Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Organocatalytic Asymmetric Ring-Opening of Aziridines

Marcio W. Paixão, Martin Nielsen, Christian Borch Jacobsen and Karl Anker Jørgensen*

Danish National Research Foundation: Center for Catalysis
Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark
e-mail: kaj@chem.au.dk

Supporting Information

Contents

General Methods …… page S2

Materials …..…..…….……. page S2

General Procedure for the Aziridine Ring-opening …...……... page S2

Data for Products **4** ..... page S3

Spectra .....……..…… page S6

General Methods. NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a Micromass LCT spectrometer using electrospray (ES^+) ionization techniques. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ dip. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD or Daicel Chiralcel OD columns). Racemic samples were prepared using BEMP or TBAI as the catalyst.

Materials. Analytical grade solvents and commercially available reagents were used as received. For flash chromatography (FC) silica gel was purchased from Fluka (Silica gel 60, 230-400 mesh). The catalyst **3c,**[1] nucleophiles **1a-h**[2] and aziridines **2a-c**[3] were synthesised according to literature procedures.

General Procedure for the Organocatalytic Aziridine Ring-opening:

To a vial equipped with a magnetic stirring bar was added the phase-transfer catalyst **3** (6 mol%, 0.006 mmol), nucleophile **1** (0.2 mmol) and aziridine **2** (0.1 mmol) in a 7:1 mixture of *o*-xylene and $CHCl_3$ (1.5 mL) and cooled to 2 ^{o}C when necessary. The reaction was started by addition of an aqueous solution of an appropriate base (0.4 mL, see Table 2 in the article). The reaction was stirred for an appropriate amount of time (see below) followed by removal of the aqueous phase and concentration of the organic phase. Purification by FC (EtOAc/hexane 1:9 to 3:7) afforded the pure product.

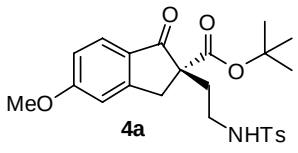
[1] See *e.g.*: a) B. Lygo and P. G. Wainwright, *Tetrahedron*, 1999, **55**, 6289. b) T. B. Poulsen, L. Bernadi, J. Alemán, J. Overgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 441.

[2] For the preparation of **1a** and **1b** see: a) J. Alemán, E. Reyes, B. Richter, J. Overgaard and K. A. Jørgensen, *Chem. Commun.*, 2007, 3921. For **1c**, **1d** and **1e** see: b) H. O. House and C. B. Hudson, *J. Org. Chem.*, 1970, **35**, 647. For **1f** see: c) L. A. Carpino, *J. Am. Chem. Soc.*, 1960, **82**, 2725 and according to reference 1b. Subsequent Bu_2SnO catalyzed transesterfication to the *t*-butyl ester was done as described by: d) M. Nakajima, S.Yamamoto, Y. Yamaguchi, S. Nakamura, S. Hashimoto, *Tetrahedron*, 2003, **59**, 7307 when necessary. **1g** and **1h** was prepared from the commercially available methyl esters as described in reference 2d.

[3] A. L. Braga, M. W. Paixão, D. S. Lüdtke, C. C. Silveira and O. E. D. Rodrigues, *Org. Lett.*, 2003, **5**, 2635.

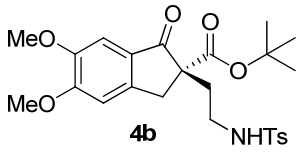
Data for Compounds 4:

(*S*)-*tert*-Butyl 2-(2-(4-methylphenylsulfonamido)ethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4a):



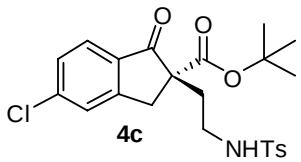
Prepared according to the general procedure (reaction time 12 h), as white crystals. Ee = 97%. Isolated yield = 87%. ^{1}H NMR ($CDCl_3$) δ 7.63 (d, *J* = 8.11 Hz, 2H), 7.59 (d, *J* = 8.49 Hz, 1H), 7.21 (d, *J* = 6.56 Hz, 2H), 6.84 (d, *J* = 8.39 Hz, 2H), 4.81 (t, *J* = 6.0 Hz, 1H), 3.83 (s, 3H), 3.46 (d, *J* = 17.3 Hz, 1H), 3.04-2.96 (m, 2H), 2.91 (d, *J* = 17.3 Hz, 1H), 2.33 (s, 3H), 2.15-2.09 (m, 1H), 1.92-1.87 (m, 1H), 1,28 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 200.7, 170.3, 166.1, 156.0, 143.5, 137.0, 129.9 (2), 128.1, 127.2 (2), 126.7, 116.2, 109.5, 82.5, 60.3, 55.9, 40.0, 37.4, 34.2, 27.9 (3), 21.7. HRMS calc.:$C_{24}H_{29}NO_6SNa^+$ 482.1603; found: 482.1607. The ee was determined by HPLC using two Chiralpak OD columns [hexane/*i*PrOH (85:15)]; flow rate 0.5 mL/min; τ_{major} = 82.8 min, τ_{minor} = 93.1 min (97% ee). $[\alpha]_D^{rt}$ +12.2^o (c = 2.0, CH_2Cl_2).

(*S*)-*tert*-Butyl 5,6-dimethoxy-2-(2-(4-methylphenylsulfonamido)ethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4b):



Prepared according to the general procedure (reaction time 12 h), as white crystals. Ee = 90%. Isolated yield = 86%. ^{1}H NMR ($CDCl_3$) δ 7.63 (d, *J* = 8.25 Hz, 2H), 7.21 (d, *J* = 7.26 Hz, 2H), 7.06 (s, 1H), 6.79 (s, 1H), 4.78 (t, *J* = 6.0 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.42 (d, *J* = 17.4 Hz, 1H), 3.09-2.92 (m, 2H), 2.88 (d, *J* = 17.5 Hz, 1H), 2.34 (s, 3H), 2.21-2.05 (m, 1H), 1.99-1.84 (m, 1H), 1,27 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 213.2, 170.4, 156.3, 149.9, 148.5, 143.5, 137.0, 129.9 (2), 127.6, 127.2 (2), 107.3, 105.1, 82.5, 60.3, 56.5, 56.3, 40.0, 37.3, 34.3, 27.9 (3), 21.7. HRMS calc.:$C_{25}H_{31}NO_7SNa^+$ 512.1719; found: 512.1710. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{minor} = 37.4 min, τ_{major} = 50.2 min (90% ee). $[\alpha]_D^{rt}$ +36.1^o (c = 0.1, CH_2Cl_2)

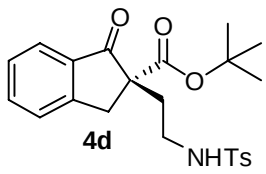
(*S*)-*tert*-Butyl 5-chloro-2-(2-(4-methylphenylsulfonamido)ethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4c):



Prepared according to the general procedure (reaction time 12 h), as yellow oil. Ee = 93%. Isolated yield = 83%. ^{1}H NMR ($CDCl_3$) δ 7.06 (t, *J* = 7.88 Hz, 2H), 7.38 (s, 1H), 7.30 (d, *J* = 8.18 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 3H), 4.65 (bs, 1H), 3.47 (d, *J* = 17.2 Hz, 1H), 3.09-2.87 (m, 3H), 2.34 (s, 3H), 2.22-2.08 (m, 1H), 1.98-1.83 (m, 1H), 1,28 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 201.3, 169.7, 154.3, 143.6, 142.2, 136.9, 133.5, 129.9 (2), 128.9, 127.2 (2), 126.7, 126.1, 83.2, 60.3, 35.9, 37,0, 34.0, 27.9 (3), 21.7. HRMS calc.:$C_{23}H_{26}ClNO_7SNa^+$ 486.1118; found: 486.1122. The ee was determined by HPLC using a Chiralpak

AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{minor} = 23.6 min, τ_{major} = 33.3 min (93% ee). $[\alpha]_D^{rt}$ +58^o (c = 1.0, CH_2Cl_2).

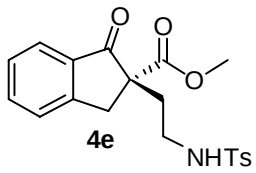
(*S*)-*tert*-Butyl 2-(2-(4-methylphenylsulfonamido)ethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4d):



4d

Prepared according to the general procedure (reaction time 12 h), as colourless oil. Ee = 87%. Isolated yield 84%. ^{1}H NMR ($CDCl_3$) δ 7.64 (dd, J^1 = 8.0, J^2 = 15.7 Hz, 3H), 7.56 (t, *J* = 7.4, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.65 (t, *J* = 6.0 Hz, 1H), 3.51 (d, *J* = 17.2 Hz, 1H), 3.13-2.81 (m, 3H), 2.34 (s, 3H), 2.21-2.02 (m, 1H), 2.00-1.82 (m, 1H), 1,28 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 202.7, 170.1, 152.9, 143.3, 137.2, 135.6, 135.0, 129.9 (2), 128.0, 127.2 (2), 126.5, 125.0, 82.7, 60.9, 40.1, 35.5, 34.1, 27.9 (3), 21.7. HRMS calc.:$C_{23}H_{27}NO_5SNa^+$ 452.1508; found: 452.1506. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{minor} = 23.4 min, τ_{major} = 29.9 min (87% ee). $[\alpha]_D^{rt}$ +7.0^o (c = 2.0, CH_2Cl_2).

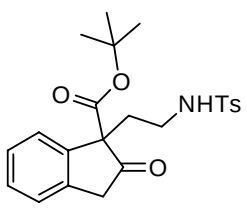
(*S*)-Methyl 2-(2-(4-methylphenylsulfonamido)ethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (4e):



4e

Prepared according to the general procedure (reaction time 12 h), as colourless oil. Ee = 70%. Isolated yield 89%. ^{1}H NMR ($CDCl_3$) δ 7.72-7.52 (m, 3H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 4.65 (t, *J* = 6.0 Hz, 1H), 3.58 (bs, 3H), 3.10-2.91 (m, 4H), 2.34 (bs, 3H), 2.27-2.14 (m, 1H), 2.04-1.87 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 202.2, 171.6, 152.9, 143.6, 137.0, 135.9, 134.8, 129.9 (2), 128.2, 127.2 (2), 126.6, 125.2, 59.1, 53.2, 39.9, 37.3, 34.6, 21.7. HRMS calc.:$C_{20}H_{21}NO_5SNa^+$ 410.1038; found: 452.1025. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 41.0 min, τ_{minor} = 50.0 min (70% ee). $[\alpha]_D^{rt}$ +26.8^o (c = 1.0, CH_2Cl_2).

***tert*-Butyl 1-(2-(4-methylphenylsulfonamido)ethyl)-2-oxo-2,3-dihydro-1H-indene-1-carboxylate (4g):**

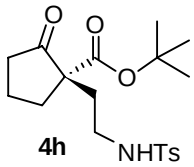


4g

Prepared according to the general procedure (reaction time 12 h), as colourless oil. Ee = 76%. Isolated yield = 74%. ^{1}H NMR ($CDCl_3$) δ 7.2 (d, *J* = 8.2 Hz, 2H), 7.37-6.98 (m, 6H), 4.26 (t, *J* = 6 Hz, 1H), 3.66 (d, *J* = 22.5 Hz, 1H), 3.46 (d, *J* = 22.5 Hz, 1H), 2.86-2.64 (m, 2H), 2.42-2.27 (m, 4H), 2.26 – 2.19 (m, 1H), 1.22 (s, 9H) . ^{13}C NMR ($CDCl_3$) δ 213.2, 169.0, 143.6, 139.9, 137.6, 136.7, 129.8 (2), 128.9, 128.1, 127.2 (2), 125.5, 123.8, 83.0, 64.8, 43.5, 39.5, 32.8, 28.0, 27.8 (3), 21.7. HRMS calc.:$C_{23}H_{27}NO_5SNa^+$

452.1508; found: 452.1512.The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 17.3 min, τ_{minor} = 18.3 min (76% ee). $[\alpha]_D^{rt}$ -4.8^o (c = 0.6, CH_2Cl_2).

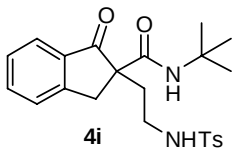
(*S*)-*tert*-Butyl 1-(2-(4-methylphenylsulfonamido)ethyl)-2-oxocyclopentanecarboxylate (4h):



4h

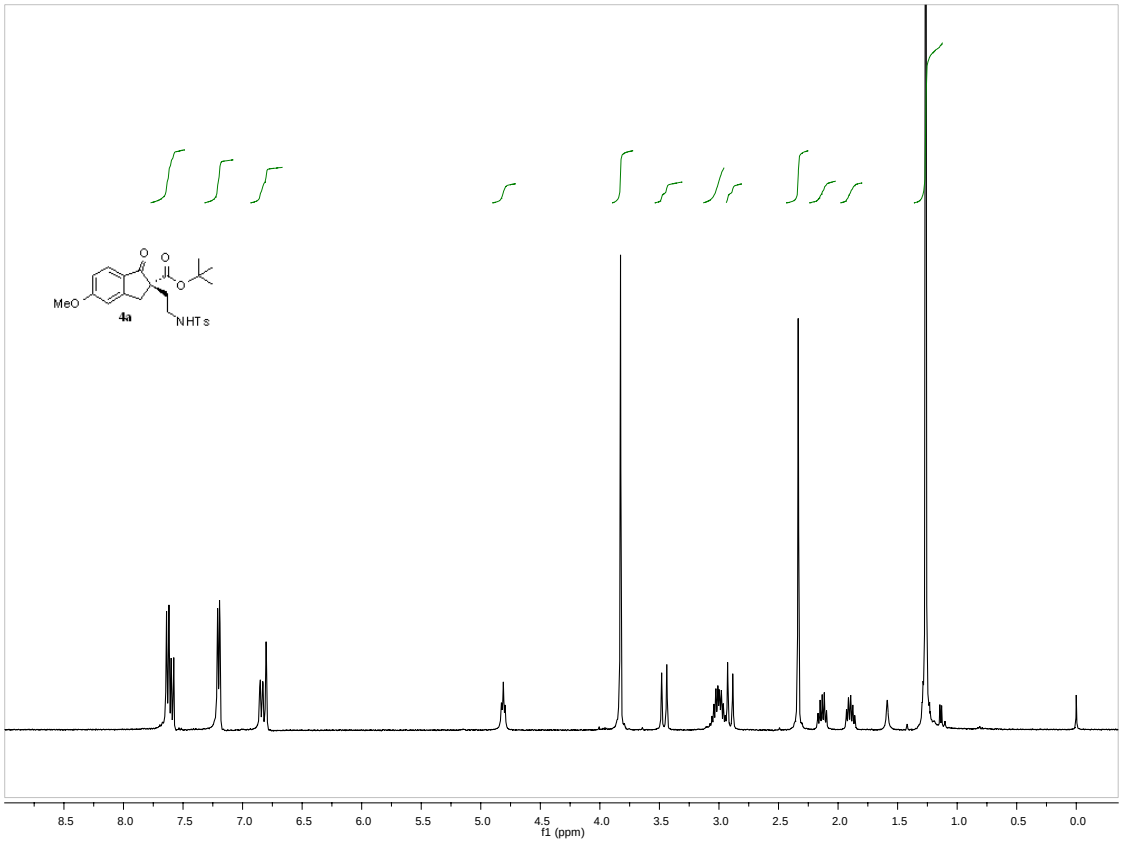
Prepared according to the general procedure (0.5 mL of o-xylene/$CHCl_3$ (7:1) used as solvent, reaction time 72 h) as colourless oil. Ee = 77%. Isolated yield = 53%. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.86 (t, *J* = 6.0 Hz, 1H), 3.06 – 3.00 (m, 2H), 2.45 – 2.34 (m, 2H), 2.42 (s, 3H), 2.30 – 2.21 (m, 1H), 2.04 – 1.76 (m, 5H), 1.39 (s, 9H) . ^{13}C NMR ($CDCl_3$) δ 215.6, 170.5, 143.3, 136.7, 129.8 (2C), 127.1 (2C), 82.6, 59.6, 39.6, 37.6, 33.8, 32.7, 27.8 (3C), 21.5, 19.6. HRMS calc.: $C_{19}H_{27}NO_5SNa^+$ 404.1502; found: 404.1516. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (92:8)]; flow rate 1.0 mL/min; τ_{minor} = 66.6 min, τ_{major} = 74.1 min (77% ee). $[\alpha]_D^{rt}$ +1.2^o (c = 1.0, CH_2Cl_2).

***N*-*tert*-Butyl-2-(2-(4-methylphenylsulfonamido)ethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (4i):**

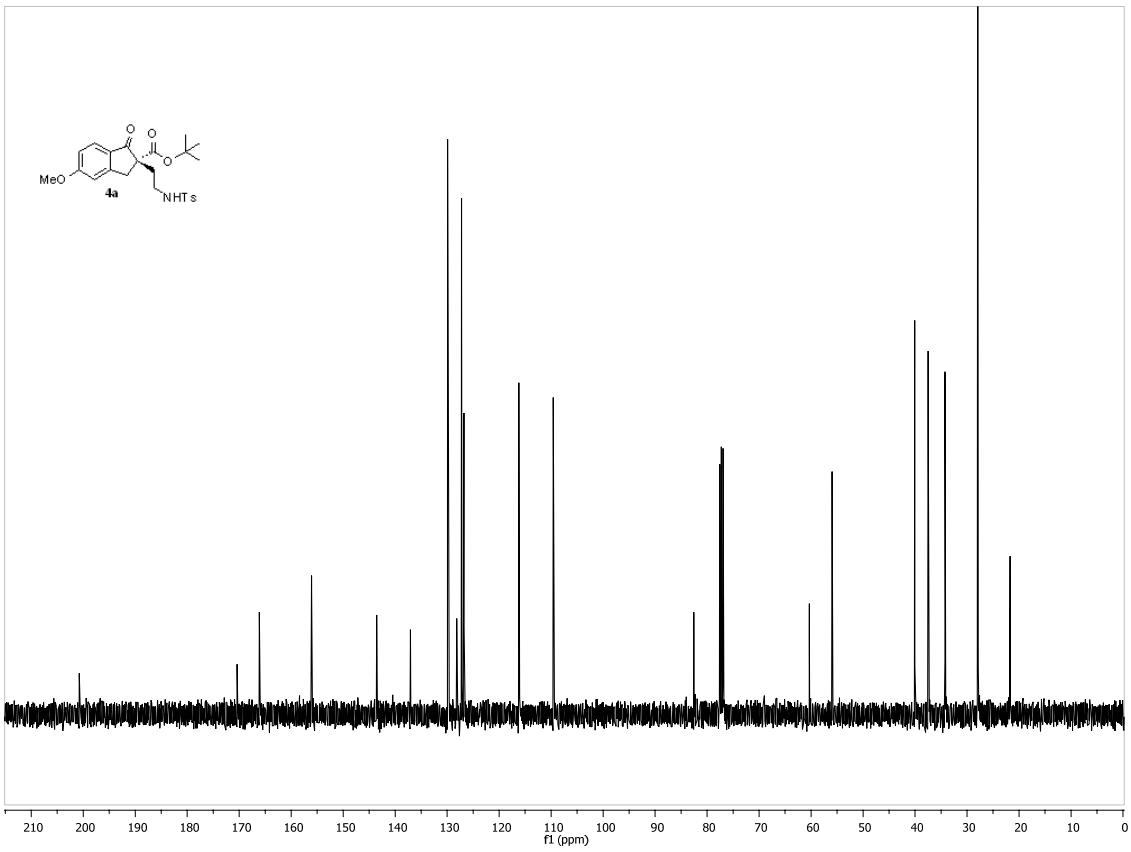


4i

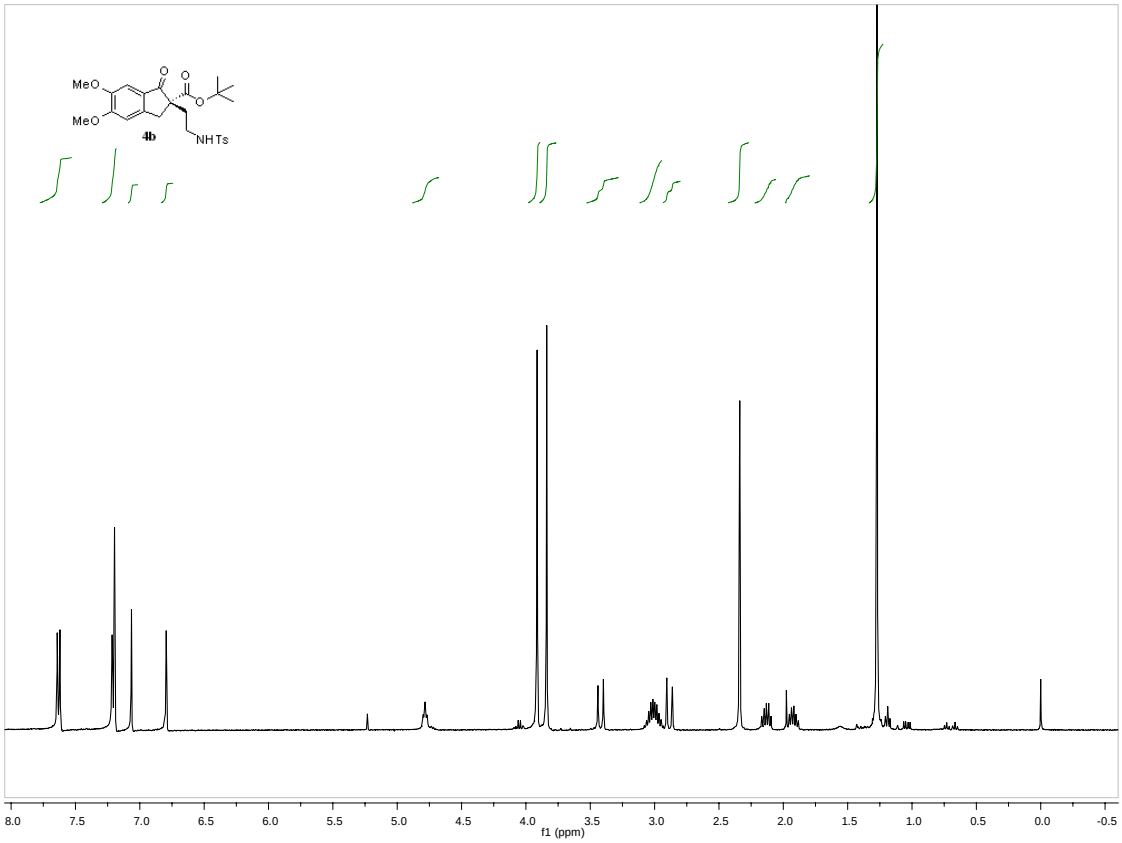
Prepared according to the general procedure (reaction time 20 h) as white crystals. Ee = 23%. Isolated yield = 82%. ^{1}H NMR ($CDCl_3$) δ 7.77 – 7.70 (m, 3H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.07 (s, 1H), 4.94 (s, 1H), 3.91 (d, *J* = 18 Hz, 1H), 3.16 – 2.95 (m, 3H), 2.41 (s, 3H), 2.14 – 2.07 (m, 1H), 1.93 – 1.86 (m, 1H), 1.28 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 207.3, 168.0, 153.3, 143.4, 136.7, 136.3, 134.3, 129.7 (2C), 127.8, 127.0 (2C), 126.7, 124.6, 59.5, 51.4, 40.3, 39.5, 36.3, 28.4 (3C), 21.5. HRMS calc.: $C_{23}H_{28}N_2O_4SNa^+$ 451.1662; found: 451.1647. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (70:30)]; flow rate 1.0 mL/min; τ_{major} = 10.1 min, τ_{minor} = 20.3 min (23% ee). $[\alpha]_D^{rt}$ -5.8^o (c = 0.12, CH_2Cl_2).



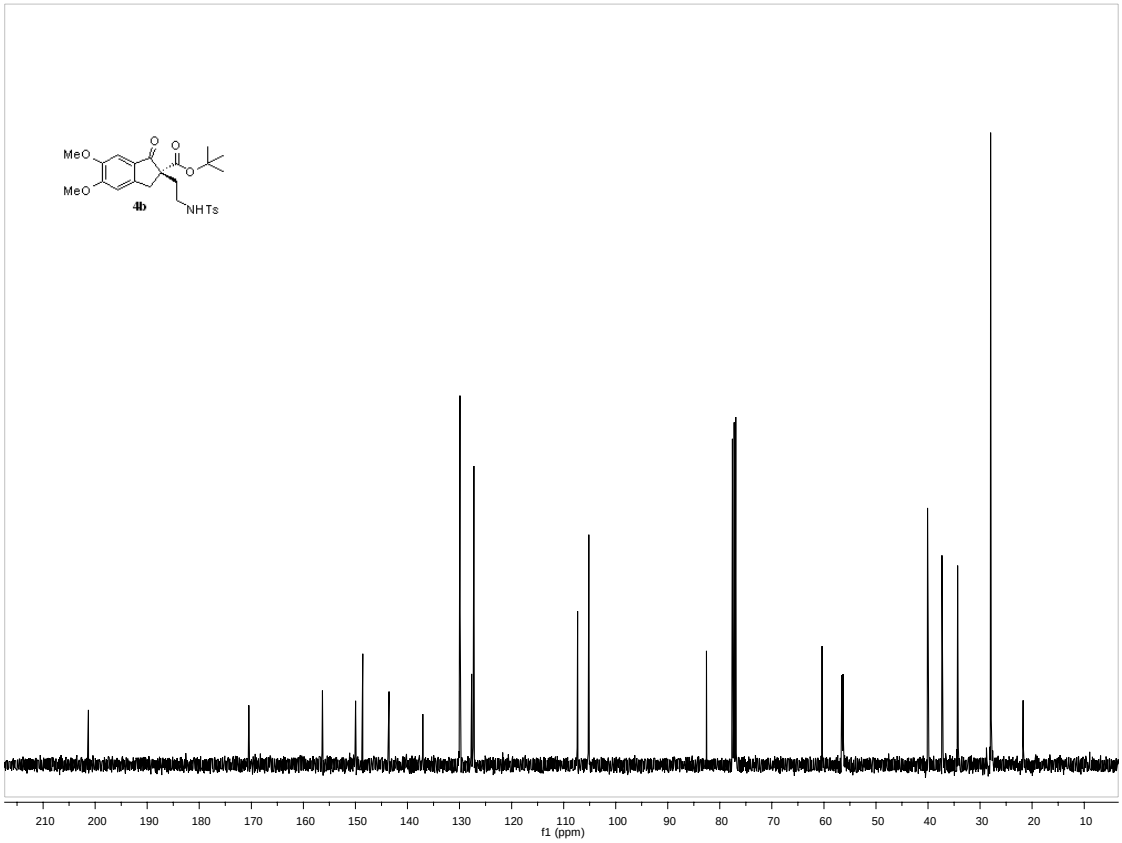
^{1}H NMR (400MHZ, $CDCl_3$) Spectrum of **4a**



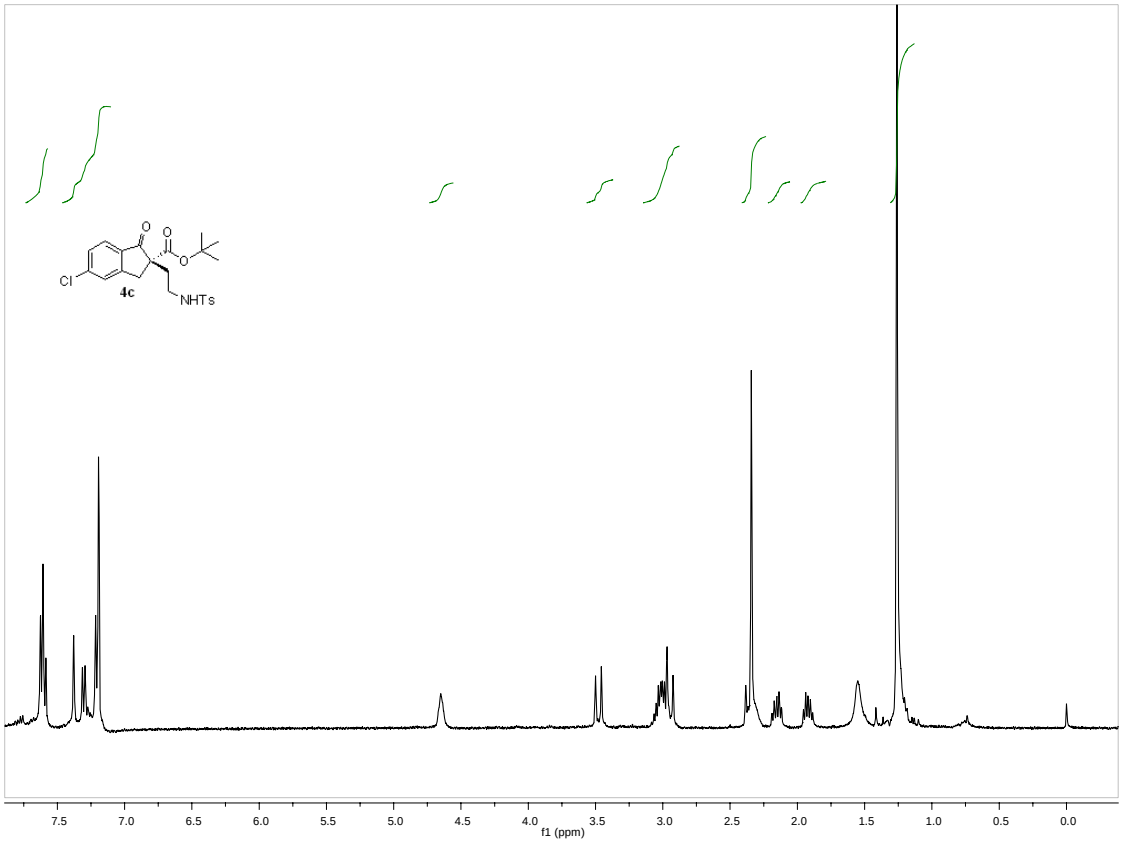
^{13}C NMR (100MHZ, $CDCl_3$) Spectrum of **4a**



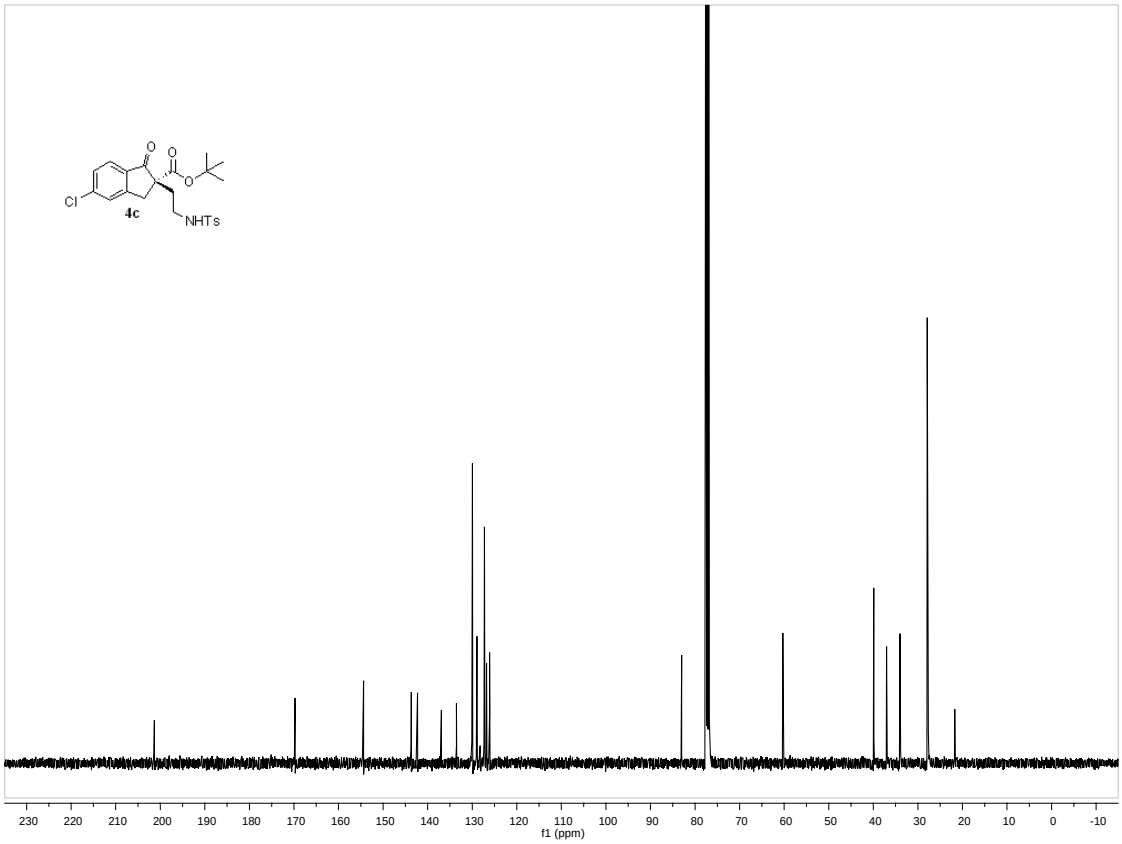
^{1}H NMR (400MHZ, $CDCl_3$) Spectrum of **4b**



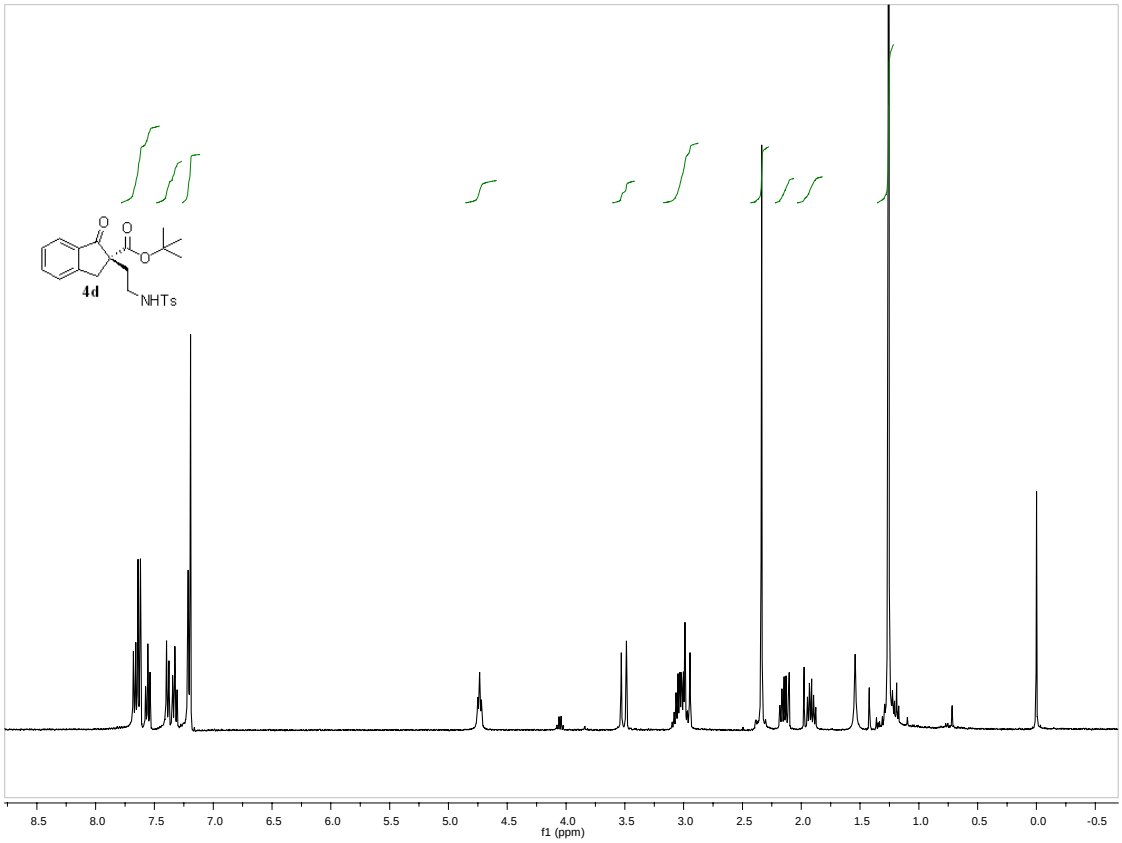
^{13}C NMR (100MHZ, $CDCl_3$) Spectrum of **4b**



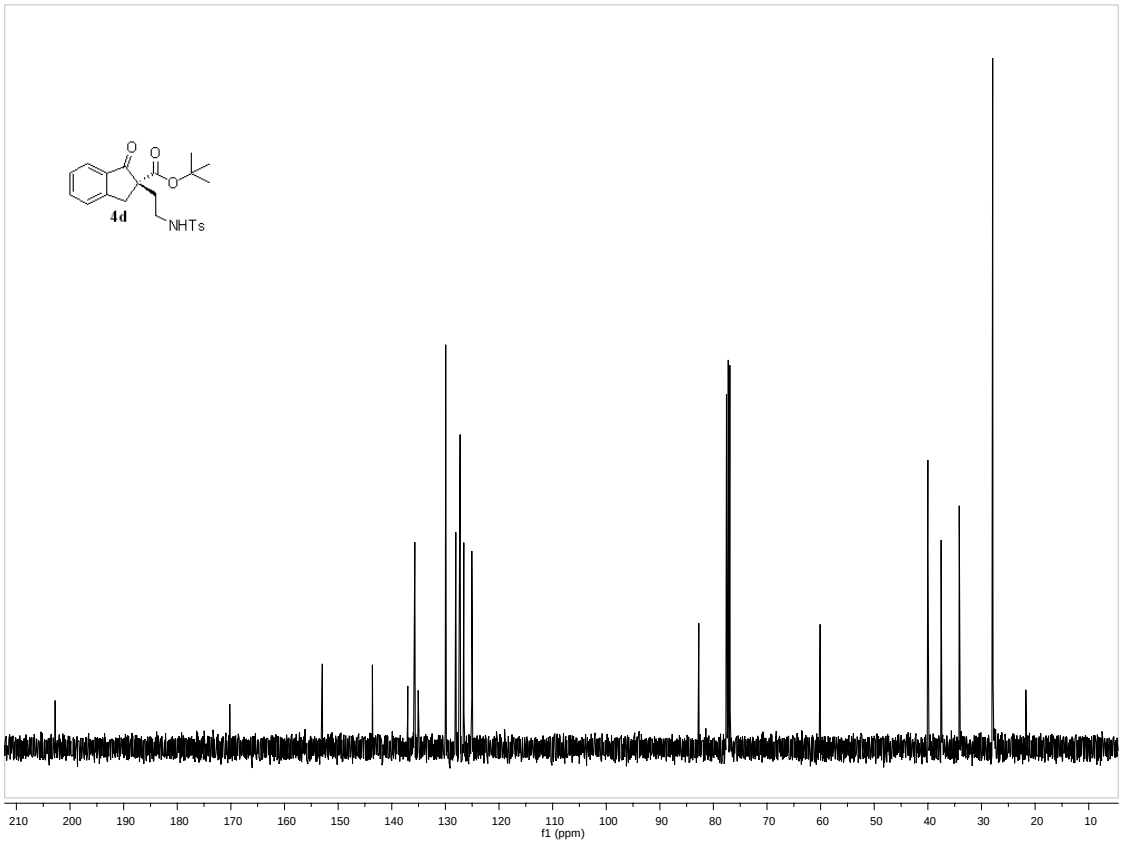
^{1}H NMR (400MHZ, $CDCl_3$) Spectrum of **4c**



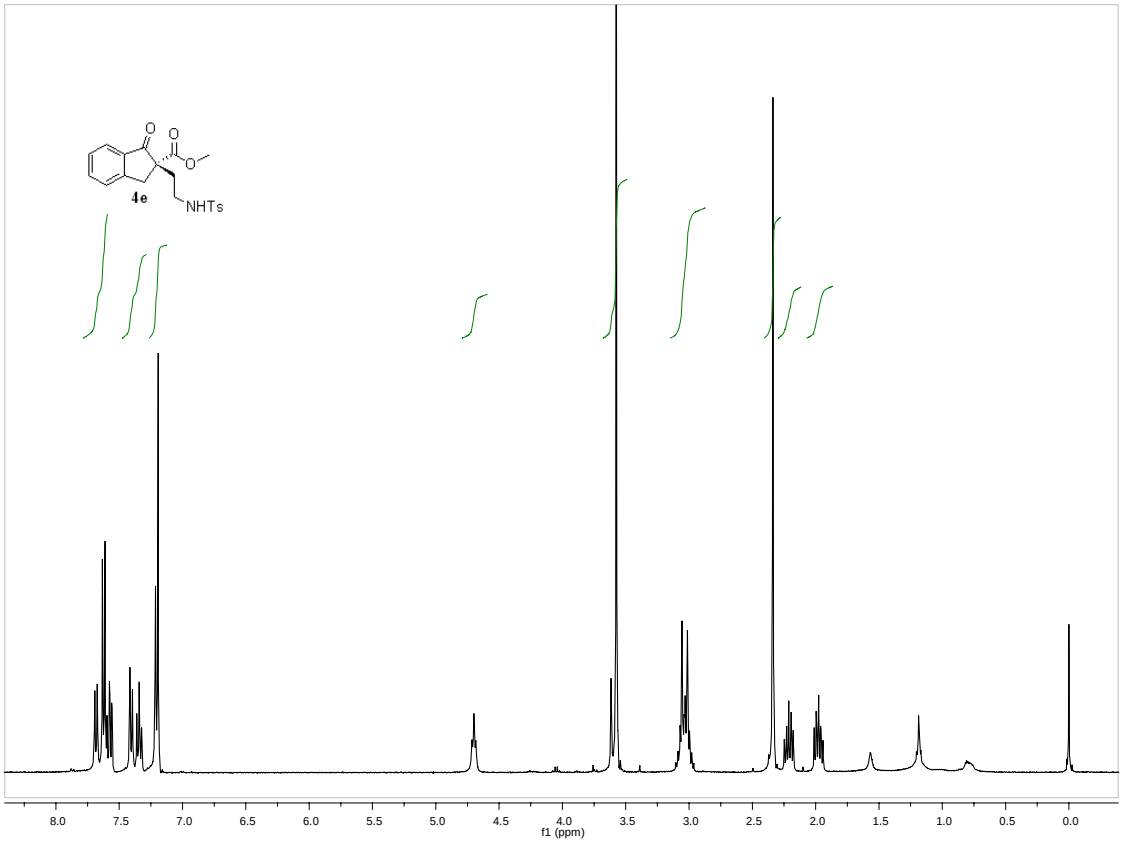
^{13}C NMR (100MHZ, $CDCl_3$) Spectrum of **4c**



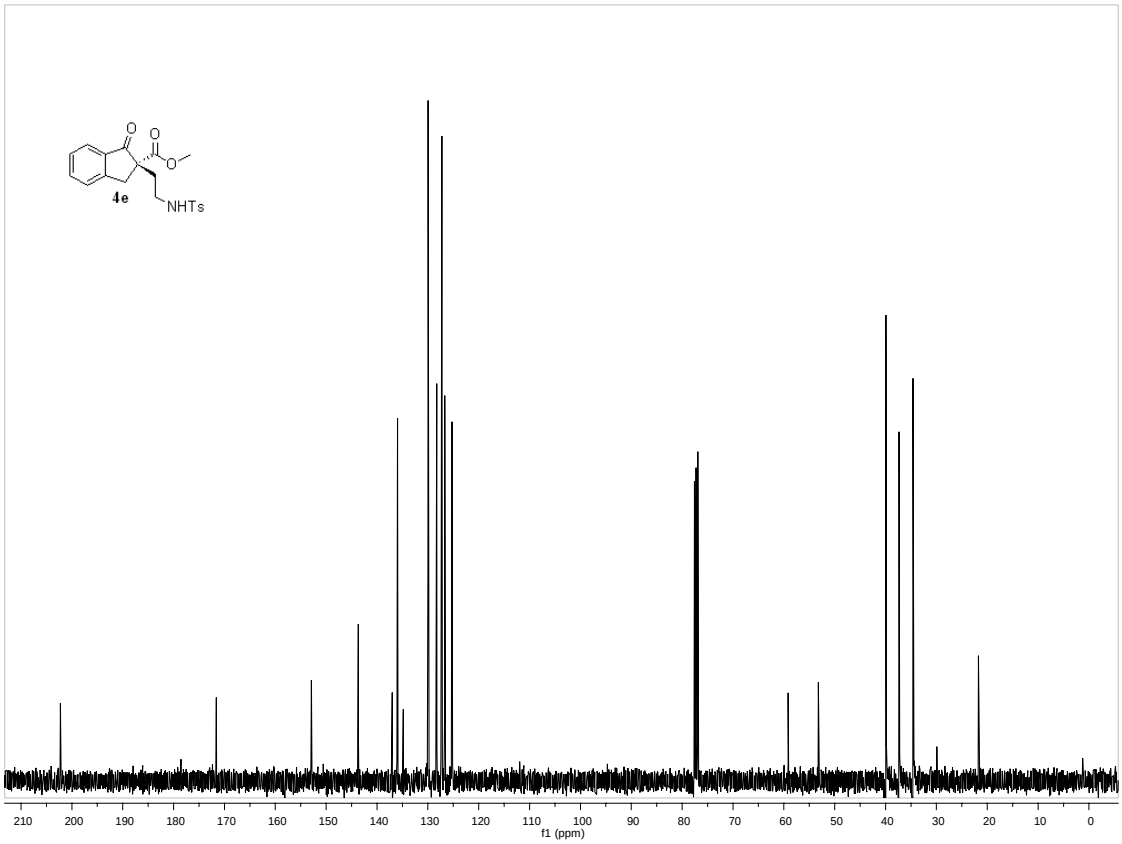
^{1}H NMR (400MHZ, $CDCl_3$) Spectrum of **4d**



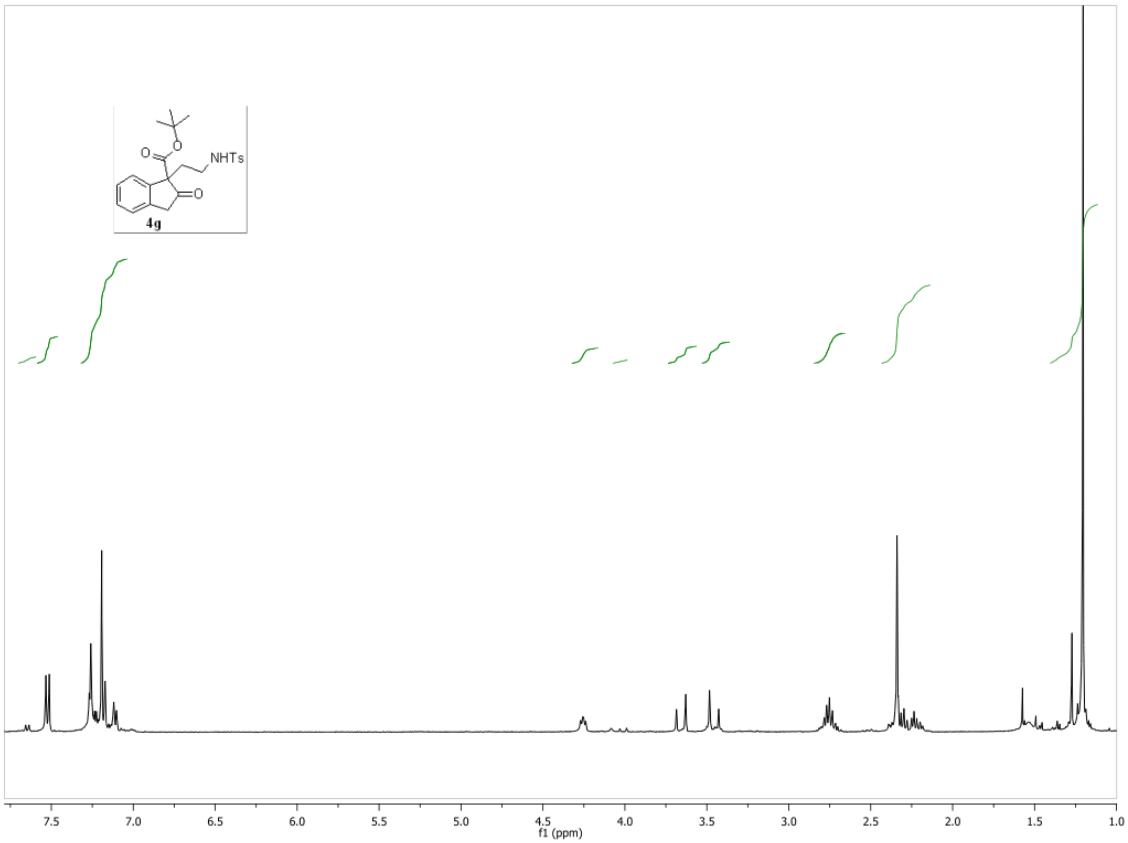
^{13}C NMR (100MHZ, $CDCl_3$) Spectrum of **4d**



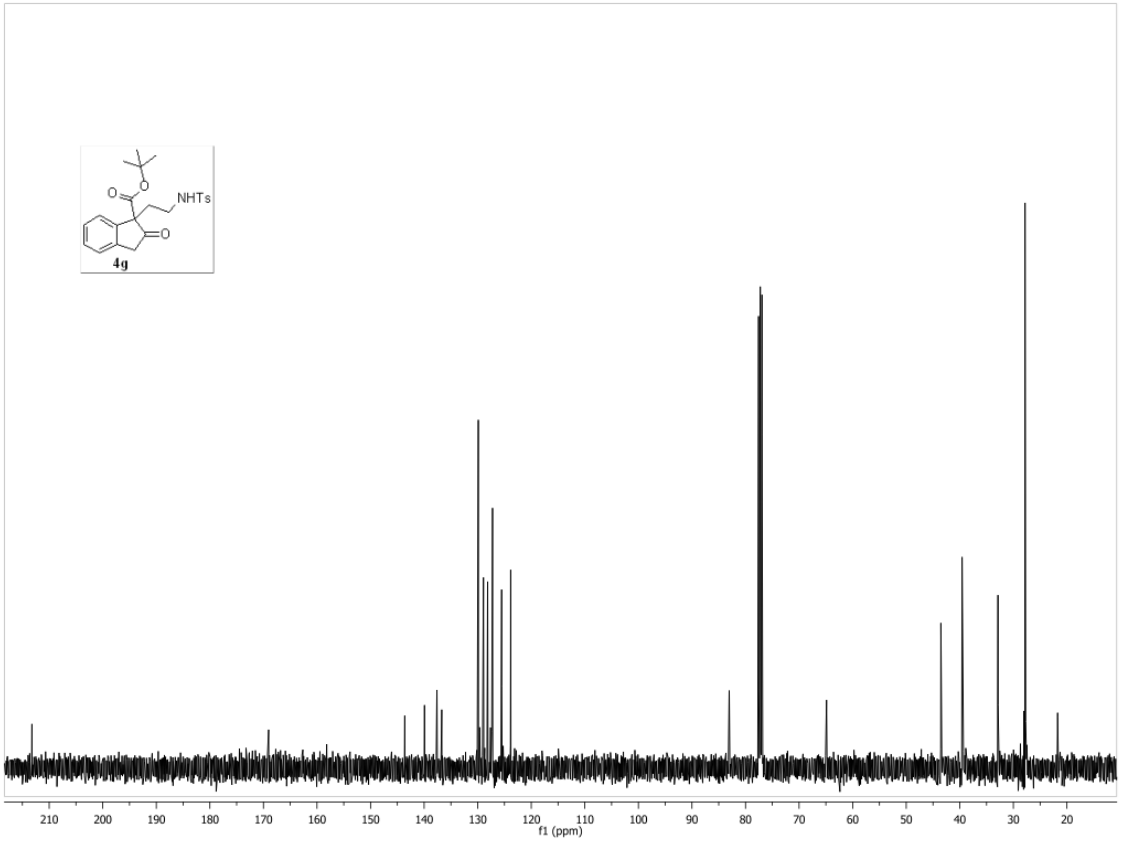
^{1}H NMR (400MHZ, $CDCl_3$) Spectrum of **4e**



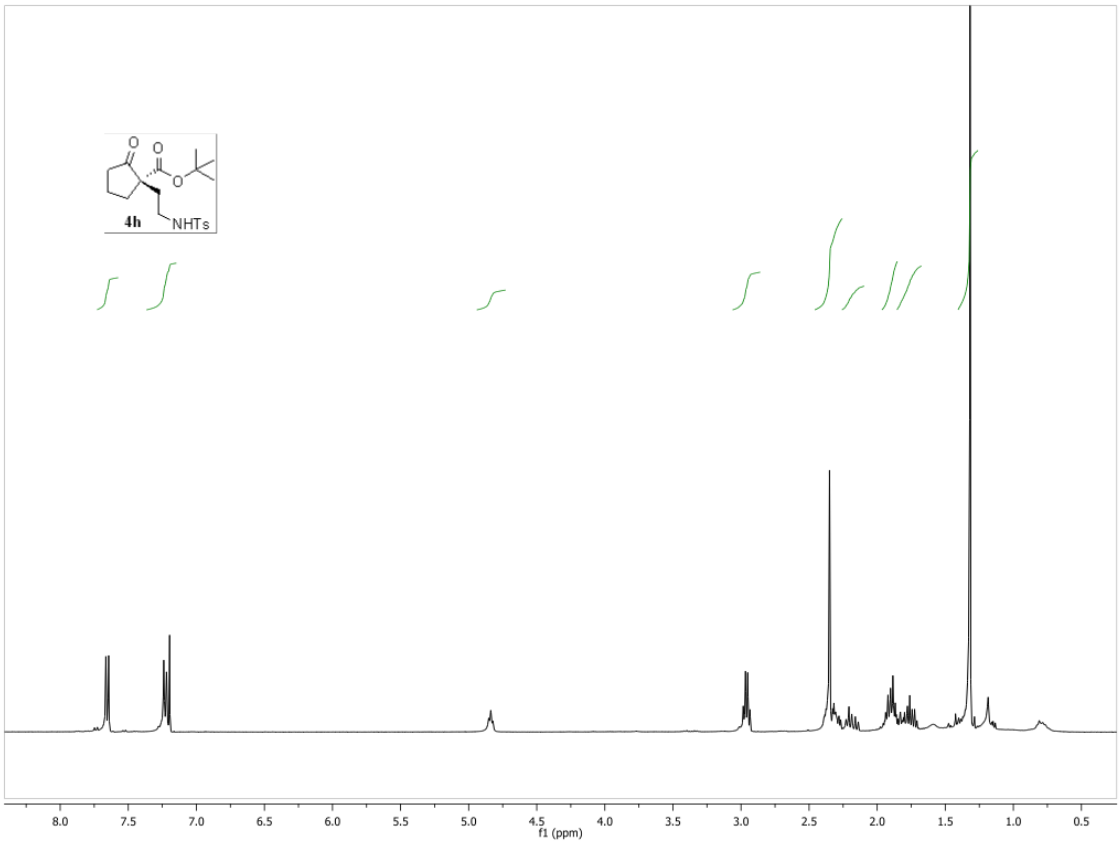
^{13}C NMR (100MHZ, $CDCl_3$) Spectrum of **4e**



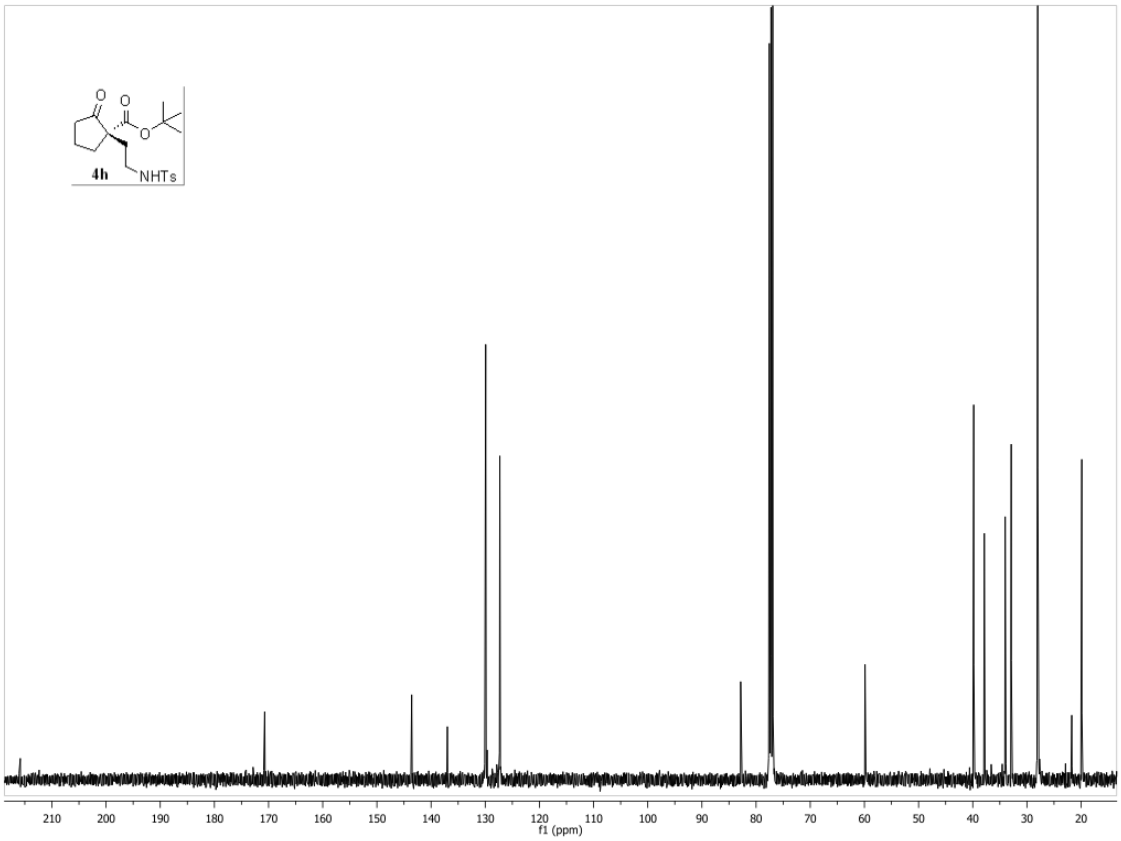
^{1}H NMR (400MHZ, $CDCl_3$) Spectrum of **4g**



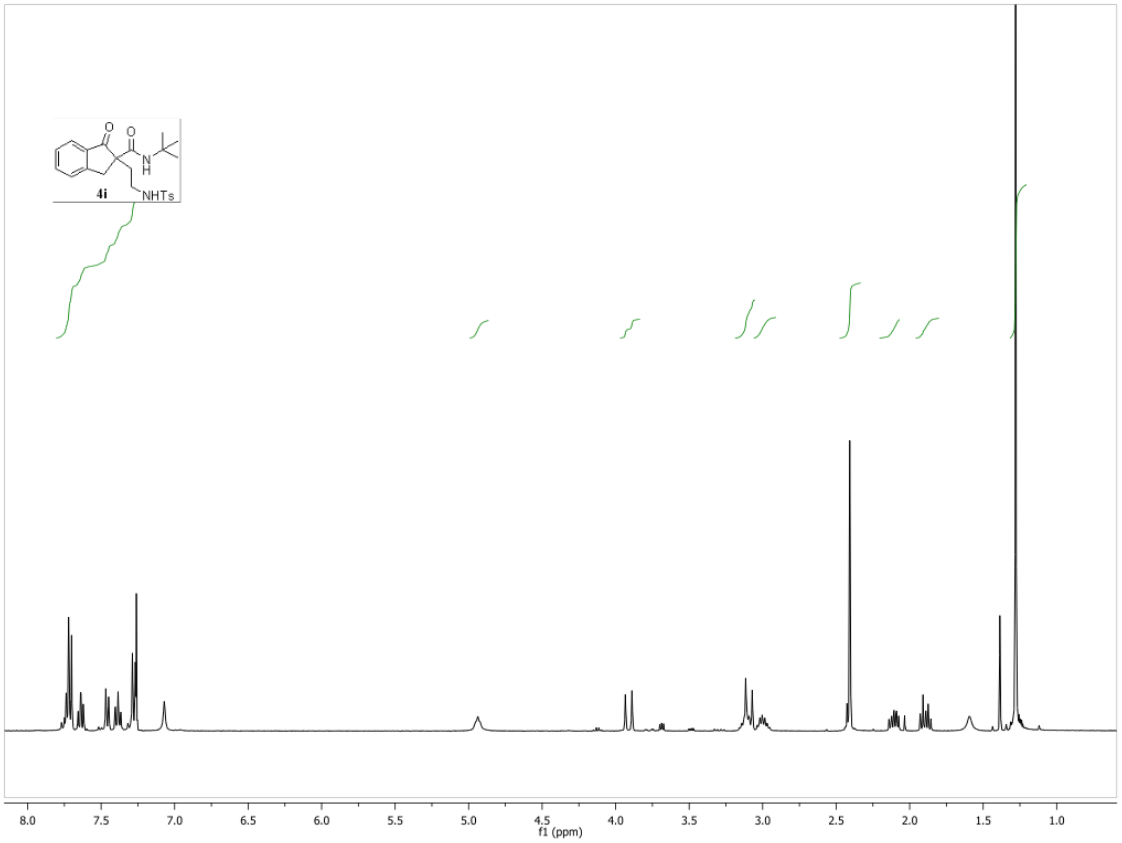
^{13}C NMR (100MHZ, $CDCl_3$) Spectrum of **4g**



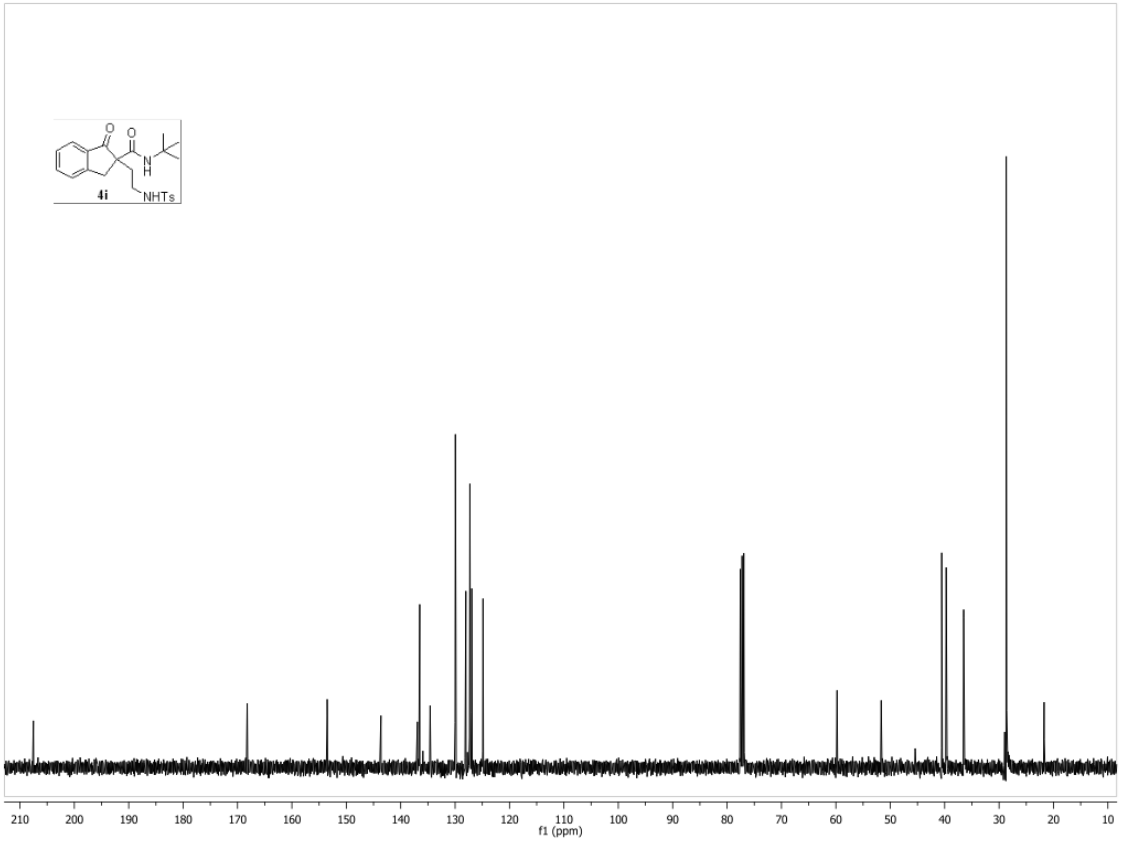
^{1}H NMR (400MHZ, $CDCl_3$) Spectrum of **4h**



^{13}C NMR (100MHZ, $CDCl_3$) Spectrum of **4h**



^{1}H NMR (400MHZ, $CDCl_3$) Spectrum of **4i**



^{13}C NMR (100MHZ, $CDCl_3$) Spectrum of **4i**