Electronic Supplementary Material (ESI) for Chemical Communications.

Supporting Information

Exploration of flow reaction conditions using machine-learning for enantioselective organocatalyzed Rauhut-Currier and [3+2] annulation sequence

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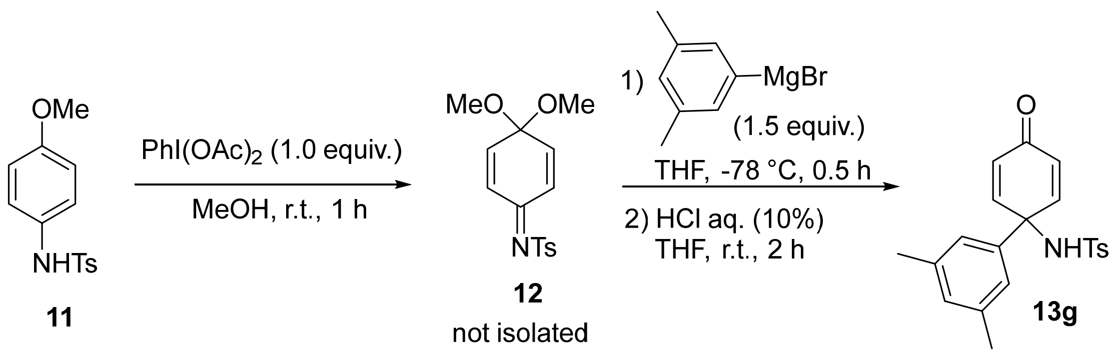
This supplementary information file replaces that originally published on 09 Dec 2019. There were some minor errors including incorrect axis scales in Figures S3B and S5B which have now been corrected in this updated version. This does not affect the results and conclusions of the article.

CONTENTS:

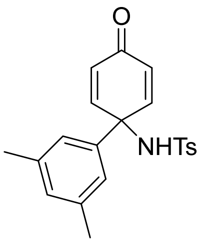
General methods

^{1}H-, ^{13}C-, and ^{19}F-NMR spectra were recorded with a JEOL JMN ECS400 FT NMR, JNM ECA600 FT NMR or Bruker AVANCE II (^{1}H-NMR 400 MHz, ^{13}C-NMR 100, 150 MHz or 175 MHz, ^{19}F-NMR 565 MHz). ^{1}H-NMR spectra are reported as follows: chemical shift in ppm relative to the chemical shift of $CHCl_3$ at 7.26 ppm, integration, multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants (Hz). ^{13}C-NMR spectra reported in ppm relative to the central line of triplet for $CDCl_3$ at 77 ppm. Benzotrifluoride was used as external standards for ^{19}F-NMR. ESI-MS spectra were obtained with JMS-T100LC (JEOL). Optical rotations were measured with JASCO P-1030 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU 980 pump and UV-975 UV/Vis detector). FT-IR spectra were recorded on a JASCO FT-IR system (FT/IR4100). Absolute configuration was determined by Rigaku R-AXIS RAPID 191R diffractometer using filtered Cu-Kα radiation. Column chromatography on SiO_2 was performed with Kanto Silica Gel 60 (40-100 μm). Commercially available organic and inorganic compounds were used without further purification. Dienones **1** were prepared according to known literature procedure.[1] Stainless steel (Comet-01-X) micromixer[2] with inner diameter of 100 μm were manufactured by Techno Application. The flow microreactor system was dipped in a cooling oil bath to control the temperature. Solutions were introduced to the flow microreactor system using syringe pumps, Harvard Model 11, equipped with gastight syringes purchased from YMC. GPy (a programming library in Python for Gaussian processes) was used to estimate yield from parameters such as quantity of **2a**, temperature, and flow rate. Jupyter Notebook was also used to visualize and analyze data (see **Figs. S3-S5**).

Procedure for the preparation of 13g



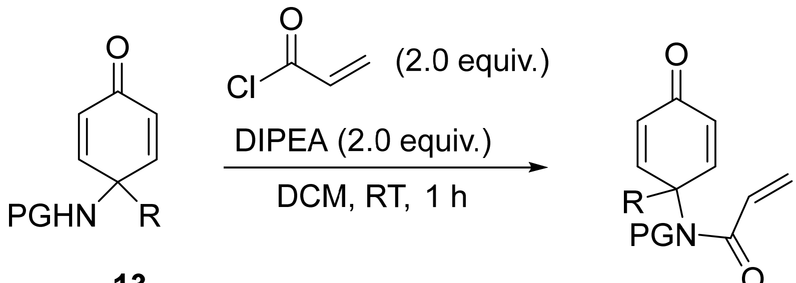
To a solution of **11** (3.08 mmol) in MeOH (15 mL) was added $PhI(OAc)_2$ (3.08 mmol) at 0 °C and stirred at room temperature. After 1 h, saturated $NaHCO_3$ aq. was added to the reaction solution to quench. EtOAc (50 mL) was added to the reaction mixture and washed with brine (30 mL). The organic layer was separated and dried over Na_2SO_4. Evaporation of solvent, followed by dried in *vacuo* gave **12** as crude mixture. This crude mixture was dissolved in THF (10 mL) and reacted with Grignard reagent (1.0 M ether solution, 5.7 mL) at -78 °C. After 0.5 h, 10% HCl aq. (10 mL) was added to reaction mixture, and then it was warmed to room temperature. After stirring for 2 h, the reaction mixture was diluted with EtOAc (30 mL) and the organic phase was washed with saturated $NaHCO_3$ aq. The separated organic layer was dried over Na_2SO_4, evaporated, then dried in *vacuo.* The crude residue was purified by silica gel column chromatography. Pure **13g** was obtained as yellow solid in 58% overall yield from **11**.



8g

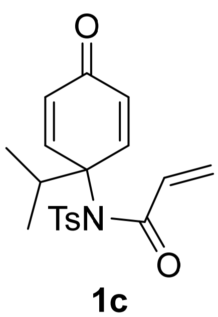
13g: yellow solid; 25% yield; ^{1}H-NMR (400 MHz, CDCl3) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.01 (s, 2H), 6.95 (s, 1H), 6.77 (d, *J* = 10.3 Hz, 2H), 6.05 (d, *J* = 10.3 Hz, 2H), 5.42 (s, 1H), 2.43 (s, 3H), 2.26 (s, 6H); ^{13}C-NMR (100 MHz $CDCl_3$) δ 185.12, 149.02, 144.29, 139.33, 137.55, 137.51, 130.89, 129.69, 127.95, 127.81, 123.52, 59.74, 21.66, 21.44; HRMS (ESI) calcd for $C_{21}H_{21}NO_3SNa$: *m/z* ([M+Na$^+$]) 390.1134, found 390.1134; IR (KBr) 3110, 2885, 1664, 1617, 1460, 1401, 1341, 1160, 1089, 818, 697, 550 cm^{-1}.

General procedure for preparation of dienones 1



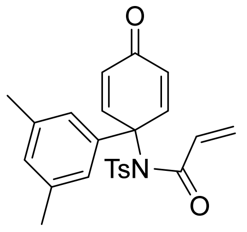
13 **1**

A round bottom flask was charged with a dichloromethane solution of dienone **13** (10 mL, 1.0 mmol) and DIEPA (2 equiv.). Then, acryloyl chloride (2.0 mmol) was added to the reaction mixture and stirred vigorously for 1 h at room temperature. The reaction was then passed through short silica pad to quench. The combined solvent was removed in *vacuo* and the obtained crude residue was quickly purified by silica gel column chromatography (hexane/EtOAc) to give the desired product **1** (**1** is not so stable in silica gel).



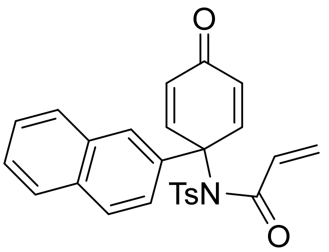
1c

1c: white solid; 40% yield; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 10.5 Hz, 2H), 6.90 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.48 (dd, *J* = 16.9, 1.2 Hz, 1H), 6.03 (d, *J* = 10.5 Hz, 2H), 5.90 (dd, *J* = 10.1, 1.2 Hz, 1H), 2.56-2.61 (m, 1H), 2.40 (s, 3H), 0.81 (d, *J* = 6.9 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 184.83, 170.82, 146.89, 145.43, 136.75, 134.68, 130.61, 130.15, 129.67, 128.67, 67.58, 32.14, 21.72, 17.15; HRMS (ESI) calcd for $C_{19}H_{21}NO_4SNa$: *m/z* ([M+Na$^+$]) 382.1083, found 382.1081; IR (KBr) 2983, 2962, 2939, 2378, 2364, 2345, 1714, 1673, 1630, 1403, 1336, 1186, 1071, 981, 920, 663 cm^{-1}.



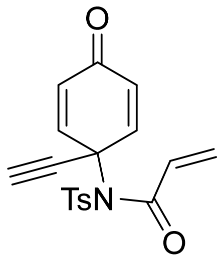
1g

1g: white solid; 64% yield; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.7 Hz, 2H), 7.26-7.31 (m, 4H), 6.93 (dd, *J* = 16.8, 10.3 Hz, 1H), 6.87 (s, 2H), 6.23 (dd, *J* = 16.8, 1.3 Hz, 1H), 6.02 (d, J = 10.1 Hz, 2H), 5.79 (dd, *J* = 10.3, 1.3 Hz, 1H), 2.44 (s, 3H), 2.22 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 185.00, 169.69, 148.33, 145.69, 139.11, 138.22, 136.48, 133.52, 130.80, 130.50, 129.81, 128.62, 127.54, 122.98, 65.67, 21.81, 21.52; HRMS (ESI) calcd for $C_{23}H_{25}NO_6SNa$: *m/z* ([M+Na$^+$]) 466.1295, found 466.1295; IR (KBr) 2984, 2962, 1712, 1669, 1625, 1401, 1354, 1341, 1185, 1170, 1117, 1068, 981, 666, 599 cm^{-1}.



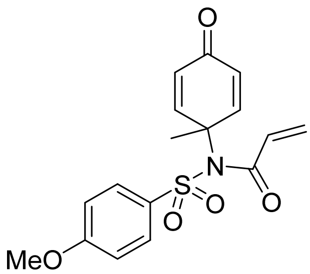
1l

1l: white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75-7.79 (m, 2H), 7.69-7.73 (m, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.41-7.48 (m, 5H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.99 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.18 (dd, *J* = 16.9, 1.0 Hz, 1H), 6.09 (d, *J* = 10.2 Hz, 2H), 5.77 (dd, *J* = 10.2, 1.0 Hz, 1H), 2.45 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 184.86, 169.47, 147.93, 145.80, 136.49, 135.72, 133.37, 133.27, 132.99, 131.07, 129.89, 129.54, 128.61, 128.25, 127.86, 127.73, 126.92, 124.53, 122.46, 65.74, 21.88 (one carbon overlapped); HRMS (ESI) calcd for $C_{26}H_{21}NO_4SNa$: *m/z* ([M+Na$^+$]) 446.1083, found 466.1080; IR (KBr) 3058, 2380, 2366, 2360, 2345, 2310, 1692, 1668, 1627, 15077, 1397, 1192, 1177, 1087, 986, 865, 660 cm^{-1}.



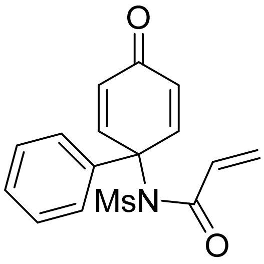
1o

1o: yellow solid; 50% yield; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 9.6 Hz, 2H), 6.79 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.46 (dd, *J* = 16.9, 0.9 Hz, 1H), 6.15 (d, *J* = 9.6 Hz, 2H), 5.91 (dd, *J* = 10.1, 0.9 Hz, 1H), 2.54 (s, 1H), 2.45 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 183.93, 168.20, 145.78, 144.66, 136.78, 132.27, 131.76, 130.00, 128.15, 128.11, 76.36, 76.20, 55.76, 21.79; HRMS (ESI) calcd for $C_{18}H_{15}NO_4SNa$: *m/z* ([M+Na$^+$]) 364.0614, found 364.0613; IR (KBr) 3274, 3098, 3063, 1704, 1667, 1625, 1608, 1398, 1348, 1173, 1014, 942, 863, 811, 662 cm^{-1}.



1p

1p: yellow solid; 40% yield; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 10.3 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.76 (dd, *J* = 16.7, 10.1 Hz, 1H), 6.47 (dd, *J* = 16.7, 1.4 Hz, 1H), 6.01 (d, *J* = 10.3 Hz, 2H), 5.95 (dd, *J* = 10.1, 0.9 Hz, 1H), 3.87 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 184.58, 170.73, 164.11, 150.62, 134.26, 131.70, 130.81, 130.77, 127.44, 114.38, 60.16, 55.90, 26.99; HRMS (ESI) calcd for $C_{17}H_{17}NO_5SNa$: *m/z* ([M+Na$^+$]) 370.0720, found 370.0718; IR (KBr) 3452, 2946, 2842, 2345, 1720, 1670, 1597, 1498, 1348, 1265, 1166, 1020, 835, 805, 560 cm^{-1}.



1q

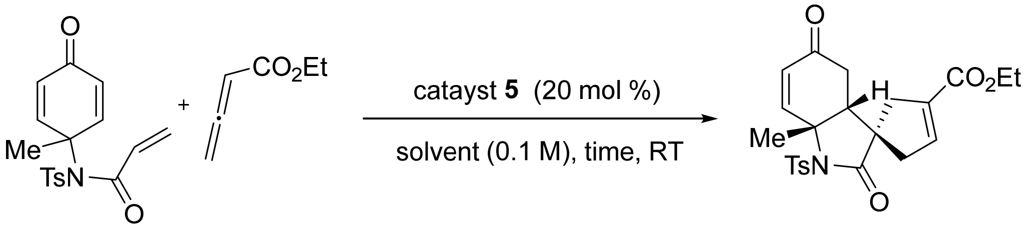
1q: white solid; 75% yield; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 10.1 Hz, 2H), 7.31-7.39 (m, 5H), 6.65 (dd, *J* = 16.7, 10.1 Hz, 1H), 6.37 (d, *J* = 10.1 Hz, 2H), 6.30 (d, *J* = 16.7 Hz, 1H), 5.80 (d, *J* = 10.1 Hz, 1H), 3.22 (s, 3H)**;** ^{13}C-NMR (100 MHz, $CDCl_3$) δ 184.59, 168.72, 148.05, 138.42, 131.83, 129.53, 128.96, 128.37, 125.39, 66.09, 44.71 (one carbon overlapped); HRMS (ESI) calcd for $C_{16}H_{15}NO_4SNa$: *m/z* ([M+Na$^+$]) 340.0614, found 340.0615; IR (KBr) 3057, 3033, 3012, 2934, 2385, 2360, 1692, 1667, 1631, 1489, 1399, 1359, 1332, 1184, 1137, 958, 787, 765 cm^{-1}.

Reaction optimization in batch system

General procedure for the RC and [3+2] annulation sequence

To a solution of acrylic amide **1a** (0.03 mmol, 10 mg) in degassed dry solvent was added allenic ester **2a** (0.06 mmol, 7 μL, 2 equiv.). Then, chiral catalyst **5** (6 μmol, 20 mol%) was added to the mixture of **1a** and **2a**. Then, a crude mixture was passed through short silica pad with EtOAc. Removal of solvent under reduced pressure gave a crude residue, which was purified by silica gel chromatography (*n*-hexane/EtOAc = 2/1) to afford product **4a**.

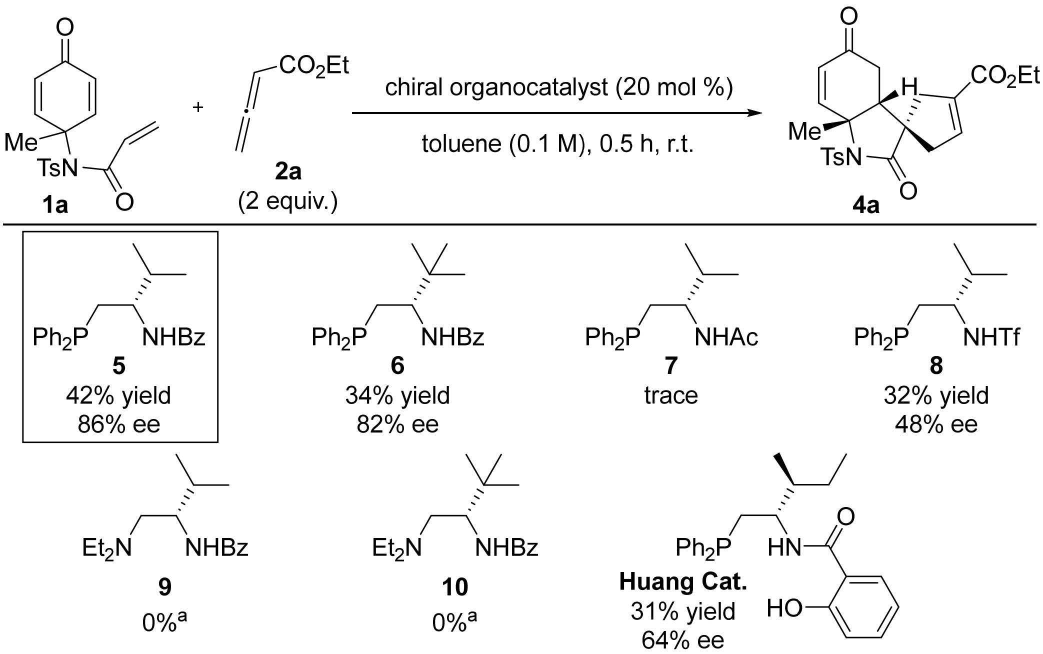
Table S1. Solvent screening



entry	solvent	time (h)	yield (%)	ee (%)
1	dioxane	0.5	20	72
2	toluene	0.5	42	86
3	DCM	0.5	36	86
4	THF	0.5	43	82
5	CH_3CN	0.5	36	72
6	MeOH	12	-	-

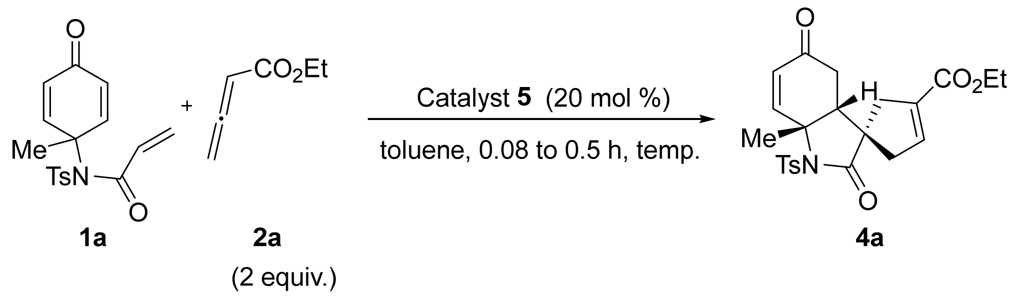
Reaction conditions: **1a** (0.03 mmol), **2a** (0.06 mmol), and catalyst (*S*)-**5** (20 mol%), in dry solvent. Yields were estimated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Ees were determined by HPLC analysis (Daicel Chiralpak ID).

Table S2. Screening of organocatalyst



Reaction conditions: **1a** (0.03 mmol), **2a** (0.06 mmol), and organocatalyst (20 mol%), in dry toluene. Yields were estimated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Ees were determined by HPLC analysis (Daicel Chiralpak ID). [a] RC product **3a** was only observed.

Table S3. Screening of concentration and temperature



entry	temp. (°C)	conc. (M)	yield (%)	ee (%)
1	RT	0.1	42	86
2	50	0.1	36	75
3	80-reflux	0.1	39-45	78-84
4	80	0.05	42	90
5	80	0.01	65 (44)[a]	92 (92)[a]

Reaction conditions: **1a** (0.03 mmol), **2a** (0.06 mmol), and catalyst (*S*)-**5** (20 mol%), in dry toluene. Yields were estimated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Ees were determined by HPLC analysis (Daicel Chiralpak ID). [a] On a 1 mmol scale of **1a** (data in parentheses, entry 5)

The domino reaction of **1a** and **2a** as prototypical substrates in the presence of chiral organocatalyst (20 mol %) was attempted in a batch process (Table S2). Among the organocatalysts examined, (S)-valine-derived catalyst **5** bearing diphenylphosphine and benzoyl units promoted the desired domino reaction to afford spiro heterocycle **4a** with high regio- and stereoselectivity, albeit in 42% yield. In 2017, we and Huang independently reported highly active organocatalyst for the enantioselective intramolecular RC reaction of **1**,[1,3] however, neither amine catalyst **9** nor Huang Cat. for the RC showed attractive outcomes on our desired domino reaction. Many unidentified products were also formed due to side reactions of dienone **1a** with the highly reactive intermediary RC product **3a**,[1] and allenoate **2a** in the presence of catalysts **5**. In terms of enantioselectivity, the use of catalyst **5** in toluene gave **4a** in 92% ee as a single diastereomer, but no significant improvement in the chemical yield of **4a** was accomplished in the batch system (Table S1-3).

Procedure for the RC and [3+2] annulation sequence (Flow)

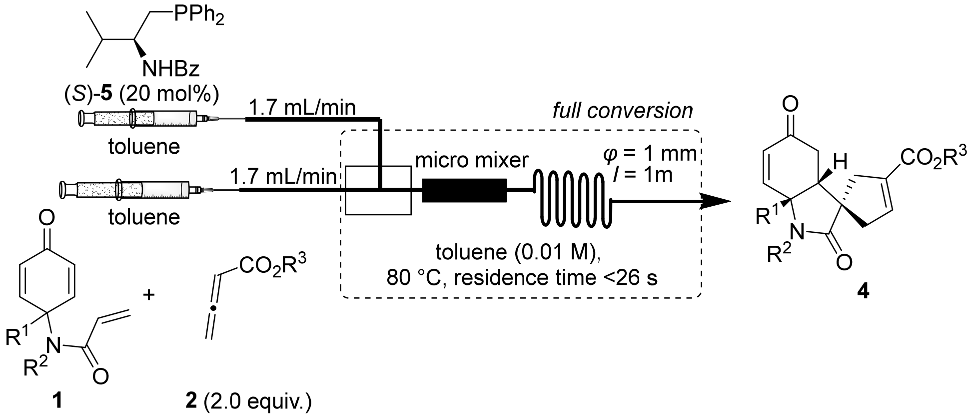


Fig. S1. The flow system of RC and [3+2] annulation.

As shown in Fig. S1, a flow microreactor system was dipped in oil bath to heat at 80 ˚C. A solution of **1** (0.03 mmol) and **2** (0.06 mmol, 2.0 equiv.) in degassed dry toluene (1.5 mL), and a solution of catalyst **5** (6 µmol, 2.3 mg, 20 mol%) in degassed dry toluene (1.5 mL) were introduced to the flow microreactor system by syringe pumps (flow rate: 1.7 mL/min). After the continuous-flow was kept within residence time, the reaction mixture was collected to a round bottom flask. The reaction mixture was passed through short silica pad with EtOAc. Removal of solvent under reduced pressure afforded a residue, which was purified by silica gel chromatography (*n*-hexane/EtOAc) to give the product **4**.

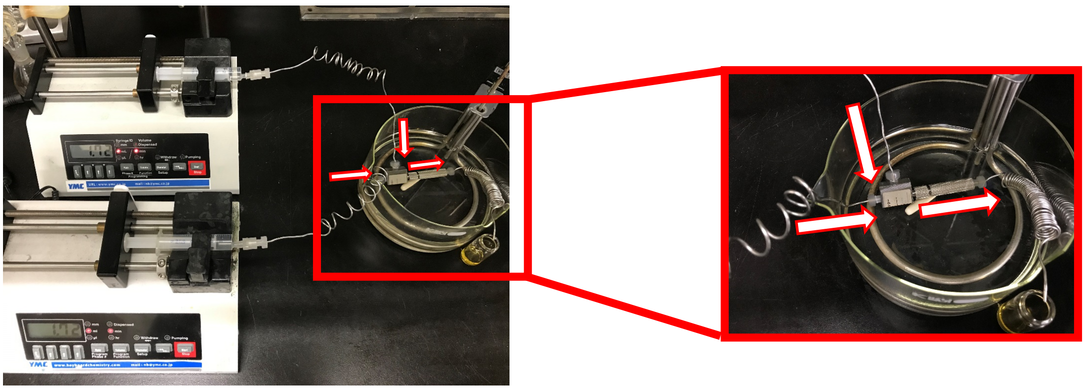
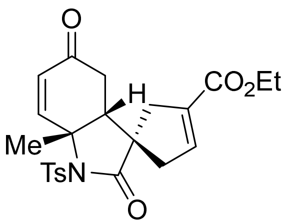
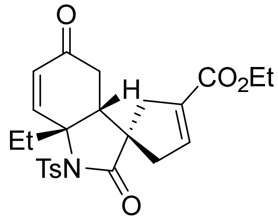


Fig. S2. Micro mixers: Comet X-01



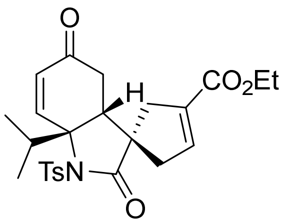
4a

4a: 76% yield (70% yield on a 1 mmol scale of **1a**); white solid; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 10.5 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.62 (t, *J* = 2.1 Hz, 1H), 6.15 (d, *J* = 10.5 Hz, 1H), 4.06-4.18 (m, 2H), 2.97 (dd, *J* = 17.4 Hz, 2.2 Hz, 1H), 2.77 (dd, *J* = 18.5, 7.6 Hz, 1H), 2.56-2.60 (m, 2H), 2.37-2.49 (m, 6H), 1.96 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 194.25, 176.36, 163.56, 148.22, 145.59, 140.30, 135.74, 134.12, 129.73, 128.72, 63.77, 60.61, 52.57, 49.02, 42.33, 37.62, 33.43, 27.13, 21.81, 14.27 (one carbon overlapped); HRMS (ESI) calcd for $C_{23}H_{25}NO_6SNa$: *m/z* ([M+Na$^+$]) 466.1295, found 466.1295; IR (KBr) 2963, 2926, 2854, 1738, 1719, 1710, 1686, 1678, 1362, 1304, 1263, 1172, 1086, 1015 cm^{-1}; $[\alpha]_D^{25}$ = -72.2 (*c* 1.0, $CHCl_3$ for 94% ee); HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 215 nm, tR = 24.0 min (major isomer) and 41.1 min (minor isomer).



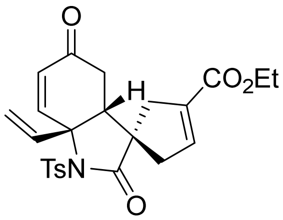
4b

4b: 68% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 10.5 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.62 (t, *J* = 2.3 Hz, 1H), 6.22 (d, *J* = 10.5 Hz, 1H), 4.06-4.14 (m, 2H), 3.04 (dd, *J* = 18.6, 2.3 Hz, 1H), 2.66-2.75 (m, 2H), 2.47-2.56 (m, 2H), 2.40-2.45 (m, 5H), 2.26 (dd, *J* = 18.6, 2.3 Hz, 1H), 2.11-2.18 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.51, 176.56, 163.41, 147.37, 145.54, 140.28, 135.11, 133.86, 129.56, 129.53, 128.78, 67.66, 60.49, 52.40, 43.83, 42.51, 37.64, 34.03, 30.87, 21.71, 14.16, 8.59 (one carbon overlapped); HRMS (ESI) calcd for $C_{24}H_{27}NO_6SNa$: *m/z* ($[M+Na]^+$) 480.1451, found 480.1447; IR (KBr) 2986, 2937, 1739, 1703, 1684, 1393, 1348, 1246, 1168 cm^{-1}; $[\alpha]_D^{20}$ = -74.8 (*c* 1.0, $CHCl_3$ for 92% ee); Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 225 nm, tR = 24.6 min (major isomer) and 41.4 min (minor isomer).



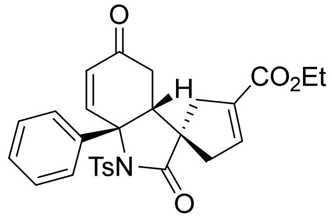
4c

4c: 92% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 10.8 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.54 (t, *J* = 2.3 Hz, 1H), 6.28 (d, *J* = 10.8 Hz, 1H), 3.99-4.06 (m, 2H), 2.99-3.04 (m, 2H), 2.56-2.68 (m, 2H), 2.47 (d, *J* = 18.3 Hz, 1H), 2.31-2.39 (m, 5H), 1.97-2.11 (m, 1H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.86, 176.47, 163.25, 146.73, 145.34, 140.63, 134.92, 133.49, 130.86, 129.59, 128.92, 71.21, 60.55, 52.86, 42.64, 40.32, 38.01, 36.01, 34.55, 21.78, 18.48, 16.91, 14.24; HRMS (ESI) calcd for $C_{25}H_{29}NO_6SNa$: *m/z* ($[M+Na]^+$) 494.1608, found 494.1603; IR (KBr) 2970, 1743, 1707, 1688, 1637, 1395, 1343, 1248, 1167 cm^{-1}; $[\alpha]_D^{20}$ = -113.2 (*c* 1.0, $CHCl_3$ for 96% ee); Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 250 nm, tR = 27.8 min (major isomer) and 45.9 min (minor isomer).



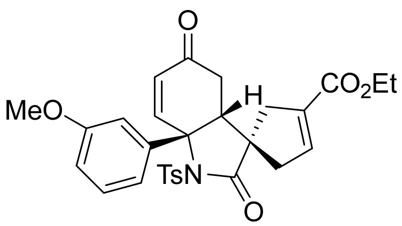
4d

4d: 61% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.34-7.38 (m, 3H), 6.63 (t, *J* = 2.3 Hz, 1H), 6.38 (d, *J* = 10.5 Hz, 1H), 6.10 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.47 (d, *J* = 10.1 Hz, 1H), 5.31 (d, *J* = 17.4 Hz, 1H), 4.10-4.17 (m, 2H), 2.98 (dd, *J* = 18.3 Hz, 2.3 Hz, 1H), 2.57-2.69 (m, 2H), 2.48-2.52 (m, 3H), 2.37-2.47 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.63, 176.10, 163.25, 145.75, 144.57, 140.42, 138.20, 135.54, 134.32, 131.27, 129.79, 128.84, 117.63, 66.91, 60.65, 52.65, 48.12, 42.52, 37.57, 32.63, 22.08, 14.28; HRMS (ESI) calcd for $C_{24}H_{25}NO_6SNa$: *m/z* ($[M+Na]^+$) 478.1295, found 478.1293; IR (KBr) 2986, 2943, 1736, 1702, 1679, 1640, 1350, 1267, 1243, 1168, 1109, 1085 cm^{-1}; $[\alpha]_D^{19}$ = -138.2(*c* 0.6, $CHCl_3$ for 91% ee); Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 225 nm, tR = 26.8 min. (major isomer) and 39.0 min min. (minor isomer).



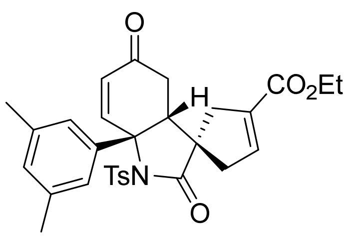
4e

4e: 78% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 10.5 Hz, 1H), 7.37-7.43 (m, 5H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.57-6.65 (m, 1H), 6.52 (d, *J* = 10.5 Hz, 1H), 4.11-4.17 (m, 2H), 3.00 (dd, *J* = 18.5, 2.3 Hz, 1H), 2.83-2.88 (m, 1H), 2.56 (s, 2H), 2.41-2.51 (m, 5H), 2.32 (dd, *J* = 18.5, 2.3 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.95, 176.90, 163.59, 145.75, 145.65, 140.59, 140.02, 135.23, 134.19, 131.15, 129.48, 129.24, 129.06, 128.84, 125.91, 68.93, 60.63, 53.16, 52.88, 42.85, 37.79, 33.43, 21.82, 14.27; HRMS (ESI) calcd for $C_{28}H_{27}NO_6SNa$: *m/z* ($[M+Na]^+$) 528.1451, found 528.1445; IR (KBr) 3063, 2980, 2938, 2378, 2346, 1738, 1711, 1683, 1360, 1265, 1244 cm^{-1}; $[\alpha]_D^{25}$ = -108.7 (*c* 1.0, $CHCl_3$ for 94% ee); Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 213 nm, tR = 55.0 min (major isomer) and 69.2 min (minor isomer).



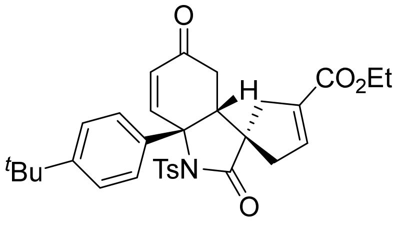
4f

4f: 54% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 10.5 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 6.89-6.97 (m, 3H), 6.61 (t, *J* = 2.1 Hz, 1H), 6.51 (d, *J* = 10.5 Hz, 1H), 4.10-4.16 (m, 2H), 3.82 (s, 3H), 3.00 (dd, *J* = 18.5, 2.2 Hz, 1H), 2.83-2.88 (m, 1H), 2.52-2.55 (m, 2H), 2.41-2.50 (m, 5H), 2.29-2.33 (m, 1H), 1.25 (t, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 195.02, 177.03, 163.72, 159.84, 145.75, 145.51, 142.23, 140.06, 135.19, 134.15, 131.12, 130.18, 129.51, 129.23, 118.51, 114.02, 111.78, 68.90, 60.65, 55.45, 53.13, 52.69, 42.83, 37.75, 33.48, 21.76, 14.29; HRMS (ESI) calcd for $C_{29}H_{29}NO_7SNa$: *m/z* ($[M+Na]^+$) 558.1557, found 558.1552; IR (KBr) 2932, 2374, 2347, 2307, 1743, 1706, 1688, 1544, 1509, 1364, 1264 cm^{-1}; $[\alpha]_D^{20}$ = +76.2 (*c* 1.0, $CHCl_3$ for 92% ee); Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 212 nm, tR = 22.5 min (minor isomer) and 26.4 min (major isomer).



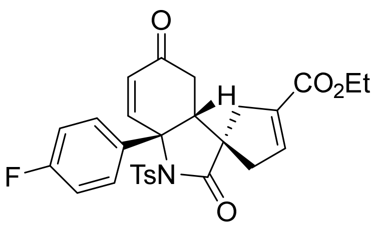
4g

4g: 75% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 10.3 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.01 (s, 1H), 6.89 (s, 2H), 6.64 (t, *J* = 2.1 Hz, 1H), 6.51 (d, *J* = 10.3 Hz, 1H), 4.12-4.17 (m, 2H), 3.02 (dd, *J* = 18.6, 2.1 Hz, 1H), 2.81-2.83 (m, 1H), 2.54-2.63 (m, 2H), 2.46-2.51 (m, 1H), 2.43-2.45 (m, 4H), 2.37 (dd, *J* = 18.6, 2.1 Hz, 1H), 2.30 (s, 6H), 1.26 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 195.13, 176.92, 163.47, 145.97, 145.52, 140.07, 138.49, 135.33, 135.18, 134.12, 130.93, 130.44, 129.31, 129.18, 123.68, 68.82, 60.65, 53.08, 52.57, 42.44, 37.81, 33.22, 21.72, 21.46, 14.20; HRMS (ESI) calcd for $C_{32}H_{35}NO_6SNa$: *m/z* ($[M+Na]^+$) 584.2077, found 584.2075; IR (KBr) 2986, 2931, 2367, 2312, 1744, 1717, 1708, 1688, 1638, 1599, 1507, 1362, 1245 cm^{-1}; $[\alpha]_D^{21}$ = -69.4 (*c* 1.0, $CHCl_3$ for 92% ee); Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 254 nm, tR = 16.5 min (major isomer) and 20.4 min (minor isomer).



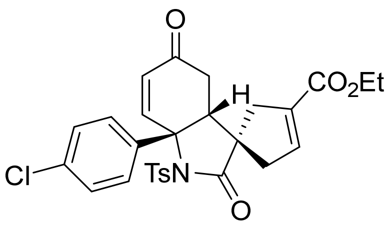
4h

4h: 70% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 10.5 Hz, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.27-7.31 (m, 4H), 6.62 (t, *J* = 2.1 Hz, 1H), 6.50 (d, *J* = 10.5 Hz, 1H), 4.11-4.17 (m, 2H), 3.01 (dd, *J* = 18.8, 2.1 Hz, 1H), 2.84-2.88 (m, 1H), 2.47-2.56 (m, 3H), 2.44 (s, 3H), 2.30-2.43 (m, 2H), 1.34 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 195.20, 176.83, 163.68, 151.79, 145.93, 145.51, 140.10, 137.28, 135.40, 134.04, 130.95, 129.43, 129.17, 125.94, 125.67, 68.77, 60.64, 53.15, 52.72, 42.74, 37.77, 34.72, 33.48, 31.36, 21.82, 14.29; HRMS (ESI) calcd for $C_{28}H_{27}NO_6SNa$: *m/z* ([M+Na]$^+$) 528.1451, found 528.1445; IR (KBr) 2970, 2378, 2312, 1742, 1712, 1687, 1506, 1362, 1244, 1166 cm^{-1}; $[\alpha]_D^{25}$ = -69.5 (*c* 1.0, $CHCl_3$ for 98% ee); Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 254 nm, tR = 18.5 min (minor isomer) and 20.5 min (major isomer).



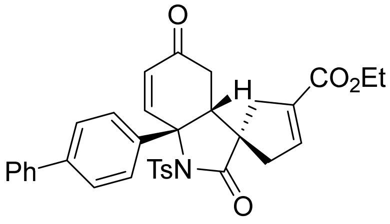
4i

4i: 81% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 10.5 Hz, 1H), 7.37-7.40 (m, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.10-7.14 (m, 2H), 6.62 (t, *J* = 2.3 Hz, 1H), 6.52 (d, *J* = 10.5 Hz, 1H), 4.11-4.17 (m, 2H), 3.01 (dd, *J* = 18.8, 2.3 Hz, 1H), 2.79-2.84 (m, 1H), 2.53-2.56 (m, 2H), 2.44-2.46 (m, 5H), 2.34 (dd, *J* = 18.8, 2.3 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (175 MHz, $CDCl_3$) δ 194.91, 177.15, 163.94, 162.98 ($J_{C\text{-}F}$ = 284 Hz), 146.20, 145.50, 140.24, 136.68 (d, $J_{C\text{-}F}$ = 2.6 Hz) , 135.28, 134.41, 131.57, 129.83, 129.43, 128.08 (d, $J_{C\text{-}F}$ = 9.2 Hz), 116.35 (d, $J_{C\text{-}F}$ = 20.8 Hz), 68.62, 60.95, 53.29, 53.16, 43.03, 38.03, 33.50, 22.12, 14.55; ^{19}F-NMR (565 MHz, $CDCl_3$) δ -113.62; HRMS (ESI) calcd for $C_{28}H_{26}FNO_6SNa$: *m/z* ([M+Na]$^+$) 546.1357, found 546.1352; IR (KBr) 3363, 2925, 2345, 1712, 1686, 1509, 1361, 1247, 1168, 1086, 866, 760, 665, 577, 560, 546 cm^{-1}; $[\alpha]_D^{22}$ = -117.83 (*c* 0.6, $CHCl_3$ for 87% ee); Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 254 nm, tR = 15.1 min. (minor isomer) and 22.3 min (major isomer).



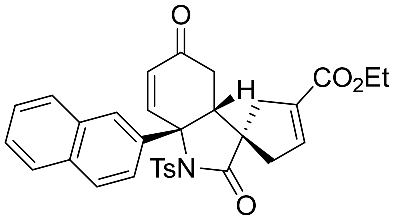
4j

4j: 85% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 10.5 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.32-7.36 (m, 4H), 6.62 (t, *J* = 2.3 Hz, 1H), 6.53 (d, *J* = 10.5 Hz, 1H), 4.11-4.16 (m, 2H), 3.01 (dd, *J* = 18.8, 2.3 Hz, 1H), 2.77-2.81 (m, 1H), 2.52-2.55 (m, 2H), 2.41-2.48 (m, 5H), 2.34 (dd, *J* = 18.8, 2.3 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (175 MHz, $CDCl_3$) δ 194.48, 176.62, 163.45, 145.92, 144.86, 139.88, 139.17, 134.87, 134.85, 131.38, 129.53, 129.22, 129.12, 127.23, 68.29, 60.62, 52.97, 52.72, 42.75, 37.70, 33.15, 21.79, 14.22 (one carbon overlapped); HRMS (ESI) calcd for $C_{28}H_{26}ClNO_6SNa$: *m/z* ($[M+Na]^+$) 562.1062, found 562.1052; IR (KBr) 2961, 2926, 2854, 1739, 1712, 1692, 1493, 1363, 1246, 1167, 1083, 664, 504, 473 cm^{-1}; $[\alpha]_D^{22}$ = -125.8 (*c* 0.45, $CHCl_3$ for 87% ee); Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 230 nm, tR = 15.0 min (minor isomer) and 23.7 min (major isomer).



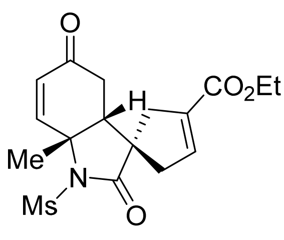
4k

4k: 58% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 10.5 Hz, 1H), 7.59-7.67 (m, 4H), 7.38-7.52 (m, 5H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.63 (t, *J* = 2.3 Hz, 1H), 6.55 (d, *J* = 10.5 Hz, 1H), 4.10-4.18 (m, 2H), 3.04 (dd, *J* = 18.8, 2.3 Hz, 1H), 2.87-2.92 (m, 1H), 2.44-2.61 (m, 7H), 2.36 (dd, *J* = 18.8, 2.3 Hz, 1H) 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 194.94, 176.90, 163.60, 145.82, 145.56, 141.74, 140.05, 140.02, 139.50, 135.18, 134.20, 131.24, 129.54, 129.27, 129.03, 127.93, 127.72, 127.22, 126.36, 68.81, 60.67, 53.16, 52.85, 42.87, 37.81, 33.46, 21.86, 14.31; HRMS (ESI) calcd for $C_{34}H_{31}NO_6SNa$: *m/z* ($[M+Na]^+$) 604.1764, found 604.1760; IR (KBr) 2921, 2367, 2306, 1746, 1720, 1711, 1687, 1510, 1487, 1362, 1246, 1166 cm^{-1}; $[\alpha]_D^{21}$ = -34.0 (*c* 1.0, $CHCl_3$ for 93% ee) ; Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 200 nm tR = 43.5 min (major isomer) and 50.7 min (minor isomer).



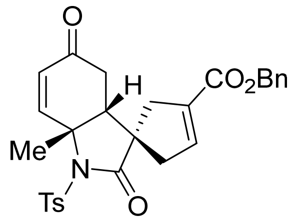
4l

4l: 60% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88-7.92 (m, 2H), 7.75-7.82 (m, 5H), 7.54-7.60 (m, 2H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 6.59-6.63 (m, 2H), 4.02-4.13 (m, 2H), 3.01-3.09 (m, 1H), 2.85-2.89 (m, 1H), 2.49-2.65 (m, 2H), 2.32-2.45 (m, 5H), 2.25-2.31 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H) (two carbons overlapped); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.00, 177.31, 163.67, 145.79, 145.58, 140.06, 137.62, 135.21, 134.20, 133.13, 132.84, 131.38, 129.48, 129.32, 128.42, 127.78, 127.11, 125.55, 123.01, 69.14, 60.65, 53.19, 52.47, 42.90, 37.90, 33.34, 21.83, 14.28; HRMS (ESI) calcd for $C_{32}H_{29}NO_6SNa$: *m/z* ($[M+Na]^+$) 555.17, found 555.65; IR (KBr) 2926, 2374, 2310, 1745, 1712, 1688, 1364, 1244, 1167, 811, 668 cm^1; $[\alpha]_D^{25}$ = -74.5 (*c* 1.0, $CHCl_3$ for 96% ee); Daicel Chiralpak IE column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 230 nm, tR = 53.7 min (minor isomer) and 75.7 min (major isomer).



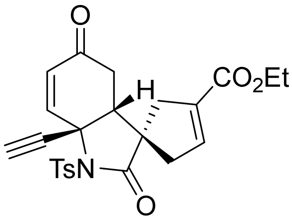
4m

4m: 59% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 10.5 Hz, 1H), 6.71 (t, *J* = 2.3 Hz, 1H), 6.12 (d, *J* = 10.5 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.37 (s, 3H), 3.11 (dd, *J* = 18.8, 2.3 Hz, 1H), 2.76-2.85 (m, 1H), 2.59-2.68 (m, 4H), 2.51 (dd, *J* = 18.8, 2.3 Hz, 1H), 1.91 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.06, 177.71, 163.59, 147.68, 140.40, 134.09, 128.85, 63.82, 60.76, 52.76, 49.08, 43.07, 42.42, 38.01, 33.33, 27.18, 14.30; HRMS (ESI) calcd for $C_{17}H_{21}NO_6SNa$: *m/z* ($[M+Na]^+$) 390.0982, found 390.0980; IR (KBr) 2931, 2855, 2361, 2345, 2318, 1748, 1717, 1705, 1689, 1681, 1508, 1257, 1131, 969 cm^{-1}; $[\alpha]_D^{21}$ = -176.3 (*c* 1.0, $CHCl_3$ for 88% ee); Daicel Chiralpak IB column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 245 nm, tR = 11.3 min (major isomer) and 14.0 min (minor isomer).



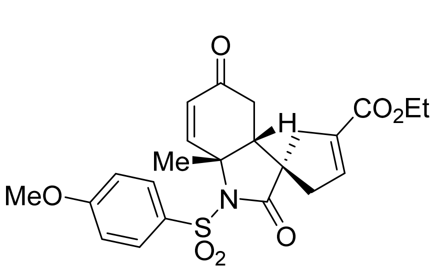
4n

4n: 64% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.48 (dd, *J* = 10.5, 1.8 Hz, 1H), 7.30-7.37 (m, 7H), 6.67 (t, *J* = 2.3 Hz, 1H), 6.14 (d, *J* = 10.5 Hz, 1H), 5.10-5.01 (m, 2H), 2.99 (dd, *J* = 20.4, 2.3 Hz, 1H), 2.77 (dd, *J* = 18.5, 7.6 Hz, 1H), 2.55-2.59 (m, 2H), 2.47-2.52 (m, 1H), 2.37-2.44 (m, 5H), 1.96 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.19, 176.38, 163.40, 148.16, 145.62, 141.03, 135.91, 135.82, 135.71, 135.65, 133.70, 129.74, 128.72, 128.61, 128.27, 66.40, 63.77, 52.55, 49.09, 42.48, 37.62, 33.43, 27.17, 21.82; HRMS (ESI) calcd for $C_{28}H_{27}NO_6SNa$: *m/z* ($[M+Na]^+$) 528.1451, found 528.1447; IR (KBr) 2959, 2373, 2340, 2312, 1746, 1716, 1707, 1687, 1679, 1544, 1509, 1362, 1246, 1173, 1083 cm^{-1}; $[\alpha]_D^{20}$ = -81.6 (*c* 1.0, $CHCl_3$ for 94% ee); Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, flow rate 1.0 mL/min, 217 nm: 16.8 min. (major isomer) and 28.8 min (minor isomer).



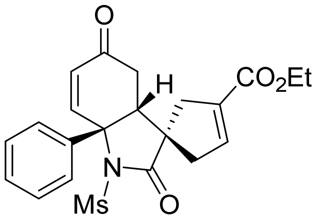
4o

4o: 45% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 2H), 7.45-7.48 (m, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.59 (t, *J* = 2.1 Hz, 1H), 6.23 (d, *J* = 10.5 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.00-3.04 (m, 1H), 2.82-2.94 (m, 3H), 2.52-2.69 (m, 3H), 2.42-2.48 (m, 4H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 193.77, 175.57, 163.52, 145.85, 143.94, 139.50, 135.03, 134.31, 129.65, 129.24, 129.04, 81.00, 76.42, 60.71, 57.32, 53.33, 49.82, 42.98, 37.04, 34.66, 21.86, 14.28; HRMS (ESI) calcd for $C_{24}H_{23}NO_6SNa$: *m/z* ($[M+Na]^+$) 476.1138, found 476.1135; IR (KBr) 2373, 2312, 1747, 1708, 1690, 1544, 1508, 1362, 1249, 1173 cm^{-1}; $[\alpha]_D^{20}$ = -15.4 (*c* 1.0, $CHCl_3$ for 92% ee); Daicel Chiralpak IE column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 212 nm, tR = 35.8 min. (minor isomer) and 57.8 min(major isomer).



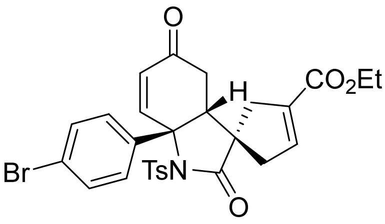
4p

4p: 54% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.2 Hz, 2H), 7.49 (dd, *J* = 10.8, 1.4 Hz, 1H), 7.00 (d, *J* = 9.2 Hz, 2H), 6.63 (t, *J* = 2.1 Hz, 1H), 6.14 (d, J = 10.8 Hz, 1H), 4.09-4.15 (m, 2H), 3.89 (s, 3H), 2.93-3.01 (m, *J* = 17.9 Hz, 1H), 2.77 (dd, *J* = 18.5, 7.6 Hz, 1H), 2.52-2.60 (m, 2H), 2.38-2.49 (m, 3H), 1.95 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.28, 176.36, 164.13, 163.48, 148.35, 140.31, 134.30, 131.12, 128.70, 114.24, 63.66, 60.61, 55.85, 52.58, 49.09, 42.34, 37.64, 33.44, 27.15, 14.34 (one carbon overlapped); HRMS (ESI) calcd for $C_{23}H_{25}NO_7SNa$: *m/z* ($[M+Na]^+$) 482.1244, found 482.1239; IR (KBr) 2980, 2373, 2312, 1744, 1710, 1685, 1594, 1497, 1362, 1262, 1163, 1088, 1018, 675 cm^{-1}; $[\alpha]_D^{19}$ = -83.1 (*c* 1.0, $CHCl_3$ for 92% ee); Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 240 nm, tR = 40.9 min, (major isomer) and 76.3 min (minor isomer).



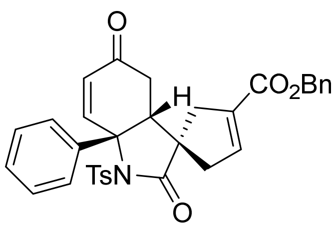
4q

4q: 89% yield; white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39-7.47 (m, 6H), 6.69-6.72 (m, 1H), 6.51 (d, *J* = 10.5 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.33 (s, 3H), 3.13-3.19 (m, 1H), 2.89-2.91 (m, 1H), 2.67-2.77 (m, 2H), 2.45-2.53 (m, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 194.66, 178.21, 163.60, 144.79, 140.45, 140.16, 134.17, 131.50, 129.31, 128.96, 125.22, 68.75, 60.79, 53.44, 52.88, 42.95, 42.83, 38.22, 33.06, 14.32; HRMS (ESI) calcd for $C_{22}H_{23}NO_6SNa$: *m/z* ($[M+Na]^+$) 452.1138, found 452.1135; IR (KBr) 2931, 2367, 2345, 2318, 1744, 1716, 1706, 1688, 1680, 1648, 1543, 1509, 1423, 1360, 1248, 1165 cm^{-1}; $[\alpha]_D^{20}$ = -87.0 (*c* 1.0, $CHCl_3$ for 88% ee); Daicel Chiralpak IB column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 254 nm, tR = 15.7 min (major isomer) and 19.3 min (minor isomer).



4r

4r: 76% yield; white yellowish solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.62 (dd, *J* = 10.5, 1.4 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.61 (t, *J* = 2.3 Hz, 1H), 6.53 (d, *J* = 10.5 Hz, 1H), 4.11-4.16 (m, 2H), 3.01 (dd, *J* = 18.5, 2.3 Hz, 1H), 2.77-2.79 (m, 1H), 2.52-2.55 (m, 2H), 2.43-2.45 (m, 5H), 2.34 (dd, *J* = 18.5, 2.3 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 194.51, 176.69, 163.59, 146.00, 144.87, 139.92, 139.86, 135.01, 134.15, 132.26, 131.48, 129.61, 129.21, 127.60, 123.08, 68.42, 60.60, 53.08, 52.83, 42.86, 37.87, 33.24, 21.84, 14.28; HRMS (ESI) calcd for $C_{28}H_{26}BrNO_6SNa$: *m/z* ($[M+Na]^+$) 606.0556, found 606.0553; IR (KBr) 2367, 2312, 1745, 1715, 1705, 1687, 1543, 1510, 1491, 1363, 1245 cm^{-1}; $[\alpha]_D^{20}$ = -105.5 (*c* 1.0, $CHCl_3$ for 86% ee); Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 245 nm, tR = 13.9 min (minor isomer) and 21.9 min (major isomer).



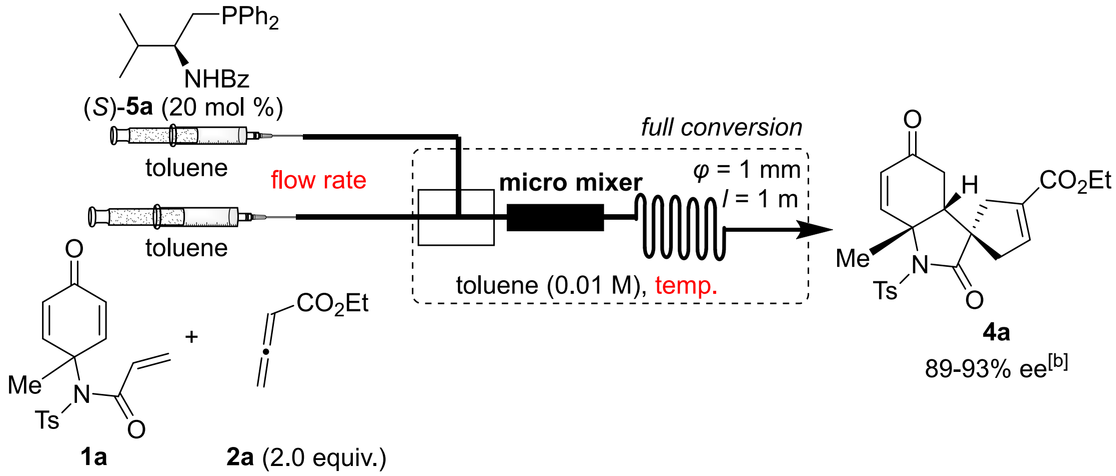
4s

4s: 73% yield; orange solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 10.5 Hz, 1H), 7.29-7.41 (m, 12H), 6.66 (s, 1H), 6.51 (d, J = 10.5 Hz, 1H), 5.12 (m, 2H), 2.97-3.05 (m, 1H), 2.82-2.88 (m, 1H), 2.55-2.60 (m, 2H), 2.40-2.51 (m, 5H), 2.27-2.38 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.91, 176.83, 163.36, 145.78, 145.61, 140.74, 140.60, 135.83, 135.18, 134.87, 133.80, 131.15, 129.51, 129.22, 129.08, 128.85, 128.62, 128.29, 125.90, 68.94, 66.42, 53.12, 52.92, 42.98, 37.77, 33.47, 21.84; HRMS (ESI) calcd for $C_{33}H_{29}NO_6SNa$: *m/z* ($[M+Na]^+$) 590.1608, found 590.1603; IR (KBr) 2964, 2921, 2373, 2312, 1744, 1598, 1489, 1460, 1389, 1363, 1246, 1164, 1081 cm^{-1}; $[\alpha]_D^{20}$ = -60.9 (*c* 1.0, $CHCl_3$ for 90% ee); Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 217 nm, 23.7 min, (minor isomer) and 31.2 min (major isomer); (*R*,*R*,*R*)-**4s** was previously synthesized and characterized.[3]

Gaussian process regression with GPy

Gaussian process regression was carried out based on experimental data (**Table S4-S6**) with GPy.

Table S4. Screening of flow rate and temperature (2.0 equiv. of **2a** was used).[a]



entry	flow rate (mL/min)	temp. (°C)	NMR yield (%)[c]
1	1.0	90	49
2	1.5	80	72
3	2.0	70	58
4	2.5	60	55
5	3.0	100	43

[a] Reaction conditions: **1a** (0.03 mmol), **2a** (2.0 equiv.) and catalyst (S)-**5a** (20 mol%), in dry toluene (3 mL). [b] Enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak ID). [c] 1,3,5-Trimethoxybenzene was used as an internal standard.

(A)

```
import GPy
import numpy as np
from matplotlib import pyplot as plt
import warnings
warnings.filterwarnings('ignore')
```

```
#flow rate, temp
X = np.array([[1.0, 90],
              [1.5, 80],
              [2.0, 70],
              [2.5, 60],
              [3.0, 100]])
    #yield
Y = np.array([49, 72, 58, 55, 43])[:, np.newaxis]
```

```
#standardization
X_std = np.copy(X)
for i in range(X.shape[1]):
    X_std[:, i:i+1] = (X[:, i:i+1] - np.mean(X[:, i:i+1]))/np.sqrt(np.var(X[:, i:i+1]))
```

```
#GPR and visualization
kernel = GPy.kern.RBF(input_dim=2)
model = GPy.models.GPRegression(X_std, Y, kernel=kernel, normalizer=True,
noise_var=0.001)
model.optimize(max_iters=3, messages=True)
model.plot()
print(model)

x0_list_law = [1.0, 1.5, 2.0, 2.5, 3.0]
x1_list_law = [60, 70, 80, 90, 100]
x0_list_std = []
x1_list_std = []
x0_list_std = (np.array(x0_list_law) - np.mean(X[:,0:1])) / np.sqrt(np.var(X[:,0:1]))
x1_list_std = (np.array(x1_list_law) - np.mean(X[:,1:2])) / np.sqrt(np.var(X[:,1:2]))
plt.xticks(x0_list_std, x0_list_law)
plt.yticks(x1_list_std, x1_list_law)
plt.xlabel("flow rate [mL/min]", fontsize=15)
plt.ylabel("temperature [℃]", fontsize=15)
plt.tick_params(labelsize=15)
plt.legend(bbox_to_anchor=(1,0.5), fontsize=15)


model.plot(fixed_inputs=[(1, 0)], plot_data=False, lower=25, upper=75)
x0_list_law = [0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0]
x0_list_std = []
x0_list_std = (np.array(x0_list_law) - np.mean(X[:,0:1])) / np.sqrt(np.var(X[:,0:1]))
x0_line = 1.7
x0_line_std = (x0_line - np.mean(X[:,0:1])) / np.sqrt(np.var(X[:,0:1]))
plt.plot([x0_line_std, x0_line_std], [30, 80], color='r', linewidth=1,
linestyle='-', label=x0_line)
plt.xticks(x0_list_std, x0_list_law)
plt.xlabel("flow rate [mL/min]", fontsize=15)
plt.ylabel("yield [%]", fontsize=15)
plt.tick_params(labelsize=15)
plt.legend(("Mean","1.7 mL/min", "Confidence"), fontsize=15)
model.plot(fixed_inputs=[(0, -0.7)], plot_data=False, lower=25, upper=75)
x1_list_law = [50, 60, 70, 80, 90, 100, 110]
x1_list_std = []
x1_list_std = (np.array(x1_list_law) - np.mean(X[:,1:2])) / np.sqrt(np.var(X[:,1:2]))
plt.xticks(x1_list_std, x1_list_law)
x1_line = 77
x1_line_std = (x1_line - np.mean(X[:,1:2])) / np.sqrt(np.var(X[:,1:2]))
plt.plot([x1_line_std, x1_line_std], [30, 80], color='r', linewidth=1,
linestyle='-', label=x1_line)
plt.xlabel("temperature [℃]", fontsize=15)
plt.ylabel("yield [%]", fontsize=15)
plt.tick_params(labelsize=15)
plt.legend(("Mean","77 ℃", "Confidence"),loc="lower right",borderaxespad=0.2, fontsize=15)
```

Optimizer: L-BFGS-B

Parameters:

GP_regression. | value | constraints |

priors

rbf.variance | 1.1158823807134526 | +ve |

rbf.lengthscale | 0.4336905033416461 | +ve |

Gaussian_noise.variance | 0.001002572382707438 | +ve |

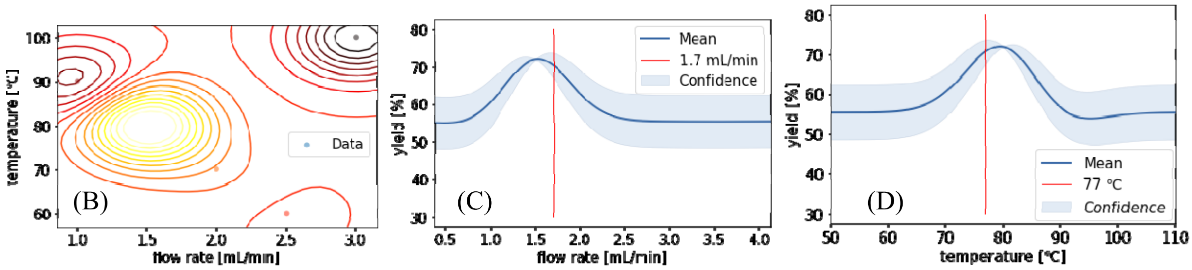
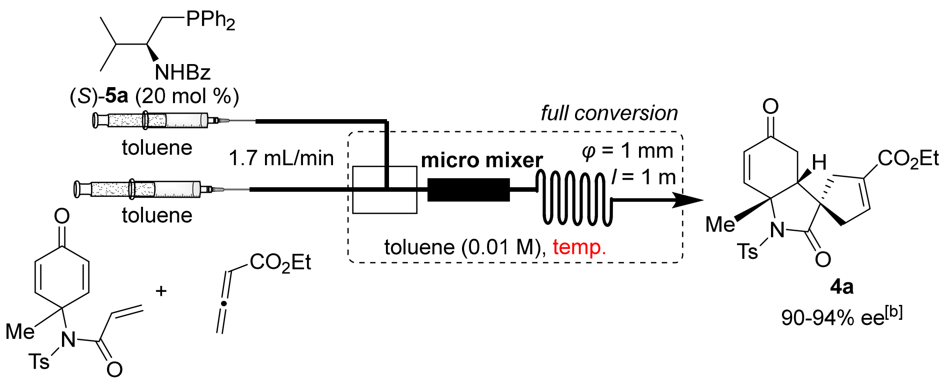


Fig. S3. Gaussian process regression GPy for Table S4. (A) Source code of GPR; (B) Estimated yield from Table S4 (entries 1-5); (C) Predicted yield for flow rates in the yellow ring in Fig. S3B; (D) Predicted yield for temperatures in the yellow ring in Fig. S3B.

Table S5. Screening of quantity of **2a** and temperature (flow rate: 1.7 mL/min).[a]



1a **2a** (X equiv.)

entry	**2a** (equiv.)	temp. (°C)	NMR yield (%)[c]
1	1.0	80	45
2	1.5	100	51
3	2.0	90	58
4	3.0	70	50
5	4.0	60	48

[a] Reaction conditions: **1a** (0.03 mmol), **2a** and catalyst (S)-**5a** (20 mol%), in dry toluene (3 mL). [b] Enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak ID). [c] 1,3,5-Trimethoxybenzene was used as an internal standard.

(A)

```
import GPy
import numpy as np
from matplotlib import pyplot as plt
import warnings
warnings.filterwarnings('ignore')
```

```
#eq, temp
X = np.array([[1.0, 80],
              [1.5, 100],
              [2.0, 90],
              [3.0, 70],
              [4.0, 60]])
#yield
Y = np.array([45, 51, 58, 50, 48])[:, np.newaxis]
```

```
#standardization
X_std = np.copy(X)
for i in range(X.shape[1]):
    X_std[:, i:i+1] = (X[:, i:i+1] - np.mean(X[:, i:i+1]))/np.sqrt(np.var(X[:, i:i+1]))
```

```
#GPR and visualization
kernel = GPy.kern.RBF(input_dim=2)
model = GPy.models.GPRegression(X_std, Y, kernel=kernel, normalizer=True,
noise_var=0.001)
model.optimize(max_iters=3)
model.plot()
x0_list_law = [1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0]
x1_list_law = [60, 70, 80, 90, 100]
x0_list_std = []
x1_list_std = []

x0_list_std = (np.array(x0_list_law) - np.mean(X[:,0:1])) / np.sqrt(np.var(X[:,0:1]))
x1_list_std = (np.array(x1_list_law) - np.mean(X[:,1:2])) / np.sqrt(np.var(X[:,1:2]))

plt.xticks(x0_list_std, x0_list_law)
plt.yticks(x1_list_std, x1_list_law)
plt.xlabel("2a [equiv.]", fontsize=15)
plt.ylabel("temperature [℃]", fontsize=15)
plt.tick_params(labelsize=15)
plt.legend(fontsize=15)
model.plot(fixed_inputs=[(1, 0.75)], plot_data=False, lower=25, upper=75)
x0_list_law = [0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5]
x0_list_std = []
x0_list_std = (np.array(x0_list_law) - np.mean(X[:,0:1])) / np.sqrt(np.var(X[:,0:1]))
x0_line = 1.7
plt.xticks(x0_list_std, x0_list_law)
x0_line = 2.0
x0_line_std = (x0_line - np.mean(X[:,0:1])) / np.sqrt(np.var(X[:,0:1]))
plt.plot([x0_line_std, x0_line_std], [30, 80], color='r', linewidth=1,
linestyle='-', label=x0_line)
plt.xlabel("2a [equiv.]", fontsize=15)
plt.ylabel("yield [%]", fontsize=15)
plt.tick_params(labelsize=15)
plt.legend( ("Mean","2.0 equiv.", "Confidence"), fontsize=15)
model.plot(fixed_inputs=[(0, -0.2)], plot_data=False, lower=25, upper=75)
x1_list_law = [50, 60, 70, 80, 90, 100, 110]
x1_list_std = []
x1_list_std = (np.array(x1_list_law) - np.mean(X[:,1:2])) / np.sqrt(np.var(X[:,1:2]))
plt.xticks(x1_list_std, x1_list_law)
x1_line = 90
x1_line_std = (x1_line - np.mean(X[:,1:2])) / np.sqrt(np.var(X[:,1:2]))
plt.plot([x1_line_std, x1_line_std], [30, 80], color='r', linewidth=1,
linestyle='-', label=x1_line)
plt.xlabel("temperature [℃]", fontsize=15)
plt.ylabel("yield [%]", fontsize=15)
plt.tick_params(labelsize=15)
plt.legend( ("Mean","90℃", "Confidence"), fontsize=15)
```

Optimizer: L-BFGS-B

Parameters:

GP_regression.	value	constraints
priors		
rbf.variance	1.100572205236196	+ve
rbf.lengthscale	0.3747925937891553	+ve
Gaussian_noise.variance	0.001002216349538893	+ve

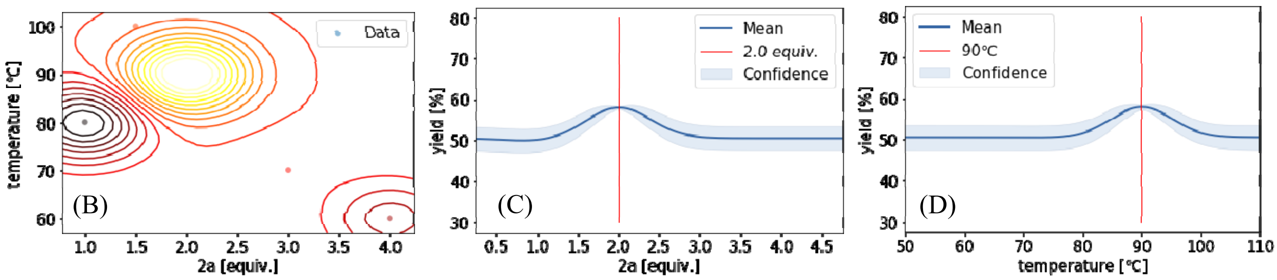
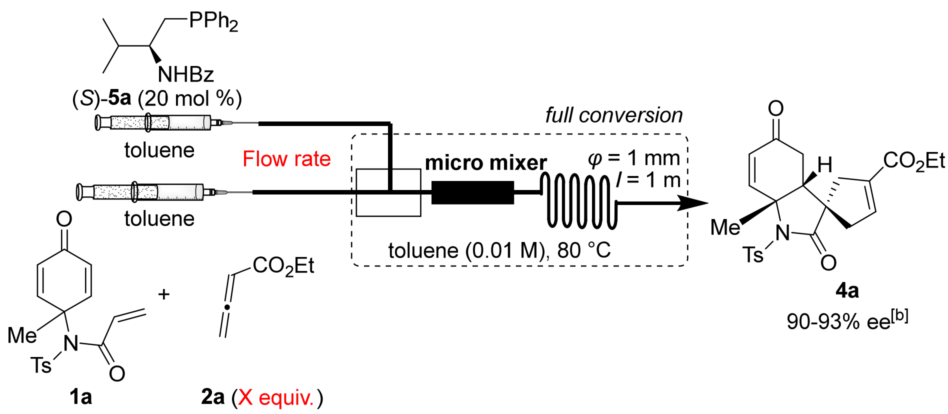


Fig. S4. Gaussian process regression GPy for Table S5. (A) Source code of GPR; (B) Estimated yield from Table S5 (entries 1-5); (C) Predicted yield for equivalents of **2a** in the yellow ring in Fig. S4B; (D) Predicted yield for temperatures in the yellow ring in Fig. S4B

Table S6. Screening of flow rate and quantity of **2a** (at 80 °C).[a]



entry	Flow rate (mL/min)	**2a** (equiv.)	NMR yield (%)[c]
1	1.0	3.0	63
2	1.5	2.0	64
3	2.0	4.0	62
4	2.5	3.5	59
5	3.0	2.5	50

[a] Reaction conditions: **1a** (0.03 mmol), **2a** and catalyst (S)-**5a** (20 mol%), in dry toluene (3 mL). [b] Enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak ID). [c] 1,3,5-Trimethoxybenzene was used as an internal standard.

(A)

```
import GPy
import numpy as np
from matplotlib import pyplot as plt
import warnings
warnings.filterwarnings('ignore')
```

```
#flow rate, eq
X = np.array([[1.0, 3],
              [1.5, 2],
              [2.0, 4],
              [2.5, 3.5],
              [3.0, 2.5]])
#yield
Y = np.array([63, 64, 62, 59, 50])[:, np.newaxis]
```

```
#standardization
X_std = np.copy(X)
for i in range(X.shape[1]):
    X_std[:, i:i+1] = (X[:, i:i+1] - np.mean(X[:, i:i+1]))/np.sqrt(np.var(X[:, i:i+1]))
```

```
#GPR and visualization
kernel = GPy.kern.RBF(input_dim=2)
model = GPy.models.GPRegression(X_std, Y, kernel=kernel, normalizer=True,
noise_var=0.001)
model.optimize(max_iters=3, messages=True)
model.plot()
print(model)
x0_list_law = [1.0, 1.5, 2.0, 2.5, 3.0]
x1_list_law = [2, 2.5, 3, 3.5, 4]
x0_list_std = []
x1_list_std = []

x0_list_std = (np.array(x0_list_law) - np.mean(X[:,0:1])) / np.sqrt(np.var(X[:,0:1]))
x1_list_std = (np.array(x1_list_law) - np.mean(X[:,1:2])) / np.sqrt(np.var(X[:,1:2]))

plt.xticks(x0_list_std, x0_list_law)
plt.yticks(x1_list_std, x1_list_law)
plt.xlabel("flow rate [mL/min]", fontsize=15)
plt.ylabel("2a [equiv.]", fontsize=15)
plt.tick_params(labelsize=15)
plt.legend(fontsize=15)

model.plot(fixed_inputs=[(1, 0.3)], plot_data=False, lower=25, upper=75)
x0_list_law = [0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5]
x0_list_std = []
x0_list_std = (np.array(x0_list_law) - np.mean(X[:,0:1])) / np.sqrt(np.var(X[:,0:1]))
plt.xticks(x0_list_std, x0_list_law)
x0_line = 1.7
x0_line_std = (x0_line - np.mean(X[:,0:1])) / np.sqrt(np.var(X[:,0:1]))
plt.plot([x0_line_std, x0_line_std], [50, 70], color='r', linewidth=1,
linestyle='-', label=x0_line)
plt.xlabel("flow rate [mL/min]", fontsize=15)
plt.ylabel("yield [%]", fontsize=15)
plt.tick_params(labelsize=15)
plt.legend( ("Mean","1.7 mL/min", "Confidence"), fontsize=15)
```

```
model.plot(fixed_inputs=[(0, -1)], plot_data=False, lower=25, upper=75)
x1_list_law = [2.0, 2.5, 3.0, 3.5, 4.0, 4.5]
x1_list_std = []
x1_list_std = (np.array(x1_list_law) - np.mean(X[:,1:2])) / np.sqrt(np.var(X[:,1:2]))
plt.xticks(x1_list_std, x1_list_law)
x1_line = 2
x1_line_std = (x1_line - np.mean(X[:,1:2])) / np.sqrt(np.var(X[:,1:2]))
plt.plot([x1_line_std, x1_line_std], [50, 70], color='r', linewidth=1,
linestyle='-', label=x1_line)
plt.xlabel("2a [equiv.]", fontsize=15)
plt.ylabel("yield [%]", fontsize=15)
plt.tick_params(labelsize=15)
plt.legend( ("Mean","2.0 equiv.", "Confidence"), fontsize=15)
```

Optimizer: L-BFGS-B

Parameters:

GP_regression.	value	constraints
priors		
rbf.variance	1.046759848795677	+ve
rbf.lengthscale	1.1471099131952978	+ve
Gaussian_noise.variance	0.0009988100555326674	+ve

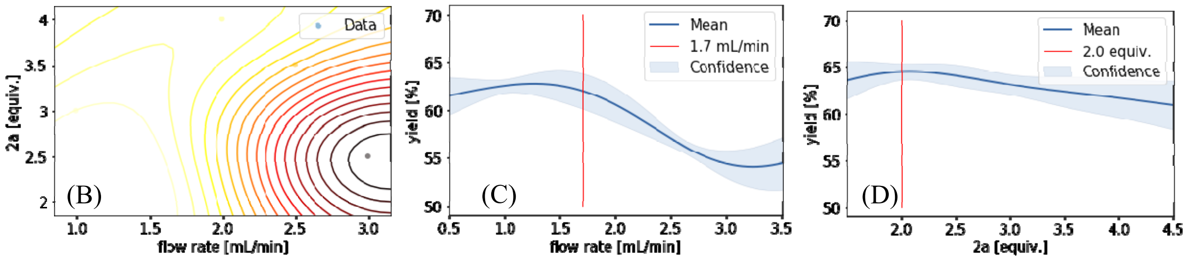


Fig. S5. Gaussian process regression GPy for Table S6. (A) Source code of GPR; (B) Estimated yield from Table S6 (entries 1-5); (C) Predicted yield for flow rates in the yellow ring in Fig. S5B; (D) Predicted yield for equivalents of **2a** in the yellow ring in Fig. S5B

X-ray structure of 4e

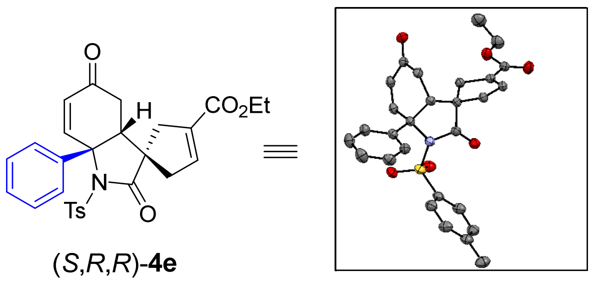


Fig. S6. ORTEP drawing of compound (*S,R,R*)-**4e** with ellipsoids at 50% probability (H atoms are omitted for clarity).

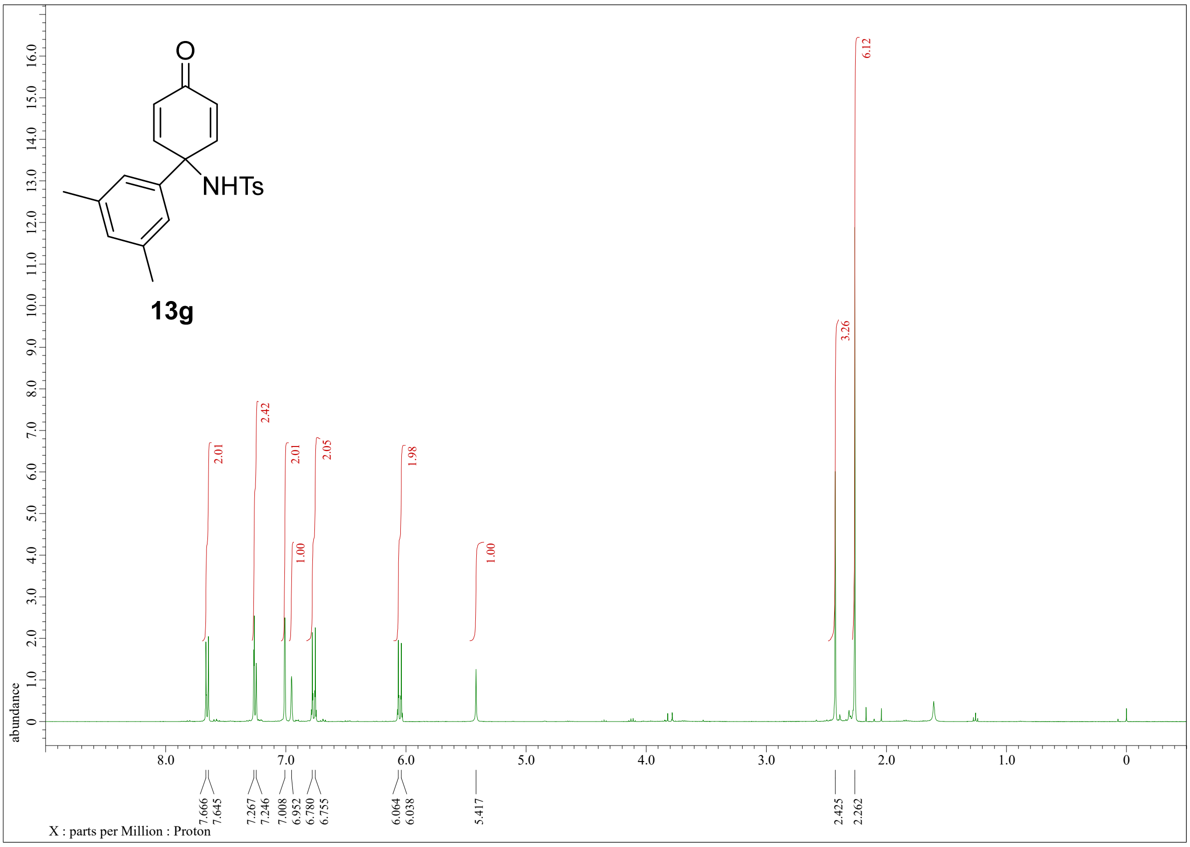
References

1. K. Kishi, F. A. Arteaga, S. Takizawa and H. Sasai, *Chem. Commun.,* 2017, **53**, 7724–7727.

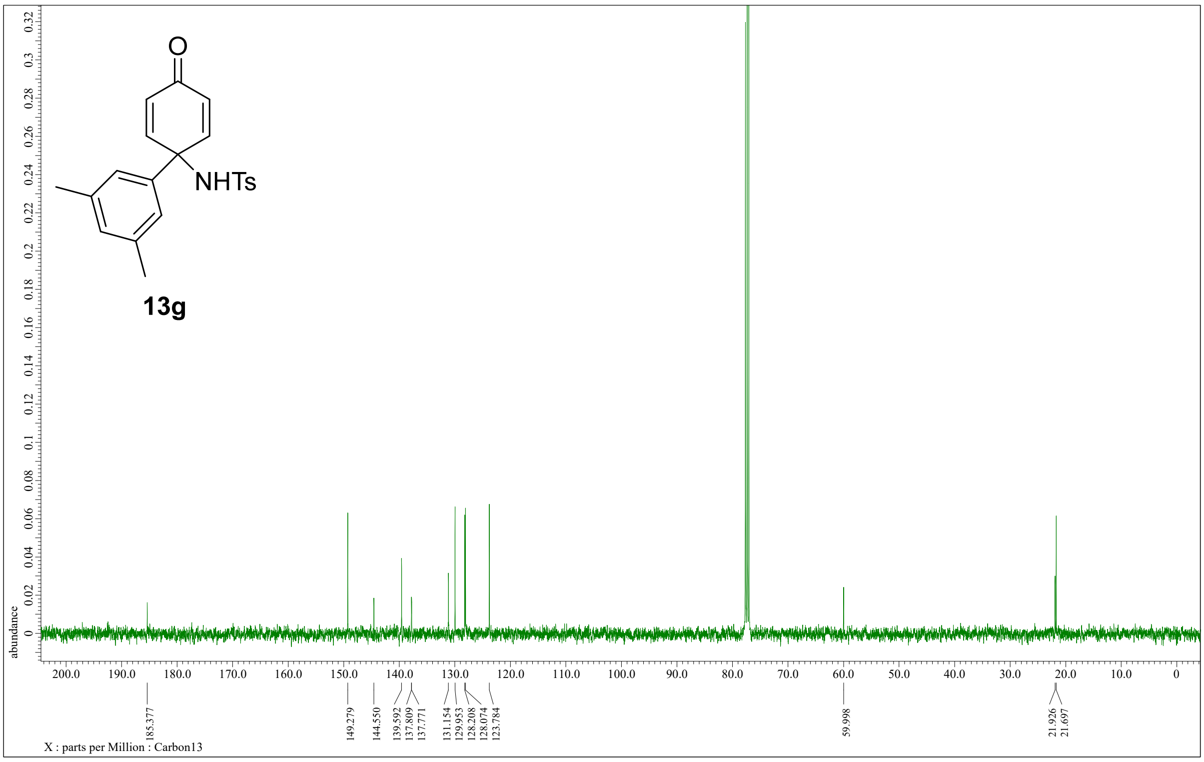
2. A micromixing device, 'Comet X-01', is available from Techno Applications Co., Ltd., 34-16-204, Hon, Denenchofu, Oota, Tokyo, 145-0072, Japan.

3. H. Jin, Q. Zhang, E. Li, P. Jia, N. Li and Y. Huang, *Org. Biomol. Chem.,* 2017, **15**, 7097–7101.

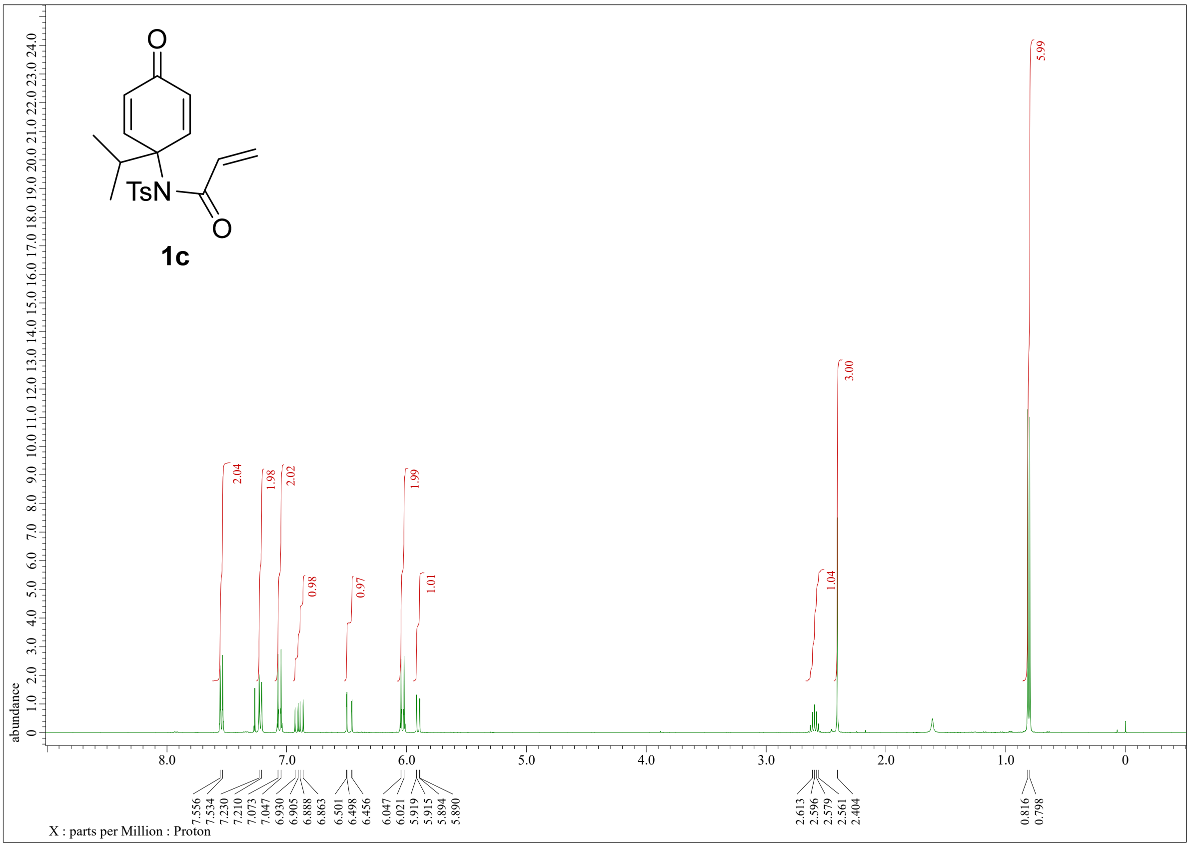
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **13g**



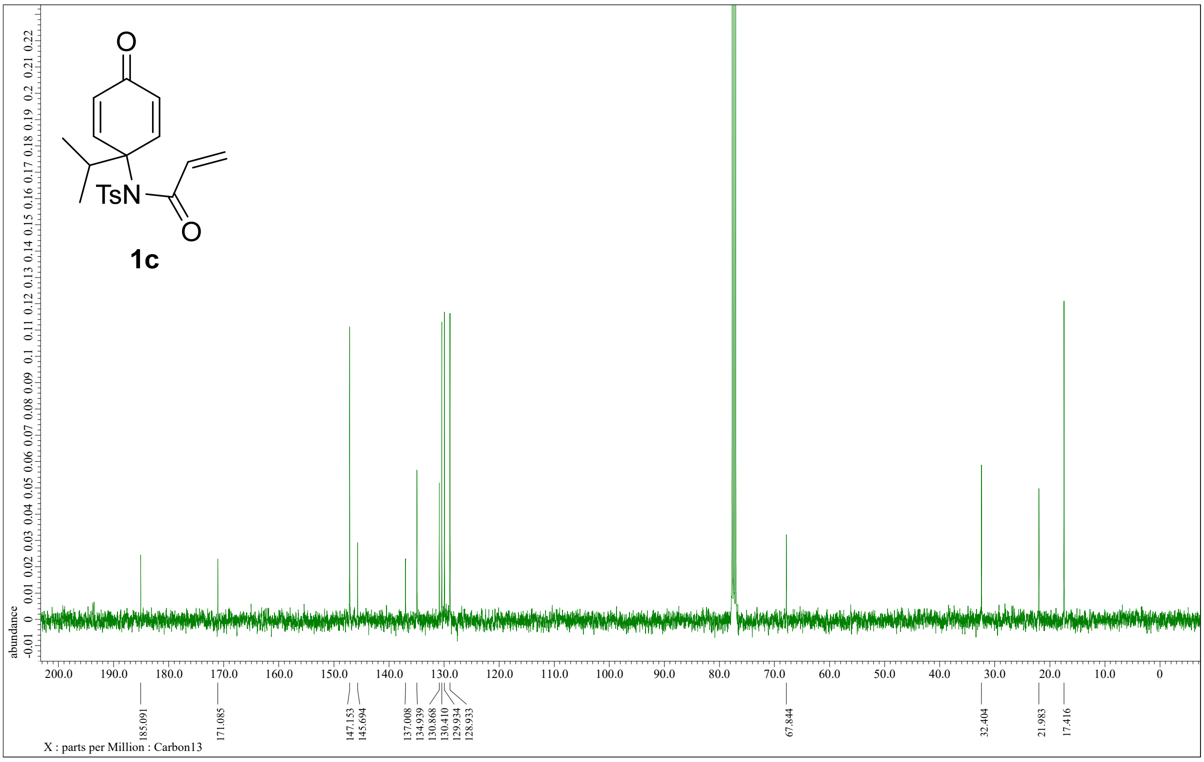
^{13}C-NMR (100 MHz, $CDCl_3$) chart of **13g**



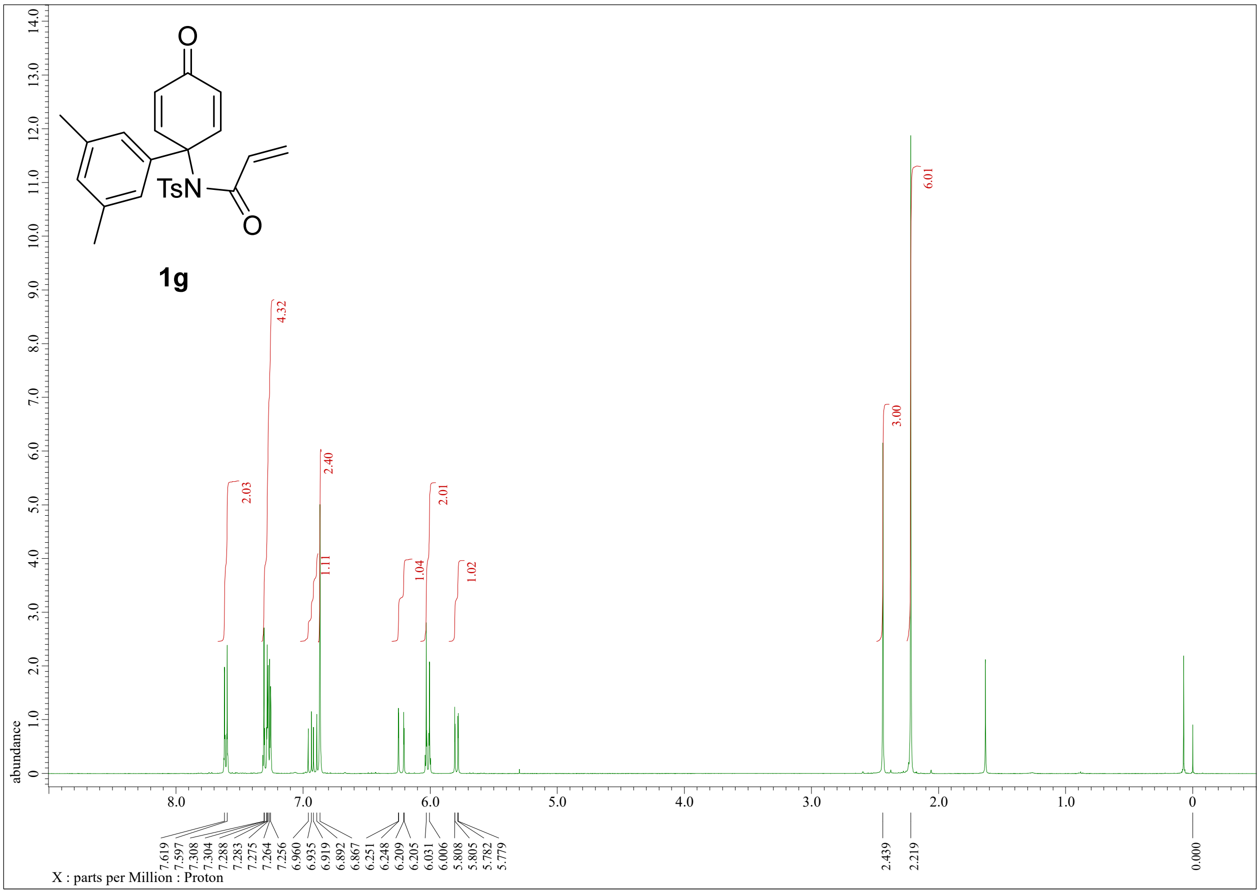
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **1c**



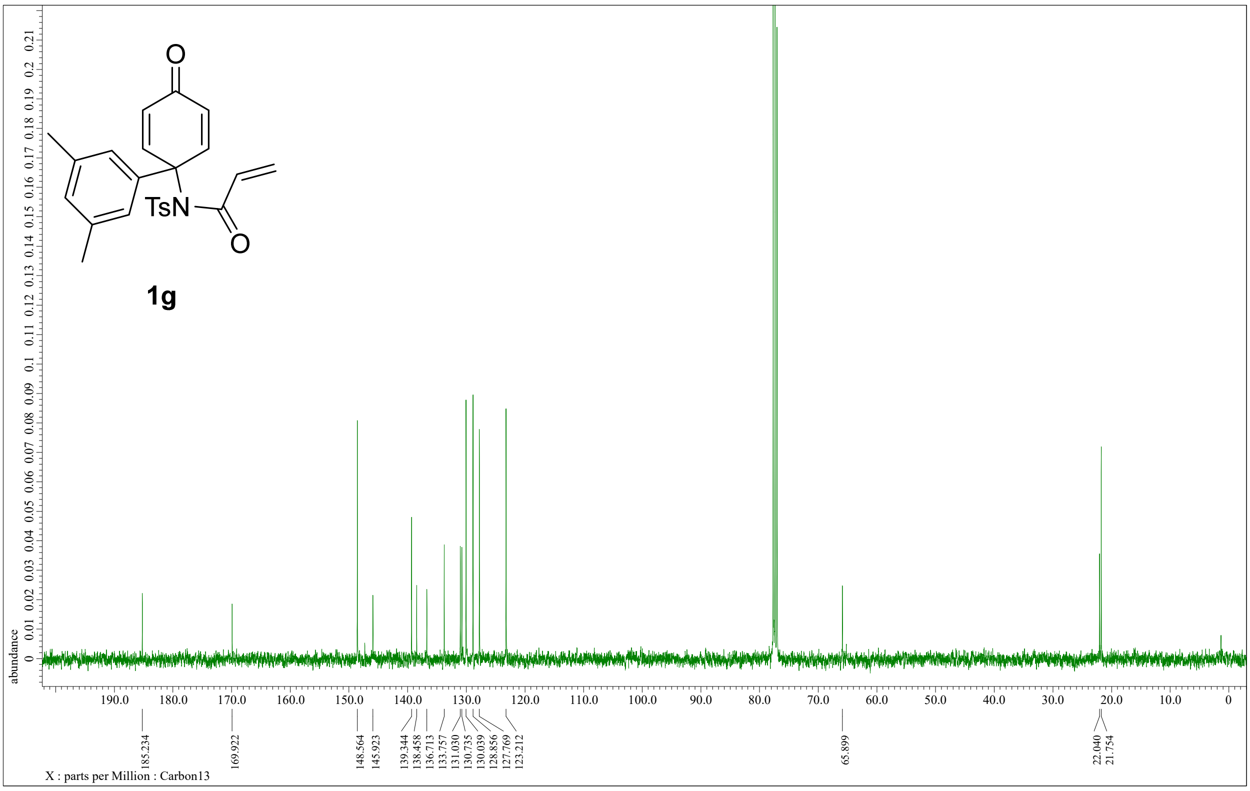
^{13}C-NMR (100 MHz, $CDCl_3$) chart of **1c**



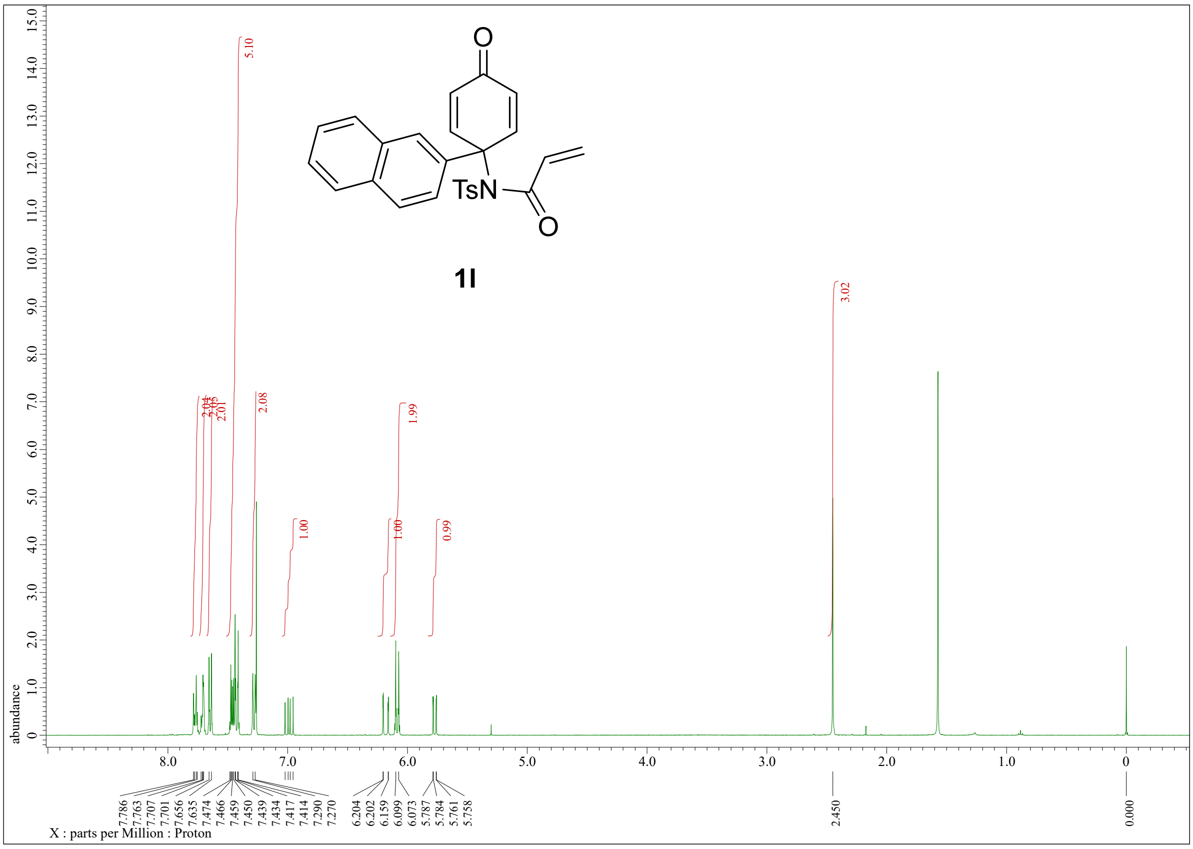
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **1g**



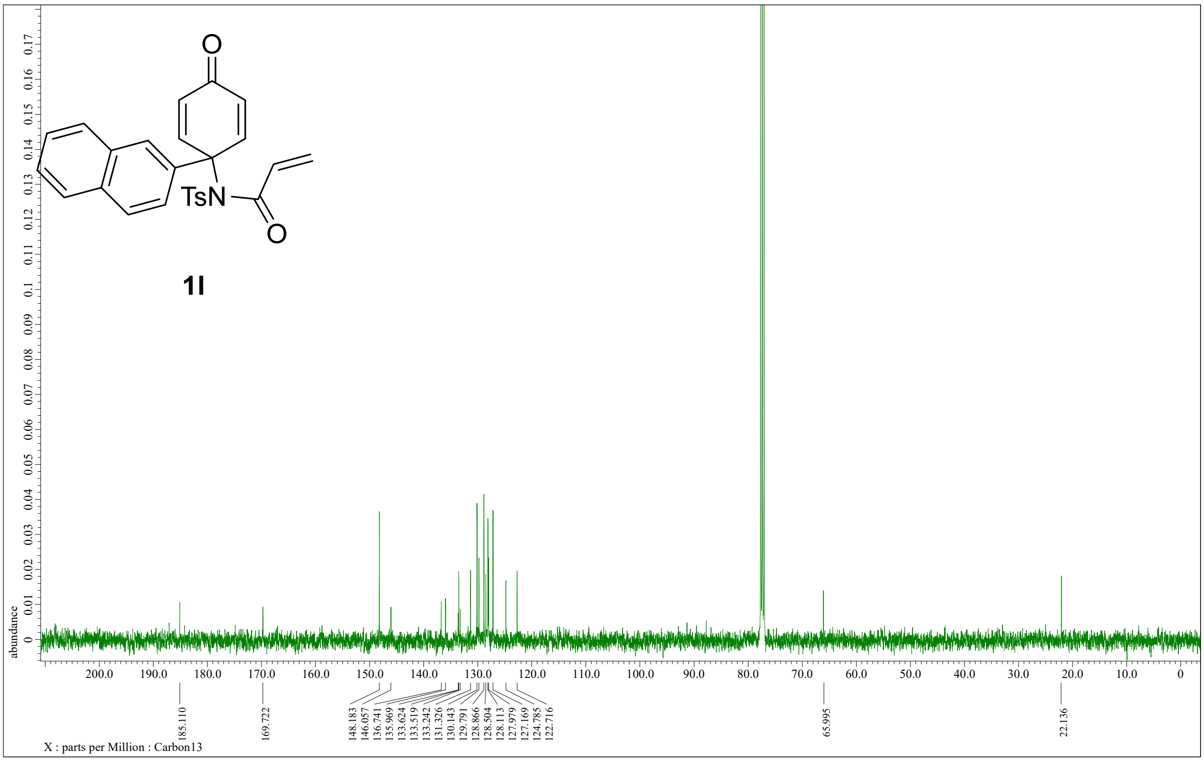
^{13}C-NMR (100 MHz, $CDCl_3$) chart of **1g**



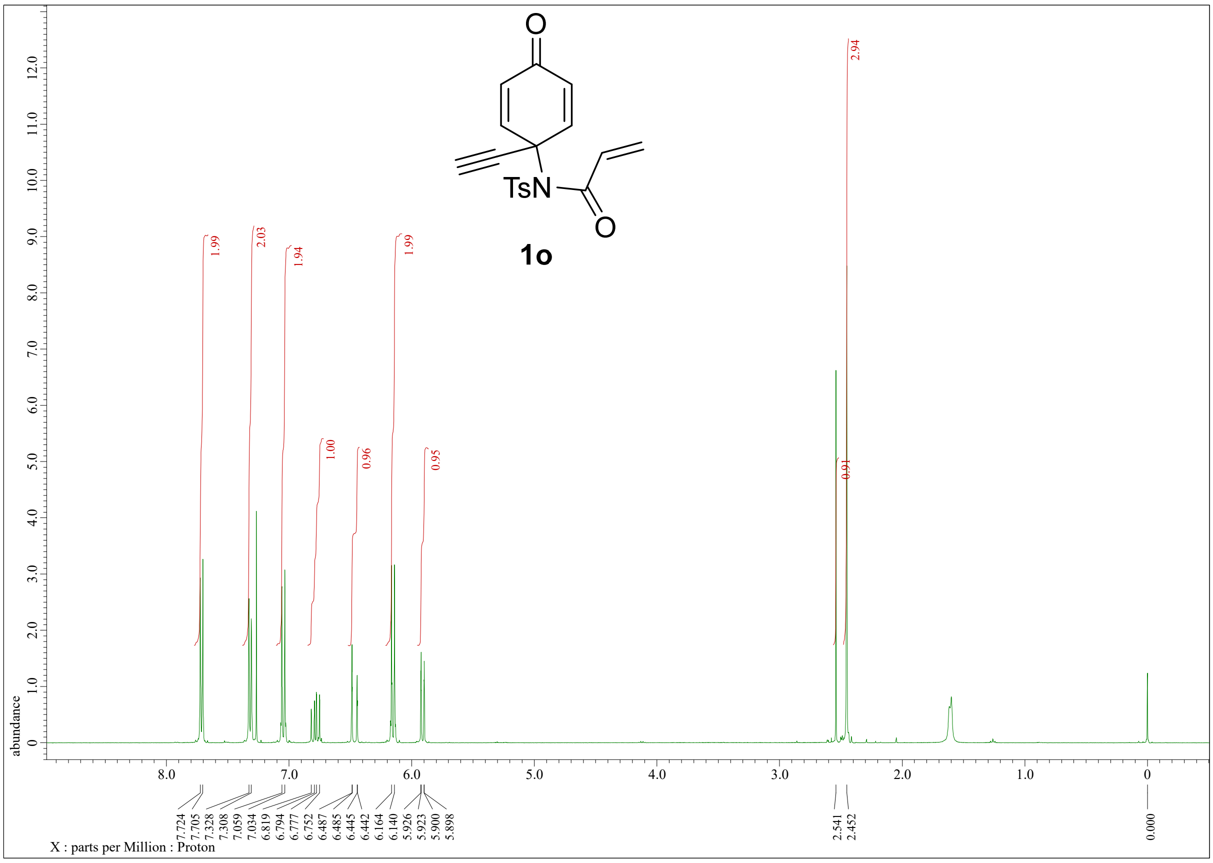
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **1l**



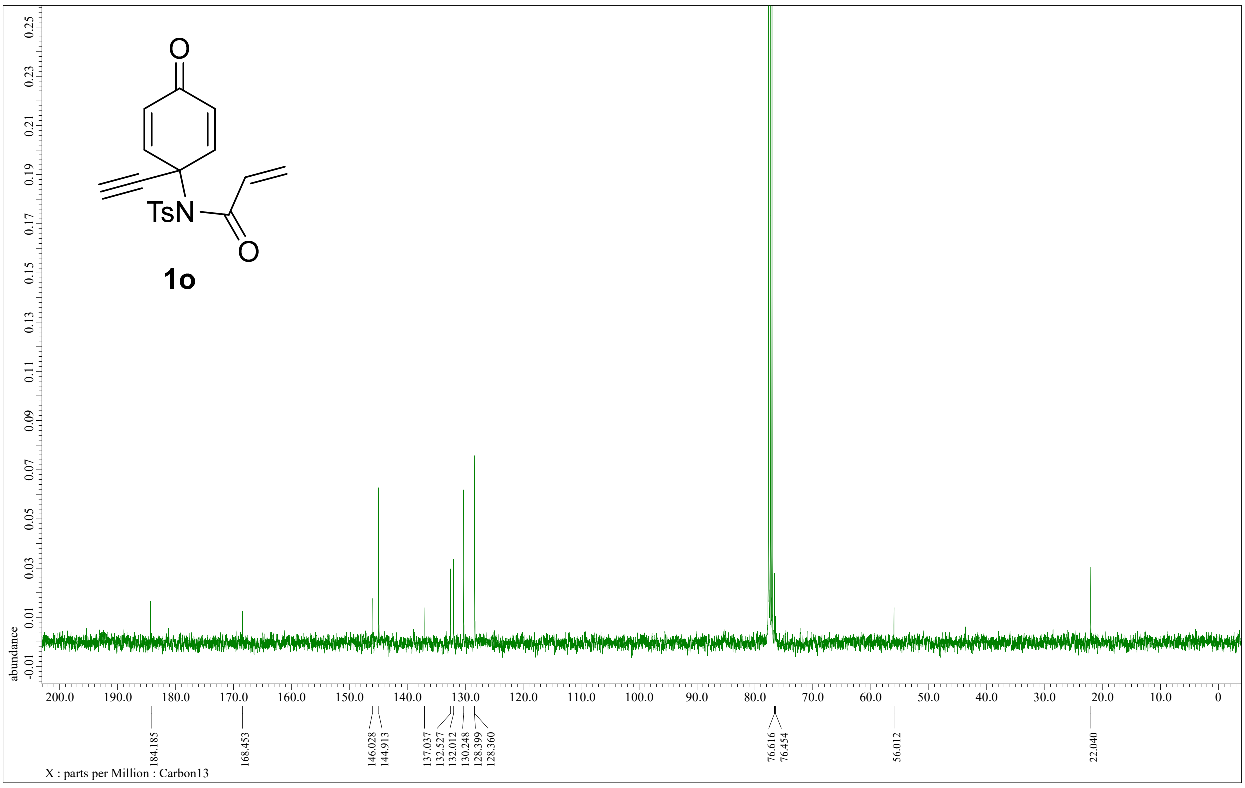
^{13}C-NMR (100 MHz, $CDCl_3$) chart of **1l**



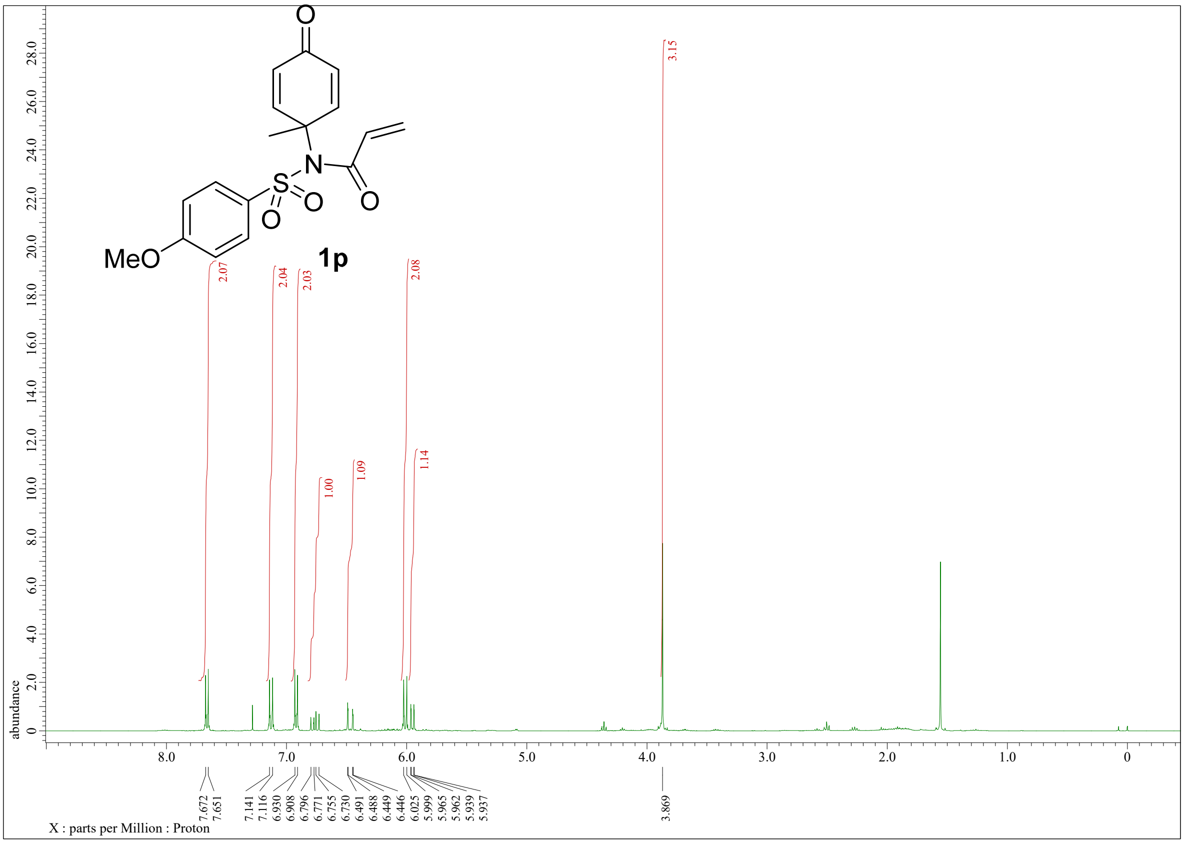
[1]H-NMR (400 MHz, $CDCl_3$) chart of **1o**



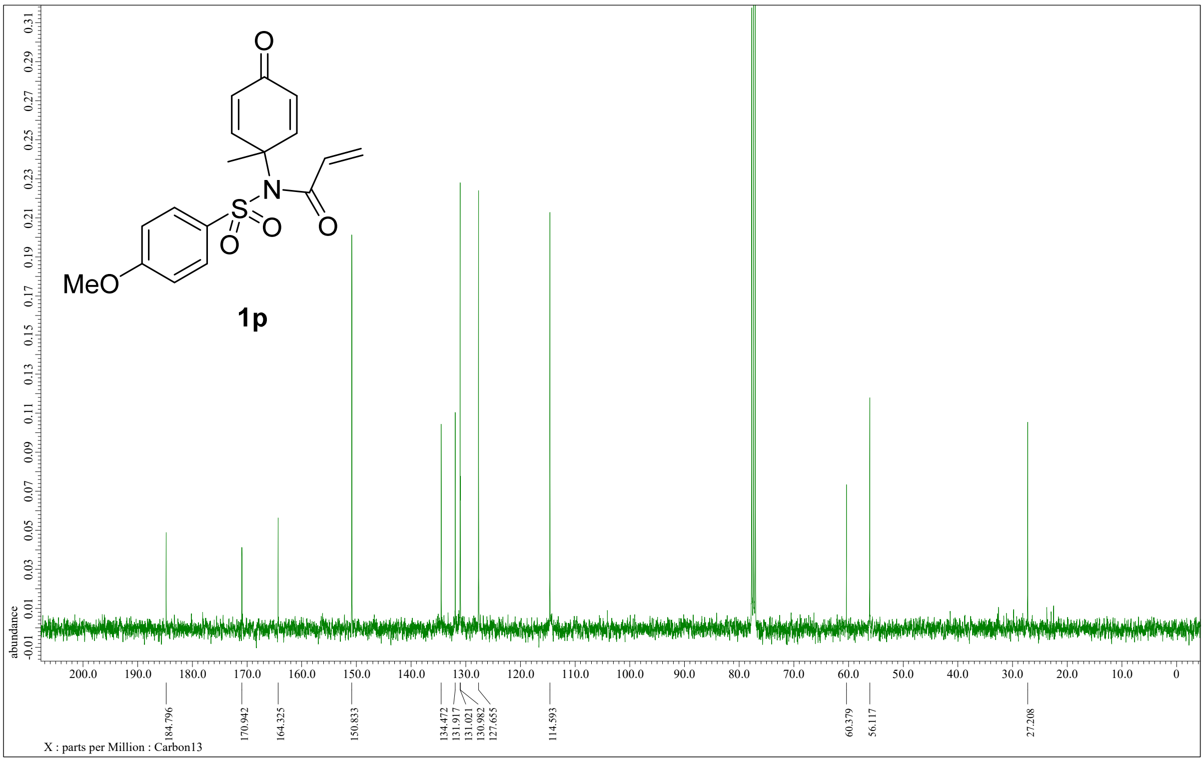
[13]C-NMR (100 MHz, $CDCl_3$) chart of **1o**



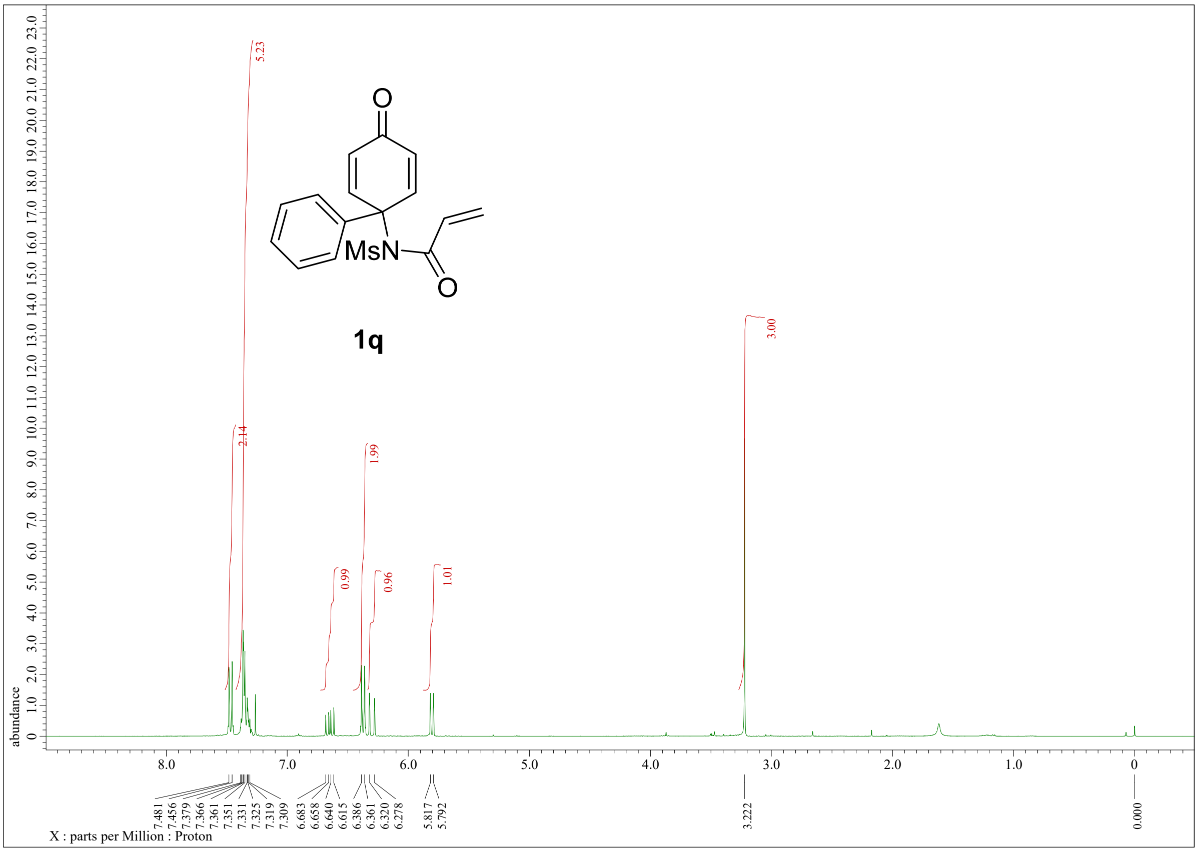
[1]H-NMR (400 MHz, $CDCl_3$) chart of **1p**



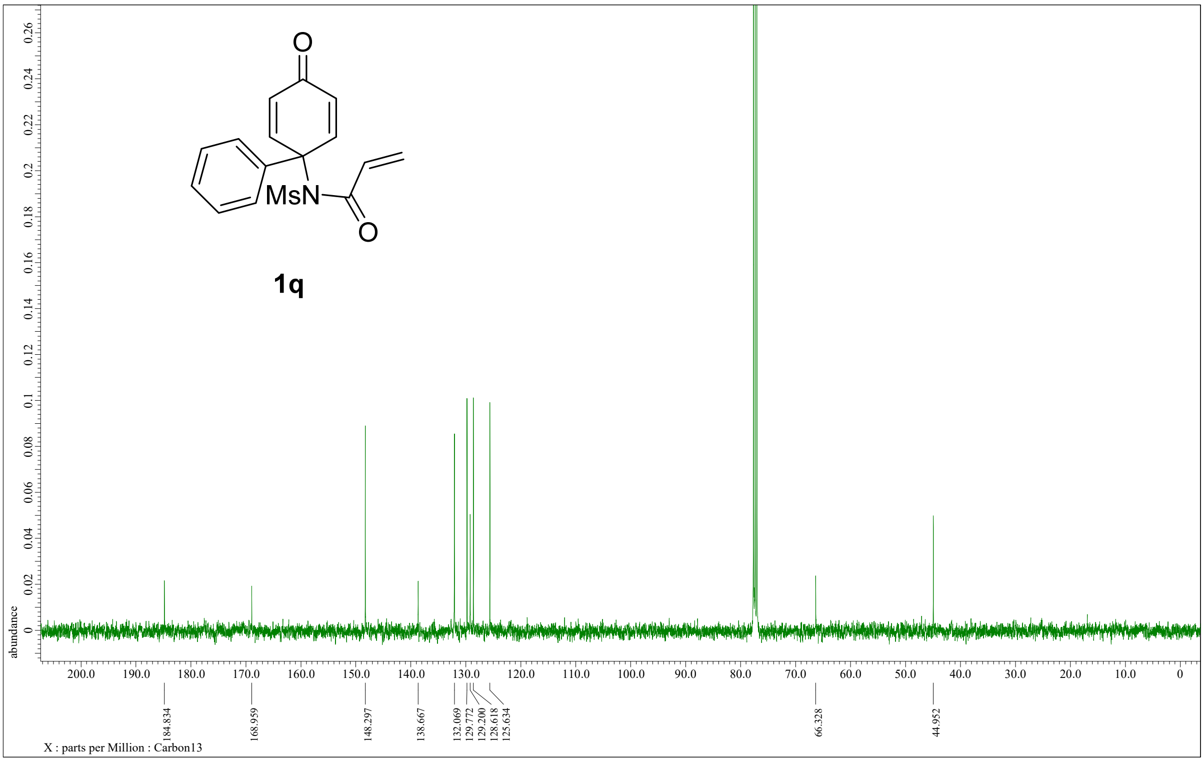
[13]C-NMR (100 MHz, $CDCl_3$) chart of **1p**



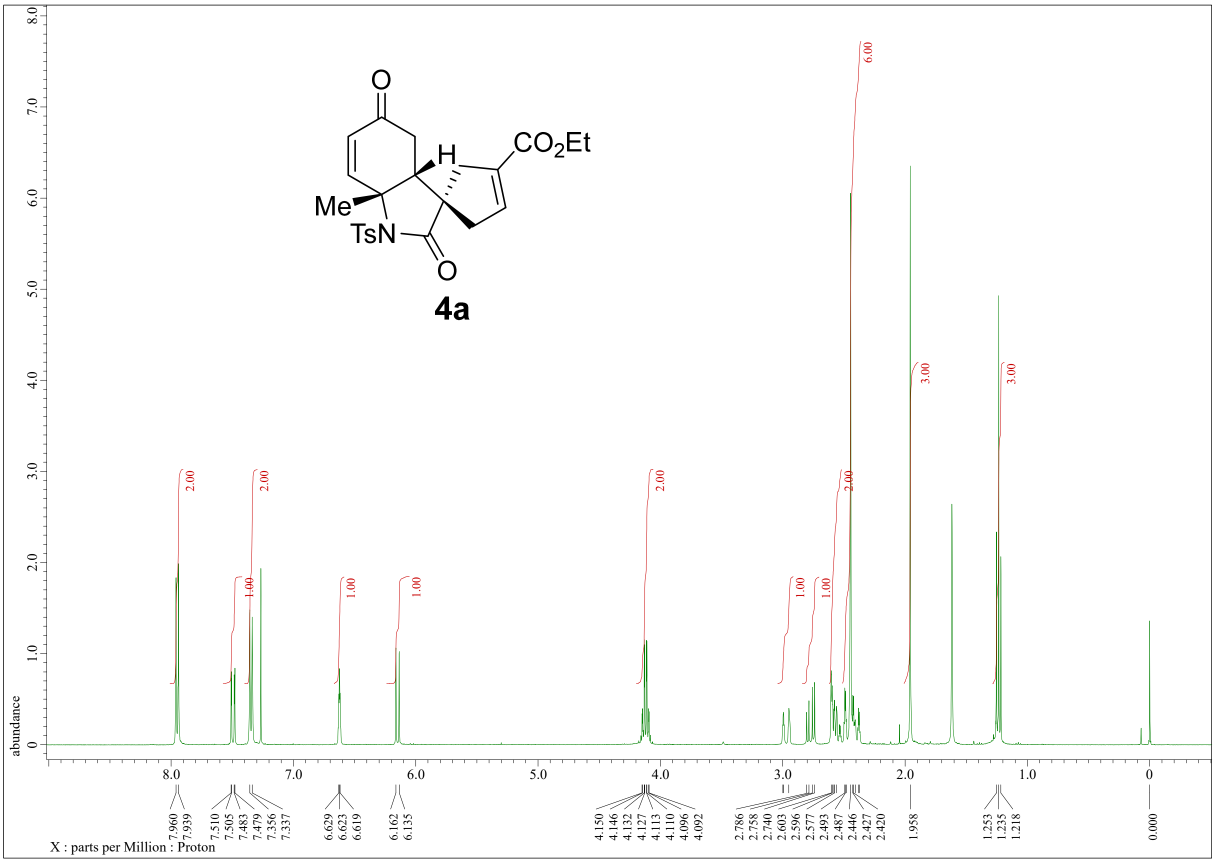
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **1q**



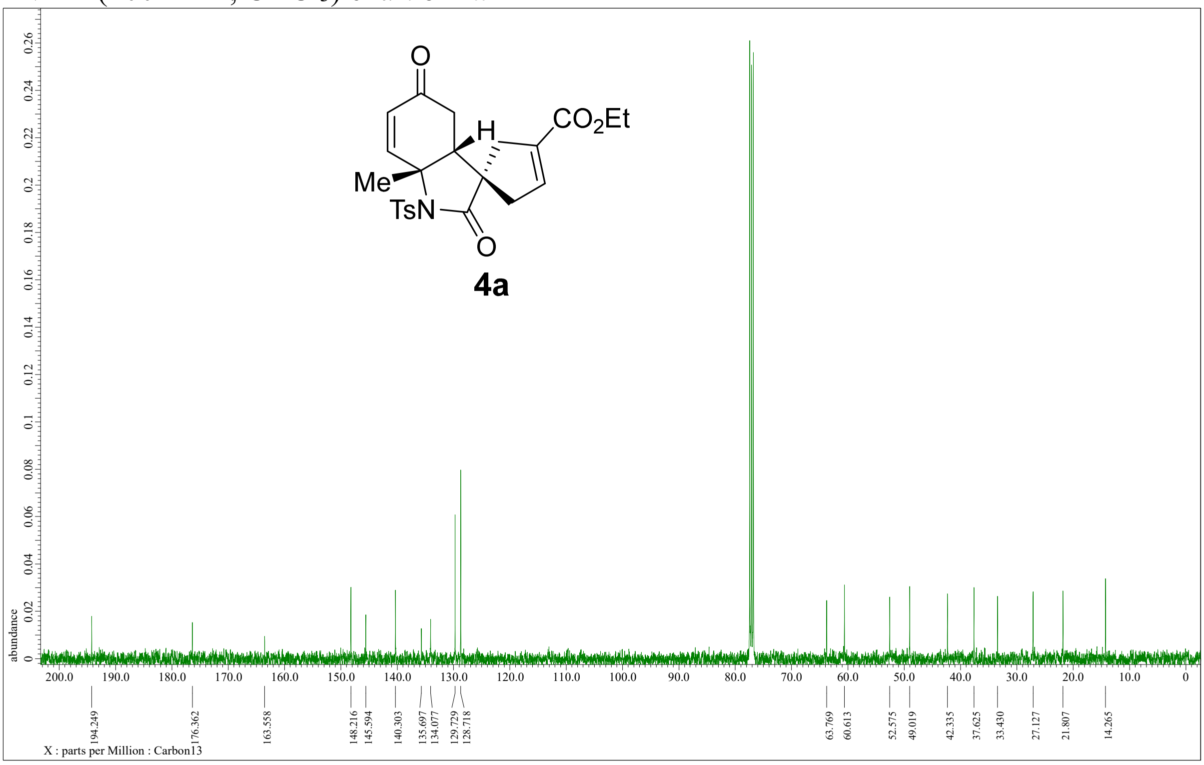
^{13}C-NMR (100 MHz, $CDCl_3$) chart of **1q**



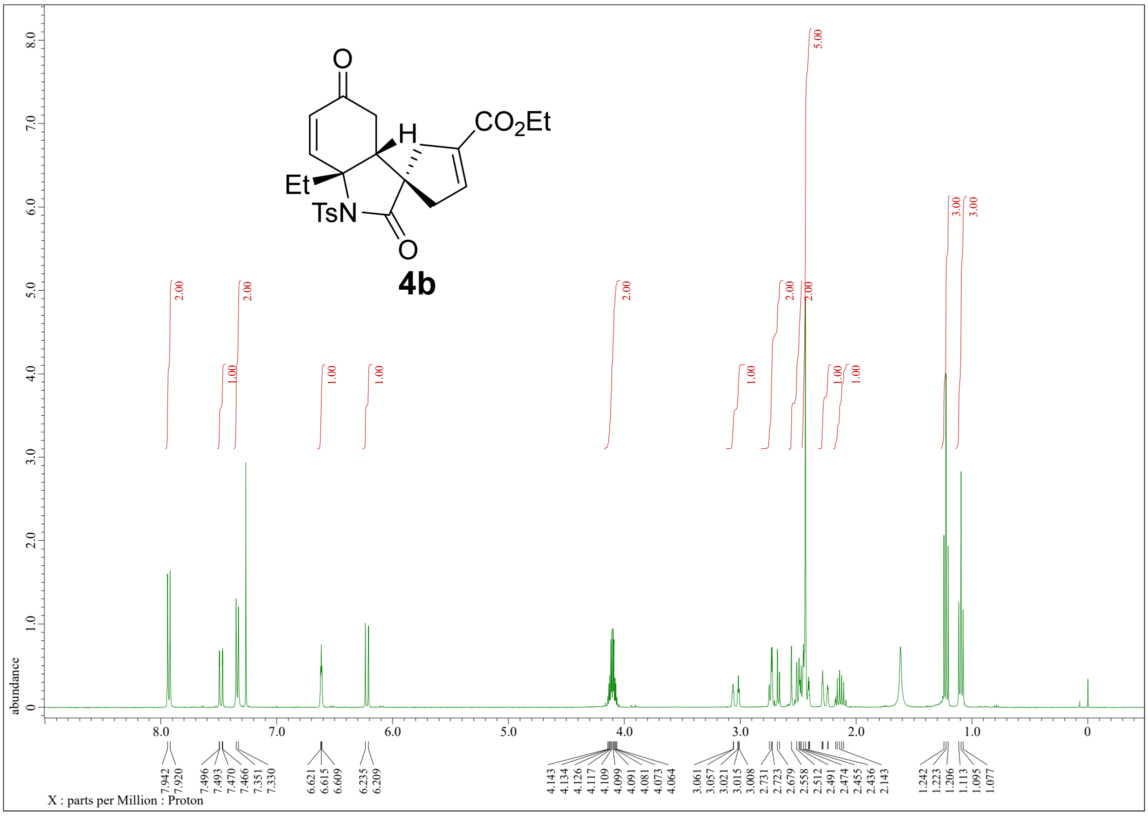
[1]H-NMR (400 MHz, $CDCl_3$) chart of **4a**



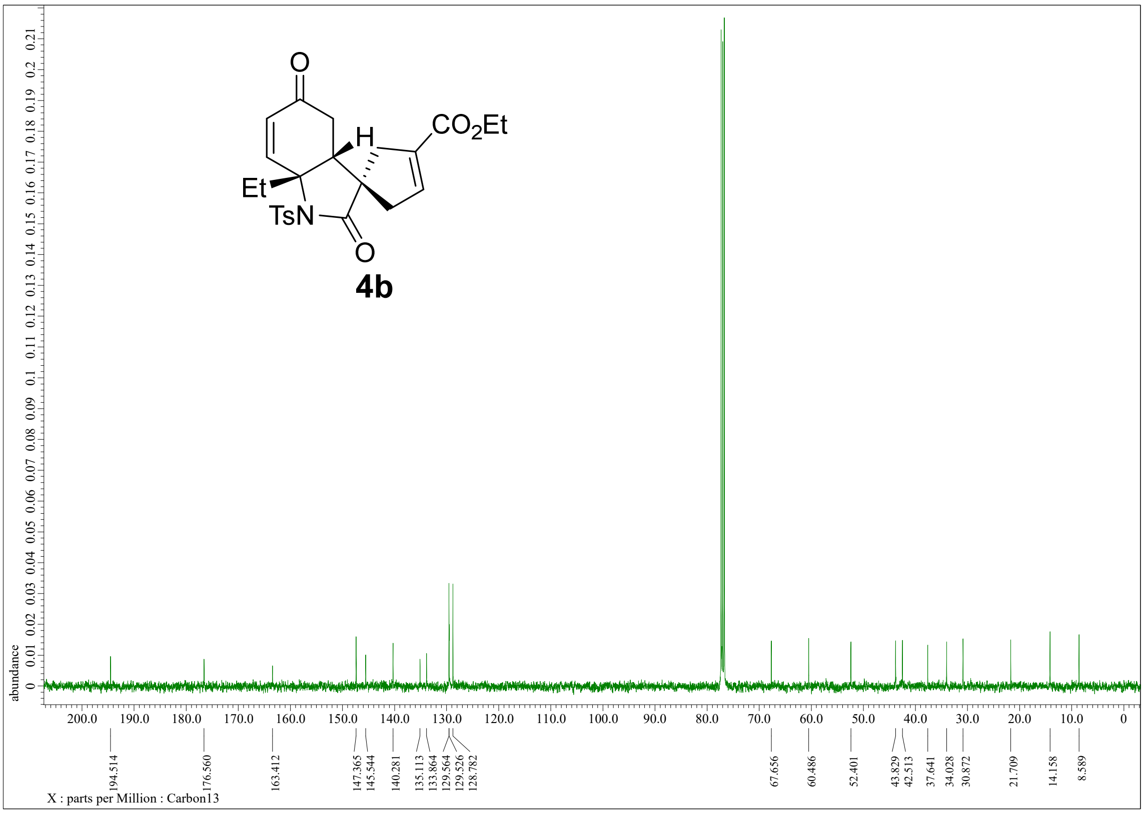
[13]C-NMR (100 MHz, $CDCl_3$) chart of **4a**



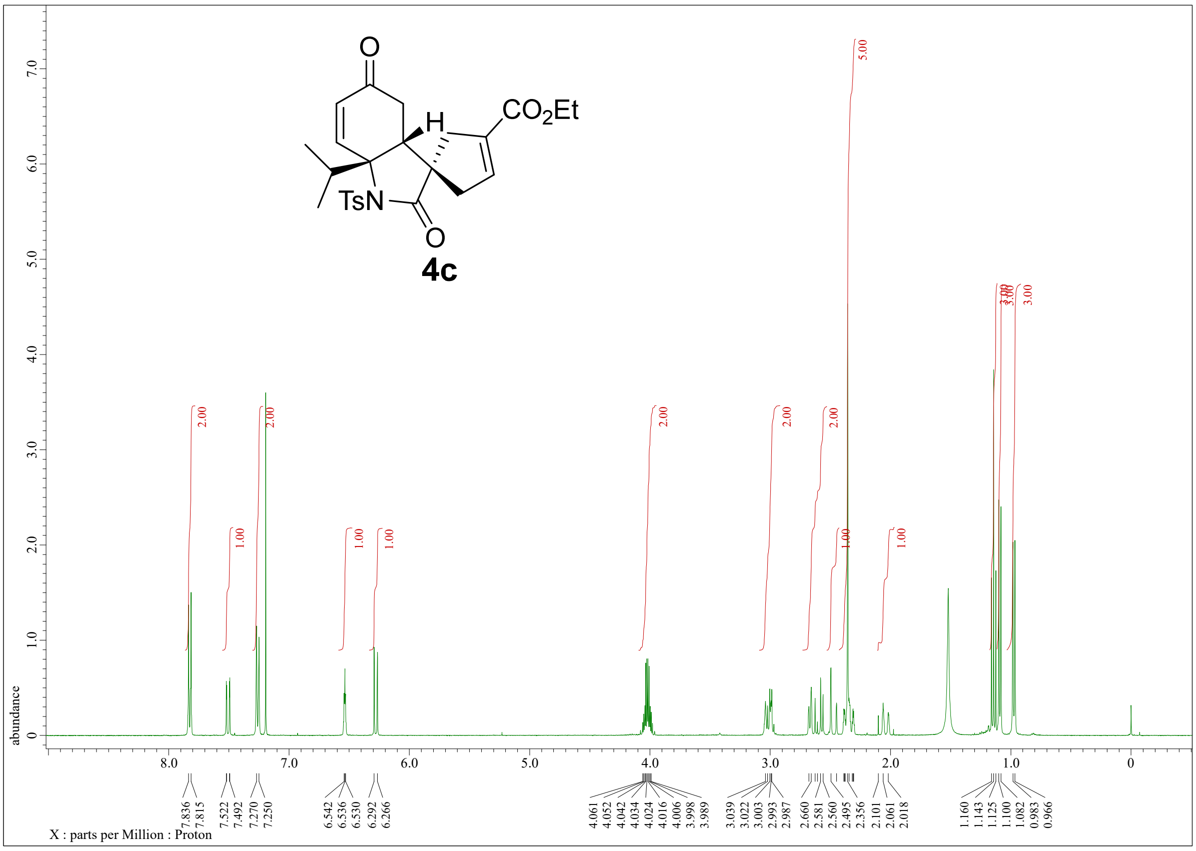
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **4b**



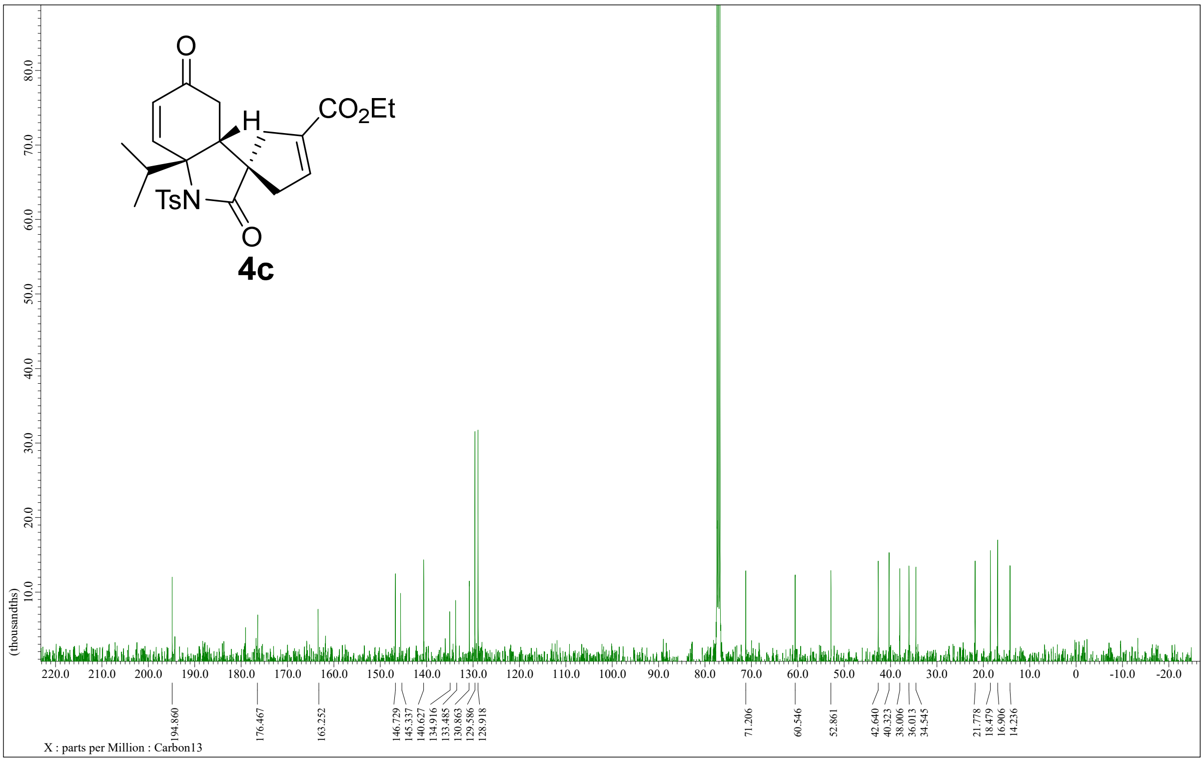
^{13}C-NMR (100 MHz, $CDCl_3$) chart of **4b**



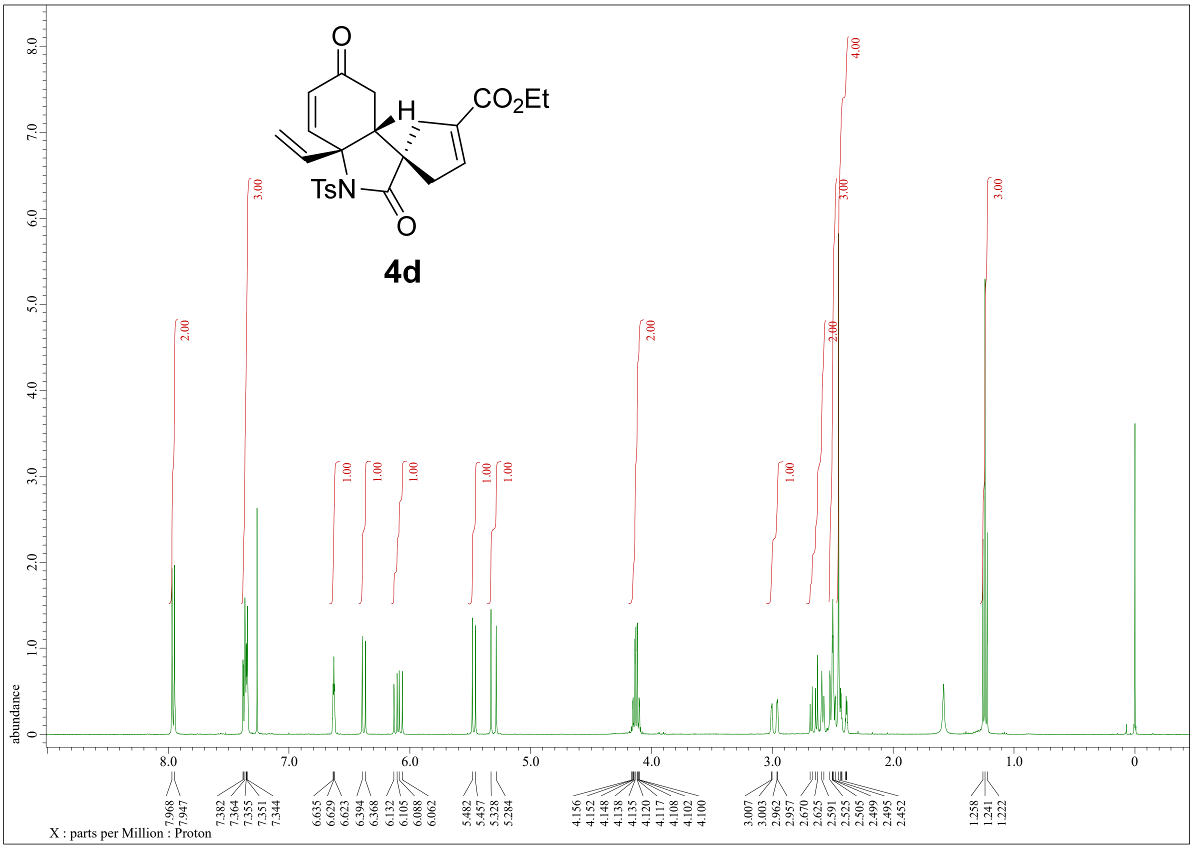
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **4c**



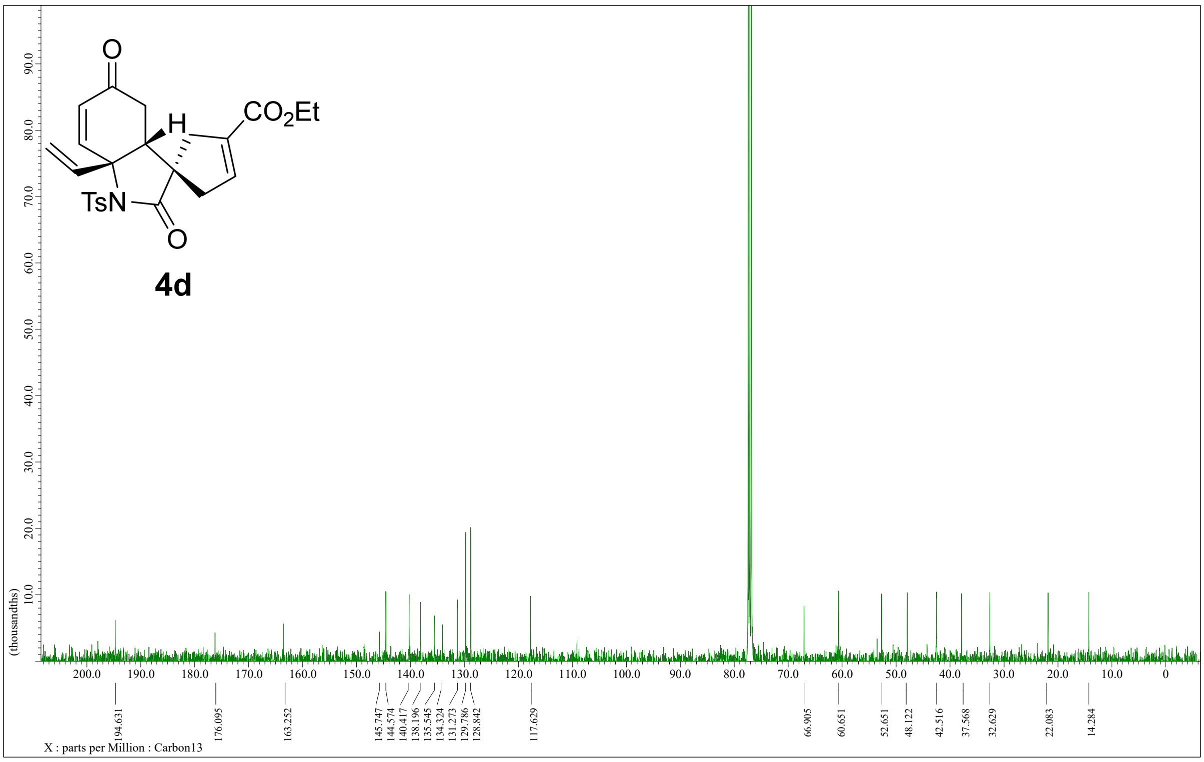
^{13}C-NMR (100 MHz, $CDCl_3$) chart of **4c**



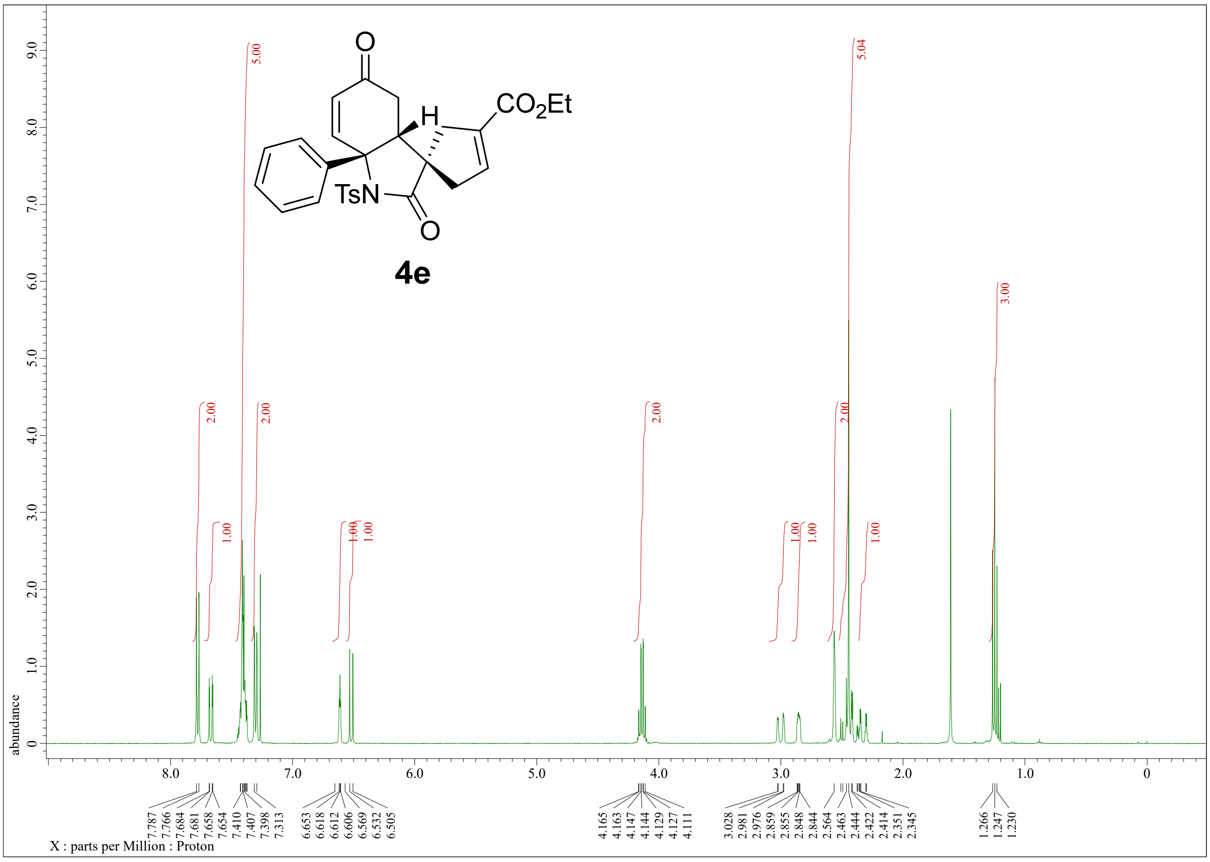
[1]H-NMR (400 MHz, $CDCl_3$) chart of **4d**



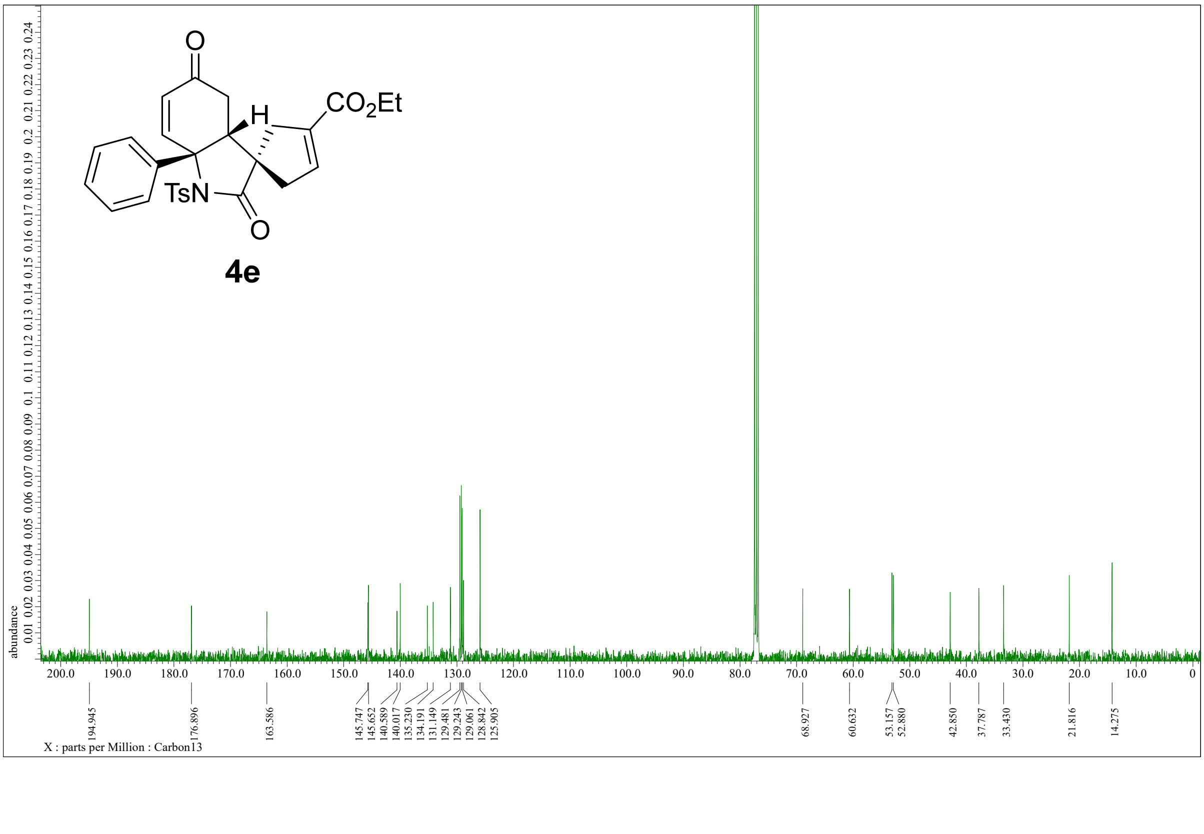
[13]C-NMR (100 MHz, $CDCl_3$) chart of **4d**



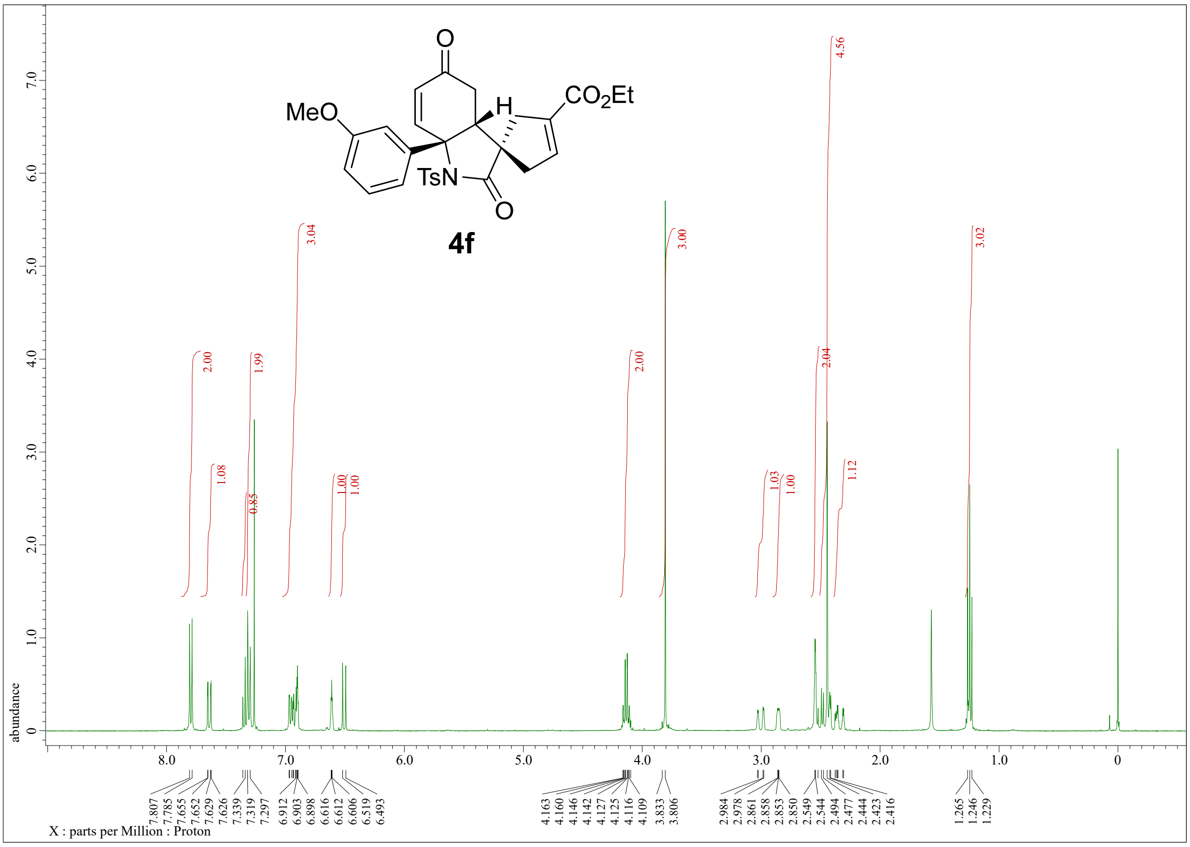
[1]H-NMR (400 MHz, $CDCl_3$) chart of **4e**



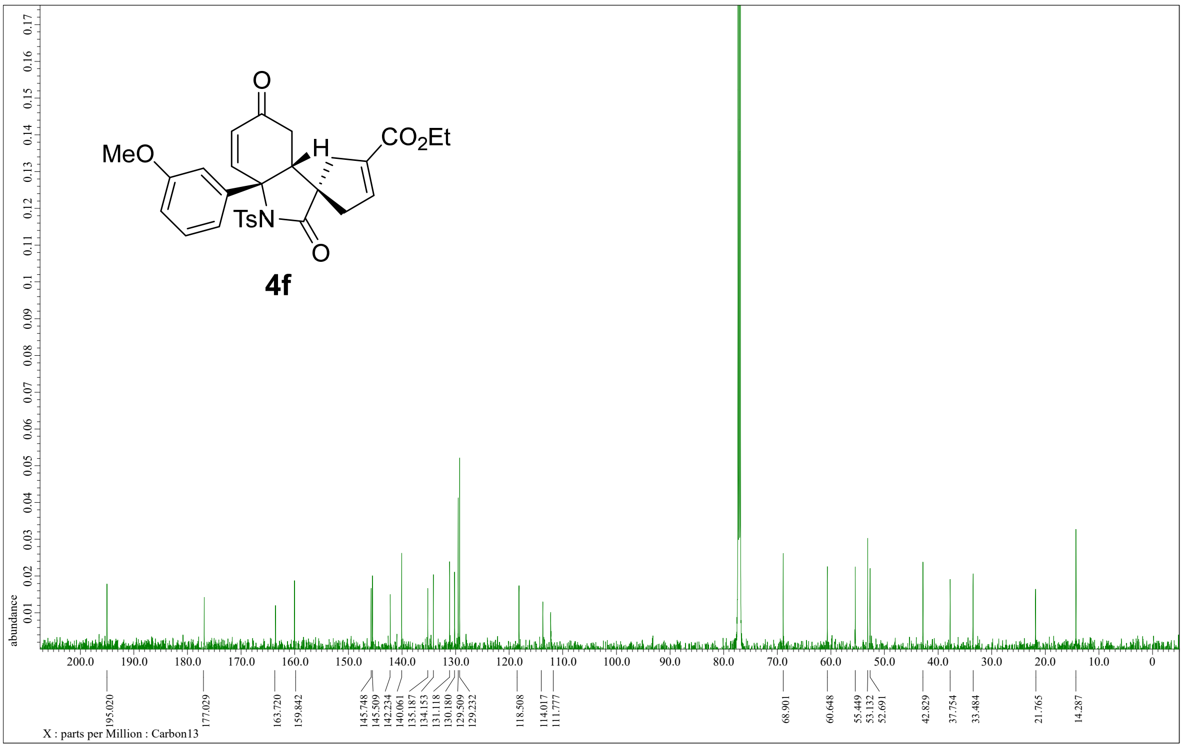
[13]C-NMR (100 MHz, $CDCl_3$) chart of **4e**



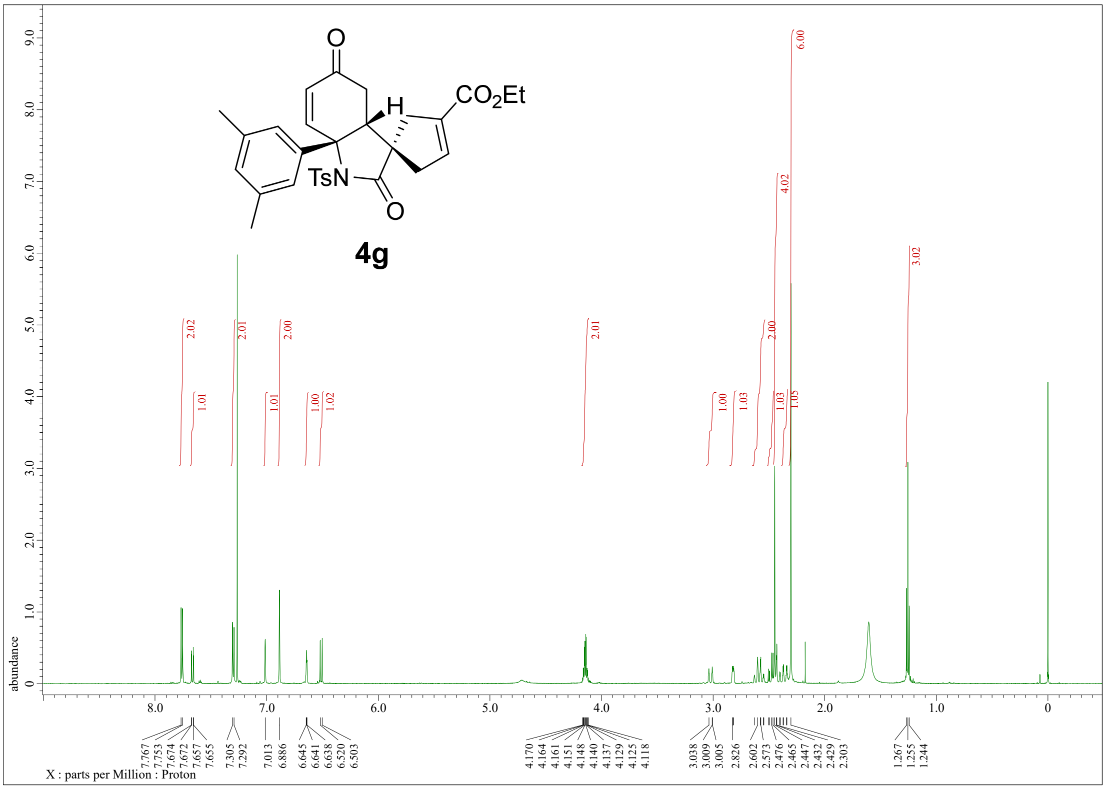
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **4f**



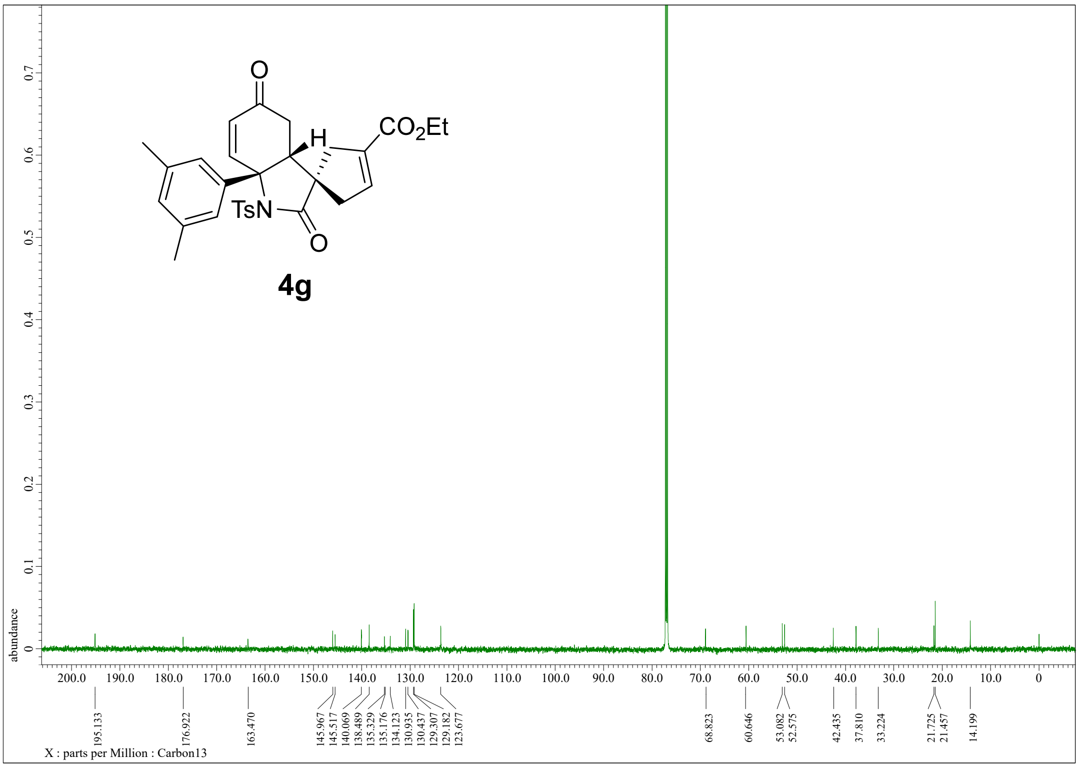
^{13}C-NMR (150 MHz, $CDCl_3$) chart of **4f**



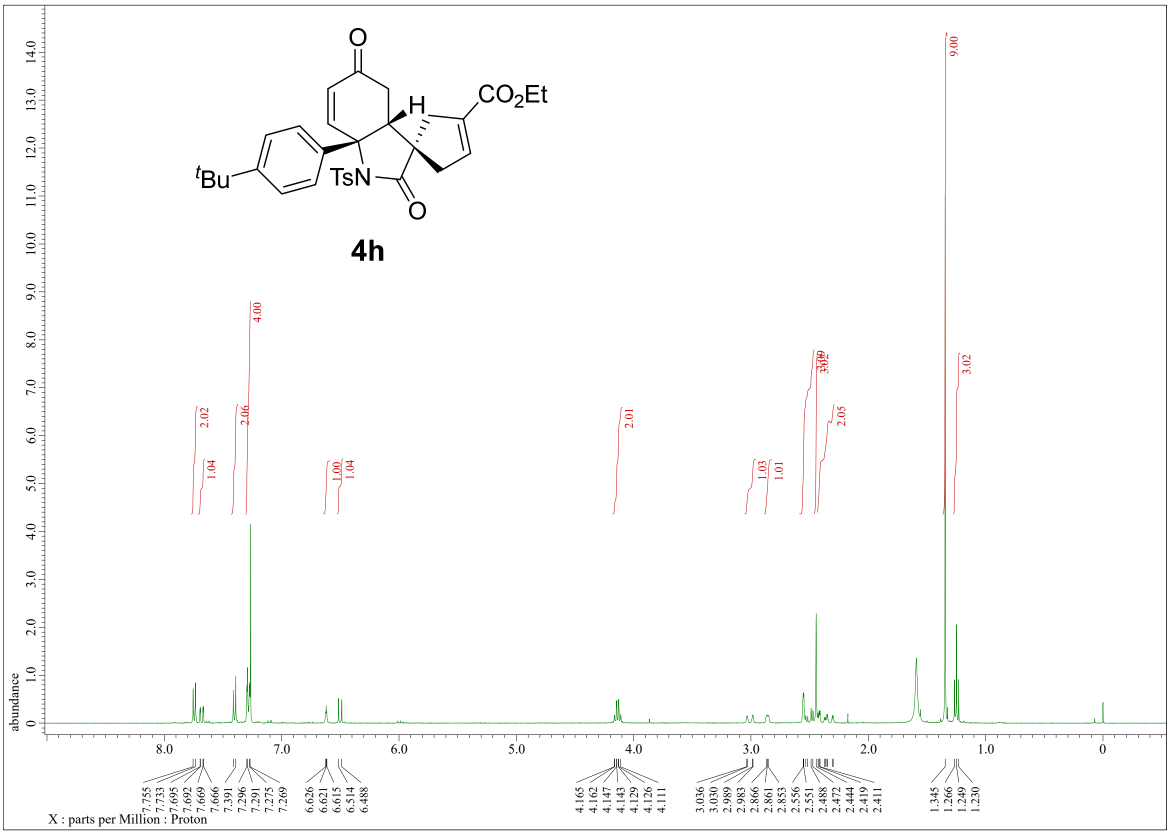
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **4g**



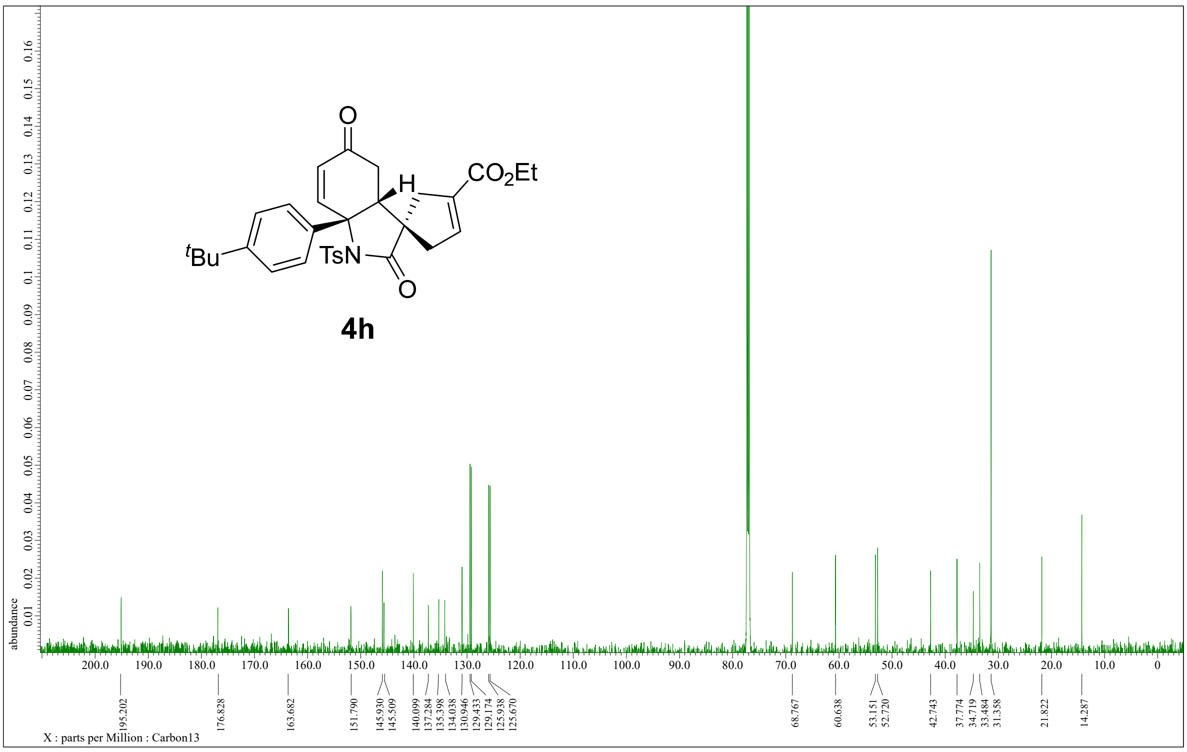
^{13}C-NMR (150 MHz, $CDCl_3$) chart of **4g**



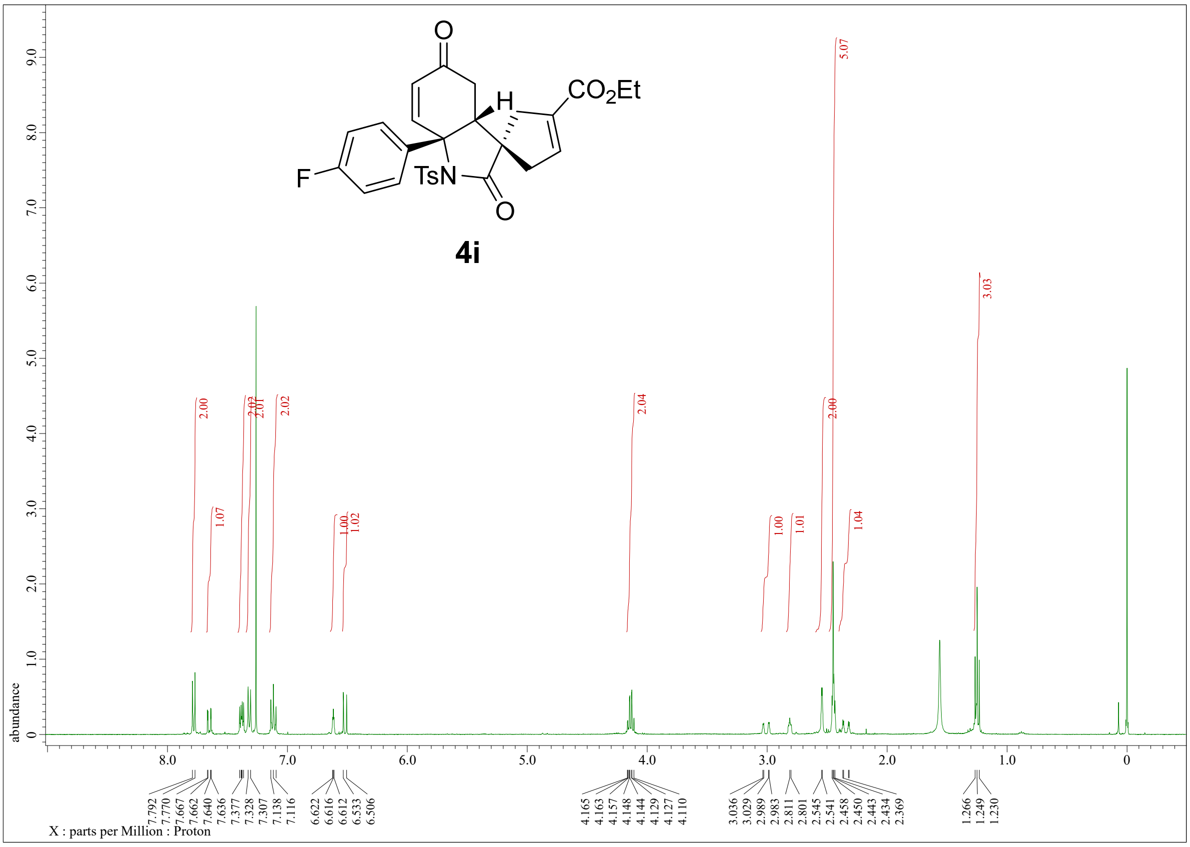
[1]H-NMR (400 MHz, $CDCl_3$) chart of **4h**



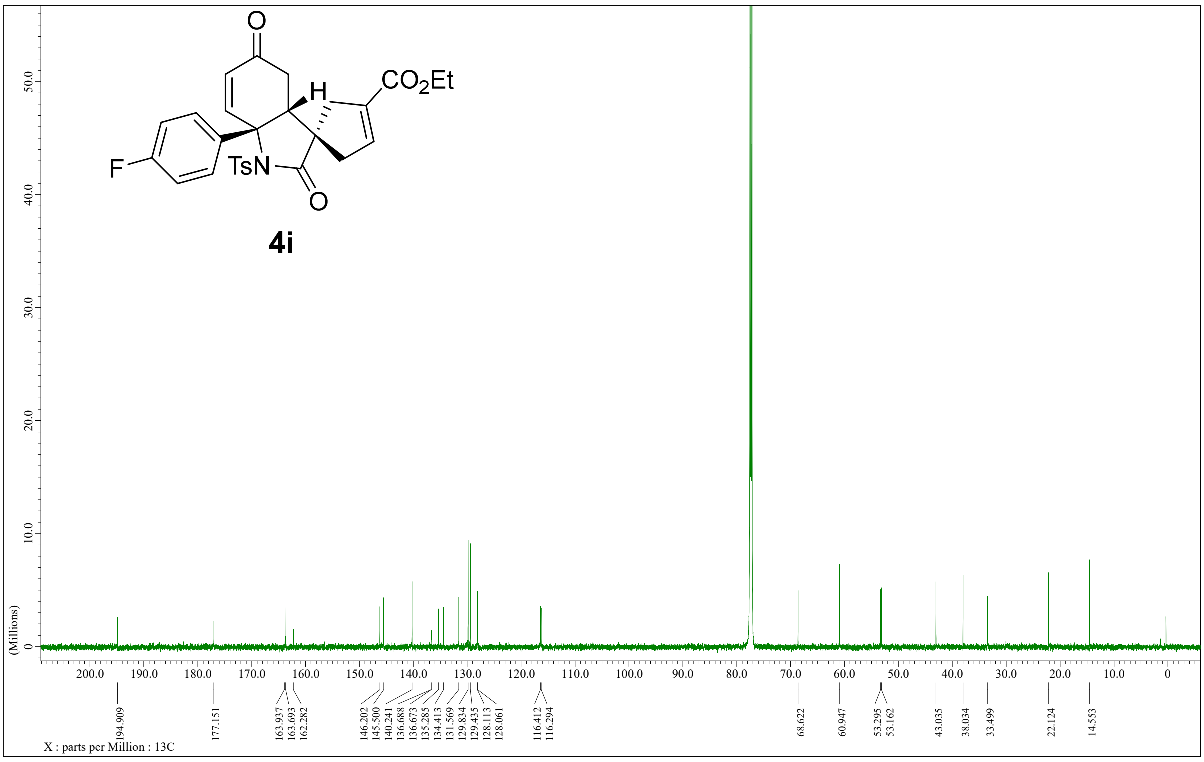
[13]C-NMR (150 MHz, $CDCl_3$) chart of **4h**



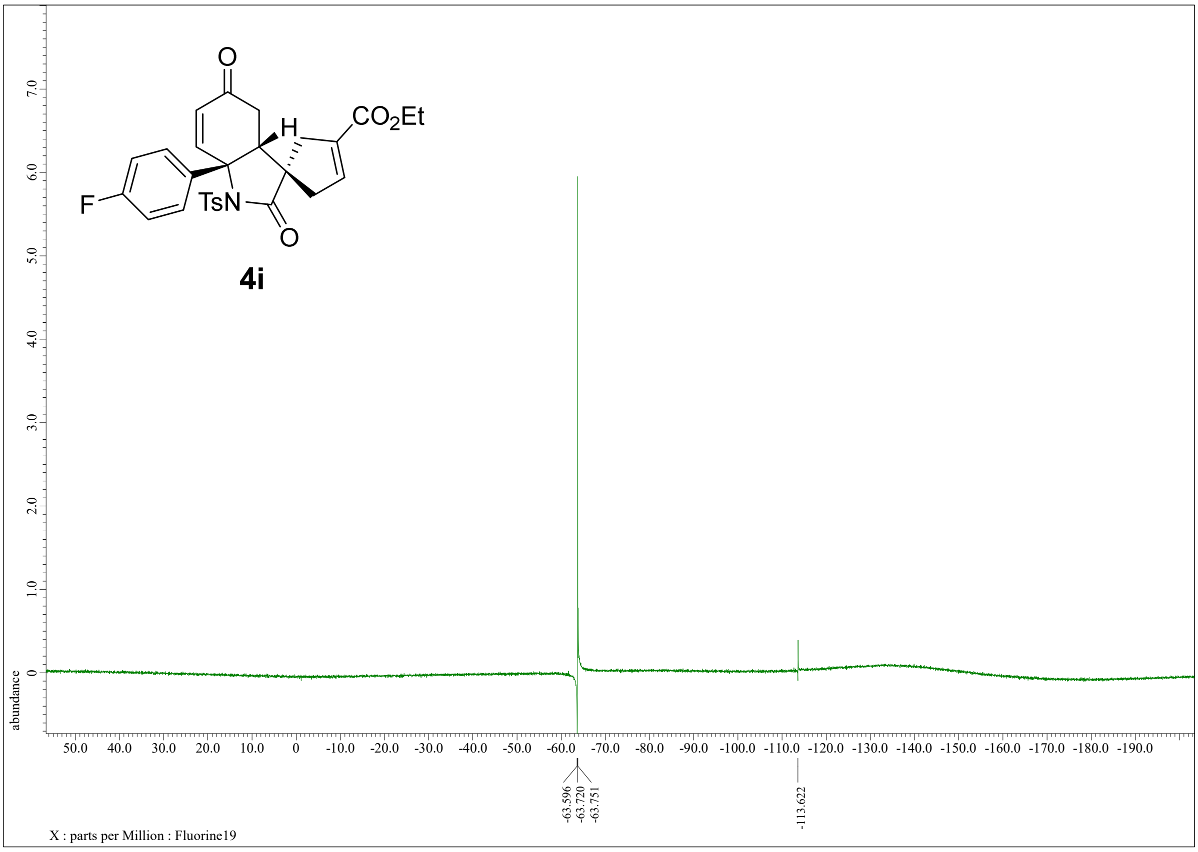
[1]H-NMR (400 MHz, $CDCl_3$) chart of **4i**



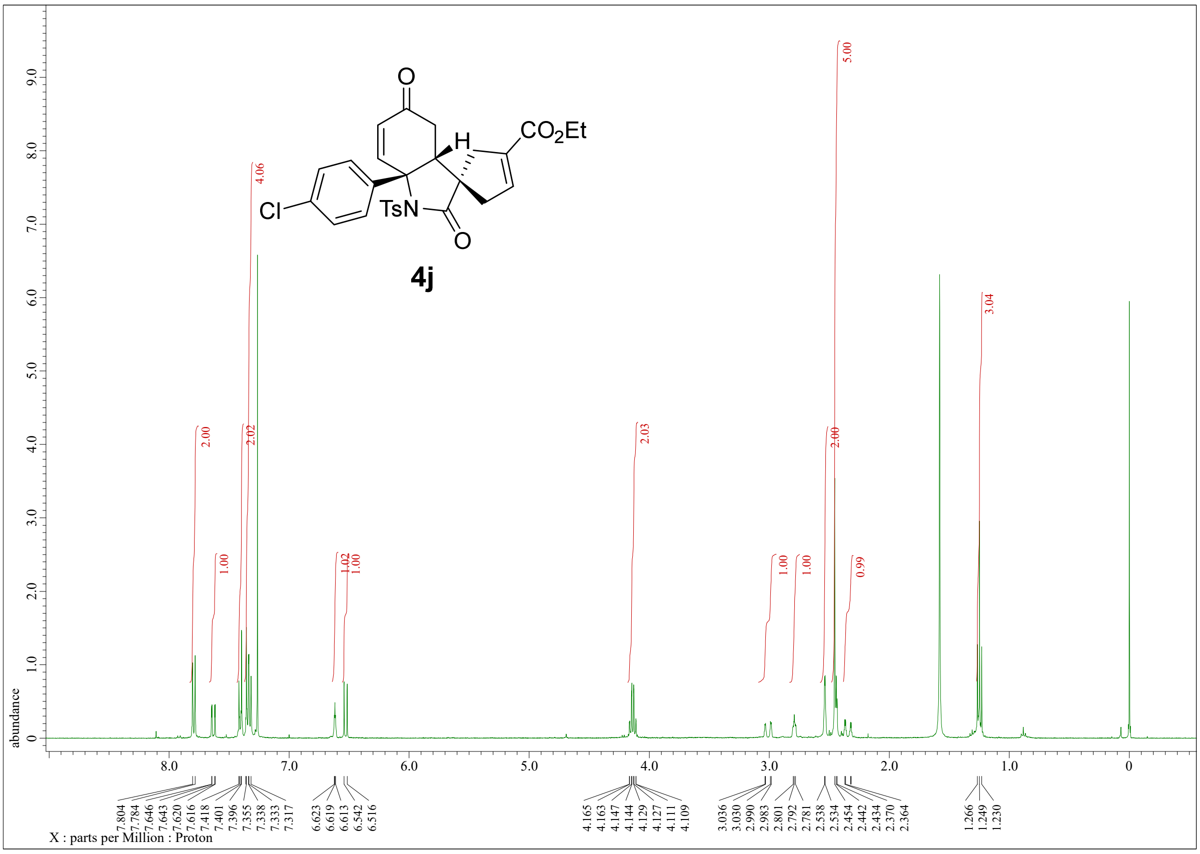
[13]C-NMR (175 MHz, $CDCl_3$) chart of **4i**



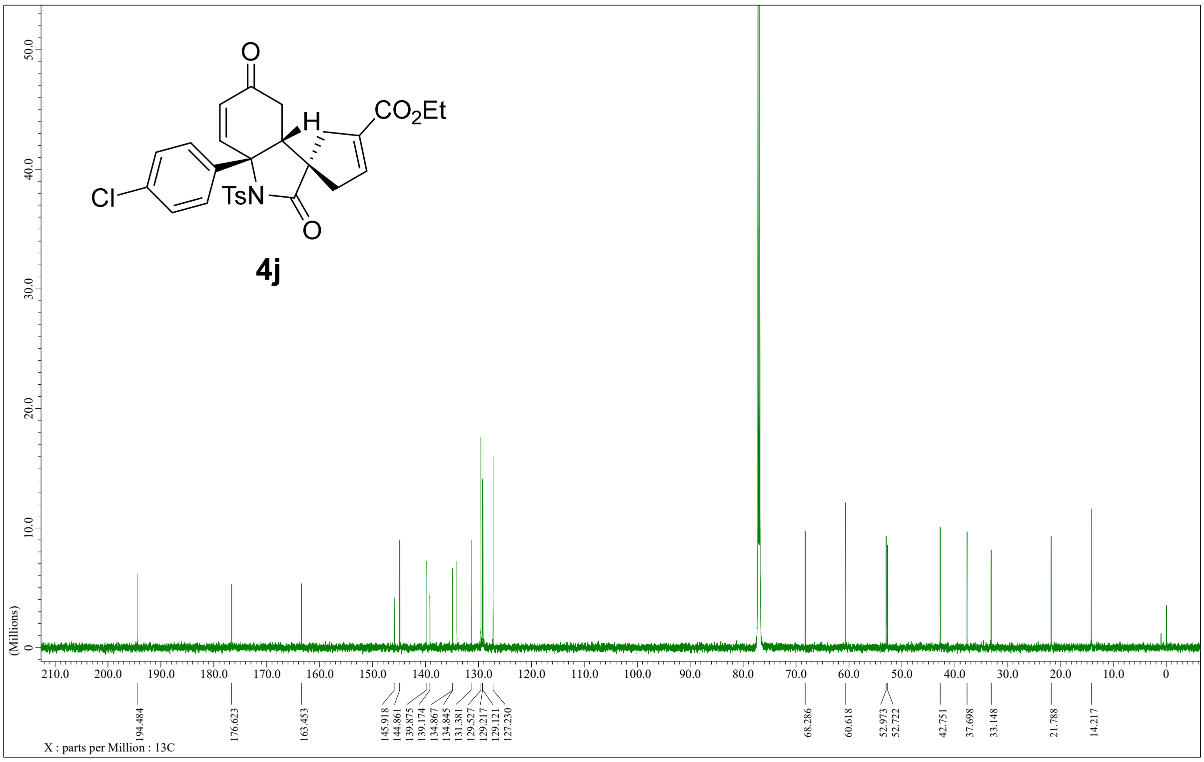
^{19}F-NMR (565 MHz, $CDCl_3$) chart of **4i**



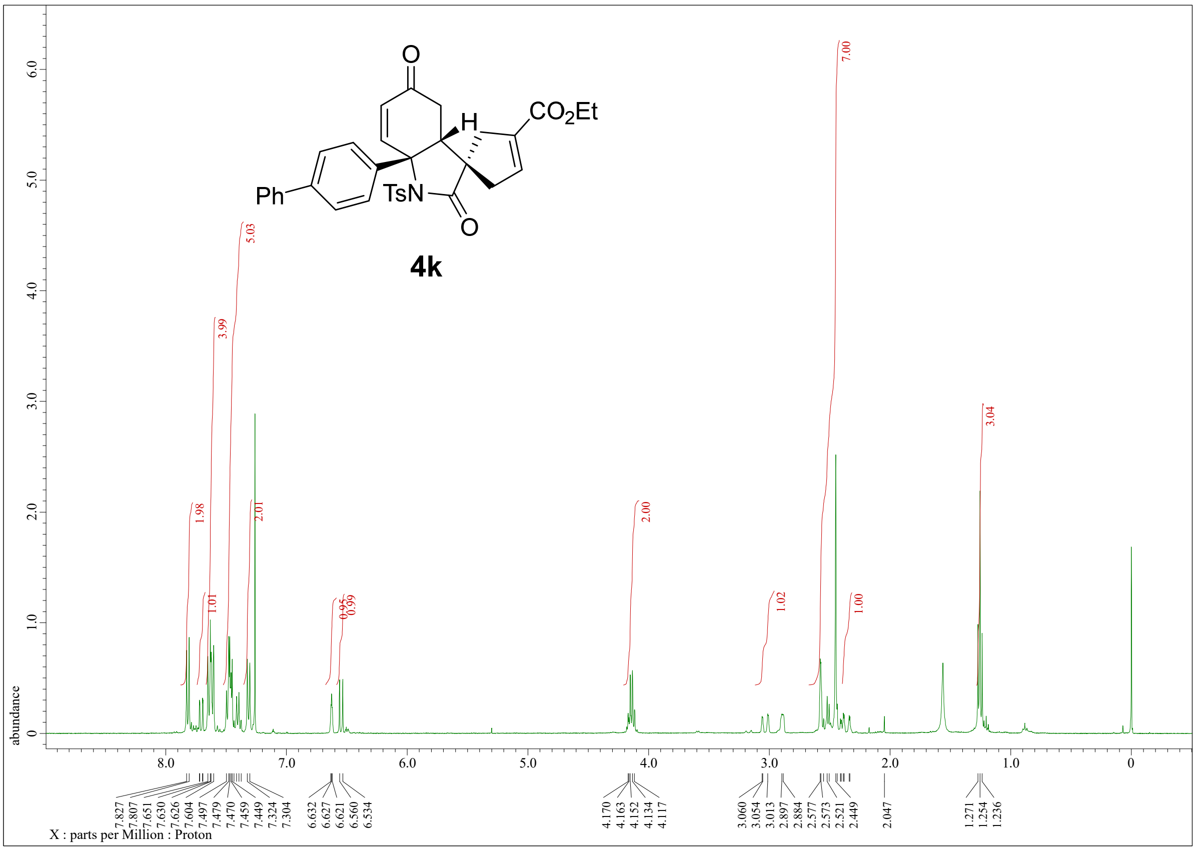
[1]H-NMR (400 MHz, $CDCl_3$) chart of **4j**



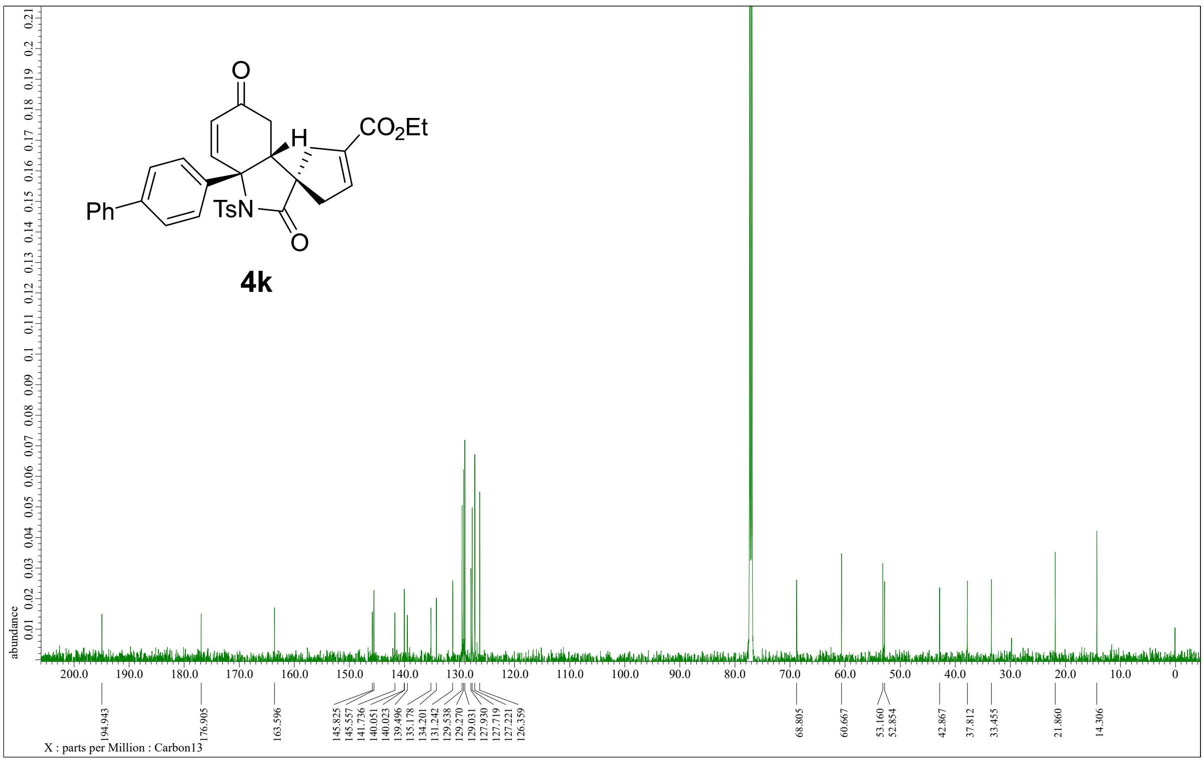
[13]C-NMR (175 MHz, $CDCl_3$) chart of **4j**



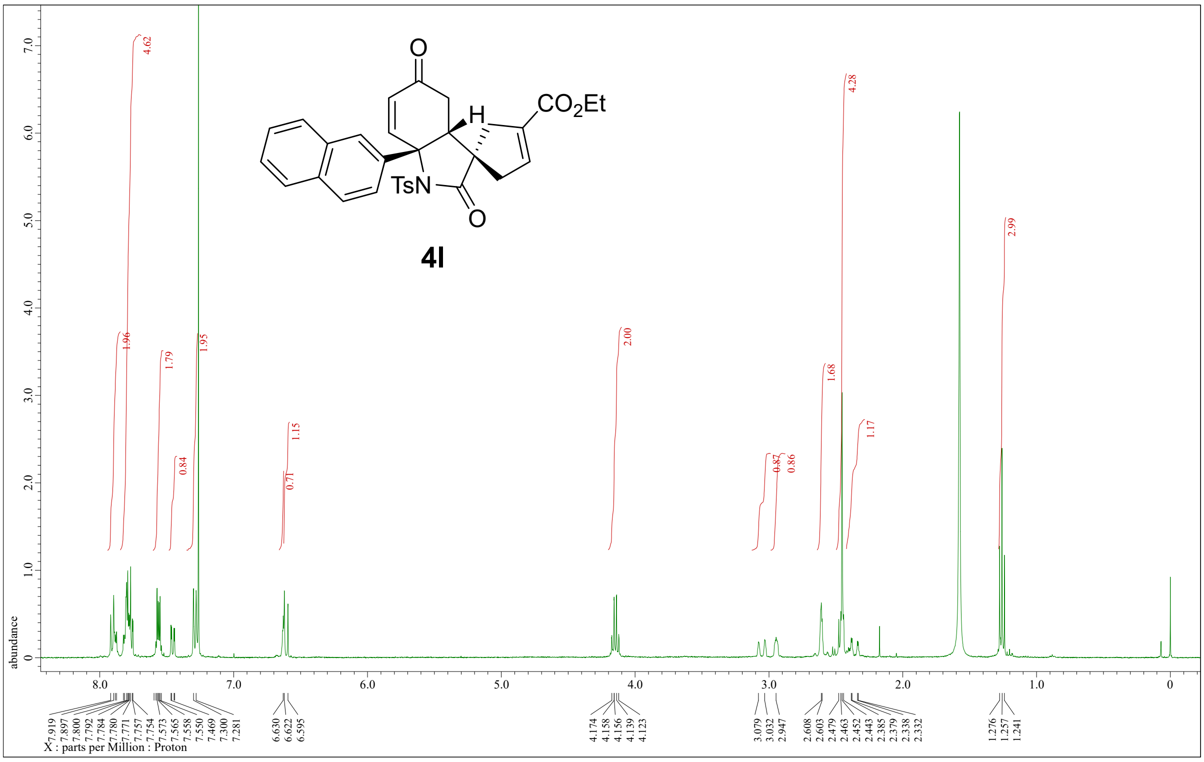
[1]H-NMR (400 MHz, CDCl3) chart of **4k**



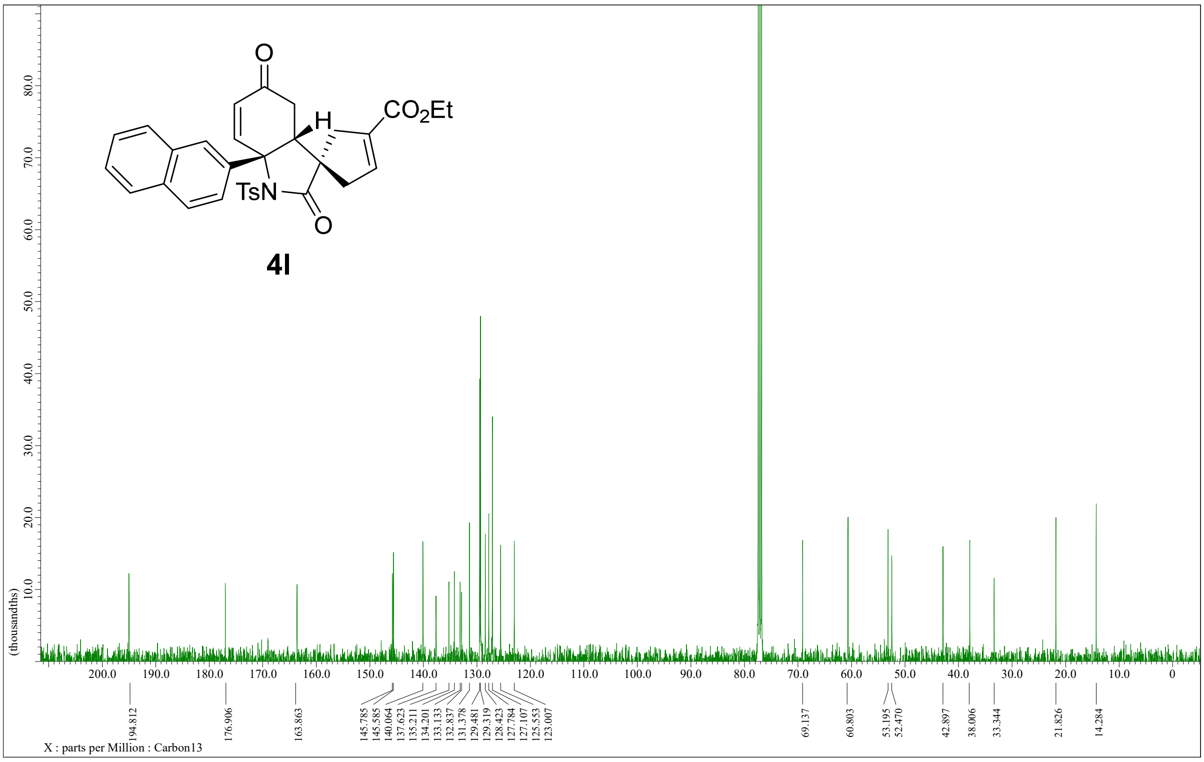
[13]C-NMR (150 MHz, CDCl3) chart of **4k**



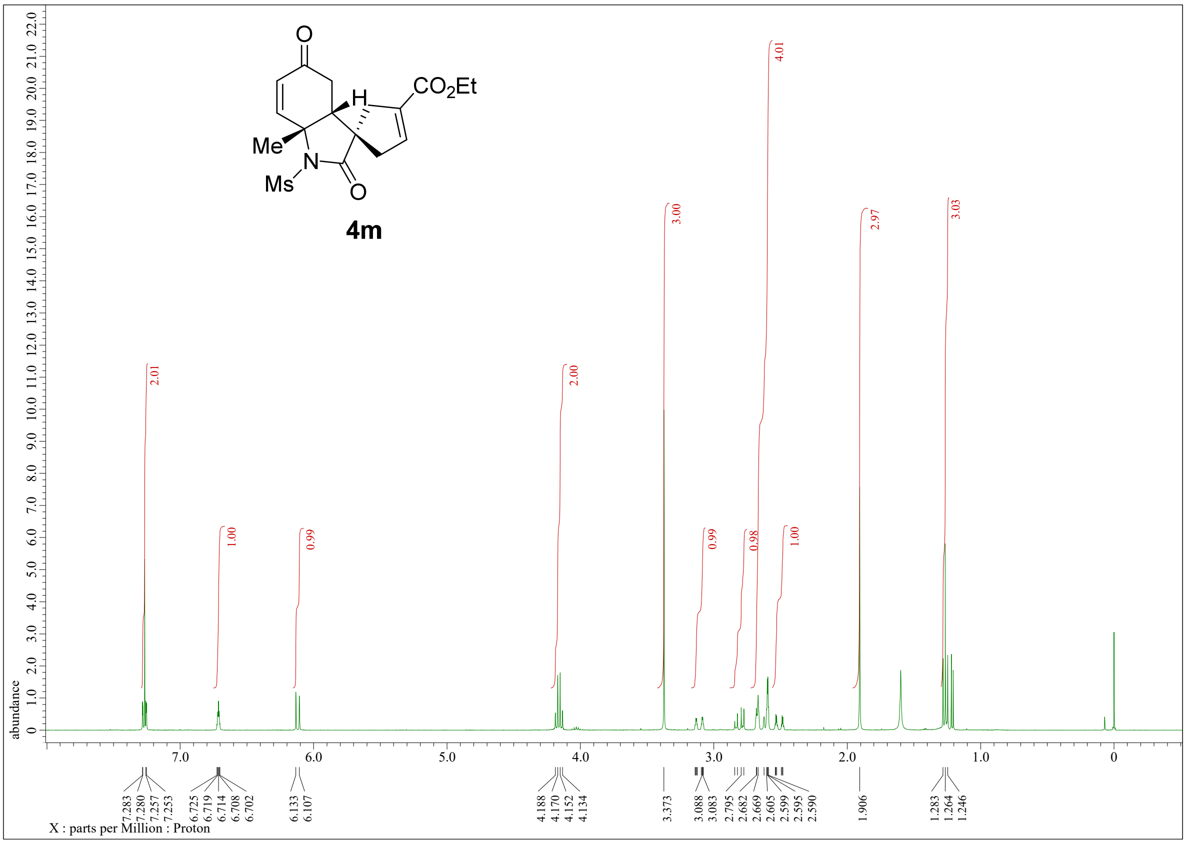
[1]H-NMR (400 MHz, $CDCl_3$) chart of **4l**



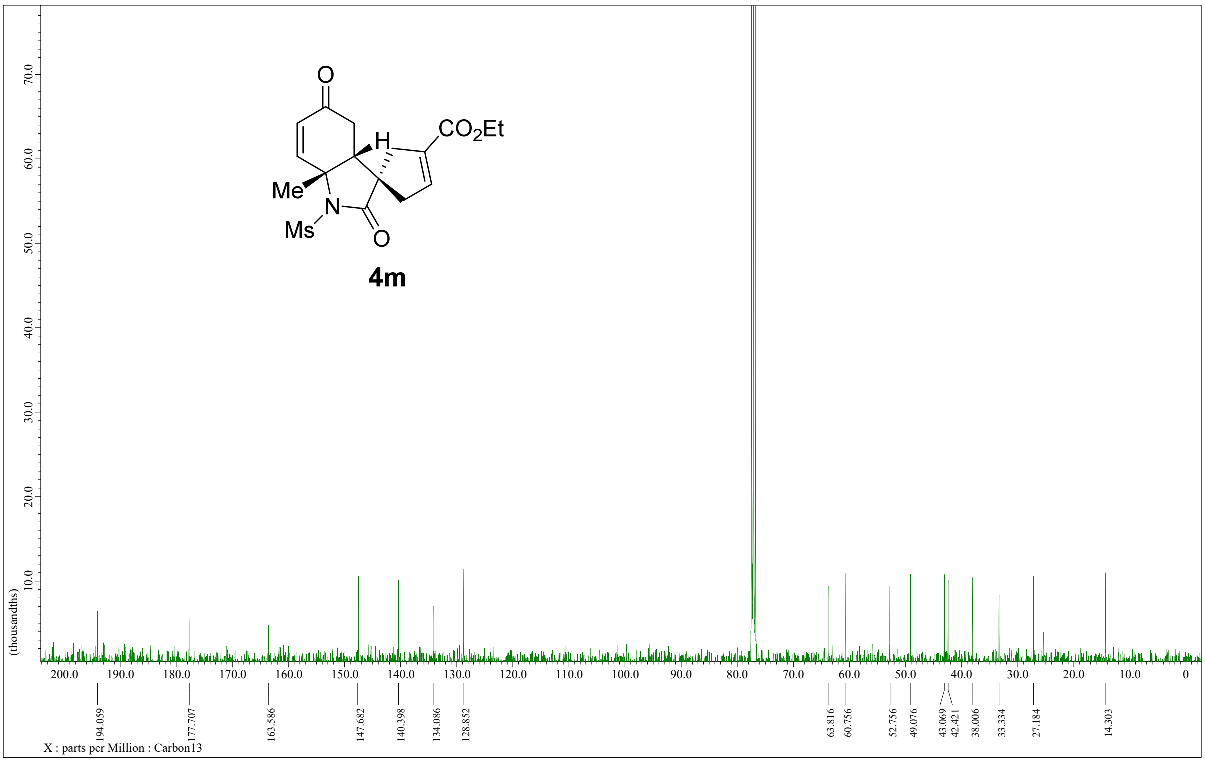
[13]C-NMR (100 MHz, $CDCl_3$) chart of **4l**



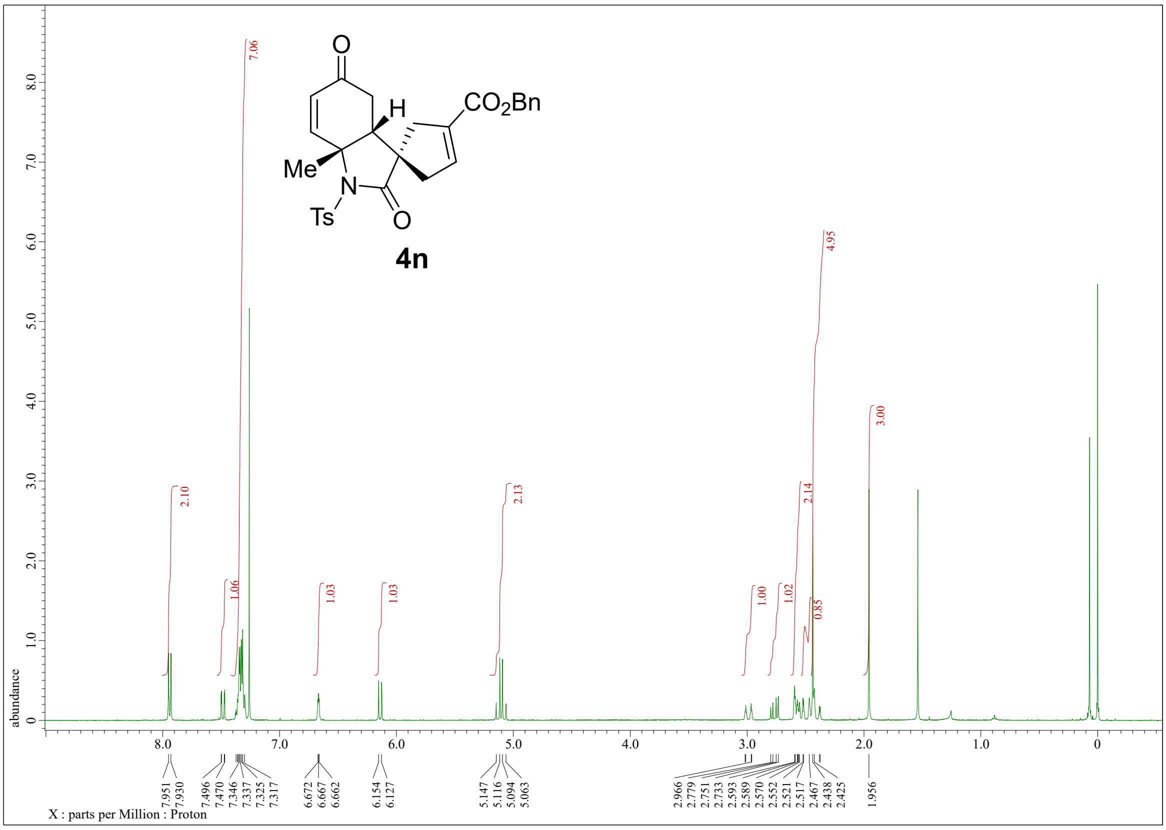
[1]H-NMR (400 MHz, CDCl3) chart of **4m**



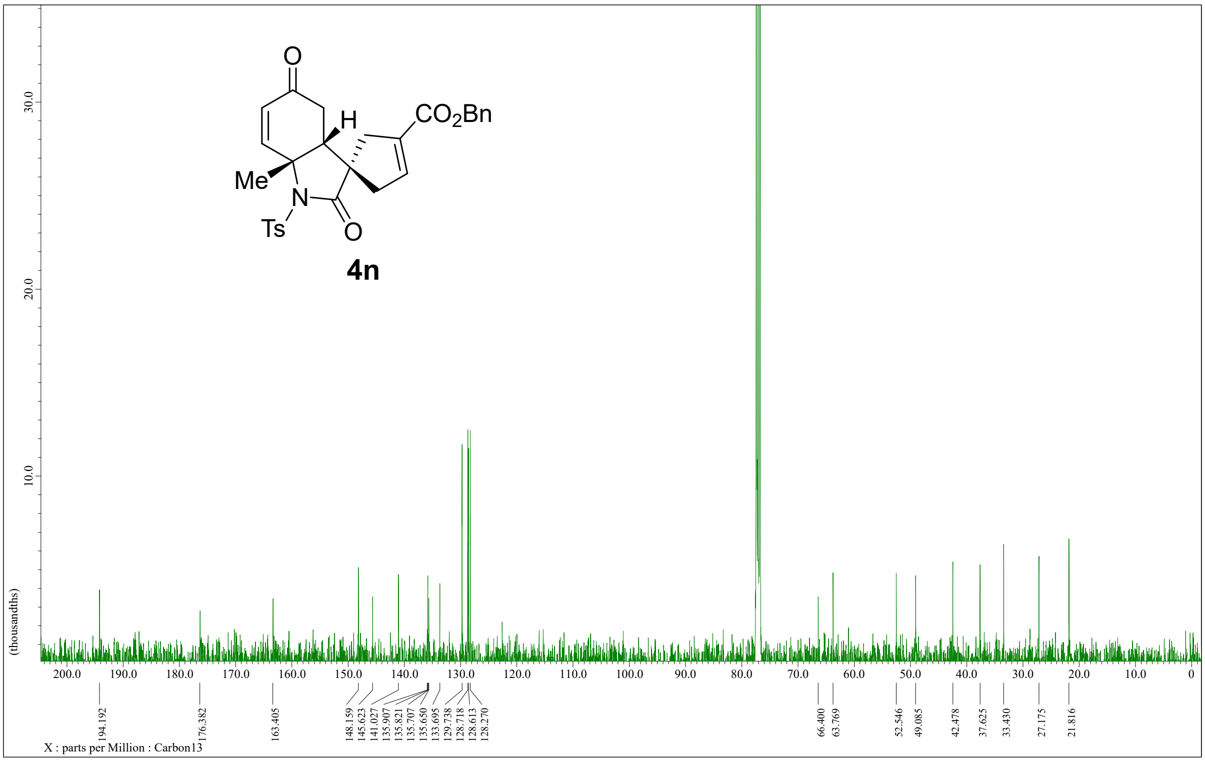
[13]C-NMR (100 MHz, CDCl3) chart of **4m**



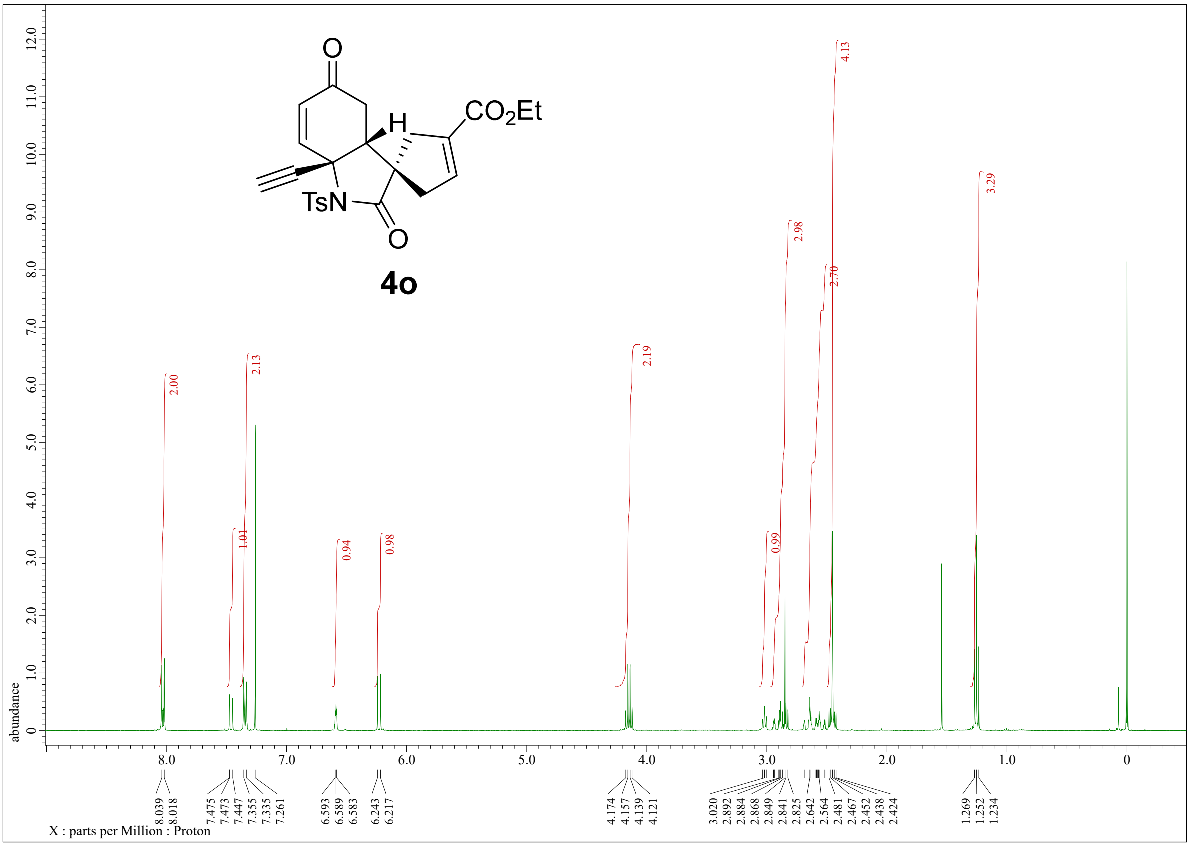
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **4n**



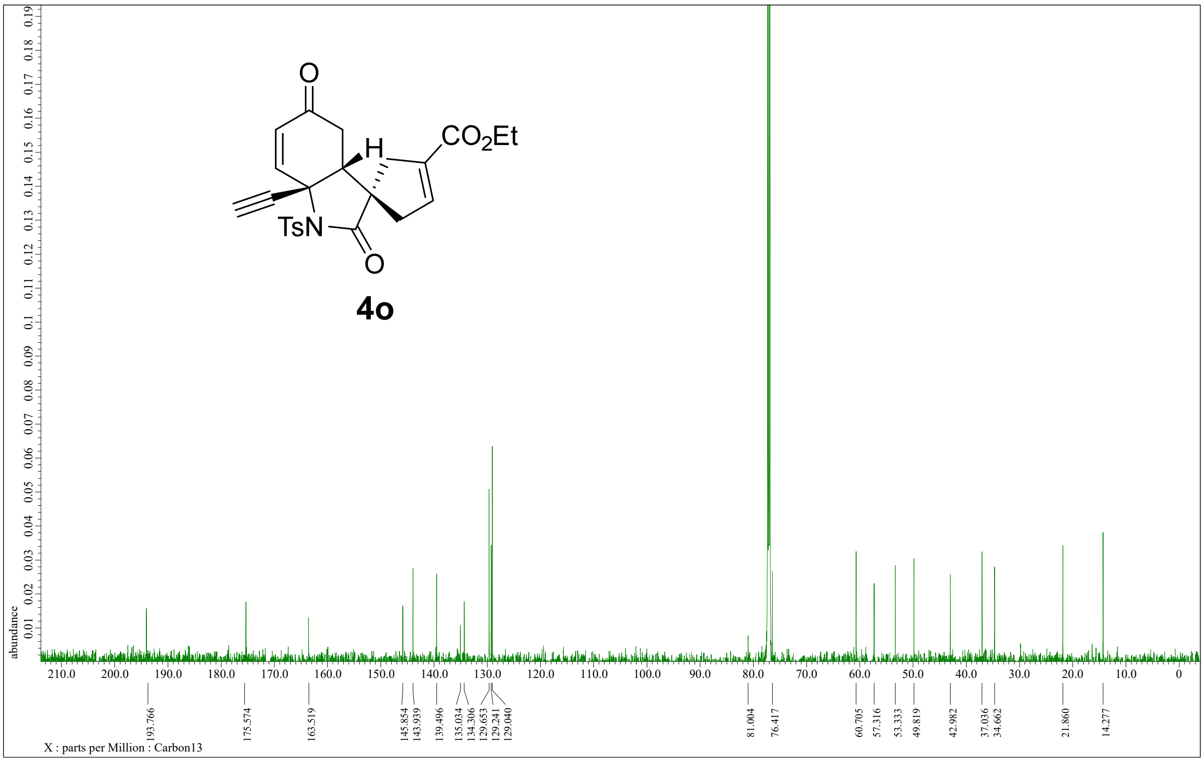
^{13}C-NMR (100 MHz, $CDCl_3$) chart of **4n**



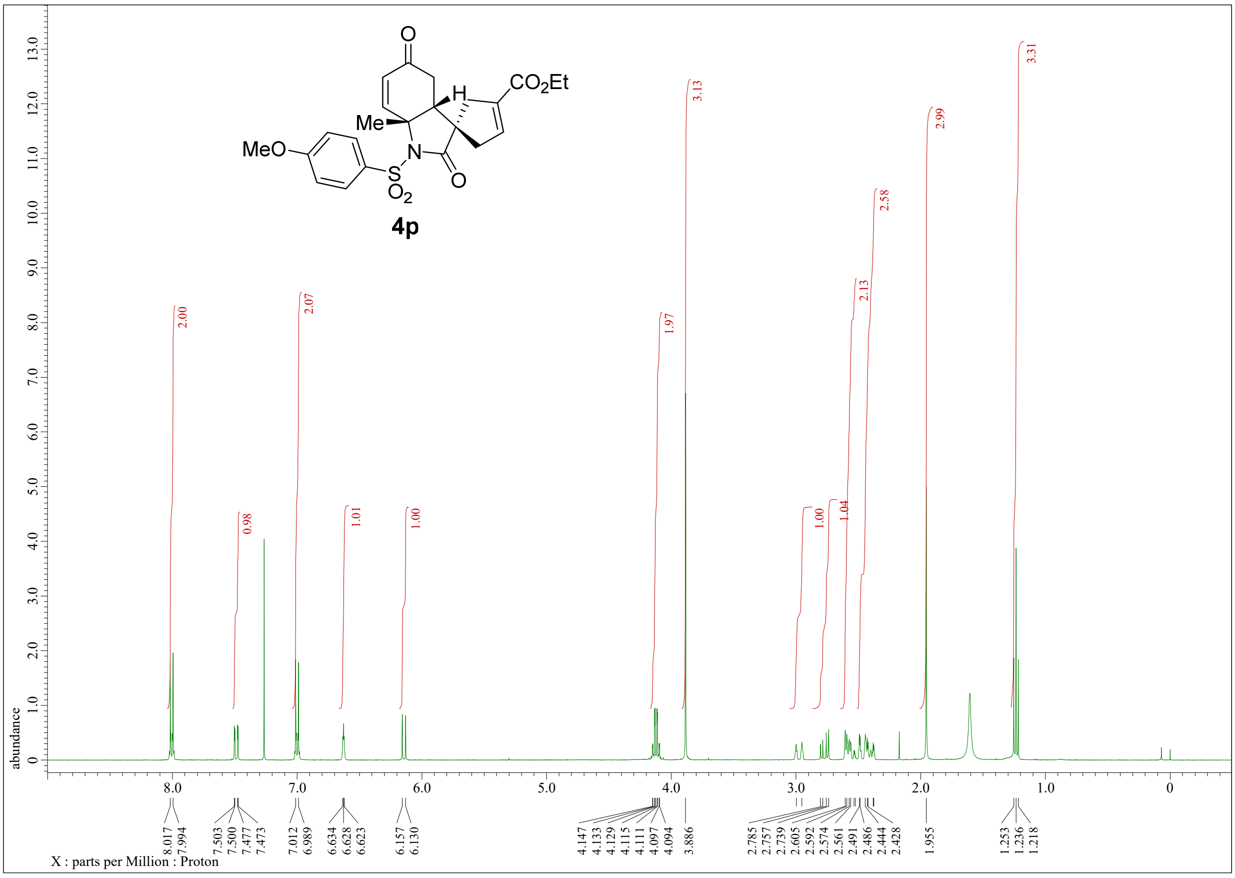
[1]H-NMR (400 MHz, $CDCl_3$) chart of **4o**



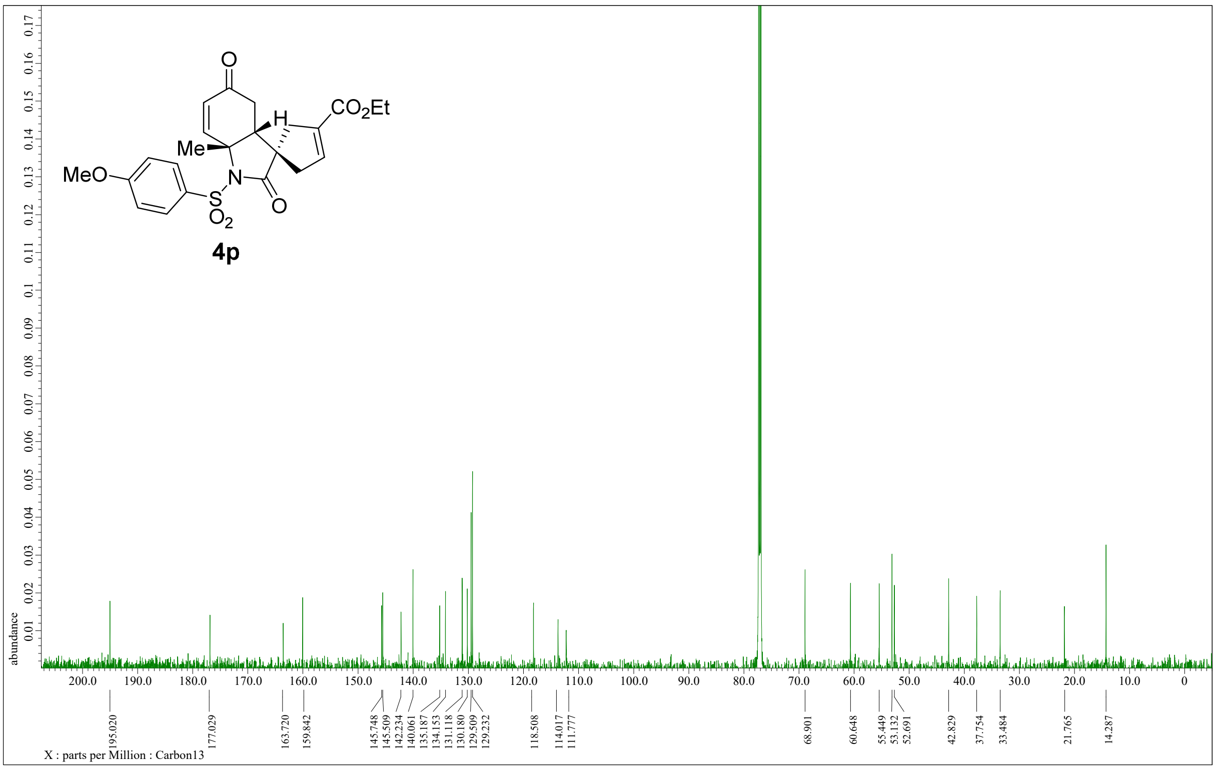
[13]C-NMR (150 MHz, $CDCl_3$) chart of **4o**



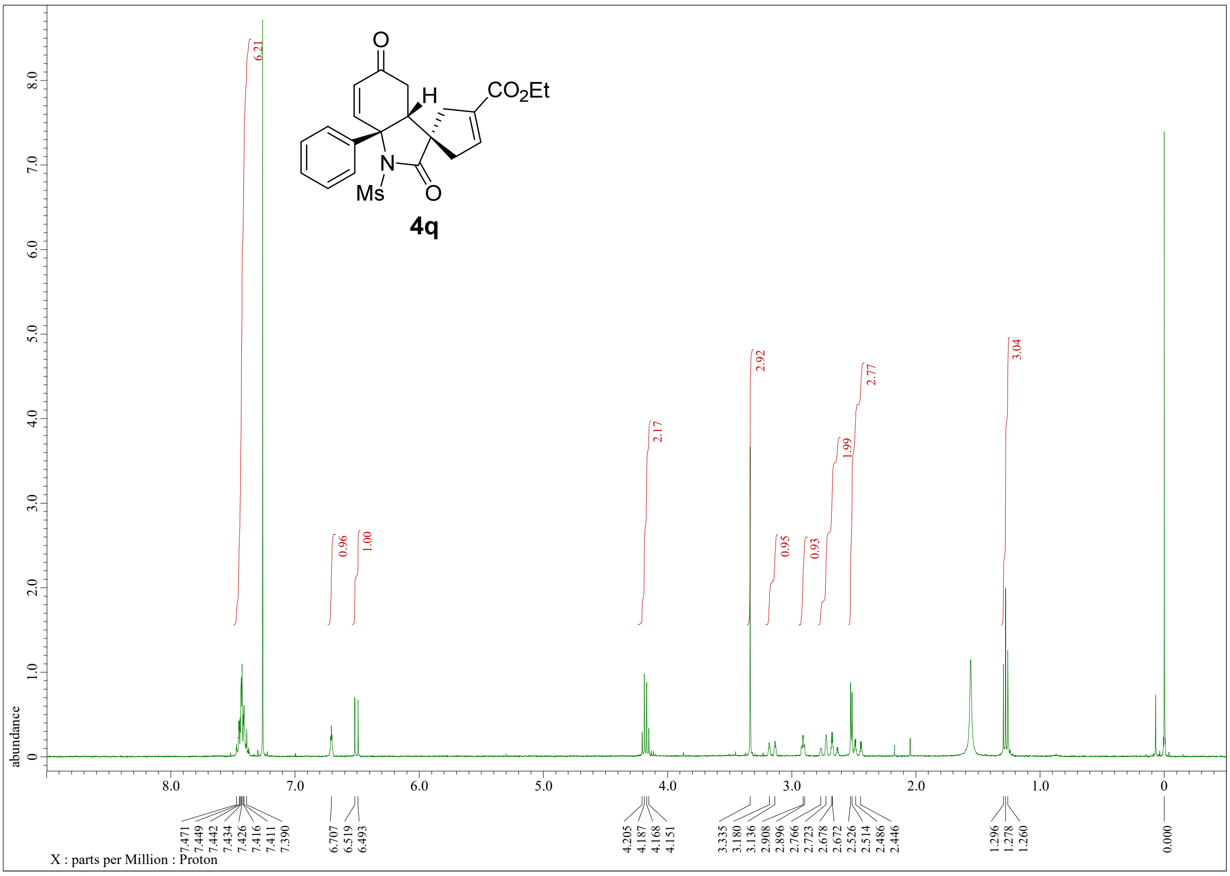
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **4p**



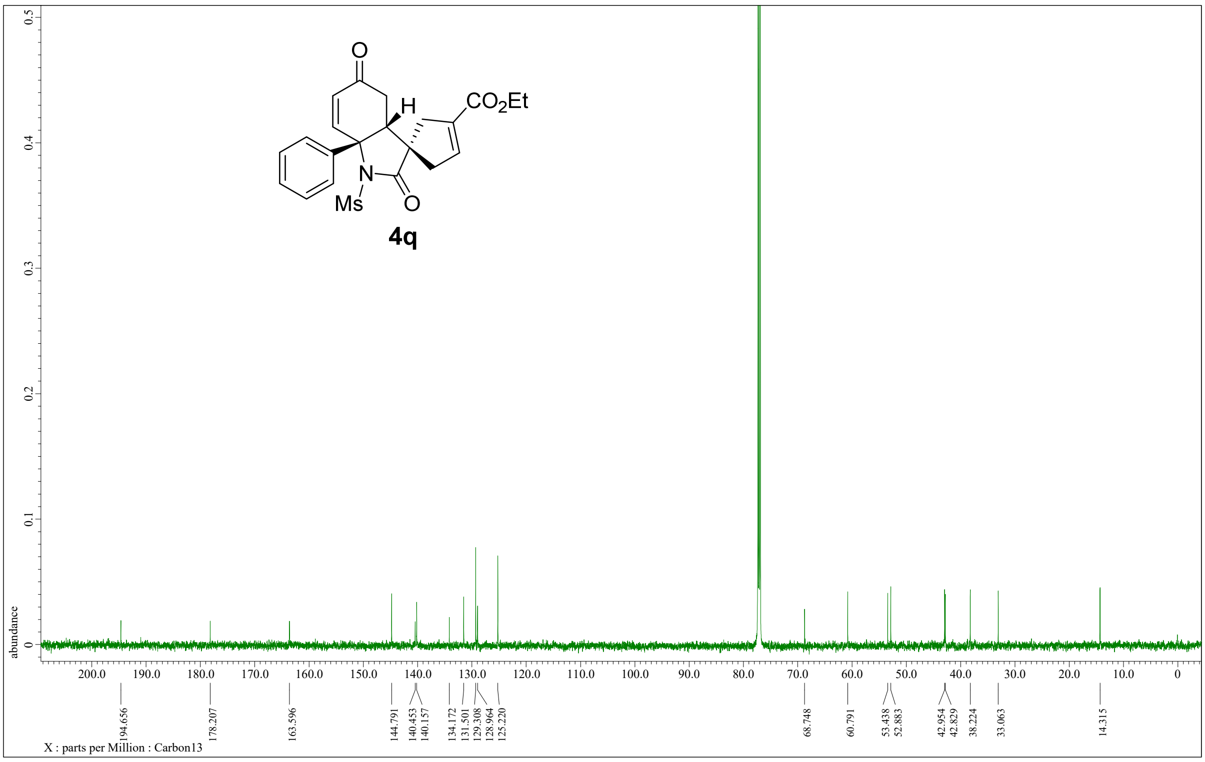
^{13}C-NMR (100 MHz, $CDCl_3$) chart of **4p**



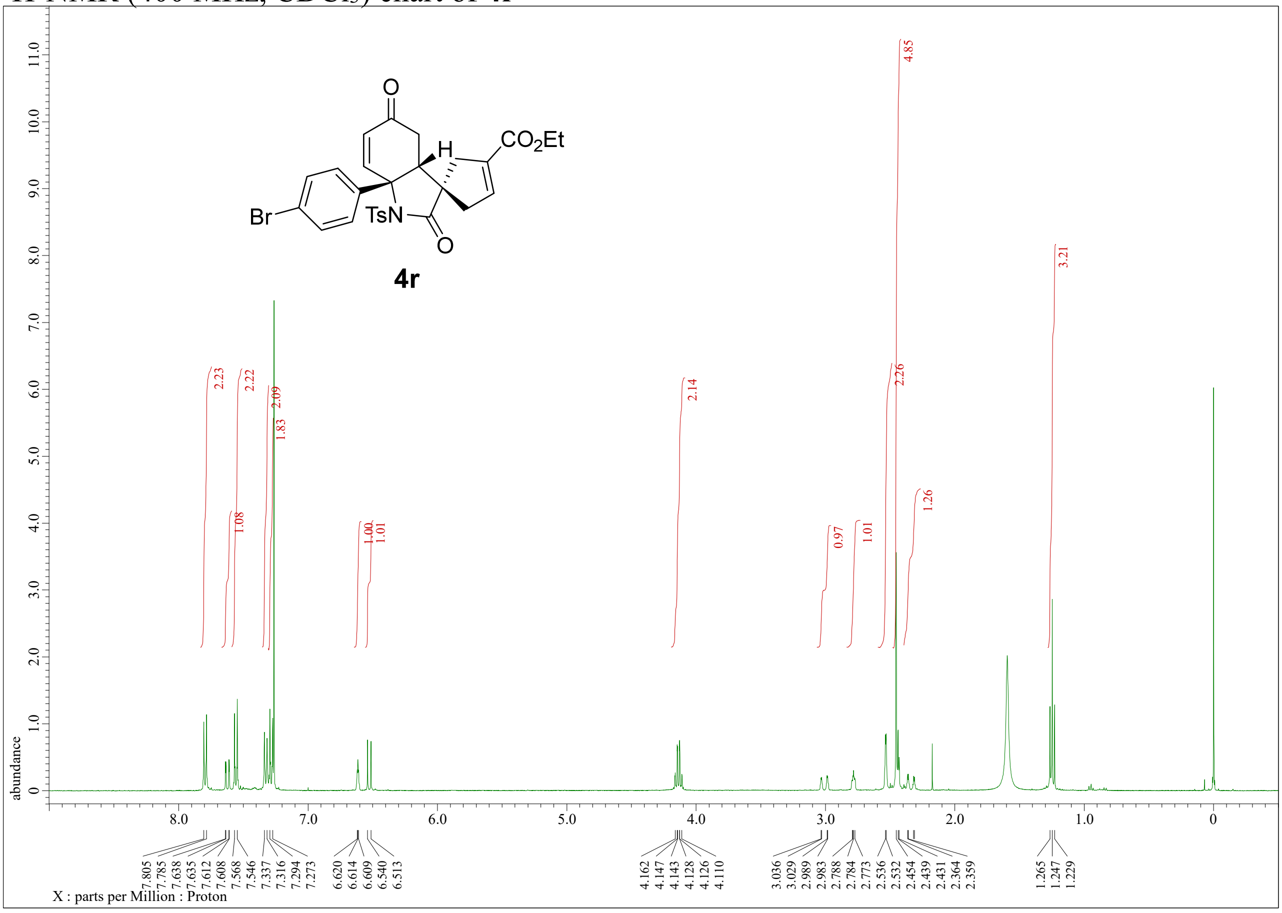
[1]H-NMR (400 MHz, $CDCl_3$) chart of **4q**



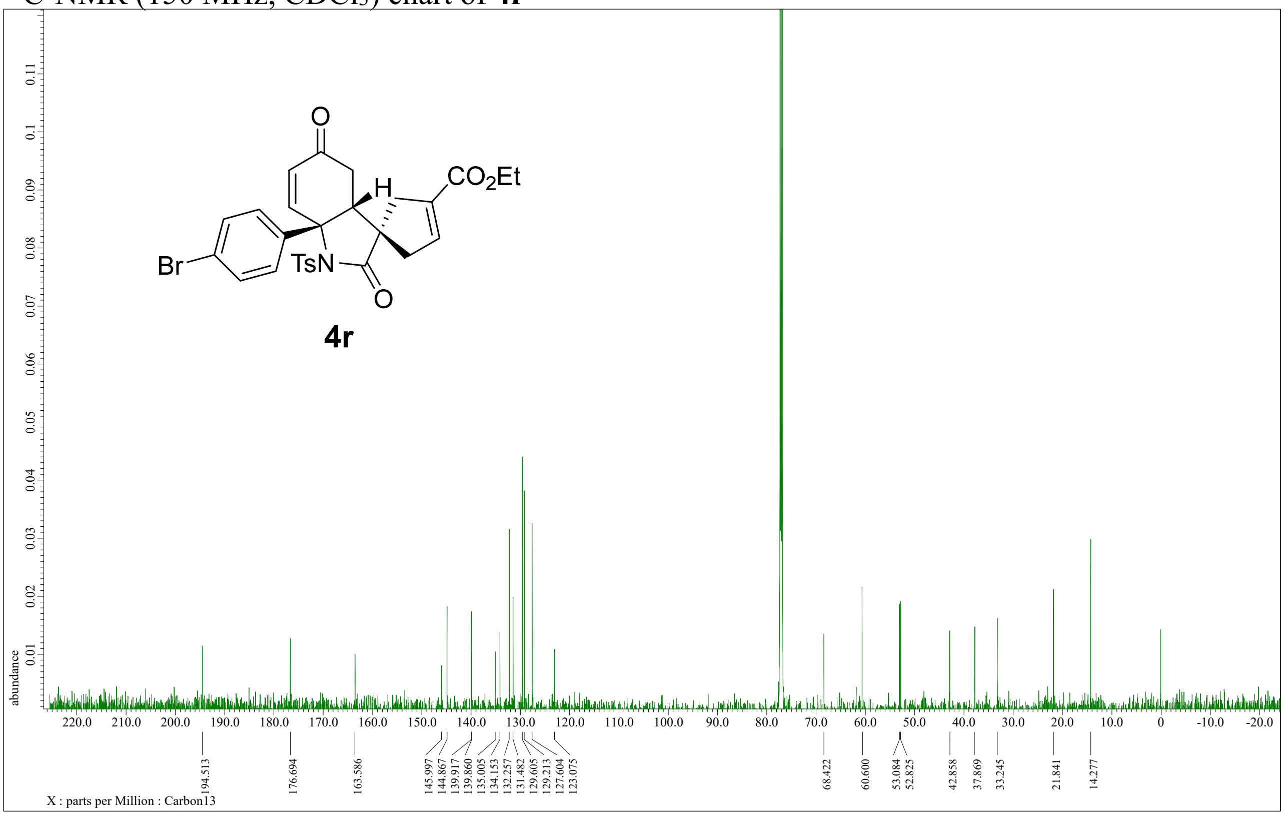
[13]C-NMR (150 MHz, $CDCl_3$) chart of **4q**



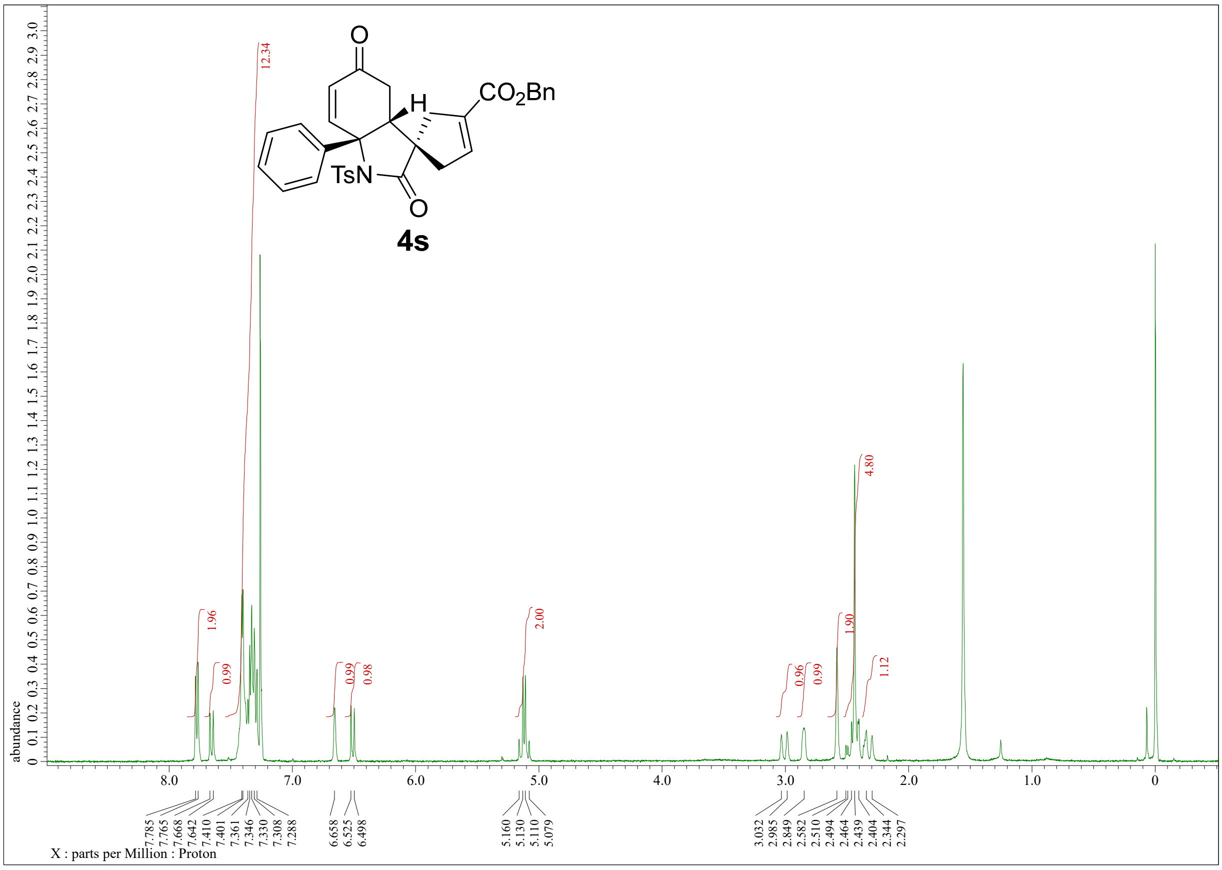
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **4r**



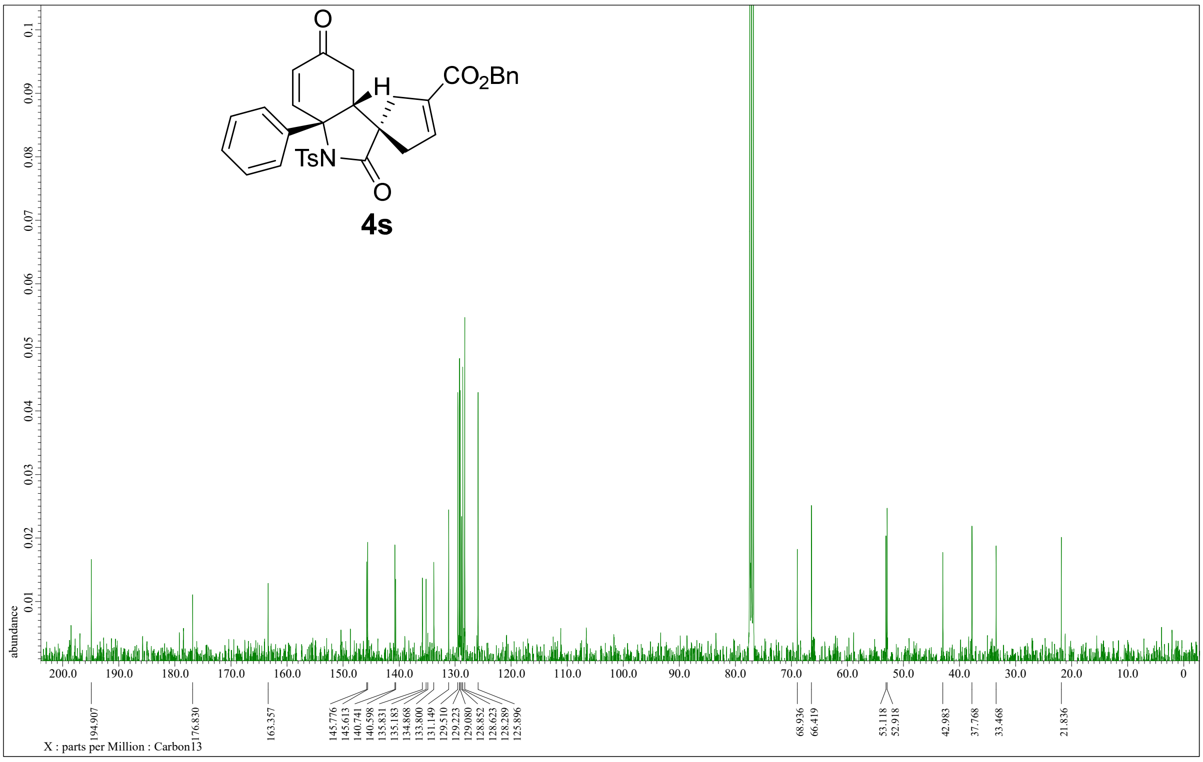
^{13}C-NMR (150 MHz, $CDCl_3$) chart of **4r**



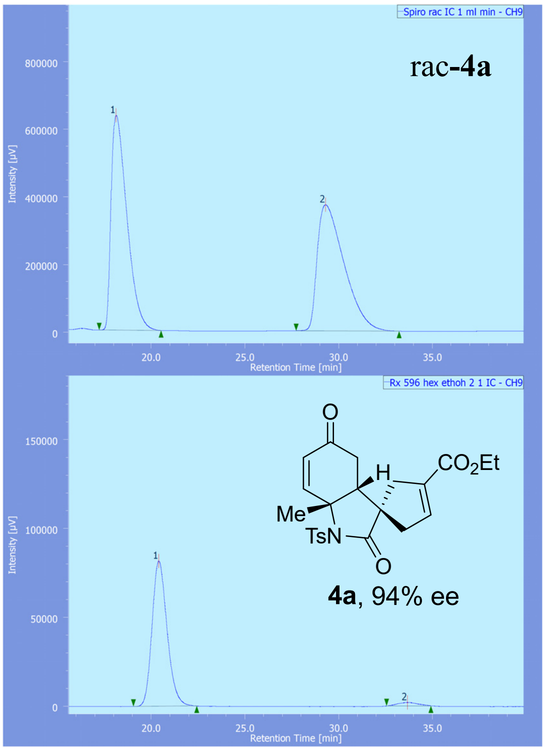
^{1}H-NMR (400 MHz, $CDCl_3$) chart of **4s**



^{13}C-NMR (100 MHz, $CDCl_3$) chart of **4s**



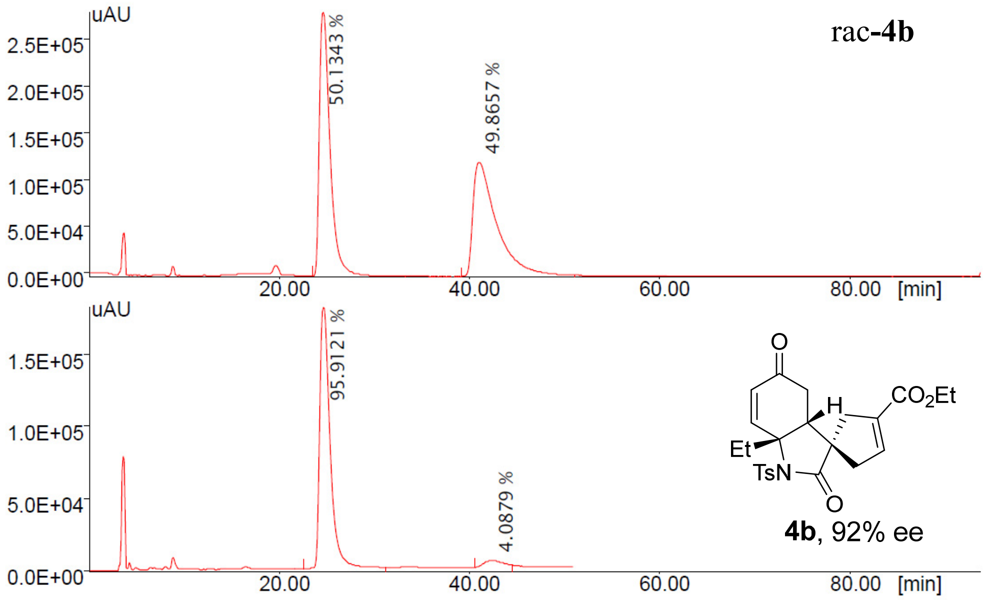
HPLC charts of **4a**



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	20.403	4555434	81718	96.926	97.705	N/A	3176	7.416	1.221	
2	Unknown	9	33.662	144469	1919	3.074	2.295	N/A	3971	N/A	1.074	

HPLC Conditions: Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 215 nm, tR = 24.0 min (major isomer) and 41.1 min (minor isomer).

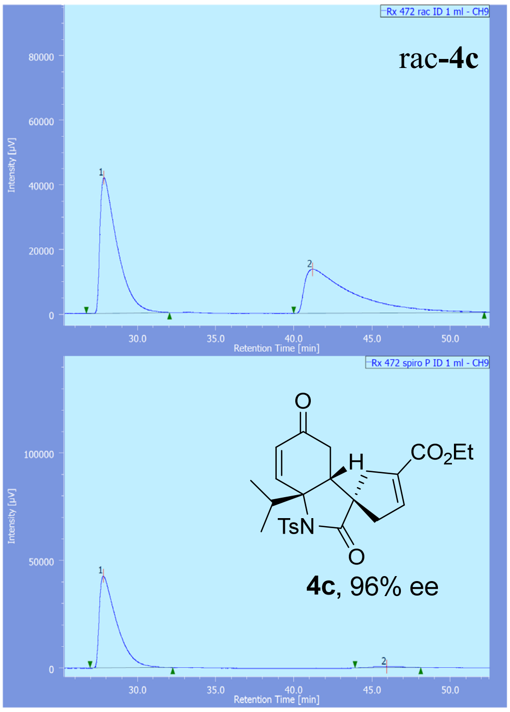
HPLC chart of **4b**



#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		24.573	180667	12440902.092	95.91
2		42.347	4225	530248.808	4.09

HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 225 nm, tR = 24.6 min (major isomer) and 41.4 min (minor isomer).

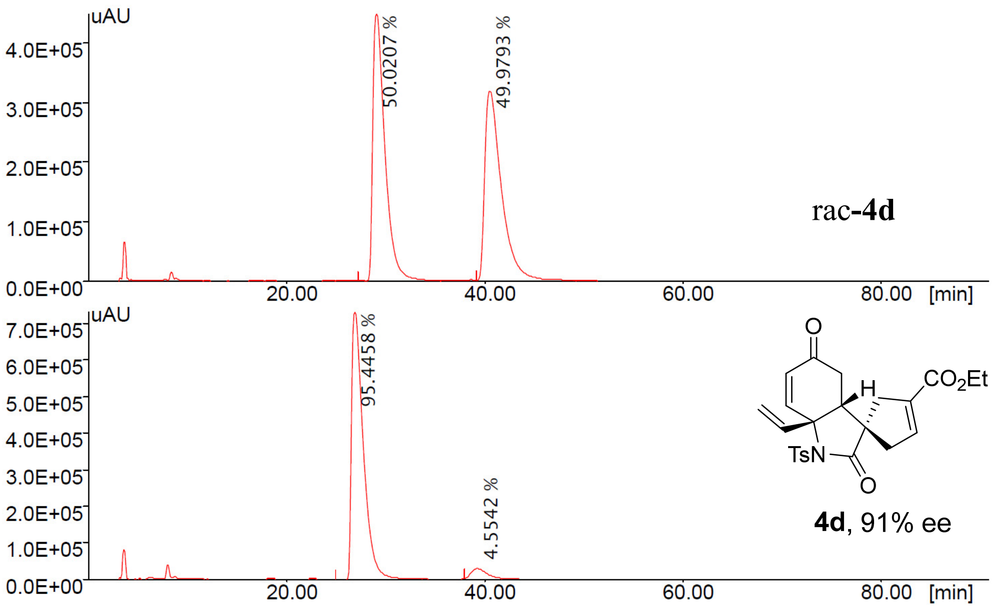
HPLC charts of **4c**



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	27.822	3301881	42851	98.148	98.956	N/A	3326	5.854	3.044	
2	Unknown	9	45.927	62320	452	1.852	1.044	N/A	1849	N/A	1.038	

HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 250 nm, tR = 27.8 min (major isomer) and 45.9 min (minor isomer).

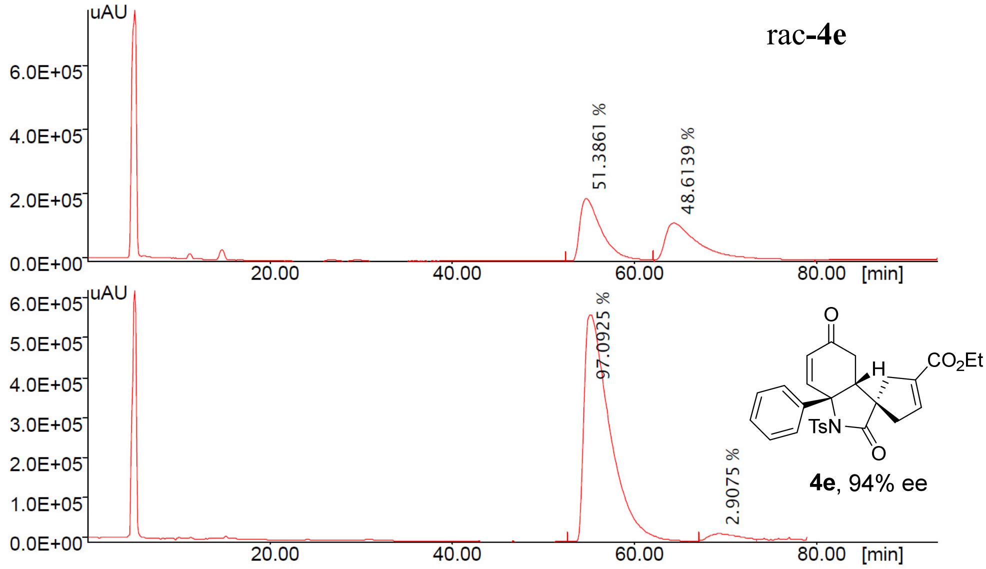
HPLC charts of **4d**



#	Name	RT	Height [uAU]	Area [uAU. Sec]	%Area
1		26.840	729283	55653754.458	95.45
2		39.187	26962	2655509.640	4.55

HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 225 nm, tR = 26.8 min. (major isomer) and 39.0 min min. (minor isomer).

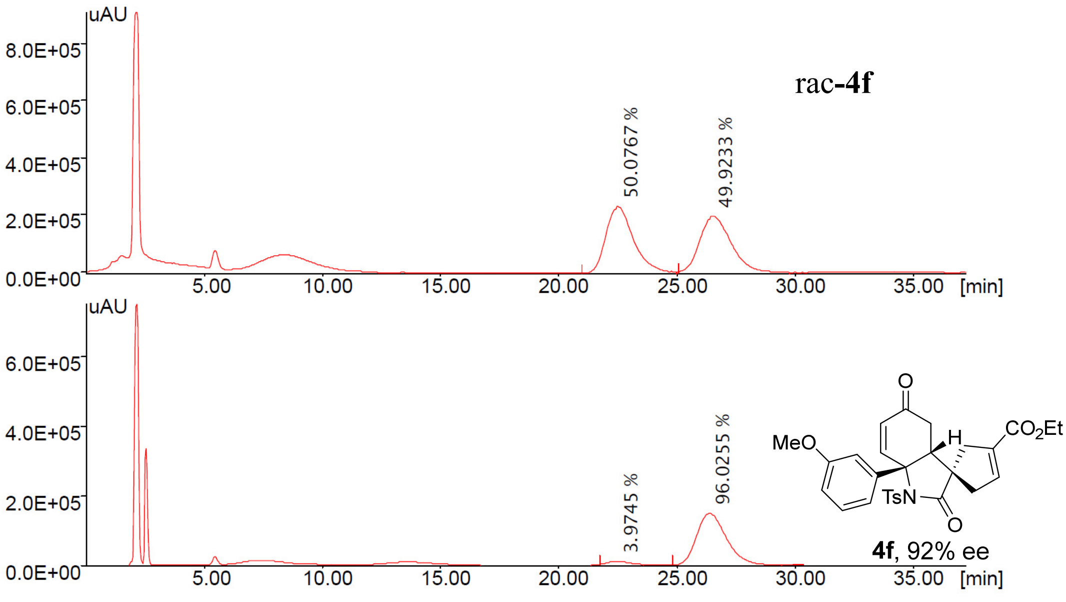
HPLC charts of **4e**



#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		55.040	568888	107672487.610	97.09
2		69.227	16240	3224325.648	2.91

HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 213 nm, tR = 55.0 min (major isomer) and 69.2 min (minor isomer).

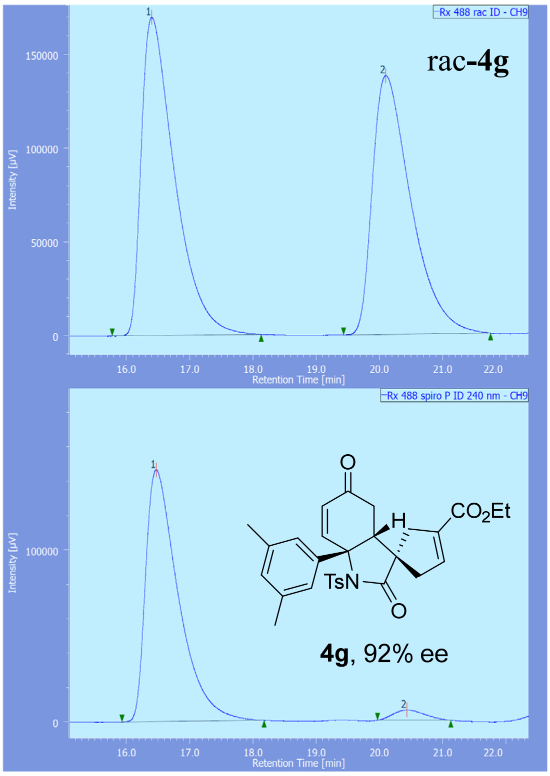
HPLC charts of **4f**



#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		22.467	9054	523688.008	3.97
2		26.347	148175	12652411.389	96.03

HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 212 nm, tR = 22.5 min (minor isomer) and 26.4 min (major isomer).

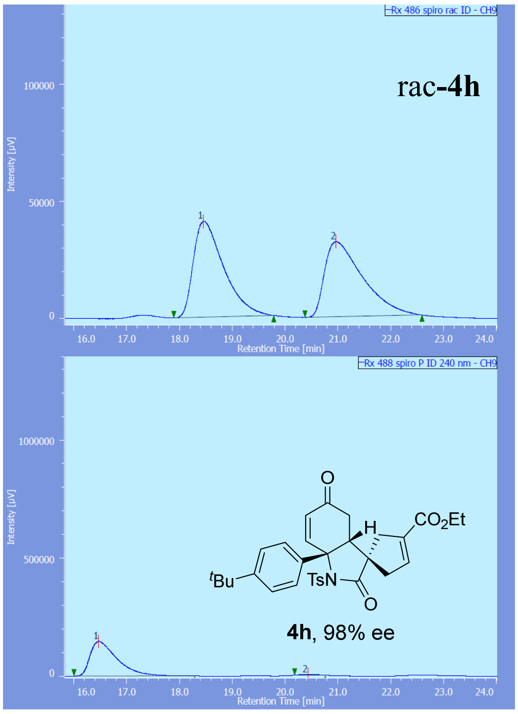
HPLC charts of **4g**



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	16.472	5253417	146457	96.187	96.074	N/A	5277	4.261	1.984	
2	Unknown	9	20.432	208264	5985	3.813	3.926	N/A	7298	N/A	1.231	

HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 254 nm, tR = 16.5 min (major isomer) and 20.4 min (minor isomer).

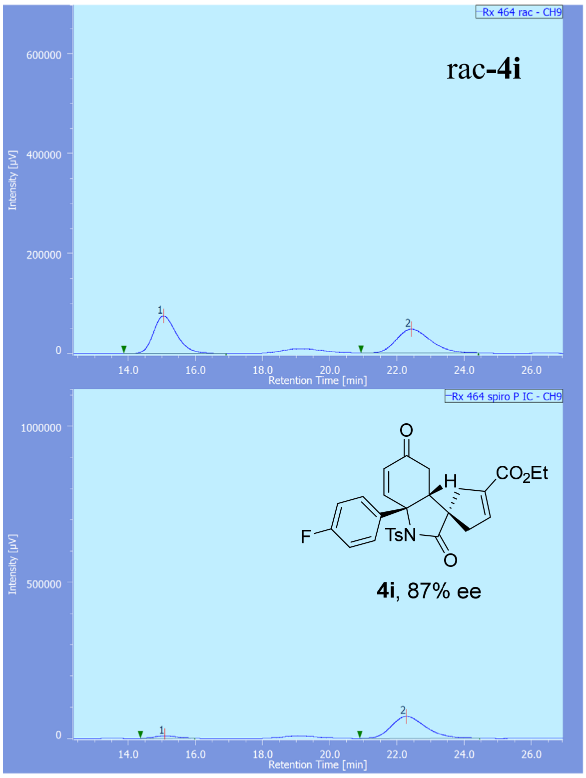
HPLC charts of **4h**



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	16.472	5260569	146408	98.770	97.946	N/A	5276	5.173	1.993	
2	Unknown	9	20.432	65521	3071	1.230	2.054	N/A	16940	N/A	1.148	

HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 254 nm, tR = 18.5 min (minor isomer) and 20.5 min (major isomer).

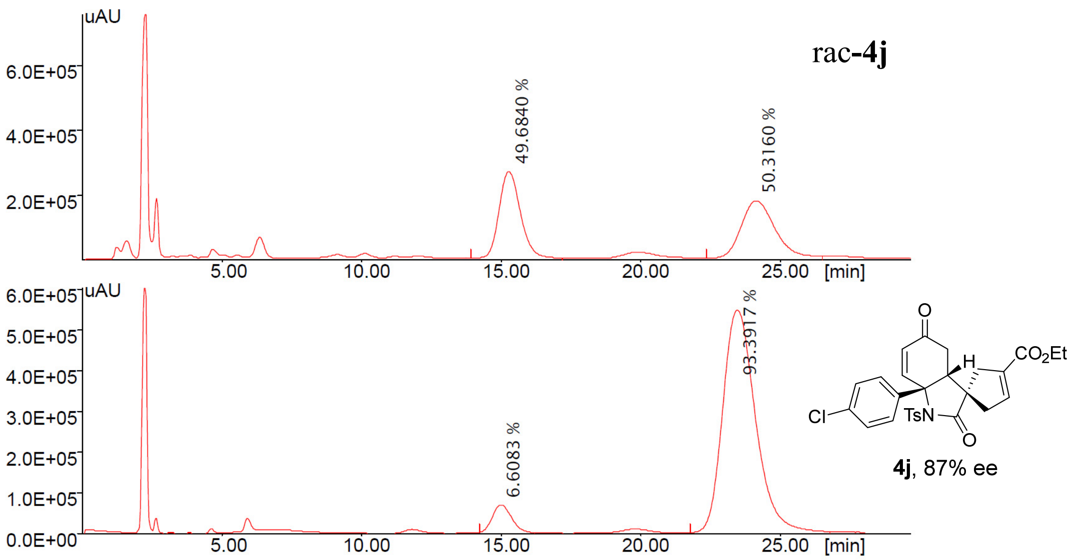
HPLC charts of **4i**



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	15.093	335388	7632	6.385	9.845	N/A	2585	4.767	1.113	
2	Unknown	9	22.273	4917687	69888	93.615	90.155	N/A	2363	N/A	1.264	

HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 254 nm, tR = 15.1 min. (minor isomer) and 22.3 min (major isomer).

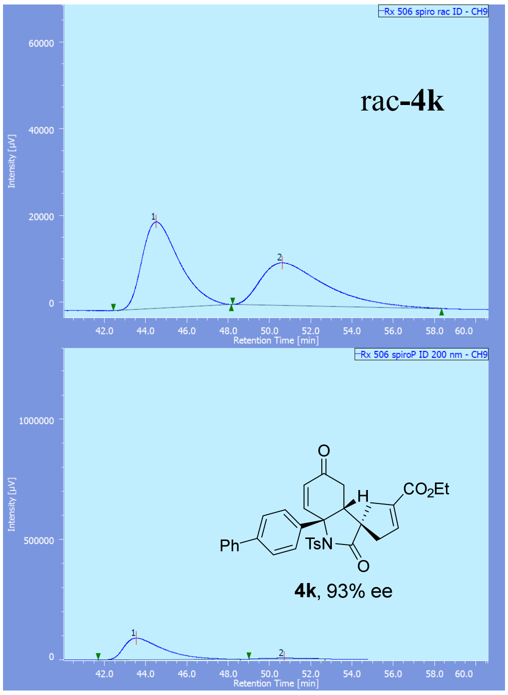
HPLC charts of **4j**



#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		14.987	67417	3048528.845	6.61
2		23.427	546498	43083258.242	93.39

HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 230 nm, tR = 15.0 min (minor isomer) and 23.7 min (major isomer).

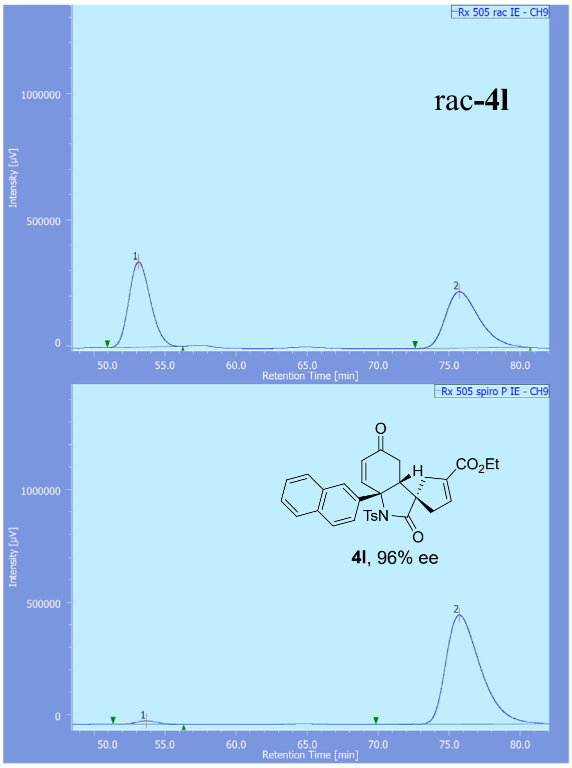
HPLC charts of **4k**



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	43.540	11681027	89380	96.423	96.362	N/A	2732	2.036	2.019	
2	Unknown	9	50.710	433269	3375	3.577	3.638	N/A	2960	N/A	1.087	

HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 200 nm tR = 43.5 min (major isomer) and 50.7 min (minor isomer).

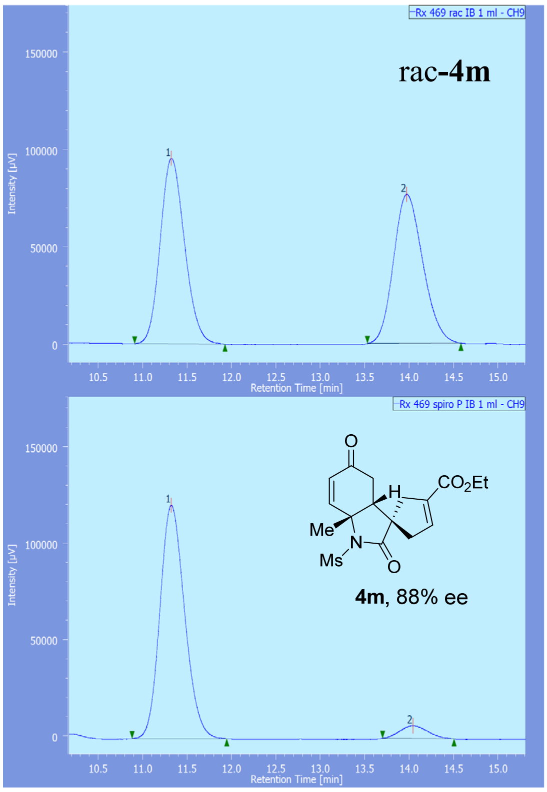
HPLC charts of **4l**



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	53.683	1602672	15261	1.919	3.054	N/A	5941	6.164	1.083	
2	Unknown	9	75.702	81910377	484427	98.081	96.946	N/A	4785	N/A	1.506	

HPLC conditions: Daicel Chiralpak IE column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 230 nm, tR = 53.7 min (minor isomer) and 75.7 min (major isomer).

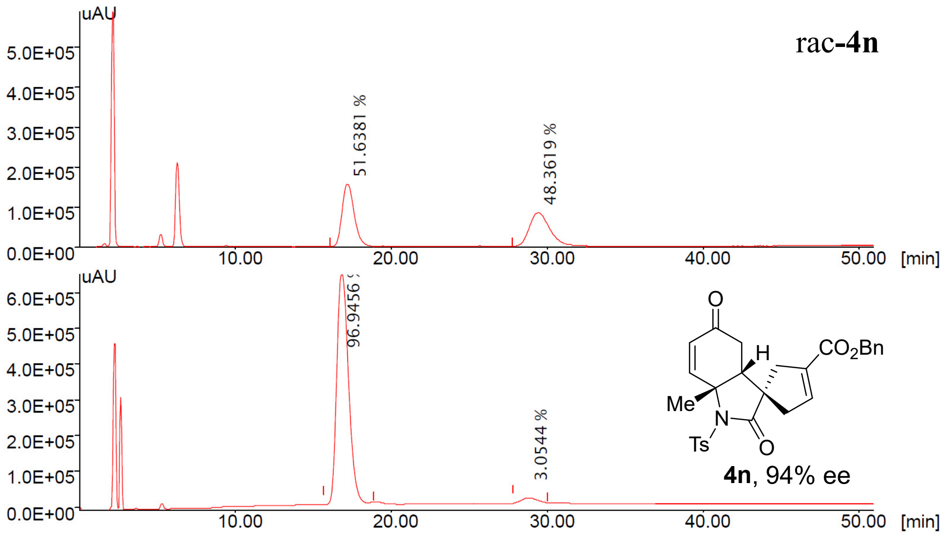
HPLC charts of **4m**



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	11.322	2333698	120877	94.129	94.782	N/A	7976	4.951	1.161	
2	Unknown	9	14.042	145569	6655	5.871	5.218	N/A	8925	N/A	1.114	

HPLC conditions: Daicel Chiralpak IB column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 245 nm, tR = 11.3 min (major isomer) and 14.0 min (minor isomer).

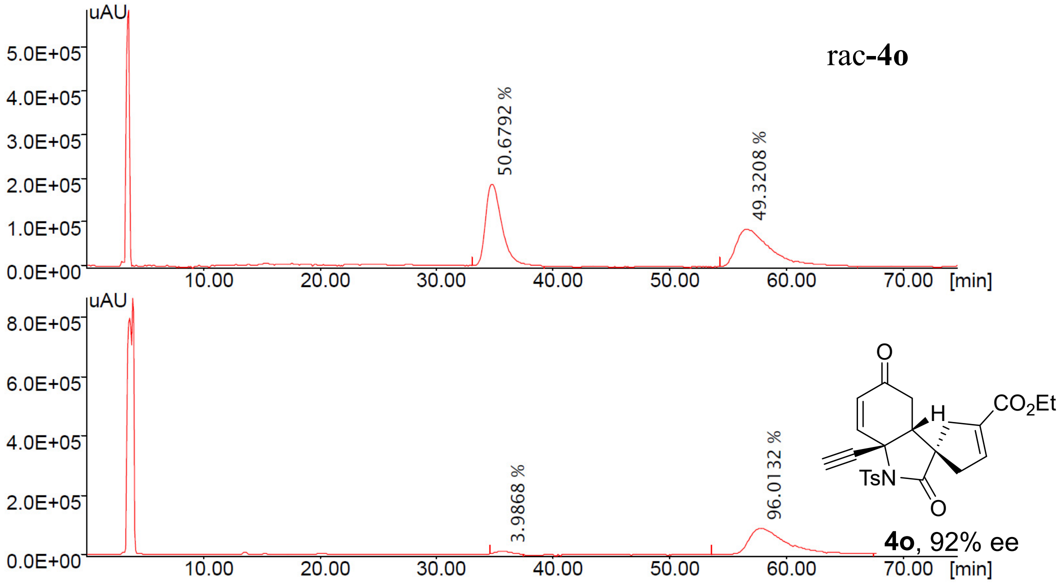
HPLC charts of **4n**



#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		16.813	641592	31254190.240	96.95
2		28.800	14197	984714.415	3.05

HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, flow rate 1.0 mL/min, 217 nm: 16.8 min. (major isomer) and 28.8 min (minor isomer).

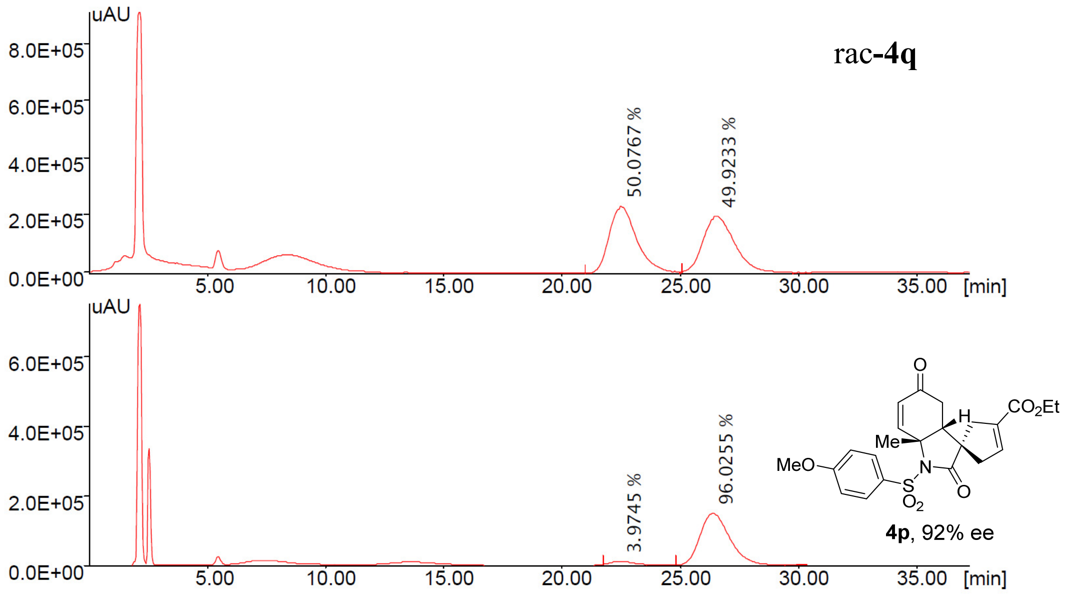
HPLC charts of **4o**



#	Name	RT	Height[uAU]	Area[uAU. Sec]	%Area
1		22.467	9054	523688.008	3.97
2		26.347	148175	12652411.389	96.03

HPLC conditions: Daicel Chiralpak IE column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 212 nm, tR = 35.8 min. (minor isomer) and 57.8 min(major isomer).

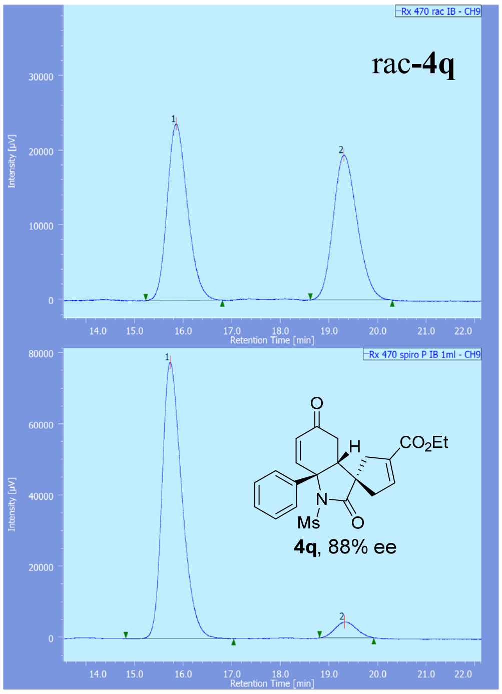
HPLC charts of **4p**



#	Name	RT	Height[uAU]	Area[uAU. Sec]	%Area
1		35.840	8817	750133.611	3.99
2		57.773	86297	18065376.815	96.01

HPLC conditions: Daicel Chiralpak ID column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 240 nm, tR = 40.9 min, (major isomer) and 76.3 min (minor isomer).

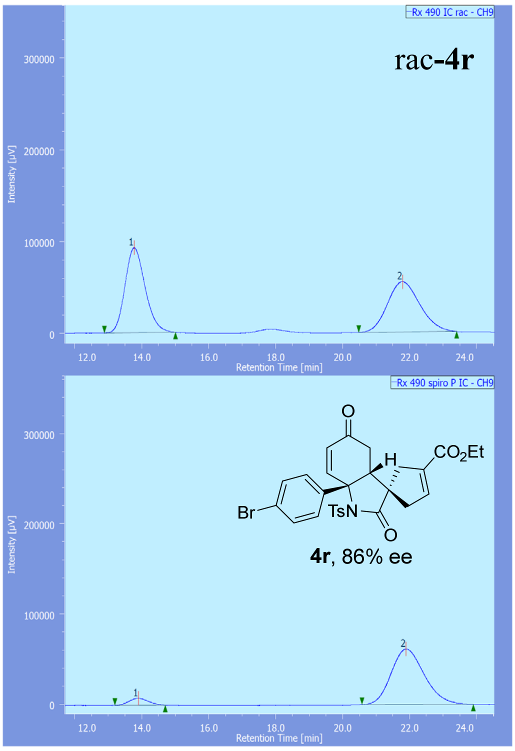
HPLC charts of **4q**



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	15.730	2183316	77609	94.024	94.541	N/A	7426	4.588	1.351	
2	Unknown	9	19.322	138758	4482	5.976	5.459	N/A	8473	N/A	1.101	

HPLC conditions: Daicel Chiralpak IB column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 254 nm, tR = 15.7 min (major isomer) and 19.3 min (minor isomer).

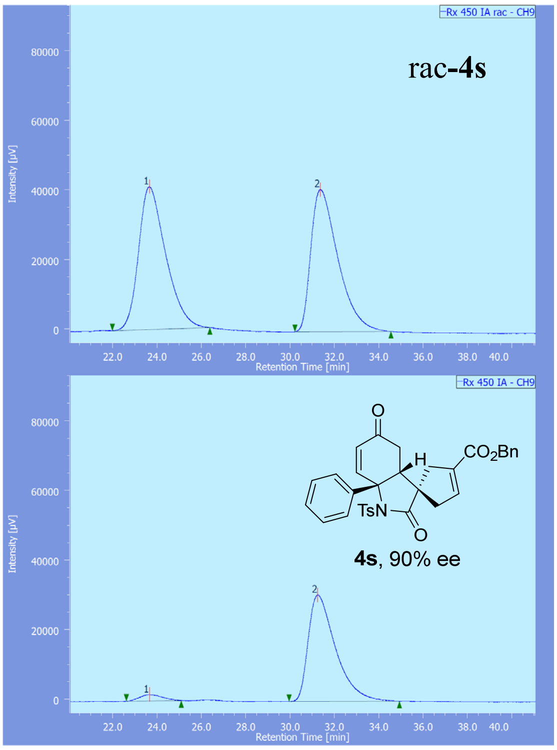
HPLC charts of **4r**



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	13.905	311497	7710	6.860	11.150	N/A	2599	5.522	1.075	
2	Unknown	9	21.892	4229344	61440	93.140	88.850	N/A	2342	N/A	1.190	

HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 245 nm, tR = 13.9 min (minor isomer) and 21.9 min (major isomer).

HPLC charts of **4s**



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	23.662	131098	1840	4.764	5.680	N/A	2405	3.703	1.210	
2	Unknown	9	31.248	2620880	30564	95.236	94.320	N/A	3291	N/A	1.764	

HPLC conditions: Daicel Chiralpak IC column, *n*-hexane/EtOH = 2/1, 1.0 mL/min, 217 nm, 23.7 min, (minor isomer) and 31.2 min (major isomer).