Asymmetric Organocatalytic α-selective Vinylogous Michael Addition/isomerization for the Synthesis of Rauhut–Currier Type Products

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General Information

Unless otherwise noted, all reactions were carried out under argon atmosphere. TLC was performed with silica gel GF254 precoated on glass plates and spots were visualized with UV. ^{1}H and ^{13}C spectra were recorded on a 400 MHz spectrometer (101 MHz for ^{13}C NMR). The following abbreviations were used to designate chemical shift, multiplicities: s = singlet, d = doublet, t = triplet, q = quartert, m = multiplet, br = broad. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Column chromatography was performed on silica gel (300-400 mesh). HPLC analysis was performed on Agilent HPLC 1100 or 1200 equipped with Daicel Chiralpak® AD-H, AS-H, or OD-H column. High resolution mass spectra for all the new compounds were done by an LTQ-Orbitrap instrument (ESI) (Thermo Fisher Scientific, USA). Dry THF and Et_2O were prepared based on the textbook "PURIFICATION OF LABORATORY CHEMICALS, FIFTH EDITION". Organocatalyst **A**, allylmagnesium bromide (1.0 M solution in diethyl ether J&K Seal), and vinylmagnesium bromide (1.0 M solution in THF J&K Seal) were purchased from J&K. Organocatalysts **C**, **D**, **E**, and **F** were purchased from Daicel Chiral Technologies (China) Co., LTD. Nitroalkenes **2a**–**2l**, and **2q** were purchased from Sigma-Aldrich or TCI. β-alkylnitroalkenes **2m**–**2p**. Dimethyl oxalate, diethyl oxalate, and Hoveyda-Grubbs II were purchased from the Energy Chemical. Other reagents and solvents were obtained from Tianjin Kemiou Chemical Reagent Co., Ltd. and directly used without further purification. The racemic products **3** were prepared under the catalysis of racemic organocatalyst **F**, which was obtained through the mixture of equal amount of (*R,R*)-**F** and (*S,S*)-**F** isomers.

The Procedure for Synthesis of Vinylogous α-Keto Ester 1

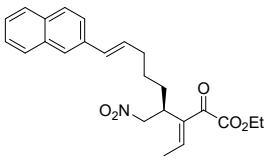
A solution of diethyl oxalate (4.38 g, 30 mmol) in anhydrous THF/Et_2O (1:1, 120 mL) under an argon atmosphere was cooled to −80 °C. Allylmagnesium bromide (30 mL of 1 M solution in diethyl ether) was added dropwise for 30 min, and the reaction was stirred for a further 30 min at the same temperature. A further small amount of allylmagnesium bromide (10 mL) was added, and the reaction was stirred for a further 10 min. The reaction was then warmed to −60 °C, and quenched by addition of 1 M H_2SO_4 (50 mL). The product was extracted into diethyl ether (3 x 50 mL), and the combined extracts were washed with brine (2 x 50 mL), dried ($MgSO_4$), and distilled under reduced pressure to give the desired product as yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.1, 10.1, 6.8 Hz, 1H), 5.28 – 5.20 (m, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.61 (d, *J* = 6.8 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.97, 160.89, 128.35, 120.41, 62.64, 43.74, 14.06; HRMS (ESI) m/z calcd for $C_7H_{10}O_3$, $[M+H]^+$ 143.0708, found 143.0705.

The Procedure for the Preparation of Rauhut-Currier Type Products

To a flame over-dried test-tube were added nitroalkene **2** (0.4 mmol), squaramide organocatalyst **F** (1.0 mol %, 0.004 mmol), and toluene (2.0 mL). The reaction mixture was stirred at -10 °C for 15 min, then vinylogous α-keto ester **1** (0.8 mmol, ~115 μL) was added in one partition by using a pipettor. The reaction mixture was stirred at the same temperature until the full conversion of nitroalkene **2** (monitored by TLC analysis). After the completion of the reaction, the reaction was directly purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 as the eluent) to afford the pure product for NMR and HPLC analysis.

The Procedure for the Transformation of 3p

(1) To a solution of **3p** (0.4 mmol, 120 mg, 95% ee) and 2-vinylnaphthalene (1.2 mmol, 186 mg) in DCM (30 mL) was added Zhan catalyst-1B (5.0 mol %, 0.02 mmol, 16 mg) at room temperature under the protection of argon. The resulting mixture was stirred at reflux temperature. After 2 h, the mixture was filtered through Celite, concentrated under reduced pressure, and purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1 as the eluent).



8

Waxy solid, 106 mg, 65% isolated yield based on **3p**.

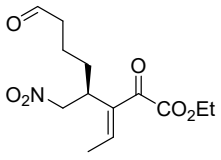
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 3H), 7.68 (s, 1H), 7.58 – 7.56 (m, 1H), 7.48 – 7.41 (m, 2H), 6.96 (q, *J* = 7.0 Hz, 1H), 6.54 (d, *J* = 15.8 Hz, 1H), 6.32 – 6.25 (m, 1H), 4.84 (dd, *J* = 12.6, 9.0 Hz, 1H), 4.61 (dd, *J* = 12.6, 5.8 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.63 – 3.55 (m, 1H), 2.27 (q, *J* = 7.0 Hz, 2H), 2.05 (d, *J* = 7.1 Hz, 3H), 1.91 – 1.84 (m, 1H), 1.73 – 1.65 (m, 1H), 1.55 – 1.41 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.07, 164.14, 152.17, 136.17, 135.08, 133.78, 132.85, 130.83, 130.23, 128.20, 127.94, 127.73, 126.28, 125.67, 125.60, 123.60, 77.60, 62.37, 36.86, 32.86, 29.57, 27.28, 15.53, 14.15.

HPLC analysis using Daicel CHIRALPAK OD-H column (*n*-Hexane/*i*PrOH = 85/15, 1.0 mL/min, $\lambda = 254$ nm, t_{major} = 27.9 min, t_{minor} = 35.0 min, 97% ee, $[\alpha]_D^{20}$ = 16.5 (c = 0.8, in EtOAc))

HRMS (ESI) m/z calcd for $C_{24}H_{27}NO_5$, $[M+H]^+$ 410.1967, found 410.1966.

(2) To a solution of **3p** (0.8 mmol, 120 mg) in DCM-H_2O (1:1, 8.0 mL) were added ruthenium (III) chloride (40 mol %, 0.32 mmol, 66.4 mg) and $NaIO_4$ (1.5 eq, 1.20 mmol, 256 mg) at 25 °C. The solution was stirred for 3 h at the same temperature until the reaction was completed. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution (10.0 mL). The solution was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered through Celite, and concentrated in vacuo to give the desired crude product. The desired product was obtained by silica gel column chromatography (PE/EA = 5/1 to 2/1 as the eluent).

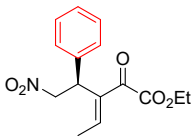


7

Light yellow oil, 94 mg, 41% isolated yield based on **3p**.

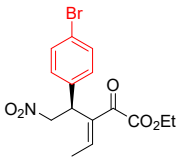
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 6.95 (q, *J* = 7.1 Hz, 1H), 4.77 (dd, *J* = 12.7, 8.9 Hz, 1H), 4.59 (dd, *J* = 12.7, 6.0 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.59 – 3.52 (m, 1H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.04 (d, *J* = 7.1 Hz, 3H), 1.85 – 1.75 (m, 1H), 1.66 – 1.51 (m, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.39, 189.02, 164.01, 152.56, 135.73, 77.39, 62.41, 43.46, 36.78, 29.38, 19.85, 15.54, 14.11.
HRMS (ESI) m/z calcd for $C_{13}H_{19}NO_6$, $[M+Na]^+$ 308.1110, found 308.1111.
$[\alpha]_D^{20}$ = 24.86 (c = 0.7, in EtOAc))

Compound Characterization Data



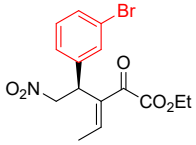
3a

Light yellow liquid, 89.7 mg, 77% isolated yield based on **2a**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 5H), 6.99 (q, *J* = 7.0 Hz, 1H), 5.23 – 5.10 (m, 2H), 4.87 (t, *J* = 7.6 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.12 (d, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.77, 164.00, 151.90, 137.30, 136.91, 129.08, 127.77, 127.67, 76.78, 62.45, 41.24, 15.63, 14.12.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 97/3, 0.5 mL/min, λ = 220 nm, t_{major} = 35.2 min, t_{minor} = 36.7 min, 97% ee, $[\alpha]_D^{20}$ = 16.7 (c = 0.8, in EtOAc))
HRMS (ESI) m/z calcd for $C_{15}H_{17}NO_5$, $[M+H]^+$ 292.1185, found 292.1181.



3b

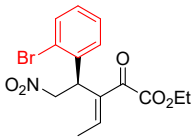
White solid, 118.5 mg, 80% isolated yield based on **2b**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.00 (q, *J* = 7.1 Hz, 1H), 5.11 (d, *J* = 7.6 Hz, 2H), 4.81 (t, *J* = 7.6 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.12 (d, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.61, 163.79, 152.11, 136.54, 136.34, 132.18, 129.42, 121.81, 76.47, 62.56, 40.71, 15.69, 14.11.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 97/3, 0.5 mL/min, λ = 220 nm, t_{major} = 47.9 min, t_{minor} = 45.7 min, 97% ee, $[\alpha]_D^{20}$ = 19.0 (c = 1.1, in EtOAc))
HRMS (ESI) m/z calcd for $C_{15}H_{16}BrNO_5$, $[M+H]^+$ 370.0290, found 370.0292.



3c

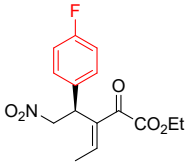
Light yellow oil, 114.0 mg, 77% isolated yield based on **2c**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.38 (m, 2H), 7.22 – 7.16 (m, 2H), 7.03 (q, *J* = 7.1 Hz, 1H), 5.16 – 5.07 (m, 2H), 4.83 (t, *J* = 7.5 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.13 (d, *J* = 7.5 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.49, 163.76, 152.30, 139.51, 136.36, 131.00, 130.81, 130.60, 126.31, 123.04, 76.37, 62.57, 40.76, 15.74, 14.11.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH =

97/3, 0.5 mL/min, λ = 220 nm, t_{major} = 37.9 min, t_{minor} = 34.4 min, 98% ee, $[\alpha]_D^{20}$ = 19.1 (c = 1.3, in EtOAc))
HRMS (ESI) m/z calcd for $C_{15}H_{16}BrNO_5$, $[M+H]^+$ 370.0290, found 370.0289.



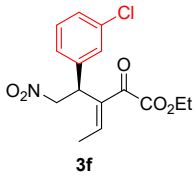
3d

Light yellow oil, 103.7 mg, 70% isolated yield based on **2d**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 7.00 (q, *J* = 7.0 Hz, 1H), 5.30 – 5.15 (m, H), 4.90 (dd, *J* = 13.0, 5.7 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.08 (d, *J* = 7.0 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 189.18, 163.86, 153.23, 135.89, 135.21, 133.48, 130.00, 129.55, 128.17, 124.33, 75.36, 62.50, 41.43, 16.26, 14.12.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 97/3, 0.5 mL/min, λ = 220 nm, t_{major} = 27.7 min, t_{minor} = 28.5 min, 97% ee, $[\alpha]_D^{20}$ = 19.5 (c = 1.0, in EtOAc))
HRMS (ESI) m/z calcd for $C_{15}H_{16}BrNO_5$, $[M+H]^+$ 370.0290, found 370.0279.



3e

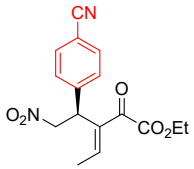
Light yellow oil, 85.4 mg, 69% isolated yield based on **2e**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 2H), 7.01 – 6.96 (m, 3H), 5.13 – 5.07 (m, 2H), 4.83 (t, *J* = 7.5 Hz, 1H), 4.31 (q, 7.5 Hz, 2H), 2.11 (d, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.76, 163.90, 162.14 ($^1J_{C\text{-}F}$ = 247 Hz), 151.90, 136.82, 133.11 ($^4J_{C\text{-}F}$ = 3.1 Hz), 129.42 ($^3J_{C\text{-}F}$ = 8.2 Hz), 115.94 ($^2J_{C\text{-}F}$ = 21.6 Hz), 76.77, 62.49, 40.61, 15.57, 14.07.
HPLC analysis using Daicel CHIRALPAK OD-H column (*n*-Hexane/*i*PrOH = 97/3, 0.8 mL/min, λ = 220 nm, t_{major} = 49.8 min, t_{minor} = 41.6 min, 97% ee, $[\alpha]_D^{20}$ = 18.9 (c = 1.1, in EtOAc))
HRMS (ESI) m/z calcd for $C_{15}H_{16}FNO_5$, $[M+H]^+$ 310.1091, found 310.1090.



3f

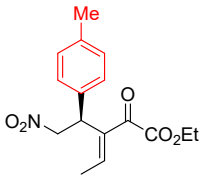
Light yellow oil, 106.8 mg, 82% isolated yield based on **2f**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 3H), 7.17 – 7.16 (m, 1H), 7.03 (q, *J* = 7.1 Hz, 1H), 5.13 (d, *J* = 7.7 Hz, 2H), 4.84 (t, *J* = 7.7 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.13 (d, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.49, 163.76, 152.23, 139.24, 136.40, 134.87, 130.32, 128.07, 127.93, 125.83, 76.40, 62.56, 40.81, 15.72, 14.11.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 97/3, 0.5 mL/min, λ = 220 nm, t_{major} = 36.3 min, t_{minor} = 32.6 min, 98% ee, $[\alpha]_D^{20}$ = 11.9 (c = 0.8, in EtOAc))
HRMS (ESI) m/z calcd for $C_{15}H_{16}ClNO_5$, $[M+H]^+$ 326.0795, found 326.0793.



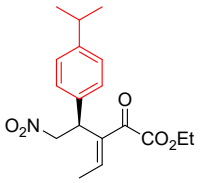
3g

Light yellow oil, 88.6 mg, 70% isolated yield based on **2g**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.04 (q, *J* = 7.1 Hz, 1H), 5.20 – 5.03 (m, 2H), 4.90 (t, *J* = 7.5 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.12 (d, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.41, 163.61, 152.82, 142.69, 136.04, 132.75, 128.48, 118.41, 111.68, 75.93, 62.64, 40.87, 15.78, 14.05.
HPLC analysis using Daicel CHIRALPAK OD-H column (*n*-Hexane/*i*PrOH = 85/15, 1.0 mL/min, λ = 220 nm, t_{major} = 46.1 min, >99% ee, $[\alpha]_D^{20}$ = 11.7 (c = 0.7, in EtOAc))
HRMS (ESI) m/z calcd for $C_{16}H_{16}N_2O_5$, $[M+H]^+$ 317.1137, found 317.1136.



3h

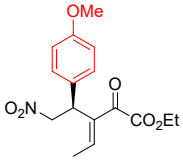
Light yellow oil, 98.0 mg, 80% isolated yield based on **2h**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (q, *J* = 8.2 Hz, 4H), 6.97 (q, *J* = 7.1 Hz, 1H), 5.21 – 5.07 (m, 2H), 4.83 (t, *J* = 7.6 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 2.11 (d, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.83, 164.04, 151.70, 137.51, 137.06, 134.27, 129.74, 127.55, 76.91, 62.41, 40.97, 21.09, 15.60, 14.12.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 97/3, 0.5 mL/min, λ = 220 nm, t_{major} = 31.3 min, t_{minor} = 32.3, 97% ee, $[\alpha]_D^{20}$ = 18.1 (c = 1.0, in EtOAc))
HRMS (ESI) m/z calcd for $C_{16}H_{19}NO_5$, $[M+H]^+$ 306.1341, found 306.1329.



3i

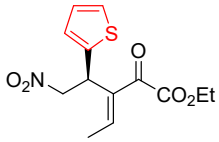
Light yellow oil, 92.0 mg, 69% isolated yield based on **2i**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 4H), 6.98 (q, *J* = 7.1 Hz, 1H), 5.23 – 5.06 (m, 2H), 4.84 (dd, *J* = 8.4, 6.9 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.87 (hept, *J* = 6.9 Hz, 1H), 2.11 (d, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.85, 164.07, 151.73, 148.36, 137.02, 134.55, 127.61, 127.10, 76.92, 62.38, 40.98, 33.75, 23.94, 15.58, 14.10.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 98/2, 0.4 mL/min, λ = 220 nm, t_{major} = 37.1 min, t_{minor} = 35.7, 98% ee, $[\alpha]_D^{20}$ = 11.0 (c = 0.5, in EtOAc))
HRMS (ESI) m/z calcd for $C_{18}H_{23}NO_5$, $[M+H]^+$ 334.1654, found 334.1650.



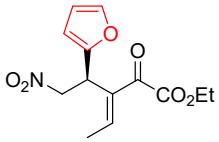
3j

Light yellow oil, 90.0 mg, 70% isolated yield based on **2j**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 2H), 6.95 (q, *J* = 7.0 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.19 – 5.05 (m, 2H), 4.80 (t, *J* = 7.6 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 2.10 (d, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.90, 164.04, 159.04, 151.55, 137.13, 129.26, 128.87, 114.40, 77.03, 62.42, 55.35, 40.71, 15.57, 14.12.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 90/10, 0.8 mL/min, λ = 220 nm, t_{major} = 20.2 min, >99% ee, $[\alpha]_D^{20}$ = 10.4 (c = 0.6, in EtOAc))
HRMS (ESI) m/z calcd for $C_{16}H_{19}NO_6$, $[M+H]^+$ 322.1291, found 322.1289.



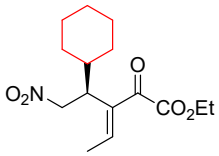
3k

Light yellow oil, 103.5 mg, 87% isolated yield based on **2k**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.18 (m, 1H), 7.01 (q, *J* = 7.1 Hz, 1H), 6.95 – 6.91 (m, 2H), 5.21 – 5.06 (m, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.13 (d, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.19, 163.74, 151.94, 139.38, 136.34, 127.17, 125.92, 125.20, 77.19, 62.51, 36.96, 15.49, 14.12.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 97/3, 0.5 mL/min, λ = 220 nm, t_{major} = 38.7 min, t_{minor} = 37.5 min, 98% ee, $[\alpha]_D^{20}$ = 10.5 (c = 0.6, in EtOAc))
HRMS (ESI) m/z calcd for $C_{13}H_{15}NO_5S$, $[M+H]^+$ 298.0749, found 298.0745.



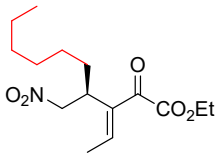
3l

Light yellow oil, 86.6 mg, 77% isolated yield based on **2l**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 1H), 7.05 (q, *J* = 7.1 Hz, 1H), 6.30 – 6.28 (m, 1H), 6.13 – 6.12 (m, 1H), 5.15 – 4.96 (m, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.09 (d, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 187.89, 163.84, 152.50, 149.96, 142.09, 134.40, 110.81, 107.15, 75.06, 62.49, 35.29, 15.51, 14.10.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 97/3, 0.5 mL/min, λ = 220 nm, t_{major} = 31.9 min, t_{minor} = 28.9 min, 94% ee, $[\alpha]_D^{20}$ = 19.0 (c = 1.2, in EtOAc))
HRMS (ESI) m/z calcd for $C_{13}H_{15}NO_6$, $[M+H]^+$ 282.0978, found 282.0977.



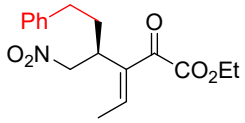
3m

Light yellow oil, 100.0 mg, 84% isolated yield based on **2m**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (q, *J* = 7.0 Hz, 1H), 4.85 – 4.66 (m, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.25 (td, *J* = 9.9, 4.9 Hz, 1H), 1.99 (d, *J* = 7.0 Hz, 3H), 1.86 – 1.75 (m, 3H), 1.69 – 1.56 (m, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.30 – 0.95 (m, 4H), 0.84 – 0.75 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 189.24, 164.28, 152.60, 136.14, 76.45, 62.30, 42.91, 37.16, 31.61, 31.44, 26.12, 26.05, 25.94, 15.58, 14.14.
HPLC analysis using Daicel CHIRALPAK OD-H column (*n*-Hexane/*i*PrOH = 98/2, 0.4 mL/min, λ = 220 nm, t_{major} = 25.4 min, t_{minor} = 27.1 min, >99% ee, $[\alpha]_D^{20}$ = 15.8 (c = 0.9, in EtOAc))
HRMS (ESI) m/z calcd for $C_{15}H_{23}NO_5$, $[M+H]^+$ 298.1654, found 298.1651.



3n

Light yellow oil, 72.1 mg, 60% isolated yield based on **2n**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (q, *J* = 7.0 Hz, 1H), 4.83 – 4.55 (m, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.56 – 3.48 (m, 1H), 2.01 (d, *J* = 7.0 Hz, 3H), 1.80 – 1.72 (m, 1H), 1.60 – 1.55 (m, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.24 (br, 8H), 0.86 (t, *J* = 6.6 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 189.09, 164.17, 152.02, 136.28, 77.65, 62.31, 36.92, 31.63, 29.93, 29.03, 27.39, 22.60, 15.46, 14.12, 14.10.
HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 97/3, 0.5 mL/min, λ = 220 nm, t_{major} = 12.7 min, t_{minor} = 13.3 min, 98% ee, $[\alpha]_D^{20}$ = 14.9 (c = 0.7, in EtOAc))
HRMS (ESI) m/z calcd for $C_{15}H_{26}NO_5$, $[M+H]^+$ 300.1811, found 300.1810.



3o

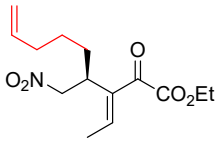
Light yellow oil, 112.4 mg, 88% isolated yield based on **2o**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 7.22 – 7.18 (m, 1H), 7.15 – 7.13 (m, 2H), 6.93 (q, *J* = 7.1 Hz, 1H), 4.85 – 4.57 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.58 – 3.50 (m, 1H), 2.68 – 2.61 (m, 1H), 2.55 – 2.47 (m, 1H), 2.19 – 2.09 (m, 1H), 2.03 – 1.94 (m, 1H), 1.83 (d, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.17, 164.16, 152.68, 140.41, 135.78, 128.66, 128.44, 126.39, 77.51, 62.41, 36.05, 33.23, 30.94, 15.35, 14.17.

HPLC analysis using Daicel CHIRALPAK AD-H column (*n*-Hexane/*i*PrOH = 97/3, 0.5 mL/min, $\lambda = 220$ nm, t_{major} = 24.8 min, t_{minor} = 23.4 min, 96% ee, $[\alpha]_D^{20}$ = 17.1 (c = 0.8, in EtOAc))

HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_5$, $[M+H]^+$ 320.1498, found 320.1490.



3p

Light yellow oil, 71.4 mg, 63% isolated yield based on **2p**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (q, *J* = 7.1 Hz, 1H), 5.72 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 – 4.93 (m, 2H), 4.82 – 4.76 (m, 1H), 4.59 – 4.55 (m, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.56 – 3.49 (m, 1H), 2.05 – 2.00 (m, 5H), 1.82 – 1.72 (m, 1H), 1.62 – 1.55 (m, 1H), 1.39 – 1.24 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.05, 164.12, 152.12, 137.91, 136.14, 115.24, 77.56, 62.32, 36.77, 33.37, 29.34, 26.65, 15.46, 14.11.

HPLC analysis using Daicel CHIRALPAK OD-H column (*n*-Hexane/*i*PrOH = 99/1, 0.4 mL/min, $\lambda = 220$ nm, t_{major} = 39.2 min, t_{minor} = 42.1 min, 95% ee, $[\alpha]_D^{20}$ = 16.1 (c = 1.0, in EtOAc))

HRMS (ESI) m/z calcd for $C_{14}H_{21}NO_5$, $[M+Na]^+$ 306.1317, found 306.1319.

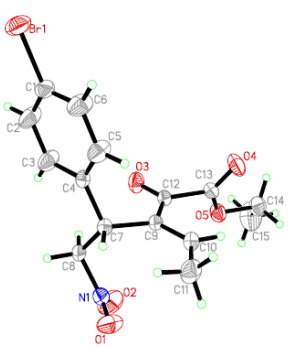
X-ray Crystal Structure of Compound 3b

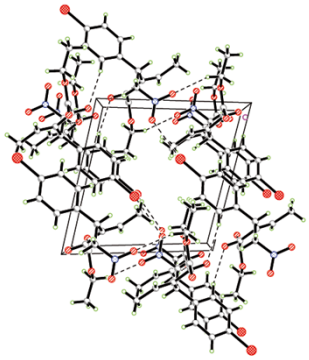
Crystal data for compound 3b

Molecular formular	C_{15} H_{16} Br N O_5
Fw	370.2
Crystal shape/color	Block/Colorless
Crystal size, mm	0.42×0.39×0.36
Crystal system	Triclinic
Space group	P-1
a(Å)	8.5887(8)
b(Å)	10.3821(10)
c(Å)	10.6032(8)
α(°)	96.304(7)
β(°)	112.149(8)
γ(°)	105.649(8)
V, Å3	819.19(13)
Z	2
T, K	298(2)
m(Mo*K*a), mm^{-1}	0.7107
ρ_{calcd}, g cm^{-3}	1.501
Reflections/parameters	3617/201
Restraints	0
Observed reflections (I ³ 2s(I))	2247
F(000)	376
T_{min}	0.57498
T_{max}	1.00000
Goodness of fit on F^2	1.063
R_1, ωr_2 ($I \geq 2\sigma(I)$)*	0.0529,0.1111
R_1, ωR_2 (all data)*	0.09994,0.1354
Largest peak and deepest hole (e $Å^{-3}$)	0.605,-0.747

Selected bond lengths (Å) and angles for 3b

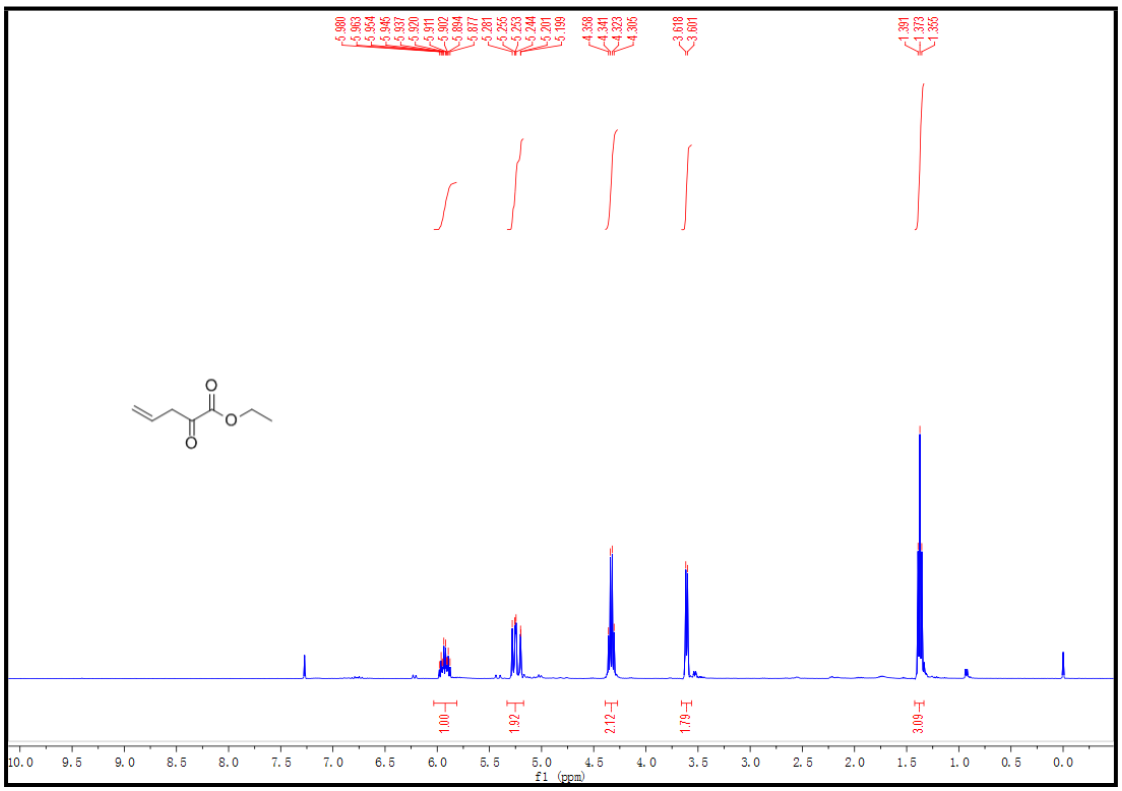
Br1-C1	1.893(4)
C1-C6	1.350(5)
C1-C2	1.361(6)
C2-C3	1.373(6)
C3-C4	1.371(5)
C4-C5	1.363(5)
C4-C7	1.528(5)
C5-C6	1.386(6)
C7-C9	1.523(4)
C7-C8	1.527(5)
C8-N1	1.490(5)
C9-C10	1.337(4)
C9-C12	1.461(5)
C10-C11	1.488(5)
C12-O3	1.212(4)
C12-C13	1.524(4)
C13-O4	1.196(4)
C13-O5	1.311(4)
C14-C15	1.454(7)
C14-O5	1.463(4)
N1-O2	1.204(5)
N1-O1	1.206(4)

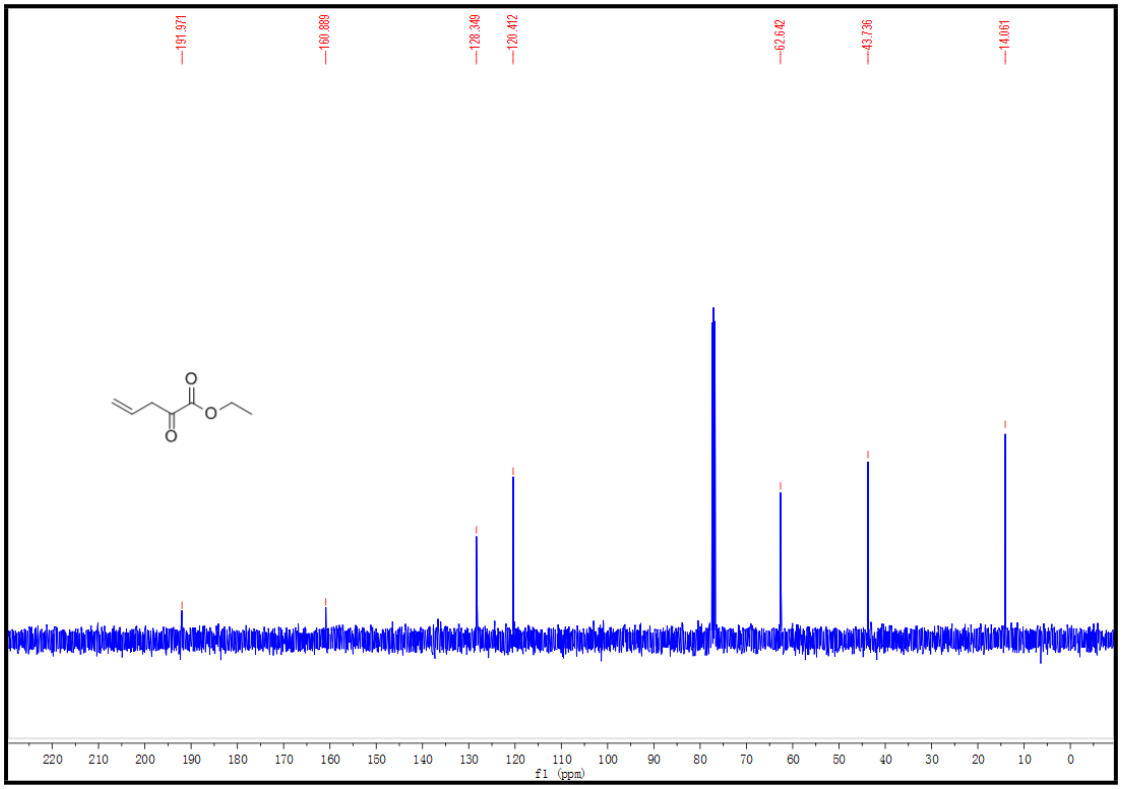


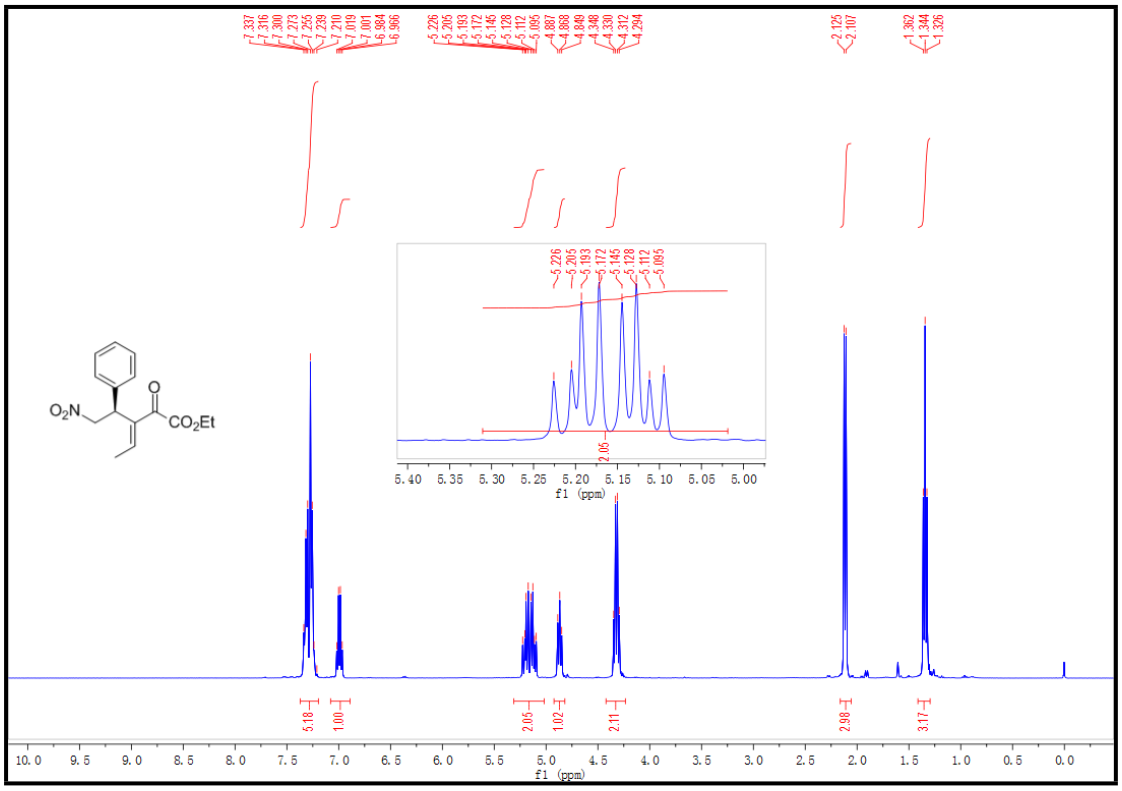


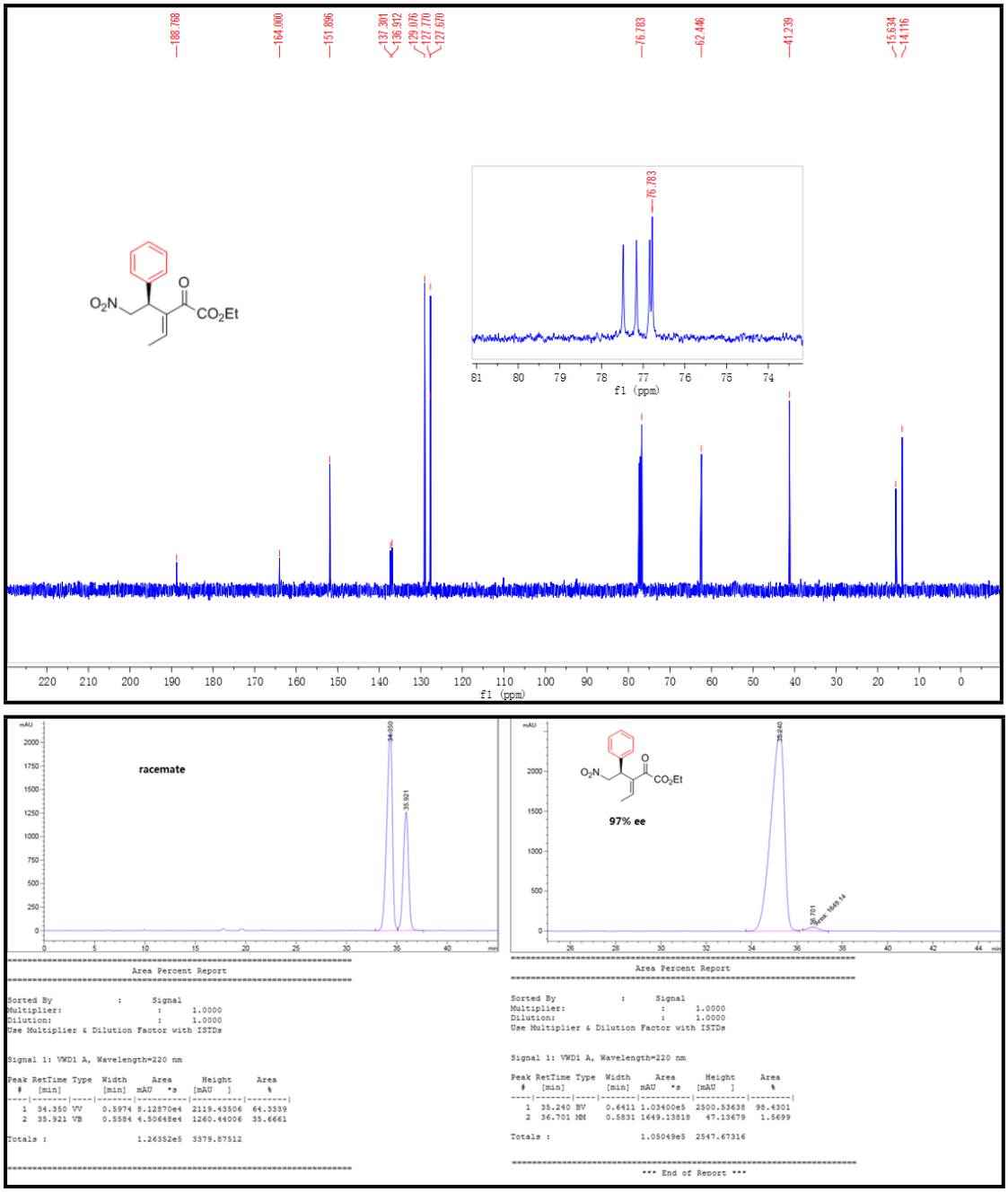
CCDC **1536616** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif

Copy of NMR Spectrum and HPLC Chromatograms

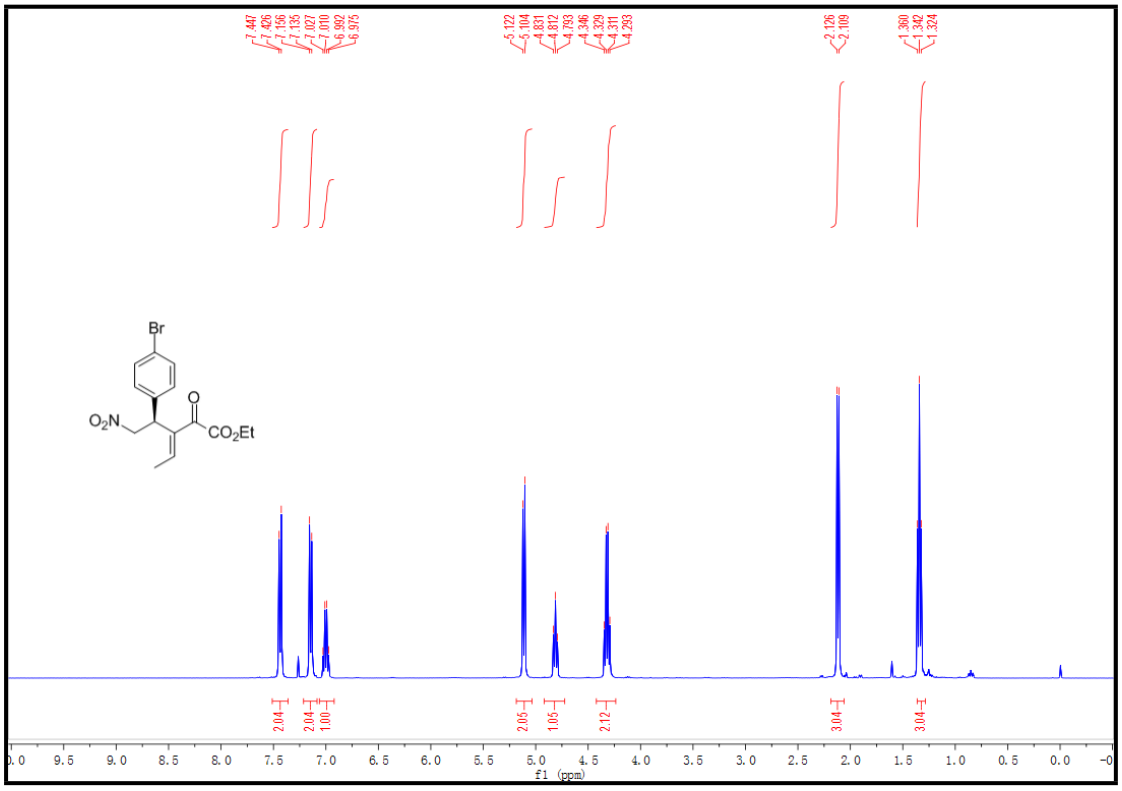


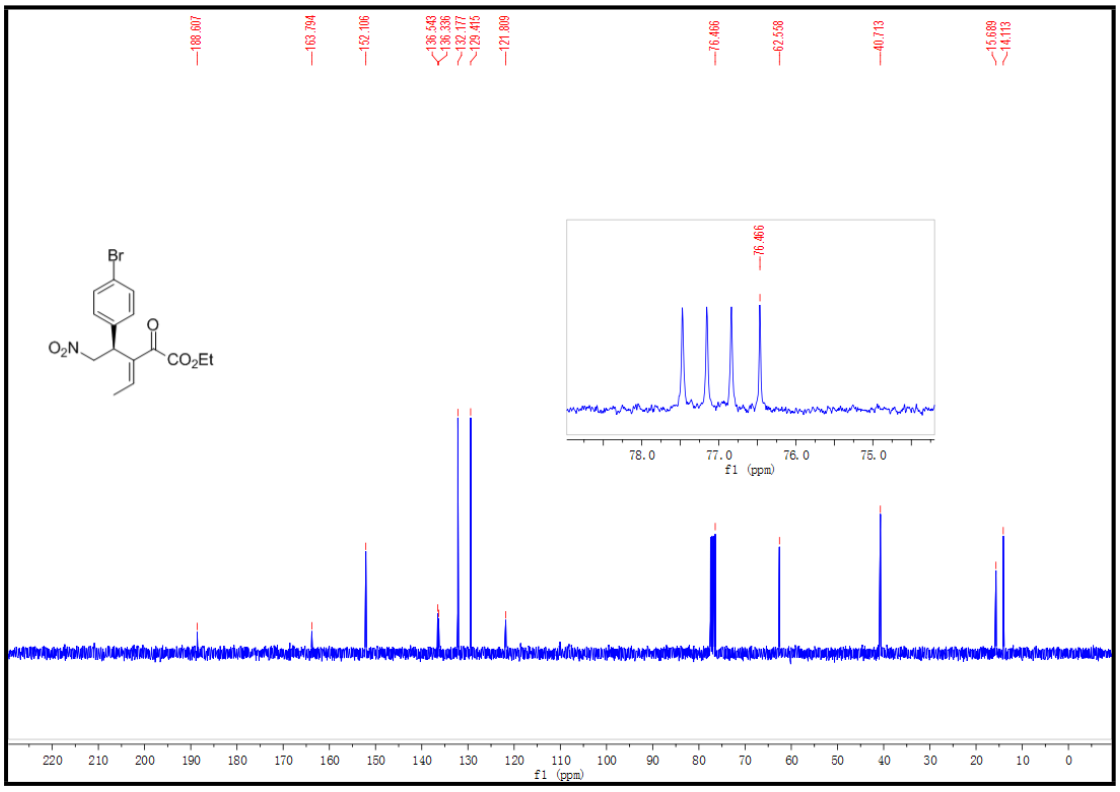

191.971
160.889
128.349
120.412
62.642
43.736
14.061
f1 (ppm)

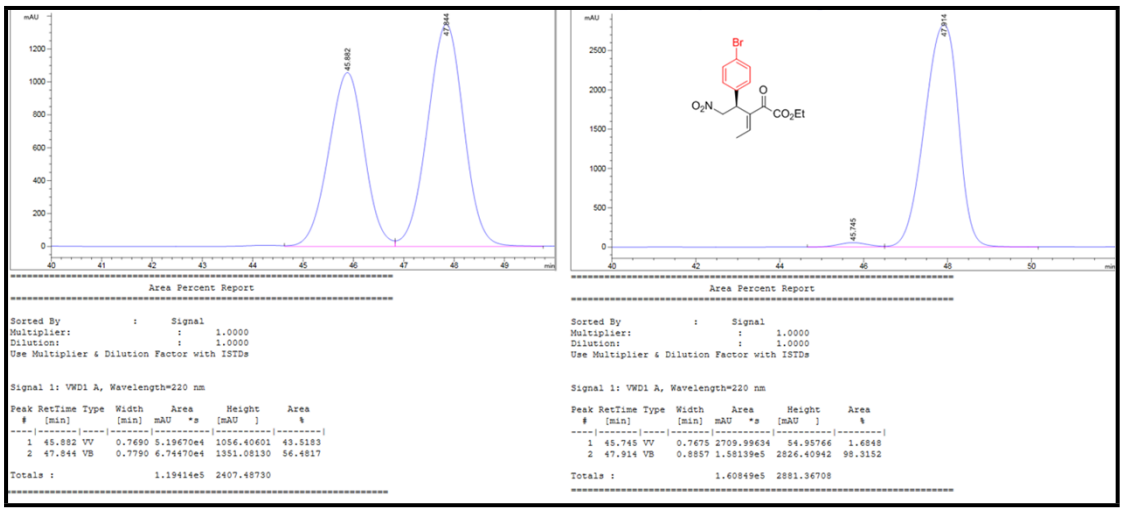

7.337
7.316
7.300
7.273
7.255
7.239
7.210
7.019
7.001
6.984
6.966
5.226
5.205
5.193
5.172
5.145
5.128
5.112
5.095
4.887
4.868
4.849
4.348
4.330
4.312
4.294
2.125
2.107
1.362
1.344
1.326
O2N
CO2Et
5.18
1.00
2.05
1.02
2.11
2.98
3.17
f1 (ppm)



Note: the racemic product was prepared under the catalysis of racemic organocatalyst **F**, which was obtained through the mixture the equial amount of (*S,S*)-**F** and (*R,R*)-**F** isomers.


7.447
7.426
7.156
7.135
7.027
7.010
6.992
6.975
5.122
5.104
4.831
4.812
4.793
4.346
4.329
4.311
4.293
2.126
2.109
1.360
1.342
1.324
Br
O2N
O
CO2Et
2.04
2.04
1.00
2.05
1.05
2.12
3.04
3.04
f1 (ppm)


188.807
163.794
152.106
136.543
136.336
132.177
129.415
121.809
76.466
62.558
40.713
15.689
14.113
Br
O2N
O
CO2Et
76.466
78.0
77.0
76.0
75.0
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

Peak	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	45.882	VV	0.7690	5.19670e4	1056.40601	43.5183
2	47.844	VB	0.7790	6.74470e4	1351.08130	56.4817

Totals : 1.19414e5 2407.48730

Area Percent Report

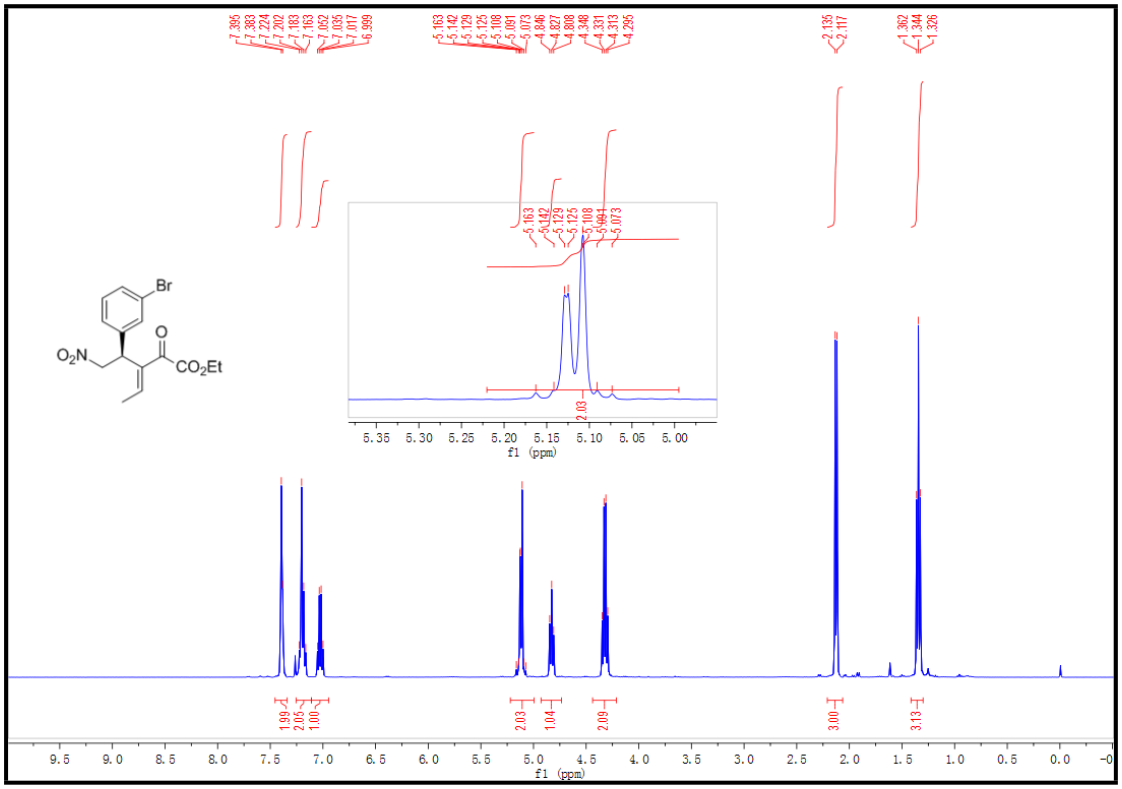
Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

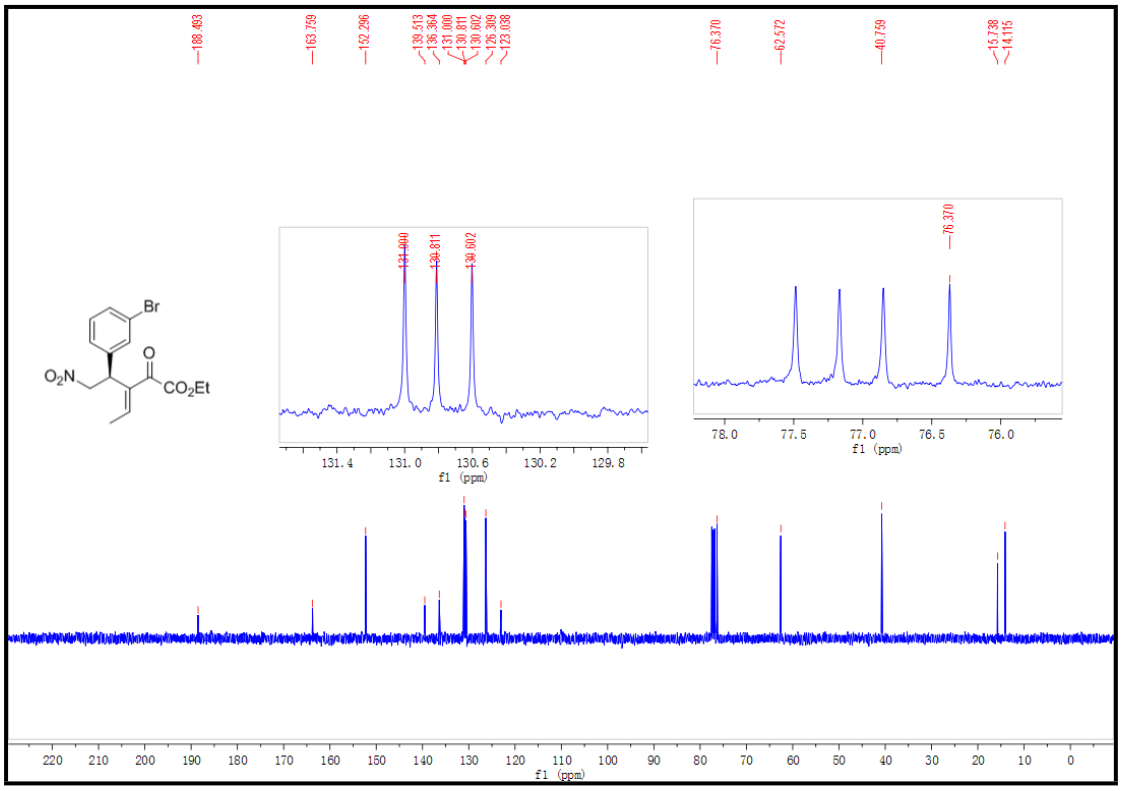
Signal 1: VWD1 A, Wavelength=220 nm

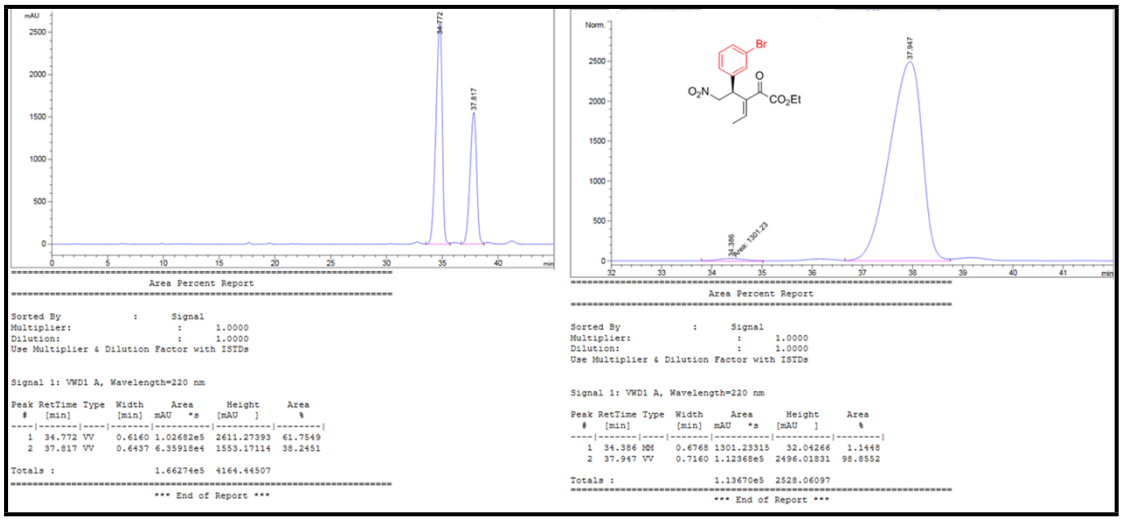
Peak	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	45.745	VV	0.7675	2709.99634	54.95766	1.6848
2	47.914	VB	0.8857	1.58139e5	2826.40942	98.3152

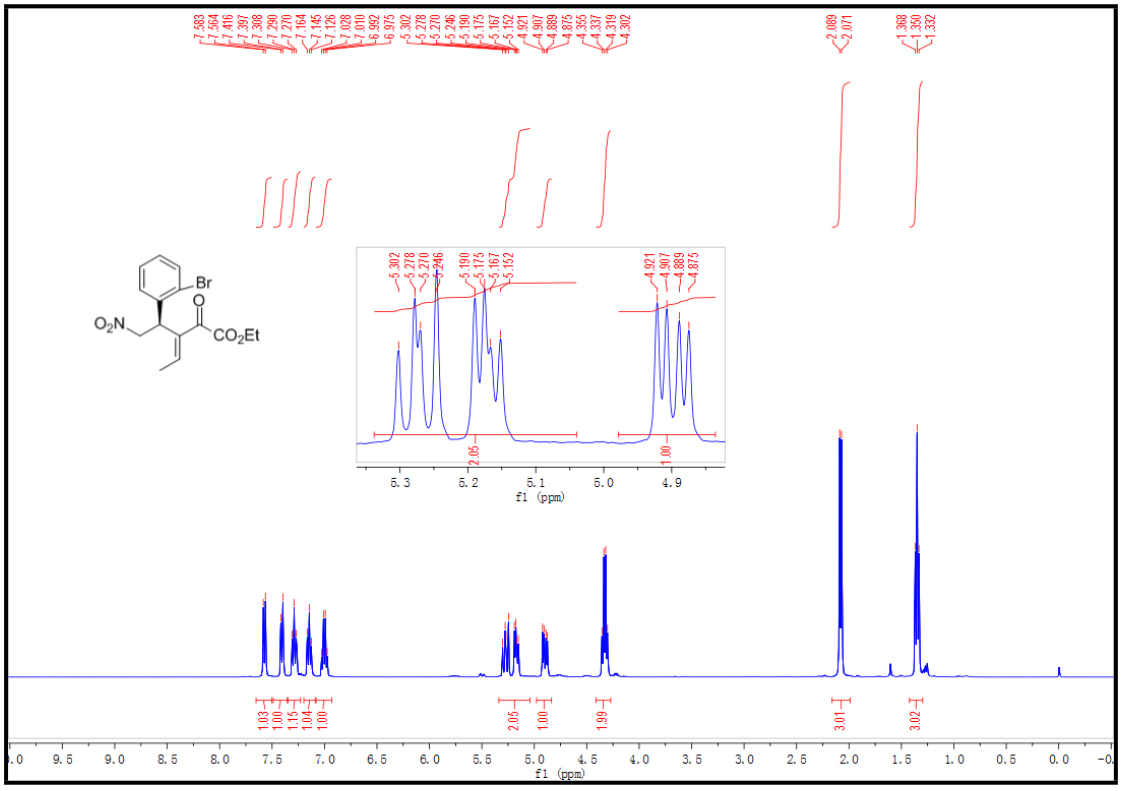
Totals : 1.60849e5 2881.36708

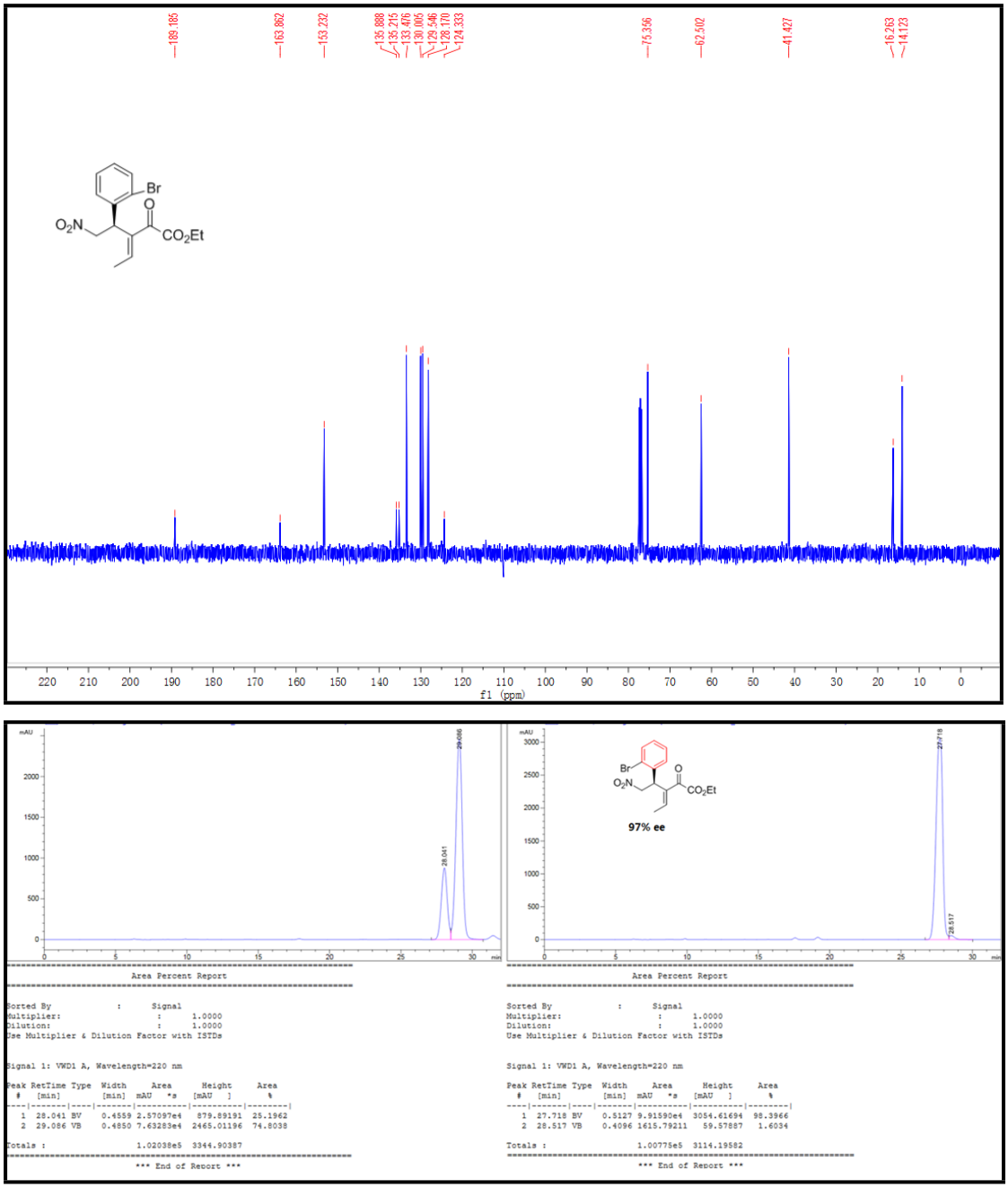
Note: the racemic product was prepared under the catalysis of racemic organocatalyst **F**, which was obtained through the mixture the equial amount of (*S,S*)-**F** and (*R,R*)-**F** isomers.


Br
O
O2N
CO2Et
f1 (ppm)

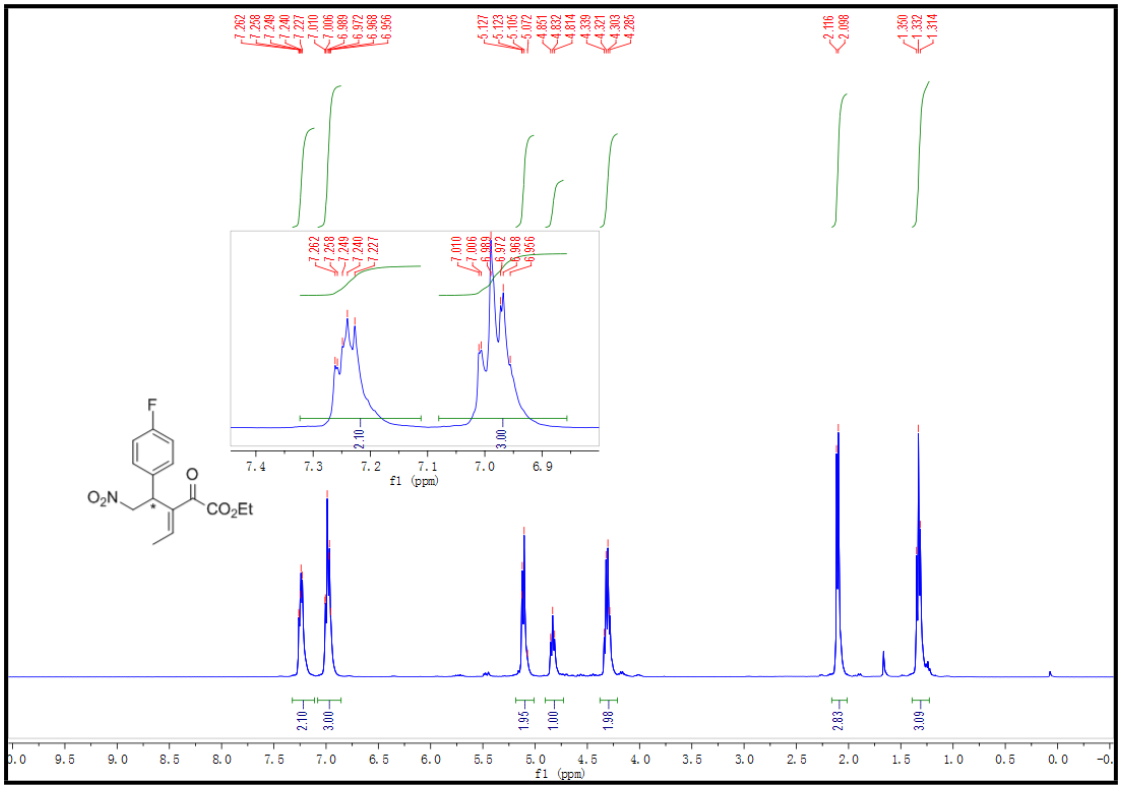

Br
O
O2N
CO2Et
f1 (ppm)

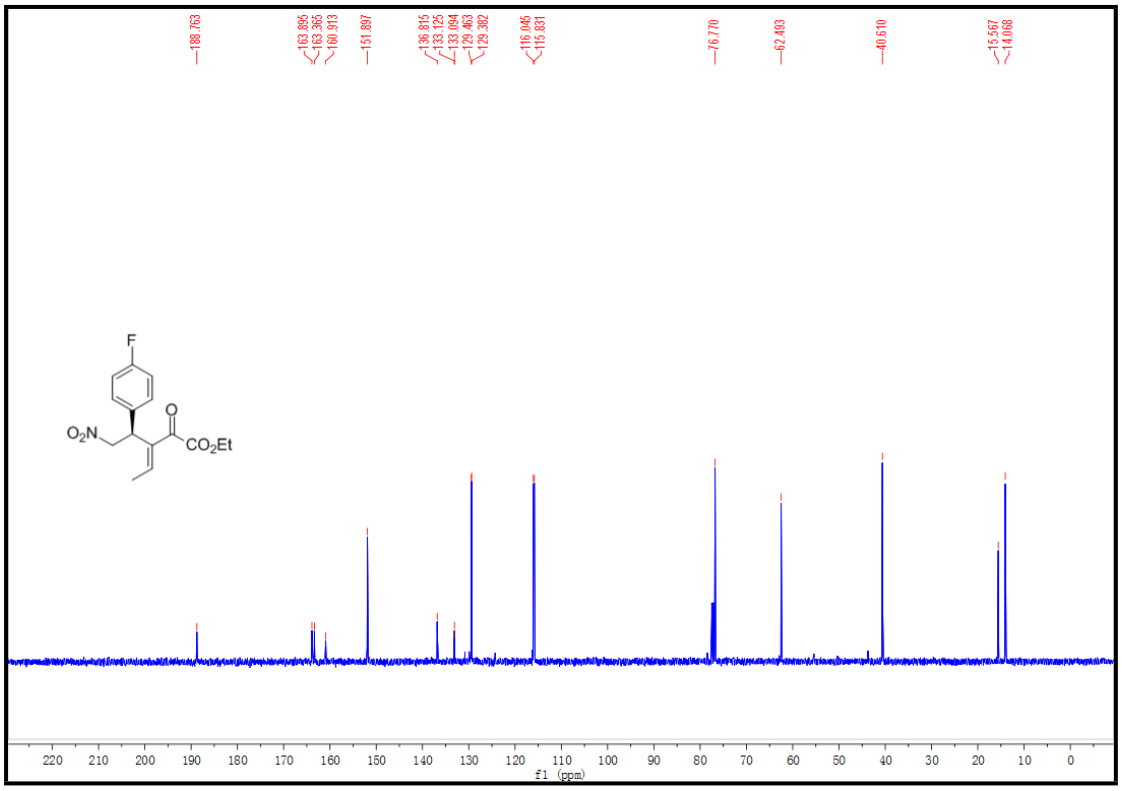

mAU
34.772
37.817
Norm.
Br
O2N
O
CO2Et
37.947
24.386
Area Percent Report
Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs
Signal 1: VWD1 A, Wavelength=220 nm
Peak RetTime Type Width Area Height Area
[min] [min] mAU *s [mAU] %
1 34.772 VV 0.6160 1.02682e5 2611.27393 61.7549
2 37.817 VV 0.6437 6.35918e4 1553.17114 38.2451
Totals : 1.66274e5 4164.44507
*** End of Report ***
Area Percent Report
Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs
Signal 1: VWD1 A, Wavelength=220 nm
Peak RetTime Type Width Area Height Area
[min] [min] mAU *s [mAU] %
1 34.386 MM 0.6768 1301.23315 32.04266 1.1448
2 37.947 VV 0.7160 1.12368e5 2496.01831 98.8552
Totals : 1.13670e5 2528.06097
*** End of Report ***

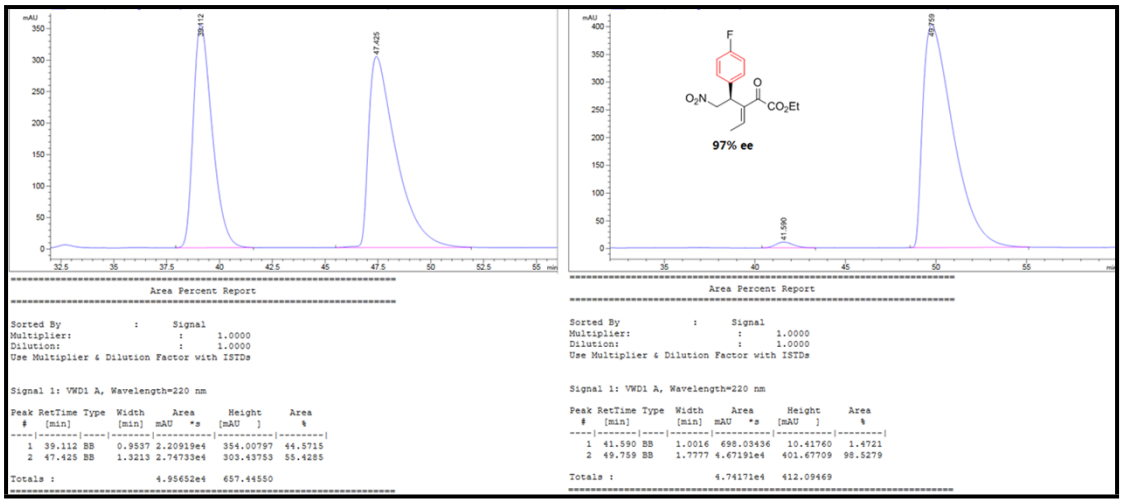

Br
O2N
O
CO2Et
f1 (ppm)
f1 (ppm)



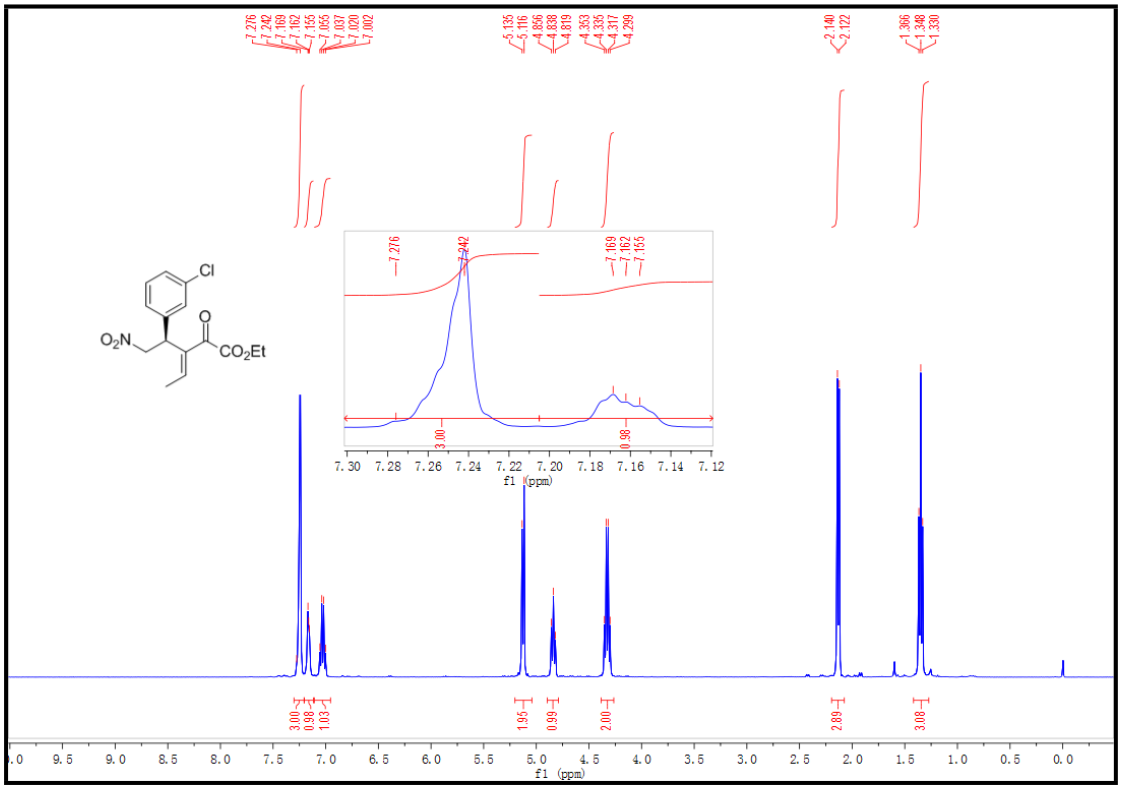
Note: the racemic product was prepared under the catalysis of racemic organocatalyst **F**, which was obtained through the mixture the equial amount of (*S,S*)-**F** and (*R,R*)-**F** isomers.

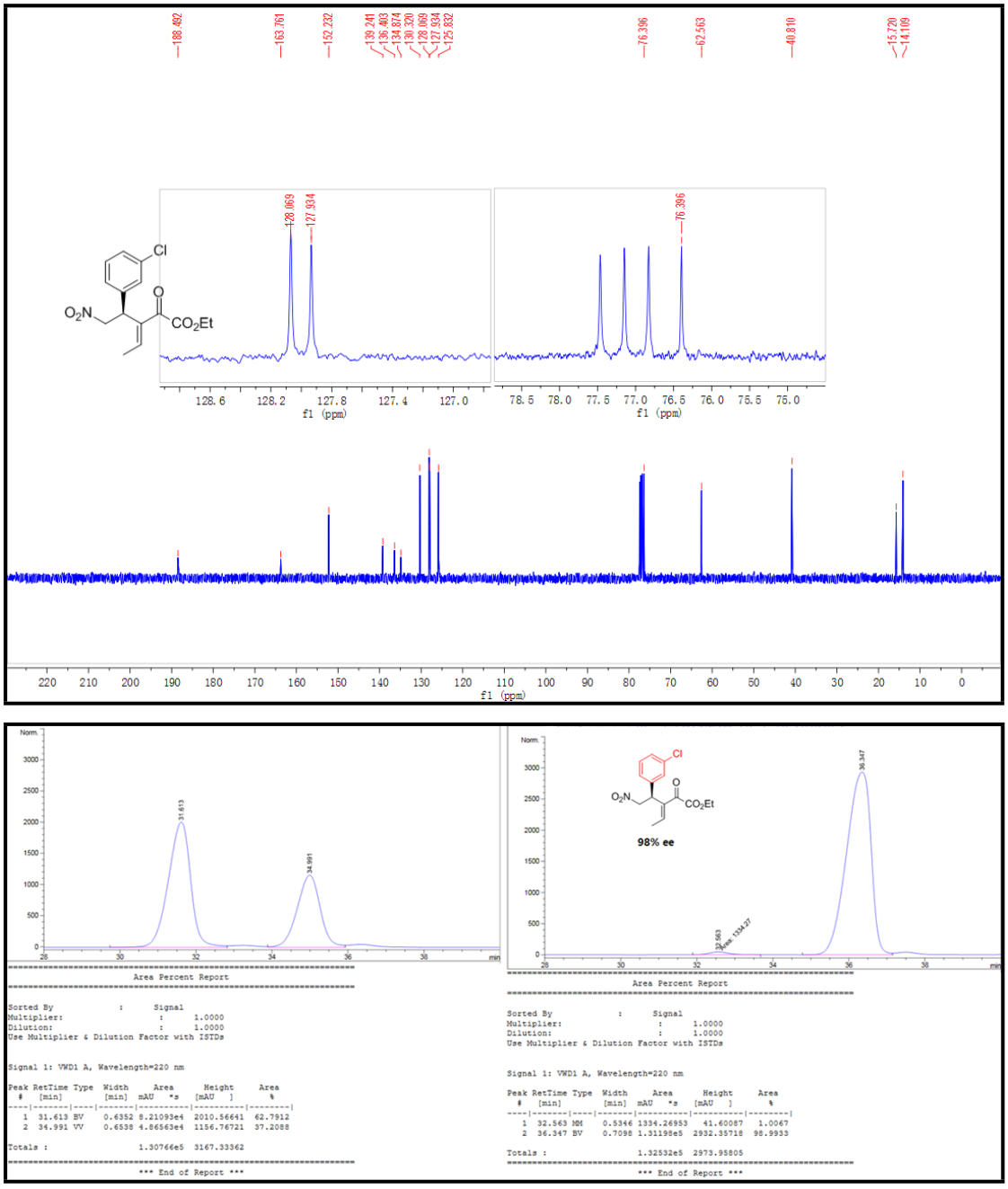

F
O
O_2N
CO_2Et
f1 (ppm)


F
O
O_2N
CO_2Et
f1 (ppm)

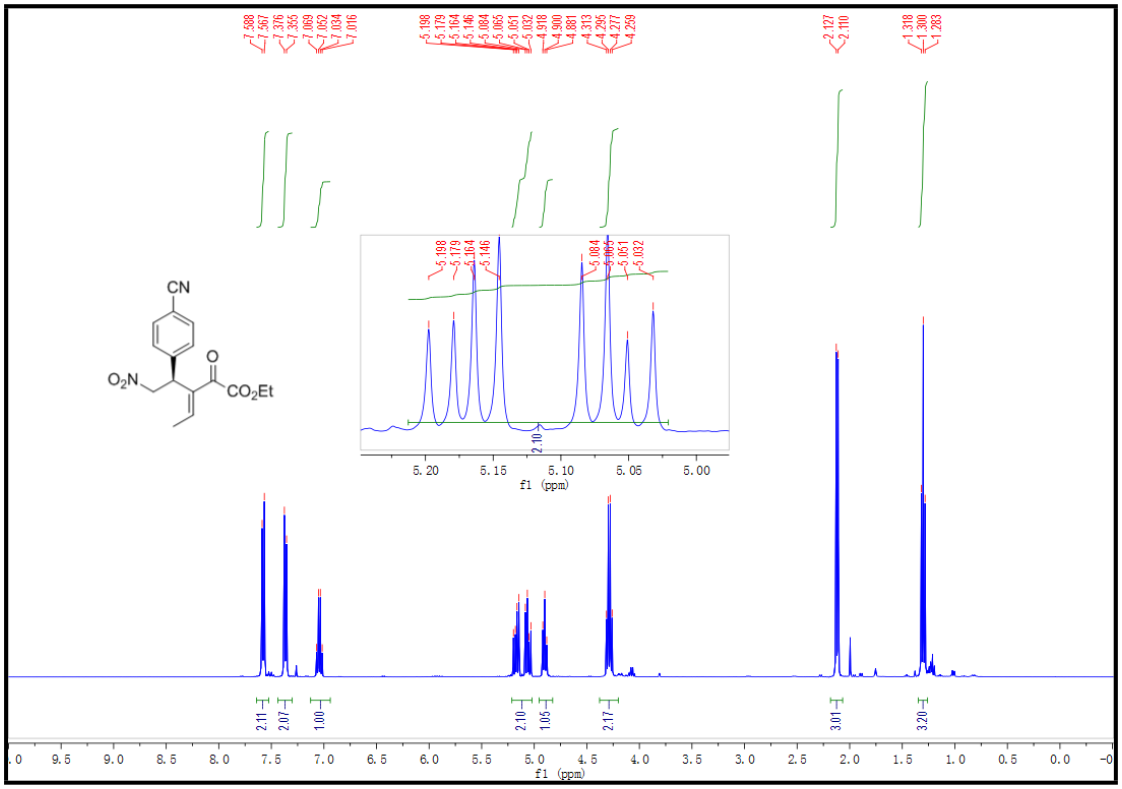


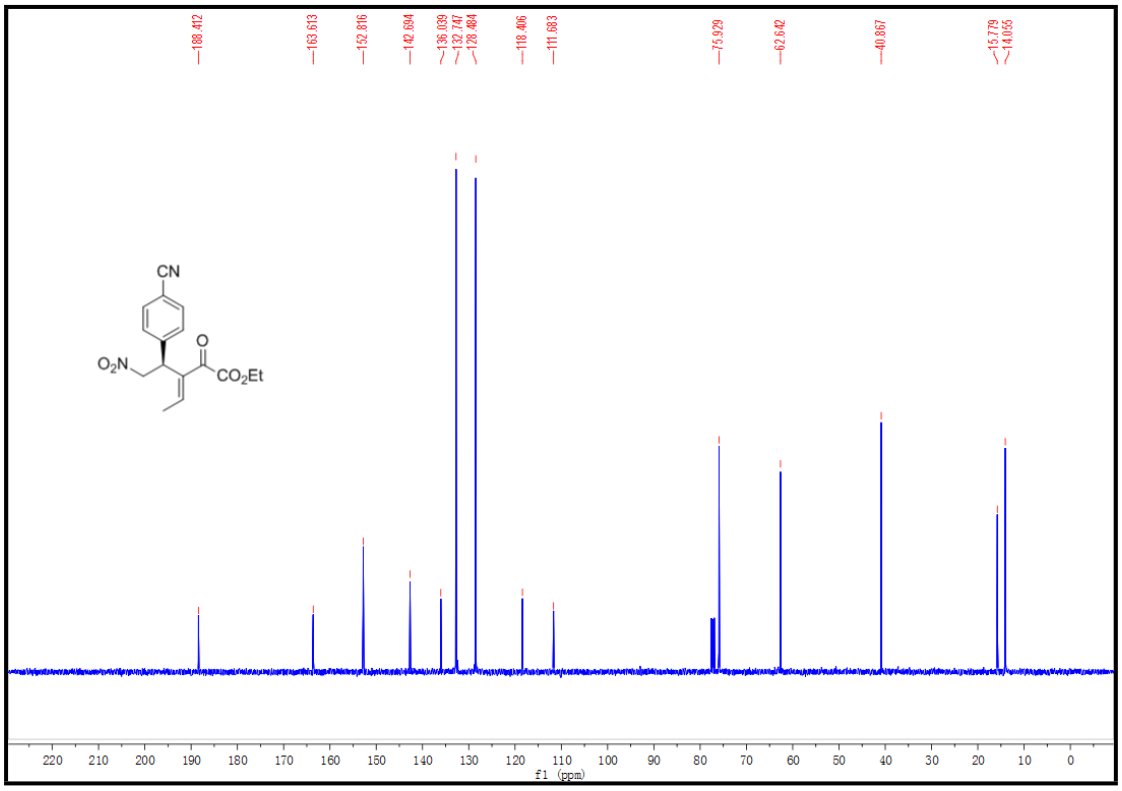
Note: the racemic product was prepared under the catalysis of racemic organocatalyst **F**, which was obtained through the mixture the equial amount of (*S,S*)-**F** and (*R,R*)-**F** isomers.

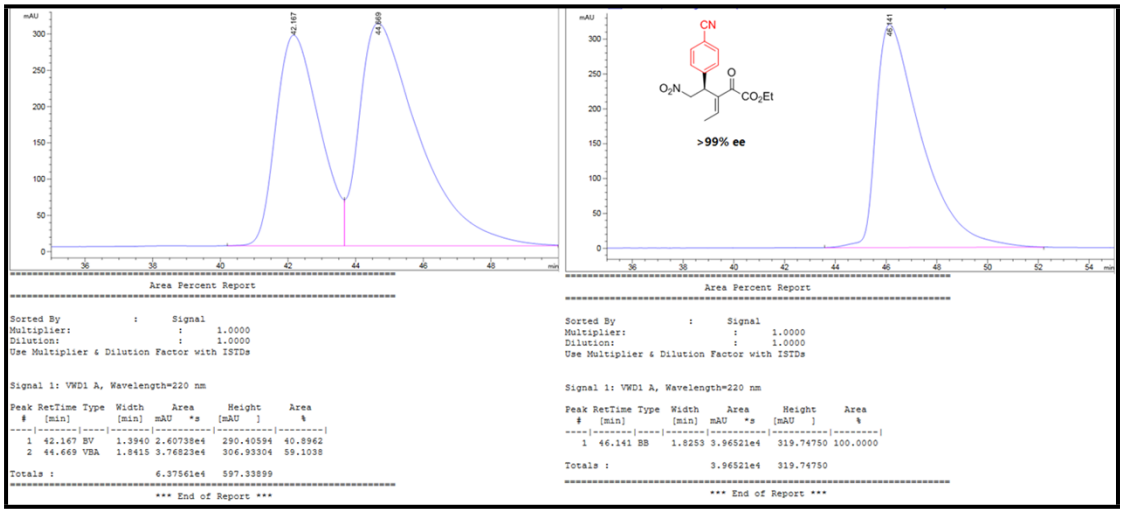




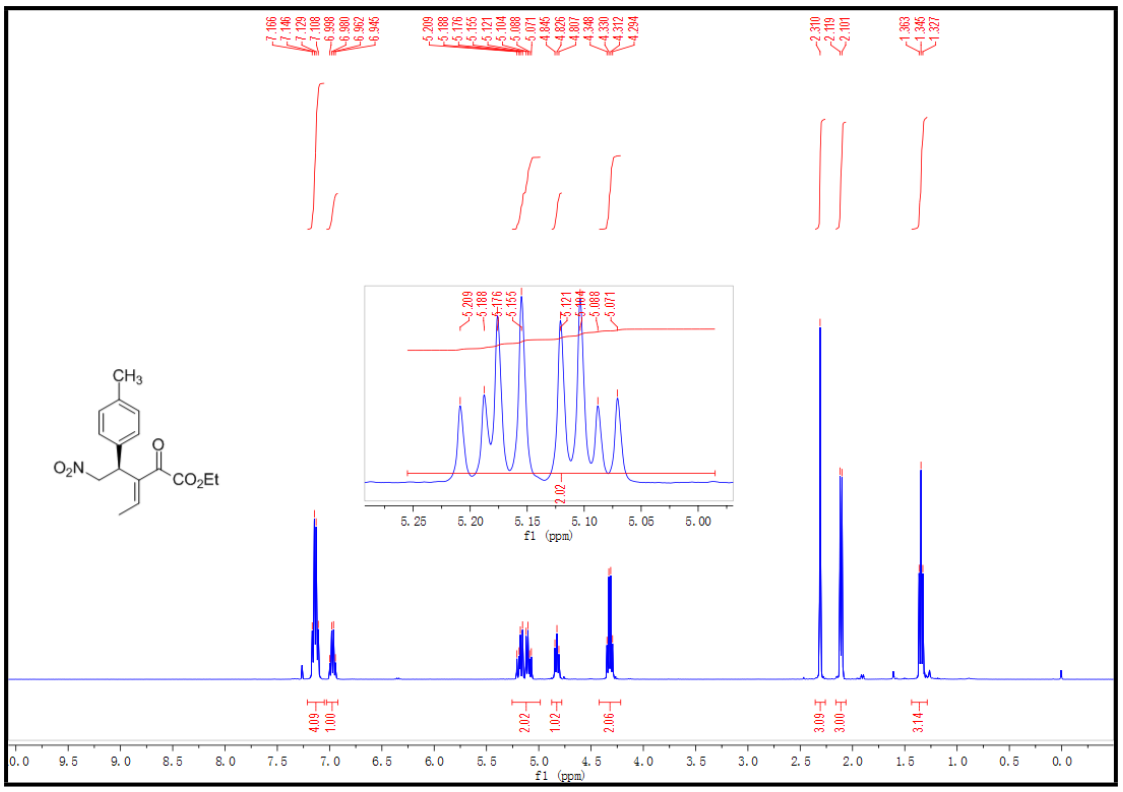
Note: the racemic product was prepared under the catalysis of racemic organocatalyst **F**, which was obtained through the mixture the equial amount of (*S,S*)-**F** and (*R,R*)-**F** isomers.

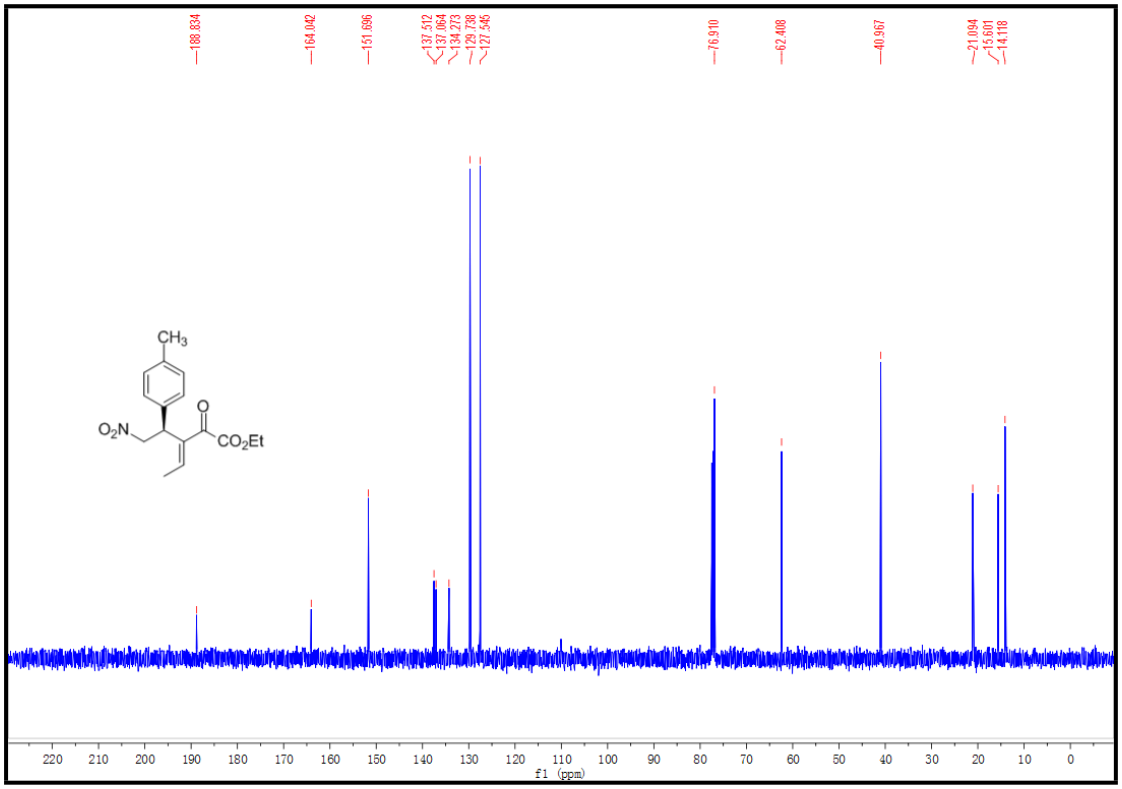

CN
O
O2N
CO2Et
f1 (ppm)

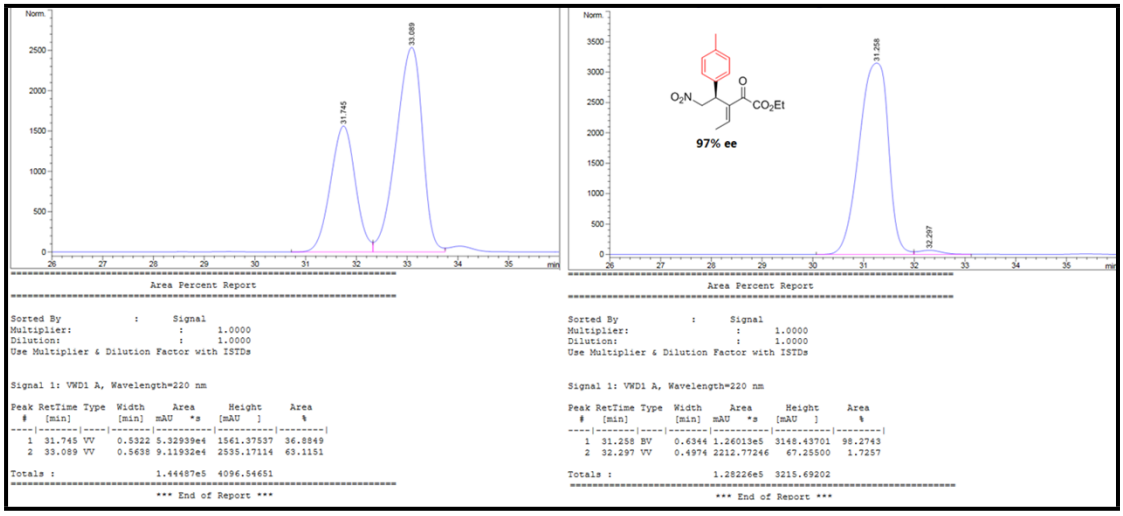

CN
O
O2N
CO2Et
f1 (ppm)



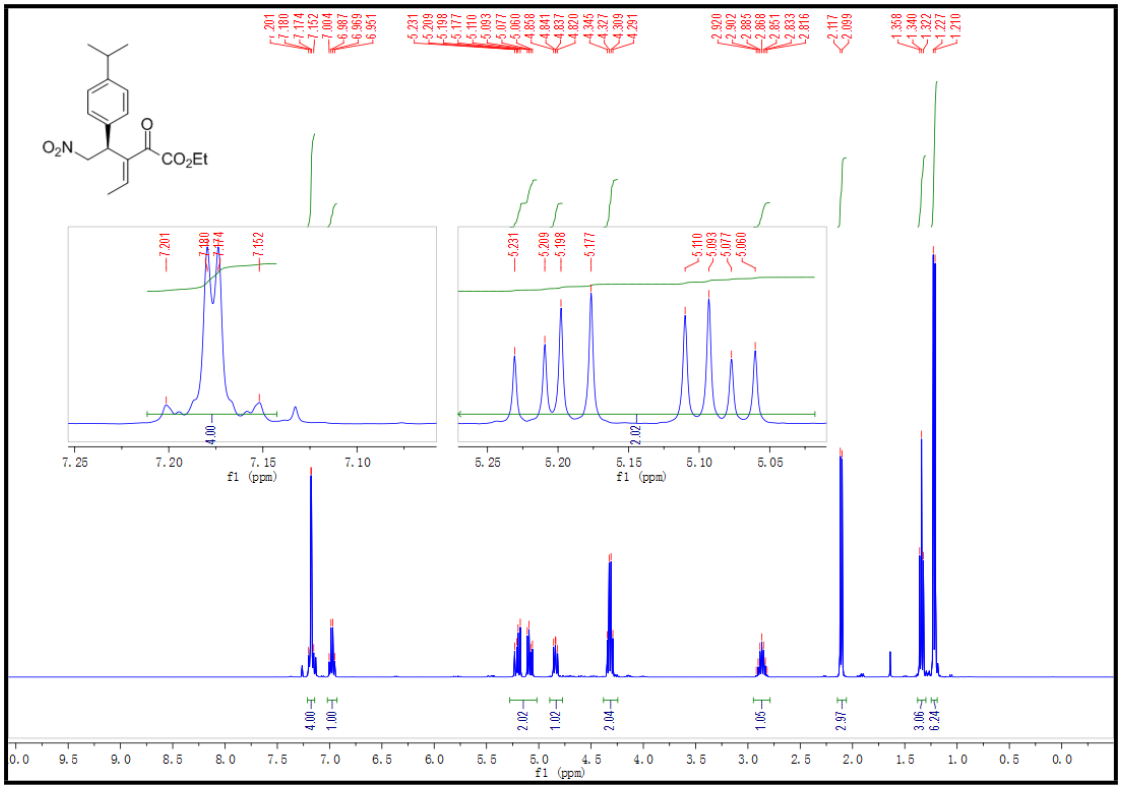
Note: the racemic product was prepared under the catalysis of racemic organocatalyst **F**, which was obtained through the mixture the equial amount of (*S,S*)-**F** and (*R,R*)-**F** isomers.

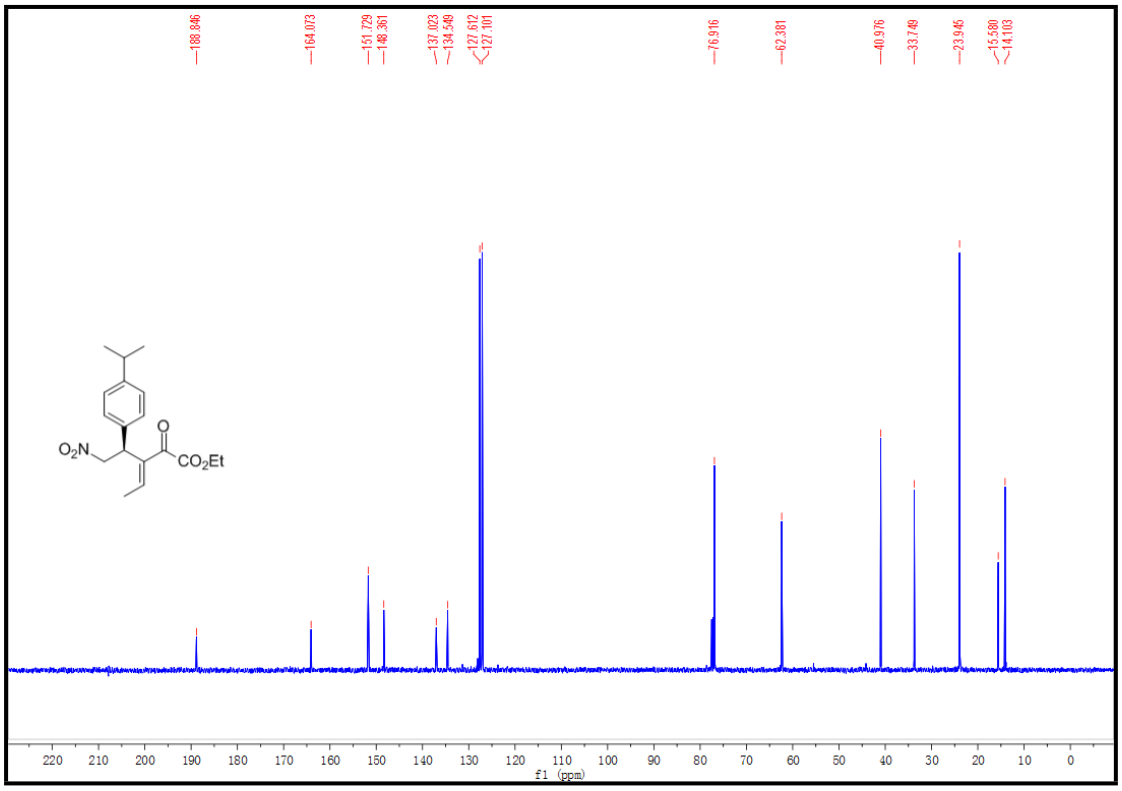


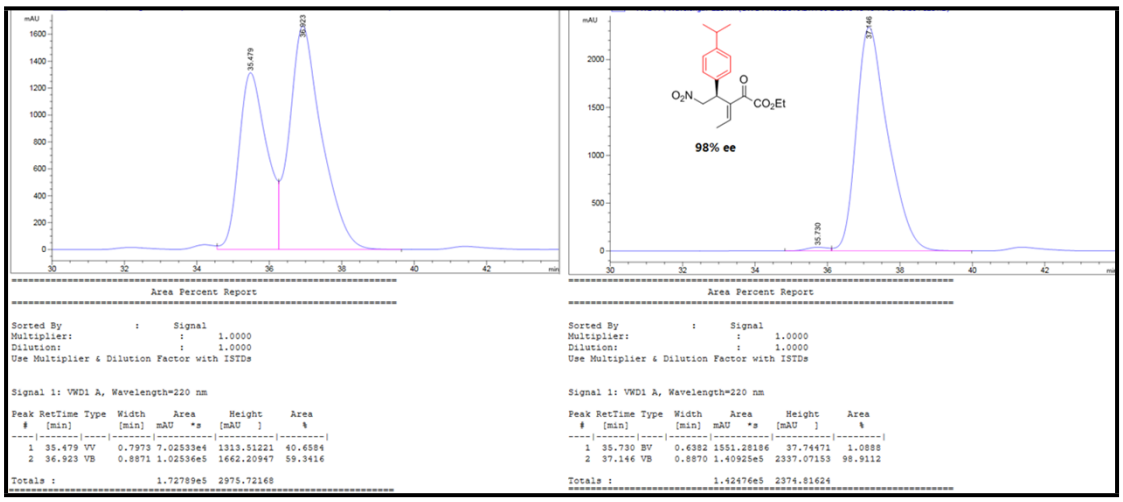




Note: the racemic product was prepared under the catalysis of racemic organocatalyst **F**, which was obtained through the mixture the equial amount of (*S,S*)-**F** and (*R,R*)-**F** isomers.


O2N
O
CO2Et
f1 (ppm)


O2N
O
CO2Et
f1 (ppm)



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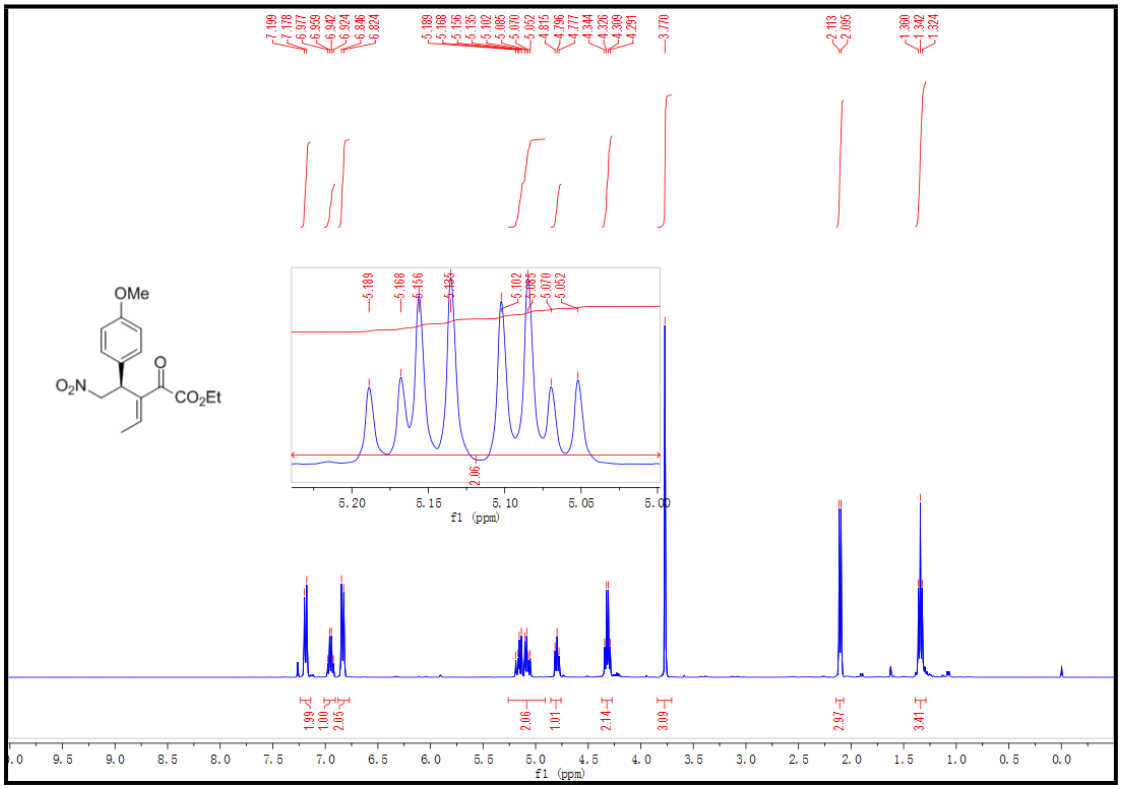

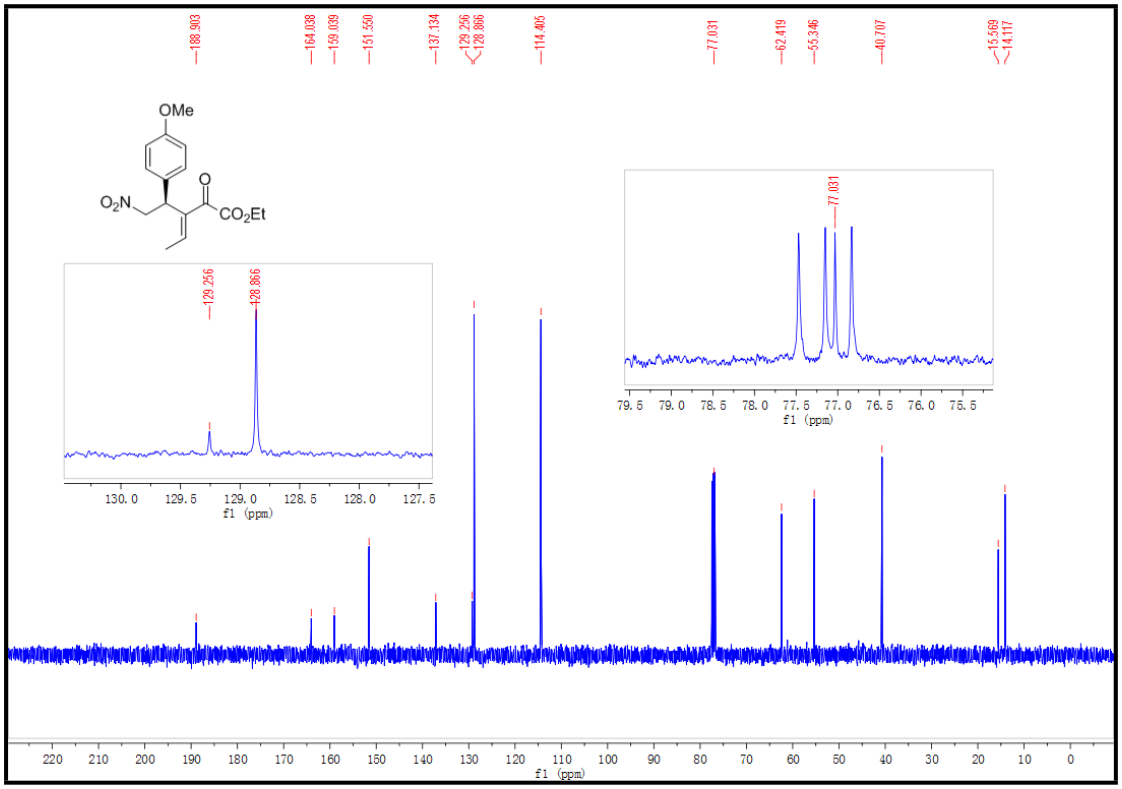

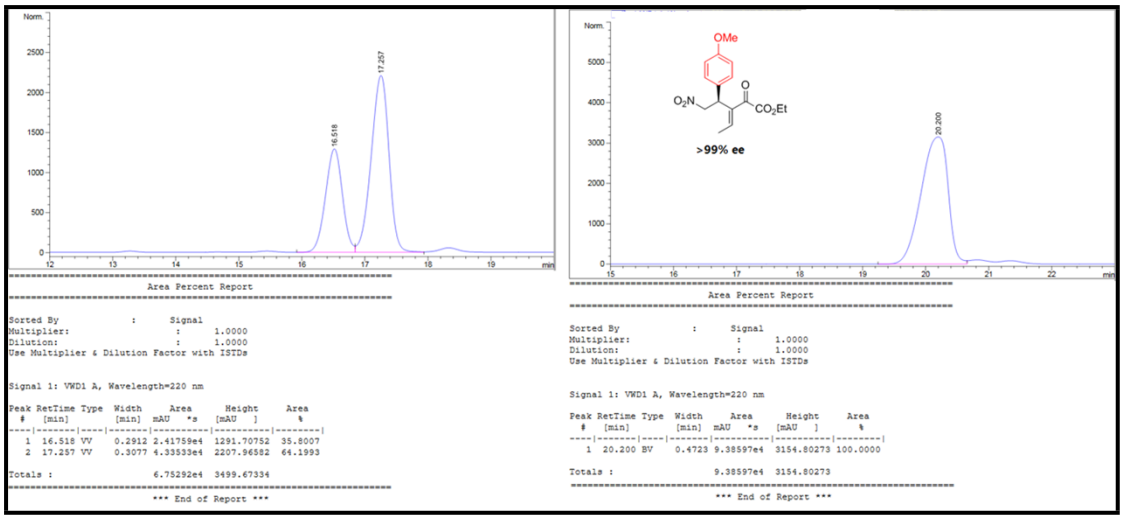

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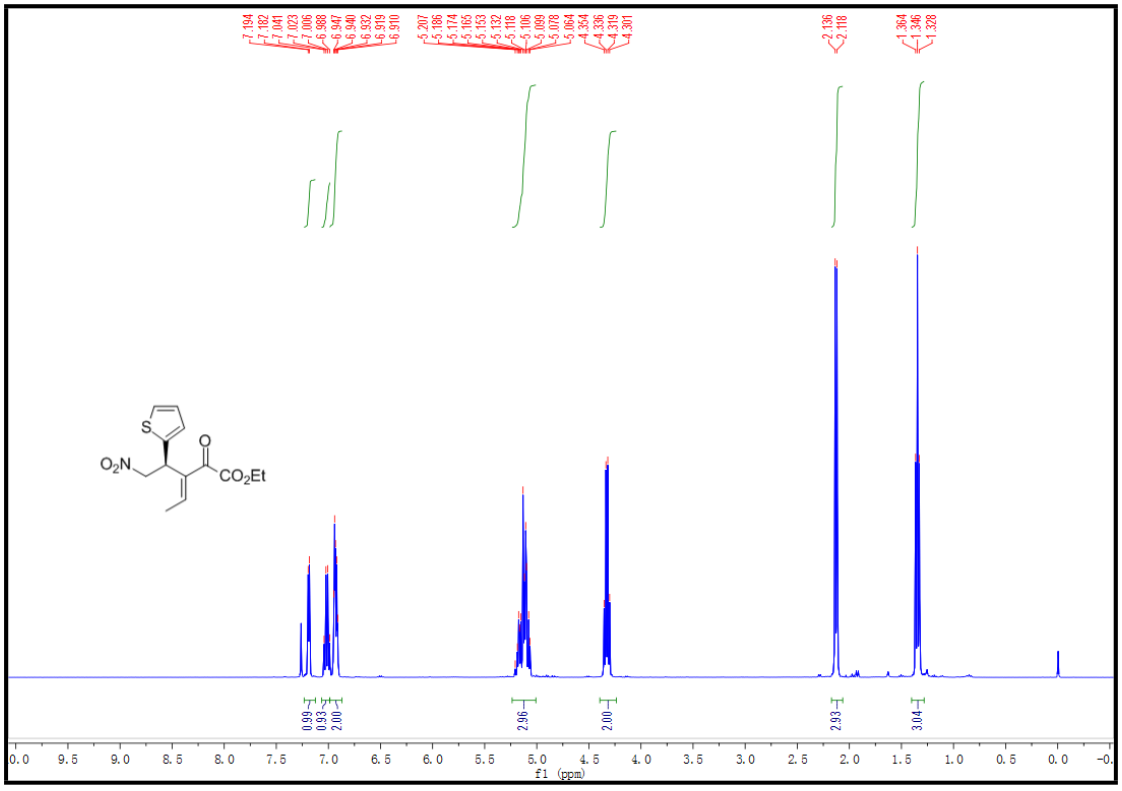
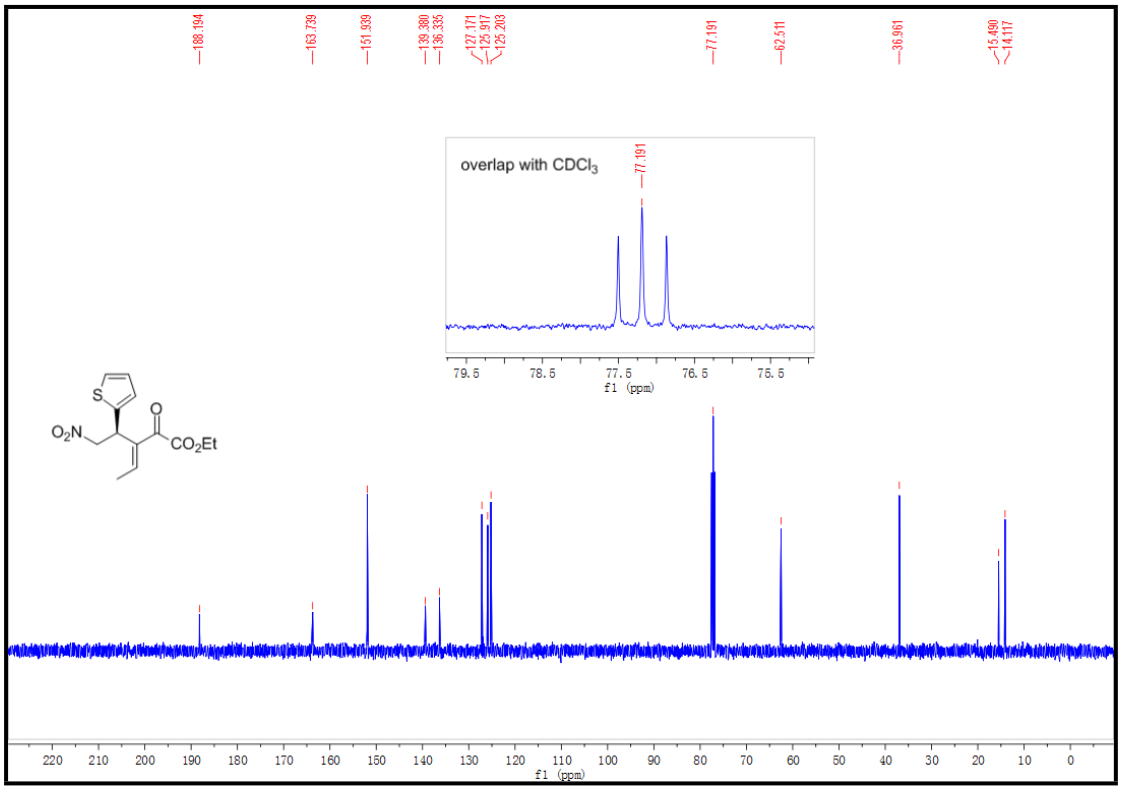
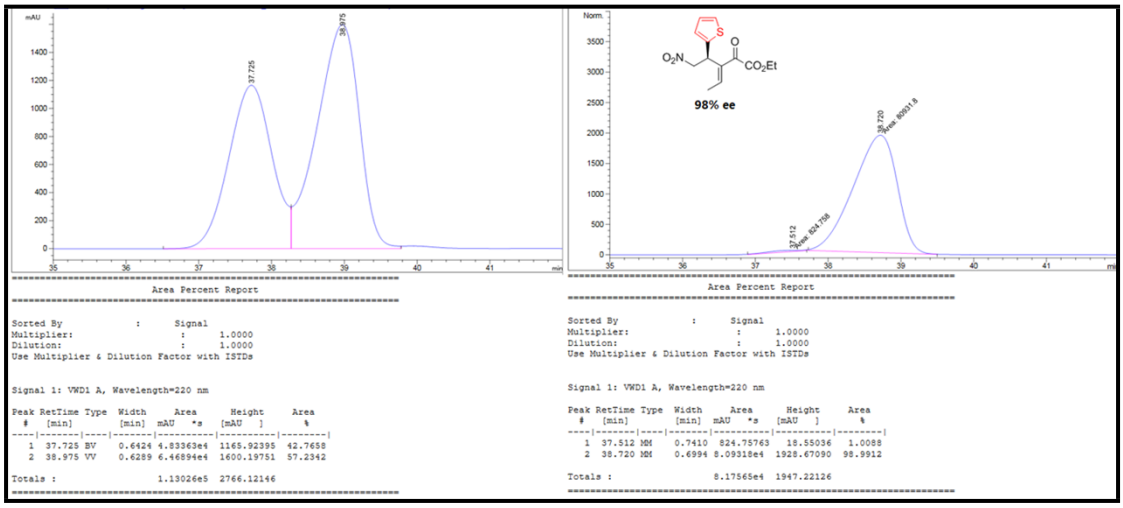
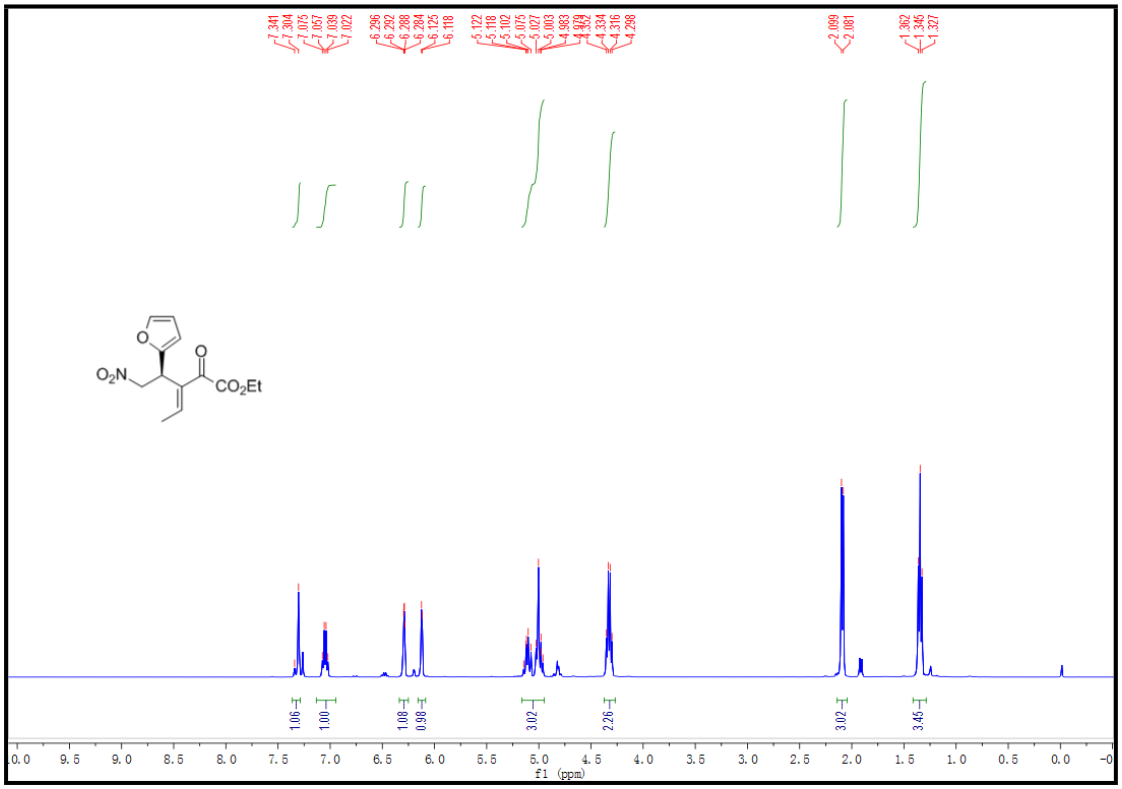
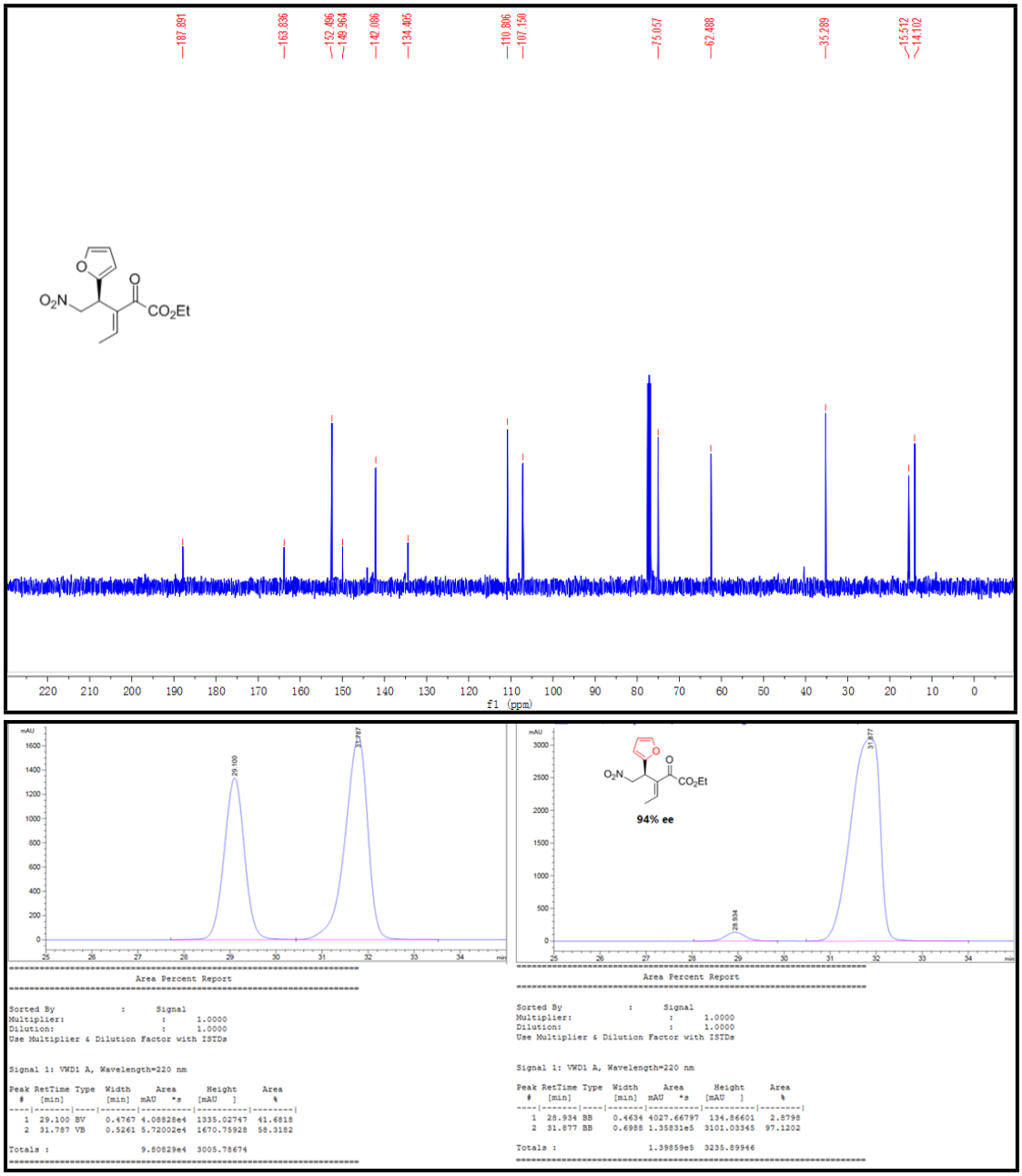

7.194
7.182
7.041
7.023
7.006
6.988
6.947
6.940
6.932
6.919
6.910
5.207
5.186
5.174
5.165
5.153
5.132
5.118
5.106
5.099
5.078
5.064
4.354
4.336
4.319
4.301
2.136
2.118
1.364
1.346
1.328
0.99
0.93
2.00
2.96
2.00
2.93
3.04
f1 (ppm)


188.194
163.739
151.939
139.380
136.335
127.171
125.917
125.203
77.191
62.511
36.961
15.490
14.117
overlap with CDCl3
77.191
f1 (ppm)



Note: the racemic product was prepared under the catalysis of racemic organocatalyst **F**, which was obtained through the mixture the equial amount of (*S,S*)-**F** and (*R,R*)-**F** isomers.





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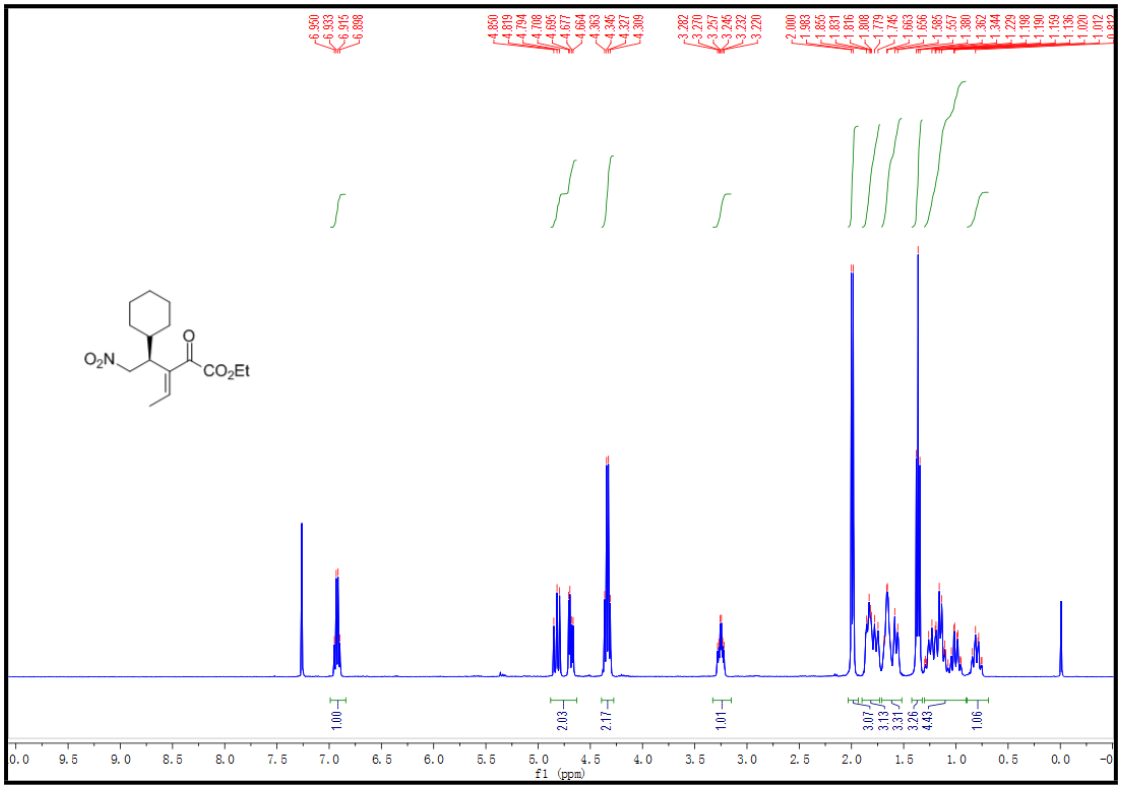
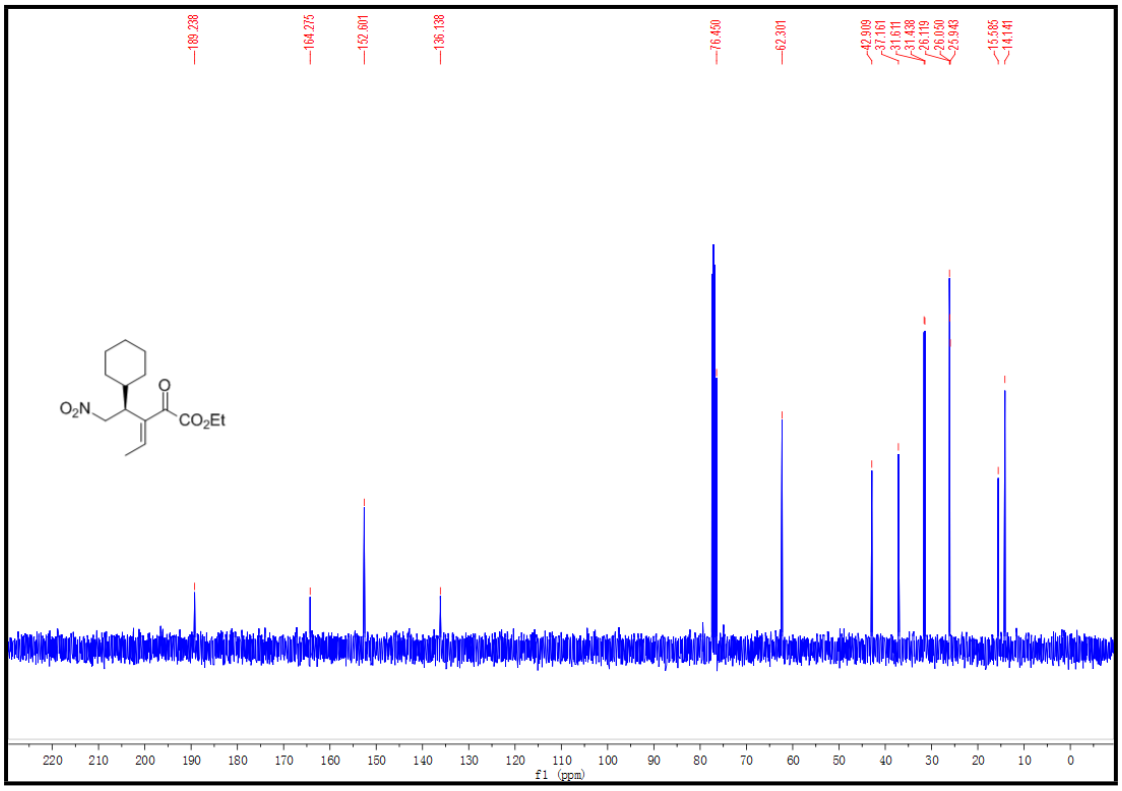
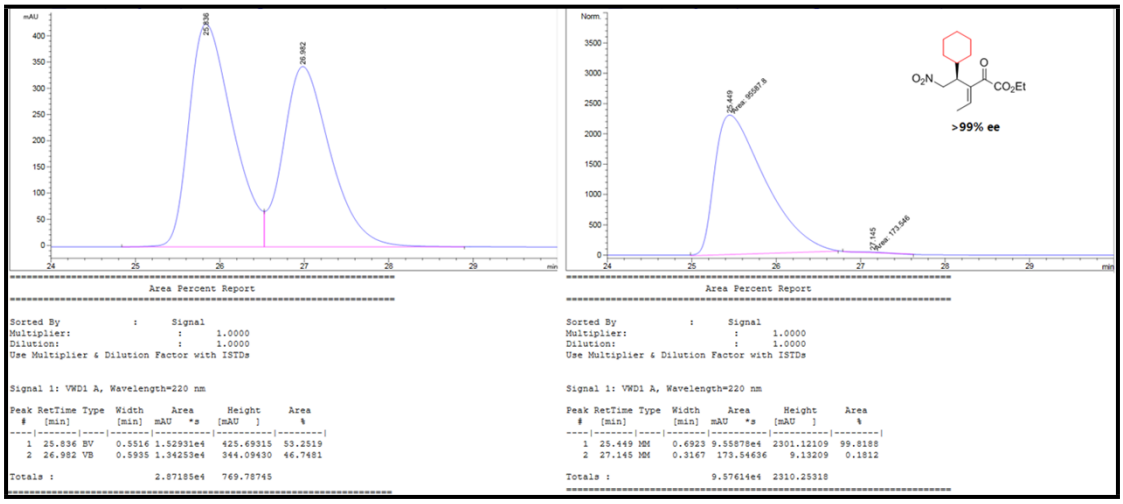

6.950
6.933
6.915
6.888
4.860
4.819
4.794
4.708
4.695
4.677
4.664
4.363
4.345
4.327
4.309
3.282
3.270
3.257
3.245
3.232
3.220
2.000
1.983
1.855
1.831
1.816
1.808
1.779
1.745
1.663
1.656
1.585
1.557
1.380
1.362
1.344
1.229
1.198
1.190
1.159
1.136
1.020
1.012
O2N
O
CO2Et
1.00
2.03
2.17
1.01
3.07
3.13
3.31
3.26
4.43
1.06
f1 (ppm)


189.238
164.275
152.601
136.138
76.450
62.301
42.909
37.161
31.611
31.438
26.119
26.050
25.943
15.585
14.141
O2N
O
CO2Et
f1 (ppm)



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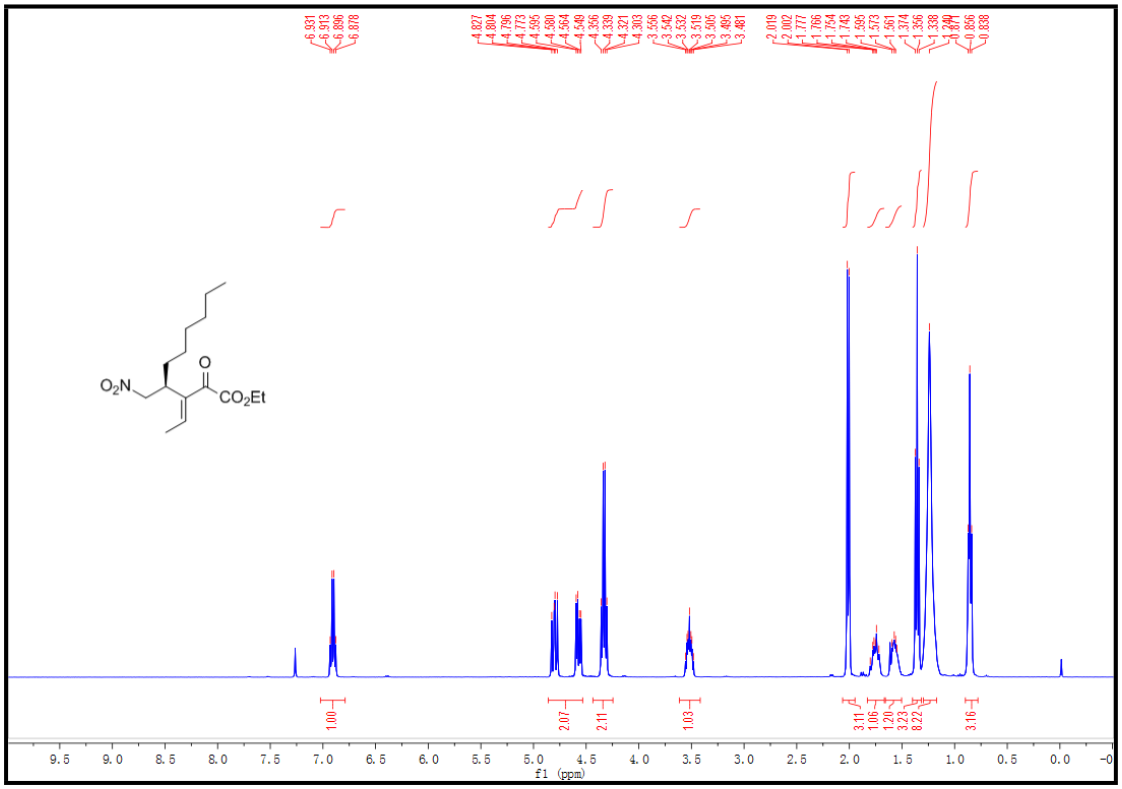

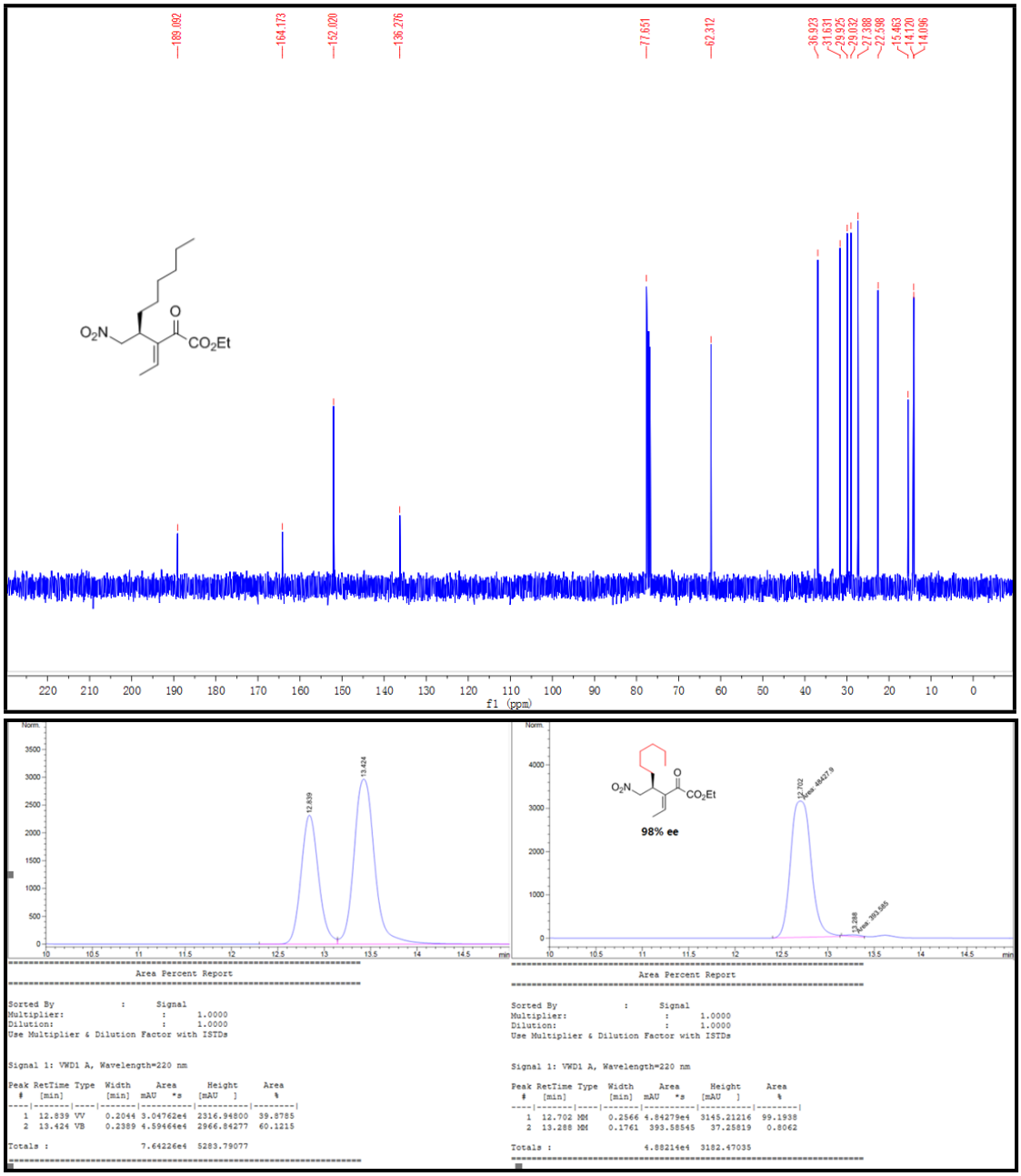

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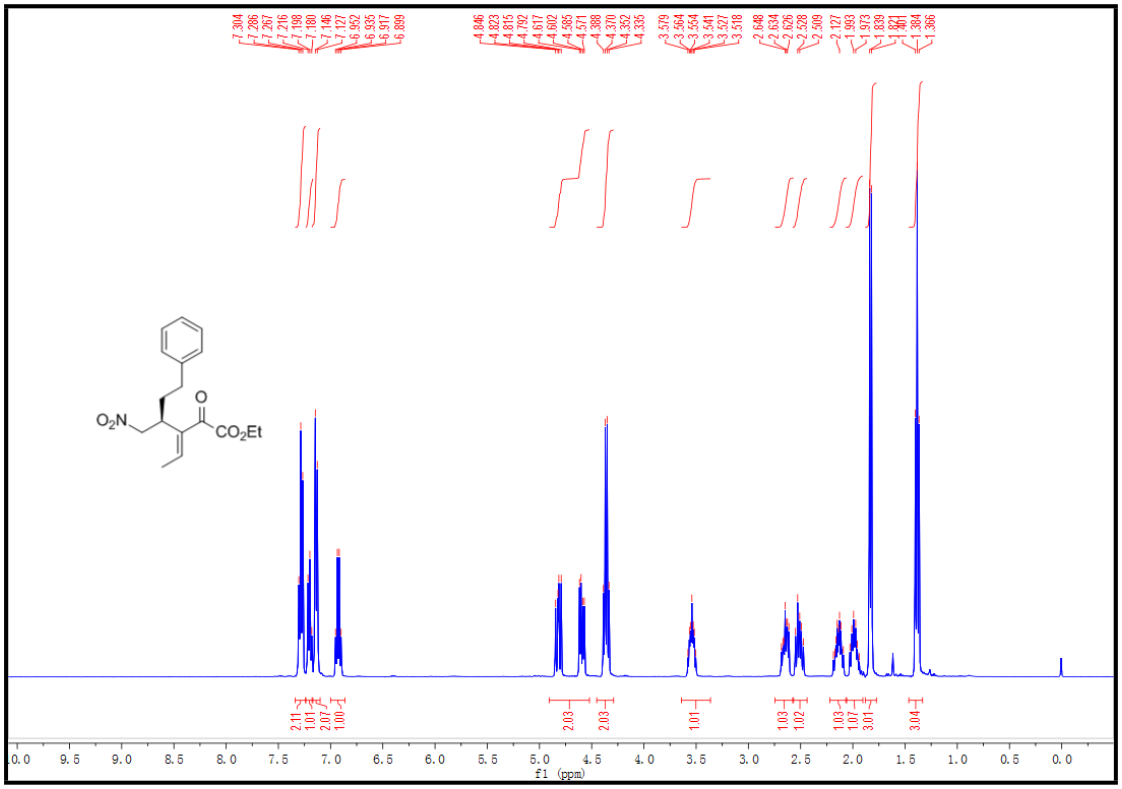
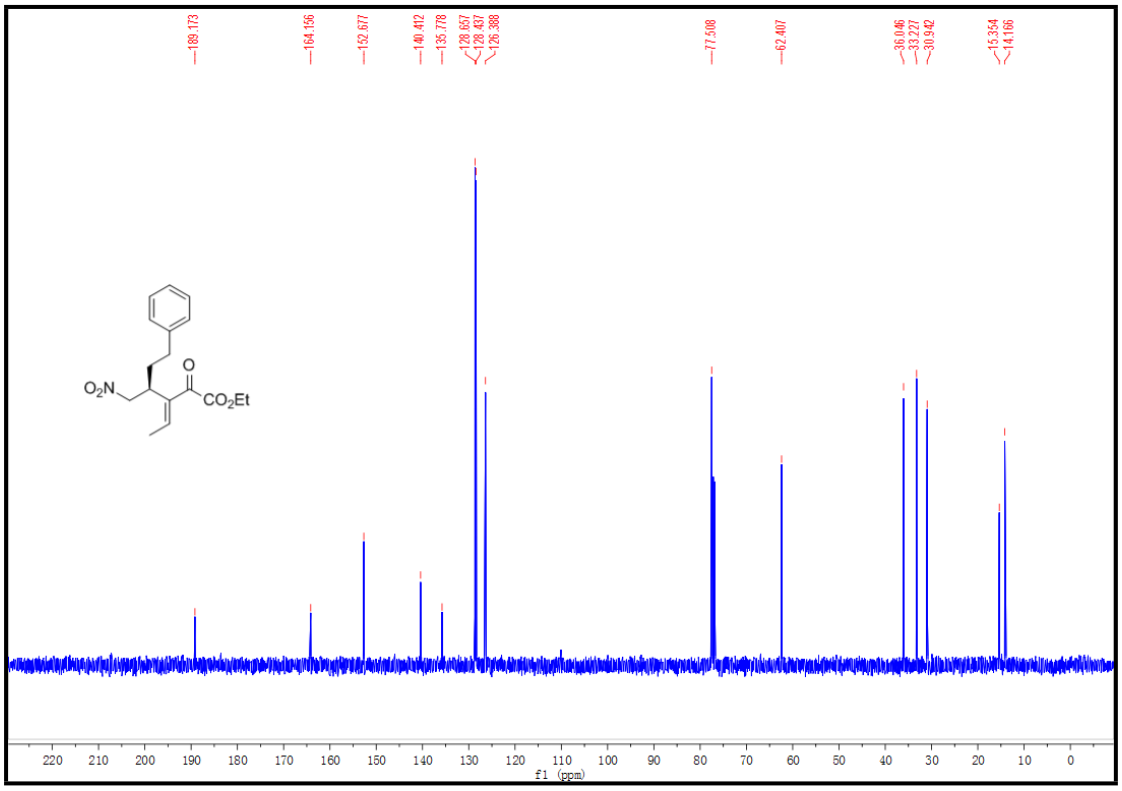
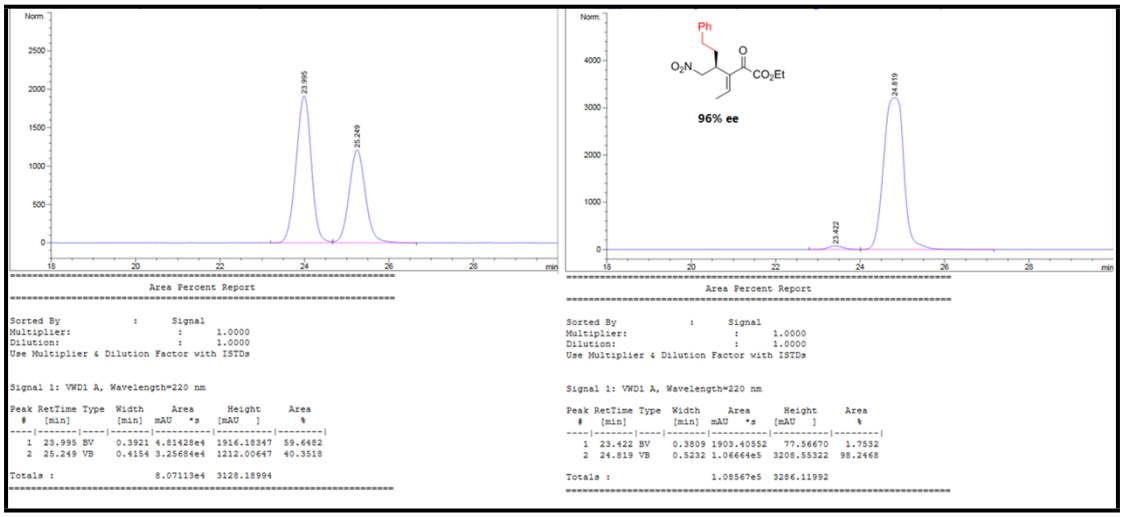

7.304
7.286
7.267
7.216
7.198
7.180
7.146
7.127
6.952
6.935
6.917
6.899
4.846
4.823
4.815
4.792
4.617
4.602
4.585
4.571
4.388
4.370
4.352
4.335
3.579
3.564
3.554
3.541
3.527
3.518
2.648
2.634
2.626
2.328
2.309
2.127
1.993
1.973
1.839
1.821
1.401
1.384
1.366
O2N
O
CO2Et
2.11
1.01
2.07
1.00
2.03
2.03
1.01
1.03
1.02
1.03
1.07
3.01
3.04
f1 (ppm)


188.173
164.156
152.677
140.412
135.778
128.657
128.437
126.388
77.508
62.407
36.046
33.227
30.942
15.354
14.166
O2N
O
CO2Et
f1 (ppm)



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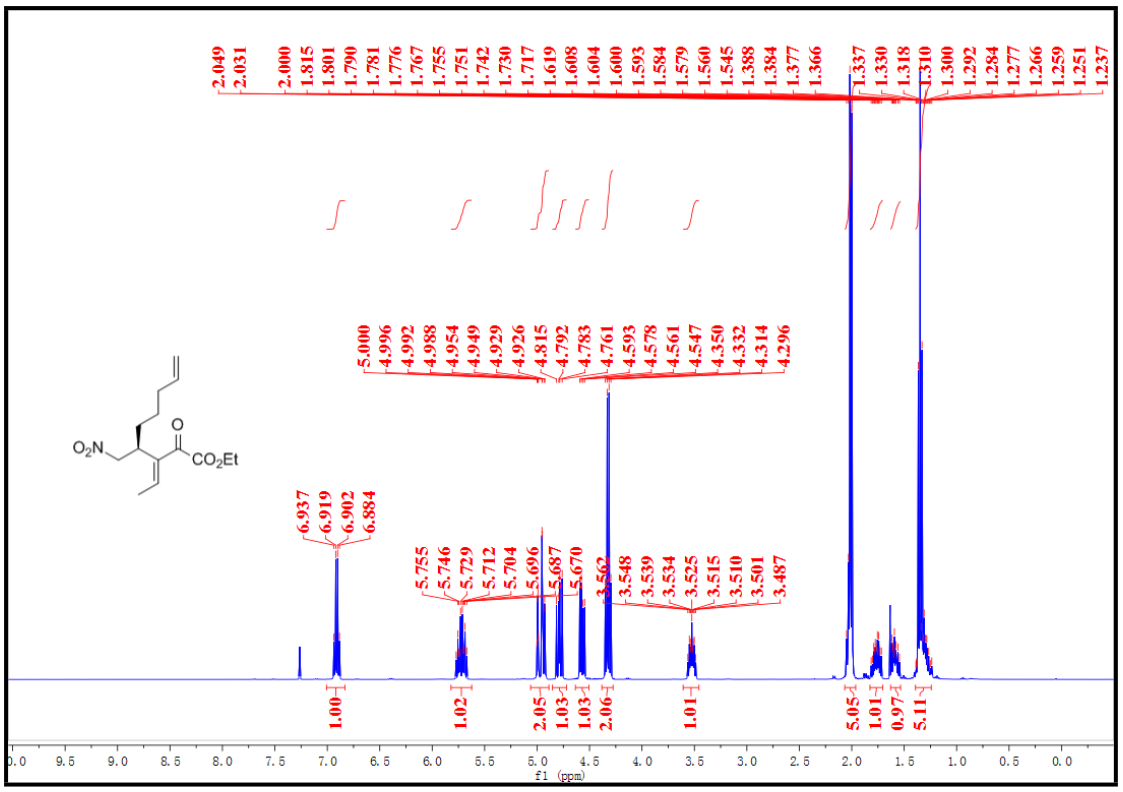

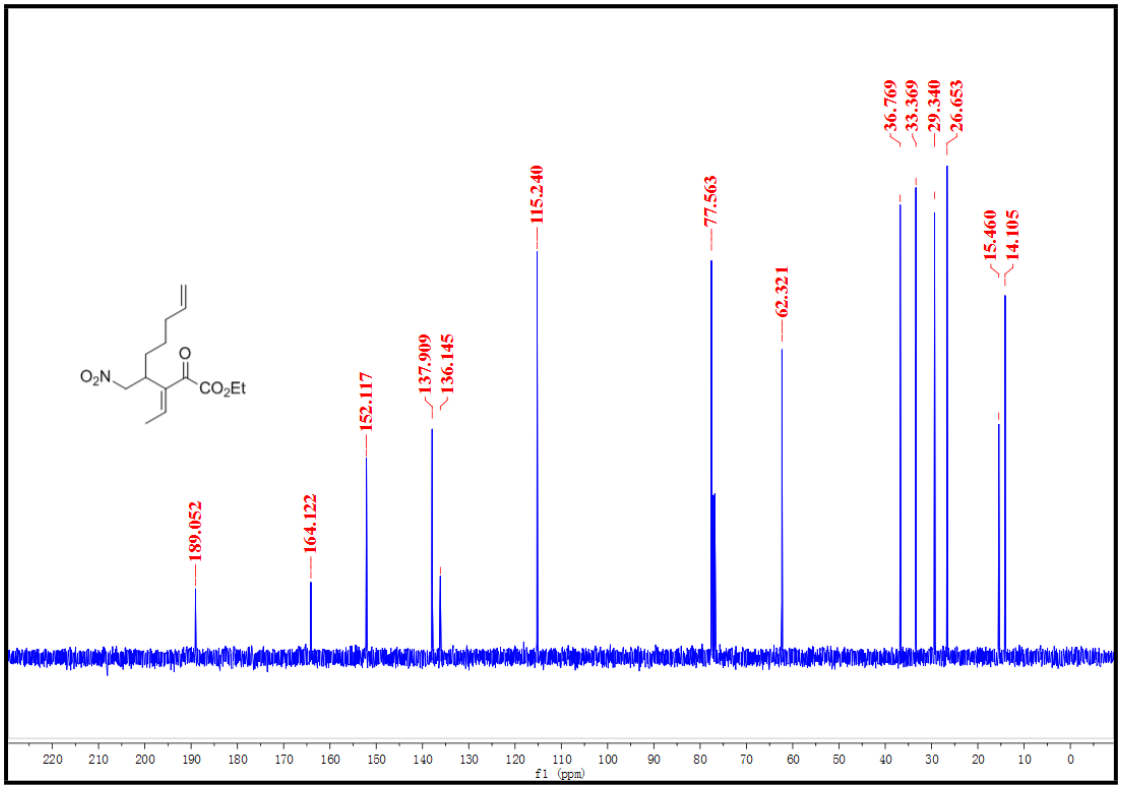

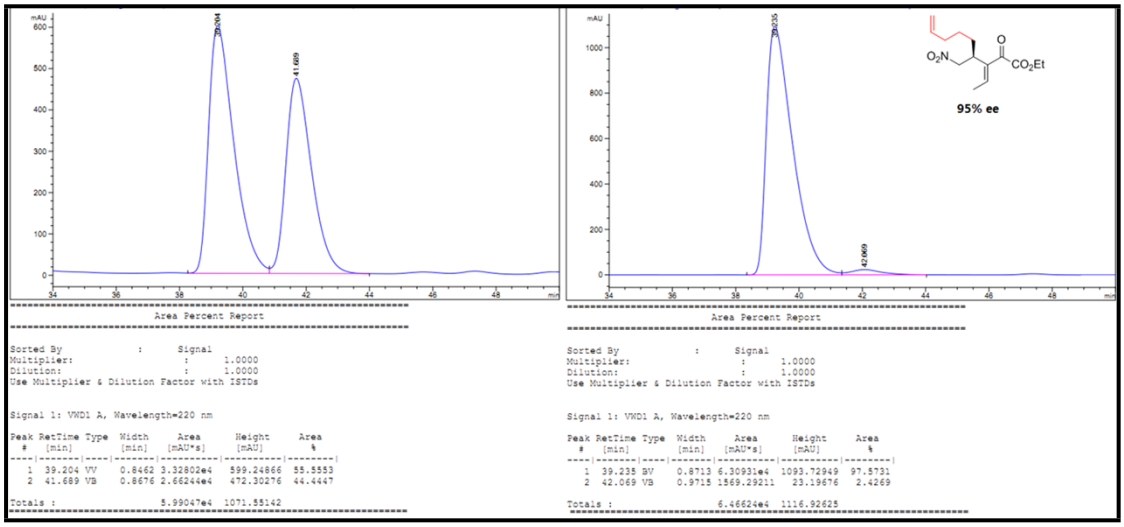

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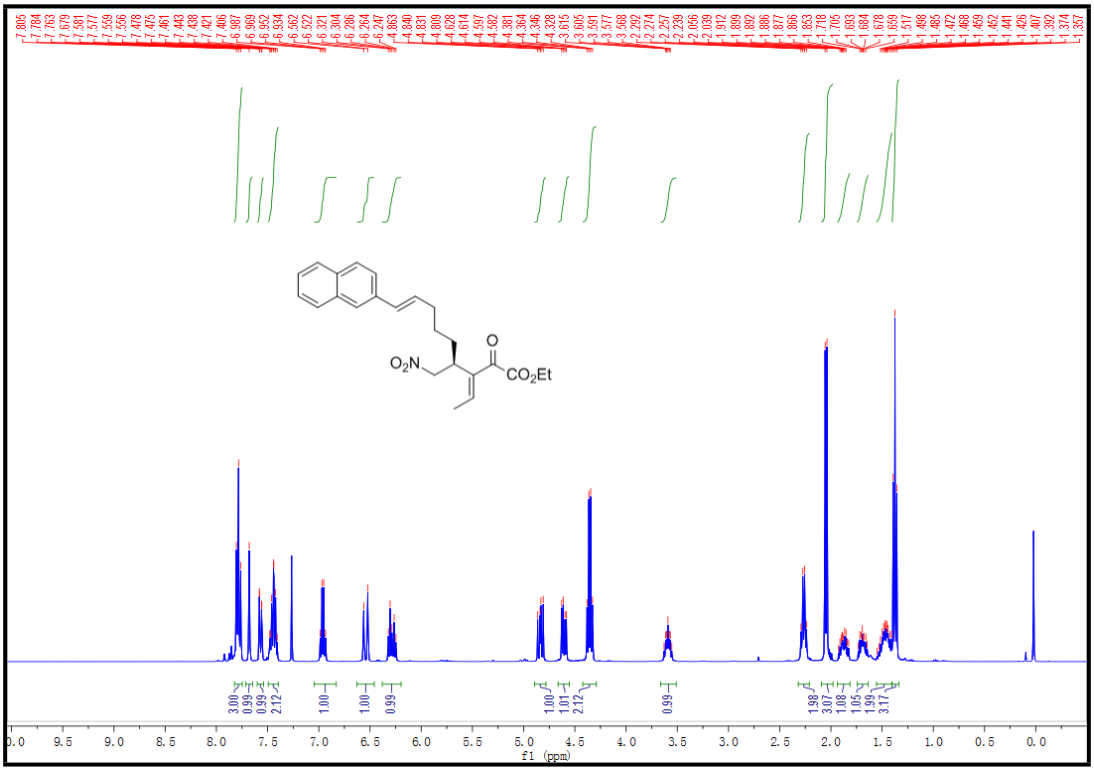
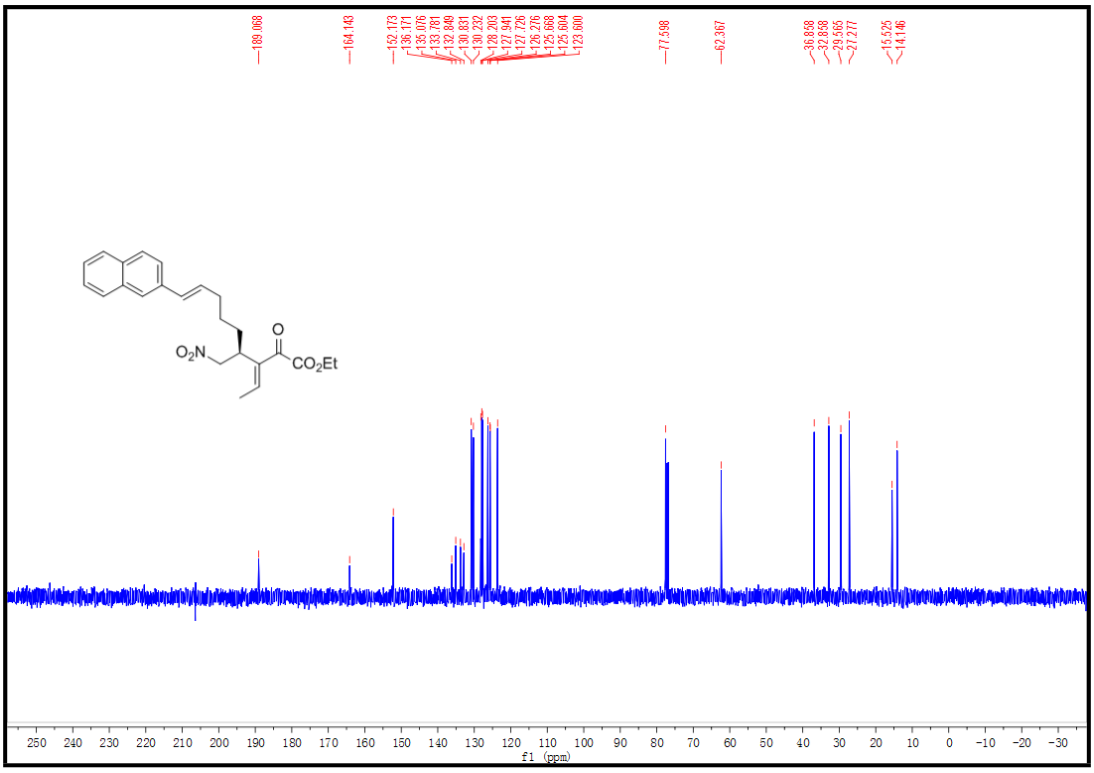
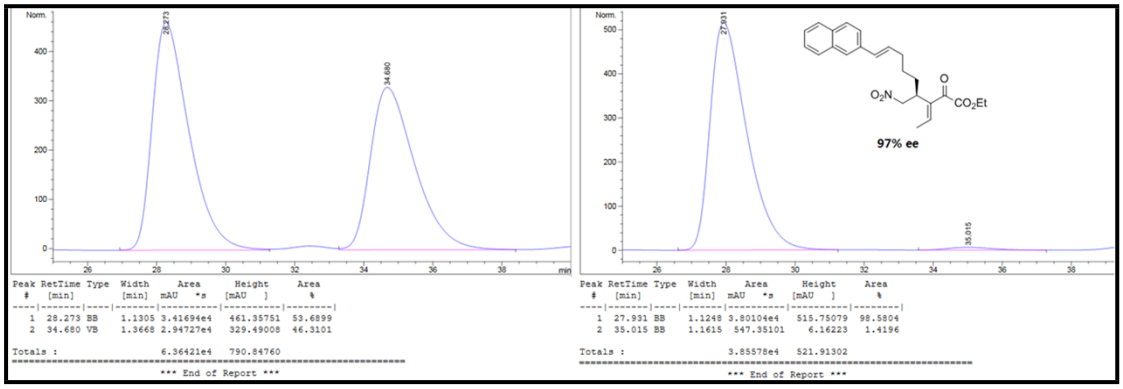

O2N
O
CO2Et
f1 (ppm)


O2N
O
CO2Et
f1 (ppm)



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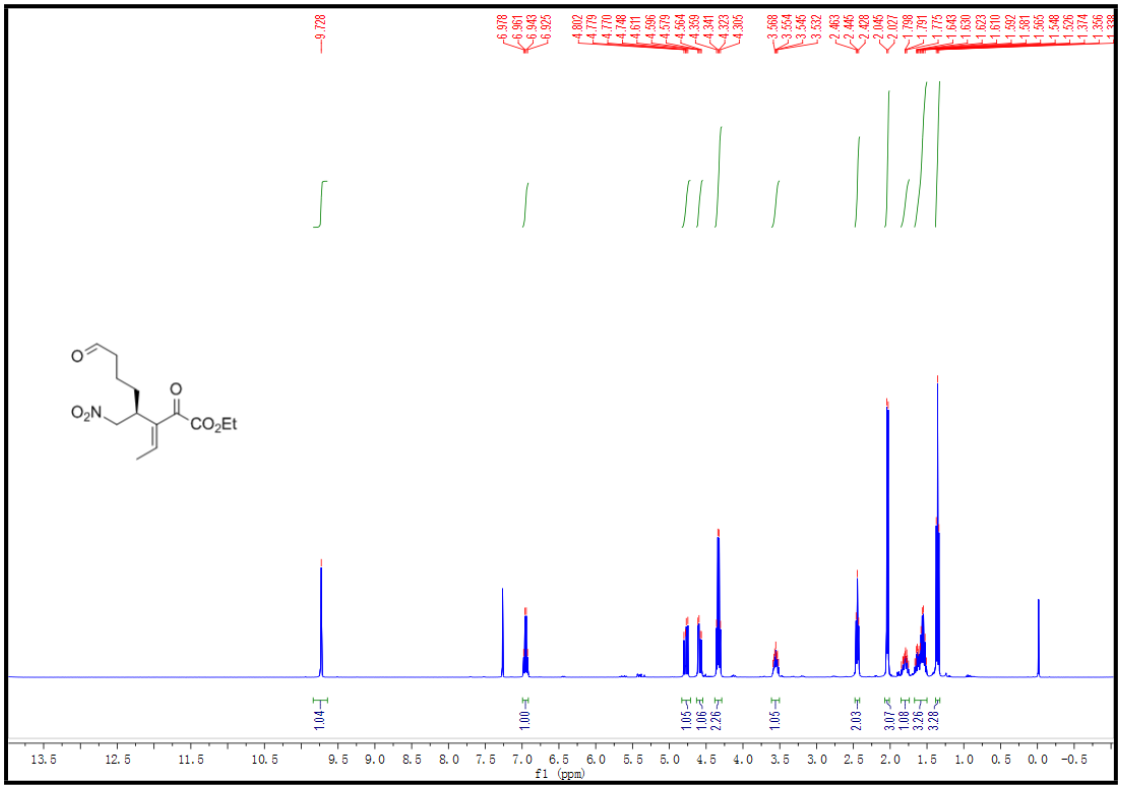

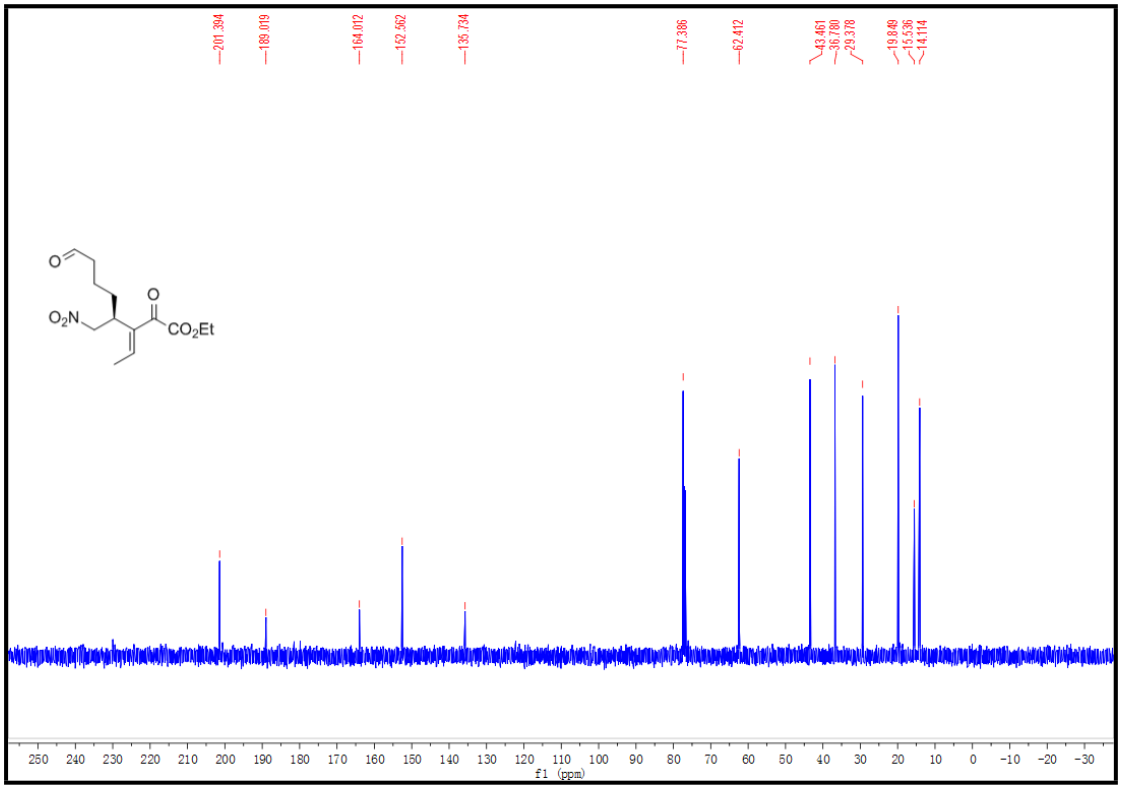
201.394
189.019
164.012
152.562
135.734
77.386
62.412
43.461
36.780
29.378
19.849
15.536
14.114
O
O2N
O
CO2Et
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)