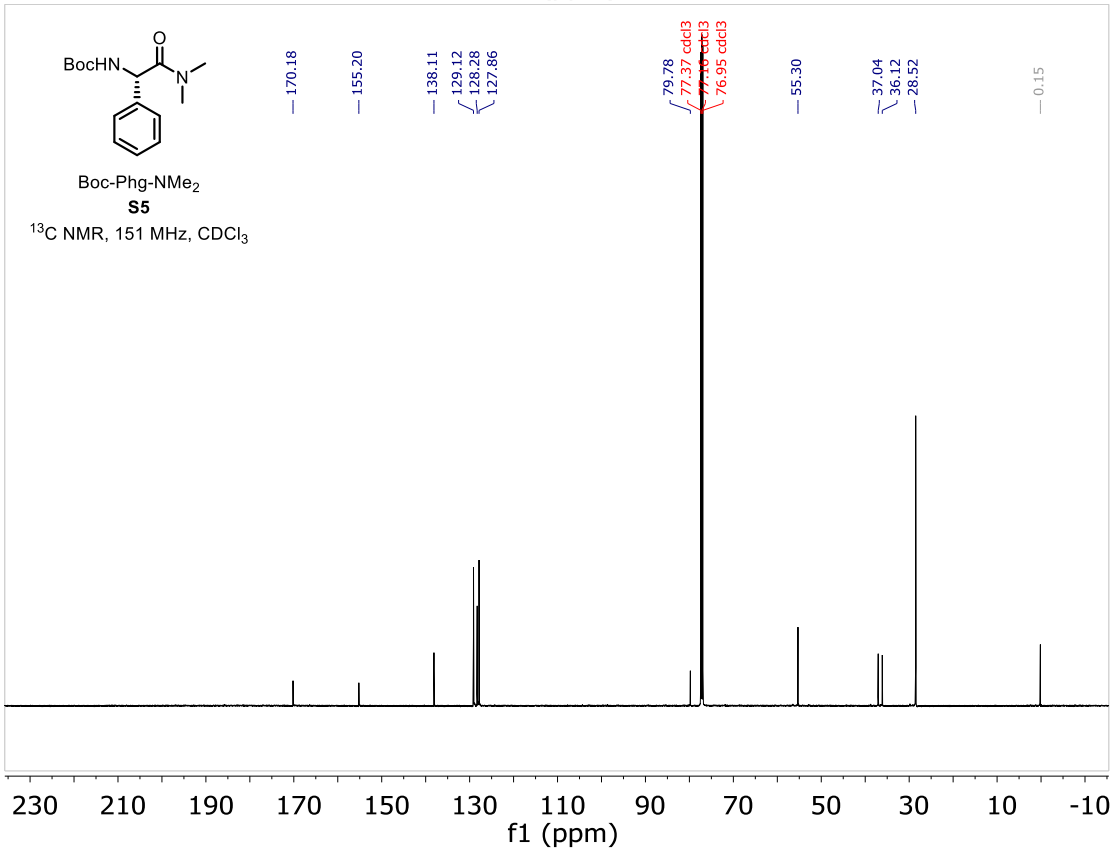
P20
HRMS: (m/z) for $[M+H]^+$ ($C_{27}H_{42}N_5O_6S$) requires 564.2856, observed 564.2841

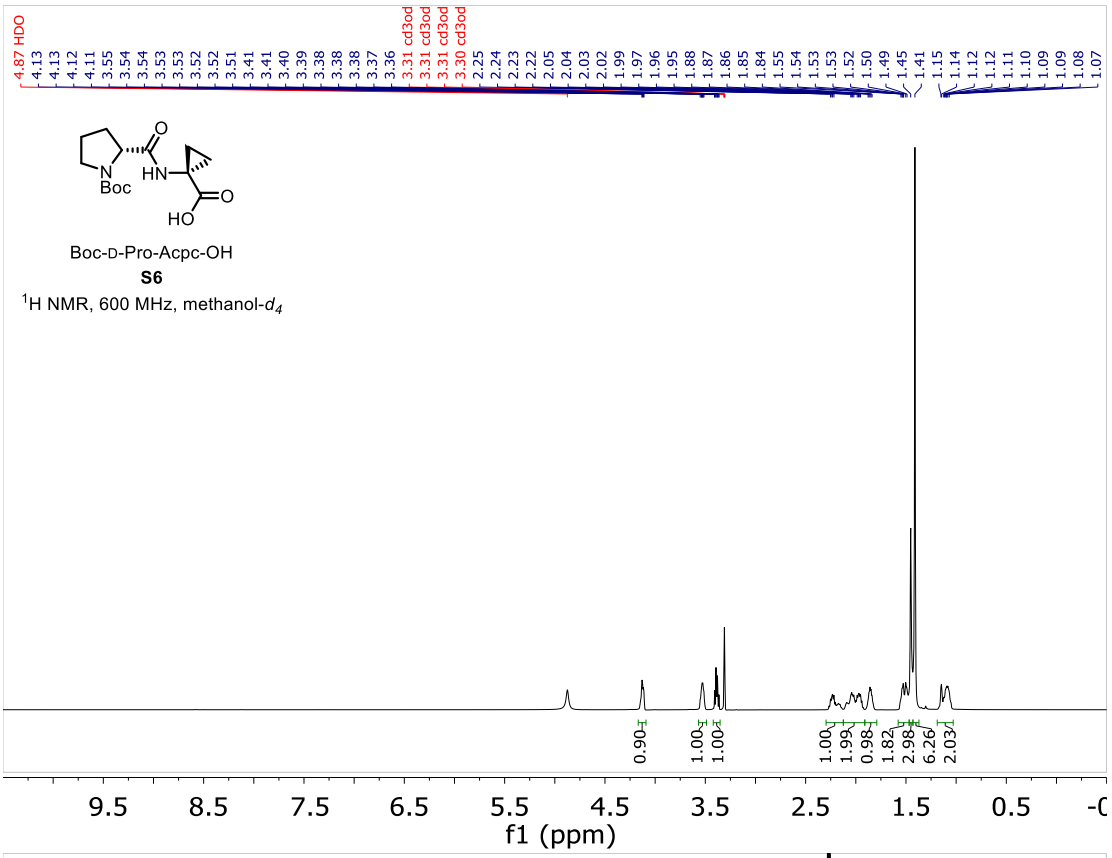


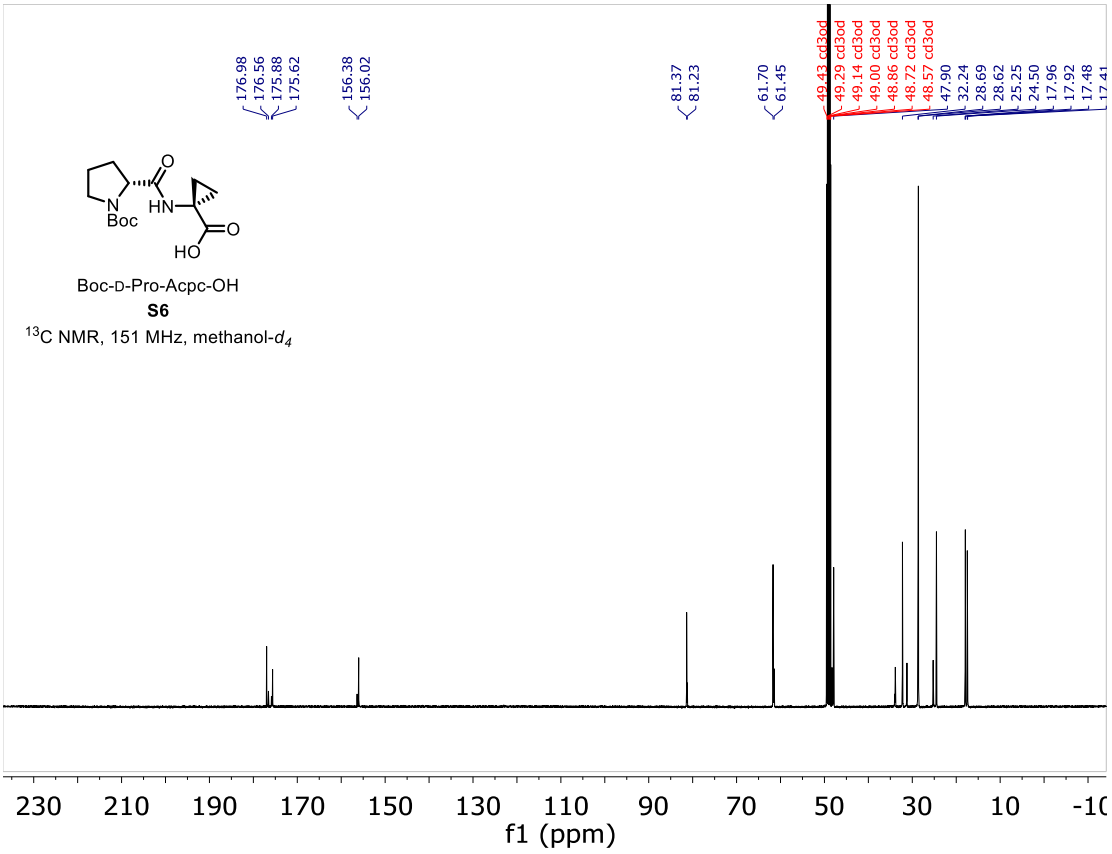
P21
HRMS: (m/z) for $[M+H]^+$ ($C_{27}H_{40}N_5O_6S$) requires 562.2699, observed 562.2697

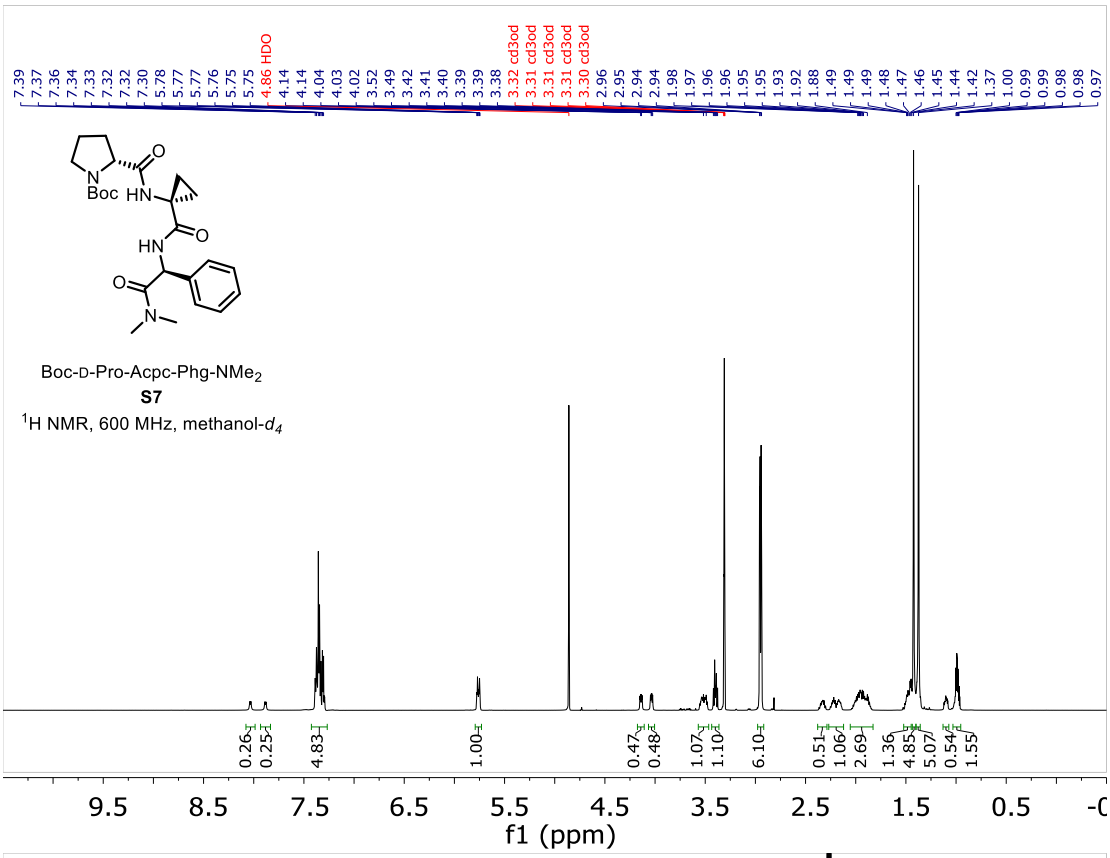
C. ^{1}H and ^{13}C NMR Spectra (Next Page)

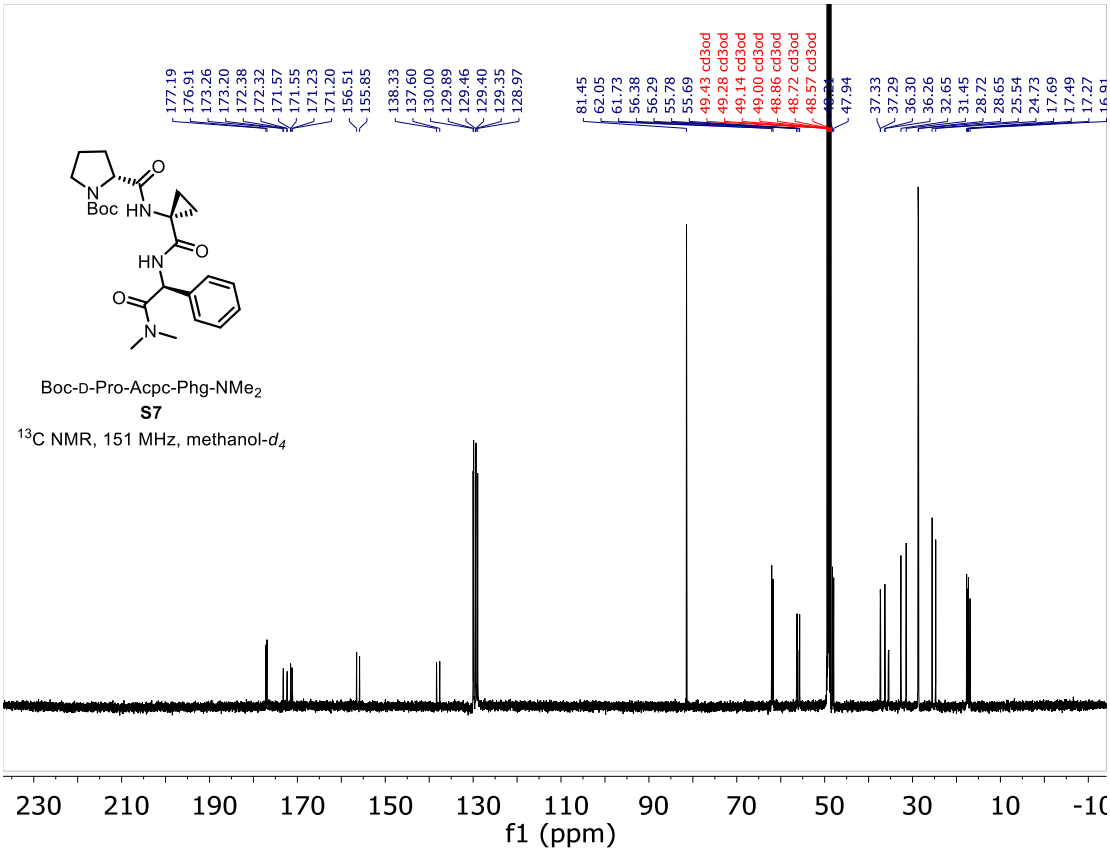

7.38
7.38
7.38
7.37
7.35
7.35
7.34
7.33
7.33
7.31
7.31
7.30
7.30
7.30
7.29
7.29
7.28
7.28
7.26 cdcl3
6.03
6.02
5.56
5.55
2.98
2.89
1.60 HDO
1.41
-0.00
BocHN
O
N
Boc-Phg-NMe2
S5
1H NMR, 600 MHz, CDCl3
4.73
0.92
0.90
3.00
3.01
9.12
f1 (ppm)

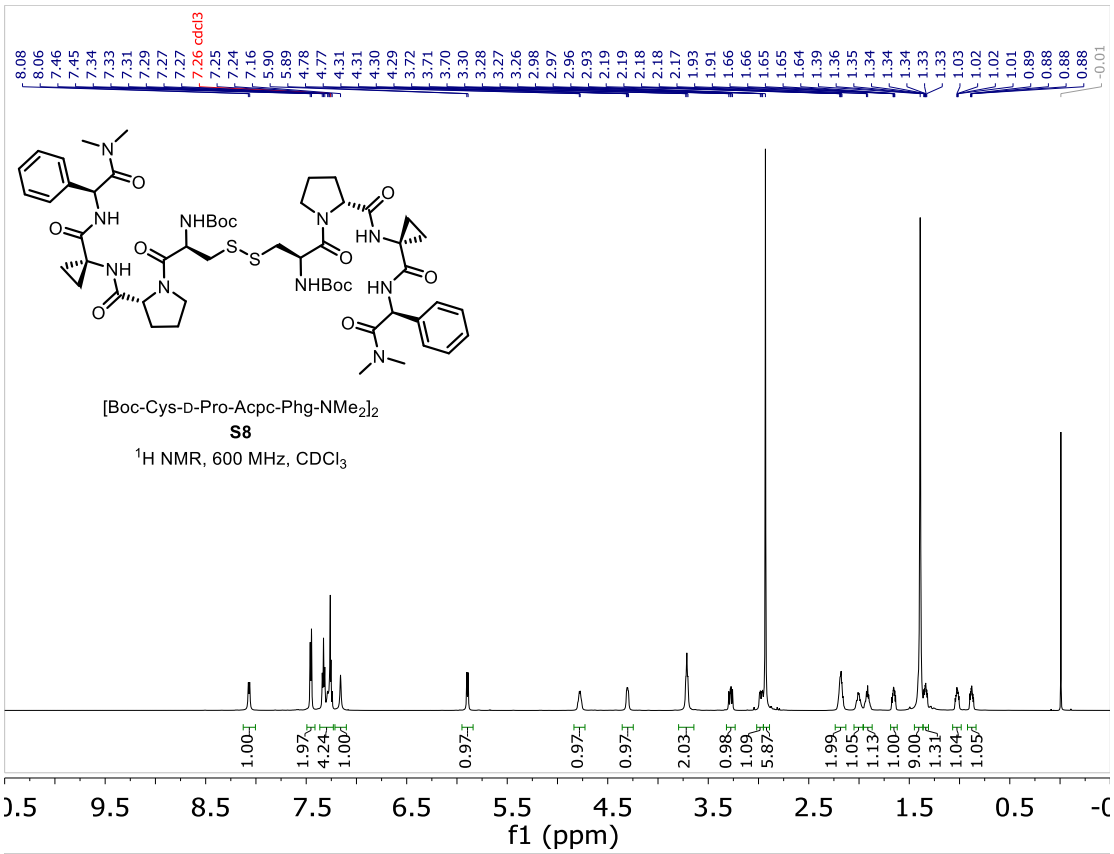

BocHN
O
N
Boc-Phg-NMe2
S5
13C NMR, 151 MHz, CDCl3
170.18
155.20
138.11
129.12
128.28
127.86
79.78
77.37 cdcl3
77.16 cdcl3
76.95 cdcl3
55.30
37.04
36.12
28.52
0.15
f1 (ppm)

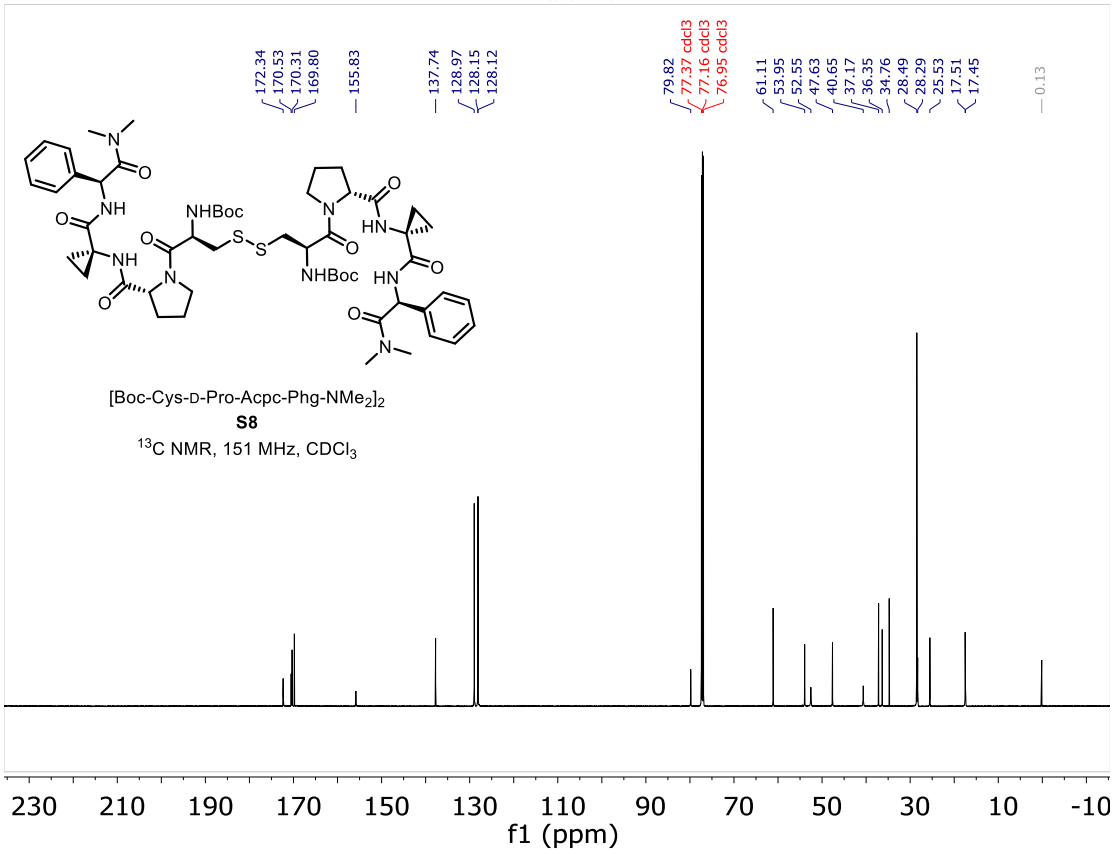

Boc-D-Pro-Acpc-OH
S6
1H NMR, 600 MHz, methanol-d4
f1 (ppm)

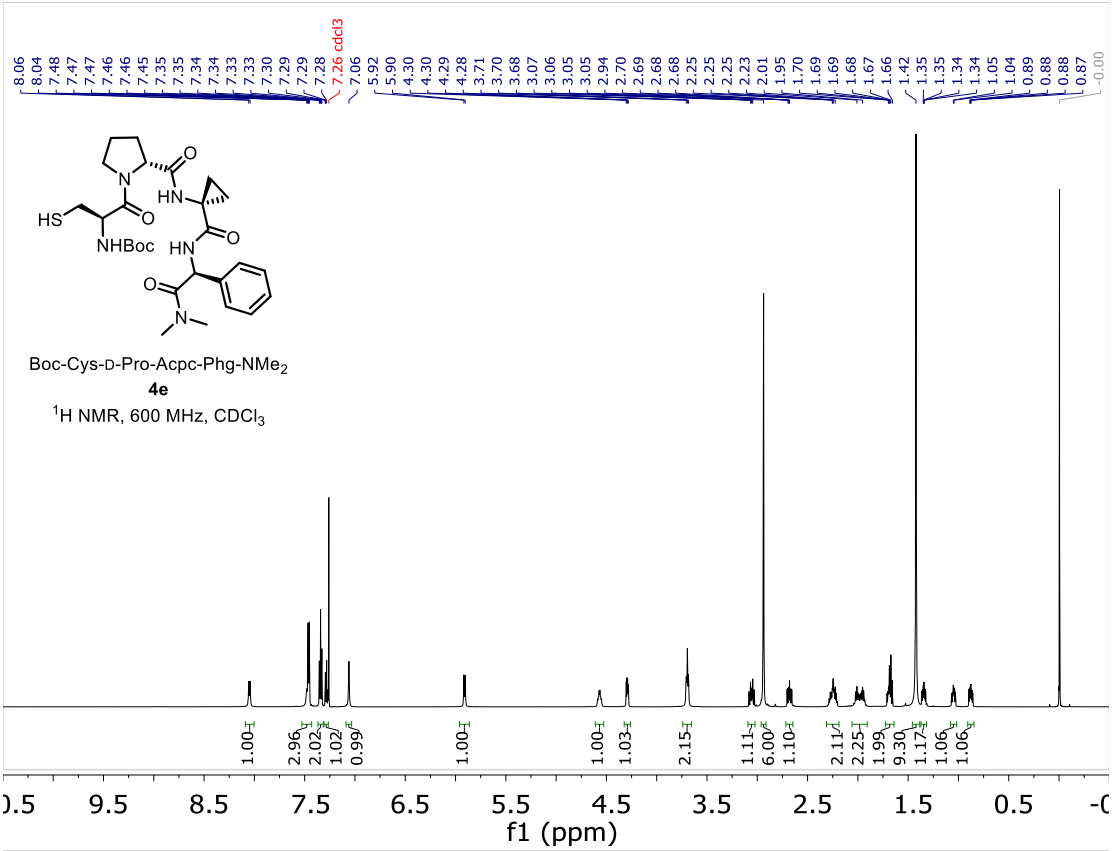

Boc-D-Pro-Acpc-OH
S6
13C NMR, 151 MHz, methanol-d4
f1 (ppm)

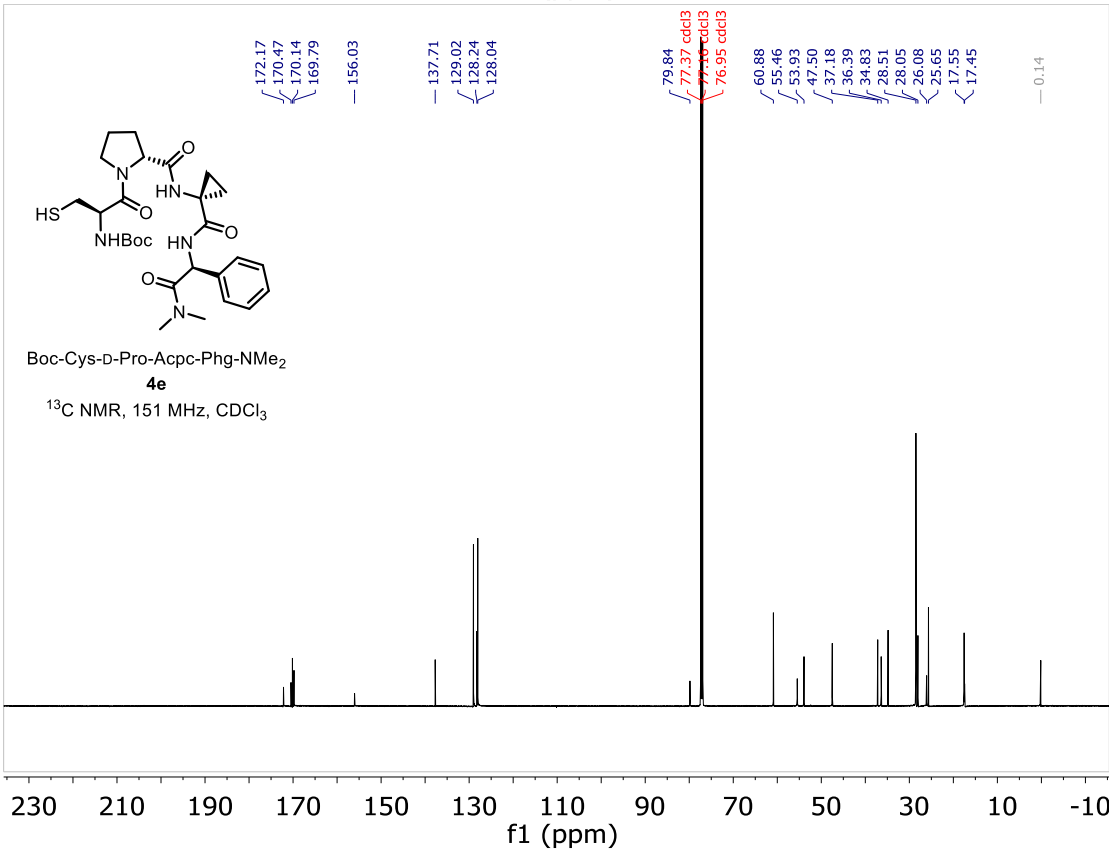

Boc-D-Pro-Acpc-Phg-NMe2
S7
1H NMR, 600 MHz, methanol-d4
f1 (ppm)


Boc-D-Pro-Acpc-Phg-NMe2
S7
13C NMR, 151 MHz, methanol-d4
f1 (ppm)

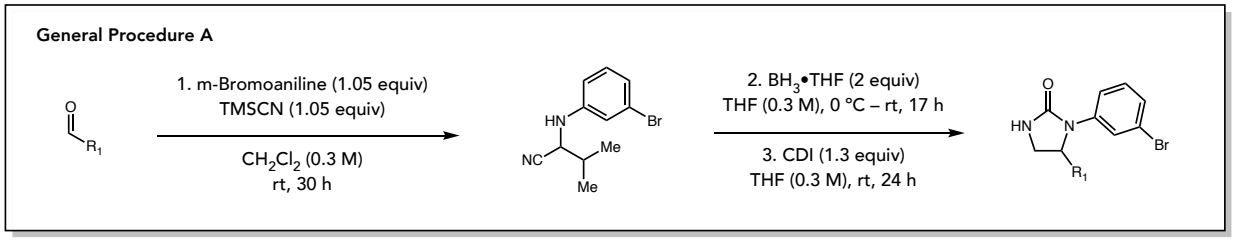

[Boc-Cys-D-Pro-Acpc-Phg-NMe2]2
S8
1H NMR, 600 MHz, CDCl3
f1 (ppm)


[Boc-Cys-D-Pro-Acpc-Phg-NMe2]2
S8
13C NMR, 151 MHz, CDCl3
f1 (ppm)


Boc-Cys-D-Pro-Acpc-Phg-NMe2
4e
1H NMR, 600 MHz, CDCl3
f1 (ppm)


Boc-Cys-D-Pro-Acpc-Phg-NMe2
4e
13C NMR, 151 MHz, CDCl3
f1 (ppm)

Synthesis of Substrates



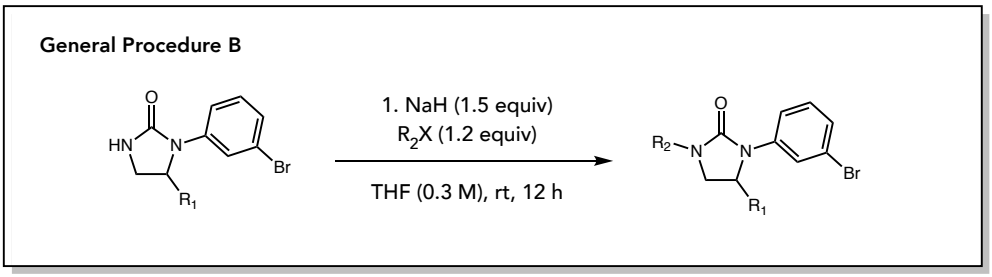
General procedure A:

This procedure was adapted and modified from previous reports (*34–35*).

To a 1 L round bottom flask were added the corresponding aldehyde (100 mmol, 1.0 equiv), 3-bromoaniline (11.4 mL, 105 mmol, 1.05 equiv), and $MgSO_4$ (~2.0 g) in CH_2Cl_2 (333 ml). The reaction mixture was stirred for 30 minutes at room temperature, followed by addition of trimethylsilyl cyanide (14.1 mL, 105 mmol, 1.05 equiv). The reaction was stirred for additional 30 hours at room temperature. Then, 6 *N* NaOH (aq) was added until the solution reaches pH of 13.5. The aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The resulting crude mixture was carried to the next step without further purification.

To an oven dried 1 L round bottom flask was added the crude starting material from the previous step in tetrahydrofuran (333 mL). The reaction vessel was evacuated and backfilled with argon three times. After the reaction was cooled down to 0 °C, borane tetrahydrofuran complex (1 M in THF, 200 mL, 200 mmol, 2.0 equiv) was added dropwise *via* cannula under an argon atmosphere, and the reaction was stirred for 17 hours as it warmed up to room temperature. Then, the reaction was quenched with water at 0 °C, and tetrahydrofuran was evaporated *in vacuo*. To the residual slurry of reaction mixture, 400 mL of 6 *N* HCl (aq) was added. The reaction was then stirred for 4 hours at 90 °C. Upon cooling to 0 °C, the reaction was neutralized with solid sodium hydroxide pellets, extracted with CH_2Cl_2 for three times, and concentrated. The crude oil was carried to the next step without further purification.

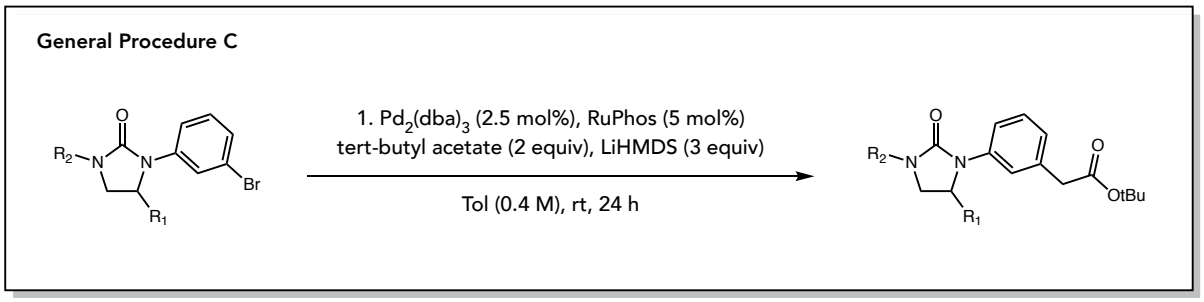
To a 1 L round bottom flask were added the crude starting material and carbonyldiimidazole (CDI, 21.1 g, 130 mmol, 1.3 equiv) in tetrahydrofuran (333 mL). The reaction mixture was stirred for 24 hours at room temperature. Then, the reaction was diluted with CH_2Cl_2, washed with 1*N* HCl (aq) three times, washed with brine, dried over $MgSO_4$, and concentrated. The crude oil was dissolved in minimal volume of hot ethyl acetate and slowly cooled down to –20 °C over 12 hours. The precipitate was isolated by vacuum filtration, and the filtrate was recrystallized with hot ethyl acetate again. Two rounds of recrystallization afforded the desired imidazolidinone product.



General procedure B:

The procedure was adapted and modified from a previous report (*36*).

To a 250 mL round bottom flask was added the corresponding imidazolidinone starting material (20.0 mmol, 1.0 equiv) in tetrahydrofuran (67 mL). The reaction was cooled to 0 °C, followed by addition of sodium hydride (60% dispersion in mineral oil, 1.20 g, 30.0 mmol, 1.5 equiv) and 30 minutes of stirring. Then, the corresponding alkyl halide (24.0 mmol, 1.2 equiv) was added, and the reaction mixture was allowed to warm up to room temperature as it was stirred for 12 hours. Then, the reaction was quenched with water at 0 °C and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate twice. The combined organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel flash column chromatography or carried to the next step without further purification.



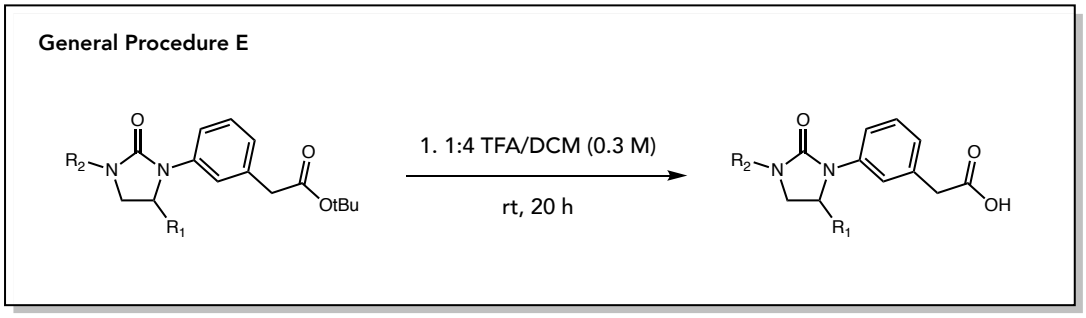
General procedure C:

The procedure was adapted and modified from a previous report. (*37*)

To a 250 mL round bottom flask were added the corresponding bromide starting material (20.0 mmol, 1.0 equiv), tris(dibenzylideneacetone)dipalladium(0) (458 mg, 0.50 mmol, 2.5 mol%), 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (RuPhos, 527 mg, 1.00 mmol, 5 mol%), and lithium bis(trimethylsilyl)amide (10.0 g, 60.0 mmol, 3.0 equiv). The reaction vessel was evacuated and backfilled with argon three times, followed by addition of toluene (50 mL) and *tert*-butyl acetate (5.36 mL, 40.0 mmol, 2.0 equiv). The reaction was stirred at room temperature under argon atmosphere for 24 hours. Then, the crude reaction was quenched with sat. NH_4Cl (aq), washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford the crude ester product, which was then purified by silica gel flash column chromatography or carried to the next step without further purification.

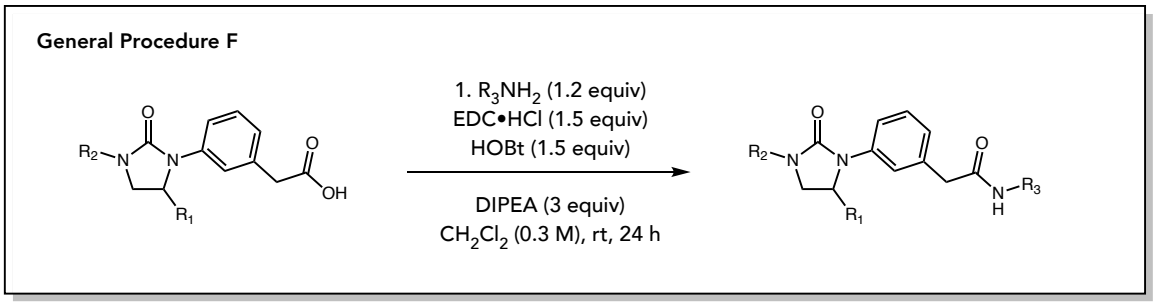
General procedure D:

The corresponding ester product (20.0 mmol, 1.0 equiv) was dissolved in water (25 mL) and methanol (25 mL), where lithium hydroxide (4.79 g, 200 mmol, 10 equiv) was added. The reaction was stirred for 24 hours at room temperature. Under reduced pressure, methanol was evaporated, leaving a slurry of crude reaction mixture with water. The aqueous mixture was then washed with CH_2Cl_2 twice, acidified with 3*N* HCl (aq), and extracted with CH_2Cl_2 three times. The combined organic layer was then dried over $MgSO_4$ and concentrated to afford the desired carboxylic acid product, which was carried to the next step without further purification.



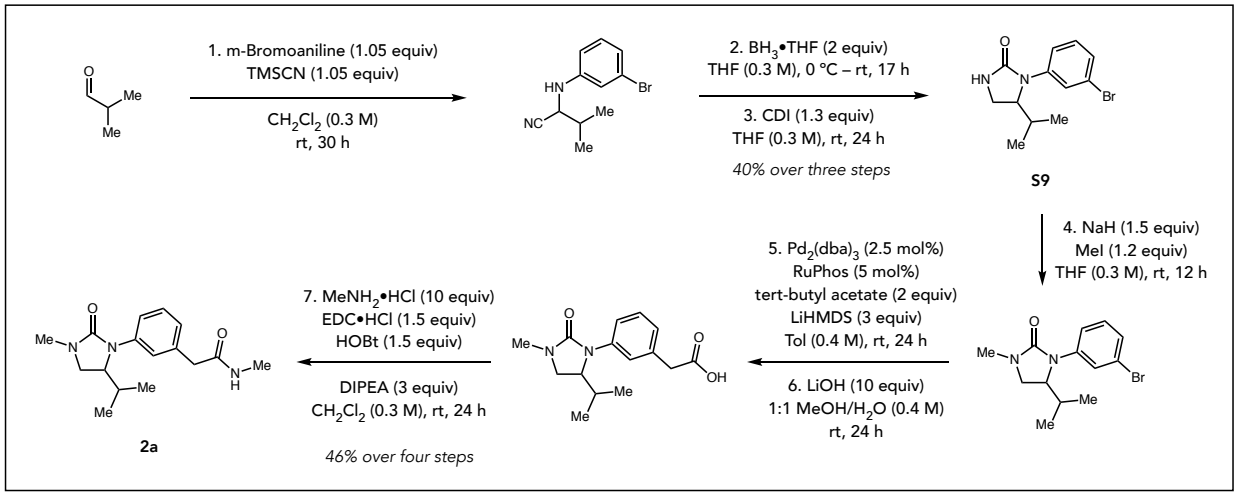
General procedure E:

The corresponding ester product (20 mmol, 1.0 equiv) was dissolved in trifluoroacetic acid (13 mL) and CH_2Cl_2 (53 mL). The reaction was stirred for 20 hours at room temperature, then diluted with water. The aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layer was then dried over $MgSO_4$ and concentrated to afford the desired carboxylic acid product, which was carried to the next step without further purification.

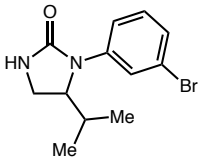


General procedure F:

To a 250 mL round bottom flask were added the corresponding carboxylic acid starting material (20.0 mmol, 1.0 equiv), *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (5.74 g, 30.0 mmol, 1.5 equiv), 1-hydroxybenzotriazole (4.60 g, 30.0 mmol, 1.5 equiv), corresponding amine (24.0 mmol, 1.2 equiv), and *N*,*N*-diisopropylethylamine (10.5 mL, 60.0 mmol, 3.0 equiv) in CH_2Cl_2 (67 mL). The reaction was stirred for 24 hours at room temperature, then washed with 10% citric acid (aq), sat. $NaHCO_3$ (aq), and brine. The organic layer was dried over $MgSO_4$, concentrated, and purified by silica gel flash column chromatography to afford the desired amide product.



1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (S9):



The title imidazolidinone was synthesized following the general procedure A described above with isobutyraldehyde (9.13 mL, 100 mmol). Two rounds of recrystallization afforded 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 11.45 g, 40.4 mmol, 40 % yield over three steps) as a white crystalline solid.

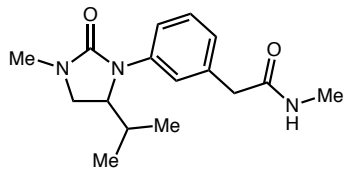
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.58 (m, 1H), 7.40–7.33 (m, 1H), 7.26–7.14 (m, 2H), 4.80 (s, 1H), 4.36 (ddd, *J* = 9.5, 5.6, 3.7 Hz, 1H), 3.53 (td, *J* = 9.3, 1.2 Hz, 1H), 3.34 (ddd, *J* = 8.9, 5.5, 1.1 Hz, 1H), 2.22–2.10 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 139.8, 130.3, 127.1, 124.8, 122.7, 120.6, 60.5, 38.0, 27.7, 18.0, 14.4.

IR (FT-ATR, cm^{-1}) ν_{max} 3250, 3111, 2960, 1702, 1590, 1565, 1479, 1407, 1389, 1372, 1320, 1254, 1152, 1116, 1072, 1023, 993, 973, 869, 774, 711, 683.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{12}H_{16}BrN_2O^+$ requires 283.0, observed 283.0.

2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (2a):



2a

The intermediate 3-(3-bromophenyl)-4-isopropyl-1-methylimidazolidin-2-one was synthesized following the general procedure B described above with 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 5.32 g, 18.8 mmol, 1.0 equiv) and methyl iodide (1.41 mL, 22.6 mmol, 1.2 equiv). The resultant orange solid was carried to the next step without further purification.

The intermediate 2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedures C and D described above with the crude product from the previous step. The crude white solid was carried to the next step without further purification.

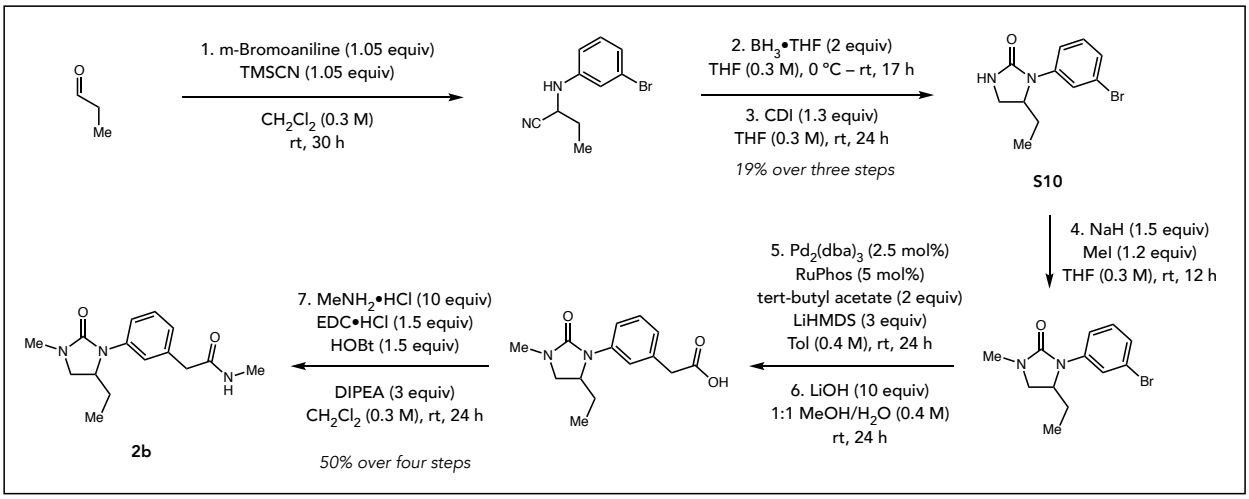
The title amide was synthesized following the general procedure F with methylamine hydrochloride (12.7 g, 188 mmol, 10 equiv). Purification by silica gel flash column chromatography (0–5% MeOH in CH_2Cl_2) afforded 2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (**2a**, 2.50 g, 8.64 mmol, 46% yield over four steps) as pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 3H), 7.04 – 6.86 (m, 1H), 5.50 (s, 1H), 4.26 (ddd, J = 9.5, 5.6, 3.7 Hz, 1H), 3.56 (s, 2H), 3.43 (t, J = 9.3 Hz, 1H), 3.22 (dd, J = 9.0, 5.7 Hz, 1H), 2.87 (s, 3H), 2.74 (d, J = 4.8 Hz, 3H), 2.21 – 2.11 (m, 1H), 0.90 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.8 Hz, 3H).

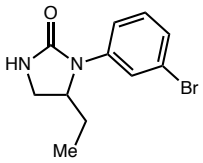
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 158.6, 139.6, 135.7, 129.6, 124.8, 122.9, 120.5, 57.4, 45.0, 44.0, 31.0, 27.5, 26.7, 18.1, 14.4.

IR (FT-ATR, cm^{-1}) ν_{max} 3302, 2959, 1674, 1604, 1556, 1494, 1435, 1404, 1383, 1326, 1269, 1161, 1112, 770, 694.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{16}H_{24}N_3O_2^+$ requires 290.18630, observed 290.18652, difference 0.76 ppm.



1-(3-bromophenyl)-5-ethylimidazolidin-2-one (S10):



S10

The title imidazolidinone was synthesized following the general procedure A described above with propionaldehyde (1.43 mL, 20.0 mmol). Two rounds of recrystallization afforded 1-(3-bromophenyl)-5-ethylimidazolidin-2-one (**S10**, 1.05 g, 3.92 mmol, 19% yield over three steps) as a white crystalline solid.

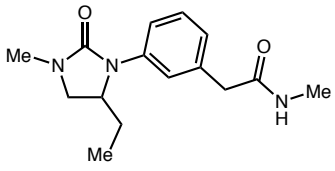
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.60 (m, 1H), 7.45 – 7.31 (m, 1H), 7.25 – 7.16 (m, 2H), 4.74 (s, 1H), 4.37 – 4.25 (m, 1H), 3.68 (td, *J* = 8.8, 1.1 Hz, 1H), 3.26 (dd, *J* = 8.6, 5.3 Hz, 1H), 1.83 – 1.69 (m, 1H), 1.69 – 1.58 (m, 1H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 139.9, 130.3, 126.9, 124.2, 122.7, 119.9, 57.2, 42.6, 24.9, 8.4.

IR (FT-ATR, cm^{-1}) ν_{max} 3254, 2965, 1705, 1591, 1480, 1432, 1314, 1250, 1150, 774, 683.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{11}H_{14}BrN_2O^+$ requires 269.0, observed 269.0.

2-(3-(5-ethyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (2b):



2b

The intermediate 3-(3-bromophenyl)-4-ethyl-1-methylimidazolidin-2-one was synthesized following the general procedure B described above with 1-(3-bromophenyl)-5-ethylimidazolidin-2-one (**S10**, 1.05 g, 3.92 mmol, 1.0 equiv) and methyl iodide (0.29 ml, 4.70 mmol, 1.2 equiv). The resultant pale yellow oil was carried to the next step without further purification.

The intermediate 2-(3-(5-ethyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedures C and D described above with the crude product from the previous step. The crude pale-yellow solid was carried to the next step without further purification.

The title amide was synthesized following the general procedure F with methylamine hydrochloride (2.65 g, 39.2 mmol, 10 equiv). Purification by silica gel flash column chromatography (0–10% MeOH in CH_2Cl_2) afforded 2-(3-(5-ethyl-3-methyl-2-oxoimidazolidin-

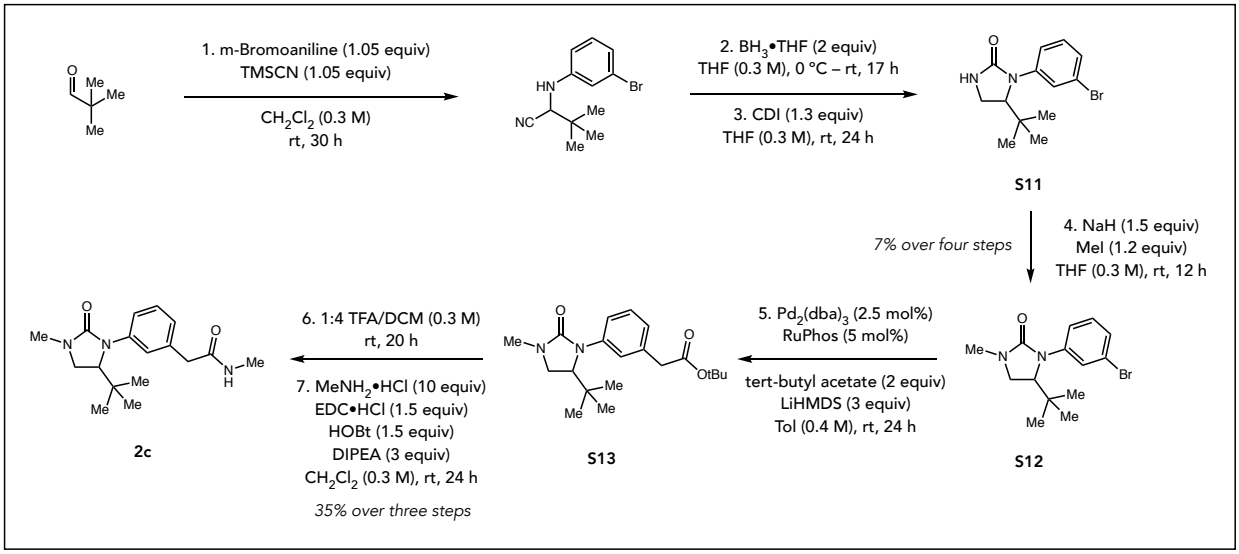
1-yl)phenyl)-*N*-methylacetamide (**2b**, 539 mg, 1.96 mmol, 50% yield over four steps) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 1H), 7.36 – 7.25 (m, 2H), 7.00 – 6.92 (m, 1H), 5.49 (s, 1H), 4.19 (tdd, *J* = 8.6, 5.5, 2.8 Hz, 1H), 3.62 – 3.53 (m, 3H), 3.16 (dd, *J* = 8.7, 5.6 Hz, 1H), 2.88 (s, 3H), 2.74 (d, *J* = 4.9 Hz, 3H), 1.81 – 1.69 (m, 1H), 1.63 – 1.50 (m, 1H), 0.88 (t, *J* = 7.5 Hz, 3H).

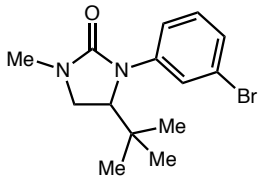
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 158.5, 139.7, 135.7, 129.6, 129.6, 124.6, 122.2, 119.8, 54.1, 49.6, 44.0, 31.2, 26.7, 25.0, 8.5.

IR (FT-ATR, cm^{-1}) ν_{max} 3304, 2932, 2360, 1690, 1654, 1604, 1585, 1554, 1493, 1435, 1404, 1376, 1325, 1271, 1161, 1108, 844, 755, 696.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{15}H_{22}N_3O_2^+$ requires 276.17065, observed 276.17023, difference 1.52 ppm.



3-(3-bromophenyl)-4-(tert-butyl)-1-methylimidazolidin-2-one (S12):



S12

The intermediate 1-(3-bromophenyl)-5-(tert-butyl)imidazolidin-2-one (**S11**) was synthesized following the general procedure A described above with 2,2-dimethylpropanal (2.72 mL, 25.0 mmol). Instead of recrystallization, the crude product was purified by silica gel flash column chromatography (0–60% EtOAc in hexanes) to afford 789 mg of the desired intermediate **S11** with minor impurities, which was then carried to the next step without further purification.

The title compound was synthesized following the general procedure B described above with the obtained intermediate **S11** and methyl iodide (0.21 mL, 3.3 mmol). Purification by silica gel flash column chromatography (0–40% EtOAc in hexanes) afforded 3-(3-bromophenyl)-4-(tert-butyl)-1-methylimidazolidin-2-one (**S12**, 0.497 g, 1.67 mmol, 7% yield over four steps) as pale yellow solid.

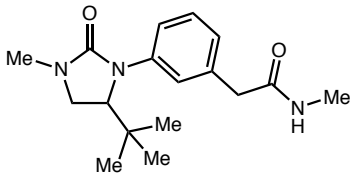
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (t, *J* = 2.0 Hz, 1H), 7.34 (ddd, *J* = 8.0, 2.1, 1.2 Hz, 1H), 7.25 – 7.15 (m, 2H), 4.07 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.50 (t, *J* = 9.4 Hz, 1H), 3.27 (dd, *J* = 9.3, 4.1 Hz, 1H), 2.84 (s, 3H), 0.81 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.90, 142.80, 130.02, 127.62, 127.04, 122.88, 122.27, 61.88, 47.22, 36.52, 30.93, 26.25.

IR (FT-ATR, cm^{-1}) ν_{max} 2960.18, 1700.08, 1590.42, 1565.91, 1497.84, 1479.54, 1429.75, 1402.82, 1366.76, 1286.40, 1253.19, 1213.09, 1121.45, 994.26, 862.74, 774.45, 739.41, 685.12.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{14}H_{20}BrN_2O^+$ requires 311.1, observed 311.1.

2-(3-(5-(*tert*-butyl)-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (2c):



2c

The intermediate tert-butyl 2-(3-(5-(tert-butyl)-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetate (**S13**) was synthesized following the general procedure C described above with 3-(3-bromophenyl)-4-(tert-butyl)-1-methylimidazolidin-2-one (**S12**, 0.490 g, 1.57 mmol) as the starting material. Purification by silica gel flash column chromatography (0–50% EtOAc in hexanes) afforded a mixture of the desired intermediate **S13** with impurities, which was then carried to the next step without further purification.

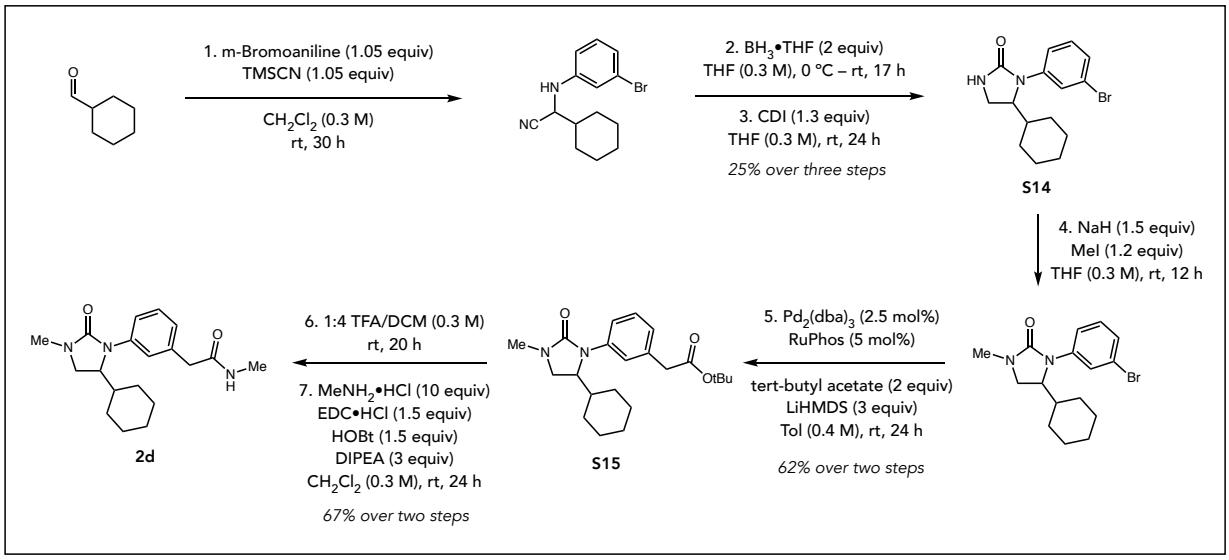
The title amide was synthesized following the general procedure E and F with methylamine hydrochloride (1.06 g, 15.7 mmol, 10 equiv). Purification by silica gel flash column chromatography (0–80% acetone in hexanes) afforded 2-(3-(5-(*tert*-butyl)-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (**2c**, 167 mg, 0.55 mmol, 35% yield over three steps) as pale yellow foamy solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, MeOD) δ 7.38 – 7.21 (m, 3H), 7.11 (dt, *J* = 7.3, 1.6 Hz, 1H), 4.25 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.59 (t, *J* = 9.7 Hz, 1H), 3.49 (s, 2H), 3.39 (dd, *J* = 9.6, 4.9 Hz, 1H), 2.82 (s, 3H), 2.71 (s, 3H), 0.80 (s, 9H).

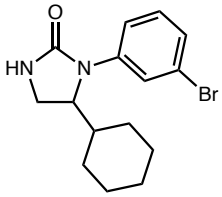
^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.55, 159.41, 142.02, 135.46, 129.57, 125.93, 125.57, 123.46, 61.96, 47.35, 43.86, 36.42, 30.98, 26.68, 26.24.

IR (FT-ATR, cm^{-1}) ν_{max} 3303.95, 2956.94, 1688.38, 1654.74, 1604.55, 1557.54, 1490.97, 1436.99, 1405.67, 1367.75, 1336.15, 1266.09, 1214.69, 1116.26, 755.87, 693.00.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{26}N_3O_2^+$ requires 304.20195, observed 304.20242, difference 1.55 ppm.



1-(3-bromophenyl)-5-cyclohexylimidazolidin-2-one (S14):



S14

The title imidazolidinone was synthesized following the general procedure A described above with cyclohexanecarboxaldehyde (2.42 ml, 20.0 mmol). Two rounds of recrystallization afforded 1-(3-bromophenyl)-5-cyclohexylimidazolidin-2-one (**S14**, 1.61 g, 5.00 mmol, 25% yield over three steps) as a white crystalline solid.

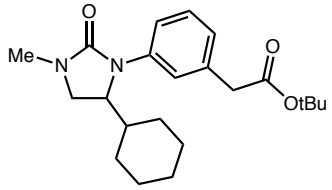
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 1H), 7.42 – 7.34 (m, 1H), 7.27 – 7.20 (m, 2H), 4.84 (s, 1H), 4.33 (ddd, *J* = 9.3, 5.1, 3.7 Hz, 1H), 3.60 – 3.47 (m, 1H), 3.41 (dd, *J* = 8.9, 5.2 Hz, 1H), 1.87 – 1.50 (m, 6H), 1.32 – 0.95 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 140.0, 130.2, 127.0, 124.8, 122.7, 120.4, 60.3, 39.2, 38.2, 28.7, 26.5, 26.2, 25.7, 25.1.

IR (FT-ATR, cm^{-1}) ν_{max} 3228, 3109, 2927, 2852, 2360, 1699, 1591, 1566, 1480, 1445, 1408, 1345, 1314, 1253, 1148, 1071, 993, 975, 862, 775, 756, 737, 682.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{15}H_{20}BrN_2O^+$ requires 323.1, observed 323.1.

***tert*-butyl 2-(3-(5-cyclohexyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetate (S15):**



S15

The intermediate 3-(3-bromophenyl)-4-cyclohexyl-1-methylimidazolidin-2-one was synthesized following the general procedure B described above with 1-(3-bromophenyl)-5-cyclohexylimidazolidin-2-one (**S14**, 1.61 g, 5.00 mmol, 1.0 equiv) and methyl iodide (0.37 ml, 6.00 mmol, 1.2 equiv). The resultant white solid was carried to the next step without further purification.

The title ester was synthesized following the general procedure C described above with the crude product from the previous step. Purification by silica gel flash column chromatography (0–50% EtOAc in hexanes) afforded *tert*-butyl 2-(3-(5-cyclohexyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetate (**S15**, 1.15 g, 3.10 mmol, 62% yield over two steps) as a brown oil.

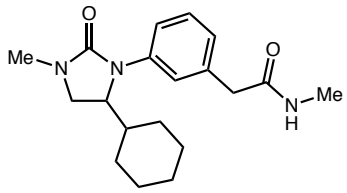
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.25 (m, 3H), 7.01 – 6.96 (m, 1H), 4.19 (ddd, *J* = 9.2, 5.2, 3.7 Hz, 1H), 3.51 (s, 2H), 3.41 (t, *J* = 9.2 Hz, 1H), 3.25 (dd, *J* = 8.9, 5.2 Hz, 1H), 2.85 (s, 3H), 1.83 – 0.86 (m, 11H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 158.7, 139.22, 135., 129.0, 124.5, 122.3, 120.3, 57.3, 46.2, 43.0, 38.1, 31.1, 28.7, 28.2, 26.6, 26.3, 25.7, 25.0.

IR (FT-ATR, cm^{-1}) ν_{max} 2926, 2853, 1705, 1604, 1587, 1494, 1449, 1432, 1402, 1367, 1264, 1142, 1032, 952, 839, 773, 753, 694.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{22}H_{33}N_2O_3^+$ requires 373.2, observed 373.2.

2-(3-(5-cyclohexyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (2d):



2d

The intermediate 2-(3-(5-cyclohexyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedure E described above with *tert*-butyl 2-(3-(5-cyclohexyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetate (**S15**, 1.15 g, 3.10 mmol, 1.0 equiv). The crude pale orange solid was carried to the next step without further purification.

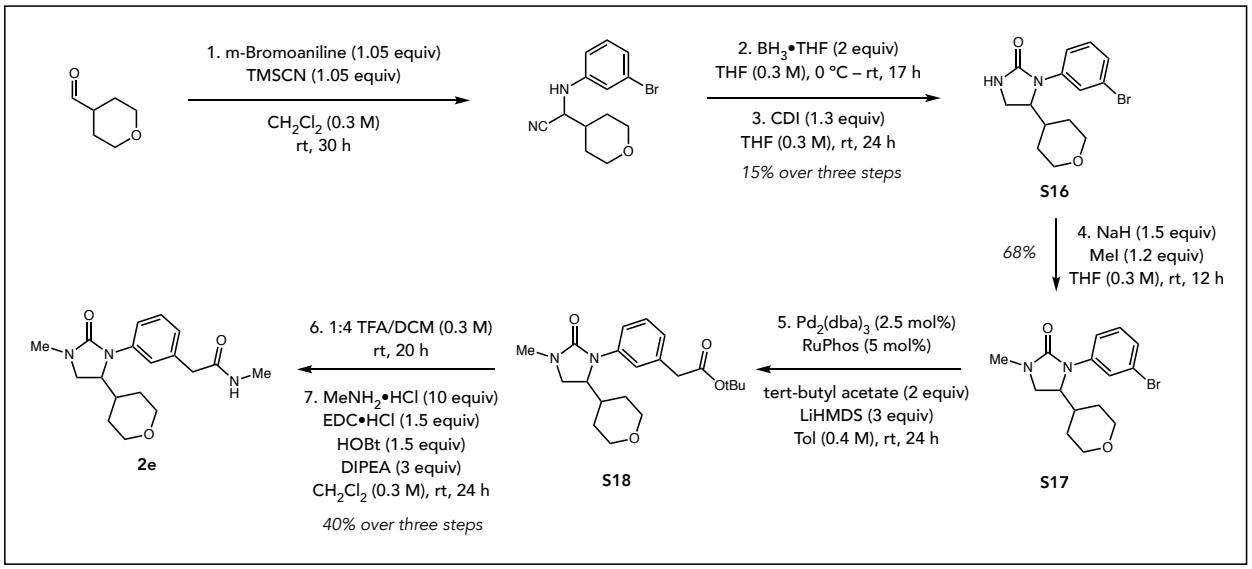
The title amide was synthesized following the general procedure F with methylamine hydrochloride (2.10 g, 31.0 mmol, 10 equiv). Purification by silica gel flash column chromatography (0–70% acetone in hexanes) afforded 2-(3-(5-cyclohexyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (**2d**, 683 mg, 2.08 mmol, 67% yield over two steps) as a pale yellow foamy solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 3H), 6.99 – 6.92 (m, 1H), 5.46 (s, 1H), 4.20 (ddd, *J* = 9.4, 5.4, 3.8 Hz, 1H), 3.58 (s, 2H), 3.43 (t, *J* = 9.3 Hz, 1H), 3.27 (dd, *J* = 9.0, 5.3 Hz, 1H), 2.86 (s, 3H), 2.74 (d, *J* = 4.8 Hz, 3H), 1.80 – 1.62 (m, 4H), 1.59 – 1.48 (m, 2H), 1.23 – 0.88 (m, 5H).

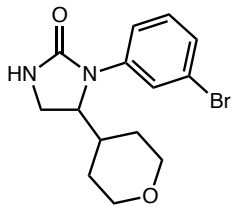
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 158.6, 139.8, 135.6, 129.7, 124.7, 122.7, 120.3, 57.1, 46.2, 44.1, 38.1, 31.0, 28.7, 26.7, 26.5, 26.3, 25.7, 25.1.

IR (FT-ATR, cm^{-1}) ν_{max} 3306, 2925, 2853, 1690, 1654, 1604, 1585, 1553, 1493, 1439, 1404, 1368, 1326, 1269, 1164, 1114, 844, 752, 696.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{19}H_{28}N_3O_2^+$ requires 330.21760, observed 330.21825, difference 1.97 ppm.



1-(3-bromophenyl)-5-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-2-one (S16):



S16

The title imidazolidinone was synthesized following the general procedure A described above with tetrahydropyran-4-carbaldehyde (2.85 g, 25.0 mmol). Two rounds of recrystallization afforded 1-(3-bromophenyl)-5-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-2-one (**S16**, 1.19 g, 3.66 mmol, 15% yield over three steps) as grey solid.

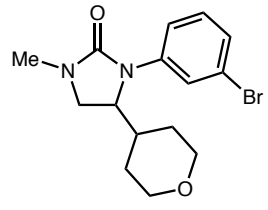
^{1}H NMR ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (t, *J* = 1.9 Hz, 1H), 7.37 (dt, *J* = 7.7, 1.8 Hz, 1H), 7.26 – 7.17 (m, 2H), 4.64 (s, 1H), 4.37 (dt, *J* = 9.1, 4.4 Hz, 1H), 3.98 (td, *J* = 13.1, 12.1, 4.3 Hz, 2H), 3.60 (td, *J* = 9.2, 1.3 Hz, 1H), 3.42 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.33 (td, *J* = 11.2, 3.5 Hz, 1H), 3.21 (td, *J* = 11.7, 2.5 Hz, 1H), 2.12 – 1.96 (m, 1H), 1.51 – 1.35 (m, 4H).

^{13}C NMR ^{13}C NMR (126 MHz, CDl_3) δ 159.30, 139.70, 130.41, 127.27, 124.63, 122.85, 120.35, 67.71, 67.65, 59.40, 39.12, 35.85, 28.32, 25.32.

IR (FT-ATR, cm^{-1}) ν_{max} 3287.38, 2933.12, 2845.67, 1700.83, 1590.61, 1565.33, 1479.34, 1427.35, 1359.70, 1317.25, 1253.58, 1237.76, 1139.05, 1087.71, 1014.76, 993.37, 983.96, 854.33, 823.27, 775.71, 758.19, 706.23, 683.39.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{14}H_{18}BrN_2O_2^+$ requires 325.1, observed 325.1.

3-(3-bromophenyl)-1-methyl-4-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-2-one (S17):



S17

The title compound was synthesized following the general procedure B described above with 1-(3-bromophenyl)-5-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-2-one (**S16**, 0.950 g, 3.35 mmol, 1.0 equiv) and methyl iodide (0.25 ml, 4.03 mmol, 1.2 equiv). Purification with silica gel flash column chromatography (0–70% EtOAc in hexanes) afforded 3-(3-bromophenyl)-1-methyl-4-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-2-one (**S17**, 0.774 g, 2.28 mmol, 68%) as a white solid.

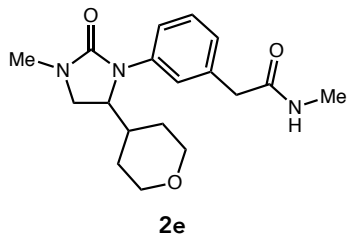
^{1}H NMR ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.63 (m, 1H), 7.41 – 7.35 (m, 1H), 7.24 – 7.18 (m, 2H), 4.24 (dt, *J* = 9.1, 4.3 Hz, 1H), 4.06 – 3.89 (m, 2H), 3.48 (t, *J* = 9.3 Hz, 1H), 3.38 – 3.28 (m, 2H), 3.28 – 3.15 (m, 1H), 2.87 (s, 3H), 2.12 – 1.99 (m, 1H), 1.49 – 1.31 (m, 4H).

^{13}C NMR ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.80, 140.19, 130.17, 126.48, 123.77, 122.66, 119.41, 67.57, 67.52, 56.12, 45.74, 35.44, 30.84, 28.17, 25.04.

IR (FT-ATR, cm^{-1}) ν_{max} 2952.60, 2927.75, 2847.25, 1686.63, 1593.22, 1566.50, 1497.56, 1482.48, 1438.81, 1427.21, 1400.84, 1387.88, 1372.24, 1356.50, 1336.74, 1318.35, 1291.79, 1270.58, 1257.17, 1235.18, 1211.82, 1141.41, 1108.95, 1088.44, 1071.80, 1008.46, 992.94, 916.77, 885.64, 865.26, 851.43, 803.65, 767.29, 751.72, 723.58, 683.39.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{15}H_{20}BrN_2O_2^+$ requires 339.1, observed 339.1.

N-methyl-2-(3-(3-methyl-2-oxo-5-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-1-yl)phenyl)acetamide (2e):



2e

The intermediate tert-butyl 2-(3-(3-methyl-2-oxo-5-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)phenyl)acetate (**S18**) was synthesized following the general procedure C described above with 3-(3-bromophenyl)-1-methyl-4-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-2-one (**S17**, 0.770 g, 2.27 mmol) as the starting material. Purification by silica gel flash column chromatography (0–70% EtOAc in hexanes) afforded a mixture of the desired intermediate **S13** with impurities, which was then carried to the next step without further purification.

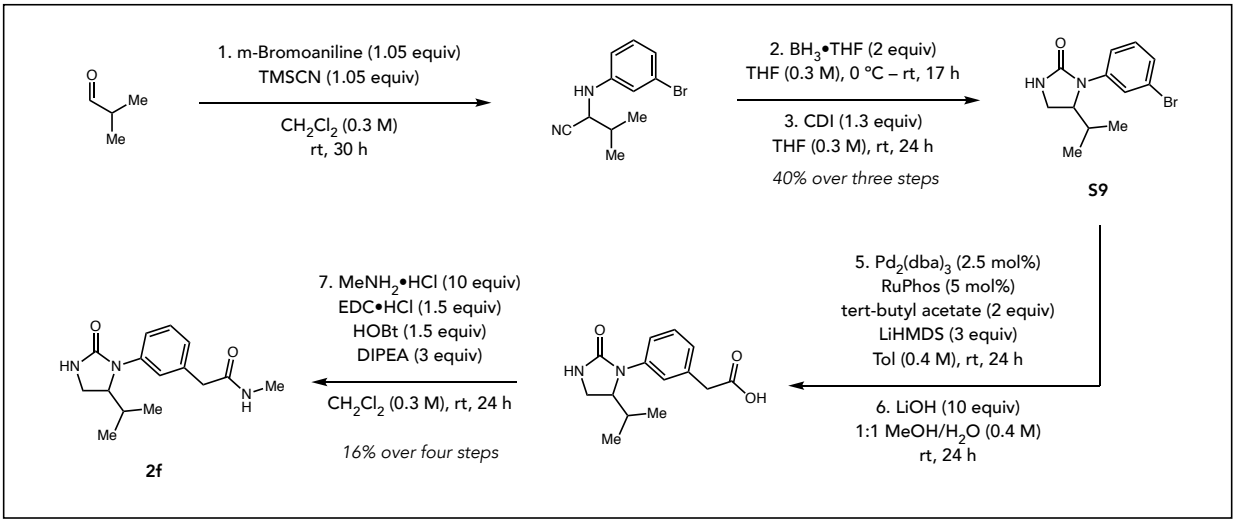
The title amide was synthesized following the general procedure E and F with methylamine hydrochloride (1.53 g, 22.7 mmol, 10 equiv). Purification by silica gel flash column chromatography (0–80% acetone in hexanes) afforded *N*-methyl-2-(3-(3-methyl-2-oxo-5-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-1-yl)phenyl)acetamide (**2e**, 303 mg, 0.914 mmol, 40% yield over three steps) as pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 3H), 7.04 – 6.92 (m, 1H), 5.47 (s, 1H), 4.27 (dt, *J* = 9.3, 4.6 Hz, 1H), 4.04 – 3.88 (m, 2H), 3.57 (s, 2H), 3.48 (t, *J* = 9.3 Hz, 1H), 3.38 – 3.26 (m, *J* = 3.5 Hz, 2H), 3.26 – 3.12 (m, 1H), 2.87 (s, 3H), 2.75 (d, *J* = 4.8 Hz, 3H), 2.05 (ddq, *J* = 15.7, 9.9, 4.8 Hz, 1H), 1.49 – 1.28 (m, 4H).

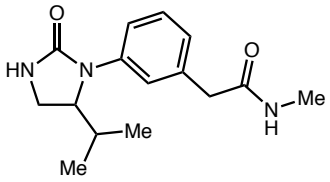
^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.49, 158.46, 139.53, 135.85, 129.76, 124.95, 122.57, 120.27, 67.73, 67.71, 56.37, 46.08, 44.01, 35.74, 31.03, 28.34, 26.71, 25.32

IR (FT-ATR, cm^{-1}) ν_{max} 3305.65, 2937.65, 2850.32, 1687.86, 1653.93, 1604.42, 1585.64, 1556.68, 1493.97, 1438.00, 1405.96, 1390.33, 1370.86, 1324.91, 1276.31, 1239.36, 1145.87, 1099.88, 1011.18, 984.76, 917.99, 852.85, 752.94, 692.79.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{18}H_{26}N_3O_3^+$ requires 332.19687, observed 332.19672, difference 0.45 ppm.



2-(3-(5-isopropyl-2-oxoimidazolidin-1-yl)phenyl)-N-methylacetamide (2f):



2f

The intermediate 2-(3-(5-isopropyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedures C and D described above with 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 1.00 g, 3.53 mmol, 1.0 equiv). The crude pale yellow foamy solid was carried to the next step without further purification.

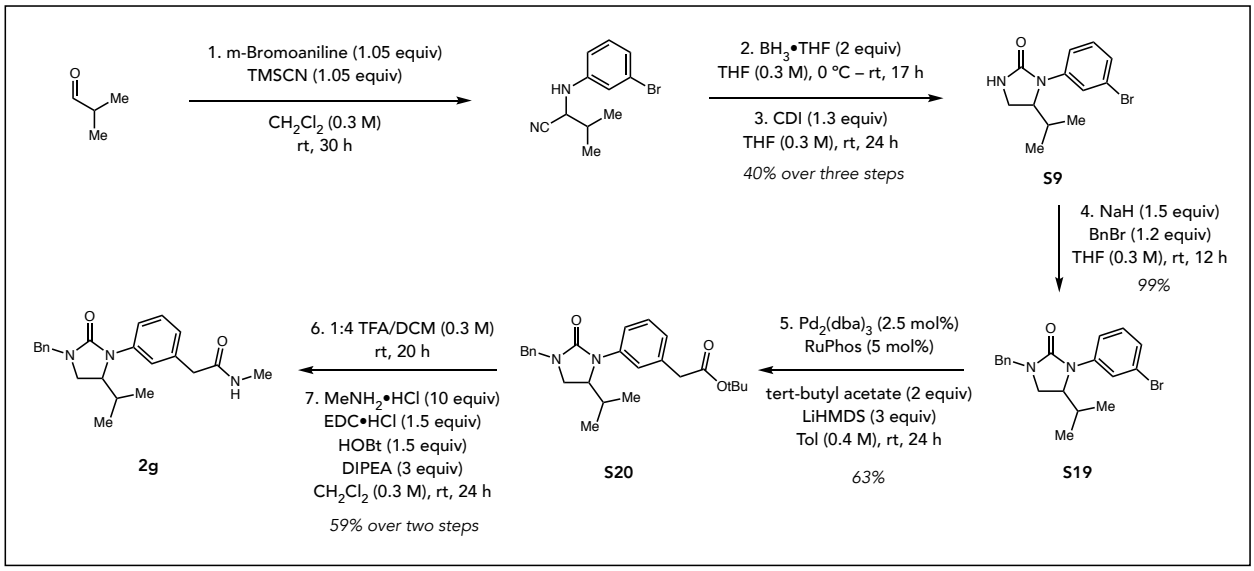
The title amide was synthesized following the general procedure F with methylamine hydrochloride (2.38 g, 35.3 mmol, 10 equiv). Purification by silica gel flash column chromatography (20–100% acetone in hexanes) afforded 2-(3-(5-isopropyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (**2f**, 155 mg, 0.56 mmol, 16% yield over three steps) as a pale yellow foamy solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 3H), 7.05 – 6.98 (m, 1H), 5.48 (s, 1H), 4.75 (s, 1H), 4.40 (ddd, *J* = 9.6, 5.8, 3.8 Hz, 1H), 3.58 (s, 2H), 3.55 – 3.51 (m, 1H), 3.35 (ddd, *J* = 9.0, 5.8, 1.2 Hz, 1H), 2.75 (d, *J* = 4.8 Hz, 3H), 2.22 – 2.07 (m, 1H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

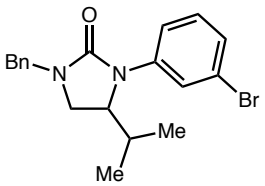
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 160.0, 139.0, 135.8, 129.7, 125.4, 123.4, 121.3, 60.6, 44.0, 38.1, 27.8, 26.7, 18.0, 14.5.

IR (FT-ATR, cm^{-1}) ν_{max} 3291, 2960, 1695, 1651, 1604, 1560, 1492, 1433, 1390, 1323, 1257, 1152, 734, 696.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{15}H_{22}N_3O_2^+$ requires 276.17065, observed 276.17057, difference 0.29 ppm.



1-benzyl-3-(3-bromophenyl)-4-isopropylimidazolidin-2-one (S19):



S19

The title compound was synthesized following the general procedure B described above with 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 1.50 g, 5.30 mmol, 1.0 equiv) and benzyl bromide (0.76 ml, 6.36 mmol, 1.2 equiv). Purification with silica gel flash column chromatography (0–25% EtOAc in hexanes) afforded 1-benzyl-3-(3-bromophenyl)-4-isopropylimidazolidin-2-one (**S19**, 1.97 g, 5.25 mmol, 99%) as a pale yellow oil.

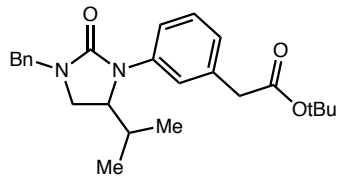
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 1H), 7.47 – 7.37 (m, 1H), 7.39 – 7.32 (m, 2H), 7.33 – 7.26 (m, 3H), 7.24 – 7.16 (m, 2H), 4.45 (s, 2H), 4.25 – 4.15 (m, 1H), 3.30 (t, *J* = 9.5 Hz, 1H), 3.09 (dd, *J* = 9.2, 5.1 Hz, 1H), 2.21 – 2.09 (m, 1H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 140.3, 136.8, 130.2, 128.8, 128.4, 127.8, 126.5, 124.2, 122.7, 119.8, 57.2, 48.1, 41.9, 27.5, 18.0, 14.2.

IR (FT-ATR, cm^{-1}) ν_{max} 2964, 2931, 1697, 1591, 1563, 1493, 1481, 1425, 1385, 1366, 1322, 1258, 1144, 1096, 1070, 1028, 992, 957, 773, 750, 700, 686.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{19}H_{22}BrN_2O^+$ requires 373.1, observed 373.1.

***tert*-butyl 2-(3-(3-benzyl-5-isopropyl-2-oxoimidazolidin-1-yl)phenyl)acetate (S20):**



S20

The title ester was synthesized following the general procedures C described above with 1-benzyl-3-(3-bromophenyl)-4-isopropylimidazolidin-2-one (**S19**, 1.97 g, 5.25 mmol). Purification by silica gel flash column chromatography (0–40% EtOAc in hexanes) afforded *tert*-butyl 2-(3-(3-benzyl-5-isopropyl-2-oxoimidazolidin-1-yl)phenyl)acetate (**S20**, 1.35 g, 3.31 mmol, 63% yield) as a brown oil.

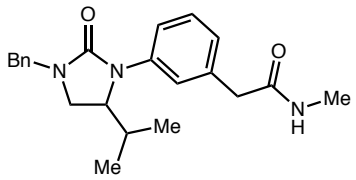
^{1}H NMR (500 MHz, CDCl3) δ 7.39 – 7.27 (m, 8H), 7.03 – 6.98 (m, 1H), 4.45 (s, 2H), 4.25 (ddd, *J* = 9.5, 5.4, 3.6 Hz, 1H), 3.52 (s, 2H), 3.29 (t, *J* = 9.4 Hz, 1H), 3.08 (dd, *J* = 9.1, 5.4 Hz, 1H), 2.20 – 2.06 (m, 1H), 1.43 (s, 9H), 0.82 (d, *J* = 7.1 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 158.2, 138.9, 137.1, 135.5, 129.0, 128.8, 128.4, 127.7, 124.7, 122.5, 120.4, 57.5, 48.2, 42.9, 42.1, 28.2, 27.5, 17.8, 14.3.

IR (FT-ATR, cm^{-1}) ν_{max} 2966, 1700, 1604, 1493, 1430, 1384, 1367, 1322, 1259, 1143, 952, 749, 700.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{25}H_{33}N_2O_3^+$ requires 409.2, observed 409.2.

2-(3-(3-benzyl-5-isopropyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (2g):



2g

The intermediate 2-(3-(3-benzyl-5-isopropyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedures E described above with *tert*-butyl 2-(3-(3-benzyl-5-isopropyl-2-oxoimidazolidin-1-yl)phenyl)acetate (**S20**, 1.35 g, 3.31 mmol, 1.0 equiv). The crude pale orange solid was carried to the next step without further purification.

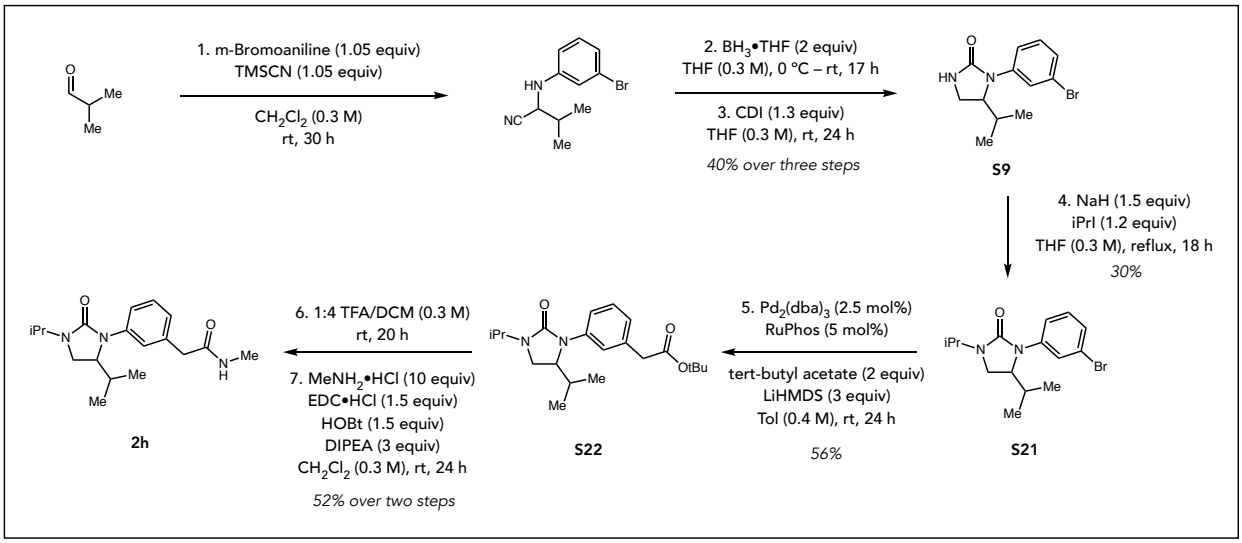
The title amide was synthesized following the general procedure F with methylamine hydrochloride (2.24 g, 33.1 mmol, 10 equiv). Purification by silica gel flash column chromatography (0–70% acetone in hexanes) afforded 2-(3-(3-benzyl-5-isopropyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (**2g**, 714 mg, 1.95 mmol, 59% yield over two steps) as a pale yellow foamy solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 8H), 6.98 (dt, *J* = 7.2, 1.6 Hz, 1H), 5.47 (s, 1H), 4.46 (s, 2H), 4.26 (ddd, *J* = 9.6, 5.4, 3.6 Hz, 1H), 3.58 (s, 2H), 3.31 (t, *J* = 9.5 Hz, 1H), 3.10 (dd, *J* = 9.1, 5.5 Hz, 1H), 2.76 (d, *J* = 4.8 Hz, 3H), 2.20 – 2.08 (m, 1H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H).

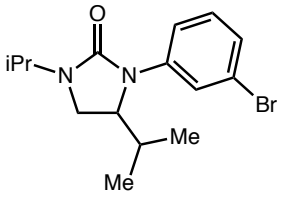
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 158.2, 139.5, 136.9, 135.67, 129.7, 128.8, 128.3, 127.8, 124.9, 122.8, 120.6, 57.3, 48.1, 44.0, 42.0, 27.5, 26.7, 18.0, 14.3.

IR (FT-ATR, cm^{-1}) ν_{max} 3306, 3031, 2960, 1671, 1603, 1586, 1553, 1493, 1435, 1385, 1358, 1323, 1261, 1210, 1156, 1115, 1097, 1028, 843, 748, 701, 657.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{22}H_{28}N_3O_2^+$ requires 366.21760, observed 366.21695, difference 1.77 ppm.



3-(3-bromophenyl)-1,4-diisopropylimidazolidin-2-one (S21):



S21

The title compound was synthesized following the general procedure B described above with 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 1.50 g, 5.30 mmol, 1.0 equiv) and isopropyl iodide (0.64 mL, 6.36 mmol, 1.2 equiv). The reaction was refluxed for 18 hours. Purification with silica gel flash column chromatography (0–60% EtOAc in hexanes) afforded 3-(3-bromophenyl)-1,4-diisopropylimidazolidin-2-one (**S21**, 510 g, 1.59 mmol, 30%) aspale yellow oil.

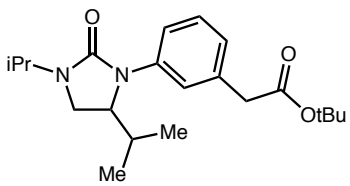
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 1H), 7.44 – 7.35 (m, 1H), 7.21 – 7.14 (m, 2H), 4.31 – 4.18 (m, 2H), 3.39 (t, *J* = 9.4 Hz, 1H), 3.19 (dd, *J* = 9.0, 4.9 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.9, 140.5, 130.1, 126.1, 123.8, 122.6, 119.5, 57.2, 43.6, 36.9, 27.7, 19.8, 19.5, 18.1, 14.2.

IR (FT-ATR, cm^{-1}) ν_{max} 2965, 2875, 1694, 1591, 1562, 1480, 1424, 1386, 1324, 1265, 1241, 1182, 1151, 1126, 1090, 1063, 991, 852, 772, 728, 684.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{15}H_{22}BrN_2O^+$ requires 325.1, observed 325.1.

***tert*-butyl 2-(3-(3,5-diisopropyl-2-oxoimidazolidin-1-yl)phenyl)acetate (S22):**



S22

The title ester was synthesized following the general procedures C described above with 3-(3-bromophenyl)-1,4-diisopropylimidazolidin-2-one (**S21**, 1.03 g, 3.21 mmol). Purification by silica gel flash column chromatography (0–40% EtOAc in hexanes) afforded *tert*-butyl 2-(3-(3,5-diisopropyl-2-oxoimidazolidin-1-yl)phenyl)acetate (**S22**, 636 mg, 1.80 mmol, 56% yield) with minor impurities as a brown oil. The product was carried forward without further purification.

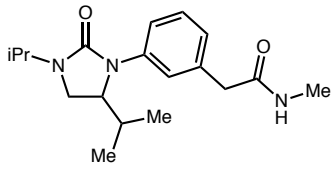
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.27 (m, 3H), 7.01 – 6.93 (m, 1H), 4.33 – 4.17 (m, 2H), 3.50 (s, 2H), 3.44 – 3.34 (m, 1H), 3.17 (dd, *J* = 8.9, 5.1 Hz, 1H), 2.22 – 2.11 (m, 1H), 1.43 (s, 9H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 157.4, 139.2, 135.4, 128.9, 124.3, 122.2, 120.1, 57.4, 43.5, 42.9, 37.0, 28.2, 27.8, 19.7, 19.5, 18.1, 14.3.

IR (FT-ATR, cm^{-1}) ν_{max} 2965, 2931, 1696, 1591, 1563, 1493, 1481, 1424, 1385, 1366, 1322, 1257, 1143, 1096, 1070, 1029, 992, 957, 843, 773, 750, 700, 686.

MS (ESI) (*m/z*) for $[M+H]^+$ $C_{21}H_{33}N_2O_3^+$ requires 361.2, observed 361.2.

2-(3-(3,5-diisopropyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (2h):



2h

The intermediate 2-(3-(3,5-diisopropyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedures E described above with *tert*-butyl 2-(3-(3,5-diisopropyl-2-oxoimidazolidin-1-yl)phenyl)acetate (**S22**, 636 mg, 1.80 mmol, 1.0 equiv). The crude pale orange solid was carried to the next step without further purification.

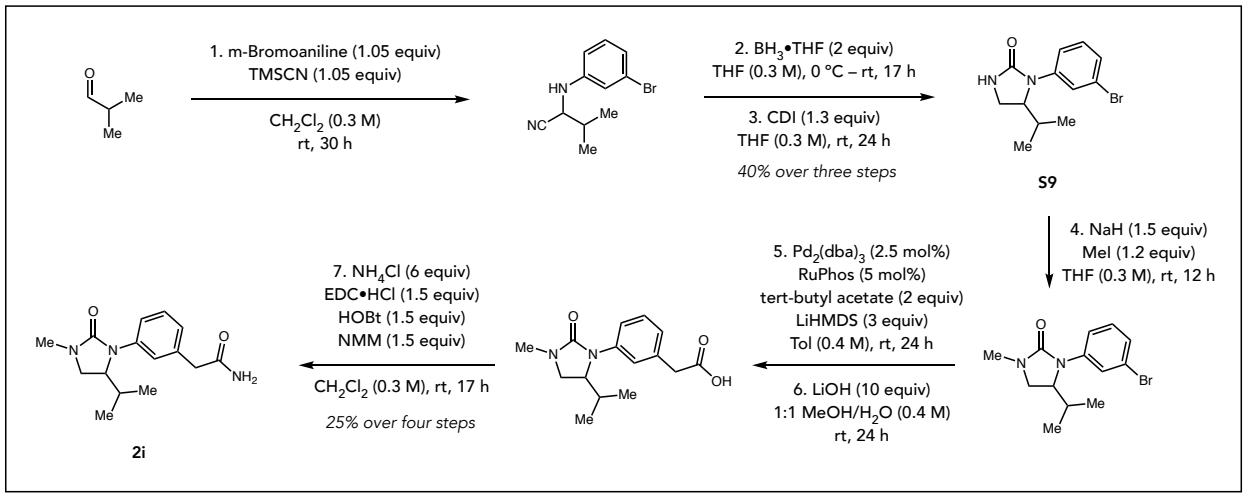
The title amide was synthesized following the general procedure F with methylamine hydrochloride (1.22 g, 18.0 mmol, 10 equiv). Purification by silica gel flash column chromatography (0–70% acetone in hexanes) afforded 2-(3-(3,5-diisopropyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (**2h**, 297 mg, 0.936 mmol, 52% yield over two steps) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 1H), 7.37 – 7.27 (m, 2H), 6.98 – 6.92 (m, 1H), 5.49 (s, 1H), 4.31 – 4.19 (m, 2H), 3.56 (s, 2H), 3.40 (t, *J* = 9.4 Hz, 1H), 3.19 (dd, *J* = 9.0, 5.2 Hz, 1H), 2.74 (d, *J* = 4.8 Hz, 3H), 2.20 – 2.10 (m, 1H), 1.18 (dd, *J* = 15.2, 6.8 Hz, 6H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

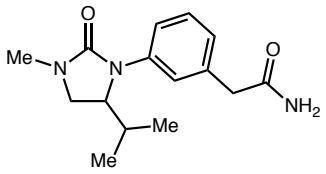
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 157.4, 139.7, 135.6, 129.6, 124.5, 122.6, 120.2, 57.3, 44.0, 43.6, 37.0, 27.8, 26.7, 19.7, 19.6, 18.1, 14.3.

IR (FT-ATR, cm^{-1}) ν_{max} 3303, 2965, 1662, 1604, 1586, 1553, 1492, 1428, 1387, 1367, 1325, 1266, 1170, 1126, 1067, 845, 769, 693.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{18}H_{28}N_3O_2^+$ requires 318.21760, observed 318.21788, difference 0.88 ppm.



2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetamide (2i):



2i

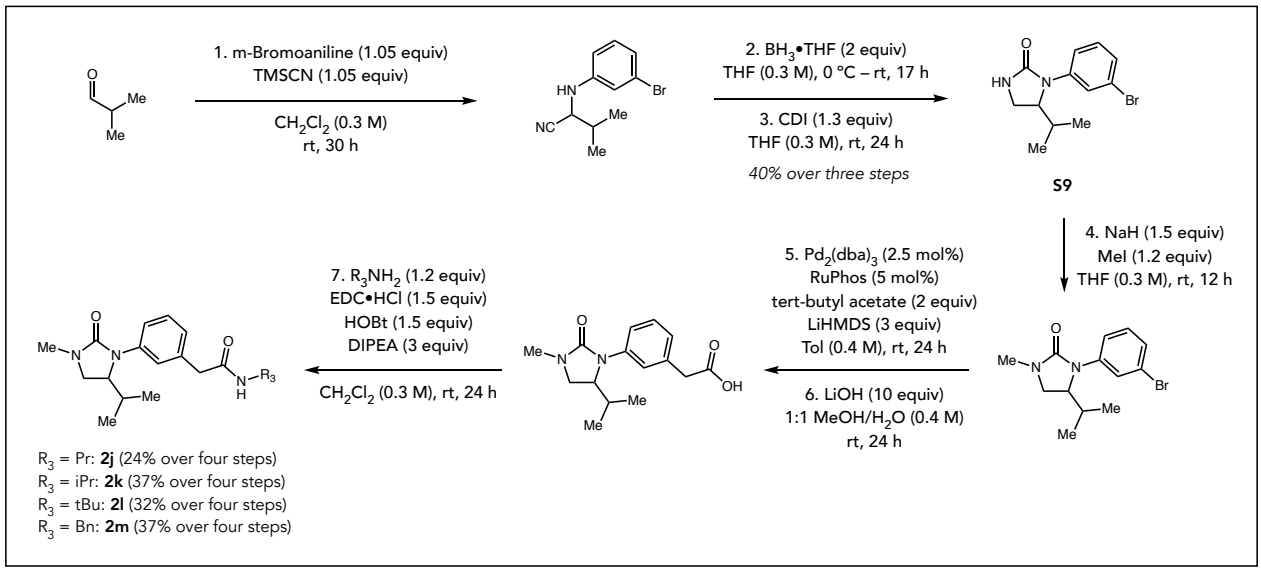
The intermediate 3-(3-bromophenyl)-4-isopropyl-1-methylimidazolidin-2-one was synthesized following the general procedure B described above with 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 2.83 g, 10.0 mmol, 1.0 equiv) and methyl iodide (0.75 ml, 12.0 mmol, 1.2 equiv). The resultant orange solid was carried to the next step without further purification.

The intermediate 2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedures C and D described above with the crude product from the previous step. The crude white solid was carried to the next step without further purification.

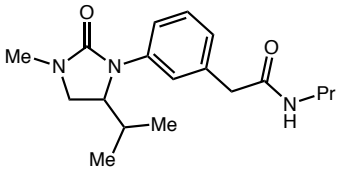
To a 100 mL round bottom flask were added the crude carboxylic acid starting material from the previous step, *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (2.33 g, 15.0 mmol, 1.5 equiv), 1-hydroxybenzotriazole (2.03 g, 15.0 mmol, 1.5 equiv), ammonium chloride (1.02 g, 60.0 mmol, 6.0 equiv), N-methylmorpholine (1.65 mL, 15.0 mmol, 1.5 equiv) in CH_2Cl_2 (32 mL). The reaction was stirred for 17 hours at room temperature, then washed with 10% citric acid (aq), sat. $NaHCO_3$ (aq), and brine. The organic layer was dried over $MgSO_4$, concentrated, and purified by silica gel flash column chromatography (0–70% acetone in hexanes) to afford 2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetamide (**2i**, 688 mg, 2.50 mmol, 25% yield over four steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (t, *J* = 2.0 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.00 (dt, *J* = 7.2, 1.6 Hz, 1H), 5.52 (s, 1H), 5.30 (s, 1H), 4.27 (ddd, *J* = 9.5, 5.7, 3.7 Hz, 1H), 3.58 (d, *J* = 2.5 Hz, 2H), 3.43 (t, *J* = 9.3 Hz, 1H), 3.23 (dd, *J* = 9.0, 5.7 Hz, 1H), 2.87 (s, 3H), 2.23 – 2.06 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.25, 158.57, 139.65, 135.65, 129.63, 124.61, 122.84, 120.27, 57.33, 44.96, 43.63, 31.00, 27.54, 18.08, 14.43.

IR (FT-ATR, cm^{-1}) ν_{max} 3351.50, 3195.60, 2960.16, 2929.98, 2874.41, 1664.06, 1603.15, 1586.63, 1493.11, 1434.25, 1402.93, 1381.68, 1326.41, 1265.52, 1215.28, 1186.67, 1111.55, 1040.18, 997.62, 894.48, 841.62, 783.35, 751.92, 696.91.
HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{15}H_{22}N_3O_2^+$ requires 276.17065, observed 276.17012, difference 1.92 ppm.



2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-propylacetamide (2j):



2j

The intermediate 3-(3-bromophenyl)-4-isopropyl-1-methylimidazolidin-2-one was synthesized following the general procedure B described above with 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 2.83 g, 10.0 mmol, 1.0 equiv) and methyl iodide (0.75 ml, 12.0 mmol, 1.2 equiv). The resultant orange solid was carried to the next step without further purification.

The intermediate 2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedures C and D described above with the crude product from the previous step. The crude white solid was carried to the next step without further purification.

The title amide was synthesized following the general procedure F with propylamine (0.99 mL, 12.0 mmol, 1.2 equiv). Purification by silica gel flash column chromatography (0–10% MeOH in CH_2Cl_2) afforded 2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-propylacetamide (**2j**, 762 mg, 2.40 mmol, 24% yield over four steps) as pale yellow oil.

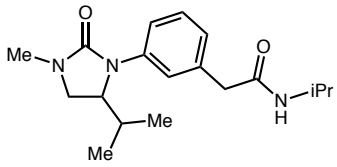
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 3H), 7.00 – 6.92 (m, 1H), 5.44 (s, 1H), 4.26 (ddd, *J* = 9.5, 5.6, 3.7 Hz, 1H), 3.56 (s, 2H), 3.43 (t, *J* = 9.3 Hz, 1H), 3.28 – 3.05 (m, 3H), 2.87 (s, 3H), 2.17 – 2.10 (m, 1H), 1.48 – 1.37 (m, 2H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 158.5, 139.6, 135.8, 129.6, 124.7, 122.7, 120.5, 57.3, 45.0, 442, 41.5, 31.0, 27.5, 22.9, 18.1, 14.4, 11.4.

IR (FT-ATR, cm^{-1}) ν_{max} 3300, 3075, 2961, 2931, 2874, 1688, 1647, 1604, 1585, 1547, 1493, 1433, 1403, 1382, 1325, 1266, 1157, 1112, 1040, 997, 957, 890, 844, 771, 750, 694.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{18}H_{28}N_3O_2^+$ requires 318.21760, observed 318.21769, difference 0.28 ppm.

***N*-isopropyl-2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetamide (2k):**



2k

The intermediate 3-(3-bromophenyl)-4-isopropyl-1-methylimidazolidin-2-one was synthesized following the general proce dure B found above with 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 2.83 g, 10.0 mmol, 1.0 equiv) and methyl iodide (0.75 ml, 12.0 mmol, 1.2 equiv). The resultant orange solid was carried to the next step without further purification.

The intermediate 2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedures C and D described above with the crude product from the previous step. The crude white solid was carried to the next step without further purification.

The title amide was synthesized following the general procedure F with isopropyl amine (0.98 mL, 12.0 mmol, 1.2 equiv). Purification by silica gel flash column chromatography (0–10% MeOH in CH_2Cl_2) afforded *N*-isopropyl-2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetamide (**2k**, 1.17 g, 3.70 mmol, 37% yield over four steps) as a pale yellow oil.

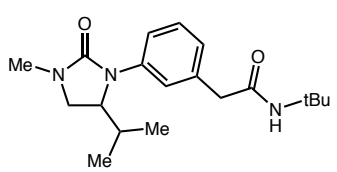
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 3H), 6.99 – 6.93 (m, 1H), 5.26 (d, *J* = 7.7 Hz, 1H), 4.26 (ddd, *J* = 9.5, 5.6, 3.7 Hz, 1H), 4.11 – 3.98 (m, 1H), 3.52 (s, 2H), 3.43 (t, *J* = 9.3 Hz, 1H), 3.22 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.87 (s, 3H), 2.20 – 2.10 (m, 1H), 1.06 (t, *J* = 6.9 Hz, 6H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 158.5, 139.5, 135.8, 129.6, 124.6, 122.6, 120.5, 57.6, 45.0, 44.2, 41.6, 31.0, 27.5, 22.7, 22.7, 18.0, 14.4.

IR (FT-ATR, cm^{-1}) ν_{max} 3295, 2965, 2931, 1691, 1645, 1604, 1586, 1544, 1493, 1434, 1404, 1383, 1327, 1267, 1174, 1112, 845, 770, 695.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{18}H_{28}N_3O_2^+$ requires 318.21760, observed 318.21743, difference 0.53 ppm.

N-(tert-butyl)-2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetamide (2l):



2l

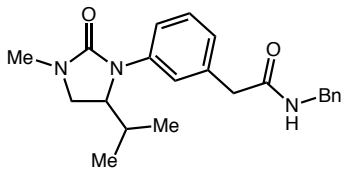
The intermediate 3-(3-bromophenyl)-4-isopropyl-1-methylimidazolidin-2-one was synthesized following the general procedure B found above with 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 2.83 g, 10.0 mmol, 1.0 equiv) and methyl iodide (0.75 ml, 12.0 mmol, 1.2 equiv). The resultant orange solid was carried to the next step without further purification.

The intermediate 2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedures C and D described above with the crude product from the previous step. The crude white solid was carried to the next step without further purification.

The title amide was synthesized following the general procedure F with tert-butylamine (1.26 mL, 12.0 mmol, 1.2 equiv). Purification by silica gel flash column chromatography (0–40% acetone in hexanes) afforded N-(tert-butyl)-2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetamide (**2l**, 1.06 g, 3.20 mmol, 32% yield over four steps) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 3H), 6.95 (dt, *J* = 7.3, 1.5 Hz, 1H), 5.24 (s, 1H), 4.26 (ddd, *J* = 9.5, 5.6, 3.8 Hz, 1H), 3.47 (s, 2H), 3.43 (t, *J* = 9.3 Hz, 1H), 3.21 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.87 (s, 3H), 2.15 (dtq, *J* = 10.6, 6.9, 3.7 Hz, 1H), 1.27 (s, 9H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.29, 158.51, 139.48, 136.22, 129.52, 124.48, 122.46, 120.33, 57.34, 51.37, 45.21, 44.96, 31.03, 28.79, 27.51, 18.04, 14.39.
IR (FT-ATR, cm^{-1}) ν_{max} 3309.60, 2962.99, 2929.32, 1686.55, 1650.73, 1604.53, 1586.32, 1546.02, 1493.43, 1452.32, 1434.06, 1403.98, 1383.20, 1364.09, 1326.48, 1267.12, 1224.57, 1157.38, 1112.11, 1041.15, 777.36, 694.18.
HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{19}H_{30}N_3O_2^+$ requires 332.23325, observed 332.23328, difference 0.09 ppm.

***N*-benzyl-2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetamide (2m):**



2m

The intermediate 3-(3-bromophenyl)-4-isopropyl-1-methylimidazolidin-2-one was synthesized following the general procedure B described above with 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 2.83 g, 10.0 mmol, 1.0 equiv) and methyl iodide (0.75 ml, 12.0 mmol, 1.2 equiv). The resultant orange solid was carried to the next step without further purification.

The intermediate 2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetic acid was synthesized following the general procedures C and D described above with the crude product from the previous step. The crude white solid was carried to the next step without further purification.

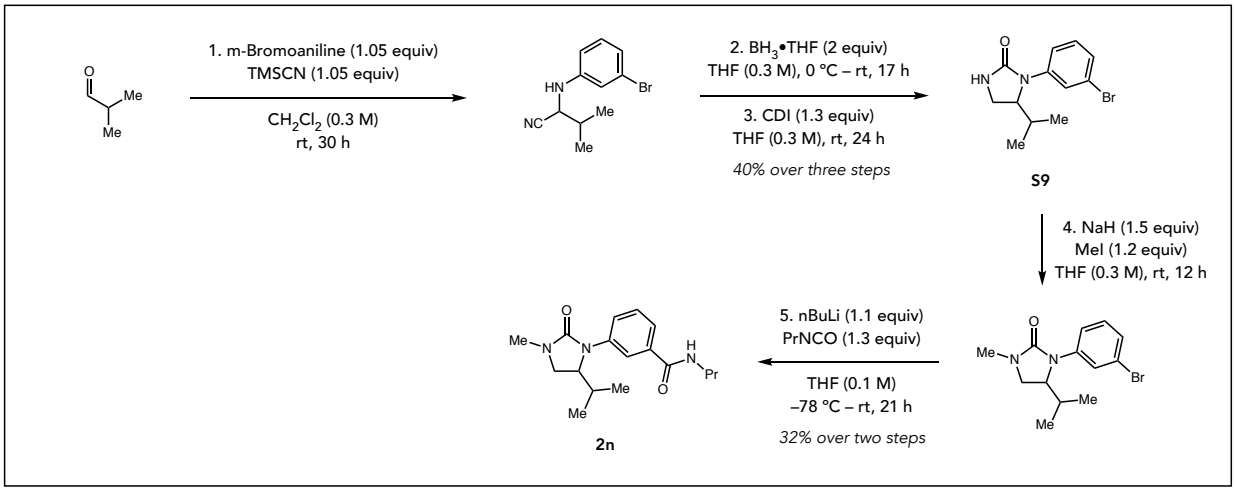
The title amide was synthesized following the general procedure F with benzylamine (1.31 mL, 12.0 mmol, 1.2 equiv). Purification by silica gel flash column chromatography (0–10% MeOH in CH_2Cl_2) afforded *N*-benzyl-2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)acetamide (**2m**, 1.36 g, 3.72 mmol, 37% yield over four steps) as a pale yellow foamy solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.15 (m, 8H), 6.98 (dt, *J* = 6.7, 1.7 Hz, 1H), 5.81 (s, 1H), 4.40 (d, *J* = 5.8 Hz, 2H), 4.23 (ddd, *J* = 9.4, 5.6, 3.7 Hz, 1H), 3.62 (s, 2H), 3.41 (t, *J* = 9.3 Hz, 1H), 3.21 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.86 (s, 3H), 2.19 – 2.07 (m, 1H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.73 (d, *J* = 6.8 Hz, 3H).

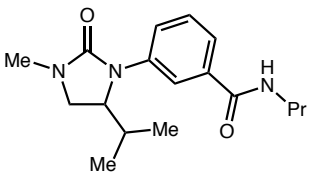
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 158.5, 139.6, 138.3, 135.5, 129.6, 128.8, 127.7, 127.5, 124.6, 122.6, 120.4, 57.3, 44.9, 44.1, 43.7, 31.0, 27.5, 18.0, 14.4.

IR (FT-ATR, cm^{-1}) ν_{max} 3297, 3060, 2960, 2928, 1672, 1604, 1586, 1493., 1453, 1434, 1404, 1383, 1326, 1267, 1157, 1112, 1029, 843, 749, 699.

HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{22}H_{28}N_3O_2^+$ requires 366.21760, observed 366.21806, difference 1.26 ppm.



3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)-*N*-propylbenzamide (2n):



2n

The intermediate 3-(3-bromophenyl)-4-isopropyl-1-methylimidazolidin-2-one was synthesized following the general proce dure B found above with 1-(3-bromophenyl)-5-isopropylimidazolidin-2-one (**S9**, 2.83 g, 10.0 mmol, 1.0 equiv) and methyl iodide (0.75 ml, 12.0 mmol, 1.2 equiv). The resultant orange solid was carried to the next step without further purification.

To a 250 mL round bottom flask was added the crude starting material from the previous step. The flask was evacuated and backfilled with argon three times, followed by addition of tetrahydrofuran (94 mL). Upon cooling to –78 ºC, n-butyllithium (2.5 M in hexanes, 4.40 mL, 11.0 mmol, 1.1 equiv) was added, and the solution was stirred for 1 hour. Propyl isocyanate (1.22 mL, 13.0 mmol, 1.3 equiv) was added dropwise, and the reaction was stirred for 21 hours as it warmed up to room temperature. The solution was then quenched with sat. NH_4Cl (aq). The aqueous layer was extracted with dichloromethane three times. The combined organic layer was dried with $MgSO_4$ and concentrated. Purification with silica gel flash column chromatography (0–50% acetone in hexanes) afforded 3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)-*N*-propylbenzamide (**2n**, 953 mg, 3.15 mmol, 32% yield over two steps) as a white solid.

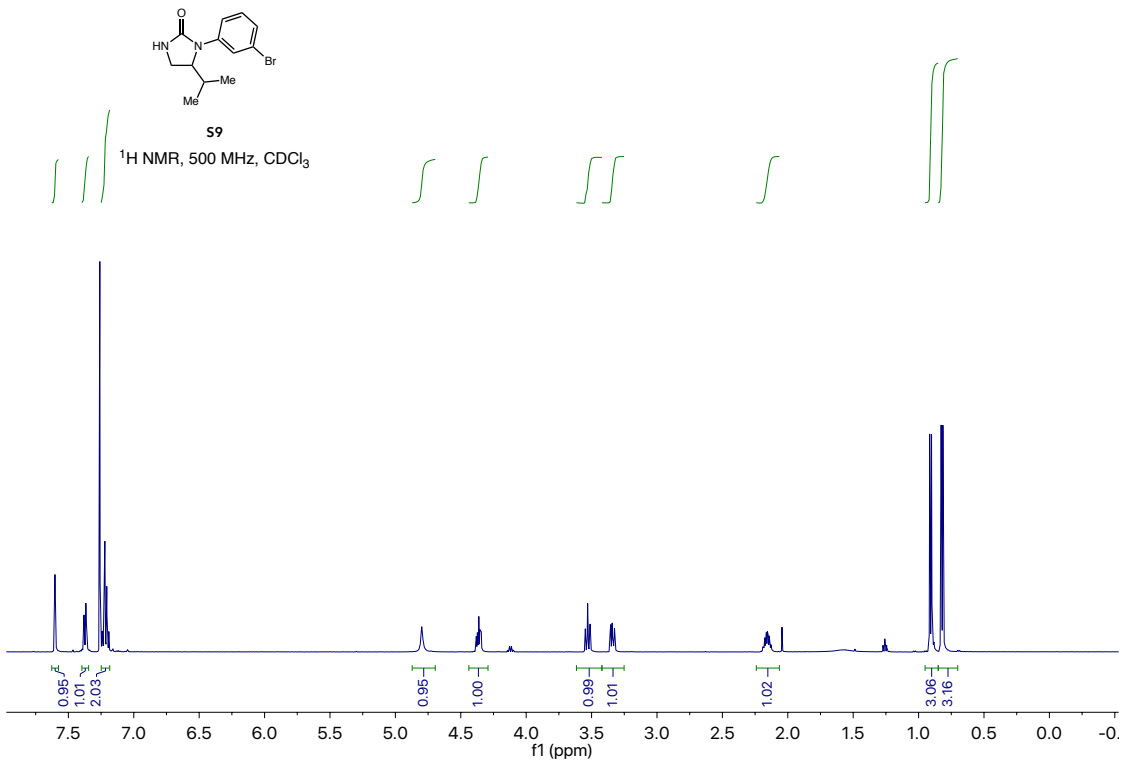
^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (t, *J* = 2.0 Hz, 1H), 7.55 (ddd, *J* = 8.1, 2.2, 1.1 Hz, 1H), 7.46 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 6.28 (s, 1H), 4.33 (ddd, *J* = 9.5, 5.4, 3.7 Hz, 1H), 3.51 – 3.35 (m, 3H), 3.23 (dd, *J* = 9.0, 5.4 Hz, 1H), 2.88 (s, 3H),

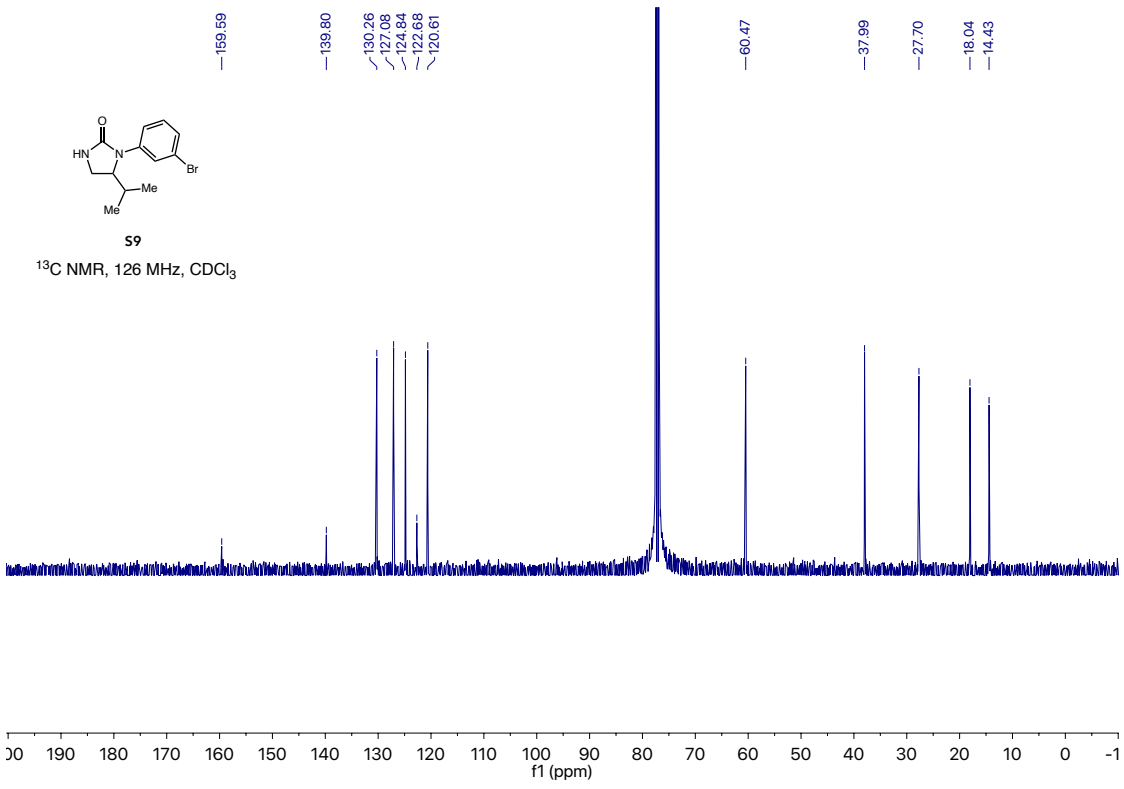
2.18 (dqd, J = 10.6, 6.8, 3.7 Hz, 1H), 1.68 – 1.59 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H).

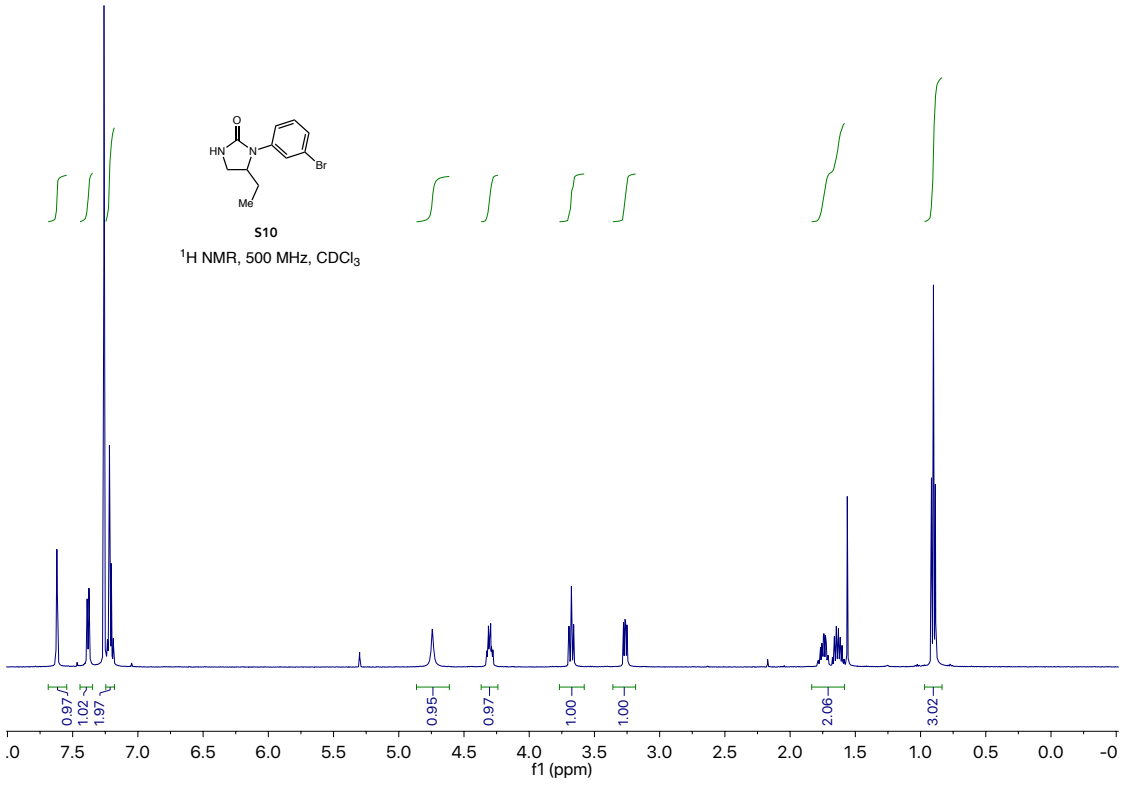
^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.57, 158.42, 139.26, 135.74, 129.15, 123.88, 121.90, 119.65, 57.25, 44.87, 41.94, 30.97, 27.37, 23.07, 18.04, 14.30, 11.64.

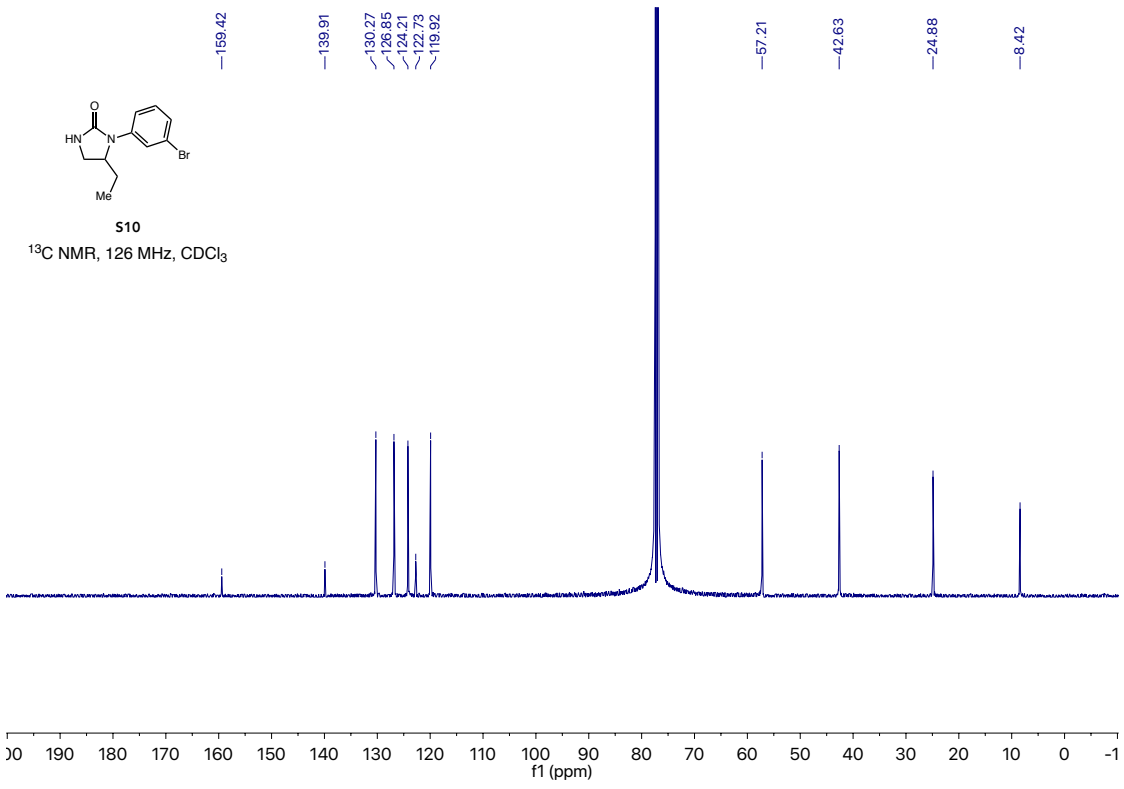
IR (FT-ATR, cm^{-1}) ν_{max} 3300.49, 3089.20, 2959.50, 1651.41, 1604.25, 1585.56, 1555.67, 1493.32, 1434.71, 1404.61, 1383.10, 1352.53, 1326.05, 1266.89, 1161.66, 1112.05, 1040.69, 997.67, 899.26, 751.56, 693.90.

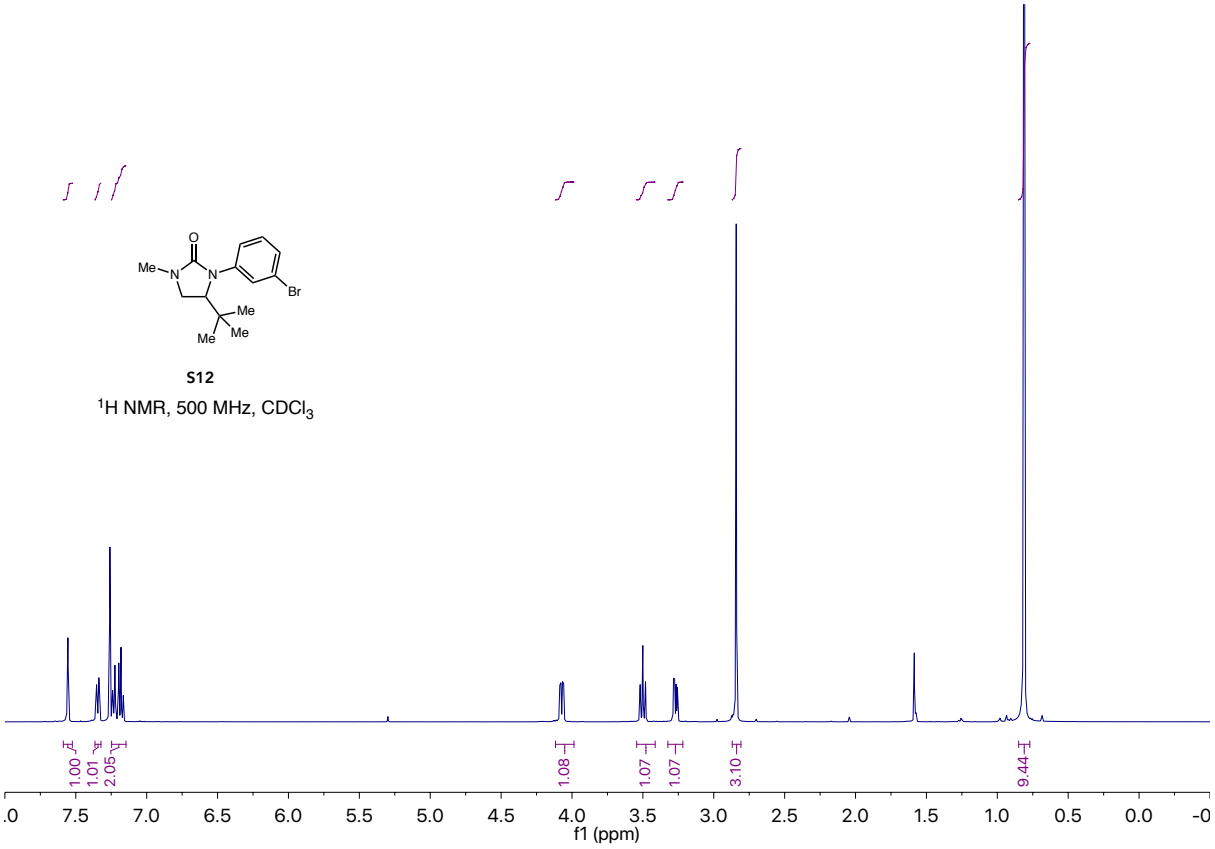
HRMS (ESI) (*m/z*) for $[M+H]^+$ $C_{17}H_{26}N_3O_2^+$ requires 304.20195, observed 304.20142, difference 1.74 ppm.


S9
^{1}H NMR, 500 MHz, $CDCl_3$
0.95
1.01
2.03
0.95
1.00
0.99
1.01
1.02
3.06
3.16
f1 (ppm)


159.59
139.80
130.26
127.08
124.84
122.68
120.61
60.47
37.99
27.70
18.04
14.43
S9
^{13}C NMR, 126 MHz, $CDCl_3$
f1 (ppm)

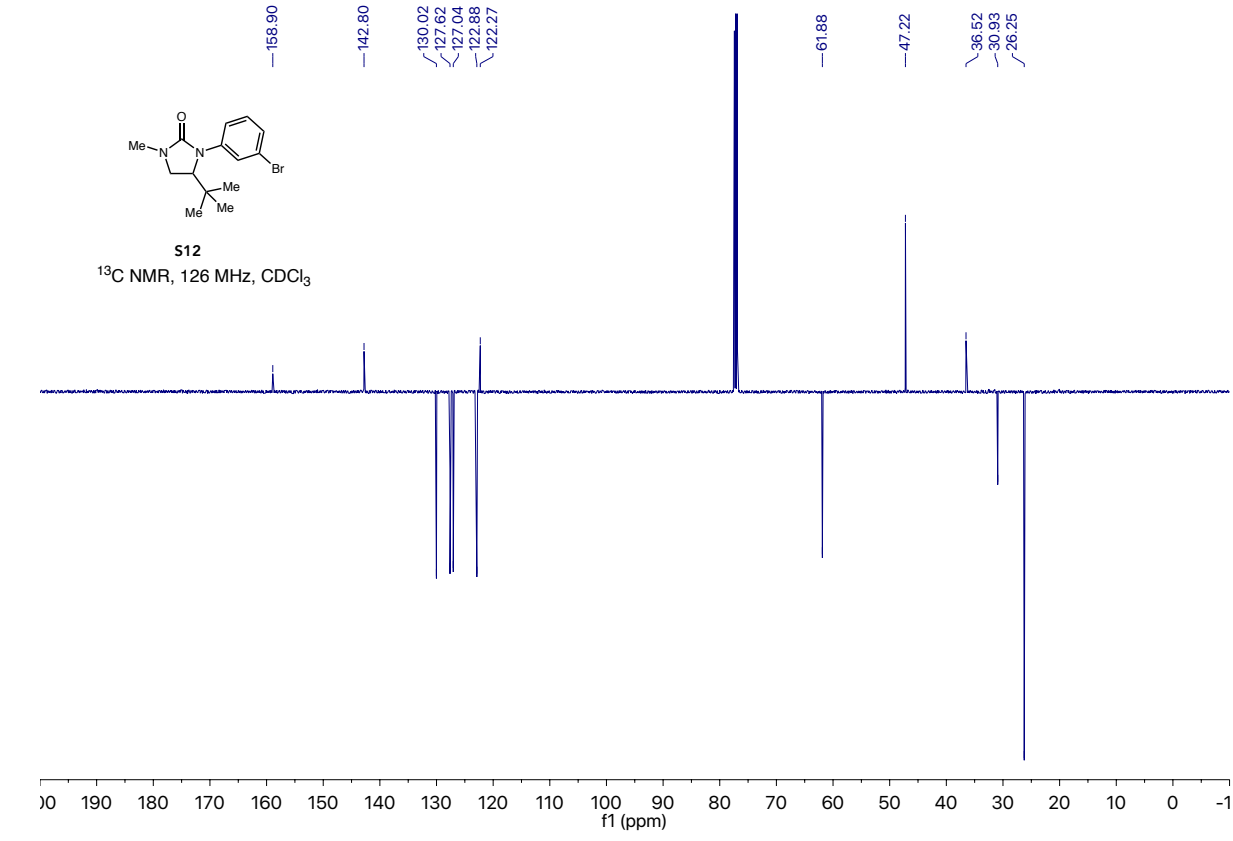

S10
^{1}H NMR, 500 MHz, $CDCl_3$
0.97
1.02
1.97
0.95
0.97
1.00
1.00
2.06
3.02
f1 (ppm)


159.42
139.91
130.27
126.85
124.21
122.73
119.92
57.21
42.63
24.88
8.42
S10
^{13}C NMR, 126 MHz, $CDCl_3$
f1 (ppm)



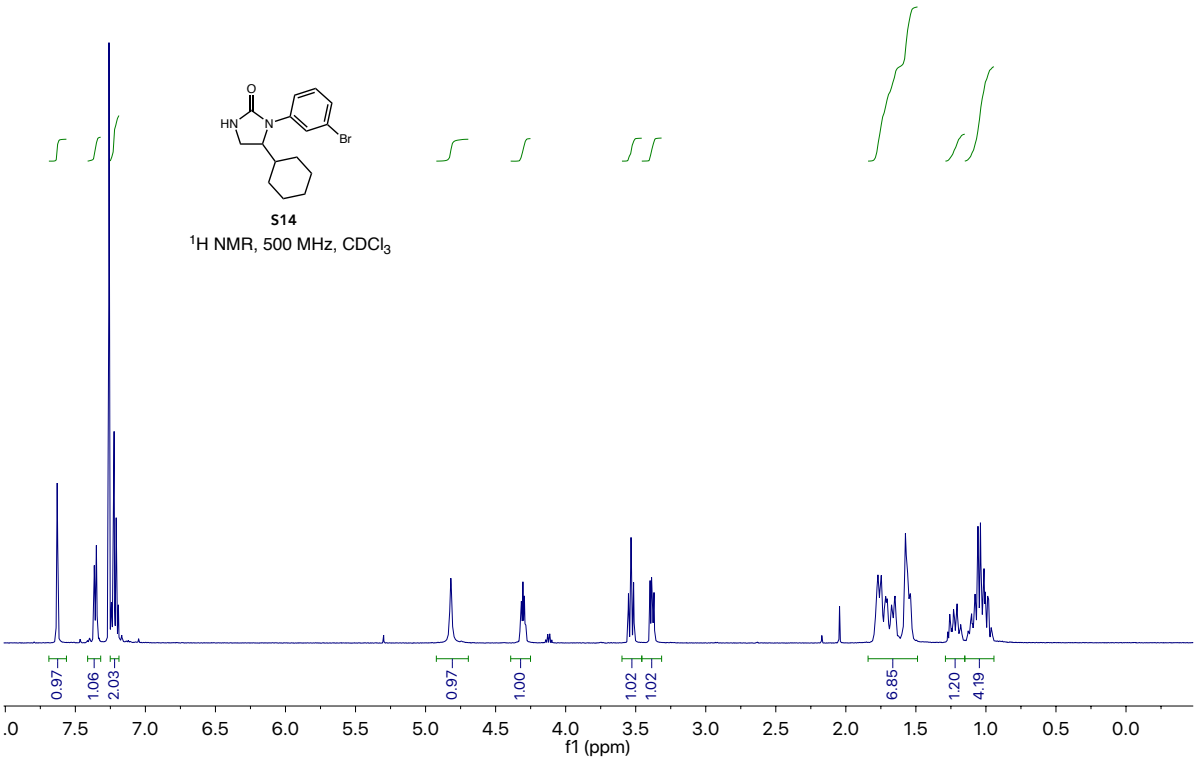
S12

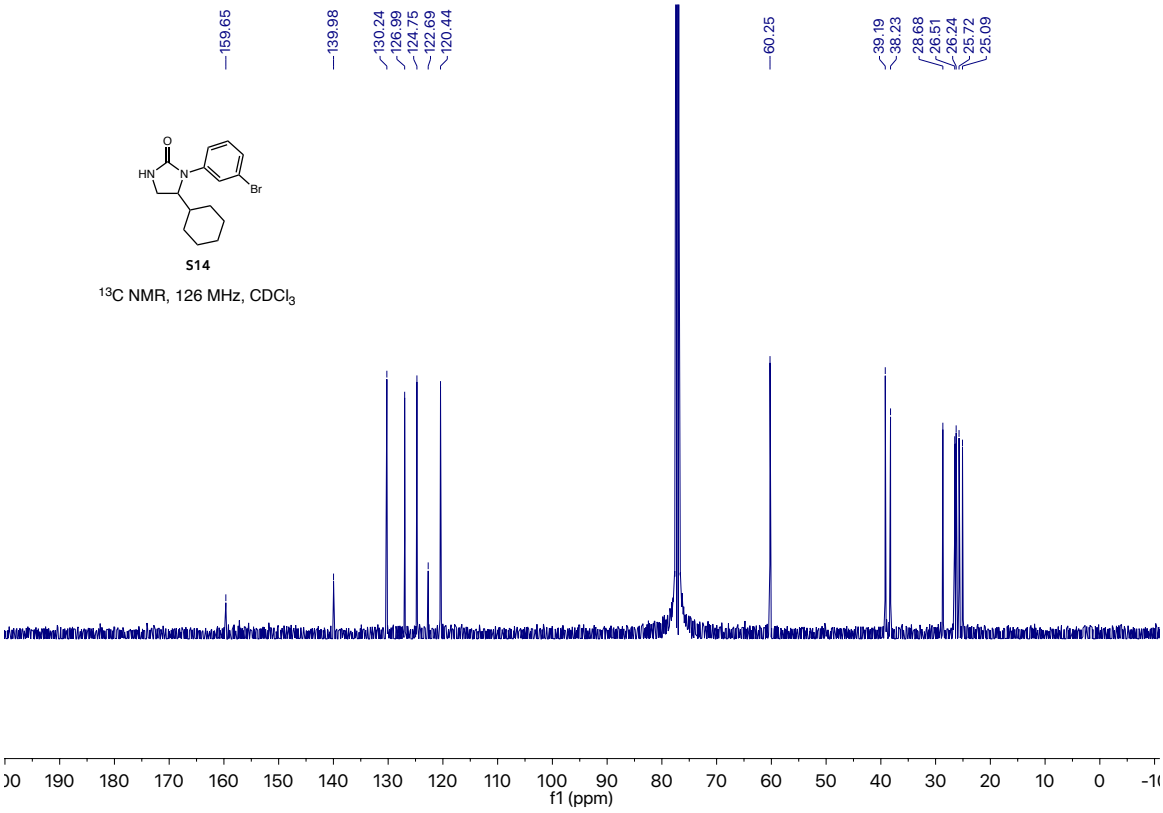
^{1}H NMR, 500 MHz, $CDCl_3$

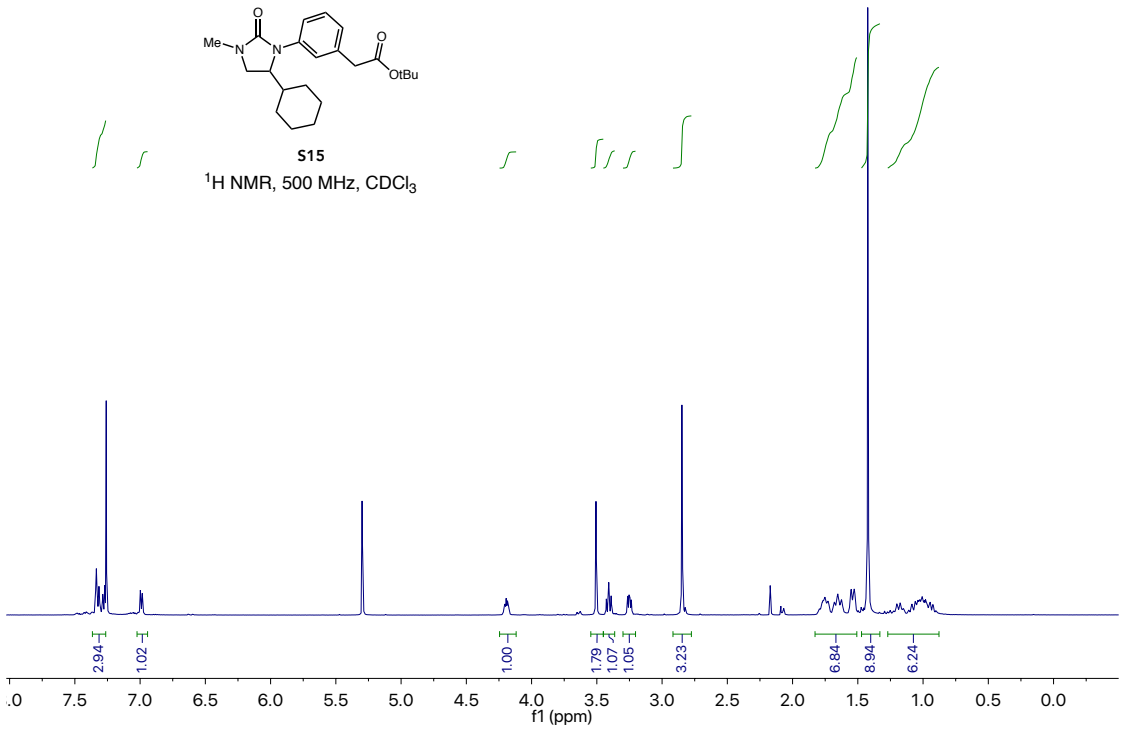


S12

^{13}C NMR, 126 MHz, $CDCl_3$

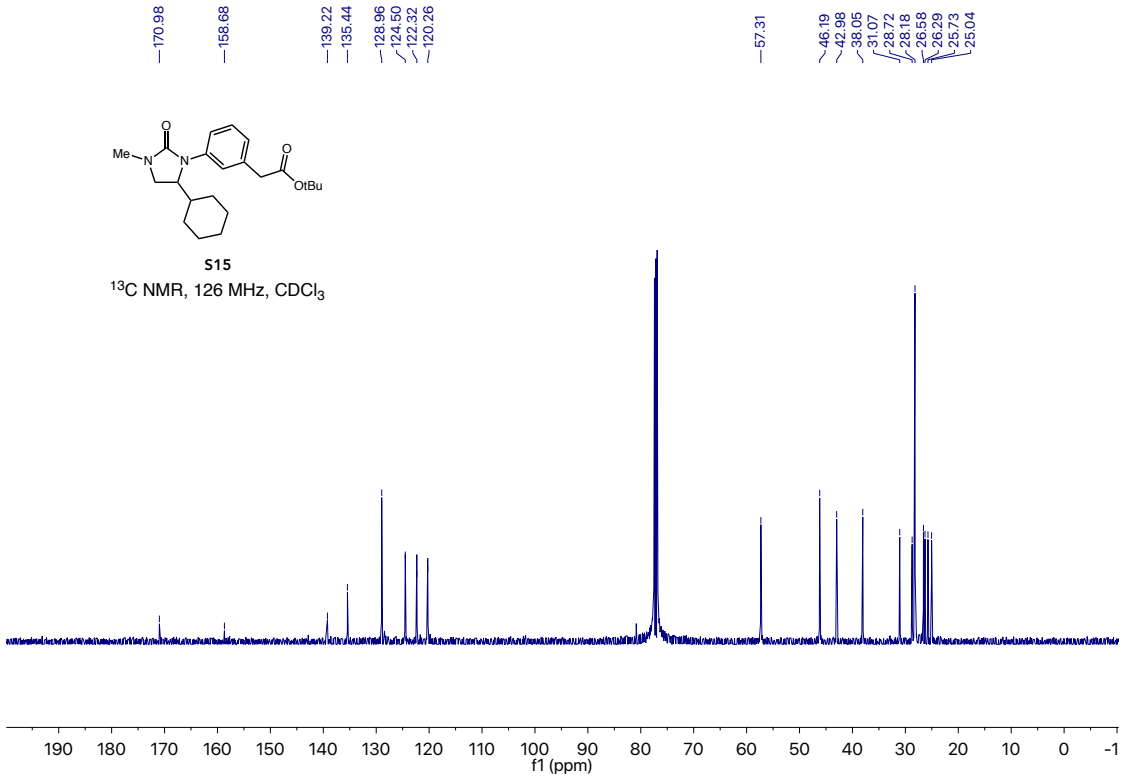

S14
^{1}H NMR, 500 MHz, $CDCl_3$
0.97
1.06
2.03
0.97
1.00
1.02
1.02
6.85
1.20
4.19
f1 (ppm)


159.65
139.98
130.24
126.99
124.75
122.69
120.44
60.25
39.19
38.23
28.68
26.51
26.24
25.72
25.09
S14
^{13}C NMR, 126 MHz, $CDCl_3$
f1 (ppm)



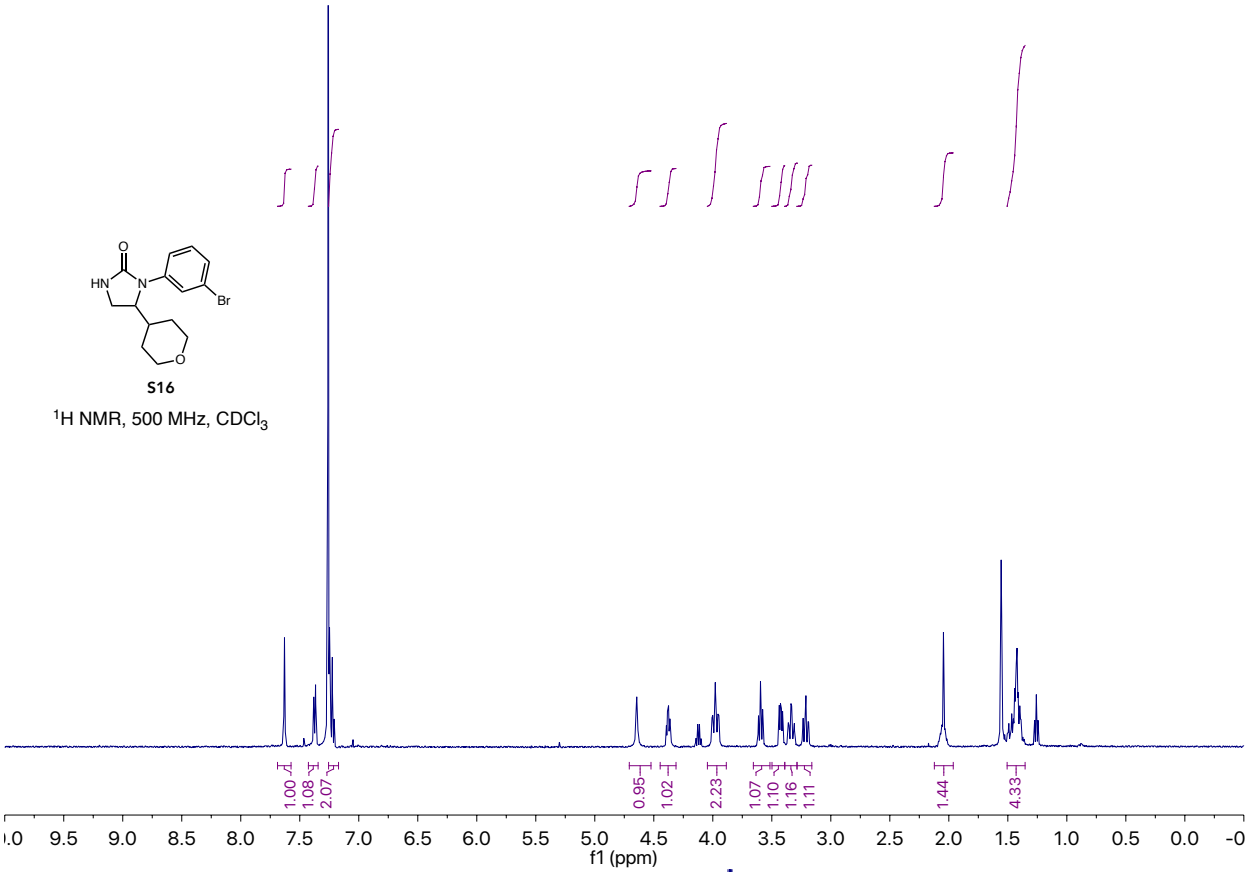
S15

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



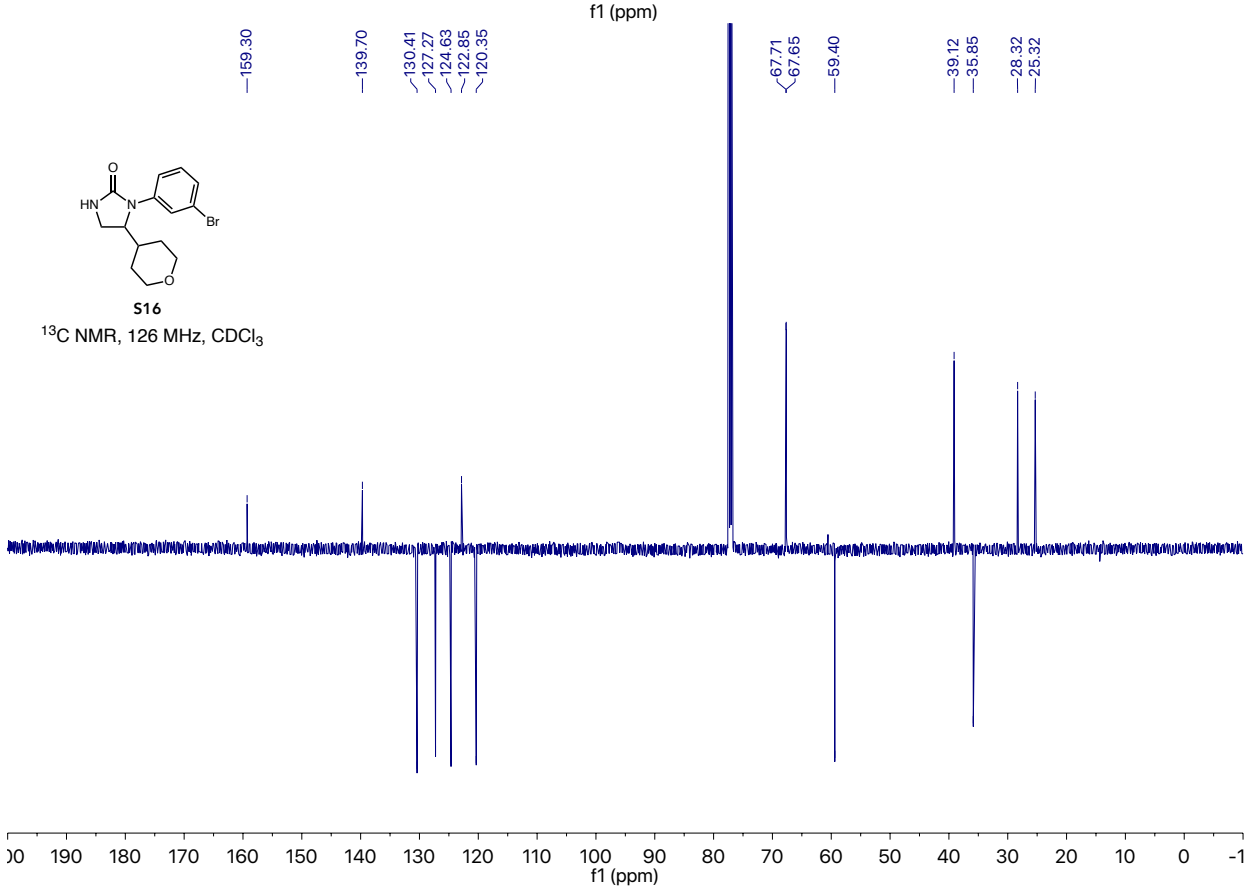
S15

^{13}C NMR, 126 MHz, $CDCl_3$



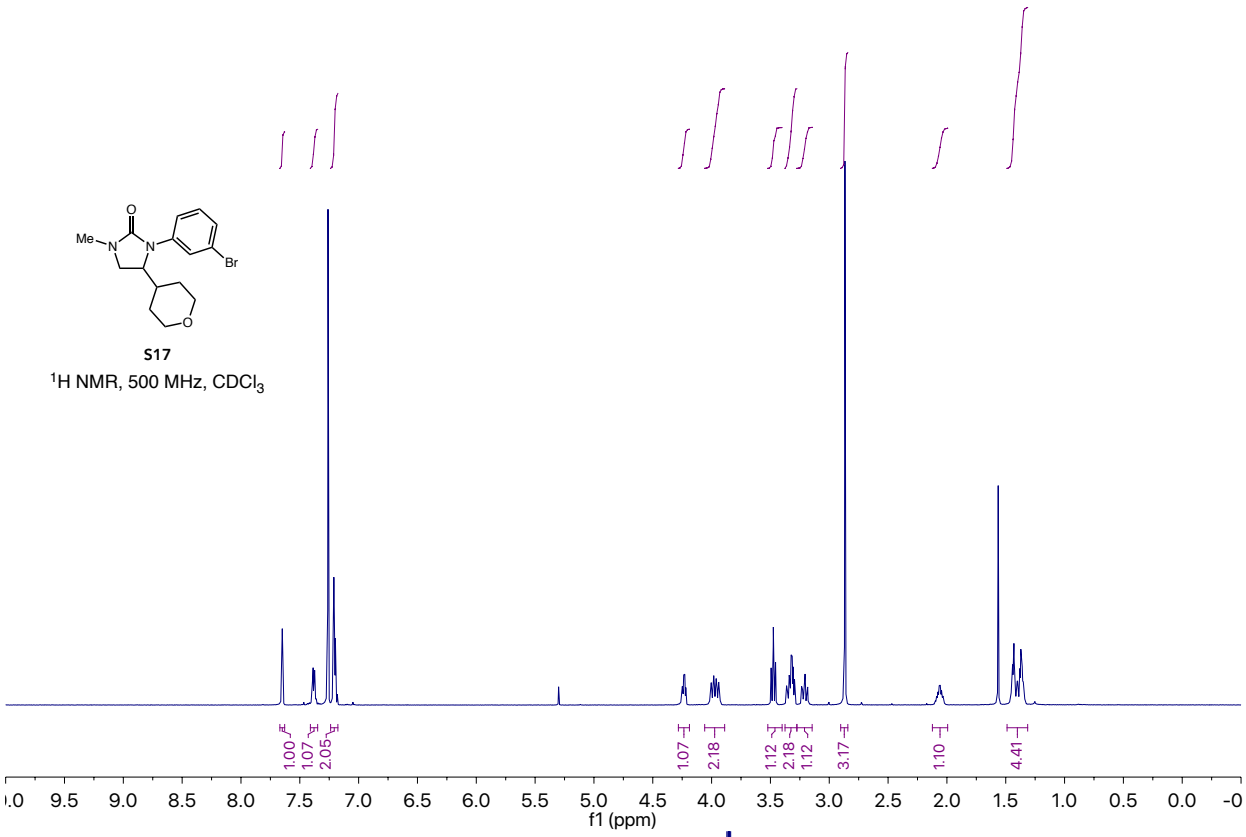
S16

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



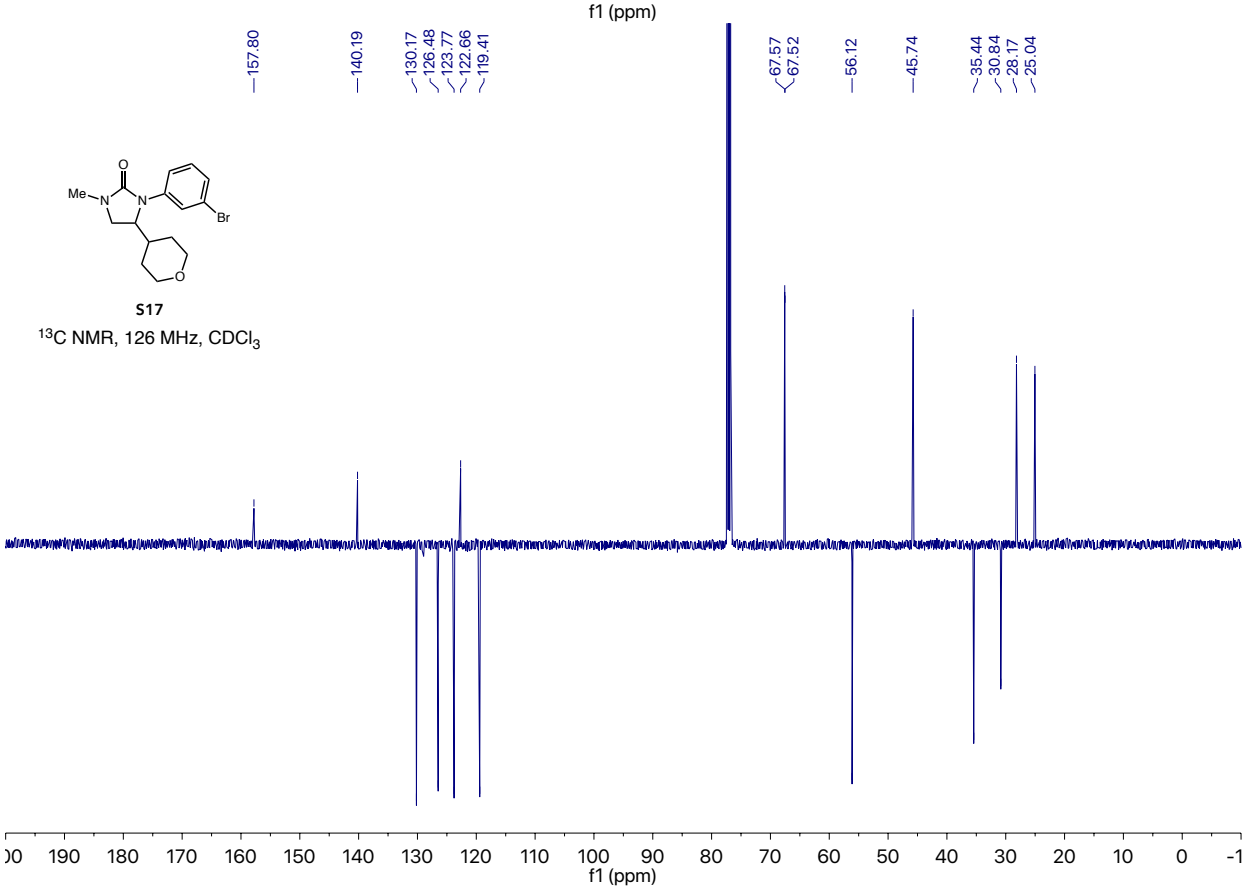
S16

^{13}C NMR, 126 MHz, $CDCl_3$



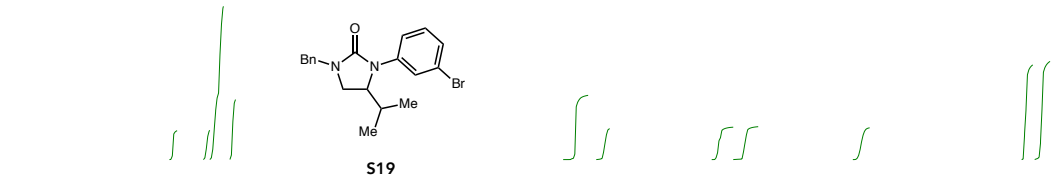
S17

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



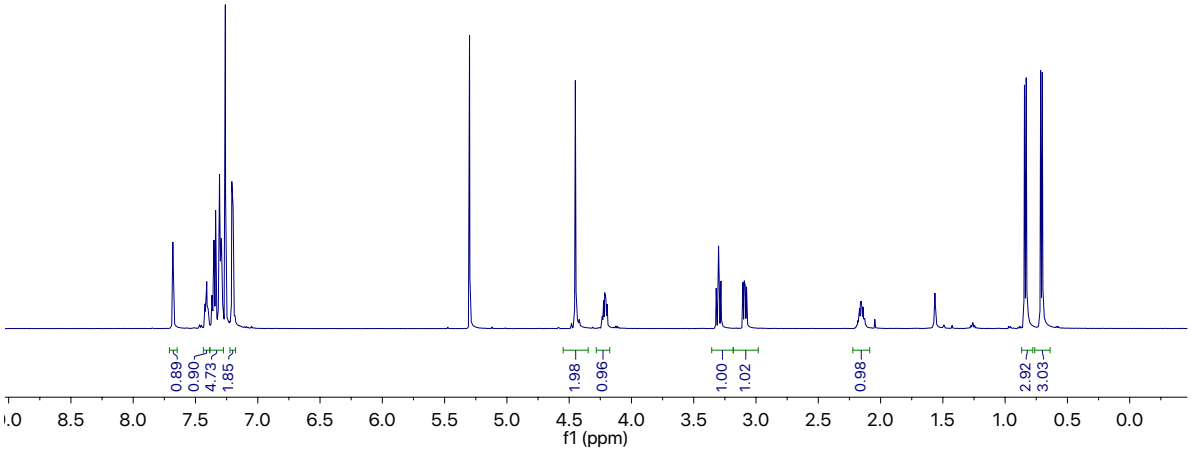
S17

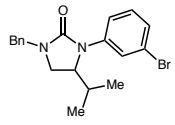
^{13}C NMR, 126 MHz, $CDCl_3$



S19

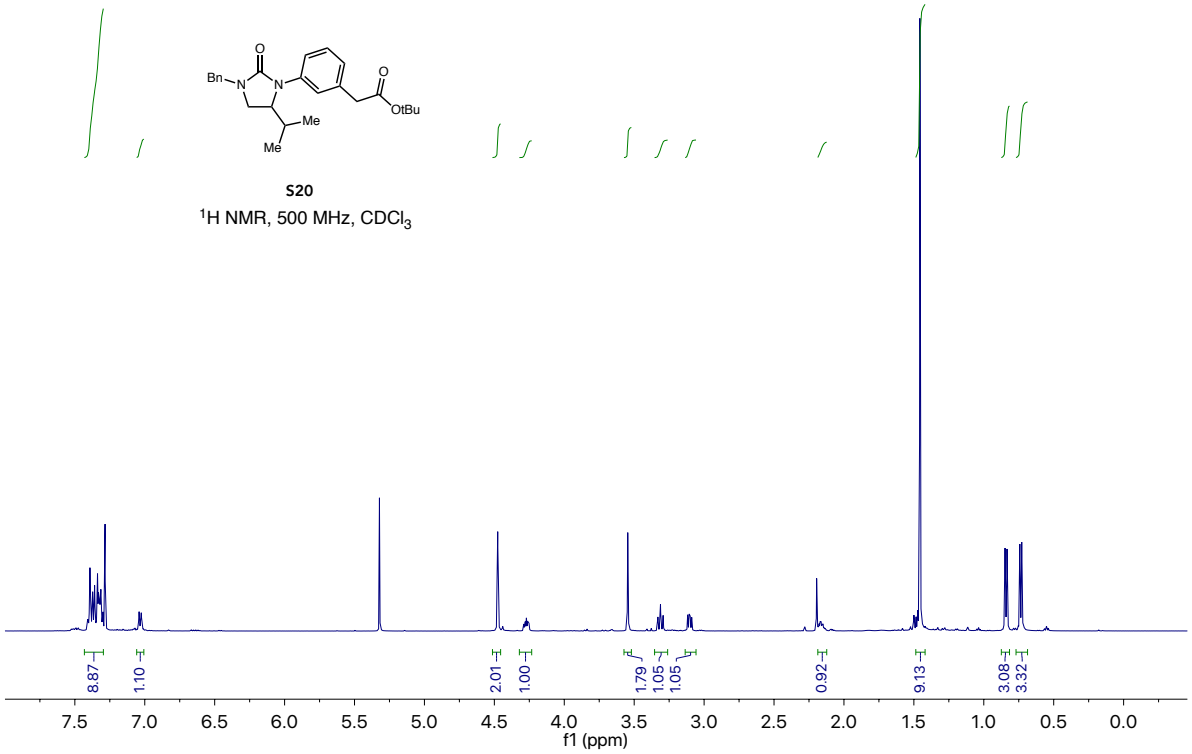
^{1}H NMR, 500 MHz, $CDCl_3$





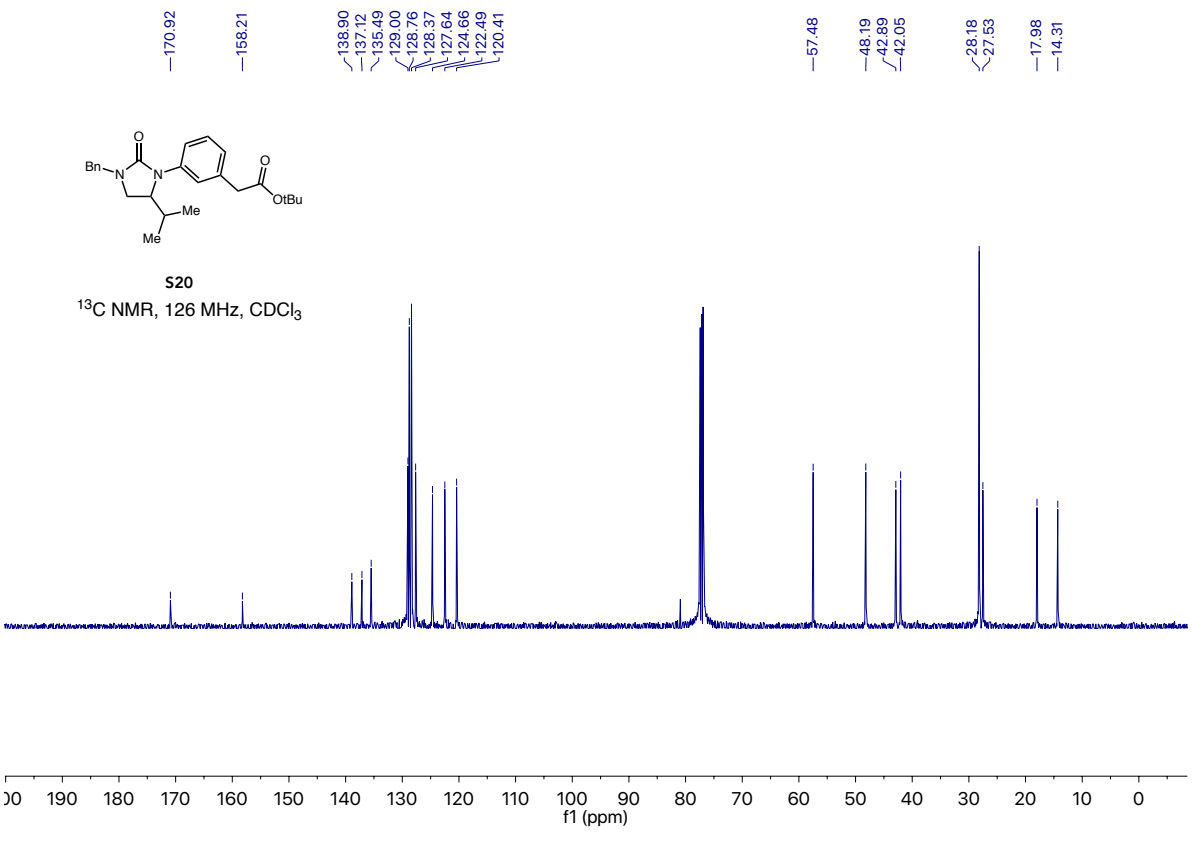
S19

^{13}C NMR, 126 MHz, $CDCl_3$



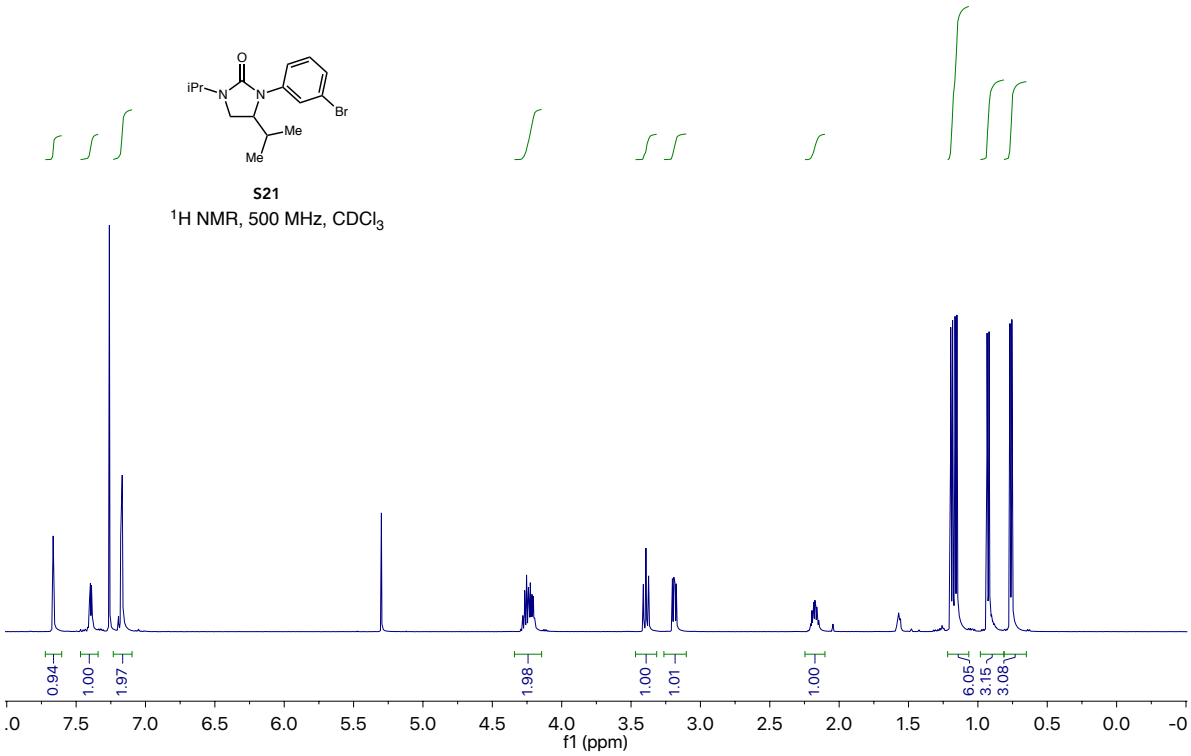
S20

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



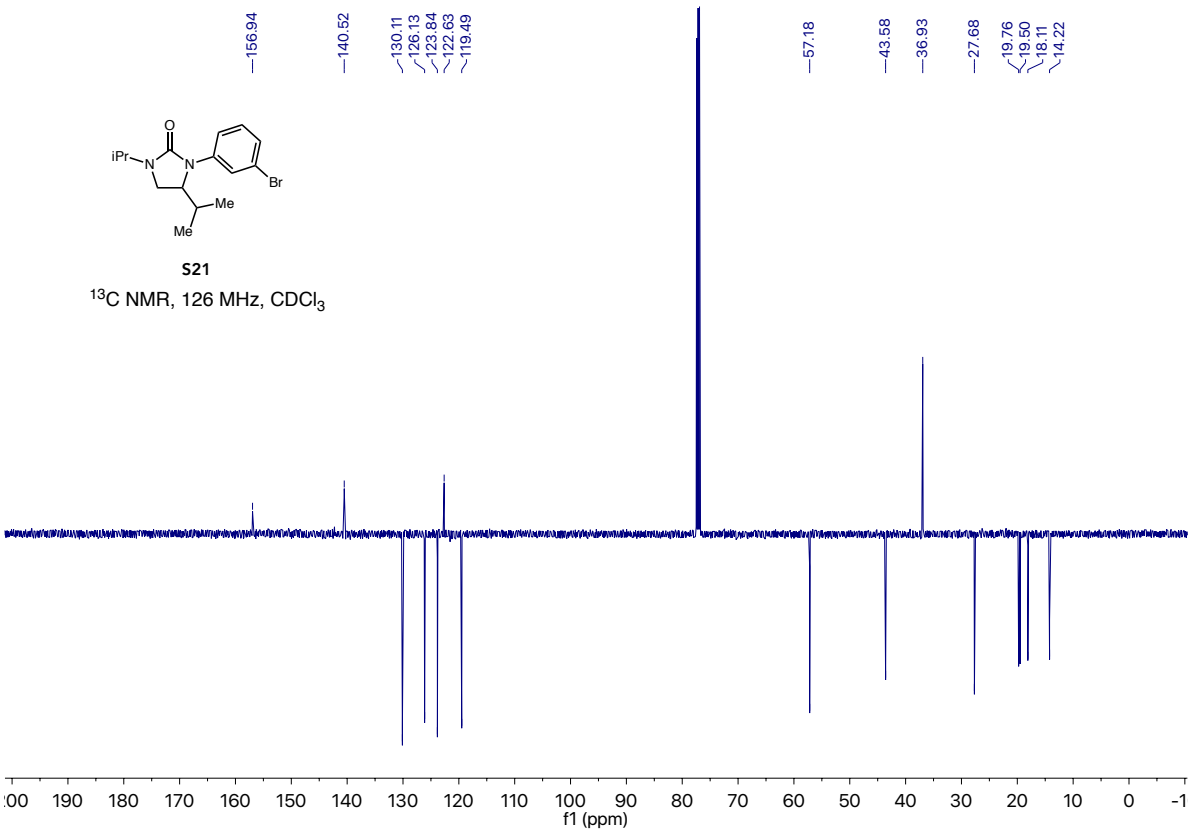
S20

^{13}C NMR, 126 MHz, $CDCl_3$



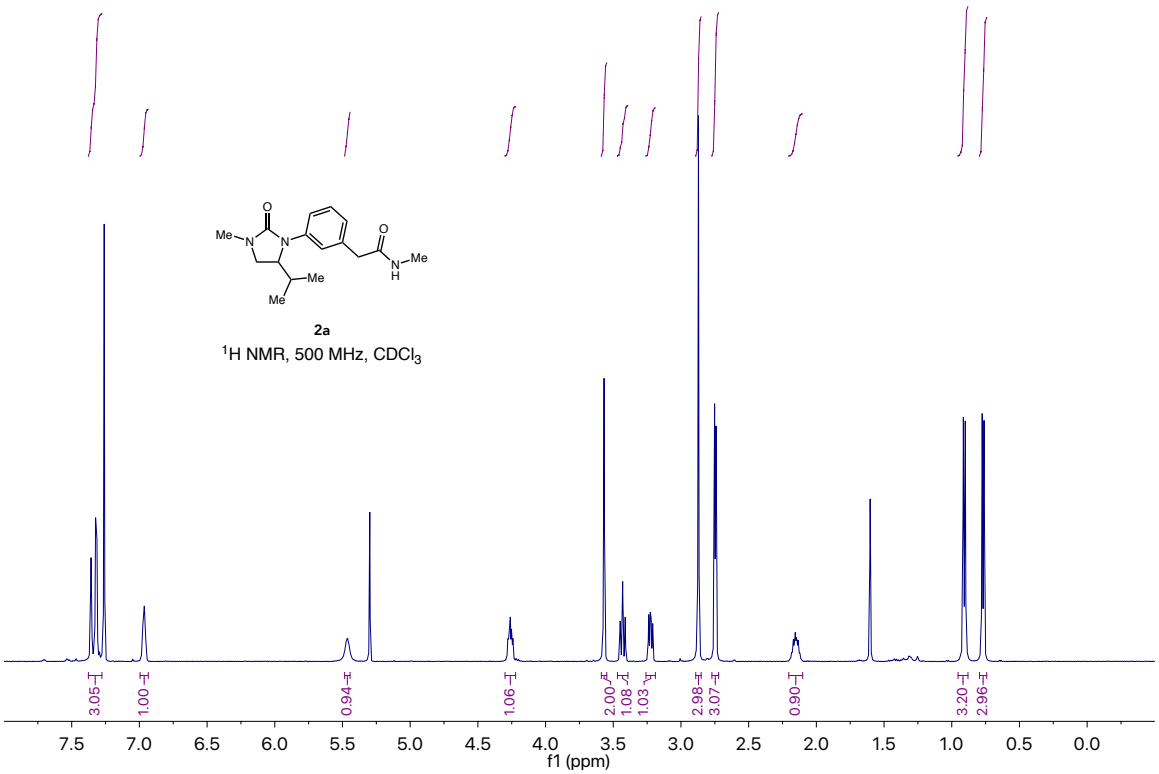
S21

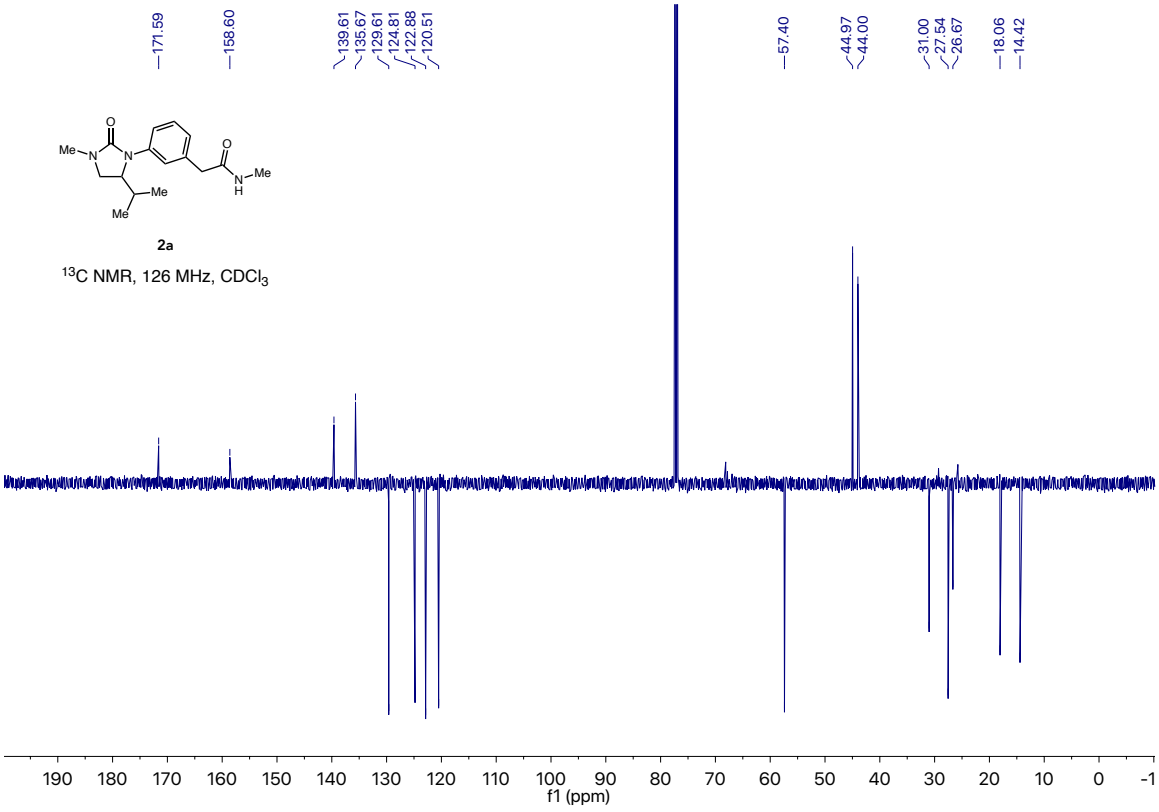
^{1}H NMR, 500 MHz, $CDCl_3$

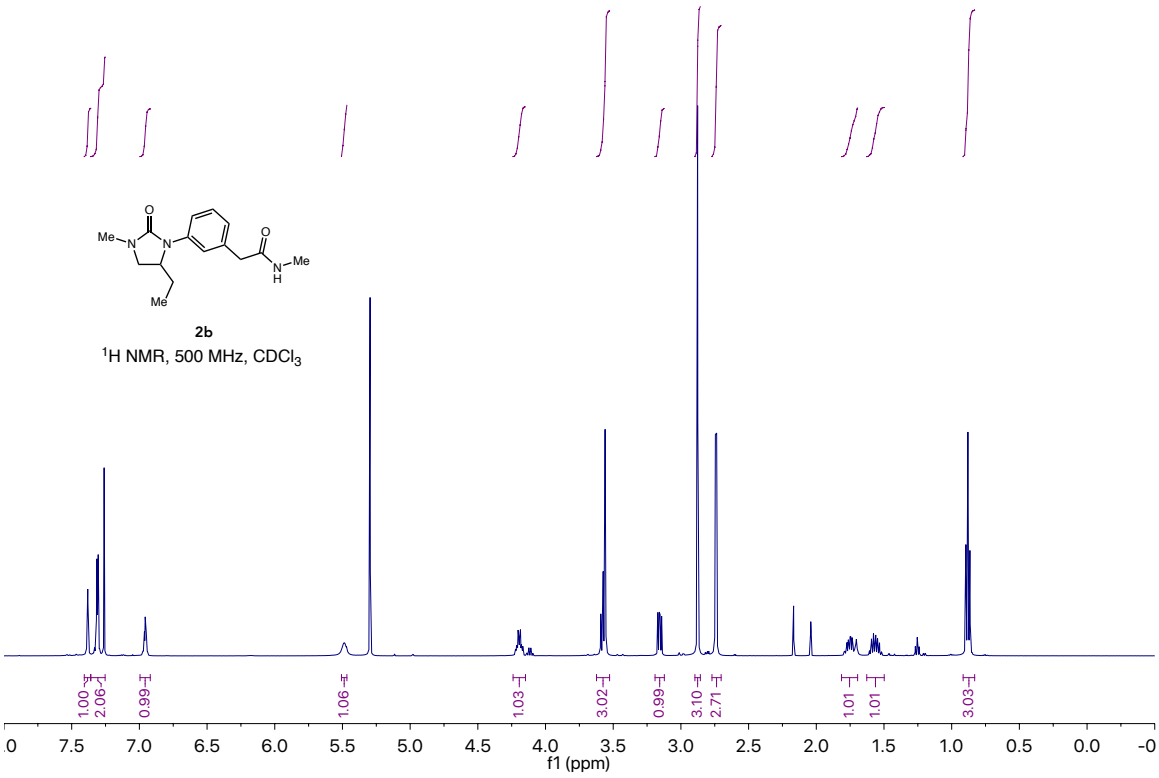


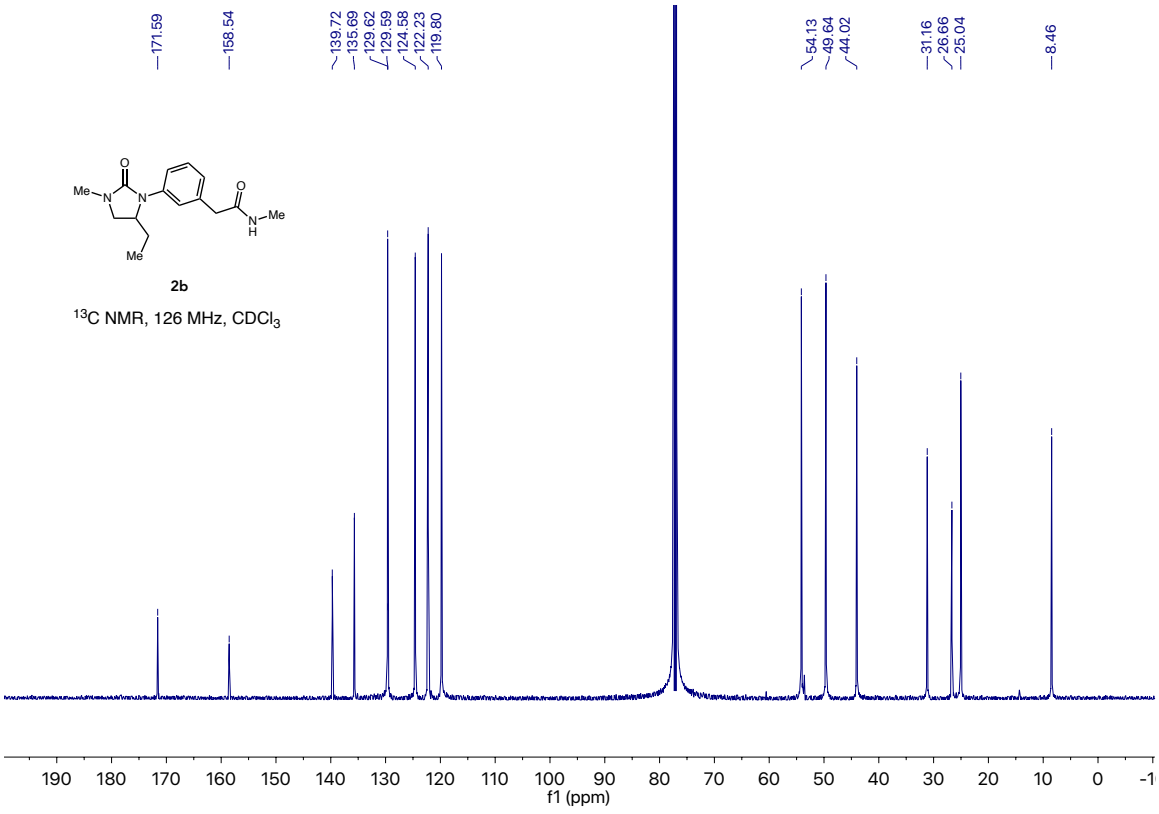
S21

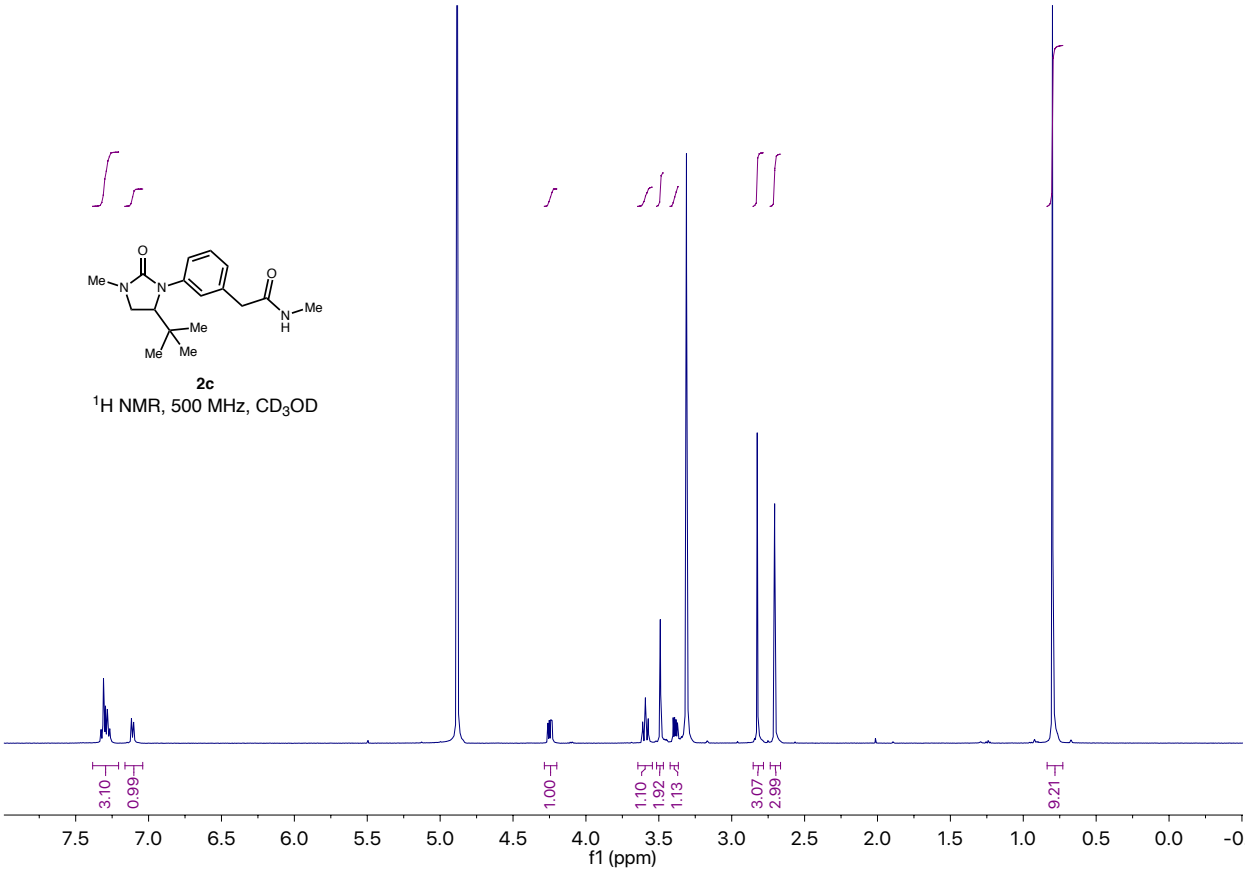
^{13}C NMR, 126 MHz, $CDCl_3$


Me
N
O
N
O
N
Me
H
Me
Me
2a
1H NMR, 500 MHz, CDCl3
3.05
1.00
0.94
1.06
2.00
1.08
1.03
2.98
3.07
0.90
3.20
2.96
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
f1 (ppm)


171.59
158.60
139.61
135.67
129.61
124.81
122.88
120.51
57.40
44.97
44.00
31.00
27.54
26.67
18.06
14.42
Me
N
O
N
O
N
Me
H
Me
Me
2a
13C NMR, 126 MHz, CDCl3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

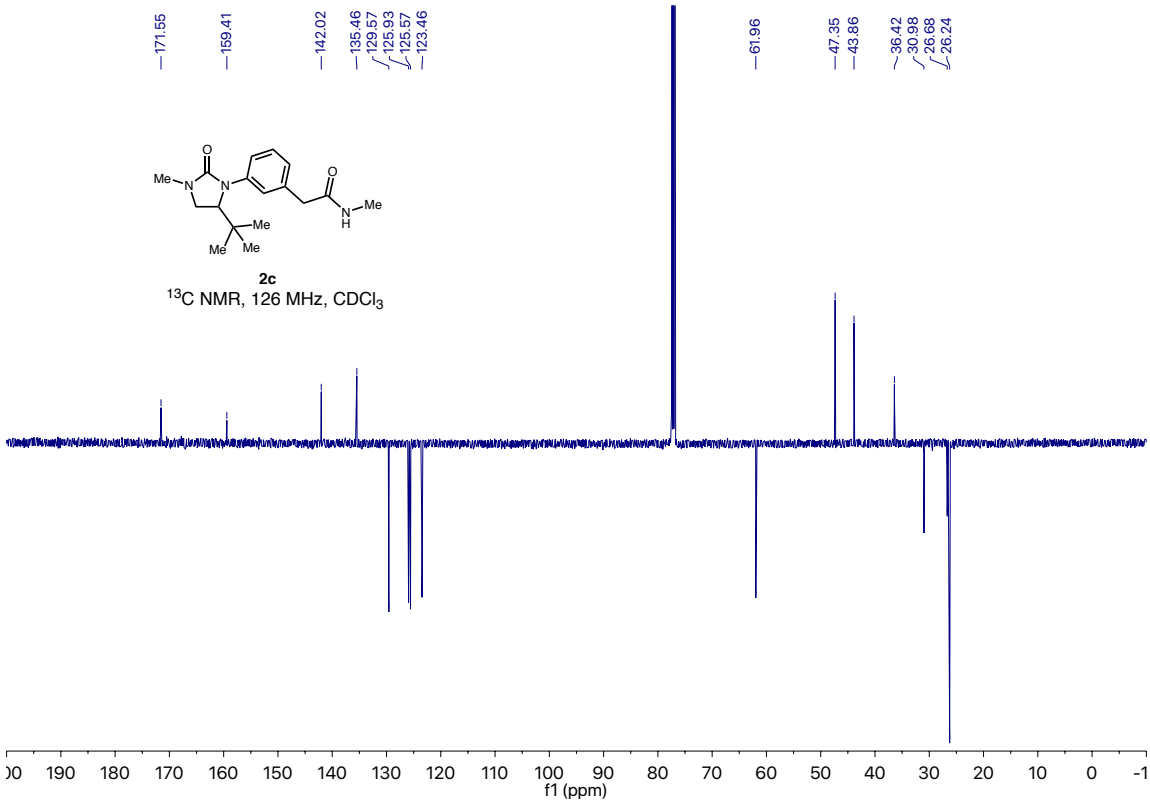

2b
1H NMR, 500 MHz, CDCl3
1.00
2.06
0.99
1.06
1.03
3.02
0.99
3.10
2.71
1.01
1.01
3.03
f1 (ppm)


171.59
158.54
139.72
135.69
129.62
129.59
124.58
122.23
119.80
54.13
49.64
44.02
31.16
26.66
25.04
8.46
2b
13C NMR, 126 MHz, CDCl3
f1 (ppm)



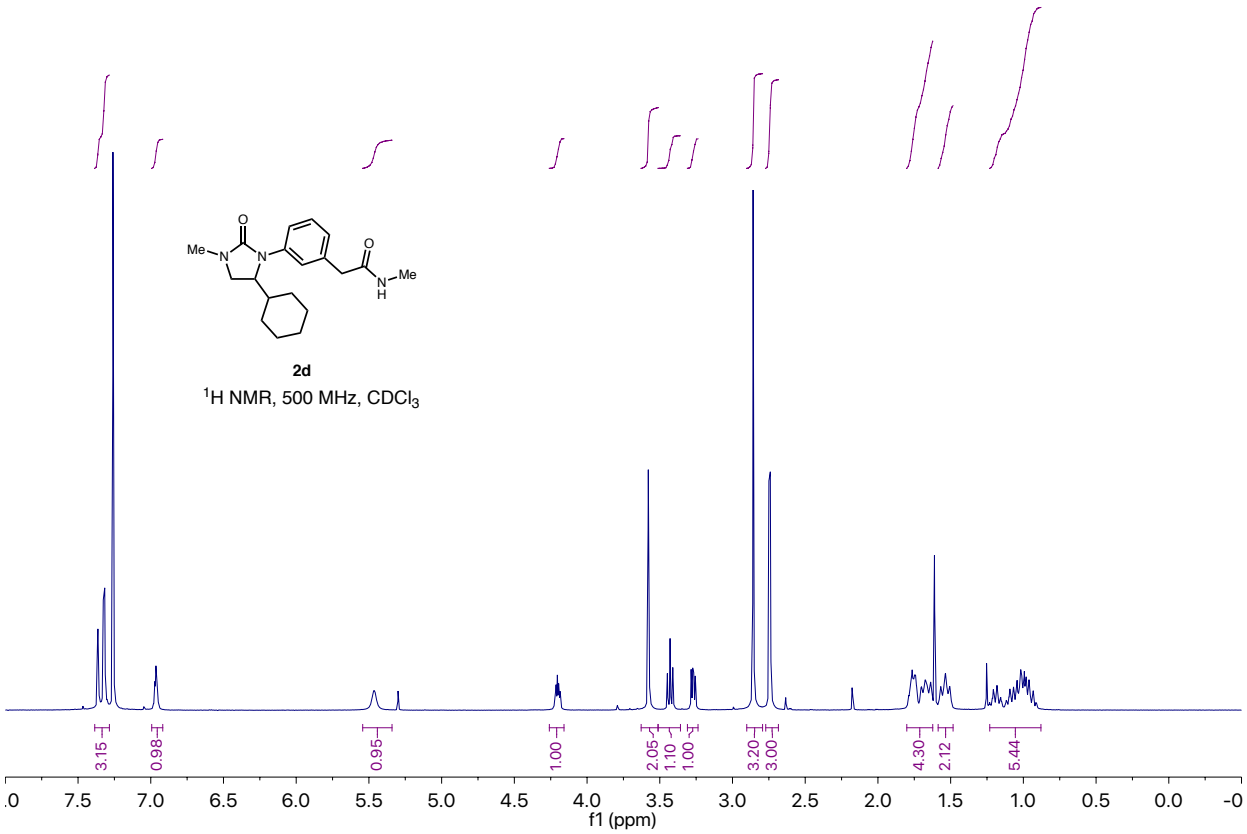
2c

^{1}H NMR, 500 MHz, CD_3OD



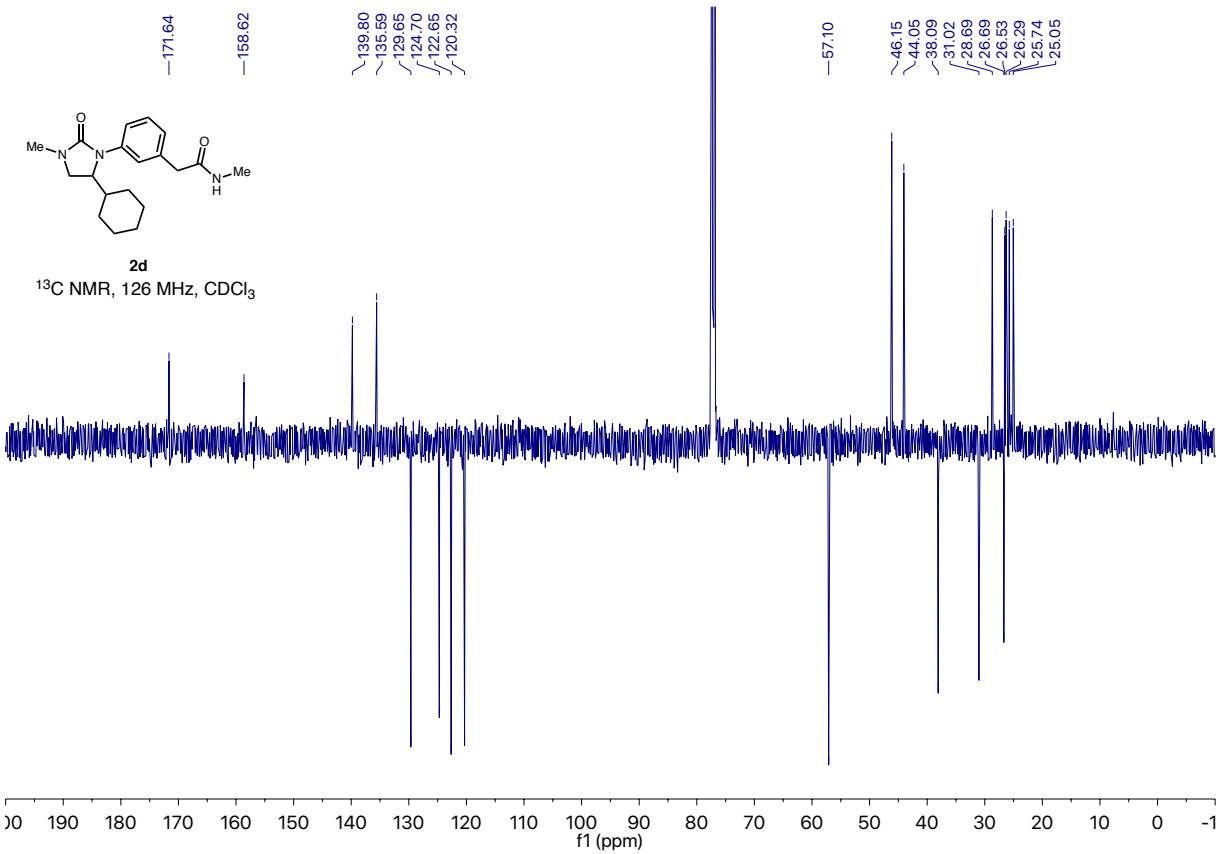
2c

^{13}C NMR, 126 MHz, $CDCl_3$



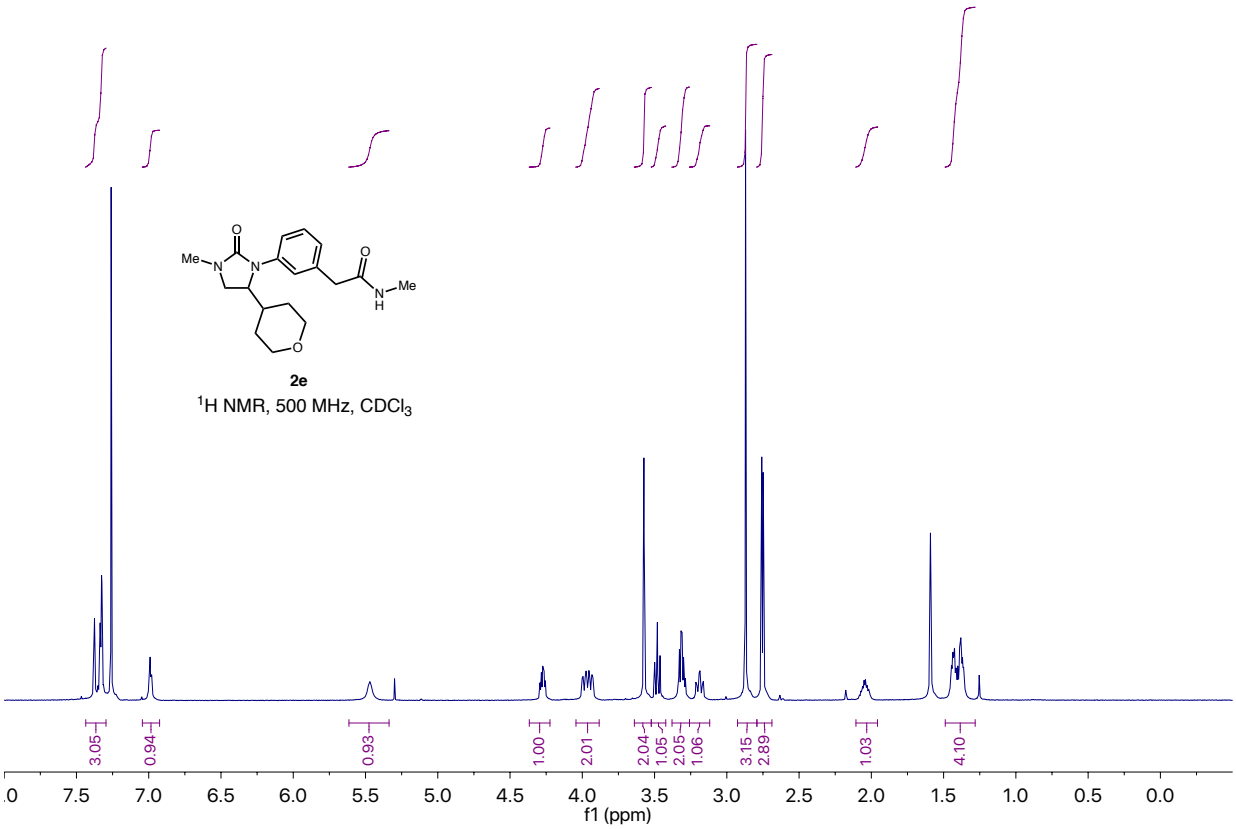
2d

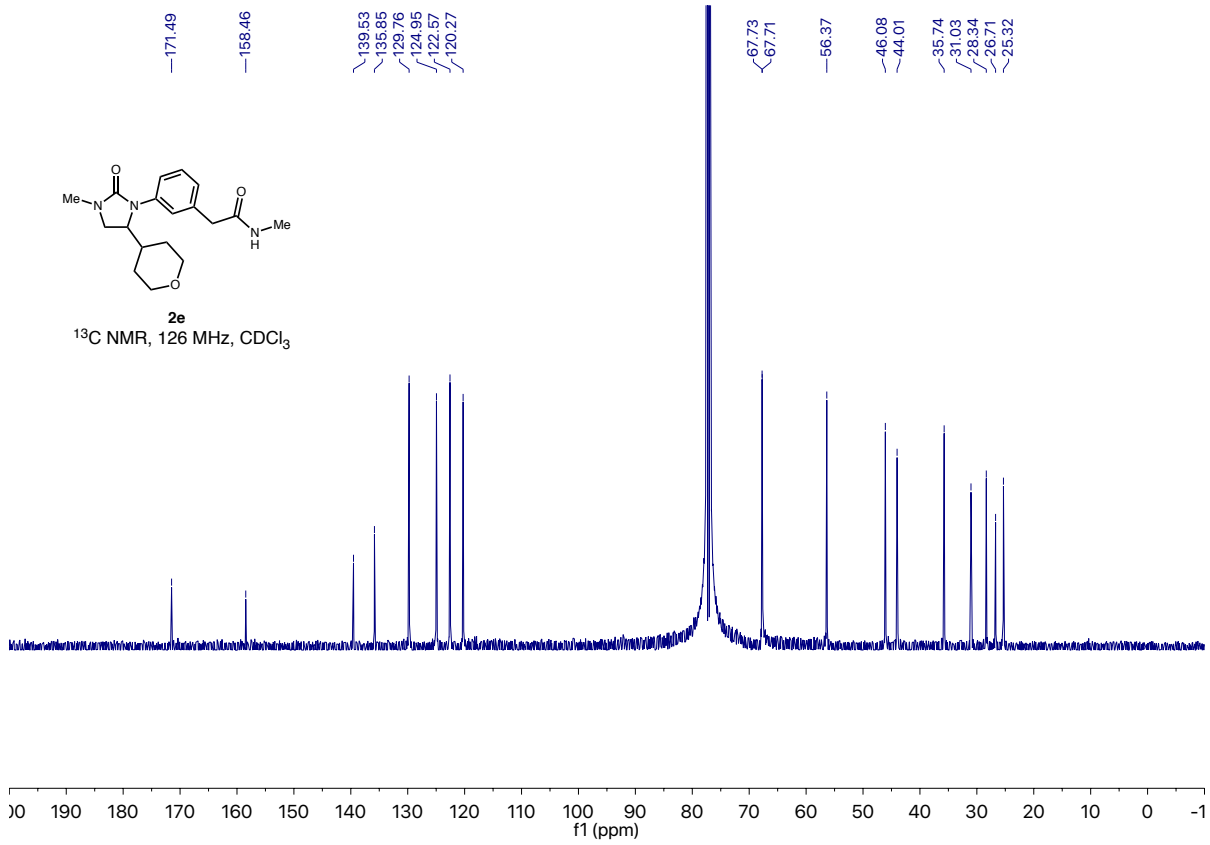
^{1}H NMR, 500 MHz, $CDCl_3$

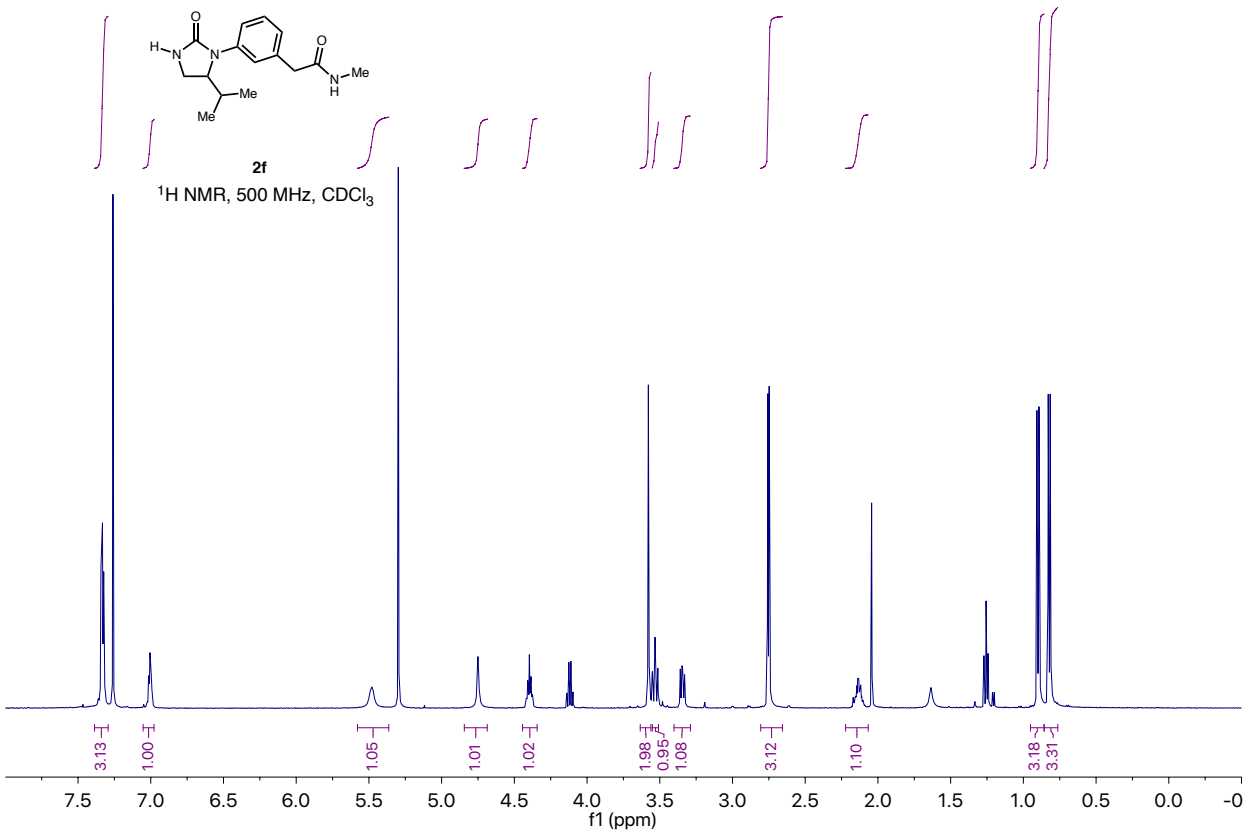


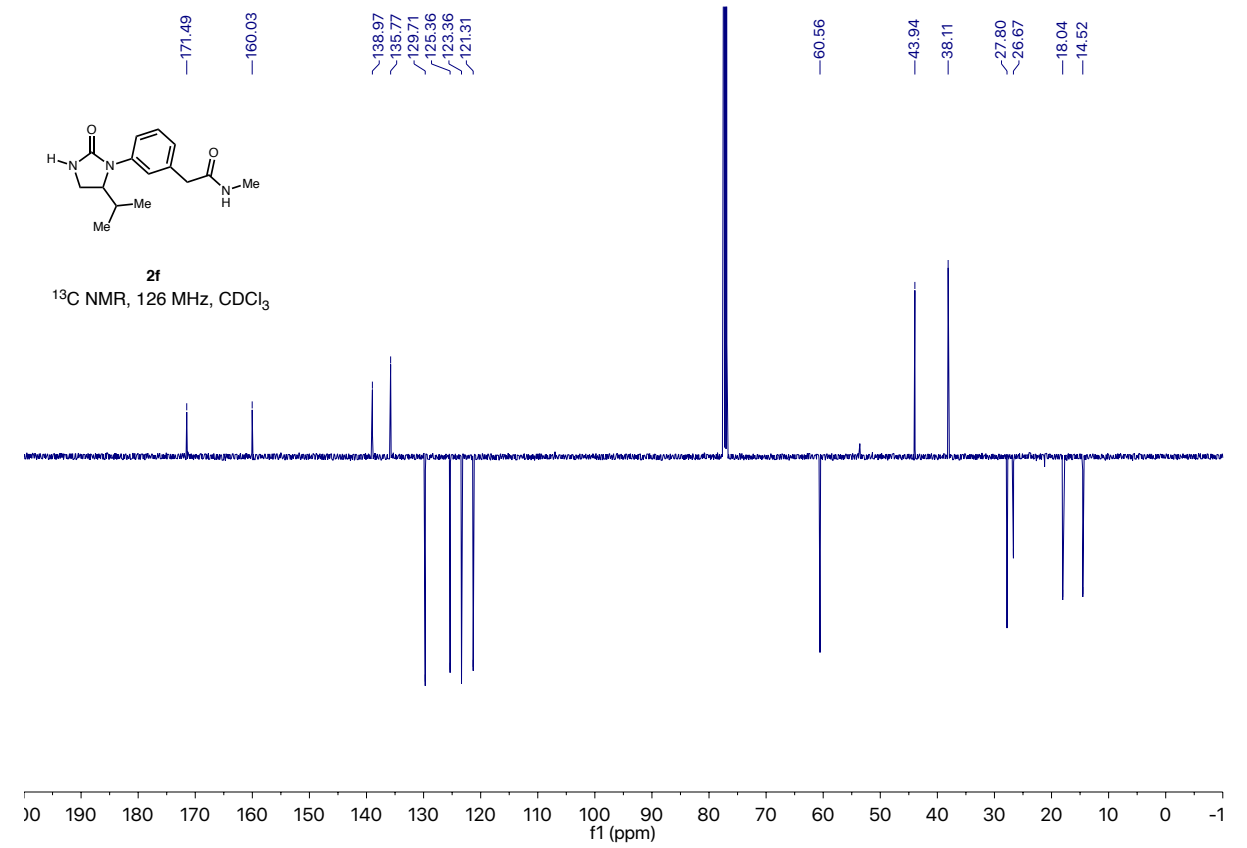
2d

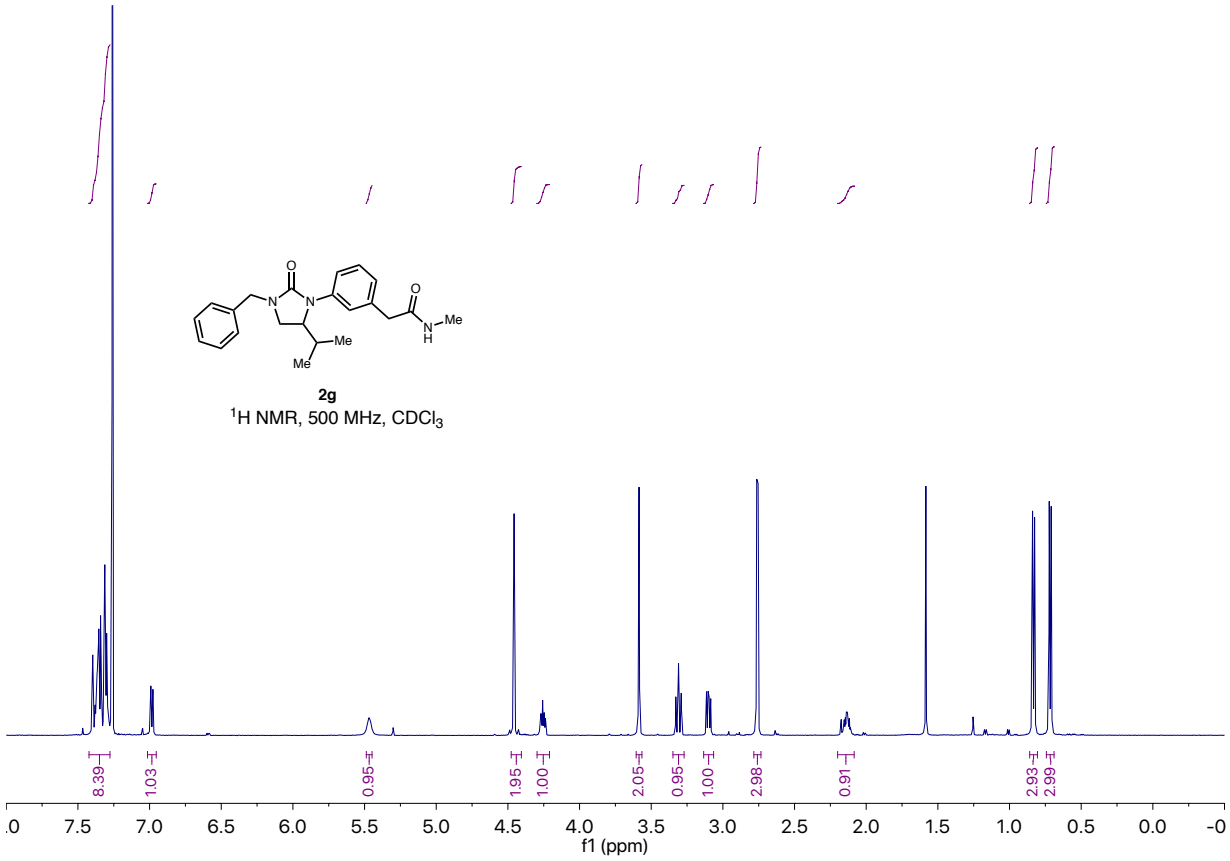
^{13}C NMR, 126 MHz, $CDCl_3$


2e
^{1}H NMR, 500 MHz, $CDCl_3$
3.05
0.94
0.93
1.00
2.01
2.04
1.05
2.05
1.06
3.15
2.89
1.03
4.10
f1 (ppm)


171.49
158.46
139.53
135.85
129.76
124.95
122.57
120.27
67.73
67.71
56.37
46.08
44.01
35.74
31.03
28.34
26.71
25.32
2e
^{13}C NMR, 126 MHz, $CDCl_3$
f1 (ppm)

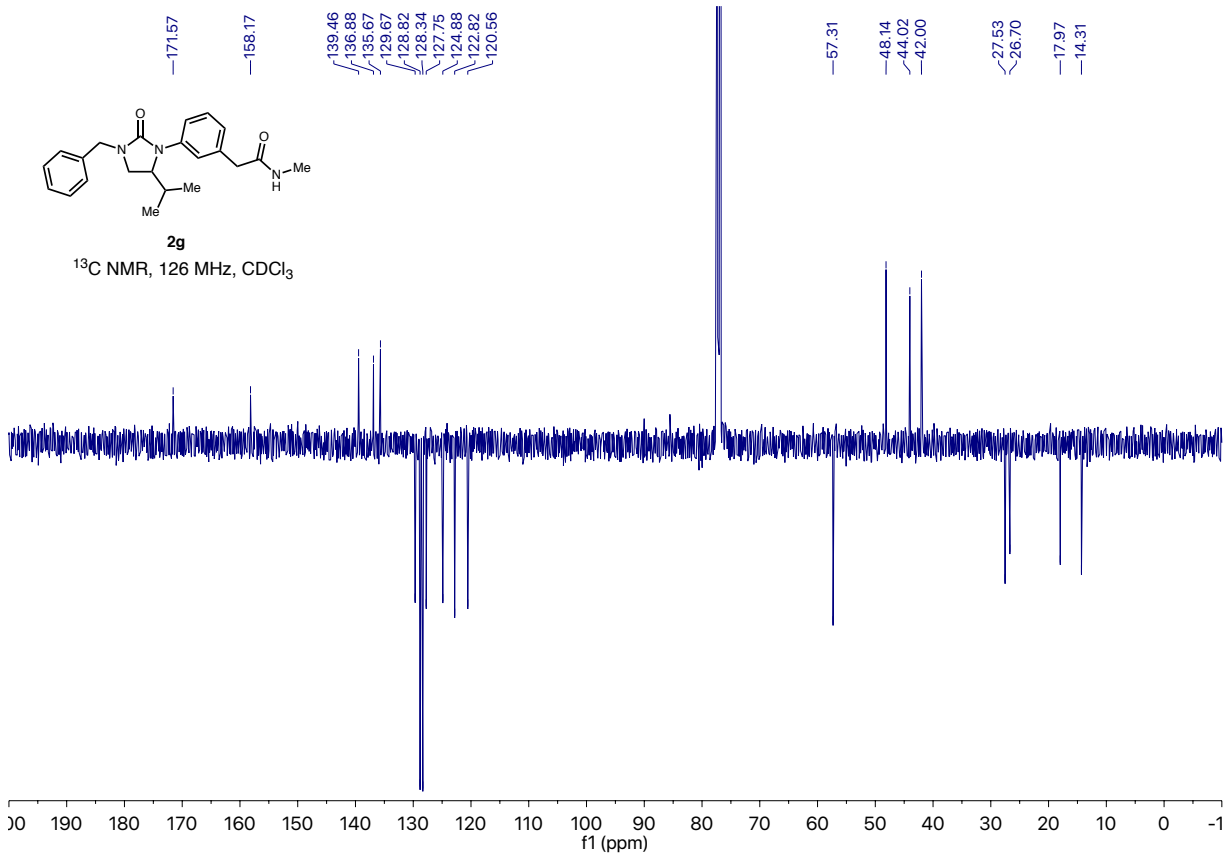

2f
^{1}H NMR, 500 MHz, $CDCl_3$
3.13
1.00
1.05
1.01
1.02
1.98
0.95
1.08
3.12
1.10
3.18
3.31
f1 (ppm)


171.49
160.03
138.97
135.77
129.71
125.36
123.36
121.31
60.56
43.94
38.11
27.80
26.67
18.04
14.52
2f
^{13}C NMR, 126 MHz, $CDCl_3$
f1 (ppm)



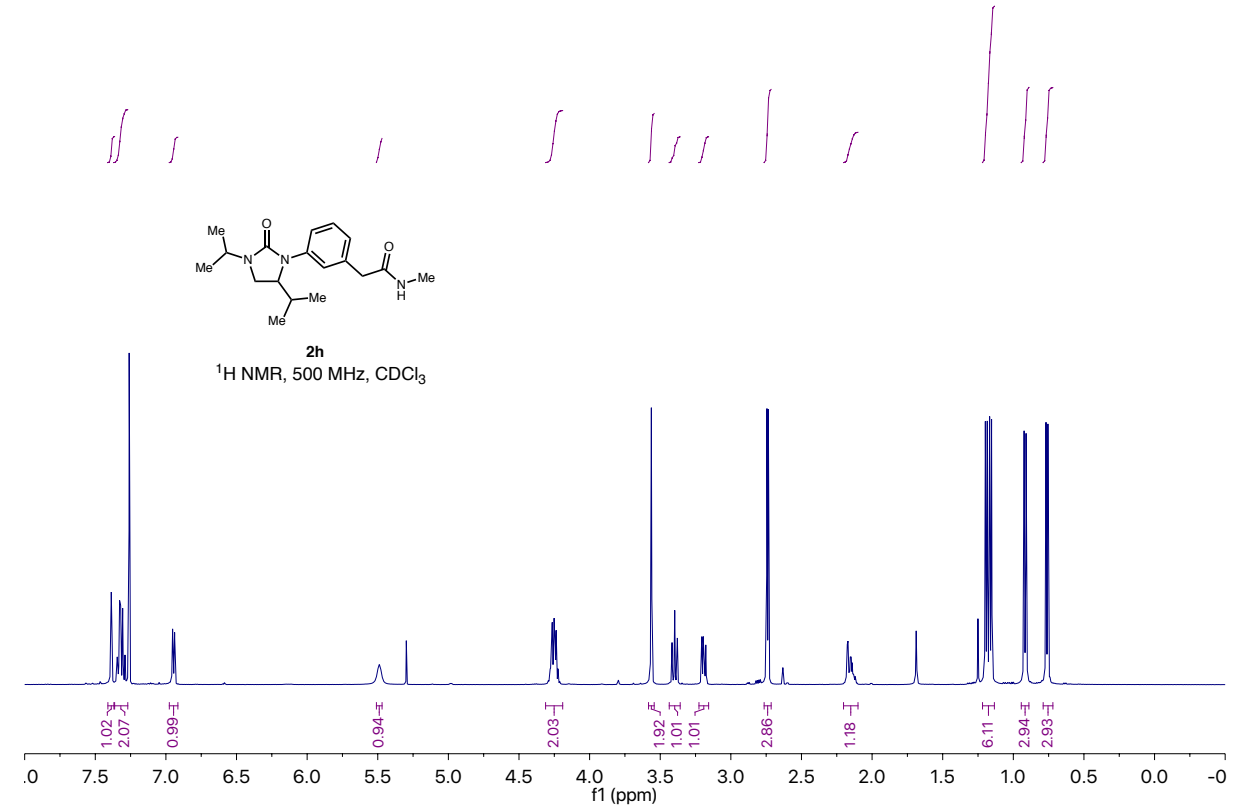
2g

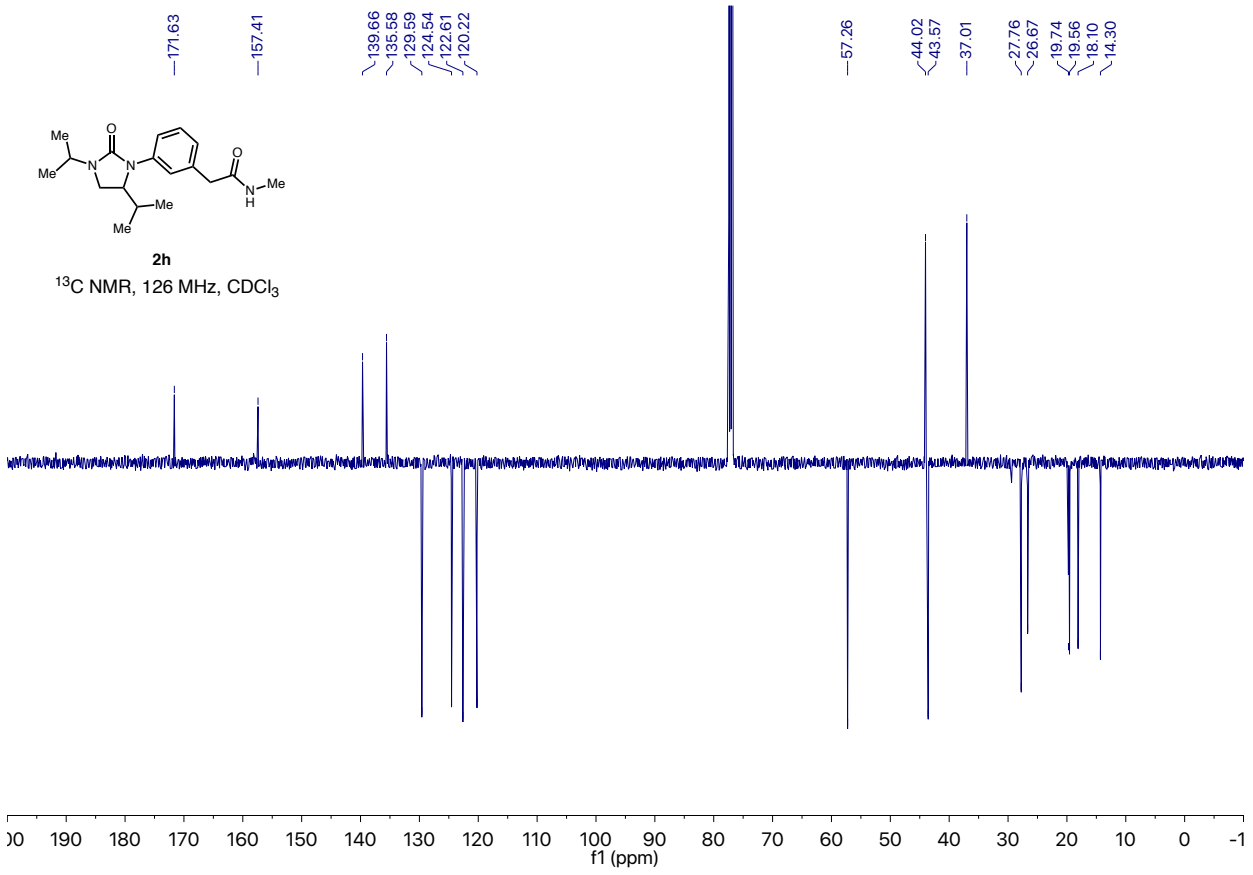
^{1}H NMR, 500 MHz, $CDCl_3$

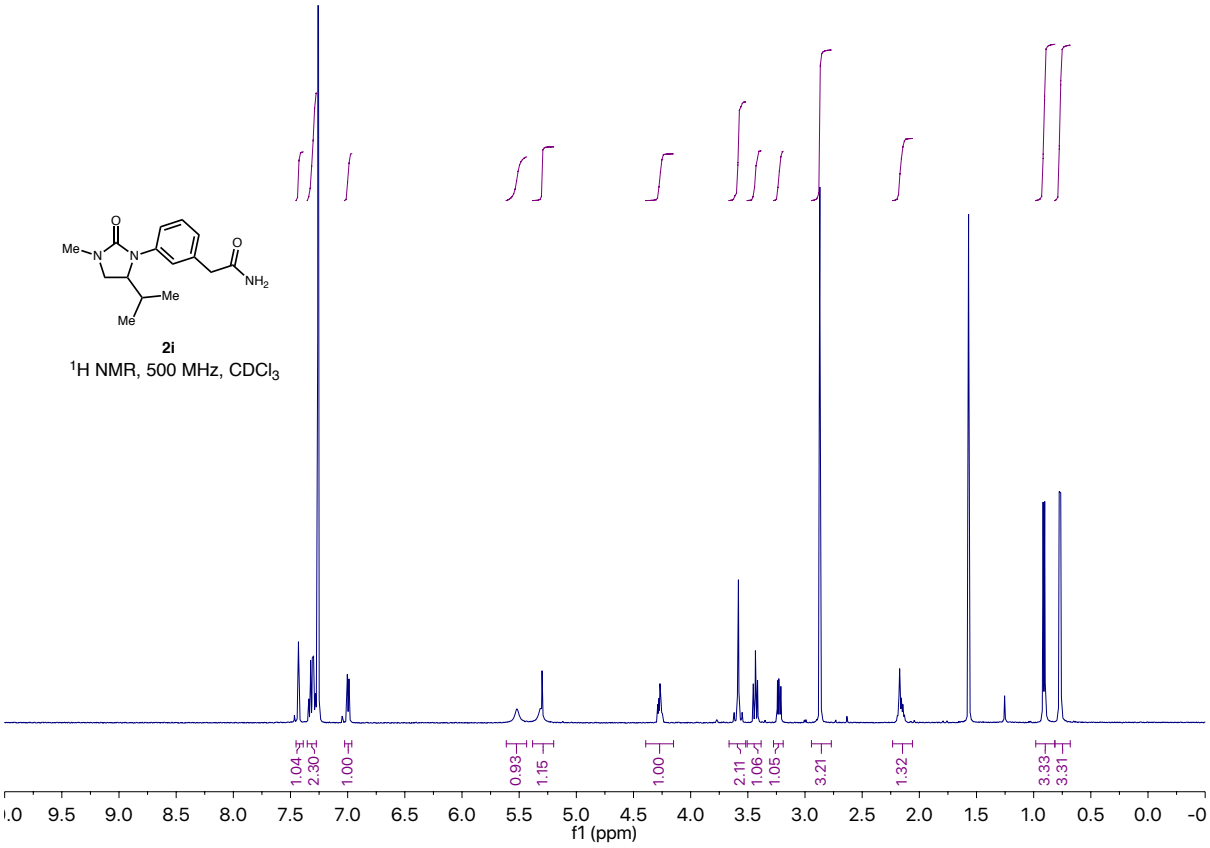


2g

^{13}C NMR, 126 MHz, $CDCl_3$

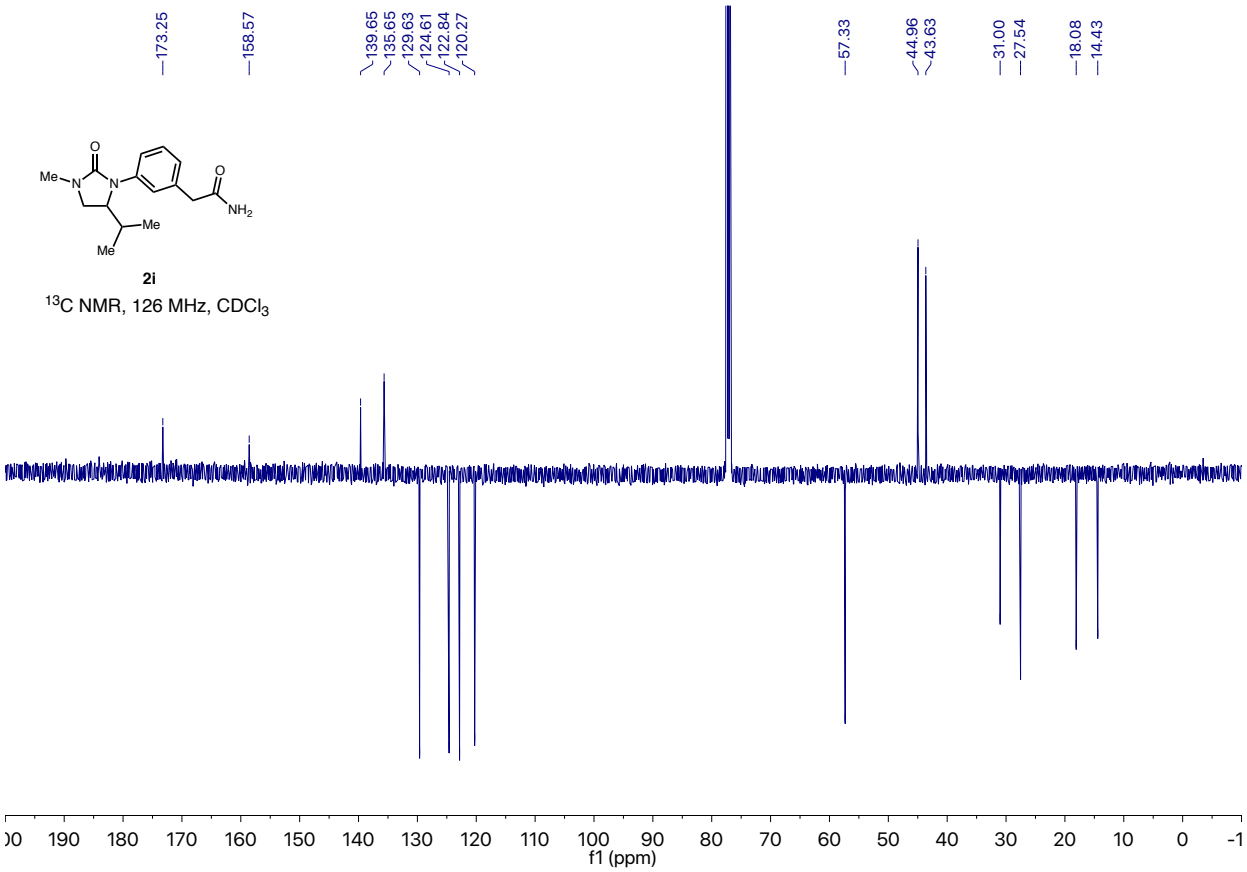

2h
1H NMR, 500 MHz, CDCl3
1.02
2.07
0.99
0.94
2.03
1.92
1.01
1.01
2.86
1.18
6.11
2.94
2.93
f1 (ppm)


171.63
157.41
139.66
135.58
129.59
124.54
122.61
120.22
57.26
44.02
43.57
37.01
27.76
26.67
19.74
19.56
18.10
14.30
2h
13C NMR, 126 MHz, CDCl3
f1 (ppm)



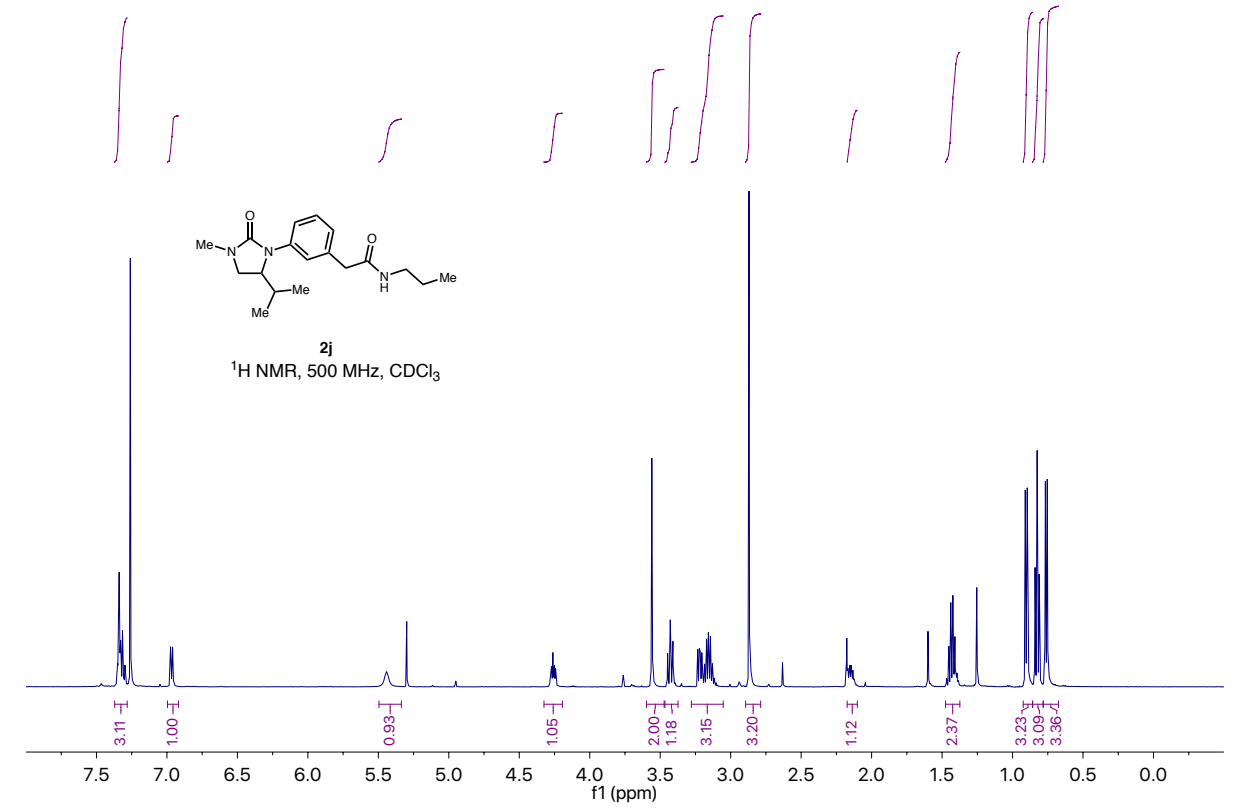
2i

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



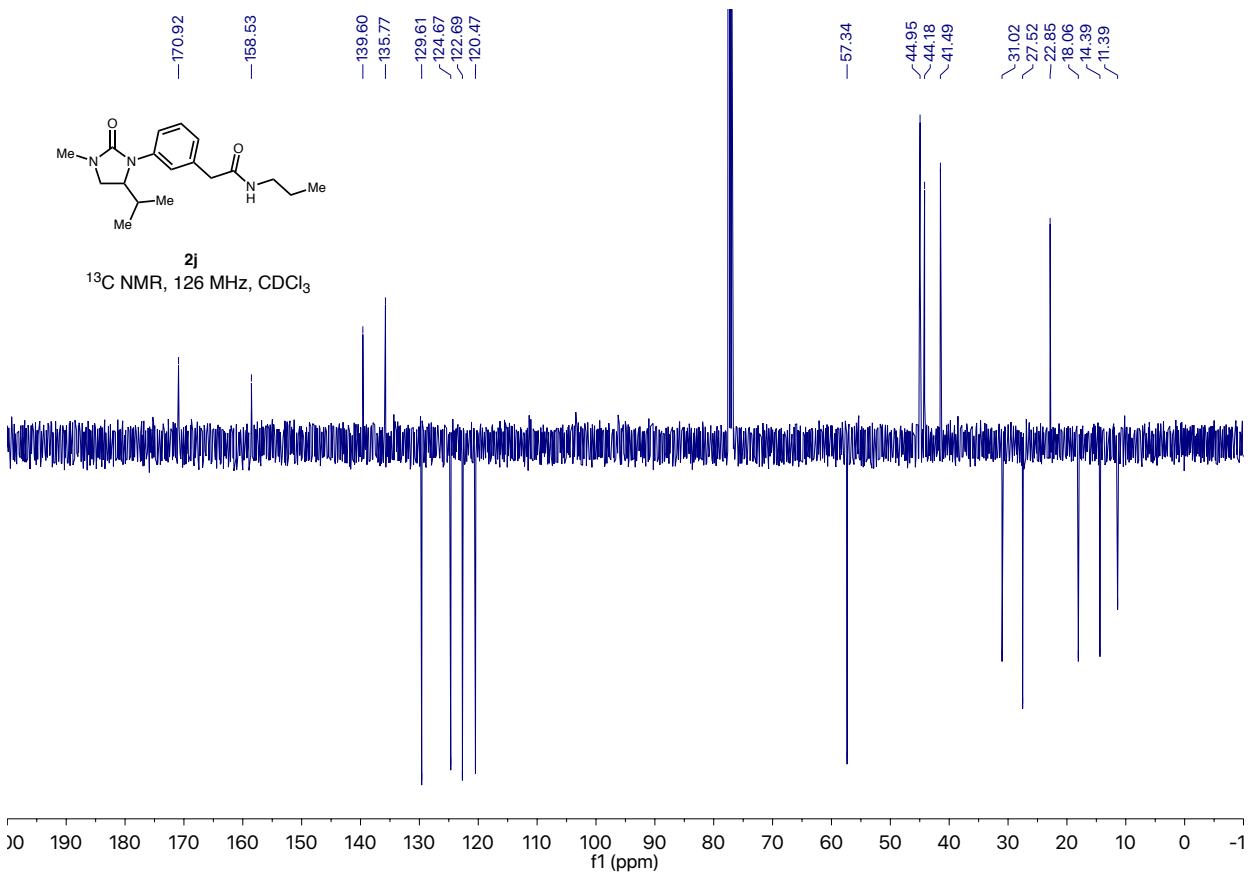
2i

^{13}C NMR, 126 MHz, $CDCl_3$



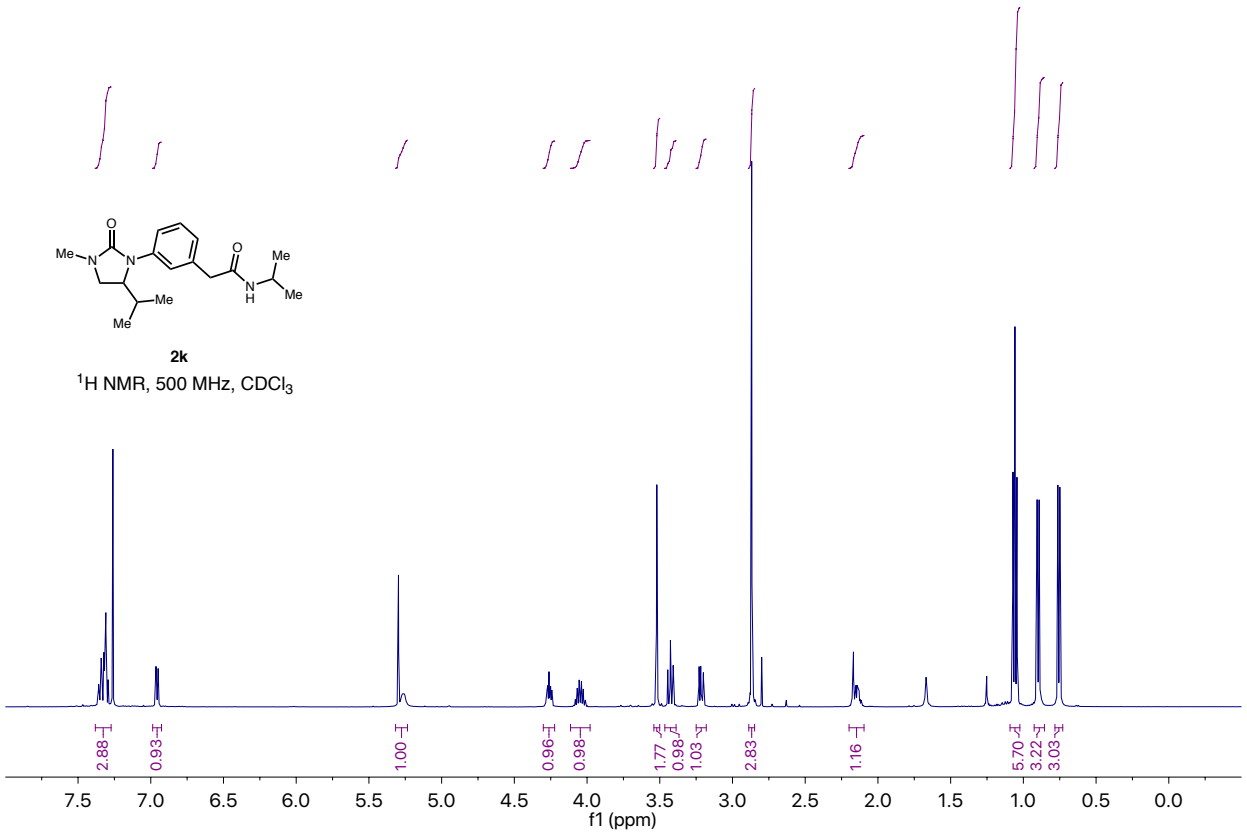
2j

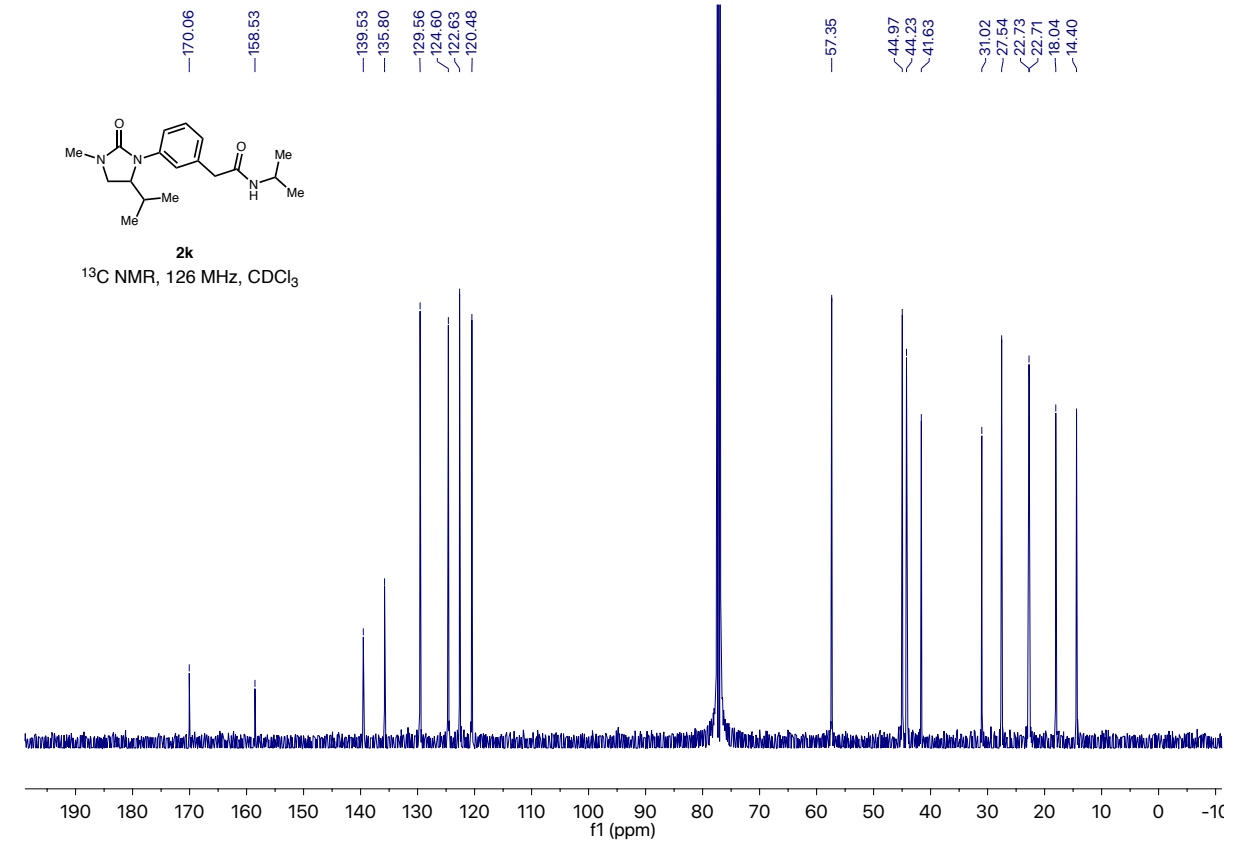
^{1}H NMR, 500 MHz, $CDCl_3$

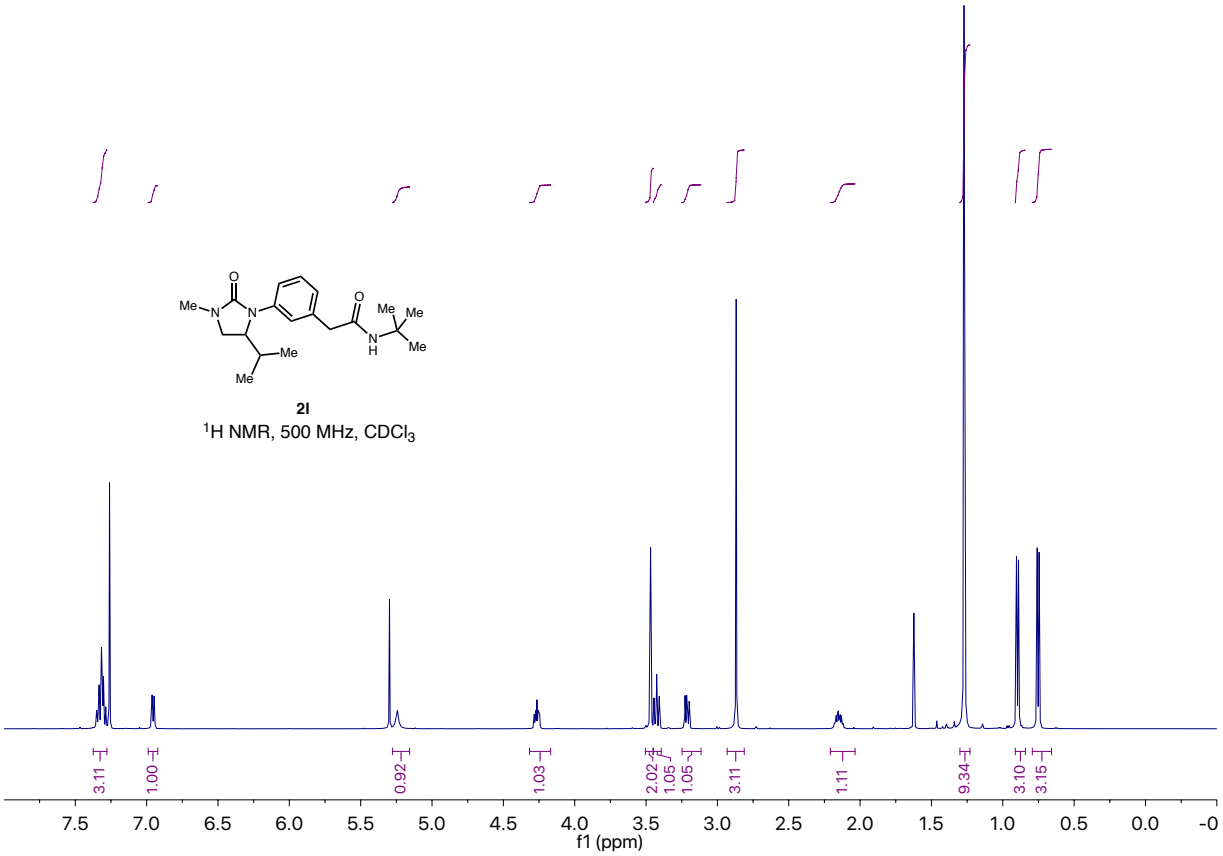


2j

^{13}C NMR, 126 MHz, $CDCl_3$

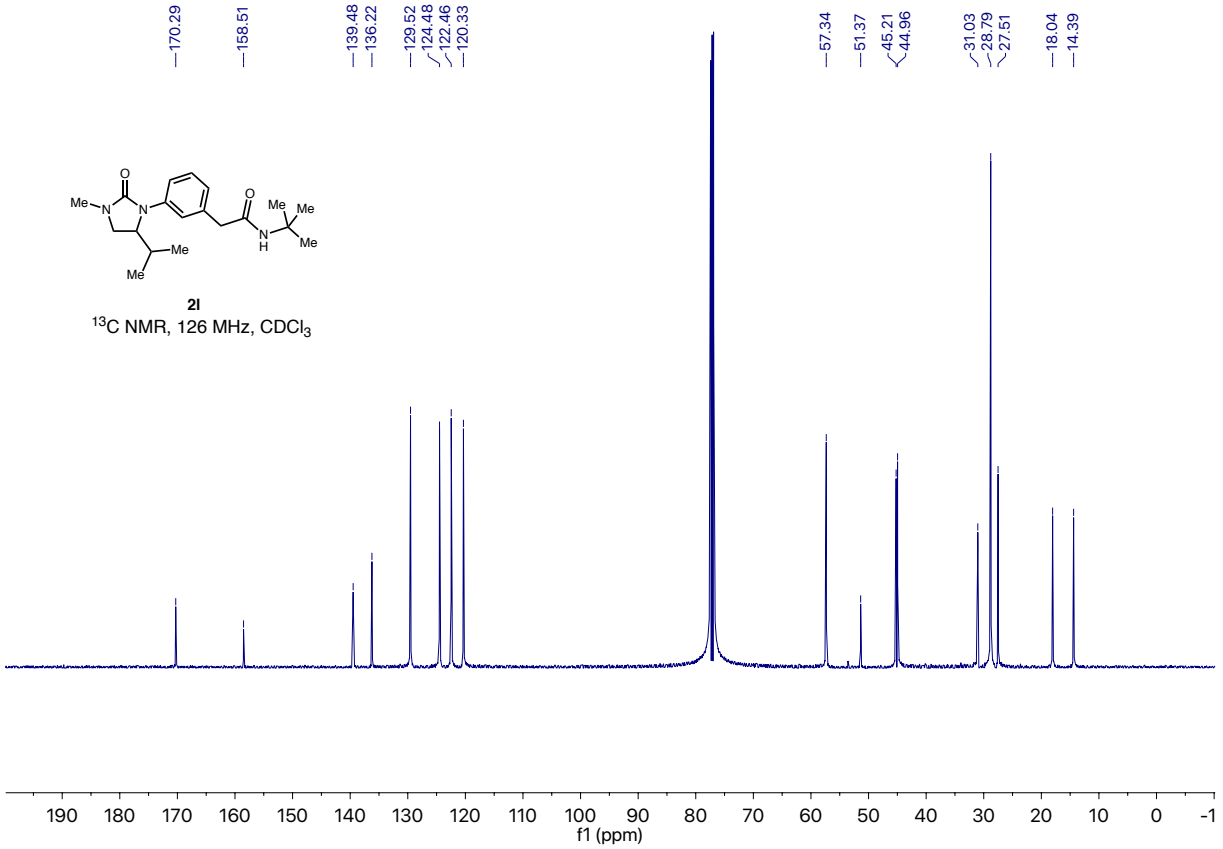

2k
1H NMR, 500 MHz, CDCl3
2.88
0.93
1.00
0.96
0.98
1.77
0.98
1.03
2.83
1.16
5.70
3.22
3.03
f1 (ppm)


170.06
158.53
139.53
135.80
129.56
124.60
122.63
120.48
57.35
44.97
44.23
41.63
31.02
27.54
22.73
22.71
18.04
14.40
2k
13C NMR, 126 MHz, CDCl3
f1 (ppm)



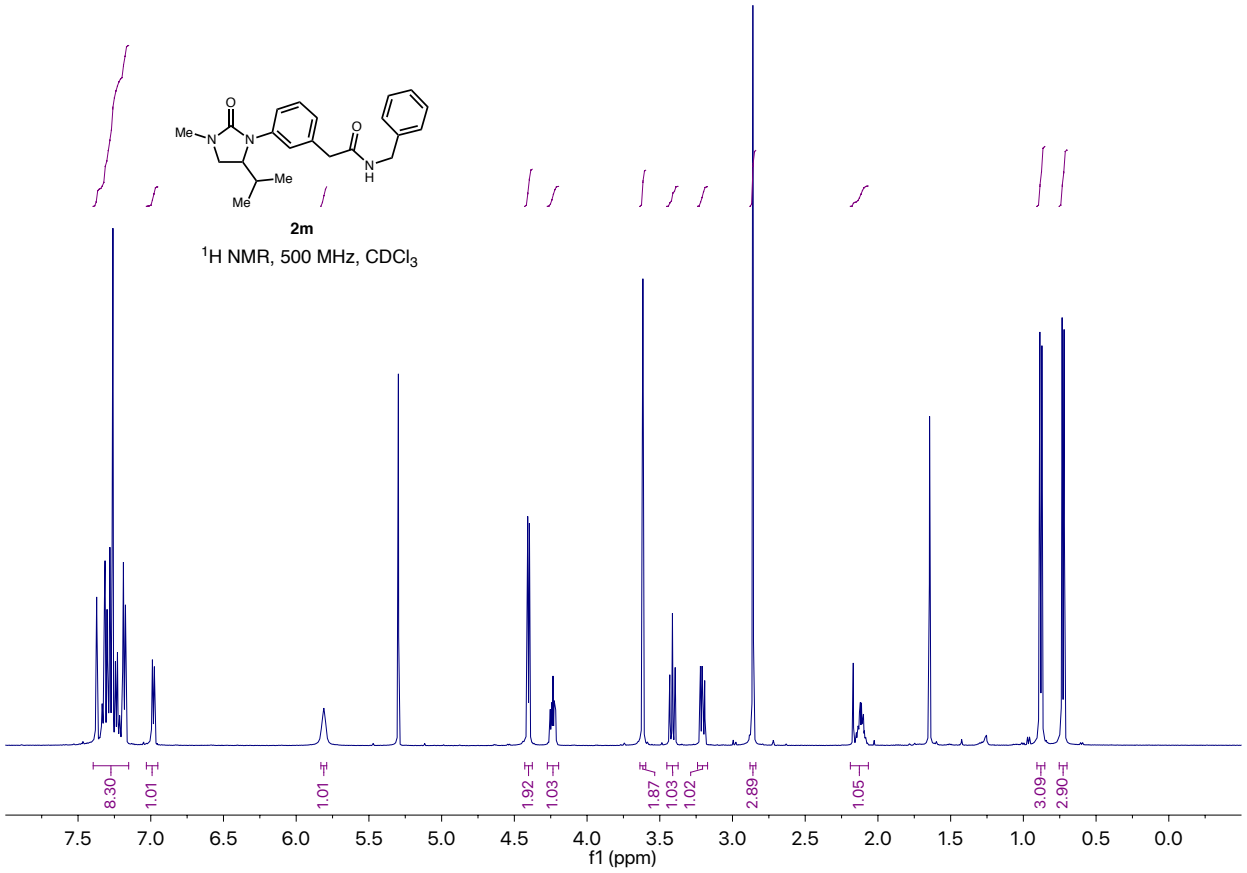
2l

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



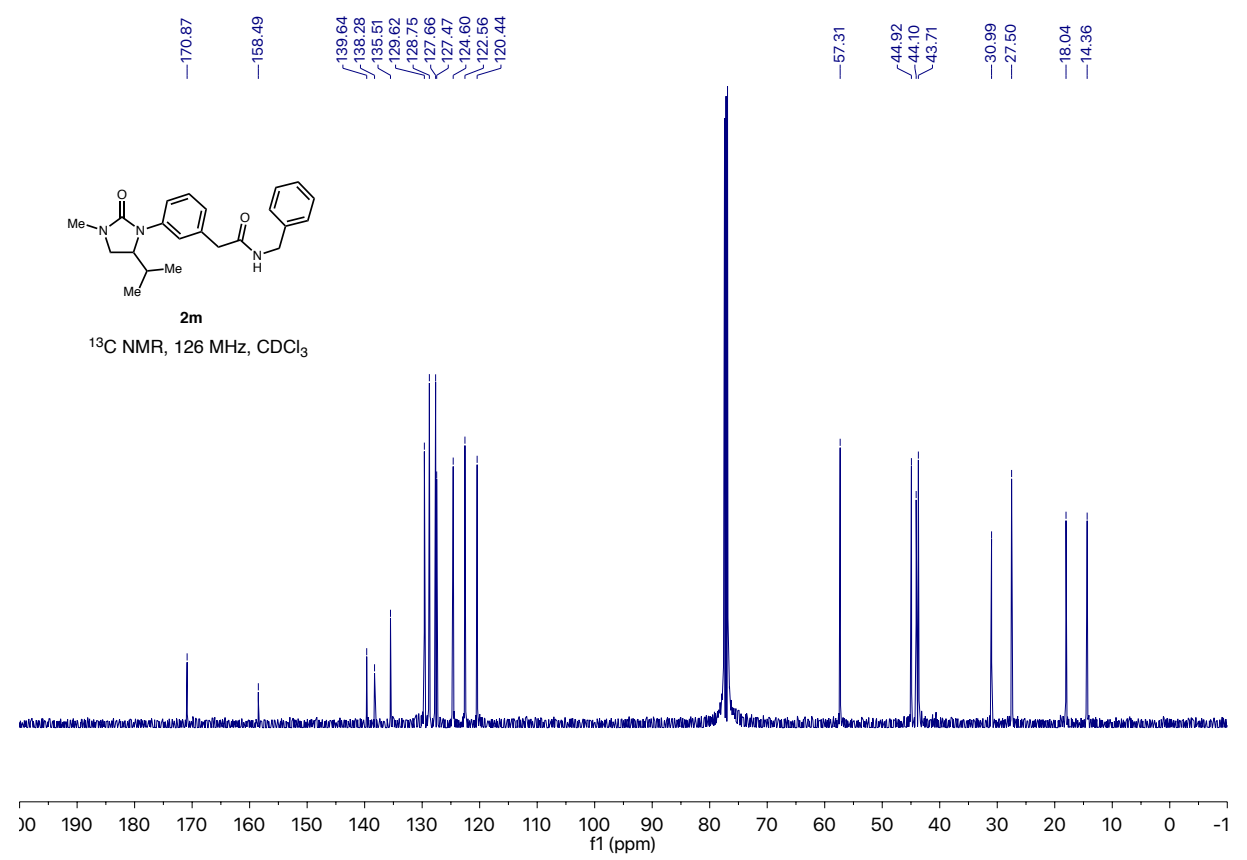
2l

^{13}C NMR, 126 MHz, $CDCl_3$



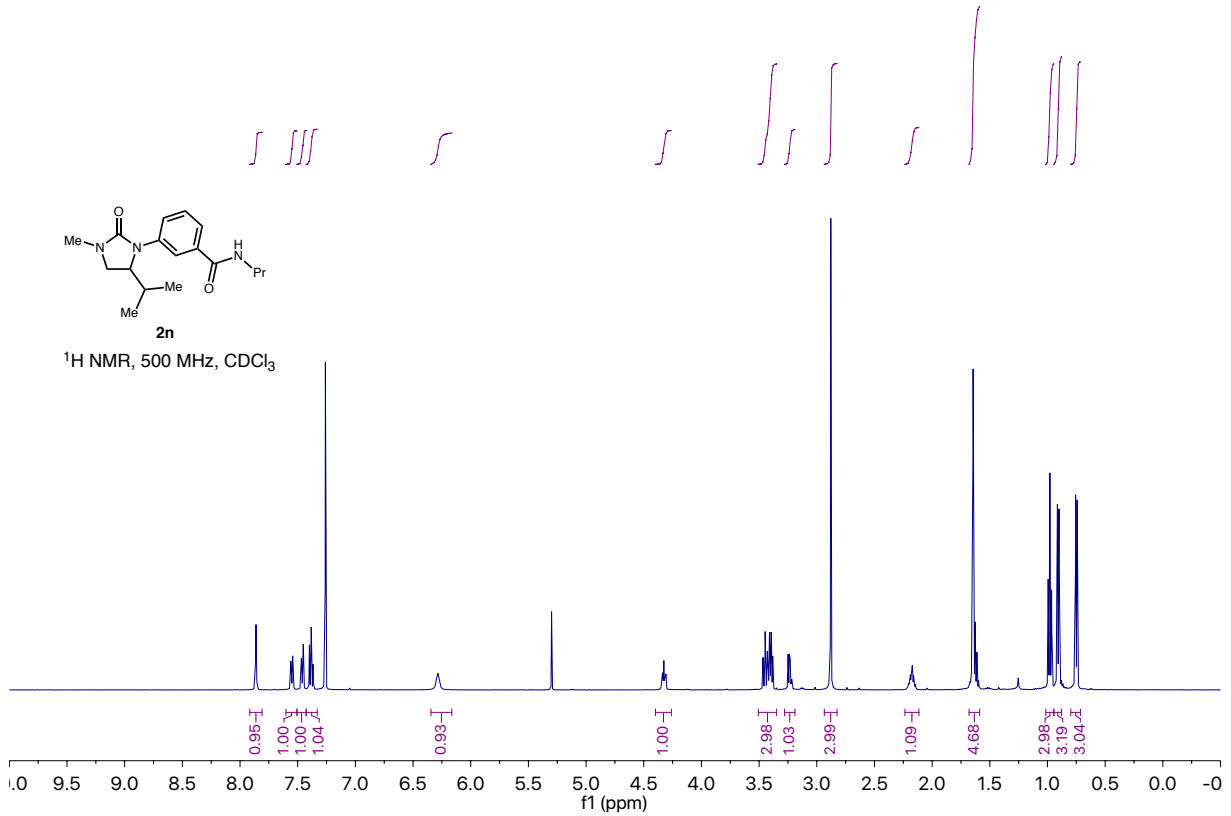
2m

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



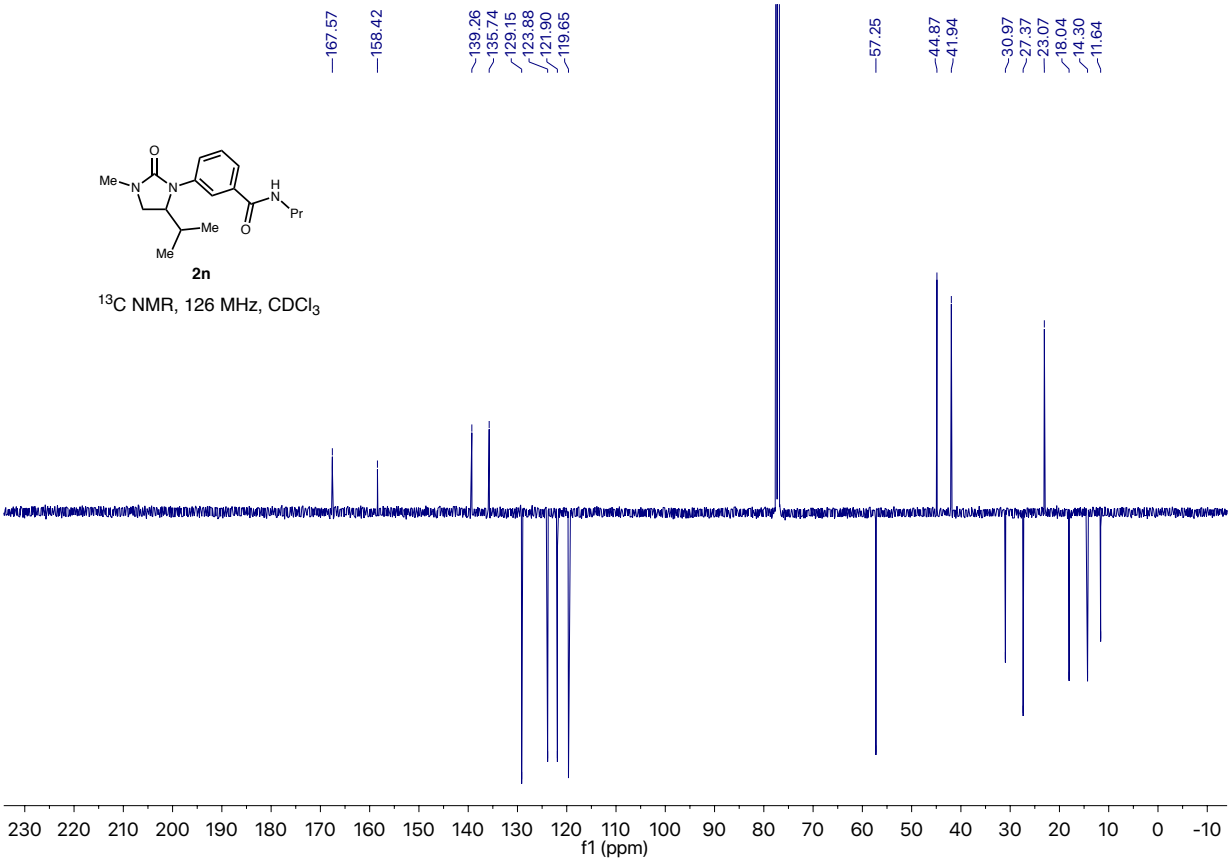
2m

^{13}C NMR, 126 MHz, $CDCl_3$



2n

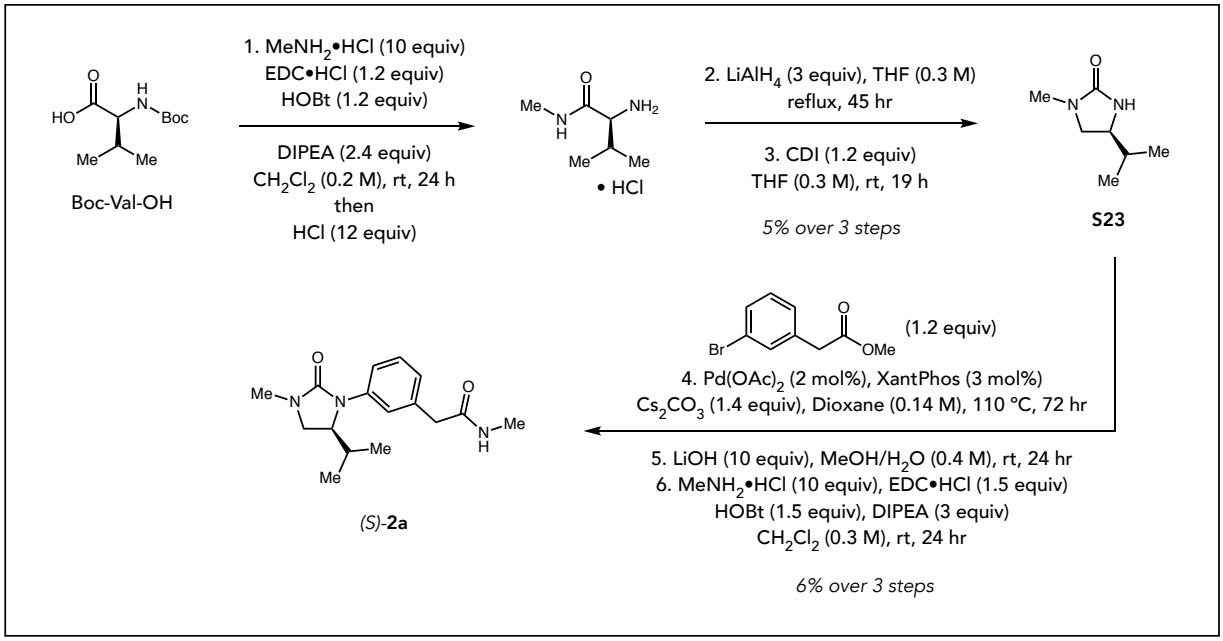
^{1}H NMR, 500 MHz, $CDCl_3$



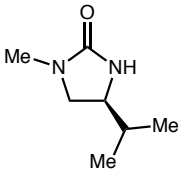
2n

^{13}C NMR, 126 MHz, $CDCl_3$

Synthesis of *(S)*-**2a** for Determination of Absolute Configuration



(*S*)-4-isopropyl-1-methylimidazolidin-2-one (S23):



S23

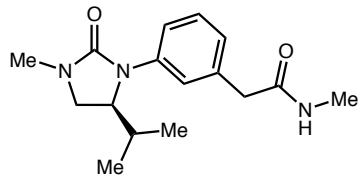
To a 50 mL round bottom flask were added (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanoic acid (0.543 g, 2.50 mmol, 1.0 equiv), methylamine hydrochloride (1.69 g, 25.0 mmol, 10 equiv), 1-hydroxybenzotriazole (0.459 g, 3.00 mmol, 1.2 equiv), *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (0.575 g, 3.00 mmol, 1.2 equiv), and *N*,*N*-diisopropylethylamine (1.05 mL, 6.00 mmol, 2.4 equiv) in CH_2Cl_2 (12.5 ml). The flask was sealed with a cap, and the reaction mixture was stirred at room temperature for 24 hours. The solution was then washed with 10% citric acid (aq), sat. $NaHCO_3$ (aq), and brine. The combined organic layer was dried over Na_2SO_4 and concentrated. The white solid was dissolved in hydrogen chloride in 1,4-dioxane (4 *N* in dioxane, 7.50 mL, 30.0 mmol, 12 equiv), stirred for 1 hour, and concentrated in *vacuo*. The resultant white solid was carried to the next step without further purification.

To a 50 mL round bottom flask was added the crude intermediate from the previous step in dry tetrahydrofuran (8.3 mL), to which lithium aluminum hydride (285 mg, 7.50 mmol, 3.0 equiv) was added in portions. After addition, the reaction mixture was refluxed for 45 hours. Upon cooling down to 0 °C, the reaction was quenched by sequential addition of 0.3 mL water, 0.3 mL 15% NaOH (aq), and 0.9 mL water. The mixture was stirred for 15 minutes at room temperature, followed by addition of a scoop of $MgSO_4$ and 15 minutes of stirring. The mixture was filtered, and the filtrate was concentrated to provide a crude yellow oil, which was carried to the next step without further purification.

To a 50 mL round bottom flask was added the crude intermediate and carbonyldiimidazole (527 mg, 3.25 mmol, 1.2 equiv) in dry tetrahydrofuran (8.3 mL). The reaction was stirred for 19 hours

at room temperature. The reaction mixture was then diluted with CH_2Cl_2, washed with 1 *N* HCl (aq) three times, washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel flash column chromatography with ethyl acetate to afford (*S*)-4-isopropyl-1-methylimidazolidin-2-one (**S23**, 19.3 mg, 0.136 mmol, 5% yield) as white solid. The spectral data matched a previous report (*38*).

(*S*)-2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (*(S)*-2a):



(S)-**2a**

The procedure is adapted and modified from a previous report (*39*).

To an oven-dried 2-dram vial were added *(S)*-4-isopropyl-1-methylimidazolidin-2-one (**S23**, 19.3 mg, 0.136 mmol, 1.0 equiv), palladium(II) acetate (0.6 mg, 2.7 μmol, 2 mol%), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos, 2.4 mg, 4.1 μmol, 3 mol%), methyl 2-(3-bromophenyl)acetate (37.4 mg, 0.163 mmol, 1.2 equiv), and cesium carbonate (61.9 mg, 0.190 mmol, 1.4 equiv). The vial was evacuated and backfilled with argon three times. Upon addition of dioxane (1.0 ml), the vial was sealed and stirred for 72 hours at 110 °C. Upon cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through a celite plug, and concentrated. The crude intermediate was carried to the next step without further purification.

The crude ester was hydrolyzed following the general procedure D described above. The crude carboxylic acid intermediate was carried to the next step without further purification.

The title amide was synthesized following the general procedure F with methylamine hydrochloride (92.0 mg, 1.36 mmol, 10 equiv). Purification by preparative TLC (80% acetone in hexanes) afforded (*S*)-2-(3-(5-isopropyl-3-methyl-2-oxoimidazolidin-1-yl)phenyl)-*N*-methylacetamide (*(S)*-**2a**, 2.3 mg, 8.0 μmol, 6% yield over three steps) as a colorless oil. The spectral data matched that of *rac*-**2a** (*vide supra*).

$[\alpha]_D^{21.0}$ = –11.8º (*c* = 0.13, CH_2Cl_2)
HPLC: (ChiralCel®, OZ-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): t_R= 20.3 min

Stereochemical Proof for the Absolute Configuration of Deracemization Products

The specific rotation and the HPLC retention time of (*S*)-**2a** were compared to those of the deracemization product formed from *rac*-**2a**, which determined that (*R*)-**2a** was the major enantiomer in the deracemization product (*vide infra*). The absolute configurations of other substrates were inferred by analogy.

General Procedures for Deracemization Reactions

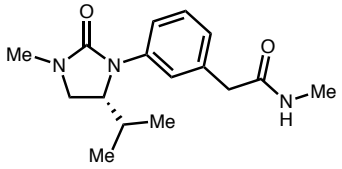
Method A (reaction optimization):

An oven-dried 2-dram vial was charged with a magnetic stir bar, substrate (25.0 μmol, 1.0 equiv), $[Ir(dF(CF_3)ppy)_2bpy]PF_6$ (0.5 mg, 0.50 μmol, 2 mol %), chiral base **3e** (2.5 mg, 2.50 μmol, 10 mol %), chiral thiol **4e** (1.4 mg, 2.50 μmol, 10 mol %), triphenylmethane (3.6 mg, 12.5 μmol, 50 mol %), and molecular sieves (50 mg, 10 % m/v). The vial was sealed with a PTFE/silicone septum, followed by three times of evacuation and backfill with Ar. Then, 0.5 mL of anhydrous THF was added. The reaction was irradiated by a blue LED lamp (Kessil H150B LED Grow Light) and stirred at room temperature with a fan to cool the reaction setup. After 4 hours, the reaction was filtered through a pipette containing 0.50 inch of silica gel and rinsed with 10 mL of acetone. The yields were determined by ^1H NMR with 1.0 μL of benzyl ether as an internal standard. The crude mixture was purified by preparative TLC. The enantiomeric ratios were then determined by HPLC analysis with chiral stationary phase.

Method B (preparative scale):

An oven-dried 2-dram vial was charged with a magnetic stir bar, substrate (0.25 mmol, 1.0 equiv), $[Ir(dF(CF_3)ppy)_2bpy]PF_6$ (5.1 mg, 5.0 μmol, 2 mol %), chiral base **3e** (12.4 mg, 12.5 μmol, 5 mol %), chiral thiol **4e** (7.0 mg, 12.5 μmol, 5 mol %), triphenylmethane (15.3 mg, 62.5 μmol, 25 mol %), and molecular sieves (125 mg, 5% m/v). The vial was sealed with a PTFE/silicone septum, followed by three times of evacuation and backfill with Ar. Then, 2.5 mL of anhydrous THF was added. The reaction was irradiated by a blue LED lamp (Kessil H150B LED Grow Light) and stirred at room temperature with a fan to cool the reaction setup. After 12 hours, the reaction was filtered through a pipette containing 0.50 inch of silica gel, rinsed with 10 mL of acetone, concentrated, and purified by flash column chromatography. The enantiomeric ratios were then determined by HPLC analysis with chiral stationary phase.

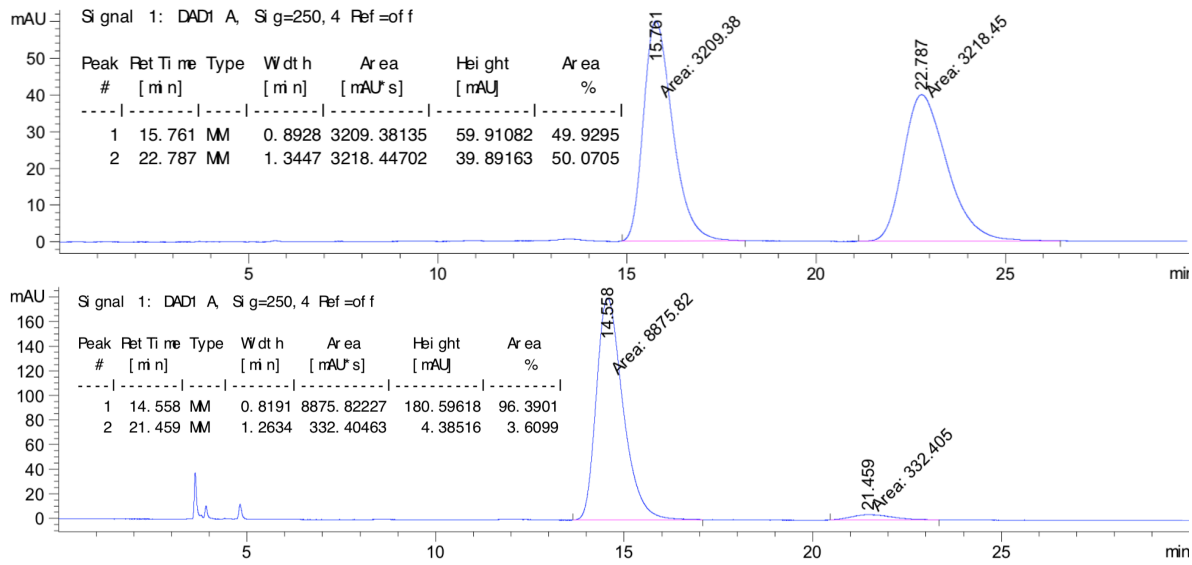
Characterization of Products

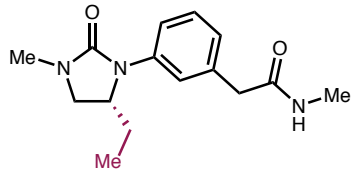


2a

$[\alpha]_D^{21.0}$ = +13.2° (*c* = 0.30 in CH_2Cl_2, 95:5 er)

HPLC (ChiralCel®, OZ-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 15.8 min, minor enantiomer t_R= 22.8 min

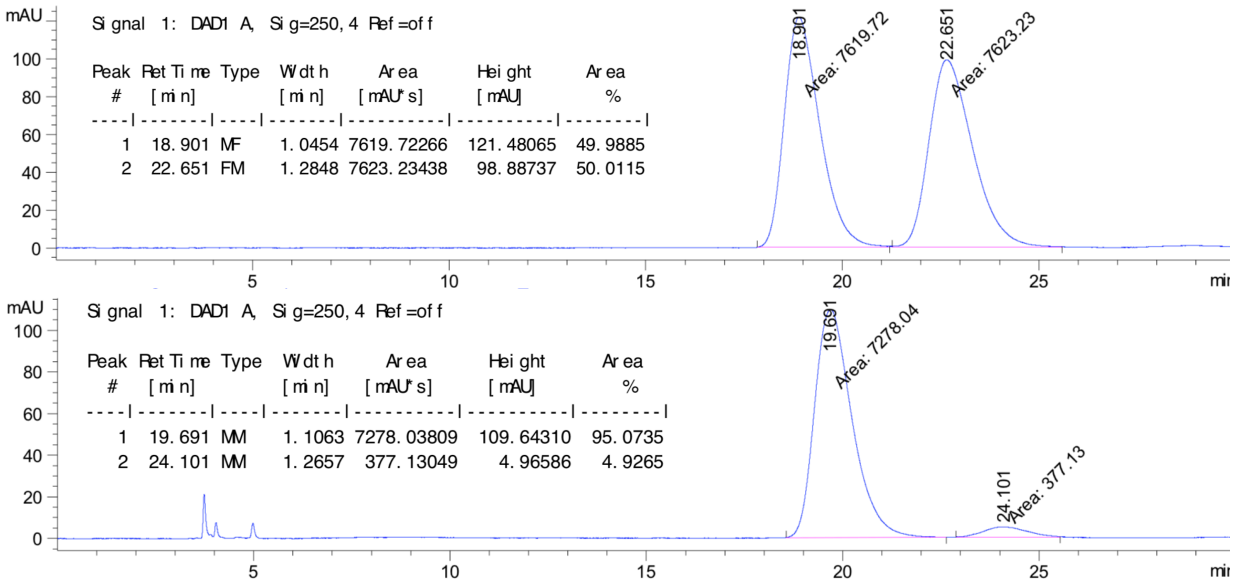


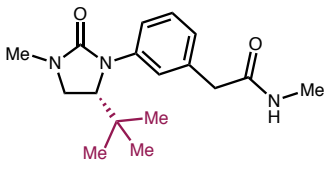


2b

$[\alpha]_D^{21.0}$ = –2.3° (*c* = 0.14 in CH_2Cl_2, 94:6 er)

HPLC (ChiralCel®, OZ-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 18.9 min, minor enantiomer t_R= 22.7 min

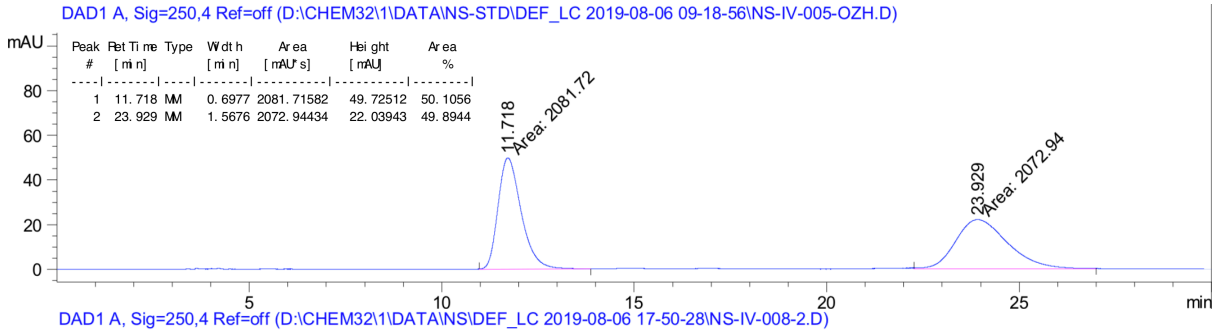


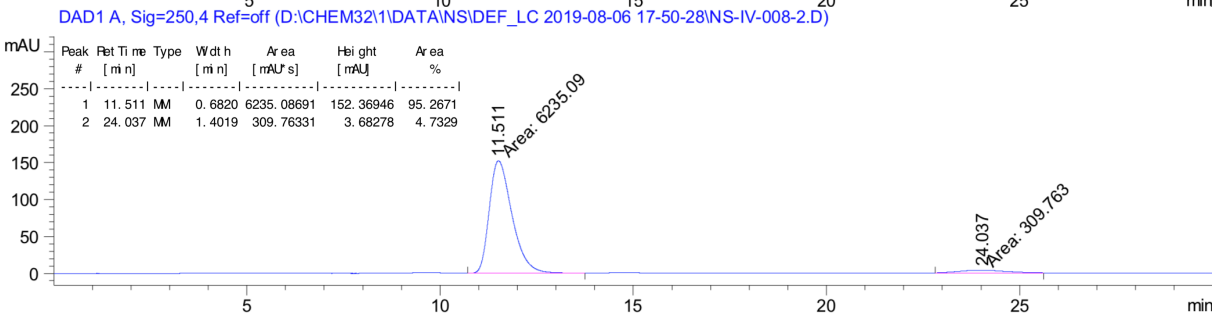


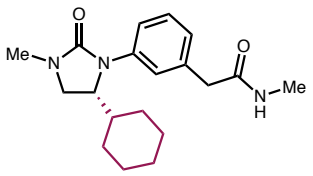
2c

$[\alpha]_D^{21.0} = 35.3^o$ (c = 0.25 in CH_2Cl_2, 94:6 er)

HPLC (ChiralCel®, OZ-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 11.7 min, minor enantiomer t_R= 23.9 min



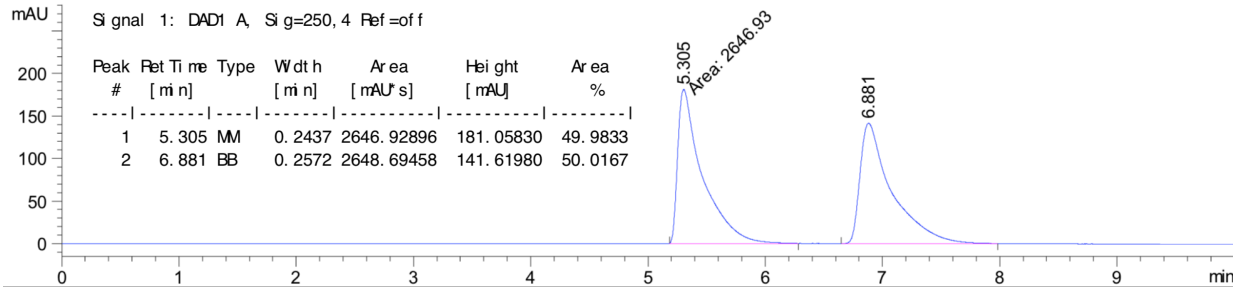


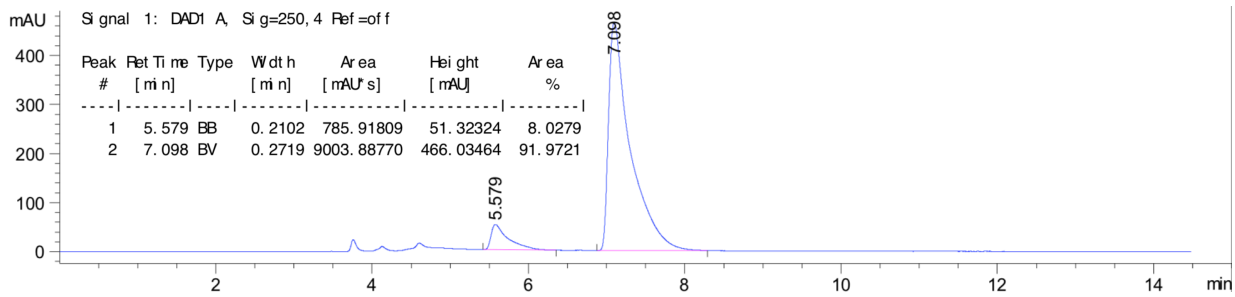


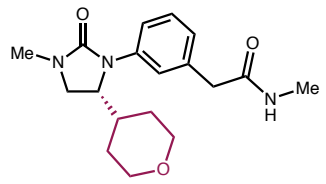
2d

$[\alpha]_D^{21.0} = 2.1^o$ (c = 0.16 in CH_2Cl_2, 90:10 er)

HPLC (ChiralPak®, AD-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 6.9 min, minor enantiomer t_R= 5.3 min



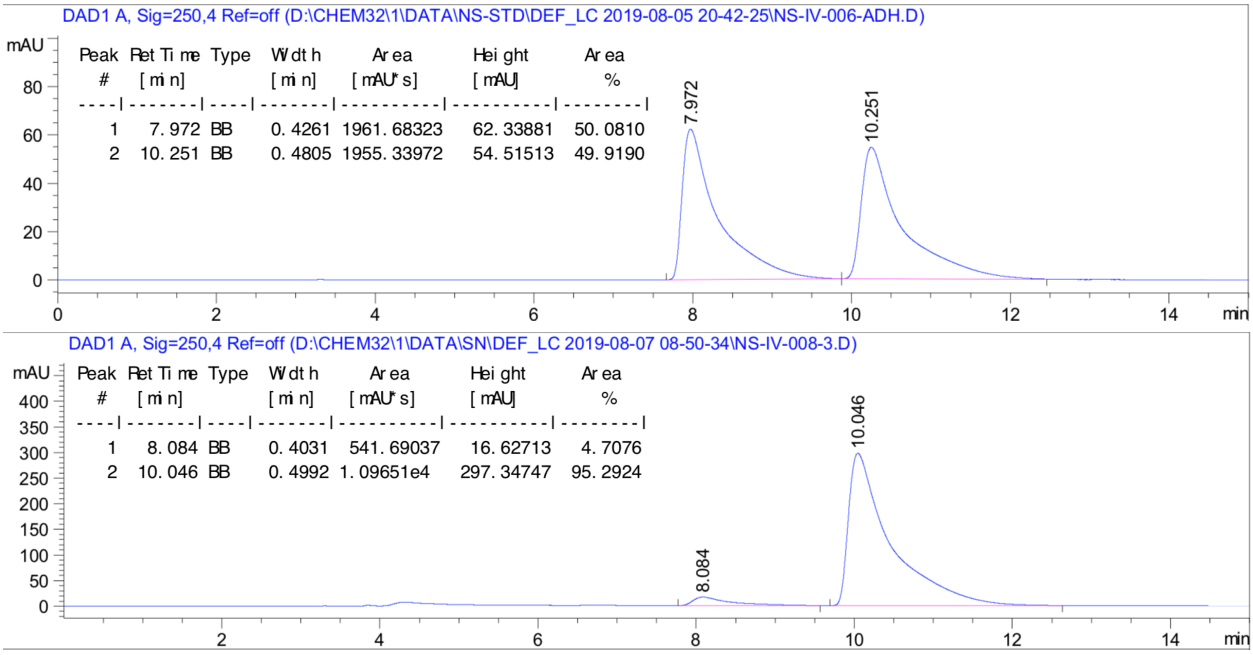


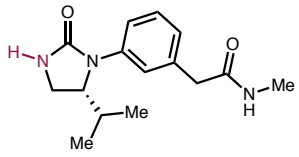


2e

$[\alpha]_D^{21.0} = -11.1^{\circ}$ (c = 0.18 in CH_2Cl_2, 94:6 er)

HPLC (ChiralPak®, AD-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 10.3 min, minor enantiomer t_R= 8.0 min

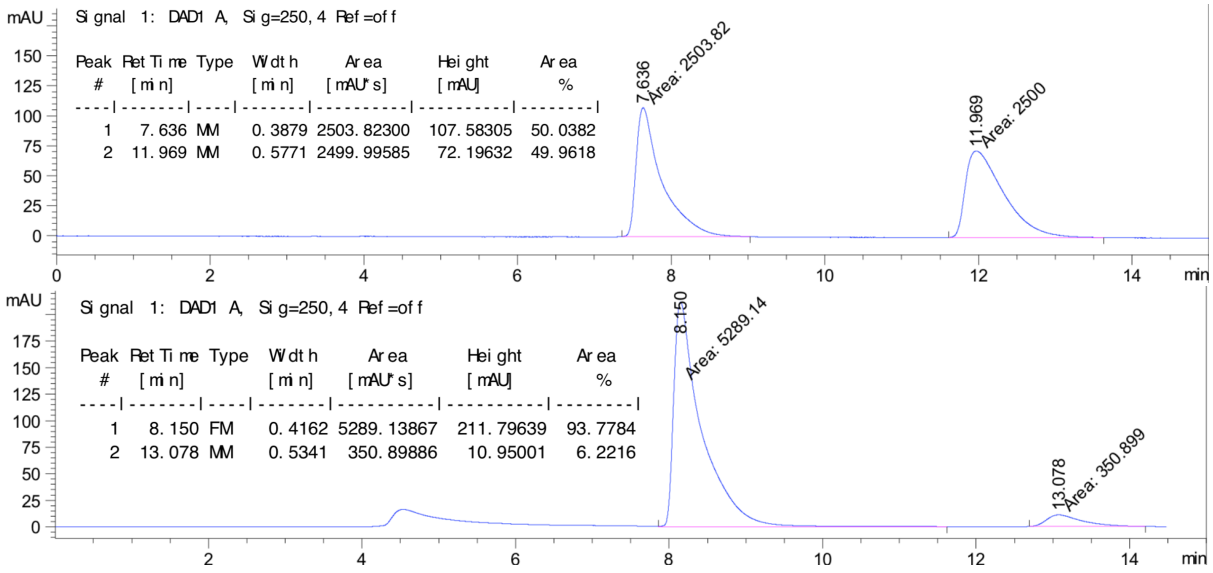


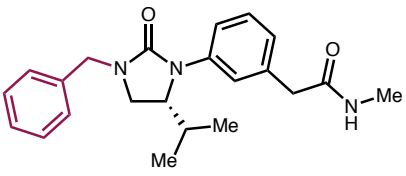


2f

$[\alpha]_D^{21.0} = 6.5^{\circ}$ (c = 0.20 in CH_2Cl_2, 92:8 er)

HPLC (ChiralPak®, AD-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 7.6 min, minor enantiomer t_R= 12.0 min

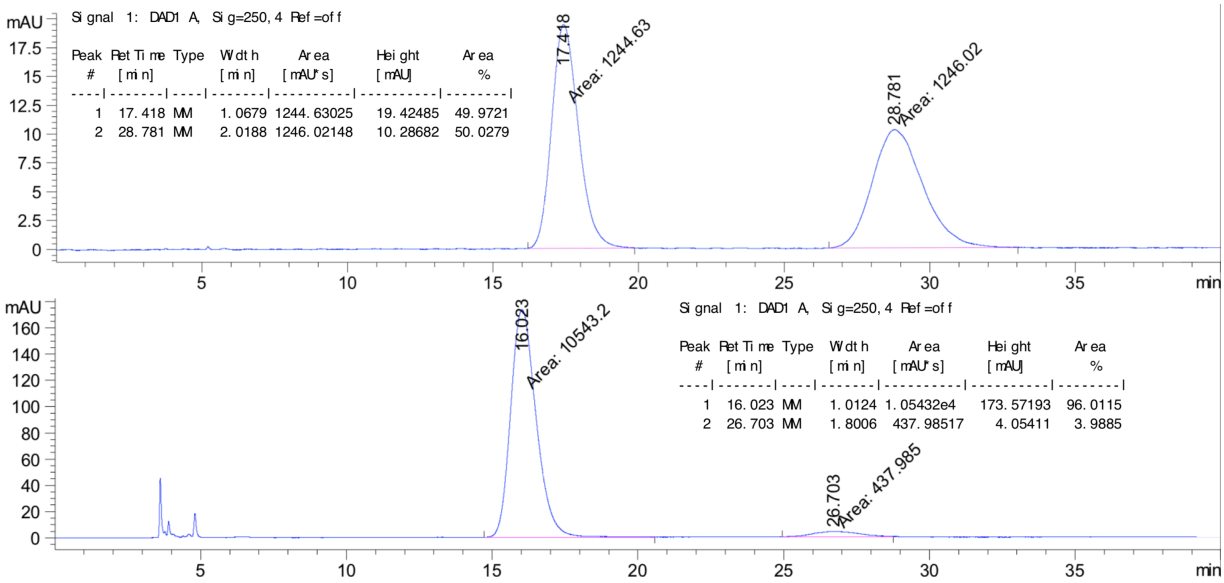


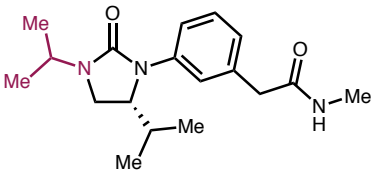


2g

$[\alpha]_D^{21.0}$ = 17.2° (*c* = 0.26 in CH_2Cl_2, 95:5 er)

HPLC (ChiralCel®, OZ-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 17.4 min, minor enantiomer t_R= 28.8 min

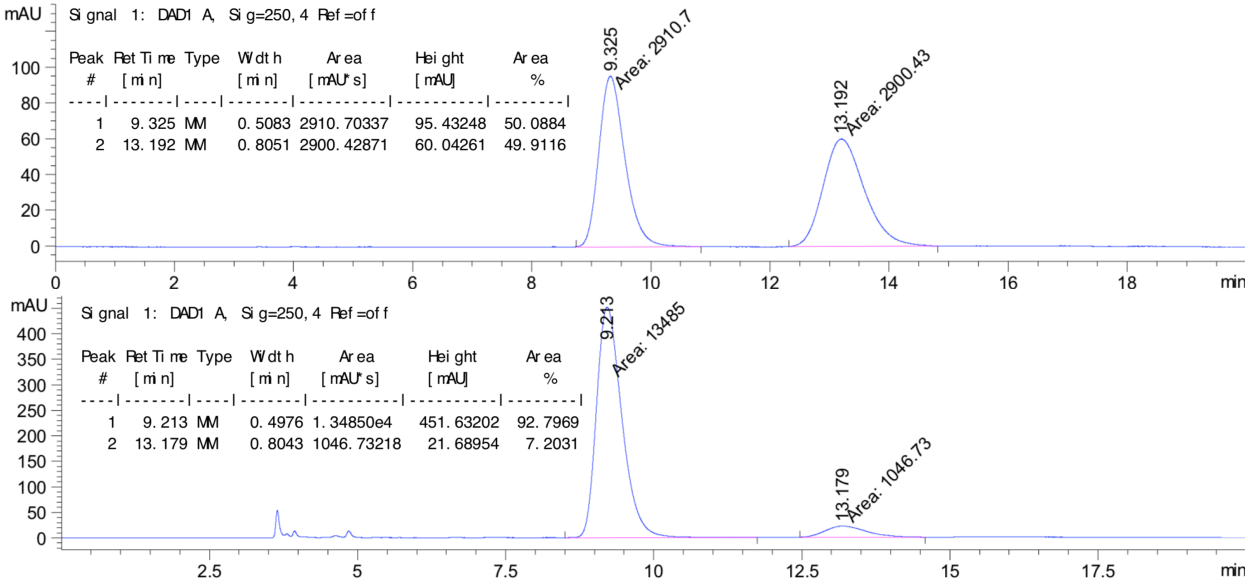


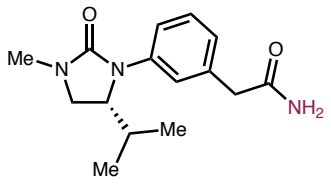


2h

$[\alpha]_D^{21.0}$ = 11.7° (*c* = 0.25 in CH_2Cl_2, 93:7 er)

HPLC (ChiralCel®, OZ-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 9.3 min, minor enantiomer t_R= 13.2 min

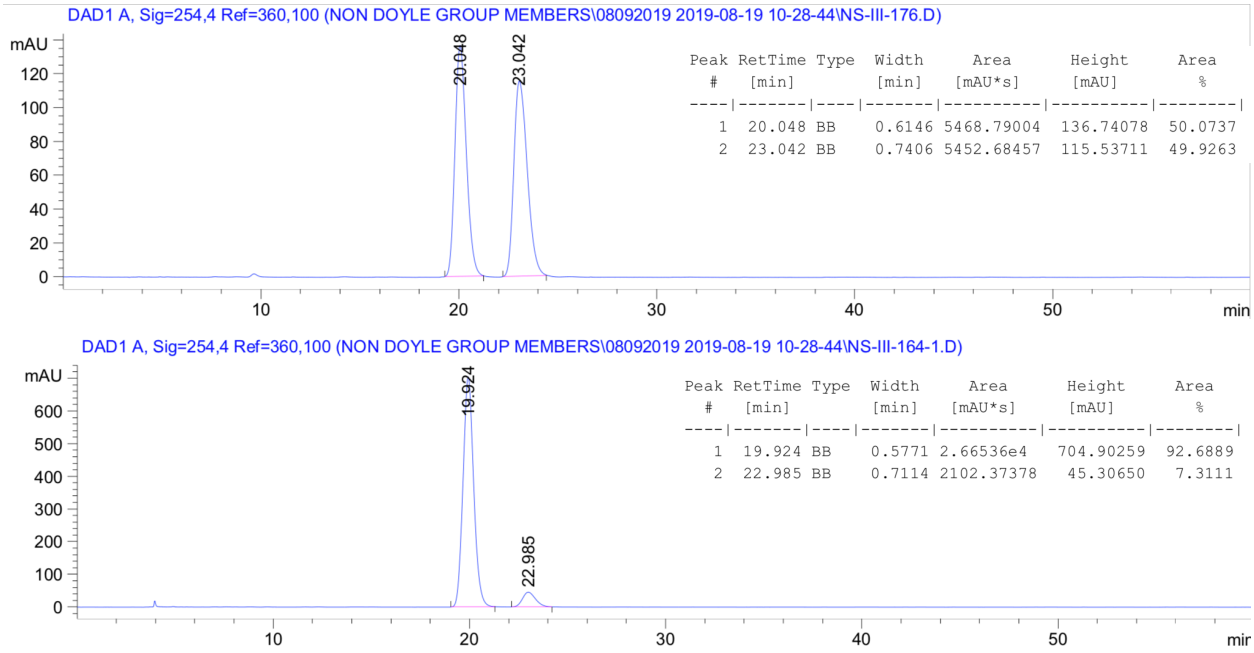


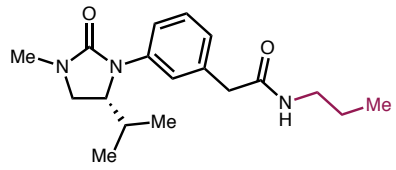


2i

$[\alpha]_D^{21.0}$ = 13.4° (*c* = 0.27 in CH_2Cl_2, 93:7 er)

HPLC (ChiralPak®, ID column, 40% IPA/Hex eluent, 1.0 mL/min flow rate, 254 nm): major enantiomer t_R= 20.0 min, minor enantiomer t_R= 23.0 min

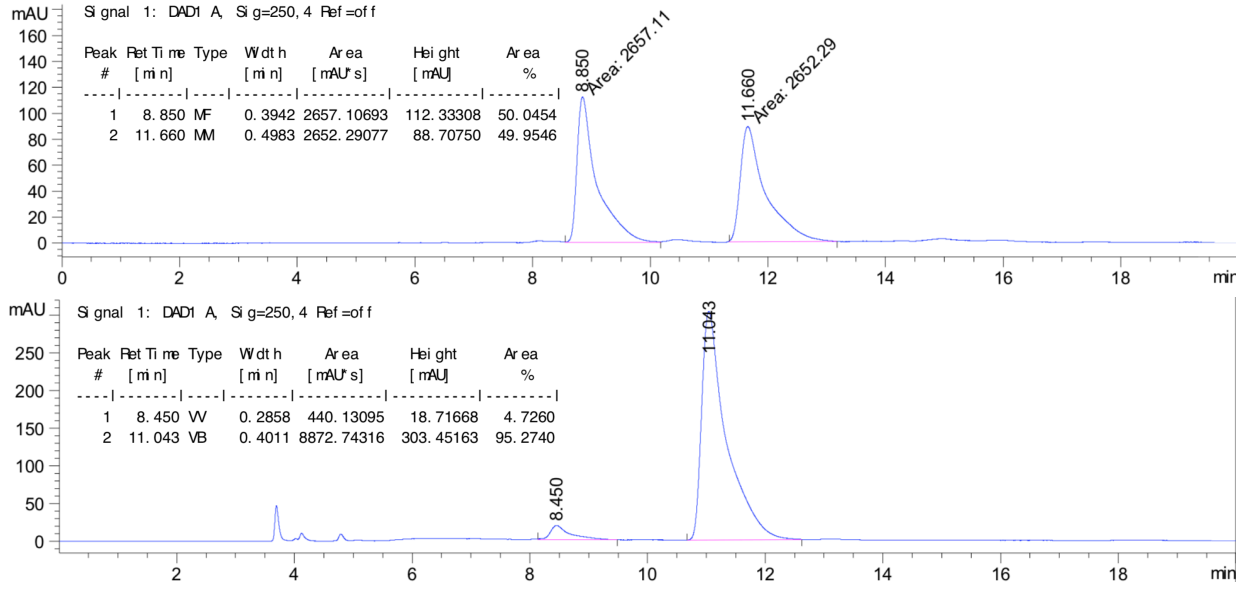


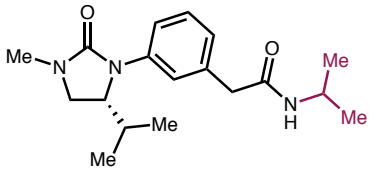


2j

$[\alpha]_D^{21.0}$ = 14.3° (*c* = 0.45 in CH_2Cl_2, 95:5 er)

HPLC (ChiralPak®, AD-H column, 15% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 11.7 min, minor enantiomer t_R= 8.9 min

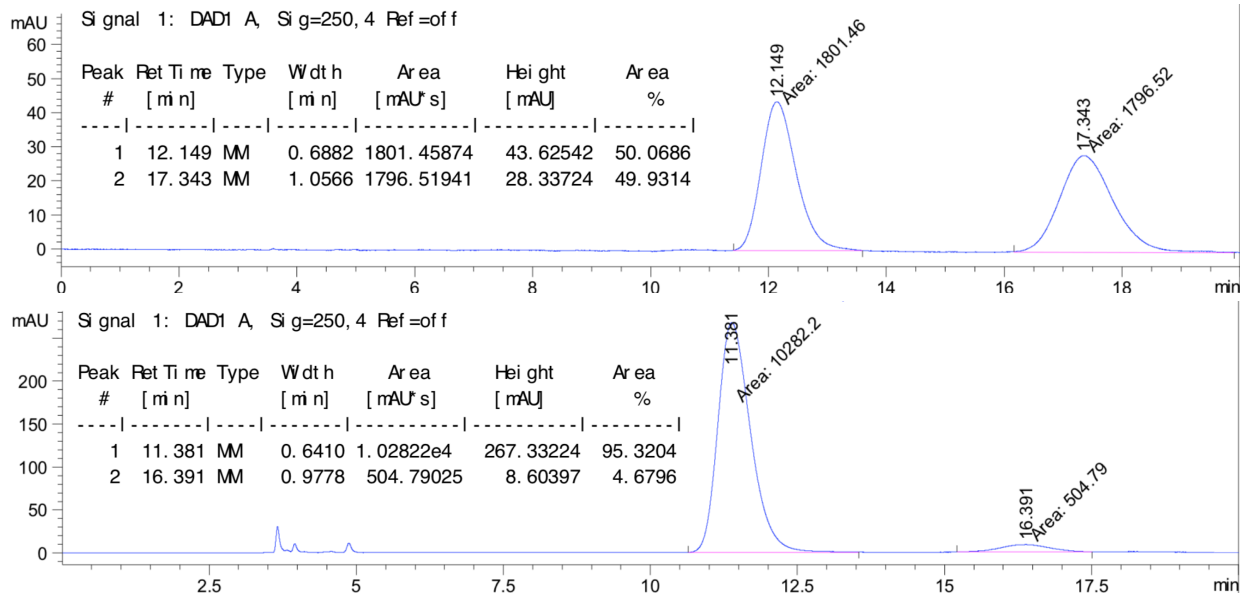


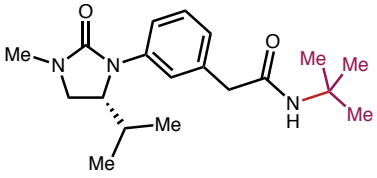


2k

$[\alpha]_D^{21.0} = 8.0^o$ (c = 0.13 in CH_2Cl_2, 93:7 er)

HPLC (ChiralCel®, OZ-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 12.1 min, minor enantiomer t_R= 17.3 min

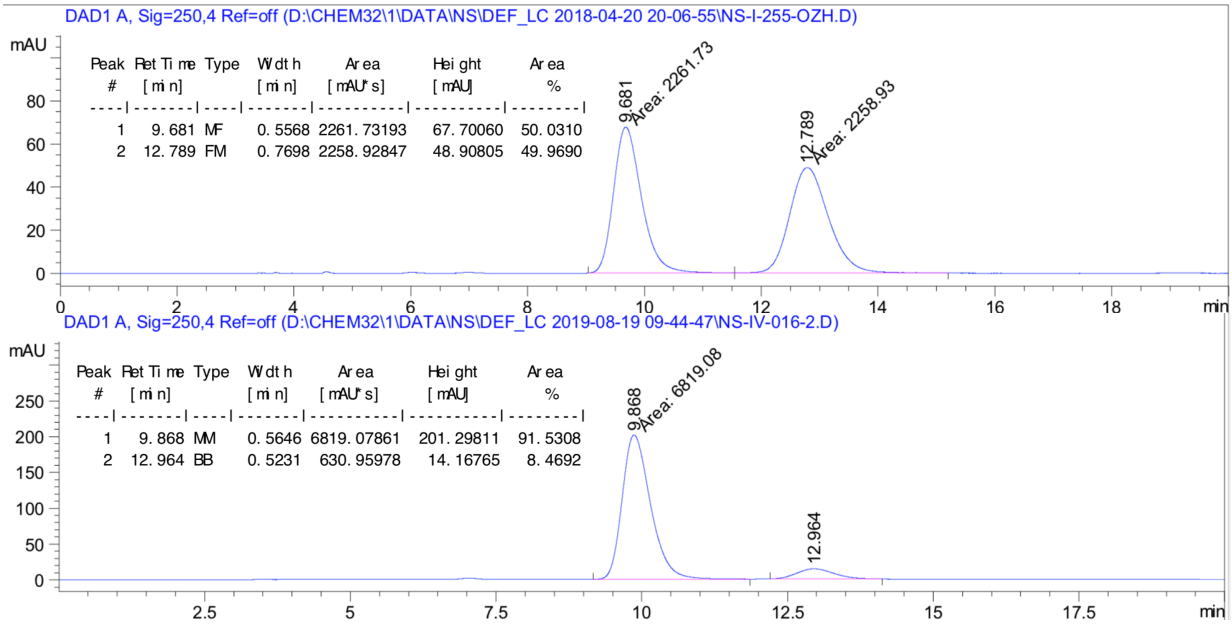


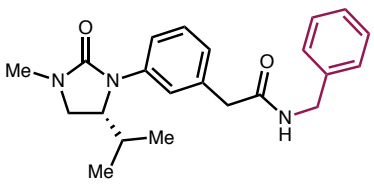


2l

$[\alpha]_D^{21.0} = 10.5^o$ (c = 0.21 in CH_2Cl_2, 92:8 er)

HPLC (ChiralCel®, OZ-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 9.7 min, minor enantiomer t_R= 12.8 min

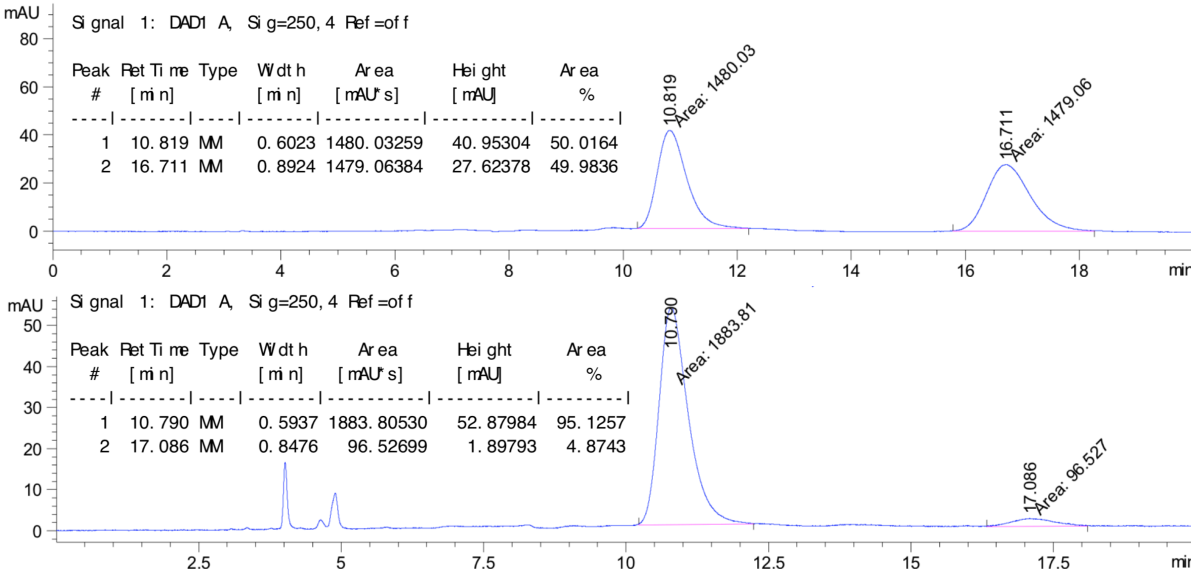


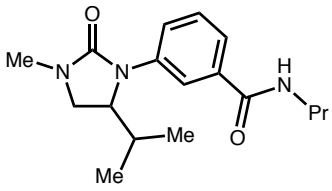


2m

$[\alpha]_D^{21.0} = 11.7^{\circ}$ (c = 0.22 in CH_2Cl_2, 95:5 er)

HPLC (ChiralCel®, OD-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 10.8 min, minor enantiomer t_R= 16.7 min

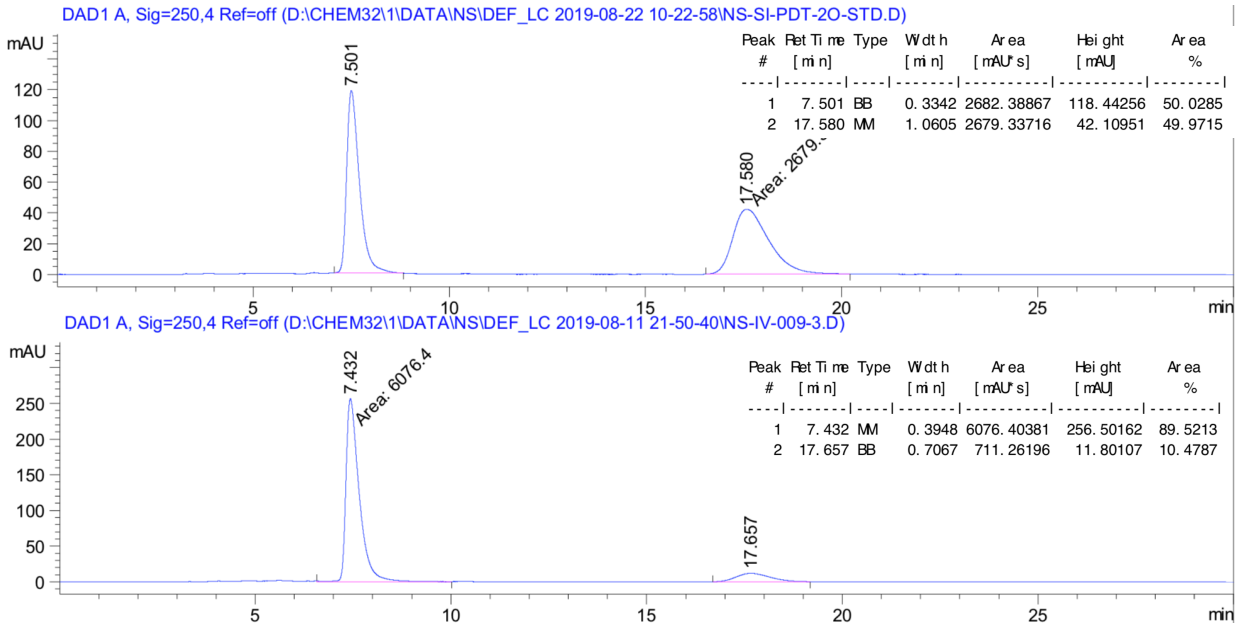


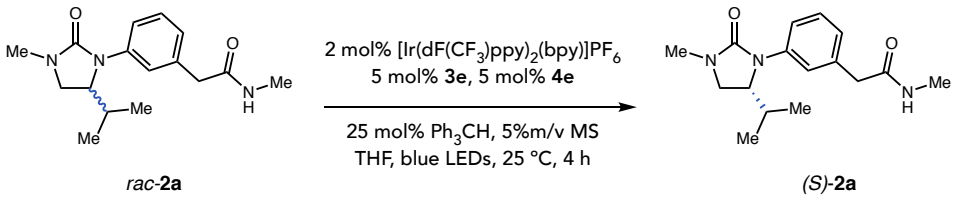


2n

$[\alpha]_D^{21.0} = -9.8^{\circ}$ (c = 0.18 in CH_2Cl_2, 90:10 er)

HPLC (ChiralCel®, OD-H column, 25% IPA/Hex eluent, 1.0 mL/min flow rate, 250 nm): major enantiomer t_R= 7.5 min, minor enantiomer t_R= 17.6 min





rac-**2a** *(S)*-**2a**

entry	change	yield (%)	er
1	None	99	96:4
2	No $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$	97	50:50
3	No **3e**	99	69:31
4	No **4e**	91	55:45
5	No Ph_3CH	96	93:7
6	No MS	99	95:5
7	No light	99	50:50

Table S1. Control experiments. Reactions were performed on 0.025 mmol scale. Yields were determined by ^1H NMR analysis of crude reaction mixtures relative to an internal standard (benzyl ether). The er was determined by HPLC analysis on a chiral stationary phase.

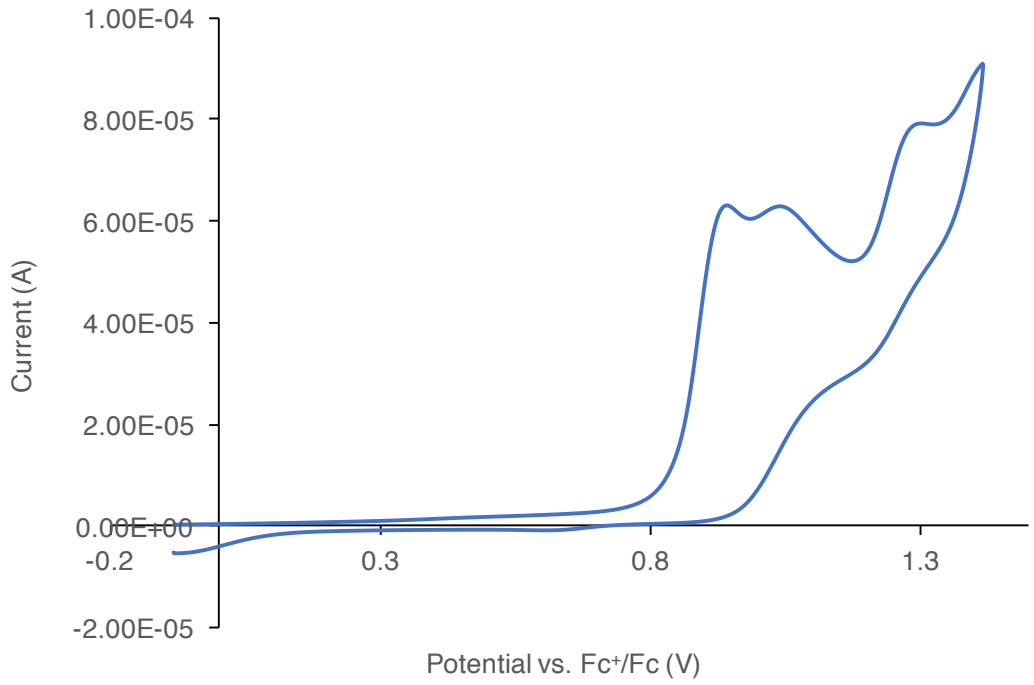


Fig. S1. Cyclic voltammogram of substrate **2a**. Cyclic voltammetry experiments were carried out with 0.1 M NBu_4PF_6 as electrolyte in acetonitrile. Experiments were run using 0.002 M of substrate, glassy carbon as working electrode, platinum mesh as counter electrode, and Ag^+/Ag (in acetonitrile) as reference electrode with a scan rate of 0.1 V/s. The reference electrode was calibrated with ferrocene.

Stern–Volmer Experiments

Stern-Volmer experiments were conducted on an Agilent Technologies Cary Eclipse Fluorescence Spectrophotometer using the Cary Eclipse Scan Application. Rigorously degassed (with argon) solutions of each component were prepared in tetrahydrofuran prior to each set of experiments. The solutions were irradiated at 380 nm and luminescence was measured at 480 nm. The luminescence of the optimized chiral base catalyst **3e** overlaps with that of iridium photocatalyst, which complicates data analysis. Instead, base **3d**, which has comparable reactivity and enantioselectivity (Fig. 3A), was used in Stern–Volmer experiments and the corresponding Time-Correlated Single Photon Counting experiments.

Species	Concentration (mM)
$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$	0.010
Base **3d**	0.100
(R)-**2a** or *(S)*-**2a**	varied

Substrate = *(R)*-**2a**			Substrate = *(S)*-**2a**		
[*(R)*-**2a**](mM)	I (AU)	I_0/I	[*(S)*-**2a**](mM)	I (AU)	I_0/I
0	873.32	1.00	0	808.77	1.00
0.30	671.60	1.30	0.30	669.80	1.21
0.60	560.30	1.56	0.60	519.51	1.56
1.20	452.08	1.93	1.20	418.70	1.93

Table S2. Fluorescence quenching data with solutions of racemic $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$, base **3d**, and substrate **2a** in tetrahydrofuran.

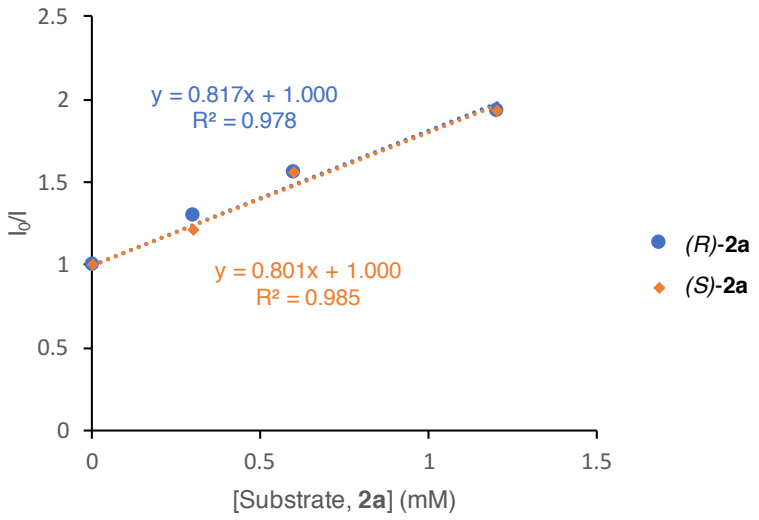


Fig. S2. Stern–Volmer plots of racemic [Ir(dF(CF$_3$)ppy)$_2$(bpy)]PF$_6$ quenched with varying concentrations of substrate *(R)*-**2a** and *(S)*-**2a** in the presence of base **3d** in tetrahydrofuran.

Time-Correlated Single Photon Counting experiments (0.010 mM racemic [Ir(dF(CF$_3$)ppy)$_2$(bpy)]PF$_6$ and 0.100 mM **3d** in tetrahydrofuran) demonstrated that the lifetime of the excited-state Ir photocatalyst (τ) is 0.908 μs.

Linear regression analysis of Stern–Volmer plots (Fig. S2) affords the K_{SV} values for each enantiomeric substrate **2a**.

(R)-**2a**: $K_{SV,(S)} = 817 \pm 80\ M^{-1}$
(S)-**2a**: $K_{SV,(R)} = 801 \pm 70\ M^{-1}$

The rate constants for electron transfer events (k_{ET}) can be obtained from the lifetime measurement and Stern-Volmer experiments with the following equation:

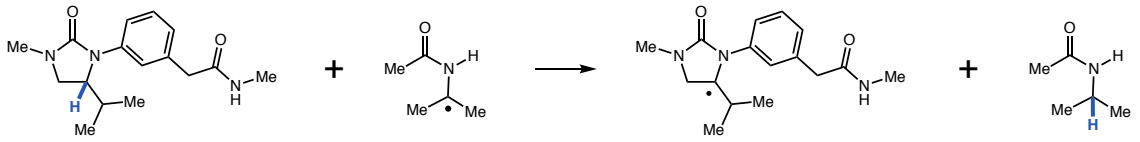
$$k_{ET} = \frac{K_{SV}}{\tau}$$

This provides the rate constants for electron transfer events from the excited-state Ir photocatalyst to each enantiomeric substrate **2a**.

(R)-**2a**: $k_{ET,(S)} = 9.0(8) \times 10^8\ M^{-1}s^{-1}$
(S)-**2a**: $k_{ET,(R)} = 8.8(7) \times 10^8\ M^{-1}s^{-1}$

Computational Evaluation of Bond Dissociation Free Energy

Computational Methods. All computations were performed with the Gaussian 16 program. (*40*) Density functional theory calculations were performed with the density functional B3LYP. (*41, 42*) The 6-31G+ (d, p) basis set was used for gas-phase geometry optimization and normal mode analyses. Frequency calculations were performed at the optimized geometries to confirm that each geometry had the appropriate number of imaginary frequencies: zero for minima. The absolute bond strength values were benchmarked with experimental bond strength of *N*-isopropylacetamide (93.1 kcal/mol). (*43*)



2a **C1** **C2** **C3**

Entry	Compound	G_{gas}, 298 K (kcal/mol)	Freq. (cm^{-1})
1	**2a**	–588635.2937	24.96, 26.55, 36.49
2	**C1**	–204830.5214	56.72, 100.57, 129.94
3	**C2**	–588235.9376	24.23, 25.67, 32.41
4	**C3**	–205233.1212	44.25, 78.01, 138.01

Table S3. Computed Gibbs free energies and the three lowest vibrational frequencies of select compounds.

$$\Delta\text{BDFE} = (-588235.9376) + (-205233.1212) - (-588635.2937) - (-204830.5214)$$
$$= -3.244 \text{ kcal/mol}$$

Thus, BDFE (**2a**, C–H) = 93.1 – 3.244 ≈ 89.9 kcal/mol.

Cartesian Coordinates for Optimized Structures.

Compound **2a**

C	2.83601200	-0.16284600	-0.34872000
C	3.47529200	1.24391400	-0.23009200
C	1.15470700	1.50997000	-0.24393200
H	4.25461500	1.40006200	-0.98380700
H	3.93076500	1.39140400	0.76156400
H	2.98631600	-0.53194800	-1.37420600
O	0.05051300	2.04593700	-0.20946000
C	2.49595500	3.58126000	-0.24410000
H	1.51407000	4.03762800	-0.37672500
H	2.87206400	3.82826700	0.76003300
H	3.18752500	3.99091700	-0.98768500
C	3.47046100	-1.18009200	0.63630200
H	4.55351800	-0.99415200	0.56172000
C	3.04847500	-0.94531100	2.09455700
H	3.61855900	-1.60073500	2.76115300
H	3.21955200	0.08594400	2.42020800
H	1.98541200	-1.16458600	2.23379800
C	3.24498700	-2.64612700	0.23046200
H	3.54579800	-2.82614000	-0.80815000
H	3.84086000	-3.30883900	0.86721600
H	2.19658600	-2.93981900	0.33410200
C	0.34210100	-0.77378400	-0.37625700
C	0.35994800	-1.68052300	-1.44370400
C	-0.79187000	-0.68871100	0.43847100
C	-0.76454500	-2.47130700	-1.69024100
H	1.23029300	-1.76313600	-2.08554100
C	-1.94763600	-1.42498700	0.15361800
H	-0.77804400	-0.00064700	1.27715300
C	-1.91802800	-2.33221000	-0.91532600
H	-0.74923200	-3.17965500	-2.51362800
H	-2.80027100	-2.92371200	-1.14403600
C	-3.21143400	-1.18560100	0.94471300
H	-3.89963700	-2.02916900	0.85528000
H	-2.97982300	-1.07814500	2.01236700
C	-4.03725600	0.06093200	0.55978500
O	-5.25255400	0.07702000	0.75847400
N	-3.36815900	1.12646600	0.05274400
H	-2.36843800	1.08506600	-0.10015000
C	-4.06271000	2.36279900	-0.27688600
H	-4.59228700	2.75511100	0.59688500
H	-3.32421900	3.09267200	-0.61250200
H	-4.79976600	2.19950200	-1.07013800

N	2.35885500	2.15046200	-0.42388700
N	1.41007000	0.13538700	-0.13013100

Compound **C1**

C	1.43960500	1.35490000	0.48570500
H	1.71981800	1.25488400	1.55044100
H	0.59058600	2.03924600	0.44493700
H	2.28095800	1.83353600	-0.02521700
C	1.15989000	0.00935800	-0.11896700
C	2.31695200	-0.91332600	-0.35932800
H	2.67383100	-1.38592000	0.57474100
H	2.05613600	-1.71884900	-1.05481600
H	3.16652900	-0.36685900	-0.77975900
N	-0.05395000	-0.64720200	0.14493400
H	-0.00573600	-1.63856400	0.36622900
C	-1.37208700	-0.23794800	0.02790000
C	-1.65697700	1.14443600	-0.51930200
H	-1.65814300	1.88323900	0.28942500
H	-0.92295500	1.45251300	-1.26896200
H	-2.65583000	1.12562200	-0.95754000
O	-2.27398000	-1.01161900	0.34374200

Compound **C2**

C	2.81901800	-0.07991600	-0.13674800
C	3.49834200	1.27121100	-0.12421300
C	1.17904500	1.58156100	-0.20068400
H	4.20777100	1.40579900	-0.95738100
H	4.07040400	1.43232900	0.80926100
O	0.07096800	2.10430300	-0.26613700
C	2.55276800	3.64265400	-0.26556300
H	1.56244700	4.09199500	-0.35437800
H	3.03477600	4.01396100	0.64829100
H	3.16111500	3.94040700	-1.12824700
C	3.46247200	-1.24200800	0.59097900
H	4.53516800	-1.00025400	0.59282300
C	3.00433900	-1.31657600	2.06724700
H	3.57211000	-2.08318800	2.60602500
H	3.15192500	-0.36194500	2.58407400
H	1.94253100	-1.57491600	2.13254100
C	3.33022900	-2.61803900	-0.09094200
H	3.64528200	-2.57274400	-1.13848800
H	3.96500600	-3.34850400	0.42296300
H	2.30268400	-2.98975100	-0.05944800
C	0.37107600	-0.71992500	-0.36307300
C	0.40941700	-1.58937700	-1.45900400

C	-0.76689100	-0.66195300	0.44654700
C	-0.70059100	-2.39017400	-1.73184200
H	1.28843500	-1.61800000	-2.09376600
C	-1.90773900	-1.41332700	0.13901800
H	-0.77009300	0.00995400	1.29885900
C	-1.85659300	-2.29206400	-0.95293300
H	-0.67539800	-3.07119500	-2.57764900
H	-2.72852600	-2.89145600	-1.20020100
C	-3.18007400	-1.21873200	0.92859300
H	-3.84496200	-2.07930500	0.82441600
H	-2.95615300	-1.12172600	1.99873100
C	-4.03823500	0.01084800	0.56106000
O	-5.24764700	0.00558100	0.79164900
N	-3.40218100	1.08552000	0.03099400
H	-2.40648200	1.05882800	-0.14661300
C	-4.12670000	2.30784300	-0.28678500
H	-4.64148800	2.69437200	0.59822700
H	-3.41029500	3.04957100	-0.64357300
H	-4.87980900	2.12742100	-1.06093000
N	2.39311400	2.20633700	-0.22420600
N	1.43587900	0.19058900	-0.10530000

Compound **C3**

C	1.67152800	1.05991900	0.88849800
H	1.96330000	0.47630500	1.76933200
H	0.92376400	1.79391300	1.20445100
H	2.55520500	1.60065200	0.53172300
C	1.11372400	0.13927700	-0.20957200
H	0.83515300	0.75262300	-1.07188500
C	2.15408600	-0.88883800	-0.67180600
H	2.44358800	-1.54863900	0.15546300
H	1.75823600	-1.50966300	-1.48089100
H	3.05989700	-0.38768100	-1.02742100
N	-0.09749100	-0.55709400	0.23173300
H	0.02149500	-1.34118900	0.86401900
C	-1.40811200	-0.19042900	0.07429300
C	-1.70414600	1.00854700	-0.81369400
H	-1.20597500	1.91505900	-0.45400100
H	-1.37430100	0.83075300	-1.84323500
H	-2.78228400	1.16747300	-0.80901500
O	-2.30976500	-0.82760100	0.61662700

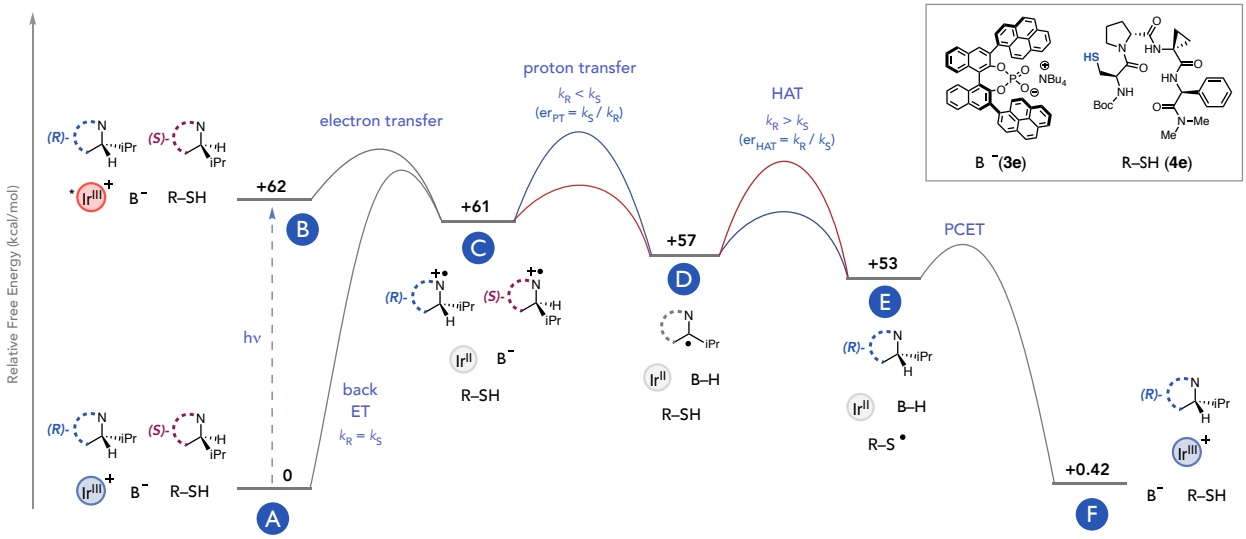


Fig. S3. Calculation of free energy values in the proposed reaction energy profile.

A → B:

The excited-state triplet energy of $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ has been previously reported to be 62 kcal/mol. (*28*)

B → C:

The excited-state potential of $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ has been previously reported ($E_{1/2}^*$ = 0.94 V vs. Fc^+/Fc in MeCN). (*28*) The oxidation potential of substrate **2a** has been measured by cyclic voltammetry ($E_{p/2}$ = 0.91 V vs. Fc^+/Fc in MeCN, Fig. S1).

$$\Delta G°_{B\to C} = (0.91 - 0.94) \times 23.06 = -0.69 \text{ kcal/mol}$$

C → D:

The BDFE(C–H) of substrate **2a** is estimated to be 89.9 kcal/mol by DFT calculations (Table S3). The oxidation potential of substrate **2a** has been measured by cyclic voltammetry ($E_{p/2}$ = 0.91 V vs. Fc^+/Fc in MeCN, Fig. S1). The pK_a of the radial cation intermediate can be estimated by the formulism of Mayer. (*44*)

$$\text{BDFE(rt in MeCN)} = 1.37\ \text{p}K_a + 23.06\ E°\ (\text{vs. } Fc^+/Fc) + 54.9 \text{ kcal/mol}$$

$$\text{p}K_a \approx 10.2$$

The pK_a of anionic phosphate base is estimated to be 13.0. (*45*) Free energy change of the proton transfer event can be calculated from the pK_a values.

$$\Delta G°_{C\to D} = -RT \ln K_{eq} \approx -3.8 \text{ kcal/mol}$$

D → E:

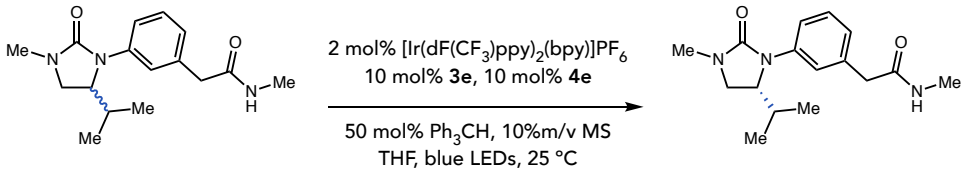
The BDFE(S–H) of cysteine has been previously reported to be 86.2 kcal/mol. (*44*) Free energy change of the H-atom transfer event can be estimated from the difference in BDFE values.

$$\Delta G°_{D\to E} = 86.2 - 89.9 \approx -3.7 \text{ kcal/mol}$$

F vs. A:

The free energy difference between a racemic ensemble and a single-enantiomer ensemble of the same molecule can be calculated from the standard Gibbs free energy equation and Boltzmann's entropy formula.

$$\Delta G^{\circ}{}_{\mathrm{F}} = \Delta H^{\circ} - T\Delta S^{\circ} = RT \ln 2 \approx 0.42 \text{ kcal/mol (at rt)}$$



rac-**2a** *(R)*-**2a**

Entry	Reaction Time (h)	Yield (%)	er
1	0.25	99	86:14
2	0.5	99	93:7
3	1	99	95:5
4	1.5	99	96:4
5	2	99	96:4
6	2.5	99	96:4
7	3	99	96:4
8	4	99	96:4
9	5	99	96:4

Table S4. Reaction conditions and results for the time-course studies. Reactions were performed on 0.025 mmol scale. Yields were determined by ^{1}H NMR analysis of crude reaction mixtures relative to an internal standard. The er was determined by HPLC analysis on a chiral stationary phase.

Quantum Yield Measurement

Chemical actinometry was carried out following the methods previously reported by Hatchard and Parker (*29, 46*). Potassium ferrioxolate ($K_3Fe(C_2O_4)_3 \cdot H_2O$) was purchased from Alfa Aeser and used without further purification. Blue LED strips (λ_{max} = 463 nm) was used for measurements.

Solution needed

0.05 M sulfuric acid stock solution

In a 100 mL volumetric flask, 0.281 mL of concentrated sulfuric acid (17.8 M) was added to 90 mL deionized water. Then, water was added until the 100 mL graduation mark was reached.

Ferrioxolate solution

A 0.15 M solution of potassium ferrioxolate was prepared by dissolving potassium ferrioxolate ($K_3Fe(C_2O_4)_3 \cdot H_2O$, MW 491.243) (1.842 g, 3.75 mmol) with the 0.05 M sulfuric acid solution prepared in a 25 mL volumetric flask. Weigh potassium ferrioxolate as fast as possible and make every precaution to prepare and store the solution in the dark.

Developer solution:

225 g of sodium acetate trihydrate was dissolved in 1 liter of 0.5 M sulfuric acid. 10 g of 1,10-phenantroline was added to this solution. Store in the dark.

Typical Experiment: Measuring Photon Flux

A 1cm × 1cm quartz cuvette was charged with 1.5 mL of 0.15 M aqueous potassium ferrioxalate solution. Two sides of the cuvette were coated with black electrical tape to ensure a minimum pathway of the light of 1 cm. To stir the ferrioxolate, the solution was continually sparged with Argon and stirred with a small stirbar. While stirring, the solution was irradiated with a blue LED (λ_{max} = 463 nm) at room temperature. 10 μL aliquots of the solution were taken at different time points between 1 and 7 minutes of irradiation. This aliquot was immediately added to 5 mL of a developer solution of sodium acetate and 1,10-phenanthroline and the flask was quickly wrapped in aluminum foil. Concurrently, a "blank" sample was prepared by diluting 10 uL of the stock solution (kept in the dark) into 5 mL of developer solution. The solutions were left in the dark for 30 min - 1 hr, becoming bright red. The solutions were transferred to a cuvette and the absorbance spectrum of the $Fe(phen)_3^{2+}$ complex was obtained. The absorbance at 510 nm (ε = 11,100 M^{-1} cm^{-1}) was measured for every sample.

Data Analysis

To calculate photon flux from your chemical actinometry data, first determine the number of Fe^{2+} ions produced by ferrioxolate photo-degradation:

$$\text{moles } of \text{ Fe}^{2+} = \frac{\Delta A_{510\,nm} V_1 V_3}{\varepsilon_{510\,nm} l V_2}$$

ΔA = difference in absorbance at 510 nm between sample and 'blank'

l = path length of cuvette (1 cm)

$\varepsilon_{510\,nm}$ = Extinction coefficient of $Fe(phen)_3$ complex at 510 nm (ε = 11,100 $M^{-1}cm^{-1}$)

V_1 = total volume of irradiated solution (1.5 mL)
V_2 = volume of aliquot taken from V_1 (10 uL)
V_3 = the volume that V_2 is diluted into (5 mL)

Now, the photon flux can be determined:

$$\text{photon flux} = \frac{\text{moles of } Fe^{2+}}{\emptyset_{468\ nm} t F}$$

$\emptyset_{468\ nm}$ = 0.92(5)
t = time of irradiation (seconds)
F = mean fraction of light absorbed by the ferrioxalate solution (F = 0.850 at 468 nm at 0.15 M ferrioxolate).

Results

Run 1			Run 2			Run 3		
Time (s)	$A_{510\,nm}$(AU)	$\Delta A_{510\ nm}$	Time (s)	$A_{510\,nm}$(AU)	$\Delta A_{510\ nm}$	Time (s)	$A_{510\,nm}$(AU)	$\Delta A_{510\ nm}$
0	0.3744	0	0	0.206	0	0	0.2118	0
80	0.4463	0.0719	60	0.2942	0.0882	66	0.2647	0.0529
130	0.5057	0.1313	195	0.4143	0.2083	126	0.3132	0.1014
265	0.6328	0.2584	370	0.5869	0.3809	184	0.4079	0.1961
330	0.6942	0.3198	420	0.6881	0.4821	240	0.4407	0.2289
						300	0.516	0.3042
Slope ($\Delta A_{510\ nm}$ / time) = $(9.79 \pm 0.27) \times 10^{-4}\ s^{-1}$			Slope ($\Delta A_{510\ nm}$ / time) = $(1.055 \pm 0.093) \times 10^{-3}\ s^{-1}$			Slope ($\Delta A_{510\ nm}$ / time) = $(1.083 \pm 0.078) \times 10^{-3}\ s^{-1}$		

Table S5. Absorbance data for the photon flux measurement using potassium ferrioxalate.

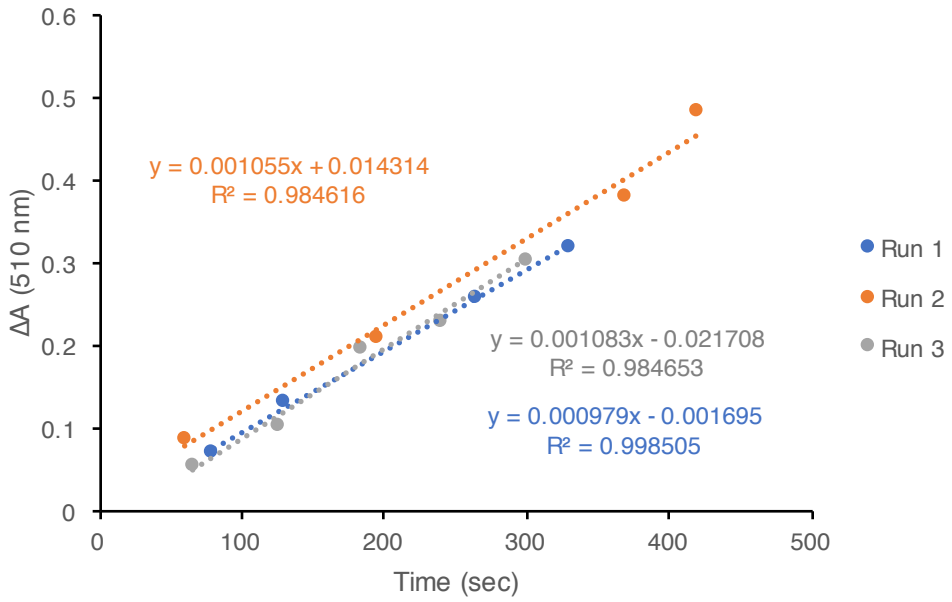


Fig. S4. UV-Vis absorbance plot for the photon flux measurement using potassium ferrioxalate.

Calculated average photon flux: **$(8.98 \pm 0.36) \times 10^{-8}$ einstein/s**

Initial-rate time-course study of deracemization reaction

An oven-dried 1cm x 1cm quartz cuvette was charged with a magnetic stir bar, racemic substrate **2a** (27.8 mg, 96.1 μmol), $[Ir(dF(CF_3)ppy)_2bpy]PF_6$ (1.5 mg, 1.50 μmol), chiral base **3e** (3.7 mg, 3.7 μmol), chiral thiol **3e** (2.1 mg, 3.7 μmol), and triphenylmethane (5.4 mg, 18.8 μmol). Two sides of the cuvette were coated with black electrical tape to ensure a minimum pathway of the light of 1 cm. The cuvette was sealed with a PTFE/silicone septum, followed by three times of evacuation and backfill with Ar. Then, 1.5 mL of anhydrous THF was added. The reaction was irradiated by a blue LED strips and stirred at room temperature with a fan to cool the reaction setup. At various time points within the first 20 minutes, 20 μl of reaction fraction was taken, which was analyzed by HPLC with chiral stationary phase after a short silica plug and acetone flush. After the last time point, substrate recovery was analyzed by ^1H NMR with 1.0 μL of benzyl ether as an internal standard. In every case, the substrate was fully recovered with quantitative yields.

Run 1		Run 2		Run 3	
Time (s)	%ee	Time (s)	%ee	Time (s)	%ee
120	2.2	150	1.9	150	1.9
240	3.3	300	3.6	300	3.7
360	5	600	6.2	600	6.3
510	6.1	900	8.8	900	8.8
600	7.4	1200	11.1	1200	11.6
900	9.9				
1200	12.3				
Slope $= (9.41 \pm 0.35) \times 10^{-3}\ s^{-1}$		Slope $= (8.70 \pm 0.26) \times 10^{-3}\ s^{-1}$		Slope $= (9.03 \pm 0.23) \times 10^{-3}\ s^{-1}$	

Table S6. Initial- rate time-course data for quantum yield measurement of deracemization reaction.

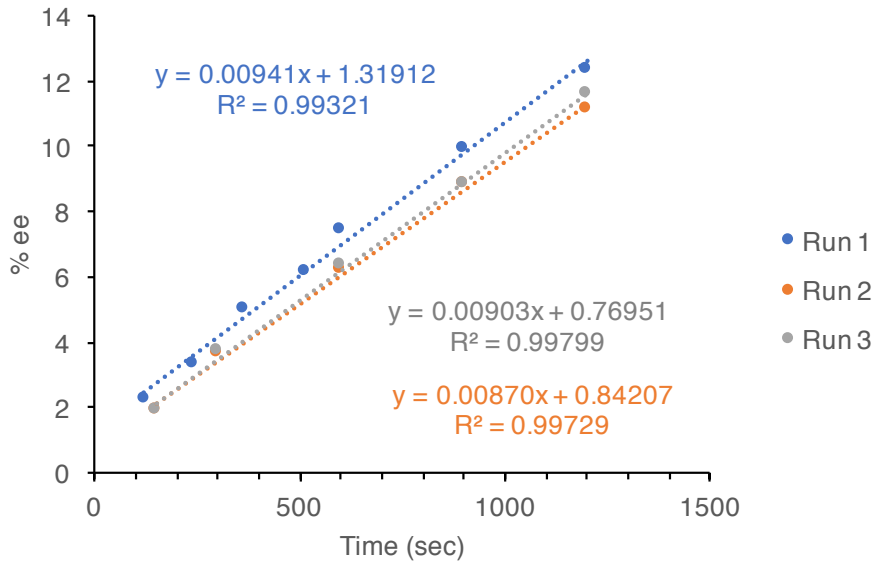


Fig. S5. Initial-rate time-course plots for quantum yield measurement of deracemization reaction.

Calculated average slope in initial-rate time-course plots: $(9.05 \pm 0.49) \times 10^{-3}$ s^{-1}

Where N_0 is the initial moles of substrate (96.1 μmol),

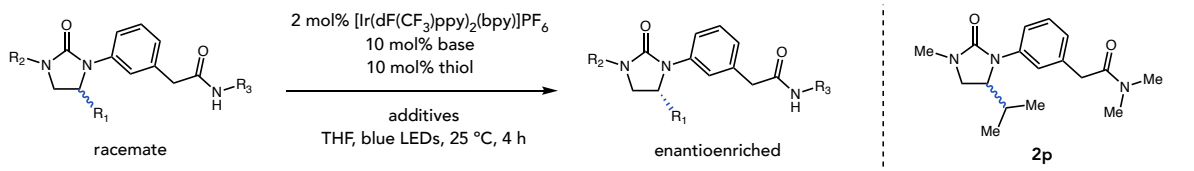
$$\text{Quantum Yield} = \frac{\text{moles of the minor enantiomer converted to the major enantiomer}}{\text{moles of incident photons}}$$

$$= \frac{\Delta[\text{moles of the (R) converted (S)}]}{\Delta t} \times \left[\frac{\Delta(\text{moles of incident photons})}{\Delta t}\right]^{-1}$$

$$= \frac{\Delta\left(N_0 \times \frac{\%ee}{2} \times \frac{1}{100}\right)}{\Delta t} \times \frac{1}{\text{Photon flux}}$$

$$= \frac{N_0}{2000 \times \text{Photon flux}} \times \frac{\Delta(\%ee)}{\Delta t}$$

Thus, calculated quantum yield: **0.048(3)**



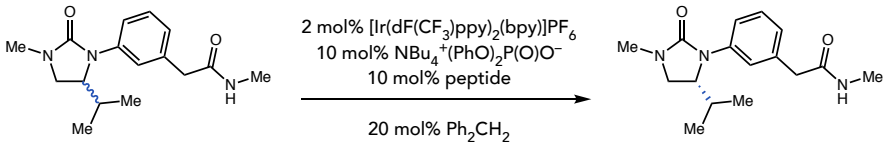
Reaction Condition A	**Reaction Condition B**	**Reaction Condition B'**	**Reaction Condition C**	**Reaction Condition C'**
base: **3e** thiol: PhSH additives: 10 %m/v MS	base: $NBu_4^+(PhO)_2P(O)O^-$ thiol: **4e** additive: 50 mol% Ph_3CH, 10 %m/v MS	base: $NBu_4^+(PhO)_2P(O)O^-$ thiol: ent-**4e** additive: 50 mol% Ph_3CH, 10 %m/v MS	base: **3e** (5 mol%) thiol: **4e** (5 mol%) additive: 25 mol% Ph_3CH, 5 %m/v MS	base: **3e** (5 mol%) thiol: ent-**4e** (5 mol%) additive: 25 mol% Ph_3CH, 5 %m/v MS

Entry	Substrate	Reaction Condition	Yield (%)	er
1	**2a**	A	92	86:14
2	**2b**	A	96	77:23
3	**2d**	A	99	80:20
4	**2f**	A	99	89:11
5	**2g**	A	99	88:12
6	**2h**	A	99	87:13
7	**2j**	A	95	85:15
8	**2k**	A	99	85:15
9	**2m**	A	96	83:17
10	**2o**	A	99	58:42
11	**1b**	A	99	49:51

Entry	Substrate	Reaction Condition	Yield (%)	er
12	**2a**	B	95	79:21
13	**2a**	B'	99	21:79
14	**2b**	B	96	85:15
15	**2d**	B	96	76:24
16	**2f**	B	99	69:31
17	**2g**	B	99	77:23
18	**2h**	B	99	69:31
19	**2j**	B	99	81:19
20	**2k**	B	99	79:21
21	**2m**	B	96	83:17
22	**2o**	B	99	79:21
23	**1b**	B	99	77:23

Entry	Substrate	Reaction Condition	Yield (%)	er
24	**2a**	C	96	96:4
25	**2a**	C'	99	53:47
26	**2b**	C	99	95:5
27	**2d**	C	99	92:8
28	**2f**	C	96	94:6
29	**2g**	C	99	96:4
30	**2h**	C	99	93:7
31	**2j**	C	99	95:5
32	**2k**	C	99	95:5
33	**2m**	C	99	95:5
34	**2o**	C	97	81:19
35	**1b**	C	99	74:26

Table S7. Reaction conditions and results for the studies on synergistic enantioselectivity. Reactions were performed on 0.025 mmol scale. Yields were determined by ^{1}H NMR analysis of crude reaction mixtures relative to an internal standard (benzyl ether). The er was determined by HPLC analysis on a chiral stationary phase.



rac-**2a** → *(R)*-**2a**

Entry		Peptide	Yield (%)	er	Entry		Peptide	Yield (%)	er
1*	**4a**	(Boc-Cys-D-Pro-Aic-Phe-OMe)$_2$	76	58:42	14	**P9**	(tBu-urea)-Cys-D-Pro-Acpc-1-Nal-NMe$_2$	99	54:46
2*	**4b**	(Boc-Cys-D-Pro-Aic-Phe-NMe$_2$)$_2$	84	60:20	15	**P10**	Boc-Cys-D-Pro-Aib-2-Nal-NMe$_2$	99	68:32
3	**4c**	Boc-Cys-D-Pro-Aic-Phe-NMe$_2$	99	68:32	16	**P11**	Boc-Cys-D-Pro-Acpc-2-Nal-NMe$_2$	99	66:34
4	**4d**	Boc-Cys-D-Pro-Aic-Gly-NMe$_2$	88	70:30	17	**P12**	Boc-Cys-D-Pro-Aib-Cha-NMe$_2$	99	69:31
5	**4e**	Boc-Cys-D-Pro-Acpc-Phg-NMe$_2$	87	80:20	18	**P13**	Boc-Cys-D-Pro-Acpc-Cha-NMe$_2$	99	67:33
6	**P1**	Boc-Cys-D-Pro-Acpc-Phe-NMe$_2$	84	68:32	19	**P14**	(2-thio-Bz)-D-Pro-Acpc-Cha-NMe$_2$	99	49:51
7	**P2**	Boc-Cys-D-Pro-Aib-Phg-NMe$_2$	92	78:22	20	**P15**	Boc-Cys(Trt)-D-Pro-Aib-Cha-NMe$_2$	99	53:47
8	**P3**	Boc-Cys-D-Pro-Aic-D-Phe-NMe$_2$	94	72:28	21	**P16**	Boc-Cys-D-Pro-Aib-Chg-NMe$_2$	99	69:31
9	**P4**	Boc-Cys-D-Pro-Aic-Dap(Cbz)-NEt$_2$	82	65:35	22	**P17**	Boc-Cys-D-Pro-Acpc-Chg-NMe$_2$	90	65:35
10	**P5**	Boc-Cys-D-Pro-Aib-Phe-N(Pip)$_2$	76	70:30	23	**P18**	Boc-L-Val-Cys-D-Pro-Aib-Phg-NMe$_2$	92	77:23
11*	**P6**	(Boc-Cys-D-Pro-Aib-Phe-N(Pip)$_2$)$_2$	99	64:36	24	**P19**	Boc-D-Val-Cys-D-Pro-Aib-Phg-NMe$_2$	83	68:32
12	**P7**	Boc-Cys-D-Pro-Aib-1-Nal-NMe$_2$	88	69:31	25	**P20**	Boc-Cys-D-Pro-Aib-D-Phg-NMe$_2$	82	65:35
13	**P8**	Boc-Cys-D-Pro-Acpc-1-Nal-NMe$_2$	89	71:29	26	**P21**	Boc-Cys-D-Pro-Acpc-D-Phg-NMe$_2$	99	59:41

Table S8. Supplementary optimization data for cysteine-embedded peptides. Reactions were performed on 0.025 mmol scale. Yields were determined by ^{1}H NMR analysis of crude reaction mixtures relative to an internal standard (benzyl ether). The er was determined by HPLC analysis on a chiral stationary phase. *Peptide = 5 mol%

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