Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Formal [3+2] Cycloaddition of α-Unsubstituted Isocyanoacetates and Methyleneindolinones: Enantioselective Synthesis of Spirooxindoles

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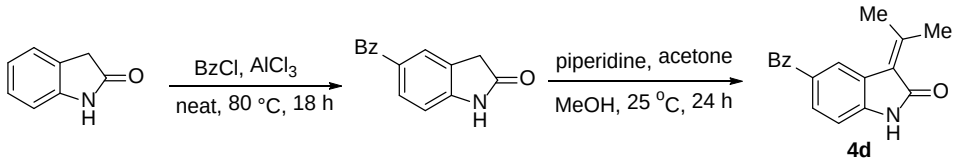
Electronic Supplementary Information

I. General information. **^{1}H** and **^{13}CNMR** spectra were recorded on Bruker AMX500 (500 MHz), Agilent 400MR (400 MHz) and 600MR (600 MHz) spectrometers. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: ^{1}H (chloroform δ 7.26; acetone δ 2.05; DMSO δ 2.50), ^{13}C (chloroform δ 77.16; acetone δ 29.84, 206.26; DMSO δ 39.52). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t =triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz) and integration. For thin layer chromatography (**TLC**), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254nm. High resolution mass spectra (**HRMS**) were obtained on a Finnigan/MAT 95XL-T spectrometer. **Optical rotations** were recorded on an mrc AP81 automatic polarimeter or a Jasco DIP-1000 polarimeter. Enantiomeric excesses (**ee**) were determined by HPLC analysis on Agilent HPLC units, including the following instruments: pump, LC-20AD; detector, SPD-20A; column, Chiralpak AD-H, IA-H, ID-H, and OJ-H.

Tetrahydrofuran (THF) and dichloromethane (DCM) were dried over a Pure Solv solvent purification system. Other solvents used such as acetone, acetonitrile, ethyl acetate (AcOEt) and methanol were of analytical grade and used as received. All chemicals were purchased from commercial suppliers and used without further purification. Methyl isocyanoacetate (**2a**) were purchased from Alfa Aesar Company. Other isocyanoacetates, ligands and catalysts were prepared according to literature procedures.[1, 2] Other chemicals were purchased from commercial suppliers and used as received without further purification.

II. Synthesis of methyleneindolinones

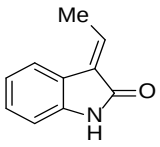
5-Benzoyl-3-Methylideneoxindole (4d)



4d

To a flask with oxindole (1 equiv) and $AlCl_3$ solid (4 equiv), acyl chloride (10 equiv) was added and heated to 80 ^oC for 18 h. The reaction mixture was poured into ice water and rapidly stirred while solid NaCl was added until the aqueous phase is saturated with observation of undissolved NaCl solid. The aqueous phase was extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The solid obtained was then dissolved in a solution of acetone and MeOH (v/v = 1:1). Piperidine (4 equiv) was then added and the reaction mixture was allowed to stir for 24 h at ambient temperature. The precipitates were collected *via* suction filtration and recrystallized to afford **4d** as a brown solid, 95% yield. mp: 245-246 ^oC, **^{1}H NMR** (500 MHz, DMSO-d6): δ 10.91 (s, 1H), 7.96 (s, 1H), 7.71 (d, *J* = 6.9 Hz, 2H), 7.66-7.61 (m, 2H), 7.55 (t, *J* = 7.6 Hz, 2H), 6.95 (d, J = 8.2 Hz, 1H), 2.54 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d6): δ 194.8, 168.6, 156.7, 144.5, 137.9, 131.9, 131.3, 129.7, 129.2, 128.4, 124.9, 123.6, 121.7, 108.6, 24.8, 22.5. **HRMS** (ESI), m/z calcd. for $[C_{18}H_{15}NO_2Na, M+Na]^+$: 300.0995; found: 300.1004.

(*E*)-3-Ethylideneindolin-2-one (*E*-4i)

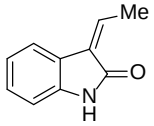


***E*-4i**

***E*-4i** was synthesized according to literature procedures.[3] Yellow solid. mp: 142-143 ^oC, **^{1}H NMR** (500 MHz, DMSO-d6): δ 10.42 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.89-6.83 (m, 2H), 2.22 (d, *J* = 7.6 Hz,

3H). **^{13}C NMR** (125 MHz, DMSO-d6): δ 167.9, 142.0, 135.8, 129.0, 128.9, 123.6, 122.3, 121.3, 109.7, 14.9. **HRMS** (ESI), m/z calcd. for [$C_{10}H_8NO$, M-H]$^-$: 158.0611; found: 158.0606.

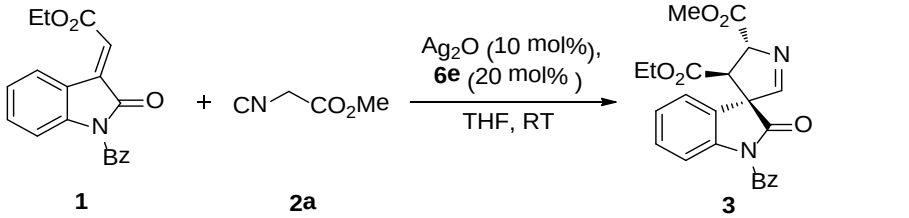
(*Z*)-3-Ethylideneindolin-2-one (*Z*-4i)



***Z*-4i**

***Z*-4i** was synthesized according to literature procedures.[3] Yellow solid. mp: 168-169 ^{o}C, **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 2.46 (dd, *J* = 7.7 Hz, 1.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.3, 139.2, 137.9, 128.4, 127.9, 123.8, 121.7, 119.1, 109.5, 14.3. **HRMS** (ESI), m/z calcd. for [$C_{10}H_9NONa$, M+Na]$^+$: 182.05777; found: 182.05764.

III. Cycloaddition of methyleneindolinone 1 with methyl isocyanoacetate 2a

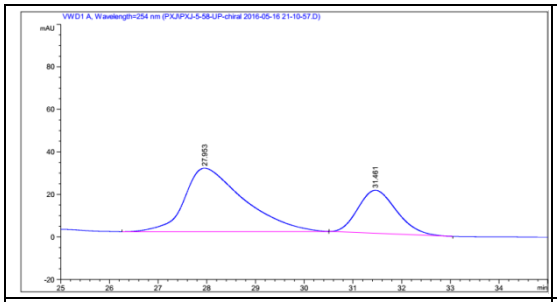


1 **2a** **3**

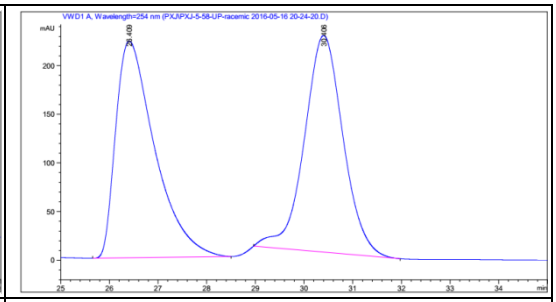
2:1:1 dr, 30%, 39% *ee* (major)

To a 10 mL vial charged with chiral ligand **6e** (48.9 mg, 0.08 mmol) and Ag_2O (9.3 mg, 0.04 mmol) was added THF (2 mL). The mixture was stirred at ambient temperature for 0.5 h. Methyleneindolinone **1**[4] (0.4 mmol) was added in one portion, followed by isocyanoacetate **2a** (0.4 mmol). The reaction mixture was stirred at ambient temperature until the starting material was consumed, and then concentrated, purified by flash chromatography (hexanes/ethyl acetate) over pre-treated silica gel (treated with 5% v/v NEt_3 in hexanes/AcOEt eluent) to give chiral product **3** as a colorless wax, 30% yield (dr: 2:1:1). **^{1}H NMR** (400 MHz, Acetone-d6): δ 7.85 (d, *J* = 8.3 Hz, 3H), 7.66-7.62 (m, 1H), 7.58 (d, *J* = 3.0 Hz, 1H), 7.54-7.48 (m, 3H), 7.44 (d, *J*

= 7.4 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 5.21 (dd, *J* = 8.2 Hz, 3.0 Hz, 1H), 4.16 (d, *J* = 8.2 Hz, 1H), 4.09-4.01 (m, 2H), 3.86 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Acetone-d6): δ 172.6, 170.7, 168.6, 168.5, 164.3, 141.2, 134.2, 132.9, 129.6, 129.5, 128.1, 127.7, 125.4, 123.6, 115.0, 76.6, 68.8, 61.4, 56.1, 52.2, 13.2. **HRMS** (ESI), m/z calcd. for $[C_{23}H_{20}N_2O_6Na, M+Na]^+$: 443.12136; found: 443.12150. **Optical Rotation**: The absolute configuration of **3** was assigned by analogy to **5e**. 39% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 28.0 min for major isomer, t_R = 31.5 min for minor isomer).

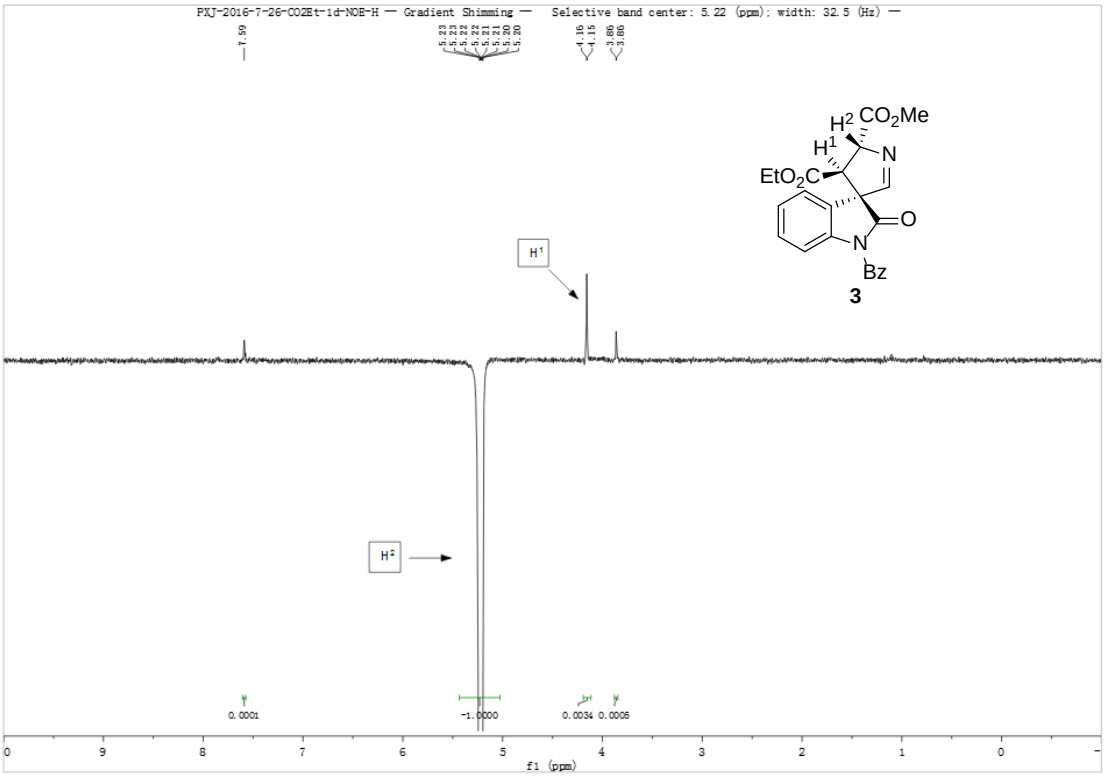


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	27.953	BB	1.0140	2515.94165	29.82953	69.3967
2	31.461	BB	0.6962	1109.50745	20.21971	30.6033

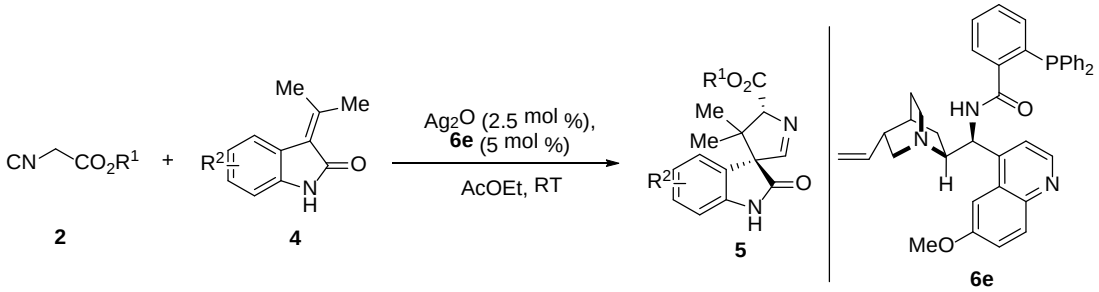


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	26.409	BB	0.8138	1.23960e4	222.73825	50.1605
2	30.406	BB	0.7826	1.23166e4	222.58041	49.8395

The *trans*-configuration of **3** was assigned by its NOE analysis. As the value of integration at δ 5.22 (H^2) is 1, the value of integration at δ 4.16 (H^1) is 0.0034 and the value of integration at δ 3.86 (Me) is 0.0005.



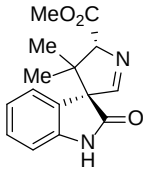
IV. Enantioselective formal [3+2] cycloaddition of 2 and 4



General procedure. To a 10 mL vial charged with chiral ligand **6e** (12.2 mg, 0.02 mmol) and Ag_2O (2.3 mg, 0.01 mmol) was added AcOEt (0.25 mL). The mixture was stirred at ambient temperature for 0.5 h. Methyleneindolinones **4** (0.4 mmol) was added in one portion. Isocyanoacetate **2** (0.4 mmol) in AcOEt (0.4 mL) was added via syringe pump over 5 h. The reaction mixture was stirred at ambient temperature until the starting material was consumed, and then concentrated, purified by flash chromatography (hexanes/ethyl acetate) over pre-treated silica gel (treated with 5% v/v NEt_3 in hexanes/AcOEt eluent) to give chiral product **5**.

V. Characterization of compounds 5a-j

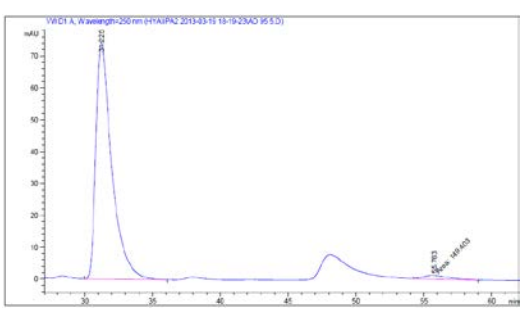
(3*R*,5'*R*)-Methyl 4',4'-Dimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5a):



5a

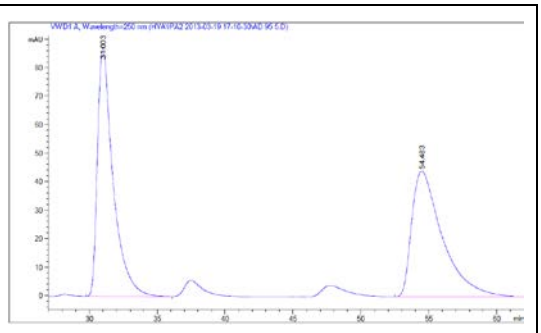
The general procedure outlined above was followed. White solid, mp: 220-222 ^{o}C, 99% yield (dr: >20:1). **^{1}H NMR** (500 MHz, Acetone-d6): δ 9.60 (s, 1H), 7.45 (d, *J* = 3.2 Hz, 1H), 7.33-7.27 (m, 2H), 7.05 (t, *J* = 7.6 Hz, 1 H), 6.99 (d, *J* = 8.2 Hz, 1H), 4.98 (d, *J* = 3.2 Hz, 1H), 3.77 (s, 3H), 1.23 (s, 3H), 0.97 (s, 3H). **^{13}C NMR** (125 MHz, Acetone-d6): δ 175.2, 171.4, 167.7, 144.1, 130.2, 127.9, 125.9, 122.5, 110.7, 81.1, 73.8, 52.3, 51.7, 22.7, 21.2; **HRMS** (ESI): m/z calcd. for [$C_{15}H_{15}N_2O_3$, M-H]$^{-}$: 271.1088; found: 271.1084.

Optical Rotation: $[\alpha]^{22}_{D}$ = -86.3 (c = 0.4, Acetone). The absolute configuration of **5a** was assigned by analogy to **5e**. 95% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 31.2 min for major isomer, t_R = 55.8 min for minor isomer).



Signal 1: VWD1 A, Wavelength=250 nm

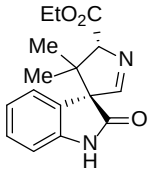
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.225	BB	1.2029	6067.06348	74.51347	97.5967
2	55.763	MM T	2.1412	149.40254	1.16294	2.4033



Signal 1: VWD1 A, Wavelength=250 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.003	BB	1.1574	6962.97314	87.21552	50.0706
2	54.483	BB	2.1492	6943.33691	44.14037	49.9294

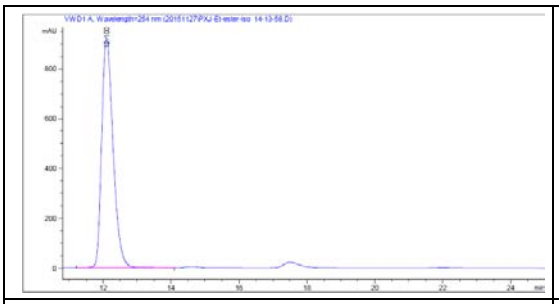
(3*R*,5'*R*)-Ethyl 4',4'-dimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5b):



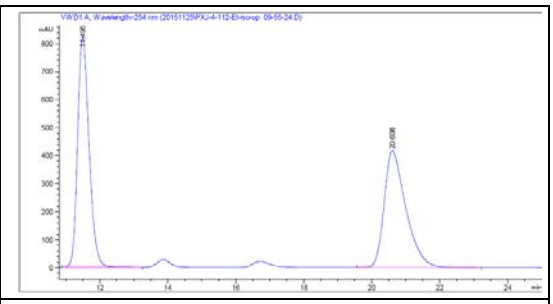
5b

The general procedure outlined above was followed. White solid, mp: 211-213 °C, 99% yield (dr: >20:1). **^{1}H NMR** (400 MHz, Acetone-d6): δ 9.85 (s, 1H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.33-7.27 (m, 2H), 7.05 (t, *J* = 7.8 Hz, 1 H), 7.00 (d, *J* = 7.8 Hz, 1H), 4.96 (d, *J* = 2.7 Hz, 1H), 4.24 (qd, *J* = 7.0 Hz, 3.5 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.24 (s, 3H), 0.98 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d6): δ 174.8, 170.4, 168.2, 143.6, 129.7, 127.4, 125.1, 121.8, 110.3, 79.9, 73.1, 60.7, 51.5, 22.4, 21.0, 14.6; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{18}N_2O_3Na, M+Na]^+$: 309.12096; found: 309.12118.

Optical Rotation: $[\alpha]^{29}_D$ = -10.0 (c = 0.3, Acetone). The absolute configuration of **5b** was assigned by analogy to **5e**. > 99% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 12.1 min for major isomer, t_R =20.6 min for minor isomer).

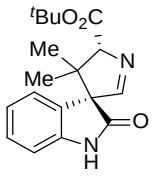


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	12.100	BV R	0.3640	2.15984e4	923.13611	100.0000



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	11.495	BV R	0.3623	1.92650e4	823.77417	51.2213
2	20.608	BV R	0.6489	1.83463e4	415.68124	48.7787

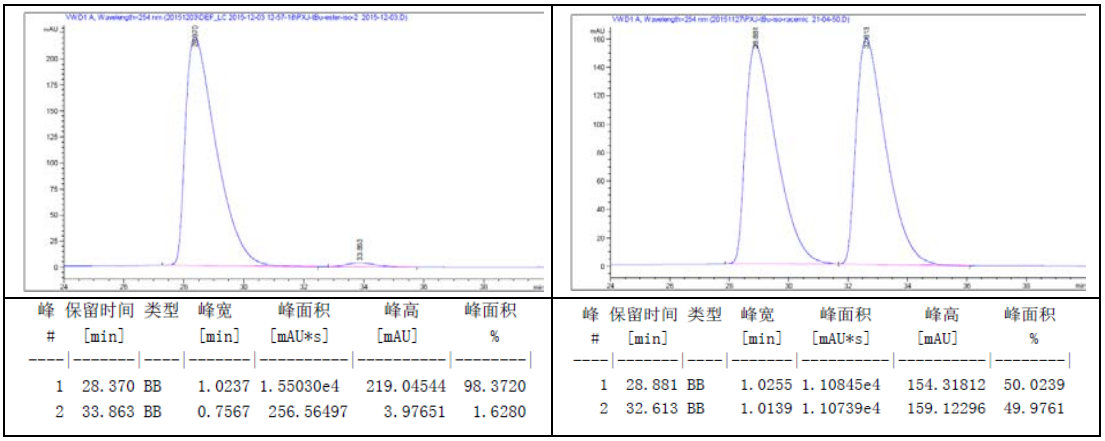
(3*R*,5'*R*)-tert-butyl 4',4'-dimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5c):



5c

The general procedure outlined above was followed. White solid, mp: 225-226 ^{o}C, 99% yield (dr: 85:15). **^{1}H NMR** (400 MHz, Acetone-d6): δ 9.60 (s, 1H), 7.42 (d, *J* = 3.0 Hz, 1H), 7.37-7.23 (m, 2H), 7.05 (t, *J* = 7.8 Hz, 1 H), 6.99 (d, *J* = 6.7 Hz, 1H), 4.87 (d, *J* = 3.0 Hz, 1H), 1.53 (s, 9H), 1.24 (s, 3H), 1.02 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d6): δ 174.9, 169.5, 167.8, 143.7, 129.7, 127.4, 125.2, 121.8, 110.3, 81.1, 80.2, 73.2, 58.7, 51.6, 28.2, 22.2, 21.1, 8.5; **HRMS** (ESI): m/z calcd. for [$C_{18}H_{22}N_2O_3Na$, M+Na]$^{+}$: 337.15226; found: 337.15220.

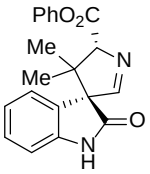
Optical Rotation: $[\alpha]^{28}_{D}$ = -5.5 (c = 0.4, Acetone). The absolute configuration of **5c** was assigned by analogy to **5e**. 97% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 28.4 min for major isomer, t_R =33.9 min for minor isomer).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	28.370	BB	1.0237	1.55030e4	219.04544	98.3720
2	33.863	BB	0.7567	256.56497	3.97651	1.6280

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	28.881	BB	1.0255	1.10845e4	154.31812	50.0239
2	32.613	BB	1.0139	1.10739e4	159.12296	49.9761

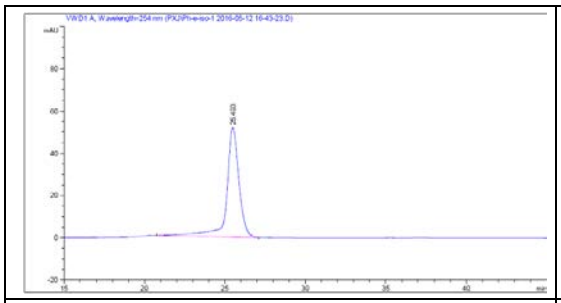
(3*R*,5'*R*)-Phenyl 4',4'-dimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5d):



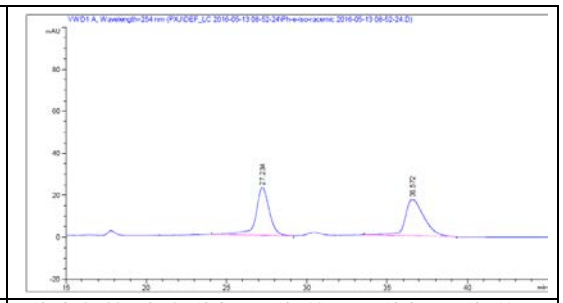
5d

The general procedure outlined above was followed. White solid, mp: 251-253 ^{o}C, 99% yield (dr: >20:1). **^{1}H NMR** (400 MHz, DMSO-d6): δ 10.77 (s, 1H), 7.61 (d, *J* = 2.5 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 2H), 7.32-7.25 (m, 3H), 7.20 (d, *J* = 7.8 Hz, 2 H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 5.15 (d, *J* = 2.6 Hz, 1H), 1.24 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d6): δ 174.8, 169.3, 168.8, 150.5, 143.7, 130.1, 129.8, 127.5, 125.6, 125.0, 122.2, 121.9, 110.4, 79.9, 73.2, 58.5, 51.9, 22.6, 21.1, 8.33; **HRMS** (ESI): m/z calcd. for $[C_{20}H_{18}N_2O_3Na, M+Na]^+$: 357.12096; found: 357.12012.

Optical Rotation: $[\alpha]^{27}_{D}$ = -67.3 (c = 0.3, Acetone). The absolute configuration of **5d** was assigned by analogy to **5e**. > 99% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 27.2 min for major isomer, t_R =36.6 min for minor isomer).

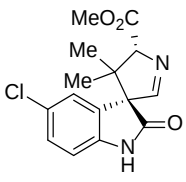


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	25.493	BB	0.7821	2750.88062	51.84112	100.0000



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	27.234	BB	0.7494	1347.17407	22.96508	48.4504
2	36.572	VV R	0.9694	1433.34851	17.34049	51.5496

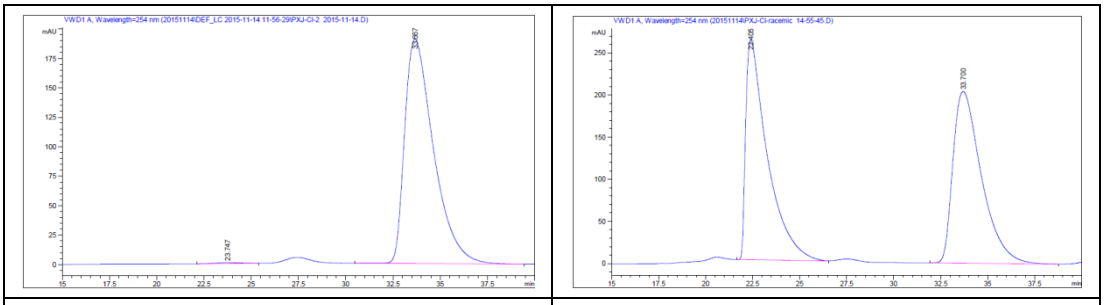
(3*R*,5'*R*)-Methyl 5-chloro-4',4'-dimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5e):



5e

The general procedure outlined above was followed. White solid, mp: 197-199 ^{o}C, 99% yield (dr: >20:1). **^{1}H NMR** (500 MHz, Acetone-d6): δ 9.76 (s, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.34 (d, *J* = 10.7 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 1H), 4.97 (d, *J* = 2.5 Hz, 1H), 3.77 (s, 3H), 1.24 (s, 3H), 0.98 (s, 3H). **^{13}C NMR** (125 MHz, Acetone-d6): δ 174.0, 170.4, 166.1, 142.2, 129.2, 127.1, 126.4, 111.0, 111.0, 80.3, 73.0, 51.7, 50.9, 21.7, 20.4; **HRMS** (ESI): m/z calcd. for $[C_{15}H_{15}ClN_2O_3Na, M+Na]^+$: 329.0663; found: 329.0677.

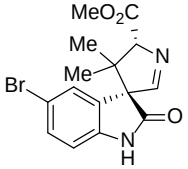
Optical Rotation: $[\alpha]^{23}_{D}$ = -43.9 (c = 0.3, Acetone).The absolute configuration of **5e** was assigned by conversion to **7** followed by x-ray analysis. 99% ee (HPLC condition: Chiralpak OD-H column, *n*-hexane/*i*-PrOH = 93:7, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 23.7 min for minor isomer, t_R = 33.7 min for major isomer).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	23.747	BB	1.0841	72.02675	7.82307e-1	0.3542
2	33.667	BB	1.6290	2.02649e4	190.82019	99.6458

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	22.405	BB	1.0974	2.08367e4	261.13651	49.2799
2	33.700	BB	1.5078	2.14456e4	203.77597	50.7201

(3*R*,5'*R*)-Methyl 5-bromo-4',4'-dimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5f):

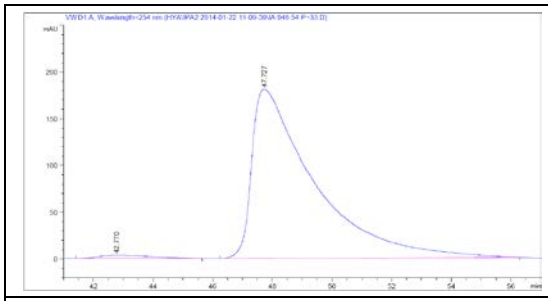


5f

The general procedure outlined above was followed. White solid, mp: 76-77 ^{o}C, 99% yield (dr: >20:1). **^{1}H NMR** (500 MHz, Acetone-d6): δ 9.73 (s, 1H), 7.50-7.48 (m, 2H), 7.45 (d, *J* = 1.9 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 4.97 (d, *J* = 3.2 Hz, 1H), 3.77 (s,

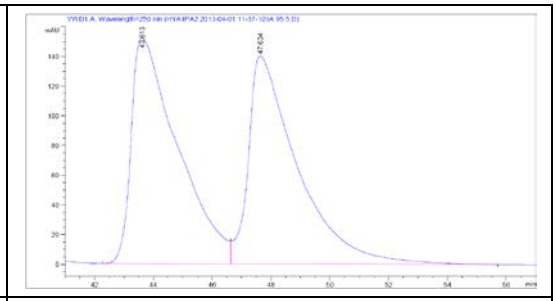
3H), 1.24 (s, 3H), 0.98 (s, 3H). **^{13}C NMR** (125 MHz, Acetone-d6): δ 174.8, 171.2, 167.0, 143.5, 133.0, 130.7, 128.4, 114.5, 112.5, 81.1, 73.9, 52.6, 51.8, 22.6, 21.3; **HRMS** (ESI): m/z calcd. for [$C_{15}H_{14}BrN_2O_3Na$, M+Na]$^+$: 349.0193; found: 340.0186.

Optical Rotation: $[\alpha]^{22}_D$ = -59.8 (c = 0.2, Acetone).The absolute configuration of **5f** was assigned by analogy to **5e**. 97% ee (HPLC condition: Chiralpak IA-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 42.8 min for minor isomer, t_R = 47.7 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

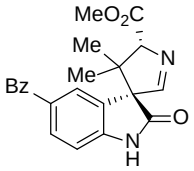
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	42.770	BB	1.4306	423.33096	1.5841
2	47.727	BB	1.8283	2.63001e4	98.4159



Signal 1: VWD1 A, Wavelength=250 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.613	BV	1.5077	1.66910e4	152.04590	50.6692
2	47.634	VB	1.5943	1.62501e4	140.09138	49.3308

(3*R*,5'*R*)-Methyl 5-benzoyl-4',4'-dimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (**5g**):

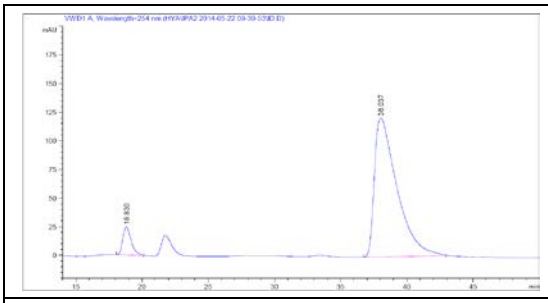


5g

The general procedure outlined above was followed. White solid, mp: 48-50 ^oC, 99% yield, (dr: >20:1). **^{1}H NMR** (500 MHz, DMSO-d6): δ 11.14 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.60-7.59 (m, 2H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 4.87 (d, *J* = 3.2 Hz, 1H), 3.71 (s, 3H), 1.18 (s, 3H), 0.89 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d6): δ 194.4, 174.7, 170.3, 167.1, 147.7, 137.6, 132.7, 132.1, 130.3, 129.2, 128.4, 128.3, 124.8, 109.7, 79.8, 72.3, 51.6,

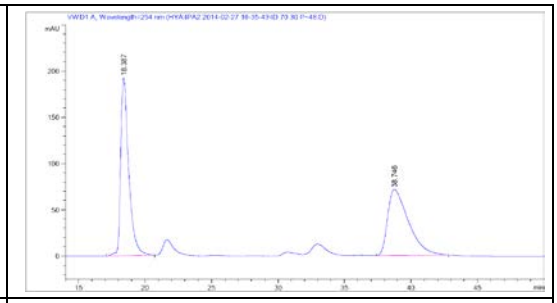
51.3, 22.0, 20.6; **HRMS** (ESI): m/z calcd. for $[C_{22}H_{19}N_2O_4, M-H]^-$: 375.1350; found: 375.1347.

Optical Rotation: $[\alpha]^{22}_D$ = -68.8 (c = 0.2, Acetone).The absolute configuration of **5g** was assigned by analogy to **5e**. 86% ee (HPLC condition: Chiralpak ID-H column, *n*-hexane/*i*-PrOH = 70:30, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 18.8 min for minor isomer, t_R = 38.0 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

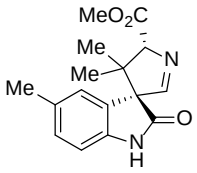
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	18.830	BB	0.6644	1071.48755	6.9692
2	38.037	BB	1.6375	1.43030e4	93.0308



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	18.387	BB	0.6123	8059.43066	50.9568
2	38.746	BB	1.2691	7756.77246	49.0432

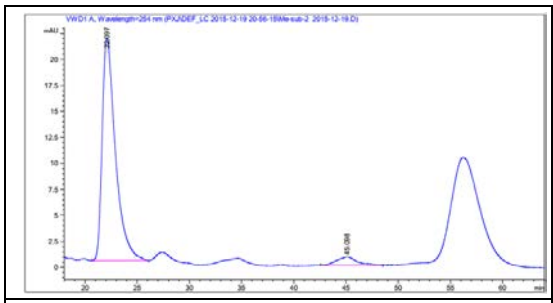
(3*R*,5'*R*)-Methyl 4',4',5-trimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5h):



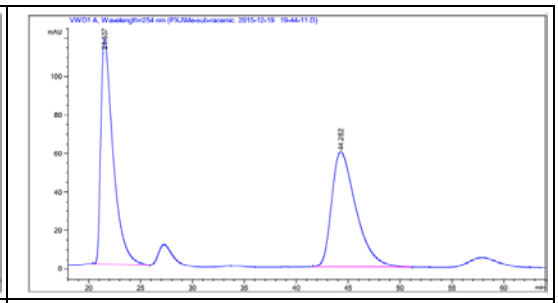
5h

The general procedure outlined above was followed. White solid, mp: 221-223 ^oC, 95% yield (dr: 87:13). **^{1}H NMR** (400 MHz, Acetone-d6): δ 9.51 (s, 1H), 7.44 (d, *J* = 3.0 Hz, 1H), 7.13 (d, *J* = 9.8 Hz, 2H), 6.88 (d, *J* = 7.8 Hz, 1H), 4.97 (d, *J* = 3.0 Hz, 1H), 3.76 (s, 3H), 2.32 (s, 3H), 1.22 (s, 3H), 0.96 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d6): δ 174.8, 171.0, 168.3, 141.1, 130.8, 130.0, 128.0, 125.1, 110.0, 80.0, 73.1, 52.0, 51.4, 22.5, 21.1, 20.9; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{17}N_2O_4Na, M+Na]^+$: 309.12096; found: 309.12098.

Optical Rotation: $[\alpha]^{30}_{D}$ = -8.1 (c = 0.2, Acetone). The absolute configuration of **5h** was assigned by analogy to **5e**. 89% ee (HPLC condition: Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 22.1 min for major isomer, t_R =45.1 min for minor isomer).

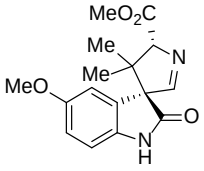


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	22.097	BB	1.3136	1885.93311	21.37001	94.5697
2	45.098	BB	1.5300	108.29250	8.30105e-1	5.4303



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	21.537	BB	1.1215	9655.73633	116.91745	49.8793
2	44.282	BB	1.8981	9702.47559	59.73183	50.1207

(3*R*,5'*R*)-Methyl 5-methoxy-4',4'-dimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5i):

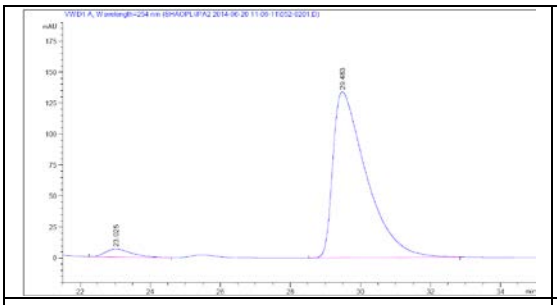


5i

The general procedure outlined above was followed (10% Ag_2O, 20% Pre-cat). White solid, mp: 203-204 ^{o}C, 99% yield (dr: 88:12). **^{1}H NMR** (500 MHz, Acetone-d6): δ 9.42 (s, 1H), 7.44 (d, *J* = 2.5 Hz, 1H), 6.92-6.87 (m, 3H), 4.98 (d, *J* = 3.2 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 1.23 (s, 3H), 0.98 (s, 3H). **^{13}C NMR** (125 MHz, Acetone-d6): δ 175.1, 171.4, 167.7, 156.2, 137.3, 127.2, 115.0, 114.9, 111.0, 81.1, 74.2, 56.1, 52.3, 51.7, 22.6, 21.3; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{17}N_2O_4, M-H]^-$: 301.1194; found: 301.1186.

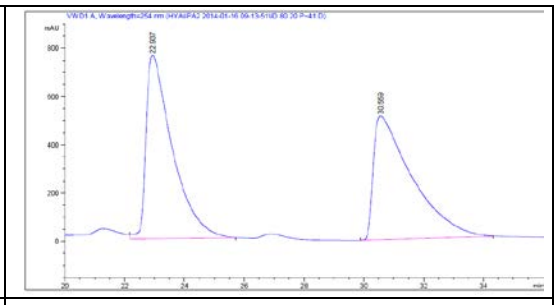
Optical Rotation: $[\alpha]^{25}_{D}$ = -49.3 (c = 0.2, Acetone). The absolute configuration of **5i** was assigned by analogy to **5e**. 93% ee (HPLC condition: Chiralpak ID-H column,

n-hexane/*i*-PrOH = 80:20, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 23.0 min for minor isomer, t_R = 29.5 min for major isomer).



Signal 1: VWD1 A, Wavelength=254 nm

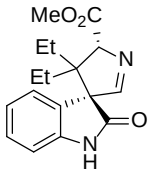
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.025	BB	0.6008	327.09286	6.39997	3.5640
2	29.483	BV	0.7880	8850.67383	133.91942	96.4360



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	22.937	VB	0.8567	4.65256e4	50.2865
2	30.559	BB	1.1763	4.59955e4	49.7135

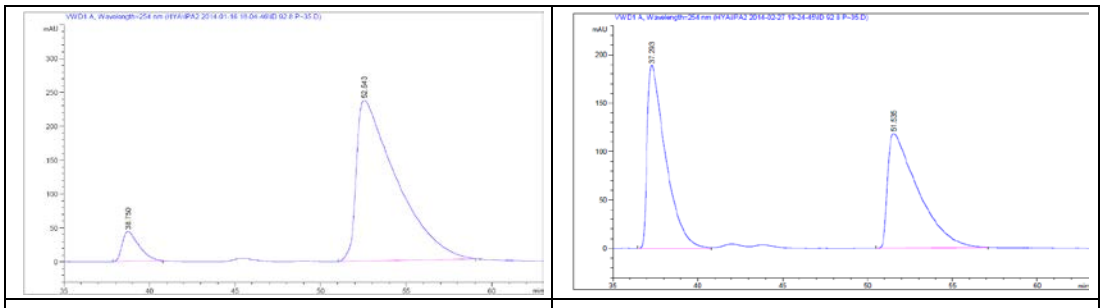
(3*R*,5'*R*)-Methyl 4',4'-diethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5j):



5j

The general procedure outlined above was followed. White solid, mp: 200-202 ^oC, 99% yield (dr: 88:12). **^{1}H NMR** (500 MHz, Acetone-d6): δ 9.68 (s, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.30-7.27 (m, 2H), 7.02 (t, *J* = 7.6 Hz, 1 H), 6.96 (d, *J* = 7.6 Hz, 1H), 4.88 (d, *J* = 2.5 Hz, 1H), 3.77 (s, 3H), 2.03-1.97 (m, 1H), 1.95-1.89 (m, 1H), 1.72-1.65 (m, 1H), 1.58-1.48 (m, 1H), 0.77 (t, *J* = 7.6 Hz, 3H), 0.51 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (125 MHz, Acetone-d6): δ 175.4, 172.3, 167.3, 143.4, 129.9, 128.1, 127.6, 122.4, 110.5, 82.0, 73.3, 57.7, 52.0, 27.2, 23.5, 9.2, 8.9; **HRMS** (ESI): m/z calcd. for $[C_{17}H_{19}N_2O_3, M\text{-}H]^-$: 299.1401; found: 299.1399.

Optical Rotation: $[\alpha]^{22}_D$ = -13.7 (c = 0.4, Acetone). The absolute configuration of **5j** was assigned by analogy to **5e**. 86% ee (HPLC condition: Chiralpak ID-H column, *n*-hexane/*i*-PrOH = 92:8, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 38.8 min for minor isomer, t_R = 52.5 min for major isomer).



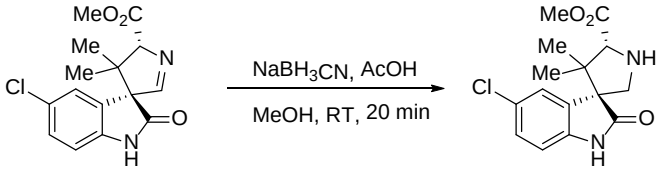
Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	38.750	BB	0.7960	2991.08081	7.1585
2	52.543	BB	2.0564	3.87924e4	92.8415

Signal 1: VWD1 A, Wavelength=254 nm

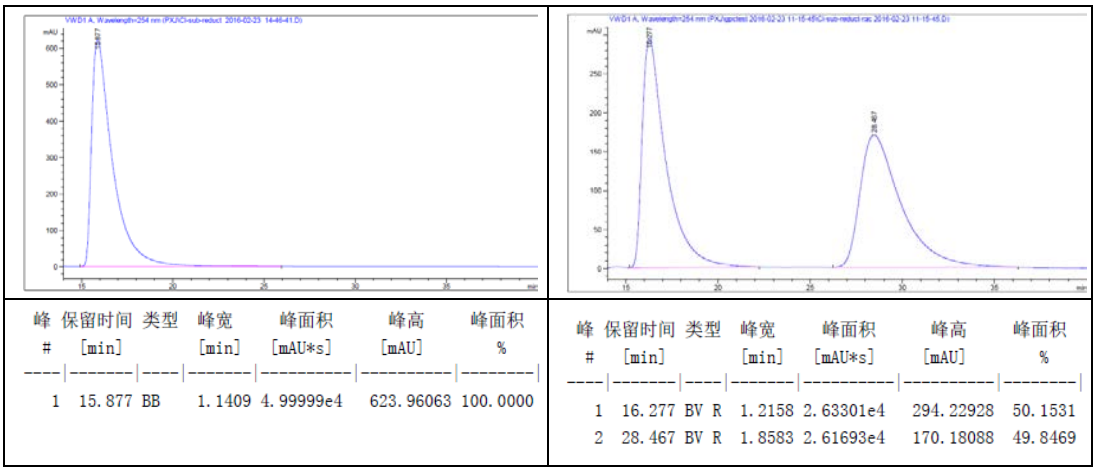
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	37.293	BB	1.1253	1.42300e4	49.2789
2	51.535	BB	1.6879	1.46465e4	50.7211

VI. Transformation of cycloadduct



5e, 99% ee **7**

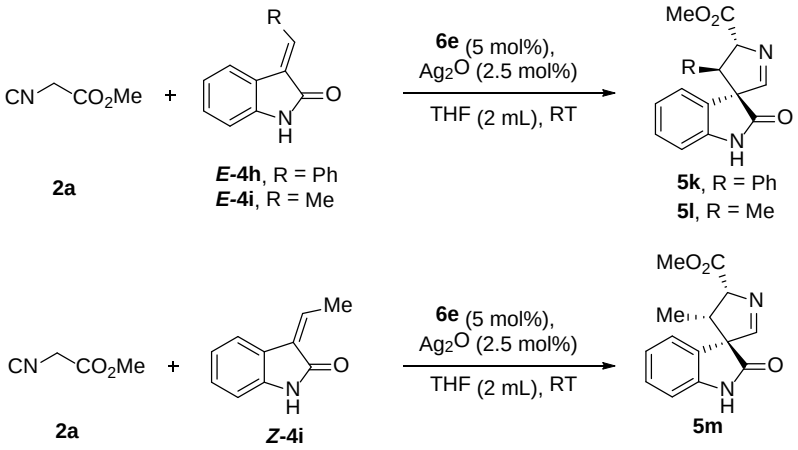
To **5e** (99% ee, 30.7 mg, 0.1 mmol) in MeOH, was added $NaBH_3CN$ (12.6 mg, 0.2 mmol) and then AcOH (11.4 µl, 0.2 mmol) at the ambient temperature. The reaction mixture was stirred for 20 min, and then concentrated, purified by flash chromatography over pre-treated silica gel (treated with 5% v/v NEt_3 in hexanes/AcOEt eluent) to give product **7** as a white solid, mp: 213-214 ^oC, 99% yield (dr: >20:1). **^{1}H NMR** (400 MHz, Acetone-d6): δ 9.49 (s, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.25 (dd, *J* = 8.3 Hz, 2.0 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 4.37 (s, 1H), 3.73 (s, 3H), 3.50 (d, *J* = 11.4 Hz, 1H), 3.21 (d, *J* = 11.4 Hz, 1H), 1.01 (s, 3H), 0.99 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d6): δ 181.2, 173.0, 142.1, 130.5, 128.5, 126.5, 125.4, 126.2, 111.0, 68.5, 62.4, 52.1, 48.5, 21.4, 20.9; **HRMS** (ESI): m/z calcd. for $[C_{15}H_{18}ClN_2O_3$, M+H$]^+$: 309.10005; found: 309.09945. **Optical Rotation**: $[\alpha]^{29}_D$ = -101.6 (c = 0.3, Acetone). > 99% ee (HPLC condition: Chiralpak OD-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 15.9 min for major isomer, t_R =28.5 min for minor isomer).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	15.877	BB	1.1409	4.99999e4	623.96063	100.0000

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	16.277	BV R	1.2158	2.63301e4	294.22928	50.1531
2	28.467	BV R	1.8583	2.61693e4	170.18088	49.8469

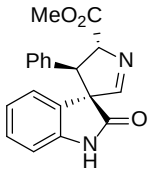
VII. [3+2] Cycloaddition of monosubstituted-4 and methyl isocyanoacetate 2a



General procedure. To a 10 mL vial charged with chiral ligand **6e** (12.2 mg, 0.02 mmol) and Ag_2O (2.3 mg, 0.01 mmol) was added THF (2 mL). The mixture was stirred at ambient temperature for 0.5 h. Methyleneindolinones **4** (0.4 mmol) was added in one portion, followed by isocyanoacetate **2a** (0.4 mmol). The reaction mixture was stirred at ambient temperature until the starting material was consumed, and then concentrated, purified by flash chromatography (hexanes/ethyl acetate) over pre-treated silica gel (treated with 5% v/v NEt_3 in hexanes/AcOEt eluent) to give chiral product **5**.

(3*R*,4'*S*,5'*R*)-Methyl 2-oxo-4'-phenyl-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-

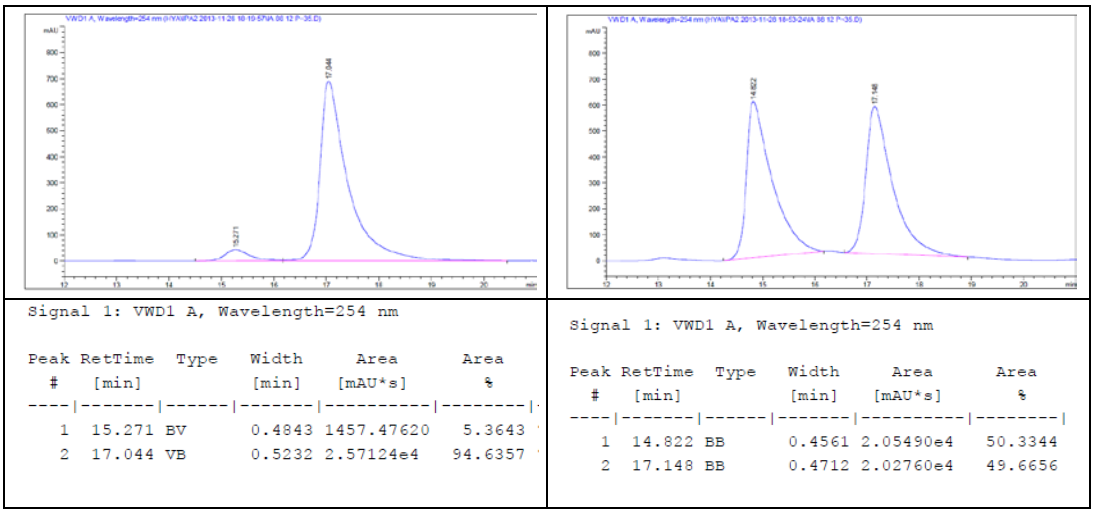
carboxylate (5k):



5k

The general procedure outlined above was followed. White solid, mp: 129-130 ^{o}C, 99% yield (dr: 69:14:17). **^{1}H NMR** (500 MHz, Acetone-d6): δ 9.30 (s, 1H), 7.53 (d, *J* = 2.5 Hz, 1H), 7.47 (d, *J* = 7.0 Hz, 1 H), 7.32-7.29 (m, 1H), 7.19-7.15 (m, 4H), 7.08-7.06 (m, 2H), 6.85 (d, *J* = 7.6 Hz, 1H), 5.42 (dd, *J* = 10.8 Hz, 3.2 Hz, 1H), 4.20 (d, *J* = 10.1 Hz, 1H), 3.73 (s, 3H). **^{13}C NMR** (125 MHz, Acetone-d6): δ 173.7, 172.2, 167.0, 143.7, 135.2, 130.2, 129.1, 129.0, 128.4, 124.6, 123.4, 110.6, 77.2, 72.2, 58.6, 52.6; **HRMS** (ESI): m/z calcd. for [$C_{19}H_{16}N_2O_3Na$, M+Na]$^{+}$: 343.1053; found: 343.1068.

Optical Rotation: $[\alpha]^{24}_{D}$ = -4.8 (c = 0.3, Acetone). The absolute configuration of **5k** was assigned by analogy to **5e**. 89% ee (HPLC condition: Chiralpak IA-H column, *n*-hexane/*i*-PrOH = 88:12, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 17.0 min for major isomer, t_R = 15.3 min for minor isomer).



Signal 1: VWD1 A, Wavelength=254 nm

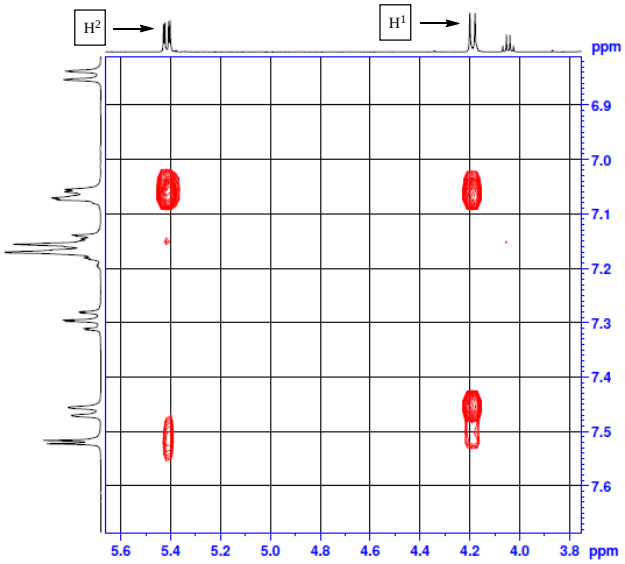
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	15.271	BV	0.4843	1457.47620	5.3643
2	17.044	VB	0.5232	2.57124e4	94.6357

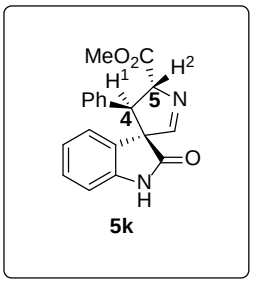
Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	14.822	BB	0.4561	2.05490e4	50.3344
2	17.148	BB	0.4712	2.02760e4	49.6656

The relative configuration of **5k** (*trans*) was determined by the NOE correlation between the CH at **C-4** and the CH on the spirooxindole phenyl ring. The coupling

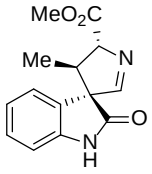
constant between CH of **C-4** and CH of **C-5** is J = 10.4.





5k

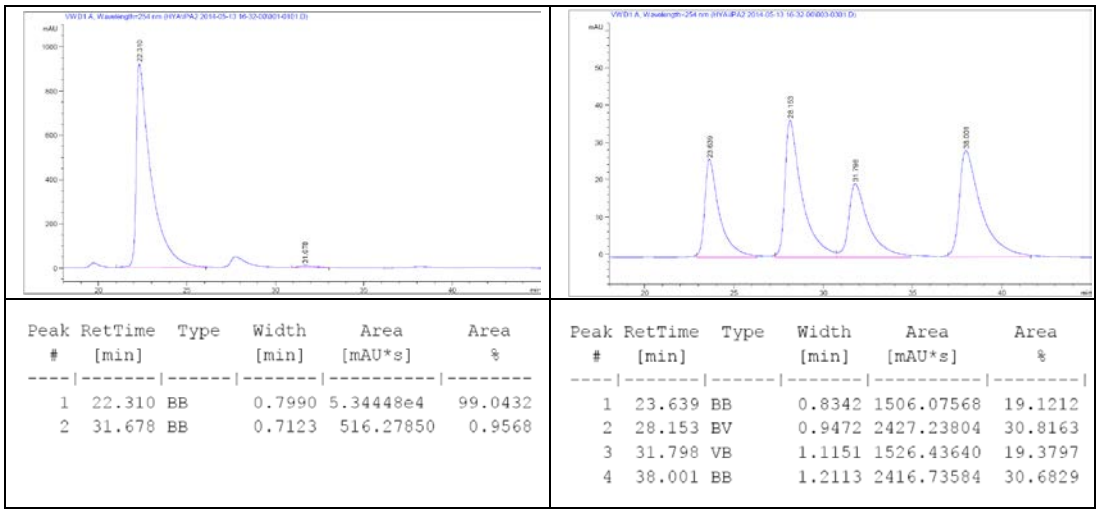
(3*R*,4'*S*,5'*R*)-Methyl 4'-methyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5l):



5l

The general procedure outlined above was followed. White solid, mp: 149-150 ^{o}C, 99% yield (dr: 73:19:8). **^{1}H NMR** (600 MHz, DMSO-d6): δ 10.66 (s, 1H), 7.47 (d, J = 2.8 Hz, 1H), 7.27-7.23 (m, 1H), 7.13 (d, J = 7.3 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 4.50 (dd, J = 9.7 Hz, 2.9 Hz, 1H), 3.72 (s, 3H), 2.73-2.71 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-d6): δ 174.0, 172.0, 167.7, 143.3, 139.6, 128.7, 124.0, 122.7, 110.2, 79.1, 69.9, 52.5, 47.4, 11.5; **HRMS** (ESI): m/z calcd. for $[C_{14}H_{14}N_2O_3Na, M+Na]^+$: 281.08966; found: 281.08927.

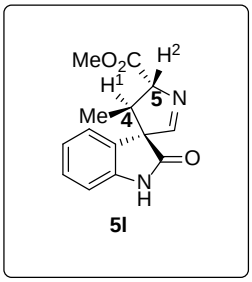
Optical Rotation: $[\alpha]^{25}_{D}$= -95.6 (c = 0.3, Isopropanol). The absolute configuration of **5l** was assigned by analogy to **5e**. 98% ee (HPLC condition: Chiralpak IA-H column, *n*-hexane/*i*-PrOH = 93:7, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 22.3 min for major isomer, t_R = 31.7 min for minor isomer).



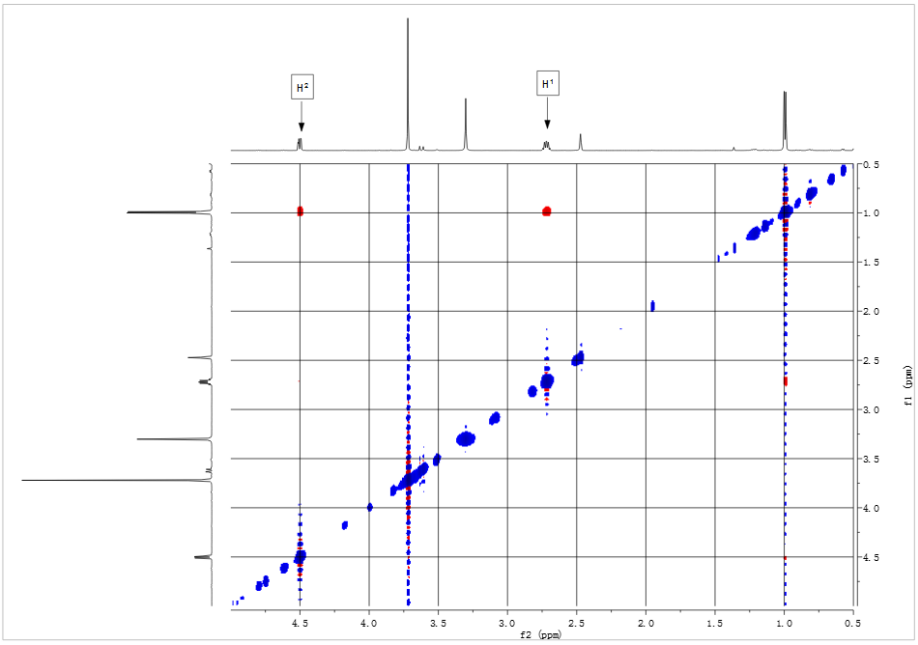
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	22.310	BB	0.7990	5.34448e4	99.0432
2	31.678	BB	0.7123	516.27850	0.9568

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	23.639	BB	0.8342	1506.07568	19.1212
2	28.153	BV	0.9472	2427.23804	30.8163
3	31.798	VB	1.1151	1526.43640	19.3797
4	38.001	BB	1.2113	2416.73584	30.6829

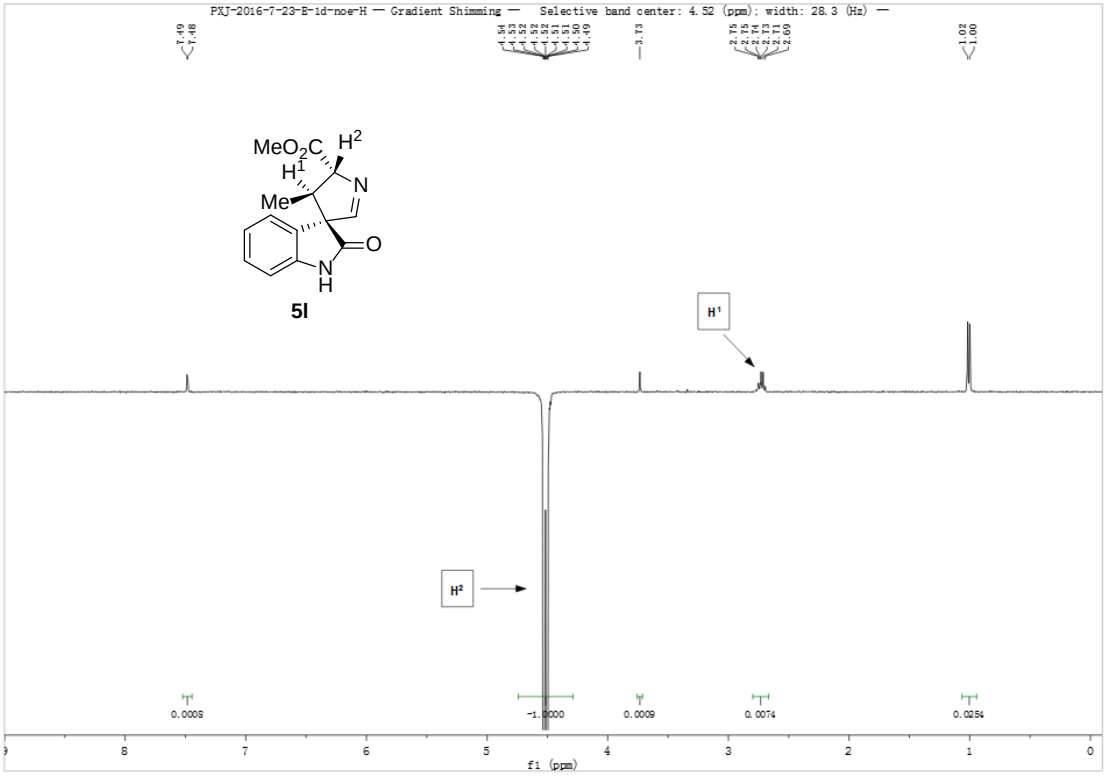
The relative configuration of **5l** (*trans*) was determined by the 2D-NOE correlation between the CH at **C-4** and the CH at **C-5**.



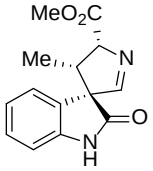
5l



The *trans*-configuration of **5l** was also assigned by its 1D-NOE analysis. As the value of integration at δ 4.52 (H^2) is 1, the value of integration at δ 2.75-2.69 (H^1) is 0.0074 and the value of integration at δ 1.01 (Me) is 0.0254.



(3*R*,4'*S*,5'*R*)-Methyl 4'-methyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5m):

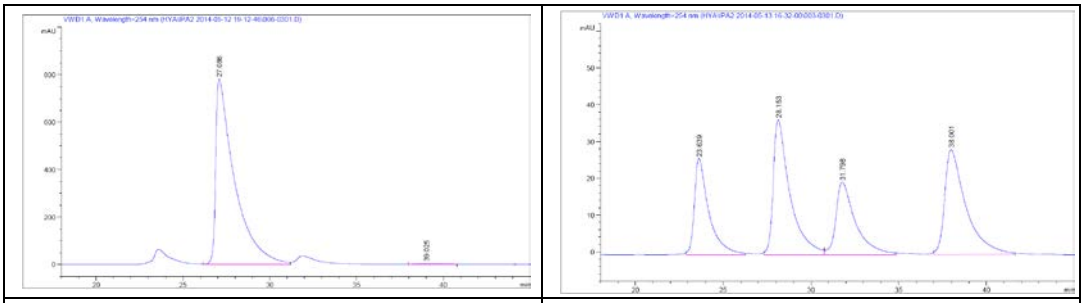


5m

The general procedure outlined above was followed. White solid, 99% yield (dr: 6:5:89). ^{1}H NMR (600 MHz, DMSO-d6): δ 10.73 (s, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.26-7.22 (m, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 5.16 (dd, *J* = 9.2 Hz, 2.1 Hz, 1H), 3.71 (s, 3H), 3.13-3.01 (m, 1H), 0.66 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d6): δ 177.1, 171.8, 167.2, 142.9, 129.6, 126.8, 125.5, 122.1, 110.4, 78.1, 70.0, 52.2, 42.1, 11.8; **HRMS** (ESI): m/z calcd. for $[C_{14}H_{14}N_2O_3Na, M+Na]^+$: 281.08966; found: 281.08991.

Optical Rotation: $[\alpha]^{26}_{D}$ = -33.8 (c = 0.4, Acetone). The absolute configuration of **5m** was assigned by analogy to **5e**. 99% ee (HPLC condition: Chiralpak IA-H column,

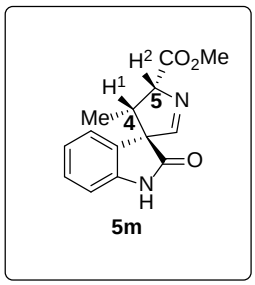
n-hexane/*i*-PrOH = 93:7, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 27.1 min for major isomer, t_R = 39.0 min for minor isomer).



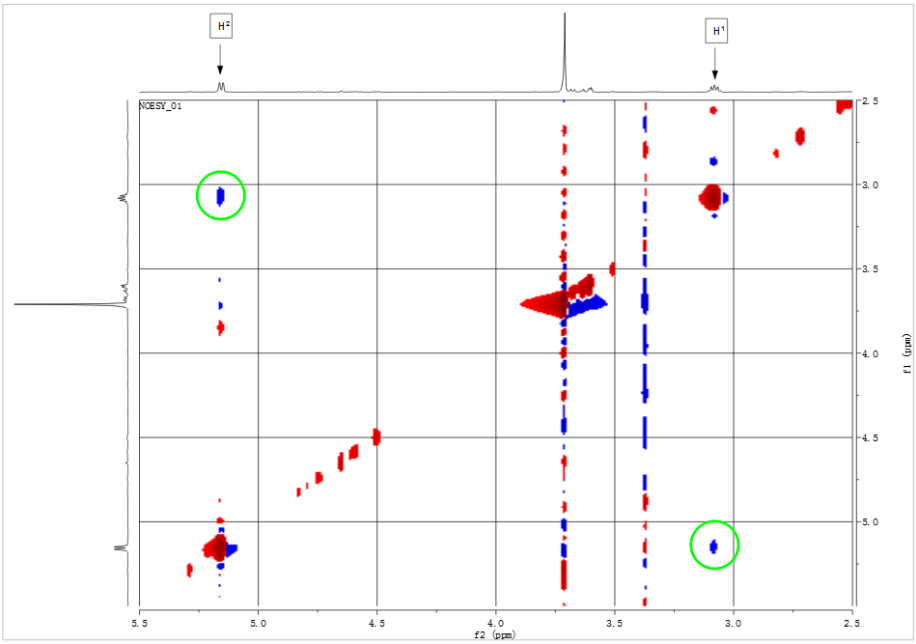
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	27.086	VV	1.0360	5.88773e4	99.6038
2	39.025	BB	0.9271	234.20013	0.3962

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	23.639	BB	0.8342	1506.07568	19.1212
2	28.153	BV	0.9472	2427.23804	30.8163
3	31.798	VB	1.1151	1526.43640	19.3797
4	38.001	BB	1.2113	2416.73584	30.6829

The relative configuration of **5m** (*cis*) was determined by the 2D-NOE correlation between the CH at **C-4** and the CH at **C-5**.

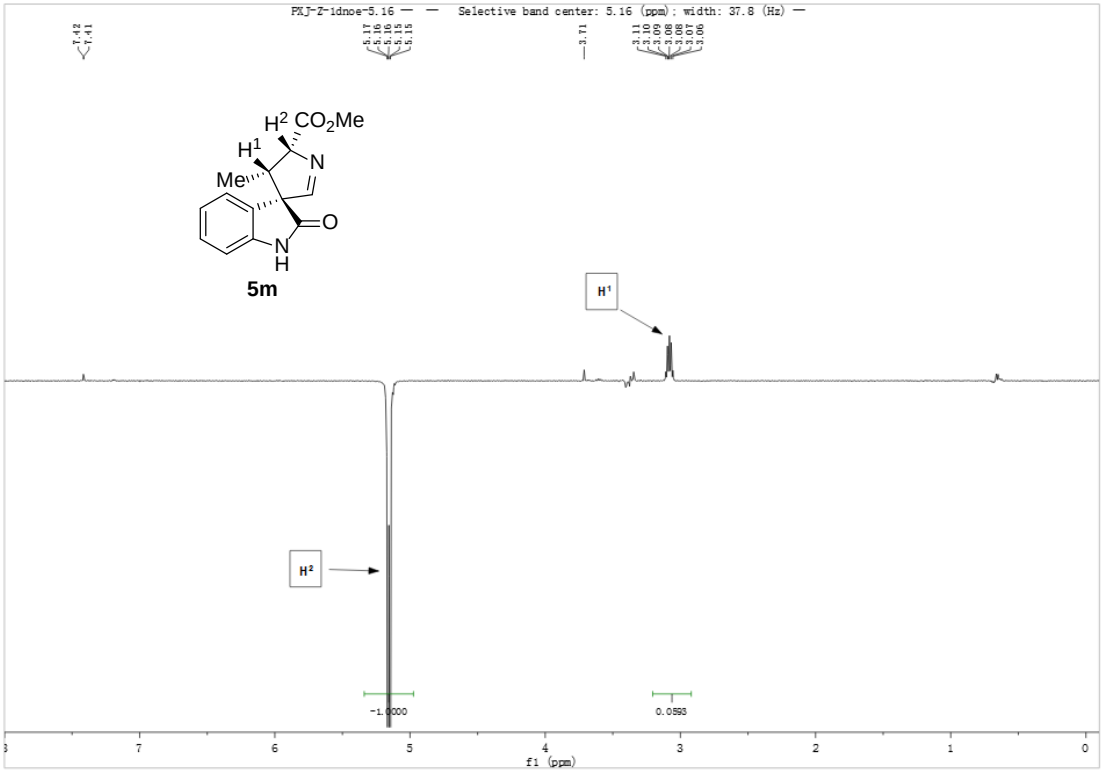


5m

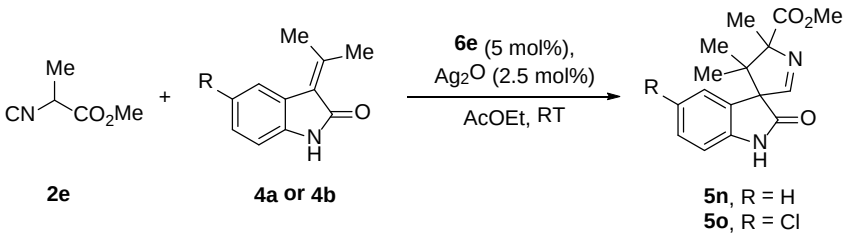


The *cis*-configuration of **5m** was also assigned by its 1D-NOE analysis. As the value

of integration at δ 5.16 (H^2) is 1, the value of integration at δ 2.75-2.69 (H^1) is 0.0593.



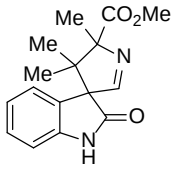
VIII. [3+2] Cycloaddition of methyleneindolinones and α-methyl isocyanoacetates



2e **4a or 4b** **5n**, R = H; **5o**, R = Cl

General procedure A. To a 10 mL vial charged with chiral ligand **6e** (12.2 mg, 0.02 mmol) and Ag_2O (2.3 mg, 0.01 mmol) was added AcOEt (0.25 mL). The mixture was stirred at ambient temperature for 0.5 h. Methyleneindolinones **4a** or **4b** (0.4 mmol) was added in one portion. Isocyanoacetate **2e** (0.4 mmol) in AcOEt (0.4 mL) was added via syringe pump over 5 h. The reaction mixture was stirred at ambient temperature until the starting material was consumed, and then concentrated, purified by flash chromatography (hexanes/ethyl acetate) over pre-treated silica gel (treated with 5% v/v NEt_3 in hexanes/AcOEt eluent) to give chiral product **5n** or **5o**.

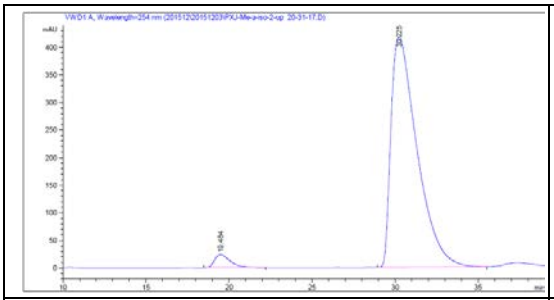
Methyl 4',4',5'-trimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5n):



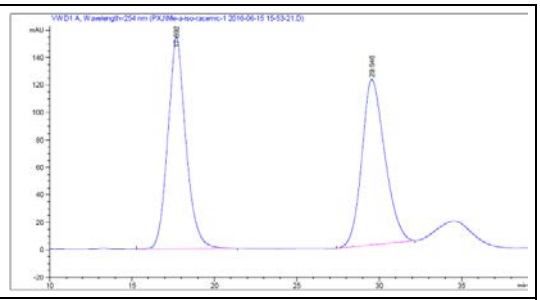
5n

The general procedure A outlined above was followed. White solid, mp: 210-211 ^{o}C, 94% yield (dr: 5:1). **^{1}H NMR** (400 MHz, Acetone-d6): δ 9.60 (s, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.24-7.14 (m, 1H), 7.07-6.98 (m, 1 H), 6.96 (d, *J* = 7.6 Hz, 1H), 3.72 (s, 3H), 1.74 (s, 3H), 1.20 (s, 3H), 0.95 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d6): δ 175.3, 173.8, 163.7, 143.4, 129.6, 127.8, 126.0, 121.7, 110.2, 85.5, 74.2, 52.0, 48.8, 25.5, 23.8, 20.2; **HRMS** (ESI): m/z calcd. for [$C_{16}H_{18}N_2O_3Na$, M+Na]$^{+}$: 309.12096; found: 309.12064.

Optical Rotation: $[\alpha]^{29}_{D}$ = -120.5 (c = 0.4, Acetone). 93% ee (HPLC condition: Chiralpak OD-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 19.5 min for minor isomer, t_R = 30.2 min for major isomer).

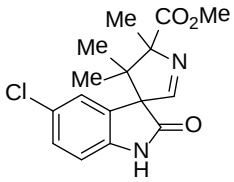


峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	19.484	BB	0.7527	1546.86499	24.25116	3.2850
2	30.225	BB	1.5076	4.55416e4	417.84674	96.7150



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	17.692	BB	1.0307	1.17021e4	154.31645	50.0217
2	29.546	BB	1.3343	1.16919e4	120.57706	49.9783

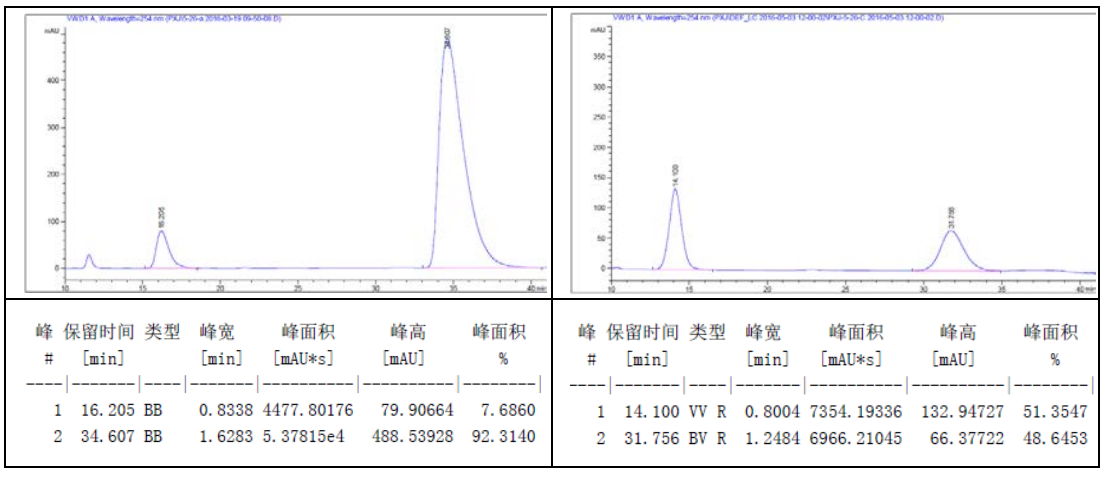
Methyl 5-chloro-4',4',5'-trimethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (5o):



5o

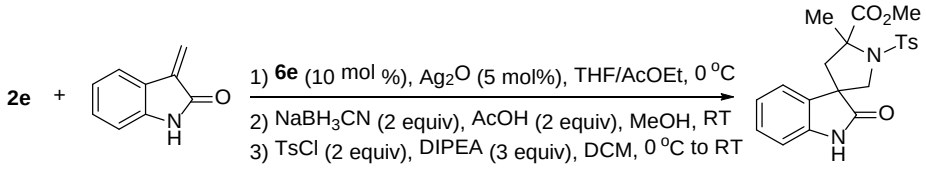
The general procedure A outlined above was followed. White solid, mp: 224-226 °C, 95% yield (dr: 13:1). **^{1}H NMR** (400 MHz, Acetone-d6): δ 9.70 (s, 1H), 7.32 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.28 (s, 1H), 7.24 (d, *J* = 2.1 Hz, 1H), 3.73 (s, 3H), 1.73 (s, 3H), 1.21 (s, 3H), 0.97 (s, 3H). **^{13}C NMR** (100 MHz, Acetone-d6): δ 174.6, 173.3, 161.7, 141.9, 129.0, 128.0, 127.4, 126.2, 110.9, 85.7, 74.2, 50.9, 49.0, 25.8, 23.0, 19.7; **HRMS** (ESI): m/z calcd. for $[C_{16}H_{17}ClN_2O_3Na, M+Na]^+$: 343.08199; found: 343.08196.

Optical Rotation: $[\alpha]^{28}_D$ = -40.0 (c = 0.4, Acetone). 85% ee (HPLC condition: Chiralpak OD-H column, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1 mL/min, wavelength = 254 nm, t_R =16.2 min for minor isomer, t_R = 34.6 min for major isomer).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	16.205	BB	0.8338	4477.80176	79.90664	7.6860
2	34.607	BB	1.6283	5.37815e4	488.53928	92.3140

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	14.100	VV R	0.8004	7354.19336	132.94727	51.3547
2	31.756	BV R	1.2484	6966.21045	66.37722	48.6453



4j **8**

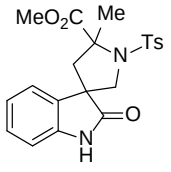
General procedure B. To a 10 mL vial charged with chiral ligand **6e** (12.2 mg, 0.02

mmol) and Ag_2O (2.3 mg, 0.01 mmol) was added AcOEt (1 mL). The mixture was stirred at ambient temperature for 0.5 h, and then cooled to 0 ^oC. α-Methyl isocyanoacetate **2e** (22.6 mg, 0.2 mmol) was added in one portion. Methyleneoxindole **4j** (43.5 mg, 0.3 mmol) in THF (0.5 mL) was added via syringe pump over 1 h. The reaction mixture was stirred at 0 ^oC until the starting material was consumed, and then concentrated to get the crude product.

The crude product was dissolved in MeOH at ambient temperature. Then $NaBH_3CN$ (2 equiv) and AcOH (2 equiv) were added successively. The mixture was stirred at ambient temperature until the starting material was consumed. The mixture was concentrated in vacuo. Purification by column chromatography on silica gel gave the reduction product.

To a solution of the reduction product in DCM, was added DIPEA (3 equiv) under nitrogen. At 0 ^oC, TsCl (2 equiv) was added and then stirred at ambient temperature. After stirring at ambient temperature at 24 h, the reaction mixture was diluted with DCM, then washed with H_2O, $NaHCO_3$ saturated solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure and the residue was purified by chromatography on silica gel to afford respective compound **8**.[5]

Methyl 5'-methyl-2-oxo-1'-tosylspiro[indoline-3,3'-pyrrolidine]-5'-carboxylate (8):

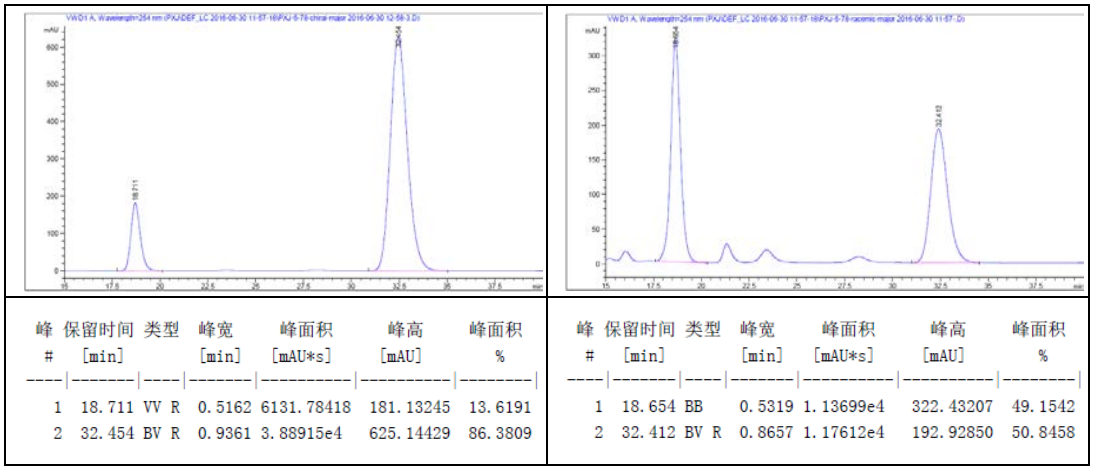


8

The general procedure B outlined above was followed. White solid, mp: 138-139 ^oC, 48% yield (dr: 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 7.5 Hz, 1H),δ 7.34-7.24 (m, 2H), 7.19 (dd, *J* = 11.2 Hz, 4.1 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 3.87 (s, 3H), 3.76 (d, *J* = 9.8 Hz, 1H), 3.66 (d, *J* = 9.8 Hz, 1H), 2.60 (d, *J* = 13.8 Hz, 1H), 2.49 (d, *J* = 13.8 Hz, 1H),

2.40 (s, 3H), 1.84 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 179.9, 174.0, 143.7, 140.0, 137.0, 132.6, 129.4, 128.6, 127.7, 123.9, 123.3, 109.9, 68.5, 57.2, 52.9, 51.6, 50.4, 23.2, 21.5; **HRMS** (ESI): m/z calcd. for $[C_{21}H_{22}N_2O_5SNa, M+Na]^+$: 437.11416; found: 437.11339.

Optical Rotation: $[\alpha]^{27}_D$ = -40.0 (c = 0.2, Isopropanol). 73% ee (HPLC condition: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 80:20, flow rate = 1 mL/min, wavelength = 254 nm, t_R = 18. min for minor isomer, t_R =32.4 min for major isomer).



峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	18.711	VV R	0.5162	6131.78418	181.13245	13.6191
2	32.454	BV R	0.9361	3.88915e4	625.14429	86.3809

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	18.654	BB	0.5319	1.13699e4	322.43207	49.1542
2	32.412	BV R	0.8657	1.17612e4	192.92850	50.8458

IX. X-ray crystallographic analysis and determination of configurations of the products

The absolute configuration of **7** (**3*R*, 5'*R***) was assigned by X-ray crystallographic analysis of a single crystal of **7** (Figure S1). The crystal was prepared from the solution of **7** in acetone/hexane at ambient temperature. The absolute configuration of **5e** (**3*R*, 5'*R***) was deduced. The configurations of **3**, **5a-d**, **5f-m** were assigned by analogy.

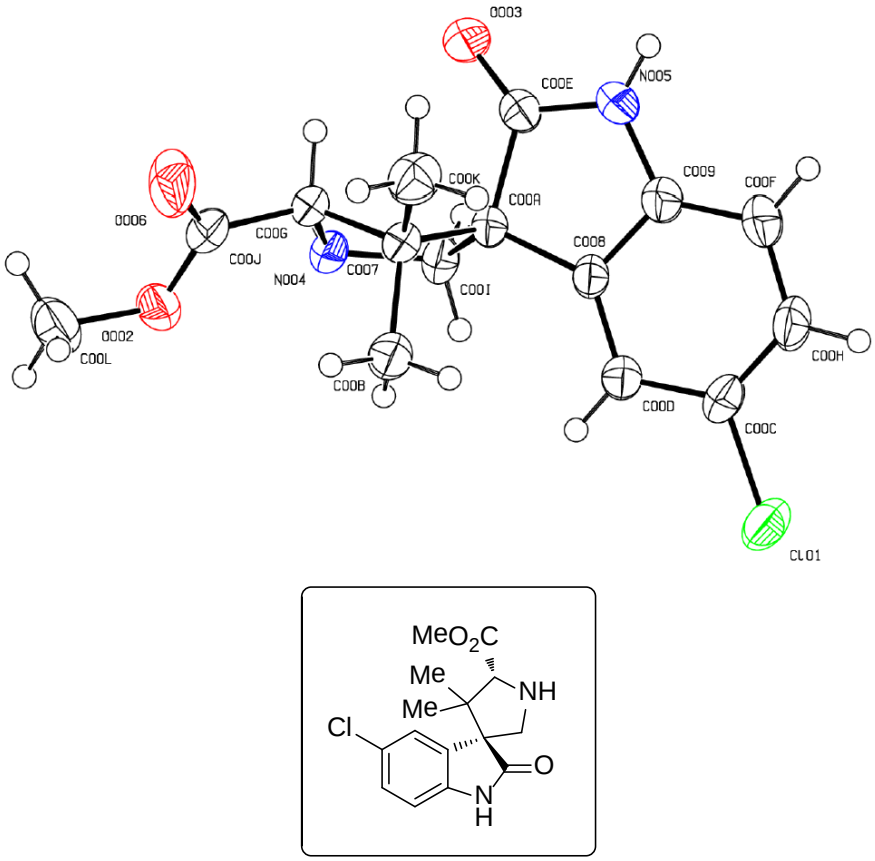


Figure S1. X-ray structure of **7**

Table 1. Crystal data and structure refinement for 1496241

Identification code	1496241
Empirical formula	$C_{15}H_{17}ClN_2O_3$
Formula weight	308.75
Temperature/K	293(2)
Crystal system	Orthorhombic
Space group	P 21 21 21
a/Å	7.2915(5)
b/Å	12.7983(10)
c/Å	15.9552(9)
α/°	90
β/°	90

γ/°	90
Volume/Å^3	1488.92(17)
Z	4
ρ_{calc}g/cm^3	1.377
μ/mm^{-1}	0.268
F(000)	648.0
Crystal size/mm^3	0.3 × 0.2 × 0.2
Radiation	MoK$^{\alpha}$ (λ = 0.71073)
2Θrange for data collection/°	6.86 to 61.174
Index ranges	-10 ≤ h ≤ 9, -12 ≤ k ≤ 18, -13 ≤ l ≤ 21
Reflections collected	6234
Independent reflections	3524 (R_{int}=0.0279, R_{sigma}= 0.0544)
Data / restraints / parameters	3524 / 0 / 196
Goodness-of-fit on F^2	1.052
Final R indexes [I>=2σ (I)]	R_1 = 0.0481, wR_2 = 0.0950
Final R indexes (all data)	R_1 = 0.0710, wR_2 = 0.1103
Largest diff. peak / hole / e Å^{-3}	0.23 / -0.24
Flack parameter	-0.08 (6)

X. References

1. P.-L. Shao, J.-Y. Liao, Y. A. Ho and Y. Zhao, *Angew. Chem., Int. Ed.*, 2014, **53**, 5435.

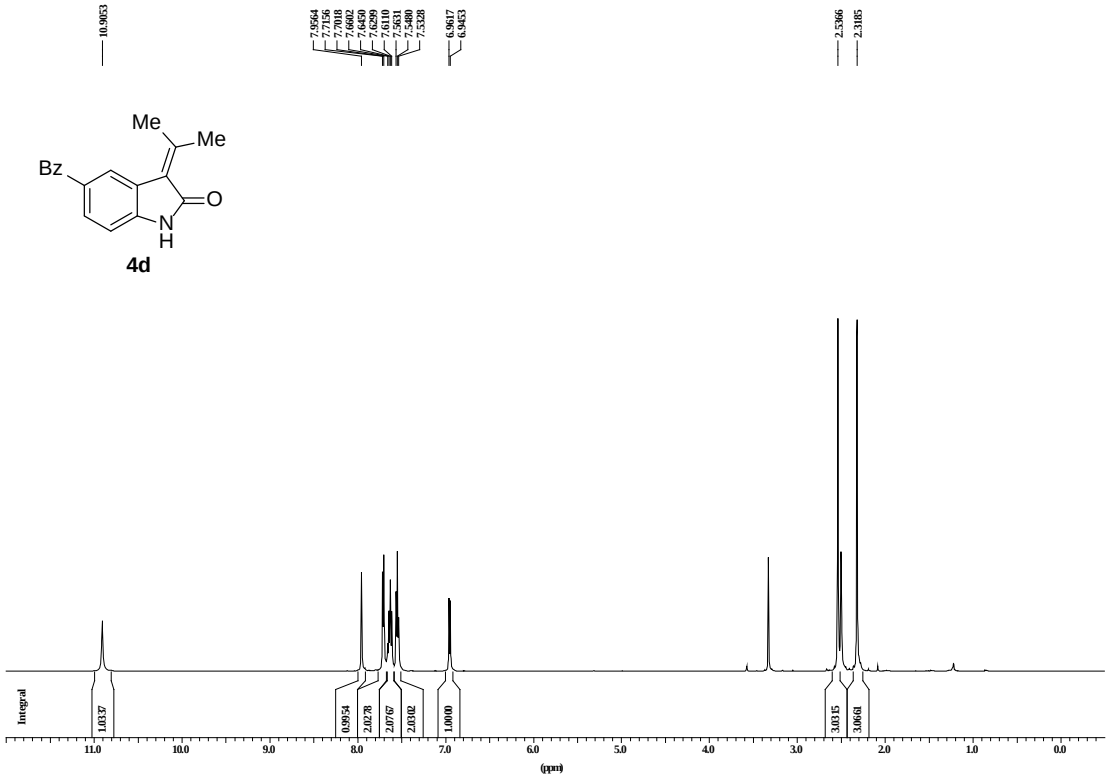
2. N. Elders, R. F. Schmitz, F. J. J. de Kanter, E. Ruijter, M. B. Groen and R. V. A. Orru, *J. Org. Chem.*, 2007, **72**, 6135.

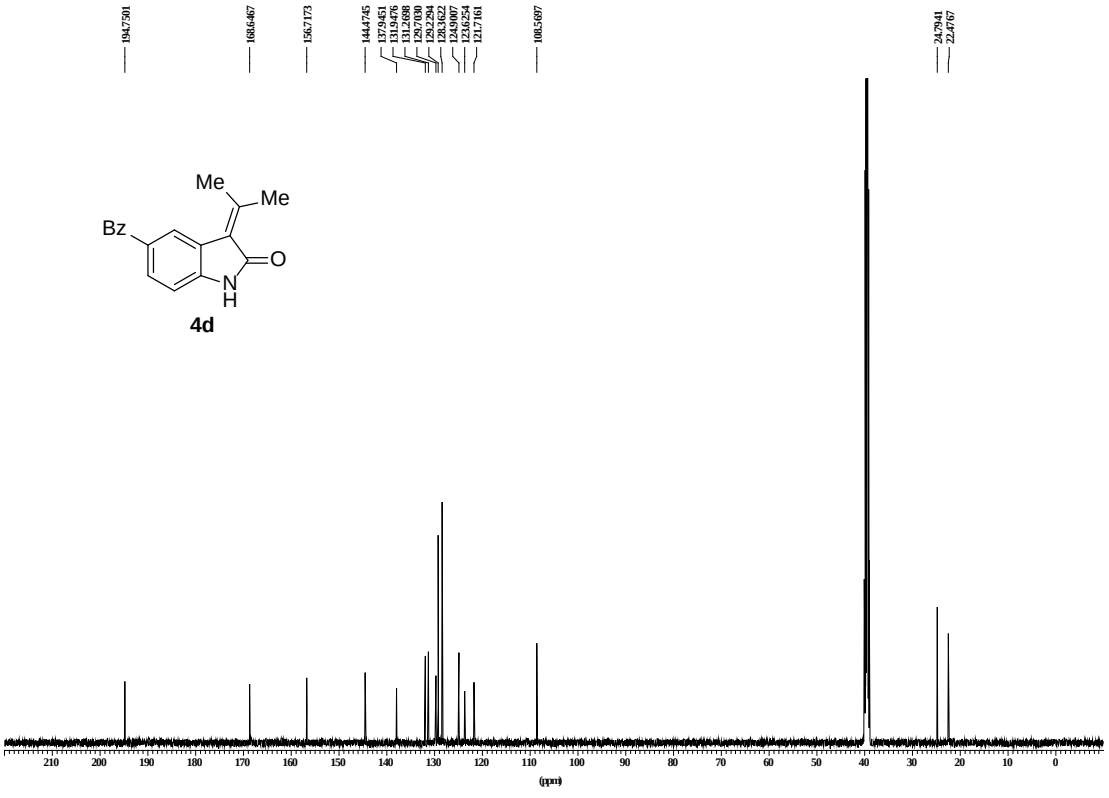
3. D. G. Mittelbiberach, G. D. AttenWeiler, H. D. Warthausen, A. H. Biberach, K. R. Warthausen, G. G. S. Warthausen and D. S. Biberach, Novel Compounds. U.S. Patent 20110195954 A1, November 21, 2008.

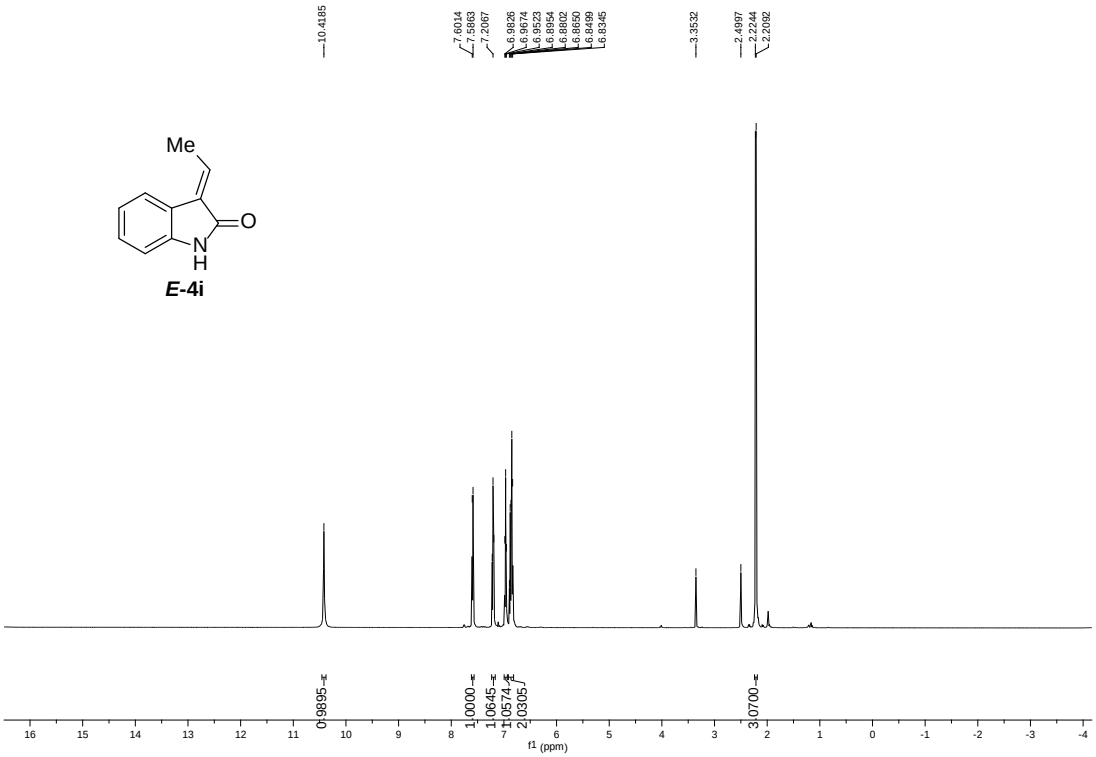
4. H. Lv, X.-Y. Chen, L.-H. Sun and S. Ye, *J. Org. Chem.*, 2010, **75**, 6973.

5. W. Ang, G. Chen, L. Xiong, Y. Chang, W. Pi, Y. Liu, C. Li, J. Zheng, L. Zhou, B. Yang, Y. Deng, S. Yang, Y. Luo and Y. Wei, *Eur. J. Med. Chem.*, 2014, **82**, 263.

XI. NMR spectra of the products



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7.2067
6.9926
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6.9523
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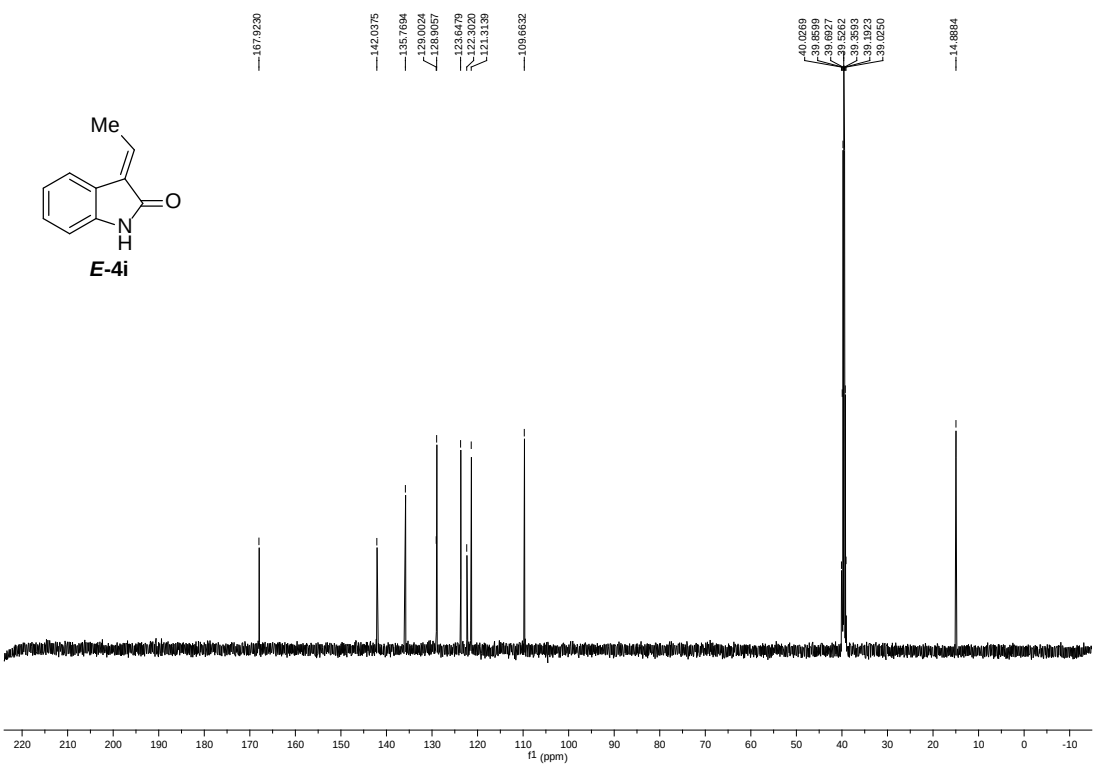
6.8802
6.8650
6.8499
6.8345
3.3532
2.4997
2.2244
2.2092
Me
O
N
H
E-4i
0.9895
1.0000
1.0645
1.0574
2.0305
3.0700
f1 (ppm)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142.0375
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129.0024
128.9057
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109.6632
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39.8599
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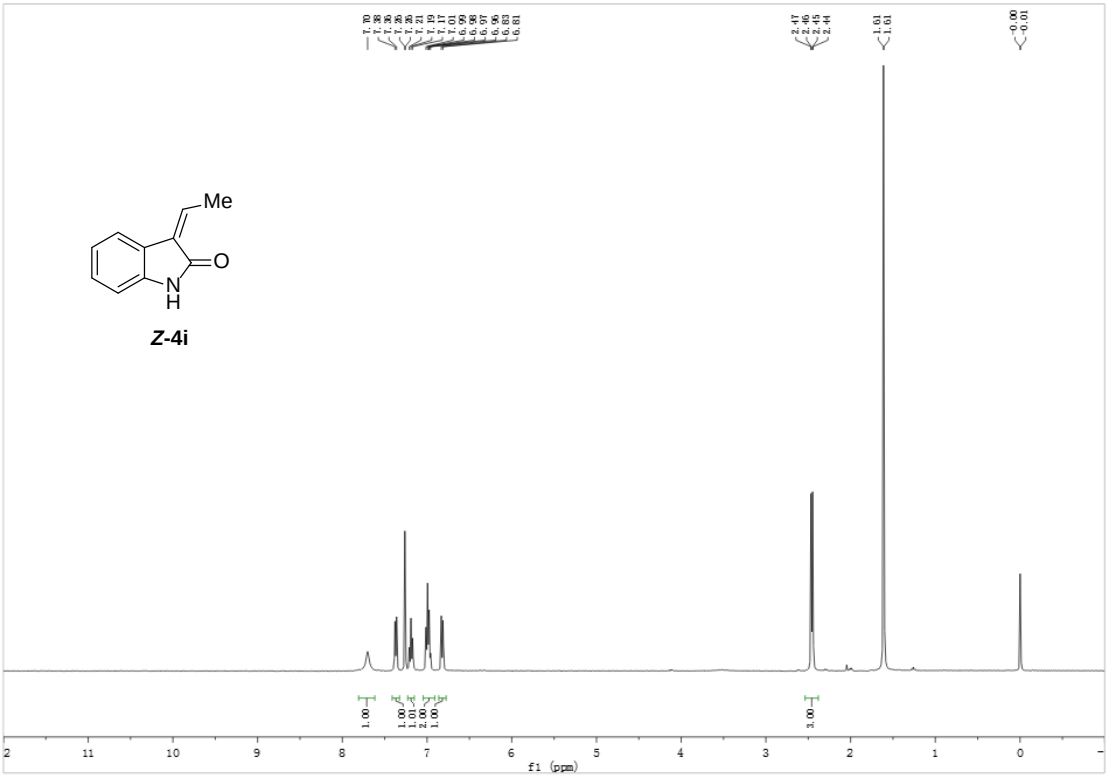
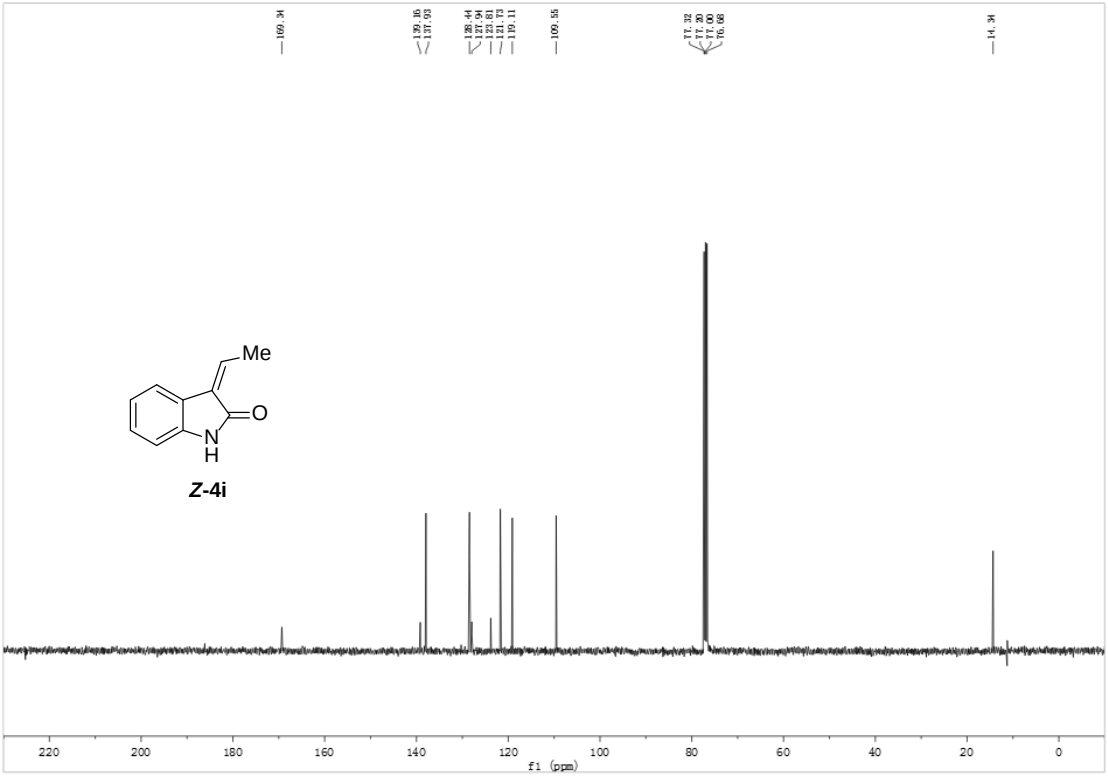
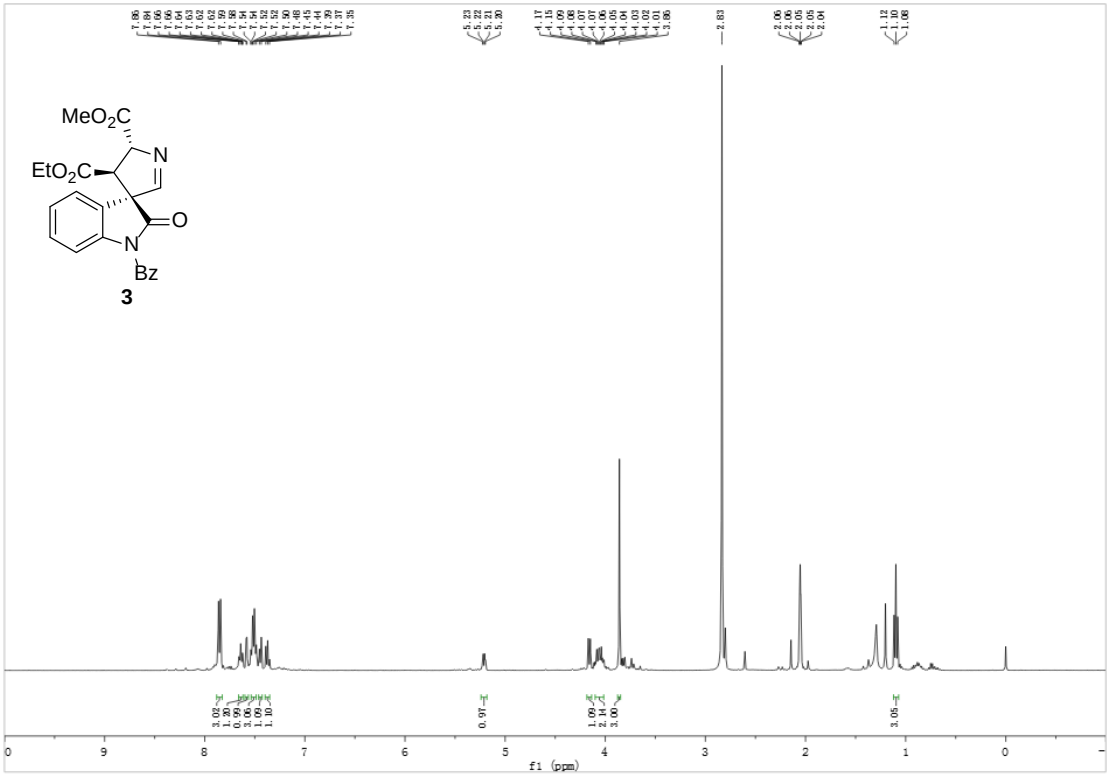
39.3593
39.1923
39.0250
14.8884
Me
O
N
H
E-4i
f1 (ppm)



***Z*-4i**



***Z*-4i**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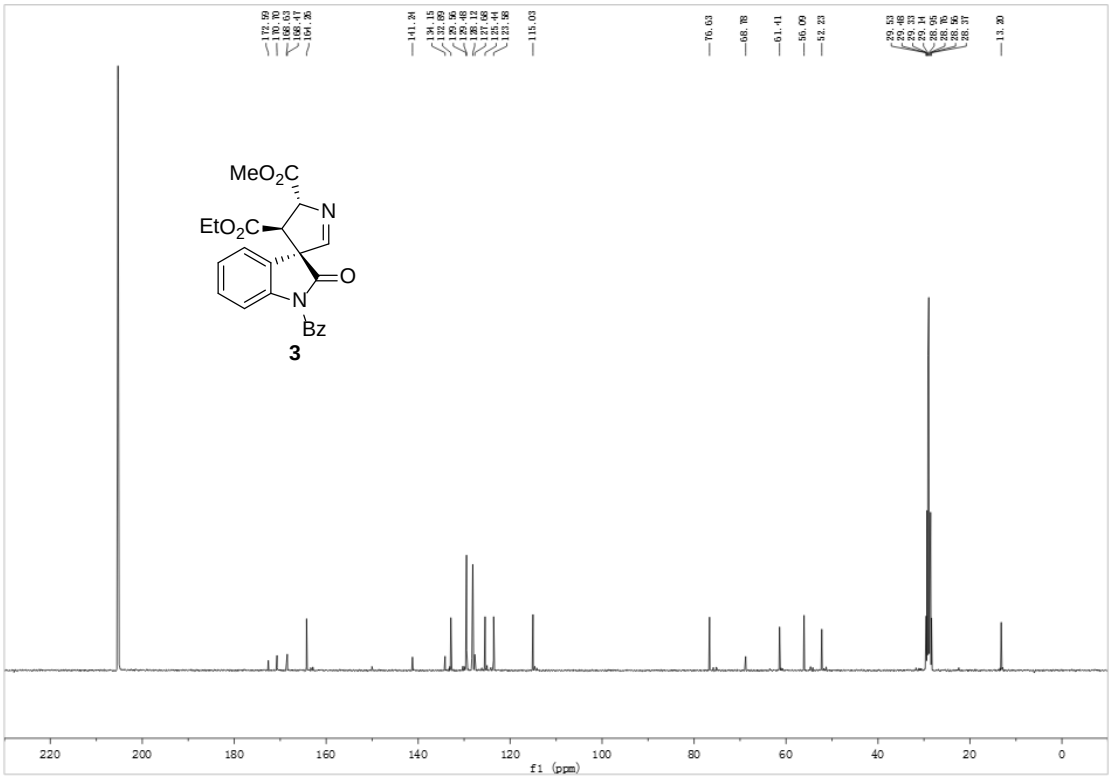
N
O
N
Bz
3
f1 (ppm)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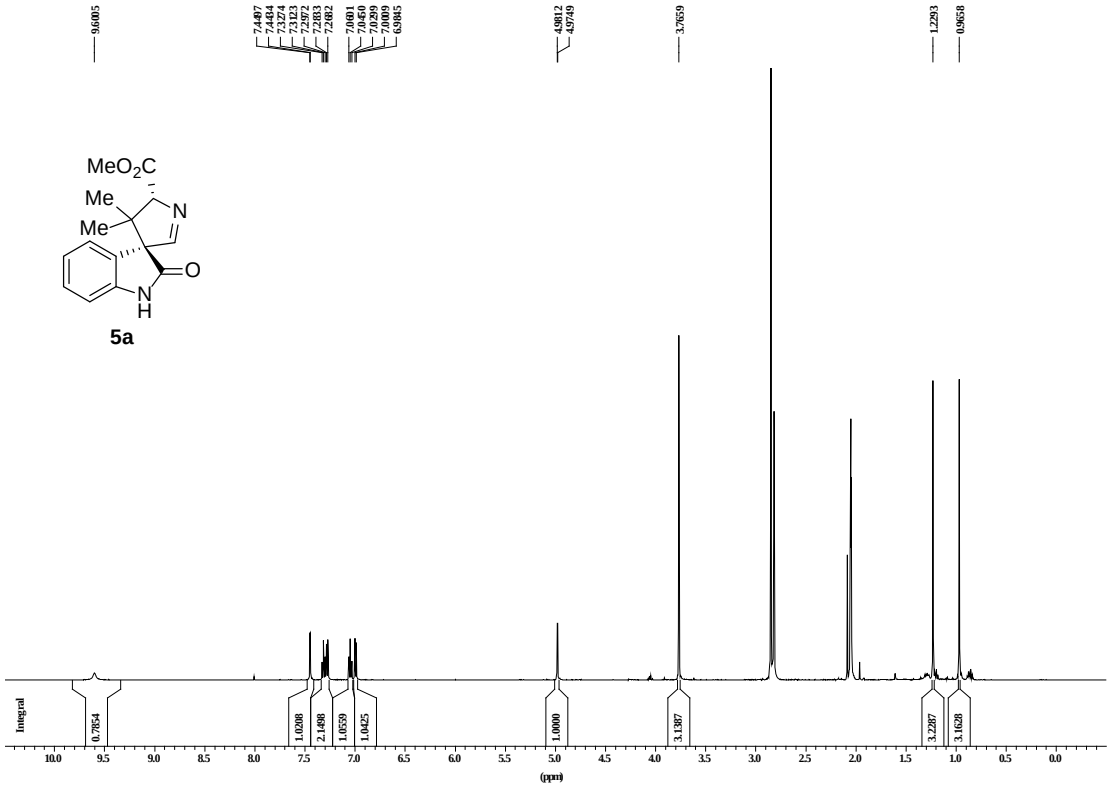
O
N
Bz
3
f1 (ppm)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7.3213
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7.0001
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7.0239
7.0099
6.9945
4.9812
4.9749
3.7659
1.2293
0.9658
MeO2C
Me
Me
N
O
N
H
5a
Integral
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1.0559
1.0425
1.0000
3.1387
3.2297
3.1628
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
3.0
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1.5
1.0
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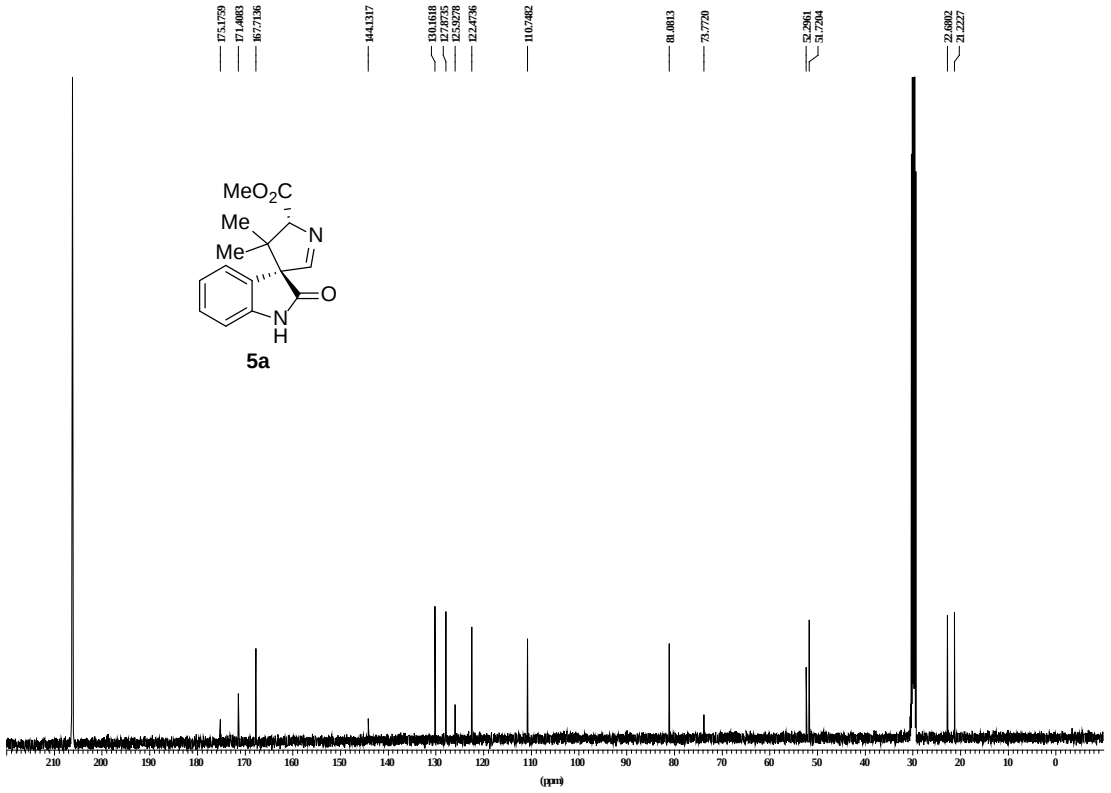
0.0
(ppm)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125.9278
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73.7720
52.2961
51.7204
22.6802
21.2227
MeO2C
Me
Me
N
O
N
H
5a
210
200
190
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120
110
100
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60
50
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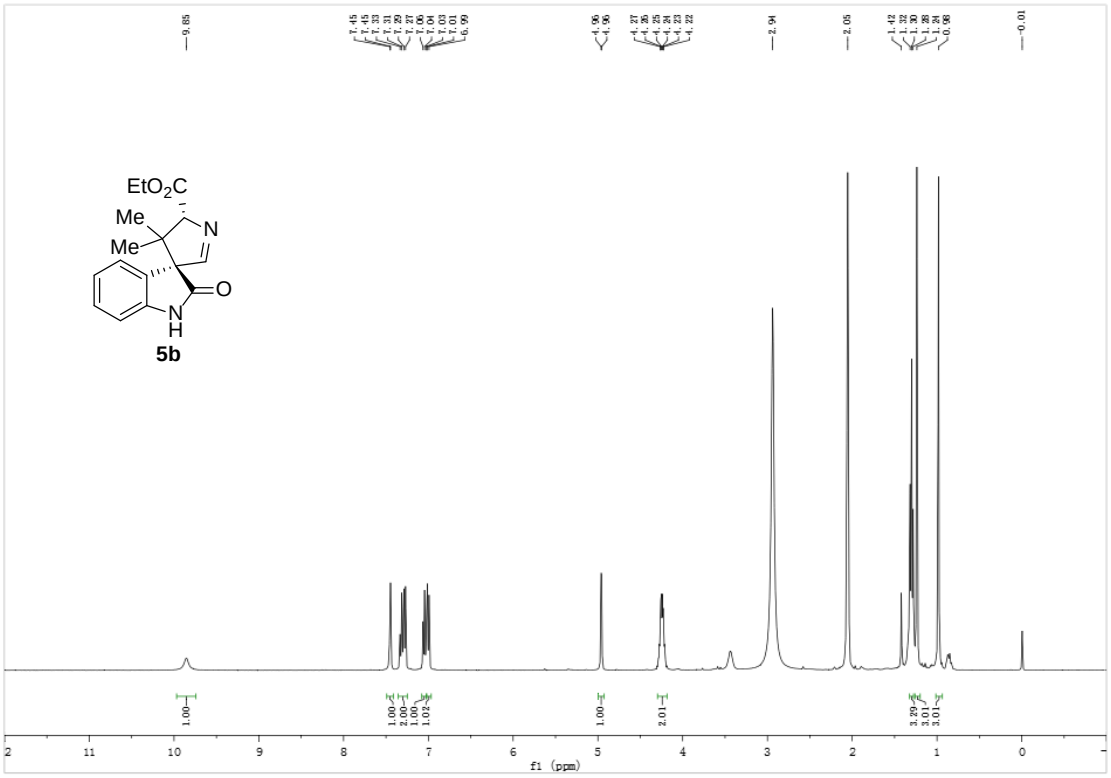
30
20
10
0
(ppm)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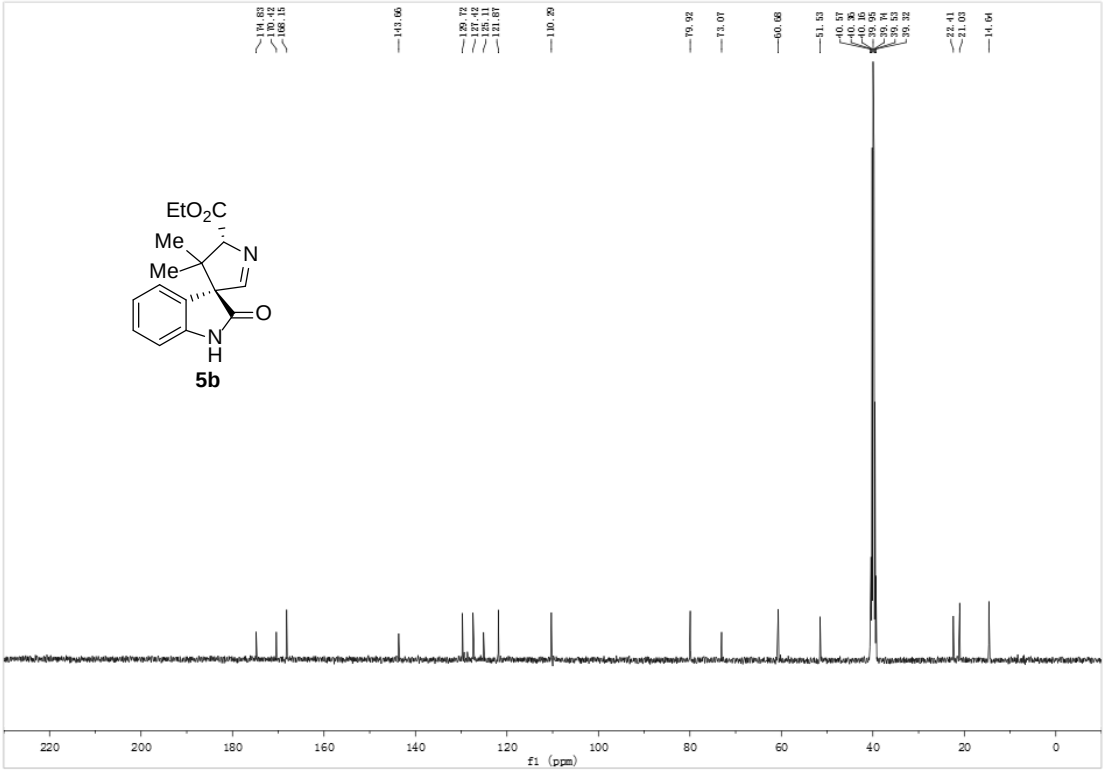
Me
N
O
N
H
5b
f1 (ppm)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H
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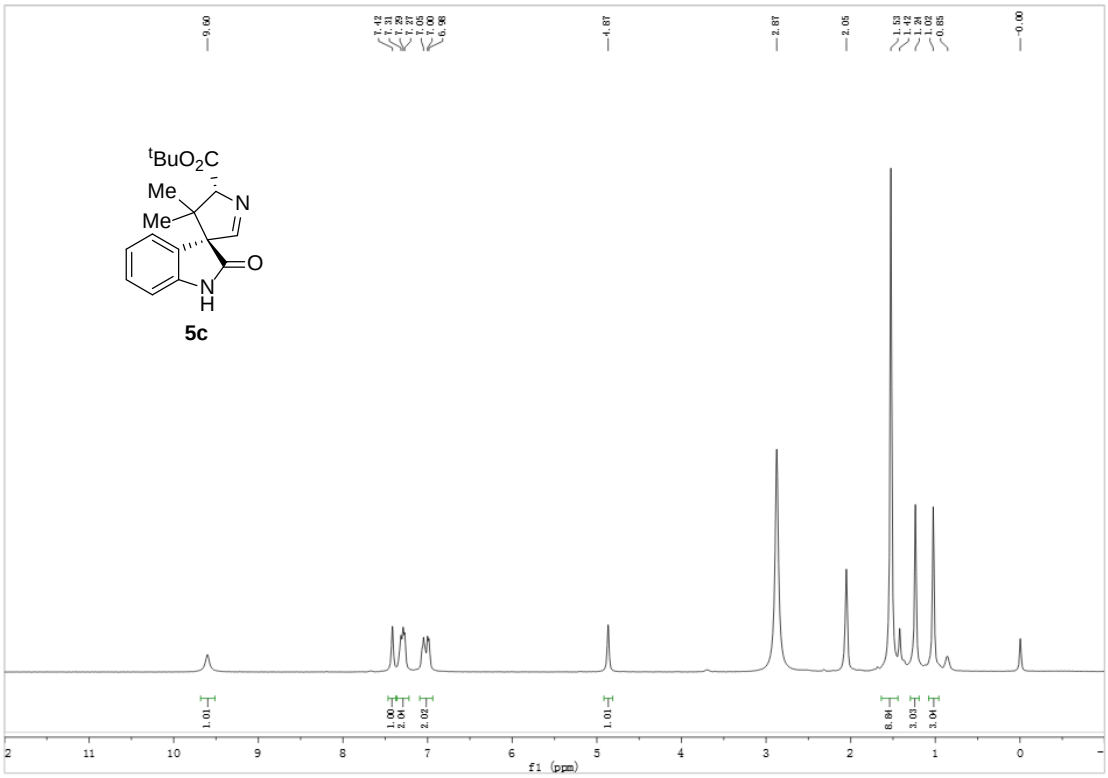
f1 (ppm)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1.47
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tBuO2C
Me
Me
N
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N
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2.02
1.01
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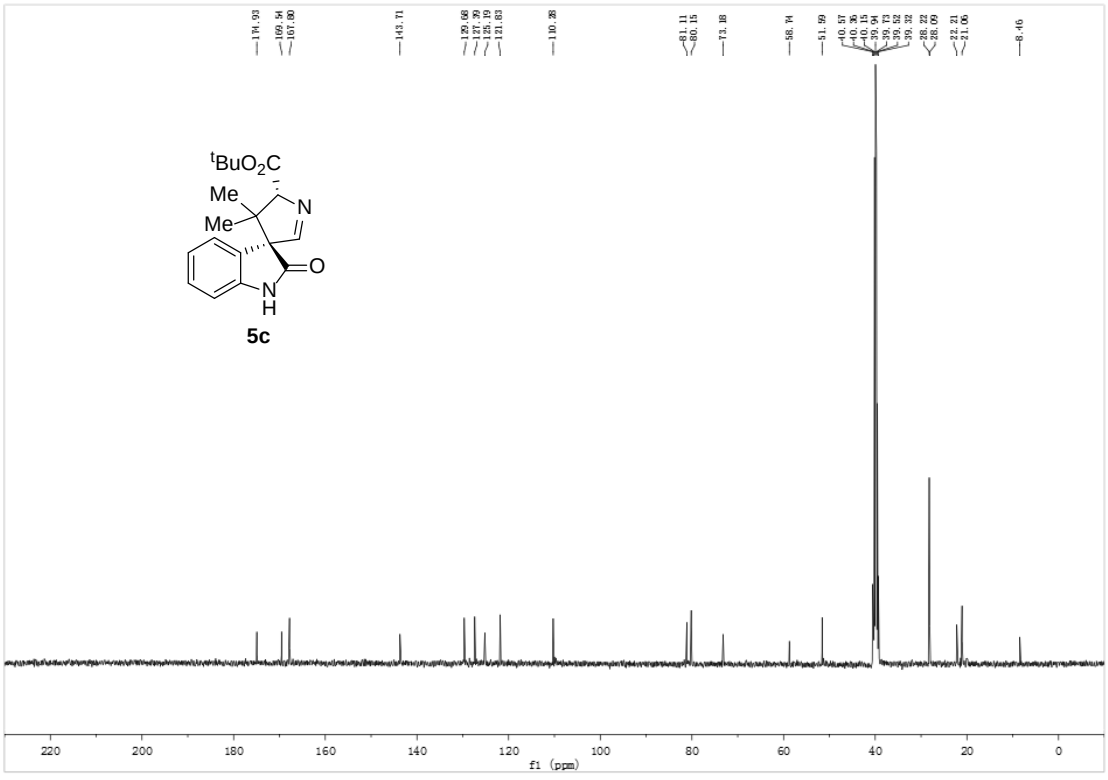
3.04
f1 (ppm)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121.83
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80.15
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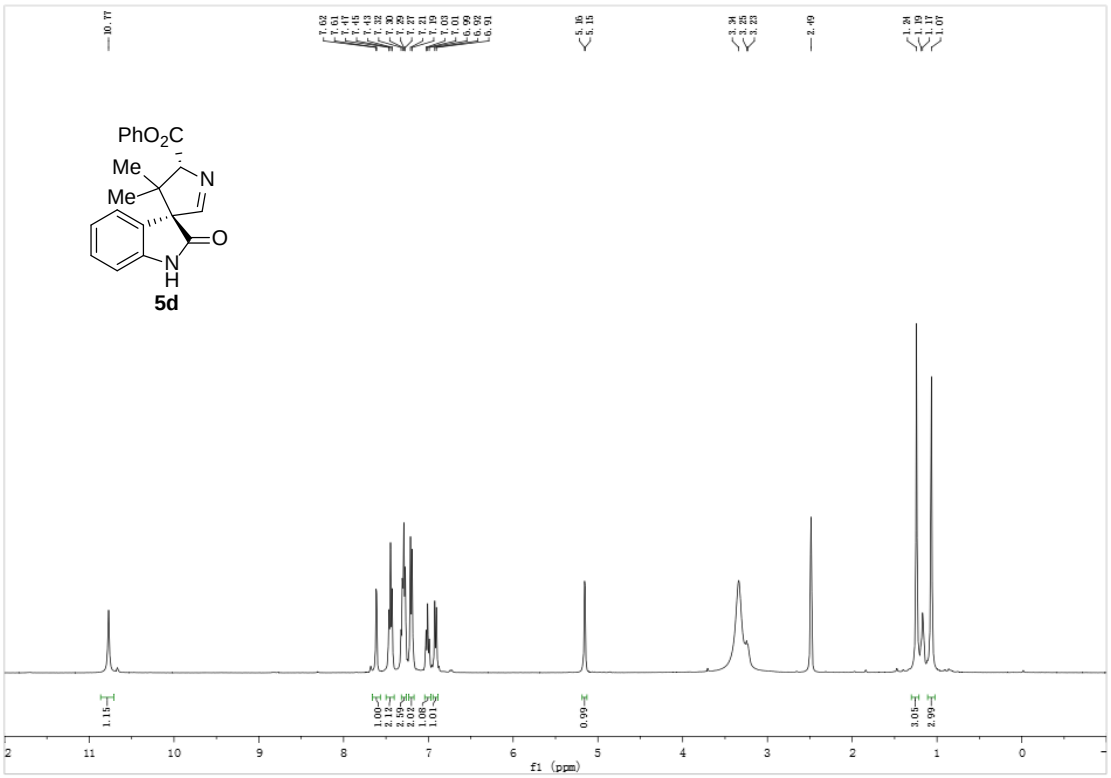
58.74
51.89
40.57
40.36
40.15
39.94
39.73
39.52
39.32
28.69
22.21
21.06
8.46
tBuO2C
Me
Me
N
O
N
H
5c
f1 (ppm)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Me
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O
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H
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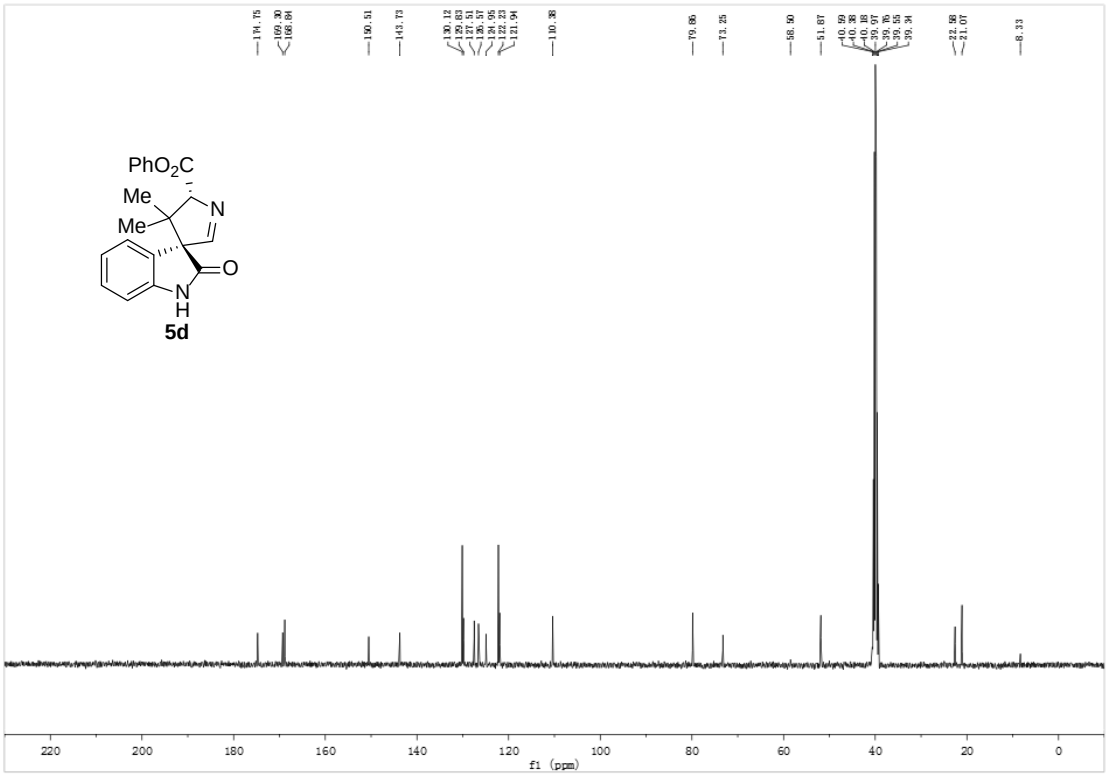
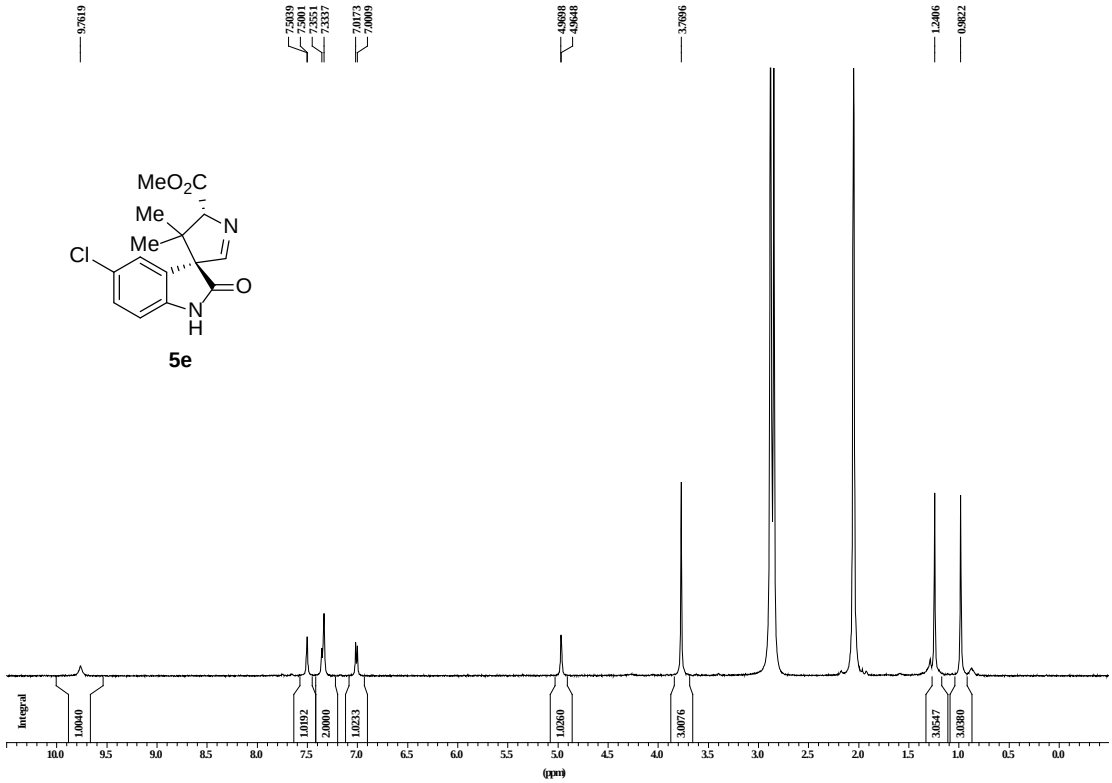
f1 (ppm)


PhO2C
Me
Me
N
O
N
H
5d
f1 (ppm)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0.9822
MeO2C
Me
Me
N
Cl
O
N
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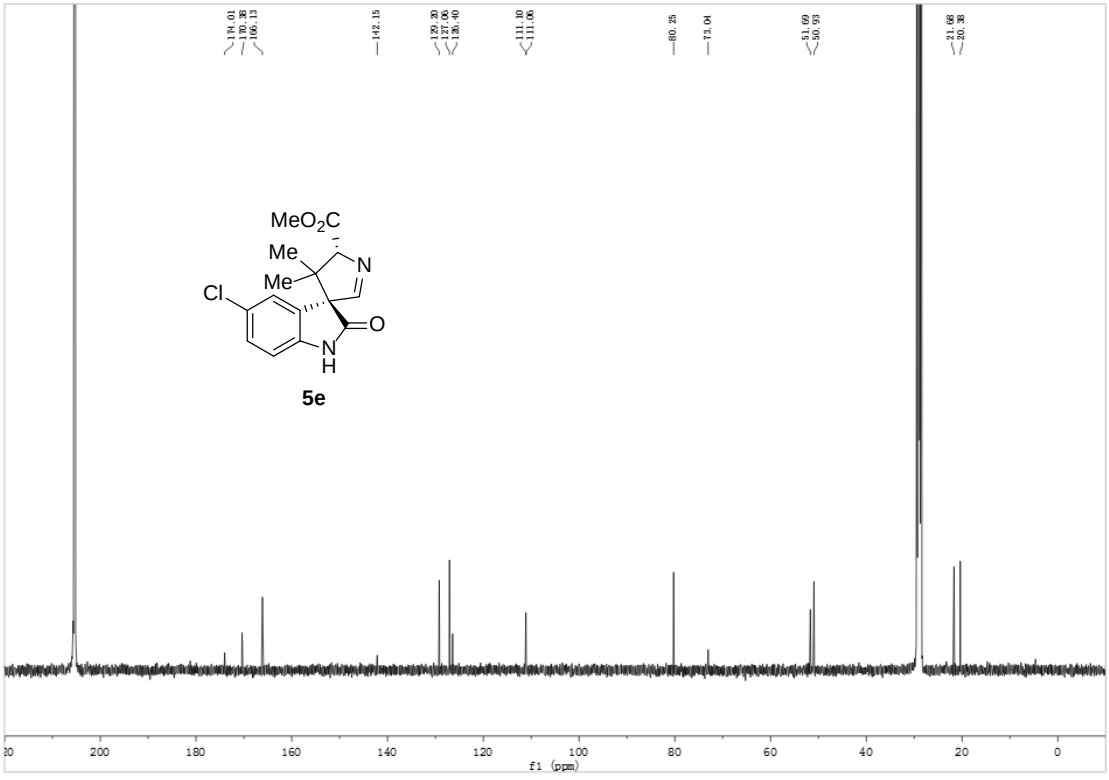
(ppm)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80.25
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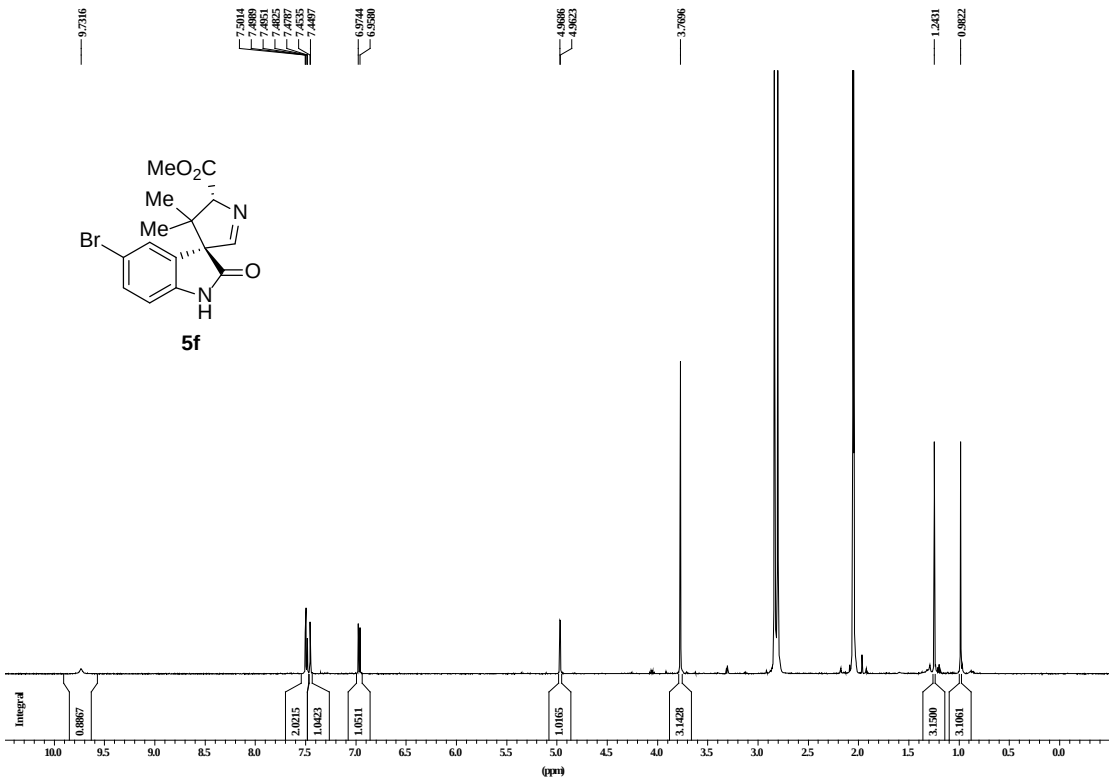
Me
N
Cl
O
N
H
5e
f1 (ppm)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Me
Me
N
Br
O
N
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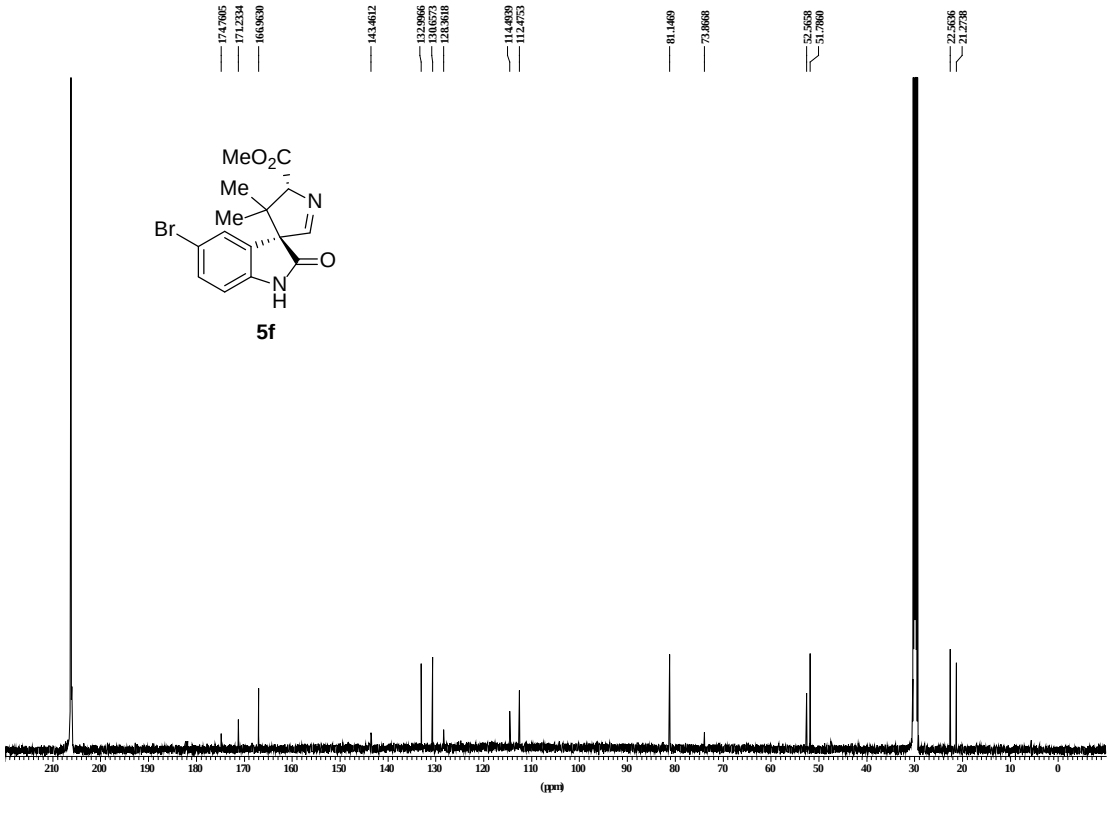
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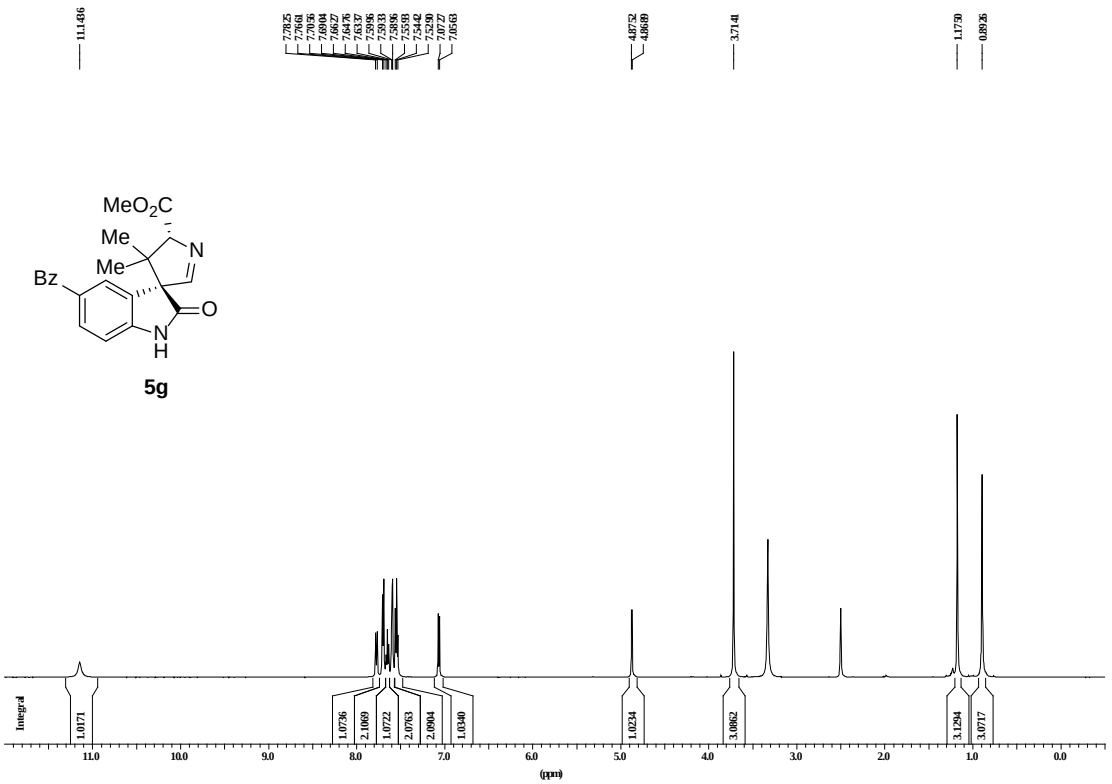
Me
Me
N
Br
O
N
H
5f
(ppm)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7.5896
7.5595
7.5442
7.5290
7.0727
7.0563
4.8732
4.8669
3.7141
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0.8926
MeO2C
Me
Me
N
Bz
O
N
H
5g
Integral
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2.0763
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3.0717
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1.0
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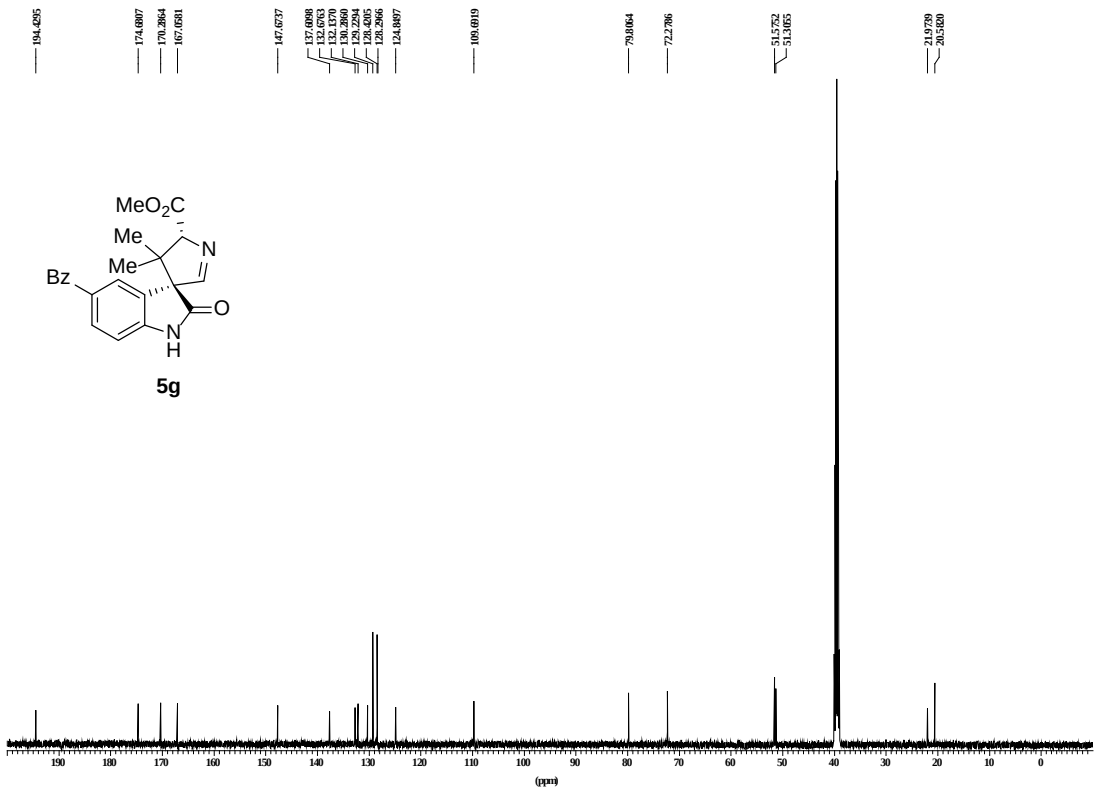
(ppm)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128.4205
128.2966
124.8497
109.6919
79.8064
72.2786
51.5752
51.3455
21.9739
20.5820
MeO2C
Me
Me
N
Bz
O
N
H
5g
190
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130
120
110
100
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20
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0
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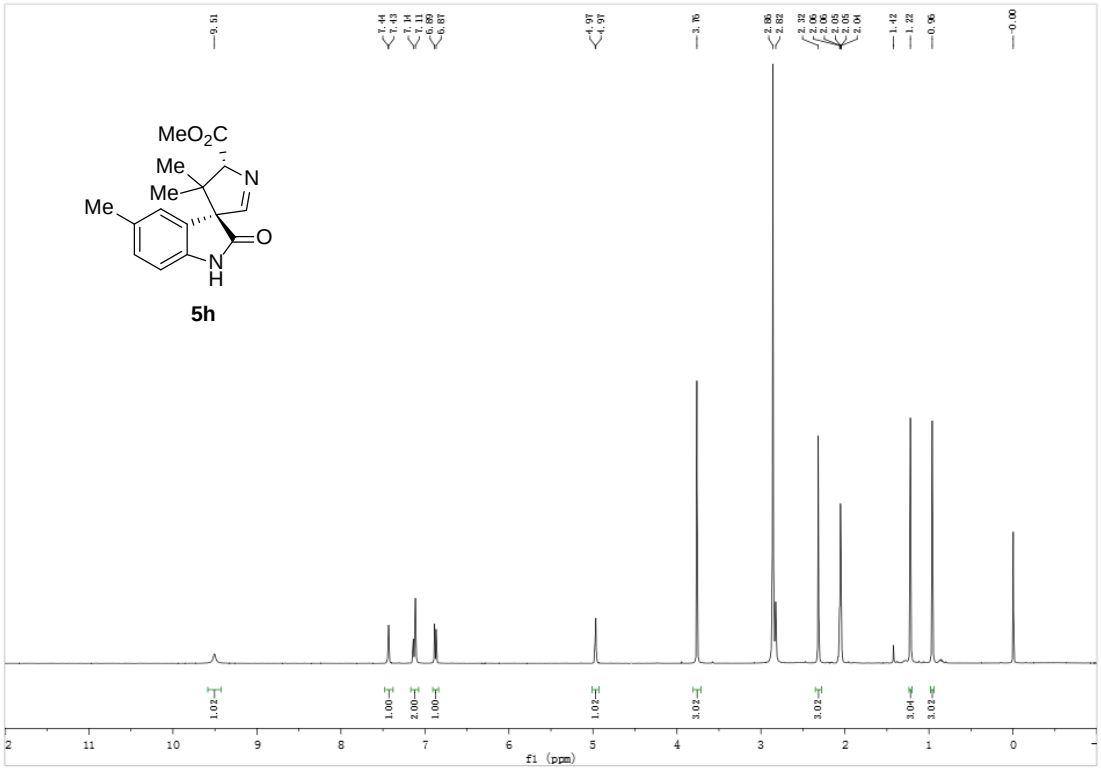
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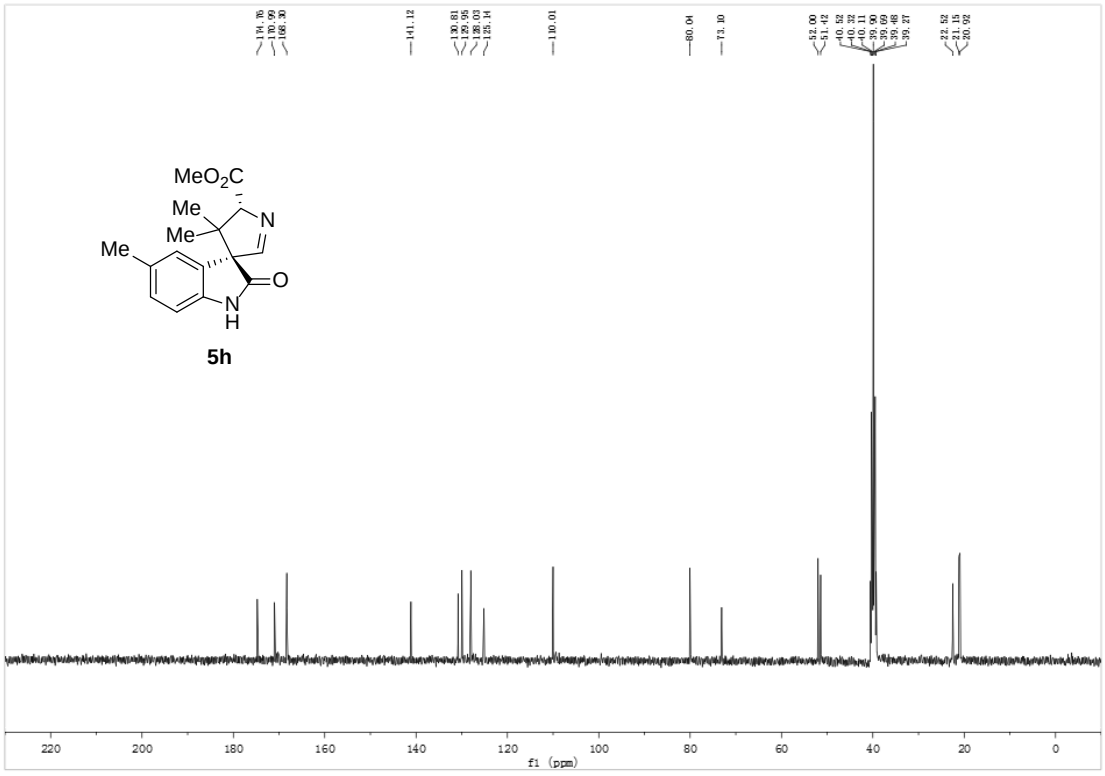
Me
Me
N
O
N
H
5h
f1 (ppm)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Me
Me
N
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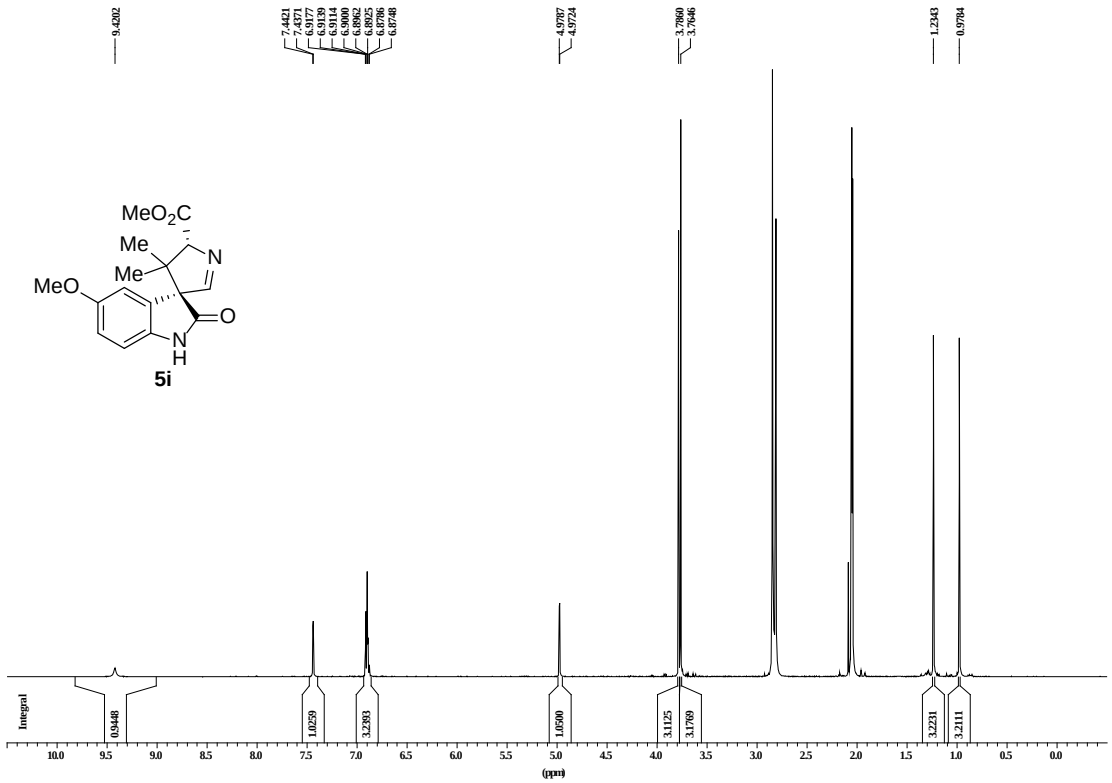
N
H
5h
f1 (ppm)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Me
N
MeO
O
N
H
5i
Integral
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3.1125
3.1769
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9.0
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8.0
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6.0
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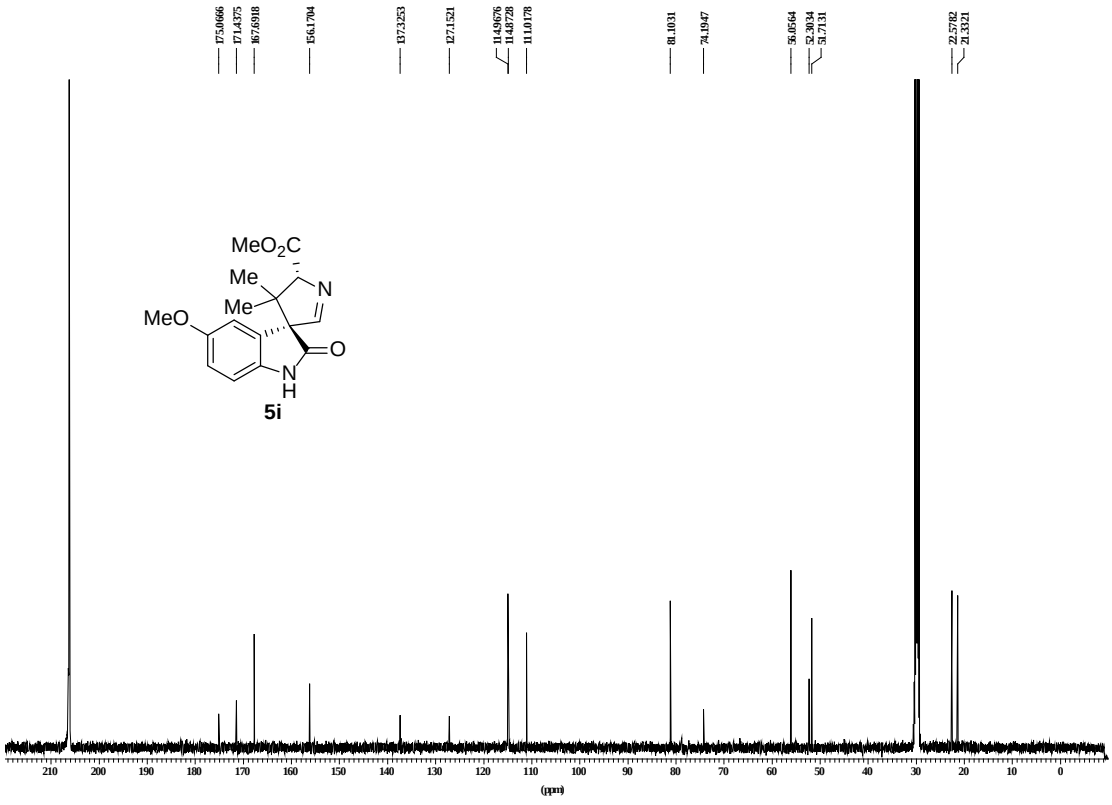
(ppm)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74.1947
56.0564
52.3034
51.7131
22.5782
21.3321
MeO2C
Me
Me
N
MeO
O
N
H
5i
210
200
190
180
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160
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140
130
120
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100
90
80
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60
50
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30
20
10
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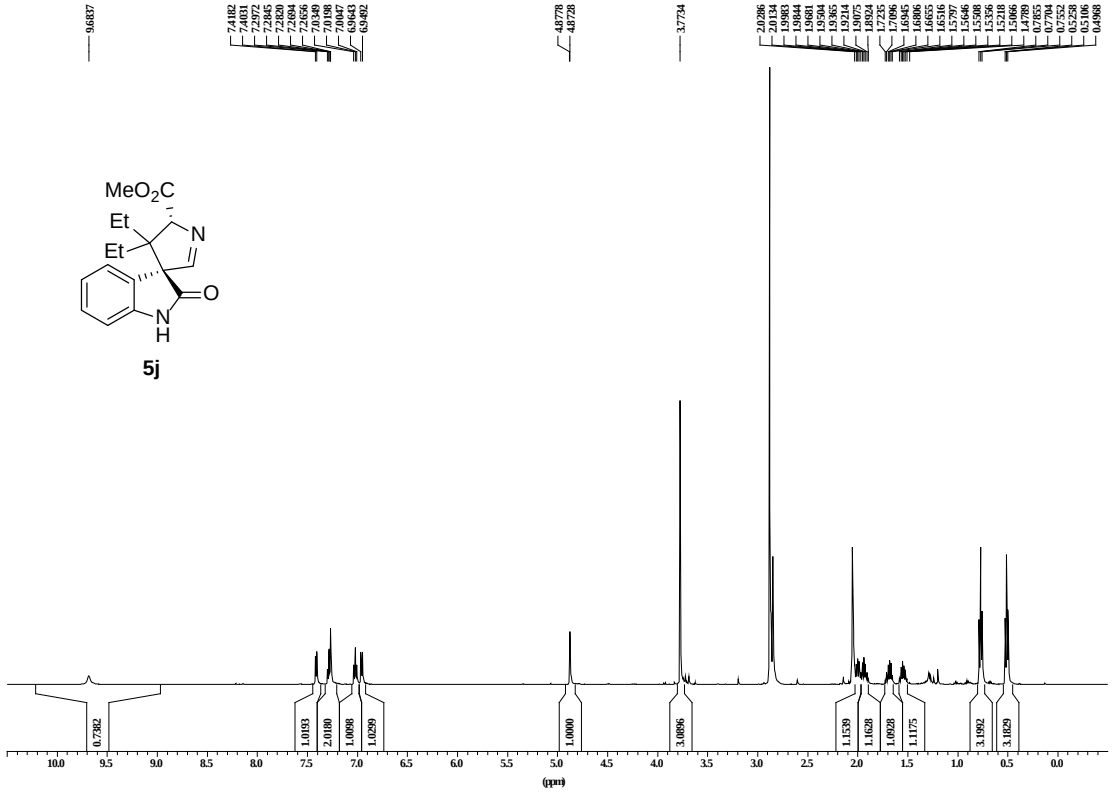
(ppm)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Et
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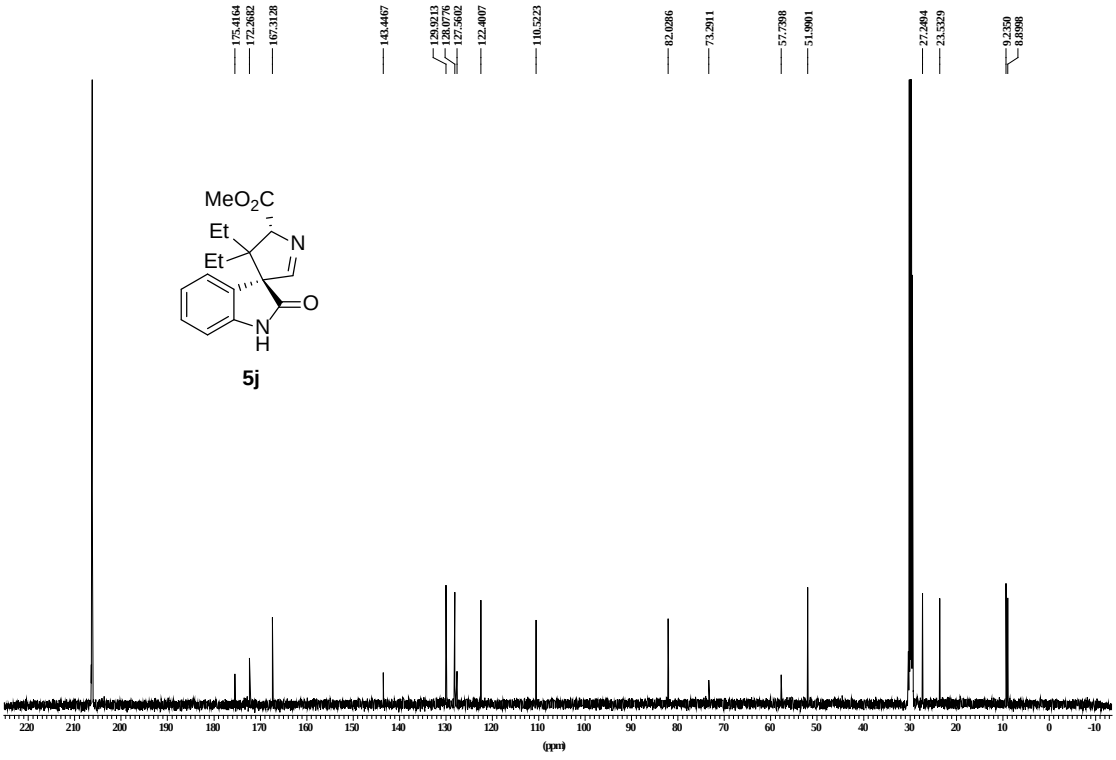
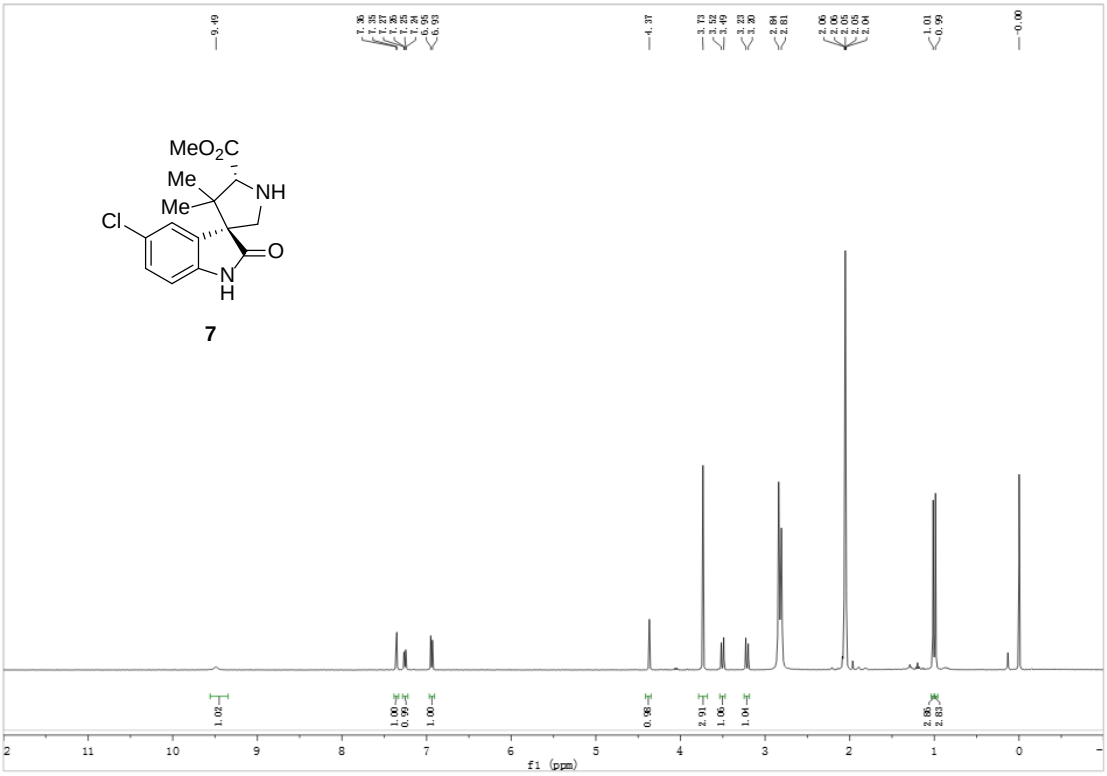
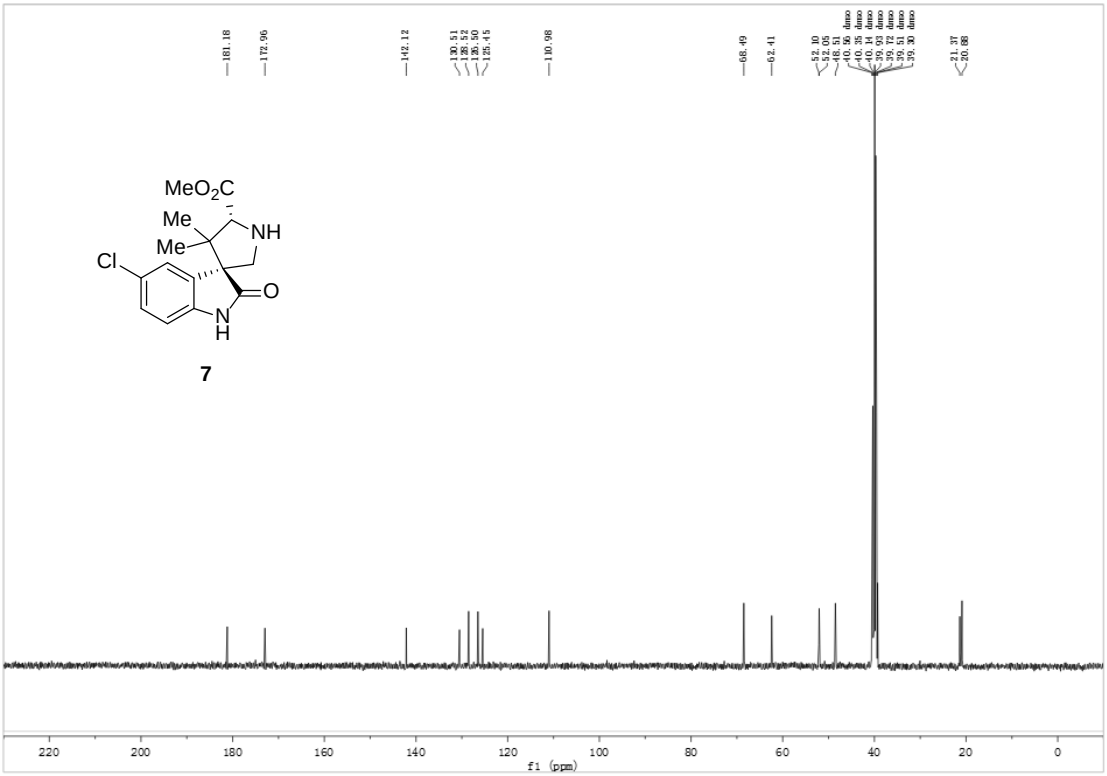
O
N
H
5j

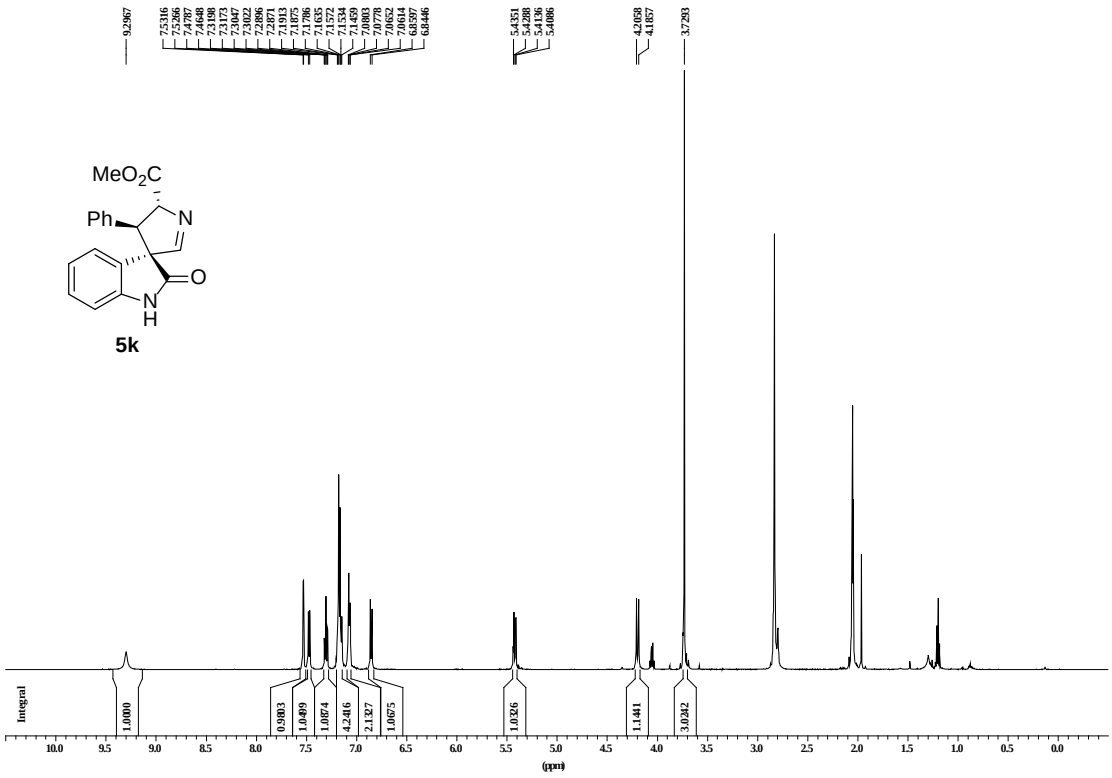

MeO2C
Et
Et
N
O
N
H
5j



7



7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7.4648
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7.3022
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7.2871
7.1913
7.1875
7.1706
7.1635
7.1572
7.1534
7.1459
7.0803
7.0778
7.0652
7.0614
6.8597
6.8446
5.4351
5.4298
5.4136
5.4086
4.2058
4.1857
3.7293
MeO2C
Ph
N
O
N
H
5k
Integral
1.0000
0.9803
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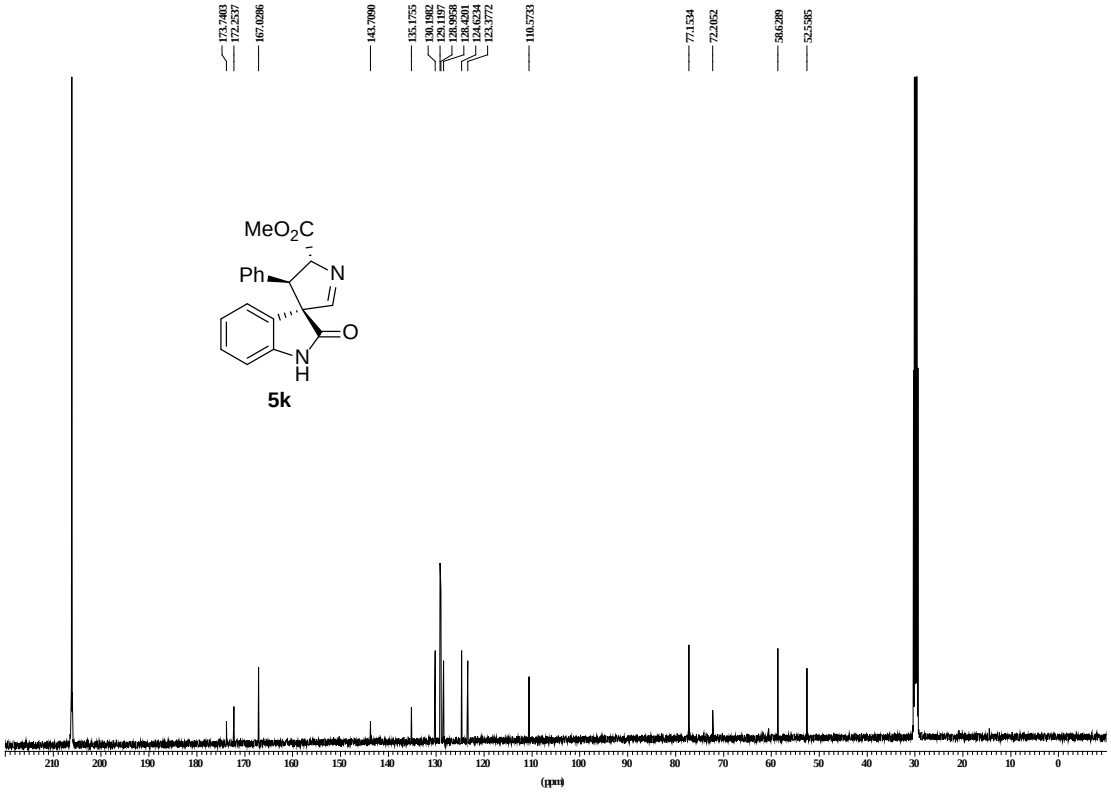
1.0874
4.2416
2.1327
1.0675
1.0326
1.1441
3.0342
(ppm)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129.1197
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128.4201
124.6234
123.3772
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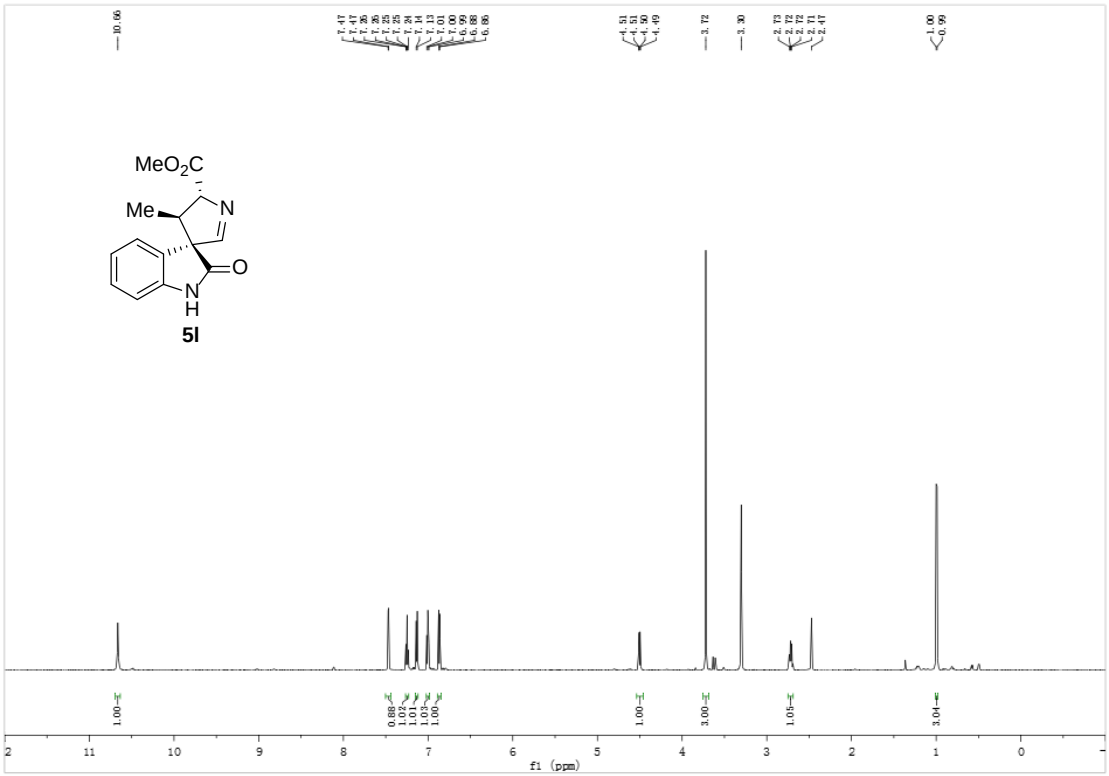
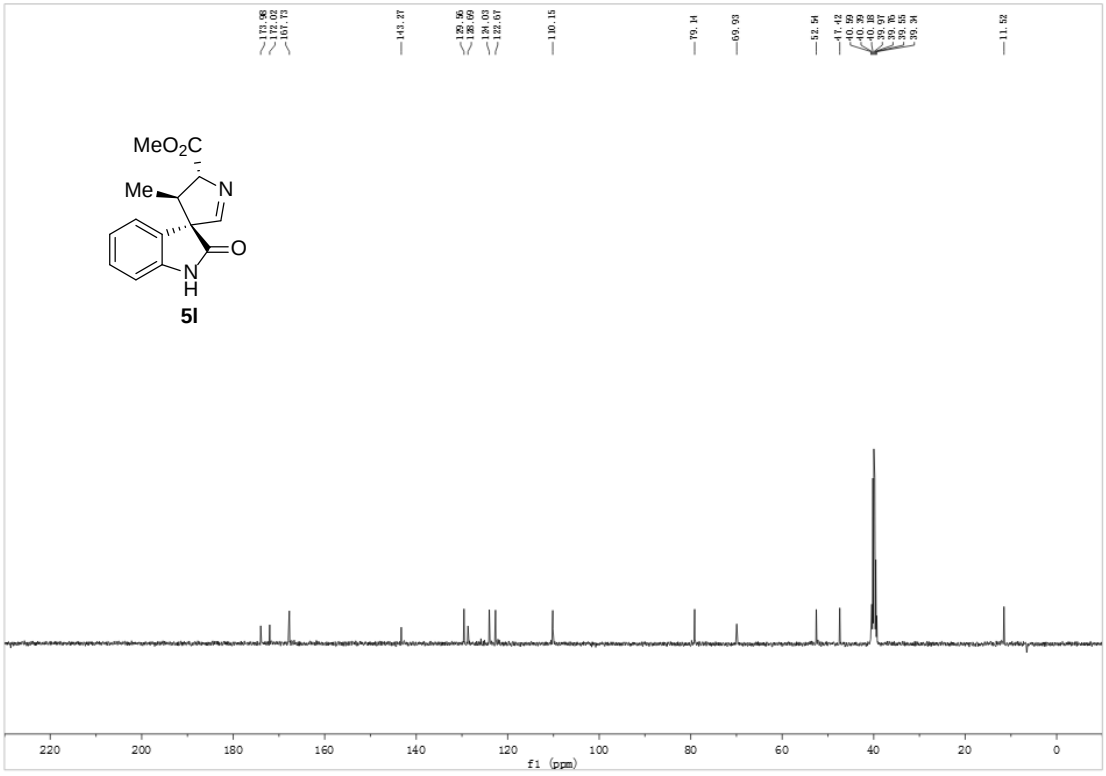
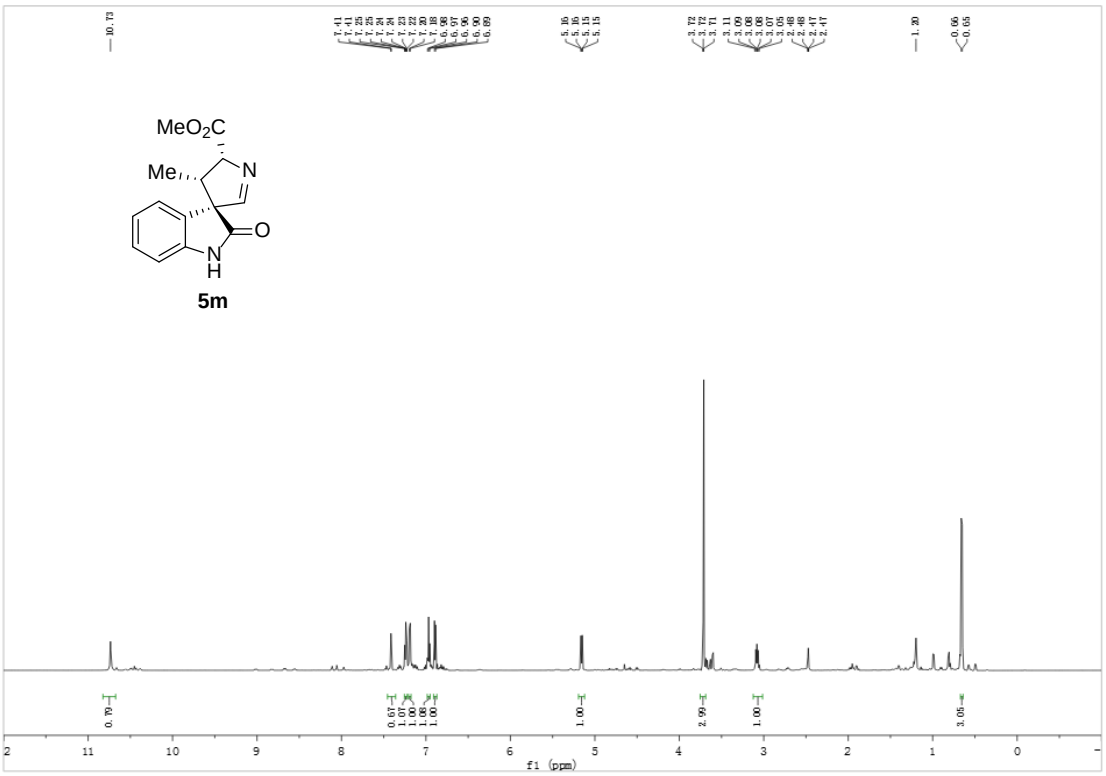
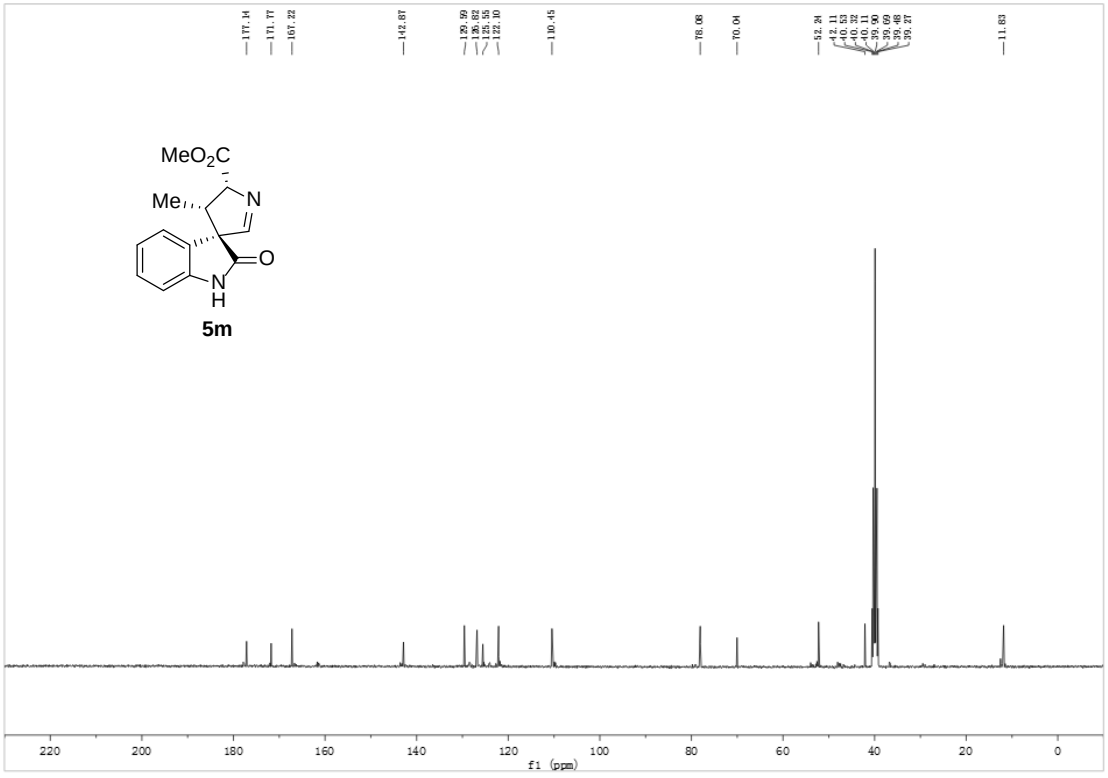
77.1534
72.2052
58.6289
52.5585
MeO2C
Ph
N
O
N
H
5k
(ppm)


MeO2C
Me
N
O
N
H
5l
f1 (ppm)


MeO2C
Me
N
O
N
H
5l
f1 (ppm)


MeO2C
Me
N
O
N
H
5m
f1 (ppm)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Me
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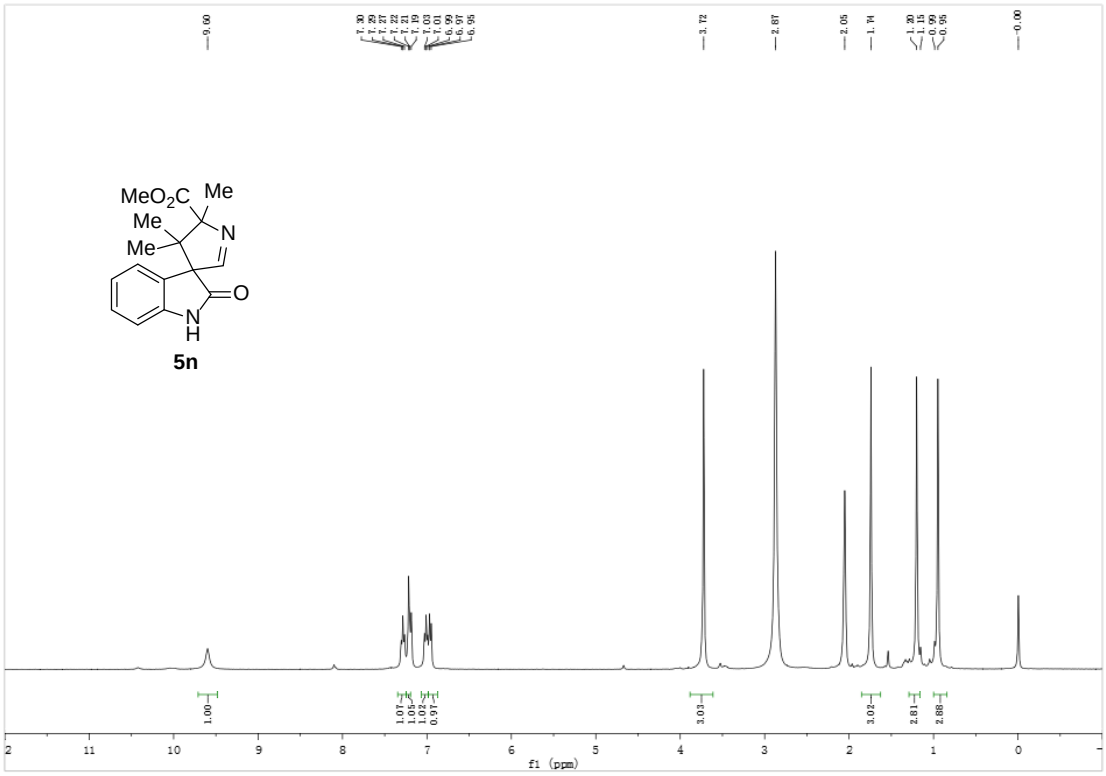
O
N
H
5m
f1 (ppm)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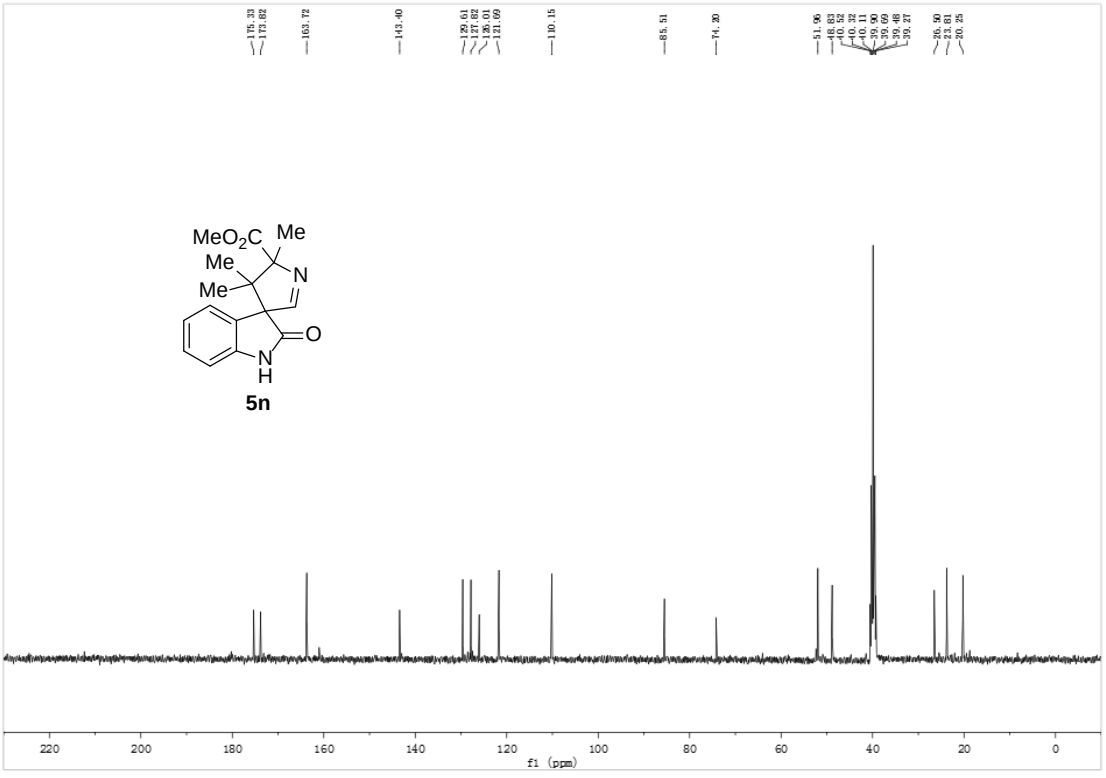
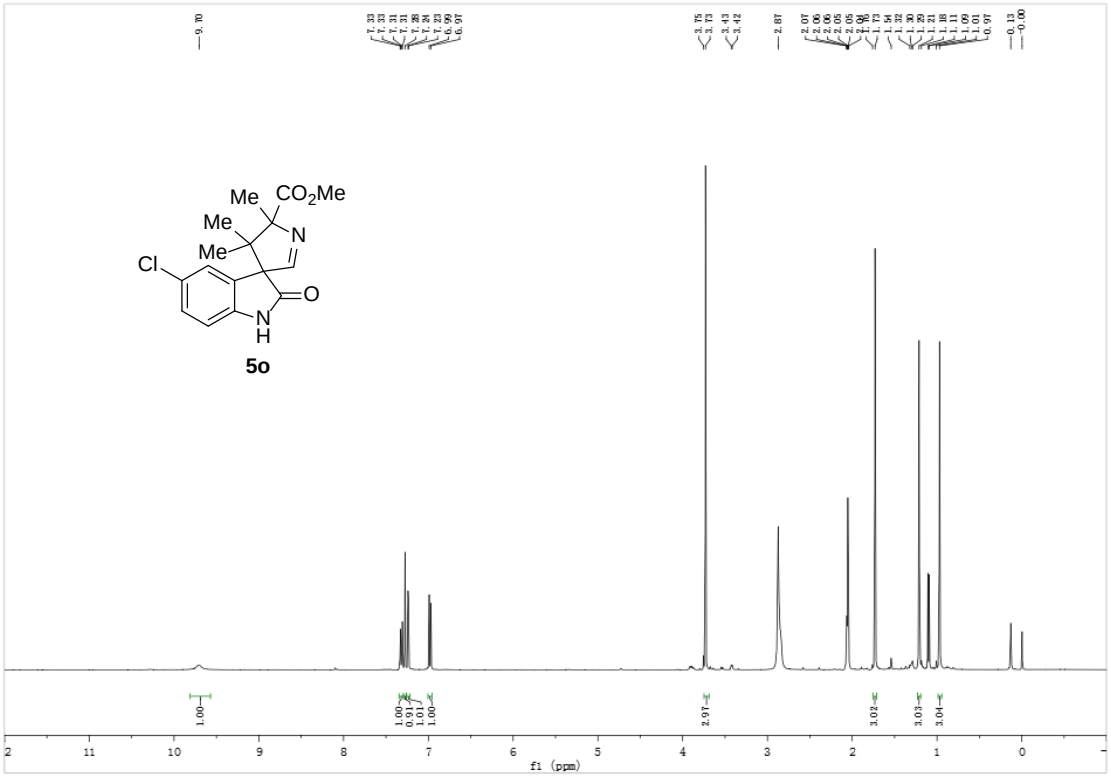
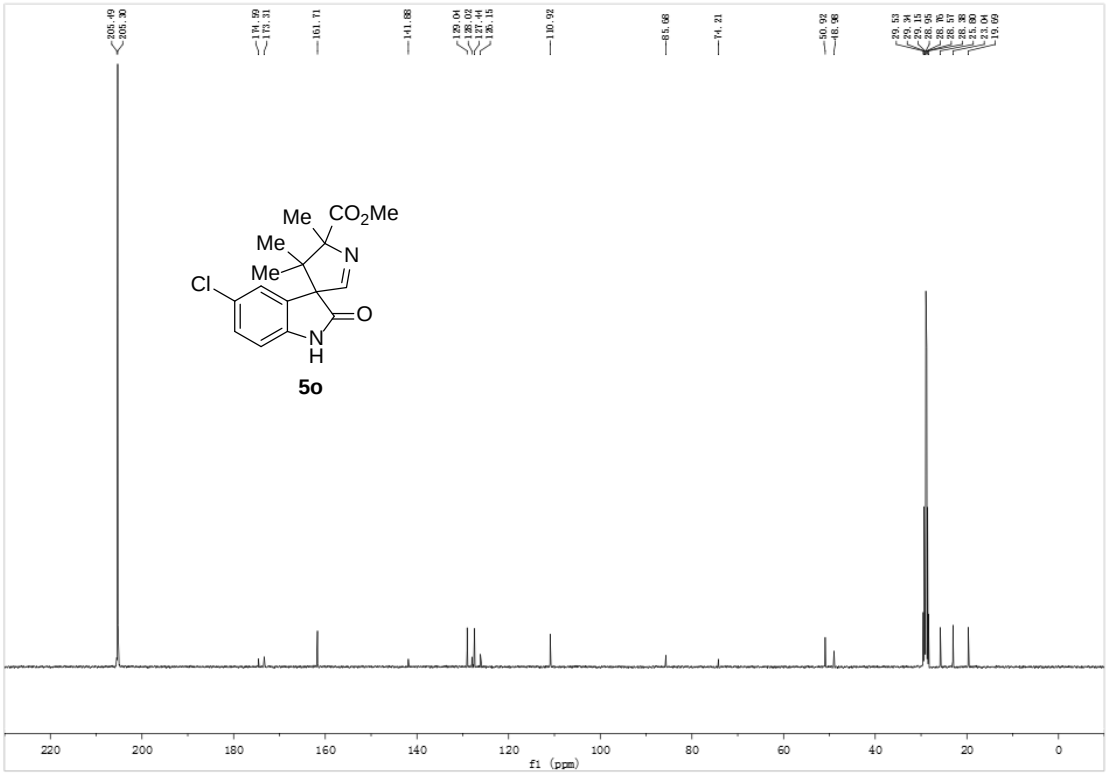
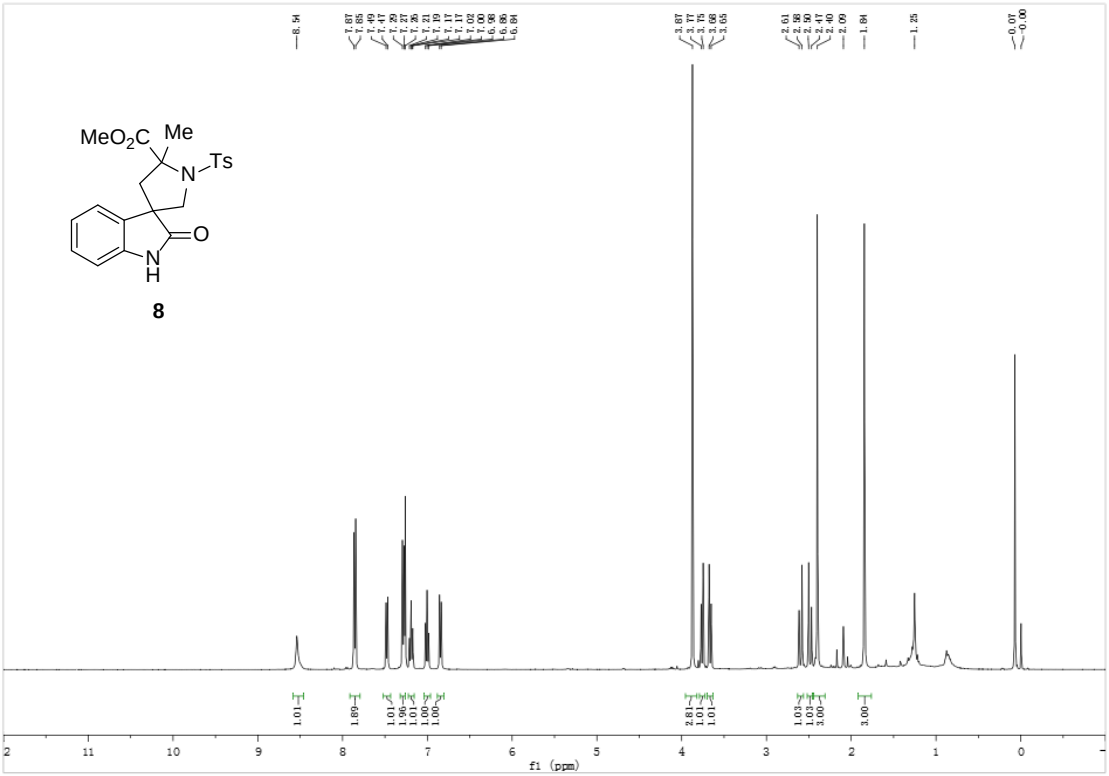
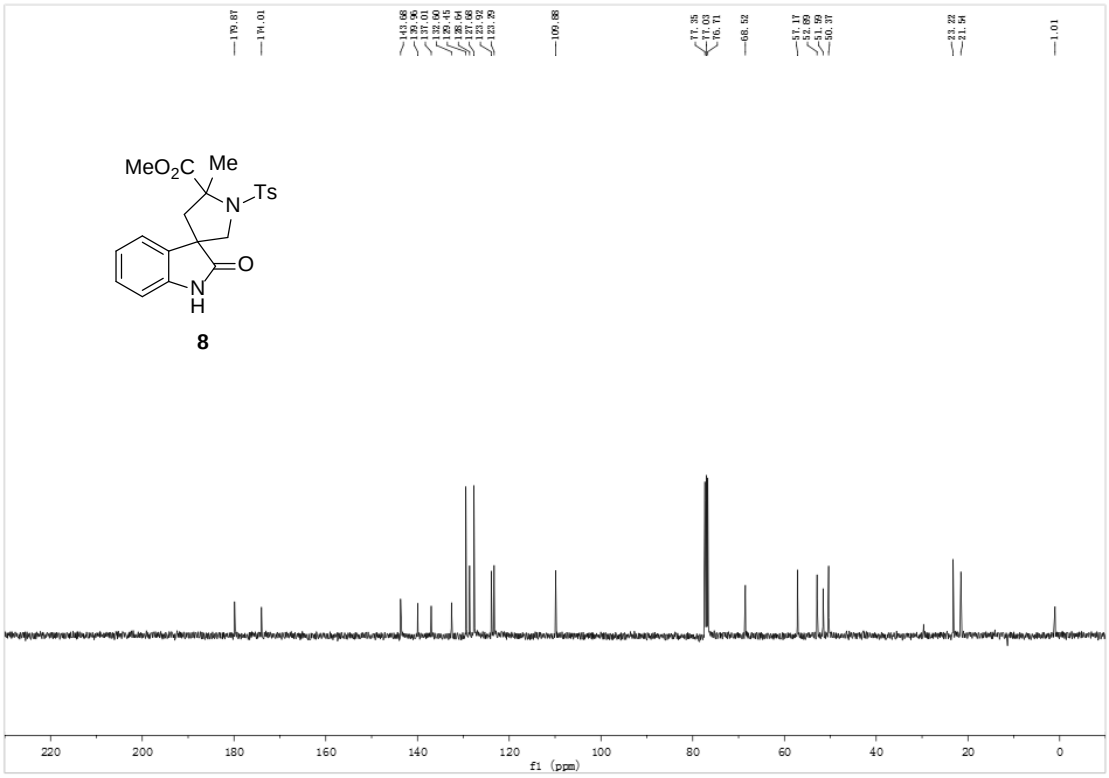
Me
Me
Me
N
O
N
H
5n
f1 (ppm)


MeO2C
Me
Me
Me
N
O
N
H
5n
f1 (ppm)


Me
CO2Me
Me
N
Me
Cl
O
N
H
5o
f1 (ppm)


Me
CO2Me
Me
N
Me
Cl
O
N
H
5o
f1 (ppm)


MeO2C
Me
N
Ts
O
N
H
8
f1 (ppm)


MeO2C
Me
N
Ts
O
N
H
8
f1 (ppm)