A Convenient Approach to Difluoromethylated All-carbon Quaternary Centers *via* Ni(II)-Catalyzed Enantioselective Michael Addition

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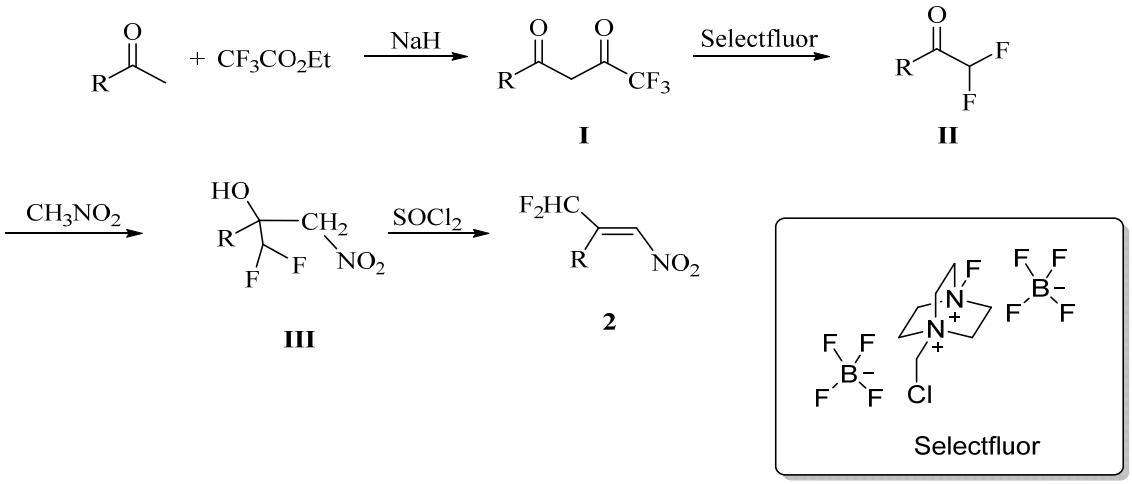
1. The typical synthesis procedure for β-difluoromethyl nitroalkene 2

β-Difluoromethylnitroalkene(**2a-2j**) was prepared according to the literatures.[1]



The synthesis of **I:**

Under nitrogen atmosphere, the mixture of NaH(60% dispersion in mineral oil, 1.2g) in THF(50mL) was stirred at 0°C for 10 min, then acetophnone(10 mmol, 1.2g) was added and stirred for another 30min, subsequently CF_3CO_2Et(15mmol, 2.13g) was added dropwise. The mixture was stirred at room temperature until the reaction proceeded to completion (monitored by TLC). A solution of HCl (1N, 10 mL) was added and extracted with ethyl acetate (20mL×3), and dried over Na_2SO_4. The solvent was removed to afford the crude product **I**, which was directly used for the next step.

The synthesis of **II:**

The product 1-trifluoromethyl-1,3-diketone **I**(1eq.) and selectfluor (2.5eq.) were dissolved in acetonitrile (60mL) and refluxed for 3h, followed by the addition of water (2eq.), then refluxing for another 15minutes. Subsequently the solution was cooled to room temperature, Et_3N (5eq.) was added and the mixture was stirred for 16h. The solvent was evaporated under vacuum and the residue was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography yielded the desired α,α-difluoromethyl ketone **II**.

The synthesis of **III:**

A solution of difluoromethyl ketone **II** (10mmol), Et_3N (6.96 mL, 50mmol) and $MeNO_2$ (20 mL) was stirred for 12h at room temperature. The organic phase was concentrated under vacuum

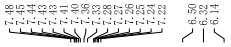
1. F.-L. Liu, J.-R. Chen, B. Feng, X.-Q. Hu, L.-H. Ye, L-Q. Lu, W.-J. Xiao, *Org. Biomol. Chem.* **2013**, *12*, 1057-1060.

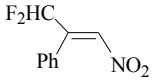
to afford the crude nitroalcohol **III**, which was directly used for the next step.

The synthesis of **2:**

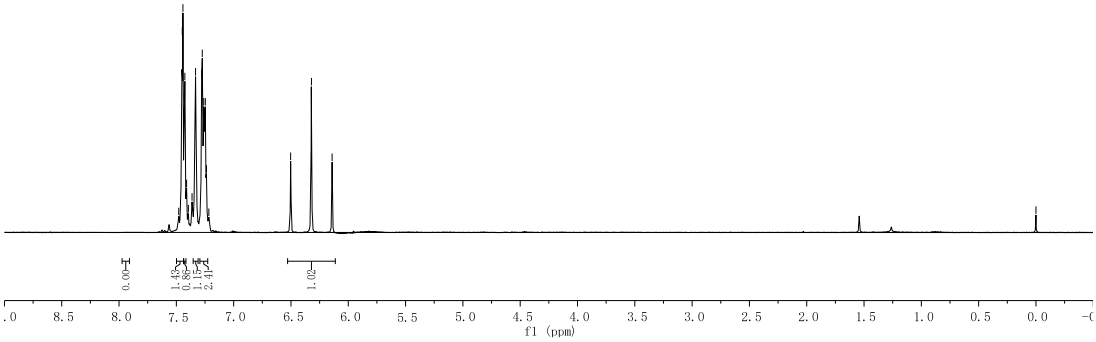
To a solution of nitroalcohol **III** and Et_3N (6.96 mL, 50 mmol) in toluene (30 mL) were added dropwise $SOCl_2$ (2.18 mL, 30 mmol) at 0 °C. The mixture was stirred for 3h at room temperature and then diluted with ethyl acetate. The organic phase was washed successively with water and brine, dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified with flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:50 (v/v), to afford the difluoromethylated nitroalkene **2**. The stereochemistry of **2d** was studied by NOESY. The correlation of the proton in CF2H group and the vinyl proton indicated that only *E*-**2** was obtained after flash chromatography.

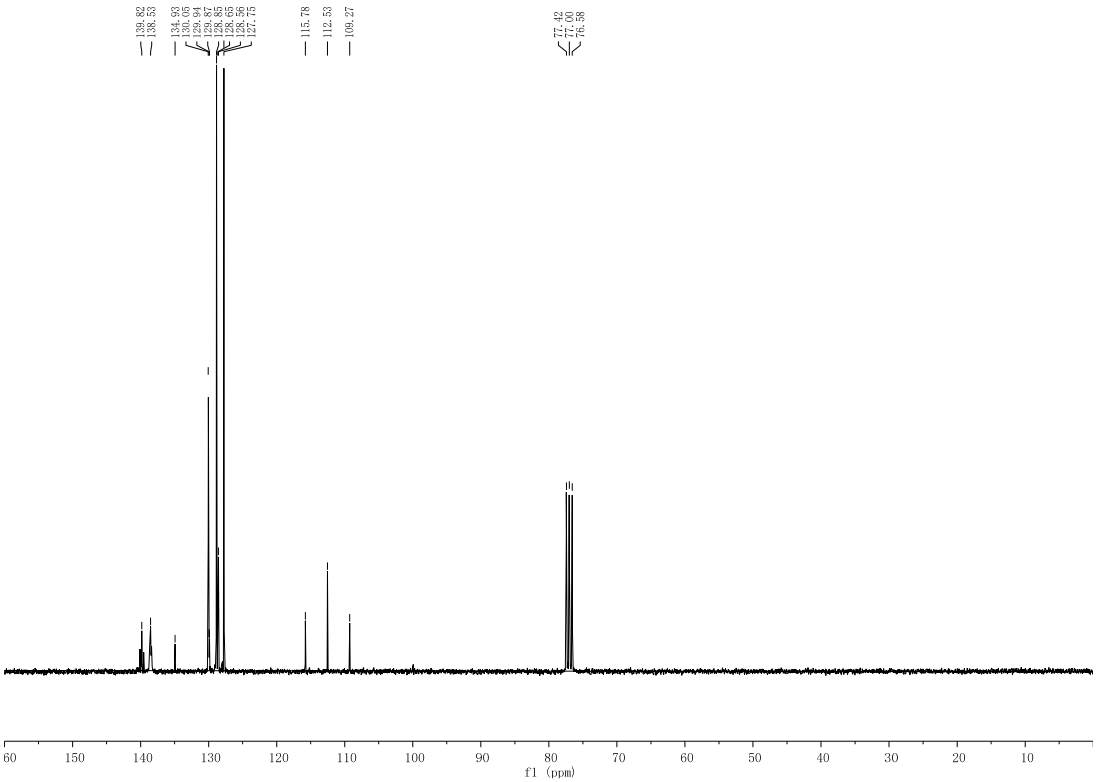
2. The NMR spectra for the products 2

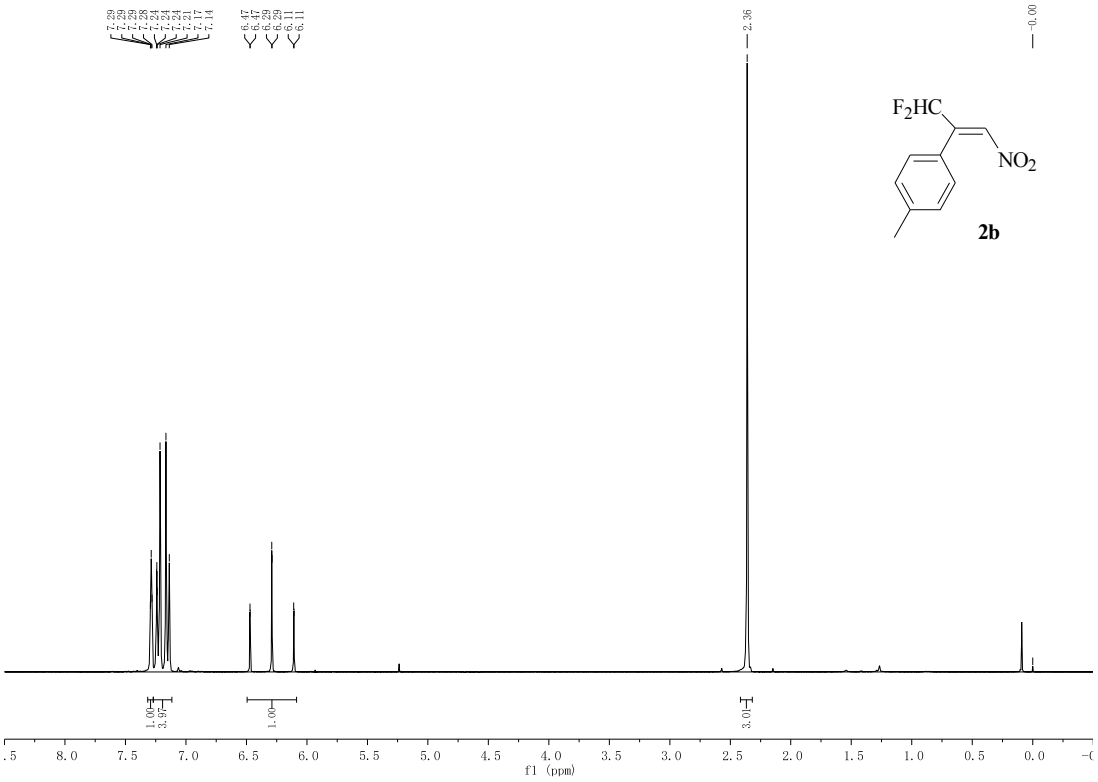




2a



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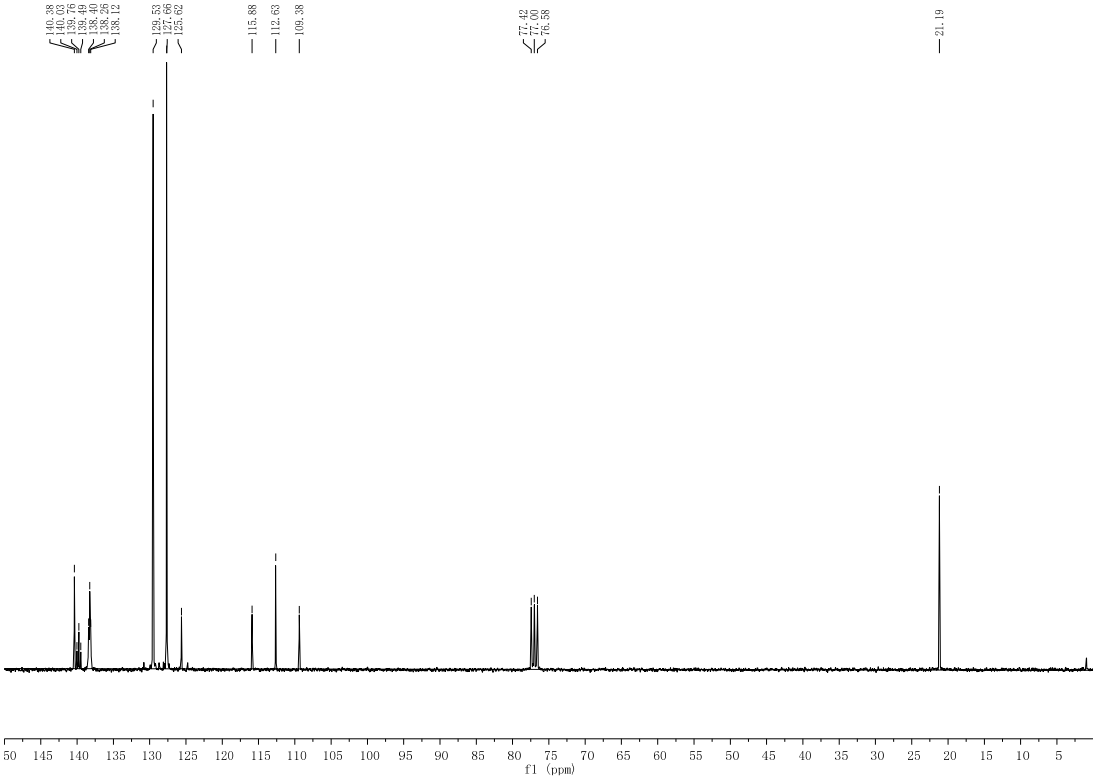
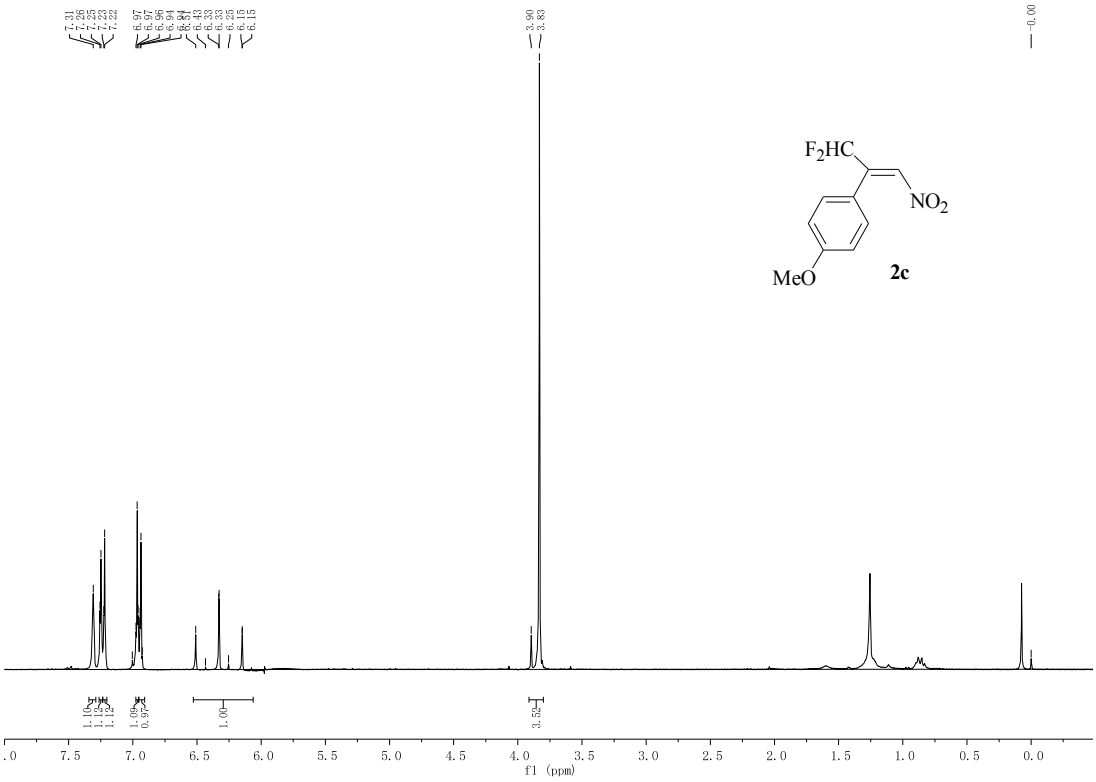
NO2
2b
f1 (ppm)


f1 (ppm)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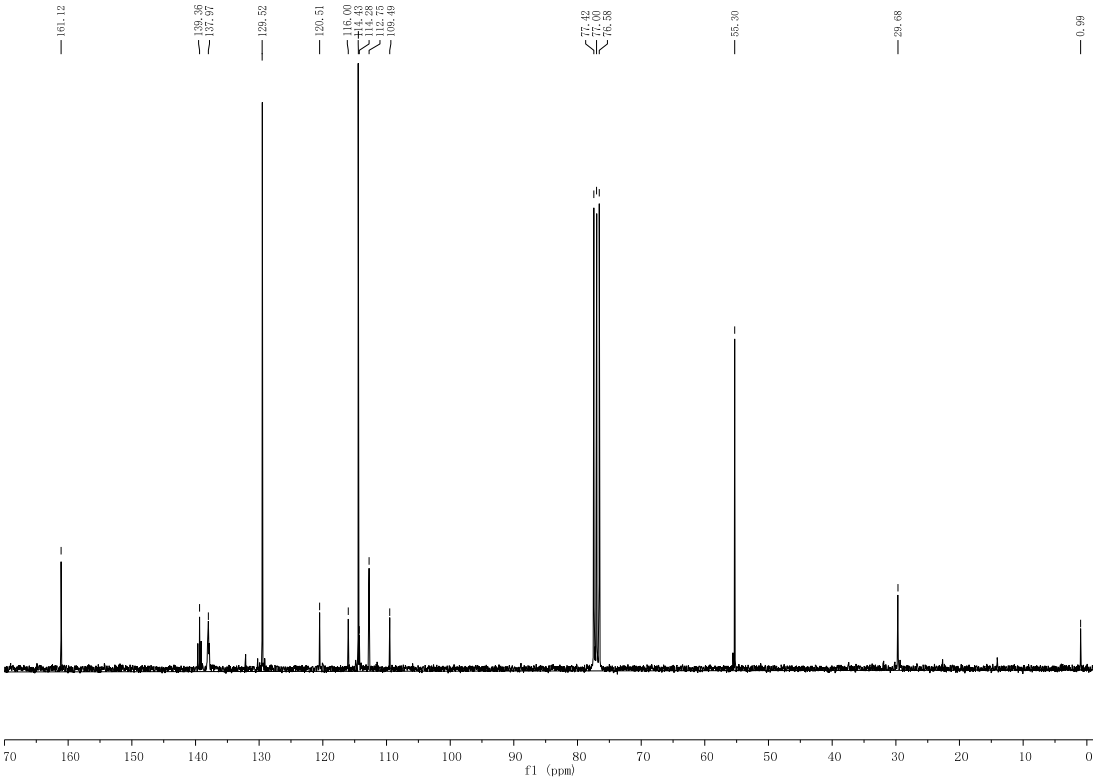
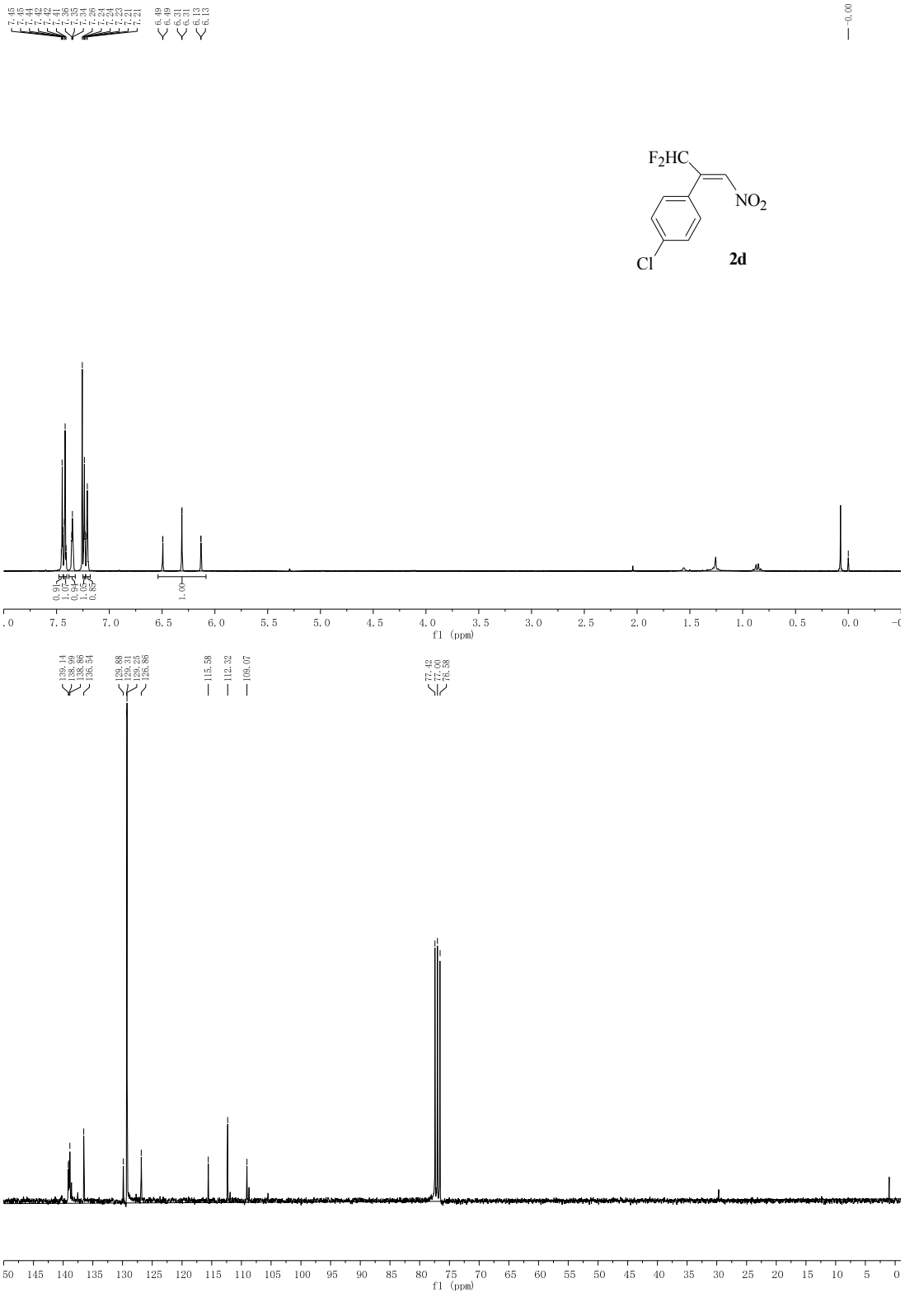
NO2
MeO
2c
f1 (ppm)


f1 (ppm)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7.42
7.42
7.41
7.36
7.35
7.34
7.25
7.24
7.23
7.21
7.21
6.49
6.49
6.31
6.31
6.13
6.13
0.00
F2HC
NO2
Cl
2d
0.91
1.07
0.94
1.05
0.87
1.00
f1 (ppm)
139.14
138.88
138.86
136.54
129.88
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129.25
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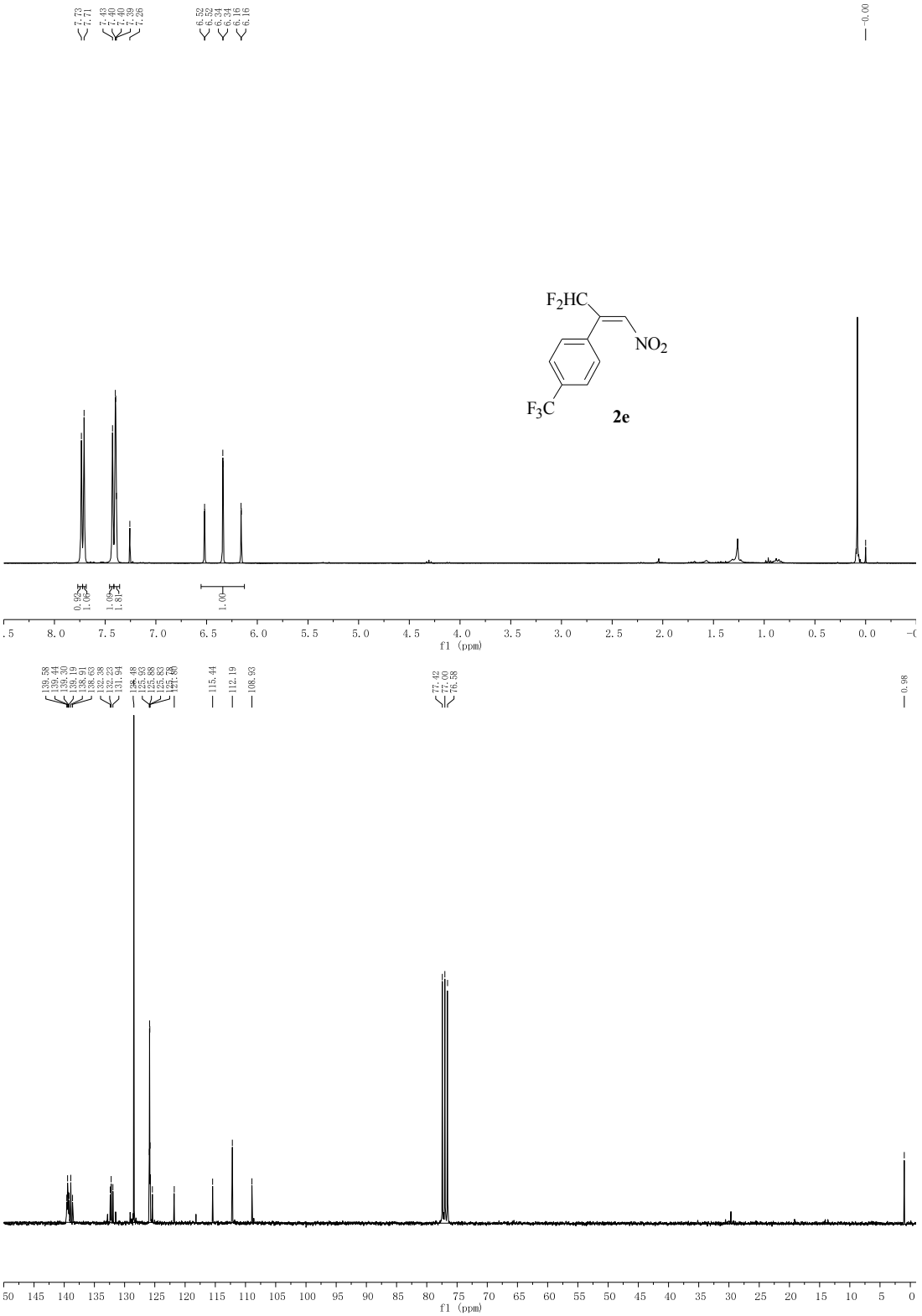
115.58
112.32
109.07
77.42
77.00
76.58
f1 (ppm)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7.40
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7.39
7.26
6.52
6.52
6.34
6.34
6.16
6.16
-0.00
F2HC
NO2
F3C
2e
0.92
1.06
1.00
1.81
1.00
f1 (ppm)
139.58
139.44
139.30
139.19
138.91
138.63
132.38
132.23
131.94
125.53
125.88
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112.19
108.93
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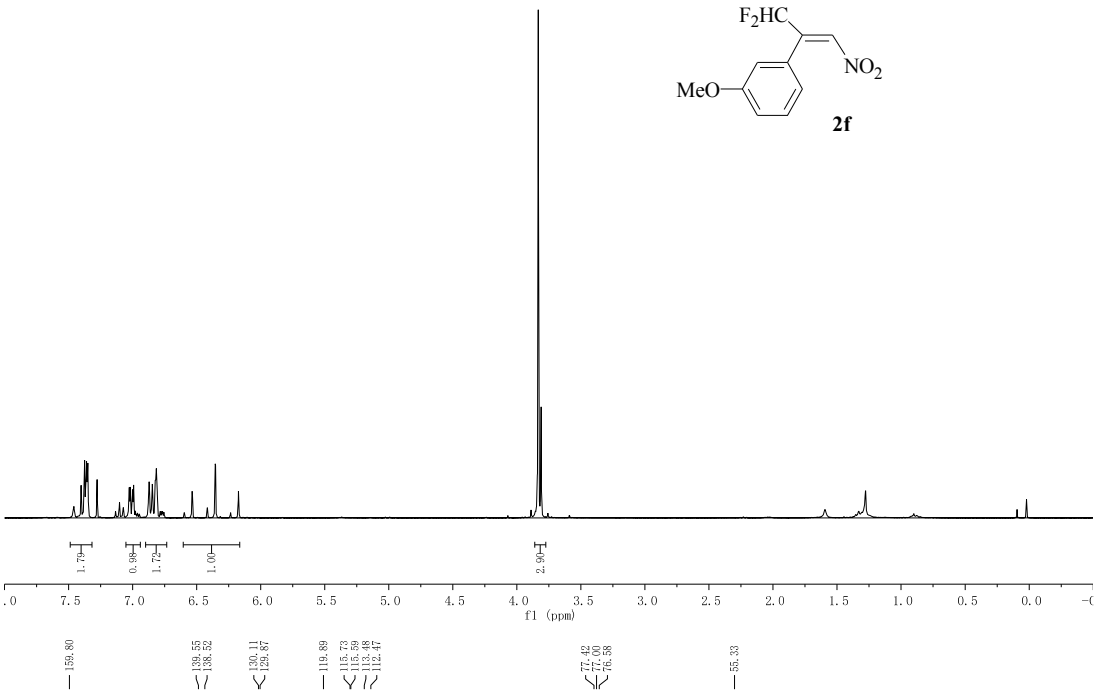
77.00
76.58
0.98
f1 (ppm)


F2HC
NO2
MeO
2f
1.79
0.98
1.72
1.00
2.90
f1 (ppm)
159.80
139.55
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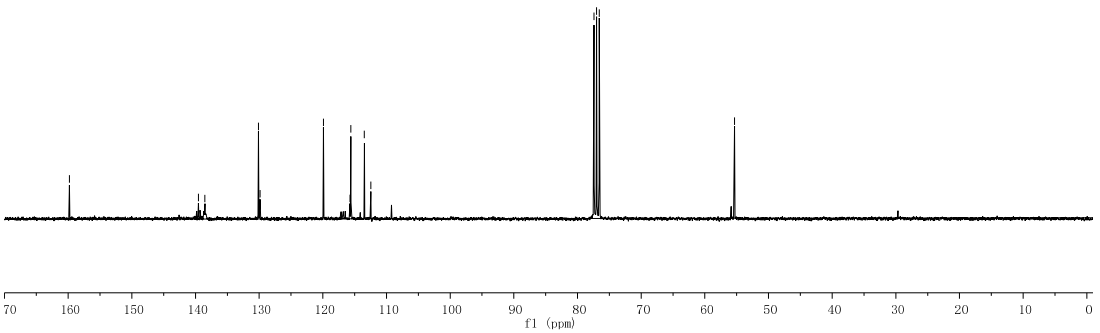
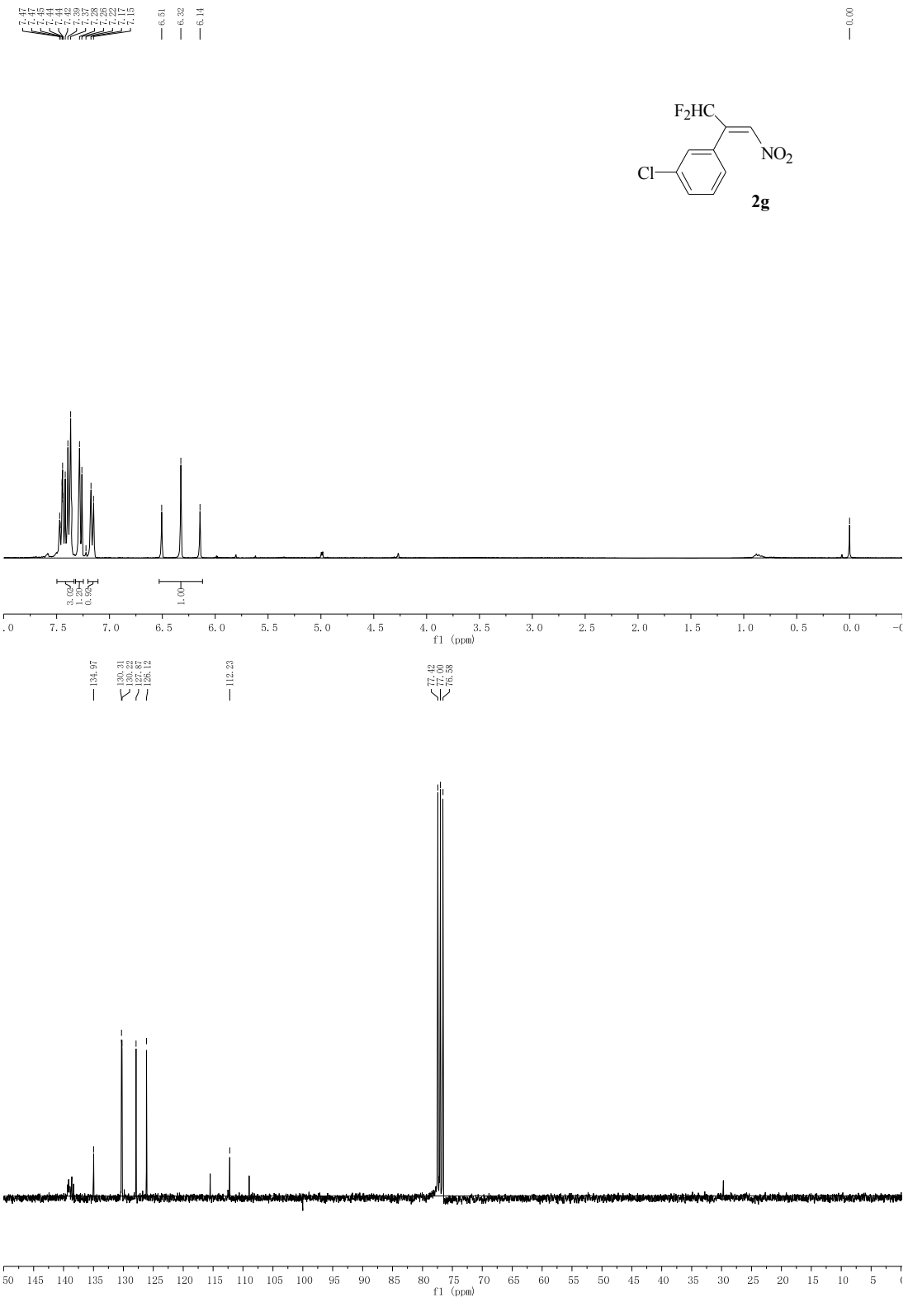
77.00
76.58
55.33


f1 (ppm)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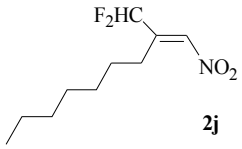
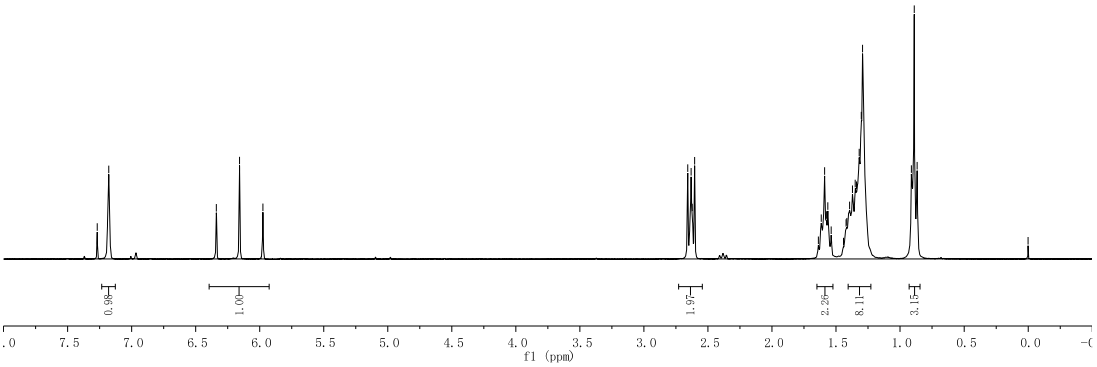
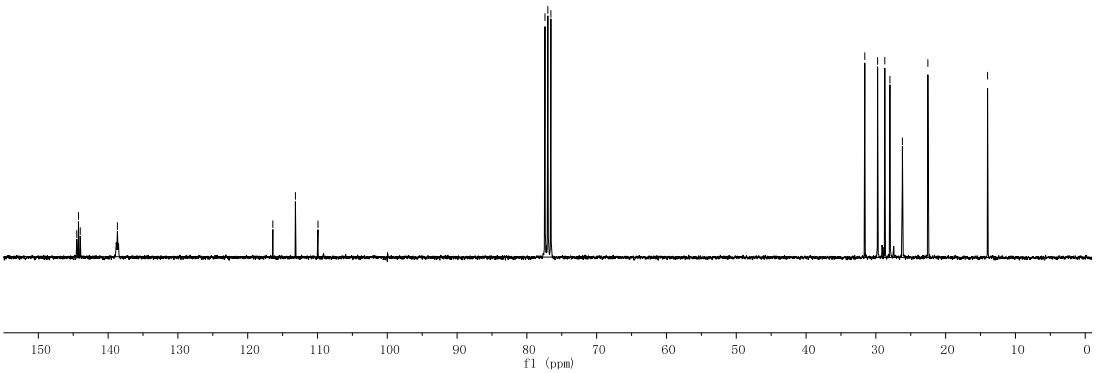
7.47
7.45
7.44
7.44
7.42
7.39
7.38
7.38
7.25
7.22
7.17
7.15
6.51
6.32
6.14
0.00
F2HC
NO2
Cl
2g
3.07
1.26
0.95
1.00
f1 (ppm)
134.97
130.31
128.22
127.82
126.12
112.23
77.42
77.00
76.58
f1 (ppm)



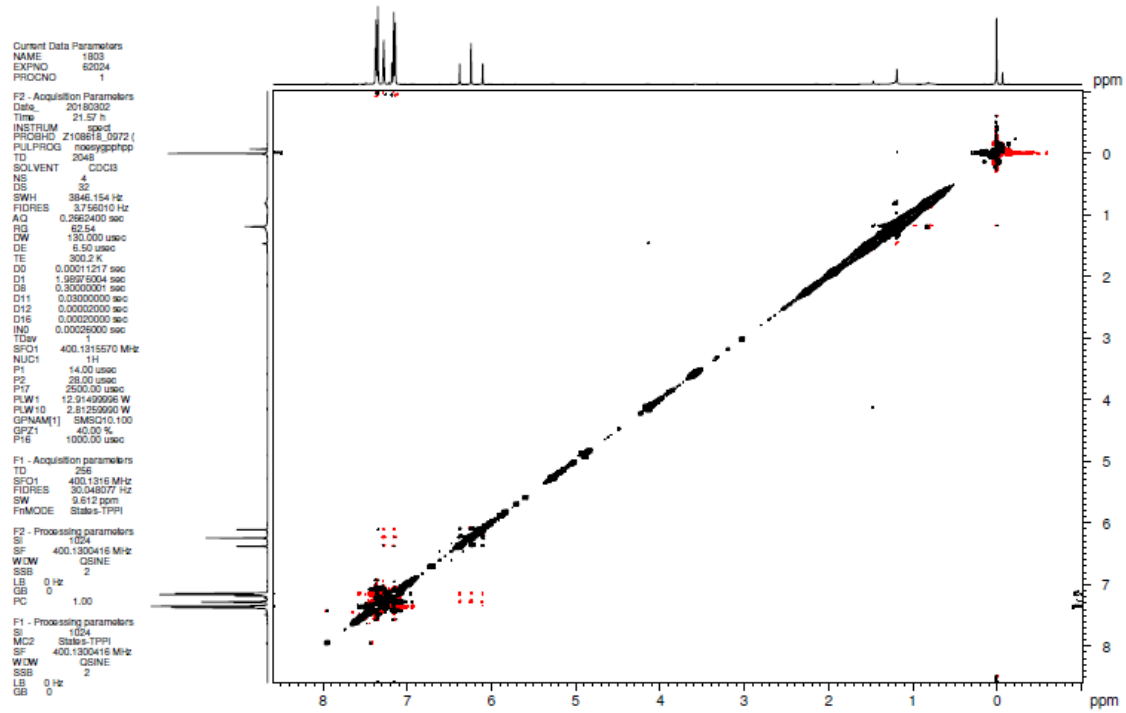
2j



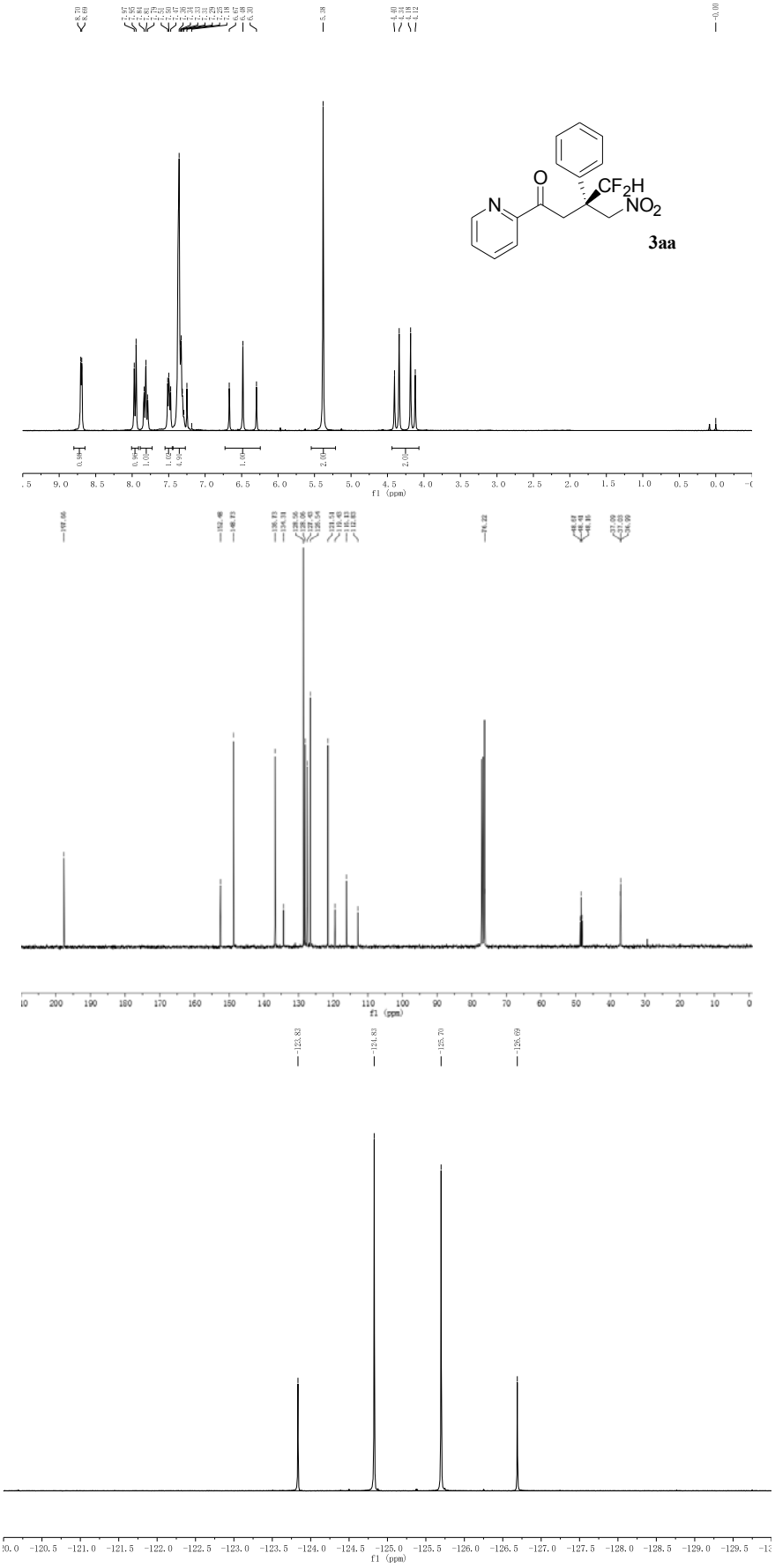


3. The NOESY spectra for 2d

NOESY-CDCL3



4. The NMR spectra for the products 3




7.82
7.36
7.26
6.63
6.44
6.26
5.39
5.35
5.33
5.28
4.17
4.11
4.06
3.99
0.00
O
O
N
CF2H
NO2
3ab
0.98
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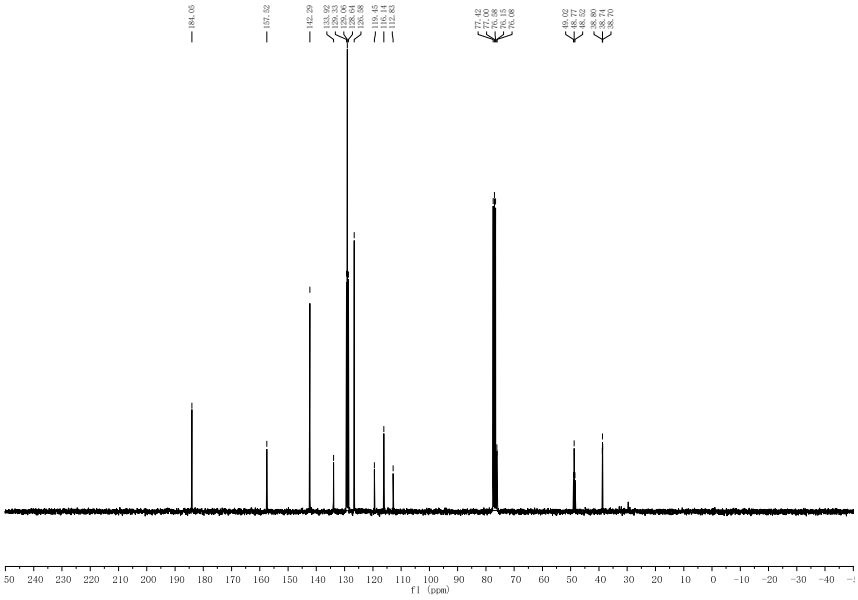
1.04
1.04
2.04
f1 (ppm)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133.92
130.33
129.66
128.64
128.36
119.45
116.14
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48.52
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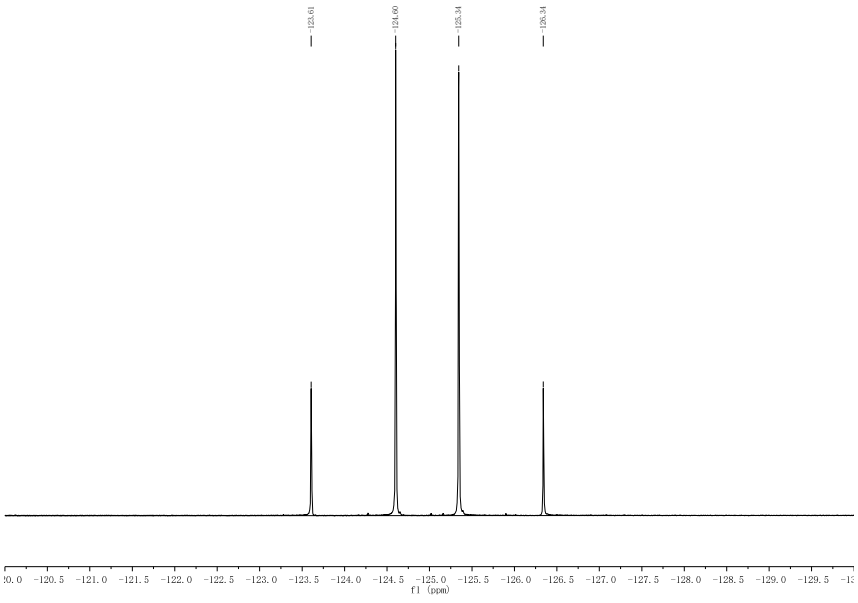
36.70
f1 (ppm)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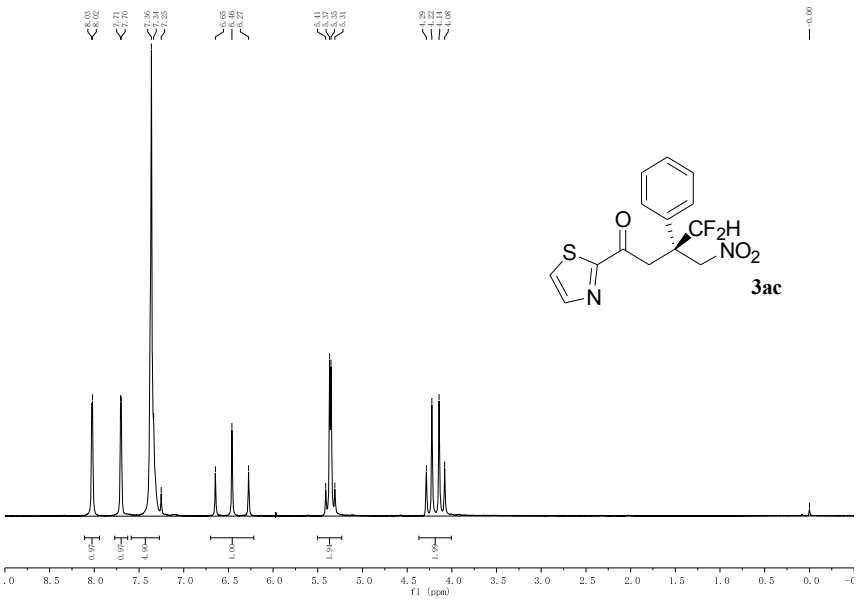
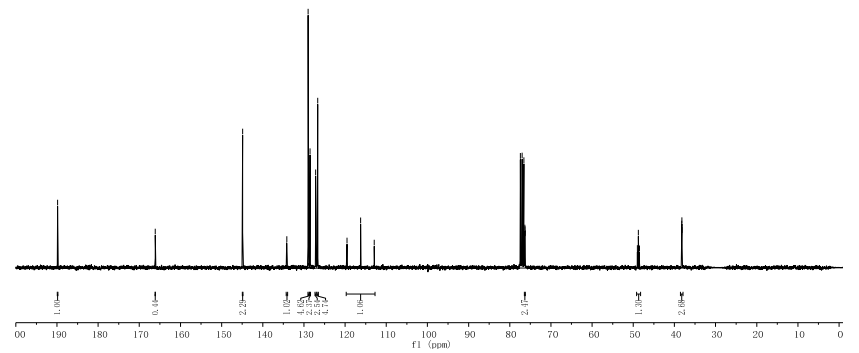
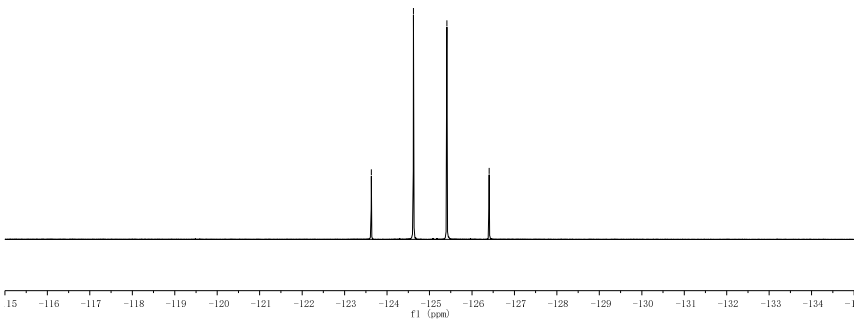
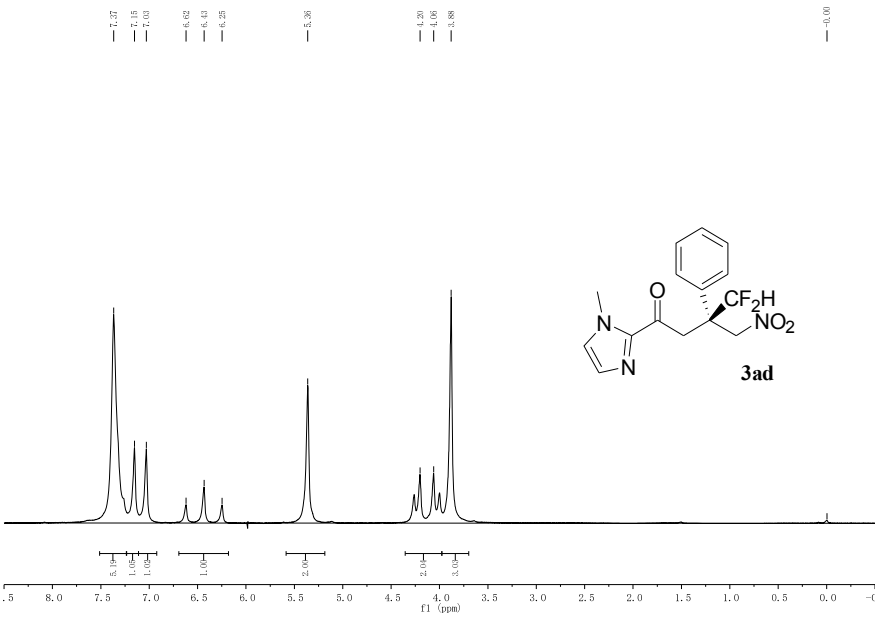
126.34
f1 (ppm)


O
CF2H
NO2
S
N
3ac






7.37
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6.43
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CF2H
NO2
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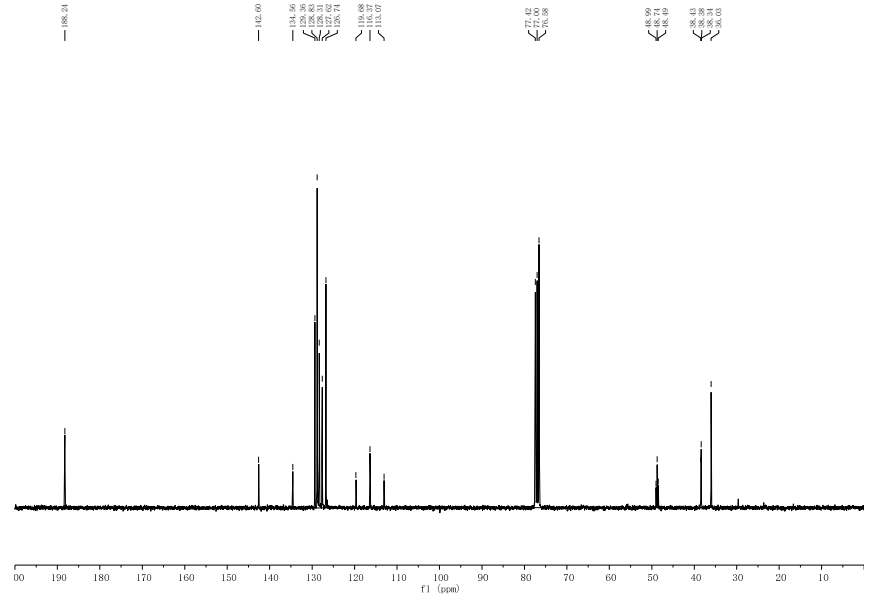
N
3ad
f1 (ppm)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36.38
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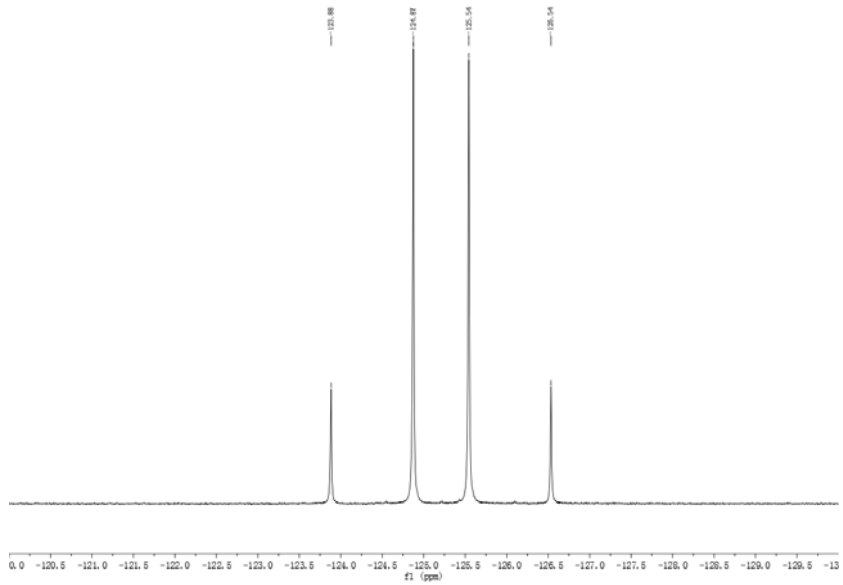
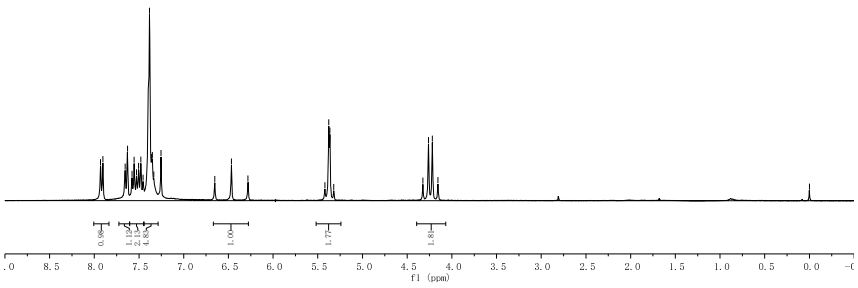
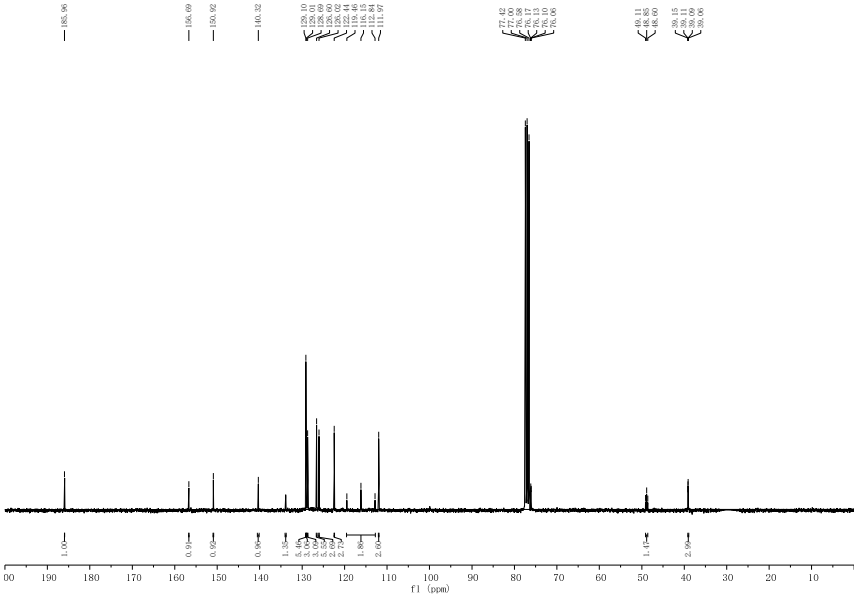
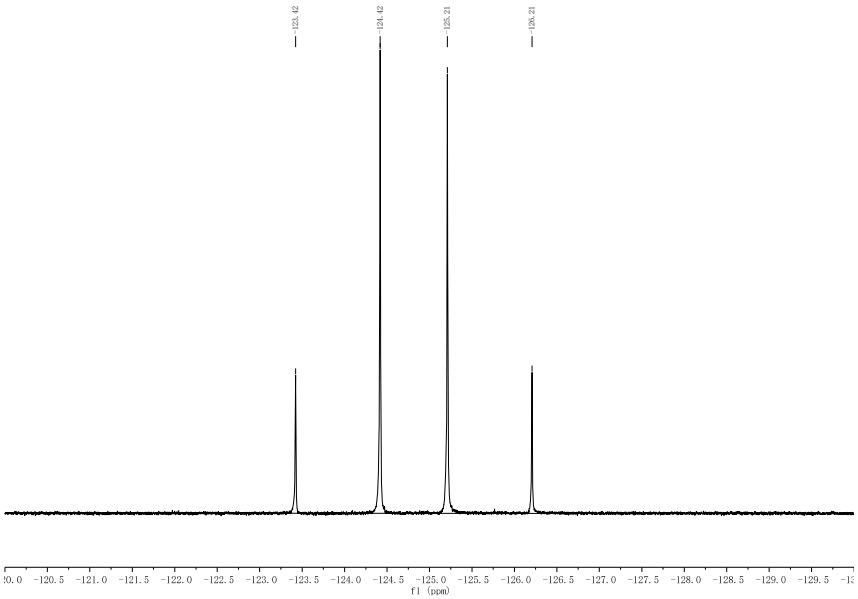
36.03
f1 (ppm)

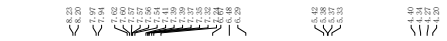

123.88
124.87
125.54
126.54
f1 (ppm)

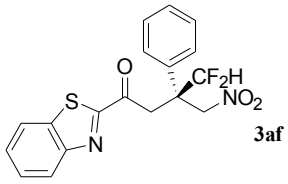
3ae











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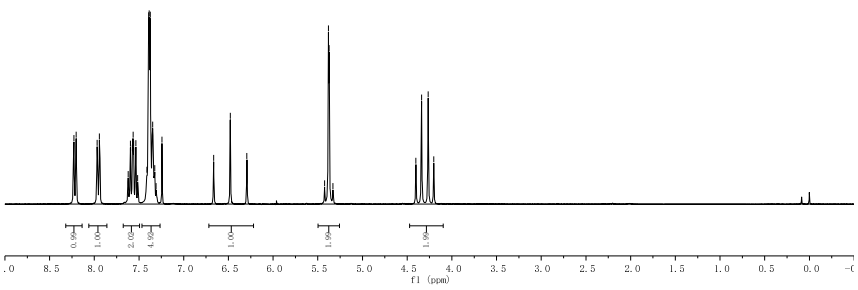

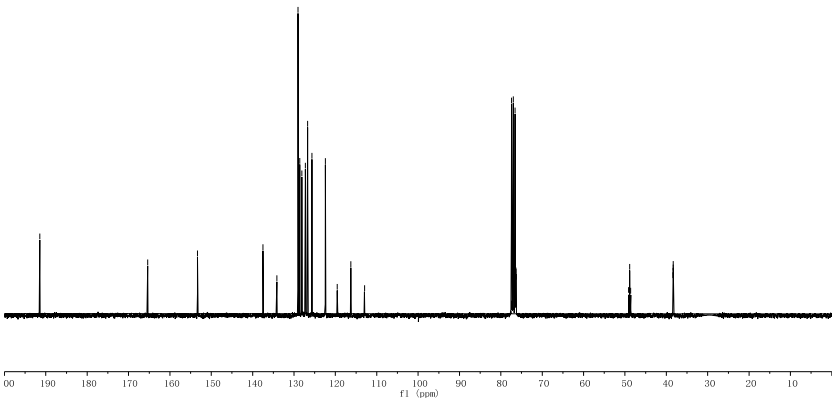

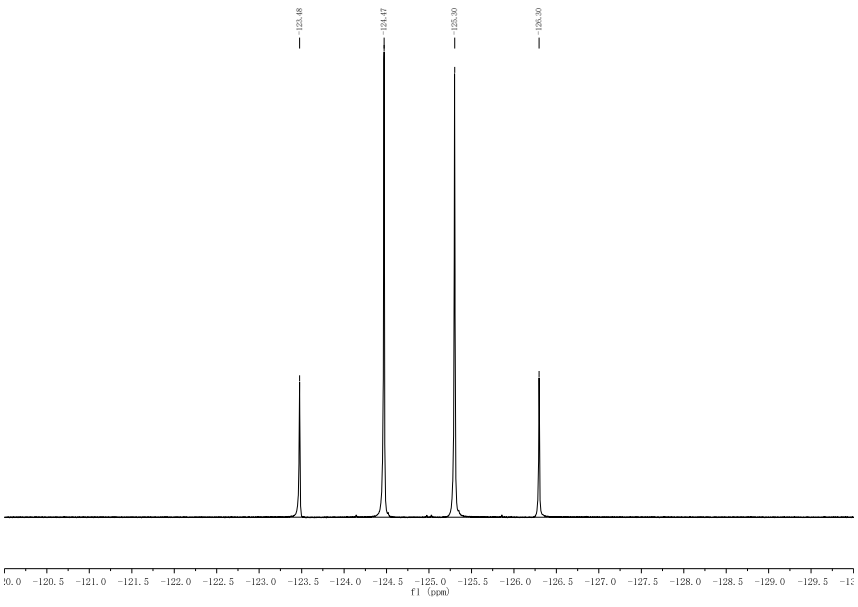

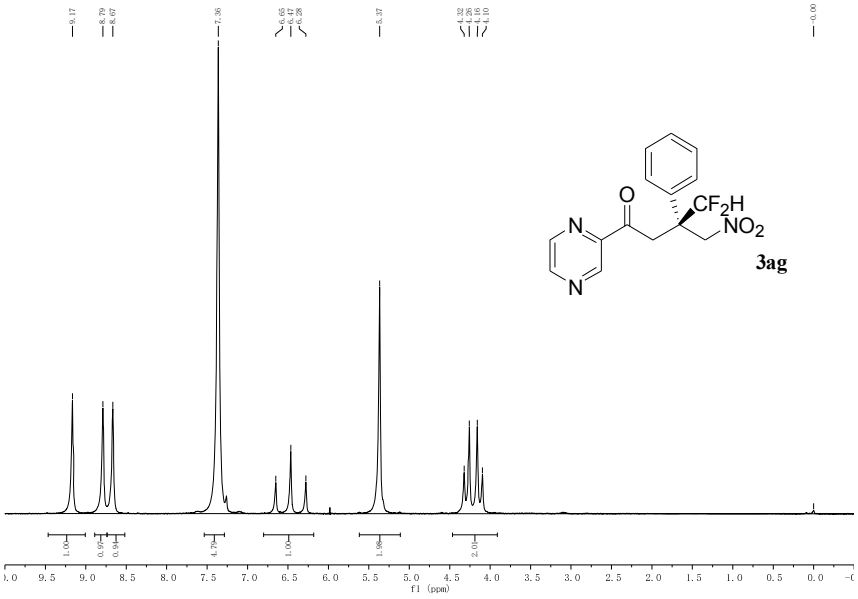
9.17
8.79
8.67
7.36
6.63
6.57
6.28
5.37
4.32
4.26
4.16
4.10
0.00
O
CF2H
NO2
N
N
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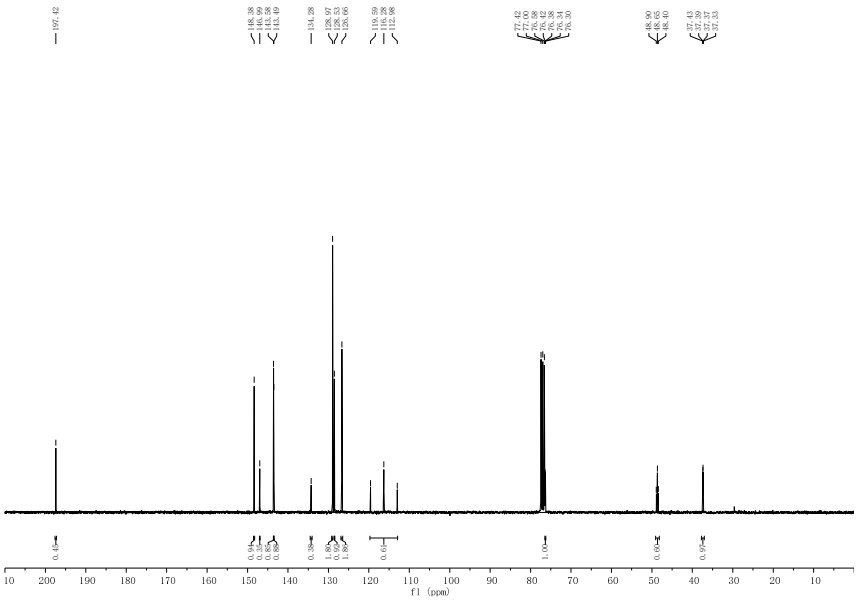
1.00
1.98
2.00
f1 (ppm)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143.09
134.28
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128.53
128.06
119.59
116.28
112.98
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77.00
76.58
76.38
76.34
76.30
48.90
48.65
48.40
37.43
37.39
37.33
0.45
0.94
0.35
0.85
0.98
0.38
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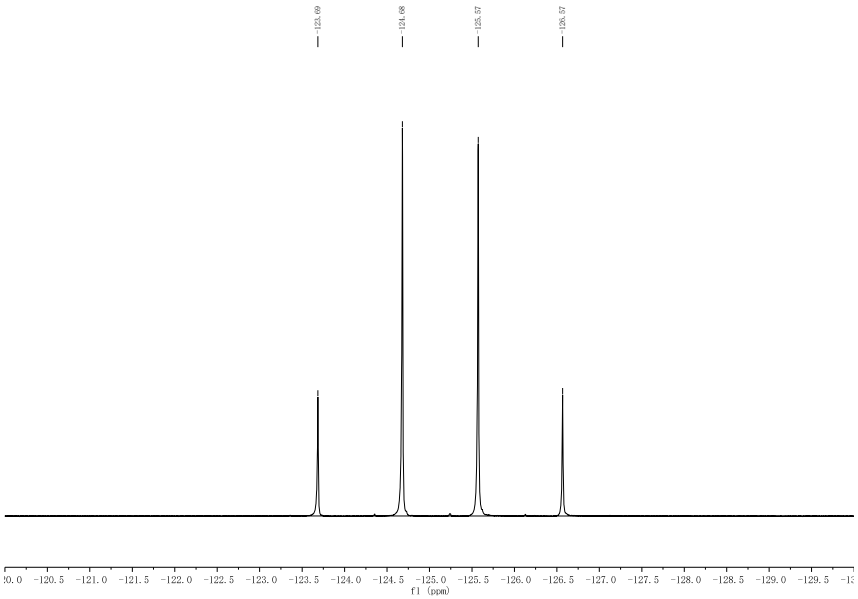
1.00
1.89
0.60
1.00
0.60
0.97
f1 (ppm)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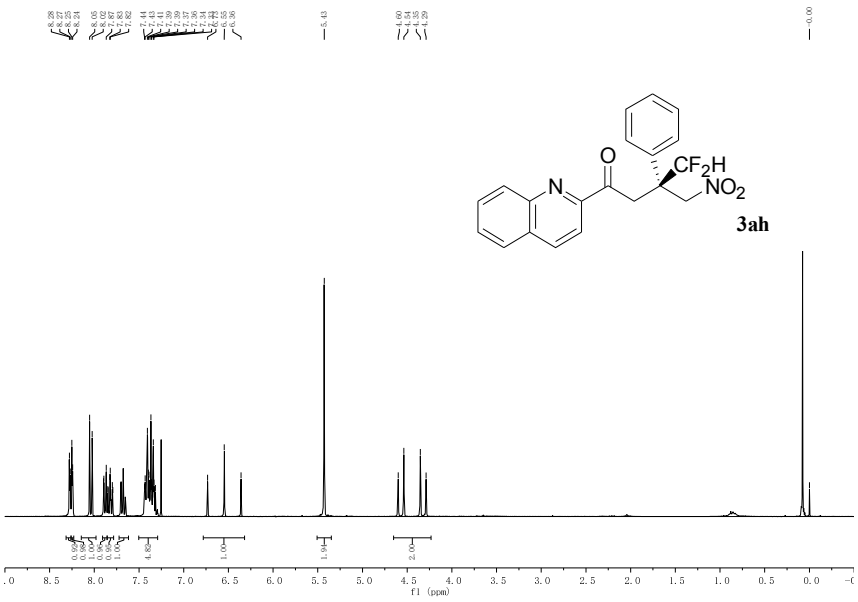
f1 (ppm)



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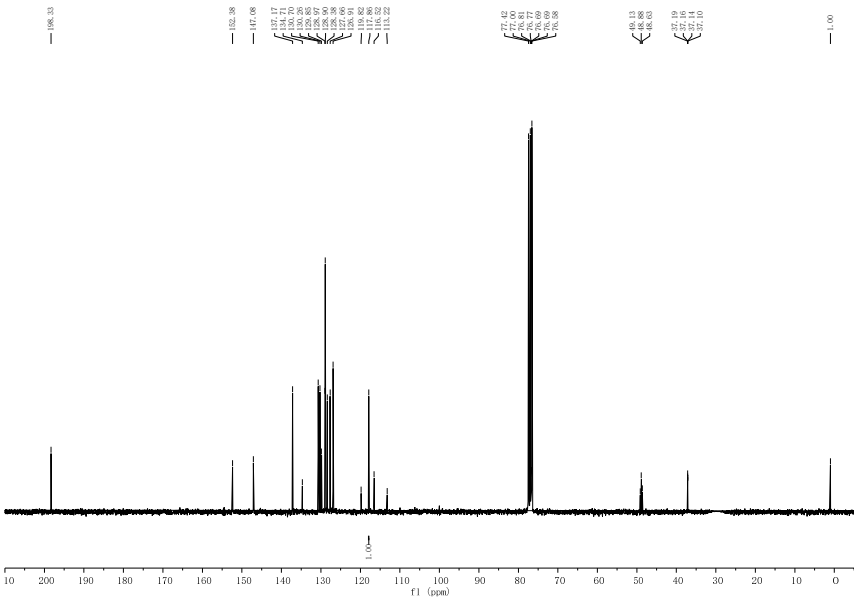
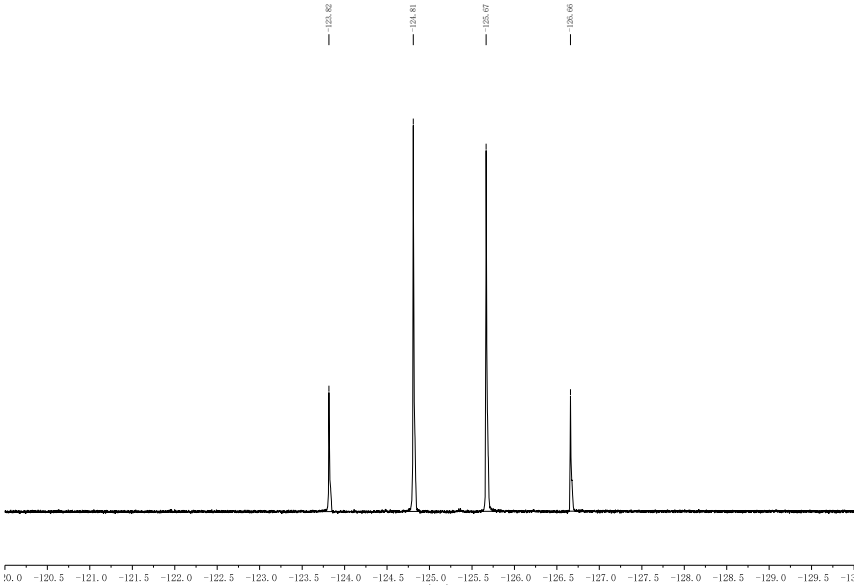
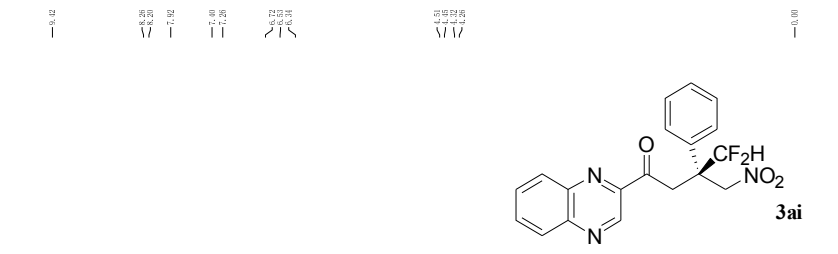
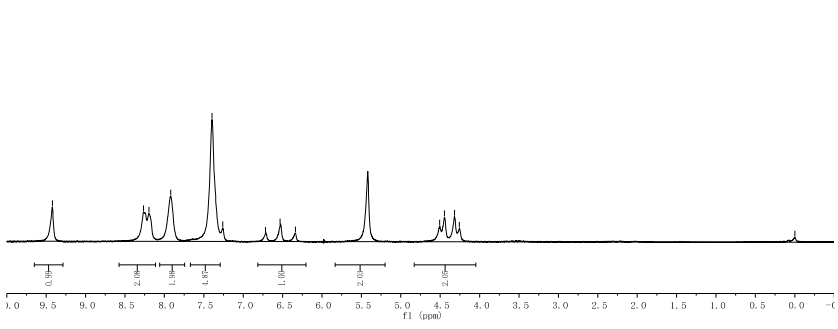
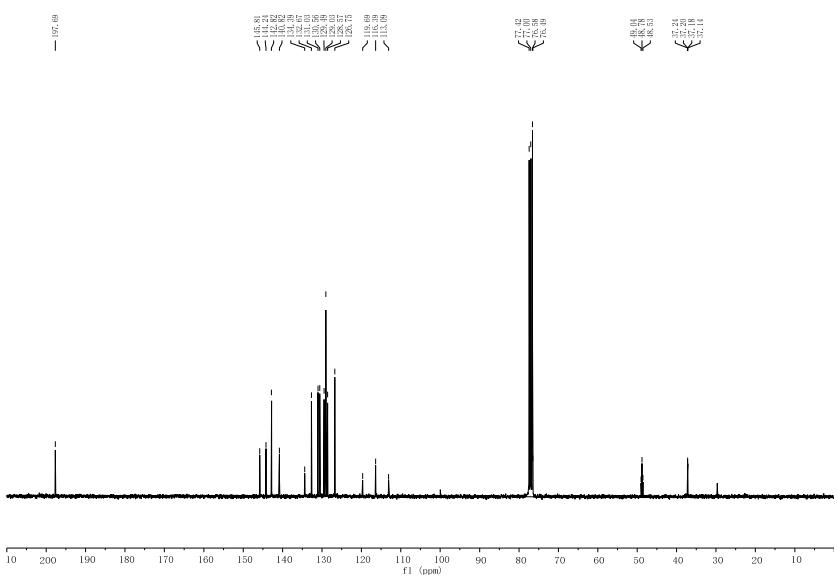
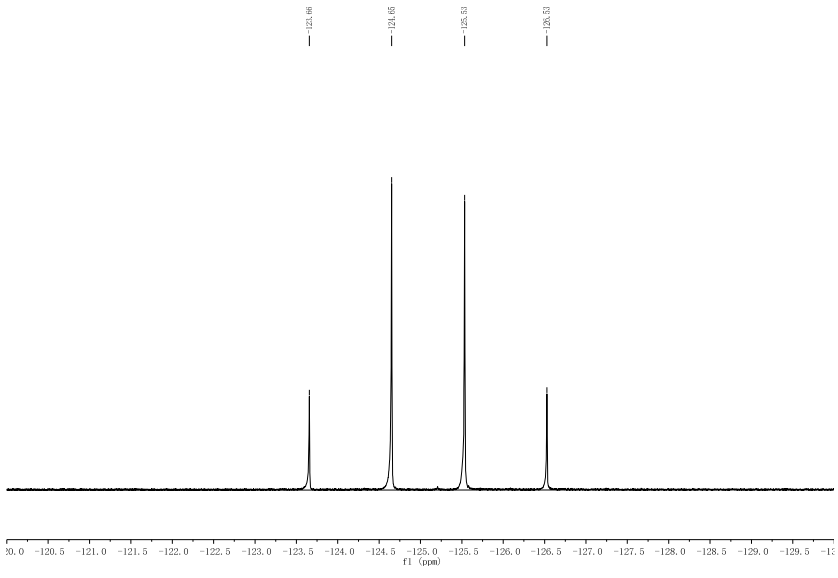


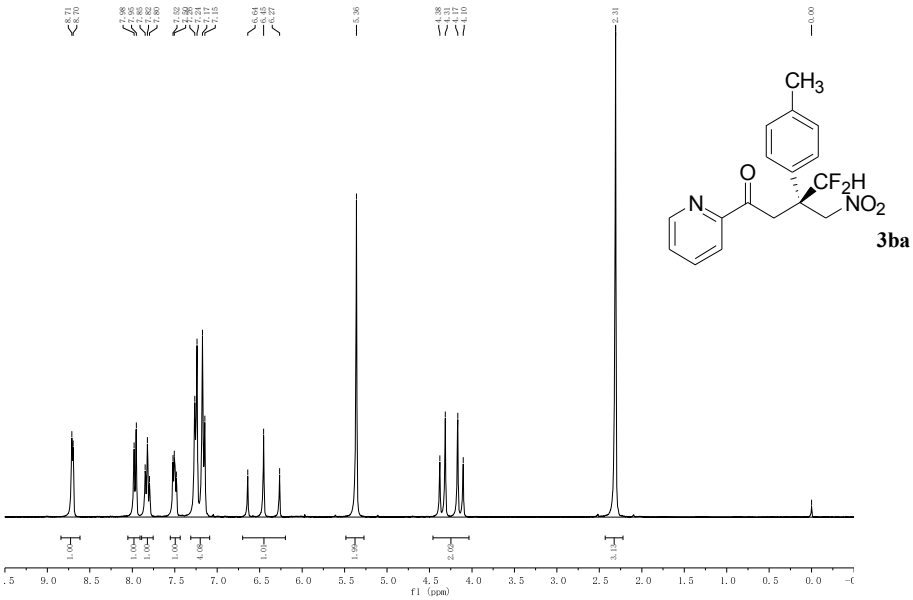




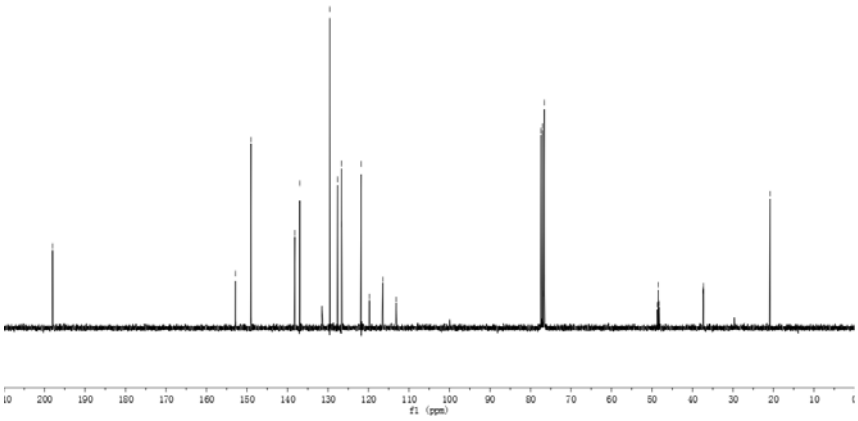


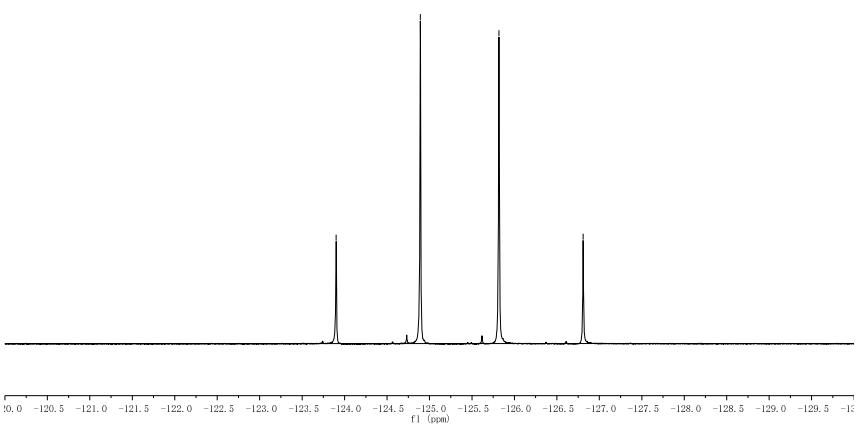


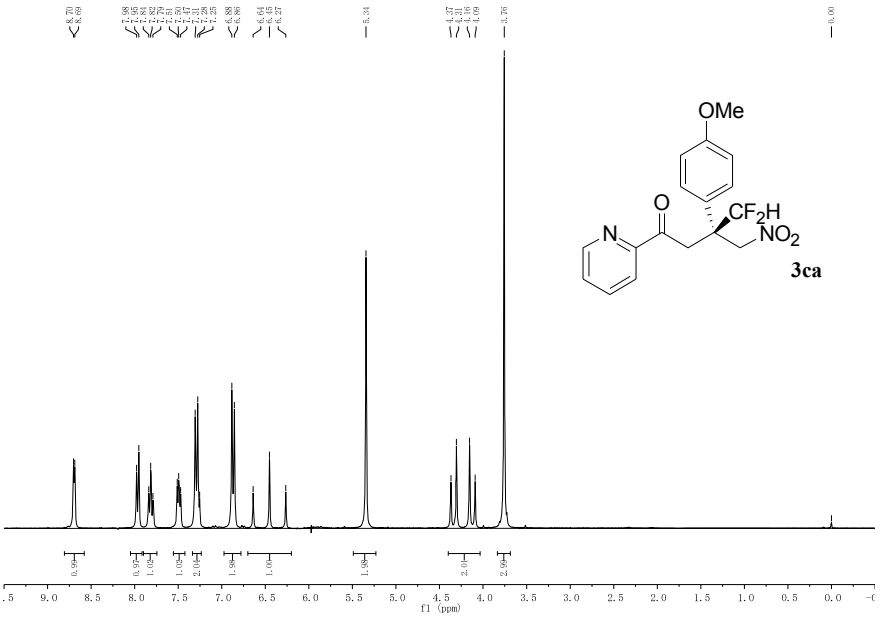


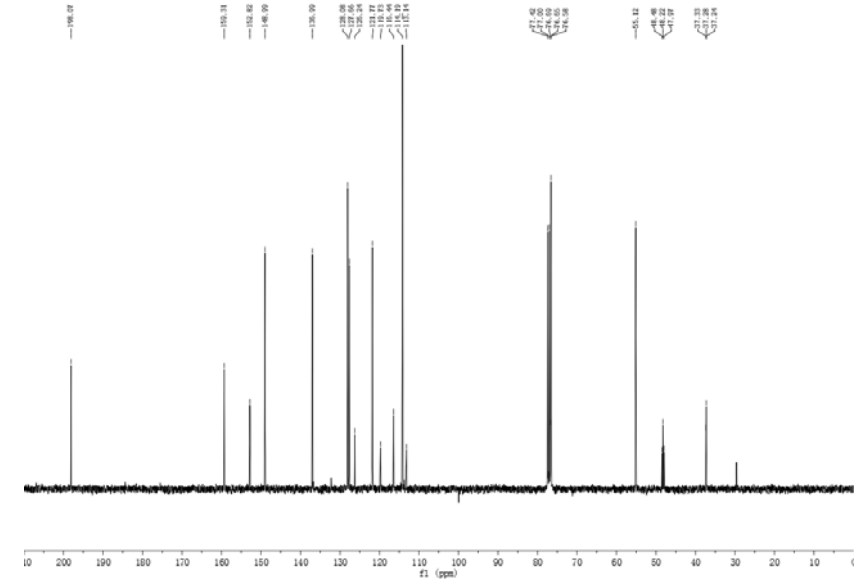


3ba






OMe
O
N
CF2H
NO2
3ca
f1 (ppm)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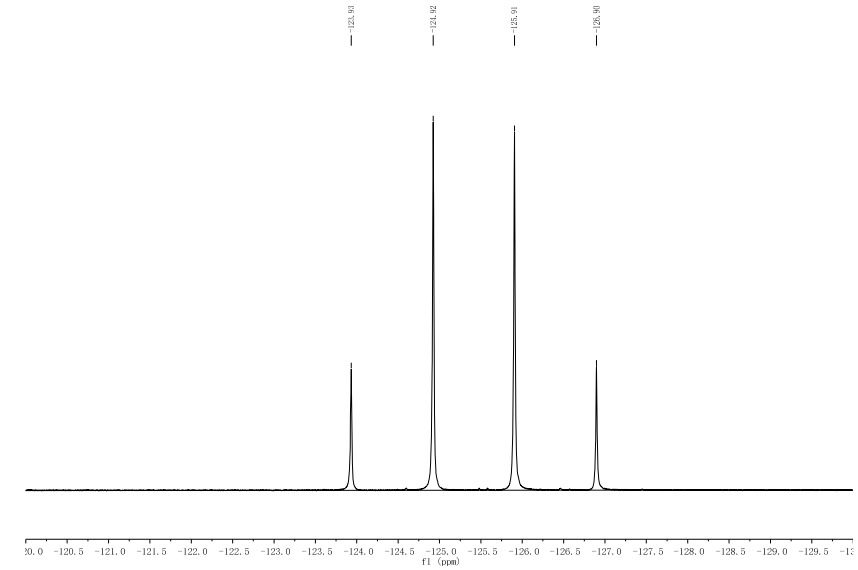
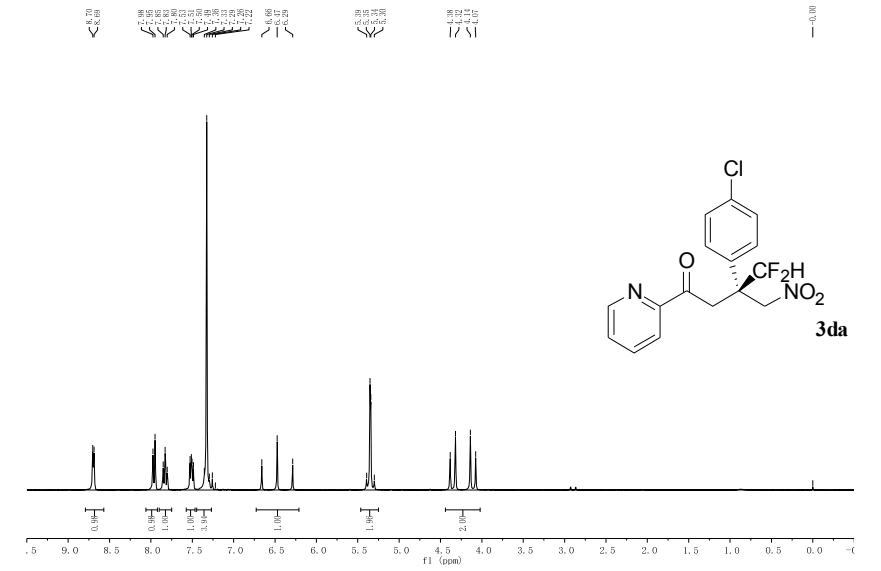
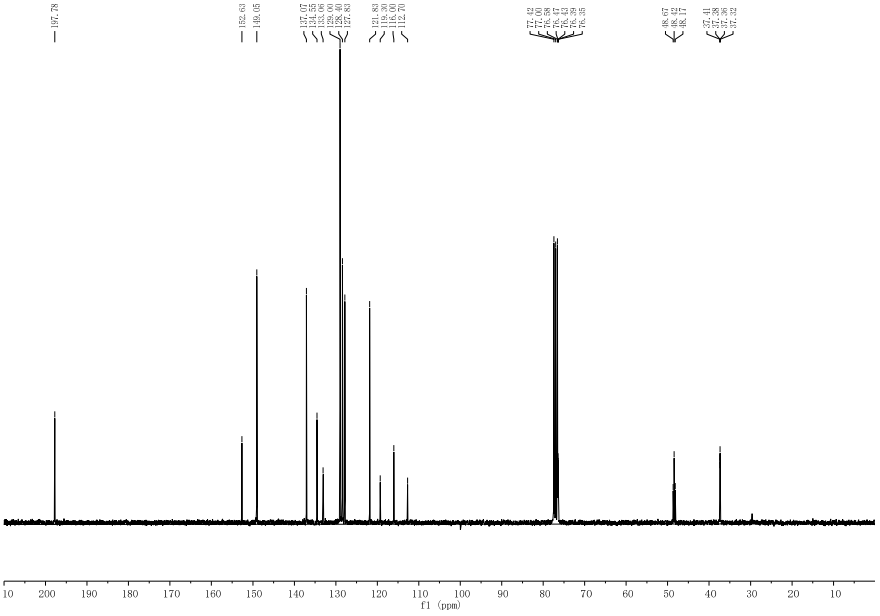

f1 (ppm)


Cl
O
N
CF2H
NO2
3da
f1 (ppm)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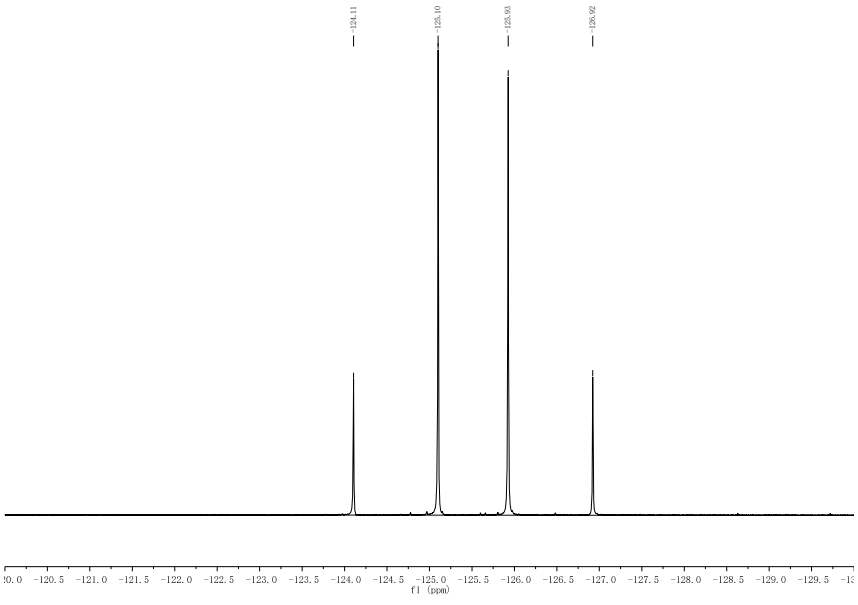
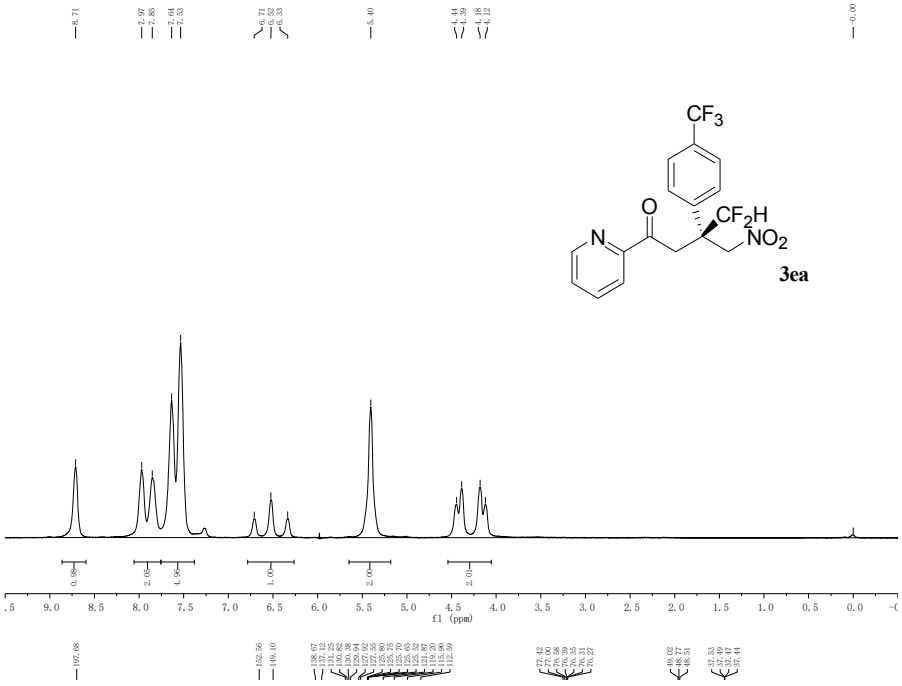
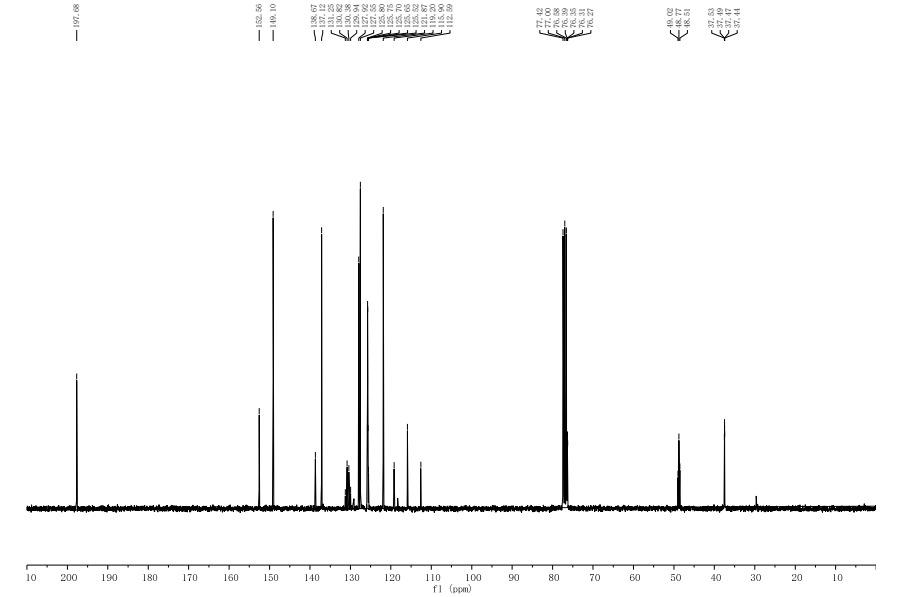
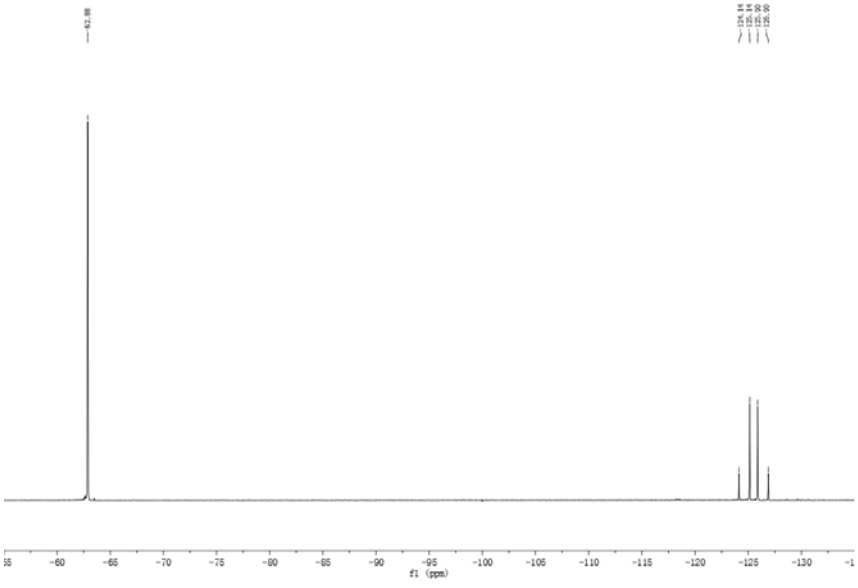
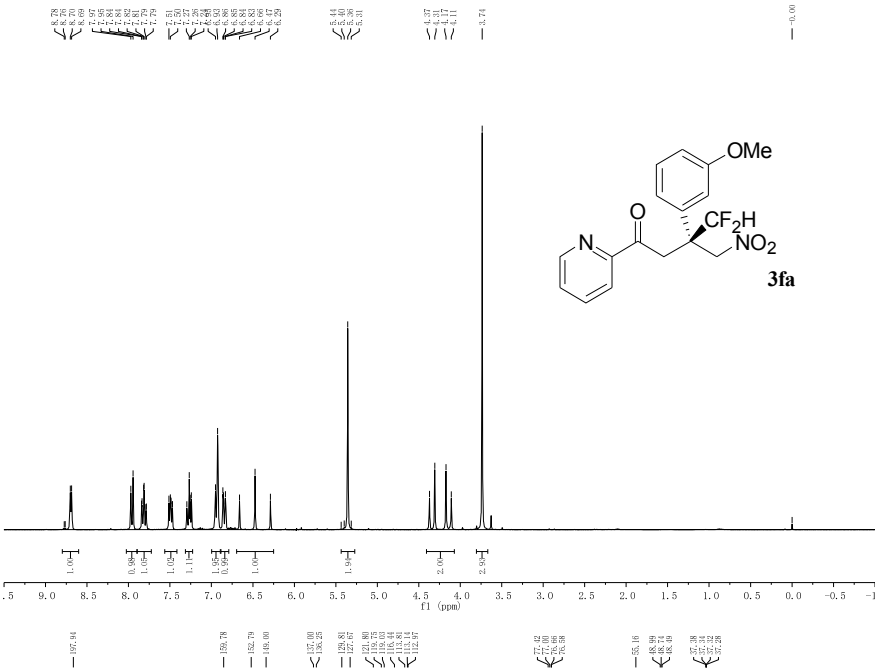

f1 (ppm)

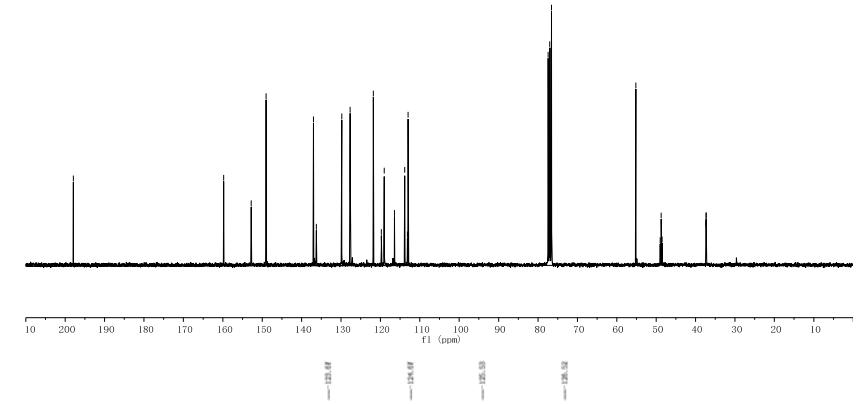

CF3
O
CF2H
NO2
N
3ea

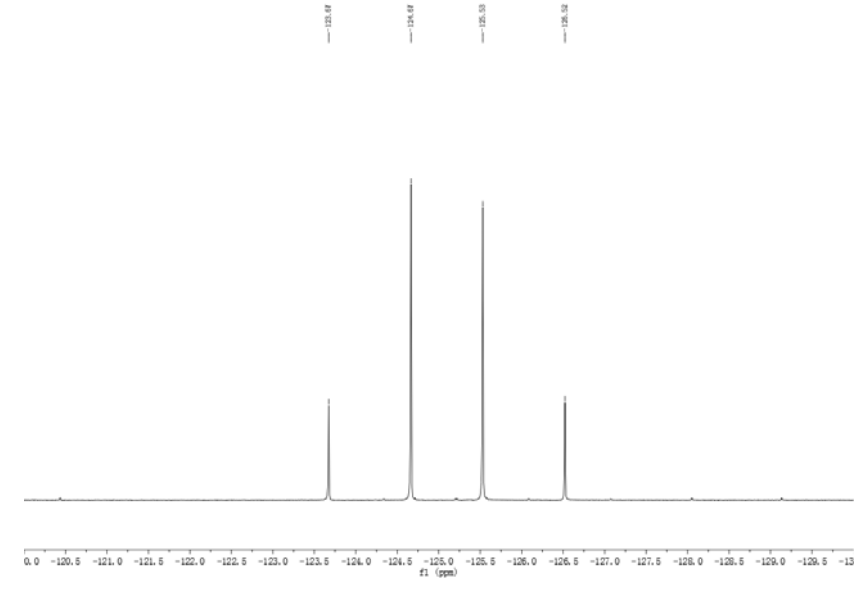


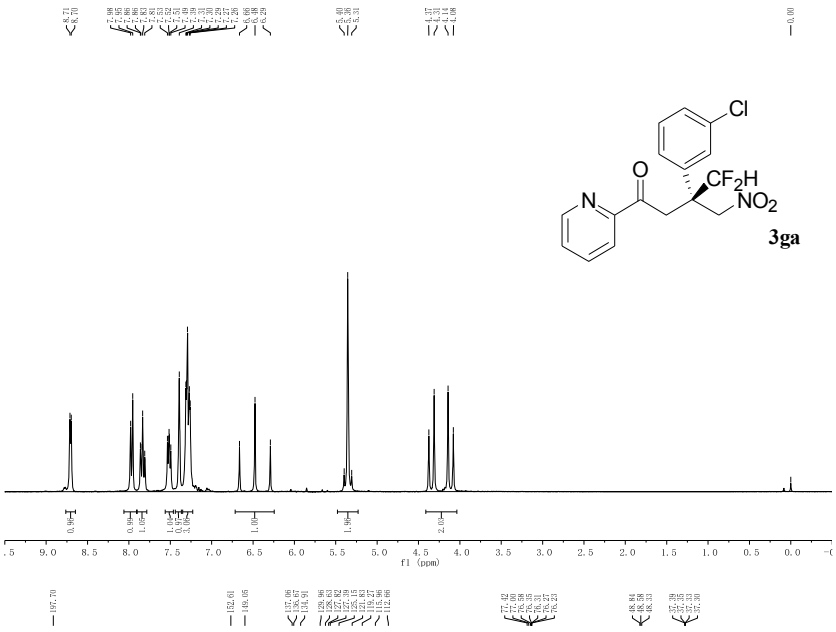


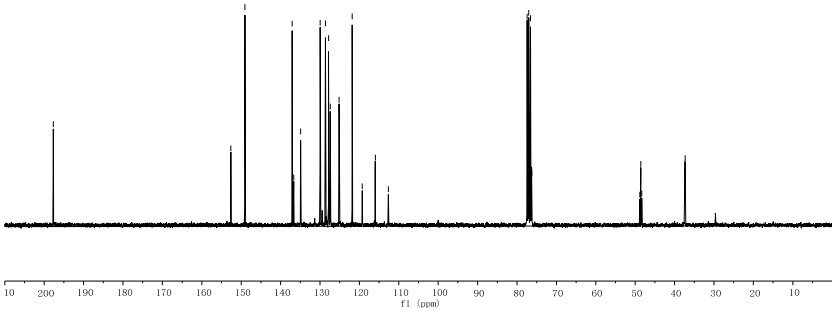


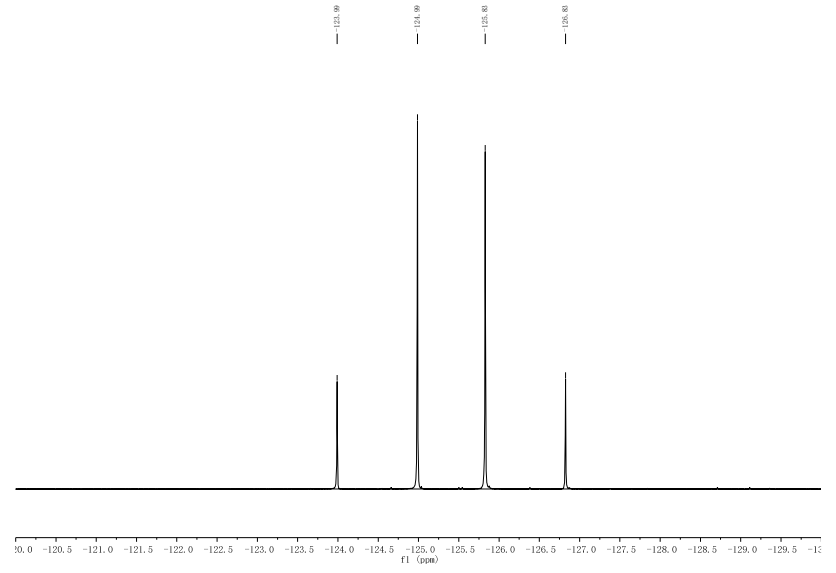
3fa

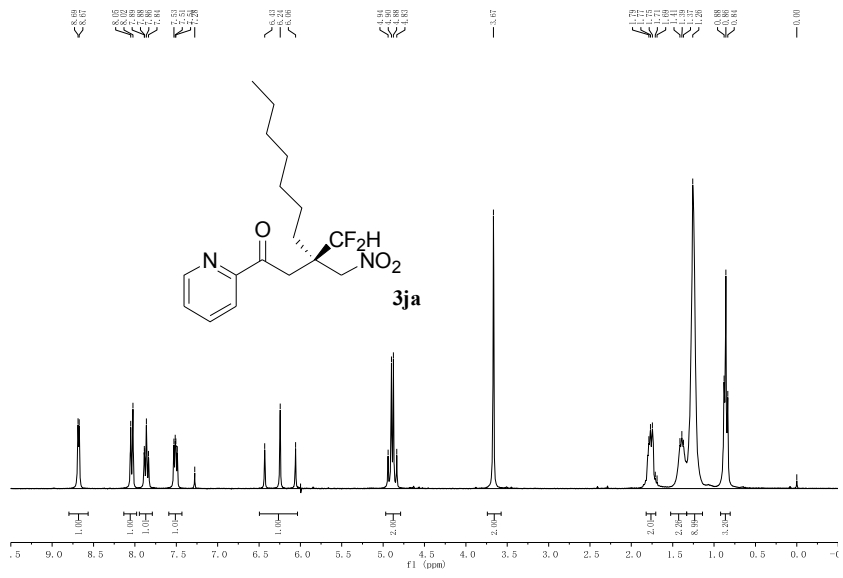




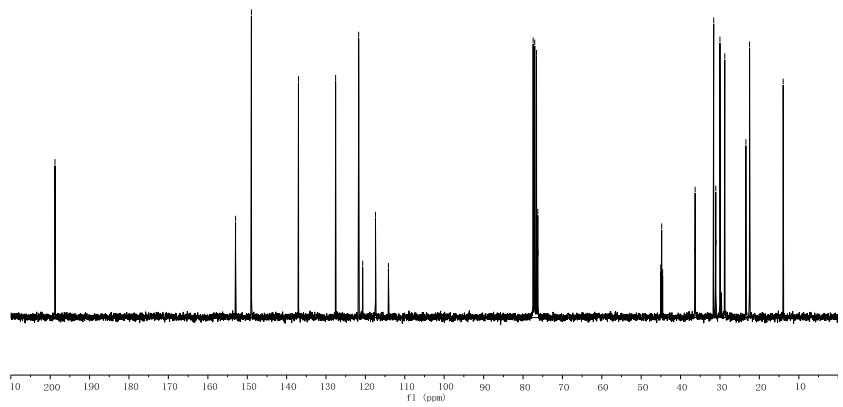

Cl
O
CF2H
N
NO2
3ga
f1 (ppm)

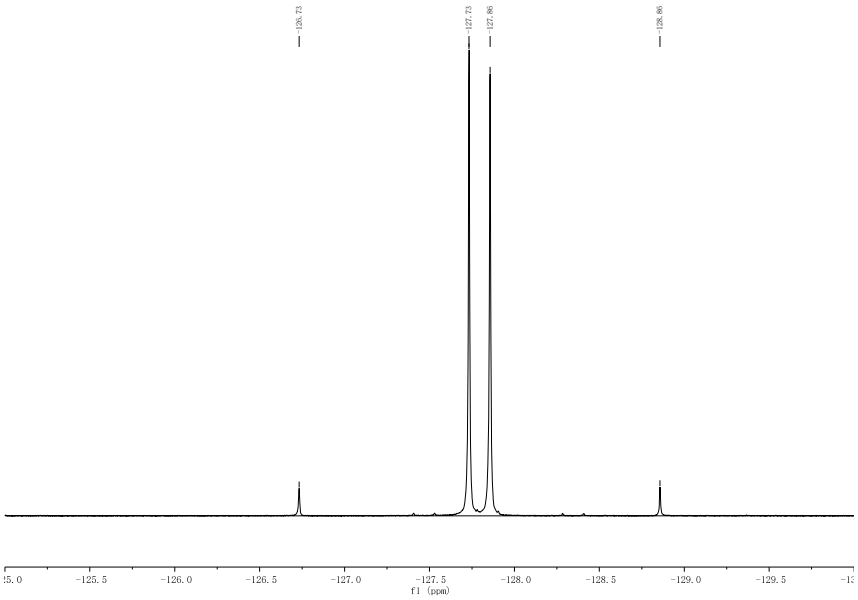

f1 (ppm)


f1 (ppm)

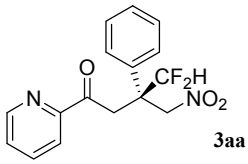


3ja



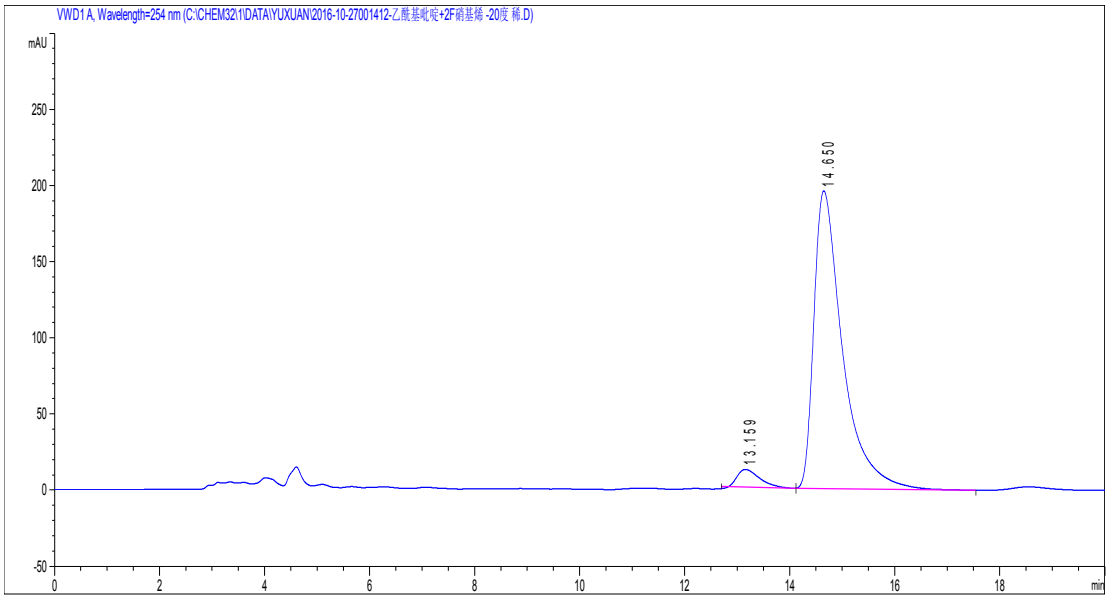


5 .HPLC spectra for the products

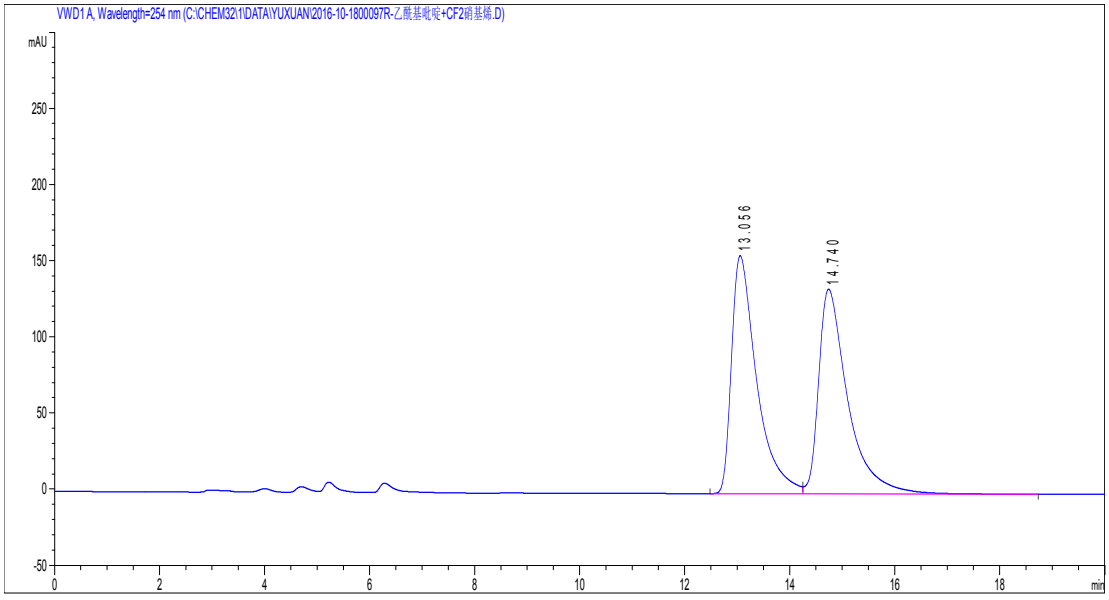


3aa

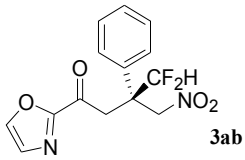
Chiracel AD-H; 90:10 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm. 91% ee



#	Time	Width	Area	Height	Area%
1	13.159	0.4982	349.32870	11.68740	4.4844
2	14.650	0.6339	7440.61865	195.63841	95.5156

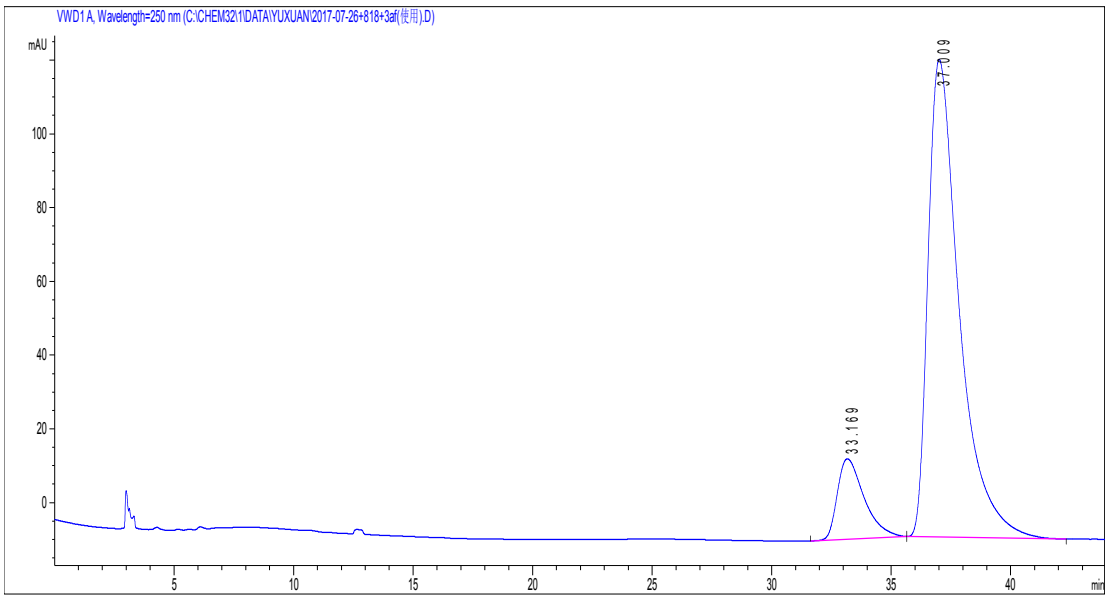


#	Time	Width	Area	Height	Area%
1	13.056	0.4974	5216.05469	156.27853	50.2015
2	14.740	0.5689	5174.18018	134.47690	49.7985

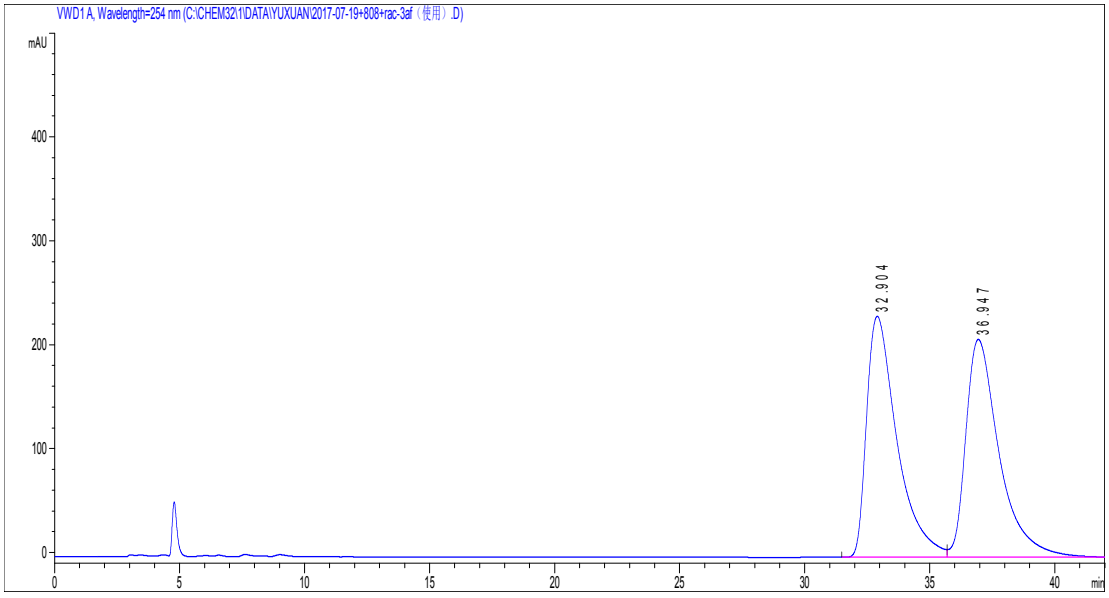


3ab

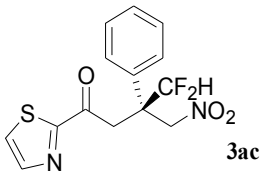
Chiracel AD-H; 95:5 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm. 75% ee



#	Time	Width	Area	Height	Area%
1	33.169	1.1627	1707.92151	21.85603	12.6650
2	37.009	1.3625	.17775e4	129.5622	87.3350

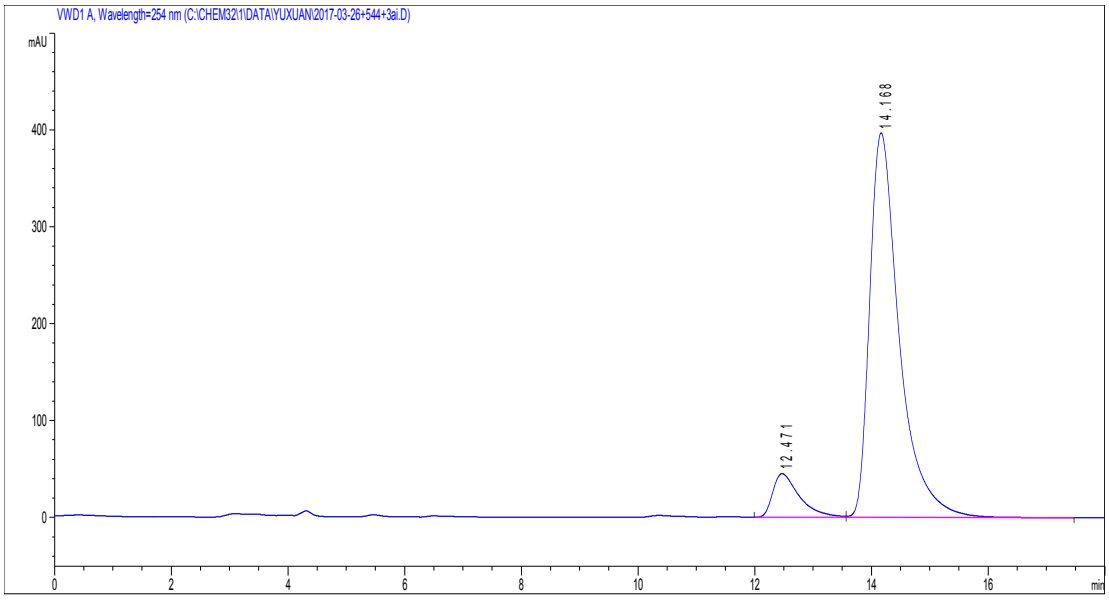


#	Time	Width	Area	Height	Area%
1	32.904	1.2682	1.95884e4	231.96864	50.1825
2	36.947	1.3956	1.94460e4	209.55565	49.8175

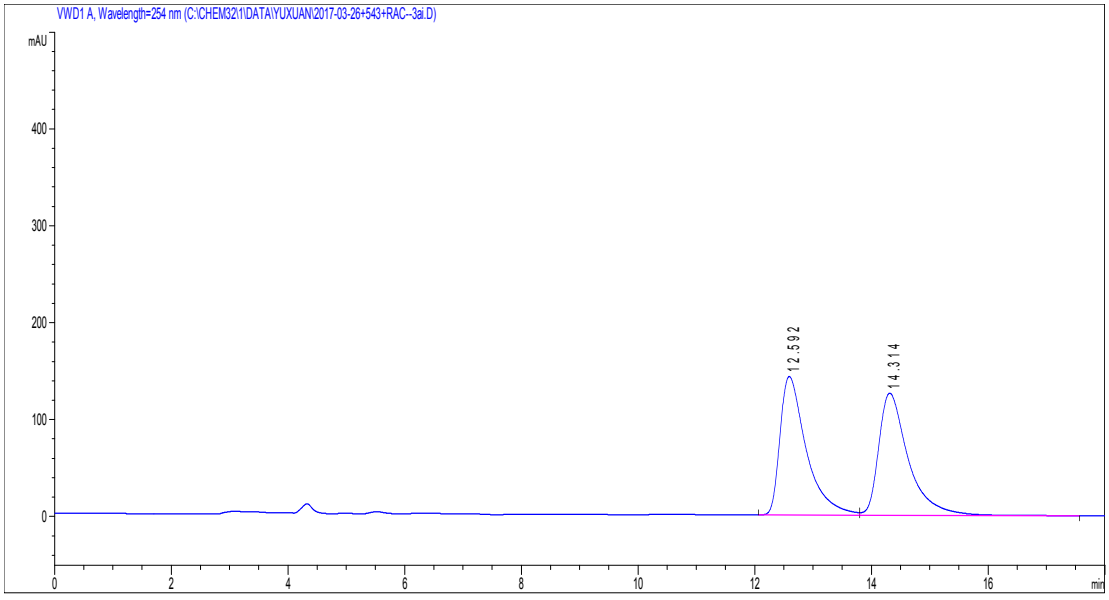


3ac

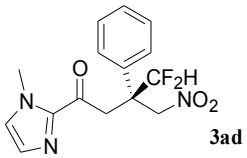
Chiracel OD-H; 80:20 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm. 81% ee



#	Time	Width	Area	Height	Area%
1	12.471	0.4752	1435.91907	45.01280	9.3057
2	14.168	0.5315	1.39946e4	396.75543	90.6943

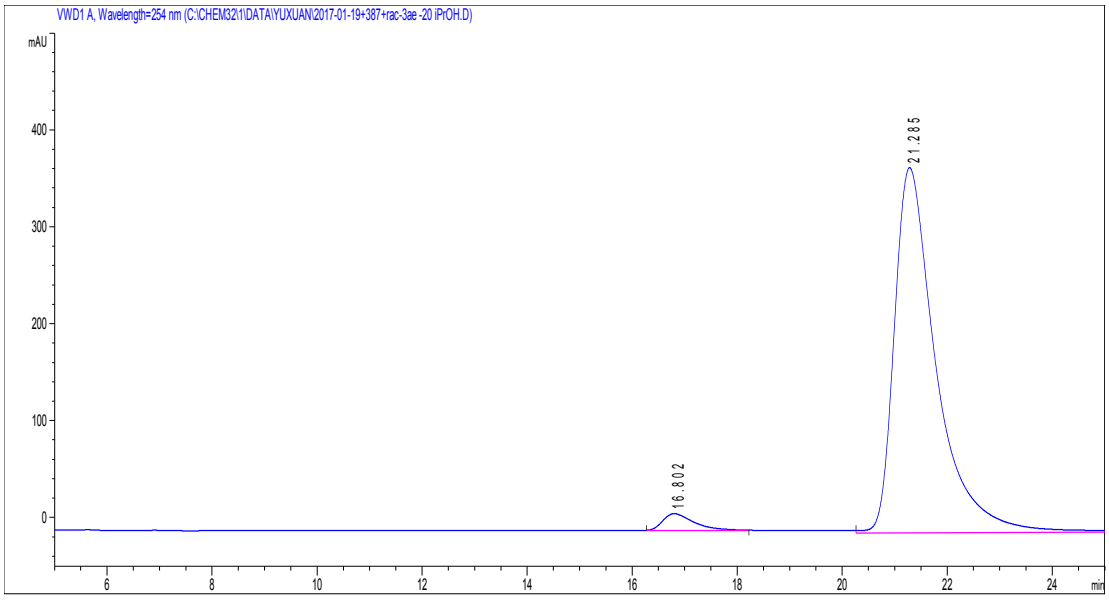


#	Time	Width	Area	Height	Area%
1	12.592	0.4672	4469.47607	142.79517	50.2753
2	14.314	0.5244	4420.53613	125.98346	49.7247

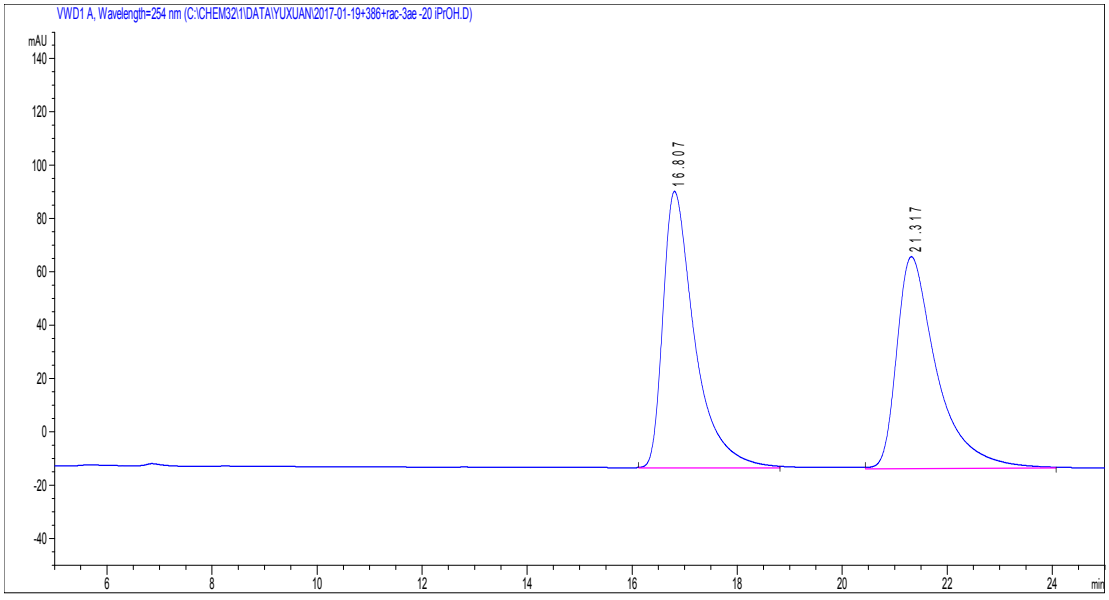


3ad

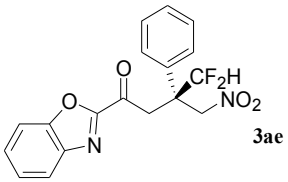
Chiracel AD-H; 90:10 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm. 93% ee



#	Time	Width	Area	Height	Area%
1	16.802	0.7145	752.91290	17.56265	3.4939
2	21.285	0.9193	2.07964e4	377.03394	96.5061

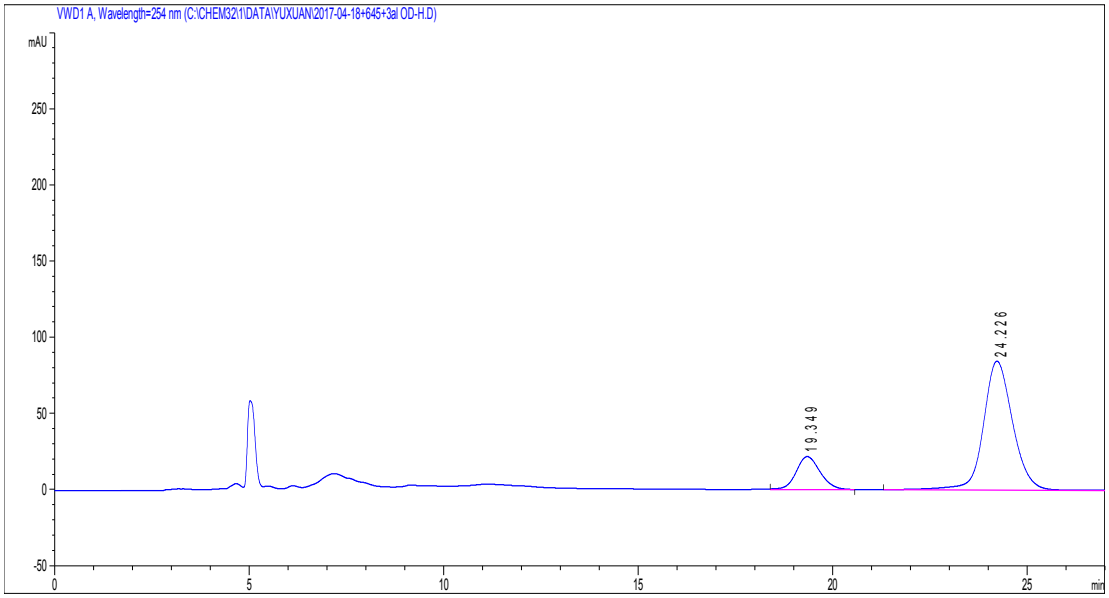


#	Time	Width	Area	Height	Area%
1	16.807	0.6976	4339.78418	103.67841	50.8828
2	21.317	0.8787	4189.19873	79.45830	49.1172

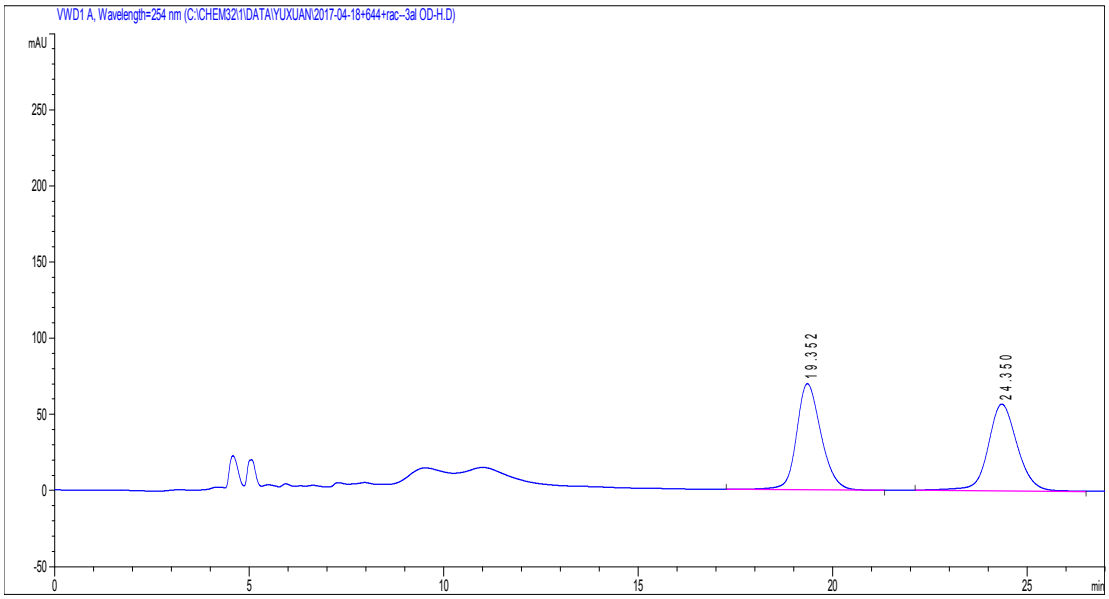


3ae

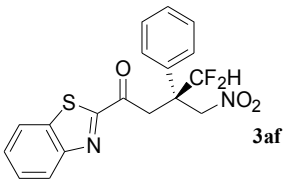
ChiracelOD-H; 80:20 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm.66% ee



#	Time	Width	Area	Height	Area%
1	19.349	0.7197	937.86792	21.72040	17.1087
2	24.226	0.8905	4543.94775	85.04855	82.8913

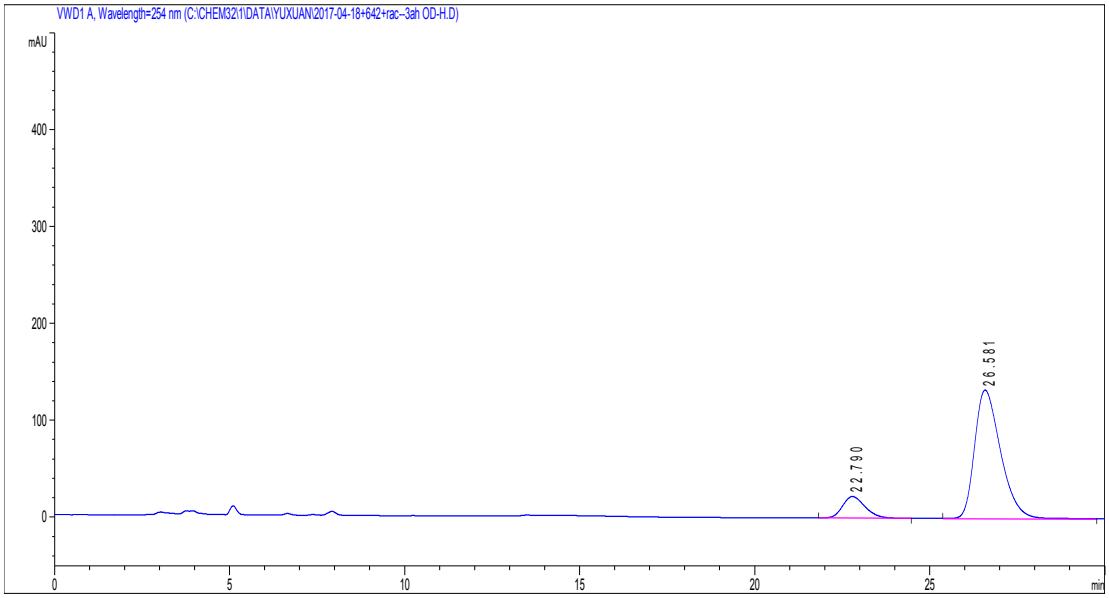


#	Time	Width	Area	Height	Area%
1	19.352	0.6680	3055.30811	69.75513	50.5888
2	24.350	0.8724	2984.18579	57.00895	49.4112

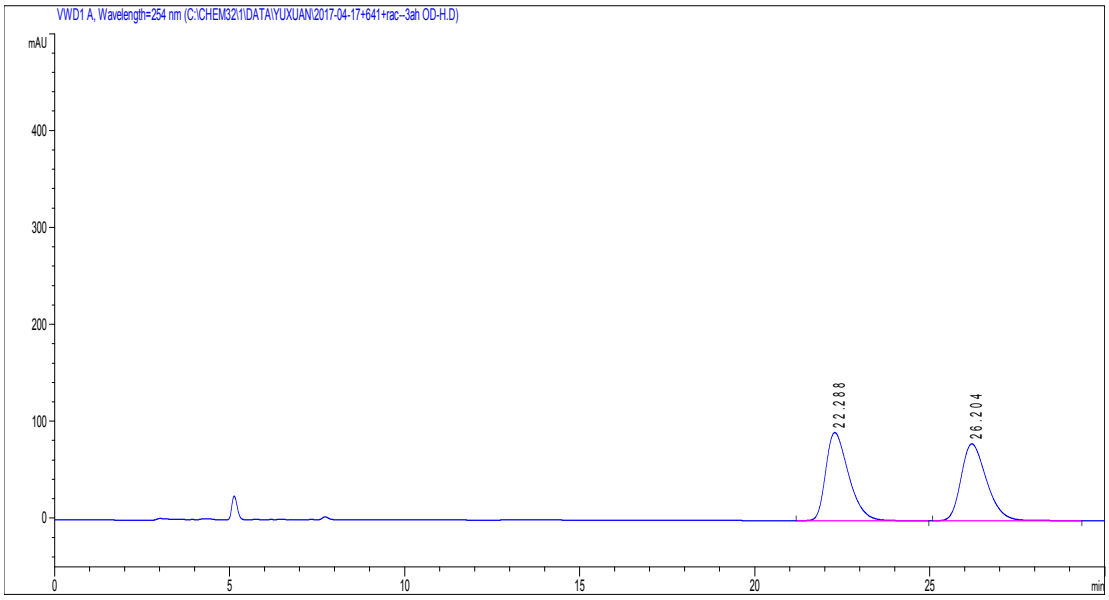


3af

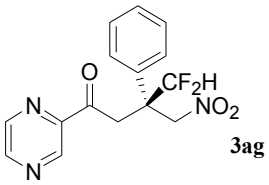
ChiracelOD-H; 90:10 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm.75% ee



#	Time	Width	Area	Height	Area%
1	22.790	0.6834	986.16931	22.19268	12.5028
2	26.581	0.8655	6901.39258	132.90556	87.4972

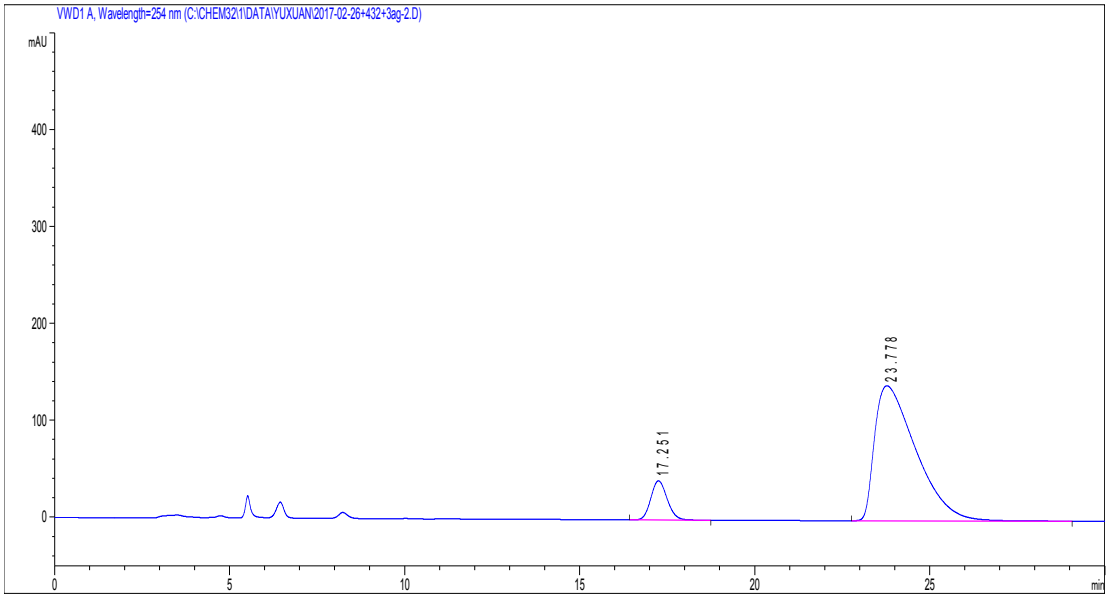


#	Time	Width	Area	Height	Area%
1	22.288	0.6972	4132.40820	90.93843	50.7341
2	26.204	0.7790	4012.82275	79.35229	49.2659

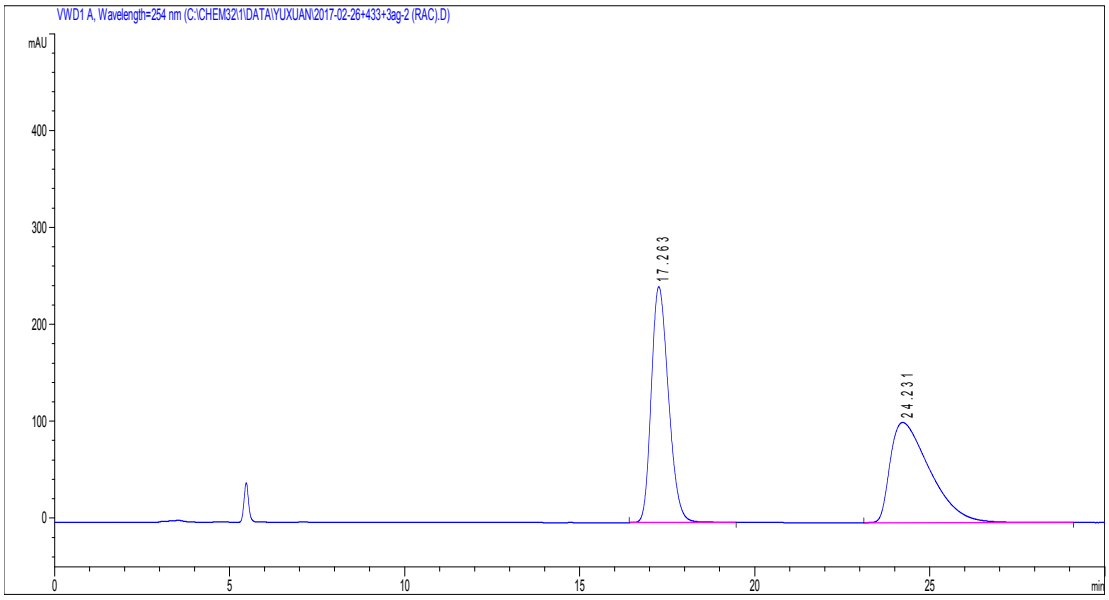


3ag

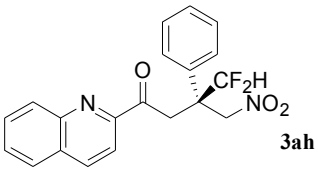
Chiracel AS-H; 80:20 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm. 79% ee



#	Time	Width	Area	Height	Area%
1	17.251	0.5472	1333.15295	40.60772	10.4745
2	23.778	1.2506	1.13945e4	139.26158	89.5255

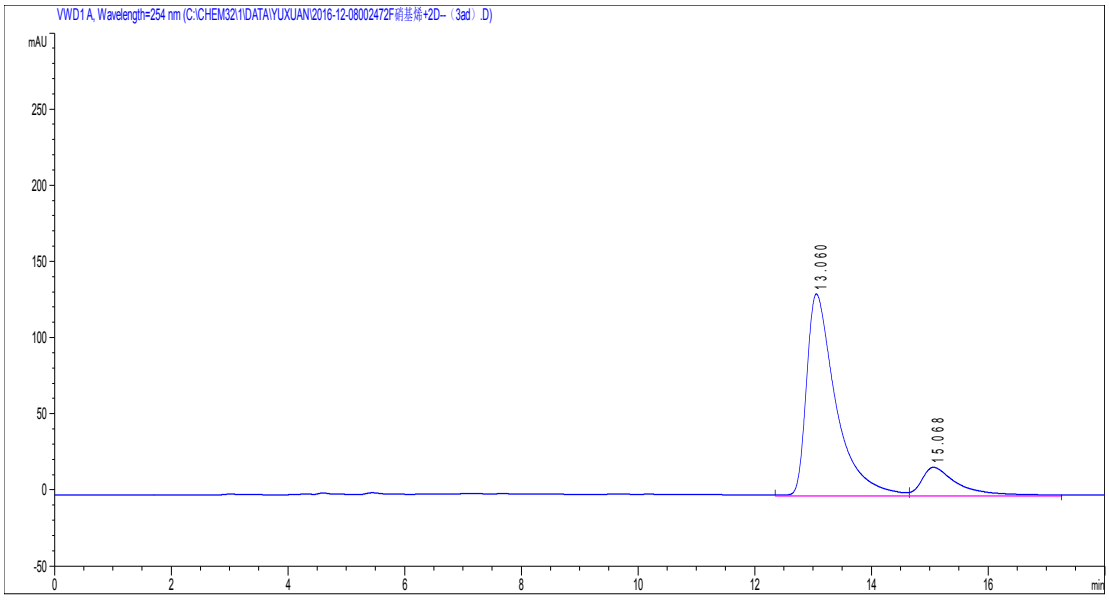


#	Time	Width	Area	Height	Area%
1	17.263	0.5300	8283.81738	243.45168	50.5131
2	24.231	1.1985	8115.51172	103.31113	49.4869

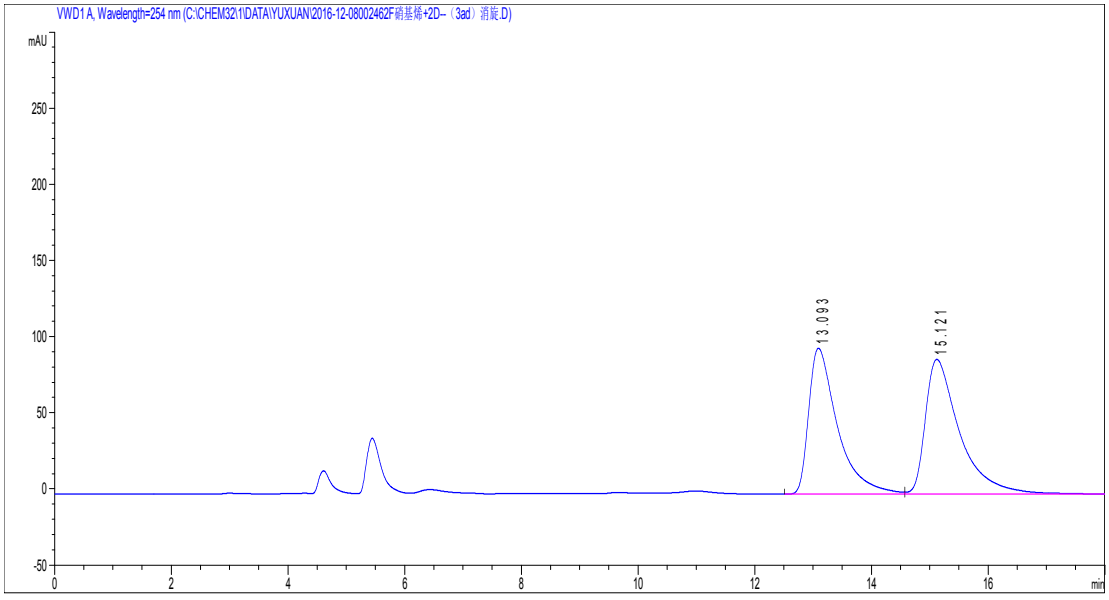


3ah

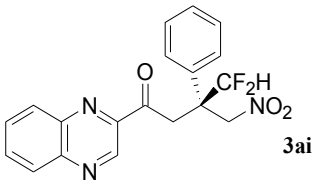
ChiracelAD-H; 90:10 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm.70% ee



#	Time	Width	Area	Height	Area%
1	13.060	0.5822	4629.21631	132.52354	85.0306
2	15.068	0.7277	814.96088	18.66513	14.9694

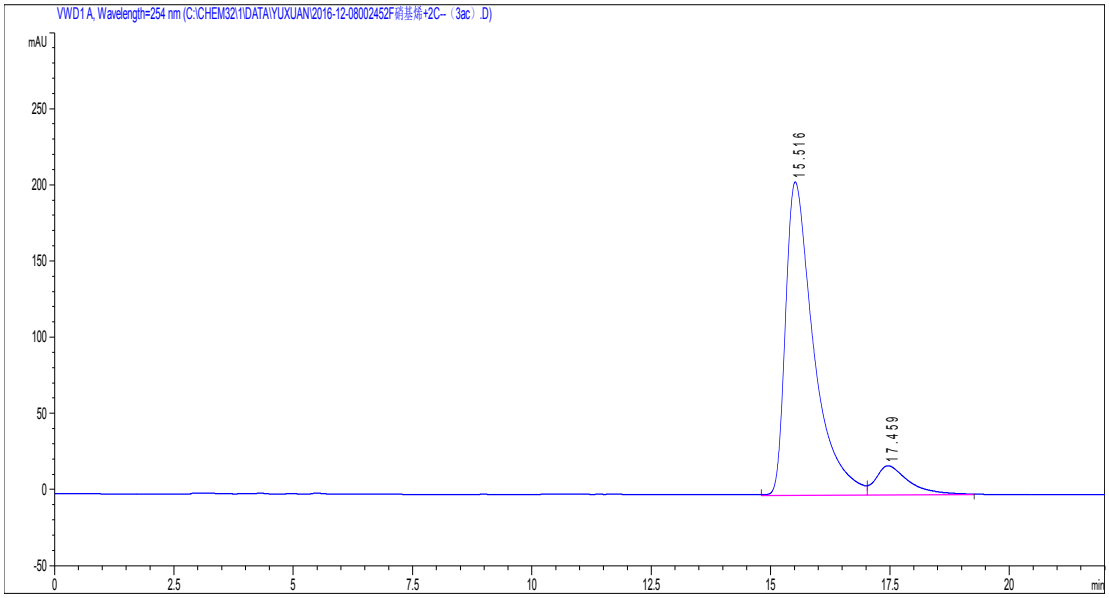


#	Time	Width	Area	Height	Area%
1	13.093	0.5078	3285.15991	95.85886	47.6164
2	15.121	0.6003	3614.06226	88.52074	52.3836

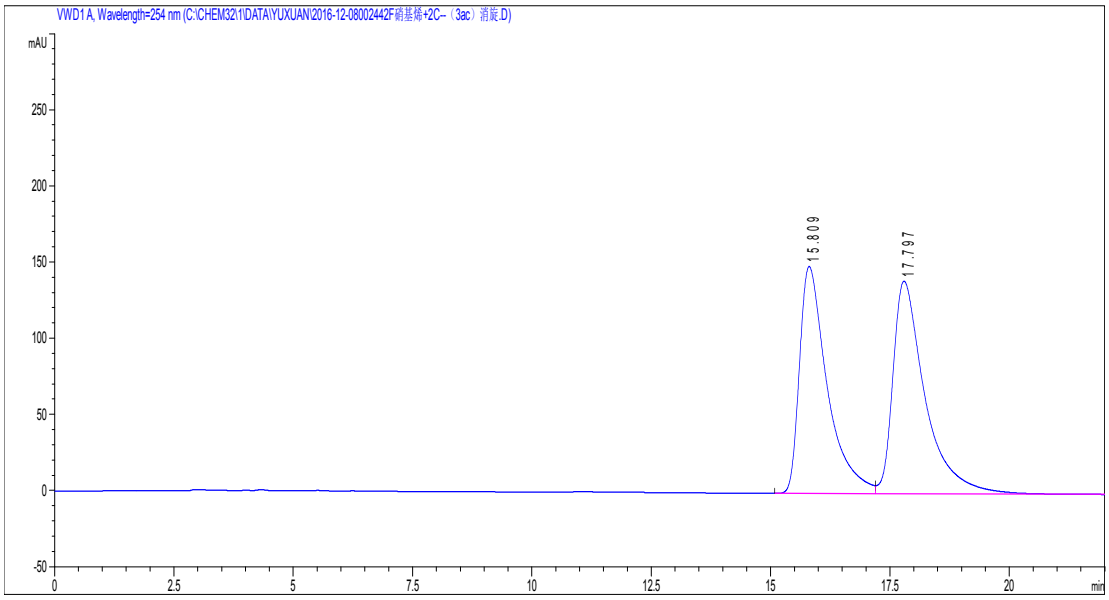


3ai

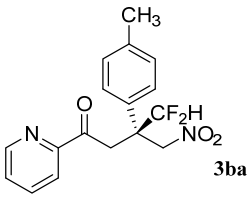
ChiracelAD-H; 90:10 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm.80% ee



#	Time	Width	Area	Height	Area%
1	15.516	0.6839	8452.73535	206.00320	90.0341
2	17.459	0.8098	935.63214	19.25626	9.9659

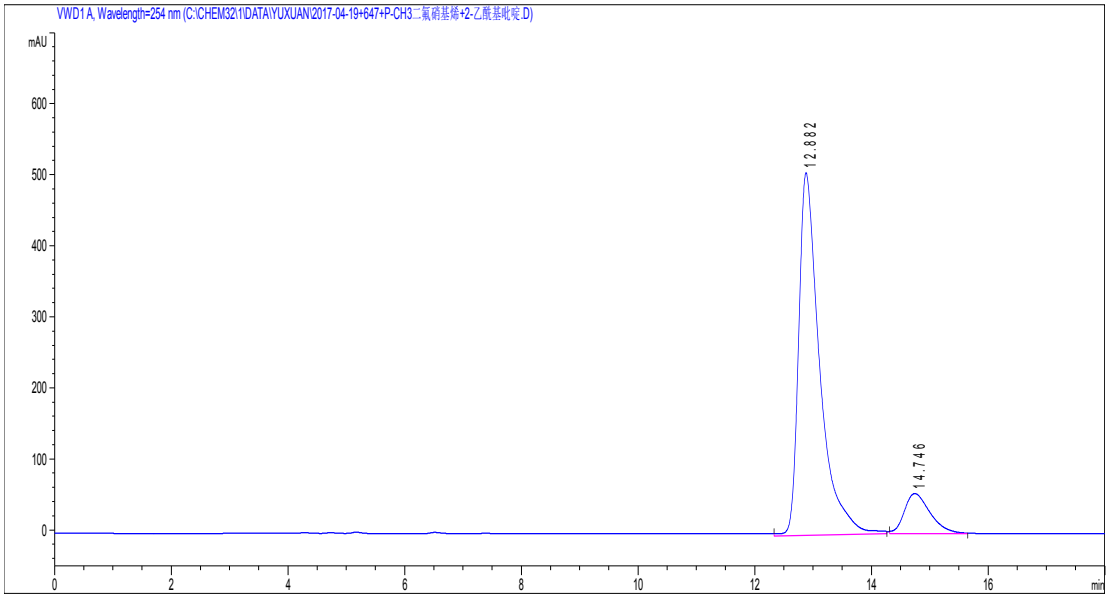


#	Time	Width	Area	Height	Area%
1	15.809	0.6008	6026.15625	149.00395	47.9625
2	17.797	0.6893	6538.16162	139.61909	52.0375

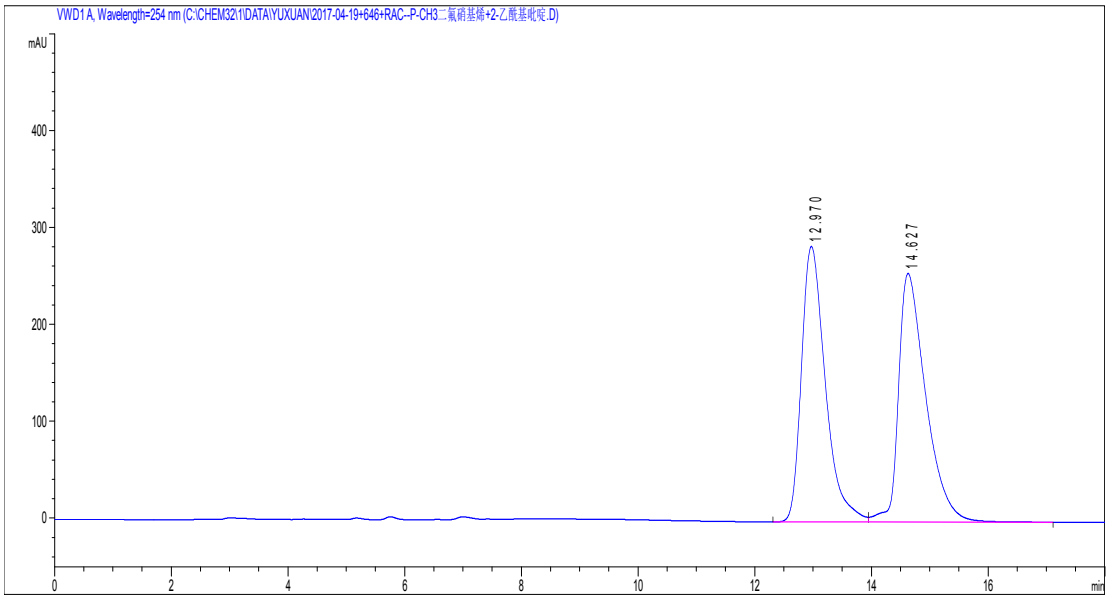


3ba

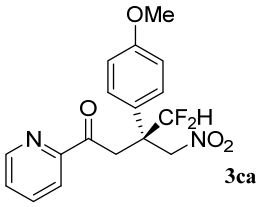
ChiracelOD-H; 90:10 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm.76% ee



#	Time	Width	Area	Height	Area%
1	12.882	0.4169	1.27652e4	510.31796	88.1814
2	14.746	0.5086	1710.87012	56.06187	11.8186

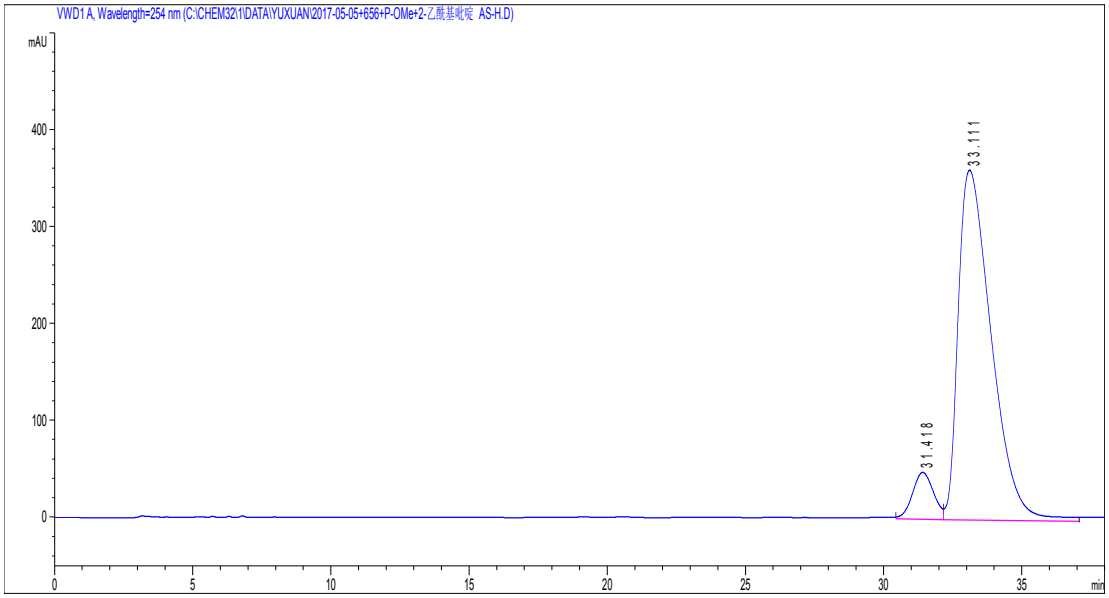


#	Time	Width	Area	Height	Area%
1	12.970	0.4367	8106.86719	284.27579	49.3999
2	14.627	0.4857	8303.81543	256.51770	50.6001

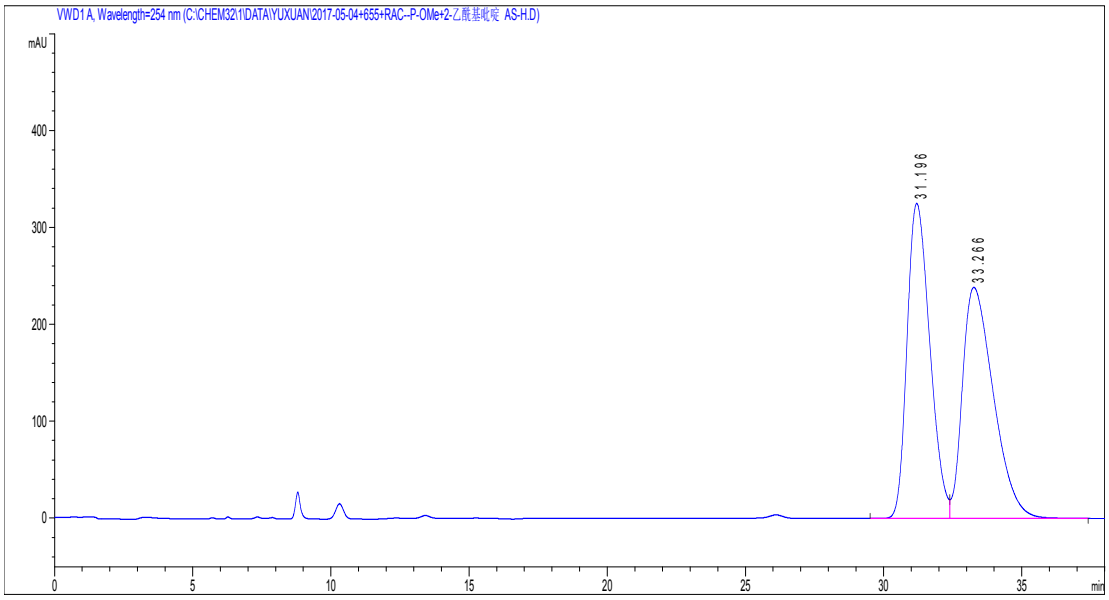


3ca

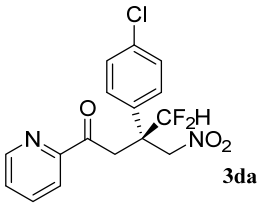
ChiracelAS-H; 90:10 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm, 84% ee



#	Time	Width	Area	Height	Area%
1	31.418	0.8863	2572.06104	48.36728	7.8727
2	33.111	1.3894	3.00988e4	361.06201	92.1273

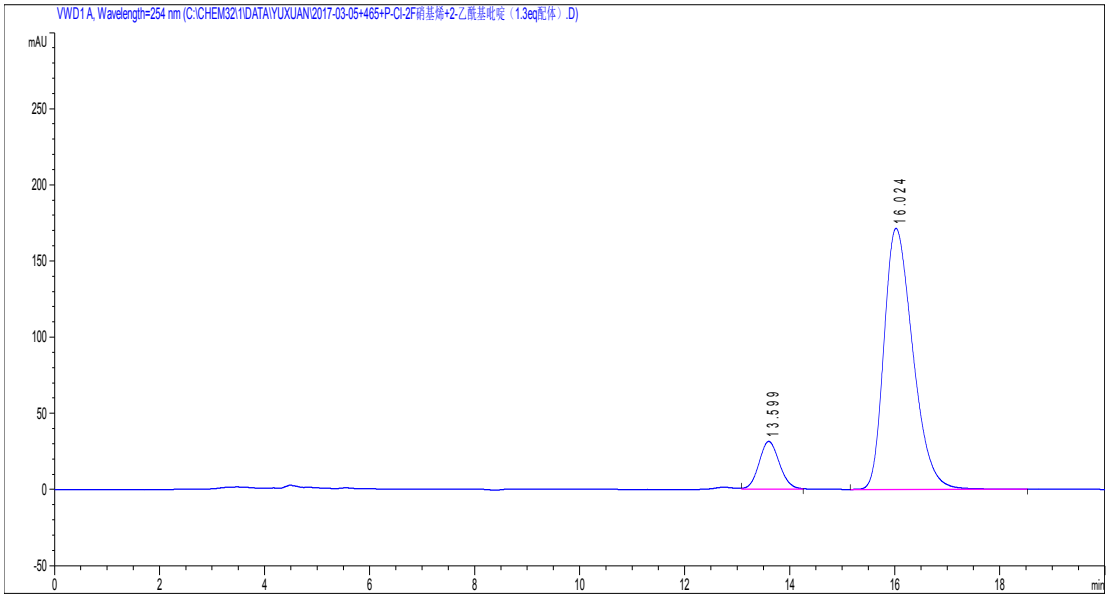


#	Time	Width	Area	Height	Area%
1	31.196	0.8989	1.86442e4	325.17123	50.0783
2	33.266	1.1920	1.85859e4	238.53084	49.9217

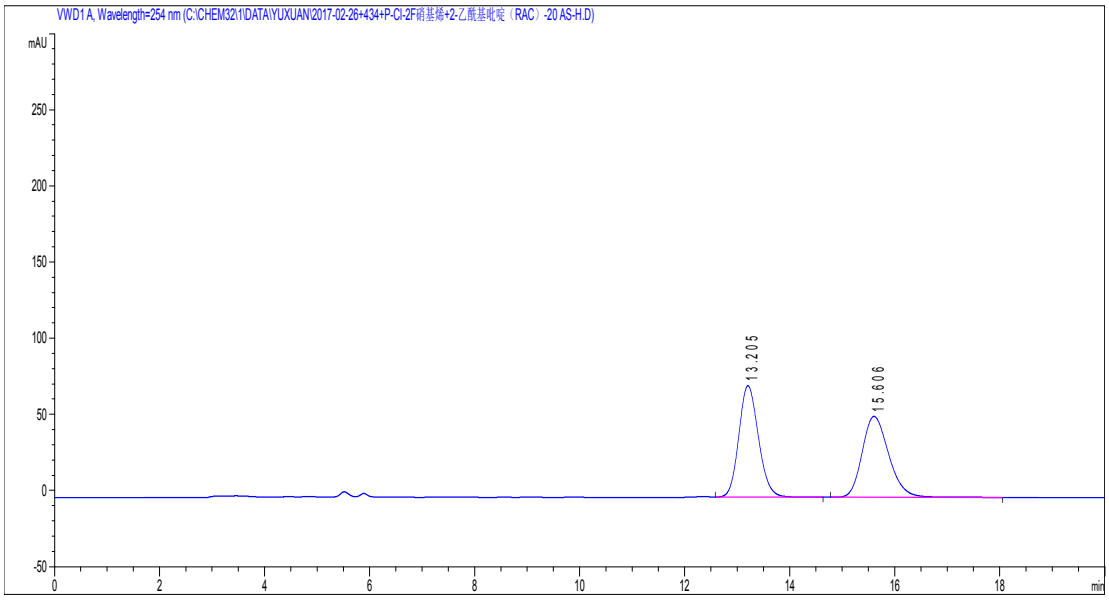


3da

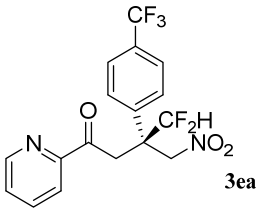
ChiracelAS-H; 80:20 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm.77% ee



#	Time	Width	Area	Height	Area%
1	13.599	0.4500	847.82196	31.40025	11.4851
2	16.024	0.5914	6534.07910	171.52586	88.5149

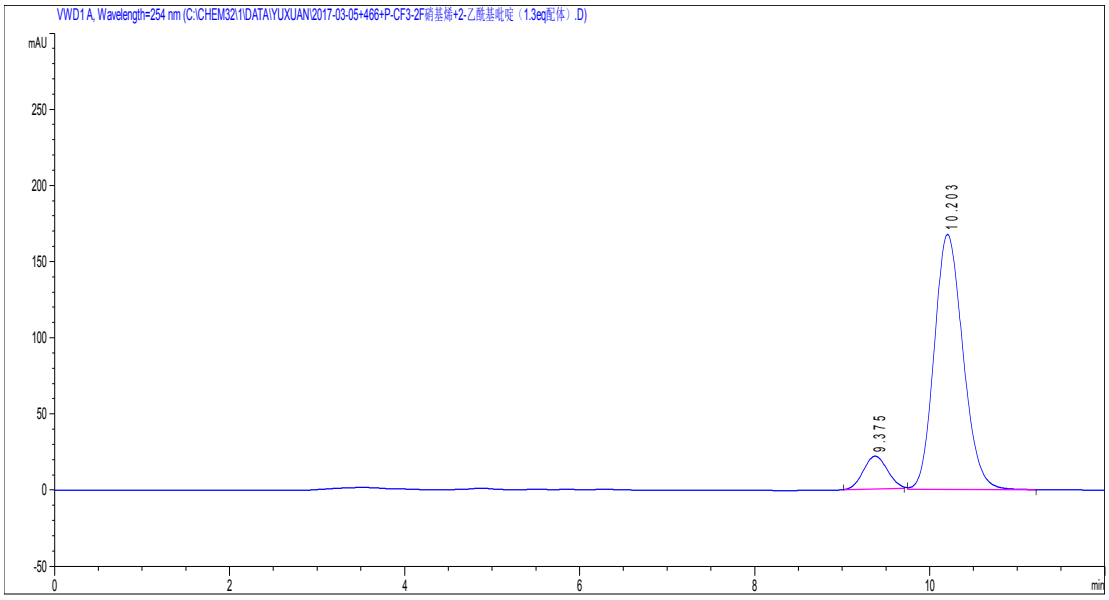


#	Time	Width	Area	Height	Area%
1	13.205	0.4023	1902.85718	73.20322	50.4459
2	15.606	0.5440	1869.22095	53.19016	49.5541

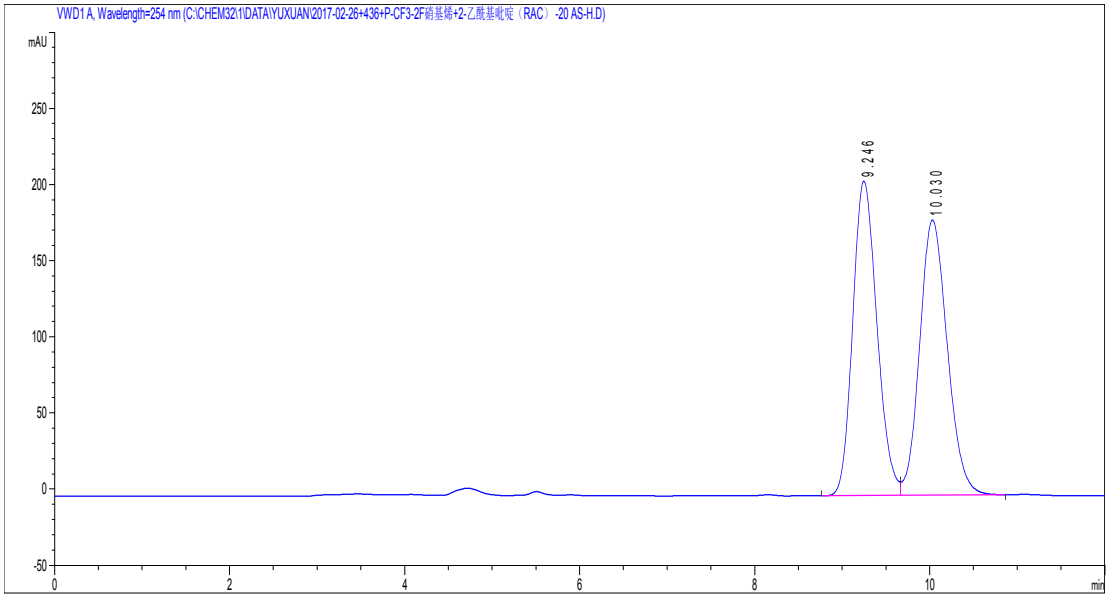


3ea

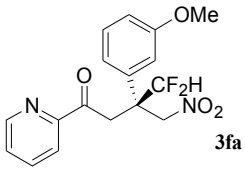
ChiracelAS-H; 80:20 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm.80% ee



#	Time	Width	Area	Height	Area%
1	9.375	0.3202	415.76651	21.63966	9.8086
2	10.203	0.3805	3823.02148	167.47557	90.1914

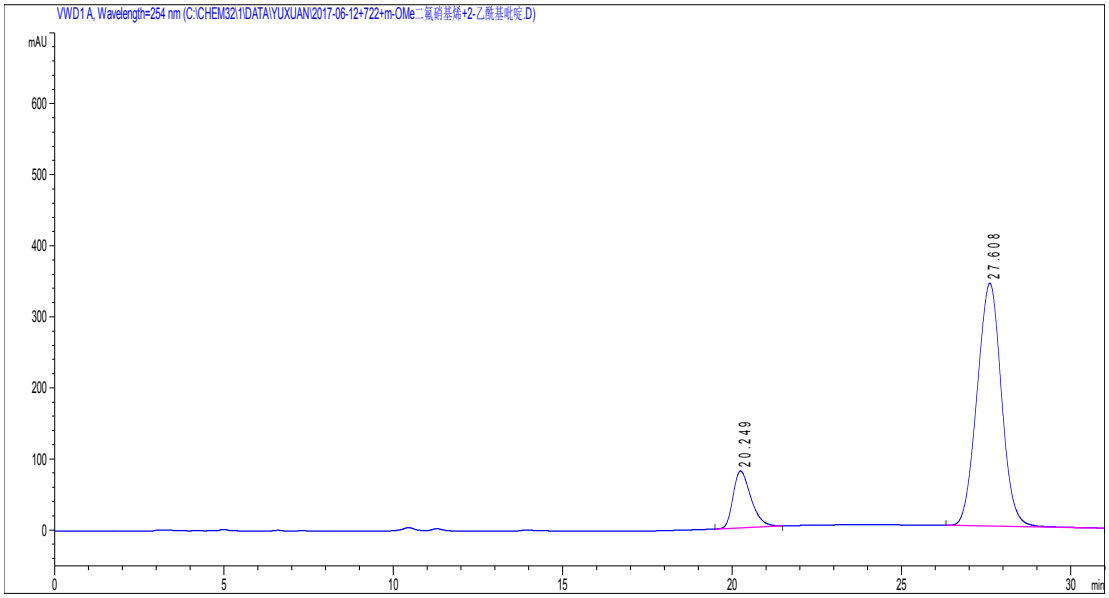


#	Time	Width	Area	Height	Area%
1	9.246	0.2994	3972.95630	206.51308	50.0330
2	10.030	0.3412	3967.70801	180.66481	49.9670

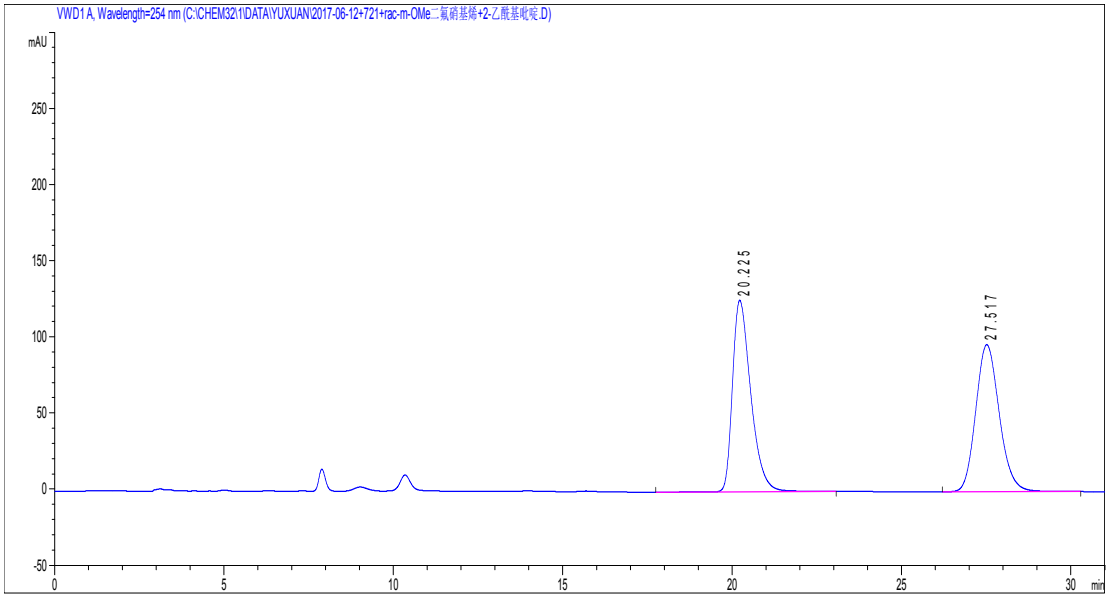


3fa

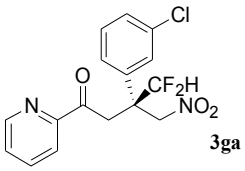
ChiracelOD-H; 90:10 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm.71% ee



#	Time	Width	Area	Height	Area%
1	20.249	0.5591	2921.83813	80.00660	14.6100
2	27.608	0.7768	1.70770e4	341.82587	85.3900

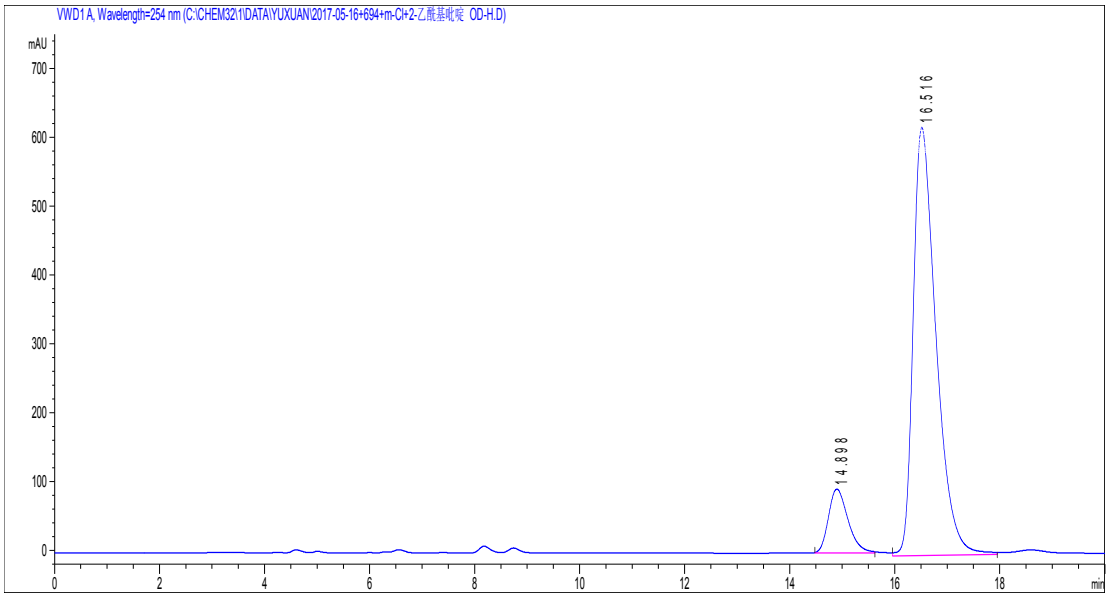


#	Time	Width	Area	Height	Area%
1	20.225	0.5734	4741.08447	125.86942	50.4647
2	27.517	0.7455	4653.75977	96.52320	49.5353

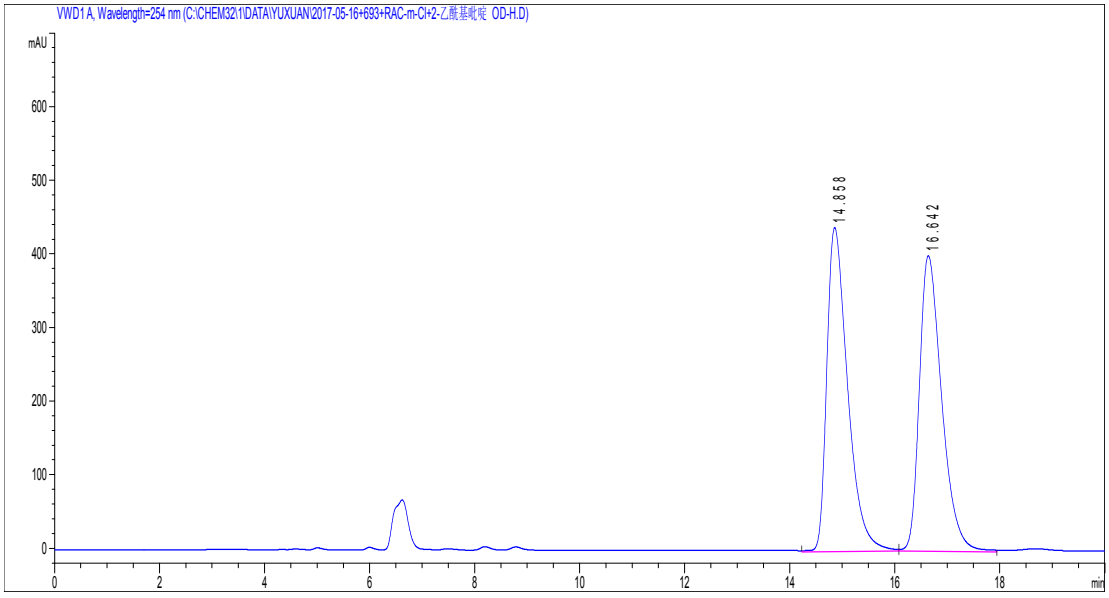


3ga

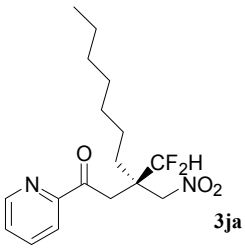
ChiracelOD-H; 90:10 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm.78% ee



#	Time	Width	Area	Height	Area%
1	14.898	0.4286	2384.26953	92.71590	11.2836
2	16.516	0.5020	1.87462e4	622.32397	88.7164

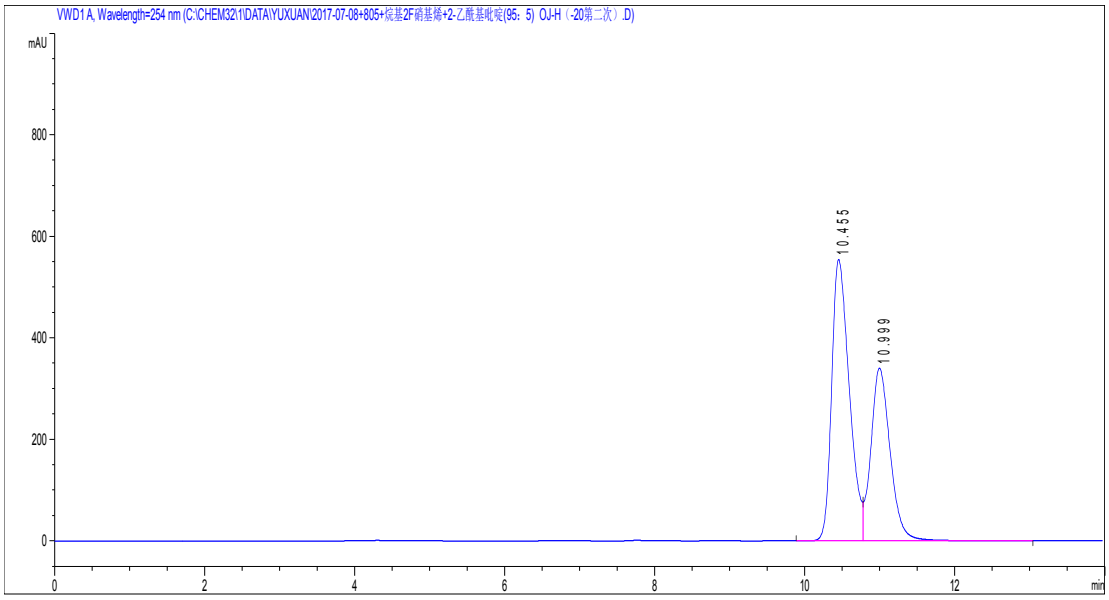


#	Time	Width	Area	Height	Area%
1	14.858	0.4584	1.21102e4	440.32550	50.5238
2	16.642	0.4923	1.18591e4	401.47272	49.4762

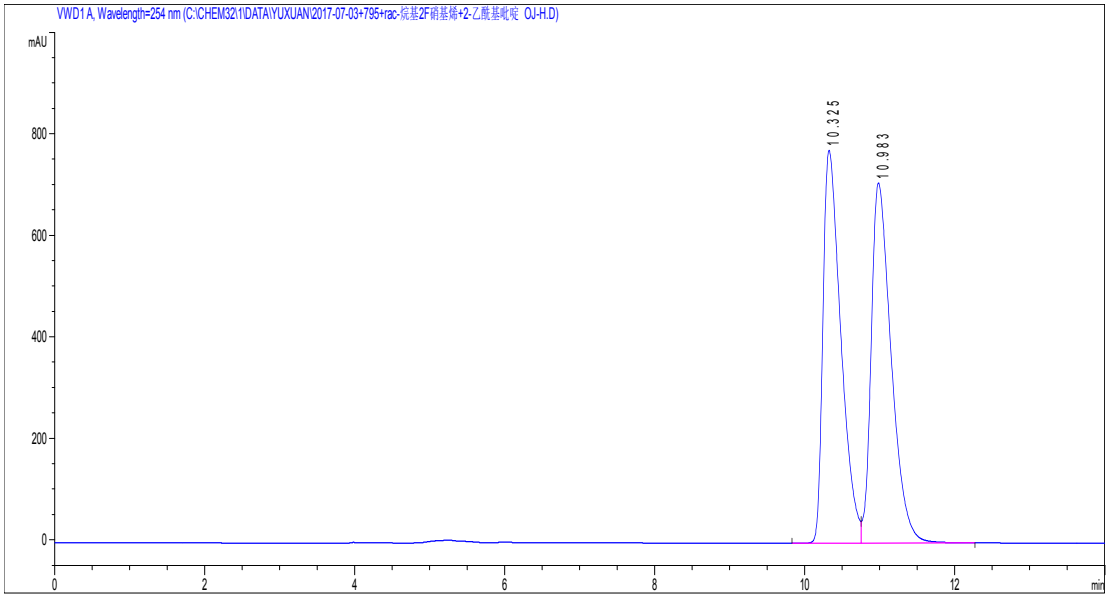


3ja

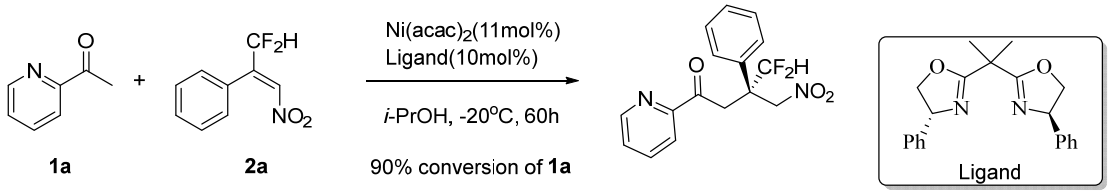
ChiracelOJ-H; 95:5 / *n*-hexane/*i*-PrOH; v = 0.8 mL/min; λ = 254 nm.19% ee



#	Time	Width	Area	Height	Area%
1	10.455	0.2490	9028.14844	554.37354	59.6657
2	10.999	0.2712	6103.07275	340.27991	40.3343

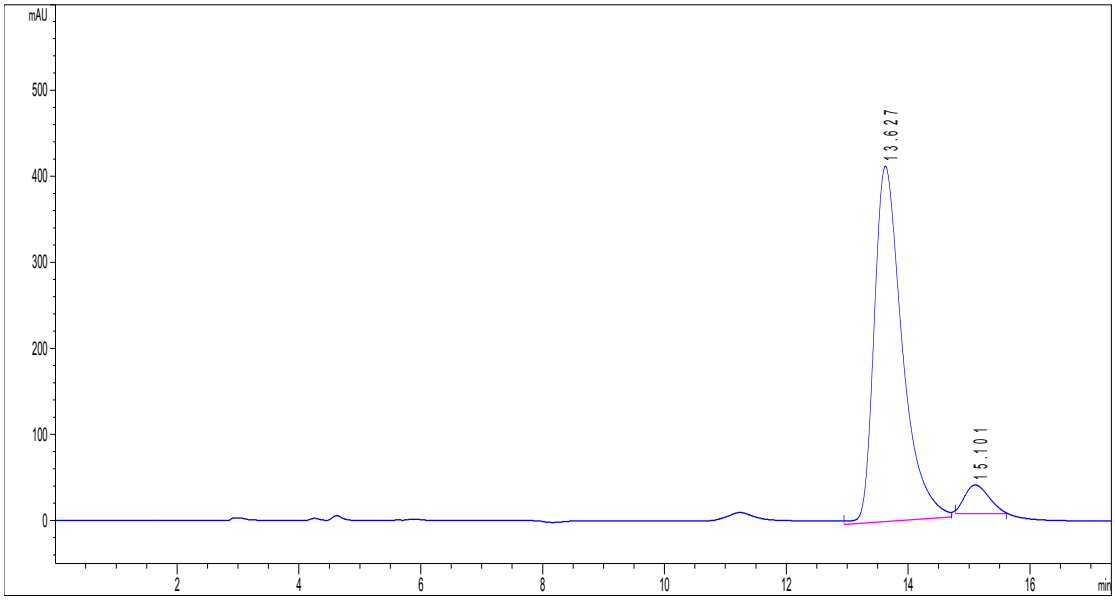


#	Time	Width	Area	Height	Area%
1	10.325	0.2512	1.28100e4	773.49530	49.3699
2	10.983	0.2811	1.31370e4	709.38373	50.6301

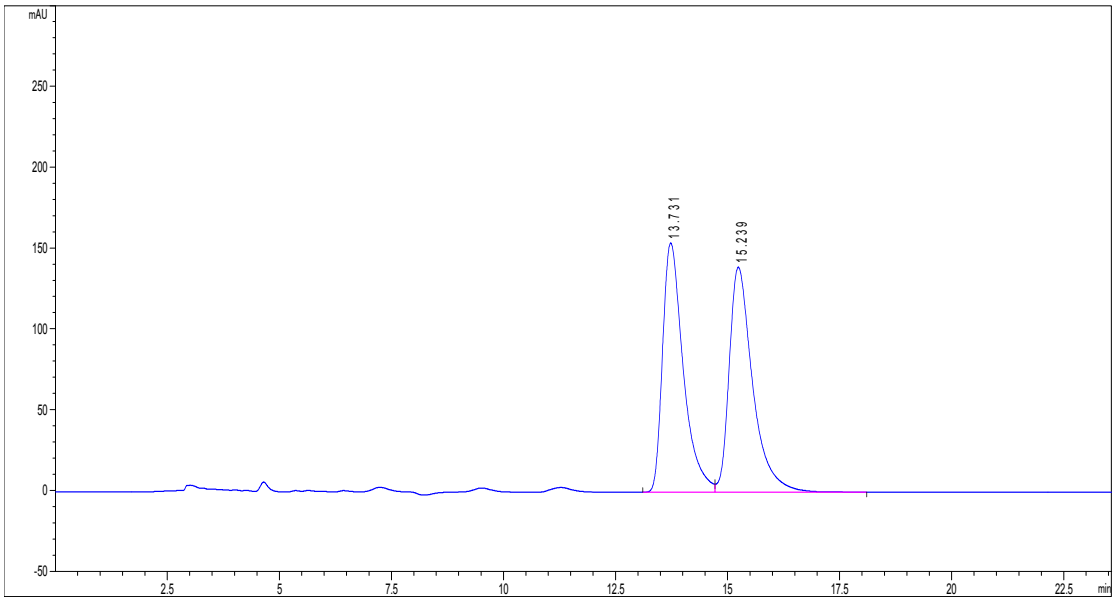


1a 3 mmol + **2a** 4.5 mmol → 0.768g, 80%yield, 87%*ee*

ChiracelAD-H; 90 : 10 / *n*-hexane/*i*-PrOH; v = 1.0 mL/min; λ = 254 nm. 87% ee



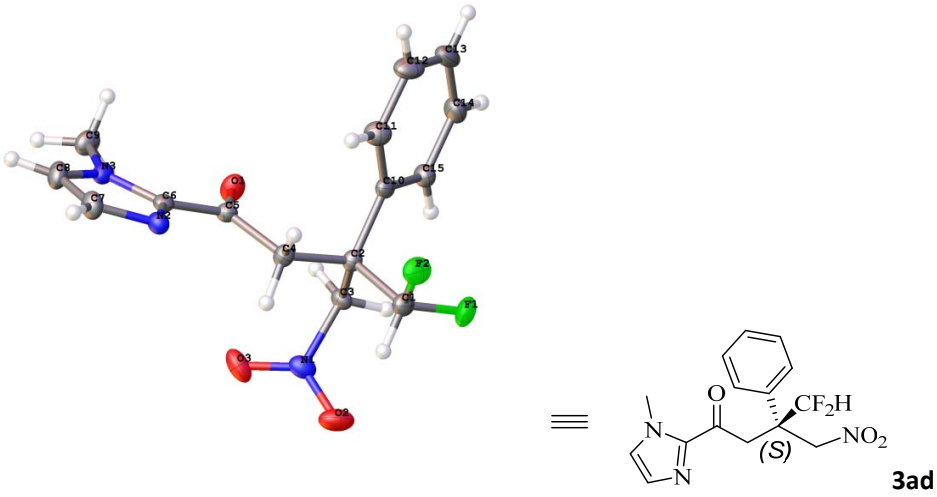
#	Time	Width	Area	Height	Area%
1	13.627	0.5326	13206.7	413.3	93.47
2	15.101	0.4607	921.9	33.4	6.525



#	Time	Width	Area	Height	Area%
1	13.731	0.4859	4957.6	154.3	49.366
2	15.239	0.5489	5085	139.3	50.634

6. The structure of 3ad

Crystallographic data of **3ab** has been deposited with the Cambridge Crystallographic Data Centre as deposition number 1575270. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK;fax: +44 1223 336033.



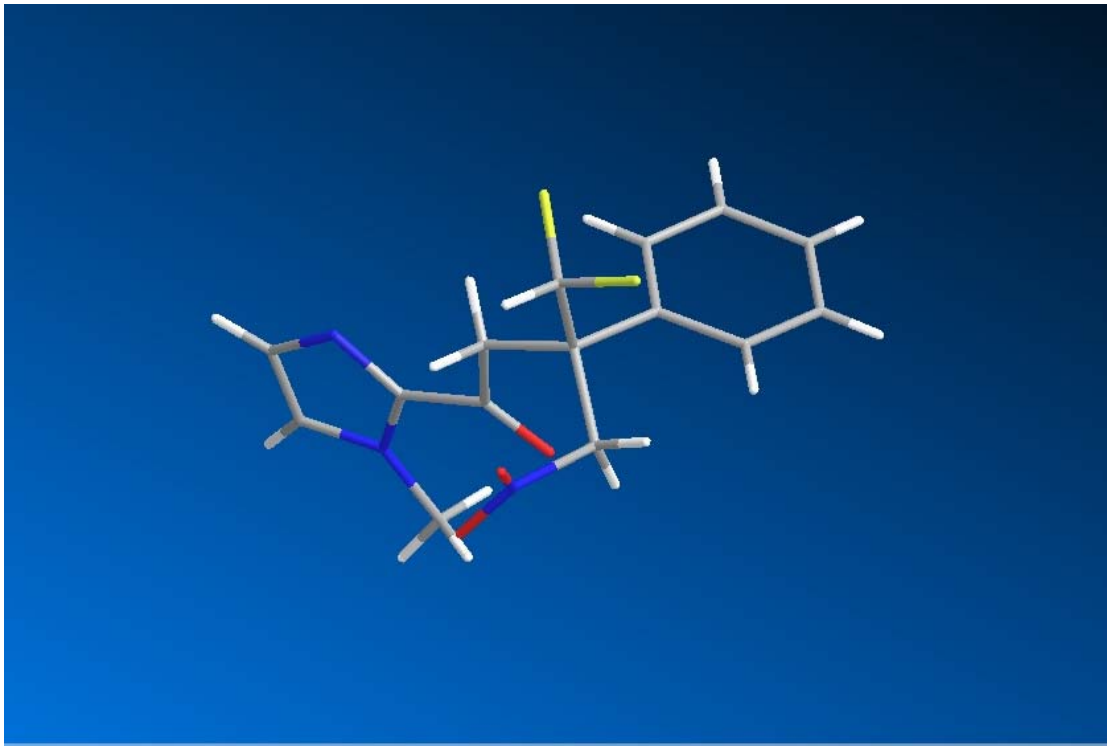


Table 1:Crystal data and structure refinement for exp_5098

Identification code	exp_5098
Empirical formula	$C_{15}H_{15}F_2N_3O_3$
Formula weight	323.30
Temperature / K	110.5
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a / Å, b / Å, c / Å	9.3745(2), 11.4530(3), 13.8901(3)
α/°, β/°, γ/°	90, 90, 90
Volume / $Å^3$	1419.34(7)
Z	4
ρ_{calc} / mg mm^{-3}	1.440
μ / mm^{-1}	1.015
F(000)	672
Crystal size / mm^3	0.400 × 0.300 × 0.250
2Θ range for data collection	10.01 to 142.064°
Index ranges	$-11 \leq h \leq 10$, $-13 \leq k \leq 14$, $-16 \leq l \leq 7$
Reflections collected	4726
Independent reflections	2805[R(int) = 0.0172 (inf-0.9Å)]
Data/restraints/parameters	2805/0/209
Goodness-of-fit on F^2	1.061
Final R indexes [I>2σ (I) i.e. F_o>4σ (F_o)]	R_1 = 0.0329, wR_2 = 0.0839
Final R indexes [all data]	R_1 = 0.0336, wR_2 = 0.0848
Largest diff. peak/hole / e $Å^{-3}$	0.175/-0.274
Flack Parameters	-0.06(7)
Completeness	0.999