3-Bromooxindoles as Nucleophiles in Asymmetric Organocatalytic Mannich Reactions with *N*-Ts-imines

Jianhao Li, Taiping Du, Gang Zhang* and Yungui Peng*

School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, P. R. China

Fax: (+86) 02368253157; E-mail: pengyungui@hotmail.com

Department of High Altitude Military Hygiene, College of High Altitude Military Medicine, Third Military Medical University, Chongqing 400038, P. R. China

E-mail: zhanggang1968@yahoo.com.cn

Table of Contents

1. General methods 2

2. Synthesis of chiral catalysts 2

3. Asymmetric Mannich reaction of 3-bromooxindole with *N*-Ts-imine catalyzed by other catalysts 7

4. Optimization of the reaction conditions 9

5. Determination of the absolute configuration of the major disastereomer 10

6. General procedure for synthesis of 3-bromo 3, 3'-disubstituted oxindoles via asymmetric *anti*-Mannich reaction 11

7. Characterization of the *anti*-Mannich reaction products 11

8. Synthesis of aziridine via the product of *anti*-Mannich reaction 17

9. References 18

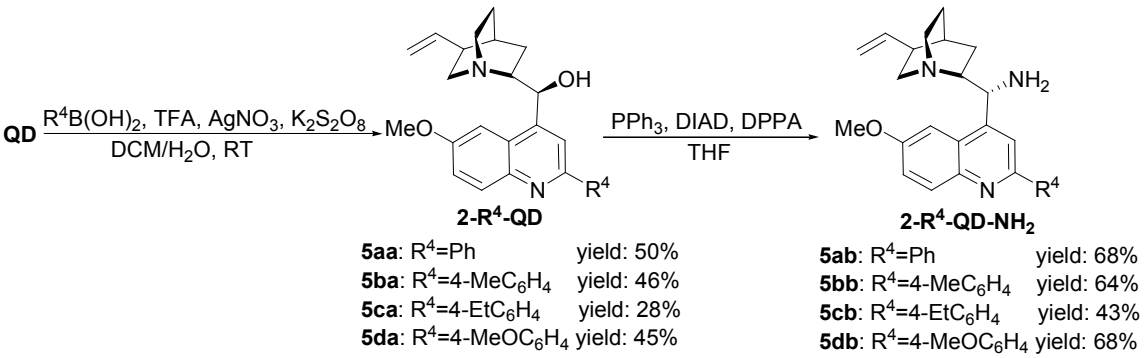
10. NMR spectra and HPLC for catalysts and *anti*-Mannich reaction products. 19

1. General methods

All solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial source were used without further purification. Petroleum ether and ethyl acetate for flash column chromatography were distilled before use. All reactions were monitored by TLC with silica gel coated plates. Flash column chromatography was performed on silica gel H (10–40 μ). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer, respectively. Chemical shifts are reported in ppm from tetramethyl silane (TMS) with the solvent resonance as the internal standard. Proton signal multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or a combination of them. *J*-values are in Hz. HRMS (Bio TOF Q) spectra were recorded on P-SIMS-Gly of Bruker Daltonics Inc. Optical rotations were measured on a Perkin Elmer 341 Polarimeter at λ = 589 nm. Analytical high performance liquid chromatography (HPLC) was carried out on WATERS 510 instrument (2487 Dual λ Absorbance Detector and 515 HPLC Pump) using chiral column, Chiralpak columns purchased from Daicel Chemical Industries, LTD.

2. Synthesis of chiral catalysts

The preparation of catalyst precursor's 2-R^4-QD-NH$_2$ [1-4]



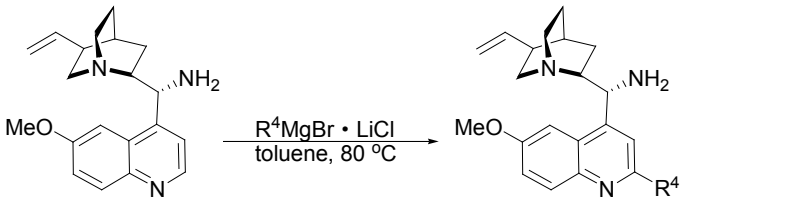
5aa: R^4=Ph yield: 50%
5ba: R^4=4-MeC$_6$H$_4$ yield: 46%
5ca: R^4=4-EtC$_6$H$_4$ yield: 28%
5da: R^4=4-MeOC$_6$H$_4$ yield: 45%

5ab: R^4=Ph yield: 68%
5bb: R^4=4-MeC$_6$H$_4$ yield: 64%
5cb: R^4=4-EtC$_6$H$_4$ yield: 43%
5db: R^4=4-MeOC$_6$H$_4$ yield: 68%

Trifluoroacetic acid (1.12 mL, 15 mmol, 3.0 equiv.) was added to the solution of **QD** (1.62 g, 5 mmol, 1.0 equiv.) in dichloromethane (25 mL), phenylboronic acid (1.22 g, 10 mmol, 2.0 equiv.) and silver (I) nitrate (170 mg, 0.1 mmol, 0.2 equiv.) in water (10 mL) were added subsequently, then potassium persulfate (2.72 g, 10 mmol, 2.0 equiv.) was added. The resulted solution was stirred vigorously at room temperature for 4 h, additional phenylboronic (0.61 mg, 0.125 mmol, 1.0 equiv.) was added, and the reaction was further stirred for 9 h, diluted with dichloromethane (40 mL) and washed with 2 M NaOH (3×30 mL). The layers were separated, and the aqueous layer was extracted with 70% $CHCl_3$, 30% isopropyl alcohol (6×30 mL), and the combined organic layers were concentrated under reduced pressure. Purification was performed by column chromatography to provide **5aa** in 50% yield.

5aa (2.5 mmol) and triphenylphosphane (0.786 g, 3 mmol, 1.2 equiv.) were dissolved in dry THF (10 mL) and the solution was cooled to 0 °C. Diisopropyl azidocarboxylate (0.62 mL, 3 mmol, 1.2 equiv.)

was added in one portion. A solution of diphenyl phosphoryl azide (0.66 mL, 3 mmol 1.2 equiv.) in dry THF (2 mL) was then added drop wise at 0 °C. The mixture was allowed to warm to room temperature. After having been stirred for 12 h, the solution was heated at 50 °C for 2h. Triphenyl phosphane (0.85 g, 3.25 mmol) was then added and heating was maintained until the gas evolution had ceased (2 h). The solution was cooled to room temperature, water (0.3 mL) was added, and the solution was stirred for 3 h. Solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2 (12 mL) and diluted hydrochloric acid (10%, 12 mL). The aqueous phase was washed with CH_2Cl_2 (3×12 mL). The aqueous phase was then alkalized with an excess of concd. aqueous ammonia and washed with CH_2Cl_2 (3×12 mL). The CH_2Cl_2 solutions were dried with Na_2SO_4 and concentrated. The concentrated organic phase was purified by column chromatography on silica gel with elution with $CHCl_3$/MeOH/aq. NH_4OH (50/1/0.1) to afford a yellow solid **5ab**. **5ab** was then directly used to the next step.



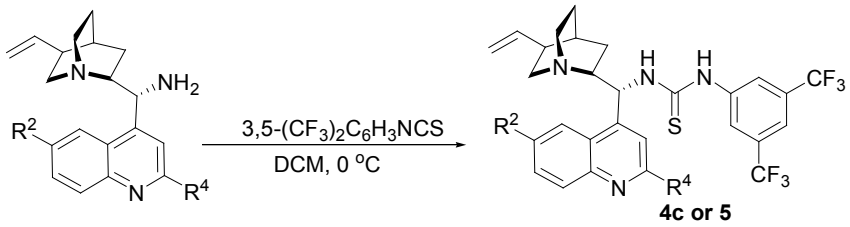
QD-NH$_2$

2-R^4-QD-NH$_2$
5eb: R^4=4-FC$_6$H$_4$ yield: 40%
5fb: R^4=4-ClC$_6$H$_4$ yield: 31%

In a 50 mL Schlenk tube flushed with argon was charged with LiCl (1.26 g, 30 mmol), magnetic stir bar and sealed with septum. Mg (1.08 g, 45 mmol) and 0.5 mL of THF were added under argon. 2 mL of a solution of aryl bromide in THF (30 mmol was dissolved in 15 mL) was added to the slurry and stirred vigorously. The formation of Grignard reagents was initiated in one minute (which was realized by the generation of heat), and then remaining aryl bromide was added slowly by maintaining the same temperature. After the addition of aryl bromide, the reaction mixture was stirred for 15 – 30 min at rt.

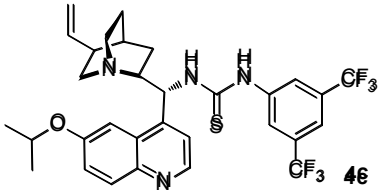
Aryl magnesium bromide (30 mmol, 0.25M in THF) was diluted with toluene and evaporated under the vacuum. After removing solvent, 10 mL of toluene was added. **QD-NH$_2$** (0.969 g, 3 mmol) was added to this solution and the mixture was heat to 80 °C for 15 h. The reaction mixture was quenched with aq. NH_4Cl and water; the organic phase was dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by column chromatography ($CHCl_3$/MeOH/aq. NH_4OH = 50/1/0.1) to provide **5eb** as a yellow solid.

General procedure for the preparation of catalysts



4c or 5

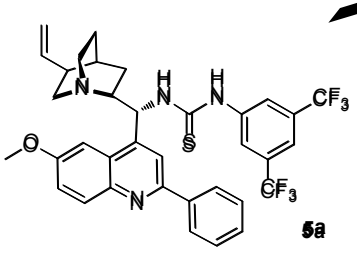
3,5-Bis(trifluoromethyl)phenyl isothiocyanate (1 mmol) in anhydrous DCM (2 mL) was added to a solution of catalyst precursors **QD-NH$_2$** of **4c** (or **5**) (1 mmol) in anhydrous DCM (5 mL) at 0 °C. TLC analysis indicated completion of the reaction. The reaction mixture was concentrated in vacuo. The residue was purified directly by column chromatography on silica gel (CH_3Cl/MeOH/cc. aq. NH_4OH = 200/1/1 as eluant) and then neutral Al_2O_3 (EA/PE = 3/1 as eluant) affording thiourea as a soild.



4c

1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-(6-isopropoxyquinolin-4-yl)((*1S, 2S, 4S, 5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (4c)

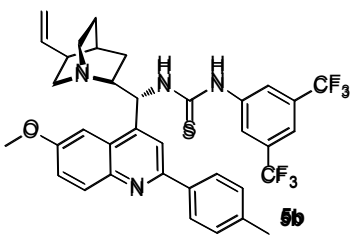
Catalyst precursor QD-NH_2 of **4c** was prepared according to literature known procedure.[1, 5] The pure product **4c** was obtained as a white solid in 94% yield. mp: 131–133 °C, $[\alpha]_D^{25}$ = +173 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 4.2 Hz, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.88 (s, 2H), 7.67 (s, 1H), 7.53 (s, 1H), 7.40 (dd, J = 9.2, 2.1 Hz, 1H), 7.37 (m, 1H), 5.83–5.78 (m, 2H), 5.17–5.11 (m, 2H), 4.76–4.72 (m, 1H), 3.04–2.93 (m, 4H), 2.38 (dd, J = 14.9, 7.8 Hz, 1H), 1.83–1.61 (m, 4H), 1.43 (d, J = 5.9 Hz, 6H), 1.22 (d, J = 5.5 Hz, 1H), 1.04 (dd, J = 17.6, 8.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 156.4, 147.1, 146.7, 144.4, 140.2, 139.7, 132.4 (q, J = 33.8 Hz), 131.5, 128.1, 123.5, 123.0 (q, J = 273.0 Hz), 122.6, 120.1, 118.6, 115.2, 104.0, 70.4, 61.4, 48.6, 47.2, 38.8, 27.2, 25.1, 25.1, 22.1, 21.8. HRMS [EI-(+H)] calcd for $C_{31}H_{33}F_6N_4OS$ 623.2274, found 623.2266.



5a

1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-(6-methoxy-2-phenylquinolin-4-yl)((*1S, 2S, 4S, 5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (5a).

The pure product **5a** was obtained as a yellow solid in 88% yield. mp: 124–126 °C, $[\alpha]_D^{25}$ = +98 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15–8.02 (m, 3H), 7.83 (s, 3H), 7.63 (s, 1H), 7.42 (t, J = 8.6 Hz, 4H), 7.26 (s, 1H), 5.87 (s, 2H), 5.22–5.15 (m, 2H), 3.96 (s, 3H), 3.36–2.93 (m, 5H), 2.38 (d, J = 6.1 Hz, 1H), 1.65 (d, J = 32.6 Hz, 3H), 1.31–1.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 158.1, 154.8, 145.0, 143.9, 142.1, 140.3, 139.2, 135.9, 132.3 (q, J = 33.0 Hz), 132.2, 129.2, 128.8, 127.2, 126.5, 123.4, 123.0 (q，J = 271.0 Hz), 122.4, 118.6, 115.6, 101.7, 60.4, 55.7, 48.6, 46.9, 38.6, 27.1, 25.8, 25.0, 21.0. HRMS [EI-(+H)] calcd for $C_{35}H_{33}F_6N_4OS$ 671.2274, found 671.2297.

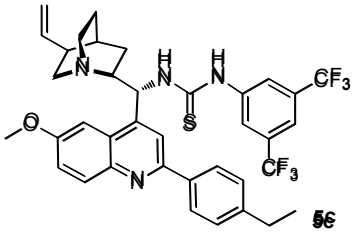


5b

1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-(6-methoxy-2-(*p*-tolyl)quinolin-4-yl)((*1S, 2S, 4S, 5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (5b).

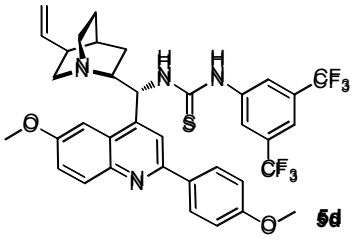
The pure product **5b** was obtained as a yellow solid in 85% yield. mp: 139–140 °C, $[\alpha]_D^{25}$ = +82 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J =

9.2 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.85 (s, 2H), 7.77 (s, 1H), 7.62 (s, 1H), 7.39 (dd, *J* = 9.2, 1.9 Hz, 1H), 7.24 (d, *J* = 6.4 Hz, 3H), 5.86 (s, 2H), 5.22–5.15 (m, 2H), 3.96 (s, 3H), 3.29 (d, *J* = 60.3 Hz, 2H), 2.97 (dd, *J* = 24.5, 10.4 Hz, 3H), 2.39 (s, 3H), 1.70–1.58 (m, 3H), 1.26 (s, 2H), 1.08 (t, *J* = 11.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 158.0, 154.8, 145.0, 143.8, 142.0, 140.2, 139.3, 139.1, 136.4, 132.2 (q, *J* = 33.5 Hz), 132.1, 129.5, 127.1, 126.5, 123.4, 123.0 (q, *J* = 272.8 Hz), 122.3, 118.5, 115.7, 101.7, 61.7, 55.7, 48.6, 46.9, 38.5, 27.1, 25.7, 25.0, 24.3, 21.3. HRMS [EI-(+H)] calcd for $C_{36}H_{35}F_6N_4OS$ 685.2430, found 685.2455.



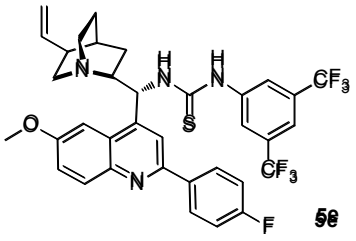
1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-(2-(4-ethylphenyl)-6-methoxyquinolin-4-yl)((*1S, 2S, 4S, 5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (5c).

The pure product **5c** was obtained as a yellow solid in 79% yield. mp: 112–114 °C, $[\alpha]_D^{25}$ = +68 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16–8.03 (m, 1H), 7.96 (t, *J* = 10.2 Hz, 2H), 7.80 (d, *J* = 19.3 Hz, 3H), 7.62 (s, 2H), 7.39 (d, *J* = 9.1 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 3H), 5.86 (s, 2H), 5.21–5.14 (m, 2H), 3.96 (s, 3H), 3.27 (dd, *J* = 48.9, 7.5 Hz, 2H), 2.96 (dd, *J* = 25.0, 11.1 Hz, 3H), 2.69 (dd, *J* = 14.9, 7.4 Hz, 2H), 2.36 (d, *J* = 6.6 Hz, 1H), 1.68 (s, 1H), 1.57 (s, 1H), 1.33–1.23 (m, 5H), 0.97 (dd, *J* = 61.8, 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.6, 158.0, 154.8, 145.7, 145.0, 144.1, 142.0, 140.3, 139.3, 136.7, 132.3 (q, *J* = 33.8 Hz), 132.2, 128.4, 127.3, 127.2, 123.4, 123.0 (q, *J* = 273.0 Hz), 122.3, 118.5, 115.6, 101.7, 61.8, 55.7, 48.6, 45.0, 38.6, 29.7, 28.7, 27.2, 25.8, 25.0, 15.5. HRMS [EI-(+H)] calcd for $C_{37}H_{37}F_6N_4OS$ 699.2587, found 699.2583.



1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-(6-methoxy-2-(4-methoxyphenyl)quinolin-4-yl)((*1S, 2S, 4S, 5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (5d).

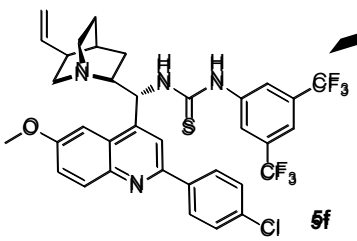
The pure product **5d** was obtained as a yellow solid in 86% yield. mp: 133–135 °C, $[\alpha]_D^{25}$ = +73 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.2 Hz, 1H), 7.96 (d, *J* = 7.0 Hz, 2H), 7.82 (s, 2H), 7.68 (d, *J* = 36.6 Hz, 3H), 7.37 (d, *J* = 9.0 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 2H), 5.87 (s, 2H), 5.22–5.15 (m, 2H), 3.95 (s, 3H), 3.83 (s, 3H), 3.28 (d, *J* = 46.3 Hz, 2H), 2.95 (dd, *J* = 25.0, 11.5 Hz, 3H), 2.36 (d, *J* = 6.2 Hz, 1H), 1.63 (d, *J* = 35.7 Hz, 3H), 1.25 (dd, *J* = 8.5, 5.7 Hz, 1H), 1.06 (t, *J* = 9.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 160.7, 157.8, 154.4, 146.9, 144.9, 144.1, 142.2, 140.4, 139.3, 132.2 (q, *J* = 34.2 Hz), 131.7, 128.5, 126.5, 123.5, 123.0 (q, *J* = 272.9 Hz), 122.4, 118.5, 115.6, 114.2, 101.8, 61.6, 55.6, 55.4, 48.6, 46.9, 38.5, 27.1, 25.8, 25.0, 24.5. HRMS [EI-(+H)] calcd for $C_{36}H_{35}F_6N_4O_2S$ 701.2379, found 701.2382.



1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-(2-(4-fluorophenyl)-6-methoxyquinolin-4-yl)((*1S, 2S, 4S, 5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (5e).

The pure product **5e** was obtained as a yellow solid in 83% yield. mp: 106–107 °C, $[\alpha]_D^{25}$ = +98 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–8.02 (m, 3H), 7.80–7.46 (m, 5H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.13 (d, *J* = 7.1 Hz, 2H), 5.87 (s, 2H), 5.17 (s, 2H), 3.95 (s, 3H), 3.38–2.78 (m, 4H), 2.38 (d, *J* = 5.6 Hz, 1H), 1.66 (d, *J* = 27.2 Hz, 3H), 1.26 (s, 2H), 1.08 (d,

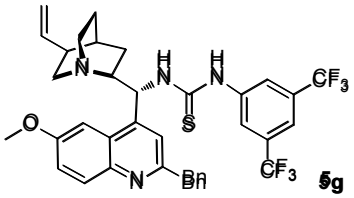
J = 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 163.6 (d, J = 248.9 Hz), 158.1, 153.6, 144.9, 143.8, 142.1, 140.0, 139.4, 135.3, 132.4 (q, J = 34.3 Hz), 129.0, 128.9, 126.6, 123.4, 122.9 (q, J = 272.9 Hz), 122.5, 118.7, 115.8, 115.6, 101.6, 61.7, 55.6, 48.5, 46.9, 38.6, 29.7, 27.2, 25.9, 25.0. HRMS [EI-(+H)] calcd for $C_{35}H_{32}F_7N_4OS$ 689.2180, found 689.2183.



5f

1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-(2-(4-chlorophenyl)-6-methoxyquinolin-4-yl)((*1S, 2S, 4S, 5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (5f)

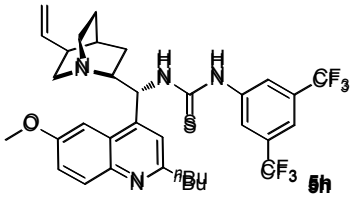
The pure product **5f** was obtained as a yellow solid in 71% yield. mp: 112–113 °C, $[\alpha]_D^{25}$ = +68 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14–8.05 (m, 1H), 7.90 (d, J = 46.4 Hz, 3H), 7.65 (t, J = 24.9 Hz, 3H), 7.33 (dt, J = 27.9, 13.7 Hz, 4H), 5.84–5.86 (m, 2H), 5.23–5.16 (m, 2H), 3.94 (d, J = 15.7 Hz, 3H), 3.14–2.96 (m, 4H), 2.33 (dd, J = 40.7, 5.0 Hz, 1H), 1.26 (s, 3H), 1.06 (s, 2H), 0.87 (d, J = 7.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.4, 158.2, 157.8, 153.2, 144.9, 143.8, 142.1, 140.0, 139.2, 137.5, 135.3, 132.4 (q, J =33.9 Hz), 128.9, 128.4, 126.6, 123.3, 123.0 (q, J = 550.0, 277.1 Hz), 118.6, 116.9, 115.6, 101.6, 61.8, 55.6, 48.6, 46.9, 38.5, 29.7, 27.1, 25.8, 25.0. HRMS [EI-(+H)] calcd for $C_{35}H_{32}ClF_6N_4OS$ 705.1884, found 705.1897.



5g

1-((*R*)-(2-benzyl-6-methoxyquinolin-4-yl)((*1S, 2S, 4S, 5R*)-5-vinylquinuclidin-2-yl)methyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (5g).[4]

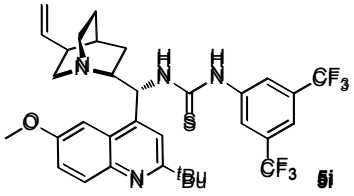
The pure product **5g** was obtained as a yellow solid in 90% yield. mp: 111–113 °C, $[\alpha]_D^{25}$ = +100 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 9.1 Hz, 1H), 7.76 (s, 2H), 7.62 (s, 2H), 7.39 (d, J = 9.1 Hz, 1H), 7.10 (s, 6H), 5.80 (s, 2H), 5.11 (d, J = 5.0 Hz, 2H), 4.20 (s, 2H), 3.95 (s, 3H), 2.96 (dd, J = 36.9, 26.9 Hz, 5H), 2.32 (d, J = 6.8 Hz, 1H), 1.60 (d, J = 24.7 Hz, 3H), 1.26–1.16 (m, 1H), 0.95–0.88 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 158.3, 157.9, 151.7, 144.5, 144.0, 141.9, 140.1, 139.2, 132.2 (q, J = 32.7 Hz), 131.4, 129.0, 128.9, 128.6, 126.4, 123.4, 123.0 (q, J = 270.2 Hz), 122.1, 118.4, 115.5, 102.0, 61.5, 55.7, 48.4, 46.9, 44.8, 38.6, 27.2, 25.8, 24.9, 24.3. HRMS [EI-(+H)] calcd for $C_{36}H_{35}F_6N_4OS$ 685.2430, found 685.2439.



5h

1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-(2-butyl-6-methoxyquinolin-4-yl)((*1S, 2S, 4S, 5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (5h).[4]

The pure product **5h** was obtained as a yellow solid in 91% yield. mp: 104–105 °C, $[\alpha]_D^{25}$ = +104 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–8.02 (m, 3H), 7.74 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 17.6 Hz, 2H), 5.96 (s, 2H), 5.33–5.27 (m, 2H), 4.06 (s, 3H), 3.17–2.96 (m, 7H), 2.52 (d, J = 5.9 Hz, 1H), 1.82 (d, J = 8.8 Hz, 5H), 1.53–1.37 (m, 3H), 1.21–1.14 (m, 1H), 1.03 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 160.2, 157.7, 144.6, 140.5, 138.8, 132.2 (q, J = 33.7 Hz), 131.3, 129.1, 126.1, 126.0, 123.2, 123.0 (q, J = 272.9 Hz), 121.9, 118.4, 115.8, 101.9, 61.7, 55.6, 48.5, 46.8, 38.6, 38.4, 32.1, 27.1, 25.6, 24.9, 24.1, 22.7, 13.9. HRMS [EI-(+H)] calcd for $C_{33}H_{37}F_6N_4OS$ 651.2587, found 651.2591.



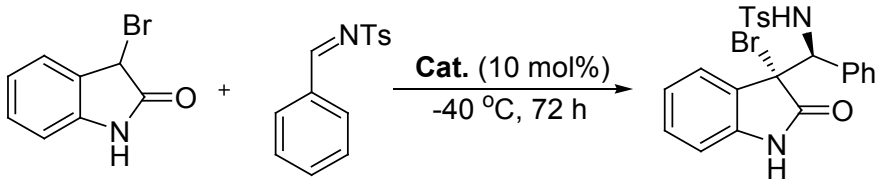
5i

1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-(2-(tert-butyl)-6-methoxyquinolin-4-yl)

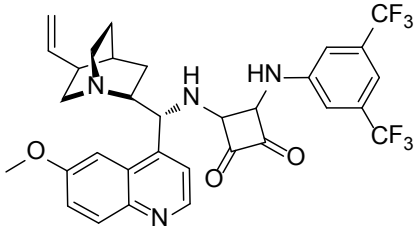
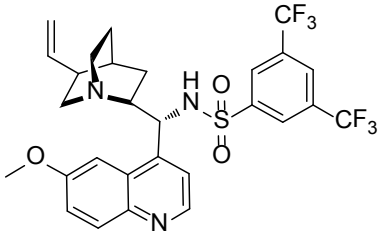
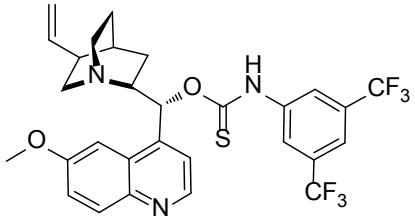
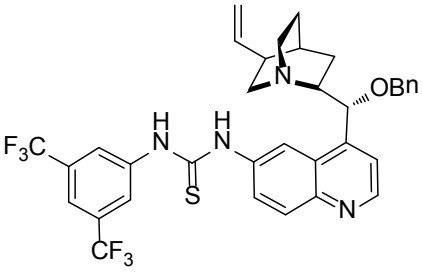
((*1S, 2S, 4S, 5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (5i).[4]

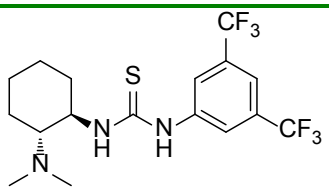
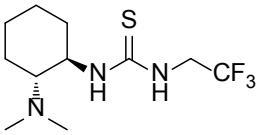
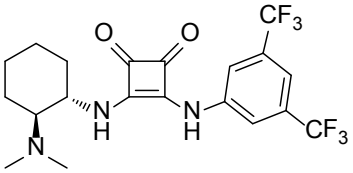
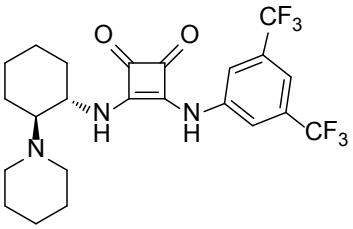
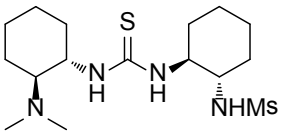
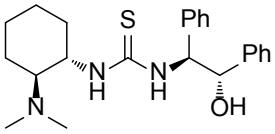
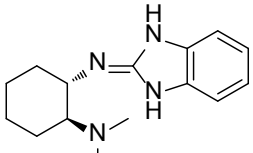
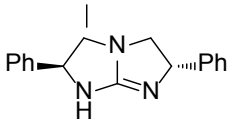
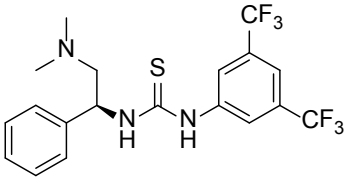
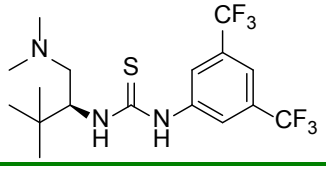
The pure product **5i** was obtained as a yellow solid in 88% yield. mp: 115–116 °C, $[\alpha]_D^{25}$ = +84 (c = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.02–7.90 (m, 3H), 7.63 (s, 1H), 7.39 (d, J = 21.2 Hz, 3H), 5.78 (s, 2H), 5.10 (d, J = 8.8 Hz, 2H), 3.92 (s, 3H), 3.42–2.97 (m, 5H), 2.36 (s, 1H), 1.68 (s, 3H), 1.43 (s, 9H), 1.26 (t, J = 7.0 Hz, 1H), 1.06 (d, J = 6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.8, 171.2, 166.5, 157.8, 157.2, 144.2, 140.8, 140.0, 135.2, 132.1 (q, J = 49.7 Hz), 125.7, 123.4, 123.1 (q, J = 272.7 Hz), 121.5, 118.3, 115.5, 101.6, 61.8, 60.4, 55.7, 48.5, 38.6, 37.9, 30.2, 27.2, 25.8, 21.0, 14.2. HRMS [EI-(+H)] calcd for $C_{33}H_{37}F_6N_4OS$ 651.2587, found 651.2584.

3. Asymmetric Mannich reaction of 3-bromooxindole with *N*-Ts-imine catalyzed by other catalysts.[a]



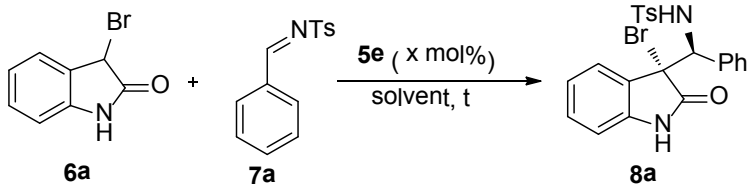
6a **7a** **8a**

Entry	Cat.	Yield(%)[b]	Dr[c]	Ee(%)[c]
1		Trace	-	-
2		NR	-	-
3		NR	-	-
4		21	89：11	43

5		55	89：11	56
6		49	88：12	51
7		42	91：9	-44
8		59	78：22	-48
9		25	84：16	-58
10		23	92：8	-10
11		66	74：26	-27
12		70	70：30	0/66
13		55	99:1	-80
14		25	99:1	-83

[a] Reaction conditions: **6a** (0.1 mmol), **7a** (0.12 mmol), **cat.** (0.01mmol), *c* = 0.20 M, -40 °C, 72 h. [b] Yield of the isolated product after purification by column chromatography on silica gel. [c] Determined by HPLC analysis on a chiral stationary phase.

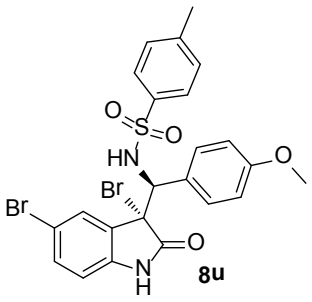
4. Optimization of the reaction conditions [a]



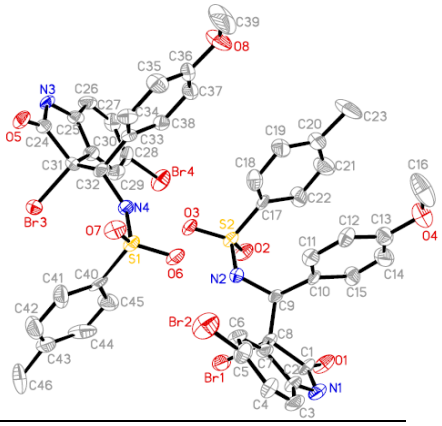
Entry	Solvent	x (mol%)	T/°C	*c*/mol/L	t (h)	Yield (%)[b]	Dr[c]	Ee (%)[c]
1	DCM	10	-40	0.20	72	76	96:4	94
2	$CHCl_3$	10	-40	0.20	72	68	96:4	92
3	C_2H_5Br	10	-40	0.20	72	70	98:2	89
4	$(CHCl_2)_2$	10	-40	0.20	72	45	94:6	90
5	toluene	10	-40	0.20	72	55	96:4	70
6	EA	10	-40	0.20	72	83	95:5	65
7	hexane	10	-40	0.20	72	Trace	-	-
8	Et_2O	10	-40	0.20	72	Trace	-	-
9	THF	10	-40	0.20	72	NR	-	-
10	CH_3CN	10	-40	0.20	72	NR	-	-
11	DMF	10	-40	0.20	72	NR	-	-
11	^{i}PrOH	10	-40	0.20	72	NR	-	-
12	DCM	5	-40	0.20	72	51	96:4	94
13	DCM	15	-40	0.20	72	76	96:4	94
14	DCM	10	-40	0.20	24	53	96:4	94
15	DCM	10	-40	0.20	48	66	96:4	94
16	DCM	10	-40	0.20	96	76	96:4	94
17	DCM	10	-40	0.20	120	74	96:4	94
18	DCM	10	-30	0.20	72	68	94:6	94
19	DCM	10	-50	0.20	72	66	97:3	94
20	DCM	10	-40	0.15	72	69	95:5	92
21	DCM	10	-40	0.25	72	70	96:4	94
22[d]	DCM	10	-40	0.20	72	62	96:4	94
23[e]	DCM	10	-40	0.20	72	87	96:4	94
24[f]	DCM	10	-40	0.20	72	91	96:4	94
25[g]	DCM	10	-40	0.20	72	89	96:4	94

[a] Reaction conditions: **6a** (0.1 mmol), **7a** (0.12 mmol). [b] Yield of the isolated product after purification by column chromatography on silica gel. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 4 Å molecular sieves (50 mg) were added. [e] **7a** (0.14 mmol). [f] **7a** (0.15 mmol). [g] **7a** (0.16 mmol).

5. Determination of the absolute configuration of the major diastereomer:

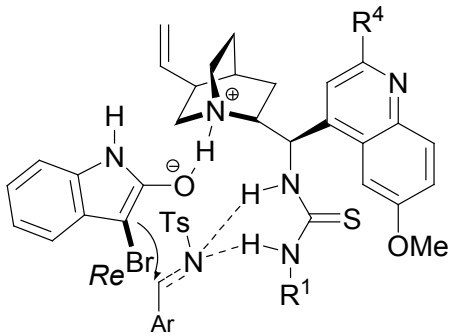


N-((*S*)-((*R*)-3,5-dibromo-2-oxoindolin-3-yl)(4-methoxyphenyl)methyl)-4-methylbenzenesulfonamide



Empirical formula	$C_{48}H_{42}Br_4N_4O_{10}S_2$
Formula weight	1218.62
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1$
a, Å	10.6545(13)
b, Å	20.649(3)
c, Å	13.3304(16)
α, °	90
β, °	99.311(2)
γ, °	90
V, Å^3	2894.1(6)
Z, Calculated density	2, 1.398 Mg/m^3
μ (mm^{-1})	2.906
F(000)	1220
GOF	1.081
R_1[a] [$I > 2\sigma(I)$]	0.0823
wR_2[b] [$I > 2\sigma(I)$]	0.2286
R_1 (all data)	0.1212
wR_2 (all data)	0.2875
Flack parameter	0.022(17)

[a] $R_1 = \sum||F_0|-|F_C||/\sum|F_0|$; [b] $wR_2 = |\sum w(|F_0|^2-|F_C|^2)^2|/\sum|w(F_0^2)^2|^{1/2}$

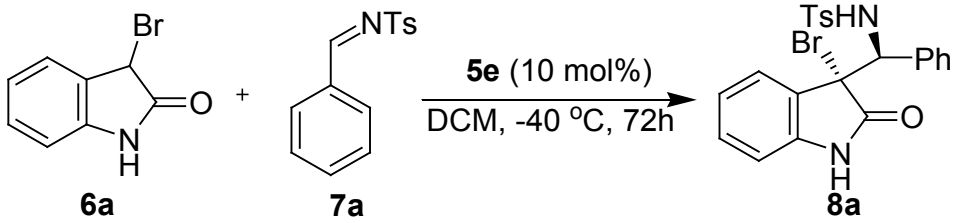


Ar = 4-MeOC$_6$H$_4$; R^1 = 3,5-(CF$_3$)$_2$C$_6$H$_3$; R^4 = 4-FC$_6$H$_4$

Proposed transition state model.

To account for the stereochemical outcome, a transition state model was proposed. The two reactive partners were activated concurrently by the catalyst and the nucleophilic attack from both the *Re*-faces of the enolate anion and the *N*-Ts-imine afford the observed products. Other product configurations were deduced based on analogy.

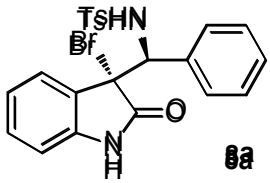
6. General procedure for synthesis of 3-bromo 3, 3'-disubstituted oxindoles via asymmetric *anti*-Mannich reaction



6a 7a 8a

3-bromooxindole **6a** (0.1 mmol, 1 equiv.) was dissolved in anhydrous DCM (0.5 mL), subsequently catalyst **5e** (0.01 mmol, 0.1 equiv.) and *N*-Ts-imine **7a** (0.15 mmol, 1.5 equiv.) were added at -40 °C. After being stirred 72 h, the reaction mixture was purified directly by flash chromatography on silica gel. (AcOEt/PE = 1:3) to give the corresponding product.

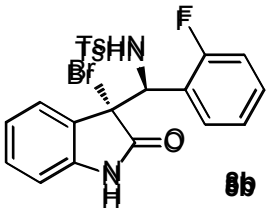
7. Characterization of the *anti*-Mannich reaction products



8a

***N*-((*S*)-((*R*)-3-bromo-2-oxoindolin-3-yl)(phenyl)methyl)-4-methylbenzenesulfonamide (8a)**

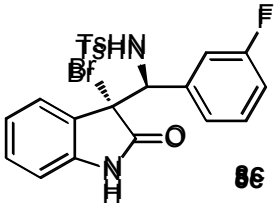
The title compound was isolated as yellow solid in 91% yield, mp: 109–111 °C, $[\alpha]_D^{25}$ = +122 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.75 (d, J = 7.4 Hz, 1H), 7.49 (d, J = 8.2 Hz, 2H), 7.24–7.17 (m, 2H), 7.02 (dd, J = 13.3, 7.7 Hz, 3H), 6.87 (t, J = 7.6 Hz, 2H), 6.76–6.68 (m, 4H), 4.88 (d, J = 7.6 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 143.4, 139.6, 136.2, 133.6, 130.8, 129.3, 128.7, 128.3, 127.7, 127.4, 127.2, 127.0, 123.8, 110.5, 63.8, 58.7, 21.4. HRMS [EI-(+Na)] calcd for $C_{22}H_{19}BrN_2NaO_3S$ 493.0192, found 493.0203. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (70/30 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 32.9 min, t_{minor} = 38.5 min).



8b

***N*-((*S*)-((*R*)-3-bromo-2-oxoindolin-3-yl)(2-fluorophenyl)methyl)-4-methylbenzenesulfonamide (8b)**

The title compound was isolated as yellow solid in 94% yield. mp: 92–94 °C, $[\alpha]_D^{25}$ = +76 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.48 (q, J = 7.9 Hz, 4H), 7.30–7.28 (m, 1H), 7.16–7.08 (m, 3H), 6.95 (dd, J = 14.6, 7.9 Hz, 3H), 6.80 (d, J = 7.8 Hz, 1H), 6.72–6.66 (m, 1H), 5.38 (d, J = 9.0 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 159.9 (d, J = 247.9 Hz), 143.5, 139.6, 135.8, 130.8, 130.2, 130.1, 129.3, 128.4, 127.1, 126.1, 124.0, 123.9, 123.8, 114.8 (d, J = 22.8 Hz), 110.8, 57.3, 55.4, 21.4. HRMS [EI-(+Na)] calcd for $C_{22}H_{18}BrFN_2NaO_3S$ 511.0098, found 511.0105. The *ee* and *dr* were determined by a chiral phase Chiralpak AD-H column (76/24 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 35.8 min, t_{minor} = 28.1 min).

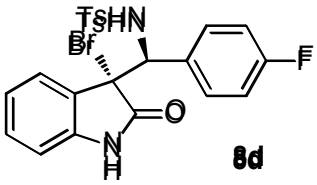


8c

***N*-((*S*)-((*R*)-3-bromo-2-oxoindolin-3-yl)(3-fluorophenyl)methyl)-4-methylbenzenesulfonamide (8c)**

The title compound was isolated as yellow solid in 99% yield, mp: 160–162 °C, $[\alpha]_D^{25}$ =

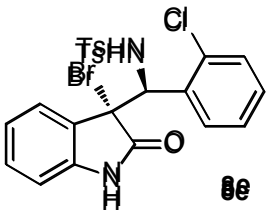
+92 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.68 (d, J = 7.3 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 7.1 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.04 (d, J = 8.2 Hz, 2H), 6.91–6.86 (m, 1H), 6.76 (dd, J = 16.6, 7.7 Hz, 3H), 6.63 (d, J = 7.8 Hz, 1H), 6.50 (d, J = 9.4 Hz, 1H), 4.87 (d, J = 7.5 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 161.7 (d, J = 246.8 Hz), 143.8, 139.5, 136.3, 136.2, 136.0, 131.0, 129.4, 127.4, 127.1, 126.8, 124.4, 123.9, 116.0 (d, J = 23.1 Hz), 115.4 (d, J = 20.8 Hz), 110.7, 63.2, 58.1, 21.4. HRMS [EI-(+Na)] calcd for $C_{22}H_{18}BrFN_2NaO_3S$ 511.0098, found 511.0111. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (60/40 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 15.6 min, t_{minor} = 29.7 min).



8d

_N_-((_S_)-((_R_)-3-bromo-2-oxoindolin-3-yl)(4-fluorophenyl)methyl)-4-methylbenzenesulfonamide (8d)

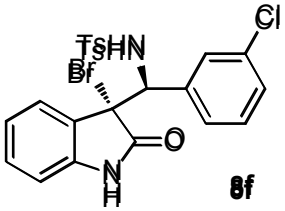
The title compound was isolated as yellow solid in 96% yield, mp: 169–171 °C, $[\alpha]_D^{25}$ = +109 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.76 (d, J = 7.0 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 7.01 (d, J = 8.1 Hz, 2H), 6.80 (d, J = 7.6 Hz, 1H), 6.73–6.68 (m, 3H), 6.54 (t, J = 8.6 Hz, 2H), 4.85 (d, J = 7.6 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 162.4 (d, J = 248.5 Hz), 143.7, 139.6, 136.2, 131.0, 130.6, 130.5, 129.4, 127.4, 127.0, 126.95, 123.9, 114.7 (d, J = 21.6 Hz), 110.7, 63.1, 58.5 (d, J = 1.2 Hz), 21.4. HRMS [EI-(+Na)] calcd for $C_{22}H_{18}BrFN_2NaO_3S$ 511.0098, found 511.0108. The *ee* and *dr* were determined by a chiral phase Chiralpak AD-H column (76/24 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 21.0 min, t_{minor} = 26.4 min).



8e

_N_-((_S_)-((_R_)-3-bromo-2-oxoindolin-3-yl)(2-chlorophenyl)methyl)-4-methylbenzenesulfonamide (8e)

The title compound was isolated as yellow solid in 84% yield, mp: 174–1176 °C, $[\alpha]_D^{25}$ = +104 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.23–7.22 (m, 1H), 7.15 (t, J = 5.4 Hz, 3H), 6.98 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 7.6 Hz, 1H), 5.77 (d, J = 8.9 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 143.4, 139.6, 135.6, 135.1, 134.4, 130.7, 130.4, 129.4, 129.4, 129.2, 128.7, 127.2, 126.8, 125.7, 123.8, 111.0, 57.5, 56.9, 21.4. HRMS [EI-(+Na)] calcd for $C_{22}H_{18}BrClN_2NaO_3S$ 526.9802, found 526.9809. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (70/30 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 56.1 min, t_{minor} = 43.5 min).

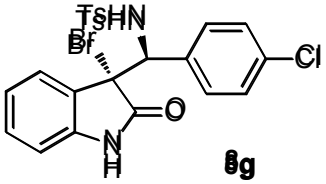


8f

_N_-((_S_)-((_R_)-3-bromo-2-oxoindolin-3-yl)(3-chlorophenyl)methyl)-4-methylbenzenesulfonamide (8f)

The title compound was isolated as yellow solid in 99% yield, mp: 192–193 °C, $[\alpha]_D^{25}$ = +116 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 7.9 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 7.7 Hz, 3H), 6.87 (t, J = 7.8 Hz, 1H), 6.77–6.66 (m, 4H), 4.82 (d, J = 7.4 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$)

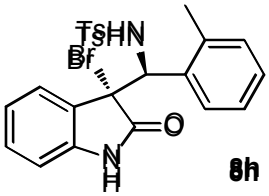
δ 174.2, 143.9, 139.5, 135.9, 135.6, 133.5, 131.1, 129.8, 129.4, 129.1, 128.5, 127.3, 127.0, 126.9, 126.6, 123.9, 110.8, 63.2, 58.0, 21.5. HRMS [EI-(+Na)] calcd for $C_{22}H_{18}BrClN_2NaO_3S$ 526.9802, found 526.9806. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (60/40 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 15.5 min, t_{minor} = 28.1 min).



8g

_N_-((_S_)-((_R_)-3-bromo-2-oxoindolin-3-yl)(4-chlorophenyl)methyl)-4-methylbenzenesulfonamide (8g)

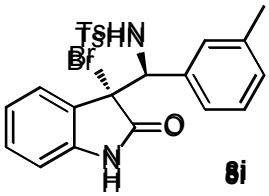
The title compound was isolated as yellow solid in 94% yield, mp: 117–119 °C, $[\alpha]_D^{25}$ = +145 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.76 (d, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.29 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.84 (t, *J* = 9.2 Hz, 3H), 6.71 (t, *J* = 8.8 Hz, 3H), 4.85 (d, *J* = 7.6 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 143.9, 139.5, 136.0, 134.4, 132.1, 131.0, 130.1, 129.4, 127.9, 127.4, 127.0, 126.9, 126.4, 124.0, 110.8, 63.2, 58.3, 21.5. HRMS [EI-(+Na)] calcd for $C_{22}H_{18}BrClN_2NaO_3S$ 526.9802, found 526.9811. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (60/40 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 18.3 min, t_{minor} = 30.1 min).



8h

_N_-((_S_)-((_R_)-3-bromo-2-oxoindolin-3-yl)(o-tolyl)methyl)-4-methylbenzenesulfonamide (8h)

The title compound was isolated as yellow solid in 89% yield, mp: 166–168 °C, $[\alpha]_D^{25}$ = +100 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 6.5 Hz, 3H), 6.86 (dd, *J* = 12.4, 7.7 Hz, 2H), 6.78 (dd, *J* = 6.9, 4.3 Hz, 2H), 6.64 (d, *J* = 7.1 Hz, 1H), 5.22 (d, *J* = 7.2 Hz, 1H), 2.28 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 143.2, 139.7, 137.2, 136.7, 133.1, 130.8, 130.0, 129.1, 128.4, 127.5, 127.1, 126.8, 126.4, 125.7, 123.7, 110.7, 58.7, 57.6, 21.5, 19.9. HRMS [EI-(+Na)] calcd for $C_{23}H_{21}BrN_2NaO_3S$ 507.0348, found 507.0348. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (60/40 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 22.7 min, t_{minor} = 26.0 min).

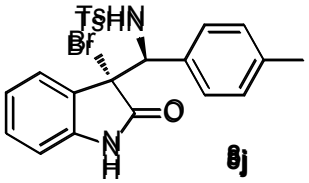


8i

_N_-((_S_)-((_R_)-3-bromo-2-oxoindolin-3-yl)(m-tolyl)methyl)-4-methylbenzenesulfonamide (8i)

The title compound was isolated as yellow solid in 99% yield, mp: 187–188 °C, $[\alpha]_D^{25}$ = +104 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.74–7.70 (m, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.24–7.16 (m, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.78 (dt, *J* = 15.2, 7.5 Hz, 2H), 6.69 (d, *J* = 7.4 Hz, 1H), 6.54 (dd, *J* = 18.4, 7.4 Hz, 2H), 6.44 (s, 1H), 4.82 (d, *J* = 7.6 Hz, 1H), 2.28 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 143.3, 139.6, 137.2, 136.4, 133.4, 130.8, 130.0, 129.7, 129.1, 129.0, 127.7, 127.4, 127.0, 125.4, 123.7, 110.5, 63.8, 58.6, 21.4, 21.0. HRMS [EI-(+Na)] calcd for $C_{23}H_{21}BrN_2NaO_3S$ 507.0348, found 507.0342. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (60/40 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254

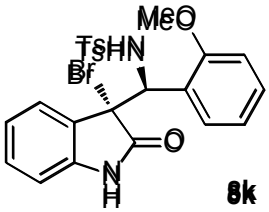
nm, t_{major} = 20.4 min, t_{minor} = 40.4 min).



8j

***N*-((*S*)-((*R*)-3-bromo-2-oxoindolin-3-yl)(p-tolyl)methyl)-4-methylbenzenesulfonamide (8j)**

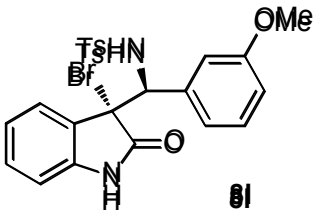
The title compound was isolated as yellow solid in 87% yield, mp: 106–107 °C, $[\alpha]_D^{25}$ = +92 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.68 (d, J = 7.4 Hz, 1H), 7.49 (d, J = 8.2 Hz, 2H), 7.28–7.24 (m, 1H), 7.17 (t, J = 7.3 Hz, 1H), 7.02 (d, J = 8.1 Hz, 2H), 6.72–6.63 (m, 5H), 6.50 (d, J = 7.1 Hz, 1H), 4.82 (d, J = 7.1 Hz, 1H), 2.30 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 143.4, 139.6, 138.2, 136.2, 130.8, 130.5, 129.2, 128.7, 128.6, 128.4, 127.5, 127.0, 123.7, 110.5, 63.5, 58.6, 21.4, 21.1. HRMS [EI-(+Na)] calcd for $C_{23}H_{21}BrN_2NaO_3S$ 507.0348, found 507.0349. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (60/40 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 25.4 min, t_{minor} = 40.8 min).



8k

***N*-((*S*)-((*R*)-3-bromo-2-oxoindolin-3-yl)(2-methoxyphenyl)methyl)-4-methylbenzenesulfonamide (8k)**

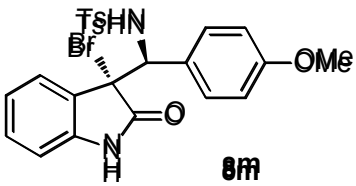
The title compound was isolated as yellow solid in 90% yield, mp: 162–164 °C, $[\alpha]_D^{25}$ = +68 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.49 (d, J = 8.2 Hz, 3H), 7.21 (t, J = 7.6 Hz, 1H), 7.12–7.02 (m, 3H), 6.96 (d, J = 8.1 Hz, 2H), 6.79–6.62 (m, 3H), 6.41 (d, J = 7.9 Hz, 1H), 5.26 (s, 1H), 3.28 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 156.5, 143.0, 139.4, 136.8, 131.5, 130.1, 129.6, 129.0, 128.9, 127.2, 123.7, 122.9, 120.4, 111.5, 110.4, 110.1, 58.8, 54.8, 21.4. HRMS [EI-(+Na)] calcd for $C_{23}H_{21}BrN_2NaO_4S$ 523.0298, found 523.0292. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (60/40 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 49.9 min, t_{minor} = 37.4 min).



8l

***N*-((*S*)-((*R*)-3-bromo-2-oxoindolin-3-yl)(3-methoxyphenyl)methyl)-4-methylbenzenesulfonamide (8l)**

The title compound was isolated as yellow solid in 99% yield, mp: 106–107 °C, $[\alpha]_D^{25}$ = +87 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.02–7.99 (m, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.31–7.28 (m, 2H), 6.97 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.71 (dd, J = 13.0, 5.5 Hz, 2H), 6.52 (dd, J = 8.0, 1.8 Hz, 1H), 6.25 (d, J = 7.6 Hz, 1H), 6.11 (s, 1H), 4.87 (d, J = 8.3 Hz, 1H), 3.33 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 158.6, 143.5, 139.7, 136.2, 134.7, 130.8, 129.2, 128.6, 127.37, 127.35, 127.2, 124.0, 121.2, 115.4, 112.0, 110.5, 63.9, 58.6, 54.8, 21.4. HRMS [EI-(+Na)] calcd for $C_{23}H_{21}BrN_2NaO_4S$ 523.0298, found 523.0315. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (60/40 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 19.9 min, t_{minor} = 49.5 min).

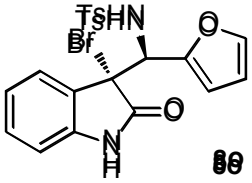


8m

***N*-((*S*)-((*R*)-3-bromo-2-oxoindolin-3-yl)(4-methoxyphenyl)methyl)-4-methylbenzenesulfonamide (8m)**

The title compound was isolated as yellow solid in 88% yield, mp: 107–109 °C, $[\alpha]_D^{25}$ = +86 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.62 (d, J

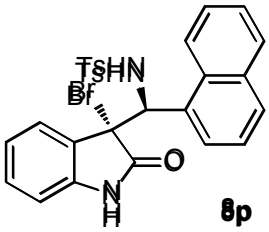
= 7.4 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 12.0 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.68 (t, *J* = 10.3 Hz, 3H), 6.38 (dd, *J* = 20.0, 7.6 Hz, 3H), 4.77 (d, *J* = 6.5 Hz, 1H), 3.63 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 159.5, 143.4, 139.5, 136.2, 130.8, 130.1, 129.3, 127.5, 127.3, 127.0, 125.4, 123.7, 113.1, 110.5, 63.2, 58.6, 55.1, 21.5. HRMS [EI-(+Na)] calcd for $C_{23}H_{21}BrN_2NaO_4S$ 523.0298, found 523.0307. The *ee* and *dr* were determined by a chiral phase Chiralpak AD-H column (76/24 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 25.1 min, t_{minor} = 28.5 min).



8o

***N*-((*S*)-((*R*)-3-bromo-2-oxoindolin-3-yl)(furan-2-yl)methyl)-4-methylbenzenesulfonamide (8o)**

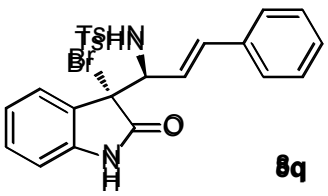
The title compound was isolated as yellow solid in 99% yield, mp: 79–82 °C, $[\alpha]_D^{25}$ = +51 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.61–7.49 (m, 3H), 7.24–7.20 (m, 1H), 7.14–7.11 (m, 3H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 9.0 Hz, 1H), 6.03 (s, 2H), 5.09 (d, *J* = 9.0 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 147.7, 143.5, 142.2, 139.6, 136.4, 130.8, 129.4, 127.9, 127.2, 126.1, 123.7, 110.8, 110.5, 110.2, 57.4, 56.9, 21.5. HRMS [EI-(+Na)] calcd for $C_{20}H_{17}BrN_2NaO_4S$ 482.9985, found 482.9970. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (60/40 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 21.7 min, t_{minor} = 27.7 min).



8p

***N*-((*S*)-((*R*)-3-bromo-2-oxoindolin-3-yl)(naphthalen-1-yl)methyl)-4-methylbenzenesulfonamide (8p)**

The title compound was isolated as yellow solid in 81% yield, mp: 130–132 °C, $[\alpha]_D^{25}$ = +99 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.79 (s, 1H), 7.52 (dd, *J* = 19.2, 8.0 Hz, 2H), 7.38 (dd, *J* = 6.7, 5.3 Hz, 2H), 7.31 (dd, *J* = 9.3, 5.7 Hz, 3H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.96–6.86 (m, 3H), 6.63 (dd, *J* = 5.6, 2.7 Hz, 1H), 6.49 (d, *J* = 8.1 Hz, 2H), 5.90 (d, *J* = 9.0 Hz, 1H), 1.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 142.7, 139.8, 135.6, 133.0, 131.3, 131.1, 130.9, 129.0, 128.5, 128.0, 127.7, 127.2, 127.0, 126.0, 125.5, 125.5, 124.6, 124.1, 123.7, 110.4, 58.5, 57.0, 21.1. HRMS [EI-(+Na)] calcd for $C_{27}H_{21}BrN_2NaO_3S$ 544.9566, found 544.9575. The *ee* and *dr* were determined by a chiral phase Chiralpak AD-H column (76/24 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 30.5 min, t_{minor} = 21.4 min).

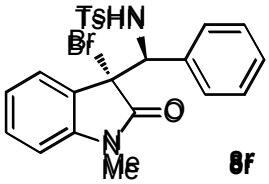


8q

***N*-((*S*,*E*)-1-((*R*)-3-bromo-2-oxoindolin-3-yl)-3-phenylallyl)-4-methylbenzenesulfonamide (8q)**

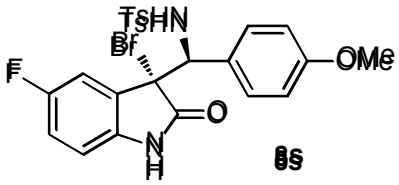
The title compound was isolated as yellow solid in 89% yield, mp: 120–121 °C, $[\alpha]_D^{25}$ = +85 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.27 (dd, *J* = 12.9, 4.7 Hz, 4H), 7.17 (d, *J* = 8.4 Hz, 3H), 7.11 (dd, *J* = 6.9, 3.7 Hz, 2H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.37 (dd, *J* = 15.8, 9.3 Hz, 1H), 5.91 (d, *J* = 15.8 Hz, 1H), 4.50-4.45 (m, 1H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 143.8, 139.9, 136.5, 135.8, 135.4, 130.6, 129.7, 128.5, 128.4, 128.1, 127.6, 126.8, 126.0, 123.6, 122.3, 110.9, 62.2, 57.0, 21.5. HRMS [EI-(+Na)] calcd for

$C_{24}H_{21}BrN_2NaO_3S$ 519.0348, found 519.0349. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (60/40 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 18.1 min, t_{minor} = 28.6 min).



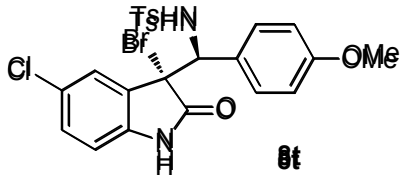
_N_-((_S_)-((_R_)-3-bromo-1-methyl-2-oxoindolin-3-yl)(phenyl)methyl)-4-methylbenzenesulfonamide (8r)

The title compound was isolated as yellow solid in 64%, mp: 61–62 °C, $[\alpha]_D^{25}$ = +33 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 7.3 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.32–7.29 (m, 1H), 7.19 (dd, J = 14.2, 7.1 Hz, 1H), 7.00 (dd, J = 9.3, 4.5 Hz, 3H), 6.87 (dd, J = 13.9, 6.2 Hz, 2H), 6.67 (d, J = 7.5 Hz, 2H), 6.57 (d, J = 7.7 Hz, 1H), 6.46 (d, J = 7.1 Hz, 1H), 4.83 (d, J = 7.1 Hz, 1H), 2.81 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 143.4, 142.4, 136.2, 133.3, 130.8, 129.3, 128.5, 128.3, 127.5, 127.5, 127.0, 126.8, 123.7, 108.5, 63.9, 58.6, 26.4 (d, J = 2.4 Hz), 21.4. HRMS [EI-(+Na)] calcd for $C_{23}H_{21}BrN_2NaO_3S$ 507.0348, found 507.0339. The *ee* and *dr* were determined by a chiral phase phenomenex Lvx 5μ Cellulose-1 column (90/10 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 16.5 min, t_{minor} = 25.1 min).



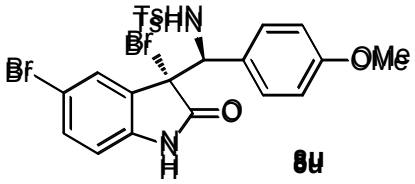
_N_-((_S_)-((_R_)-3-bromo-5-fluoro-2-oxoindolin-3-yl)(4-methoxyphenyl)methyl)-4-methylbenzenesulfonamide (8s)

The title compound was isolated as yellow solid in 89% yield, mp: 158–159 °C, $[\alpha]_D^{25}$ = +126 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.49 (d, J = 8.2 Hz, 2H), 7.16 (dd, J = 7.6, 1.7 Hz, 1H), 7.07 (d, J = 8.1 Hz, 2H), 6.96 (td, J = 8.8, 2.5 Hz, 1H), 6.78 (d, J = 8.7 Hz, 2H), 6.68 (dd, J = 8.6, 4.2 Hz, 1H), 6.48 (d, J = 8.7 Hz, 2H), 6.42 (d, J = 6.3 Hz, 1H), 4.79 (d, J = 6.4 Hz, 1H), 3.67 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 160.6, 159.7, 157.4, 143.5, 136.4, 135.6 (d, J = 2.3 Hz), 130.2, 129.3, 129.0 (d, J = 8.5 Hz), 127.4, 125.2, 117.4 (d, J = 23.8 Hz), 114.4 (d, J = 25.6 Hz), 113.2, 111.5 (d, J = 7.9 Hz), 62.8, 58.3, 55.1, 21.5. HRMS [EI-(+Na)] calcd for $C_{23}H_{20}BrFN_2NaO_4S$ 541.0203, found 541.0214. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (70/30 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 34.7 min, t_{minor} = 57.3 min).



_N_-((_S_)-((_R_)-3-bromo-5-chloro-2-oxoindolin-3-yl)(4-methoxyphenyl)methyl)-4-methylbenzenesulfonamide (8t)

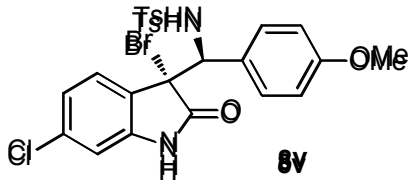
The title compound was isolated as yellow solid in 90%, mp: 170–171 °C, $[\alpha]_D^{25}$ = +229 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.36 (s, 1H), 7.19 (dd, J = 8.4, 2.0 Hz, 1H), 7.09 (d, J = 8.1 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.7 Hz, 2H), 6.37 (d, J = 6.5 Hz, 1H), 4.79 (d, J = 6.5 Hz, 1H), 3.67 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 159.7, 143.5, 138.2, 136.4, 130.7, 130.2, 129.3, 129.2, 128.7, 127.4, 126.8, 125.3, 113.3, 111.7, 62.8, 58.0, 55.1, 21.5. HRMS [EI-(+Na)] calcd for $C_{23}H_{20}BrClN_2NaO_4S$ 556.9908, found 556.9923. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (70/30 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 33.2 min, t_{minor} = 54.5 min).



8u

***N*-((*S*)-((*R*)-3,5-dibromo-2-oxoindolin-3-yl)(4-methoxyphenyl)methyl)-4-methylbenzenesulfonamide (8u)**

The title compound was isolated as yellow solid in 93%, mp: 179–181 °C, $[\alpha]_D^{25}$ = +189 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.52–7.49 (m, 3H), 7.33 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 8.3 Hz, 1H), 6.49 (d, *J* = 8.7 Hz, 2H), 6.40 (d, *J* = 6.5 Hz, 1H), 4.80 (d, *J* = 6.6 Hz, 1H), 3.67 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 159.6, 143.6, 138.7, 136.3, 133.6, 130.2, 129.5, 129.5, 129.4, 127.4, 125.3, 115.8, 113.2, 112.2, 62.8, 58.0, 55.2, 21.5. HRMS [EI-(+Na)] calcd for $C_{23}H_{20}Br_2N_2NaO_4S$ 600.9403, found 600.9428. The *ee* and *dr* were determined by a chiral phase Chiralpak IC column (70/30 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 254 nm, t_{major} = 34.3 min, t_{minor} = 56.4 min).

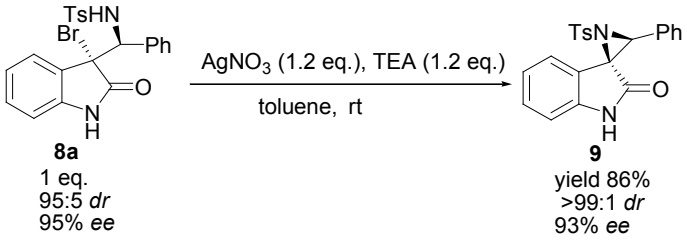


8v

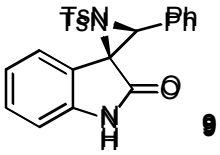
***N*-((*S*)-((*R*)-3-bromo-6-chloro-2-oxoindolin-3-yl)(4-methoxyphenyl)methyl)-4-methylbenzenesulfonamide (8v)**

The title compound was isolated as yellow solid in 75%, mp: 104–106 °C, $[\alpha]_D^{25}$ = +140 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.17 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.70 (dd, *J* = 8.7, 5.2 Hz, 3H), 6.61 (d, *J* = 7.3 Hz, 1H), 6.45 (d, *J* = 8.7 Hz, 2H), 4.80 (d, *J* = 7.3 Hz, 1H), 3.66 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 159.5, 143.5, 140.6, 136.6, 130.0, 129.95, 129.3, 128.0, 127.4, 125.8, 125.2, 123.8, 113.2, 111.2, 63.1, 58.0, 55.1, 21.4. HRMS [EI-(+Na)] calcd for $C_{23}H_{20}BrClN_2NaO_4S$ 556.9908, found 556.9920. The *ee* and *dr* were determined by a chiral phase Chiralpak AD-H column (76/24 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 30.8 min, t_{minor} = 55.7 min).

8. Synthesis of aziridine via the product of *anti*-Mannich reaction



The produce of *anti*-Mannich Reaction **8a** (0.2 mmol, 1 equiv.) was dissolved in anhydrous toluene (0.1 mL), subsequently $AgNO_3$ (0.24 mmol, 1.2 equiv.) and TEA (0.24 mmol, 1.2 equiv.) were added at room temperature. TLC analysis indicated completion of the reaction. The reaction mixture was purified directly by flash chromatography on silica gel. (AcOEt/PE = 1 : 5) to give **9** as a yellow soild.



9

(*2S, 3S*)-3-phenyl-1-tosylspiro[aziridine-2,3'-indolin]-2'-one (9)

The product was obtained as a yellow solid in 86% yield, mp: 71–74 °C, $[\alpha]_D^{25}$ = -27 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.92 (t, J = 7.8 Hz, 3H), 7.32 (d, J = 8.1 Hz, 2H), 7.23 (s, 5H), 7.12 (t, J = 7.6 Hz, 2H), 6.78 (d, J = 7.7 Hz, 1H), 4.85 (s, 1H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 145.0, 142.0, 136.4, 130.5, 129.9, 129.8, 128.5, 128.2, 127.9, 127.8, 125.4, 122.8, 121.1, 110.8, 55.8 (d, J = 2.6 Hz), 53.5, 21.7. HRMS [EI-(+Na)] calcd for $C_{22}H_{18}N_2NaO_3S$ 413.0930, found 413.0922. The *ee* and *dr* were determined by a chiral phase Chiralpak AD-H column (76/24 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 35.2 min, t_{minor} = 58.6 min).

9. References

[1] I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, and P. S. Baran. *J. Am. Chem. Soc*. 2010, **132**, 13194.

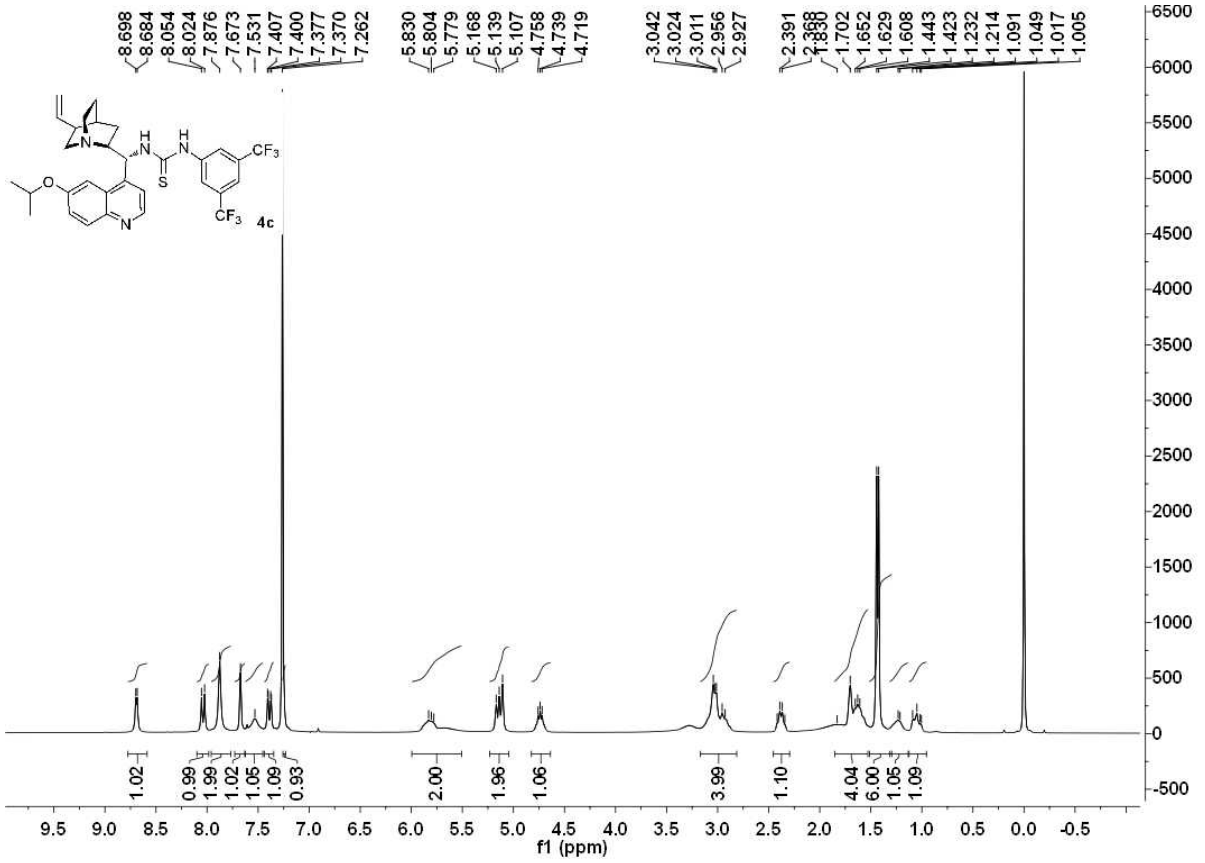
[2] V. Benedek, V. Szilard, C. Antal and S. Tibor. *Org. Lett*. 2005, **7**, 1967.

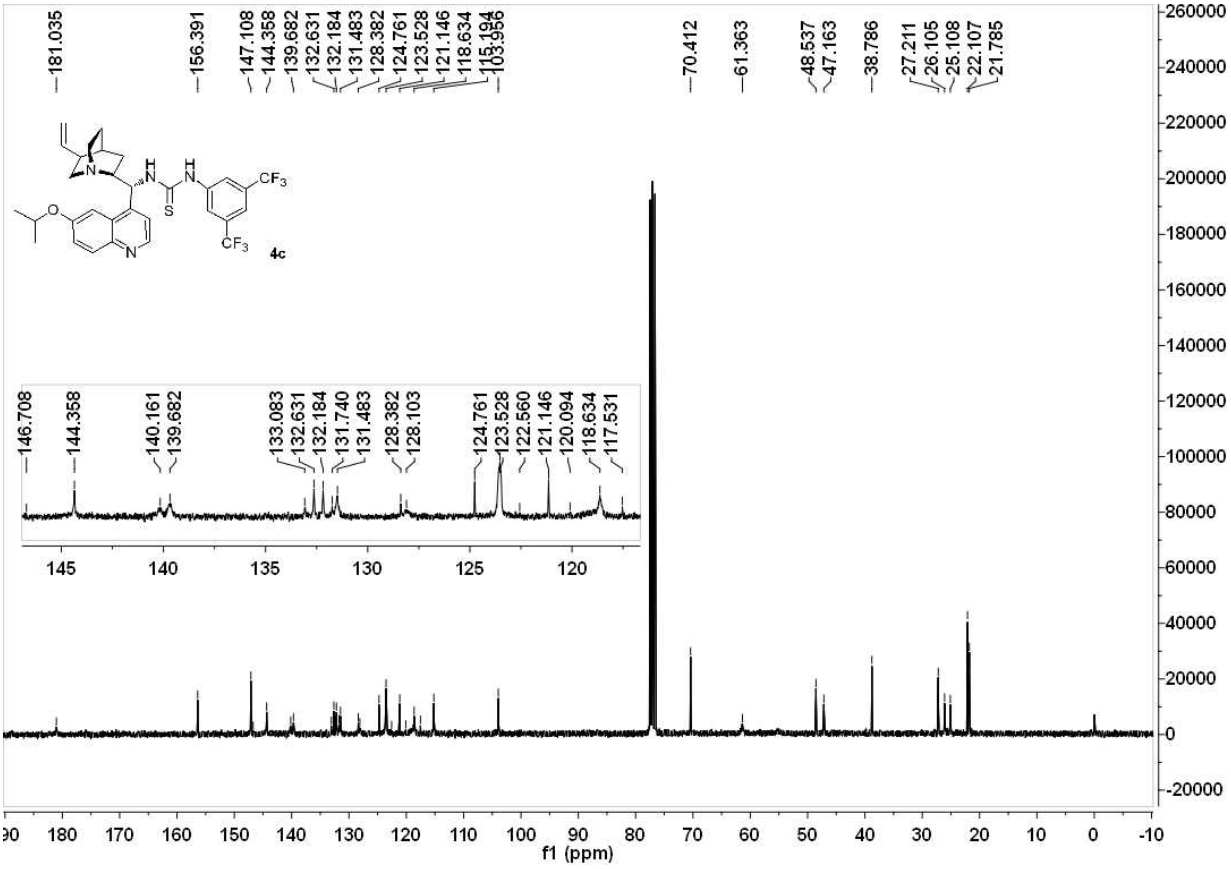
[3] P. Anbarasan, H. Neumann and M. Beller, *Chem. Eur. J*. 2011, **17**, 4217.

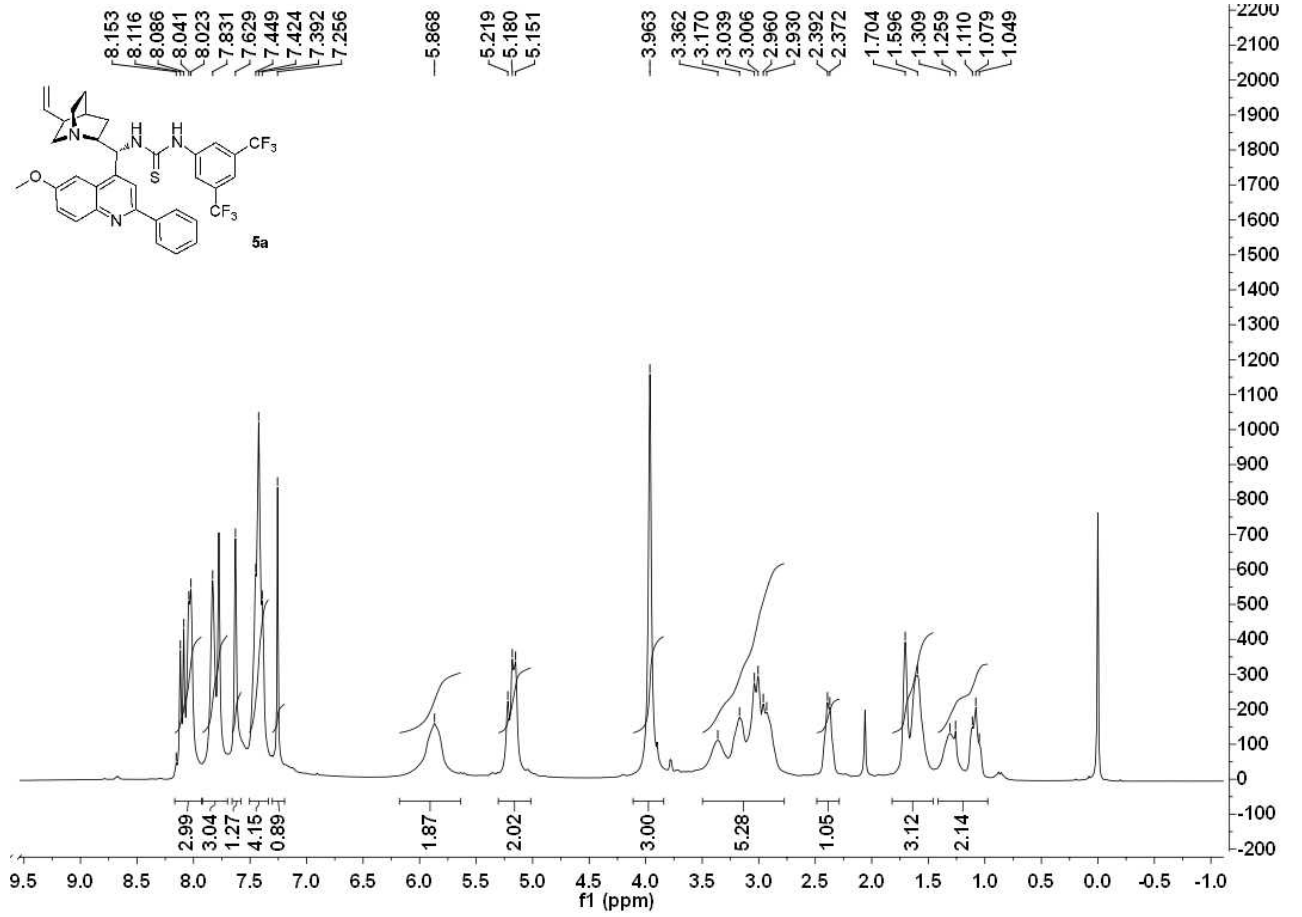
[4] A. Lee, A. Michrowska, S. S. Mosse, and B. List. *Angew. Chem. Int. Ed*. 2011, **50**, 1707.

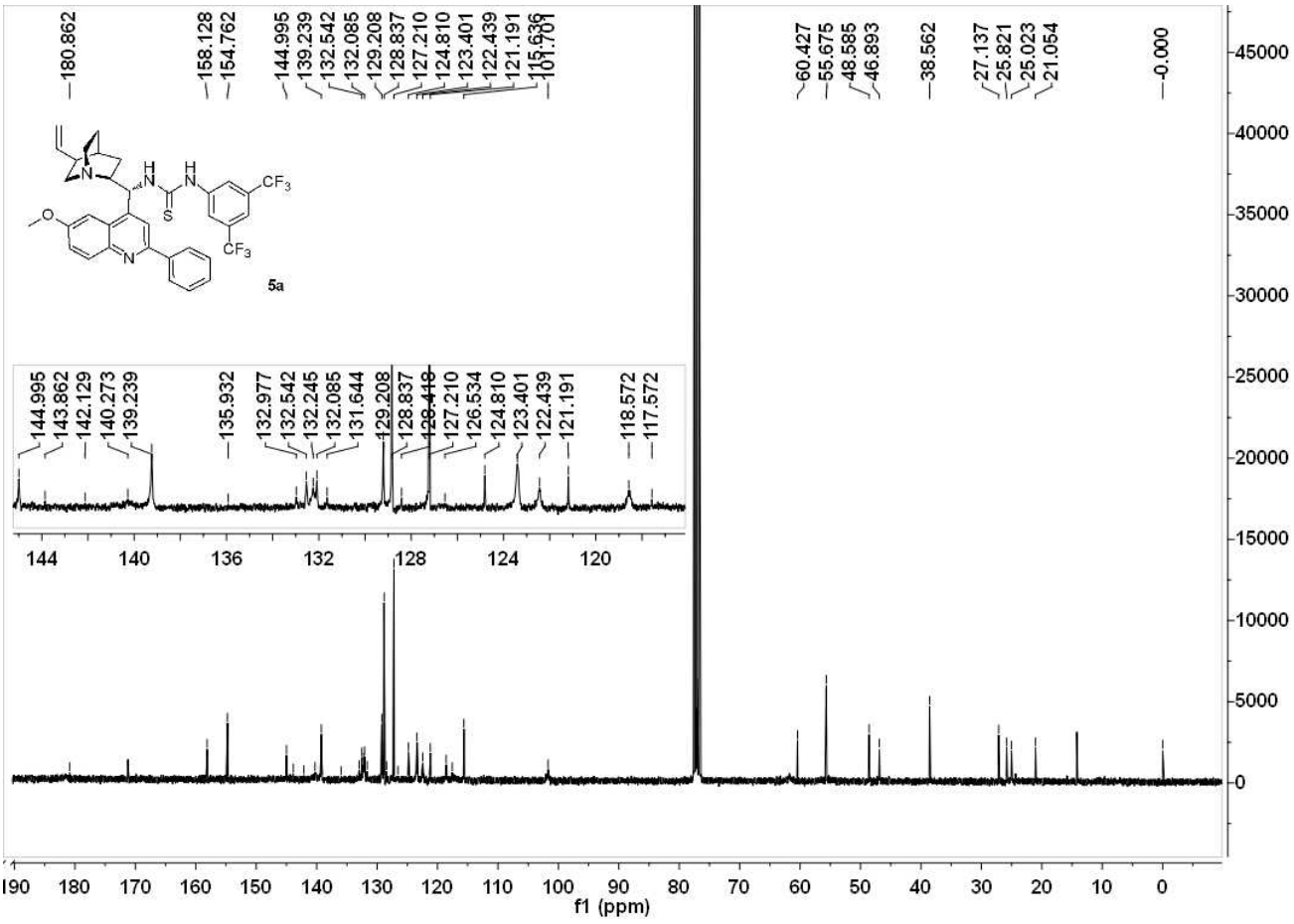
[5] A. Berkessel, B. Seelig, S. Schwengberg, J. Hescheler, and A. Sachinidis, *ChemBioChem*. 2010, **11**, 208.

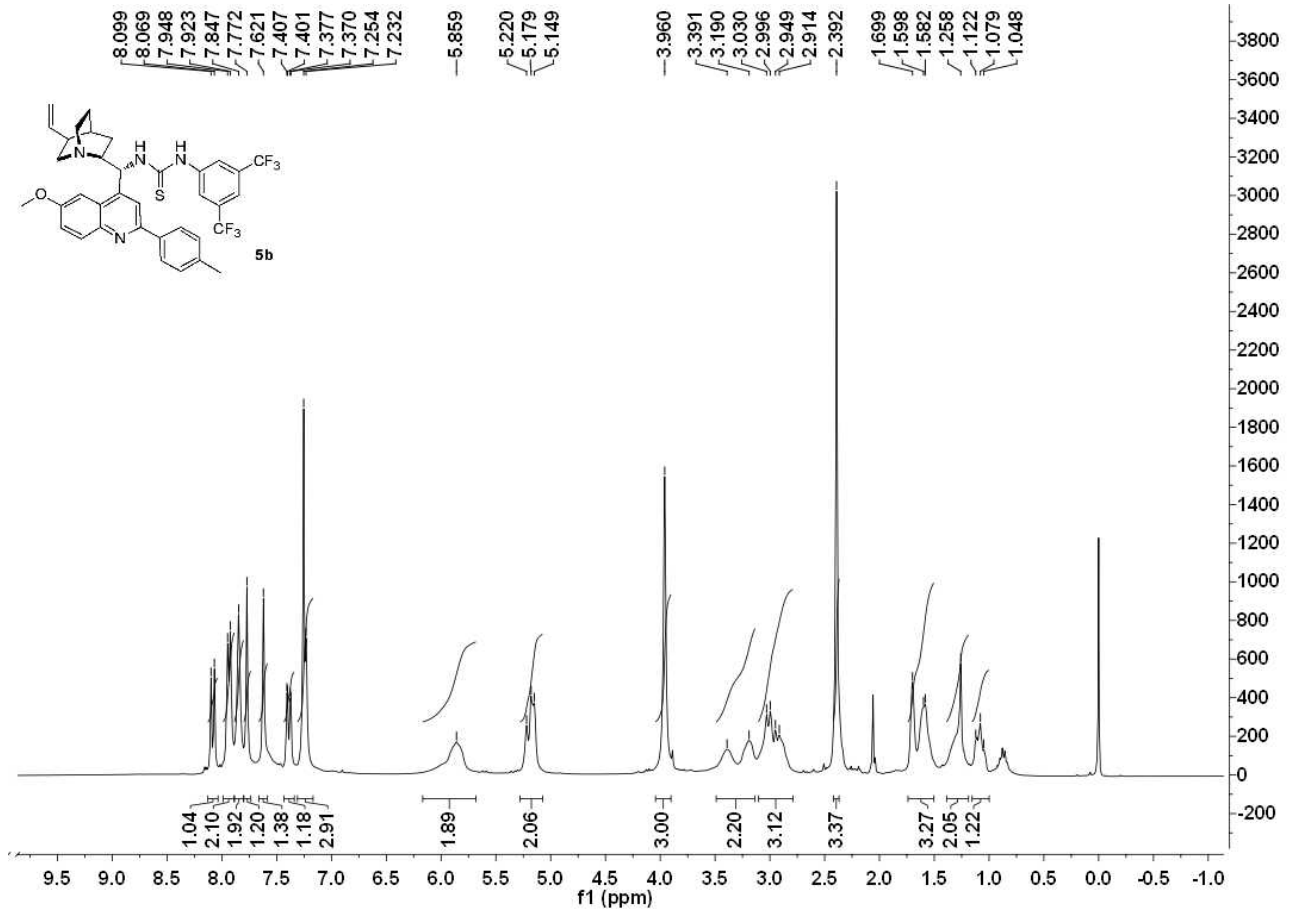
10. NMR spectra and HPLC for catalysts and *anti*-Mannich reaction products.

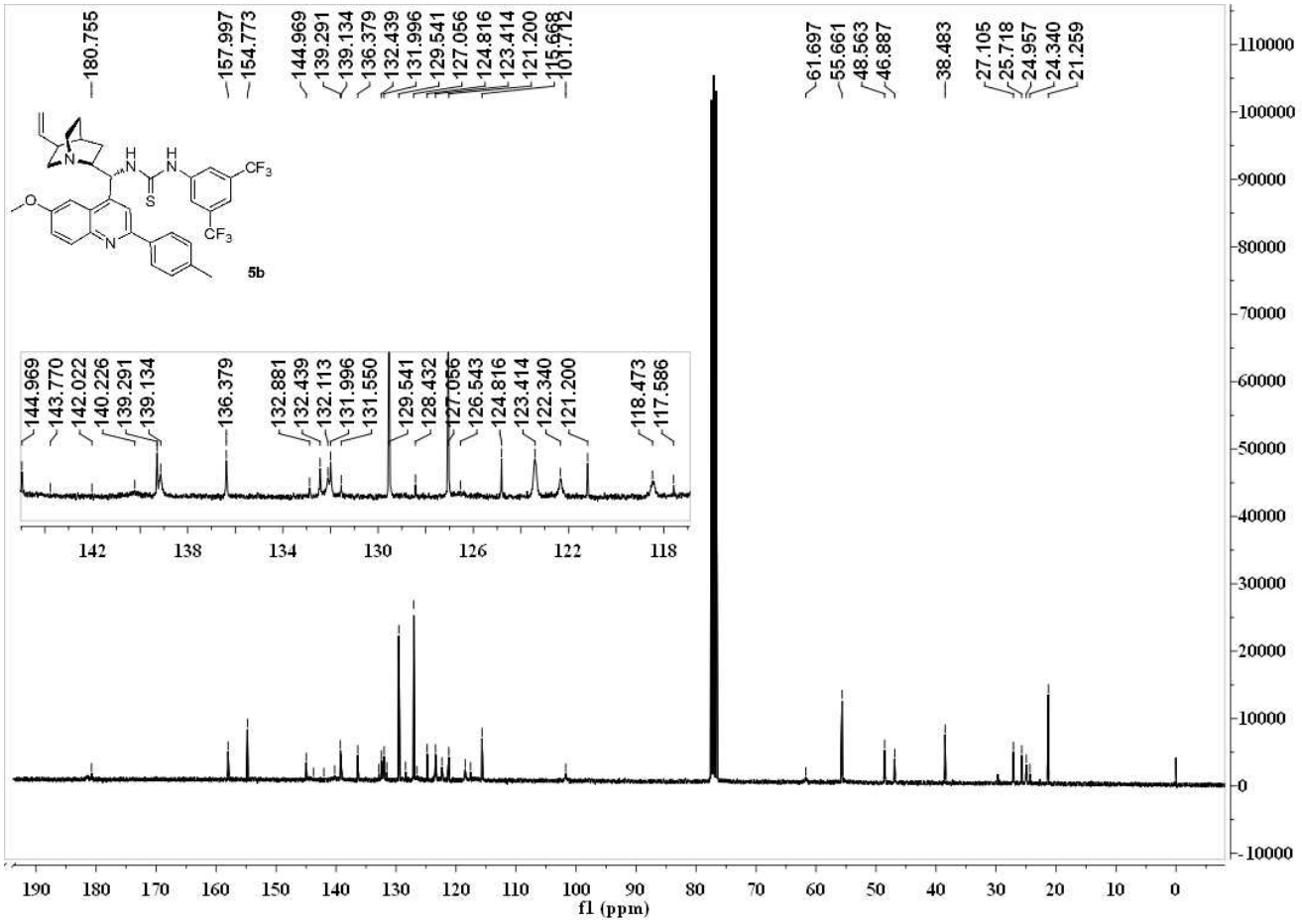


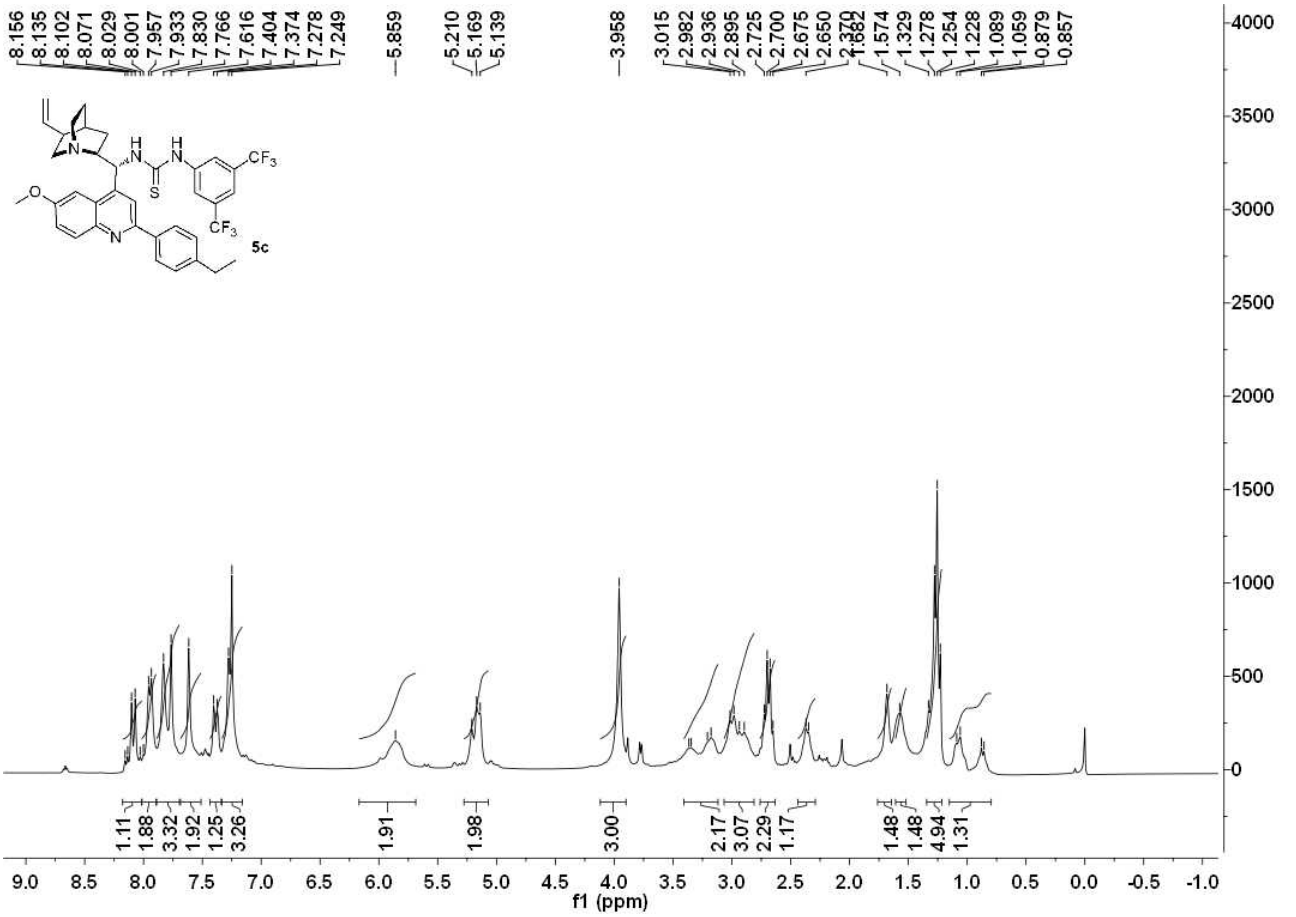


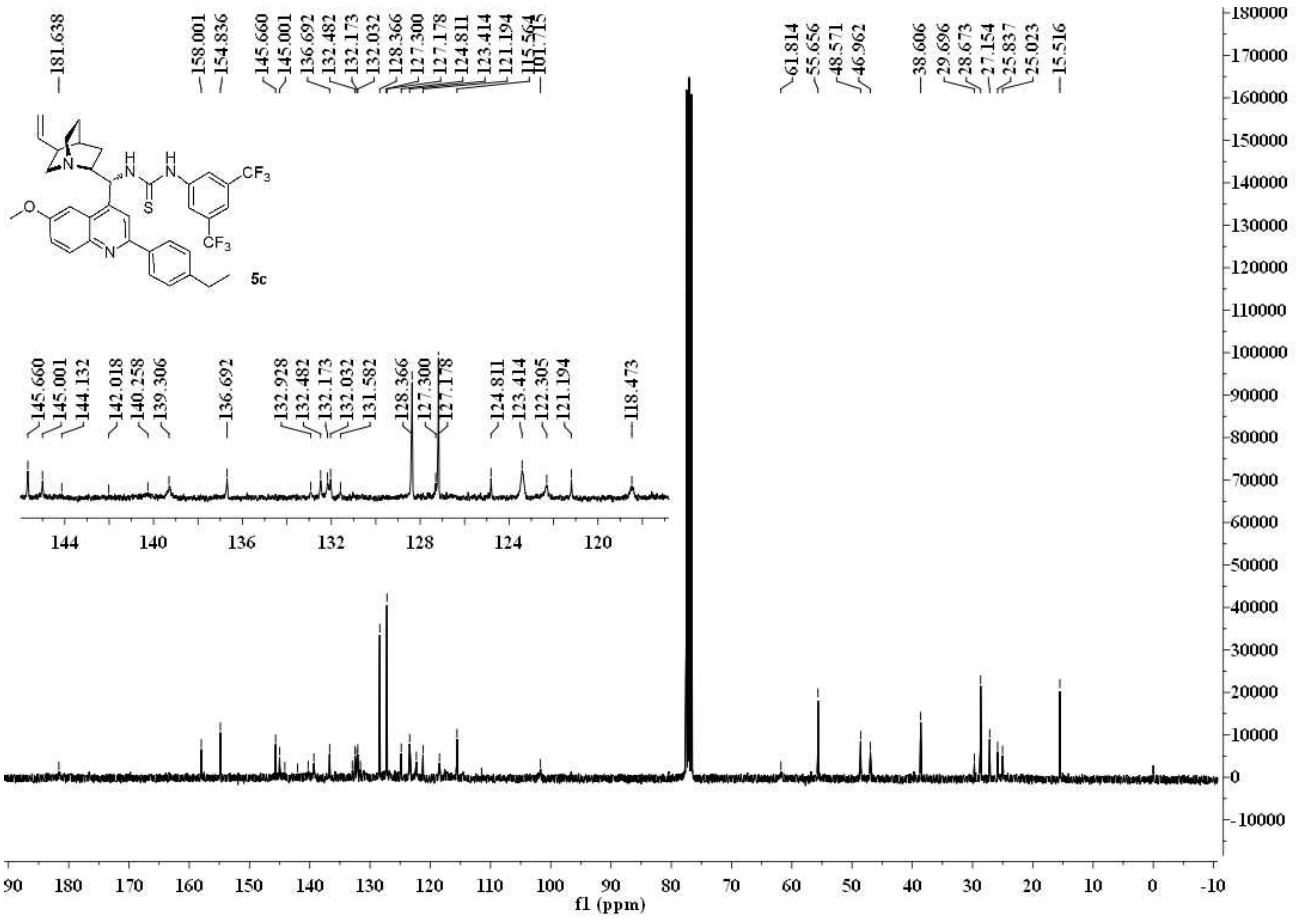

8.153
8.116
8.086
8.041
8.023
7.831
7.629
7.449
7.424
7.392
7.256
5.868
5.219
5.180
5.151
3.963
3.362
3.170
3.039
3.006
2.960
2.930
2.392
2.372
1.704
1.596
1.309
1.259
1.110
1.079
1.049
5a
2.99
3.04
1.27
4.15
0.89
1.87
2.02
3.00
5.28
1.05
3.12
2.14
f1 (ppm)

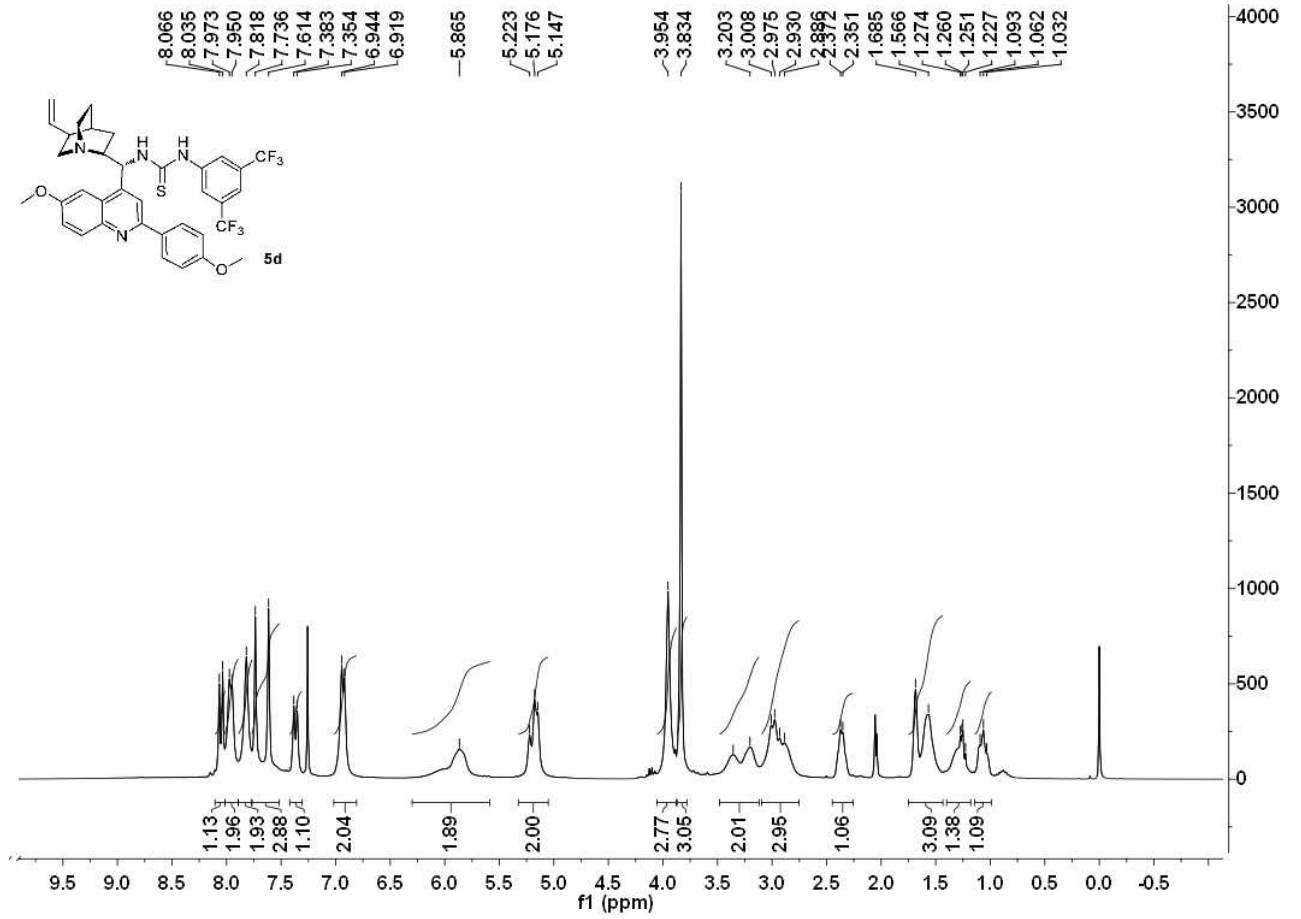

180.862
158.128
154.762
144.995
139.239
132.542
132.085
129.208
128.837
127.210
124.810
123.401
122.439
121.191
115.636
101.701
60.427
55.675
48.585
46.893
38.562
27.137
25.821
25.023
21.054
-0.000
5a
144.995
143.862
142.129
140.273
139.239
135.932
132.977
132.542
132.245
132.085
131.644
129.208
128.837
128.448
127.210
126.534
124.810
123.401
122.439
121.191
118.572
117.572
f1 (ppm)

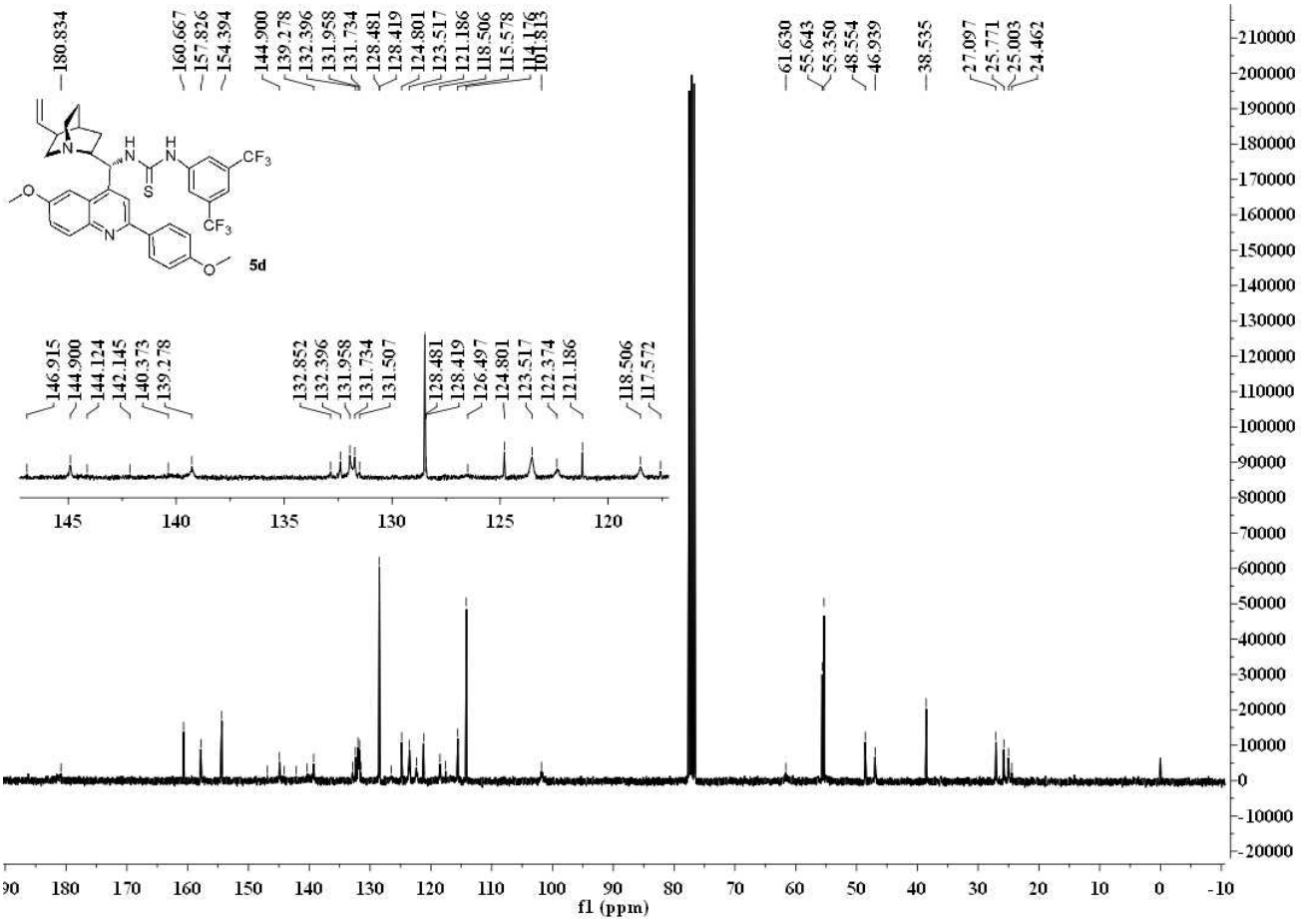

8.099
8.069
7.948
7.923
7.847
7.772
7.621
7.407
7.401
7.377
7.370
7.254
7.232
5.859
5.220
5.179
5.149
3.960
3.391
3.190
3.030
2.996
2.949
2.914
2.392
1.699
1.598
1.582
1.258
1.122
1.079
1.048
5b
1.04
2.10
1.92
1.20
1.38
1.18
2.91
1.89
2.06
3.00
2.20
3.12
3.37
3.27
2.05
1.22
f1 (ppm)

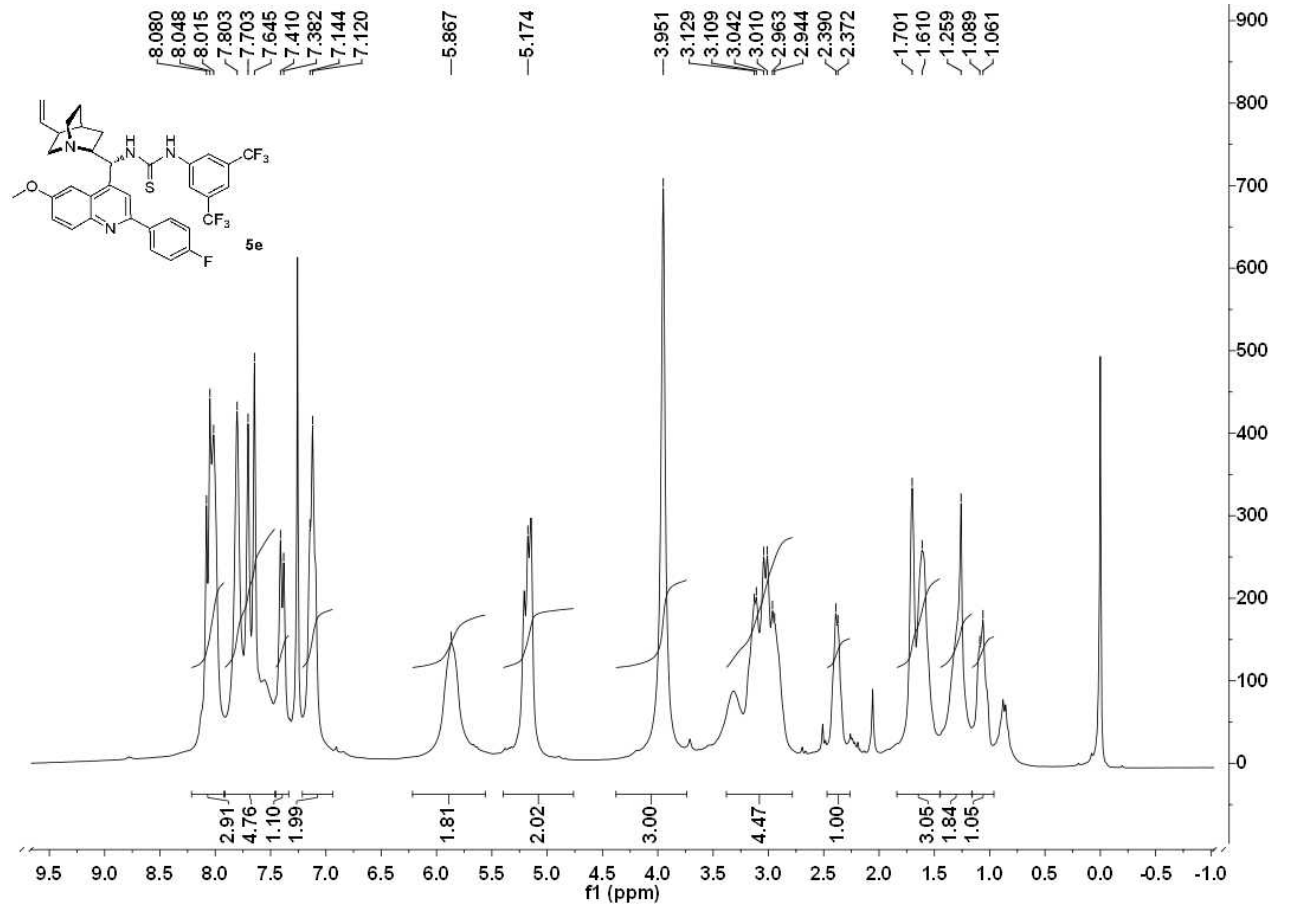

180.755
157.997
154.773
144.969
139.291
139.134
136.379
132.439
131.996
129.541
127.056
124.816
123.414
121.200
115.668
101.712
61.697
55.661
48.563
46.887
38.483
27.105
25.718
24.957
24.340
21.259
5b
144.969
143.770
142.022
140.226
139.291
139.134
136.379
132.881
132.439
132.113
131.996
131.550
129.541
128.432
127.056
126.543
124.816
123.414
122.340
121.200
118.473
117.586
f1 (ppm)

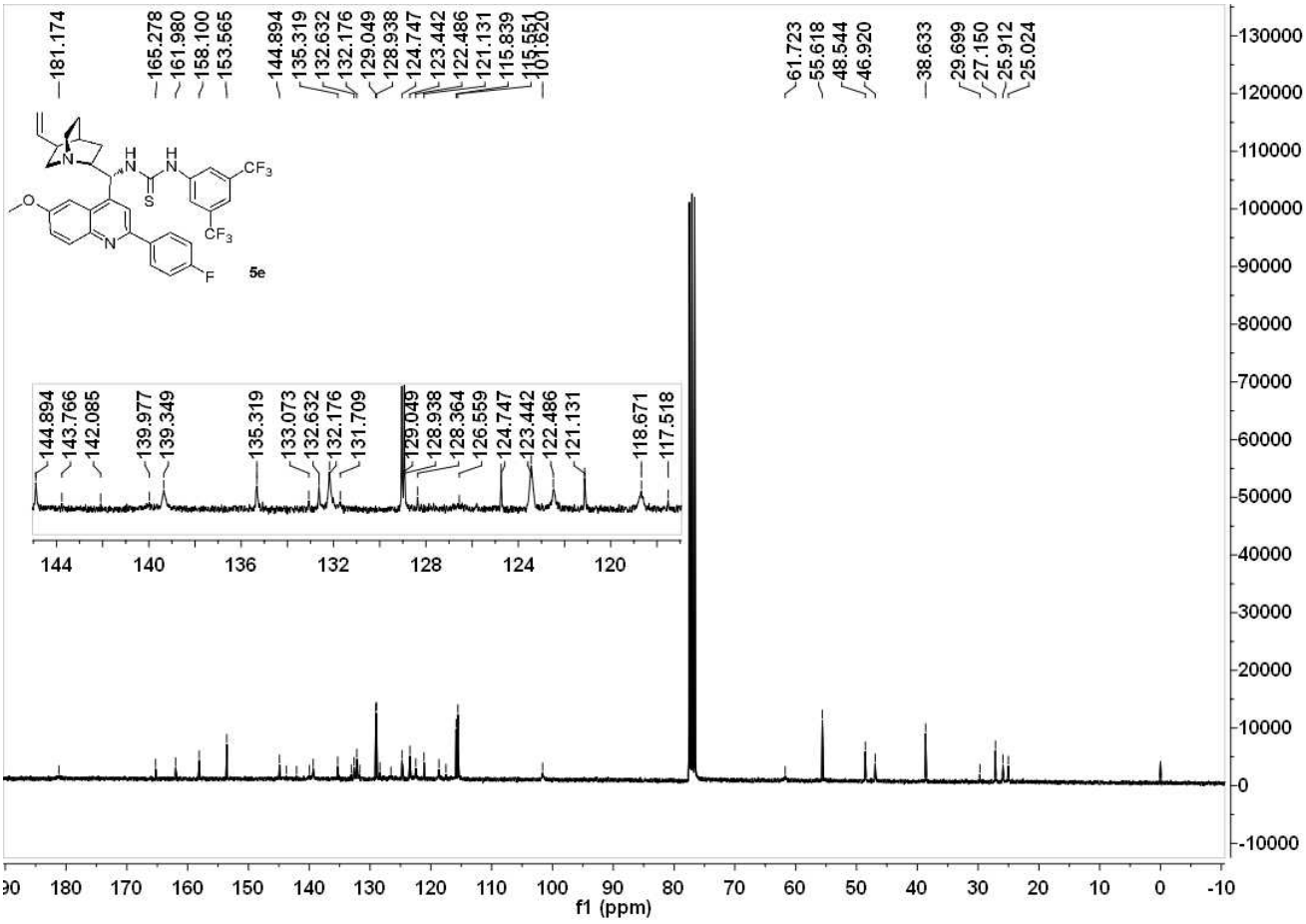

8.156
8.135
8.102
8.071
8.029
8.001
7.957
7.933
7.830
7.766
7.616
7.404
7.374
7.278
7.249
5.859
5.210
5.169
5.139
3.958
3.015
2.982
2.936
2.895
2.725
2.700
2.675
2.650
2.370
1.682
1.574
1.329
1.278
1.254
1.228
1.089
1.059
0.879
0.857
CF3
CF3
5c
1.11
1.88
3.32
1.92
1.25
3.26
1.91
1.98
3.00
2.17
3.07
2.29
1.17
1.48
1.48
4.94
1.31
f1 (ppm)

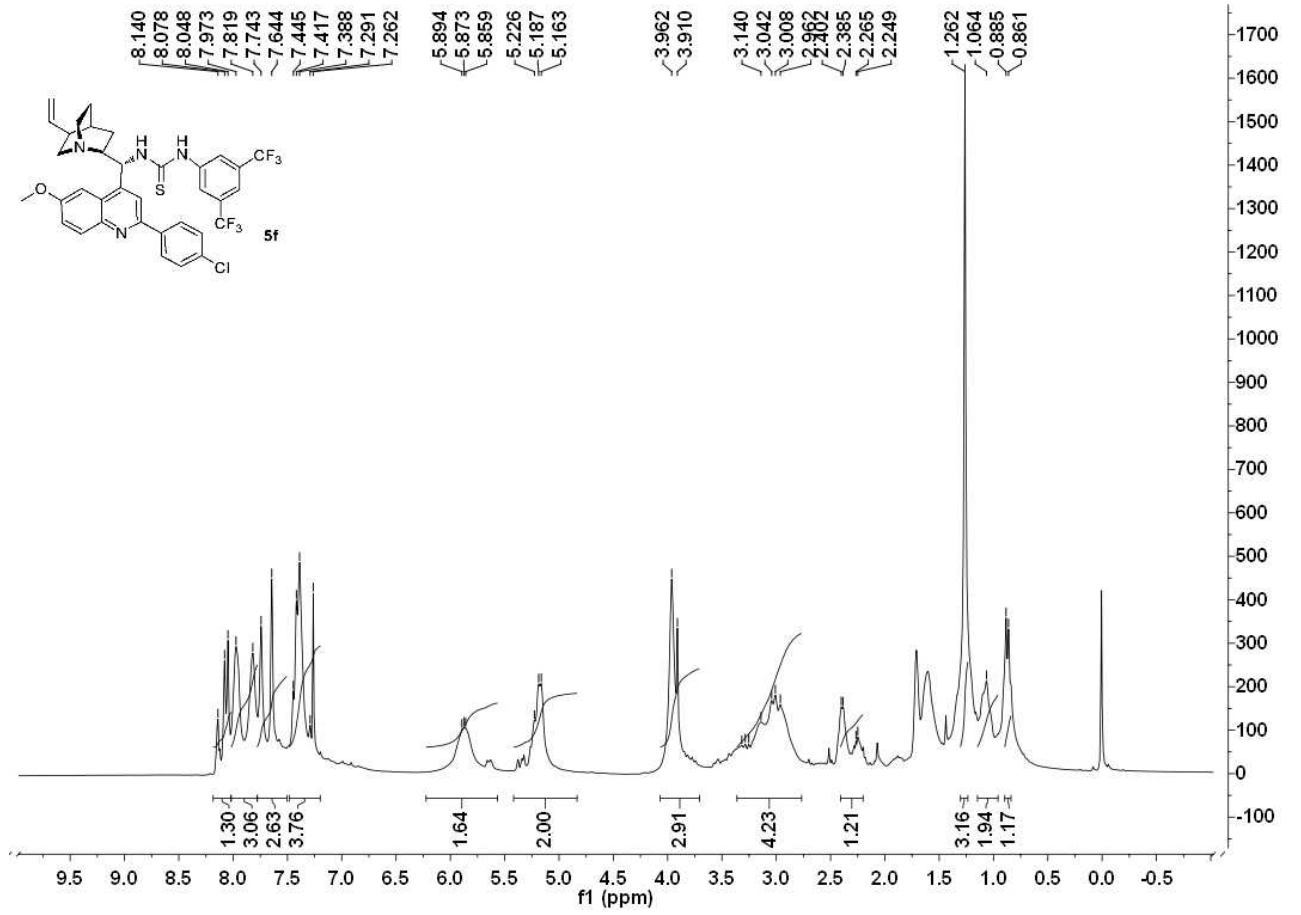

181.638
158.001
154.836
145.660
145.001
136.692
132.482
132.173
132.032
128.366
127.300
127.178
124.811
123.414
121.194
61.814
55.656
48.571
46.962
38.606
29.696
28.673
27.154
25.837
25.023
15.516
CF3
CF3
5c
145.660
145.001
144.132
142.018
140.258
139.306
136.692
132.928
132.482
132.173
132.032
131.582
128.366
127.300
127.178
124.811
123.414
122.305
121.194
118.473
f1 (ppm)

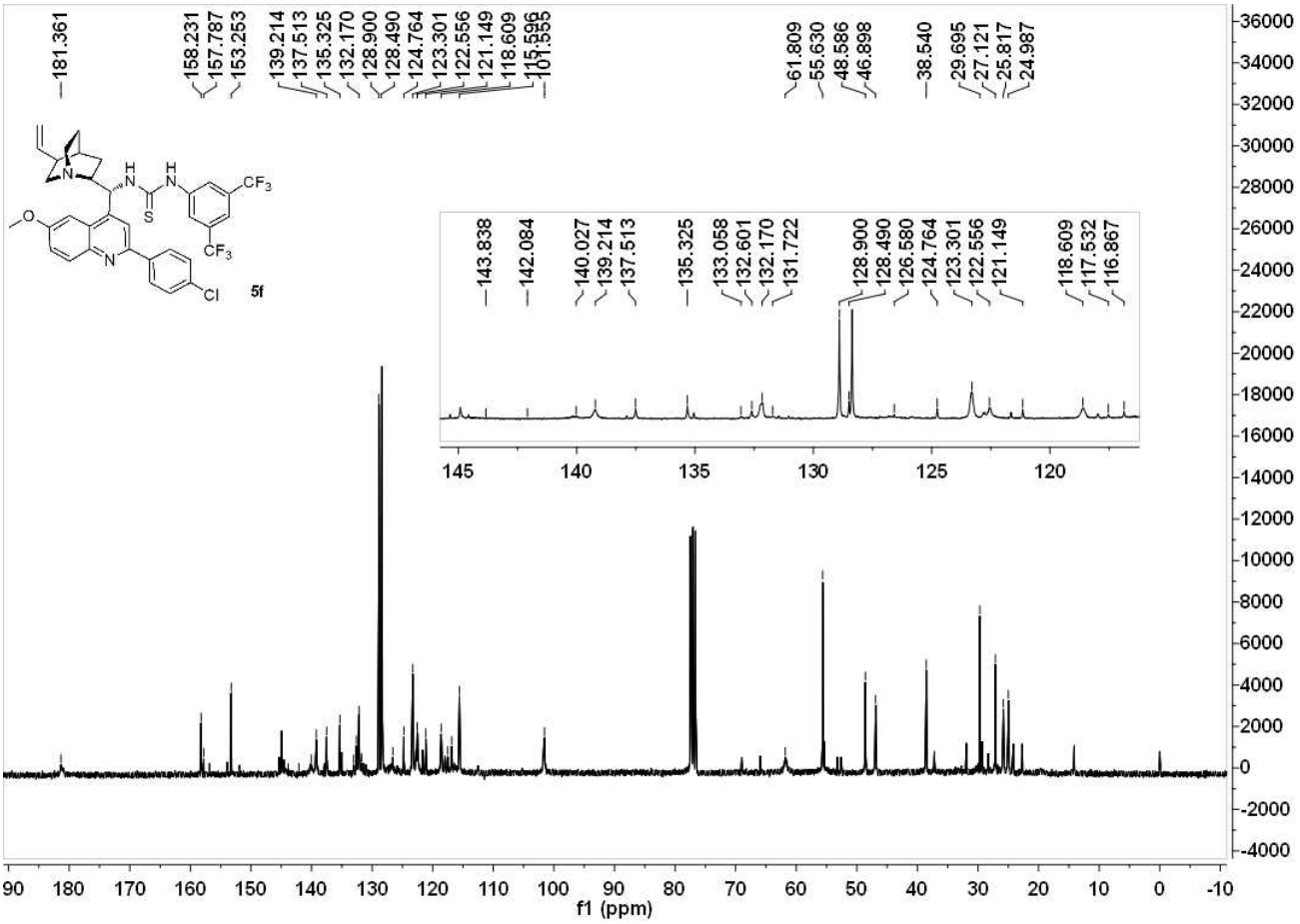


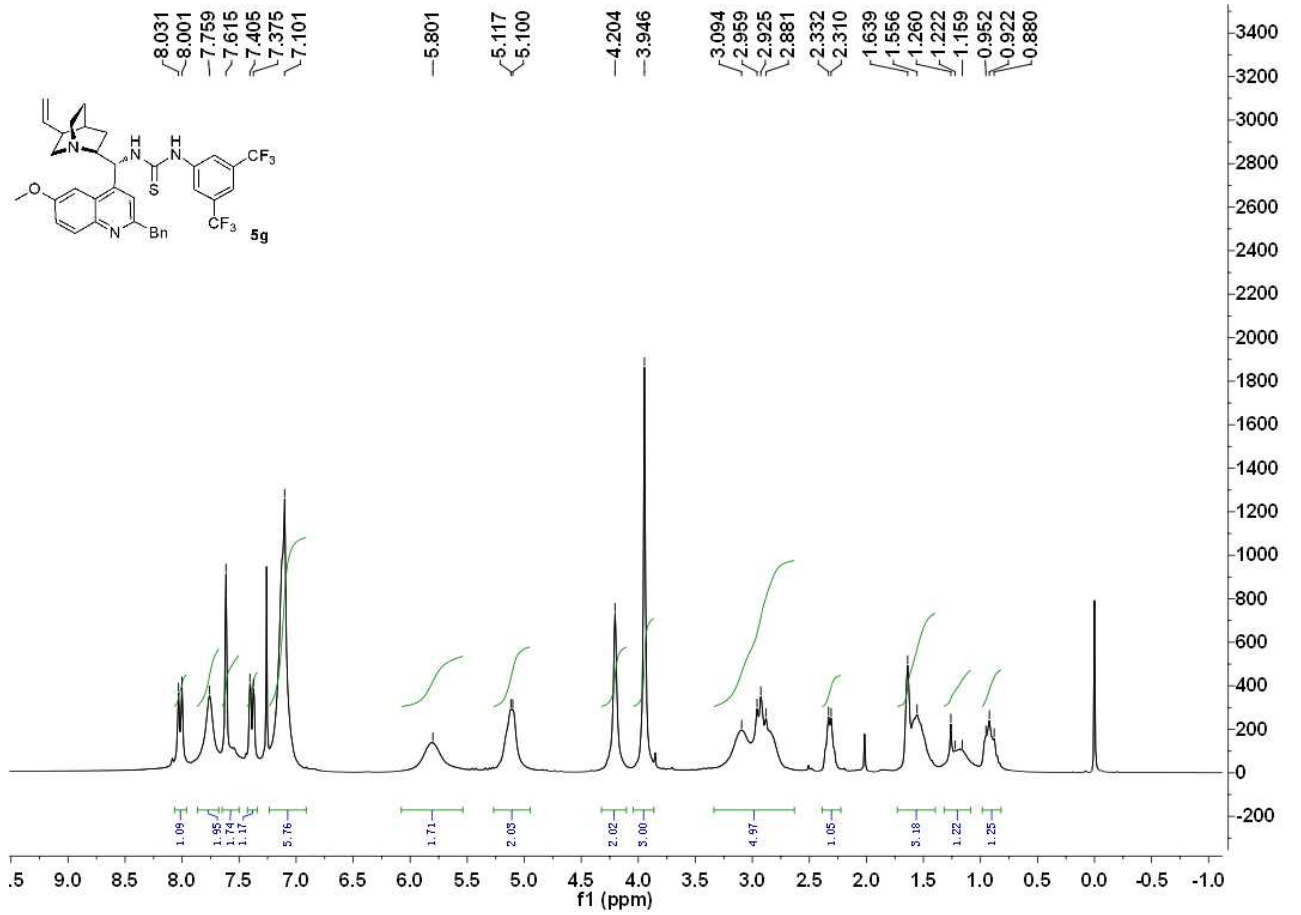


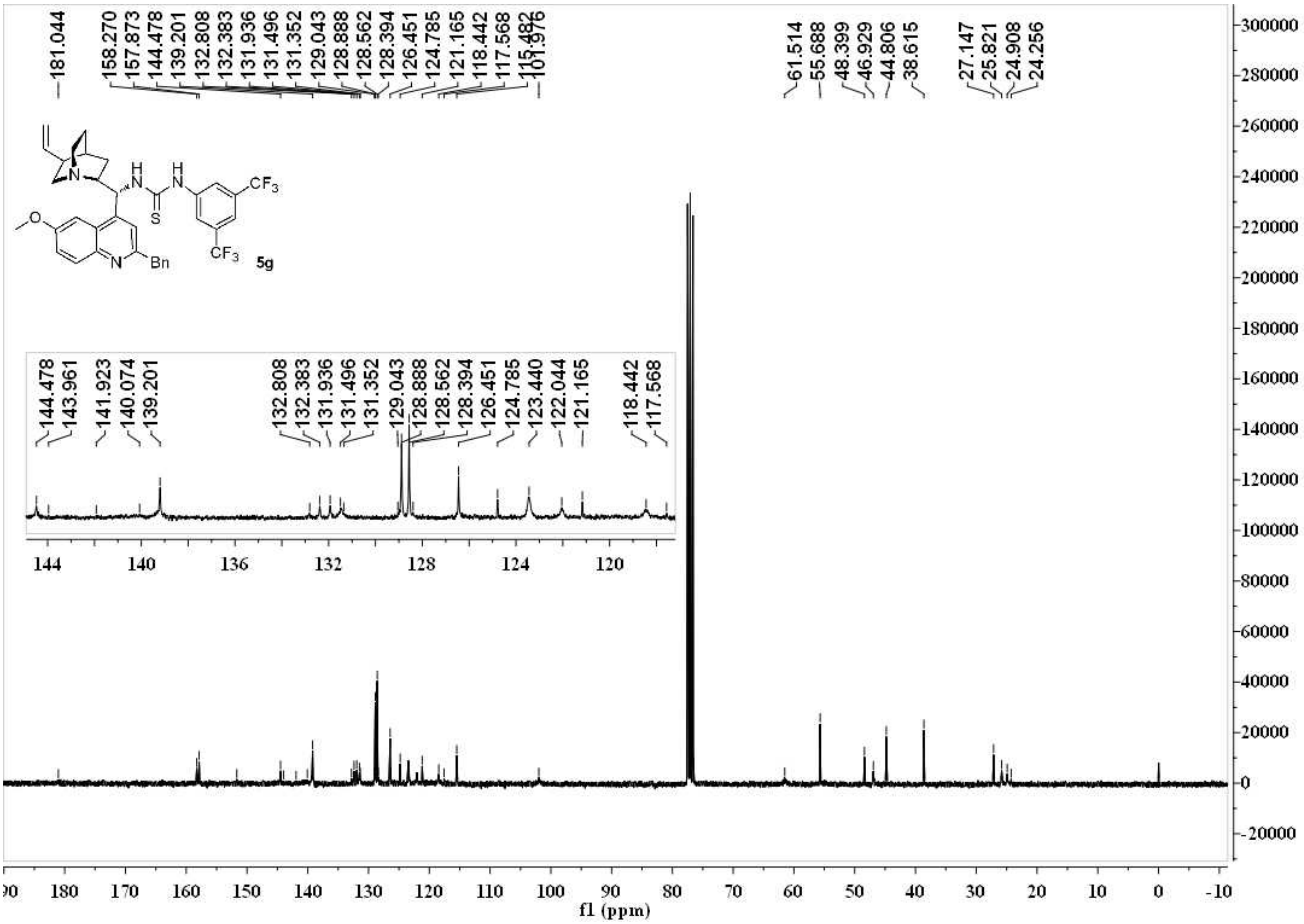


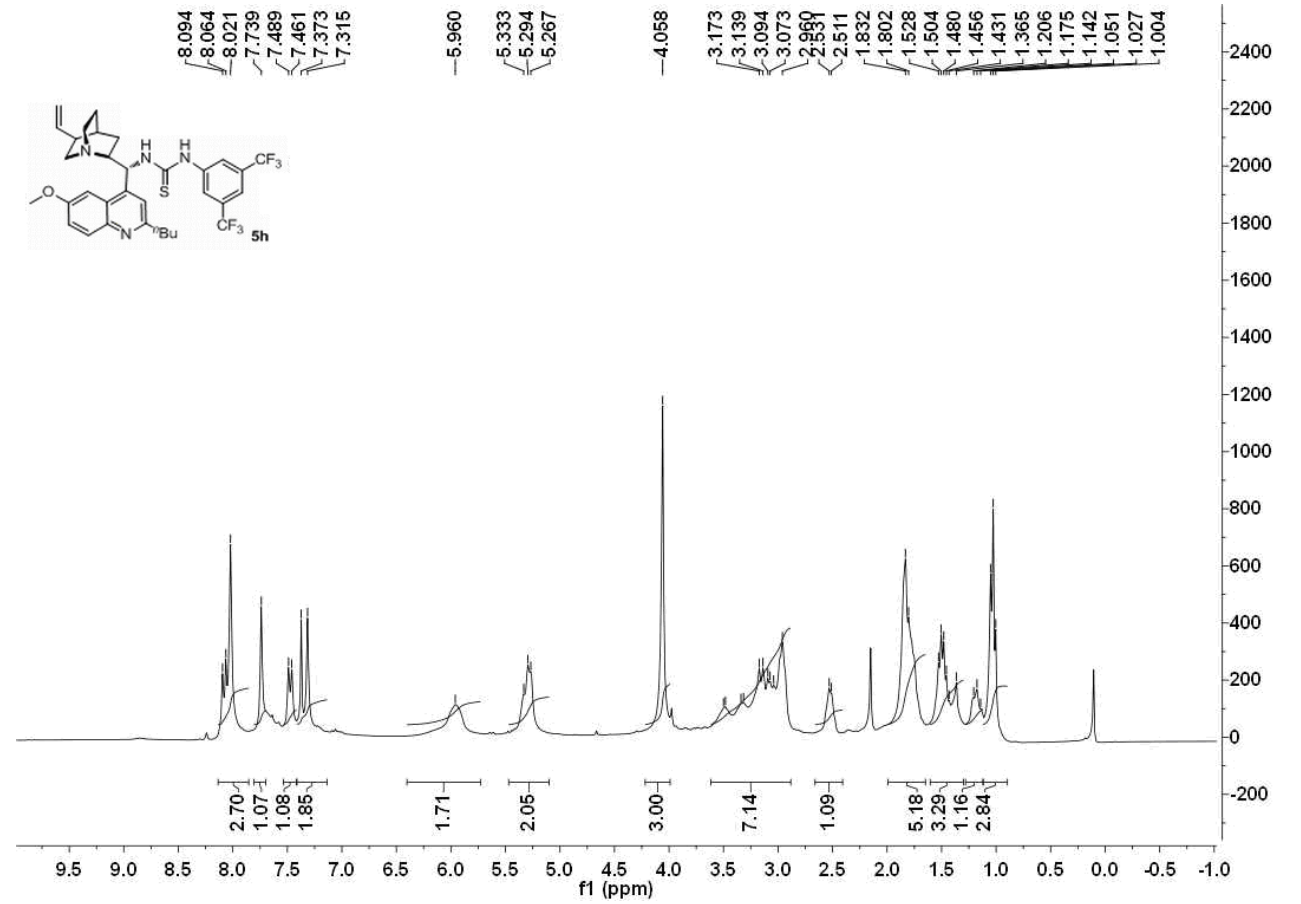


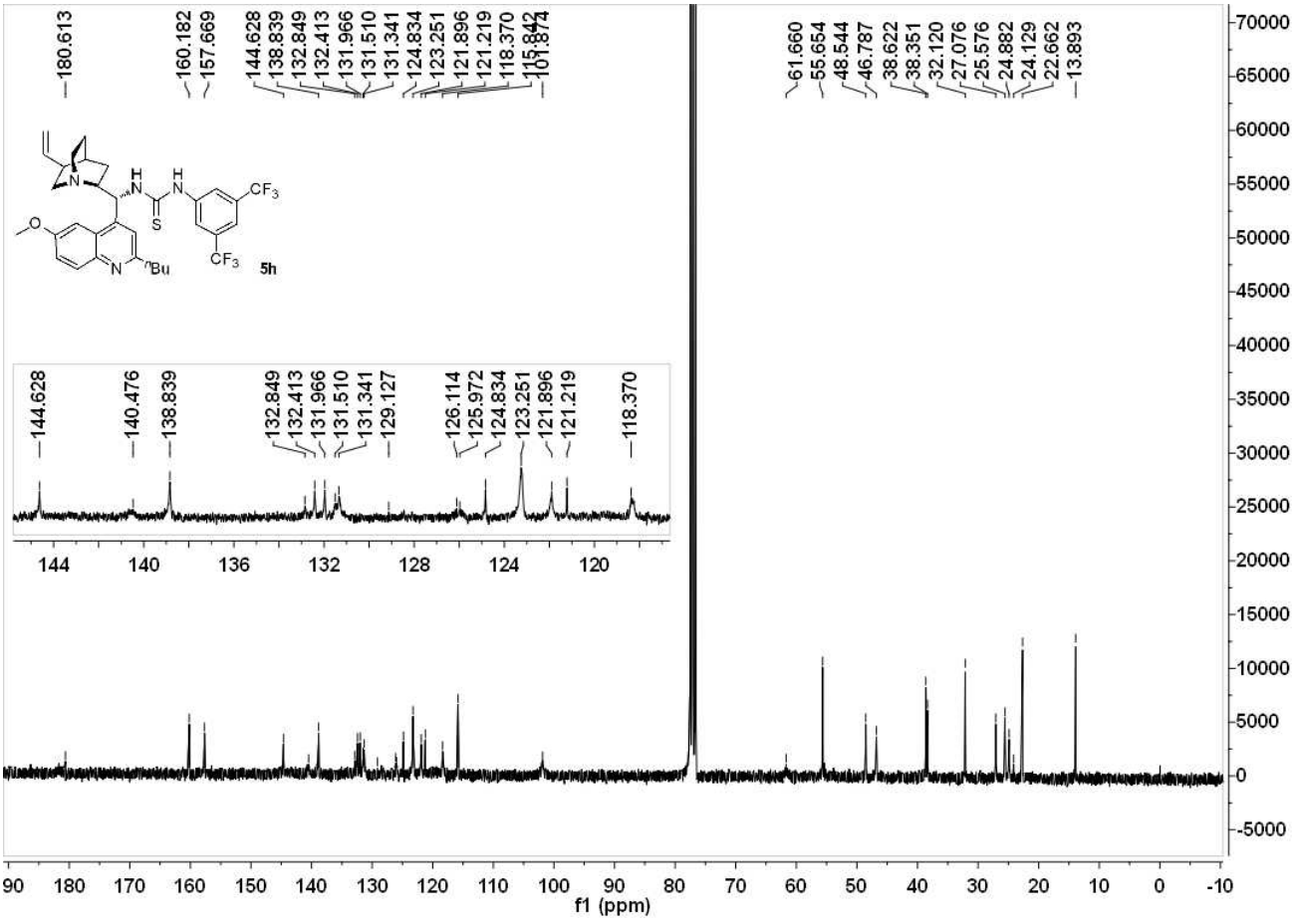


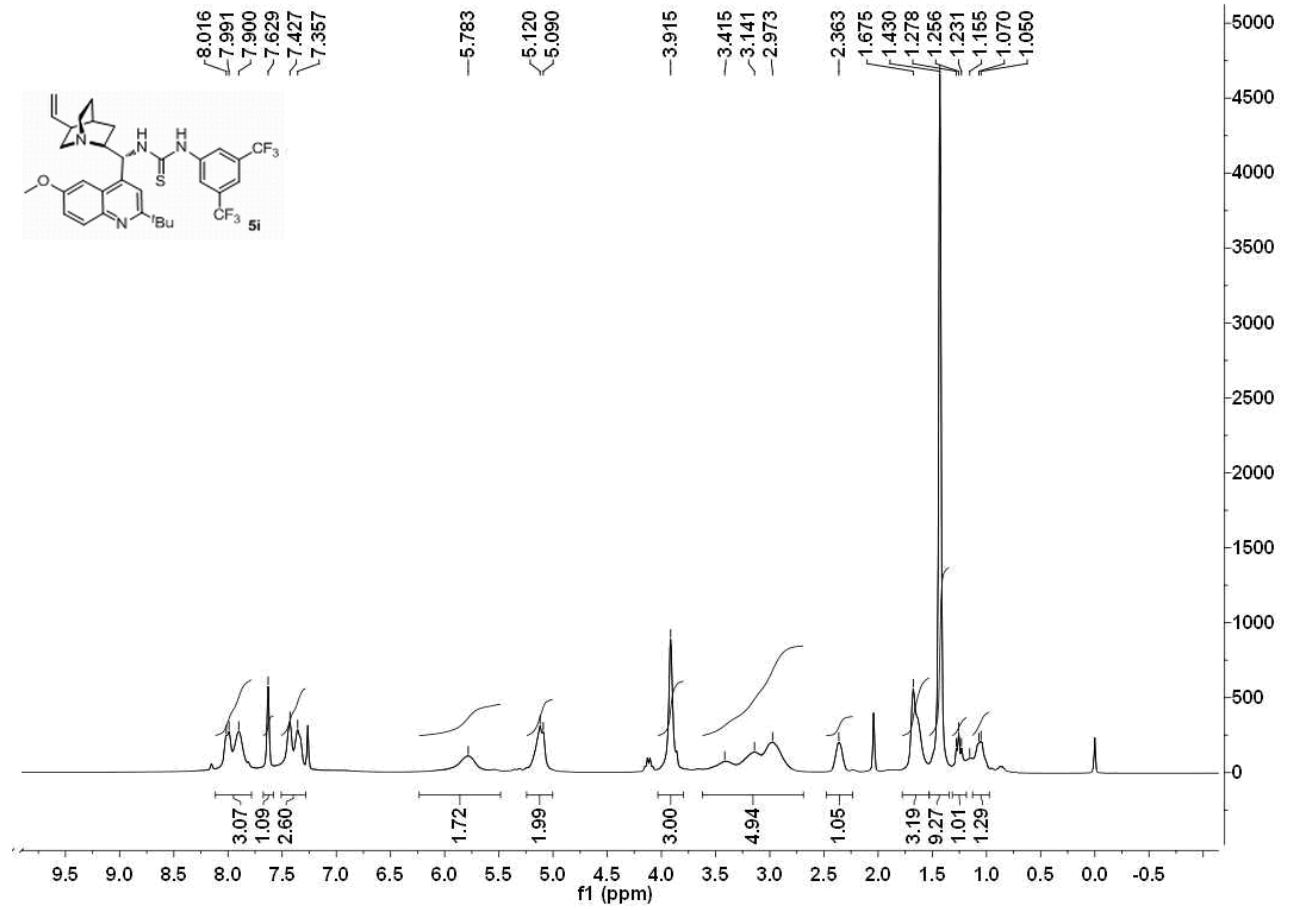


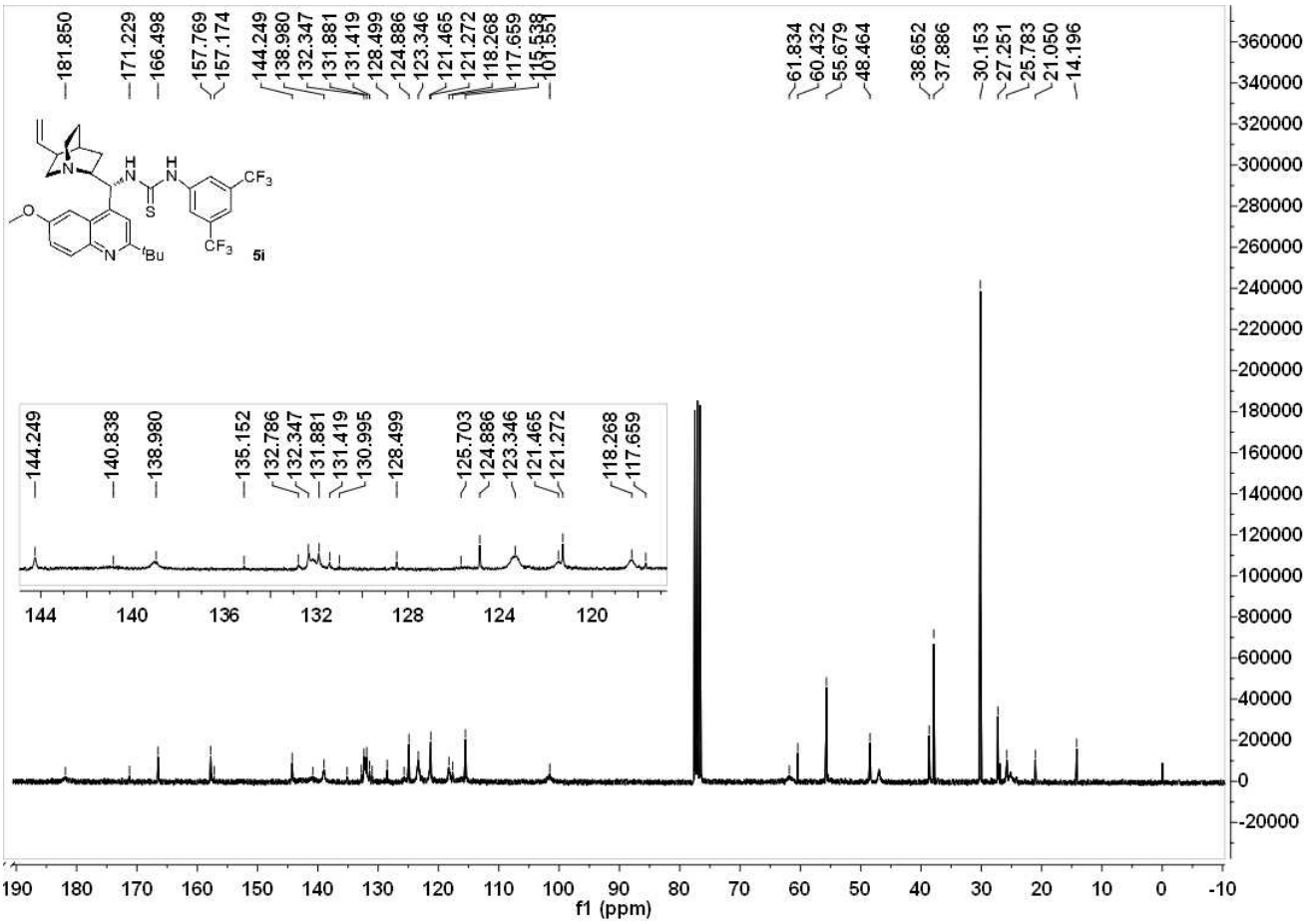


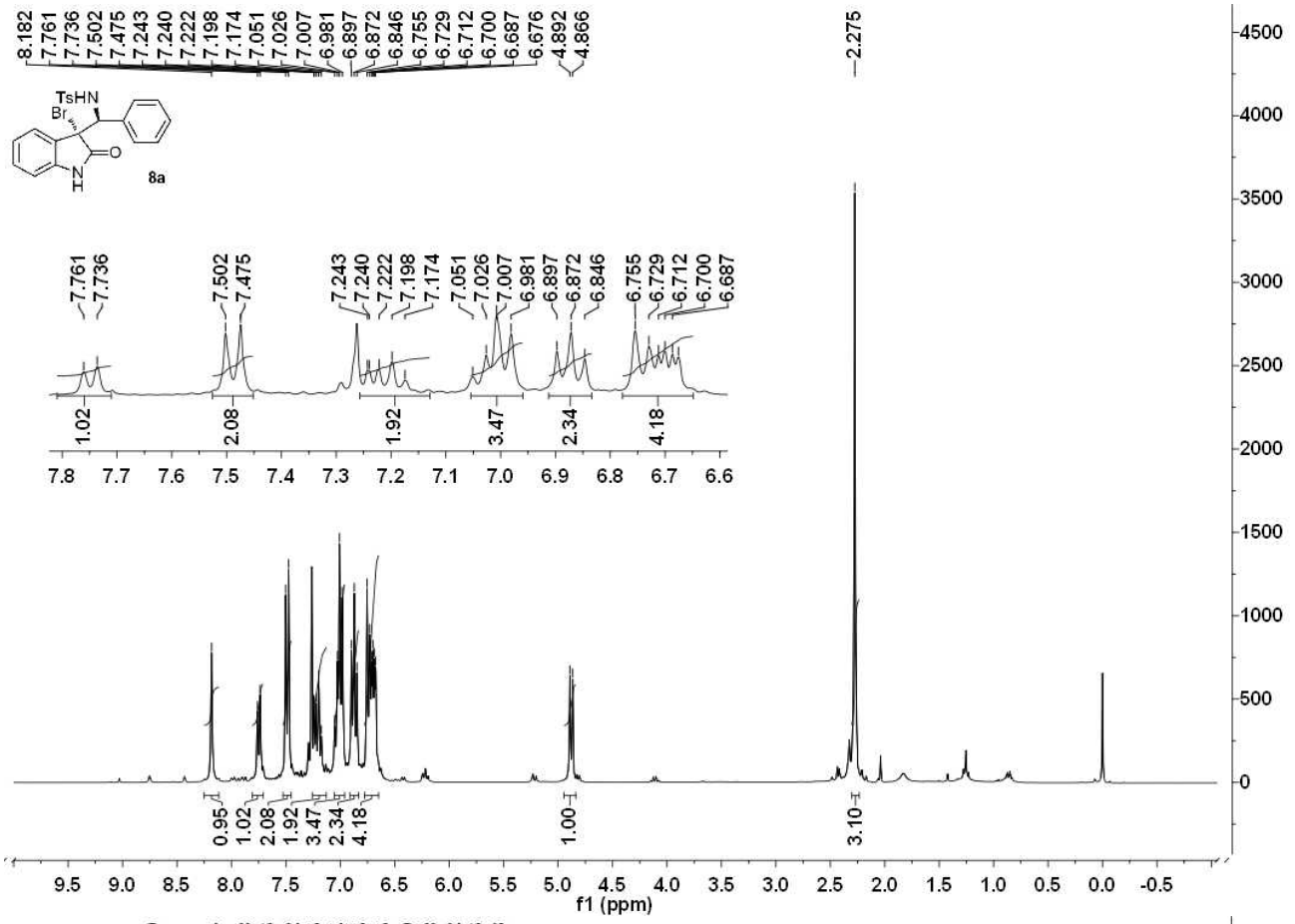


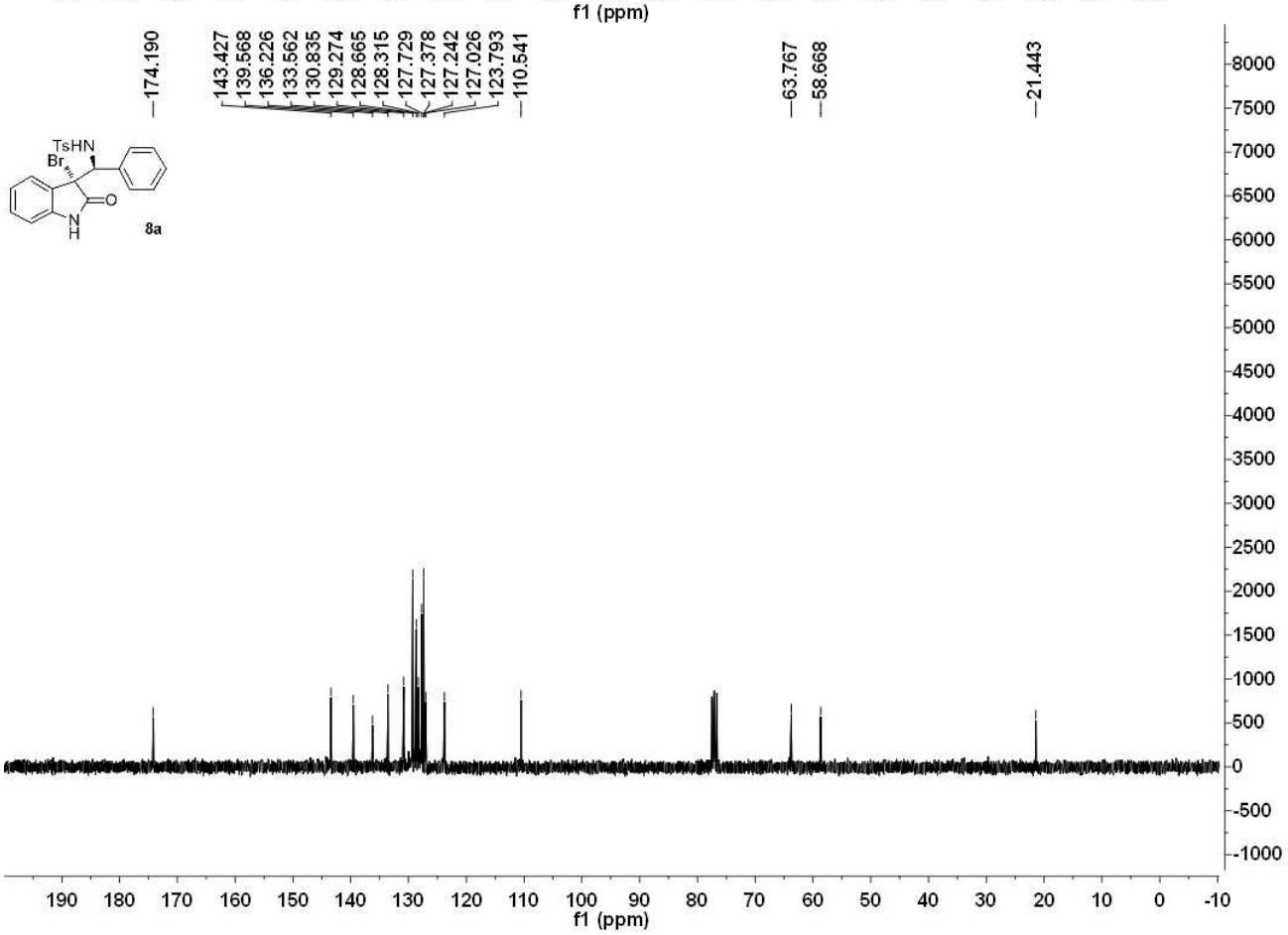


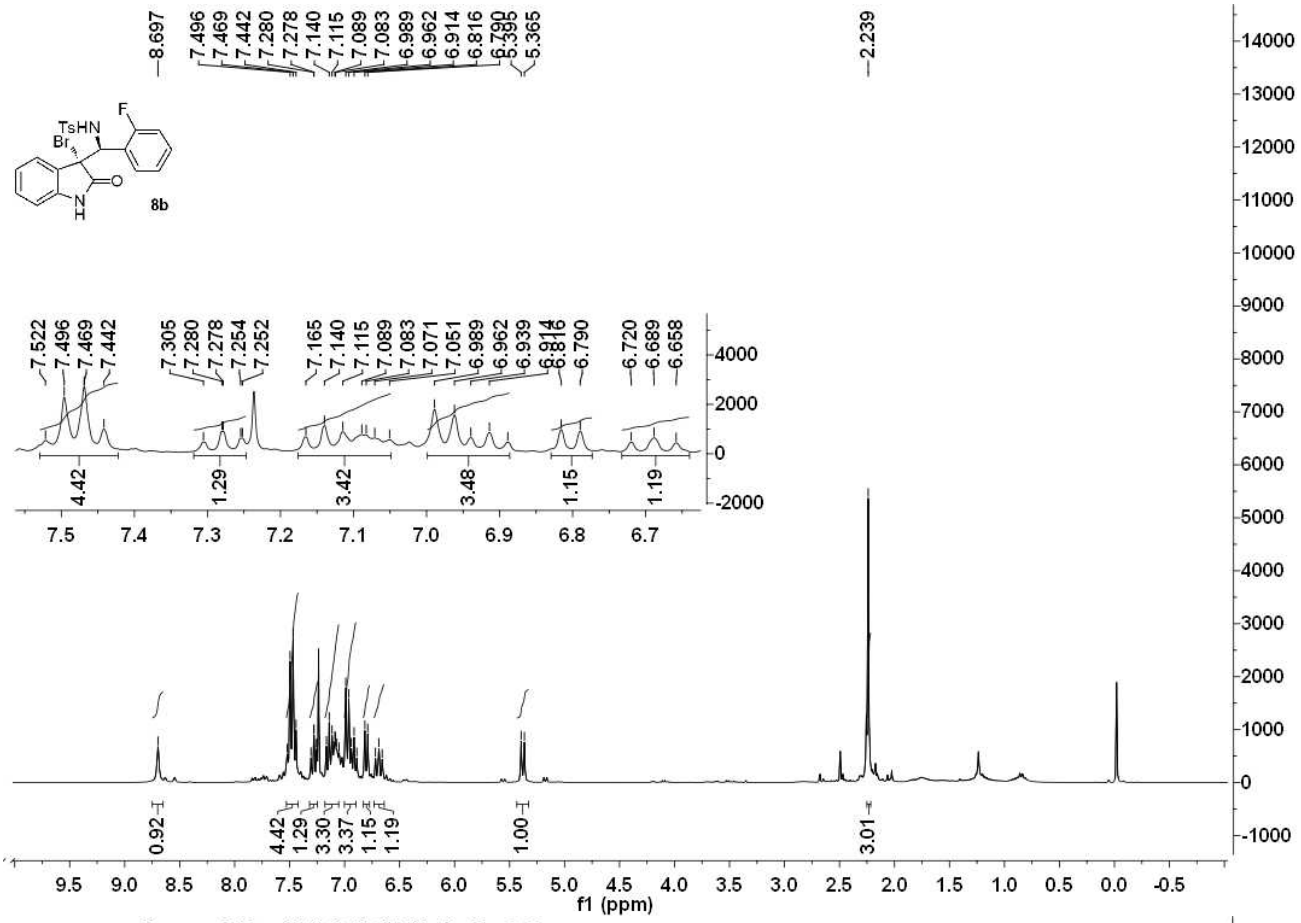


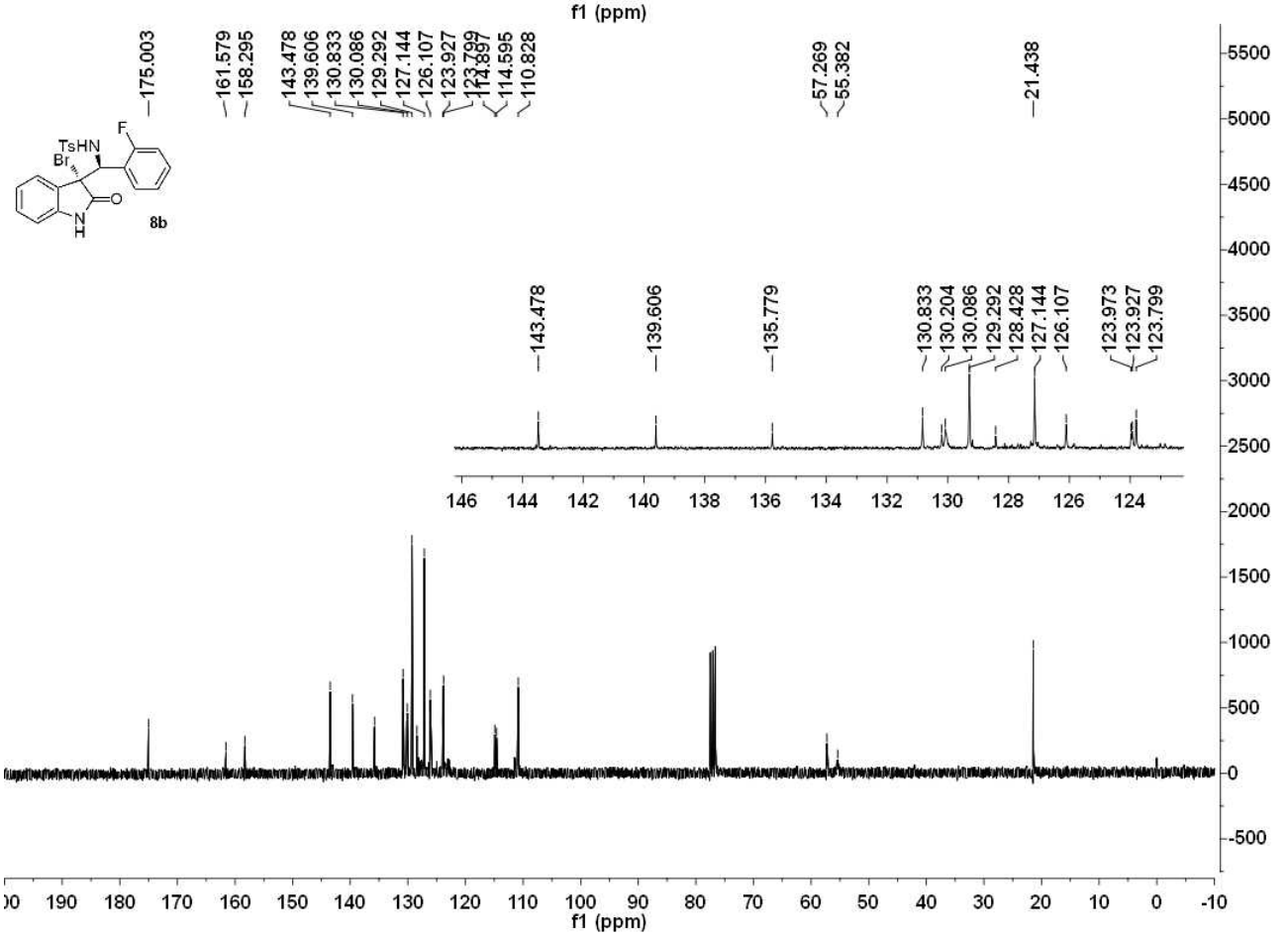


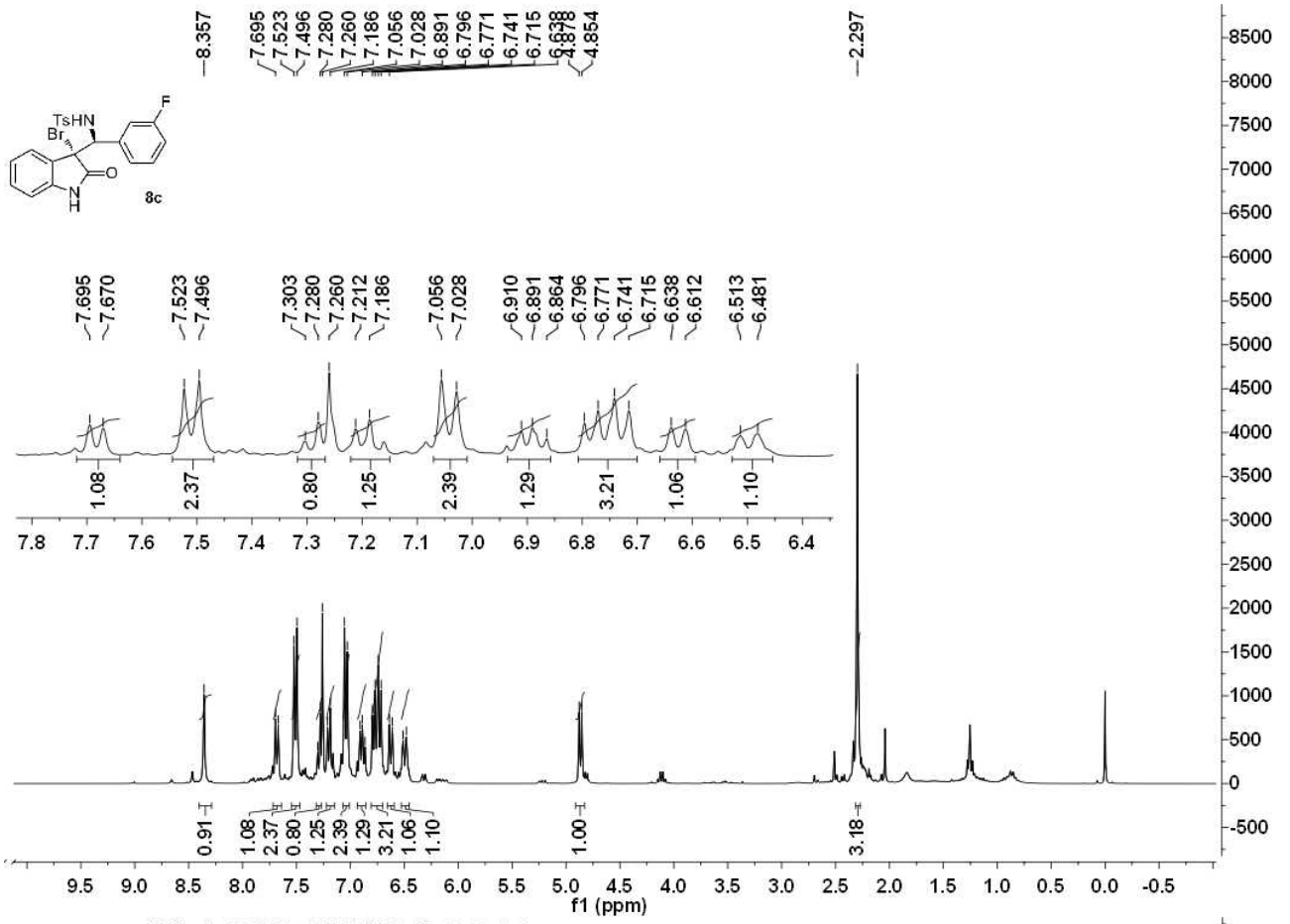


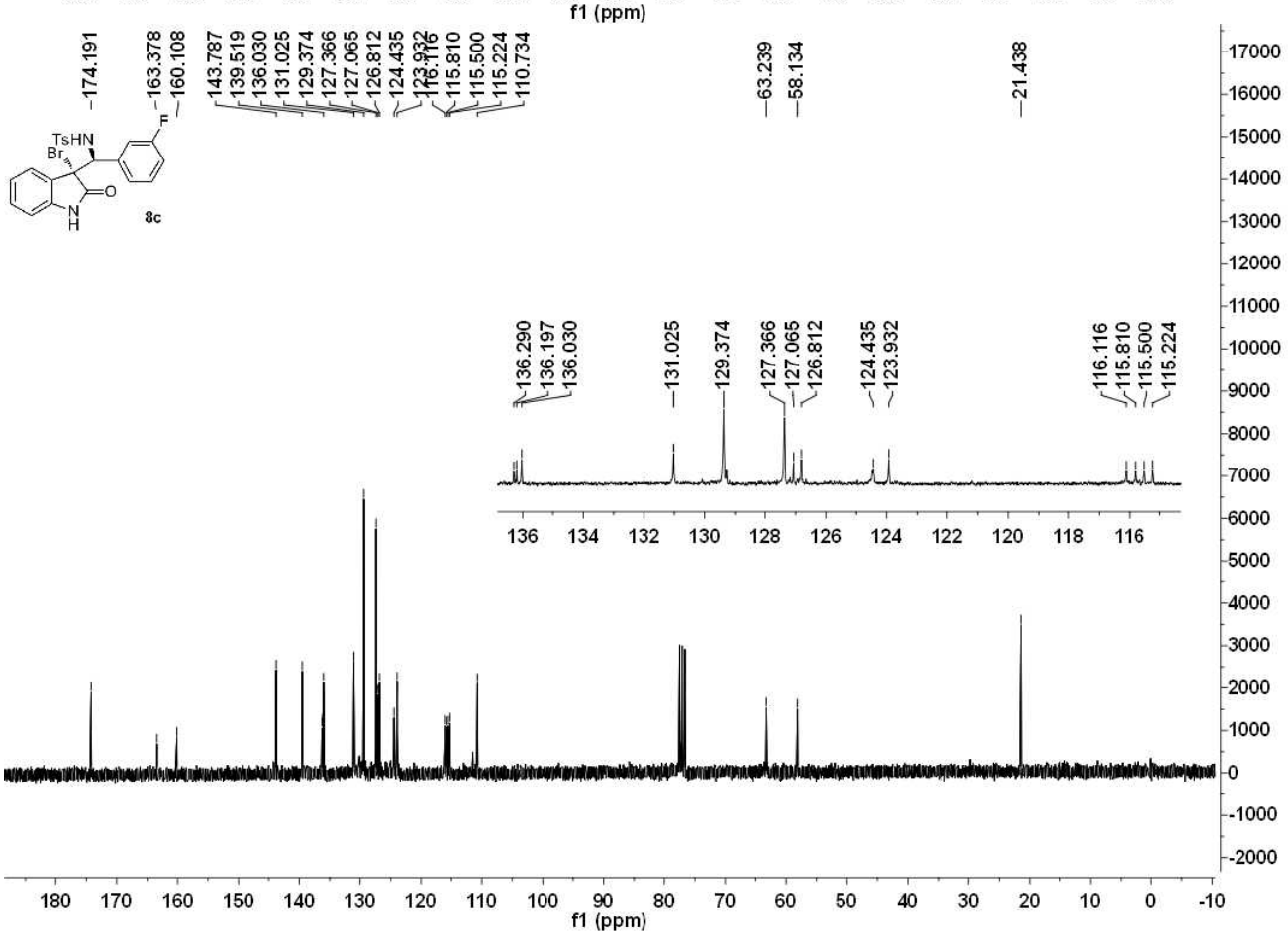


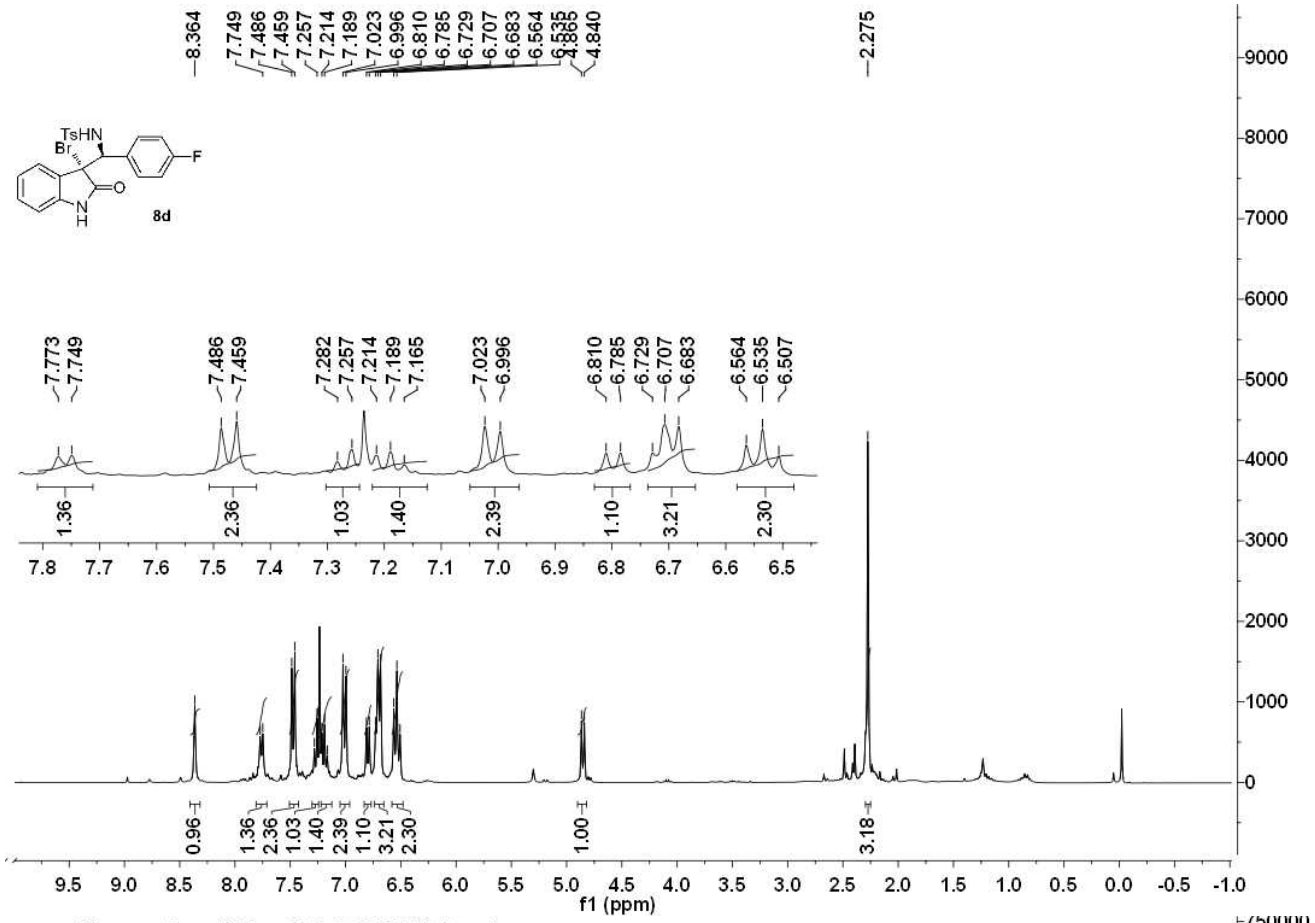


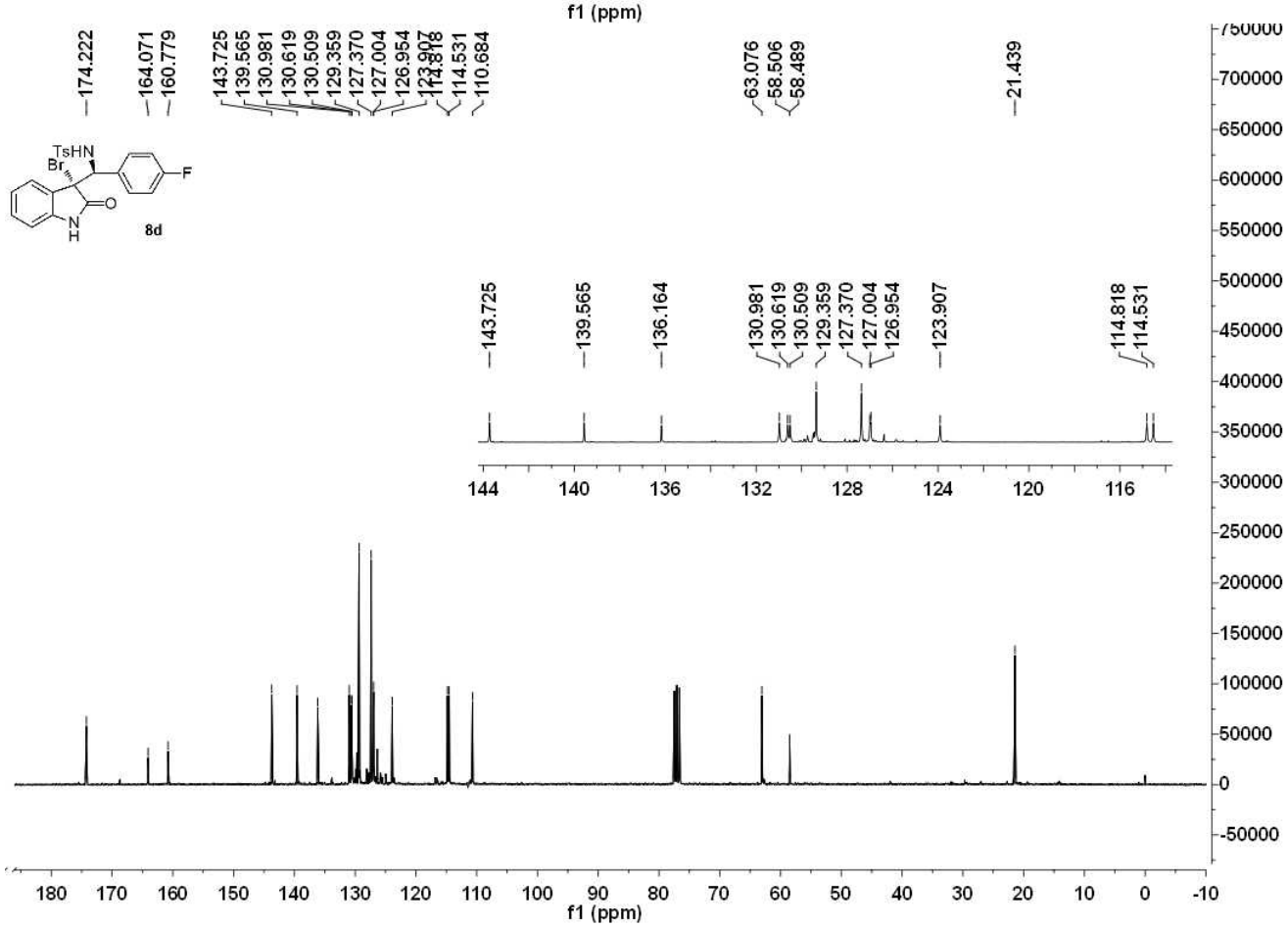


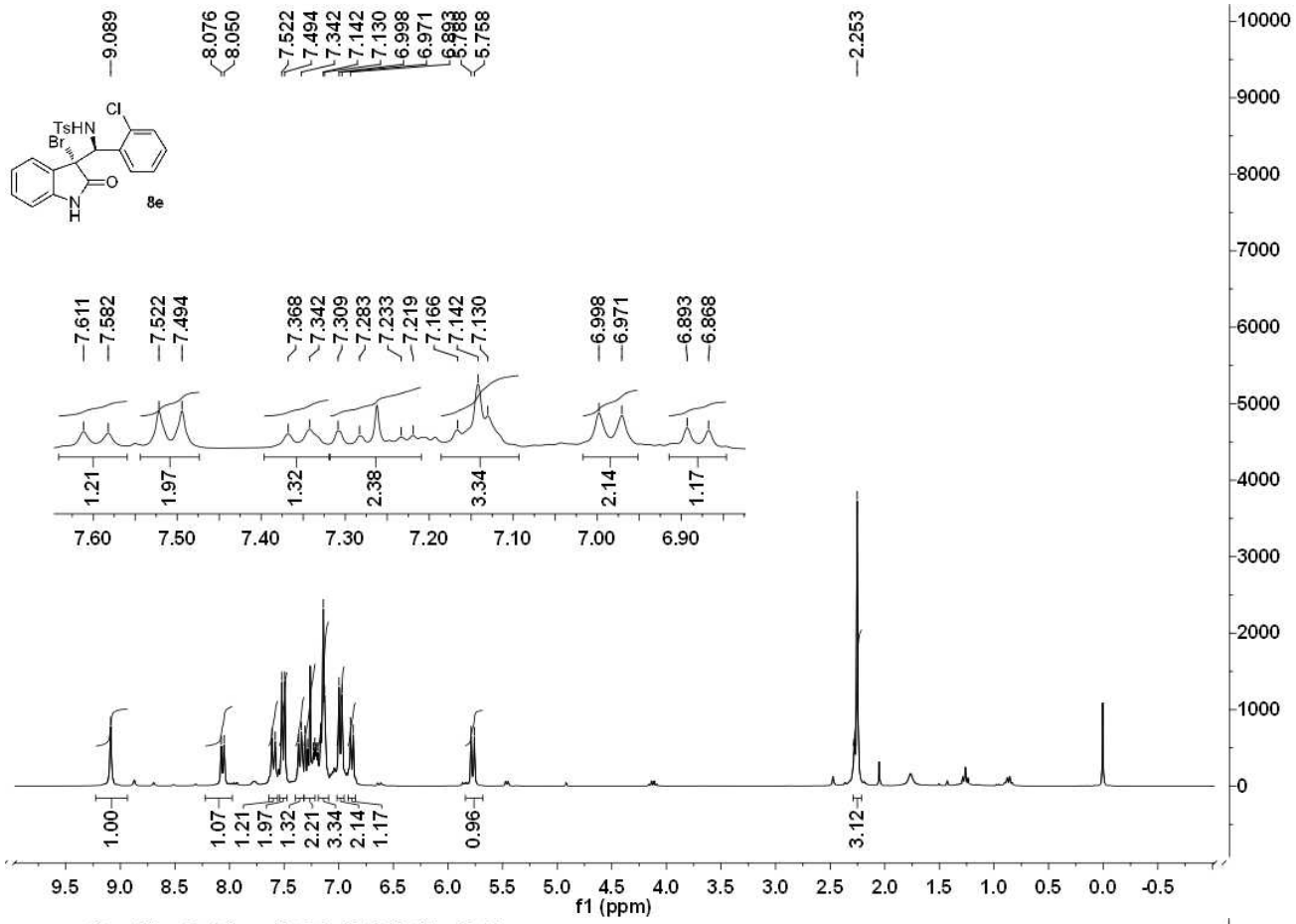


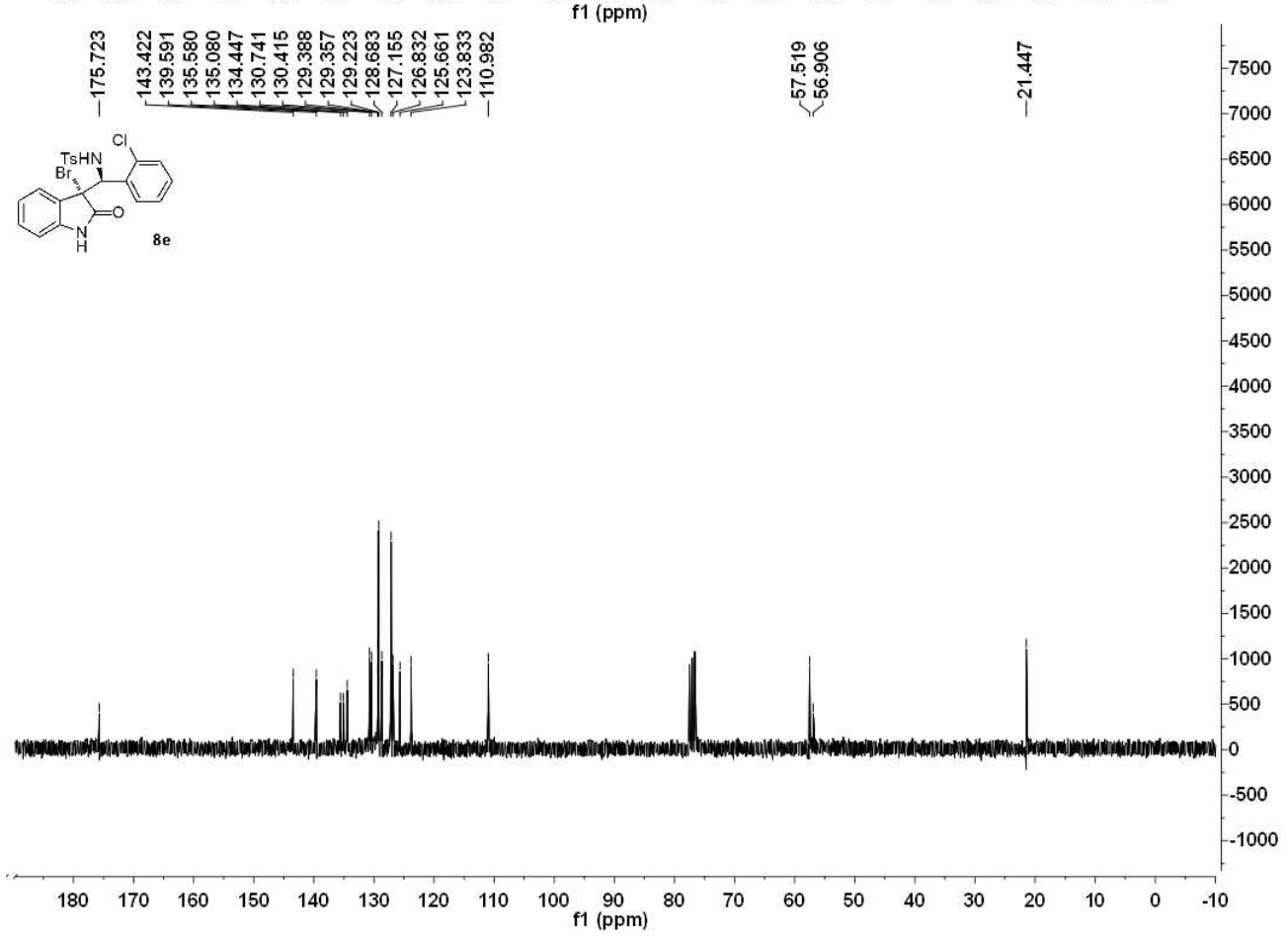


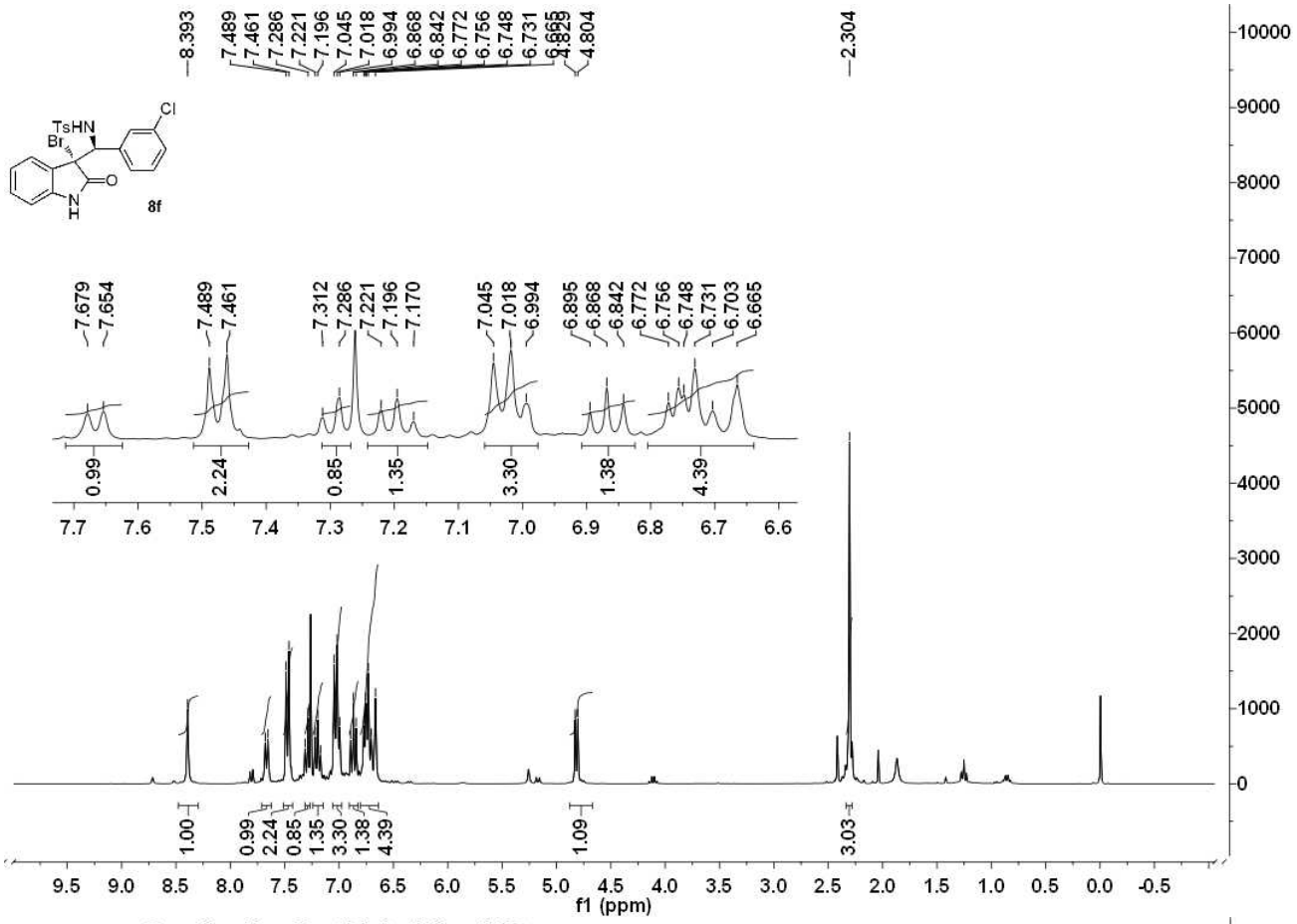


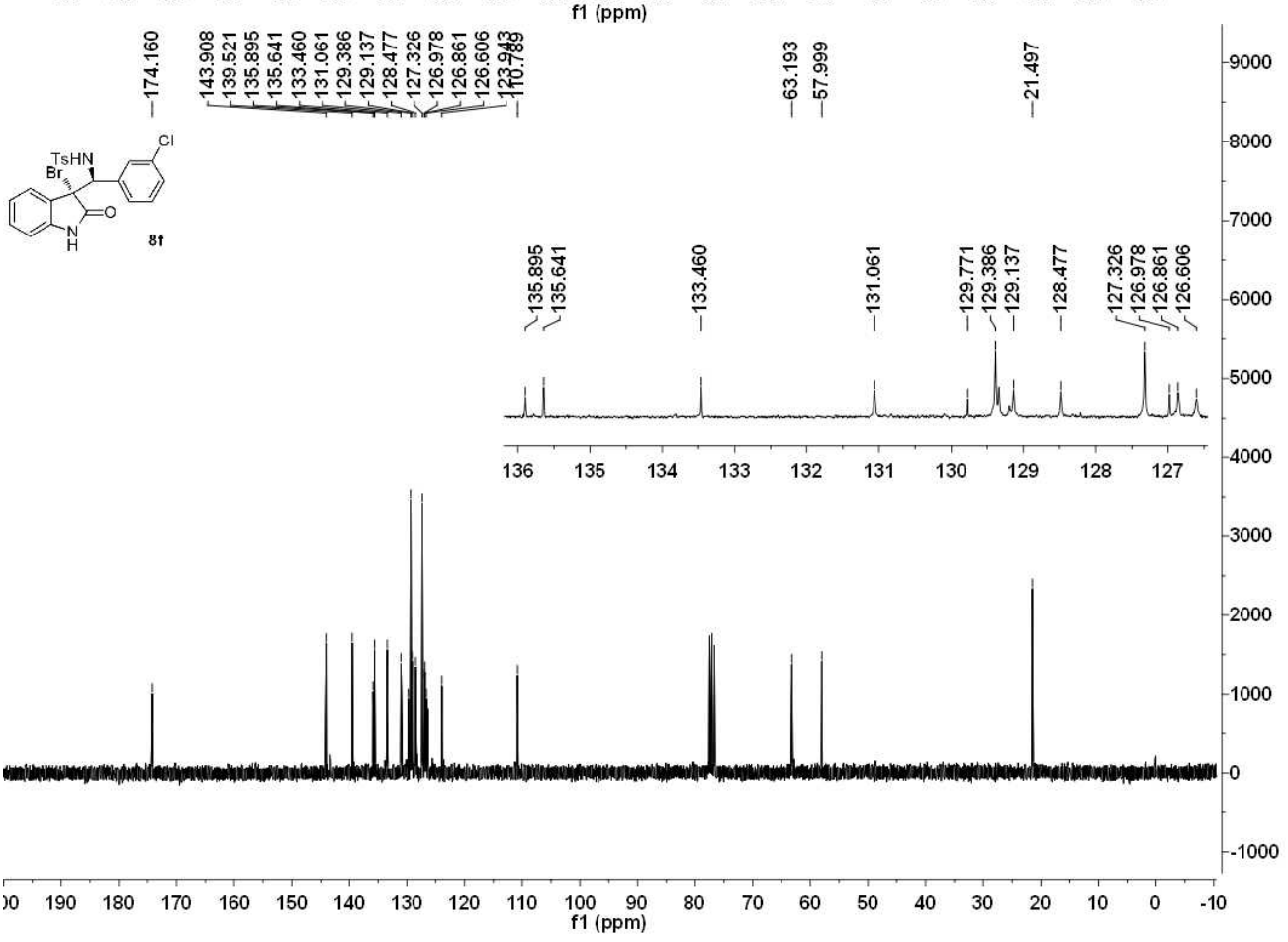


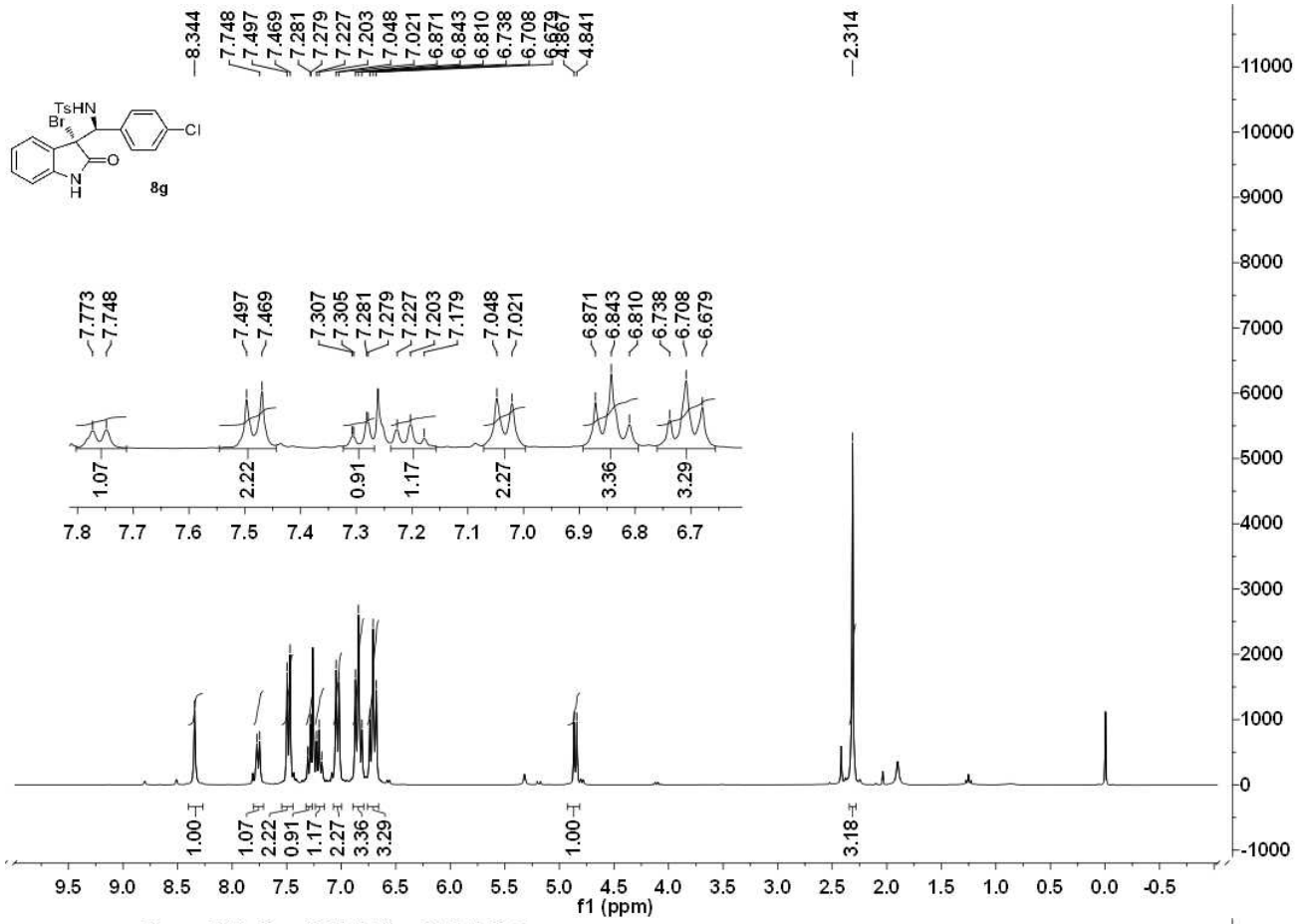


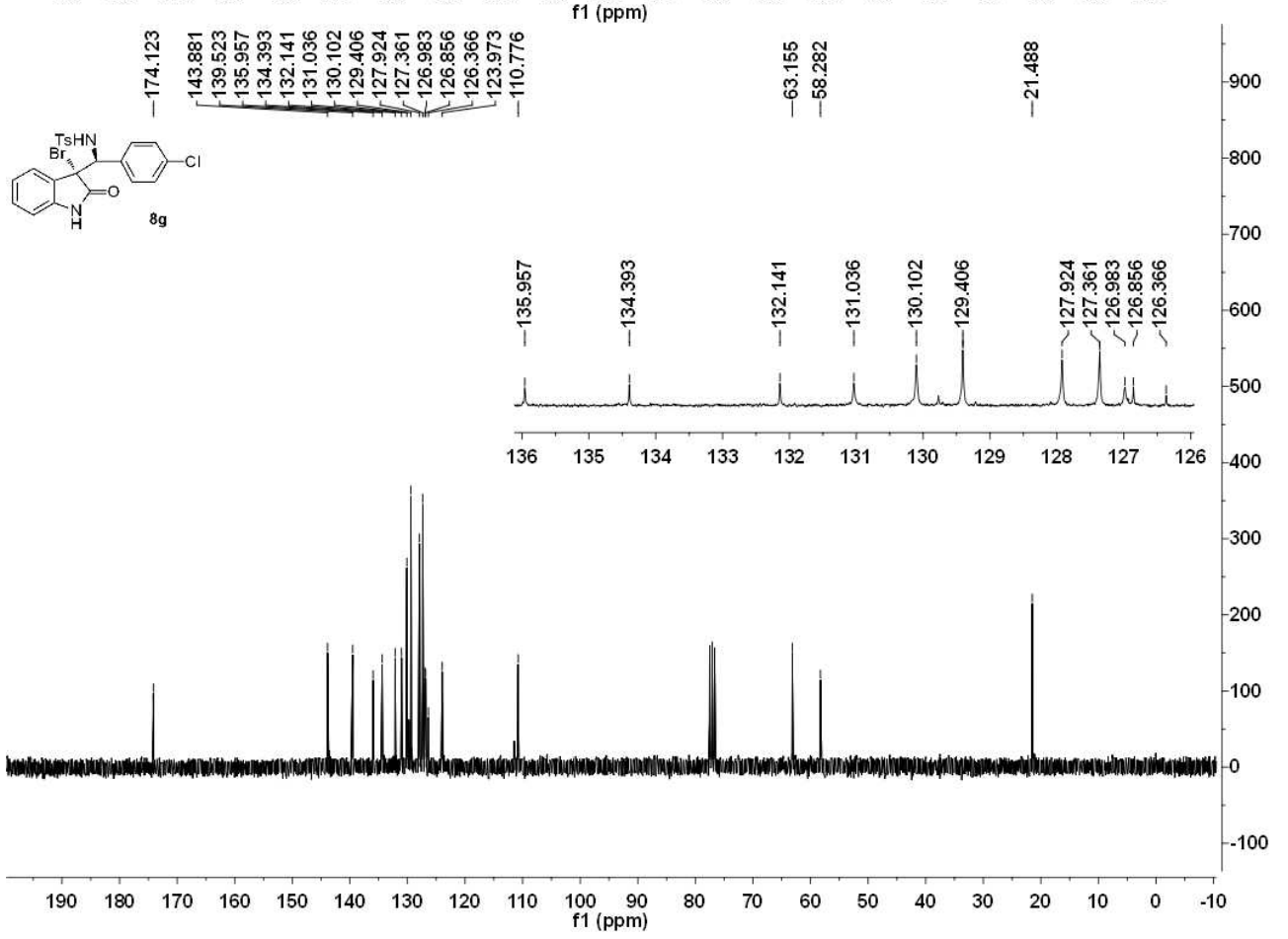


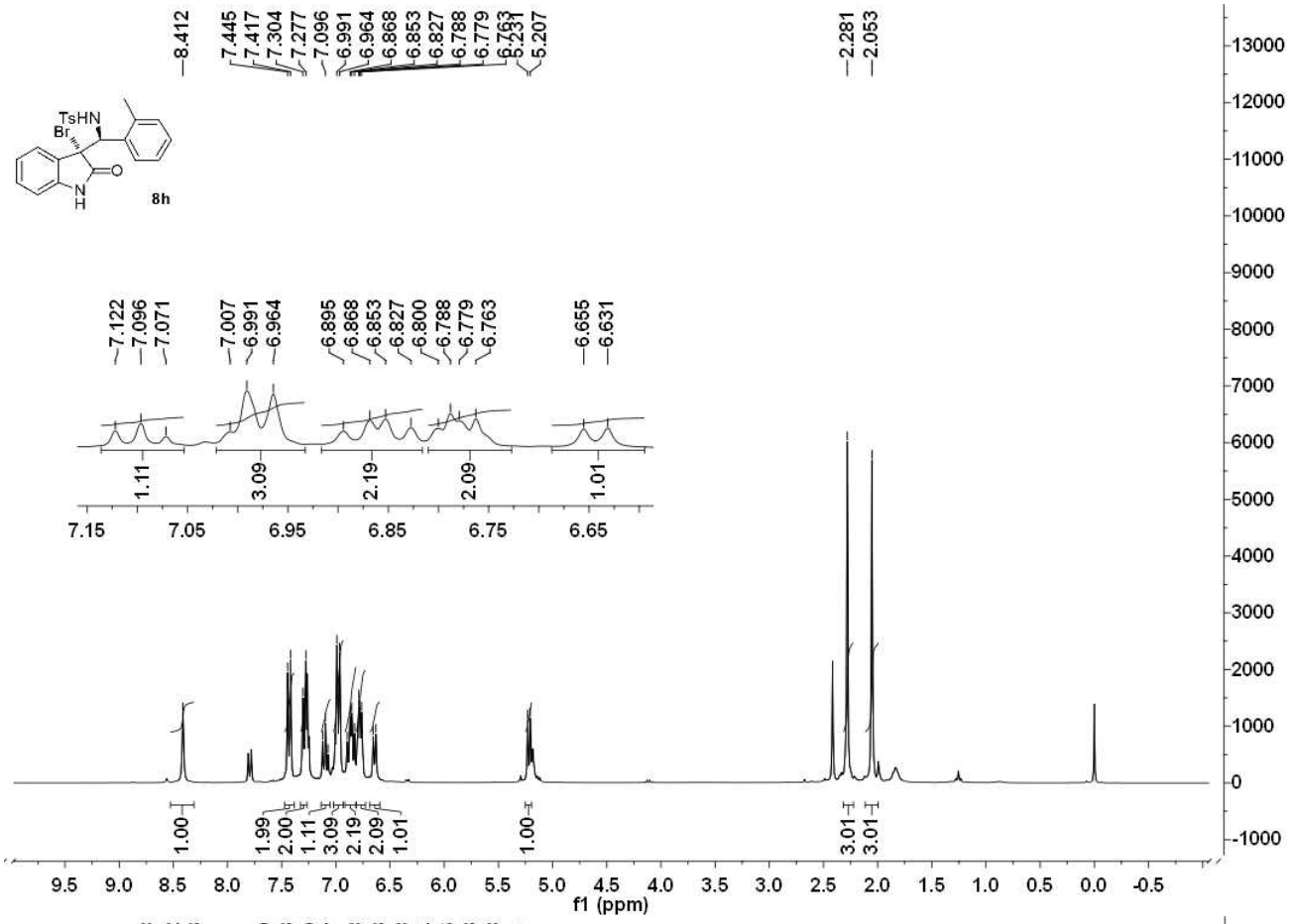


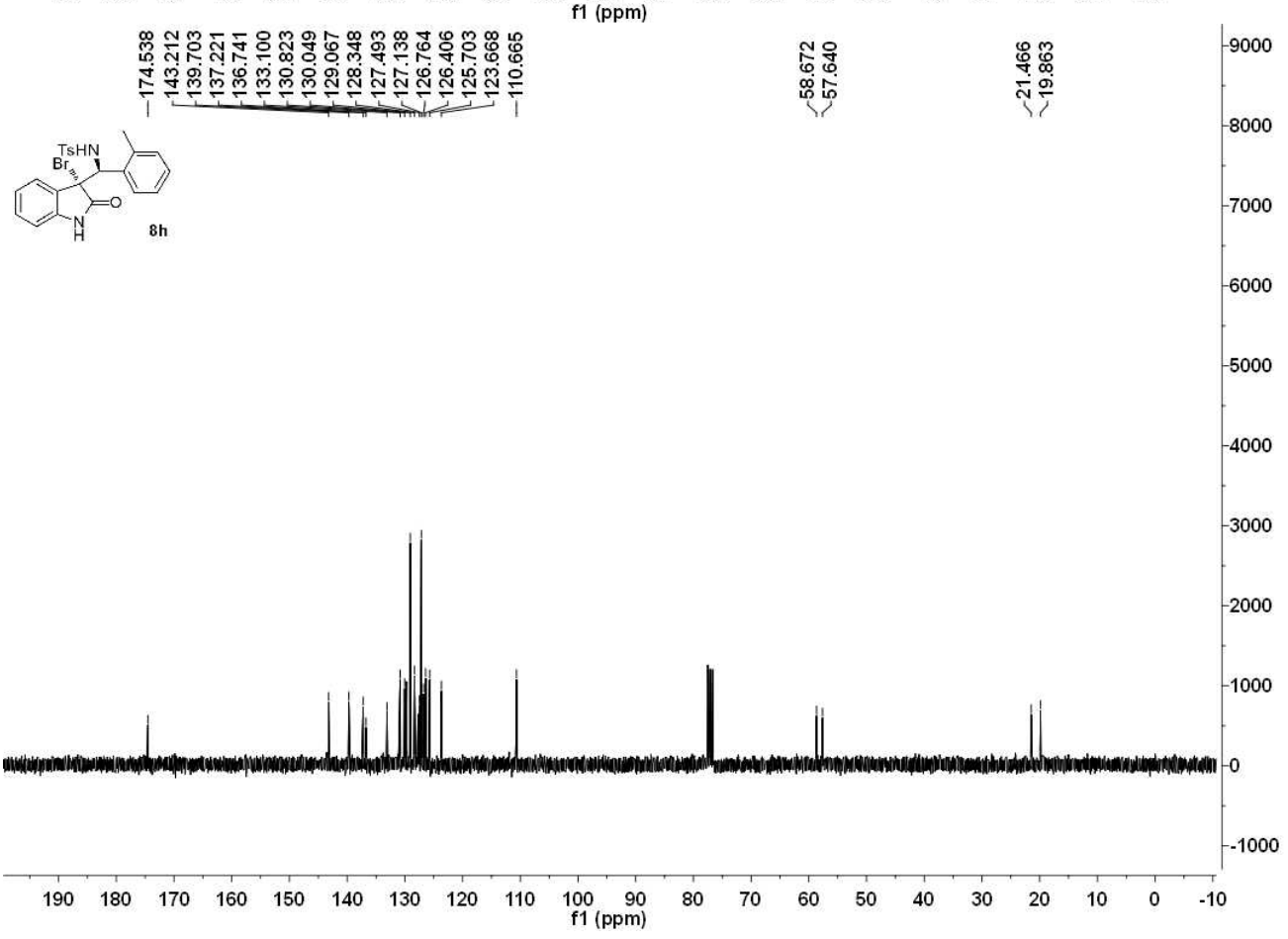


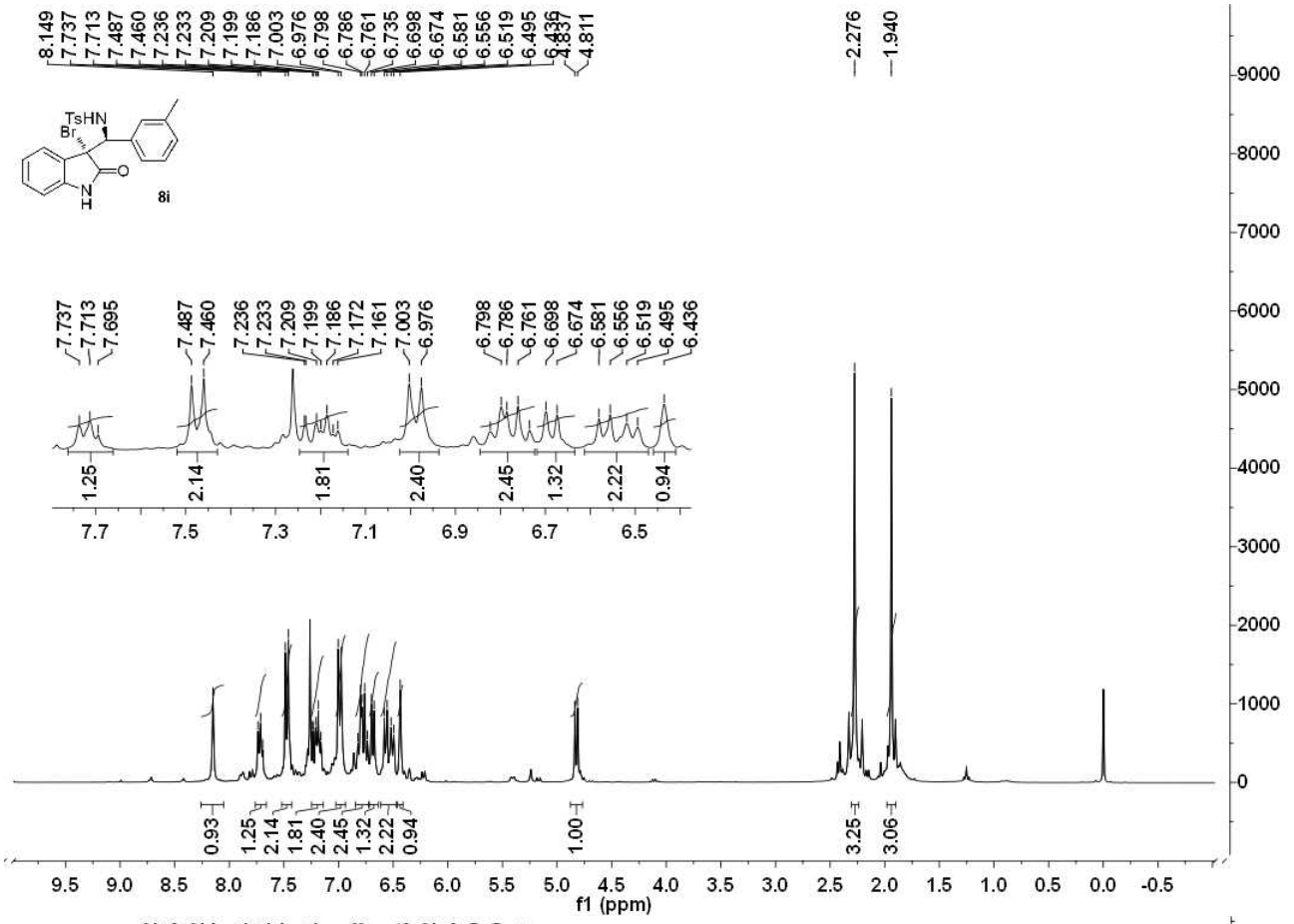


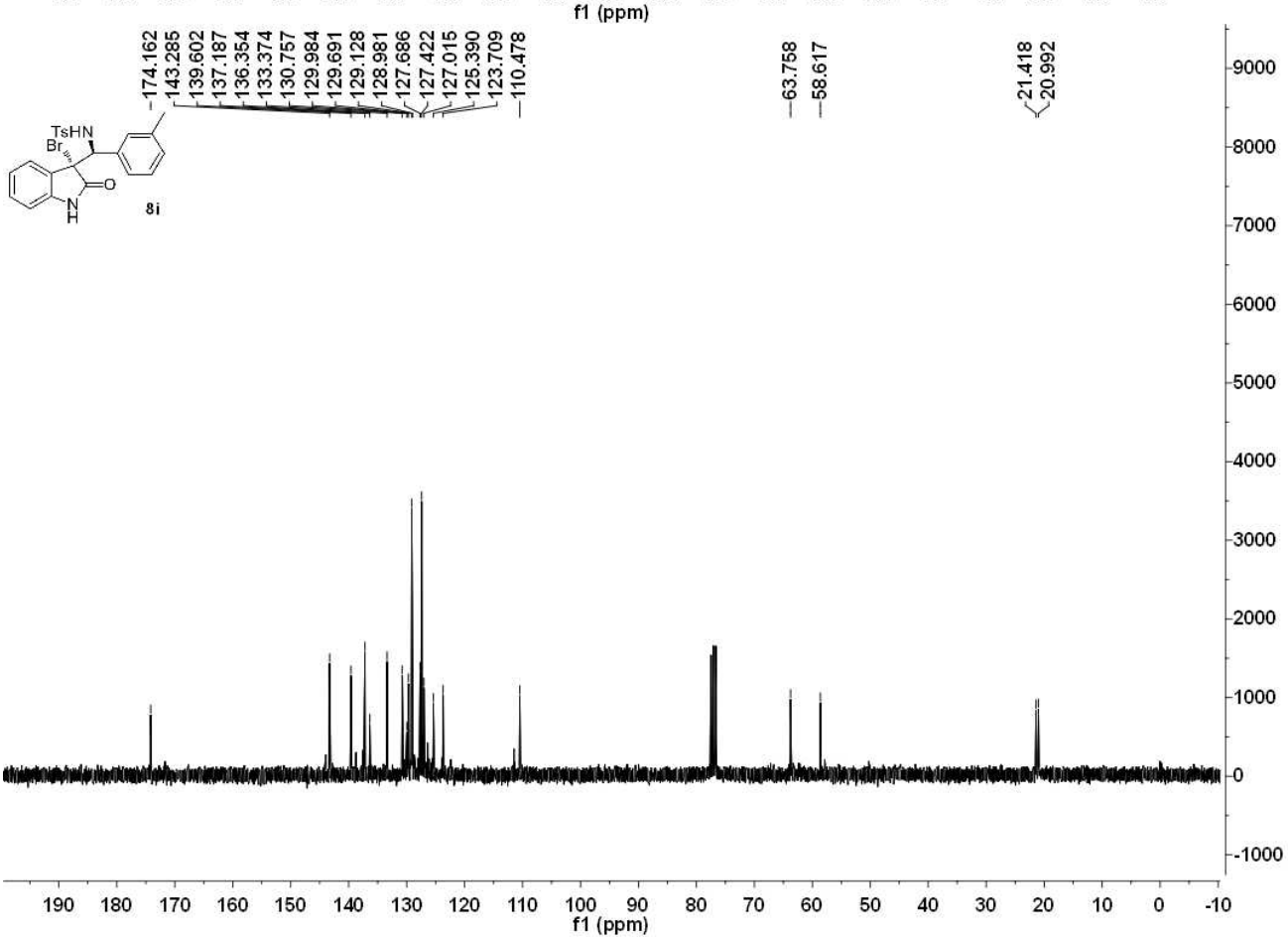


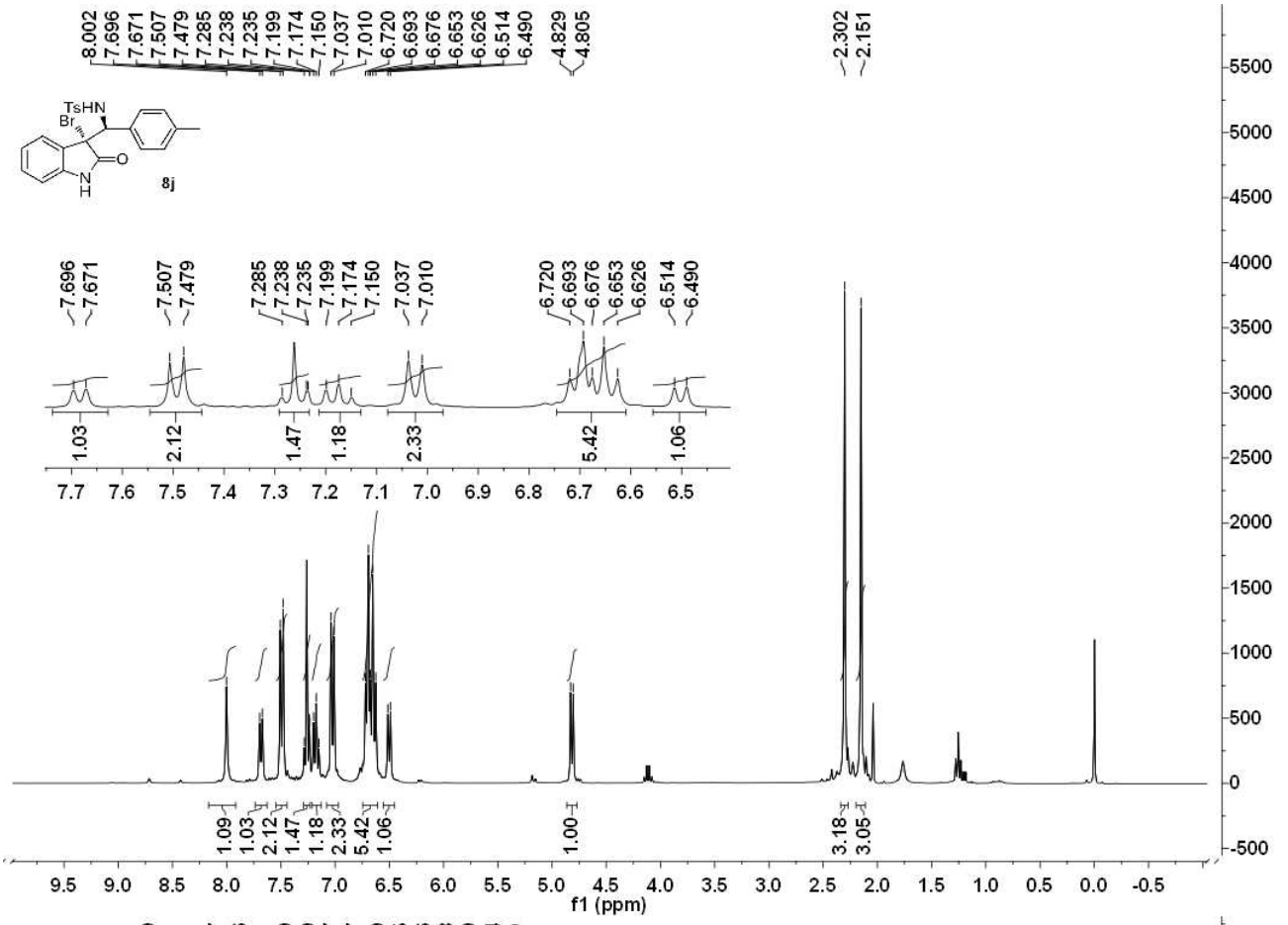


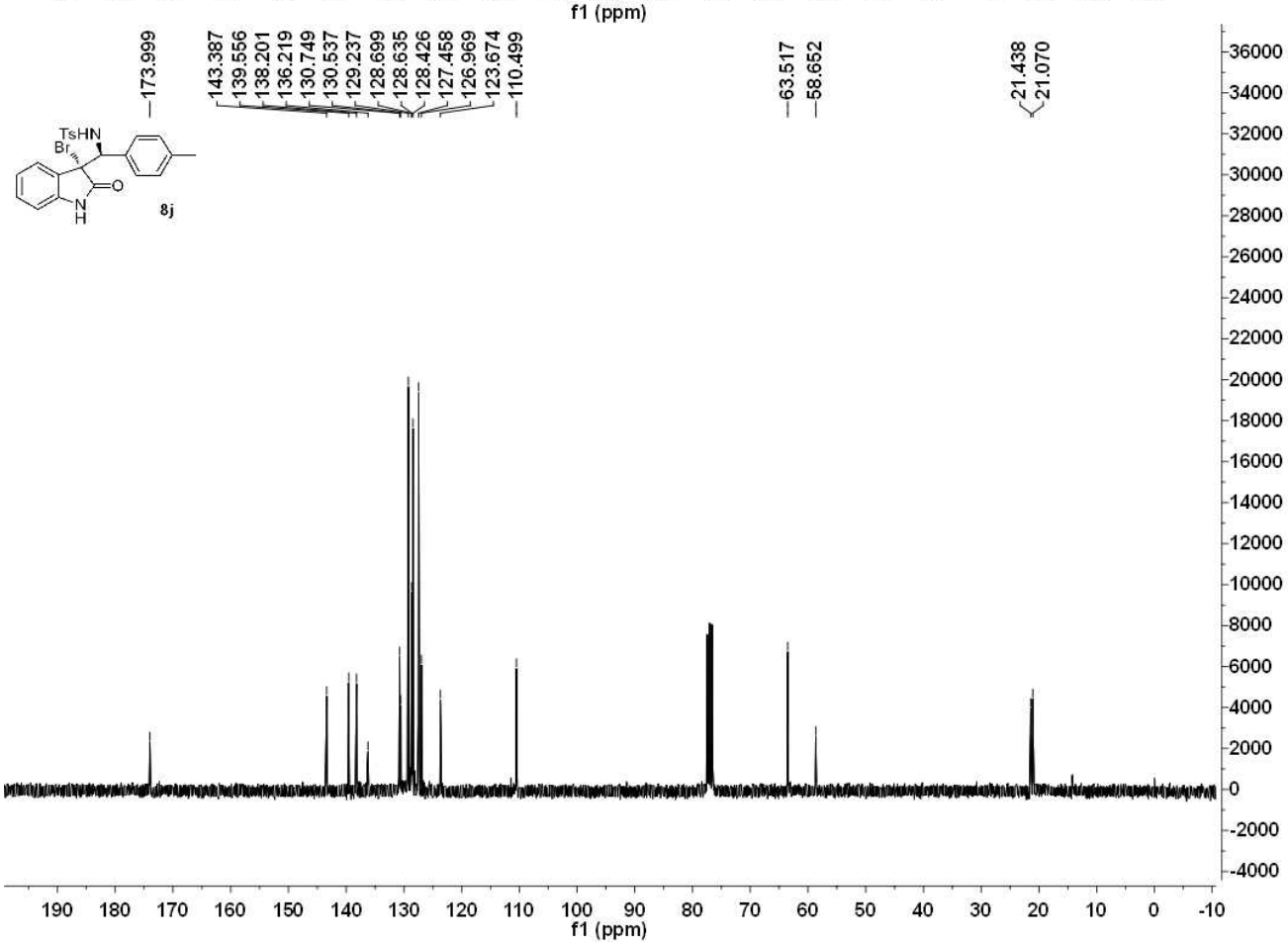


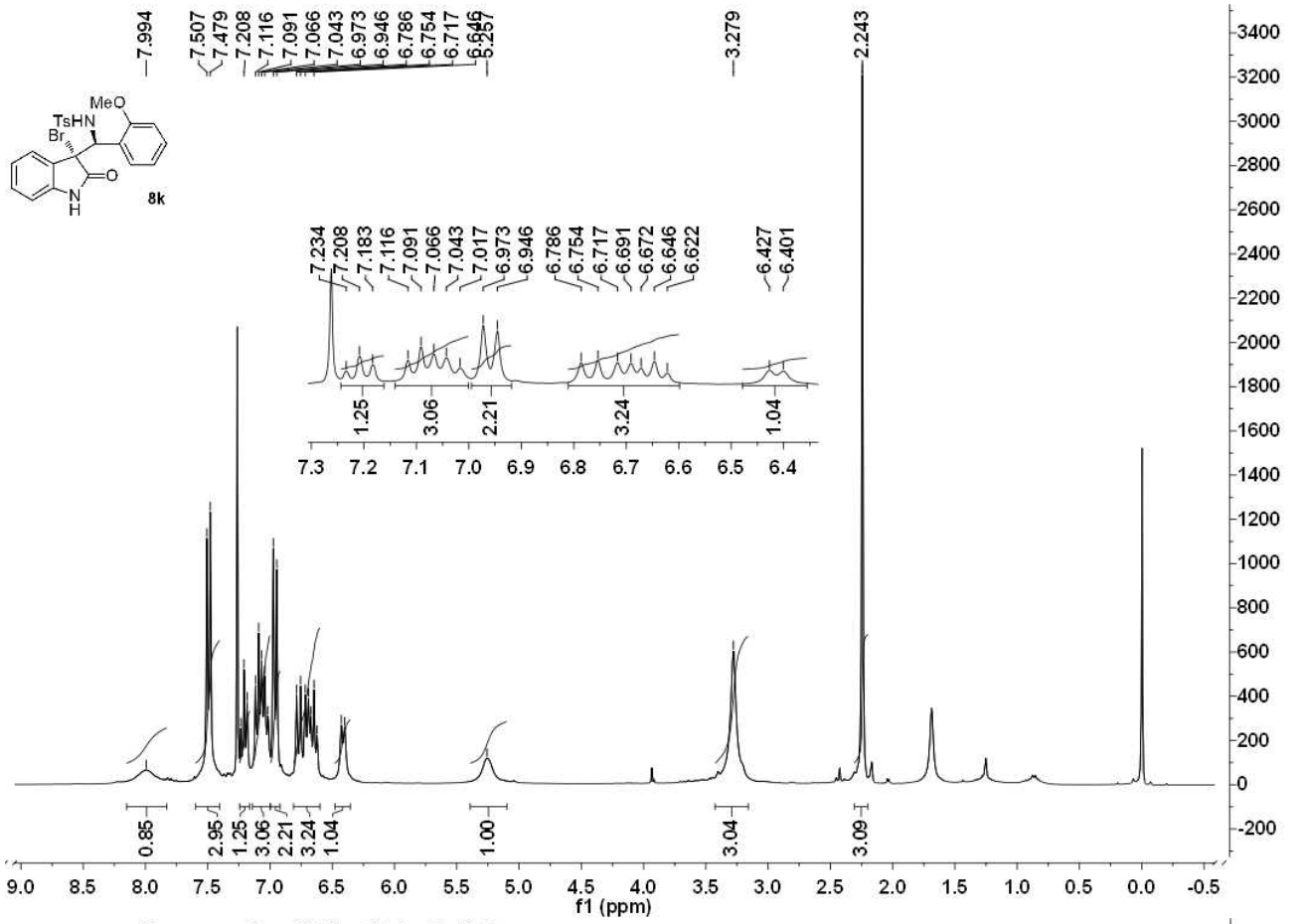


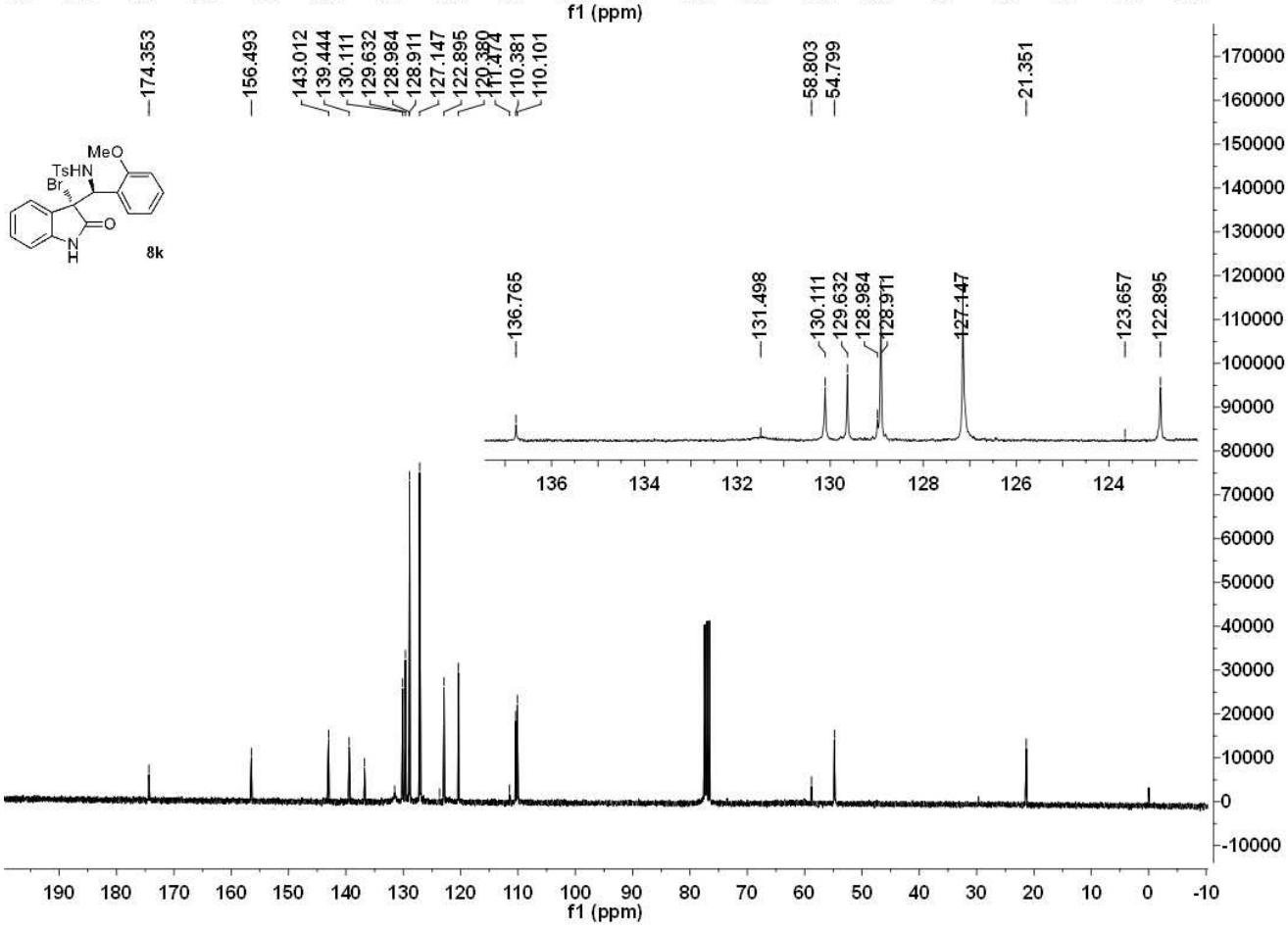


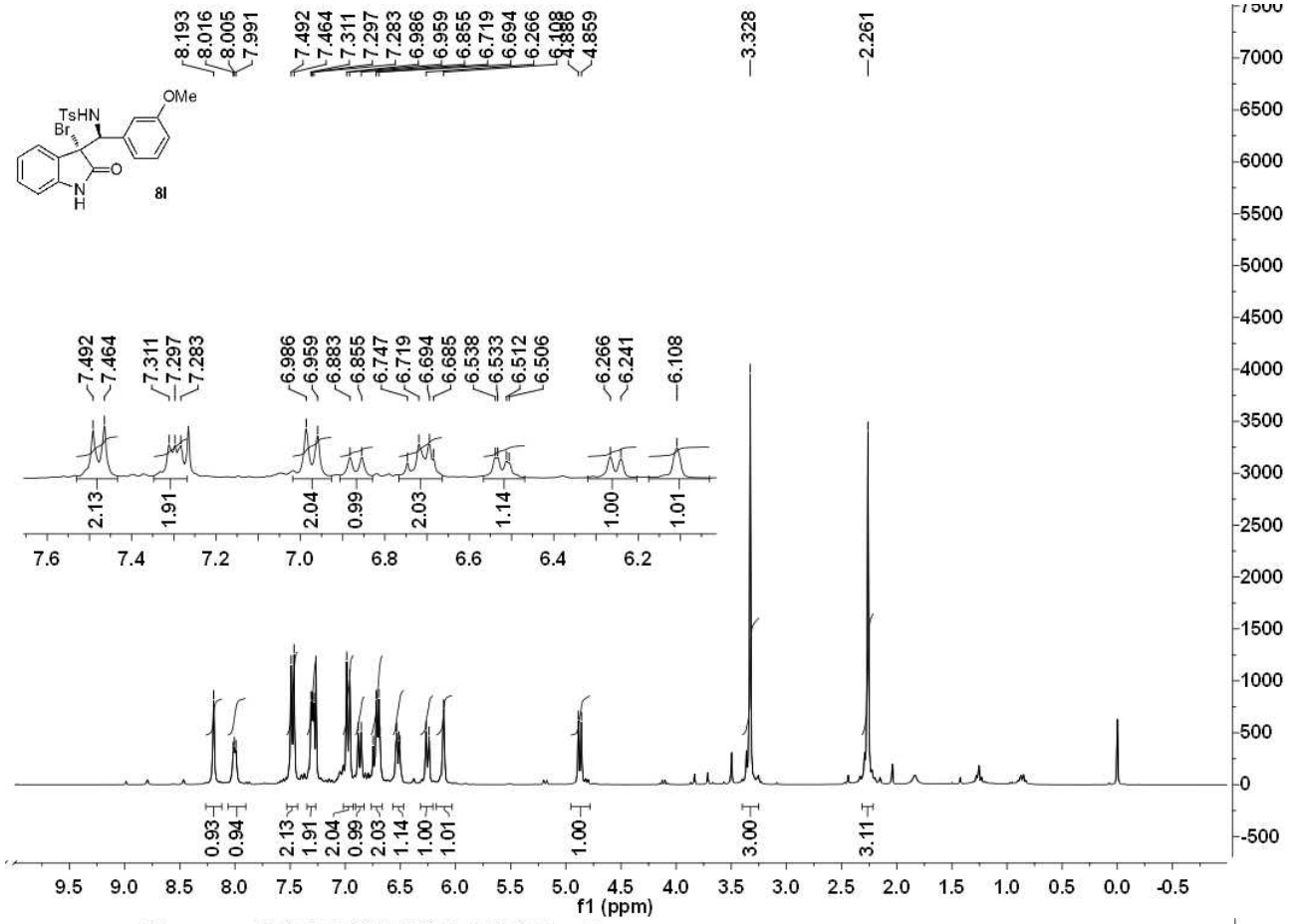


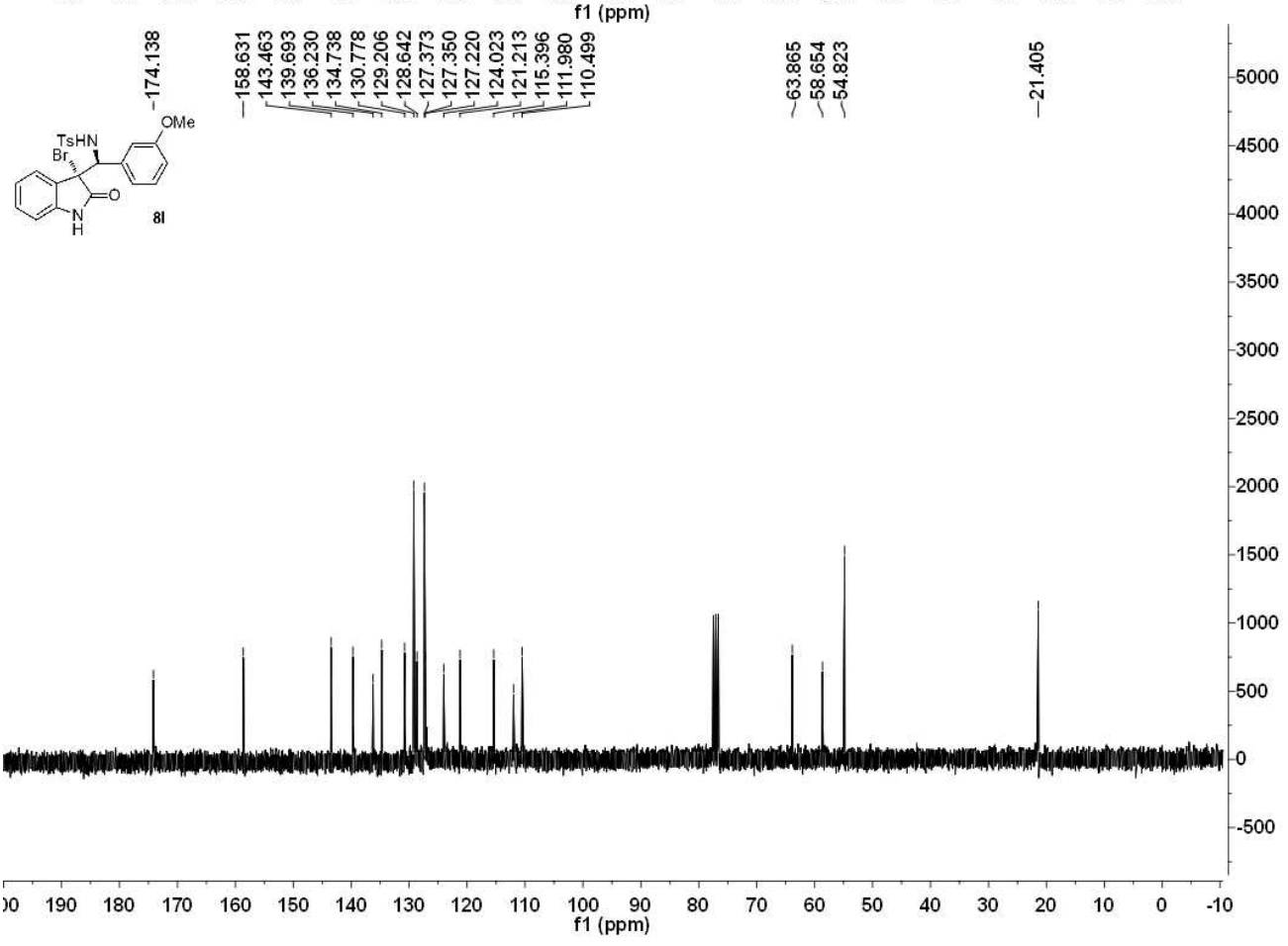


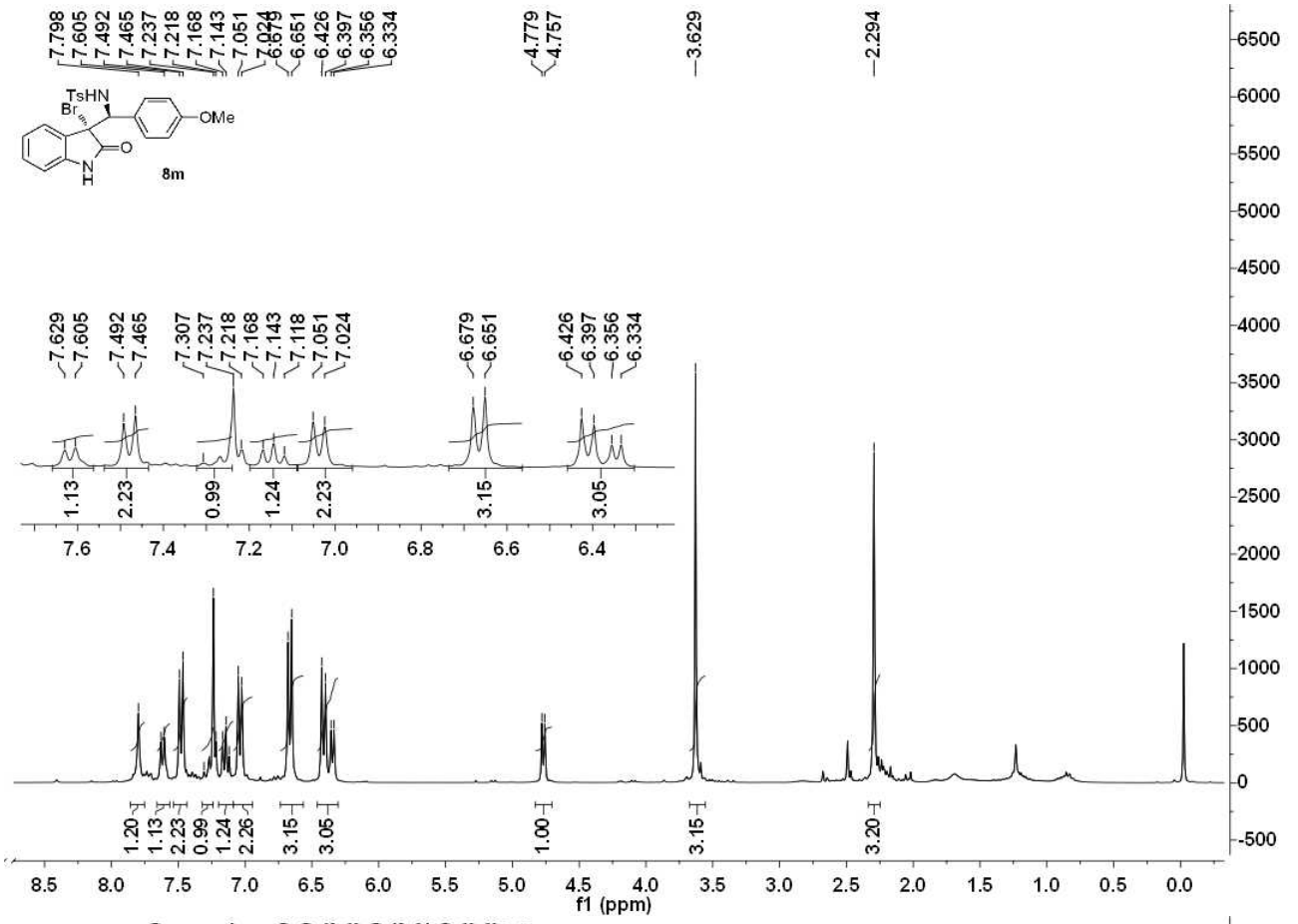


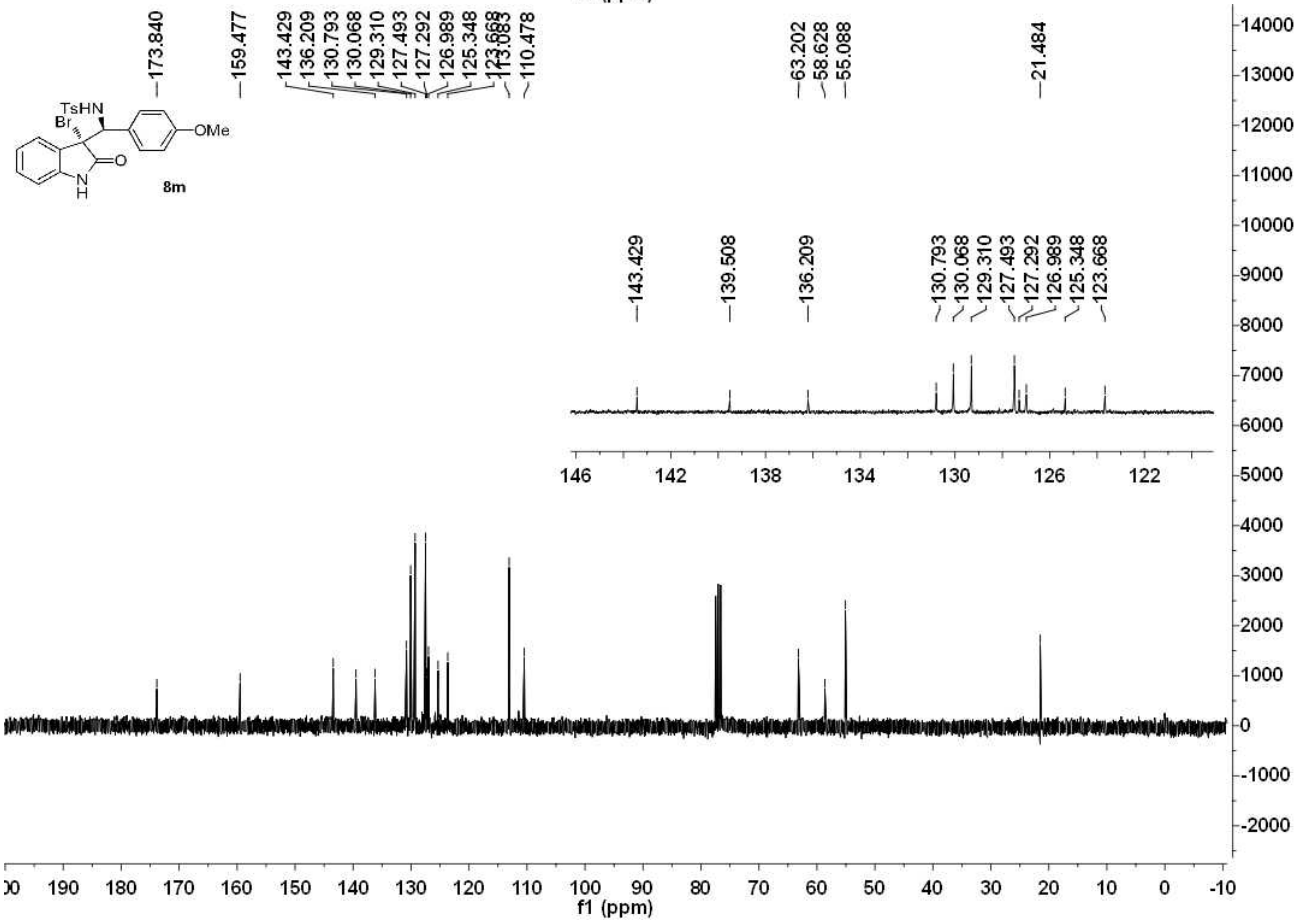


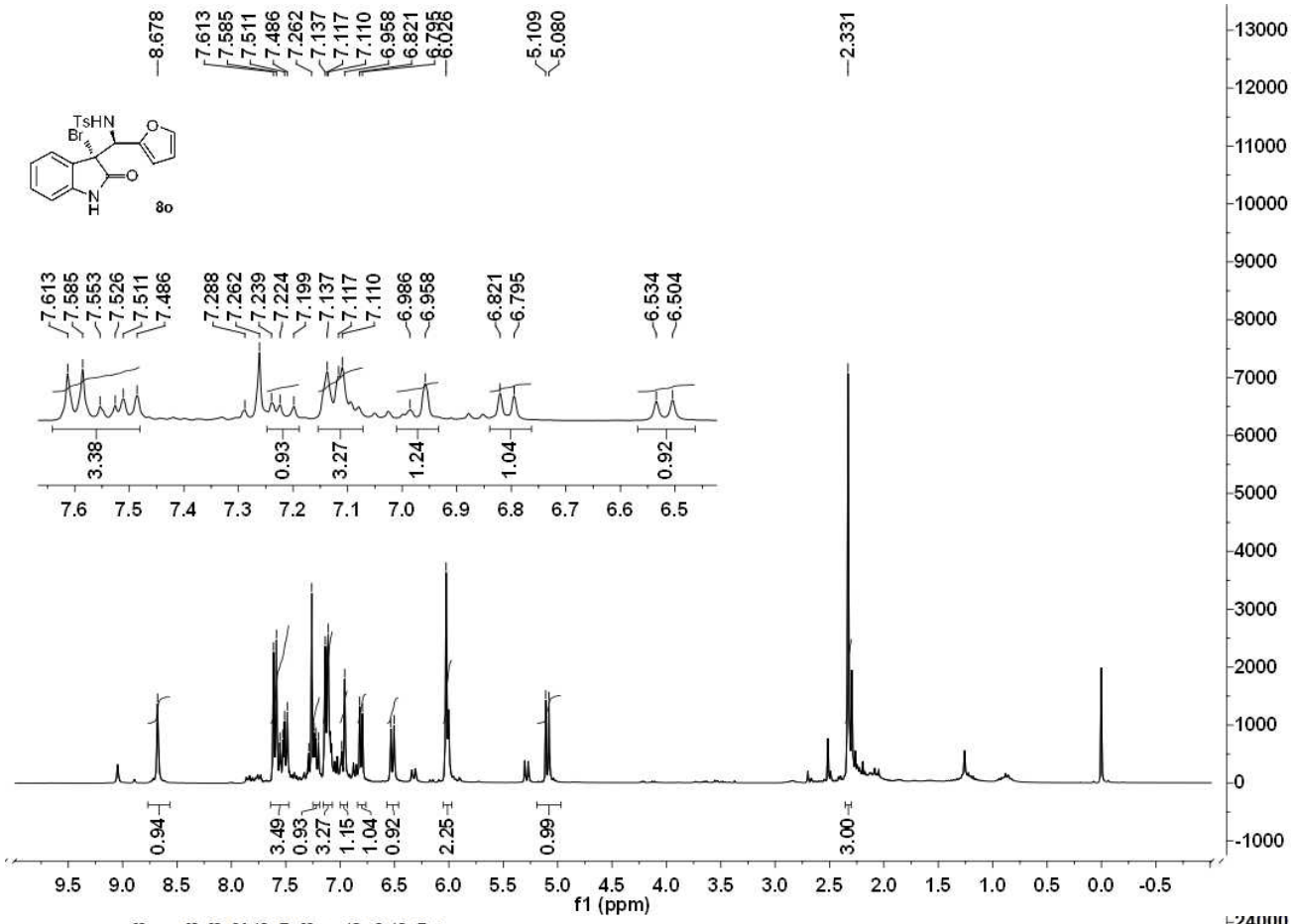


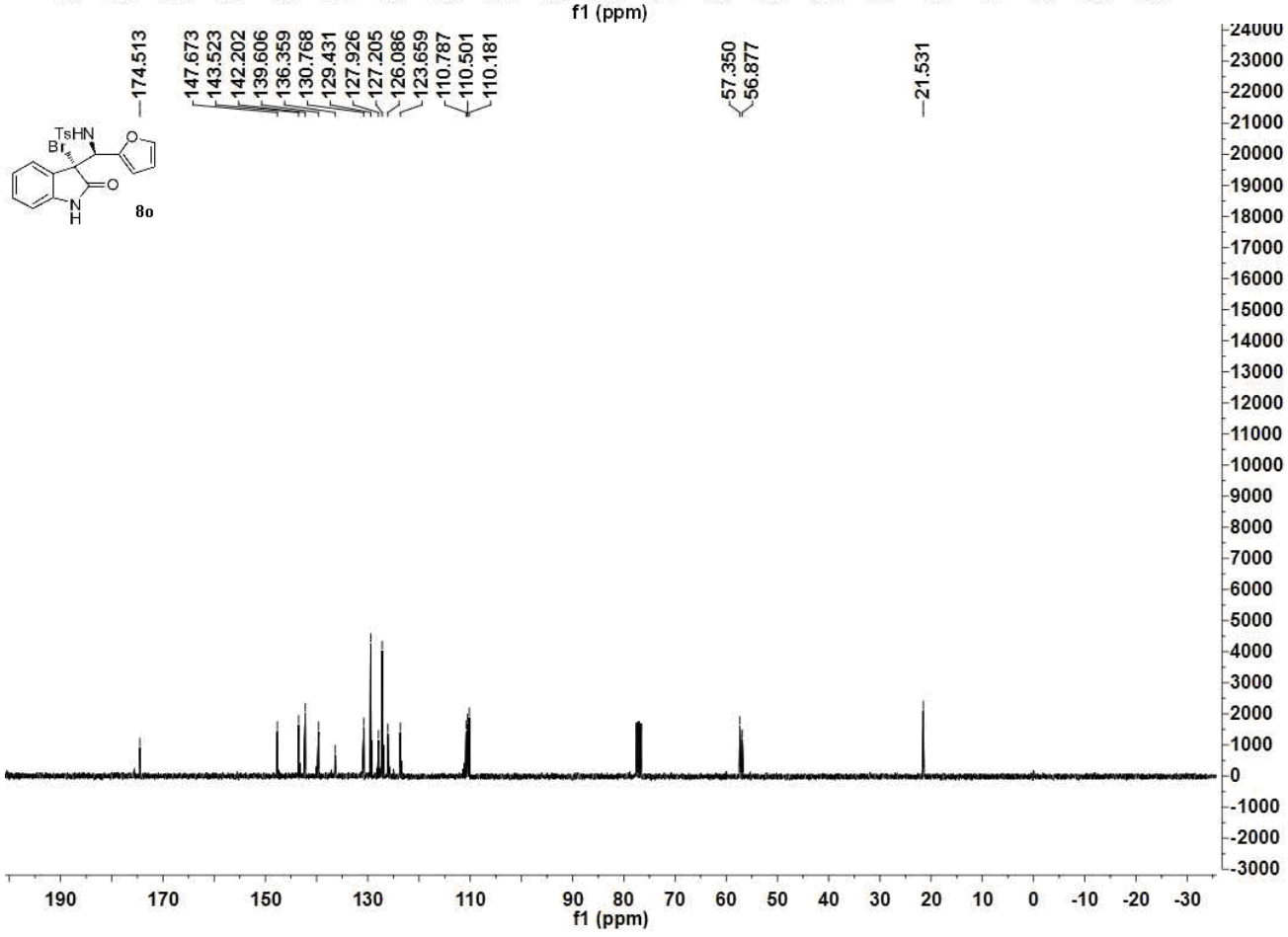


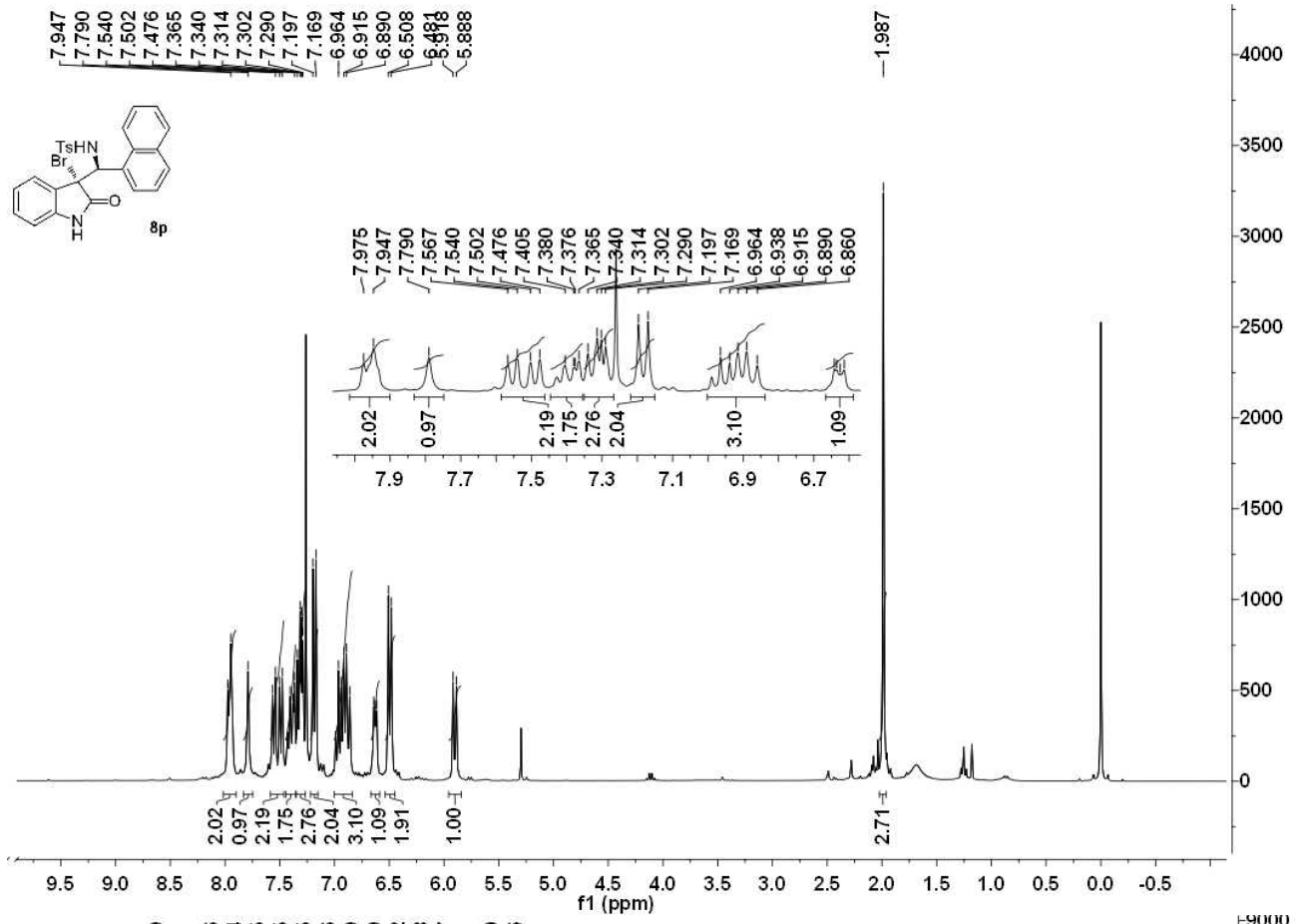


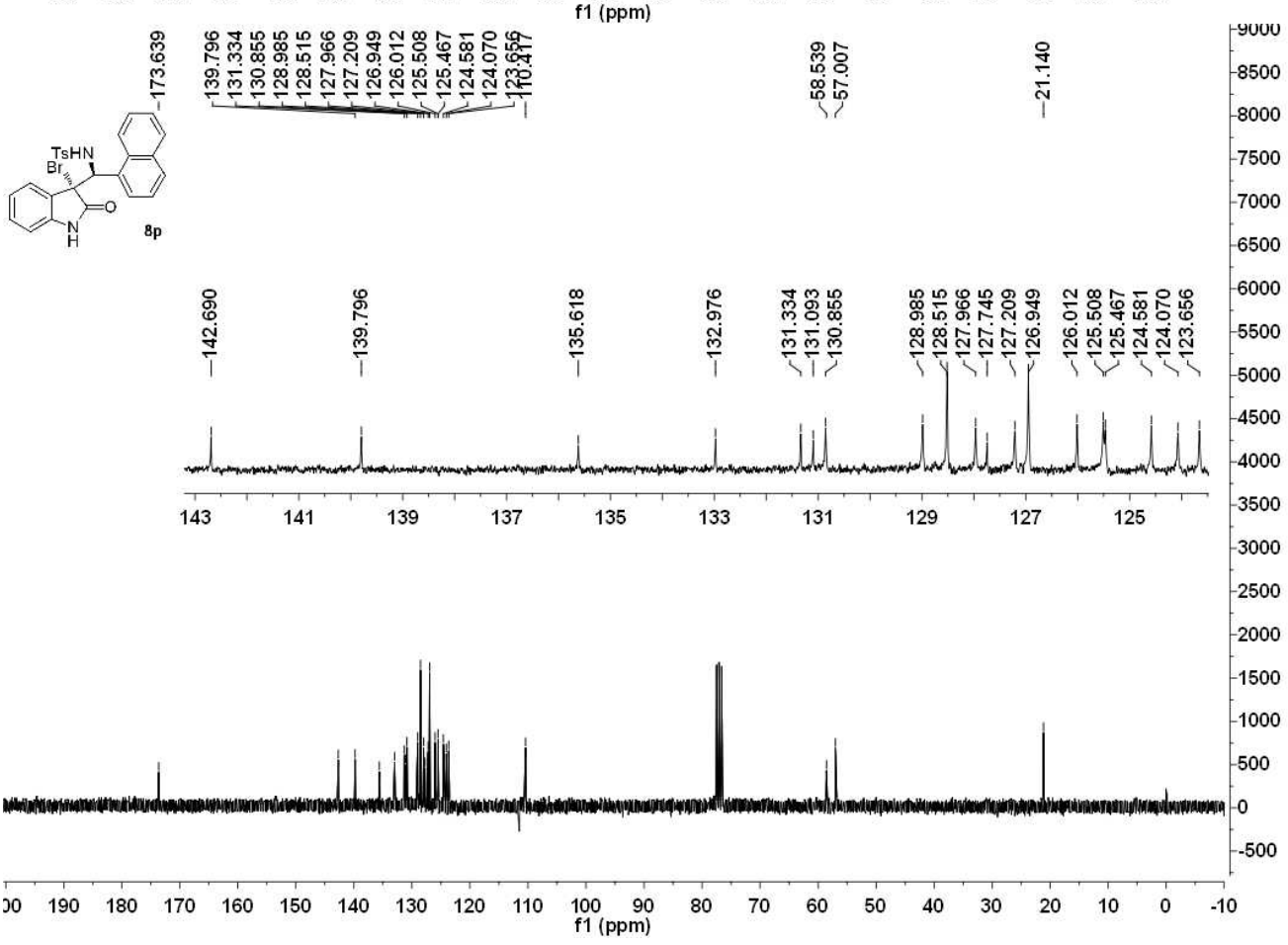


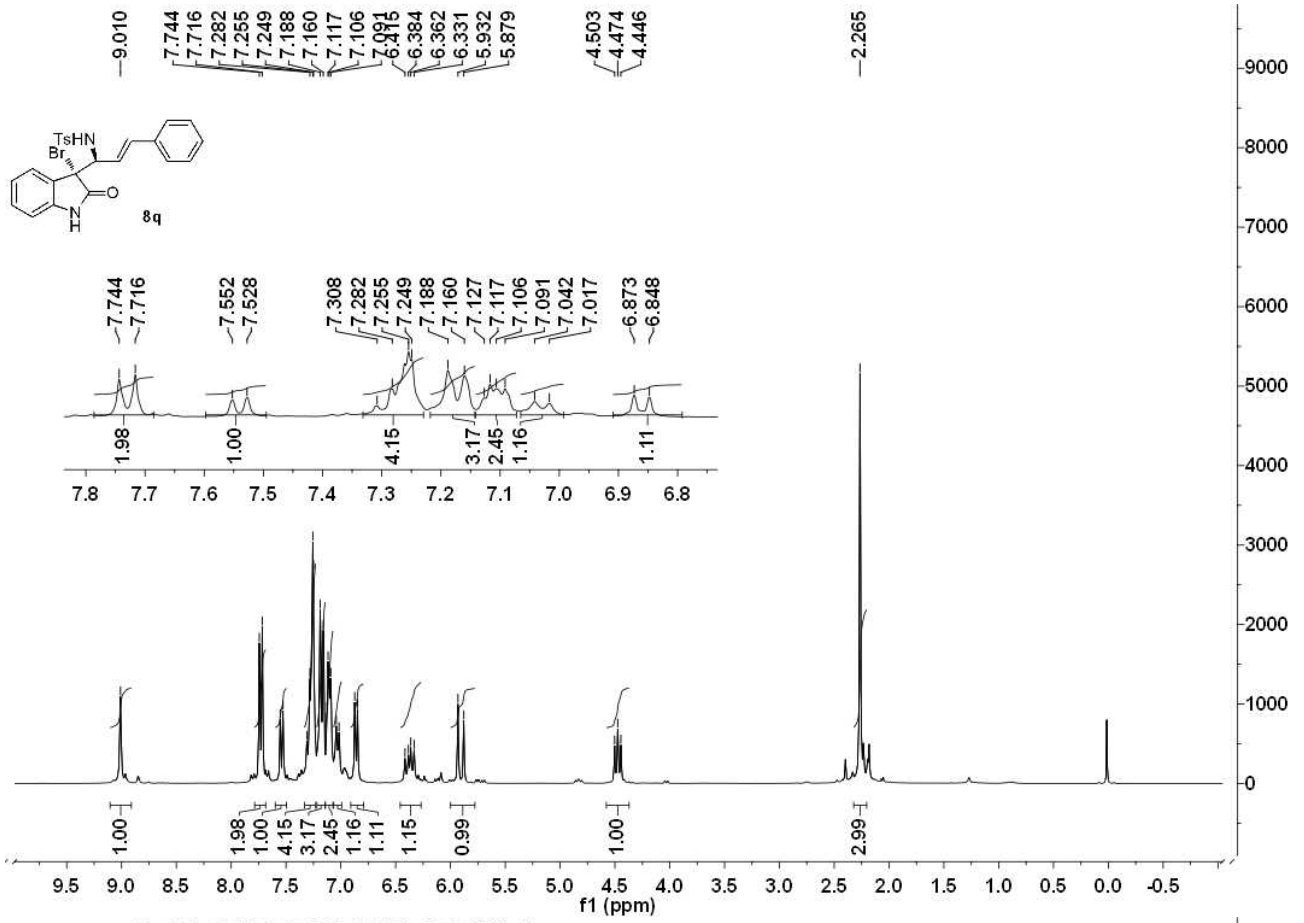


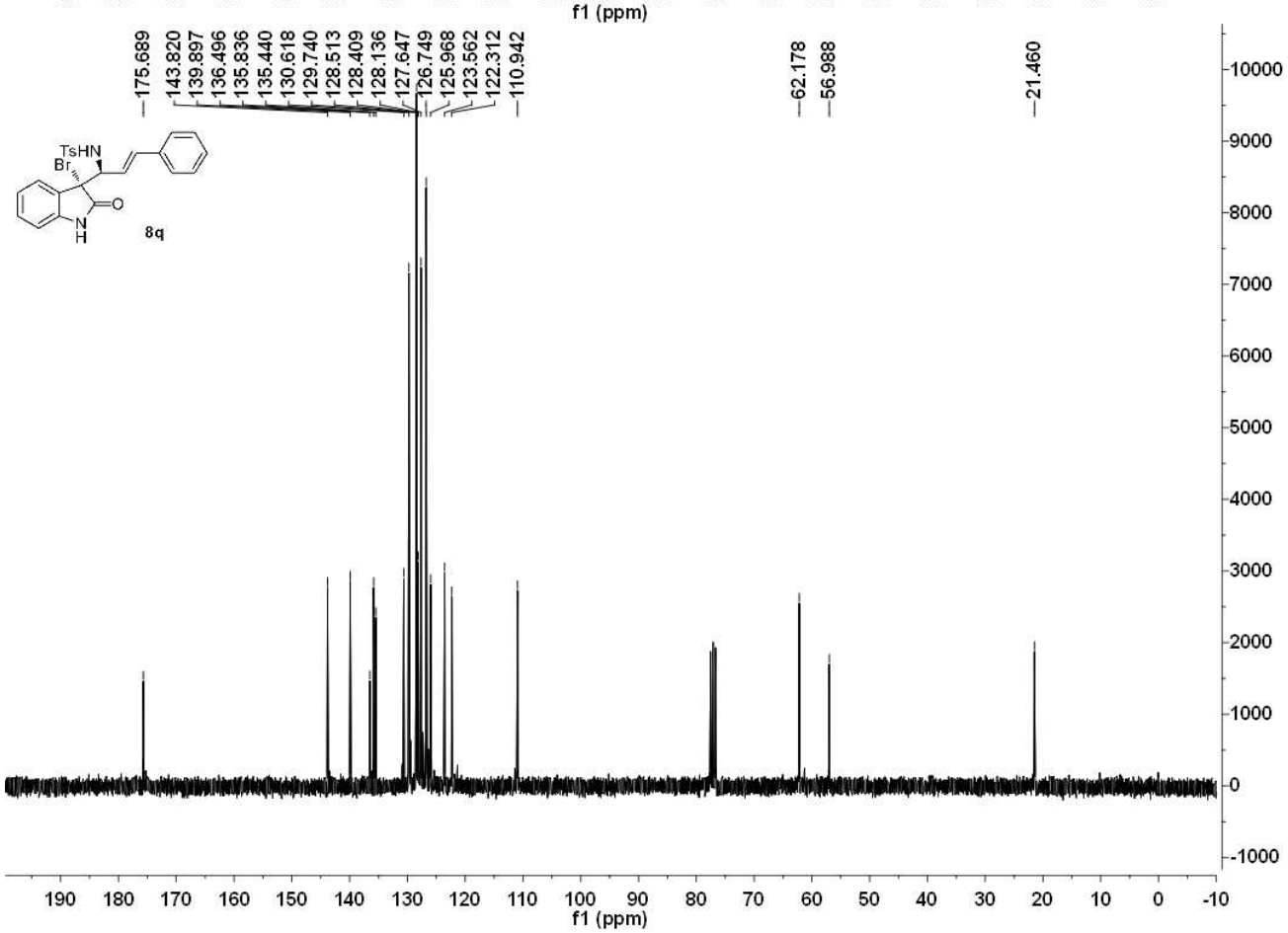


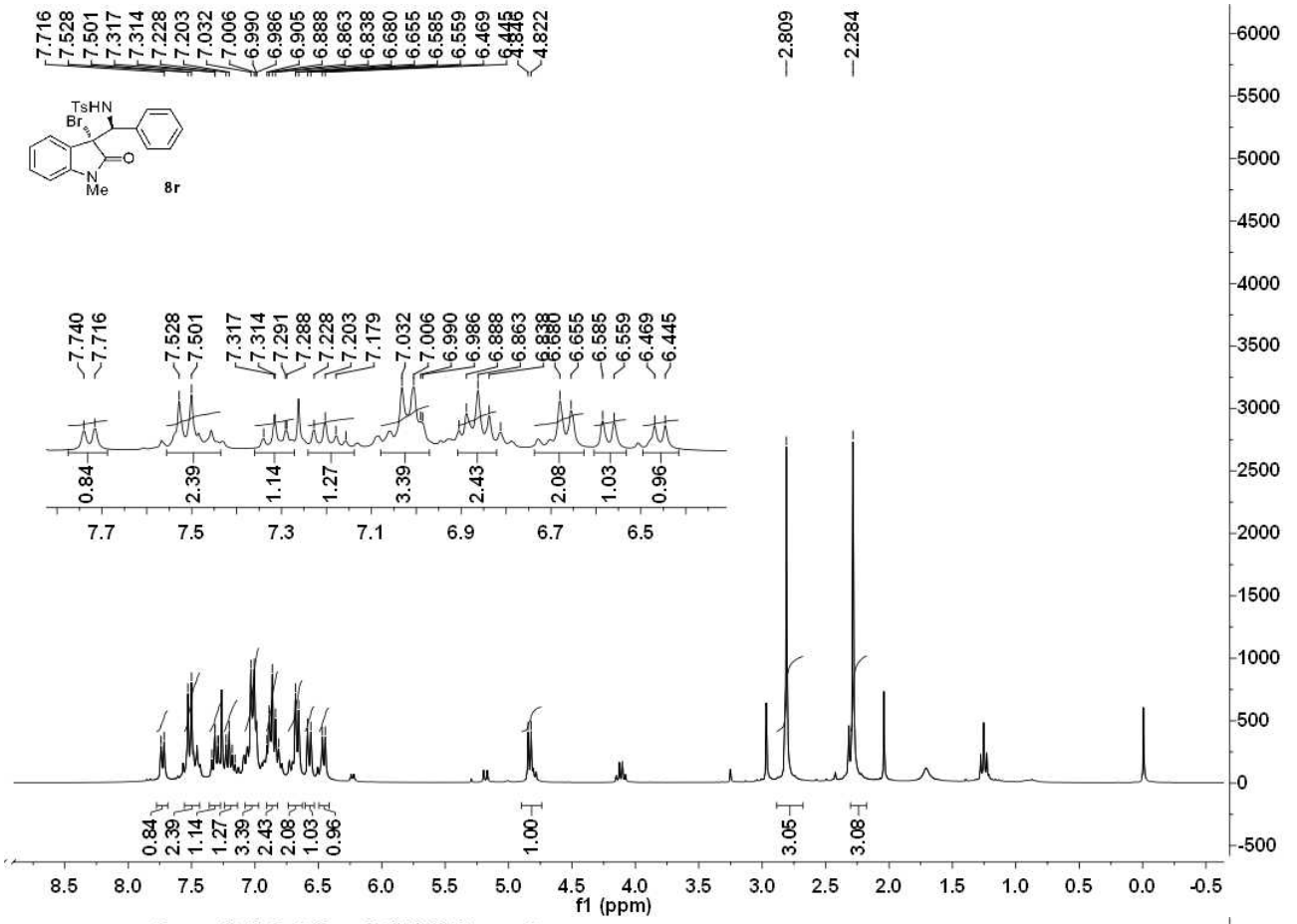


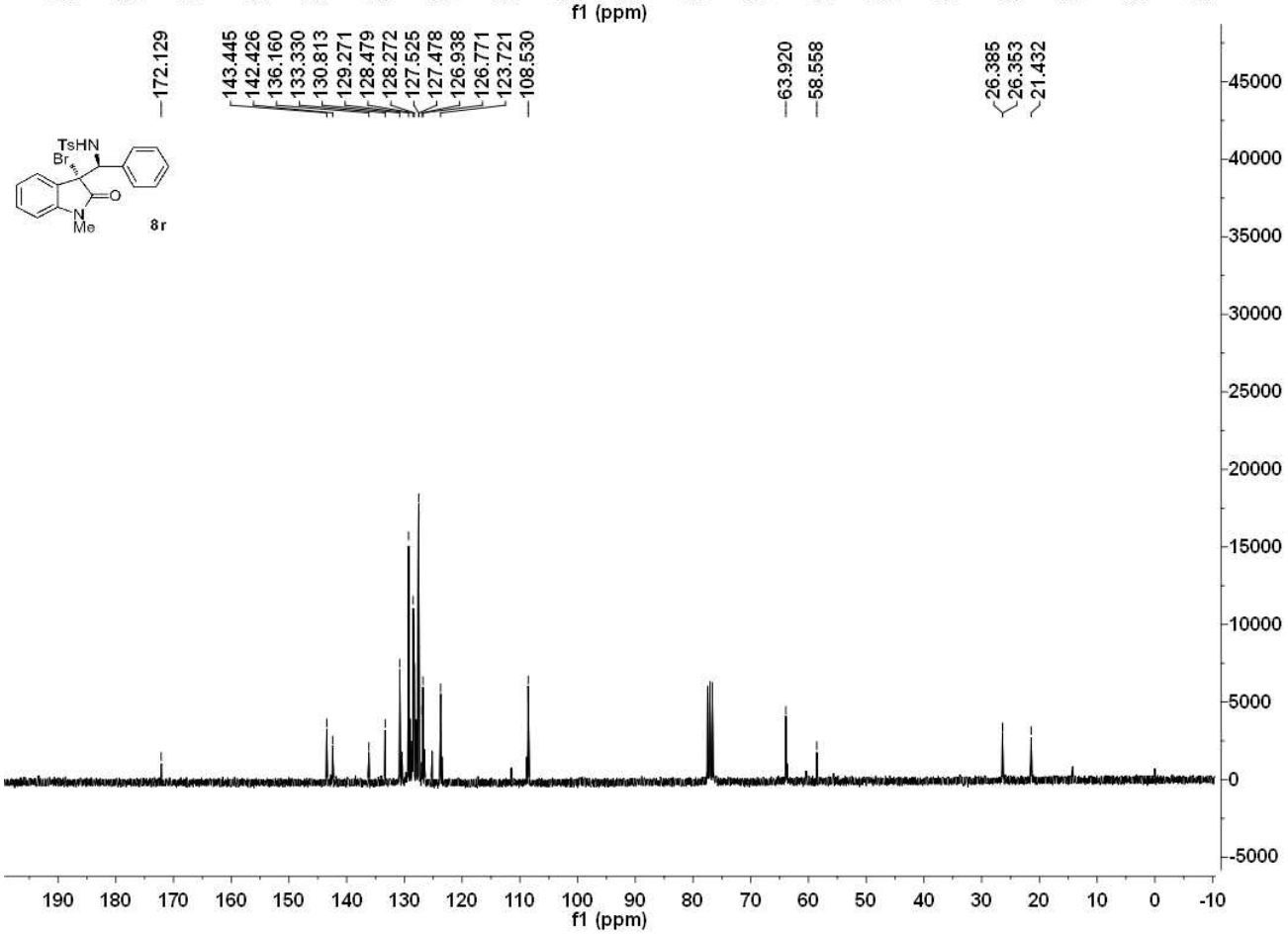

7.947
7.790
7.540
7.502
7.476
7.365
7.340
7.314
7.302
7.290
7.197
7.169
6.964
6.915
6.890
6.508
5.888
1.987
TsHN
Br
O
N
H
8p
7.975
7.947
7.790
7.567
7.540
7.502
7.476
7.405
7.380
7.376
7.365
7.340
7.314
7.302
7.290
7.197
7.169
6.964
6.938
6.915
6.890
6.860
2.02
0.97
2.19
1.75
2.76
2.04
3.10
1.09
1.91
1.00
2.71
f1 (ppm)

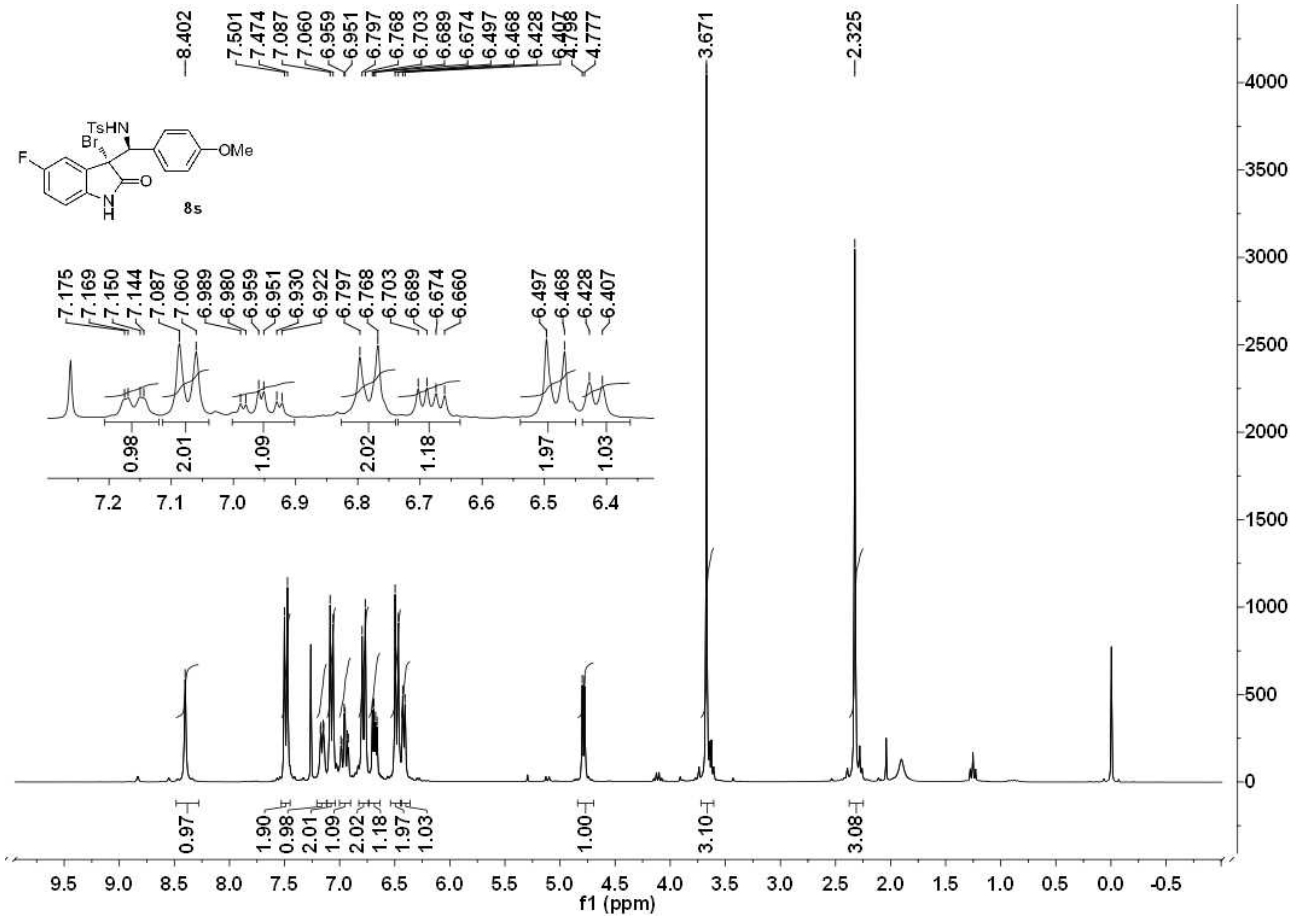

173.639
139.796
131.334
130.855
128.985
128.515
127.966
127.209
126.949
126.012
125.508
125.467
124.581
124.070
123.656
58.539
57.007
21.140
TsHN
Br
O
N
H
8p
142.690
139.796
135.618
132.976
131.334
131.093
130.855
128.985
128.515
127.966
127.745
127.209
126.949
126.012
125.508
125.467
124.581
124.070
123.656
f1 (ppm)

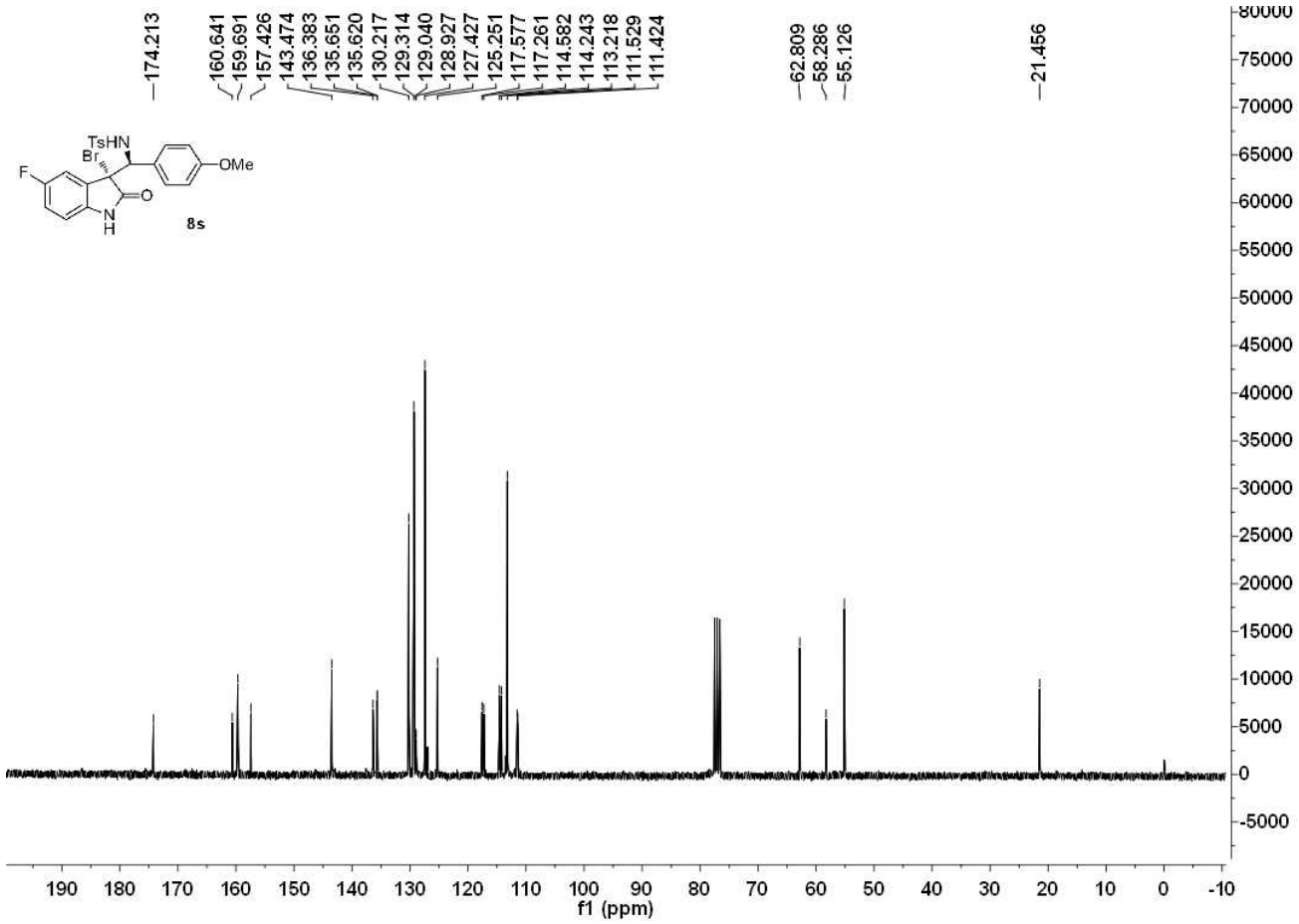

9.010
7.744
7.716
7.282
7.255
7.249
7.188
7.160
7.117
7.106
7.091
6.415
6.384
6.362
6.331
5.932
5.879
4.503
4.474
4.446
2.265
TsHN
Br
O
N
H
8q
7.744
7.716
7.552
7.528
7.308
7.282
7.255
7.249
7.188
7.160
7.127
7.117
7.106
7.091
7.042
7.017
6.873
6.848
1.98
1.00
4.15
3.17
2.45
1.16
1.11
1.00
1.98
1.00
4.15
3.17
2.45
1.16
1.11
1.15
0.99
1.00
2.99
f1 (ppm)

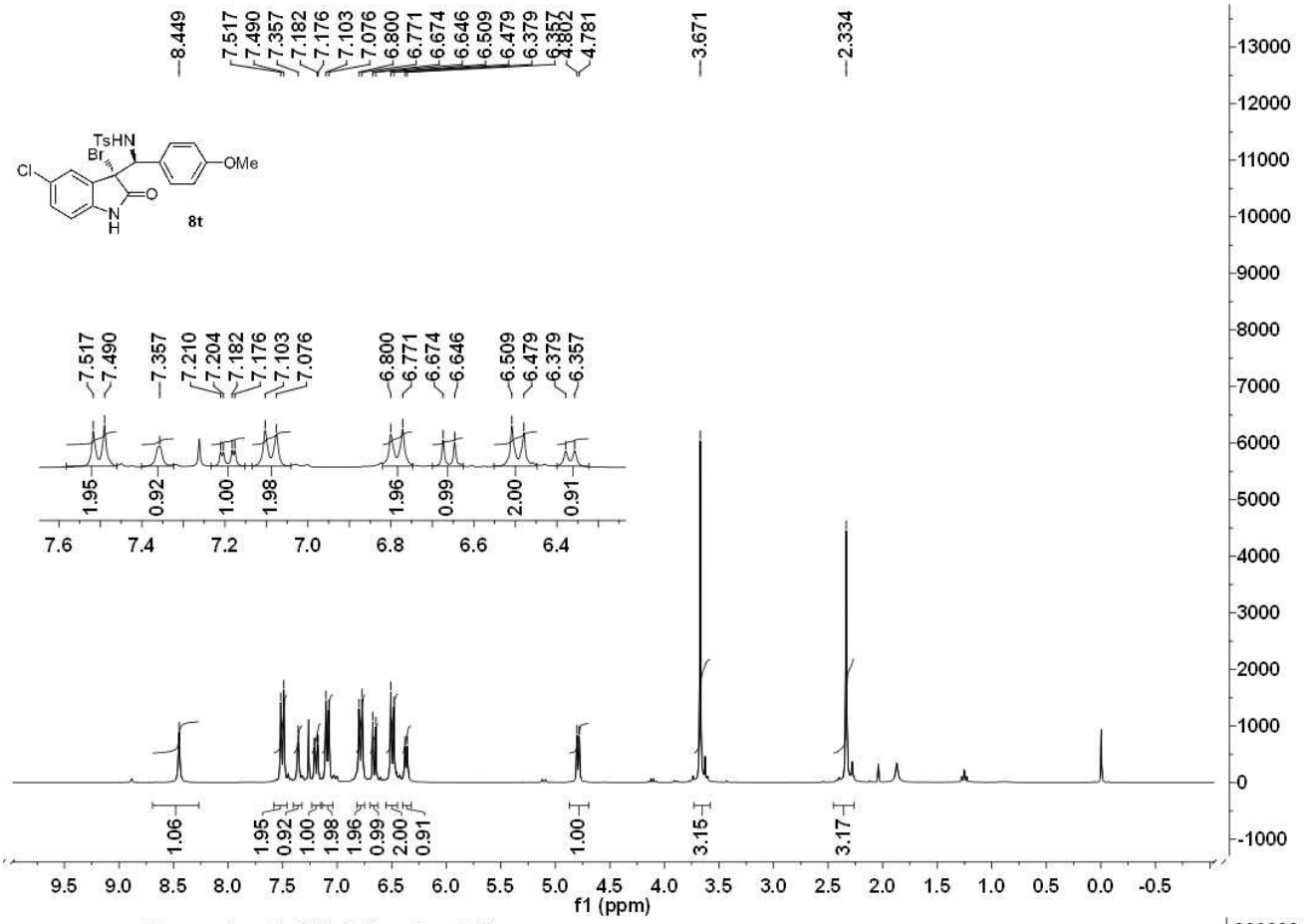

175.689
143.820
139.897
136.496
135.836
135.440
130.618
129.740
128.513
128.409
128.136
127.647
126.749
125.968
123.562
122.312
110.942
62.178
56.988
21.460
TsHN
Br
O
N
H
8q
f1 (ppm)

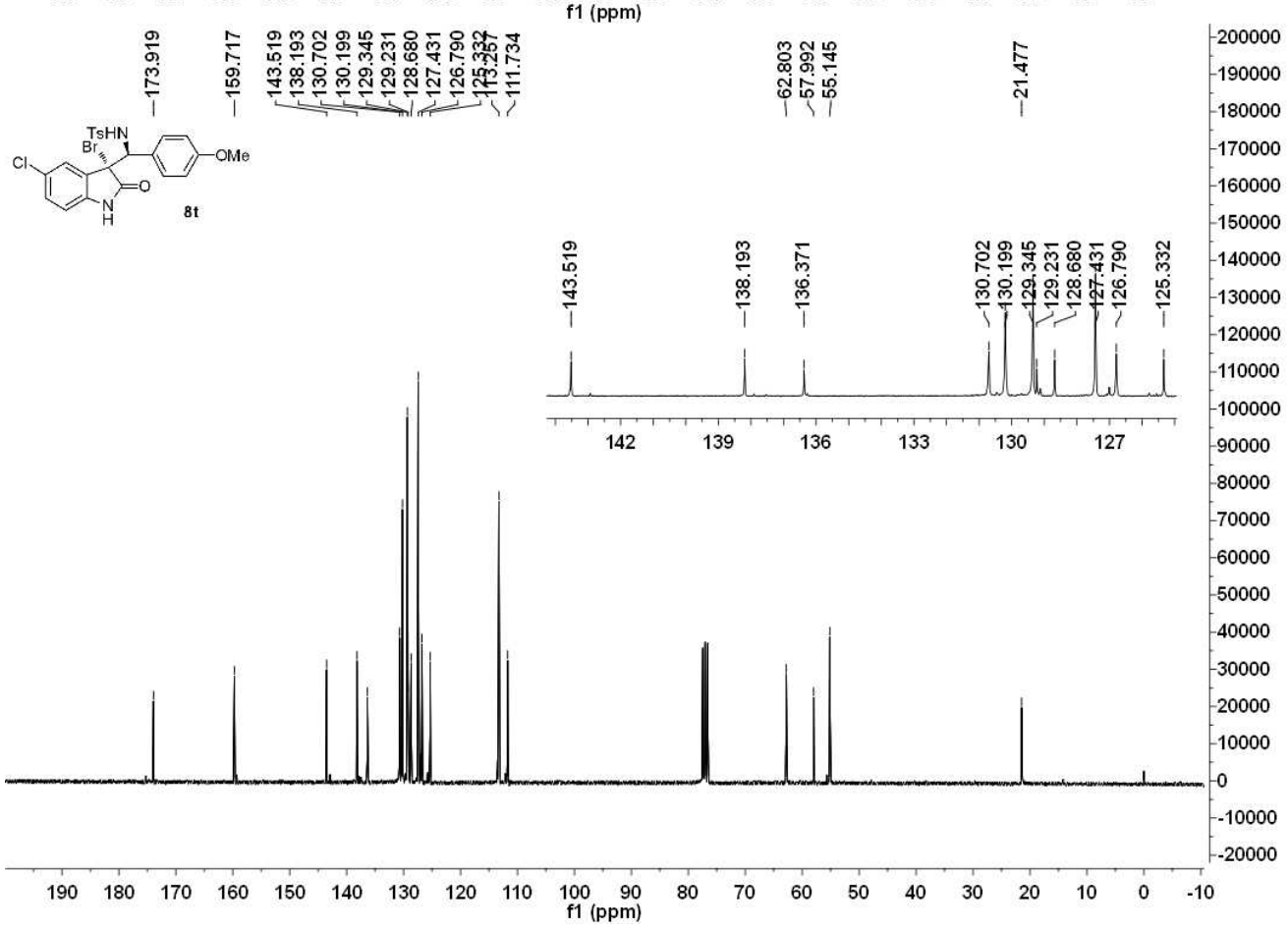


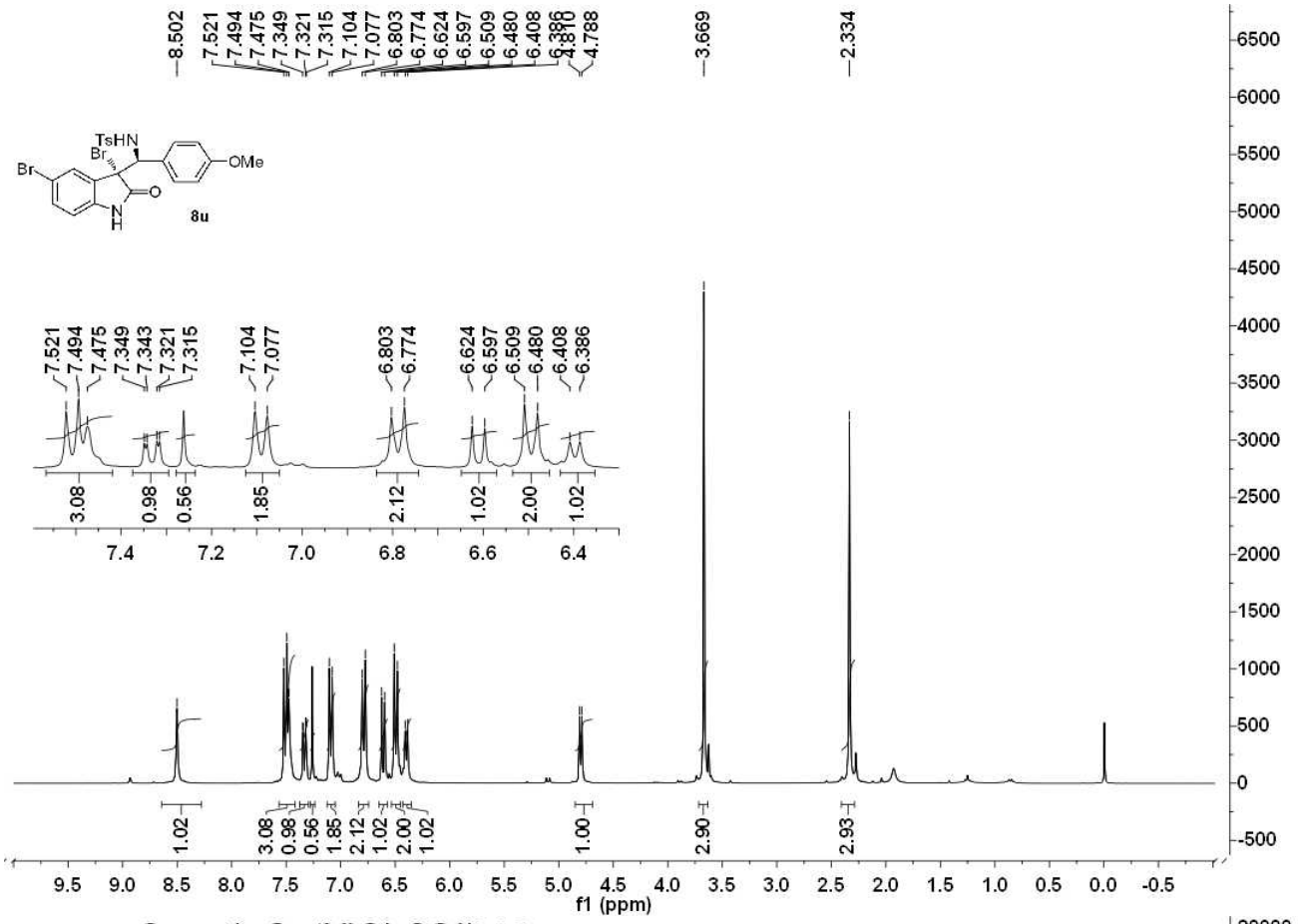


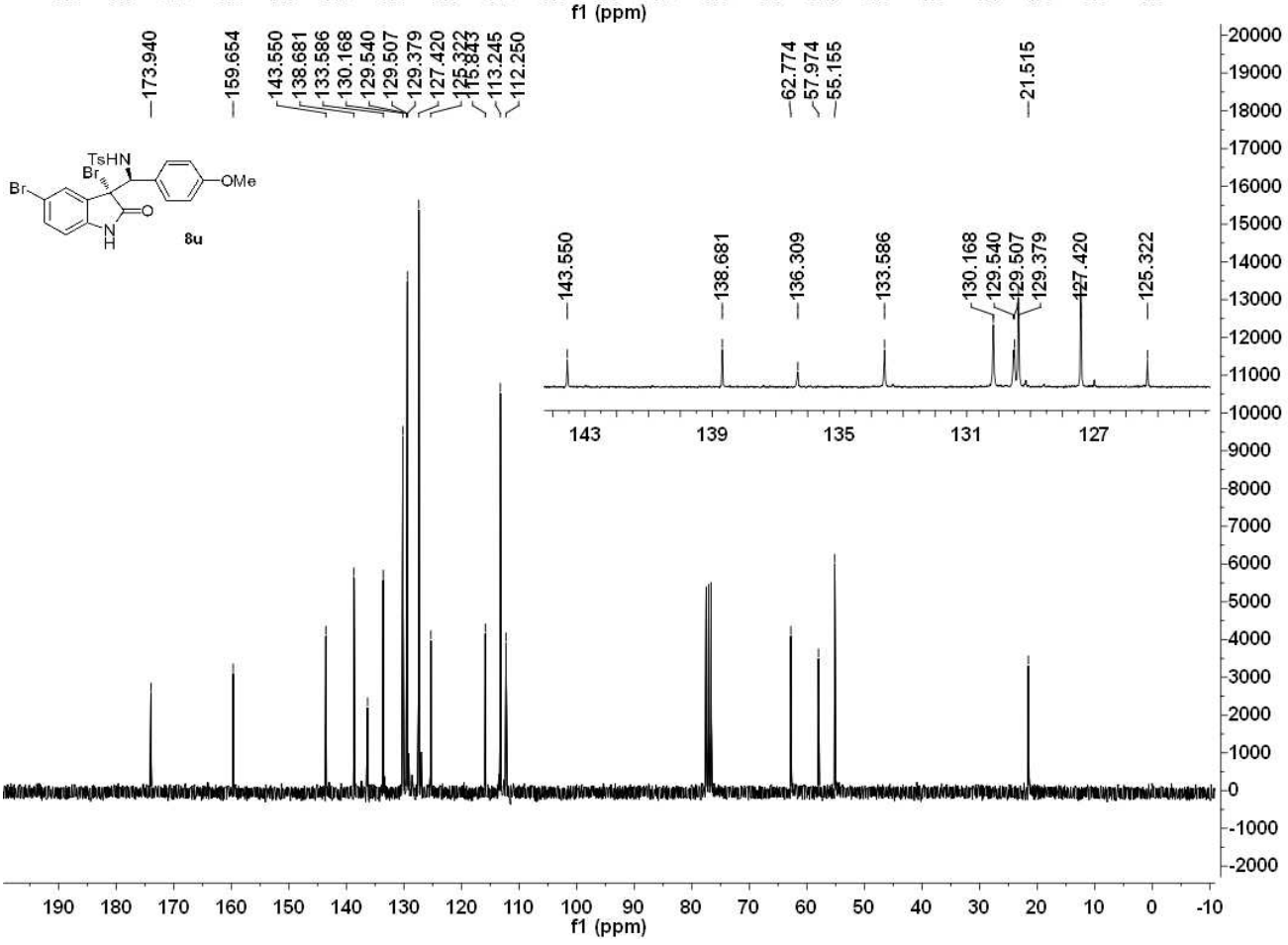

8.402
7.501
7.474
7.087
7.060
6.959
6.951
6.797
6.768
6.703
6.689
6.674
6.497
6.468
6.428
6.407
4.798
4.777
3.671
2.325
TsHN
Br
F
OMe
O
N
H
8s
7.175
7.169
7.150
7.144
7.087
7.060
6.989
6.980
6.959
6.951
6.930
6.922
6.797
6.768
6.703
6.689
6.674
6.660
6.497
6.468
6.428
6.407
0.98
2.01
1.09
2.02
1.18
1.97
1.03
0.97
1.90
0.98
2.01
1.09
2.02
1.18
1.97
1.03
1.00
3.10
3.08
f1 (ppm)

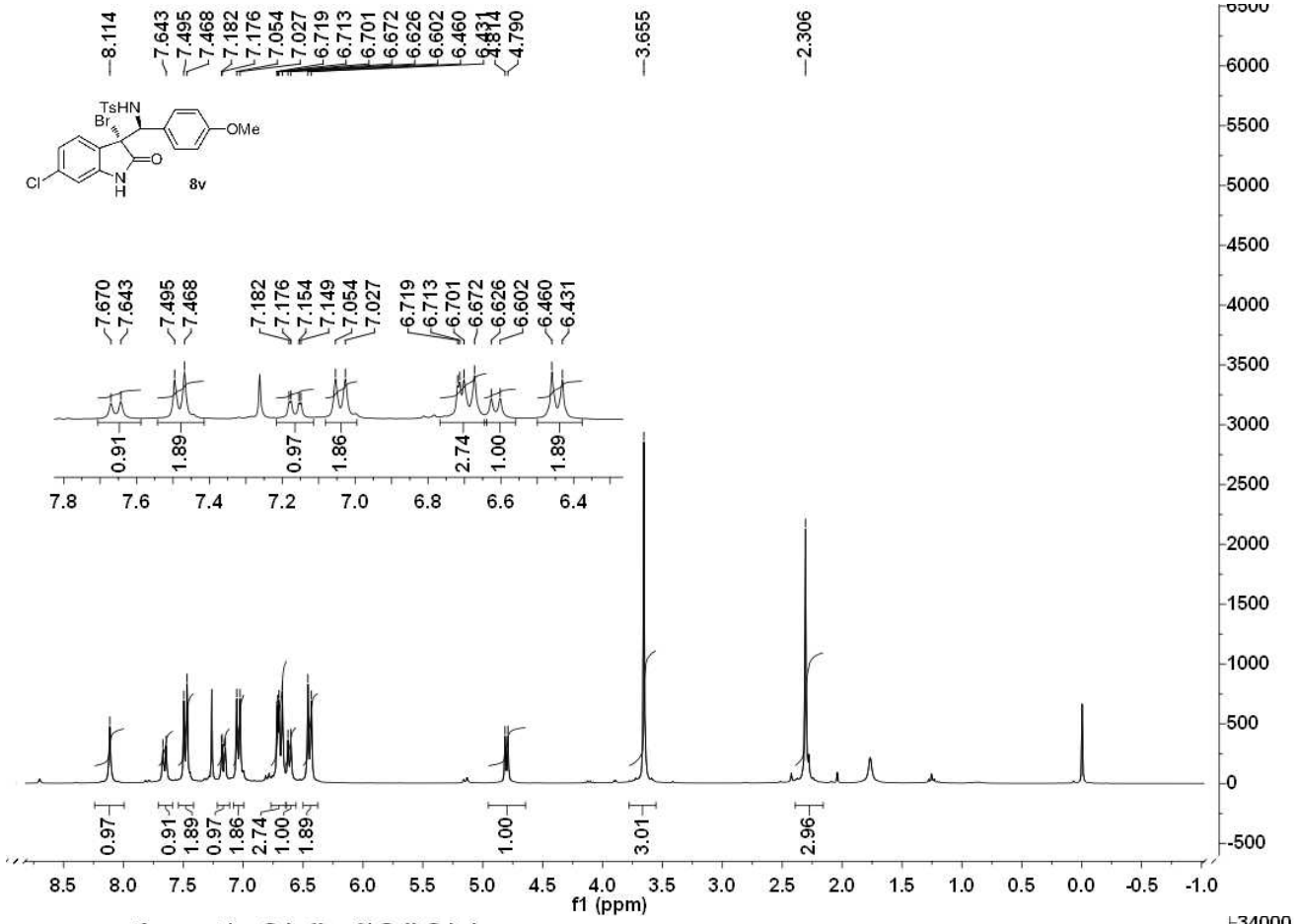

174.213
160.641
159.691
157.426
143.474
136.383
135.651
135.620
130.217
129.314
129.040
128.927
127.427
125.251
117.577
117.261
114.582
114.243
113.218
111.529
111.424
62.809
58.286
55.126
21.456
TsHN
Br
F
OMe
O
N
H
8s
f1 (ppm)

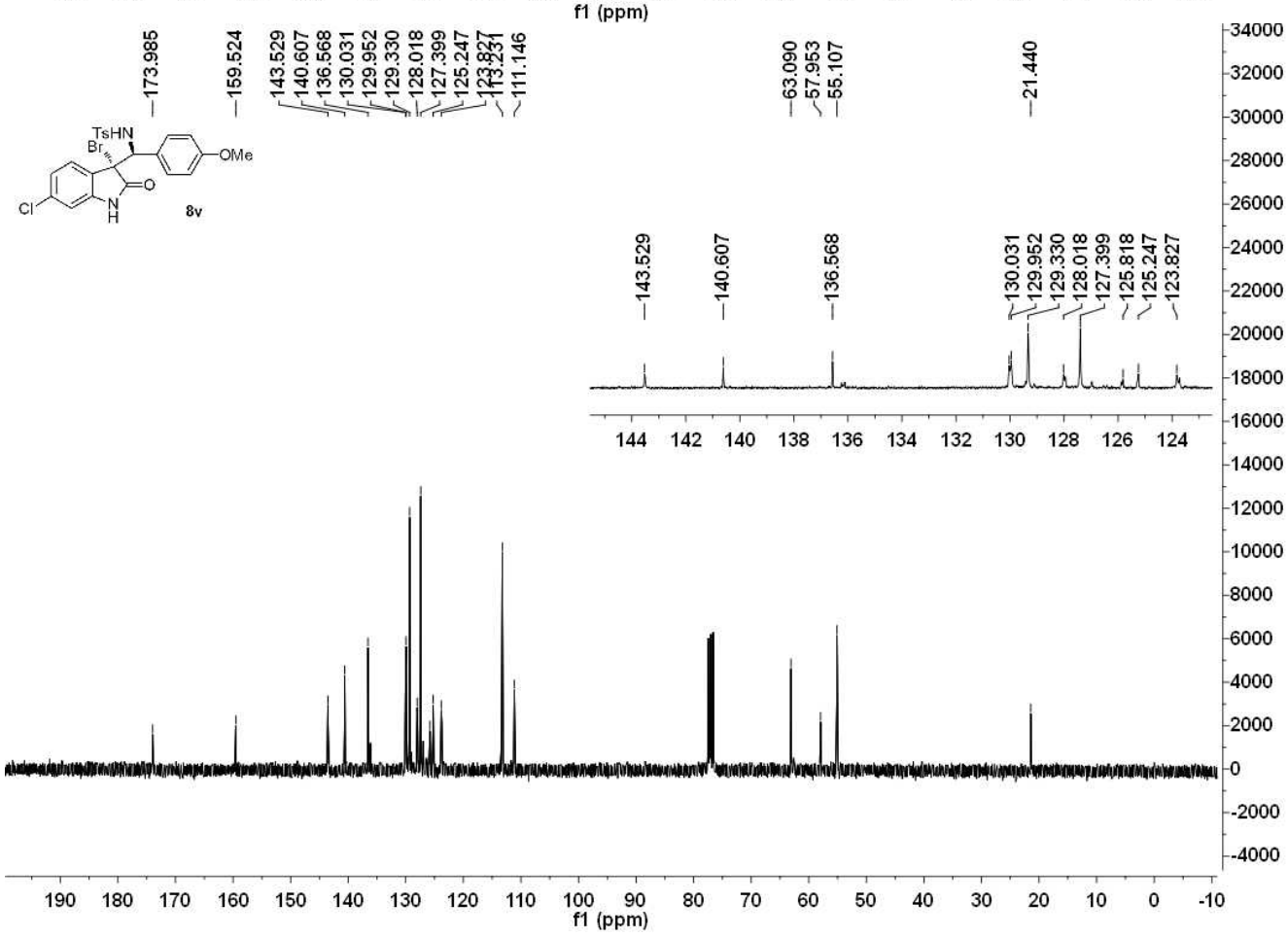

8.449
7.517
7.490
7.357
7.182
7.176
7.103
7.076
6.800
6.771
6.674
6.646
6.509
6.479
6.379
6.357
4.802
4.781
3.671
2.334
TsHN
Br
Cl
OMe
O
N
H
8t
1.06
1.95
0.92
1.00
1.98
1.96
0.99
2.00
0.91
1.00
3.15
3.17
f1 (ppm)

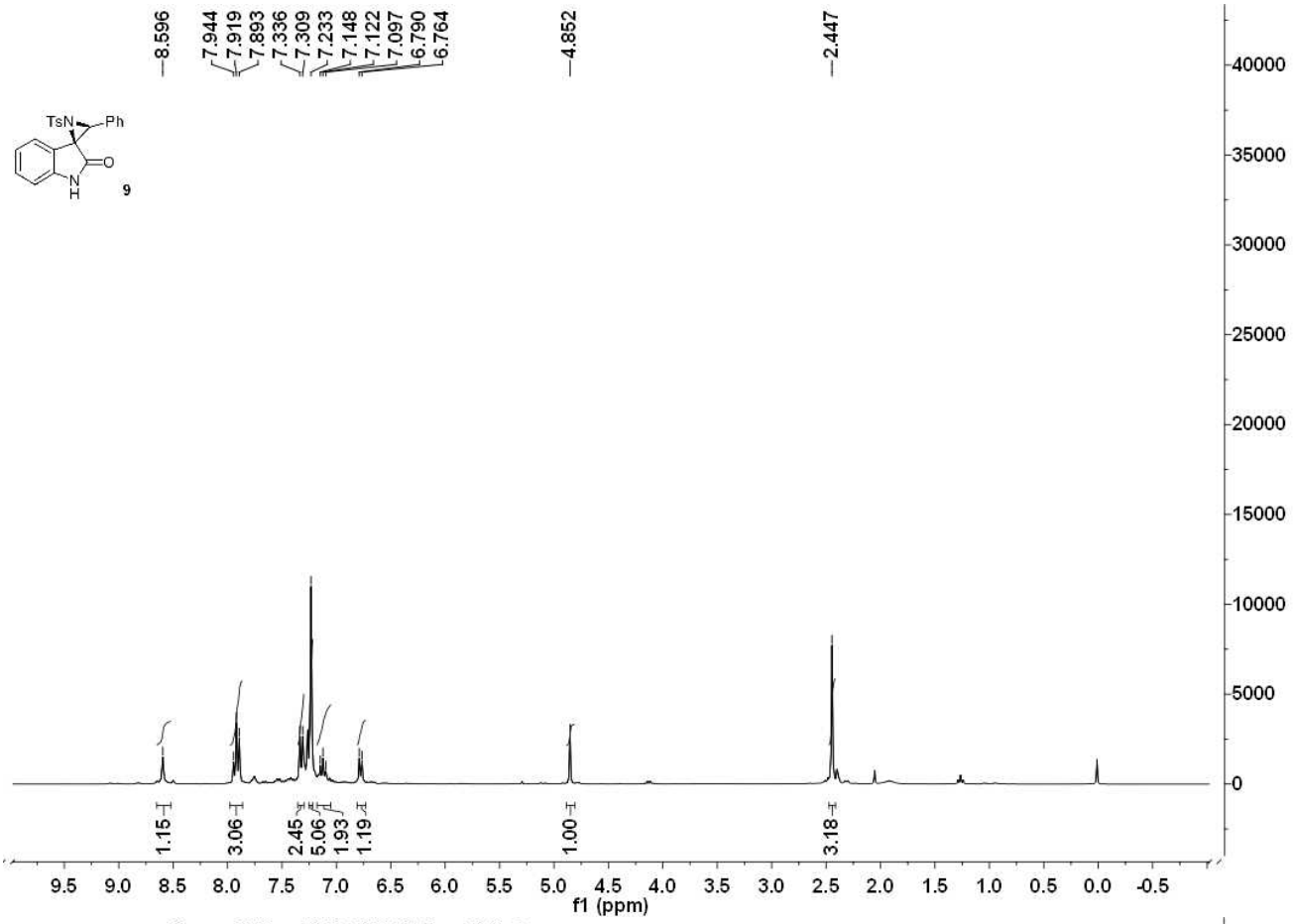

173.919
159.717
143.519
138.193
130.702
130.199
129.345
129.231
128.680
127.431
126.790
125.332
113.287
111.734
62.803
57.992
55.145
21.477
TsHN
Br
Cl
OMe
O
N
H
8t
f1 (ppm)

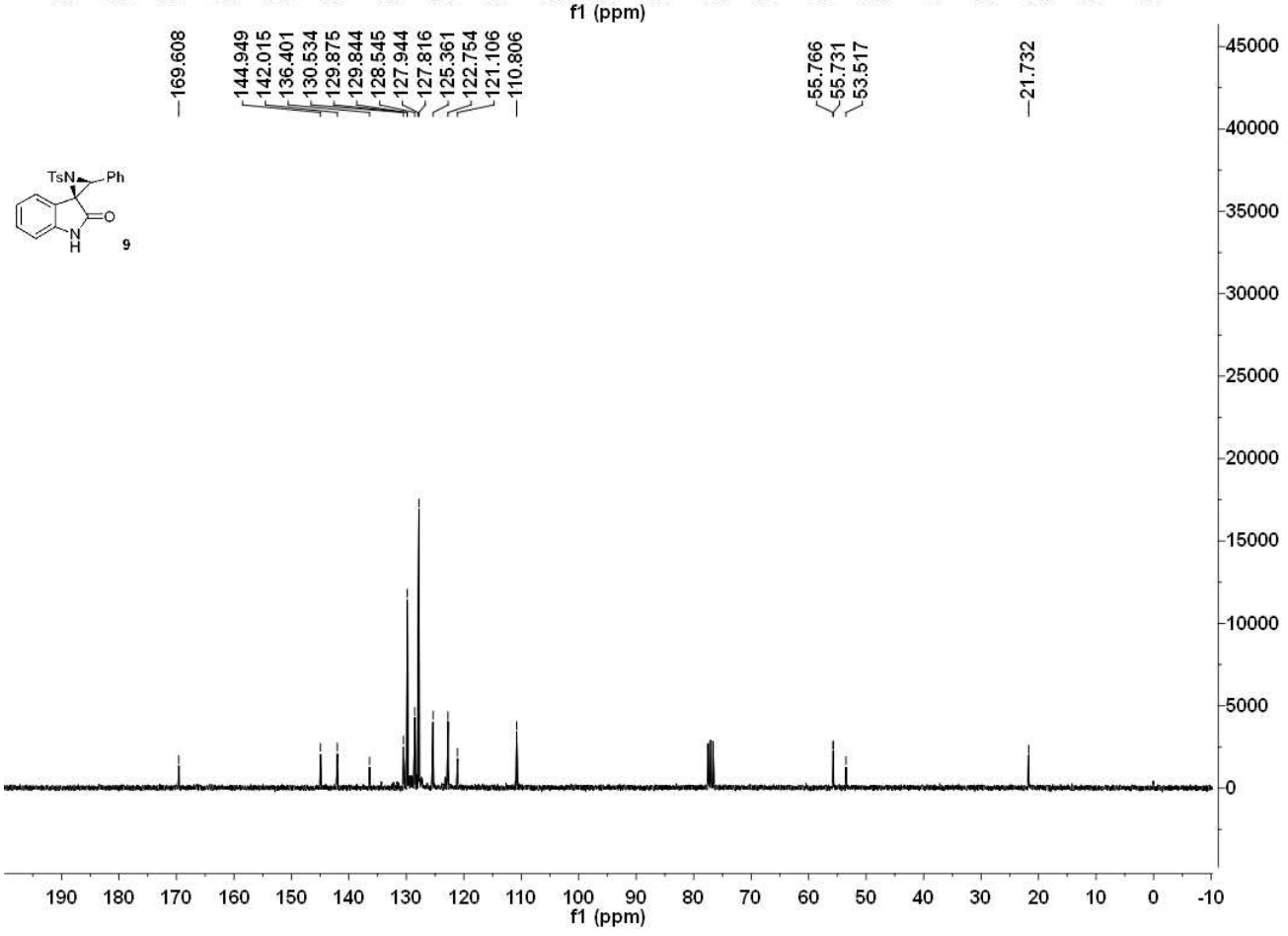


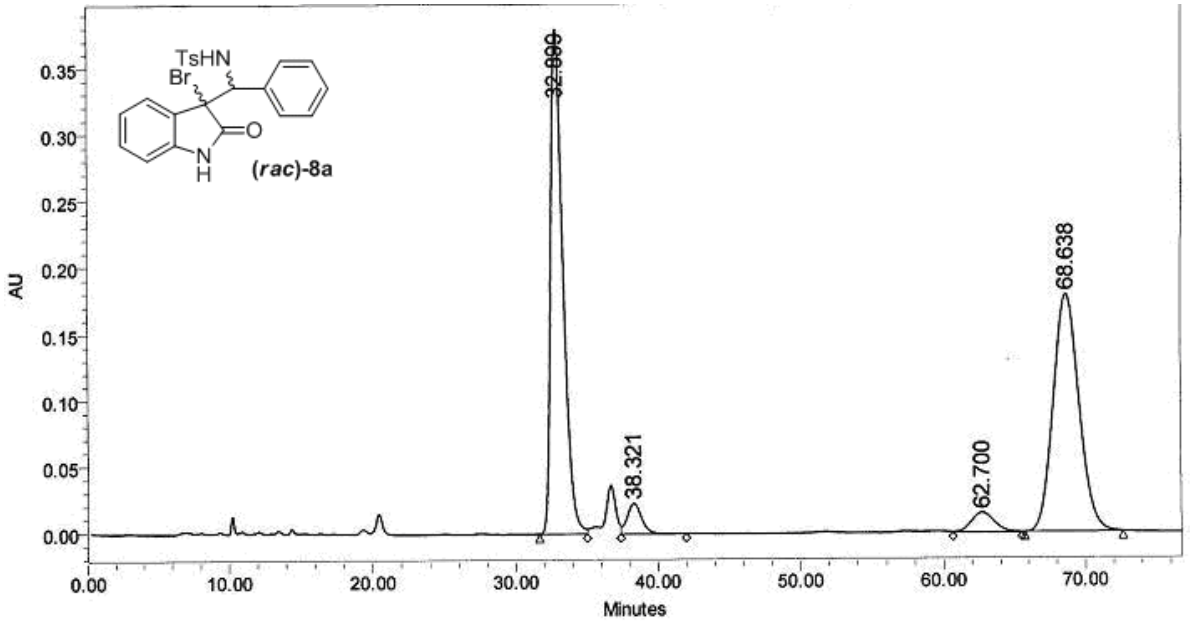




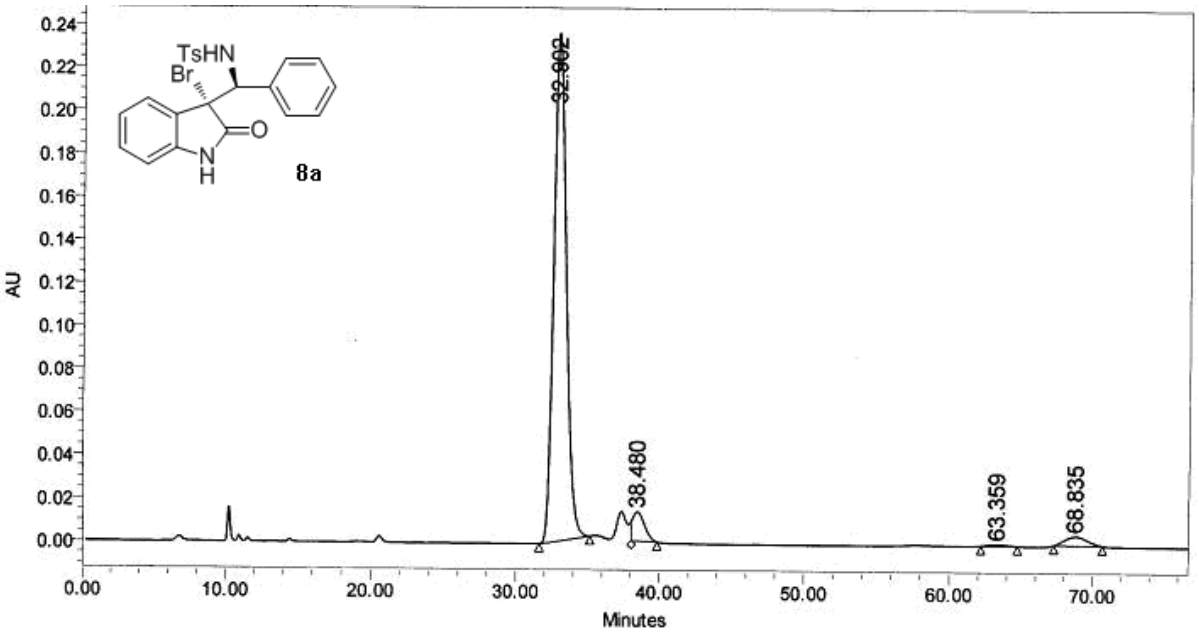




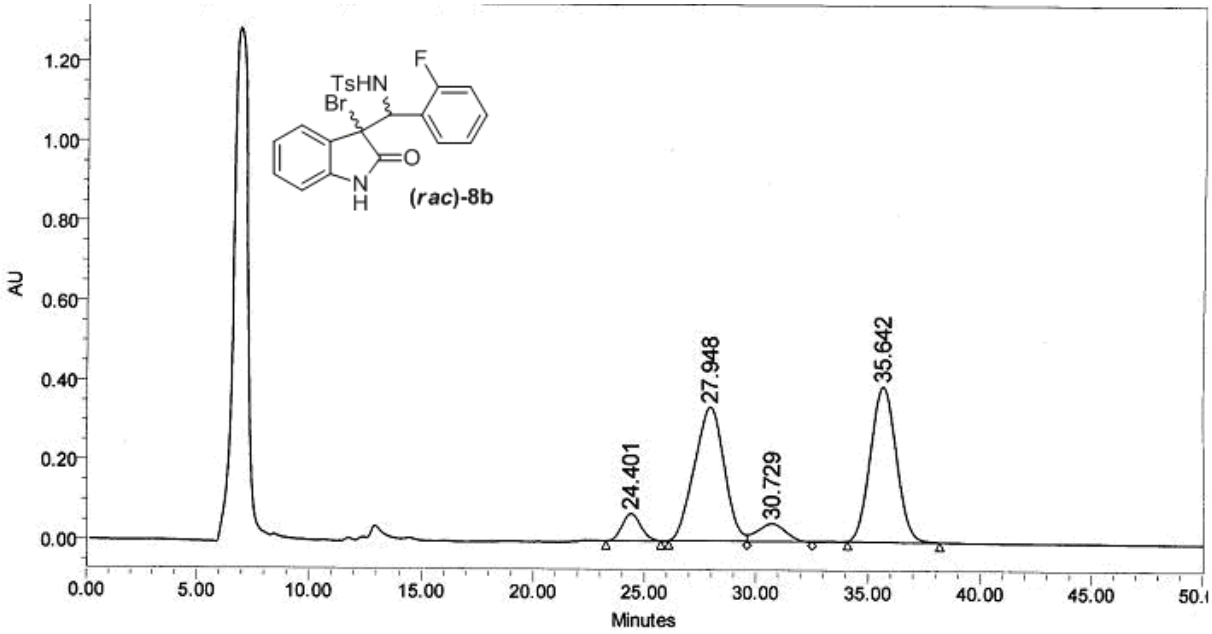




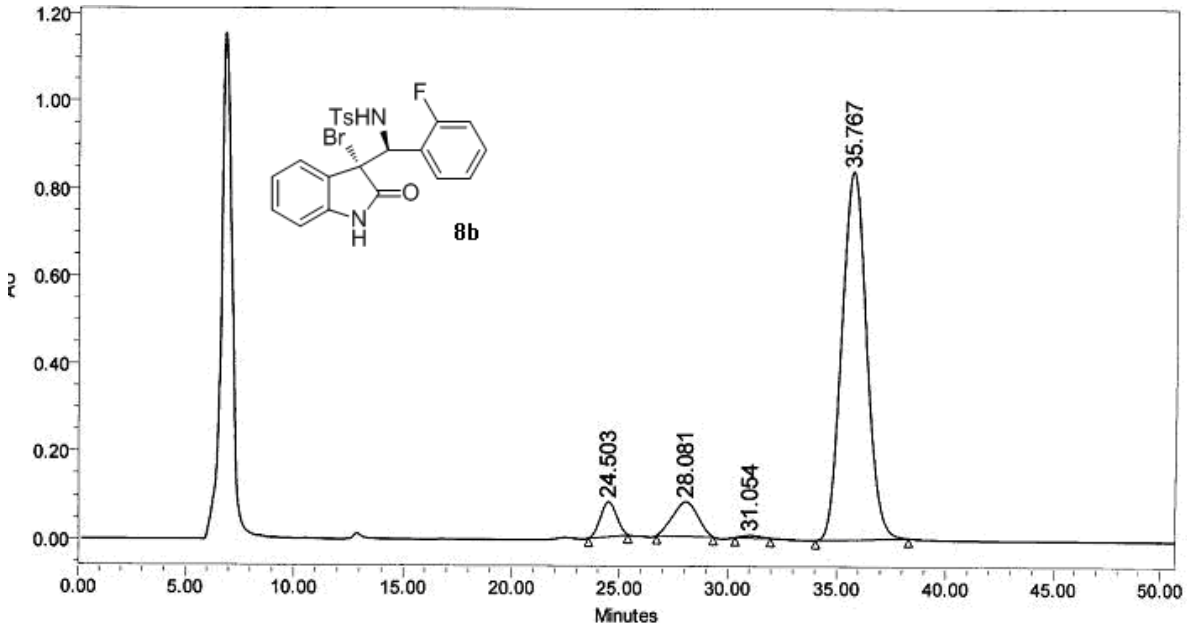
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	32.899	22881727	46.81	380311	63.78
2	38.321	1625522	3.33	22822	3.83
3	62.700	1702279	3.48	14959	2.51
4	68.638	22670066	46.38	178207	29.89



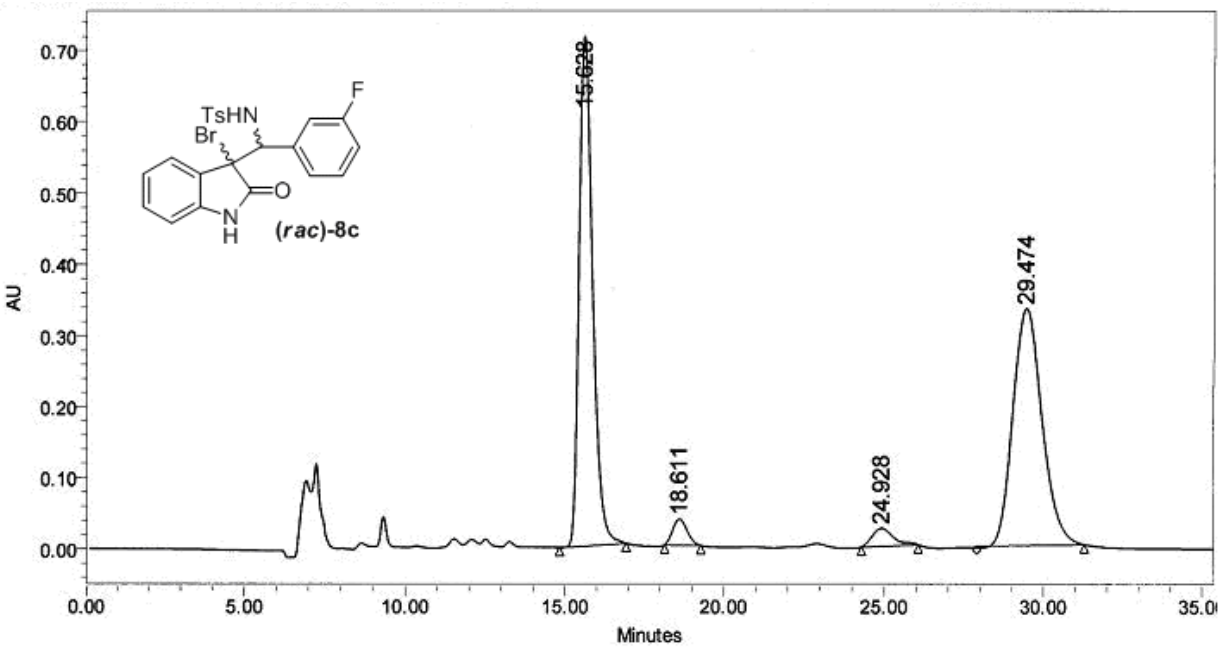
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	32.902	14152791	91.78	235767	92.86
2	38.480	755067	4.90	13283	5.23
3	63.359	59588	0.39	690	0.27
4	68.835	452427	2.93	4151	1.63



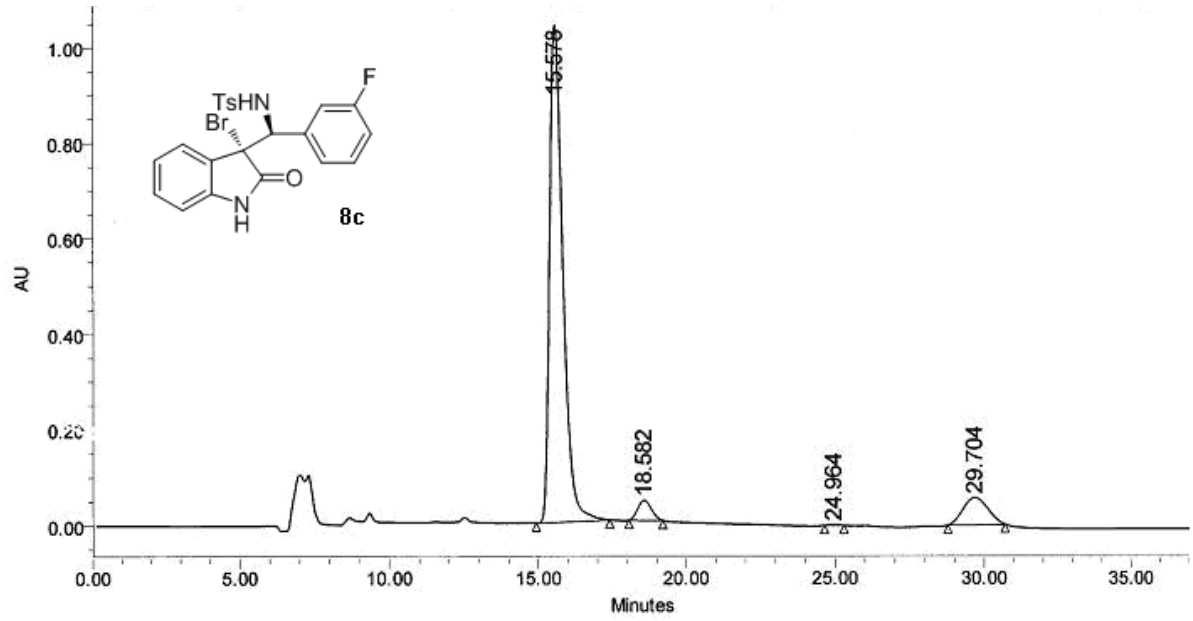
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	24.401	3993139	5.70	68650	8.21
2	27.948	31162312	44.47	334822	40.03
3	30.729	3884417	5.54	44601	5.33
4	35.642	31028445	44.28	388284	46.43



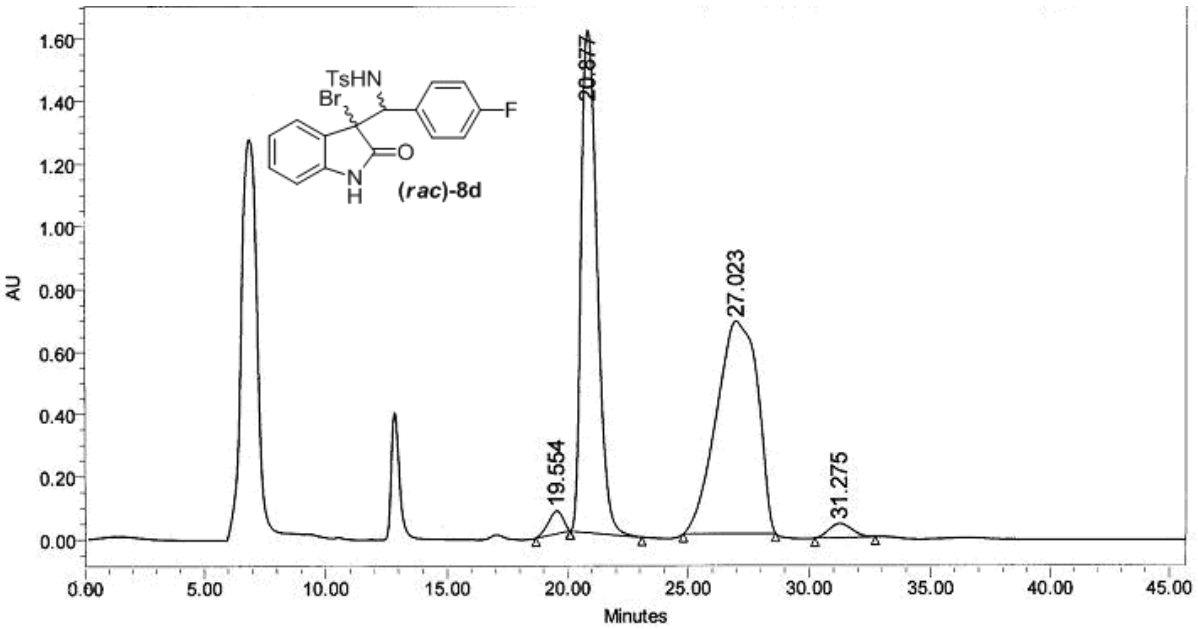
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	24.503	4042584	5.27	78447	7.84
2	28.081	6254806	8.16	77789	7.77
3	31.054	307222	0.40	5517	0.55
4	35.767	66040223	86.16	838932	83.84



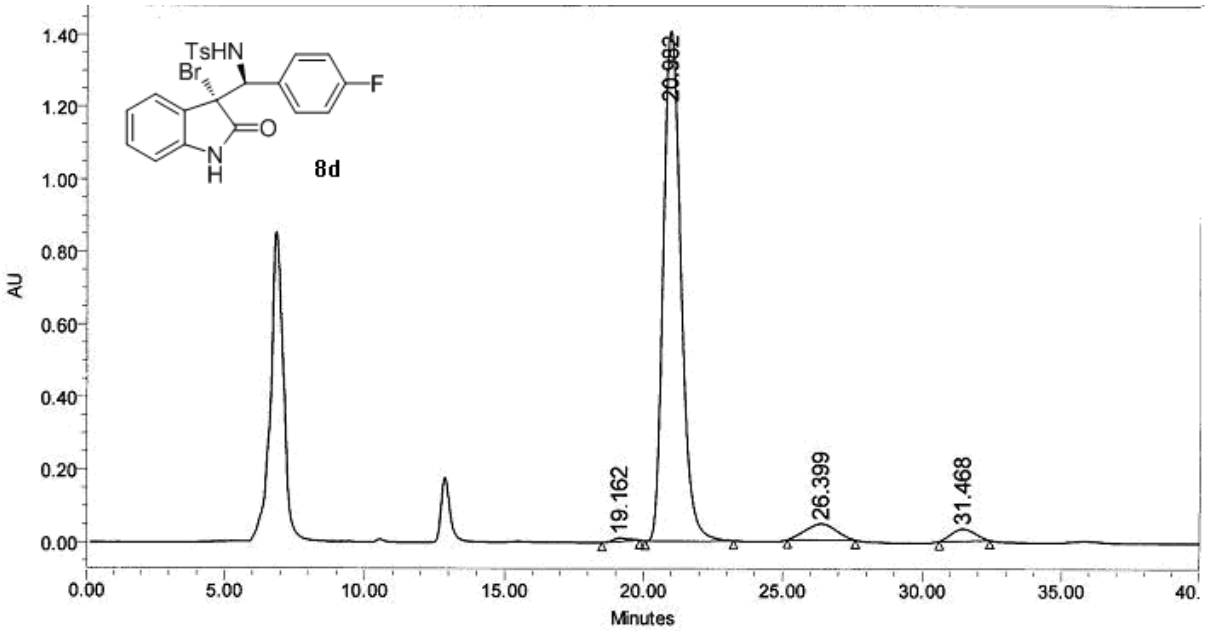
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	15.628	21229578	47.42	716166	64.47
2	18.611	1133515	2.53	36265	3.26
3	24.928	1135814	2.54	24919	2.24
4	29.474	21268512	47.51	333432	30.02



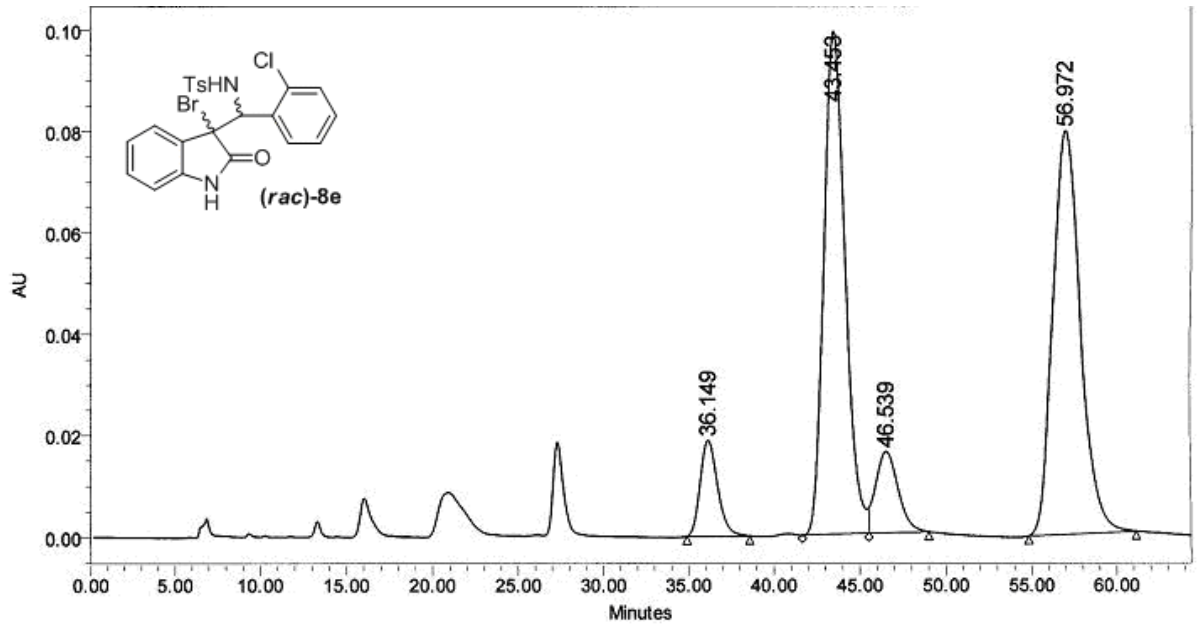
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	15.578	32083514	87.43	1039171	91.29
2	18.582	1311847	3.57	41224	3.62
3	24.964	42897	0.12	1768	0.16
4	29.704	3257474	8.88	56205	4.94



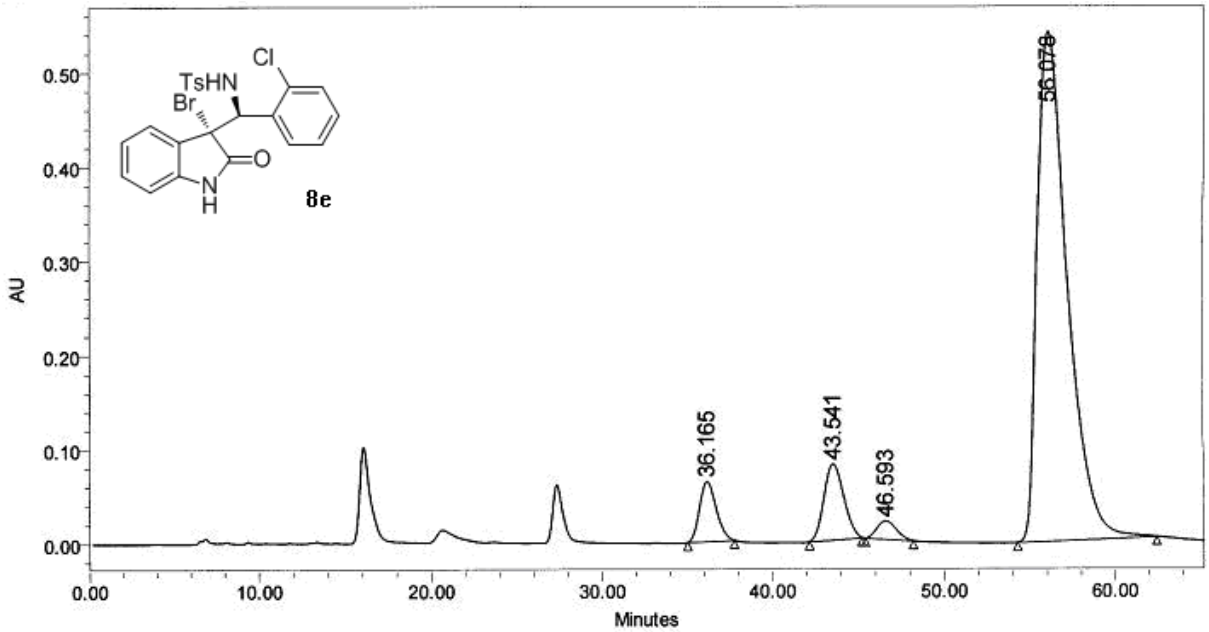
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	19.554	3002859	1.87	71441	2.98
2	20.877	74180166	46.19	1602886	66.82
3	27.023	80495464	50.13	680074	28.35
4	31.275	2903997	1.81	44465	1.85



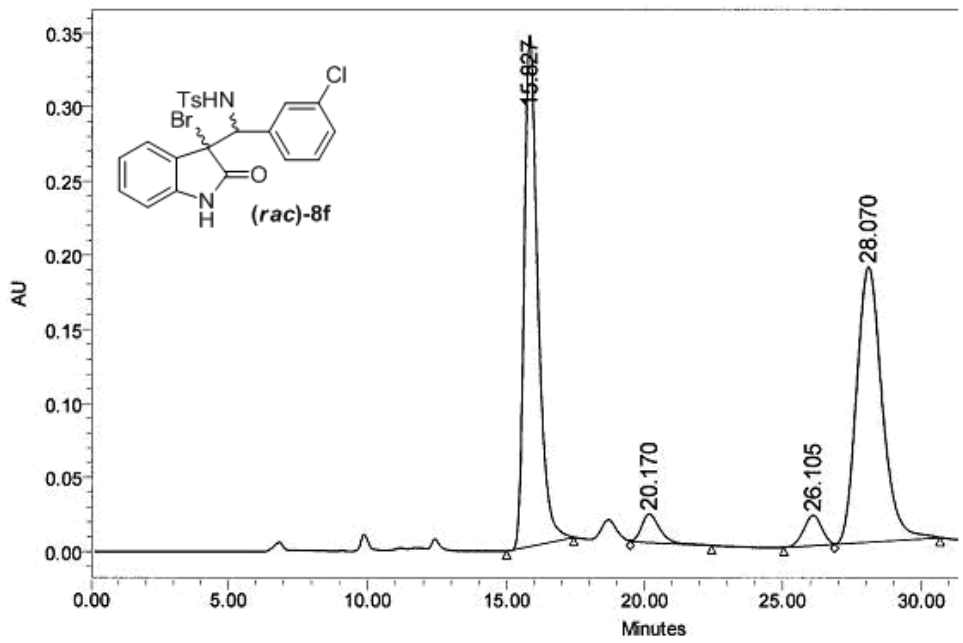
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	19.162	335294	0.50	9231	0.62
2	20.982	61974034	91.69	1405527	94.23
3	26.399	3372525	4.99	44105	2.96
4	31.468	1910766	2.83	32700	2.19



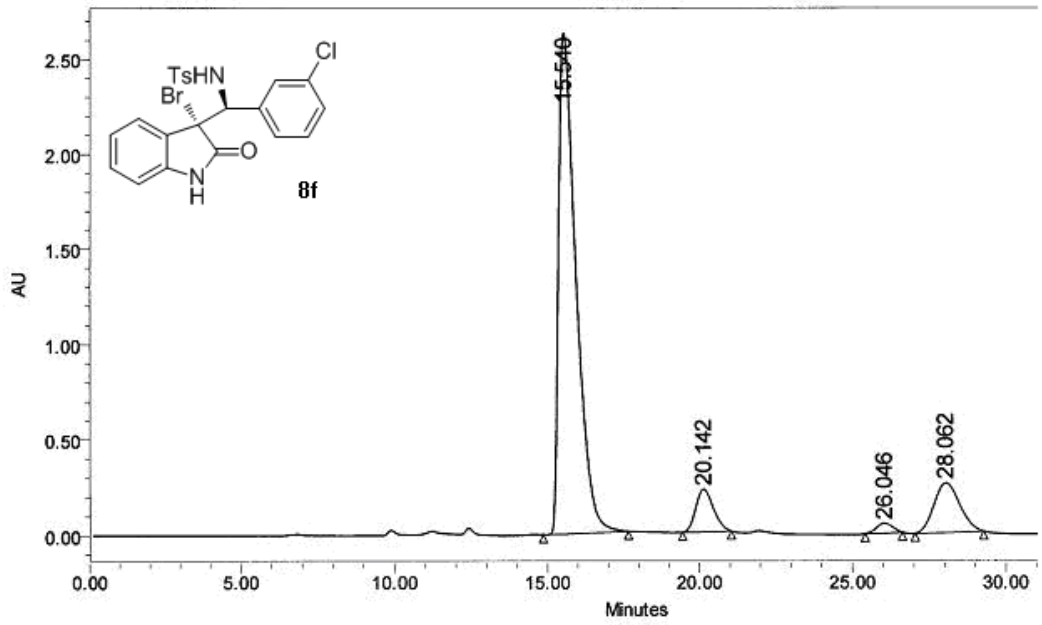
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	36.149	1329603	6.58	18740	8.79
2	43.453	8499326	42.03	99106	46.49
3	46.539	1436302	7.10	15870	7.44
4	56.972	8956730	44.29	79473	37.28



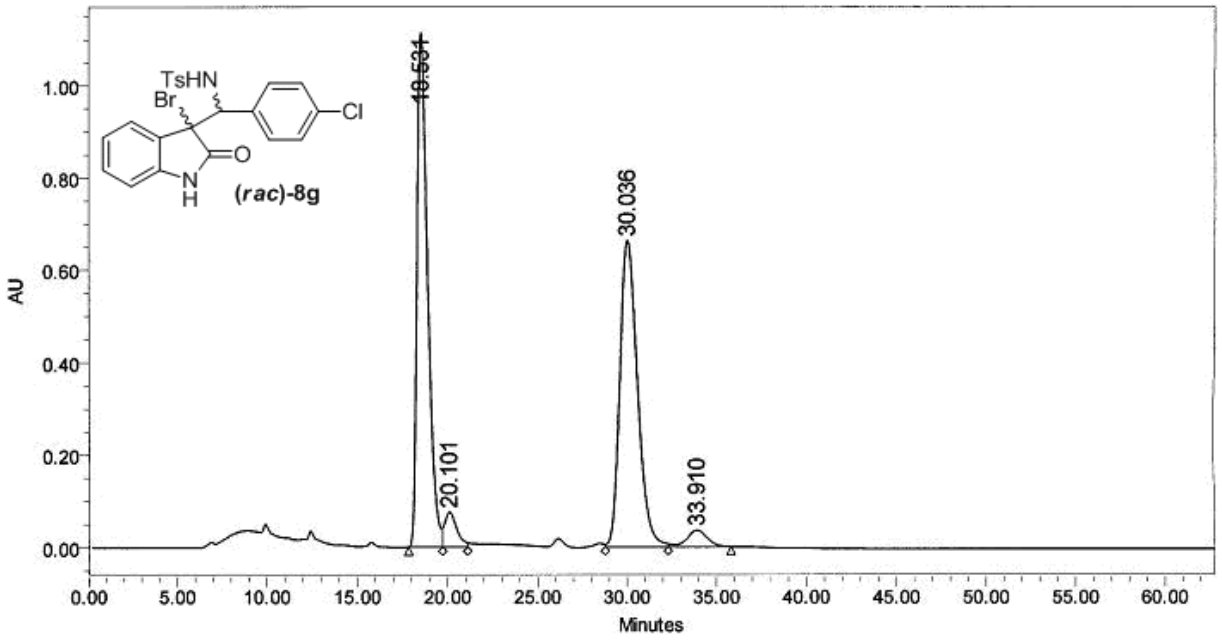
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	36.165	4297851	5.46	63323	9.00
2	43.541	6408536	8.15	79979	11.37
3	46.593	1507620	1.92	19355	2.75
4	56.078	66456653	84.47	540813	76.88



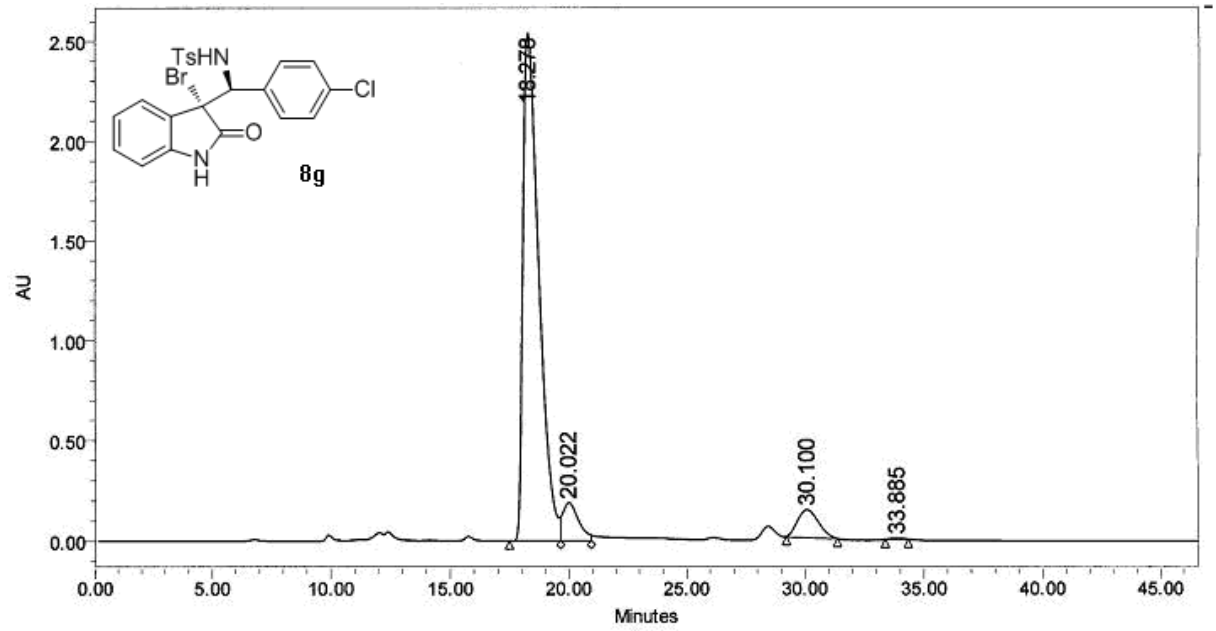
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	15.827	11844962	46.61	344740	60.53
2	20.170	862014	3.39	19033	3.34
3	26.105	914678	3.60	20350	3.57
4	28.070	11789077	46.39	185458	32.56



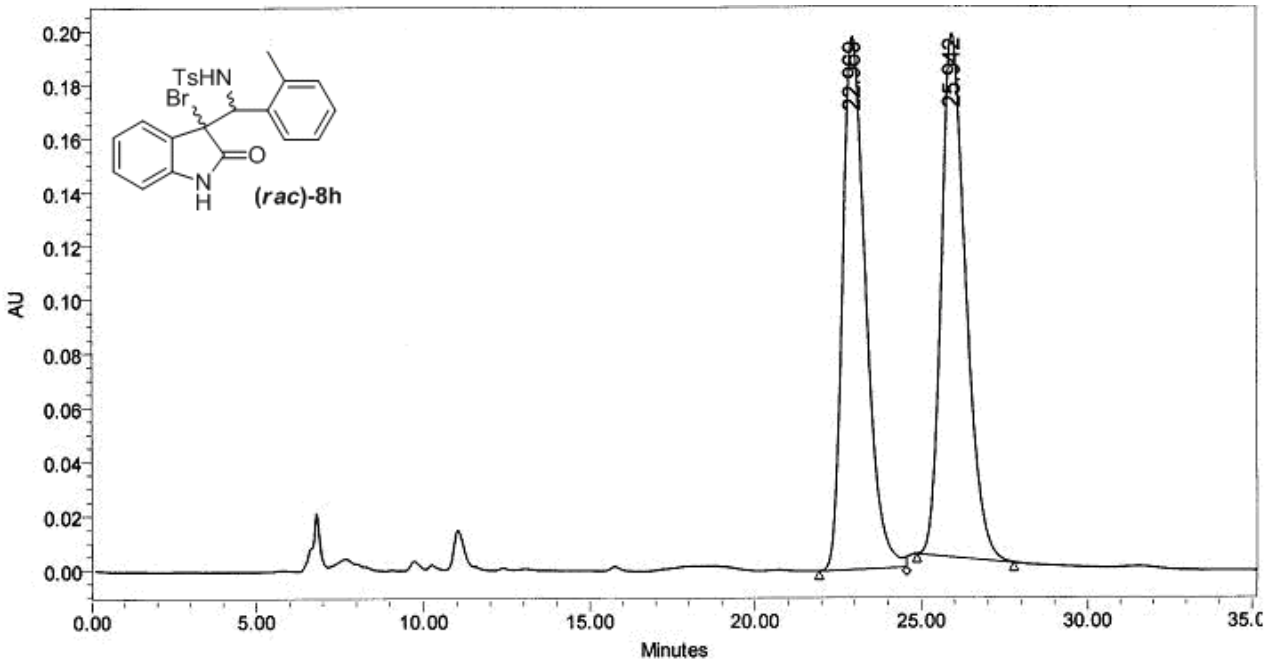
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	15.540	104165949	80.16	2627819	83.23
2	20.142	8947106	6.88	221540	7.02
3	26.046	1859627	1.43	51436	1.63
4	28.062	14978029	11.53	256656	8.13



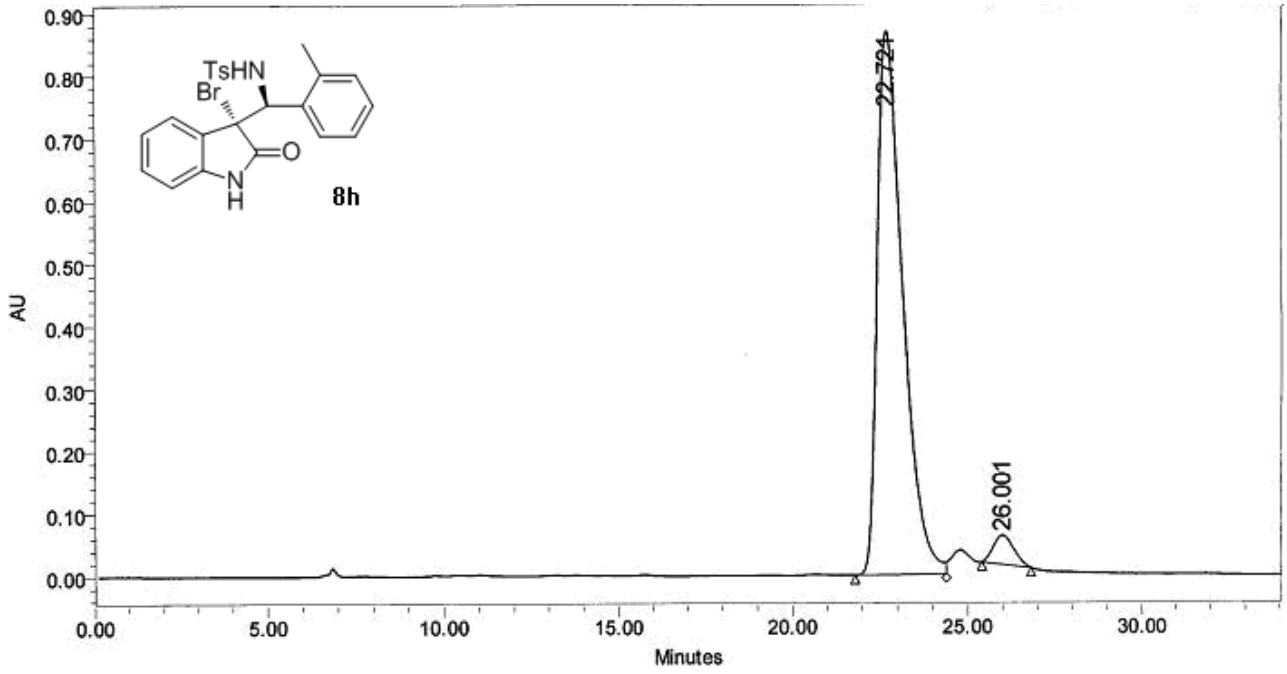
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	18.531	45173926	46.56	1113917	59.02
2	20.101	3541881	3.65	75681	4.01
3	30.036	45427711	46.82	661344	35.04
4	33.910	2874591	2.96	36349	1.93



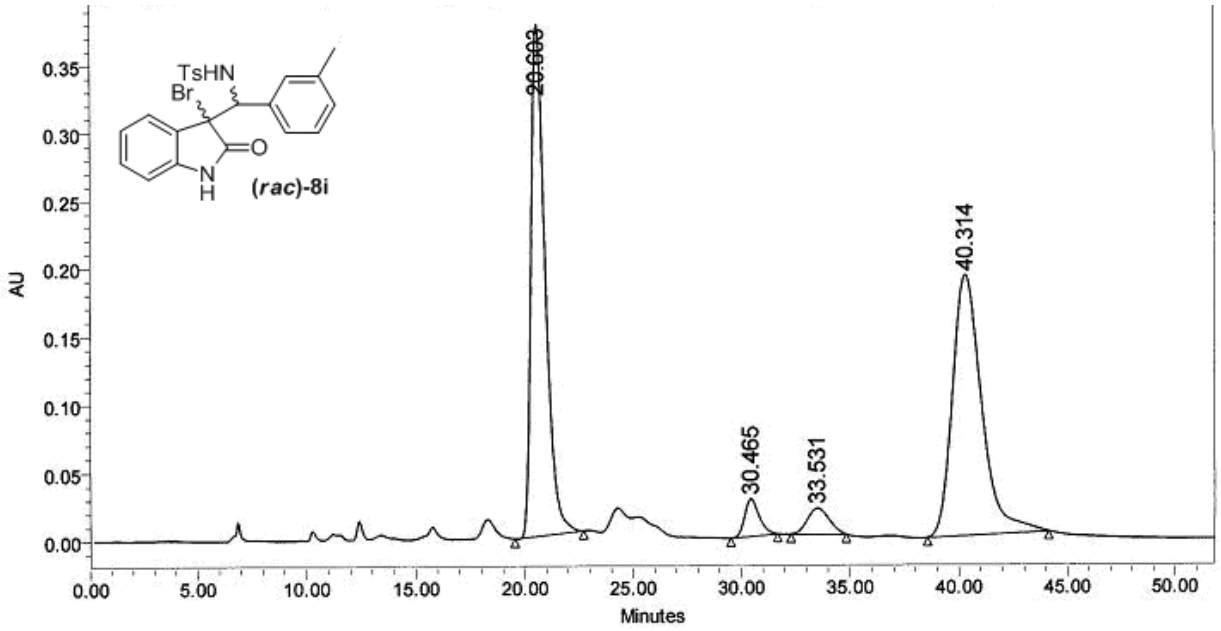
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	18.278	118079549	87.29	2538276	88.53
2	20.022	8713490	6.44	187297	6.53
3	30.100	8318646	6.15	137091	4.78
4	33.885	165890	0.12	4554	0.16



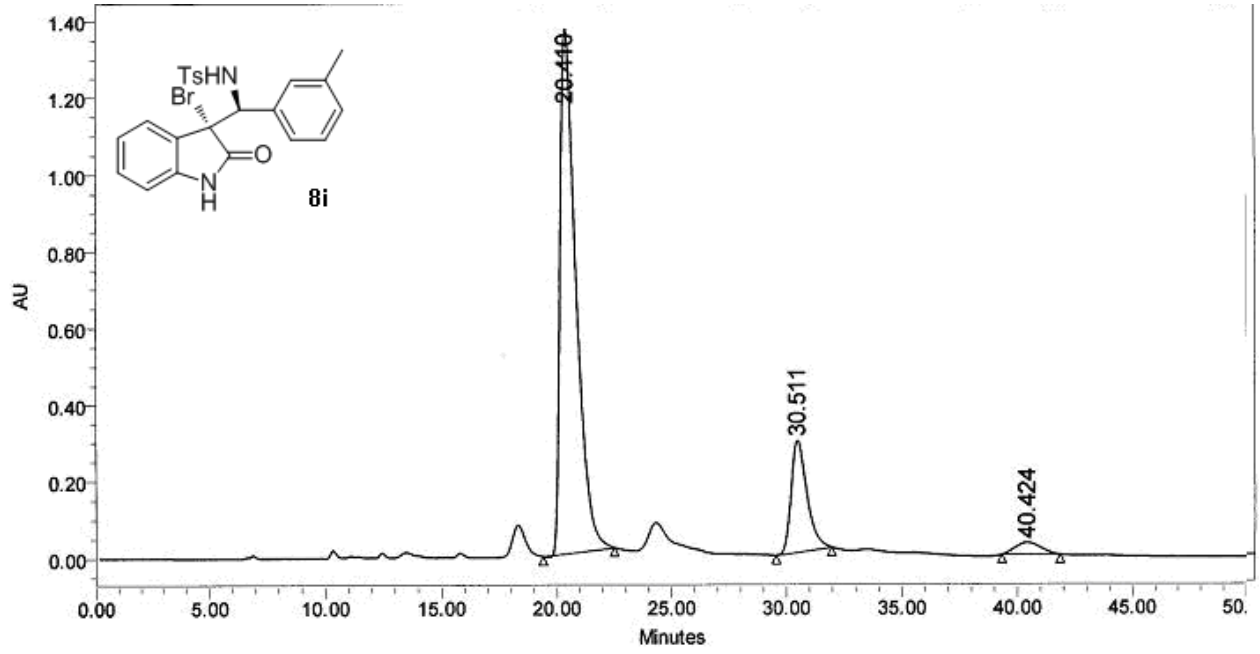
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	22.969	9500256	49.19	197478	50.44
2	25.942	9811977	50.81	194050	49.56



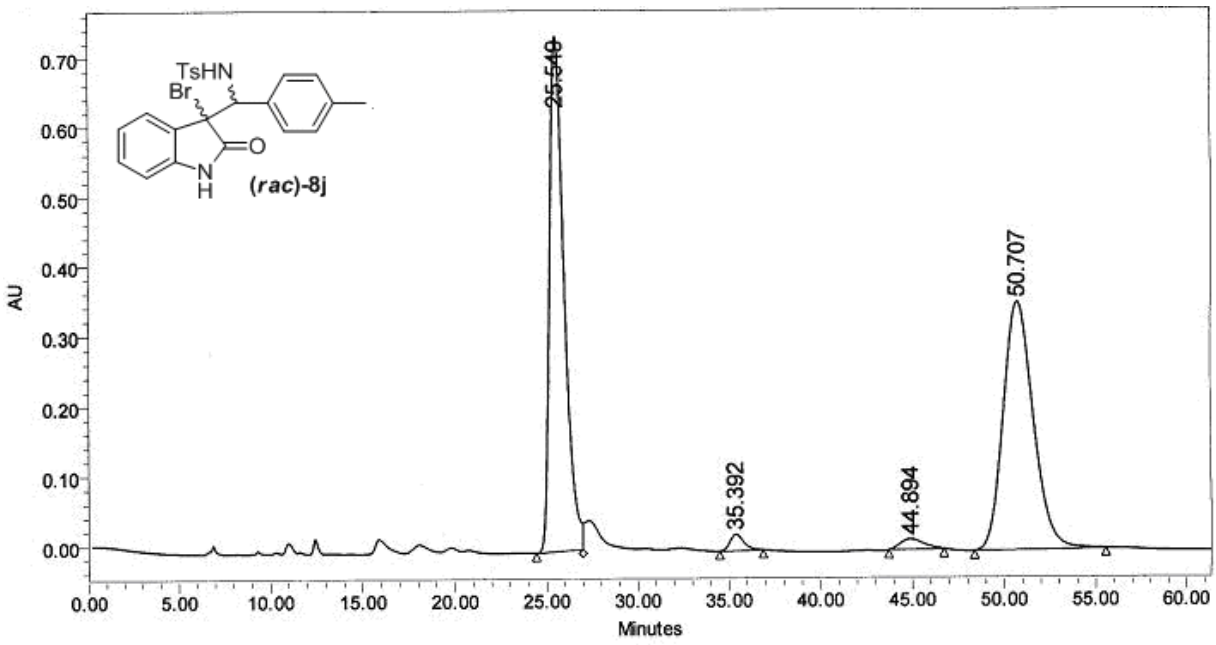
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	22.721	43628899	95.94	867667	94.97
2	26.001	1848444	4.06	46001	5.03



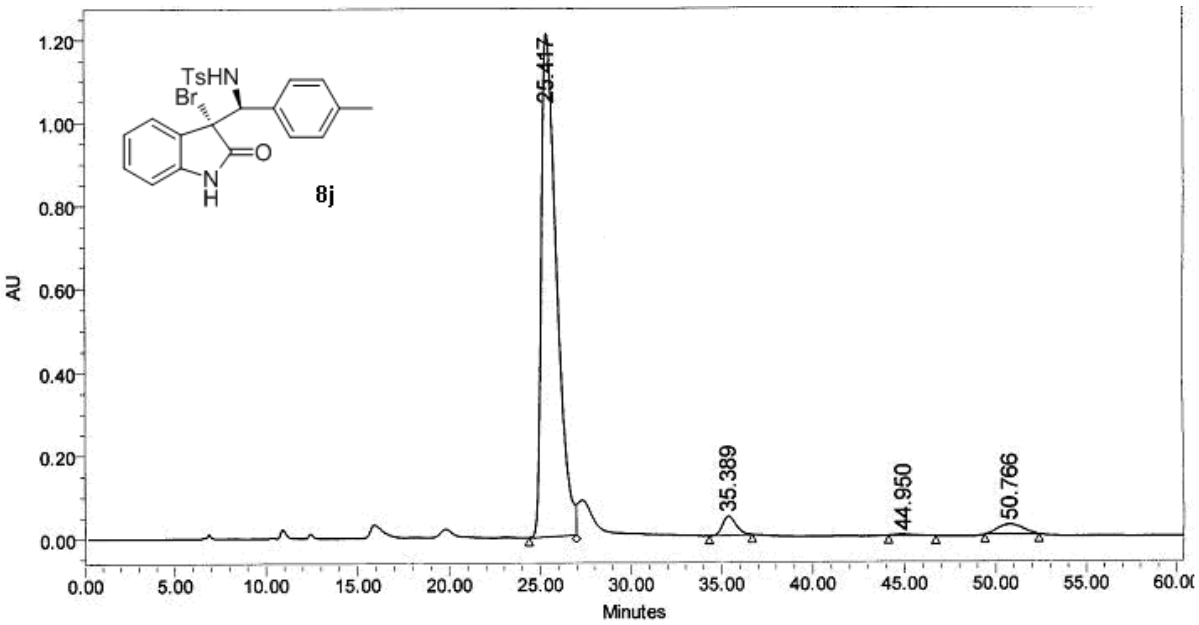
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	20.603	17009767	45.56	376794	61.40
2	30.465	1274964	3.42	27489	4.48
3	33.531	1324557	3.55	19073	3.11
4	40.314	17724931	47.48	190330	31.01



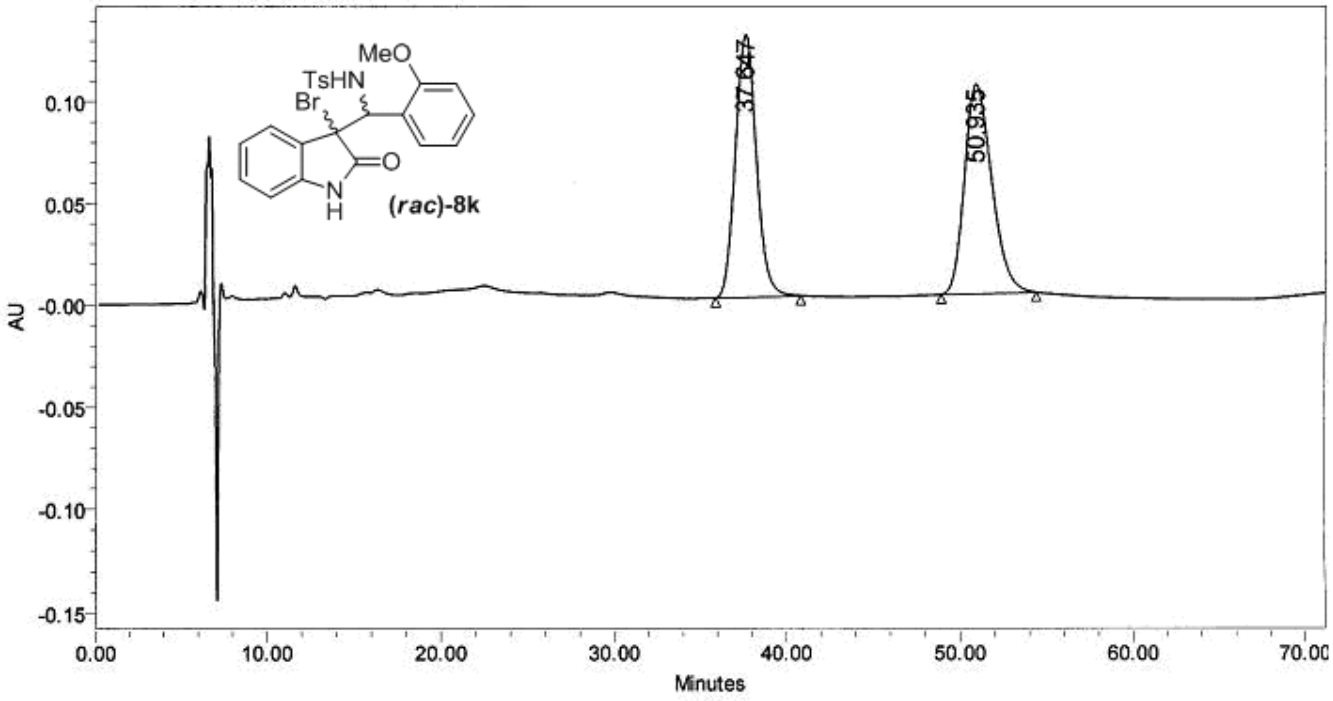
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	20.410	65572600	80.27	1364838	81.02
2	30.511	13759357	16.84	289176	17.17
3	40.424	2355723	2.88	30593	1.82



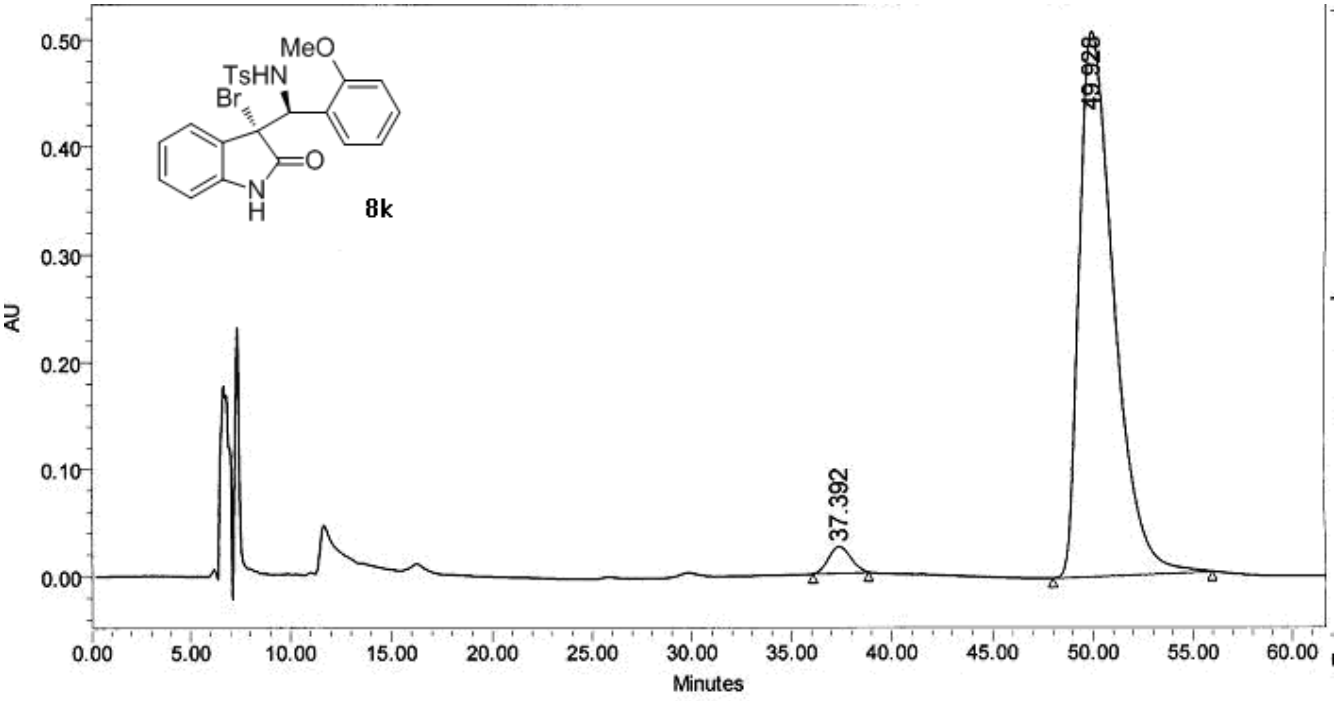
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	25.549	40692041	48.61	739161	65.33
2	35.392	1222542	1.46	23455	2.07
3	44.894	1322269	1.58	15037	1.33
4	50.707	40471244	48.35	353805	31.27



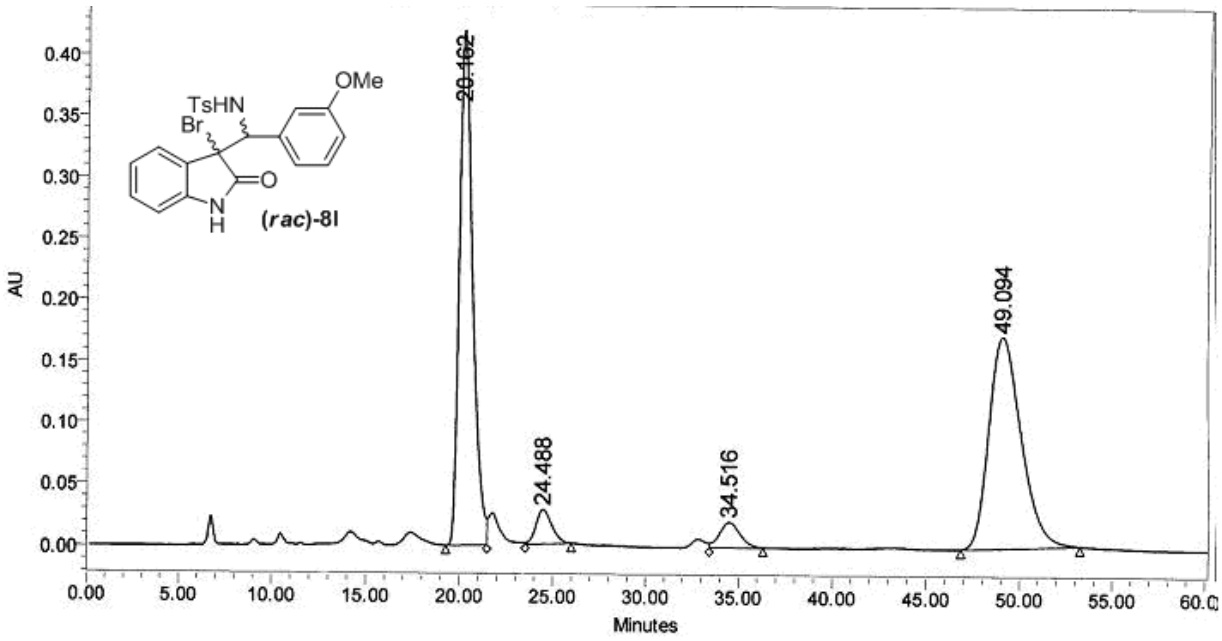
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	25.417	70519207	93.58	1209501	94.34
2	35.389	2347465	3.12	45820	3.57
3	44.950	209029	0.28	2799	0.22
4	50.766	2283370	3.03	23989	1.87



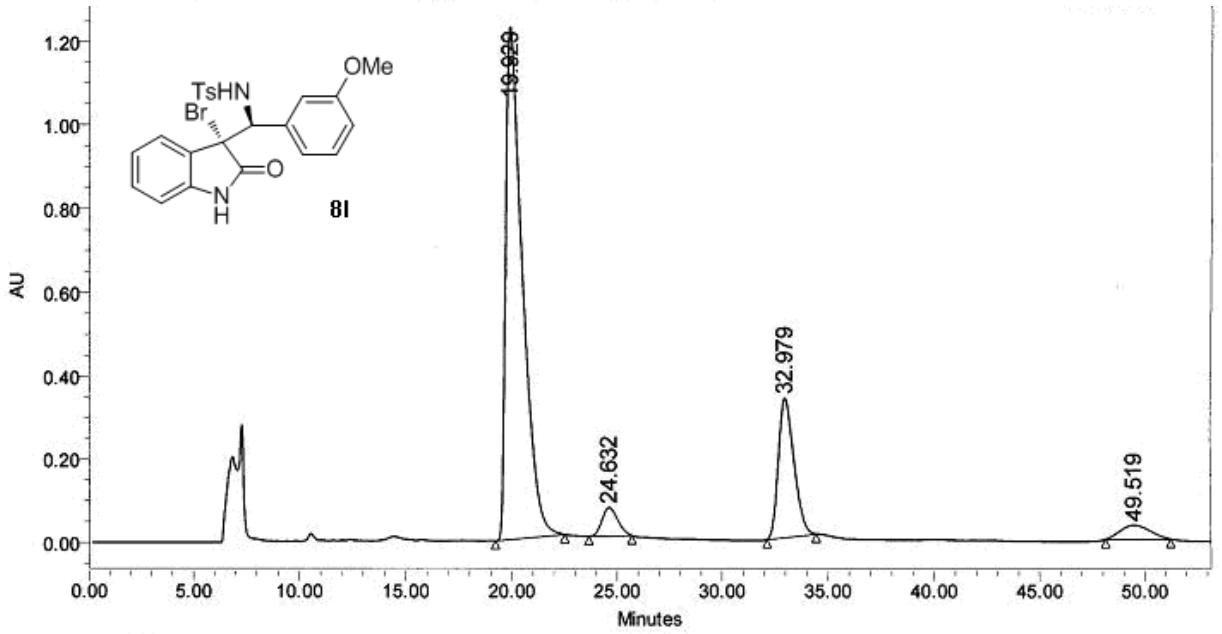
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	37.647	10910317	49.30	129386	55.68
2	50.935	11220608	50.70	102980	44.32



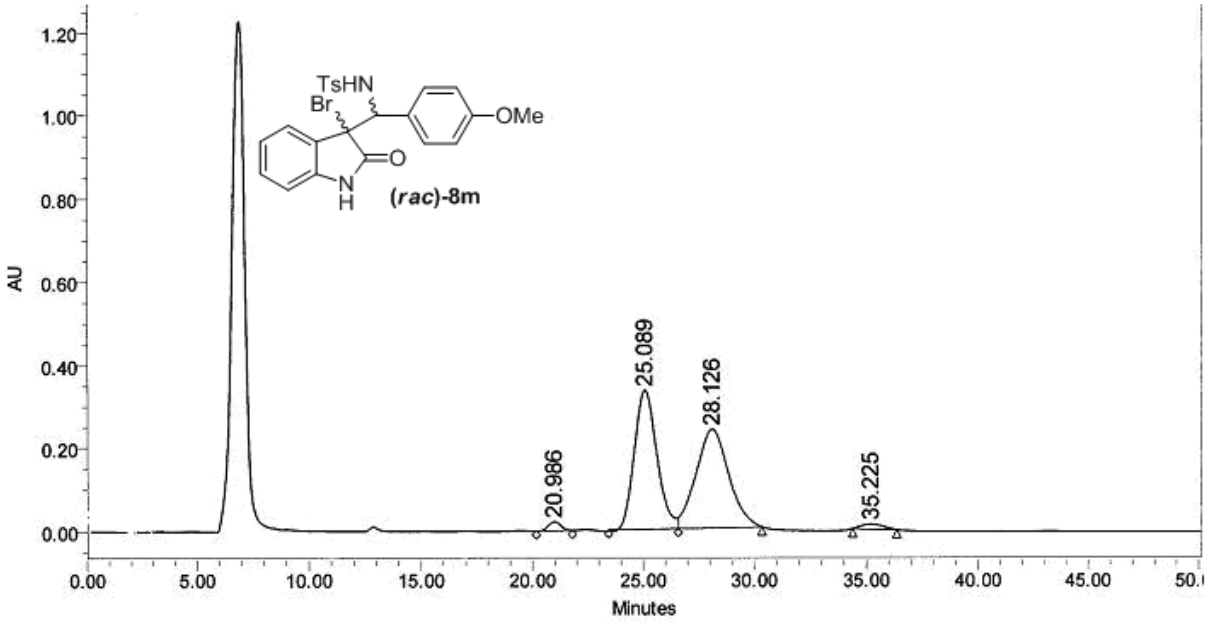
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	37.392	1842354	2.92	24181	4.55
2	49.928	61287570	97.08	507190	95.45



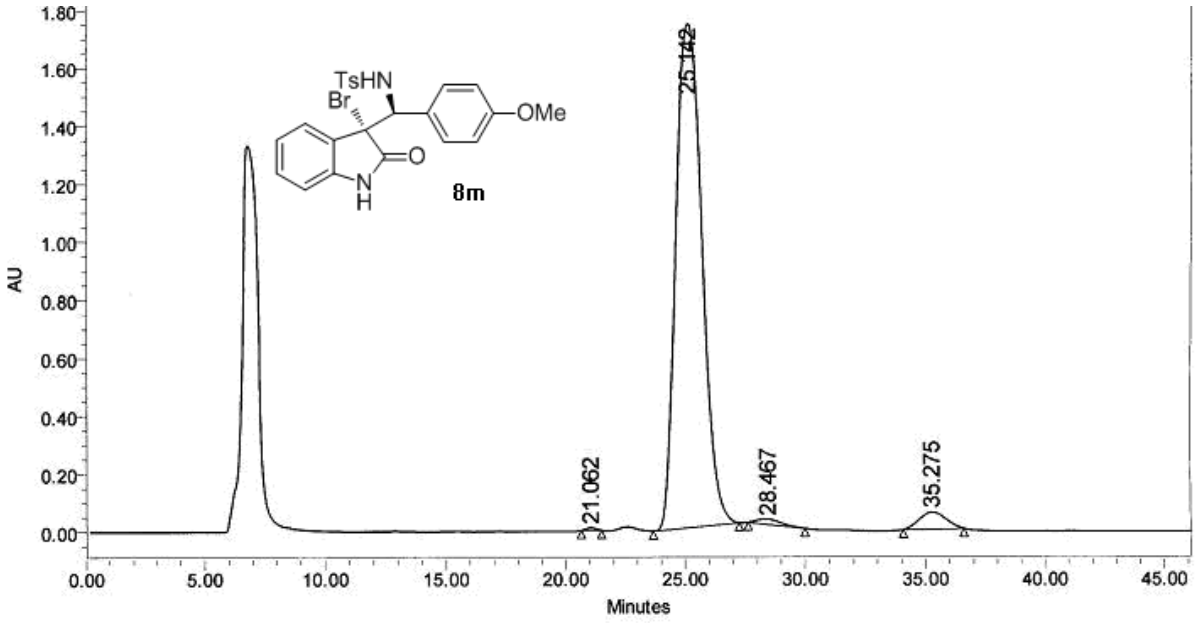
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	20.162	20555698	46.38	419433	65.67
2	24.488	1594969	3.60	27332	4.28
3	34.516	1545600	3.49	20250	3.17
4	49.094	20620889	46.53	171703	26.88



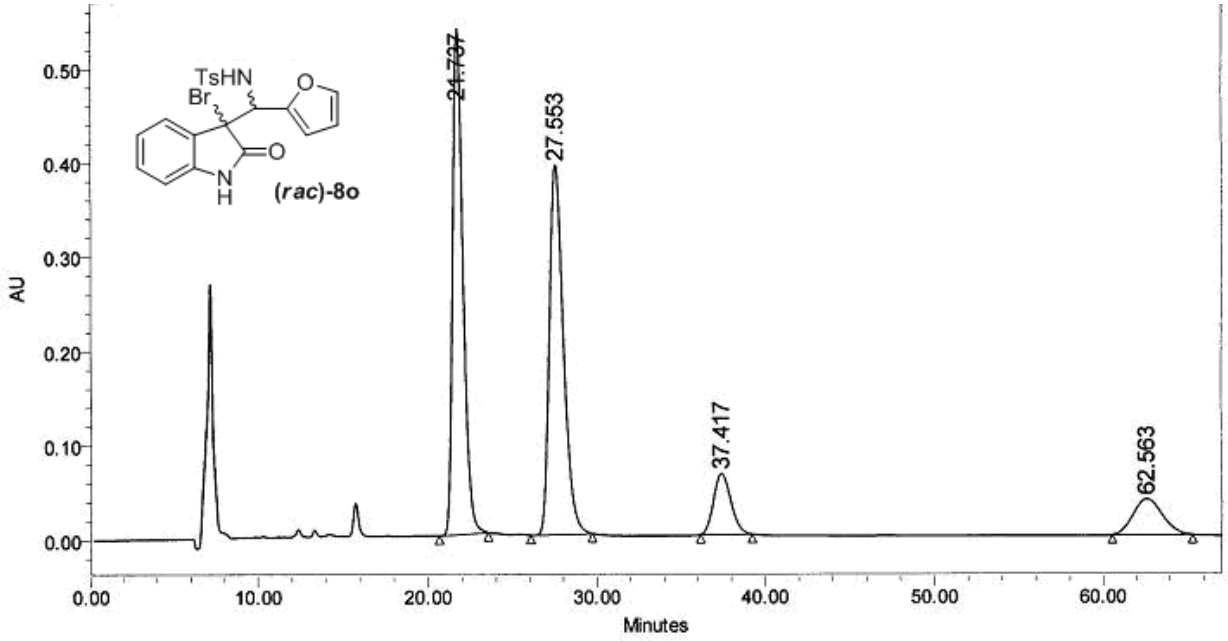
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	19.929	67499456	73.95	1228643	73.82
2	24.632	3516603	3.85	68098	4.09
3	32.979	16970680	18.59	334399	20.09
4	49.519	3295230	3.61	33302	2.00



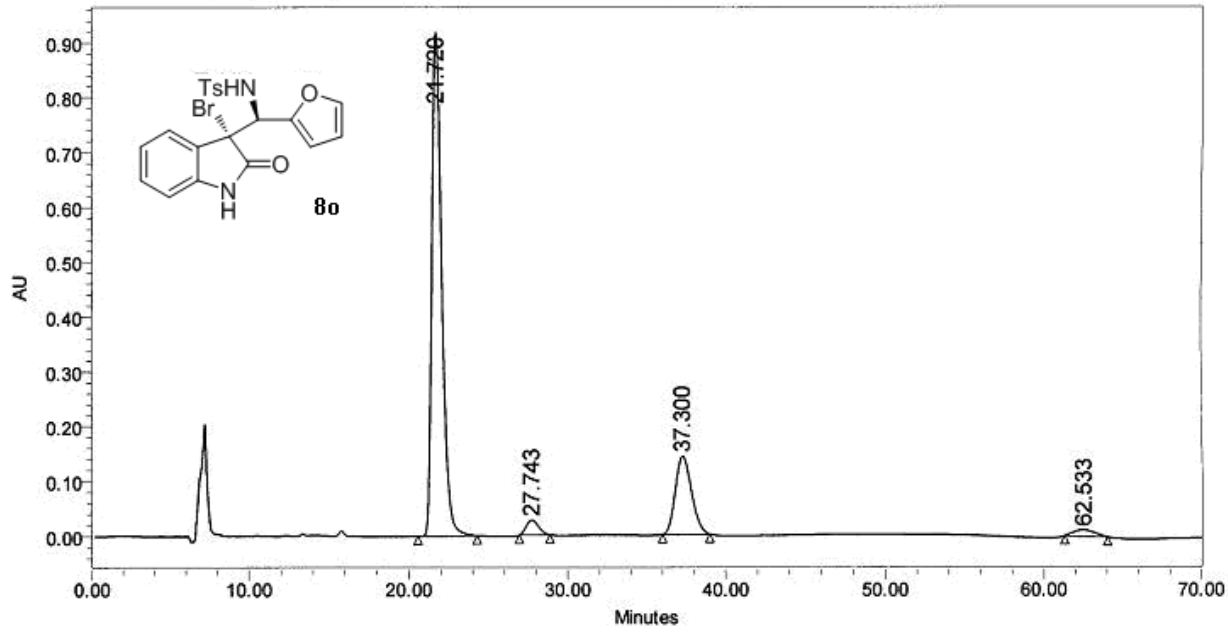
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	20.986	775427	1.58	20706	3.44
2	25.089	23484531	47.88	332918	55.37
3	28.126	24003316	48.93	235827	39.22
4	35.225	789556	1.61	11798	1.96



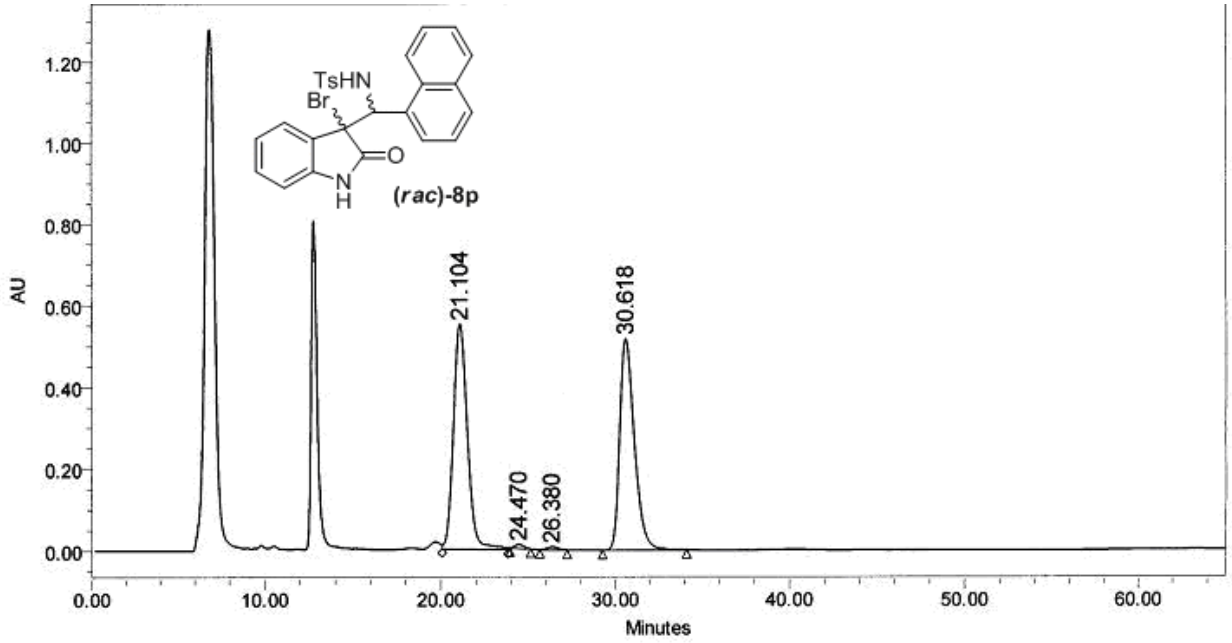
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	21.062	265663	0.19	9044	0.50
2	25.142	131711314	95.65	1737599	95.27
3	28.467	1226798	0.89	18398	1.01
4	35.275	4495210	3.26	58830	3.23



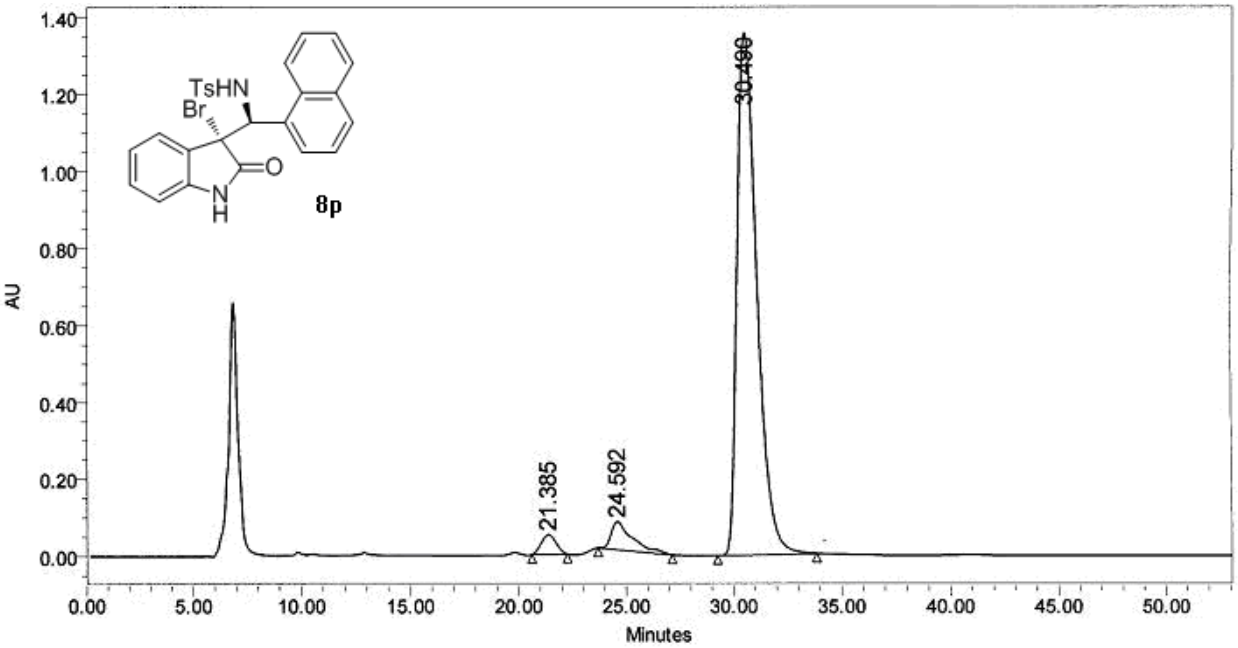
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	21.737	22696334	41.65	536875	52.11
2	27.553	22621103	41.51	391396	37.99
3	37.417	4581728	8.41	63959	6.21
4	62.563	4592811	8.43	37995	3.69



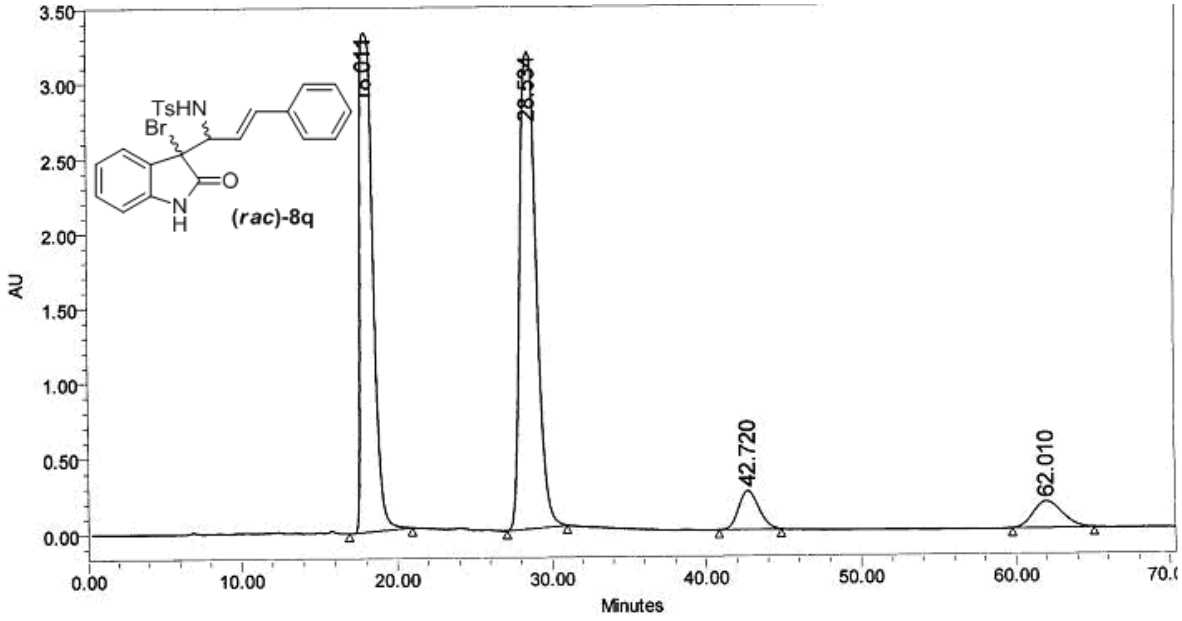
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	21.720	39619213	75.95	918309	83.62
2	27.743	1450542	2.78	27018	2.46
3	37.300	10027211	19.22	141348	12.87
4	62.533	1068324	2.05	11492	1.05



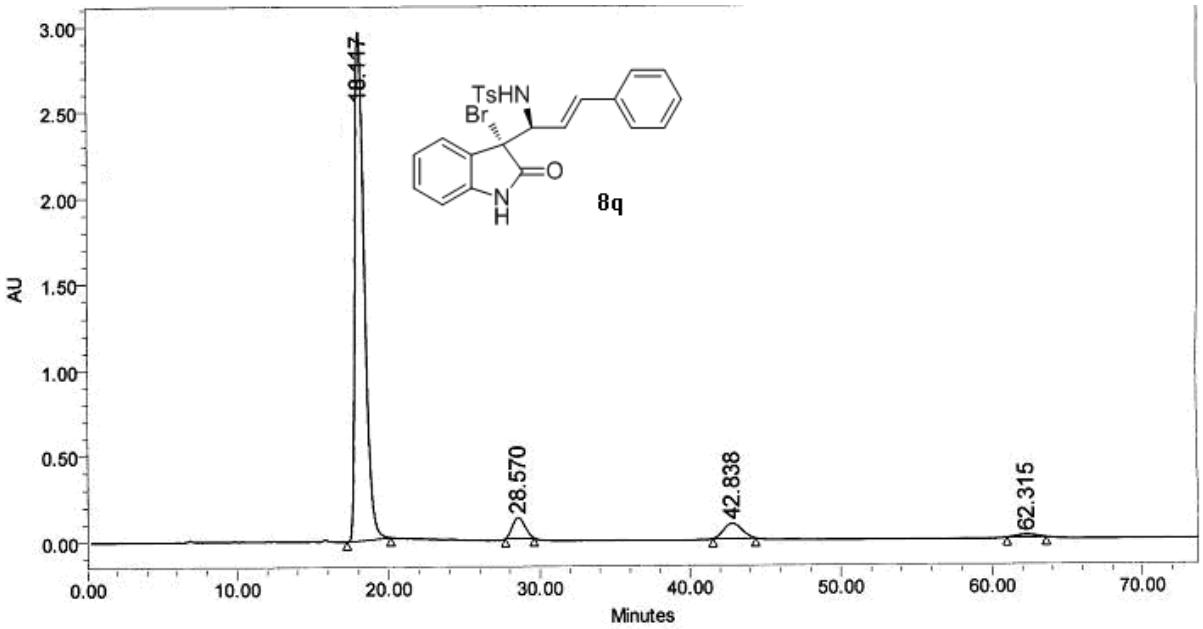
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	21.104	30246494	49.52	549371	50.75
2	24.470	343895	0.56	9511	0.88
3	26.380	297242	0.49	7000	0.65
4	30.618	30190080	49.43	516538	47.72



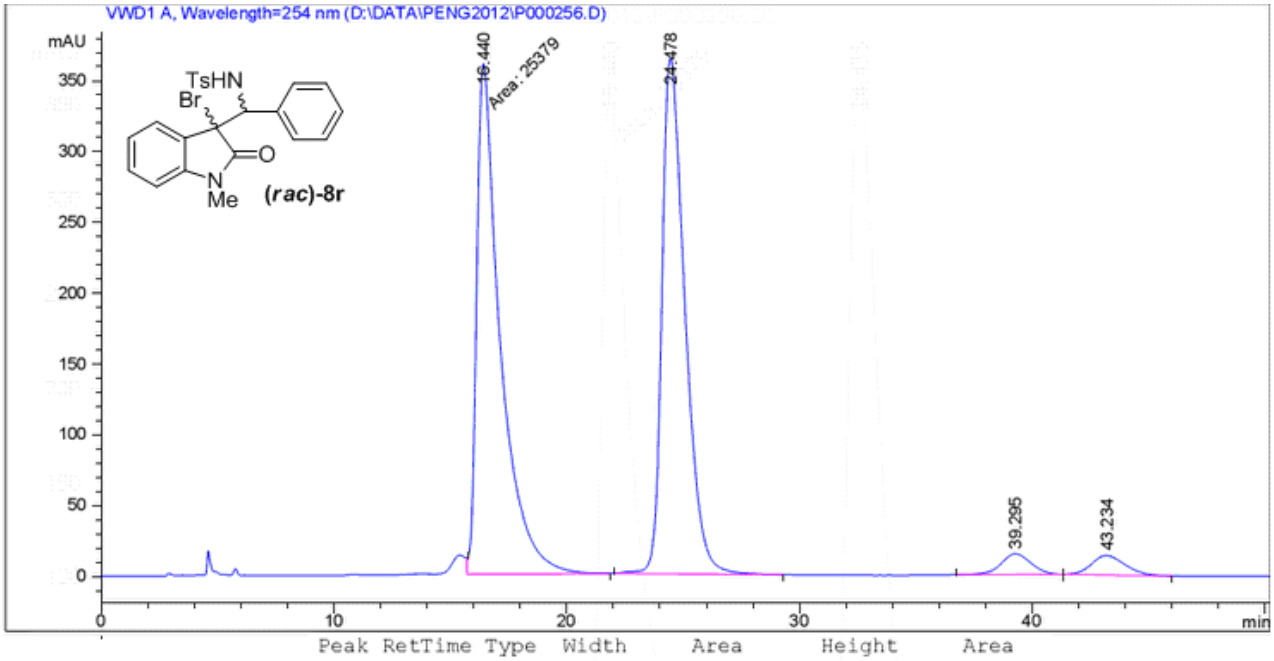
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	21.385	2389367	2.56	50277	3.40
2	24.592	4884385	5.23	72173	4.88
3	30.490	86190812	92.22	1356900	91.72



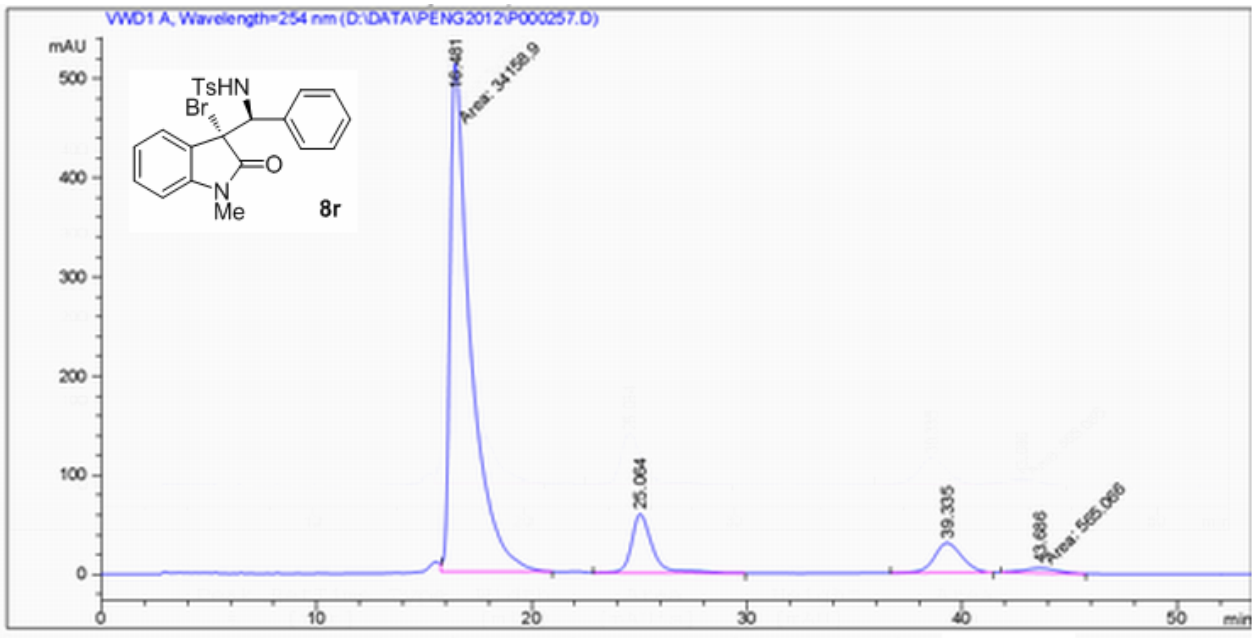
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	18.011	190838492	40.53	3321998	47.98
2	28.534	234173788	49.74	3173782	45.84
3	42.720	23008748	4.89	253989	3.67
4	62.010	22782637	4.84	173734	2.51



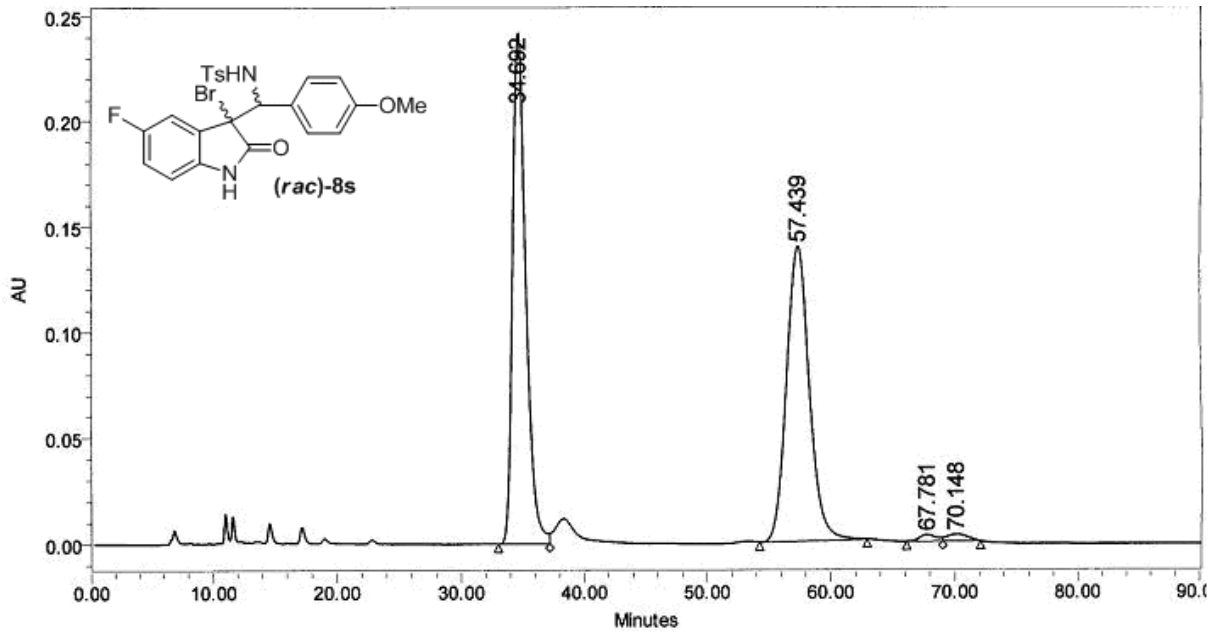
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	18.117	126453446	89.03	2958795	92.99
2	28.570	6917905	4.87	120498	3.79
3	42.838	7300599	5.14	87688	2.76
4	62.315	1370020	0.96	14835	0.47



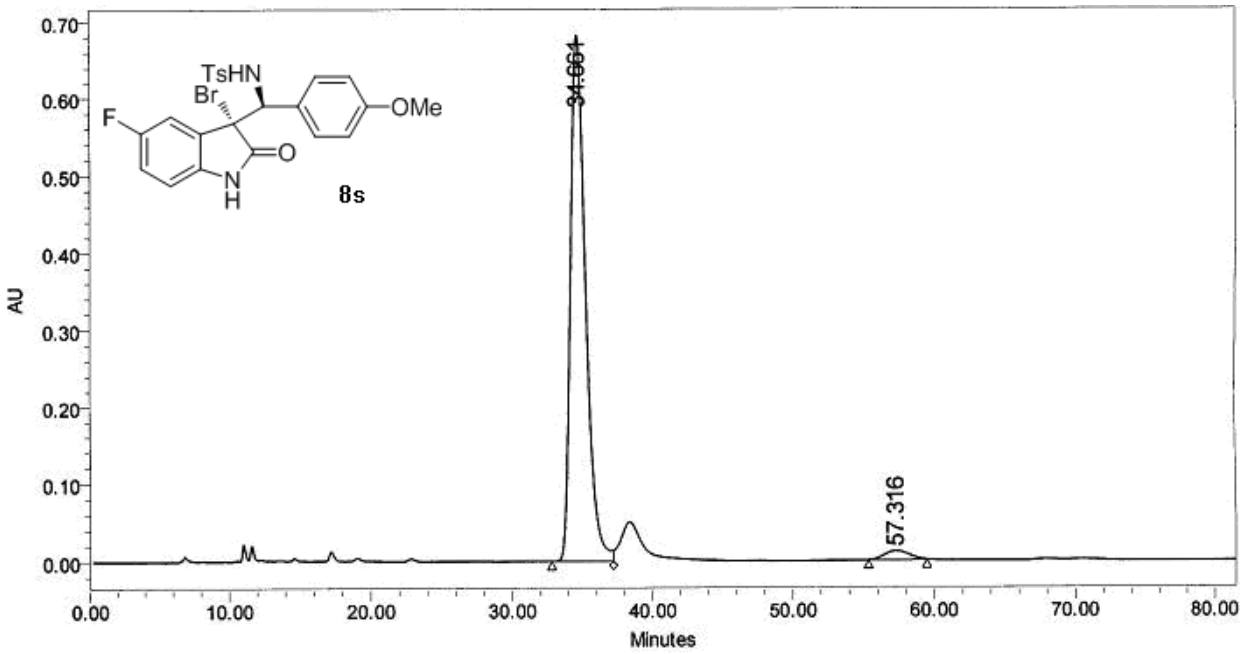
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.440	FM	1.1741	2.53790e4	360.27612	47.8567
2	24.478	BB	1.0217	2.49705e4	363.95850	47.0865
3	39.295	BB	1.3057	1303.49207	14.61313	2.4580
4	43.234	BB	1.4020	1378.18762	13.61833	2.5988



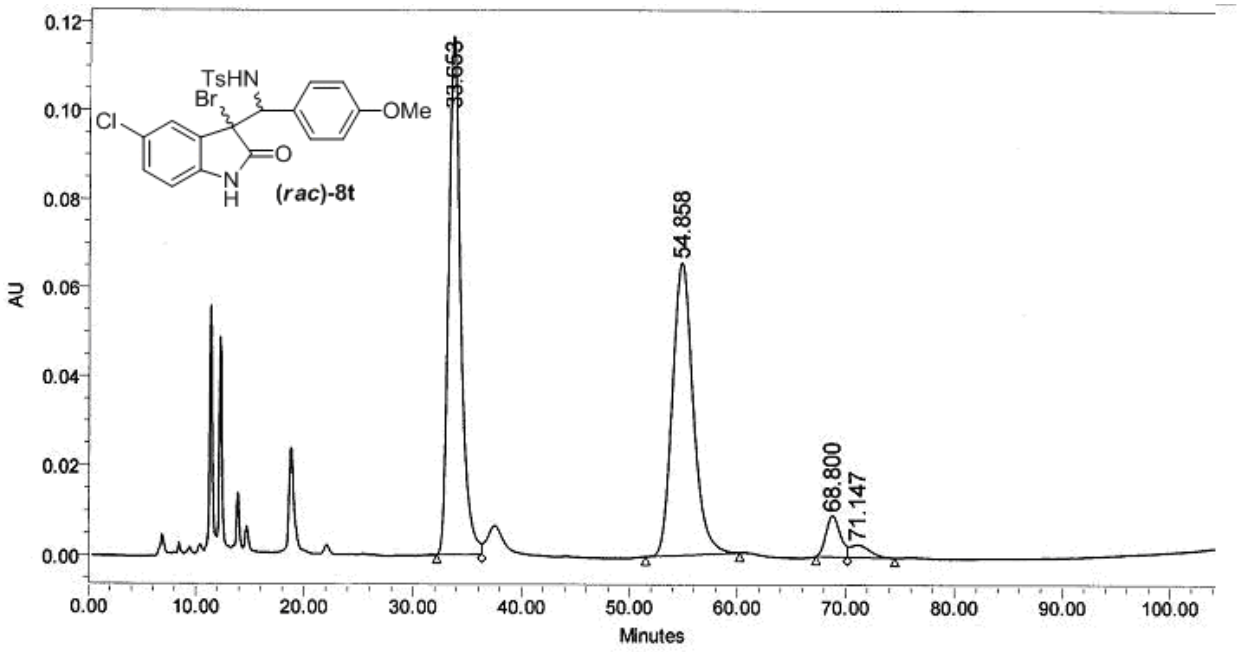
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.481	FM	1.1092	3.41589e4	513.26581	82.6153
2	25.064	BB	0.9900	3964.67603	59.27349	9.5888
3	39.335	BB	1.3374	2658.28418	29.89411	6.4292
4	43.686	MM	1.9051	565.06622	4.94342	1.3666



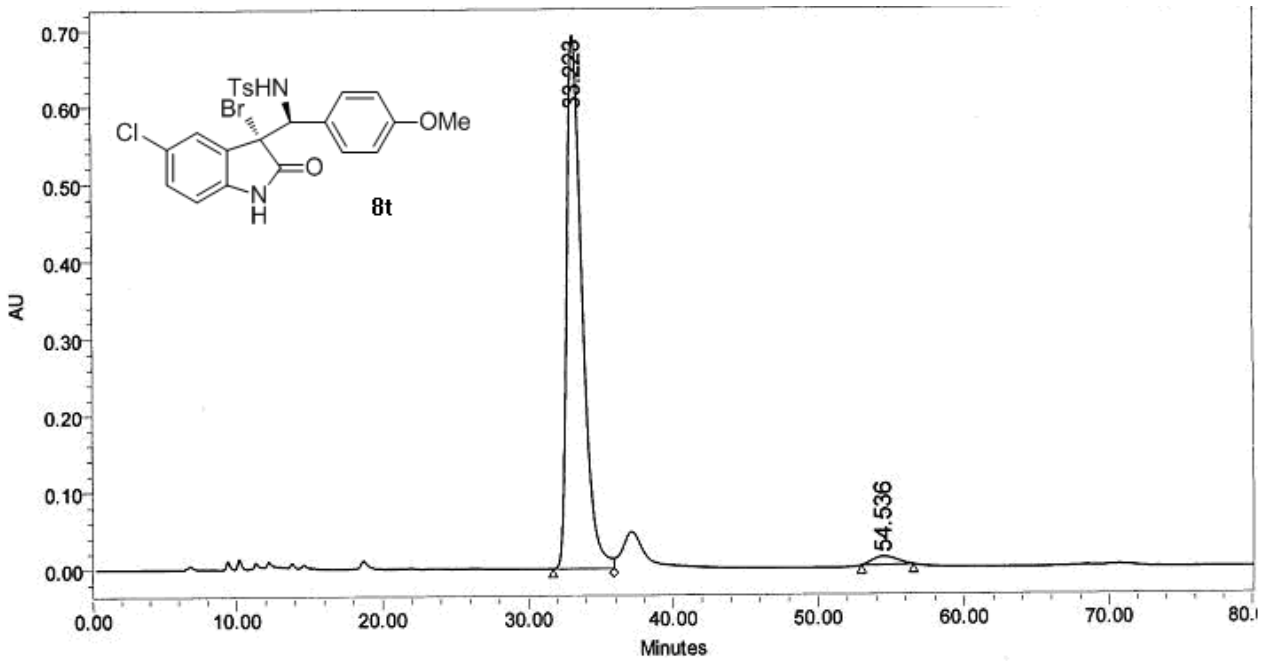
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	34.692	18036271	49.52	241836	62.44
2	57.439	17720691	48.65	139114	35.92
3	67.781	292297	0.80	3159	0.82
4	70.148	375552	1.03	3213	0.83



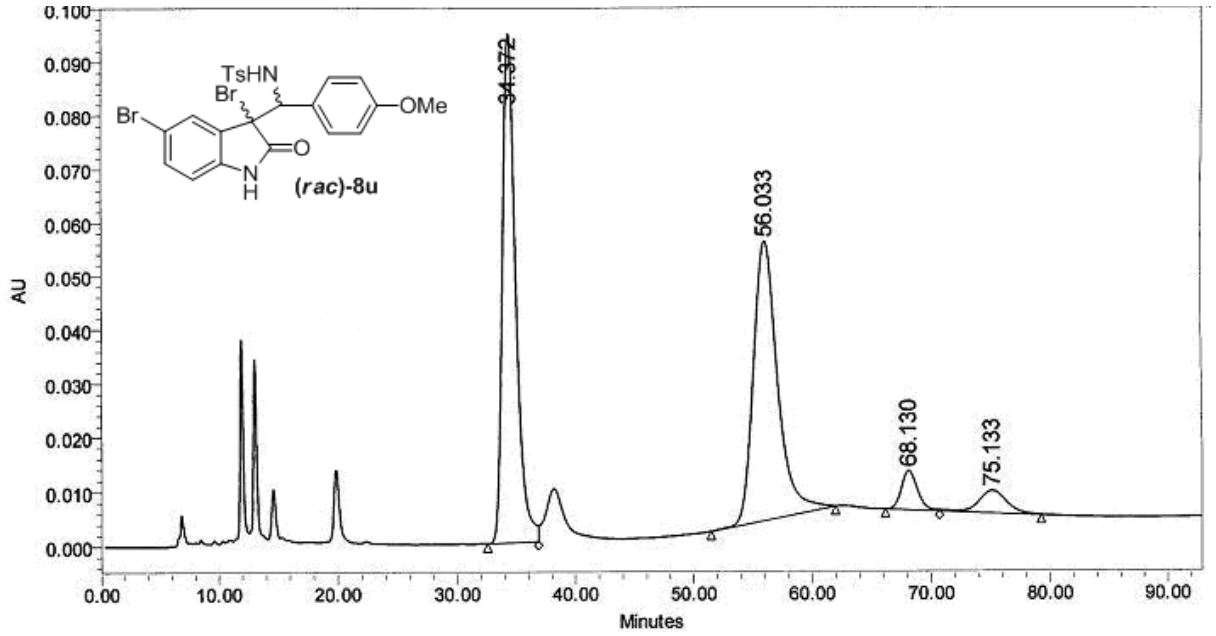
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	34.661	50551185	97.38	681665	98.35
2	57.316	1358715	2.62	11414	1.65



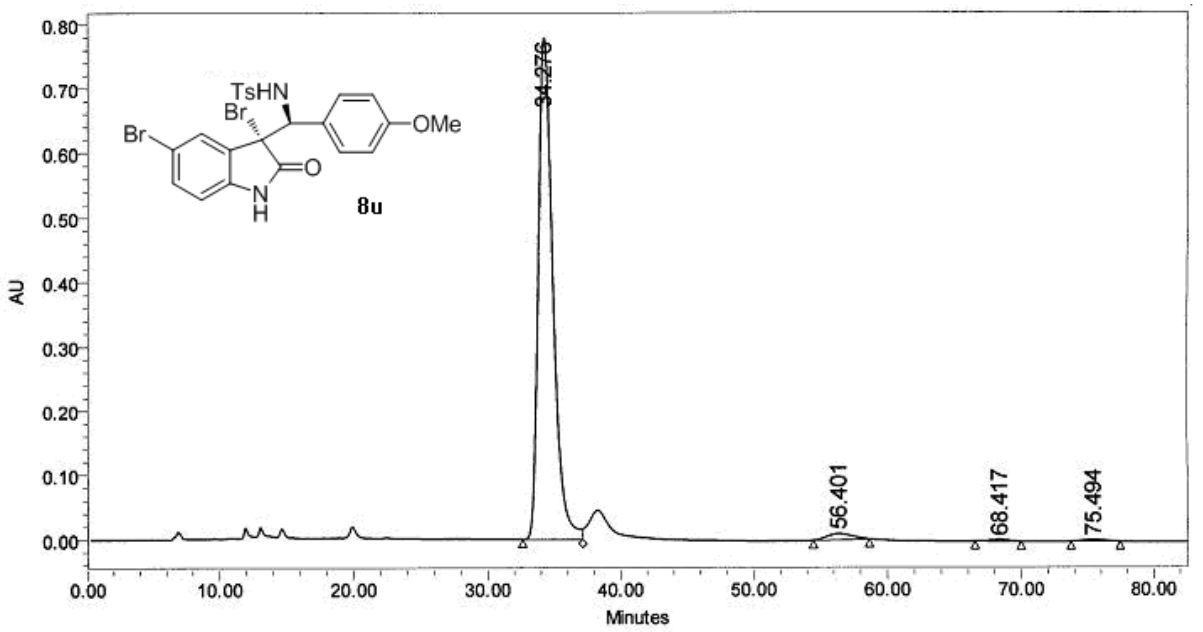
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	33.653	9040764	47.69	116433	60.09
2	54.858	8745412	46.13	65514	33.81
3	68.800	822468	4.34	9086	4.69
4	71.147	348074	1.84	2718	1.40



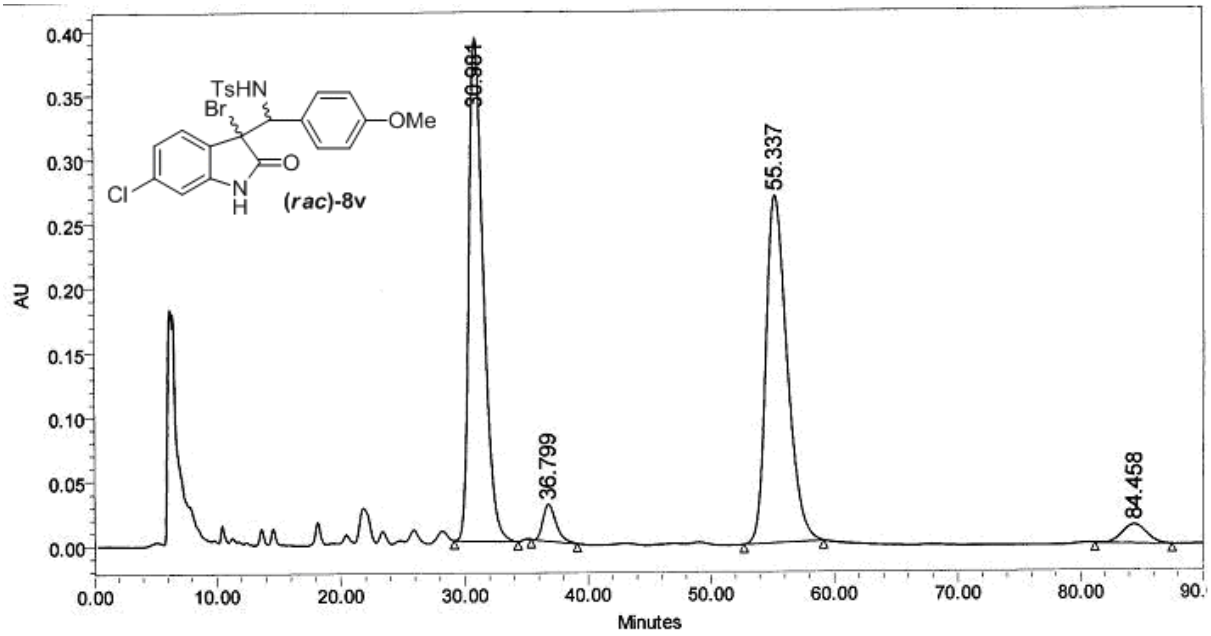
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	33.223	50811431	97.61	691959	98.47
2	54.536	1242235	2.39	10730	1.53



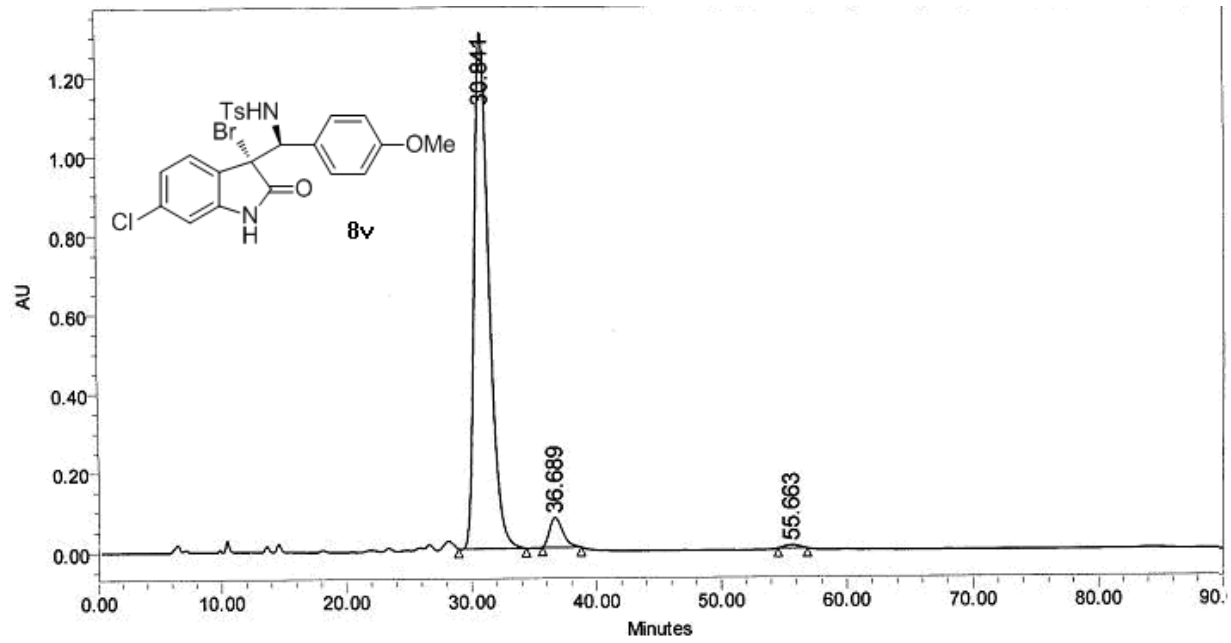
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	34.372	7332982	45.97	94598	60.06
2	56.033	7302331	45.78	51761	32.86
3	68.130	658280	4.13	7092	4.50
4	75.133	658721	4.13	4054	2.57



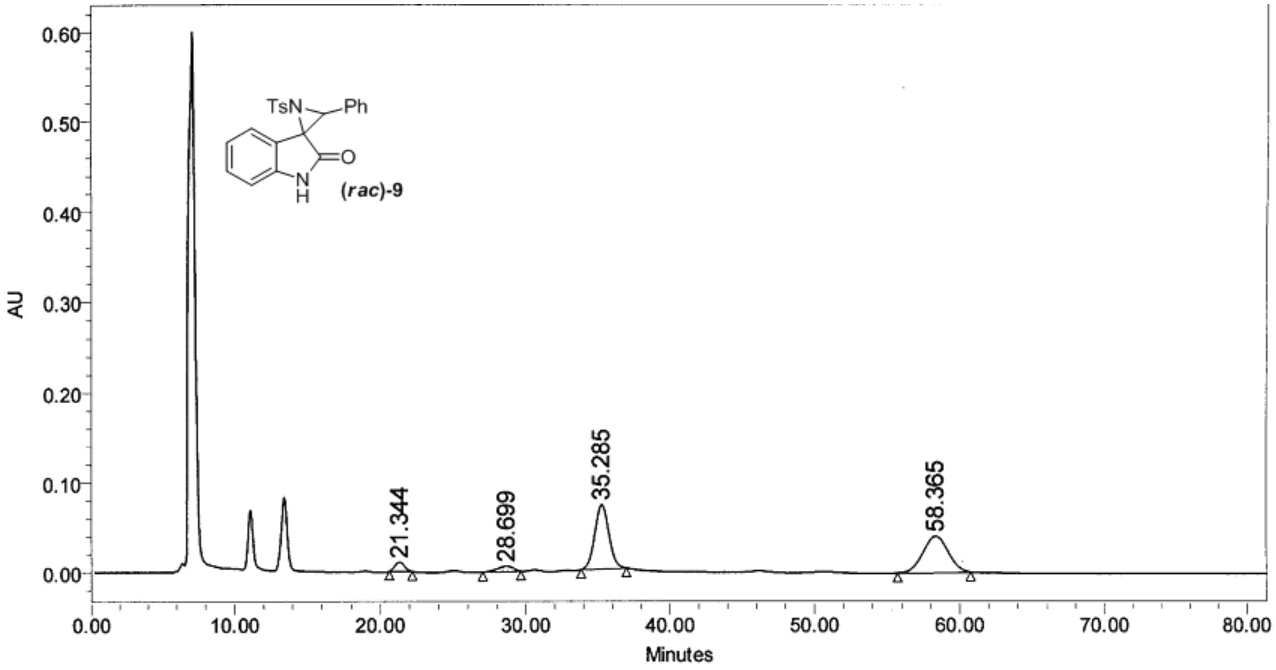
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	34.276	59395550	97.02	778465	98.10
2	56.401	1210169	1.98	9361	1.18
3	68.417	280757	0.46	2961	0.37
4	75.494	332869	0.54	2717	0.34



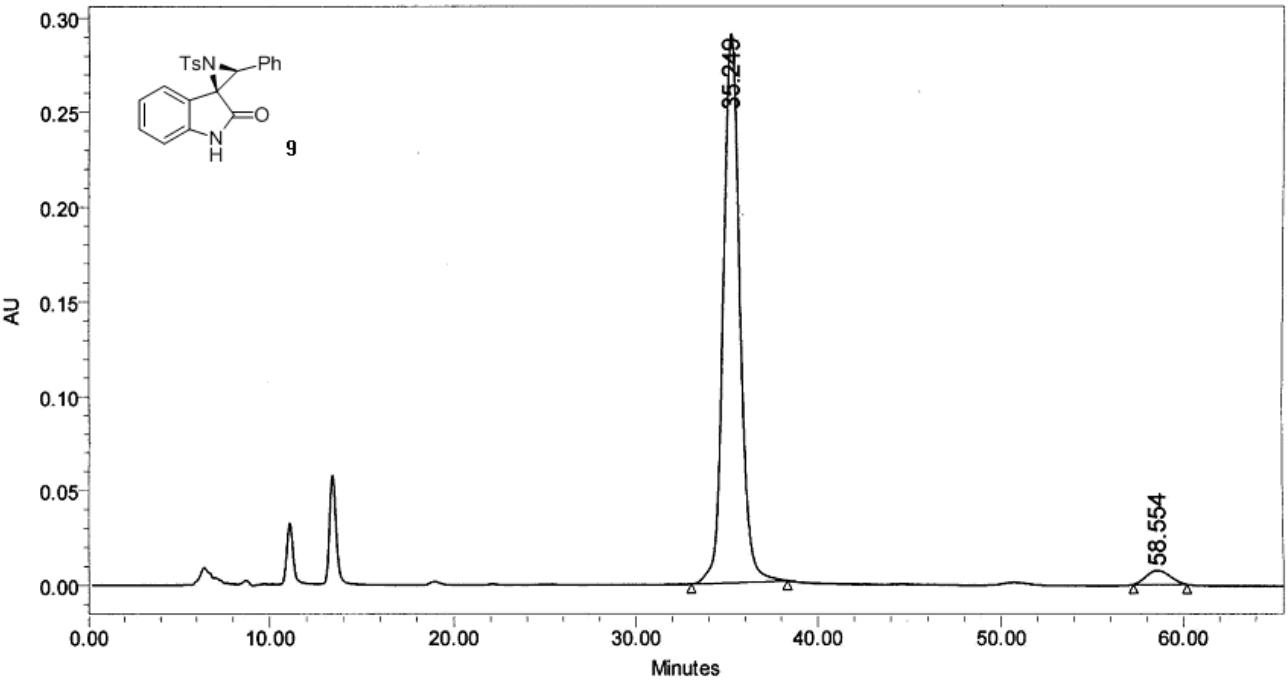
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	30.981	31685442	46.73	391074	55.62
2	36.799	2068942	3.05	28231	4.02
3	55.337	32054767	47.28	269358	38.31
4	84.458	1990209	2.94	14429	2.05



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	30.841	105748942	94.62	1301154	94.13
2	36.689	5379894	4.81	73364	5.31
3	55.663	636694	0.57	7788	0.56



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	21.344	459184	4.32	10408	8.11
2	28.699	458782	4.32	6119	4.77
3	35.285	4846813	45.61	71413	55.65
4	58.365	4861194	45.75	40396	31.48



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	35.249	18301404	96.52	290347	97.53
2	58.554	660122	3.48	7346	2.47