

Supporting Information  
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## Supporting Information

### **Bifunctional Thiourea Catalyzed Asymmetric Mannich Reaction Using Trifluoromethyl Alimine as Trifluoromethyl Building Blocks**

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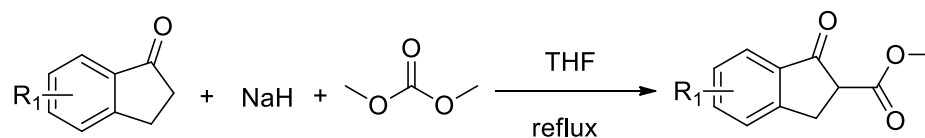
## Index

I - General Remarks .....	3
II – General procedure B: preparation of $\beta$ -ketoesters 2a .....	4
III – General procedure C: Preparation of aldimine 3.....	4
IV - General procedure D: General procedure for Asymmetric trifluoromethylation of $\beta$ -keto esters .....	4
V – Datas, NMR copies and HPLC copies .....	6
Compound 4a:.....	6
Compound 4b:.....	10
Compound 4c: .....	14
Compound 4d:.....	18
Compound 4e: .....	22
Compound 4f: .....	26
Compound 4g:.....	30
Compound 4h:.....	34
Compound 4i:.....	38
Compound 4n:.....	42
Compound 4o:.....	46

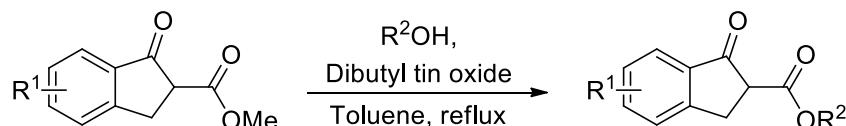
## I - General Remarks

All reactions were performed in flame-dried glassware with magnetic stirring bar, under argon atmosphere, and sealed with a rubber septum. The solvents were distilled by standard methods. Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Flash column chromatography was carried out using Qingdao silica Gel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was done using Qingdao silica Gel (silica gel 60 F254). TLC plates were analyzed by an exposure to ultraviolet (UV) light and/or submersion in phosphomolybdic acid solution or in I<sub>2</sub>. NMR experiments were carried out in deuteriochloroform (CDCl<sub>3</sub>). <sup>1</sup>H NMR, <sup>13</sup>C and <sup>19</sup>F NMR spectra were recorded at 400 MHz or 600 MHz, 100 MHz or 150 MHz and 376 MHz spectrometers Bruker (400 MHz) and Agilent (600 MHz). Chemical shifts are reported as  $\delta$  values relative to internal chloroform ( $\delta$  7.26 for <sup>1</sup>H NMR and 77.0 for <sup>13</sup>C NMR) in parts per million (ppm). The following abbreviations are used for the multiplicities : s: singlet, d: doublet, dd: doublet of doublet, t: triplet, q: quadruplet, m: multiplet, br: broad signal for proton spectra; Coupling constants (*J*) are reported in Hertz (Hz). Melting points were uncorrected. Infrared spectra were recorded on an IR spectrometer (Perkin Elmer BX FT-IR), and absorption frequencies were reported in reciprocal centimeters (cm<sup>-1</sup>). The HRMS data were measured on MALDI-TOF type of instrument for the high resolution mass spectra. The enantio- and diastereomeric excesses [(ee's) & (de's)] of products were determined by chiral HPLC analysis was measured at 254 nm using the indicated chiral column.

## II – General procedure B: preparation of $\beta$ -ketoesters 2a



NaH (60% suspension in mineral oil, 2.86g, 71.5mmol) and THF(40 mL) were added into a flame-dried round-bottom flask equipped with a stir bar under argon atmosphere. Then dimethyl carbonate (14.4 mL, 171.6 mmol) was added, and the mixture was warmed to 60 °C. A solution of 1-indanone (3.78 g, 28.6 mmol) in THF (40 mL) was added dropwise into the flask over 1 h. The mixture was refluxed until complete conversion by TLC. After cooled to room temperature, it was quenched by 2 M HCl (60 mL). The mixture was extracted with DCM. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether /EtOAc = 5/1) to afford the desired compound.



Methyl 1-indanone-2-carboxylate (1.00 g, 5.26 mmol), the alcohol (10 mL) and dibutyl tin oxide (131 mg, 0.526mmol) were dissolved into toluene. The mixture was then refluxed until completion of the reaction, and then cooled to room temperature. After concentrated in vacuo, the residue was purified by flash column chromatography (petroleum ether /EtOAc = 5/1) to afford the desired compound.

## III – General procedure C: Preparation of aldimine 3

*p*-Methoxy aniline (4 g, 0.032 mol) and *p*-toluenesulfonic acid (0.02 g) were added into a solution of methyl trifluoroacetaldehyde hemiacetal (5.6 g, 0.0385 mol) in toluene (50 mL). The reaction mixture was then refluxed under Ar for 4 hours in Dean-Stark apparatus, and then concentrated under reduced pressure. The residue was distilled to give the desired product **3** (5.3 g) under 5 mmHg at 80 °C.

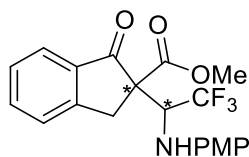
## IV - General procedure D: General procedure for Asymmetric trifluoromethylation of $\beta$ -keto esters

$\beta$ -Ketoesters **2** (0.158 mmol , 1 eq) and aldimine **3** (0.189 mmol, 1.2 eq) were dissolved in *i*Pr<sub>2</sub>O (2 mL) at 10 °C under Ar atmosphere in a flam-dried flask. DIPEA (0.237 mmol, 1.5 eq) and thiourea catalyst **1g** (9.4 mg, 10 mol%) were added successively. The mixture was stirred at 10 °C for 72 h. When the reaction was completed, the reaction mixture was concentrated under reduced

pressure. The residue was purified by flash column chromatography using mixture of petroleum ether: EtOAc:DCM=7:1:1 as eluent to obtain the desired product **4**.

## V – Datas, NMR copies and HPLC copies

### Compound 4a:



**Compound 4a:** 80% yield; white solid; mp: 148-150 °C;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ (ppm): 7.80~7.78 (d, *J* = 7.6 Hz, 1H), 7.68~7.64 (t, *J* = 7.6 Hz 1H), 7.55~7.53 (d, *J* = 8 Hz, 1H), 7.43~7.39 (t, *J* = 7.6 Hz 1H), 6.81 (s, 4H), 5.23~5.15(m, 1H), 4.07~4.03 (d, *J* = 17.2 Hz, 1H), 3.76 (s, 3H), 3.71~3.68 (d, *J* = 11.6 Hz, 1H), 3.56 (s, 3H), 3.43~3.39 (d, *J* = 17.2 Hz, 1H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm): 196.7, 167.5, 153.7, 152.3, 139.4, 135.8, 133.9, 129.4-120.9 (q, *J*<sub>C-F</sub> = 284.3 Hz), 128.0, 126.4, 125.1, 116.1, 114.7, 63.9, 60.9-60.1 (q, *J*<sub>C-F</sub> = 27.8 Hz), 55.5, 53.3, 31.4;

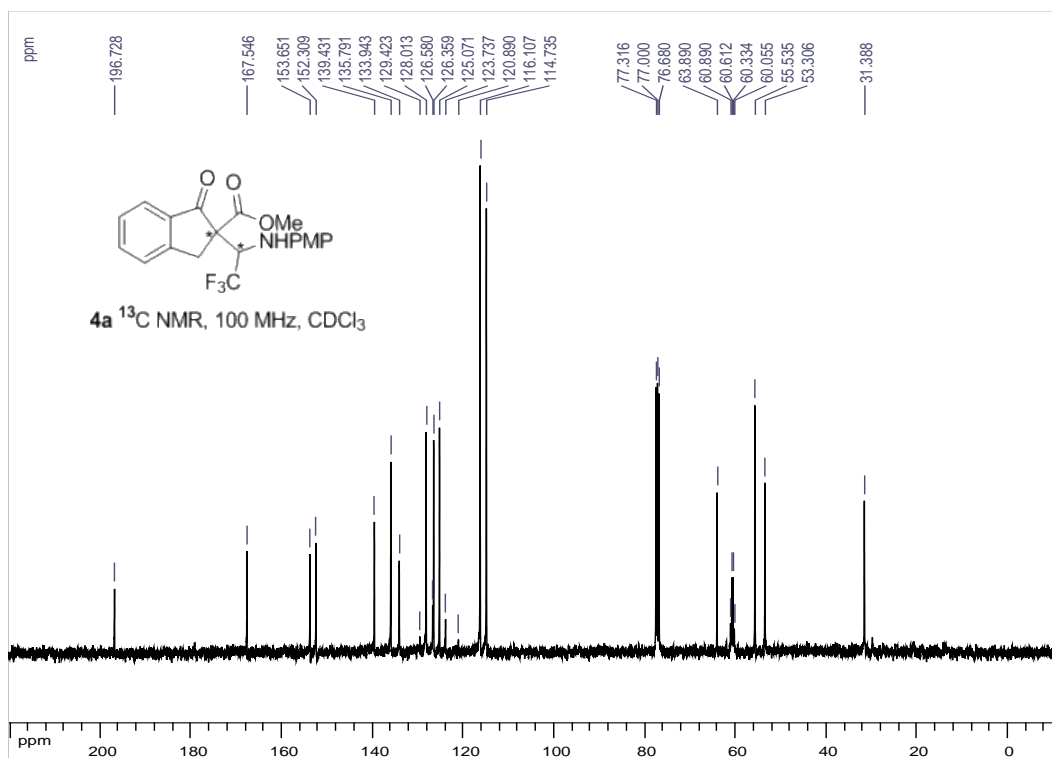
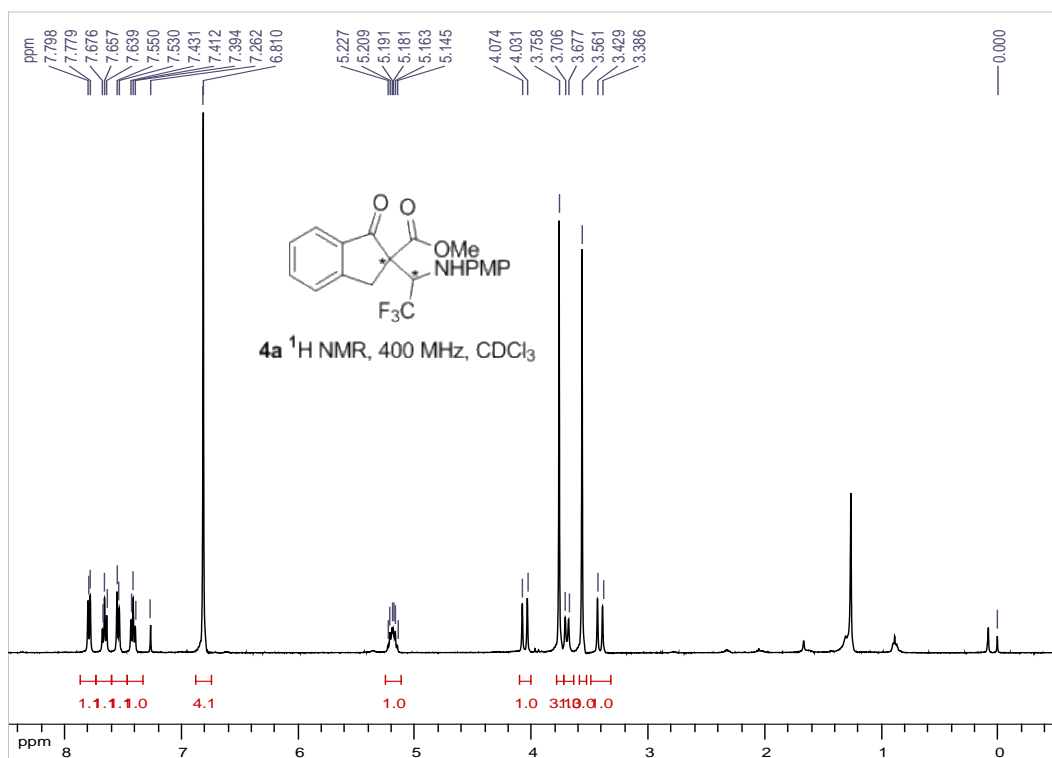
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -70.36~ -70.38 (d, *J* = 6.8 Hz);

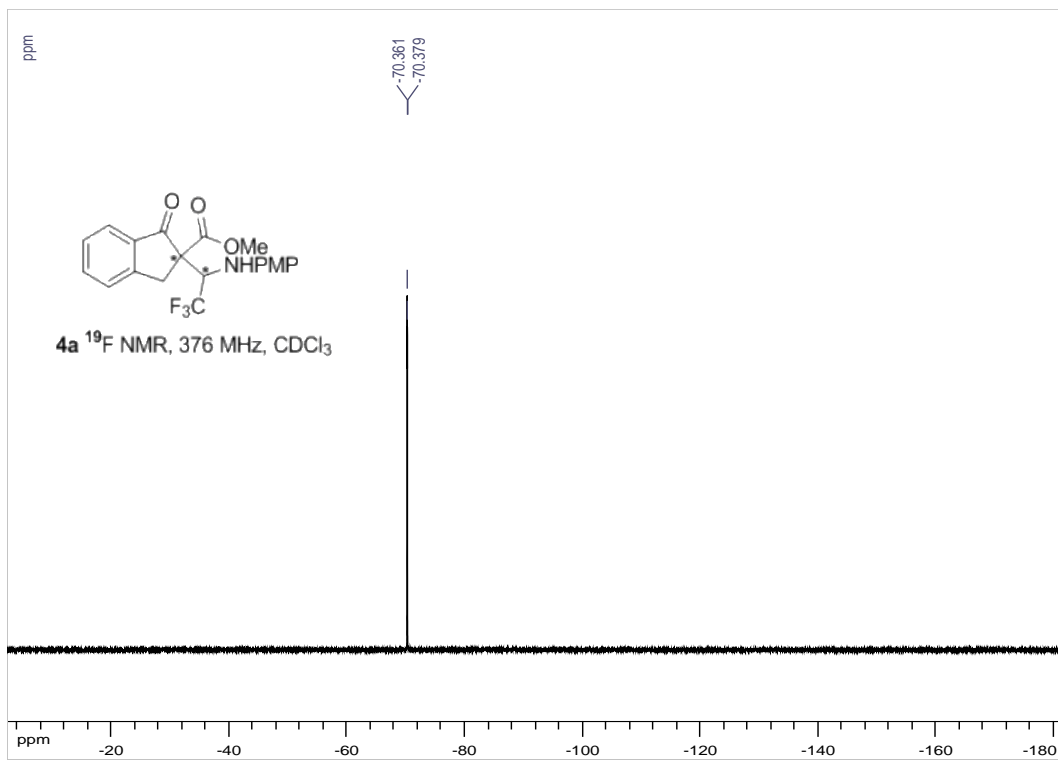
**HRMS** (ESIMS) calcd for C<sub>20</sub>H<sub>18</sub>F<sub>3</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 394.1261, found 394.1258.

**IR** (thin film, cm<sup>-1</sup>): 3370, 3032, 2961, 1745, 1514, 1465, 1245, 1033, 828, 760;

**HPLC** major ee: 84%; minor ee: 88%; dr: 80:20 ; (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, 1 mL/min, 254 nm, major isomer: *t*<sub>1</sub> = 17.70 min, *t*<sub>2</sub> = 29.28 min; minor isomer: *t*<sub>3</sub> = 11.97 min, *t*<sub>4</sub> = 22.82 min).

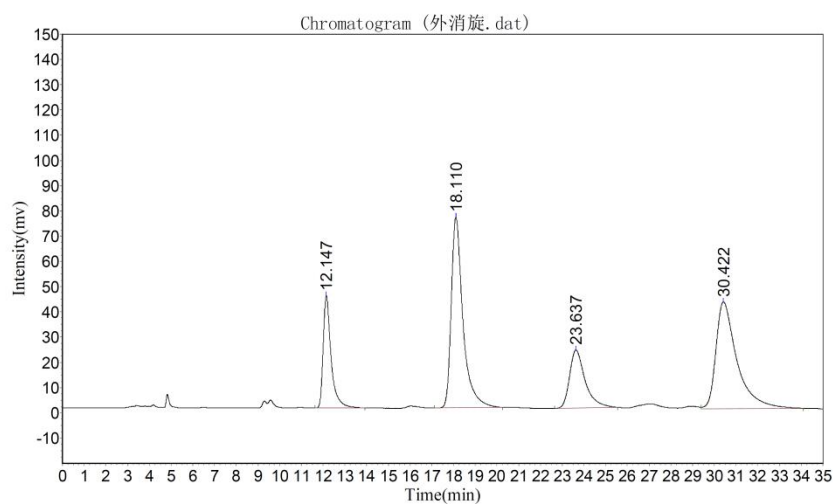
NMR copies of major product of compound **4a**





HPLC copies of compound 4a:

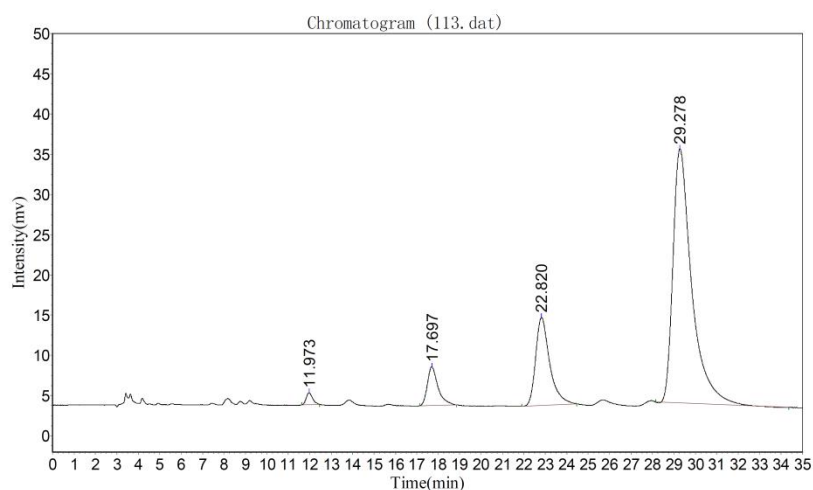
### rac Hex/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		12.147	44607.402	1126686.250	13.9640
2		18.110	75555.961	2827196.750	35.0399
3		23.637	22998.309	1145437.125	14.1964
4		30.422	42280.914	2836665.500	35.1572
Total			187332.803	8068510.750	100.0000

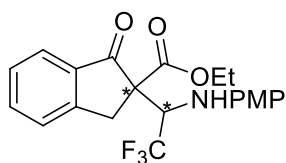
### 4a Hex/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		11.973	1475.857	30564.500	1.1683
2		17.697	4794.087	165612.469	6.3303
3		22.820	10923.311	496306.406	18.9705
4		29.278	31603.586	1923720.375	73.5310
Total			48796.841	2616203.750	100.0000

**Compound 4b:**



**Compound 4b:** 85% yield; white solid; mp: 127-129 °C;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ (ppm): 7.74~7.72(d, *J* = 7.6 Hz, 1H), 7.65~7.61(t, *J* = 7.2 Hz, 1H), 7.55~7.53(d, *J* = 7.6 Hz, 1H), 7.39~7.35(t, *J* = 7.6 Hz, 1H), 6.81~6.75(m, 4H), 5.24~5.16(m, 1H), 4.26~4.13(m, 2H), 3.98~3.94(d, *J* = 17.6 Hz, 1H), 3.73(s, 3H), 3.62~3.59(d, *J* = 11.2 Hz, 1H), 3.36~3.31(d, *J* = 17.6 Hz, 1H), 1.26~1.23(t, *J* = 6.8 Hz, 3H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm): 197.8, 167.1, 153.9, 153.2, 139.7, 135.7, 134.4, 130.1~124.4(q, *J*<sub>C-F</sub> = 285.1 Hz), 127.9, 126.2, 125.1, 116.8, 114.7, 62.6, 62.5, 61.2~60.3 (q, *J*<sub>C-F</sub> = 27.8 Hz), 55.6, 31.6, 13.8;

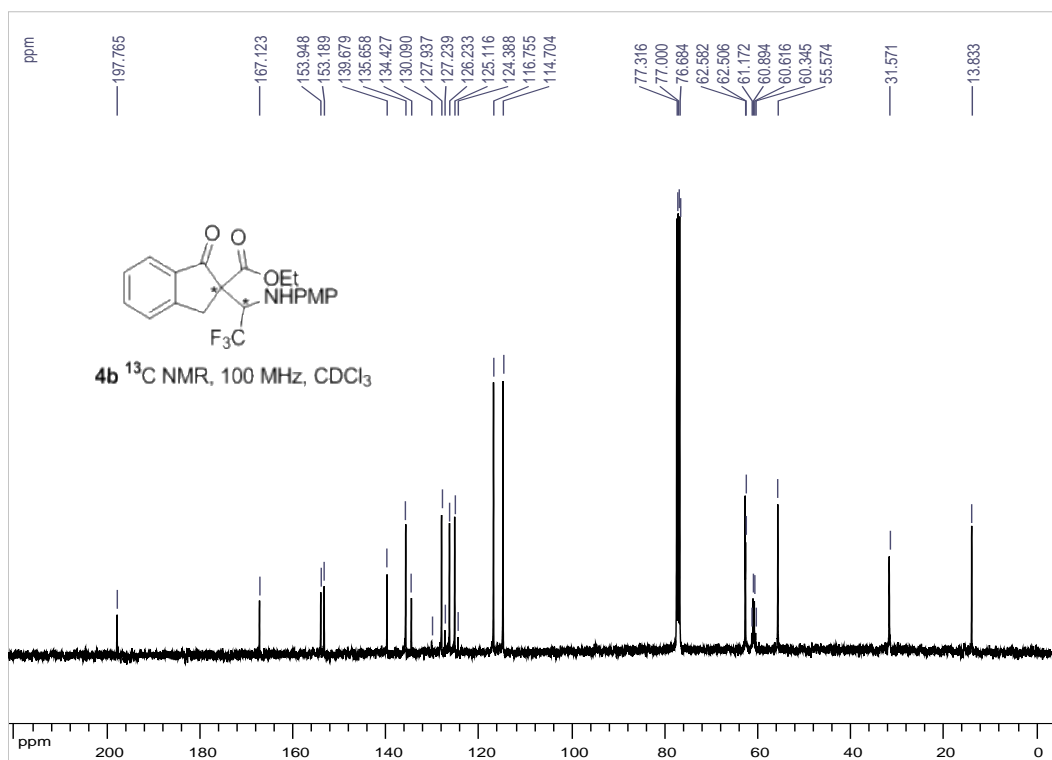
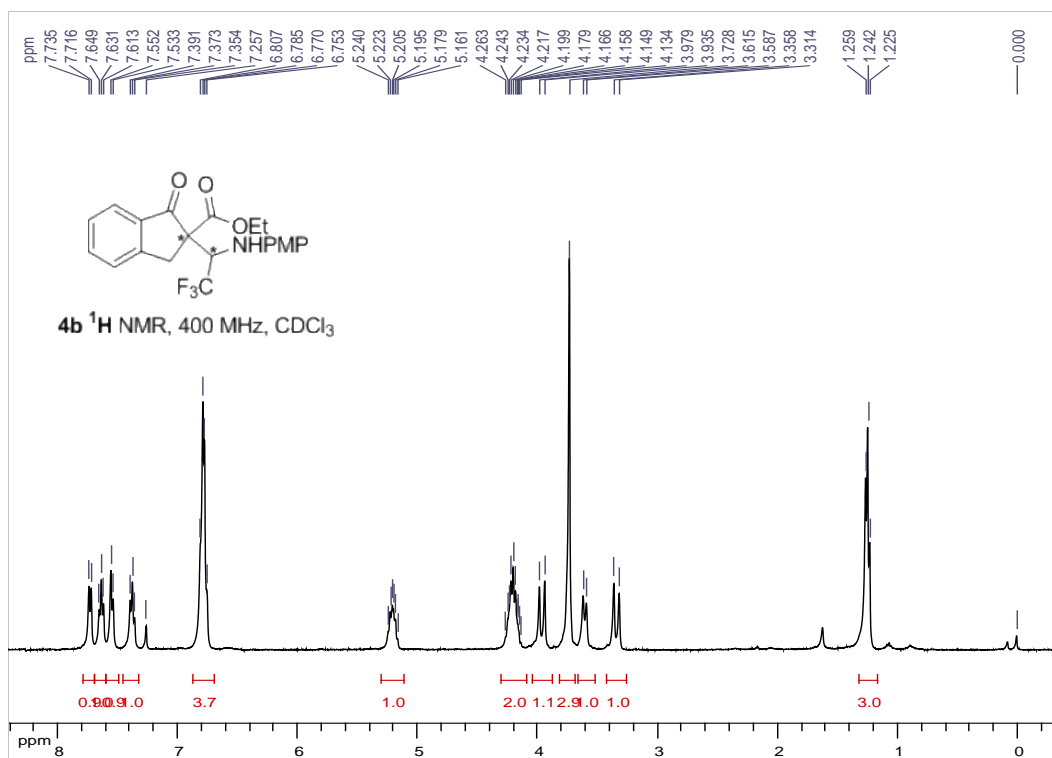
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -70.02~-70.04(d, *J* = 7.5 Hz);

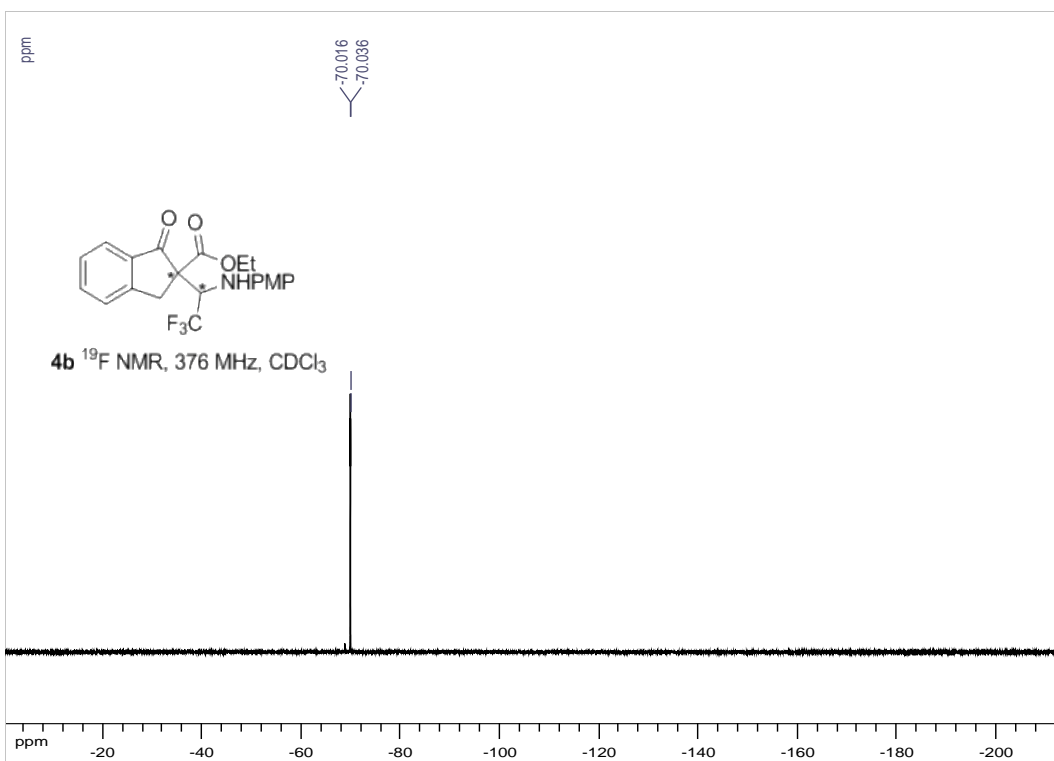
**HRMS** (ESIMS) calcd for C<sub>21</sub>H<sub>20</sub>F<sub>3</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 408.1417, found 408.1412

**IR** (thin film, cm<sup>-1</sup>): 3389.5, 2924.3, 1722.1, 1606.6, 1518.8, 1465.6, 1244.4, 1144.8, 1031.9, 829.2;

**HPLC** major ee: 77%; minor ee: 80%; dr: 86:14 (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 95/5, 1 mL/min, 254 nm, major isomer: t<sub>1</sub> = 22.26 min; t<sub>2</sub> = 28.68 min; minor isomer: t<sub>3</sub> = 13.99 min; t<sub>4</sub> = 25.39 min).

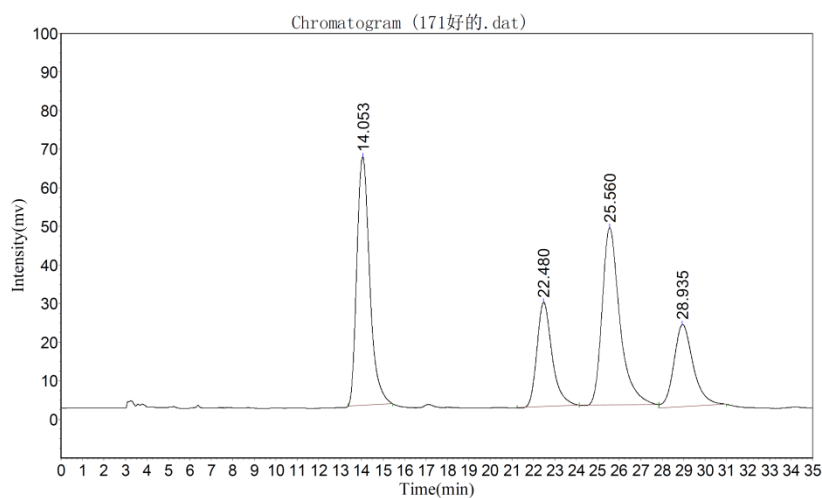
NMR copies of major product of compound **4b**:





HPLC copies of compound **4b**:

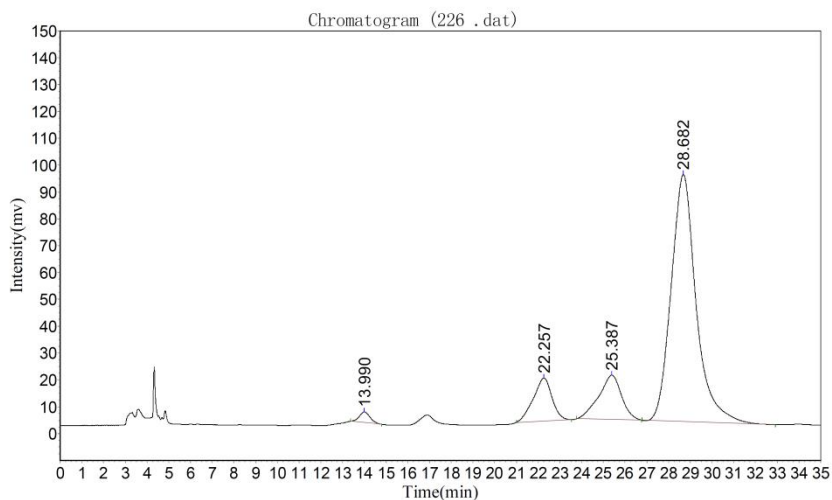
**rac Hex/iPrOH 95/5 AD-H**



**Results**

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		14.053	64404.070	2678943.250	33.6250
2		22.480	27066.238	1322629.000	16.6011
3		25.560	45975.020	2625833.750	32.9584
4		28.935	21297.789	1339702.875	16.8154
Total			158743.117	7967108.875	100.0000

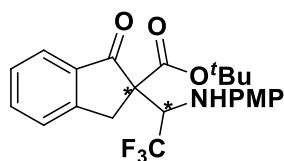
**4b Hex/iPrOH 95/5 AD-H**



**Results**

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		13.990	3959.224	136290.500	1.4125
2		22.257	15988.847	952750.688	9.8740
3		25.387	16482.209	1202264.000	12.4598
4		28.682	92077.789	7357806.000	76.2537
Total			128508.069	9649111.188	100.0000

**Compound 4c:**



**Compound 4c:** 72% yield, white solid; mp: 165-167 °C;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ (ppm): 7.78~7.76(d, *J* = 7.2 Hz, 1H), 7.64~7.61(t, *J* = 7.2 Hz, 1H), 7.52~7.50(d, *J* = 7.6 Hz, 1H), 7.40~7.37(t, *J* = 7.2 Hz, 1H), 6.80(s, 4H), 5.22~5.14(m, 1H), 4.02~3.98(d, *J* = 17.2 Hz, 1H), 3.85~3.83(d, *J* = 10.8 Hz, 1H), 3.75(s, 3H), 3.37~3.32(d, *J* = 17.2 Hz, 1H), 1.27(s, 9H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm): 197.0, 165.7, 153.4, 152.5, 139.7, 135.6, 134.1, 129.7~121.1(q, *J*<sub>C-F</sub> = 284.7 Hz), 127.9, 126.3, 125.0, 115.3, 114.8, 83.6, 64.8, 59.8~58.9(q, *J*<sub>C-F</sub> = 28.2 Hz), 55.7, 31.4, 27.5;

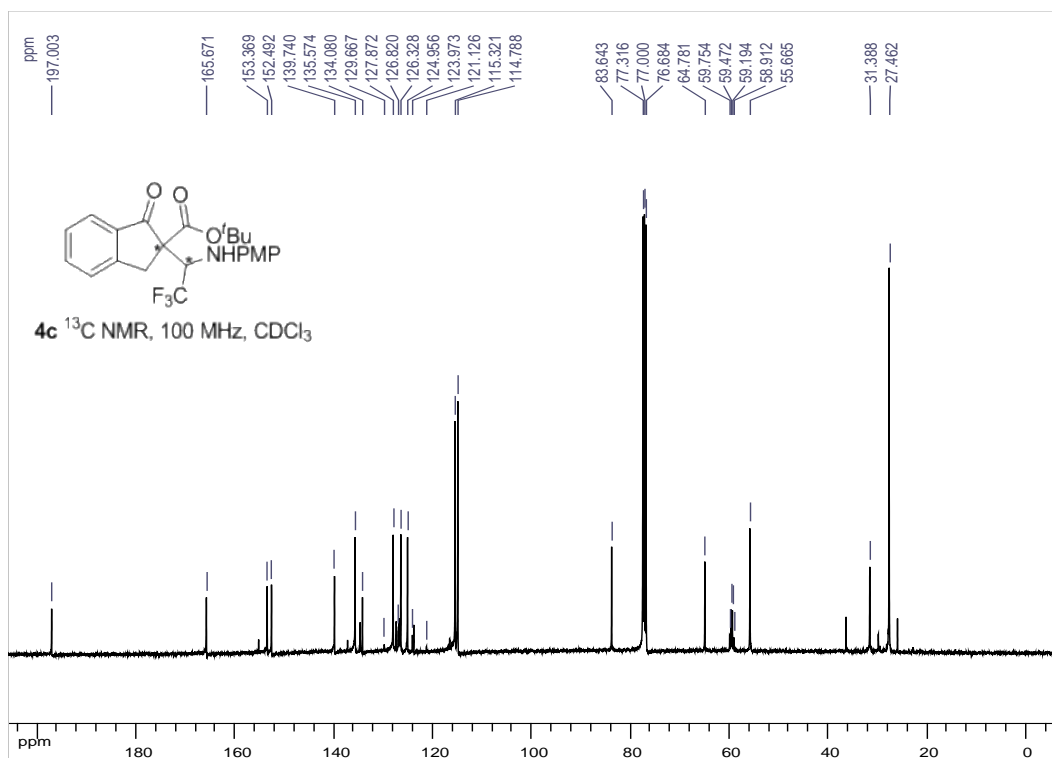
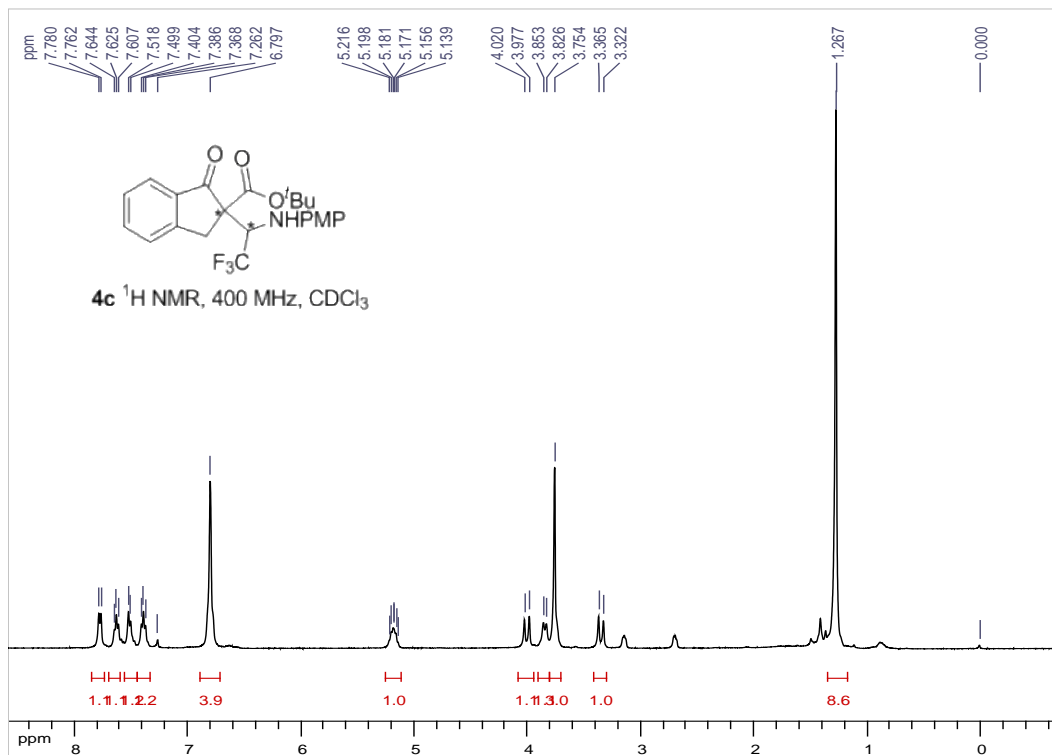
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -68.77~-68.79(d, *J* = 6.8 Hz);

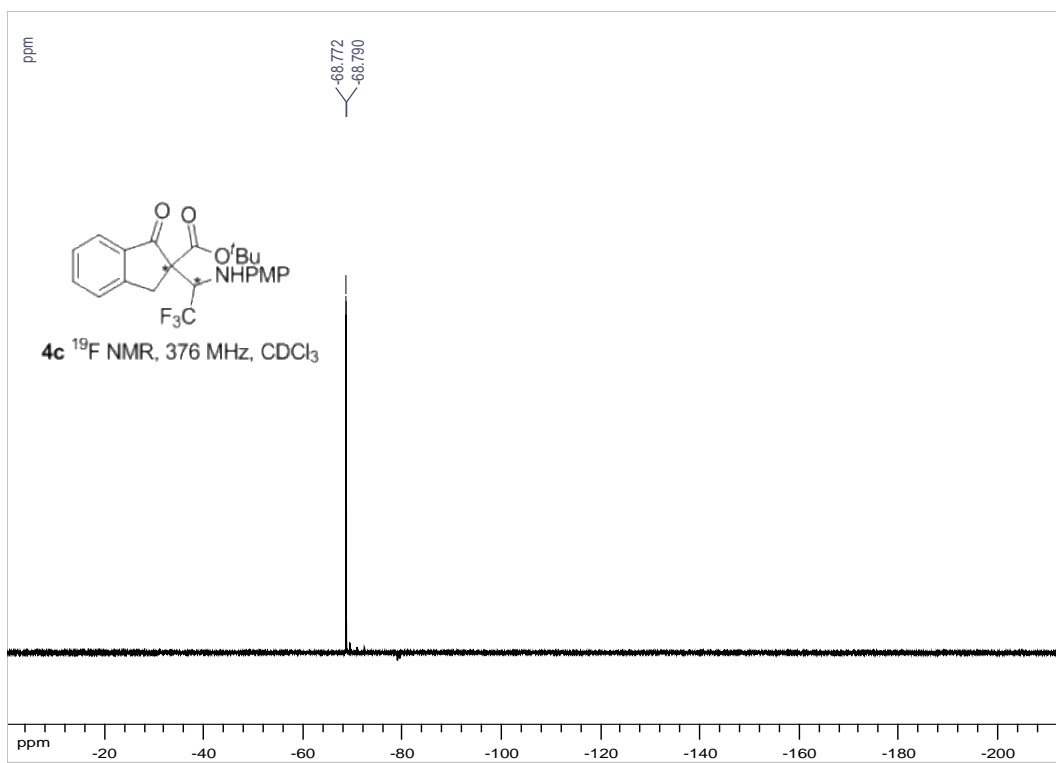
**HRMS** (ESIMS) calcd for C<sub>23</sub>H<sub>24</sub>F<sub>3</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 436.1730, found 436.1725

**IR** (thin film, cm<sup>-1</sup>): 3784.3, 3431.4, 2921.3, 2851.5, 1718.6, 1513.5, 1462.0, 1244.8, 1150.5, 1030.6, 839.0, 747.8, 670.0;

**HPLC** ee: 76% (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, 1 mL/min, 254 nm, major isomer: *t*<sub>1</sub> = 10.62 min; minor isomer: *t*<sub>2</sub> = 12.67 min).

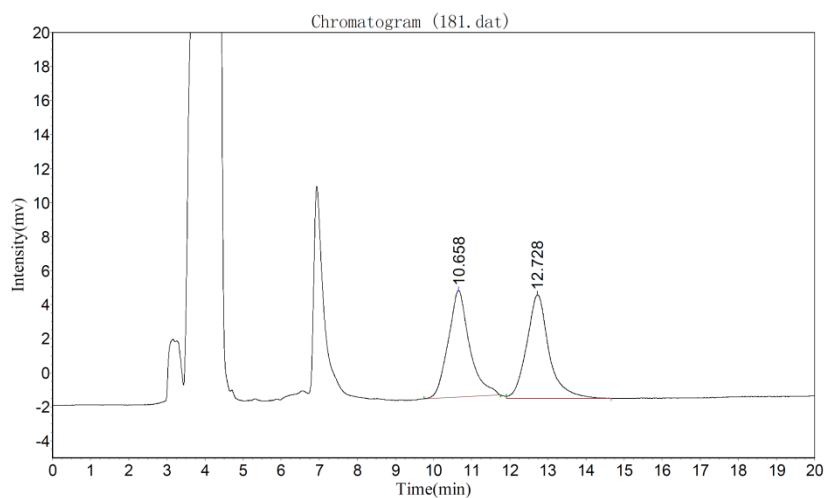
NMR copies of compound **4c**:





HPLC copies of compound **4c**:

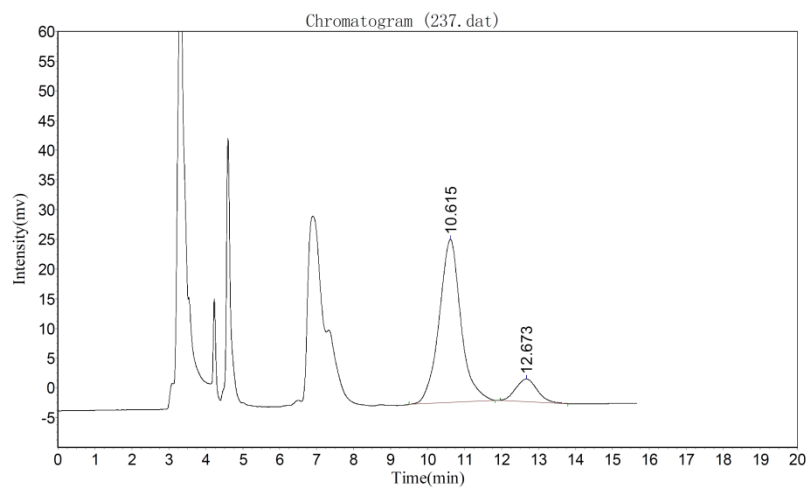
**rac Hex/iPrOH 90/10 AD-H**



**Results**

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		10.658	6257.580	243037.813	49.4878
2		12.728	6089.085	248068.328	50.5122
Total			12346.666	491106.141	100.0000

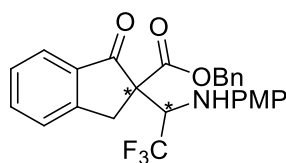
**4c Hex/iPrOH 90/10 AD-H**



**Results**

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		10.615	27448.758	1117439.375	88.0708
2		12.673	3799.027	151356.594	11.9292
Total			31247.785	1268795.969	100.0000

**Compound 4d:**



**Compound 4d:** 81% yield; white solid; mp: 137-139 °C;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ (ppm): 7.80~7.78(d, *J* = 7.6 Hz, 1H), 7.68~7.64(t, *J* = 7.6 Hz, 1H), 7.56~7.54(d, *J* = 7.6 Hz, 1H), 7.44~7.40(t, *J* = 7.6 Hz, 1H), 7.28~7.26(m, 3H), 7.16~7.14(m, 2H), 6.70(s, 4H), 5.24~5.17(m, 1H), 5.08~5.05(d, *J* = 12.4 Hz, 1H), 4.90~4.87(d, *J* = 12.4 Hz, 1H), 4.09~4.04(d, *J* = 17.2 Hz, 1H), 3.75(s, 3H), 3.68~3.65(d, *J* = 10.4 Hz, 1H), 3.43~3.39(d, *J* = 17.2 Hz, 1H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm): 196.5, 167.0, 153.6, 152.3, 139.3, 135.8, 134.7, 134.0, 128.4, 128.3, 128.1, 126.6~123.8(q, *J*<sub>C-F</sub> = 285.4 Hz), 126.4, 125.2, 116.1, 114.7, 68.4, 64.1, 60.6~59.7(q, *J*<sub>C-F</sub> = 27.8 Hz), 55.6, 31.4;

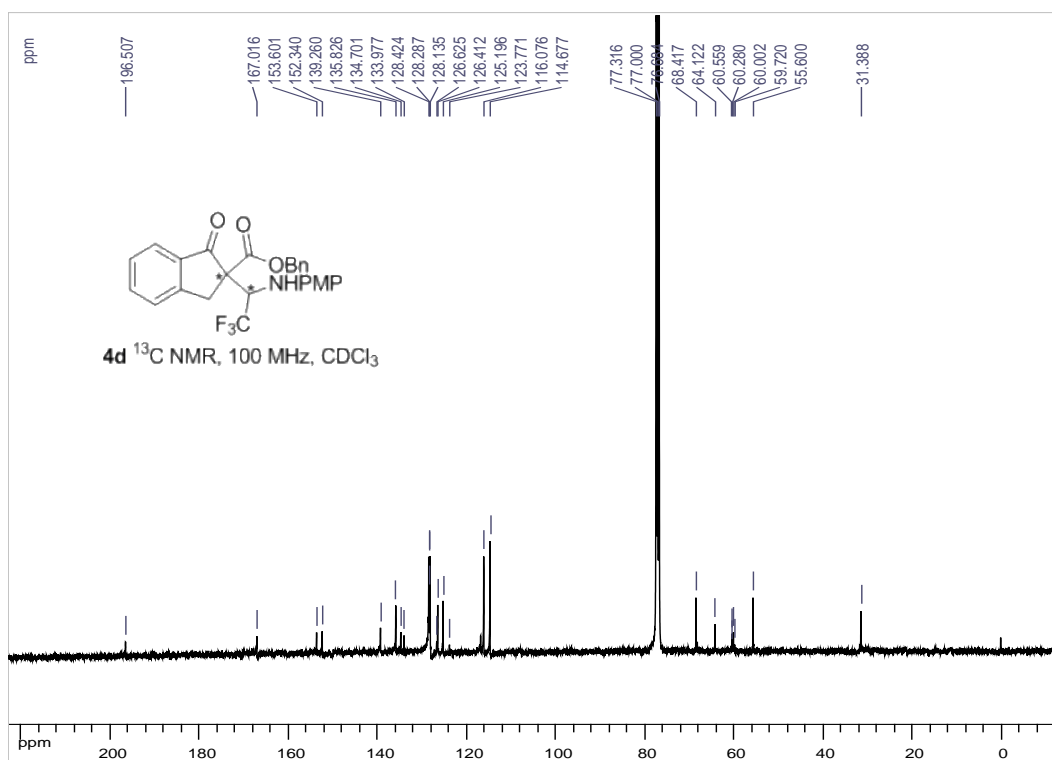
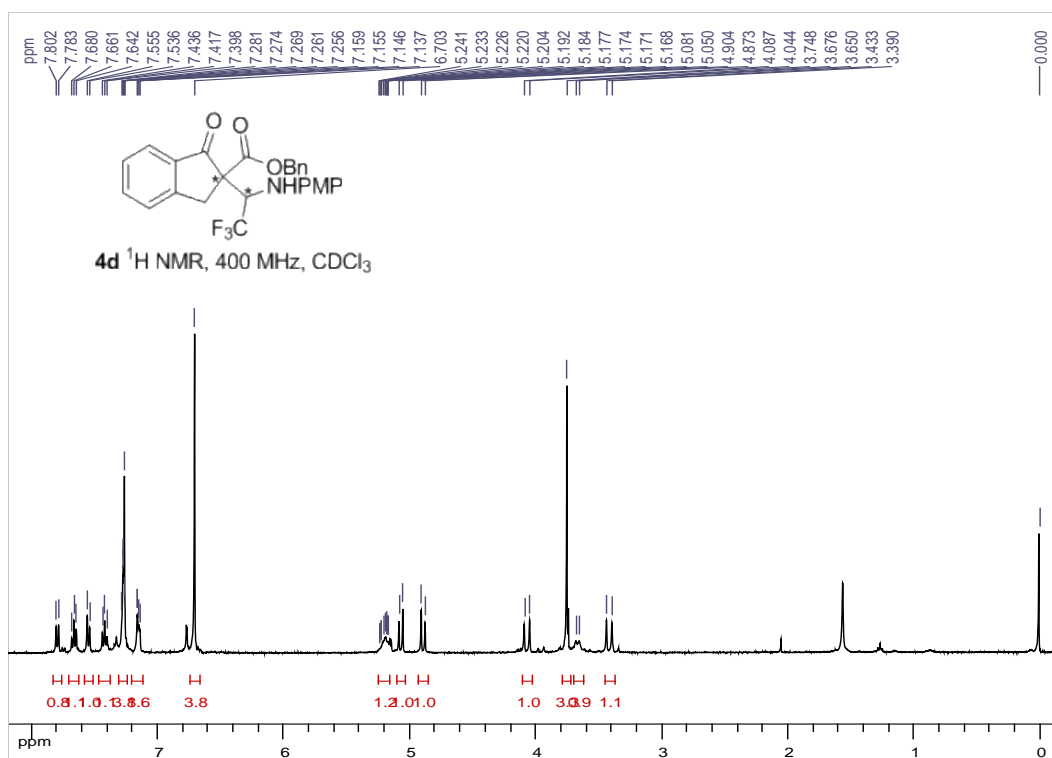
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -77.49~-77.50(d, *J* = 6.8 Hz);

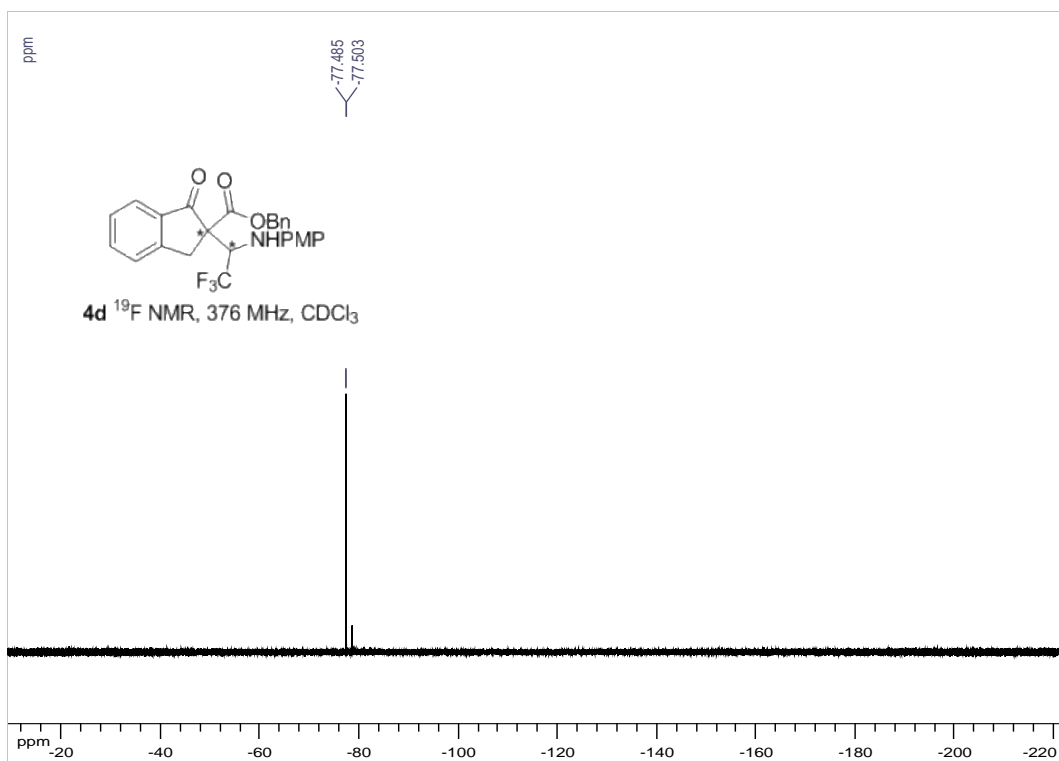
**HRMS** (ESIMS) calcd for C<sub>26</sub>H<sub>22</sub>F<sub>3</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 470.1574, found 470.1573

**IR** (thin film, cm<sup>-1</sup>): 3401.7, 2924.6, 2854.1, 1711.3, 1516.0, 1462.0, 1244.3, 1033.8, 916.1;

**HPLC** major ee: 79%; minor ee: 65%; dr: 81:19; (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, 1 mL/min, 254 nm, major isomer: *t*<sub>1</sub> = 36.96 min, *t*<sub>2</sub> = 43.79 min; minor isomer: *t*<sub>3</sub> = 19.00 min, *t*<sub>4</sub> = 29.46 min).

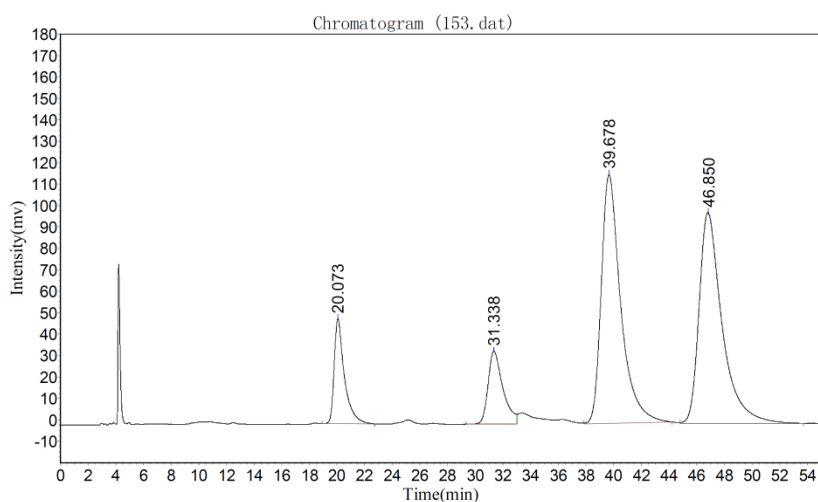
NMR copies of major product of compound **4d**:





HPLC copies of compound **4d**:

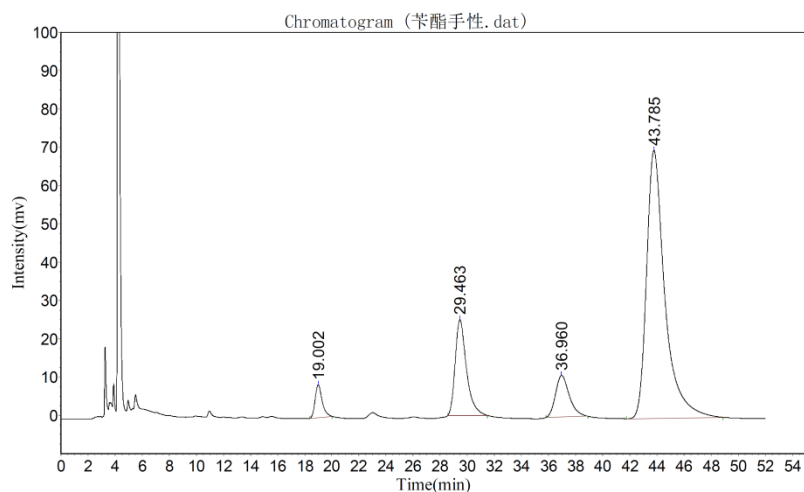
### rac Hex/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		20.073	49063.641	2501779.750	9.0070
2		31.338	34170.922	2541426.250	9.1497
3		39.678	116355.266	11338516.000	40.8211
4		46.850	98586.313	11394377.000	41.0222
Total			298176.141	27776099.000	100.0000

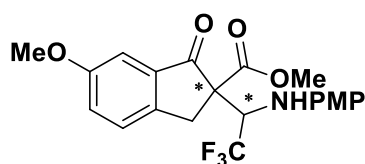
### 4d Hex/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		19.002	8544.613	307376.000	3.3900
2		29.463	24953.186	1435670.250	15.8339
3		36.960	10861.914	764118.313	8.4274
4		43.785	69967.906	6559899.500	72.3487
Total			114327.619	9067064.063	100.0000

**Compound 4e:**



**Compound 4e:** 93% yield, white solid; mp: 143-145 °C;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ (ppm): 7.44~7.42(d, *J* = 8.4 Hz, 1H), 7.27~7.24(dd, *J* = 2 Hz, 8.4 Hz, 1H), 7.20(s, 1H), 6.81(s, 4H), 5.20~5.12(m, 1H), 3.98~3.94(d, *J* = 16.8 Hz, 1H), 3.84(s, 3H), 3.76(s, 3H), 3.66~3.63(d, *J* = 11.2 Hz, 1H), 3.56(s, 3H), 3.35~3.30(d, *J* = 16.8 Hz, 1H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm): 196.7, 167.6, 159.9, 153.7, 145.3, 139.4, 135.2, 127.1, 125.4, 126.6~123.8(q, *J*<sub>C-F</sub> = 284.7 Hz), 116.2, 114.8, 106.0, 64.6, 61.0~60.2(q, *J*<sub>C-F</sub> = 27.4 Hz), 55.6, 53.4, 41.0, 30.8;

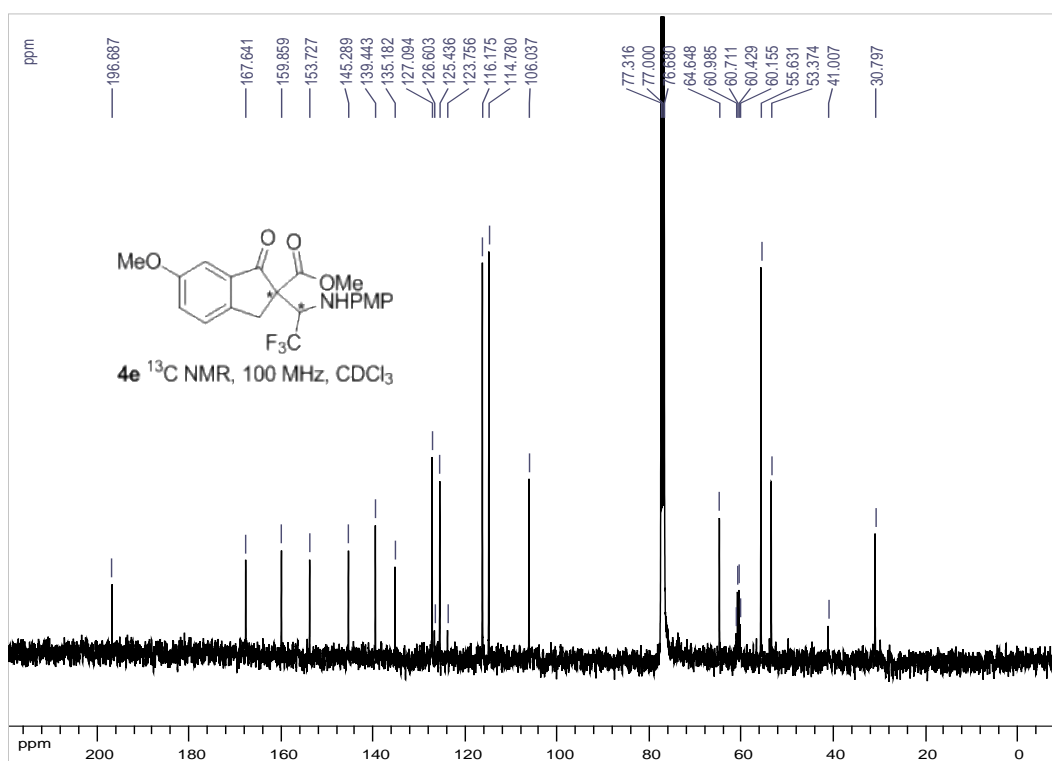
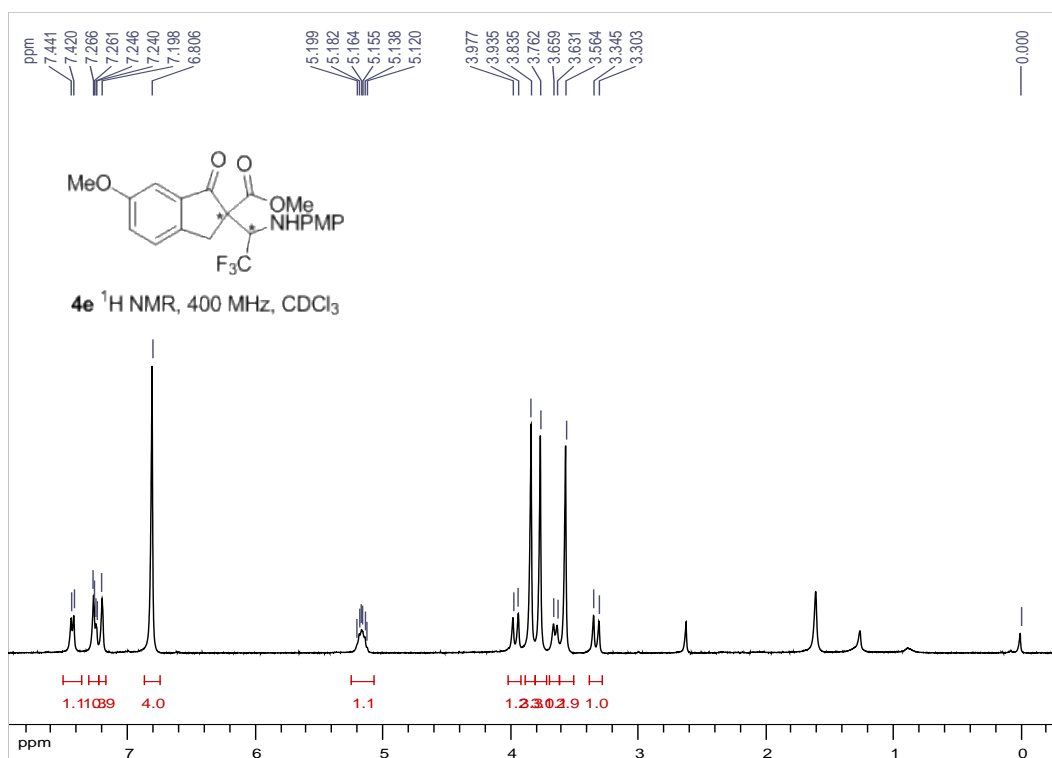
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -69.03~-69.05(d, *J* = 7.2 Hz);

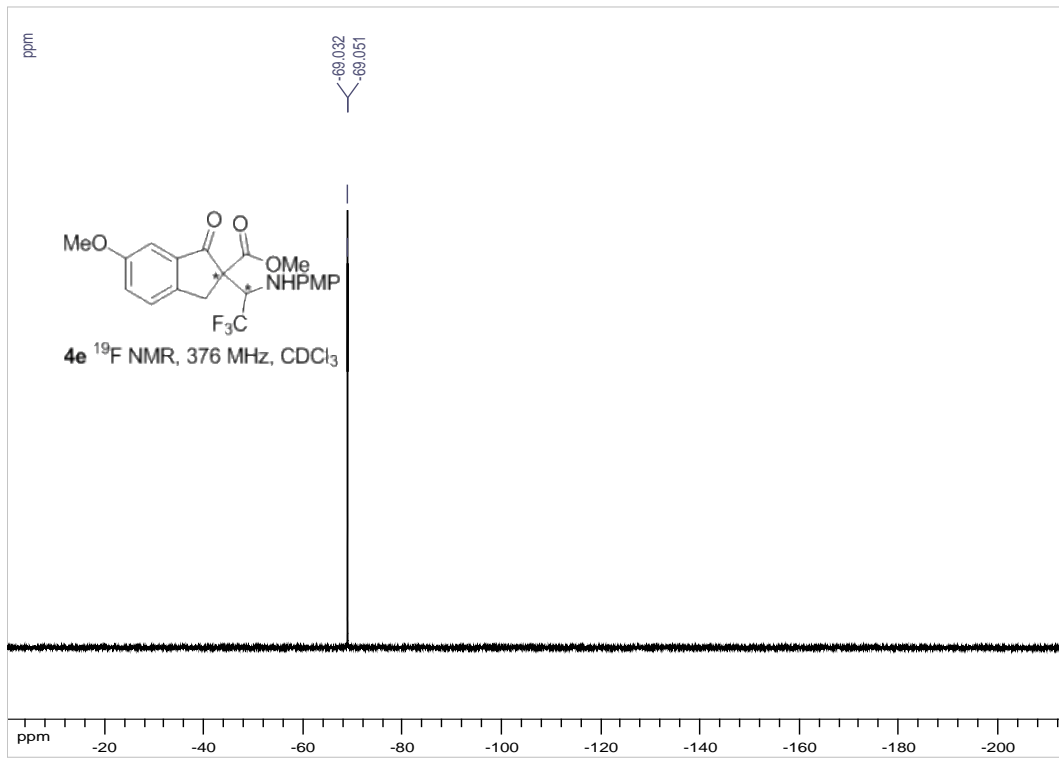
**HRMS** (ESIMS) calcd for C<sub>21</sub>H<sub>20</sub>F<sub>3</sub>NO<sub>5</sub> [M + H]<sup>+</sup> 424.1366, found 424.1371

**IR** (thin film, cm<sup>-1</sup>): 3369.7, 2924.9, 1719.2, 1614.4, 1513.6, 1458.2, 1238.4, 1030.2, 826.0, 726.3, 667.8

**HPLC** major ee: 76%; minor ee: 84%; dr: 81:19; (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, 1 mL/min, 254 nm, major isomer: t<sub>1</sub> = 30.36 min, t<sub>2</sub> = 36.38 min; minor isomer: t<sub>3</sub> = 16.85 min, t<sub>4</sub> = 25.68 min).

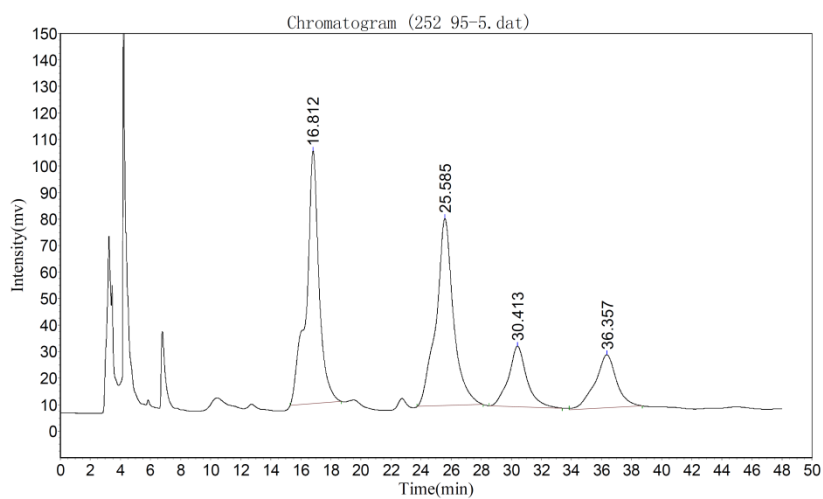
NMR copies of major product of compound **4e**:





HPLC copies of compound 4e:

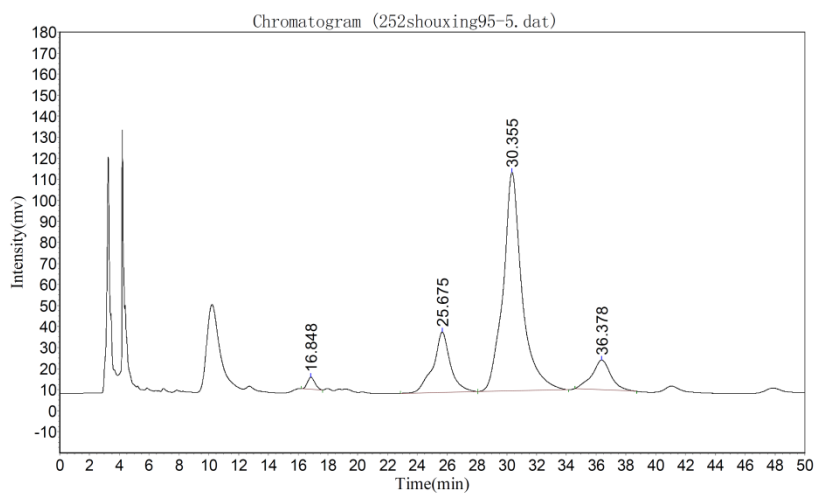
### rac Hex/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		16.812	95376.734	5638816.500	36.9921
2		25.585	70631.297	5677243.000	37.2441
3		30.413	22830.045	1928965.625	12.6545
4		36.357	19989.604	1998294.250	13.1093
Total			208827.680	15243319.375	100.0000

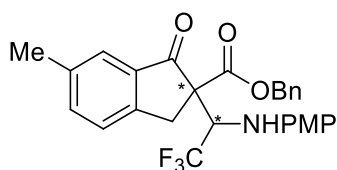
### 4e Hex/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		16.848	5775.752	204134.859	1.5811
2		25.675	28738.439	2299614.000	17.8114
3		30.355	103965.742	9170629.000	71.0300
4		36.378	14069.855	1236536.625	9.5775
Total			152549.790	12910914.484	100.0000

**Compound 4f:**



**Compound 4f:** 82% yield; white solid; mp: 140-141 °C;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ (ppm): 7.58(s, 1H), 7.46~7.44(d, *J* = 7.6 Hz, 1H), 7.40~7.38(d, *J* = 7.6 Hz, 1H), 7.26~7.25(m, 3H), 7.15~7.14(m, 2H), 6.70(s, 4H), 5.22~5.17(m, 1H), 5.07~5.04(d, *J* = 12.4 Hz, 1H), 4.89~4.86(d, *J* = 12.4 Hz, 1H), 4.02~3.98(d, *J* = 17.2 Hz, 1H), 3.75~3.71(m, 4H), 3.37~3.33(d, *J* = 17.2 Hz, 1H), 2.38(s, 3H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm): 196.5, 167.1, 153.6, 149.8, 139.4, 138.1, 137.1, 134.8, 134.2, 129.5~121.0(q, *J*<sub>C-F</sub> = 285.1 Hz), 128.4, 128.2, 128.1, 126.0, 125.0, 116.0, 114.7, 68.3, 64.4, 60.6~59.8(q, *J*<sub>C-F</sub> = 27.8 Hz), 55.6, 31.1, 21.0;

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -68.71~-68.73(d, *J* = 6.8 Hz);

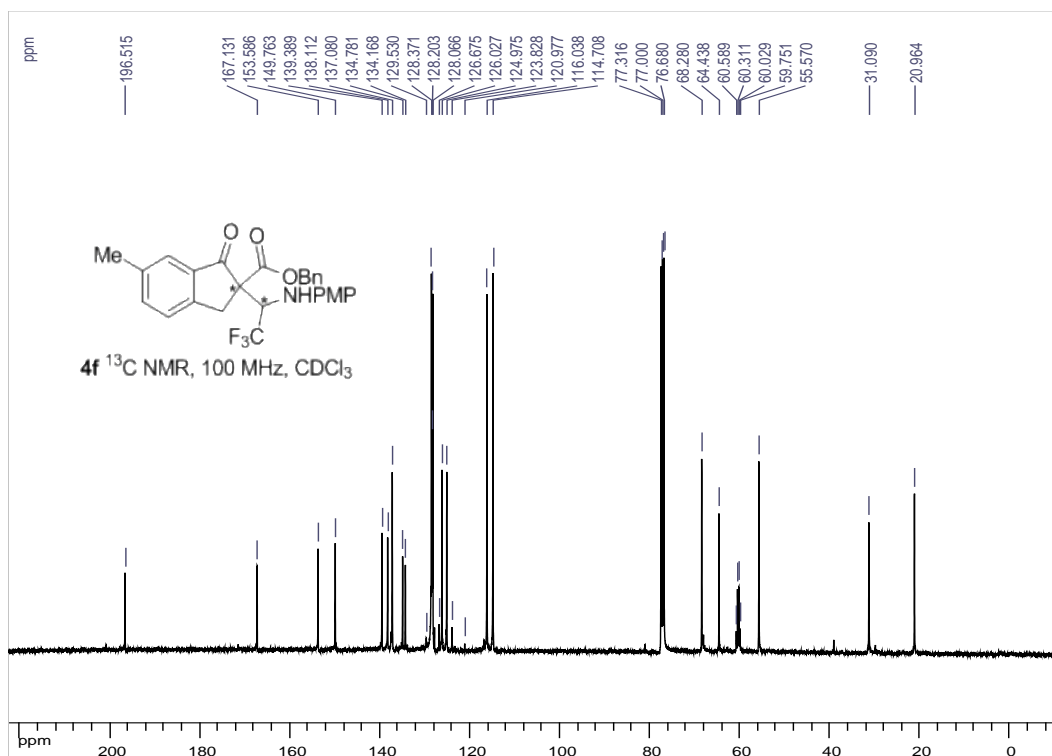
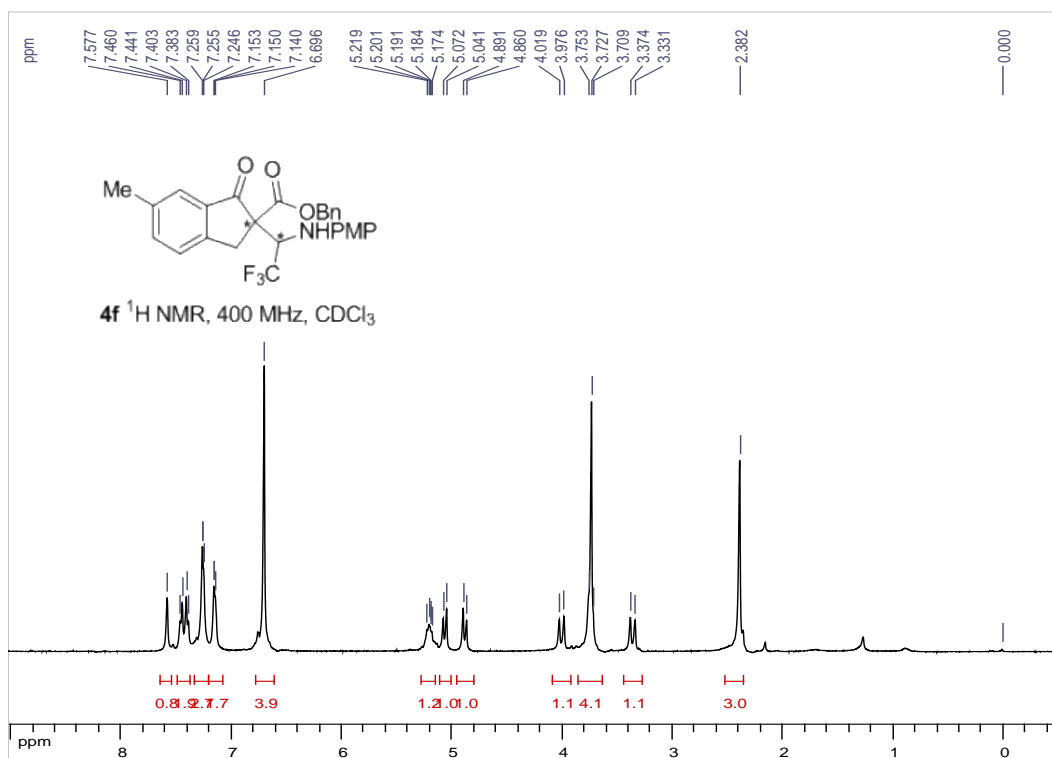
**HRMS** (ESIMS) calcd for C<sub>27</sub>H<sub>24</sub>F<sub>3</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 484.1730, found 484.1726

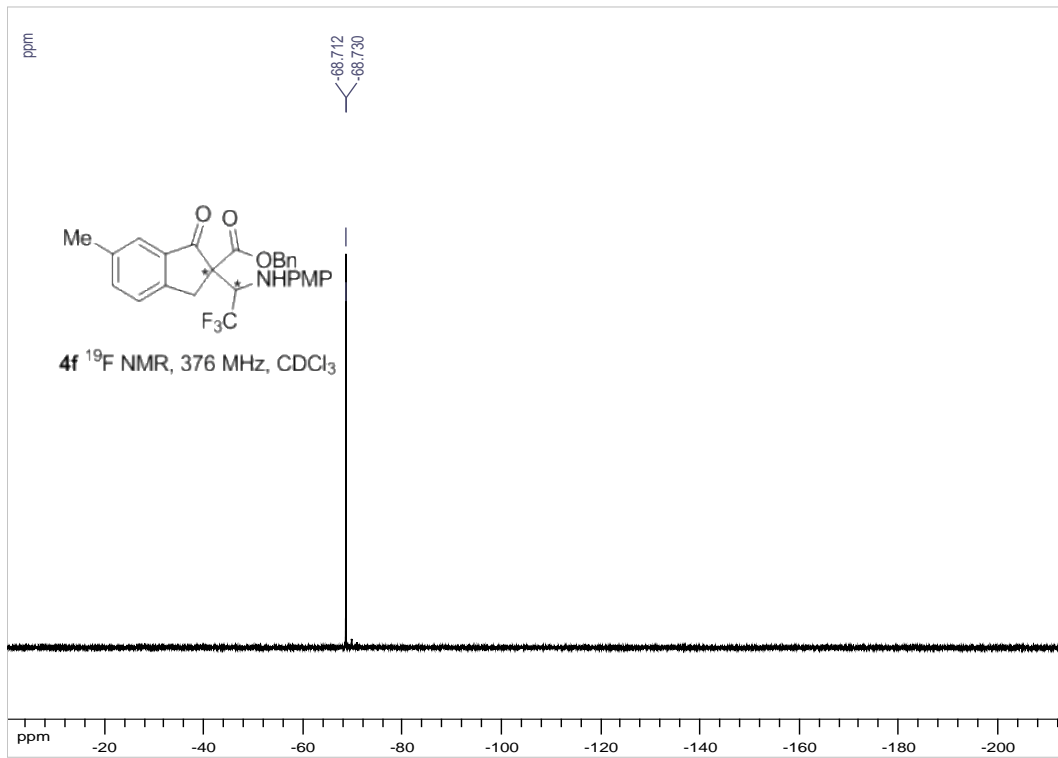
**IR** (thin film, cm<sup>-1</sup>): 3427.0, 3365.8, 3037.0, 1714.9, 1620.8, 1511.2, 1454.3, 1278.8, 1232.7, 1155.5, 1037.7, 820.4;

**IR** (neat) ν (cm<sup>-1</sup>) 2961, 1627, 1601, 1509, 1384, 1329, 1203, 1176, 1108, 1021, 965, 853, 771, 758, 731, 691.

**HPLC** major ee: 86%; minor ee: 47%; dr:87:13 (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, 1 mL/min, 254 nm, major isomer: *t*<sub>1</sub> = 20.44 min, *t*<sub>2</sub> = 30.42 min; minor isomer: *t*<sub>3</sub> = 26.74 min, *t*<sub>4</sub> = 46.56 min).

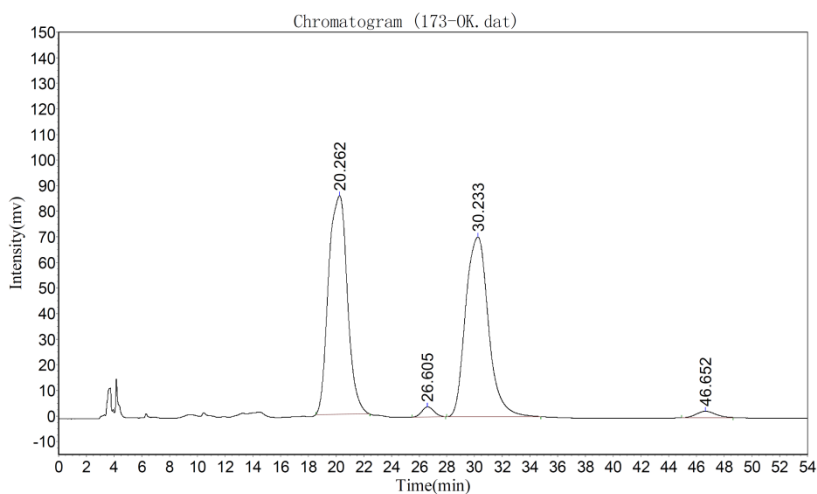
NMR copies of major product of compound **4f**:





HPLC copies of compound **4f**:

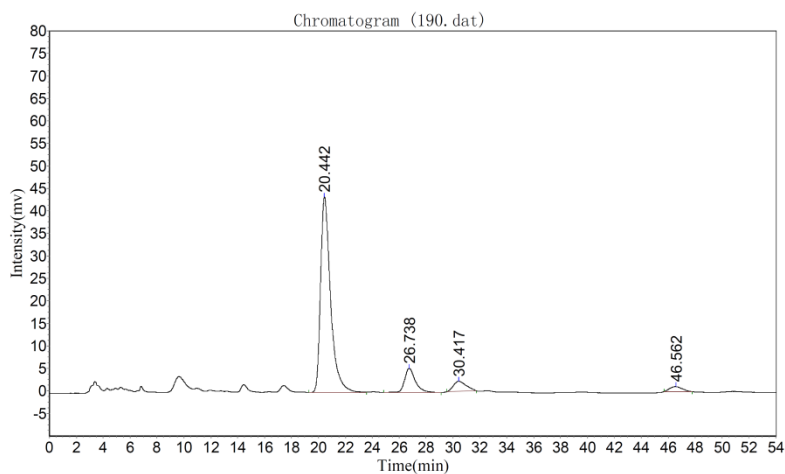
### rac Hex/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		20.262	85398.156	8061062.000	48.5985
2		26.605	3979.074	239504.703	1.4439
3		30.233	70218.664	8051124.000	48.5386
4		46.652	2507.015	235377.438	1.4190
Total			162102.909	16587068.141	100.0000

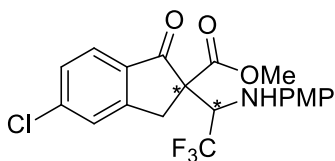
### 4f Hex/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		20.442	43486.242	2249287.250	81.3938
2		26.738	5403.189	299766.563	10.8475
3		30.417	2246.845	145648.797	5.2705
4		46.562	1106.619	68759.648	2.4882
Total			52242.895	2763462.258	100.0000

**Compound 4g:**



**Compound 4g:** 78% yield; yellow solid; mp: 128-130 °C;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ (ppm): 7.65~7.63(d, *J* = 8.4 Hz, 1H), 7.53(s, 1H), 7.36~7.34(d, *J* = 8.4 Hz, 1H), 6.81~6.75(m, 4H), 5.23~5.15(m, 1H), 3.97~3.93(d, *J* = 18.0 Hz, 1H), 3.75(s, 3H), 3.73(s, 3H), 3.56~3.53(d, *J* = 10.8 Hz, 1H), 3.33~3.29(d, *J* = 17.6 Hz, 1H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm): 196.2, 167.3, 154.6, 154.1, 142.5, 139.5, 132.8, 129.9~121.4(q, *J*<sub>C-F</sub> = 284.7 Hz), 128.9, 126.6, 126.2, 123.1, 116.9, 114.7, 62.8, 61.2~60.4(q, *J*<sub>C-F</sub> = 27.4 Hz), 55.6, 53.5, 31.2;

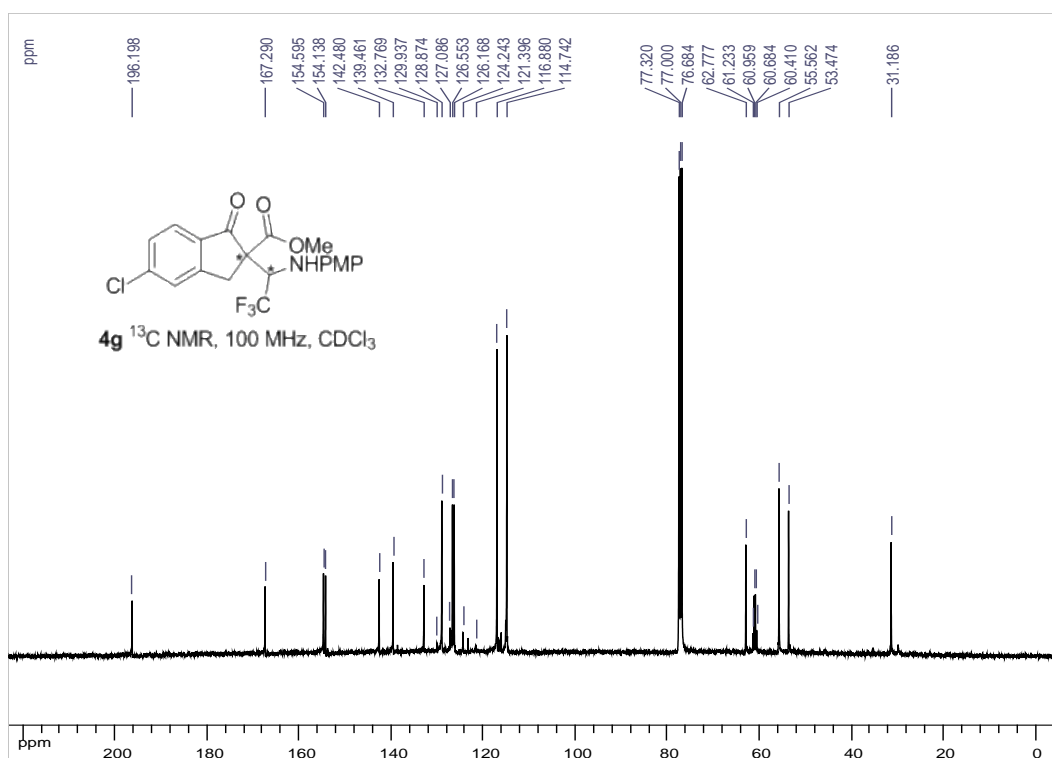
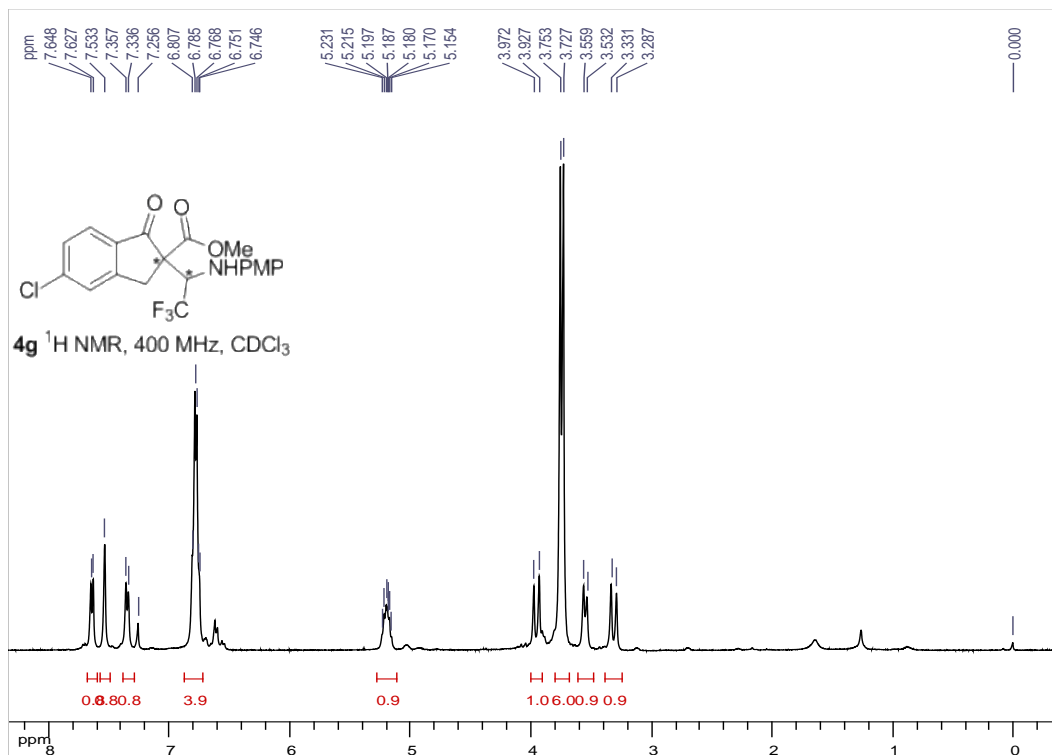
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -70.37~-70.38(d, *J* = 6.0 Hz);

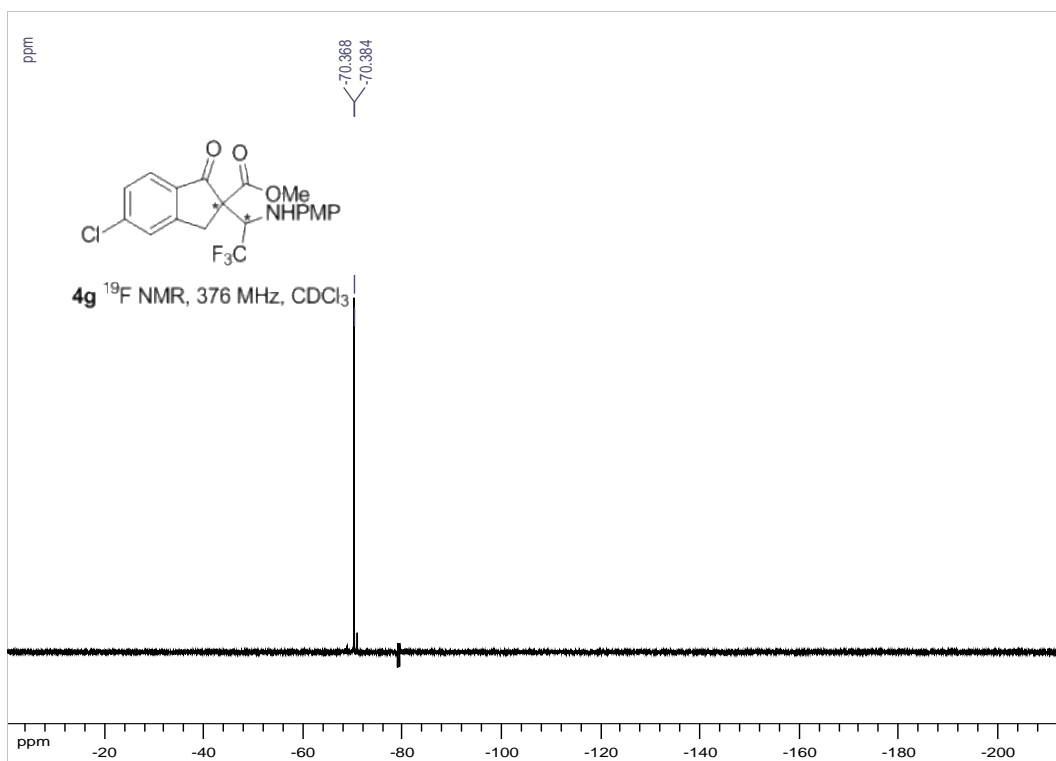
**HRMS** (ESIMS) calcd for C<sub>20</sub>H<sub>17</sub>ClF<sub>3</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 428.0871, found 428.0868

**IR** (thin film, cm<sup>-1</sup>): 3432.2, 2923.1, 1719.1, 1514.6, 1447.5, 1246.1, 1178.4, 1030.5, 825.1, 670.3;

**HPLC** major ee: 30%; minor ee: 35%; dr: 73:27; (Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, 25 °C, 1 mL/min, 254 nm, major isomer: t<sub>1</sub> = 31.49 min, t<sub>2</sub> = 43.86 min; minor isomer: t<sub>3</sub> = 23.47 min, t<sub>4</sub> = 27.40 min).

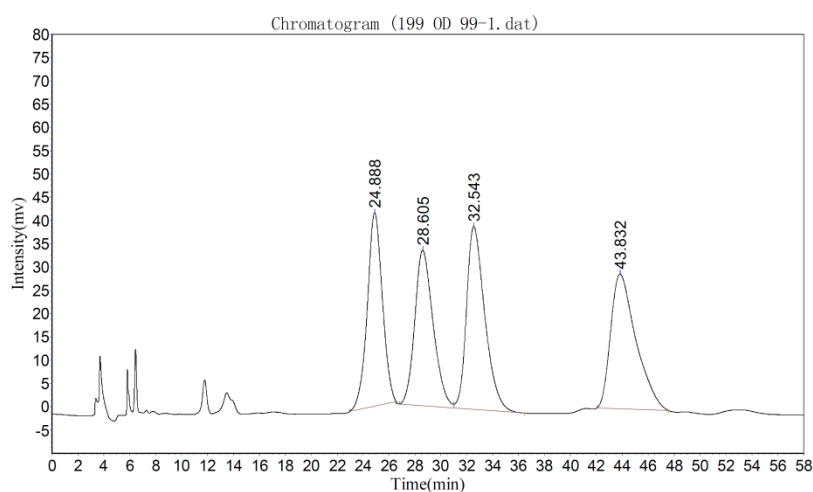
NMR copies of major product of compound **4g**:





HPLC copies of compound **4g**:

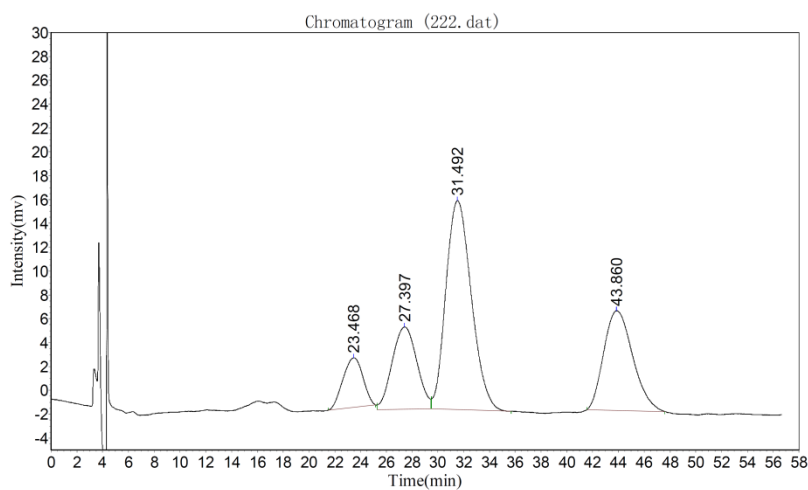
**rac Hex/iPrOH 99/1 OD-H**



**Results**

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		24.888	41563.070	3356666.750	23.3008
2		28.605	33399.156	3284695.500	22.8012
3		32.543	39295.547	3842335.000	26.6722
4		43.832	28956.018	3922090.250	27.2258
Total			143213.791	14405787.500	100.0000

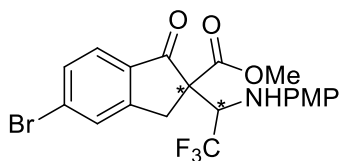
**4g Hex/iPrOH 99/1 OD-H**



**Results**

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		23.468	4177.403	448670.375	8.8427
2		27.397	6922.674	923006.625	18.1913
3		31.492	17522.010	2399136.000	47.2839
4		43.860	8351.272	1303080.250	25.6821
Total			36973.359	5073893.250	100.0000

**Compound 4h:**



**Compound 4h:** 85% yield; pale solid; mp: 155-157 °C;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ (ppm): 7.72(s, 1H), 7.57~7.55(d, *J* = 8.0 Hz, 1H), 7.52~7.50(d, *J* = 8.0 Hz, 1H), 6.81~6.75(m, 4H), 5.23~5.15(m, 1H), 3.98~3.93(d, *J* = 18.0 Hz, 1H), 3.75(s, 3H), 3.73(s, 3H), 3.56~3.53(d, *J* = 11.2 Hz, 1H), 3.34~3.29(d, *J* = 18.0 Hz, 1H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm): 196.5, 167.2, 154.7, 154.1, 139.4, 133.2, 131.7, 131.4, 129.9~124.2(q, *J*<sub>C-F</sub> = 285.8 Hz), 129.7, 126.2, , 116.9, 114.7, 62.7, 61.2~60.4(q, *J*<sub>C-F</sub> = 27.4 Hz), 55.6, 53.5, 31.1;

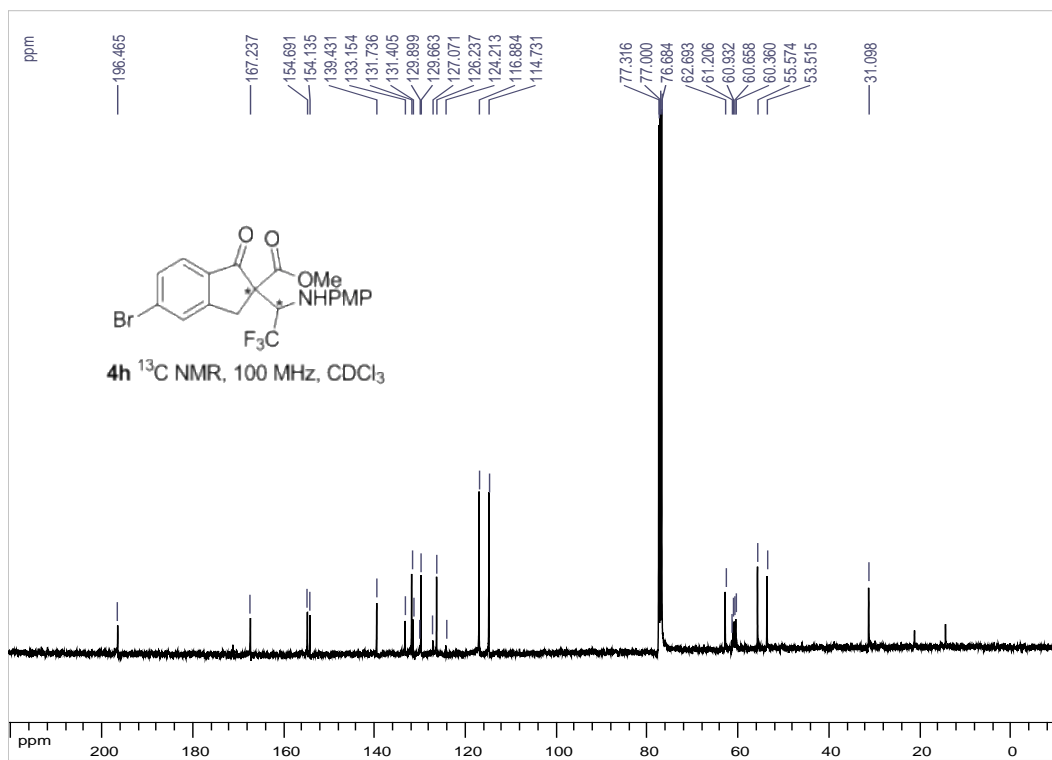
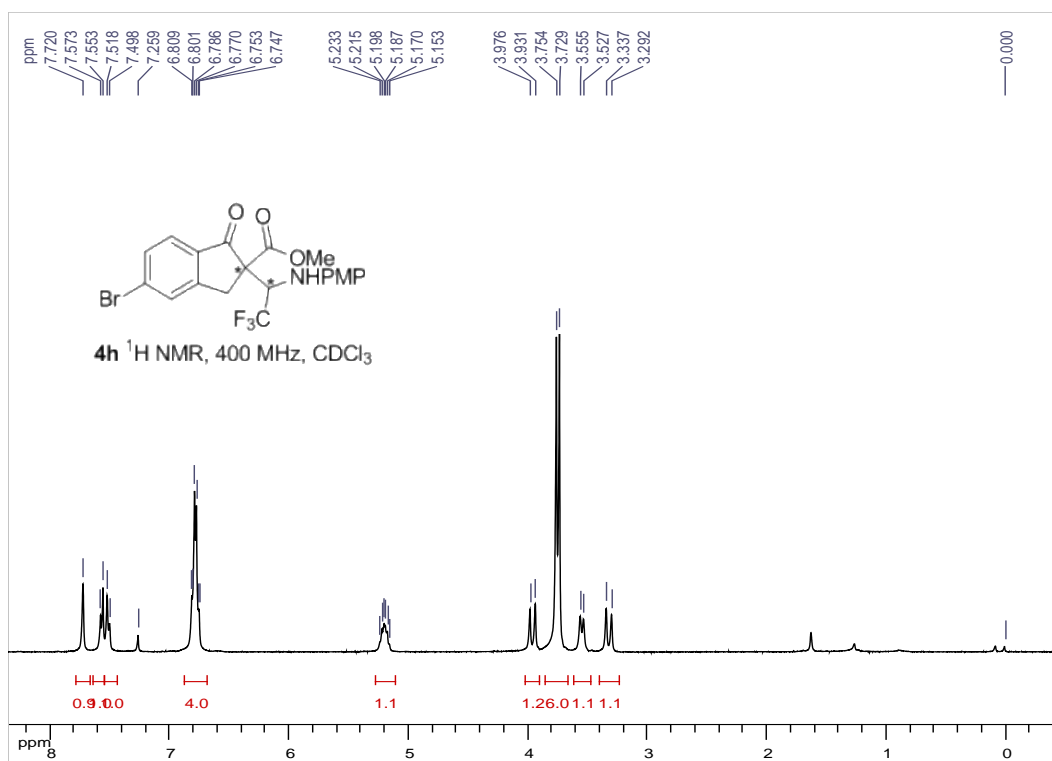
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -70.39~-70.41(d, *J* = 7.5 Hz);

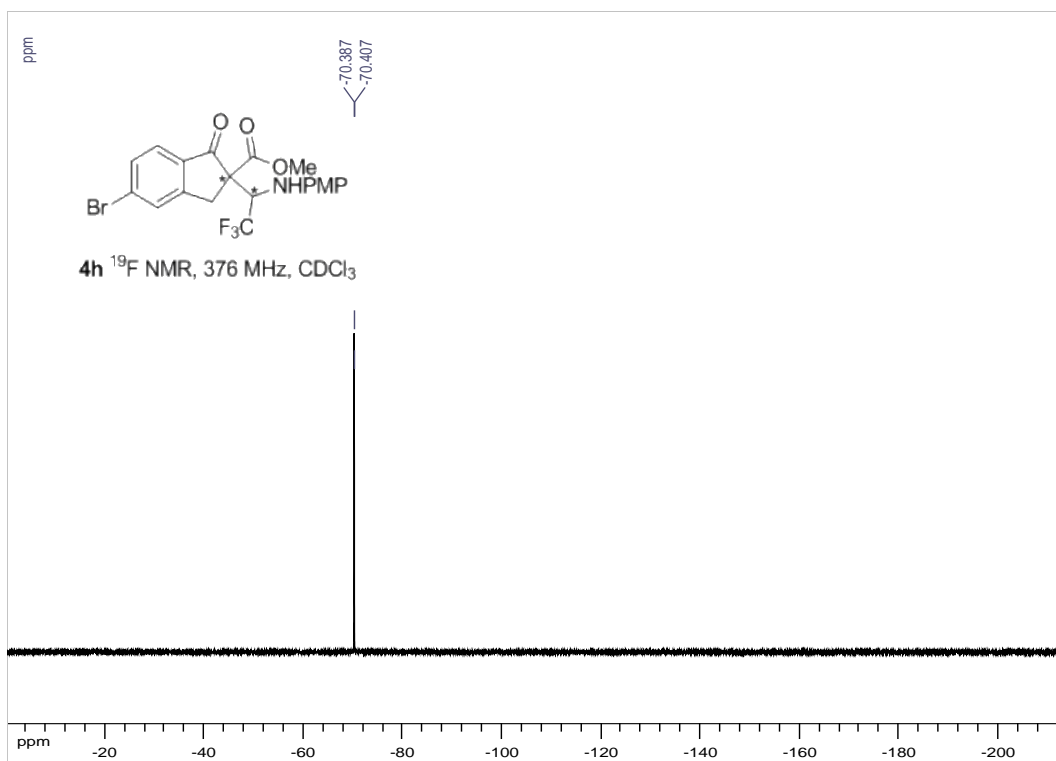
**IR** (thin film, cm<sup>-1</sup>): 3439.1, 3382.9, 2950.1, 1720.4, 1595.8, 1513.1, 1244.5, 1144.0, 1028.1, 826.3, 673.9;

**HRMS** (ESIMS) calcd for C<sub>20</sub>H<sub>17</sub>BrF<sub>3</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 472.0366, found 472.0367

**HPLC** major ee: 25%; minor ee: 10%; dr: 59:41; (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, 25 °C, 1 mL/min, 254 nm, major isomer: *t*<sub>1</sub> = 22.71 min, *t*<sub>2</sub> = 29.57 min; minor isomer: *t*<sub>3</sub> = 13.80 min, *t*<sub>4</sub> = 32.36 min).

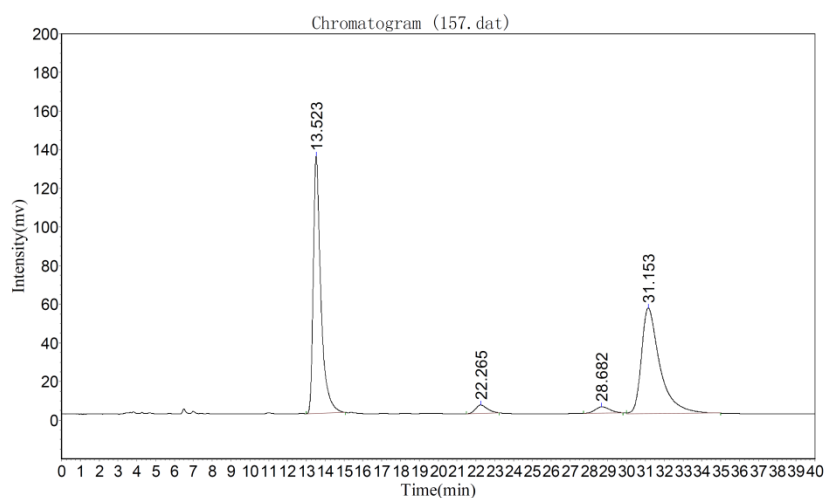
NMR copies of major product of compound **4h**:





HPLC copies of compound **4h**:

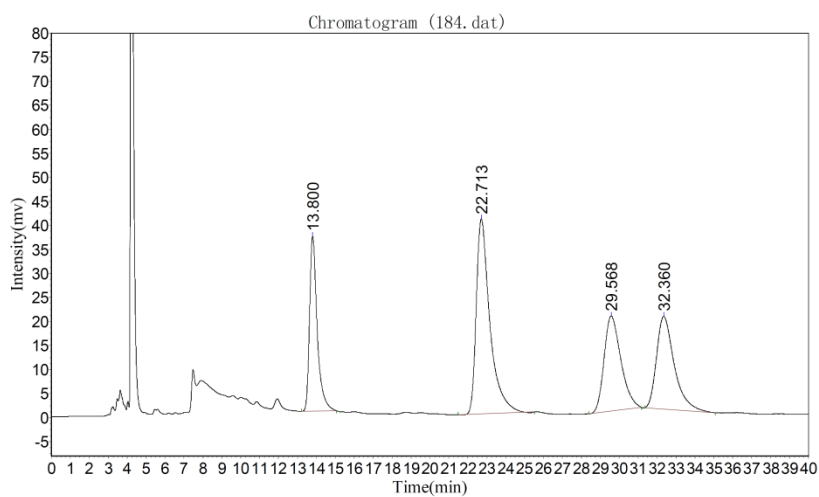
### rac Hex/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		13.523	133239.672	3713635.250	47.6373
2		22.265	4330.450	187941.406	2.4109
3		28.682	3235.626	168803.078	2.1654
4		31.153	54717.246	3725263.500	47.7865
Total			195522.994	7795643.234	100.0000

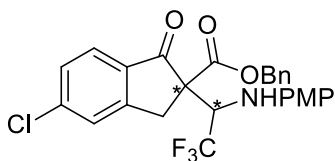
### 4h Hex/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		13.800	36408.402	1020681.063	18.4882
2		22.713	40591.629	2026044.125	36.6990
3		29.568	19809.988	1221033.750	22.1173
4		32.360	19310.734	1252946.875	22.6954
Total			116120.754	5520705.813	100.0000

**Compound 4i:**



**Compound 4i:** 80% yield; violet solid; mp: 176-178 °C;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ (ppm): 7.73~7.71(d, *J* = 8.4 Hz, 1H), 7.54(s, 1H), 7.41~7.39(d, *J* = 8.4 Hz, 1H), 7.29~7.24(m, 3H), 7.16~7.14(m, 2H), 6.70(s, 4H), 5.23~5.14(m, 1H), 5.08~5.05(d, *J* = 12.4 Hz, 1H), 4.90~4.87(d, *J* = 12.4 Hz, 1H), 4.07~4.02(d, *J* = 17.6 Hz, 1H), 3.75(s, 3H), 3.65~3.62(d, *J* = 11.6 Hz, 1H), 3.41~3.36(d, *J* = 17.2 Hz, 1H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm): 195.1, 166.7, 153.7, 142.6, 139.1, 134.5, 132.4, 129.0, 128.5, 128.4, 128.2, 126.7, 126.2, 116.1, 114.7, 68.6, 64.3, 60.5-59.7(q, *J*<sub>C-F</sub> = 28.2 Hz), 55.6, 31.1;

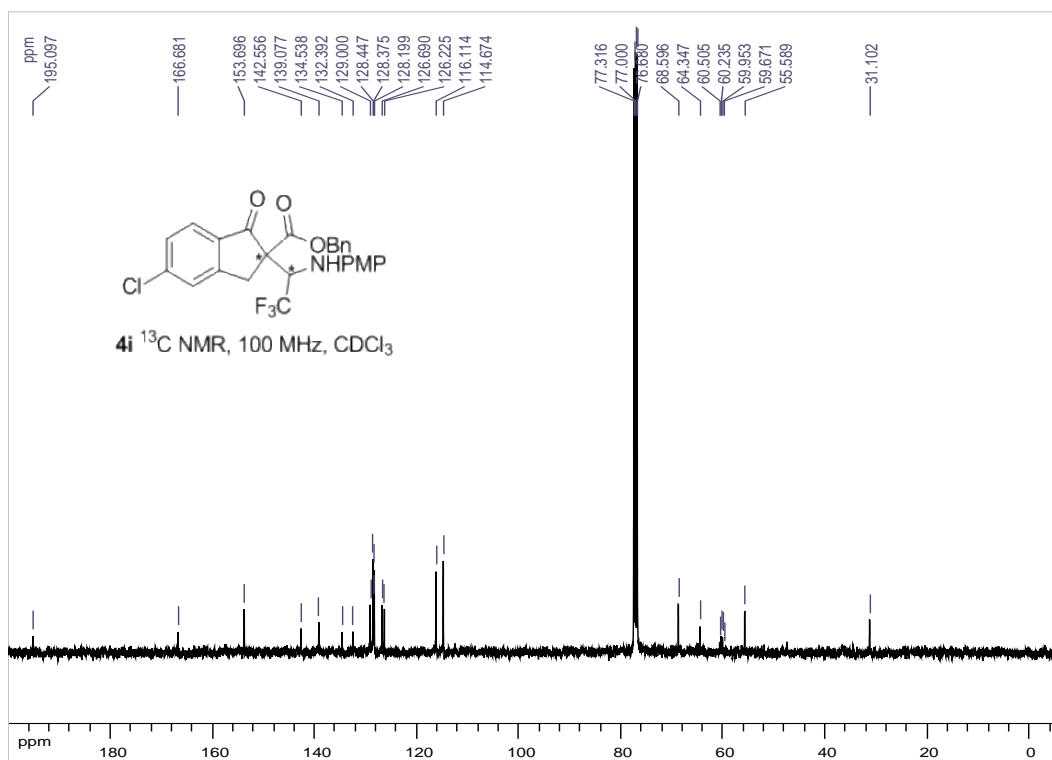
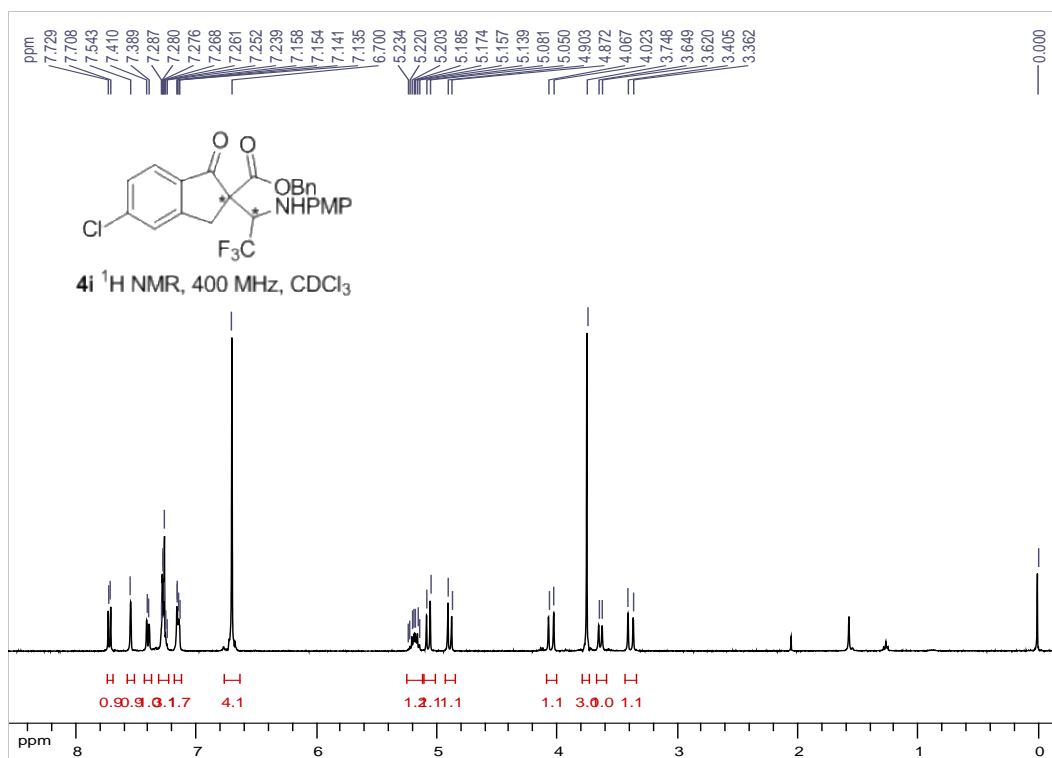
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -68.75~-68.77(d, *J* = 6.8 Hz);

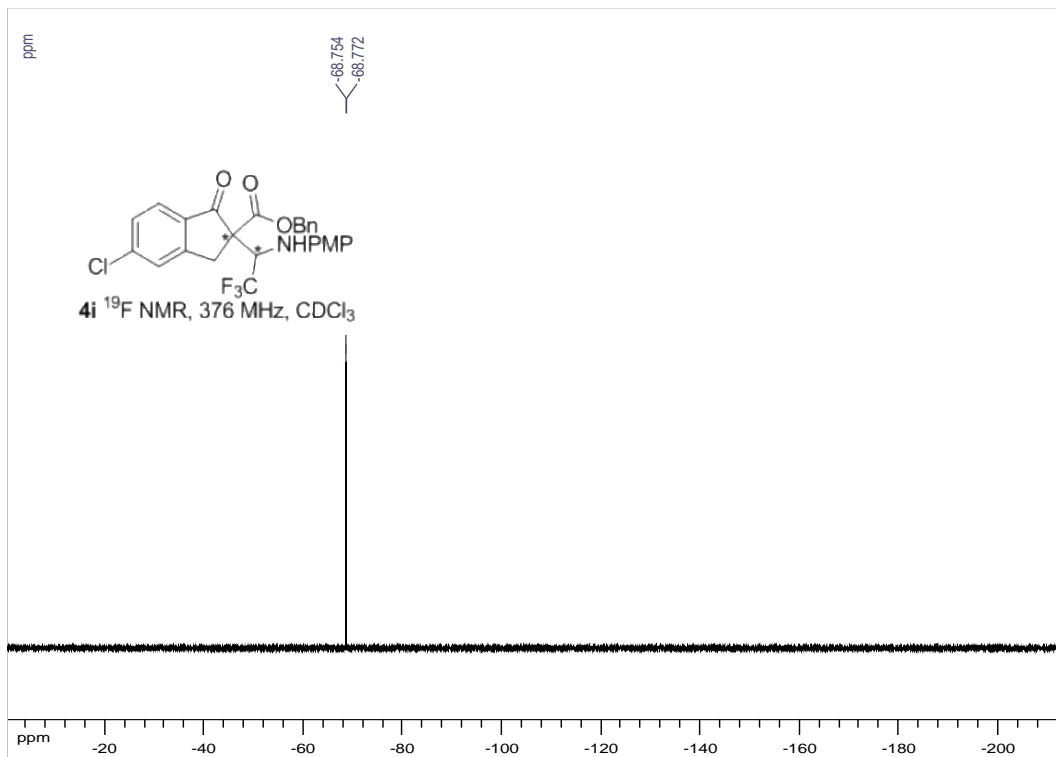
**HRMS** (ESIMS) calcd for C<sub>26</sub>H<sub>21</sub>ClF<sub>3</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 504.1184, found 504.1178

**IR** (thin film, cm<sup>-1</sup>): 3399.6, 2926.5, 1708.8, 1600.9, 1520.5, 1459.1, 1243.6, 1180.2, 1151.3, 1034.4, 908.6, 830.2, 750.6, 697.7;

**HPLC** major ee: 81%; minor ee: 65%; dr: 72:28; (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 98/2, 1 mL/min, 254 nm, major isomer: *t*<sub>1</sub> = 100.05 min, *t*<sub>2</sub> = 181.44 min; minor isomer: *t*<sub>3</sub> = 47.29 min, *t*<sub>4</sub> = 91.09 min).

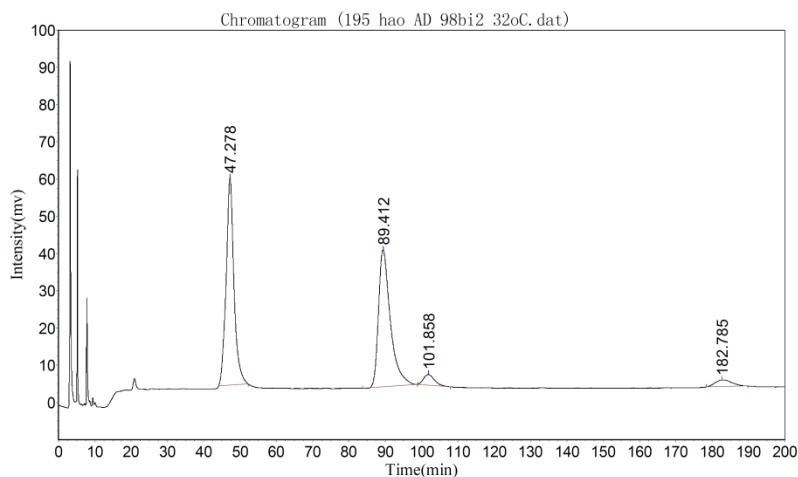
NMR copies of major product of compound **4i**:





HPLC copies of compound 4i:

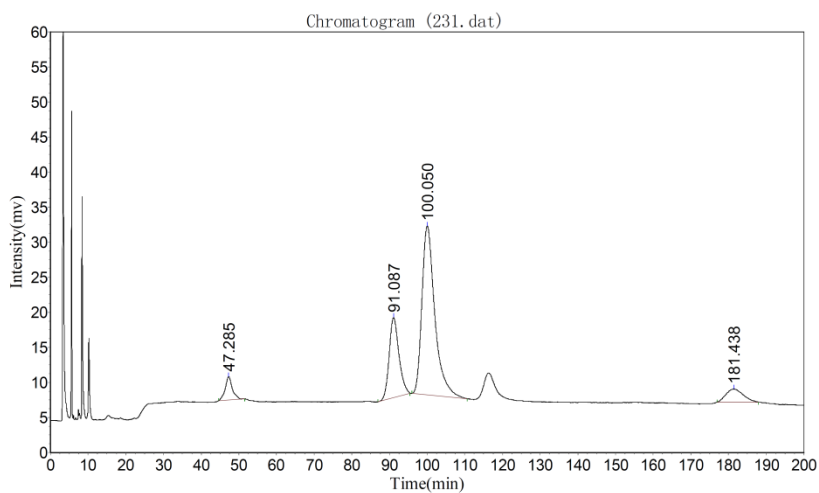
### rac Hex/iPrOH 98/2 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		47.278	55700.070	8342927.500	46.7732
2		89.412	36870.957	8339722.000	46.7553
3		101.858	2849.108	585948.125	3.2850
4		182.785	1772.300	568370.125	3.1865
Total			97192.436	17836967.750	100.0000

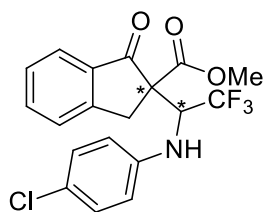
### 4i Hex/iPrOH 98/2 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		47.285	3334.780	434910.656	4.9278
2		91.087	11431.988	2049800.625	23.2257
3		100.050	24133.064	5749443.500	65.1453
4		181.438	1874.388	591418.375	6.7012
Total			40774.221	8825573.156	100.0000

**Compound 4n:**



**Compound 4n:** 83% yield; white solid; mp: 185-186 °C;

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>): δ (ppm): 7.72~7.71 (d, *J* = 7.2 Hz, 1H), 7.66~7.63 (t, *J* = 7.2 Hz 1H), 7.55~7.54 (d, *J* = 7.8 Hz, 1H), 7.40~7.37 (t, *J* = 7.8 Hz 1H), 7.14~7.12 (d, *J* = 7.8 Hz, 2H), 6.75~6.73 (d, *J* = 8.4 Hz, 2H), 5.28~5.23 (m, 1H), 3.96~3.93 (m, 2H), 3.74 (s, 3H), 3.38~3.35 (d, *J* = 17.4 Hz, 1H);

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm): 197.6, 167.5, 153.0, 144.2, 136.0, 134.2, 129.7~124.0 (q, *J*<sub>C-F</sub> = 284), 129.2, 128.2, 126.3, 125.2, 124.9, 115.9, 62.1, 59.6~58.7 (q, *J*<sub>C-F</sub> = 28.2), 53.5, 31.6;

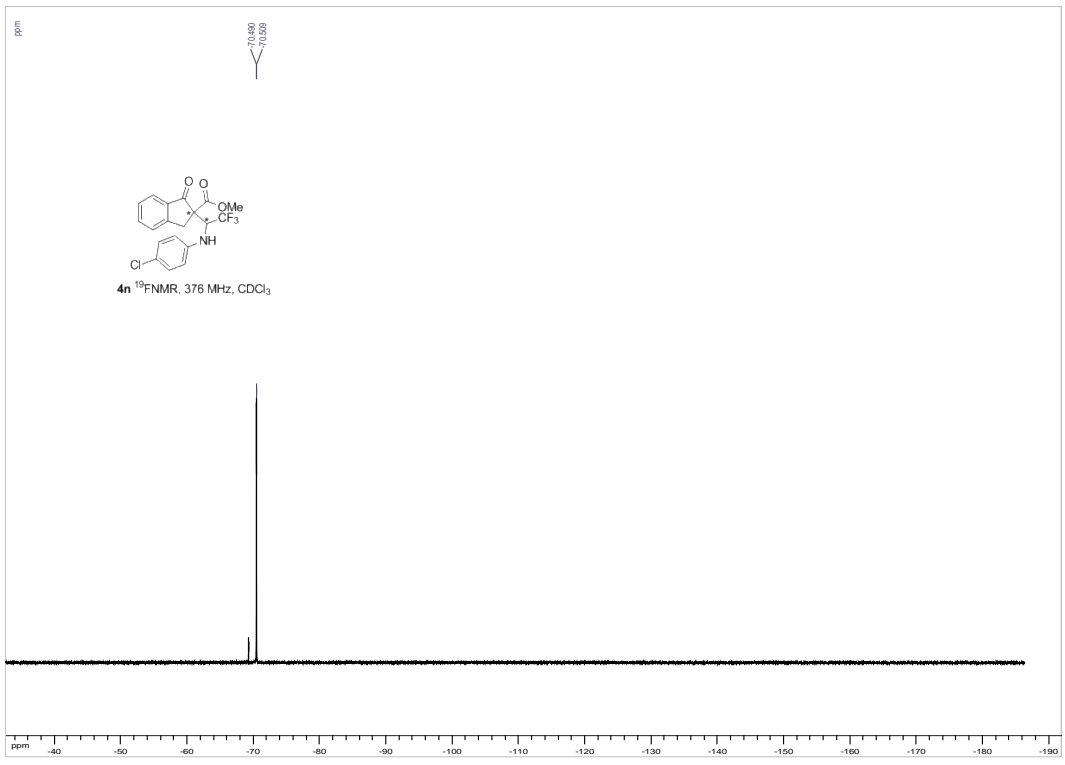
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -70.49~-70.51 (d, *J* = 7.1 Hz);;

**HRMS** (ESIMS) calcd for C<sub>19</sub>H<sub>15</sub>ClF<sub>3</sub>NO<sub>3</sub>Na [M + Na]<sup>+</sup> 420.0585, found 420.0589;

**IR** (thin film, cm<sup>-1</sup>): 3393, 3042, 1740, 1603, 1493, 1435, 1284, 876, 762;

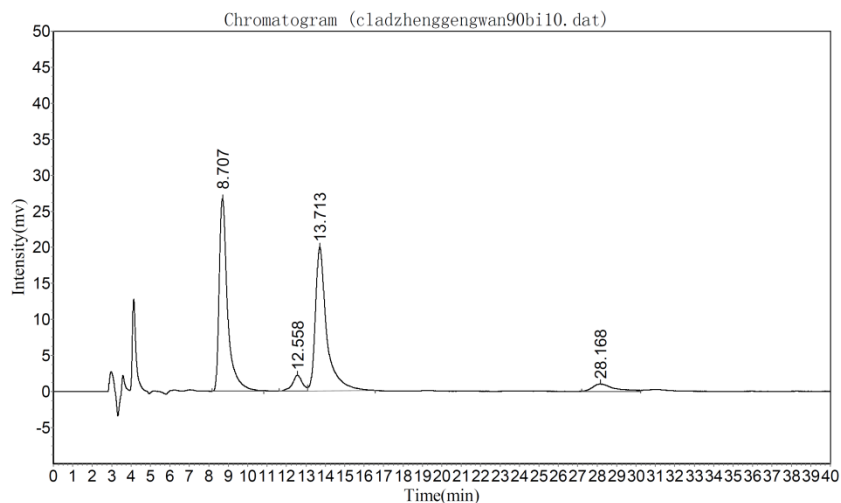
**HPLC** major ee: 94%; minor ee: 42%; dr: 97:3; (Chiralpak AD-H, *n*-heptane/*i*-PrOH = 90/10, 1 mL/min, 254 nm, major isomer: *t*<sub>1</sub> = 8.50 min, *t*<sub>2</sub> = 13.37 min; minor isomer: *t*<sub>3</sub> = 12.22 min, *t*<sub>4</sub> = 28.50 min).





HPLC copies of compound 4n:

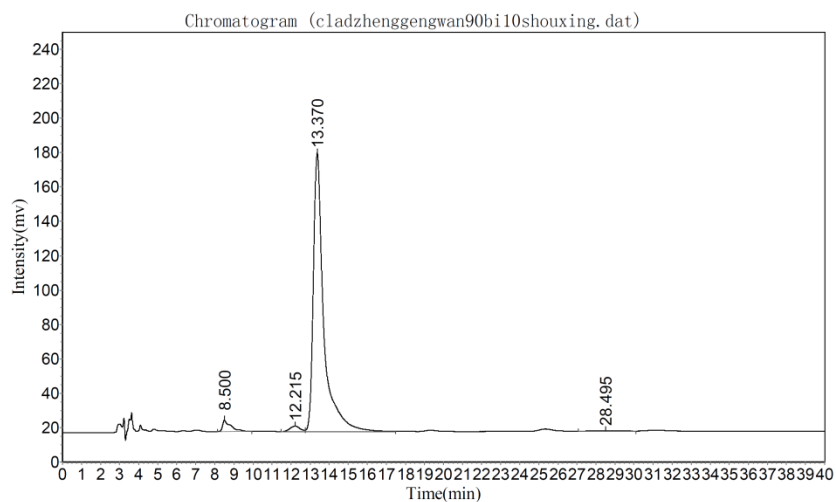
### rac n-Hept/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		8.707	26705.607	802358.313	45.4514
2		12.558	2224.487	77602.164	4.3960
3		13.713	19950.965	806649.500	45.6945
4		28.168	1011.168	78699.844	4.4581
Total			49892.227	1765309.820	100.0000

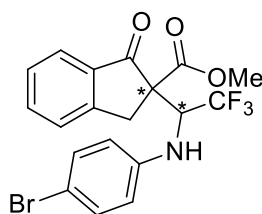
### 4n n-Hept/iPrOH 90/10 AD-H



#### Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		8.500	6531.187	198054.172	3.0368
2		12.215	3183.272	118045.023	1.8100
3		13.370	162145.391	6157746.500	94.4163
4		28.495	430.813	48062.918	0.7369
Total			172290.663	6521908.613	100.0000

**Compound 4o:**



**Compound 4o:** 95% yield; white solid; mp: 194-196 °C;;

**<sup>1</sup>H NMR** δ (ppm): 7.72~7.71 (d, *J* = 7.8 Hz, 1H), 7.66~7.63 (t, *J* = 7.8 Hz 1H), 7.55~7.53 (d, *J* = 7.8 Hz, 1H), 7.40~7.37 (t, *J* = 7.8 Hz 1H), 7.27~7.26 (d, *J* = 8.4 Hz, 2H), 6.70~6.68 (d, *J* = 9.0 Hz, 2H), 5.29~5.23 (m, 1H), 4.00~3.98 (d, *J* = 10.8 Hz, 1H), 3.96~3.93 (d, *J* = 17.4 Hz, 1H), 3.73 (s, 3H), 3.38~3.35 (d, *J* = 17.4 Hz, 1H);

**<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>): δ (ppm): 197.6, 167.5, 153.0, 144.7, 136.0, 134.2, 132.0, 128.2, 126.3, 125.2, 123.5 (q, *J*<sub>C-F</sub> = 284.4), 116.3, 115.8, 112.0, 62.0, 59.3~58.7 (q, *J*<sub>C-F</sub> = 28.2), 53.5, 31.7;;

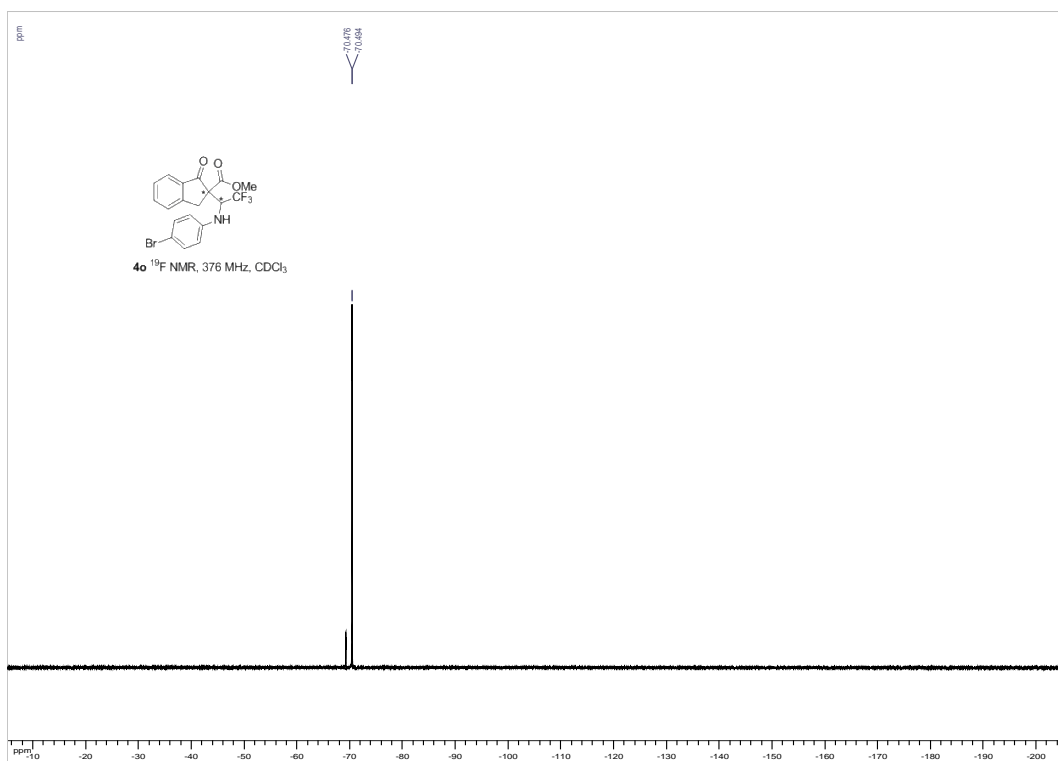
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>): δ (ppm): -70.48~ -70.49 (d, *J* = 6.8 Hz);

**HRMS** (ESIMS) calcd for C<sub>19</sub>H<sub>15</sub>BrF<sub>3</sub>NO<sub>3</sub>Na [M + Na]<sup>+</sup> 464.0079, found 464.0096;

**IR** (thin film, cm<sup>-1</sup>): 3389, 3040, 2951, 1738, 1598, 1526, 1491, 1225, 1156, 1127, 822, 761;

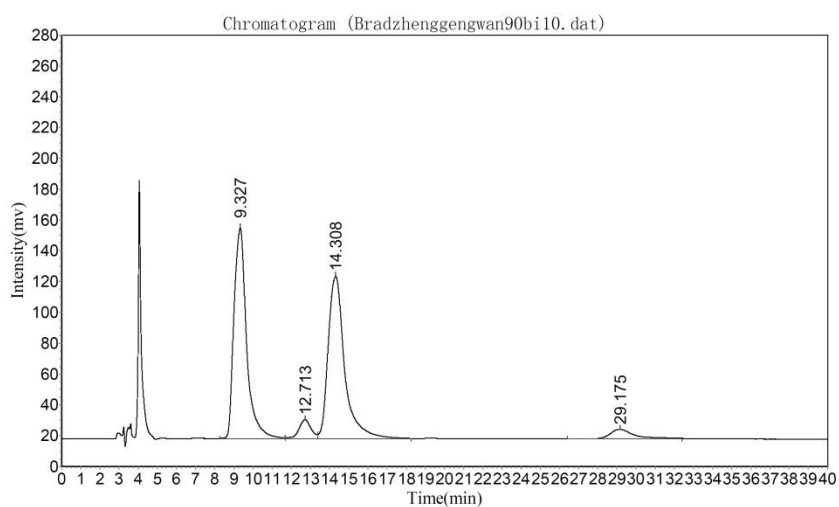
**HPLC** major ee: 94%; minor ee: 90%; dr: 85:15; (Chiralpak AD-H, *n*-heptane/*i*-PrOH = 90/10, 1 mL/min, 254 nm, major isomer: t<sub>1</sub> = 12.70 min, t<sub>2</sub> = 28.50 min; minor isomer: t<sub>3</sub> = 9.35 min, t<sub>4</sub> = 14.30 min).





HPLC copies of compound **4o**:

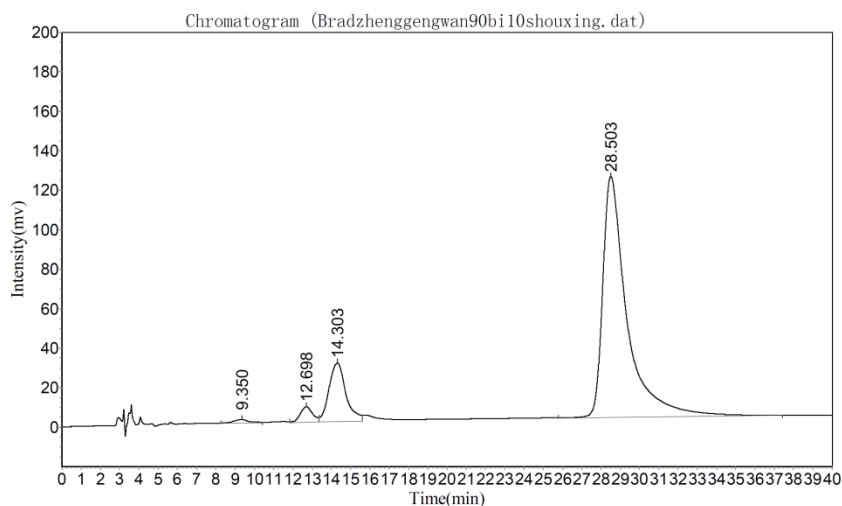
**rac n-Hept/iPrOH 90/10 AD-H**



**Results**

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		9.327	136711.500	6239829.000	46.0628
2		12.713	12107.607	526581.125	3.8873
3		14.308	105374.727	6280351.000	46.3619
4		29.175	6002.620	499598.719	3.6881
Total			260196.454	13546359.844	100.0000

**4o n-Hept/iPrOH 90/10 AD-H**



**Results**

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		9.350	1631.917	92227.992	0.7081
2		12.698	7758.478	350659.313	2.6922
3		14.303	29643.949	1811320.125	13.9064
4		28.503	122135.445	10770832.000	82.6933
Total			161169.789	13025039.430	100.0000