Organocatalytic Enantioselective Mannich Reaction of Isoxazol-5(4*H*)-ones to Isatin-derived Ketimines

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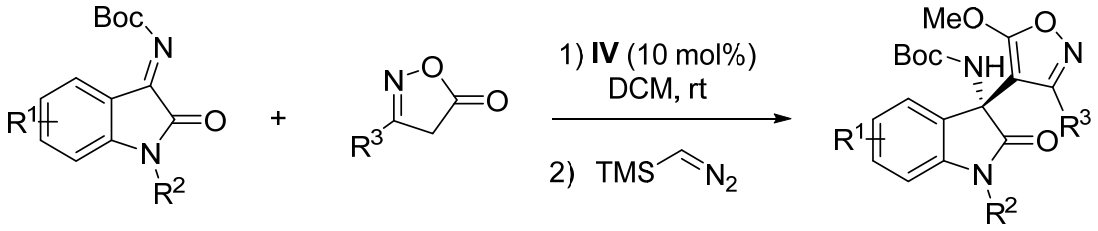
Materials and methods

All reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR using residual nondeuterated solvent ($CHCl_3$) as internal standard (δ 7.26 and 77.0 ppm, respectively). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI). Specific optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary phase columns from Daicel or Phenomenex.

N-Boc isatin ketimines,[1] isoxazol-5-ones,[2-4] and squaramide **IV**[5] were prepared according to the previous literature.

General procedure for the enantioselective Mannich reaction

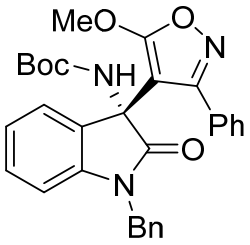


1 **2** **3**

An oven dried test tube was charged with isatin ketimine **1** (0.2 mmol), isoxazol-5-one **2** (0.2 mmol) and squaramide **IV** (12.0 mg, 0.02 mmol). The test tube was purged with N_2 10 minutes. Dichloromethane (2 mL) was added, and the mixture was stirred at room temperature until completion (TLC). A 1 M solution of TMS-diazomethane in diethyl ether (0.4 mmol) was added via syringe and the reaction was stirred for 2 hours at room temperature. The reaction mixture was chromatographed on silica gel eluting with hexane:EtOAc mixtures to give compound **3**.

Characterization data for compounds 3

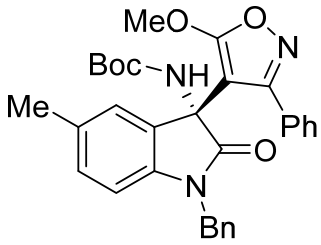
***tert*-Butyl (*R*)-(1-benzyl-3-(5-methoxy-3-phenylisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3aa)**



69.5 mg (70%) of **3aa** were obtained from **1a** (67.2 mg) and **2a** (32.1 mg). Enantiomeric excess (93%) was measured by HPLC (Chiralpak AD-H), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 17.9 min, minor enantiomer: t_r = 23.1 min

Pale yellow solid, m.p. = 156.3-157.4 ºC; $[\alpha]_D^{25}$ = –6.2 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.15 (9H, m, Ar), 7.08-7.00 (3H, m, Ar), 6.91 (1H, td, *J* = 9, 1.2 Hz, Ar), 6.35 (1H, d, *J* = 9 Hz, Ar), 6.15 (1H, s, NH), 4.8 (1H, d, *J* = 15.9 Hz, CH-Ph), 4.15 (3H, s, MeO), 4.09 (1H, d, *J* = 15.9 Hz, CH-Ph), 1.26 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.6 (C), 168.6 (C), 164.3 (C), 153.5 (C), 142.8 (C), 135.3 (C), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 124.2 (CH) 122.8 (CH), 109.1 (CH), 90.2 (C), 80.3 (C), 59.0 (C), 58.6 (CH_3), 44.0 (CH_2), 28.1 (CH_3); **IR** (ATR) ν 3442, 1720 (C=O), 1615, 1405, 1168, 749, 695 cm^{-1}; **HRMS** (ESI) *m/z*: 512.2198 $[M+H]^+$, $C_{30}H_{30}N_3O5^+$ requires 512.2180.

***tert*-Butyl (*R*)-(1-benzyl-3-(5-methoxy-3-phenylisoxazol-4-yl)-5-methyl-2-oxoindolin-3-yl)carbamate (3ba)**

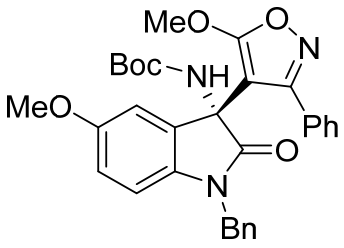


71,5 mg (67%) of **3ba** were obtained from **1b** (74.5 mg) and **2a** (32.2 mg). Enantiomeric excess (97%) was measured by HPLC (Chiralcel OD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 10.1 min, minor enantiomer: t_r = 8.0 min.

Yellow solid, m.p. = 65.2-67.1 ºC; $[\alpha]_D^{25}$ = +5.4 (*c* = 0.78, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.12 (9H, m, Ar), 7.05 (1H, s, Ar), 6.99 (2H, dd, *J* = 8.2, 1.3 Hz, Ar),6.82 (1H, ddd, *J* = 8.2, 1.6, 0.7 Hz, Ar), 6.23 (1H, d, *J* = 7.9 Hz, Ar), 6.17 (1H, s, N-H), 4.77 (1H, d, *J* = 15.7 Hz, CH-Ph), 4.17 (3H, s, MeO), 4.04 (1H, d, *J* = 15.7 Hz, CH-Ph),2.20 (3H, s, Ar-CH_3), 1.28 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.8 (C), 169.0 (C), 164.7 (C), 153.9 (C), 140.6 (C), 135.8 (C), 132.7 (CH), 130.4 (C), 129.7 (CH), 129.4 (CH), 128.9 (C), 128.0 (CH), 127.9 (CH), 127.7 (CH), 125.3 (CH), 109.2 (CH), 90.7 (C), 80.6 (C), 59.4 (C), 58.9 (CH_3), 44.3 (CH_2), 28.1 (CH_3), 21.3 (CH_3); **IR** (ATR) ν 3431,

1718 (C=O), 1623, 1477, 1407, 1161, 920, 697 cm^{-1}; **HRMS** (ESI) *m/z*: 526.2330 $[M+H]^+$, $C_{31}H_{32}N_3O_5^+$ requires 526.2336.

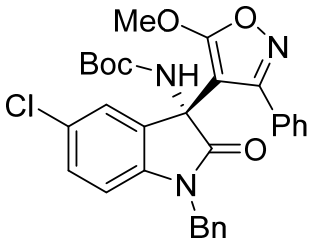
***tert*-Butyl (*R*)-(1-benzyl-5-methoxy-3-(5-methoxy-3-phenylisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ca)**



66,6 mg (62%) of **3ca** were obtained from **1c** (73.3 mg) and **2a** (32.6 mg). Enantiomeric excess (96%) was measured by HPLC (Chiralcel OD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 12.3 min, minor enantiomer: t_r = 9.3 min.

Orange solid, m.p. = 71.3-72.4 ºC ; $[\alpha]_D^{25}$ = +10.5 (*c* =1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40-7.12 (9H, m, Ar), 7.08-7.00 (2H, m, Ar), 6.88 (1H, d, *J* =2.4 Hz, Ar), 6.55 (1H, dd, *J* = 8.4, 2.7 Hz, Ar), 6.24 (1H, d, *J* = 8.8 Hz, Ar), 6,14 (1H, s, NH), 4.77 (1H, d, *J* = 15.9 Hz, CH-Ph), 4.17 (3H, s, MeO), 4.09 (1H, d, *J* = 15.9 Hz, CH-Ph), 3.68 (3H, s, MeO), 1.28 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.4 (C), 168.7 (C), 164.4 (C), 156.1 (C), 153.5 (C), 136.2 (C), 135.4 (C), 131.2 (C), 129.1 (CH), 128.61 (C), 128.55 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 113.9 (CH), 111.3 (CH), 109.6 (CH), 90.1 (C), 80.4 (C), 59.4 (C), 58.6 (CH_3), 55.7 (CH_3), 44.1 (CH_2), 28.1 (CH_3); **IR** (ATR) ν 3427, 1714 (C=O), 1617, 1490, 1403, 1272, 1006, 695 cm^{-1}; **HRMS** (ESI) *m/z*: 542.2269 $[M+H]^+$, $C_{31}H_{32}N_3O_6^+$ requires 542.2286.

***tert*-Butyl (*R*)-(1-benzyl-5-chloro-3-(5-methoxy-3-phenylisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3da)**

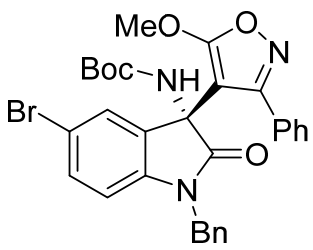


68.7 mg (63%) of **3da** were obtained from **1d** (74.4 mg) and **2a** (32.2 mg). Enantiomeric excess (95%) was measured by HPLC (Chiralcel OD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 11.8 min, minor enantiomer: t_r = 8.7 min.

Pale yellow solid, m.p. = 76.0-79.7 ºC; $[\alpha]_D^{25}$ = +8.3 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m, Ar), 7.25-7.17 (4H, m, Ar), 7.04 (2H, dd, *J* = 8.2, 1.3 Hz, Ar), 6.98 (1H, dd, *J* = 8.3, 2.1 Hz, Ar), 6.29-6.15 (2H, m, Ar + NH), 4.80 (1H, d, *J* = 15.9 Hz, CH-Ph), 4.19 (3H, s, MeO), 4.06 (1H, d, *J* = 15.9 Hz, CH-Ph, 1.30 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.3 (C), 168.7 (C), 164.2 (C), 153.4 (C), 141.3 (C), 134.9 (C), 131.7 (C), 129.3 (CH), 129.1 (CH), 129.0 (C), 128.6 (CH), 128.4 (C),

128.2 (C), 127.8 (CH), 127.6 (CH), 127.5 (CH), 124.6 (CH), 110.1 (CH),84.5 (C), 80.7 (C), 59.0 (C), 58.7 (CH_3), 55.7 (CH_3), 44.1 (CH_2), 28.1 (CH_3); **IR** (ATR) ν 3427, 2967, 1716 (C=O), 1610, 1477, 1403, 1155, 1008, 697 cm^{-1}; **HRMS** (ESI) *m/z*: 546.1769 $[M+H]^+$, $C_{30}H_{29}ClN_3O_5^+$ requires 546.1790.

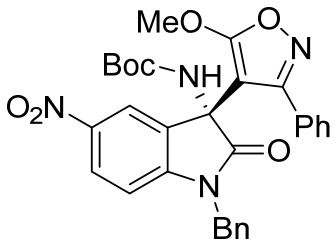
***tert*-Butyl (*R*)-(1-benzyl-5-bromo-3-(5-methoxy-3-phenylisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ea)**



75.8 mg (64%) of **3ea** were obtained from **1e** (83.1 mg) and **2a** (32.2 mg). Enantiomeric excess (94%) was measured by HPLC (Chiralcel AD-H), hexane:*i*PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 12.1 min, minor enantiomer: t_r = 16.0 min.

White solid, m.p. = 143.3-144.0 °C; $[\alpha]_D^{25}$ = +15.2 (*c* = 0.82, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32-7.15 (9H, m, Ar), 7.08 (1H, dd, J = 8.3, 2.0 Hz, Ar), 7.02-6.98 (2H, m, Ar), 6.16-6.13 (2H, m, NH+Ar), 4.77 (1H, d, *J* = 15.9 Hz, CH-Ph), 4.15 (3H, s, MeO), 4.01 (2H, d, *J* = 15.9 Hz, CH-Ph), 1.26 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.2 (C), 168.7 (C), 164.2 (C), 153,4 (C), 141,8 (C), 134.9 (C), 132.1 (C), 131.8 (CH), 129.3 (CH), 129.1 (CH), 128.6 (CH), 128.4 (C), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 115.5 (C), 110.6 (CH), 89.5 (C), 80.7 (C), 58.9 (C), 58.8 (CH_3), 44.1 (CH_2), 28.1 (CH_3); **IR** (ATR) ν 3431, 1722 (C=O), 1623, 1474, 1405, 1155, 1006, 695 cm^{-1}; **HRMS** (ESI) *m/z*: 590.1279 $[M+H]^+$, $C_{30}H_{29}BrN_3O_5^+$ requires 590.1285.

***tert*-Butyl (*R*)-(1-benzyl-5-nitro-3-(5-methoxy-3-phenylisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3da)**

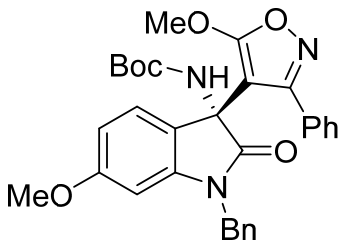


77.8 mg (70%) of **3da** were obtained from **1d** (76.5 mg) and **2a** (32.2 mg). Enantiomeric excess (96%) was measured by HPLC (Chiralcel OD-H), hexane:*i*PrOH 90:10, 1.0 mL min^{-1}, major enantiomer: t_r = 34.4 min, minor enantiomer: t_r = 41.3 min.

Orange solid, m.p. = 78.4-81.9 °C; $[\alpha]_D^{25}$ = +30.8 (*c* = 0.79, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.0 (1H, d, *J* = 2.1 Hz, Ar), 7.93 (1H, dd, *J* = 8.7, 2.1 Hz, Ar) 7.35-7.21 (6H, m, Ar), 7.17 (2H, t, J = 7.5 Hz, Ar), 7.03-6.93 (1H, m, Ar), 6.35 (1H, d, *J* = 8.7 Hz, Ar), 6.30 (1H, s, NH), 4.80 (1H, d, *J* = 15.9 Hz, CH-Ph), 4.17 (4H, m, MeO + CH-Ph), 1.30

(9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.2 (C), 169.0 (C), 16402 (C), 153.6 (C), 148.6 (C), 143.9 (C), 131.2 (C), 129.7 (CH), 129.2 (CH), 128.9(CH), 128.3 (C), 128.1 (CH), 128.0 (CH), 127.6 (CH), 126.2 (CH), 119.8 (CH), 108.9(CH),88.7 (C), 81.2 (C), 59.0 (CH_3), 58.7 (C), 58.7 (CH_3), 44.6 (CH_2), 28.2 (CH_3); **IR** (ATR) ν 1716 (C=O), 1610, 1477, 1330, 1153, 1067, 1006, 698 cm^{-1}; **HRMS** (ESI) *m/z*: 557.2017 $[M+H]^+$, $C_{30}H_9N_4O_7^+$ requires 557.2031.

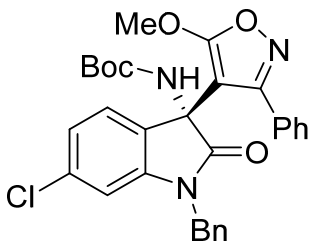
***tert*-Butyl (*R*)-(1-benzyl-6-methoxy-3-(5-methoxy-3-phenylisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ga)**



56.3 mg (52%) of **3ga** were obtained from **1h** (52.4 mg) and **2a** (32.2 mg). Enantiomeric excess (55%) was measured by HPLC (Chiralcel AS-H), hexane:^{i}PrOH 90:10, 1.0 mL min^{-1}, major enantiomer: t_r = 15.6 min, minor enantiomer: t_r = 12.4 min

Yellow solid, m.p. = 63.5-66.8 ºC; **$[\alpha]_D^{25}$** = +5.8 (*c* =0.87, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.10 (9H, m, Ar), 7.02 (1H , s, Ar), 7.00 (1H, d, *J* = 8.2, 7.6, 0.8 Hz, Ar), 6.36 (1H, dd, *J* = 7.1, 2.3 Hz, Ar), 6.09 (1H, s, N-H), 4.76 (1H, d, *J* = 15.7 Hz, CH-Ph), 4.18-4.01 (4H, m, MeO + CH-Ph), 3.64 (3H, s, OCH_3), 1.26 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.2 (C), 168.6 (C), 164.5 (C), 153.6 (C), 144.0 (C), 135.3 (C), 129.1 (CH), 129.0 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 125.2 (CH), 122.2 (C), 106.4 (CH), 97.2 (CH), 90.6 (C) , 80.2 (C), 58.7 (C), 58.6 (CH_3), 44.17 (CH_2), 28.1 (CH_3); **IR** (ATR) ν 3438, 1716 (C=O), 1619, 1477, 1403, 1159, 1006, 697 cm^{-1}; **HRMS** (ESI) *m/z*: 542.2285 $[M+H]^+$, $C_{31}H_{32}N_3O_6^+$ requires 542.2286.

***tert*-Butyl (*R*)-(1-benzyl-6-chloro-3-(5-methoxy-3-phenylisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ia)**

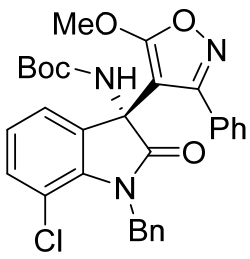


68.0 mg (63%) of **3ha** were obtained from **1h** (74.5 mg) and **2a** (32.2 mg). Enantiomeric excess (92%) was measured by HPLC (Chiralcel OD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 9.9 min, minor enantiomer: t_r = 7.7 min.

Pale yellow solid, m.p. = 75.4-77.3 °C; **$[\alpha]_D^{25}$** = +10.8 (*c* = 0.82, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48-7.04 (9H, m, Ar), 6.98 (1H, m, Ar), 6.84 (1H, dd, *J* = 8.0, 1.8 Hz), 4.78 (1H, d, *J* = 15.6 Hz, CH-Ph), 4.13 (3H, s, MeO), 4.04

(1H, d, J = 15.6 Hz, CH-Ph), 1.24 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.7 (C), 168.6 (C), 164.2 (C), 153.5 (C), 143.9 (C), 134.7 (C), 129.2 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.3 (C), 127.8 (CH), 127.7 (CH), 127.5 (CH), 125.0 (CH), 122.7 (CH) 109.6 (CH),89.7 (C), 80.6 (C), 58.7 (CH_3), 55.7 (CH_3), 53.4 (C), 44.1 (CH_2), 28.1 (CH_3); **IR** (ATR) ν 3431, 1738 (C=O), 1710, 1608, 1476, 1403, 1284, 1162, 1006, 698 cm^{-1}; **HRMS** (ESI) *m/z*: 546.1791 $[M+H]^+$, $C_{30}H_{29}ClN_3O_5^+$ requires 546.1790.

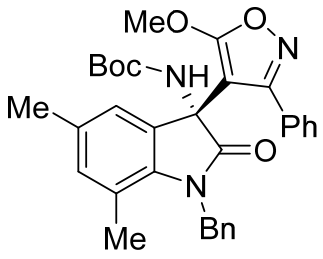
***tert*-Butyl (*R*)-(1-benzyl-7-chloro-3-(5-methoxy-3-phenylisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ia)**



68.2 mg (67%) of **3ia** were obtained from **1i** (74.2 mg) and **2a** (32.2 mg). Enantiomeric excess (95%) was measured by HPLC (Chiralcel OD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 15.9 min, minor enantiomer: t_r = 13.7 min.

Yellow solid, m.p. = 68.4-71.0 ºC; $[\alpha]_D^{25}$ = –42.1 (c = 0.76, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56-7.08 (9H, m, Ar), 6.87 (1H, dd , J = 8.1, 7.3 Hz Ar), 6.35 (1H, s, N-H), 5.01 (1H, d, J = 15.8 Hz, CH-Ph), 4.04 (1H, d, J = 15.8 Hz, CH-Ph) 4.20 (3H, s, MeO), 1.30 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.6(C), 168.6 (C), 164.3 (C), 153.4 (C), 139.1 (C), 137.3 (C), 133.5 (CH), 131.8 (C), 129.7 (CH), 129.1 (CH), 128.3 (C), 127.9 (CH), 127.0 (CH), 123.8 (CH), 122.5 (CH), 115.5 (CH), 90.0 (C), 80.8 (C), 58.9 (CH_3), 58.8 (C), 45.1 (CH_2), 28.2 (CH_3); **IR** (ATR) ν 3425, 1718 (C=O), 1617, 1451, 1403, 1157, 1123, 1008, 697 cm^{-1}; **HRMS** (ESI) *m/z*: 546.1781 $[M+H]^+$, $C_{30}H_{29}ClN_3O_5^+$ requires 546.1790.

***tert*-Butyl (*R*)-(1-benzyl-3-(5-methoxy-3-phenylisoxazol-4-yl)-5,7-dimethyl-2-oxoindolin-3-yl)carbamate (3ga)**

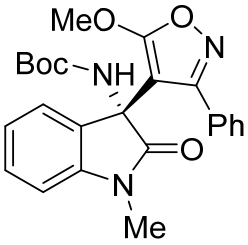


68.7 mg (64%) of **3ja** were obtained from **1j** (72.9 mg) and **2a** (32.2 mg). Enantiomeric excess (97%) was measured by HPLC (Chiralcel OD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 9.8 min, minor enantiomer: t_r = 7.4 min.

Yellow oil. $[\alpha]_D^{25}$ = –7.2 (c =1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 (1H,tt, J= 7.5, 2.1 Hz, Ar), 7.31-7.13 (7H, m, Ar), 6.91 (3H, m, Ar), 6.31 (1H, s, Ar), 6,46 (1H, s, NH), 4.93 (1H, d, J = 17.1 Hz, CH-Ph), 4.25 (3H, s, MeO), 4.08 (1H, d, J = 17.1 Hz, CH-Ph), 2.20 (3H, s, CH_3-Ph), 1.89 (3H, s, CH_3-Ph), 1.28 (9H, s, *t*-BuO); **^{13}C NMR**

(75 MHz, $CDCl_3$) δ 175.5 (C), 168.3 (C), 164.3 (C), 153.5 (C), 138.3 (C), 137.4 (C), 133.6 (CH), 132.4 (C), 131.3 (CH), 129.2 (C), 129.1 (CH), 128.5 (CH), 127.4 (CH), 126.8 (CH), 126.1(CH), 122.5 (CH), 119.3 (C), 90.9 (C), 80.3 (C), 58.7 (CH_3), 45.2 (CH_2), 28.1 (CH_3), 20.7 (CH_3), 18.3 (CH_3); **IR** (ATR) ν 3442, 2920, 1716 (C=O), 1623, 1477, 1403, 1161, 1008, 695 cm^{-1}; **HRMS** (ESI) *m/z*: 540.2490 $[M+H]^+$, $C_{32}H_{34}N_3O_5^+$ requires 540.2493.

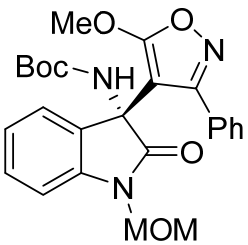
***tert*-Butyl (*R*)-(3-(5-methoxy-3-phenylisoxazol-4-yl)-1methyl-2-oxoindolin-3-yl)carbamate (3ka)**



55.2 mg (64%) of **3ka** were obtained from **1k** (52.4 mg) and **2a** (32.2 mg). Enantiomeric excess (94%) was measured by HPLC (Chiralcel AS-H), hexane:^{i}PrOH 90:10, 1.0 mL min^{-1}, major enantiomer: t_r = 11.2 min, minor enantiomer: t_r = 13.9 min

Yellow oil; $[\alpha]_D^{25}$ = +11.7 (*c* =1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 – 7.29 (2H, m, Ar), 7.30 – 7.16 (2H , m, Ar), 7.07 (1H, td, *J* = 8.2, 7.6, 0.8 Hz, Ar), 6.93 (1H, d, *J* = 7.1 Hz, Ar), 6.49 (1H, s, Ar), 6.46 (1H, s, N-H), 4.34 (3H, s, MeO), 2.8 (3H, s, MeN), 1.31 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.2 (C), 168.6 (C), 164.5 (C), 153.5 (C), 143.5 (C), 143.5 (C), 129.4 (CH), 129.2 (CH), 129.1 (CH), 128.5 (C), 127.7 (CH), 123.8 (CH), 123.0 (CH), 108.2 (CH), 90.3 (C), 80.5 (C), 59.0 (CH_3), 28.1 (CH_3), 26.1 (CH_3); **IR** (ATR) ν 3425, 1712 (C=O), 1612, 1472, 1403, 1284, 1153, 764, 697 cm^{-1}; **HRMS** (ESI) *m/z*: 438.1869 $[M+H]^+$, $C_{24}H_{26}N_3O_5^+$ requires 438.1867.

***tert*-Butyl (*R*)-(3-(5-methoxy-3-phenylisoxazol-4-yl)-1-(methoxymethyl)-2-oxoindolin-3-yl)carbamate (3la)**

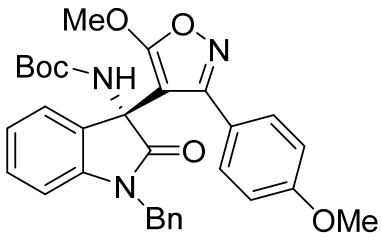


53.4 mg (57%) of **3la** were obtained from **1l** (58.6 mg) and **2a** (32.2 mg). Enantiomeric excess (92%) was measured by HPLC (Chiralpak AS-H), hexane;^{i}PrOH 90:10, 1.0 mL min^{-1}, major enantiomer: t_r = 8.9 min, minor enantiomer: t_r = 10.3 min.

Brown solid, m.p. = 66.1-66.5 ºC; $[\alpha]_D^{25}$ = +51.8 (*c* = 0.80, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34-7.13 (5H, m, Ar), 7.03-6,92 (3H, m, Ar), 6.67 (1H, d, *J* = 7.1 Hz, Ar), 6.31 (1H, s, NH), 4.78 (1H, d, *J* = 11.0 Hz, CH-OMe), 4.33 (1H, d, *J* = 11.0 Hz, CH-OMe), 4.20 (3H, s, MeO), 3.31 (3H, s, Me), 1.26 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.0 (C), 168.4 (C), 164.2 (C), 153.3 (C), 141.9 (C), 129.9

(C), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.3 (C), 127.7 (CH), 123.7 (CH), 123.3 (CH), 109.6 (CH), 90.2 (C), 80.4 (C), 71.5 (C), 59.2 (C), 58.8 (CH_3), 56.6 (CH_3), 28.1 (CH_3); **IR** (ATR) ν 3429, 2978, 1716 (C=O), 1612, 1477, 1401, 1153, 1008, 915, 751, 697 cm^{-1}; **HRMS** (ESI) *m/z*: 466.1957 $[M+H]^+$, $C_{25}H_{28}N_3O_6^+$ requires 466.1973.

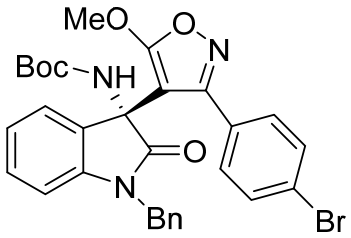
***tert*-Butyl (*R*)-(1-benzyl-3-(5-methoxy-3-(4-methoxyphenyl)isoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ab)**



59.0 mg (55%) of **3ab** were obtained from **1a** (67.3 mg) and **2b** (38.2 mg). Enantiomeric excess (94%) was measured by HPLC (Phenomenex Lux® 5µm Amylose-1), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 19.9 min, minor enantiomer: t_r = 17.9 min.

Pale yellow solid, m.p.= 148.0-148.3 ºC; $[\alpha]_D^{25}$ = +20.2 (*c* = 0.78, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29-7.12 (9H, m, Ar), 7.01-6.95 (3H, m, Ar), 6.84 (1H, td, *J* = 7.5, 1.0 Hz, Ar), 6.64 (2H, m, Ar), 6.34 (1H, d, *J* = 7.8 Hz, Ar), 6.01 (1H, s, NH), 4.72 (1H, d, *J* = 15.9 Hz, CH-Ph), 4.21 (1H, d, *J* = 15.8 Hz, CH-Ph), 4.00 (3H, s, MeO), 3.72 (3H, s, MeO), 1.17 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.8 (C), 168.6 (C), 164.2 (C), 160.4 (C), 153.5 (C), 142.9 (C), 135.4 (C), 130.6 (CH), 130.3 (C), 129.0 (CH), 128.6 (CH), 127.6 (CH), 127.5 (CH), 125.2 (CH), 122.8 (CH), 120,8 (C), 113.3 (CH), 109.1 (CH), 90.1 (C), 80.3 (C), 59.1 (C), 58.5 (CH_3), 55.3 (CH_3), 44.2 (CH_2), 28.1 (CH_3); **IR** (ATR) ν 3436, 1716 (C=O), 1613, 1479, 1401, 1244, 1155, 993, 751, 697, 577 cm^{-1}; **HRMS** (ESI) *m/z*: 542.2271 $[M+H]^+$, $C_{31}H_{32}N_3O_6^+$ requires 542.2286.

***tert*-Butyl (*R*)-(1-benzyl-3-(3-(4-bromophenyl)-5-methoxyisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ac)**

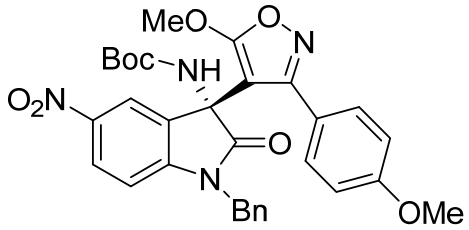


87.1 mg (76%) of **1a** were obtained from **1a** (67.3 mg) and **2c** (48.0 mg). Enantiomeric excess (85%) was measured by HPLC (Chiralpak AD-H), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 17.3 min, minor enantiomer: t_r = 14.3 min.

Yellow oil, $[\alpha]_D^{25}$ = +27.8 (*c* = 0.94, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38-7.25 (6H, m, Ar), 7.09 (1H, td, J_1 = 7.7, J_2 = 1.3 Hz), 6.94-6.89 (3H, m, Ar), 6.43 (1H, d, *J* = 7.8 Hz, Ar), 6.04 (1H, s, NH), 4.78 (1H, d, *J* = 15.6 Hz, CH-Ph), 4.29 (1H, d, *J* = 15.6 Hz, CH-Ph), 4.13 (3H, s, MeO), 1.26 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.6 (C), 168.9 (C), 163.4 (C), 153.5 (C), 142.7 (C), 135.2 (C), 130.9 (CH), 130.8 (CH), 130.0

(C), 129.2 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 127.5 (C), 124.5 (CH), 123.7 (C), 122.9 (CH), 109.1 (CH), 90.2 (C), 80.4 (C), 59.0 (C), 58.7 (CH_3), 44.1 (CH_2), 28.1 (CH_3); **IR** (ATR) ν 3432, 1716 (C=O), 1615, 1477, 1403, 1066, 993, 749 cm^{-1}; **HRMS** (ESI) *m/z*: 590.1279 $[M+H]^+$, $C_{30}H_{29}BrN_3O_5^+$ requires 590.1285.

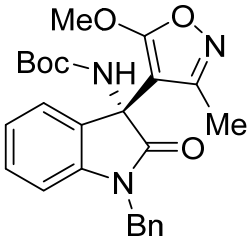
***tert*-Butyl (*R*)-(1-benzyl-3-(5-methoxy-3-(4-methoxyphenyl)isoxazol-4-yl)-5-nitro-2-oxoindolin-3-yl)carbamate (3fb)**



32.7 mg (56%) of **3db** were obtained from **1d** (38.1 mg) and **2b** (19.1 mg). Enantiomeric excess (95%) was measured by HPLC (Phenomenex Lux® 5µm Amylose-1), hexane;^{i}PrOH 90:10, 1.0 mL min^{-1}, major enantiomer: t_r = 62.2 min, minor enantiomer: t_r = 58.0 min.

Yellow oil; $[\alpha]_D^{25}$ = +54.7 (*c* = 0.78, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03-7.98 (2H, m, Ar), 7.37-7.27 (5H, m, Ar), 7.06-7.01 (2H, m, Ar), 6.76-6.71 (2H, m, Ar), 6.24 (1H, s, NH), 4.92 (1H, d, *J* = 15.9 Hz, CH-Ph), 4.35 (1H, d, *J* = 15.8 Hz, CH-Ph), 4.15 (3H, s, MeO), 3.80 (3H, s, MeO), 1.30 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.2 (C), 168.7 (C), 163.7 (C), 160.6 (C), 153.4 (C), 148.5 (C), 143.5 (C), 134.3 (C), 131.1 (C), 130.5 (CH), 128.8 (CH), 127.9 (CH), 127.5 (CH), 126.1 (CH), 120.3 (C), 119.7 (CH), 113.5 (CH), 108.7 (CH), 88.5 (C), 81.0 (C), 58.7 (CH), 58.6 (C), 58.4 (CH_3), 44.6 (CH_2), 28.1 (CH_3); **IR** (ATR) ν 3432, 1716 (C=O), 1615, 1477, 1403, 1066, 993, 749 cm^{-1}; . **IR** (ATR) ν 3432, 1716 (C=O), 1615, 1477, 1403, 1066, 993, 749 cm^{-1}; **HRMS** (ESI) *m/z*: 587.2112 $[M+H]^+$, $C_{31}H_{31}N_4O_8^+$ requires 587.2136.

***tert*-Butyl (*R*)-(1-benzyl-3-(5-methoxy-3-methylisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ad)**

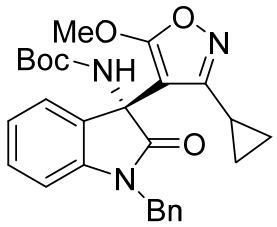


53.2 mg (59%) of **3ad** were obtained from **1a** (67.3 mg) and **2d** (19.8 mg). Enantiomeric excess (41%) was measured by HPLC (Chiralpak AD-H), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 23.8 min, minor enantiomer: t_r = 14.0 min.

Yellow oil; $[\alpha]_D^{25}$ = +10.7, (*c* = 0.81, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.37 (9H, m, Ar), 7.34-7.27 (4H, m, Ar), 7.21 (1H, td, *J* = 7.5, 1.0 Hz, Ar), 7.02 (1H, td, *J* = 7.5, 1.0 Hz, Ar), 6.77 (1H, d, *J* = 7.7 Hz, Ar), 6.21 (1H, s, NH), 5.01 (1H, d, *J* = 15.4 Hz, CH-Ph), 4.83 (1H, d, *J* = 15.4 Hz, CH-Ph), 4.11 (3H, s, MeO),

1.53 (3H, s, MeO), 1.31 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.0 (C), 168.8 (C), 160.7 (C), 153.8 (C), 142.9 (C), 135.6 (C), 129.8 (C), 129.4 (CH), 128.7 (CH), 127.7 (CH), 124.2 (CH), 123.0 (CH), 109.1 (CH), 89.3 (C), 80.6 (C), 58.9 (C), 58.5 (CH_3), 44.4 (CH_2), 28.1 (CH_3), 11.5 (CH_3); **IR** (ATR) ν 3421, 2976, 1712 (C=O), 1608, 1455, 1284, 1161, 944, 751, 700 cm^{-1}; **HRMS** (ESI) *m/z*: 450.2020 $[M+H]^+$, $C_{25}H_{28}N_3O_5^+$ requires 450.2023.

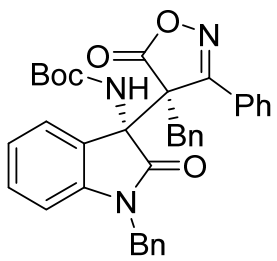
***tert*-Butyl (*R*)-(1-benzyl-3-(3-cyclopropyl-5-methoxyisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ae)**



27.0 mg (57%) of **3ae** were obtained from **1a** (33.6 mg) and **2e** (12.5 mg). Enantiomeric excess (65%) was measured by HPLC (Chiralpak AD-H), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 17.5 min, minor enantiomer: t_r = 14.6 min.

Yellow solid, m.p. = 141.5-141.9 ºC; **$[\alpha]_D^{25}$** = +8.2 (*c* = 0.89, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43-7.27 (5H, m, Ar), 7.19 (1H, td, *J* = 7.7, 1.3 Hz, Ar), 7.02 (1H, td, *J* = 7.5, 1.0 Hz, Ar), 6.74 (1H, d, *J* =7.8 Hz, Ar), 6.26 (1H, bs, NH), 5.00-4.90 (1H, m, Ar), 4.02 (3H, s, MeO), 1.30-1.16 (10H, m, *t*-BuO + CH), 0.79-0.68 (2H, m, CH_2), 0.56-0.41 (2H, m, CH_2), **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.1 (C), 168.6 (C), 165.1 (C), 153.7 (C), 143.1 (C), 135.6 (C), 129.9 (C), 129.2 (CH), 128.7 (CH), 127.8 (CH), 127.6 (CH), 124.2 (CH), 122.9 (CH), 108.9 (CH), 90.2 (C), 80.5 (C), 59.1 (C), 58.4 (CH_3), 44.5 (CH_2), 28.1 (CH_3), 7.1 (CH_2), 7.01 (CH), 6.11 (CH_2); **IR** (ATR) ν 3423, 1735, 1710 (C=O), 1627, 1468, 1422, 1164, 1047, 754, 702 cm^{-1}; **HRMS** (ESI) *m/z*: 476.2189 $[M+H]^+$, $C_{27}H_{30}N_3O_5^+$ requires 476.2180.

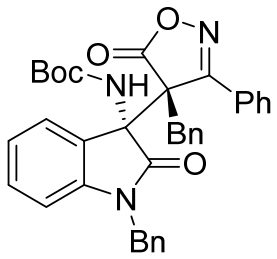
***tert*-butyl (1-benzyl-3-(4-benzyl-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3af)**



49.7 mg (85% overall yield) of product **3af** were obtained in a 41:59 diastereoisomeric ratio.

***Syn* diastereoisomer:** 20.6 mg (35%) were obtained from **1a** (33.6 mg) and **2h** (25.1 mg). Enantiomeric excess (>99%) was measured by HPLC (Chiralpak AD-H), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 24.1 min, minor enantiomer: t_r = 25.7 min

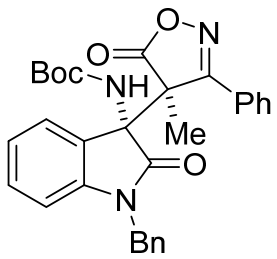
Orange solid, m.p. = 133.4-134.3ºC; $[\alpha]_D^{25}$ = +87.5 (*c* = 0.82, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61-7.55 (1H, m, Ar), 7.49-7.38 (4H, m, Ar), 7.37-7.25 (6H, m, Ar), 7.22-6.94 (8H, m, Ar), 6.14 (1H, d, *J* = 7.8 Hz, Ar), 4.83 (1H, d, *J* = 16.2 Hz, CH-Ph), 4.58 (1H, d, *J* =14.9 Hz, CH-Ph), 3.84 (1H, d, *J* =14.9 Hz, CH-Ph), 2.85 (1H, d *J* = 16.0 Hz, CH-Ph), 1.37 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.9 (C), 171.2 (C), 165.1 (C), 153.5 (C), 141.9 (C), 134.6 (C), 131.7 (CH), 130.1 (CH), 129.7 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 128.1 (C), 128.0 (CH), 127.9 (CH), 127.3 (CH), 127.2 (CH), 123.3 (CH), 121.6 (CH), 109.8 (CH), 80.9 (C), 61.6 (C), 60.8 (C), 43.2 (CH_2), 33.9 (CH_2), 28.2 (CH_3); **IR** (ATR) ν 3391, 2976, 1768, 1718 (C=O), 1610, 1487, 1366, 1157, 889, 752, 695 cm^{-1}; **HRMS** (ESI) *m/z*: 528.2488 $[M+H]^+$, $C_{36}H_{34}N_3O5^+$ requires 528.2493.



***Anti* diastereoisòmer:** 29.1 mg (50%) were obtained from **1a** (33.6 mg) and **2h** (25.1 mg). Enantiomeric excess (72%) was measured by HPLC (Chiralpak AD-H), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 14.3 min, minor enantiomer: t_r = 7.8 min

Yellow solid, m.p. = 142.8-144.0 ºC; $[\alpha]_D^{25}$ = +9.1 (*c* = 0.97, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.53 (1H, dd, *J* = 7.1, 1.5 Hz, Ar), 7.35-6.99 (18H, m, Ar), 5.99 (1H, d, *J* = 7.4, 1.3 Ar), 5.04 (1H, d, *J* = 15.6 Hz, CH-Ph), 4.01-3.83 (3H, m, CH-Ph), 1.27 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.1 (C), 174.1 (C), 163.9 (C), 154.4 (C), 143.6 (C), 134.6 (C), 131.7 (C), 130.7 (CH), 130.1 (CH), 129.8 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 128.1 (C), 127.9 (CH), 127.6 (CH), 127.5 (C), 127.4 (CH), 125.7 (C), 124.6 (CH), 122.6 (CH), 109.5 (CH), 81.0 (C), 64.9 (C), 58.6 (C), 44.1 (CH_2), 36.4 (CH_2), 27.9 (CH_3); **IR** (ATR) ν 3384, 2976, 1768, 1716 (C=O), 1612, 1480, 1366, 1155, 900, 728, 695, 505 cm^{-1}; **HRMS** (ESI) *m/z*: 528.2488 $[M+H]^+$, $C_{36}H_{34}N_3O5^+$ requires 528.2493.

***tert*-butyl (1-benzyl-3-(4-methyl-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ag)**

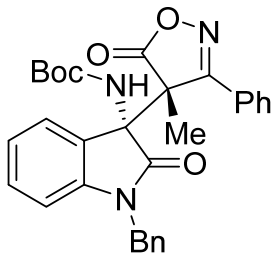


47.4 mg (93% overall yield) of product **3ag** were obtained in a 32:68 diastereoisomeric ratio.

***Syn* diastereoisomer:** 15.4 mg (30%) were obtained from **1a** (33.6 mg) and **2g** (17.5 mg). Enantiomeric excess (27%) was

measured by HPLC (Chiralpak AD-H), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 11.8 min, minor enantiomer: t_r = 28.1 min

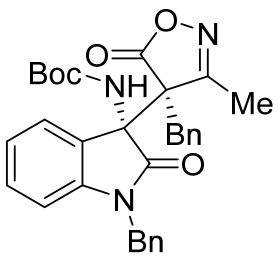
Yellow solid, m.p. = 161.1-162.6ºC; $[\alpha]_D^{25}$ = +17.4 (c = 0.96, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58-7.53 (1H, m, Ar), 7.47-7.41 (1H, m, 2H), 7.22-7.11 (9H, m, Ar), 7.00 (1H, td, J = 7.6 Hz, J = 1.0 Hz, Ar), 6.60 (1H, bs, NH), 6.23 (d, J = 7.8 Hz, Ar), 4.58 (1H, d, J = 16.2 Hz), CH-Ph), 2.86 (1H, d J = 16.2 Hz, CH-Ph), 2.23 (3H, s, CH_3), 1.33 (9H, s, t-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 179.7 (C), 170.9 (C), 167.2 (C), 153.5 (C), 141.8 (C), 134.6 (C), 131.7 (CH), 130.1 (CH), 129.0 (C), 128.7 (CH), 128.4 (CH), 127.5 (CH), 127.4 (C), 127.3 (CH), 127.2 (C), 126.0 (C),123.2 (CH), 121.6 (CH), 109.7 (CH), 80.8 (C), 60.9 (C), 54.2 (C), 42.7 (CH_2), 28.2 (C), 28.1 (CH_3), 15.2 (CH_3); **IR** (ATR) ν 3395, 2924, 1776, 1718 (C=O), 1612, 1489, 1366, 1157, 898, 751, 695 cm^{-1}; **HRMS** (ESI) *m/z*: 512.2172 $[M+H]^+$, $C_{30}H_{30}N_3O_5^+$ requires 512.2180.



***Anti* diastereoisomer:** 32.0 mg (63%) were obtained from **1a** (33.6 mg) and **2g** (17.5 mg). Enantiomeric excess (86%) was measured by HPLC (Chiralpak AD-H), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 17.9 min, minor enantiomer: t_r = 10.9 min

Yellow oil, $[\alpha]_D^{25}$ = –56.9 (c = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (1H, dd, J = 6.8, 1.7 Hz, Ar), 7.30-7.18 (7H, m, Ar), 7.05-6.89 (7H, m, Ar), 6.00 (1H, dd, J = 7.3, Ar), 5.04 (1H, d, J = 15.5 Hz, CH-Ph), 4.07 (1H, d, J = 15.5 Hz, CH-Ph), 2.07 (3H, s, CH_3), 1.23 (9H, s, t-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 179.3 (C), 174.1 (C), 166.3 (C), 154.2 (C), 143.2 (C), 134.7 (C), 130.6 (CH), 130.0 (CH), 128.6 (CH), 127.9 (CH), 127.8 (C), 127.7 (CH), 127.6 (CH), 126.9 (CH), 125.4 (C), 124.2 (CH), 122.4 (CH). 109.7 (CH), 80.9 (C), 64.4 (C), 51.9 (C), 44.2 (CH_2), 27.9 (CH_3), 17.9 (CH_3); **IR** (ATR) ν 3362, 2980, 1774, 1716 (C=O), 1612, 1487, 1366, 1250, 1157, 894, 728, 691 cm^{-1}; **HRMS** (ESI) *m/z*: 512.2172 $[M+H]^+$, $C_{30}H_{30}N_3O_5^+$ requires 512.2180.

tert-butyl (1-benzyl-3-(4-benzyl-3-methyl-5-oxo-4,5-dihydroisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (3ah)

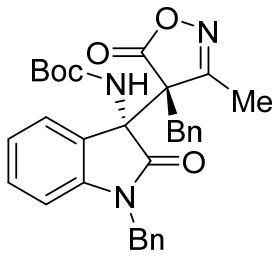


97.7 mg (93% overall yield) of product **3ah** were obtained in a 48:52 diastereoisomeric ratio.

***Syn* diastereoisomer:** 47.1 mg (45%) were obtained from **1a** (67.2 mg) and **2f** (37.8 mg). Enantiomeric excess (46%) was

measured by HPLC (Chiralpak AD-H), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 13.9 min, minor enantiomer: t_r = 15.4 min

Yellow solid, m.p. = 155.4-156.5 ºC; **[α]$_D^{25}$** = +48.5 (c = 0.79, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58-7.54 (2H, m, Ar), 7.38-7.21 (8H, m, Ar), 7.19-7.16 (1H, m, Ar), 7.11-7.07 (2H, m, Ar), 7.01 (1H, td, J = 7.6, 1.0 Hz, Ar), 6.86 (1H, s, NH), 6.83-6.80 (1H, m, Ar), 5.16 (1H, d, J = 15.3 Hz, CH-Ph), 4.81 (1H, d, J = 15.3 Hz, CH-Ph), 4.03 (1H, d, J = 14.4 Hz, CH-Ph), 3.65 (1H, d, J = 14.4 Hz, CH-Ph), 1.62 (3H, s, CH_3), 1.35 (9H, s, t-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.9 (C), 171.9 (C), 164.5 (C),153.7 (C), 142.3 (C), 134.8 (C), 132.9 (C), 129.5 (CH), 128.8 (CH), 128.4 (CH), 127.9 (CH), 126.2 (C), 123.7 (CH), 122.5 (CH), 109.4 (CH), 81.0 (C), 60.9 (C), 60.7 (C), 44.9 (CH_2), 33.2 (CH_2), 28.2 (CH_3), 12.7 (CH_3); **IR** (ATR) ν 3382, 1772, 1716 (C=O), 1608, 1481, 1153, 756, 700 cm^{-1}; **HRMS** (ESI) m/z: 526.2334 $[M+H]^+$, $C_{31}H_{32}N_3O_5^+$ requires 526.2336.



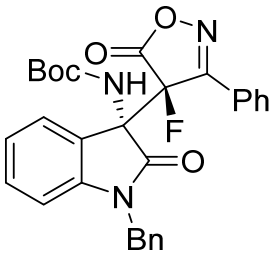
***Anti* diastereoisomer:** 50.6 mg (48%) were obtained from **1a** (67.2 mg) and **2f** (37.8 mg). Enantiomeric excess (64%) was measured by HPLC (Chiralpak AD-H), hexane;^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 36.7 min, minor enantiomer: t_r = 12.0 min

Yellow solid, m.p. = 93.3-96.6 ºC; **[α]$_D^{25}$** = +10.6 (c = 0.76, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 (1H, dd, J = 7.9, 1.0 Hz, Ar), 7.42-7.21 (9H, m, Ar), 7.15 (1H, td, J = 7.6, 1.0 Hz, Ar), 7.05-7.00 (2H, m, Ar), 6.98 (1H, s, NH), 6.87 (1H, dd, J = 7.9, 1.0 Hz, Ar), 5.09 (1H, d, J = 15.2 Hz, CH-Ph), 4.66 (1H, d, J = 15.2 Hz, CH-Ph), 3.72 (1H, d, J = 13.6 Hz, CH-Ph), 3.32 (1H, d, J = 13.6 Hz, CH-Ph), 1.31 (9H, s, t-BuO), 1.20 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.7 (C), 173.8 (C), 163.9 (C), 154.3 (C), 143.8 (C), 135.0 (C), 131.7 (C), 130.5 (CH), 129.6 (CH), 128.9 (CH), 128.8 (CH), 128.2 (CH), 128.0 (CH), 125.5 (C), 125.1 (CH), 123.0 (CH), 109.6 (CH), 81.2 (C), 64.0 (C), 58.8(C), 44.6 (CH_2), 34.8 (CH_2), 28.0 (CH_3), 13.2 (CH_3); **IR** (ATR) ν 3365, 1777, 1716 (C=O), 1610, 1485, 1366, 1157, 883, 697 cm^{-1}; **HRMS** (ESI) m/z: 526.2334 $[M+H]^+$, $C_{31}H_{32}N_3O_5^+$ requires 526.2336.

Synthesis of compound 3aa at one mmol scale

An oven dried round bottom flask was charged with isatin ketimine **1a** (337 mg, 1.0 mmol), isoxazol-5-one **2a** (162 mg, 1.0 mmol) and squaramide **IV** (60.0 mg, 0.1 mmol). The flask was purged with N_2 for 10 minutes. Dichloromethane (10 mL) was added, and the mixture was stirred at room temperature until completion (TLC). 1 M solution of TMS-diazomethane in diethyl ether (2.0 mL, 2 mmol) was added via a syringe and the reaction was stirred 2 hours at room temperature. The reaction mixture was chromatographed on silica gel eluting with hexane:EtOAc (8:2) to give 333 mg (65%) of compound **3aa** with 94% ee.

Synthesis of *tert*-butyl ((*S*)-1-benzyl-3-((*R*)-4-fluoro-5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)-2-oxoindolin-3-yl)carbamate (4)

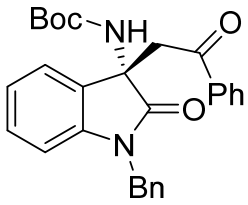


An oven dried test tube was charged with isatin ketimine **1a** (33.6 mg, 0.1 mmol), isoxazol-5-one **2** (16.1 mg, 0.1 mmol) and squaramide **IV** (6.0 mg, 0.01 mmol). The test tube was purged with N_2 and dichloromethane (1 mL) was added. The mixture was stirred at room temperature for 20 hours. NFSI (41.0 mg, 0.13 mmol) and K_2CO_3 (18.0 mg, 0.13 mmol) were added and the reaction was stirred vigorously 5 more hours. Upon completion, the reaction mixture was chromatographed on silica gel eluting with hexane:EtOAc mixtures to give compound **4** **(**33.1 mg, 64%) as a single diastereomer (dr>20:1) with identical spectroscopical features to those described in the literature.[6] Enantiomeric excess (93%) was measured by HPLC (Phenomenex Lux® *i*-Amylose-1), 90:10 Hexane/*i*PrOH, 0.5 mL min^{-1}, major enantiomer: t_r = 27.8 min, minor enantiomer: t_r = 18.5 min; lit.[6] (Chiralpak IA, same stationary phase as Lux® *i*-Amylose-1, 90:10 Hexane/iPrOH, 0.5 mL/min, major enantiomer: t_r = 21.2 min, minor enantiomer t_r = 15.2 min.

Pale yellow solid; $[\alpha]_D^{25}$ = –70.7 (*c* = 0.89, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45-7.42 (1H, m, Ar), 7.37-7.28 (5H, m, Ar), 7.18 (1H, t, *J* = 7.5 Hz, Ar), 7.00-6.91 (4H, m, Ar), 6.83 (1H, d, *J* = 7.5 Hz, Ar), 6.75 (1H, bs, NH), 6.12 (1H, d, *J* = 7.1 Hz, Ar), 4.85 (1H, d, *J* = 15.3 Hz, CH-Ph), 4.41 (1H, d, *J* = 15.3 Hz, CH-Ph), 1.28 (9H, s, *t*-BuO); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -176.1 ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8 (d, *J* = 8.2 Hz, C), 169.6 (d, *J* = 22.6 Hz, C), 160.2 (d, *J* = 13.9 Hz, C), 153.4 (C), 143.2 (C), 134.7 (C), 131.0 (CH), 130.6 (CH), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.0

(CH), 125.6 (CH), 125.5 (CH), 123.8 (C), 123.0 (CH), 108.9 (CH), 89.2 (C), 81.3 (CH), 65.7 (d, J = 22.6 Hz, C), 44.6 (CH_2), 28.0 (CH_3); **HRMS** (ESI) *m/z*: 516.1937 $[M+H]^+$, $C_{29}H_{27}FN_3O_5^+$ requires 516.1929.

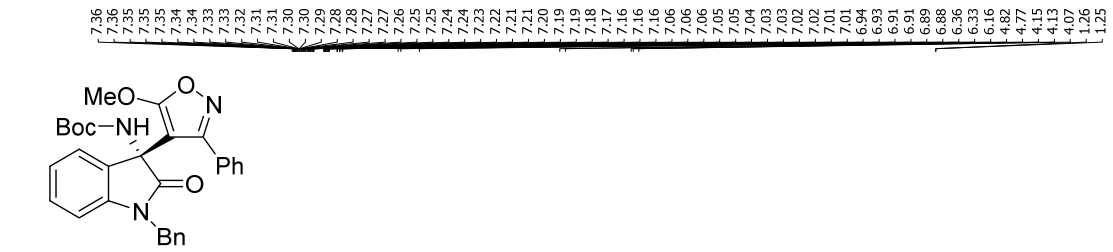
Synthesis of *tert*-butyl (*S*)-(1-benzyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)carbamate (5)



Compounds **1a** (33.6 mg) and **2a** (16.1 mg) were reacted in the presence of catalyst **IV** (6.0 mg, 0.01 mmol) as described in the general procedure omitting the methylation step. The crude was concentrated under reduced pressure and suspended in MeOH:H_2O (1:1). Then, iron powder (56.1 mg, 1.0 mmol) and NH_4Cl (53.5 mg, 1.0 mmol) were added, and the reaction was stirred at 60 ºC overnight. The reaction mixture was filtered through a short celite pad eluting with DCM. The filtrate was concentrated under reduced pressure and purified by flash column chromatography eluting with 6:4 hexane:EtOAc to afford 41.2 mg (87%) of **5** were obtained from 3aa (49.7 mg). Enantiomeric excess (91%) was measured by HPLC (Phenomenex Lux® *i*-Amylose-1 (90:10 Hexane/*i*PrOH, 0.5 mL min^{-1}), major enantiomer: t_r = 41.1 min, minor enantiomer: t_r = 10.8 min.

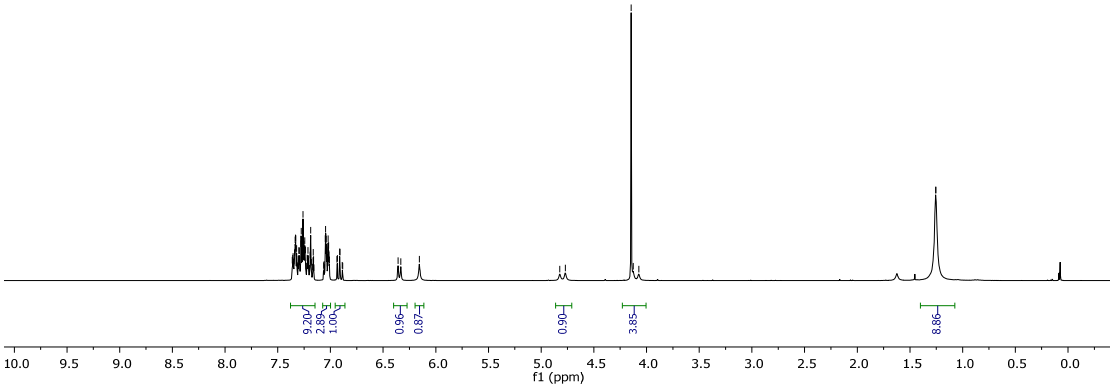
Yellow oil; $[\alpha]_D^{25}$ = –65.7 (c = 0.95, $CHCl_3$), Lit.[7] $[\alpha]_D^{25}$ = –50.7 (c = 0.1, $CHCl_3$, 90% ee, for the *S* enantiomer), Lit.[8] $[\alpha]_D^{25}$ = +52.34 (c = 0.34, $CHCl_3$, 95% ee, for the *R* enantiomer); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 (1H, m, Ar), 7.54 (1H, m, Ar), 7.45-7.27 (7H, m, Ar), 7.14 (H, td, J = 7.7, 1.3 Hz, Ar), 6.92 (1H, td, J = 7.6, 1.0 Hz, Ar), 6.72 (1H, d, J = 7.8 Hz, Ar), 6.48 (1H, bs, Ar), 5.10 (1H, d, J = 15.7 Hz, CH-CO), 4.89 (1H, d, J = 15.7 Hz, CH-CO), 3.70 (1H, d, J = 15.3 Hz, CH-Ph), 3.36 (1H, d, J = 16.6 Hz, CH-Ph), 1.33 (9H, s, *t*-BuO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.4 (C), 176.1 (C), 154.0 (C), 142.5 (C), 136.6 (C), 135.9 (C), 133.7 (CH), 129.9 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 127.5 (CH), 127.4 (CH), 124.2 (CH), 122.7 (CH), 109.3 (CH), 80.2 (C), 60.0 (C), 44.2 (CH_2), 43.7 (CH_2), 28.1 (CH_3); **HRMS** (ESI) *m/z*: 457.2141 $[M+H]^+$, $C_{28}H_{29}N_2O_4^+$ requires 457.2122.

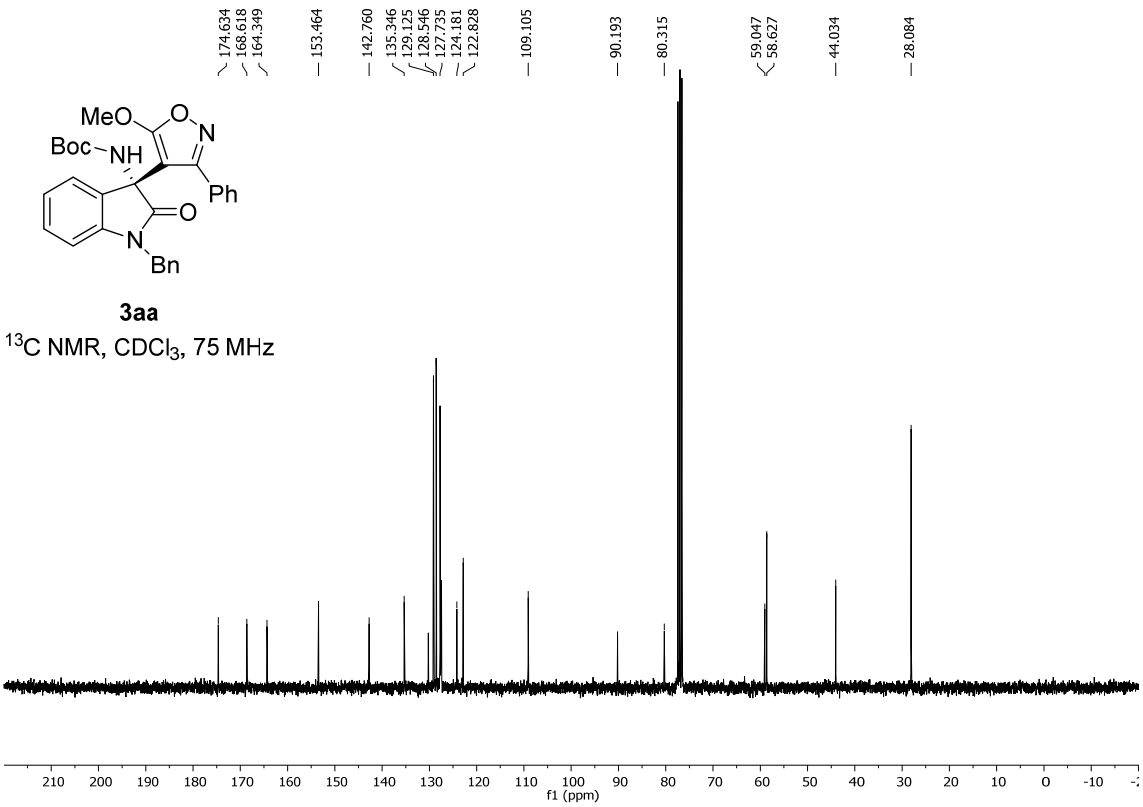
^{1}H NMR and ^{13}C NMR spectra for compounds 3-5



3aa

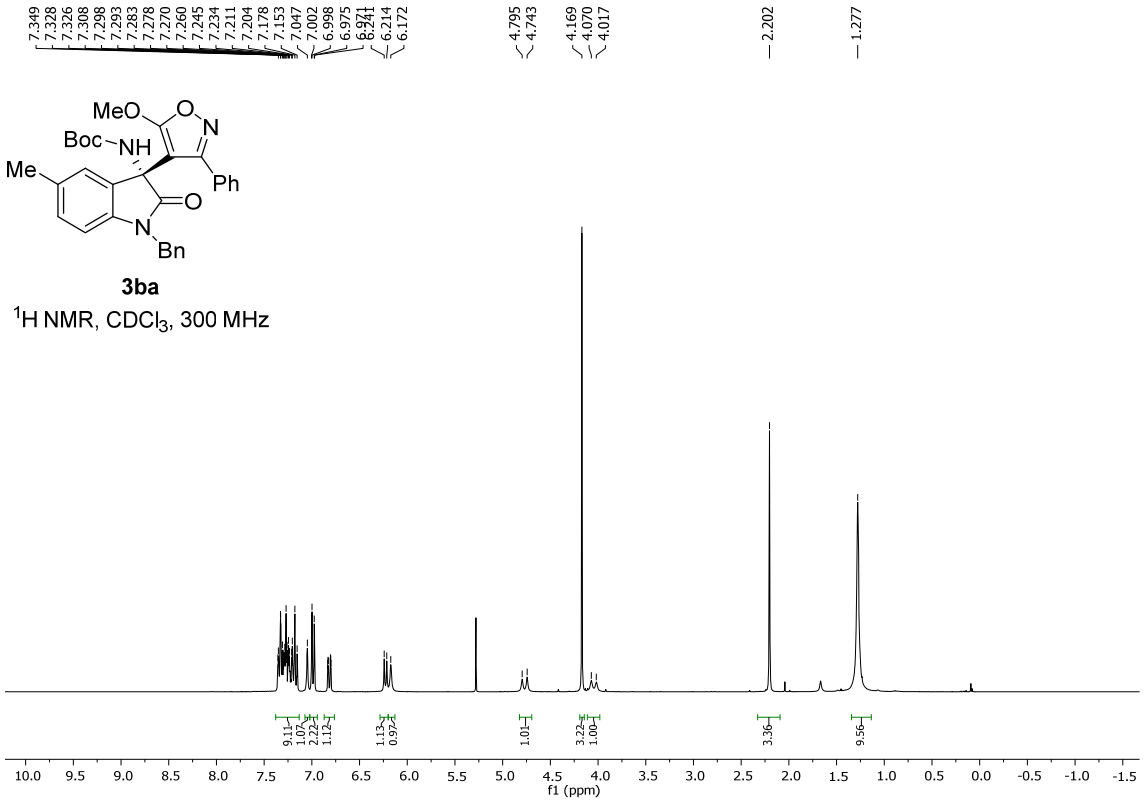
^{1}H NMR, $CDCl_3$, 300 MHz





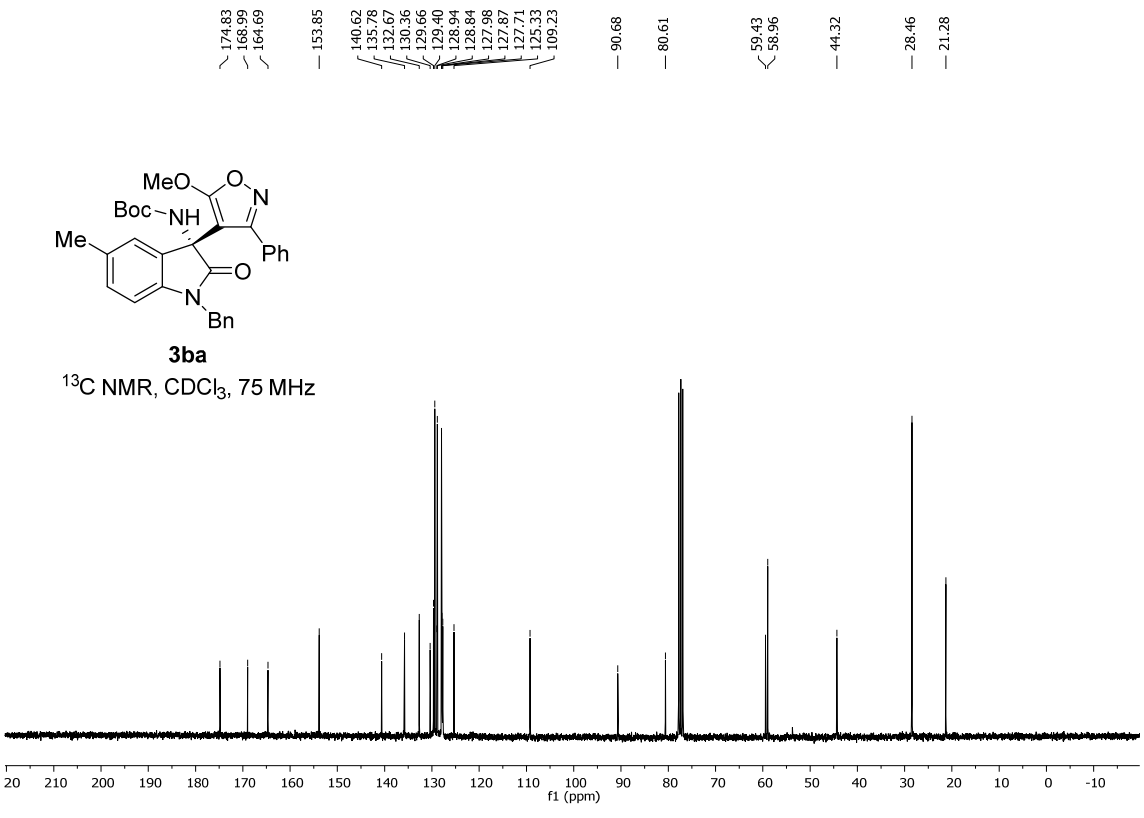
3aa

^{13}C NMR, $CDCl_3$, 75 MHz



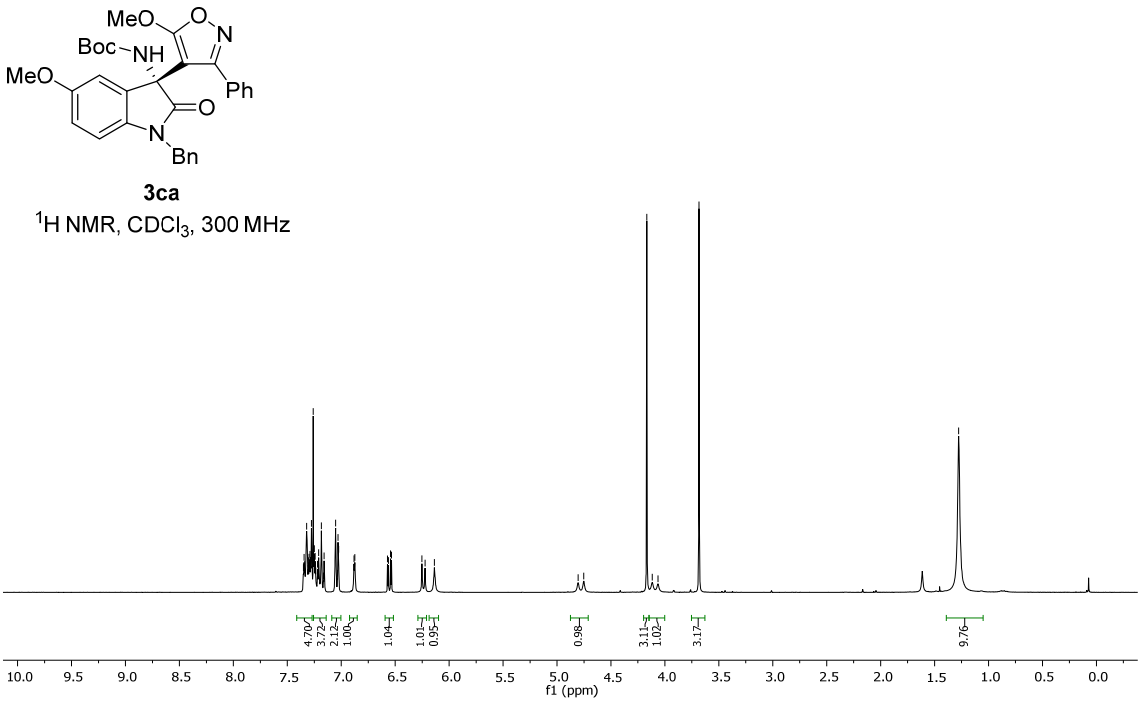
3ba

^{1}H NMR, $CDCl_3$, 300 MHz



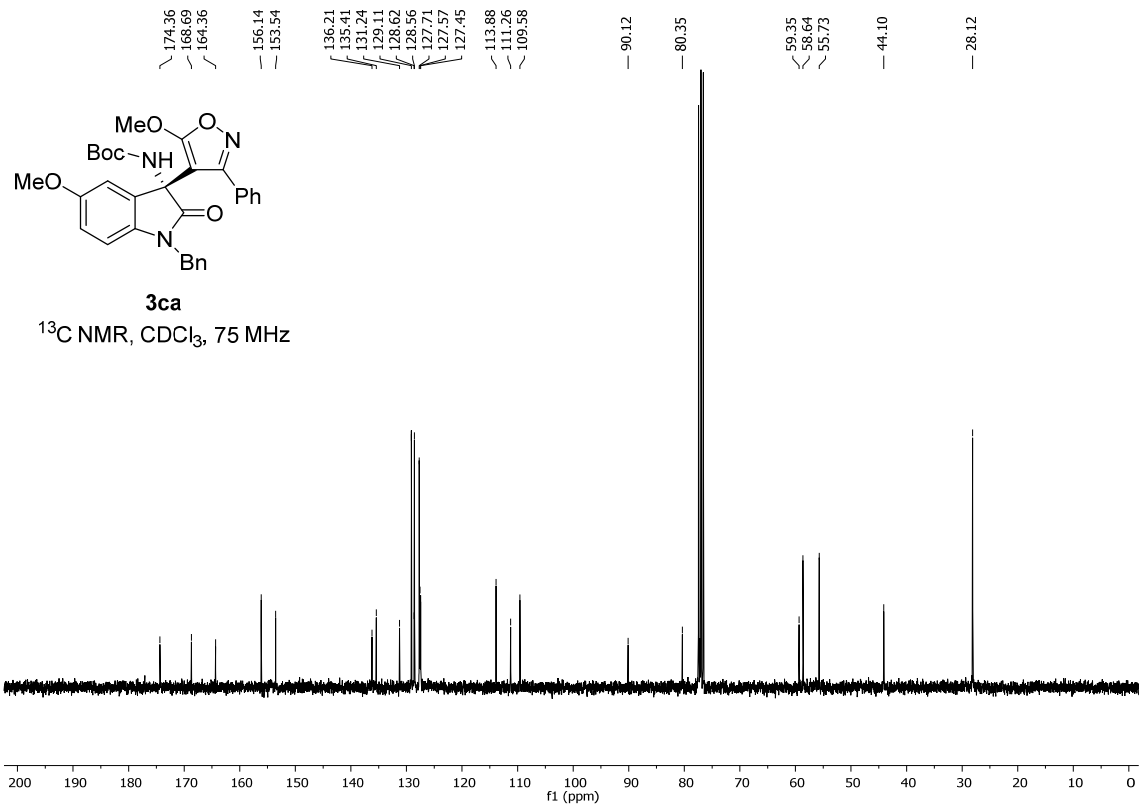
3ba

^{13}C NMR, $CDCl_3$, 75 MHz



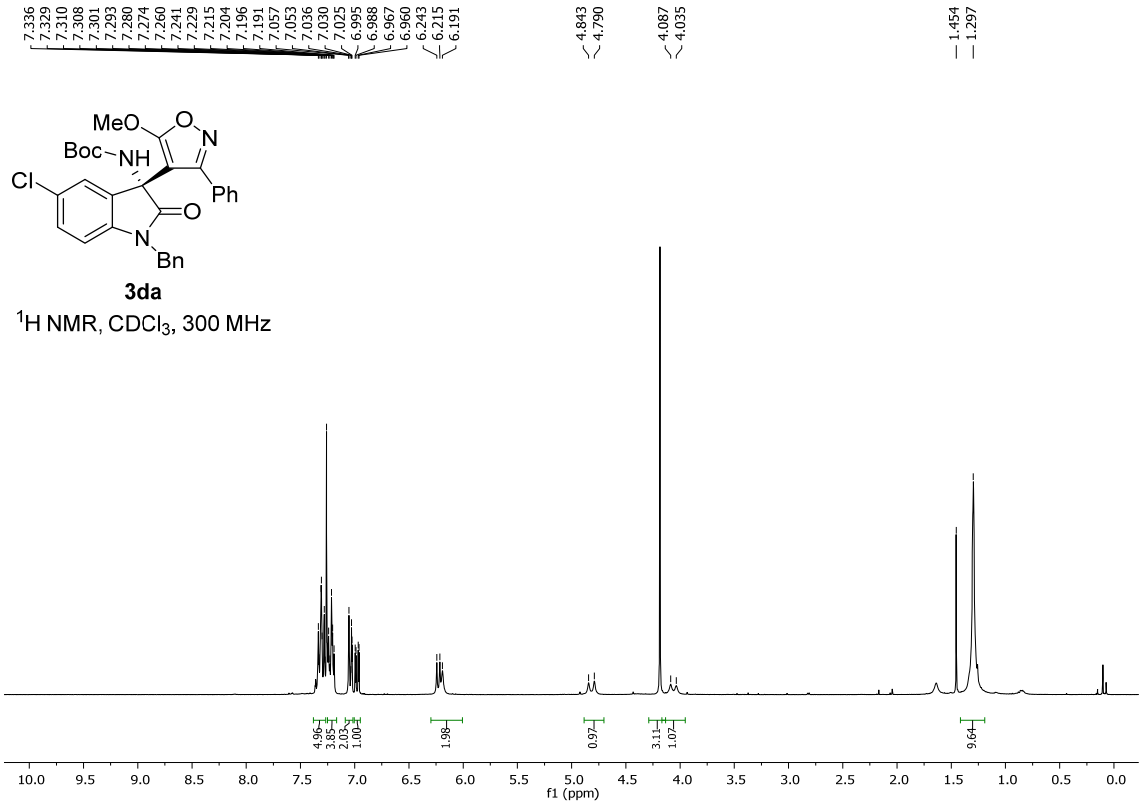
3ca

^{1}H NMR, $CDCl_3$, 300 MHz



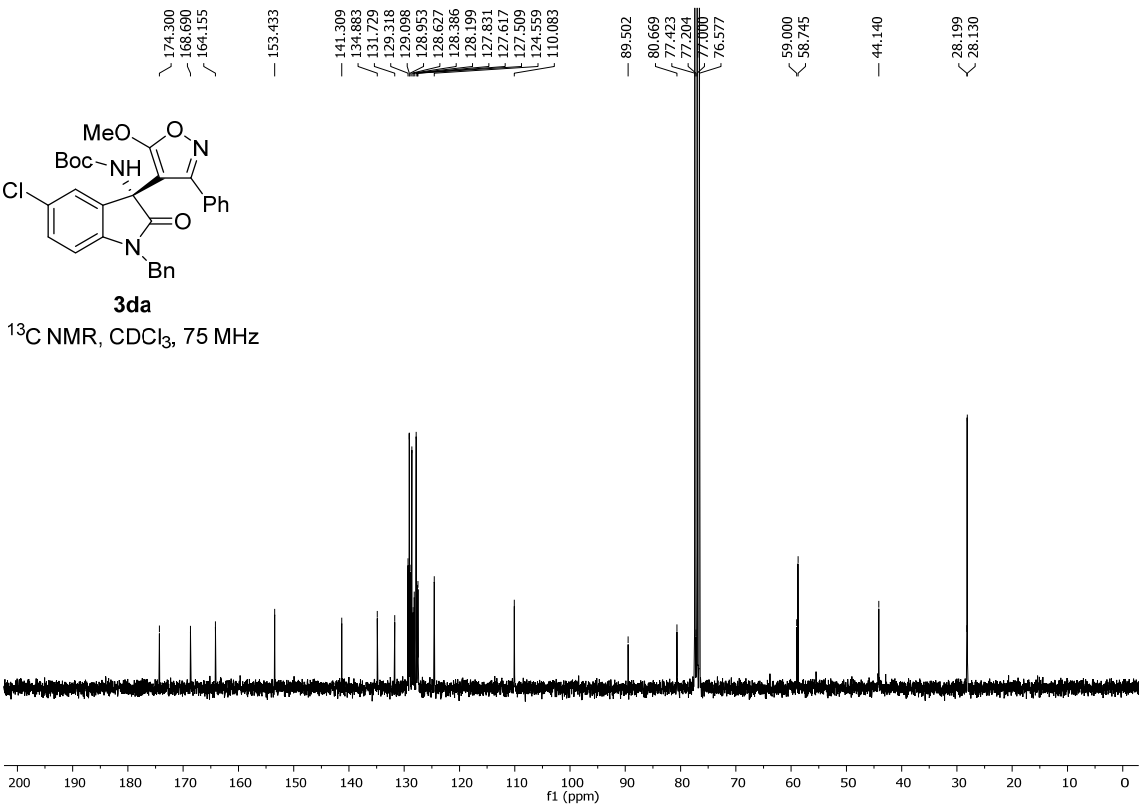
3ca

^{13}C NMR, $CDCl_3$, 75 MHz



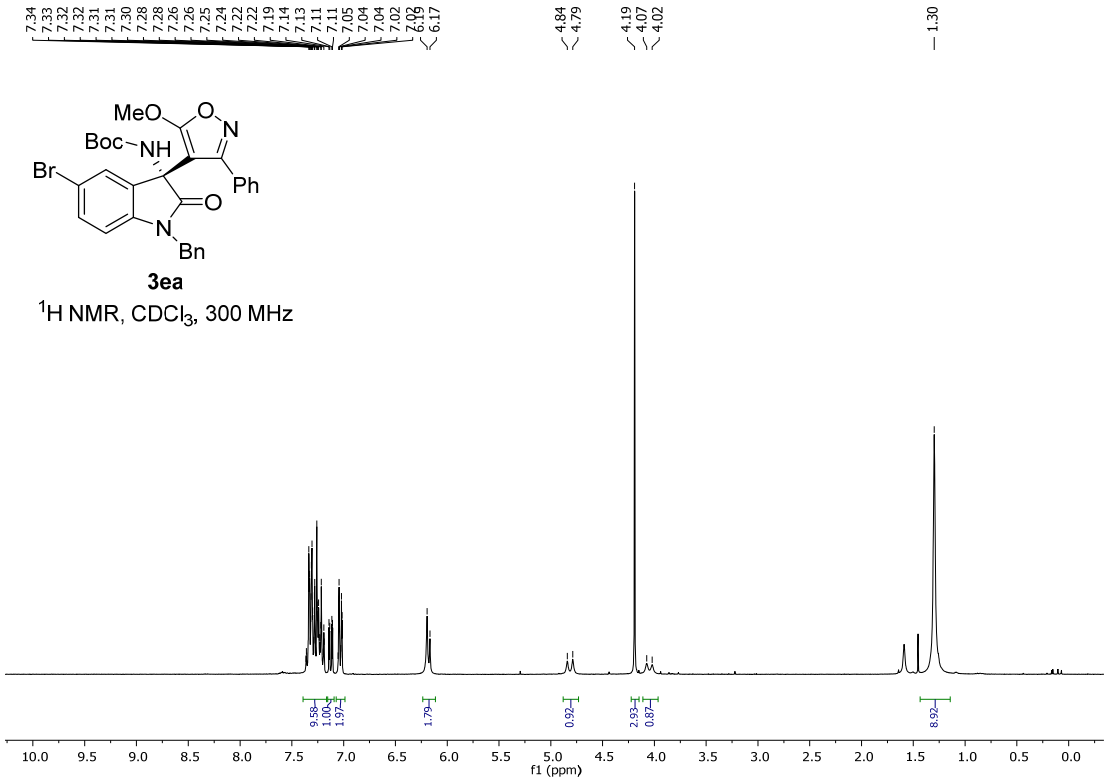
3da

^{1}H NMR, $CDCl_3$, 300 MHz



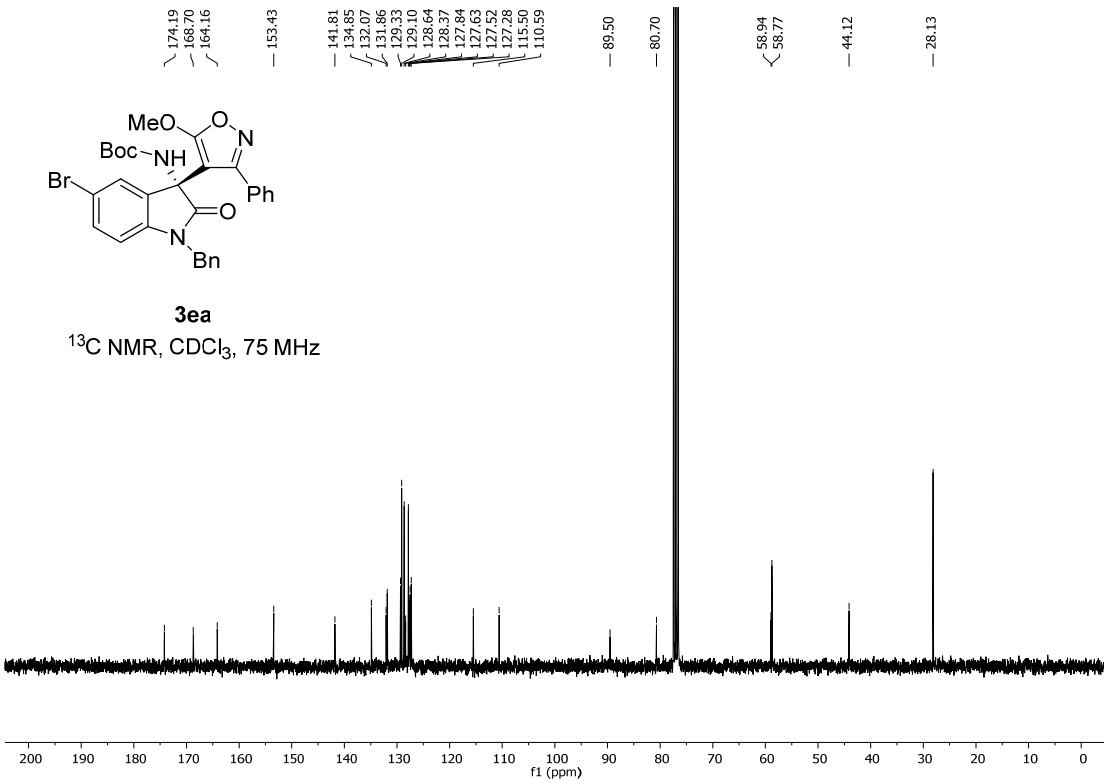
3da

^{13}C NMR, $CDCl_3$, 75 MHz



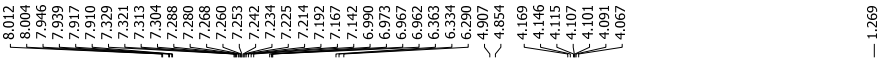
3ea

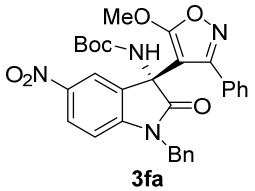
^{1}H NMR, $CDCl_3$, 300 MHz



3ea

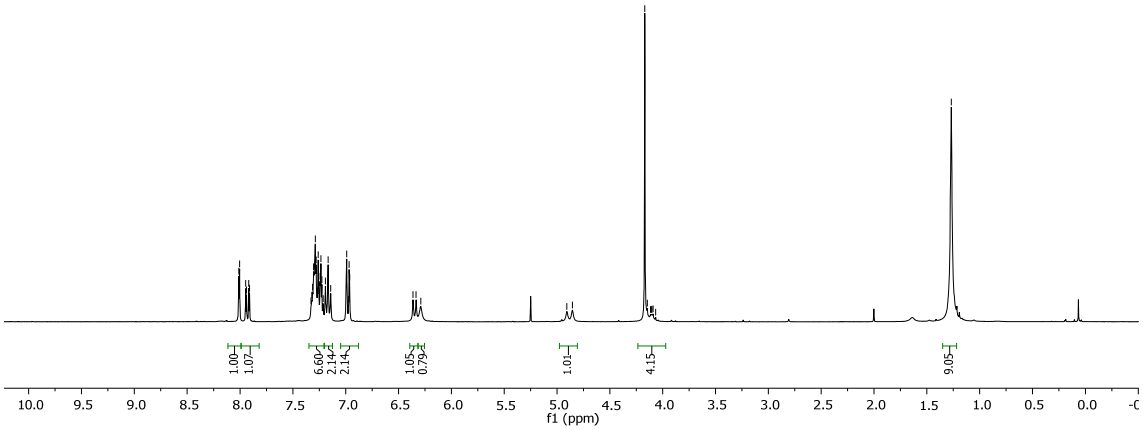
^{13}C NMR, $CDCl_3$, 75 MHz

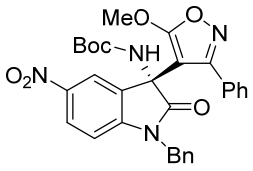




3fa

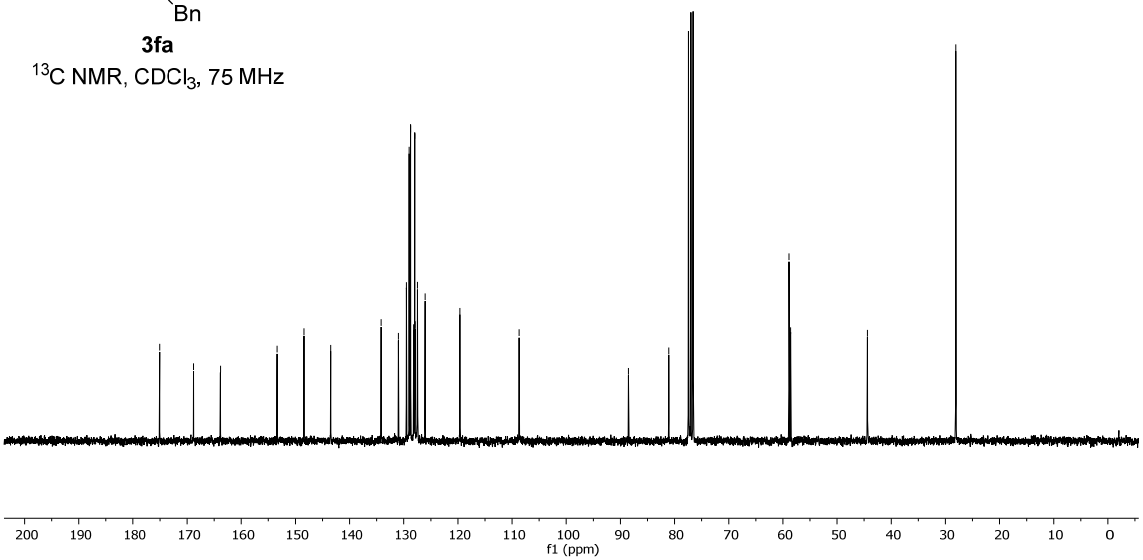
^{1}H NMR, $CDCl_3$, 300 MHz

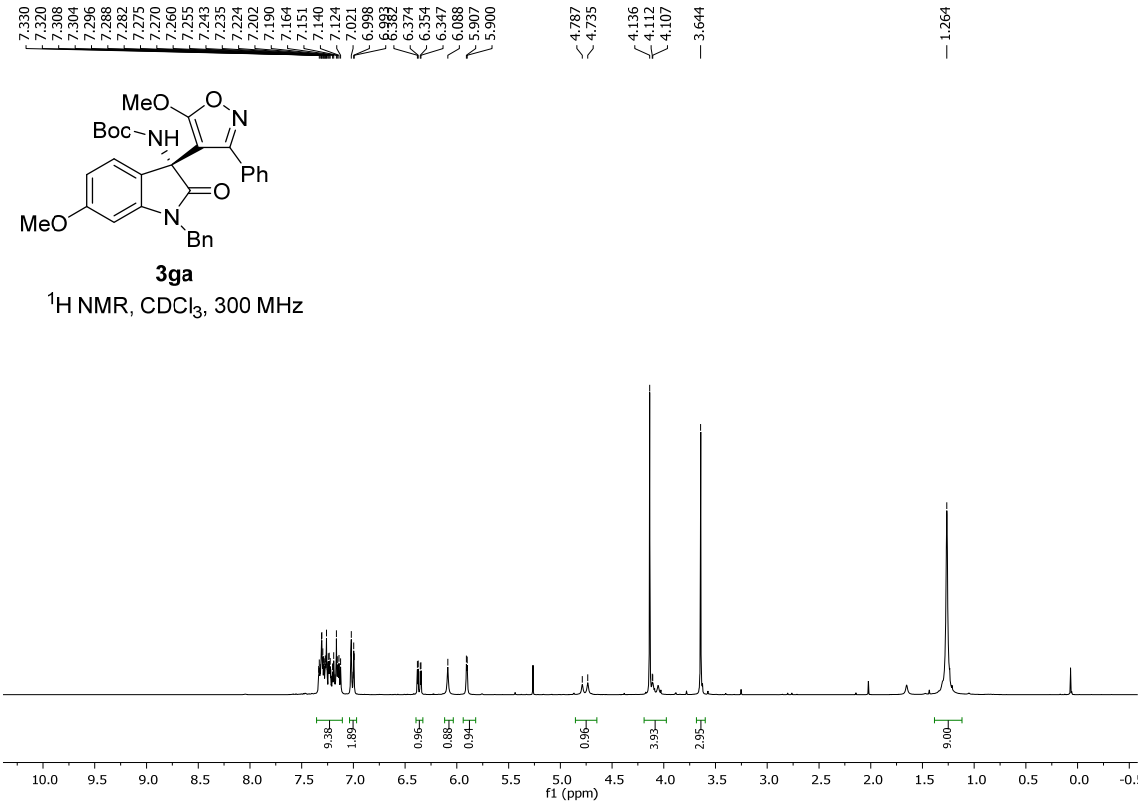




3fa

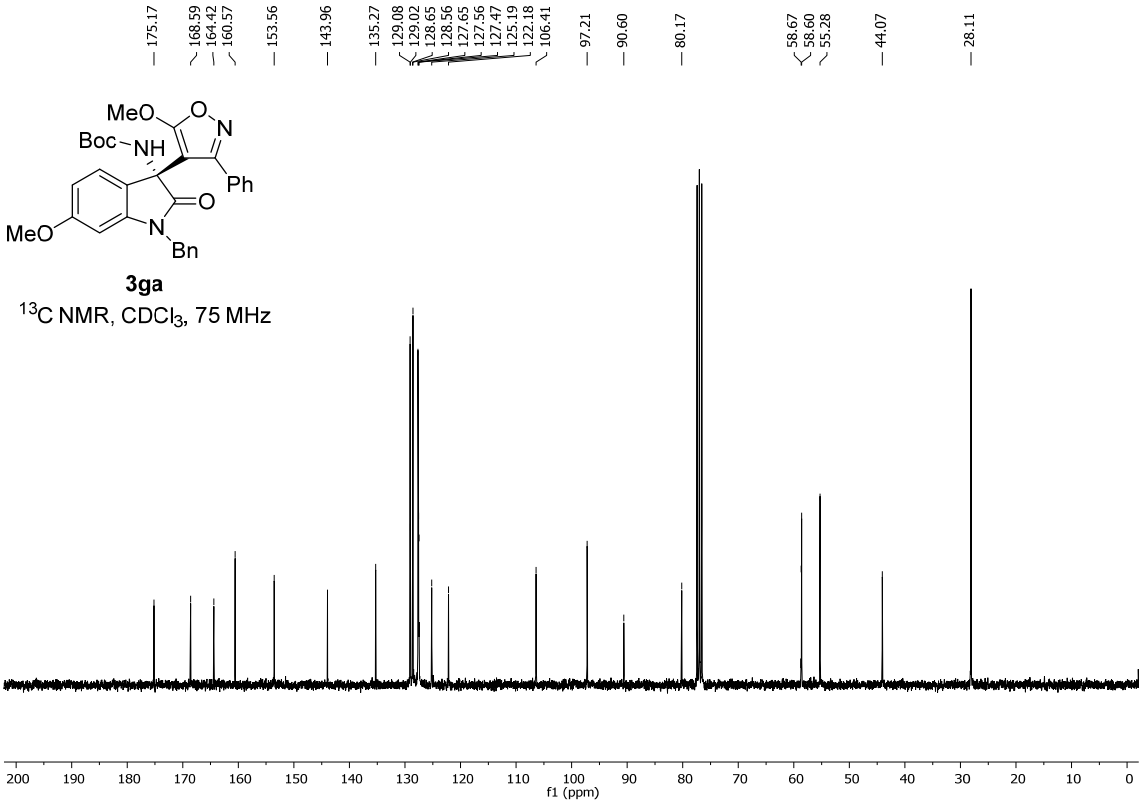
^{13}C NMR, $CDCl_3$, 75 MHz





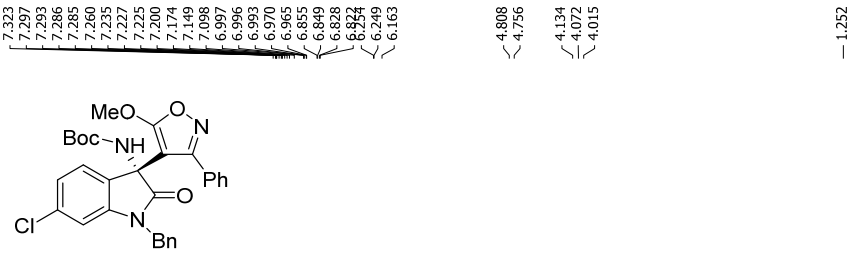
3ga

^{1}H NMR, $CDCl_3$, 300 MHz



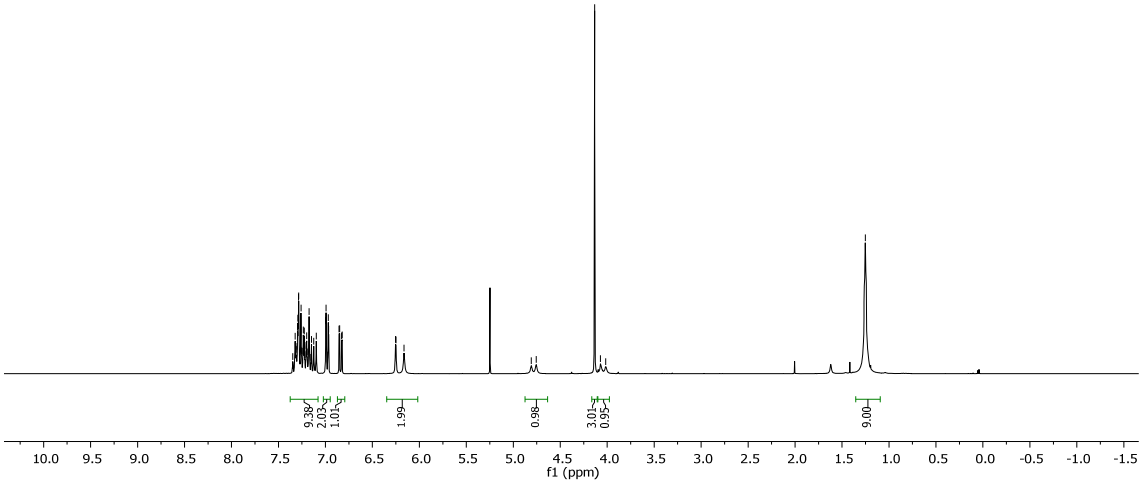
3ga

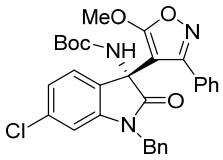
^{13}C NMR, $CDCl_3$, 75 MHz



3ha

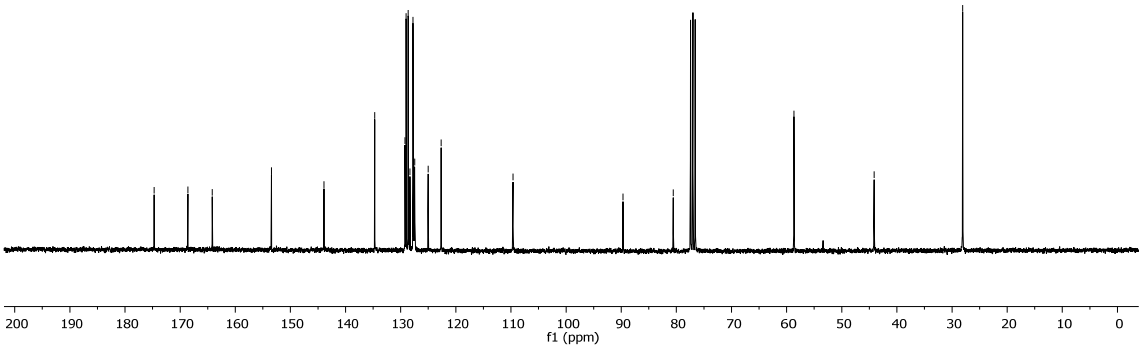
^{1}H NMR, $CDCl_3$, 300 MHz

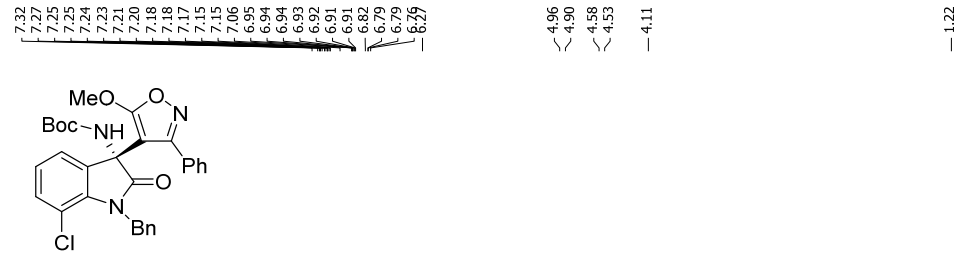




3ha

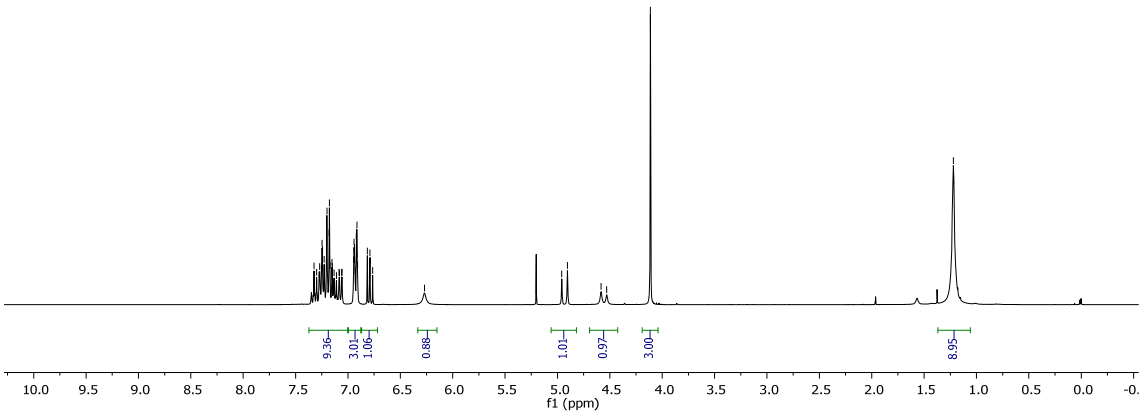
^{13}C NMR, $CDCl_3$, 75 MHz

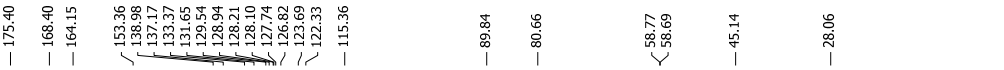


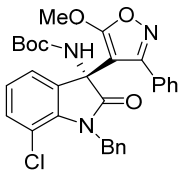


3ia

^{1}H NMR, $CDCl_3$, 300 MHz

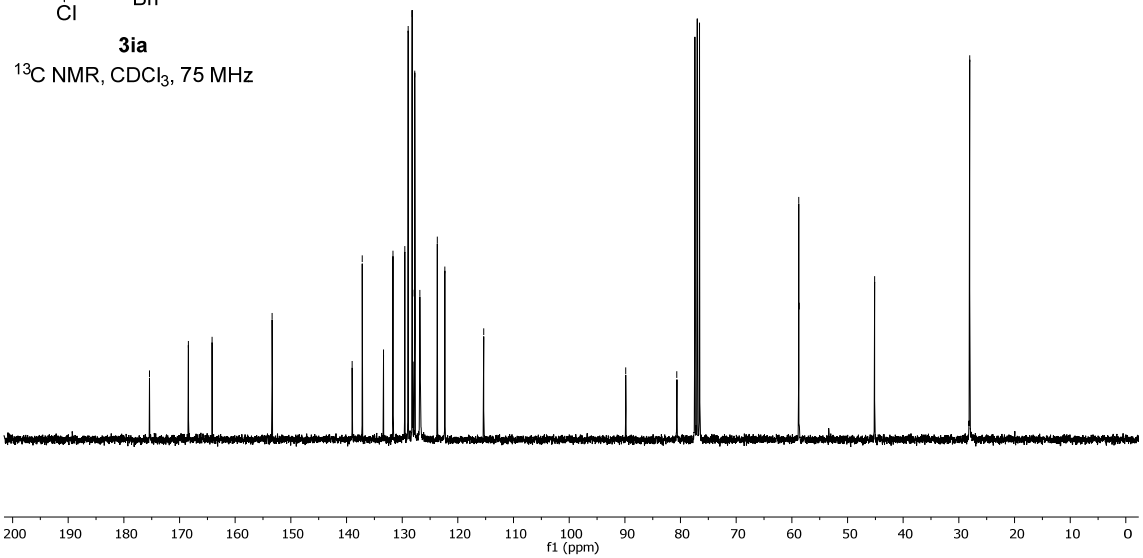


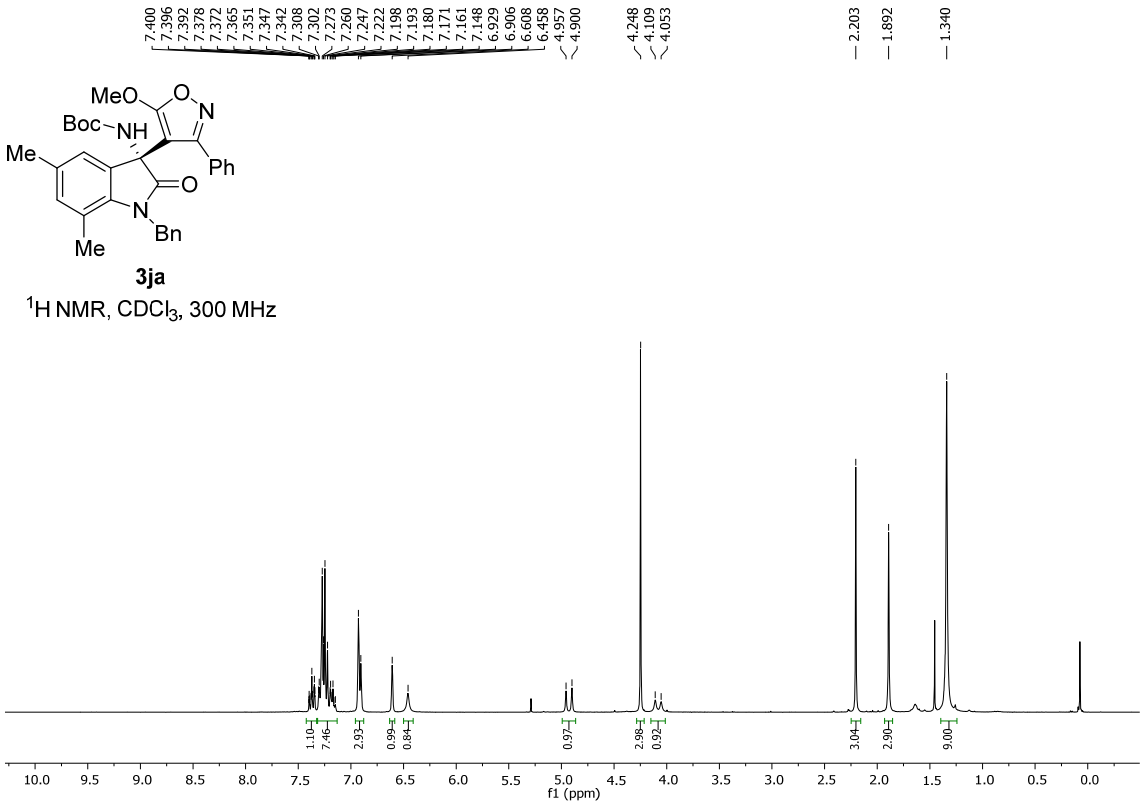




3ia

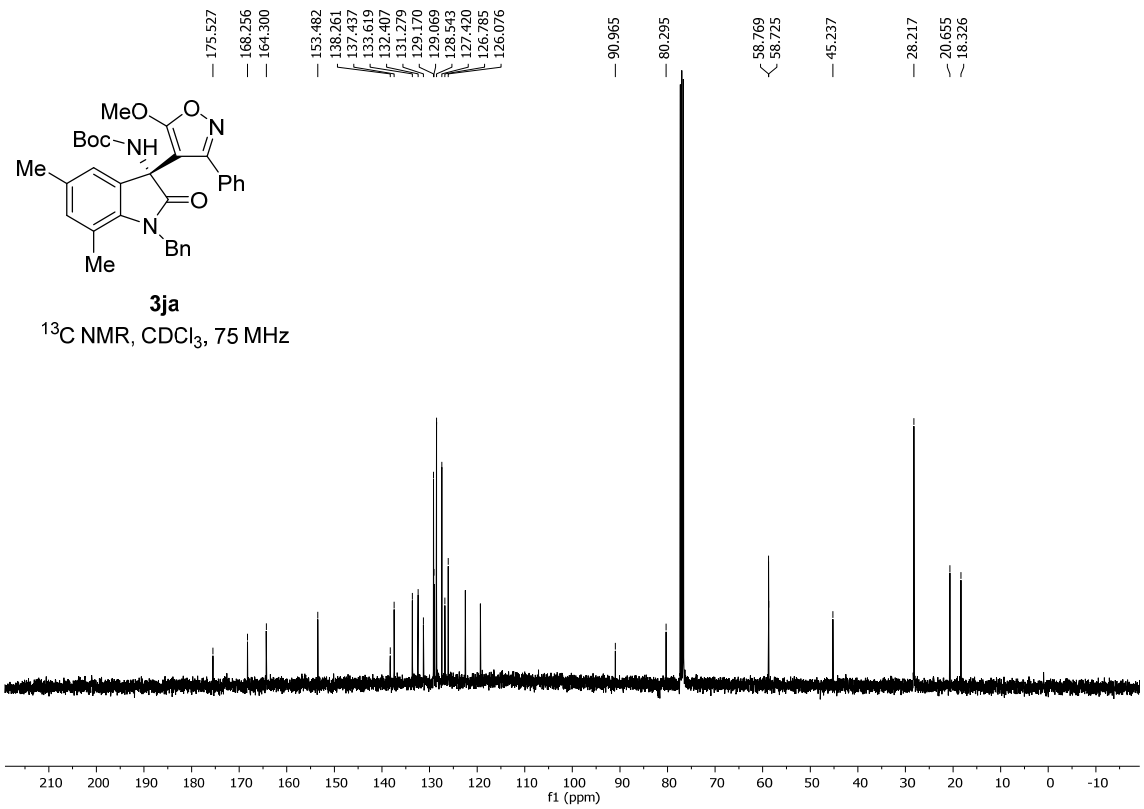
^{13}C NMR, $CDCl_3$, 75 MHz





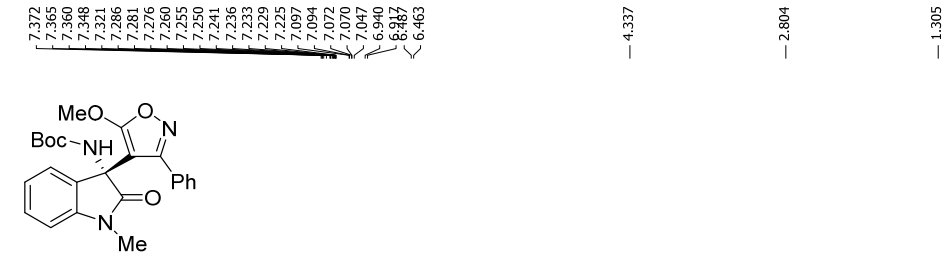
3ja

^{1}H NMR, $CDCl_3$, 300 MHz



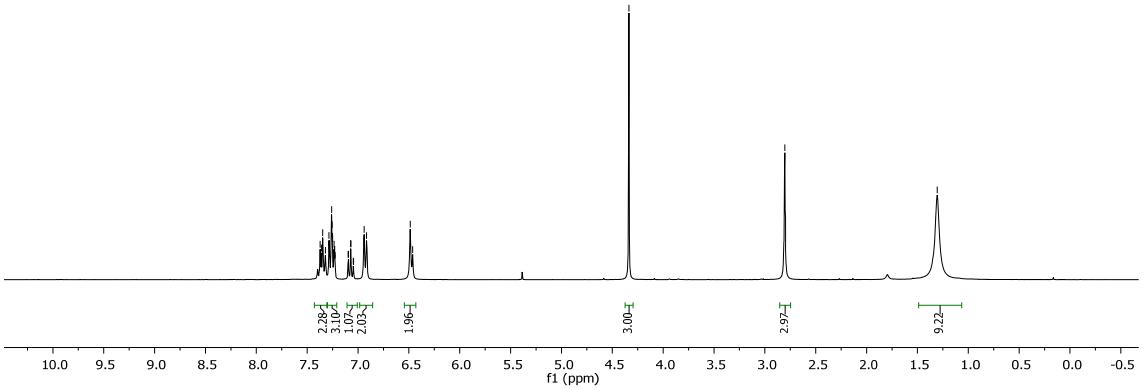
3ja

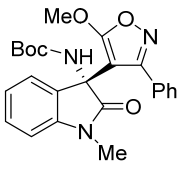
^{13}C NMR, $CDCl_3$, 75 MHz



3ka

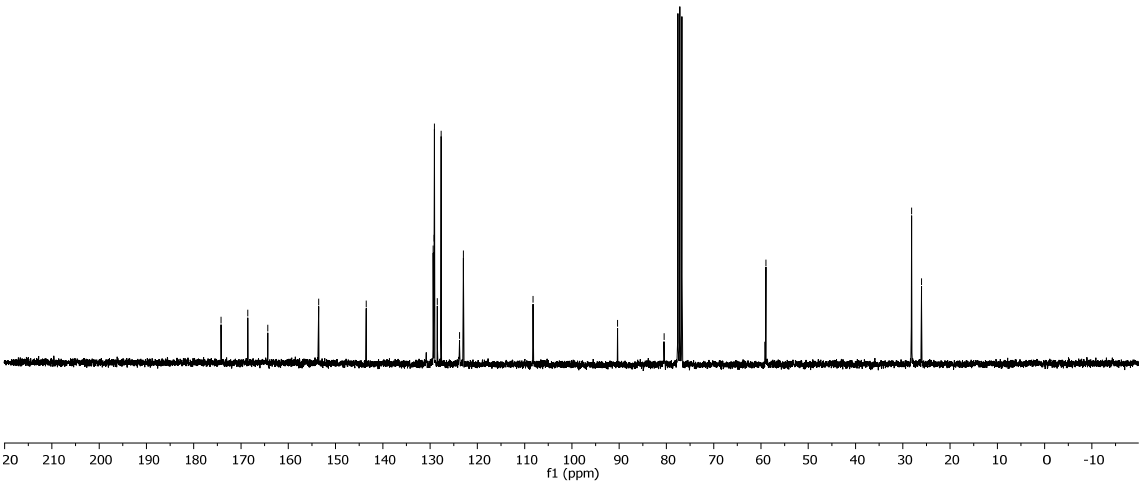
^{1}H NMR, $CDCl_3$, 300 MHz

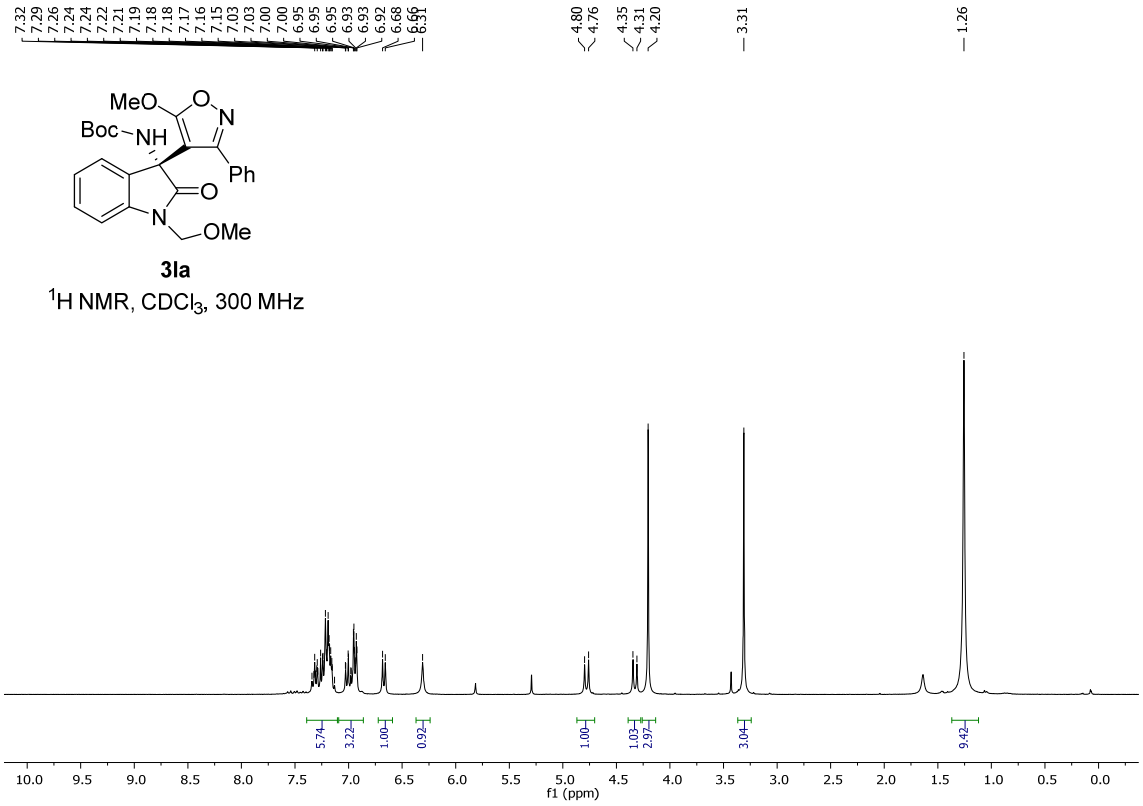




3ka

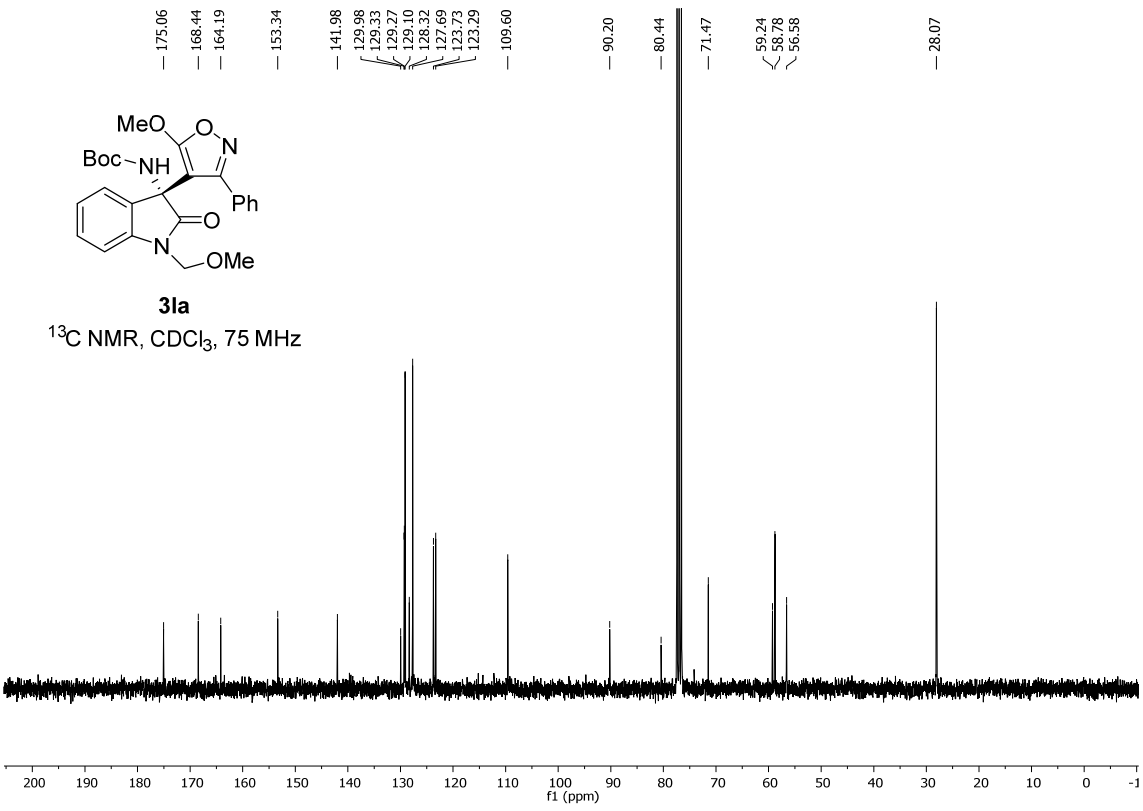
^{13}C NMR, $CDCl_3$, 75 MHz





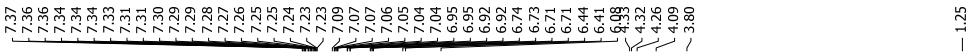
3la

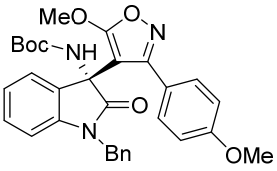
^{1}H NMR, $CDCl_3$, 300 MHz



3la

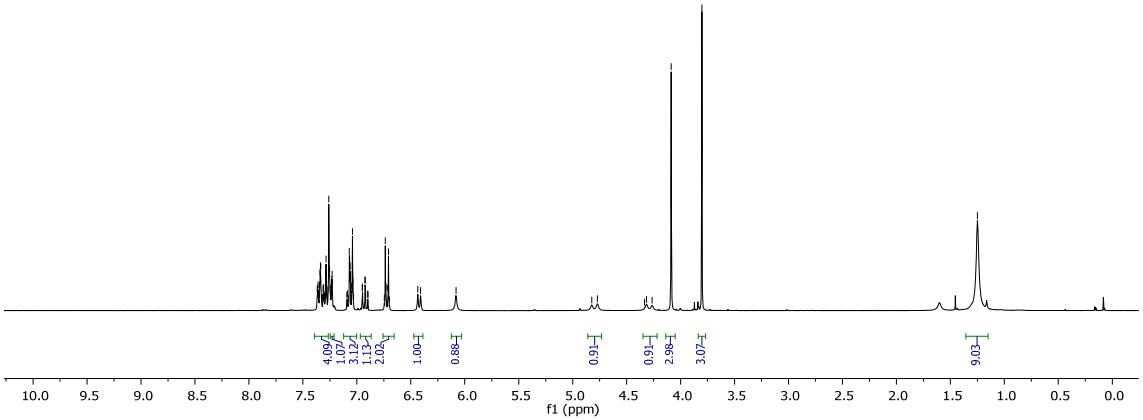
^{13}C NMR, $CDCl_3$, 75 MHz

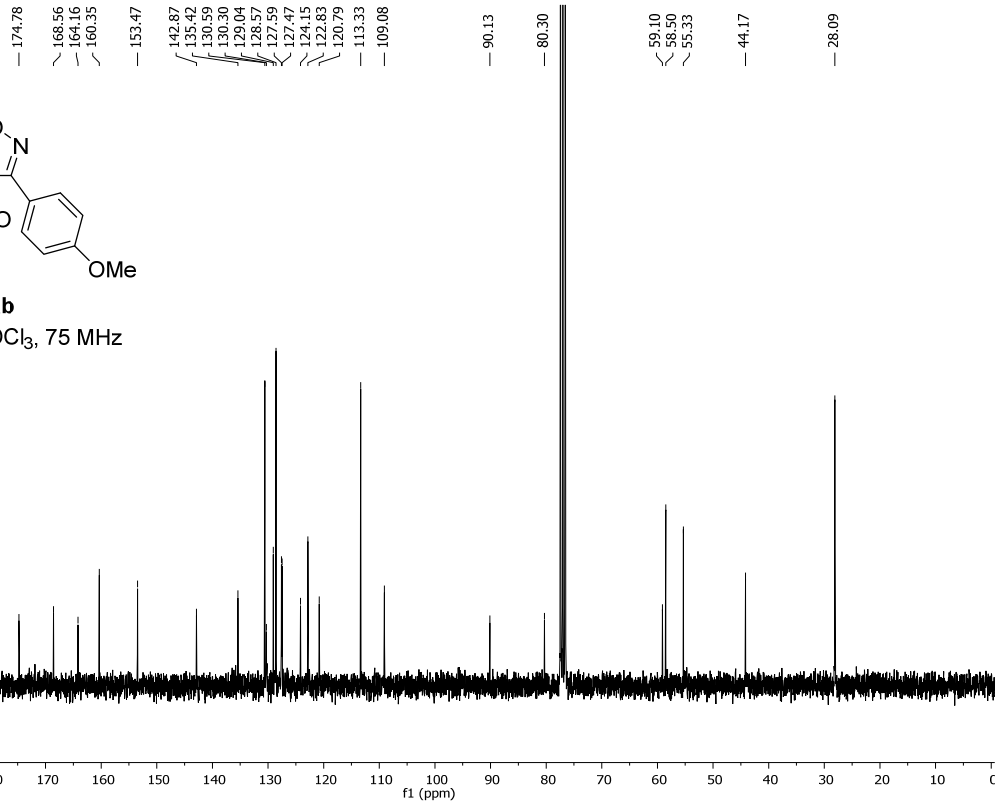


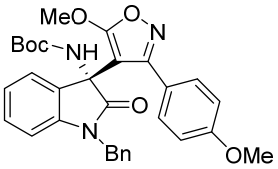


3ab

^{1}H NMR, $CDCl_3$, 300 MHz

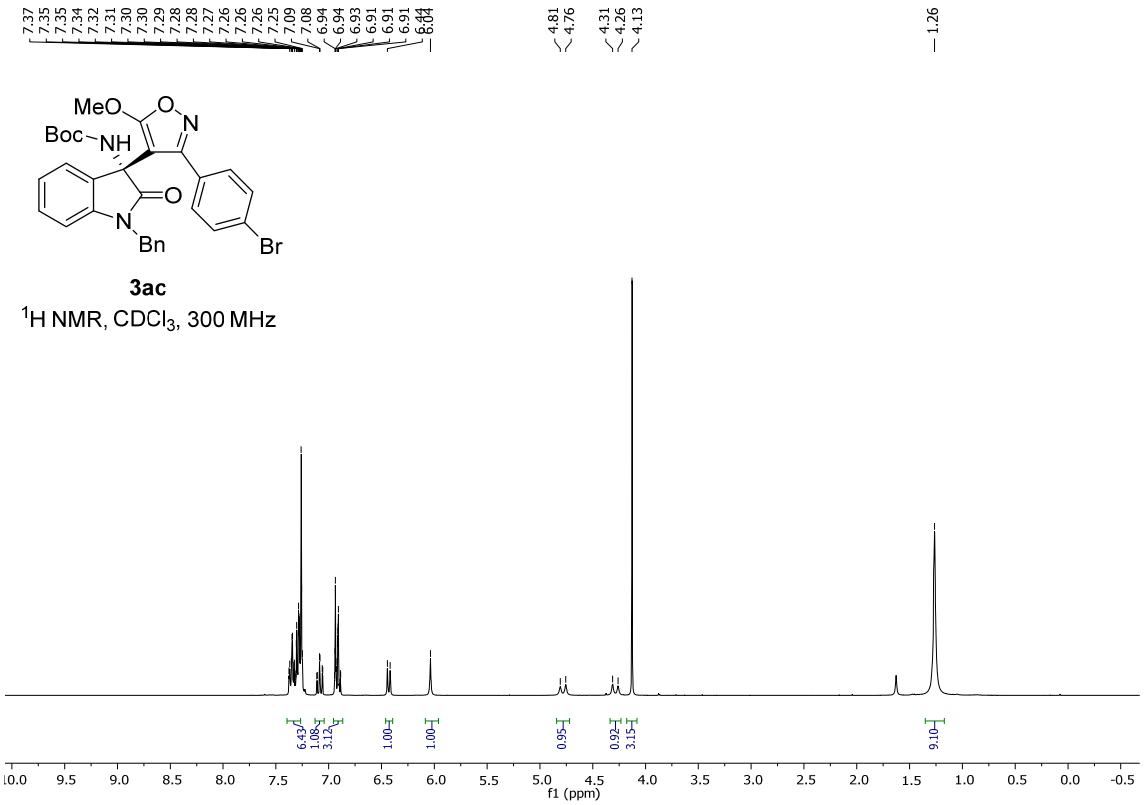






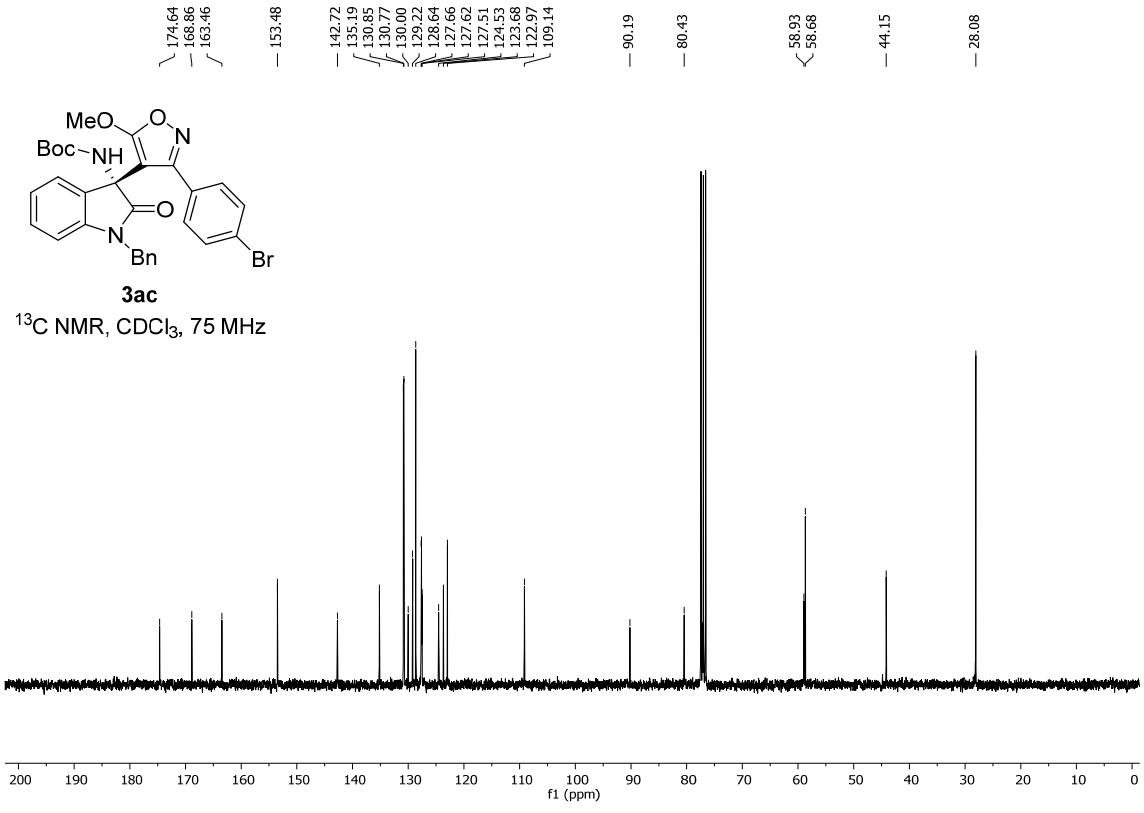
3ab

^{13}C NMR, $CDCl_3$, 75 MHz



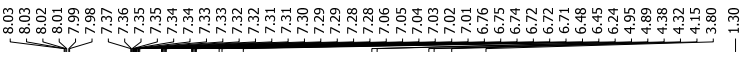
3ac

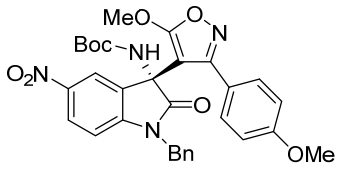
^{1}H NMR, $CDCl_3$, 300 MHz



3ac

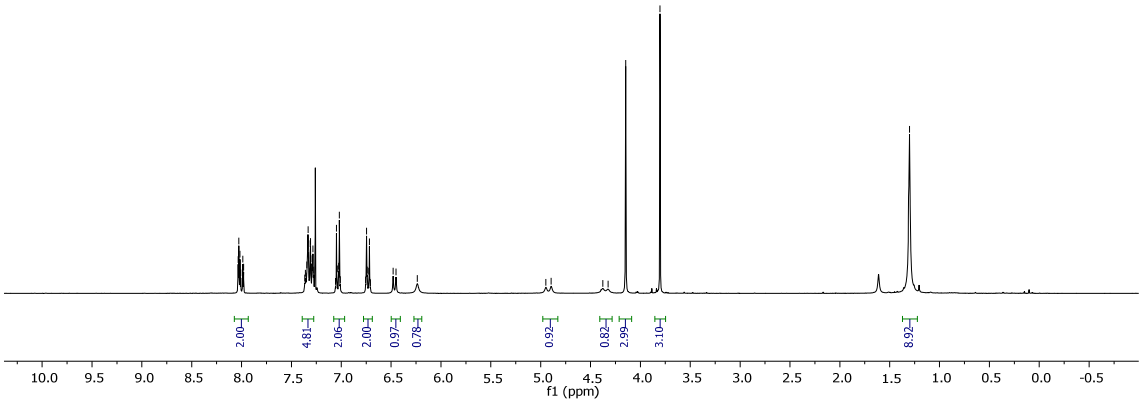
^{13}C NMR, $CDCl_3$, 75 MHz

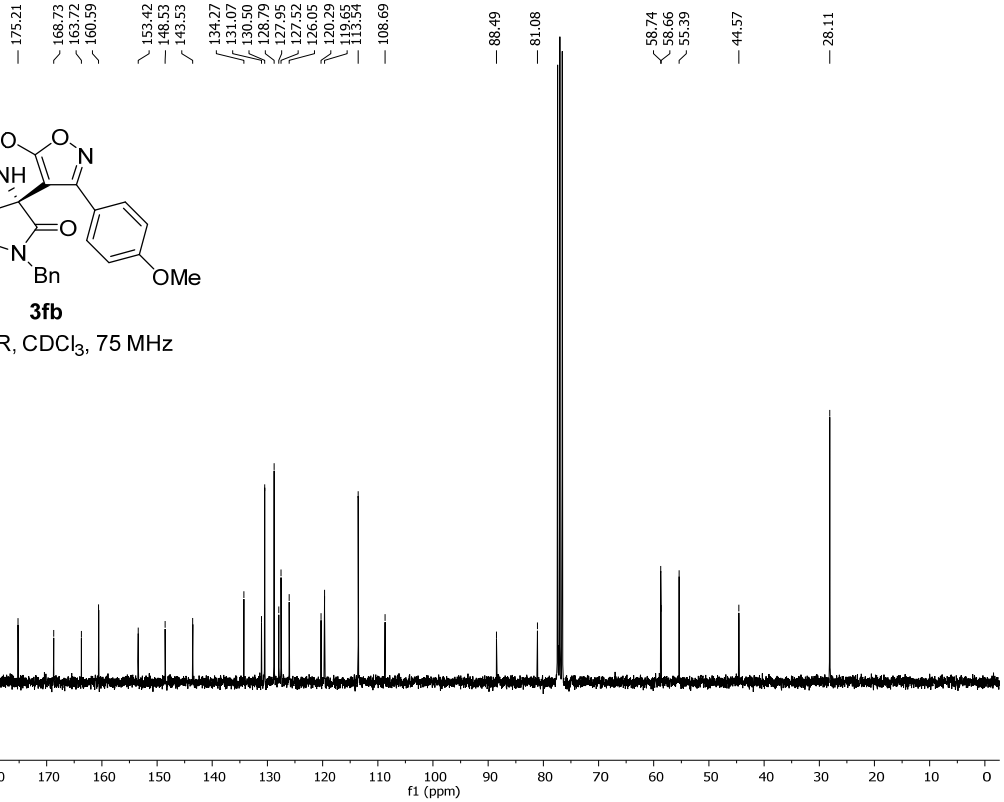




3fb

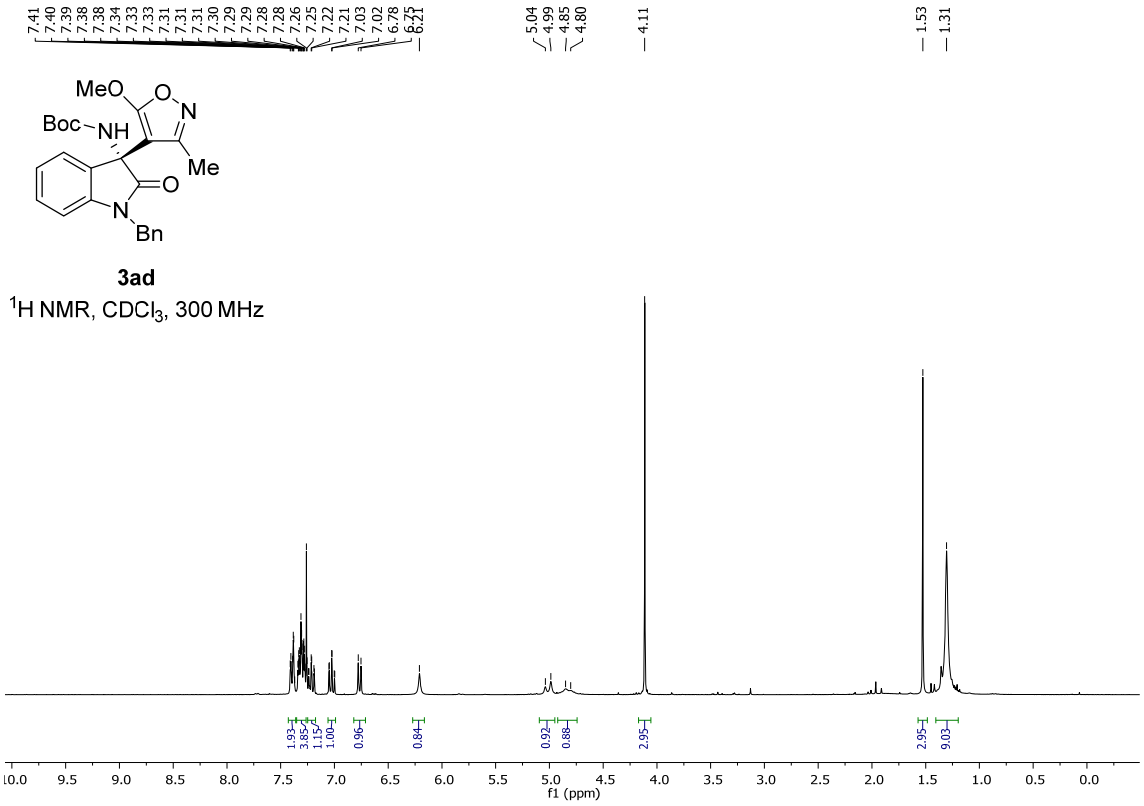
^{1}H NMR, $CDCl_3$, 300 MHz





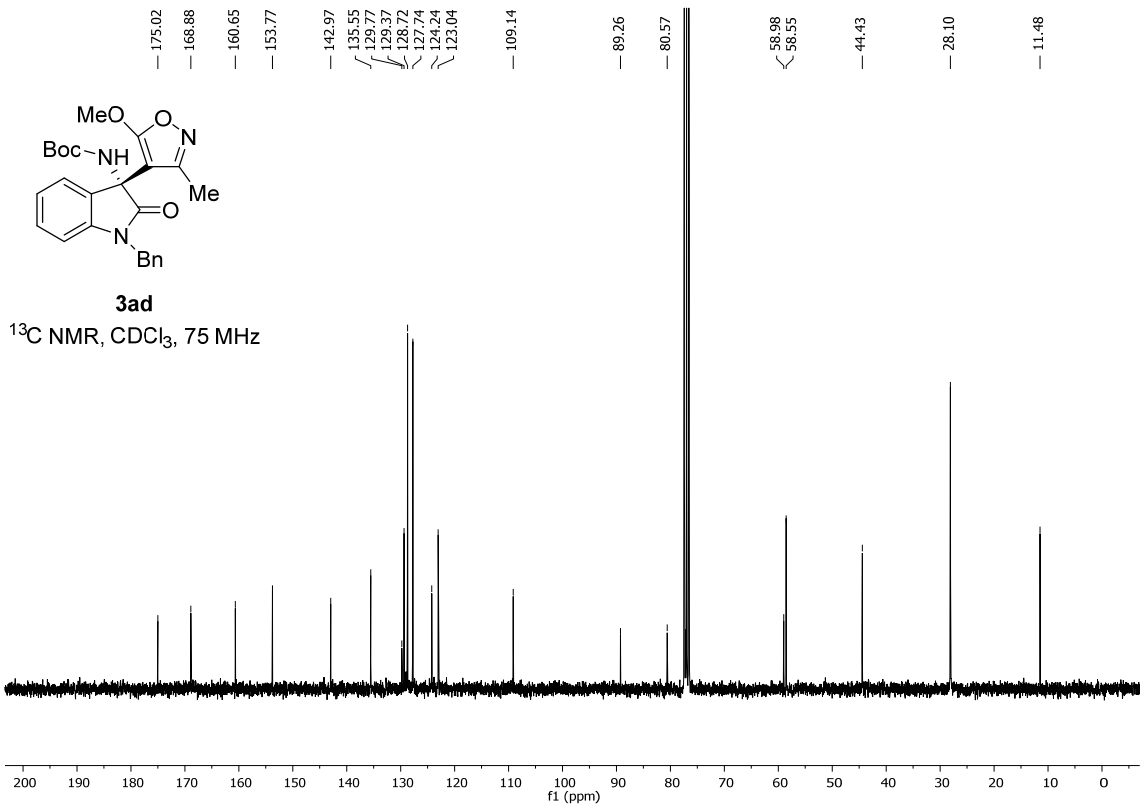
3fb

^{13}C NMR, $CDCl_3$, 75 MHz



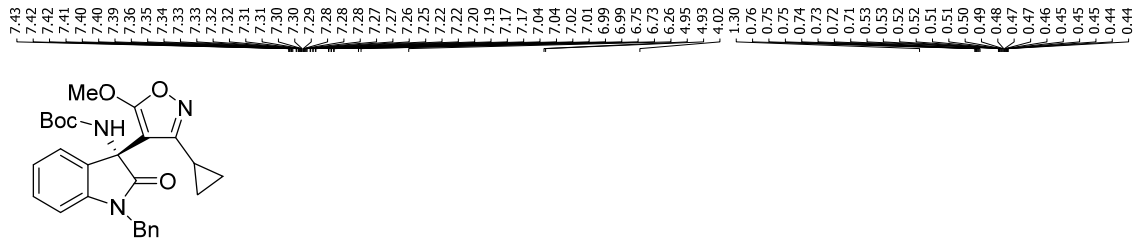
3ad

^{1}H NMR, $CDCl_3$, 300 MHz



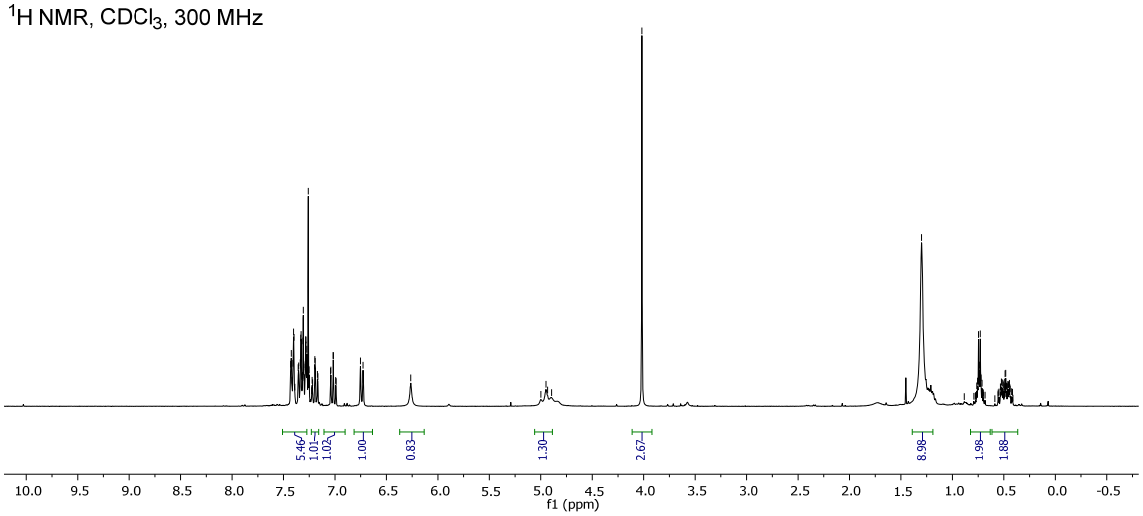
3ad

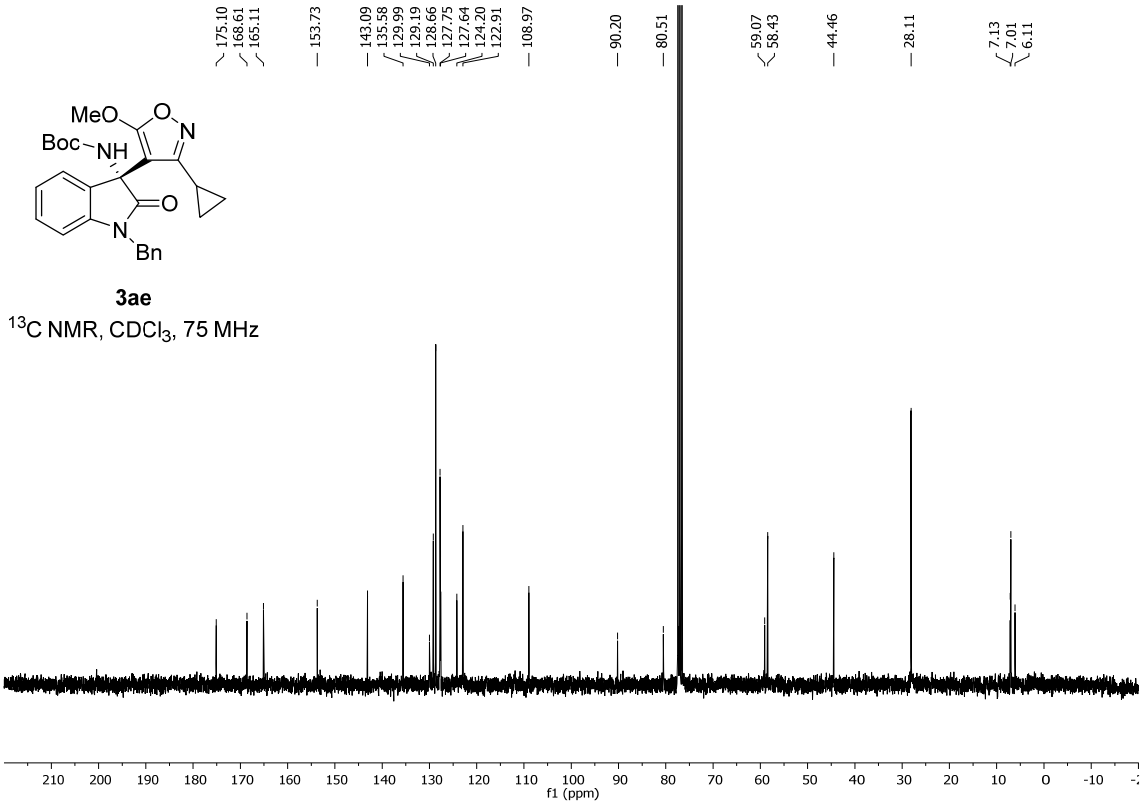
^{13}C NMR, $CDCl_3$, 75 MHz



3ae

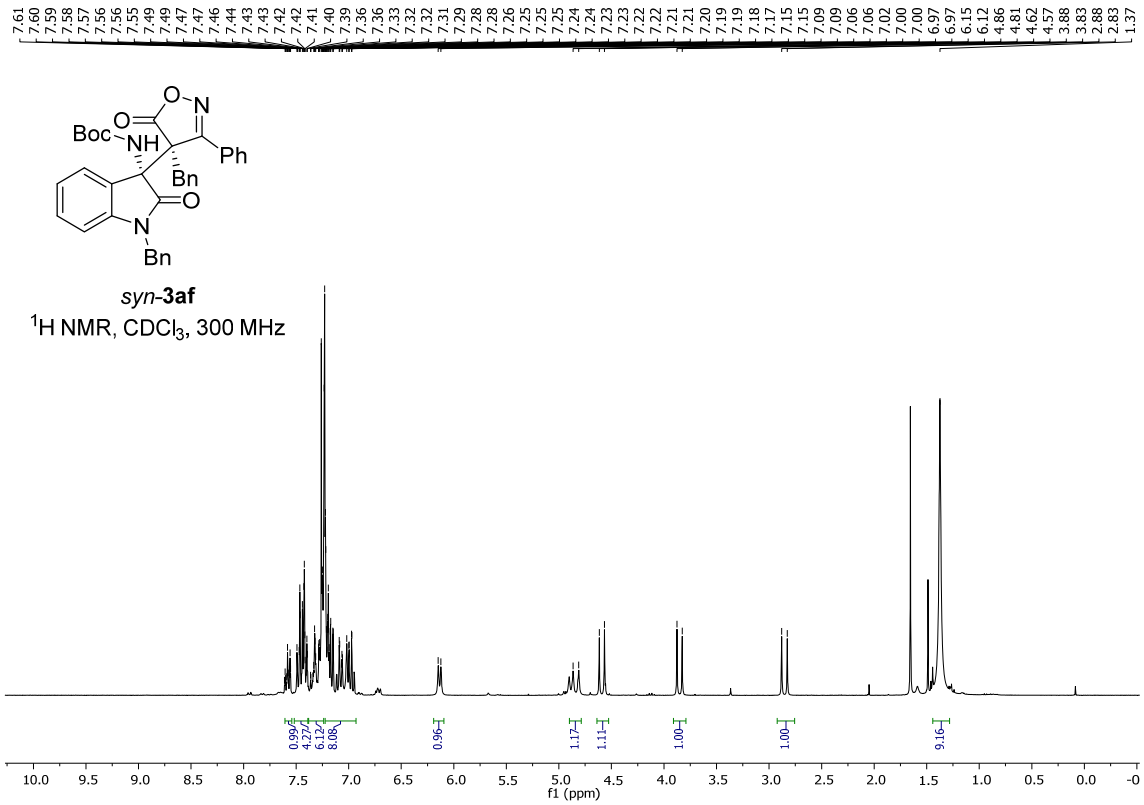
^{1}H NMR, $CDCl_3$, 300 MHz

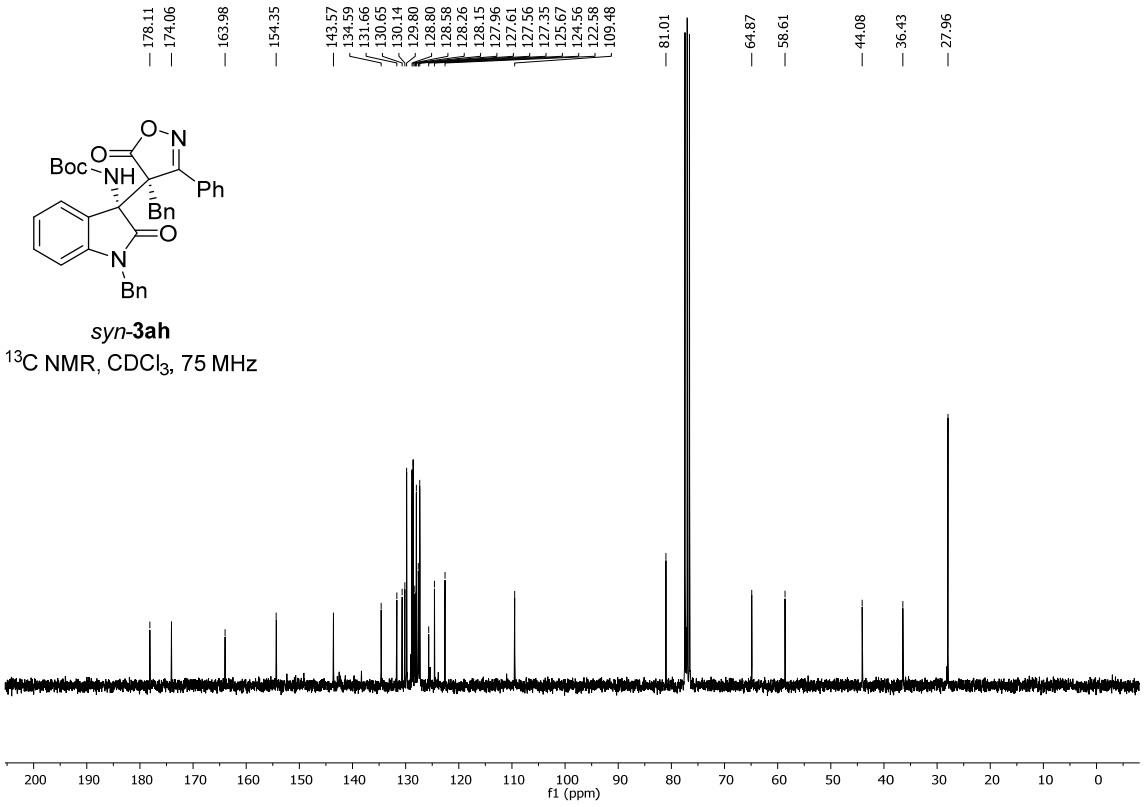


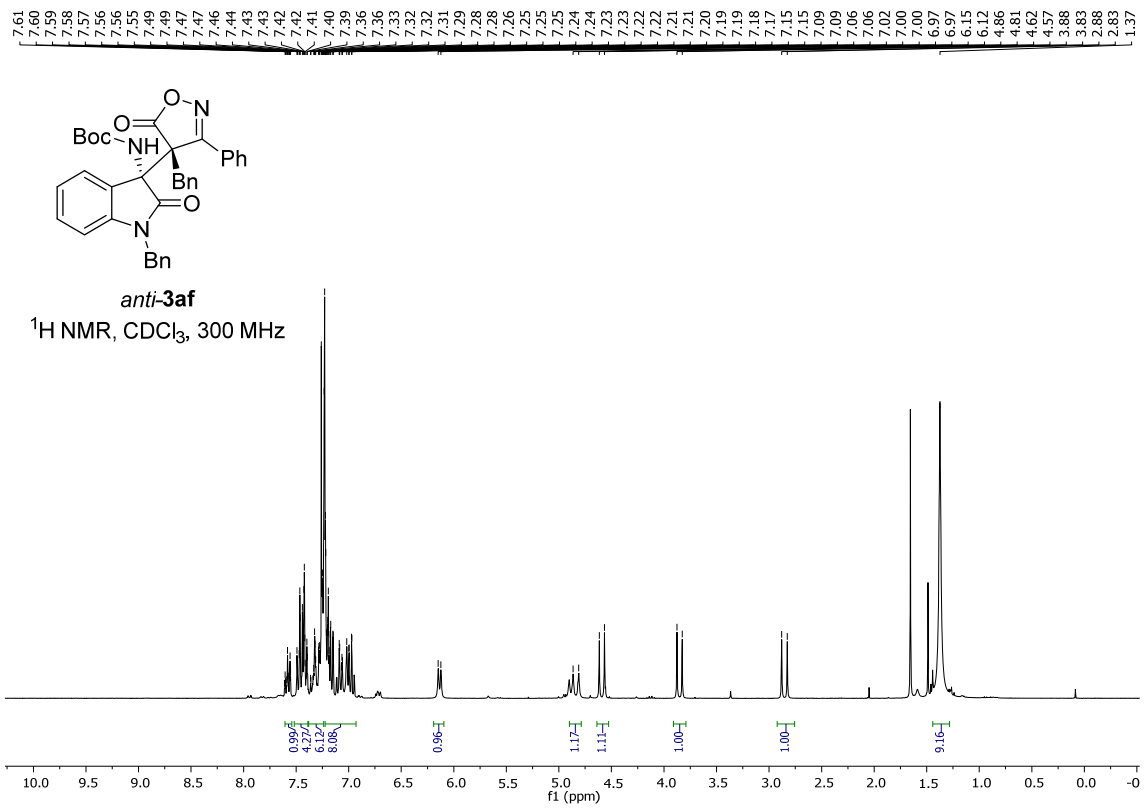


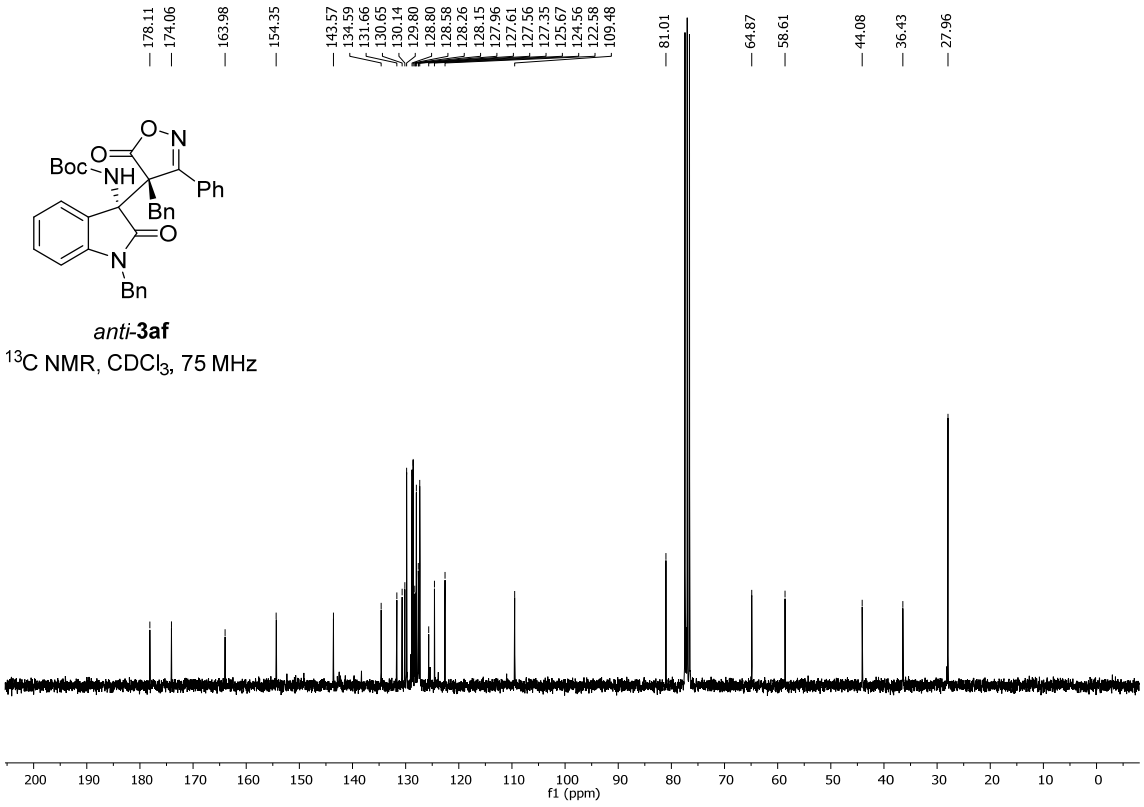
3ae

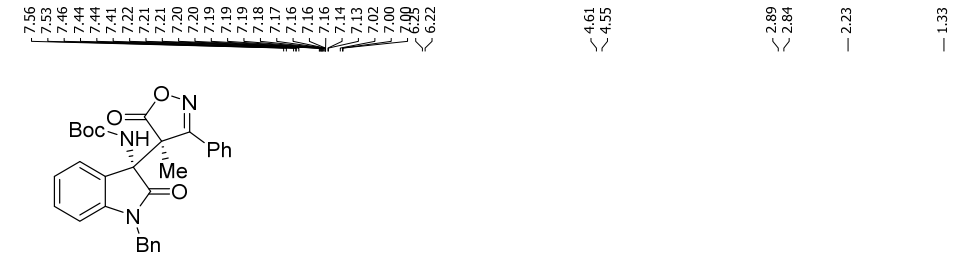
^{13}C NMR, $CDCl_3$, 75 MHz


Boc
NH
O
N
Ph
Bn
O
N
Bn
syn-3af
1H NMR, CDCl3, 300 MHz
f1 (ppm)


Boc
NH
O
N
Ph
Bn
O
N
Bn
syn-3ah
13C NMR, CDCl3, 75 MHz
f1 (ppm)

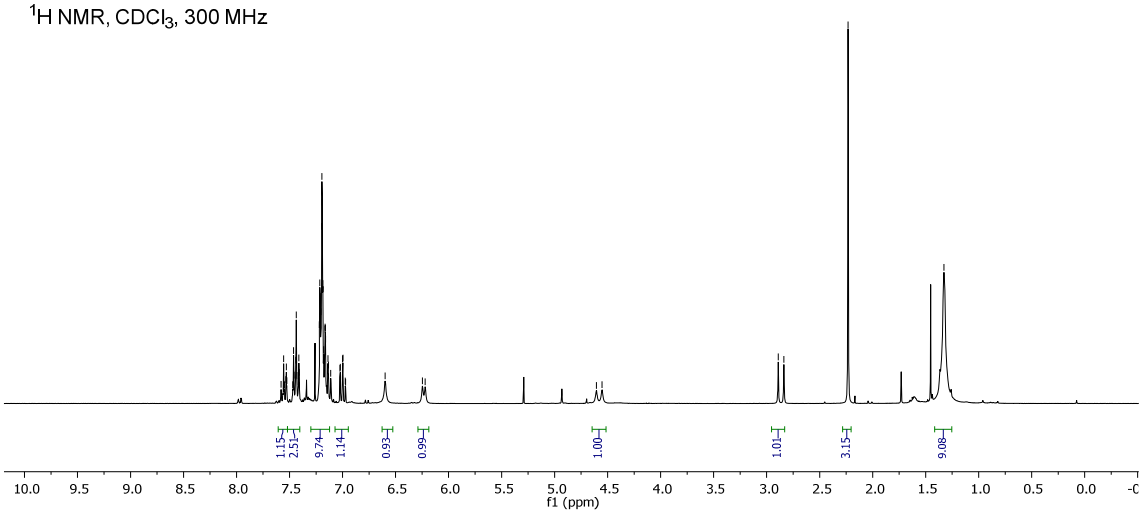

7.61 7.60 7.59 7.58 7.57 7.56 7.56 7.55 7.49 7.49 7.47 7.47 7.46 7.44 7.43 7.43 7.42 7.42 7.41 7.40 7.39 7.36 7.33 7.32 7.31 7.29 7.28 7.28 7.26 7.25 7.25 7.25 7.24 7.24 7.23 7.23 7.22 7.22 7.21 7.21 7.20 7.19 7.19 7.18 7.17 7.15 7.15 7.09 7.09 7.06 7.06 7.02 7.00 7.00 6.97 6.97 6.15 6.12 4.86 4.81 4.62 4.57 3.88 3.83 2.88 2.83 1.37
Boc
NH
O
O
N
Ph
Bn
O
N
Bn
anti-3af
1H NMR, CDCl3, 300 MHz
0.99 4.27 6.12 8.08 0.96 1.17 1.11 1.00 1.00 9.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

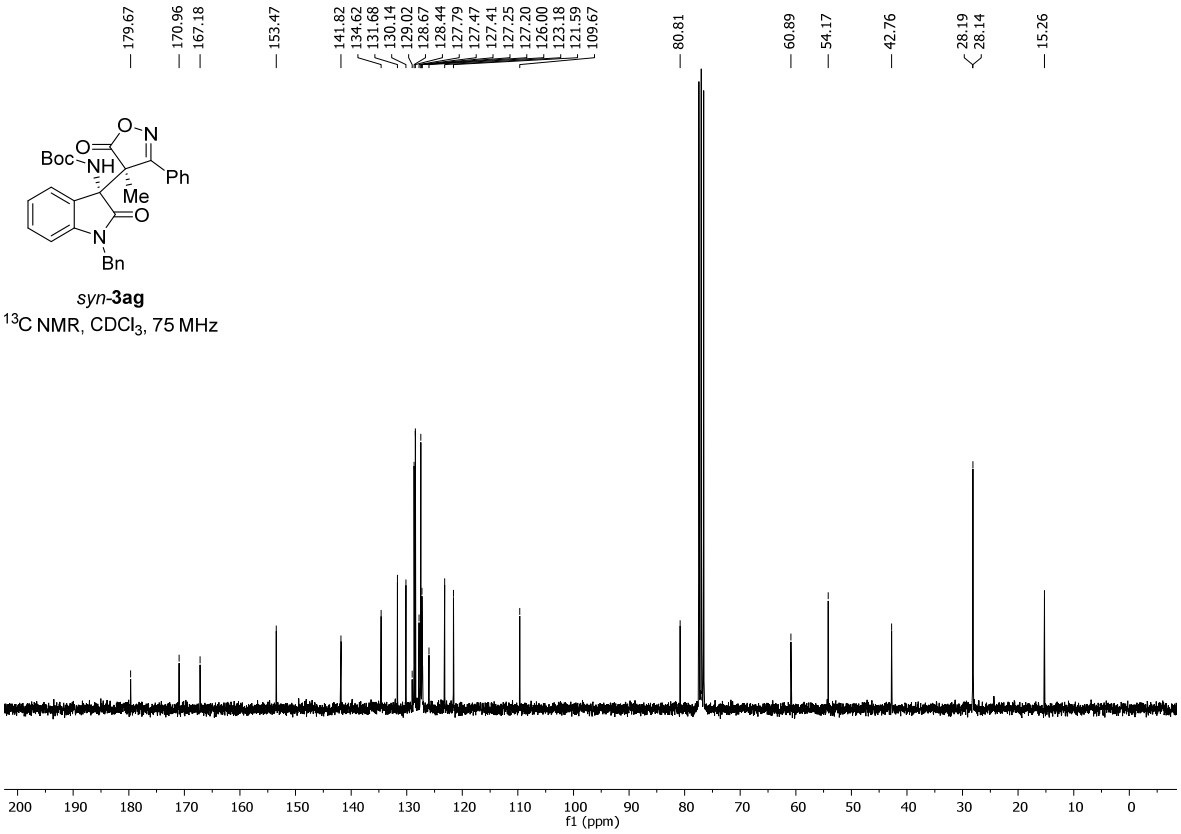

178.11 174.06 163.98 154.35 143.57 134.59 131.66 130.65 130.14 129.80 128.80 128.58 128.26 128.15 127.96 127.61 127.56 127.35 125.67 124.56 122.58 109.48 81.01 64.87 58.61 44.08 36.43 27.96
Boc
NH
O
O
N
Ph
Bn
O
N
Bn
anti-3af
13C NMR, CDCl3, 75 MHz
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



syn-**3ag**

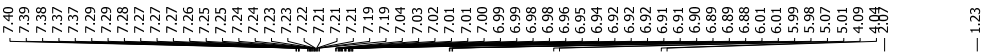
^{1}H NMR, $CDCl_3$, 300 MHz

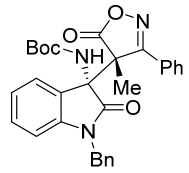




syn-**3ag**

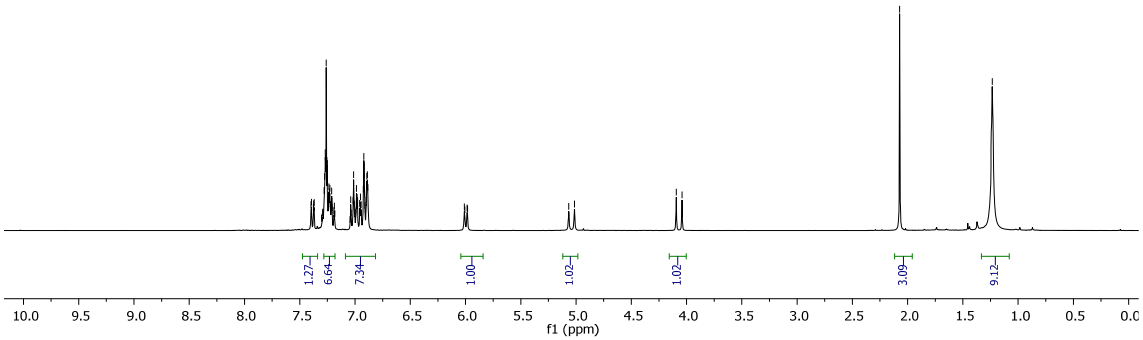
^{13}C NMR, $CDCl_3$, 75 MHz

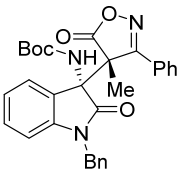




anti-**3ag**

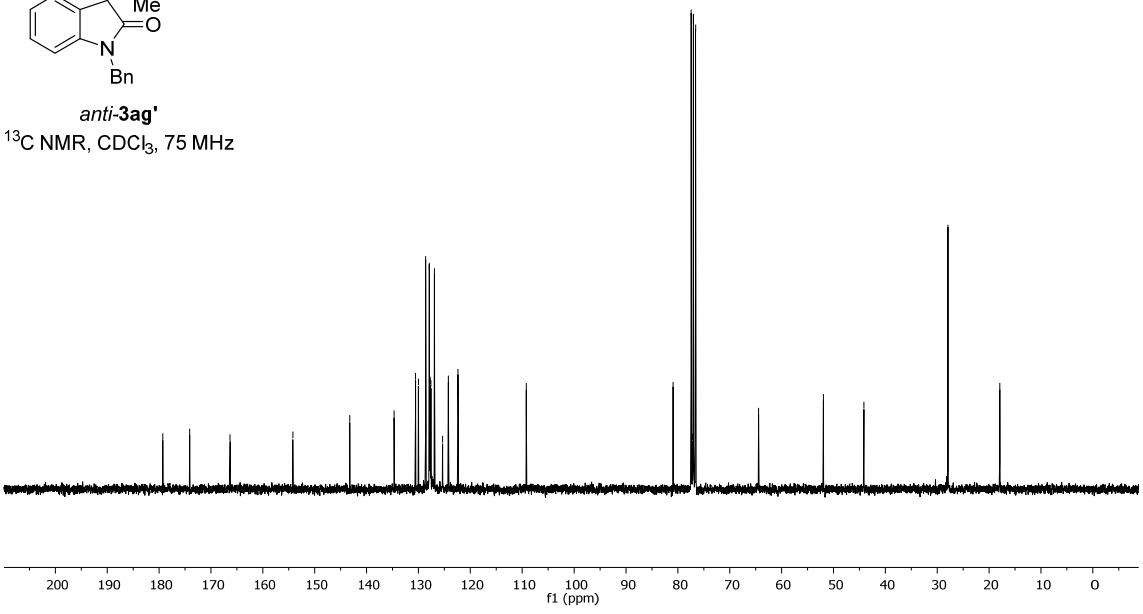
^{1}H NMR, $CDCl_3$, 300 MHz

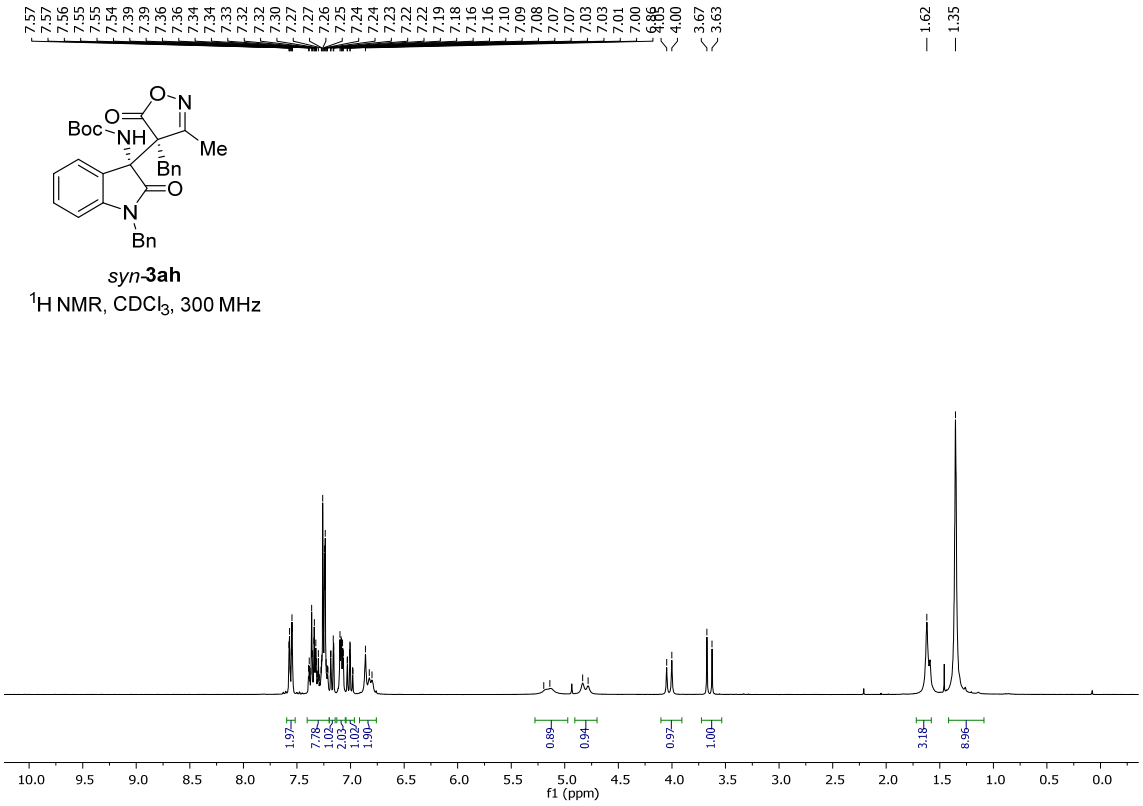




anti-**3ag'**

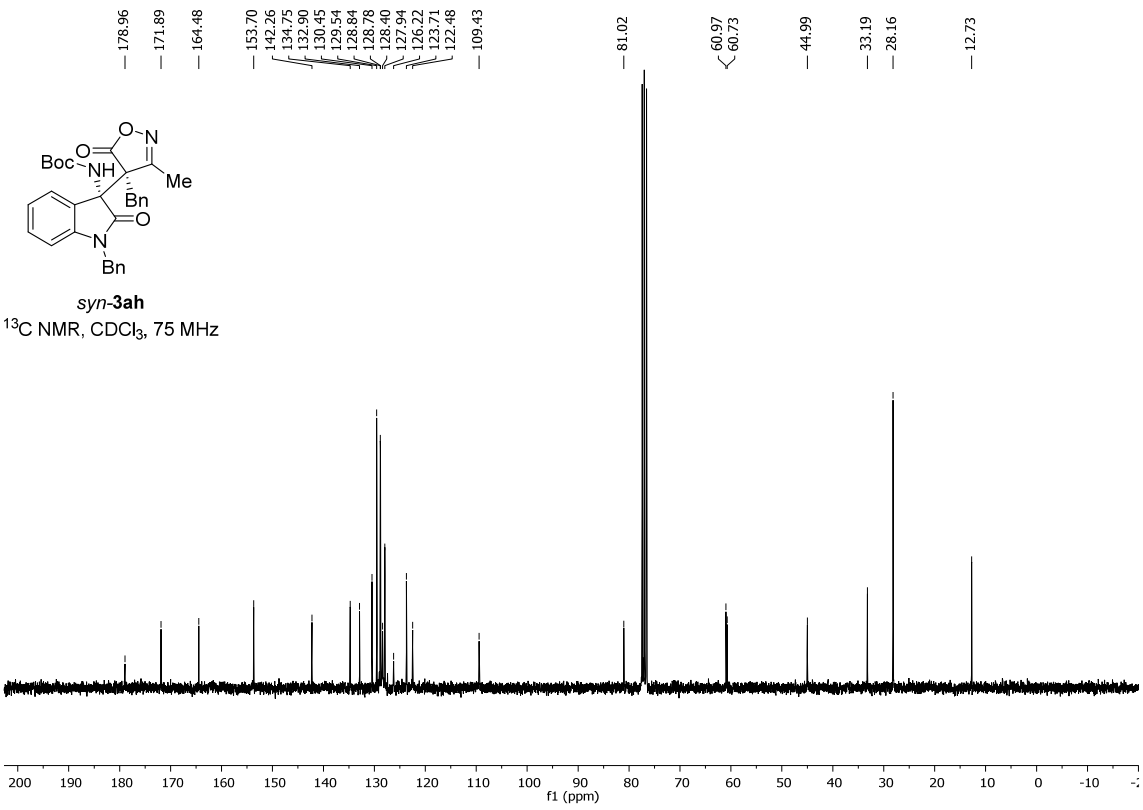
^{13}C NMR, $CDCl_3$, 75 MHz





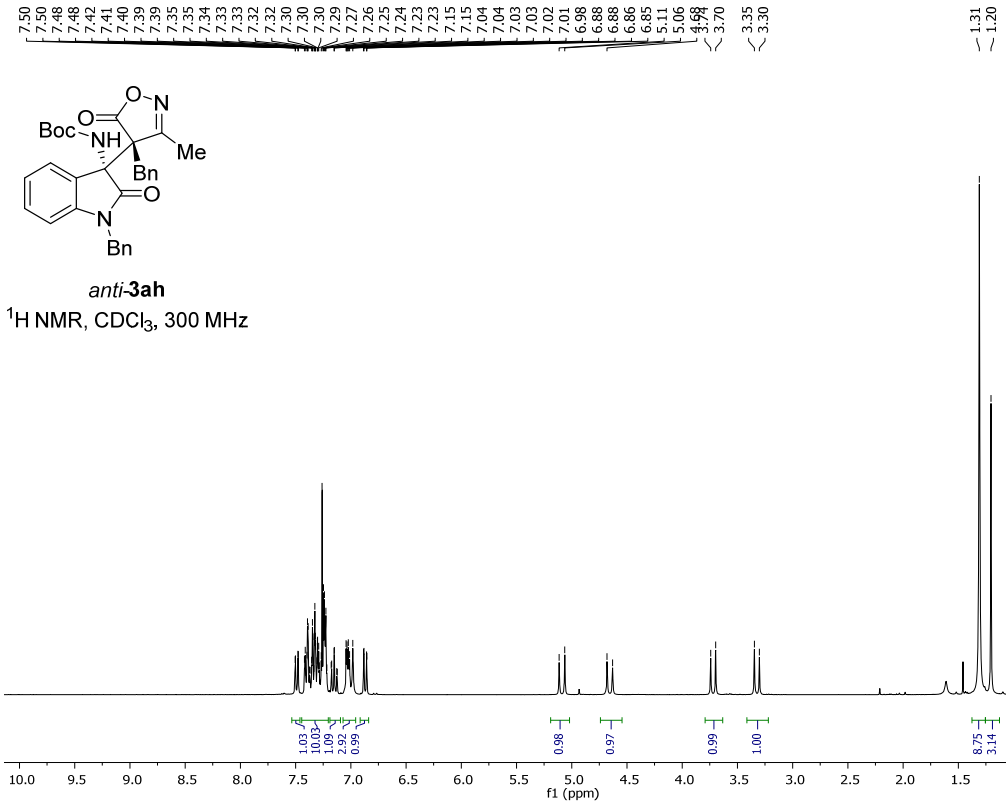
syn-**3ah**

^{1}H NMR, $CDCl_3$, 300 MHz



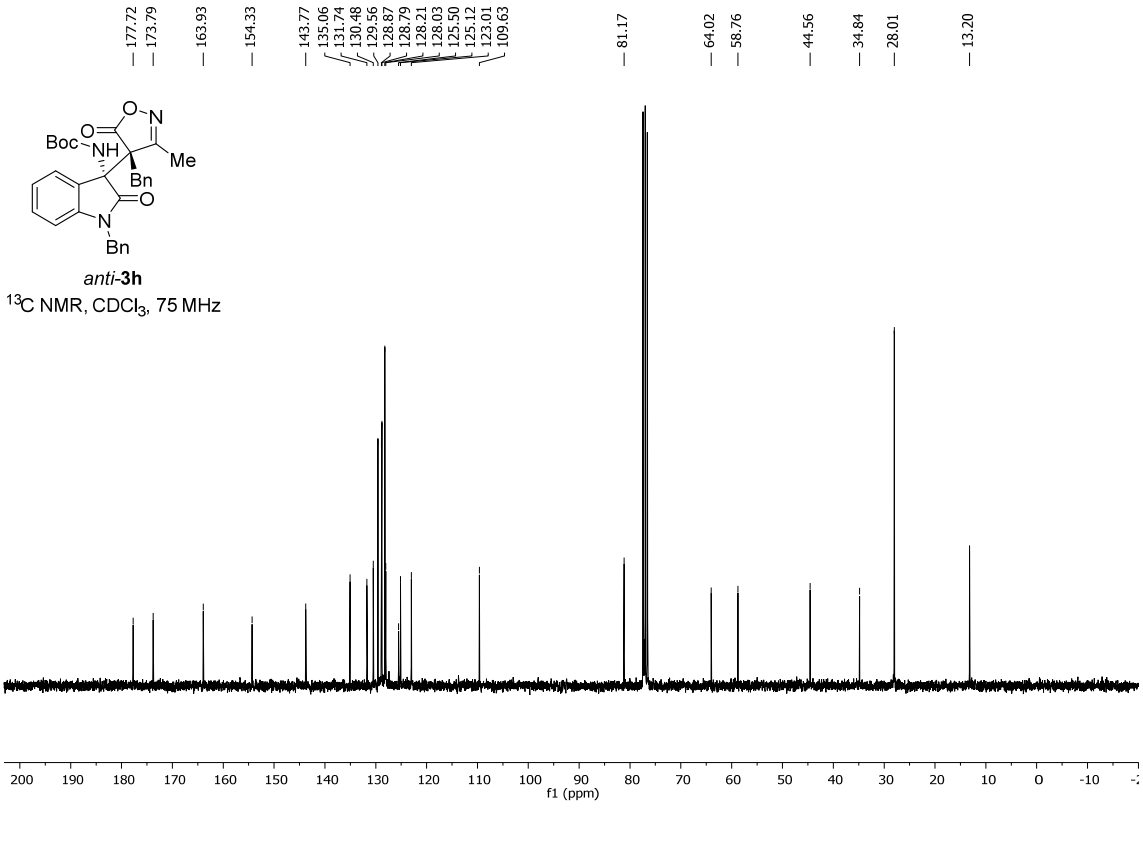
syn-**3ah**

^{13}C NMR, $CDCl_3$, 75 MHz



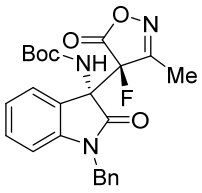
anti-**3ah**

^{1}H NMR, $CDCl_3$, 300 MHz



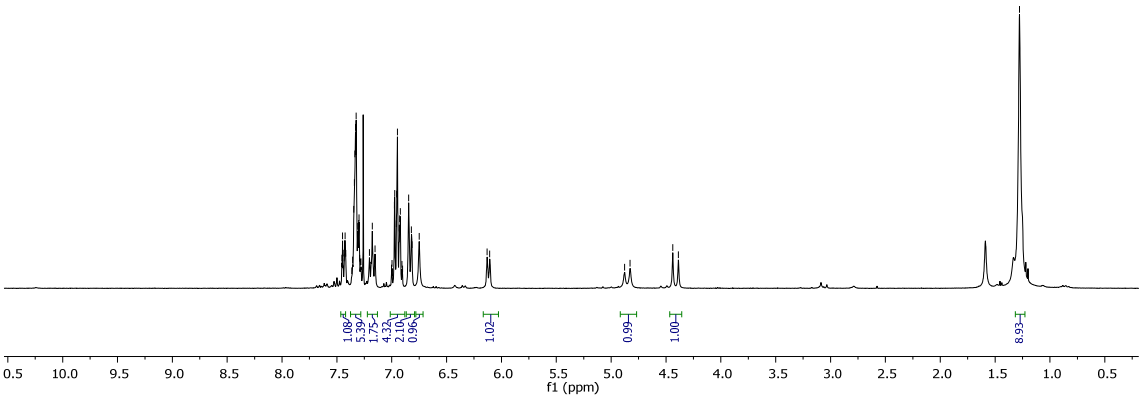
anti-**3h**

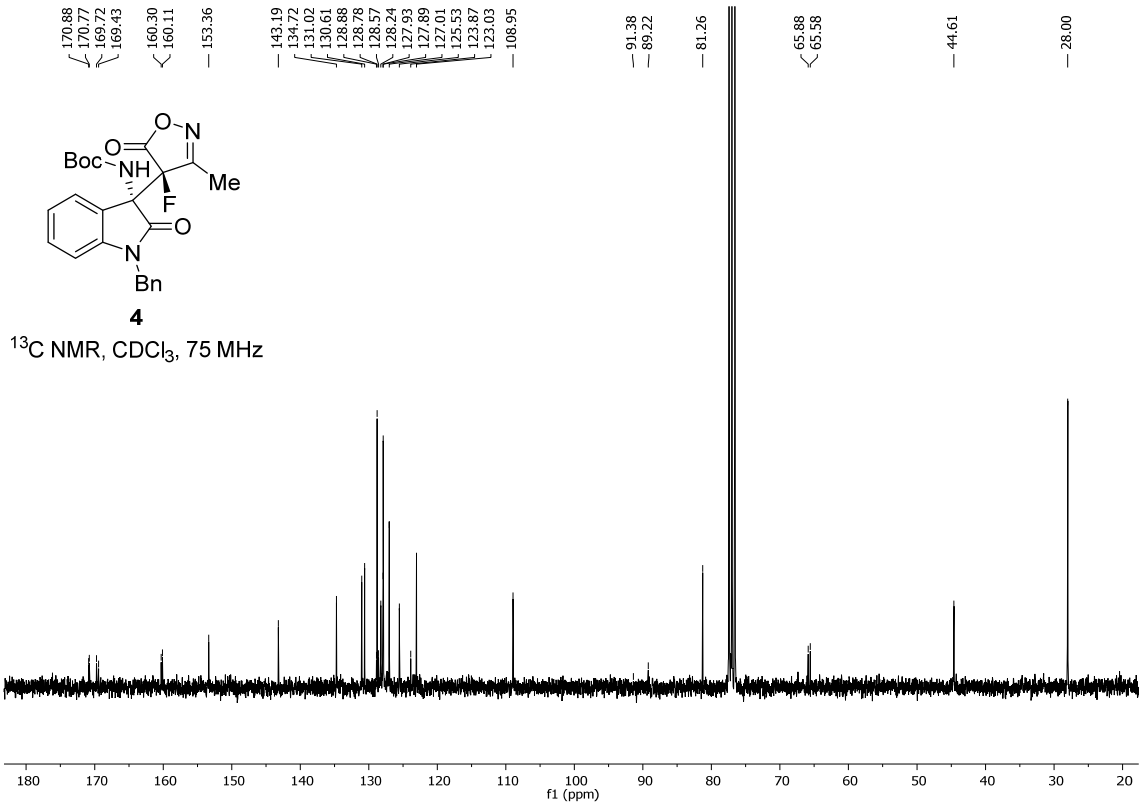
^{13}C NMR, $CDCl_3$, 75 MHz



4

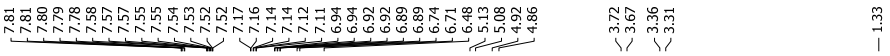
^{1}H NMR, $CDCl_3$, 300 MHz

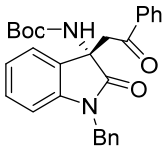




4

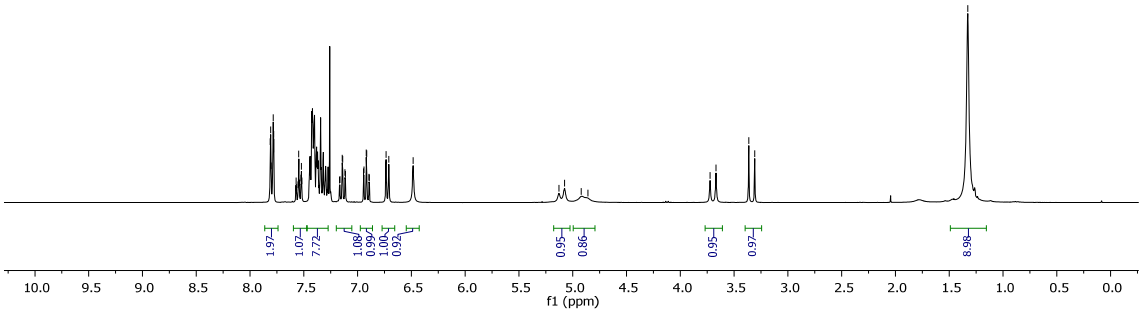
^{13}C NMR, $CDCl_3$, 75 MHz

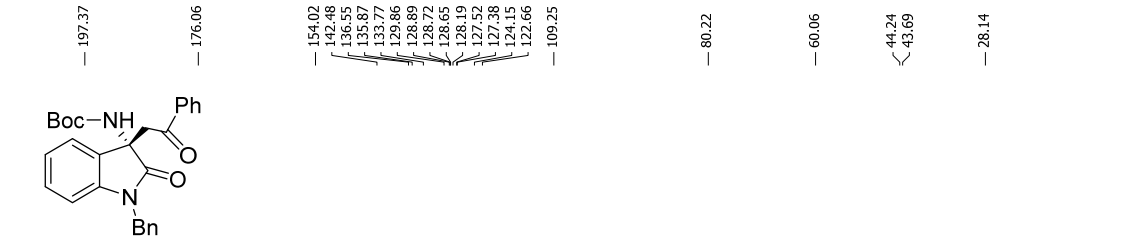




5

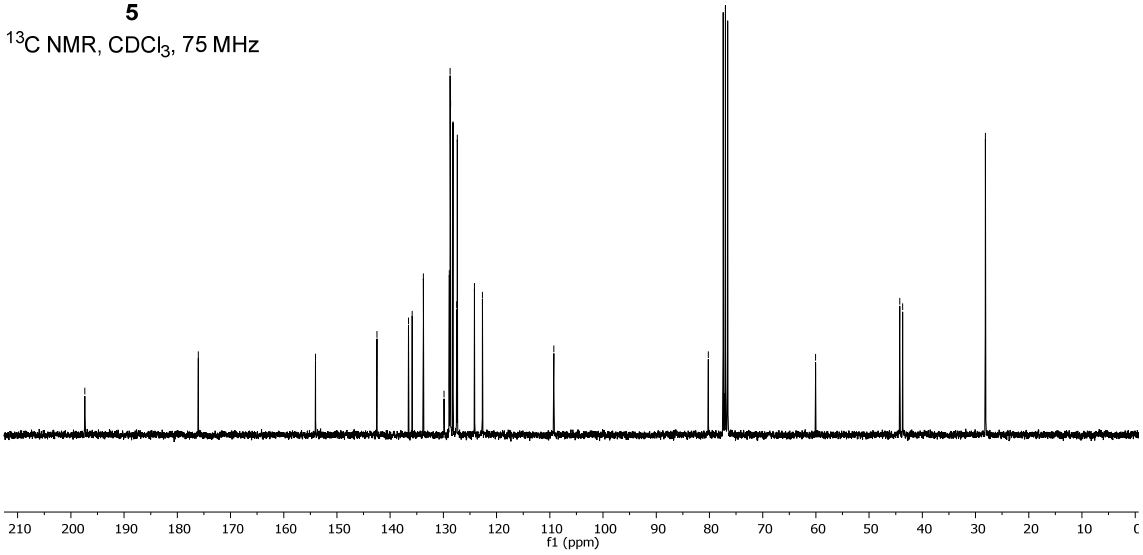
^{1}H, $CDCl_3$, 300 MHz



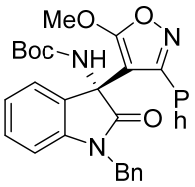


5

^{13}C NMR, $CDCl_3$, 75 MHz

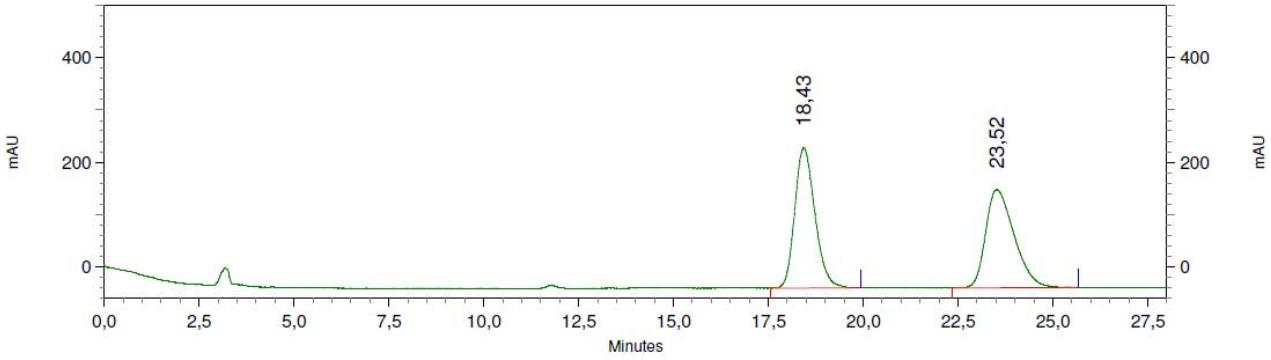


HPLC traces for compounds 3-5



3aa

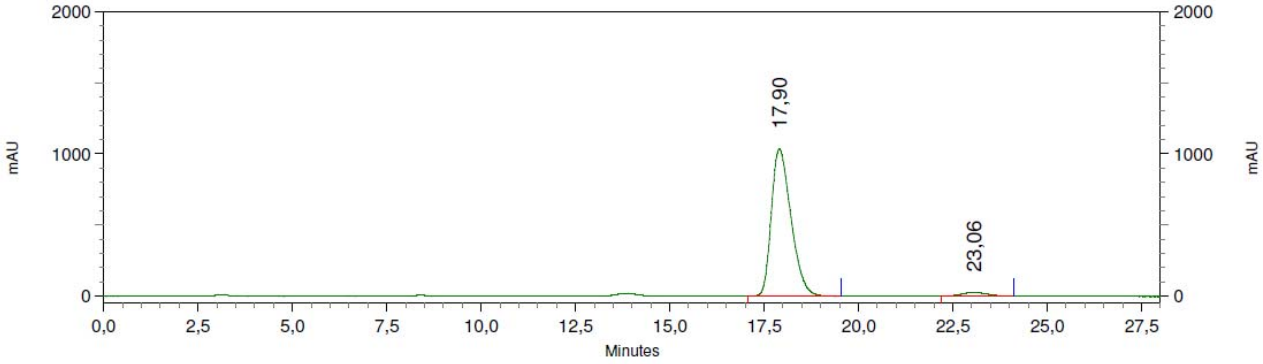
Racemic



54: 212 nm, 4 nm
Results

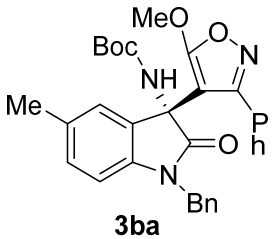
Retention Time	Area	Area Percent
18,43	39632183	50,332
23,52	39108574	49,668

Enantioenriched



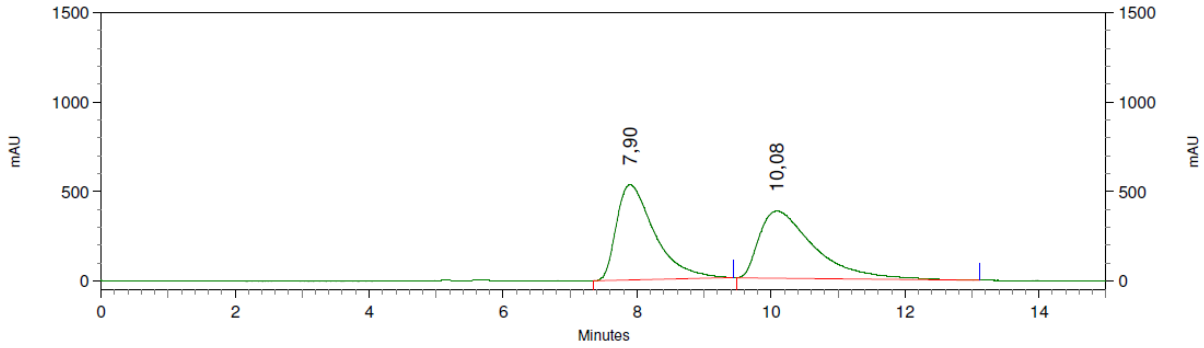
54: 212 nm, 4 nm
Results

Retention Time	Area	Area Percent
17,90	150107162	96,552
23,06	5360105	3,448



3ba

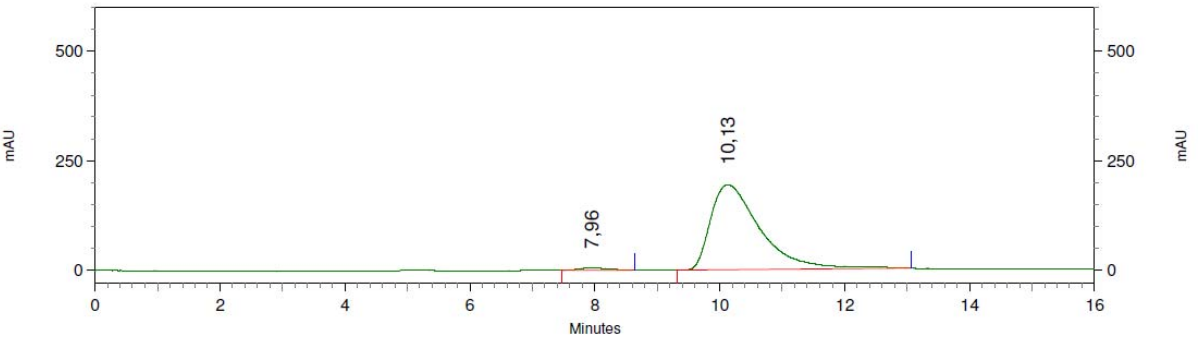
Racemic



25: 266 nm, 4 nm
Results

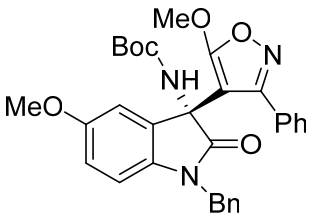
Retention Time	Area	Area Percent
7,90	84259018	49,678
10,08	85350792	50,322

Enantioenriched



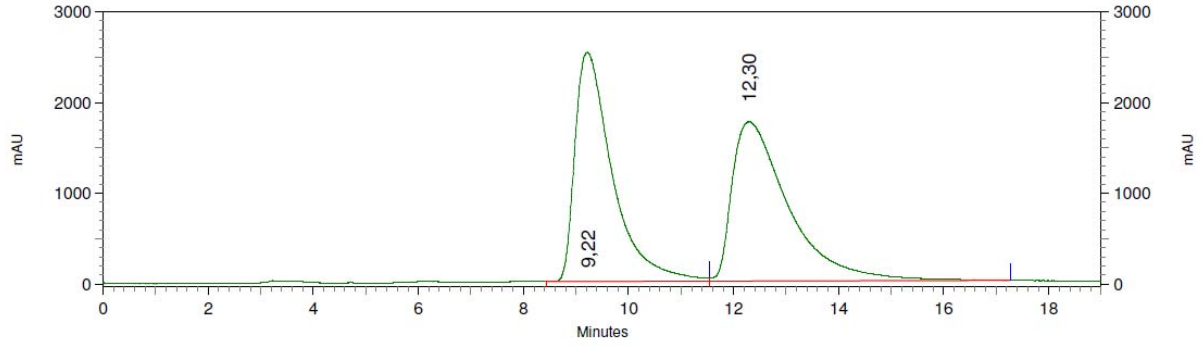
42: 256 nm, 4 nm
Results

Retention Time	Area	Area Percent
7,96	764558	1,753
10,13	42846882	98,247



3ca

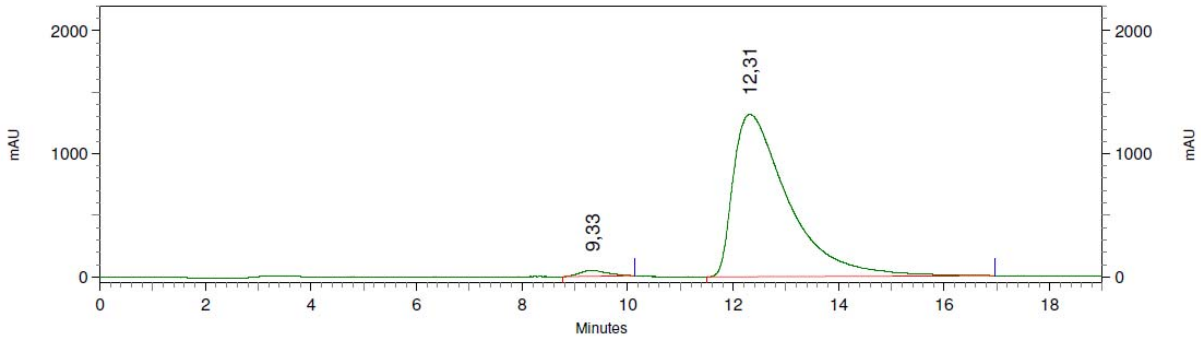
Racemic



28: 205 nm, 4 nm
Results

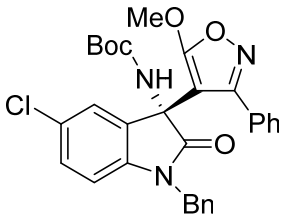
Retention Time	Area	Area Percent
9,22	498769376	48,846
12,30	522339026	51,154

Enantioenriched



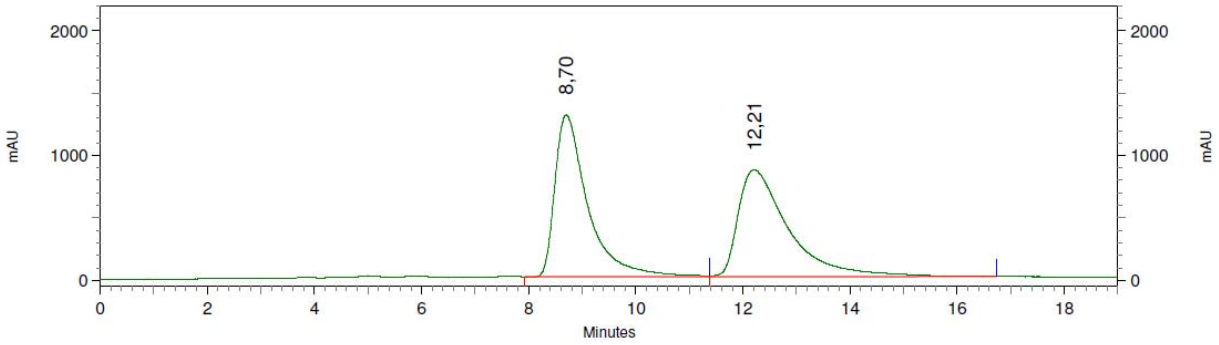
44: 209 nm, 4 nm
Results

Retention Time	Area	Area Percent
9,33	6939638	1,783
12,31	382216435	98,217



3da

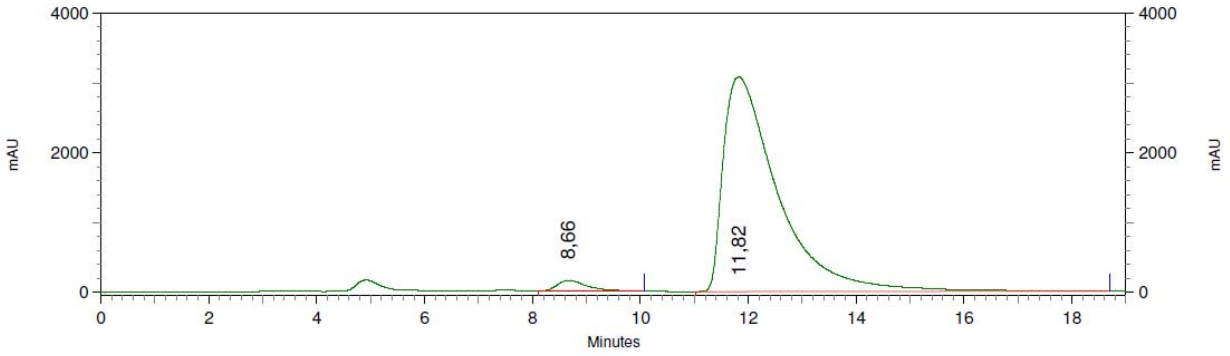
Racemic



54: 211 nm, 4 nm
Results

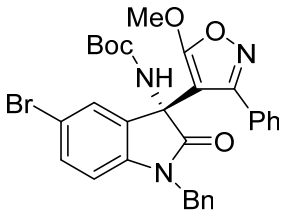
Retention Time	Area	Area Percent
8,70	220983773	49,730
12,21	223387724	50,270

Enantioenriched



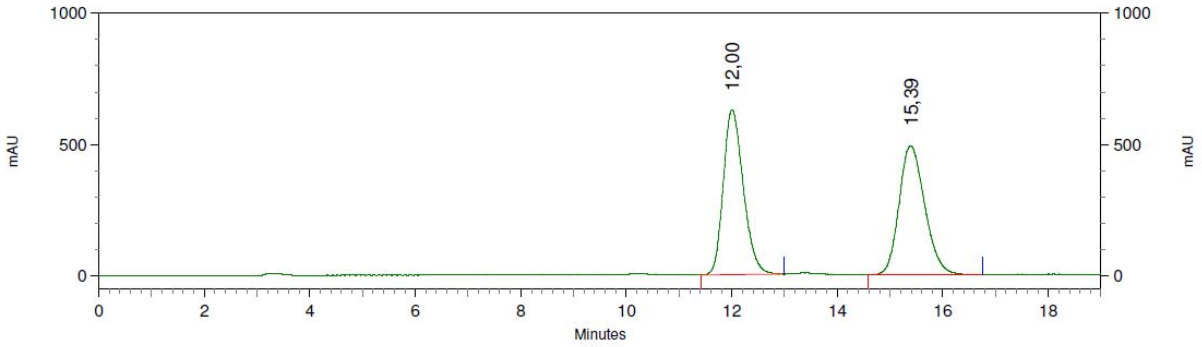
54: 211 nm, 4 nm
Results

Retention Time	Area	Area Percent
8,66	23870589	2,673
11,82	868996614	97,327



3ea

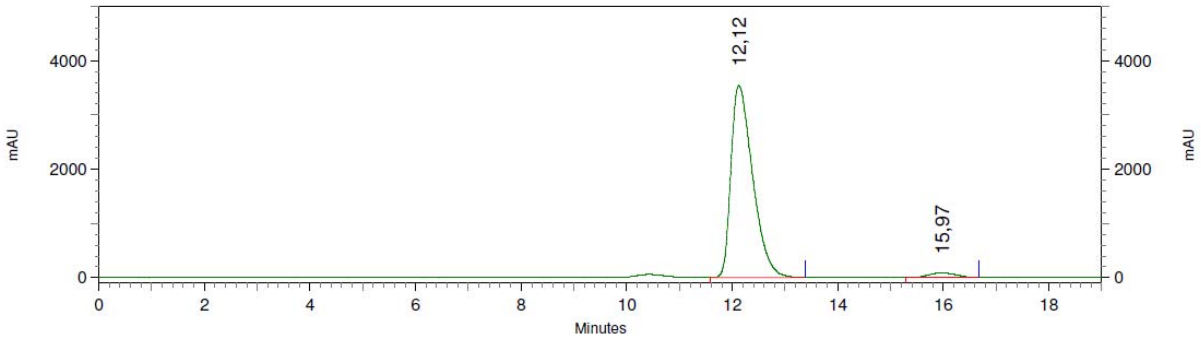
Racemic



49: 217 nm, 4 nm
Results

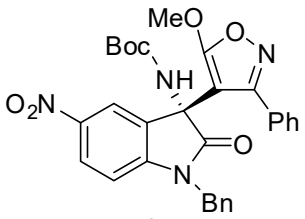
Retention Time	Area	Area Percent
12,00	66180482	49,901
15,39	66443009	50,099

Enantioenriched



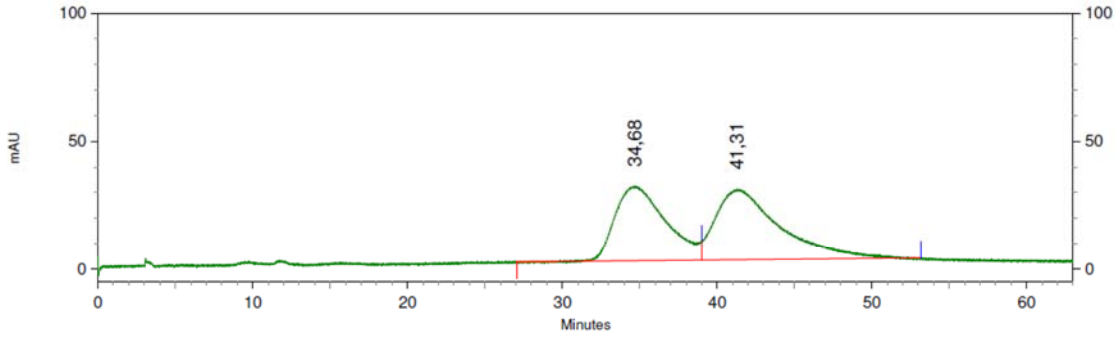
49: 217 nm, 4 nm
Results

Retention Time	Area	Area Percent
12,12	404757078	97,167
15,97	11800511	2,833



3fa

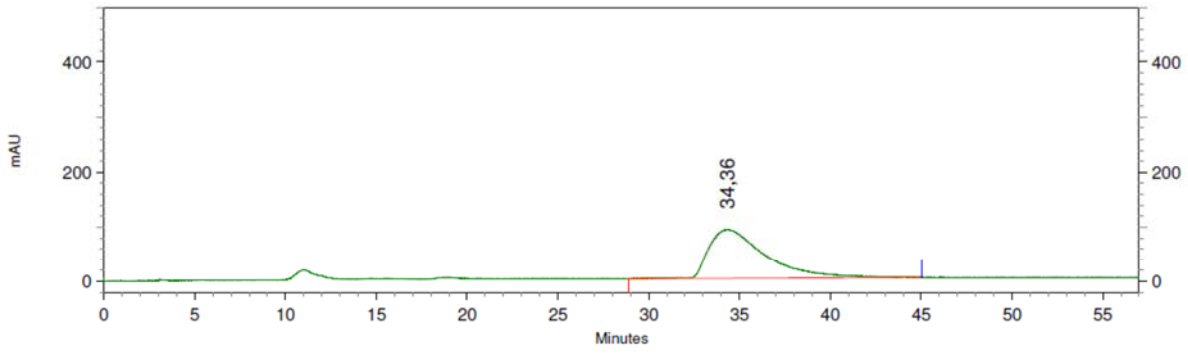
Racemic



21: 279 nm, 4 nm
Results

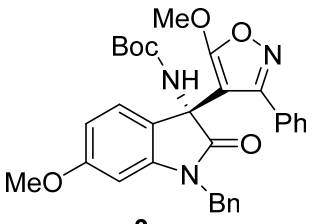
Retention Time	Area	Area Percent
34,68	26800448	45,585
41,31	31991659	54,415

Enantioenriched



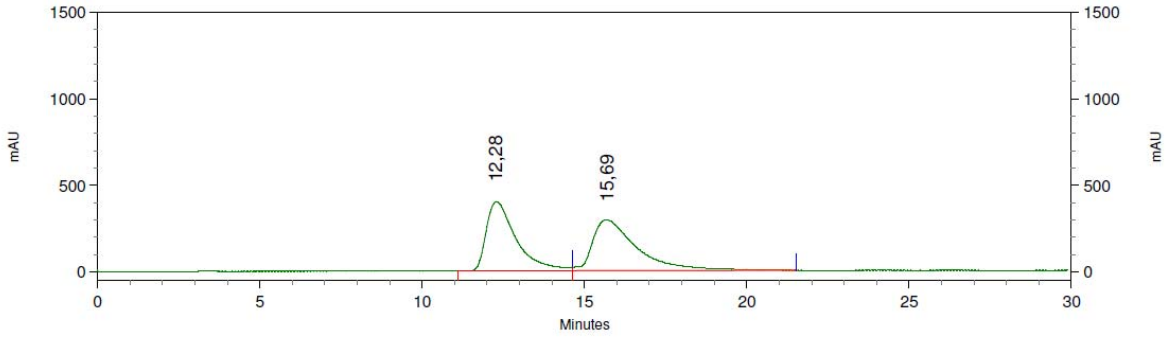
28: 279 nm, 4 nm
Results

Retention Time	Area	Area Percent
34,36	78932085	100,000



3ga

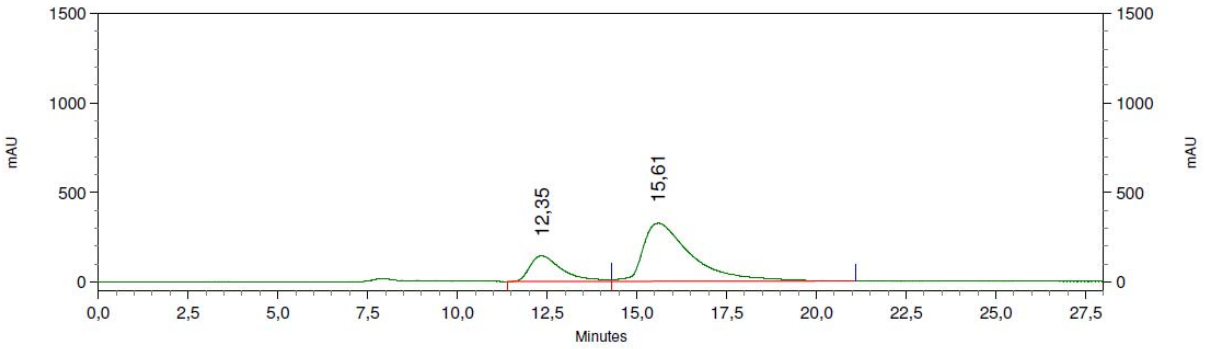
Racemic



14: 247 nm, 4 nm
Results

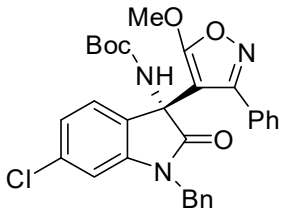
Retention Time	Area	Area Percent
12,28	101416892	47,912
15,69	110258468	52,088

Enantioenriched



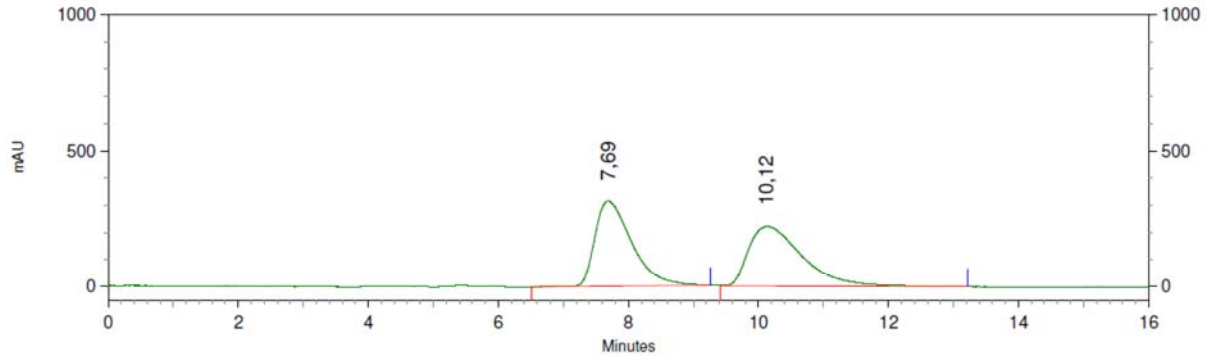
14: 247 nm, 4 nm
Results

Retention Time	Area	Area Percent
12,35	35710775	22,791
15,61	120977072	77,209



3ha

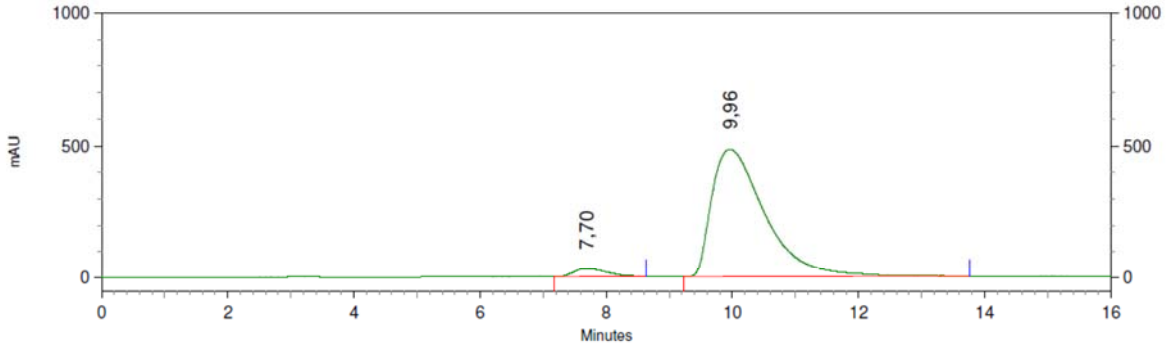
Racemic



20: 237 nm, 4 nm
Results

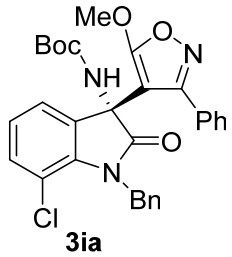
Retention Time	Area	Area Percent
7,69	49928294	49,538
10,12	50858890	50,462

Enantioenriched



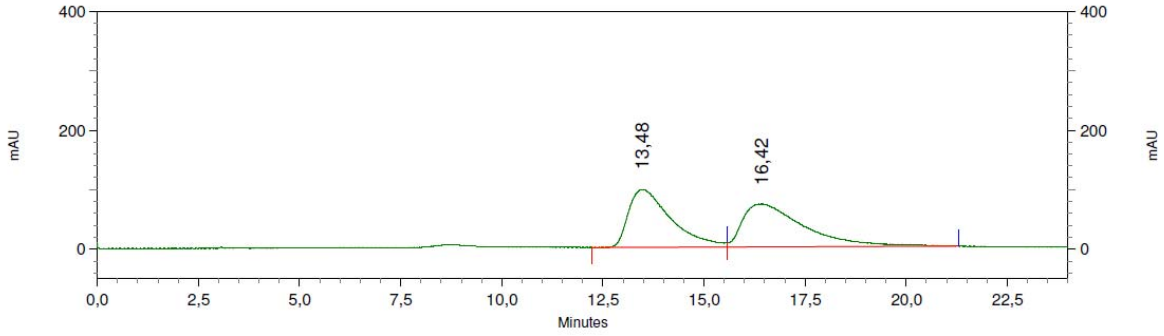
20: 237 nm, 4 nm
Results

Retention Time	Area	Area Percent
7,70	4480681	3,784
9,96	113944625	96,216



3ia

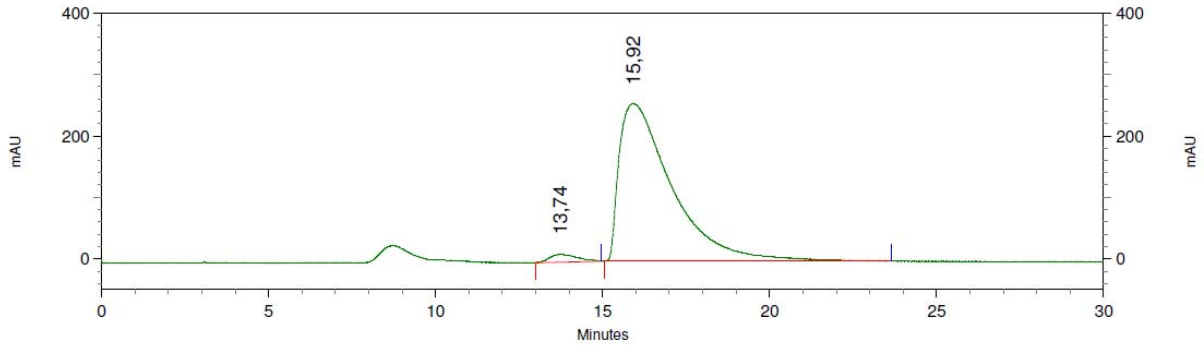
Racemic



28: 279 nm, 4 nm
Results

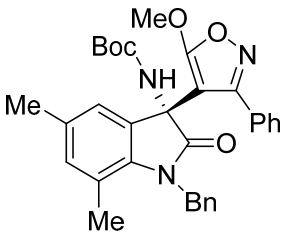
Retention Time	Area	Area Percent
13,48	28500135	48,196
16,42	30633391	51,804

Enantioenriched



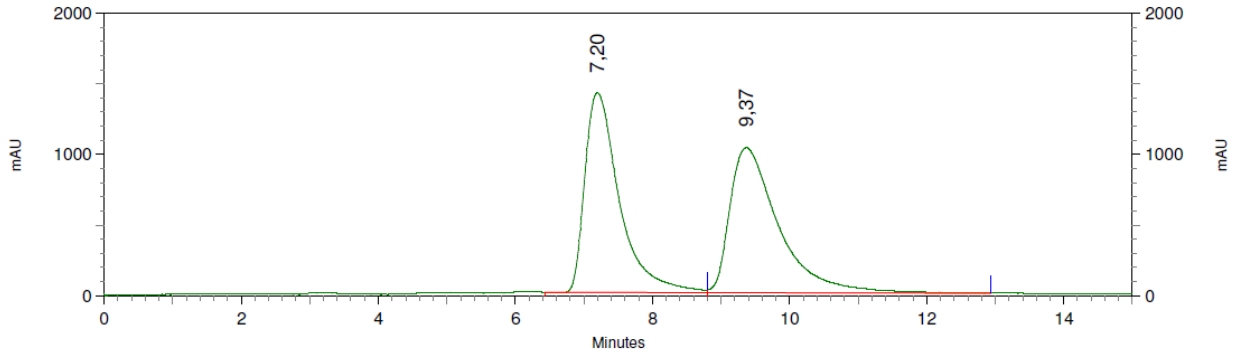
28: 279 nm, 4 nm
Results

Retention Time	Area	Area Percent
13,74	2953943	2,539
15,92	113386040	97,461



3ja

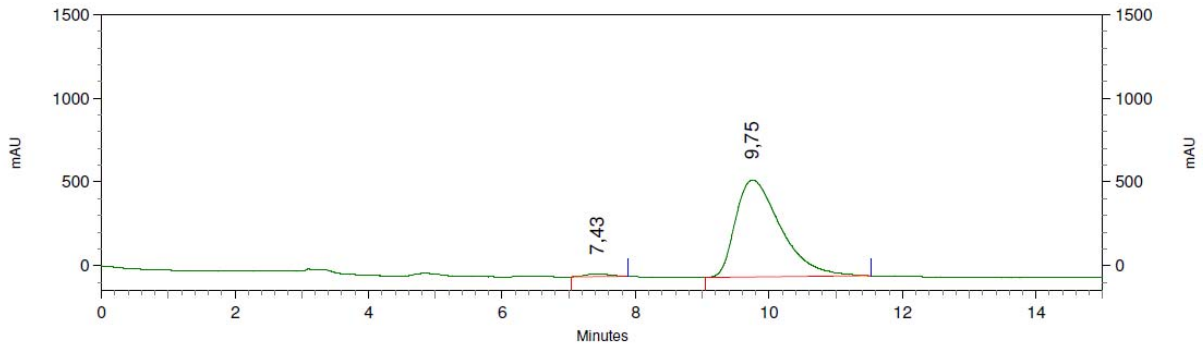
Racemic



56: 212 nm, 4 nm
Results

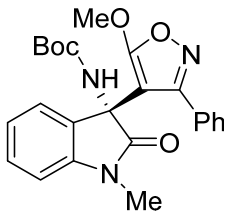
Retention Time	Area	Area Percent
7,20	198311944	49,356
9,37	203484970	50,644

Enantioenriched



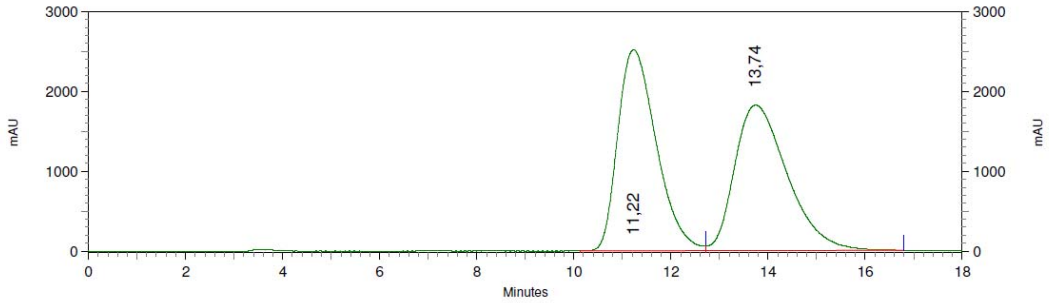
37: 222 nm, 4 nm
Results

Retention Time	Area	Area Percent
7,43	1617495	1,465
9,75	108816823	98,535



3ka

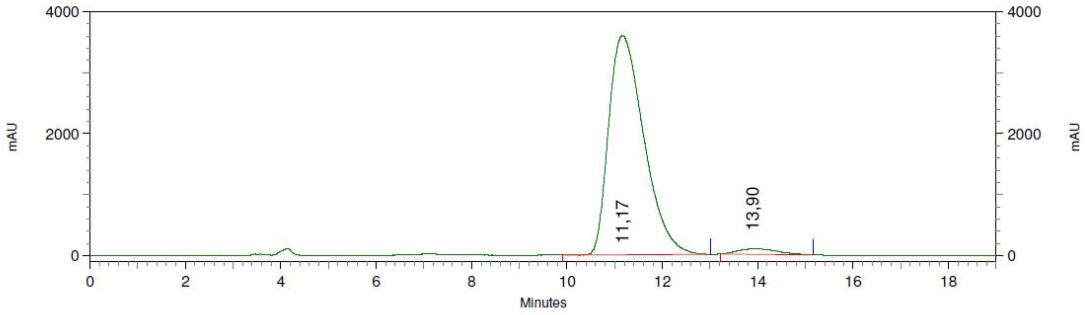
Racemic



23: 220 nm, 4 nm
Results

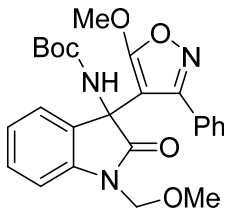
Retention Time	Area	Area Percent
11,22	555679283	50,354
13,74	547856376	49,646

Enantioenriched



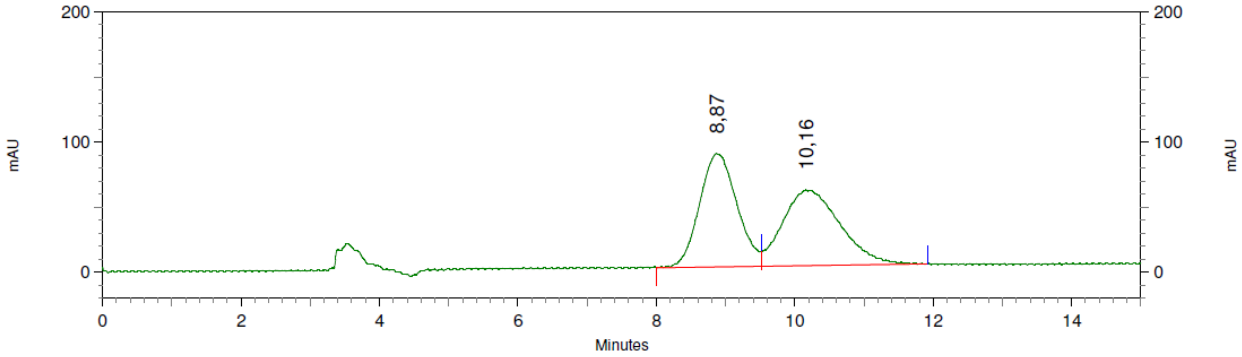
23: 220 nm, 4 nm
Results

Retention Time	Area	Area Percent
11,17	737131966	97,232
13,90	20982460	2,768



3la

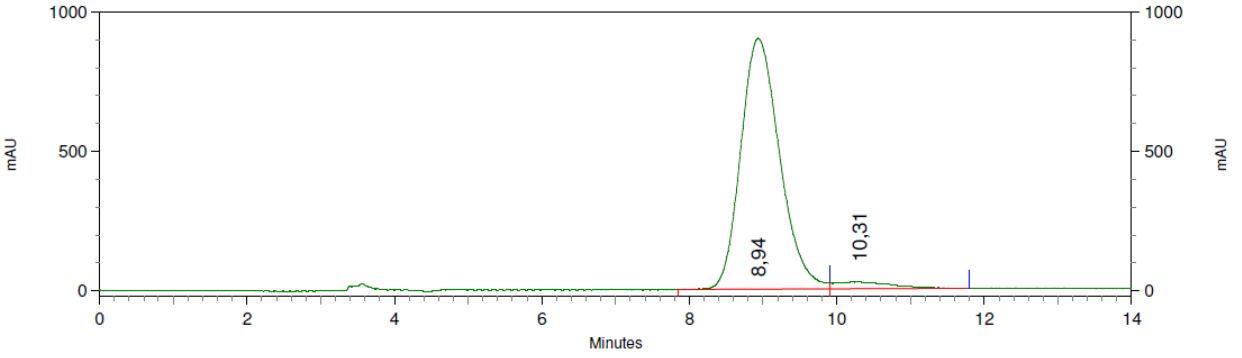
Racemic



12: 217 nm, 4 nm
Results

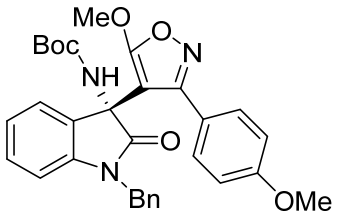
Retention Time	Area	Area Percent
8,87	13049126	49,525
10,16	13299416	50,475

Enantioenriched



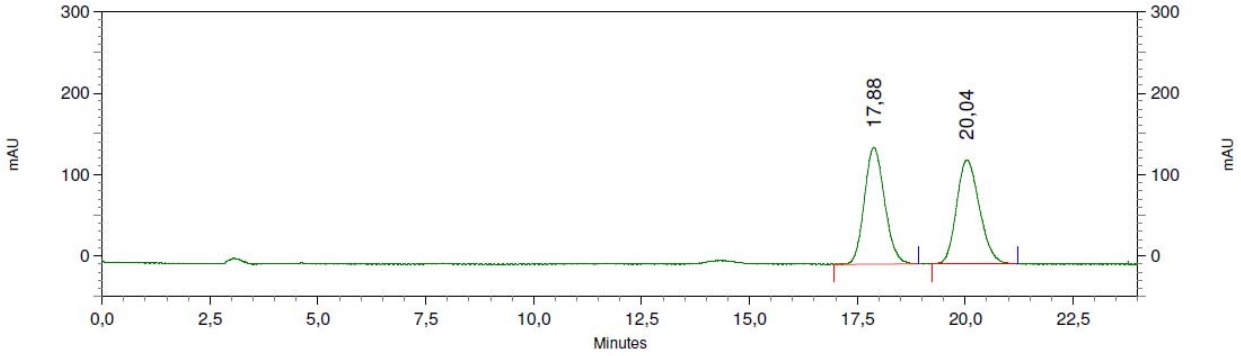
12: 217 nm, 4 nm
Results

Retention Time	Area	Area Percent
8,94	131923917	96,118
10,31	5327665	3,882



3ab

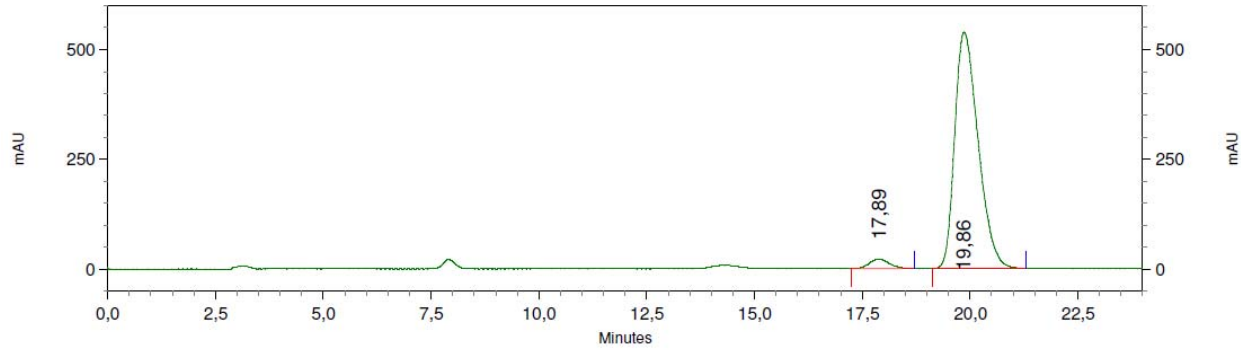
Racemic



43: 226 nm, 4 nm
Results

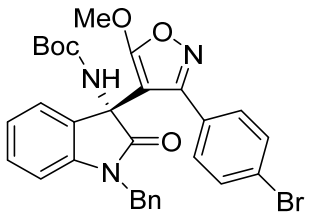
Retention Time	Area	Area Percent
17,88	18770722	49,727
20,04	18976536	50,273

Enantioenriched



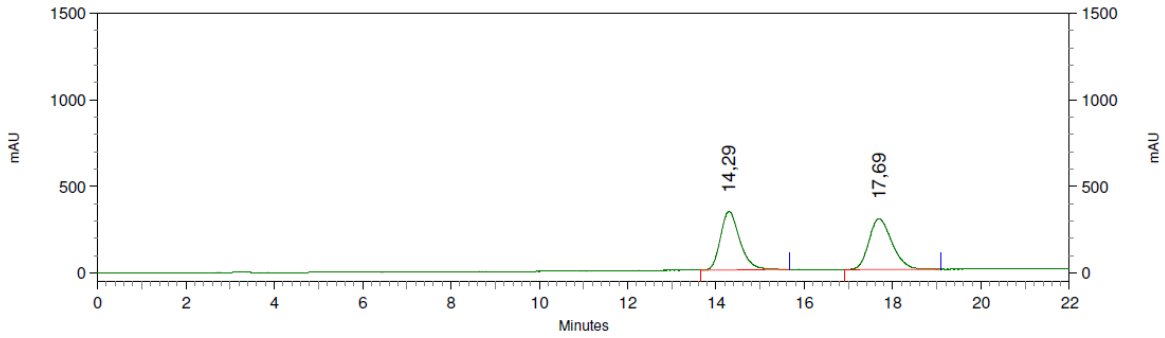
43: 226 nm, 4 nm
Results

Retention Time	Area	Area Percent
17,89	2858070	3,396
19,86	81303137	96,604



3ac

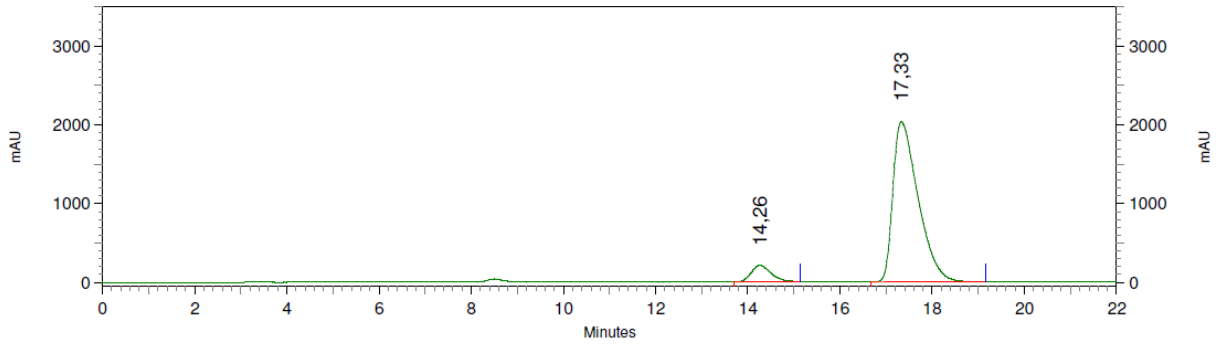
Racemic



63: 227 nm, 4 nm
Results

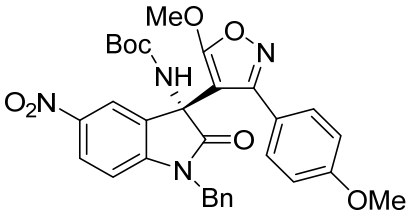
Retention Time	Area	Area Percent
14,29	41268832	49,221
17,69	42575831	50,779

Enantioenriched



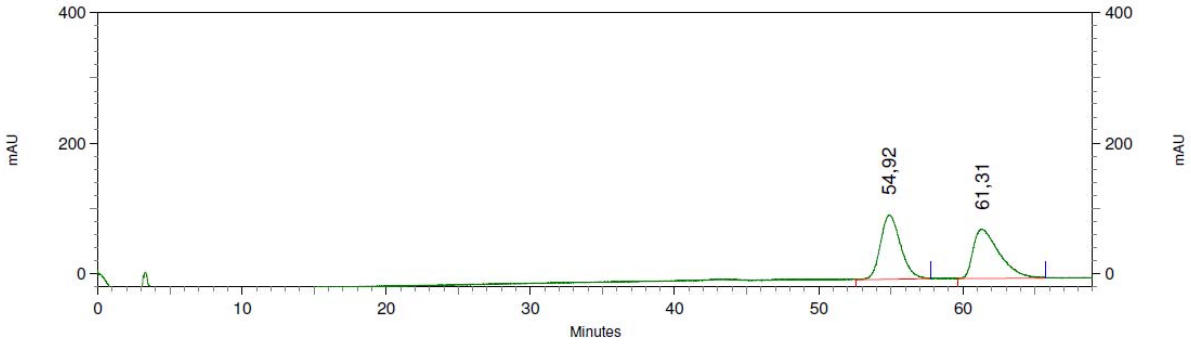
63: 227 nm, 4 nm
Results

Retention Time	Area	Area Percent
14,26	24968261	7,506
17,33	307690687	92,494



3fb

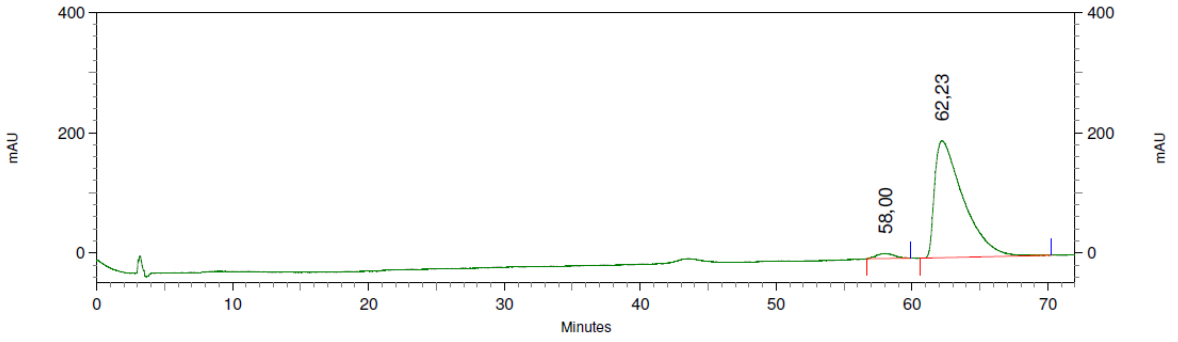
Racemic



9: 210 nm, 4 nm Results

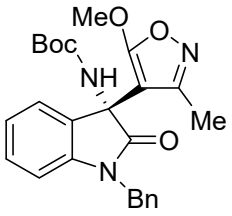
Retention Time	Area	Area Percent
54,92	37902529	49,943
61,31	37988309	50,057

Enantioenriched



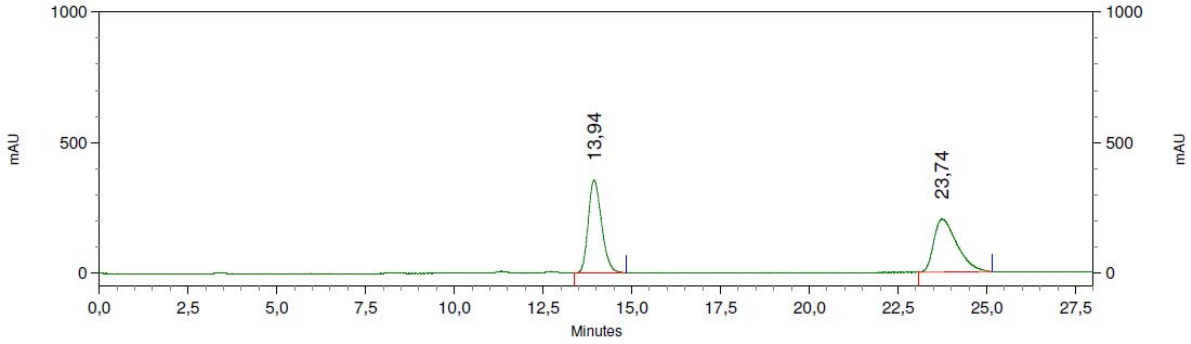
9: 210 nm, 4 nm Results

Retention Time	Area	Area Percent
58,00	3156335	2,685
62,23	114389246	97,315



3ad

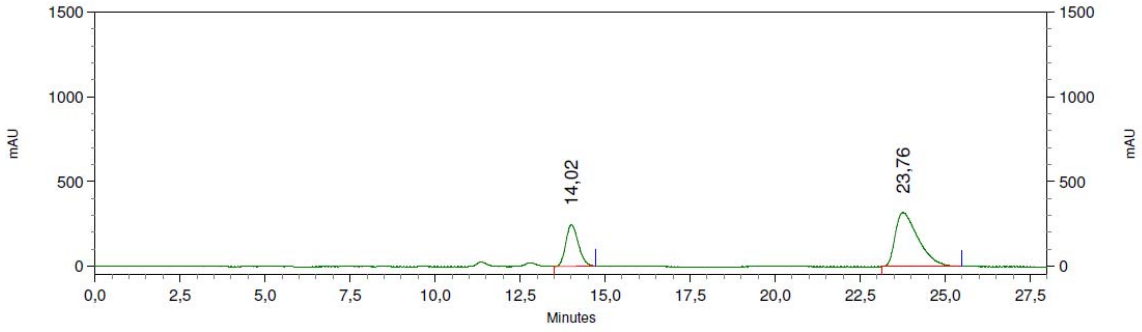
Racemic



15: 234 nm, 4 nm
Results

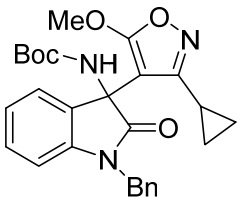
Retention Time	Area	Area Percent
13,94	36884217	50,205
23,74	36582424	49,795

Enantioenriched



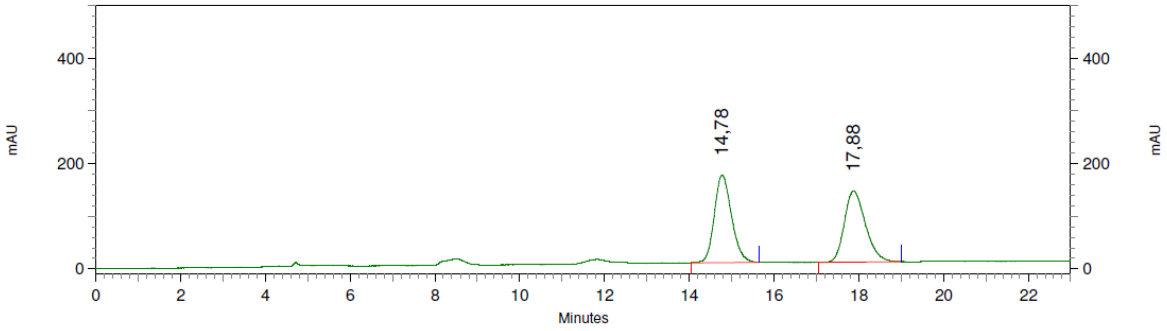
15: 234 nm, 4 nm
Results

Retention Time	Area	Area Percent
14,02	25081267	29,539
23,76	59826363	70,461



3ae

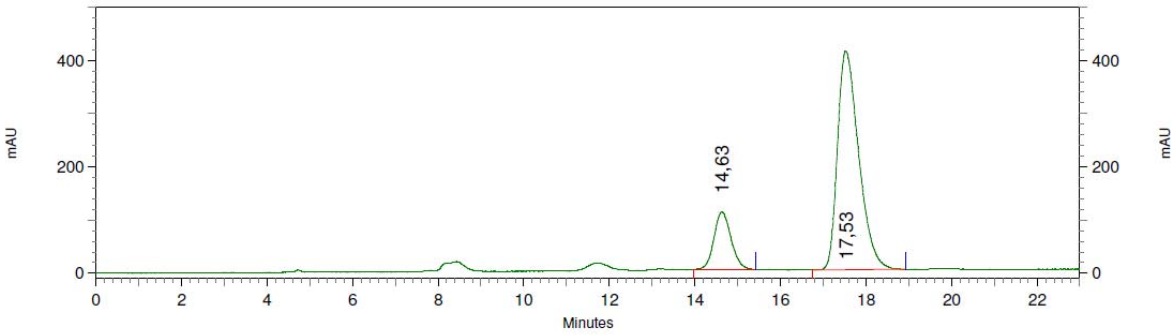
Racemic



38: 258 nm, 4 nm
Results

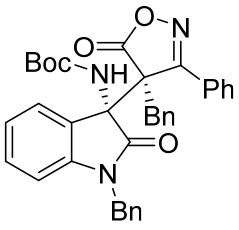
Retention Time	Area	Area Percent
14,78	18769040	50,085
17,88	18705367	49,915

Enantioenriched



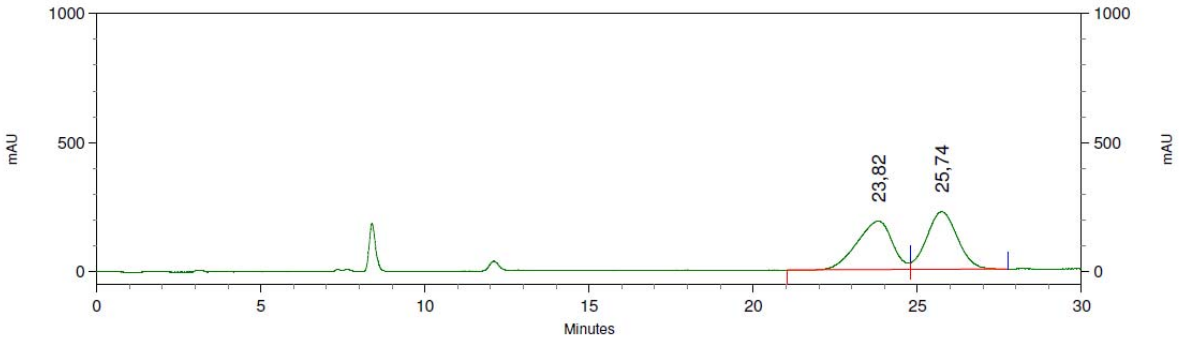
38: 258 nm, 4 nm
Results

Retention Time	Area	Area Percent
14,63	12040376	17,493
17,53	56787999	82,507



syn-**3af**

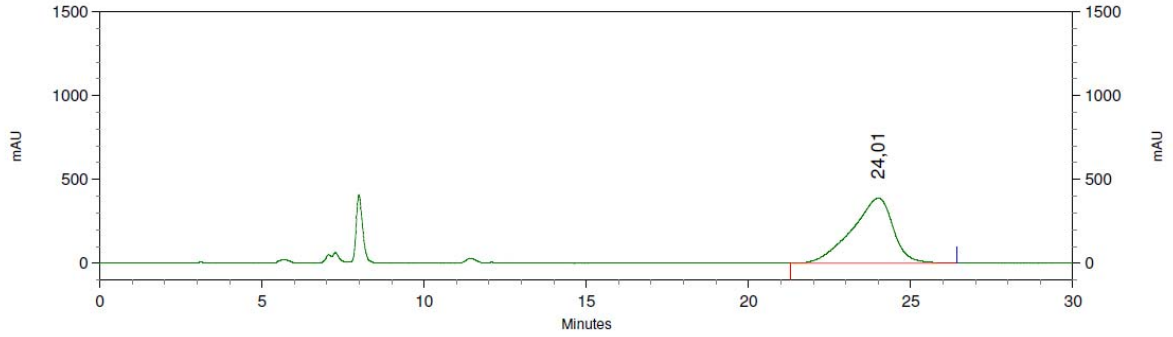
Racemic



68: 219 nm, 4 nm
Results

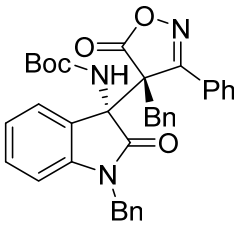
Retention Time	Area	Area Percent
23,82	56166252	49,347
25,74	57653452	50,653

Enantioenriched



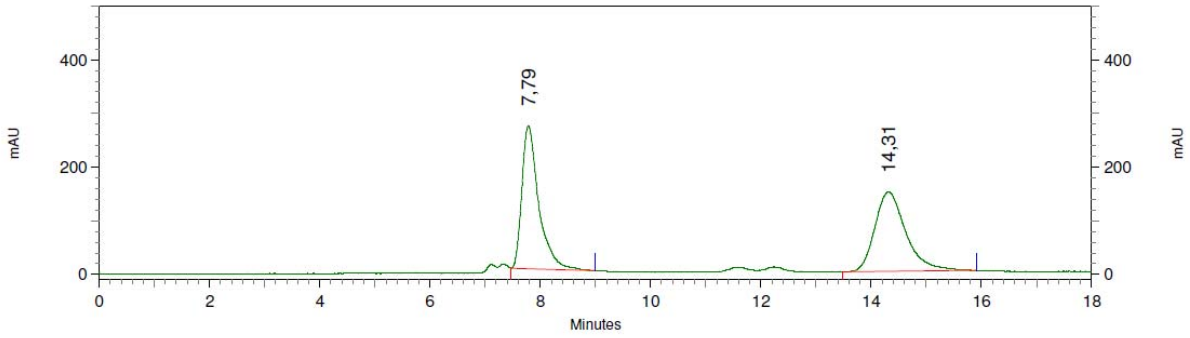
68: 219 nm, 4 nm
Results

Retention Time	Area	Area Percent
24,01	136870293	100,000



anti-**3af**

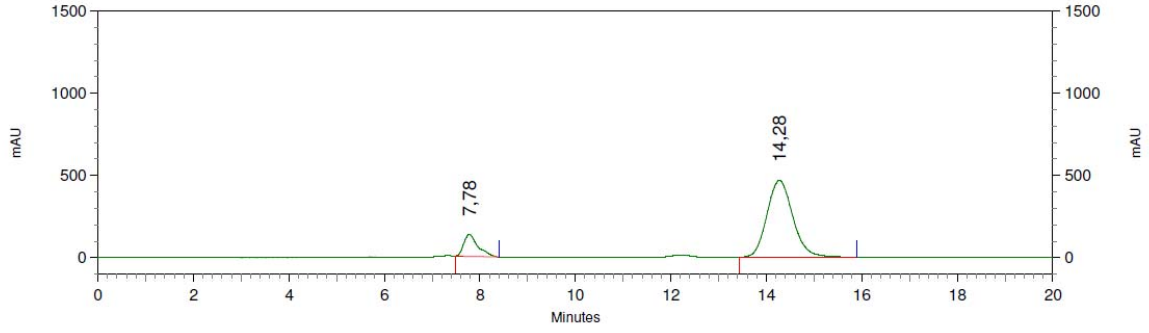
Racemic



38: 258 nm, 4 nm
Results

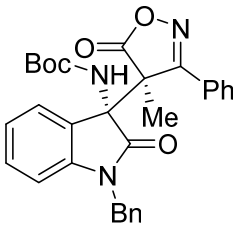
Retention Time	Area	Area Percent
7,79	22667667	49,426
14,31	23194392	50,574

Enantioenriched



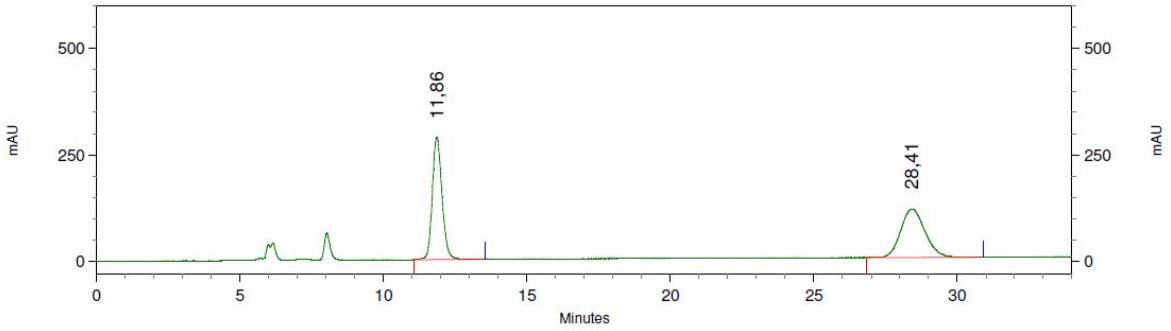
38: 258 nm, 4 nm
Results

Retention Time	Area	Area Percent
7,78	11161166	13,860
14,28	69365927	86,140



syn-**3ag**

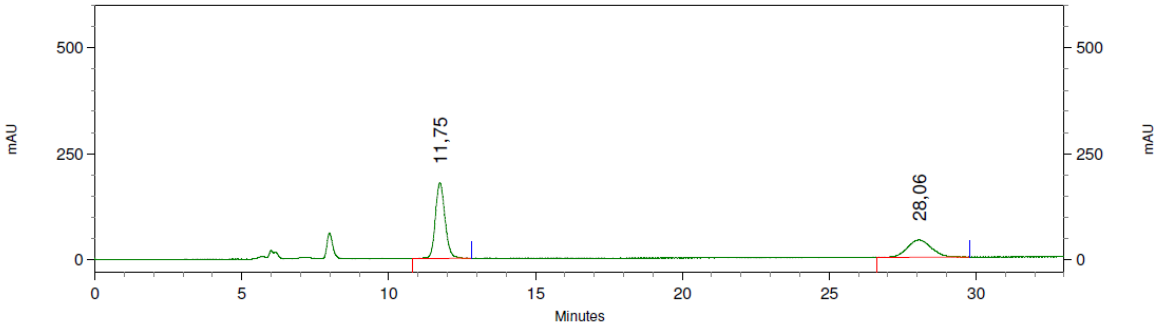
Racemic



42: 256 nm, 4 nm
Results

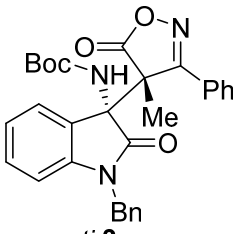
Retention Time	Area	Area Percent
11,86	27023477	50,165
28,41	26845558	49,835

Enantioenriched



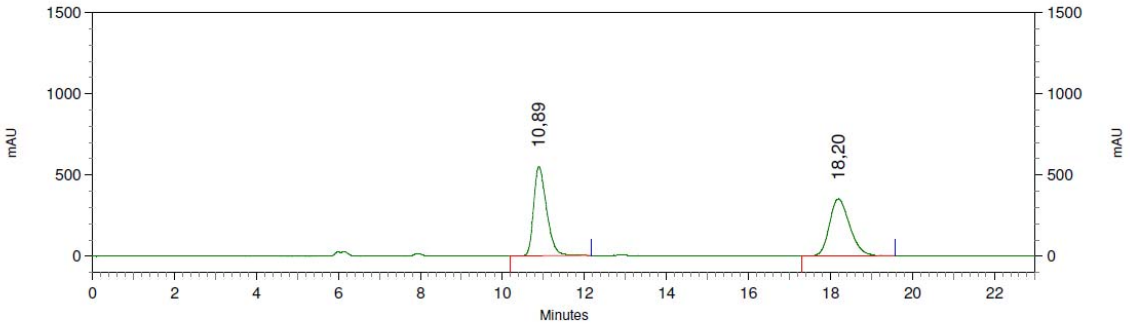
42: 256 nm, 4 nm
Results

Retention Time	Area	Area Percent
11,75	16348660	63,440
28,06	9421506	36,560



anti-**3ag**

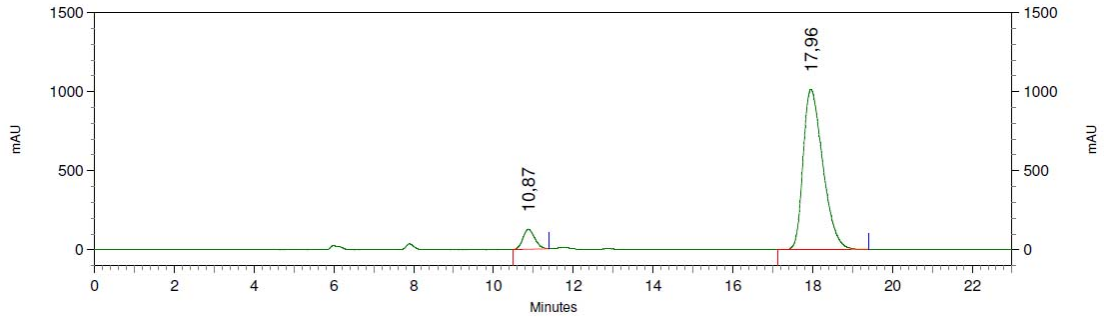
Racemic



42: 256 nm, 4 nm
Results

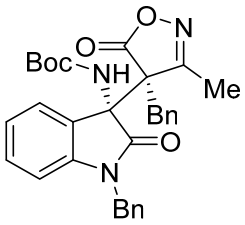
Retention Time	Area	Area Percent
10,89	48504299	50,343
18,20	47844022	49,657

Enantioenriched



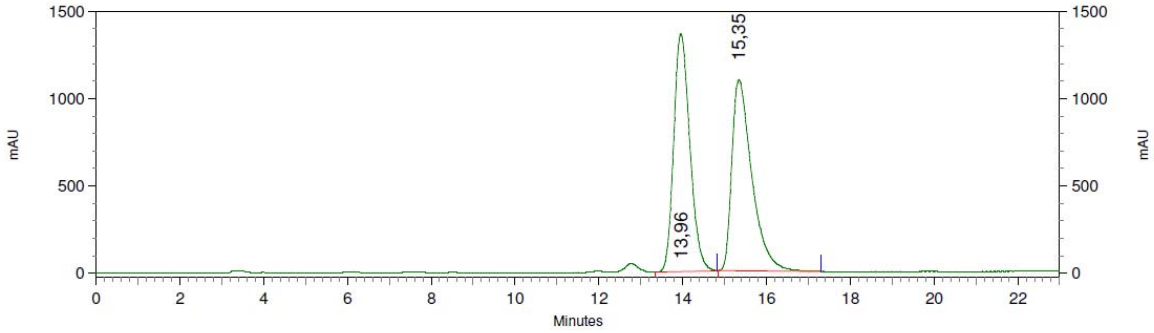
42: 256 nm, 4 nm
Results

Retention Time	Area	Area Percent
10,87	10293009	6,906
17,96	138760363	93,094



syn-**3ah**

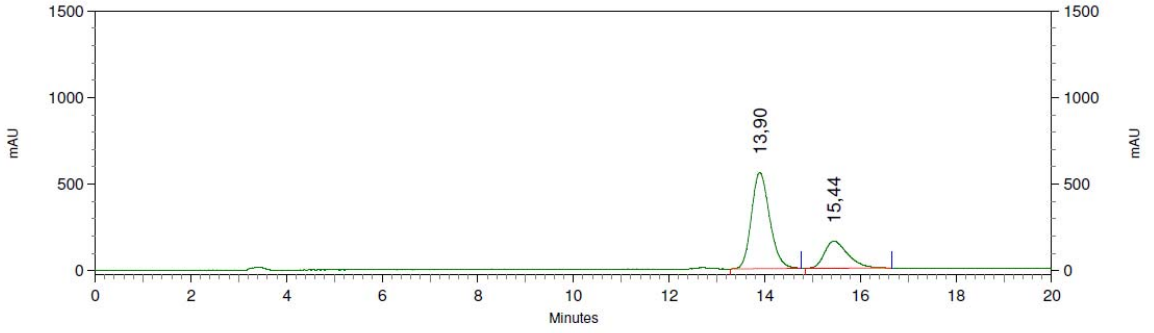
Racemic



54: 211 nm, 4 nm
Results

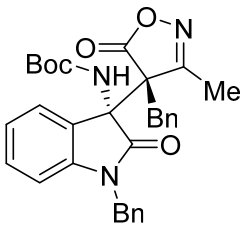
Retention Time	Area	Area Percent
13,96	146059544	50,106
15,35	145444332	49,894

Enantioenriched



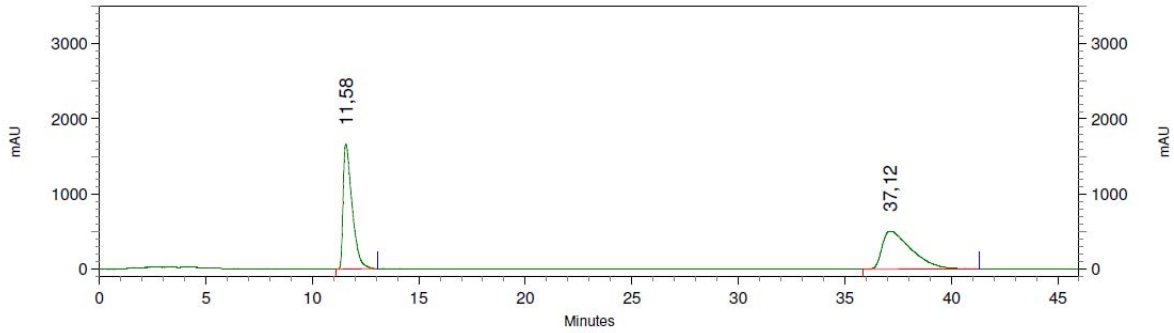
54: 211 nm, 4 nm
Results

Retention Time	Area	Area Percent
13,90	58738242	73,082
15,44	21634557	26,918



anti-**3ah**

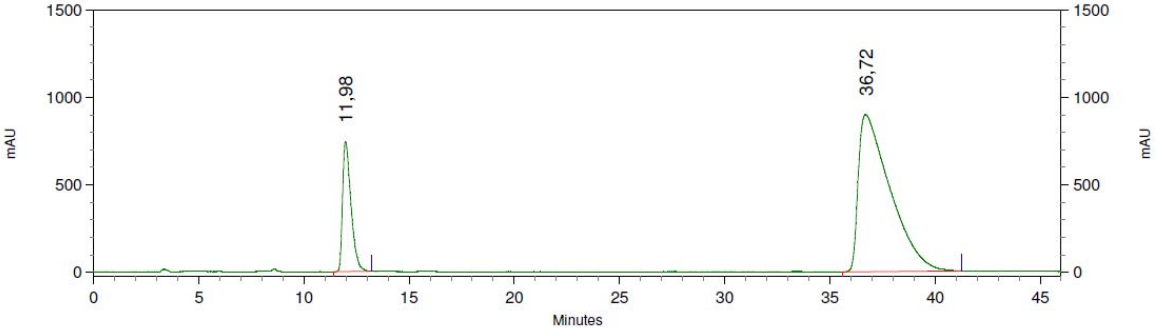
Racemic



54: 211 nm, 4 nm
Results

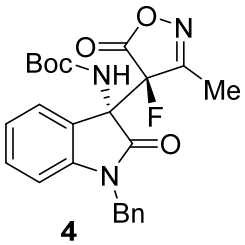
Retention Time	Area	Area Percent
11,58	194501285	49,977
37,12	194676937	50,023

Enantioenriched



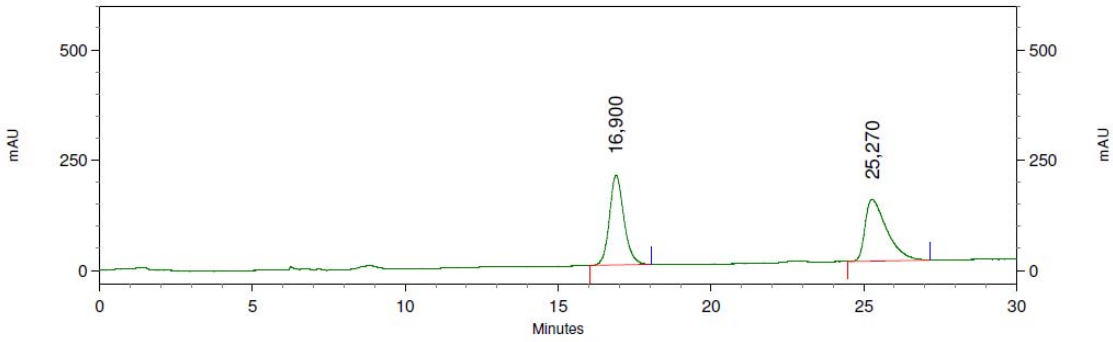
54: 211 nm, 4 nm
Results

Retention Time	Area	Area Percent
11,98	83197926	18,054
36,72	377634261	81,946



4

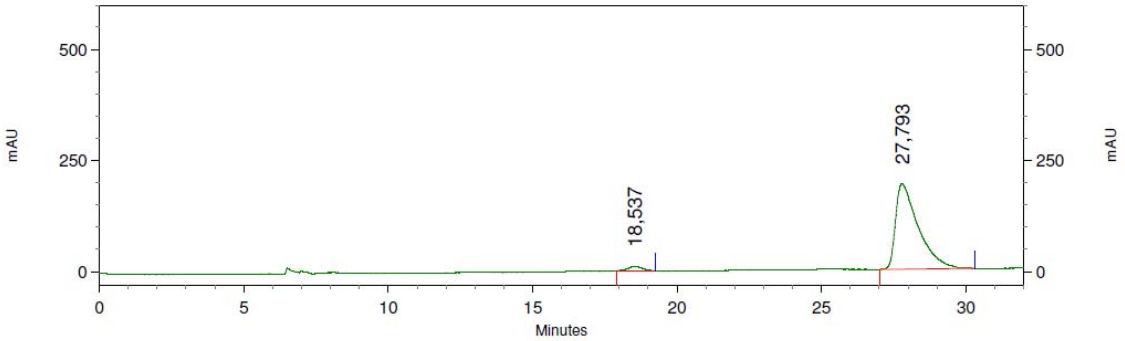
Racemic



1: 268 nm, 4 nm Results

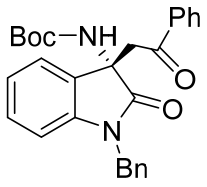
Retention Time	Area	Area Percent
16,900	26755918	49,330
25,270	27483222	50,670

Enantioenriched



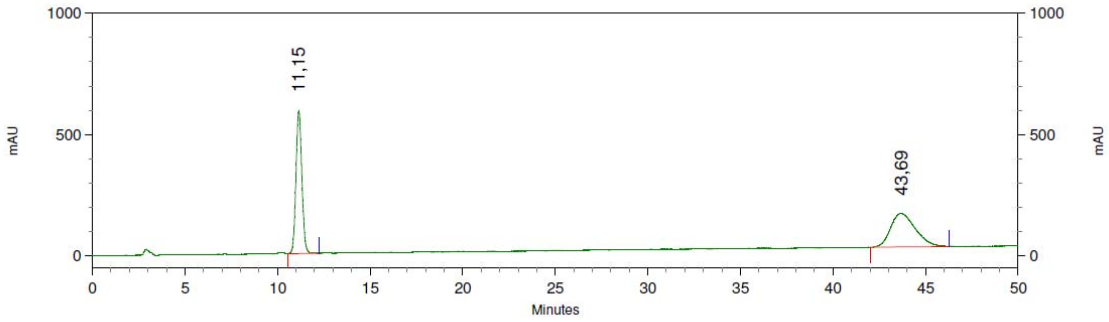
1: 268 nm, 4 nm Results

Retention Time	Area	Area Percent
18,537	1394891	3,213
27,793	42018313	96,787



5

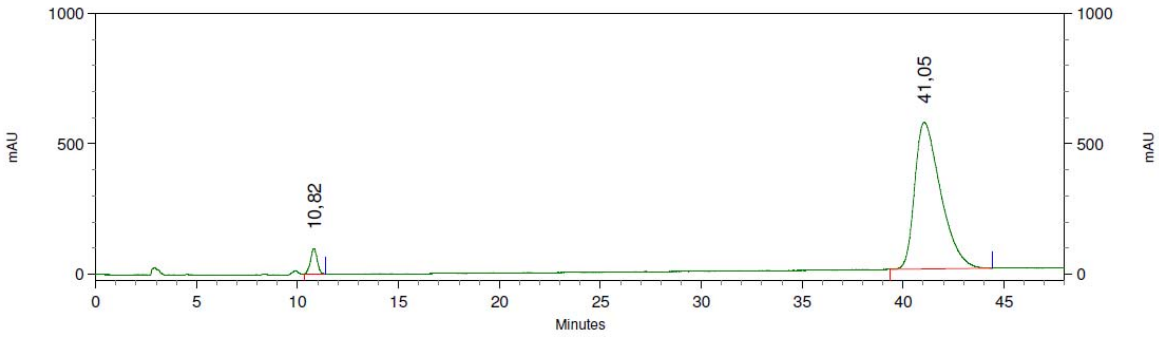
Racemic



65: 210 nm, 4 nm
Results

Retention Time	Area	Area Percent
11,15	52101686	50,386
43,69	51302539	49,614

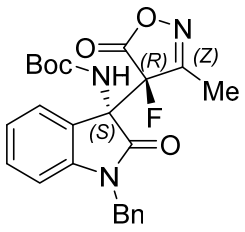
Enantioenriched



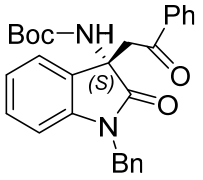
65: 210 nm, 4 nm
Results

Retention Time	Area	Area Percent
10,82	9031039	4,289
41,05	201507233	95,711

Absolute configuration analysis



4



5

Šebesta and co-workers describe the synthesis of compound **4** [6] with (*S,R*) configuration. They reported chiral HPLC chromatography as follows:

Authors	Column	Chiral Phase	Conditions	Retention times (min)
Šebesta	Chiralpak IA	Amylose tris-(3,5-dimethylphenylcarbamate) immobilized on SiO_2	90:10 Hexane/*i*PrOH, 0.5 mL/min, λ = 210 nm)	t_{major} = 21.2 t_{minor} =15.2
This work	Phenomenex Lux® *i*-amylose-1	Amylose tris-(3,5-dimethylphenylcarbamate) immobilized on SiO_2	90:10 Hexane/*i*PrOH, 0.5 mL/min, λ = 210 nm)	t_{major} = 27.9 t_{minor} = 18.5

As the stationary phase and HPLC conditions are the same, one can consider than the same enantiomer is obtained. Unfortunately, the authors did not provide the $[\alpha]_D$ of this compound to be used as further evidence.

On the other hand compounds (*S*)-**5** and (*R*)-**5** have been described by Chimni[7] and by Wu and Cao, [8] respectively. The absolute stereochemistry of compound **5** obtained in our work was ascertained by comparison of the optical rotation values as well as by comparison of the HPLC chiral chromatography.

Authors	Column	Chiral Phase	Conditions	Retention times (min)
Wu and Cao	Chiralpak IA	Amylose tris-(3,5-dimethylphenylcarbamate) immobilized on SiO_2	80:20 Hexane/*i*PrOH, 1 mL/min, λ = 210 nm)	(*R*) t_{major} = 8.9 t_{minor} = 32.9
This work	Phenomenex Lux® *i*-amylose-1	Amylose tris-(3,5-dimethylphenylcarbamate) immobilized on SiO_2	80:20 Hexane/*i*PrOH, 1 mL/min, λ = 210 nm)	t_{major} = 41.0 t_{minor} = 10.8

While the stationary phase and HPLC conditions are the same, one can consider than the opposite enantiomer is obtained.

This can be further proved by checking the specific rotation:

Authors	Specific rotation	C	Solvent	Enantiomer
Wu and Cao	$[\alpha]^{28}_D = +52.3$	0,34	$CHCl_3$	(*R*)
Chimni	$[\alpha]^{25}_D = -50.7$	0.1	$CHCl_3$	(*S*)
This work	$[\alpha]^{25}_D = -65.7$	0,95	$CHCl_3$	(*S*)

References

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[6] D. Krištofíková, M. Mečiarová, E. Rakovský, R. Šebesta, *ACS Sustainable Chem. Eng.* 2020, **8**, 14417−14424

[7] J. Kaur, A. Kumari, V. K. Bhardwaj, S. S. Chimni, *Adv. Synth. Catal.* 2017, **359**, 1725–1734.

[8] C. Cheng, X. Lu, L. Ge, J. Chen, W. Cao, X. X. Wu, G. Zhao, *Org. Chem. Front*. 2017, **4**, 101–114.