Supporting Information

Chemoenzymatic Dynamic Kinetic Resolution of α-Trifluoromethylated Amines: Influence of Substitutions on the Reversed Stereoselectivity

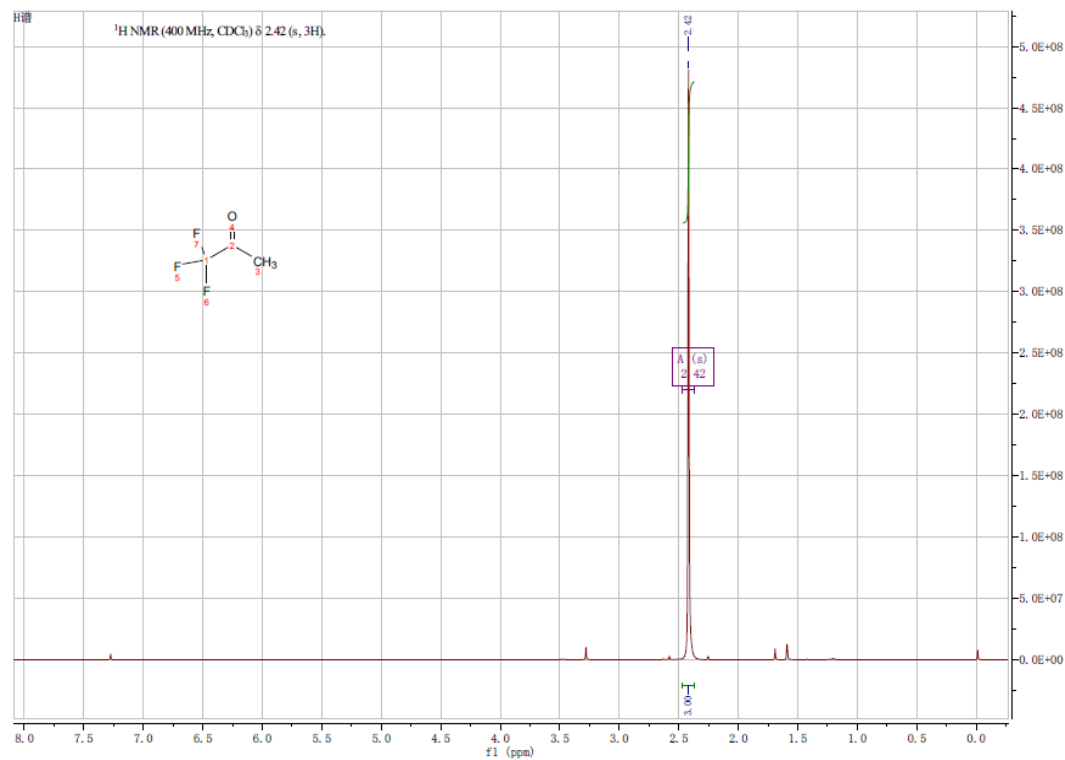**Guilin Cheng, Bo Xia, Qi Wu* and Xianfu Lin***

1. Computational methods

Docking calculations were carried out using the Autodock 4.0 package. For the docking the lipase B from C. antarctica was chosen (PDB Code 1TCA). The protein structure was checked and prepared for the use in the docking experiments. We utilized the NQ-Flipper server to recognize unfavorable rotamers of Asn and Gln residues in the protein structure. The results were checked and the protonation states of the histidines were assigned by visual inspection. All water molecules were discarded from the structure before docking. Chem3D Ultra 8.0 was used to construct the product amides for docking in both enantiomeric forms. Gasteiger partial charges were assigned to the atoms.

Autodock 4.0 was used to dock the product amides to the receptor protein applying a genetic algorithm augmented by a local search (Solis & Wets). The Genetic Algorithm (GA) parameters were set as follows: The number of individuals in the population was set to 50 and the maximum number of energy evaluations was set to medium 500,000 leading to a typical number of generations of 250. The results of 50 independent runs were clustered.
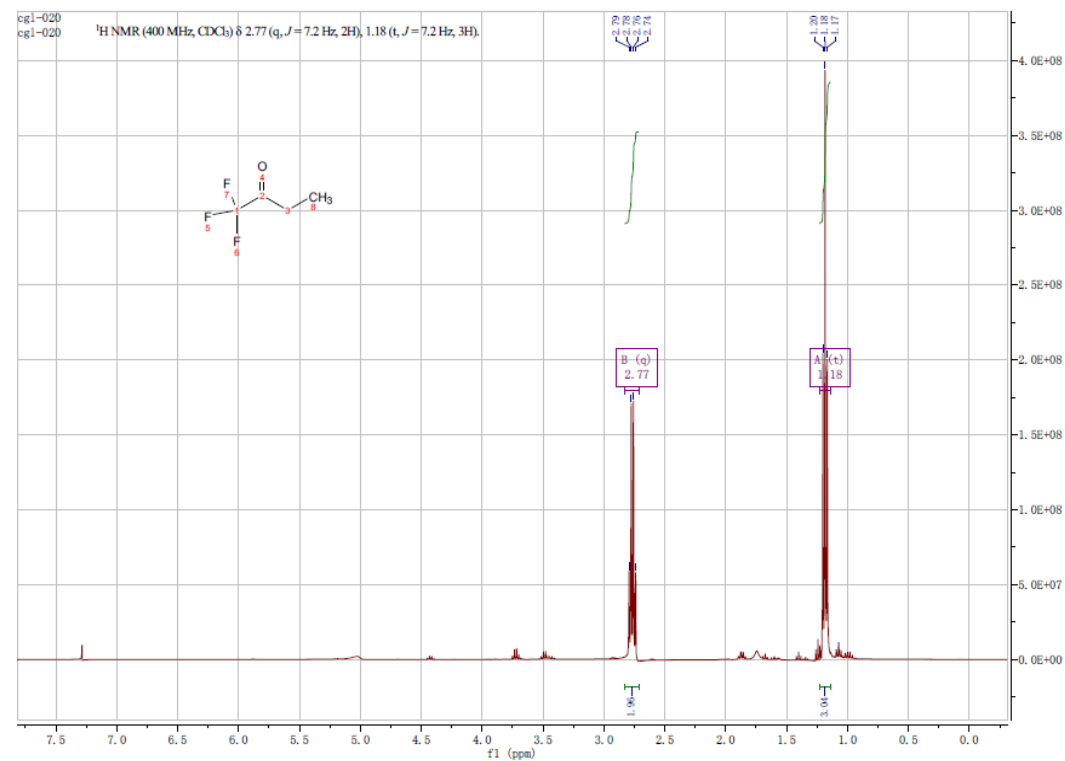
2. Data of ^{1}H NMR (CDCl$_3$, δ, ppm, 400 MHz)
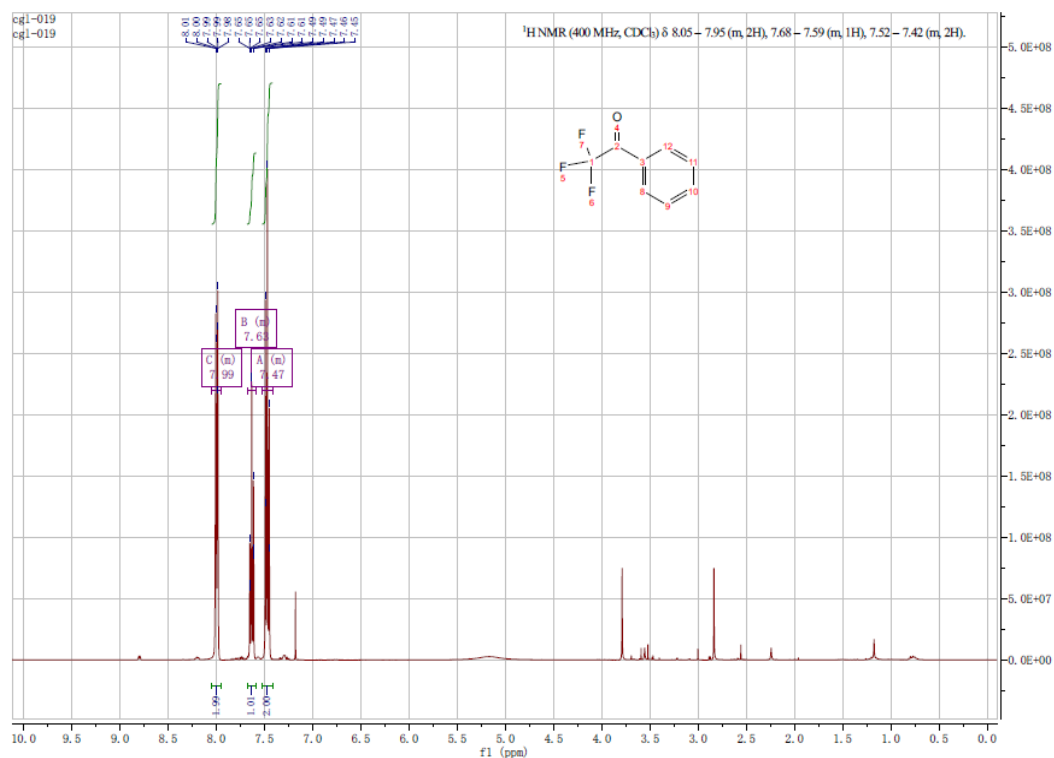
2.1. ^{1}H NMR of α-trifluoromethylated ketones
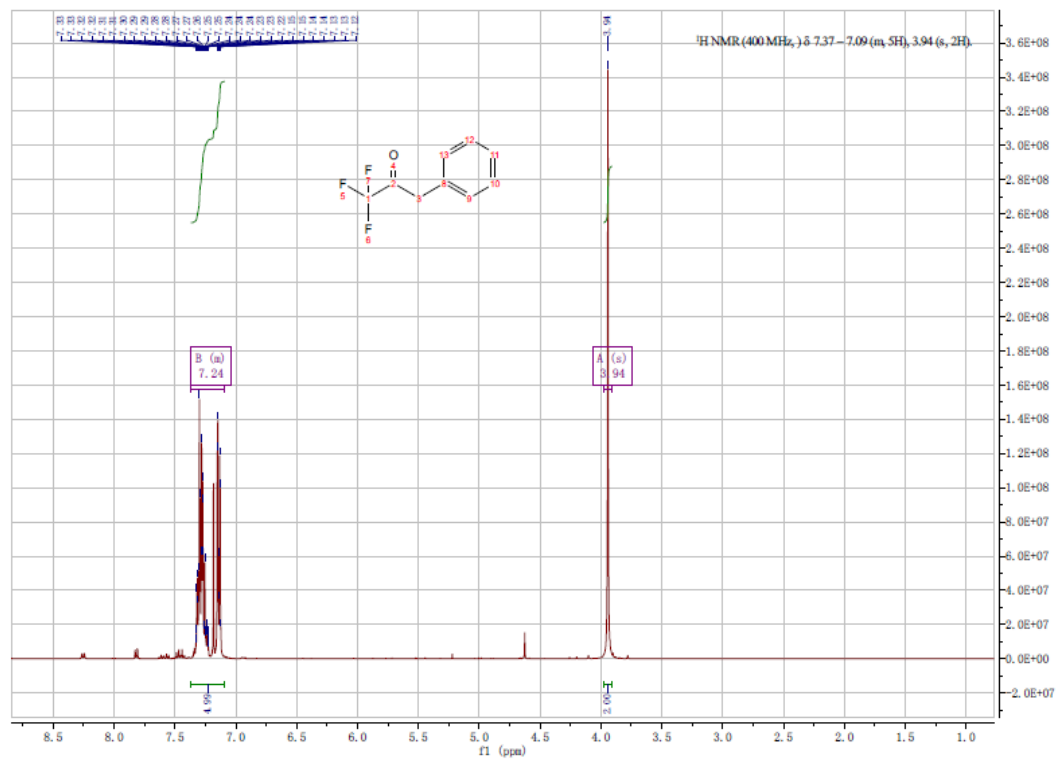
1,1,1-trifluoroacetone (**3a**)

^{1}H NMR (400 MHz, CDCl$_3$) δ 2.42 (s, 3H).

1,1,1-trifluoro-2-butanone (**3b**)

^{1}H NMR (400 MHz, CDCl$_3$) δ 2.77 (q, J = 7.2 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H).

2,2,2-trifluoroacetophenone (**3d**)

¹H NMR (400 MHz, CDCl₃) δ 8.05 – 7.95 (m, 2H), 7.68 – 7.59 (m, 1H), 7.52 – 7.42 (m, 2H).

1,1,1-trifluoro-3-phenyl-2-propanone (**3e**)

¹H NMR (400 MHz,) δ 7.37 – 7.09 (m, 5H), 3.94 (s, 2H).

2.2. ¹H NMR of α-trifluoromethylated amines

2,2,2-trifluoro-1-propylamine (**1a**)

¹H NMR (400 MHz, CDCl₃) δ 3.44 – 3.17 (m, 1H), 1.38 (s, 2H), 1.25 (d, J = 6.8 Hz, 3H).

2,2,2-trifluoro-1-butylamine (**1b**)

¹H NMR (400 MHz, CDCl₃) δ 3.04 (s, 1H), 1.77 (dtd, J = 11.4, 7.4, 4.0 Hz, 1H), 1.36 (ddd, J = 63.8, 35.5, 19.5 Hz, 3H), 1.05 (t, J = 7.5 Hz, 3H).

1,1,1-trifluoro-3-methyl-2-butylamine (**1c**)

¹H NMR (400 MHz,) δ 3.00 (ddd, J = 12.0, 8.2, 4.2 Hz, 1H), 2.15 – 1.93 (m, 1H), 1.32 (s, 2H), 1.06 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H).

2,2,2-trifluoro-1-phenylethanamine (**1d**)

¹H NMR (400 MHz, D₂O) δ 7.43 (dd, J = 18.9, 9.3 Hz, 5H), 4.41 (q, J = 7.4 Hz, 1H), 2.05 (d, J = 9.6 Hz, 2H).

3,3,3-trifluoro-1-phenyl-2-propylamine (**1e**)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.25 (m, 5H), 3.49 (ddd, J = 10.5, 7.1, 3.4 Hz, 1H), 3.16 (dd, J = 13.9, 3.4 Hz, 1H), 2.65 (dd, J = 13.9, 10.4 Hz, 1H), 1.55 (s, 2H).

2.3. ^{1}H NMR of α-trifluoromethylated amides

N-(1,1,1-trifluoropropan-2-yl)acetamide (**2a**)

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.01 (s, 1H), 4.70 (dd, J = 15.7, 7.7 Hz, 1H), 2.04 (s, 3H), 1.31 (d, J = 7.0 Hz, 3H).

N-(1,1,1-trifluorobutan-2-yl)acetamide (**2b**)

¹H NMR (500 MHz, CDCl₃) δ 5.51 (s, 1H), 4.64 – 4.48 (m, 1H), 2.07 (s, 3H), 1.88 (ddd, J = 14.3, 7.4, 4.0 Hz, 1H), 1.50 (ddd, J = 14.3, 10.3, 7.3 Hz, 1H), 1.00 (t, J = 7.5 Hz, 3H).

N-(1,1,1-trifluoro-3-methylbutan-2-yl)acetamide (**2c**)

¹H NMR (400 MHz,) δ 4.73 – 4.39 (m, 1H), 2.16 (dtd, J = 11.6, 7.0, 4.5 Hz, 1H), 2.11 – 2.04 (m, 3H), 1.71 (s, 1H), 1.02 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H).

N-(2,2,2-trifluoro-1-phenylethyl)acetamide (**2d**)

^{1}H NMR (400 MHz,) δ 7.43 – 7.18 (m, 5H), 6.07 (d, J = 8.0 Hz, 1H), 5.76 – 5.55 (m, 1H), 2.10 – 1.90 (m, 3H).

N-(1,1,1-trifluoro-3-phenylpropan-2-yl)acetamide (**2e**)

^{1}H NMR (400 MHz, CDCl₃) δ 7.30 – 7.07 (m, 5H), 5.63 – 5.32 (m, 1H), 4.93 – 4.84 (m, 1H), 3.13 (dd, J = 14.6, 4.4 Hz, 1H), 2.70 (dd, J = 14.6, 10.1 Hz, 1H), 1.83 (d, J = 2.0 Hz, 3H).

3. Data of ^{13}C NMR (CDCl$_3$, δ, ppm, 100 MHz)

3.1. ^{13}C NMR of α-trifluoromethylated ketones
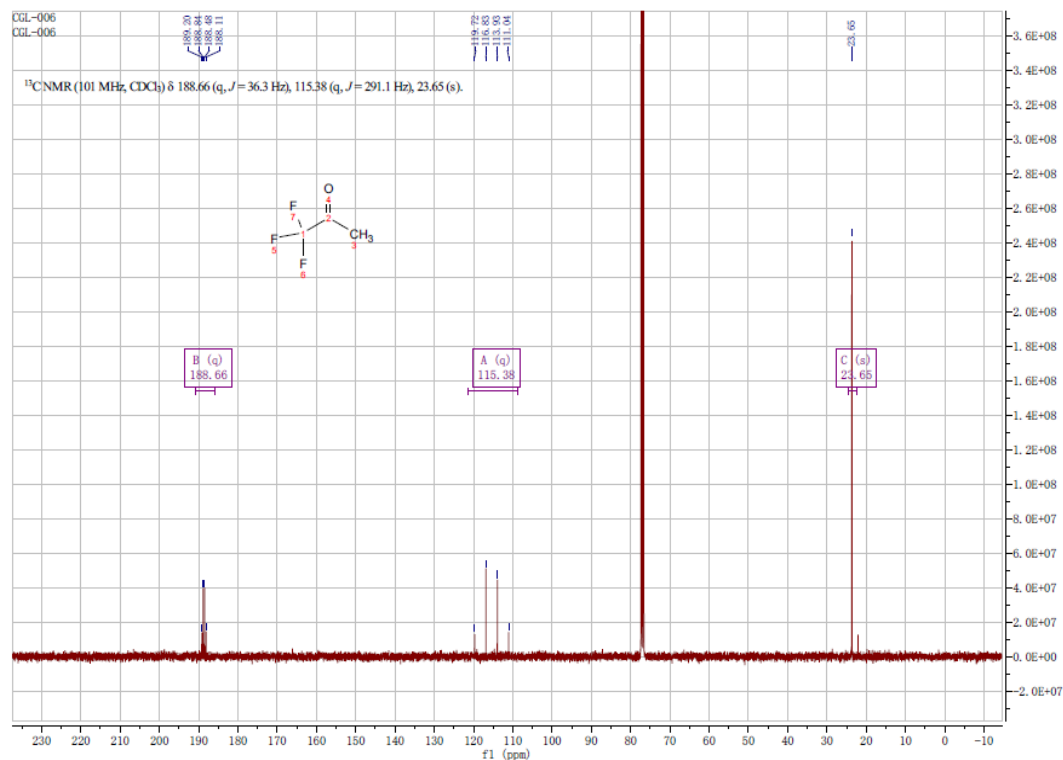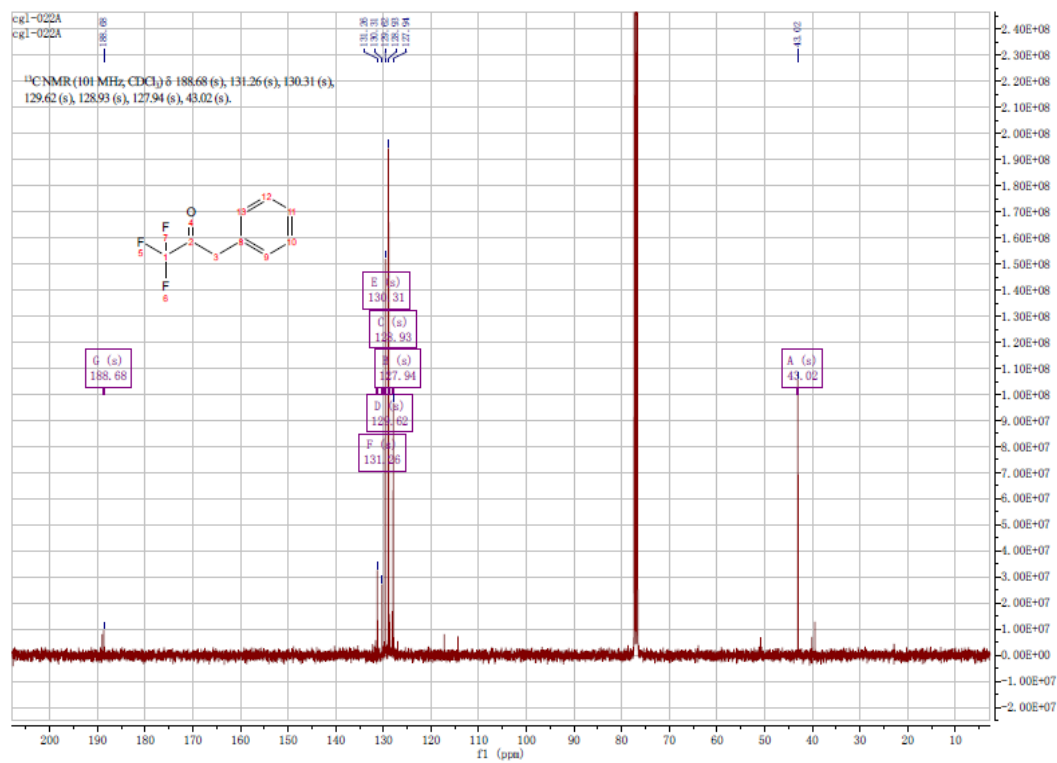
1,1,1-trifluoroacetone (**3a**)

^{13}C NMR (101 MHz, CDCl$_3$) δ 188.66 (q, J = 36.3 Hz), 115.38 (q, J = 291.1 Hz), 23.65 (s).

1,1,1-trifluoro-2-butanone (**3b**)

^{13}C NMR (101 MHz, CDCl$_3$) δ 192.14 (q, J = 34.8 Hz), 115.63 (q, J = 292.0 Hz), 29.87 (s), 6.27 (s).

2,2,2-trifluoroacetophenone (**3d**)

cgl-019
cgl-019

^{13}C NMR (101 MHz, CDCl$_3$) δ 182.37 – 177.43 (m), 135.53 (s), 130.11 (d, *J* = 1.8 Hz), 129.92 (s), 129.10 (s), 116.68 (q, *J* = 291.3 Hz).

A (m) 180.35
B (s) 135.53
F (s) 129.92
D (s) 129.10
E (d) 130.11
C (q) 116.68

1,1,1-trifluoro-3-phenyl-2-propanone (**3e**)

cgl-022A
cgl-022A

^{13}C NMR (101 MHz, CDCl$_3$) δ 188.68 (s), 131.26 (s), 130.31 (s), 129.62 (s), 128.93 (s), 127.94 (s), 43.02 (s).

G (s) 188.68
E (s) 130.31
C (s) 128.93
B (s) 127.94
D (s) 129.62
F (s) 131.26
A (s) 43.02

3.2. ^{13}C NMR of α-trifluoromethylated amines

2,2,2-trifluoro-1-propylamine (**1a**)

^{13}C NMR (101 MHz, CDCl$_3$) δ 126.83 (q, J = 280.9 Hz), 49.46 (q, J = 30.0 Hz), 15.66 (d, J = 2.2 Hz).

2,2,2-trifluoro-1-butylamine (**1b**)

^{13}C NMR (101 MHz, CDCl$_3$) δ 126.80 (q, J = 281.5 Hz), 55.13 (q, J = 28.4 Hz), 23.02 (d, J = 1.6 Hz), 10.18 (s).
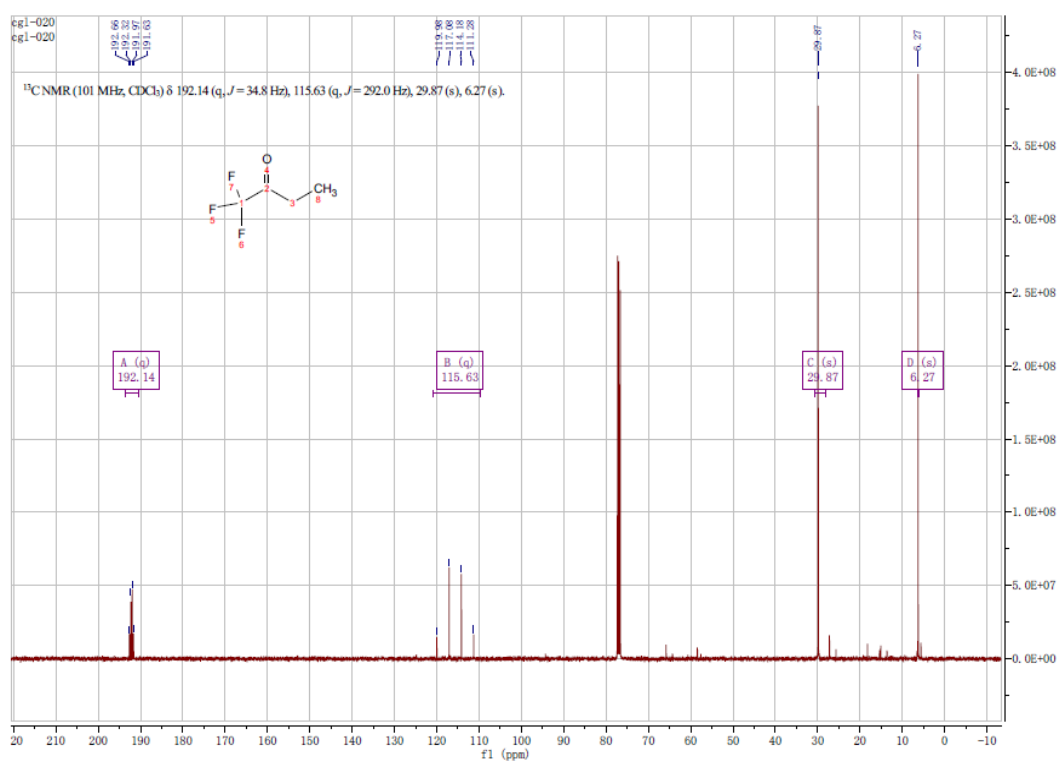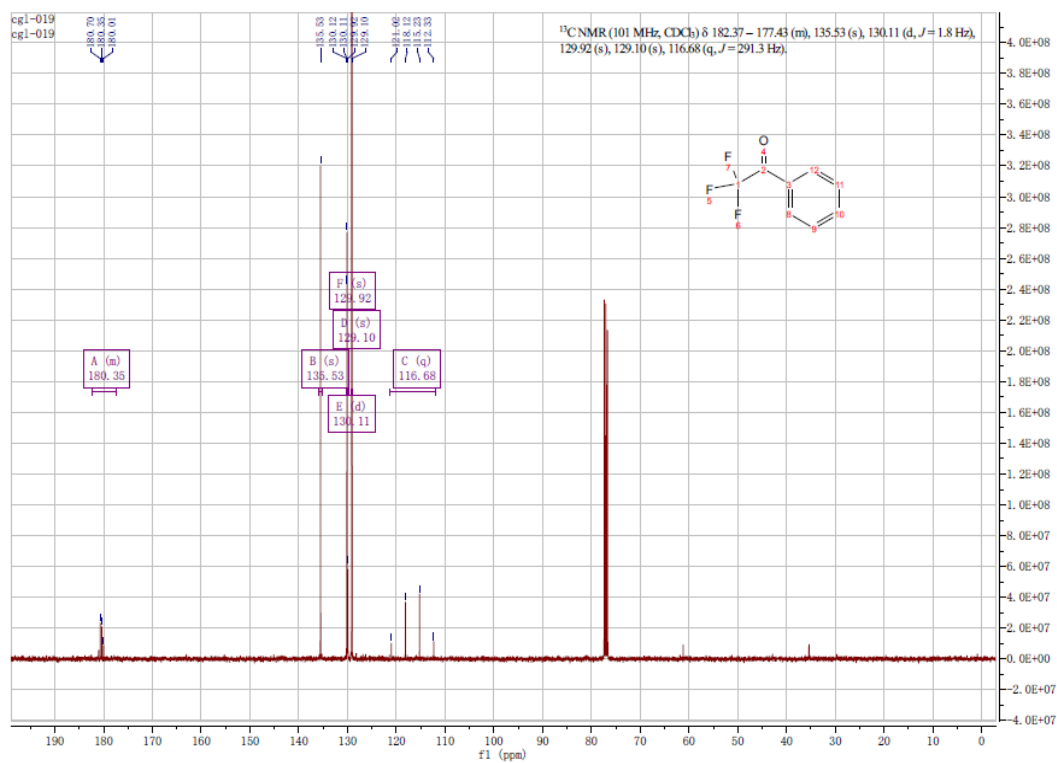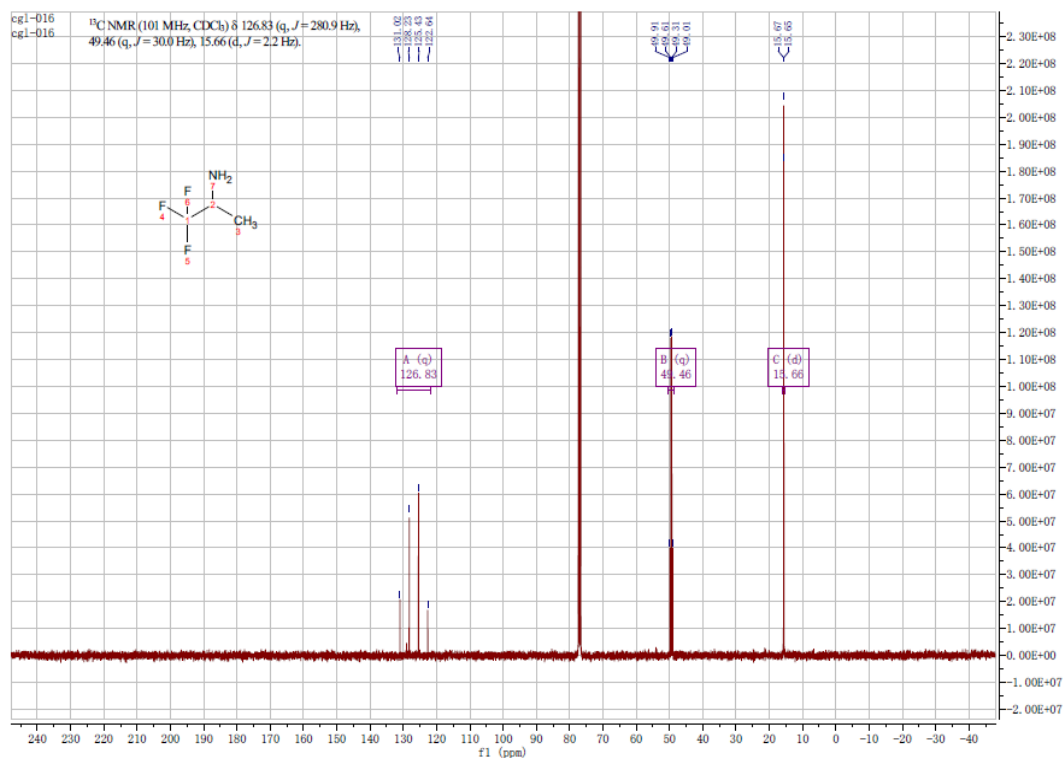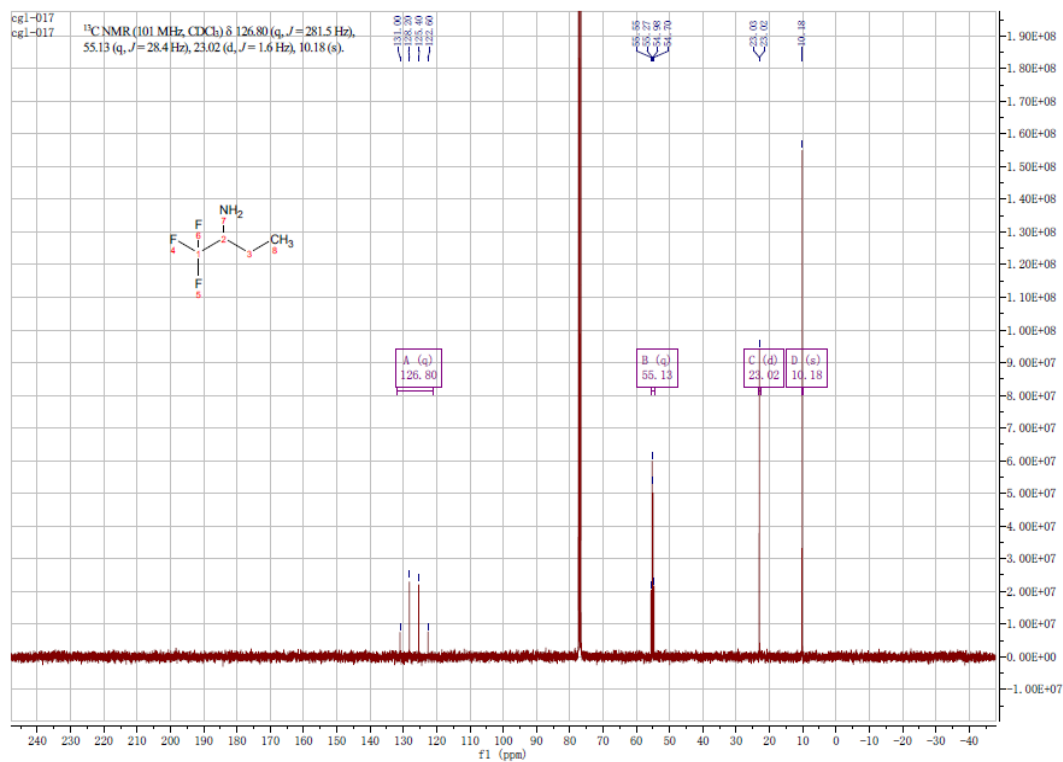
1,1,1-trifluoro-3-methyl-2-butylamine (**1c**)
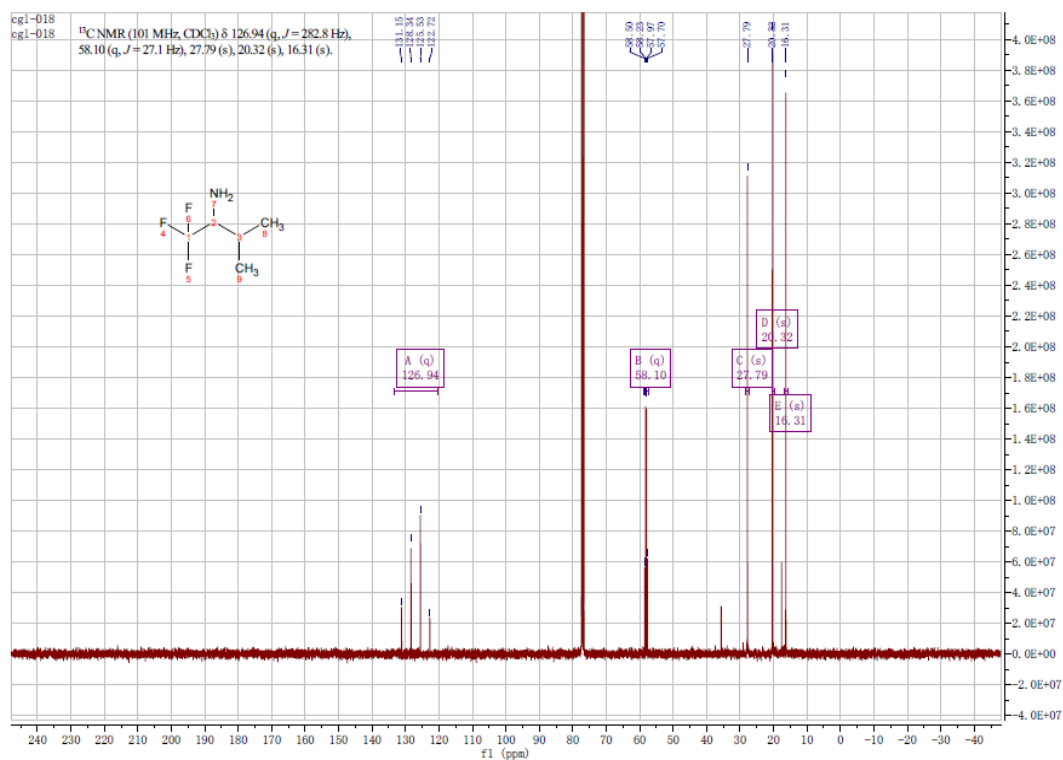
2,2,2-trifluoro-1-phenylethanamine (**1d**)
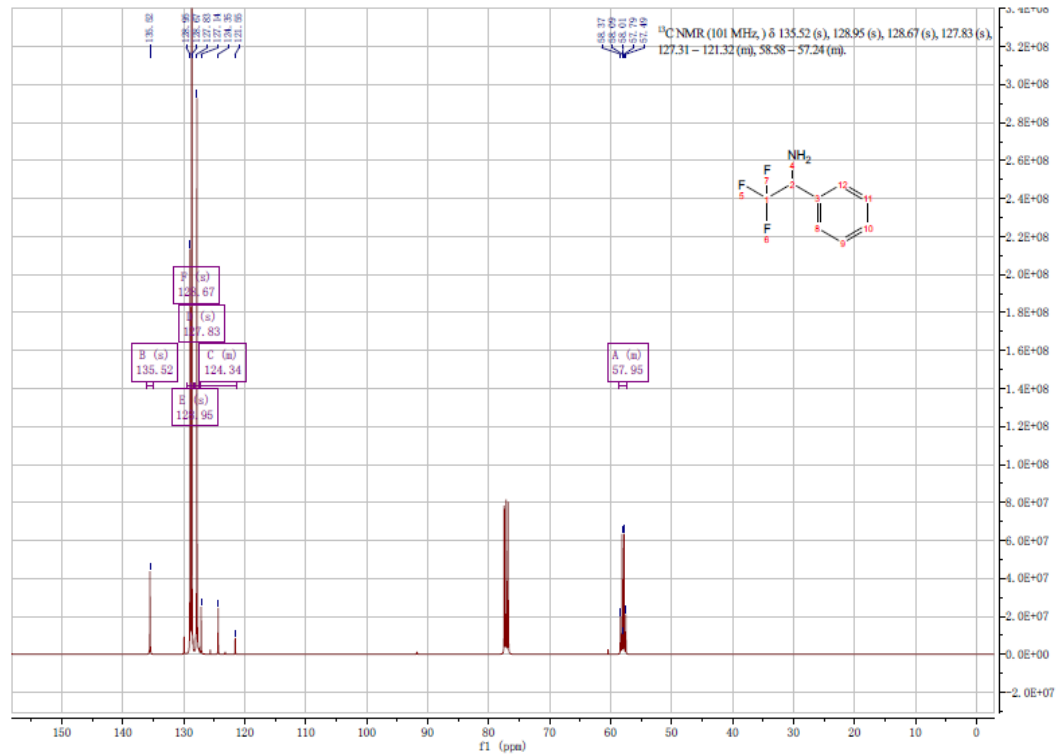
3,3,3-trifluoro-1-phenyl-2-propylamine (**1e**)
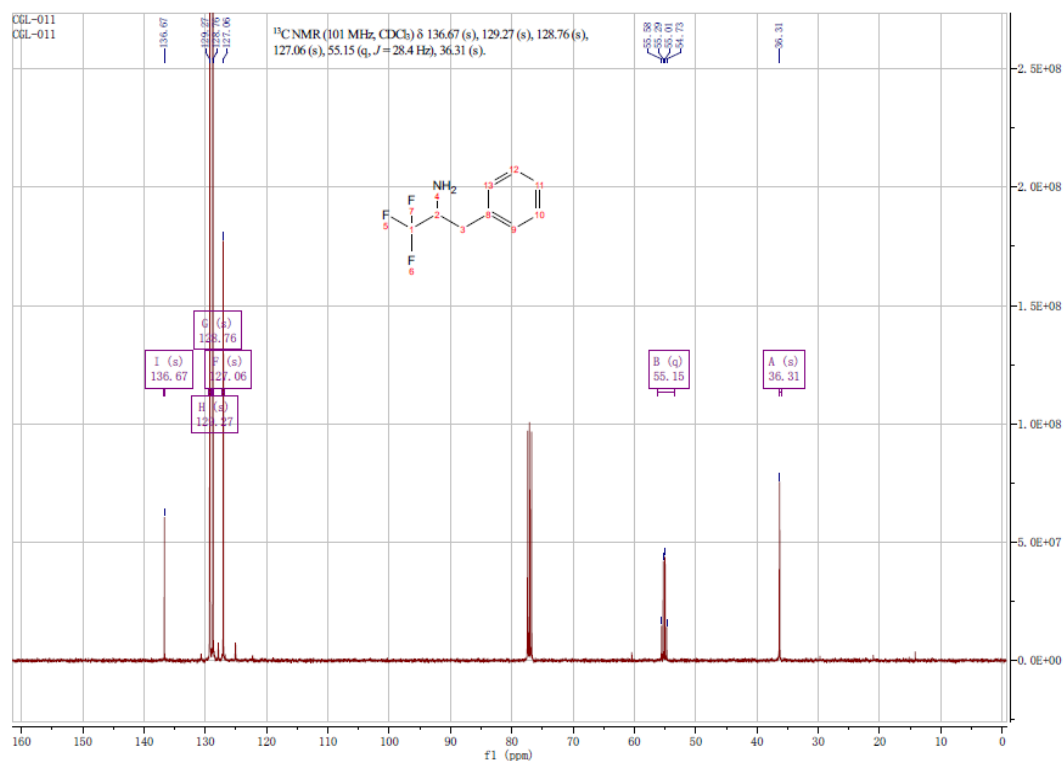
^{13}C NMR (101 MHz, CDCl$_3$) δ 136.67 (s), 129.27 (s), 128.76 (s), 127.06 (s), 55.15 (q, J = 28.4 Hz), 36.31 (s).

3.3. ^{13}C NMR of α-trifluoromethylated amides

N-(1,1,1-trifluoropropan-2-yl)acetamide (**2a**)

^{13}C NMR (101 MHz, CDCl$_3$) δ 170.01 (s), 125.30 (q, J = 280.9 Hz), 46.26 (q, J = 31.5 Hz), 22.95 (s), 14.19 (d, J = 1.7 Hz).

N-(1,1,1-trifluorobutan-2-yl)acetamide (**2b**)

^{13}C NMR (101 MHz, CDCl$_3$) δ 170.82 (s), 125.19 (q, J = 281.4 Hz), 51.74 (q, J = 30.2 Hz), 22.76 (s), 21.38 (s), 9.62 (s).

N-(1,1,1-trifluoro-3-methylbutan-2-yl)acetamide (**2c**)

^{13}C NMR (101 MHz, CDCl$_3$) δ 170.36 (s), 125.27 (q, J = 282.4 Hz), 27.43 (s), 23.00 (s), 19.80 (s), 17.06 (s).

N-(2,2,2-trifluoro-1-phenylethyl)acetamide (**2d**)

^{13}C NMR (101 MHz, CDCl$_3$) δ 169.48 (s), 132.84 (s), 129.32 (s), 129.02 (s), 127.90 (s), 125.91 (s), 54.26 (d, J = 31.5 Hz), 23.15 (s).

N-(1,1,1-trifluoro-3-phenylpropan-2-yl)acetamide (**2e**)

^{13}C NMR (101 MHz, CDCl$_3$) δ 170.13 (s), 134.91 (s), 128.99 (s), 128.72 (s), 127.26 (s), 125.04 (d, J = 282.1 Hz), 51.03 (q, J = 30.0 Hz), 34.26 (s), 22.82 (s).
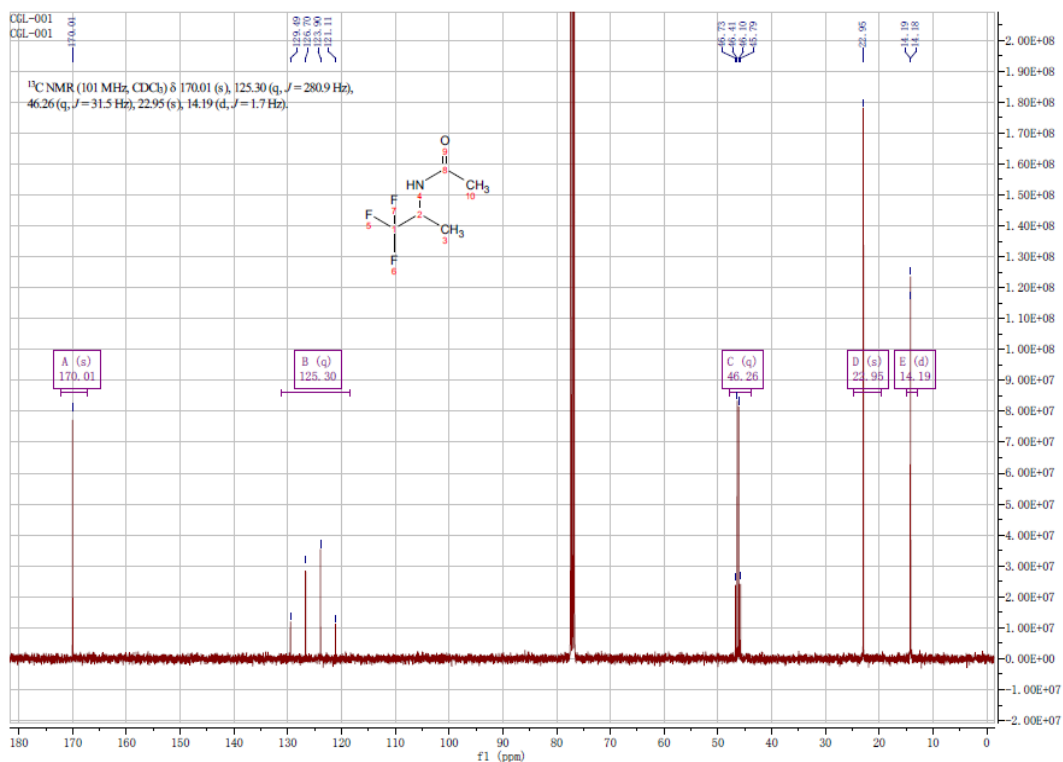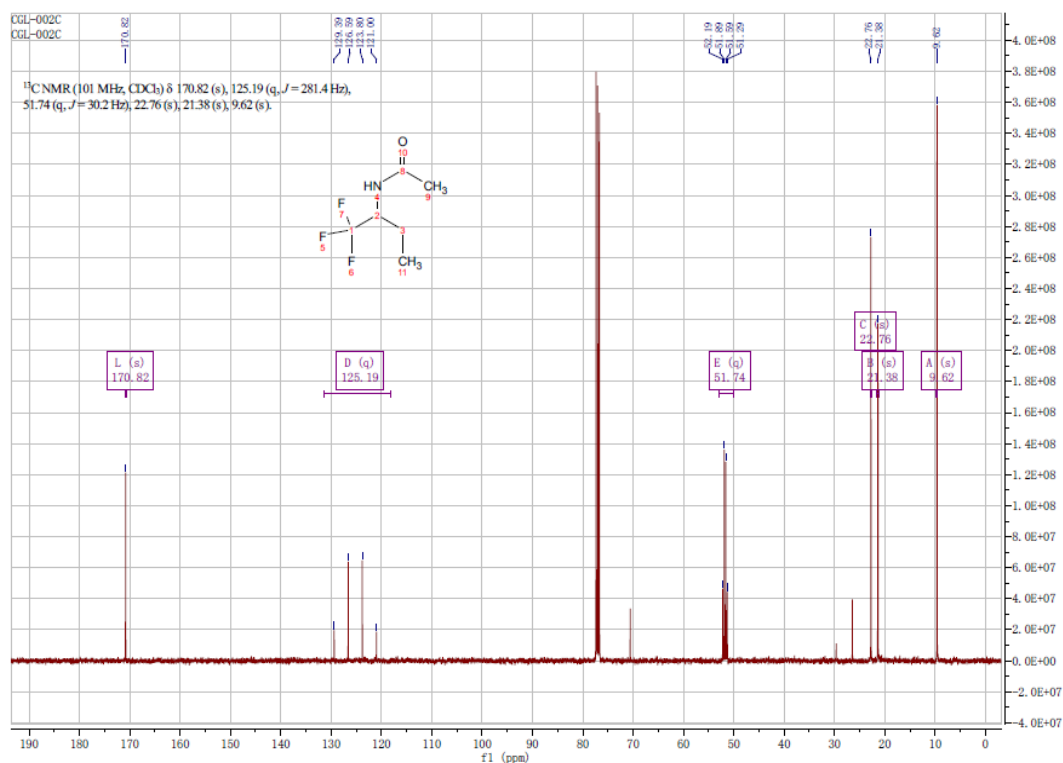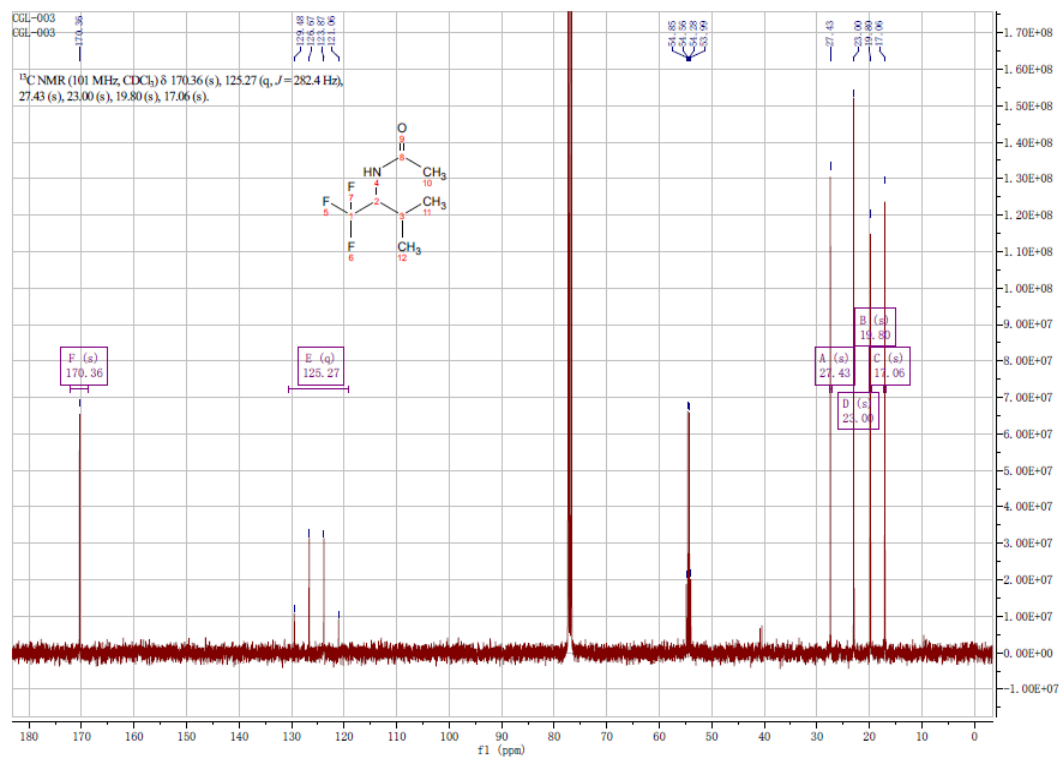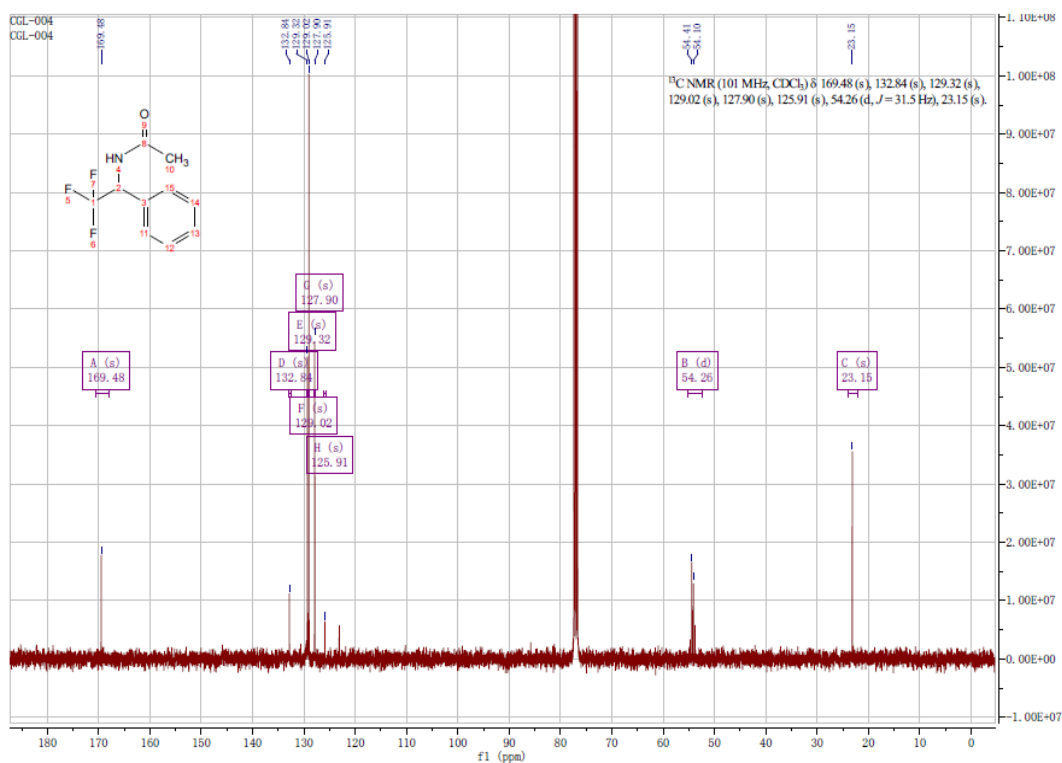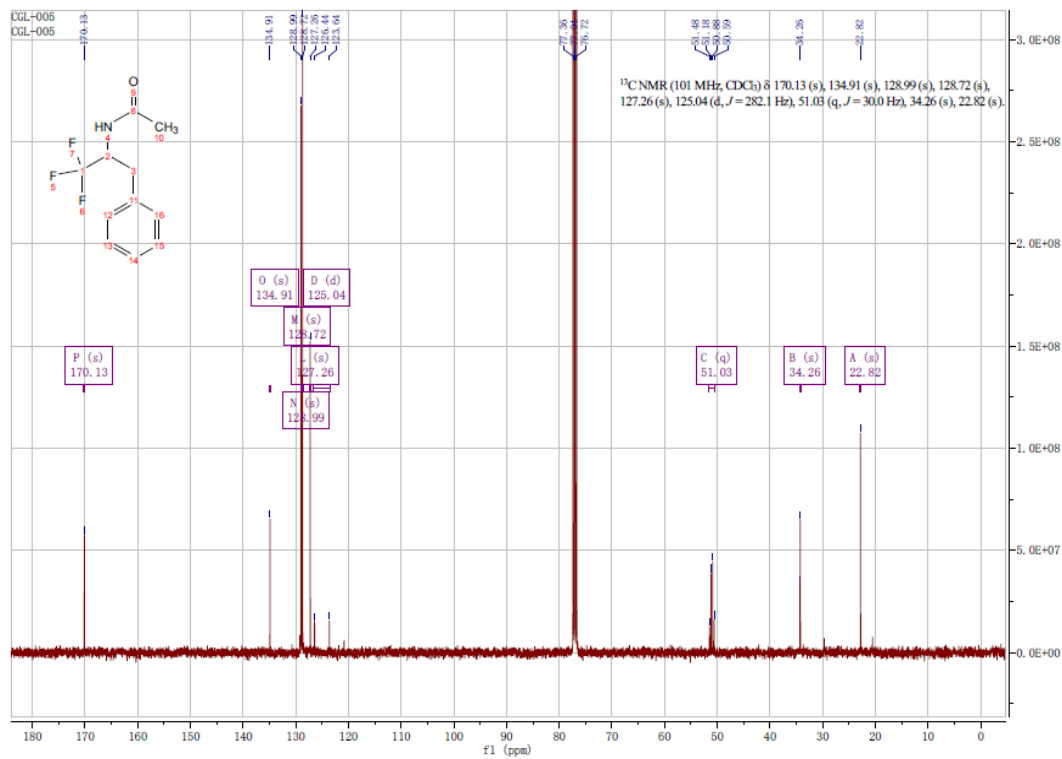
4. Data of Chiral-GC

Dynamic Kinetic Resolution of **1a**

RT:

(R)-Product: 11.25 min;   (S)-Product: 12.35 min

Standard:
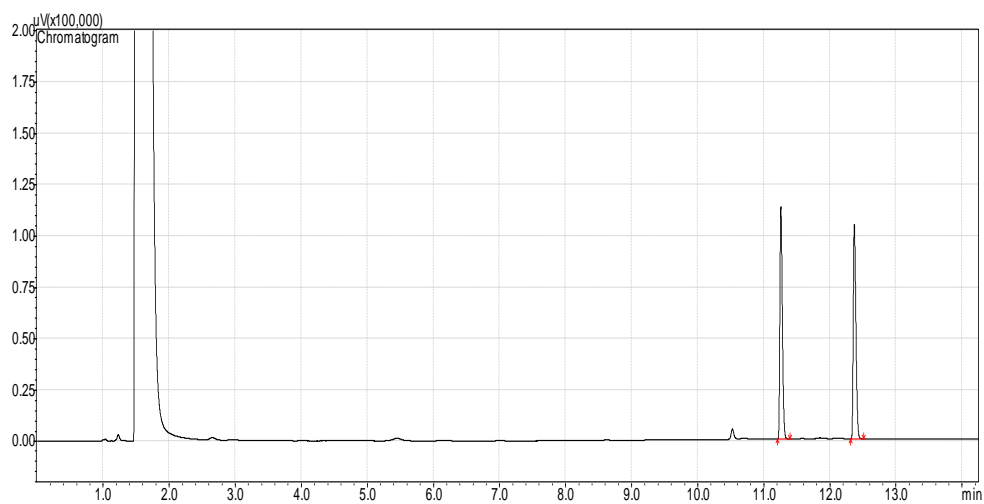
Reaction mixture:
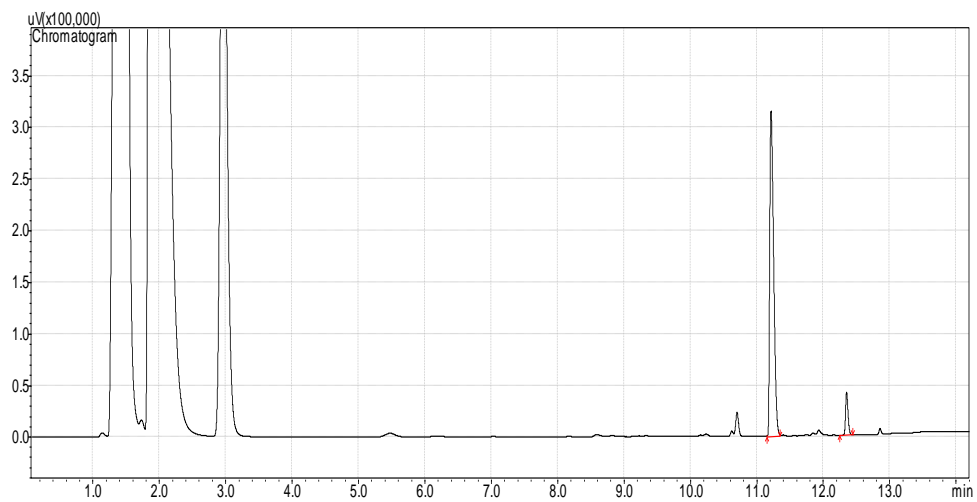
Dynamic Kinetic Resolution of **1b**

RT:

(R)-Product: 11.46 min;   (S)-Product: 12.48 min
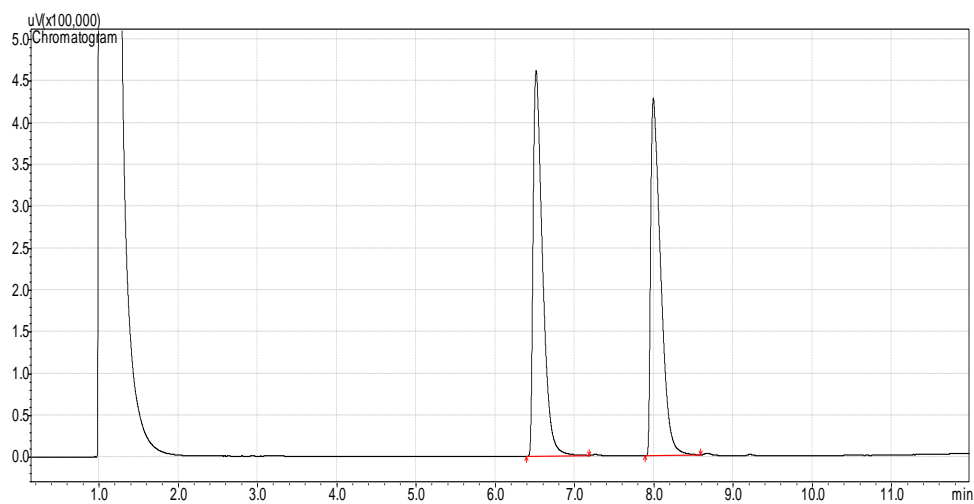
Standard:
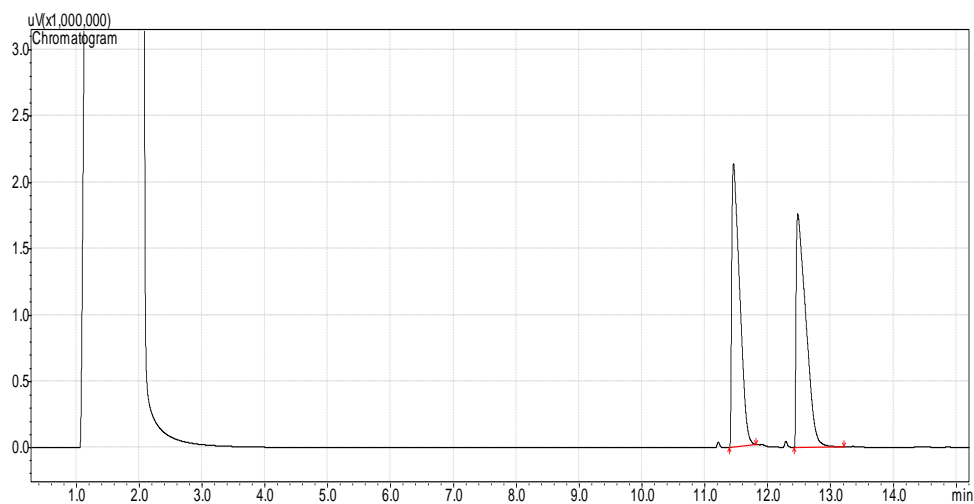
Reaction mixture:
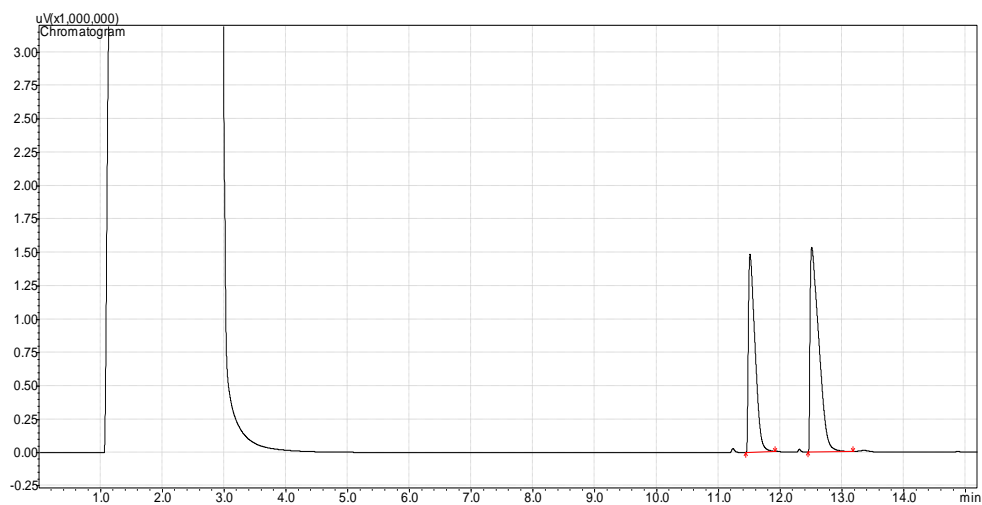
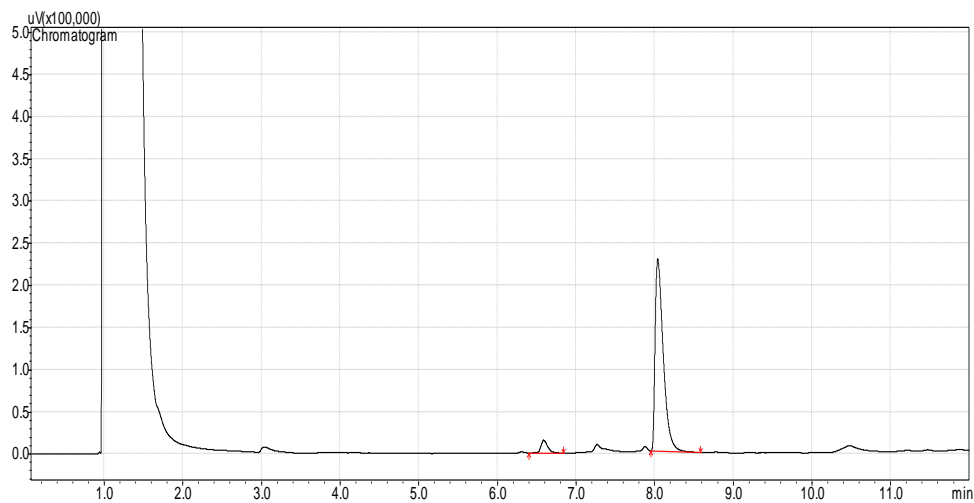Dynamic Kinetic Resolution of **1c**

RT:

(R)-Product: 6.51 min;   (S)-Product: 8.00 min

Standard:
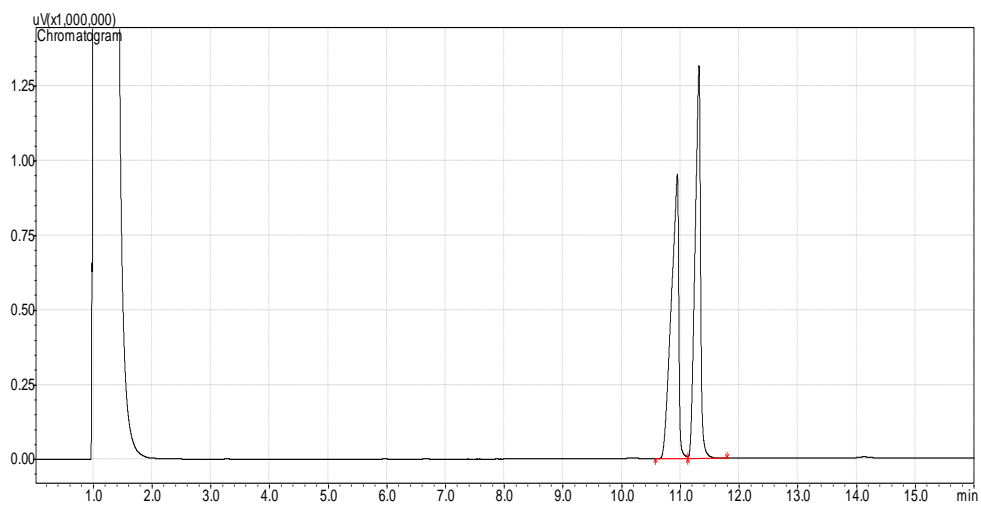

Reaction mixture:

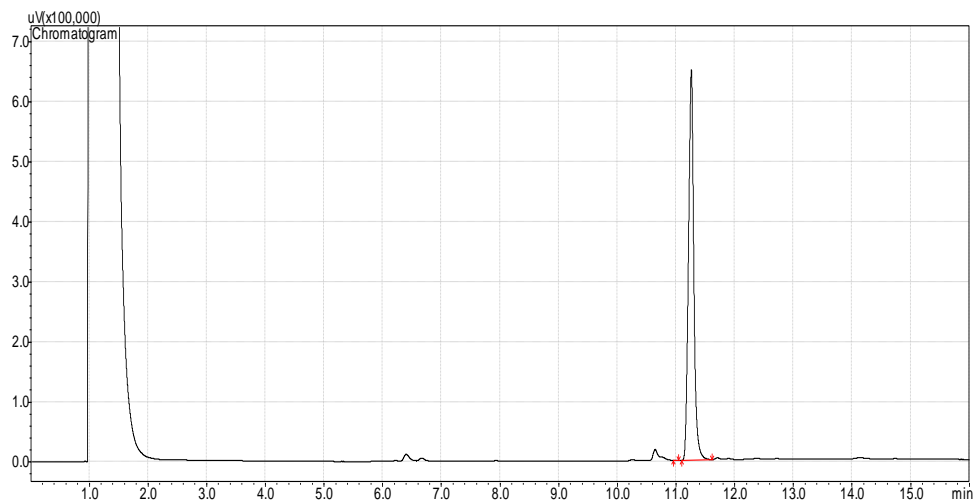Dynamic Kinetic Resolution of **1d**

RT:

(R)-Product: 10.95 min; (S)-Product: 11.26 min
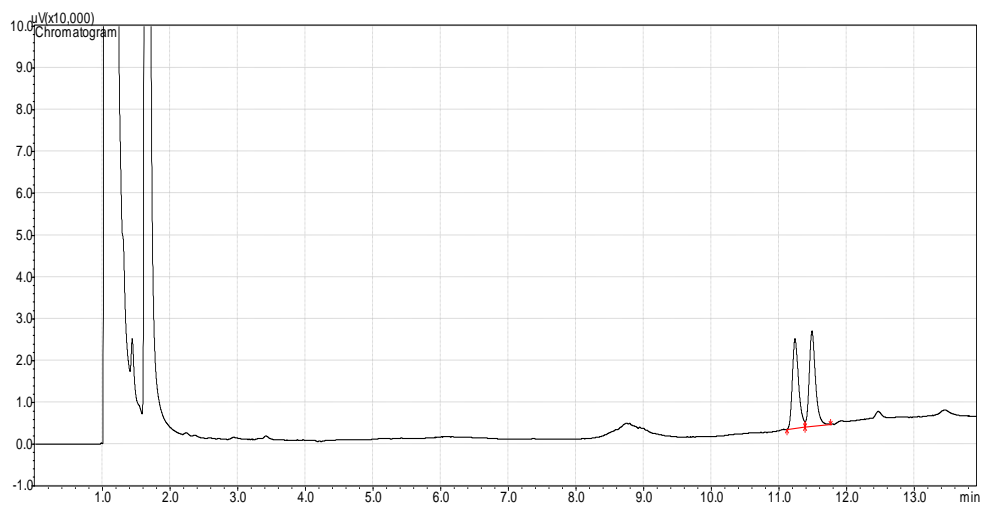
Standard:

Reaction mixture:

Dynamic Kinetic Resolution of **1e**

RT:

(R)-Product: 11.23 min;   (S)-Product: 11.49 min

Standard:

Reaction mixture: