Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

Pyrrolidine Modified PANF Catalyst for Asymmetric Michael Addition of Ketones to Nitrostyrenes in Aqueous Phase

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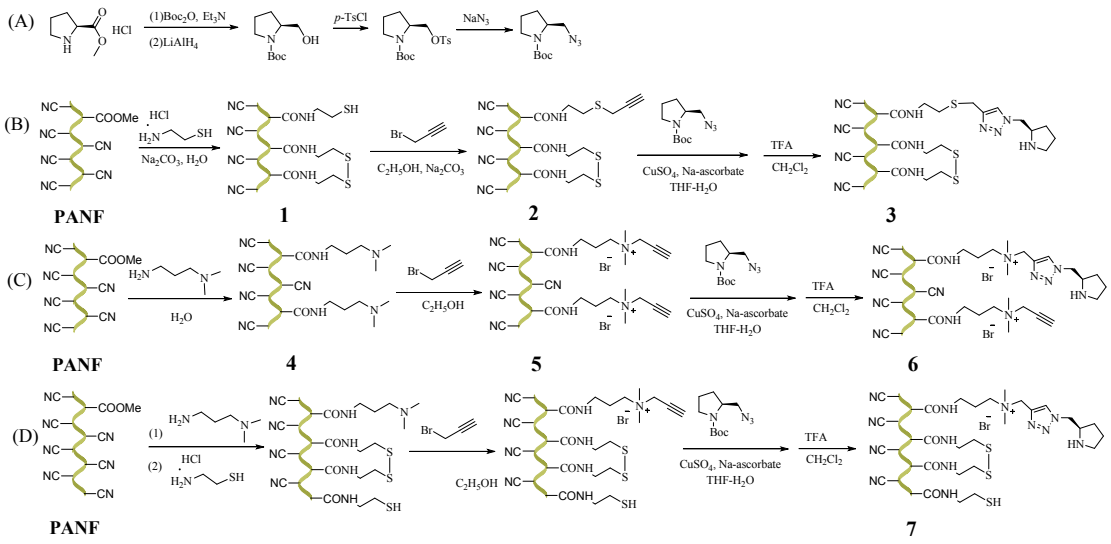
1. General Information

A commercially available polyacrylonitrile fiber (PANF) with a length of 10 cm and a diameter of 30 ± 0.5 μm (from the Fushun Petrochemical Corporation of China) was used. The aldehydes, ketones, *N*,*N*-dimethyl-1,3-propanediamine and all the other reagents were of analytical grade and used without further purification. Non-commercial materials were prepared and then purified by column chromatography.

FTIR spectra (Fourier Transform infrared spectroscopy) were obtained with an AVATAR360 FTIR spectrometer (Thermo Nicolet). Elemental analyses were performed on an Elementar vario EL analyzer. A Hitachi S-4800 scanning electron microscopy (SEM) was used to characterize the surface of the modified fibers. ^{1}H NMR spectra were recorded on BRUKER-AVANCE III (600 MHz) and BRUKER-AVANCE III (400MHz) instruments using tetramethyl silane as the internal standard. HPLC analysis was performed on Waters-Modol 510 using ChiralPak columns purchased from Daicel Chemical Industries, LTD. Racemic standard products were prepared under the catalysis of DL-proline to optimize the HPLC conditions. Optical rotations were determined using an Autopol IV automatic polarimeter. Contact angle measurements were conducted with a POWEREACH-JC2000DI contact angle system under room temperature. BET surface was determined by low pressure adsorption device with a pressure sensor of Microsensor-MPM480. The UV spectrophotometer was Pgeneral-t6newcentury.

2. Synthesis of the fiber catalysts



Scheme 1. Preparation of polyacrylonitrile fiber supported catalyst **3**, **6**, and **7**.

(A) Synthesis of *N*-Boc-2-azidomethylpyrrolidine

***N*-Boc-(*L*)-prolinol.**[1] L-proline methyl ester hydrochloride (8.28 g, 50 mmol), Boc_2O (12 g, 55 mmol) and Et_3N (15.2 mL, 110 mmol) were added to 80 mL of dry CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 18 h, and then washed with 0.5 mol/L of HCl aqueous solution, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, filtered, concentrated in vacuo to give a colorless oil (*N*-Boc- *L*-proline methyl ester).

The above colorless oil was added to a stirred suspension of $LiAlH_4$ (1.80 g, 48.03 mmol) in THF (40 mL) at 0 °C and stirred for 3 h. Then the reaction mixture was quenched with H_2O (1.8 mL), 15% aqueous NaOH (1.8 mL) and H_2O (5.4 mL). The precipitate was filtered and washed with ethyl acetate (100 mL). The filtrate was concentrated under vacuo and purified by flash column chromatography (ethyl acetate/hexane, 1:5) to give *N*-Boc-(*L*)-prolinol as a liquid (9.17 g, 95%).$[\alpha]_D^{20}$= -33.8° (c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.96 (m, 1H), 3.69-3.53 (m, 2H), 3.51-3.39 (m, 1H), 3.37-3.24 (m, 1H), 2.07-1.94 (m, 1H), 1.92-1.73 (m, 2H), 1.54 (s, 1H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.01, 80.12, 67.40, 60.09, 47.48, 28.61, 28.42, 24.23, 24.00.

O-tosyl-*N*-Boc-prolinol.[2] In a 50 mL round-bottom flask, *N*-Boc-(*L*)-prolinol (604 mg, 3 mmol) was dissolved in 3 mL of pyridine, and cooled to 0 °C. Then, *p*-toluenesulfonyl chloride (696 mg, 3.6 mmol) was added and the mixture was stirred at

0 ºC for 16 h. The reaction mixture was diluted with 150 mL of ethyl acetate and washed with 1 mol/L of HCl aqueous solution, saturated $NaHCO_3$ and finally with water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained colourless oil was purified by flash chromathography (hexane-ethyl acetate 5:1) (704 mg, 66%). $[\alpha]_D^{20}$= -53.0° (c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 7.3 Hz, 2H), 4.12-3.83 (m, 3H), 3.38-3.23 (m, 2H), 2.44 (s, 3H), 2.00-1.75 (m, 4H), 1.39 (s, 9H).

***N*-Boc-2-azidomethylpyrrolidine.**[2] O-tosyl-*N*-Boc-prolinol (703.5 mg, 1.98 mmol) and sodium azide (776 mg, 12 mmol) was added into 21 mL of DMSO and the resulting mixture was heated to 65 ºC for 12 h. Then, it was allowed to cool to room temperature, diluted with ethyl acetate (50 mL),washed with H_2O (3×30 mL) and brine (20 mL) and dried over Na_2SO_4. After removal of the ethyl acetate under reduced pressure, the *N*-Boc-2-azidomethylpyrrolidine was obtained as a colourless oil (355 mg, 80%). $[\alpha]_D^{20}$= -57.8° (c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.91 (m, 1H), 3.63-3.24 (m, 4H), 2.05-1.76 (m, 4H), 1.47 (s, 9H).

(B) Synthesis of catalyst 3

Fiber 1.

Dried **PANF** (1.000 g), cysteamine hydrochloride (1.36 g), deionized water (15 mL) and Na_2CO_3 (1.27 g) were added to a three-necked flask. The mixture was stirred and refluxed for 5 h. The treated fiber was filtered out and washed with 0.2 mol/L of HCl solution and then hot water (60-70 °C) until neutral. It was then dried overnight at 60 °C under vacuum to give the modified fiber **1**. The weight gain of fiber **1** based on **PANF** was 23%.

Fiber 2

Dried fiber **1** (1.000 g, 2.43 mmol/g cysteamine functions calculated by the weight gain), 3-bromopropyne (9.2 mmol), Na_2CO_3 (0.254 g) and 30 mL of ethanol were added to a three-necked flask. The mixture was stirred and heated at reflux for 6 h. The modified fiber was filtered out and washed with ethanol, 0.2 mol/L of HCl solution and hot water (60-70 °C) until neutral. The fiber was then dried overnight at

60 °C under vacuum to give the fiber **2** with an alkynyl functionality of 0.93 mmol/g.

Catalyst 3[3]

Fiber **2** (1.000 g), *N*-boc-2-azidomethylpyrrolidine (454 mg, 2 mmol), sodium ascorbate (118 mg, 0.6 mmol) and $CuSO_4 \cdot 5H_2O$ (75 mg, 0.3 mmol) were added to a solution of THF:H_2O=3:1 (35 mL) at room temperature for 24 h. Then the fiber was filtered and directly added to a mixture of CH_2Cl_2:TFA (trifluoroacetic acid) = 1:1 (30 mL) at room temperature for 12 h. After filtration, the fiber was added to a mixture of Et_3N:THF=2:98 (30 mL) for 1h. Then the catalyst **3** was sequentially washed with THF (with 2 % of Et_3N, 250 mL), water (250 mL), MeOH (250 mL). The weight gain of catalyst **3** based on fiber **2** was 5.5 % (0.46 mmol/g of chiral pyrrolidinyl groups). The loadings of disulfide bond, alkynyl, and chiral pyrrolidinyl groups of catalyst **3** are 0.66 mmol/g, 0.42 mmol/g, and 0.46mmol/g, respectively.

(C) Synthesis of catalyst 6

Aminated **fiber 4.**

Dried **PANF** (5.000 g), *N*,*N*-dimethyl-1,3-propanediamine (70 mL) and deionized water (30 mL) were added to a three-necked flask. The mixture was stirred and heated at reflux for 280 min. The treated fiber was filtered out and repeatedly washed with hot water (60-70 °C) until neutral. It was then dried overnight at 60 °C under vacuum to give the tertiary amine aminated fiber **4**. The weight gain of fiber **4** based on **PANF** was 24.0% (2.29 mmol/g tertiary amine functions calculated by weight gain and acid exchange capacity).[4]

Quaternized **fiber 5.**

Dried aminated fiber **4** (1.000 g), 3-bromopropyne (9.2 mmol) and 30 mL of ethanol were added to a three-necked flask. The mixture was stirred and heated at reflux for 5 h. The modified fiber was filtered out and washed with ethanol and deionized water. The fiber was then dried overnight at 60 °C under vacuum to give the fiber **5** with an alkynyl functionality of 1.57 mmol/g.

Catalyst 6

Quaternized fiber **5** (1.000 g), *N*-boc-2-azidomethylpyrrolidine (454 mg, 2 mmol),

sodium ascorbate (118 mg, 0.6 mmol) and $CuSO_4 \cdot 5H_2O$ (75 mg, 0.3 mmol) were added to a solution of THF:H_2O=3:1 (35 mL) at room temperature for 24 h. Then the fiber was filtered and directly added to a mixture of CH_2Cl_2:TFA (trifluoroacetic acid)=1:1 (30 mL) at room temperature for 12 h. After filtration, the fiber was added to a mixture of Et_3N:THF=2:98 (30 mL) for 1h. Then the catalyst **3** was sequentially washed with THF (containing 2 % of Et_3N, 250 mL), water (250 mL), MeOH (250 mL). The weight gain of catalyst **6** based on fiber **5** was 6.8% (0.58 mmol/g of chiral pyrrolidinyl groups). The loadings of tertiary amine, alkynyl, and chiral pyrrolidinyl group of catalyst **6** are 0.28 mmol/g, 0.89 mmol/g, and 0.58 mmol/g, respectively.

(D) Synthesis of catalyst 7

Dried fiber **4** (1.000 g), cysteamine hydrochloride (1.13 g), deionized water (15 mL) and Na_2CO_3 (1.07 g) were added to a three-necked flask. The mixture was stirred and refluxed for 3 h. The treated fiber was filtered out and washed with 0.2 mol/L of HCl solution, 0.2 mol/L of NEt_3 aqueous solution, and hot water (60-70 °C) until neutral. It was then dried overnight at 60 °C under vacuum to give the bi-functional fiber. The weight gain of bi-functional fiber based on fiber **4** was 13% (1.49 mmol/g).

The bi-functional fiber (1.000 g), 3-bromopropyne (9.2 mmol) and 30 mL of ethanol were added to a three-necked flask. The mixture was stirred and heated at reflux for 5 h. The modified fiber was filtered out and washed with ethanol and deionized water. The fiber was then dried overnight at 60 °C under vacuum to give the quaternization bi-functional fiber with an alkynyl functionality of 1.52 mmol/g. Then the fiber cycloaddition with *N*-boc-2-azidomethyl pyrrolidine, and deprotection with trifluoroacetic acid (TFA) to afford catalyst **7** (0.54 mmol/g). The loadings of thiol, disulfide bond, tertiary amine, alkynyl, and chiral pyrrolidinyl groups of catalyst **7** are 0.44 mmol/g, 0.36 mmol/g, 0.30 mmol/g, 0.89 mmol/g, and 0.54 mmol/g, respectively.

For the quaternization process, the 3-bromopropyne can only reacted with tertiary amine group. Because the quaternization between tertiary amine and 3-bromopropyne can be easily occurred without extra base. However, the reaction between thiol and 3-

bromopropyne must use adequate amount of Na_2CO_3 to neutralize the thiol to form thiol anion which was much easier to react with 3-bromopropyne. Therefore, without addition of Na_2CO_3, the 3-bromopropyne can only reacted with tertiary amine group.

3. The determination of disulfide formation

The disulfide formation was determined by Ellman reagent.

Method:

1. Prepare 10 mmol/L DTNB (5,5'-dithiobis-(2-nitrobenzoic acid) stock solution by dissolving 40 mg DTNB in 10 mL DMSO. Dilute the stock solution 100 fold with 0.1 mol/L Tris-HCl pH 7.5 to make 0.1 mmol/L DTNB working solution.

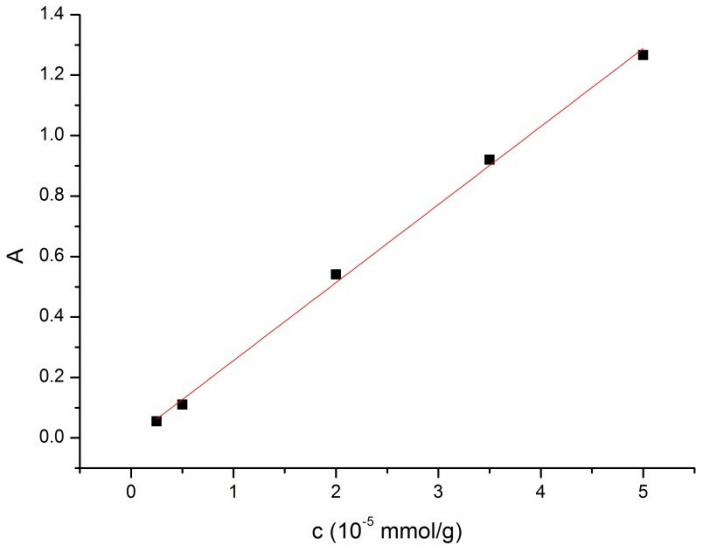
2. A series of DTT (DL-Dithiothreitol) (starting at 0.1 mmol/L) was prepared. 10 mL of DTT standard solutions and 10 mL of 0.1mM DTNB were mixed . A standard SH calibration curve was set up by UV spectrophotometer (UV wavelength 412 nm).

3. Sample 1: Appropriate amount of fiber **1** (**3** and **7**) was added to 10 mL of 0.1mmol/L DTNB working solution at 30 ^oC for 2 h. The filtrates of samples 1 was determined by UV spectrophotometer.

Sample 2: Appropriate amount of fiber **1** (**3** and **7**) was added to a mixture of 10 mL (0.063 mmol/L) of TCEP (tris(2-carboxyethyl)phosphine) stirred at 30 ^oC for 2 h. Then 10 mL of 0.1 mmol/L DTNB working solution was added and stirred at 30 ^oC for 2 h. The filtrate of samples 2 was determined by UV spectrophotometer. The results were list in Table 1.

Table 1. The preparation of standard S-H calibration curve.

Entry	1	2	3	4	5
C (10^{-5} M)	0.25	0.5	2	3.5	5
A	0.055	0.110	0.541	0.920	1.266

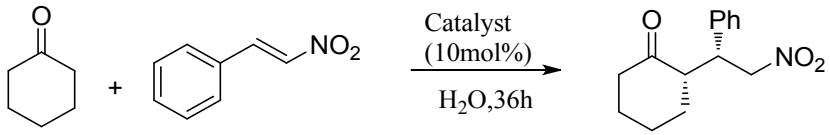


Results:

Table 2. the functional groups of free thiol and S-S bond.

	Fiber **1**	Catalyst **3**	Catalyst **7**
Free thiol (mmol/g)	0.97	0.00	0.44
S-S bond (mmol/g)	0.73	0.66	0.36

4. Typical procedure for the Michael reaction



Trans-β-nitrostyrene (120 mg, 0.8 mmol), cyclohexanone (1.5 mL, 16 mmol), catalyst **6** (0.14 g, 10 mol %) and 9 mol% *p*-toluenesulfonic acid were added to 20 mL of water. The suspension was stirred at 20 °C for 36 h and then directly filtered. The fiber washed with water and the organic filtrate was concentrated under reduced pressure. Its ^{1}H NMR spectrum was integrated to calculate the diasteromeric ratio (syn/anti = 97:3) and the product was purified by flash chromatography on silica gel (EtOAc/Hexane) to afford the syn Michael adduct (164 mg, 83%) as a white solid. The enantiomeric excess was determined by HPLC on a chiral phase chiralpak AD-H column (99% ee).

5. The BET surfaces of fiber catalyst

Table 3. The BET surfaces of PANF, catalyst **3**, **6**, and **7**.

	PANF	**Catalyst 3**	**Catalyst 6**	**Catalyst 7**
BET surface (m^2/g)	43	48	44	52

The BET surfaces of PANF, catalyst **3**, **6**, and **7** are 43 m^2/g, 48 m^2/g, 44 m^2/g, and 52 m^2/g, respectively. The results showed that the modified catalysts **3, 6,** and **7** have similar surface areas to PANF, demonstrating that the surface areas change slightly after the modification and the high catalytic activities of the catalyst suggest that the reaction performed beneath the surface of the modified fiber .

6. The absorption capacity of catalyst 6 for reactants

Trans-β-nitrostyrene (120 mg, 0.8 mmol), cyclohexanone (1.5 mL, 16 mmol), and catalyst **6** (0.14 g, 10 mol %) were added to 20 mL of water and stirred at 20 ^oC for 1 h. The fibers was directly filtered and washed with water. The absorption capacities of *trans-β*-nitrostyrene and cyclohexanone were characterized by HPLC and GC using phenol as internal standard. Finally, the absorption capacity of catalyst **6** for *trans-β*-nitrostyrene is 1.58 mmol/g and the absorption capacity for cyclohexanone is 11.20 mmol/g under the optimized condition.

7. The time-on-stream of the flow system

The flow system was consisted of a 13 cm silica column between flask and peristaltic pump. The silica column packed with 210 mg of catalyst **6** (0.48 mmol/g) which was kept at 20 ^oC in thermostatic bath. A solution of *trans-β*-nitrostyrene (447 mg, 3 mmol), cyclohexanone (3 mL), and 20 mg *p*-toluenesulfonic acid in 30 mL of ethanol and 30 mL of water was pumped into the system at 0.028 mL/min. Both the conversion and enantiomeric ratio of the final product were determined by HPLC analysis of periodically collected samples using naphthalene as internal standard. The experiment was run for 36 h and samples were collected every 3 hours from 3 h to 36 h. The result was listed in Table 4.

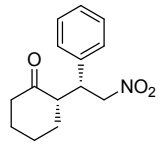
Table 4. The result of time-on-stream of the flow system.

Time (h)	Conversion (%)	Ee (%)	Time (h)	Conversion (%)	Ee %
3	62	98	21	69	99
6	70	99	24	62	99

9	76	99	27	60	98
12	71	99	30	58	98
15	58	98	33	62	99
18	60	99	36	60	98

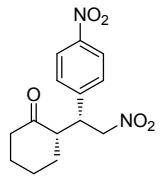
8. Spectroscopic and chromatographic data for Michael adducts

(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclohexanone[2] (entry 1, Table 3):



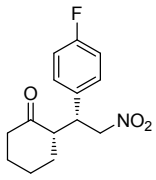
$[\alpha]_D^{20}$ = -22.4° (99% ee, c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.23 (m, 3H), 7.17 (d, J = 7.5 Hz, 2H), 4.94 (dd, J = 12.5, 4.5 Hz, 1H), 4.63 (m, 1H), 3.76 (td, J = 9.9, 4.5 Hz, 1H), 2.75-2.64 (m, 1H), 2.53-2.43 (m, 1H), 2.38 (m, J = 12.5, 6.0 Hz, 1H), 2.12-2.02 (m, 1H), 1.81-1.51 (m, 4H)，1.23 (m, 1H). The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 1 mL·min^{-1}): t_R = 11.2 min (minor), 14.6 min (major).

(*S*)-2-[(*R*)-2-Nitro-1-(4-nitrophenyl)ethyl]cyclohexanone [5] (entry 2, Table 3):



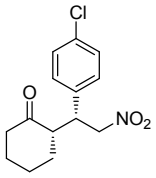
$[\alpha]_D^{20}$ = -10.4° (91% ee, c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 5.00 (dd, J = 13.0, 4.3 Hz, 1H), 4.81-4.60 (m, 1H), 3.94 (td, J = 9.7, 4.3 Hz, 1H), 2.78-2.66 (m, 1H), 2.50 (d, J = 12.9 Hz, 1H), 2.38 (ddd, J = 27.1, 16.7, 5.8 Hz, 1H), 2.11 (m, 1H), 1.81 (t, J = 23.5 Hz, 1H), 1.76-1.52 (m, 3H), 1.33-1.20 (m, 1H). The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 2 mL·min^{-1}): t_R = 15.8 min (minor), 20.7 min (major).

(*S*)-2-[(*R*)-1-(4-Fluorophenyl)-2-nitroethyl]cyclohexanone[5] (entry 3, Table 3):



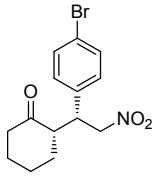
$[\alpha]_D^{20}$ = -15.2° (91% ee, c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21-7.11 (m, 2H), 7.09-6.97 (m, 2H), 4.93 (dd, *J* = 12.5, 4.3 Hz, 1H), 4.68-4.54 (m, 1H), 3.77 (s, 1H), 2.77-2.58 (m, 1H), 2.58-2.26 (m, 2H), 2.09 (m, 1H), 1.90-1.52 (m, 4H), 1.37-1.13 (m, 1H). The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 1 mL·min^{-1}): t_R = 9.4 min (minor), 12.1 min (major).

(*S*)-2-[(*R*)-1-(4-Chlorophenyl)-2-nitroethyl]cyclohexanone[5] (entry 4, Table 3)



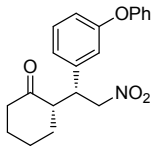
$[\alpha]_D^{20}$ = -14.8° (94% ee, c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 4.94 (dd, *J* = 12.6, 4.5 Hz, 1H), 4.60 (m, 1H), 3.76 (td, *J* = 9.9, 4.4 Hz, 1H), 2.74-2.61 (m, 1H), 2.47 (d, *J* = 12.8 Hz, 1H), 2.42-2.28 (m, 1H), 2.15-2.04 (m, 1H), 1.88-1.53 (m, 4H), 1.38-1.15 (m, 1H). The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 1.5 mL·min^{-1}): t_R = 5.3 min (minor), 5.9 min (major).

(*S*)-2-[(*R*)-1-(4-Bromophenyl)-2-nitroethyl]cyclohexanone[5] (entry 5, Table 3):



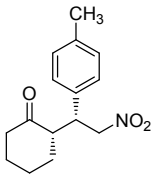
$[\alpha]_D^{20}$ = -12.2° (91% ee, c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 4.94 (dd, *J* = 12.6, 4.5 Hz, 1H), 4.63-4.57 (m, 1H), 3.76 (td, *J* = 9.9, 4.4 Hz, 1H), 2.73-2.60 (m, 1H), 2.47 (d, *J* = 13.0 Hz, 1H), 2.42-2.27 (m, 1H), 2.08 (dt, *J* = 22.3, 11.4 Hz, 1H), 1.84-1.52 (m, 4H), 1.35-1.14 (m, 1H). The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 1.0 mL·min^{-1}): t_R = 11.1 min (minor), 14.5 min (major).

(*S*)-2-[(*R*)-2-Nitro-1-(3-phenoxyphenyl)ethyl]cyclohexanone (entry 6, Table 3)



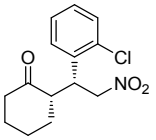
$[\alpha]_D^{20}$ = -9.4° (85% ee, c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.26 (m, 1H), 7.11 (m, 1H), 7.00-6.96 (m, 2H), 6.89 (m, 3H), 4.93 (dd, *J* = 12.5, 4.4 Hz, 1H), 4.62-4.54 (m, 1H), 3.73 (td, *J* = 10.0, 4.4 Hz, 1H), 2.63 (td, *J* = 11.5, 4.9 Hz, 1H), 2.46 (d, *J* = 12.9 Hz, 1H), 2.41-2.28 (m, 1H), 2.16-2.02 (m, 1H), 1.86-1.53 (m, 4H), 1.37-1.13 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 211.75, 157.60, 156.87, 139.80, 130.28, 129.86, 123.50, 123.13, 118.86, 118.55, 118.02, 78.77, 52.42, 43.86, 42.77, 33.28, 28.82, 28.55, 25.47, 25.08.The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 1.0 mL·min^{-1}): t_R = 10.1 min (minor), 15.8 min (major).

(*S*)-2-[(*R*)-2-Nitroethyl -1-(4-tolyl)]cyclohexanone[5] (entry 7, Table 3):



$[\alpha]_D^{20}$ = -12.0° (87% ee, c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 4.96-4.88 (m, 1H), 4.65-4.56 (m, 1H), 3.74 (dt, *J* = 14.4, 9.9, 4.5 Hz, 1H), 2.66 (td, *J* = 11.3, 5.0 Hz, 1H), 2.47 (dd, *J* = 9.6, 3.3 Hz, 1H), 2.42-2.34 (m, 1H), 2.31 (s, 3H), 2.12-2.03 (m, 1H), 1.81-1.53 (m, 4H), 1.31-1.15 (m, 1H). The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 1.0 mL·min^{-1}): t_R = 13.3 min (minor), 20.3 min (major).

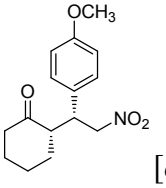
(*S*)-2-[(*R*)-1-(2-Chlorophenyl)-2-nitroethyl] cyclohexanone[6] (entry 8, Table 3)



$[\alpha]_D^{20}$ = -34.2° (90% ee, c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 1H), 7.26-7.18 (m, 3H), 4.92-4.89 (m, 2H), 4.29 (d, *J* = 4.9 Hz, 1H), 2.92 (s, 1H), 2.48 (d, *J* = 12.9 Hz, 1H), 2.39 (td, *J* = 12.9, 6.0 Hz, 1H), 2.17-2.06 (m, 1H), 1.86-1.53 (m, 4H), 1.41-1.27 (m, 1H). The enantiomeric excess was

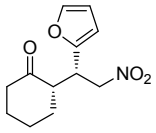
determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 1.0 mL·min-1): t_R = 8.5 min (minor), 10.6 min (major).

(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone[2] (entry 9, Table 3)



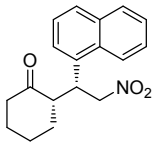
$[\alpha]_D^{20}$ = -14.2° (93% ee, c = 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.5 Hz, 2H), 6.41 (d, *J* = 13.1 Hz, 2H), 5.86 (dd, *J* = 15.7, 9.6 Hz, 1H), 4.59-4.51 (m, 1H), 3.80 (s, 3H), 3.31 (qd, *J* = 8.6, 4.9 Hz, 1H), 2.57-2.48 (m, 1H), 2.43 (t, *J* = 16.0 Hz, 1H), 2.35 (m, 1H), 2.17 (d, *J* = 13.7 Hz, 1H), 2.08 (dd, *J* = 18.8, 14.8 Hz, 1H), 1.90 (d, *J* = 5.0 Hz, 1H), 1.73-1.60 (m, 2H), 1.45 (dt, *J* = 21.6, 10.7 Hz, 1H). The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 1.0 mL·min-1): t_R = 10.9 min (minor), 13.6 min (major).

(*S*)-2-[(*R*)-1-(2-Furanyl)-2-nitroethyl]cyclohexanone[5] (entry 10, Table 3):



$[\alpha]_D^{20}$ = -7.4° (83% ee, c = 1.0, CH_2Cl_2).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 10.8 Hz, 1H), 6.29 (s, 1H), 6.18 (d, *J* = 2.9 Hz, 1H), 4.79 (dd, *J* = 12.5, 4.7 Hz, 1H), 4.67 (dd, *J* = 12.2, 9.7 Hz, 1H), 3.97 (td, *J* = 9.2, 4.7 Hz, 1H), 2.82-2.70 (m, 1H), 2.45 (t, *J* = 17.8 Hz, 1H), 2.37 (td, *J* = 12.8, 6.2 Hz, 1H), 2.07 (d, *J* = 33.2 Hz, 1H), 1.90-1.58 (m, 4H), 1.41-1.21 (m, 1H). The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 1.0 mL·min^{-1}): t_R = 11.1 min (major), 13.5 min (minor).

(*S*)-2-[(*R*)-1-(1-Naphthyl)-2-nitroethyl]cyclohexanone[7] (entry 11, Table 3)

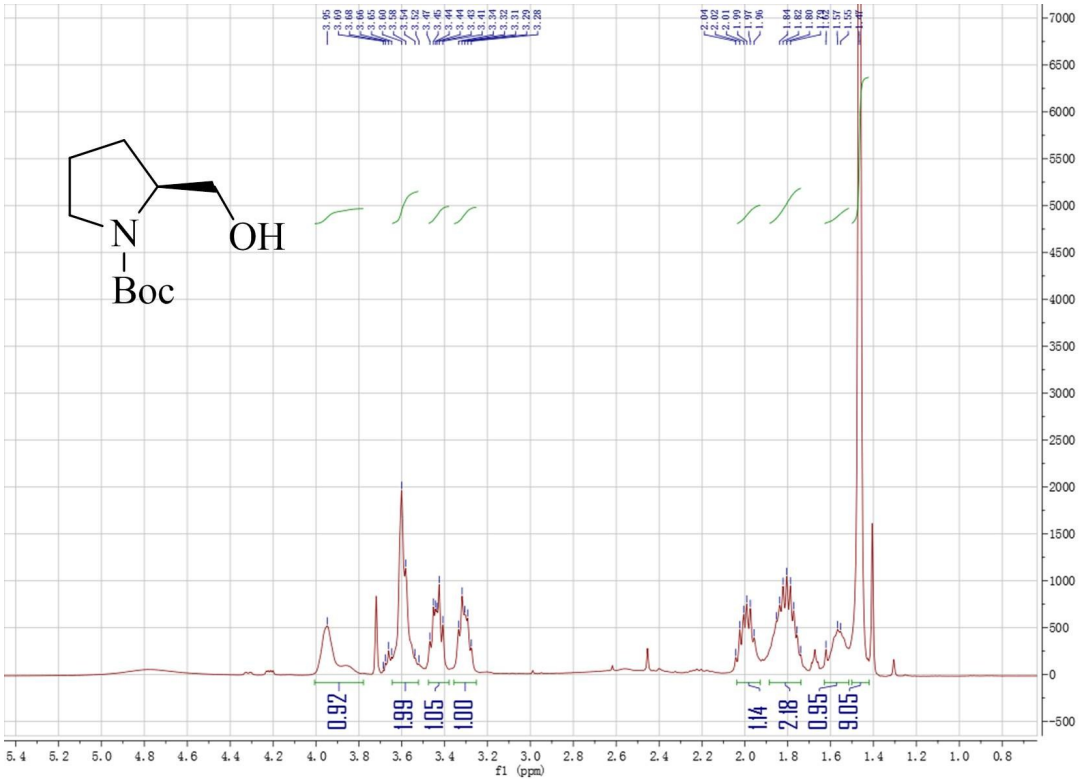


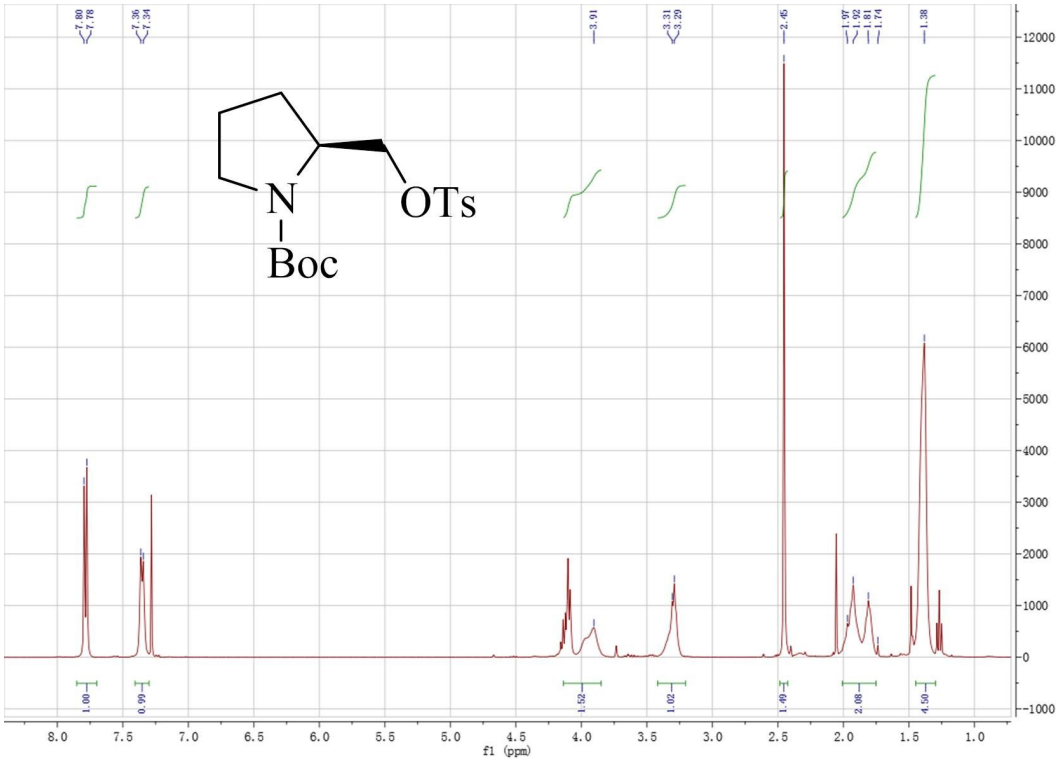
$[\alpha]_D^{20}$ = -14.0° (84% ee, c = 1.0, CH_2Cl_2).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (m, 3H), 7.63 (s, 1H), 7.57-7.44 (m, 2H), 7.29 (m, 1H), 5.02 (dd, *J* = 12.6, 4.4 Hz, 1H), 4.87-4.67 (m, 1H), 3.95 (td, *J* = 10.0, 4.4 Hz, 1H), 2.86-2.73 (m, 1H), 2.50 (d, *J* = 13.0 Hz, 1H), 2.40 (td, *J* = 12.9, 6.0 Hz, 1H), 2.08 (dd, *J* = 21.6, 15.2

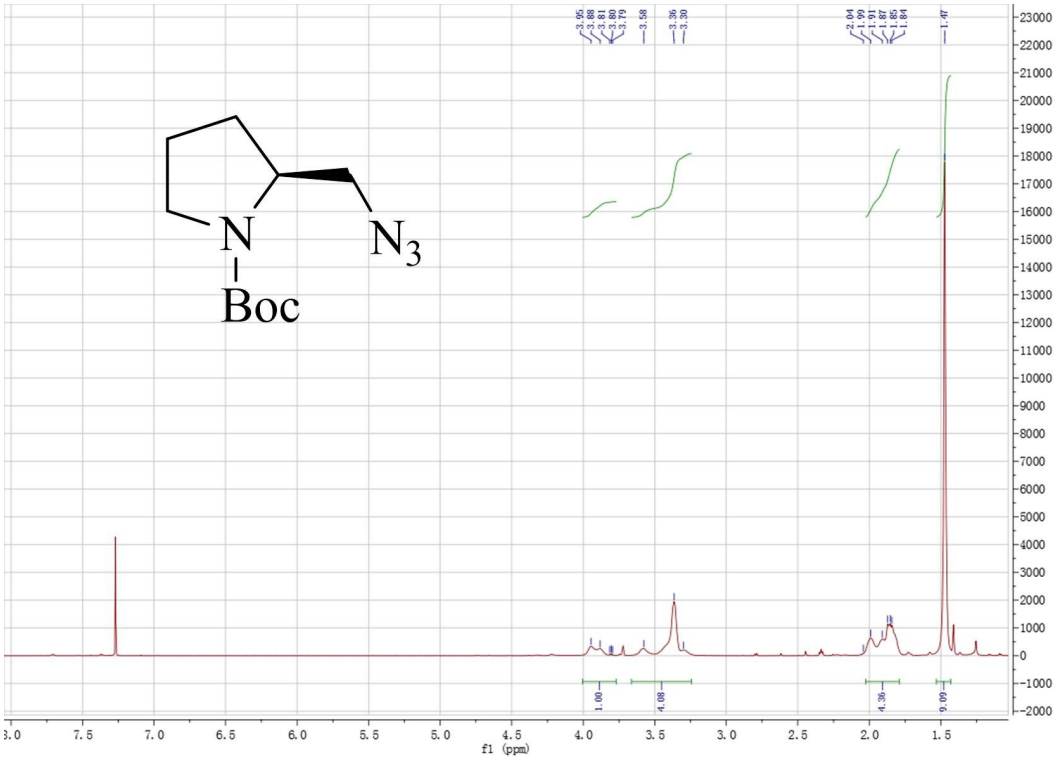
Hz, 1H), 1.81-1.50 (m, 4H), 1.32-1.20 (m, 1H). The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane: 2-propanol = 90:10, 1.0 mL·min^{-1}): t_R = 12.7 min (minor), 17.6 min (major).

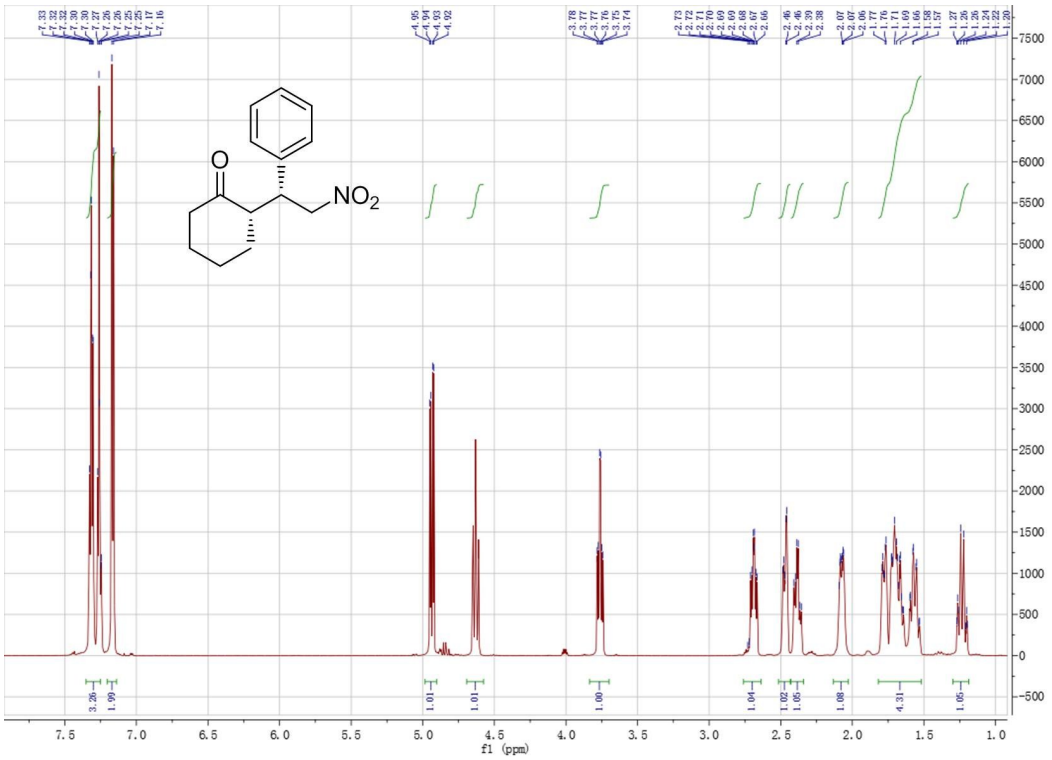
9. NMR and HPLC spectra for Michael adducts

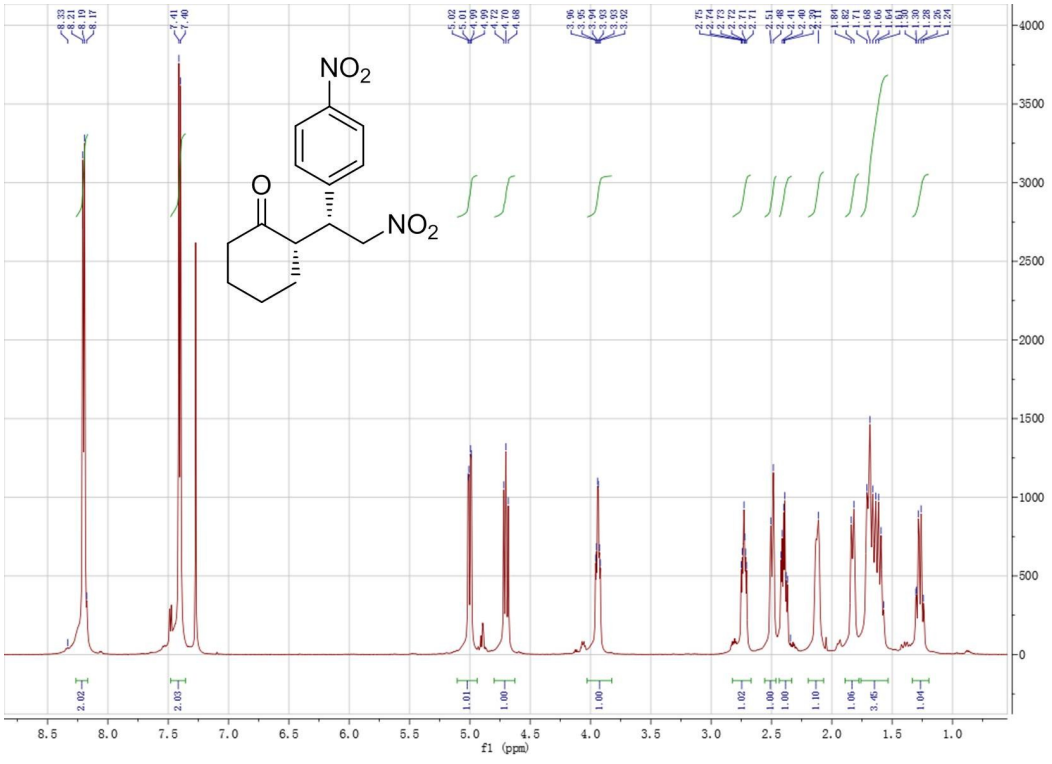
(A) NMR spectra

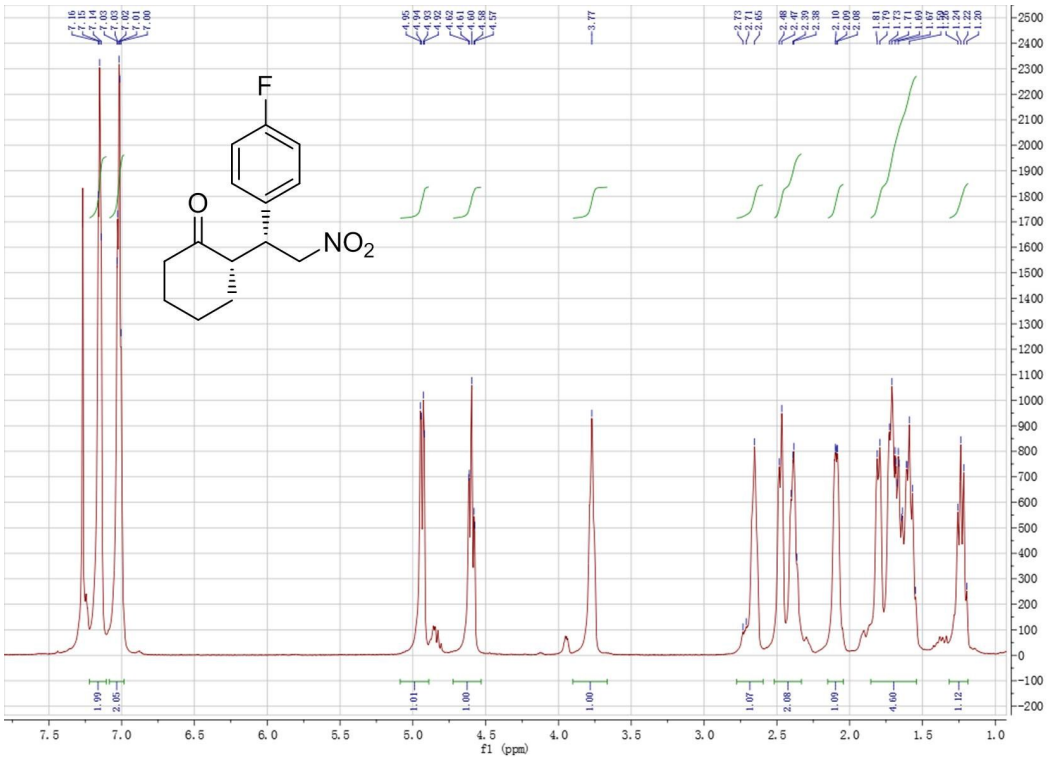


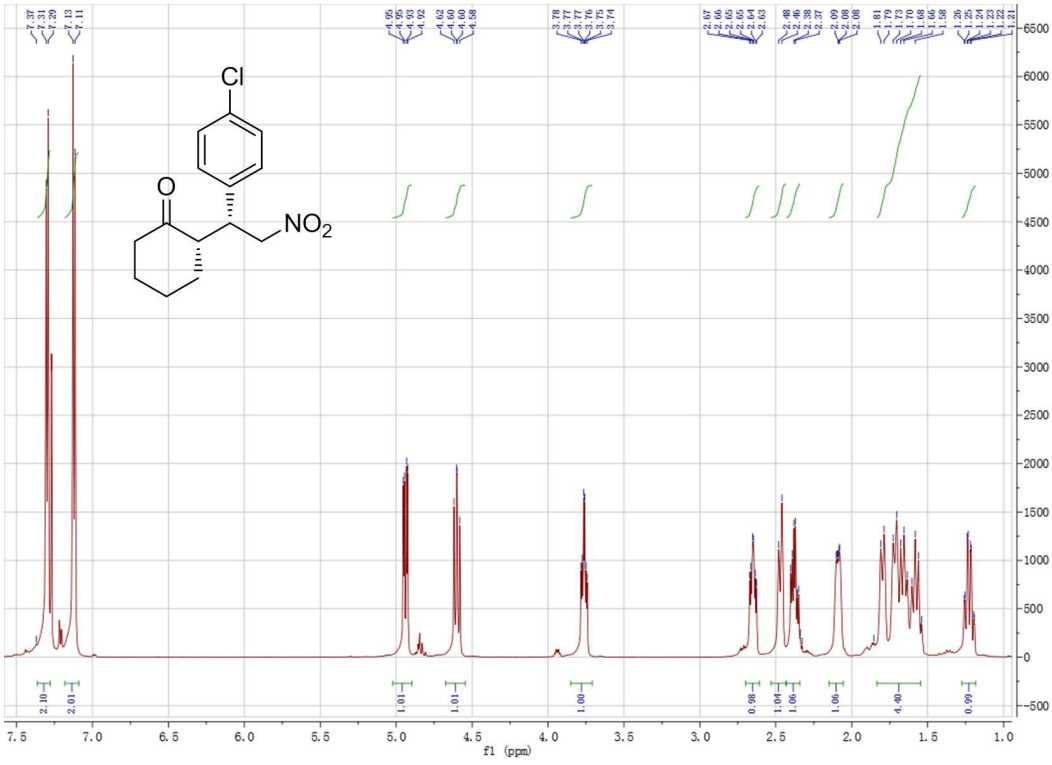

7.80
7.78
7.36
7.34
3.91
3.31
3.29
2.45
1.97
1.92
1.81
1.74
1.38
N
OTs
Boc
1.00
0.99
1.52
1.02
1.49
2.08
4.50
f1 (ppm)

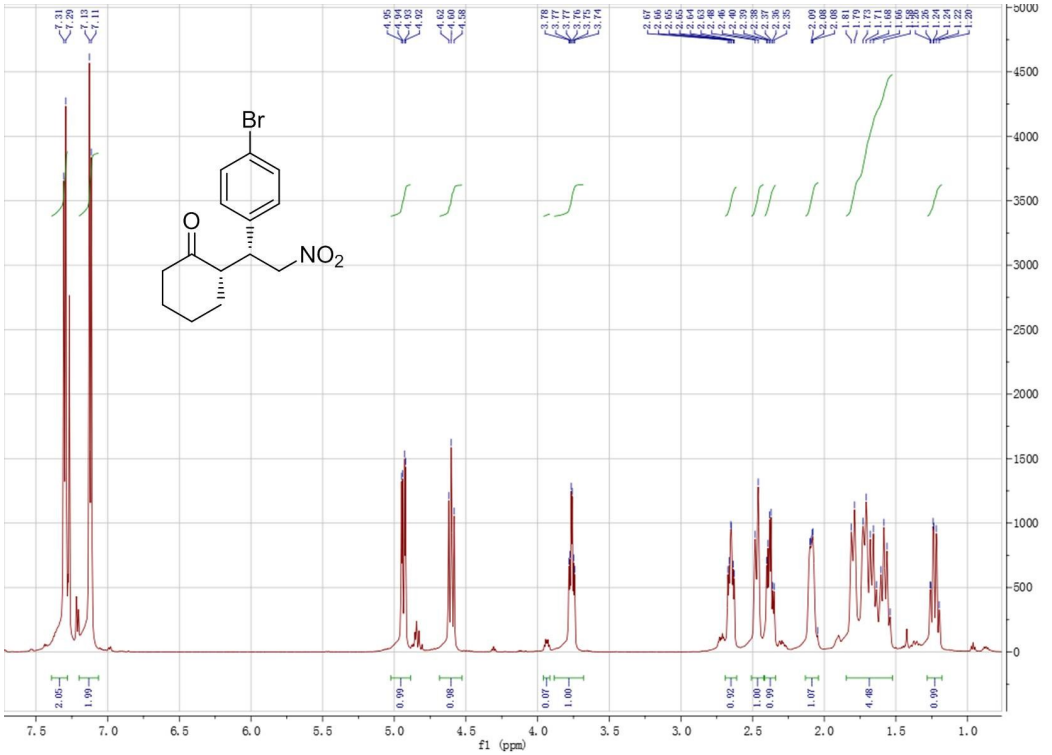

3.95
3.88
3.81
3.80
3.79
3.58
3.36
3.30
2.04
1.99
1.91
1.87
1.85
1.84
1.47
N
N3
Boc
1.00
4.08
4.36
9.09
f1 (ppm)

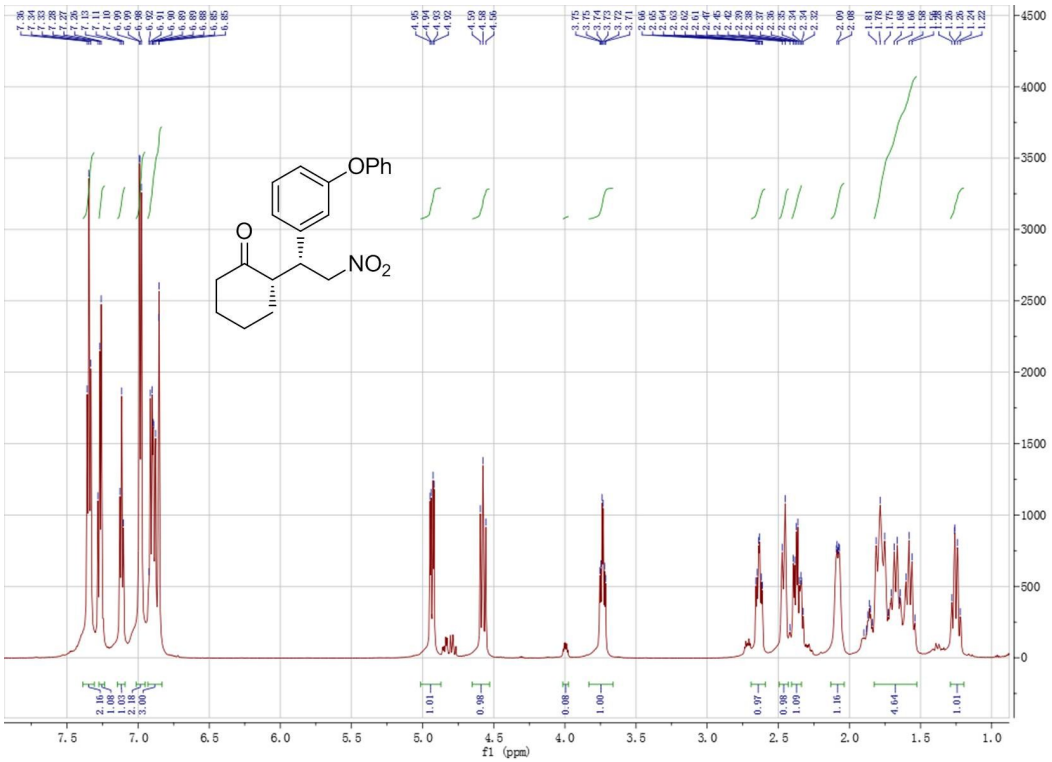

O
NO2
f1 (ppm)

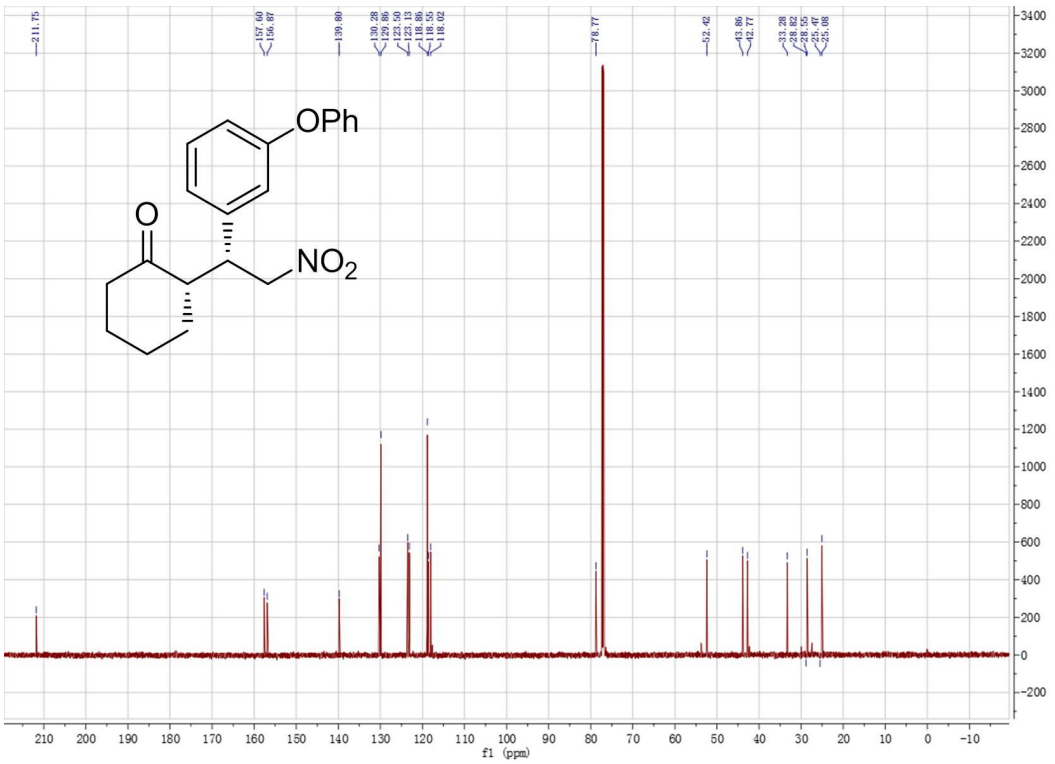

NO2
O
NO2
f1 (ppm)

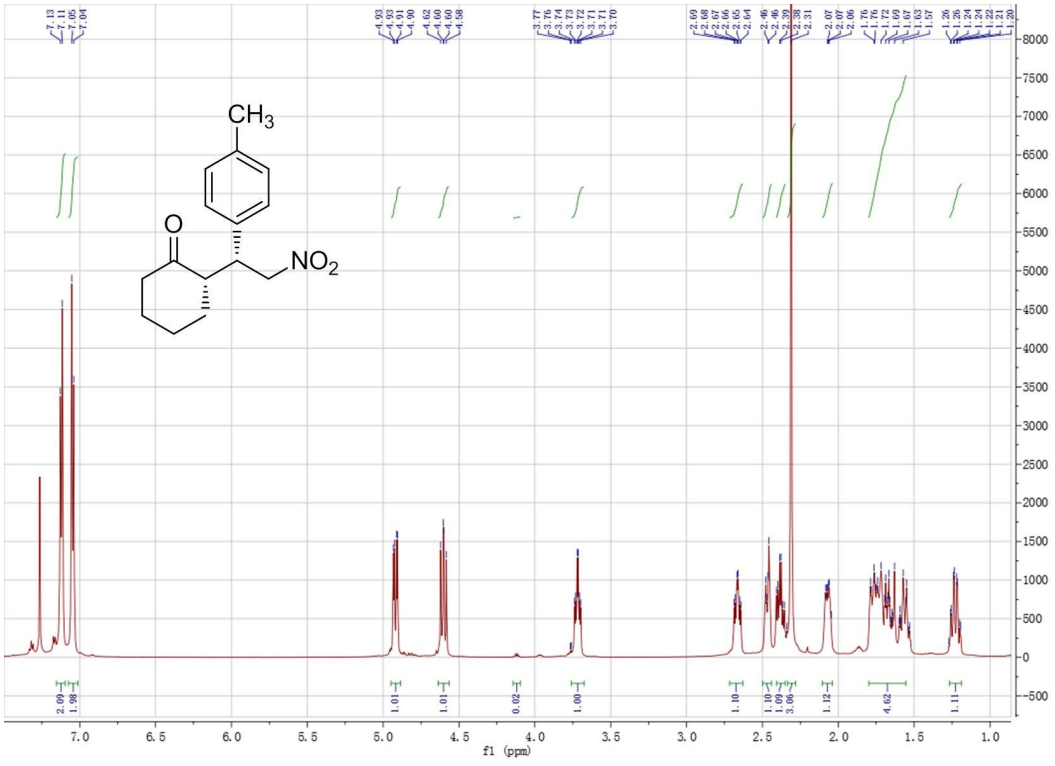

F
O
NO2
f1 (ppm)

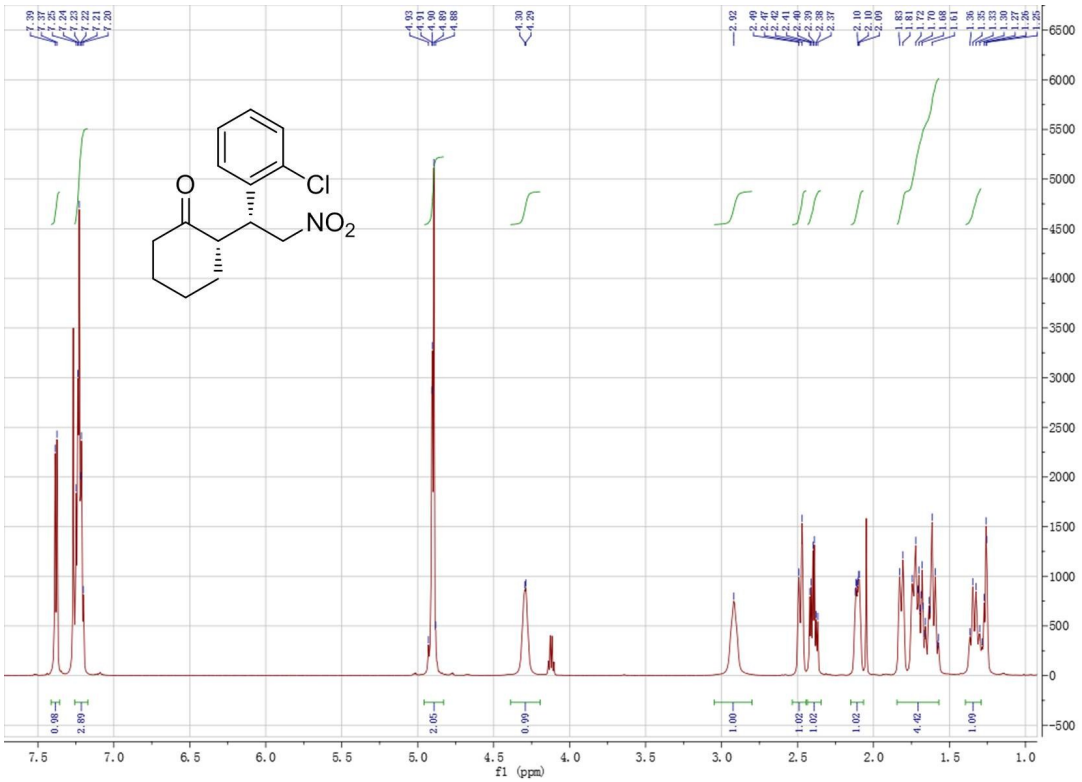

Cl
O
NO2
f1 (ppm)

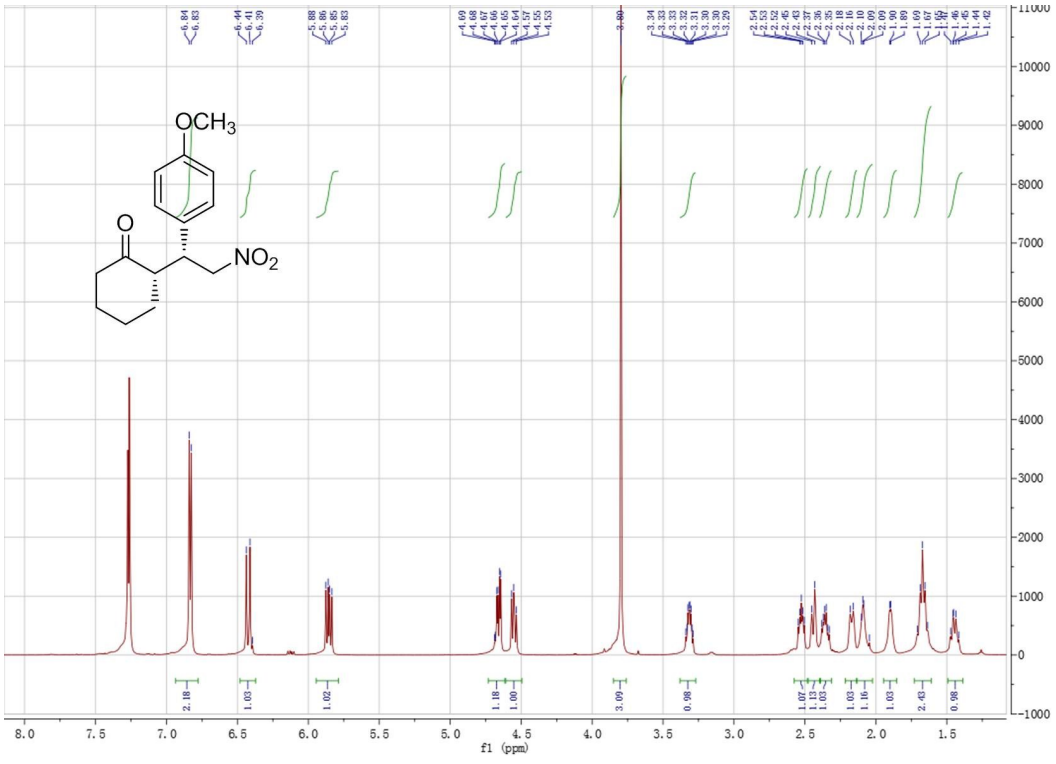

Br
O
NO2
f1 (ppm)

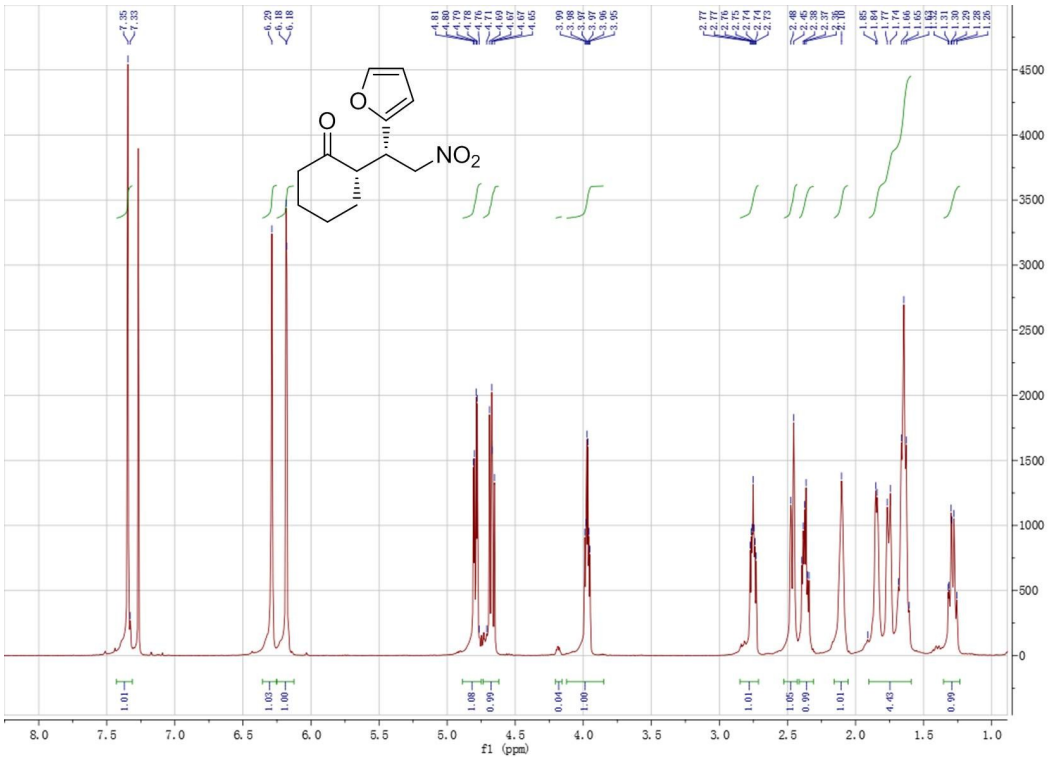

OPh
O
NO2
f1 (ppm)

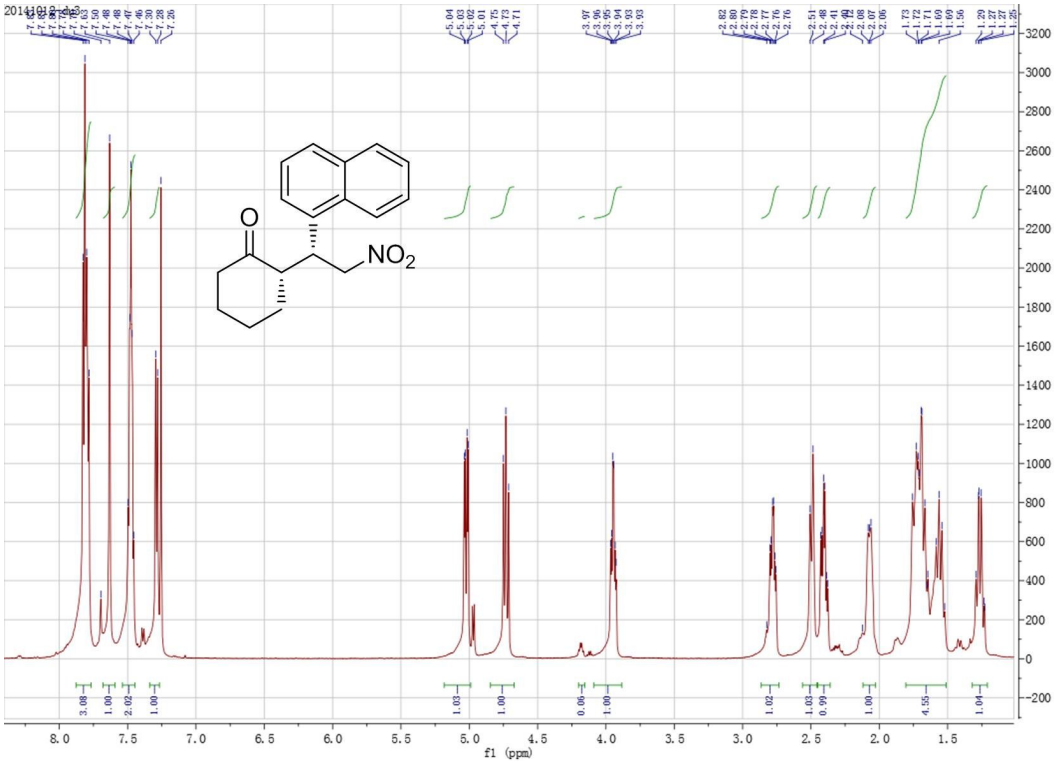

OPh
O
NO2
f1 (ppm)


CH3
O
NO2
f1 (ppm)


O
Cl
NO2
f1 (ppm)

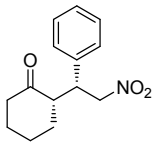

OCH3
O
NO2
f1 (ppm)



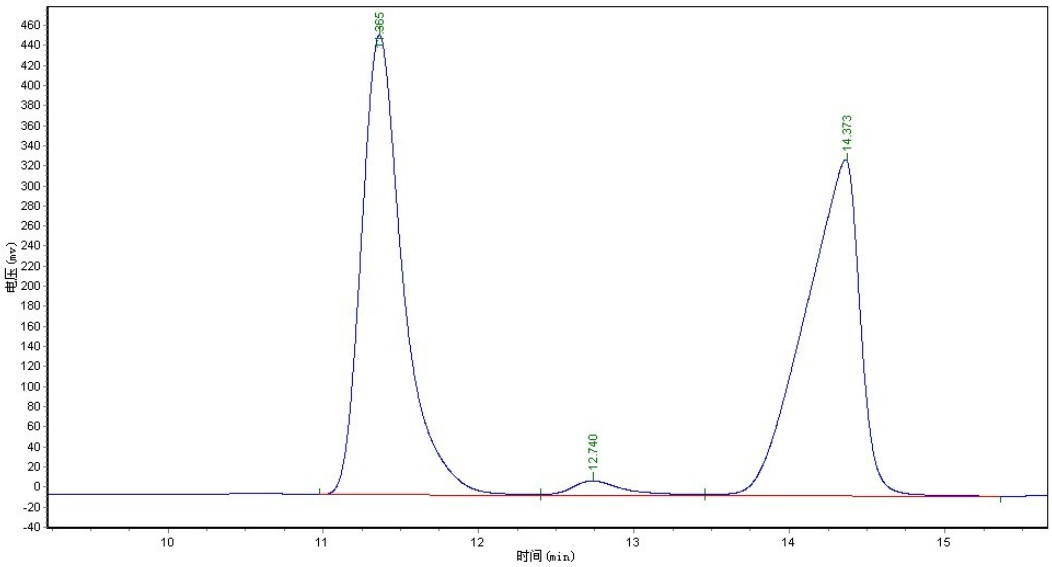


(B) HPLC spectra

(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclohexanone (4a):

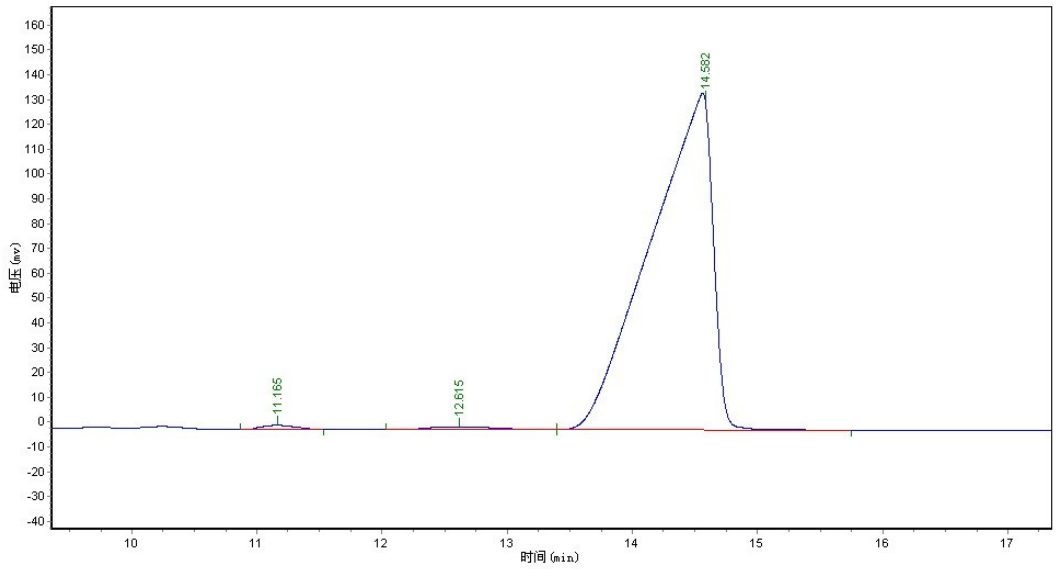


Racemic:



entry	R.T. (min)	Height	Area	Area %
1	11.365	458158	8511790	50.0117
2	12.740	14456	332384	1.9530
3	14.373	334280	8175413	48.0353

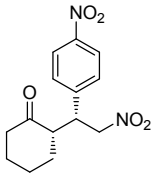
Nonracemic: Table 3, entry 1



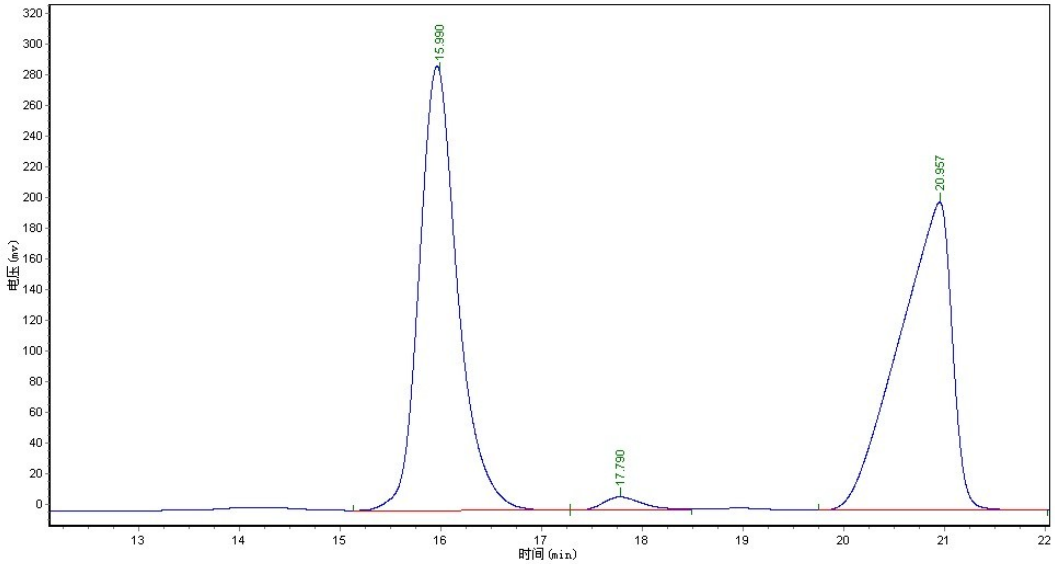
entry	R.T. (min)	Height	Area	Area %
1	11.165	1655	29836	0.6278

2	12.615	1104	41960	0.8829
3	14.582	135086	4680611	98.4893

(*S*)-2-[(*R*)-2-Nitroethyl-1-(4-nitrophenyl)]cyclohexanone (4b):

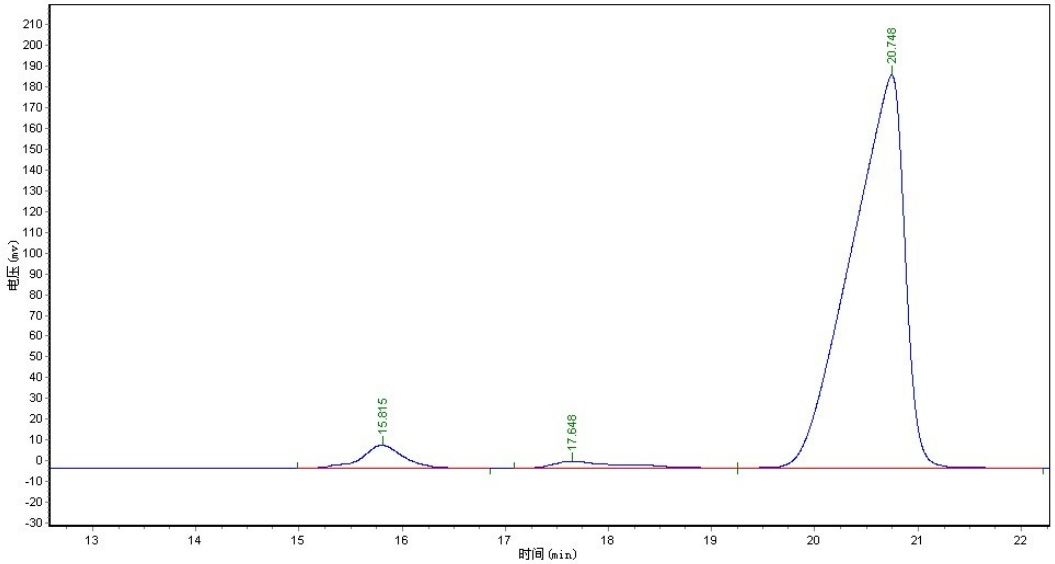


Racemic:



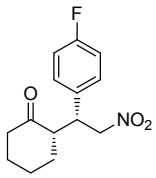
entry	R.T. (min)	Height	Area	Area %
1	15.990	288796	7703755	50.3775
2	17.790	8732	247181	1.6164
3	20.957	200100	7341127	48.0061

Nonracemic: Table 3, entry 2

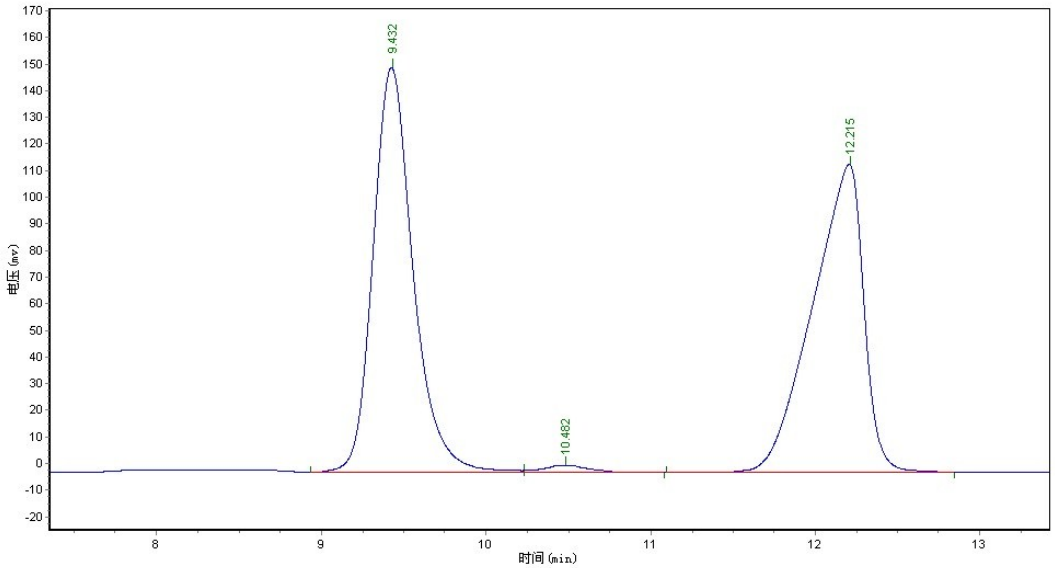


entry	R.T. (min)	Height	Area	Area %
1	15.815	11010	317087	4.3206
2	17.648	3347	166963	2.2750
3	20.748	188513	6854952	93.4044

(*S*)-2-[(*R*)-1-(4-Fluorophenyl)-2-nitroethyl]cyclohexanone (4c):



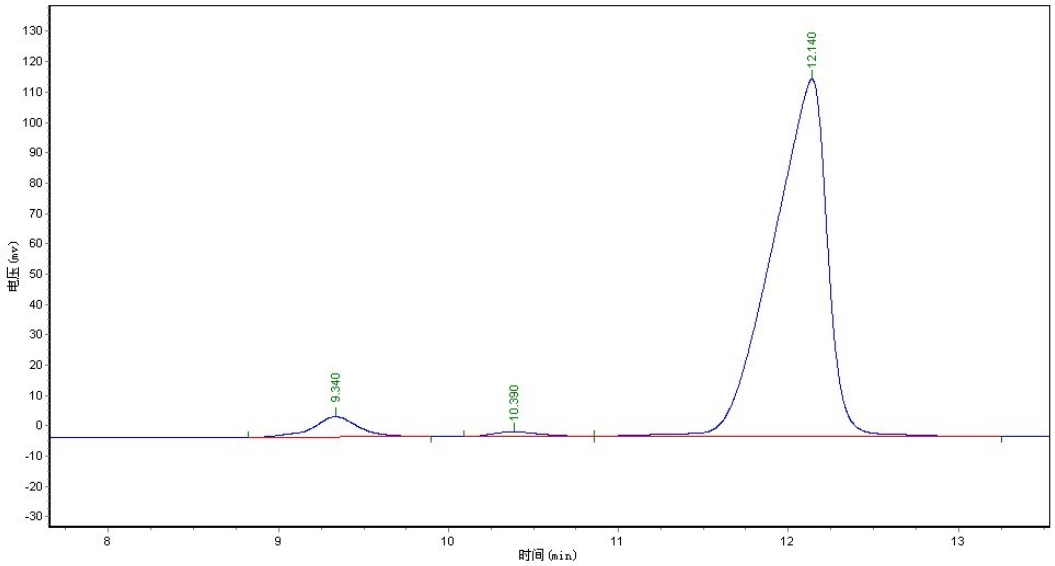
Racemic:



entry	R.T. (min)	Height	Area	Area %
1	9.432	151778	2566206	50.2029
2	10.482	2707	50752	0.9929

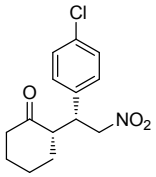
3	12.215	115366	2494707	48.8042

Nonracemic: Table 3, entry 3

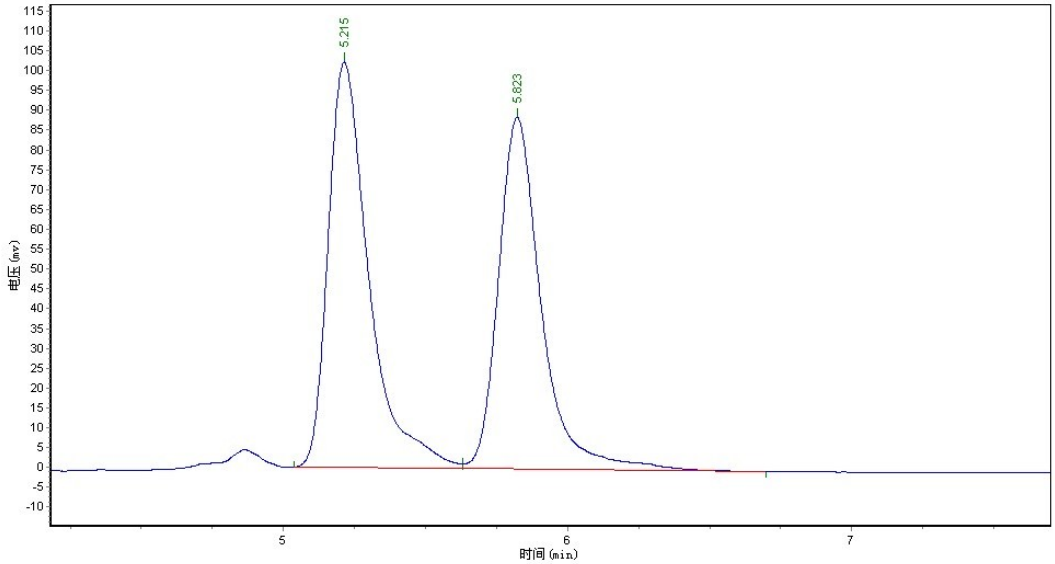


entry	R.T. (min)	Height	Area	Area %
1	9.340	6690	126032	4.5069
2	10.390	1705	34489	1.2333
3	12.140	117463	2635899	94.2598

(*S*)-2-[(*R*)-1-(4-Chlorophenyl)-2-nitroethyl]cyclohexanone (4d):

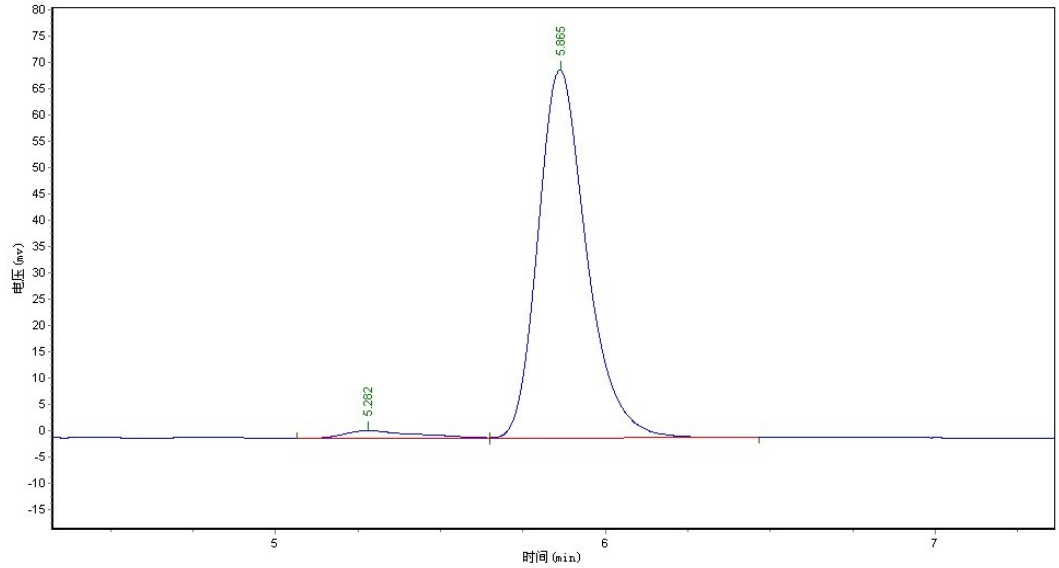


Racemic:



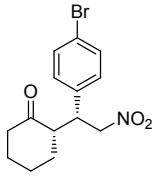
entry	R.T. (min)	Height	Area	Area %
1	5.215	101931	1017520	52.2363
2	5.823	88480	930298	47.7637

Nonracemic: Table 3, entry 4

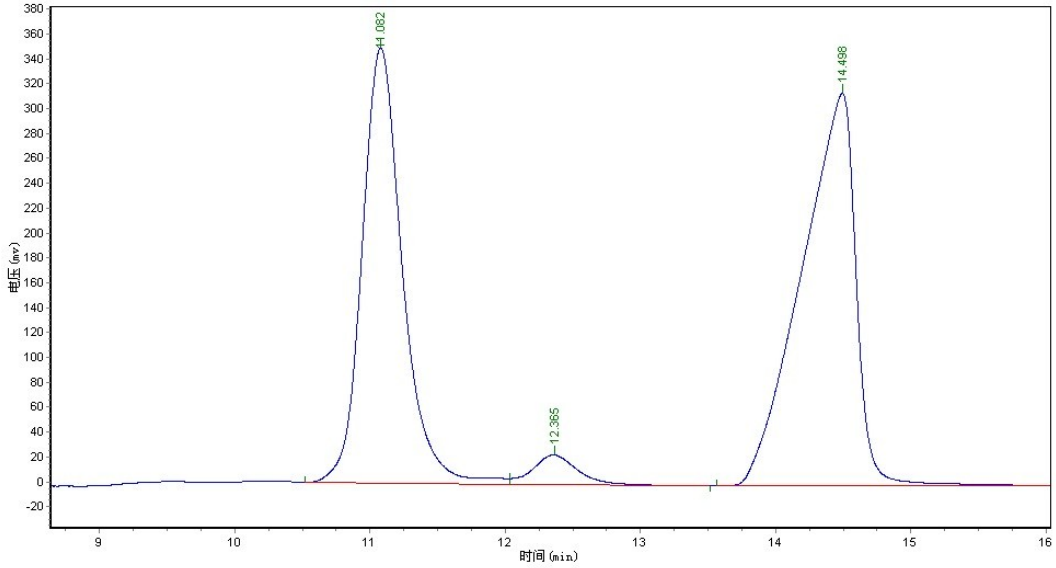


entry	R.T. (min)	Height	Area	Area %
1	5.282	1505	21309	2.8994
2	5.865	70043	713657	97.1006

(*S*)-2-[(*R*)-1-(4-Bromophenyl)-2-nitroethyl]cyclohexanone (4e):

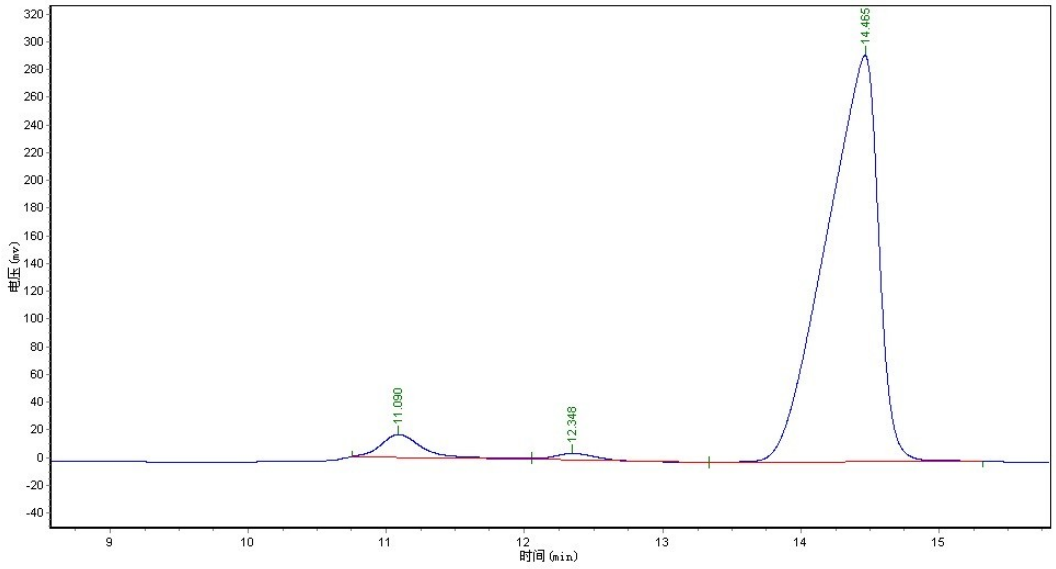


Racemic:



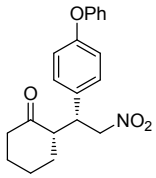
entry	R.T. (min)	Height	Area	Area %
1	11.090	350679	7463922	44.2103
2	12.357	24558	609961	3.6129
3	14.523	312399	8808878	52.1768

Nonracemic: Table 3, entry 5



entry	R.T. (min)	Height	Area	Area %
1	11.090	16442	351219	4.3062
2	12.348	4816	86738	1.0635
3	14.465	292851	7718239	94.6304

(*S*)-2-[(*R*)-2-Nitroethyl-1-(3-phenoxy)] cyclohexanone (4f):



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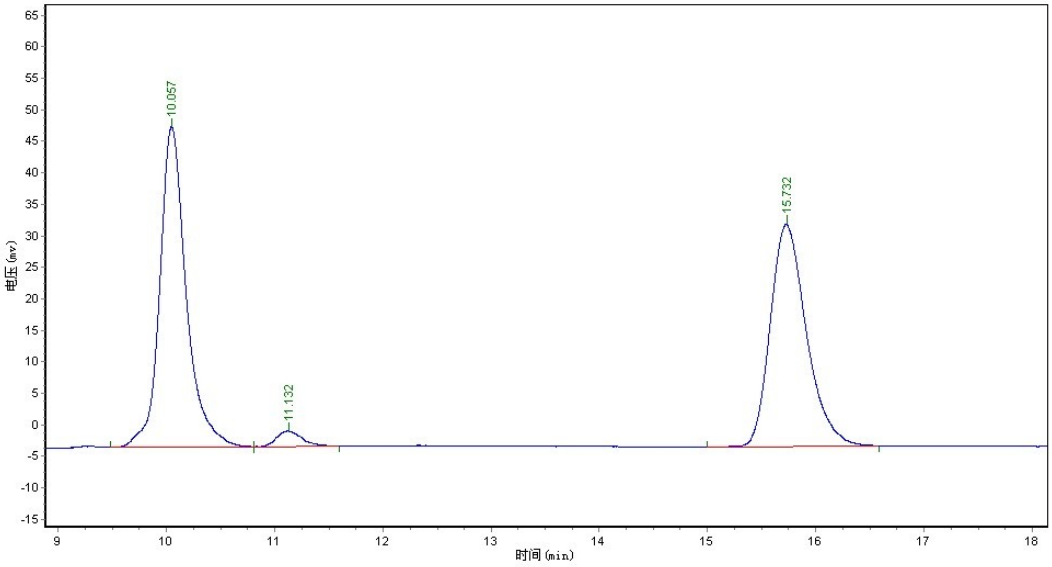
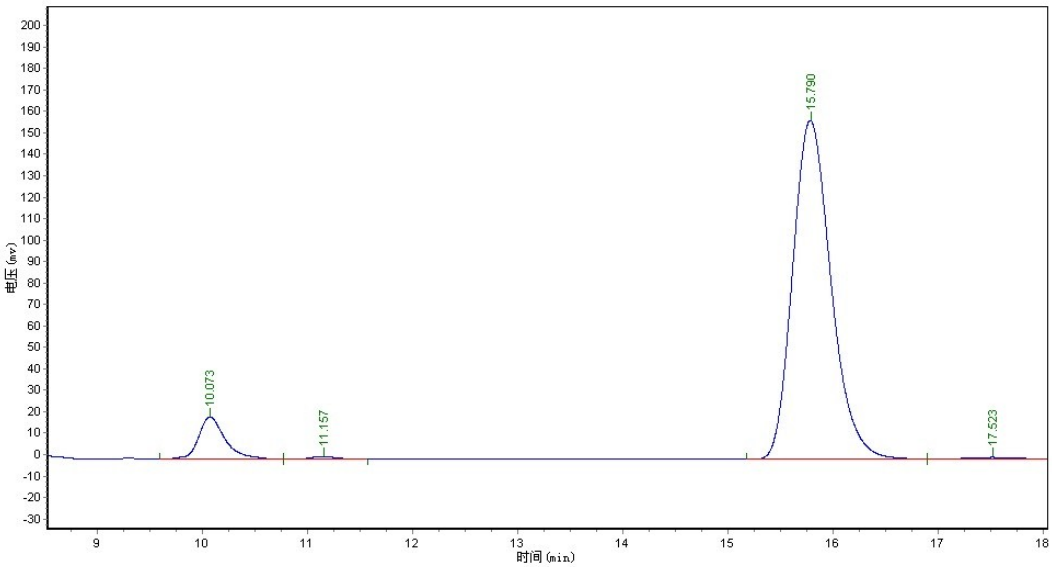


entry	R.T. (min)	Height	Area	Area %
1	10.057	50983	871796	50.2566
2	11.132	2553	45843	2.6427
3	15.732	35246	817091	47.1007

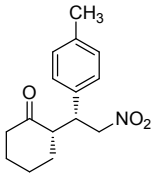
Nonracemic: Table 3, entry 6



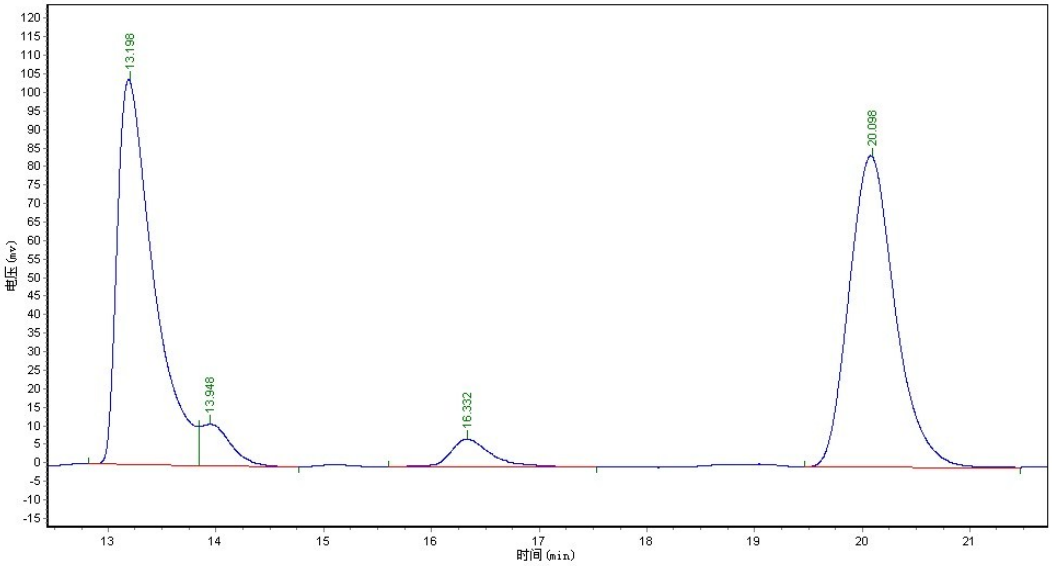
entry	R.T. (min)	Height	Area	Area %
1	10.073	19613	342332	7.8062

2	11.157	1117	20659	0.4711
3	15.790	147847	3998965	91.1885
4	17.523	723	23427	0.5342

(*S*)-2-[(*R*)-2-Nitro-1-(*p*-tolyl)ethyl]cyclohexanone (4g):

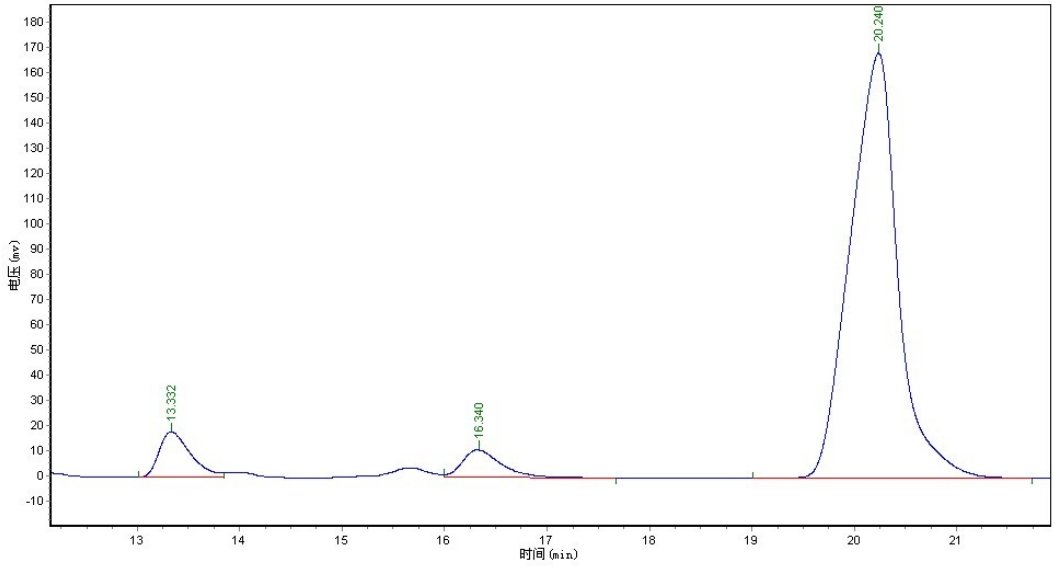


Racemic:



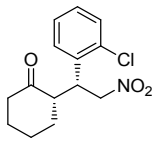
entry	R.T. (min)	Height	Area	Area %
1	13.198	104438	2465060	45.7891
2	13.948	11466	223032	4.1429
3	16.332	7492	200674	3.7276
4	20.098	84062	2494738	46.3404

Nonracemic: Table 3, entry 7

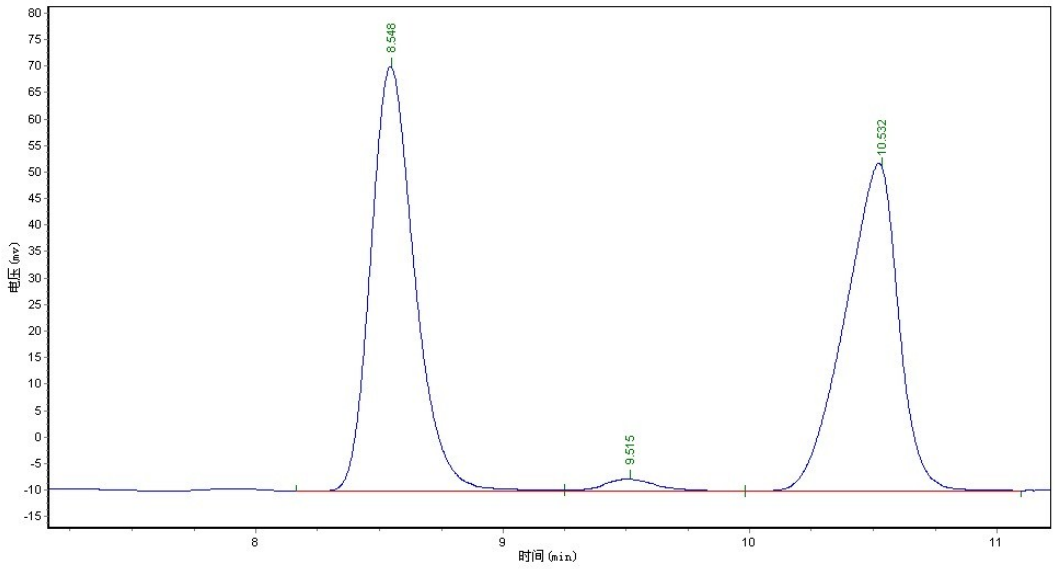


entry	R.T. (min)	Height	Area	Area %
1	13.332	18096	402050	6.5520
2	16.332	11127	307177	5.0059
3	20.265	167689	5427117	88.4422

(*S*)-2-[(*R*)-1-(2-Chlorophenyl)-2-nitroethyl] cyclohexanone (4h):

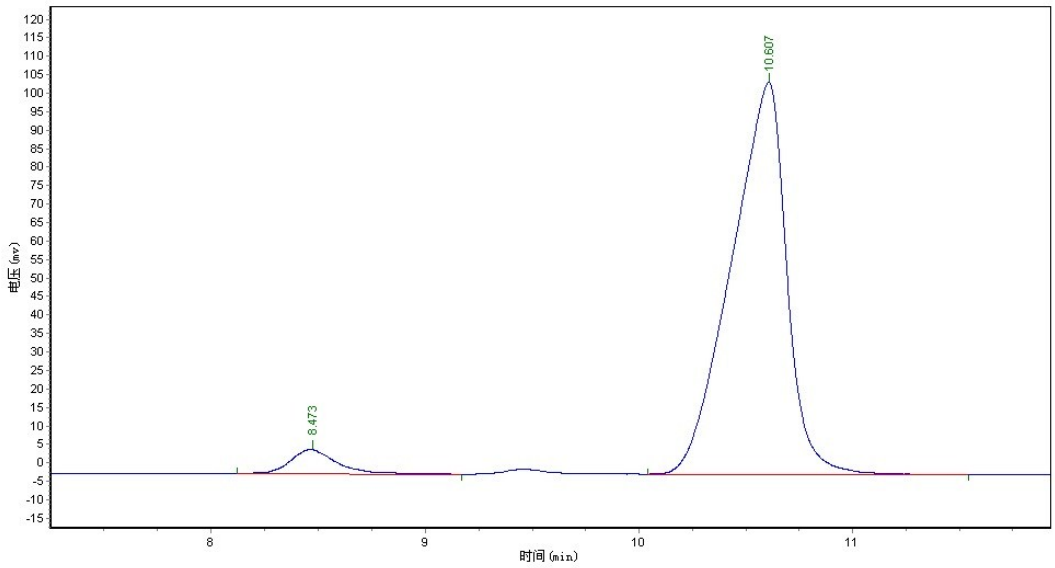


Racemic:



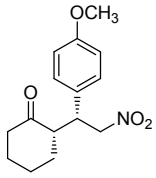
entry	R.T. (min)	Height	Area	Area %
1	8.548	80020	982452	50.6310
2	9.507	2128	9645	1.5278
3	10.523	61794	928320	47.8413

Nonracemic: Table 3, entry 8

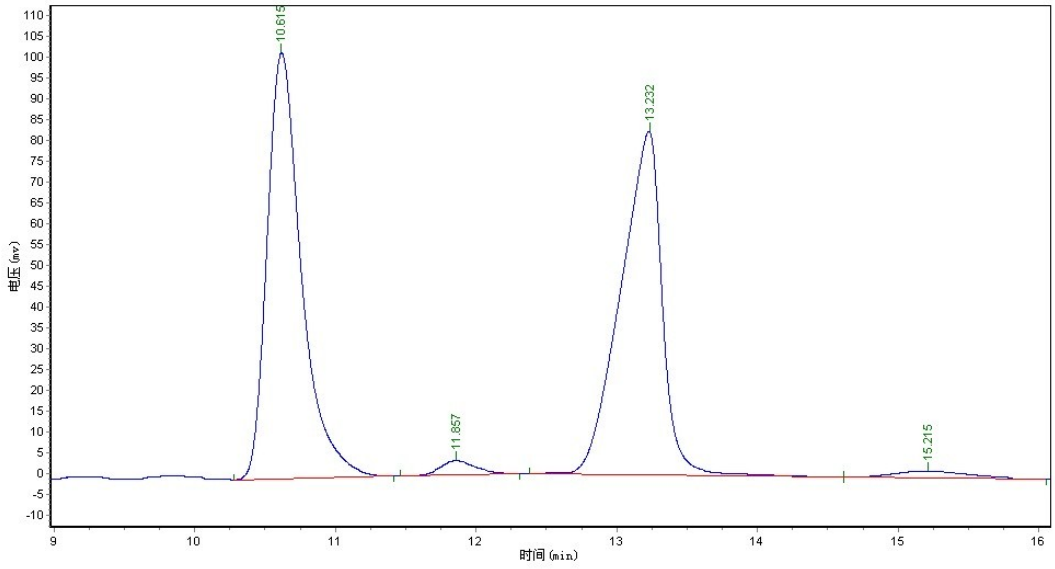


entry	R.T. (min)	Height	Area	Area %
1	8.473	6584	101989	5.0332
2	9.473	1287	19570	0.9658
3	10.607	105678	1904791	94.0010

***(S)*-2-(*(R)*-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (4i):**



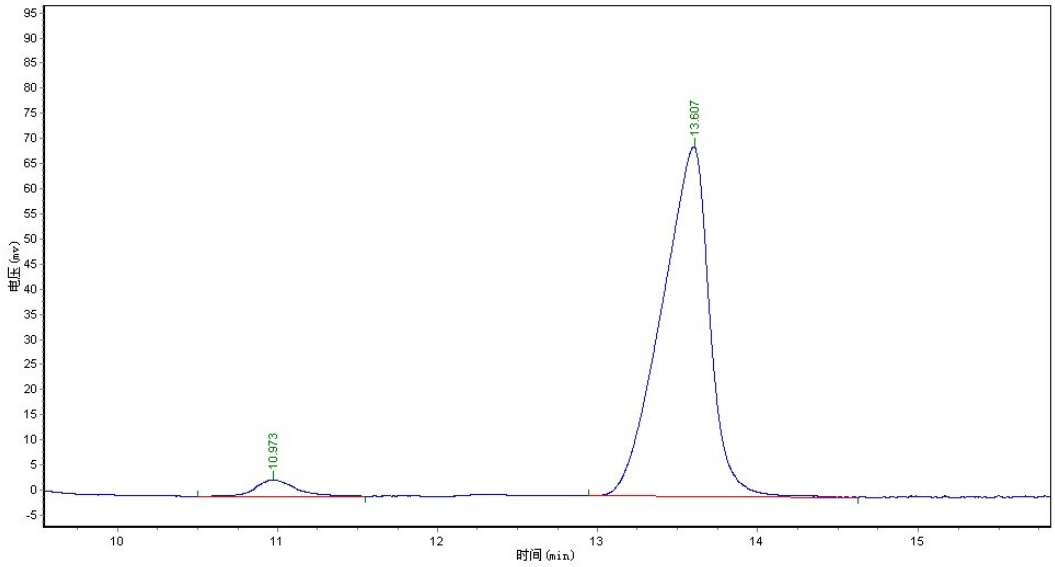
Racemic:



entry	R.T. (min)	Height	Area	Area %

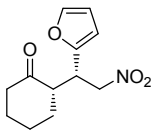
1	10.615	102010	1732744	48.8421
2	11.857	3441	60135	1.6951
3	13.232	82306	1691280	47.6733
4	15.215	1689	63484	1.7895

Nonracemic: Table 3, entry 9

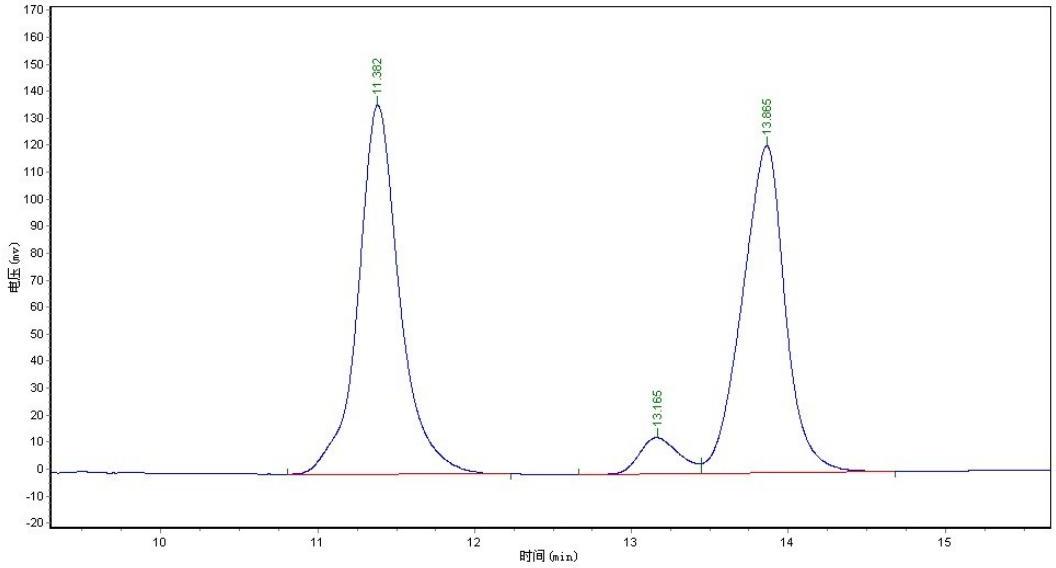


entry	R.T. (min)	Height	Area	Area %
1	10.973	3242	56890	3.7486
2	13.607	69708	1460742	96.2514

(*S*)-2-[(*S*)-1-(Furan-2-yl)-2-nitroethyl]cyclohexanone (4j)

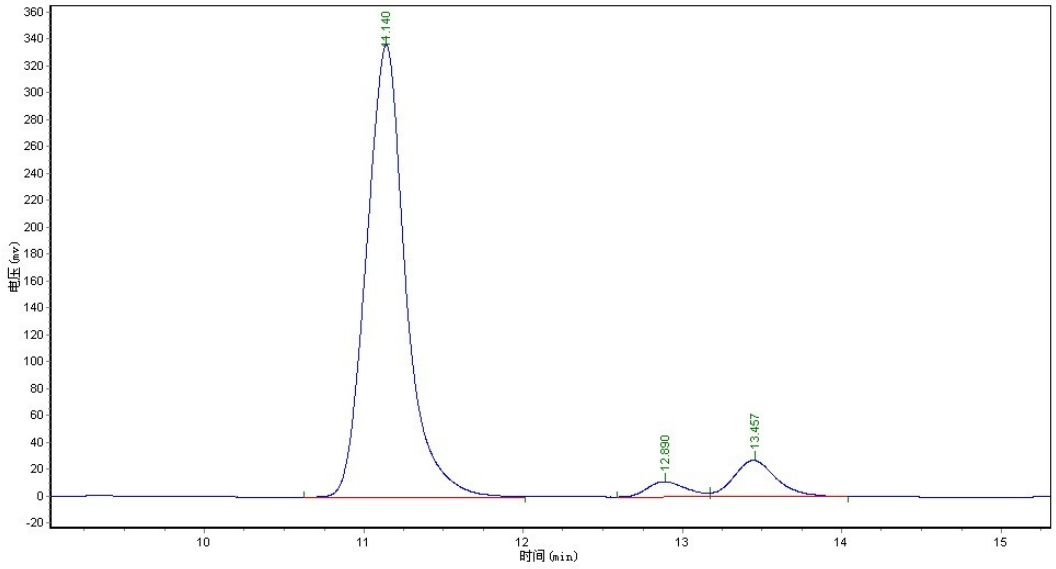


Racemic:



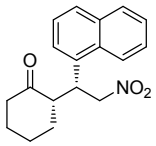
entry	R.T. (min)	Height	Area	Area %
1	11.382	136624	2518906	49.8406
2	13.165	13249	230930	4.5693
3	13.865	120829	2304085	45.5900

Nonracemic: Table 3, entry 10

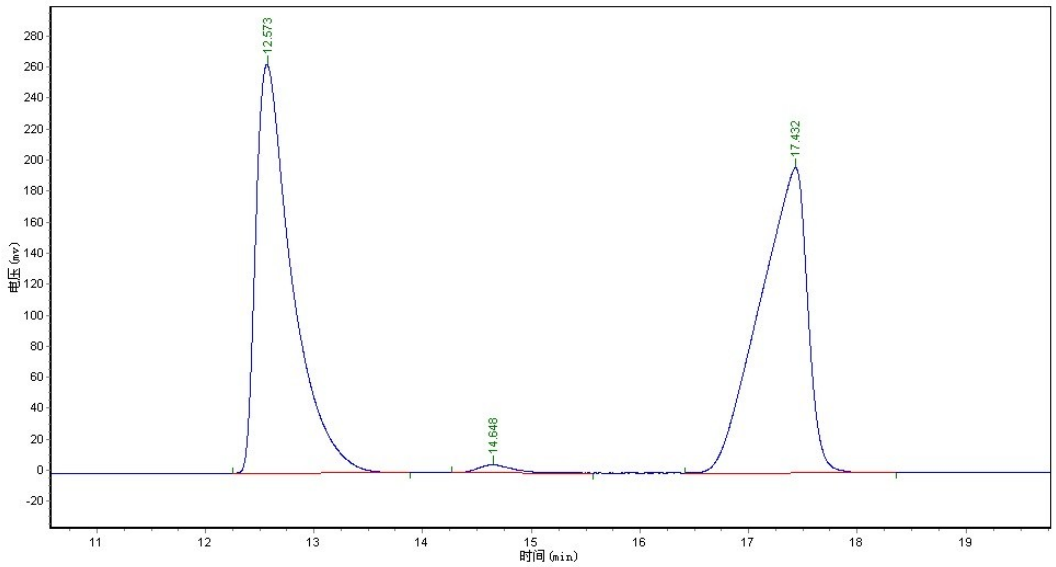


entry	R.T. (min)	Height	Area	Area %
1	11.140	335957	5753808	88.7646
2	12.890	11581	203717	3.1428
3	13.457	22447	524573	8.0927

(*S*)-2-[(*R*)-(1-Naphthalen-1-yl)-2-nitroethyl]cyclohexanone (4k):

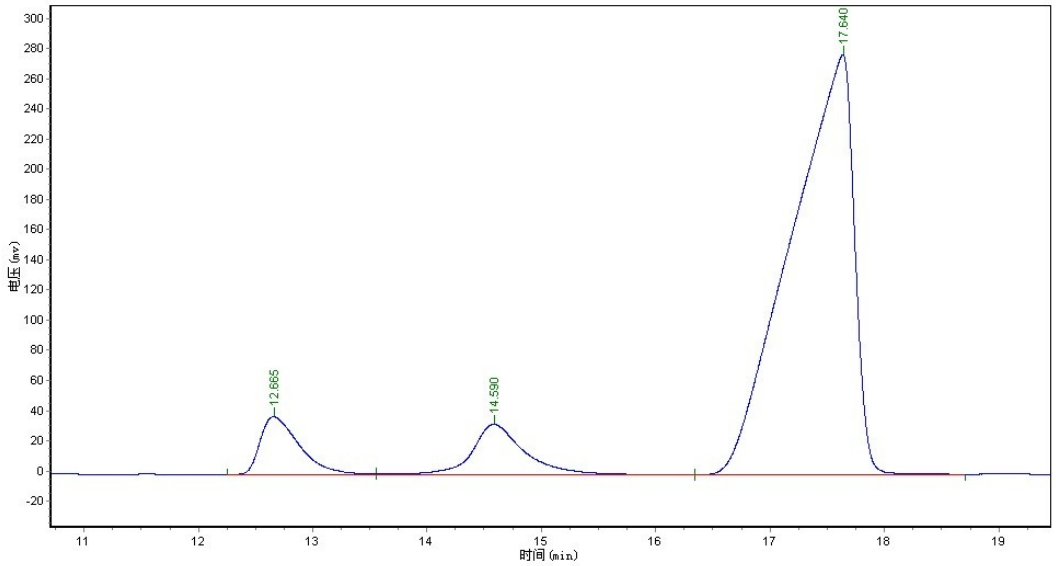


Racemic:



entry	R.T. (min)	Height	Area	Area %
1	12.573	263435	6084497	49.9246
2	14.648	5152	116814	0.9585
3	17.432	196251	5986060	49.1169

Nonracemic: Table 3, entry 11



entry	R.T. (min)	Height	Area	Area %
1	12.665	38321	911333	7.2161
2	14.590	33137	1064762	8.4310

3	17.640	277350	10653023	84.3529

(1) Lawandi, J.; Toumieux, S.; Seyer, V.; Campbell, P.; Thielges, S.; Juillerat-Jeanneret, L.; Moitessier, N. *J. Med. Chem.* **2009**, *52*, 6672.

(2) Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericàs, M. A. *Org Lett* **2007**, *9*, 3717.

(3) Font, D.; Jimeno, C.; Pericàs, M. A. *Org Lett* **2006**, *8*, 4653.

(4) Shunkevich, A.; Akulich, Z.; Mediak, G.; Soldatov, V. *Reactive and Functional Polymers* **2005**, *63*, 27.

(5) Zhao, H.-W.; Li, H.-L.; Yue, Y.-Y.; Sheng, Z.-H. *Eur. J. Org. Chem.* **2013**, *2013*, 1740.

(6) Lin, J.; Tian, H.; Jiang, Y.-J.; Huang, W.-B.; Zheng, L.-Y.; Zhang, S.-Q. *Tetrahedron: Asymmetry* **2011**, *22*, 1434.

(7) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J Am Chem Soc* **2004**, *126*, 9558.