Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Copper(I)-catalyzed Asymmetric Mannich Reaction of Glycine Schiff Bases with Isatin-derived Ketimines: Enantioselective Synthesis of 3-Substituted 3-Aminooxindoles

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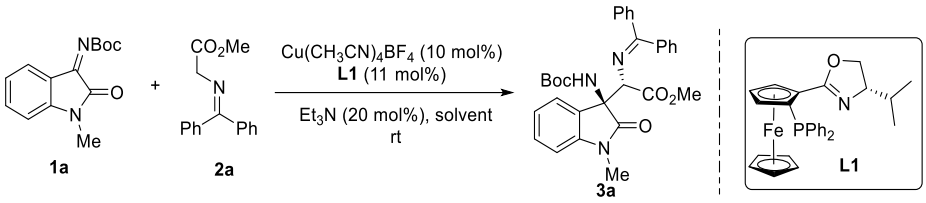
Contents

1. General information

^{1}H NMR spectrum were recorded on a Bruker DPX 400 MHz spectrometer in $CDCl_3$. Chemical shifts were reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The spectra are interpreted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, coupling constant(s) *J* are reported in Hz and relative integrations are reported. ^{13}C NMR (100 MHz) spectrum were recorded on a Bruker DPX 400 MHz spectrometer in $CDCl_3$. Chemical shifts were reported in ppm with the internal chloroform signal at 77.16 ppm as a standard. Optical rotations were measured on an AUTOPOL V. Diastereomeric ratios were determined by analysis of ^{1}H NMR spectroscopy and HPLC traces, obtained by using Chiralpak AD-H, IF, IA or Chiralcel OD-H columns with *n*-hexane and *i*-propanol or ethanol as solvents. Enantiomeric excesses were determined by analysis of HPLC traces, obtained by using Chiralpak AD-H, IF, IA or Chiralcel OD-H columns with *n*-hexane and *i*-propanol or ethanol as solvents. (Chiralpak AD-H, IF, IA and Chiralcel OD-H columns were purchased from Daicel Chemical Industries, LTD.) Melting points were obtained in open capillary tubes using SGW X-4 micro melting point apparatus which were uncorrected. Mass spectrum were recorded on TOF mass spectrometer. All reagents and starting materials were purchased from Adamas-beta and other suppliers and used without further purification. Isatin-derived ketimines **1a-1p** were prepared according to the literature procedure.[1]

2. Reaction optimization

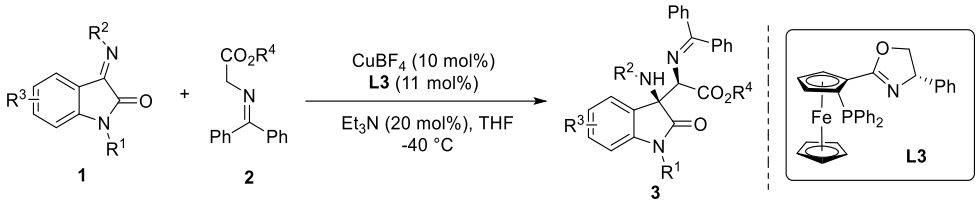
Table S1. Evaluation of solvent.[a]



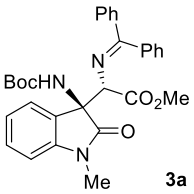
entry	solvent	yield (%)[b]	dr[c]	ee (%)[c]	t (h)
1	CPME	91	56:44	92/96	4
2	Et_2O	61	56:44	92/96	5
3	*i*Pr_2O	20	29:71	48/12	5
4	CH_3CN	38	15:85	30/8	3
5	toluene	92	51:49	86/80	3
6	CH_2Cl_2	99	57:43	92/94	0.5
7	$CHCl_3$	99	56:44	90/96	0.5
8	EtOAc	92	53:47	89/98	0.5

[a]All reactions were carried out with 0.1 mmol of **1a** and 0.11 mmol of **2a** in 1.5 mL of indicated solvent. [b]Combined yield of two diastereomers. [c]Determined by ^1H NMR spectroscopy and chiral HPLC analysis. [d]Determined by chiral HPLC analysis.

3. Preparation and characterization data of Mannich products

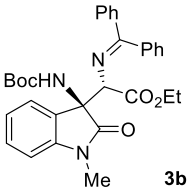


General procedure: Under a nitrogen atmosphere, $Cu(CH_3CN)_4BF_4$ (3.1 mg, 0.01 mmol), ligand **L3** (5.7 mg, 0.011 mmol) and Et_3N (20 μL, 1.0 M Et_3N dissolved in THF) were dissolved in THF (1.5 mL), and stirred at room temperature for approximately 1 h. Then, Schiff bases **1** (0.11 mmol) were added, the mixture was cooled to -40 °C and isatin-derived ketimines **2** (0.1 mmol) were then added. Once starting material was consumed (monitored by TLC), the mixture was concentrated and purified by column chromatography (petroleum ether/ethyl acetate = 3:1 to 2:1) to give the corresponding product.



Methyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

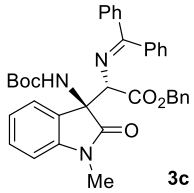
White solid; m.p: 122-124 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.7 Hz, 2H), 7.44-7.35 (m, 4H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.28-7.23 (m, 2H),7.02-6.95 (m, 3H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.31 (s, 1H), 4.39 (s, 1H), 3.75 (s, 3H), 3.59 (s, 3H), 3.25 (s, 3H), 3.17 (d, *J* = 3.9 Hz, 3H), 1.22 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.7, 174.0, 169.3, 154.0, 144.4, 138.9, 135.6, 131.0, 129.4, 129.2, 129.1, 129.1, 128. 8, 128. 8,128.2, 128.2, 127.6, 127.6, 123.5, 122.5, 107.8, 80.3, 69.0, 63.5, 52.6, 28.1, 28.1, 28.1, 26.6; **HRMS** (ESI-TOF) calcd for $C_{30}H_{31}N_3O_5$ $[M+H]^+$: 514.2336, found: 514.2341; $[\alpha]_D^{25}$ = -49.7 (*c* 1.00, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, 0.8 mL/min, 254 nm) t_R = 6.98 min (*anti*-minor), 8.40 min (*syn*-major), 11.23 min (*anti*-major), 12.76 (*syn*-minor).



Ethyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

White solid; m.p: 146-148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7 Hz, 2H), 7.43-7.39 (m, 4H), 7.35 (d, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.25 (t, 1H), 7.03-7.00 (m, 3H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.25 (s, 1H), 4.39 (s, 1H), 4.06-3.94 (m, 2H), 3.24 (s, 3H), 1.22 (s, 9H), 1.07 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.6, 174.0, 168.4, 154.0, 144.4, 134.0, 135.7, 131.0, 129.3, 129.1(4), 129.0(8), 129.0(8), 128.7, 128.7, 128.2, 128.2, 127.6, 127.6, 123.8,

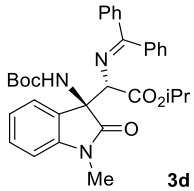
122.4, 107.8, 80.3, 69.0, 63.3, 61.6, 28.1, 28.1, 28.1, 26.5, 14.0; **HRMS** (ESI-TOF) calcd for $C_{31}H_{33}N_3O_5$ $[M+H]^+$: 528.2493, found: 528.2496; $[\alpha]_D^{25}$ = -37.0 (*c* 0.96, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm) t_R = 11.66 min (*anti*-major), 14.44 min (anti- minor), 18.00 min (*syn*-minor), 24.24 min (*syn*-major).



3c

Benzyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

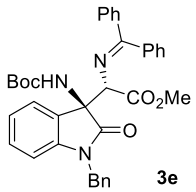
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 2H, major), 7.43-7.37(4) (m, 2H, major+minor), 7.36(6)-7.34 (m, 2H, major+minor), 7.33-7.27 (m, 7H, major+minor), 7.50-6.96 (m, 1H, major+minor), 7.23-7.17 (m, 2H, major+minor), 6.90 (d, *J* = 7.1 Hz, 2H, major), 6.72-6.67 (m, 1H, major+minor), 6.20(s, 1H, major), 5.20 (s, 2H, minor), 5.06 (d, *J* = 12.1 Hz, 1H, major), 4.87 (d, *J* = 12.1 Hz, 1H, major), 4.43 (s, 1H, major), 4.21 (s, 1H, minor), 3.15 (s, 3H, minor), 3.07 (s, 3H, major), 1.20 (s, 9H, major+minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major+minor) 174.5, 174.2, 173.4, 168.2, 153.9, 144.3, 138.9, 135.5, 135.1, 131.0, 129.2, 129.1, 129.1, 129.1, 129.1, 129.0, 128.9, 128.9, 128.7, 128.7, 128.6(0), 128.5(5), 128.5(5), 128.5, 128.2, 128.1, 128.1, 127.5, 127.5, 127.3, 123.7, 122.4, 107.9, 80.2, 69.0, 67.4, 67.2, 63.2, 28.1, 28.1, 28.1, 26.3; **HRMS** (ESI-TOF) calcd for $C_{36}H_{35}N_3O_5$ $[M+H]^+$: 590.2649, found: 590.2656; $[\alpha]_D^{25}$ = -47.1 (*c* 1.00, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm) t_R = 14.07 min (*anti*-minor), 16.34 min (*syn*-major), 17.91 min (*anti*-major), 23.82 min (*syn*-minor).



3d

Isopropyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

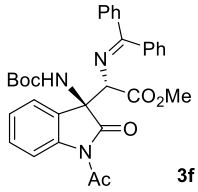
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.7 Hz, 2H, major), 7.50(d, *J* = 7.4Hz, 2H, minor) 7.43-7.40 (m, 5H, major+minor), 7.33 (t, *J* = 7.6 Hz, 2H, major+minor), 7.27-7.23 (m, 1H, major+minor), 7.16 (d, *J* = 7.4 Hz, 1H, minor), 7.06-6.98 (m, 3H, major+minor), 6.85-6.82 (m, 3H, minor), 6.77 (d, *J* = 7.8 Hz, 1H, major), 6.20 (s, 1H, major), 5.20-5.10 (m, 1H, minor), 4.86-4.80 (m, 1H, major), 4.37 (s, 3H, major), 4.15 (s, 3H, minor), 3.23 (s, 3H, major), 3.15(s, 3H, minor), 1.23-1.21 (m, 9H, major+minor), 1.03 (m, 6H, major+minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major+minor) 174.6, 174.0, 172.9 , 167.6 , 154.1 , 144.6 , 139.1 , 135.8 , 131.0 , 129.3 , 129.1, 129.1, 128.7, 128.7, 128.6 , 128.4 , 128.2, 128.2, 127.6, 127.6, 123.9 , 122.4 , 107.8 , 80.3 , 69.4 , 69.0 , 63.2 , 28.2 , 26.6 , 21.8, 21.8, 21.8, 21.5, 21.5; **HRMS** (ESI-TOF) calcd for $C_{32}H_{35}N_3O_5$ $[M+H]^+$: 542.2649, found: 542.2656; $[\alpha]_D^{25}$ = -91.1 (*c* 1.02, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm) t_R = 9.14 min (*anti*-minor), 12.81 min (*anti*-major), 16.26 min (*syn*-minor), 21.15 min (*syn*-major).



3e

Methyl (*S*)-2-((*S*)-1-benzyl-3-((*tert*-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

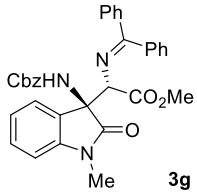
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.8 Hz, 1H, major), 7.44-7.34 (m, 4H, major+minor), 7.32-7.27 (m, 4H, major+minor), 7.23-7.19(5) (m, 1H, major+minor), 7.18(8)-7.11 (m, 4H, major+minor), 7.09-7.03 (m, 1H, major+minor), 6.99-6.94 (m, 2H, major+minor), 6.72 (s, 1H, major+minor), 6.66 (d, *J* = 7.8 Hz, 1H, minor), 6.62 (d, *J* = 7.8 Hz, 1H, major), 6.53 (s, 1H, minor), 5.12-4.76 (m, 2H, major+minor), 4.42 (s, 1H, minor), 4.29 (s, 1H, major), 3.74 (s, 3H, major), 3.64 (s, 3H, minor), 1.35 (s, 9H, minor), 1.26 (s, 9H, major); **^{13}C NMR** (100 MHz, $CDCl_3$) δ(major+minor) 175.0, 174.6, 173.6, 154.1, 154.0, 143.8, 139.1, 138.6, 136.0, 135.8, 135.4, 131.1, 130.8, 129.3, 129.2(2),129.2(2), 129.1(9), 129.0, 128.8(3), 128.8(1), 128.8(1), 128.8(0), 128.6(1), 128.5(5), 128.5(5), 128.3, 128.3, 128.1, 127.8, 127.7, 127.5, 127.3, 127.3, 127.0, 127.0, 123.8, 123.3, 122.5, 122.5, 109.0, 80.3, 69.0 , 68.7, 63.5, 52.7, 52.6, 44.5, 44.2, 28.2, 28.2, 28.2; **HRMS** (ESI-TOF) calcd for $C_{36}H_{35}N_3O_5$ $[M+H]^+$: 590.2649, found: 590.2654; $[\alpha]_D^{25}$ = -99.0 (*c* 1.07, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, 1.0 mL/min, 254 nm) t_R = 5.24 min (*syn*-minor), 8.97 min (*anti*-major), 12.69 min (*syn*-major), 36.13 min (*anti*-minor).



3f

Methyl (*S*)-2-((*S*)-1-acetyl-3-((*tert*-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

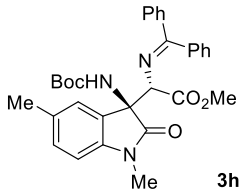
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.2 Hz, 1H, minor), 8.25 (d, *J* = 8.0 Hz, 1H, major), 7.46-7.43 (m, 3H, major+minor), 7.41-7.38 (m, 3H, major+minor), 7.33-7.28 (m, 3H, major+minor), 7.19-7.16 (m, 2H, major+minor), 6.93 (dd, *J* = 6.5, 2.9 Hz, 2H, major), 6.86 (dd, *J* = 7.4, 2.1 Hz, 2H, minor), 4.44 (s, 1H, major), 4.36 (s, 1H, minor), 3.75 (s, 3H, major), 3.60 (s, 3H, minor), 2.73 (s, 3H, minor), 2.54 (s, 3H, major), 1.32 (s, 9H, minor), 1.22 (s, 9H, major); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.0 , 175.5 , 174.6 , 174.2 , 170.7 , 170.6 , 168.9 , 153.9 , 141.0 , 138.5 , 138.2 , 135.3 , 131.4 , 129.7 , 129.7 , 129.4 , 129.2, 129.2, 129.1 ,129.1, 129.0, 129.0, 128.9, 128.9, 128.8, 128.8, 128.4, 128.4, 128.3, 128.3, 127.4,127.4, 127.1, 127.1, 125.2 , 123.0 , 116.5 , 116.4 , 81.1, 69.6, 69.4, 64.6, 63.8, 52.8, 29.8, 28.2 , 28.0, 28.0, 28.0, 26.7, 26.6; **HRMS** (ESI-TOF) calcd for $C_{31}H_{31}N_3O_6$ $[M+H]^+$: 542.2286, found: 542.2292; $[\alpha]_D^{25}$ = -83.1 (*c* 1.04, $CHCl_3$); **HPLC** (Chiralpak IF, hexane/*i*-PrOH = 100/5, 0.8 mL/min, 254 nm) t_R = 5.24 min (*syn*-minor), 8.97 min (*anti*-major), 12.69 min (*syn*-major), 36.13 min (*anti*-minor).



3g

Methyl (*S*)-2-((*S*)-3-(((benzyloxy)carbonyl)amino)-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

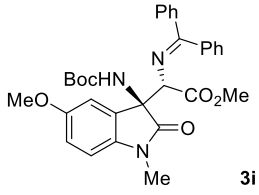
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.6 Hz, 2H, major+minor), 7.43-7.37 (m, 4H, major+minor), 7.35-7.27 (m, 9H, majro+minor), 7.16 (d, *J* = 7.3 Hz, 1H, minor), 7.04 -6.96 (m, 3H, major+minor), 6.88-6.78 (m, 1H, major+minor), 6.64 (s, 1H, major), 4.97 (s, 2H, minor), 4.92 (s, 2H, major), 4.45 (s, 1H, major), 4.26 (s, 1H, minor), 3.75 (s, 3H, minor), 3.56 (s, 3H, major), 3.22 (s, 3H, major+minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.3 , 174.3 , 173.8 , 169.1 , 154.6 , 144.5 , 138.8 , 131.2 , 131.1 , 129.7 , 129.2 , 129.1, 129.1, 129.0 , 128.8, 128.8, 128.6 , 128.5, 128.5, 128.3, 128.3, 128.2(7) , 128.1(9), 128.1(7), 128.1(7), 127.8 , 127.5, 127.5, 127.3 , 123.7 , 122.7 , 122.6 , 108.2 , 108.1 , 68.8 , 67.3 , 63.3 , 52.7 , 52.6 , 26.5; **HRMS** (ESI-TOF) calcd for $C_{33}H_{29}N_3O_5$ $[M+H]^+$: 548.2180, found: 548.2186; $[\alpha]_D^{25}$ = -74.1 (*c* 1.00, $CHCl_3$); **HPLC** (Chiralcel OD-H, hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm) t_R = 16.02 min (*anti*-minor), 21.43 min (*syn*-major), 32.53 min (*syn*-minor) 43.22 min (*anti*-major).



3h

Methyl (*S*)-2-((S*)*-3-((*tert*-butoxycarbonyl)amino)-1,5-dimethyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.7 Hz, 2H, major+minor), 7.43-7.35 (m,5H, major+minor), 7.29 (t, *J* = 7.6 Hz, 2H, major+minor), 7.06-6.97 (m, 2H, major+minor), 6.96-6.90 (m, 2H, major+minor), 6.66 (d, *J* = 7.8 Hz, 1H, major), 6.39(s, 1H, major) 4.37 (s, 1H, major), 4.27 (s, 1H, minor), 3.76 (s, 3H, minor), 3.63 (s, 3, major), 3.24 (s, 3H, major), 3.15 (s, 3H, minor), 2.29 (s, 3H, major), 2.26 (s, 3H, minor), 1.22 (s, 9H, major+minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.6, 173.7, 169.6, 154.1, 142.0, 139.0, 135.6, 131.8, 131.0, 129.5, 129.2, 129.1, 129.1, 128.7, 128.7, 128.1, 128.1, 127.7, 127.7, 124.2, 107.6, 80.3, 68.9, 63.6, 52.7, 28.2, 28.2, 28.2, 26.6, 21.3; **HRMS** (ESI-TOF) calcd for $C_{31}H_{33}N_3O_5$ $[M+H]^+$: 528.2493, found: 528.2499; $[\alpha]_D^{25}$ = -54.4 (*c* 0.99, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, 0.8 mL/min, 254 nm) t_R = 6.36 min (*anti*-minor), 7.24 min (*syn*-major), 9.23 min (*anti*-major), 11.80 min (*syn*-minor).

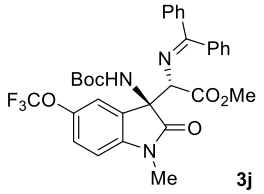


3i

Methyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-5-methoxy-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

White solid; m.p: 175-177 °C;**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47-7.37 (m, 6H), 7.29 (t, *J* =

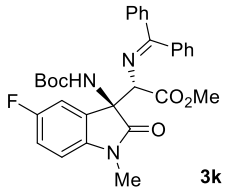
7.6 Hz, 2H), 6.95 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.85 (s, 1H), 6.77 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.37 (s, 1H), 4.38 (s, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 3.24 (s, 3H), 1.24 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.3, 173.7, 169.4, 155.9, 153.9, 138.9, 137.9, 135.5, 131.0, 129.2, 129.0, 129.0, 128.7, 128.7, 128.1, 128.1, 127.6, 127.6, 113.7, 110.6, 108.2, 80.3, 68.9, 63.8, 55.8, 52.6, 28.1, 28.1, 26.6; **HRMS** (ESI-TOF) calcd for $C_{31}H_{33}N_3O_6$ $[M+H]^+$: 544.2442, found: 544.2449; $[\alpha]_D^{25}$ = -72.8 (*c* 1.05, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, 1.0 mL/min, 254 nm) t_R = 4.82 min (*syn*-major), 5.22 min (*syn*-minor), 9.12 min (*anti*-major), 16.88 min (*anti*-minor).



3j

Methyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-1-methyl-2-oxo-5-(trifluoromethoxy)indolin-3-yl)-2-((diphenylmethylene)amino)acetate

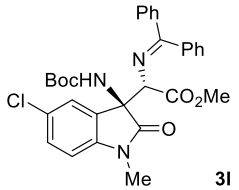
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.8 Hz, 2H, major+minor), 7.44-7.37 (m,4H, major+minor), 7.31 (t, *J* = 7.5 Hz, 2H, major+minor), 7.17-7.09 (m, 2H, major+minor), 6.97-6.93 (m, 2H, major+minor), 6.77 (d, *J* = 8.3 Hz, 1H, major), 6.37 (s, 1H, maojr), 4.37 (s, 1H, major), 4.30 (s, 1H, minor), 3.75 (s, 3H, minor), 3.62 (s, 3H, major), 3.26 (s, 3H, major), 3.18 (s, 3H, minor), 1.26 (s, 9H, major+minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major+minor) 174.6 , 174.2 , 169.1 , 153.9 , 144.7 (d, *J* = 2.1 Hz), 143.2, 138.7, 135.4, 131.2, 129.4, 129.1(3), 129.0(7), 129.0(7), 129.0, 128.9, 128.9, 128.8, 128.3, 128.2, 128.2, 127.4, 127.4, 127.3, 122.5, 122.4, 120.7 (q, *J* = 256.4 Hz), 108.3, 80.7, 68.8, 68.5, 63.6, 52.7, 28.1, 28.1, 28.1, 26.7; **HRMS** (ESI-TOF) calcd for $C_{31}H_{30}F_3N_3O_6$ $[M+H]^+$: 598.2159, found: 598.2166; $[\alpha]_D^{25}$ = -50.2 (*c* 1.02, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 100/5, 0.8 mL/min, 254 nm) t_R = 13.02 min (*anti*-minor), 19.40 min (*syn*-major), 21.50 min (*anti*-major), 25.30 min (*syn*-minor).



3k

Methyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-5-fluoro-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

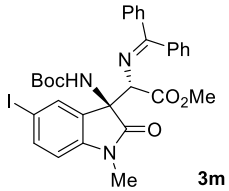
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 2H, major+minor), 7.44-7.37 (m, 4H, major+minor), 7.31 (dd, *J* = 8.3, 6.9 Hz, 2H, major+minor), 7.09-6.87 (m, 4H, major+minor), 6.71 (dd, *J* = 8.4, 4.0 Hz, 1H, major+minor), 6.30 (s, 1H, major), 4.40 (s, 1H, major), 3.76 (s, 3H, minor), 3.61 (s, 3H, major), 3.26 (s, 3H, major), 3.17 (s, 3H, minor), 1.26 (s, 9H, major+minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major+minor) δ 174.5, 174.2, 169.1, 159.2 (d, *J* = 240.6 Hz), 153.9, 140.5 (d, *J* = 1.3 Hz), 138.8, 135.5, 131.2, 129.3, 129.1, 129.1, 128.9, 128.9, 128.2, 128.2, 127.5, 127.5, 115.5 (d, *J* = 23.4 Hz), 111.8 (d, *J* = 25.2 Hz), 108.3 (d, *J* = 7.7 Hz), 80.6, 68.9, 63.7, 52.8, 28.2, 28.2, 28.2, 26.8. **HRMS** (ESI-TOF) calcd for $C_{30}H_{30}FN_3O_5$ $[M+H]^+$: 532.2242, found: 532.2249; $[\alpha]_D^{25}$ = -40.9 (*c* 0.99, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, 0.8 mL/min, 254 nm) t_R = 10.52 min (*syn*-major), 13.80 min (*anti*-major), 15.22 min (*syn*-minor), 21.05 min (*anti*-minor).



3l

Methyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-5-chloro-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.1 Hz, 5H, major+minor), 7.39 (d, *J* = 6.9 Hz, 1H, major+minor), 7.30 (t, *J* = 7.6 Hz, 2H, major+minor), 7.21 (dd, *J* = 8.2, 1.8 Hz, 1H, major+minor), 7.14 (s, 1H, major+minor), 6.95-6.91 (m, 2H, major+minor), 6.71 (d, *J* = 8.3 Hz, 1H, major+minor), 6.41 (s, 1H, major+minor), 4.38 (s, 1H, major), 4.32 (s, 1H, minor), 3.77 (s, 3H, minor), 3.66 (s, 3H, major), 3.27 (s, 3H, major), 3.16 (s, 3H, minor), 1.25 (s, 9H, major+minor). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major+minor) 174.3, 173.9, 173.9, 169.3, 153.8, 143.1, 138.7, 135.3, 131.1, 129.3, 129.1, 129.0, 129.0, 128.9, 128.9, 128.7, 128.3, 128.2, 128.2, 127.7, 127.5, 127.5, 127.4, 123.9, 108.8, 80.6, 68.7, 68.5, 63.5, 52.8, 29.8, 28.2, 28.2, 28.2, 26.7; **HRMS** (ESI-TOF) calcd for $C_{30}H_{30}ClN_3O_5$ $[M+H]^+$: 548.1947, found: 548.1953; $[\alpha]_D^{25}$ = -20.0 (*c* 0.99, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm) t_R = 10.00 min (*anti*-minor), 10.98 min (*syn*-major), 14.12 min (*anti*-major), 20.37 min (*syn*-minor).

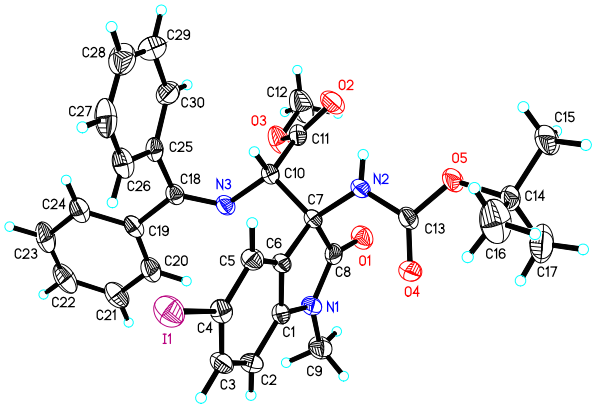


3m

Methyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-5-iodo-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.1, 1.8 Hz, 1H, major+minor), 7.49-7.36 (m,6H, major+minor), 7.32-7.25 (m, 3H, major+minor), 6.93-6.88 (m, 2H, major+minor), 6.57 (d, *J* = 8.2 Hz, 1H, major), 4.35 (s, 1H, major), 4.28 (s, 1H, minor), 3.77 (s, 3H, minor), 3.70 (s, 3H, major), 3.26 (s, 3H, major), 3.14 (s, 3H, minor), 1.26 (s, 9H, major+minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major+minor) 174.0, 173.8, 169.5, 153.8, 144.3 , 138.6, 138.0, 135.3, 131.1, 129.3, 129.0, 129.0, 128.9, 128.9, 128.7, 128.3, 128.2, 128.2, 127.6, 127.6, 127.4, 109.9, 84.8, 80.6, 68.6, 63.3, 52.9, 28.2, 28.2, 28.2, 26.6; **HRMS** (ESI-TOF) calcd for $C_{30}H_{30}IN_3O_5$ $[M+H]^+$: 640.1303, found: 640.1309; $[\alpha]_D^{25}$ = -90.1 (*c* 1.01, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R = 9.18 min (*anti*-minor), 10.47 min (*syn*-major), 15.55 min (anti-major), 19.32 min (*syn*-minor).

(CCDC 1565164 (**3m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.)



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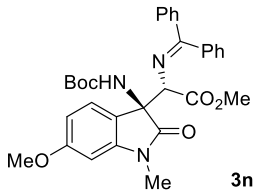
Formula weight	639.47	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 12.1518(14) Å	= 90°.
	b = 12.3848(15) Å	= 90°.
	c = 19.412(2) Å	= 90°.
Volume	2921.5(6) $Å^3$	
Z	4	
Density (calculated)	1.454 Mg/m^3	
Absorption coefficient	1.138 mm^{-1}	
F(000)	1296	
Crystal size	0.200 x 0.170 x 0.130 mm^3	
Theta range for data collection	1.950 to 25.499°.	
Index ranges	-13<=h<=14, -12<=k<=15, -21<=l<=23	
Reflections collected	16812	
Independent reflections	5433 [R(int) = 0.0315]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.6755	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5433 / 1 / 361	
Goodness-of-fit on F^2	1.038	

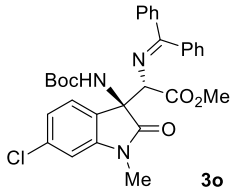
Final R indices [I>2sigma(I)]	R1 = 0.0336, wR2 = 0.0775
R indices (all data)	R1 = 0.0383, wR2 = 0.0799
Absolute structure parameter	-0.019(8)
Extinction coefficient	n/a
Largest diff. peak and hole	0.648 and -0.185 e.Å^{-3}



3n

Methyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-6-methoxy-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

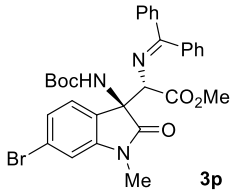
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 2H, major), 7.48 (d, *J* = 7.6 Hz, 2H, minor), 7.43-7.36 (m, 5H, major), 7.32 (t, *J* = 7.6 Hz, 2H, major+minor), 7.20 (d, *J* = 8.2 Hz, 5H, minor), 7.01-6.98 (m, 2H, major), 6.90-6.88 (m, 2H, minor), 6.50 (dd, *J* = 8.2, 2.3 Hz, 1H, major+minor), 6.45 (s, 1H, minor), 6.37 (d, *J* = 2.3 Hz, 1H, major), 6.22 (s, 1H, major+minor), 4.38 (s, 1H, major), 4.25 (s, 1H, minor), 3.84 (s, 3H, minor), 3.79 (s, 3H, major), 3.75 (s, 3H, minor), 3.57 (s, 3H, major), 3.22 (s, 3H, major), 3.15 (s, 3H, minor), 1.24 (s, 9H, major+minor). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major+minor) 175.2, 174.0, 173.4, 169.2, 161.1, 161.0, 154.0, 153.9, 145.7, 139.0, 138.7, 135.6, 135.5, 131.0, 129.2, 129.1, 129.1, 129.0, 128.8, 128.8, 128.7, 128.2(3), 128.1(8), 127.6, 128.1(8), 127.6, 127.4, 124.4, 106.1, 95.9, 80.2, 69.1, 68.8, 63.1, 55.6, 55.5, 52.7, 52.5, 28.2, 28.2, 28.2, 26.5; **HRMS** (ESI-TOF) calcd for $C_{31}H_{33}N_3O_6$ $[M+H]^+$: 544.2442, found: 544.2449; $[\alpha]_D^{25}$ = -36.1 (*c* 1.00, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, 0.8 mL/min, 254 nm) t_R = 8.69 min (*syn*-major), 10.78 min (*anti*-major), 12.29 min (*anti*-minor), 13.86 min (*syn*- minor).



3o

Methyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-6-chloro-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

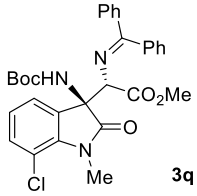
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H, major+minor), 7.47-7.38 (m, 4H, major+minor), 7.33 (t, *J* = 7.6 Hz, 2H, major+minor), 7.21 (d, *J* = 7.9 Hz, 1H, major+minor), 7.05-6.93 (m, 3H, major+minor), 6.82-6.76 (m, 1H, major+minor), 4.38 (s, 1H, major), 3.75 (s, 3H, minor), 3.59 (s, 3H, major), 3.23 (s, 3H, major), 3.16 (s, 3H, minor), 1.26 (s, 9H, major+minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.7, 174.3, 169.1, 153.9, 145.7, 138.8, 131.2, 129.3, 129.1, 129.1, 129.0, 128.8, 128.8, 128.7, 128.2, 128.2, 127.5, 127.5, 127.3, 126.9, 124.5, 122.3, 108.6, 80.6, 68.8, 63.1, 52.7, 28.2, 28.2, 28.2, 26.7; **HRMS** (ESI-TOF) calcd for $C_{30}H_{30}ClN_3O_5$ $[M+H]^+$: 548.1947, found: 548.1953; $[\alpha]_D^{25}$ = -102.7 (*c* 1.02, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm) t_R = 9.15 min (*anti*-minor), 10.26 min (*anti*-major), 11.33 min (*syn*-major), 14.99 min (*syn*-minor).



3p

Methyl (*S*)-2-((*S*)-6-bromo-3-((*tert*-butoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

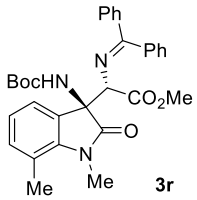
White solid; m.p: 116-118 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7 Hz, 2H), 7.45-7.40 (m, 4H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.15 (s, 2H), 6.99-6.97 (m, 2H), 6.94 (s, 1H), 6.28 (s, 1H), 4.38 (s, 1H), 3.59 (s, 3H), 3.23 (s, 3H), 1.26 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.5, 174.3, 169.0, 153.9, 145.8, 138.8, 135.5, 131.2, 129.3, 129.1, 129.1, 128.8, 128.8, 128.2, 128.2, 127.5, 127.5, 125.2, 124.8, 123.0, 111.4, 80.6, 68.8, 63.1, 52.7, 28.2, 28.2, 28.2, 26.7; **HRMS** (ESI-TOF) calcd for $C_{30}H_{30}BrN_3O_5$ $[M+H]^+$: 592.1442, found: 592.1445; $[\alpha]_D^{25}$ = -27.3 (*c* 1.00, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 100/5, 0.8 mL/min, 254 nm) t_R = 17.88 min (*anti*-minor), 20.19 min (*anti*-major), 24.34 min (*syn*-major), 34.07 min (*syn*-minor).



3q

Methyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-7-chloro-1-methyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53-7.45 (m, 2H, major+minor), 7.43-7.38 (m, 4H, major+minor), 7.34-7.25 (m, 3H, major+minor), 7.16 (d, 1H, minor), 7.05 (d, *J* = 7.3 Hz, 1H, major), 6.95-6.85 (m, 3H, major+minor), 4.34 (s, 1H, minor), 4.26 (s, 1H, major), 3.74 (s, 3H, major), 3.64 (s, 3H, minor), 3.64 (s, 3H, minor), 3.54 (s, 3H, major), 1.34 (s, 9H, minor), 1.26 (s, 9H, major); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major+minor) 175.2, 174.7, 173.8, 153.9, 140.4, 138.8, 138.6, 135.5, 135.4, 131.6, 131.6, 131.2, 131.2, 129.3, 129.1, 129.1, 129.1, 128.9, 128.8, 128.3, 128.2, 127.5, 127.3, 123.3, 123.3, 121.7, 115.5, 80.7, 69.1, 68.6, 63.2, 52.8, 30.2, 30.0, 28.3, 28.2, 28.2, 28.2; **HRMS** (ESI-TOF) calcd for $C_{30}H_{30}ClN_3O_5$ $[M+H]^+$: 548.1947, found: 548.1951; $[\alpha]_D^{25}$ = -103.6 (*c* 1.06, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 90/10, 0.8 mL/min, 254 nm) t_R = 8.80 min (*syn*-minor), 12.40 min (*anti*-major), 18.11 min (*syn*-major), 26.50 min (*anti*-minor).



3r

Methyl (*S*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-1,7-dimethyl-2-oxoindolin-3-yl)-2-((diphenylmethylene)amino)acetate

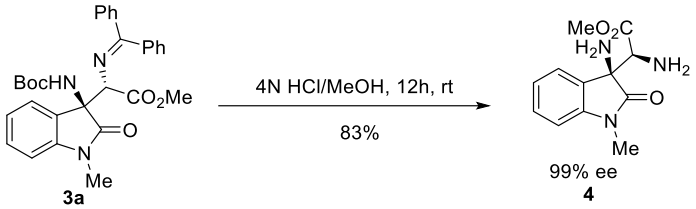
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.3 Hz, 1H, minor), 7.46 (d, *J* = 7.7 Hz, 2H, major), 7.42-7.27 (m, 6H, major+minor), 7.08-6.91 (m, 3H, major+minor), 6.89 (d, *J* = 3.1 Hz, 1H, minor), 6.87 (d, *J* = 3.0 Hz, 1H, major), 6.85 (d, *J* = 3.1 Hz, 1H, minor), 6.81 (d, *J* = 6.4 Hz, 1H, major), 6.59(s, 1H, minor), 6.40(s, 1H, major), 4.31 (s, 1H, major), 4.18 (s, 1H,

minor), 3.74 (s, 3H, minor), 3.64 (s, 3H, major), 3.54 (s, 3H, major), 3.43 (s, 3H, minor), 2.58 (s, 3H, minor), 2.54 (s, 3H, major), 1.33 (s, 9H, minor), 1.24 (s, 9H, major); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (major+minor) 175.5, 175.0, 173.6, 173.2, 169.6, 154.0, 153.9, 142.1, 139.0, 138.7, 135.6, 135.4, 133.0, 131.0, 130.9, 129.2, 129.1, 129.1, 128.9, 128.7, 128.7, 128.6, 128.2, 128.1, 128.1, 127.6,127.6, 127.4, 122.4, 121.2, 119.3, 80.2, 69.2, 68.8 , 63.0, 52.6 (d, *J* = 2.4 Hz), 30.0, 28.1, 28.1, 28.1, 19.2, 19.1; **HRMS** (ESI-TOF) calcd for $C_{31}H_{33}N_3O_5$ $[M+H]^+$: 528.2493, found: 528.2499; $[\alpha]_D^{25}$ = -380.0 (*c* 1.06, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R = 8.18 min (*anti*-minor), 11.50 min (*syn*-major), 18.78 min (*anti*-major), 29.26 min ((*syn*-minor).

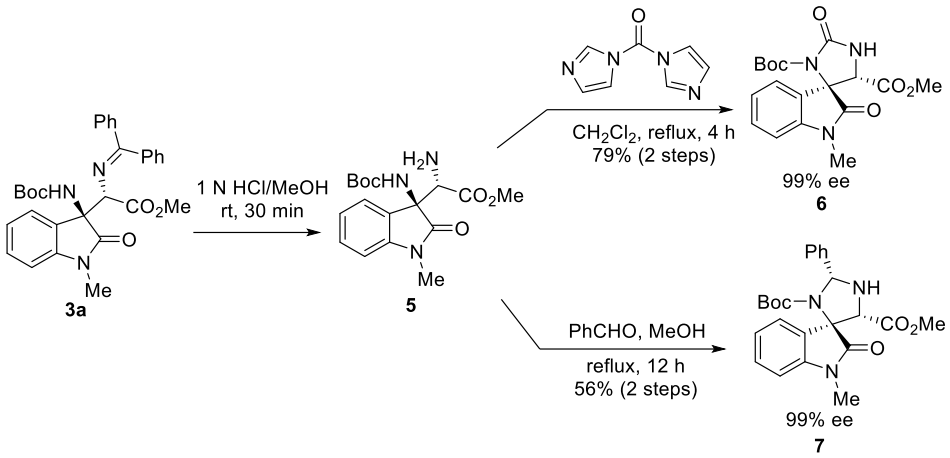
For *syn*-**3s**: White solid; m.p: 155-157 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.7 Hz, 2H), 7.43-7.35 (m, 4H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.96-6.92 (m, 3H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.40 (s, 1H), 4.31 (s, 1H), 3.64 (s, 3H), 3.53 (s, 3H), 2.54 (s, 3H), 1.23 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.6, 173.7, 169.5, 154.0, 142.1, 139.0, 135.6, 133.1, 131.0, 129.2, 129.1, 129.1, 128.7, 128.7, 128.1, 128.1, 127.7, 127.7, 122.4, 121.2, 119.4, 80.3, 69.2, 63.1, 52.6, 30.1, 28.2, 28.2, 28.2, 19.2.

For *anti*-**3s**: White solid; m.p: 178-180 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.6 Hz, 2H), 7.40 (q, *J* = 7.1 Hz, 2H), 7.35-7.29 (m, 5H), 7.04 (d, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.0 Hz, 2H), 4.17 (s, 1H), 3.74 (s, 3H), 3.43 (s, 3H), 2.58 (s, 3H), 1.33 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.1, 173.3, 170.2, 168.7, 138.7, 135.5, 133.1, 132.6, 131.1, 130.2, 129.1, 129.1, 129.0, 128.6, 128.6, 128.4, 128.3, 128.3, 127.4, 127.4, 122.5, 121.3, 80.1, 68.9, 52.7, 45.9, 29.8, 28.4, 28.4, 28.4, 19.2.

4. Transformation of Mannich adduct 3a



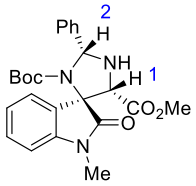
Compound **3a** (51.4 mg, 0.1 mmol) was dissolved in 4.0 N HCl/MeOH solution and stirred at room temperature. After 12 h, the mixture was neutralized by adding sat. aq $NaHCO_3$ solution and then extracted by ethyl acetate. The organic phase was separated, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH/NH_4OH = 100:10:1) to afford methyl (*S*)-2-amino-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)acetate **4** as colorless oil (20.7 mg, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.32 (td, *J* = 7.8, 1.3 Hz, 1H), 7.06 (td, *J* = 7.6, 1.0 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 3.92 (s, 1H), 3.49 (s, 3H), 3.22 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.3, 171.6, 143.5, 129.5, 129.3, 123.9, 122.9, 108.3, 62.8, 60.4, 52.2, 26.3; **HRMS** (ESI-TOF) calcd for $C_{17}H_{23}N_3O_5$ $[M+H]^+$: 350.1710, found: 350.1714; $[\alpha]_D^{25}$ = -86.6 (*c* 1.00, $CHCl_3$); **HPLC** (Chiralpak AD-H, hexane/EtOH = 80/20, 1.0 mL/min, 254 nm) t_R = 65.55 min (major), 73.07 min (minor).

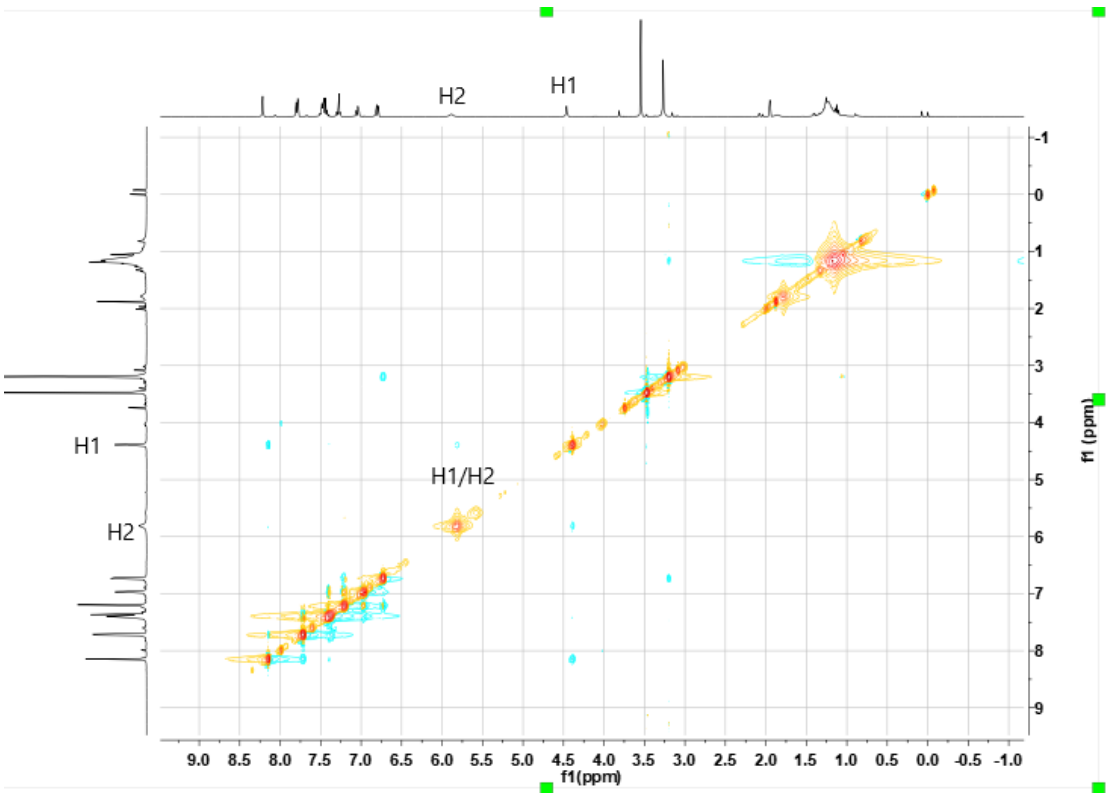


Compound **3a** (102.8 mg, 0.2 mmol) was dissolved in 1.0 N HCl/MeOH solution and stirred at room temperature. After 30 min, the mixture was neutralized by adding sat. aq $NaHCO_3$ solution and then extracted by ethyl acetate. The organic phase was separated, dried over Na_2SO4, and concentrated. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 3:1) to afford methyl (*S*)-2-amino-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)acetate **5**. Under a nitrogen atmosphere, compound **5** (34.9 mg, 0.1 mmol), and 1,1-carbonyldiimidazole (20.3 mg, 0.13 mmol) were dissolved in CH_2Cl_2 (4 mL). The reaction mixture was refluxed for 4 h, then cooled to rt and concentrated. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 1:1) to afford 3-(*tert*-butyl) 5-methyl (4*S*,5*S*)-1'-methyl-2'-oxo-2-phenylspiro[imidazolidine-4,3'-indoline]-3,5-dicarboxylate **6** as colorless oil (29.6 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.8 Hz, 1H), 7.32-7.22 (m, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.73 (s, 1H), 4.63 (s, 1H), 3.27 (s, 3H), 3.23 (s, 3H), 1.15 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.2, 167.4, 154.8, 147.9, 143.9, 130.7, 125.6, 123.5, 123.2, 108.2, 83.6, 65.8, 59.2, 52.4, 27.6, 27.6, 27.6, 26.9; **HRMS** (ESI-TOF) calcd for $C_{17}H_{23}N_3O_5$ $[M+H]^+$: 376.1503, found: 376.1509; $[\alpha]_D^{25}$ = -45.7 (*c* 1.00, $CHCl_3$); **HPLC** (Chiralpak IA, hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm) t_R = 16.29 min (major), 20.15 min (minor).

To a solution of compound **5** (34.9 mg, 0.1 mmol) in MeOH (1.5 mL) was added benzaldehyde (10 μL, 0.11 mmol) at room temperature. The mixture was refluxed under a nitrogen atmosphere for 12 h, then cooled to rt and concentrated. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate/triethylamine = 100:30:5) to afford 3-(*tert*-butyl) 5-methyl (4*S*,5*S*)-1'-methyl-2'-oxo-2-phenylspiro[imidazolidine-4,3'-indoline]-3,5-dicarboxylate **7** as white solid (22.5 mg, 56 %); mp: 177-179 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.79 (d, *J* = 7.0 Hz, 2H), 7.53-7.39 (m, 4H), 7.32-7.24 (m, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.86 (s, 1H), 4.46 (s, 1H), 3.55 (s, 3H), 3.27 (s, 3H), 1.23 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.4, 168.4, 167.5, 153.8, 144.4, 135.1, 132.0, 129.5, 129.0, 129.0, 128.8, 128.8, 124.2, 122.6, 107.9, 80.5, 75.2, 62.7, 52.6, 28.1, 28.1, 28.1, 26.7; **HRMS** (ESI-TOF) calcd for $C_{17}H_{23}N_3O_5$ $[M+H]^+$: 376.1503, found: 376.1509; $[\alpha]_D^{25}$ = +112.8 (*c* 1.00, $CHCl_3$); **HPLC** (Chiralpak IA, hexane/EtOH = 90/10, 0.8 mL/min, 254 nm) t_R = 19.87 min (major), 26.18 min (minor).

^{1}H,^{1}H-NOESY spectrum of **7** ($CDCl_3$)

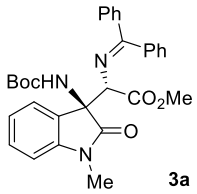




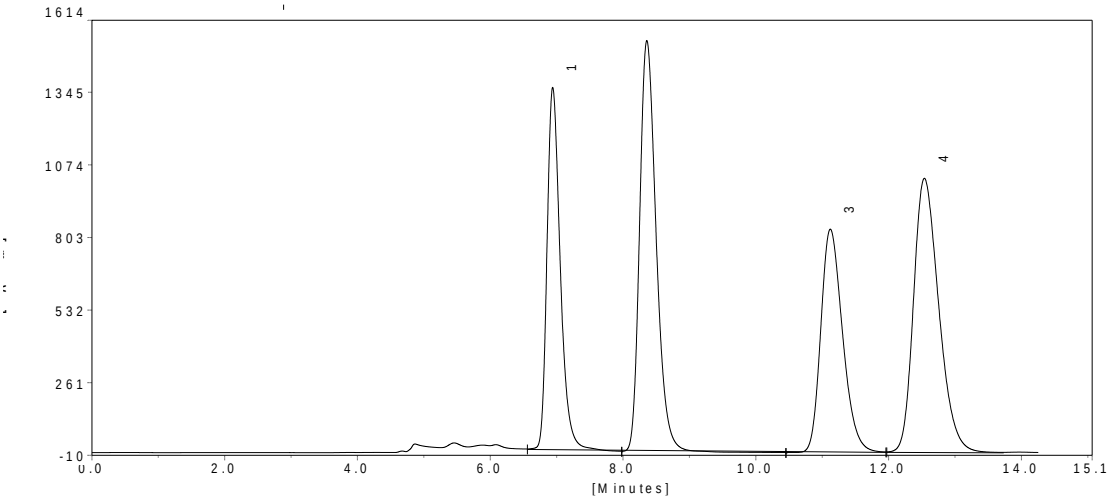
5. References

1. (a) N. Hara, S. Nakamura, M. Sano, R. Tamura, Y. Funahashi and N. Shibata, *Chem. Eur. J.*, 2012, **18**, 9276; (b) W. Yan, D. Wang, J. Feng, P. Li, D. Zhao and R. Wang, *Org. Lett.*, 2012, **14**, 2512; (c) S. Nakamura and S. Takahashi, *Org. Lett.*, 2015, **17**, 2590.

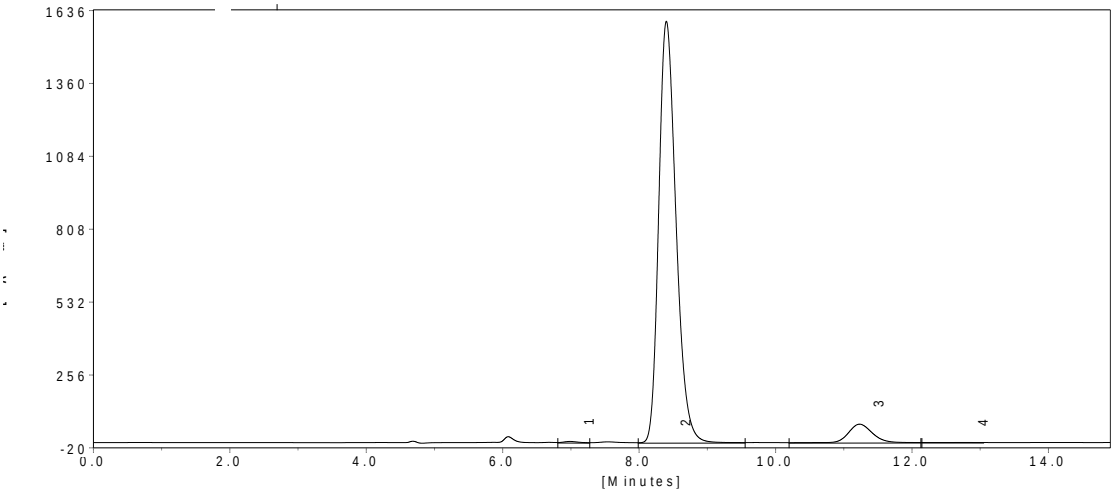
6. HPLC chromatograms



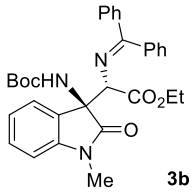
3a



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	6.93917	1350.39	18528.84	20.6428
2	8.35833	1528.30	25699.24	28.6312
3	11.12167	829.83	18657.50	20.7861
4	12.53917	1021.83	26873.93	29.9399



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	6.98417	4.26	51.77	0.1741
2	8.39917	1596.18	28025.69	94.2552
3	11.23167	69.71	1651.96	5.5558
4	12.76083	0.23	4.42	0.0149



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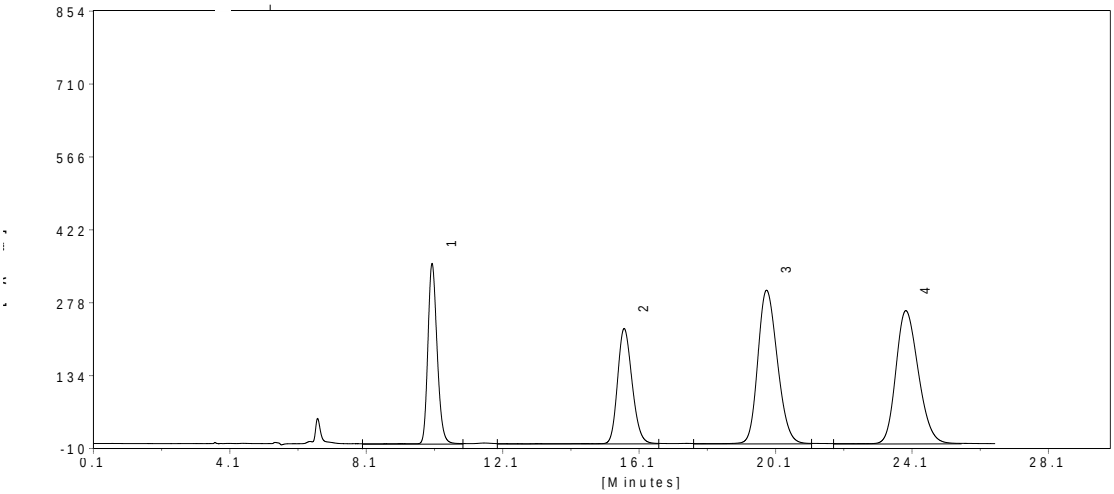
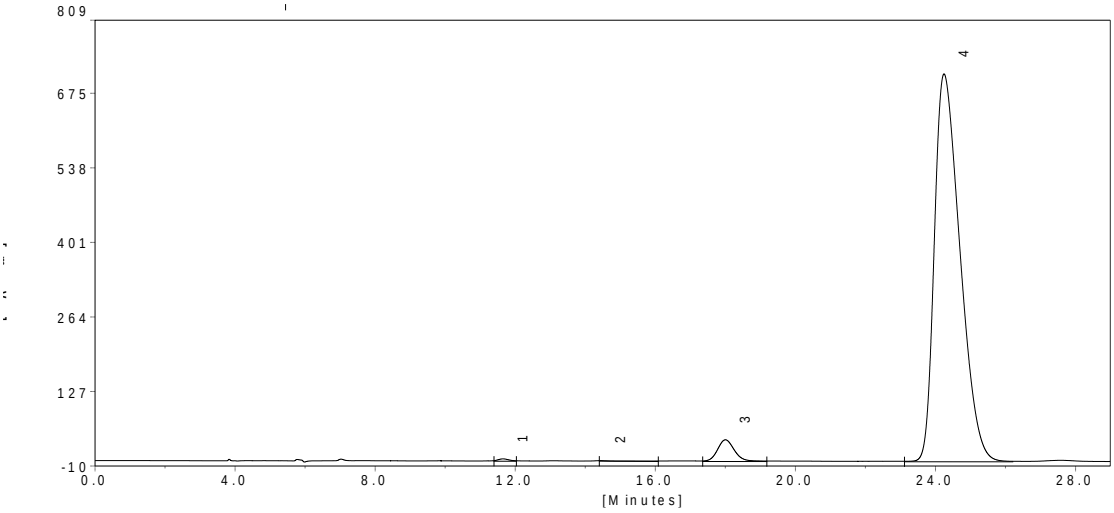
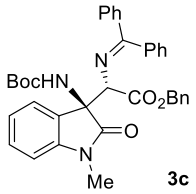


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	10.04417	356.19	6639.44	17.9030
2	15.67500	227.20	6586.05	17.7591
3	19.85167	302.87	11949.56	32.2216
4	23.93417	262.56	11910.46	32.1162



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	11.65667	3.44	64.28	0.1720
2	14.44333	0.10	24.23	0.0648
3	18.00250	38.97	1256.97	3.3627
4	24.24583	711.96	36034.63	96.4005



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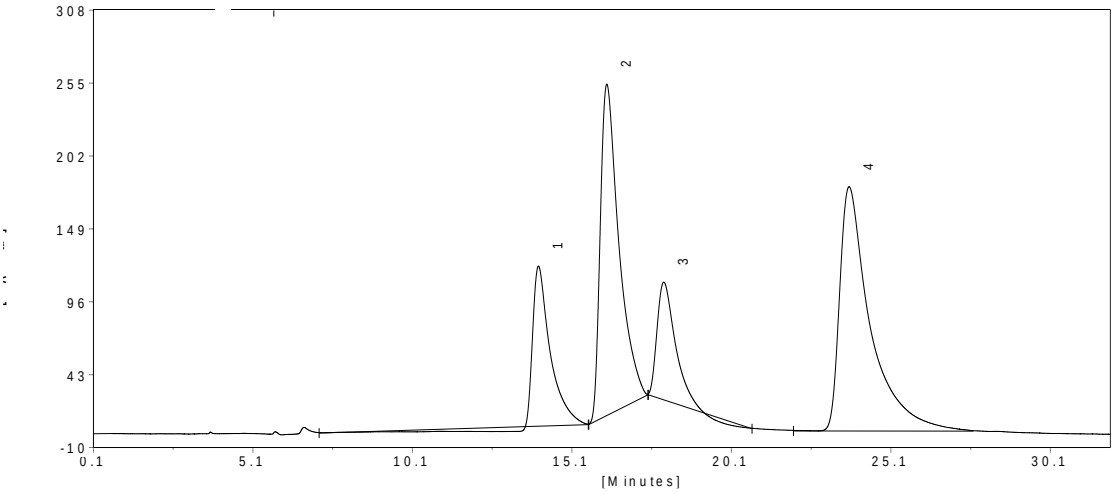
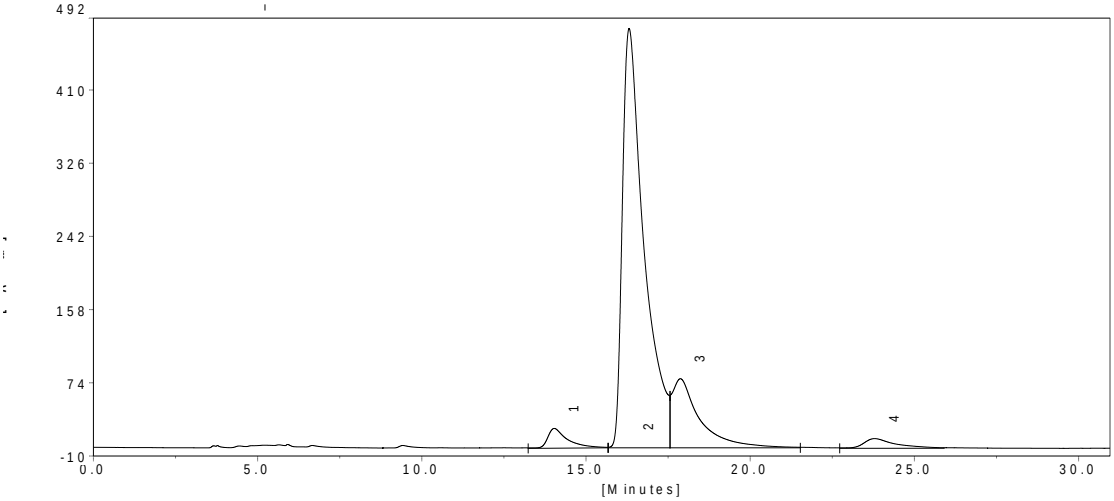
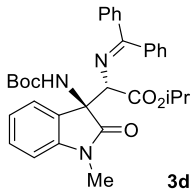


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	14.01000	116.13	3744.93	13.1146
2	16.15250	240.54	9785.30	34.2677
3	17.93500	85.38	3275.71	11.4714
4	23.74833	177.33	11749.52	41.1463



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	14.06750	22.09	867.83	3.0881
2	16.34583	480.59	22004.42	78.3006
3	17.90750	78.72	4581.30	16.3021
4	23.82583	10.55	648.94	2.3092



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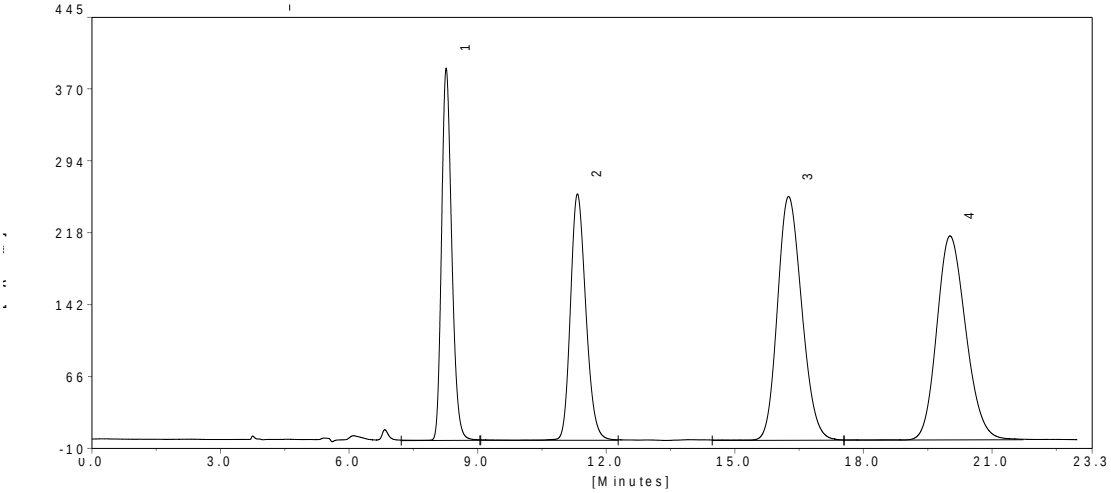
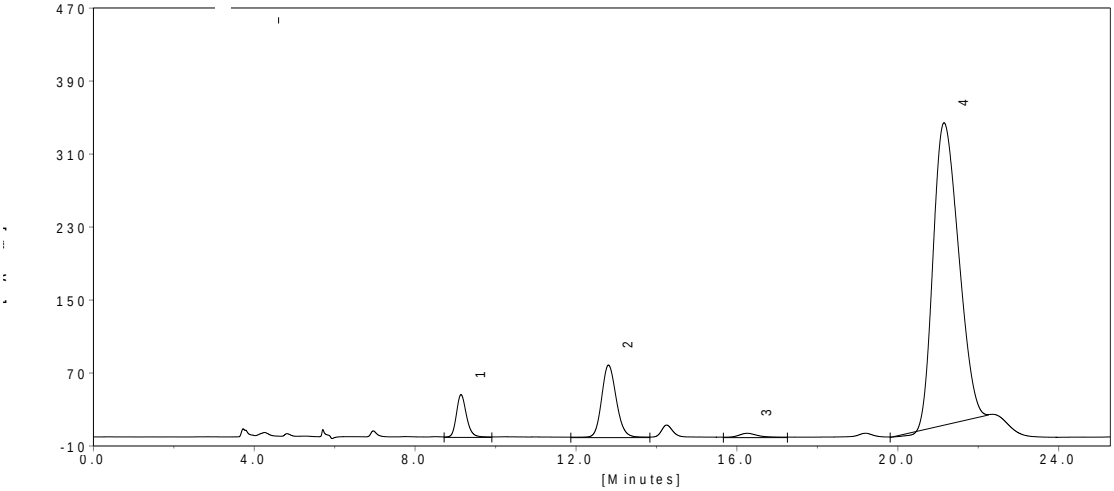


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	8.26500	392.93	6443.55	19.5891
2	11.32750	259.90	6392.02	19.4324
3	16.25333	257.11	10056.92	30.5741
4	20.02167	215.08	10001.06	30.4043



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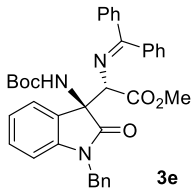
1	9.14000	46.42	788.89	4.5558
2	12.80667	79.09	1972.34	11.3901
3	16.25667	4.24	124.61	0.7196
4	21.15000	330.96	14430.36	83.3345



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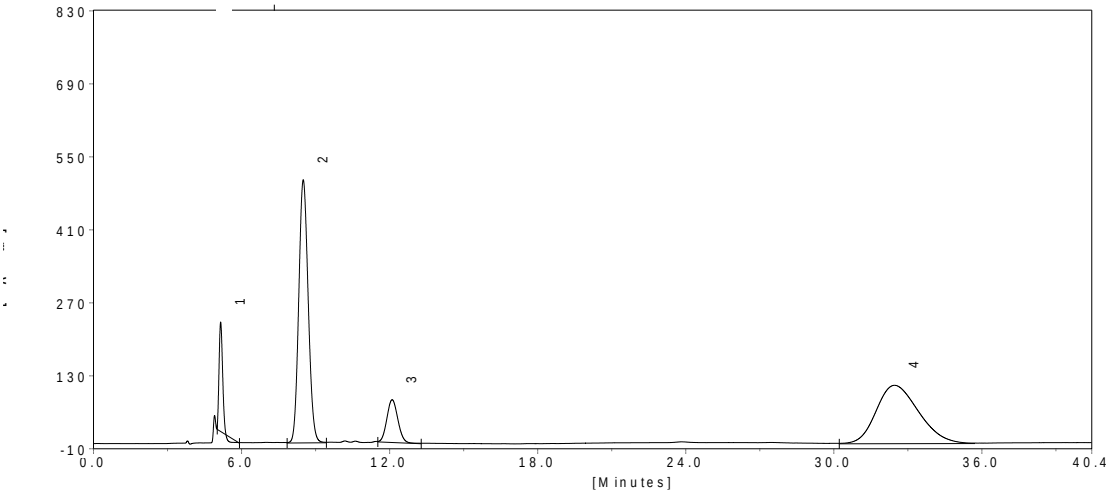
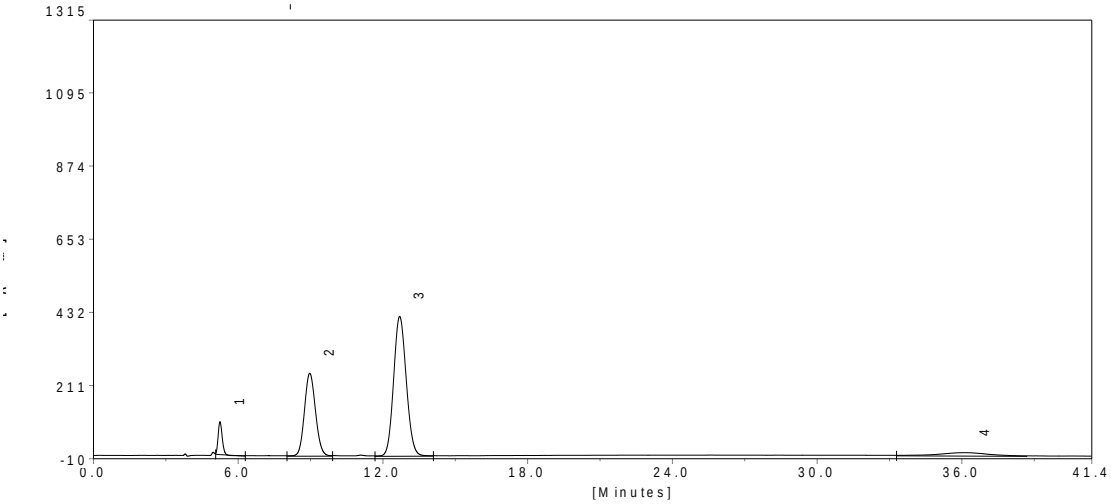
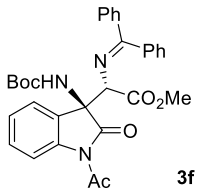


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	5.15417	209.73	1900.45	6.1789
2	8.50167	503.96	13285.12	43.1940
3	12.10333	81.30	2454.84	7.9814
4	32.45750	111.12	13116.47	42.6457



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	5.24583	98.08	1063.85	4.2083
2	8.96750	249.20	7845.90	31.0366
3	12.69417	421.30	15227.32	60.2359
4	36.13417	8.83	1142.41	4.5191



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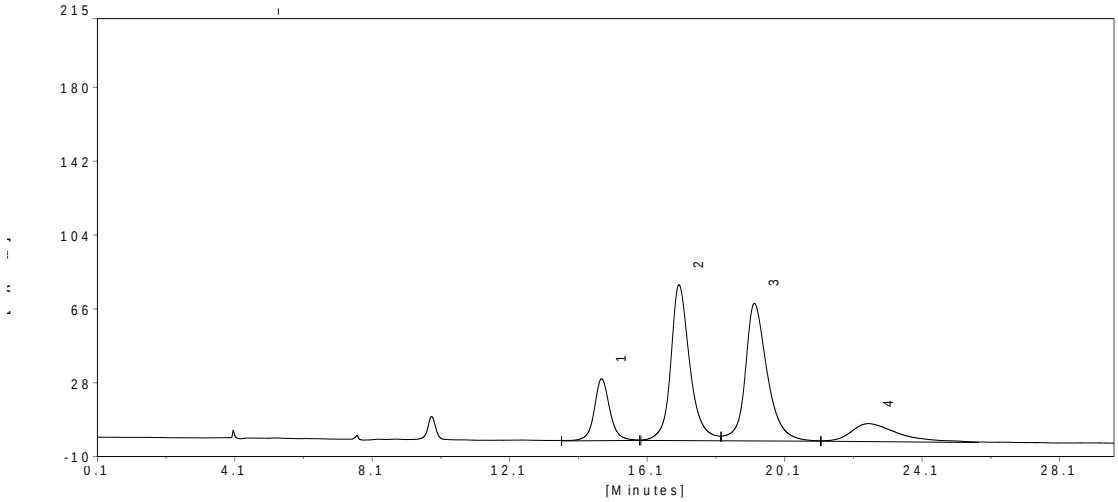
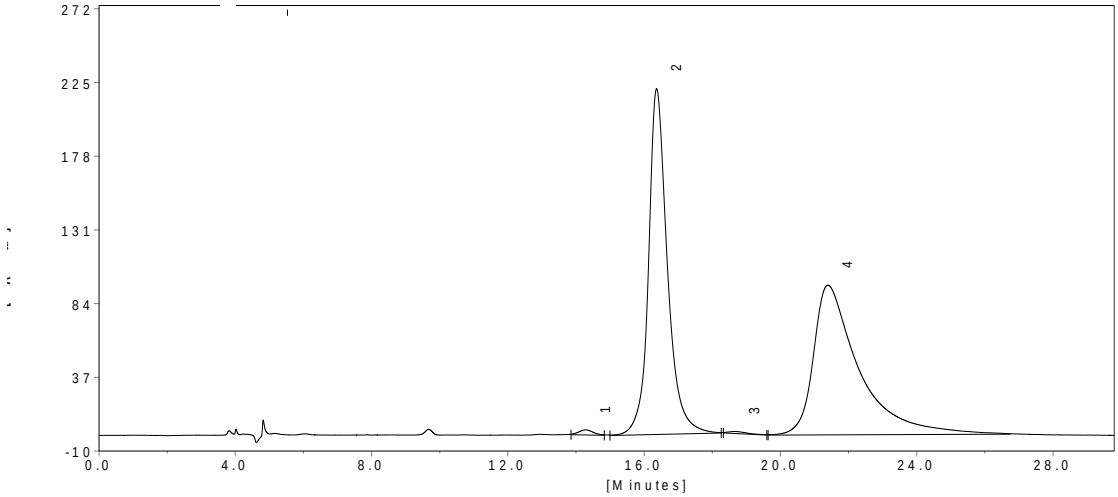
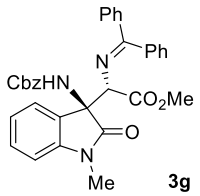


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	14.78750	31.69	970.07	12.1826
2	17.04000	79.98	3059.36	38.4209
3	19.23167	70.57	3114.53	39.1138
4	22.56333	9.00	818.78	10.2827



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	14.31750	2.95	79.62	0.4606
2	16.39750	220.22	8429.64	48.7666
3	18.68750	0.96	28.31	0.1638
4	21.42417	95.15	8748.14	50.6091



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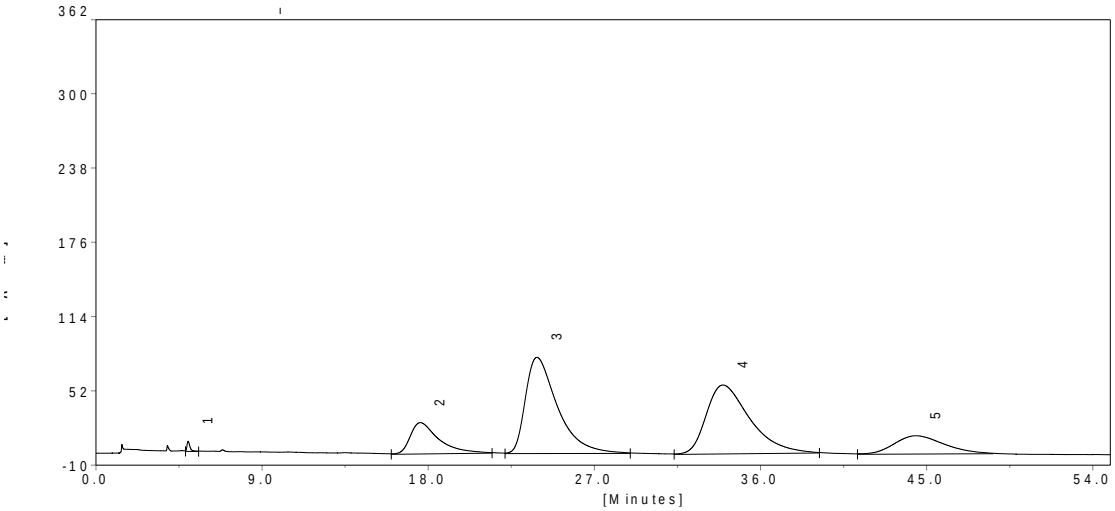
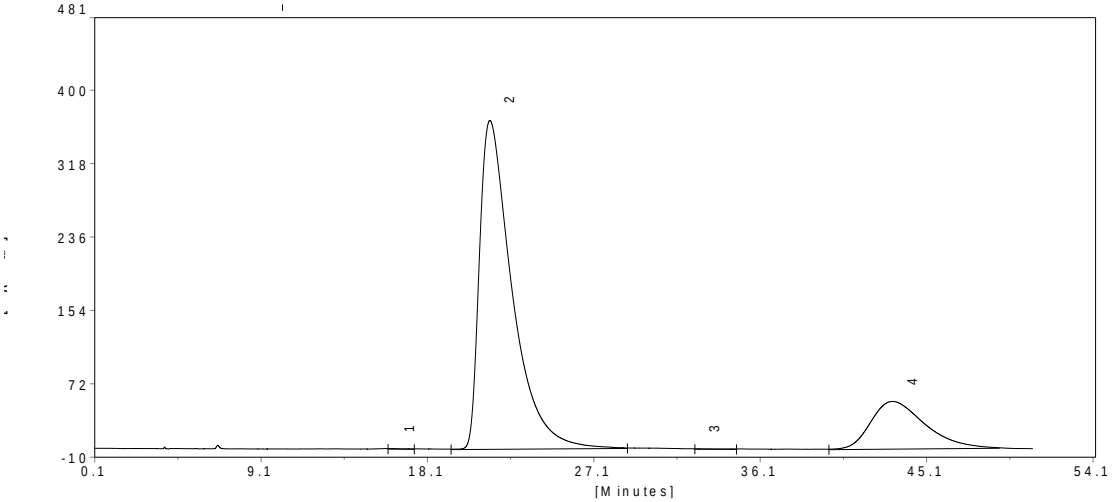
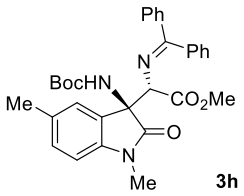


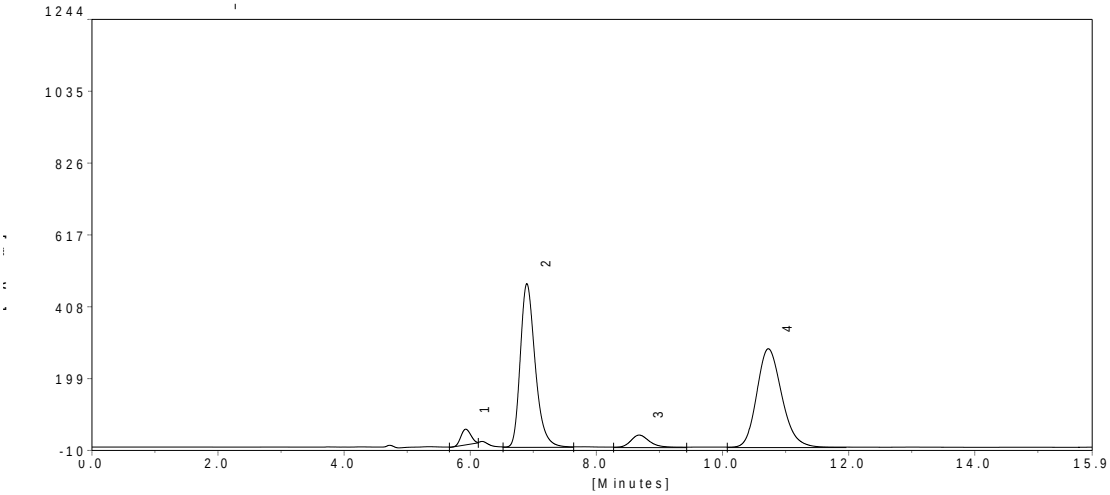
#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	17.56708	25.73	2691.72	11.1259
2	23.89167	79.87	9538.35	39.4255
3	33.96833	57.11	9260.54	38.2772
4	44.40750	14.87	2702.74	11.1714



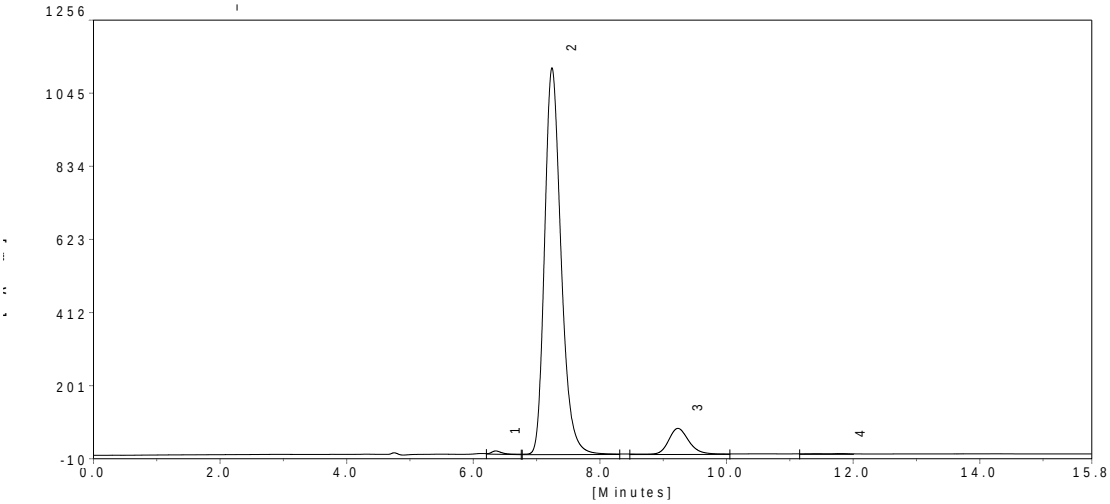
#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	16.02583	0.03	2.91	0.0053
2	21.43083	366.90	44724.17	80.8528
3	32.53250	0.01	4.91	0.0089
4	43.22750	52.74	10583.53	19.1330



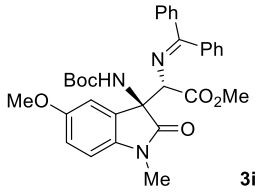
3h



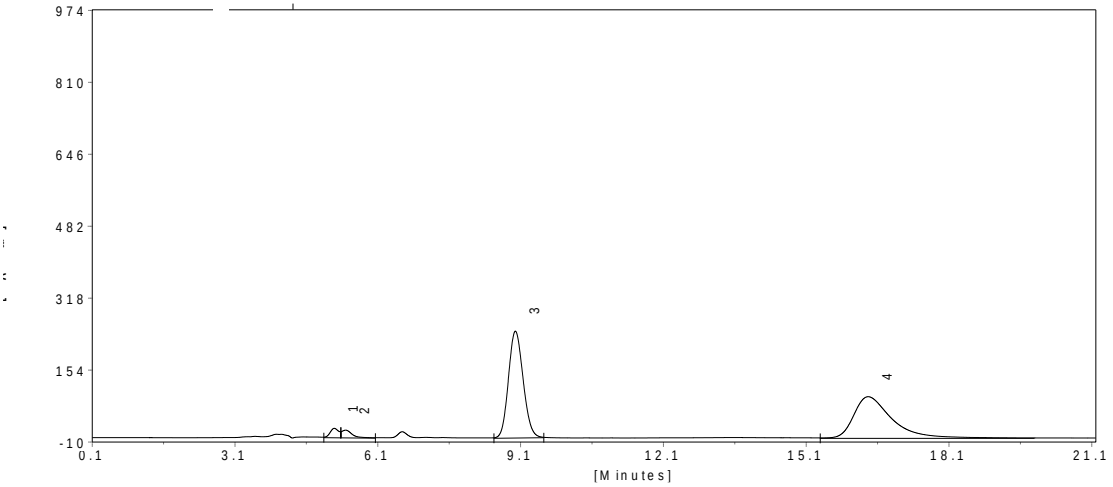
#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	5.92750	44.18	607.61	3.6030
2	6.89750	475.10	7752.88	45.9728
3	8.67833	35.09	688.04	4.0799
4	10.72667	286.31	7815.54	46.3443



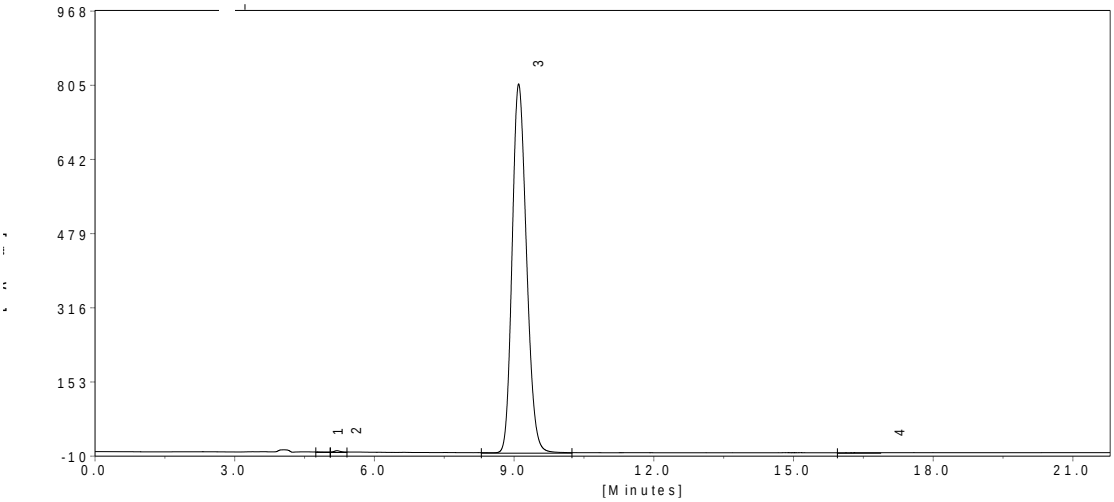
#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	6.35500	8.20	77.01	0.3542
2	7.24333	1114.89	20055.74	92.2429
3	9.23250	73.94	1587.82	7.3029
4	11.80583	0.95	21.74	0.1000



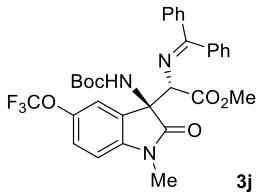
3i



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	5.19917	20.50	243.60	2.2627
2	5.43750	16.60	238.84	2.2184
3	9.00500	242.61	5163.42	47.9603
4	16.41583	93.90	5120.18	47.5586



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	4.82250	0.14	0.50	0.0029
2	5.21833	2.72	22.41	0.1294
3	9.12250	810.43	17292.87	99.8676
4	16.88000	0.02	0.00	0.0000



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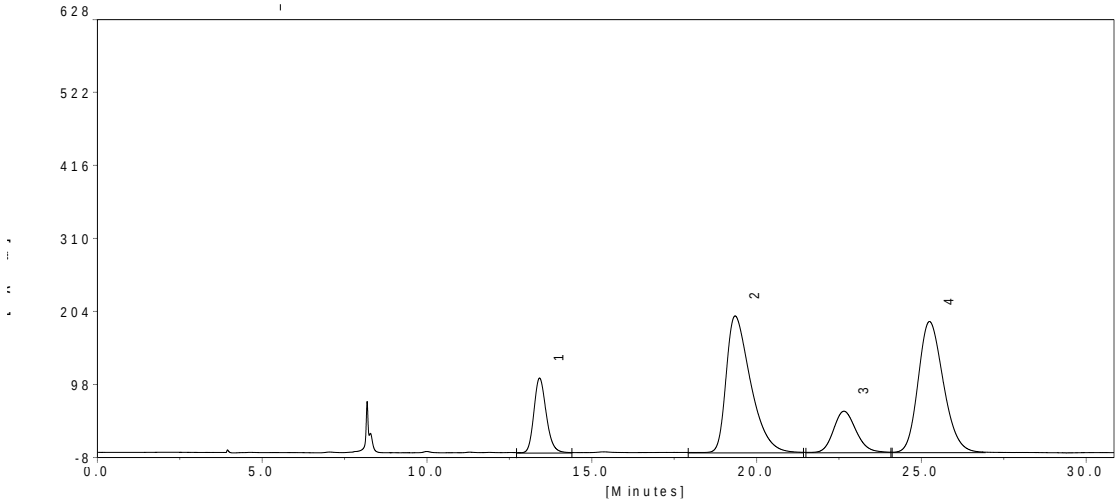
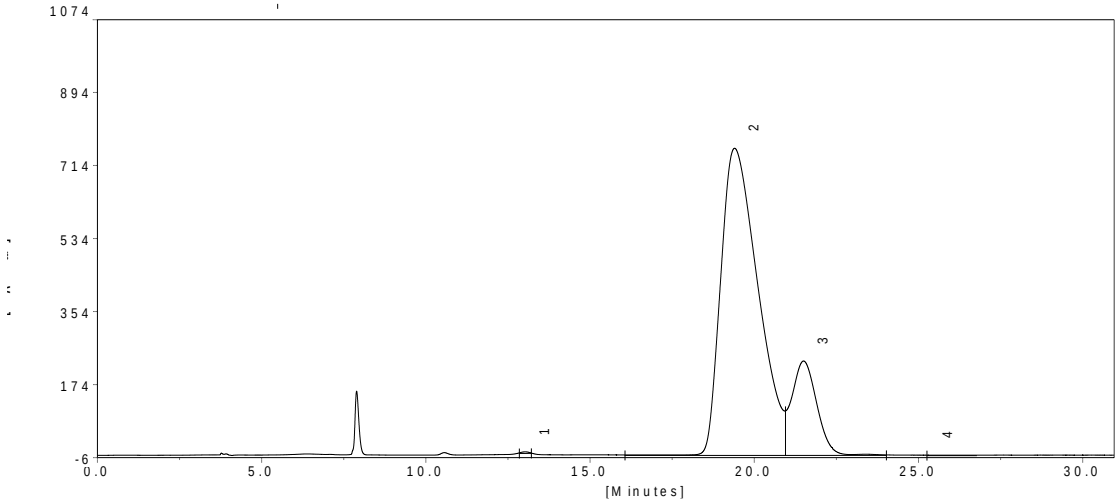
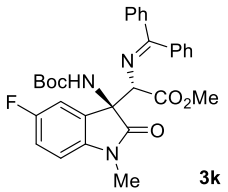


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	13.41667	108.28	2789.10	10.8643
2	19.35167	198.16	10110.28	39.3824
3	22.65333	59.67	2791.26	10.8727
4	25.24833	189.70	9981.46	38.8806



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	13.02583	2.78	38.14	0.0535
2	19.40250	755.88	58987.96	82.7068
3	21.50167	231.52	12294.04	17.2374
4	25.29750	0.02	1.67	0.0023



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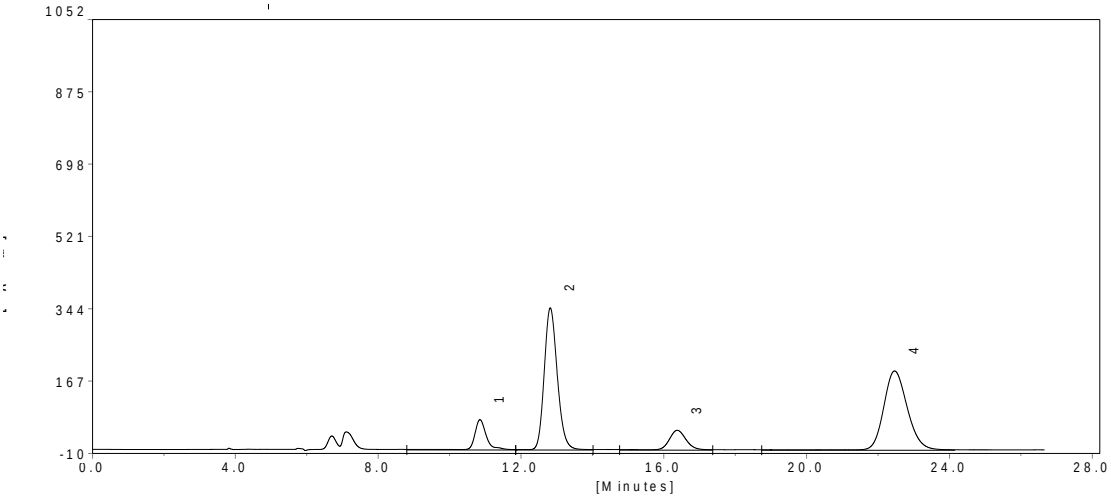
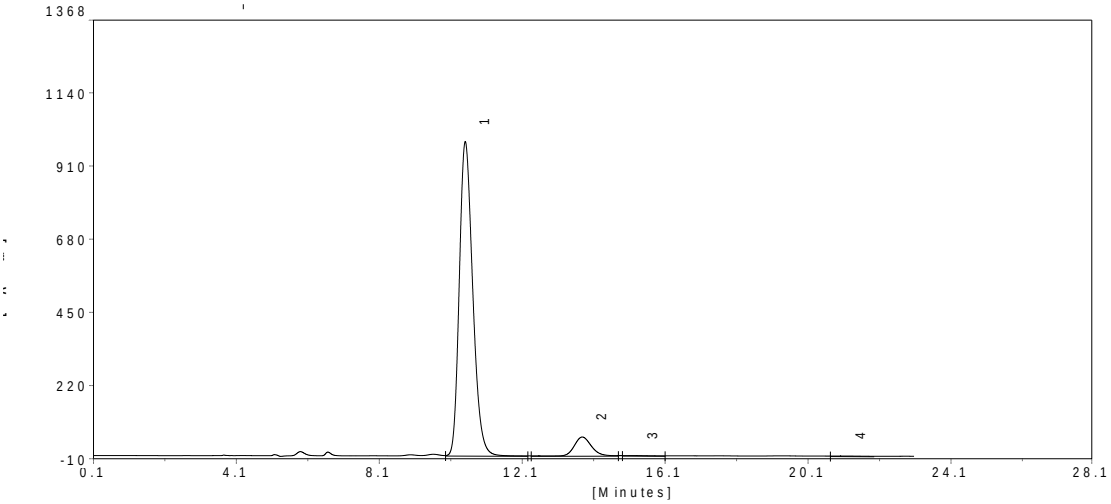
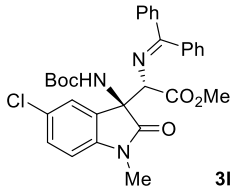


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	10.85167	73.12	1550.68	7.5766
2	12.81917	346.83	8732.07	42.6647
3	16.37750	47.48	1479.82	7.2304
4	22.46500	192.97	8704.15	42.5283



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	10.52333	987.32	25640.33	93.1096
2	13.79667	58.98	1874.95	6.8087
3	15.22250	0.40	10.87	0.0395
4	21.04750	0.32	11.64	0.0423



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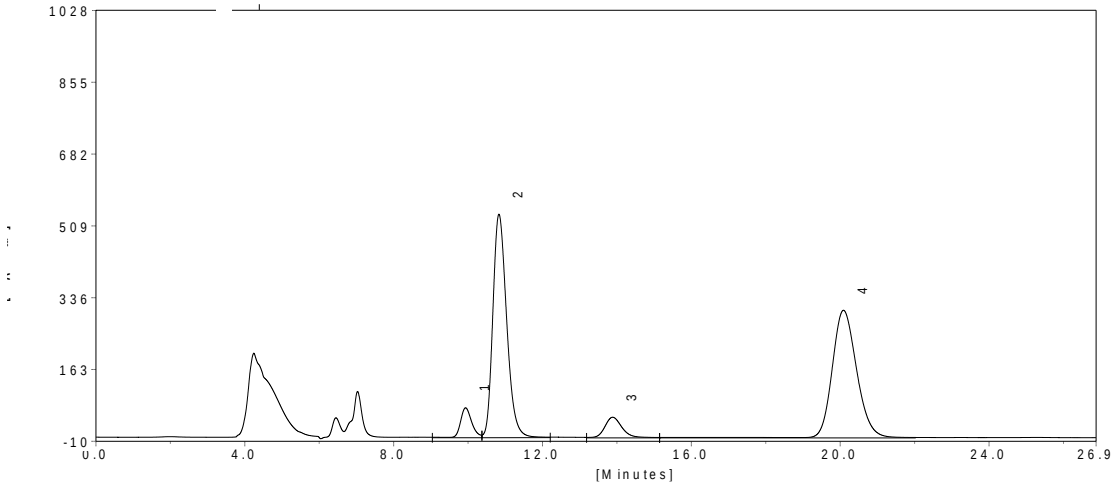
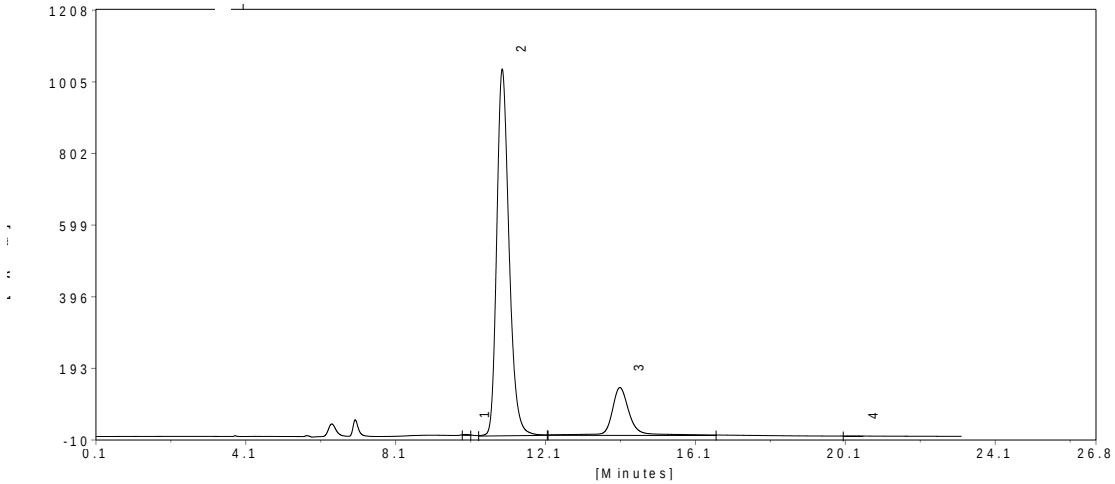
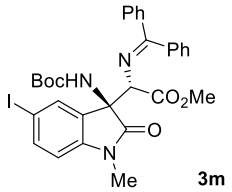


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	9.93417	71.05	1431.29	4.7010
2	10.83000	537.50	13788.21	45.2866
3	13.88583	48.60	1481.29	4.8652
4	20.08833	306.56	13745.78	45.1472



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	10.00583	1.26	10.78	0.0388
2	10.98417	1038.53	23556.79	84.8522
3	14.12500	134.44	4190.67	15.0949
4	20.37250	0.20	3.91	0.0141



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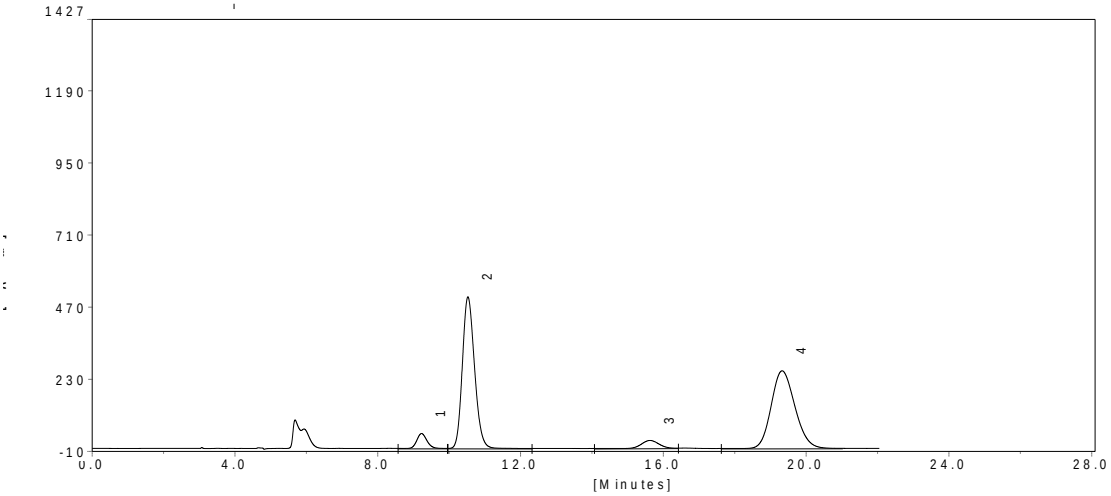
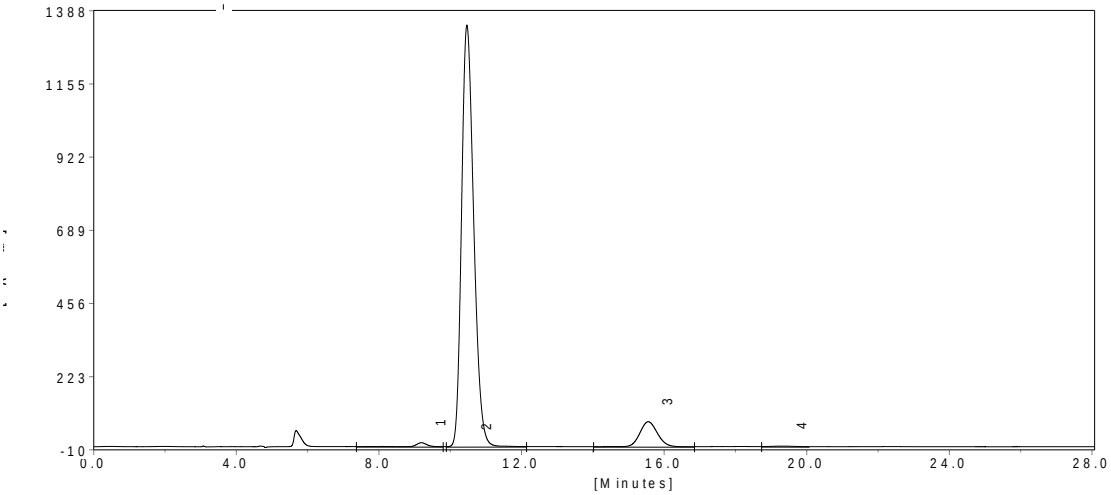
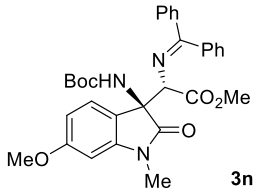


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	9.22917	49.59	963.25	3.6961
2	10.52750	504.60	11922.45	46.5336
3	15.62917	25.97	842.51	3.3731
4	19.32750	258.31	11858.91	46.3952



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	9.18667	12.51	257.82	0.7412
2	10.46833	1342.32	31754.57	91.2946
3	15.55417	79.51	2710.51	7.7927
4	19.32167	1.49	59.61	0.1714



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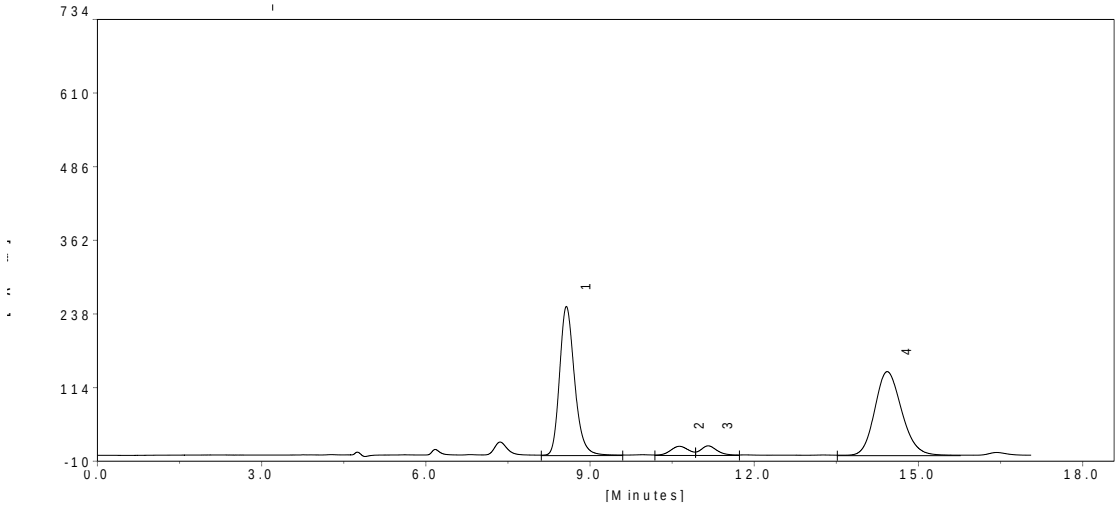
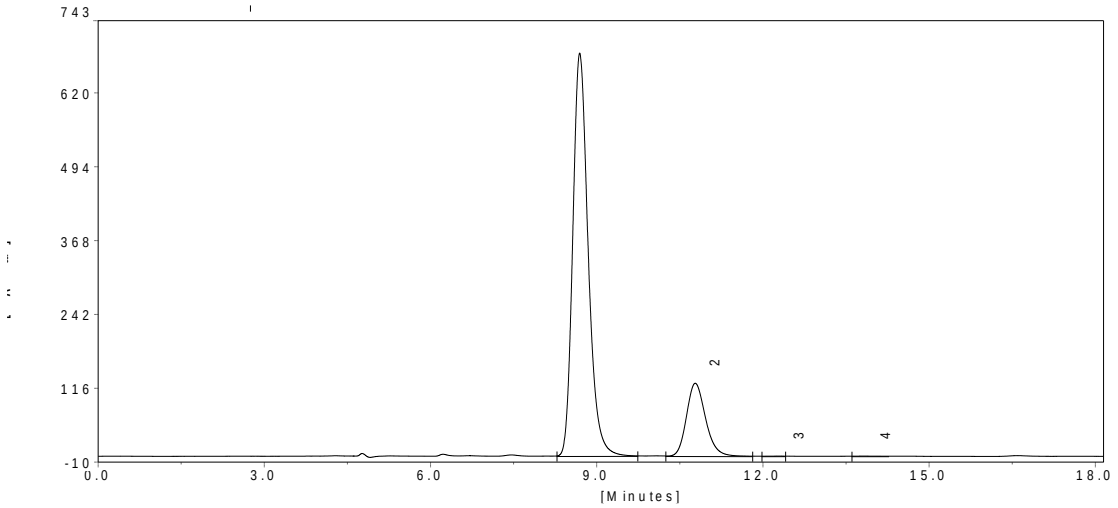
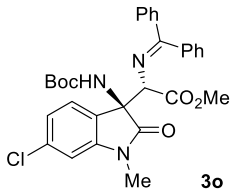


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	8.56833	250.39	4721.03	46.6487
2	10.63917	14.63	322.33	3.1850
3	11.15833	15.43	310.60	3.0690
4	14.43167	140.76	4766.44	47.0973



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	8.69333	687.49	13221.22	81.7272
2	10.77917	124.32	2950.58	18.2391
3	12.29083	0.11	1.26	0.0078
4	13.85667	0.22	4.20	0.0260



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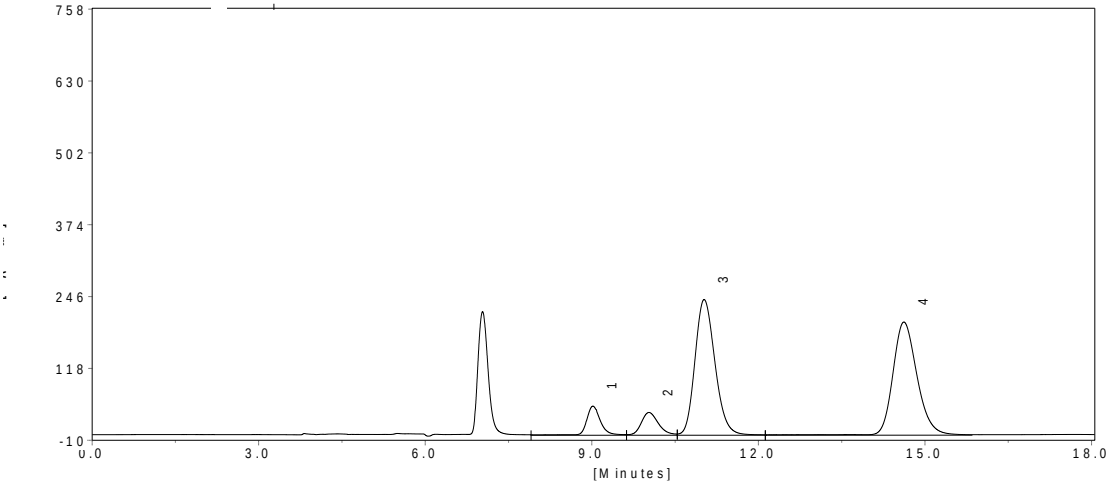
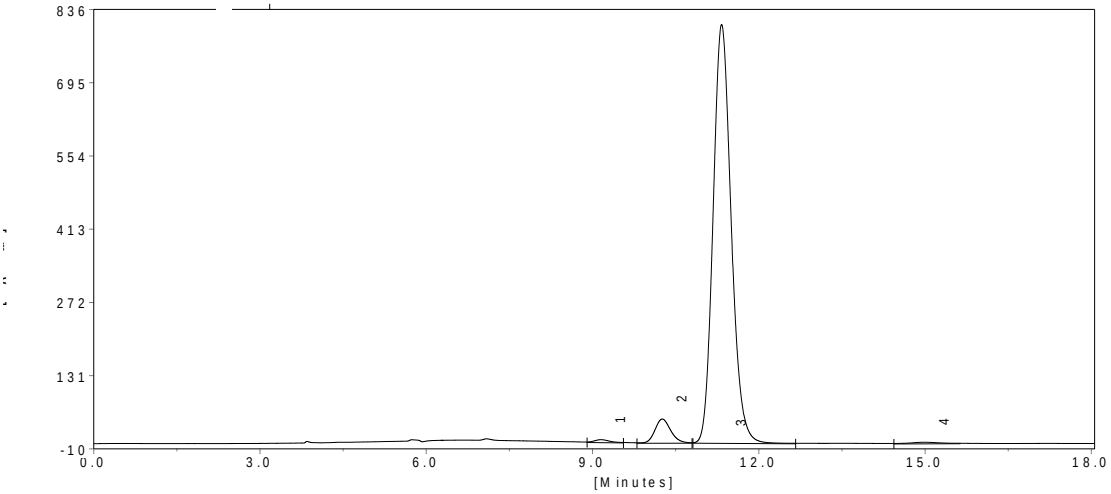
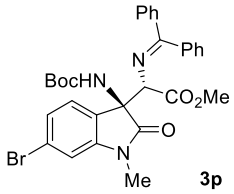


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	9.01833	51.11	831.37	6.1058
2	10.02750	39.80	825.19	6.0604
3	11.02167	240.98	5987.99	43.9778
4	14.62167	200.85	5971.41	43.8560



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	9.15250	4.88	81.74	0.4251
2	10.25917	45.79	878.77	4.5694
3	11.33000	805.81	18206.06	94.6680
4	14.99333	2.18	64.91	0.3375



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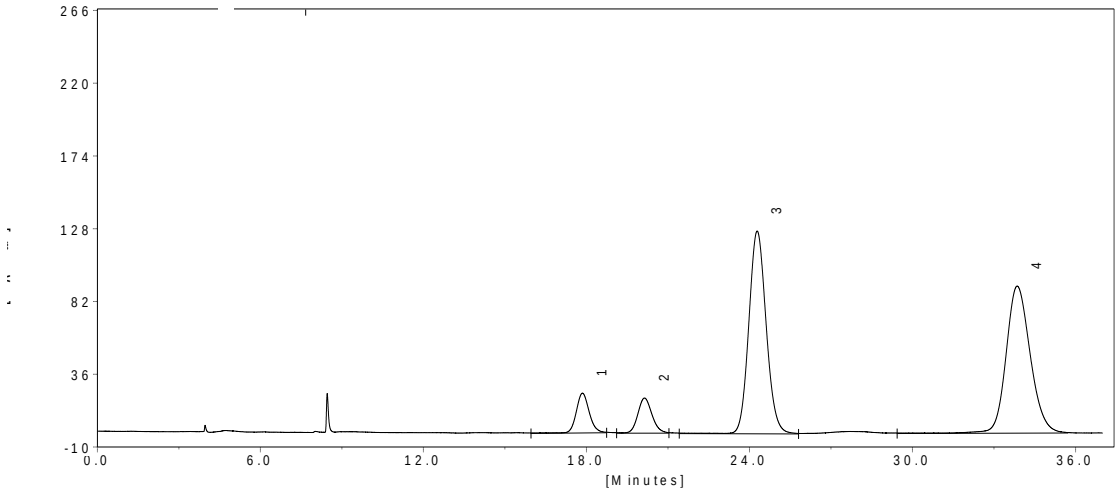
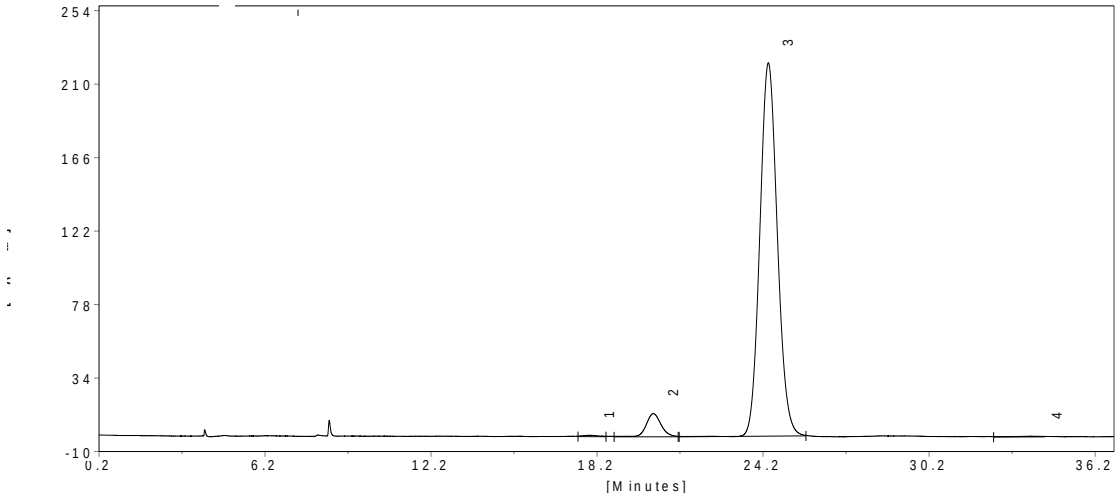
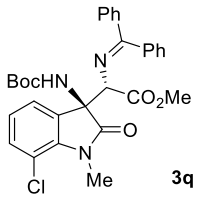


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	17.85833	24.90	792.57	6.1797
2	20.14583	21.92	768.58	5.9925
3	24.28750	127.94	5619.48	43.8147
4	33.85417	92.74	5644.92	44.0131



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	17.88500	0.58	17.03	0.1657
2	20.19417	13.62	482.83	4.6974
3	24.34250	223.31	9728.24	94.6440
4	34.06833	0.12	4.16	0.0405



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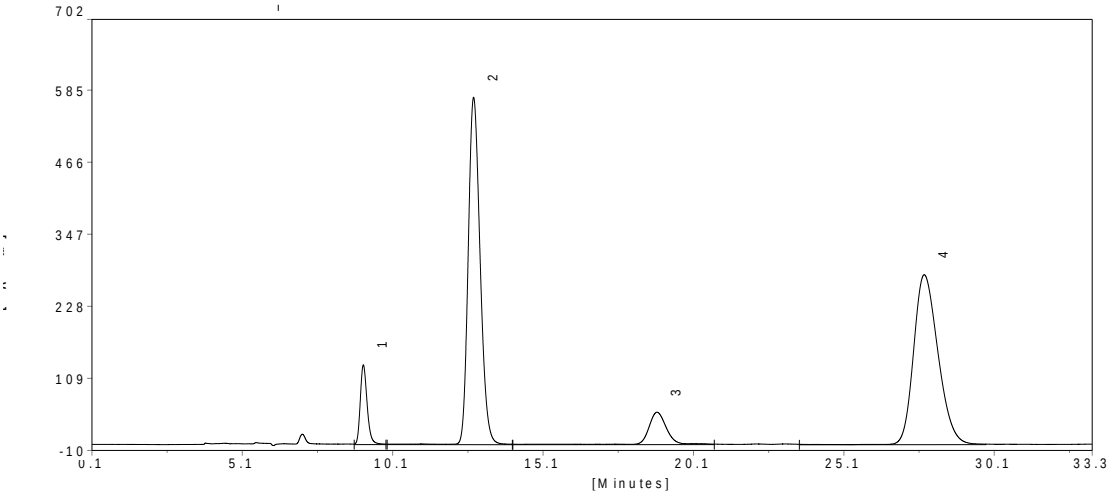
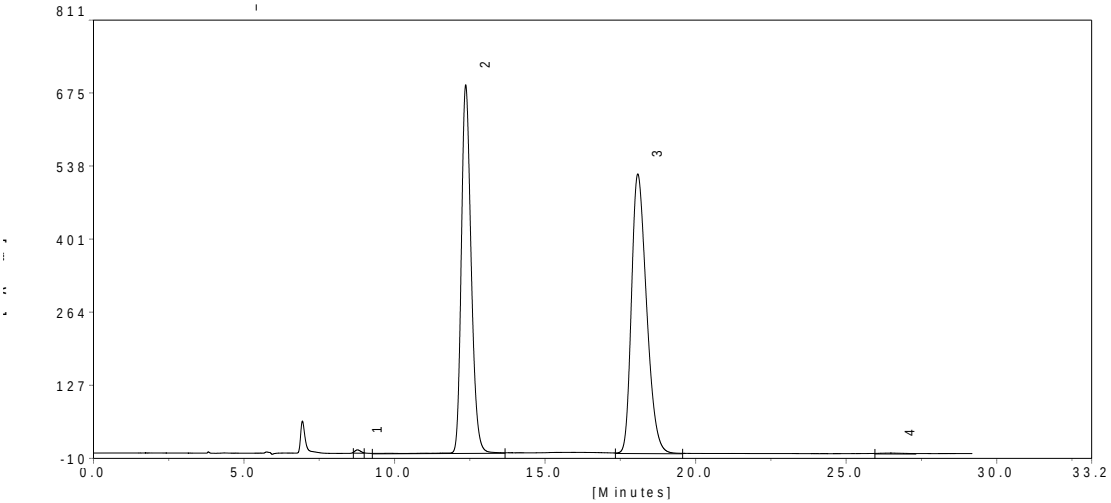
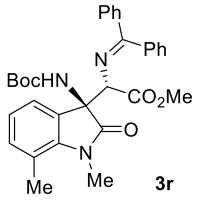


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	9.08167	130.99	2040.25	5.7862
2	12.74833	573.08	15616.74	44.2894
3	18.84083	52.81	2027.36	5.7496
4	27.73083	279.95	15576.29	44.1747



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	8.80583	5.26	61.09	0.1815
2	12.39667	690.13	15466.82	45.9475
3	18.11250	523.27	18102.37	53.7769
4	26.50333	0.76	31.69	0.0941



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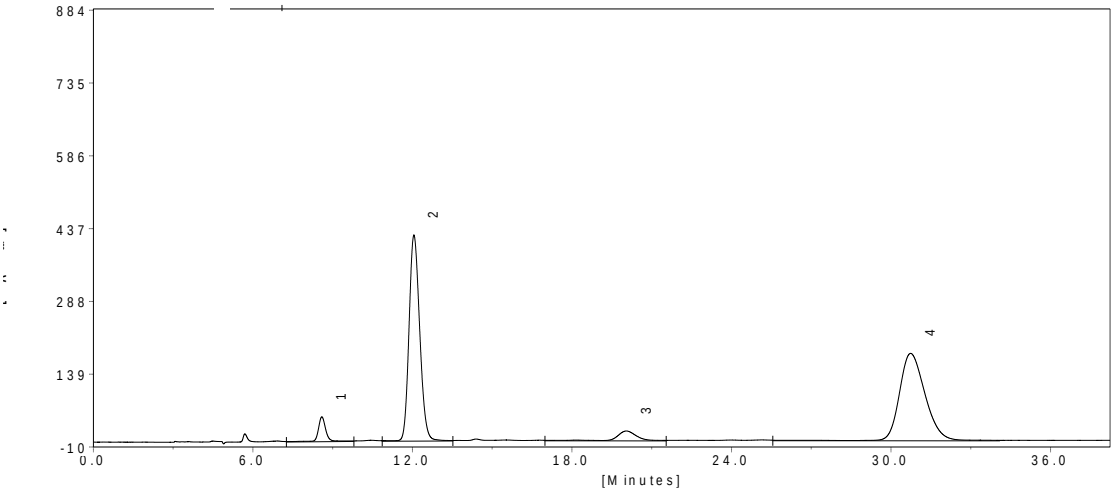
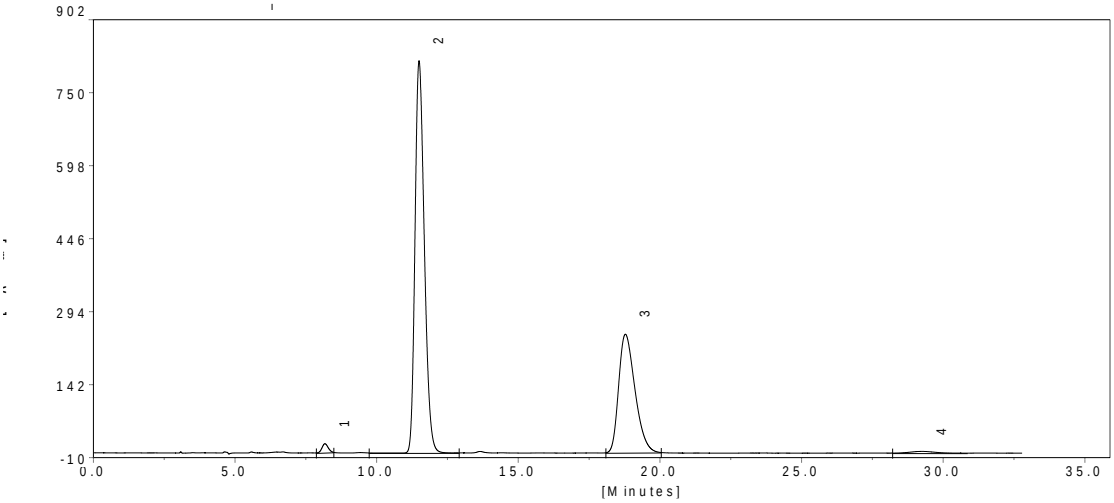
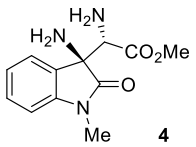


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	8.59333	50.00	895.89	3.5855
2	12.05667	420.74	11630.70	46.5476
3	20.05750	19.19	845.35	3.3832
4	30.74083	177.96	11614.71	46.4837



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	8.17583	18.57	275.02	0.9492
2	11.49750	816.77	18634.77	64.3165
3	19.78167	246.79	9854.57	34.0123
4	29.25500	3.57	209.17	0.7219



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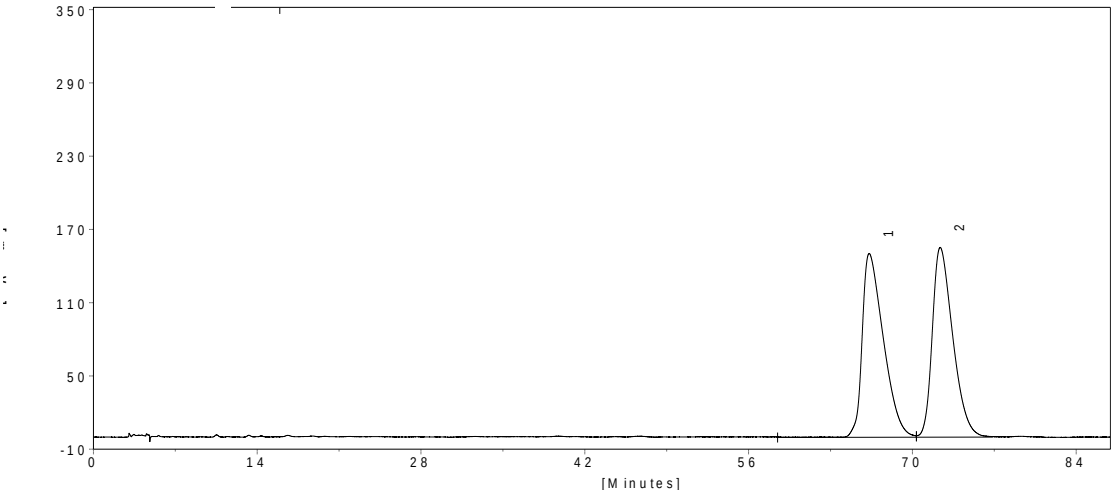
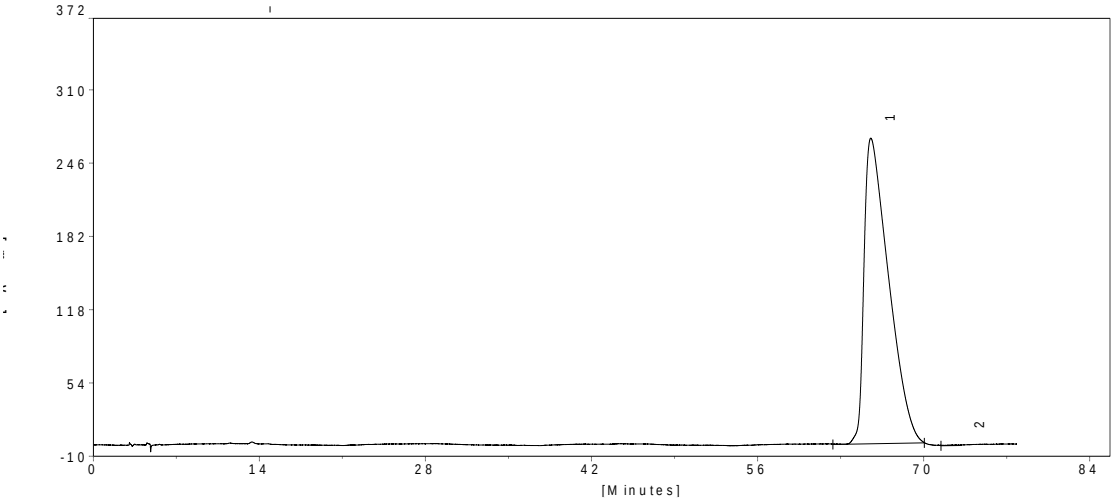
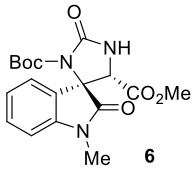


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	66.30333	150.19	18694.26	49.9146
2	72.37500	155.07	18758.20	50.0854



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	65.54750	266.53	38182.33	99.9882
2	73.06917	0.02	4.49	0.0118



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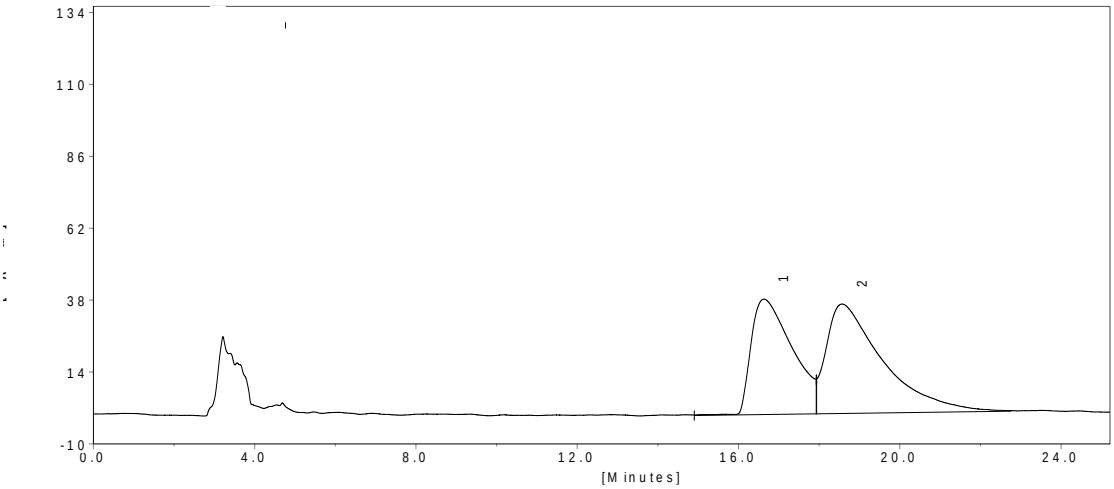
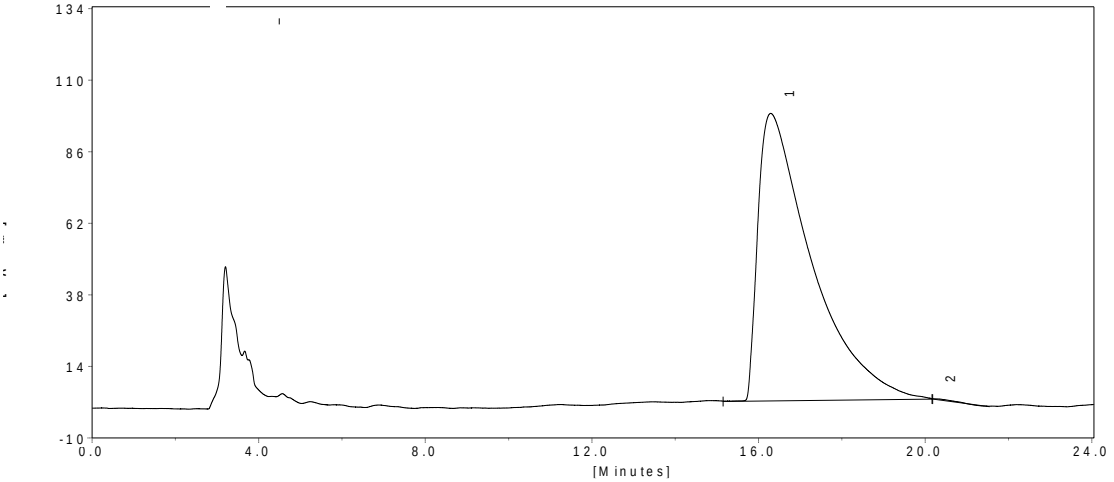
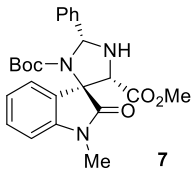


#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	16.63333	38.37	2699.11	43.4301
2	18.58917	36.33	3515.74	56.5699



#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	16.29083	96.29	8562.64	99.9828
2	20.15250	0.00	1.48	0.0172



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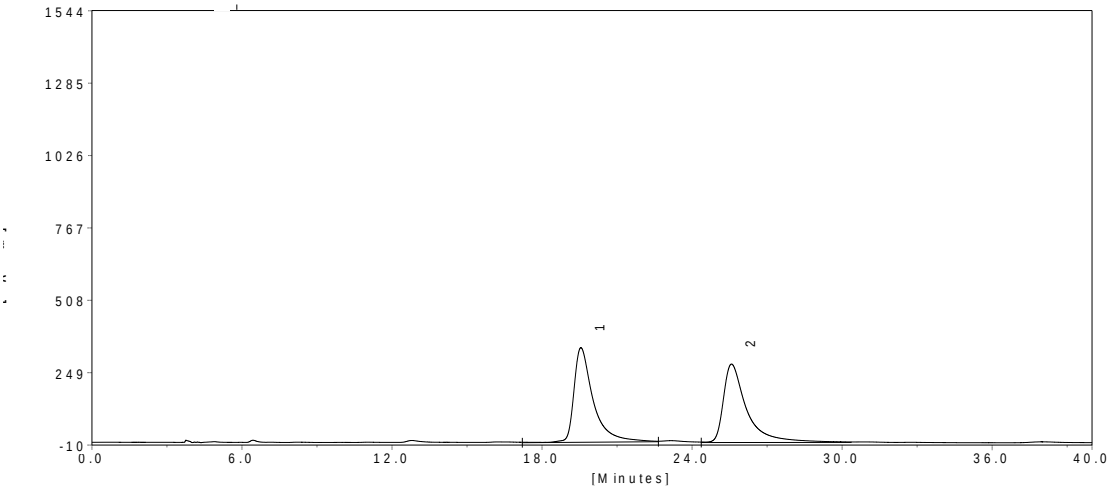
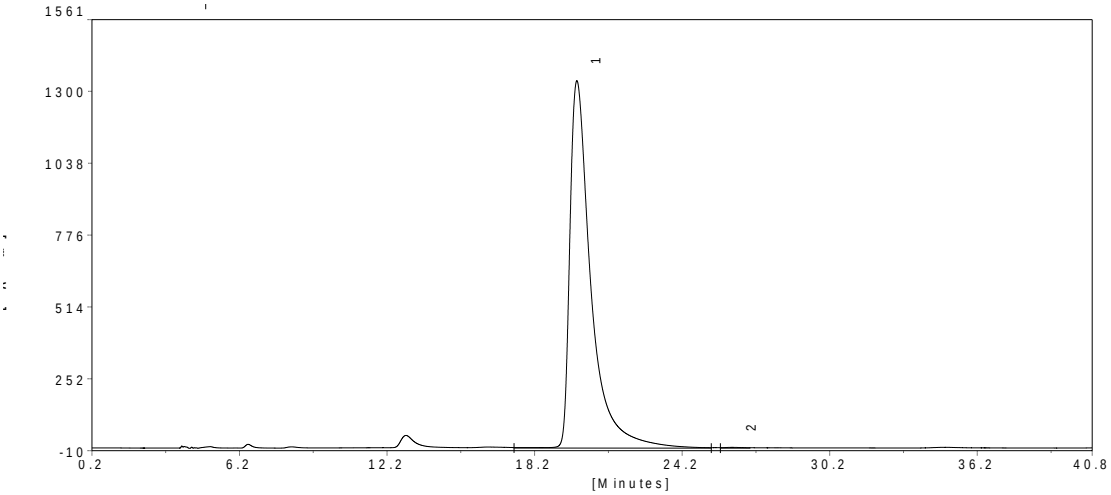


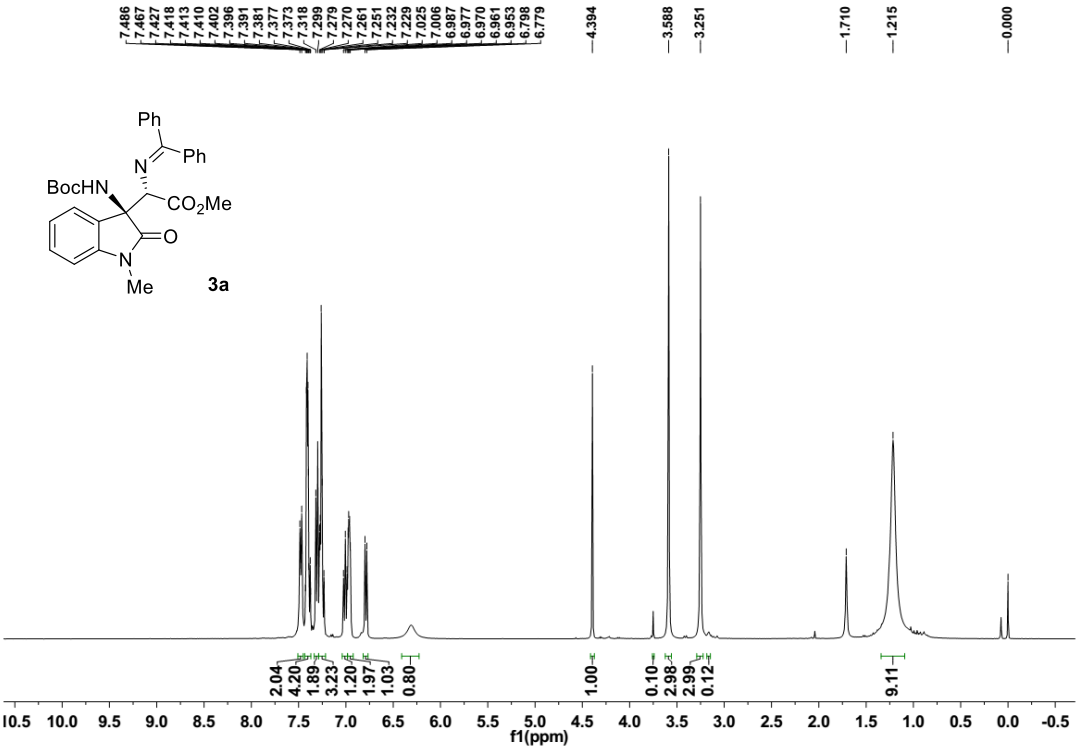
#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	19.59417	337.10	17697.42	50.0469
2	25.61833	279.29	17664.22	49.9531



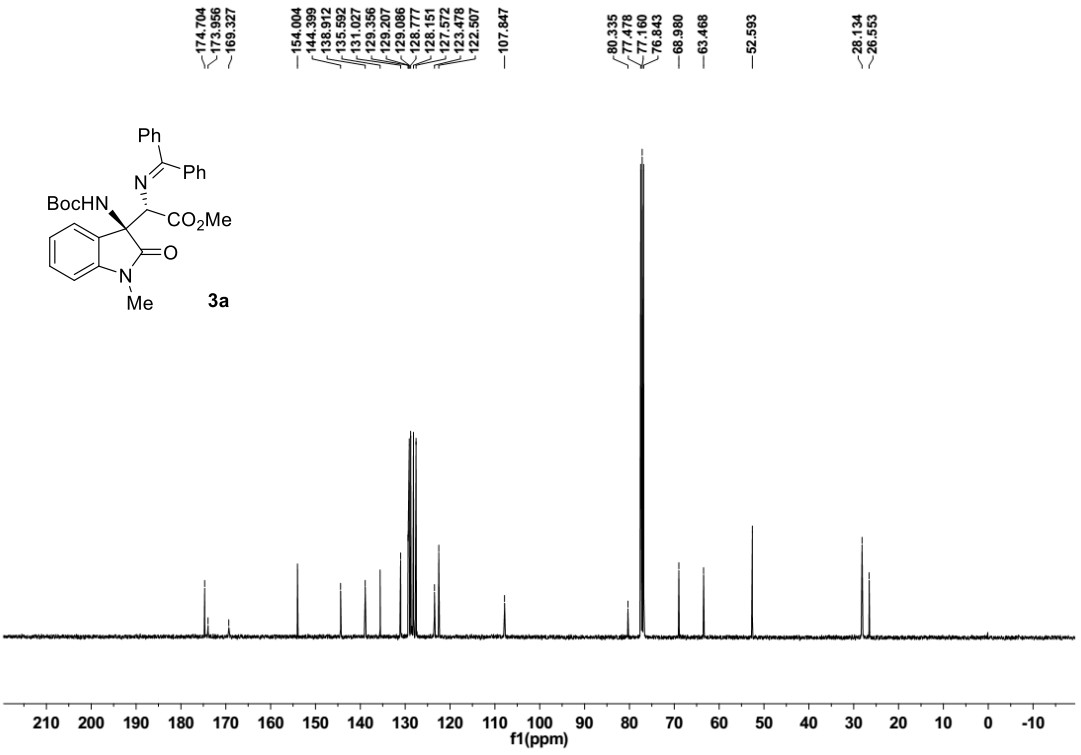
#	Ret Time(min)	Height(mV)	Area (mV.sec)	Area (%)
1	19.87250	1337.65	79253.33	99.9476
2	26.18417	1.09	41.55	0.0524

7. ^{1}H NMR and ^{13}C NMR spectra

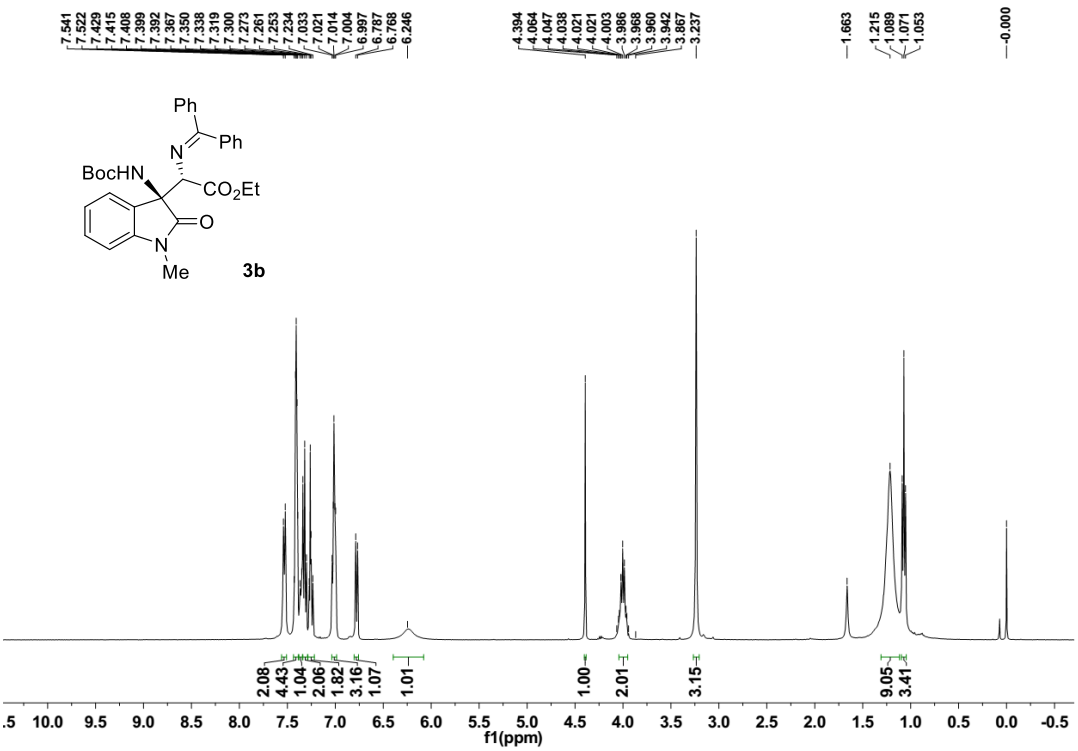
^{1}H NMR spectrum of compound **3a** ($CDCl_3$)



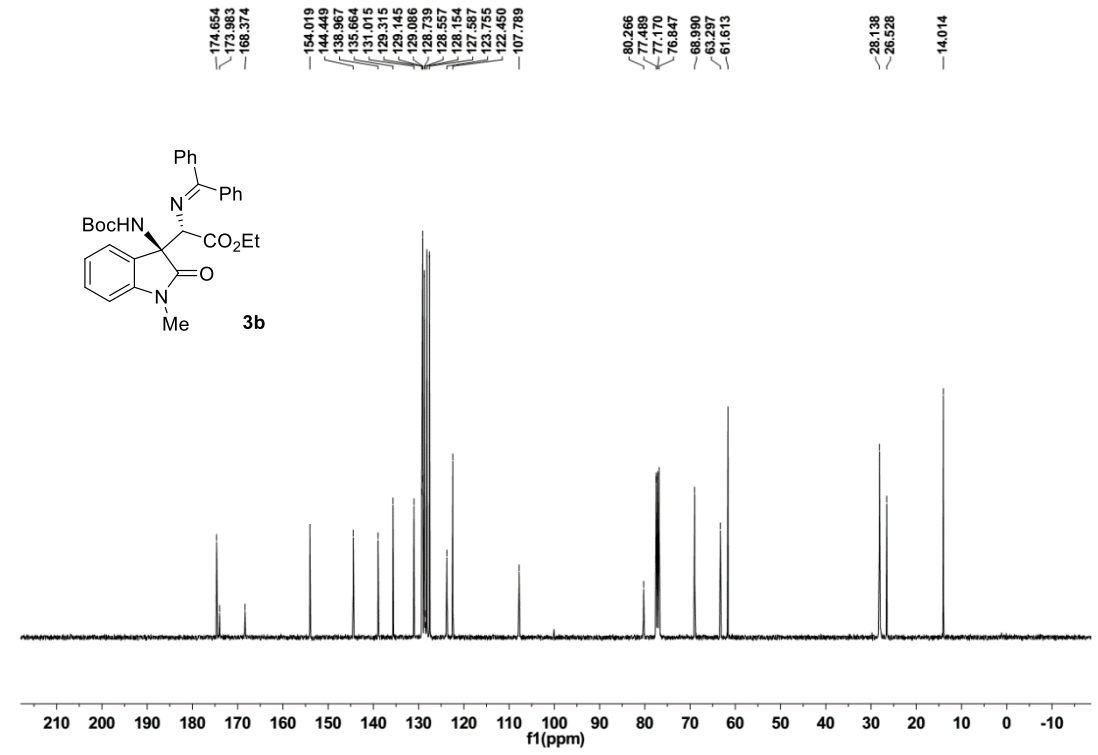
^{13}C NMR spectrum of compound **3a** ($CDCl_3$)



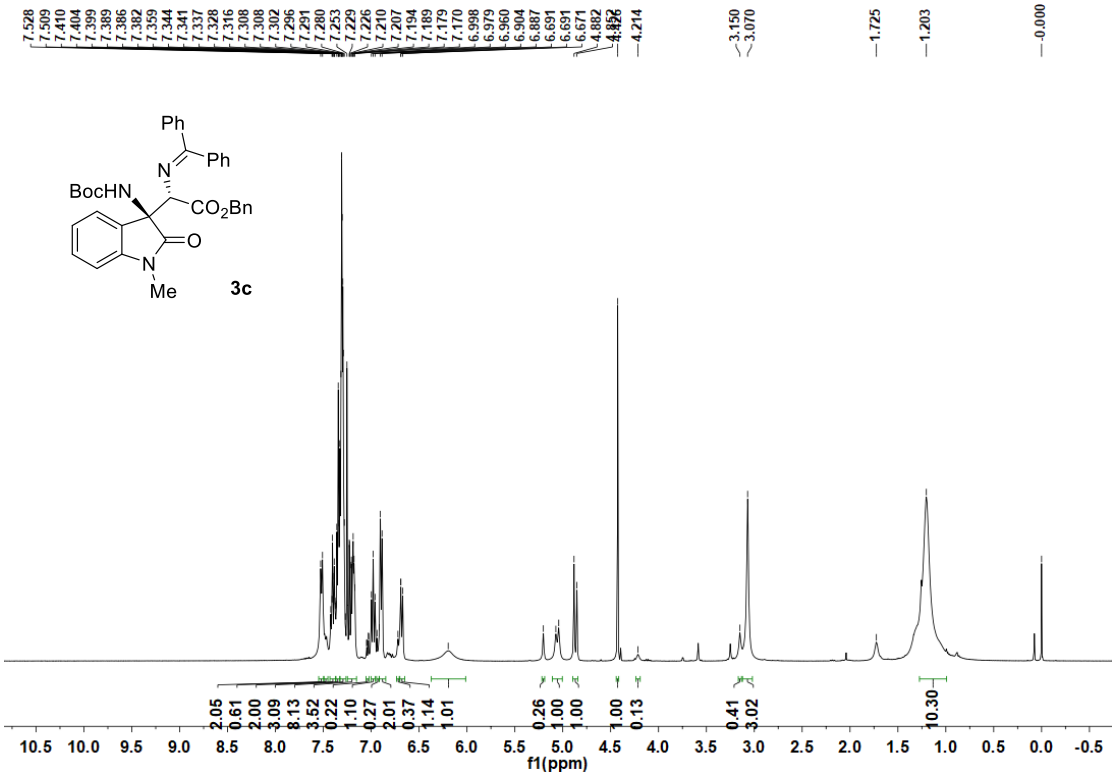
^{1}H NMR spectrum of compound **3b** ($CDCl_3$)



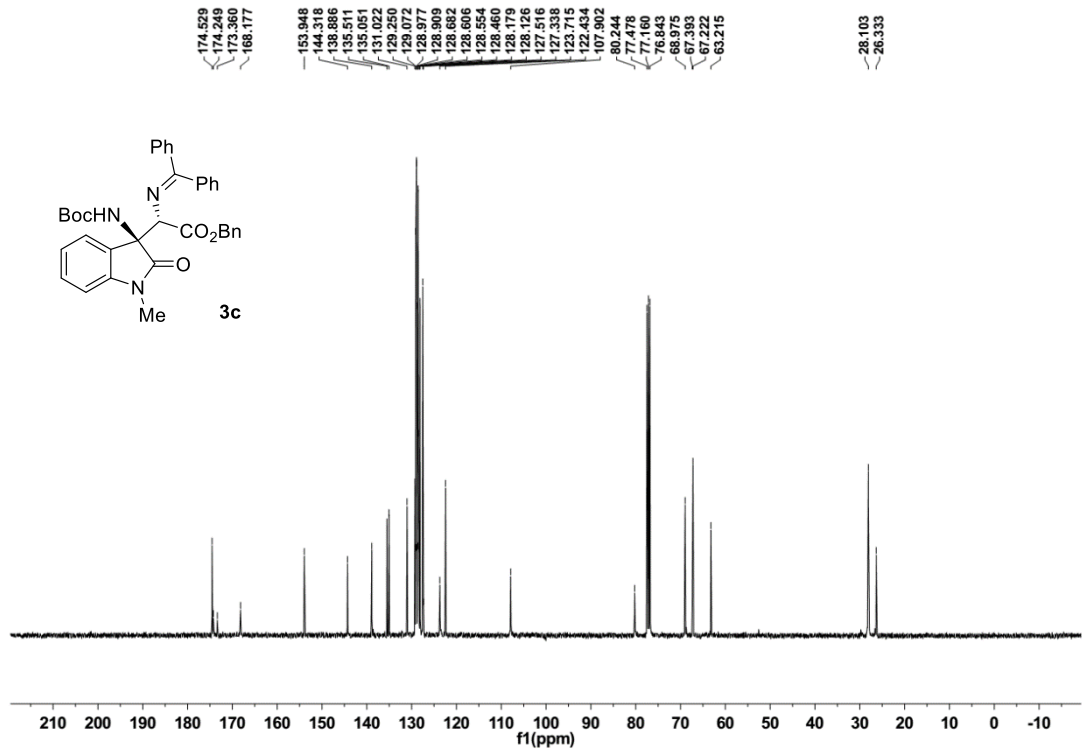
^{13}C NMR spectrum of compound **3b** ($CDCl_3$)



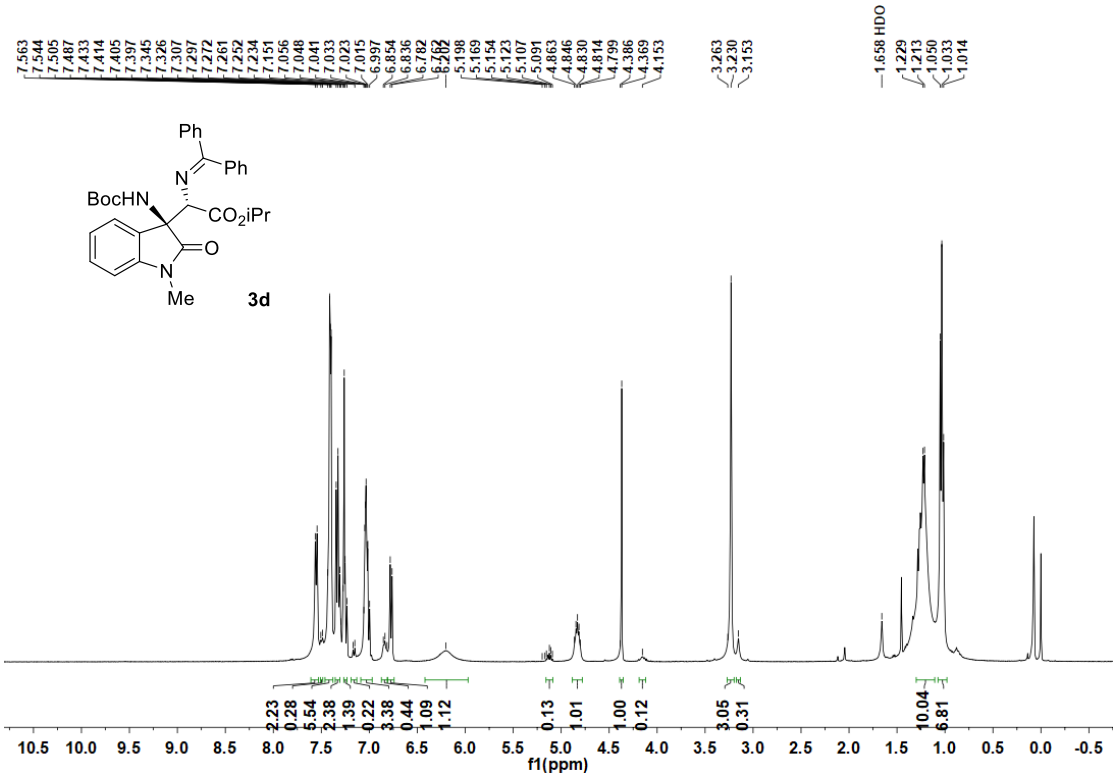
^{1}H NMR spectrum of compound **3c** ($CDCl_3$)



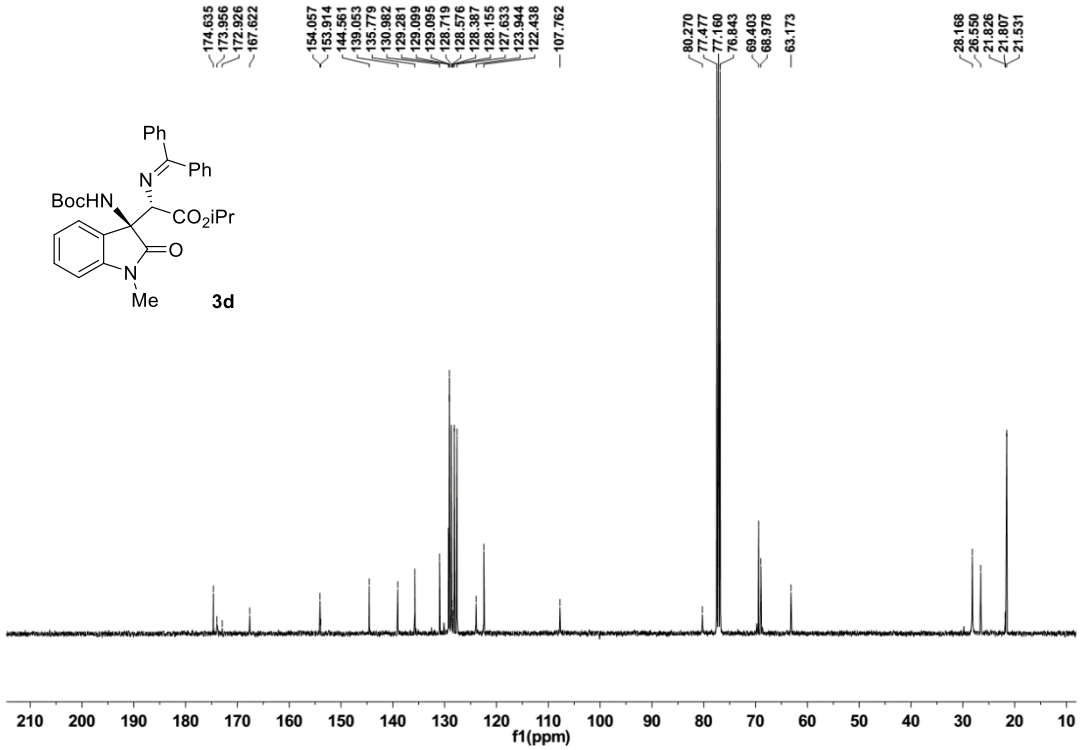
^{13}C NMR spectrum of compound **3c** ($CDCl_3$)



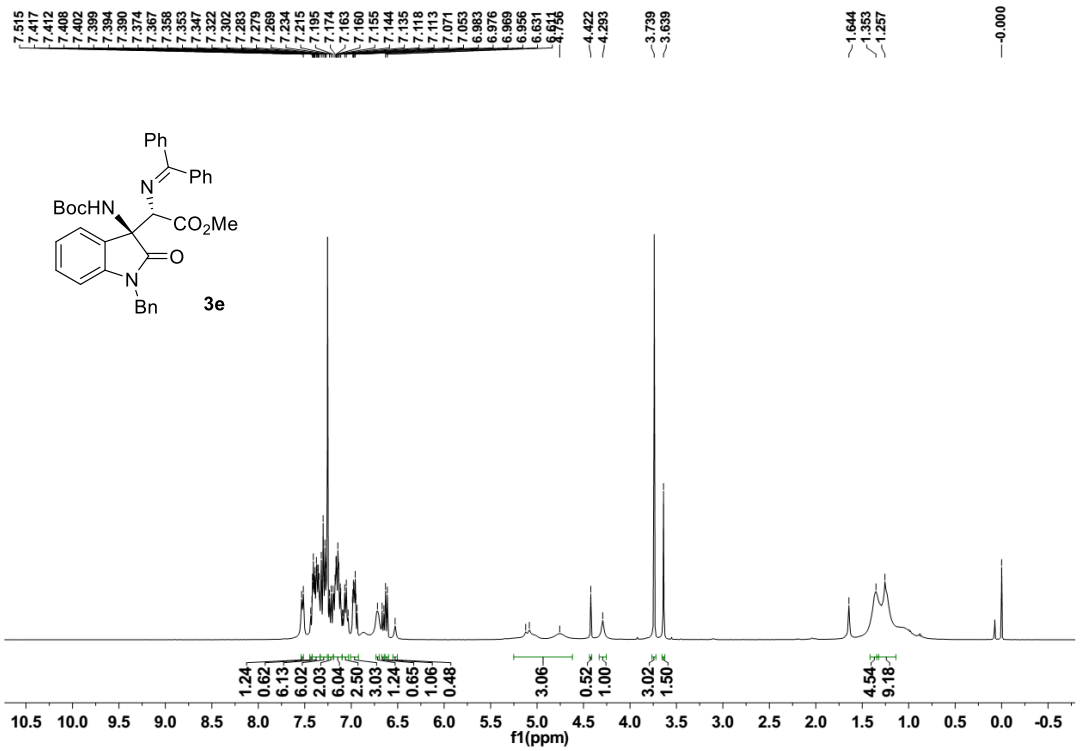
^{1}H NMR spectrum of compound **3d** ($CDCl_3$)



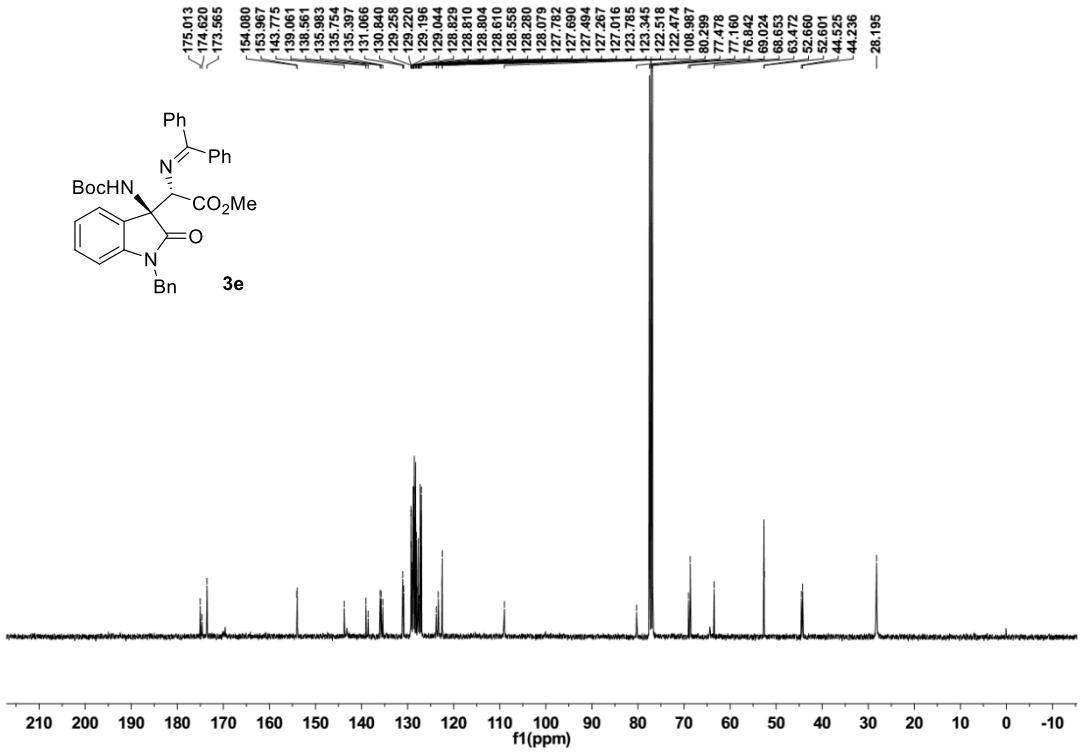
^{13}C NMR spectrum of compound **3d** ($CDCl_3$)



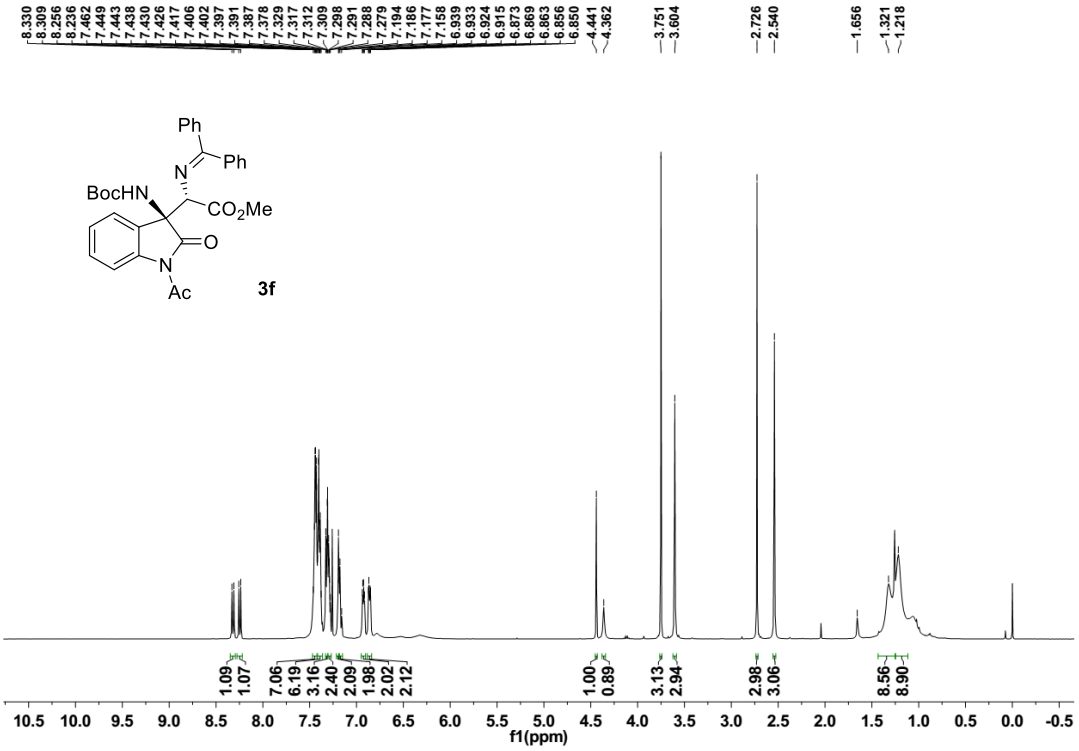
^{1}H NMR spectrum of compound **3e** ($CDCl_3$)



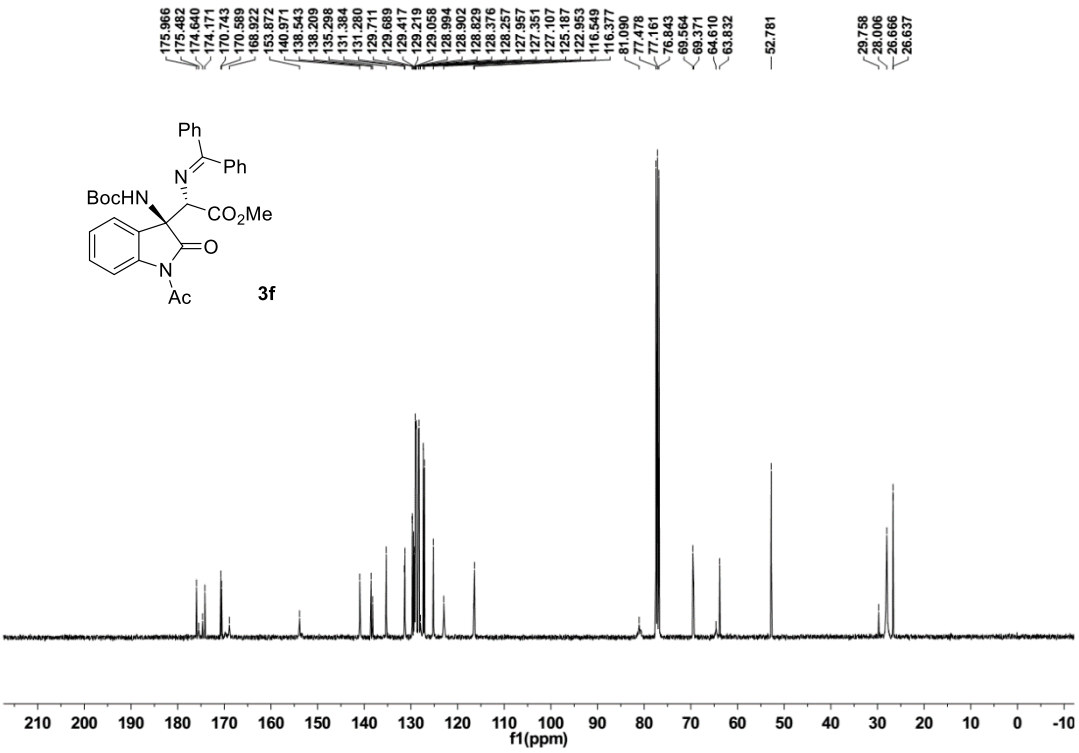
^{13}C NMR spectrum of compound **3e** ($CDCl_3$)



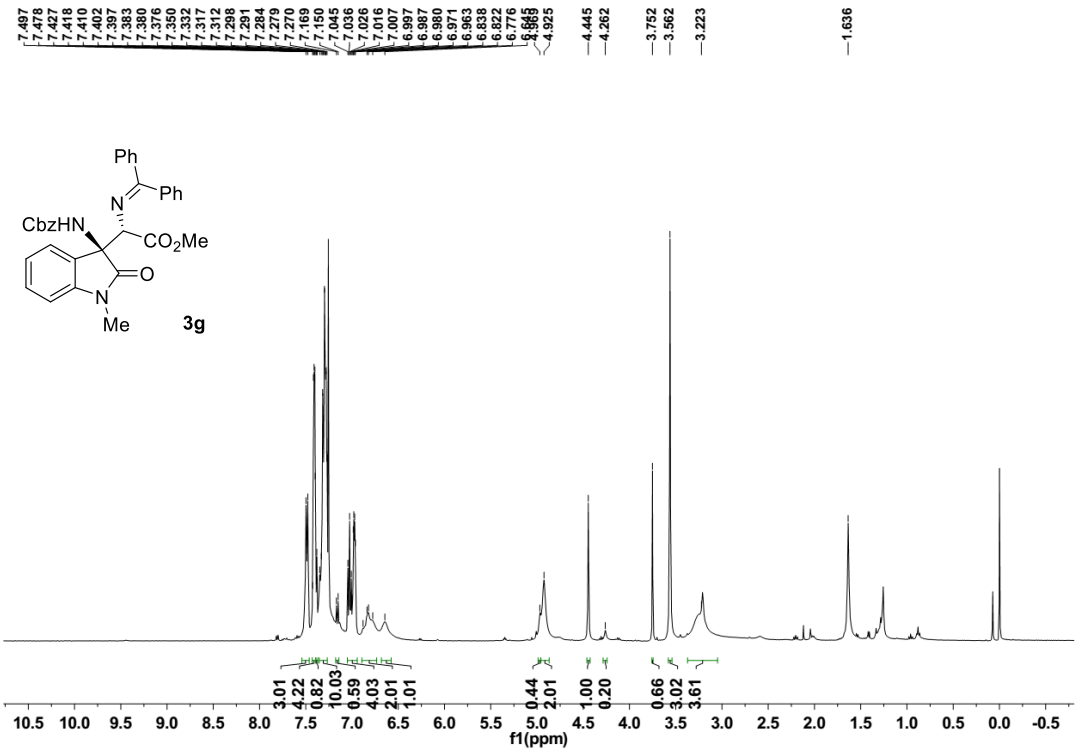
^{1}H NMR spectrum of compound **3f** ($CDCl_3$)



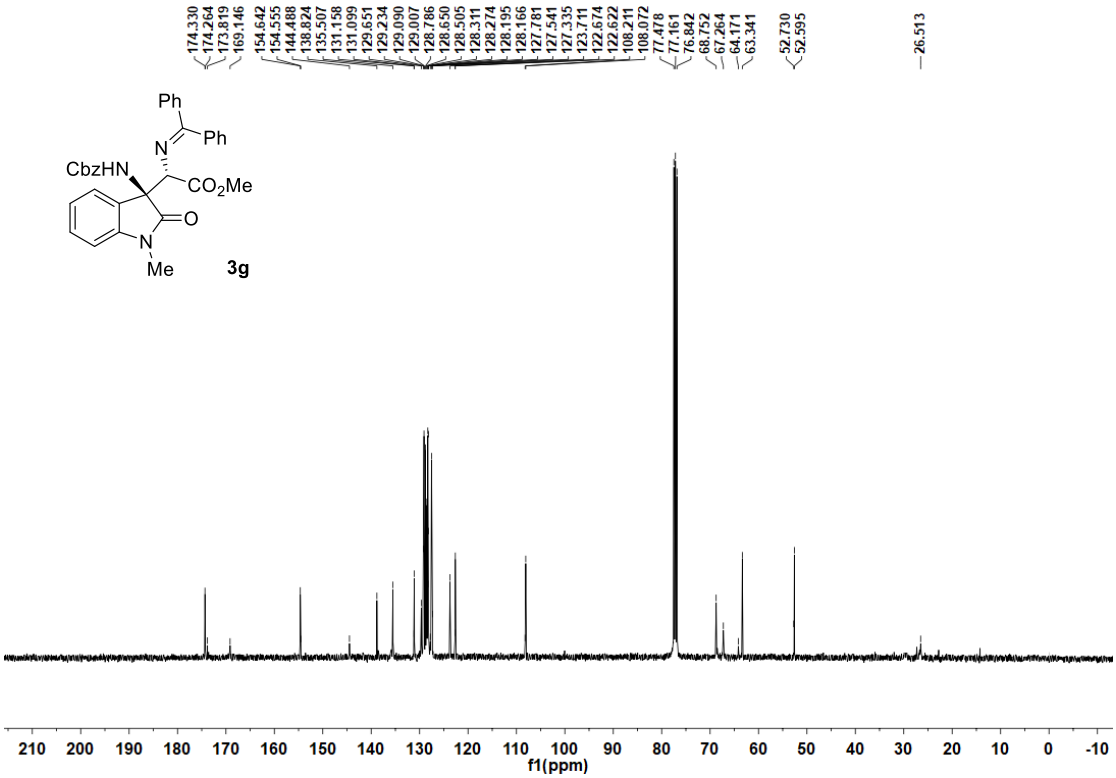
^{13}C NMR spectrum of compound **3f** ($CDCl_3$)



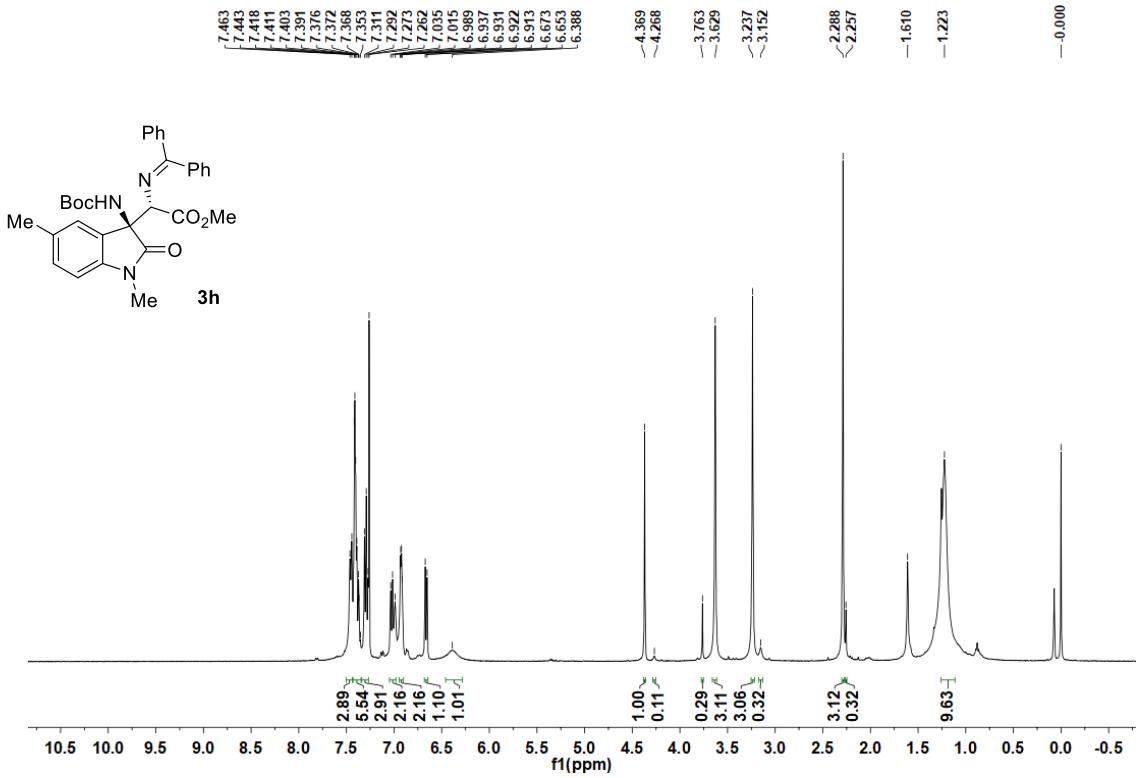
^{1}H NMR spectrum of compound **3g** ($CDCl_3$)



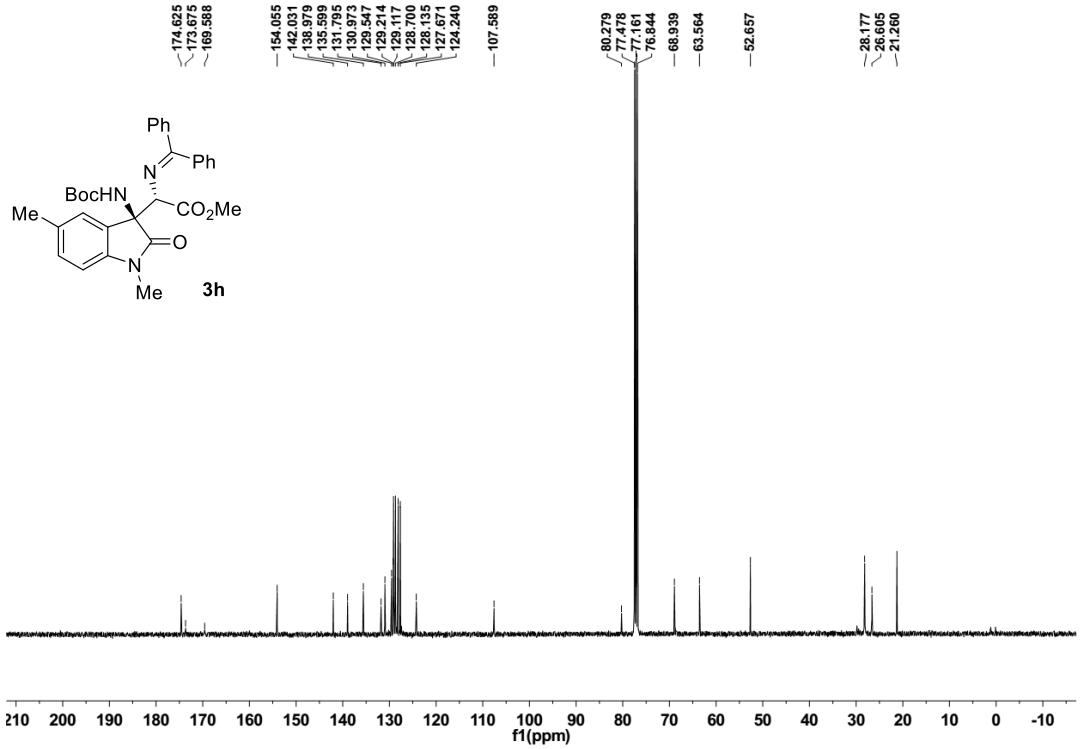
^{13}C NMR spectrum of compound **3g** ($CDCl_3$)



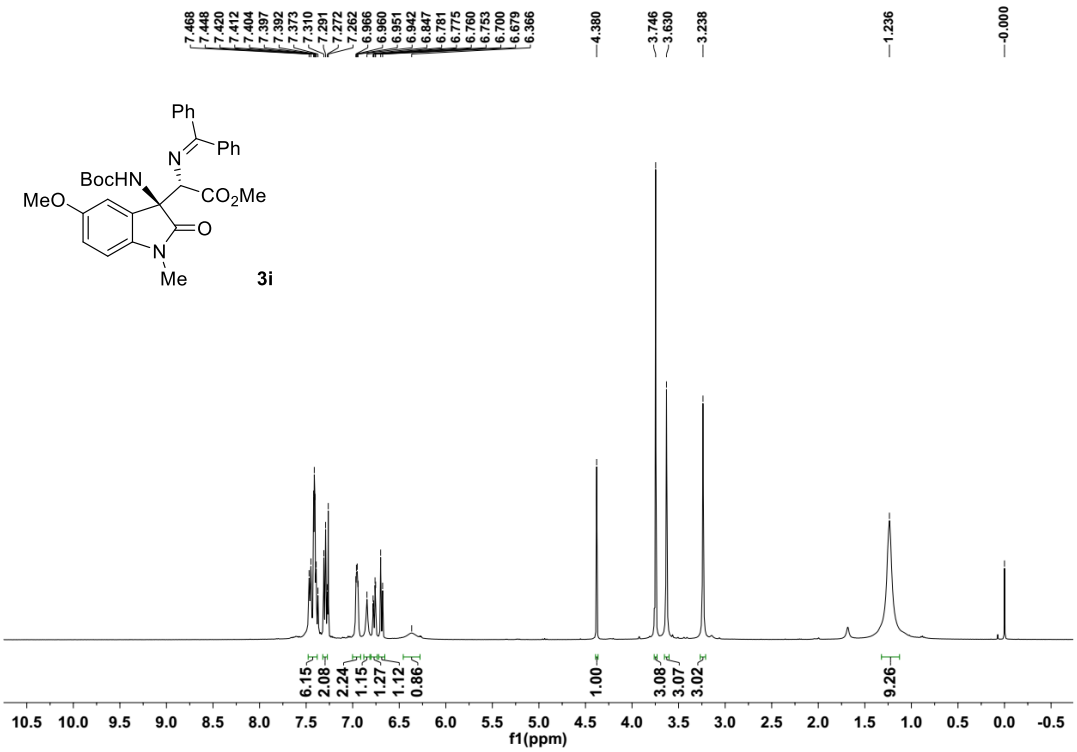
^{1}H NMR spectrum of compound **3h** ($CDCl_3$)



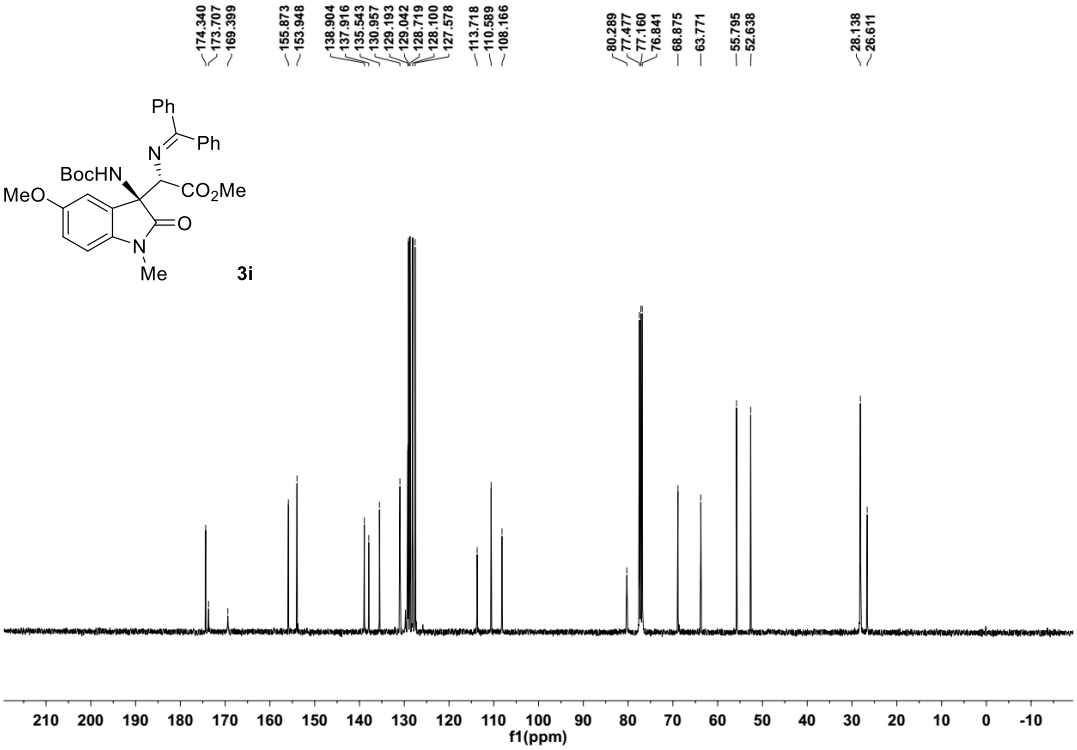
^{13}C NMR spectrum of compound **3h** ($CDCl_3$)



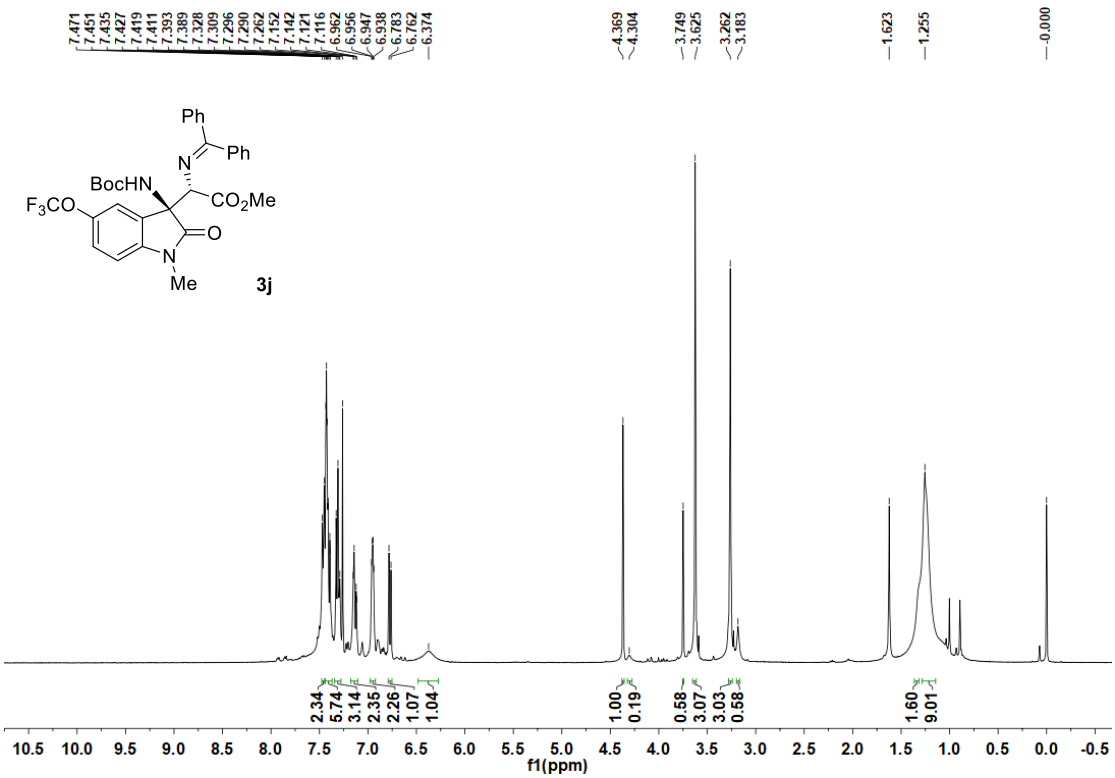
^{1}H NMR spectrum of compound **3i** ($CDCl_3$)



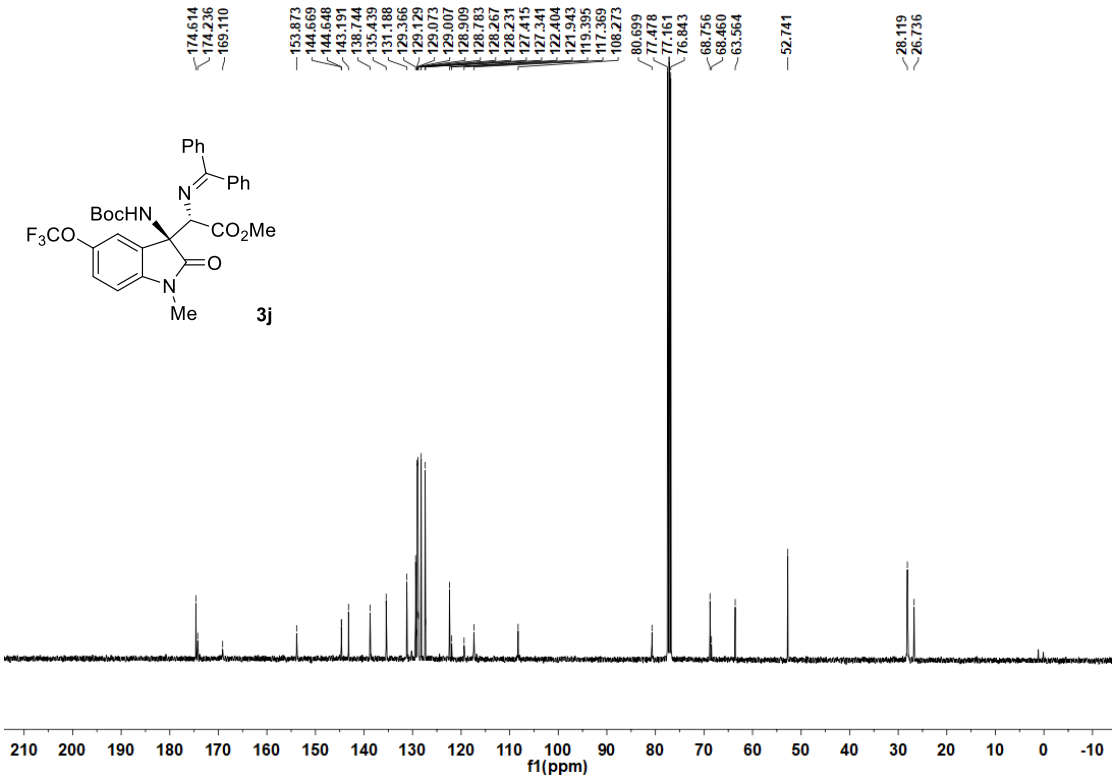
^{13}C NMR spectrum of compound **3i** ($CDCl_3$)



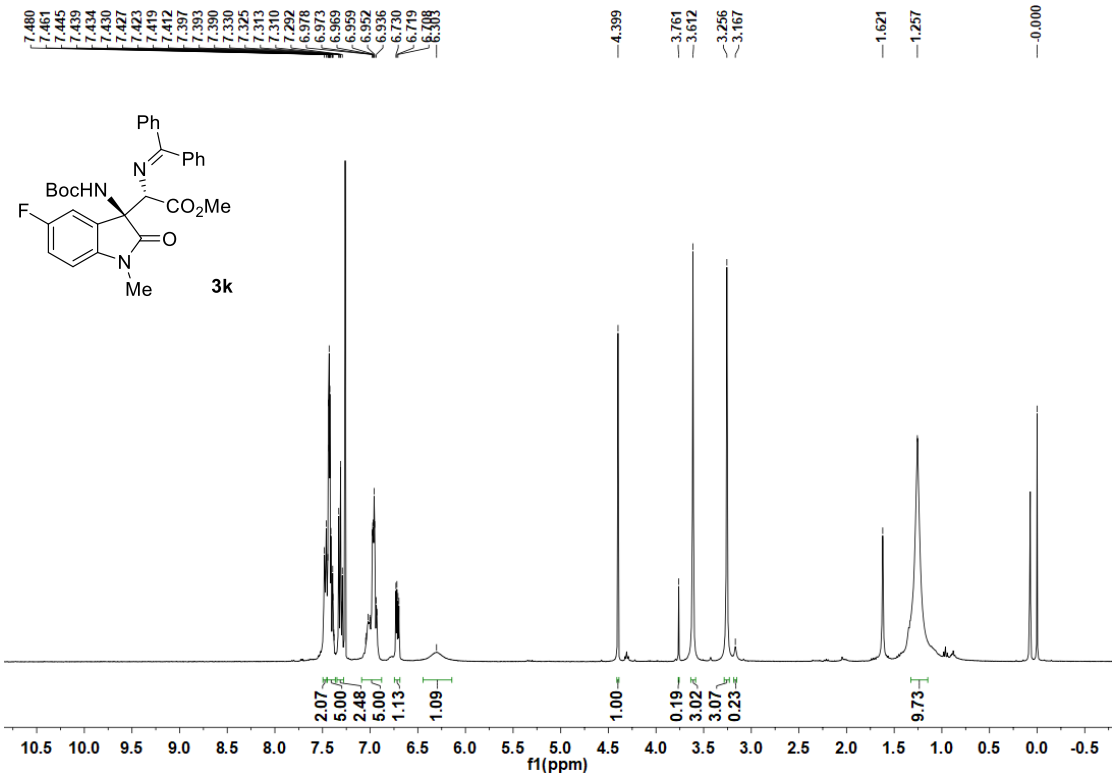
^{1}H NMR spectrum of compound **3j** ($CDCl_3$)



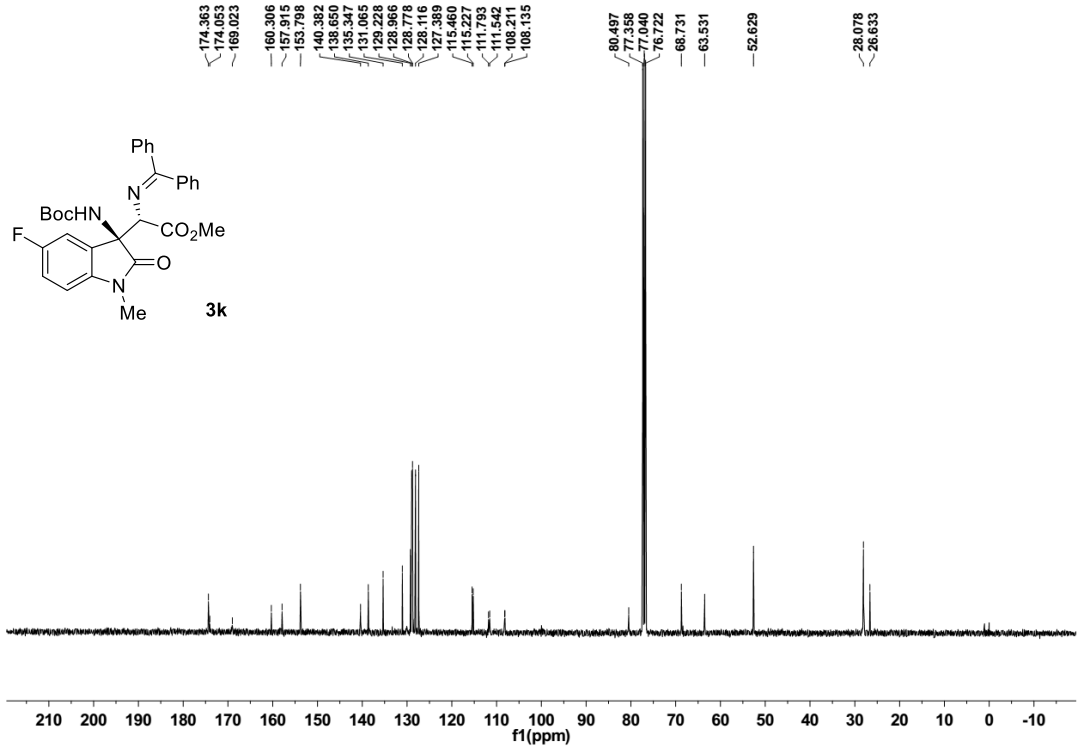
^{13}C NMR spectrum of compound **3j** ($CDCl_3$)



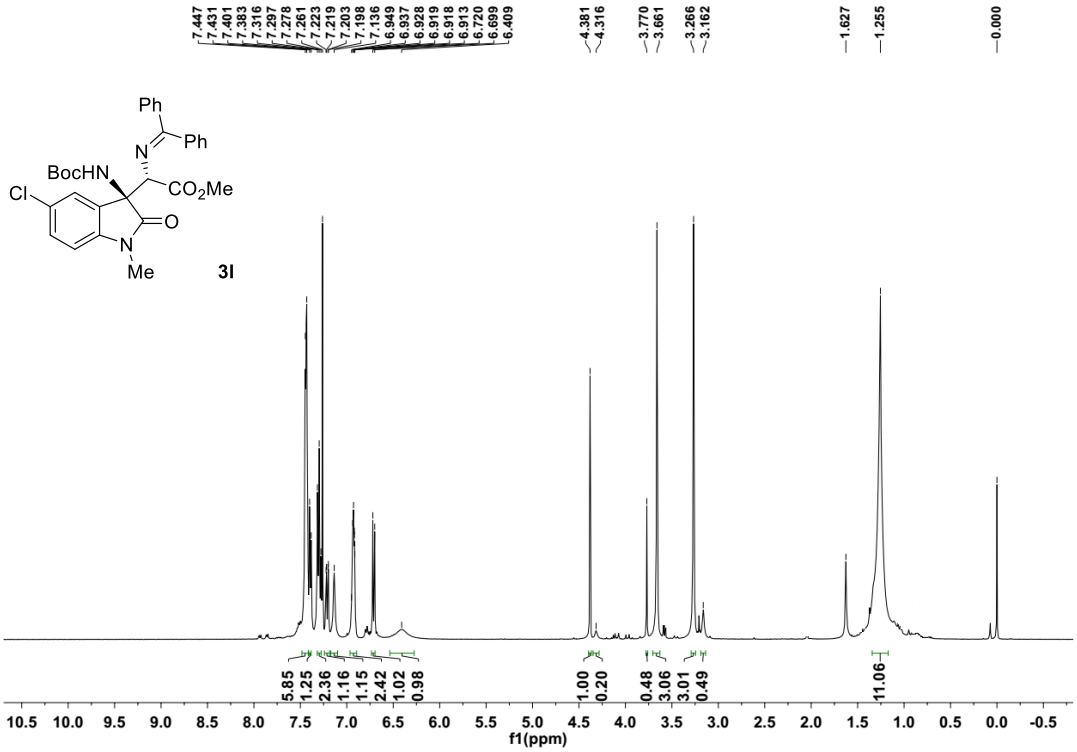
^{1}H NMR spectrum of compound **3k** ($CDCl_3$)



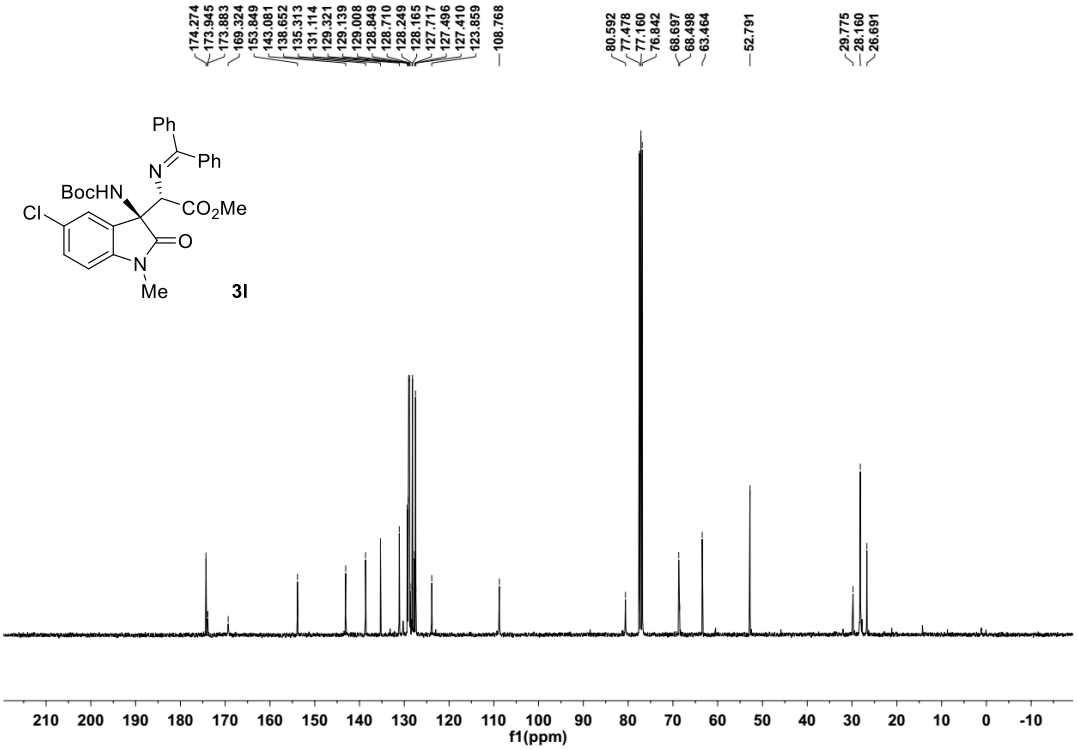
^{13}C NMR spectrum of compound **3k** ($CDCl_3$)



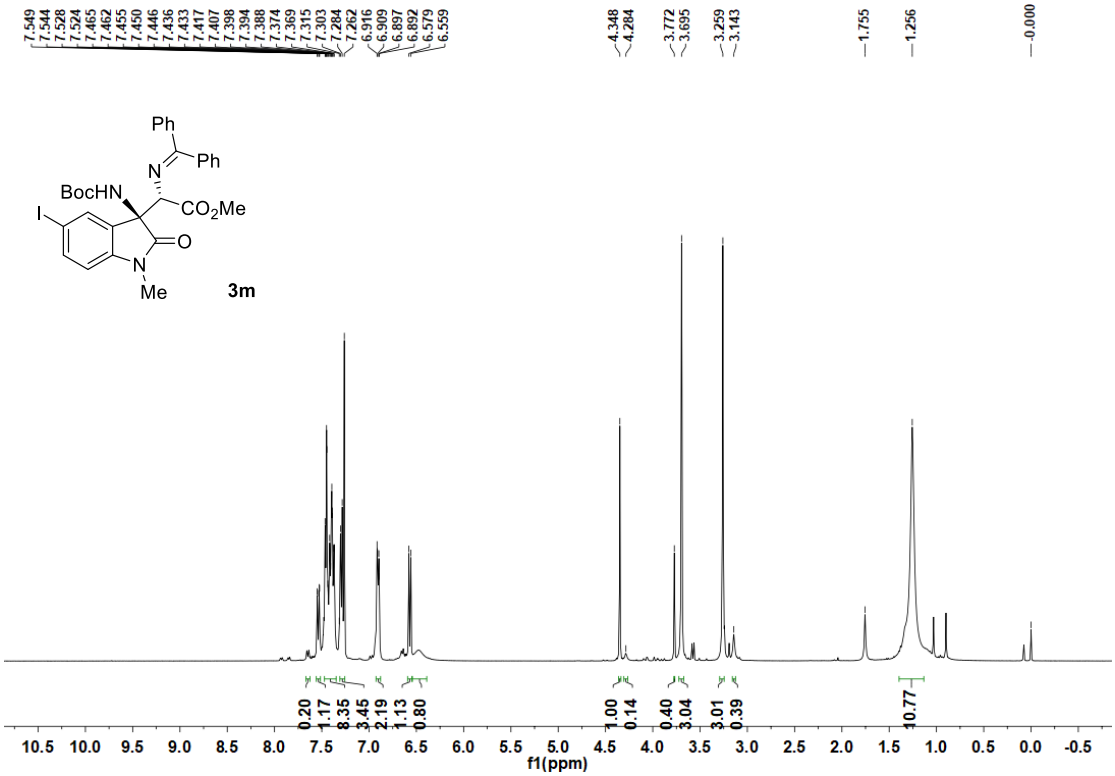
^{1}H NMR spectrum of compound **3l** ($CDCl_3$)



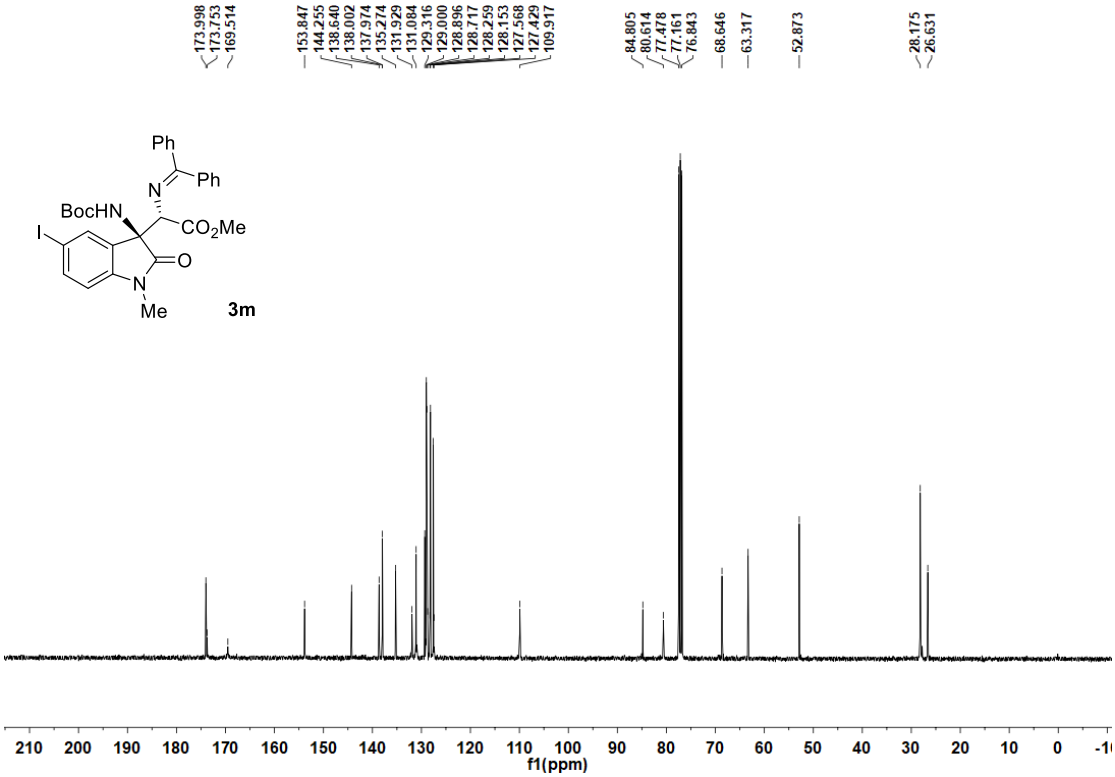
^{13}C NMR spectrum of compound **3l** ($CDCl_3$)



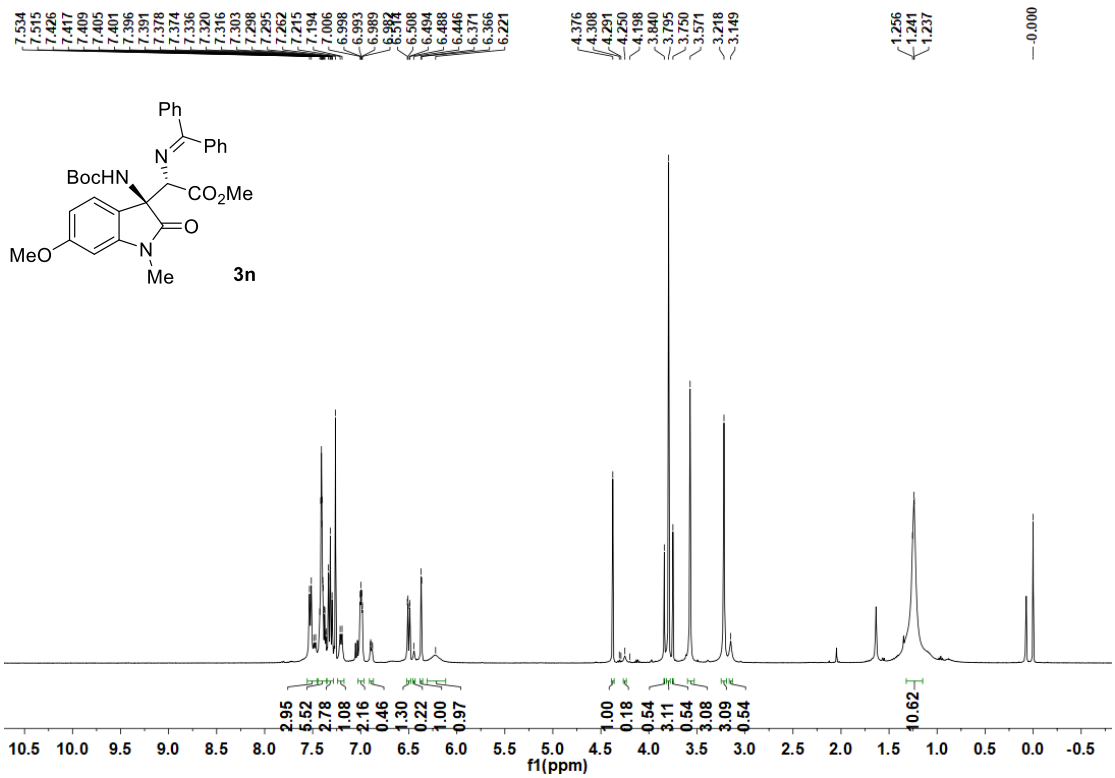
^{1}H NMR spectrum of compound **3m** ($CDCl_3$)



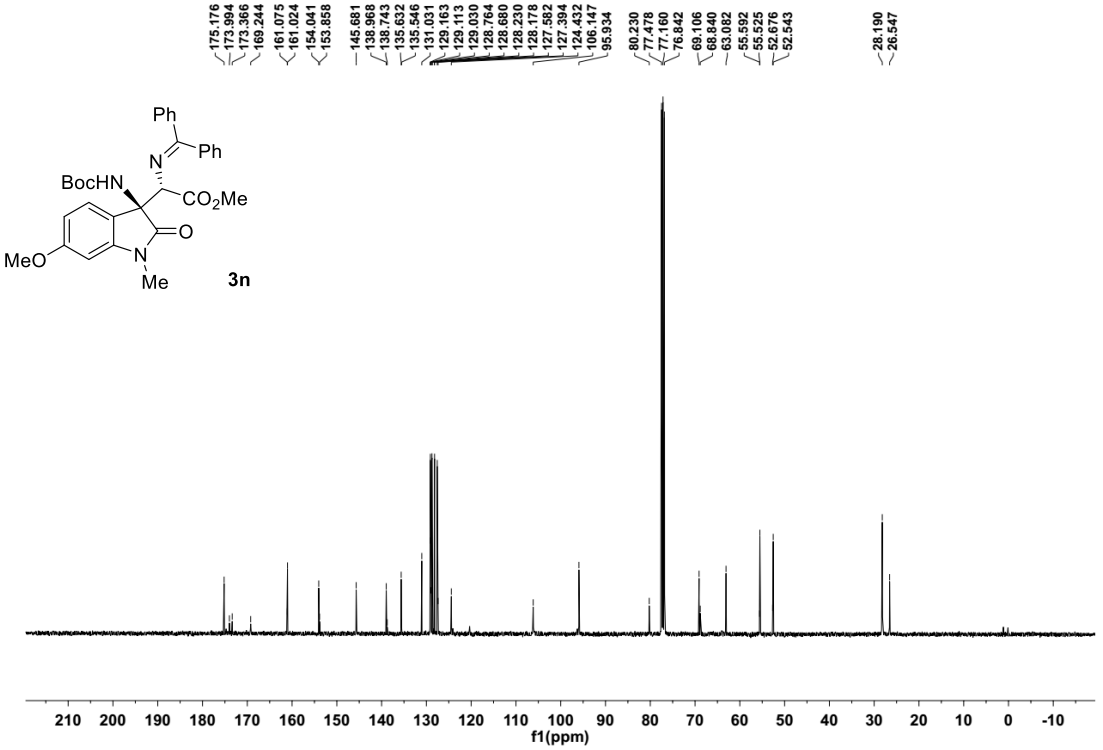
^{13}C NMR spectrum of compound **3m** ($CDCl_3$)



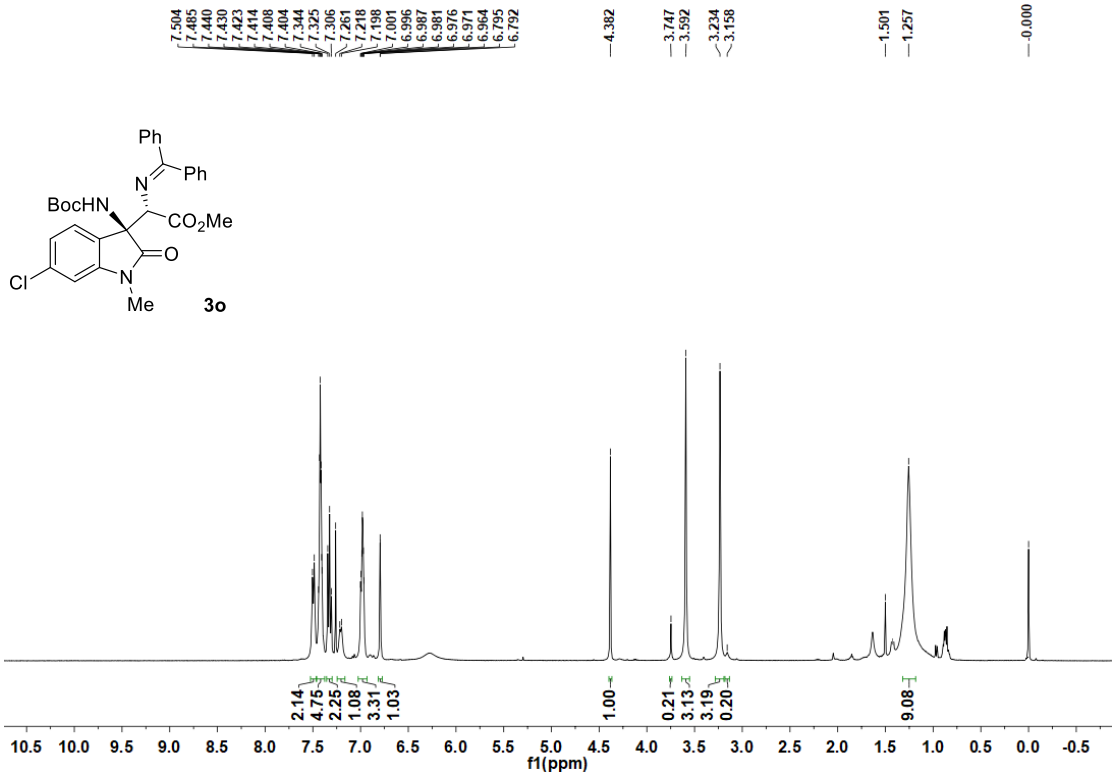
^{1}H NMR spectrum of compound **3n** ($CDCl_3$)



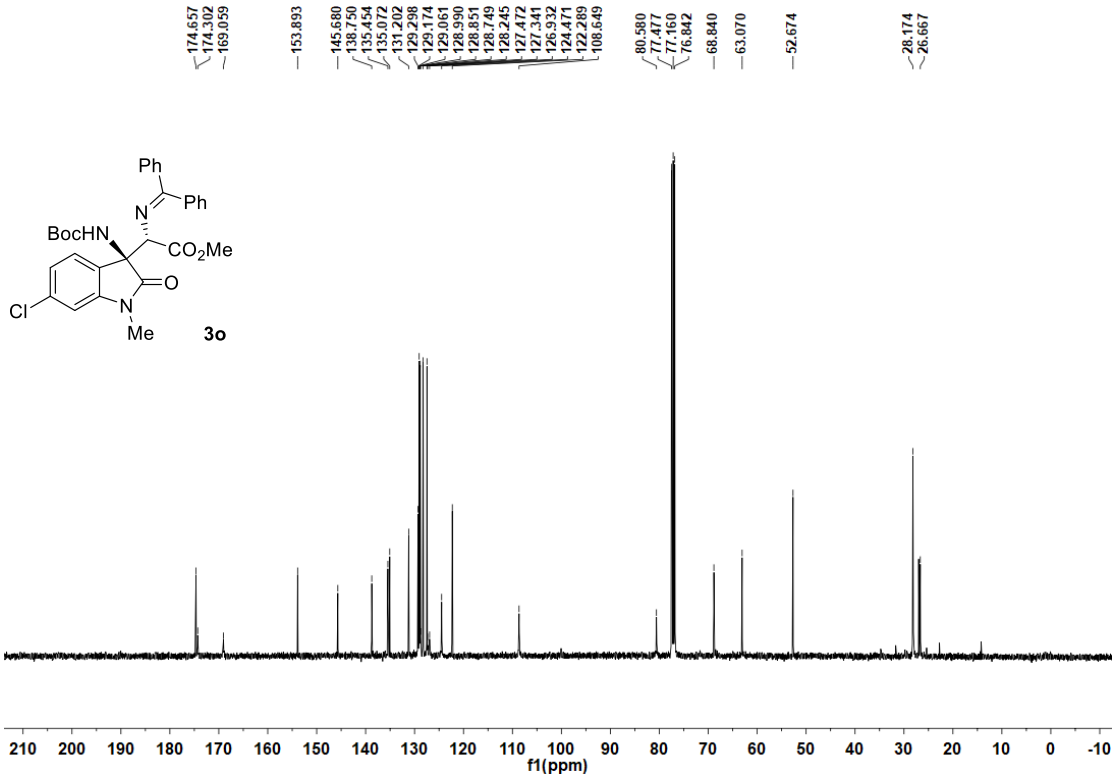
^{13}C NMR spectrum of compound **3n** ($CDCl_3$)



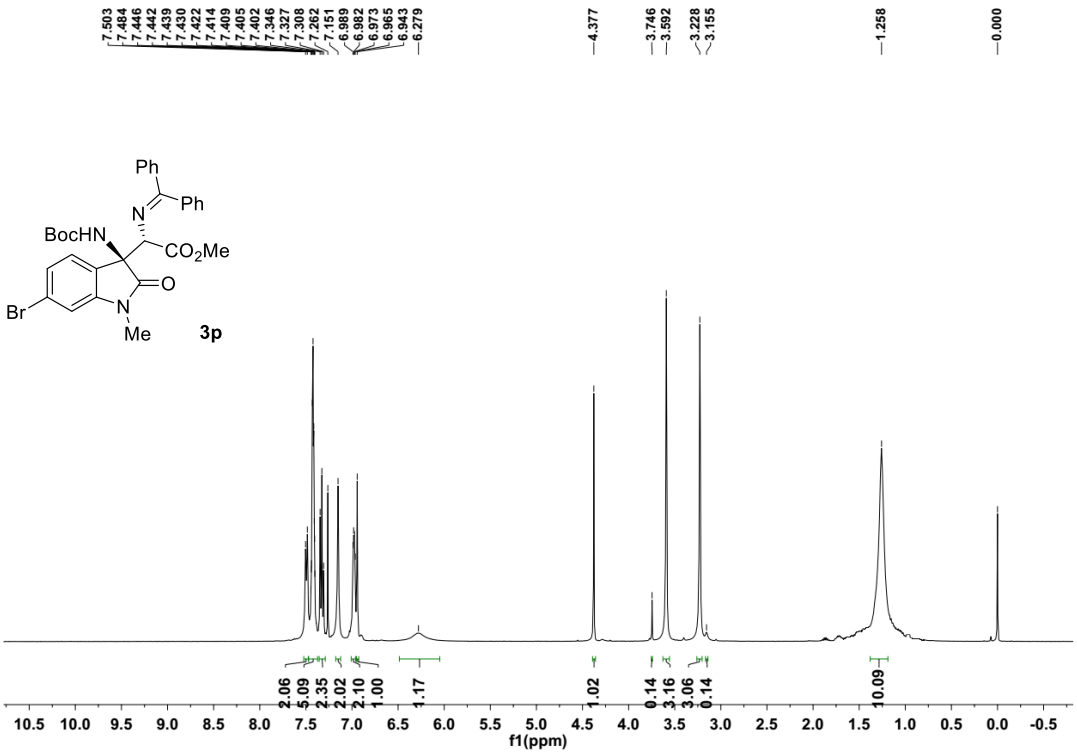
^{1}H NMR spectrum of compound **3o** ($CDCl_3$)



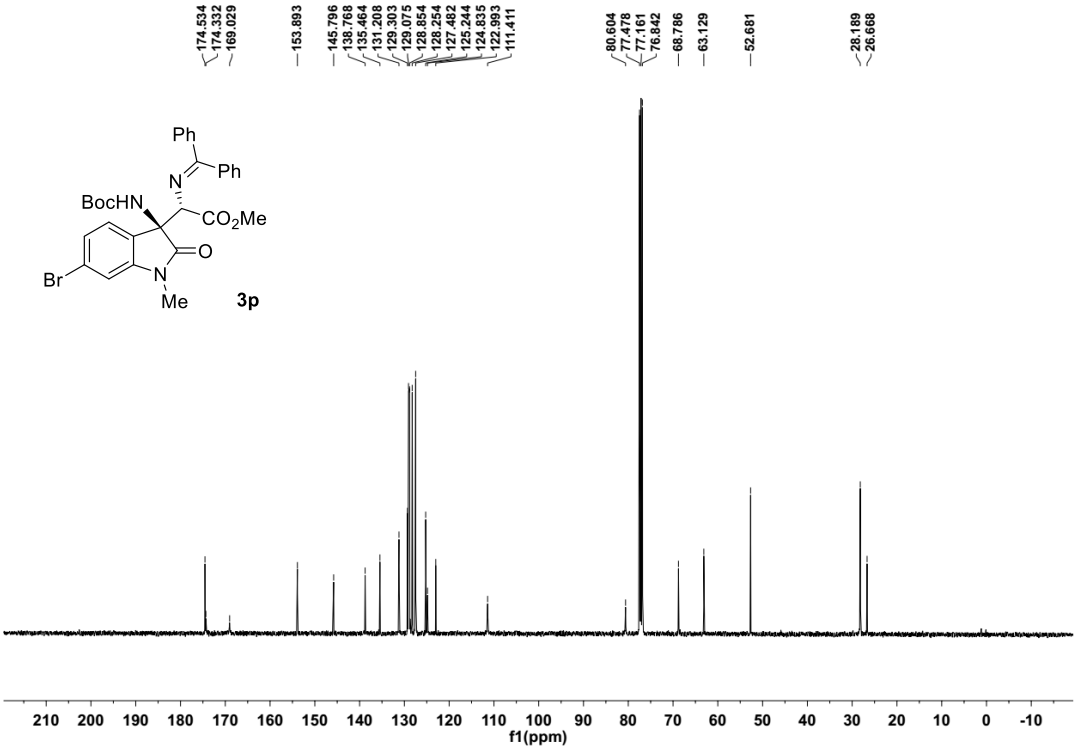
^{13}C NMR spectrum of compound **3o** ($CDCl_3$)



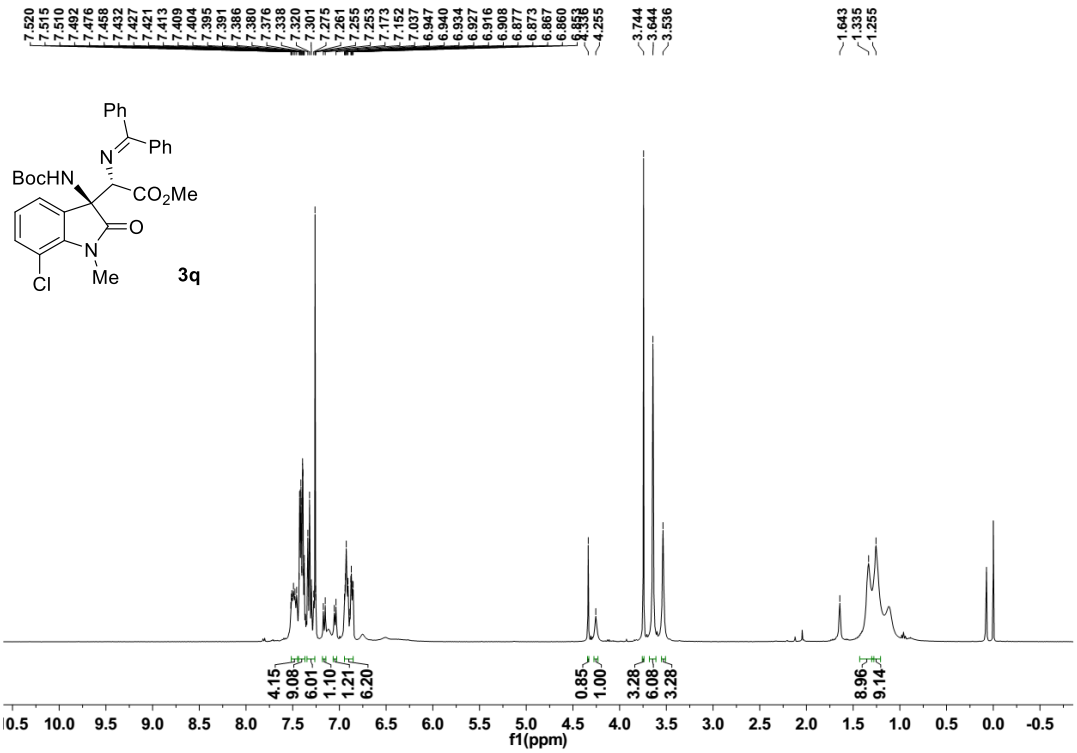
^{1}H NMR spectrum of compound **3p** ($CDCl_3$)



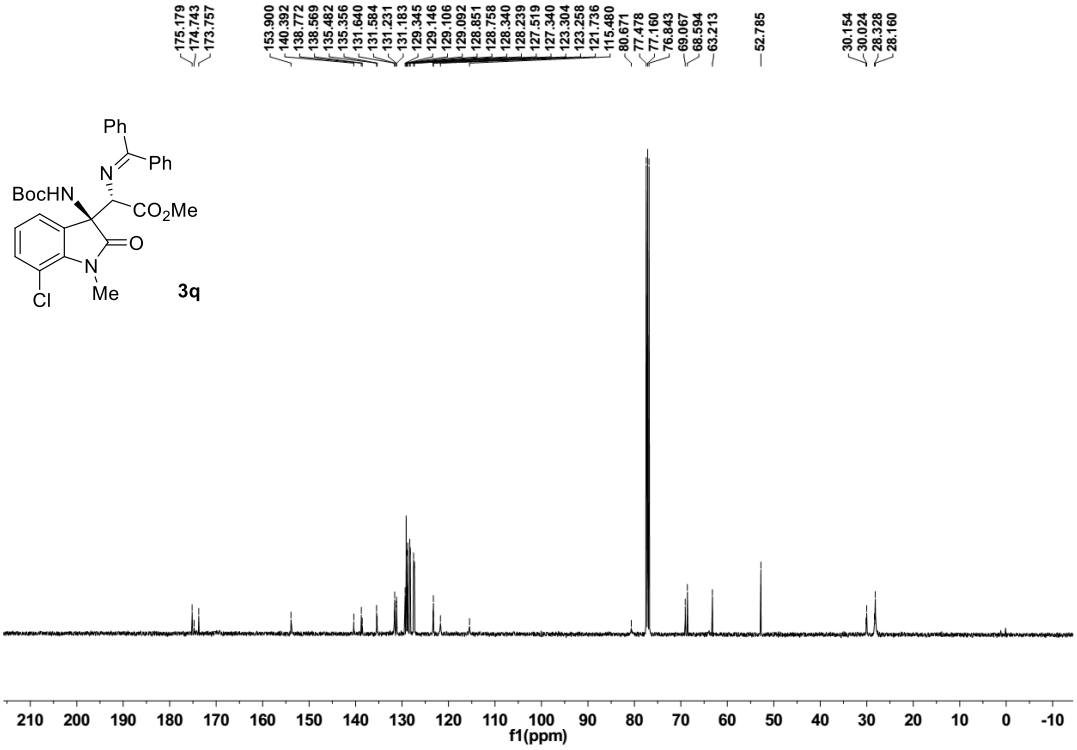
^{13}C NMR spectrum of compound **3p** ($CDCl_3$)



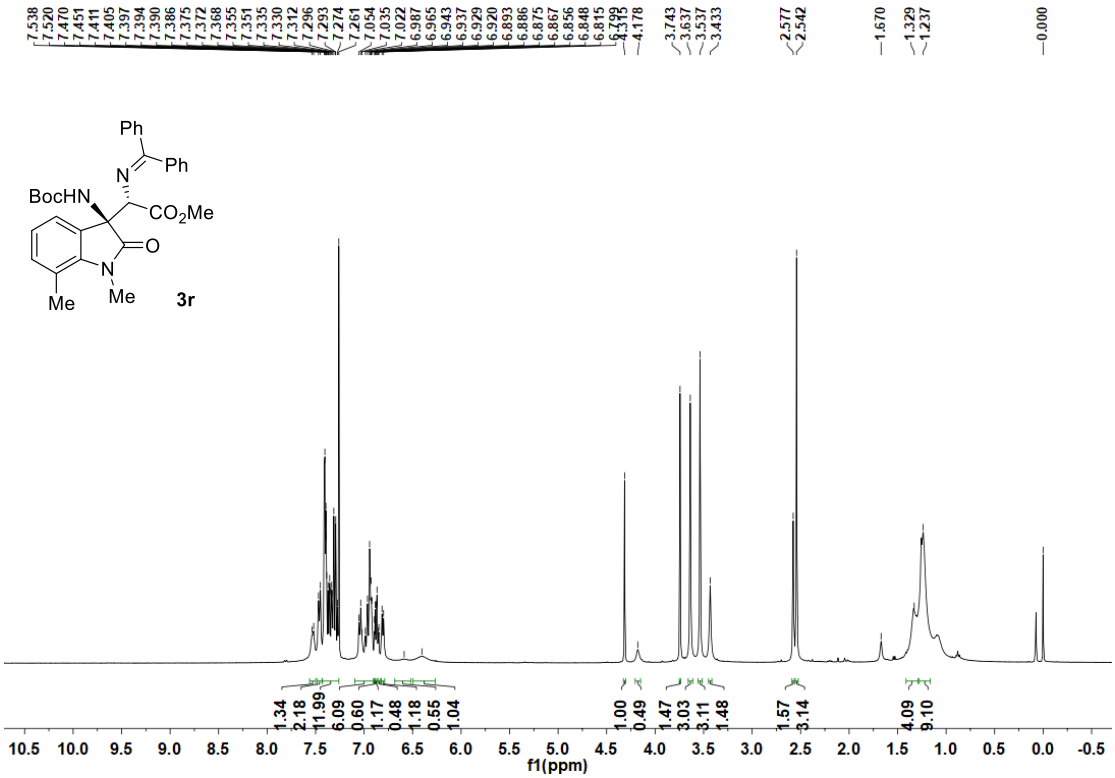
^{1}H NMR spectrum of compound **3q** ($CDCl_3$)



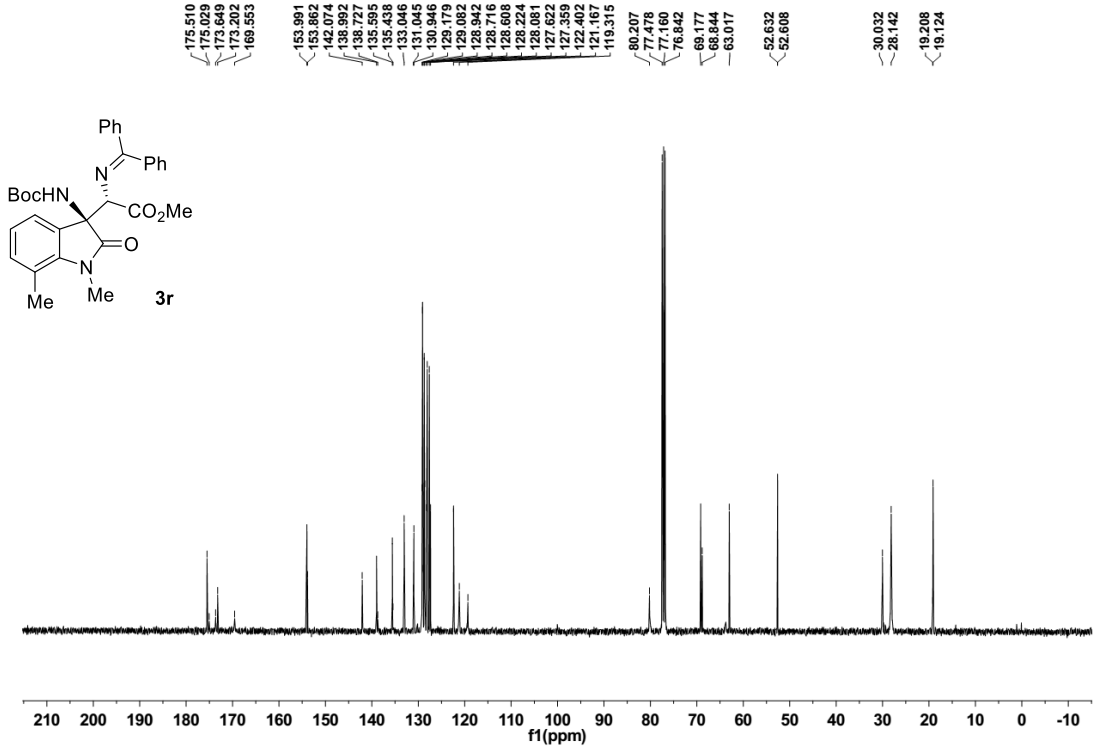
^{13}C NMR spectrum of compound **3q** ($CDCl_3$)



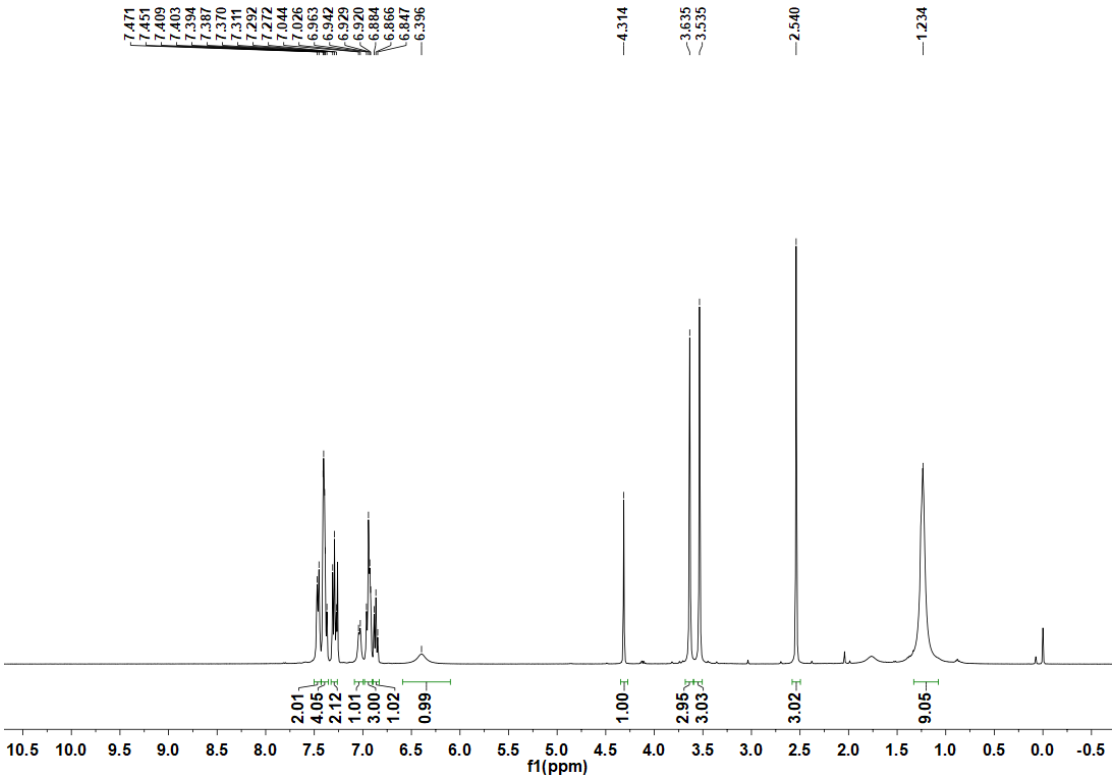
^{1}H NMR spectrum of compound **3r** ($CDCl_3$)



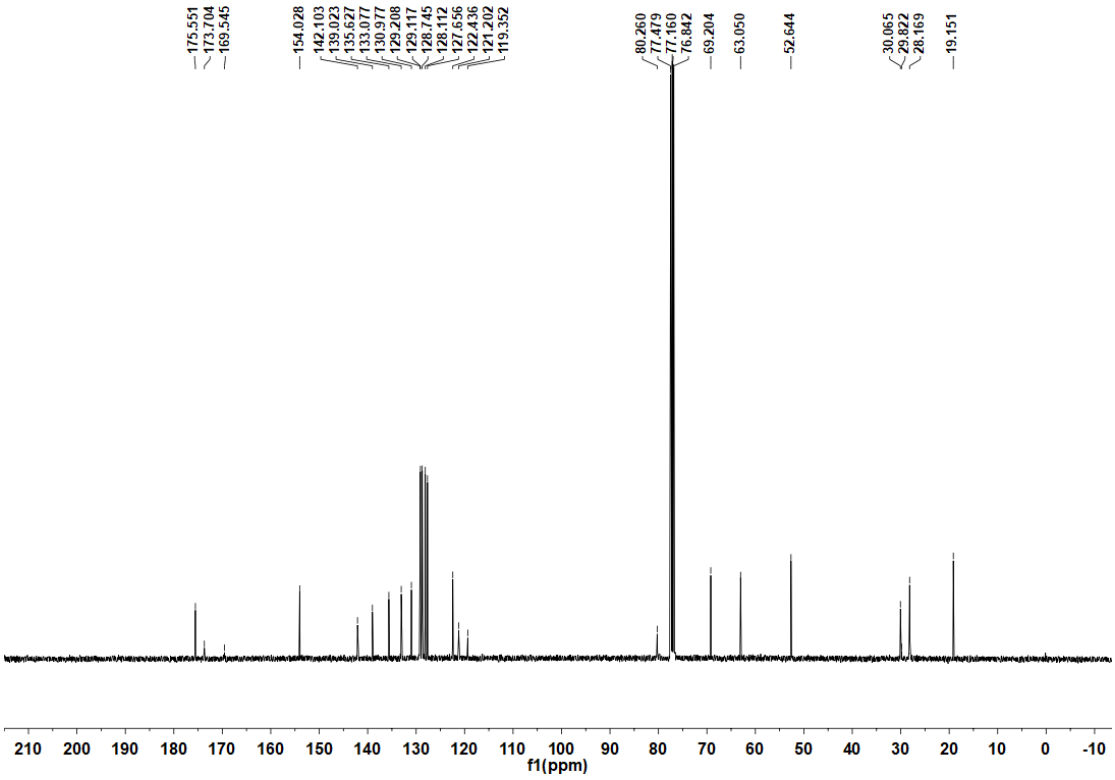
^{13}C NMR spectrum of compound **3r** ($CDCl_3$)



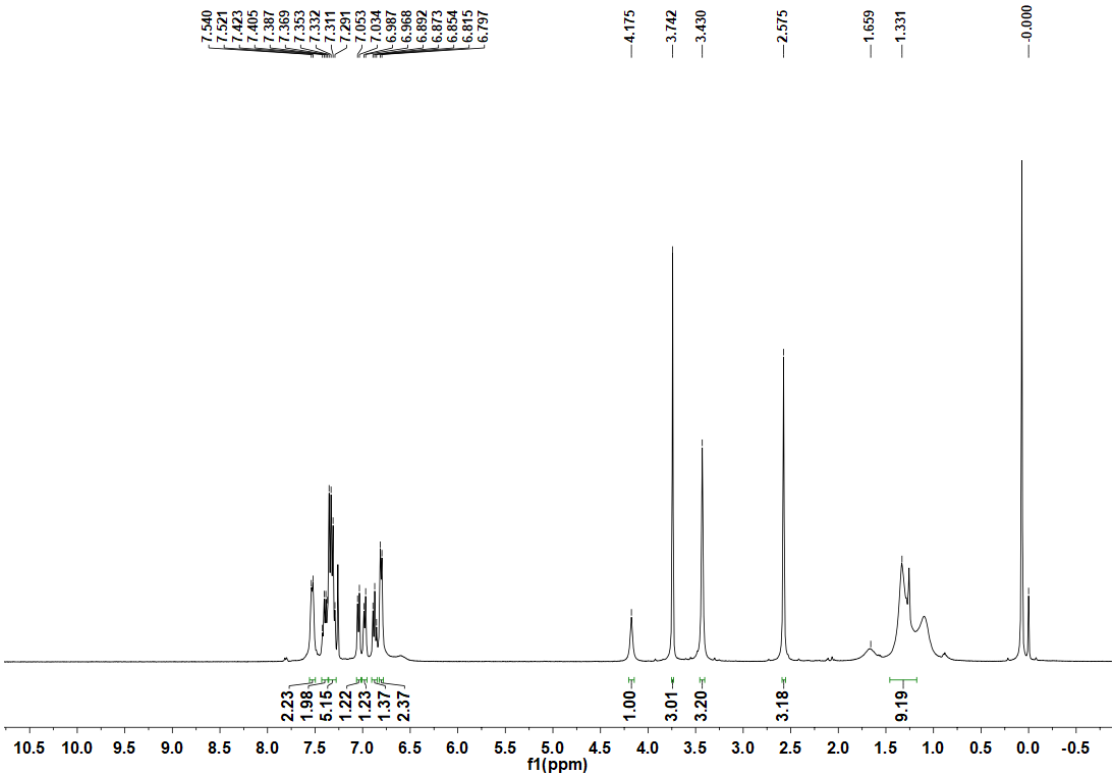
^{1}H NMR spectrum of compound *syn*-**3r** (major) ($CDCl_3$)



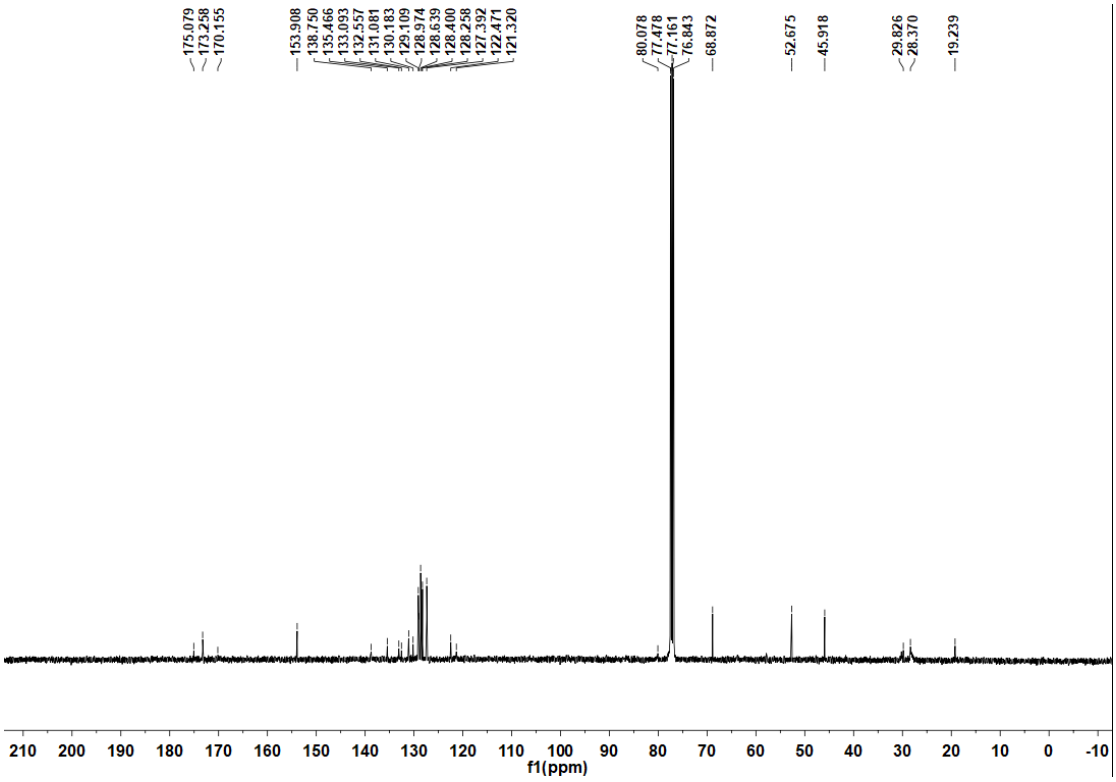
^{13}C NMR spectrum of compound *syn*-**3r** (major) ($CDCl_3$)



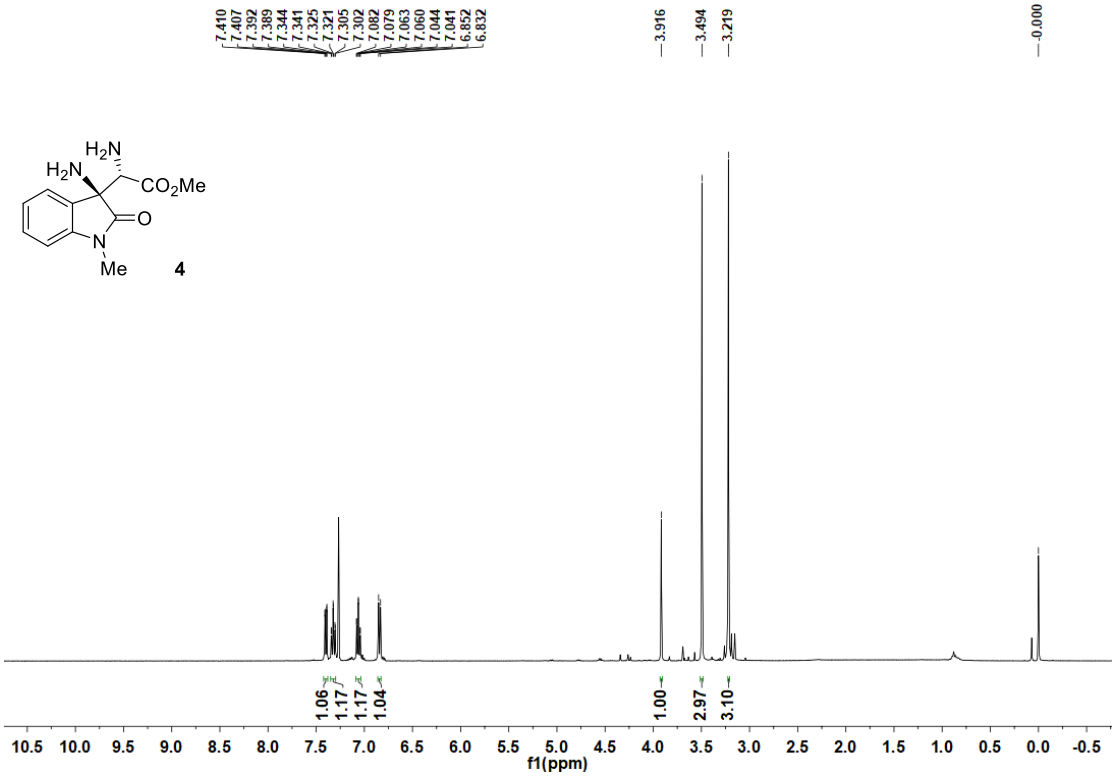
^{1}H NMR spectrum of compound *anti*-**3r** (minor) ($CDCl_3$)



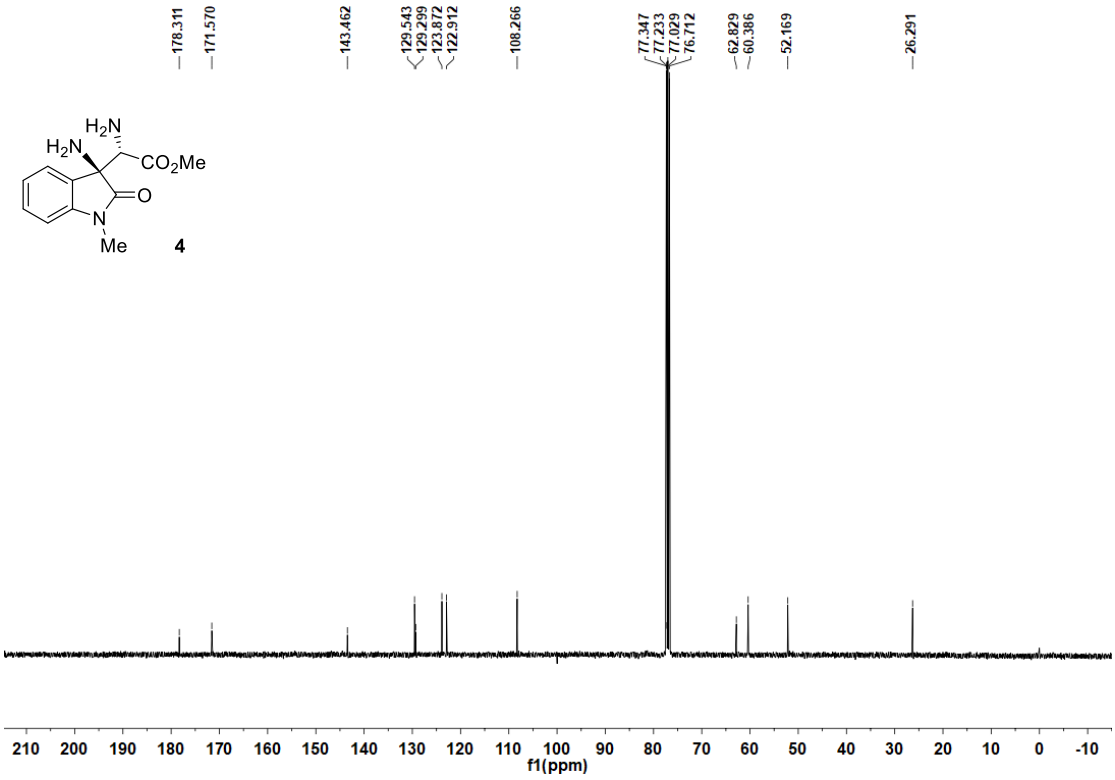
^{13}C NMR spectrum of compound *anti*-**3r** (minor) ($CDCl_3$)



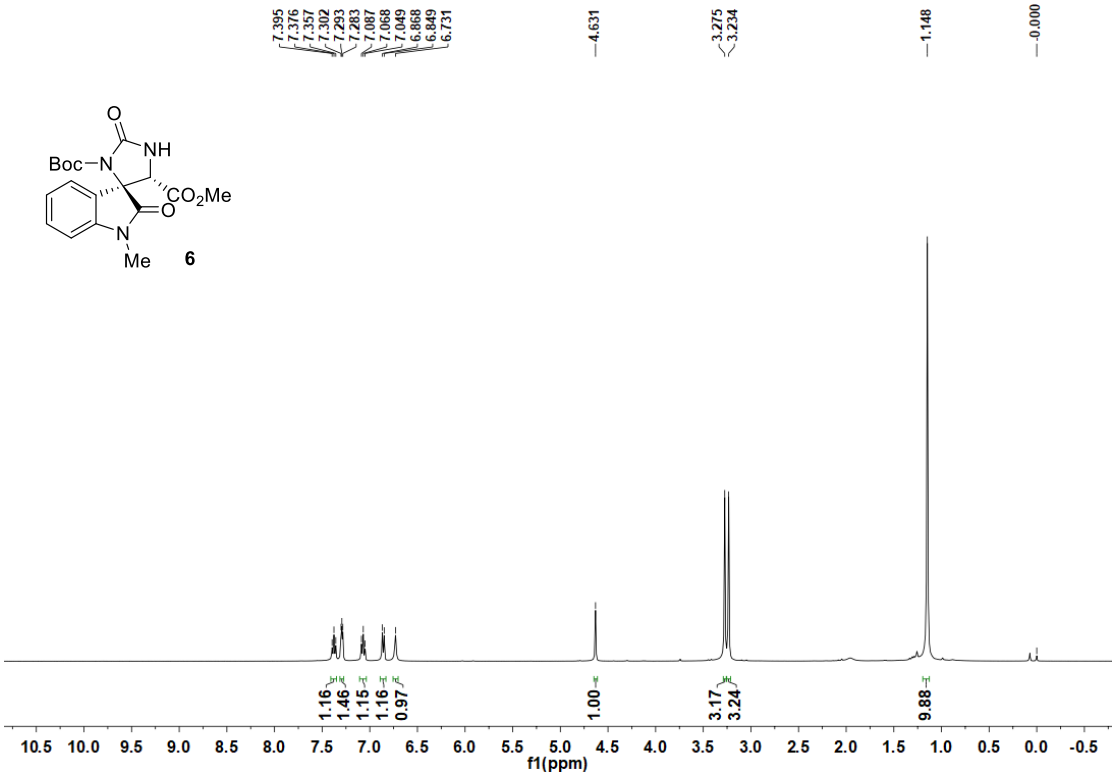
^{1}H NMR spectrum of compound **4** ($CDCl_3$)



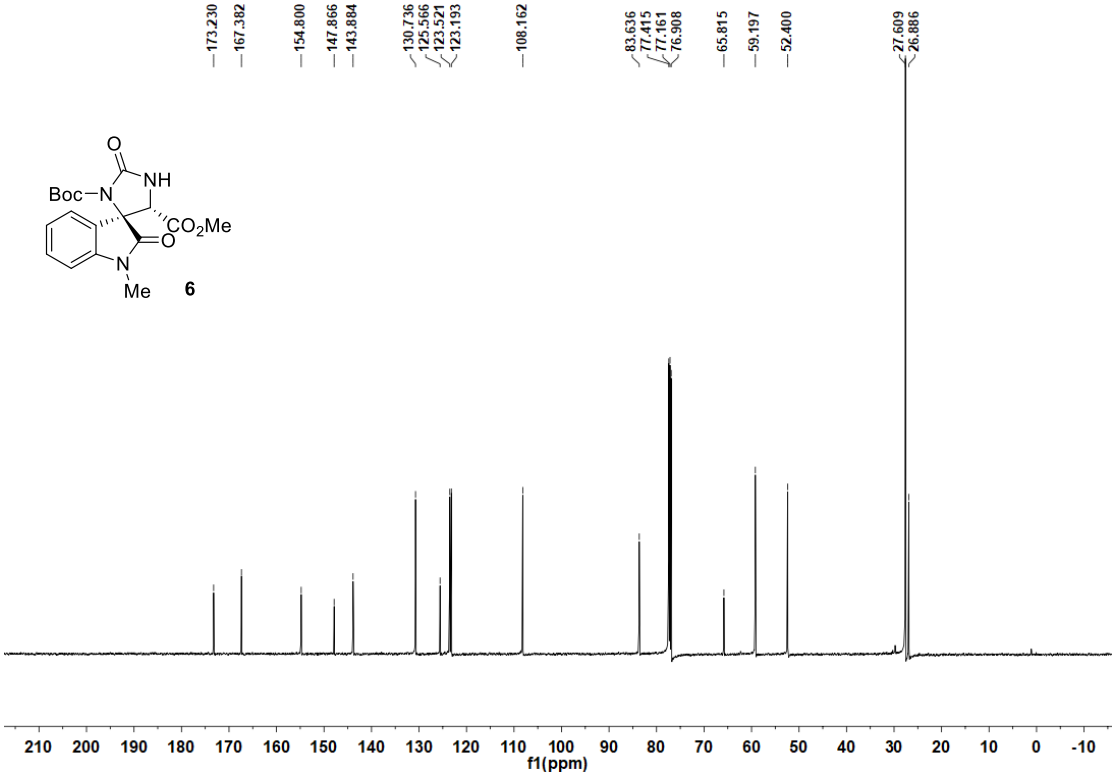
^{13}C NMR spectrum of compound **4** ($CDCl_3$)



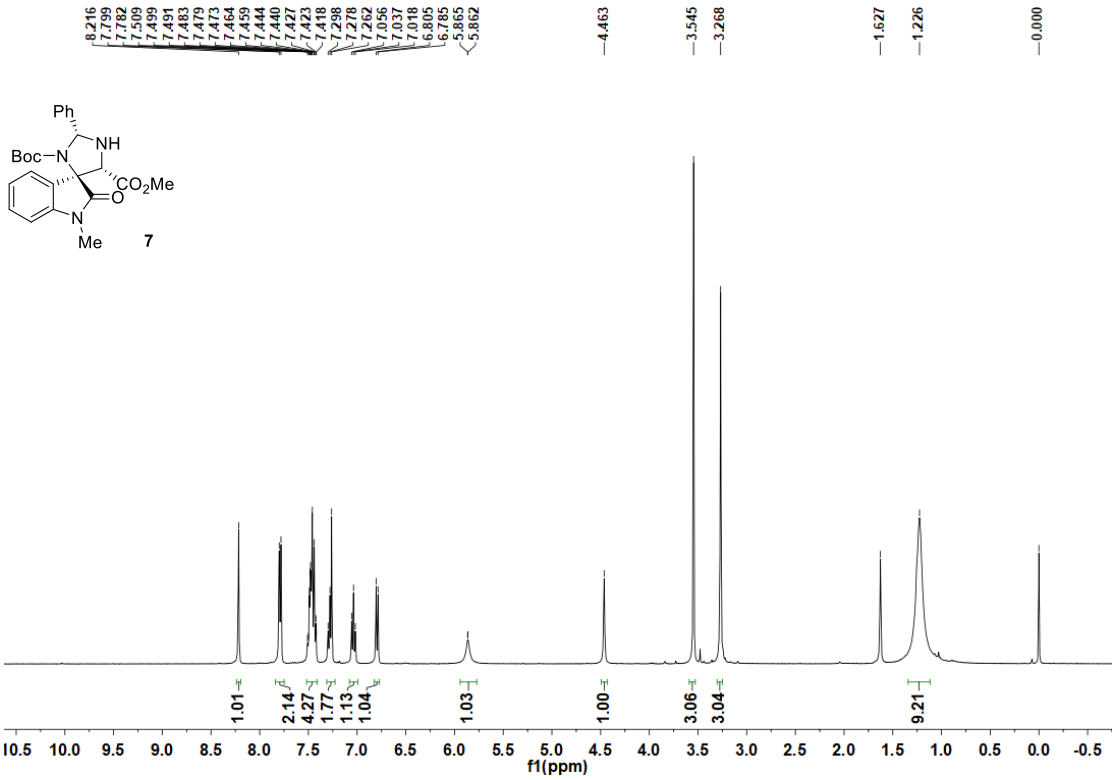
^{1}H NMR spectrum of compound **6** ($CDCl_3$)



^{13}C NMR spectrum of compound **6** ($CDCl_3$)



^{1}H NMR spectrum of compound **7** ($CDCl_3$)



^{13}C NMR spectrum of compound **7** ($CDCl_3$)