Asymmetric α-Electrophilic Difluoromethylation of β-Keto Esters by Phase Transfer Catalysis

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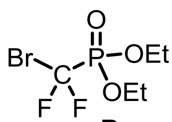
A. General Information:

Unless otherwise stated, all commercial reagents and solvents were used without further additional purification. Analytical TLC was visualized with UV light at 254 nm. Thin layer chromatography was carried out on TLC aluminum sheets with silica gel 60 F_{254}. Purification of reaction products was carried out with chromatography on silica gel 60 (200-300 mesh). ^{1}H NMR (400 MHz) spectra was obtained at 25 ℃; ^{13}C NMR (126 MHz) were recorded on a VARIAN INOVA-400M and AVANCE II 400 spectrometer at 25 ℃. Chemical shifts are reported as δ (ppm) values relative to TMS as internal standard and coupling constants (J) in Hz. The enantiomeric excesses (*ee*) were determined by HPLC. HPLC analyses were performed on equipped with Diacel Chiralpak AD-H or OJ-H chiral column (0.46 cm × 25 cm), using mixtures of n-hexane/isopropyl alcohol as mobile phase, at 25 ℃. Mass spectra are reported by using electron ionization and electrospray ionization techniques. Melting points were determined with a hot plate apparatus. Optical rotations were measured on a digital polarimeter with a sodium lamp at 15 ^{o}C. **Cat-1-Cat-4** were purchased from Sinocompound.

Materials:

1. Difluoromethylation reagents

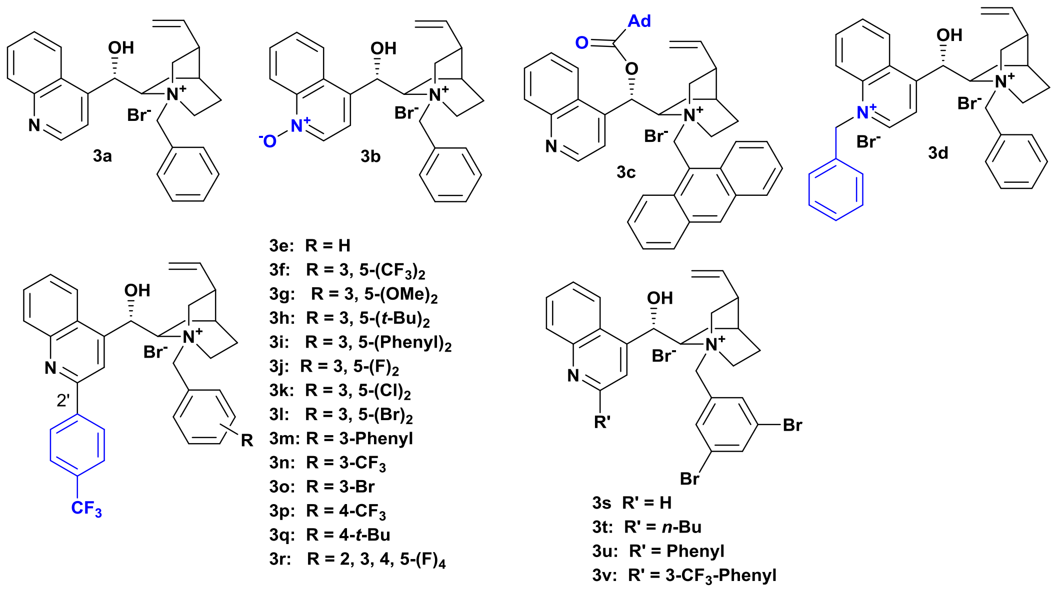
$TMSCF_2Br$ and $TMSCF_2Cl$ was purchased from innochem. HCF_2OTf (**B2**) was prepared according to the method of Hartwig (*Angew. Chem. Int. Ed.* 2013, *52,* 1 – 5). $Ph_3P^+CF_2CO_2^-$ (B3) was prepared according to the method of Xiao’s group (*Chem. Commun.* **2013**, *49*, 7513-7515.)



B_4 were purchased from TCI.

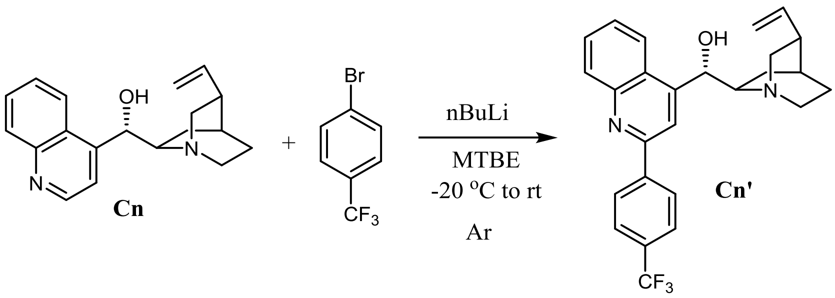
2. Phase transfer catalysts

Cinchona alkaloid catalysts 3a, **3b**, **3c**, **3d, 3k, 3s** were easily prepared according to the previous papers (*Eur. J. Org. Chem.* **2010**, *34,* 6525–6530; *J. Org.Chem.* **2012**, 77, 9601–9608. *J. Am. Chem. Soc,* **2015**, *137*, 5678-5681, *J. Org.Chem.* **2016**, *81*, 7042-7050,).



2.1 Synthesis of C-2' modified Catalysts

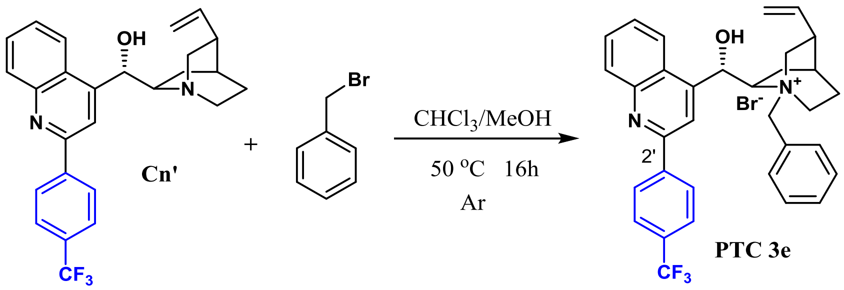
Synthesis of Cn'



Cn' was prepared partly according to Hintermann and Melchiorre's method (*Angew. Chem. Int. Ed.* **2007**, *46*, 5164 –5167; *J. Am. Chem. Soc*, **2015**, *137*, 5678-5681). Cinchonine (5.88 g, 10 mmol) was suspended in 75mL of dry MTBE (dried over molecular sieves) and cooled to -20 ℃ under Ar. The organo-lithium compound was prepared in a separate flask by adding *n*-BuLi (21 mL, 52.5 mmol, 2.5 M) to a 15 mL MTBE solution of 4-bromobenzotrifluoride (11.26 g, 50 mmol). The organo-lithium compound was added at once to the vigorously stirred MTBE solution of cinchonine and stirred at -20 ℃ for 60 min. Then the mixture was warmed to ambient temperature and stirred over another 2 h. The reaction was quenched by dropwise addition of acetic acid (30 mL) with rapid stirring and cooling, followed by the addition of water (60 mL) and ethyl acetate (60 mL). Solid iodine (5 g) was added in several portions and the mixture shaken vigorously after each addition until all the solids had dissolved. A solution of sodium metabisulfite ($Na_2S_2O_5$, 2 g) in water (20 mL) was added to quench the excess of iodine. The mixture was made basic (pH = 10) with the addition of aqueous ammonia (concentrated, 28%) and shaken thoroughly. The aqueous phase was extracted with ethyl acetate twice and the collected organic phases were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (EA/MeOH=9:1) to give the product **Cn'** as orange solid (4.35 g, 48% yield).

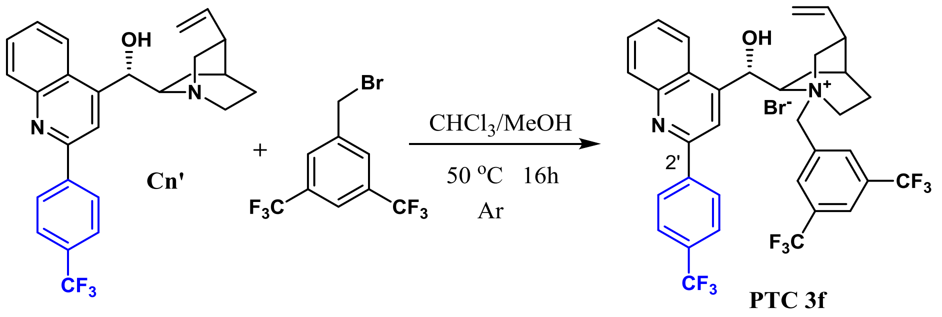
2.2 Synthesis of C-2' modified phase transfer catalysts

Preparation of PTC 3e



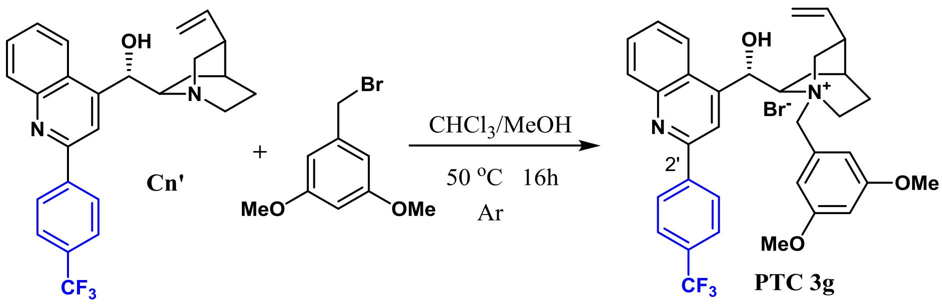
To a flame-dried flask equipped with a magnetic stirring bar and a reflux condenser was added **Cn'** (0.44 g, 1 mmol), CH_3CN (8 mL),$CHCl_3$ (6 mL) and benzyl bromide (0.22 g, 1.3 eq). The mixture was heated to 50 °C under Ar for 16 hours and then cooled to room temperature.After complete consumption of **Cn'** (inferred by TLC analysis) the solvent was evaporated under reduced pressure. Et_2O was added and the mixture was slowly concentrated under reduced pressure. The resulting suspension was stirred for 30 min and the precipitated solids were isolated by filtration, which was recrystallized from MeOH/Et_2O to afford the product **3e** (0.44 g, 71% yield) as a light yellow solid. m. p. 173-178 ℃, $[\alpha]_D^{25}$ +82.3 (*c* 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.4 Hz, 1H), 8.33 (d, *J* = 7.7 Hz, 3H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.65 – 7.60 (m, 2H), 7.20 – 7.01 (m, 5H), 6.76 (d, *J* = 5.7 Hz, 1H), 6.59 – 6.49 (m, 1H), 6.15 (d, *J* = 11.8 Hz, 1H), 5.85 (ddd, *J* = 17.4, 10.5, 7.1 Hz, 1H), 5.41 (d, *J* = 11.8 Hz, 1H), 5.30 – 5.10 (m, 2H), 4.46 (ddd, *J* = 12.4, 9.1, 2.3 Hz, 1H), 4.30 – 4.04 (m, 2H), 3.31 (t, *J* = 11.5 Hz, 1H), 2.76 (q, *J* = 10.1 Hz, 1H), 2.28 (q, *J* = 9.0 Hz, 1H), 2.18 – 1.99 (m, 1H), 1.75 (dt, *J* = 32.2, 12.0 Hz, 6H), 0.81 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.61, 147.41, 145.20, 135.22, 134.00, 129.97 (d, *J* = 7.1 Hz), 128.67 (d, *J* = 3.4 Hz), 127.92, 127.54, 126.83, 125.71 (d, *J* = 3.9 Hz), 124.11 (q, J = 275.5 Hz), 123.46, 118.18, 117.30, 66.95, 61.43, 56.25, 53.57, 38.07, 27.16, 23.77, 21.76. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.49 (s, 3F). HRMS Calcd. for $[C_{33}H_{32}BrF_3N_2O\text{-}Br]^+$requires m/z 529.2461, found m/z 529.2463.

Preparation of PTC 3f



PTC 3f was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a light yellow solid (0.42 g, 56% yield). m. p. 203-207 ℃, $[\alpha]_D^{25}$ +92.4 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (d, *J* = 1.6 Hz, 2H), 8.49 – 8.33 (m, 4H), 8.22 (s, 1H), 8.16 – 8.09 (m, 1H), 7.89 – 7.71 (m, 4H), 6.63 (d, *J* = 2.5 Hz, 1H), 6.09 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.59 – 5.44 (m, 1H), 5.43 – 5.22 (m, 3H), 4.56 (ddd, *J* = 11.7, 8.4, 2.7 Hz, 1H), 4.17 (dt, *J* = 9.9, 5.3 Hz, 2H), 3.69 – 3.47 (m, 1H), 3.13 (dt, *J* = 11.6, 9.1 Hz, 1H), 2.76 – 2.41 (m, 2H), 2.03 – 1.76 (m, 3H), 1.15 – 1.02 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.18, 148.00, 146.18, 142.62, 136.16, 134.26, 132.19 (q, *J* = 33.7 Hz), 130.75, 129.87 (d, *J* = 12.6 Hz), 127.92, 127.90, 125.70 – 125.09 (m), 124.51, 123.83, 123.27, 121.81, 117.25, 116.73, 68.33, 65.89, 61.17, 56.53, 54.95, 37.49, 27.04, 23.29, 20.95. ^{19}F NMR (376 MHz, CD_3OD) δ -63.99 (d, *J* = 10.5 Hz, 9F). HRMS Calcd. for $[C_{35}H_{30}BrF_9N_2O\text{-}Br]^+$requires m/z 665.2209, found m/z 665.2214.

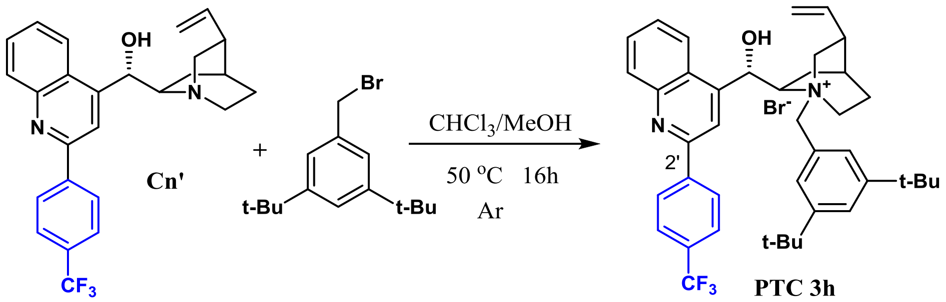
Preparation of PTC 3g



PTC 3g was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a yellow solid (0.45 g, 67% yield). m. p. 194-197 ℃, $[\alpha]_D^{25}$ +98.3 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 – 8.27 (m, 4H), 8.18 – 8.05 (m, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.79 – 7.64 (m, 2H), 6.95 (d, *J* = 2.3 Hz, 2H), 6.71 – 6.54 (m, 2H), 6.06 (ddd, *J* = 17.4, 10.5, 7.2 Hz, 1H), 5.35 – 5.22 (m, 2H), 5.15 (d, *J* = 12.1 Hz, 1H), 4.99 (d, *J* = 12.1 Hz, 1H), 4.40 (td, *J* = 10.2, 9.4, 4.8 Hz, 1H), 4.19 – 4.01 (m, 2H), 3.84 (s, 6H), 3.70 (t, *J* = 11.5 Hz, 1H), 3.11 (dt, *J* = 11.9, 9.3 Hz, 1H), 2.63 – 2.42 (m, 2H), 1.98 – 1.70 (m, 3H), 1.16 – 0.96 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 161.31, 155.16, 148.00, 146.38, 142.66, 136.32, 131.83 – 130.32

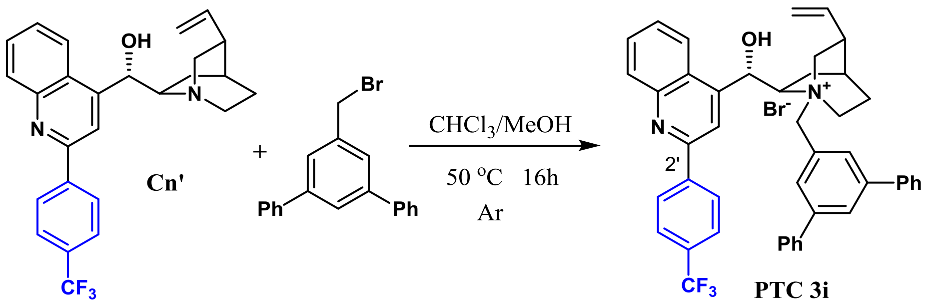
(m), 129.12, 127.92, 127.87, 125.64 – 125.40 (m), 124.29 (q, J = 271.4 Hz), 123.87, 123.21, 117.26, 116.60, 111.52, 101.76, 67.71, 65.94, 63.09, 56.90, 54.87, 54.70, 37.62, 26.98, 23.36, 20.96. ^{19}F NMR (376 MHz, CD_3OD) δ -63.96 (s, 3F). HRMS Calcd. For $[C_{35}H_{36}BrF_3N_2O_3\text{-}Br]^+$requires m/z 589.2673, found m/z 589.2668.

Preparation of PTC 3h



PTC 3h was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a white solid (0.32 g, 45% yield). m. p. 167-170 ℃, $[\alpha]_D^{25}$ +77.6 (c 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.24 (m, 3H), 8.19 – 8.10 (m, 1H), 7.94 (dd, J = 7.9, 1.9 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.66 (dd, J = 11.3, 1.7 Hz, 2H), 7.53 – 7.33 (m, 3H), 6.57 (s, 1H), 5.89 (ddd, J = 17.5, 10.4, 7.4 Hz, 1H), 5.59 – 5.37 (m, 2H), 5.24 – 4.95 (m, 2H), 4.52 (t, J = 10.8 Hz, 1H), 4.29 – 3.97 (m, 2H), 3.51 (t, J = 11.5 Hz, 1H), 2.91 (q, J = 7.1 Hz, 3H), 2.51 – 2.21 (m, 2H), 1.90 – 1.62 (m, 3H), 1.31 (s, 18H), 1.27 – 1.19 (m, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 154.96, 151.73, 151.66, 147.87, 145.64, 142.81, 135.61, 130.96 (q, J = 32.7 Hz),130.31, 129.41, 128.47, 127.96, 126.49, 125.64 (d, J = 4.0 Hz), 124.07, 123.53, 123.46 – 123.11 (m), 122.85, 118.10, 117.69, 70.54, 67.38, 65.45, 63.49, 56.45, 54.26, 45.90, 38.22, 35.00, 31.50, 29.70, 27.24, 24.02, 21.51, 11.33, 8.97. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.52 (s, 3F). HRMS Calcd. For $[C_{41}H_{48}BrF_3N_2O\text{-}Br]^+$requires m/z 641.3713, found m/z 641.3710.

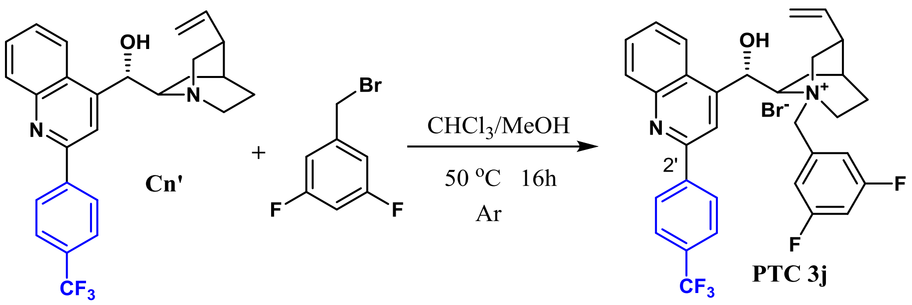
Preparation of PTC 3i



PTC 3i was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a white solid (0.58 g, 78% yield). m. p. 182-186 ℃, $[\alpha]_D^{25}$ +145.3 (c 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (t, J = 7.0 Hz, 4H), 8.20 – 8.06 (m, 1H), 7.98 (d, J = 34.4 Hz, 3H),

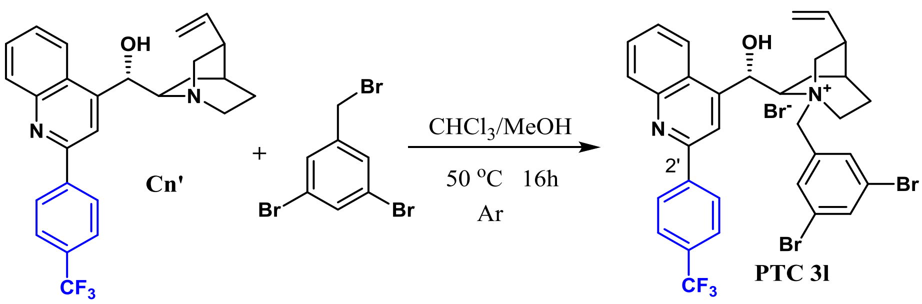
7.88 – 7.67 (m, 8H), 7.53 – 7.29 (m, 6H), 6.65 (d, J = 11.4 Hz, 1H), 6.19 – 5.95 (m, 1H), 5.51 – 5.07 (m, 4H), 4.56 – 4.40 (m, 1H), 4.24 – 4.03 (m, 2H), 3.76 – 3.52 (m, 3H), 3.16 (d, J = 12.7 Hz, 1H), 2.79 – 2.36 (m, 2H), 2.02 – 1.63 (m, 4H), 1.26 (s, 2H), 1.13 – 0.76 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.18, 148.00, 146.36, 142.67, 139.69, 139.67, 136.29, 130.90, 129.86, 128.76, 127.93, 127.75, 127.19, 126.98, 125.47 (d, J = 3.8 Hz), 125.45, 124.30 (q, J = 271.4 Hz), 123.87, 117.29, 116.60, 70.13, 67.83, 65.96, 62.93, 56.78, 54.79, 37.56, 29.41, 27.06, 23.37, 20.95. ^{19}F NMR (376 MHz, CD_3OD) δ -63.94(s, 3H). HRMS Calcd. For $[C_{45}H_{40}BrF_3N_2O\text{-}Br]^+$requires m/z 681.3087, found m/z 681.3084.

Preparation of PTC 3j



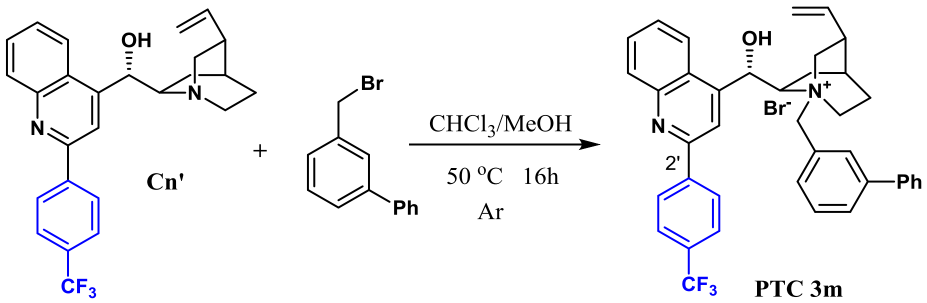
PTC 3j was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a white solid (0.53 g, 83% yield). m. p. 193-197 ℃, $[\alpha]_D^{25}$ +101.0 (c 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (d, J = 8.4 Hz, 4H), 8.21 (d, J = 8.1 Hz, 1H), 7.96 – 7.70 (m, 4H), 7.57 – 7.48 (m, 2H), 7.24 (t, J = 2.4 Hz, 1H), 6.63 (d, J = 2.5 Hz, 1H), 6.10 (ddd, J = 17.3, 10.4, 7.1 Hz, 1H), 5.41 – 5.19 (m, 3H), 5.06 (d, J = 12.7 Hz, 1H), 4.46 (ddd, J = 11.9, 8.4, 2.7 Hz, 1H), 4.15 – 3.92 (m, 2H), 3.67 (t, J = 11.3 Hz, 1H), 3.25 – 3.07 (m, 1H), 2.77 – 2.39 (m, 2H), 1.90 (dd, J = 29.7, 15.9 Hz, 3H), 1.14 (q, J = 13.1, 9.4 Hz, 1H).^{13}C NMR (101 MHz, CD_3OD) δ 164.41 (d, J = 12.8 Hz), 161.93 (d, J = 12.7 Hz), 155.29, 148.10, 146.31, 142.70, 136.19, 131.89 – 130.64 (m), 127.95, 127.92, 127.86, 123.92, 123.00, 117.26, 116.64, 105.72 (t, J = 25.6 Hz), 68.16, 68.14, 65.92, 61.70, 56.84, 54.89, 37.55, 26.94, 23.29, 20.92. ^{19}F NMR (376 MHz, CD_3OD) δ -64.11(s, 3H), -109.72 (s, 2H). HRMS Calcd. For $[C_{33}H_{30}BrF_5N_2O\text{-}Br]^+$requires m/z 565.2273, found m/z 565.2276.

Preparation of PTC 3l



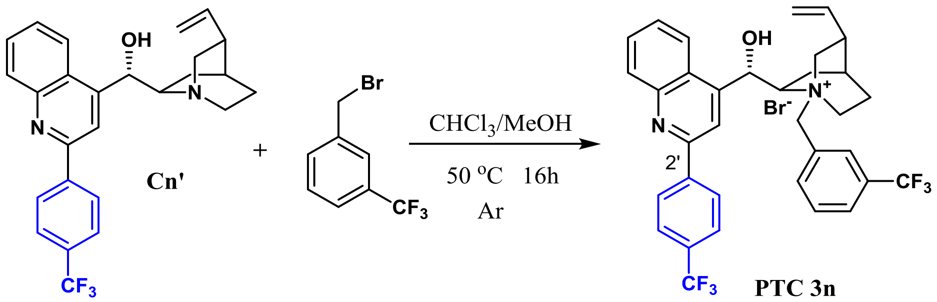
PTC 3l was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a light yellow solid (0.60 g, 78% yield). m. p. 229-232 ℃, $[\alpha]_D^{25}$ +101.0 (*c* 0.1, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD) δ 8.40 (d, *J* = 8.6 Hz, 4H), 8.17 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.05 (d, *J* = 1.7 Hz, 2H), 7.96 (d, *J* = 1.6 Hz, 1H), 7.91 – 7.70 (m, 4H), 6.60 (d, *J* = 2.5 Hz, 1H), 6.09 (ddd, *J* = 17.4, 10.4, 7.1 Hz, 1H), 5.37 – 5.18 (m, 3H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.45 (ddd, *J* = 11.8, 8.5, 2.6 Hz, 1H), 4.20 – 3.99 (m, 2H), 3.60 (t, *J* = 11.3 Hz, 1H), 3.14 (dt, *J* = 11.8, 9.3 Hz, 1H), 2.76 – 2.45 (m, 2H), 2.02 – 1.80 (m, 3H), 1.19 – 1.02 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.30, 148.11, 146.29, 142.69, 136.19, 135.90, 135.28, 131.61, 130.02, 129.98 (d, *J* = 6.9 Hz), 127.89 (d, *J* = 6.8 Hz), 125.48, 123.91, 123.25, 122.94, 117.24, 116.69, 68.20, 65.89, 61.45, 56.73, 54.94, 37.57, 27.01, 23.30, 20.90. ^{19}F NMR (376 MHz, CD_3OD) δ -64.08 (s, 3H). HRMS Calcd. For $[C_{33}H_{30}Br_3F_3N_2O\text{-}Br]^+$ requires m/z 685.0671, found m/z 685.0677.

Preparation of PTC 3m



PTC 3m was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a light yellow solid (0.47 g, 69% yield). m. p. 239-242 ℃, $[\alpha]_D^{25}$ +138.4 (*c* 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.31 (d, *J* = 8.0 Hz, 3H), 7.94 – 7.73 (m, 3H), 7.64 (t, *J* = 9.3 Hz, 2H), 7.53 (d, *J* = 7.4 Hz, 2H), 7.39 (dt, *J* = 13.0, 7.1 Hz, 3H), 7.16 (q, *J* = 7.7, 6.5 Hz, 1H), 7.00 (q, *J* = 7.9 Hz, 2H), 6.83 (dd, *J* = 20.4, 6.0 Hz, 1H), 6.59 (s, 1H), 6.33 (d, *J* = 11.9 Hz, 1H), 5.84 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.59 (d, *J* = 11.8 Hz, 1H), 5.25 – 5.10 (m, 2H), 4.50 (ddd, *J* = 12.1, 9.0, 2.4 Hz, 1H), 4.28 – 4.01 (m, 2H), 3.35 (t, *J* = 11.6 Hz, 1H), 2.80 (q, *J* = 10.2 Hz, 1H), 2.38 – 2.04 (m, 2H), 1.82 – 1.61 (m, 3H), 1.53 – 1.17 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.52, 147.37, 145.11, 140.92, 140.88, 139.19, 135.15, 132.84, 132.03, 130.90 (q, *J* = 32.2 Hz), 129.99, 128.99, 128.56, 128.27, 127.91, 127.79, 127.56, 127.44, 126.99, 126.01 – 125.15 (m), 122.91, 118.26, 117.21, 67.11, 61.51, 56.40, 53.69, 38.09, 36.01, 29.70, 27.18, 23.77, 21.75, 11.40. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.48 (s, 3F) . HRMS Calcd. For $[C_{39}H_{36}BrF_3N_2O\text{-}Br]^+$ requires m/z 605.2774, found m/z 605.2778.

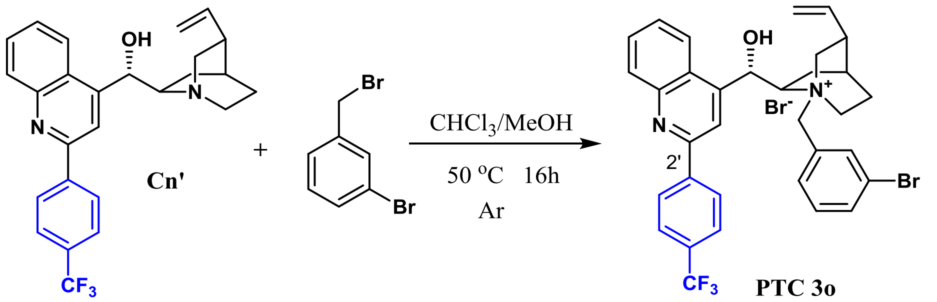
Preparation of PTC 3n



PTC 3n

PTC 3n was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a light yellow solid (0.39 g, 58% yield). m. p. 223-226 ℃, $[\alpha]_D^{25}$ +103.5 (*c* 0.1, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD) δ 8.50 – 8.32 (m, 4H), 8.28 – 8.14 (m, 2H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.97 – 7.75 (m, 6H), 6.66 (d, *J* = 9.5 Hz, 1H), 6.11 (ddd, *J* = 17.4, 10.6, 7.2 Hz, 1H), 5.33 – 5.23 (m, 2H), 5.25 – 5.03 (m, 1H), 4.49 (ddd, *J* = 11.8, 8.5, 2.7 Hz, 1H), 4.25 – 4.03 (m, 2H), 3.76 – 3.53 (m, 1H), 3.16 – 2.99 (m, 1H), 2.74 – 2.38 (m, 2H), 1.99 – 1.78 (m, 3H), 1.20 – 1.07 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.31, 148.12, 146.36, 142.71, 137.43, 136.23, 131.11 (dd, *J* = 32.6, 19.6 Hz), 130.37 – 129.60 (m), 128.83, 127.95, 127.93, 127.85, 127.08, 123.93, 122.95, 117.25, 116.65, 68.10, 65.90, 62.23, 56.64, 54.75, 37.54, 27.08, 23.29, 20.89. ^{19}F NMR (376 MHz, CD_3OD) δ -63.95 –64.04 (m, 3F), -64.04 –64.11 (m, 3F). HRMS Calcd. For $[C_{34}H_{31}BrF_6N_2O\text{-}Br]^+$requires m/z 597.2335, found m/z 597.2339.

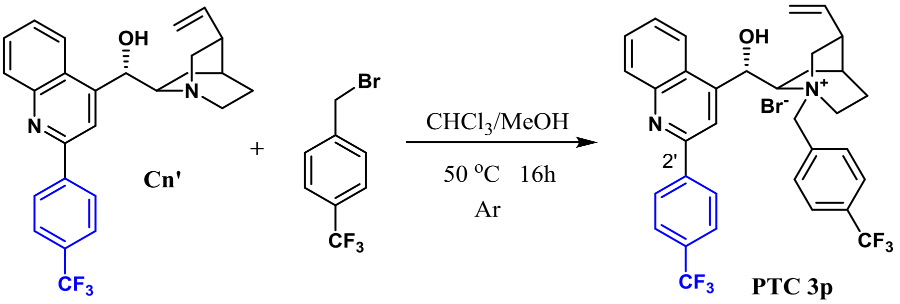
Preparation of PTC 3o



PTC 3o

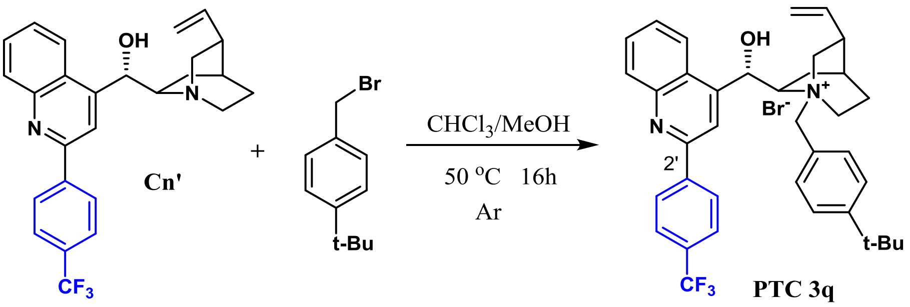
PTC 3o was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a light yellow solid (0.58 g, 85% yield). m. p. 229-234 ℃, $[\alpha]_D^{25}$ +105.2 (*c* 0.1, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD) δ 8.50 – 8.31 (m, 4H), 8.22 (d, *J* = 8.2 Hz, 1H), 8.02 (s, 1H), 7.91 – 7.72 (m, 6H), 7.52 (td, *J* = 7.9, 1.7 Hz, 1H), 6.65 (s, 1H), 6.11 (ddd, *J* = 17.5, 10.5, 7.4 Hz, 1H), 5.36 – 5.23 (m, 2H), 5.20 – 4.96 (m, 2H), 4.45 (ddd, *J* = 11.8, 8.4, 2.7 Hz, 1H), 4.14 – 3.89 (m, 2H), 3.63 (t, *J* = 11.3 Hz, 1H), 3.13 (q, *J* = 9.9 Hz, 1H), 2.73 – 2.44 (m, 2H), 1.98 – 1.80 (m, 3H), 1.20 – 1.08 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.33, 148.14, 146.38, 142.71, 136.22 (d, *J* = 3.1 Hz), 133.46, 132.40, 130.72, 127.92, 127.82, 126.01 – 125.26 (m), 123.93, 123.25 – 122.05 (m), 117.23, 116.64, 68.01, 65.86, 62.29, 56.73, 54.74, 37.58, 27.06, 23.31, 20.87. ^{19}F NMR (376 MHz, CD_3OD) δ -64.09 (s, 3F). HRMS Calcd. For $[C_{34}H_{31}Br_2F_3N_2O\text{-}Br]^+$requires m/z 607.1566, found m/z 607.1570.

Preparation of PTC 3p



PTC 3p was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a yellow solid (0.44 g, 65% yield). m. p. 223-227 ℃, $[\alpha]_D^{25}$ +102.6 (*c* 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.5 Hz, 1H), 8.40 – 8.25 (m, 3H), 7.83 (dd, *J* = 14.5, 7.8 Hz, 4H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.01 (dt, *J* = 43.8, 7.5 Hz, 2H), 6.86 – 6.73 (m, 1H), 6.62 – 6.40 (m, 2H), 5.84 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.46 (dd, *J* = 24.3, 11.8 Hz, 1H), 5.29 – 5.10 (m, 2H), 4.51 (ddd, *J* = 12.1, 8.9, 2.5 Hz, 1H), 4.32 – 4.03 (m, 2H), 3.23 – 3.03 (m, 2H), 2.66 (dd, *J* = 15.2, 6.5 Hz, 1H), 2.32 (q, *J* = 8.9 Hz, 1H), 2.11 (d, *J* = 52.3 Hz, 1H), 1.85 – 1.68 (m, 3H), 1.56 – 1.44 (m, 1H), 1.26 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 154.55, 147.36, 144.75, 142.83, 134.79, 134.41, 134.38, 132.80 – 131.64 (m), 131.01 (q, *J* = 32.1 Hz), 130.99, 130.14, 128.57, 127.90, 125.99 – 125.13 (m), 127.47, 123.32 (q, *J* = 271.0 Hz), 123.12, 118.51, 117.12, 67.51, 60.35, 56.54, 54.03, 45.96, 38.01, 29.71, 27.00, 23.72, 21.77, 11.35, 8.60. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.51(s, 3H) , -63.10 (s, 3H) . HRMS Calcd. For $[C_{34}H_{31}BrF_6N_2O\text{-}Br]^+$requires m/z 597.2335, found m/z 597.2331.

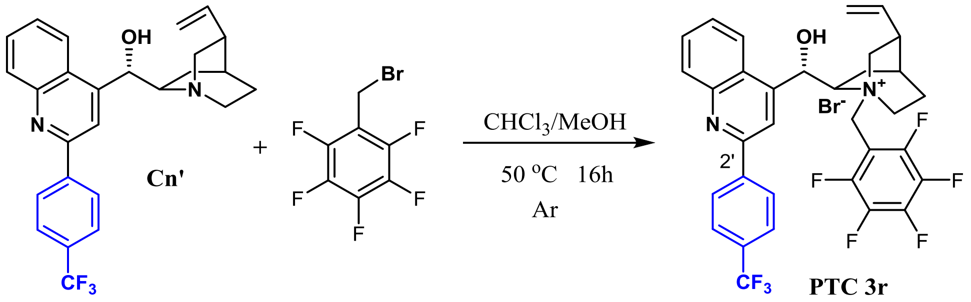
Preparation of PTC 3q



PTC 3q was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a white solid (0.47 g, 71% yield). m. p. 187-190 ℃, $[\alpha]_D^{25}$ +83.1(*c* 0.1, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD) δ 8.43 (d, *J* = 6.6 Hz, 3H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 7.95 – 7.76 (m, 4H), 7.73 – 7.56 (m, 4H), 6.73 – 6.57 (m, 1H), 6.26 – 5.90 (m, 1H), 5.30 – 5.23 (m, 1H), 5.16 – 4.95 (m, 2H), 4.51 – 4.31 (m, 1H), 4.16 – 3.85 (m, 2H), 3.74 – 3.51 (m, 1H), 2.76 – 2.43 (m, 2H), 2.01 – 1.75 (m, 4H), 1.38 (s, 9H), 1.10 (t, *J* = 7.3 Hz, 2H). ^{13}C

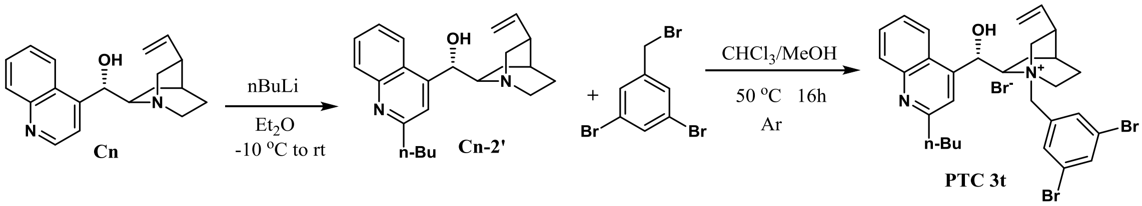
NMR (101 MHz, CD_3OD) δ 155.31, 153.77, 148.13, 146.53, 142.72, 136.33, 133.29, 131.82 – 130.38 (m), 130.02, 129.99 (d, J = 6.4 Hz), 127.95, 127.93, 127.81, 126.02, 125.50 (q, J = 3.7 Hz), 124.38, 123.97, 123.37 – 122.41 (m), 117.24, 116.56, 67.61, 65.86, 62.91, 56.63, 54.42, 37.60, 34.37, 30.22, 27.13, 23.33, 20.88, 8.04. ^{19}F NMR (376 MHz, CD_3OD) δ -64.07 (s, 3F). HRMS Calcd. For $[C_{37}H_{40}BrF_3N_2O\text{-}Br]^+$requires m/z 585.3087, found m/z 585.3082.

Preparation of PTC 3r



PTC 3r was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn'** as a white solid (0.61 g, 88% yield). m. p. 198-201 ℃, $[\alpha]_D^{25}$ +102.4(c 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (d, J = 7.3 Hz, 4H), 8.23 (d, J = 8.4 Hz, 1H), 7.85 (dd, J = 32.4, 7.9 Hz, 4H), 6.75 – 6.59 (m, 1H), 6.11 (ddd, J = 17.4, 10.6, 7.3 Hz, 1H), 5.36 – 5.24 (m, 3H), 5.17 (d, J = 13.7 Hz, 1H), 4.47 (t, J = 9.8 Hz, 1H), 4.24 (t, J = 10.4 Hz, 1H), 3.93 (q, J = 13.5, 12.2 Hz, 1H), 3.66 – 3.50 (m, 2H), 2.73 (q, J = 8.8 Hz, 1H), 2.52 (t, J = 12.1 Hz, 1H), 1.97 (dd, J = 16.3, 8.9 Hz, 4H), 1.48 – 1.14 (m, 5H), 1.09 – 0.90 (m, 2H).^{13}C NMR (101 MHz, CD_3OD) δ 155.33, 148.17, 146.04, 142.68, 136.07, 131.05 (q, J = 33.1 Hz), 130.11, 129.97, 127.93, 127.75, 125.53, 125.49, 125.45, 124.26 (q, J = 271.0 Hz), 123.99, 117.30, 116.75, 103.56 – 101.84 (m),68.09, 66.21, 56.81, 55.23, 51.09, 37.79, 26.44, 23.40, 21.03. ^{19}F NMR (376 MHz, CD_3OD) δ -64.08 (s, 3F), -136.80 (s, 1F), -151.31 (d, J = 4.7 Hz, 1F), -162.67 (d, J = 7.5 Hz, 1F). HRMS Calcd. For $[C_{33}H_{27}BrF_8N_2O\text{-}Br]^+$requires m/z 619.1990, found m/z 619.1986.

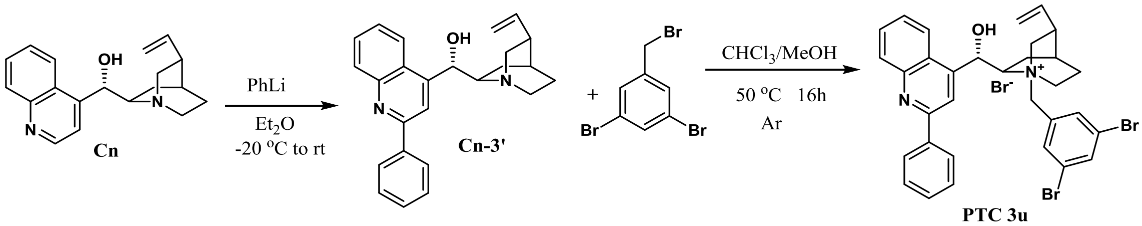
Preparation of PTC 3t



Cn-2' was prepared according to Hintermann's method (*Angew. Chem. Int. Ed.* **2007**, *46*,) as white solid (2.10 g, 56% yield). **PTC 3t** was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn-2'** as a white solid (0.58 g, 86% yield). m. p. 215-218 ℃, $[\alpha]_D^{25}$ +137.6 (c 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 5.9 Hz, 2H), 8.18

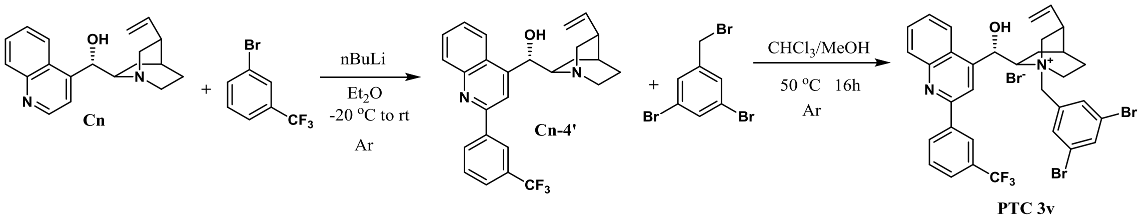
(ddd, *J* = 13.7, 8.2, 1.2 Hz, 3H), 8.01 (dd, *J* = 9.3, 1.7 Hz, 3H), 7.81 (dddd, *J* = 30.6, 8.3, 6.9, 1.3 Hz, 2H), 7.63 – 7.48 (m, 3H), 6.60 (d, *J* = 2.5 Hz, 1H), 6.08 (ddd, *J* = 17.4, 10.5, 7.1 Hz, 1H), 5.39 – 5.20 (m, 2H), 5.18 – 4.94 (m, 2H), 4.46 (ddd, *J* = 11.8, 8.5, 2.7 Hz, 1H), 4.12 – 3.84 (m, 2H), 3.72 – 3.55 (m, 1H), 3.15 (dt, *J* = 11.9, 9.4 Hz, 1H), 2.67 (q, *J* = 8.8 Hz, 1H), 2.58 – 2.37 (m, 1H), 2.00 – 1.83 (m, 3H), 1.35 – 1.27 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.91, 146.65, 143.89, 136.35, 135.02, 134.82, 130.85, 128.75, 128.00, 125.94, 123.47, 122.91, 121.78, 119.70, 118.46, 67.13, 65.53, 59.50, 56.42, 54.07, 39.24, 38.00, 32.55, 27.06, 23.70, 22.92, 21.76, 14.09. HRMS Calcd. For $[C_{30}H_{35}Br_3N_2O\text{-}Br]$+requires m/z 597.1111, found m/z 597.1115.

Preparation of PTC 3e



Cn-3' was prepared according to Hintermann's method (*Angew. Chem. Int. Ed.* **2007**, *46*, 5164 –5167) as white solid (0.55g, 21% yield). **PTC 3u** was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn-3'** as a white solid (0.58 g, 83% yield). m. p. 257-259 ℃, $[\alpha]_D^{25}$ +127.3 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (d, *J* = 5.9 Hz, 2H), 8.18 (ddd, *J* = 13.7, 8.2, 1.2 Hz, 3H), 8.01 (dd, *J* = 9.3, 1.7 Hz, 3H), 7.92 – 7.73 (m, 2H), 7.65 – 7.40 (m, 3H), 6.60 (d, *J* = 2.5 Hz, 1H), 6.08 (ddd, *J* = 17.4, 10.5, 7.1 Hz, 1H), 5.37 – 5.27 (m, 2H), 5.14 (d, *J* = 12.5 Hz, 1H), 5.00 (d, *J* = 12.6 Hz, 1H), 4.46 (ddd, *J* = 11.8, 8.5, 2.7 Hz, 1H), 4.11 – 3.84 (m, 2H), 3.68 – 3.50 (m, 1H), 3.14 (dd, *J* = 11.8, 9.2 Hz, 1H), 2.68 (t, *J* = 8.8 Hz, 1H), 2.58 – 2.44 (m, 1H), 1.99 – 1.83 (m, 3H), 1.34 – 1.26 (m, 1H), 1.20 – 1.06 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 157.27, 148.06, 145.92, 139.12, 136.17, 135.91, 135.23, 131.61, 129.87, 129.58, 129.53, 128.65, 127.36, 127.31, 123.60, 123.27, 122.64, 117.49, 116.64, 68.25, 65.76, 61.56, 56.75, 54.93, 37.51, 31.36, 26.97, 23.30, 22.32, 20.85, 13.05. HRMS Calcd. For $[C_{32}H_{31}Br_3N_2O\text{-}Br]^+$requires m/z 617.0798, found m/z 617.0792.

Preparation of PTC 3v



Cn-4' was prepared according to Hintermann and Melchiorre's method (*Angew. Chem. Int.*

Ed. **2007**, *46*, 5164 –5167; *J. Am. Chem. Soc*, **2015**, *137*, 5678-5681) as light yellow solid (1.53g, 55% yield). . **PTC 3v** was synthesized by the same procedure as mentioned above for catalyst **3e** from **Cn-4'** as a white solid (0.60 g, 79% yield). m. p. 197-201 ℃, $[\alpha]_D^{25}$ +118.0 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.47 (d, *J* = 7.5 Hz, 1H), 8.37 (d, *J* = 12.2 Hz, 2H), 8.23 (dt, *J* = 8.7, 2.0 Hz, 1H), 8.08 – 7.96 (m, 3H), 7.91 – 7.77 (m, 4H), 6.62 (d, *J* = 2.5 Hz, 1H), 6.10 (ddd, *J* = 17.4, 10.5, 7.2 Hz, 1H), 5.42 – 5.11 (m, 3H), 5.02 (d, *J* = 12.4 Hz, 1H), 4.55 – 4.43 (m, 1H), 4.18 – 3.90 (m, 2H), 3.61 (t, *J* = 11.4 Hz, 1H), 3.16 (q, *J* = 9.7 Hz, 1H), 2.78 – 2.45 (m, 2H), 2.04 – 1.81 (m, 3H), 1.20– 1.03 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.18, 148.12, 146.34, 140.04, 136.19, 135.90, 135.26, 133.30, 131.61, 130.78 (d, *J* = 11.4 Hz), 130.00 (d, *J* = 11.5 Hz)，129.59, 127.78, 125.90 (d, *J* = 3.9 Hz), 123.26, 122.86, 116.98, 116.62, 68.21, 65.92, 61.49, 56.75, 54.94, 37.54, 29.95, 26.97, 23.30, 20.89. ^{19}F NMR (376 MHz, CD_3OD) δ -64.07 (s, 3F). HRMS Calcd. For $[C_{33}H_{30}Br_3F_3N_2O\text{-}Br]^+$requires m/z 685.0671, found m/z 685.0676.

3. β-Keto esters:

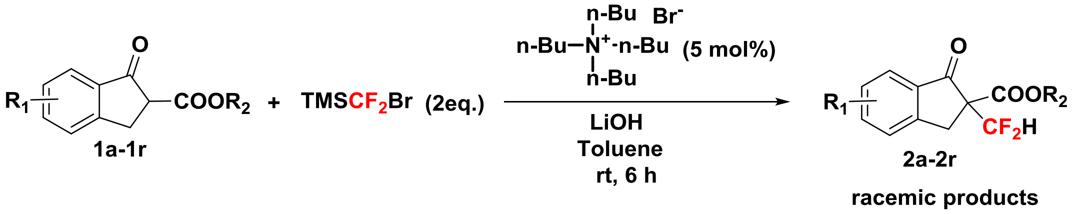
β-keto esters **1a-1t** were prepared according to the literature procedure（*Eur. J. Org. Chem*. **2010**, *34*, 6525–6530; *Green Chemistry* **2016**, *18*, 5493-5499）

4. Commercial grade reagents and solvents:

Commercial grade reagents, bases and solvents were purchased from Sinoreagent, Meryer and Energy-Chemical without further purifications.

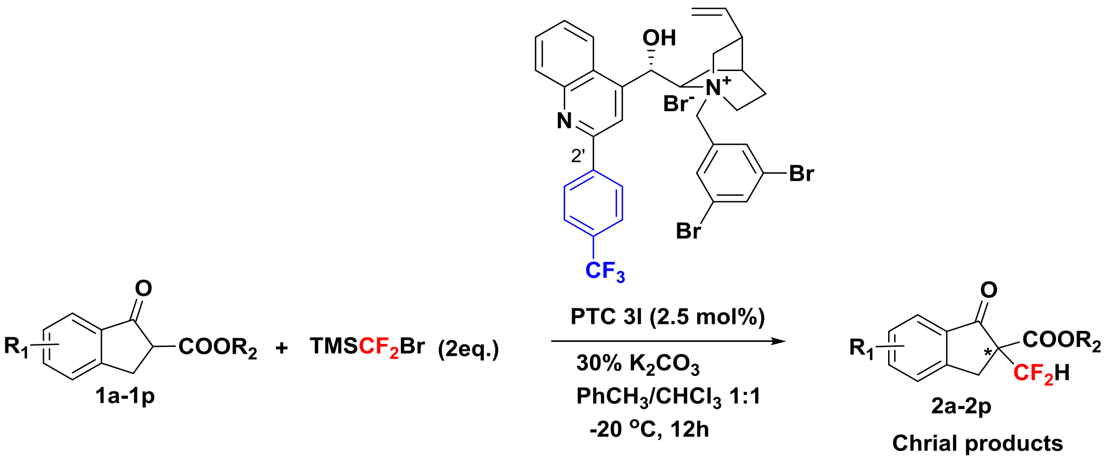
B. General proceduce for the *α*-difluoromethylation of β-keto esters:

Achiral α-difluoromethylation of β-keto esters



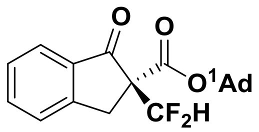
The reaction was conducted with substrate **1a-1r** (0.1 mmol) in the presence of tetrabutylammonium bromide (5 mol%) in toluene. Then $TMSCF_2Br$ (0.2 mmol) was added slowly,and the reaction was stirred at room temperaturefor 6 h. After completion of the reaction (confirmed by TLC analysis), the mixture was diluted with EtOAc (30 mL), washed with water (3×20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to give **2a-2s**. The *ee* of the product was determined by chiral HPLC.

Asymmetric α-difluoromethylation of β-keto esters



The reaction was conducted with β-keto esters **1a-1p** (0.1 mmol) in the presence of PTC **3l** (0.0025 mmol) in a mixture containing $PhCH_3/CHCl_3$ =1:1 (8 mL) and 30%K_2CO_3 (0.5 mL) at -20 ℃. Then $TMSCF_2Br$ (0.2 mmol) was added slowly,and the reaction was stirred at this temperaturefor 12 h. After the reaction was completed (confirmed by TLC analysis), the mixture was diluted with EtOAc (30 mL), washed with water (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was subject to crude ^{19}F-NMR to give the C/O isomer ratio (trifluoromethyl benzene 8 μL as internal standard). Subsequently, the residue was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate=50:1–20:1) to afford the α-difluoromethylation products.

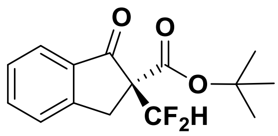
1-Adamantyl 2-difluoromethyl -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2a)



2a

(Light yellow solid, 31.3 mg, 87% yield, 80% ee); m. p. 73-76 ℃, $[\alpha]_D^{25}$ 73.6 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.72 – 7.53 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 6.54 (t, *J* = 55.4 Hz, 1H), 3.67 (d, *J* = 17.4 Hz, 1H), 3.49 (d, *J* = 17.4 Hz, 1H), 2.22 – 2.06 (m, 9H), 1.73 – 1.56 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.36 (d, *J* = 7.1 Hz), 164.37 (d, *J* = 11.6 Hz), 154.03, 135.90, 134.20 (d, *J* = 3.6 Hz), 127.89, 126.41, 125.13, 115.72 (d, *J* = 5.8 Hz), 83.91, 65.57 (dd, *J* = 23.0, 21.2 Hz), 40.97, 35.94, 30.86, 29.88. ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.62 (dd, *J* = 286.5, 55.0 Hz, 1F), -128.78 (dd, *J* = 286.3, 55.9 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / *i*-PrOH = 98 / 12, 0.6 mL / min, 254 nm, τ_R (major) = 12.25 min, τ_R (minor) = 10.99 min. HRMS Calcd. for $[C_{21}H_{22}F_2O_3+Na]^+$ requires m/z 383.1435, found m/z 383.1438.

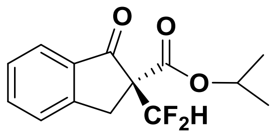
1-tert-butyl 2-difluoromethyl -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2b)



2b

(Colorless oil, 22.0 mg, 78% yield, 67% ee); $[\alpha]_D^{25}$ 63.2 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.44 – 7.35 (m, 1H), 6.54 (t, *J* = 55.4 Hz, 1H), 3.68 (d, *J* = 17.5 Hz, 1H), 3.50 (d, *J* = 17.5 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δδ 196.31 (d, *J* = 6.6 Hz), 164.75 (d, *J* = 11.4 Hz), 154.03, 135.95, 134.17 (d, *J* = 3.6 Hz), 127.94, 126.44, 125.17, 115.70 (dd, *J* = 246.5, 240.8 Hz), 83.91, 65.52 (dd, *J* = 23.0, 21.2 Hz), 27.77. ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.65 (dd, *J* = 286.8, 55.1 Hz, 1F), -128.71 (dd, *J* = 286.8, 55.1 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / *i*-PrOH = 99 / 1, 0.6 mL / min, 254 nm, τ_R (major) = 9.26 min, τ_R (minor) = 8.24 min. HRMS Calcd. for $[C_{15}H_{16}F_2O_3+Na]^+$ requires m/z 305.0965, found m/z 305.0962.

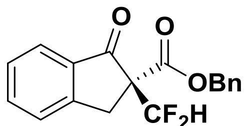
1-isopropyl 2-difluoromethyl -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2c)



2c

(Colorless oil, 22.8 mg, 85% yield, 71% ee); $[\alpha]_D^{25}$ 56.3(*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.67 (td, *J* = 7.5, 1.2 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 6.59 (t, *J* = 55.3 Hz, 1H), 5.09 (p, *J* = 6.3 Hz, 1H), 3.71 (d, *J* = 17.6 Hz, 1H), 3.54 (d, *J* = 17.5 Hz, 1H), 1.26 (dd, *J* = 10.5, 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.95 (d, *J* = 7.0 Hz), 165.38 (d, *J* = 12.0 Hz), 153.98, 136.03, 134.08 (d, *J* = 3.6 Hz), 128.00, 126.47, 125.24, 117.97, 115.55 (d, *J* = 6.1 Hz), 113.12, 70.66, 66.90 – 59.15 (m), 29.81 (t, *J* = 2.7 Hz), 21.47 (d, *J* = 7.5 Hz).^{19}F NMR (376 MHz, $CDCl_3$) δ -126.33 (dd, *J* = 287.1, 55.0 Hz, 1F), -129.11 (dd, *J* = 287.1, 55.6 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / *i*-PrOH = 98 / 2, 0.6 mL / min, 254 nm, τ_R (major) = 10.82 min, τ_R (minor) = 9.76 min. HRMS Calcd. for $[C_{14}H_{14}F_2O_3+Na]^+$ requires m/z 291.0809, found m/z 291.0814.

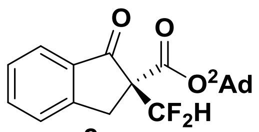
Benzyl 2-difluoromethyl -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2d)



2d

(Colorless oil, 24.6 mg, 78% yield, 67% ee); $[\alpha]_D^{25}$ 76.3(*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.26 (m, 6H), 6.63 (t, *J* = 55.2 Hz, 1H), 5.32 – 5.08 (m, 2H), 3.73 (d, *J* = 17.4 Hz, 1H), 3.56 (d, *J* = 17.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.64 (d, *J* = 6.8 Hz), 165.82 (d, *J* = 12.1 Hz), 153.88, 136.20, 134.83, 134.03 (d, *J* = 3.6 Hz), 128.66, 128.51, 128.14, 127.87, 126.53, 125.35, 117.87, 115.45 (d, *J* = 6.1 Hz), 113.02, 68.07, 64.81 (dd, *J* = 24.2, 20.8 Hz), 31.35 – 28.68 (m). ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.86 (d, *J* = 287.5 Hz), -129.07 (d, *J* = 287.5 Hz). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / *i*-PrOH = 98 / 2, 0.6 mL / min, 254 nm, τ_R (major) = 41.58 min, τ_R (minor) = 27.07 min. HRMS Calcd. for $[C_{18}H_{14}F_2O_3+Na]^+$ requires m/z 339.0809, found m/z 339.0803.

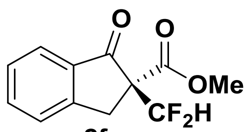
2-Adamantyl 2-difluoromethyl -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2e)



2e

(White solid, 33.1 mg, 92% yield, 83% ee); m. p. 56-58 ℃, $[\alpha]_D^{25}$ 77.5 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.67 (td, *J* = 7.5, 1.2 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 6.66 (t, *J* = 55.3 Hz, 1H), 5.00 (t, *J* = 3.5 Hz, 1H), 3.74 (d, *J* = 17.5 Hz, 1H), 3.56 (d, *J* = 17.5 Hz, 1H), 2.05 – 1.48 (m, 14H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.10 (d, *J* = 6.9 Hz), 165.09 (d, *J* = 11.9 Hz), 153.95, 136.02, 134.19 (d, *J* = 3.6 Hz), 153.95, 136.02, 115.60 (d, *J* = 5.8 Hz), 113.17, 79.68, 65.13 (dd, *J* = 23.7, 21.1 Hz), 37.18, 36.13, 31.66 (d, *J* = 2.9 Hz), 26.99, 26.78. ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.29 (dd, *J* = 287.2, 55.0 Hz, 1F), -128.91 (dd, *J* = 287.2, 55.0 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / *i*-PrOH = 98 / 2, 0.6 mL / min, 254 nm, τ_R (major) = 14.81 min, τ_R (minor) = 10.54 min. HRMS Calcd. for $[C_{21}H_{22}F_2O_3+Na]^+$ requires m/z 383.1435, found m/z 383.1438.

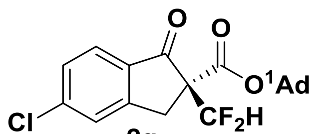
Methyl 2-difluoromethyl -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2f)



2f

(White wax, 21.4 mg, 89% yield, 81% ee); $[\alpha]_D^{25}$ 56.3 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.64 (m, 2H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 6.60 (t, *J* = 55.2 Hz, 1H), 3.89– 3.64 (m, 4H), 3.56 (d, *J* = 17.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.75 (d, *J* = 7.1 Hz), 166.43 (d, *J* = 12.1 Hz), 153.88, 136.19, 134.01 (d, *J* = 3.6 Hz), 128.12, 126.52, 125.33, 117.84, 115.42 (d, *J* = 6.2 Hz), 112.99, 64.61 (dd, *J* = 24.3, 20.8 Hz), 53.47, 29.91, 29.89, 29.86, 29.71. ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.01 (dd, *J* = 287.6, 55.1 Hz, 1F), -129.29 (dd, *J* = 287.5, 55.2 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / *i*-PrOH = 98 / 2, 0.6 mL / min, 254 nm, τ_R (major) = 16.56 min, τ_R (minor) = 13.18 min. HRMS Calcd. for $[C_{12}H_{10}F_2O_3+Na]^+$ requires m/z 263.0496, found m/z 263.0493.

1-Adamantyl 2- difluoromethyl -5-chloro -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2g)

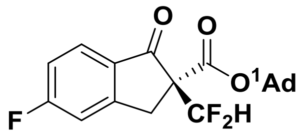


2g

(White solid, 33.9 mg, 86% yield, 74% ee); m. p. 93-96 ℃, $[\alpha]_D^{25}$62.1(*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.50 (m, 1H), 7.43 – 7.32 (m, 1H), 6.52 (dd, *J* = 55.8, 54.9 Hz, 1H), 3.64 (d, *J* = 17.7 Hz, 1H), 3.47 (d, *J* = 17.6 Hz, 1H), 2.25 – 1.98 (m, 9H), 1.66 – 1.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.92 (d, *J* = 6.7 Hz), 163.99 (d, *J* = 11.4 Hz), 155.36, 142.67, 132.65 (d, *J* = 3.6 Hz), 128.84, 126.69, 126.17, 117.90, 115.48 (d, *J* = 6.0 Hz), 113.05, 84.25, 68.33 – 60.80 (m), 40.96, 35.92, 30.86. ^{19}F NMR (376 MHz, $CDCl_3$) δ

-126.61 (d, J = 287.2 Hz, 1F), -128.64 (d, J = 287.2 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / i-PrOH = 99 / 1, 0.8 mL / min, 254 nm, τ_R (major) = 7.55 min, τ_R (minor) = 6.34 min. HRMS Calcd. for $[C_{21}H_{21}ClF_2O_3+Na]^+$ requires m/z 417.1045, found m/z 417.1047.

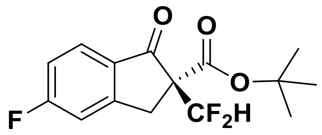
1-Adamantyl 2-difluoromethyl -5- fluorine -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2h)



2h

(Light yellow solid, 33.2 mg, 88% yield, 78% ee); m. p. 89-92 ℃ $[\alpha]_D^{25}$69.7(c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 8.5, 5.2 Hz, 1H), 7.14 (dd, J = 8.3, 2.1 Hz, 1H), 7.04 (td, J = 8.6, 2.2 Hz, 1H), 6.52 (d, J = 55.4 Hz, 1H), 3.58 (d, J = 17.7 Hz, 1H), 3.40 (d, J = 17.7 Hz, 1H), 2.17 – 2.01 (m, 9H), 1.69 – 1.43 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.39 (d, J = 7.4 Hz), 168.04, 165.47, 163.11, 163.00, 155.95 (d, J = 10.6 Hz), 129.54 (d, J = 2.0 Hz), 126.55, 126.44, 116.92, 115.43 (d, J = 24.1 Hz), 114.53, 112.22 (d, J = 22.8 Hz), 83.15, 64.86 (dd, J = 22.8, 21.2 Hz), 39.95, 34.90, 29.84. ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.17 (s, 1F), -126.72 (d, J = 286.8 Hz, 1F), -128.72 (d, J = 287.1 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / i-PrOH = 99 / 1, 0.6 mL / min, 254 nm, τ_R (major) = 12.87 min, τ_R (minor) = 11.41 min. HRMS Calcd. for $[C_{21}H_{21}F_3O_3+Na]^+$ requires m/z 401.1340, found m/z 401.1334.

1-tert-Butyl 2-difluoromethyl -5- fluorine -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2i)

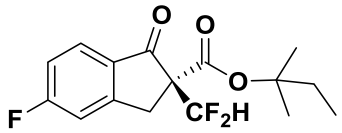


2i

(Colorless oil, 26.4 mg, 88% yield, 63% ee); $[\alpha]_D^{25}$ 46.2(c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.5, 5.3 Hz, 1H), 7.26 – 7.18 (m, 1H), 7.12 (td, J = 8.6, 2.2 Hz, 1H), 6.52 (dd, J = 55.8, 54.9 Hz, 1H), 3.67 (d, J = 17.7 Hz, 1H), 3.48 (d, J = 17.7 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.34 (d, J = 6.9 Hz), 169.10, 166.53, 164.46 (d, J = 11.3 Hz), 156.97 (d, J = 10.6 Hz), 130.53 (d, J = 1.9 Hz), 127.60, 127.49, 117.93, 116.49 (d, J = 24.0 Hz), 113.27 (d, J = 22.8 Hz), 84.15, 65.82 (dd, J = 22.9, 21.3 Hz), 27.76. ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.10 (s, 1F) , -126.74 (d, J = 286.8 Hz, 1F), -128.65 (d, J = 286.8 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / i-PrOH = 98 / 2, 0.6 mL / min, 254 nm, τ_R

(major) = 9.85 min, τ_R (minor) = 8.84 min. HRMS Calcd. for $[C_{15}H_{15}F_3O_3+Na]^+$ requires m/z 323.0871, found m/z 323.0869.

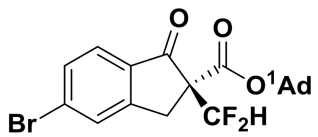
1-tert-Pentyl 2-difluoromethyl -5- fluorine -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2j)



2j

(Colorless oil, 25.4 mg, 81% yield, 55% ee); $[\alpha]_D^{25}$ 42.8(*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (dd, *J* = 8.5, 5.2 Hz, 1H), 7.22 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.12 (td, *J* = 8.6, 2.2 Hz, 1H), 6.53 (t, *J* = 55.4 Hz, 1H), 3.66 (d, *J* = 17.7 Hz, 1H), 3.49 (d, *J* = 17.6 Hz, 1H), 1.76 (q, *J* = 7.5 Hz, 2H), 1.43 (s, 6H), 0.85 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.39 (d, *J* = 7.2 Hz), 169.10, 166.52, 164.35 (d, *J* = 11.4 Hz), 156.96 (d, *J* = 10.6 Hz), 130.57, 127.53 (d, *J* = 10.9 Hz), 117.93, 116.50 (d, *J* = 24.2 Hz), 115.50 (d, *J* = 5.7 Hz), 113.26 (d, *J* = 22.9 Hz), 86.66, 69.64 – 62.48 (m), 33.50, 30.97 – 27.80 (m), 25.26, 25.19, 7.96. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -100.09 (s, 1F), -126.66 (d, *J* = 287.4 Hz, 1F), -128.65 (d, *J* = 287.4 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / *i*-PrOH = 98 / 2, 0.6 mL / min, 254 nm, τ_R (major) = 8.95 min, τ_R (minor) = 8.07 min. HRMS Calcd. for $[C_{16}H_{17}F_3O_3+Na]^+$ requires m/z 337.1027, found m/z 337.1031.

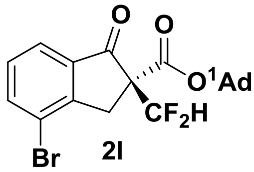
1-Adamantyl 2-difluoromethyl-5-bromine -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2k)



2k

(White solid, 36.3 mg, 83% yield, 78% ee); m. p. 113-115 ℃, $[\alpha]_D^{25}$ 73.2(*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (dt, *J* = 1.6, 0.8 Hz, 1H), 7.66 – 7.46 (m, 2H), 6.51 (dd, *J* = 55.7, 54.9 Hz, 1H), 3.65 (d, *J* = 17.7 Hz, 1H), 3.47 (d, *J* = 17.7 Hz, 1H), 2.26 – 1.87 (m, 8H), 1.69 – 1.49 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.13, 163.94 (d, *J* = 11.3 Hz), 155.43, 133.05 (d, *J* = 3.5 Hz), 131.67, 29.78, 126.21, 117.87, 115.45 (d, *J* = 6.0 Hz), 113.02, 84.27, 69.76 – 62.45 (m), 40.96, 35.91, 30.86. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -126.58 (d, *J* = 286.9 Hz, 1F), -128.61 (d, *J* = 286.9 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / *i*-PrOH = 98 / 2, 0.6 mL / min, 254 nm, τ_R (major) = 12.25 min, τ_R (minor) = 10.99 min. HRMS Calcd. for $[C_{21}H_{21}BrF_2O_3+Na]^+$ requires m/z 461.0540, found m/z 461.0545.

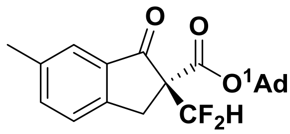
1-Adamantyl 2-difluoromethyl-4-bromine -1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2l)



2l

(White solid, 33.7 mg, 77% yield, 63% ee); m. p. 105-107 ℃, $[\alpha]_D^{25}$ 67.8(c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.8, 1.0 Hz, 1H), 7.72 (dd, J = 7.7, 0.9 Hz, 1H), 7.43 – 7.28 (m, 1H), 6.53 (dd, J = 55.7, 54.9 Hz, 1H), 3.61 (d, J = 18.0 Hz, 1H), 3.42 (d, J = 18.0 Hz, 1H), 2.18 – 1.97 (m, 8H), 1.71 – 1.47 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ195.71 (d, J = 6.7 Hz), 163.86 (d, J = 11.3 Hz), 153.63, 138.66, 136.08 (d, J = 3.5 Hz), 129.66, 123.93, 121.83, 117.84, 115.42 (d, J = 6.1 Hz), 112.99, 84.35, 69.54 – 62.85 (m), 40.96, 35.92, 30.86. ^{19}F NMR (376 MHz, $CDCl_3$ δ -126.41 (d, J = 287.5 Hz, 1F), -128.51 (d, J = 287.5 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / i-PrOH = 99.5 / 0.5, 0.6 mL / min, 254 nm, τR (major) = 21.04 min, τR (minor) = 19.67 min. HRMS Calcd. for $[C_{21}H_{21}BrF_2O_3+Na]^+$ requires m/z 461.0540, found m/z 461.0543.

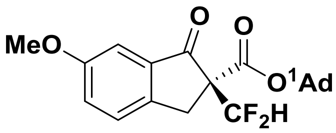
1-Adamantyl 2-difluoromethyl-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2m)



2m

(White wax, 28.4 mg, 76% yield, 63% ee); $[\alpha]_D^{25}$ 54.8(c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.51 – 7.38 (m, 2H), 6.53 (t, J = 55.5 Hz, 1H), 3.60 (d, J = 17.2 Hz, 1H), 3.44 (d, J = 17.3 Hz, 1H), 2.40 (s, 3H), 2.12 (dd, J = 28.6, 3.1 Hz, 9H), 1.67 – 1.55 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.40 (d, J = 7.2 Hz), 164.52 (d, J = 11.6 Hz), 151.52, 137.94, 137.22, 134.38 (d, J = 3.6 Hz), 126.05, 124.97, 118.17, 115.75 (d, J = 5.9 Hz), 113.33, 83.80, 65.86 (dd, J = 23.1, 21.1 Hz), 40.96, 35.95, 30.85, 29.94 – 28.85 (m), 21.03. ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.66 (dd, J = 286.5, 55.2 Hz, 1F), -128.93 (dd, J = 286.5, 55.2 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / i-PrOH = 98 / 2, 0.6 mL / min, 254 nm, τ_R (major) = 14.93 min, τ_R (minor) = 11.19 min. HRMS Calcd. for $[C_{22}H_{24}F_2O_3+Na]^+$ requires m/z 397.1591, found m/z 397.1594.

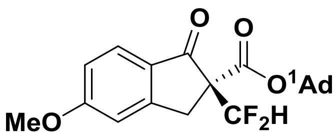
1-Adamantyl 2-difluoromethyl-6-methoxyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2n)



2n

(Light yellow solid, 28.9 mg, 74% yield, 73% ee); m. p. 93-95 ℃, $[\alpha]_D^{25}$55.6(c 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.4 Hz, 1H), 7.31 – 7.22 (m, 2H), 7.17 (d, J = 2.5 Hz, 1H), 6.53 (t, J = 55.5 Hz, 1H), 3.83 (s, 3H), 3.64 – 3.32 (m, 2H), 2.25 – 2.07 (m, 9H), 1.73 – 1.56 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.33 (d, J = 7.2 Hz), 164.47 (d, J = 11.5 Hz), 159.68, 147.13, 135.38 (d, J = 3.6 Hz), 125.50, 118.12, 115.70 (d, J = 5.8 Hz), 105.92, 83.86, 66.28 (dd, J = 23.1, 21.1 Hz), 55.62, 40.97, 35.95, 30.86, 29.25. ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.65 (dd, J = 286.5, 55.1 Hz, 1F), -129.01 (dd, J = 286.5, 55.8 Hz, 1F). Chiralcel OJ-H column (250 × 4.6 mm), hexane / i-PrOH = 99 / 1, 1 mL / min, 254 nm, τ_R (major) = 8.88 min, τ_R (minor) = 11.28 min. HRMS Calcd. for $[C_{22}H_{24}F_2O_4+Na]^+$ requires m/z 413.1540, found m/z 413.1544.

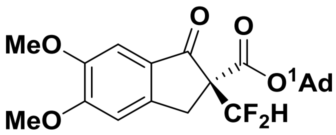
1-Adamantyl 2-difluoromethyl-5-methoxyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2o)



2o

(Light yellow solid, 29.2 mg, 75% yield, 63% ee); m. p. 103-105 ℃, $[\alpha]_D^{25}$54.3(c 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.5 Hz, 1H), 7.04 – 6.85 (m, 2H), 6.52 (t, J = 55.5 Hz, 1H), 3.91 (s, 3H), 3.61 (d, J = 17.4 Hz, 1H), 3.42 (d, J = 17.5 Hz, 1H), 2.23 – 2.03 (m, 9H), 1.63 – 1.47 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.25, 166.25, 164.71 (d, J = 11.5 Hz), 157.19, 127.29 (d, J = 3.7 Hz), 126.84, 118.23, 116.27, 115.81 (d, J = 5.3 Hz), 113.39, 109.37, 83.75, 65.81 (dd, J = 23.0, 20.8 Hz), 55.79, 40.99, 35.97, 30.86, 30.23 – 29.22 (m).^{19}F NMR (376 MHz, $CDCl_3$) δ -126.89 (dd, J = 286.0, 55.8 Hz, 1F), -128.97 (dd, J = 286.0, 55.8 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / i-PrOH = 99 / 1, 0.6 mL / min, 254 nm, τ_R (major) = 11.73 min, τ_R (minor) = 15.87 min. HRMS Calcd. for $[C_{22}H_{24}F_2O_4+Na]^+$ requires m/z 413.1540, found m/z 413.1543.

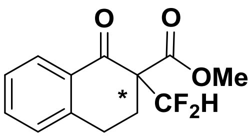
1-Adamantyl 2-difluoromethyl-5,6-di-methoxyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2o)



2p

2p was obtained by the same procedure as mentioned above for **2a-2p** using 25% KOH instead of 30% K_2CO_3 as the base. (Light yellow solid, 26.4 mg, 63% yield, 58% ee); m. p. 146-148 ℃, $[\alpha]_D^{25}$46.2(c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.96 (s, 1H), 6.53 (t, J = 55.5 Hz, 1H), 4.00 (s, 3H), 3.91 (s, 3H), 3.56 (d, J = 17.2 Hz, 1H), 3.38 (d, J = 17.2 Hz, 1H), 2.20 – 2.05 (m, 9H), 1.72 – 1.61 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.67 (d, J = 7.3 Hz), 164.78 (d, J = 11.7 Hz), 156.48, 149.89 (d, J = 13.3 Hz), 126.83, 126.79, 118.22, 115.80 (d, J = 5.5 Hz), 113.38, 107.18, 105.07, 83.75, 65.89 (dd, J = 23.1, 20.9 Hz), 56.40, 56.11, 45.33, 41.00, 35.98, 30.86, 29.57.^{19}F NMR (376 MHz, $CDCl_3$) δ -126.79 (dd, J = 285.6, 55.1 Hz, 1F), -129.19 (dd, J = 285.6, 55.1 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / i-PrOH = 98 / 2, 0.8 mL / min, 254 nm, τ_R (major) = 29.10 min, τ_R (minor) = 37.61 min. HRMS Calcd. for $[C_{23}H_{26}F_2O_5+Na]^+$ requires m/z 443.1646, found m/z 443.1643.

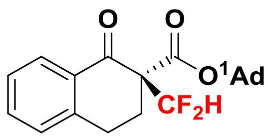
1-Methyl 2- difluoromethyl -1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (2q)



2q

2q was obtained by the same procedure as mentioned above for **2a-2p** using 25% KOH instead of 30% K_2CO_3 as the base. (colourless oil, 18.5 mg, 73% yield, 19% ee); $[\alpha]_D^{25}$5.3(c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, J = 7.9, 1.4 Hz, 1H), 7.53 (td, J = 7.5, 1.4 Hz, 1H), 7.38 – 7.26 (m, 2H), 6.61 (t, J = 55.3 Hz, 1H), 3.75 (s, 3H), 3.46 – 3.23 (m, 1H), 3.04 (dt, J = 17.3, 4.6 Hz, 1H), 2.67 (dt, J = 13.9, 4.4 Hz, 1H), 2.46 (ddd, J = 13.9, 11.6, 5.1 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 190.01 (d, J = 6.0 Hz), 166.78 (d, J = 9.0 Hz), 143.56, 134.56, 130.99 (d, J = 2.7 Hz), 128.94, 128.24, 126.99, 118.24, 115.78, 113.33, 66.67 – 55.83 (m), 53.28, 24.97, 23.08. ^{19}F NMR (376 MHz, $CDCl_3$) δ -127.32 (d, J = 283.3 Hz, 1F), -131.82 (d, J = 283.2 Hz, 1F). HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane / i-PrOH = 99 / 1, 0.8 mL / min, 254 nm, τ_R (major) = 16.58 min, τ_R (minor) = 12.52 min. HRMS Calcd. for $[C_{13}H_{12}F_2O_3+Na]^+$ requires m/z 277.0652, found m/z 277.0655.

1-Adamantyl 2- difluoromethyl -1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (2r)



2r

2r was obtained by the same procedure as mentioned above for **2a-2p** using 25% KOH instead of 30% K_2CO_3 as the base. (colourless oil, 25.0 mg, 67% yield, 47% ee); $[\alpha]_D^{25}$10.5(*c* 0.20, $CHCl_3$); ^{11}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.51 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.24 (s, 1H), 6.53 (t, *J* = 55.4 Hz, 1H), 3.33 (ddd, *J* = 17.1, 11.8, 5.1 Hz, 1H), 3.01 (ddd, *J* = 17.2, 5.1, 3.6 Hz, 1H), 2.60 (ddd, *J* = 13.9, 5.1, 3.5 Hz, 1H), 2.40 (ddd, *J* = 13.9, 11.8, 5.2 Hz, 1H), 2.20 – 2.02 (m, 9H), 1.68 – 1.53 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.60 (d, *J* = 5.8 Hz), 164.99 (d, *J* = 8.3 Hz), 143.31, 134.19, 131.36 (d, *J* = 2.4 Hz), 128.82, 128.02, 126.87, 118.47, 116.02, 113.57, 83.93, 61.41 (t, *J* = 21.0 Hz), 40.97, 35.93, 30.81, 25.09, 23.38. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -127.41 (d, *J* = 282.7 Hz, 1F), -132.08 (d, *J* = 282.7 Hz, 1F). HPLC conditions: Chiralcel OJ-H column (250 × 4.6 mm), hexane / *i*-PrOH = 99.5 / 0.5, 1 mL / min, 254 nm, τ_R (major) = 9.89 min, τ_R (minor) = 11.43 min. HRMS Calcd. for $[C_{22}H_{24}F_2O_3+Na]^+$ requires m/z 397.1591, found m/z 397.1588.

C. General proceduce for the O-difluoromethylation of β-keto ester 1f

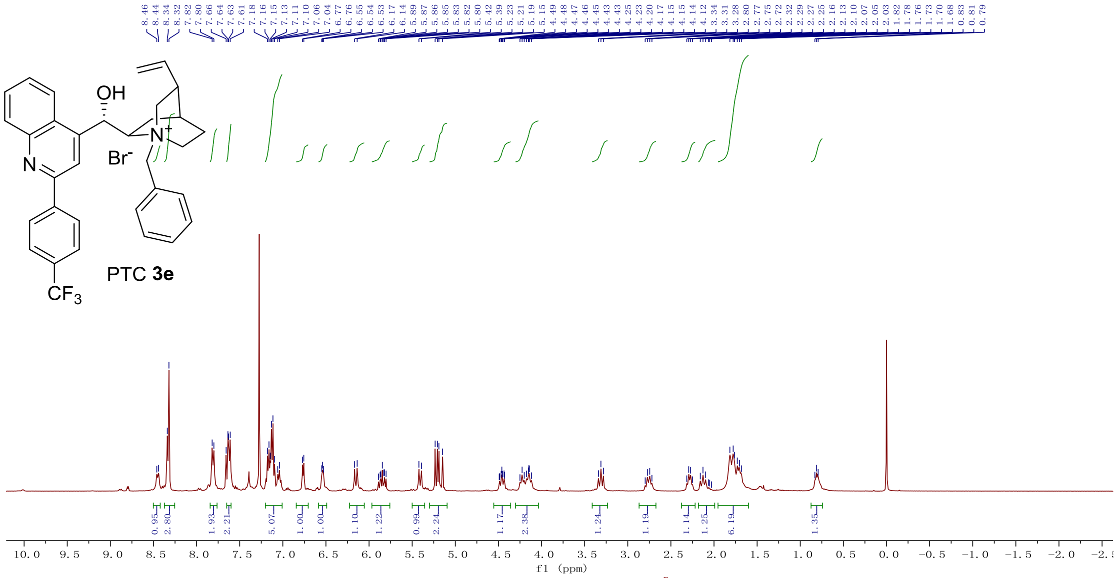
The reaction was conducted with β-keto esters **1f** (0.3 mmol) in the presence of KHF_2 (1.8 mmol) in a mixture containing CH_2Cl_2/H_2O =1:1 (0.4 mL) in pressure tubing at rt. Then $TMSCF_2Br$ (0.9 mmol) was added slowly, and the reaction was stirred at this 60 ^oC for 12 h. After the reaction was completed (confirmed by TLC analysis), the mixture was diluted with EtOAc (30 mL), washed with water (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was subject to crude ^{19}F-NMR to give the C/O isomer ratio (trifluoromethyl benzene 8 μL as internal standard). Subsequently, the residue was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate=20:1) to afford the O-difluoromethylation product **2f'**. (colourless oil, 56.2 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.56 (m, 1H), 7.50 – 7.38 (m, 3H), 7.12 ((t, *J* = 55.4 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 156.1, 141.5, 138.5, 129.3, 127.3, 124.4, 121.0, 119.2, 116.9, 116.6, 114.0, 51.8, 36.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.61(s, 1F), -81.81(s, 1F). HRMS Calcd. for $[C_{12}H_{10}F_2O_3+Na]^+$ requires m/z 263.0496, found m/z 263.0491.

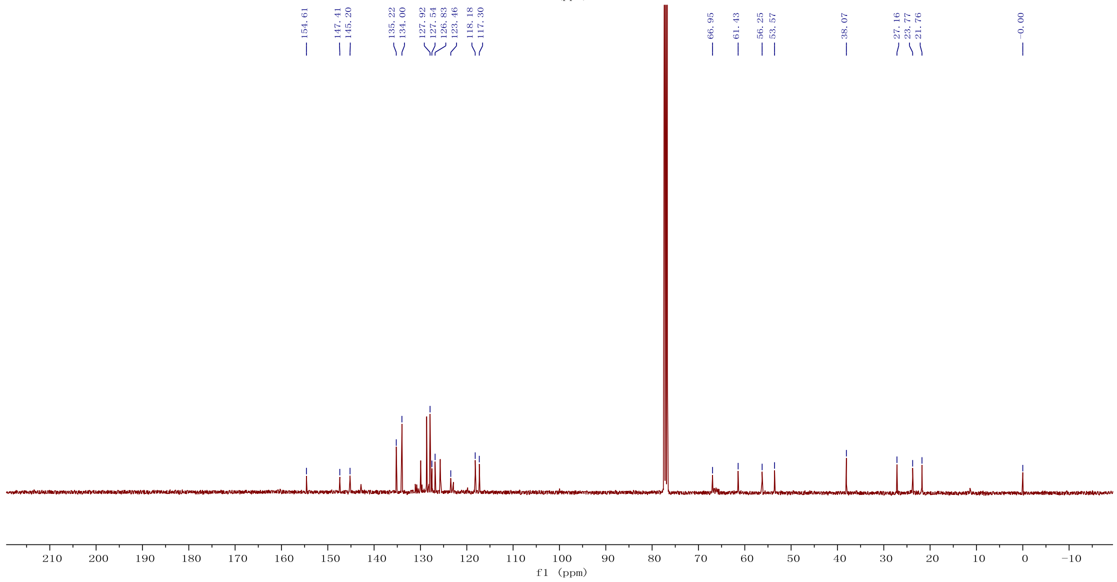
D. General proceduce for the derivatization of 1f

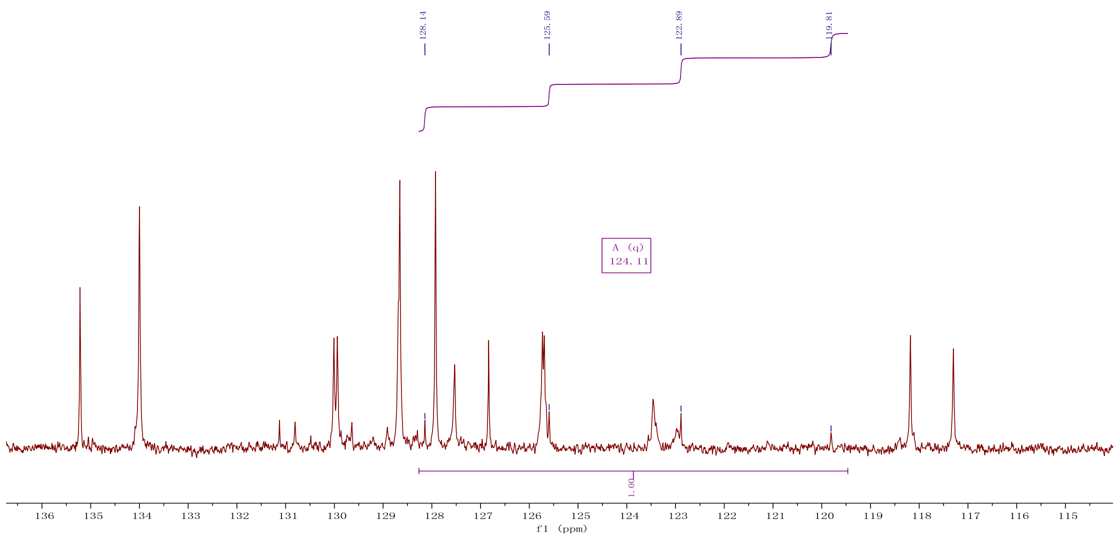
The difluoromethylated compound **1f** (48.0 mg, 0.2 mmol) in anhydrous THF (1 mL) was added slowly to the mixture of lithium aluminum hydride (17.3 mg, 0.45 mmol) in anhydrous THF (1 mL) at 0 ^{o}C. After stirring for another 1 hour at the same temperature, the reaction was allowed to warm to room temperature and stirred for another 5 h. After that, the reaction was quenched by the dropwise addition of EtOAc followed by a 10% HCl. After vigorous stirring for another 20 min, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc = 3:1) to give product **4f** (colourless oil, 32.1 mg, 75% yield, dr> 20:1). $[\alpha]_D^{25}$ +95.6 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 6.9, 1.7 Hz, 1H), 7.37 – 7.22 (m, 3H), 6.28 (t, *J* = 55.7 Hz, 1H), 5.31 (s, 1H), 3.89 (d, *J* = 11.4 Hz, 1H), 3.62 (dd, *J* = 11.4, 1.8 Hz, 1H), 3.24 (d, *J* = 16.8 Hz, 1H), 2.69 (d, *J* = 16.8 Hz, 1H), 2.04 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 140.4, 129.2, 125.0 (d, *J* = 16.6 Hz), 127.4, 121.3, 118.9, 116.5, 78.8, 64.0 (dd, *J* = 5.8, 4.1 Hz), 54.5 (t, *J* = 17.1 Hz), 33.5 (dd, *J* = 5.0, 3.6 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -126.58 (dd, *J* = 285.3, 55.8 Hz, 1F), -130.09 (dd, *J* = 285.3, 55.8 Hz, 1F). HRMS Calcd. for $[C_{11}H_{12}F_2O_2+Na]^+$ requires m/z 237.0703, found m/z 237.0710.

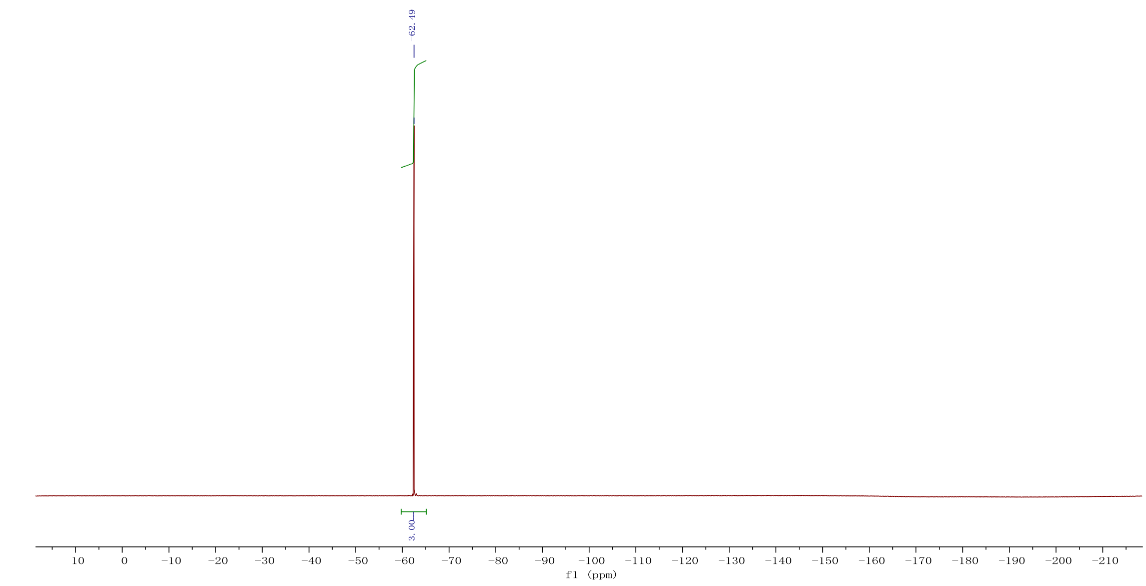
The difluoromethylated compound **1f** (48.0 mg, 0.2 mmol) was added slowly to anhydrous cyclohexylamine (0.3 mL) at 120 ^{o}C. After stirring for another 3 hour at the same temperature, the reaction was allowed to cool down to room temperature. After that, the reaction was quenched by the dropwise addition of EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc =10:1) to give product **5f** (light yellow solid, 32.1 mg, 84% yield, 80% ee); m. p.78-81 ℃, $[\alpha]_D^{25}$ +57.3(*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.61 (m, 2H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.12 (t, *J* = 55.7 Hz, 1H), 4.03 (d, *J* = 18.2 Hz, 1H), 3.95 – 3.67 (m, 1H), 3.46 (d, *J* = 18.2 Hz, 1H), 2.03 – 1.90 (m, 1H), 1.91 – 1.51 (m, 4H), 1.47 – 1.11 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8 (d, *J* = 5.7 Hz), 162.0 (d, *J* = 2.4 Hz), 154.1, 136.6, 134.7 (d, *J* = 2.2 Hz), 127.9, 126.6, 124.8, 120.8 – 110.2 (m), 64.3 (d, *J* = 19.9 Hz), 49.0, 32.6, 32.5, 29.9, 29.9, 25.5, 24.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.39 (dd, *J* = 279.4, 55.3 Hz), -124.86 (dd, *J* = 279.4, 55.3 Hz). HPLC conditions: Chiralcel OJ-H column (250 × 4.6 mm), hexane / *i*-PrOH = 98 / 2, 0.6 mL / min, 254 nm, τ_R (major) = 12.29 min, τ_R (minor) = 15.84 min. HRMS Calcd. for $[C_{17}H_{19}F_2O_2+Na]^+$ requires m/z 330.1282, found m/z 330.1289.

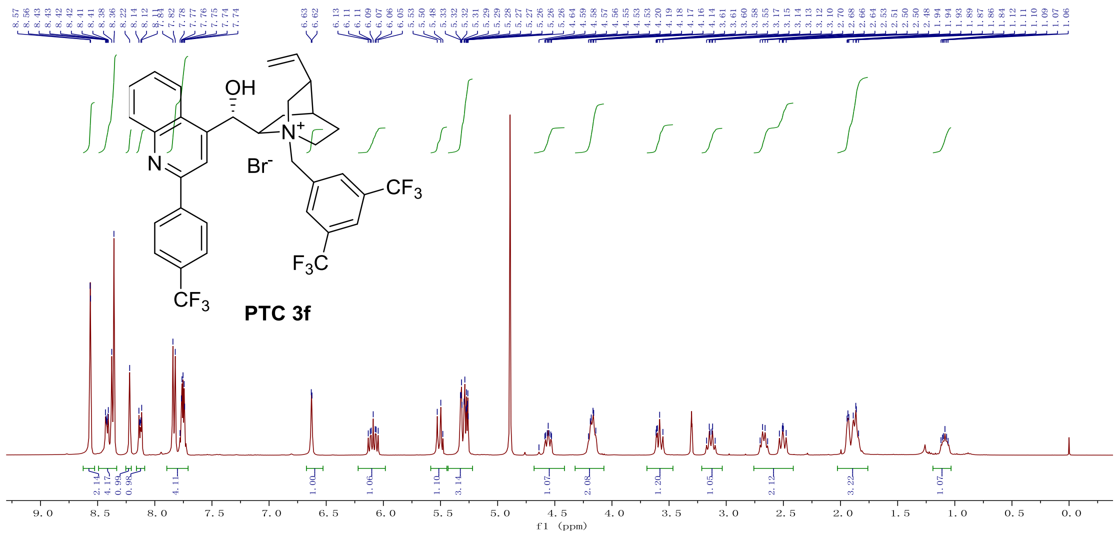
E. NMR spectra



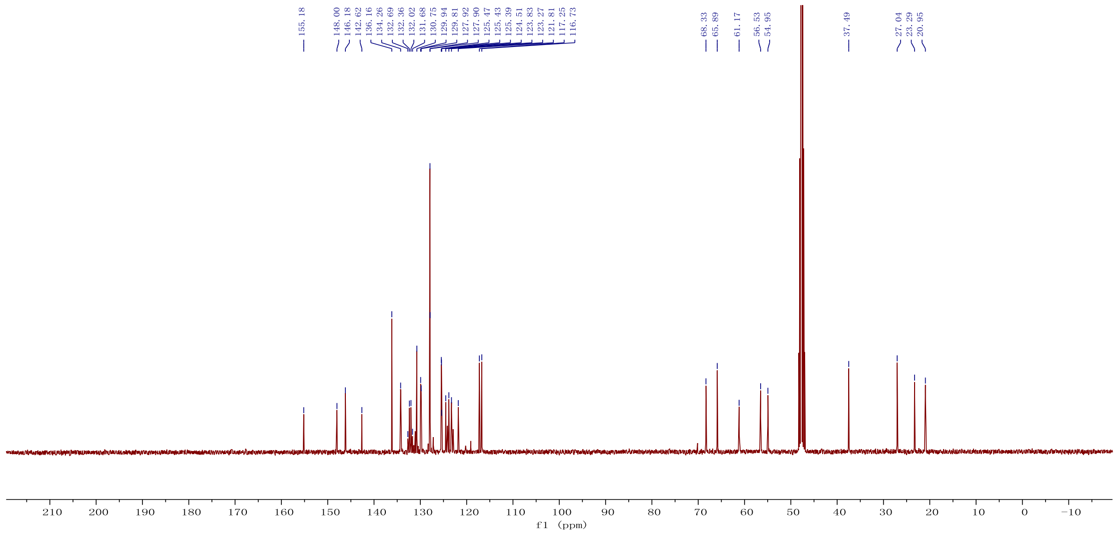


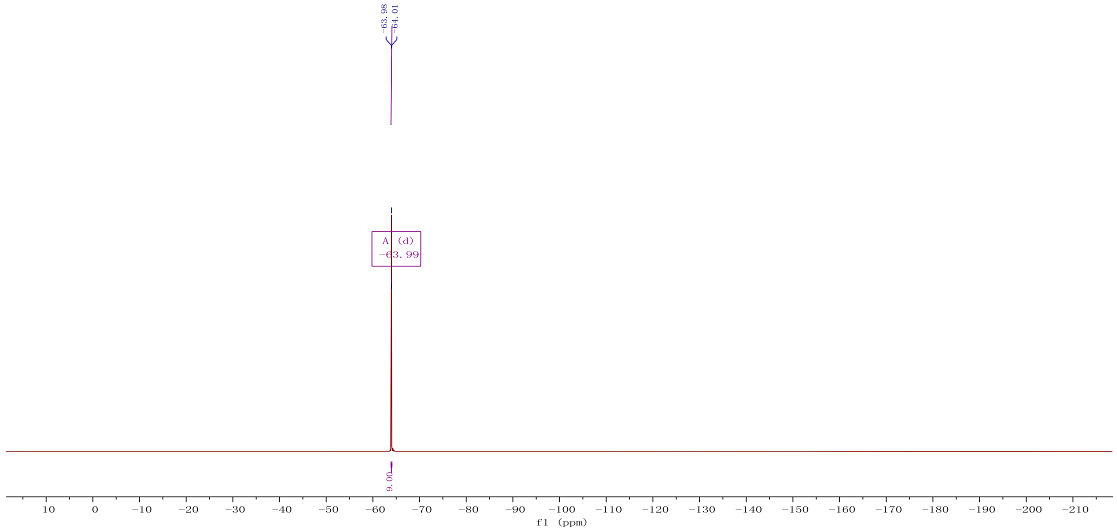






PTC 3f

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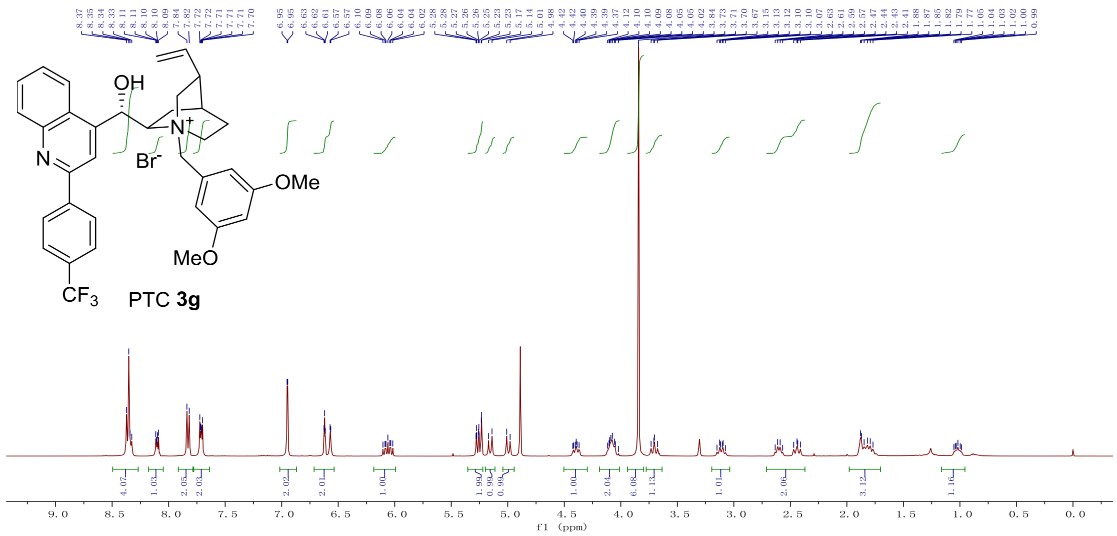
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6.95 6.95 6.63 6.62 6.61 6.57 6.57 6.10 6.09 6.08 6.06 6.04 6.04 6.02
5.28 5.28 5.27 5.26 5.25 5.23 5.23 5.17 5.14 5.01 4.98
4.42 4.42 4.40 4.39 4.37 4.12 4.10 4.10 4.09 4.08 4.05 4.05 4.02 3.84 3.73 3.71 3.70 3.67
3.15 3.13 3.12 3.10 3.07 2.63 2.61 2.59 2.57 2.47 2.44 2.43 2.41 1.88 1.87 1.85 1.82 1.79 1.77
1.05 1.04 1.03 1.02 1.00 0.99
OH
N
N+
Br-
OMe
MeO
CF3
PTC 3g
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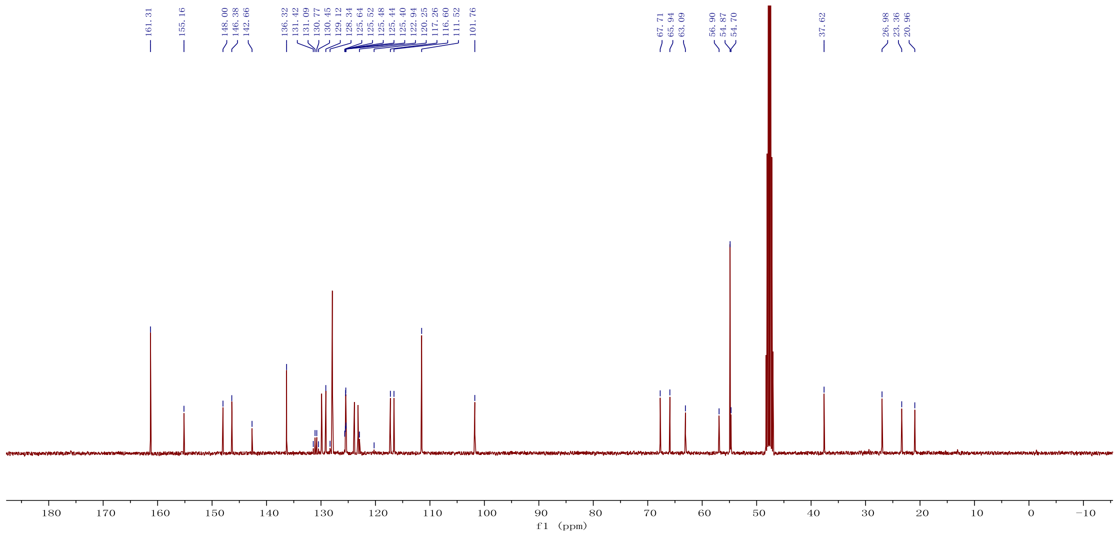
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37.62
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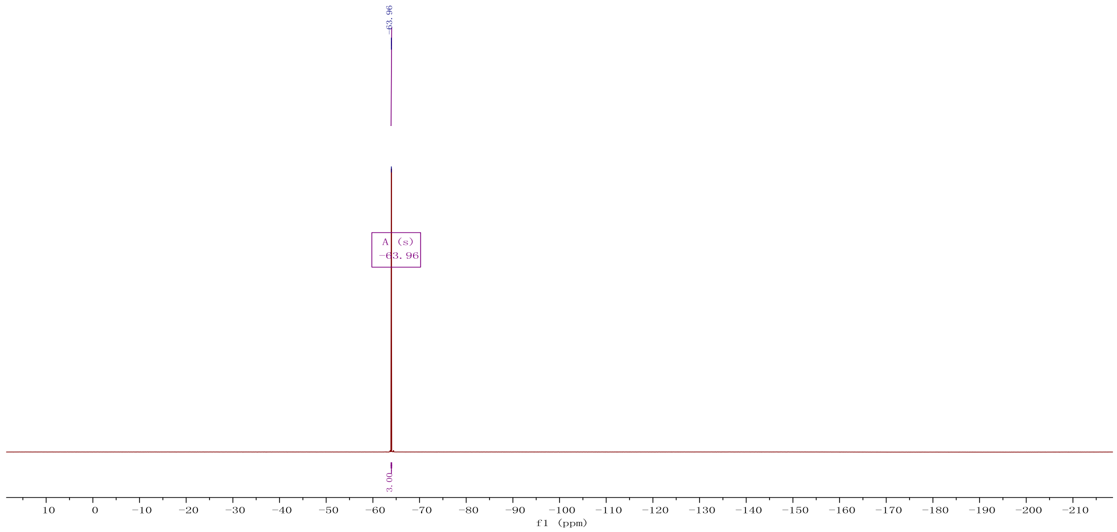
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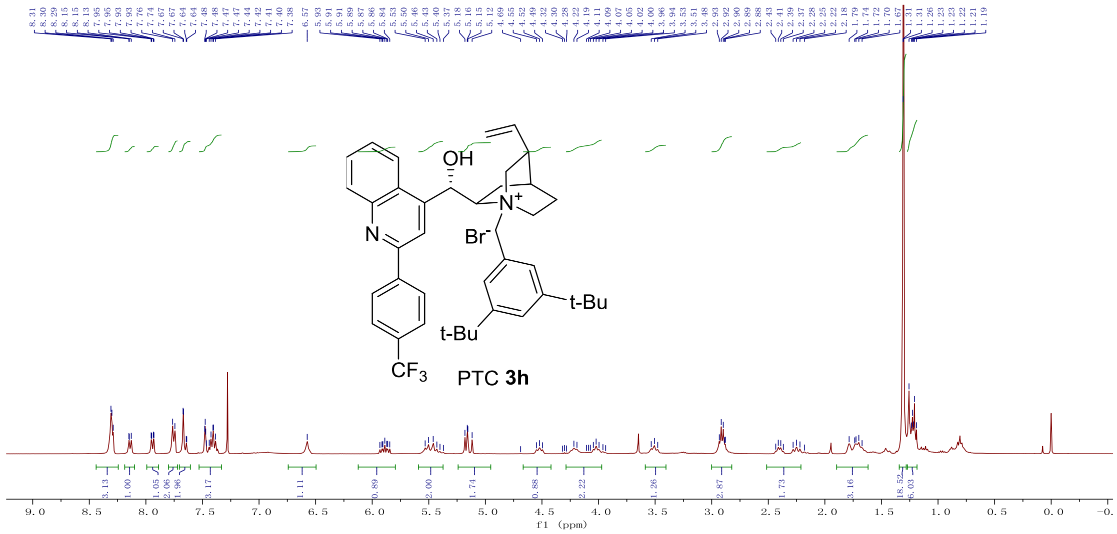
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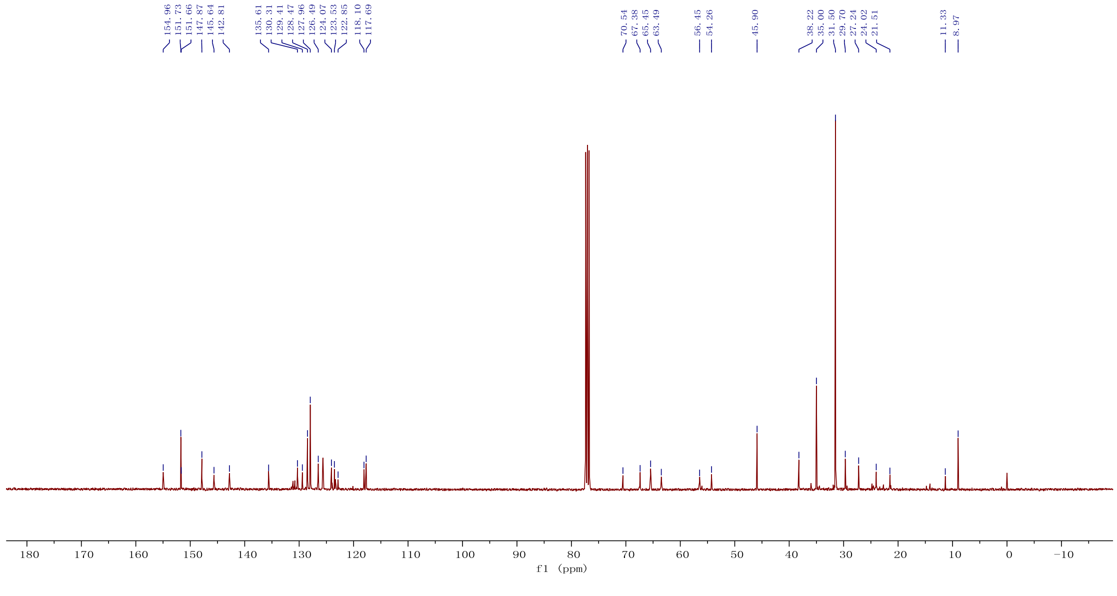
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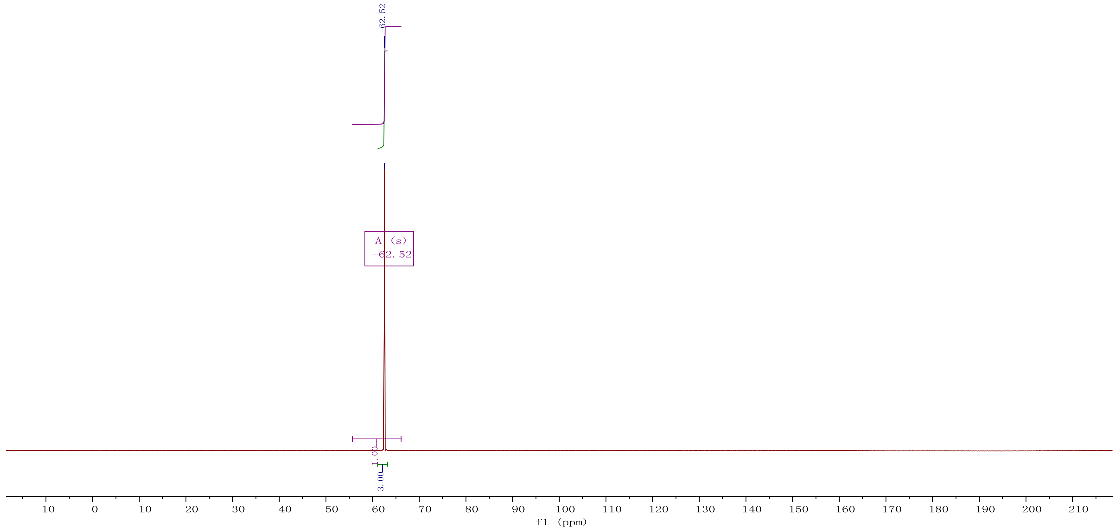
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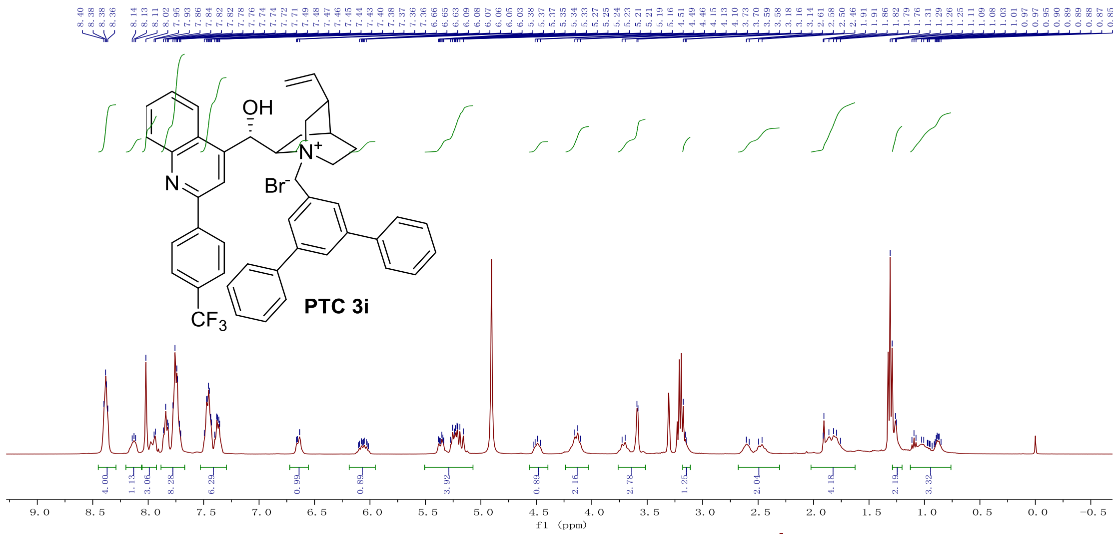
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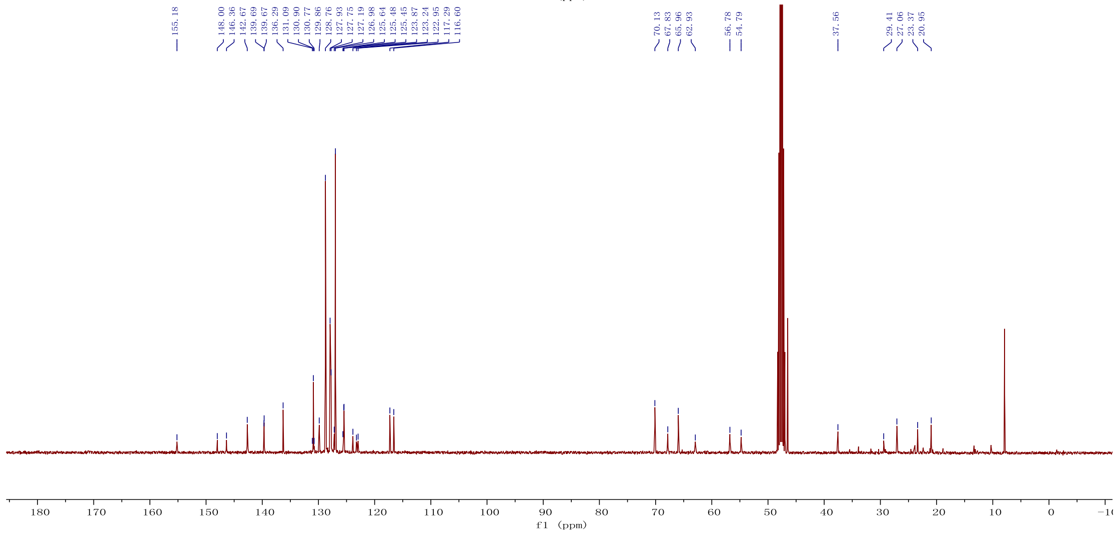
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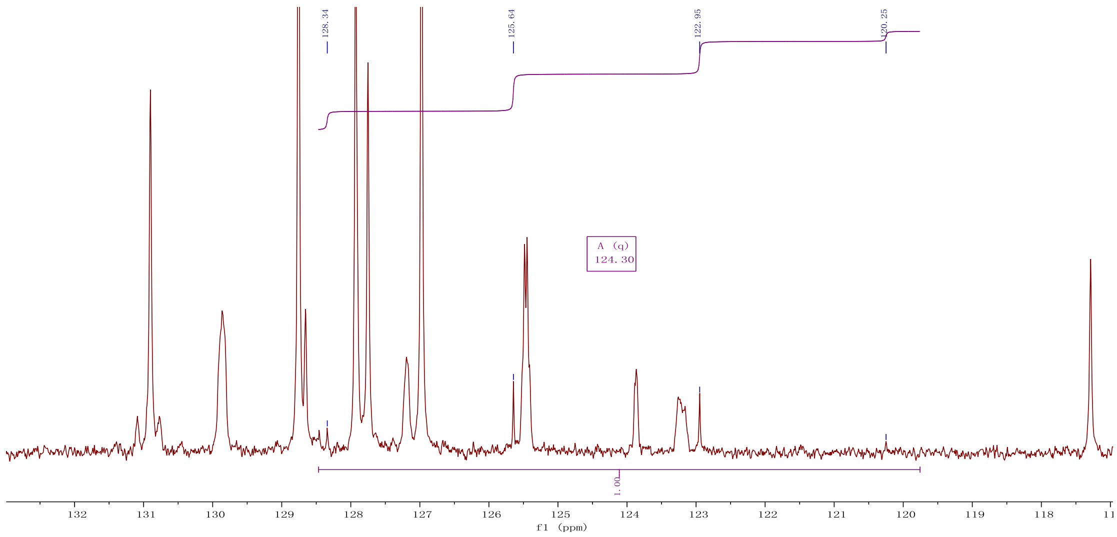
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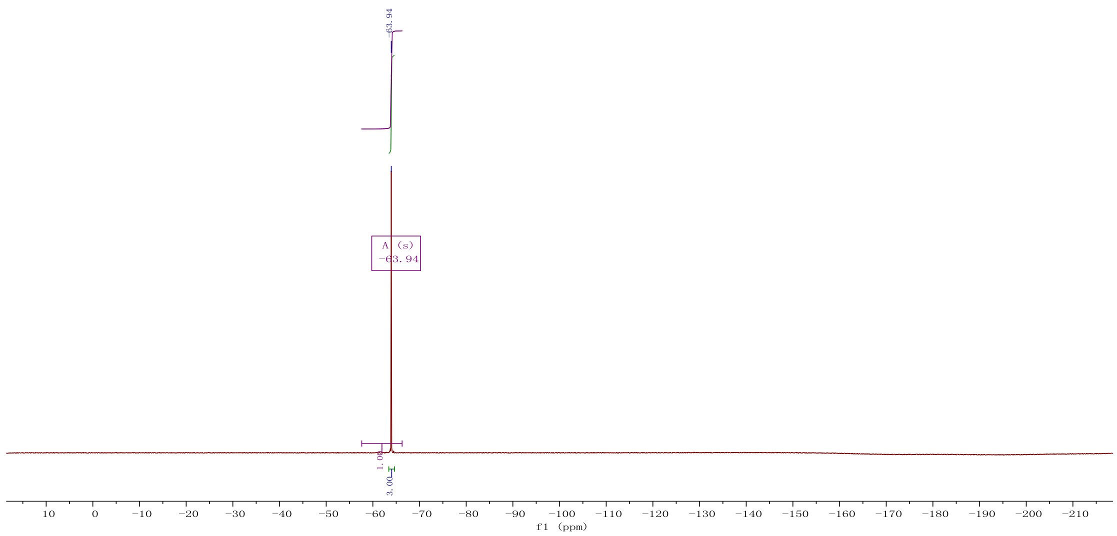
119
118
f1 (ppm)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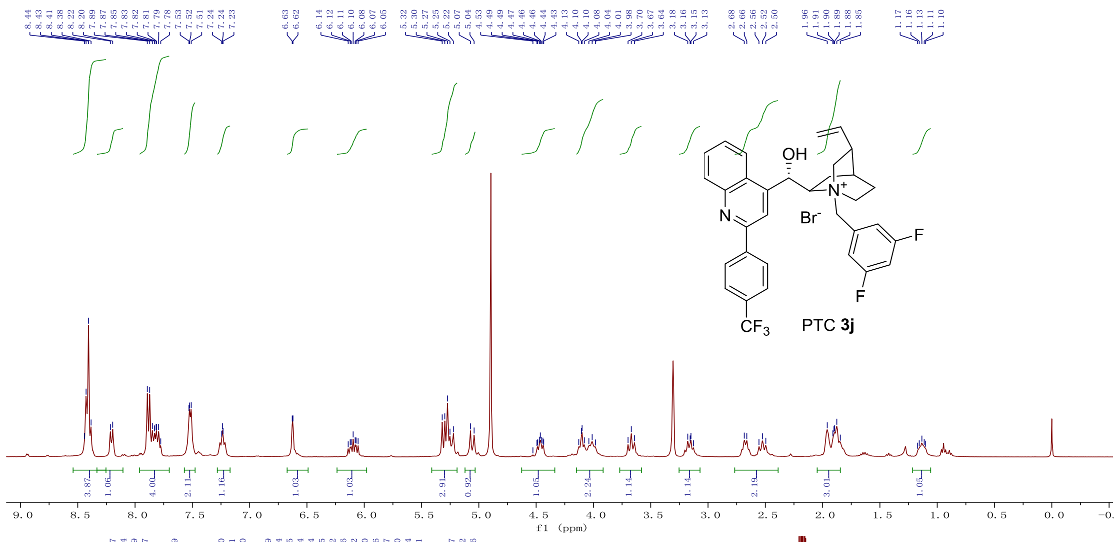
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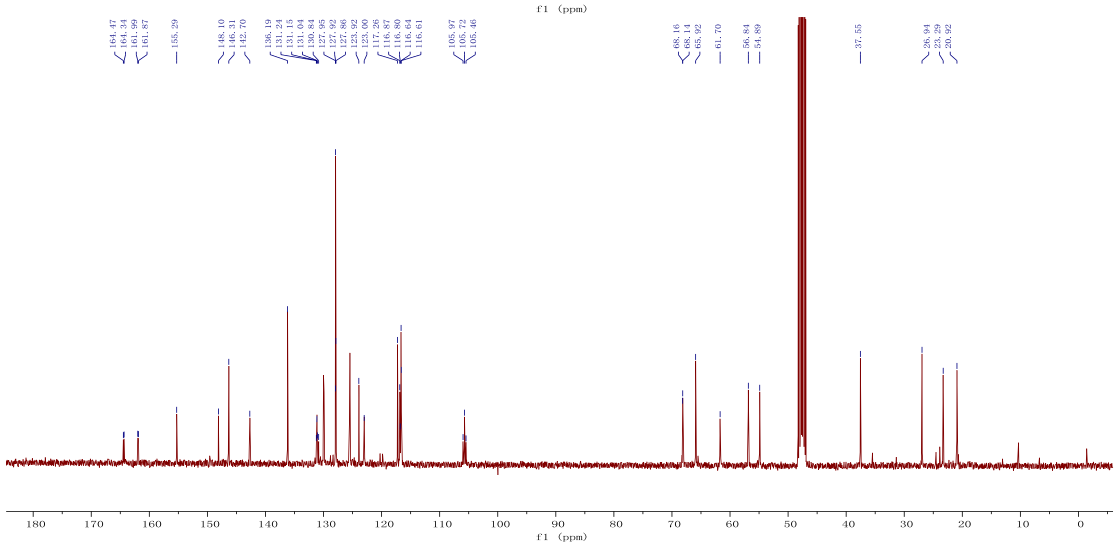
F
F
CF3
PTC 3j
f1 (ppm)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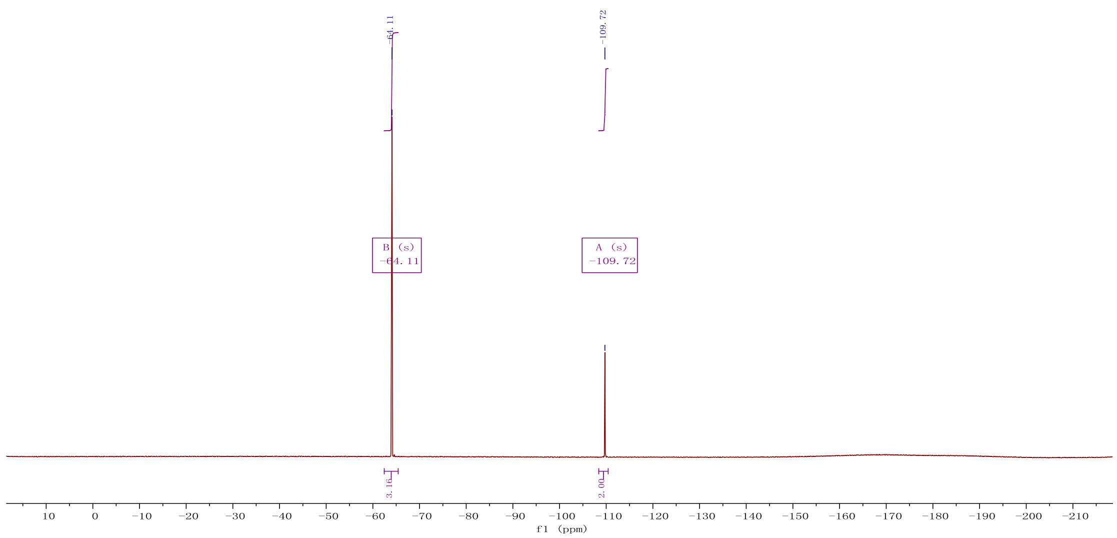
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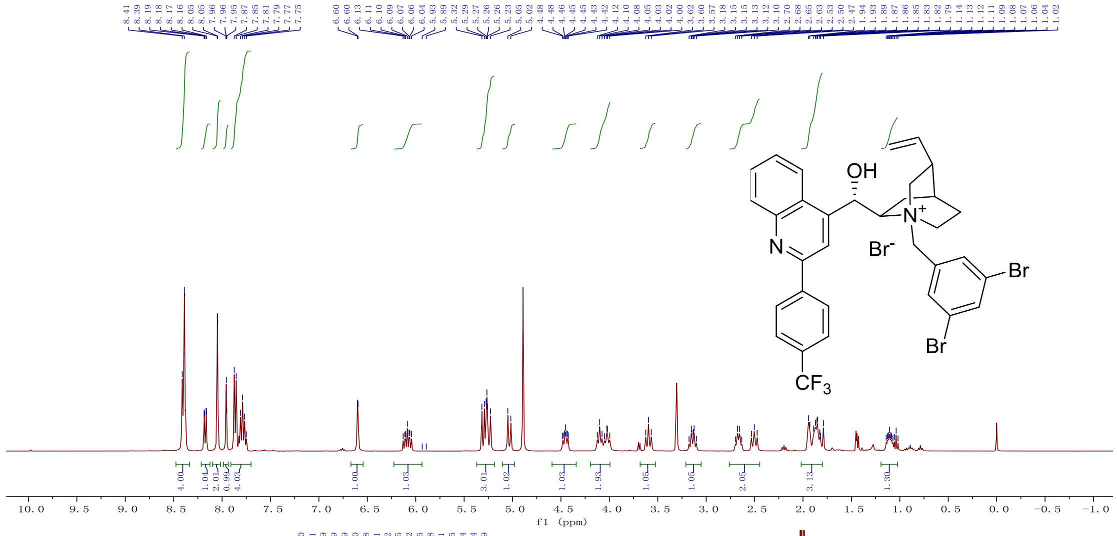
f1 (ppm)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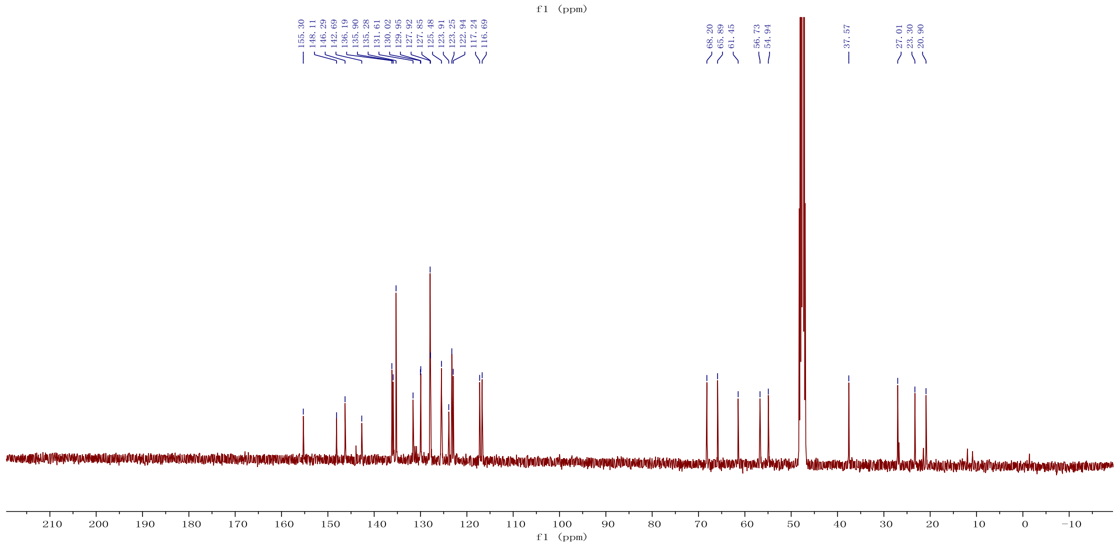
N
N+
Br-
Br
Br
CF3
f1 (ppm)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123.91
123.25
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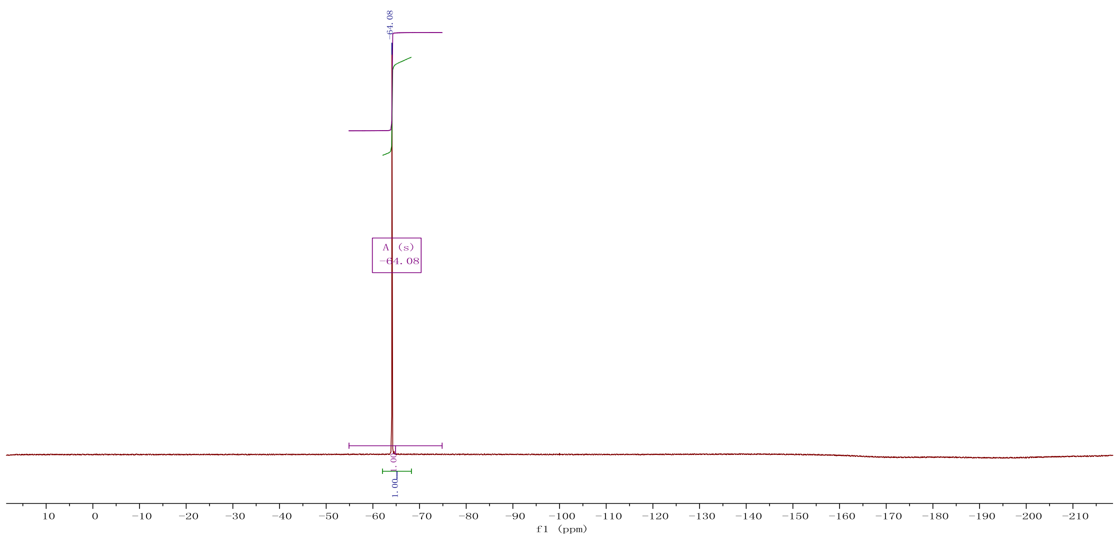
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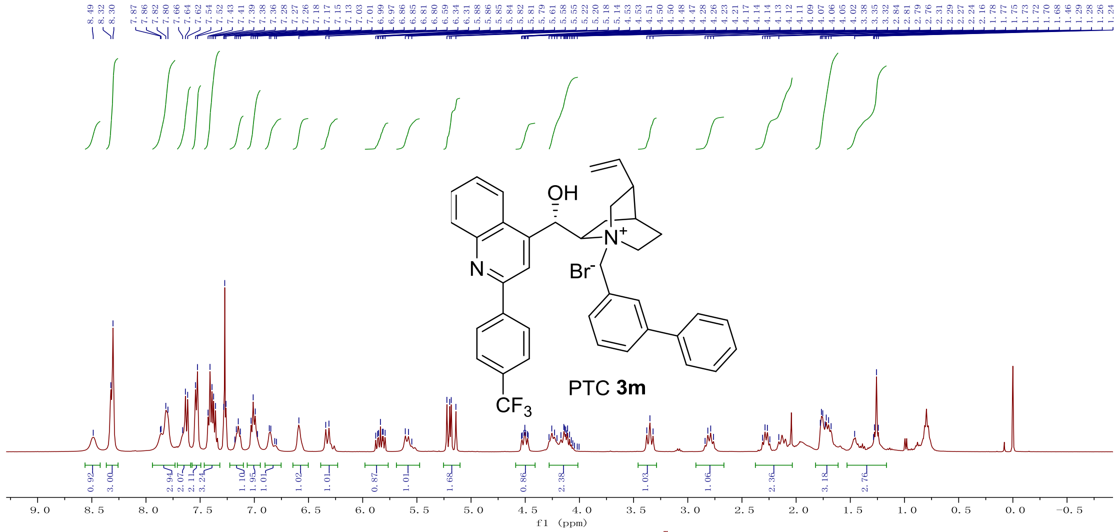
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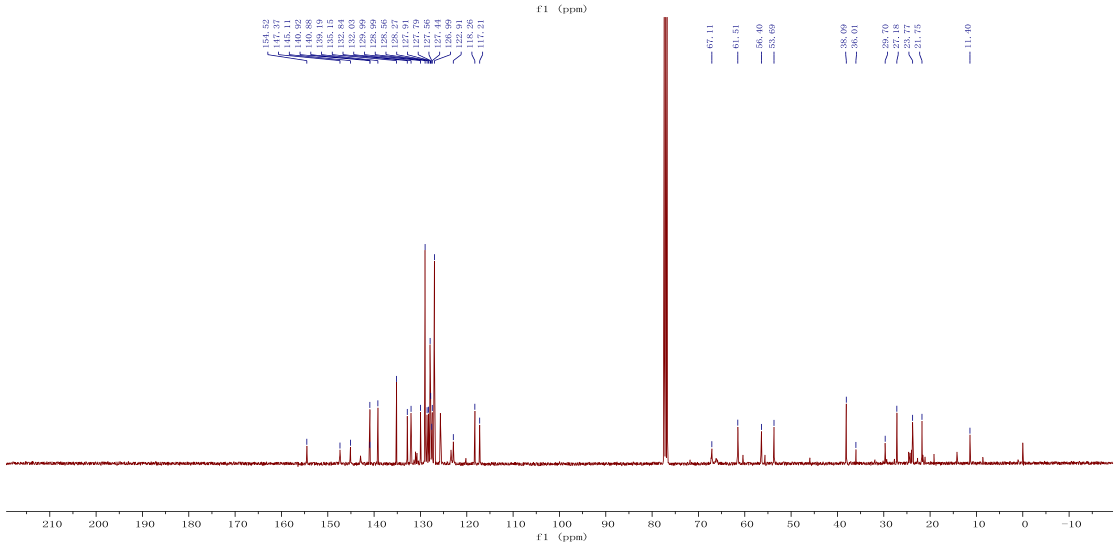
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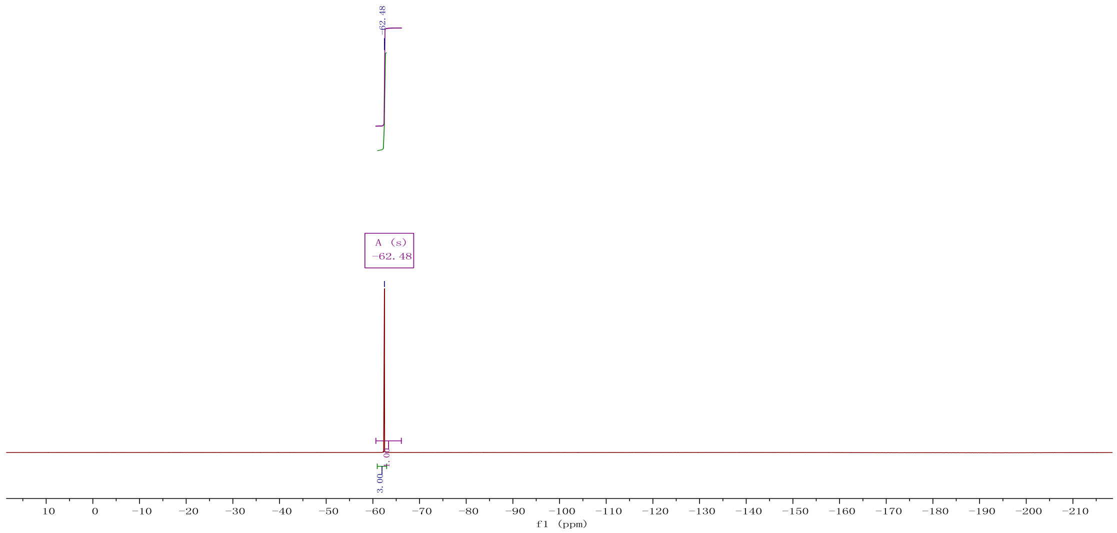
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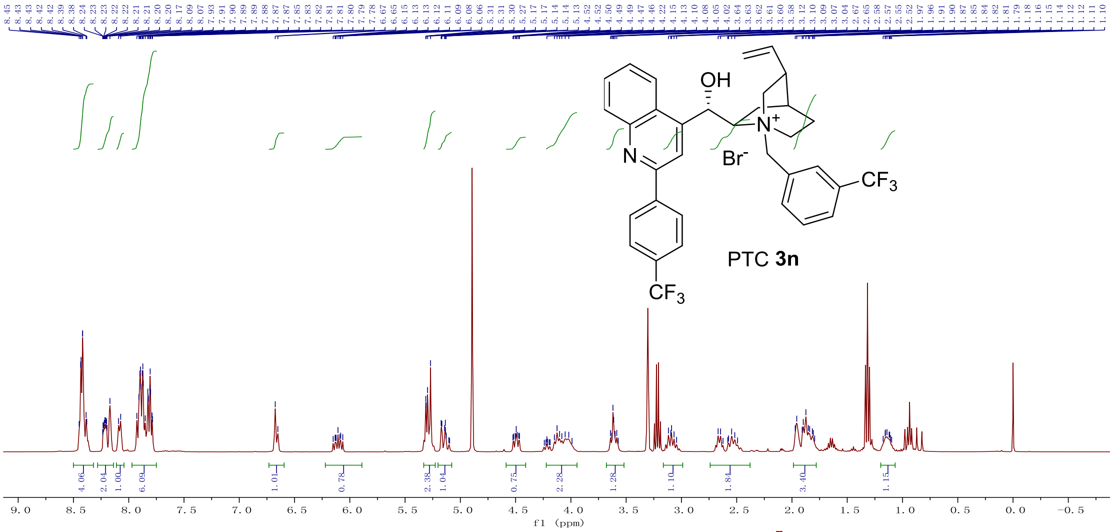
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Br⁻
CF3
CF3
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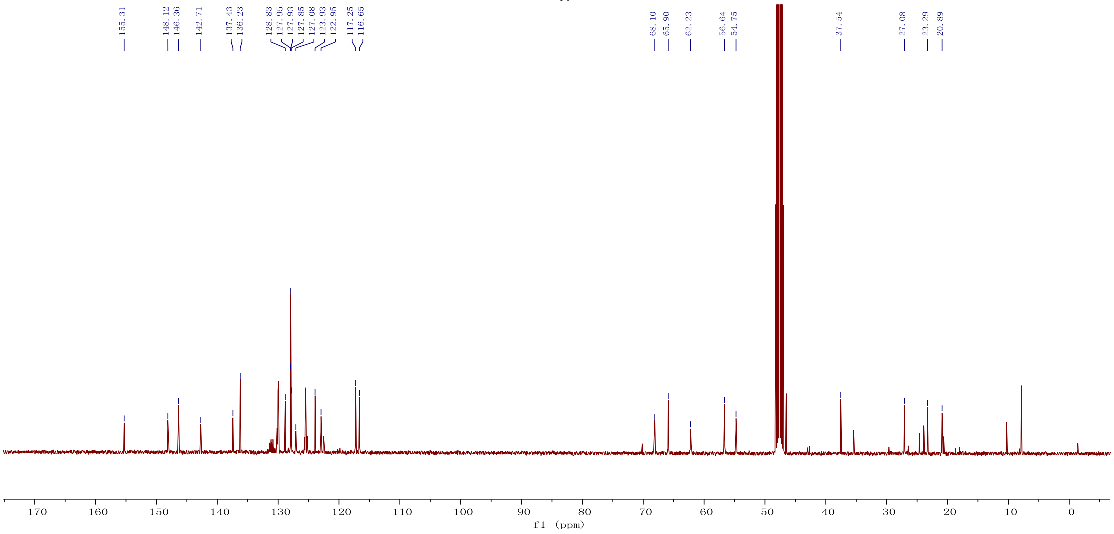
f1 (ppm)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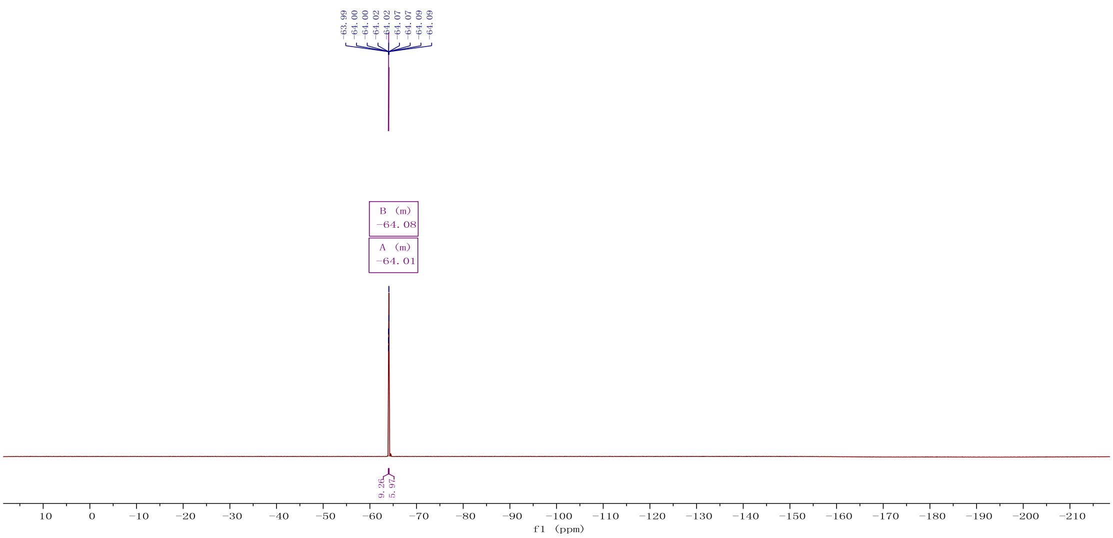
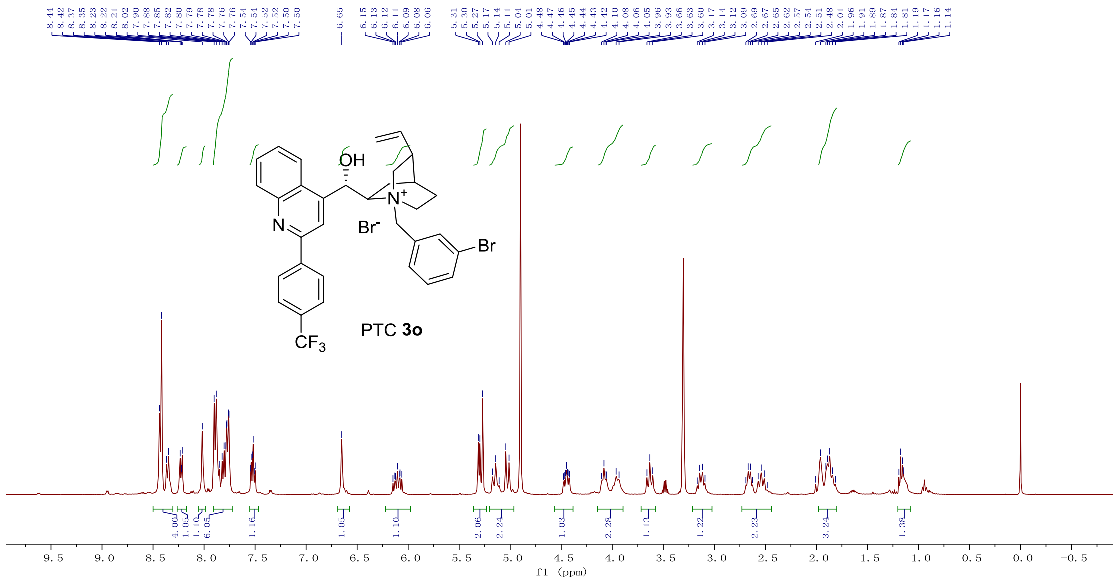
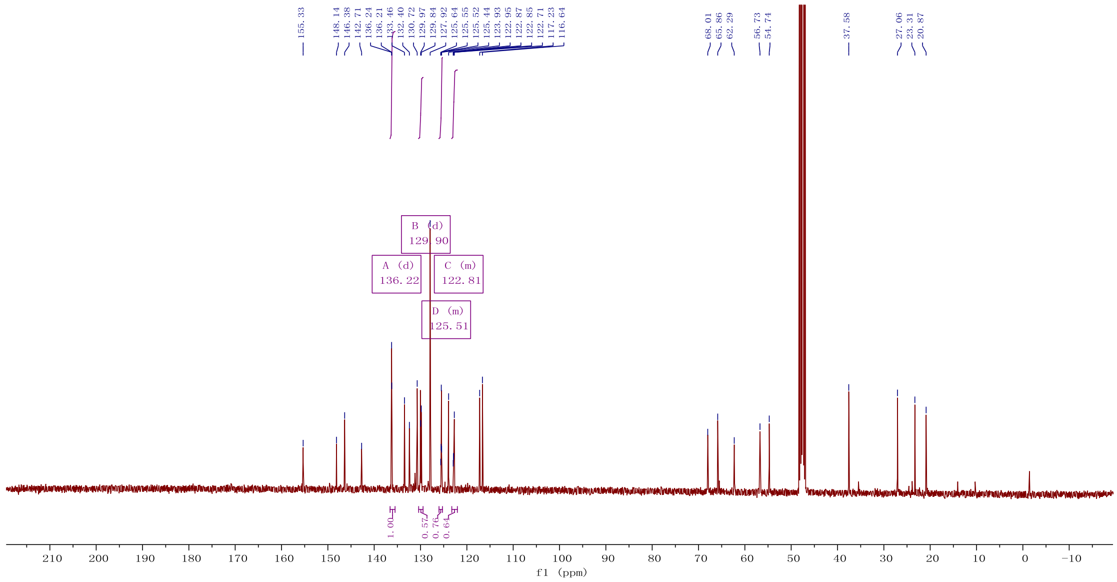
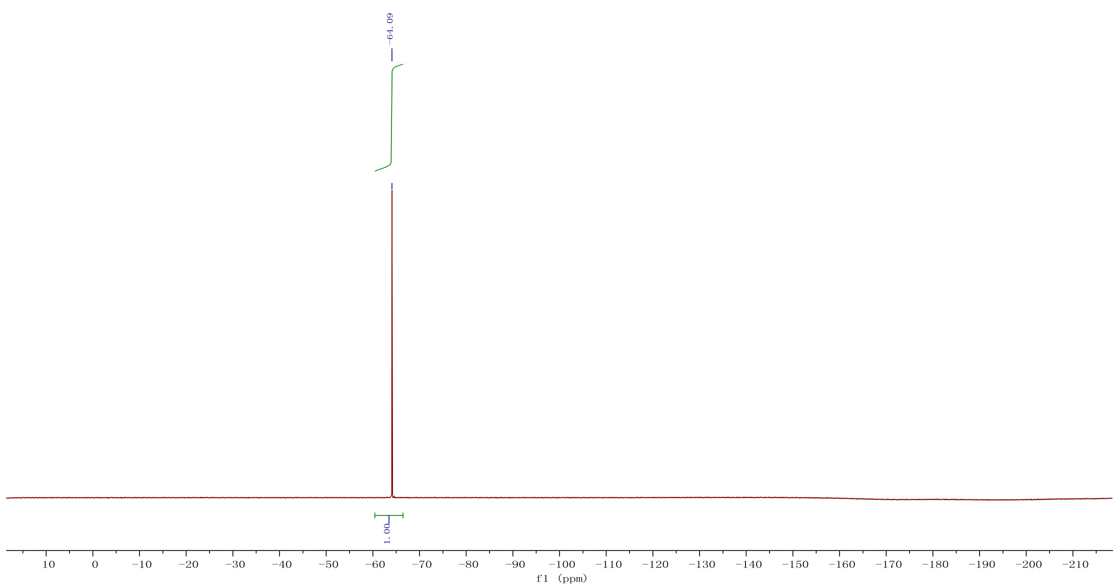
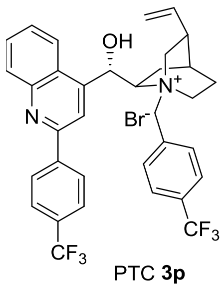
56.64
54.75
37.54
27.08
23.29
20.89
f1 (ppm)


-63.99
-64.00
-64.00
-64.02
-64.02
-64.07
-64.07
-64.09
-64.09
B (m)
-64.08
A (m)
-64.01
f1 (ppm)

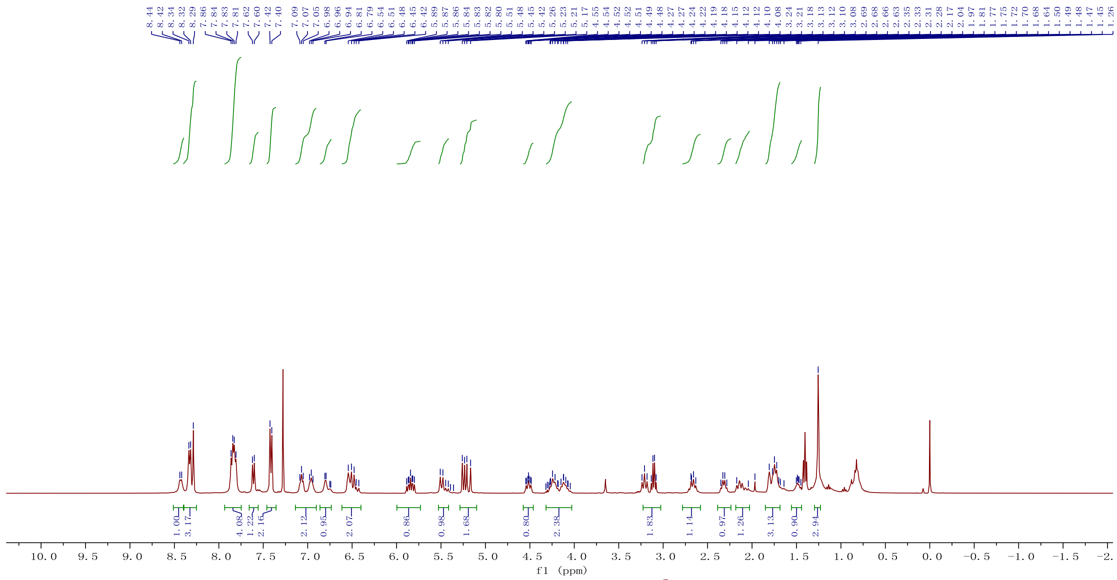

8.44 8.42 8.37 8.35 8.23 8.22 8.21 8.02 7.90 7.88 7.85 7.82 7.80 7.79 7.78 7.78 7.76 7.76 7.54 7.54 7.52 7.52 7.50 7.50
6.65
6.15 6.13 6.12 6.11 6.09 6.08 6.06
5.31 5.30 5.27 5.17 5.14 5.11 5.04 5.01
4.48 4.47 4.46 4.45 4.44 4.43 4.42 4.10 4.08 4.06 4.05 3.96 3.93 3.66 3.63 3.60 3.17 3.14 3.12 3.09
2.69 2.67 2.65 2.62 2.57 2.54 2.51 2.48 2.01 1.96 1.91 1.89 1.87 1.84 1.81 1.19 1.17 1.16 1.14
OH
N
N+
Br-
Br
CF3
PTC 3o
4.00 1.05 1.10 6.05 1.10 1.05 1.10 2.06 2.24 1.03 2.28 1.13 1.22 2.23 3.24 1.38
f1 (ppm)

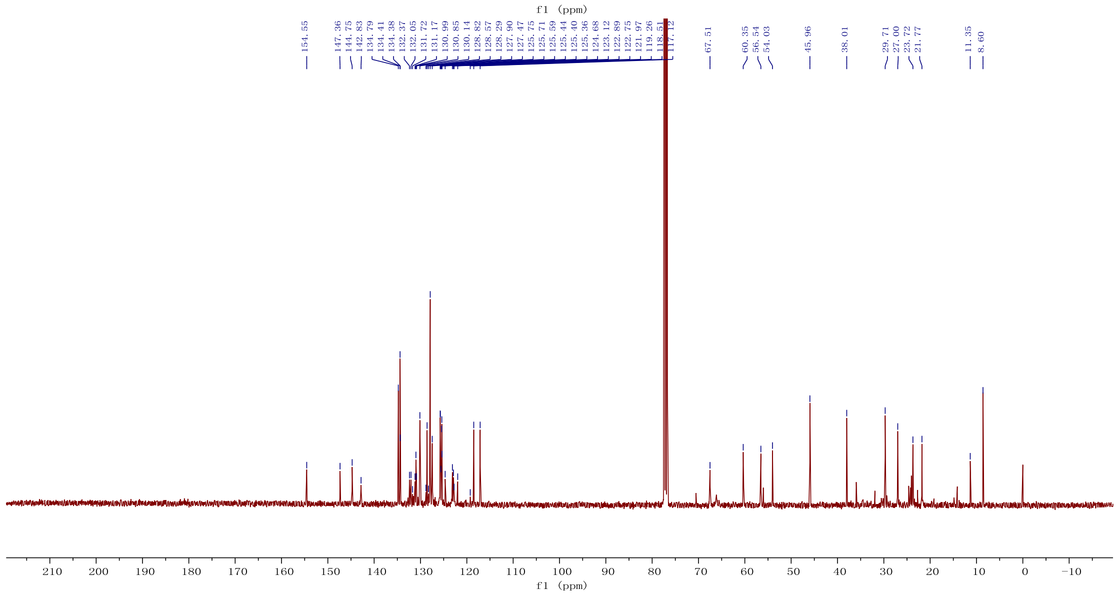

155.33
148.14 146.38 142.71 136.24 136.21 133.46 132.40 130.72 129.97 129.84 127.92 125.64 125.55 125.52 125.44 123.93 122.95 122.87 122.85 122.71 117.23 116.64
68.01 65.86 62.29
56.73 54.74
37.58
27.06 23.31 20.87
A (d) 136.22
B (d) 129.90
C (m) 122.81
D (m) 125.51
1.00 0.57 0.76 0.64
f1 (ppm)

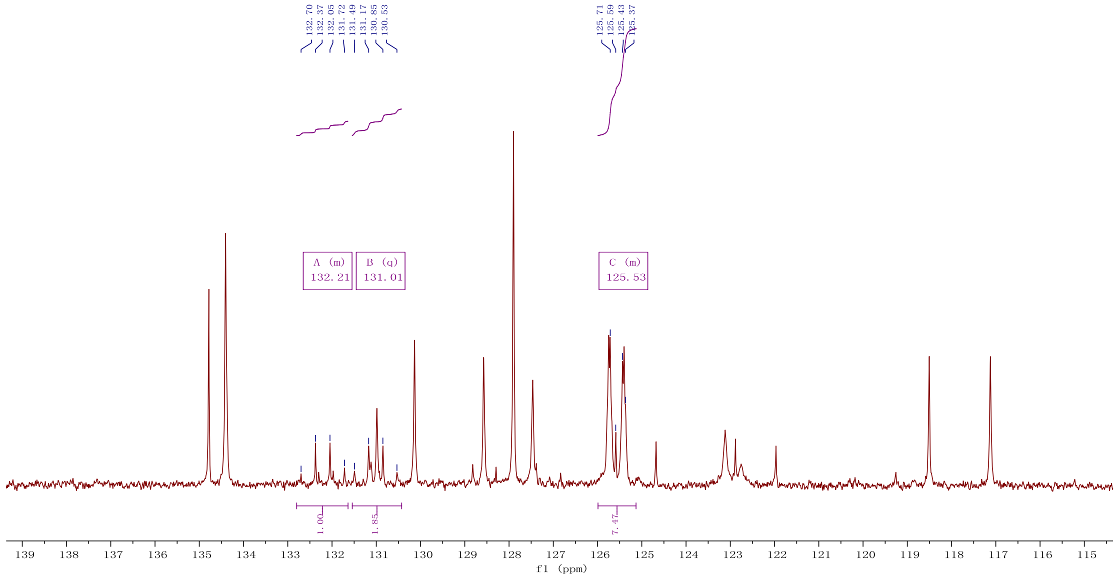

-64.09
1.00
f1 (ppm)

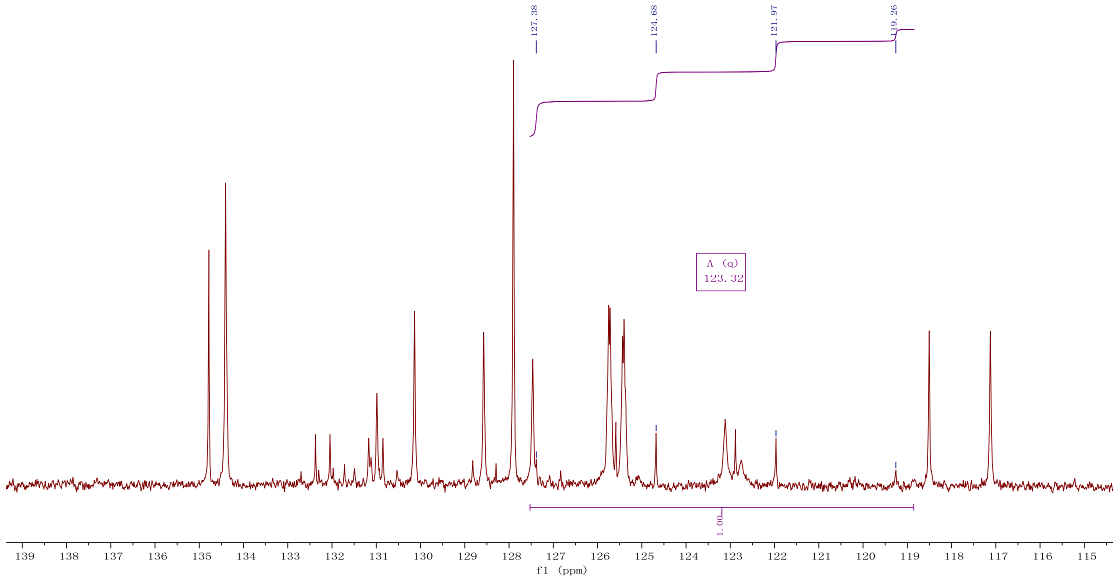


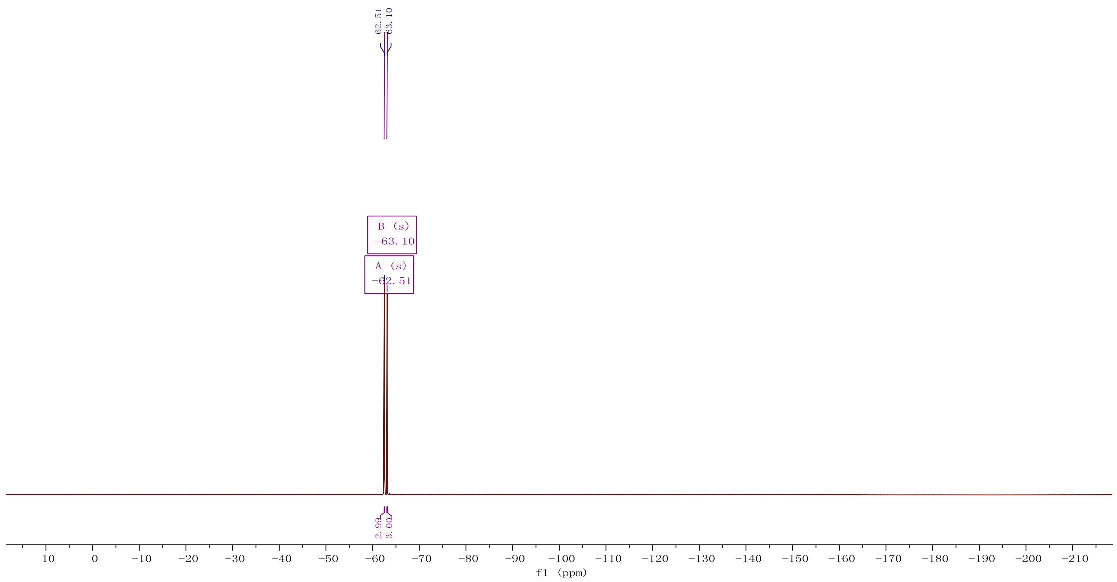
PTC **3p**

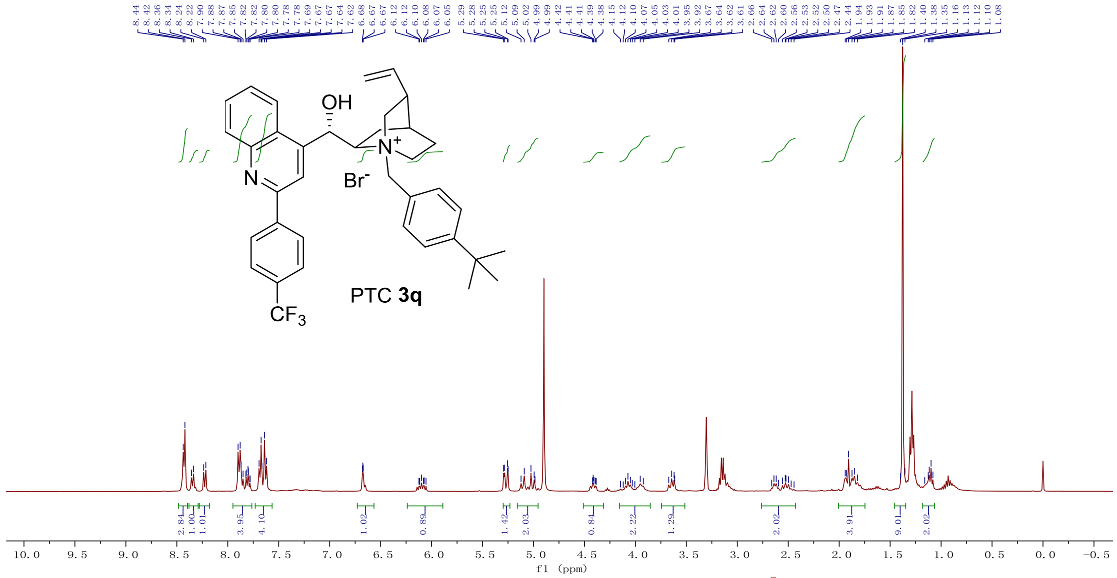


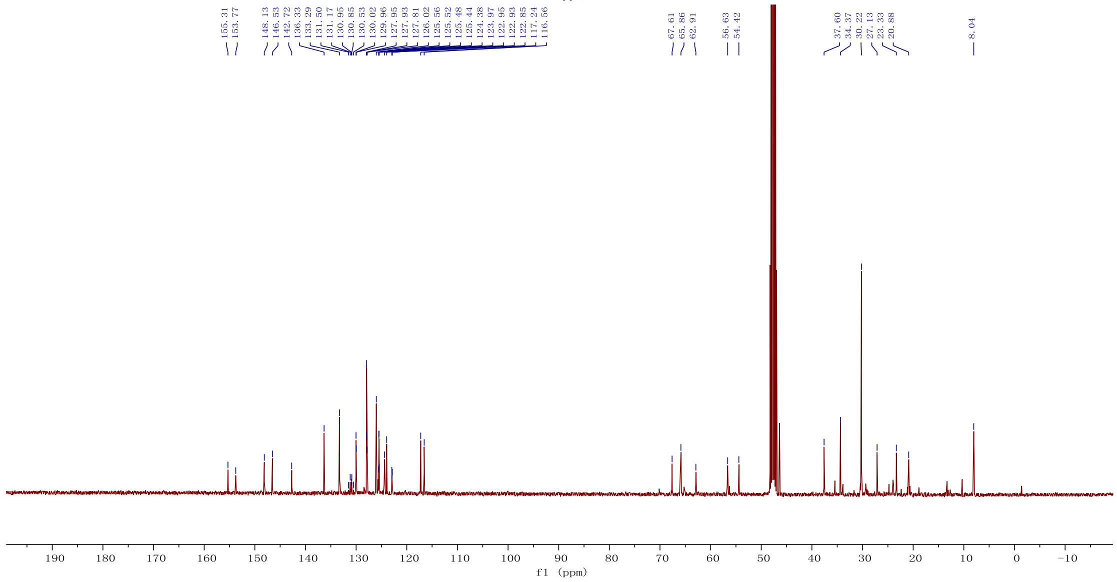


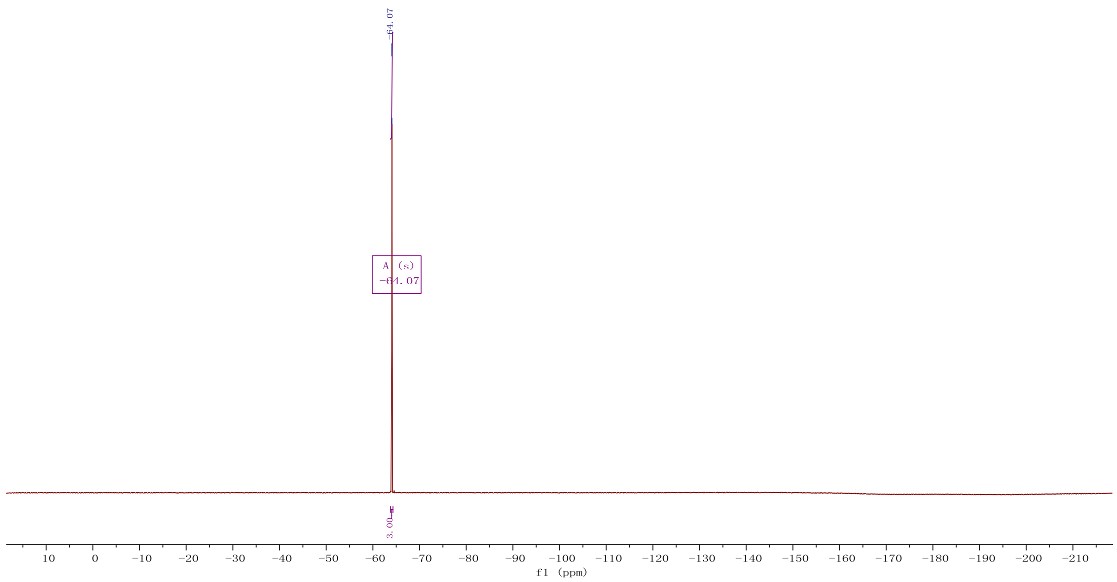

132.70
132.37
132.05
131.72
131.49
131.17
130.85
130.53
125.71
125.59
125.43
125.37
A (m)
132.21
B (q)
131.01
C (m)
125.53
1.00
1.85
7.47
f1 (ppm)

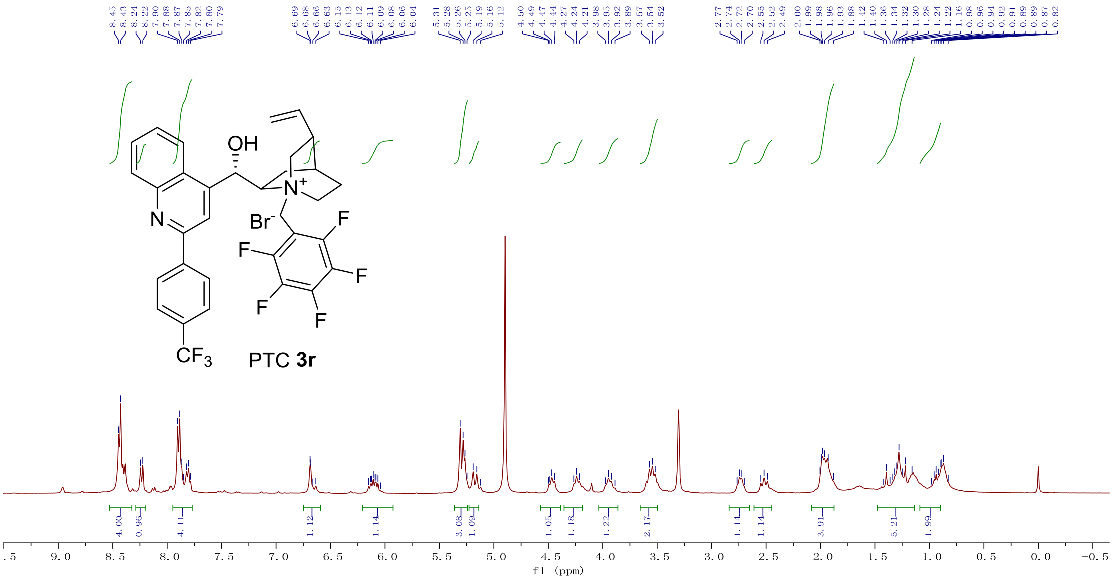

127.38
124.68
121.97
119.26
A (q)
123.32
1.00
f1 (ppm)


-62.51
-63.10
B (s)
-63.10
A (s)
-62.51
2.99
3.00
f1 (ppm)

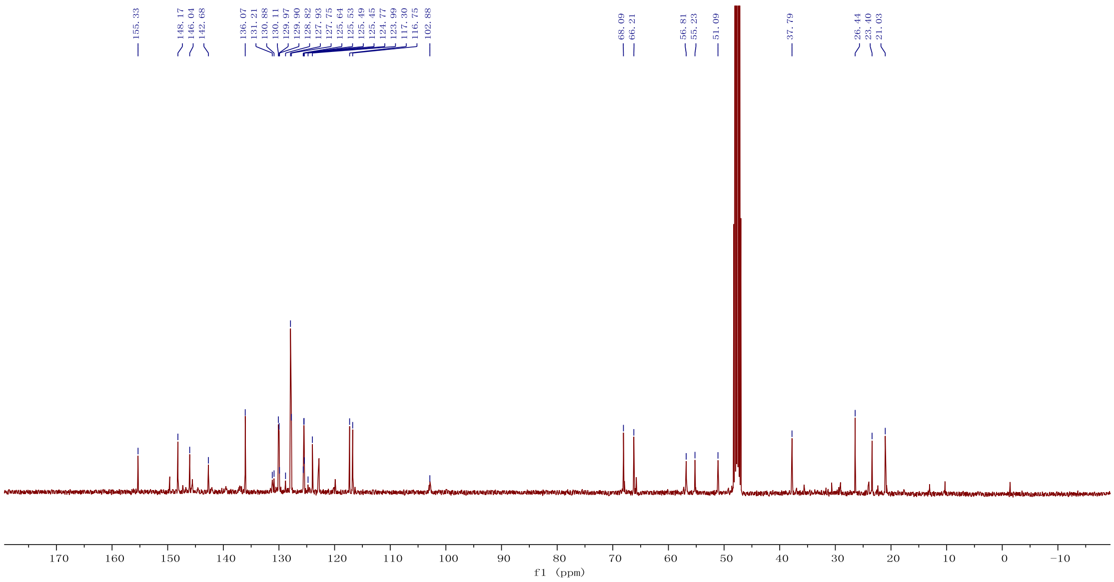

8.44 8.42 8.36 8.34 8.24 8.22 7.90 7.88 7.87 7.85 7.82 7.82 7.80 7.80 7.78 7.78 7.69 7.67 7.67 7.64 7.62 6.68 6.67 6.67 6.12 6.12 6.10 6.08 6.07 6.05 5.29 5.28 5.25 5.25 5.12 5.09 5.02 4.99 4.99 4.42 4.41 4.41 4.39 4.38 4.15 4.12 4.10 4.07 4.05 4.03 4.01 3.95 3.92 3.67 3.64 3.62 3.61 2.66 2.64 2.62 2.60 2.56 2.53 2.52 2.50 2.47 2.44 1.94 1.93 1.91 1.87 1.85 1.82 1.40 1.38 1.35 1.16 1.13 1.12 1.10 1.08
OH
N
N+
Br-
CF3
PTC 3q
2.84 1.00 1.01 3.95 4.10 1.02 0.89 1.42 2.03 0.84 2.22 1.29 2.02 3.91 9.01 2.02
f1 (ppm)

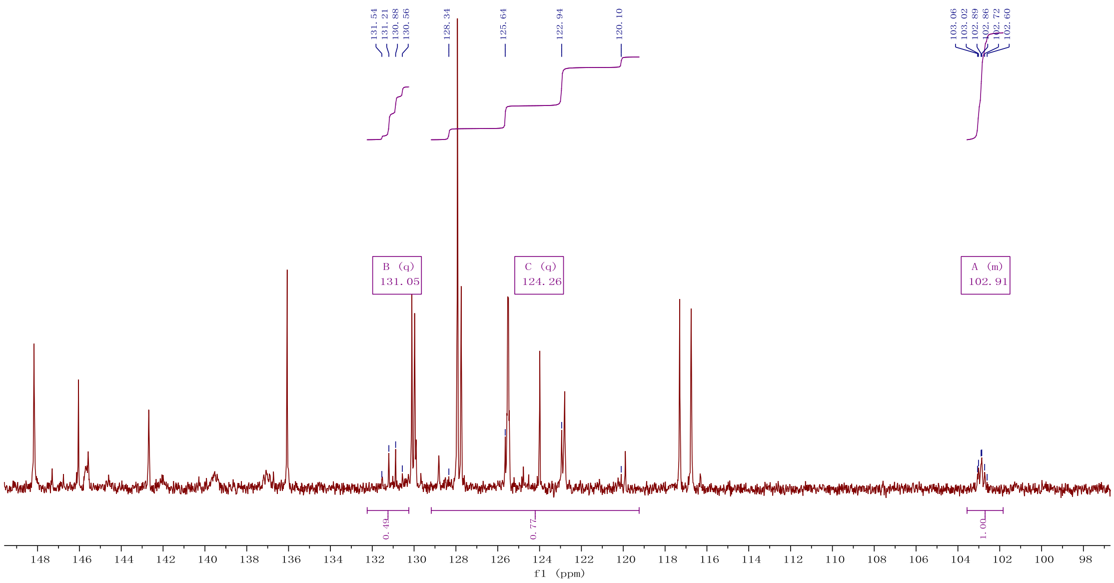

155.31 153.77 148.13 146.53 142.72 136.33 133.29 131.50 131.17 130.95 130.85 130.53 130.02 129.96 127.95 127.93 127.81 126.02 125.56 125.52 125.48 125.44 124.38 123.97 122.95 122.93 122.85 117.24 116.56
67.61 65.86 62.91 56.63 54.42
37.60 34.37 30.22 27.13 23.33 20.88
8.04
f1 (ppm)

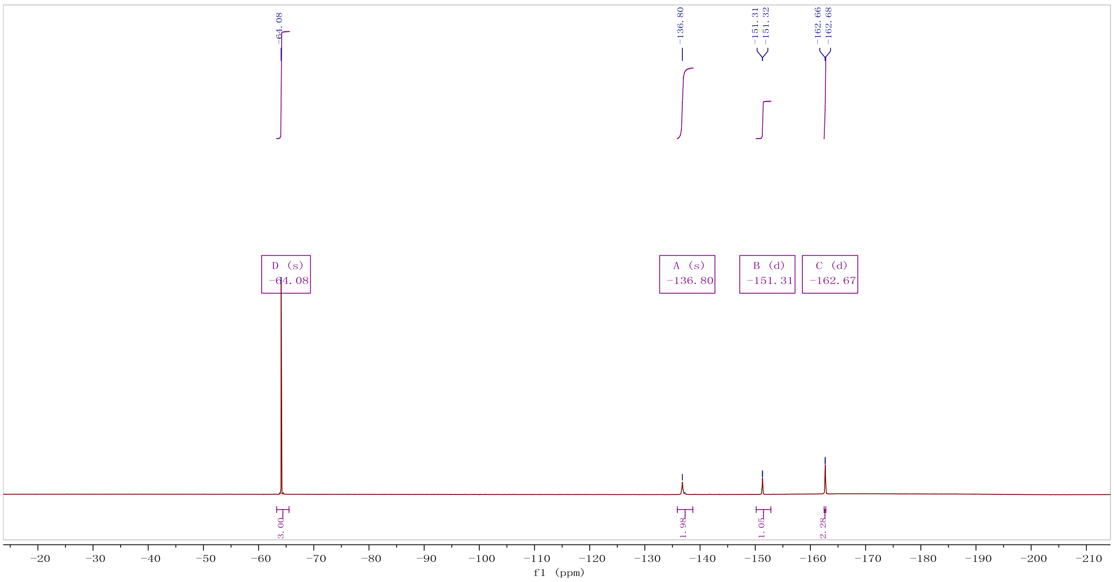

-64.07
A (s)
-64.07
3.00
f1 (ppm)

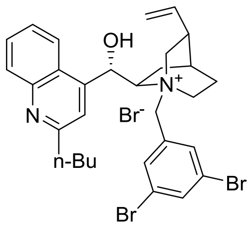


PTC 3r

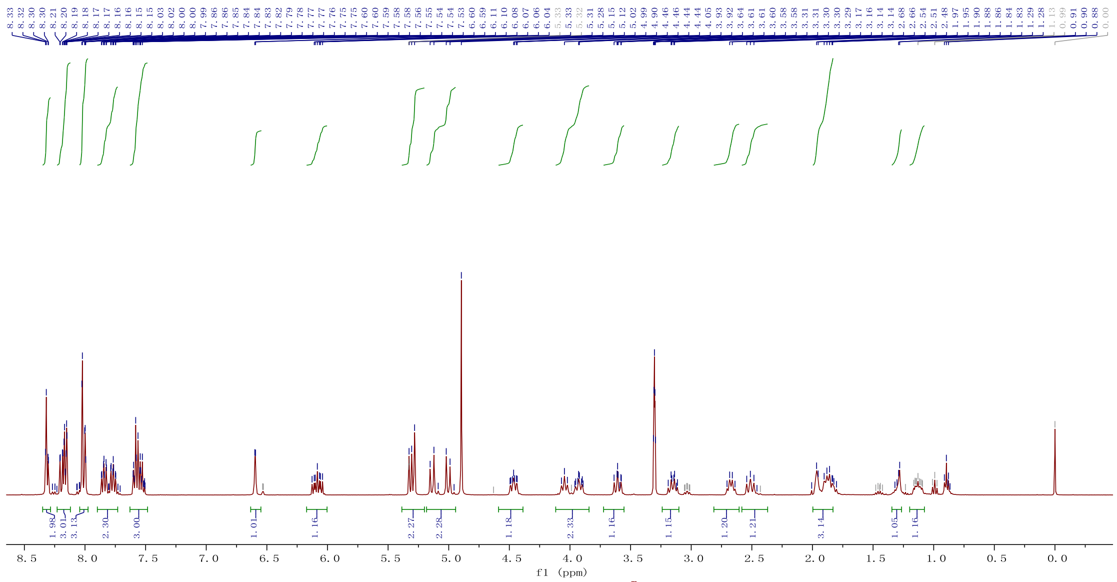


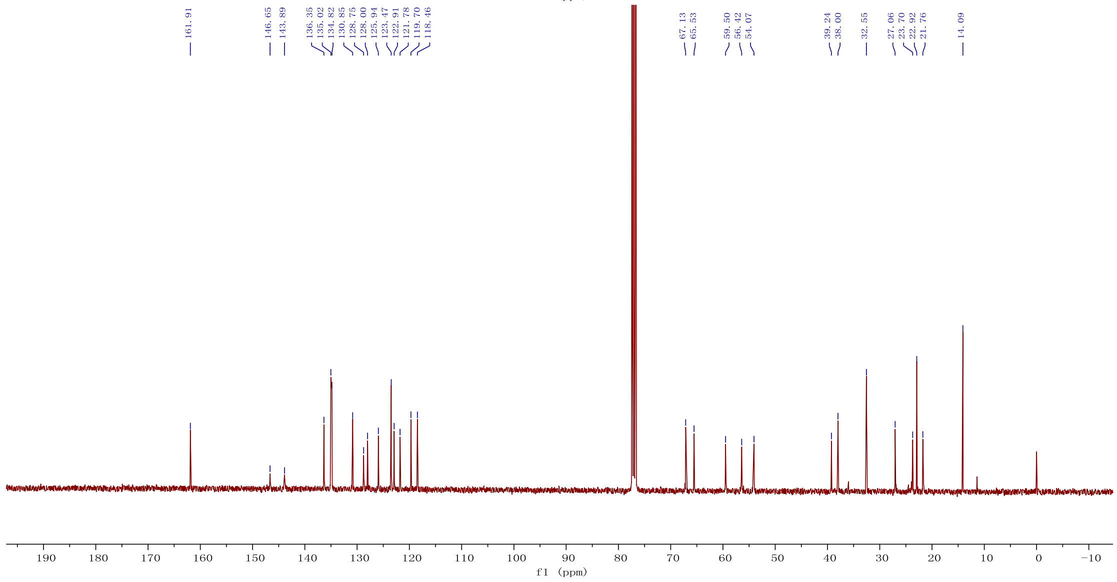


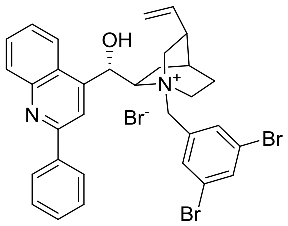

-64.08
-136.80
-151.31
-151.32
-162.66
-162.68
D (s)
-64.08
A (s)
-136.80
B (d)
-151.31
C (d)
-162.67
3.00
1.98
1.05
2.28
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


OH
N
N+
Br-
n-Bu
Br
Br

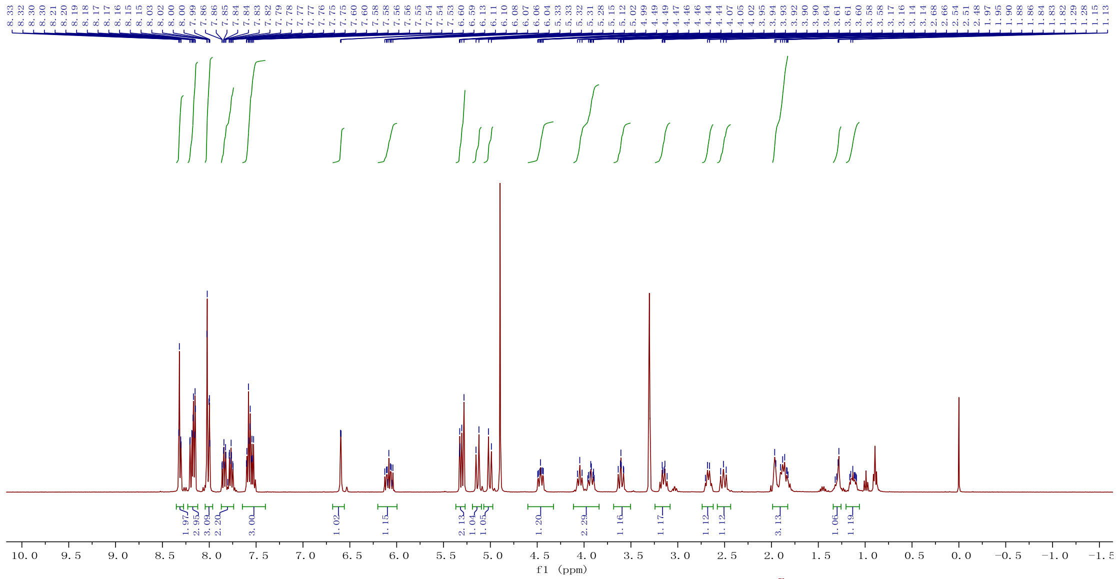
PTC **3t**

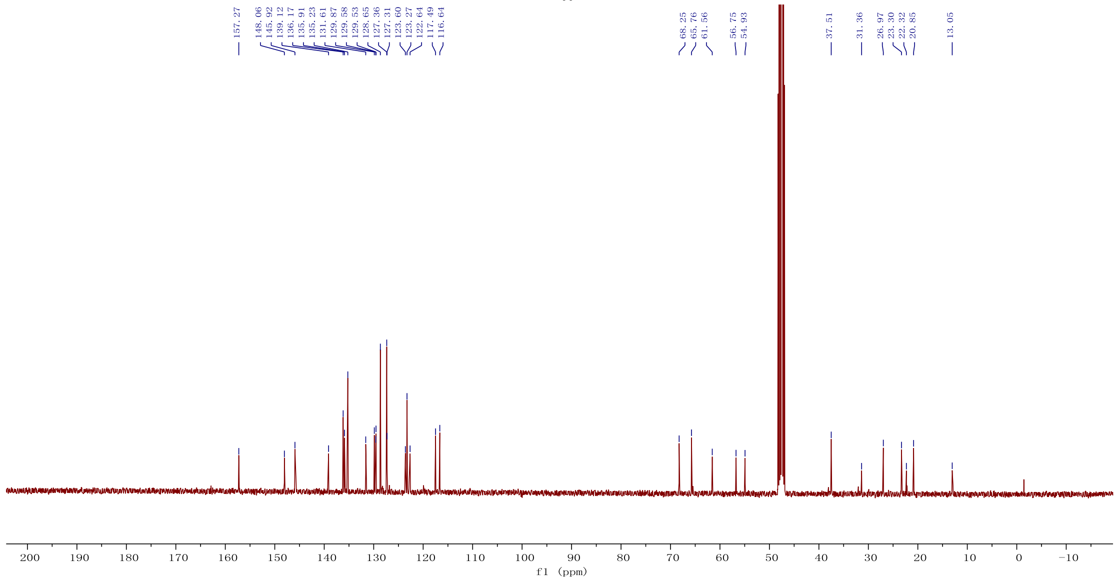

f1 (ppm)

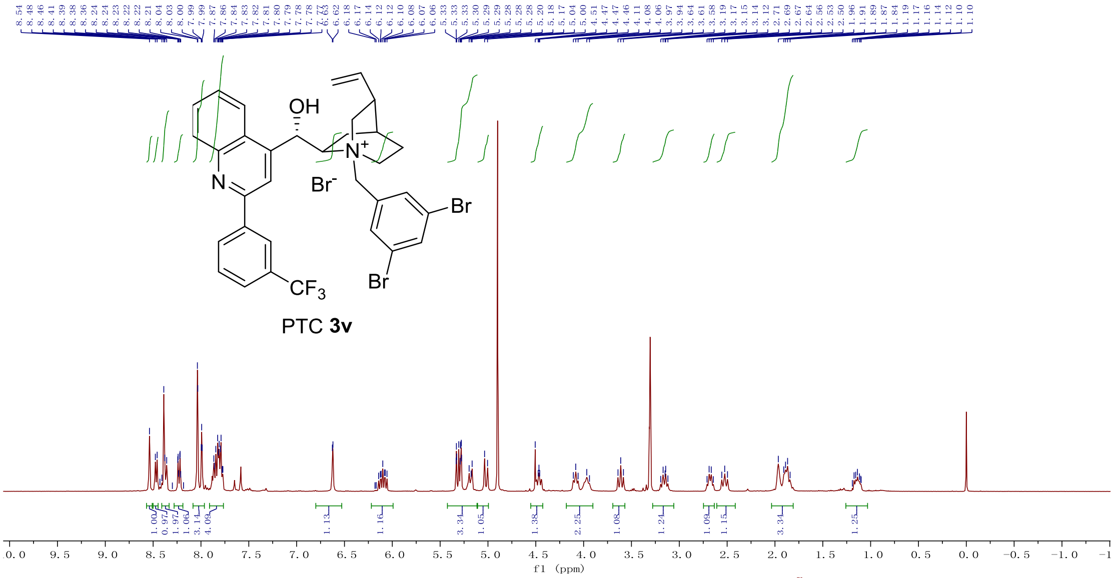

161.91
146.65
143.89
136.35
135.02
134.82
130.85
128.75
128.00
125.94
123.47
122.91
121.78
119.70
118.46
67.13
65.53
59.50
56.42
54.07
39.24
38.00
32.55
27.06
23.70
22.92
21.76
14.09
f1 (ppm)

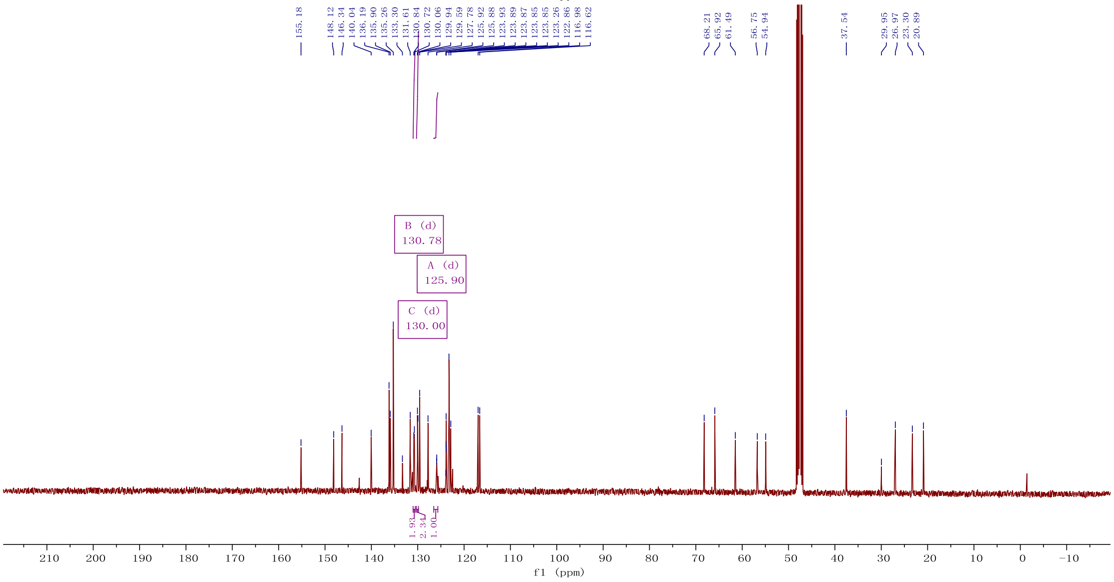


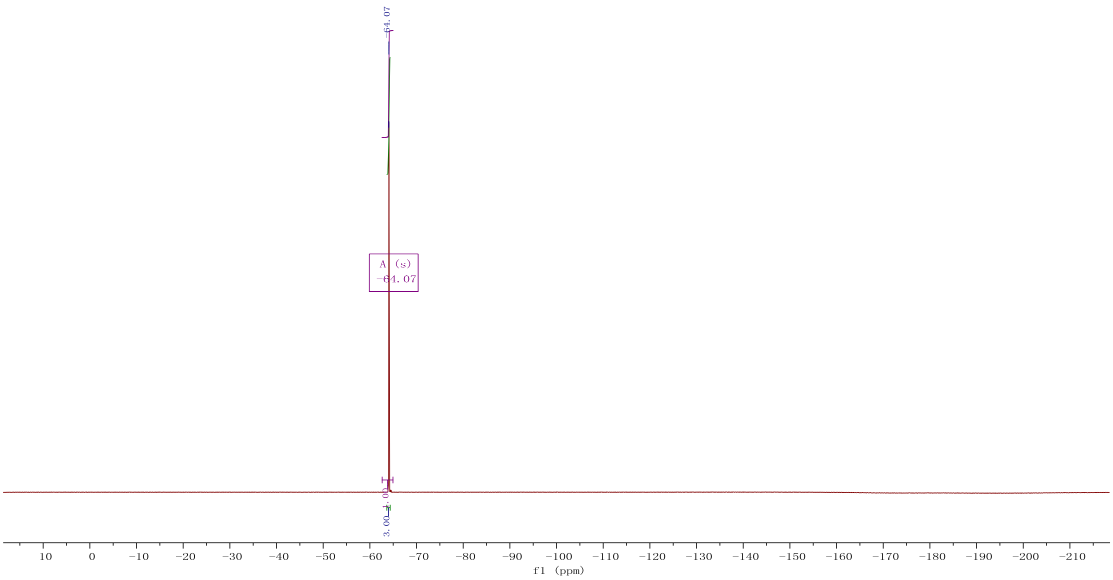
PTC **3u**

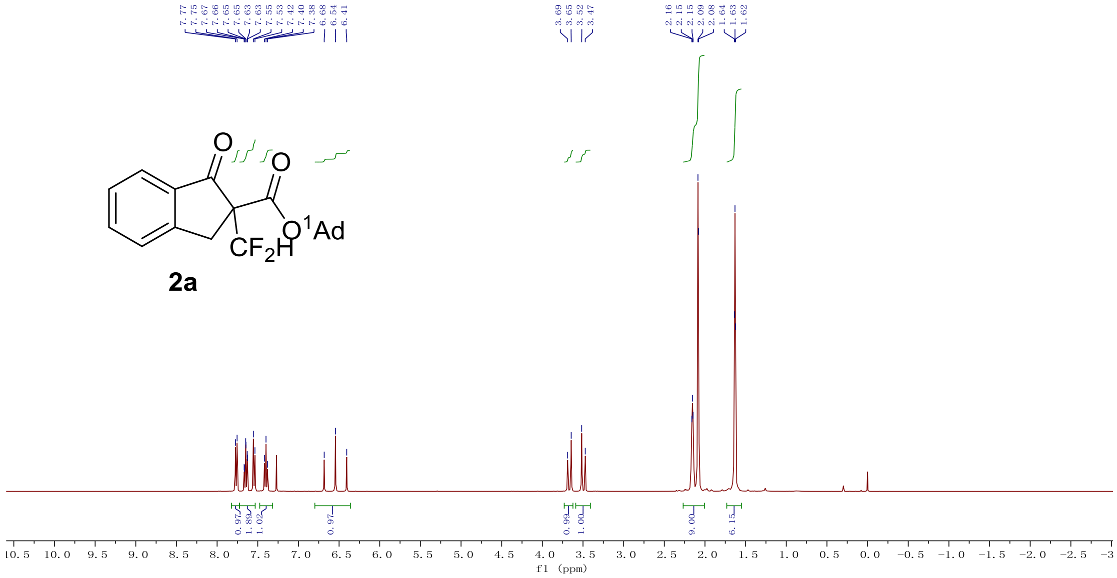


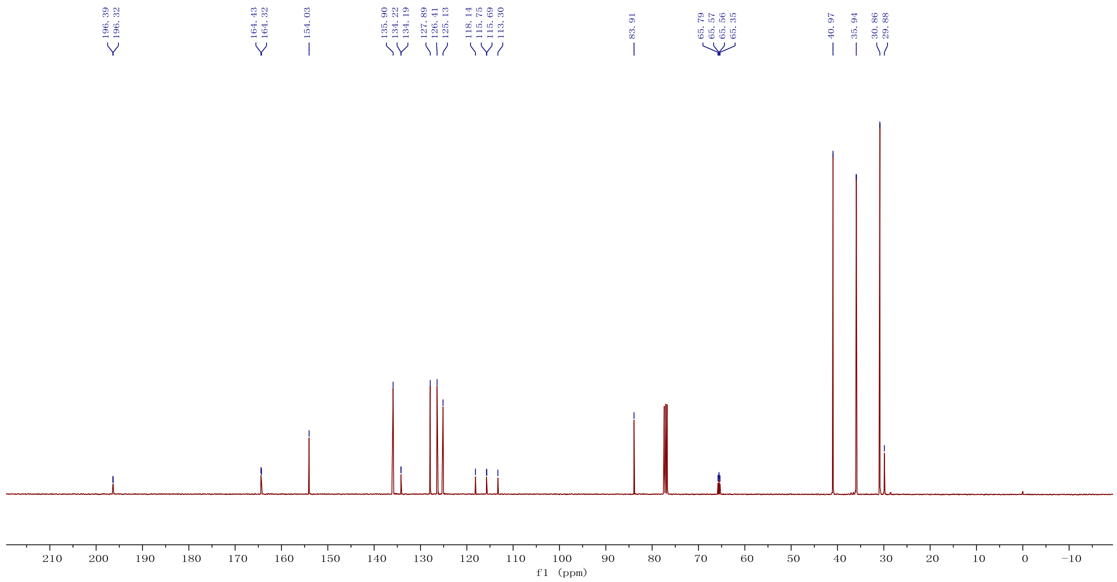


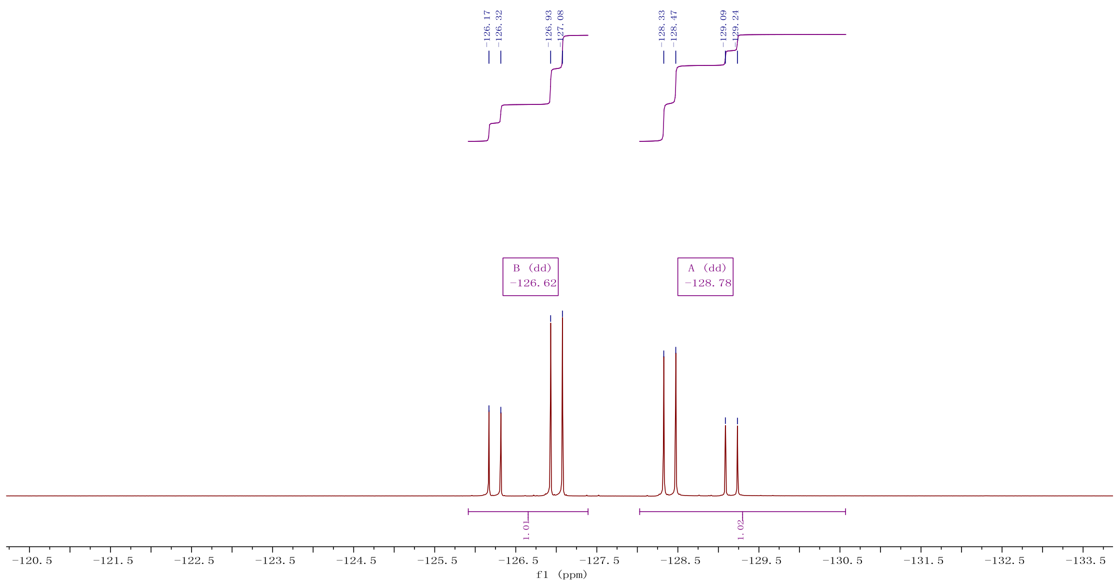

8.54, 8.48, 8.46, 8.41, 8.39, 8.38, 8.36, 8.24, 8.24, 8.23, 8.22, 8.22, 8.21, 8.04, 8.03, 8.00, 7.99, 7.99, 7.87, 7.86, 7.84, 7.83, 7.82, 7.81, 7.80, 7.79, 7.78, 7.78, 7.77, 6.63, 6.62, 6.18, 6.17, 6.14, 6.12, 6.12, 6.10, 6.08, 6.07, 6.06, 5.33, 5.33, 5.33, 5.30, 5.29, 5.29, 5.28, 5.28, 5.28, 5.20, 5.18, 5.17, 5.04, 5.00, 4.51, 4.47, 4.47, 4.46, 4.11, 4.08, 4.06, 3.97, 3.94, 3.64, 3.61, 3.58, 3.19, 3.17, 3.15, 3.14, 3.12, 2.71, 2.69, 2.67, 2.64, 2.56, 2.53, 2.50, 1.96, 1.91, 1.89, 1.87, 1.84, 1.19, 1.17, 1.16, 1.14, 1.12, 1.10, 1.10
OH
N
N+
Br-
Br
Br
CF3
PTC 3v
f1 (ppm)

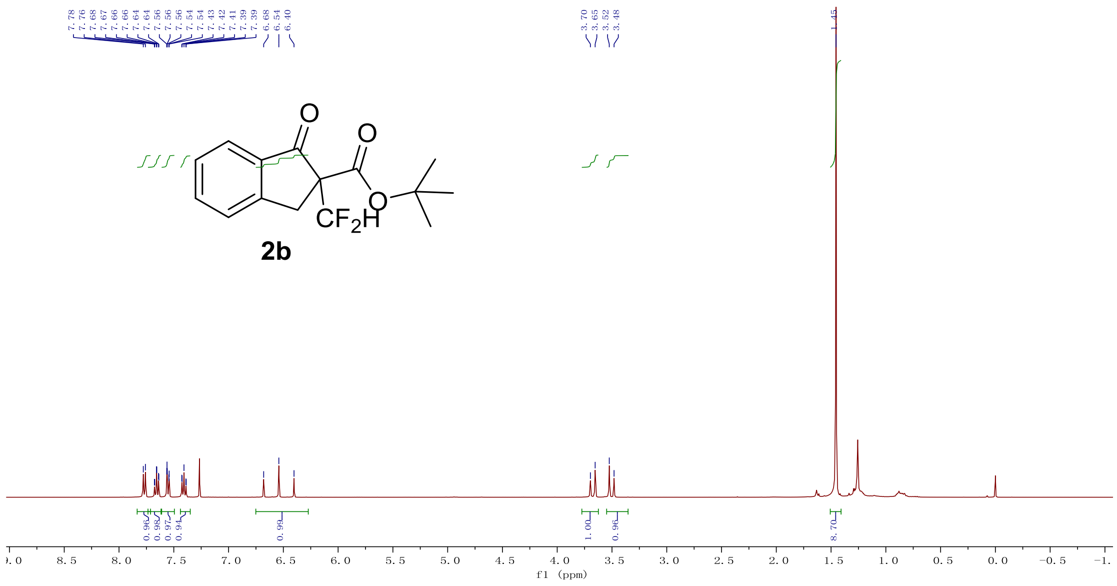

155.18, 148.12, 146.34, 140.04, 136.19, 135.90, 135.26, 133.30, 131.61, 130.84, 130.72, 130.06, 129.94, 129.59, 127.78, 125.92, 125.88, 123.93, 123.89, 123.87, 123.85, 123.26, 122.86, 116.98, 116.62, 68.21, 65.92, 61.49, 56.75, 54.94, 37.54, 29.95, 26.97, 23.30, 20.89
B (d) 130.78
A (d) 125.90
C (d) 130.00
f1 (ppm)

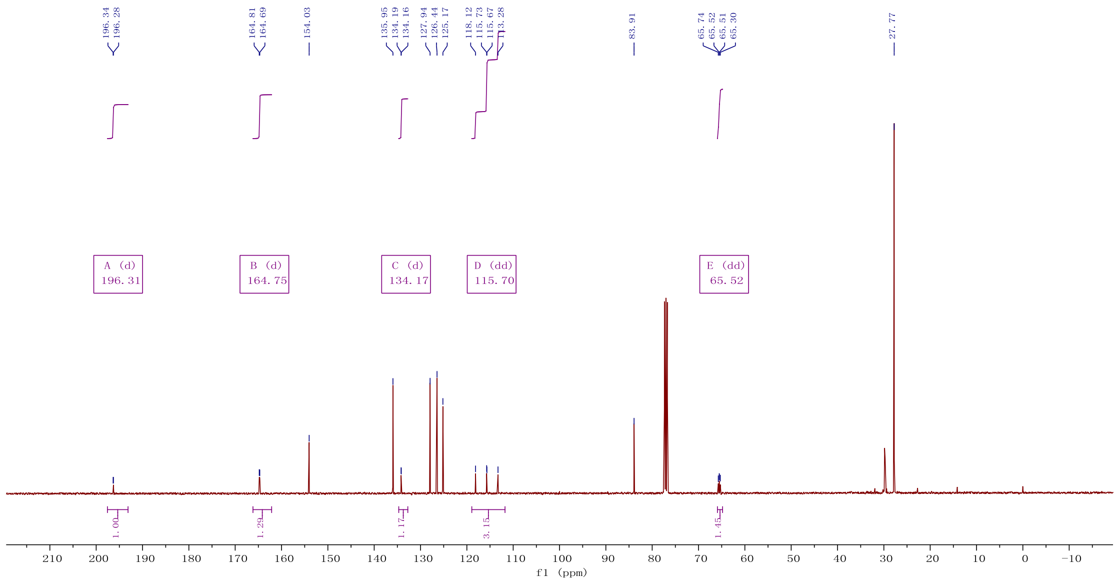

-64.07
A (s) -64.07
f1 (ppm)

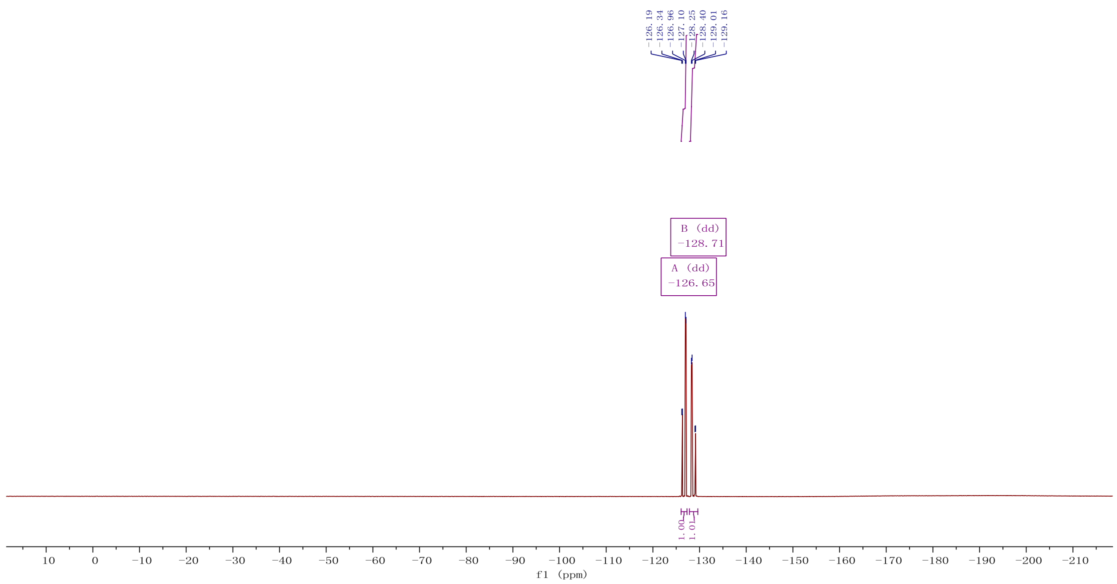

7.77 7.75 7.67 7.66 7.65 7.65 7.63 7.63 7.55 7.53 7.42 7.40 7.38 6.68 6.54 6.41
3.69 3.65 3.52 3.47
2.16 2.15 2.15 2.09 2.08 1.64 1.63 1.62
O
O
O¹Ad
CF₂H
2a
0.97 1.89 1.02 0.97 0.99 1.00 9.00 6.15
f1 (ppm)

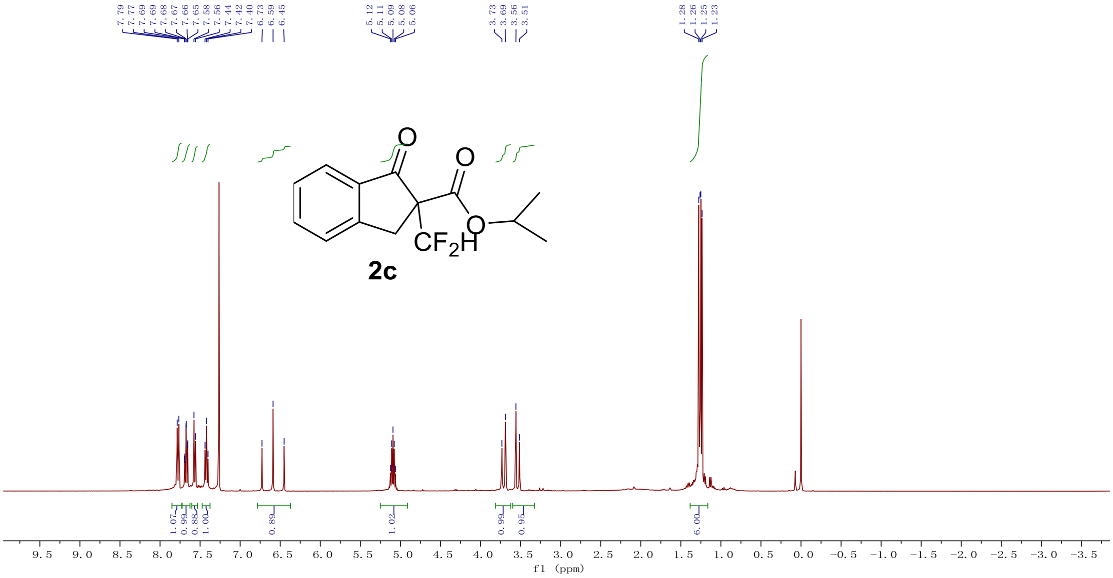

196.39 196.32
164.43 164.32
154.03
135.90 134.22 134.19 127.89 126.41 125.13 118.14 115.75 115.69 113.30
83.91
65.79 65.57 65.56 65.35
40.97 35.94 30.86 29.88
f1 (ppm)

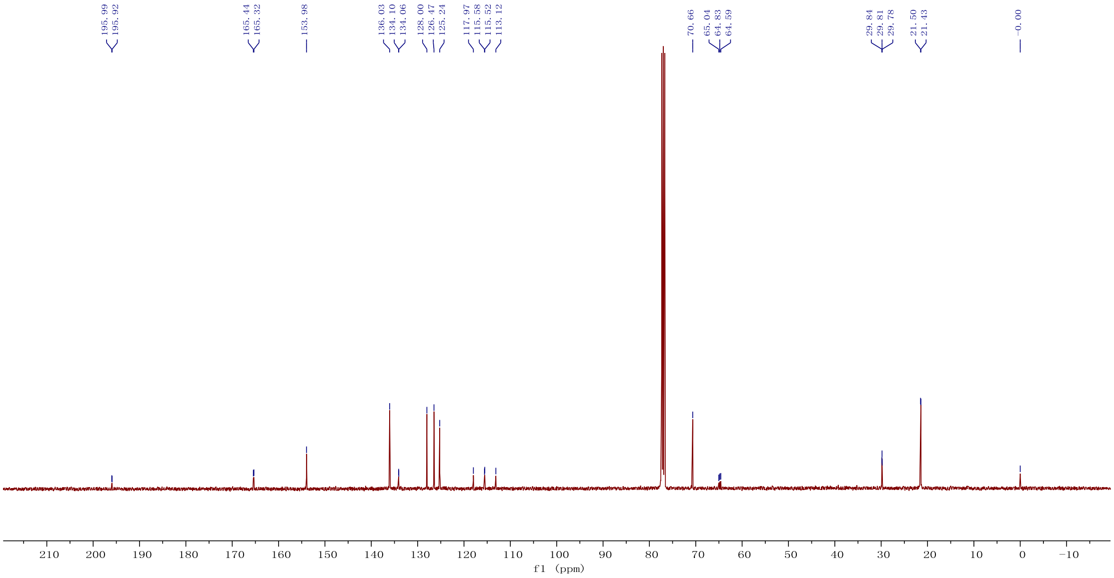

-126.17 -126.32 -126.93 -127.08
-128.33 -128.47 -129.09 -129.24
B (dd) -126.62
A (dd) -128.78
1.01
1.02
f1 (ppm)


2b
f1 (ppm)


A (d)
196.31
B (d)
164.75
C (d)
134.17
D (dd)
115.70
E (dd)
65.52
f1 (ppm)


B (dd)
-128.71
A (dd)
-126.65
f1 (ppm)


7.79
7.77
7.69
7.69
7.68
7.67
7.66
7.65
7.58
7.56
7.41
7.42
7.40
6.73
6.59
6.45
5.12
5.11
5.09
5.08
5.06
3.73
3.69
3.56
3.51
1.28
1.26
1.25
1.23
O
O
O
CF2H
2c
1.07
0.99
0.88
1.00
0.89
1.02
0.99
0.95
6.00
f1 (ppm)


195.99
195.92
165.44
165.32
153.98
136.03
134.10
134.06
128.00
126.47
125.24
117.97
115.58
115.52
113.12
70.66
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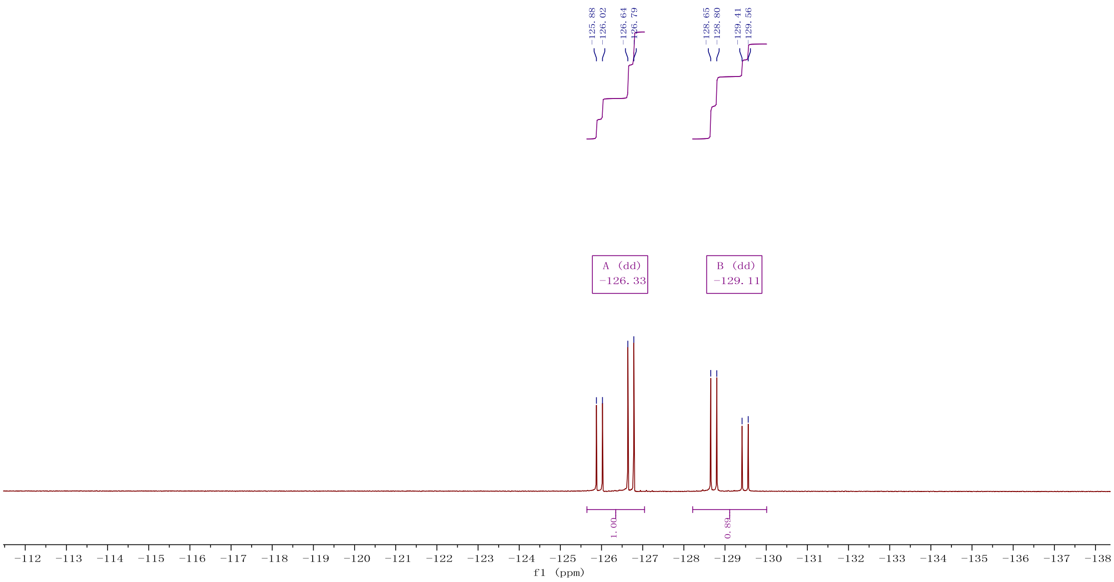
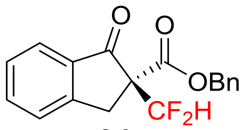
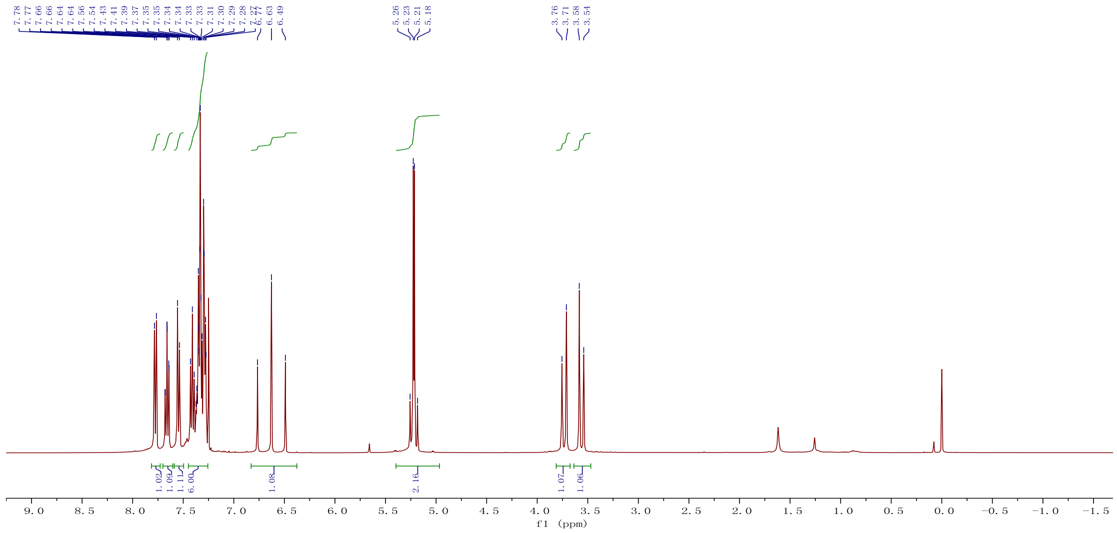
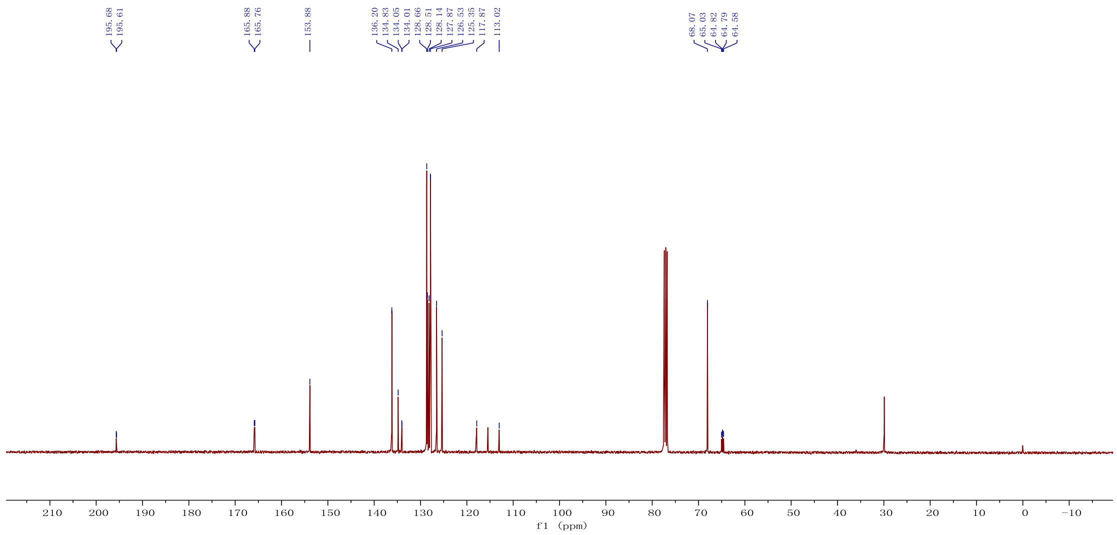
64.83
64.59
29.84
29.81
29.78
21.50
21.43
-0.00
f1 (ppm)

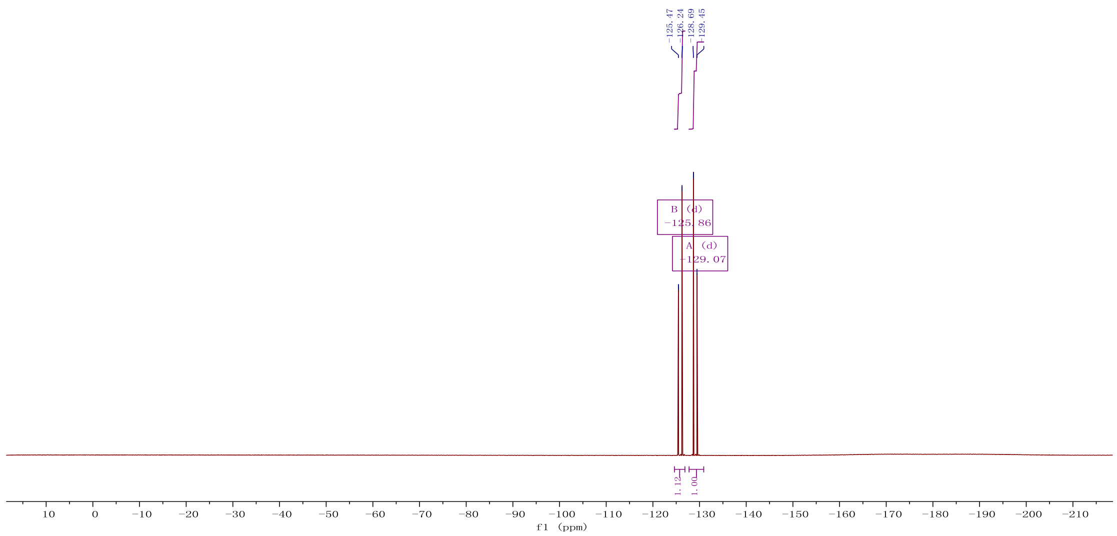

-125.88
-126.02
-126.64
-126.79
-128.65
-128.80
-129.41
-129.56
A (dd)
-126.33
B (dd)
-129.11
1.00
0.89
f1 (ppm)

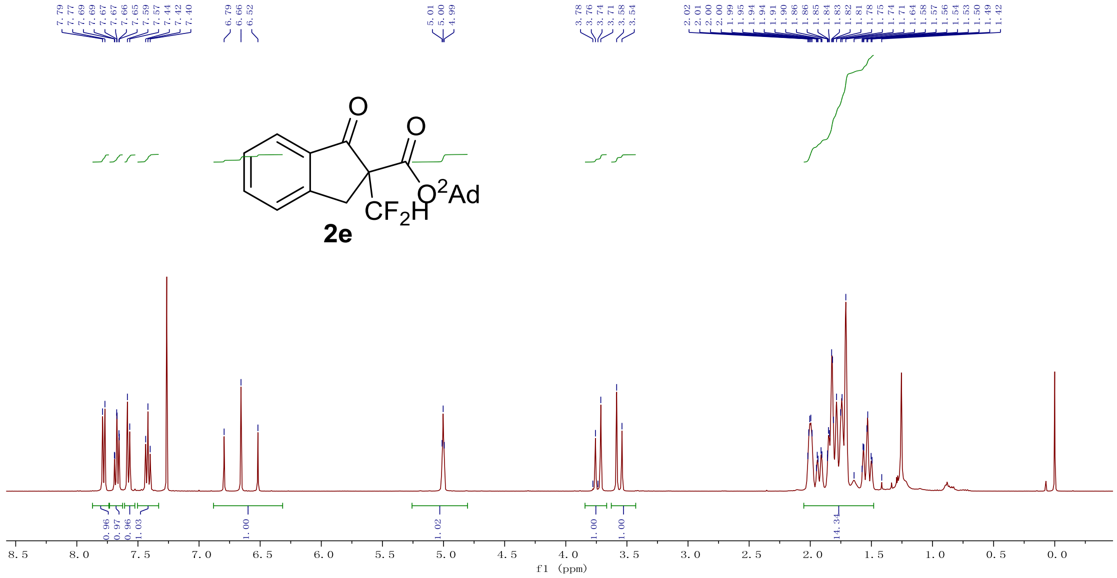

O
O
OBn
CF2H

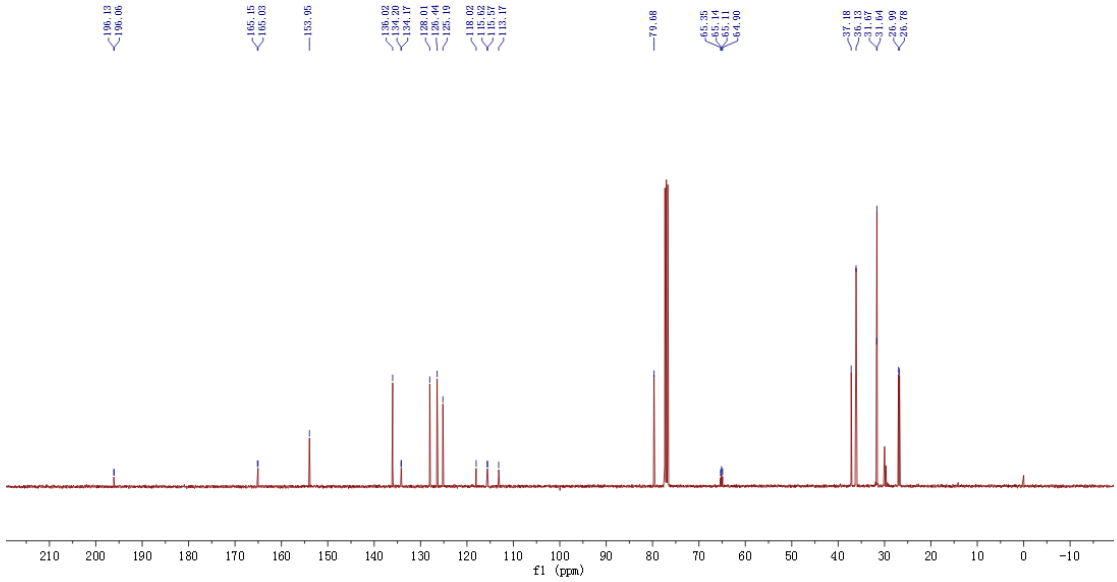
2d

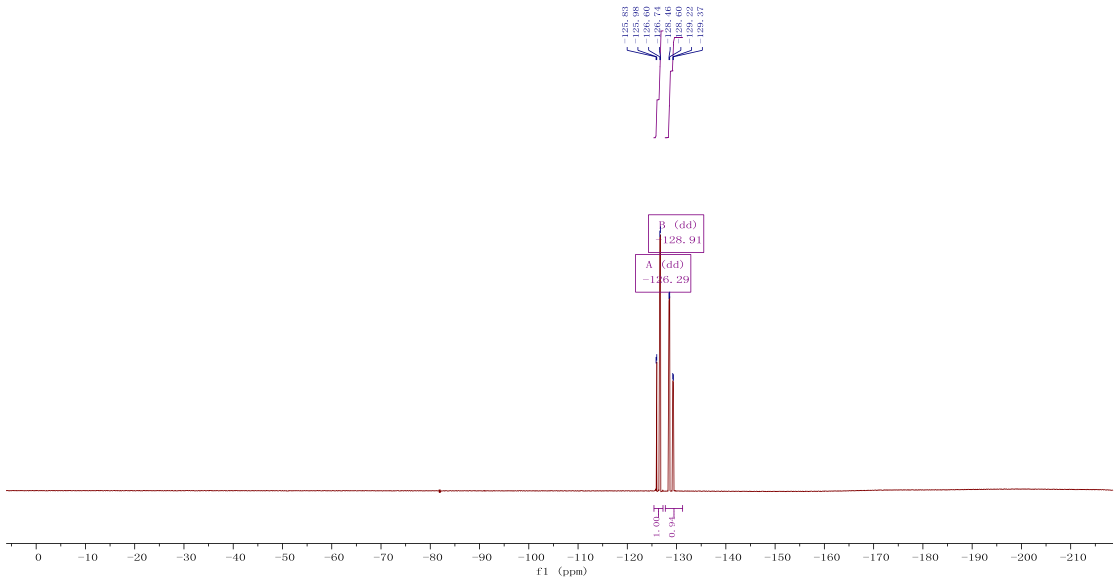

7.78 7.77 7.66 7.66 7.64 7.64 7.56 7.54 7.43 7.41 7.39 7.37 7.35 7.35 7.34 7.34 7.33 7.33 7.31 7.30 7.29 7.28 7.27 7.27 6.63 6.49
5.26 5.23 5.21 5.18
3.76 3.71 3.58 3.54
1.02 1.09 1.11 6.00 1.08 2.16 1.07 1.06
f1 (ppm)

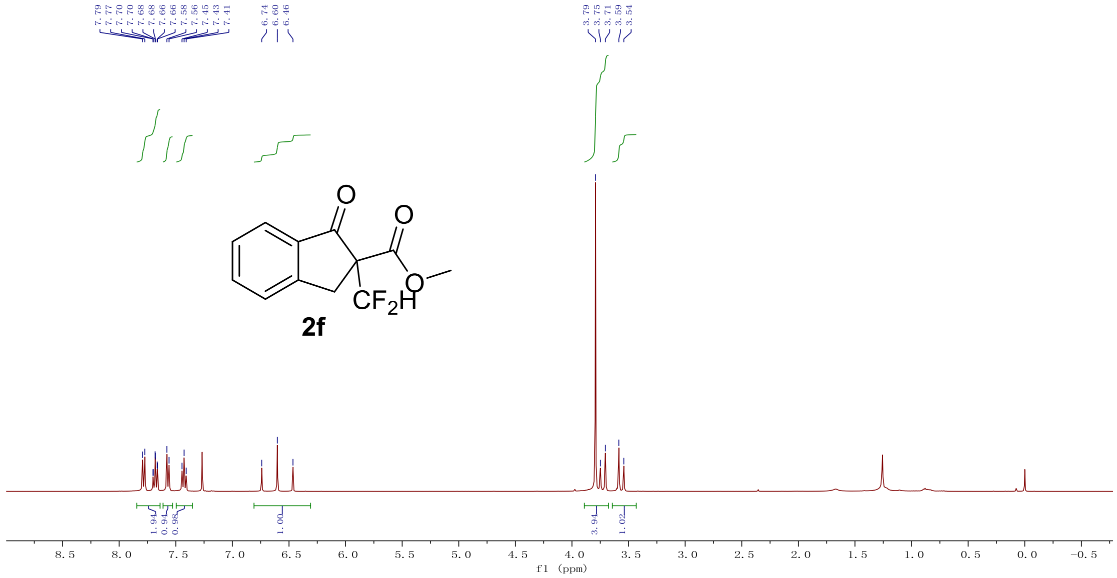

195.68 195.61
165.88 165.76
153.88
136.20 134.83 134.65 134.01 128.66 128.51 128.14 127.87 126.53 125.35 117.87 113.02
68.07 65.03 64.82 64.79 64.58
f1 (ppm)

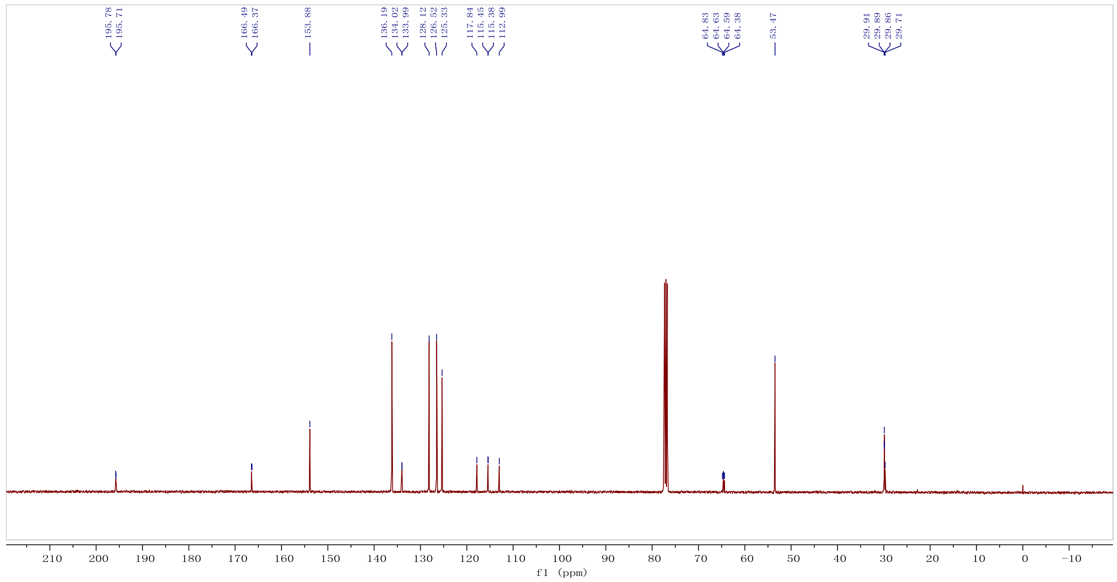

-125.47 -126.24 -128.69 -129.45
B (d) -125.86
A (d) -129.07
1.12 1.00
f1 (ppm)


7.79 7.77 7.69 7.69 7.67 7.67 7.66 7.65 7.59 7.57 7.57 7.44 7.42 7.40
6.79 6.66 6.52
5.01 5.00 4.99
3.78 3.76 3.74 3.71 3.58 3.54
2.02 2.01 2.00 2.00 1.99 1.95 1.94 1.94 1.91 1.90 1.86 1.85 1.84 1.83 1.82 1.81 1.78 1.75 1.74 1.71 1.64 1.58 1.57 1.56 1.54 1.53 1.50 1.49 1.42
O
O
CF_2H
O^2Ad
2e
0.96 0.97 0.96 1.03
1.00
1.02
1.00 1.00
14.34
f1 (ppm)


196.13 196.06
165.15 165.03
153.95
136.02 134.20 134.17 128.01 126.44 125.19
118.02 115.62 115.57 113.17
79.68
65.35 65.14 65.11 64.90
37.18 36.13 31.67 31.64 26.99 26.78
f1 (ppm)


-125.83 -125.98 -126.60 -126.74 -128.46 -128.60 -129.22 -129.37
B (dd) -128.91
A (dd) -126.29
1.00 0.94
f1 (ppm)


7.79
7.77
7.70
7.68
7.68
7.66
7.66
7.58
7.56
7.45
7.43
7.41
6.74
6.60
6.46
3.79
3.75
3.71
3.59
3.54
CF2H
2f
1.91
0.94
0.98
1.00
3.94
1.02
f1 (ppm)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195.71
166.49
166.37
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133.99
128.12
126.52
125.33
117.84
115.45
115.38
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64.63
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64.38
53.47
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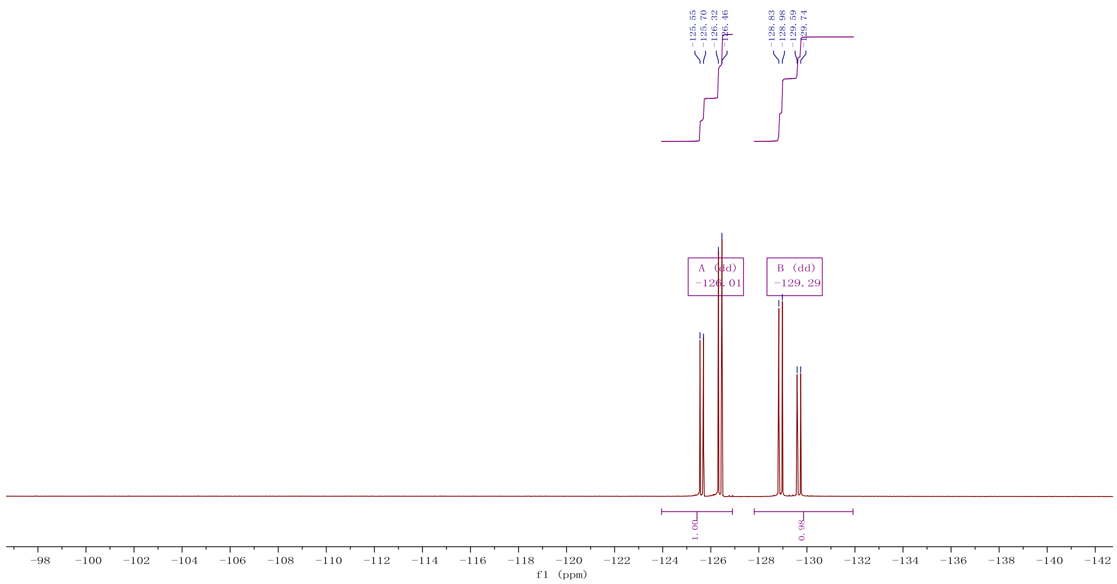
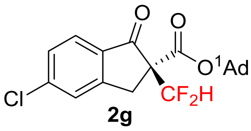
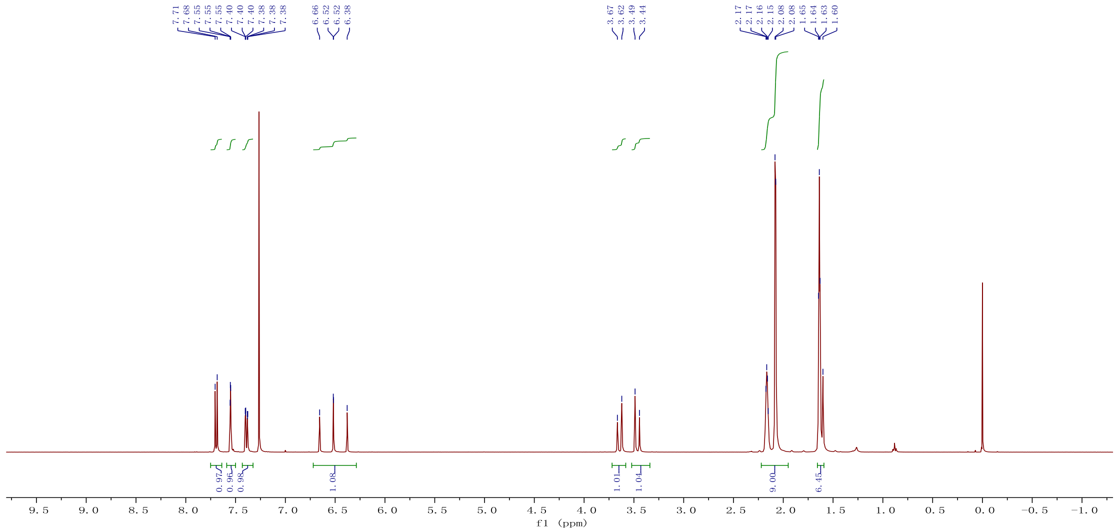
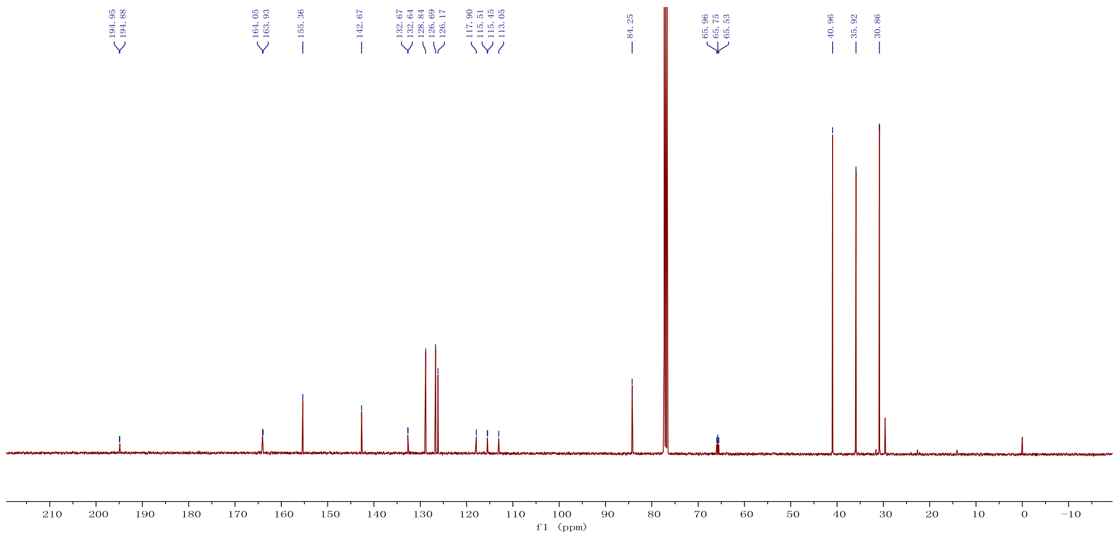
29.89
29.86
29.71
f1 (ppm)

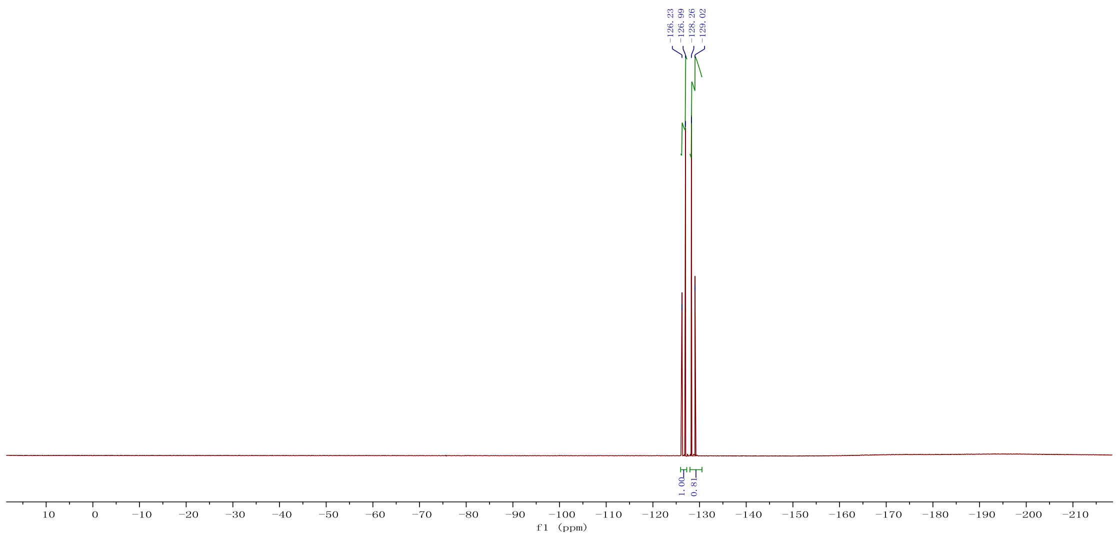

-125.55
-125.70
-126.32
-126.46
-128.83
-128.98
-129.59
-129.74
A (dd)
-126.01
B (dd)
-129.29
1.00
0.98
f1 (ppm)

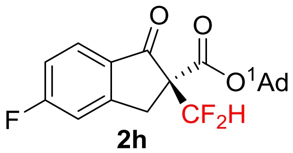


2g









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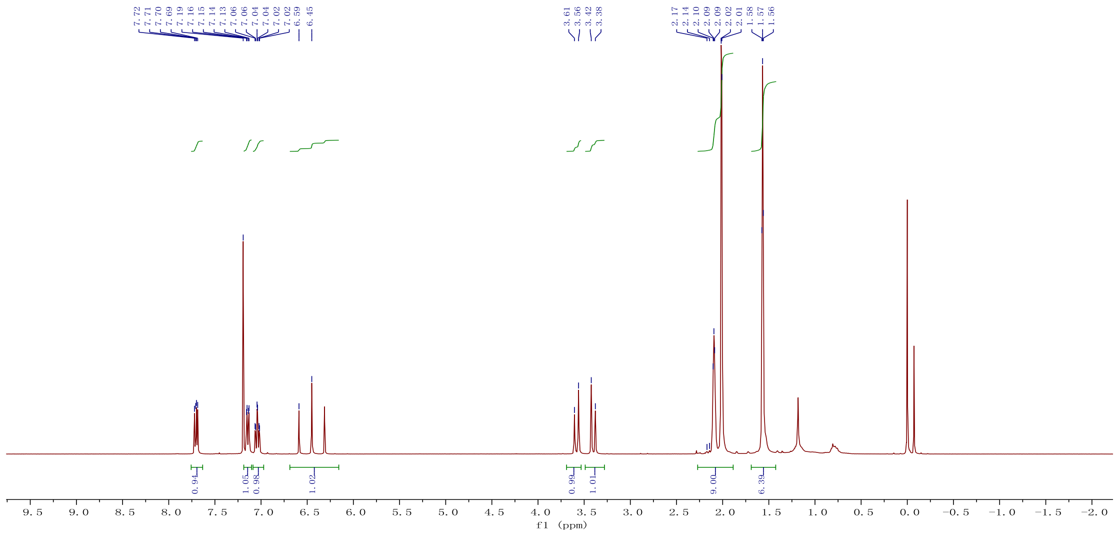

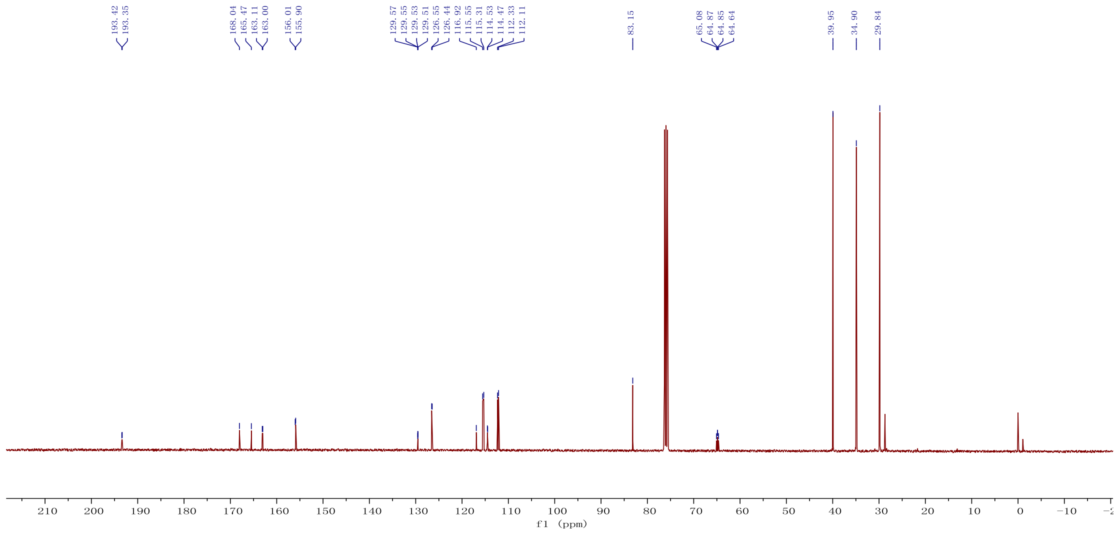

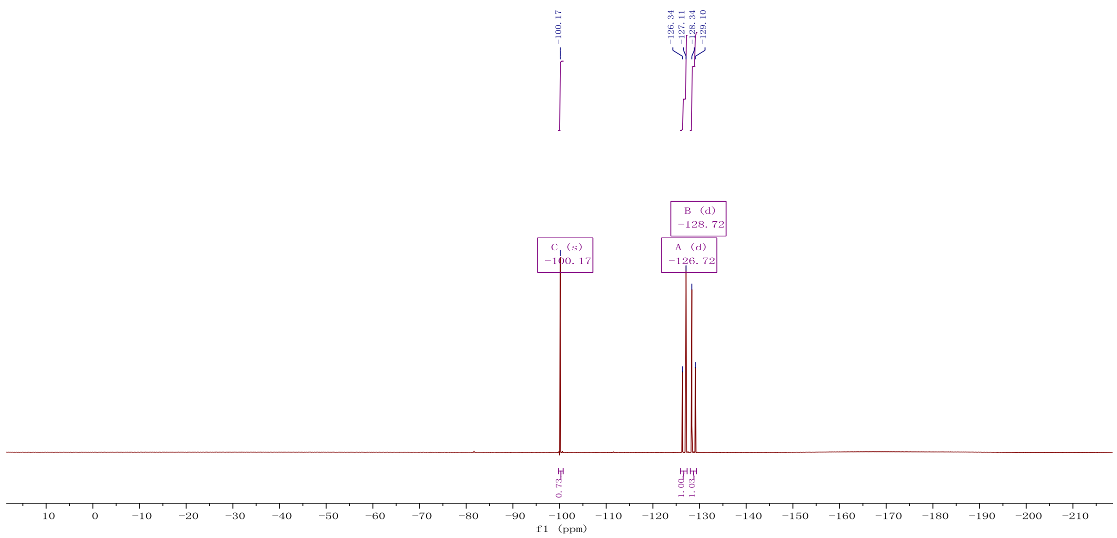

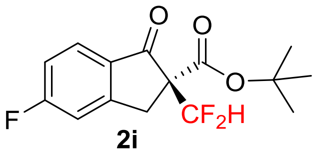

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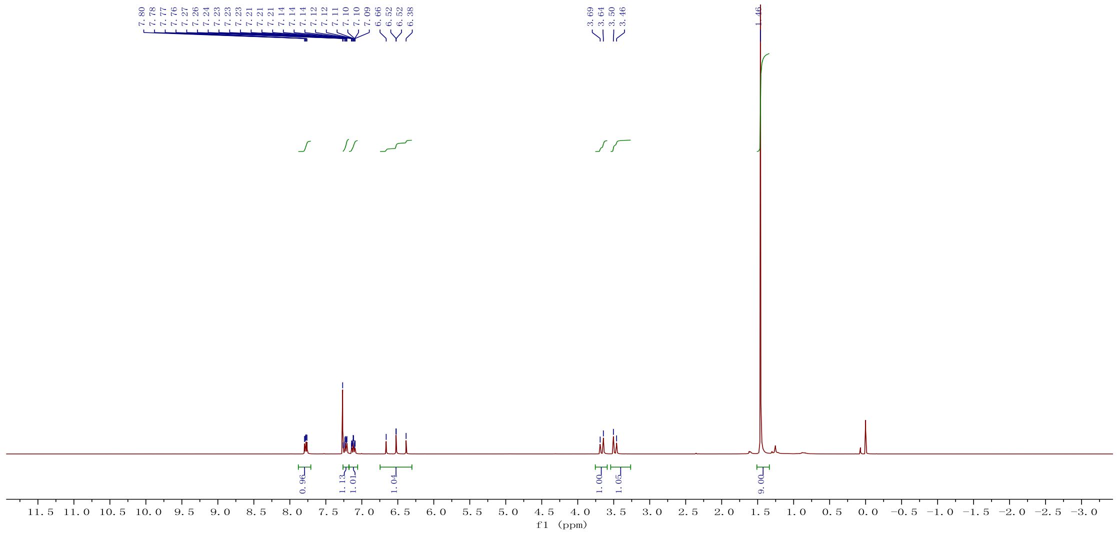
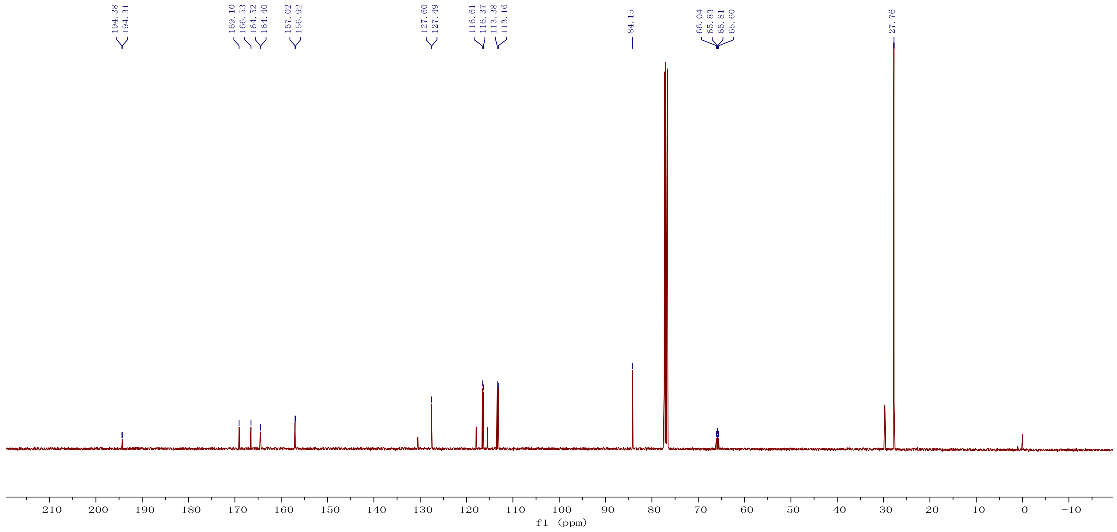
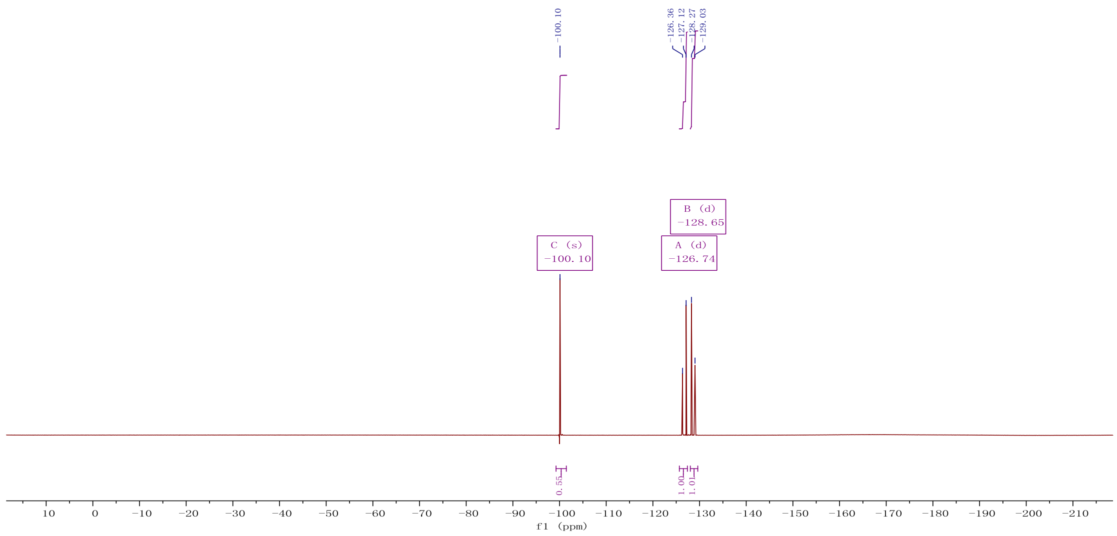
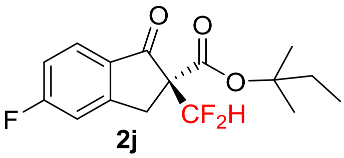
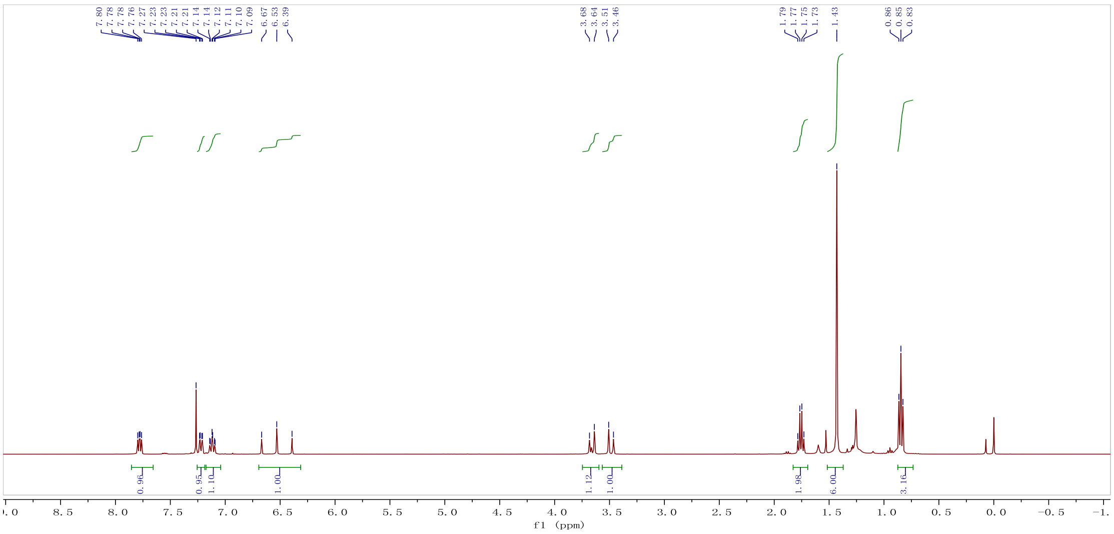


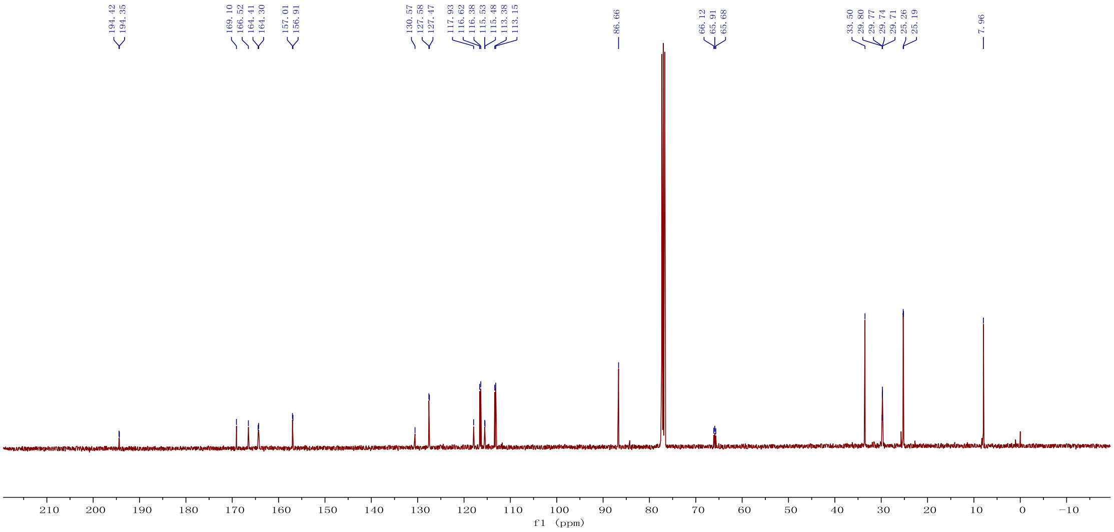


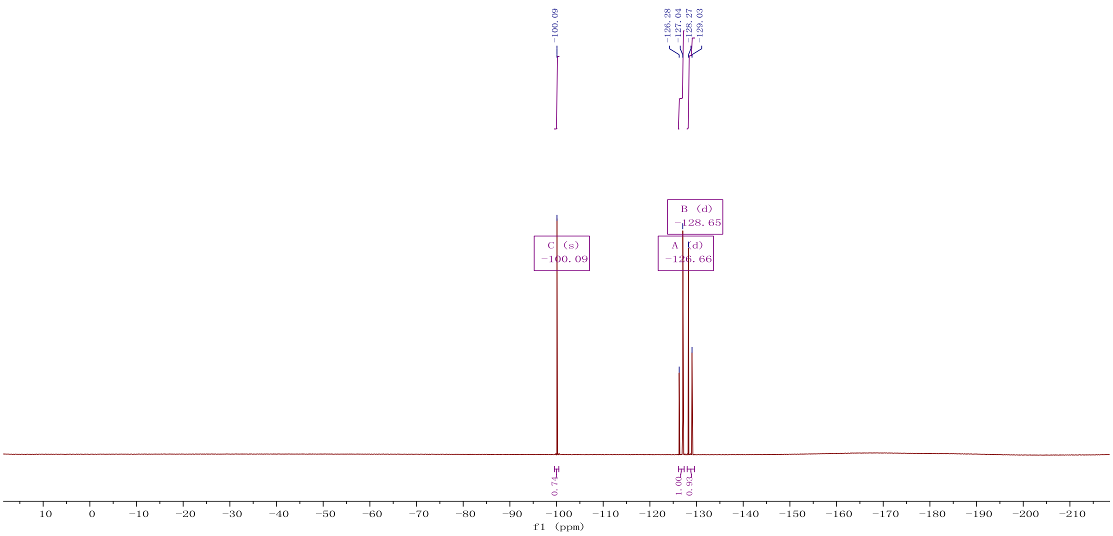


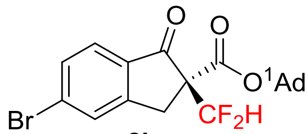

O
O
O
F
CF2H

2j

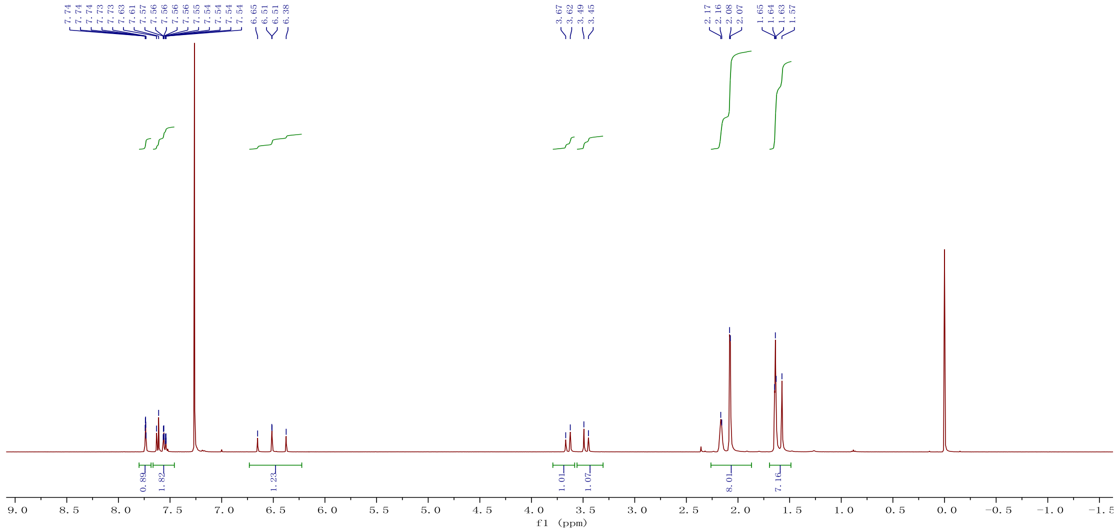

7.80 7.78 7.78 7.76 7.27 7.23 7.23 7.21 7.21 7.14 7.14 7.12 7.11 7.10 7.09 6.67 6.53 6.39
3.68 3.64 3.51 3.46
1.79 1.77 1.75 1.73 1.43 0.86 0.85 0.83
0.96 0.95 1.10 1.00 1.12 1.00 1.98 6.00 3.16
f1 (ppm)

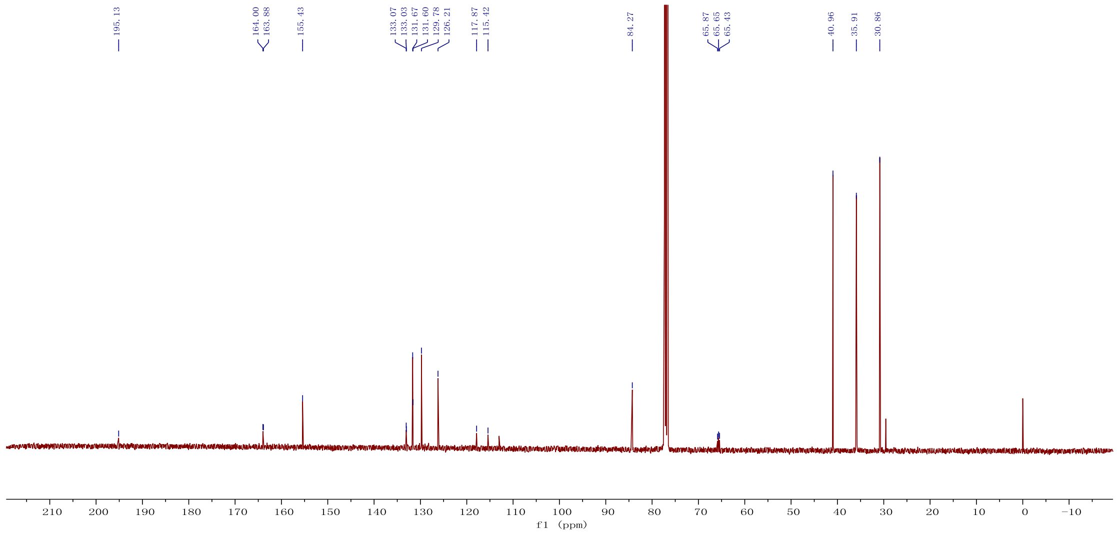

194.42 194.35 169.10 166.52 164.41 164.30 157.01 156.91 130.57 127.58 127.47 117.93 116.62 116.38 115.53 115.48 113.38 113.15 86.66 66.12 65.91 65.68 33.50 29.80 29.77 29.74 29.71 25.26 25.19 7.96
f1 (ppm)

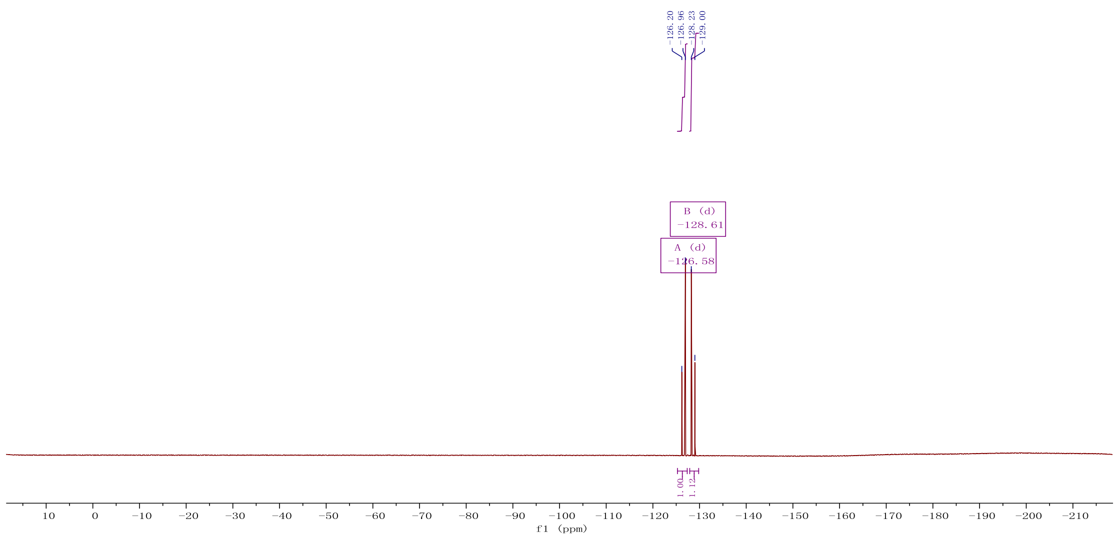

-100.09
-126.28 -127.04 -128.27 -129.03
B (d) -128.65
C (s) -100.09
A (d) -126.66
0.74 1.00 0.93
f1 (ppm)

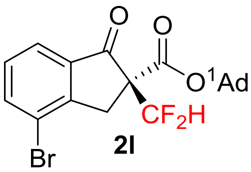


2k









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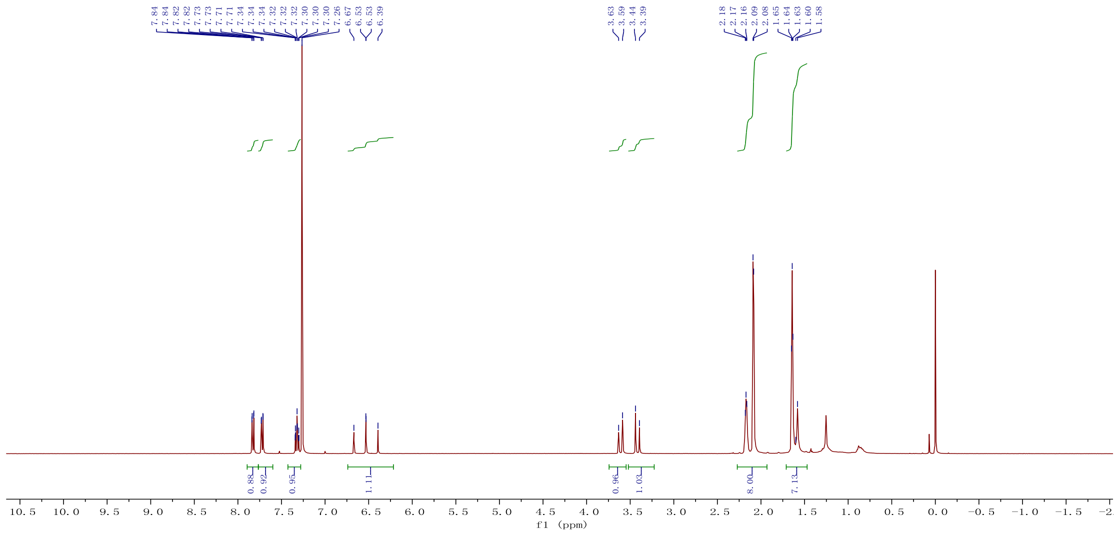

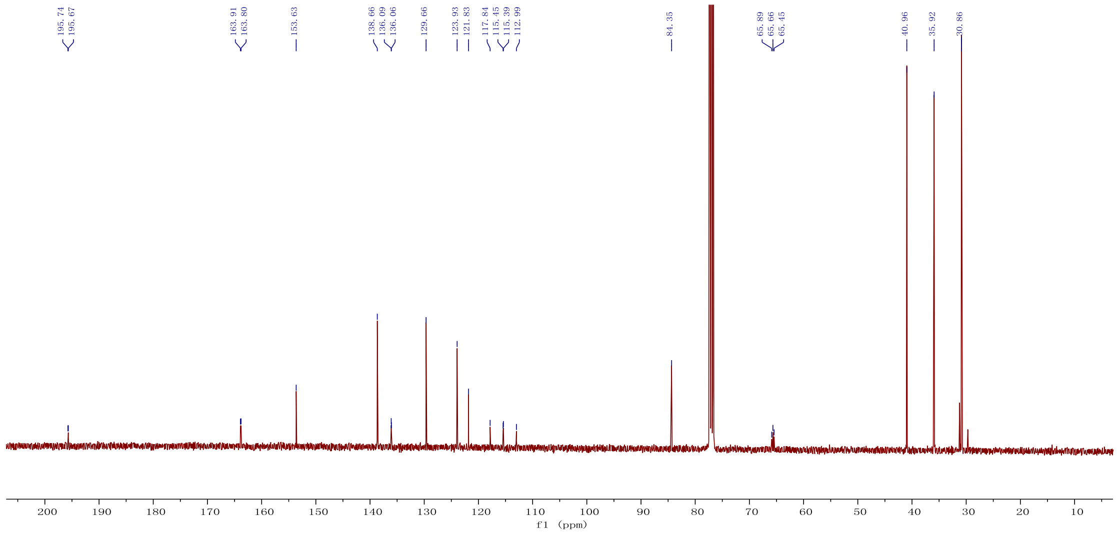

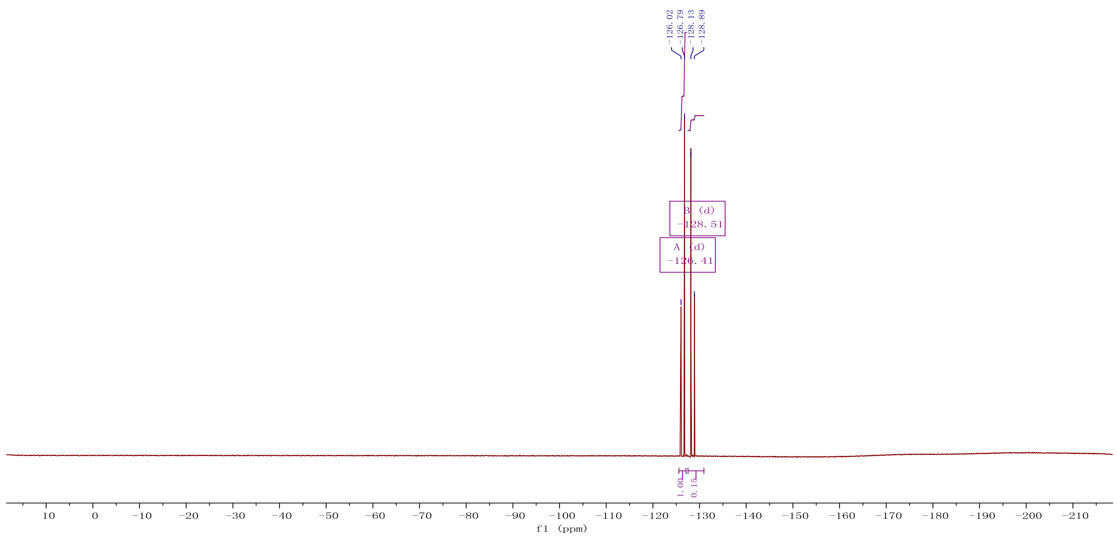

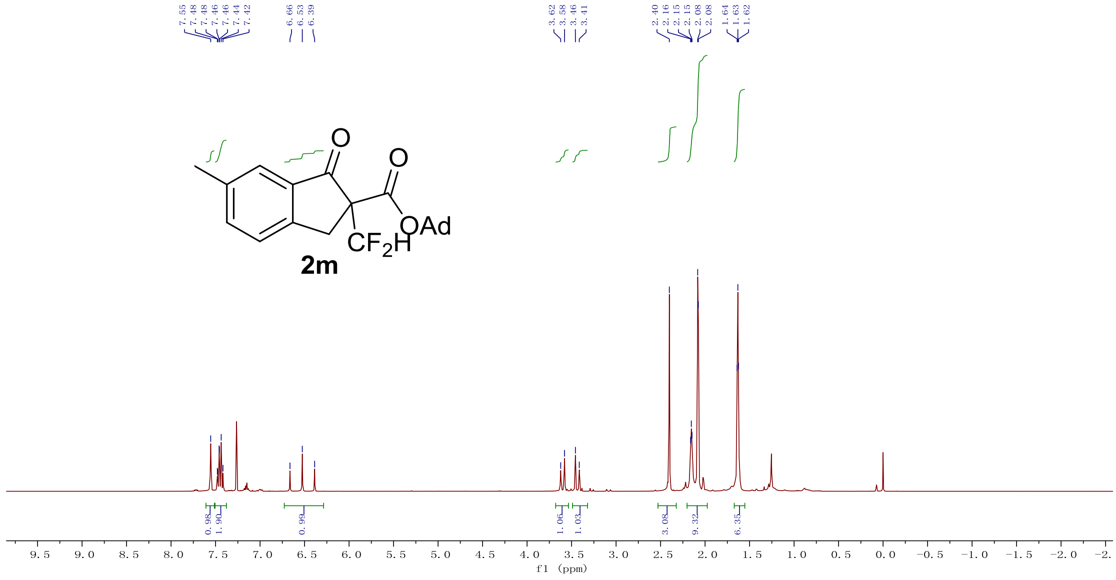
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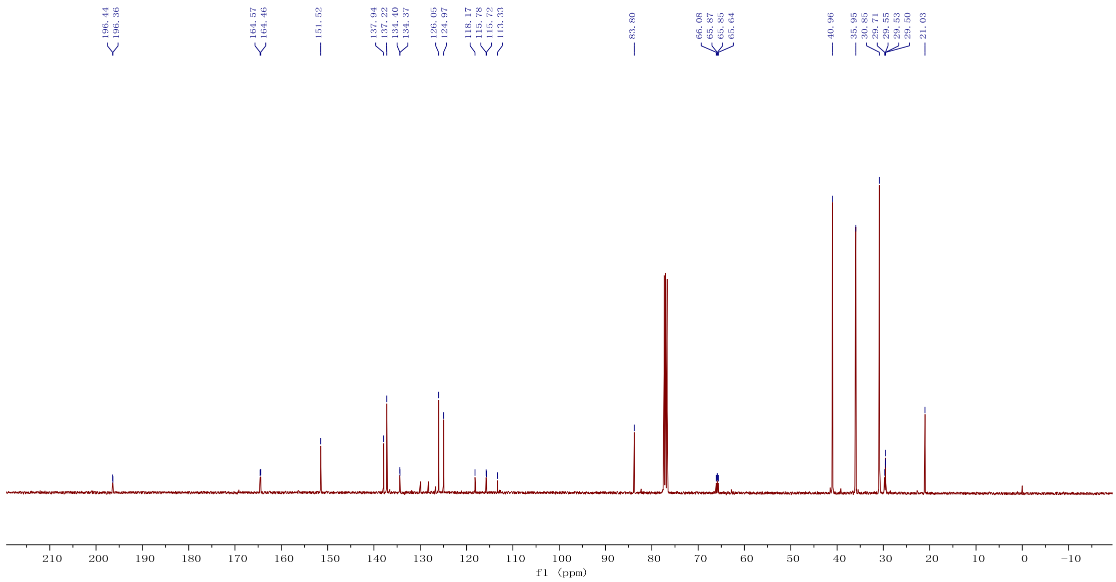
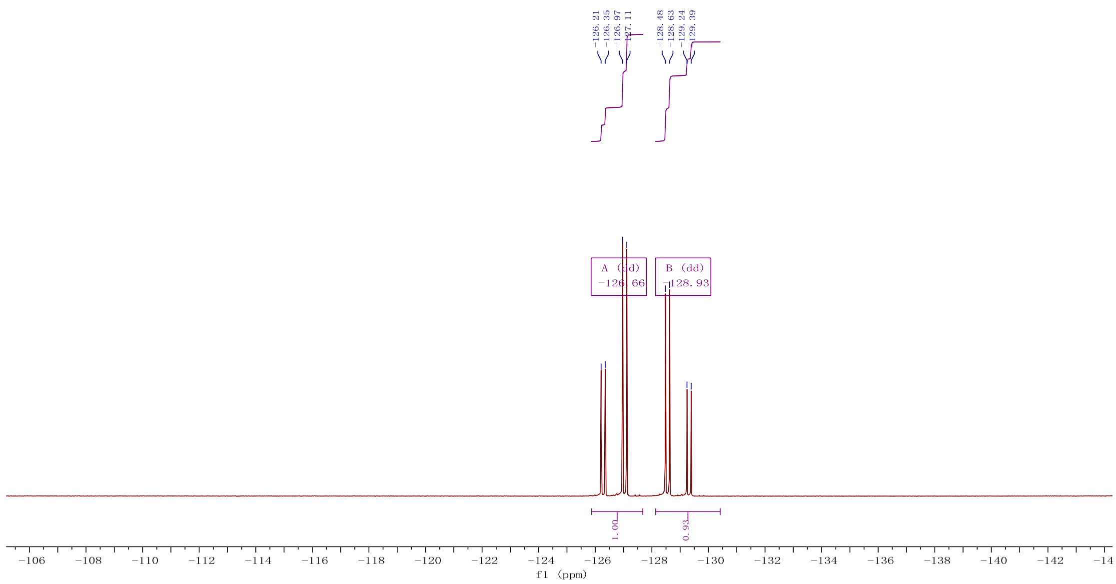
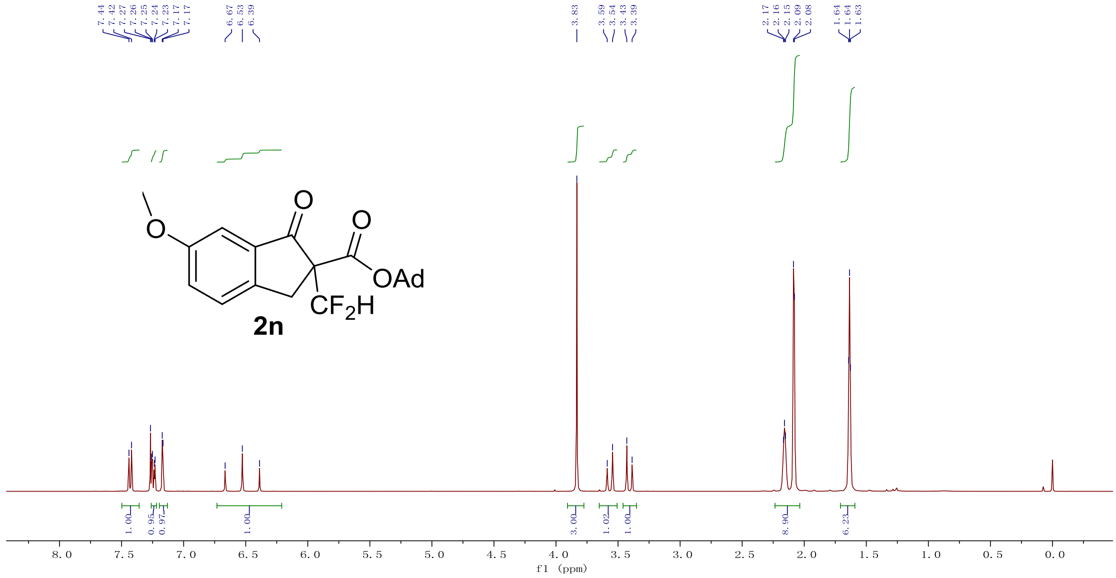
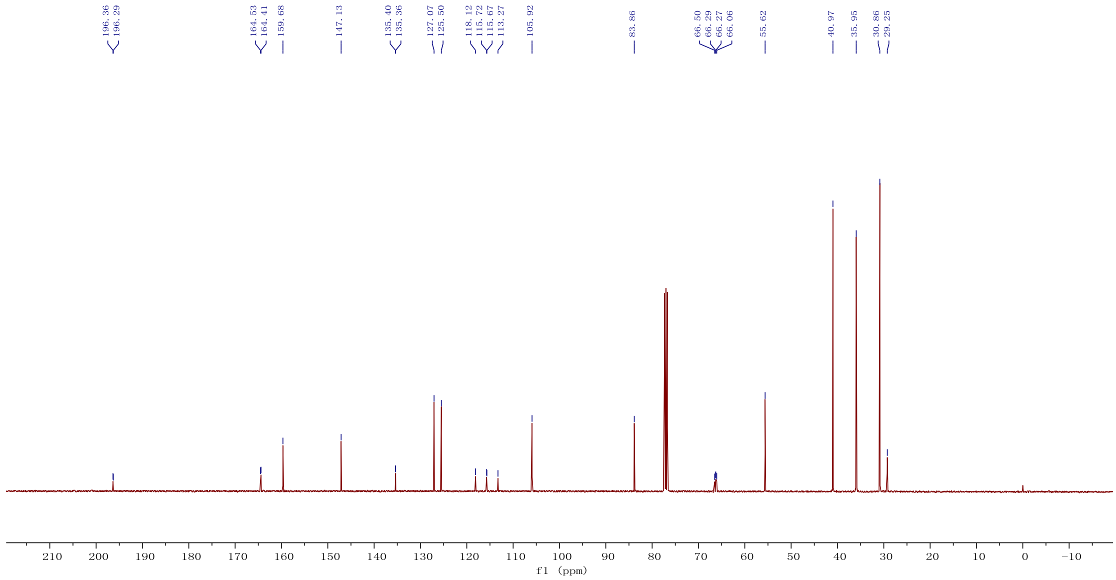
6.66 6.53 6.39
3.62 3.58 3.46 3.41
2.40 2.16 2.15 2.15 2.08 2.08
1.64 1.63 1.62
O
O
OAd
CF2H
2m
0.98 1.90 0.99 1.06 1.03 3.08 9.32 6.35
f1 (ppm)


196.44 196.36
164.57 164.46
151.52
137.94 137.22 134.40 134.37
126.05 124.97
118.17 115.78 115.72 113.33
83.80
66.08 65.87 65.85 65.64
40.96 35.95 30.85 29.71 29.55 29.53 29.50
21.03
f1 (ppm)


-126.21 -126.35 -126.97 -127.11
-128.48 -128.63 -129.24 -129.39
A (dd) -126.66
B (dd) -128.93
1.00 0.93
f1 (ppm)


7.44 7.42 7.27 7.26 7.25 7.24 7.23 7.17 7.17
6.67 6.53 6.39
3.83
3.59 3.54 3.43 3.39
2.17 2.16 2.15 2.09 2.08
1.64 1.64 1.63
O
O
OAd
CF2H
2n
1.00 0.95 0.97 1.00 3.00 1.02 1.00 8.90 6.23
f1 (ppm)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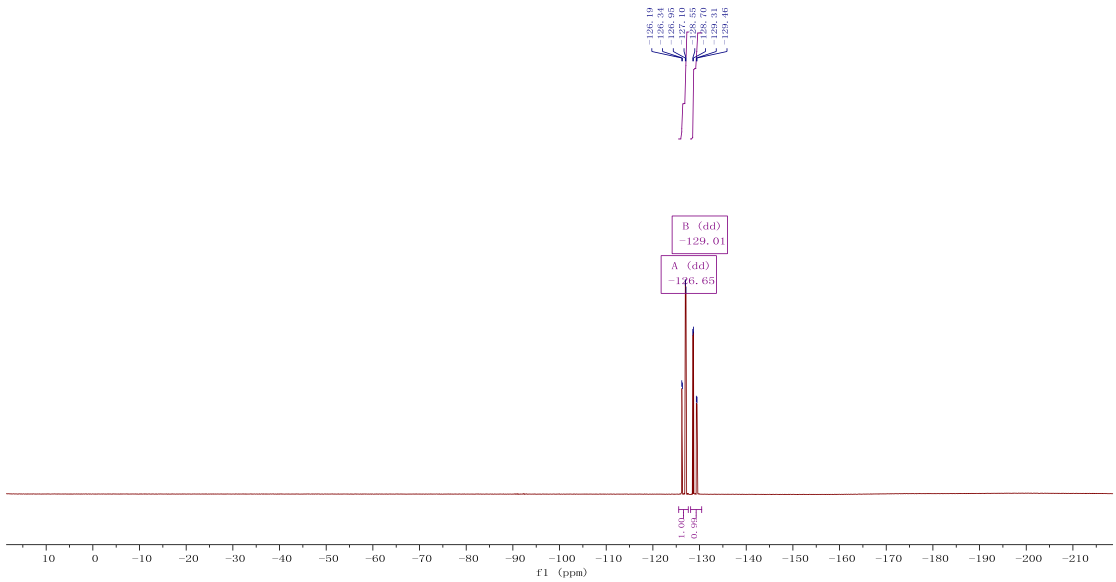
164.53 164.41 159.68
147.13
135.40 135.36
127.07 125.50
118.12 115.72 115.67 113.27
105.92
83.86
66.50 66.29 66.27 66.06
55.62
40.97
35.95
30.86 29.25
f1 (ppm)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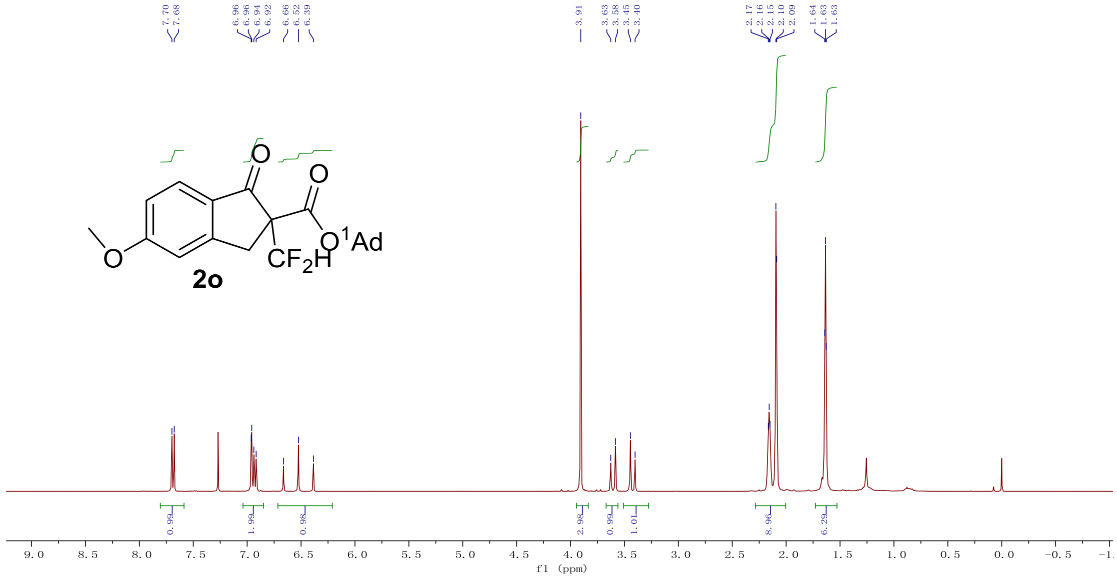
B (dd)
-129.01
A (dd)
-126.65
1.00 0.99
f1 (ppm)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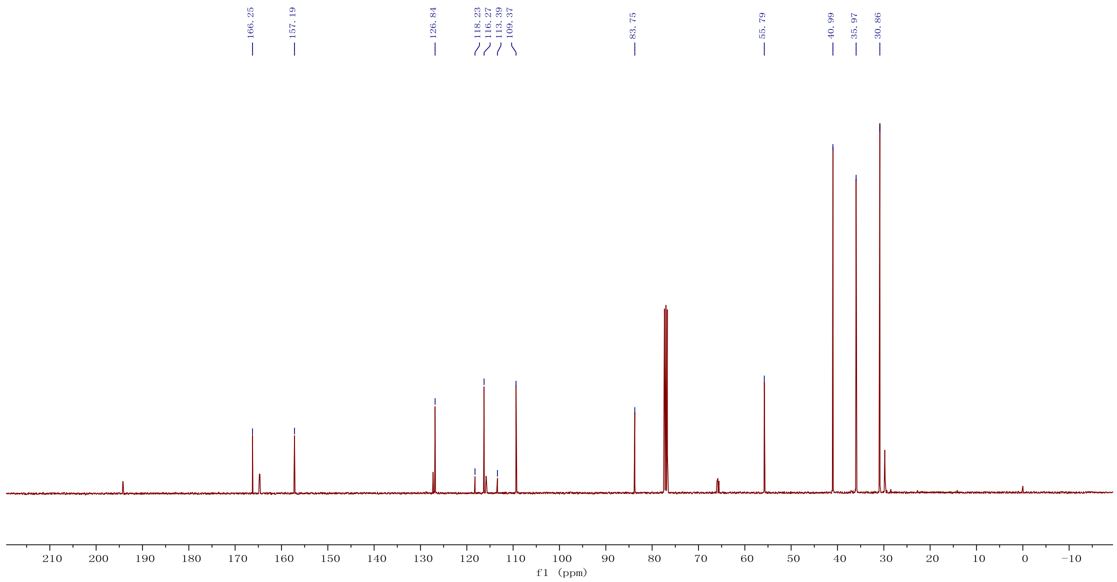
7.68
6.96
6.96
6.94
6.92
6.66
6.52
6.39
3.91
3.63
3.58
3.45
3.40
2.17
2.16
2.15
2.10
2.09
1.64
1.63
1.63
O
O
O
1Ad
CF2H
2o
0.99
1.99
0.98
2.98
0.99
1.01
8.96
6.29
f1 (ppm)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109.37
83.75
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40.99
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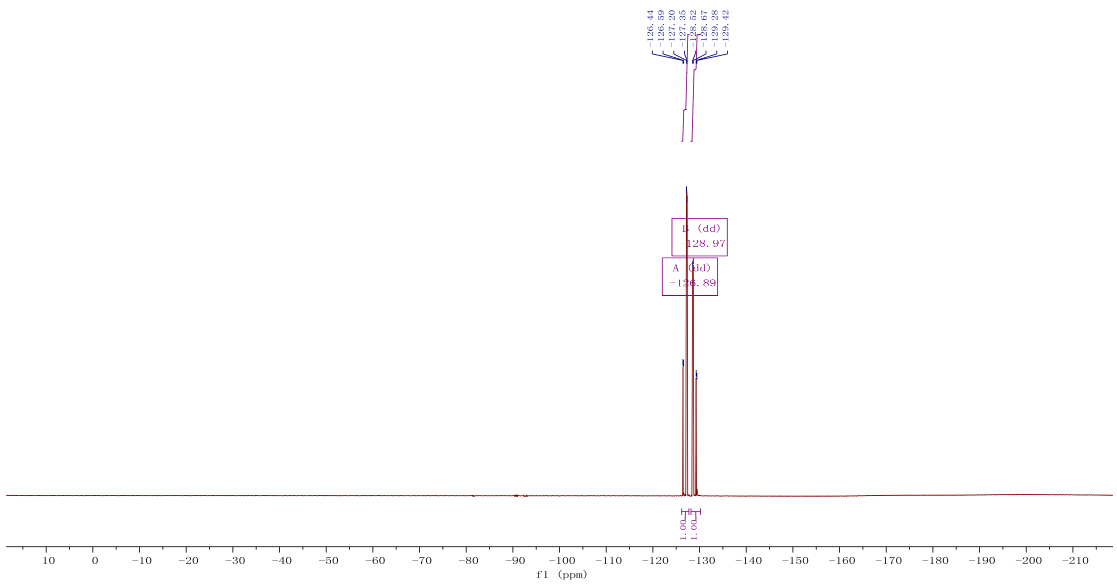
30.86
f1 (ppm)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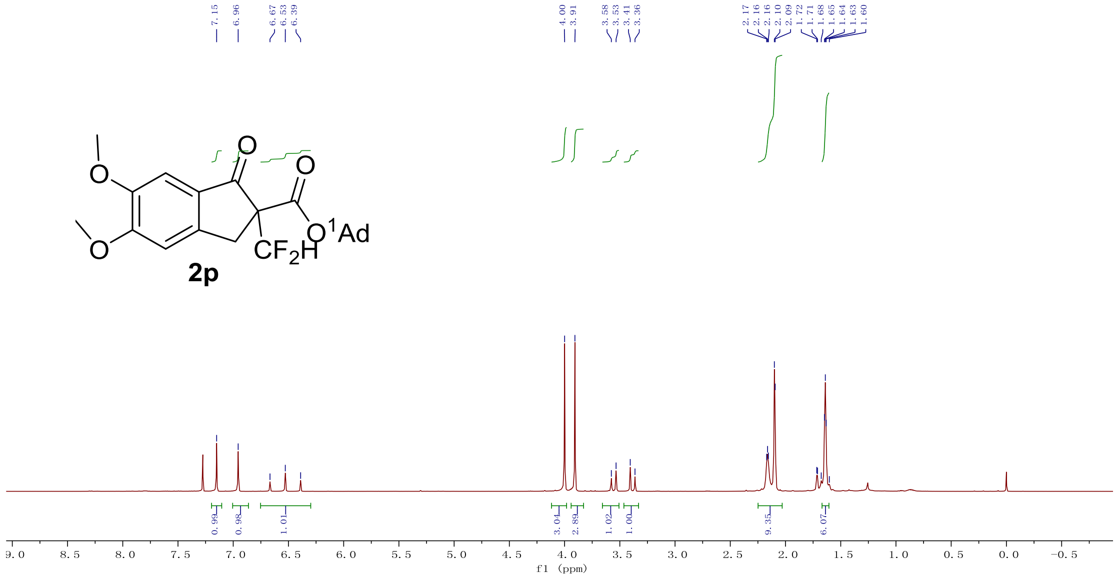
-126.59
-127.20
-127.35
-128.52
-128.67
-129.28
-129.42
B (dd)
-128.97
A (dd)
-126.89
1.00
1.00
f1 (ppm)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6.67
6.53
6.39
4.00
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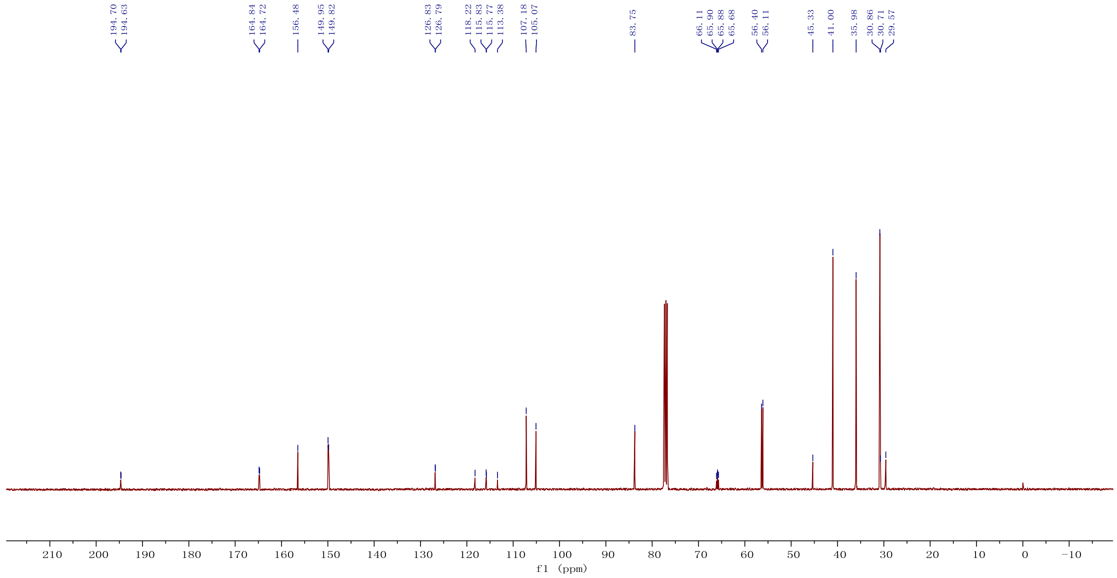
3.58
3.53
3.41
3.36
2.17
2.16
2.16
2.10
2.09
1.72
1.71
1.68
1.65
1.64
1.63
1.60
O
O
O
O
O
CF2H
1Ad
2p
0.99
0.98
1.01
3.04
2.89
1.02
1.00
9.35
6.07
f1 (ppm)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164.72
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113.38
107.18
105.07
83.75
66.11
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56.40
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45.33
41.00
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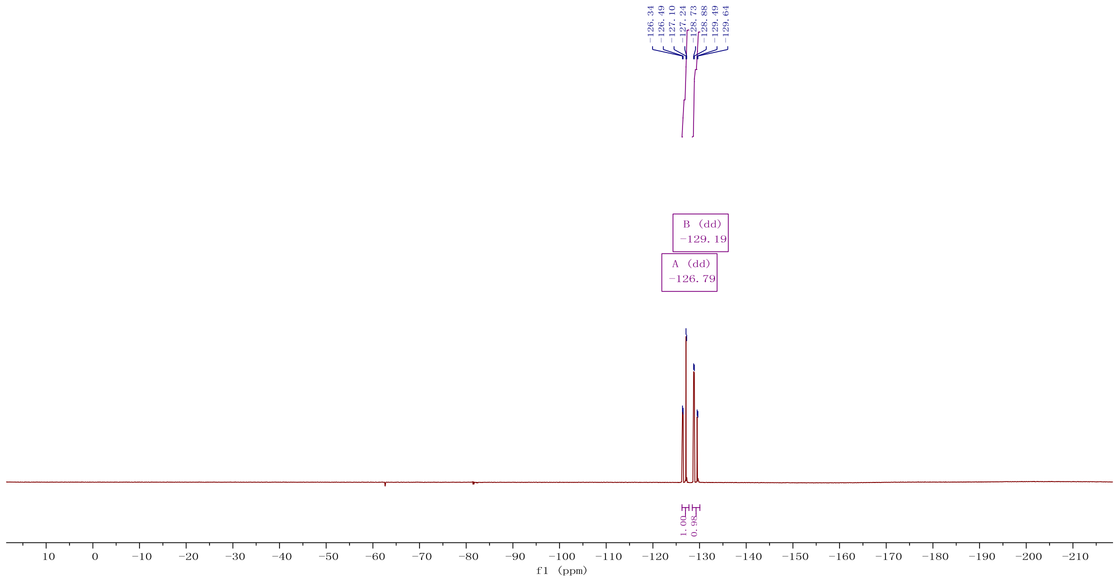
30.86
30.71
29.57
f1 (ppm)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-126.49
-127.10
-127.24
-128.73
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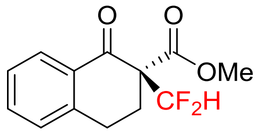
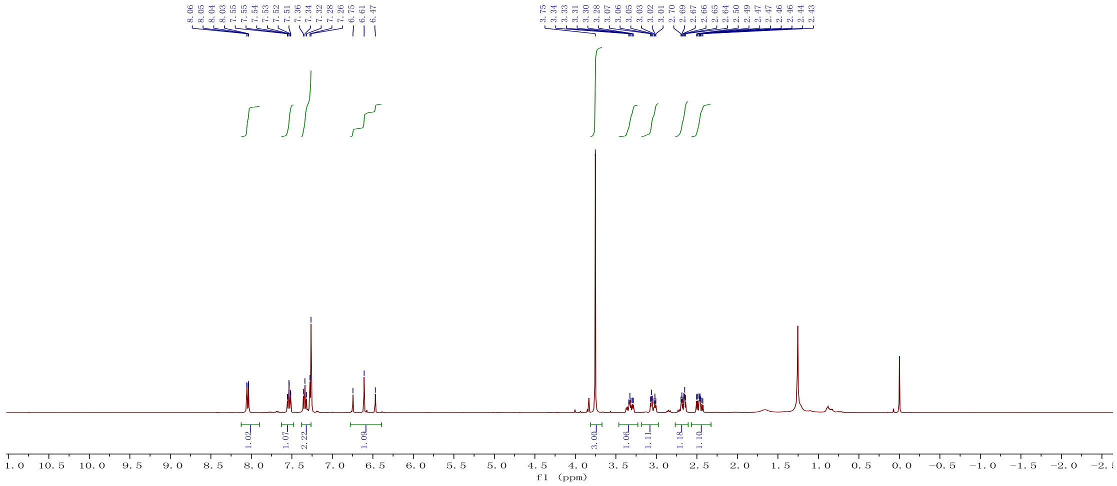
-129.64
B (dd)
-129.19
A (dd)
-126.79
1.00
0.98
f1 (ppm)


O
O
OMe
CF2H

2q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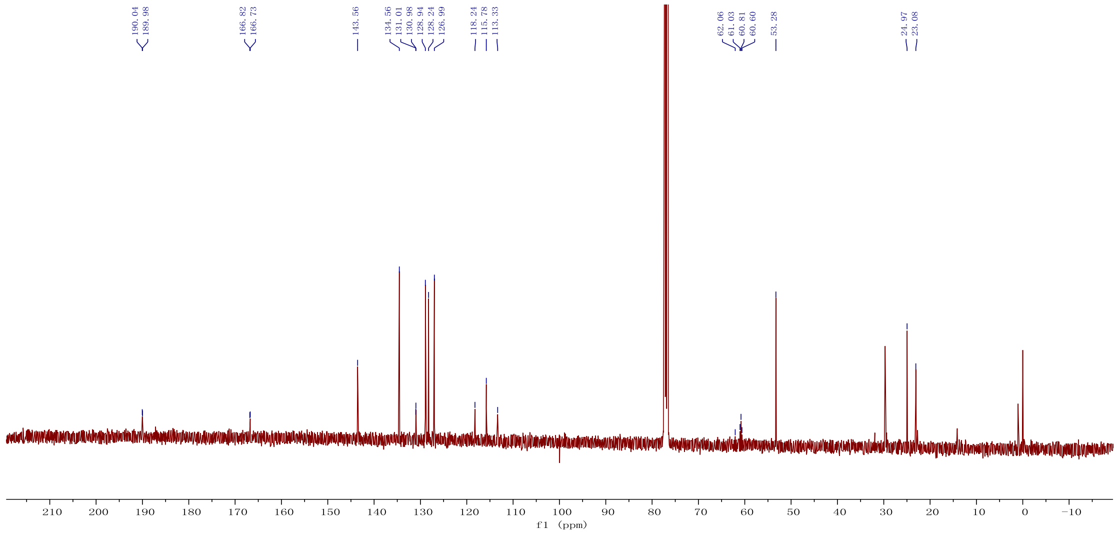
3.75 3.34 3.33 3.31 3.30 3.28 3.07 3.06 3.05 3.03 3.02 3.01 2.70 2.69 2.67 2.66 2.65 2.64 2.50 2.49 2.47 2.47 2.46 2.46 2.44 2.43
1.02 1.07 2.22 1.09 3.00 1.06 1.11 1.18 1.10
f1 (ppm)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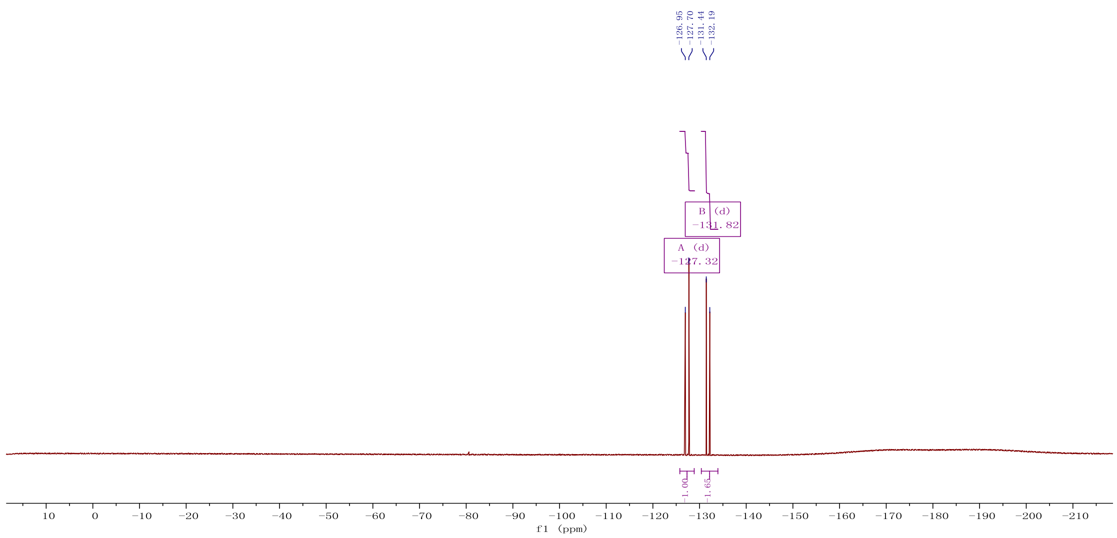
166.82 166.73
143.56
134.56 131.01 130.98 128.94 128.24 126.99
118.24 115.78 113.33
62.06 61.03 60.81 60.60
53.28
24.97 23.08
f1 (ppm)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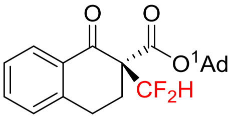
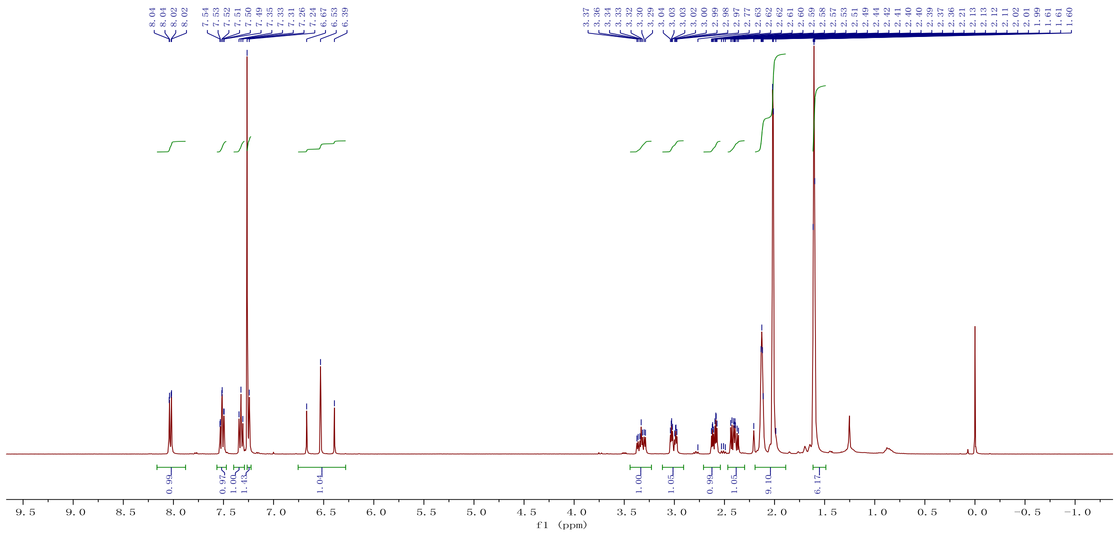
B (d) -131.82
A (d) -127.32
1.00 1.65
f1 (ppm)


O
O
O1Ad
CF2H

2r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8.04
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8.02
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7.49
7.35
7.33
7.31
7.26
7.24
6.67
6.53
6.39
3.37
3.36
3.34
3.33
3.32
3.30
3.29
3.04
3.03
3.03
3.02
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2.12
2.11
2.02
2.01
1.99
1.61
1.61
1.60
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1.04
1.00
1.05
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1.05
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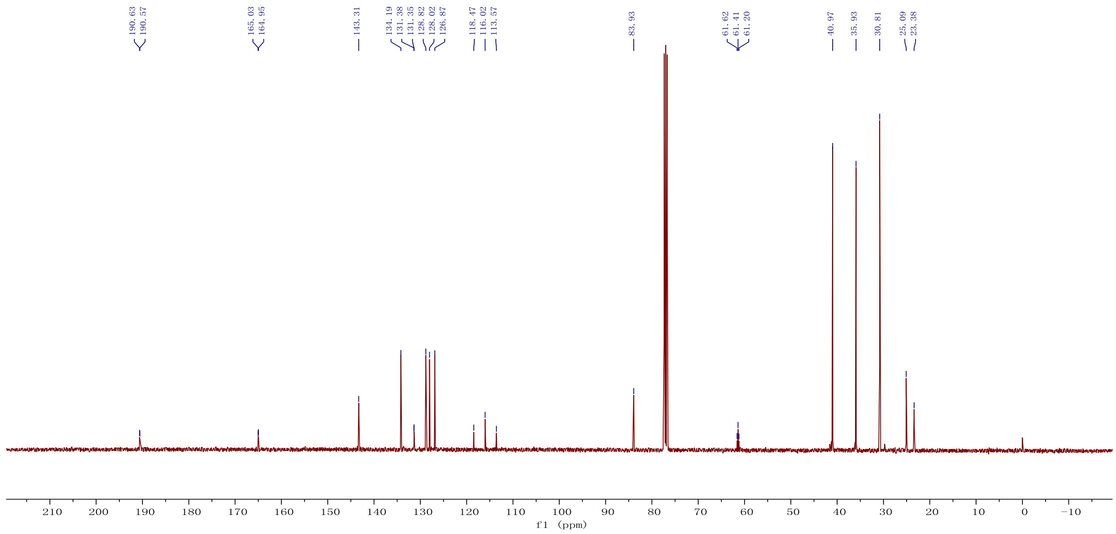
6.17
f1 (ppm)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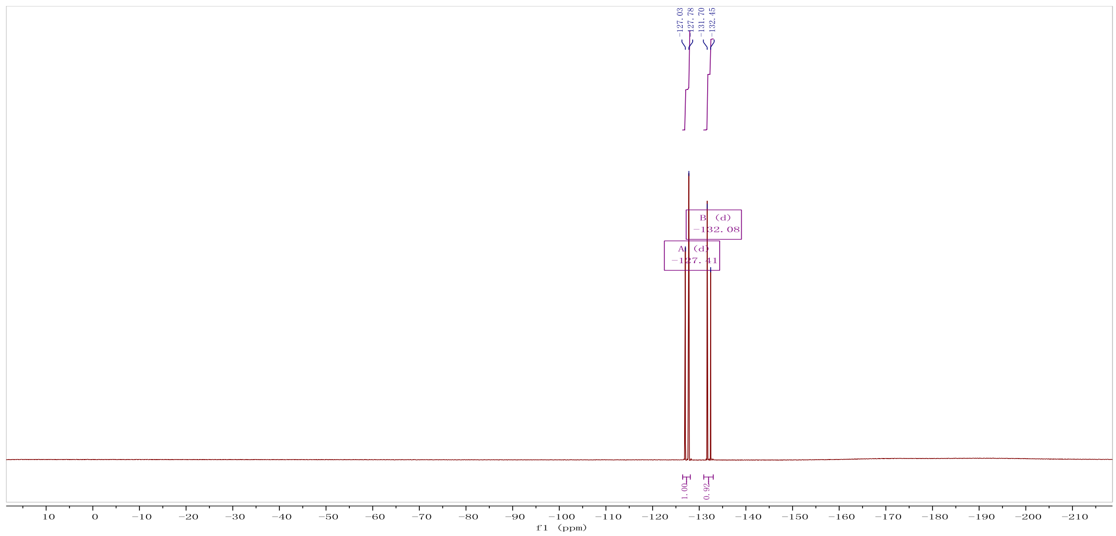
30.81
25.09
23.38
f1 (ppm)


-127.03
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-132.45
B (d)
-132.08
A (d)
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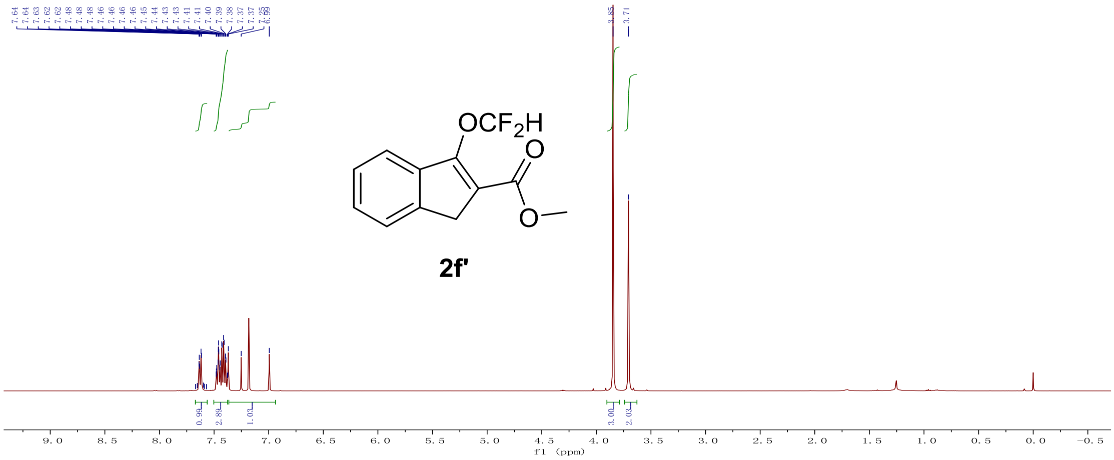
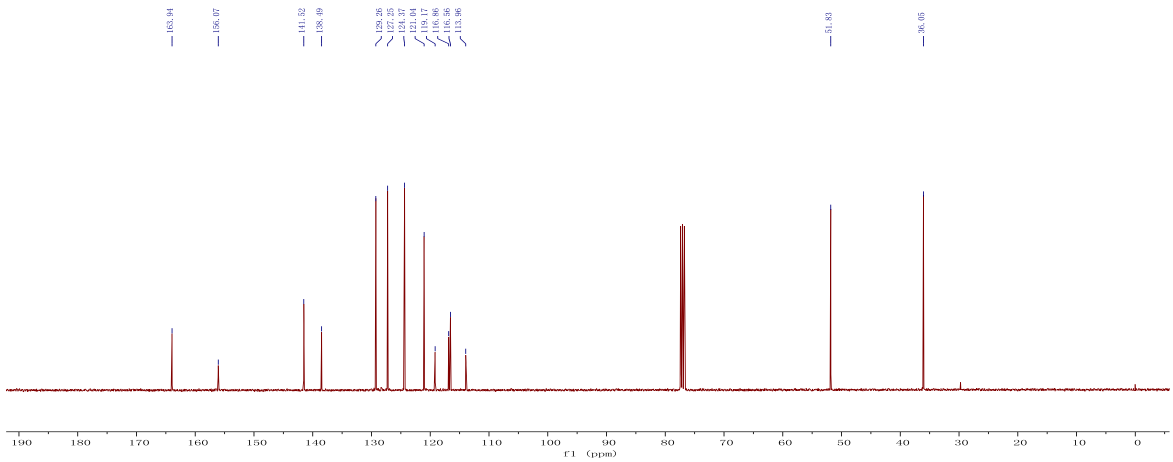
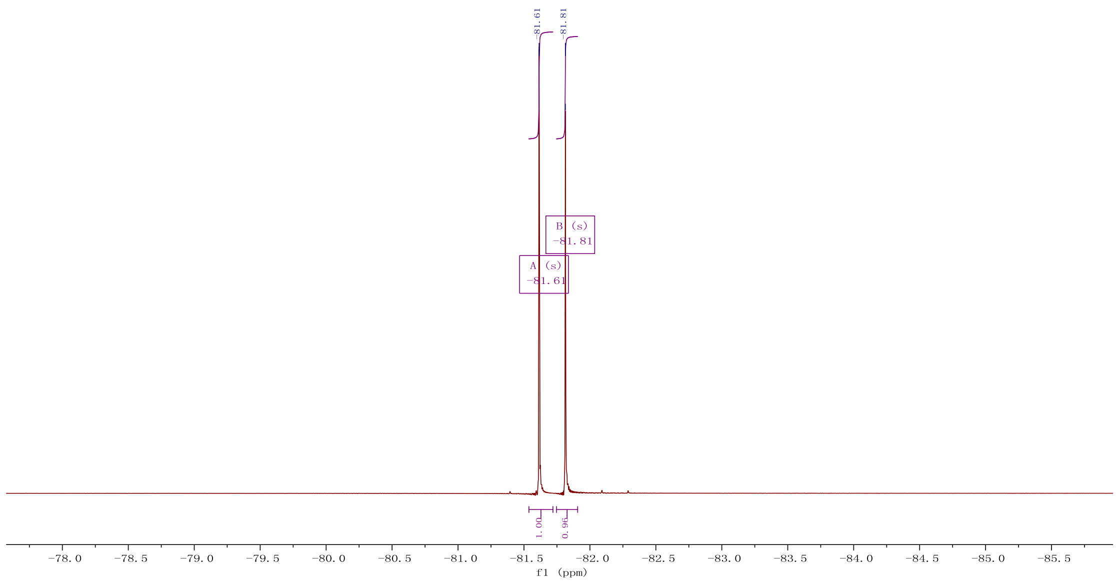
1.00
0.92
f1 (ppm)



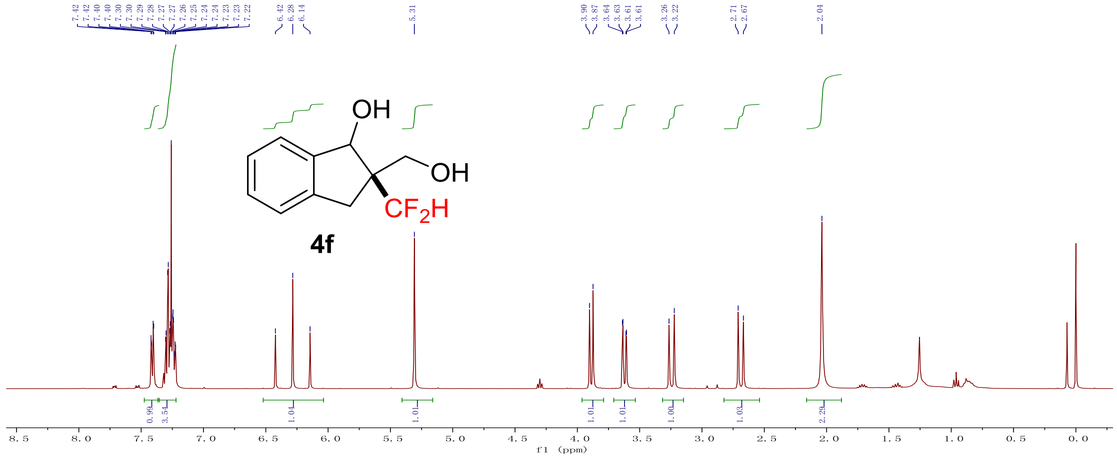
7.64 7.64 7.63 7.62 7.48 7.48 7.48 7.46 7.46 7.46 7.45 7.44 7.43 7.43 7.41 7.41 7.40 7.39 7.38 7.37 7.37 7.25 6.99
3.85 3.71
OCF2H
O
O
2f'
0.99 2.89 1.03 3.00 2.03
f1 (ppm)

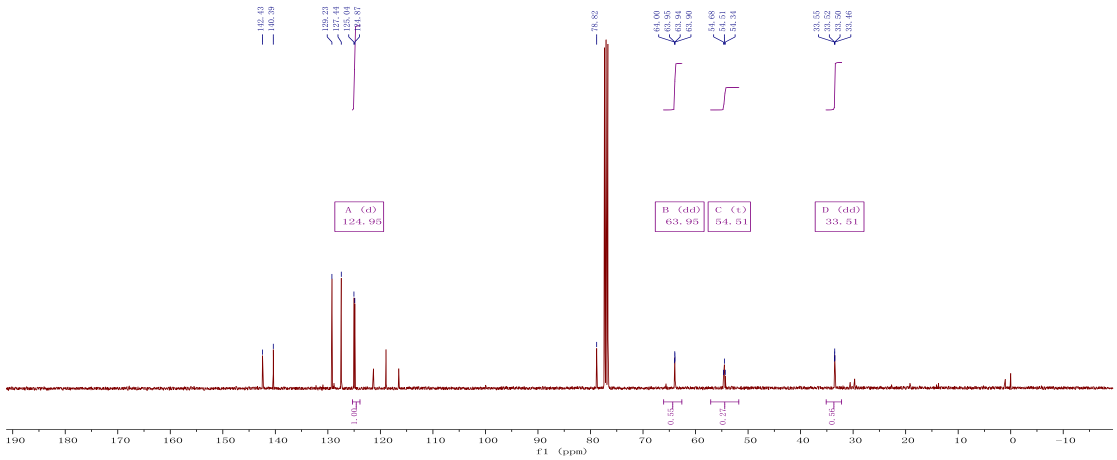


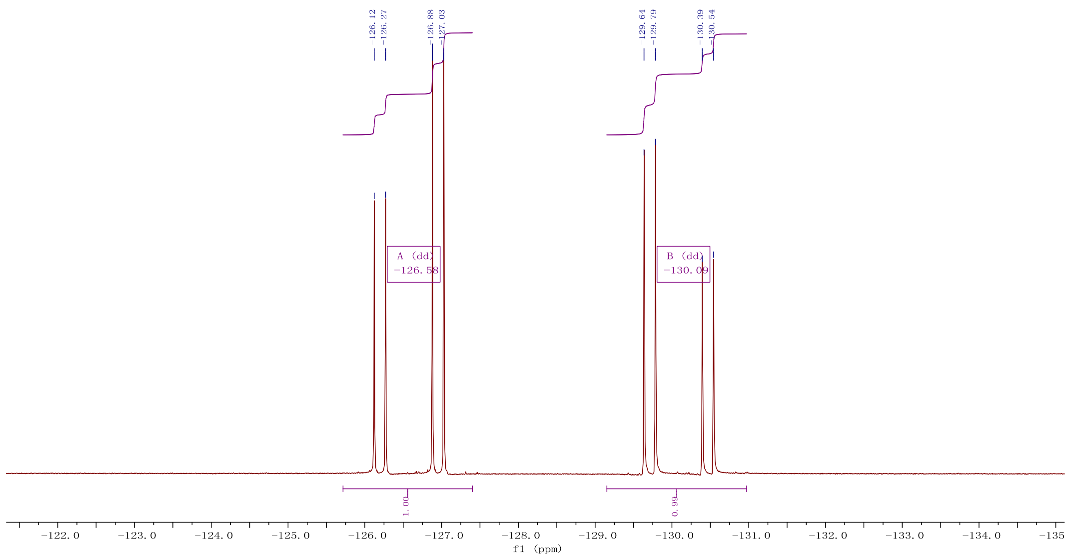
163.94 156.07 141.52 138.49 129.26 127.25 124.37 121.04 119.17 116.86 116.56 113.96 51.83 36.05
f1 (ppm)

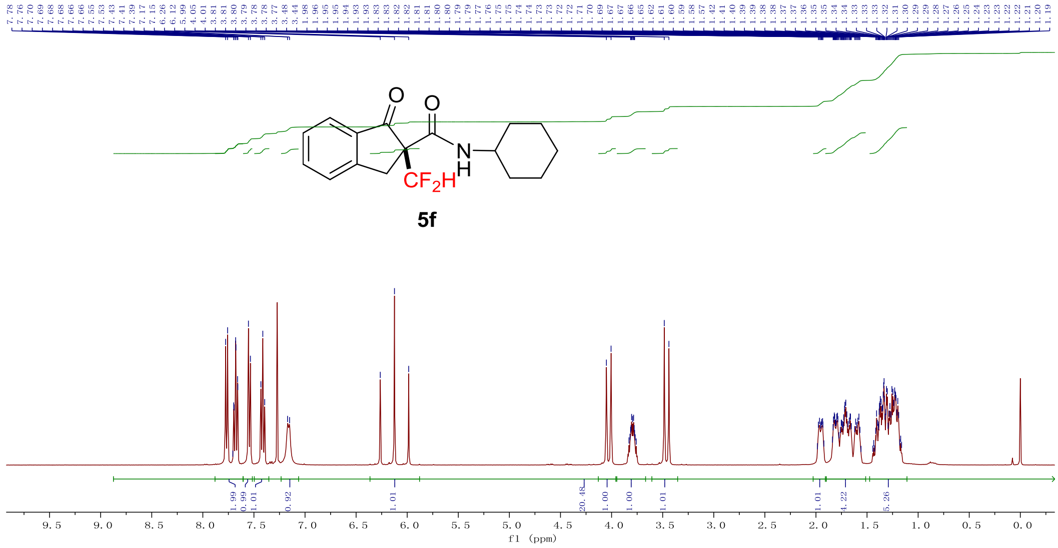


-81.61 -81.81
B (s)
-81.81
A (s)
-81.61
1.00 0.96
f1 (ppm)

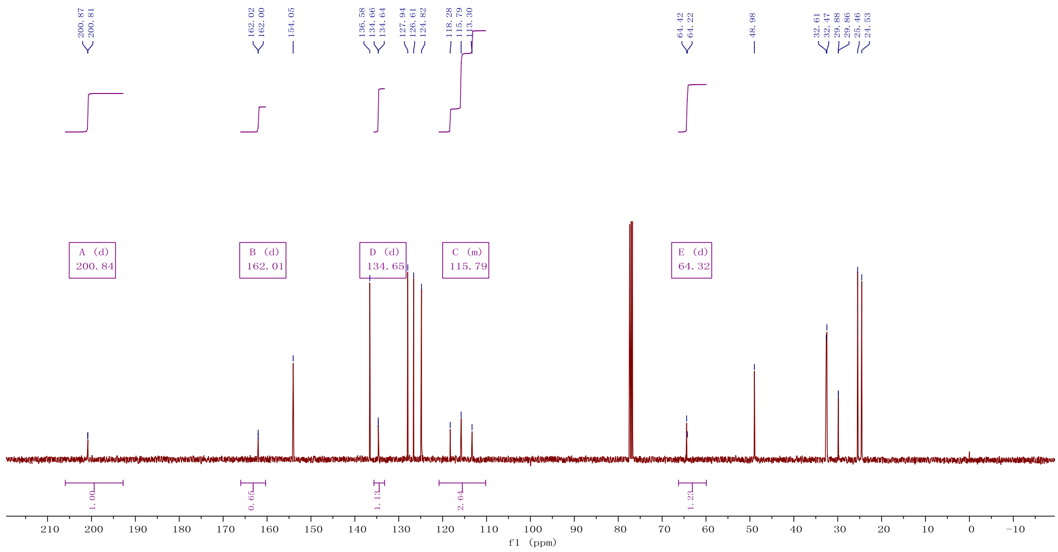

OH
OH
CF2H
4f
f1 (ppm)


A (d)
124.95
B (dd)
63.95
C (t)
54.51
D (dd)
33.51
f1 (ppm)

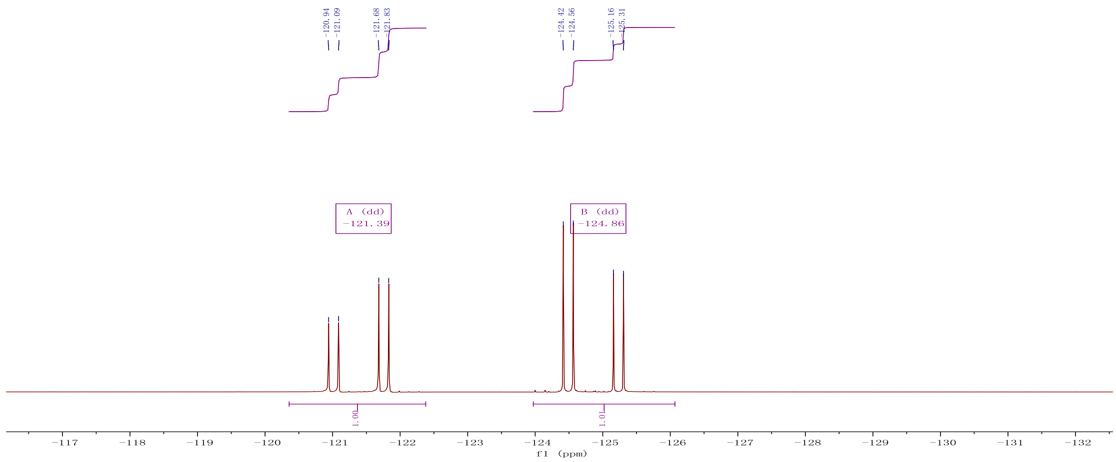

A (dd)
-126.58
B (dd)
-130.09
f1 (ppm)



5f
f1 (ppm)

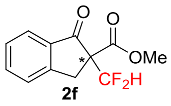


A (d)
200.84
B (d)
162.01
D (d)
134.65
C (m)
115.79
E (d)
64.32
f1 (ppm)

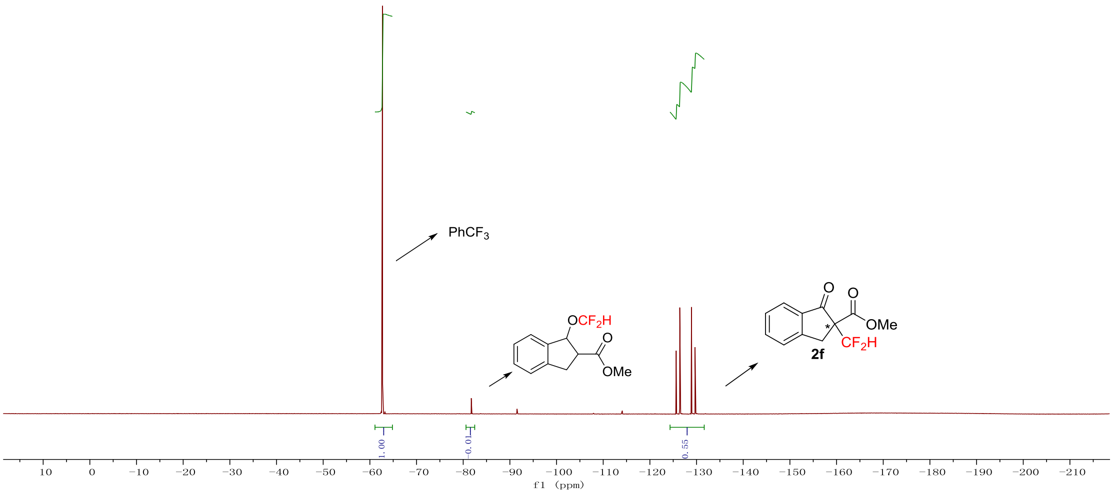


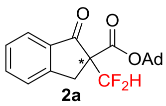
A (dd)
−121.39
B (dd)
−124.86
f1 (ppm)

Copies of some representative ^{19}F NMR spectras of crude mixtures for determining the high C/O selectivities

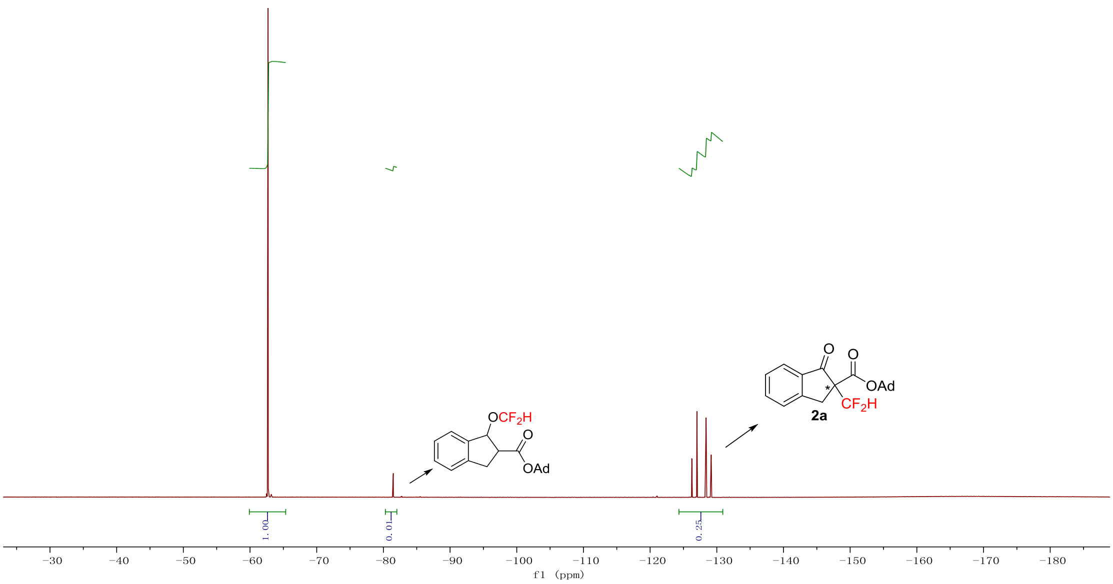


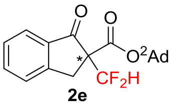
C/O = 98:2



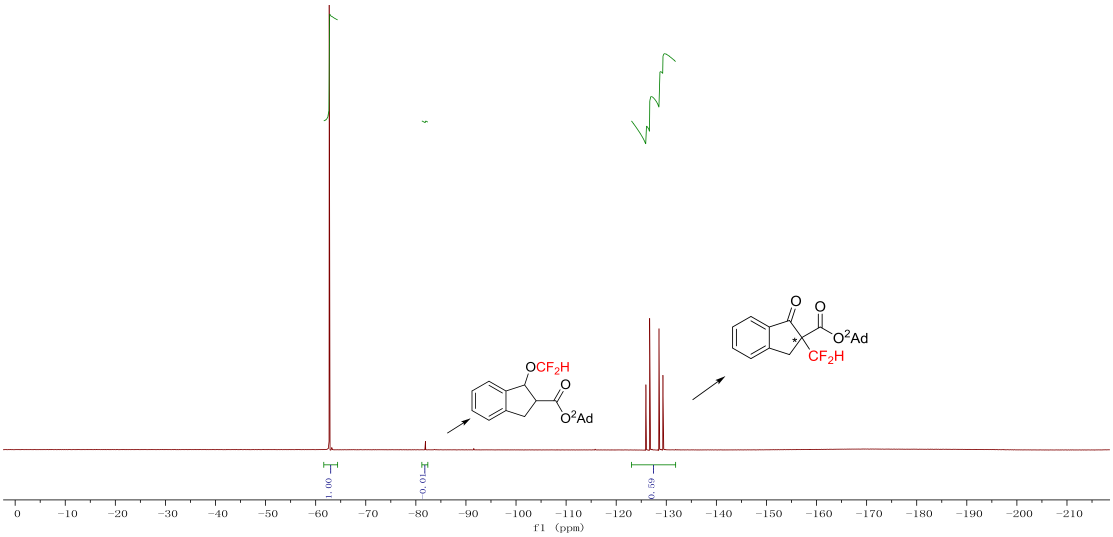


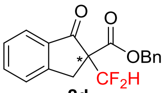
C/O = 96:4



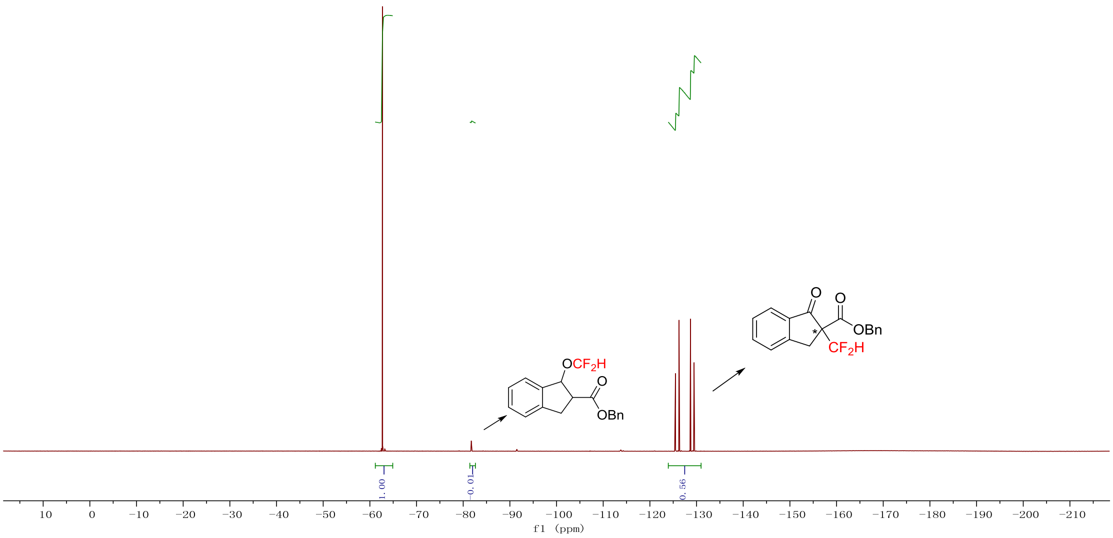


2e C/O=98:2

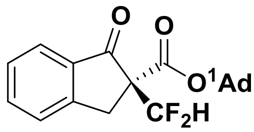




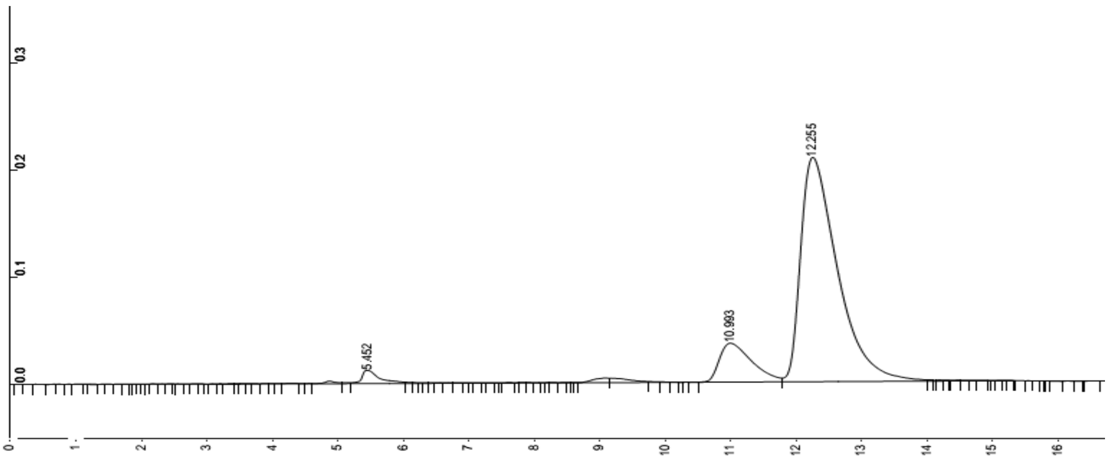
2d C/O=98:2



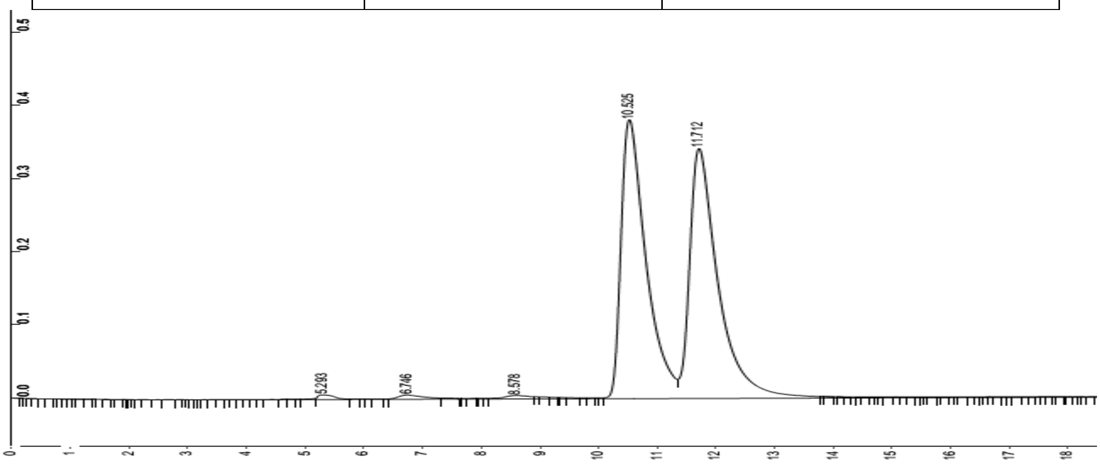
F. HPLC spectra



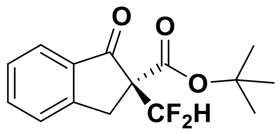
2a



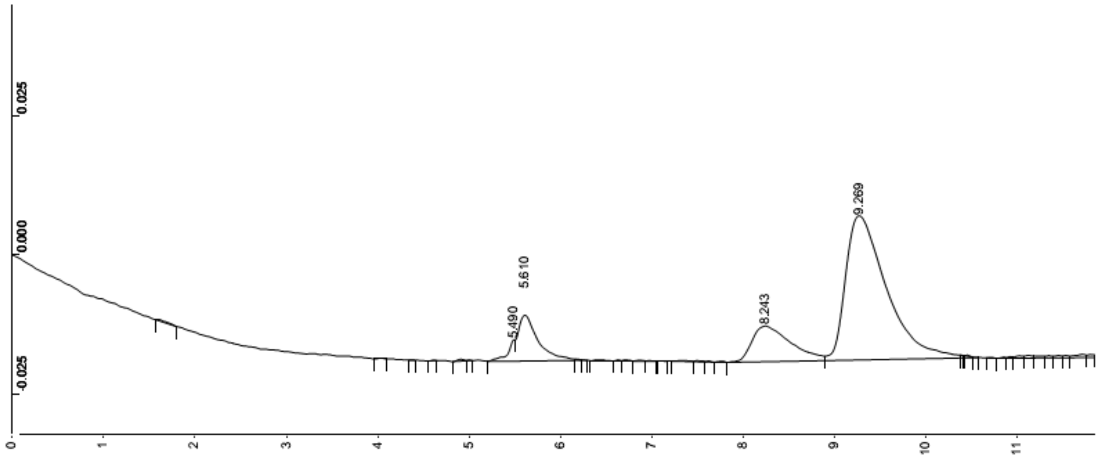
R.Time	Area	Area%
10.993	**12457557**	**10.0423**
12.255	**111593278**	**89.9577**



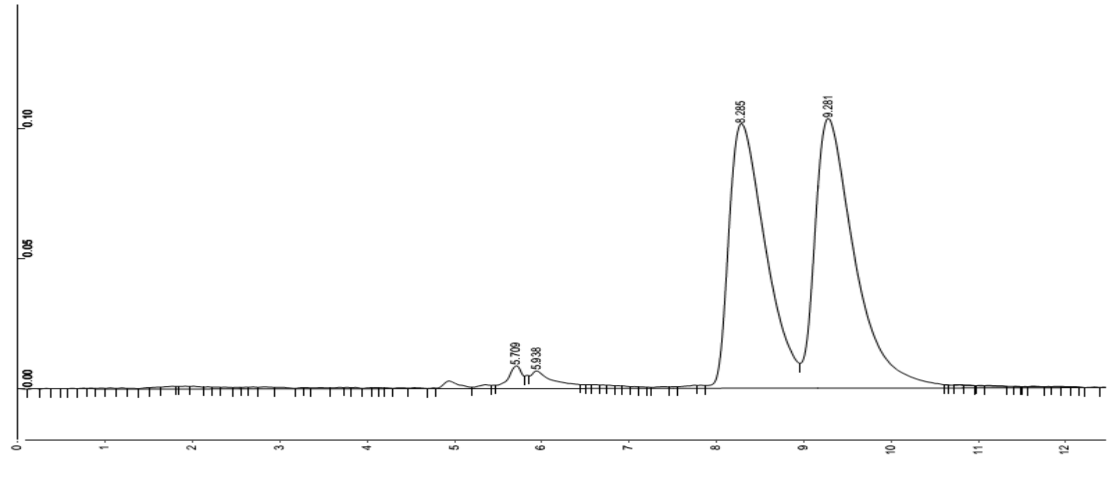
R.Time	Area	Area%
10.525	**111996656**	**50.4323**
11.712	**110076610**	**49.5677**



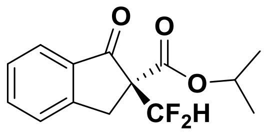
2b



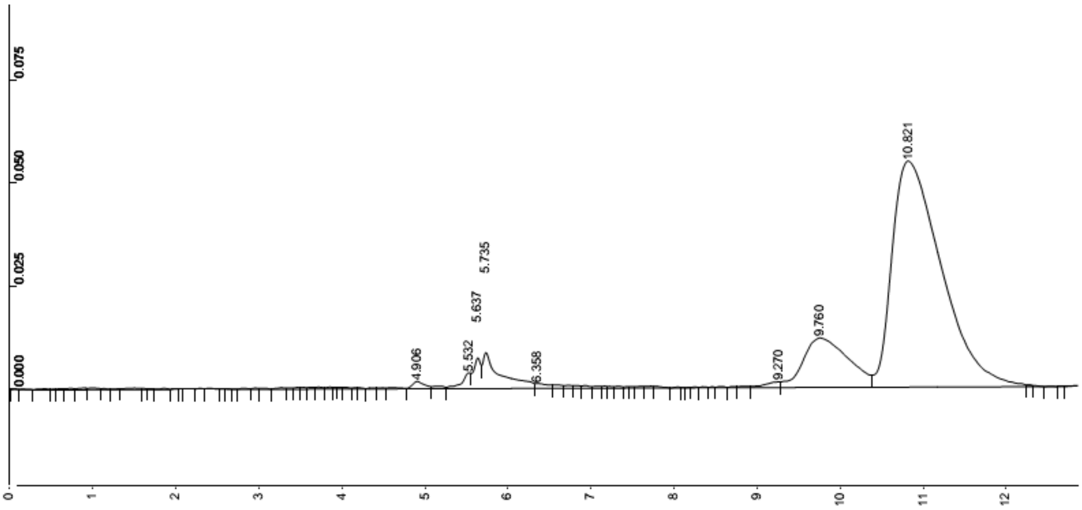
R.Time	Area	Area%
8.243	**1869104**	**16.4870**
9.269	**8630407**	**83.5130**



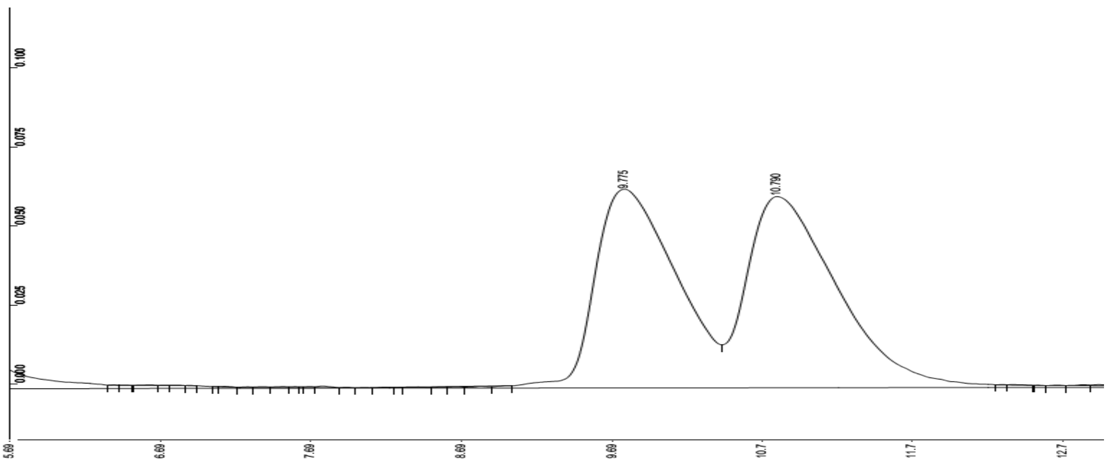
R.Time	Area	Area%
8.285	**29545488**	**49.4394**
9.281	**30215528**	**50.5606**



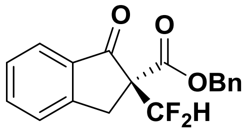
2c



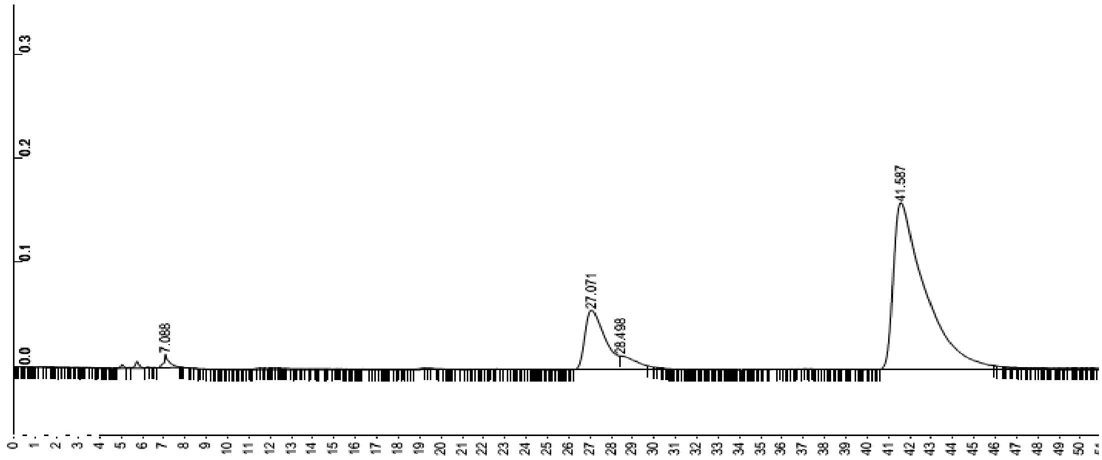
R.Time	Area	Area%
9.760	**4522232**	**14.5**
10.821	**26665575**	**85.5**



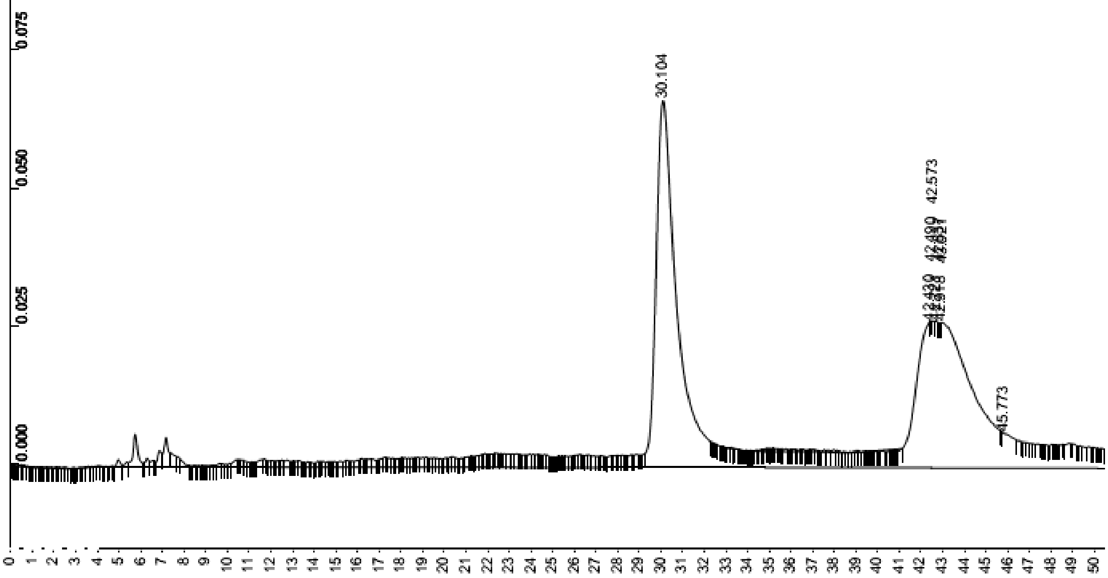
R.Time	Area	Area%
9.775	**23246980**	**49.8020**
10.790	**23436495**	**50.1980**



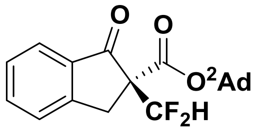
2d



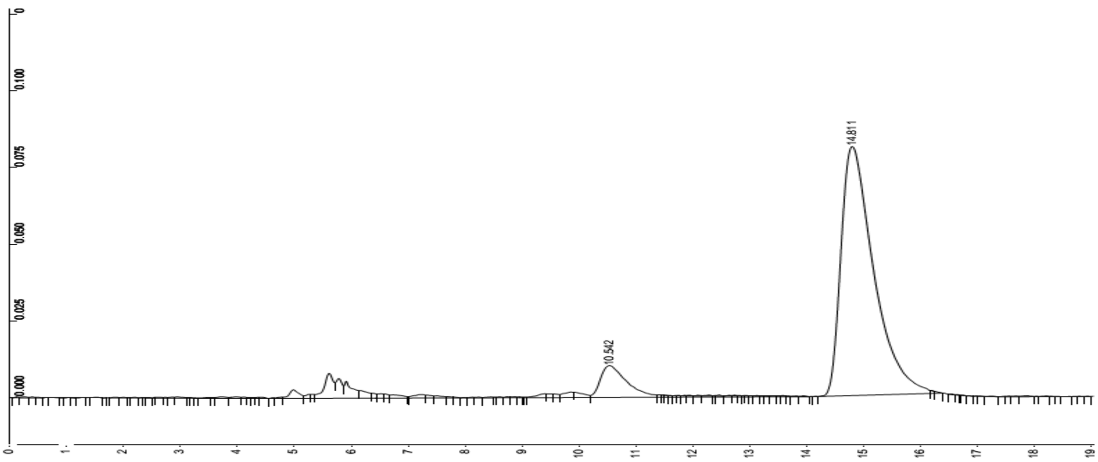
R.Time	Area	Area%
27.071	**37587524**	**16.5043**
41.587	**1901563003**	**83.4957**



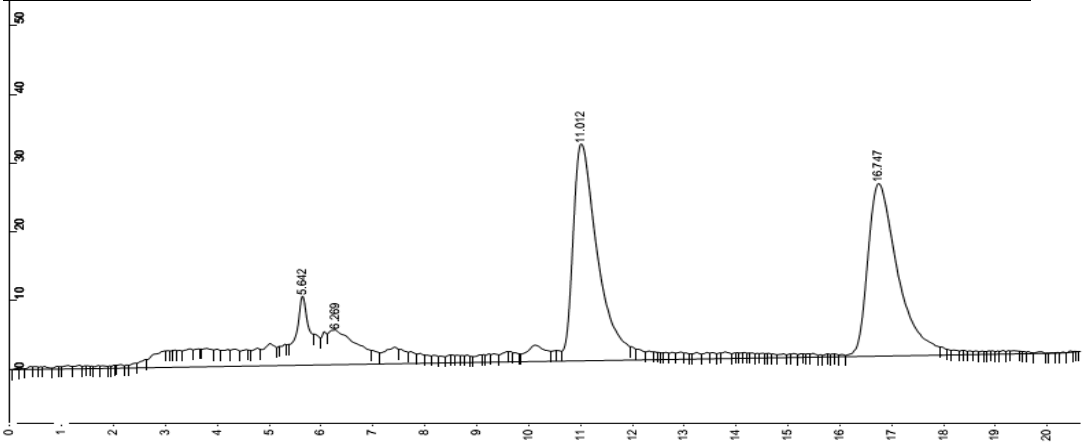
R.Time	Area	Area%
30.104	**60007588**	**48.0550**
42.573	**64865137**	**51.9450**



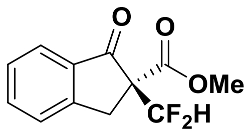
2e



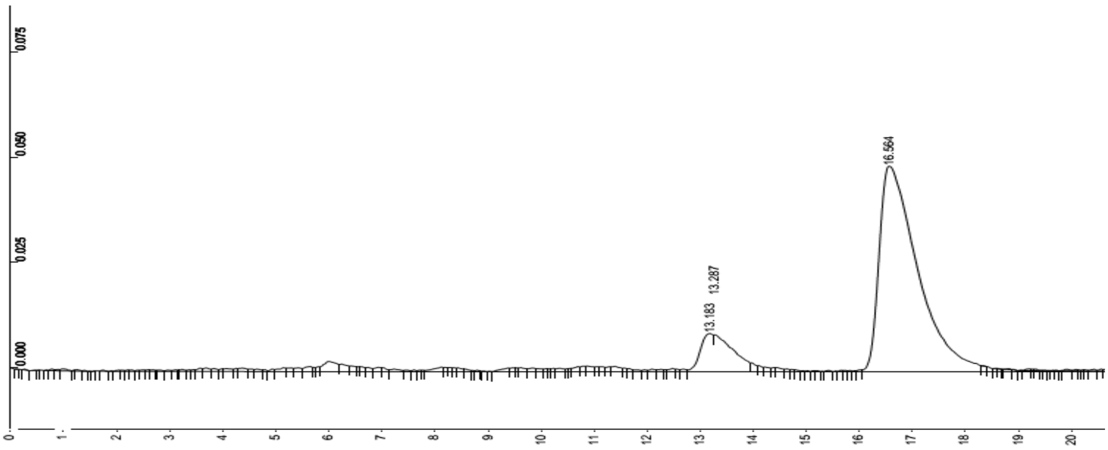
R.Time	Area	Area%
10.542	**3751933**	**8.5030**
14.811	**40388455**	**91.4970**



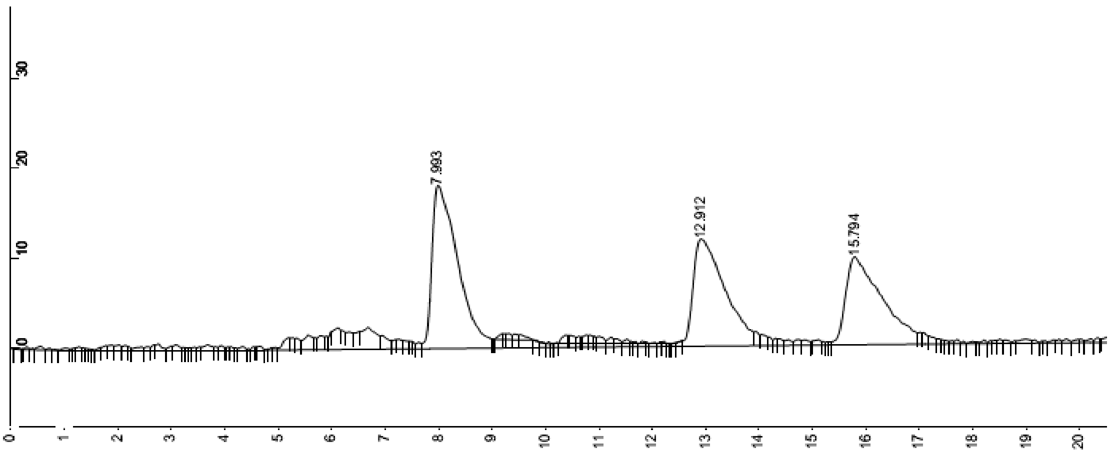
R.Time	Area	Area%
11.012	**10293782**	**49.8800**
16.747	**10343311**	**50.1200**



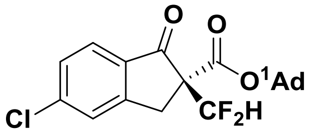
2f



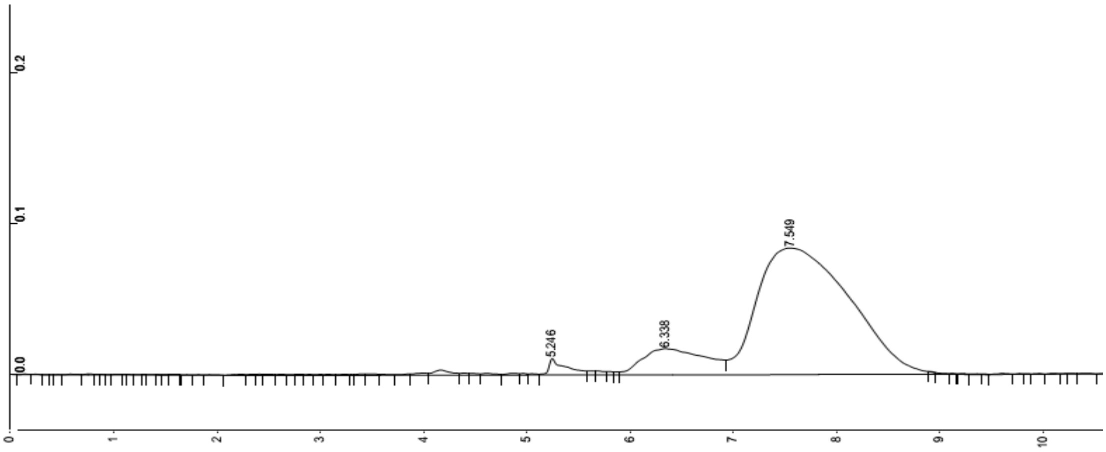
R.Time	Area	Area%
13.183	**2767981**	**10.0130**
16.564	**24874784**	**89.9830**



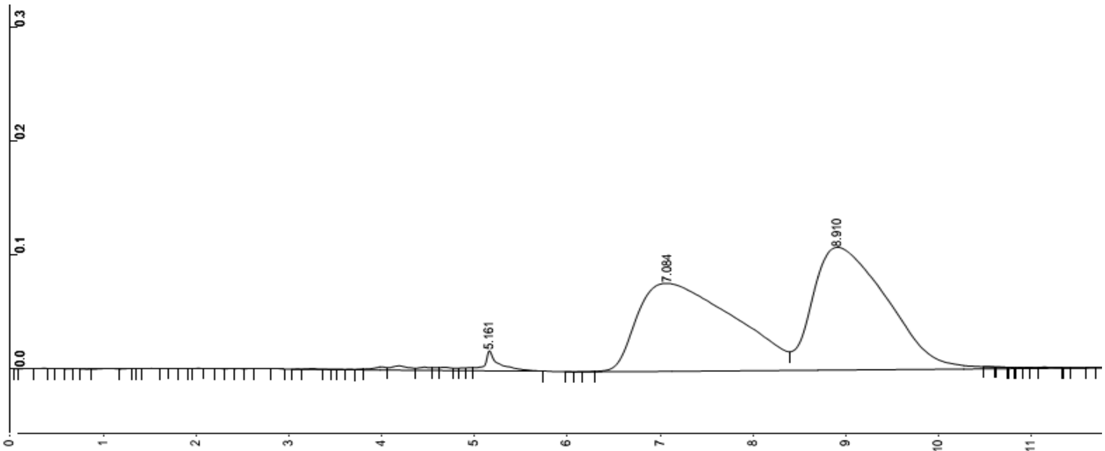
R.Time	Area	Area%
12.912	**4868761**	**49.4695**
15.794	**4973184**	**50.5305**



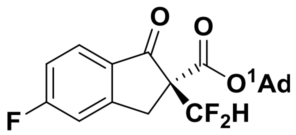
2g



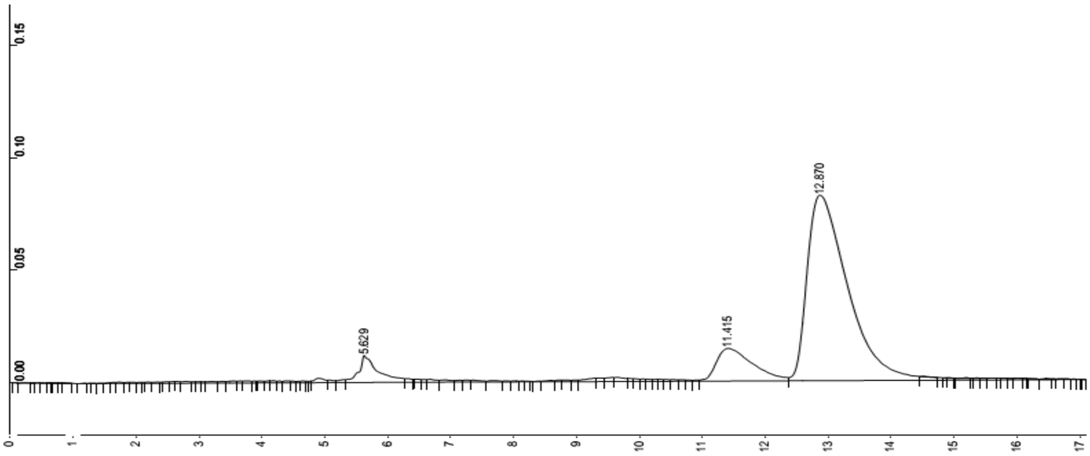
R.Time	Area	Area%
6.338	**7370727**	**12.9815**
7.549	**49407973**	**87.0185**



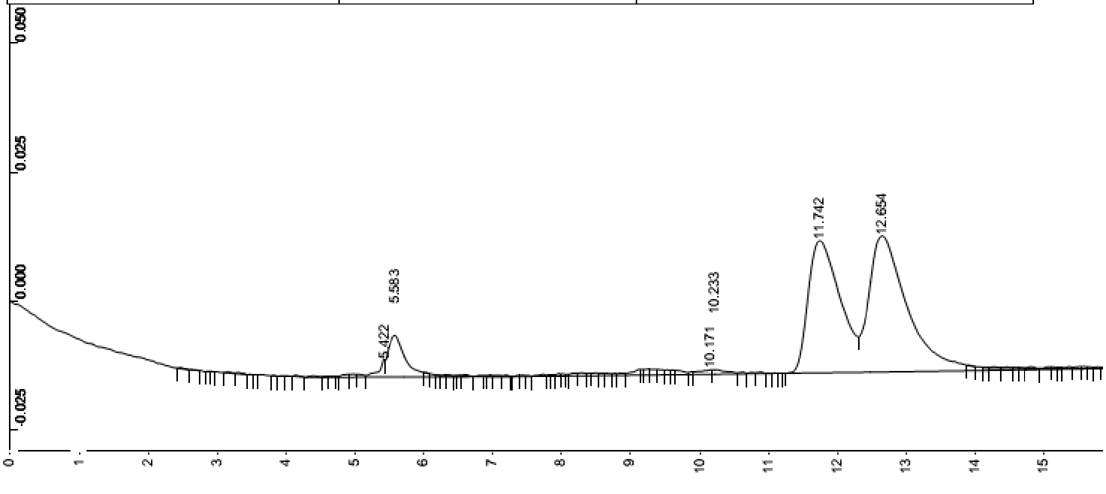
R.Time	Area	Area%
7.084	**56007124**	**48.3482**
8.910	**59834053**	**51.6518**



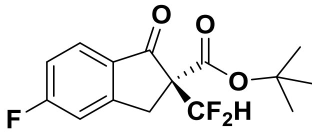
2h



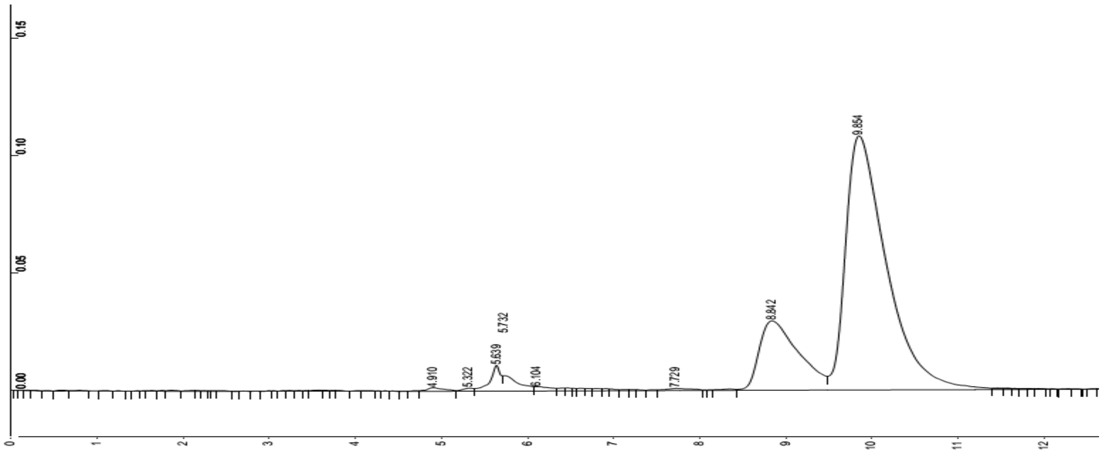
R.Time	Area	Area%
11.415	**5795442**	**10.9630**
12.870	**47068208**	**89.0370**



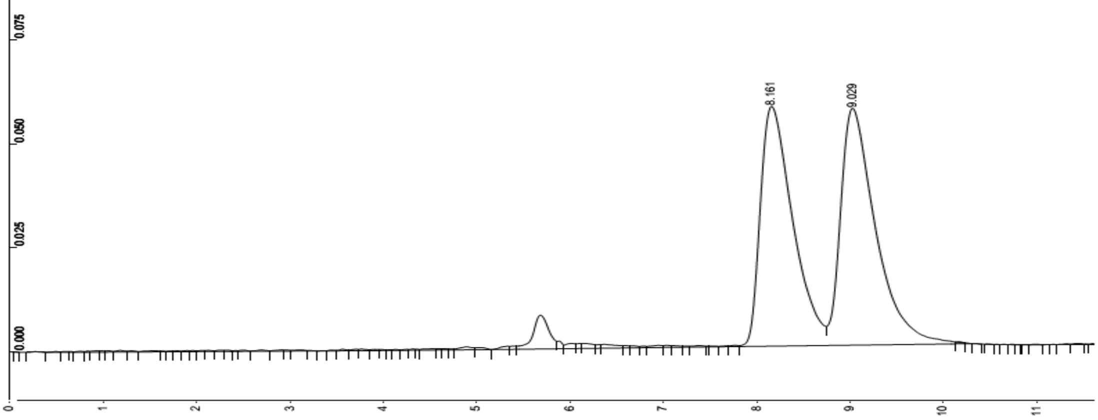
R.Time	Area	Area%
11.742	**8173717**	**49.5360**
12.664	**8326842**	**50.4640**



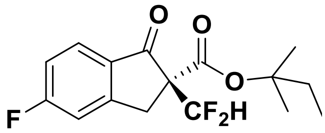
2i



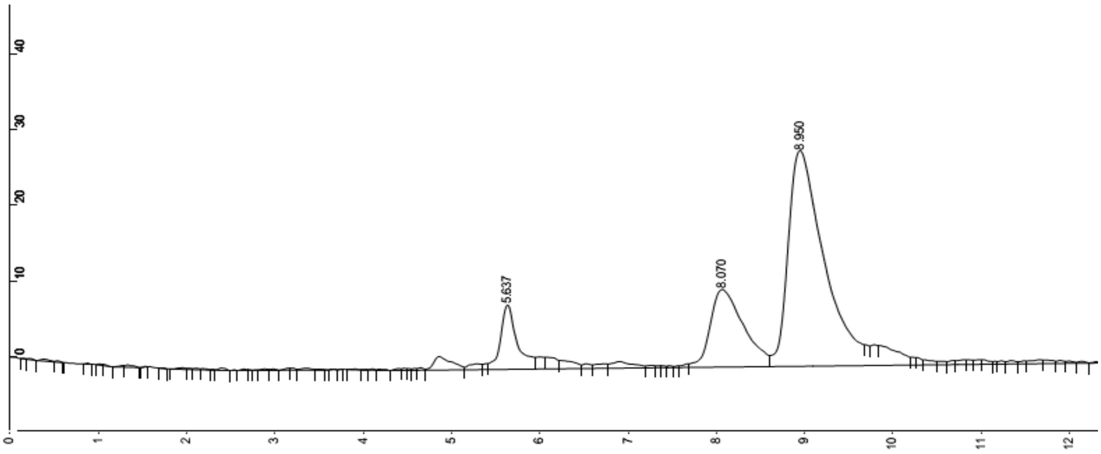
R.Time	Area	Area%
8.842	**2123787**	**18.4700**
9.854	**9374789**	**81.5300**



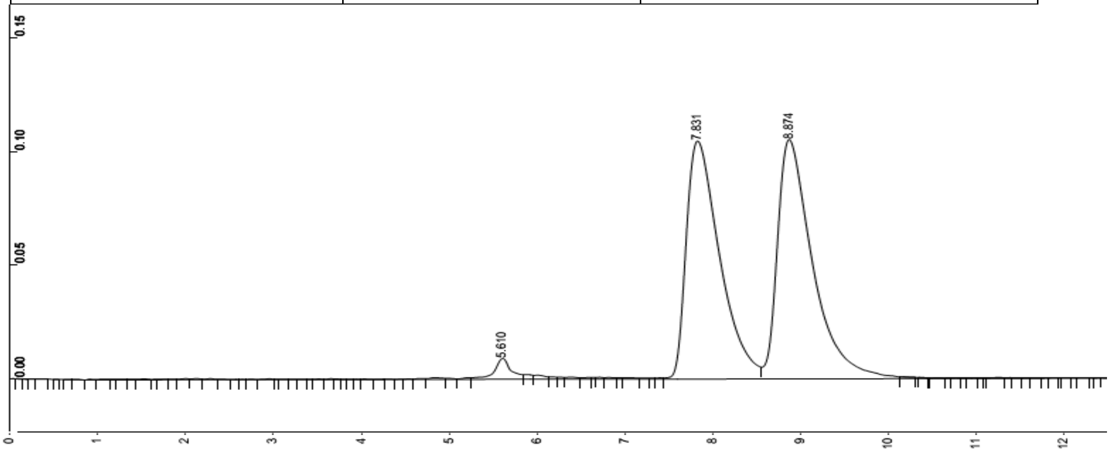
R.Time	Area	Area%
8.161	**13884401**	**48.2541**
9.029	**14889106**	**51.7459**



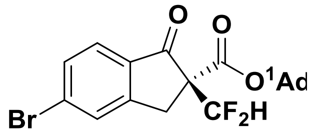
2j



R.Time	Area	Area%
8.070	**2675207**	**22.4970**
8.950	**9215830**	**77.5030**



R.Time	Area	Area%
7.831	**27569514**	**50.1542**
8.874	**27399988**	**49.8458**



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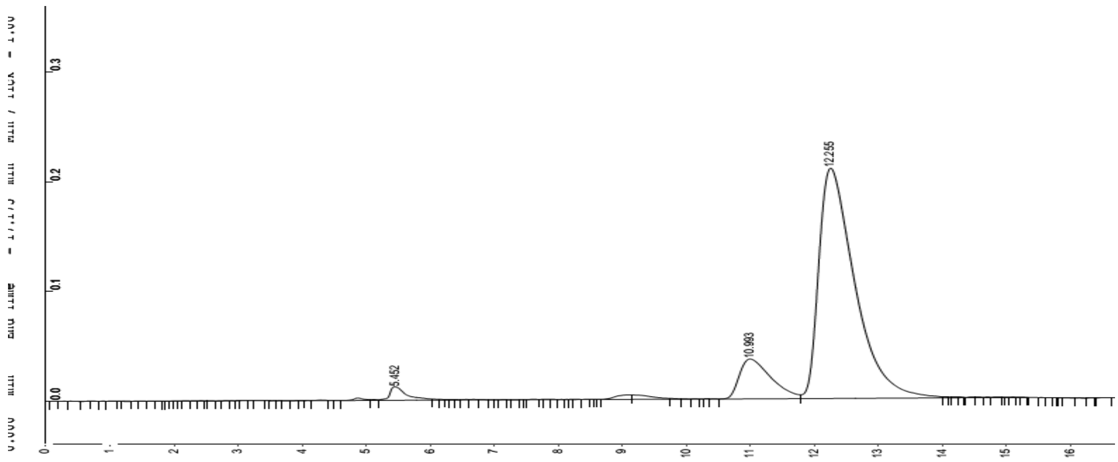
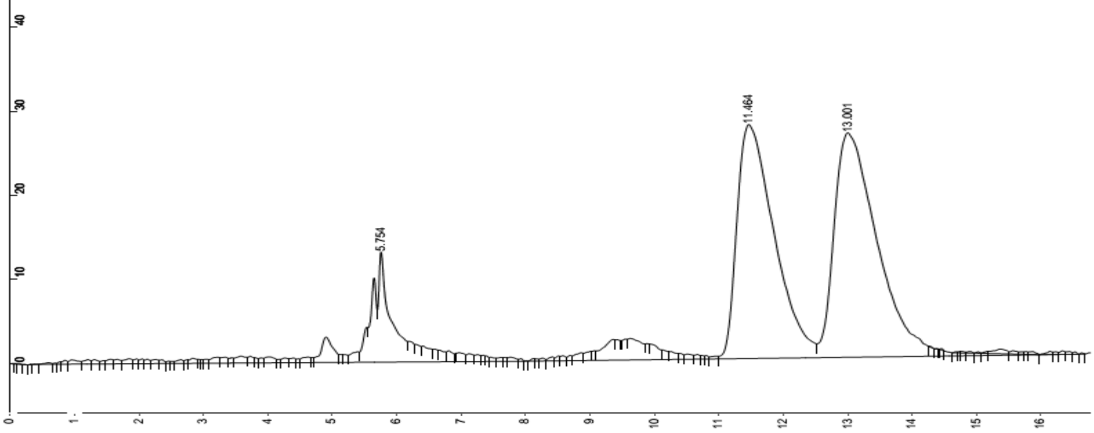
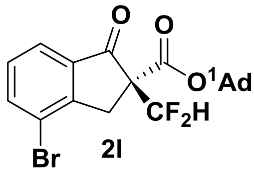


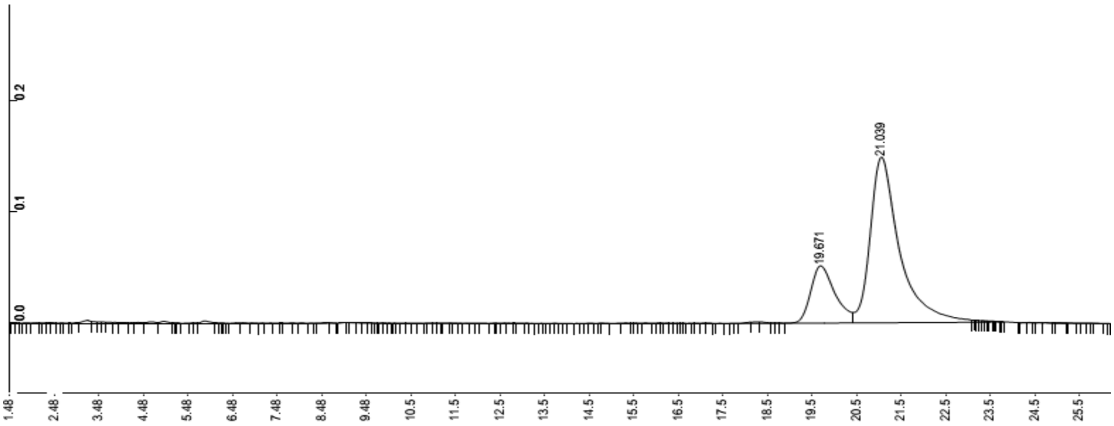
R.Time	Area	Area%
10.993	**12457557**	**10.9180**
12.225	**101643532**	**89.0820**



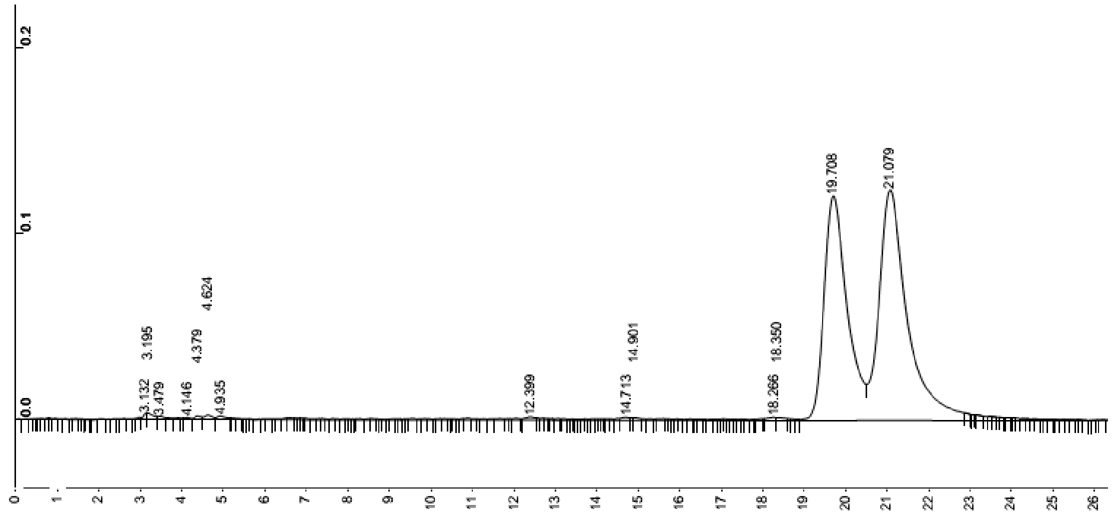
R.Time	Area	Area%
11.464	**11138592**	**49.0050**
13.001	**11848280**	**50.9950**



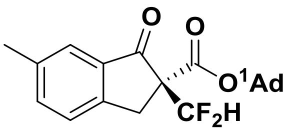
2l



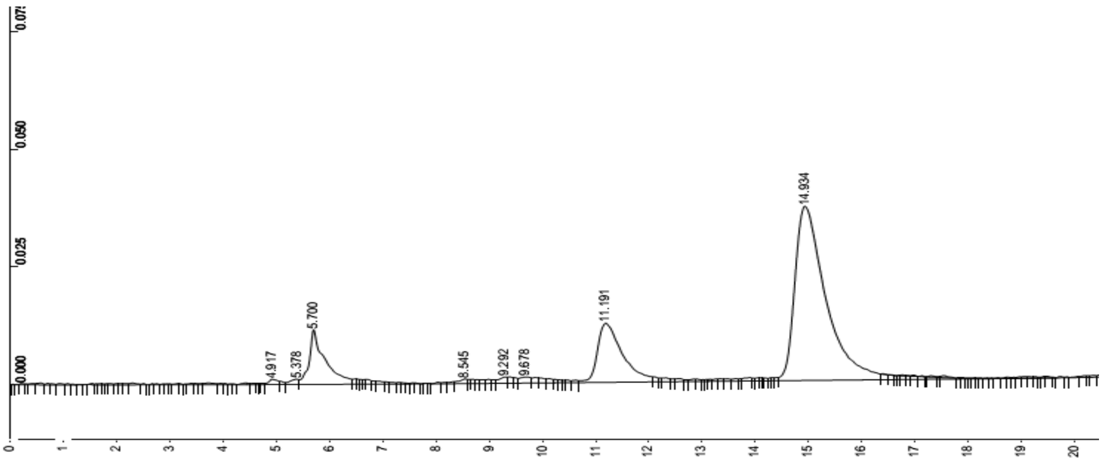
R.Time	Area	Area%
19.671	**15587770**	**18.4970**
21.039	**68684112**	**81.5030**



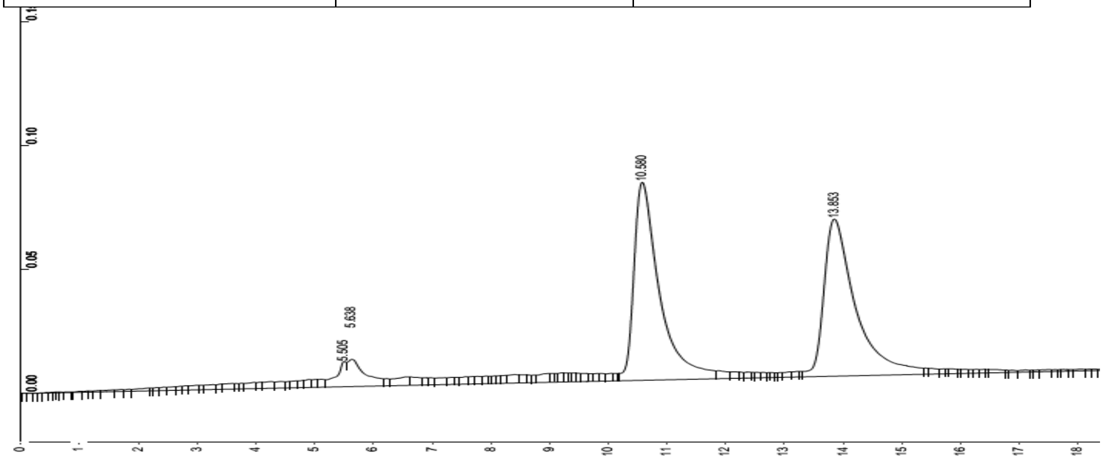
R.Time	Area	Area%
19.708	**46621080**	**48.4320**
21.079	**49639811**	**51.5680**



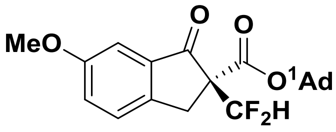
2m



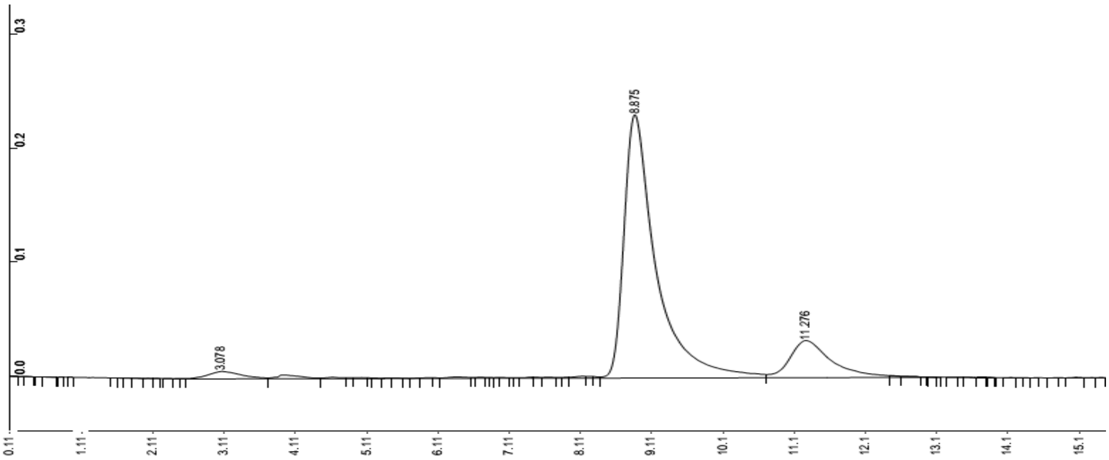
R.Time	Area	Area%
11.191	**4053561**	**18.4970**
14.934	**17861133**	**81.5030**



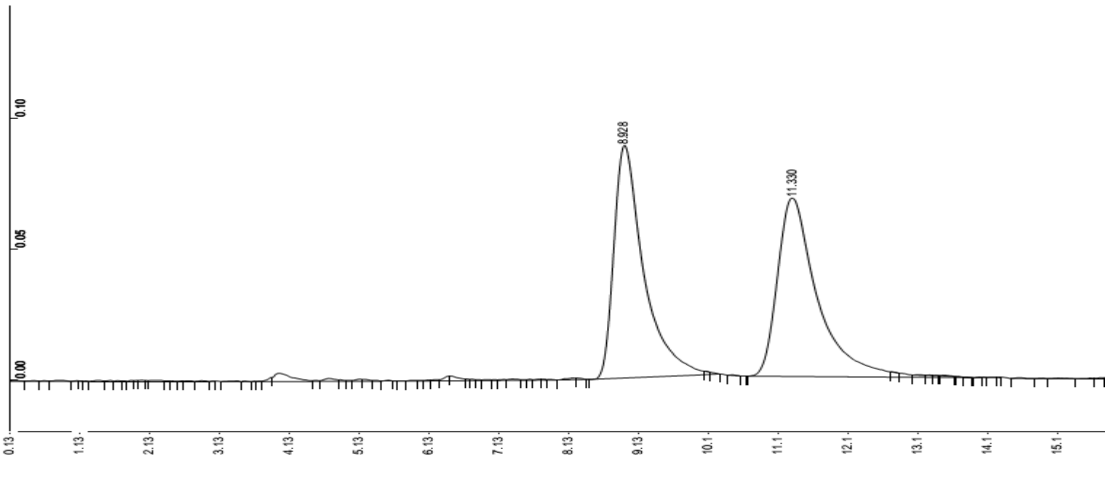
R.Time	Area	Area%
10.580	**24099084**	**50.6655**
13.853	**23465992**	**49.3345**



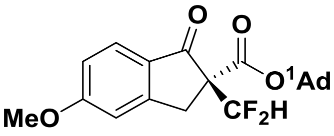
2n



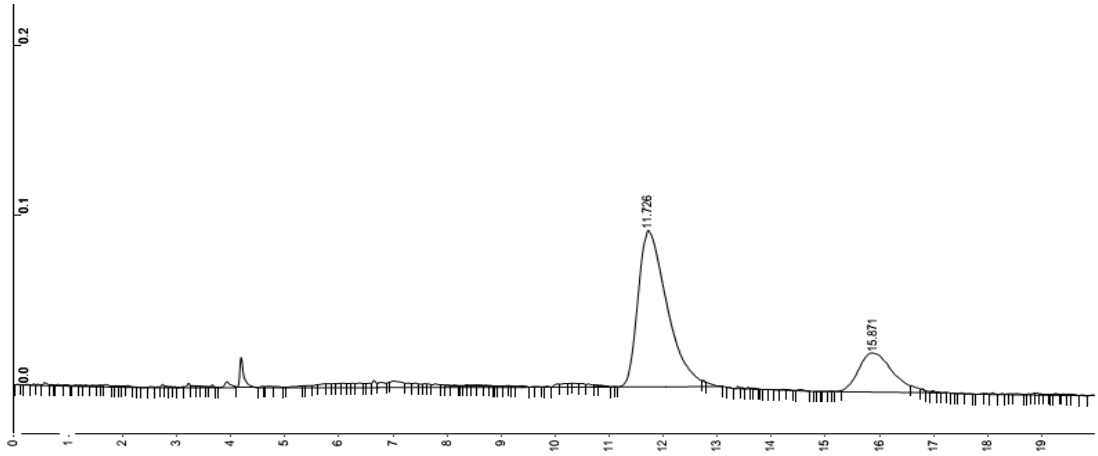
R.Time	Area	Area%
8.875	**72017816**	**86.5145**
11.276	**2901457**	**13.4855**



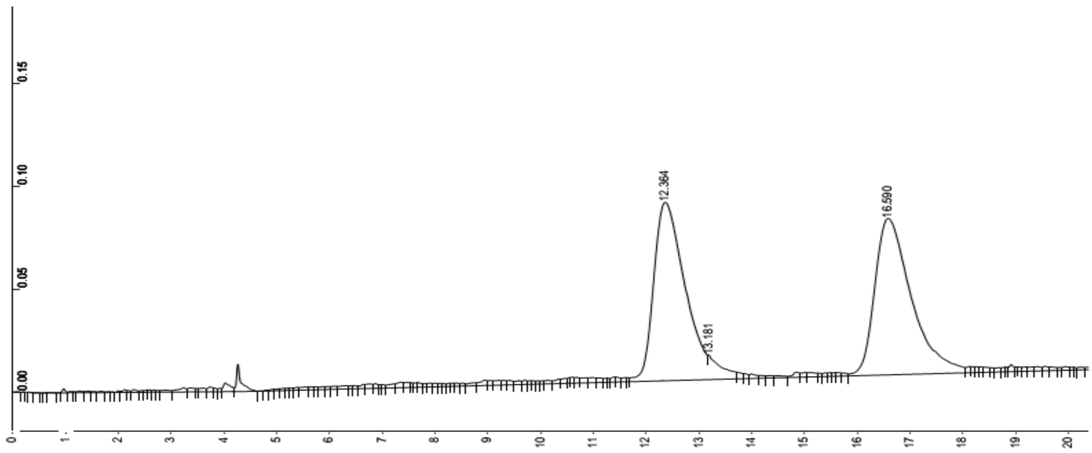
R.Time	Area	Area%
8.928	**26371764**	**49.2052**
11.330	**27223720**	**50.7948**



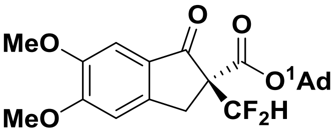
2o



R.Time	Area	Area%
11.726	**34553488**	**81.5340**
15.871	**7825750**	**18.4660**



R.Time	Area	Area%
12.364	**35083132**	**49.5391**
16.590	**35741678**	**50.4690**



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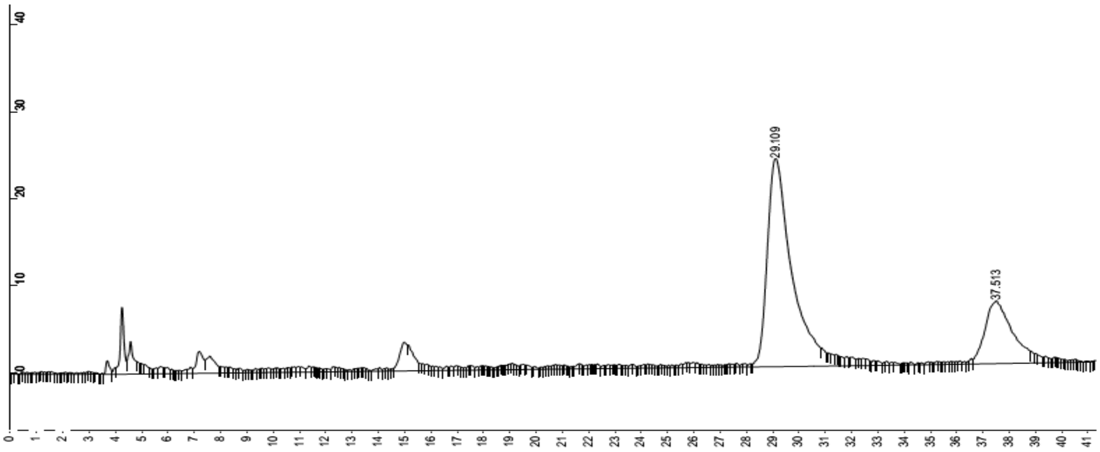
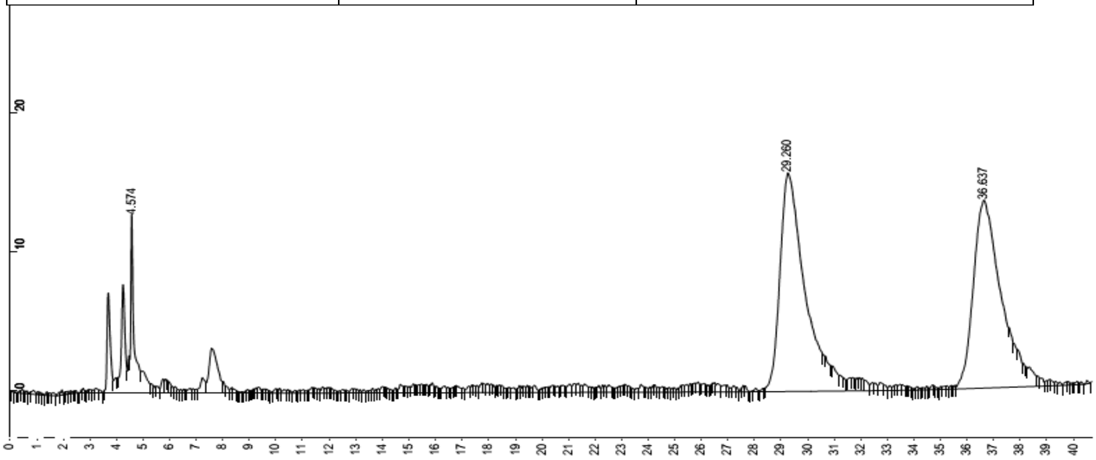
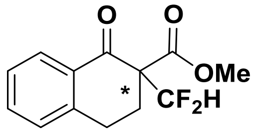


R.Time	Area	Area%
29.109	**15066944**	**78.9550**
37.513	**4016007**	**21.0450**



R.Time	Area	Area%
29.260	**9602190**	**49.9027**
36.637	**9639634**	**50.0973**



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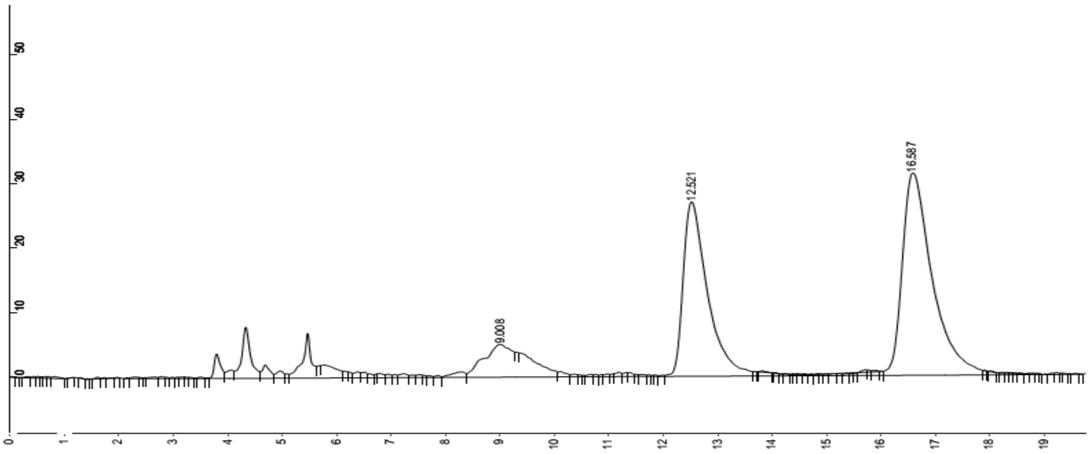
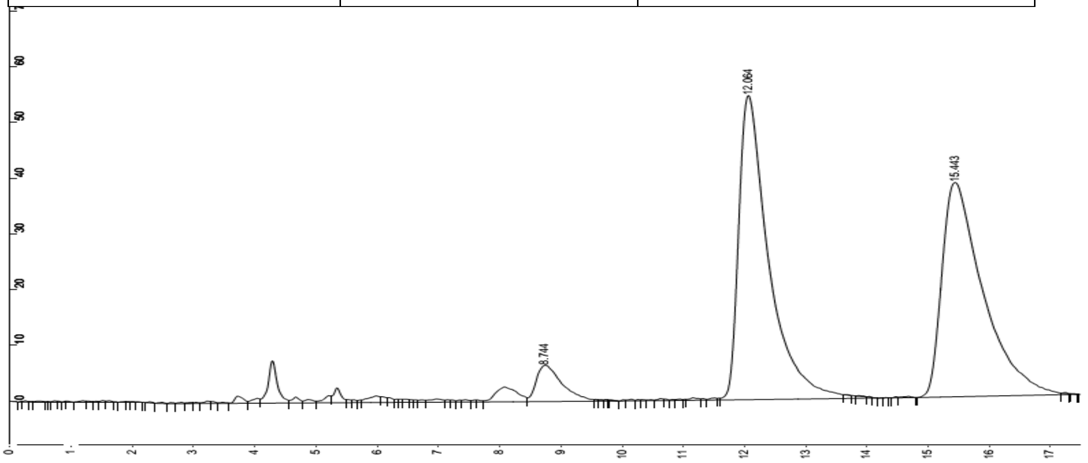
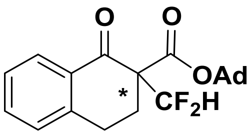


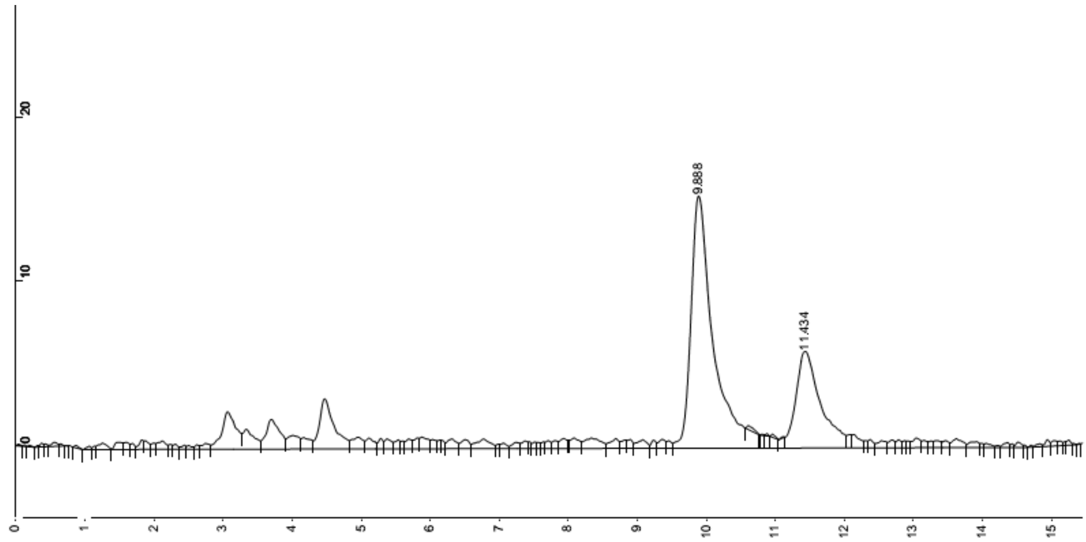
R.Time	Area	Area%
12.521	**8872778**	**40.4638**
16.587	**130549153**	**59.5362**



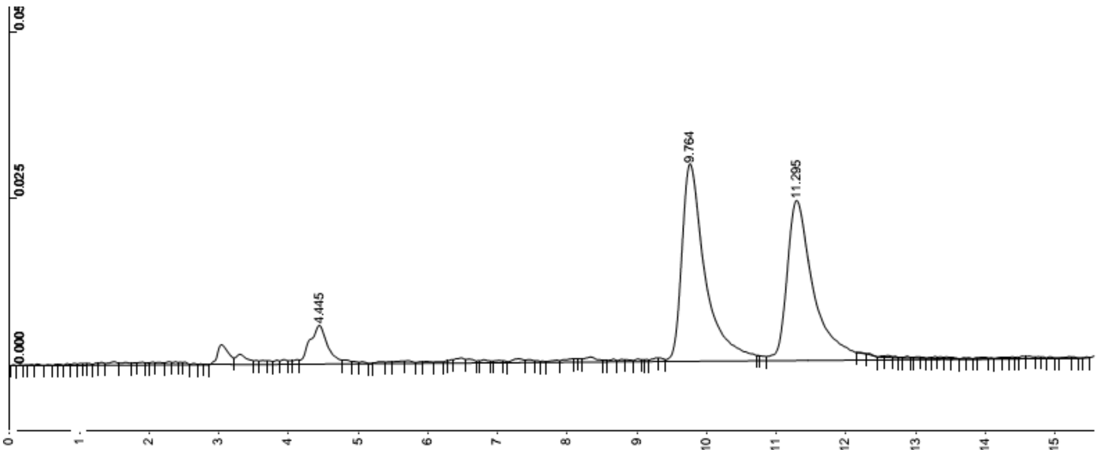
R.Time	Area	Area%
12.064	**18567074**	**49.3390**
15.443	**19064564**	**50.6610**



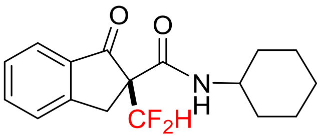
2r



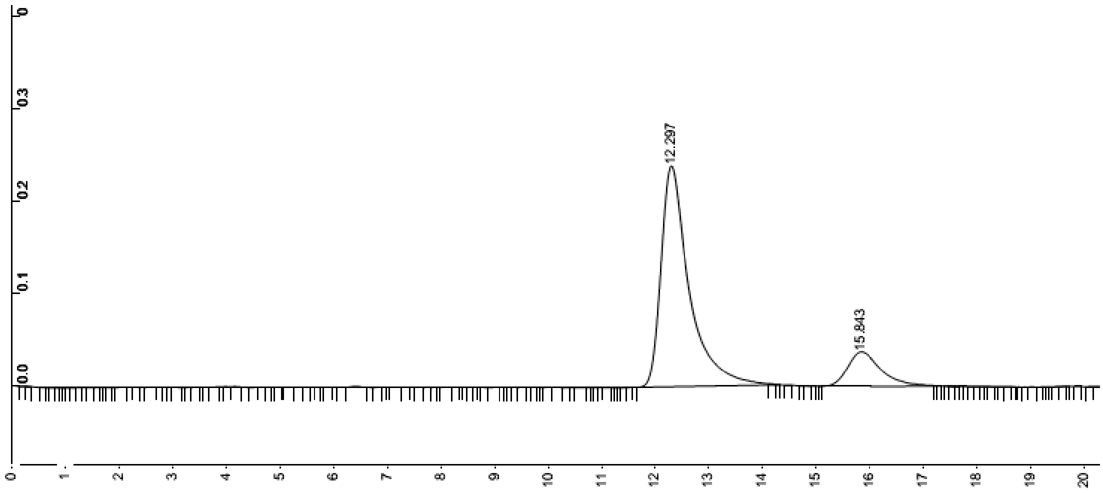
R.Time	Area	Area%
9.888	**3594220**	**73.2851**
11.434	**1310215**	**26.7149**



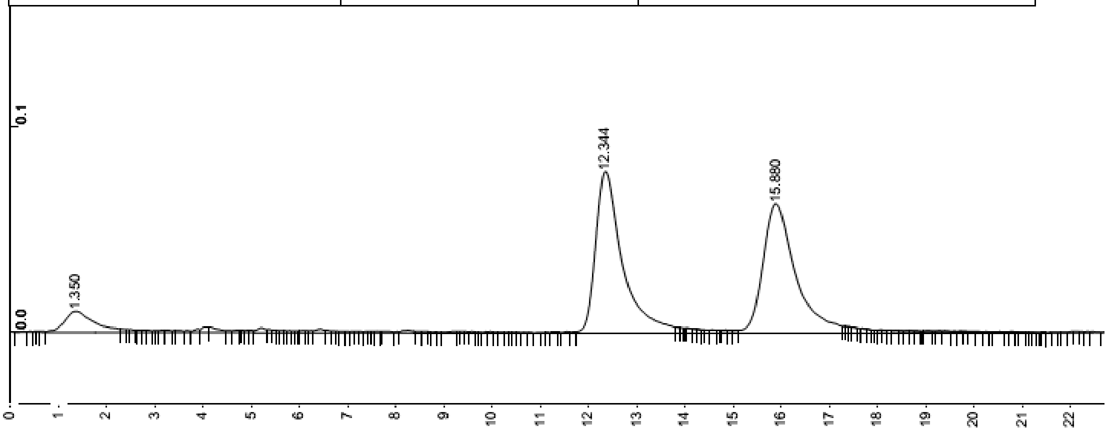
R.Time	Area	Area%
9.764	**6917868**	**50.7367**
11.295	**6712840**	**49.2633**



5f



R.Time	Area	Area%
12.297	**87857488**	**89.9150**
15.843	**9854226**	**10.0850**



R.Time	Area	Area%
12.344	**31520598**	**50.7528**
15.880	**30585528**	**49.2472**