# Redox-neutral zinc-catalyzed cascade [1,4]-H shift/annulation of diaziridines with donor-acceptor aziridines

## Table of Contents

**General Information.** Aldehydes, $Zn(OTf)_2$ (≥98%), $Sc(OTf)_3$ (99%), $Yb(OTf)_3$ (>99%), $Ni(OTf)_2$ (>96%), $Mg(OTf)_2$ (98%), $Ni(ClO_4)_2.6H_2O$ (98%), $Pd(PPh_3)_4$ (99%) and TEMPO (98%) were purchased from Aldrich and used as received. Methanol, dichloromethane, toluene and acetonitrile were dried prior as per the standard procedure. Diaziridines and DA aziridines were prepared according to the reported procedure.[1,2] Merck silica gel G/GF254 plates were used for analytical TLC and Rankem silica gel (60-120 mesh) was utilized for column chromatography. NMR spectra were recorded with Bruker Avance III 600, 500 and 400 MHz instruments using $CDCl_3$ as solvent and $Me_4Si$ as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in Hz, respectively, and to describe peak patterns following abbreviations were used when appropriate: s = singlet, d = doublet, t = triplet and m = multiplet. MestReNova software was used throughout the spectral analysis. Melting points were determined using a Büchi B-540 apparatus. FT-IR spectra were collected on Perkin Elmer IR instrument. Q-Tof ESI-MS instrument was used for recording mass spectra (model: 6546 LC/Q-TOF). Optical rotation was determined using a Rudolph Autopol I Automatic Polarimeter. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OJ-H and Daicel Chiralpak AD using *iso*-propanol and hexane as eluent. Single crystal *X*-ray data was collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using SHELXT-2018/2 (Göttingen, Germany).

**Sample Preparation for Crystal Growth.** The compound **3am** was dissolved in minimum volume of acetonitrile and chloroform and kept at room temperature for slow evaporation (2 days). Needle shaped crystals were formed, which were then subjected to *X*-ray diffraction.

**Crystal Structure and Data of 3am.**

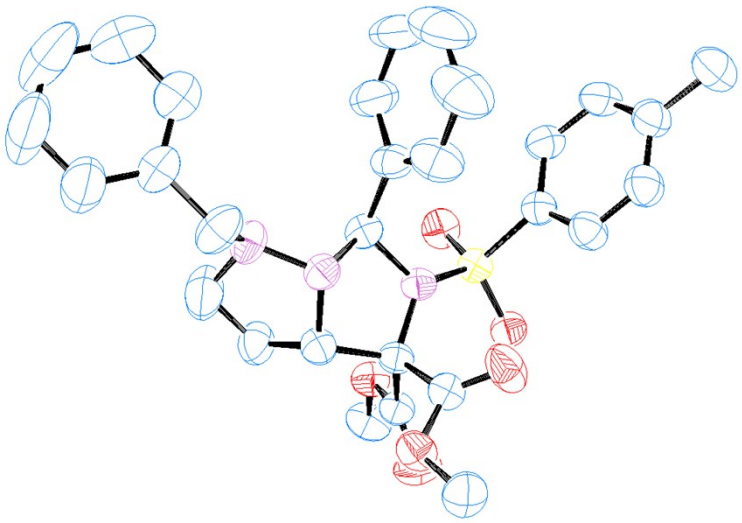
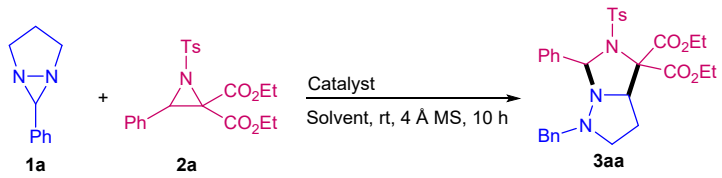


**Figure S1.** ORTEP diagram of Dimethyl 1-benzyl-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate **3am** (CCDC No 2293903) with 50% ellipsoid. H-Atoms are omitted for clarity.

| | |
|---|---|
| CCDC No. | 2293903 |
| Identification code | **3am** |
| Empirical formula | $C_{29}H_{31}N_3O_6S$ |
| Formula weight | 549.63 |
| Crystal habit, colour | Needle, Colourless |
| Temperature, *T*/K | 297K |
| Wavelength, λ/Å | 0.71073 Å |
| Crystal system | Triclinic |
| Space group | P -1 |
| Unit cell dimensions | a = 8.2702(12) Å<br>b = 12.5620(19) Å<br>c = 13.769(2) Å<br>α= 89.503(4)<br>β=79.822(4)<br>γ = 87.707)4) |
| Volume, *V*/Å$^3$ | 1406.8(4) Å$^3$ |
| *Z* | 2 |

| | |
|---|---|
| Calculated density, $Mg \cdot m^{-3}$ | 1.298 |
| Absorption coefficient, $\mu/mm^{-1}$ | 0.162 |
| $F$ (000) | 580 |
| $\theta$ range for data collection | 26.06 |
| Limiting indices | $-9 \leq h \leq 9$, $-14 \leq k \leq 14$, $-16 \leq l \leq 16$ |
| Reflection collected / unique | 4913/3926 |
| Completeness to $\theta$ | 99.3 % |
| Absorption correction | Multi-scan |
| Refinement method | 'SHELXL-2019/1 (Sheldrick, 2019)' |
| Data / restraints / parameters | 4913/ 0 / 356 |
| Goodness-of-fit on $F^2$ | 1.14 |
| Final $R$ indices [$I$ >2sigma($I$)] | R1 = 0.0456, $w$R2 = 0.1126 |
| R indices (all data) | R1 = 0.0621, $w$R2 = 0.1345 |

**Table S1. Optimization of Reaction Conditions**[a]

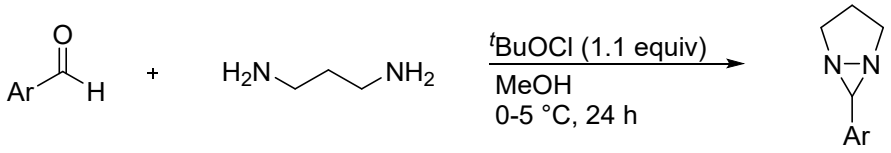



| Entry | Catalyst | Solvent | Yield (%)[b] |
|---|---|---|---|
| 1 | $Sc(OTf)_3$ | toluene | 51 |
| 2 | $Zn(OTf)_2$ | toluene | 80 |
| 3 | $Ni(OTf)_2$ | toluene | 38 |
| 4 | $Yb(OTf)_3$ | toluene | 25 |
| 5 | $Mg(OTf)_2$ | toluene | 20 |
| 6 | $Ni(ClO_4)_2.6H_2O$ | toluene | 35 |
| 7 | $Zn(OAc)_2$ | toluene | 42 |
| 8 | $ZnBr_2$ | toluene | 21 |
| 8 | $ZnCl_2$ | toluene | 30 |
| 10 | $Zn(OTf)_2$ | THF | trace |
| 11 | $Zn(OTf)_2$ | $CH_3CN$ | trace |
| 12 | $Zn(OTf)_2$ | MeOH | 12 |
| 13 | $Zn(OTf)_2$ | $(CH_2Cl)_2$ | 32 |

| | | | |
|---|---|---|---|
| 14 | $Zn(OTf)_2$ | DMSO | trace |
| 15 | PTSA | toluene | n.d. |
| 16[d] | $Zn(OTf)_2$ | toluene | 39 |

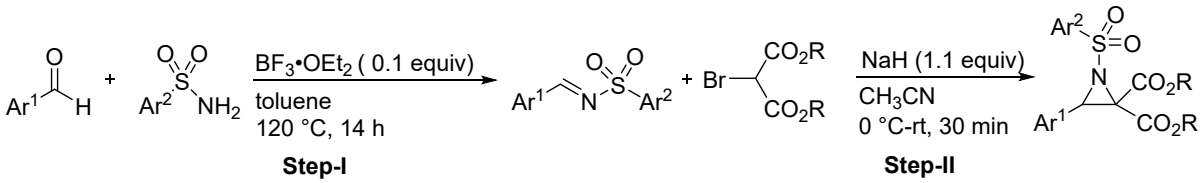
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (10 mol %), solvent (1 mL), rt, 10 h. [b]Isolated yield, [c]At 60 °C, n.d.= not detected.

**General Procedure for the Preparation of Diaziridines.**[1]




To a solution of 1,3-diaminopropane (148 mg, 2 mmol) in MeOH (10 mL), $^t$BuOCl (118 mg, 1.1 mmol) in MeOH (1 mL) was added dropwise under stirring at 0 to 5 ºC. Then, the aldehyde (1 mmol) in MeOH (2 mL) was added and the reaction was continued for 24 h at 0 to 5 ºC under $N_2$ atmosphere. After completion of the reaction, the solvent was evaporated under vacuum and the residue was dissolved with $CHCl_3$ (10 mL). Then the solution was washed with water and dried over $Na_2SO_4$. Evaporation of the solvent gave a residue that was purified by using silica gel chromatography to afford the corresponding diaziridines.

**General Procedure for the Preparation of DA Aziridines.**[2]




**Step-I:** To the stirred solution of arylsulfonamide (3 mmol) and aldehyde (3.3 mmol) in toluene (10 mL), $BF_3 \cdot Et_2O$ (43 mg, 0.3 mmol) was added. The flask was equipped with a dean-stark trap, which was attached to a reflux condenser. The reaction mixture was stirred at 120 °C for 14 h under $N_2$ atmosphere. After completion of the reaction, the resulting reaction mixture was concentrated under vacuum to afford the corresponding imine.

**Step-II**: To a suspension of NaH (88 mg, 2.2 mmol, 60 % dispersion in mineral oil), 2-bromomalonate (2.2 mmol) and imine solution (2 mmol) (obtained by **step-I**) were added in $CH_3CN$ (20 mL) under $N_2$ atmosphere at 0 °C. The resulting mixture was stirred at room temperature for 30 minutes. After completion, the mixture was filtered through a short pad of silica gel using EtOAc (40 mL). Evaporation of the solvent gave a residue that was purified by silica gel chromatography to afford the corresponding aziridines.

**General Procedure for the Annulation of Diaziridines with DA Aziridines.** Diaziridine **1** (0.1 mmol), DA aziridine **2** (0.12 mmol), $Zn(OTf)_2$ (3.62 mg, 0.01 mmol) and 4 Å molecular sieves (100 mg) were stirred in toluene (2 mL) at room temperature for 10 h. After completion, the reaction mixture was diluted with EtOAc (5 mL) and passed through a short pad of celite using EtOAc (10 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography to afford the corresponding annulated **3**.

**Synthesis of 1-Benzyl-4,5-dihydro-1H-pyrazole II**.[3] To a stirred solution of diaziridine **1a** (32 mg, 0.2 mmol) in toluene (3 mL), $Zn(OTf)_2$ (3.62 mg, 0.01 mmol) was added. The reaction was allowed to stir at room temperature for 8 h. Then, the suspension was diluted using EtOAc (5 mL) and passed through a short pad of celite using EtOAc (10 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography (hexane/ethyl acetate = 7:3) to afford **II** in 87% yield (28 mg).

**Scale-up Synthesis of 3am**. Diaziridine **1a** (480 mg, 3 mmol), DA aziridine **2m** (1.5 g, 3.6 mmol), $Zn(OTf)_2$ (108 mg, 0.3 mmol) and 4 Å molecular sieves (3 g) in toluene (10 mL) were stirred at room temperature for 12 h. Then, the reaction mixture was diluted with EtOAc (15 mL) and passed through a short pad of celite using EtOAc (20 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography (hexane/ethyl acetate = 4:1) to give **3am** in 65% yield (1.07 g).

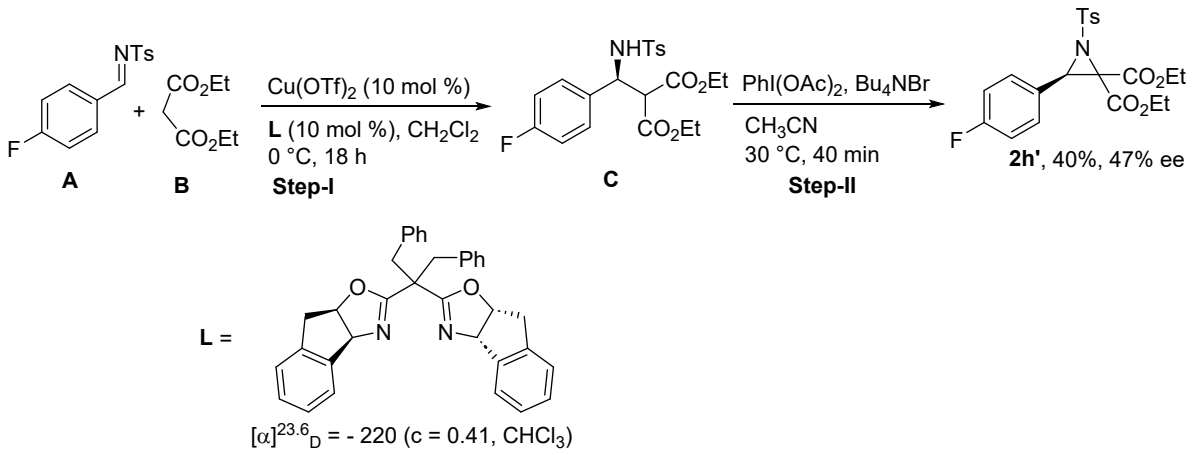
**Procedures for the Post-Synthetic Modifications**

**Synthesis of 4**[4]**.** To a stirred solution of **3am** (55 mg, 0.1mmol) in $CH_3CN$:$H_2O$ (1:1, 4 mL), aqueous 2 M NaOH (0.2 mL) was added dropwise at 0 °C and then allowed to stir at room temperature for 1 h. After completion (monitored by TLC), the reaction mixture was acidified using 2 M HCl, and extracted using ethyl acetate (10 mL). The combined organic layer was dried over $Na_2SO_4$. Evaporation of the solvent gave a residue that was purified using silica gel chromatography (hexane/ethyl acetate = 7:3) to afford **4** in 72% (35 mg) yield.

**Synthesis of 5.** To a stirred solution of **3am** (55 mg, 0.1mmol) in THF (4 mL), $LiAlH_4$ (11 mg, 0.3 mmol) was added portion wise under $N_2$ flow over 5 min at 0 °C. Then, it was slowly warmed to room temperature and allowed to stir for 3 h. After completion (monitored by TLC), the reaction mixture was diluted with ethyl acetate (10 mL), washed with aqueous $NH_4Cl$. The combined organic layer was dried over $Na_2SO_4$. Evaporation of the solvent gave a residue that was purified using silica gel chromatography (hexane/ethyl acetate = 3:2) to afford **5** in 82% (40 mg) yield.

**Synthesis of 6**[5]**.** To a stirred solution of **3af** (55 mg, 0.1 mmol) in toluene:ethanol (1:1, 4 mL), $Pd(PPh_3)_4$ (4 mg, 0.003 mmol), phenylboronic acid (18 mg, 0.1 mmol), $Na_2CO_3$ (22 mg, 0.2 mmol) and $H_2O$ (0.05 mL) were added and allowed to stir at 90 °C for 12 h under $N_2$ atmosphere. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), washed with water (5 mL) and dried over $Na_2SO_4$. Evaporation of the solvent gave a residue that was purified using silica gel chromatography (hexane/ethyl acetate = 4:1) to afford **6** in 78% (51 mg) yield.

**Procedure for the Preparation of DA Aziridine 2h'.**[6]



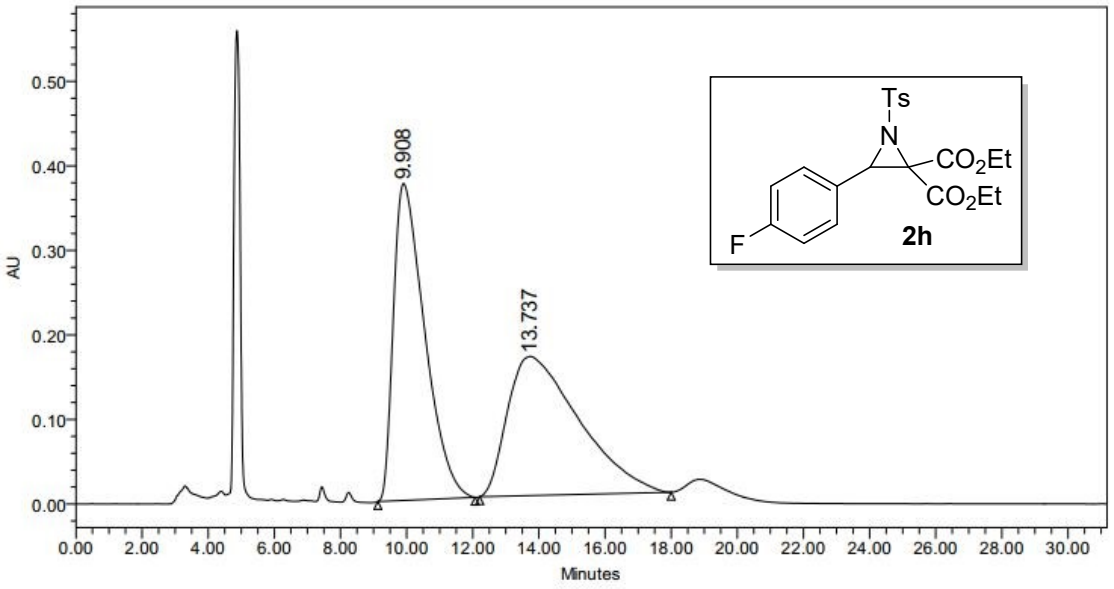

**Step-I:** $Cu(OTf)_2$ (72 mg, 0.2 mmol) and **L** (102 mg, 0.2 mmol) were stirred $CH_2Cl_2$ (8 ml) for 2 h at room temperature under nitrogen atmosphere. Then imine **A** (664 mg, 2.4 mmol) was added followed by the diethylmalonate **B** (320 mg, 2 mmol) and the resulting mixture was stirred for an additional 18 h at 0 ºC under $N_2$ atmosphere. The reaction mixture was diluted with $CH_2Cl_2$ (10 mL) and passed through a short pad of celite using $CH_2Cl_2$ (20 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography (hexane/ethyl acetate = 5:1) to afford *N*-Ts-β-amino ester **C** in 65% (328 mg) yield.

**Step-II**: To a stirred solution of **C** (217 mg, 0.5 mmol) (obtained by **step-I**) in $CH_3CN$ (3 mL), $PhI(OAc)_2$ (322 mg, 1 mmol) and $Bu_4NBr$ (322 mg, 1 mmol) were added and allowed to stir for 40 min at room temperature under $N_2$ atmosphere. The reaction mixture was diluted with EtOAc (10 mL) and passed through a short pad of celite using EtOAc (15 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography (hexane/ethyl acetate = 5:1) to furnish **2h'** in 40% (86 mg) yield.

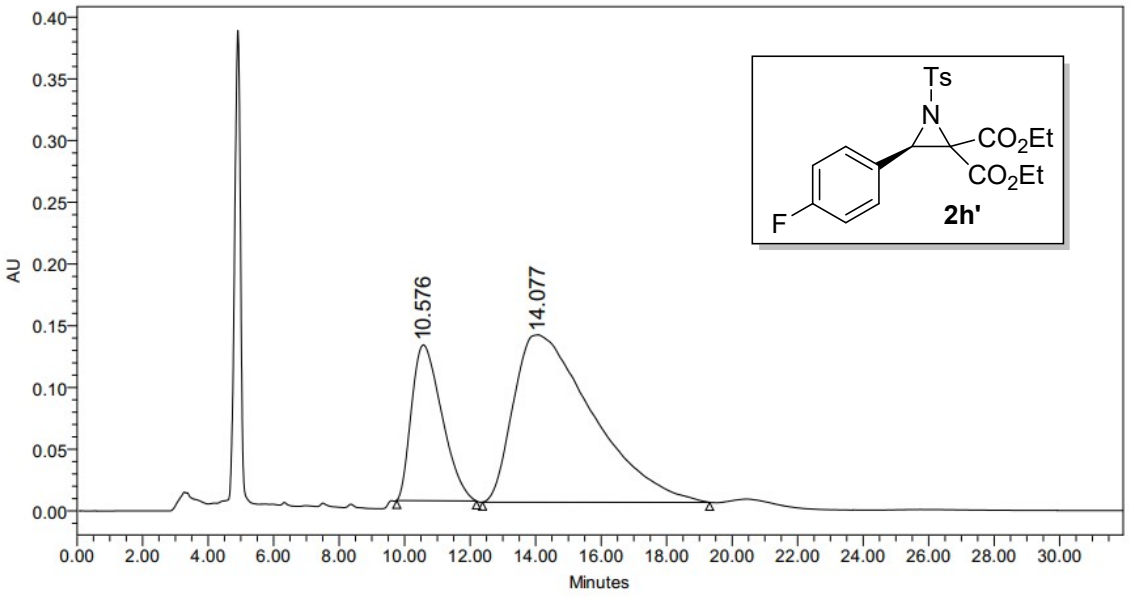
**Preparation of 3ah' using 2h'.** Diaziridine **1** (16 mg, 0.1 mmol), DA aziridine **2h'** (52 mg, 0.12 mmol), $Zn(OTf)_2$ (3.62 mg, 0.01 mmol) and 4 Å molecular sieves (100 mg) were stirred

in toluene (2 mL) for 10 h at room temperature. The reaction mixture was diluted with EtOAc (5 mL) and passed through a short pad of celite using EtOAc (10 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography to afford **3ah'** in 70% (42 mg) yield.

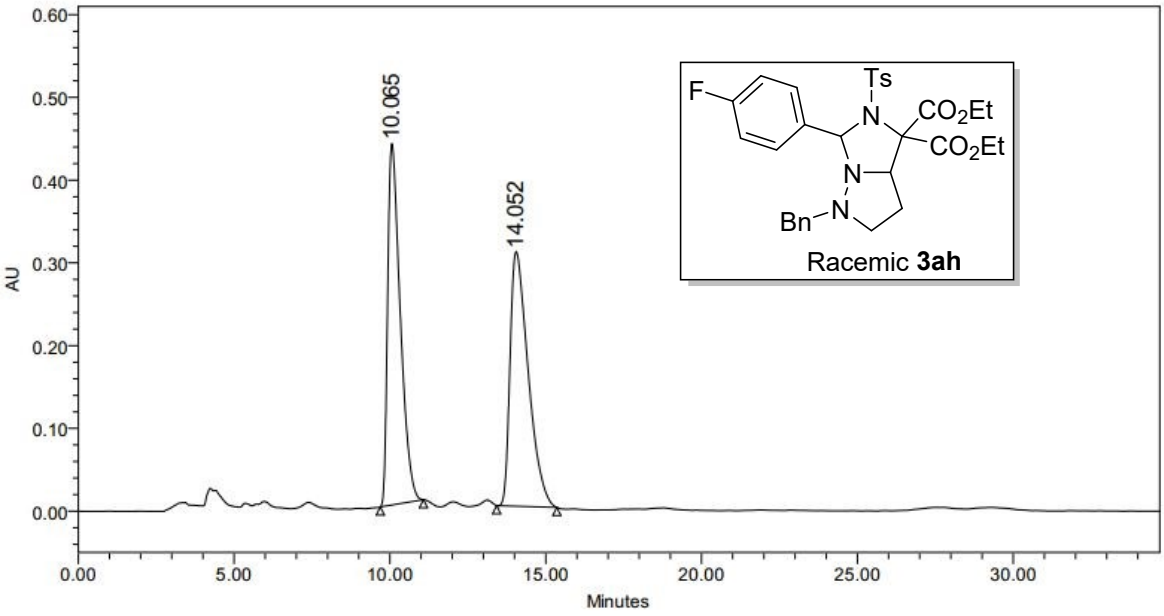
## HPLC Chromatogram



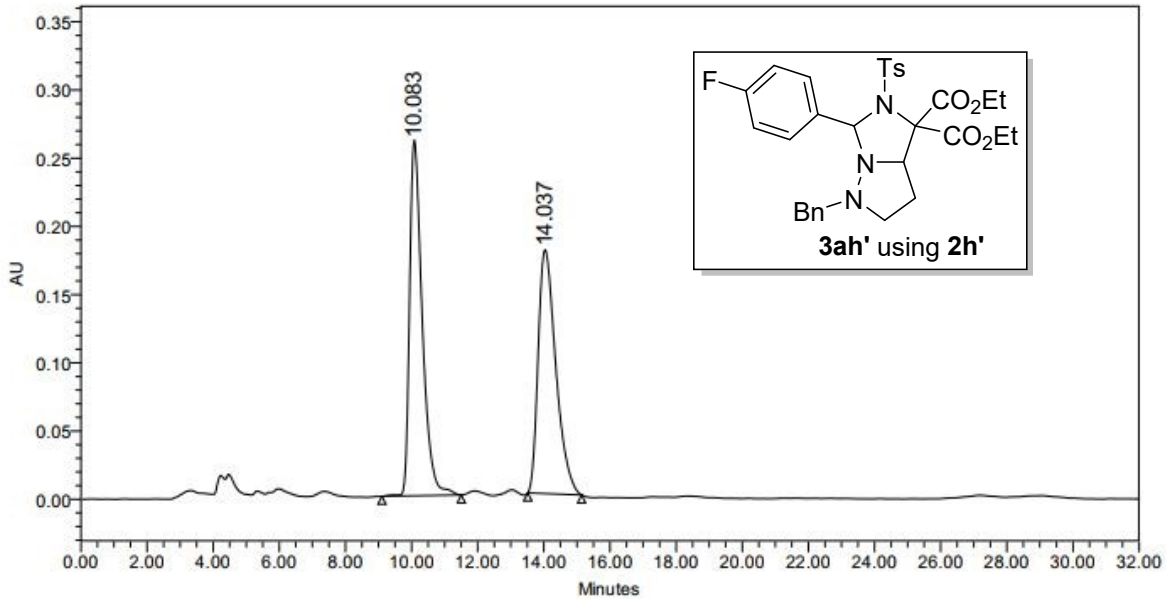

| | RT | Area | % Area | Height |
|---|---|---|---|---|
| 1 | 9.908 | 24538914 | 49.84 | 374788 |
| 2 | 13.737 | 24698290 | 50.16 | 164461 |




| | RT | Area | % Area | Height |
|---|---|---|---|---|
| 1 | 10.576 | 8125931 | 26.23 | 126092 |
| 2 | 14.077 | 22854871 | 73.77 | 135492 |

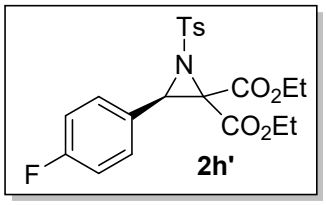



| | RT | Area | % Area | Height |
|---|---|---|---|---|
| 1 | 10.065 | 12236920 | 49.64 | 436497 |
| 2 | 14.052 | 12414465 | 50.36 | 307570 |

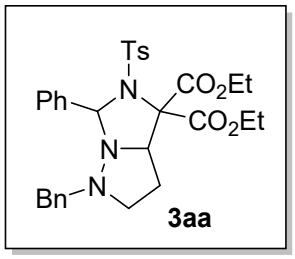



| | RT | Area | % Area | Height |
|---|---|---|---|---|
| 1 | 10.083 | 6930396 | 51.15 | 260438 |
| 2 | 14.037 | 6619063 | 48.85 | 178525 |

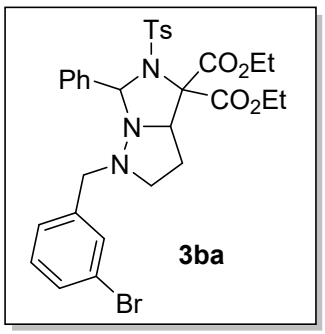
**Characterization Data of the Products**




**Diethyl (*R*)-3-(4-fluorophenyl)-1-tosylaziridine-2,2-dicarboxylate 2h'.** Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f$ = 0.43; Colourless liquid; yield 40% (86 mg); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.24 (m, 4H), 4.89 (s, 1H), 4.40-4.38 (q, *J* = 4.2 Hz, 2H), 3.95 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H). $[\alpha]_D^{21.8}$ = -2.67 (c = 0.15, $CH_2Cl_2$); HPLC: 47% *ee* [CHIRALCEL OJ-H, hexane/$^i$PrOH = 70:30, flow rate: 1 mL/min, λ = 254nm, $t_R$= 10.57 min (minor), 14.07 min (major)].

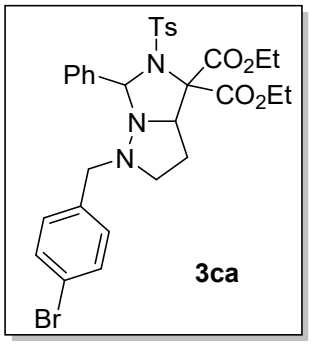



**Diethyl 1-benzyl-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3aa.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; pale yellow thick liquid; yield 80% (46 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.14-7.13 (m, 5H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.05-7.04 (m, 2H), 6.98 (t, *J* = 7.2 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.42 (s, 1H), 4.49-4.43 (m, 1H), 4.41-4.33 (m, 4H), 3.67 (d, *J* = 12.4 Hz, 1H), 3.38 (d, *J* = 12.8 Hz, 1H), 3.23-3.17 (m, 1H), 2.63-2.57 (m, 1H), 2.54-2.45 (m, 1H), 2.28 (s, 3H), 2.17-2.09 (d, *J* = 18.3 Hz, 1H), 1.42-1.38 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.3, 142.7, 138.0, 137.8, 137.1, 129.6, 129.2, 128.5, 128.4, 128.3, 128.1, 127.7, 127.1, 84.7, 76.1, 68.8, 63.0, 62.84, 62.80, 52.6, 28.3, 21.6, 14.2, 14.0; FT-IR (neat) 2982, 2929, 1750, 1456, 1344, 1263, 1158, 1090, 699, 581 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{31}H_{36}N_3O_6S$: 578.2319; Found 578.2310.

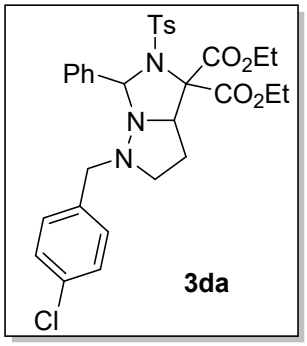



**Diethyl 1-(3-bromobenzyl)-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ba.** Analytical TLC on silica gel, 1:4 ethyl

acetate/hexane $R_f$ = 0.47; thick liquid; yield 62% (41 mg); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.27-7.26 (m, 3H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.14 (s, 1H), 7.09-7.07 (m, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 6.95 (t, *J* = 7.8 Hz, 2H), 6.92-6.91 (m, 1H), 6.89 (d, *J* = 7.8 Hz, 2H), 5.34 (s, 1H), 4.49-4.44 (m, 1H), 4.41-4.36 (m, 4H), 3.57 (d, *J* = 12.6 Hz, 1H), 3.34 (d, *J* = 12.6 Hz, 1H), 3.30-3.26 (m, 1H), 2.65-2.61 (m, 1H), 2.55-2.41 (m, 1H), 2.28 (s, 3H), 2.21-2.16 (m, 1H), 1.43-1.38 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.2, 142.7, 140.4, 138.0, 136.9, 132.3, 130.2, 129.9, 129.7 129.6, 128.6, 128.4, 127.8, 127.7, 122.1, 84.7, 76.1, 68.4, 62.8, 62.6, 53.0, 31.4, 28.7, 21.5, 14.3, 14.1; FT-IR (neat) 2958, 2923, 1747, 1457, 1344, 1235, 1157, 1091, 646, 554 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{31}H_{35}BrN_3O_6S$: 656.1424; Found 656.1441.

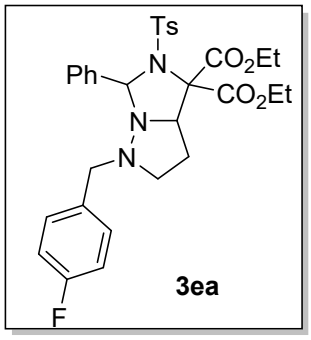



**Diethyl 1-benzyl-6-(4-bromopheny l)-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ca.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 70% (45 mg); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.13-7.05 (m, 3H), 7.00-6.92 (m, 6H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.25 (s, 1H), 4.49-4.43 (m, 1H), 4.41-4.31 (m, 4H), 3.55 (d, *J* = 12.5 Hz, 1H), 3.40 (d, *J* = 12.5 Hz, 1H), 3.31-3.26 (m, 1H), 2.69-2.64 (m, 1H), 2.54-2.47 (m, 1H), 2.33 (s, 3H), 2.19-2.13 (m, 1H), 1.42-1.38 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.1, 143.2, 137.9, 137.8, 136.1, 131.5, 130.6, 129.2, 128.6, 128.5, 128.0, 127.0, 122.6, 83.8, 75.9, 68.2, 63.1, 62.9, 62.8, 52.9, 28.8, 21.6, 14.3, 14.0; FT-IR (neat) 2962, 2929, 1746, 1456, 1344, 1263, 1158, 1091, 699, 582 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{31}H_{35}BrN_3O_6S$: 656.1424; Found 656.1426.

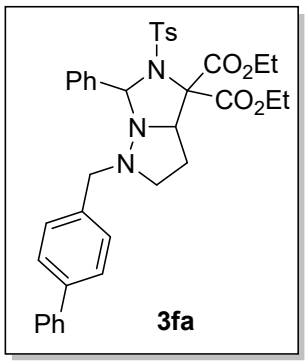



**Diethyl 1-(4-chlorobenzyl)-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3da.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 74% (47 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.14-7.13 (m, 4H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.05-7.03 (m, 2H), 6.97 (t, *J*

= 7.6 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.41 (s, 1H), 4.47-4.43 (m, 1H), 4.40- 4.33 (m, 4H), 3.66 (d, *J* = 12.8 Hz, 1H), 3.38 (d, *J* = 12.8 Hz, 1H), 3.23-3.17 (m, 1H), 2.63-2.57 (m, 1H), 2.54-2.45 (m, 1H), 2.28 (s, 3H), 2.17-2.08 (m, 1H), 1.42-1.37 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.3, 142.7, 138.1, 137.9, 137.2, 129.7, 129.3, 128.6, 128.4, 128.3, 128.1, 127.7, 127.1, 84.8, 76.2, 68.8, 63.1, 62.8, 62.7, 52.7, 28.4, 21.5, 14.2, 14.0; FT-IR (neat) 2963, 2925, 1744, 1455, 1344, 1265, 1158, 1091, 700, 581 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{34}ClN_3O_6SNa$: 634.1749; Found 634.1751.

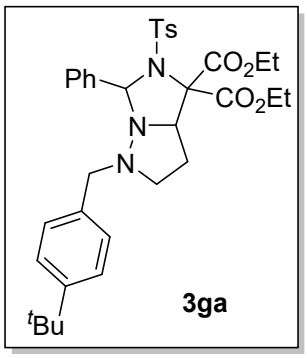



**Diethyl 1-(4-fluorobenzyl)-6-phenyl-5-tosylhexa-hydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ea.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 66% (39 mg); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.14-7.13 (m, 4H), 7.11-7.08 (m, 1H), 7.05-7.04 (m, 2H), 6.98 (t, *J* = 7.5 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 5.41 (s, 1H), 4.46-4.41 (m, 1H), 4.39-4.33 (m, 4H), 3.66 (d, *J* = 12.5 Hz, 1H), 3.37 (d, *J* = 12.5 Hz, 1H), 3.23-3.18 (m, 1H), 2.63-2.58 (m, 1H), 2.53-2.47 (m, 1H), 2.28 (s, 3H), 2.16-2.11 (m, 1H), 1.42-1.37 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.2, 142.7, 138.1, 137.9, 137.2, 131.5 ($J_{C\text{-}F}$ = 237.0), 129.9, 129.7, 129.3, 128.8 ($J_{C\text{-}F}$ = 3.7), 128.7, 128.6, 128.4, 128.3, 128.1, 127.7, 127.1, 84.8, 76.2, 68.8, 63.1, 62.8, 62.7, 52.7, 28.4, 21.5, 14.2, 14.1; $^{19}$F NMR (377 MHz, $CDCl_3$) δ -114.22; FT-IR (neat) 2960, 2918, 1746, 1455, 1344, 1265, 1158, 1091, 700, 579 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{31}H_{35}FN_3O_6S$: 596.2225; Found 596.2238.

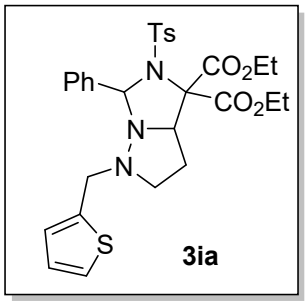



**Diethyl 1-([1,1'-biphenyl]-4-ylmethyl)-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3fa.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 72% (47 mg); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.48-7.43 (m, 4H), 7.37-7.33 (m, 3H), 7.13 (s, 4H), 7.10-7.09 (m, 3H), 7.05-

7.03 (m, 2H), 6.86 (d, $J$ = 8.5 Hz, 2H), 5.43 (s, 1H), 4.51-4.44 (m, 1H), 4.42-4.34 (m, 4H), 3.68 (d, $J$ = 12.5 Hz, 1H), 3.42 (d, $J$ = 12.5 Hz, 1H), 3.29-3.24 (m, 1H), 2.68-2.63 (m, 1H), 2.58-2.51 (m, 1H), 2.20 (s, 3H), 2.17-2.13 (m, 1H), 1.43-1.39 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.2, 142.6, 141.3, 141.2, 138.2, 137.9, 136.1, 130.1, 129.3, 128.9, 128.6, 128.4, 128.0, 127.4, 127.2, 127.0, 126.4, 84.4, 76.1, 68.8, 63.1, 62.84, 62.80, 52.9, 28.5, 21.5, 14.3, 14.0; FT-IR (KBr) 2981, 2929, 1747, 1487, 1456, 1344, 1265, 1157, 1091, 698, 580 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{37}H_{40}N_3O_6S$: 654.2632; Found 654.2632.

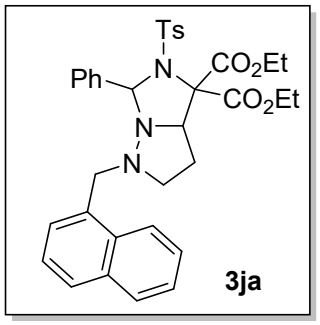



**Diethyl 1-(4-(*tert*-butyl)benzyl)-6-phenyl-5-tosylhexa-hydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ga.** Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f$ = 0.45; yellow solid; mp 123-124 °C; yield 62% (39 mg); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, $J$ = 8.4 Hz, 2H), 7.13 (t, $J$ = 7.8 Hz, 4H), 7.08 (t, $J$ = 7.2 Hz, 1H), 6.97 -6.94 (m, 4H), 6.89 (d, $J$ = 8.4 Hz, 2H), 5.40 (s, 1H), 4.46-4.42 (m, 1H), 4.40-4.34 (m, 4H), 3.61 (d, $J$ = 12.6 Hz, 1H), 3.35 (d, $J$ = 12.6 Hz, 1H), 3.24-3.20 (m, 1H), 2.63-2.59 (m, 1H), 2.51-2.45 (m, 1H), 2.28 (s, 3H), 2.17-2.13 (m, 1H), 1.42-1.37 (m, 6H), 1.26 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.3, 149.9, 142.6, 138.2, 137.3, 135.0, 129.8, 128.9, 128.6, 128.4, 128.3, 127.7, 125.0, 84.9, 76.2, 68.7, 62.8, 62.7, 52.8, 34.5, 31.5, 28.6, 21.5, 14.3, 14.0; FT-IR (neat) 2952, 2926, 1743, 1454, 1343, 1269, 1155, 1088, 699, 578 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{35}H_{44}N_3O_6S$: 634.2945; Found 634.2945.

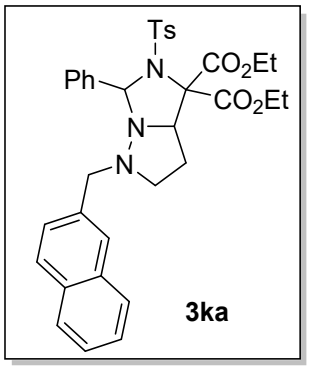



**Diethyl 6-phenyl-1-(thiophen-2-ylmethyl)-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ia.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 65% (37 mg); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, $J$ = 8.5 Hz, 2H), 7.22 (d, $J$ = 7.0 Hz, 2H), 7.13-7.06 (m, 2H), 7.02 (t, $J$ = 7.5 Hz, 2H), 6.90 (d, $J$ = 8.0 Hz, 2H), 6.82-6.81 (m, 1H), 6.71-6.70 (m, 1H), 5.39 (s, 1H), 4.46-4.34 (m, 4H),

4.22 (t, $J$ = 7.5 Hz, 1H), 3.69-3.66 (m, 1H), 3.58-3.56 (m, 1H), 3.29-3.25 (m, 1H), 2.71-2.66 (m, 1H), 2.55-2.48 (m, 1H), 2.28 (s, 3H), 2.05-1.98 (m, 1H), 1.42-1.37 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.5, 167.1, 142.7, 139.7, 138.1, 137.2, 130.0, 128.6, 128.5, 128.4, 127.8, 126.8, 126.1, 125.8, 85.1, 75.7, 68.7, 62.9, 62.7, 56.8, 52.0, 28.9, 21.5, 14.3, 14.1.; FT-IR (neat) 2981, 2924, 1743, 1456, 1343, 1265, 1157, 1089, 698, 579 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{29}H_{34}N_3O_6S_2$: 584.1884; Found 584.1896.

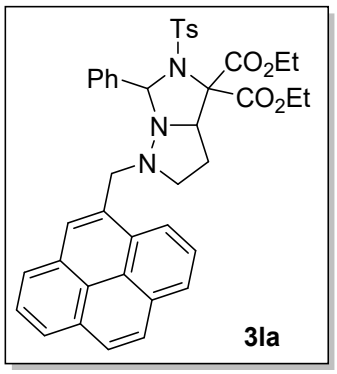



**Diethyl 1-(naphthalen-1-ylmethyl)-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*] pyrazole-4,4-dicarboxylate 3ja.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.48; yellow solid; mp 126-127 °C; yield 75% (48 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.72-7.65 (m, 2H), 7.53 (d, $J$ = 8.4 Hz, 1H), 7.37 (t, $J$ = 7.2 Hz, 1H), 7.32 (d, $J$ = 8.0 Hz, 2H), 7.24-7.19 (m, 4H), 7.17-7.14 (m, 2H), 7.05-7.01 (m, 2H), 6.91 (d, $J$ = 7.6 Hz, 2H), 5.37 (s, 1H), 4.52-4.35 (m, 5H), 4.17 (d, $J$ = 12.0 Hz, 1H), 3.69 (d, $J$ = 12.0 Hz, 1H), 3.11-3.05 (m, 1H), 2.79-2.73 (m, 1H), 2.53-2.45 (m, 1H), 2.28-2.23 (m, 4H), 1.43-1.36 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.3, 142.6, 138.0, 137.2, 133.7, 133.6, 132.2, 130.2, 129.6, 129.2, 128.54, 128.52, 128.4, 128.3, 128.1, 128.0, 127.7, 127.6, 127.5, 125.7, 125.5, 125.1, 124.9, 84.4, 76.0, 67.8, 62.8, 62.7, 61.8, 52.2, 28.9, 21.5, 14.2, 14.0; FT-IR (neat) 2981, 2926, 1745, 1456, 1342, 1265, 1156, 1089, 670, 579 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{35}H_{37}N_3O_6SNa$: 650.2295; Found 650.2320.

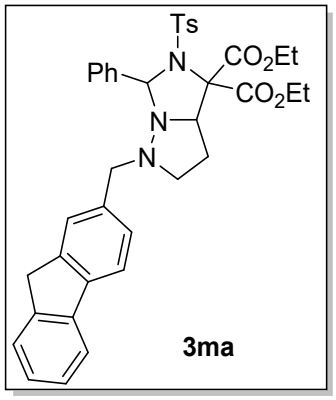



**Diethyl 1-(naphthalen-2-ylmethyl)-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*] pyrazole-4,4-dicarboxylate 3ka.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.48; thick liquid; yield 68% (42 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74-7.65 (m, 2H), 7.57 (d, $J$ = 8.4 Hz, 1H), 7.44-7.39 (m, 3H), 7.27 (s, 2H), 7.17 (d, $J$ = 8.4 Hz, 1H), 7.07-7.05 (m, 2H), 6.97 (t, $J$ = 7.2 Hz, 1H), 6.87-6.81 (m, 4H), 5.42 (s, 1H), 4.49-4.43 (m,

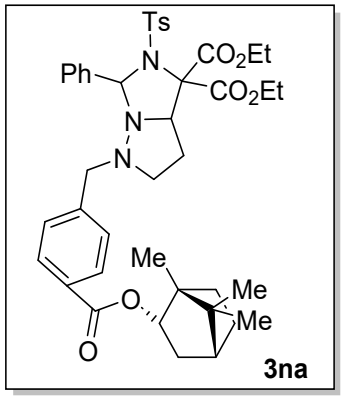
1H), 4.39-4.33 (m, 4H), 3.80 (d, *J* = 12.4 Hz, 1H), 3.54 (d, *J* = 12.4 Hz, 1H), 3.28-3.22 (m, 1H), 2.72-2.66 (m, 1H), 2.56-2.47 (m, 1H), 2.25 (s, 3H), 2.21-2.15 (m, 1H), 1.43-1.35 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.5, 167.1, 142.5, 137.9, 136.9, 135.4, 133.1, 132.7, 129.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5, 127.48, 127.43, 125.7, 125.5, 84.7, 76.0, 68.6, 63.1, 62.7, 62.6, 52.7, 28.4, 21.4, 14.1, 13.9; FT-IR (neat) 2979, 2926, 1746, 1456, 1343, 1265, 1157, 1090, 670, 583 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{35}H_{38}N_3O_6S$: 628.2476; Found 628.2477.




**Diethyl 6-phenyl-1-(pyren-4-ylmethyl)-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3la.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; yellow solid; mp 124-125 °C; yield 57% (39 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.6 Hz, 2H), 8.00-7.92 (m, 3H), 7.90-7.87 (m, 2H), 7.84-7.82 (m, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 7.2 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.74-6.70 (m, 1H), 6.66-6.62 (m, 2H), 5.32 (s, 1H), 4.52-4.45 (m, 2H), 4.39-4.30 (m, 4H), 4.04 (d, *J* = 12.4 Hz, 1H), 3.25-3.19 (m, 1H), 2.91-2.85 (m, 1H), 2.57-2.49 (m, 1H), 2.34-2.28 (m, 1H), 2.23 (s, 3H), 1.40-1.35 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.7, 167.3, 142.6, 138.0, 136.7, 131.5, 131.3, 131.1, 131.0, 129.9, 129.8, 128.6, 128.5, 128.3, 128.0, 127.4, 127.2, 127.1, 126.9, 125.8, 125.0, 124.9, 124.8, 124.7, 124.6, 124.2, 84.6, 76.0, 67.9, 62.9, 62.7, 61.6, 52.8, 29.1, 21.5, 14.3, 14.0; FT-IR(neat) 2960, 2925, 1746, 1456, 1343, 1263, 1157, 1090, 670, 583 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{41}H_{40}N_3O_6S$: 702.2632; Found 702.2633.

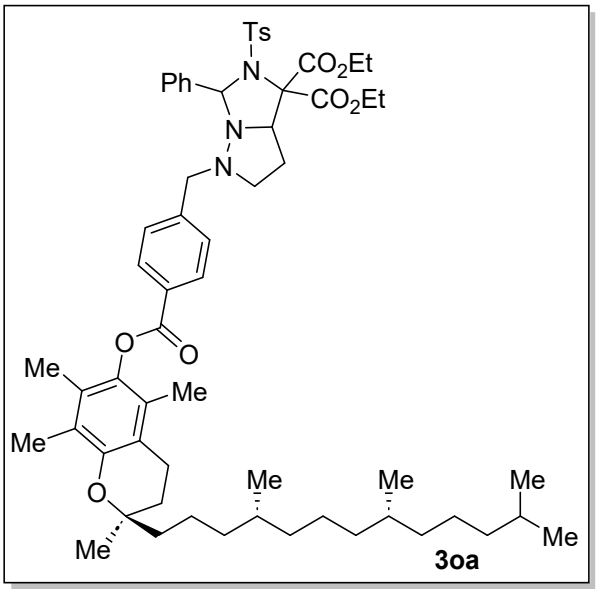



**Diethyl 1-((9H-fluoren-2-yl)methyl)-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ma.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 73% (48 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.52-7.50 (m, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.31-7.27 (m, 2H), 7.24 (s, 1H), 7.16 (s, 1H), 7.08-7.02 (m, 3H), 6.97-6.93 (m, 1H), 6.88-6.84 (m, 4H), 5.41 (s, 1H), 4.50-4.43 (m, 1H), 4.40-4.34 (m, 4H), 3.72-3.67 (m, 3H), 3.46 (d, *J* = 12.4 Hz, 1H), 3.30-3.24 (m, 1H), 2.72-2.66 (m, 1H), 2.55-2.42 (m, 1H), 2.25 (s, 3H), 2.21-2.14 (m, 1H), 1.43-1.36 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.3, 143.4, 143.1, 142.6, 141.7, 140.7, 138.1, 137.1, 136.6, 129.7, 128.5, 128.4, 128.1, 128.0, 127.5, 126.8, 126.6, 126.0, 125.1, 119.8, 119.3, 84.7, 76.2, 68.7, 63.2, 62.8, 62.7, 52.8, 36.8, 28.5, 21.5, 14.2, 14.1; FT-IR (neat) 2981, 2926, 1742, 1456, 1343, 1264, 1156, 1090, 697, 582 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{38}H_{40}N_3O_6S$: 666.2632; Found 666.2637.

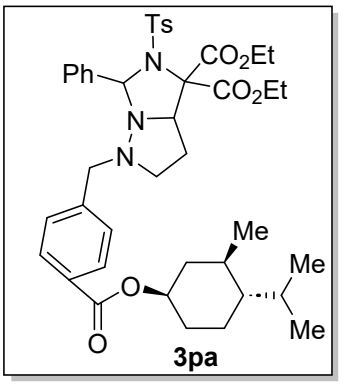



**Diethyl 6-phenyl-5-tosyl-1-(4-((((1S,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)carbonyl)benzyl) hexahydro-4H-imidazo[1,5-*b*] pyrazole-4,4-dicarboxylate 3na.** Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f$ = 0.45; thick liquid; yield 55% (41 mg); $^1$H NMR (500 MHz, CDCl3) δ 7.72-7.70 (m, 1H), 7.52-7.50 (m, 1H), 7.15-7.13 (m, 2H), 7.11-7.10 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.01 (t, *J* = 7.5 Hz, 3H), 6.89-6.85 (m, 2H), 6.35 (d, *J* = 9.0 Hz, 1H), 5.32 (s, 1H), 5.17-5.14 (m, 1H), 5.09-5.07 (m, 1H), 4.48-4.44 (m, 1H), 4.38-4.33 (m, 4H), 4.14-4.01 (m, 3H), 3.76-3.75 (m, 1H), 3.61 (d, *J* = 13.0 Hz, 1H), 3.45 (d, *J* = 13.0 Hz, 1H), 3.34-3.29 (m, 1H), 2.69-2.64 (m, 1H), 2.52-2.43 (m, 1H), 2.32 (s, 3H), 2.26 (s, 2H), 2.22-2.17 (m, 1H), 2.11-2.04 (m, 1H), 1.74-1.73 (m, 1H), 1.42-

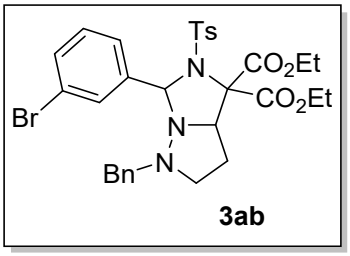
1.36 (m, 6H), 1.20-1.18 (m, 2H), 1.15-1.12 (m, 2H), 0.97 (s, 1H), 0.92 (s, 1H), 0.90 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.9, 166.6, 143.0, 142.7, 138.1, 137.7, 129.8, 129.3, 129.1, 128.6, 128.5, 128.4, 127.8, 127.6, 127.1, 126.8, 84.7, 80.4, 76.0, 68.1, 62.8, 62.3, 62.0, 57.9, 57.1, 53.0, 49.2, 48.0, 45.1, 37.1, 28.9, 27.5, 21.5, 19.9, 19.1, 14.3, 14.0; FT-IR (neat) 2957, 2935, 1735, 1455, 1340, 1271, 1157, 1092, 668, 582 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{42}H_{52}N_3O_8S$: 758.3470; Found 758.3488.



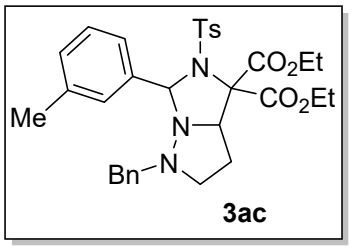

**Diethyl (3aR,6R)-6-phenyl-1-(4-((((R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl) chroman-6-yl)oxy)carbonyl)-benzyl)-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3oa.** Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f$ = 0.45; thick liquid; yield 60% (61 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.25 (s, 1H), 7.15-7.00 (m, 6H), 6.91-6.86 (m, 4H), 5.33 (s, 1H), 4.50-4.44 (m, 1H), 4.42-4.35 (m, 4H), 4.15-3.99 (m, 1H), 3.66 (d, *J* = 12.8 Hz, 1H), 3.49 (d, *J* = 12.0 Hz, 1H), 3.40-3.34 (m, 1H), 2.74-2.68 (m, 1H), 2.62 (t, *J* = 6.0 Hz, 2H), 2.58-2.49 (m, 1H), 2.32 (s, 1H), 2.27-2.21 (m, 4H), 2.12 (s, 3H), 2.05-2.00 (m, 6H), 1.86-1.77 (m, 3H), 1.57-1.49 (m, 8H), 1.44-1.37 (m, 10H), 1.21-1.06 (m, 9H), 0.88-0.84 (m, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.3, 165.2, 149.6, 143.9, 142.7, 140.8, 138.0, 136.9, 129.9, 129.8, 129.3, 129.2, 128.6, 128.5, 128.4, 128.3, 128.2, 127.6, 127.1, 127.0, 126.9, 125.2, 123.3, 117.6, 84.7, 76.0, 75.2, 68.0, 62.9, 62.8, 62.7, 53.2, 39.5, 37.6, 37.5, 37.4, 33.0, 32.9, 32.8, 29.8, 29.0, 28.1, 25.0, 24.9, 24.6, 22.9, 22.8, 21.5, 21.2, 20.8, 19.9, 19.8, 19.7, 14.3, 14.1, 13.2, 12.3, 12.0; FT-IR (neat) 2925, 2867, 1732, 1457, 1343, 1235, 1159, 1090, 667, 582 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{61}H_{84}N_3O_9S$: 1034.5923; Found 1034.5924.




**Diethyl 1-(4-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-oxy)carbonyl)benzyl)-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*] pyrazole-4,4-dicarboxylate 3pa.** Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f$ = 0.45; thick liquid; yield 68% (51 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.24 (s, 2H), 7.02-6.99 (m, 5H), 6.89-6.85 (m, 4H), 5.32 (d, *J* = 2.8 Hz, 1H), 4.93-4.86 (m, 1H), 4.47-4.42 (m, 1H), 4.40-4.33 (m, 4H), 3.62-3.58 (m, 1H), 3.44 (d, *J* = 12.8 Hz, 1H), 3.34-3.28 (m, 1H), 2.68-2.62 (m, 1H), 2.55-2.46 (m, 1H), 2.26 (s, 3H), 2.22-2.15 (m, 1H), 2.13-2.07 (m, 1H), 1.97-1.91 (m, 1H), 1.74 (d, *J* = 11.2 Hz, 2H), 1.43-1.36 (m, 6H), 1.19-1.03 (m, 4H), 0.94-0.91 (m, 7H), 0.81-0.78 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.4, 167.1, 166.0, 142.9, 142.6, 137.9, 136.7, 129.7, 129.1, 129.0, 128.9, 128.4, 128.3, 128.1, 127.4, 84.6, 75.9 74.6, 68.0, 62.8, 62.6, 52.9, 47.3, 41.0, 34.3, 31.5, 29.7, 28.8, 26.5, 23.6, 22.1, 21.4, 20.8, 16.5, 14.1, 13.9; FT-IR (neat) 2925, 2854, 1711, 1456, 1345, 1269, 1159, 1096, 696, 583 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{42}H_{54}N_3O_8S$: 760.3626; Found 760.3626.

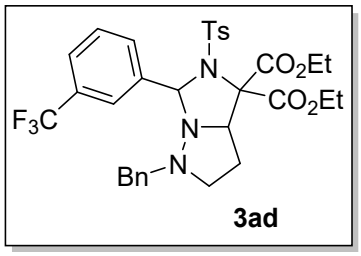



**Diethyl 1-benzyl-6-(3-bromophenyl)-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ab.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 72% (49 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.06 (s, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.92-6.83 (m, 7H), 5.19 (s, 1H), 4.52-4.46 (m, 1H), 4.42-4.35 (m, 4H), 3.47 (d, *J* = 12.4 Hz, 1H), 3.38-3.31 (m, 2H), 2.73-2.67 (m, 1H), 2.56-2.47 (m, 1H), 2.30 (s, 3H), 2.27-2.19 (m, 1H), 1.42 (t, *J* = 7.2 Hz, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.4, 167.1, 143.4, 140.2, 138.8, 137.5, 132.4, 132.2, 131.5, 130.3, 129.3, 128.9, 128.6, 128.5, 128.4, 127.8, 122.03, 122.00, 83.8, 75.9, 68.0, 63.0, 62.9, 62.5, 53.3, 29.0, 21.6, 14.3, 14.1; FT-IR (KBr) 2980, 2935, 1750, 1473, 1344, 1263, 1158, 1090, 670, 581 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{31}H_{35}BrN_3O_6S$: 656.1424; Found 656.1424.



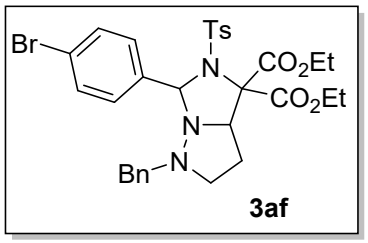
3ac

**Diethyl 1-benzyl-6-(m-tolyl)-5-tosyl-hexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ac.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 65% (42 mg); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.8 Hz, 2H), 7.14-7.13 (m, 3H), 7.06-7.05 (m, 2H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.89-6.86 (m, 3H), 6.77 (s, 1H), 5.40 (s, 1H), 4.49-4.43 (m, 1H), 4.40- 4.33 (m, 4H), 3.70 (d, *J* = 12.6 Hz, 1H), 3.37 (d, *J* = 12.6 Hz, 1H), 3.21-3.17 (m, 1H), 2.61-2.57 (m, 1H), 2.55-2.49 (m, 1H), 2.28 (s, 3H), 2.16-2.10 (m, 1H), 2.01 (s, 3H), 1.42-1.38 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.3, 142.5, 138.2, 137.9, 137.3, 136.8, 130.1, 129.2, 129.1, 128.5, 128.3, 128.0, 127.6, 127.1, 127.0, 84.7, 76.1, 69.1, 63.0, 62.8, 52.7, 28.0, 21.5, 21.2, 14.3, 14.0; FT-IR (KBr) 2960, 2924, 1747, 1454, 1344, 1263, 1157, 1092, 670, 580 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{38}N_3O_6S$: 592.2476; Found 592.2504.



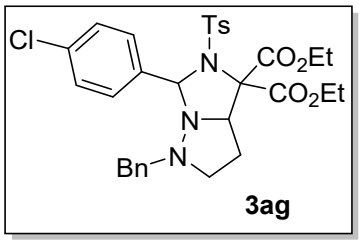
3ad

**Diethyl 1-benzyl-5-tosyl-6-(3-(trifluoromethyl)phenyl)-hexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ad.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.45; thick liquid; yield 70% (45 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 4H), 7.18 (s, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.05-7.00 (m, 3H), 6.93-6.91 (m, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.35 (s, 1H), 4.49-4.44 (m, 1H), 4.42-4.36 (m, 4H), 3.52 (d, *J* = 12.4 Hz, 1H), 3.39 (d, *J* = 12.4 Hz, 1H), 3.34-3.28 (m, 1H), 2.74-2.68 (m, 1H), 2.54-2.46 (m, 1H), 2.25 (s, 3H), 2.22-2.17 (m, 1H), 1.43-1.39 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.4, 167.1, 143.3, 138.3, 137.7, 137.6, 133.3, 130.3 ($J_{C-F}$ = 32.1), 130.1, 129.9, 129.7, 129.1, 128.6, 128.4, 128.0, 127.9, 127.1, 126.6 ($J_{C-F}$ = 270.7), 126.54 ($J_{C-F}$ = 3.6), 126.52, 126.5, 126.4, 125.2 ($J_{C-F}$ = 3.1), 125.17, 125.15, 125.1, 124.8, 123.0, 121.2, 84.1, 76.1, 68.2, 63.2, 63.0, 62.9, 53.0, 29.0, 21.4, 14.2, 14.0; $^{19}$F NMR (377 MHz, $CDCl_3$) δ -62.59; FT-IR(neat) 2985, 2929, 1749, 1454, 1329, 1268, 1161, 1093, 701, 580 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{35}F_3N_3O_6S$: 646.2193; Found 646.2200.



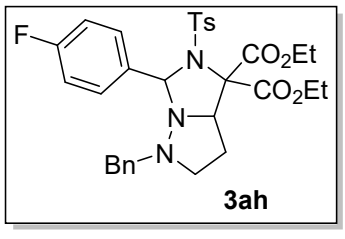
**3af**

**Diethyl 1-(4-bromobenzyl)-6-phenyl-5-tosylhexa-hydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3af.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 60% (39 mg); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.09-7.08 (m, 1H), 6.99 (d, *J* = 7.5 Hz, 2H), 6.91 (t, *J* = 7.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.30 (s, 1H), 4.48- 4.41 (m, 1H), 4.39-4.32 (m, 4H), 3.51 (d, *J* = 12.5 Hz, 1H), 3.34-3.27 (m, 2H), 2.67-2.62 (m, 1H), 2.54-2.47 (m, 1H), 2.27 (s, 3H), 2.22-2.16 (m, 1H), 1.42-1.37 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.3, 142.7, 138.0, 137.0, 136.8, 131.0, 130.9, 129.8, 128.6, 128.4, 128.2, 127.6, 120.9, 84.7, 76.0, 68.2, 62.9, 62.8, 62.4, 53.0, 28.9, 21.5, 14.3, 14.0; FT-IR (neat) 2960, 2924, 1746, 1457, 1344, 1264, 1158, 1091, 670, 582 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{31}H_{35}BrN_3O_6S$: 656.1424; Found 656.1423.



**3ag**

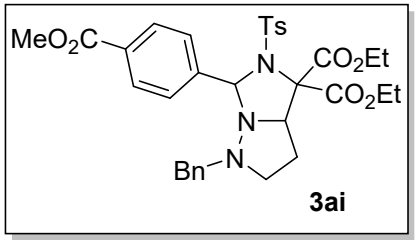
**Diethyl 1-benzyl-6-(4-chlorophenyl)-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ag.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 66% (40 mg); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.13-7.05 (m, 3H), 6.96-6.92 (m, 6H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.27 (s, 1H), 4.49-4.42 (m, 1H), 4.41-4.31 (m, 4H), 3.55 (d, *J* = 12.5 Hz, 1H), 3.39 (d, *J* = 13.0 Hz, 1H), 3.30-3.25 (m, 1H), 2.69-2.64 (m, 1H), 2.53-2.46 (m, 1H), 2.32 (s, 3H), 2.19-2.12 (m, 1H), 1.42-1.38 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.1, 143.1, 137.9, 137.8, 135.6, 134.3, 131.1, 129.2, 128.6, 128.5, 128.0, 127.7, 127.0, 83.8, 75.9, 68.2, 63.1, 62.9, 62.8, 52.9, 28.8, 21.5, 14.3, 14.0; FT-IR (neat) 2981, 2926, 1745, 1454, 1344, 1265 1157, 1088, 670, 579 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{31}H_{35}ClN_3O_6S$: 612.1930; Found 612.1939.



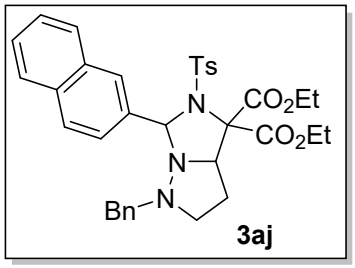
**3ah**

**Diethyl 1-benzyl-6-(4-fluorophenyl)-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ah.** Analytical TLC on silica gel, 1:4 ethyl

acetate/hexane $R_f$ = 0.47; thick liquid; yield 75% (44 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.11-7.08 (m, 3H), 7.05-7.01 (m, 2H), 6.99-6.96 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.59 (t, *J* = 8.8 Hz, 2H), 5.31 (s, 1H), 4.48-4.43 (m, 1H), 4.39-4.31 (m, 4H), 3.57 (d, *J* = 12.4 Hz, 1H), 3.39 (d, *J* = 12.4 Hz, 1H), 3.29-3.23 (m, 1H), 2.69-2.63 (m, 1H), 2.54-2.47 (m, 1H), 2.30 (s, 3H), 2.20-2.12 (m, 1H), 1.42-1.37 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.2, 144.2, 143.0, 138.1, 137.8, 132.9 ($J_{C-F}$ = 2.9), 132.8, 131.6 ($J_{C-F}$ = 8.5), 131.5, 129.8 ($J_{C-F}$ = 236.7), 129.2, 128.6, 128.4, 128.0, 127.5, 127.1, 114.5 ($J_{C-F}$ = 21.4), 114.3, 83.8, 75.9, 68.2, 63.1, 62.9, 62.8, 52.8, 28.8, 21.5, 14.3, 14.0; $^{19}$F NMR (377 MHz, $CDCl_3$) δ -114.21; FT-IR (KBr) 2982, 2926, 1743, 1454, 1343, 1225, 1158, 1093, 671, 579 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd $C_{31}H_{35}FN_3O_6S$: 596.2225; Found 596.2227.

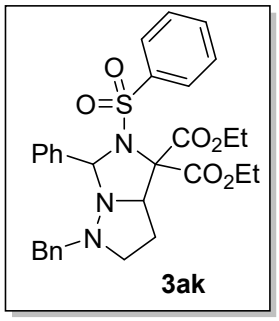



**Diethyl 1-benzyl-6-(4-(methoxycarbonyl)phenyl)-5-tosyl-hexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ai.** Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f$ = 0.47; colorless solid; mp 123-124 °C; yield 76% (48 mg); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.09-7.04 (m, 3H), 6.97-6.96 (m, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.36 (s, 1H), 4.48-4.43 (m, 1H), 4.39-4.34 (m, 4H), 3.91 (s, 3H), 3.56 (d, *J* = 12.5 Hz, 1H), 3.37 (d, *J* = 12.5 Hz, 1H), 3.28-3.23 (m, 1H), 2.68-2.63 (m, 1H), 2.53-2.41 (m, 1H), 2.26 (s, 3H), 2.20-2.13 (m, 1H), 1.42-1.38 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.5, 167.0, 143.2, 142.3, 137.74, 137.71, 129.9, 129.7, 129.2, 128.8, 128.6, 128.5, 128.0, 127.1, 84.1, 76.1, 68.5, 63.2, 62.9, 62.8, 52.8, 52.2, 28.7, 21.4, 14.2, 14.0; FT-IR (KBr) 2982, 2954, 1745, 1721, 1436, 1344, 1273, 1158, 1020, 668, 580 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{33}H_{38}N_3O_6S$: 636.2374; Found 636.2379.

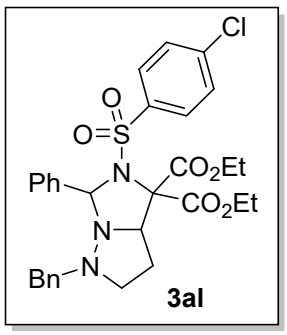



**Diethyl 1-benzyl-6-(naphthalen-2-yl)-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3aj.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.48; thick liquid; yield 58% (36 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.58-7.54 (m, 3H), 7.53-7.50 (m, 2H), 7.40-7.36 (m, 2H), 7.34-7.31 (m, 2H), 7.19 (d, *J* = 8.4 Hz,

2H), 7.06 (d, *J* = 10.0 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 10.0 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 2H), 5.48 (s, 1H), 4.54-4.48 (m, 1H), 4.45-4.37 (m, 4H), 3.74 (d, *J* = 12.8 Hz, 1H), 3.56 (d, *J* = 12.4 Hz, 1H), 3.39-3.33 (m, 1H), 2.79-2.73 (m, 1H), 2.64-2.56 (m, 1H), 2.32-2.17 (m, 1H), 2.02 (s, 3H), 1.45-1.40 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.3, 142.6, 137.7, 135.4, 134.1, 133.5, 133.0, 132.6, 132.5, 129.6, 128.5, 128.0, 127.9, 127.6, 127.5, 127.4, 127.3, 127.2, 126.3, 126.1, 125.7, 125.6, 125.5, 84.7, 76.0, 68.5, 63.3, 62.9, 62.8, 53.1, 28.7, 21.2, 14.3, 14.1; FT-IR (KBr) 2963, 2926, 1745, 1456, 1342, 1263, 1158, 1090, 667, 583 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{35}H_{38}N_3O_6S$: 628.2476; Found 628.2477.

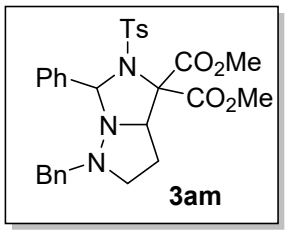



**Diethyl 1-benzyl-6-phenyl-5-(phenylsulfonyl)hexa-hydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ak.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; orange solid; mp 99-100 ˚C; yield 68% (38 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 2H), 7.30-7.28 (m, 1H), 7.14-7.05 (m, 10H), 6.98-6.94 (m, 2H), 5.44 (s, 1H), 4.49-4.43 (m, 1H), 4.39-4.34 (m, 4H), 3.67 (d, *J* = 12.4 Hz, 1H), 3.38 (d, *J* = 12.4 Hz, 1H), 3.23-3.17 (m, 1H), 2.64-2.58 (m, 1H), 2.55-2.47 (m, 1H), 2.18-2.09 (m, 1H), 1.43-1.37 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.5, 167.2, 141.1, 137.9, 137.0, 131.9, 129.7, 129.2, 128.5, 128.4, 128.1, 127.8, 127.7, 127.1, 84.8, 76.2, 68.9, 63.1, 62.8, 62.7, 52.6, 28.4, 14.2, 14.0; FT-IR (neat) 2981, 2950, 1743, 1448, 1346, 1265, 1159, 1089, 687, 588 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{30}H_{34}N_3O_6S$: 564.2163; Found 564.2153.



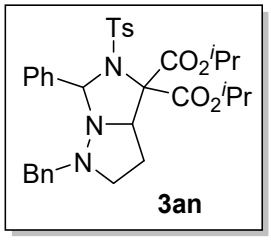

**Diethyl 1-benzyl-5-((4-chlorophenyl)sulfonyl)-6-phenylhexa-hydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3al.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 73% (43 mg); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.13-7.11 (m, 6H), 7.05-7.02 (m, 4H), 6.99 (t, *J* = 7.2 Hz, 2H), 5.42 (s, 1H), 4.48-4.42 (m, 1H), 4.39- 4.33 (m, 4H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.38 (d, *J* = 12.6 Hz,

1H), 3.24-3.20 (m, 1H), 2.65-2.61 (m, 1H), 2.54-2.48 (m, 1H), 2.17-2.11(m, 1H), 1.42-1.38 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.5, 167.1, 139.6, 138.5, 137.8, 136.8, 130.1, 129.8, 129.2, 128.6, 128.1, 128.0, 127.9, 127.2, 84.8, 76.2, 68.8, 63.1, 62.9, 62.8, 52.7, 28.5, 14.3, 14.0; FT-IR (KBr) 2981, 2955, 1746, 1477, 1348, 1266, 1162, 1089, 699, 566 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{30}H_{33}ClN_3O_6S$: 598.1773; Found 598.1802.



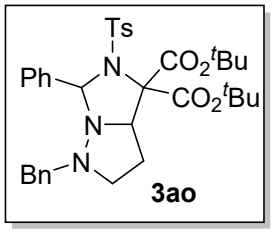
**3am**

**Dimethyl 1-benzyl-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3am.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.45; colorless solid; mp 123-124 °C; yield 85% (46 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 2H), 7.15-7.13 (m, 5H), 7.11-7.09 (m, 1H), 7.06-7.05 (m, 2H), 7.01-6.97 (m, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 5.45 (s, 1H), 4.36 (t, *J* = 6.4 Hz, 1H), 3.93 (d, *J* = 12.4 Hz, 6H), 3.70 (d, *J* = 12.8 Hz, 1H), 3.36 (d, *J* = 1.4 Hz, 1H), 3.19-3.13 (m, 1H), 2.61-2.55 (m, 1H), 2.53-2.45 (m, 1H), 2.28 (s, 3H), 2.16-2.08 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 169.1, 167.7, 142.8, 138.0, 137.8, 137.1, 129.6, 129.2, 128.5, 128.4, 128.3, 128.1, 127.8, 127.2, 84.8, 76.1, 69.2, 63.0, 53.6, 53.4, 52.6, 28.1, 21.5; FT-IR (KBr) 3030, 2952, 1748, 1454, 1344, 1272, 1157, 1089, 700, 580 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_6S$: 550.2006; Found 550.2004.

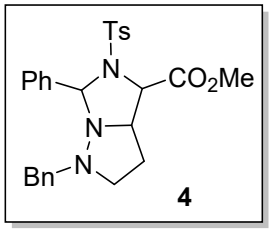


**3an**

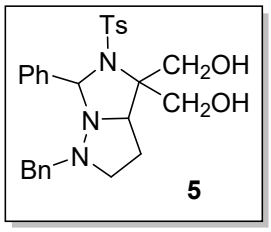
**Di-*iso*-propyl 1-benzyl-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3an.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.45; thick liquid; yield 70% (42 mg); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 2H), 7.13-7.10 (m, 5H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.03-7.02 (m, 2H), 6.97 (t, *J* = 7.5 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 5.35 (s, 1H), 5.28-5.19 (m, 2H), 4.34 (t, *J* = 7.0 Hz, 1H), 3.63 (d, *J* = 12.5 Hz, 1H), 3.37 (d, *J* = 12.5 Hz, 1H), 3.26-3.21 (m, 1H), 2.63-2.58 (m, 1H), 2.50-2.43 (m, 1H), 2.28 (s, 3H), 2.14-2.08 (m, 1H), 1.40-1.36 (m, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 168.0, 166.6, 142.5, 138.1, 137.9, 137.2, 129.7, 129.1, 128.5, 128.3, 128.1, 127.9, 127.4, 126.9, 84.7, 76.2, 70.9, 70.4, 68.3, 63.1, 52.6, 28.6, 21.8, 21.7, 21.63, 21.60, 21.4; FT-IR (KBr) 2983, 2925, 1741, 1454, 1345, 1277, 1159, 1089, 699, 577 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{33}H_{40}N_3O_6S$: 606.2632; Found 606.2632.




**Di-*tert*-butyl 1-benzyl-6-phenyl-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 3ao.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.45; thick liquid; yield 65% (41 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.14-7.13 (d, *J* = 7.2 Hz, 5H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.04-7.03 (m, 2H), 6.98 (t, *J* = 7.6 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 5.28 (s, 1H), 4.33 (t, *J* = 6.8 Hz, 1H), 3.64 (d, *J* = 12.8 Hz, 1H), 3.40 (d, *J* = 12.4 Hz, 1H), 3.26-3.20 (m, 1H), 2.64-2.58 (m, 1H), 2.47-2.39 (m, 1H), 2.29 (s, 3H), 2.13-2.05 (m, 1H), 1.59-1.58 (m, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.3, 165.9, 142.3, 138.2, 137.9, 137.5, 129.6, 129.3, 128.5, 128.4, 128.0, 127.9, 127.4, 126.9, 84.8, 83.8, 83.0, 68.6, 63.2, 52.5, 28.4, 28.0, 27.9, 21.4; FT-IR (KBr) 2975, 2926, 1742, 1455, 1345, 1250, 1154, 1089, 699, 584 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{35}H_{44}N_3O_6S$: 634.2945; Found 634.2948.

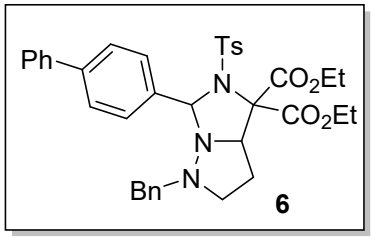



**Methyl 1-benzyl-6-phenyl-5-tosylhexahydro-1H-imidazo[1,5-*b*]pyrazole-4-carboxylate 4.** Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f$ = 0.49; colorless solid; yield 72% (35 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.29-7.27 (m, 4H), 7.25-7.23 (m, 4H), 7.16-7.14 (m, 2H), 5.94 (s, 1H), 4.26 (d, *J* = 7.2 Hz, 1H), 4.12 (d, *J* = 12.4 Hz, 1H), 3.85 (t, *J* = 8.0 Hz, 1H), 3.72 (s, 3H), 3.54 (d, *J* = 12.8 Hz, 1H), 2.82-2.76 (m, 1H), 2.52-2.46 (m, 1H), 2.43 (s, 3H), 2.24-2.17 (m, 1H), 2.05-1.97 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.5, 143.9, 139.1, 138.1, 135.6, 129.6, 129.2, 128.4, 128.3, 128.2, 128.1, 127.6, 127.4, 86.5, 67.4, 66.1, 63.3, 52.7, 51.1, 28.8, 21.8; FT-IR (neat) 2953, 2925, 1748, 1454, 1344, 1265, 1157, 1089, 701, 580 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{30}N_3O_4S$: 492.1952; Found 492.1966.

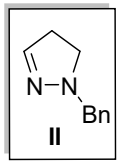



**(1-benzyl-6-phenyl-5-tosylhexahydro-1H-imidazo[1,5-*b*]pyrazole-4,4-diyl)dimethanol 5.** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane $R_f$ = 0.49; thick

liquid; yield 82% (40 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.35 (m, 2H), 7.20-7.19 (m, 6H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.99-6.98 (m, 2H), 5.58 (s, 1H), 4.09-3.99 (m, 3H), 3.91-3.85 (m, 3H), 3.43 (d, *J* = 12.4 Hz, 1H), 3.13-3.08 (m, 1H), 2.85 (s, 1H), 2.51-2.44 (m, 1H), 2.37 (s, 3H), 2.11-2.05 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.9, 137.7, 136.6, 129.3, 129.1, 128.6, 128.4, 128.2, 127.8, 127.7, 83.2, 74.5, 66.9, 66.5, 62.4, 61.2, 53.7, 24.7, 21.6; FT-IR (neat) 3368, 3031, 2924, 1453, 1373, 1289, 1121, 1090, 738, 571 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{32}N_3O_4S$: 494.2108; Found 494.2107.




**Diethyl 6-([1,1'-biphenyl]-4-yl)-1-benzyl-5-tosylhexahydro-4H-imidazo[1,5-*b*]pyrazole-4,4-dicarboxylate 6.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f$ = 0.47; thick liquid; yield 78% (51 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.24-7.22 (m, 3H), 7.21-7.18 (m, 2H), 7.02-6.96 (m, 5H), 6.85 (t, *J* = 7.6 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 5.32 (s, 1H), 4.40-4.35 (m, 1H), 4.33-4.25 (m, 4H), 3.58 (d, *J* = 12.8 Hz, 1H), 3.35 (d, *J* = 12.4 Hz, 1H), 3.24-3.18 (m, 1H), 2.63-2.56 (m, 1H), 2.48-2.39 (m, 1H), 2.18 (s, 3H), 2.15-2.07 (m, 1H), 1.35-1.28 (m, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.3, 142.7, 141.1, 139.9, 138.1, 137.1, 137.0, 129.8, 129.6, 128.8, 128.6, 128.4, 128.2, 127.6, 127.2, 127.1, 126.7, 84.8, 76.1, 68.6, 62.8, 62.77, 62.75, 52.9, 28.6, 21.5, 14.3, 14.1; FT-IR (neat) 2963, 2924, 1745, 1454, 1343, 1264, 1157, 1093, 699, 579 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{37}H_{40}N_3O_6S$: 654.2632; Found 654.2629.




**1-benzyl-4,5-dihydro-1H-pyrazole II.** Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f$ = 0.49; thick liquid; yield 87% (28 mg); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2H), 7.35-7.32 (m, 2H), 7.29-7.27 (m, 1H), 6.82 (s, 1H), 4.21 (s, 2H), 2.92 (t, *J* = 9.6 Hz, 2H), 2.66-2.61 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 143.5, 137.7, 129.1, 128.5, 127.4, 60.8, 52.3, 34.3; FT-IR (neat) 2923, 2823, 1454, 840, 734, 698 cm$^{-1}$; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{10}H_{13}N_2$: 161.1073; Found 161.1073.

**ADMET and Molecular Docking Studies**

The ADMET (adsorption, distribution, metabolism, excretion, and toxicity) properties were examined to study the drug likeness and physicochemical property of all the synthesized compounds using pkCSM tool,[7e] among which compound **4** satisfies the Lipinski's rule and Veber rule (Table S2).[7a,b] The analysis revealed that the gastrointestinal tract (GIT) absorption value for **4** is 98.021, which infers that the corresponding compound may show good absorbance in human intestine. Accounting metabolism, compound **4** was examined for inhibition of the Cytochrome P450 isomers, such as CYP3A4, CYP2D6, CYP2C9, CYP1A2 and CYP2C19 where it emerged as inhibitor of CYP3A4, the key enzyme responsible for drug metabolism. Moreover, compound **4** is not a OCT2 substrate and has good clearance rate compared to Fluconazole, hence it might have shorter dose interval period. Eventually, the final examined factor *i.e*. toxicity was documented in Table S2 where compound **4** has maximum tolerable dose. Also, the Chronic toxic activity (LOAEL) was less, however, the acute toxic activity (LD50) is nearly same with Fluconazole. The aforementioned data suggests that the synthesized **4** has good medicinal implication.

**Table S2. ADMET Properties of Compound 4.**

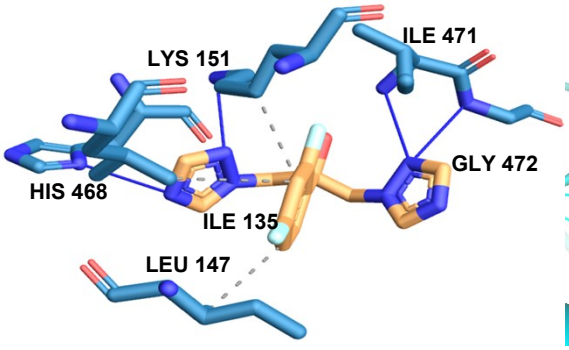
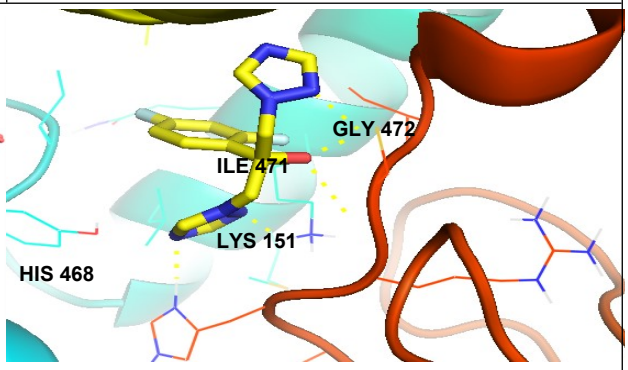
| Parameter | Compound 4 | Fluconazole |
|---|---|---|
| **Absorption** | | |
| Water solubiliy (log mol/L) | -5.763 | -2.411 |
| Caco2 permeability (log Papp in $10^{-6}$ cm/s) | 1.272 | 0.754 |
| GIT absorption[a] (%) | 98.021 | 72.188 |
| Inhibitor of *p*-glycoprotien II | Yes | No |
| Inhibitor of *p*-glycoprotien I | Yes | No |
| Substrate for *p*-glycoprotien | No | No |
| Skin Permeability (log Kp) | -2.711 | -2.736 |
| **Distribution** | | |
| BBB permeability[b] (log BB) | -0.820 | -0.706 |
| CNS permeability [c] (log PS) | -2.175 | -3.785 |
| VDss (human) [d] (log L/kg) | -0.071 | 0.438 |
| | | |

| **Metabolism** | | |
|---|---|---|
| CYP3A4 substrate | Yes | No |
| CYP2D6 substrate | No | No |
| CYP2C9 inhibitor | Yes | No |
| CYP1A2 inhibitor | No | No |
| CYP2C19 inhibitor | Yes | No |
| **Excretion** | | |
| Renal OCT2 substrate[e] | No | No |
| Total clearance (log ml/min/kg) | 0.960 | 0.851 |
| **Toxicity** | | |
| Skin sensitization | No | No |
| Hepatotoxic effect | Yes | Yes |
| Oral rat chronic toxicity (LOAEL) (log mg/kg_bw/day) | 1.334 | 1.281 |
| Oral rat acute toxicity (LD50) (mol/kg) | 2.332 | 2.321 |
| hERG II inhibitor | No | No |
| hERG I inhibitor | No | No |
| Max. Tolerated dose (log mg/kg/day) | 0.458 | 0.608 |
| AMES toxicity | No | No |

[a]Gastro intestinal tract; [b]blood brain barrier permeant; [c]central nervous system permeant; [d]VDss: volume of distribution; [e]Renal organic cation transporter 2.

Here we exhibit the best docking pose of **4** and compare it with standard ligand Fluconazole to study antifungal activity of synthesized moiety. Here the interactions between **4** and amino acid residues of target protein lanosterol 14$\alpha$-demethylase (**CYP51**) **(**PDB ID: 4WMZ)[7d] was unveiled using AutoDock Suite.[7c] The results revealed that the binding energy/docking score of docked **4** with target protein is -7.46 kcal/mol while for Fluconazole the corresponding energy/ score is -4.27 kcal/mol. Again, H-bonding interactions was found between **4** and nearby residues, such as TYR140, GLY314, GLY315 while Fluconazole forms H-bonding with LYS151, HIS468, ILE471, GLY472 amino acid residues of target protein **CYP51** (Figure S2).

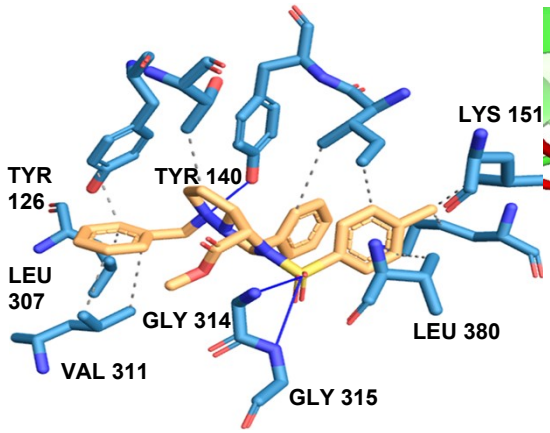
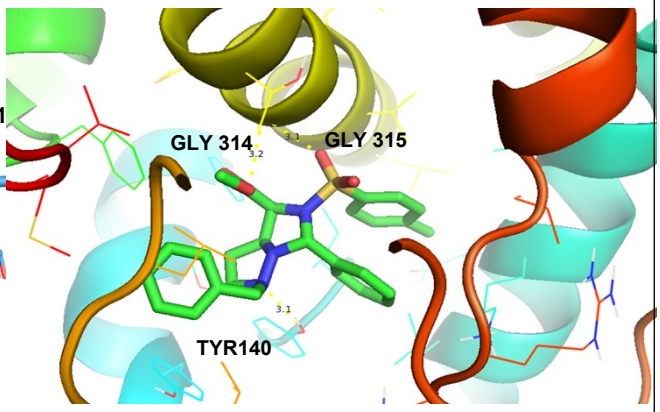
**(a)**

| 2D Interaction diagram of Fluconazole | 3D Interaction diagram of Fluconazole |
|---|---|
|  |  |



| Inhibitors | Docking Score (kcal/mol) | Hydrogen Bond interactions | Hydrophobic Interactions |
|---|---|---|---|
| **Fluconazole** | -4.27 kcal/mol | LYS151, HIS468, ILE471, GLY472 | ILE135, LEU147, LYS151 |

**(b)**

| 2D Interaction diagram of compound 4 | 3D Interaction diagram of compound 4 |
|---|---|
|  |  |



| Inhibitors | Docking Score (kcal/mol) | Hydrogen Bonding Interaction | Hydrophobic Interaction |
|---|---|---|---|
| **Compound 4** | -7.46 kcal/mol | TYR140, GLY314, GLY315 | TYR126, THR130, ILE139, LYS151, LEU307, VAL311, LEU380 |

**(c)**

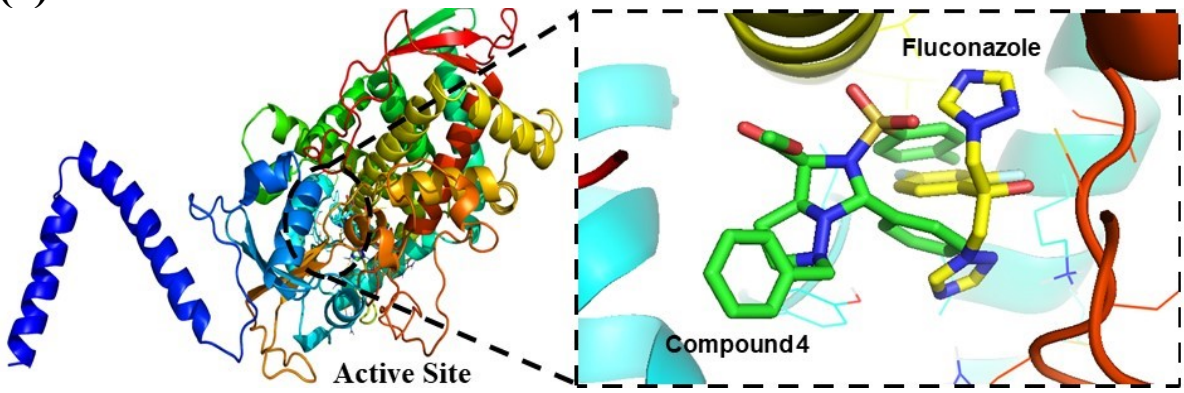



**Figure S2. The Result of Docking Experiment.** Schematic representations of binding mode of Fluconazole (**a**) and compound **4** (**b**) with target enzyme **CYP51** (blue bonds showing H-bond interactions and dotted white bonds showing hydrophobic interactions with the binding site residues) (**C)** Best docking pose of compound **4** (green) and comparison with the initial ligand Fluconazole (yellow) with **CYP51** pocket.

## References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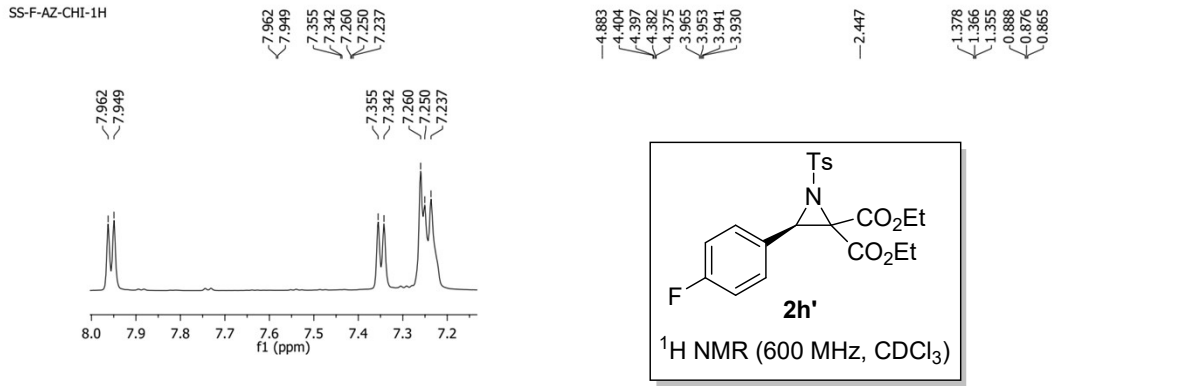
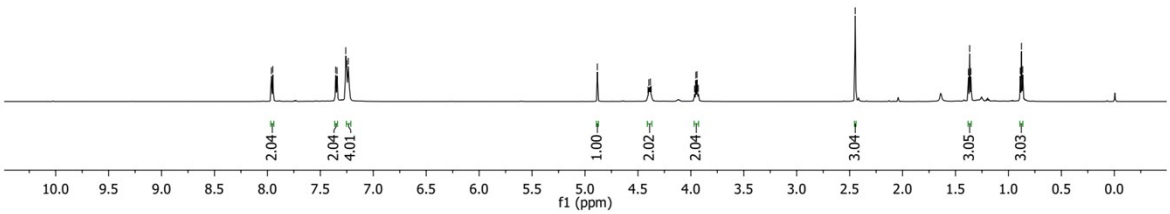
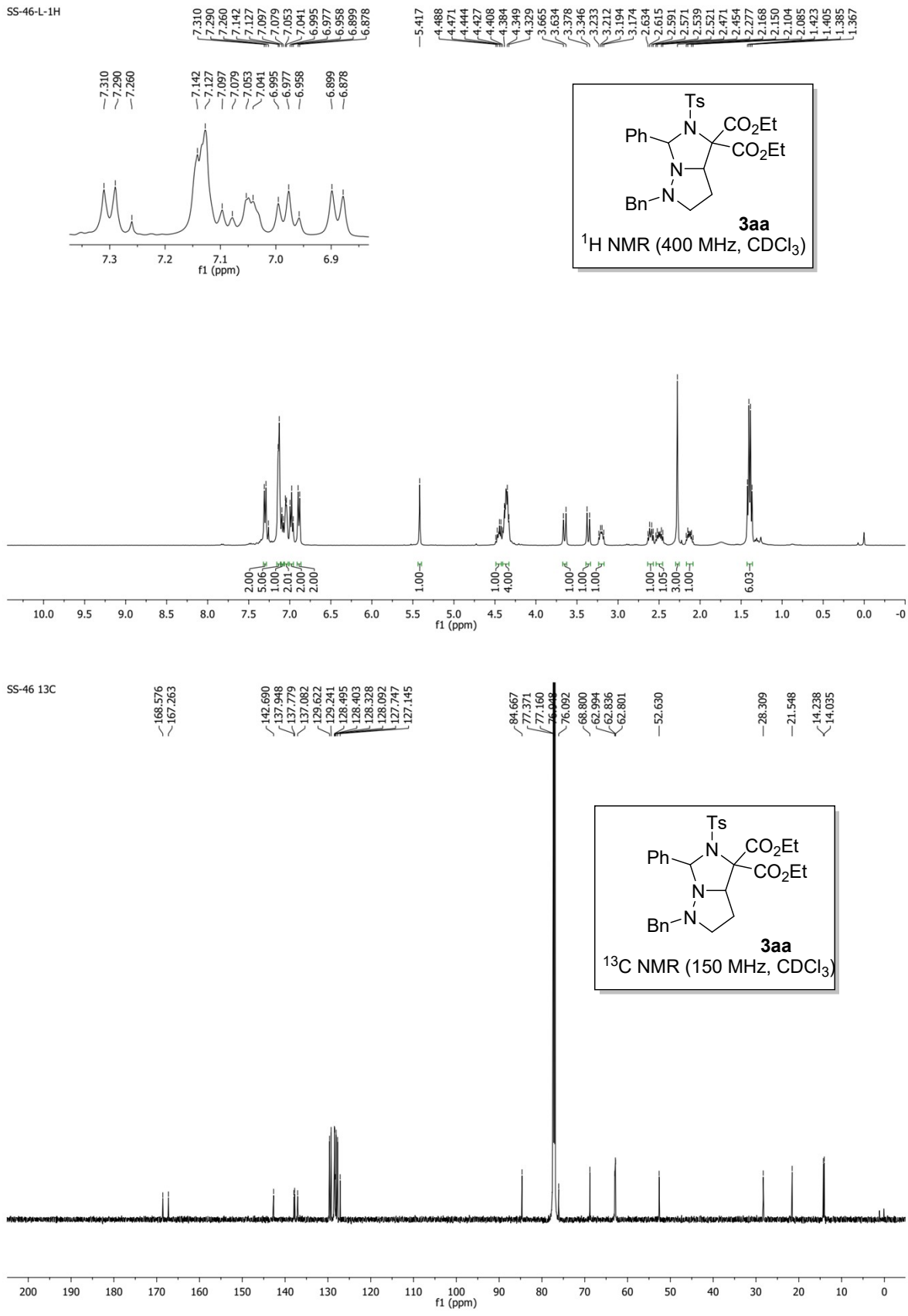
## NMR ($^{1}$H, $^{13}$C and $^{19}$F) Spectra

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7.041
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6.977
6.958
6.899
6.878
5.417
4.488
4.471
4.444
4.427
4.408
4.384
4.349
4.329
3.665
3.634
3.378
3.346
3.233
3.212
3.194
3.174
2.634
2.615
2.591
2.571
2.539
2.521
2.471
2.454
2.277
2.168
2.150
2.104
2.085
1.423
1.405
1.385
1.367
f1 (ppm)
Ts
N
CO2Et
Ph
CO2Et
N
Bn
N
3aa
1H NMR (400 MHz, CDCl3)
2.00
5.06
1.00
2.01
2.00
2.00
1.00
1.00
4.00
1.00
1.00
1.00
1.05
3.00
1.00
6.03
f1 (ppm)
SS-46 13C
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167.263
142.690
137.948
137.779
137.082
129.622
129.241
128.495
128.403
128.328
128.092
127.747
127.145
84.667
77.371
77.160
76.848
76.092
68.800
62.994
62.836
62.801
52.630
28.309
21.548
14.238
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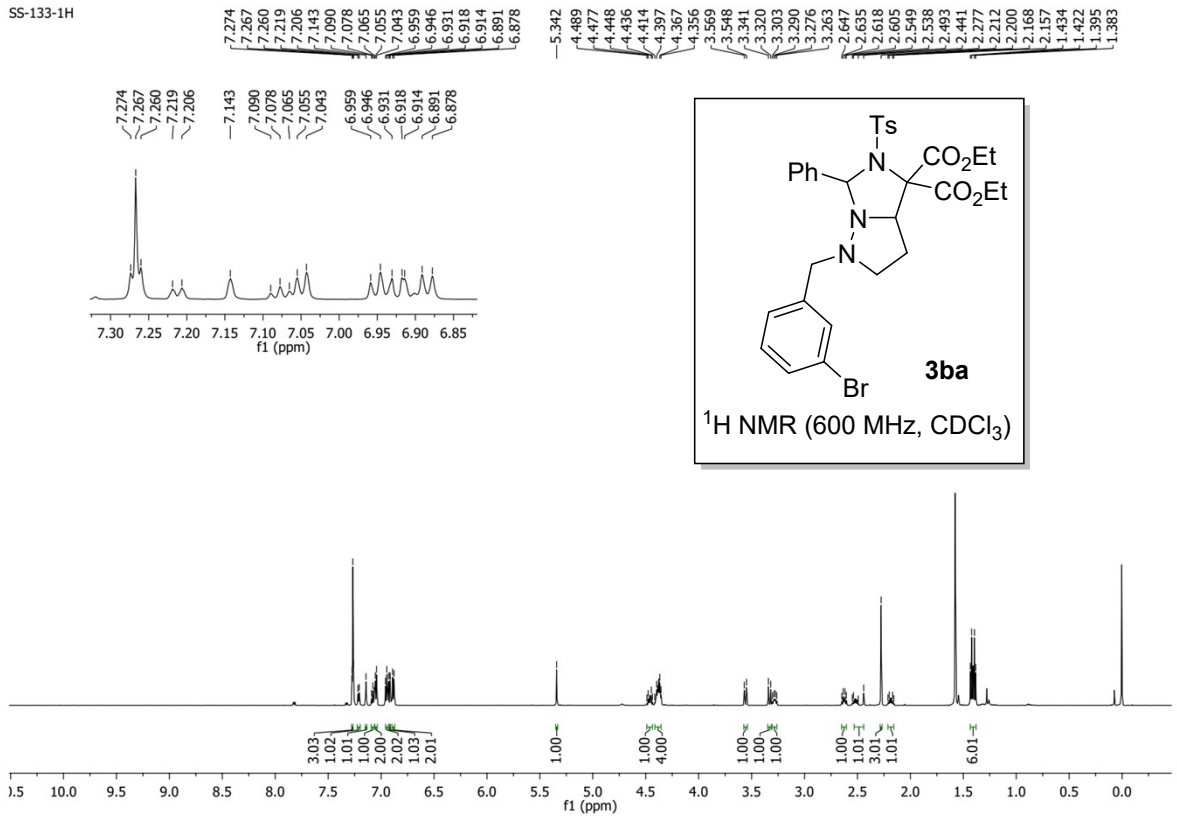
CO2Et
Ph
CO2Et
N
Bn
N
3aa
13C NMR (150 MHz, CDCl3)
f1 (ppm)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Br
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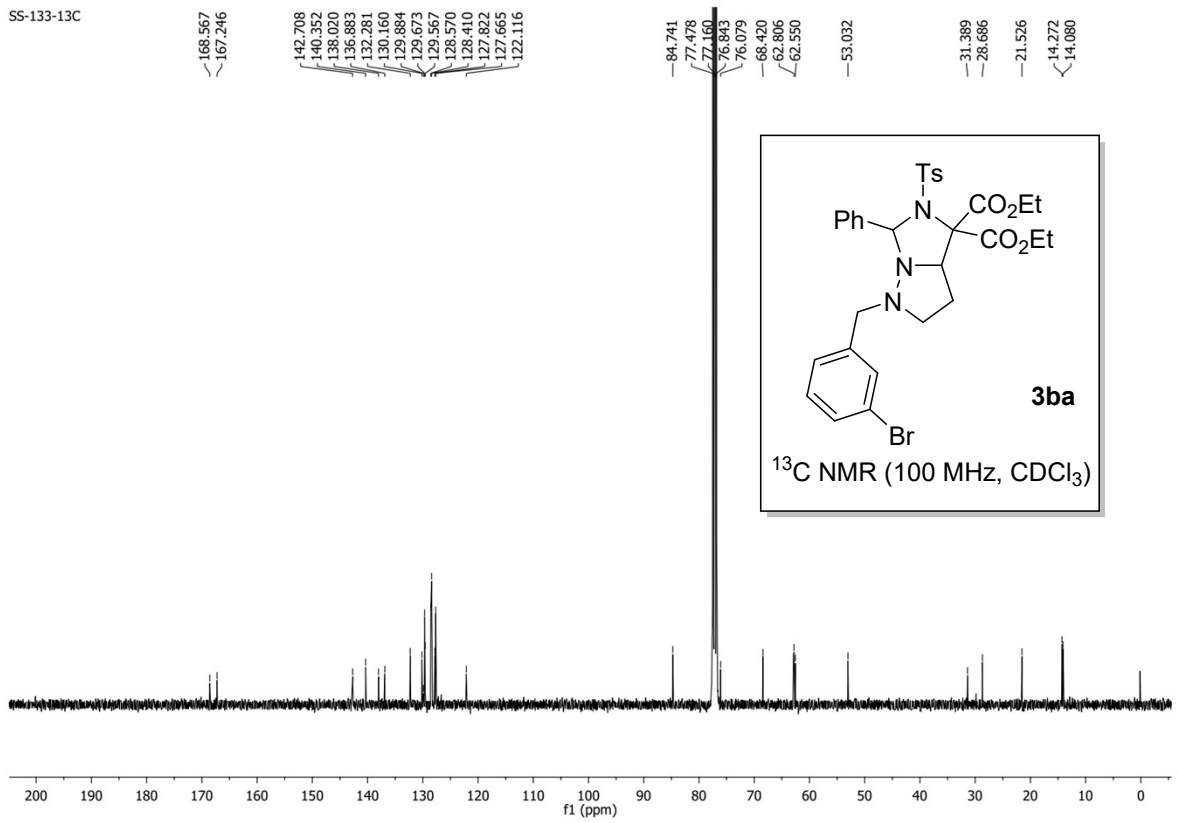
f1 (ppm)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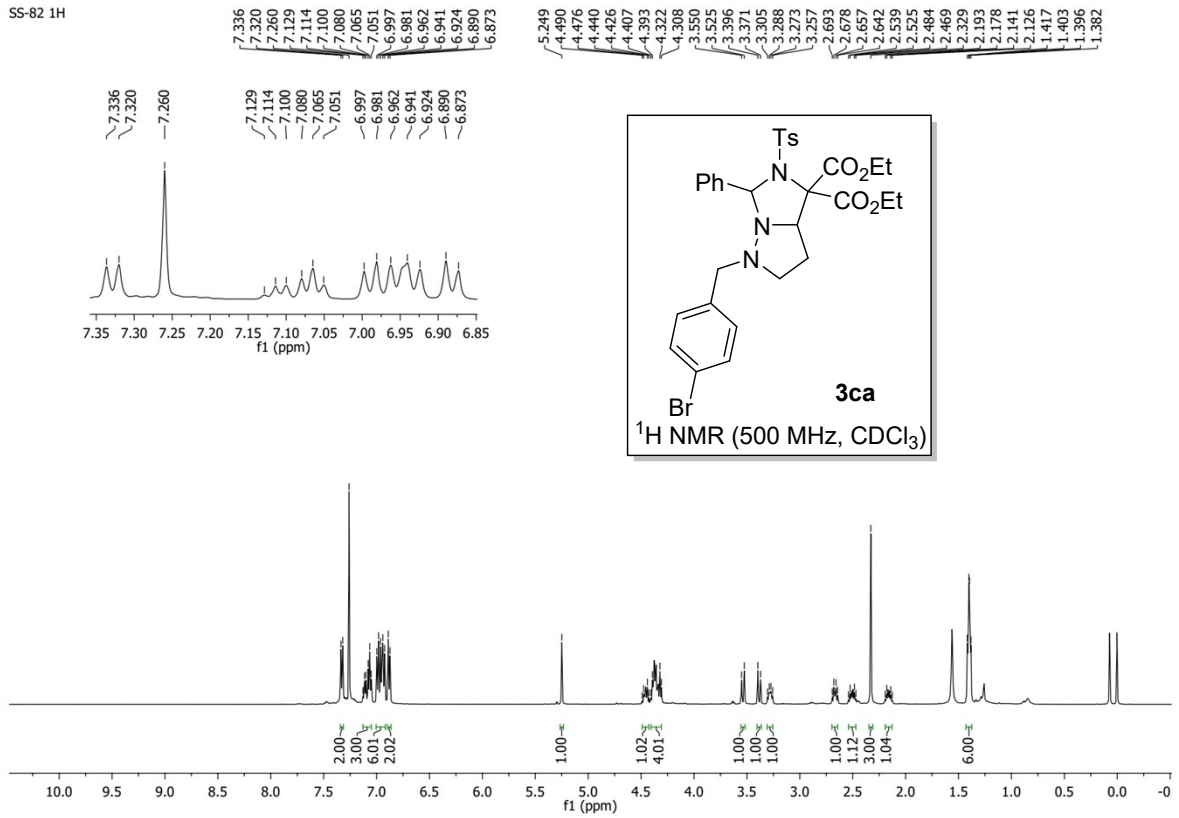
CO2Et
N
N
Br
3ba
13C NMR (100 MHz, CDCl3)
f1 (ppm)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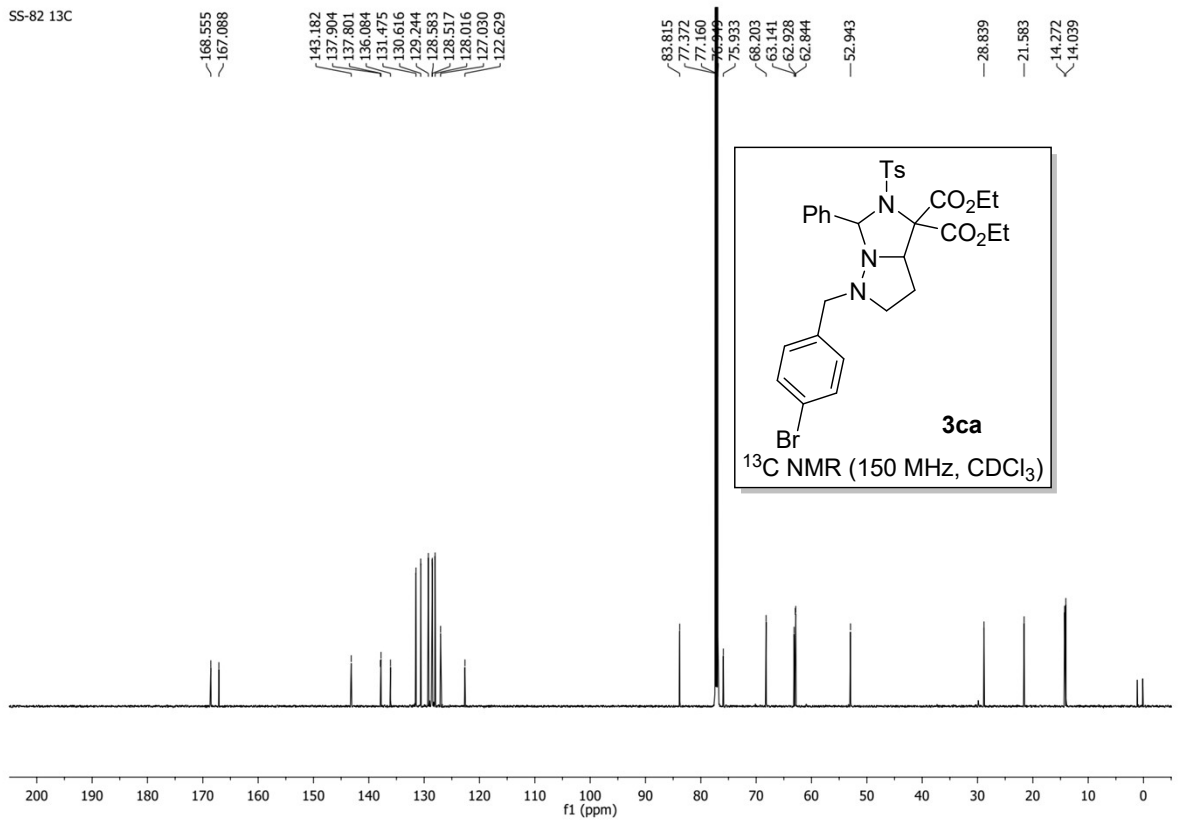
CO2Et
N
N
Br
3ca
1H NMR (500 MHz, CDCl3)
f1 (ppm)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Ts
Ph
N
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CO2Et
N
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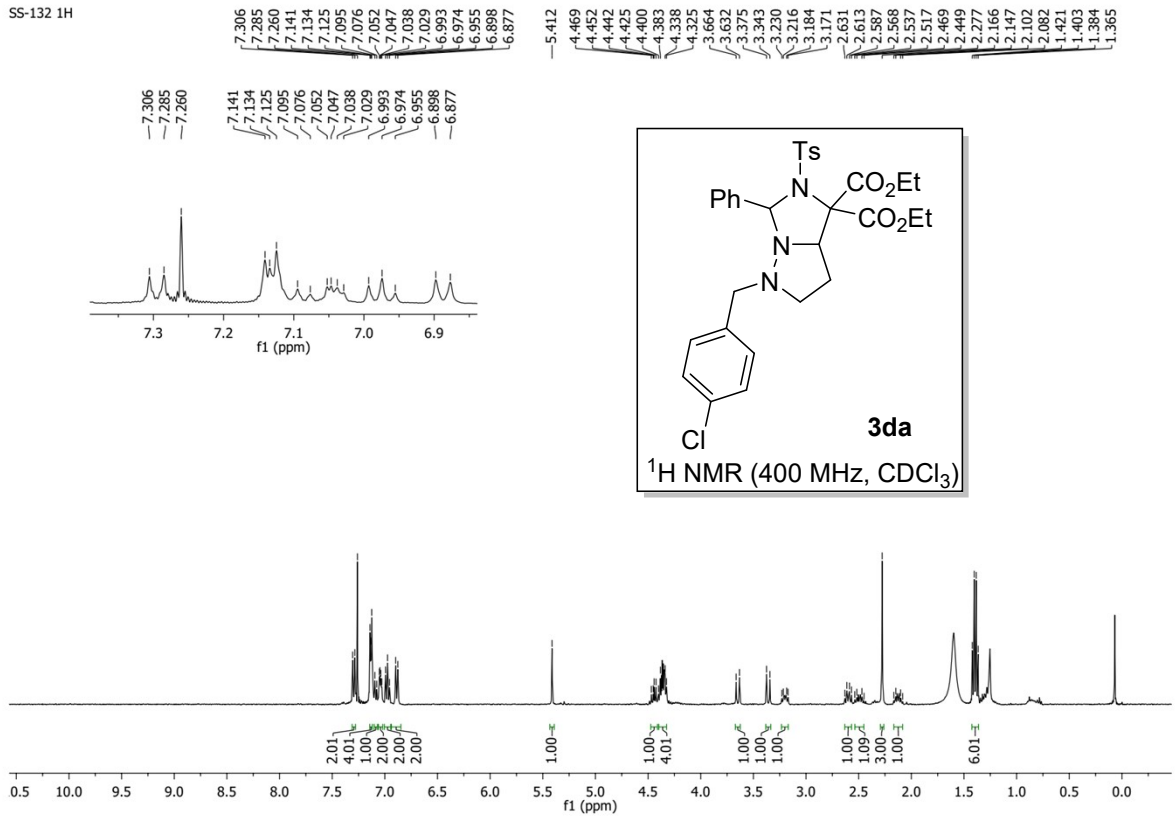
Br
3ca
13C NMR (150 MHz, CDCl3)
f1 (ppm)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Ts
Ph
CO2Et
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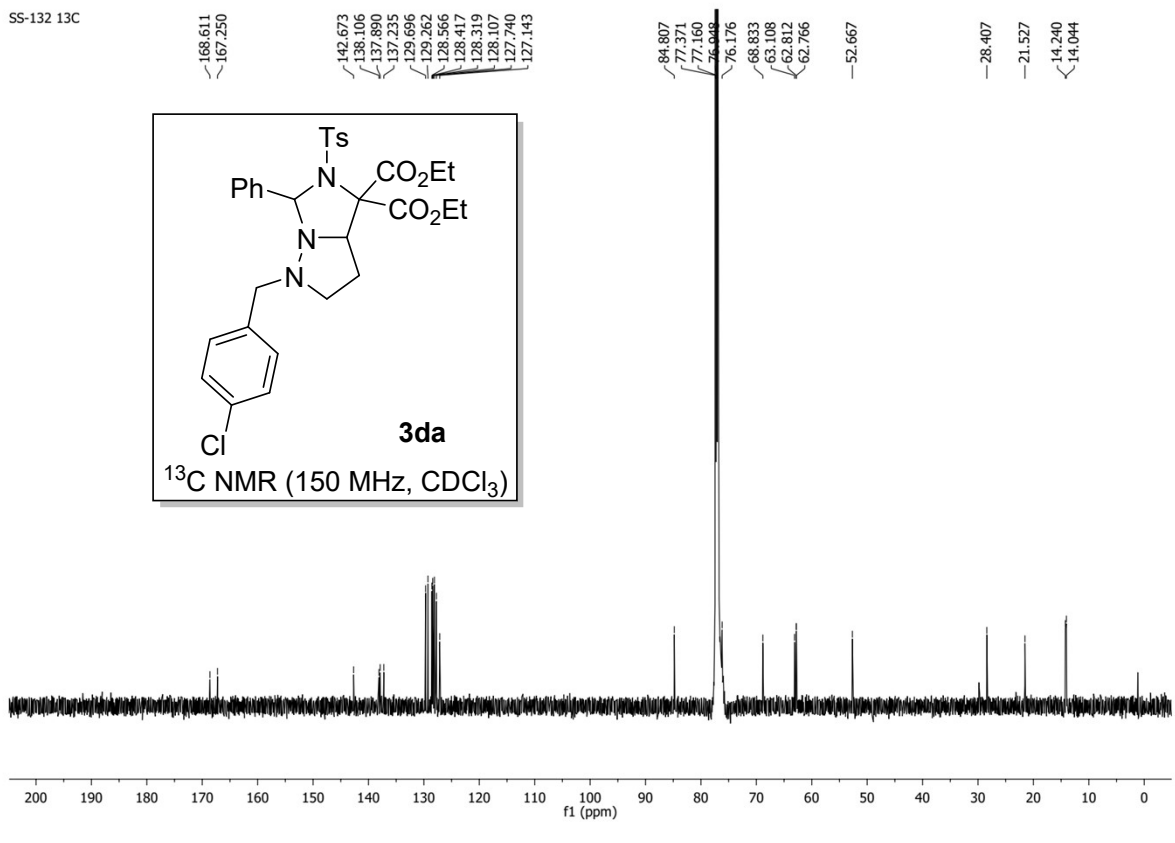
N
N
Cl
3da
1H NMR (400 MHz, CDCl3)
f1 (ppm)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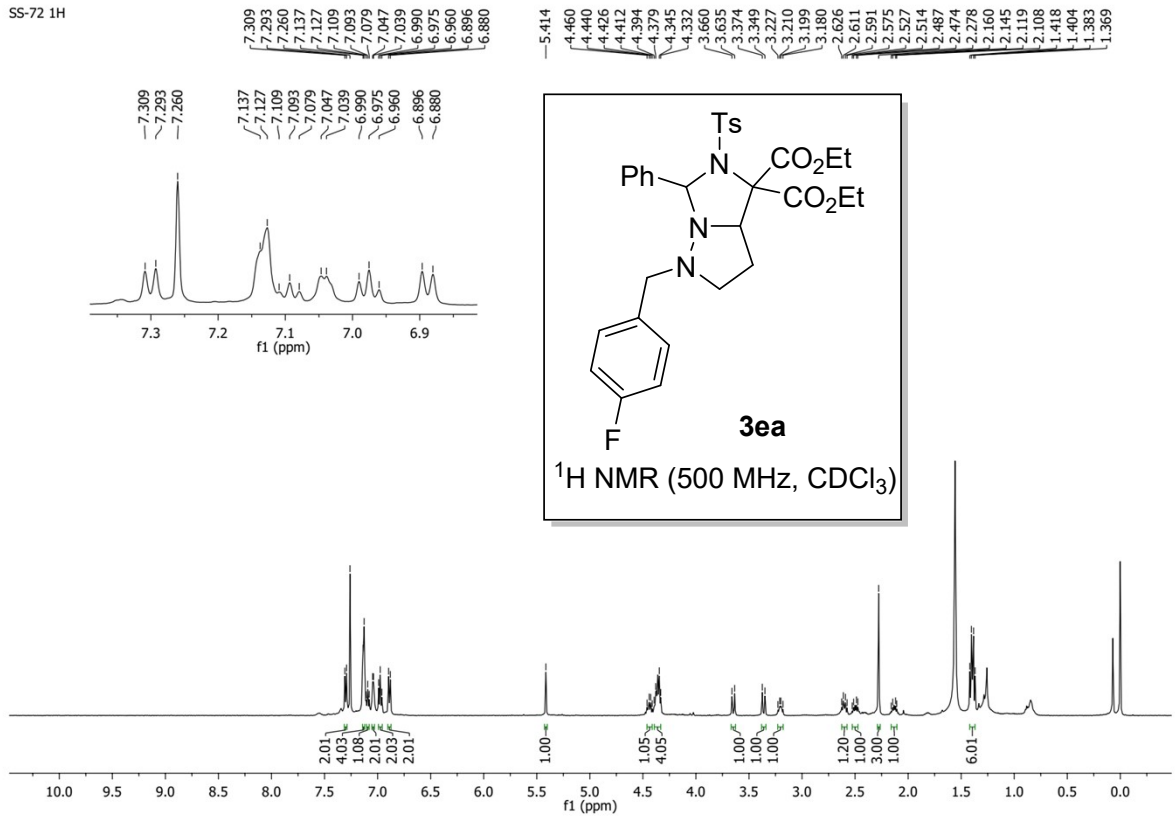
Ts
Ph
CO2Et
CO2Et
N
N
Cl
3da
13C NMR (150 MHz, CDCl3)
f1 (ppm)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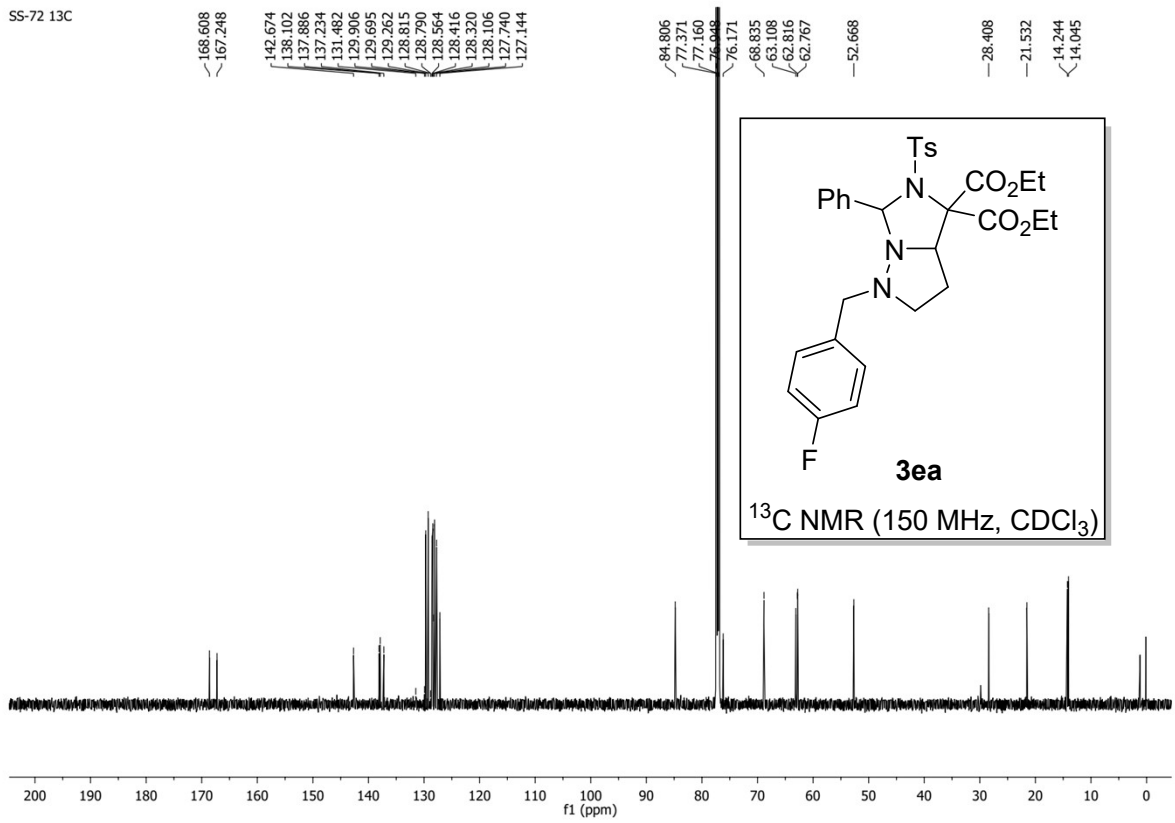
Ph
N
CO2Et
CO2Et
F
3ea
1H NMR (500 MHz, CDCl3)
f1 (ppm)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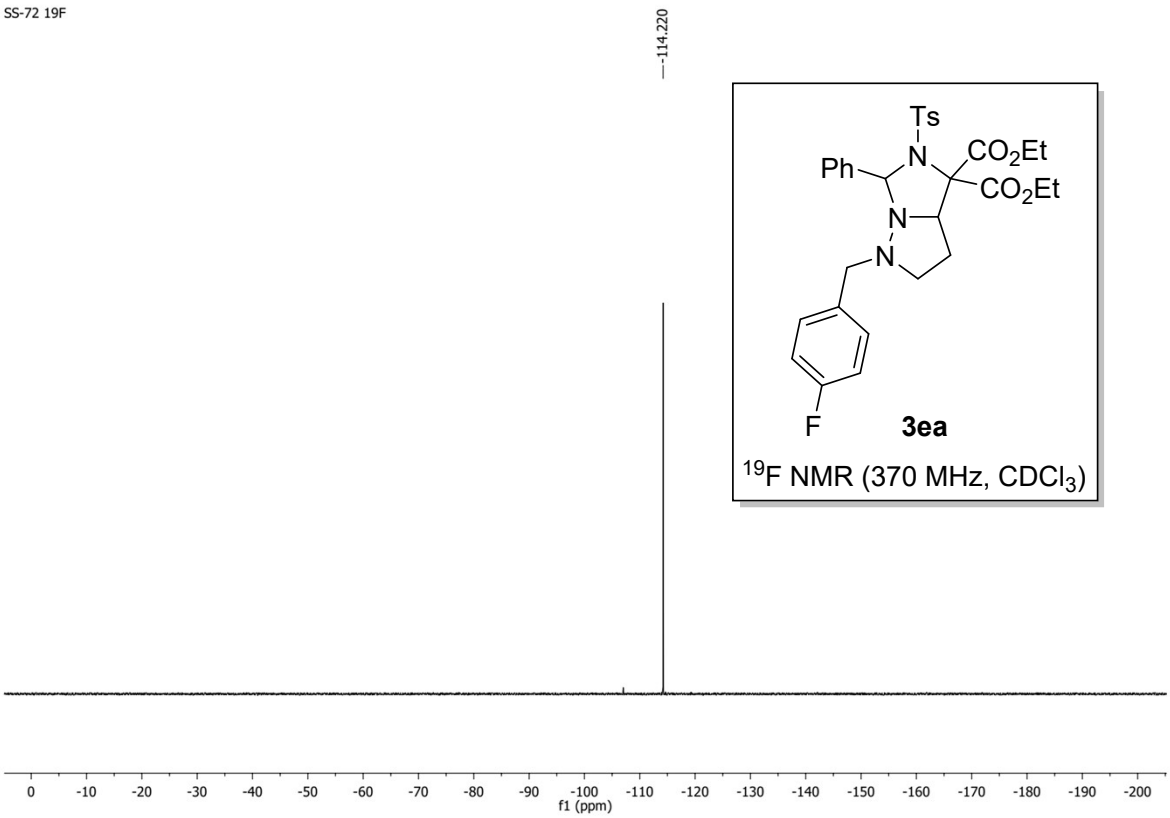
Ts
Ph
N
CO2Et
CO2Et
F
3ea
13C NMR (150 MHz, CDCl3)
f1 (ppm)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F
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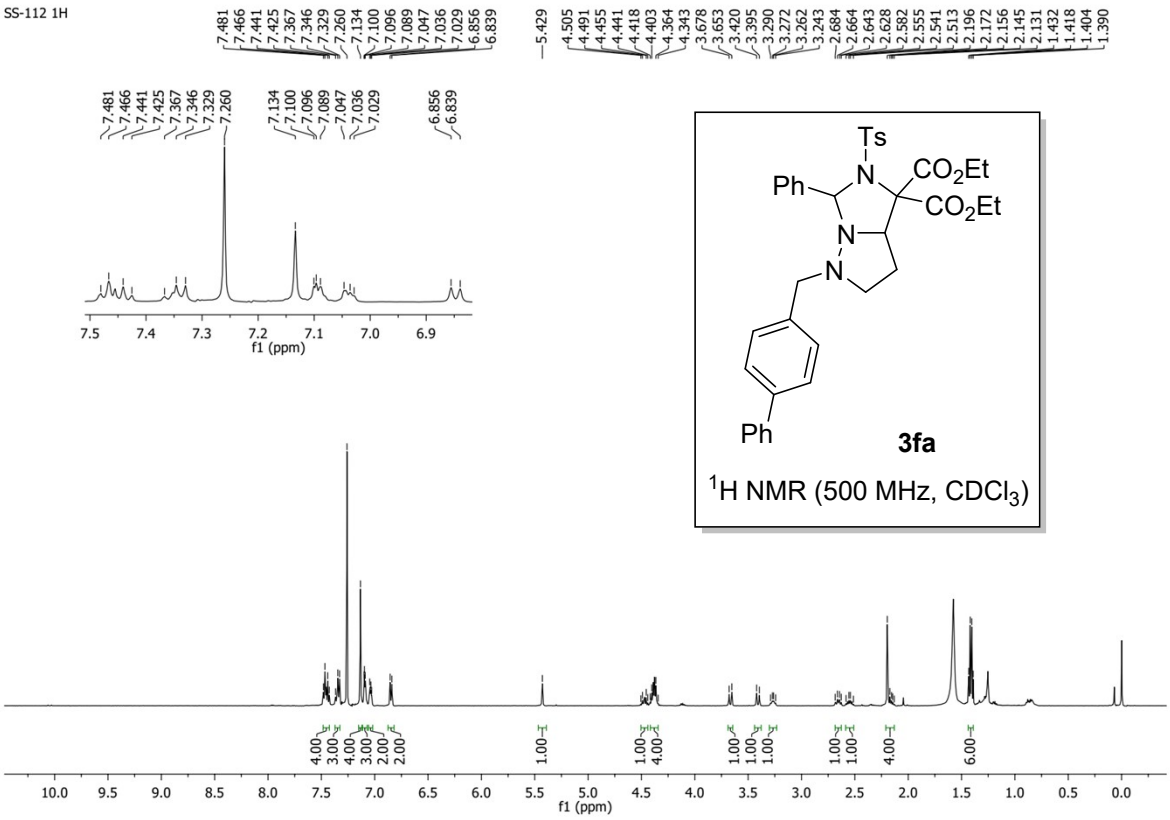
f1 (ppm)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Ph
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N
N
Ph
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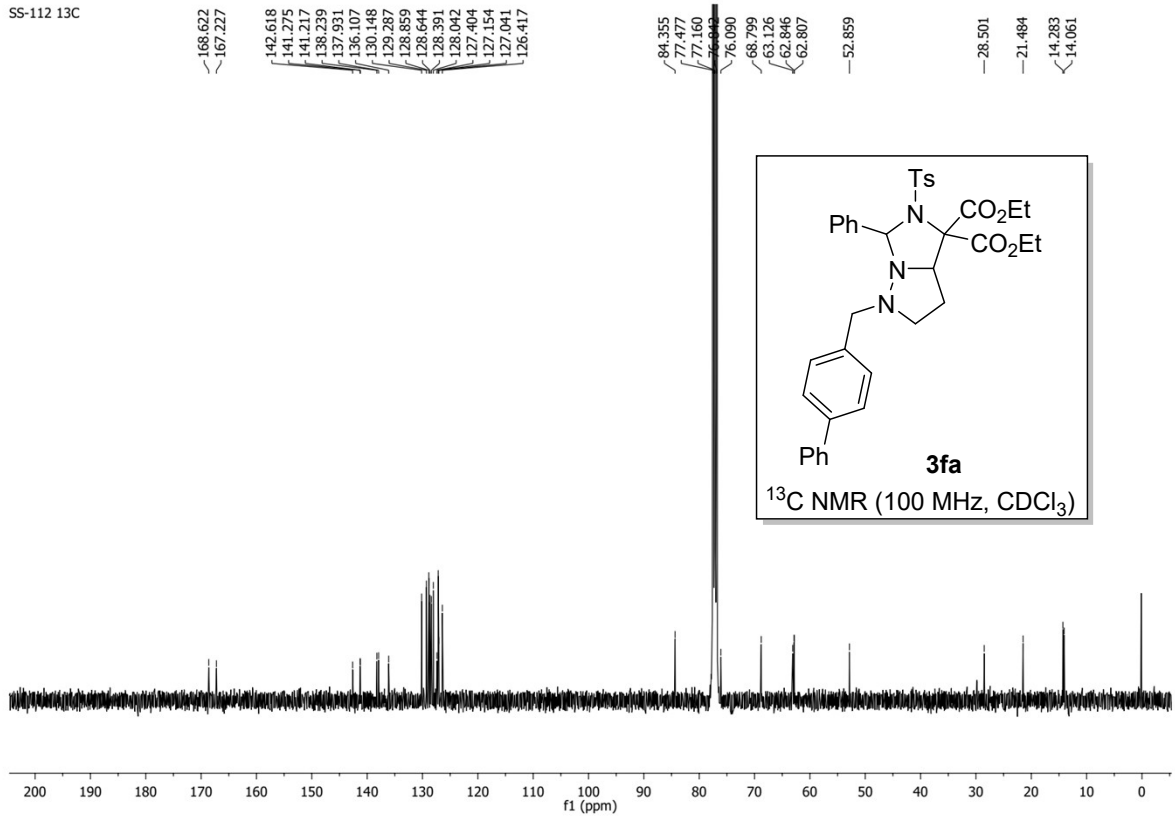
f1 (ppm)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136.107
130.148
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128.859
128.644
128.391
128.042
127.404
127.154
127.041
126.417
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77.477
77.160
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28.501
21.484
14.283
14.061
Ts
N
Ph
CO2Et
CO2Et
N
N
Ph
3fa
13C NMR (100 MHz, CDCl3)
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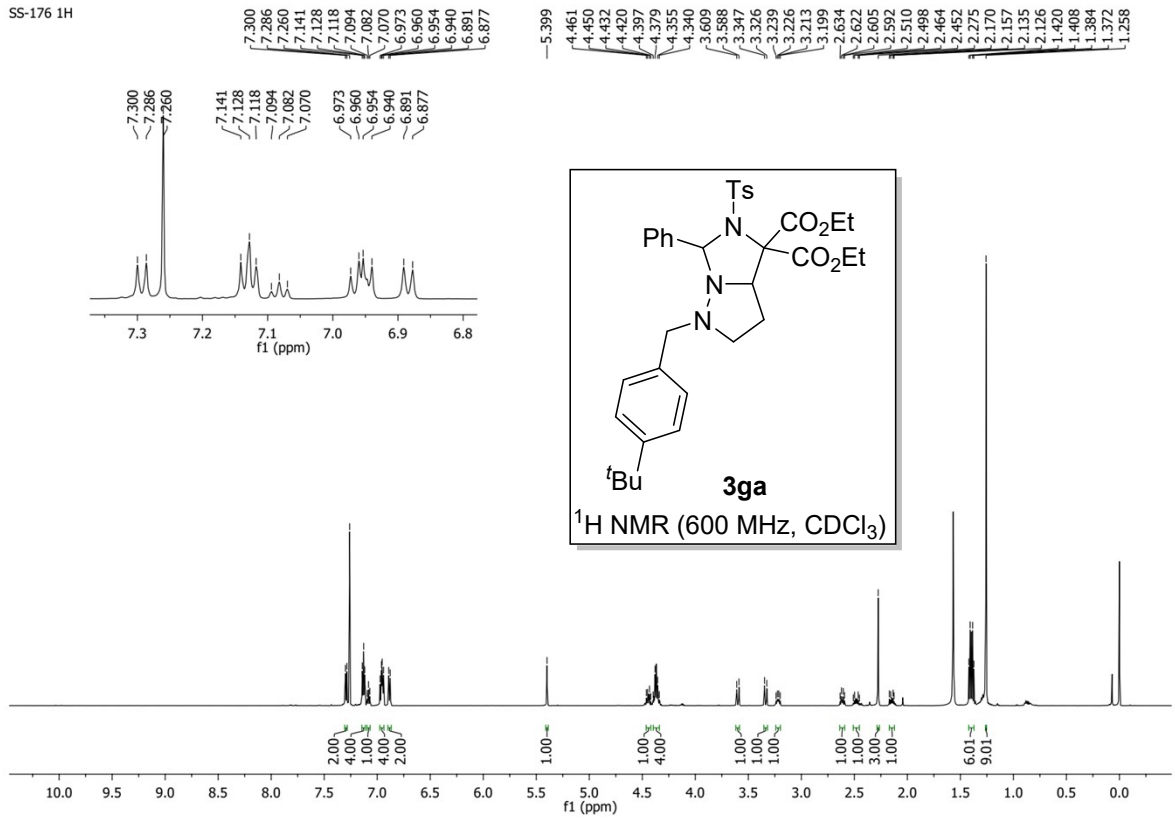
f1 (ppm)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7.118
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7.082
7.070
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6.960
6.954
6.940
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5.399
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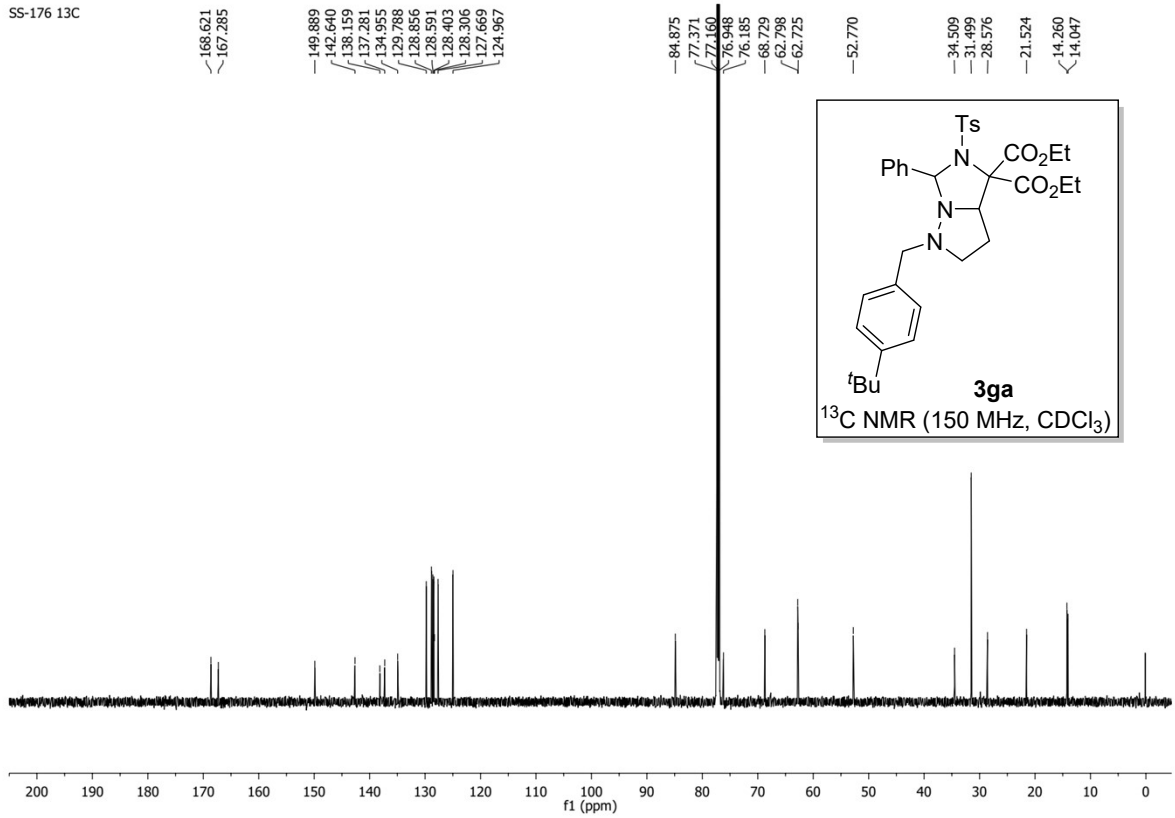
2.452
2.275
2.170
2.157
2.135
2.126
1.420
1.408
1.384
1.372
1.258
7.3 7.2 7.1 7.0 6.9 6.8
f1 (ppm)
Ts
N
Ph
CO2Et
CO2Et
N
N
tBu
3ga
1H NMR (600 MHz, CDCl3)
2.00 4.00 1.00 4.00 2.00
1.00
1.00 4.00
1.00 1.00
1.00 1.00 3.00 1.00
6.01 9.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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62.798
62.725
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34.509
31.499
28.576
21.524
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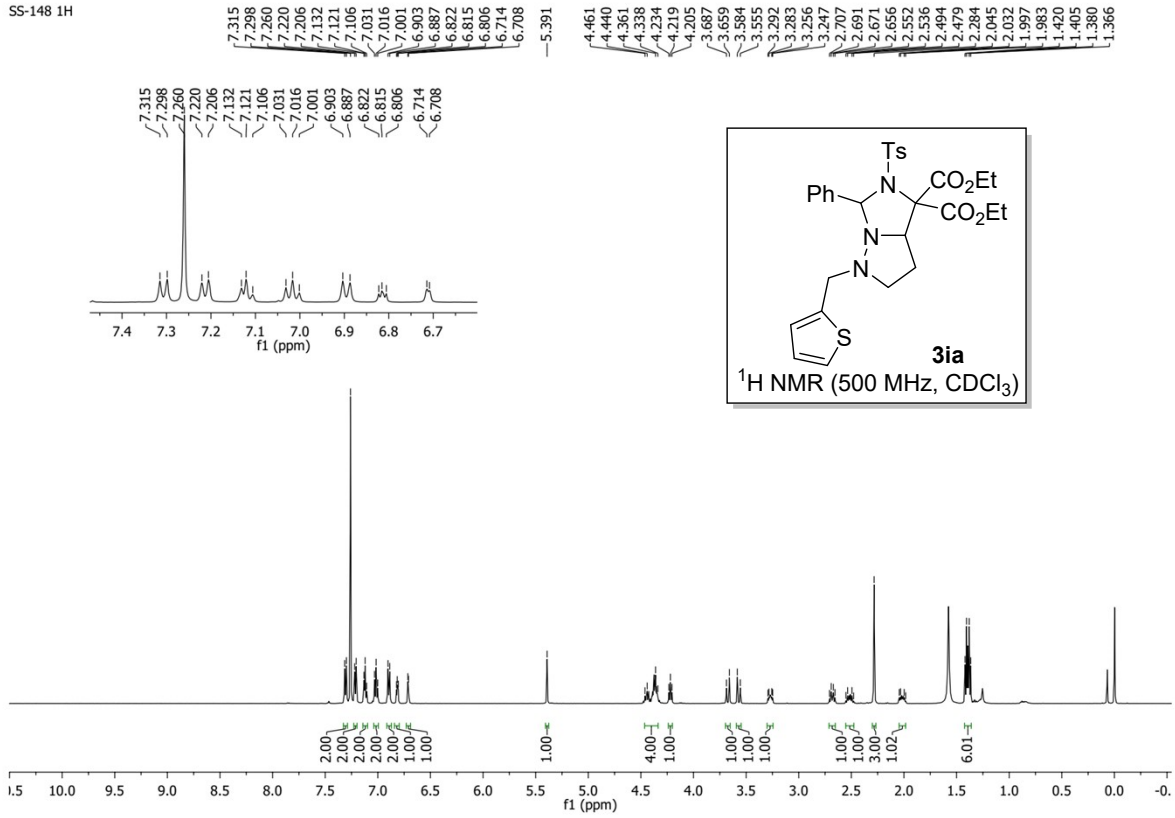
N
tBu
3ga
13C NMR (150 MHz, CDCl3)
f1 (ppm)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7.121
7.106
7.031
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6.887
6.822
6.815
6.806
6.714
6.708
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4.361
4.338
4.234
4.219
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3.584
3.555
3.292
3.283
3.256
3.247
2.707
2.691
2.671
2.656
2.552
2.536
2.494
2.479
2.284
2.045
2.032
1.997
1.983
1.420
1.405
1.380
1.366
Ts
N
Ph
CO2Et
CO2Et
N
N
S
3ia
1H NMR (500 MHz, CDCl3)
2.00
2.00
2.00
2.00
2.00
1.00
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1.00
3.00
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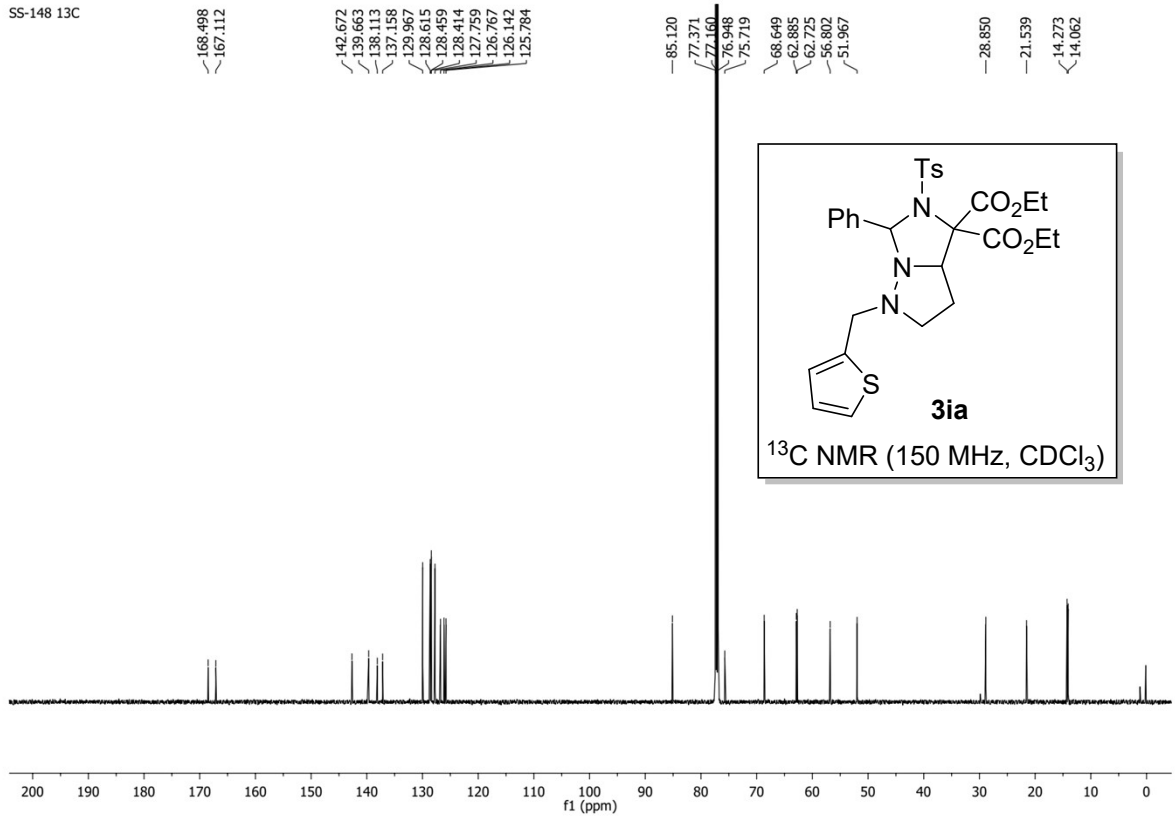
6.01
f1 (ppm)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126.142
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76.948
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62.885
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28.850
21.539
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N
S
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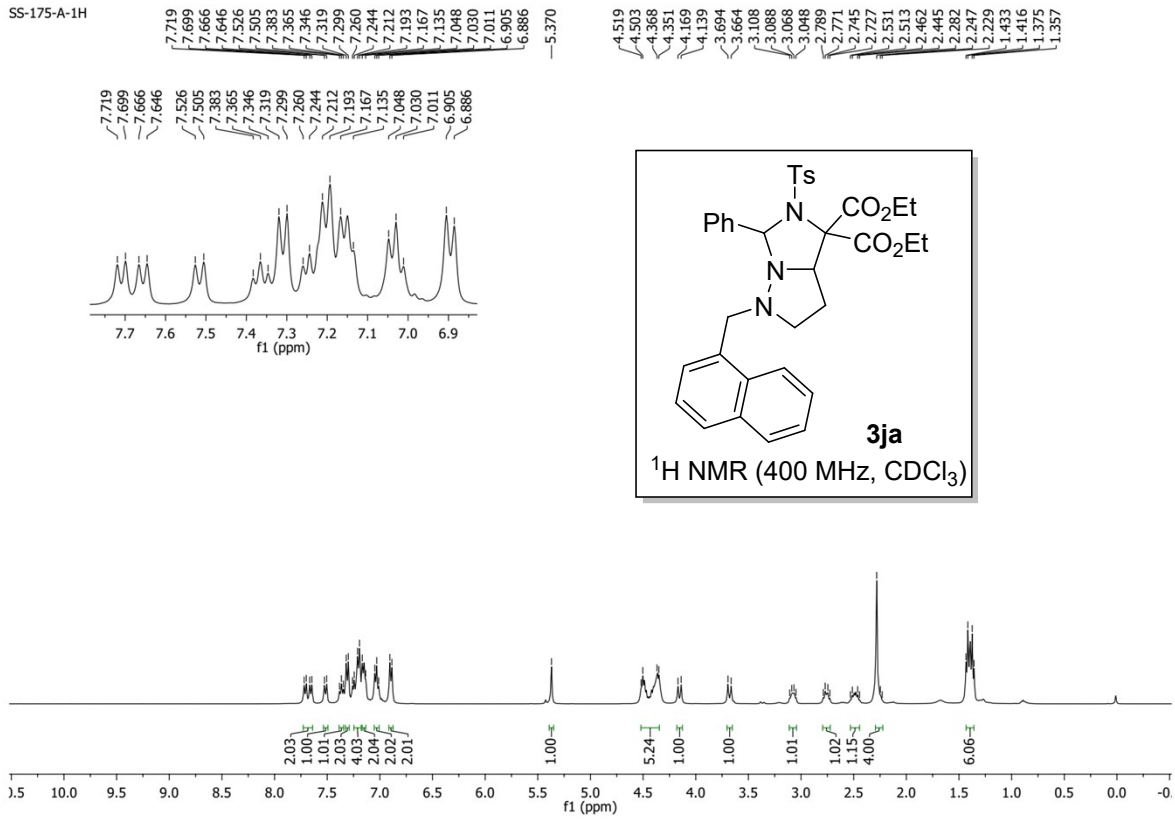
13C NMR (150 MHz, CDCl3)
f1 (ppm)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7.365
7.346
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7.299
7.260
7.244
7.212
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7.135
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4.169
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3.108
3.088
3.068
3.048
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2.771
2.745
2.727
2.531
2.513
2.462
2.445
2.282
2.247
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1.433
1.416
1.375
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Ts
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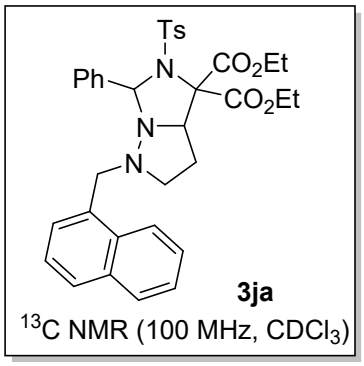
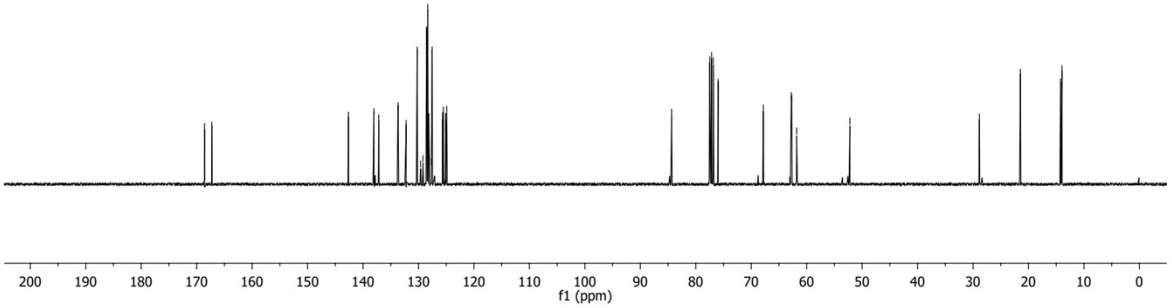
Ph
CO2Et
CO2Et
N
N
3ja
1H NMR (400 MHz, CDCl3)
f1 (ppm)

SS-175 13C

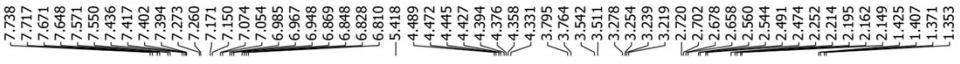



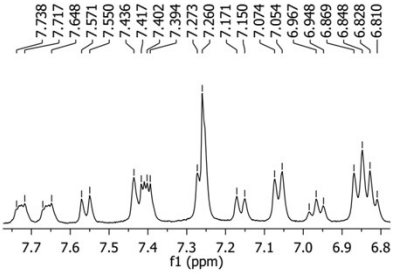

**3ja**

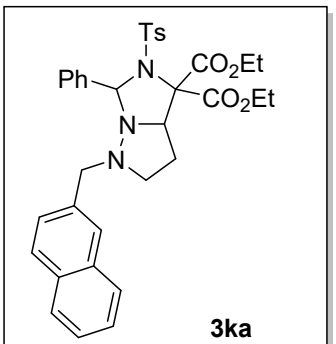
$^{13}C$ NMR (100 MHz, $CDCl_3$)




SS-151-A-1H

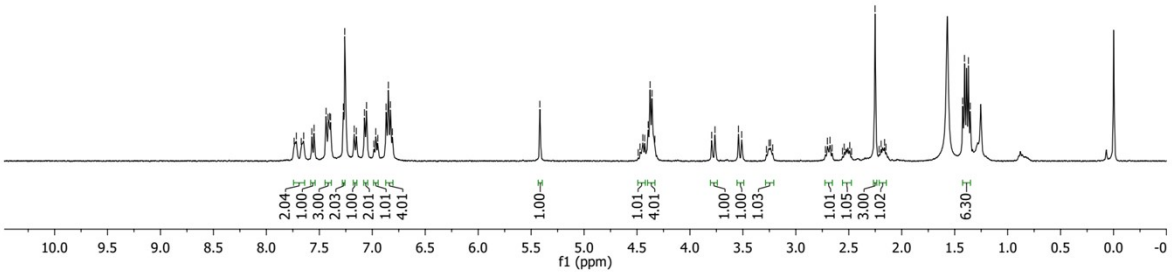


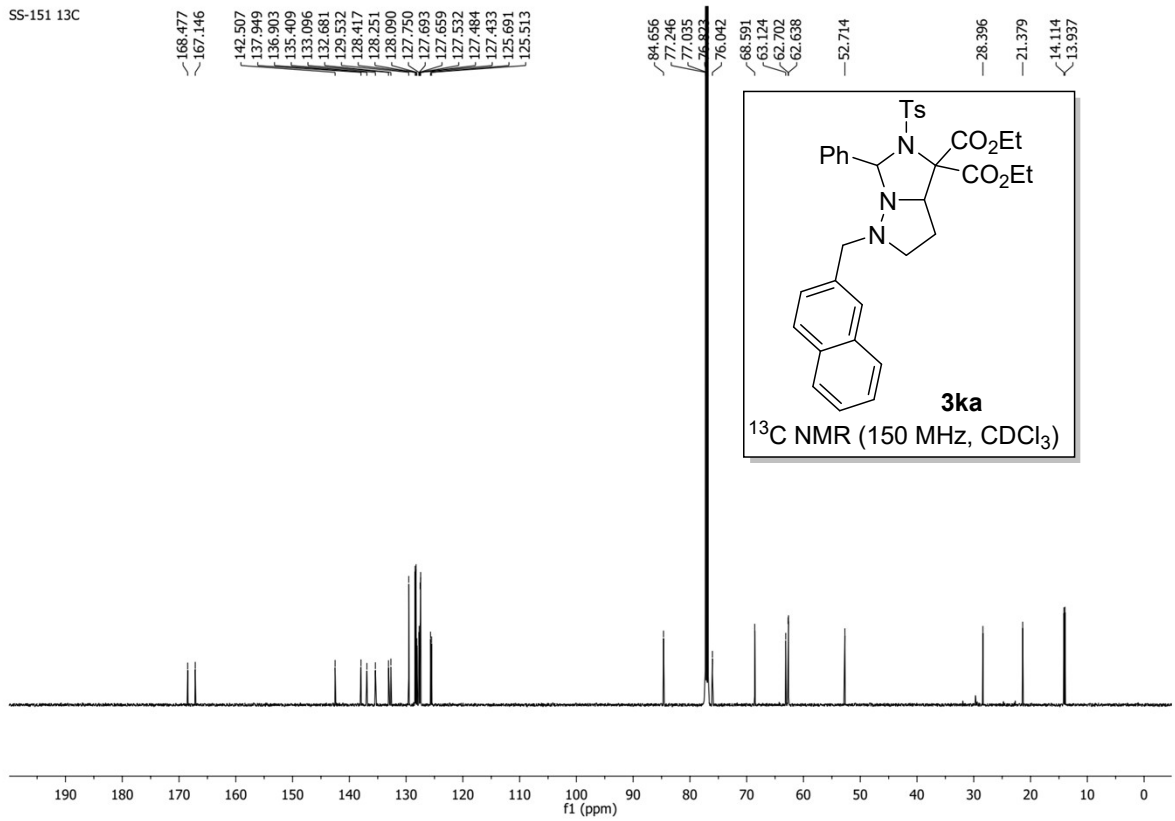



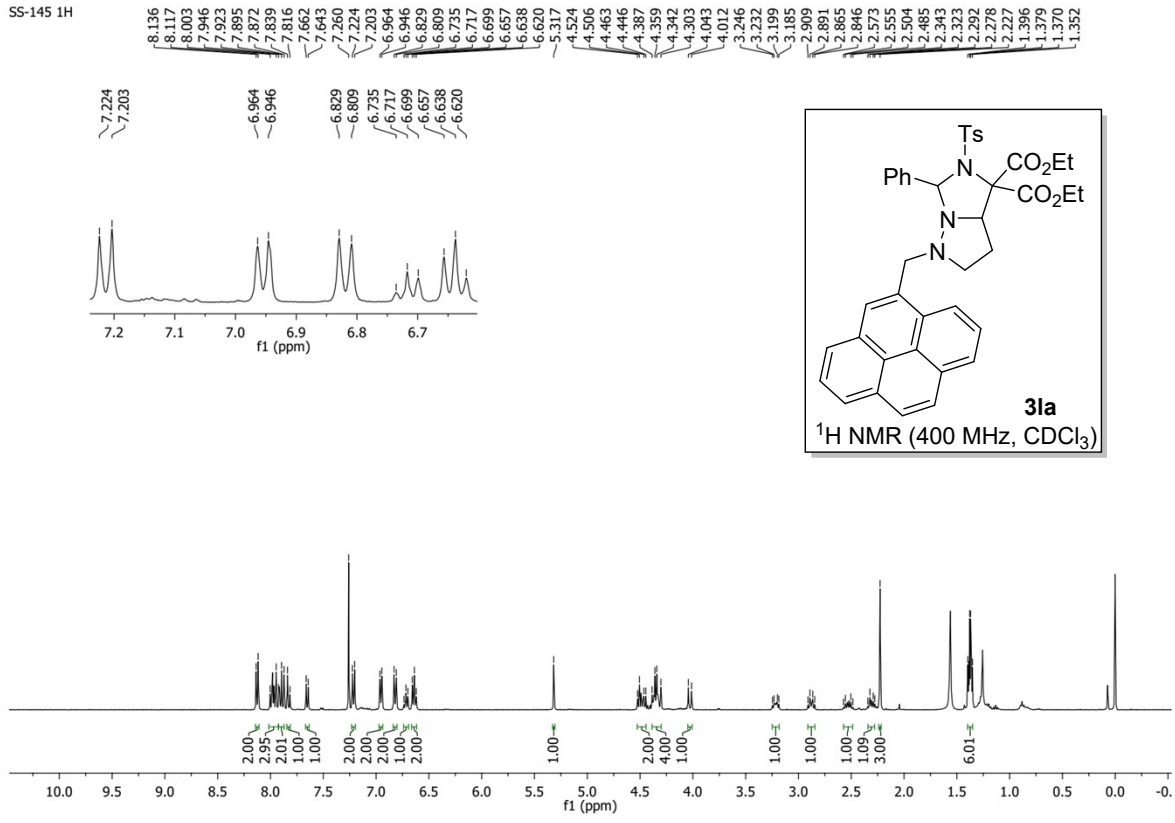



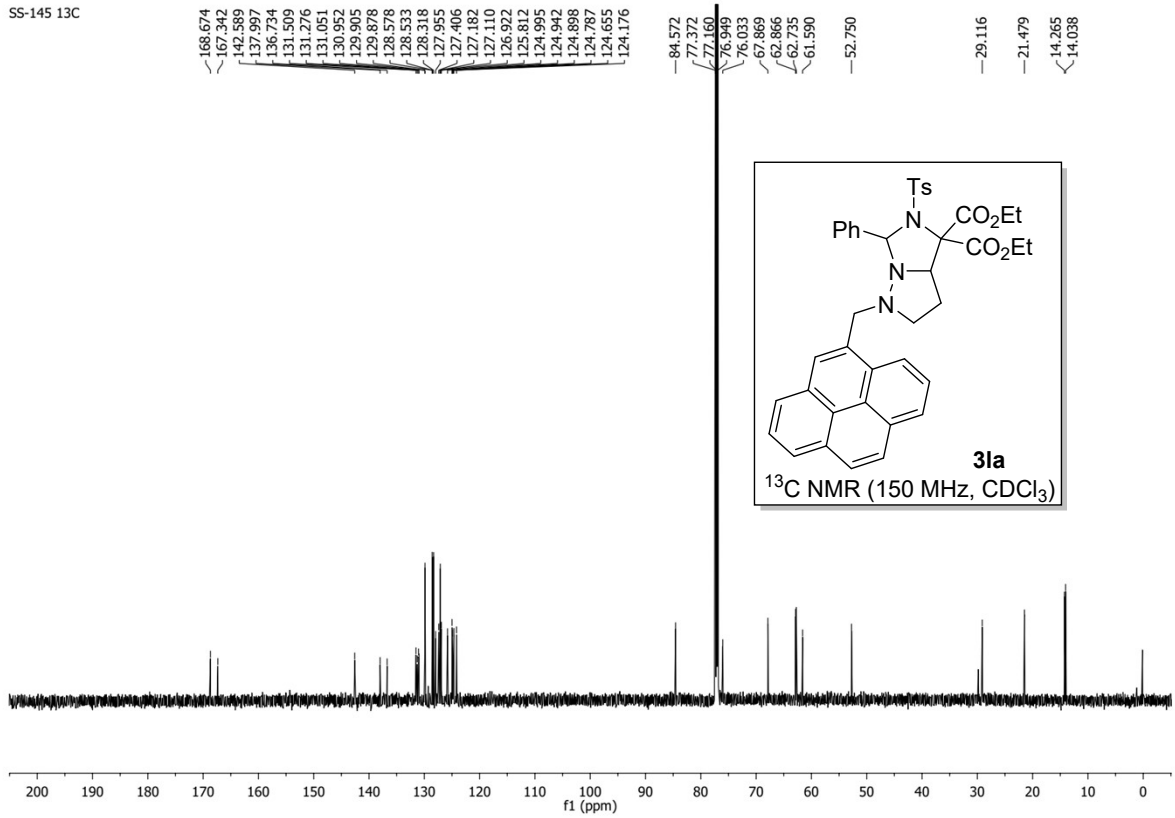

**3ka**

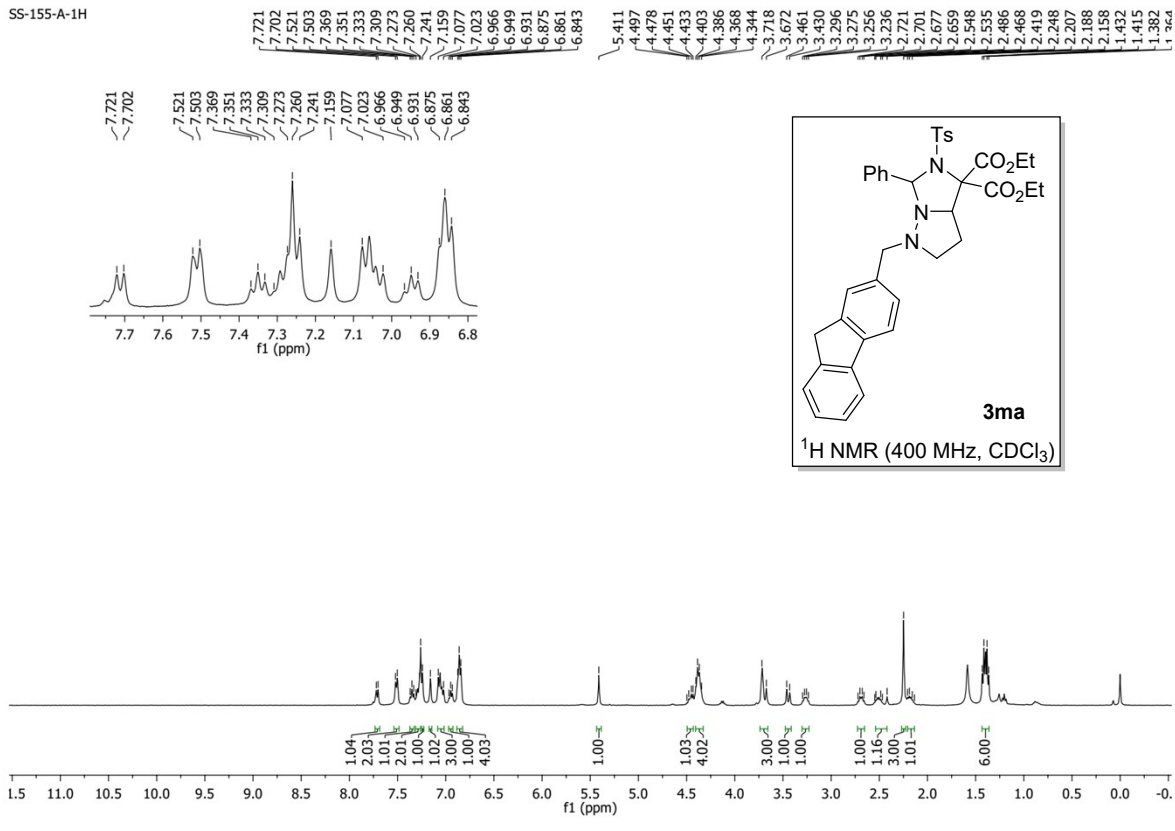
$^{1}H$ NMR (400 MHz, $CDCl_3$)

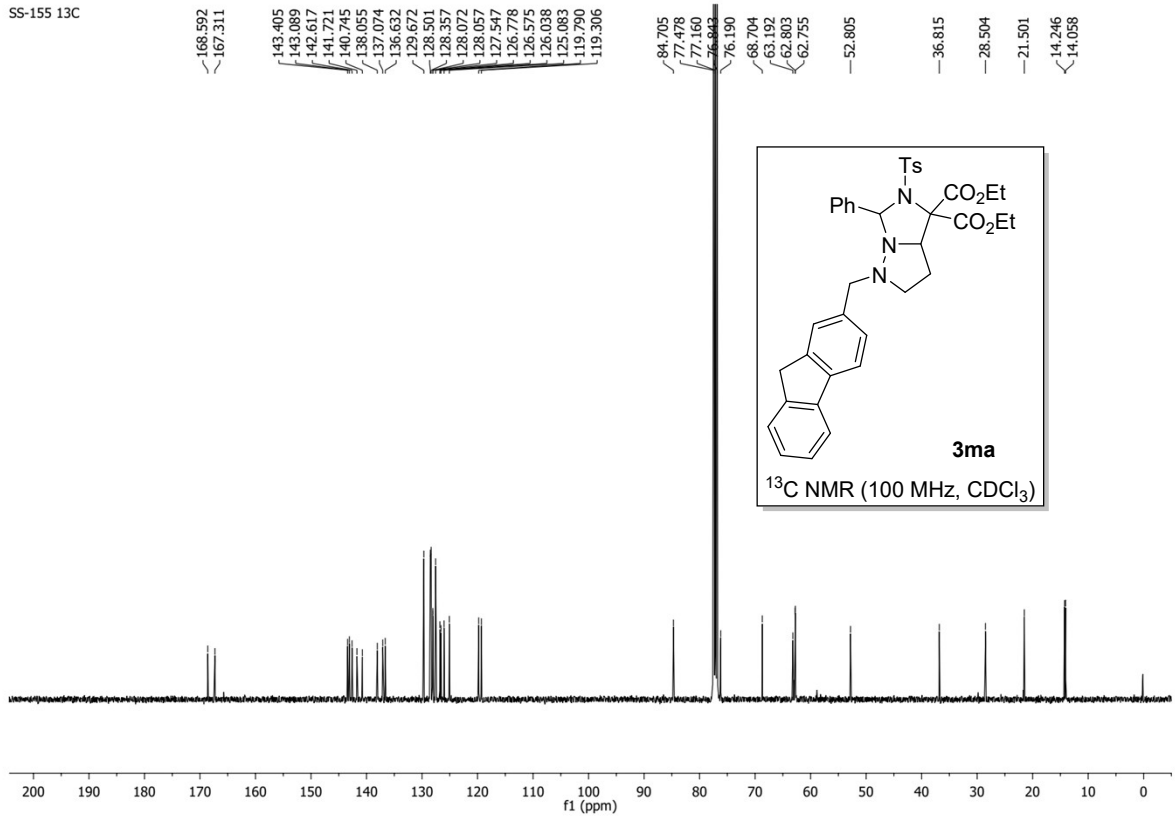


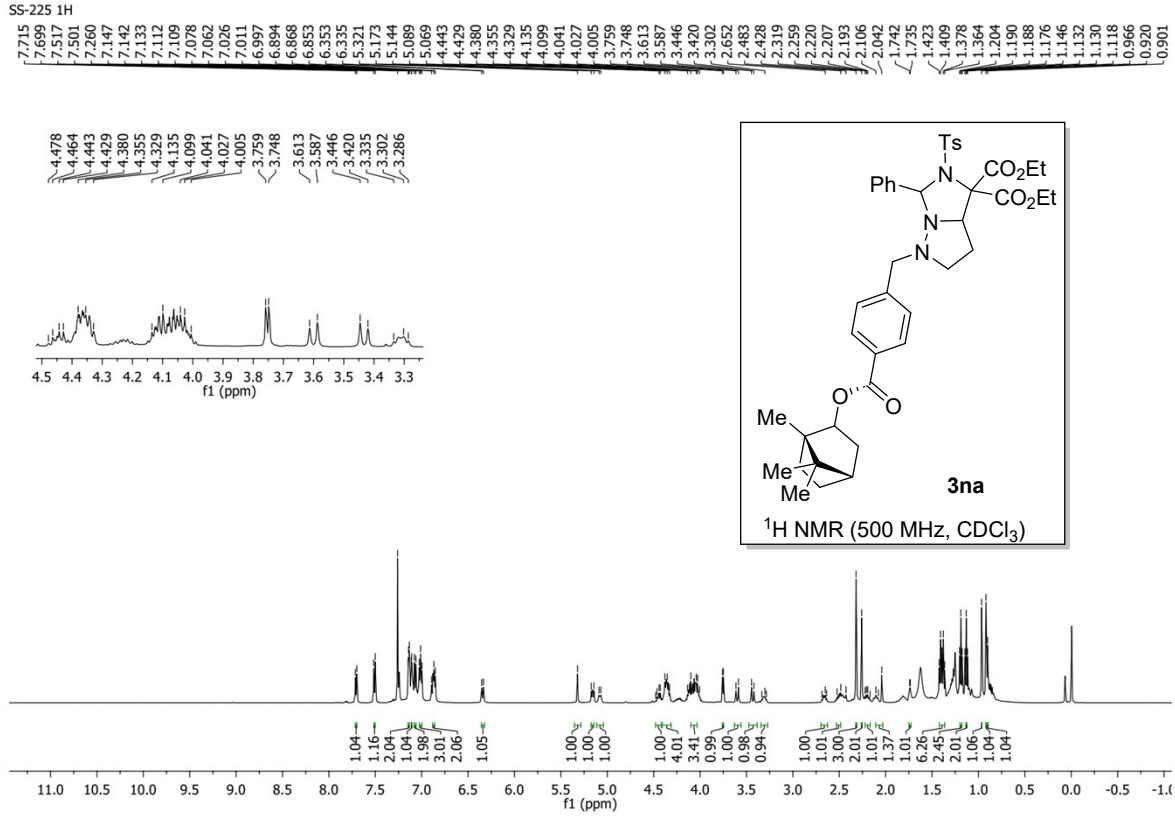

SS-151 13C
168.477
167.146
142.507
137.949
136.903
135.409
133.096
132.681
129.532
128.417
128.251
128.090
127.750
127.693
127.659
127.532
127.484
127.433
125.691
125.513
84.656
77.246
77.035
76.042
68.591
63.124
62.702
62.638
52.714
28.396
21.379
14.114
13.937
Ts
Ph
N
CO2Et
CO2Et
3ka
13C NMR (150 MHz, CDCl3)
f1 (ppm)

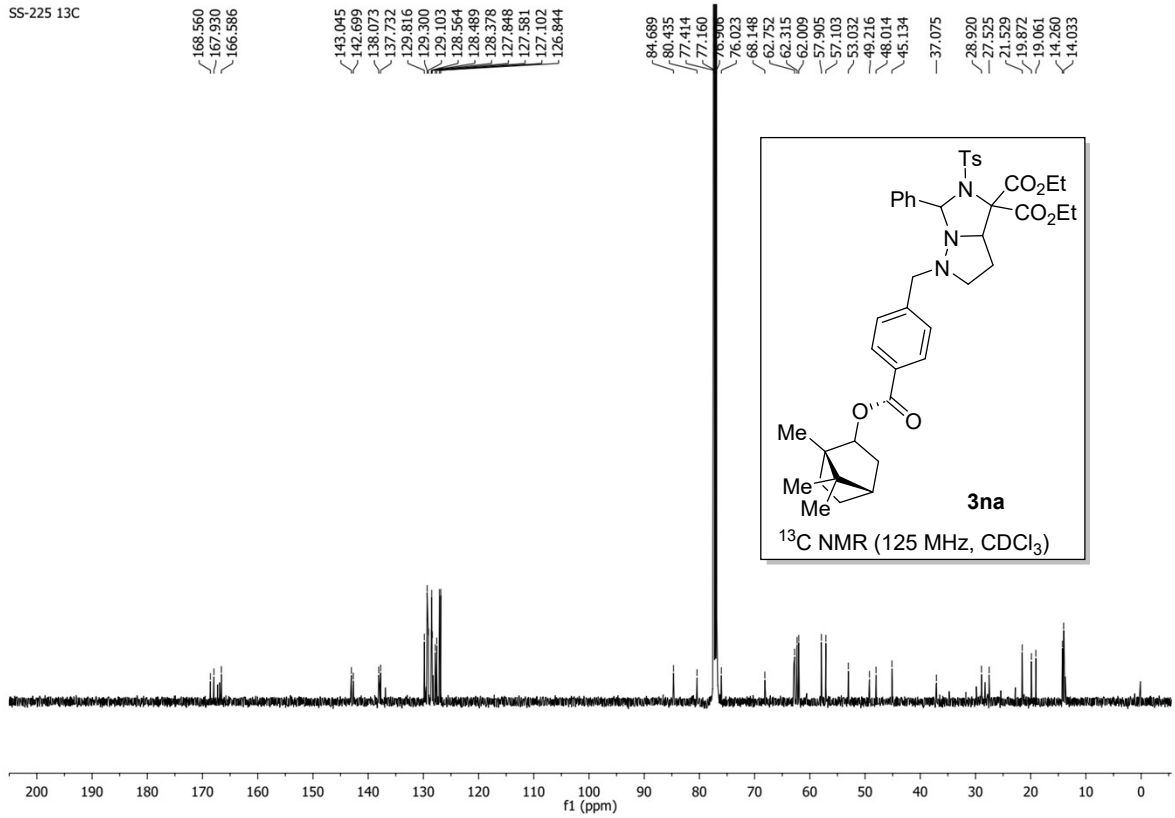

SS-145 1H
8.136
8.117
8.003
7.946
7.923
7.895
7.872
7.839
7.816
7.662
7.643
7.260
7.224
7.203
6.964
6.946
6.829
6.809
6.735
6.717
6.699
6.657
6.638
6.620
5.317
4.524
4.506
4.463
4.446
4.387
4.359
4.342
4.303
4.043
4.012
3.246
3.232
3.199
3.185
2.909
2.891
2.865
2.846
2.573
2.555
2.504
2.485
2.343
2.323
2.292
2.278
2.227
1.396
1.379
1.370
1.352
Ts
Ph
N
CO2Et
CO2Et
3la
1H NMR (400 MHz, CDCl3)
f1 (ppm)

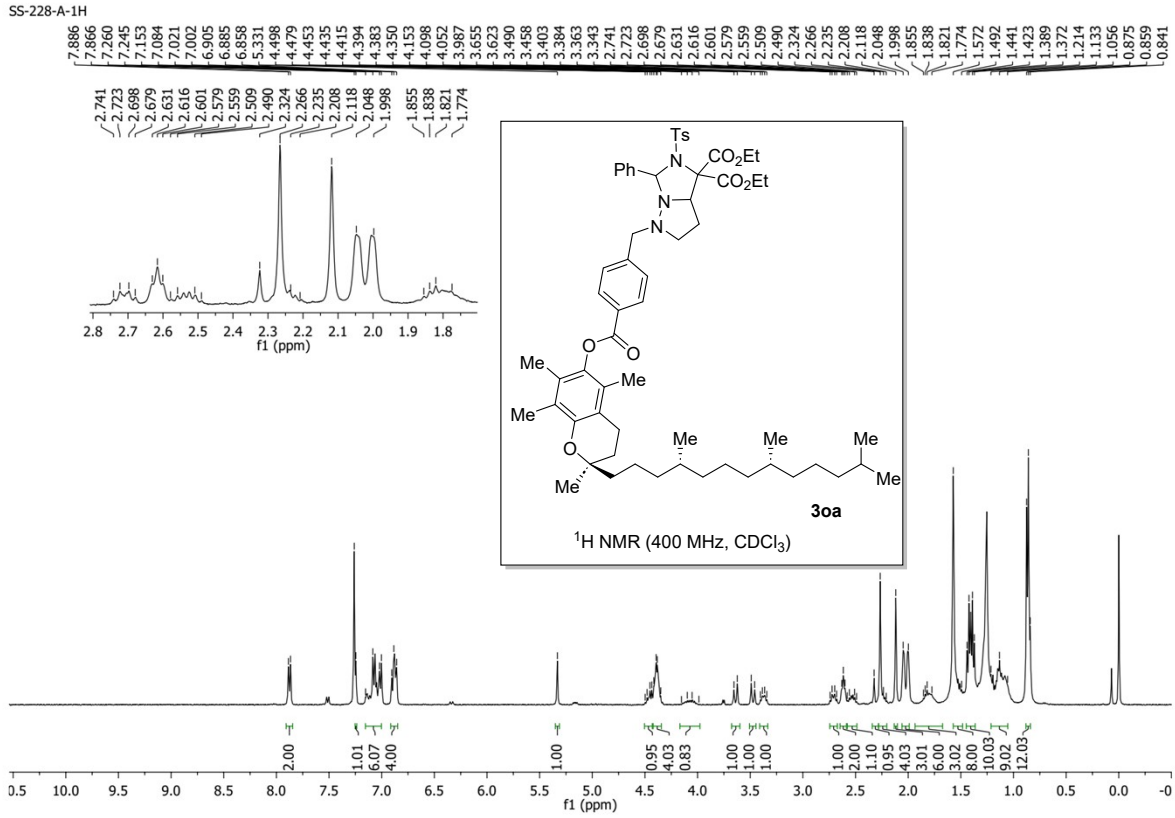

SS-145 13C
168.674
167.342
142.589
137.997
136.734
131.509
131.276
131.051
130.952
129.905
129.878
128.578
128.533
128.318
127.955
127.406
127.182
127.110
126.922
125.812
124.995
124.942
124.898
124.787
124.655
124.176
84.572
77.372
77.160
76.949
76.033
67.869
62.866
62.735
61.590
52.750
29.116
21.479
14.265
14.038
Ts
N
CO2Et
Ph
CO2Et
N
N
3la
13C NMR (150 MHz, CDCl3)
f1 (ppm)

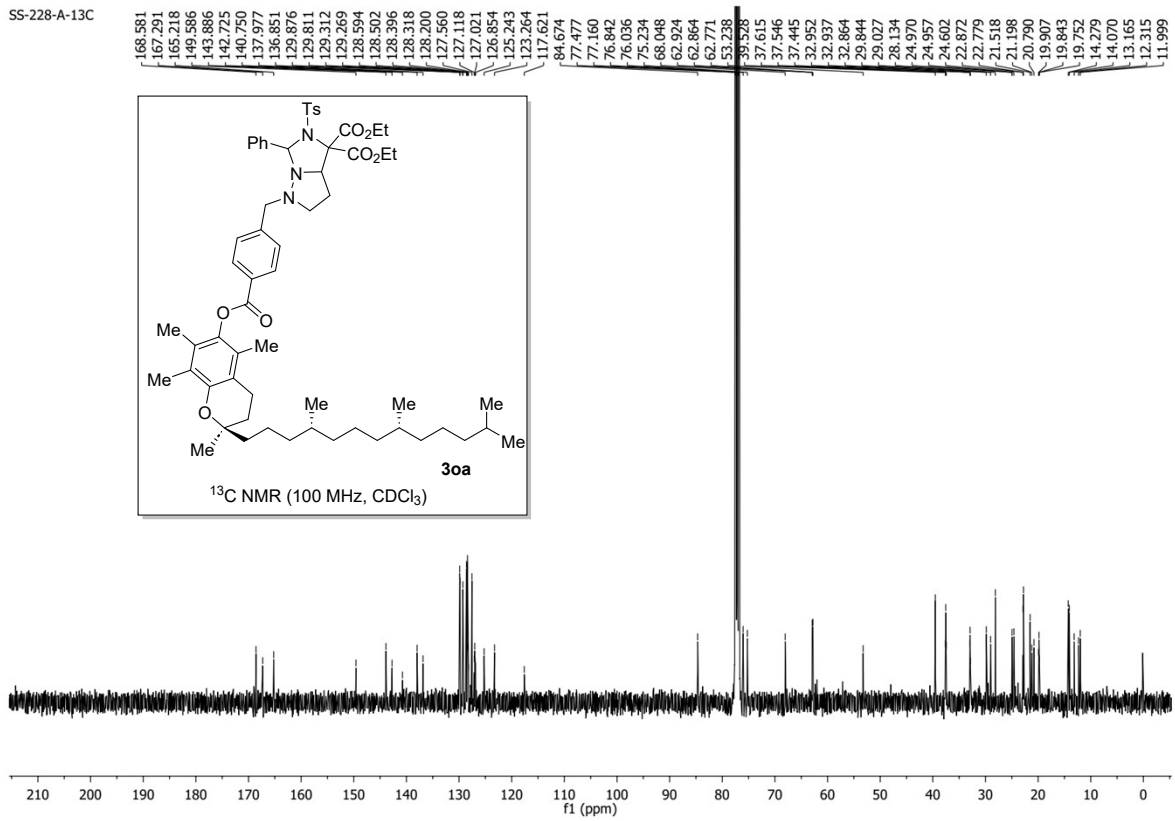

SS-155-A-1H
7.721
7.702
7.521
7.503
7.369
7.351
7.333
7.309
7.273
7.260
7.241
7.159
7.077
7.023
6.966
6.949
6.931
6.875
6.861
6.843
5.411
4.497
4.478
4.451
4.433
4.403
4.386
4.368
4.344
3.718
3.672
3.461
3.430
3.296
3.275
3.256
3.236
2.721
2.701
2.677
2.659
2.548
2.535
2.486
2.468
2.419
2.248
2.207
2.188
2.158
1.432
1.415
1.382
Ts
N
CO2Et
Ph
CO2Et
N
N
3ma
1H NMR (400 MHz, CDCl3)
1.04
2.03
1.01
2.01
1.00
1.02
3.00
1.00
4.03
1.00
1.03
4.02
3.00
1.00
1.00
1.00
1.16
3.00
1.01
6.00
f1 (ppm)

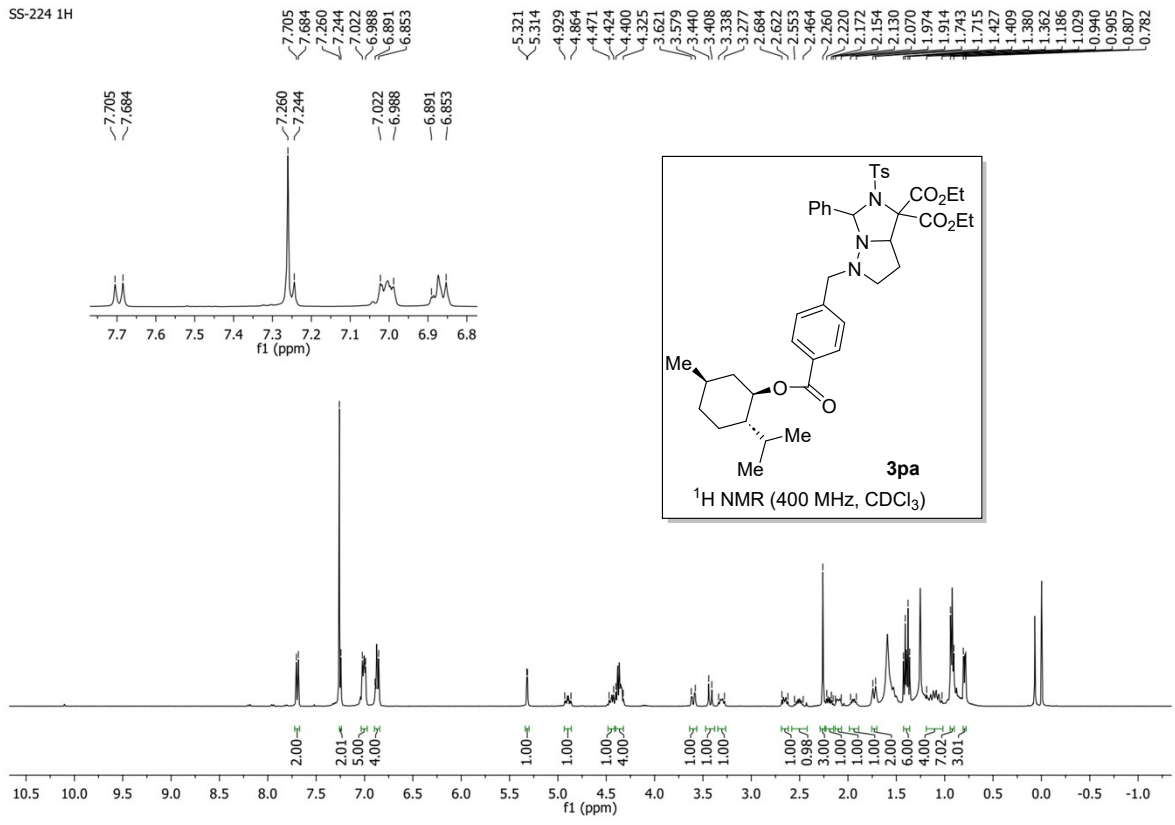

SS-155 13C
168.592
167.311
143.405
143.089
142.617
141.721
140.745
138.055
137.074
136.632
129.672
128.501
128.357
128.072
128.057
127.547
126.778
126.575
126.038
125.083
119.790
119.306
84.705
77.478
77.160
76.843
76.190
68.704
63.192
62.803
62.755
52.805
36.815
28.504
21.501
14.246
14.058
Ts
N
Ph
CO2Et
CO2Et
N
N
3ma
13C NMR (100 MHz, CDCl3)
f1 (ppm)

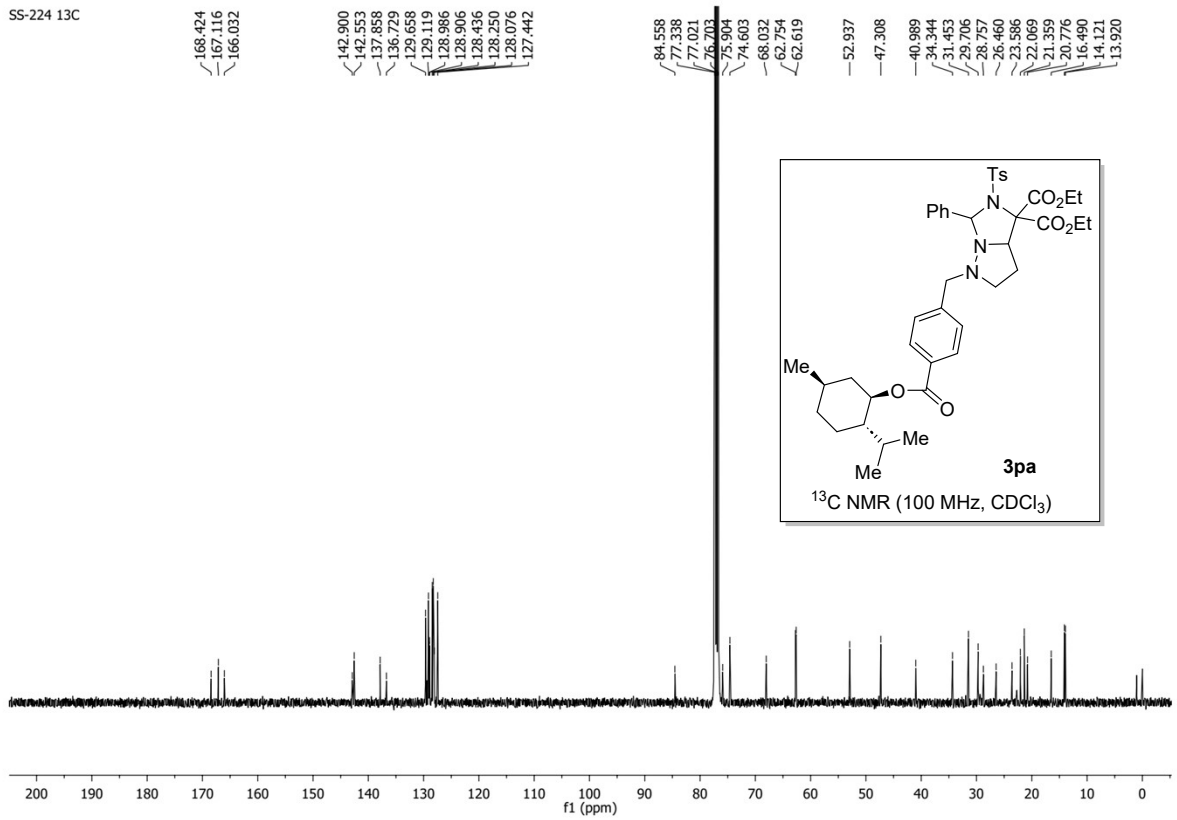

SS-225 1H
7.715
7.699
7.517
7.501
7.260
7.147
7.142
7.133
7.112
7.109
7.078
7.062
7.026
7.011
6.997
6.894
6.868
6.853
6.353
6.335
5.321
5.173
5.144
5.089
5.069
4.443
4.429
4.380
4.355
4.329
4.135
4.099
4.041
4.027
4.005
3.759
3.748
3.613
3.587
3.446
3.420
3.302
2.652
2.483
2.428
2.319
2.259
2.220
2.207
2.193
2.106
2.042
1.742
1.735
1.423
1.409
1.378
1.364
1.204
1.190
1.188
1.176
1.146
1.132
1.130
1.118
0.966
0.920
0.901
4.478
4.464
4.443
4.429
4.380
4.355
4.329
4.135
4.099
4.041
4.027
4.005
3.759
3.748
3.613
3.587
3.446
3.420
3.335
3.302
3.286
f1 (ppm)
Ts
N
Ph
CO2Et
CO2Et
N
N
O
O
Me
Me
Me
3na
1H NMR (500 MHz, CDCl3)
1.04
1.16
2.04
1.04
1.98
3.01
2.06
1.05
1.00
1.00
1.00
4.01
3.41
0.99
1.00
0.98
0.94
1.00
1.01
3.00
2.01
1.01
1.37
1.01
6.26
2.45
2.01
1.06
1.04
1.04
f1 (ppm)

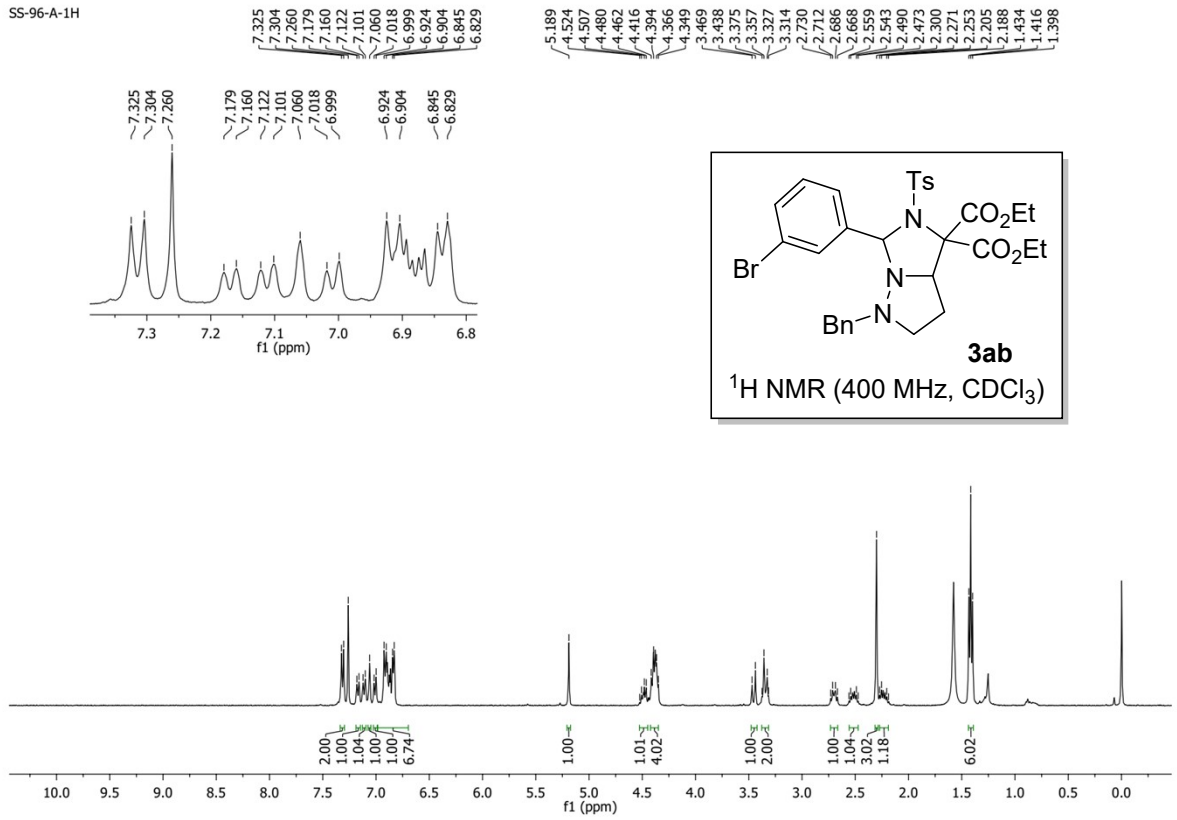

SS-225 13C
168.560
167.930
166.586
143.045
142.699
138.073
137.732
129.816
129.300
129.103
128.564
128.489
128.378
127.848
127.581
127.102
126.844
84.689
80.435
77.414
77.160
76.906
76.023
68.148
62.752
62.315
62.009
57.905
57.103
53.032
49.216
48.014
45.134
37.075
28.920
27.525
21.529
19.872
19.061
14.260
14.033
Ts
N
Ph
CO2Et
CO2Et
N
N
O
O
Me
Me
Me
3na
13C NMR (125 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

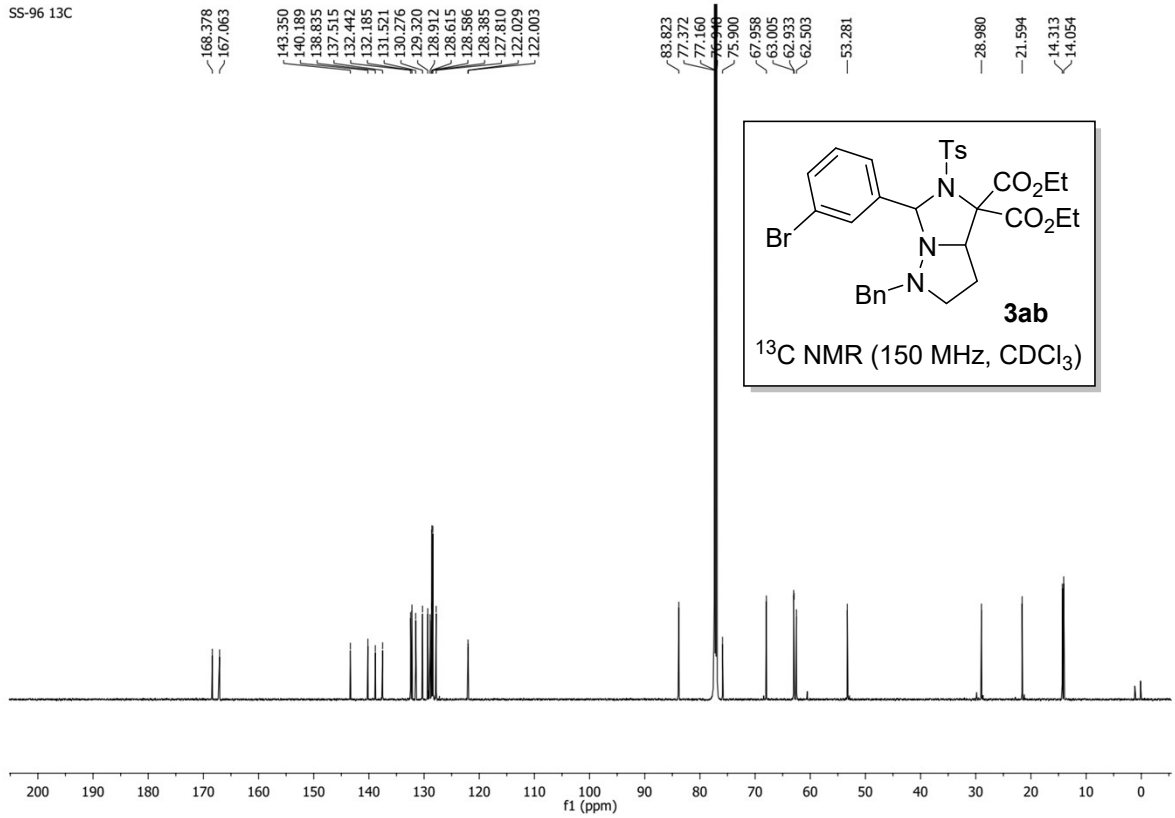

SS-228-A-1H
7.886
7.866
7.260
7.245
7.153
7.084
7.021
7.002
6.905
6.885
6.858
5.331
4.498
4.479
4.453
4.435
4.415
4.394
4.383
4.350
4.153
4.098
4.052
3.987
3.655
3.623
3.490
3.458
3.403
3.384
3.363
3.343
2.741
2.723
2.698
2.679
2.631
2.616
2.601
2.579
2.559
2.509
2.490
2.324
2.266
2.235
2.208
2.118
2.048
1.998
1.855
1.838
1.821
1.774
1.572
1.492
1.441
1.423
1.389
1.372
1.214
1.133
1.056
0.875
0.859
0.841
2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8
f1 (ppm)
Ts
N
Ph
CO2Et
CO2Et
N
N
O
O
Me
Me
Me
O
Me
Me
Me
Me
3oa
1H NMR (400 MHz, CDCl3)
2.00
1.01
6.07
4.00
1.00
0.95
4.03
0.83
1.00
1.00
1.00
1.00
2.00
1.10
0.95
4.03
3.01
6.00
3.02
8.00
10.03
9.02
12.03
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

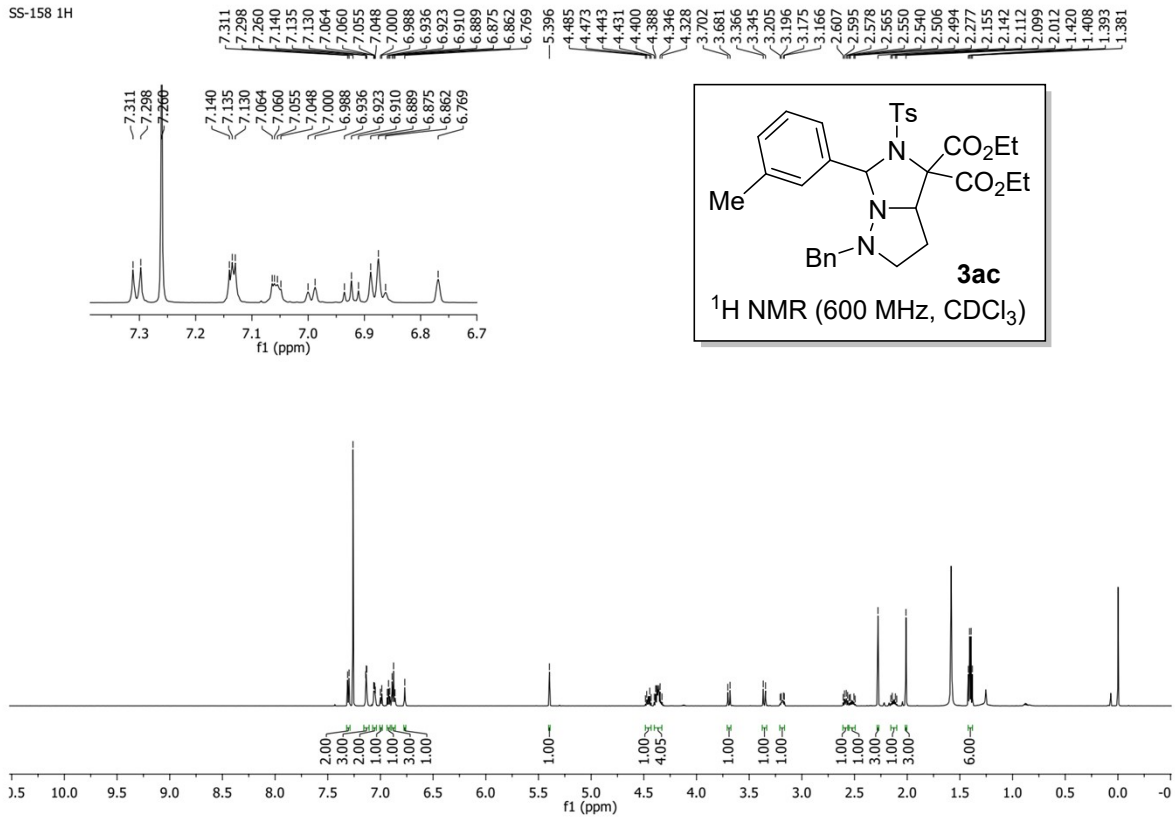

SS-228-A-13C
168.581
167.291
165.218
149.586
143.886
142.725
140.750
137.977
136.851
129.876
129.811
129.312
129.269
128.594
128.502
128.396
128.318
128.200
127.560
127.118
127.021
126.854
125.243
123.264
117.621
84.674
77.477
77.160
76.842
76.036
75.234
68.048
62.924
62.864
62.771
53.238
39.528
37.615
37.546
37.445
32.952
32.937
32.864
29.844
29.027
28.134
24.970
24.957
24.602
22.872
22.779
21.518
21.198
20.790
19.907
19.843
19.752
14.279
14.070
13.165
12.315
11.999
Ts
Ph
N
CO2Et
CO2Et
N
N
O
O
Me
Me
Me
O
Me
Me
Me
Me
Me
3oa
13C NMR (100 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

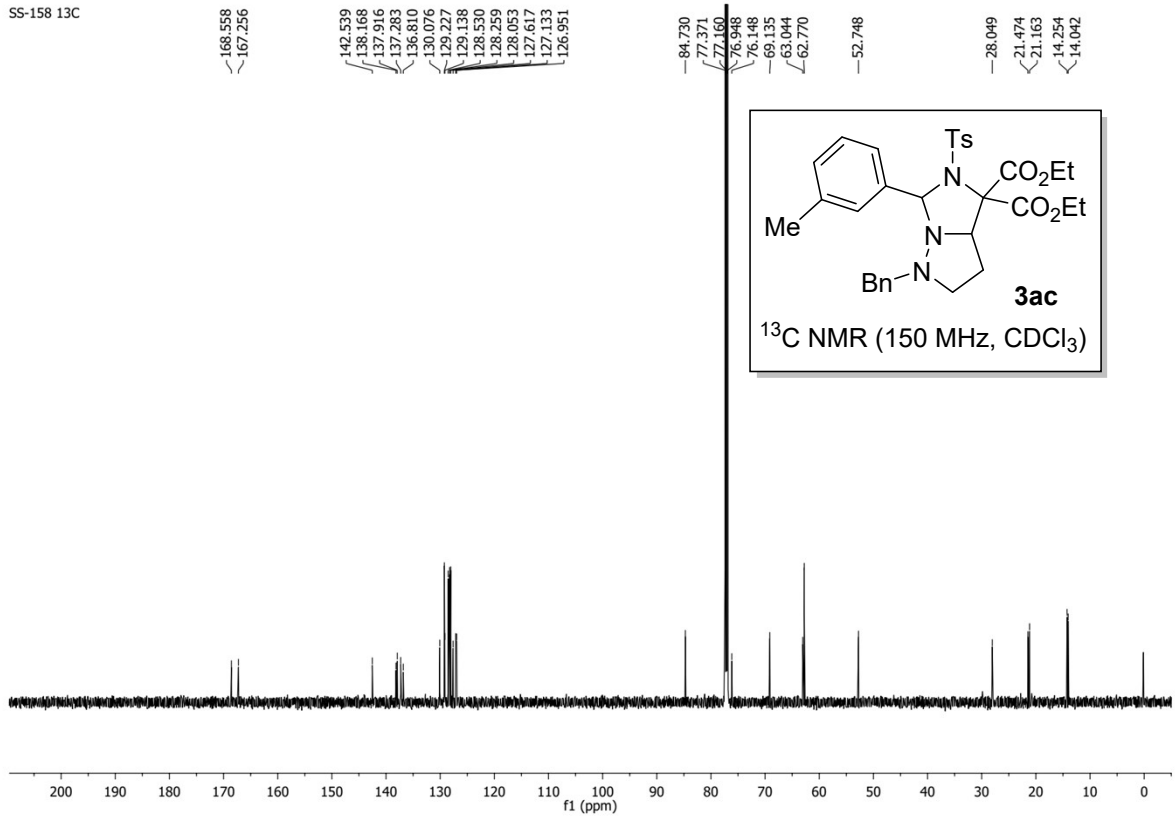

SS-224 1H
7.705
7.684
7.260
7.244
7.022
6.988
6.891
6.853
5.321
5.314
4.929
4.864
4.471
4.424
4.400
4.325
3.621
3.579
3.440
3.408
3.338
3.277
2.684
2.622
2.553
2.464
2.260
2.220
2.172
2.154
2.130
2.070
1.974
1.914
1.743
1.715
1.427
1.409
1.380
1.362
1.186
1.029
0.940
0.905
0.807
0.782
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
f1 (ppm)
Ts
Ph
N
CO2Et
CO2Et
N
N
Me
O
O
Me
Me
3pa
1H NMR (400 MHz, CDCl3)
2.00
2.01
5.00
4.00
1.00
1.00
1.00
4.00
1.00
1.00
1.00
1.00
0.98
3.00
1.00
1.00
2.00
6.00
4.00
7.02
3.01
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

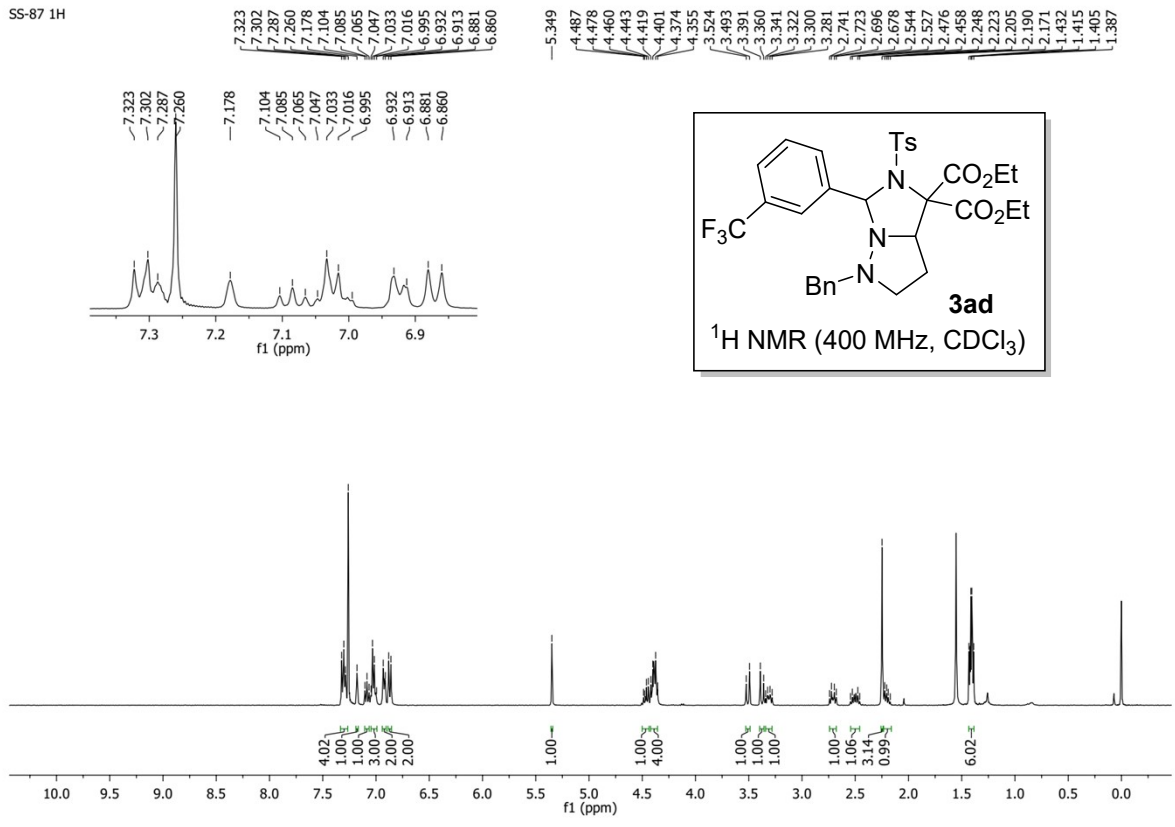

SS-224 13C
168.424
167.116
166.032
142.900
142.553
137.858
136.729
129.658
129.119
128.986
128.906
128.436
128.250
128.076
127.442
84.558
77.338
77.021
76.703
75.904
74.603
68.032
62.754
62.619
52.937
47.308
40.989
34.344
31.453
29.706
28.757
26.460
23.586
22.069
21.359
20.776
16.490
14.121
13.920
Ts
N
CO2Et
CO2Et
Ph
N
N
Me
O
O
Me
Me
3pa
13C NMR (100 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

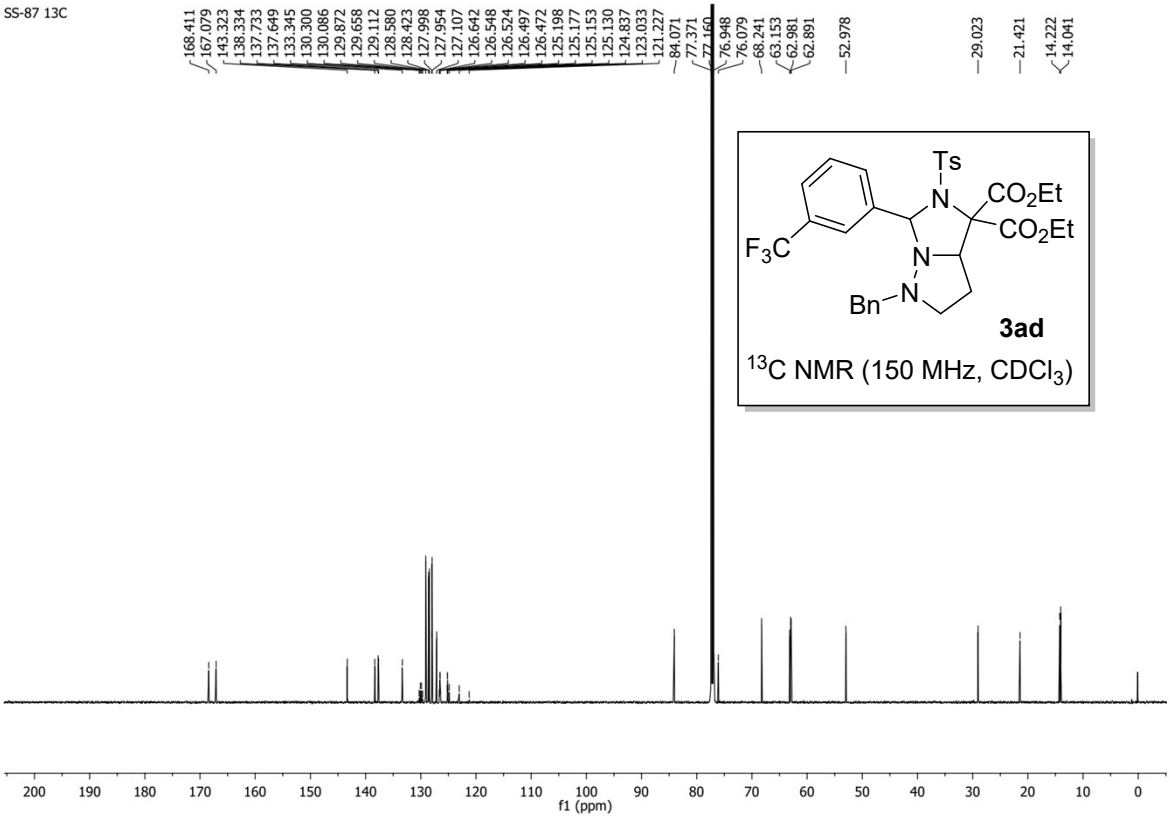

SS-96-A-1H
7.325
7.304
7.260
7.179
7.160
7.122
7.101
7.060
7.018
6.999
6.924
6.904
6.845
6.829
5.189
4.524
4.507
4.480
4.462
4.416
4.394
4.366
4.349
3.469
3.438
3.375
3.357
3.327
3.314
2.730
2.712
2.686
2.668
2.559
2.543
2.490
2.473
2.300
2.271
2.253
2.205
2.188
1.434
1.416
1.398
7.3
7.2
7.1
7.0
6.9
6.8
f1 (ppm)
Ts
N
CO2Et
CO2Et
Br
N
Bn
N
3ab
1H NMR (400 MHz, CDCl3)
2.00
1.00
1.04
1.00
1.00
6.74
1.00
1.01
4.02
1.00
2.00
1.00
1.04
3.02
1.18
6.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

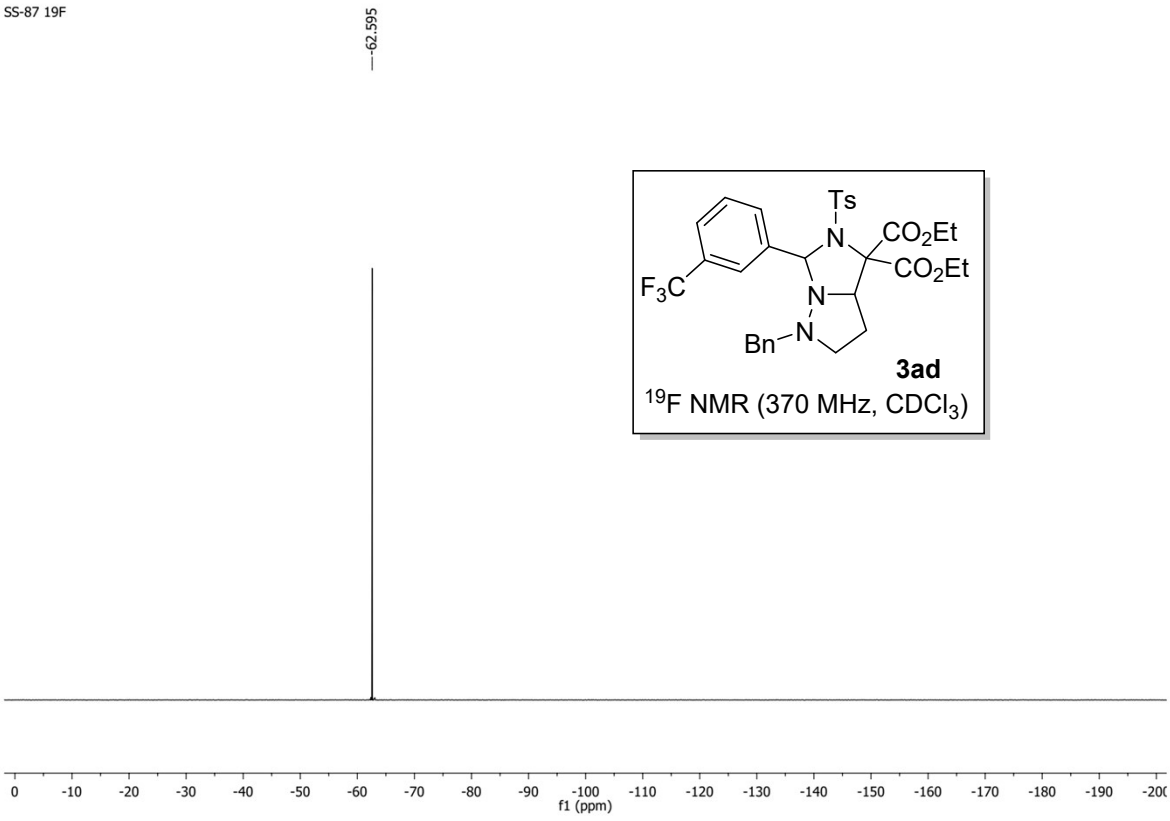

SS-96 13C
168.378
167.063
143.350
140.189
138.835
137.515
132.442
132.185
131.521
130.276
129.320
128.912
128.615
128.586
128.385
127.810
122.029
122.003
83.823
77.372
77.160
76.948
75.900
67.958
63.005
62.933
62.503
53.281
28.980
21.594
14.313
14.054
Ts
N
CO2Et
CO2Et
Br
N
Bn
N
3ab
13C NMR (150 MHz, CDCl3)
f1 (ppm)

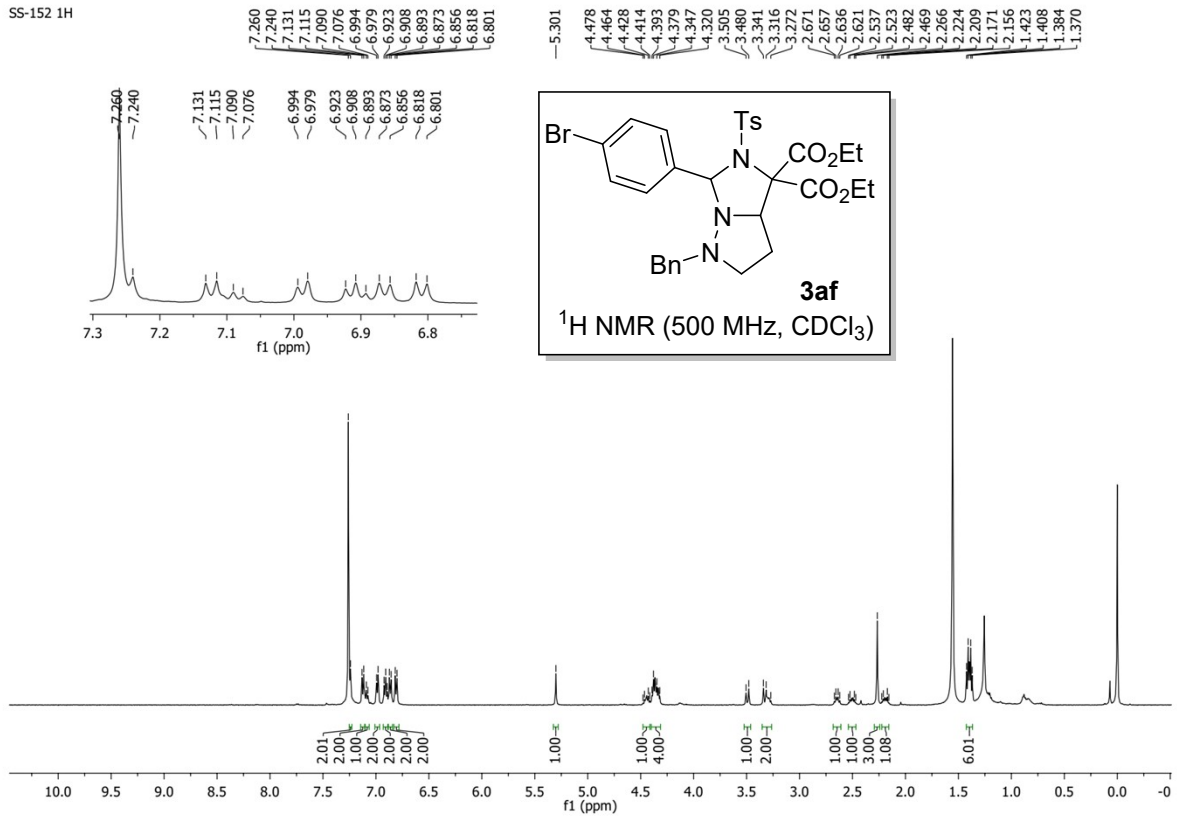

SS-158 1H
7.311
7.298
7.260
7.140
7.135
7.130
7.064
7.060
7.055
7.048
7.000
6.988
6.936
6.923
6.910
6.889
6.875
6.862
6.769
5.396
4.485
4.473
4.443
4.431
4.400
4.388
4.346
4.328
3.702
3.681
3.366
3.345
3.205
3.196
3.175
3.166
2.607
2.595
2.578
2.565
2.550
2.540
2.506
2.494
2.277
2.155
2.142
2.112
2.099
2.012
1.420
1.408
1.393
1.381
Ts
N
CO2Et
CO2Et
Me
N
Bn
N
3ac
1H NMR (600 MHz, CDCl3)
f1 (ppm)

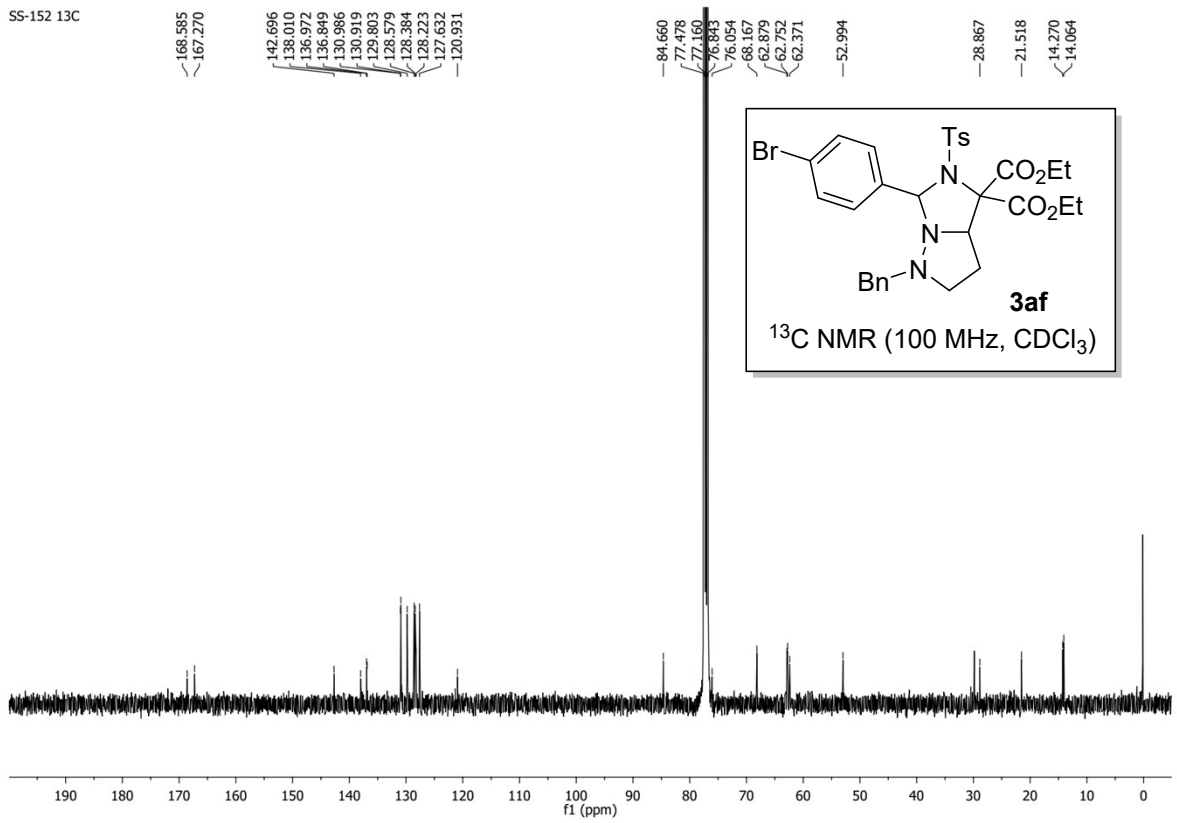

SS-158 13C
168.558
167.256
142.539
138.168
137.916
137.283
136.810
130.076
129.227
129.138
128.530
128.259
128.053
127.617
127.133
126.951
84.730
77.371
77.160
76.948
76.148
69.135
63.044
62.770
52.748
28.049
21.474
21.163
14.254
14.042
Ts
N
CO2Et
CO2Et
Me
N
Bn
N
3ac
13C NMR (150 MHz, CDCl3)
f1 (ppm)

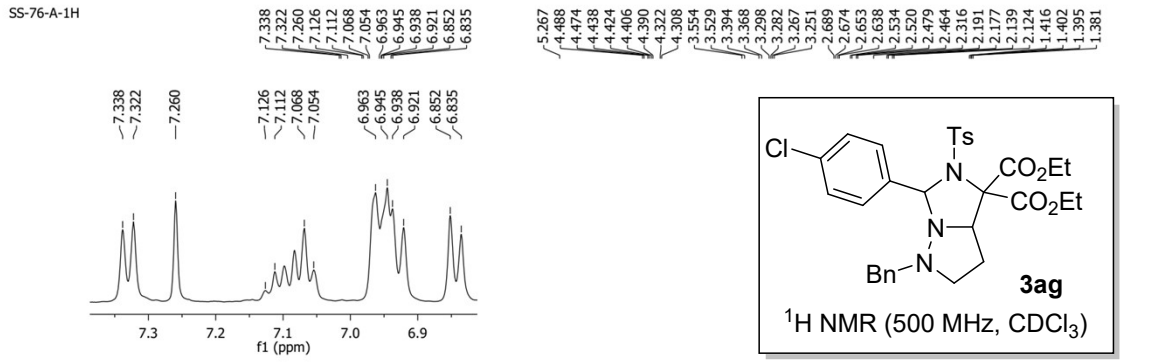

SS-87 1H
7.323
7.302
7.287
7.260
7.178
7.104
7.085
7.065
7.047
7.033
7.016
6.995
6.932
6.913
6.881
6.860
5.349
4.487
4.478
4.460
4.443
4.419
4.401
4.374
4.355
3.524
3.493
3.391
3.360
3.341
3.322
3.300
3.281
2.741
2.723
2.696
2.678
2.544
2.527
2.476
2.458
2.248
2.223
2.205
2.190
2.171
1.432
1.415
1.405
1.387
f1 (ppm)
Ts
N
CO2Et
CO2Et
F3C
N
Bn
N
3ad
1H NMR (400 MHz, CDCl3)
4.02
1.00
1.00
3.00
2.00
2.00
1.00
1.00
4.00
1.00
1.00
1.00
1.06
3.14
0.99
6.02
f1 (ppm)

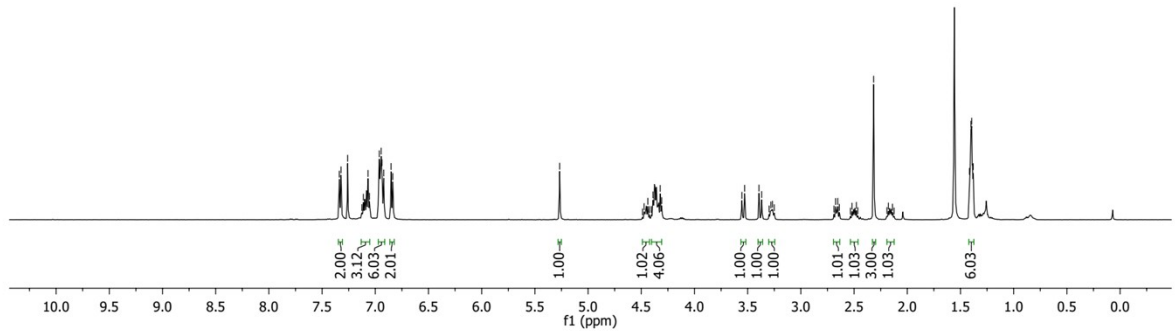

SS-87 13C
168.411
167.079
143.323
138.334
137.733
137.649
133.345
130.300
130.086
129.872
129.658
129.112
128.580
128.423
127.998
127.954
127.107
126.642
126.548
126.524
126.497
126.472
125.198
125.177
125.153
125.130
124.837
123.033
121.227
84.071
77.371
77.160
76.948
76.079
68.241
63.153
62.981
62.891
52.978
29.023
21.421
14.222
14.041
Ts
N
CO2Et
CO2Et
F3C
N
Bn
N
3ad
13C NMR (150 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

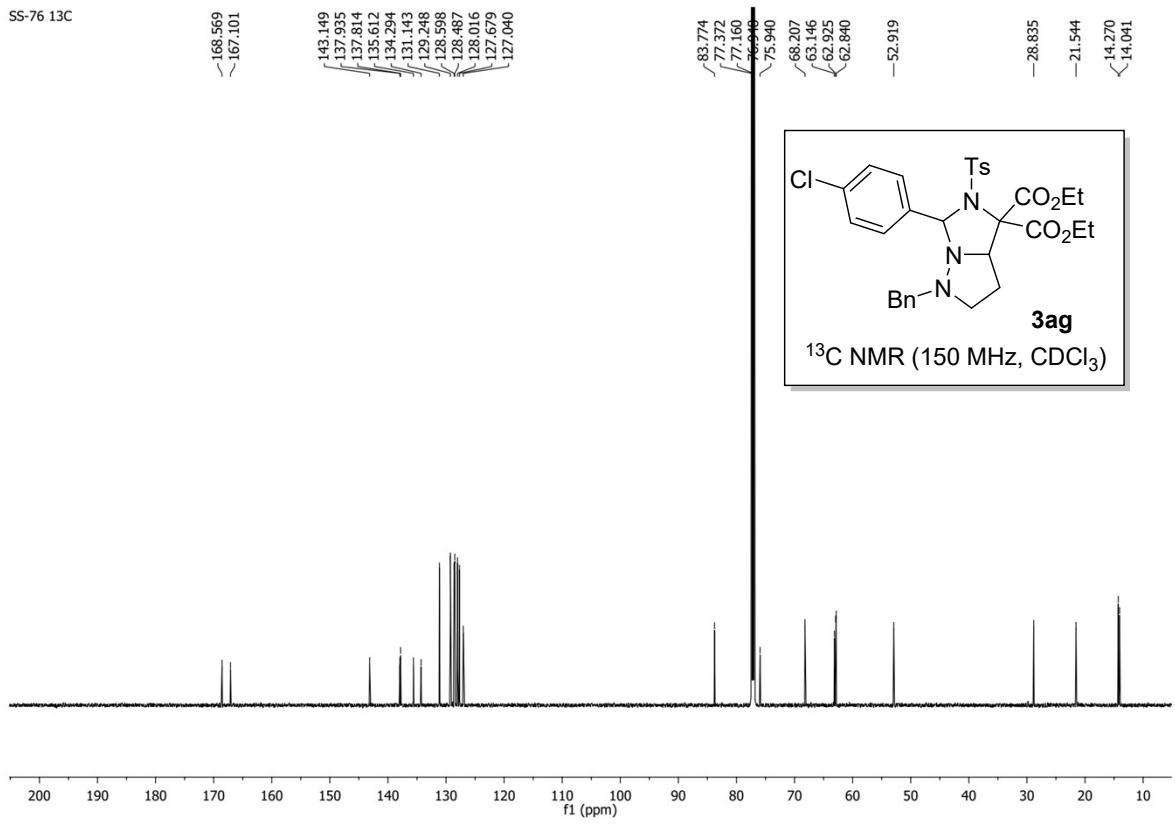

SS-87 19F
-62.595
Ts
N
CO2Et
CO2Et
F3C
N
Bn
N
3ad
19F NMR (370 MHz, CDCl3)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

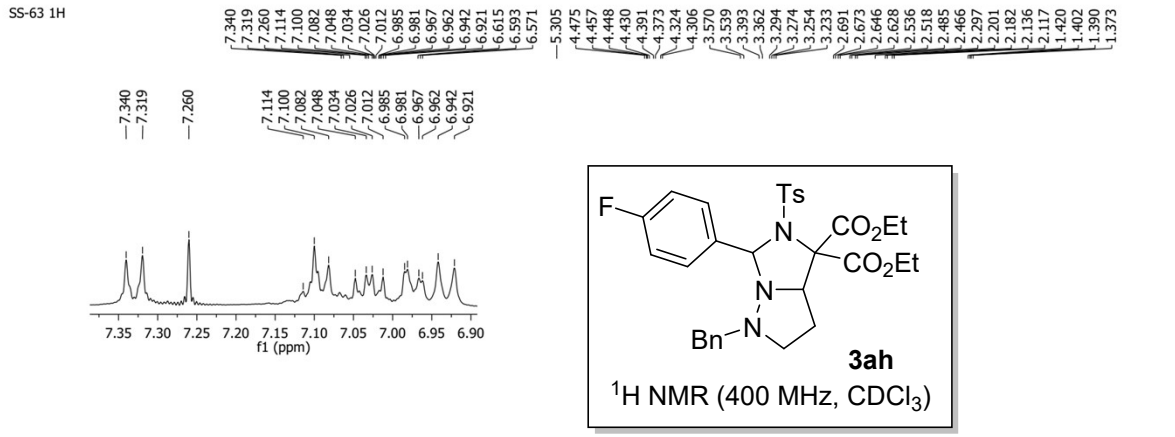

SS-152 1H
Br
Ts
N
CO2Et
CO2Et
N
Bn
N
3af
1H NMR (500 MHz, CDCl3)
f1 (ppm)

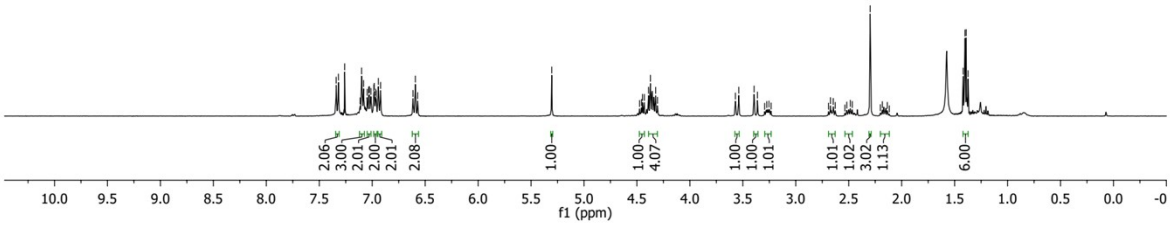

SS-152 13C
Br
Ts
N
CO2Et
CO2Et
N
Bn
N
3af
13C NMR (100 MHz, CDCl3)
f1 (ppm)

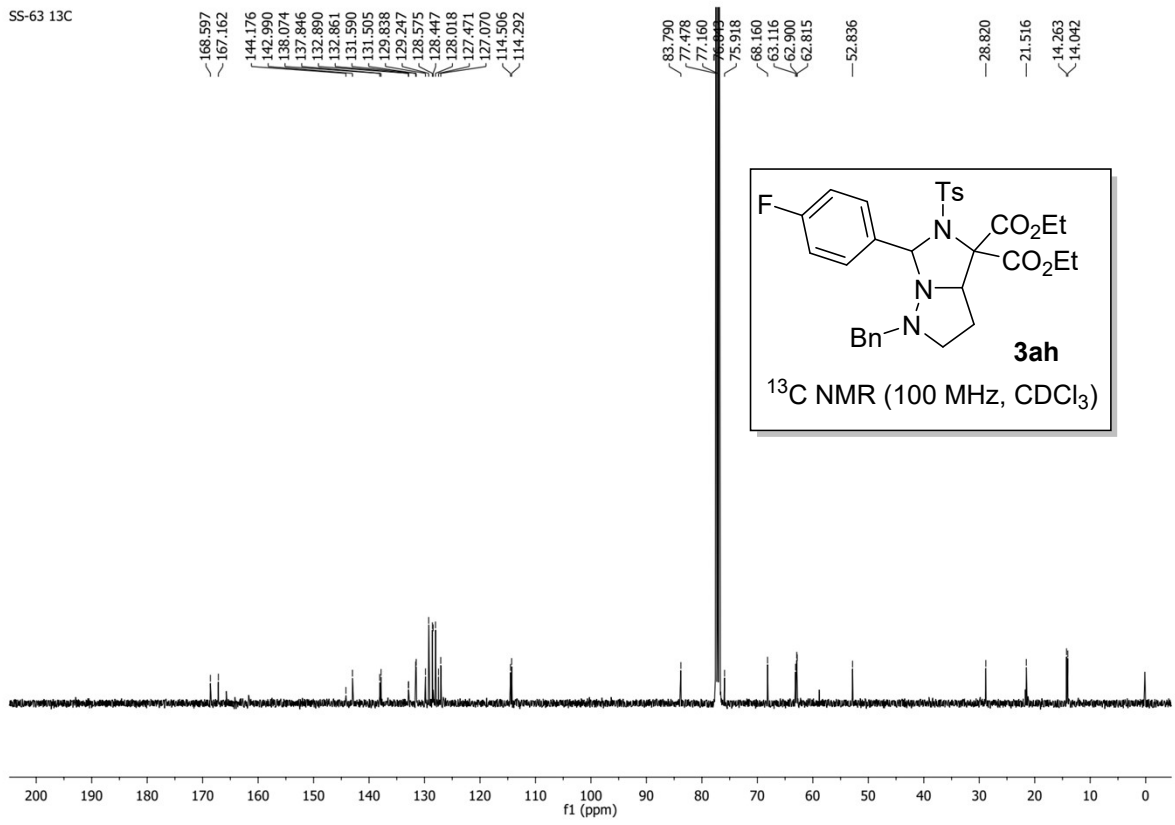

SS-76-A-1H
7.338
7.322
7.260
7.126
7.112
7.068
7.054
6.963
6.945
6.938
6.921
6.852
6.835
5.267
4.488
4.474
4.438
4.424
4.406
4.390
4.322
4.308
3.554
3.529
3.394
3.368
3.298
3.282
3.267
3.251
2.689
2.674
2.653
2.638
2.534
2.520
2.479
2.464
2.316
2.191
2.177
2.139
2.124
1.416
1.402
1.395
1.381
f1 (ppm)
Cl
Ts
N
CO2Et
CO2Et
N
Bn
N
3ag
1H NMR (500 MHz, CDCl3)


2.00
3.12
6.03
2.01
1.00
1.02
4.06
1.00
1.00
1.00
1.01
1.03
3.00
1.03
6.03
f1 (ppm)

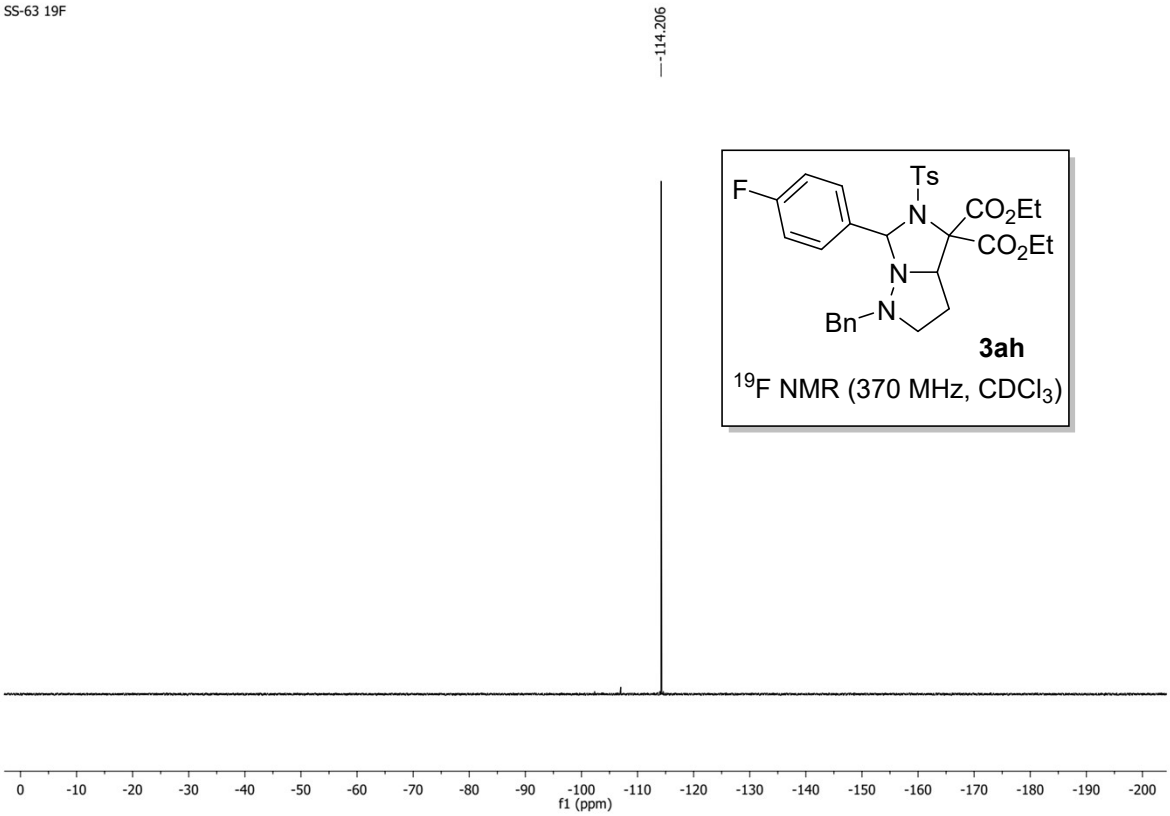

SS-76 13C
168.569
167.101
143.149
137.935
137.814
135.612
134.294
131.143
129.248
128.598
128.487
128.016
127.679
127.040
83.774
77.372
77.160
76.948
75.940
68.207
63.146
62.925
62.840
52.919
28.835
21.544
14.270
14.041
Cl
Ts
N
CO2Et
CO2Et
N
Bn
N
3ag
13C NMR (150 MHz, CDCl3)
f1 (ppm)


SS-63 1H
7.340
7.319
7.260
7.114
7.100
7.082
7.048
7.034
7.026
7.012
6.985
6.981
6.967
6.962
6.942
6.921
6.615
6.593
6.571
5.305
4.475
4.457
4.448
4.430
4.391
4.373
4.324
4.306
3.570
3.539
3.393
3.362
3.294
3.274
3.254
3.233
2.691
2.673
2.646
2.628
2.536
2.518
2.485
2.466
2.297
2.201
2.182
2.136
2.117
1.420
1.402
1.390
1.373
7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95 6.90
f1 (ppm)
F
Ts
N
CO2Et
CO2Et
N
Bn
N
3ah
1H NMR (400 MHz, CDCl3)


2.06
3.00
2.01
2.00
2.01
2.08
1.00
1.00
4.07
1.00
1.00
1.01
1.01
1.02
3.02
1.13
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


SS-63 13C
168.597
167.162
144.176
142.990
138.074
137.846
132.890
132.861
131.590
131.505
129.838
129.247
128.575
128.447
128.018
127.471
127.070
114.506
114.292
83.790
77.478
77.160
76.843
75.918
68.160
63.116
62.900
62.815
52.836
28.820
21.516
14.263
14.042
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
F
Ts
N
CO2Et
CO2Et
N
Bn
N
3ah
13C NMR (100 MHz, CDCl3)

SS-63 19F



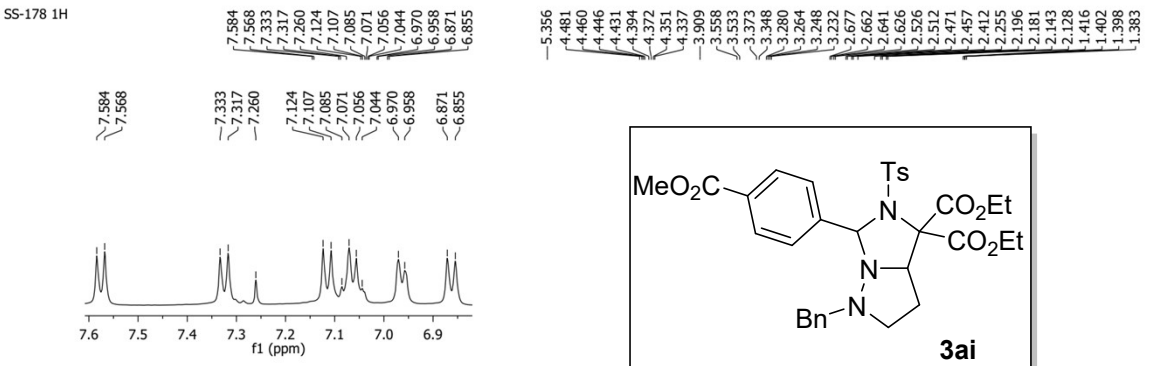




**3ah**

$^{19}$F NMR (370 MHz, $CDCl_3$)

SS-178 1H

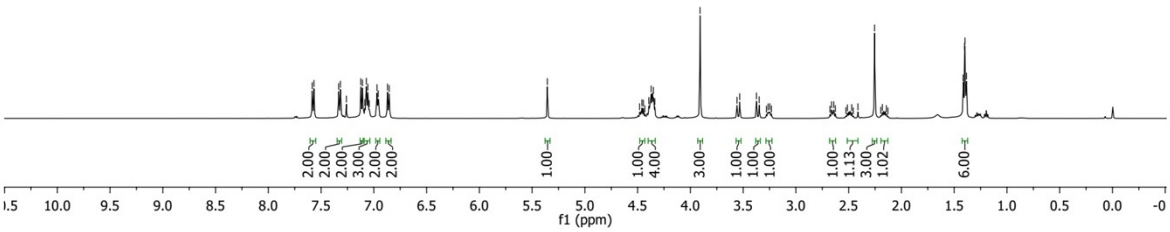


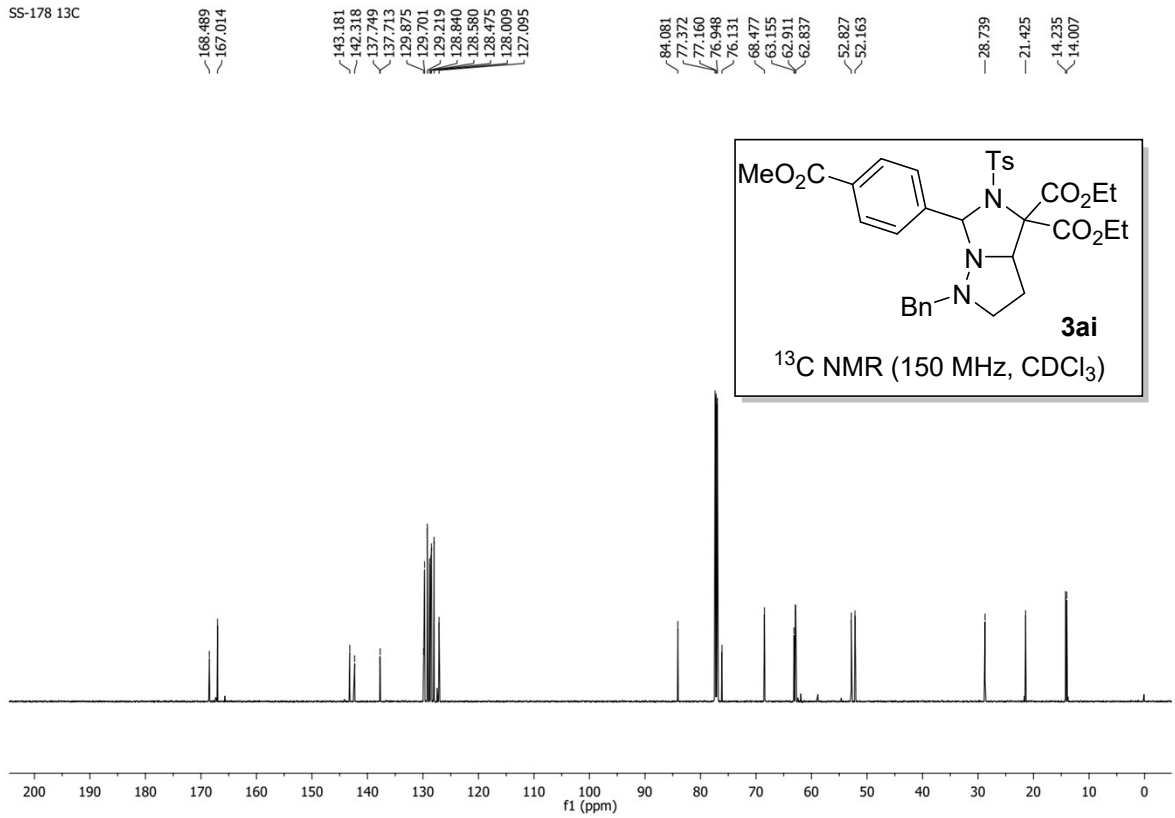


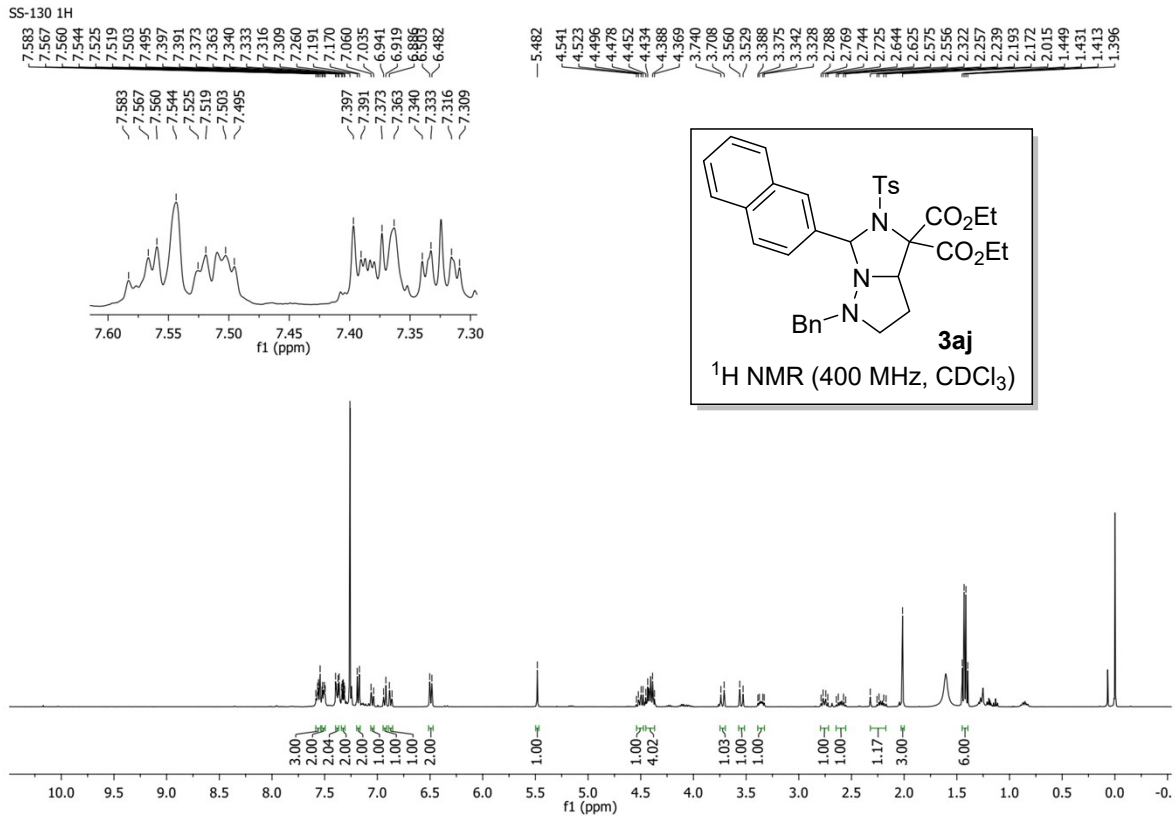


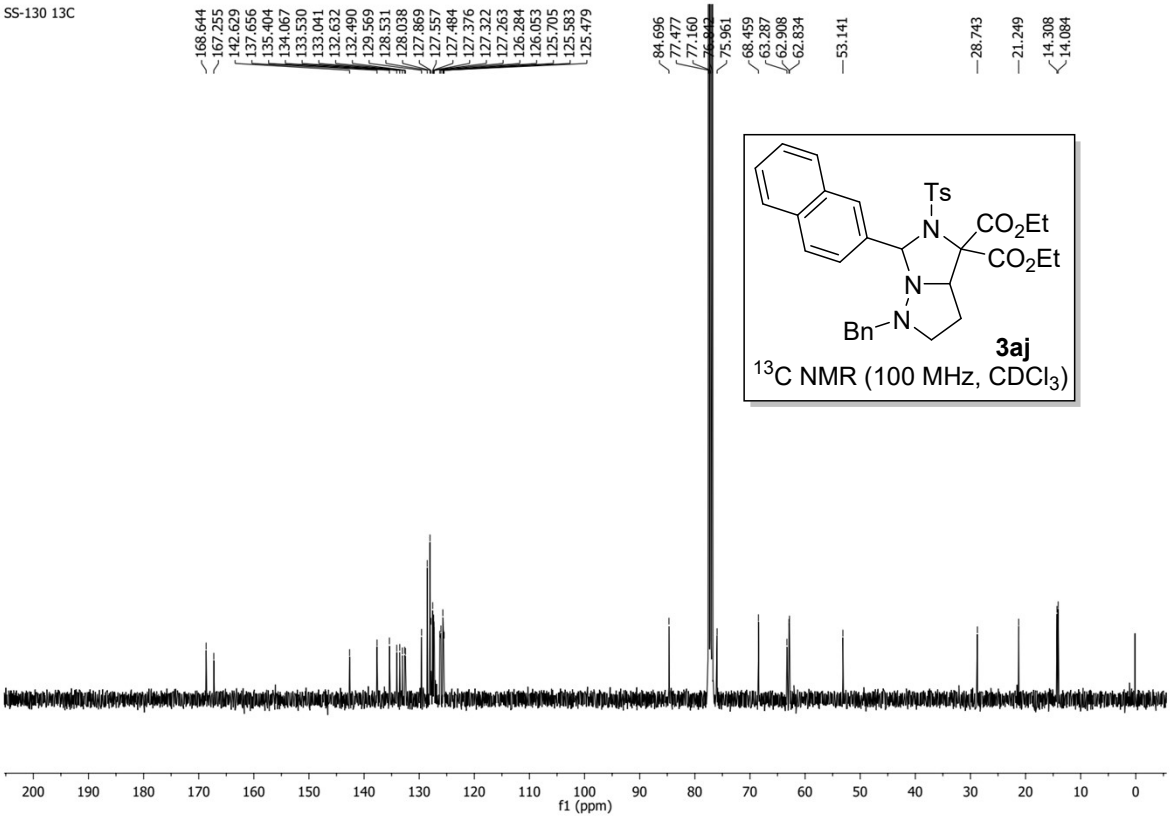
**3ai**

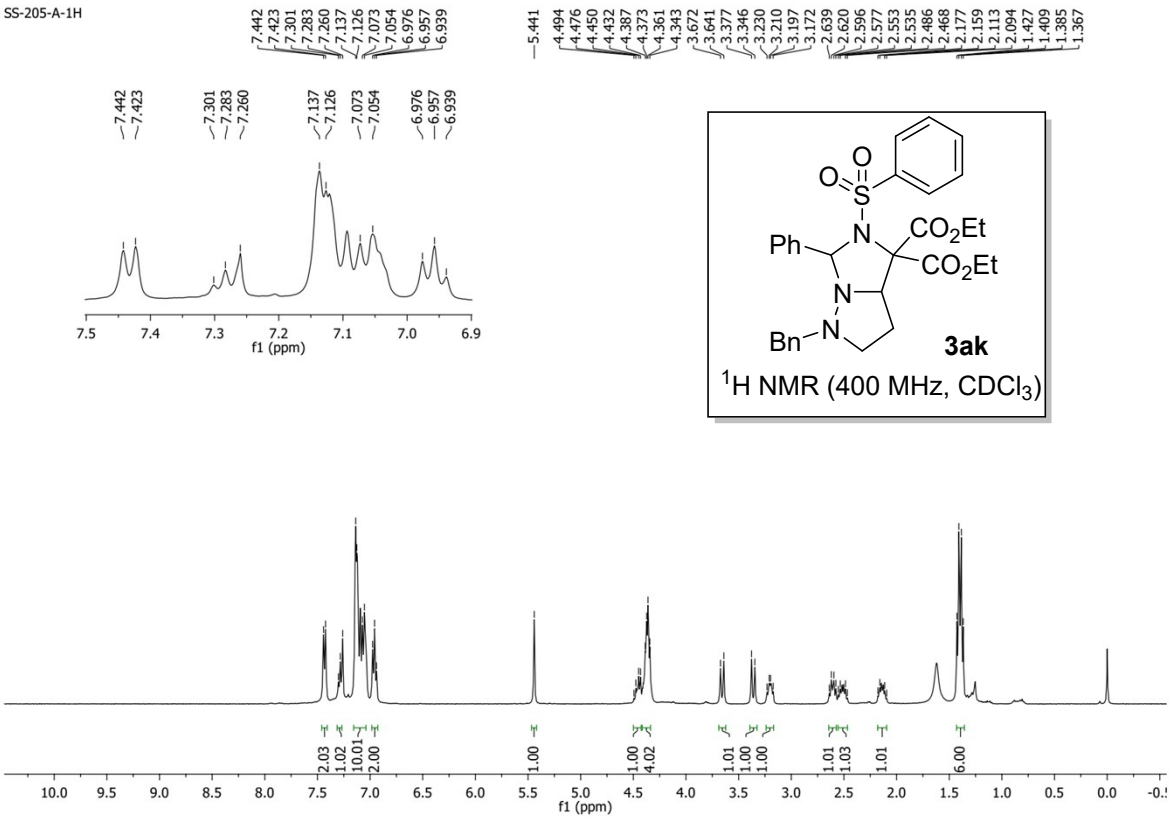
$^{1}$H NMR (500 MHz, $CDCl_3$)

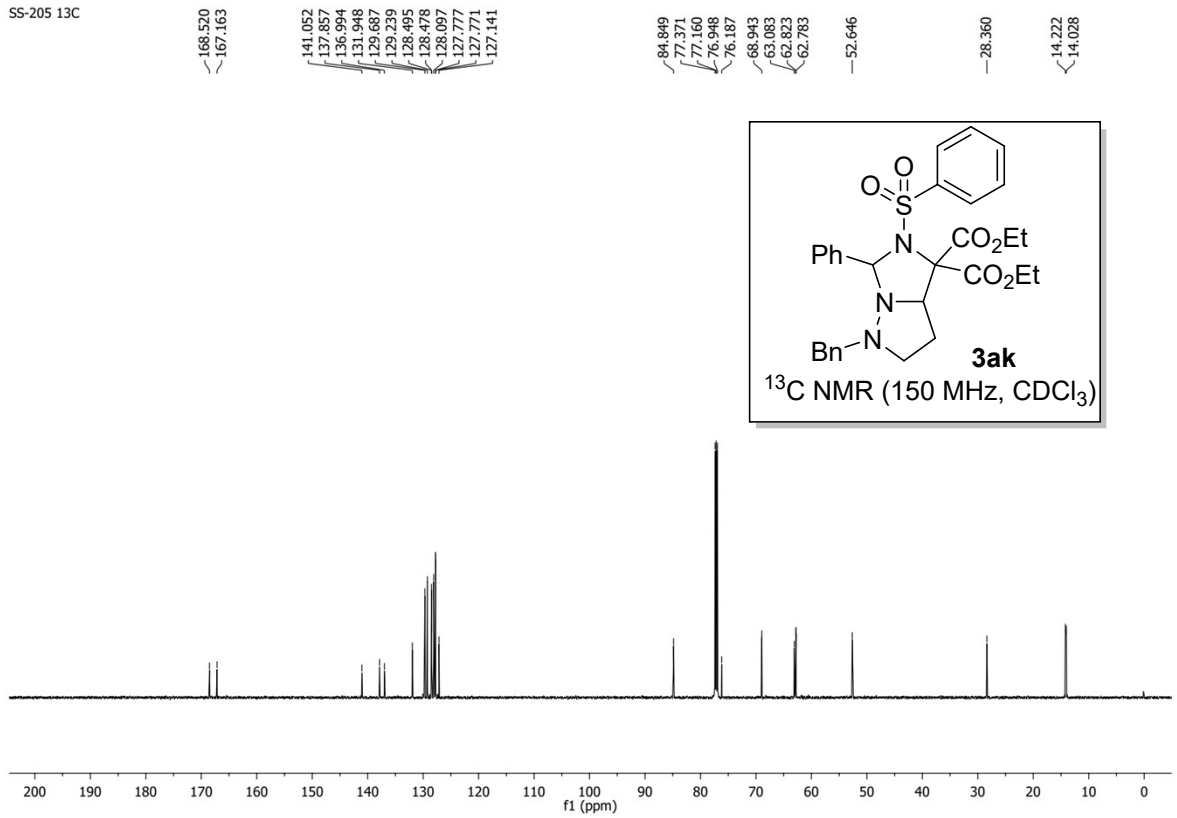


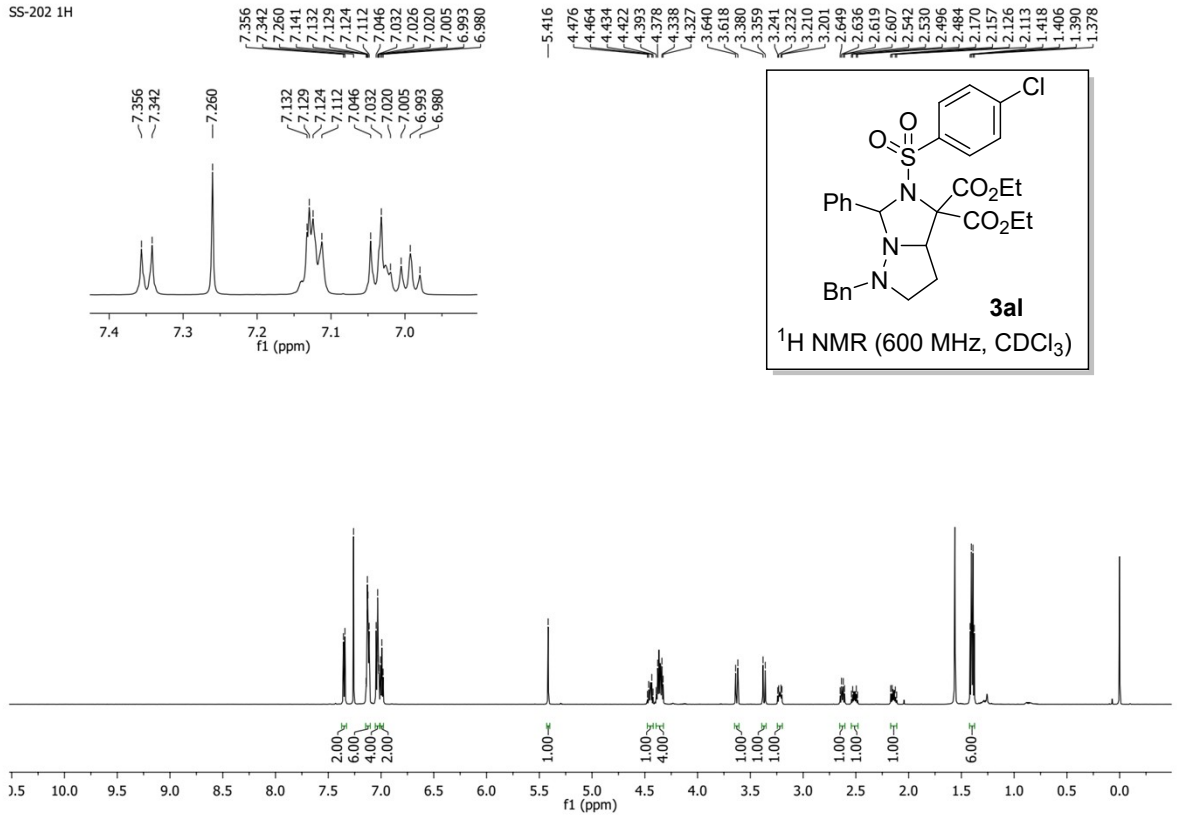

SS-178 13C
168.489
167.014
143.181
142.318
137.749
137.713
129.875
129.701
129.219
128.840
128.580
128.475
128.009
127.095
84.081
77.372
77.160
76.948
76.131
68.477
63.155
62.911
62.837
52.827
52.163
28.739
21.425
14.235
14.007
MeO2C
Ts
N
CO2Et
CO2Et
N
Bn
N
3ai
13C NMR (150 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

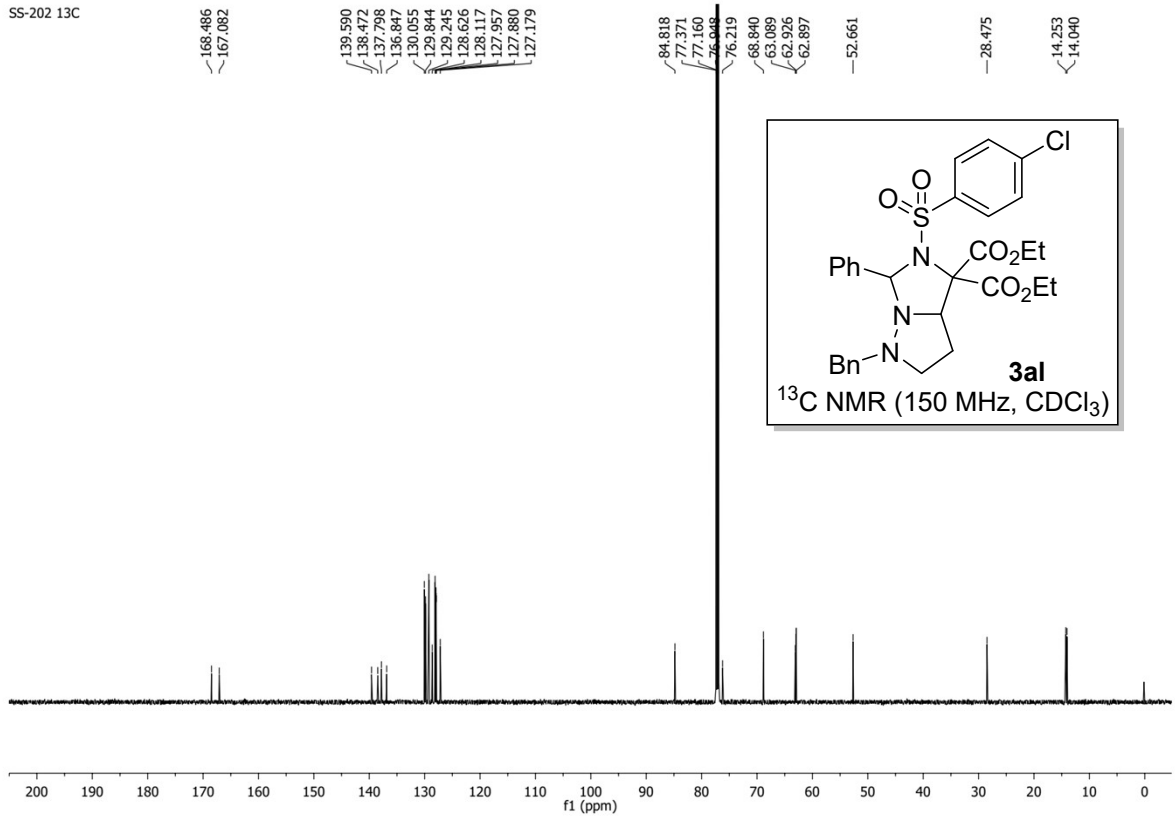

SS-130 1H
7.583
7.567
7.560
7.544
7.525
7.519
7.503
7.495
7.397
7.391
7.373
7.363
7.340
7.333
7.316
7.309
7.260
7.191
7.170
7.060
7.035
6.941
6.919
6.886
6.863
6.482
5.482
4.541
4.523
4.496
4.478
4.452
4.434
4.388
4.369
3.740
3.708
3.560
3.529
3.388
3.375
3.342
3.328
2.788
2.769
2.744
2.725
2.644
2.625
2.575
2.556
2.322
2.257
2.239
2.193
2.172
2.015
1.449
1.431
1.413
1.396
7.60
7.55
7.50
7.45
7.40
7.35
7.30
f1 (ppm)
Ts
N
CO2Et
CO2Et
N
Bn
N
3aj
1H NMR (400 MHz, CDCl3)
3.00
2.00
2.04
2.00
2.00
1.00
1.00
2.00
1.00
1.00
4.02
1.03
1.00
1.00
1.00
1.00
1.17
3.00
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)

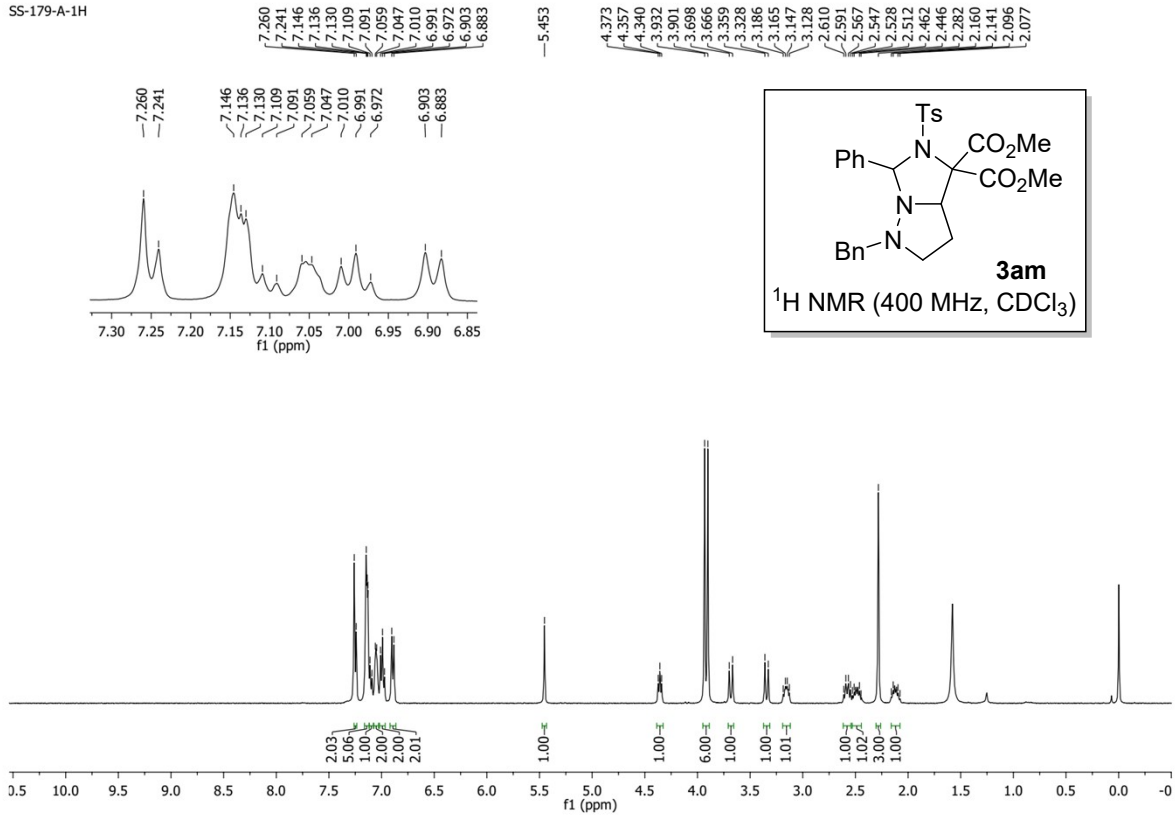

SS-130 13C
168.644
167.255
142.629
137.656
135.404
134.067
133.530
133.041
132.632
132.490
129.569
128.531
128.038
127.869
127.557
127.484
127.376
127.322
127.263
126.284
126.053
125.705
125.583
125.479
84.696
77.477
77.160
76.842
75.961
68.459
63.287
62.908
62.834
53.141
28.743
21.249
14.308
14.084
Ts
N
CO2Et
CO2Et
N
Bn
N
3aj
13C NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


SS-205-A-1H
7.442
7.423
7.301
7.283
7.260
7.137
7.126
7.073
7.054
6.976
6.957
6.939
5.441
4.494
4.476
4.450
4.432
4.387
4.373
4.361
4.343
3.672
3.641
3.377
3.346
3.230
3.210
3.197
3.172
2.639
2.620
2.596
2.577
2.553
2.535
2.486
2.468
2.177
2.159
2.113
2.094
1.427
1.409
1.385
1.367
7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
O
O
S
N
Ph
CO2Et
CO2Et
N
Bn
N
3ak
1H NMR (400 MHz, CDCl3)
2.03
1.02
10.01
2.00
1.00
1.00
4.02
1.01
1.00
1.00
1.01
1.03
1.01
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

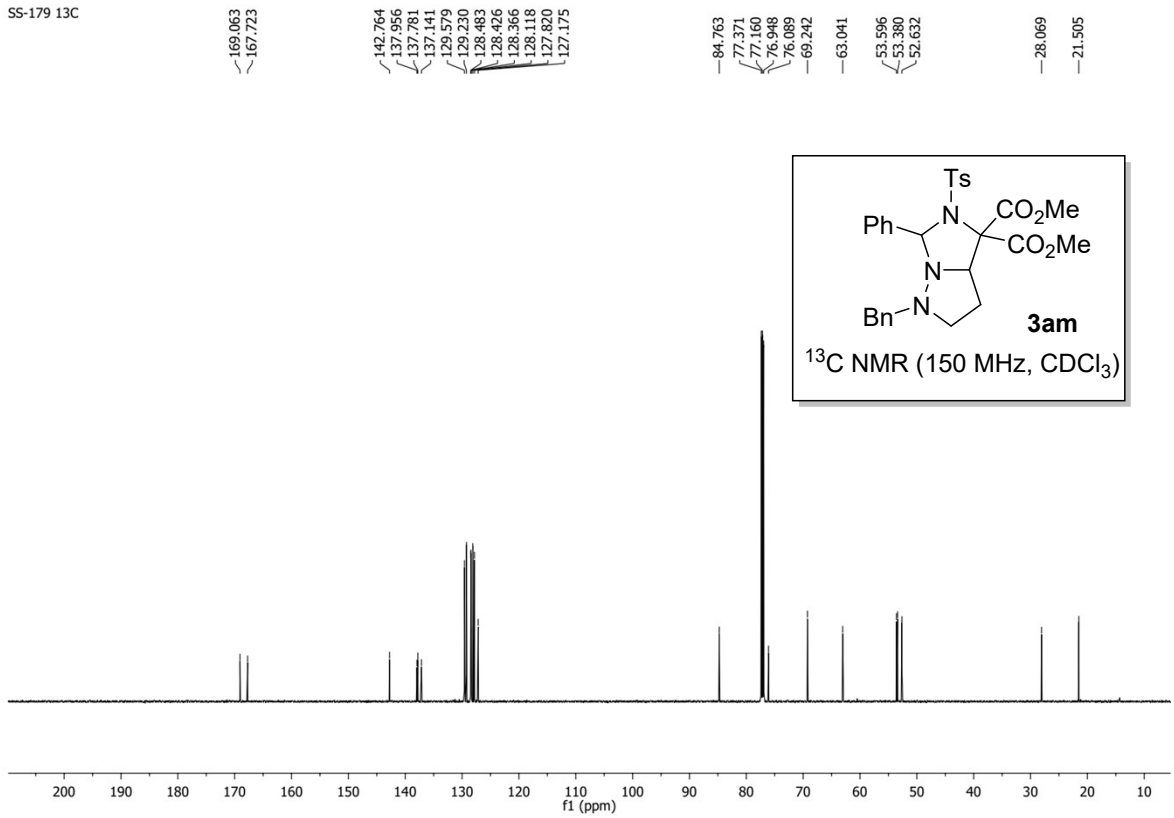

SS-205 13C
168.520
167.163
141.052
137.857
136.994
131.948
129.687
129.239
128.495
128.478
128.097
127.777
127.771
127.141
84.849
77.371
77.160
76.948
76.187
68.943
63.083
62.823
62.783
52.646
28.360
14.222
14.028
O
O
S
N
Ph
CO2Et
CO2Et
N
Bn
N
3ak
13C NMR (150 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


SS-202 1H
7.356
7.342
7.260
7.141
7.132
7.129
7.124
7.112
7.046
7.032
7.026
7.020
7.005
6.993
6.980
5.416
4.476
4.464
4.434
4.422
4.393
4.378
4.338
4.327
3.640
3.618
3.380
3.359
3.241
3.232
3.210
3.201
2.649
2.636
2.619
2.607
2.542
2.530
2.496
2.484
2.170
2.157
2.126
2.113
1.418
1.406
1.390
1.378
Cl
O
O
S
N
Ph
CO2Et
CO2Et
N
Bn
N
3al
1H NMR (600 MHz, CDCl3)
7.4 7.3 7.2 7.1 7.0
f1 (ppm)
2.00
6.00
4.00
2.00
1.00
1.00
4.00
1.00
1.00
1.00
1.00
1.00
1.00
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

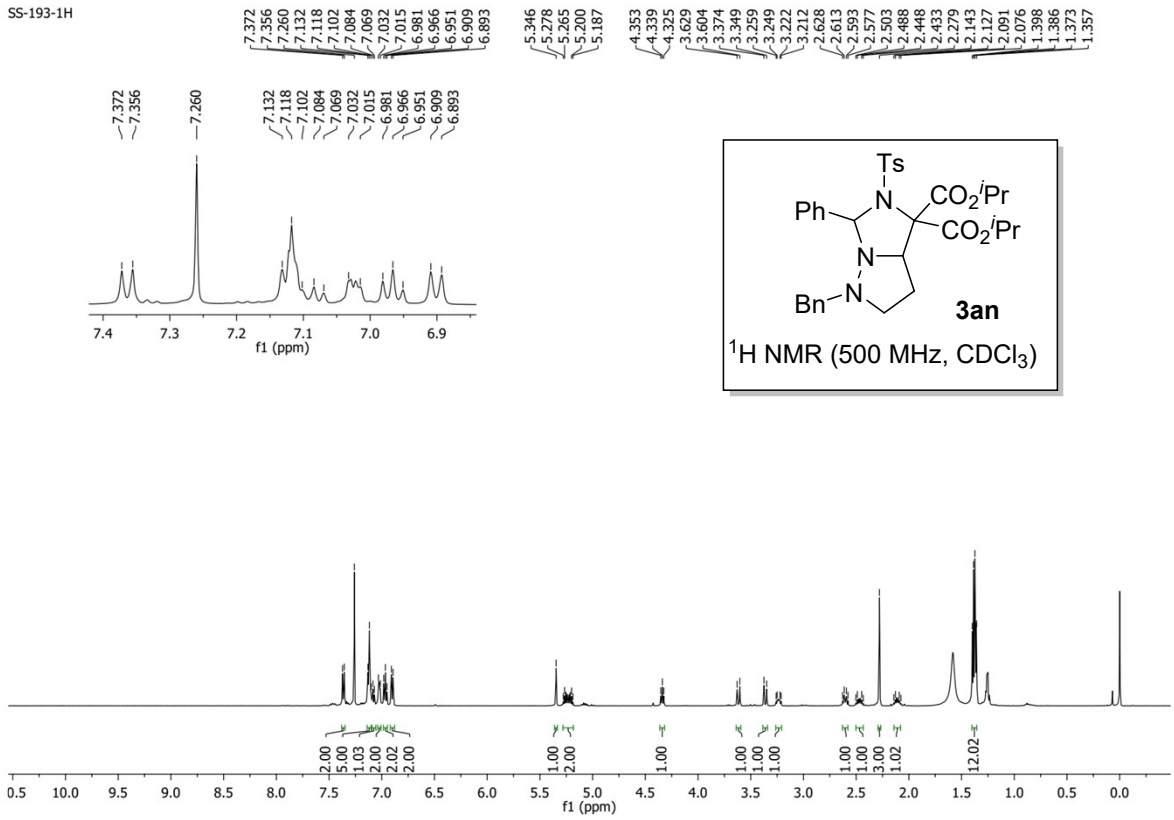

SS-202 13C
168.486
167.082
139.590
138.472
137.798
136.847
130.055
129.844
129.245
128.626
128.117
127.957
127.880
127.179
84.818
77.371
77.160
76.948
76.219
68.840
63.089
62.926
62.897
52.661
28.475
14.253
14.040
Cl
O
O
S
N
Ph
CO2Et
CO2Et
N
Bn
N
3al
13C NMR (150 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

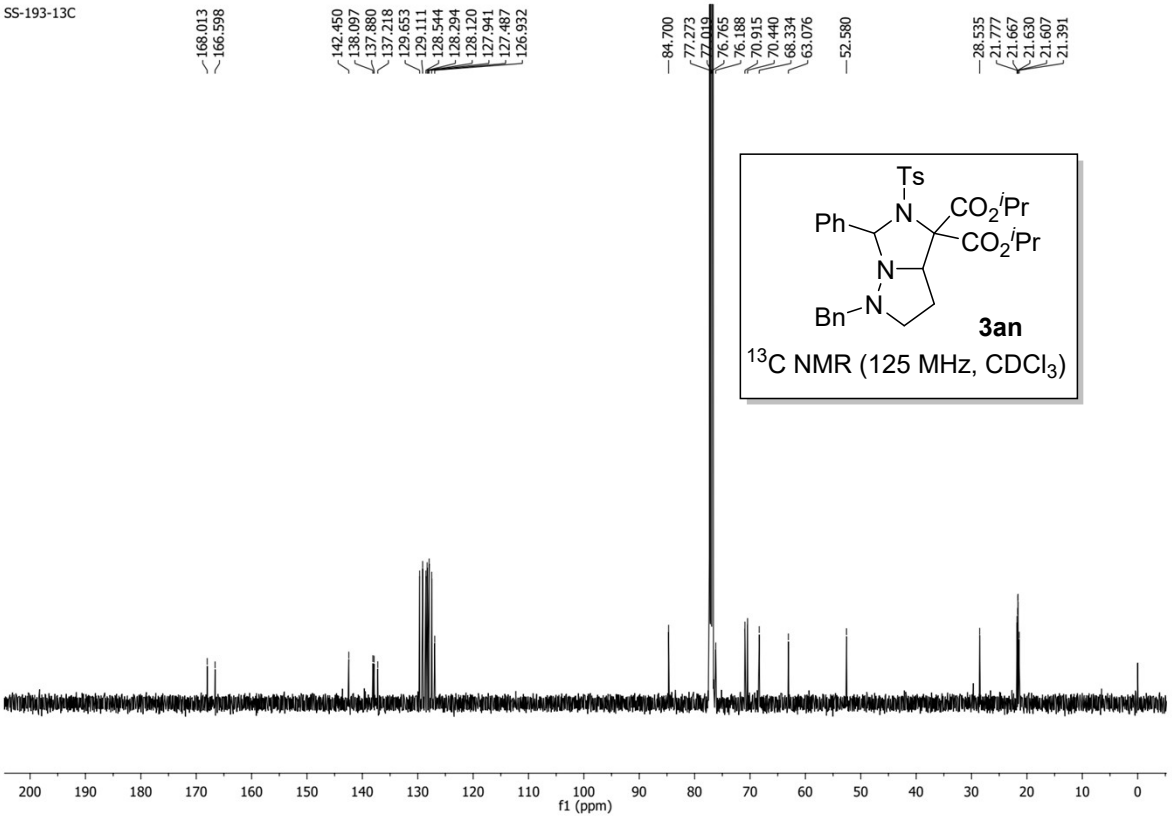

SS-179-A-1H
7.260
7.241
7.146
7.136
7.130
7.109
7.091
7.059
7.047
7.010
6.991
6.972
6.903
6.883
5.453
4.373
4.357
4.340
3.932
3.901
3.698
3.666
3.359
3.328
3.186
3.165
3.147
3.128
2.610
2.591
2.567
2.547
2.528
2.512
2.462
2.446
2.282
2.160
2.141
2.096
2.077
Ts
N
Ph
CO2Me
CO2Me
N
Bn
N
3am
1H NMR (400 MHz, CDCl3)
7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95 6.90 6.85
f1 (ppm)
2.03
5.06
1.00
2.00
2.00
2.01
1.00
1.00
6.00
1.00
1.00
1.01
1.00
1.02
3.00
1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

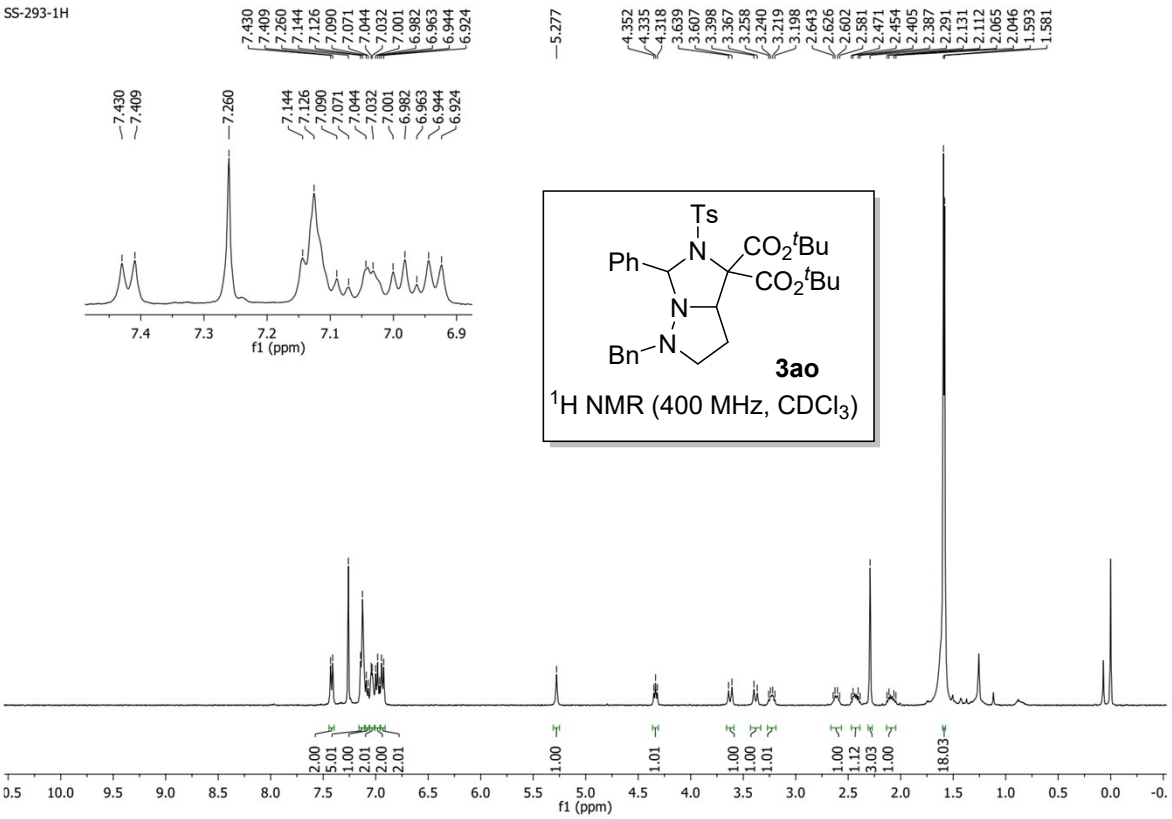
SS-179 13C

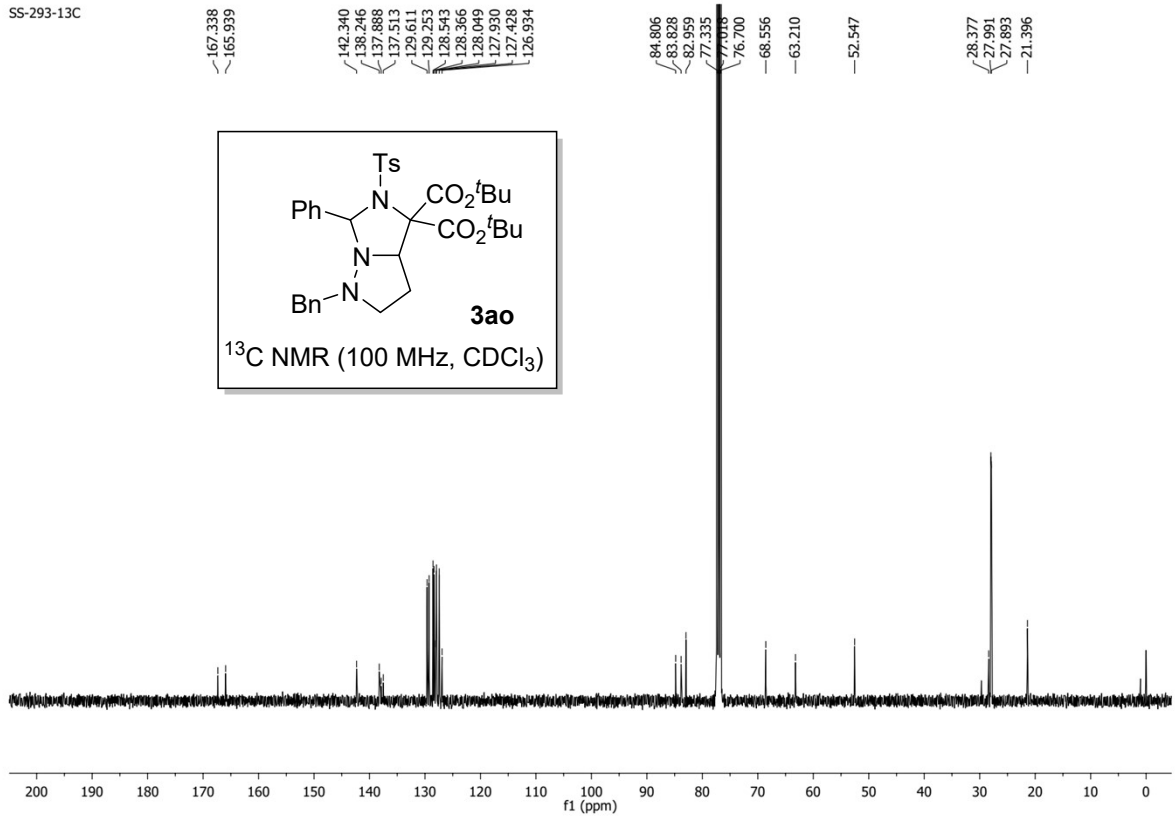


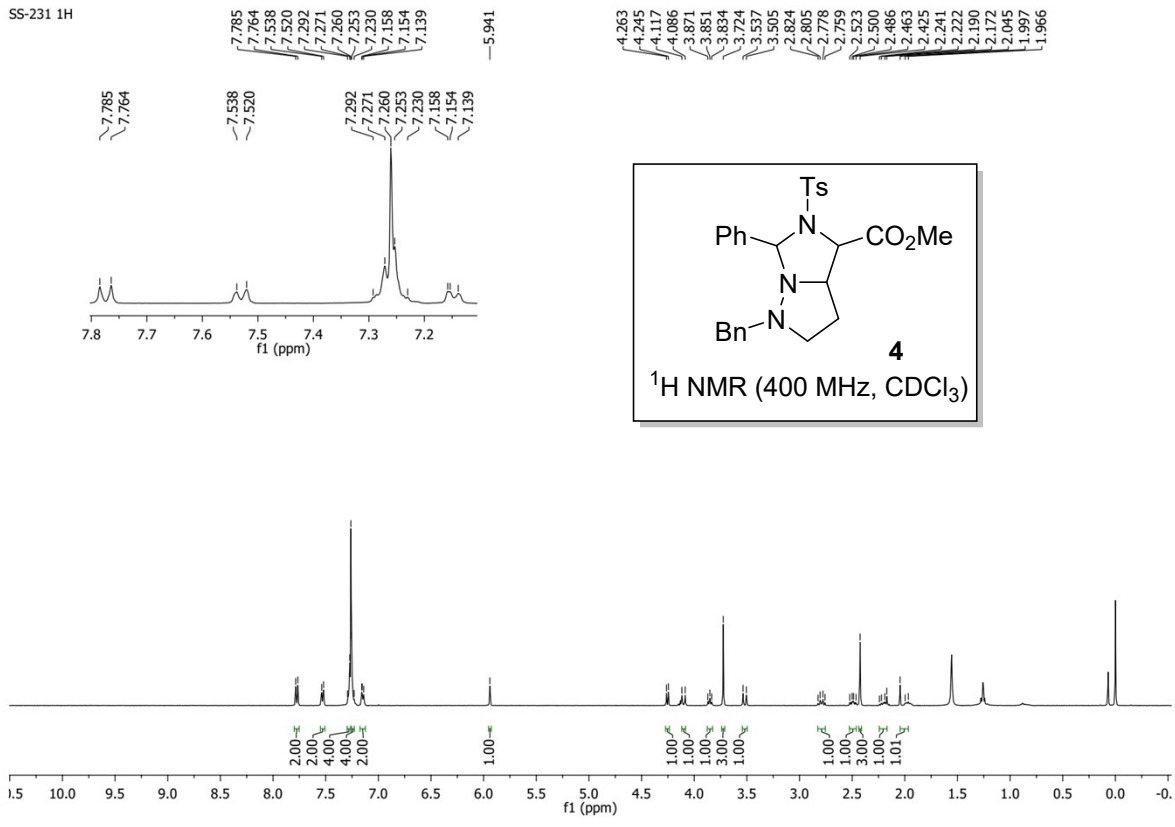

SS-193-1H

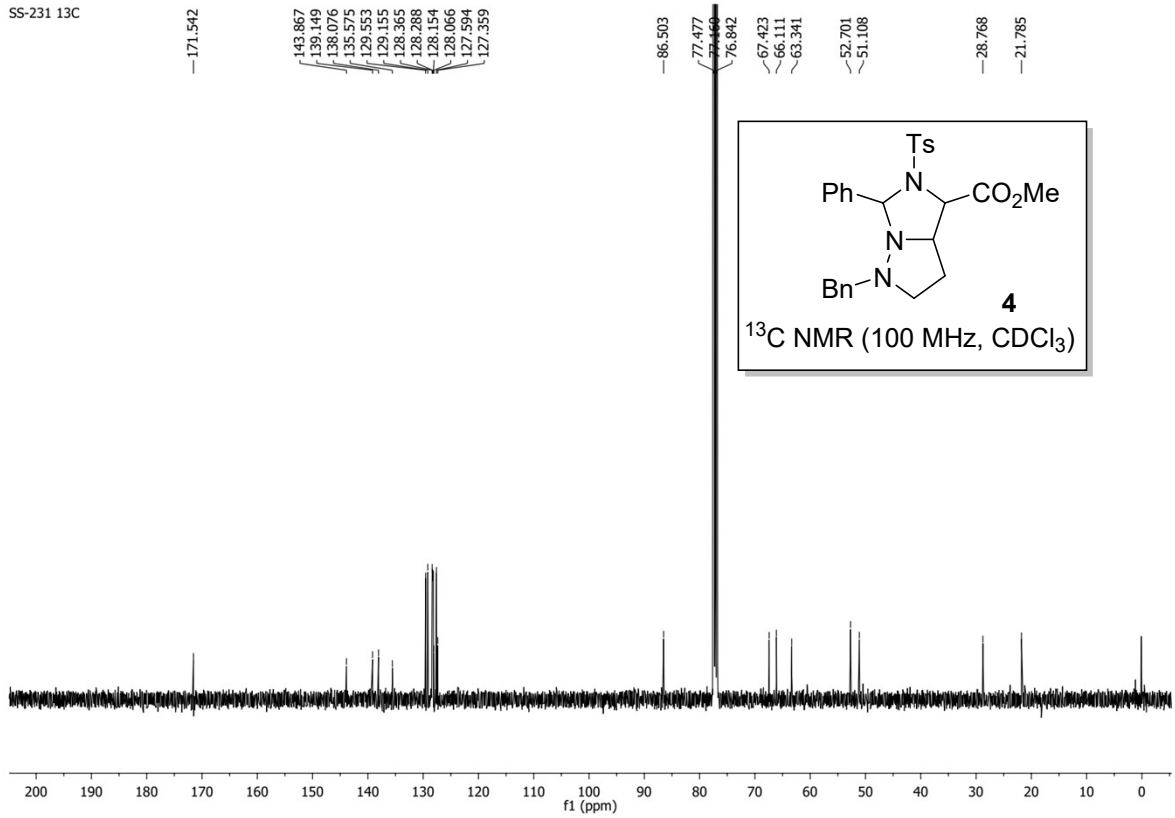


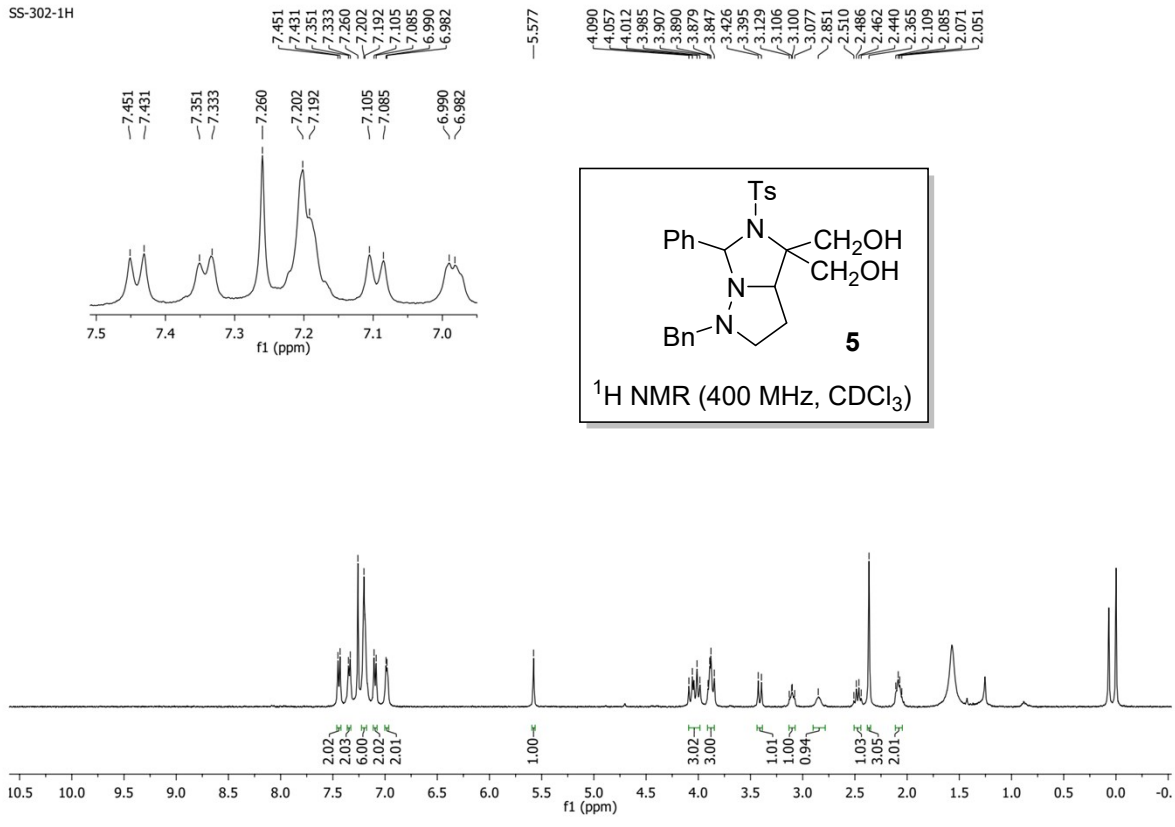

SS-193-13C
168.013
166.598
142.450
138.097
137.880
137.218
129.653
129.111
128.544
128.294
128.120
127.941
127.487
126.932
84.700
77.273
77.019
76.765
76.188
70.915
70.440
68.334
63.076
52.580
28.535
21.777
21.667
21.630
21.607
21.391
Ts
Ph
N
CO2iPr
CO2iPr
N
Bn
N
3an
13C NMR (125 MHz, CDCl3)
f1 (ppm)

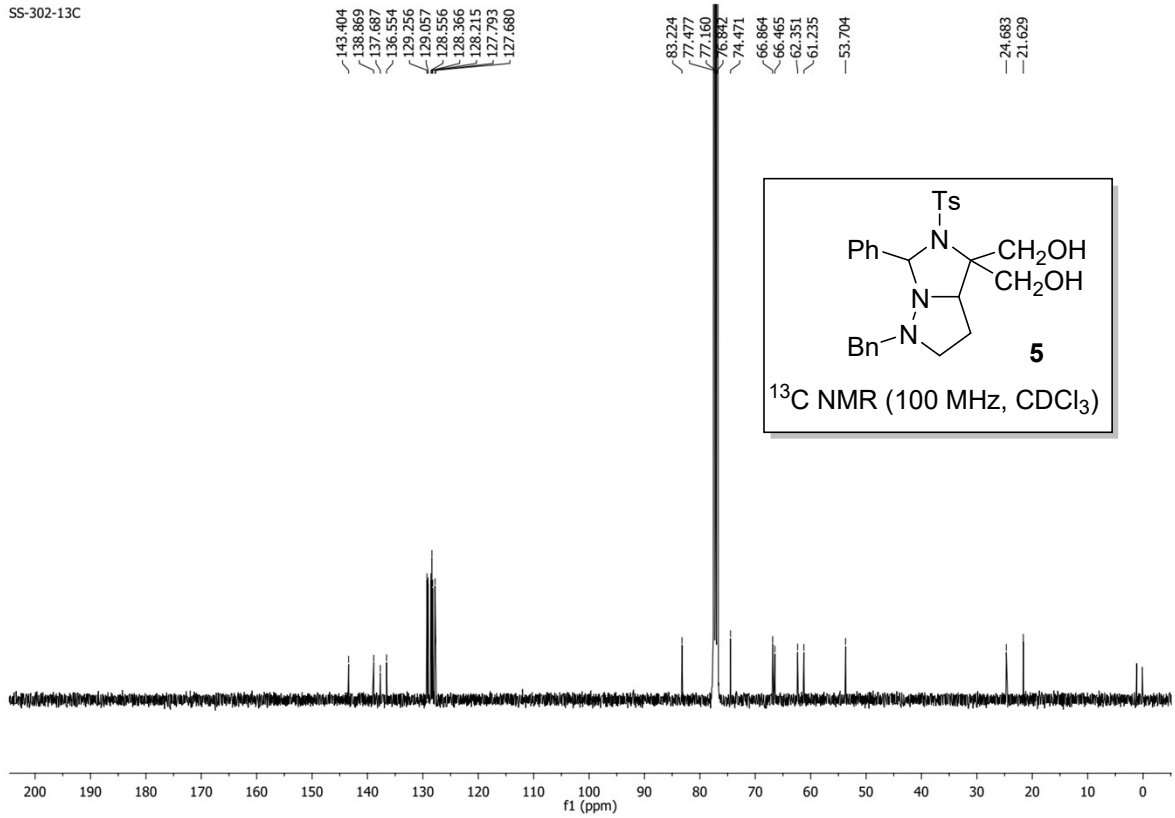

SS-293-1H
7.430
7.409
7.260
7.144
7.126
7.090
7.071
7.044
7.032
7.001
6.982
6.963
6.944
6.924
5.277
4.352
4.335
4.318
3.639
3.607
3.398
3.367
3.258
3.240
3.219
3.198
2.643
2.626
2.602
2.581
2.471
2.454
2.405
2.387
2.291
2.131
2.112
2.065
2.046
1.593
1.581
f1 (ppm)
Ts
Ph
N
CO2tBu
CO2tBu
N
Bn
N
3ao
1H NMR (400 MHz, CDCl3)
2.00
5.01
1.00
2.01
2.00
2.01
1.00
1.01
1.00
1.00
1.01
1.00
1.12
3.03
1.00
18.03
f1 (ppm)

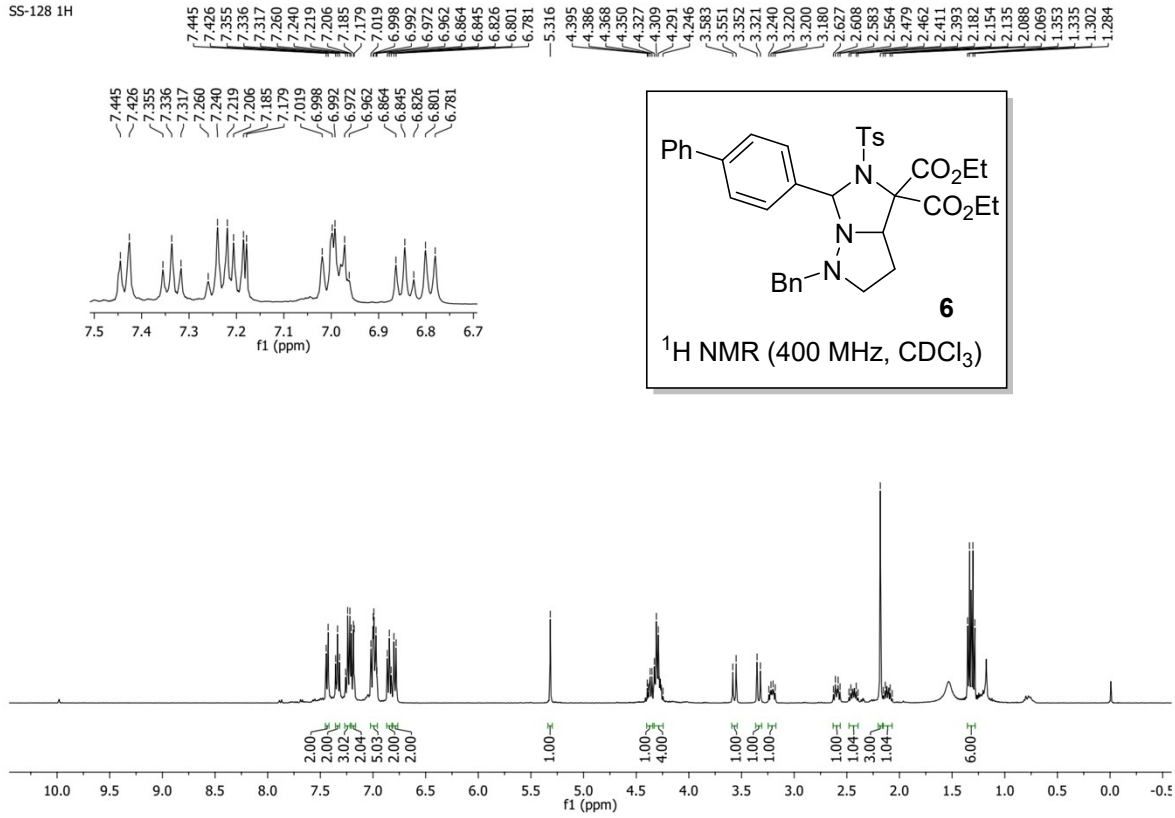

SS-293-13C
167.338
165.939
142.340
138.246
137.888
137.513
129.611
129.253
128.543
128.366
128.049
127.930
127.428
126.934
84.806
83.828
82.959
77.335
77.018
76.700
68.556
63.210
52.547
28.377
27.991
27.893
21.396
Ts
Ph
N
CO2tBu
CO2tBu
N
Bn
N
3ao
13C NMR (100 MHz, CDCl3)
f1 (ppm)

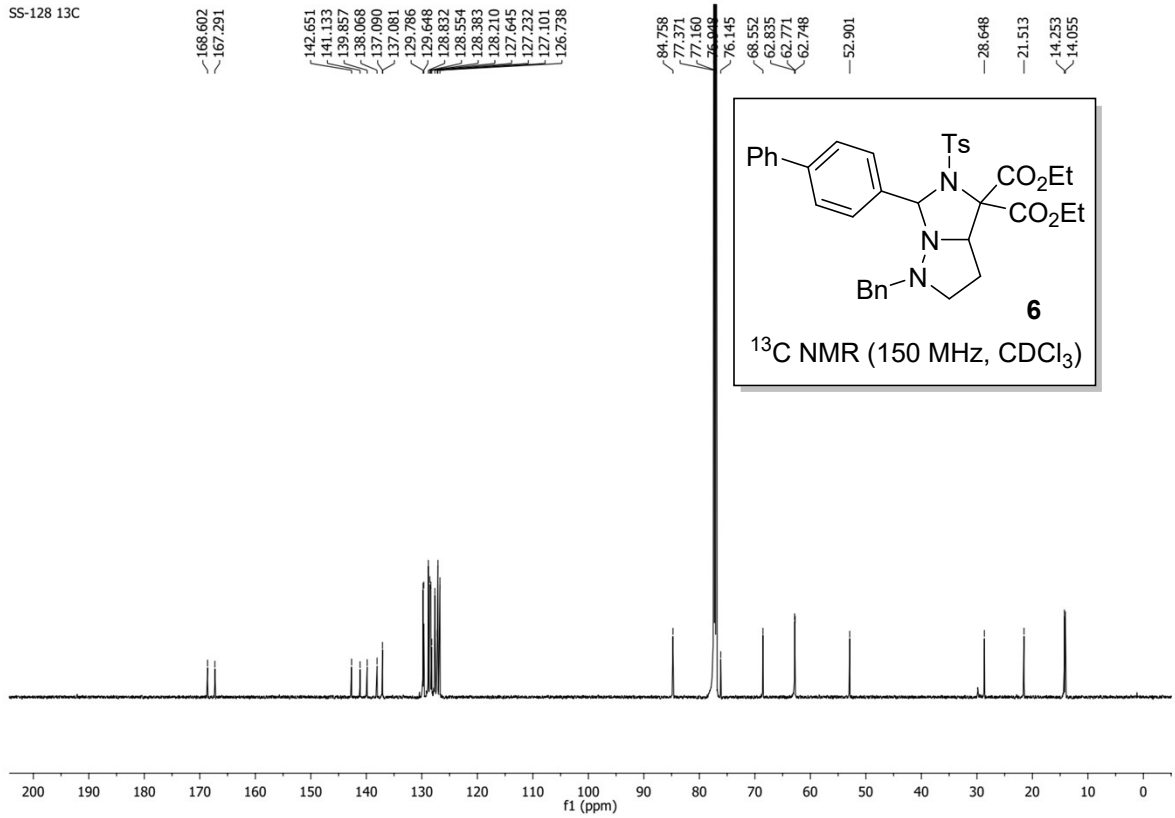

SS-231 1H
7.785
7.764
7.538
7.520
7.292
7.271
7.260
7.253
7.230
7.158
7.154
7.139
5.941
4.263
4.245
4.117
4.086
3.871
3.851
3.834
3.724
3.537
3.505
2.824
2.805
2.778
2.759
2.523
2.500
2.486
2.463
2.425
2.241
2.222
2.190
2.172
2.045
1.997
1.966
f1 (ppm)
Ts
Ph
N
CO2Me
N
Bn
N
4
1H NMR (400 MHz, CDCl3)
f1 (ppm)

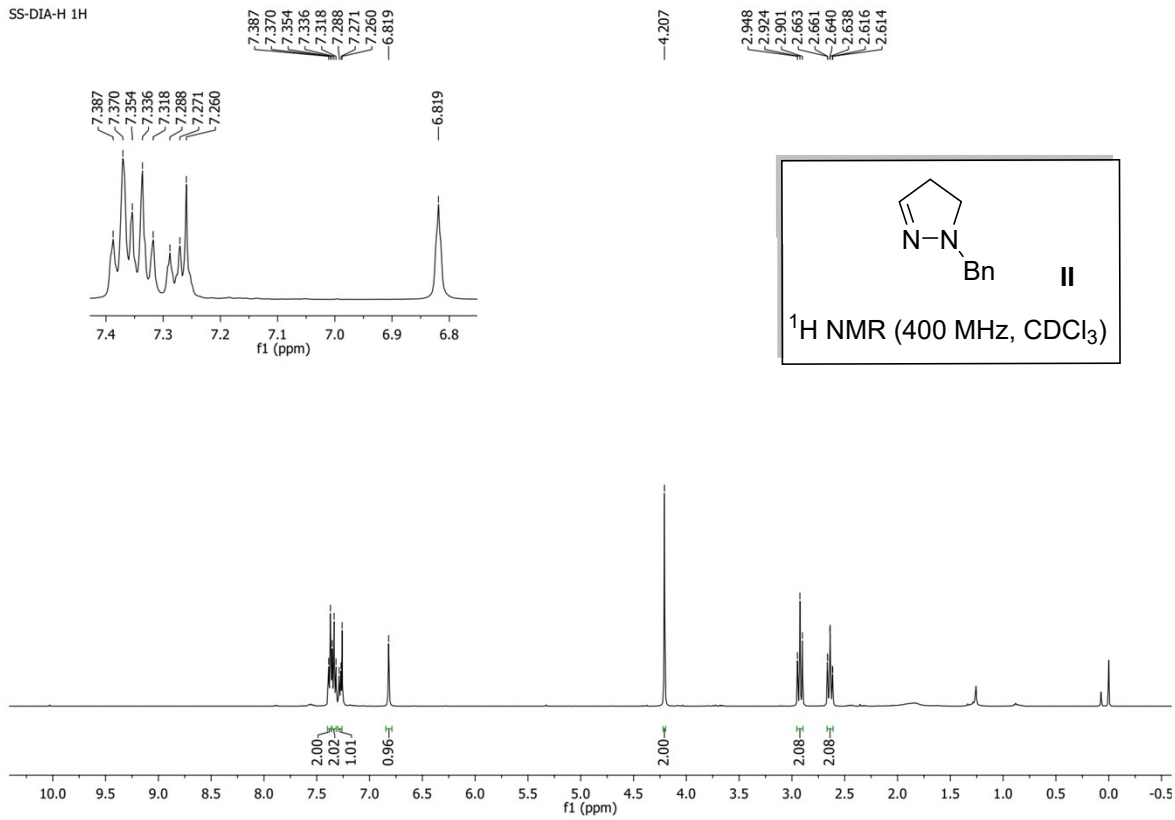

SS-231 13C
171.542
143.867
139.149
138.076
135.575
129.553
129.155
128.365
128.288
128.154
128.066
127.594
127.359
86.503
77.477
77.160
76.842
67.423
66.111
63.341
52.701
51.108
28.768
21.785
Ts
N
Ph
CO2Me
N
Bn
N
4
13C NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

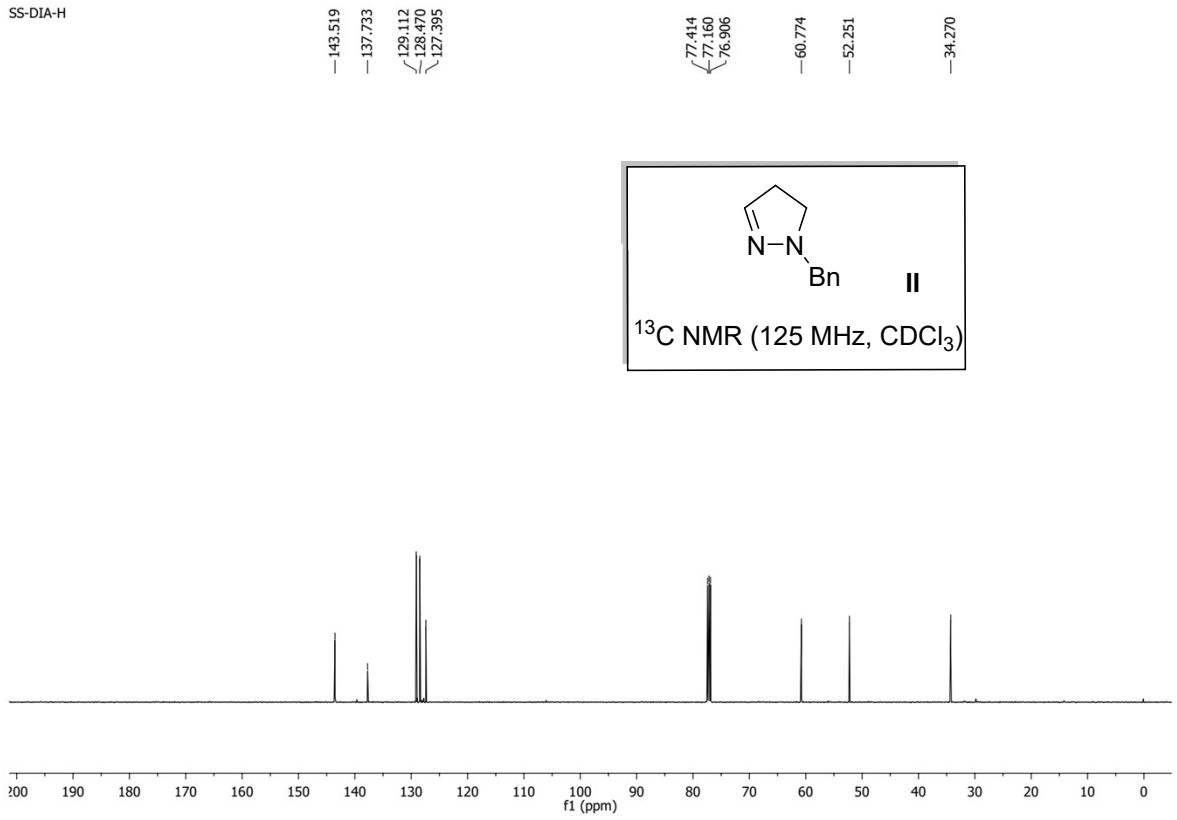

SS-302-1H
7.451
7.431
7.351
7.333
7.260
7.202
7.192
7.105
7.085
6.990
6.982
5.577
4.090
4.057
4.012
3.985
3.907
3.890
3.879
3.847
3.426
3.395
3.129
3.106
3.100
3.077
2.851
2.510
2.486
2.462
2.440
2.365
2.109
2.085
2.071
2.051
7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
Ts
N
Ph
CH2OH
CH2OH
N
Bn
N
5
1H NMR (400 MHz, CDCl3)
2.02
2.03
6.00
2.02
2.01
1.00
3.02
3.00
1.01
1.00
0.94
1.03
3.05
2.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)


SS-302-13C
143.404
138.869
137.687
136.554
129.256
129.057
128.556
128.366
128.215
127.793
127.680
83.224
77.477
77.160
76.842
74.471
66.864
66.465
62.351
61.235
53.704
24.683
21.629
Ts
N
Ph
CH2OH
CH2OH
N
Bn
N
5
13C NMR (100 MHz, CDCl3)
f1 (ppm)


SS-128 1H
7.445
7.426
7.355
7.336
7.317
7.260
7.240
7.219
7.206
7.185
7.179
7.019
6.998
6.992
6.972
6.962
6.864
6.845
6.826
6.801
6.781
5.316
4.395
4.386
4.368
4.350
4.327
4.309
4.291
4.246
3.583
3.551
3.352
3.321
3.240
3.220
3.200
3.180
2.627
2.608
2.583
2.564
2.479
2.462
2.411
2.393
2.182
2.154
2.135
2.088
2.069
1.353
1.335
1.302
1.284
f1 (ppm)
Ph
Ts
N
CO2Et
CO2Et
N
Bn
N
6
1H NMR (400 MHz, CDCl3)
2.00
2.00
3.02
2.04
5.03
2.00
2.00
1.00
1.00
4.00
1.00
1.00
1.00
1.00
1.04
3.00
1.04
6.00
f1 (ppm)


SS-128 13C
168.602
167.291
142.651
141.133
139.857
138.068
137.090
137.081
129.786
129.648
128.832
128.554
128.383
128.210
127.645
127.232
127.101
126.738
84.758
77.371
77.160
76.948
76.145
68.552
62.835
62.771
62.748
52.901
28.648
21.513
14.253
14.055
Ph
Ts
N
CO2Et
CO2Et
N
Bn
N
6
13C NMR (150 MHz, CDCl3)
f1 (ppm)


SS-DIA-H 1H
7.387
7.370
7.354
7.336
7.318
7.288
7.271
7.260
6.819
4.207
2.948
2.924
2.901
2.663
2.661
2.640
2.638
2.616
2.614
N–N
Bn
II
1H NMR (400 MHz, CDCl3)
2.00
2.02
1.01
0.96
2.00
2.08
2.08
f1 (ppm)


SS-DIA-H
143.519
137.733
129.112
128.470
127.395
77.414
77.160
76.906
60.774
52.251
34.270
N–N
Bn
II
$^{13}$C NMR (125 MHz, $CDCl_3$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)