Supporting Information:

Ni(II)-Catalyzed Enantioselective *α*-Hydrazination of *α*-Fluoroesters: Access to Chiral Quaternary *α*-Fluorinated *α*-Amino Acid Derivatives

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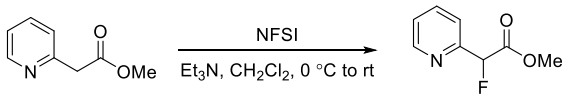
General information

^{1}H NMR spectra were recorded on Bruker Avance III HD 600 or Avance 400 MHz spectrometer. Chemical shifts are recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet; t = triplet; m = multiplet; br = broad), coupling constants (Hz), integration. ^{13}C NMR data were collected on Bruker Avance III HD 150 or Avance 100 MHz spectrometer. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. Enantiomer excesses were determined by chiral HPLC analysis on Chiralcel IA/ODH/IC/AS-H in comparison with the authentic racemates. Chiral HPLC analysis recorded on Thermo scientific Dionex Ultimate 3000 and Agilent Technologies 1260 Infinity. Optical rotations were reported as follows: $[\alpha]_D^T$ (c: g/100 mL, in solvent). Optical rotations recorded on Autopol Automatic Polarimeter. HRMS was recorded on an ABI/Sciex QStar Mass Spectrometer (ESI). EtOAc and DCM were purchased extra dry solvents. Other solvents used for work-up and purification purposes were purchased in technical grade quality and distilled by rotary evaporator before use. Single crystal X-ray crystallography data were obtained on Supernova Atlas S2 CCD detector. These ligands **L2-L17** were prepared by previous reported methods.[1-3] The preparation of fluorinated substrates was prepared according to the literature procedure reported and made some changes.

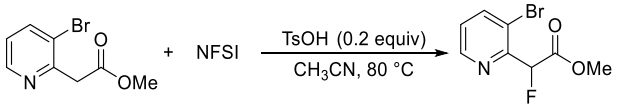
General procedures for the preparation of substrates

1a-1c, 1e-1n are known compounds.[4-9] Our modified synthesis method is as follows.



In a round-bottomed flask containing a stir bar, methyl 2-pyridylacetate (755 mg, 5.0 mmol) was dissolved in dichloromethane (30 mL), followed by triethylamine (0.15 mL, 1.0 mmol) was added. The mixture was cooled to 0 °C and then N-fluorobenzenesulfonimide (NFSI) (1.58 g, 5.0 mmol) was added. The reaction was then warmed to room temperature and stirred for 10 hours. After concentrating in vacuo, the residue was subjected to flash chromatograph on silica gel to afford 2-fluoro-2-(2-pyridyl) acetic acid methyl ester **1a**.

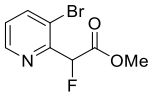
The synthesis method of substrate **1d**



S1d **1d**

In a round-bottomed flask containing a stir bar, compound **S1d** (1.15 g, 5.0 mmol), NFSI (1.89 g, 6.0 mmol), p-toluensulfonic acid (175 mg, 1.02 mmol), and acetonitrile (30 mL) were added. Then, the mixture was stirred under reflux at 80 °C for 10 hours. After that, the reaction solution was cooled to room temperature, extracted with dichloromethane for three times, washed with water and saturated sodium chloride solution. The organic phases were combined and dried with anhydrous sodium sulfate. After removing the solvent under reduced pressure, the product **1d** was obtained by column chromatography as a yellow oil.

Methyl 2-(3-bromopyridin-2-yl)-2-fluoroacetate (1d)



Yellow oil: 963.1 mg, 78% yield; R_f = 0.25 (Pet/EtOAc, 5/1, v/v).

^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 8.59 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.93 (td, *J* = 8.0, 1.6 Hz, 1H), 7.27 – 7.24 (m, 1H), 6.33 (d, *J* = 47.6 Hz, 1H), 3.86 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt) δ 167.8 (d, *J* = 26.0 Hz), 151.9 (d, *J* = 18.0 Hz), 148.5, 141.4 (d, *J*

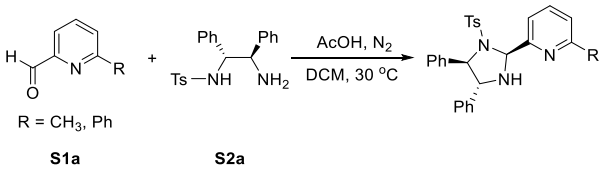
= 1.0 Hz), 126.0 (d, J = 3.0 Hz), 121.9 (d, J = 3.0 Hz), 88.5 (d, $J_{C\text{-}F}$ = 187.0 Hz), 52.9.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$, rt), δ -182.0.

HRMS (ESI): exact mass calcd for $C_8H_7Br^{79}FNNaO_2^+$ $(M+Na)^+$ requires m/z 269.9536, found m/z 269.9543 (Δ = +7 ppm), $C_8H_7Br^{81}FNNaO_2^+$ $(M+Na)^+$ requires m/z 271.9516, found m/z 271.9523 (Δ = +7 ppm).

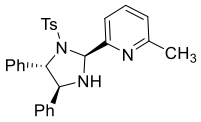
Synthesis of the ligands

Synthesis of the chiral ligand L14 and L15



In a round-bottomed flask containing a stir bar, compound **S1a** (605.7 mg, 5.0 mmol), (*R*, *R*)-TSDPEN **S2a** (1.83 g, 5.0 mmol), AcOH (429.3 μL, 7.5 mmol), and dichloromethane (50.0 mL) were added. Then, the reaction was stirred at 30 °C under N_2 for 6 h. After that, the reaction mixture was quenched by aqueous $NaHCO_3$. The organic layers were extracted with dichloromethane for 3 times, and the collected organic layers were dried over Na_2SO_4. After removing the solvent under reduced pressure, ligand **L14 and L15** could be obtained by recrystallization (recrystallization solvent: Pet/EtOAc) as a white solid.

2-((2*S*,4*S*,5*S*)-4,5-diphenyl-1-tosylimidazolidin-2-yl)-6-methylpyridine (L14)



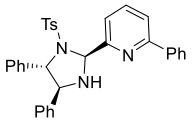
White solid, 1.7326 g, 74% yield; R_f = 0.4 (Pet/EtOAc, 1/1, v/v); m.p.: 126.4-128.5 °C; $[\alpha]_D^{24}$ = -3.27 (c = 0.535, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.34 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.23 – 7.01 (m, 12H), 5.84 (s, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.33 (d, *J* = 6.0 Hz, 1H), 2.49 (s, 3H), 2.34 (s, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 157.9, 157.4, 143.5, 140.1, 139.2, 137.0, 134.4, 129.4, 128.4, 128.2, 127.8, 127.4, 126.8, 122.9, 120.7, 78.3, 71.7, 69.5, 24.3, 21.5.

HRMS (ESI): exact mass calcd for $C_{28}H_{27}N_3NaO_2S^+$ $(M+Na)^+$ requires m/z 492.1716, found m/z 492.1724 (Δ = +8 ppm).

2-((2*S*,4*S*,5*S*)-4,5-diphenyl-1-tosylimidazolidin-2-yl)-6-phenylpyridine (L15)



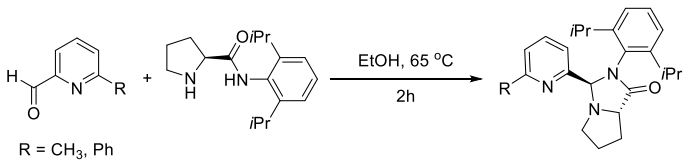
White solid, 1.844 g, 87% yield; R_f = 0.6 (Pet/EtOAc, 2/1, v/v); m.p.: 125.6-127.7 °C; $[\alpha]_D^{24}$ = 22.48 (c = 0.525, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 7.95 – 7.94 (m, 2H), 7.90 – 7.87 (m, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.44 – 7.37 (m, 5H), 7.33 – 7.16 (m, 6H), 7.11 – 7.08 (m, 4H), 5.92 (s, 1H), 4.84 (d, *J* = 5.4 Hz, 1H), 4.42 (d, *J* = 5.4 Hz, 1H), 2.34 (s, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 157.8, 156.8, 143.6, 140.3, 139.5, 138.9, 137.9, 134.8, 129.5, 129.2, 128.8, 128.6, 128.4, 127.8, 127.6, 127.4, 127.1, 127.0, 122.8, 120.3, 78.5, 71.6, 69.9, 21.6.

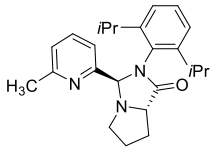
HRMS (ESI): exact mass calcd for $C_{33}H_{29}N_3NaO_2S^+$ $(M+Na)^+$ requires m/z 554.1873, found m/z 554.1866(Δ = -7 ppm).

Synthesis of the chiral ligand L16 and L17



In a round-bottomed flask containing a stir bar, 2-pyridinecarboxaldehyde **S1a** (2.4 mmol, 290.7 mg) and *L*-prolinamide **S3a** (2 mmol, 548 mg) were added. Then, anhydrous ethanol (5.0 mL) was added and the reaction was heated with stirring at 65 °C for 2 h. After that, the reaction mixture was concentrated in vacuo to remove ethanol. The residue was purified by flash column chromatography (Pet/EtOAc, 10/1-1/1, v/v) to give the **L16 and L17** ligand as a white solid.

(3*R*,7a*S*)-2-(2,6-diisopropylphenyl)-3-(6-methylpyridin-2-yl)hexahydro-1H-pyrrolo[1,2-c]imidazol-1-one (L16)



White solid, 648.9 mg, 86% yield; R_f = 0.56 (EtOAc); m.p.: 126.4-129.0 °C; $[\alpha]_D^{24}$ = -30.49 (c = 0.515, $CHCl_3$)

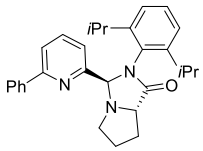
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 7.39 (t, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.16 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 5.30 (s, 1H), 4.69 (q, *J* = 4.2 Hz, 1H), 3.50 – 3.46 (m, 1H), 3.16 – 3.07 (m, 2H), 2.62 (quin, *J* = 6.6 Hz, 1H), 2.47 (s,

1H), 2.33 – 2.27 (m, 1H), 2.25 – 2.19 (m, 1H), 2.01 – 1.91 (m, 2H), 1.43 (d, *J* = 7.2 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.14 (d, *J* = 6.6 Hz, 3H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rt) δ 175.6, 159.3, 157.6, 148.5, 146.4, 136.5, 130.1, 129.0, 124.6, 123.7, 123.2, 119.4, 87.7, 65.6, 57.0, 28.8, 28.6, 28.5, 25.4, 25.3, 24.8, 23.5, 23.1.

HRMS (ESI): exact mass calcd for $C_{24}H_{31}N_3NaO^+$ $(M+Na)^+$ requires m/z 400.2359, found m/z 400.2365 (Δ = +6 ppm).

(3*R*,7a*S*)-2-(2,6-diisopropylphenyl)-3-(6-phenylpyridin-2-yl)hexahydro-1H-pyrrolo[1,2-c]imidazol-1-one (L17)



White solid, 809 mg, 92% yield; R_f = 0.52 (Pet/EtOAc, 1/1, v/v); m.p.: 145.5-148.3 °C; $[\alpha]_D^{24}$ = -26.54 (c = 0.535, $CHCl_3$)

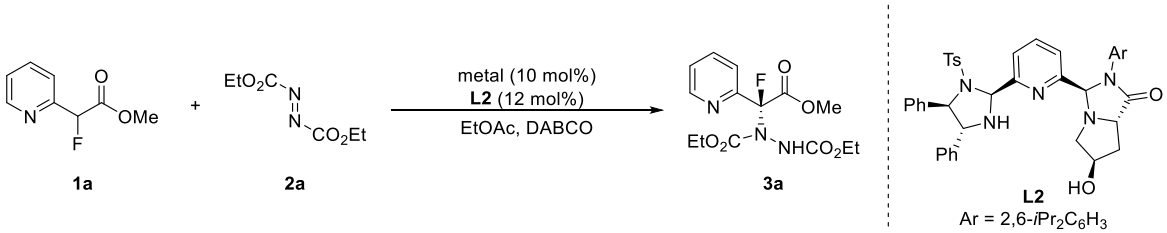
^1H NMR (600 MHz, $CDCl_3$, rt) δ 7.73 – 7.71 (m, 2H), 7.65 – 7.60 (m, 2H), 7.39 – 7.33 (m, 3H), 7.25 – 7.23 (m, 2H), 7.22 – 7.20 (m, 2H), 6.92 (dd, *J* = 7.2, 1.8 Hz, 1H), 5.44 (s, 1H), 4.66 (s, 1H), 3.46 (s, 1H), 3.18 – 3.08 (m, 2H), 2.60 – 2.53 (m, 1H), 2.35 – 2.39 (m, 1H), 2.28 – 2.22 (m, 1H), 1.99 – 1.93 (m, 2H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H), 0.02 (d, *J* = 6.6 Hz, 3H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rt) δ 157.4, 148.3, 146.5, 138.9, 137.5, 129.2, 129.1, 128.7, 127.0, 124.7, 123.7, 120.5, 120.0, 87.3, 65.6, 57.0, 29.0, 28.9, 28.8, 25.5, 25.2, 24.8, 23.6, 22.9.

HRMS (ESI): exact mass calcd for $C_{29}H_{33}N_3NaO^+$ $(M+Na)^+$ requires m/z 462.2516, found m/z 462.2520 (Δ = +4 ppm).

Optimization of the reaction conditions

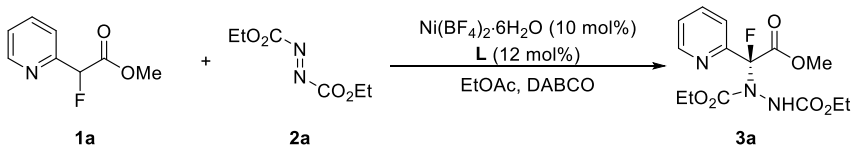
Table S1. Screening of metal[a]



entry	metal	yield (**3a**) (%)[b]	ee (**3a**) (%)[c]
1	$Fe(OTf)_2$	43	0
2	$Co(OTf)_2$	63	-13
3	$Ni(OTf)_2$	92	71
4	$Cu(OTf)_2$	93	3
5	$Zn(OTf)_2$	43	3
6	$Sc(OTf)_3$	48	0
7	$Ni(acac)_2$	32	0
8	$Ni(ClO_4)_2·6H_2O$	92	70
9	$Ni(BF_4)_2·6H_2O$	94	88

[a]Reactions were carried out with metal (10 mol%), **L2** (12 mol%), **1a** (0.05 mmol), **2a** (0.06 mmol), DABCO (1.0 equiv.) in EtOAc (1.0 mL) at 35 °C for 24 h. [b]NMR yield of **3a**. [c]The ee of **3a** was determined by chiral HPLC analysis.

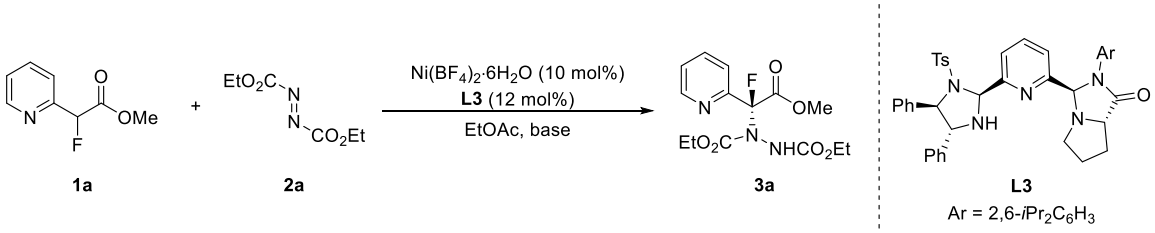
Table S2. Screening of ligand[a]



entry	ligand	yield (**3a**) (%)[b]	ee (**3a**) (%)[c]
1	**L3**	95	94
2	**L4**	82	64
3	**L5**	95	90
4	**L6**	95	-62
5	**L7**	85	5
6	**L8**	95	64

[a]Reactions were carried out with $Ni(BF_4)_2·6H_2O$ (10 mol%), **L** (10 mol%), **1a** (0.05 mmol), **2a** (0.06 mmol), DABCO (1.0 equiv.) in EtOAc (1.0 mL) at 35 °C for 24 h. [b]NMR yield of **3a**. [c]The ee of **3a** was determined by chiral HPLC analysis.

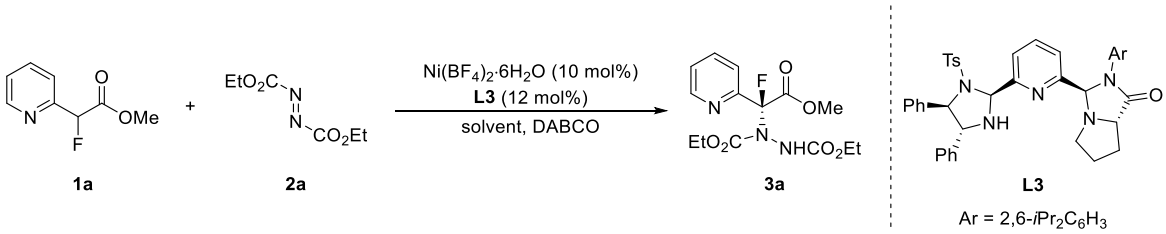
Table S3: Screening of base[a]



entry	base	x	yield (**3a**) (%)[b]	ee (**3a**) (%)[c]
1	DIPEA	1	52	92
2	Et_3N	1	40	94
3	DBU	1	-	-
4	K_2CO_3	1	84	92
5	DABCO	0.5	95	96
6	DABCO	0.25	95	98
7	DABCO	0.1	46	40
8	-	-	29	15

[a]Reactions were carried out with $Ni(BF_4)_2·6H_2O$ (10 mol%), **L3** (12 mol%), **1a** (0.05 mmol), **2a** (0.06 mmol), base (x equiv.) in EtOAc (1.0 mL) at 35 °C for 24 h. [b]NMR yield of **3a**. [c]The ee of **3a** was determined by chiral HPLC analysis.

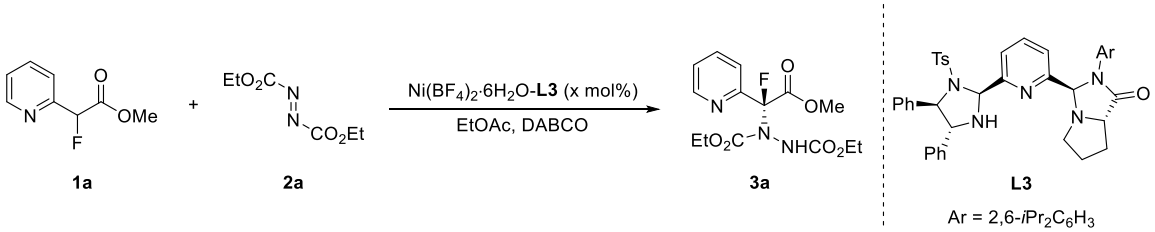
Table S4: Screening of solvent[a]



entry	slovent	yield (**3a**) (%)[b]	ee (**3a**) (%)[c]
1	DCE	58	57
2	DCM	67	77
3	THF	95	93
4	CH_3CN	95	86
5	PhMe	53	20
6	MTBE	42	62

[a]Reactions were carried out with $Ni(BF_4)_2·6H_2O$ (10 mol%), **L3** (12 mol%), **1a** (0.05 mmol), **2a** (0.06 mmol), DABCO (0.25 equiv.) in solvent (1.0 mL) at 35 °C for 24 h. [b]NMR yield of **3a**. [c]The ee of **3a** was determined by chiral HPLC analysis.

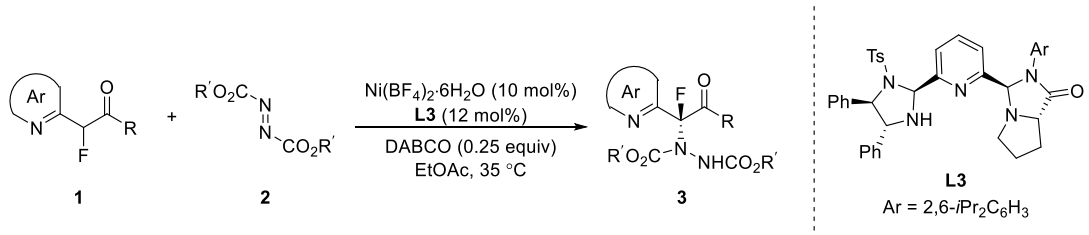
Table S5: Screening the amount of metal and ligand[a]



entry	x	yield (**3a**) (%)[b]	ee (**3a**) (%)[c]
1	5	54	55
2	2.5	55	12
3	1	33	2

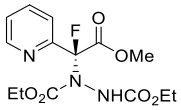
[a]Reactions were carried out with $Ni(BF_4)_2·6H_2O$ (x mol%), **L3** (1.2x mol%), **1a** (0.05 mmol), **2a** (0.06 mmol), DABCO (0.25 equiv.) in EtOAc (1.0 mL) at 35 °C. [b]NMR yield of **3a**. [c]The ee of **3a** was determined by chiral HPLC analysis.

Procedure for the catalytic reaction



In the reaction tube, a mixture of $Ni(BF_4)_2 \cdot 6H_2O$ (3.4 mg, 10 mol%), **L3** (8.9 mg, 12 mol%) and fluorinated substrate **1** (0.1 mmol) in EtOAc (2.0 mL) was stirred at 35 °C for 0.5 h. Subsequently, azodicarboxylate substrate **2** (0.12 mmol) and DABCO (2.8 mg, 0.025 mmol) were added to the reaction tube. After disappearance of fluorinated substrate (monitored by TLC, Pet/EtOAc, 1/1, v/v), product **3** was obtained by column chromatography (Pet/EtOAc, 10/1-5/1, v/v).

Diethyl (*S*)-1-(1-fluoro-2-methoxy-2-oxo-1-(pyridin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (3a)



Colorless oil, 33.3 mg, 97% yield, 98% ee; R_f = 0.29 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -14.21 (c = 1.19, $CHCl_3$); reaction time: 12 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 14.130 min (minor), 20.262 min (major).

^{1}H NMR (600 MHz, $CDCl_3$, **55** °C) δ 8.57 (d, *J* = 4.8 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.29 (dd, *J* = 8.4, 4.8 Hz, 1H), 6.82 (br, 1H), 4.31 – 4.20 (m, 2H), 4.11 – 4.03 (m, 2H), 3.78 (s, 3H), 1.30 – 1.25 (m, 3H), 1.23 – 1.15 (m, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, **55** °C) δ 165.4, 165.2, 155.3, 154.7, 153.1, 149.4, 137.6, 124.5, 122.0, 63.8, 53.5, 14.4, 14.3.

^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, **55** °C), δ -130.0, -131.6.

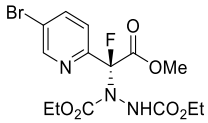
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.60 – 8.49 (m, 1H), 7.80 – 7.69 (m, 2H), 7.30 (s, 1H), 7.24 – 6.98 (m, 1H), 4.32 – 4.19 (m, 2H), 4.13 – 3.98 (m, 2H), 3.80 – 3.77 (m, 3H), 1.27 – 1.25 (m, 3H), 1.20 – 1.09 (m, 3H)

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 165.2, 155.3, 154.8, 152.5, 149.6, 149.3, 149.0, 137.7, 137.1, 124.5, 124.3, 121.9, 101.5 (d, $J_{C\text{-}F}$ = 220.0 Hz), 63.8, 62.4, 62.2, 53.7, 14.4, 14.3. (The additional peaks that appear are caused by hindered rotational isomerism.)

$^{19}F\{^{1}H\}$ NMR (565 MHz, $CDCl_3$, rt), δ -132.6, -133.7.

HRMS (ESI): exact mass calcd for $C_{14}H_{18}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 366.1072, found m/z 366.1063 (Δ = -9 ppm).

Diethyl (*S*)-1-(1-(5-bromopyridin-2-yl)-1-fluoro-2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (3b)



Colorless oil, 37.1 mg, 88% yield, 93% ee; R_f = 0.46 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{25}$ = -18.74 (c = 0.27, $CHCl_3$); reaction time: 60 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 11.382 min (minor), 16.835 min (major).

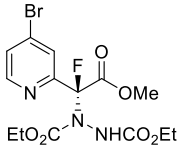
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.64 – 8.57 (m, 1H), 7.93 – 7.86 (m, 1H), 7.74 – 7.59 (m, 1H), 7.12 – 6.92 (m, 1H), 4.31 – 4.18 (m, 2H), 4.15 – 3.99 (m, 2H), 3.78 – 3.77 (m, 3H), 1.26 – 1.22 (m, 3H), 1.22 – 1.12 (m, 3H).

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, rt) δ 164.7, 155.4, 154.6, 151.2, 151.0, 150.8, 150.5, 150.1, 140.3, 139.7, 123.4, 122.0, 121.8, 101.4 (d, $J_{C\text{-}F}$ = 226.5 Hz), 64.0, 62.6, 62.4, 53.9, 53.8, 14.4, 14.2. (The additional peaks that appear are caused by hindered rotational isomerism.)

$^{19}F\{^{1}H\}$ NMR (565 MHz, $CDCl_3$, rt), δ -131.8, -132.9.

HRMS (ESI): exact mass calcd for $C_{14}H_{17}Br^{79}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 444.0177, found m/z 444.0180 (Δ = +3 ppm), $C_{14}H_{17}Br^{81}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 446.0157, found m/z 446.0161 (Δ = +4 ppm).

Diethyl (*S*)-1-(1-(4-bromopyridin-2-yl)-1-fluoro-2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (3c)



Colorless oil, 36.2 mg, 86% yield, 96% ee; R_f = 0.23 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -20.11 (c = 0.95, $CHCl_3$); reaction time: 4 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 16.667 min (minor), 27.422 min (major).

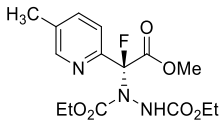
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.42 – 8.37 (m, 1H), 7.96 – 7.87 (m, 1H), 7.50 – 7.47 (m, 1H), 7.05 – 6.83 (m, 1H), 4.32 – 4.19 (m, 2H), 4.14 – 4.03 (m, 2H), 3.81 – 3.79 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.23 – 1.13 (m, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 164.6, 155.3, 154.6, 154.2, 153.9, 153.7, 150.3, 150.1, 149.7, 134.6, 133.8, 128.0, 127.7, 125.6, 101.1 (d, $J_{C\text{-}F}$ = 226.5 Hz), 64.0, 62.7, 62.5, 54.0, 53.9, 14.4, 14.3. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, rt), δ -132.1, -133.1.

HRMS (ESI): exact mass calcd for $C_{14}H_{17}Br^{79}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 444.0177, found m/z 444.0180 (Δ = +3 ppm), $C_{14}H_{17}Br^{81}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 446.0157, found m/z 446.0161 (Δ = +4 ppm)

Diethyl (*S*)-1-(1-fluoro-2-methoxy-1-(5-methylpyridin-2-yl)-2-oxoethyl)hydrazine-1,2 dicarboxylate (3e)



Colorless oil, 33.0 mg, 95% yield, 94% ee; R_f = 0.21 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -20.58 (c = 0.29, $CHCl_3$); reaction time: 16 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 12.242 min (minor), 16.553 min (major).

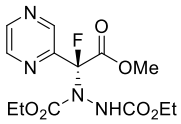
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.40 (s, 1H), 7.67 – 7.57 (m, 2H), 7.00 – 6.79 (m, 1H), 4.31 – 4.21 (m, 2H), 4.15 – 3.99 (m, 2H), 4.13 – 3.98 (m, 2H), 3.80 – 3.78 (m, 3H), 2.35 (s, 3H), 1.27 (t, *J* = 4.8 Hz, 3H), 1.20 – 1.12 (m, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 165.6, 155.3, 154.8, 150.3, 150.0, 138.1, 137.6, 134.7, 134.5, 121.5, 121.3, 63.9, 62.5, 62.3, 53.7, 18.4, 14.4, 14.3. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, rt), δ -132.3, -133.4.

HRMS (ESI): exact mass calcd for $C_{15}H_{20}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 380.1228, found m/z 380.1230 (Δ = +2 ppm).

Diethyl (*S*)-1-(1-fluoro-2-methoxy-2-oxo-1-(pyrazin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (3f)



Colorless oil, 31.0 mg, 90% yield, 97% ee; R_f = 0.13 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -7.33 (c = 0.50, $CHCl_3$); reaction time: 2 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 15.978 min (minor), 20.757 min (major).

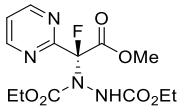
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 9.03 – 8.97 (m, 1H), 8.66 – 8.58 (m, 2H), 6.97 – 6.64 (m, 1H), 4.32 – 4.18 (m, 2H), 4.16 – 4.04 (m, 2H), 3.83 – 3.81 (m, 3H), 1.29 – 1.25 (m, 3H), 1.21 –1.15 (m, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ, 155.4, 154.5, 154.1, 145.8, 145.2, 143.8, 143.4, 64.2, 62.7, 54.0, 14.4, 14.3, 14.1. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, rt), δ -133.7, -134.6.

HRMS (ESI): exact mass calcd for $C_{13}H_{17}FN_4NaO_6^+$ $(M+Na)^+$ requires m/z 367.1024, found m/z 367.1023 (Δ = -1 ppm).

Diethyl (*S*)-1-(1-fluoro-2-methoxy-2-oxo-1-(pyrimidin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (3g)



Colorless oil, 27.5 mg, 80% yield, 89% ee; R_f = 0.37 (EtOAc); $[\alpha]_D^{25}$ = -7.07 (c = 0.53, $CHCl_3$); reaction time: 1 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 21.345 min (minor), 25.195 min (major).

^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.83 – 8.81 (m, 2H), 7.37 – 7.33 (m, 1H), 7.20 – 6.83 (m, 1H), 4.28 – 4.03 (m, 4H), 3.80 – 3.78 (m, 3H), 1.26 – 1.21 (m, 3H), 1.20 – 1.07 (m, 3H).

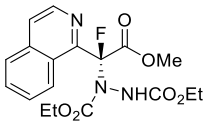
^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 164.4, 161.3, 158.0, 157.6, 155.5, 154.5, 154.0, 121.5, 121.2, 63.9, 63.6, 62.7, 62.4, 53.8, 14.3, 14.2, 14.1. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, rt), δ -126.3, -130.7, -132.5, -133.7.

HRMS (ESI): exact mass calcd for $C_{13}H_{17}FN_4NaO_6^+$ $(M+Na)^+$ requires m/z 367.1024, found m/z

367.1030 (Δ = +6 ppm).

Diethyl (*S*)-1-(1-fluoro-1-(isoquinolin-1-yl)-2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (3h)



Colorless oil, 20.4 mg, 52% yield, 90% ee; R_f = 0.55 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{25}$ = -18.32 (c = 0.48, $CHCl_3$); reaction time: 48 h; reaction temperature: 35 ºC.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 15.958 min (major), 23.458 min (minor).

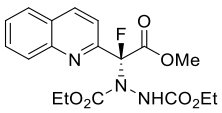
^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 8.93 – 8.62 (m, 1H), 8.43 (dd, *J* = 24.4, 5.6 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.59 (m, 3H), 6.94 – 6.57 (m, 1H), 4.37 – 3.83 (m, 7H), 1.38 – 0.81 (m, 6H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt) δ 156.6, 155.2, 140.6, 140.4, 140.3, 137.4, 136.8, 130.6, 130.4, 128.1, 127.3, 126.8, 123.2, 123.0, 63.9, 63.4, 62.3, 62.2, 53.8, 53.7, 14.5, 14.3. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$, rt), δ -116.8, -121.8.

HRMS (ESI): exact mass calcd for $C_{18}H_{20}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 416.1228, found m/z 416.1223 (Δ = -5 ppm).

Diethyl (*S*)-1-(1-fluoro-2-methoxy-2-oxo-1-(quinolin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (3i)



Colorless oil, 17.7 mg, 45% yield, 0% ee; R_f = 0.52 (Pet/EtOAc, 1/1, v/v); reaction time: 48 h; reaction temperature: 35 ºC.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 12.918 min, 18.010 min.

^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 8.24 (dd, *J* = 21.6, 13.2 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 6.87 – 6.45 (m, 1H), 4.38 – 4.11 (m, 4H), 3.83 (s, 3H), 1.31 – 1.29 (m, 3H), 1.27 – 1.24 (m, 3H).

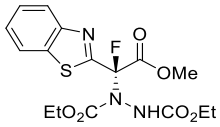
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt) δ 155.3, 154.8, 147.3, 137.8, 137.1, 130.2, 130.0, 129.9, 128.1, 128.0, 127.9, 127.8, 118.9, 64.0, 62.4, 53.8, 14.5, 14.4, 14.3. (The additional peaks that appear are caused

by hindered rotational isomerism.)

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$, rt), δ -129.9, -131.2.

HRMS (ESI): exact mass calcd for $C_{18}H_{20}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 416.1228, found m/z 416.1223 (Δ = -5 ppm).

Diethyl (*R*)-1-(1-(benzo[d]thiazol-2-yl)-1-fluoro-2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (3j)



Colorless oil, 36.3 mg, 91% yield, 23% ee; R_f = 0.55 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -1.59 (c = 0.55, $CHCl_3$); reaction time: 2 h; reaction temperature: 35 °C.

HPLC CHIRALPAK OD-H, n-hexane/2-propanol = 70/30, flow rate 1.0 mL/min, λ = 254 nm, retention time: 7.782 min (minor), 9.578 min (major).

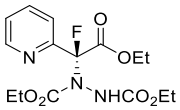
^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 8.10 – 7.98 (m, 1H), 7.93 – 7.90 (m, 1H), 7.52 – 7.42 (m, 2H), 4.38 – 4.23 (m, 2H), 4.21 – 4.05 (m, 2H), 3.89 – 3.88 (m, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.25 – 1.10 (m, 3H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, rt) δ 163.1, 155.3, 154.2, 152.9, 135.4, 126.8, 126.4, 124.3, 121.9, 121.8, 64.4, 62.9, 62.7, 54.4, 54.3, 14.4, 14.3. (The additional peaks that appear are caused by hindered rotational isomerism.)

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$, rt), δ -121.0.

HRMS (ESI): exact mass calcd for $C_{16}H_{18}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 422.0793, found m/z 422.0785 (Δ = -8 ppm).

Diethyl (*S*)-1-(2-ethoxy-1-fluoro-2-oxo-1-(pyridin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (3k)



Colorless oil, 28.6 mg, 80% yield, 98% ee; R_f = 0.18 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -16.13 (c = 0.50, $CHCl_3$); reaction time: 12 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 12.725 min (minor), 19.068 min (major).

^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.58 (d, *J* = 4.8 Hz, 1H), 7.80 – 7.68 (m, 2H), 7.30 (dd, *J* = 9.0, 4.8 Hz,

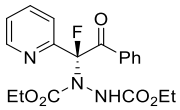
1H), 7.00 – 6.75 (m, 1H), 4.28 – 4.19 (m, 4H), 4.13 – 3.96 (m, 2H), 1.26 – 1.09 (m, 9H).

$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, rt) δ 164.5, 164.3,155.2, 154.7, 152.9, 152.6, 149.6, 149.3, 148.9, 137.5, 136.9, 124.4, 124.2, 121.9, 121.7, 101.5 (d, $J_{C\text{-}F}$ = 226.5 Hz), 63.7, 63.0, 62.9, 62.4, 62.1, 14.4, 14.3, 14.2, 13.8. (The additional peaks that appear are caused by hindered rotational isomerism.)

$^{19}F\{^{1}H\}$ NMR (565 MHz, $CDCl_3$, rt), δ -132.4, -133.6.

HRMS (ESI): exact mass calcd for $C_{15}H_{20}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 380.1228, found m/z 380.1233 (Δ = +5 ppm).

Diethyl (*S*)-1-(1-fluoro-2-oxo-2-phenyl-1-(pyridin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (3l)



Colorless oil, 37.4 mg, 96% yield, 57% ee; R_f = 0.55 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -2.42 (c = 0.75, $CHCl_3$); reaction time: 3 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 60/40, flow rate 1.0 mL/min, λ = 254 nm, retention time: 8.963 min (minor), 12.687 min (major).

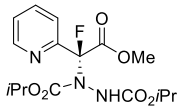
^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 8.60 (dd, *J* = 18.8, 4.8 Hz, 1H), 8.17 (dd, *J* = 79.6, 7.2 Hz, 2H), 7.83 – 7.69 (m, 2H), 750 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.29 (m, 1H), 6.85 – 6.52 (m, 1H), 4.23 – 4.06 (m, 4H), 1.35 – 1.24 (m, 3H), 1.17 (t, *J* = 7.2 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, rt) δ 155.6, 155.0, 149.3, 148.9, 137.6, 137.1, 134.5, 133.2, 133.0, 130.2, 128.3, 124.4, 122.6, 63.9, 62.6, 62.3, 14.5, 14.2. (The additional peaks that appear are caused by hindered rotational isomerism.)

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$, rt), δ -120.6, -125.5, -127.0.

HRMS (ESI): exact mass calcd for $C_{19}H_{20}FN_3NaO_5^+$ $(M+Na)^+$ requires m/z 412.1279, found m/z 412.1269 (Δ = -10 ppm).

Diisopropyl (*S*)-1-(1-fluoro-2-methoxy-2-oxo-1-(pyridin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (3m)



Colorless oil, 35.6 mg, 96% yield, 98% ee; R_f = 0.24 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -13.90 (c = 0.77,

$CHCl_3$); reaction time: 16 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 11.113 min (minor), 15.112 min (major).

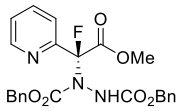
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.61 – 8.59 (m, 1H), 7.81 – 7.68 (m, 2H), 7.32 – 7.28 (m, 1H), 6.81 – 6.57 (m, 1H), 5.04 – 4.94 (m, 1H), 4.88 – 4.80 (m, 1H), 3.79 (s, 3H), 1.26 – 1.24 (m, 6H), 1.22 – 1.00 (m, 6H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 165.5, 154.9, 154.3, 152.8, 149.8, 149.4, 149.0, 137.7, 137.6, 137.0, 124.6, 124.5, 124.2, 122.0, 121.7, 72.2, 70.5, 70.1, 53.7, 22.0, 21.9, 21.8, 21.7. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, rt), δ -127.8, -130.2, -132.1, -132.8.

HRMS (ESI): exact mass calcd for $C_{16}H_{22}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 394.1385, found m/z 394.1380 (Δ = -5 ppm).

Dibenzyl (*S*)-1-(1-fluoro-2-methoxy-2-oxo-1-(pyridin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (3n)



Colorless oil, 30.4 mg, 65% yield, 93% ee; R_f = 0.26 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -10.06 (c = 0.54, $CHCl_3$); reaction time: 24 h; reaction temperature: 30 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, λ = 254 nm, retention time: 25.053 min (minor), 32.047 min (major).

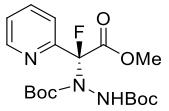
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.62 – 8.52 (m, 1H), 7.78 – 7.52 (m, 2H), 7.33 – 7.27 (m, 9H), 7.14 (d, *J* = 9.6 Hz, 1H), 7.03 – 6.75 (m, 1H), 5.30 – 4.95 (m, 4H), 3.71 – 3.66 (m, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 165.2, 165.0, 155.2, 154.7, 152.6, 149.7, 149.5, 149.1, 137.7, 137.0, 135.5, 134.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 124.6, 124.4, 122.0, 121.8, 69.5, 69.3, 68.0, 67.9, 53.8, 53.7. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$, rt), δ -131.6, -132.4.

HRMS (ESI): exact mass calcd for $C_{24}H_{22}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 490.1385, found m/z 490.1379 (Δ = -6 ppm).

Di-tert-butyl (*S*)-1-(1-fluoro-2-methoxy-2-oxo-1-(pyridin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (3o)



White solid, 20.4 mg, 51% yield, 91% ee; R_f = 0.43 (Pet/EtOAc, 1/1, v/v); m.p.: 123.6-125.3 °C; $[\alpha]_D^{25}$ = -5.23 (c = 0.65, $CHCl_3$); reaction time: 36 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, λ = 254 nm, retention time: 25.178 min (minor), 31.147 min (major).

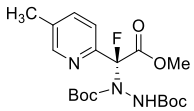
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.65 – 8.61 (m, 1H), 7.81 – 7.69 (m, 2H), 7.33 – 7.28 (m, 1H), 6.51 – 6.21 (m, 1H), 3.80 (s, 3H), 1.50 – 1.34 (m, 18H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 154.3, 153.4, 149.8, 149.4, 149.0, 137.6, 137.4, 137.0, 124.5, 124.4, 124.1, 122.0, 121.6, 84.0, 82.1, 81.6, 53.7, 53.6, 28.1, 28.0, 27.8. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$, rt), δ -126.1, -129.5, -131.7, -132.6.

HRMS (ESI): exact mass calcd for $C_{16}H_{22}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 422.1698, found m/z 422.1693 (Δ = -5 ppm).

Di-tert-butyl (*S*)-1-(1-fluoro-2-methoxy-1-(5-methylpyridin-2-yl)-2-oxoethyl)hydrazine-1,2-dicarboxylate (3p)



Colorless oil, 30.6 mg, 74% yield, 90% ee; R_f = 0.37 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{25}$ = -8.68 (c = 0.38, $CHCl_3$); reaction time: 24 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IC, n-hexane/2-propanol = 60/40, flow rate 1.0 mL/min, λ = 254 nm, retention time: 8.535 min (minor), 18.317 min (major).

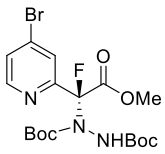
^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 8.46 – 8.43 (m, 1H), 7.68 – 7.52 (m, 2H), 6.49 – 6.42 (m, 1H), 3.80 (s, 3H), 2.36 (s, 3H), 1.50 – 1.35 (m, 18H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt) δ 154.3, 150.4, 149.9, 149.3, 138.0, 137.9, 137.4, 134.5, 134.2, 121.6, 121.0, 119.4, 83.9, 82.0, 81.5, 53.6, 53.5, 28.1, 28.0, 27.9, 18.4, 18.3. (The additional peaks that appear are caused by hindered rotational isomerism.)

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$, rt), δ -126.1, -129.4, -131.5, -132.5.

HRMS (ESI): exact mass calcd for $C_{19}H_{28}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 436.1854, found m/z 436.1857 (Δ = +3 ppm).

Di-tert-butyl (*S*)-1-(1-(4-bromopyridin-2-yl)-1-fluoro-2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (3q)



White solid, 32.4 mg, 68% yield, 85% ee; R_f = 0.45 (Pet/EtOAc, 1/1, v/v); m.p.: 159.9.2-162.7 °C; $[\alpha]_D^{25}$ = -9.37 (c = 0.82, $CHCl_3$); reaction time: 24 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IC, n-hexane/2-propanol = 60/40, flow rate 1.0 mL/min, λ = 254 nm, retention time: 6.833 min (minor), 10.962 min (major).

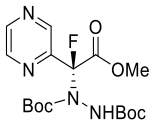
^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 8.44 (dd, *J* = 11.6, 6.4 Hz, 1H), 8.03 – 7.89 (m, 1H), 7.51 – 7.49 (m, 1H), 6.50 – 6.17 (m, 1H), 3.82 (s, 3H), 1.49 – 1.37 (m, 18H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, rt) δ 154.4, 150.6, 150.4, 150.0, 149.6, 134.3, 133.7, 127.9, 127.6, 125.7, 125.3, 84.3, 82.0, 53.9, 53.8, 28.1, 28.0, 27.9. (The additional peaks that appear are caused by hindered rotational isomerism.)

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$, rt), δ -124.6, -128.0, -130.7, -131.6.

HRMS (ESI): exact mass calcd for $C_{18}H_{25}Br^{79}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 500.0803, found m/z 500.0804 (Δ = +1 ppm), $C_{18}H_{25}Br^{81}FN_3NaO_6^+$ $(M+Na)^+$ requires m/z 502.0783, found m/z 502.0786 (Δ = +3 ppm).

Di-tert-butyl (*S*)-1-(1-fluoro-2-methoxy-2-oxo-1-(pyrazin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (3r)



Colorless oil, 27.6 mg, 69% yield, 71% ee; R_f = 0.32 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{25}$ = -3.05 (c = 0.54, $CHCl_3$); reaction time: 24 h; reaction temperature: 35 °C.

HPLC CHIRALPAK IC, n-hexane/2-propanol = 60/40, flow rate 1.0 mL/min, λ = 254 nm, retention

time: 8.420 min (minor), 13.728 min (major).

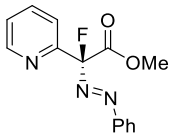
^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 9.02 (d, *J* = 22.8 Hz, 1H), 8.65 – 8.58 (m, 2H), 6.50 – 6.16 (m, 1H), 3.84 – 3.82 (m, 3H), 1.56 – 1.38 (m, 18H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt) δ 154.5, 145.6, 145.5, 145.0, 143.9, 143.6, 143.3, 84.6, 82.3, 54.0, 53.9, 28.1, 28.0, 27.9. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$, rt), δ -126.8, -129.4, -132.8, -133.7.

HRMS (ESI): exact mass calcd for $C_{17}H_{25}FN_4NaO_6^+$ $(M+Na)^+$ requires m/z 423.1650, found m/z 423.1657 (Δ = +7 ppm).

methyl (*S*, *E*)-2-fluoro-2-(phenyldiazenyl)-2-(pyridin-2-yl)acetate (3s)



Yellow oil, 10.1 mg, 40% yield, 0% ee; R_f = 0.61 (Pet/EtOAc, 1/1, v/v); reaction time: 48 h; reaction temperature: 35 °C.

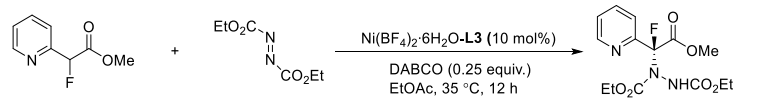
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.71 (d, *J* = 4.8 Hz, 1H), 7.89 – 7.87 (m, 2H), 7.80 (td, *J* = 7.8, 1.8 Hz, 1H), 7.63 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.54 – 7.48 (m, 3H), 7.38 – 7.35 (m, 1H), 3.91 (s, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 165.9 (d, *J* = 30.0 Hz), 153.9 (d, *J* = 25.5 Hz), 151.3, 149.7, 137.2, 132.7, 129.3, 124.7, 123.6, 122.0, 108.0 (d, $J_{C\text{-}F}$ = 219.0 Hz), 53.7.

^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, rt), δ -136.3.

HRMS (ESI): exact mass calcd for $C_{14}H_{12}FN_3NaO_2^+$ $(M+Na)^+$ requires m/z 296.0806, found m/z 296.0808 (Δ = +2 ppm).

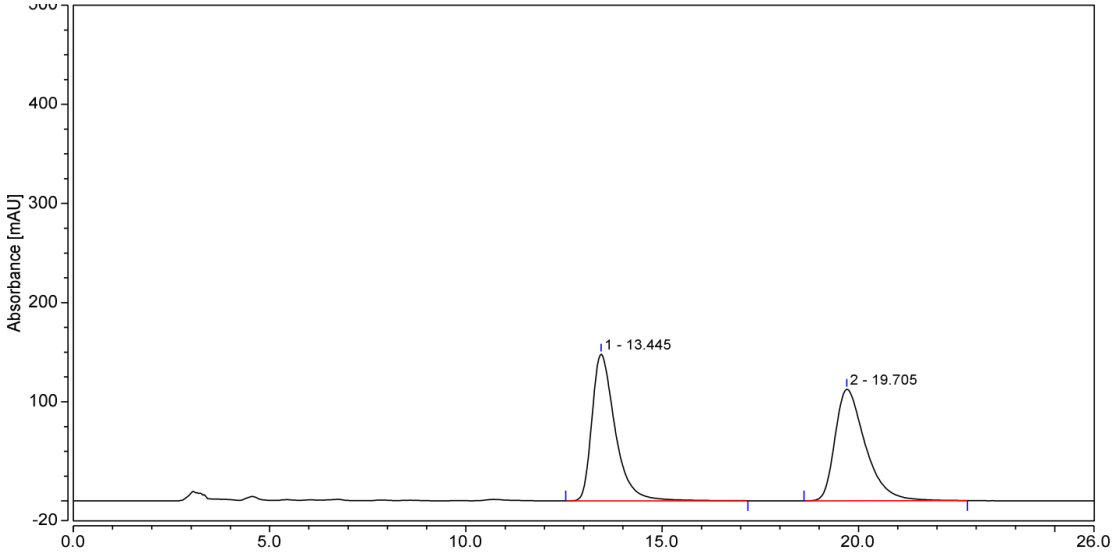
Gram-scale synthesis of 3a



In a dry reaction tube, a mixture of methyl 2-fluoro-2-(pyridin-2-yl)acetate **1a** (588.2 mg, 3.5 mmol), $Ni(BF_4)_2{\cdot}6H_2O$ (119 mg, 0.35 mmol, 10 mol%) and **L3** (310.8 mg, 0.42 mmol, 12 mol%) in EtOAc (70.0 mL) were stirred at 35 ºC for 12 h. After that, diethyl azodicarboxylate **2a** (731.1 mg, 4.2 mmol) and DABCO (98.2 mg, 0.875 mmol) were added. Subsequently, the reaction was stirred at 35 ºC for 12 h. After the reaction was complete monitored by TLC (R_f = 0.29, Pet/EtOAc, 1/1, v/v), the reaction was purified by flash column chromatography (Pet/EtOAc, 10/1-5/1, v/v) to give the product **3a** as a colorless oli (1.063 g, 89% yield, 98% ee).

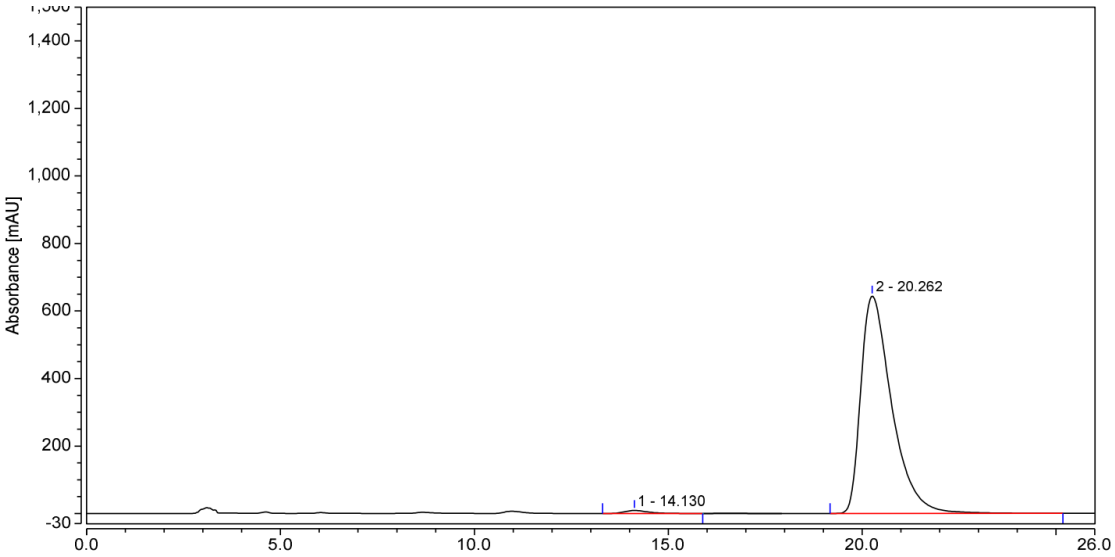
Figure S1. HPLC spectra of **3a** on a gram-scale

HPLC Spectrum of **3a**



Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	13.445	101.402	147.973	50.18	56.82
2	19.705	100.670	112.447	49.82	43.18
Total		**202.072**	**260.421**	**100.00**	**100.00**

HPLC Spectrum of **3a**



Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	14.130	6.603	9.055	1.10	1.39
2	20.262	595.819	644.175	98.90	98.61
Total:		**602.423**	**653.229**	**100.00**	**100.00**

Nonlinear effect experiment

Nonlinear effect experiment between the ee value of ligand **L3** and product **3a**

a) Preparation of ligand **L3** solution: in a 5.0 mL volumetric flask, **L3** (44.4 mg, 0.1 mmol) was added, then EtOAc was added to make the total volume up to 5.0 mL.

b) Preparation of catalyst *ent*-**L3** solution: in a 5.0 mL volumetric flask, *ent*-**L3** (44.4 mg, 0.1 mmol) was added, then EtOAc was added to make the total volume up to 5.0 mL.

For 0% ee of **L3**: 250 μL **L3** was mixed with 250 μL *ent*-**L3**;

For 20% ee of **L3**: 300 μL **L3** was mixed with 200 μL *ent*-**L3**;

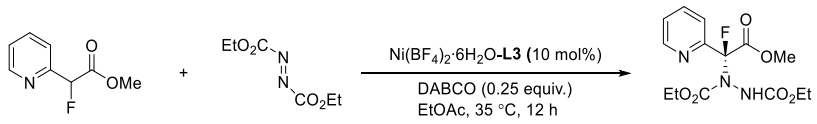
For 40% ee of **L3**: 350 μL **L3** was mixed with 150 μL *ent*-**L3**;

For 60% ee of **L3**: 400 μL **L3** was mixed with 100 μL *ent*-**L3**;

For 80% ee of **L3**: 450 μL **L3** was mixed with 50 μL *ent*-**L3**;

In a dry reaction tube, 10 mol% of $Ni(BF_4)_2{\cdot}6H_2O$ solution and 12 mol% of **L3** (0-99% ee) solution were added. Then, methyl 2-fluoro-2-(pyridin-2-yl)acetate **1a** (16.9 mg, 0.1 mmol) and EtOAc (1.5 mL) were added and the reaction was stirred at 35 °C for 0.5 h. Subsequently, diethyl azodicarboxylate **2a** (20.9 mg, 0.1 mmol) and DABCO (2.8 mg, 0.025 mmol) were added and the reaction was stirred at 35 °C until **1a** was consumed (detected by TLC, Pet/EtOAc, 1/1, v/v). Finally, the corresponding product **3a** was purified directly by flask column chromatography (Pet/EtOAc, 10/1-5/1, v/v).

Table S6: the ee value of ligand **L3** and product **3a**



1a **2a** **3a**

entry	ee of **L3** (%)	ee **(3a)** (%)
1	0	0
2	20	24
3	40	40
4	60	63
5	80	79
6	>99	98

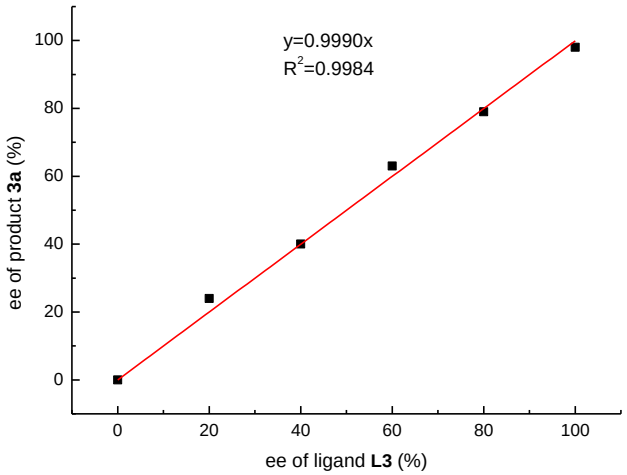
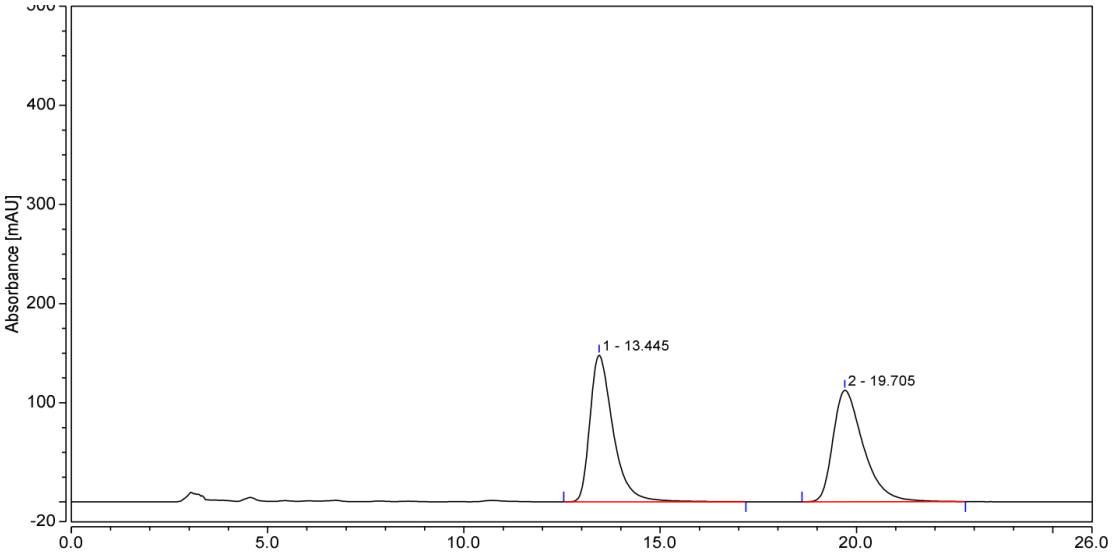


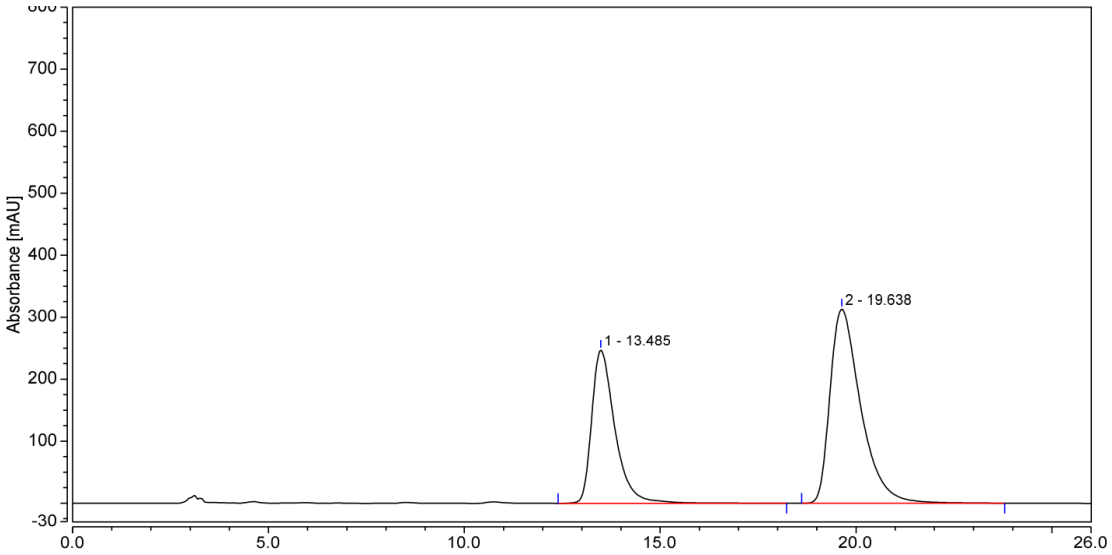
Figure S2. Determination of the linearity between ee values of ligand **L3** and product **3a**.

In the presence of ligand **L3** with 0% ee



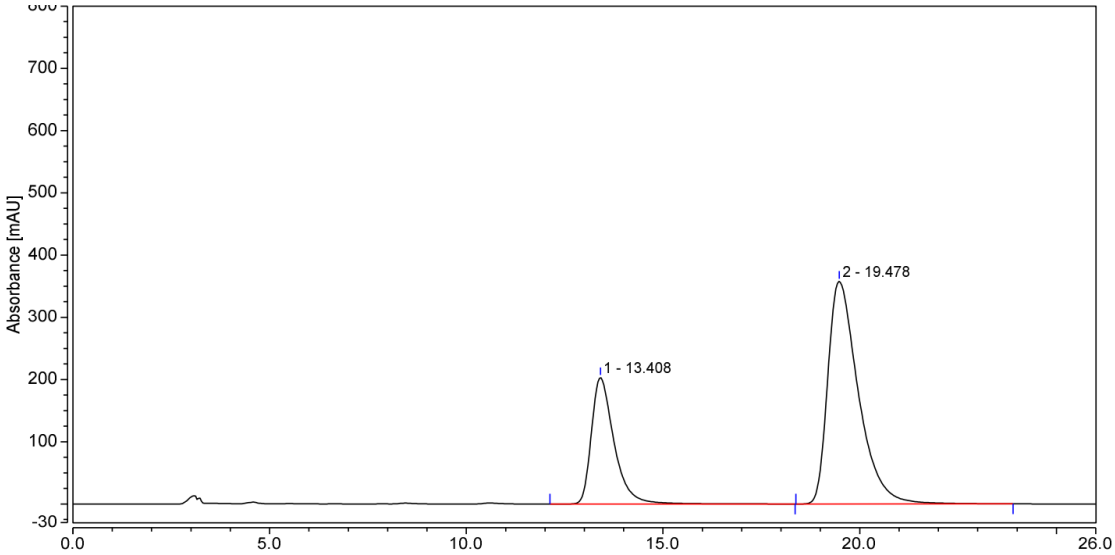
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	13.445	101.402	147.973	50.18	56.82
2	19.705	100.670	112.447	49.82	43.18
Total		**202.072**	**260.421**	**100.00**	**100.00**

In the presence of ligand **L3** with 20% ee



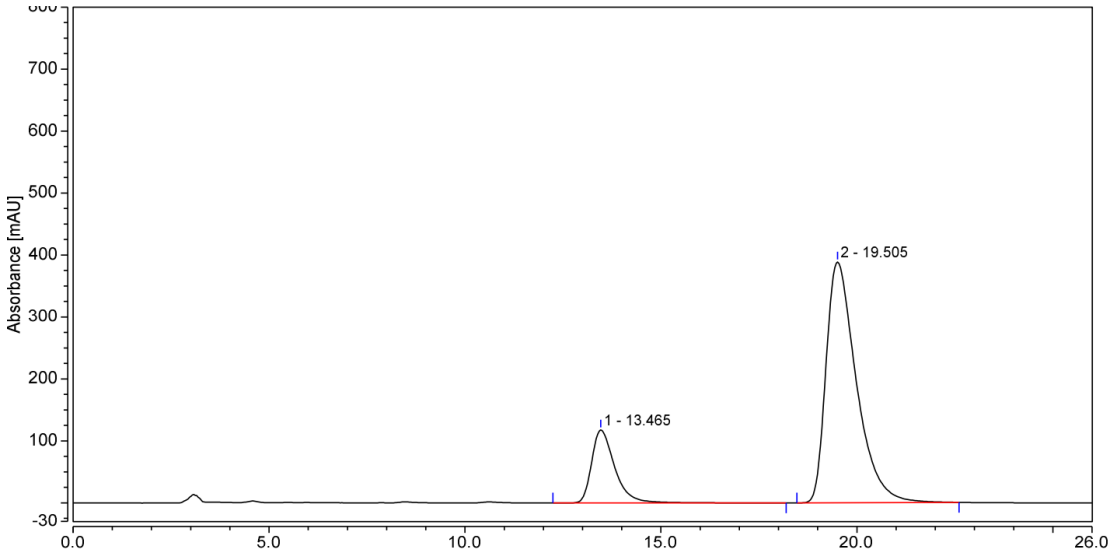
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	13.485	170.732	247.022	37.53	44.09
2	19.638	284.238	313.254	62.47	55.91
Total		**454.970**	**560.276**	**100.00**	**100.00**

In the presence of ligand **L3** with 40% ee



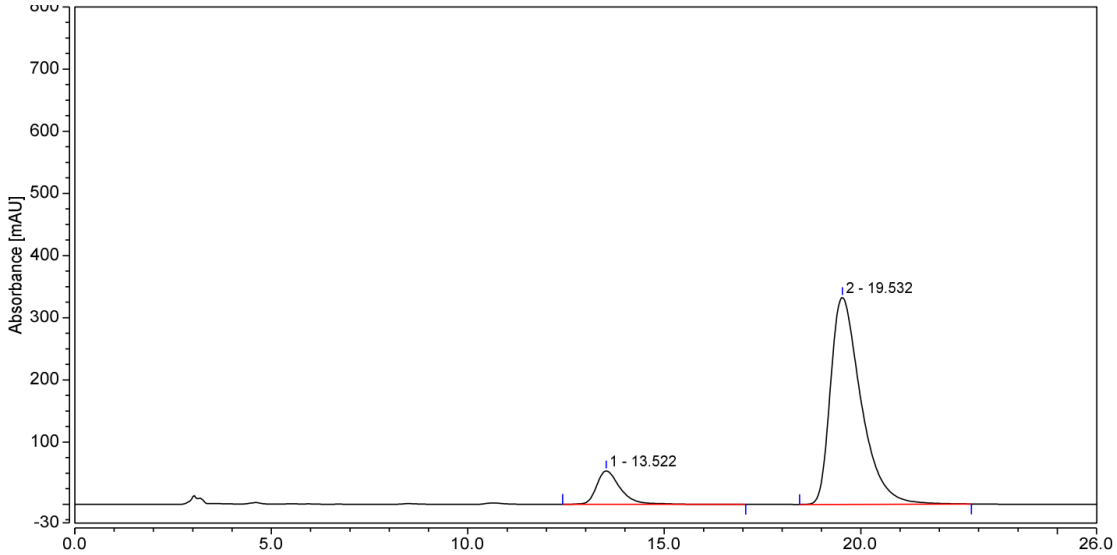
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	13.408	136.667	203.133	29.81	36.22
2	19.478	321.802	357.652	70.19	63.78
Total		**458.469**	**560.785**	**100.00**	**100.00**

In the presence of ligand **L3** with 60% ee



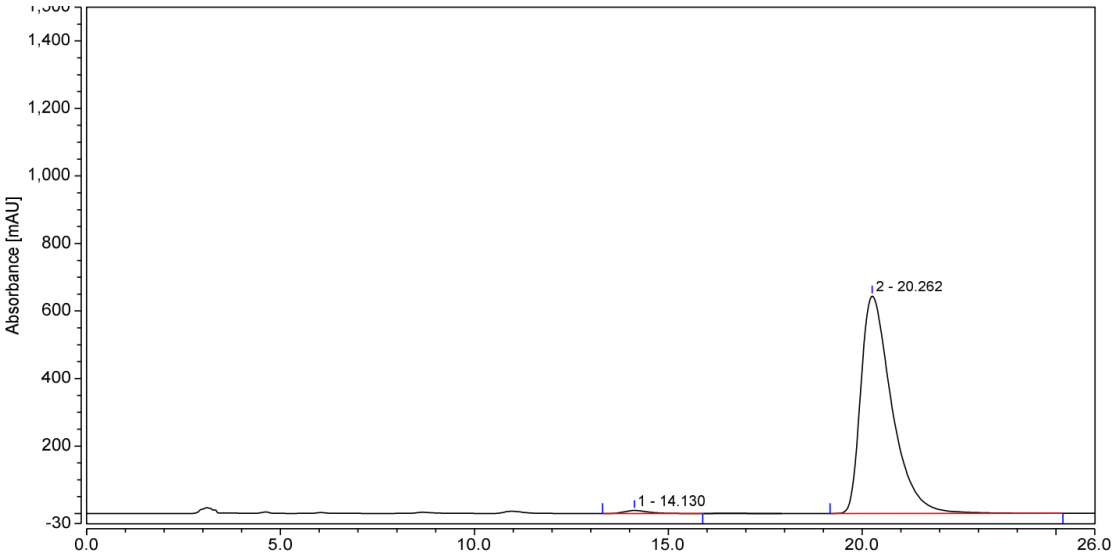
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	13.465	80.726	117.771	18.83	23.25
2	19.505	347.952	388.686	81.17	76.75
Total		**428.677**	**506.457**	**100.00**	**100.00**

In the presence of ligand **L3** with 80% ee



Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	13.522	37.897	53.889	11.24	13.94
2	19.532	299.144	332.744	88.76	86.06
Total		**337.041**	**386.633**	**100.00**	**100.00**

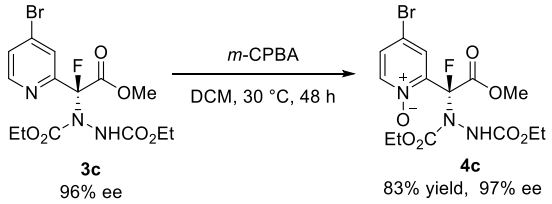
In the presence of ligand **L3** with >99% ee



Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	14.130	6.603	9.055	1.10	1.39
2	20.262	595.819	644.175	98.90	98.61
Total:		**602.423**	**653.229**	**100.00**	**100.00**

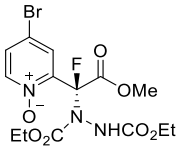
Figure S3. HPLC of **3a** with different ee value of ligand **L3**

Transformation of the product 3c



In the reaction tube, *m*-CPBA (40.6 mg, 0.2 mmol) and **3c** (42.2 mg, 0.1 mmol) were added to DCM (2.0 mL). Then, the mixture was stirred for 48 h at 30 °C until **3c** was consumed (monitored by TLC). After the reaction, the reaction solution was quenched with saturated sodium carbonate solution, extracted with dichloromethane. The organic phases were combined, dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. Finally, the corresponding product **4c** (36.3 mg, 83% yield, 97% ee) was purified directly by flask column chromatography (Pet/EtOAc, 5/1-1/1, v/v) as a colorless oil.

(*S*)-2-(1-(1,2-bis(ethoxycarbonyl)hydrazineyl)-1-fluoro-2-methoxy-2-oxoethyl)-4-bromopyridine 1-oxide (4c)



Colorless oil, 36.3 mg, 83% yield, 97% ee; R_f = 0.1 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -6.08 (c = 0.57, $CHCl_3$); reaction time: 48 h; reaction temperature: 30 °C.

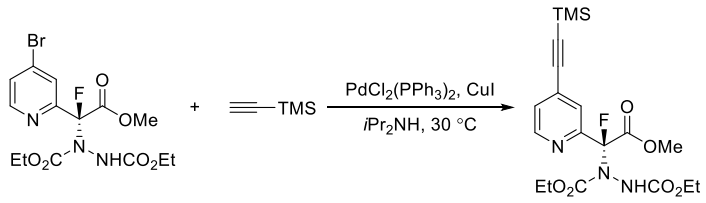
HPLC CHIRALPAK AS-H, n-hexane/2-propanol = 70/30, flow rate 1.0 mL/min, λ = 254 nm, retention time: 21.127 min (major), 32.918 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 8.03 – 7.89 (m, 2H), 7.49 – 7.35 (m, 2H), 4.35 – 4.22 (m, 2H), 4.14 – 4.01 (m, 2H), 3.81 (s, 3H), 1.29, (t, *J* = 7.2 Hz, 3H), 1.17 – 1.11 (m, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rt) δ 162.5, 161.7, 150.9, 150.8, 145.8, 145.5, 140.5, 140.0, 130.6, 130.2, 130.0, 128.5, 127.9, 119.8, 117.8, 64.9, 63.8, 63.7, 62.5, 53.9, 14.6, 14.5, 14.3, 14.1, 14.0. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$, rt) δ -122.6, -124.1, -125.7, -126.8.

HRMS (ESI): exact mass calcd for $C_{14}H_{17}Br^{79}FN_3NaO_7^+$ $(M+Na)^+$ requires m/z 460.0126, found m/z 460.0129 (Δ = +3 ppm), $C_{14}H_{17}Br^{81}FN_3NaO_7^+$ $(M+Na)^+$ requires m/z 462.0106, found m/z 462.0111 (Δ = +5 ppm)

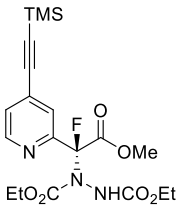


3c
96% ee

5c
54% yield, 92% ee

Diphenyl phosphorus palladium dichloride (1.7 mg, 2.5 mol%), cuprous iodide (0.5 mg, 2.5 mol%) and **3c** (42.2 mg, 0.1 mmol) were added into a reaction tube, *i*Pr$_2$Et was added under nitrogen condition, then trimethylsilyl acetylene was added and reacted overnight under nitrogen. The reaction solution was quenched with water and extracted with dichloromethane. The organic phases were combined, dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. Finally, the corresponding product **5c** (23.7 mg, 54% yield, 92% ee) was purified directly by flask column chromatography (Pet/EtOAc, 10/1-2/1, v/v) as a colorless oil.

Diethyl (*S*)-1-(1-fluoro-2-methoxy-2-oxo-1-(4-((trimethylsilyl)ethynyl)pyridin-2-yl)ethyl)hydrazine-1,2-dicarboxylate (5c)



Colorless oil, 23.6 mg, 54% yield, 92% ee; R_f = 0.5 (Pet/EtOAc, 1/1, v/v); $[\alpha]_D^{24}$ = -4.29 (c = 0.73, $CHCl_3$); reaction time: 12 h; reaction temperature: 30 ºC.

HPLC CHIRALPAK IA, n-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, λ = 254 nm, retention time: 22.515 min (minor), 26.527 min (major).

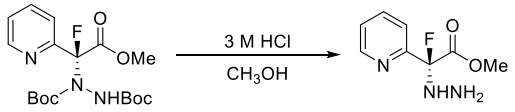
^{1}H NMR (600 MHz, $CDCl_3$, rt) δ 8.58 (dd, *J* = 31.8, 4.8 Hz, 1H), 7.81 – 7.73 (m, 1H), 7.33 (dd, *J* = 5.4, 3.6 Hz, 1H), 4.34 – 4.05 (m, 4H), 3.83 – 3.81 (m, 3H), 1.30 – 1.27 (m, 4H), 1.18 – 1.17 (m, 2H), 0.26 – 0.25 (m, 9H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, rt) δ 186.0, 183.5, 156.0, 155.3, 155.2, 154.7, 150.0, 133.3, 101.7 (d, *J* = 118.5 Hz), 64.1, 63.9, 62.5, 53.9, 32.1, 29.8, 14.5, 0.13, 0.28. (The additional peaks that appear are caused by hindered rotational isomerism.)

^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, rt) δ -132.3, -133.5.

HRMS (ESI): exact mass calcd for $C_{19}H_{26}FN_3NaO_6Si^+$ $(M+Na)^+$ requires m/z 462.1467, found m/z 462.1475 (Δ = +8 ppm).

Transformation of the product 3o

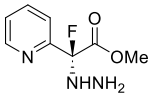


3o **6o**

95% yield

In a dry reaction tube, **3o** (39.9 mg, 0.1 mmol) was dissolved in 1.0 mL methanol, subsequently, 3 M HCl (1.0 mL) was added to the solution and stirred overnight at room temperature. The product **6o** was obtained by evaporating the solvent.

Methyl 2-fluoro-2-hydrazineyl-2-(pyridin-2-yl)acetate (6o)



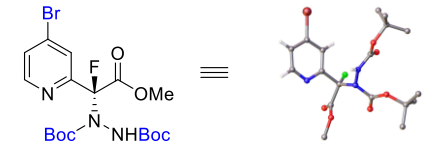
^{1}H NMR (600 MHz, DMSO-d^6, rt) δ 10.85 (br, 2H), 8.72 (d, J = 5.4 Hz, 1H), 8.50 (t, J = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.85 (t, J = 7.2Hz, 1H), 3.83 (s, 3H), 3.78 – 3.69 (m, 1H).

^{13}C{^{1}H} NMR (150 MHz, DMSO-d^6, rt) δ 161.0, 148.2, 145.6, 141.0, 124.6 (d, $J_{C\text{-}F}$ = 183.0 Hz), 118.0, 52.0.

^{19}F{^{1}H} NMR (565 MHz, DMSO-d^6, rt) δ -139.6, -147.6, -148.2, -148.3.

X-ray data of 3q

Figure S4. X-Ray crystal structure of **3q** (Recrystallization solvent: EtOAc/Pet).

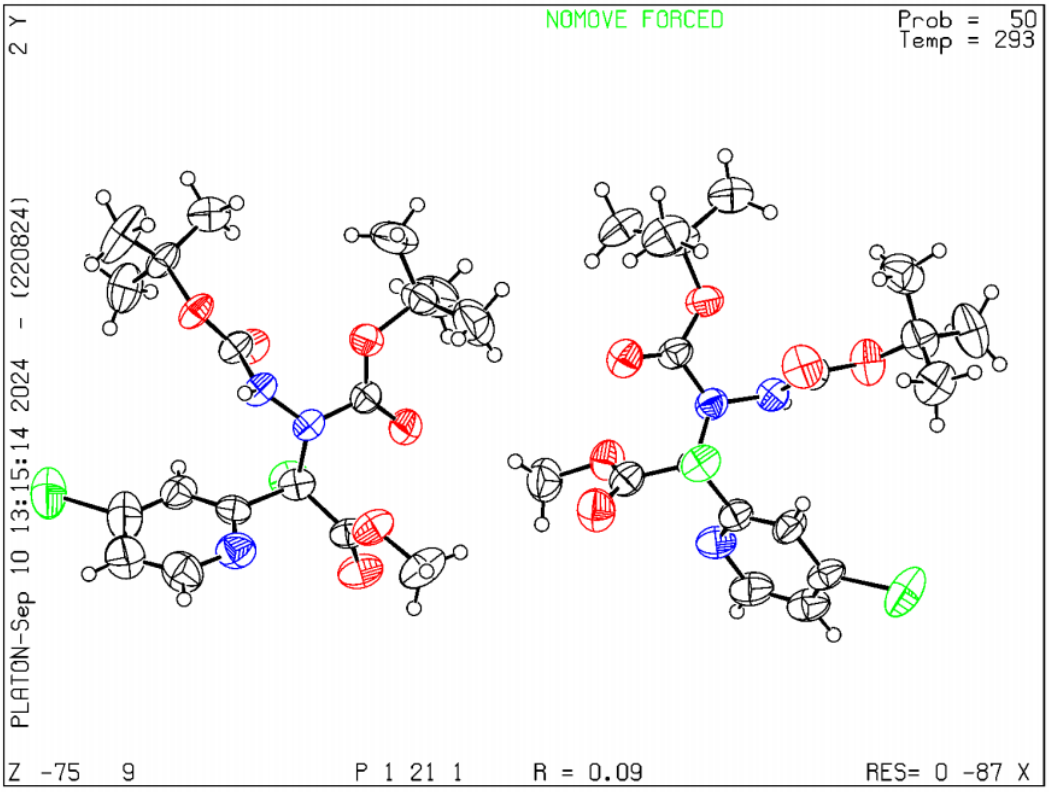


3q, 68% yield, 85% ee CCDC: 2391754

Table S7. Crystal data and structure refinement for 3q

Identification code	**3q**
Empirical formula	$C_{18}H_{25}BrFN_3O_6$
Formula weight	478.32
Temperature/K	292.97(16)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.5596(3)
b/Å	9.8290(2)
c/Å	22.2609(4)
α/°	90
β/°	103.72
γ/°	90
Volume/Å^3	2244.54(9)
Z	4
ρcalcg/cm^3	1.415
μ/mm^{-1}	2.900
F(000)	984.0
Crystal size/mm^3	0.15 × 0.12 × 0.09
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	8.176 to 133.126
Index ranges	-12 ≤ h ≤ 12, -11 ≤ k ≤ 11, -26 ≤ l ≤ 26
Reflections collected	7830
Independent reflections	7830 [Rint = ?, Rsigma = 0.0665]
Data/restraints/parameters	7830/453/538
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0442, wR_2 = 0.1176
Final R indexes [all data]	R_1 = 0.0450, wR_2 = 0.1190
Largest diff. peak/hole / e Å^{-3}	0.19/-0.24
Flack/Hooft parameter	0.03(6)

Datablock 9 - ellipsoid plot



Variable temperature NMR experiment of 3a

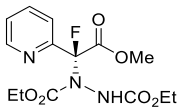


Figure S5. ^{1}H NMR Spectrum comparison

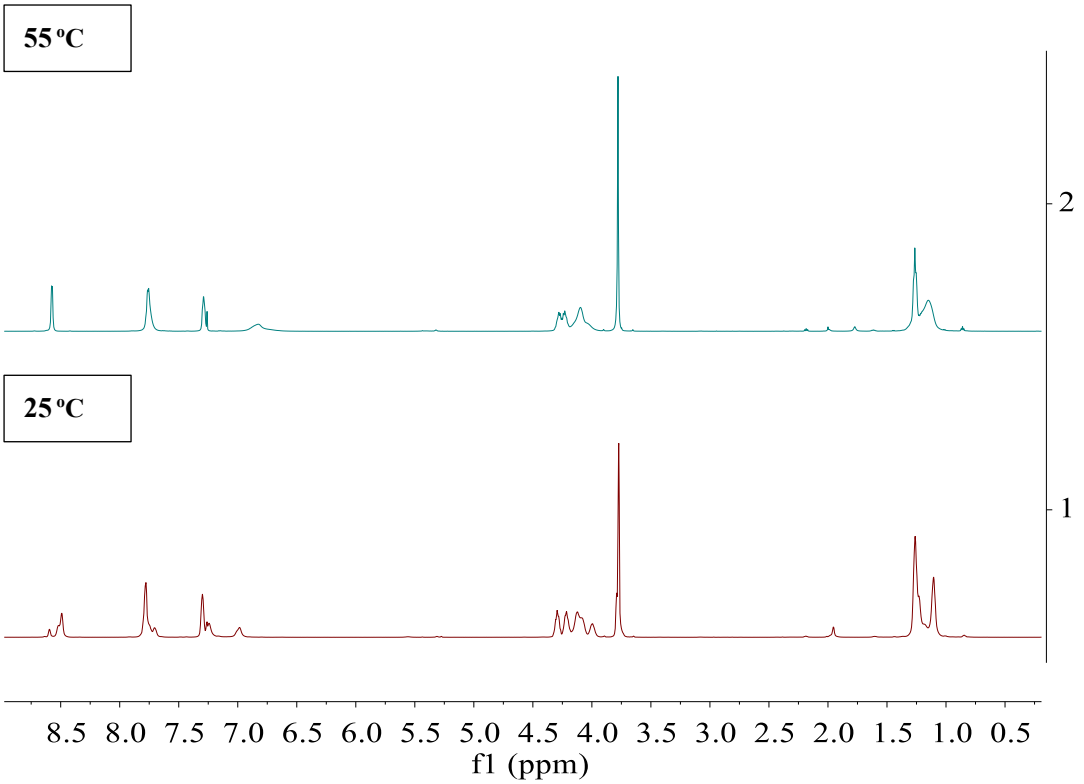


Figure S6. ^{13}C{^{1}H} NMR Spectrum comparison

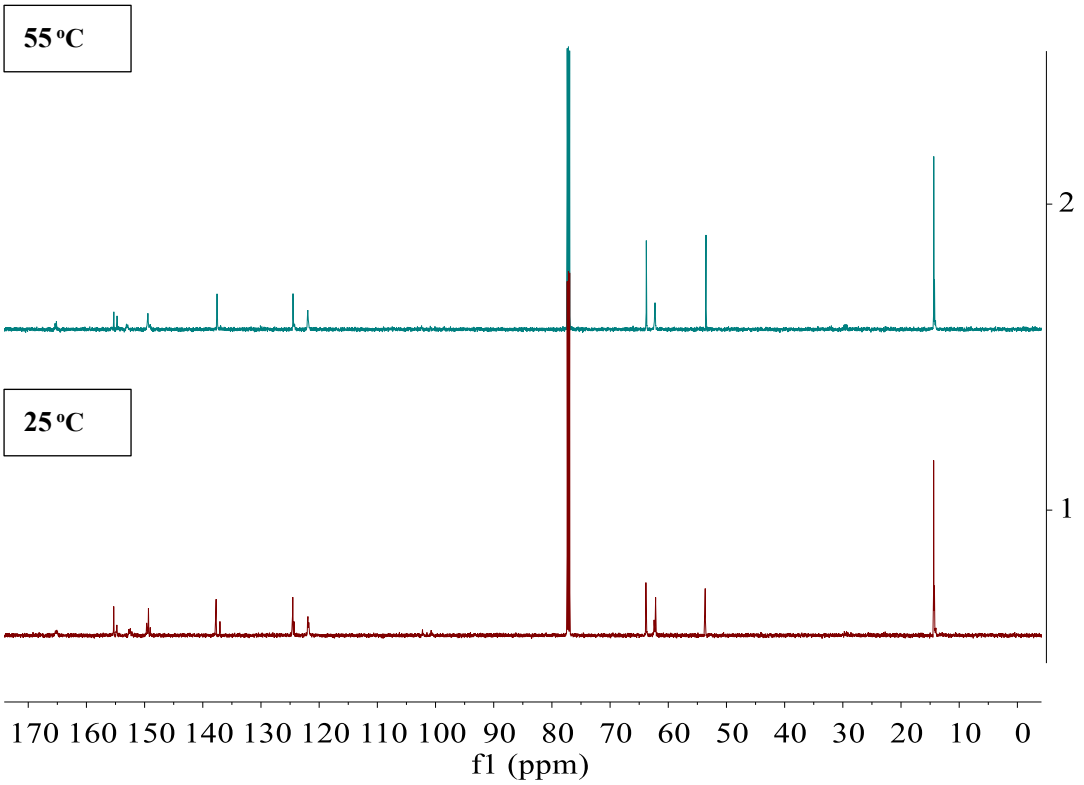
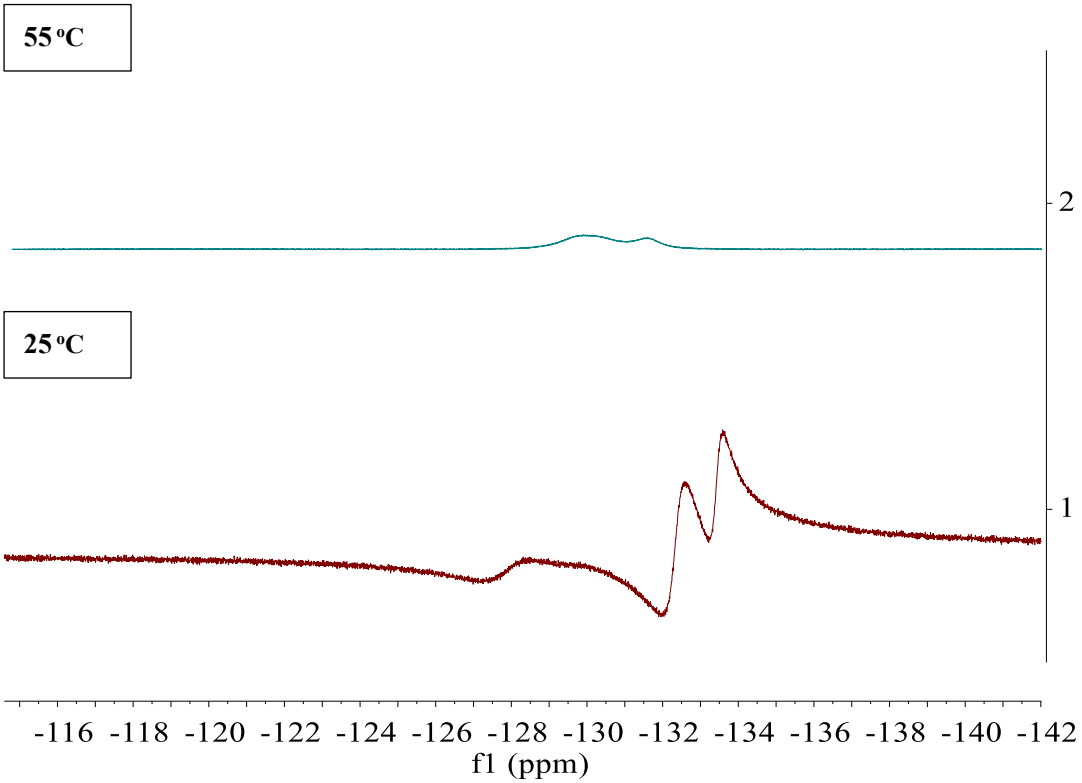


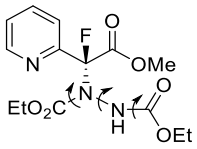
Figure S7. $^{19}F\{^{1}H\}$ NMR Spectrum comparison



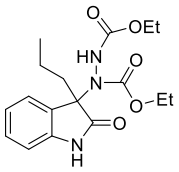
Conclusion:

The NMR spectra of **3a** were generated multiple signals at 25 °C, but aggregated into broad resonance peaks at 55 °C.

The distinct signals in the NMR spectra are very much likely due to restricted rotation around the N–CO and N–N bonds generating different isomeric forms.[10]



Similar NMR data with multiple signals due to restricted rotation around the N-CO and N-N bonds are listed as follows.[11-15]

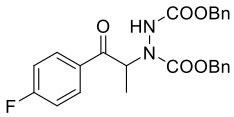


Ref: *Chem. Eur. J*. **2010**, *16*, 6632 – 6637.

Chemical Formula: $C_{17}H_{23}N_3O_5$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 22.0, 1H), 7.70 (d, *J* = 7.4, 1H), 7.20 (t, *J* = 7.6, 1H), 7.07 – 6.97 (m, 2H), 6.81 (d, *J* = 7.7, 1H), 4.36 - 4.20 (m, 2H), 4.05 – 3.95 (m, 2H), 1.98 (m, 9.5, 1H), 2.02 – 1.95 (m, 1H), 1.34 (t, *J* = 7.1, 3H), 1.19 (m, 1H), 1.04 (t, *J* = 7.0, 3H), 0.81 (dd, *J* = 7.0, 3.6, 4H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 178.90, 157.15, 154.28, 140.56, 130.83, 128.55, 124.48, 123.09, 109.44, 69.46, 62.76, 62.26, 37.71, 16.00, 14.53, 14.06, 13.98.

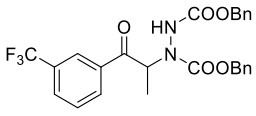


Ref: *Org. Lett*. **2010**, *12*, 2214 – 2217.

Chemical Formula: $C_{25}H_{23}FN_2O_5$

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (d, 3H, *J* = 7.2 Hz), 5.09 – 5.20 (m, 4H), 5.62 – 5.84 (1H), 7.04 – 7.30 (m, 13H), 7.82 – 7.96 (2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.51, 57.96, 67.68, 68.36, 115.92, 116.14, 127.57, 128.06, 128.35, 128.50, 128.55, 131.23, 135.66, 156.18, 164.76, 167.31, 198.56.

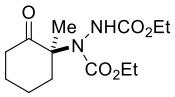


Ref: *Org. Lett*. **2010**, *12*, 2214 – 2217.

Chemical Formula: $C_{26}H_{23}F_3N_2O_5$

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (d, 3H, *J* = 7.2 Hz), 5.09 – 5.20 (m, 4H), 5.64 – 5.89 (1H), 6.82 – 7.01 (1H), 7.17 – 7.35 (10H), 7.51 – 7.63 (1H), 7.83 – 8.19 (3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.32, 58.19, 67.78, 68.49, 125.38, 127.63, 128.11, 128.21, 128.41, 128.54, 128.59, 129.54, 130.09, 131.39, 131.67, 135.59, 156.21, 198.85.

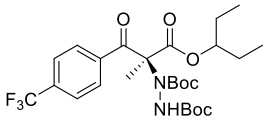


Ref: *Synlett* **2015**, *26*, 1413 – 1416.

Chemical Formula: $C_{13}H_{22}N_2O_5$

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 – 6.31 (m, 1H), 4.27 – 4.08 (m, 4H), 2.85 – 2.26 (m, 3H), 2.0 – 1.13 (m, 14H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 209.4, 156.9, 156.0, 69.5, 62.9, 62.3, 62.2, 39.7, 38.9, 38.3, 29.7, 29.3, 26.6, 21.9, 21.7, 21.0, 19.8, 14.5, 14.3.



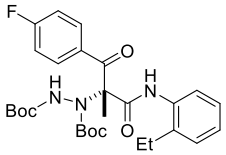
Ref: *J. Org. Chem*. **2018**, *83*, 303 – 313.

Chemical Formula: $C_{26}H_{37}F_3N_2O_7$

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 – 1.82 (complex abs., 31H), 4.92 (broad s, 1H,), 6.20 (s, 1H), 7.31 (broad s, 2H), 8.60 (broad s, 2H).

^{13}C {1H} NMR ($CDCl_3$, 101 MHz) δ (ppm): 9.4, 9.5, 26.2, 26.3 – 28.1, 79.6, 81.6, 116.5, 119.0, 119.8, 121.6, 124.1, 131.3, 1542.1, 155.6, 169.2, 189.4, 190.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -63.1 (s, 3F).



Ref: *Org. Lett.* **2020**, *22*, 468 – 473.

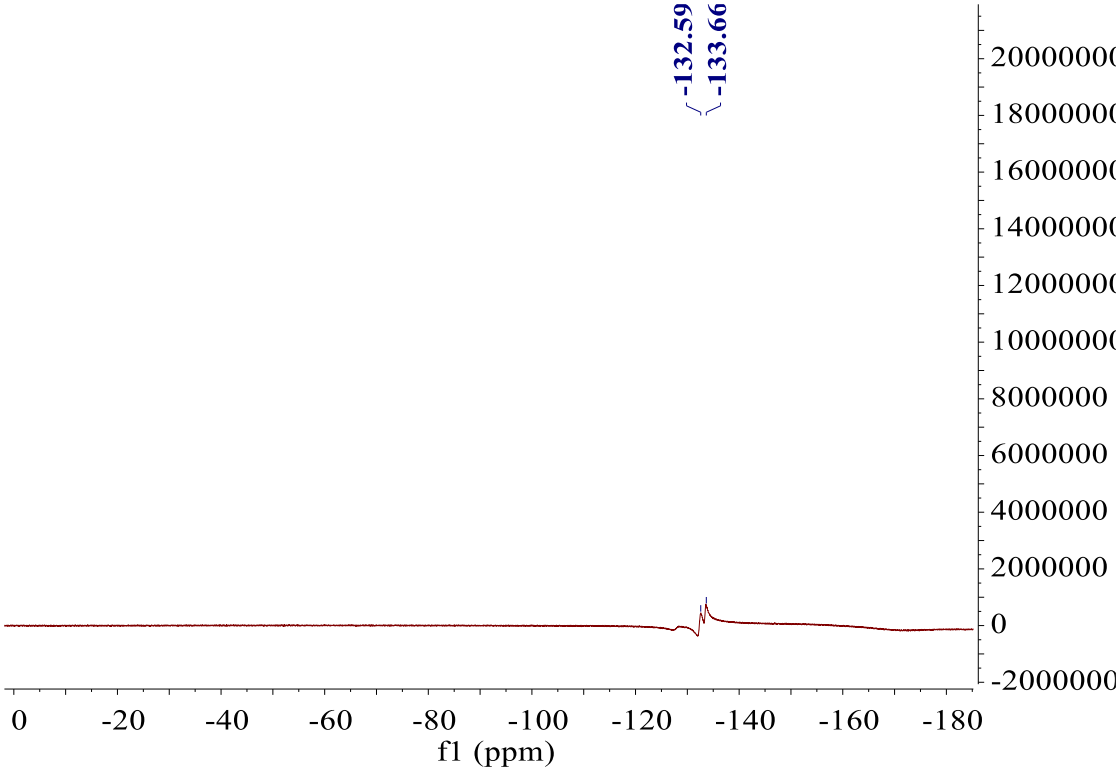
Chemical Formula: $C_{28}H_{36}FN_3O_6$

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 – 9.67 (m, 1H), 9.01 – 8.42 (m, 2H), 7.95 – 7.70 (m, 1H), 7.30 – 6.99 (m, 6H), 2.85 – 2.68 (m, 2H), 1.96 (s, 3H), 1.65 – 1.43 (m, 9H), 1.37 – 1.03 (m, 12H) ppm.

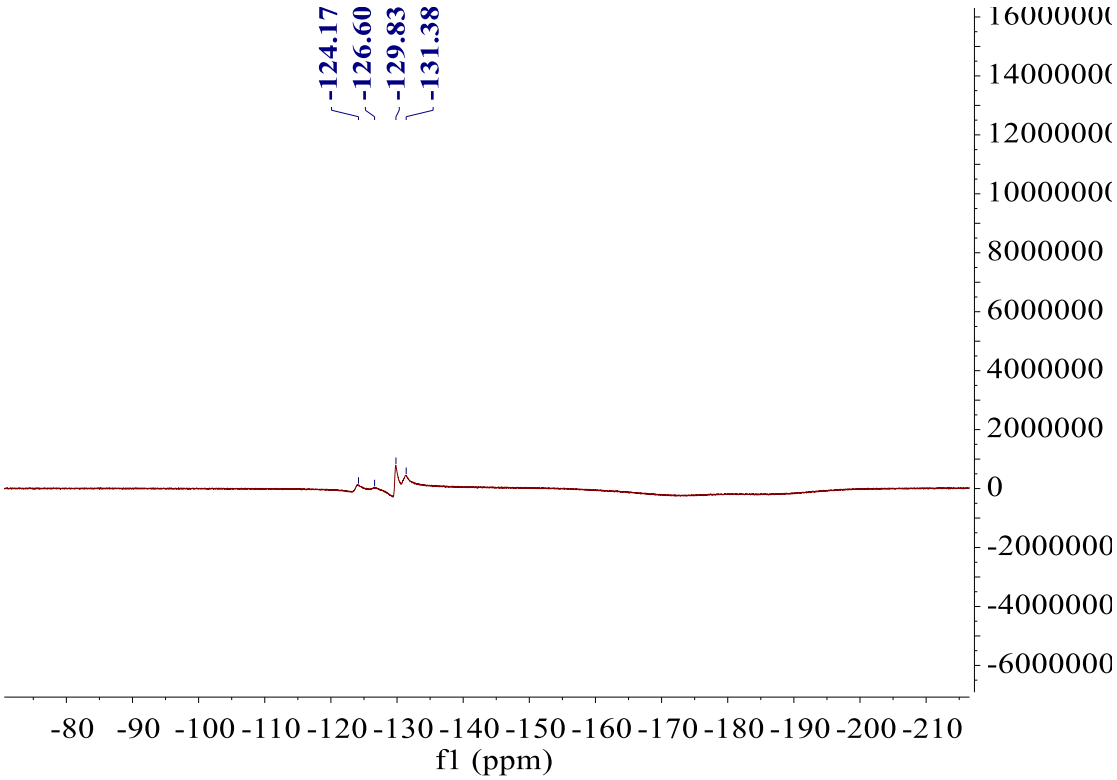
^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 170.6, 165.4 (d, J = 251.3 Hz), 157.2, 155.7, 135.4, 135.1, 132.6, 131.3, 128.7, 126.4, 125.3, 122.9, 115.1, 83.0, 80.7, 72.7, 28.2, 27.6, 24.6, 23.7, 14.1 ppm (only major peaks are reported).

$^{19}F\{^{1}H\}$ NMR Spectrum of products 3a in different solvents

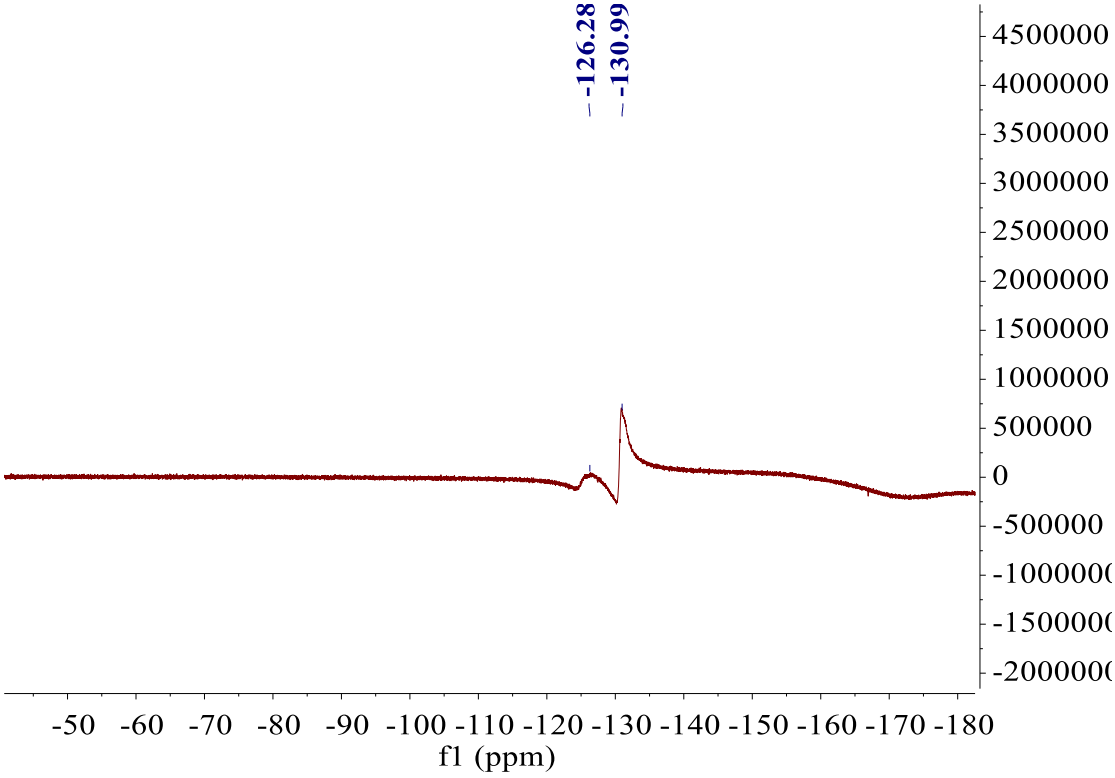
$^{19}F\{^{1}H\}$ NMR Spectrum of (565 MHz, $CDCl_3$, rt)



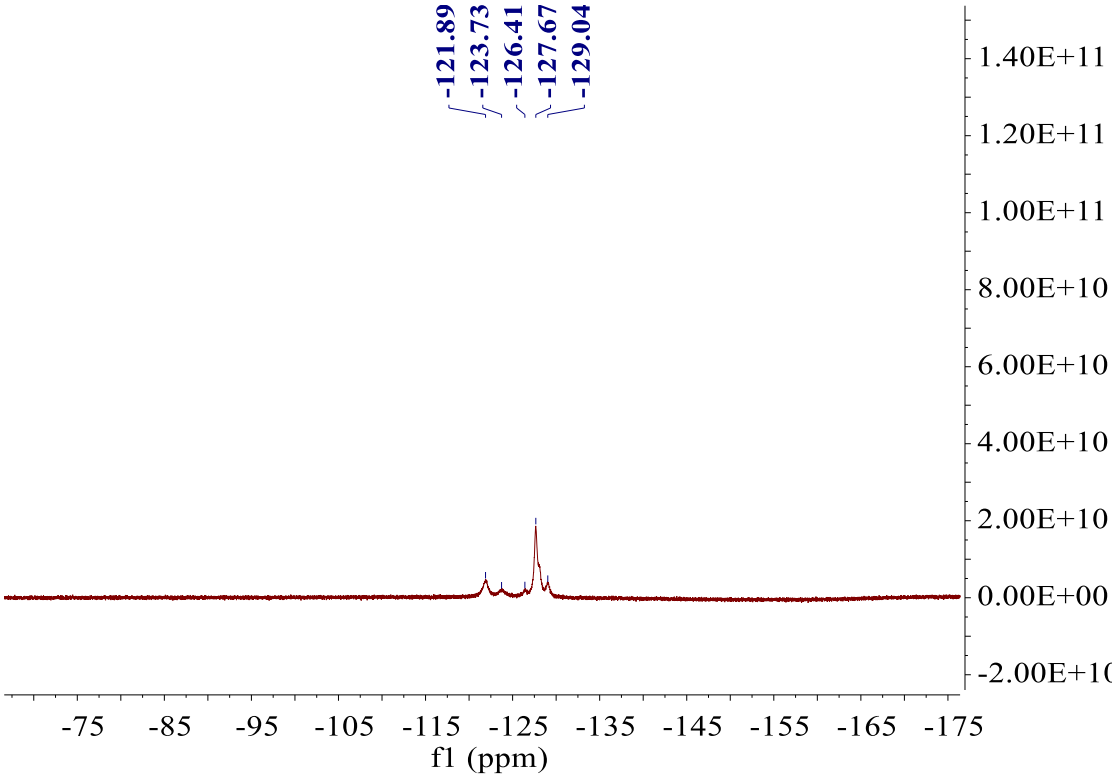
$^{19}F\{^{1}H\}$ NMR Spectrum of **3a** (565 MHz, Acetone-d^6, rt)



$^{19}F\{^{1}H\}$ NMR (564 MHz, CD_3CN, rt)

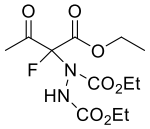


$^{19}F\{^{1}H\}$ NMR (564 MHz, DMSO-d^6, rt)



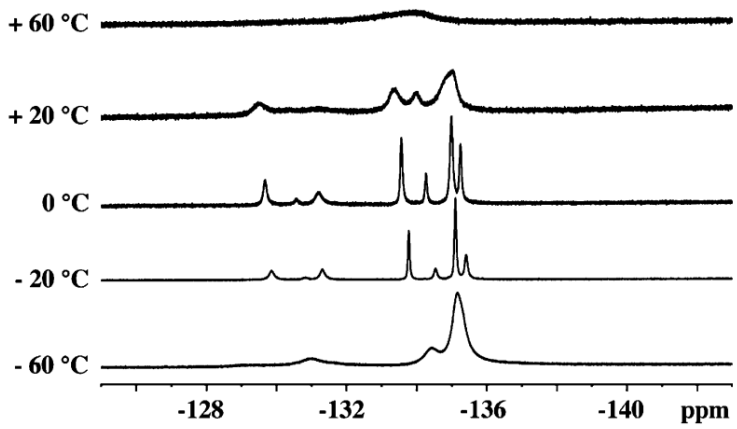
Similar reference:

The ^{19}F NMR spectra show several broad signal peaks. The reason for this phenomenon is very much likely due to restricted rotation around the N–CO and N–N bonds generating different isomeric forms,^{19}F NMR data with multiple signals due to restricted rotation around the N-CO and N-N bonds are listed as follows. [10]Assuming that the O=C–N–N–C=O structural unit is planar, then eight different isomers may be generated because of this restricted rotation. Seven of these species can be observed in the ^{19}F NMR spectrum at -20 °C, one signal possibly being superposed by another one.[10]



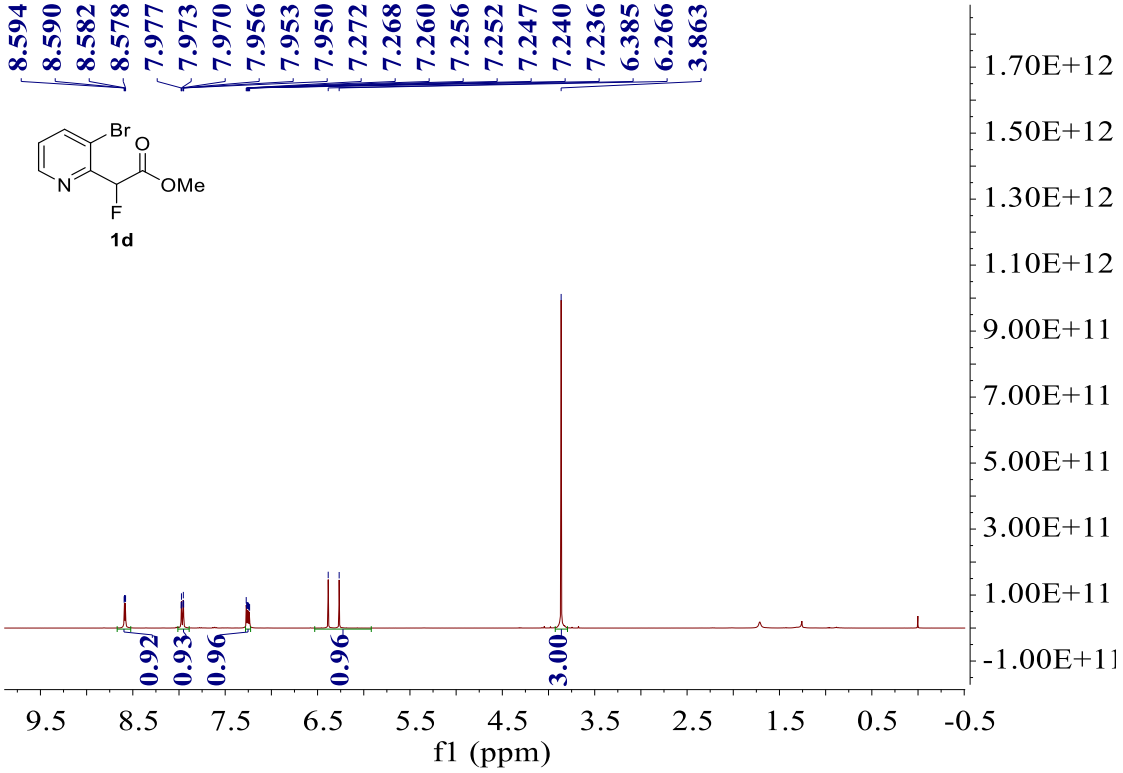
Ref: *Tetrahedron: Asymmetry* **2006**, *17*, 658 – 664.

Figure S8 Variable temperature ^{19}F NMR experiment in $CDCl_3$ in the reference 10:

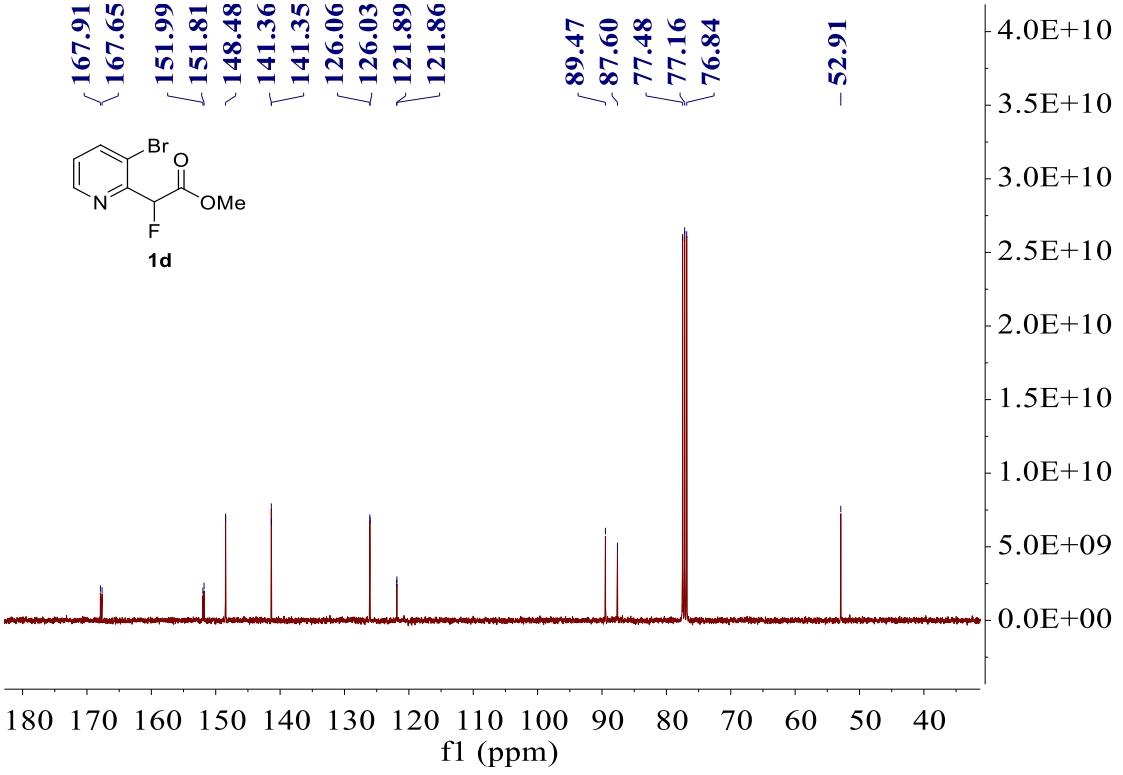


NMR Spectra

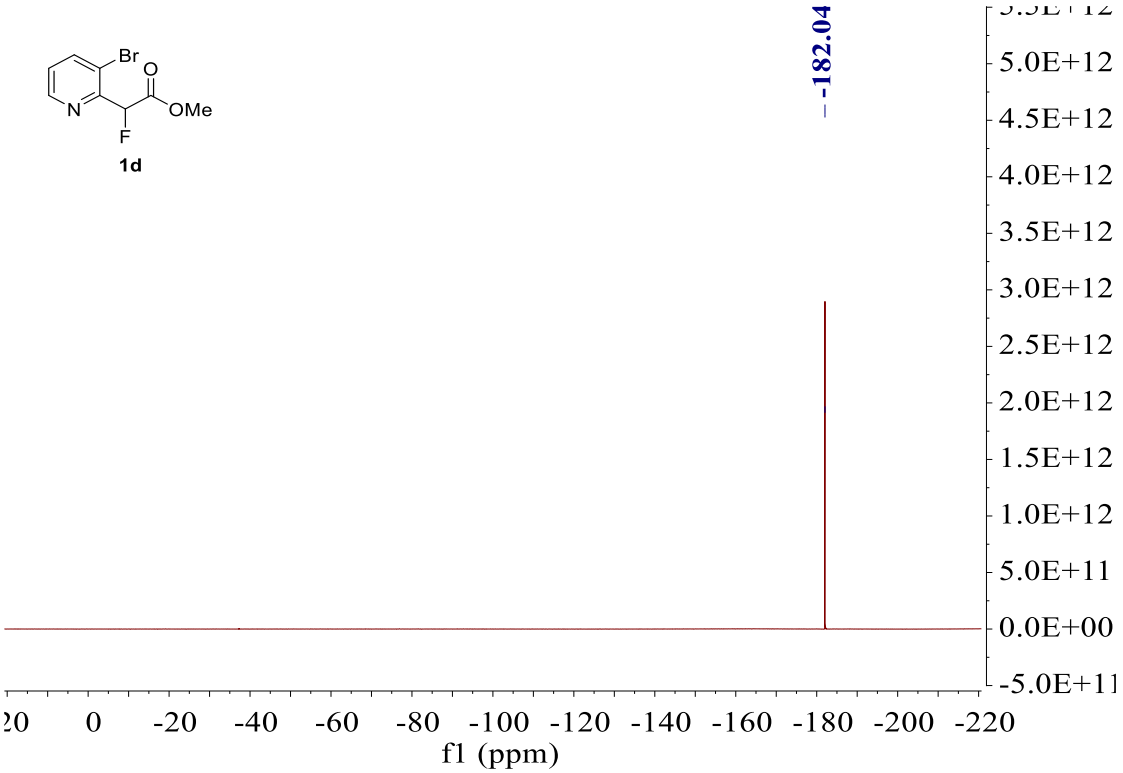
^{1}H NMR Spectrum of **1d** (400 MHz, $CDCl_3$, rt)



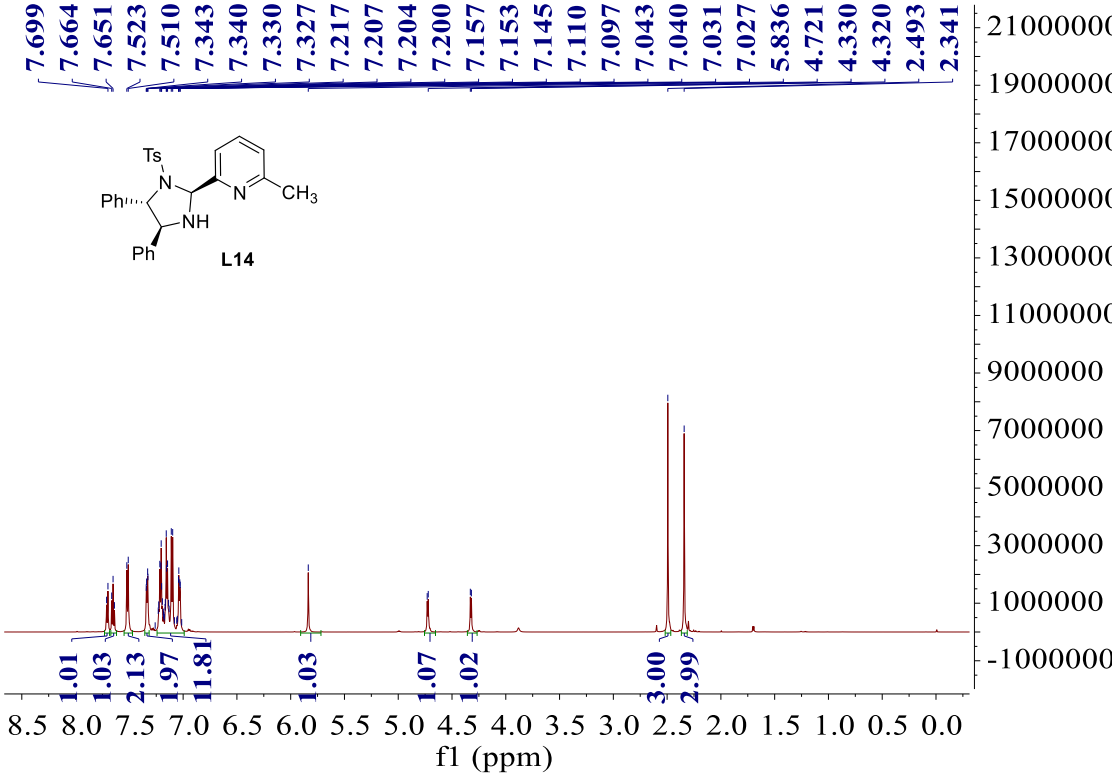
^{13}C{^{1}H} NMR Spectrum of **1d** (100 MHz, $CDCl_3$, rt)



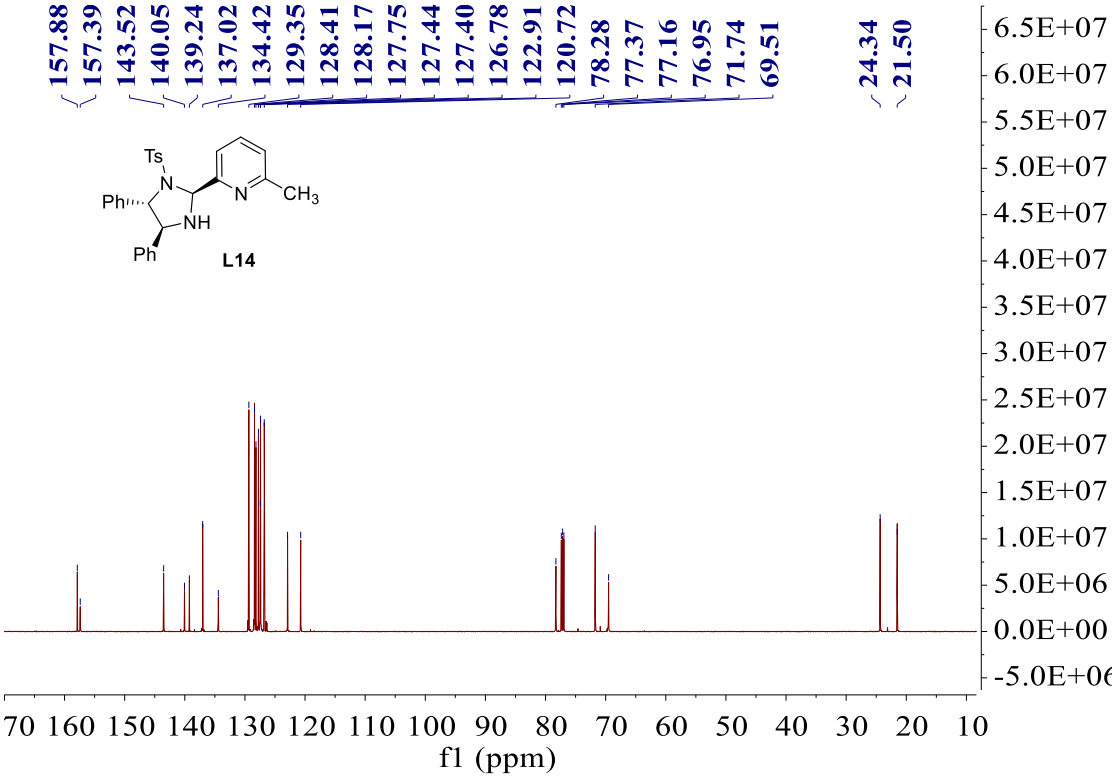
$^{19}F\{^{1}H\}$ NMR Spectrum of **1d** (376 MHz, $CDCl_3$, rt)



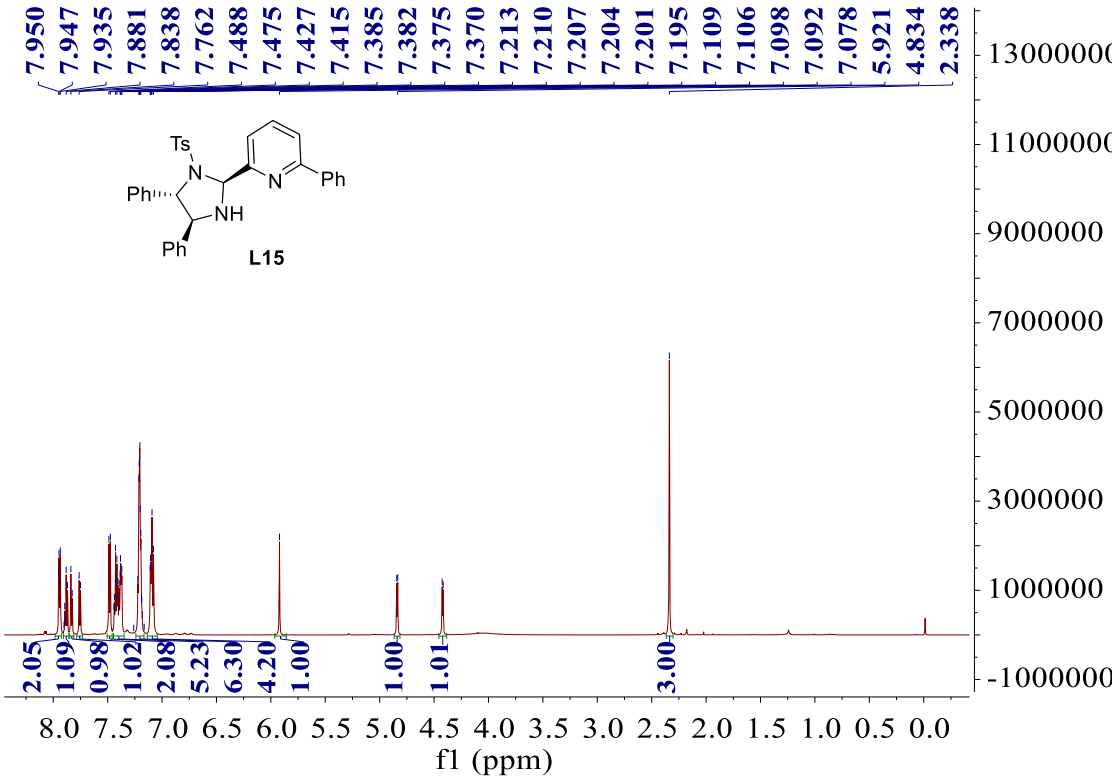
^{1}H NMR Spectrum of **L14** (600 MHz, $CDCl_3$, rt)



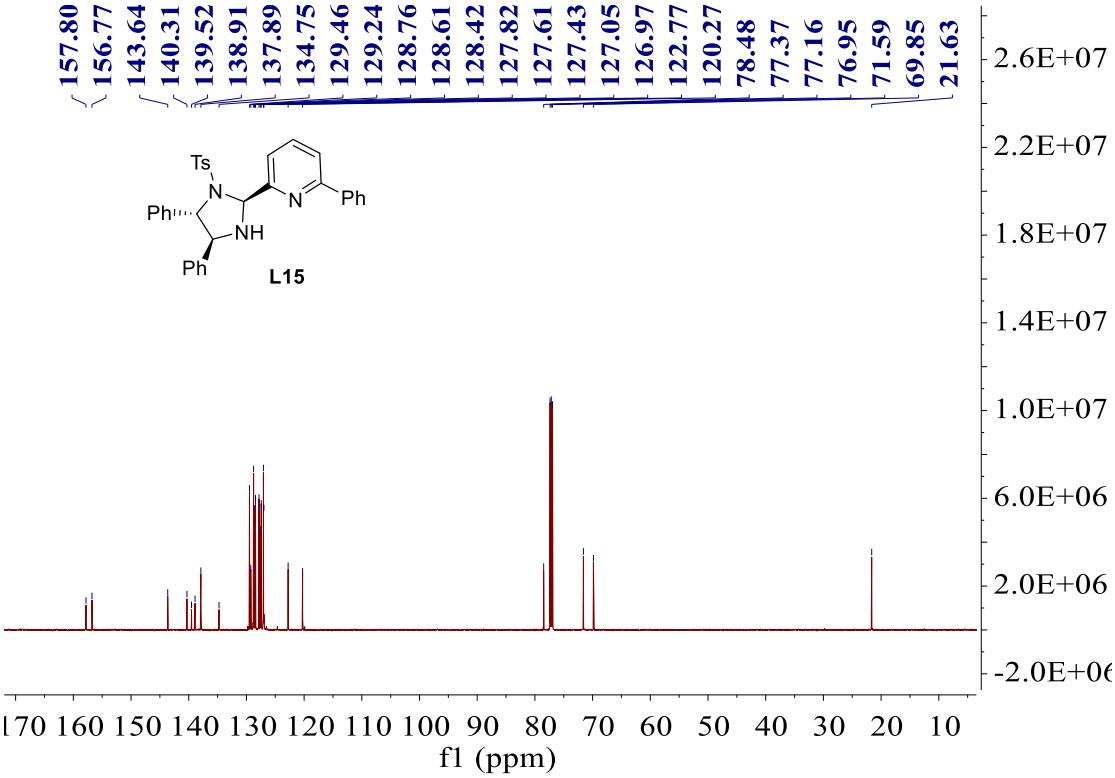
^{13}C{^{1}H} NMR Spectrum of **L14** (150 MHz, $CDCl_3$, rt)



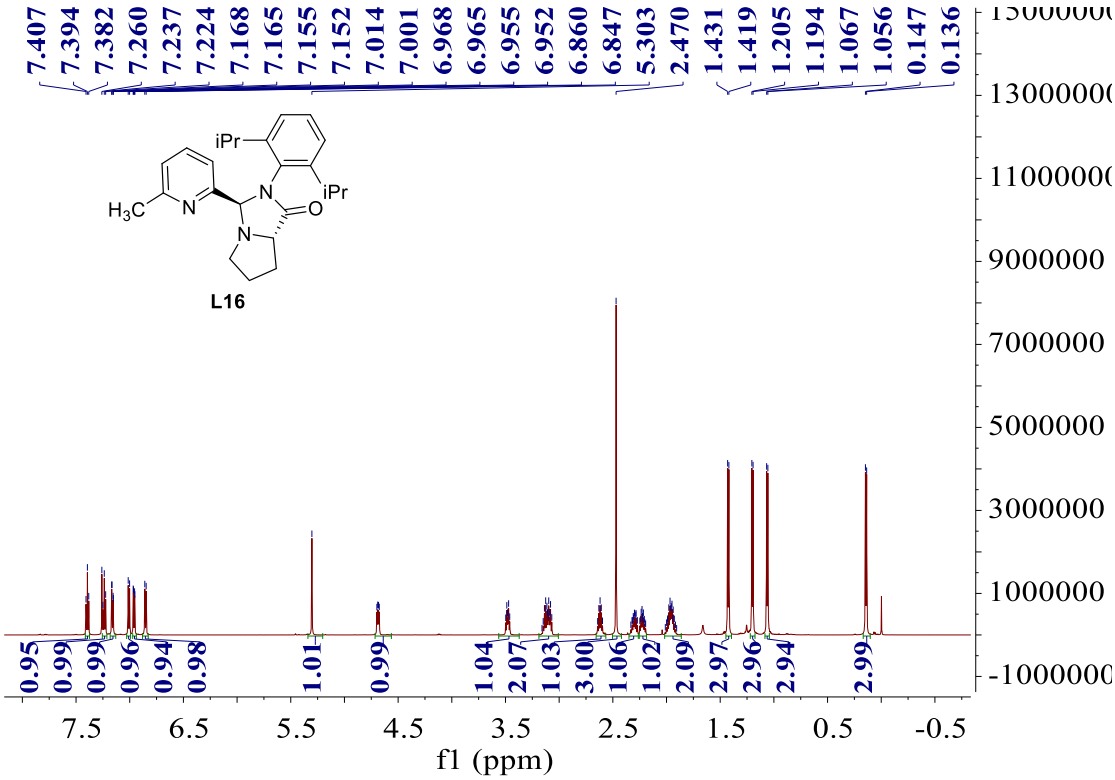
^{1}H NMR Spectrum of **L15** (600 MHz, $CDCl_3$, rt)



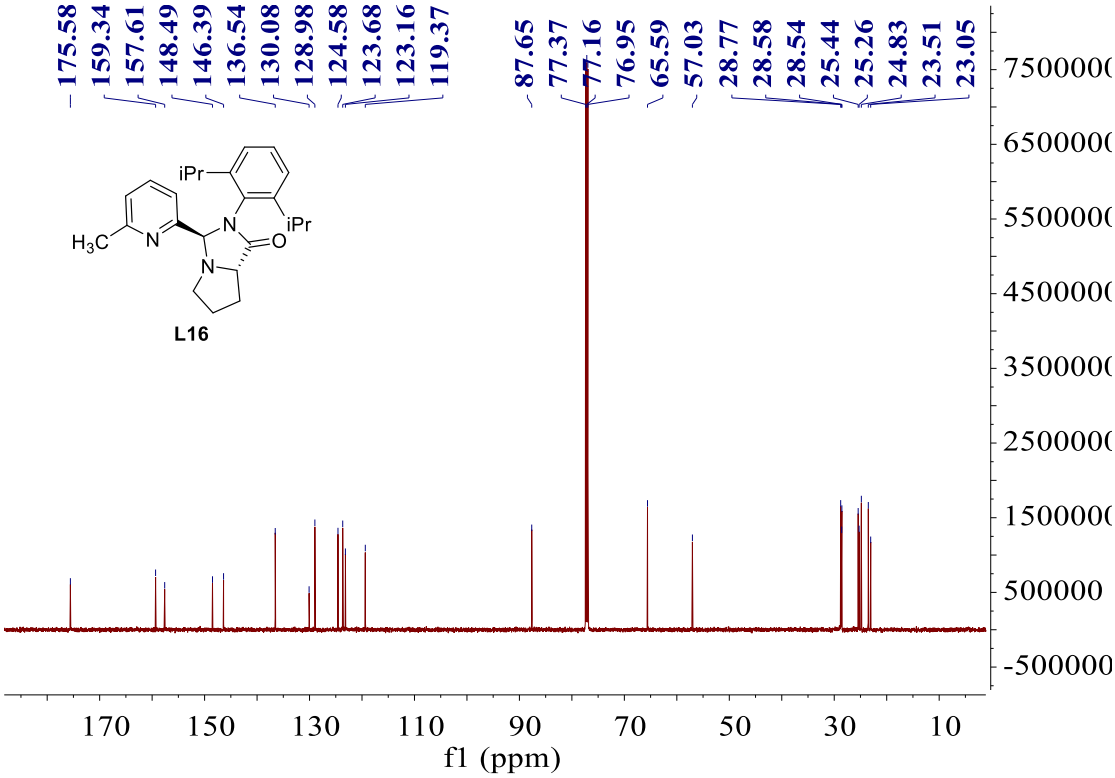
^{13}C{^{1}H} NMR Spectrum of **L15** (150 MHz, $CDCl_3$, rt)



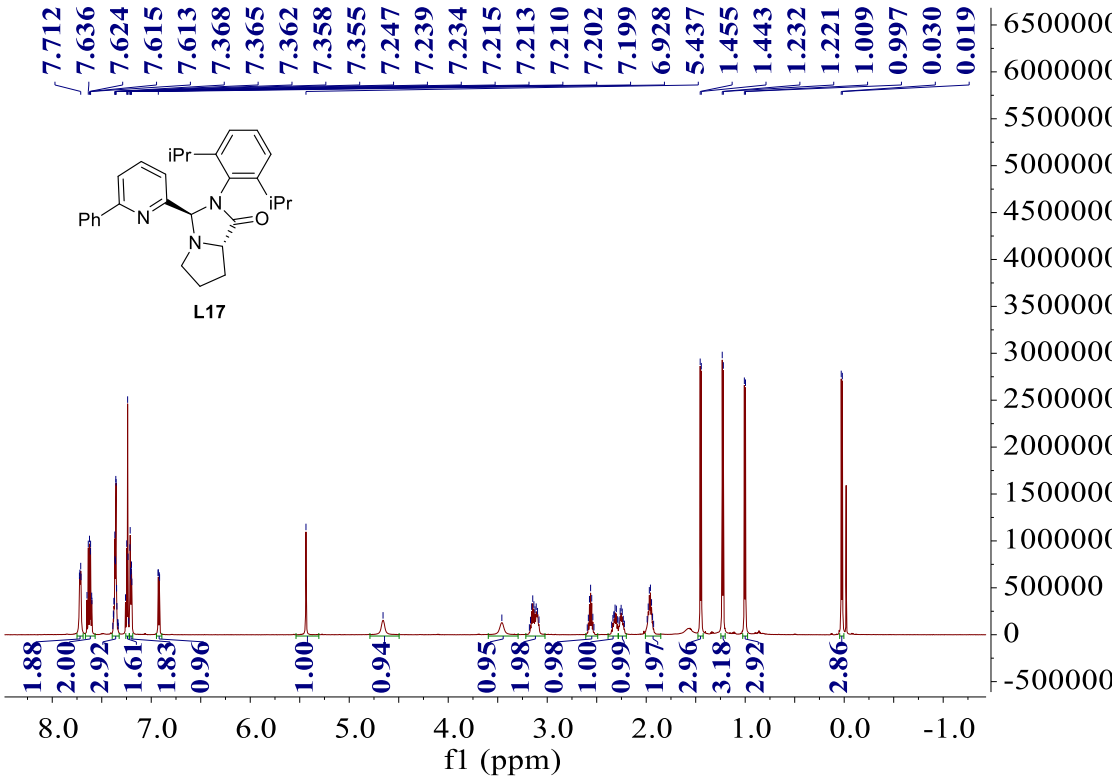
^{1}H NMR Spectrum of **L16** (600 MHz, $CDCl_3$, rt)



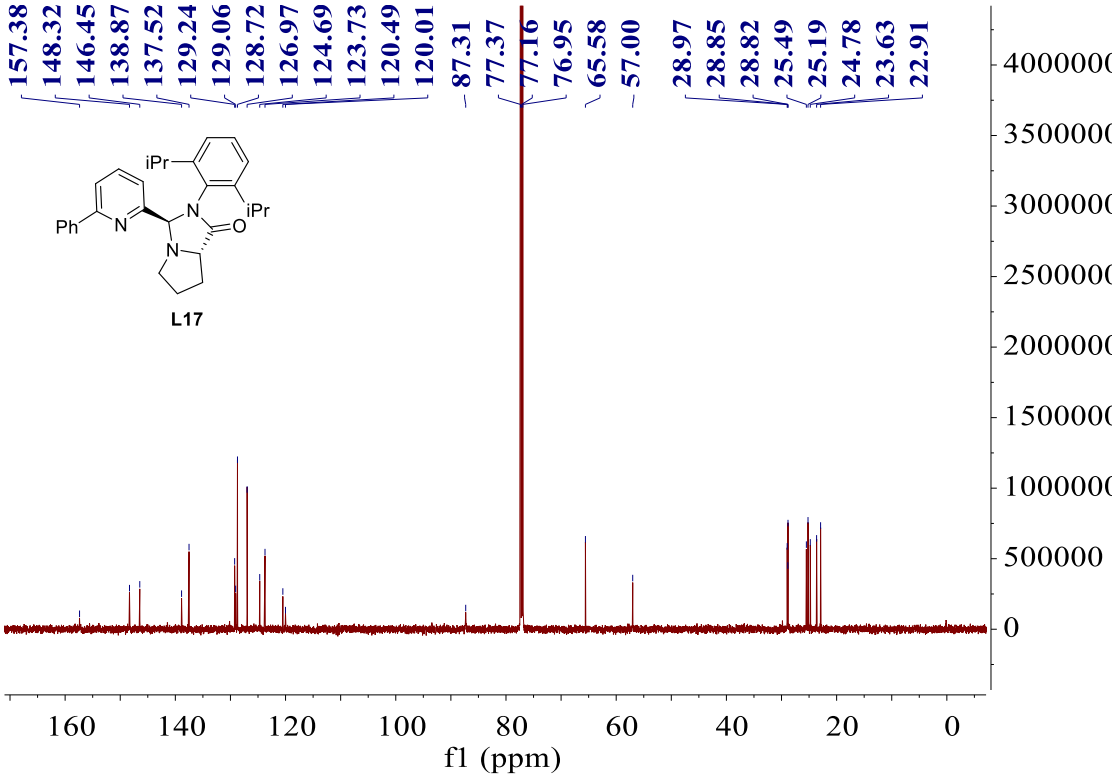
^{13}C{^{1}H} NMR Spectrum of **L16** (150 MHz, $CDCl_3$, rt)



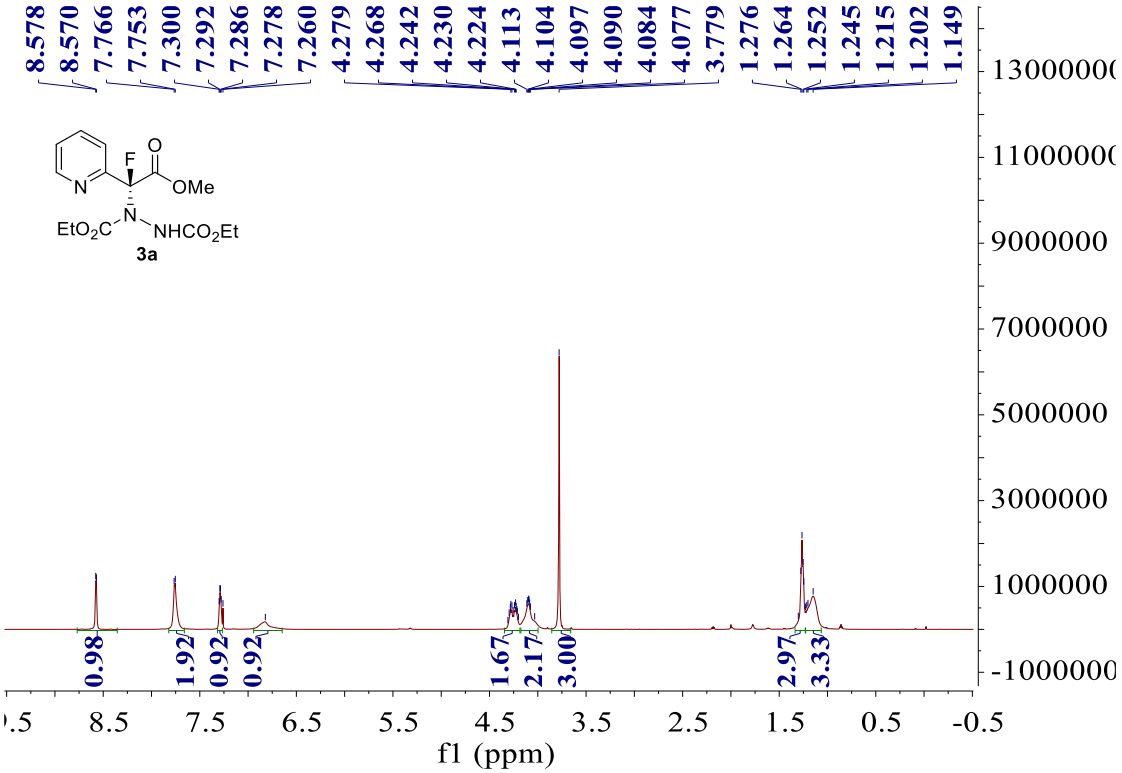
^{1}H NMR Spectrum of **L17** (600 MHz, $CDCl_3$, rt)



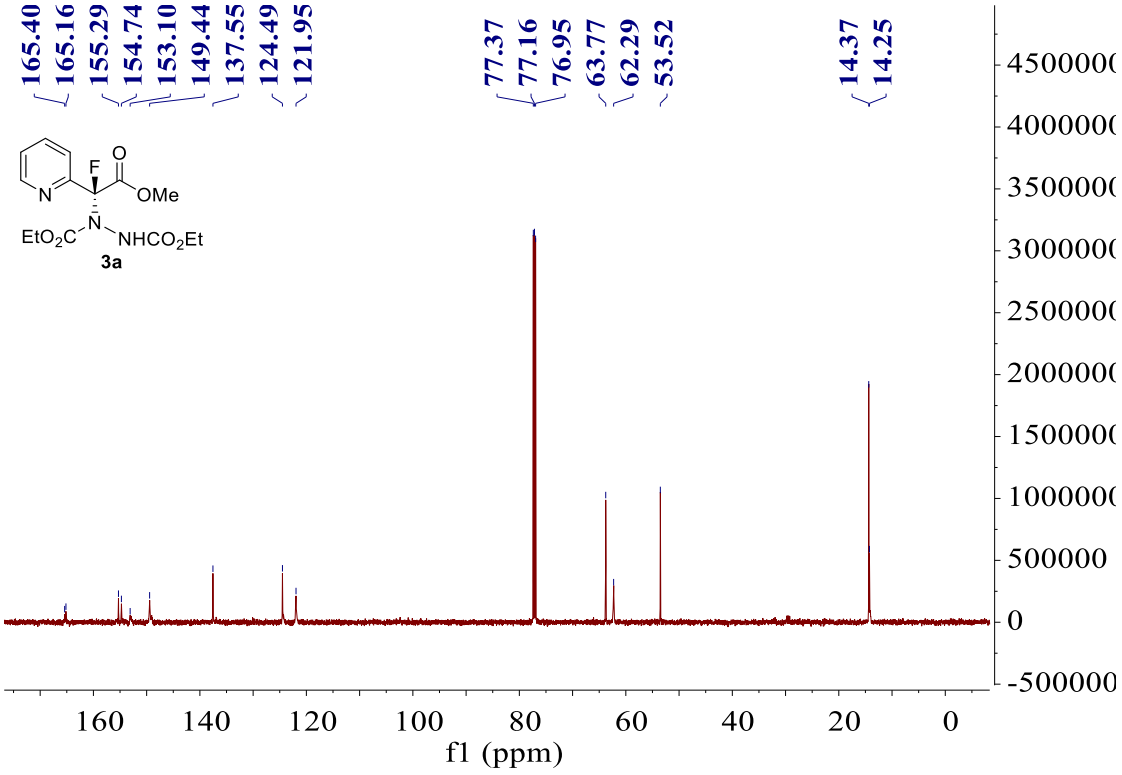
^{13}C{^{1}H} NMR Spectrum of **L17** (150 MHz, $CDCl_3$, rt)



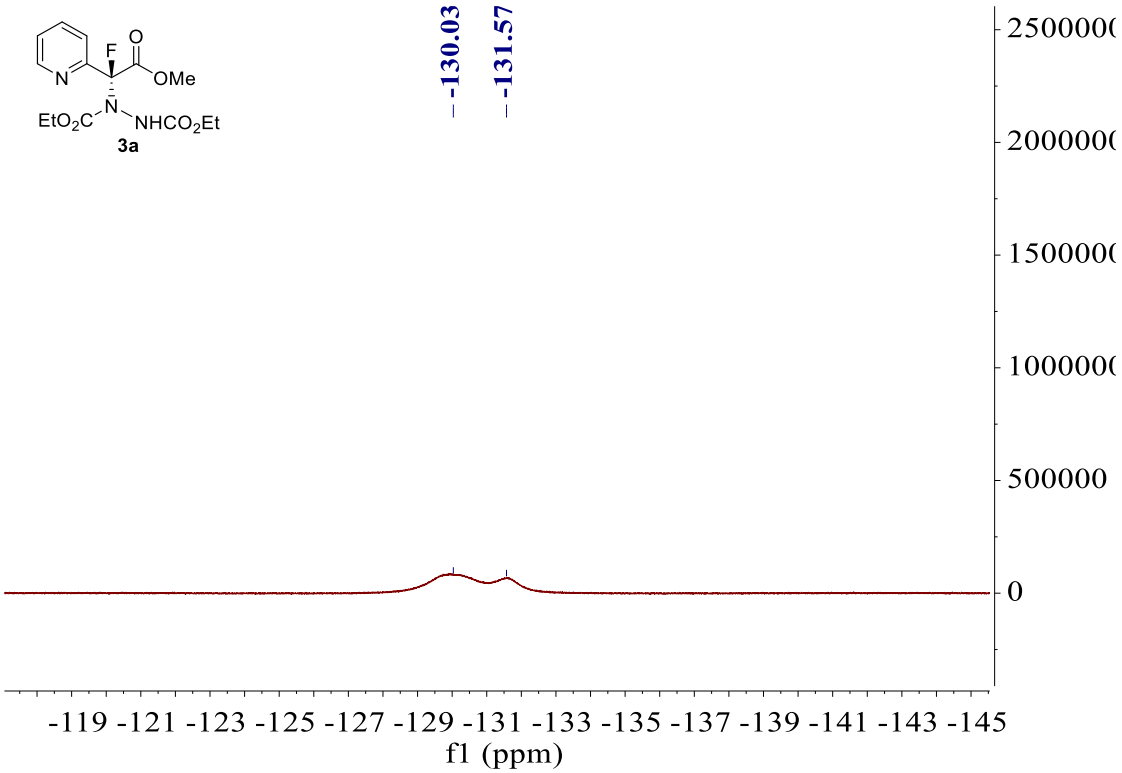
^{1}H NMR Spectrum of **3a** (600 MHz, $CDCl_3$, **55** °C)



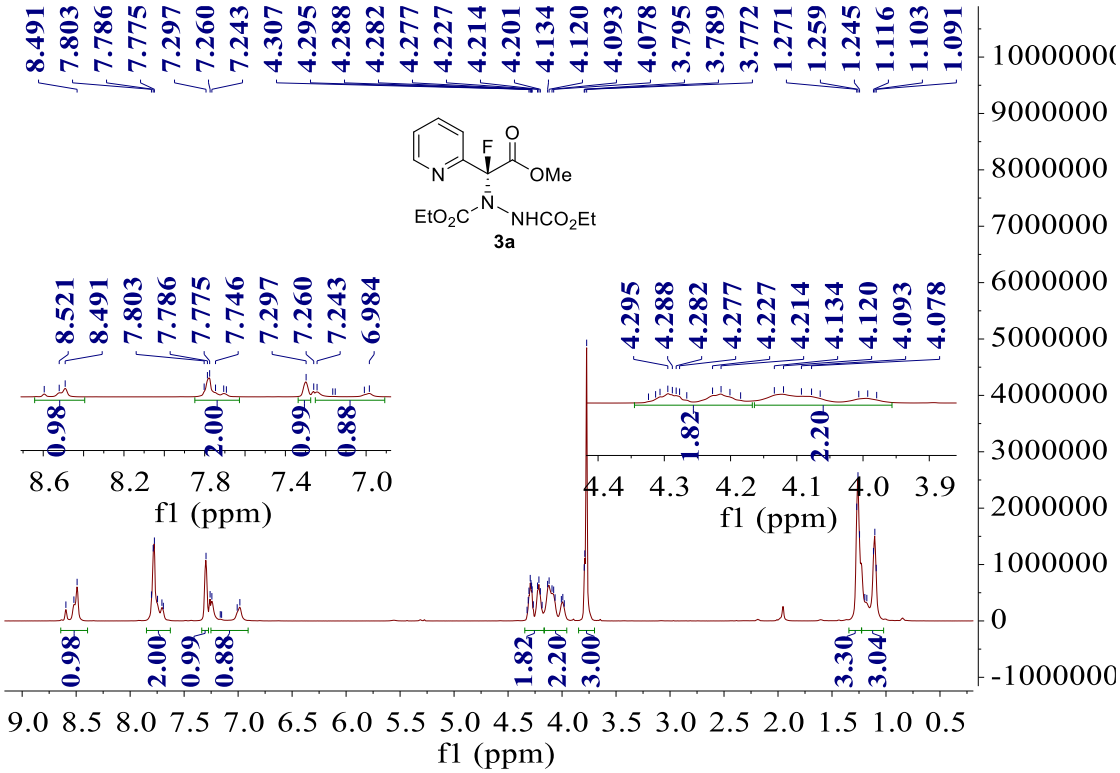
^{13}C{^{1}H} NMR Spectrum of **3a** (150 MHz, $CDCl_3$, **55** °C)



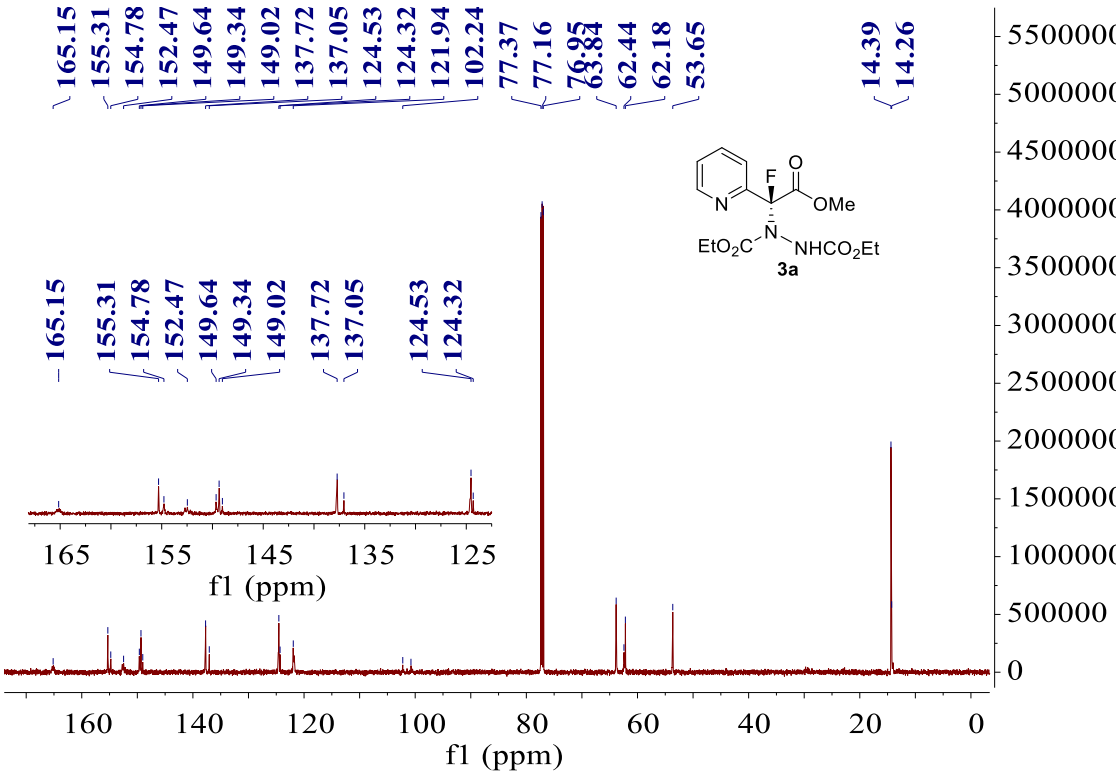
$^{19}F\{^{1}H\}$ NMR Spectrum of **3a** (565 MHz, $CDCl_3$, **55** °C)



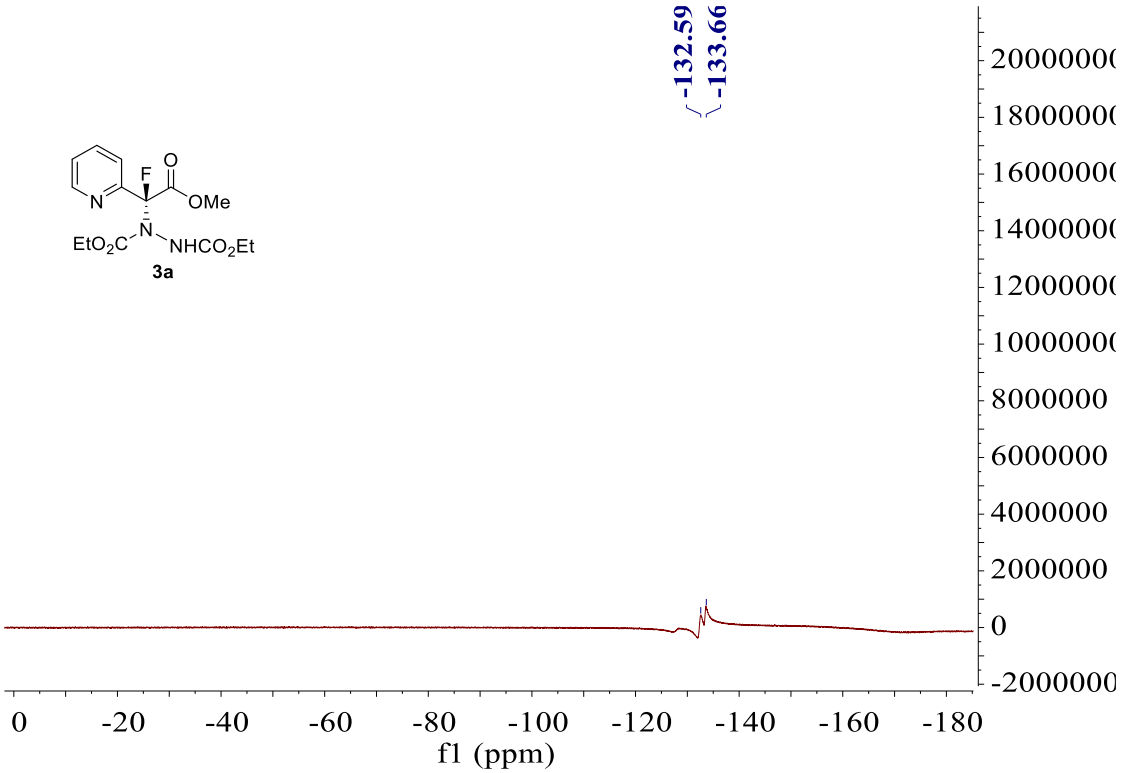
^{1}H NMR Spectrum of **3a** (600 MHz, $CDCl_3$, rt)



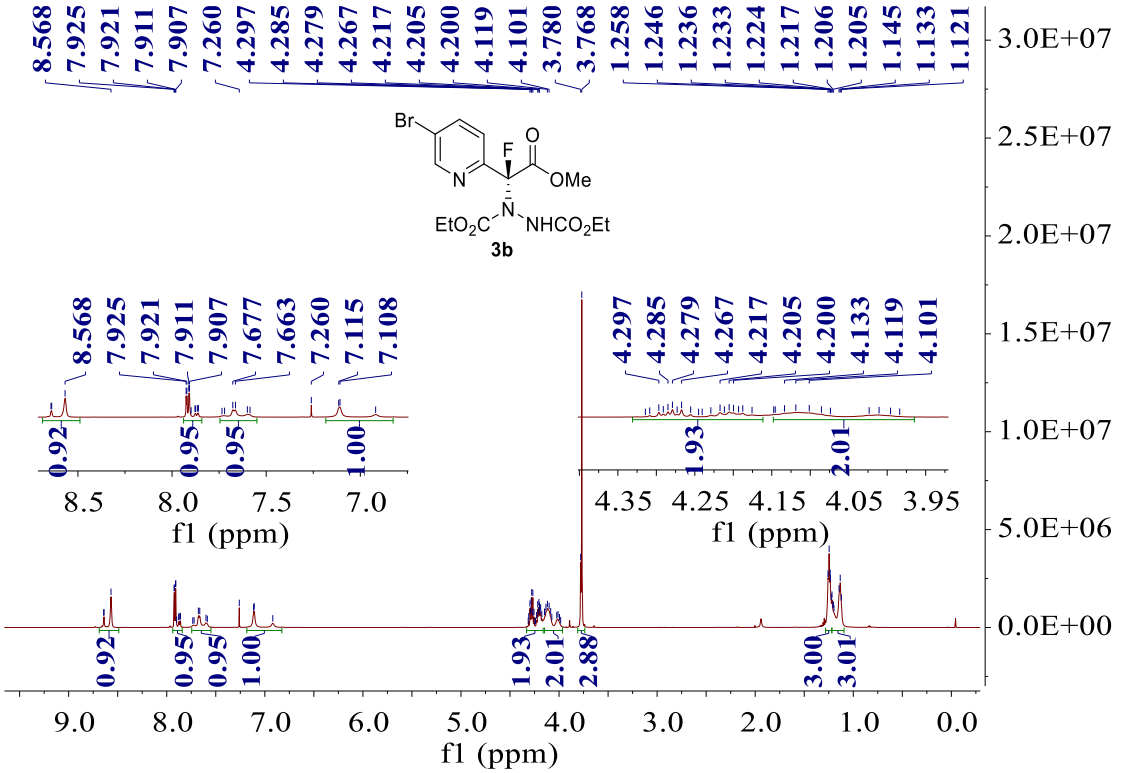
^{13}C{^{1}H} NMR Spectrum of **3a** (150 MHz, $CDCl_3$, rt)



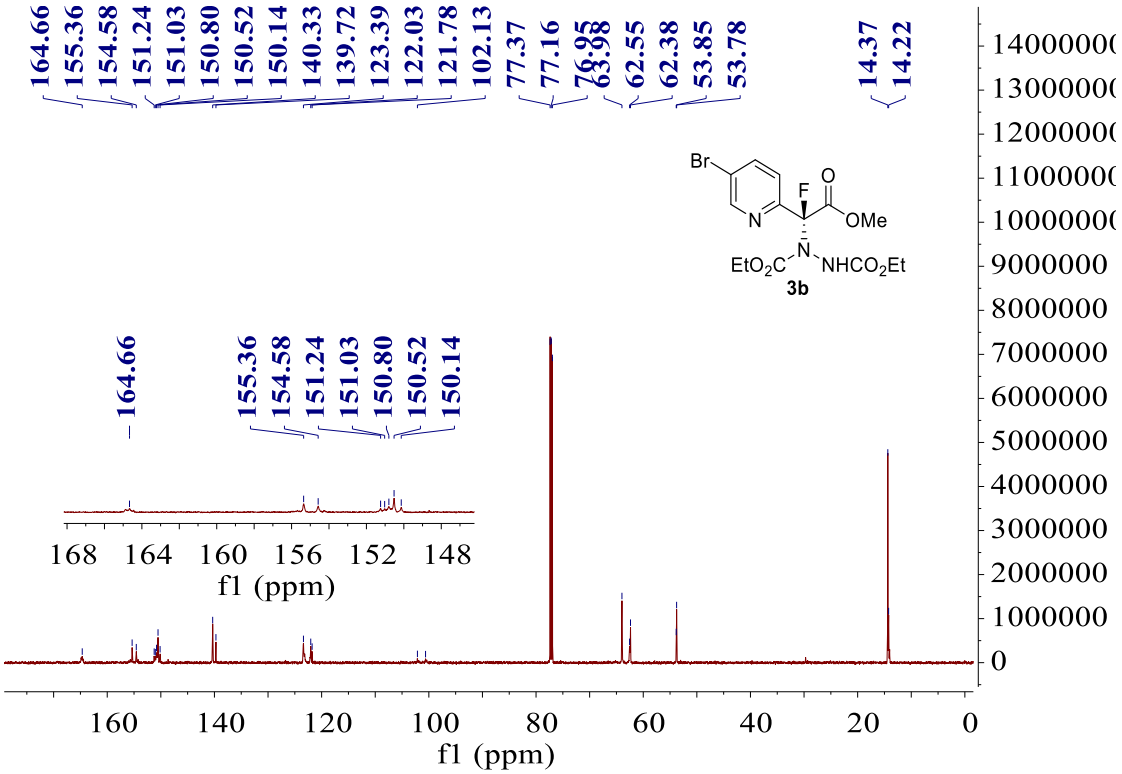
$^{19}F\{^{1}H\}$ NMR Spectrum of **3a** (565 MHz, $CDCl_3$, rt)



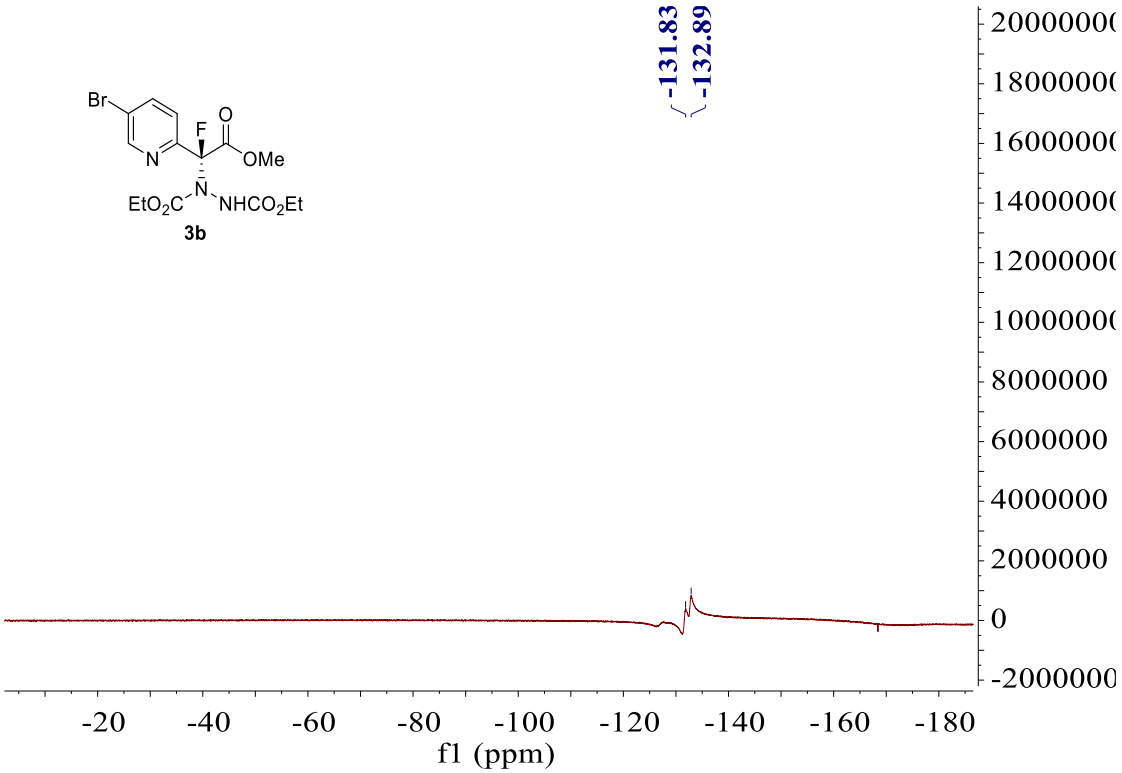
^{1}H NMR Spectrum of **3b** (600 MHz, $CDCl_3$, rt)



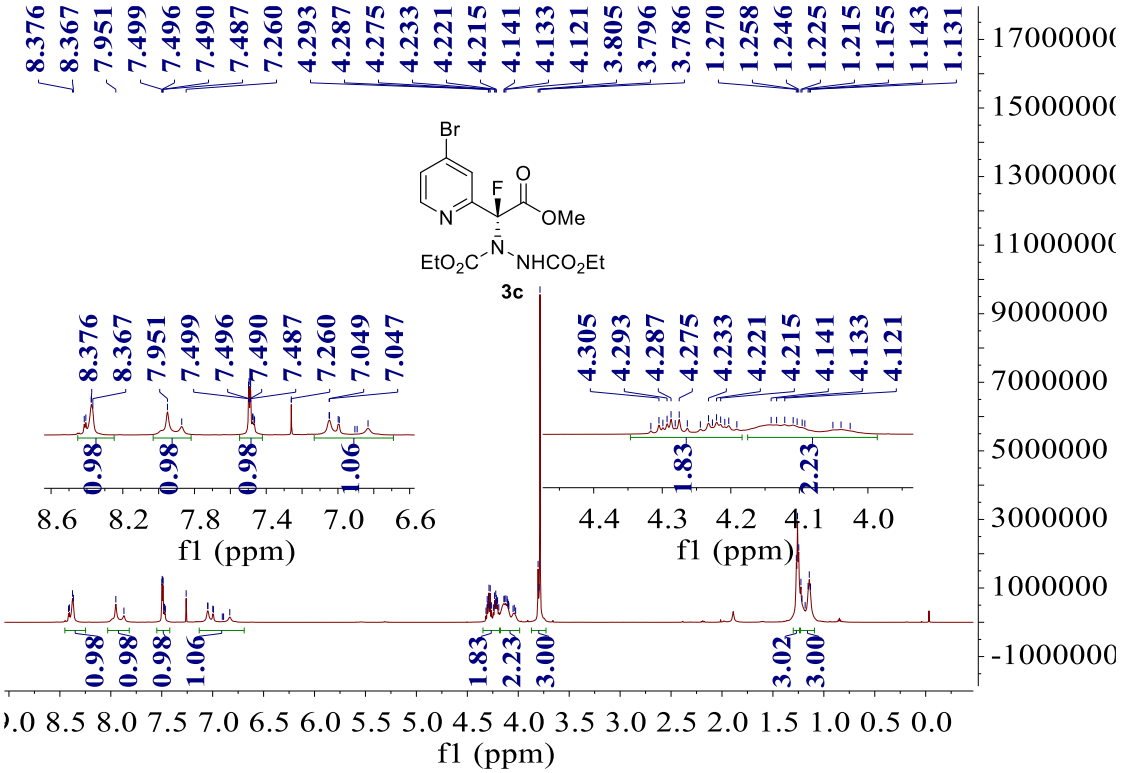
^{13}C{^{1}H} NMR Spectrum of **3b** (150 MHz, $CDCl_3$, rt)



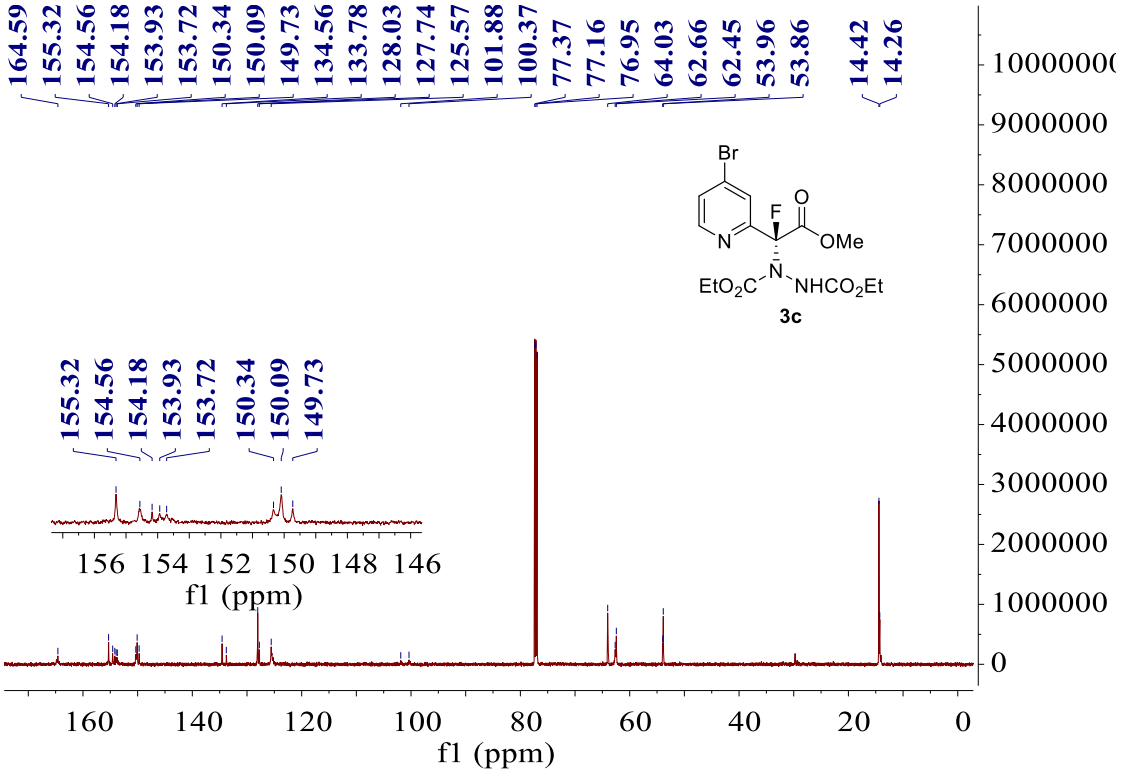
$^{19}F\{^{1}H\}$ NMR Spectrum of **3b** (565 MHz, $CDCl_3$, rt)



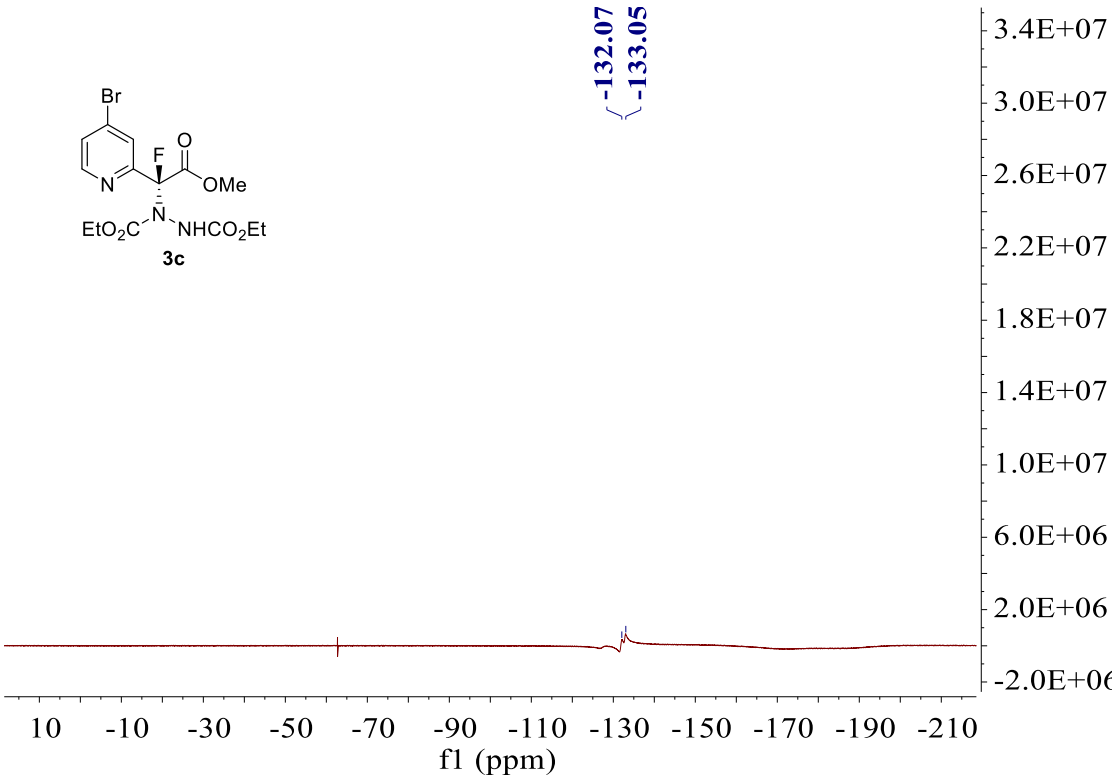
^{1}H NMR Spectrum of **3c** (600 MHz, $CDCl_3$, rt)



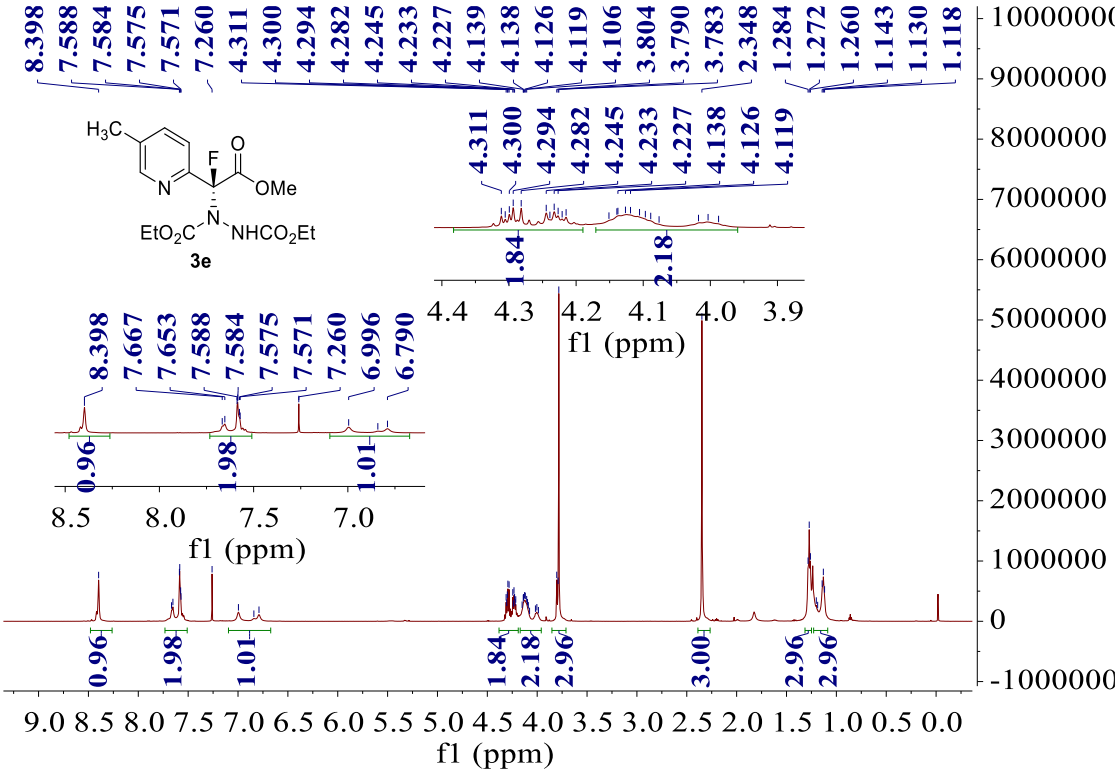
^{13}C{^{1}H} NMR Spectrum of **3c** (150 MHz, $CDCl_3$, rt)



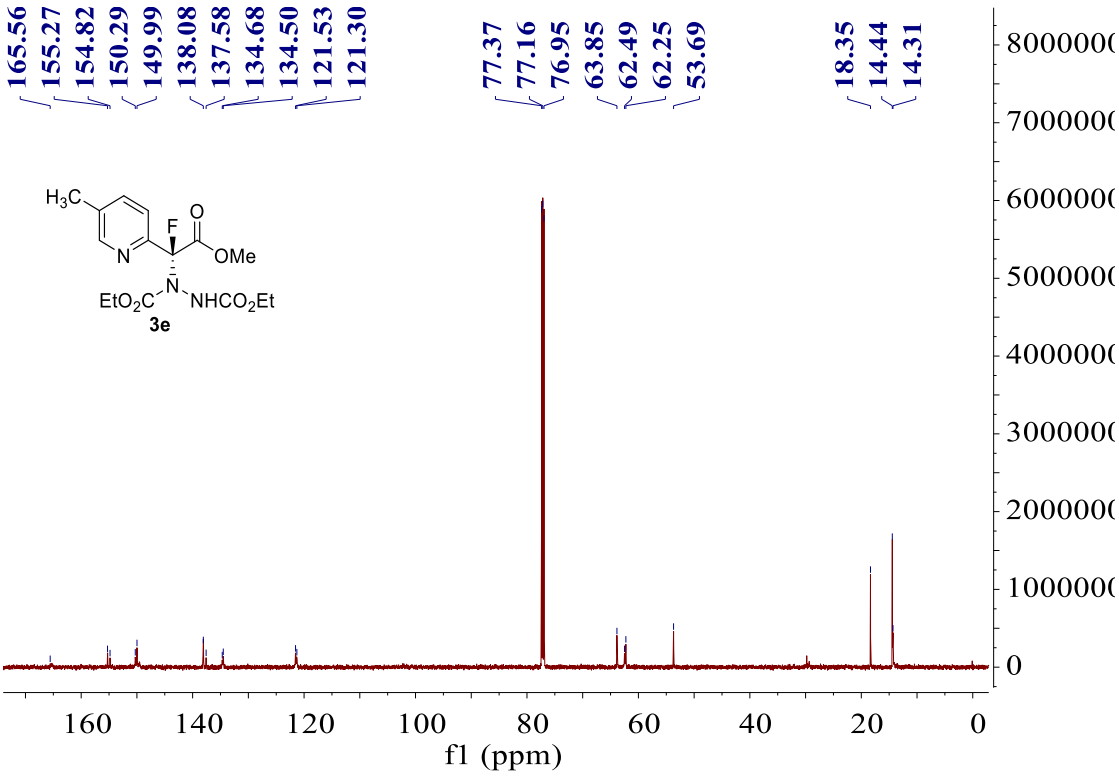
$^{19}F\{^{1}H\}$ NMR Spectrum of **3c** (565 MHz, $CDCl_3$, rt)



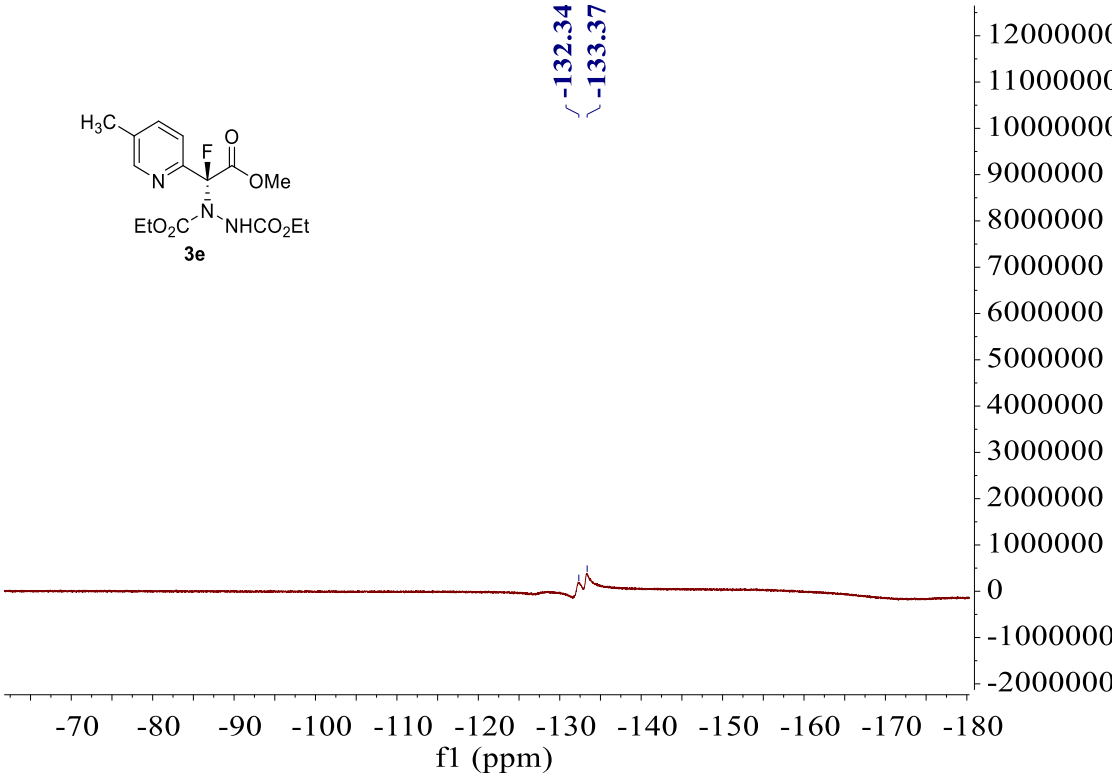
^{1}H NMR Spectrum of **3e** (600 MHz, $CDCl_3$, rt)



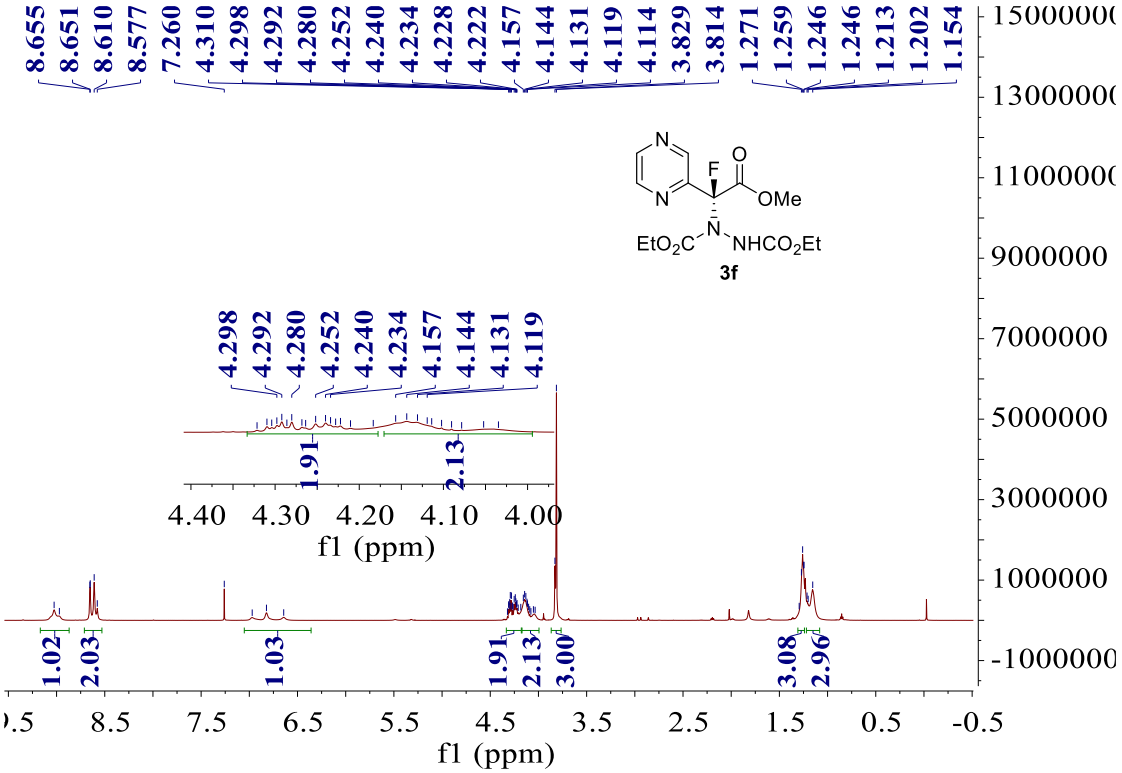
^{13}C{^{1}H} NMR Spectrum of **3e** (150 MHz, $CDCl_3$, rt)



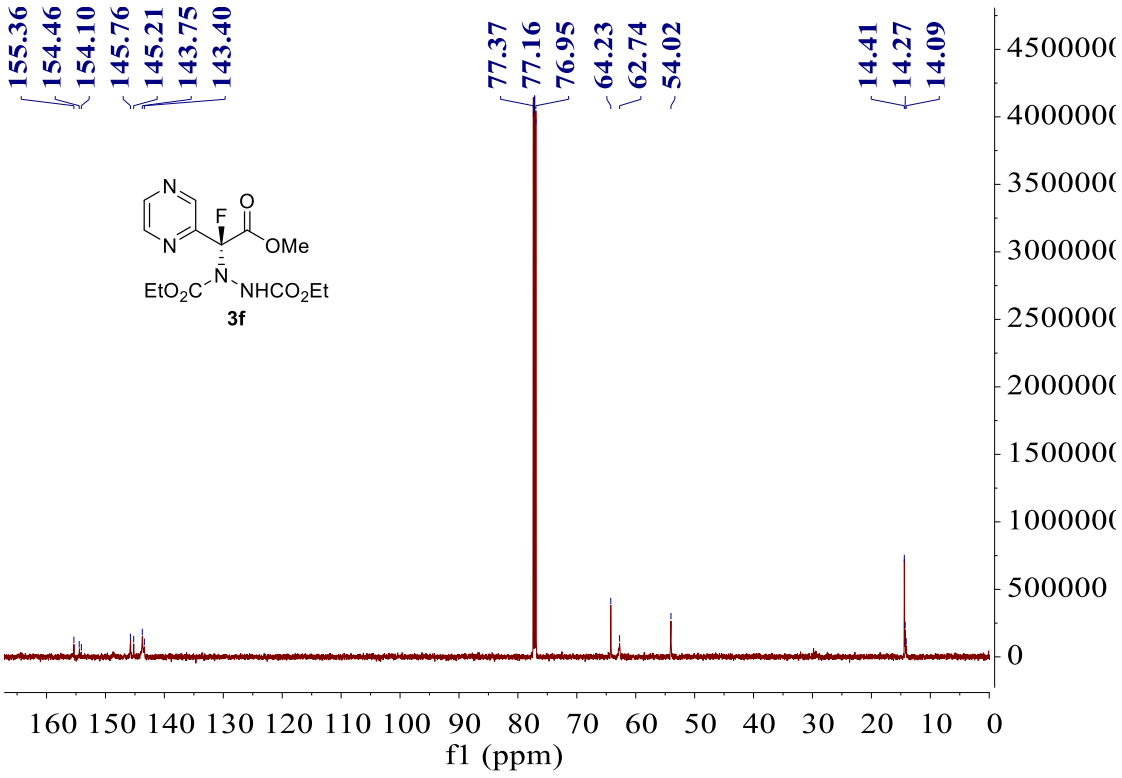
$^{19}F\{^{1}H\}$ NMR Spectrum of **3e** (565 MHz, $CDCl_3$, rt)



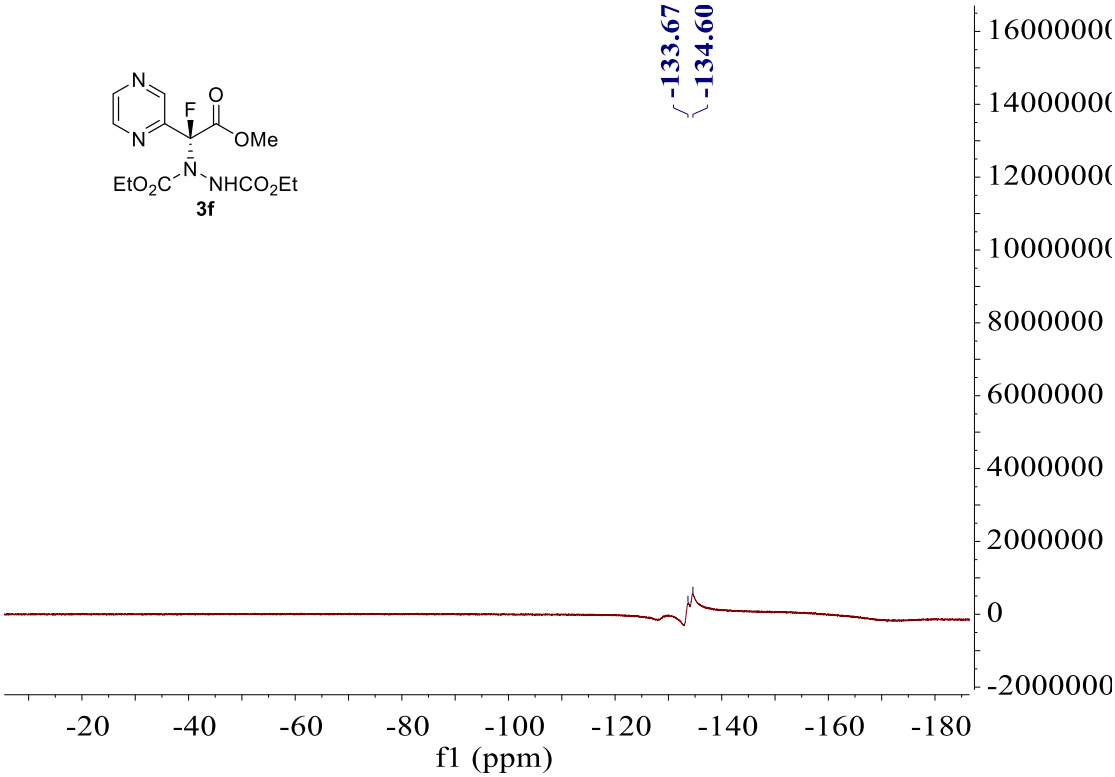
^{1}H NMR Spectrum of **3f** (600 MHz, $CDCl_3$, rt)



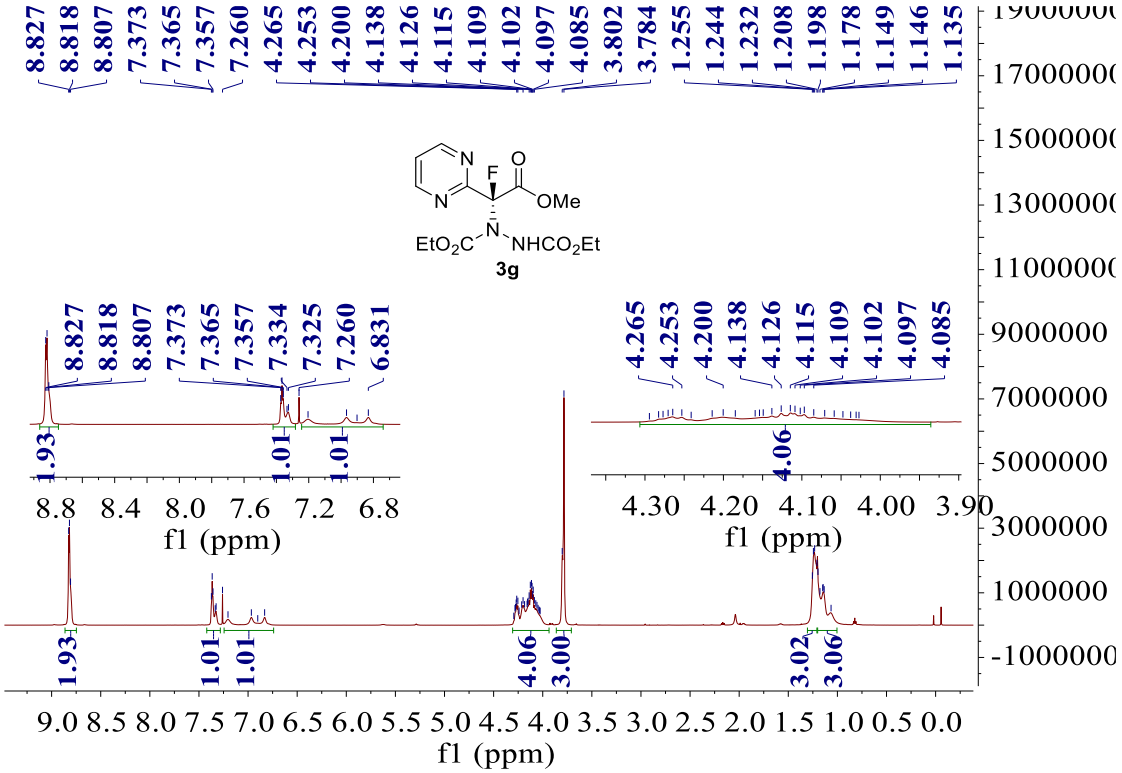
^{13}C{^{1}H} NMR Spectrum of **3f** (150 MHz, $CDCl_3$, rt)



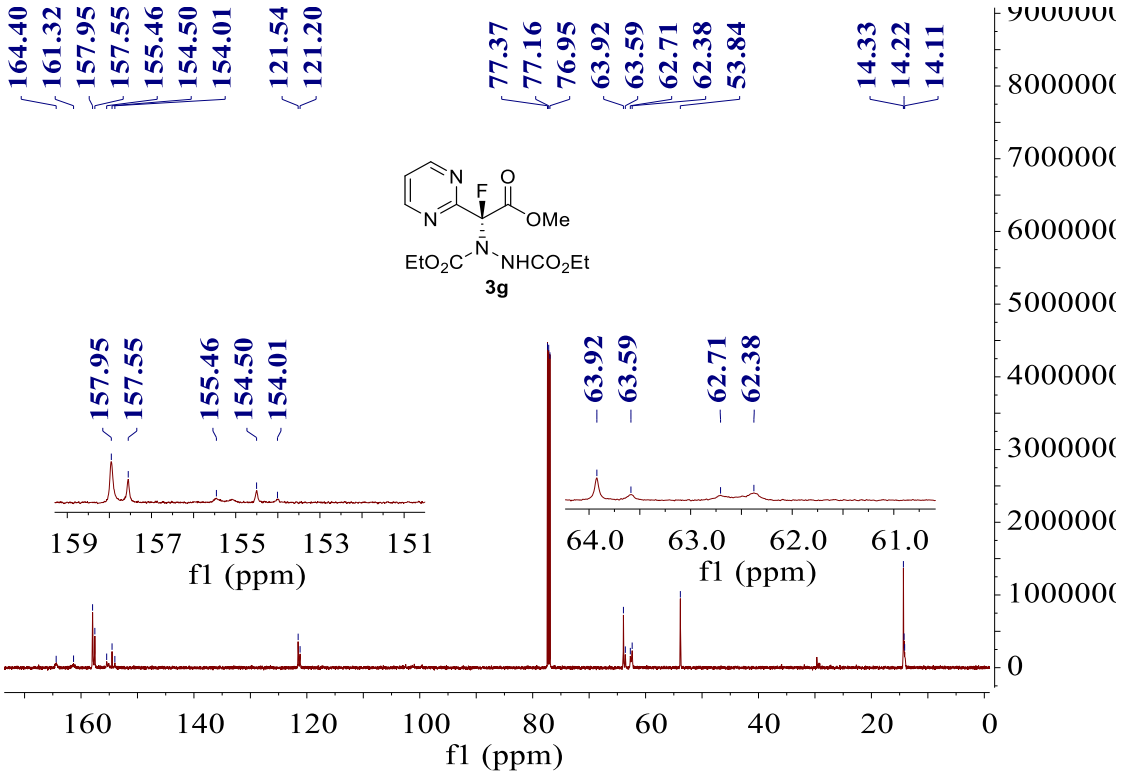
$^{19}F\{^{1}H\}$ NMR Spectrum of **3f** (565 MHz, $CDCl_3$, rt)



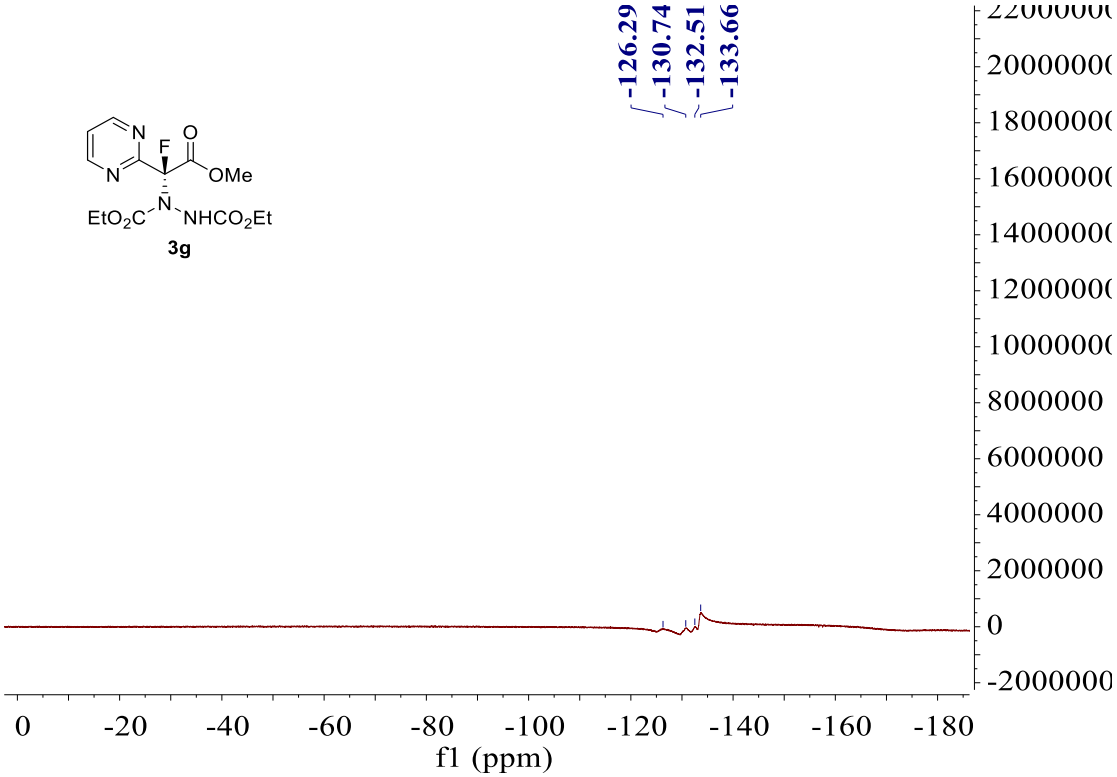
^{1}H NMR Spectrum of **3g** (600 MHz, $CDCl_3$, rt)



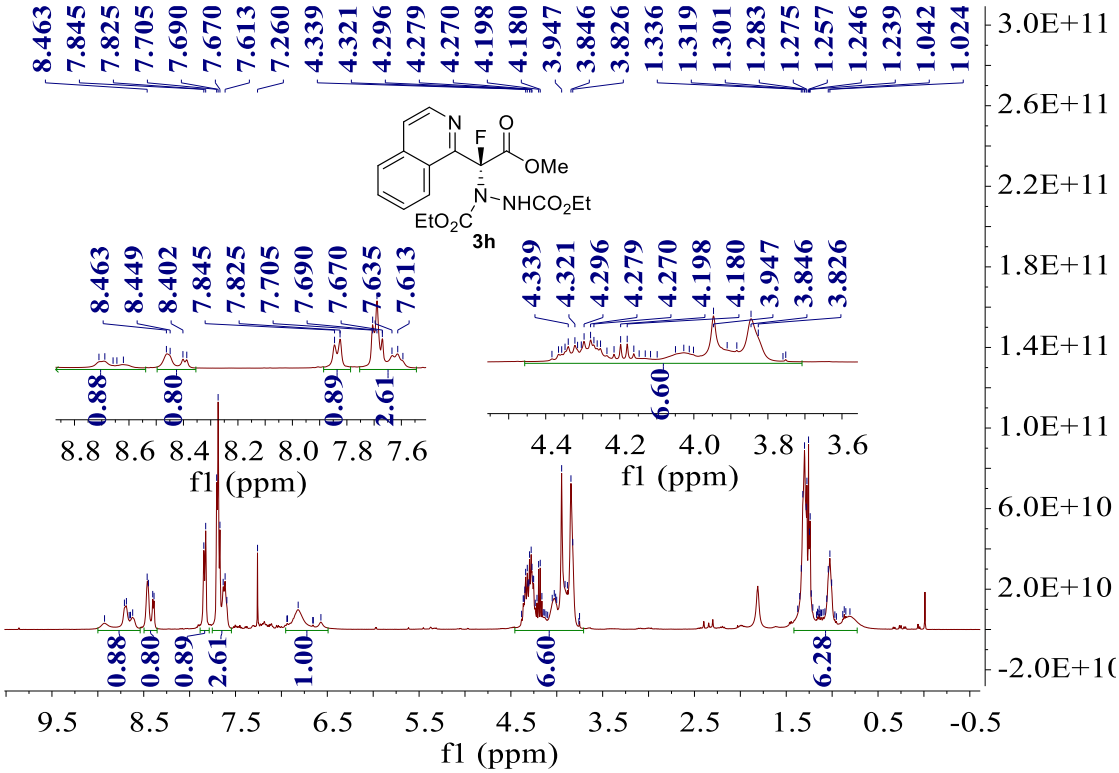
^{13}C{^{1}H} NMR Spectrum of **3g** (150 MHz, $CDCl_3$, rt)



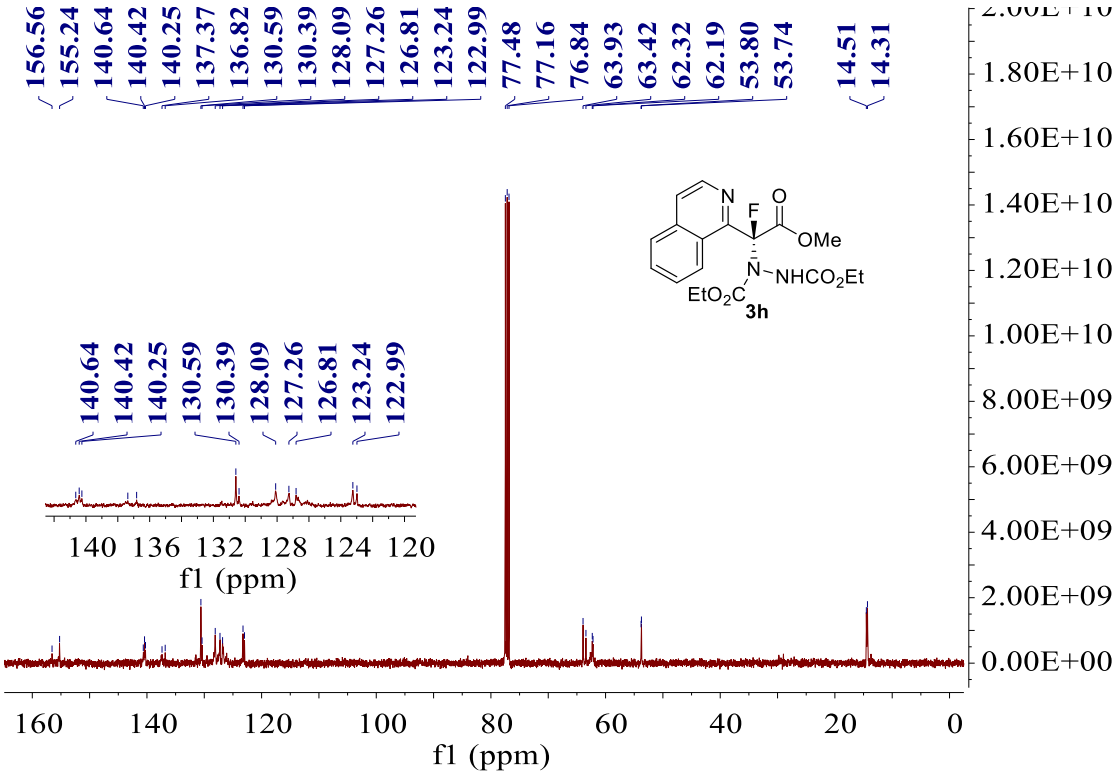
$^{19}F\{^{1}H\}$ NMR Spectrum of **3g** (565 MHz, $CDCl_3$, rt)



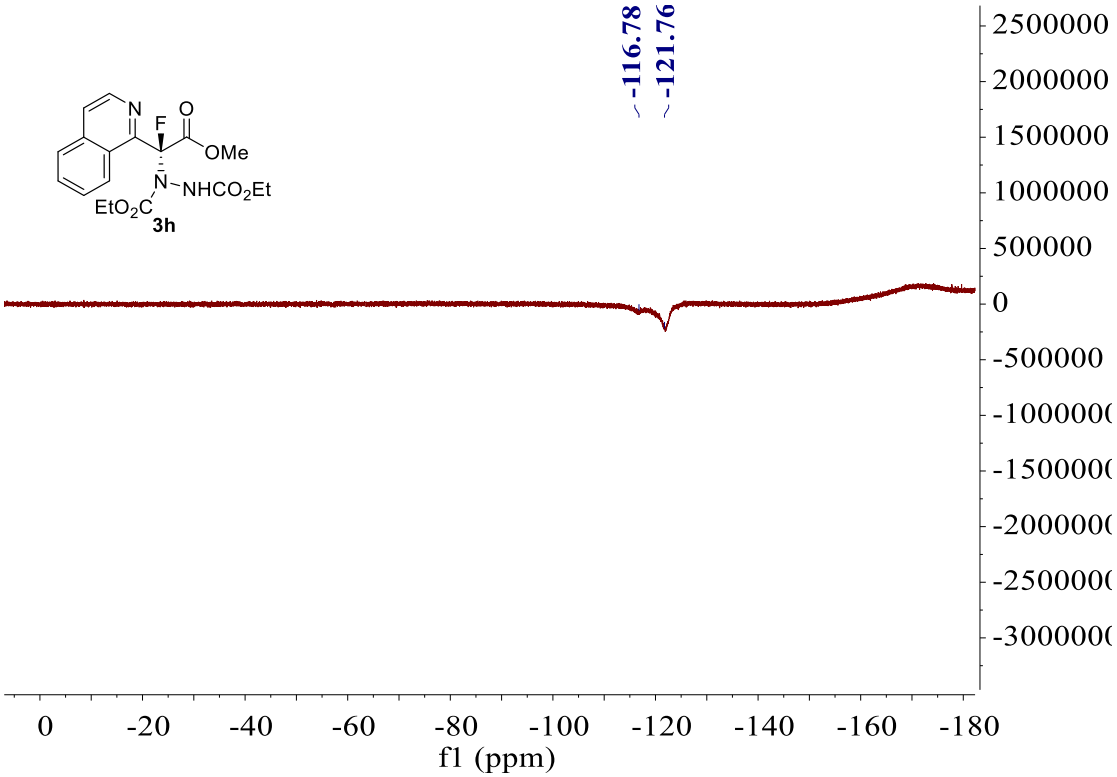
^{1}H NMR Spectrum of **3h** (400 MHz, $CDCl_3$, rt)



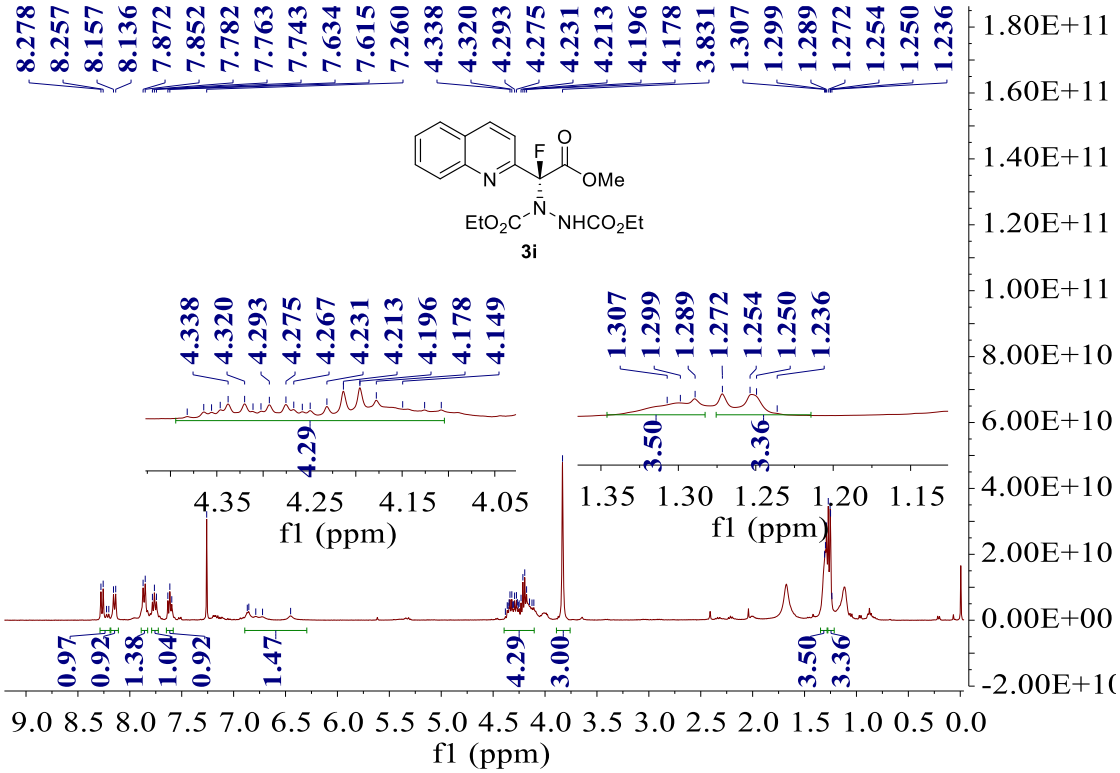
^{13}C{^{1}H} NMR Spectrum of **3h** (100 MHz, $CDCl_3$, rt)



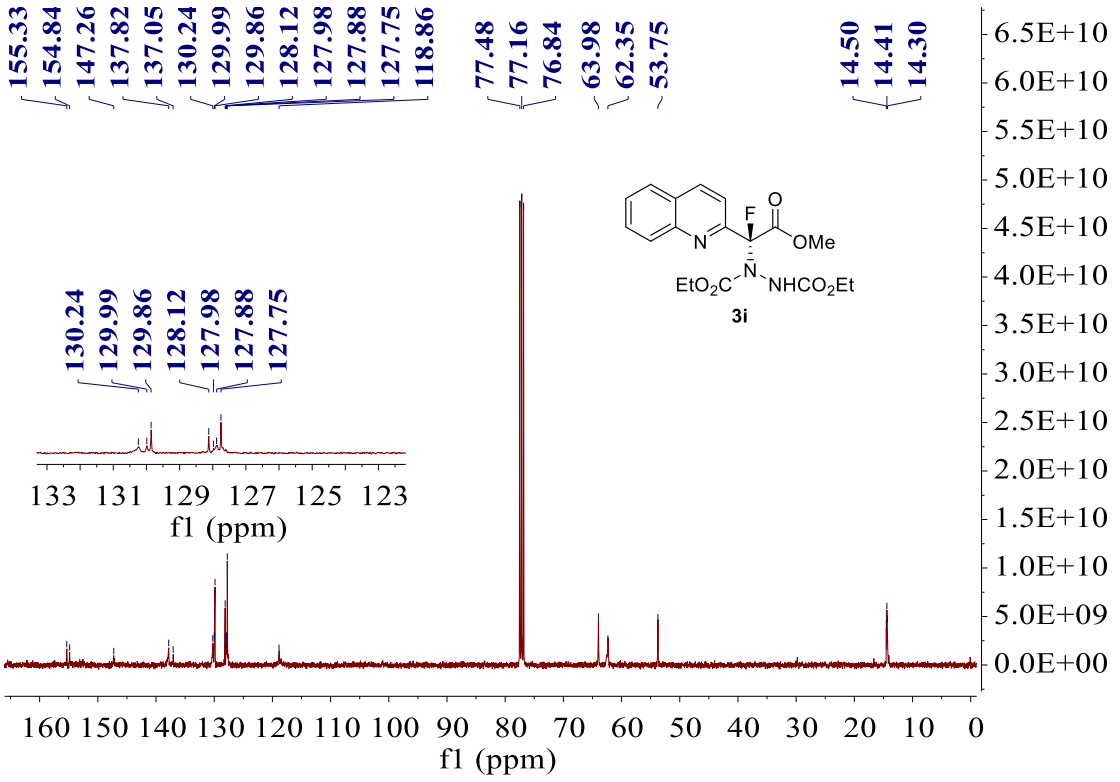
$^{19}F\{^{1}H\}$ NMR Spectrum of **3h** (376 MHz, $CDCl_3$, rt)



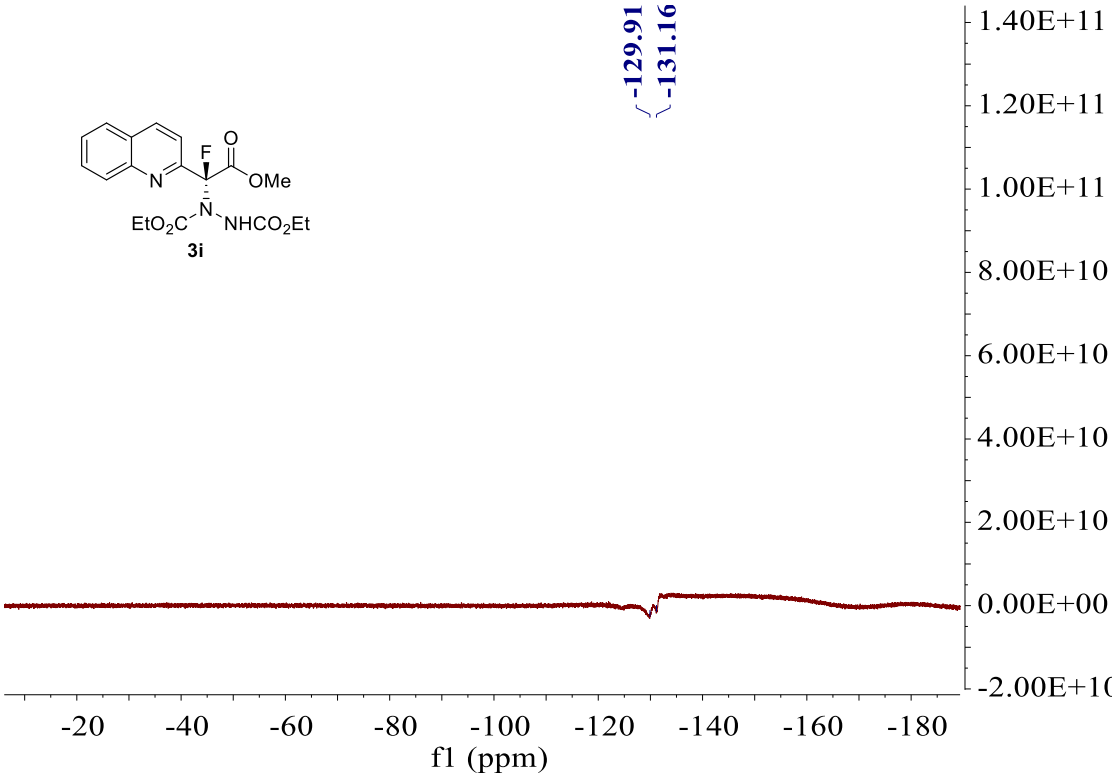
^{1}H NMR Spectrum of **3i** (400 MHz, $CDCl_3$, rt)



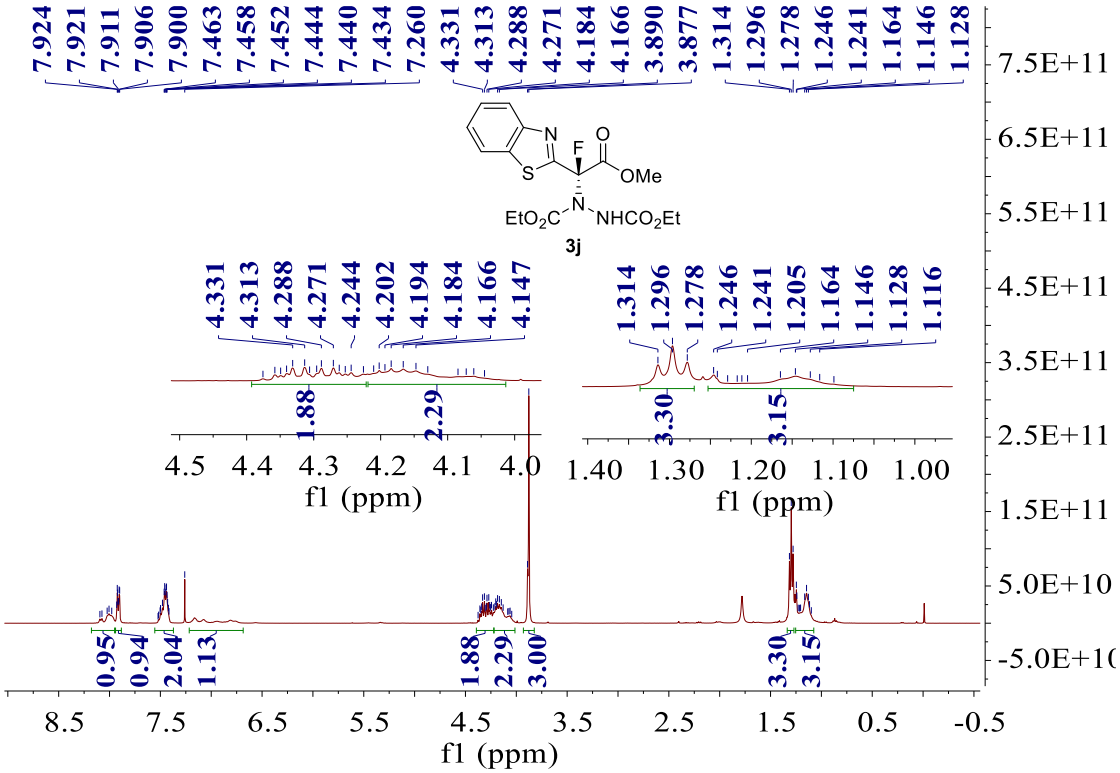
^{13}C{^{1}H} NMR Spectrum of **3i** (100 MHz, $CDCl_3$, rt)



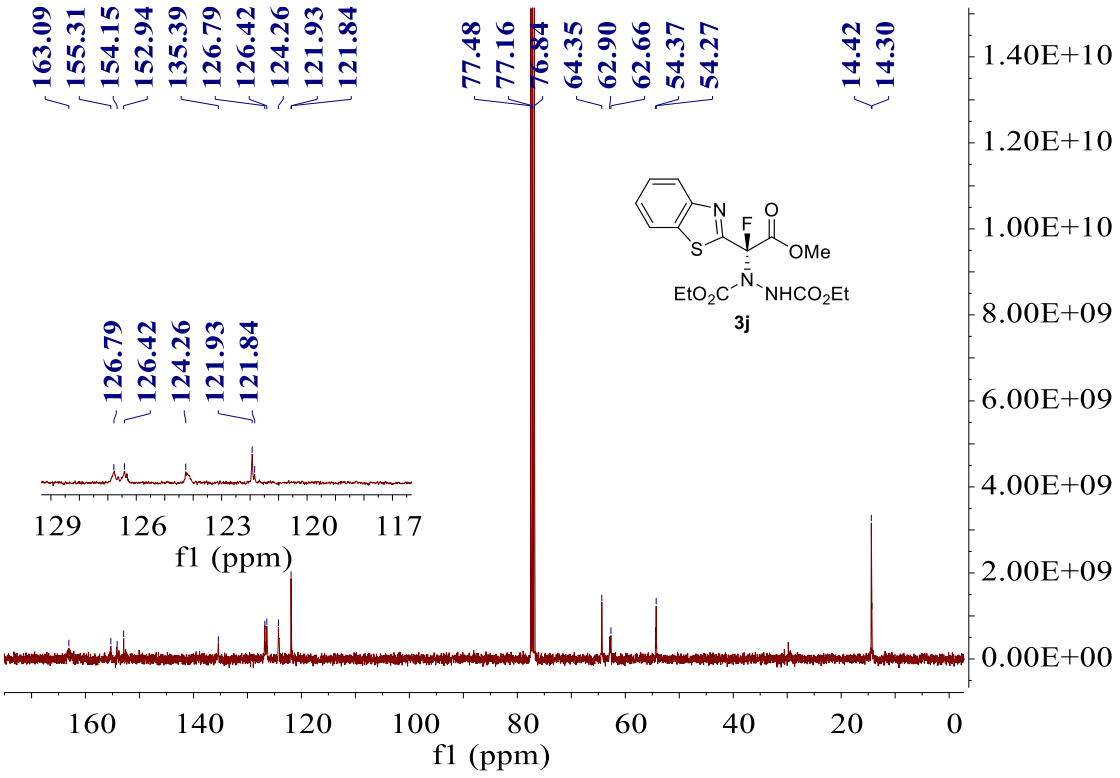
$^{19}F\{^{1}H\}$ NMR Spectrum of **3i** (376 MHz, $CDCl_3$, rt)



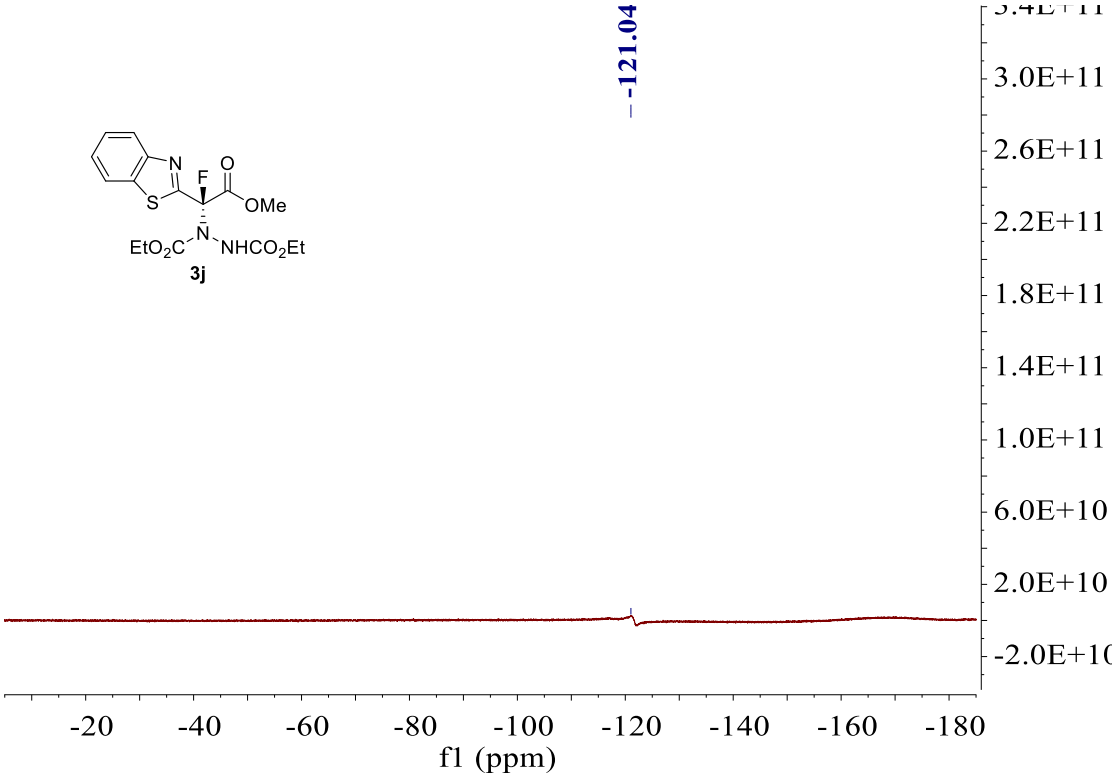
^{1}H NMR Spectrum of **3j** (400 MHz, $CDCl_3$, rt)



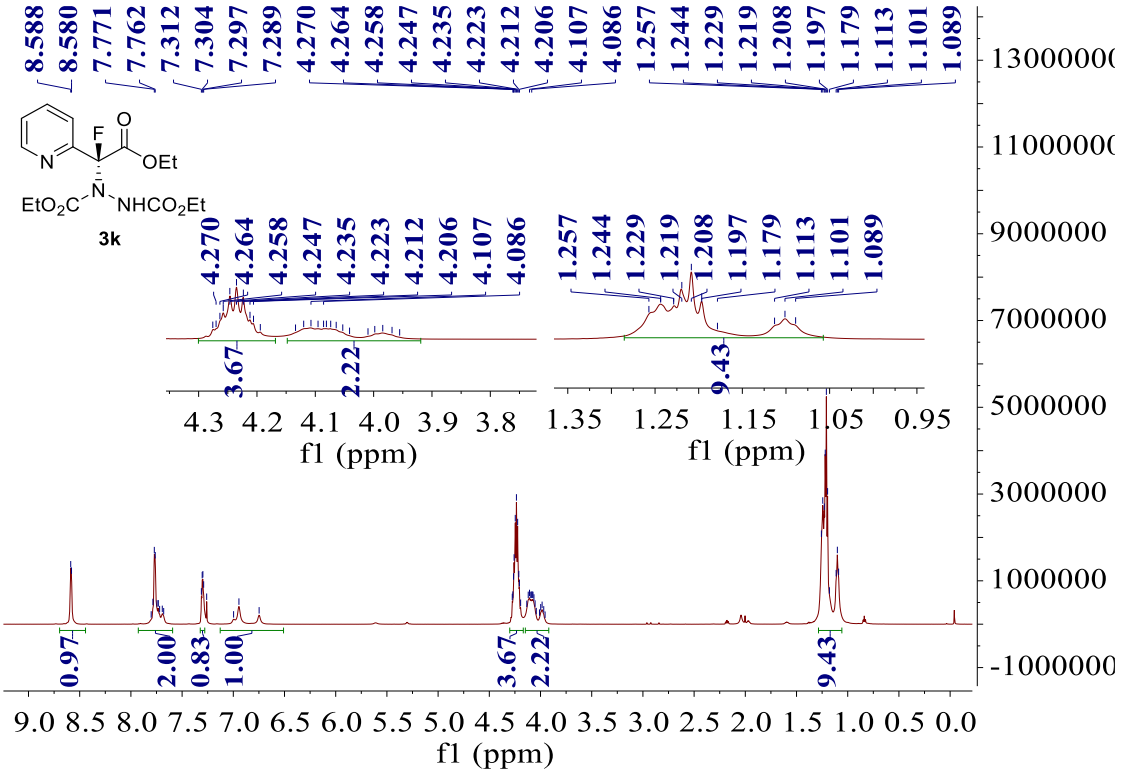
^{13}C{^{1}H} NMR Spectrum of **3j** (100 MHz, $CDCl_3$, rt)



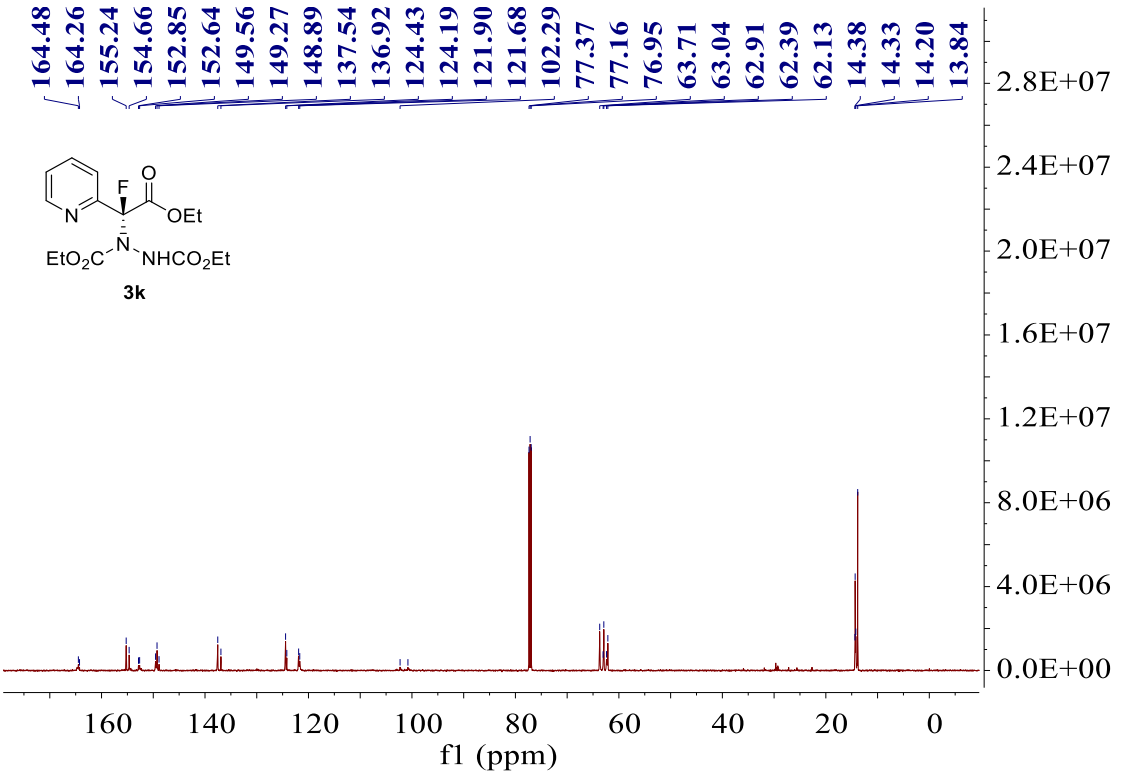
$^{19}F\{^{1}H\}$ NMR Spectrum of **3j** (376 MHz, $CDCl_3$, rt)



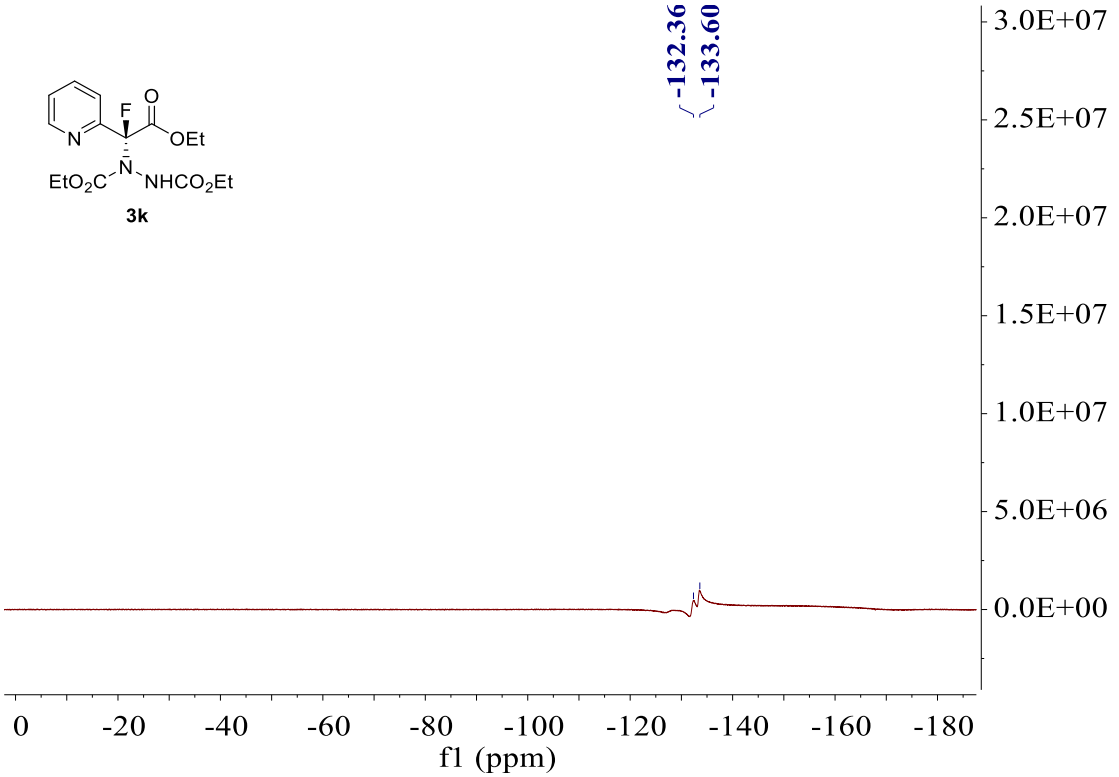
^{1}H NMR Spectrum of **3k** (600 MHz, $CDCl_3$, rt)



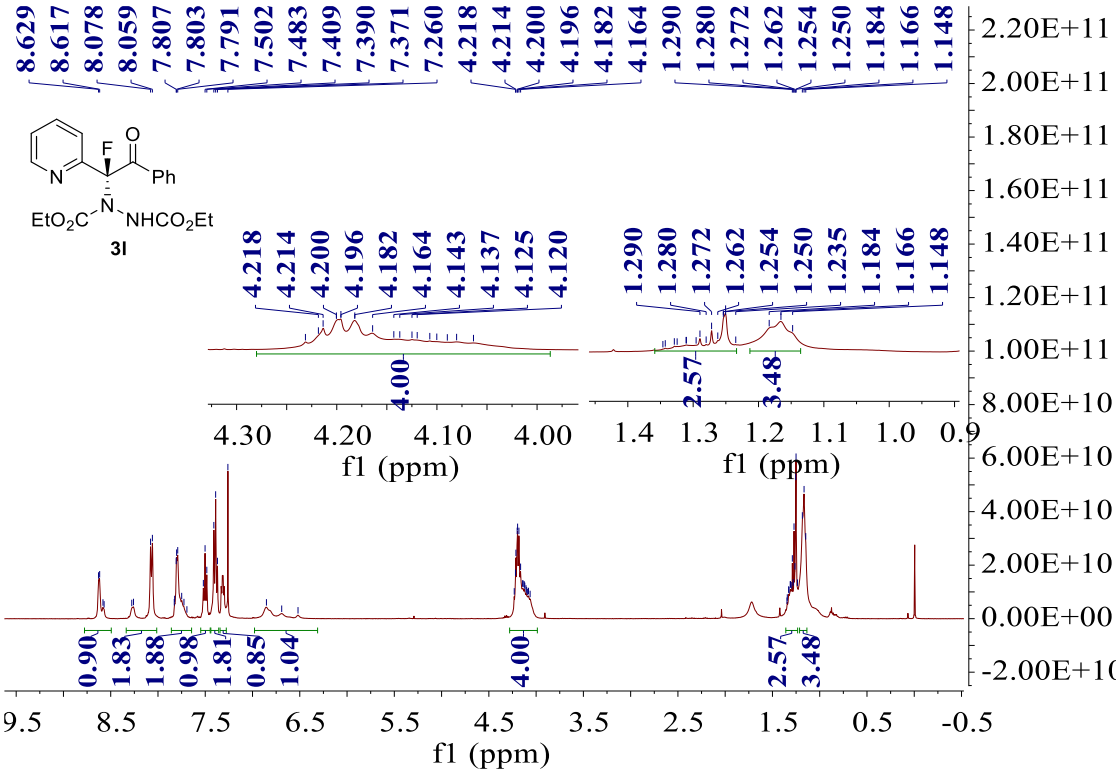
^{13}C{^{1}H} NMR Spectrum of **3k** (150 MHz, $CDCl_3$, rt)



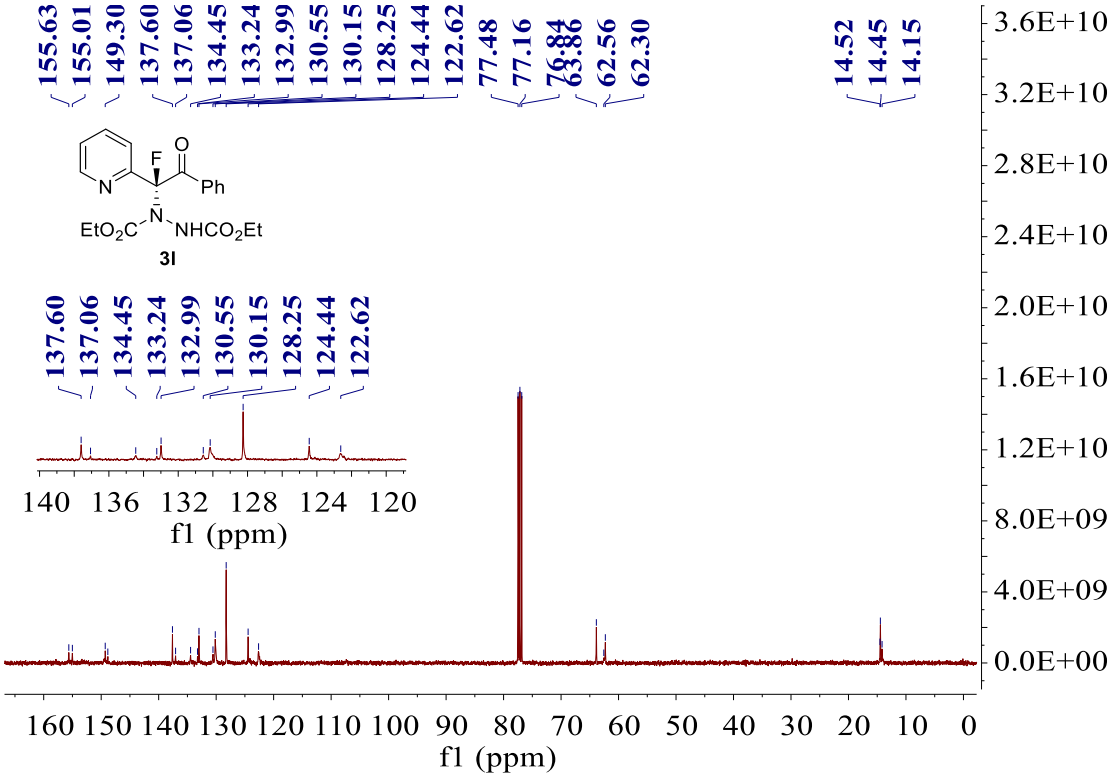
$^{19}F\{^{1}H\}$ NMR Spectrum of **3k** (565 MHz, $CDCl_3$, rt)



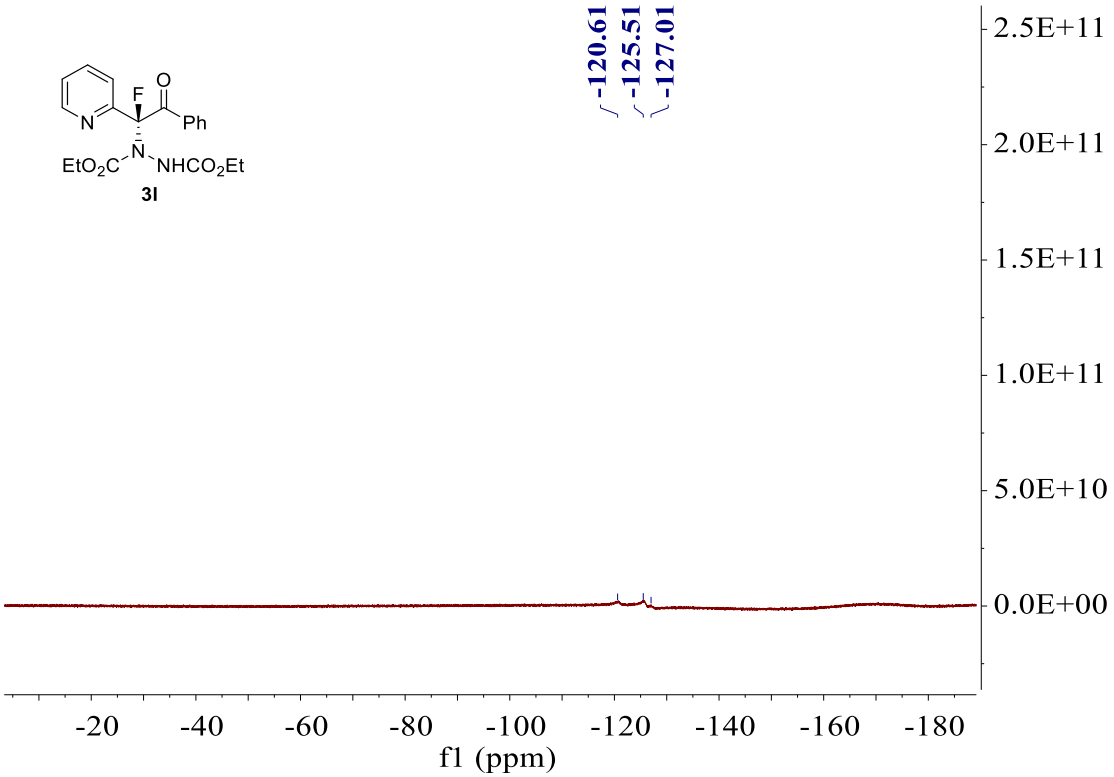
^{1}H NMR Spectrum of **3l** (400 MHz, $CDCl_3$, rt)



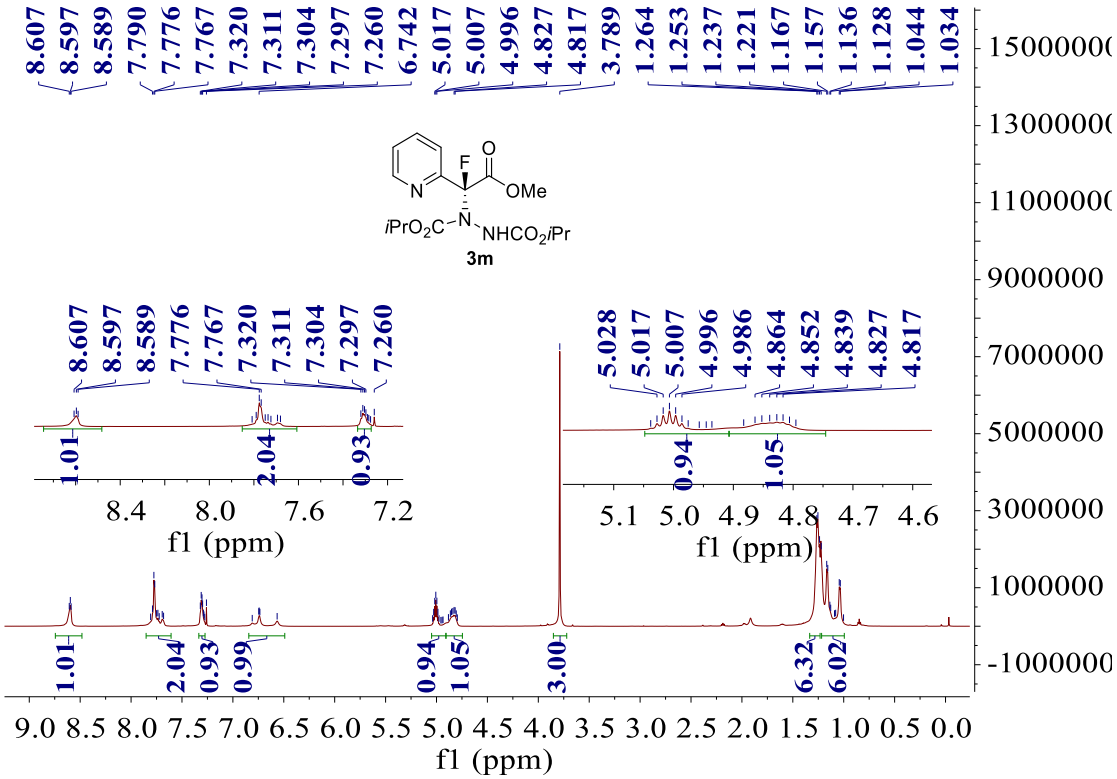
^{13}C{^{1}H} NMR Spectrum of **3l** (100 MHz, $CDCl_3$, rt)



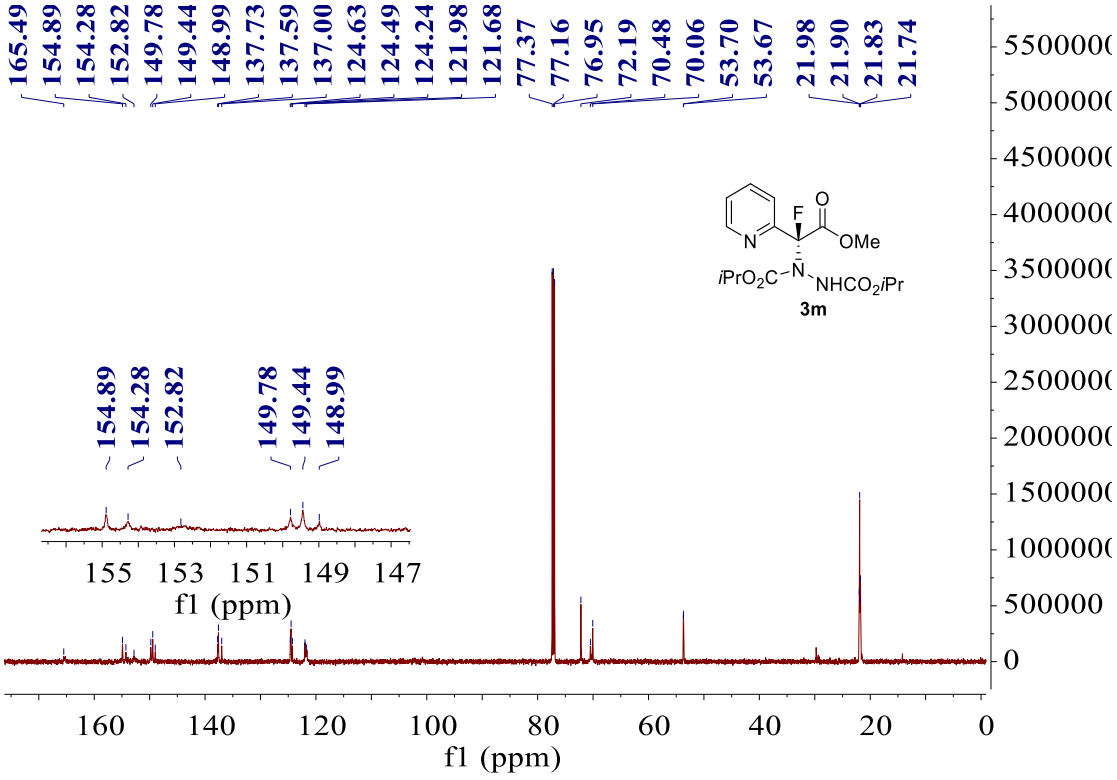
$^{19}F\{^{1}H\}$ NMR Spectrum of **3l** (376 MHz, $CDCl_3$, rt)



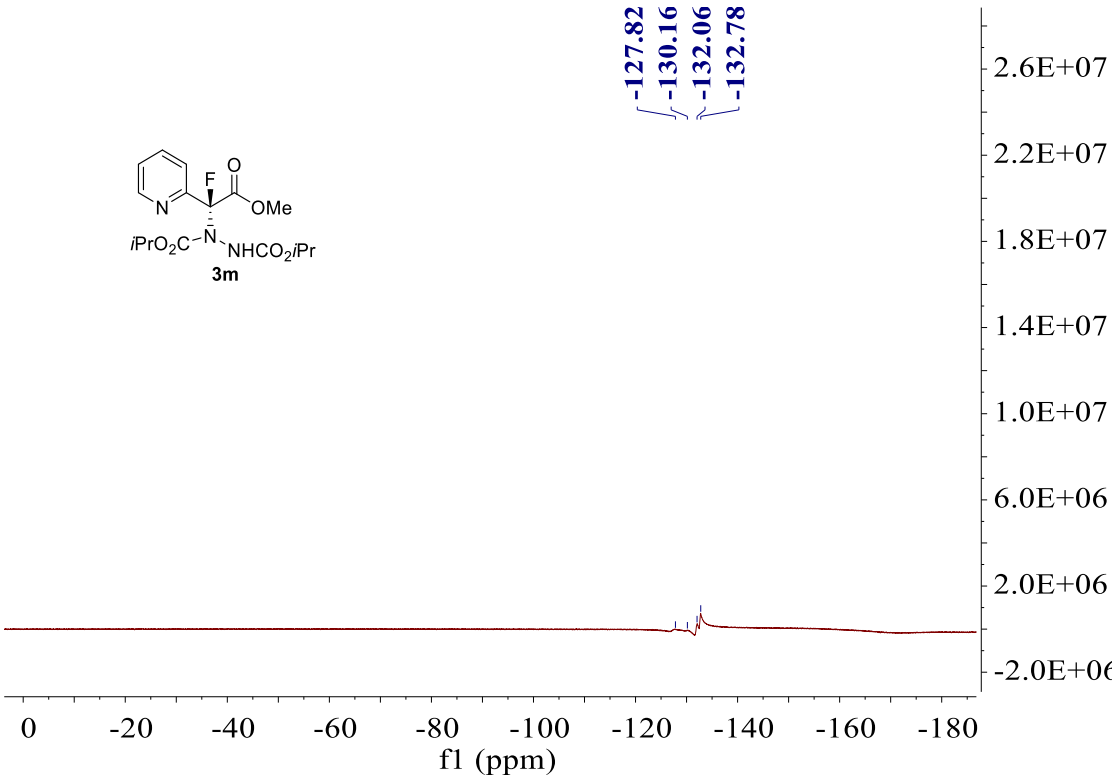
^{1}H NMR Spectrum of **3m** (600 MHz, $CDCl_3$, rt)



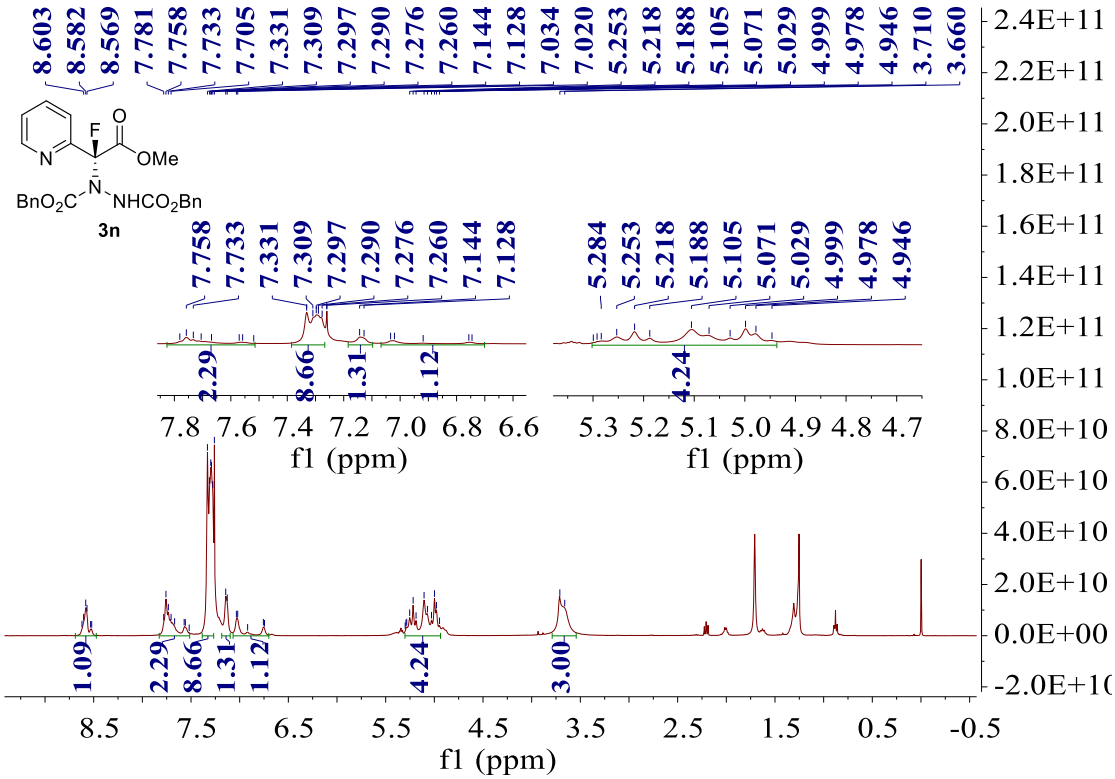
^{13}C{^{1}H} NMR Spectrum of **3m** (150 MHz, $CDCl_3$, rt)



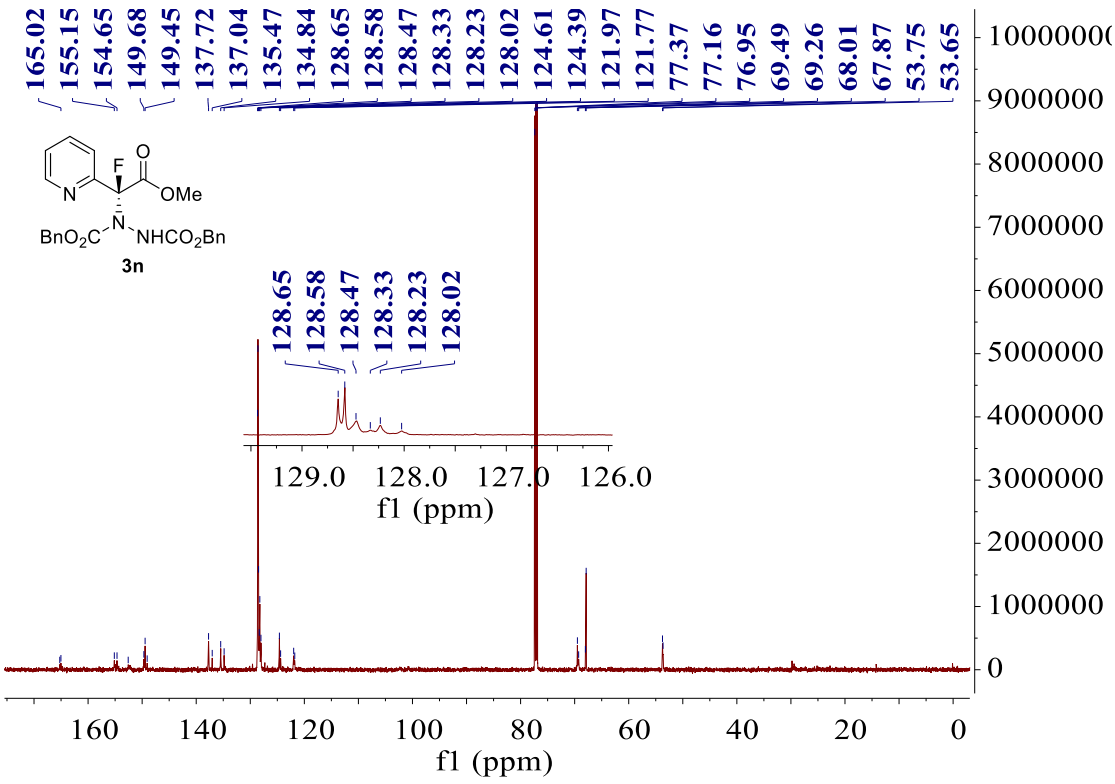
$^{19}F\{^{1}H\}$ NMR Spectrum of **3m** (565 MHz, $CDCl_3$, rt)



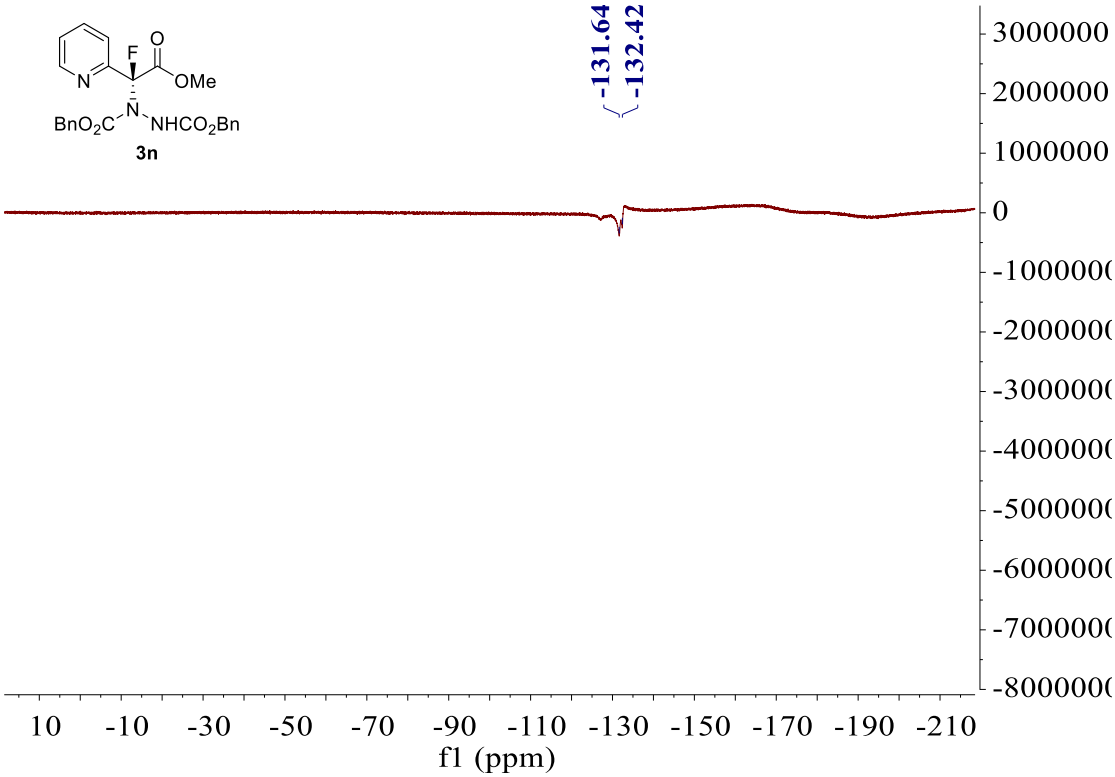
^{1}H NMR Spectrum of **3n** (600 MHz, $CDCl_3$, rt)



^{13}C{^{1}H} NMR Spectrum of **3n** (150 MHz, $CDCl_3$, rt)

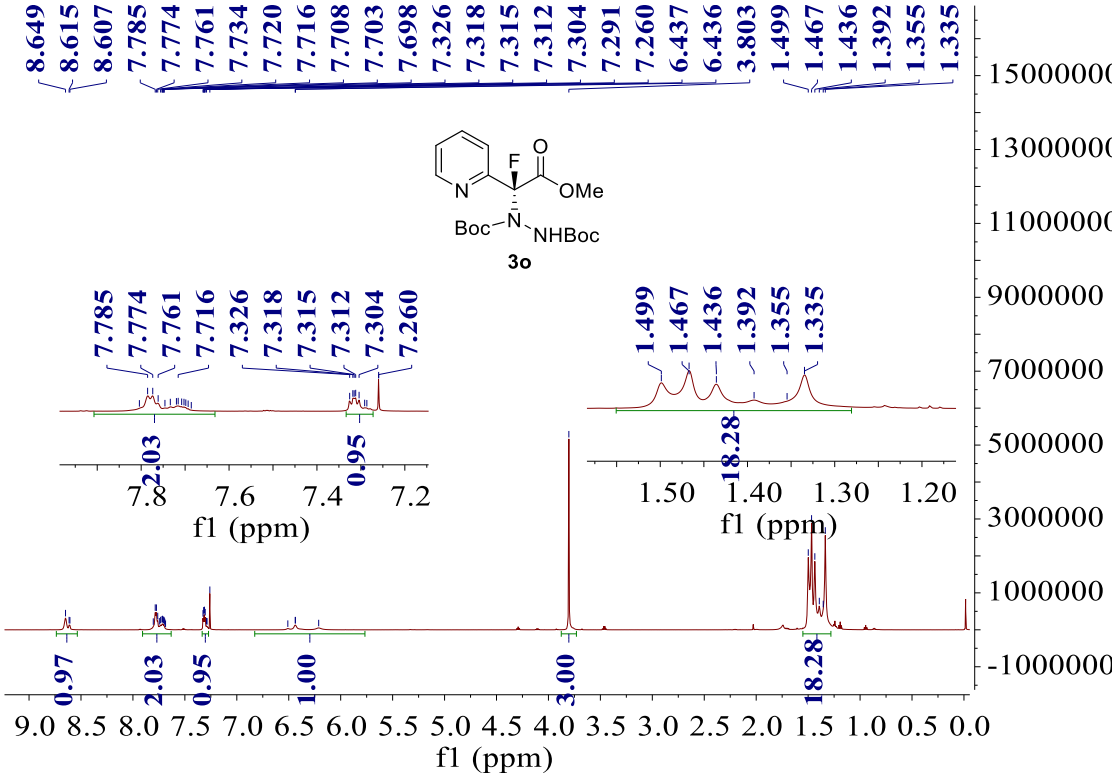


$^{19}F\{^{1}H\}$ NMR Spectrum of **3n** (565 MHz, $CDCl_3$, rt)

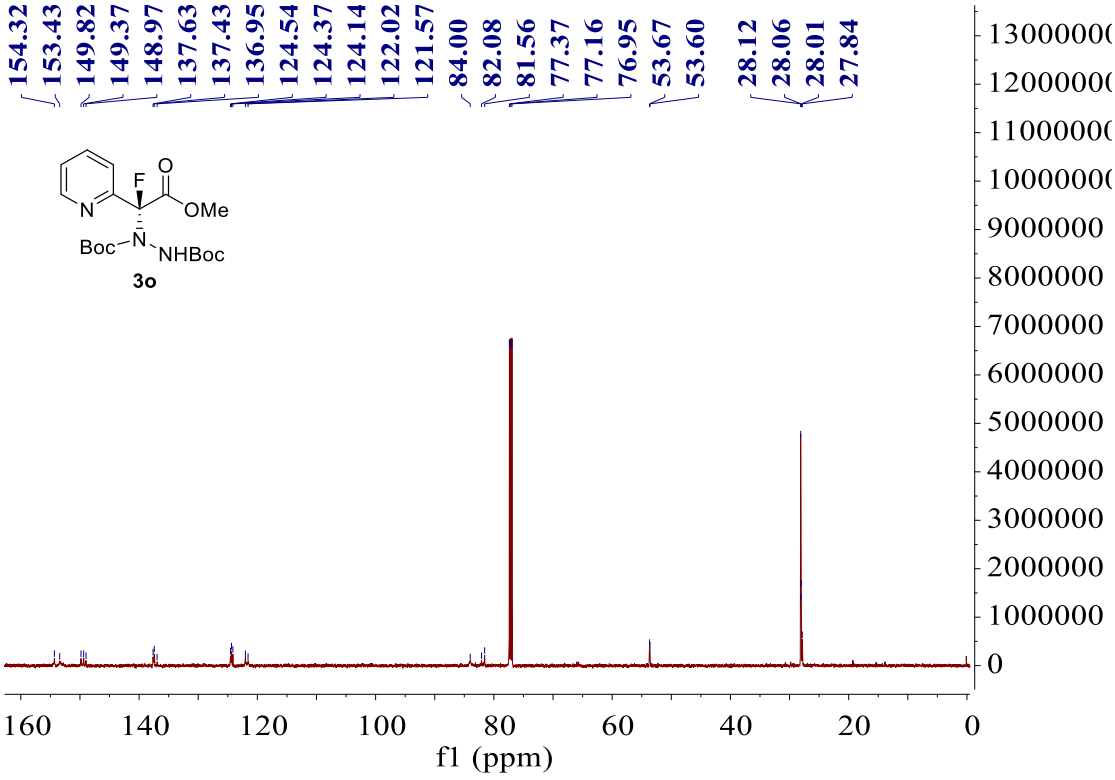


3n

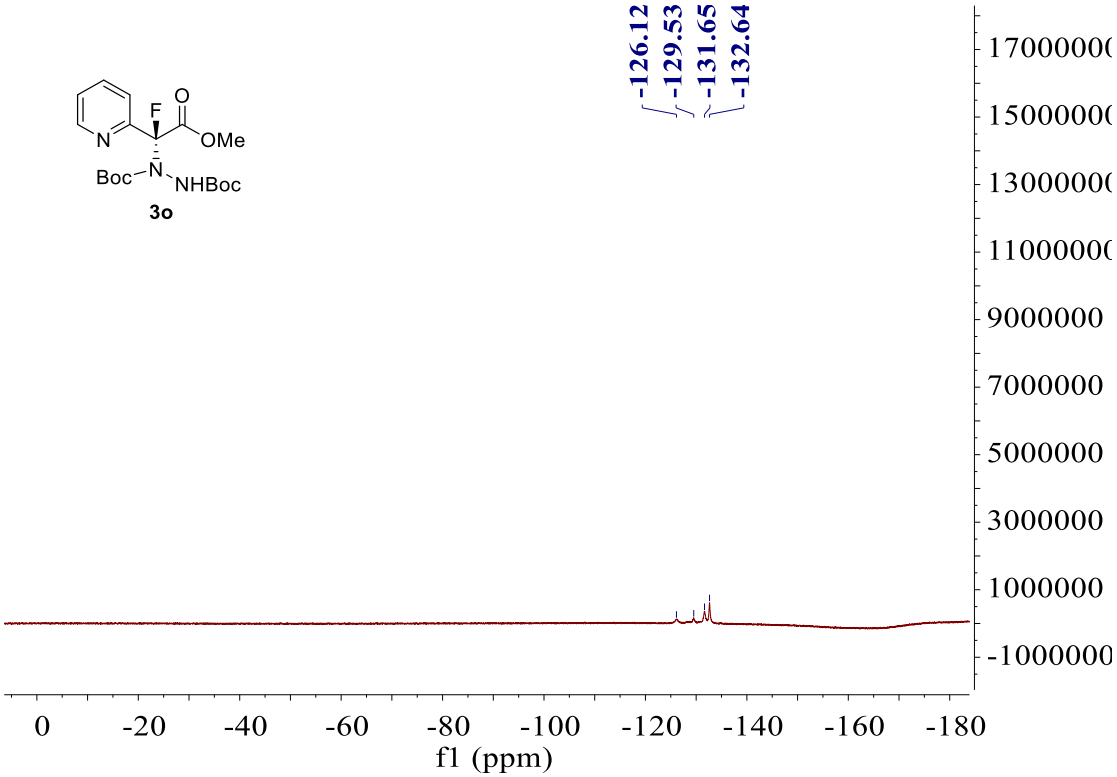
^{1}H NMR Spectrum of **3o** (600 MHz, $CDCl_3$, rt)



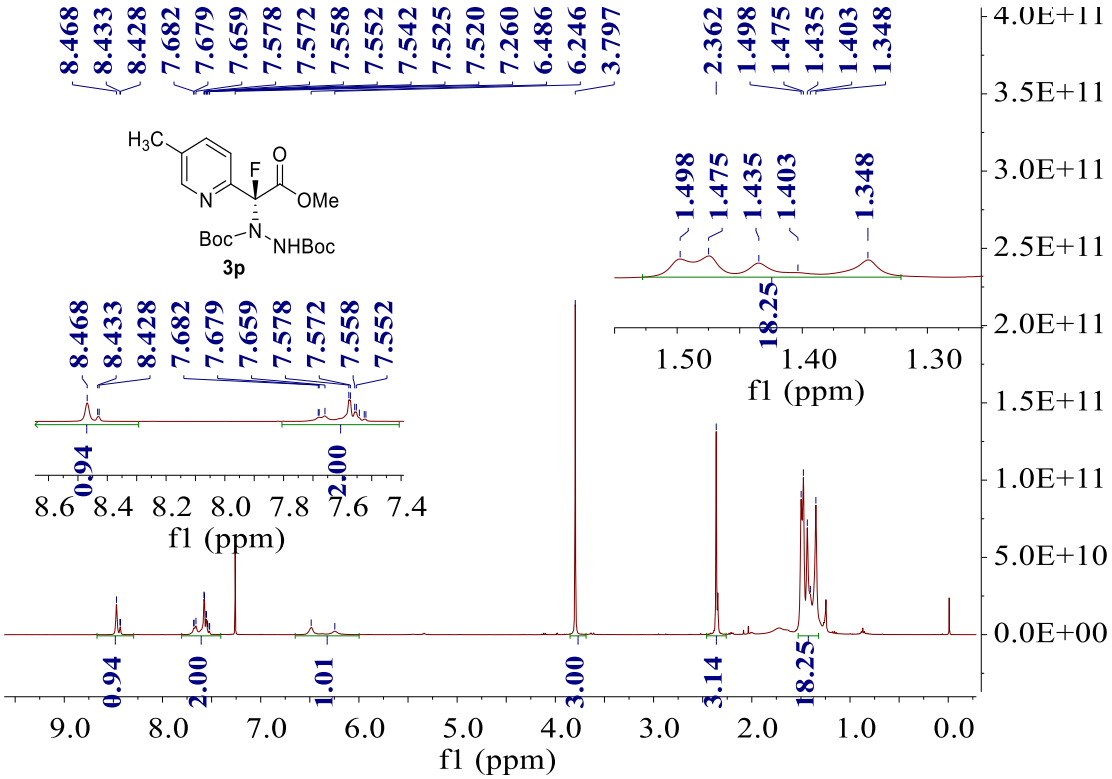
^{13}C{^{1}H} NMR Spectrum of **3o** (150 MHz, $CDCl_3$, rt)



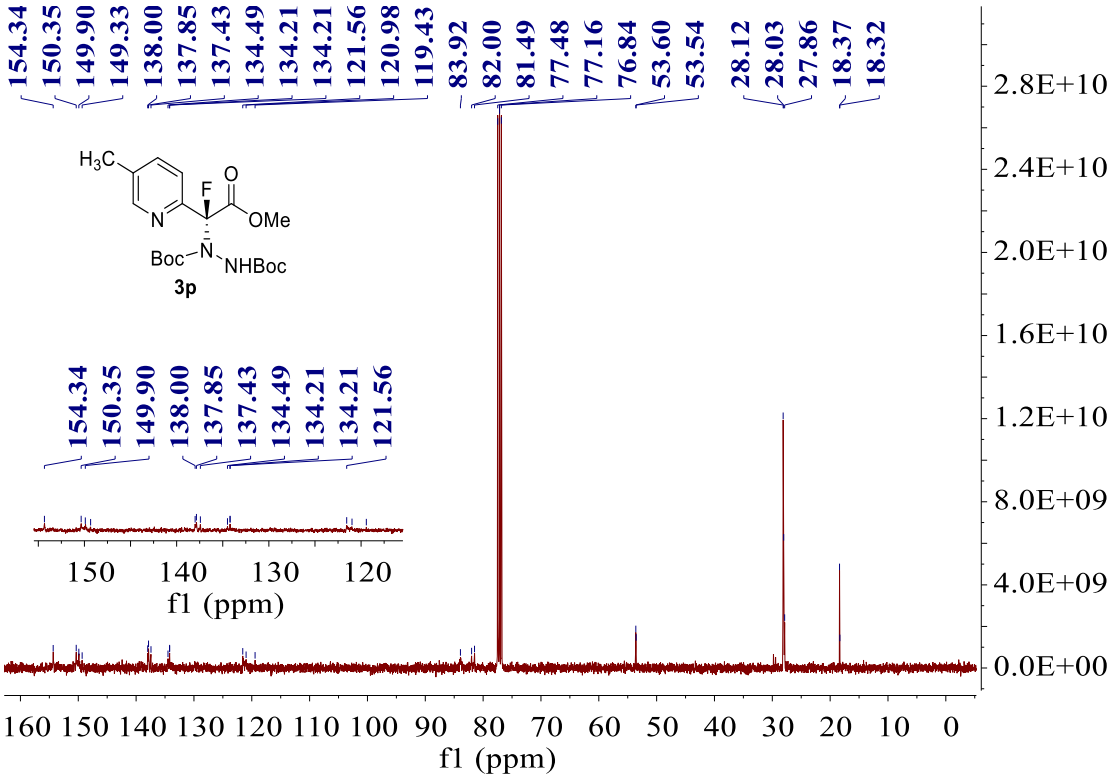
$^{19}F\{^{1}H\}$ NMR Spectrum of **3o** (565 MHz, $CDCl_3$, rt)



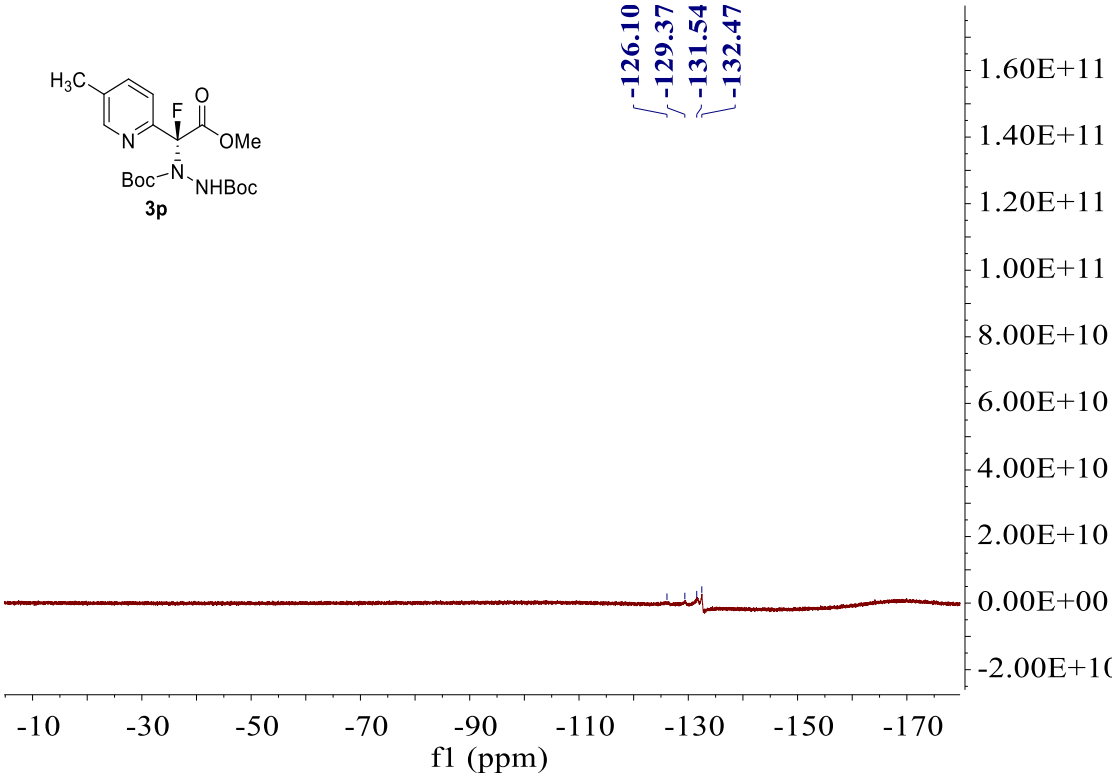
^{1}H NMR Spectrum of **3p** (400 MHz, $CDCl_3$, rt)



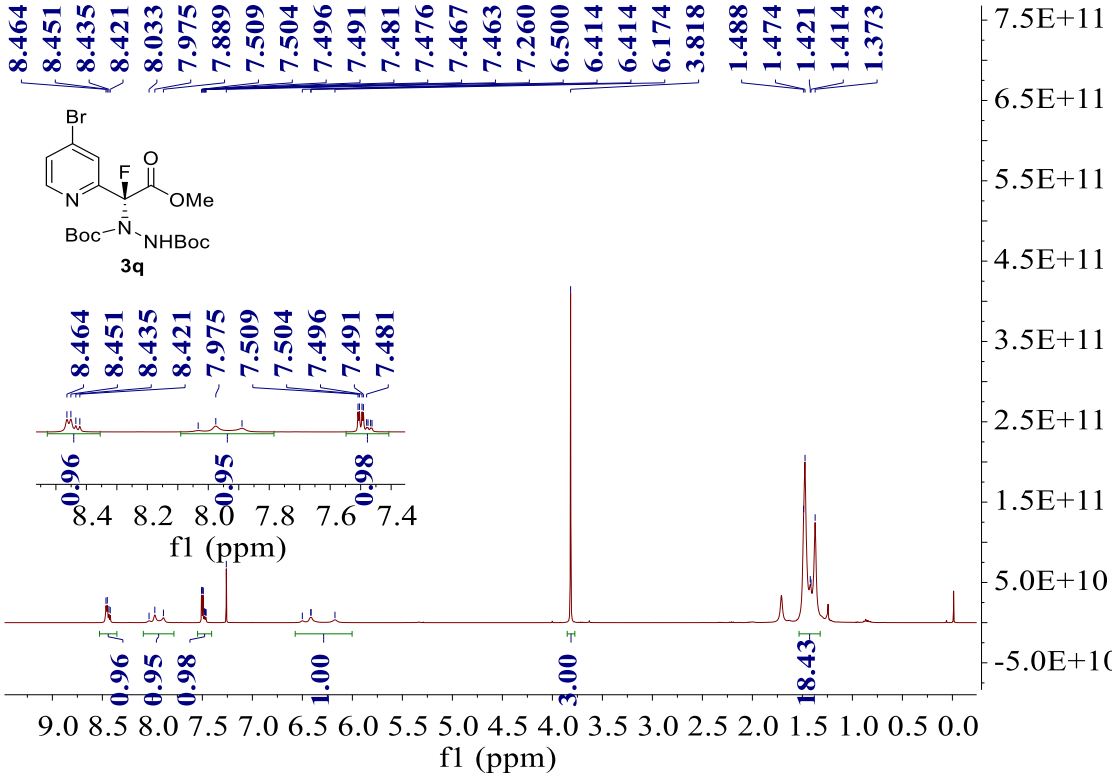
^{13}C{^{1}H} NMR Spectrum of **3p** (100 MHz, $CDCl_3$, rt)



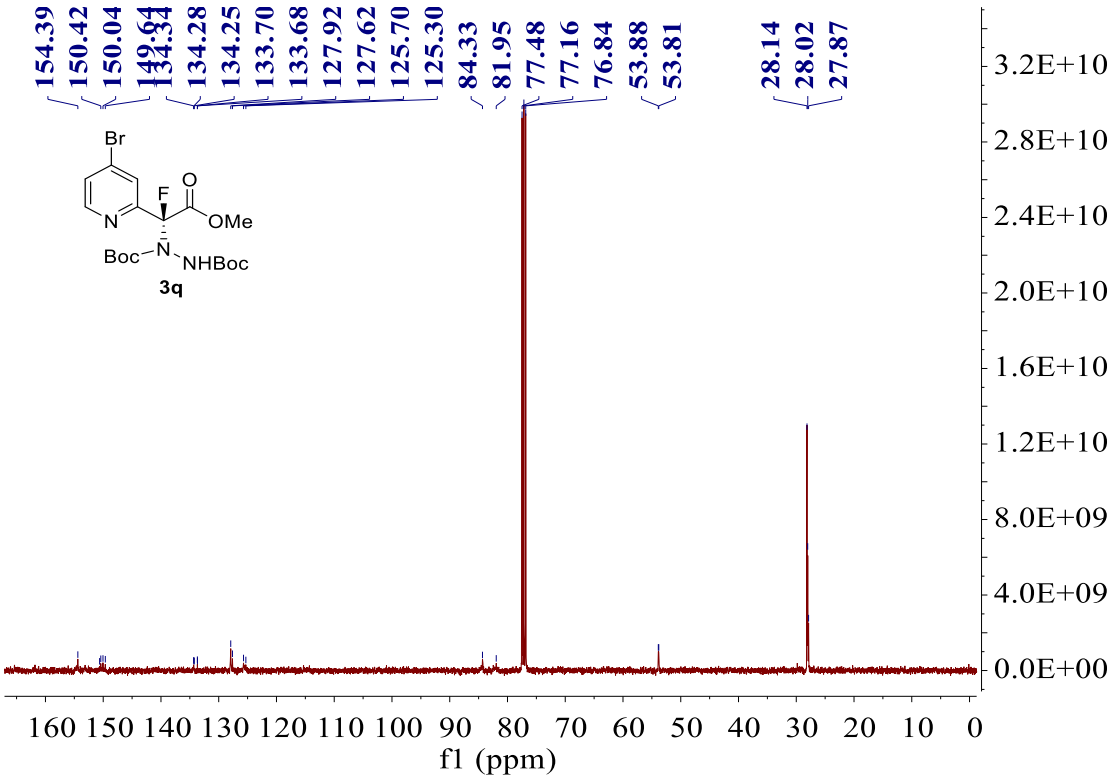
$^{19}F\{^{1}H\}$ NMR Spectrum of **3p** (376 MHz, $CDCl_3$, rt)



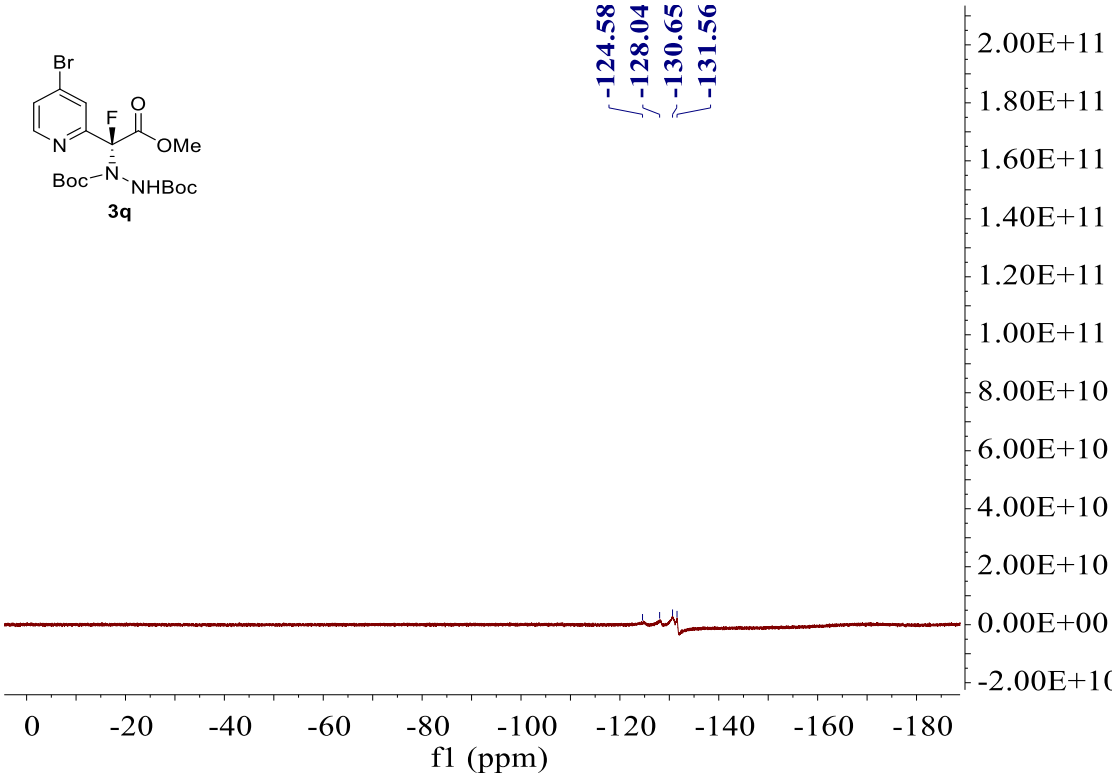
^{1}H NMR Spectrum of **3q** (400 MHz, $CDCl_3$, rt)



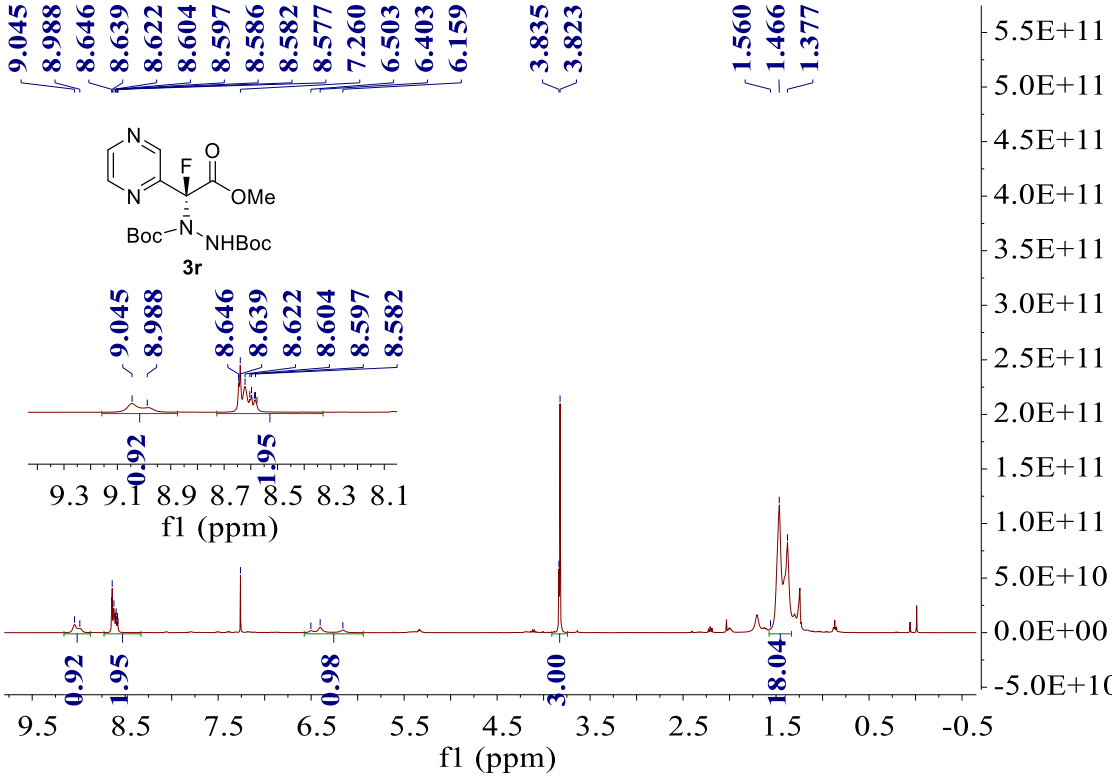
^{13}C{^{1}H} NMR Spectrum of **3q** (100 MHz, $CDCl_3$, rt)



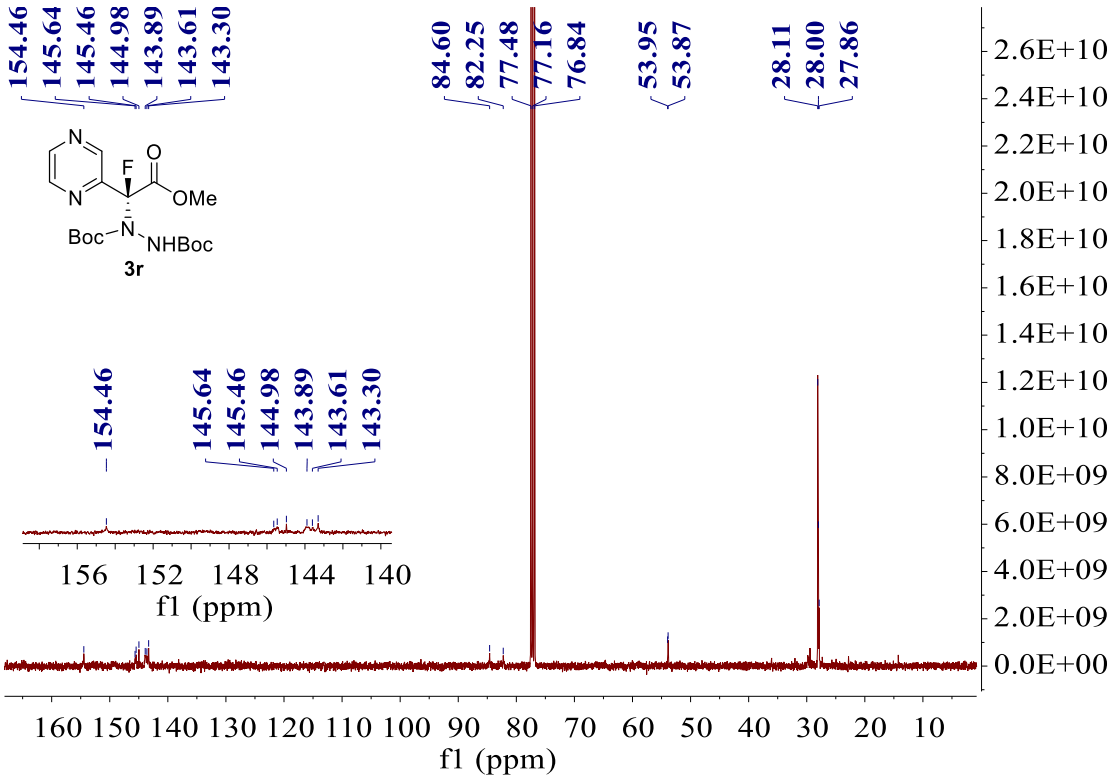
$^{19}F\{^{1}H\}$ NMR Spectrum of **3q** (376 MHz, $CDCl_3$, rt)



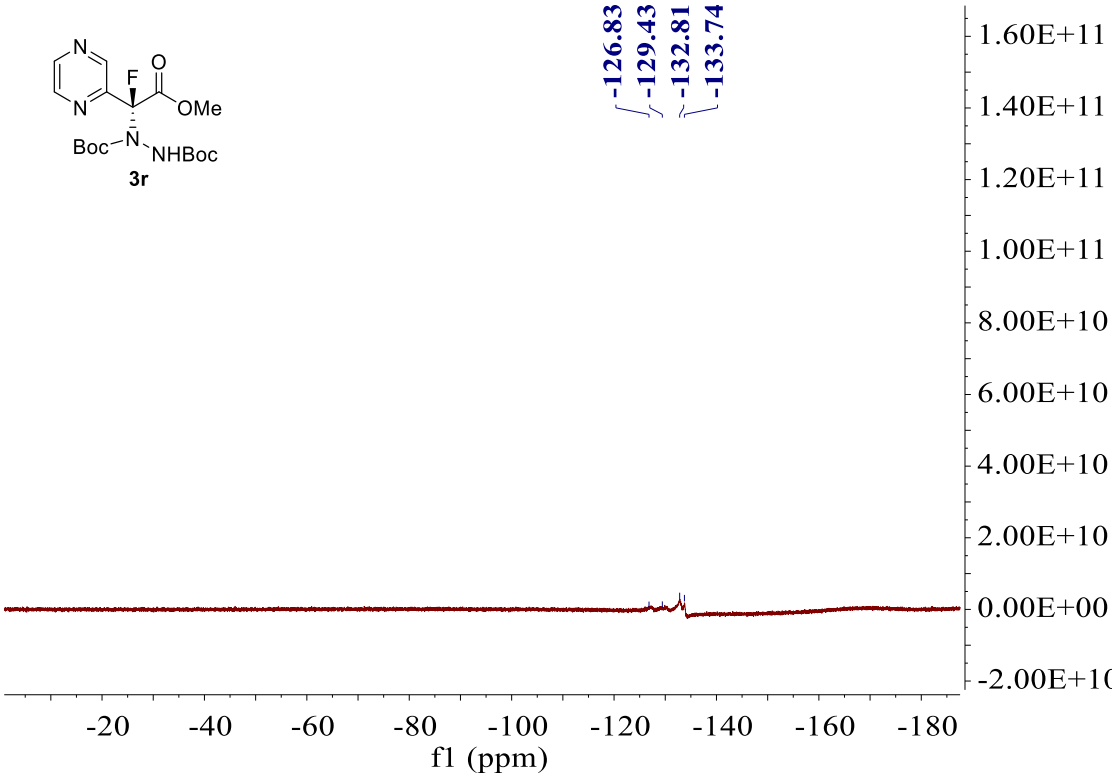
^{1}H NMR Spectrum of **3r** (400 MHz, $CDCl_3$, rt)



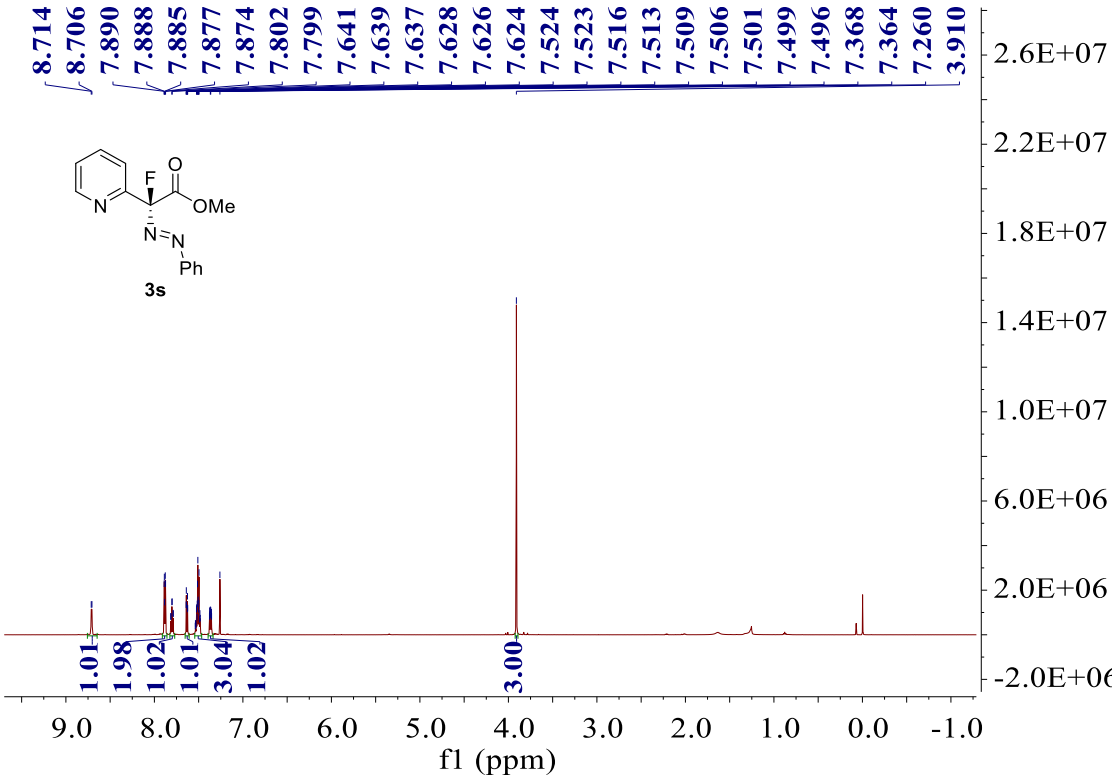
^{13}C{^{1}H} NMR Spectrum of **3r** (100 MHz, $CDCl_3$, rt)



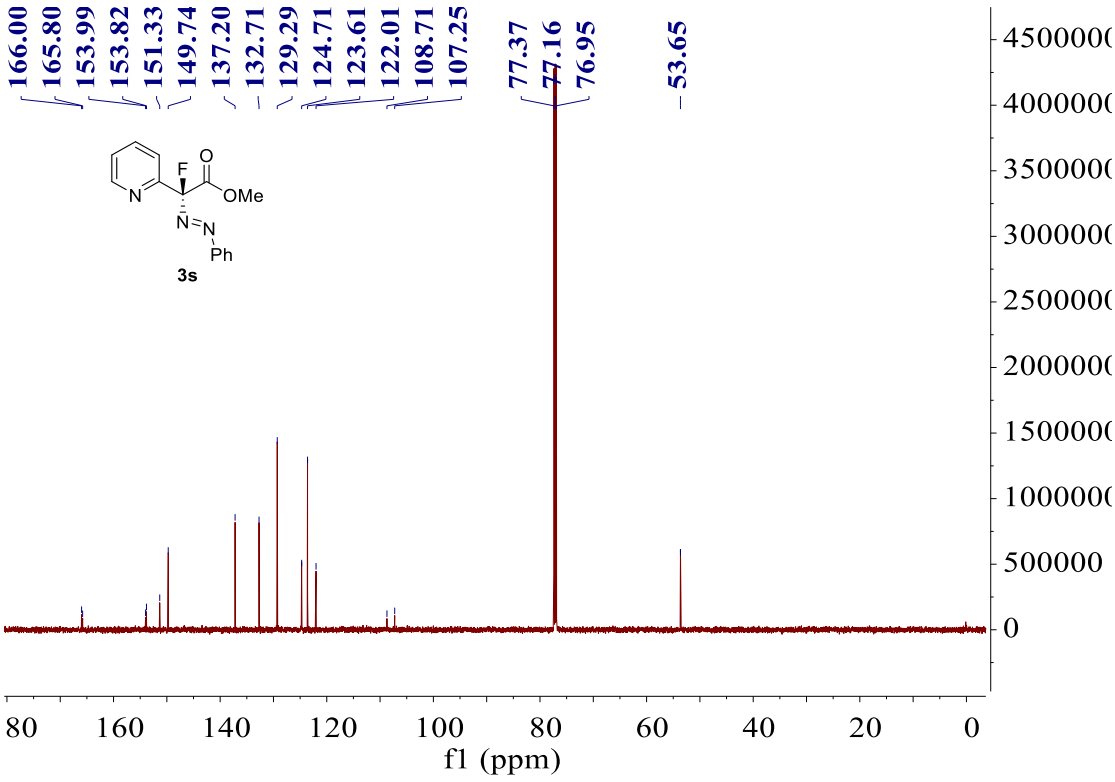
$^{19}F\{^{1}H\}$ NMR Spectrum of **3r** (376 MHz, $CDCl_3$, rt)



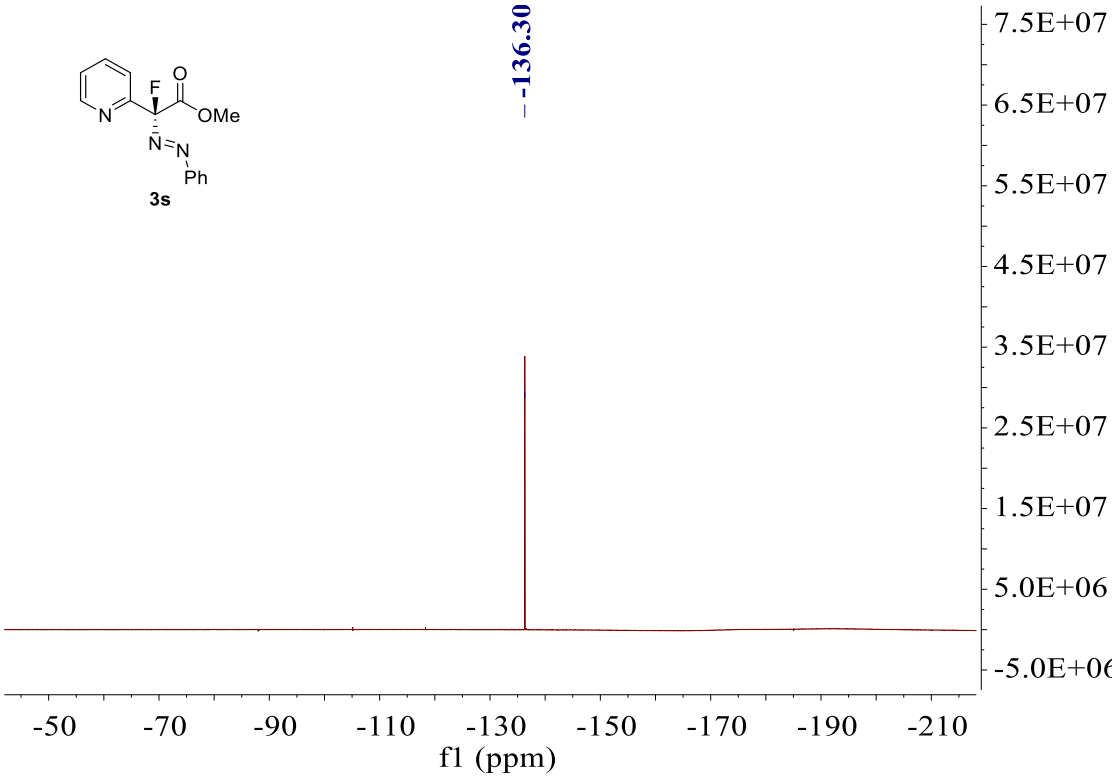
^{1}H NMR Spectrum of **3s** (600 MHz, $CDCl_3$, rt)



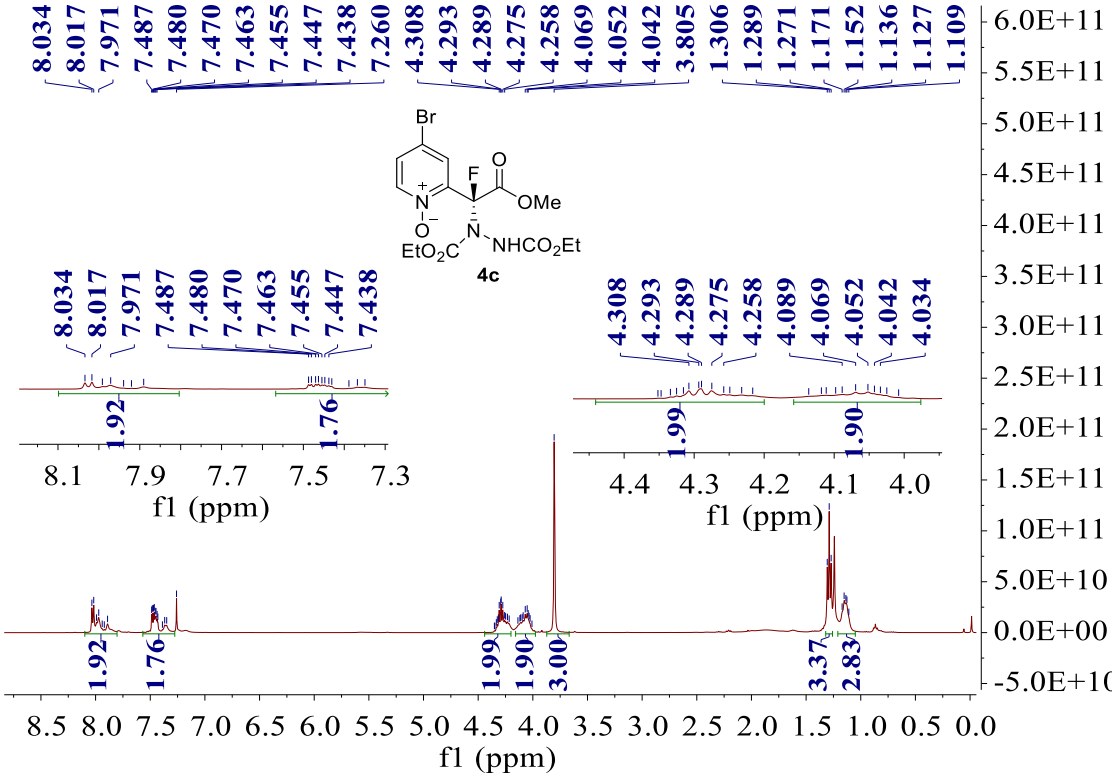
^{13}C{^{1}H} NMR Spectrum of **3s** (150 MHz, $CDCl_3$, rt)



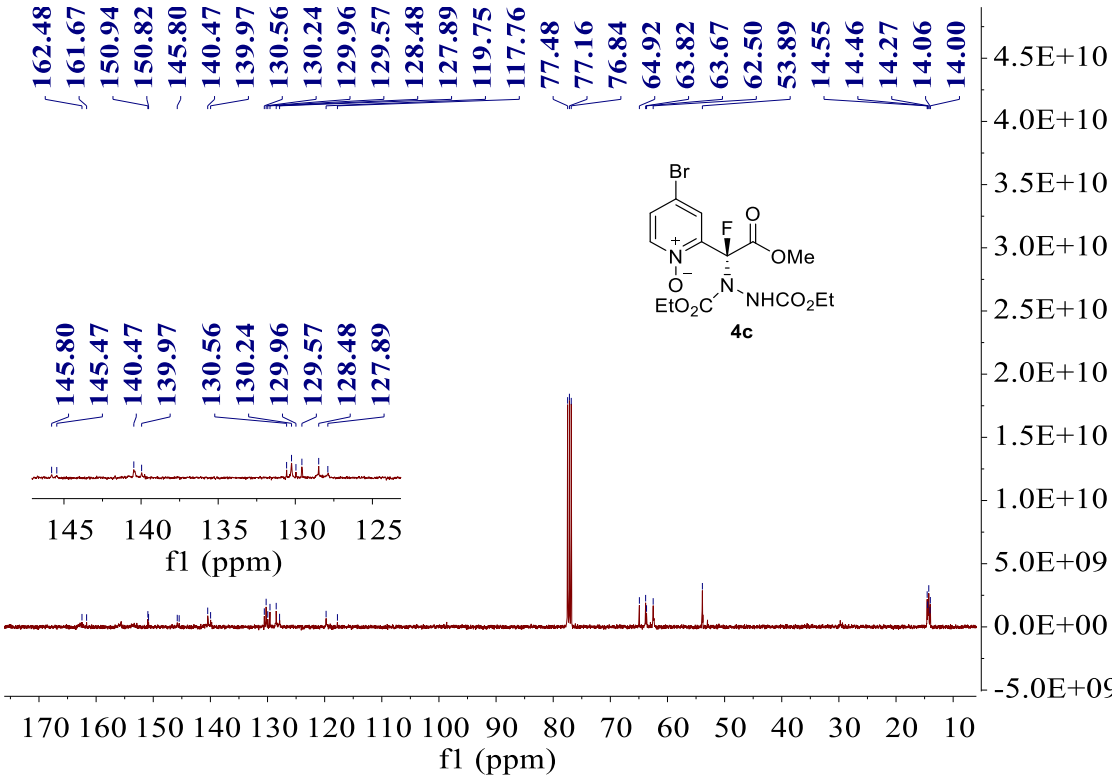
$^{19}F\{^{1}H\}$ NMR Spectrum of **3s** (565 MHz, $CDCl_3$, rt)



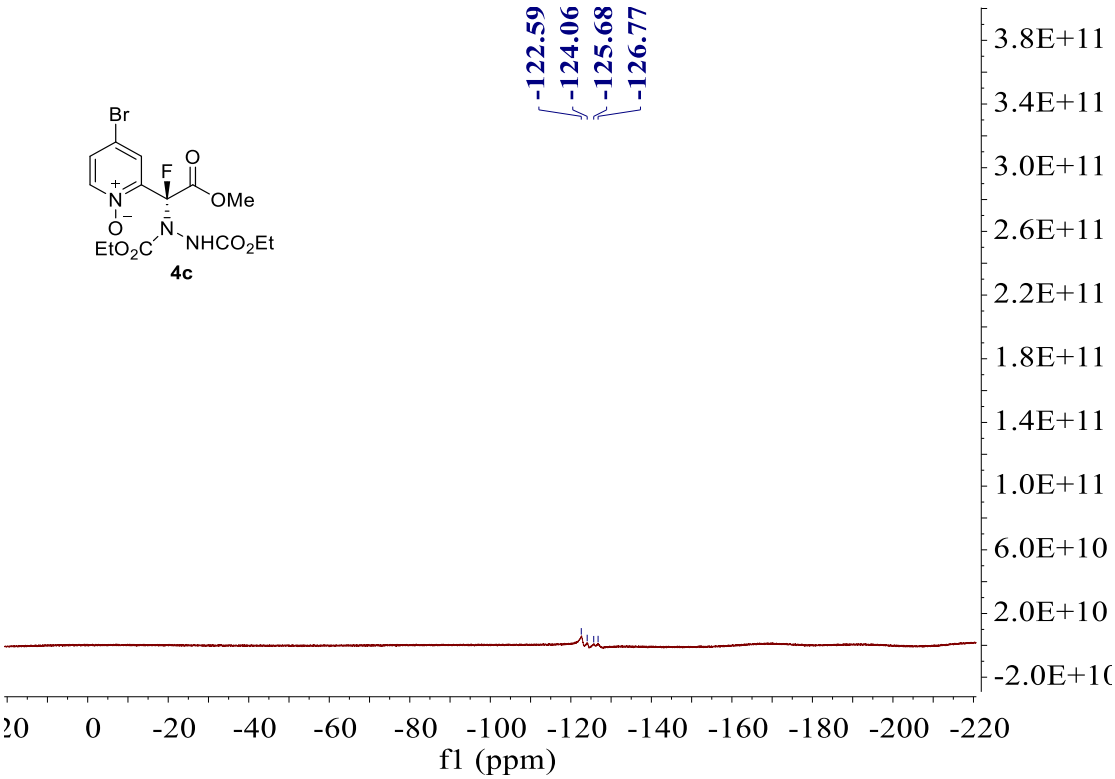
^{1}H NMR Spectrum of **4c** (400 MHz, $CDCl_3$, rt)



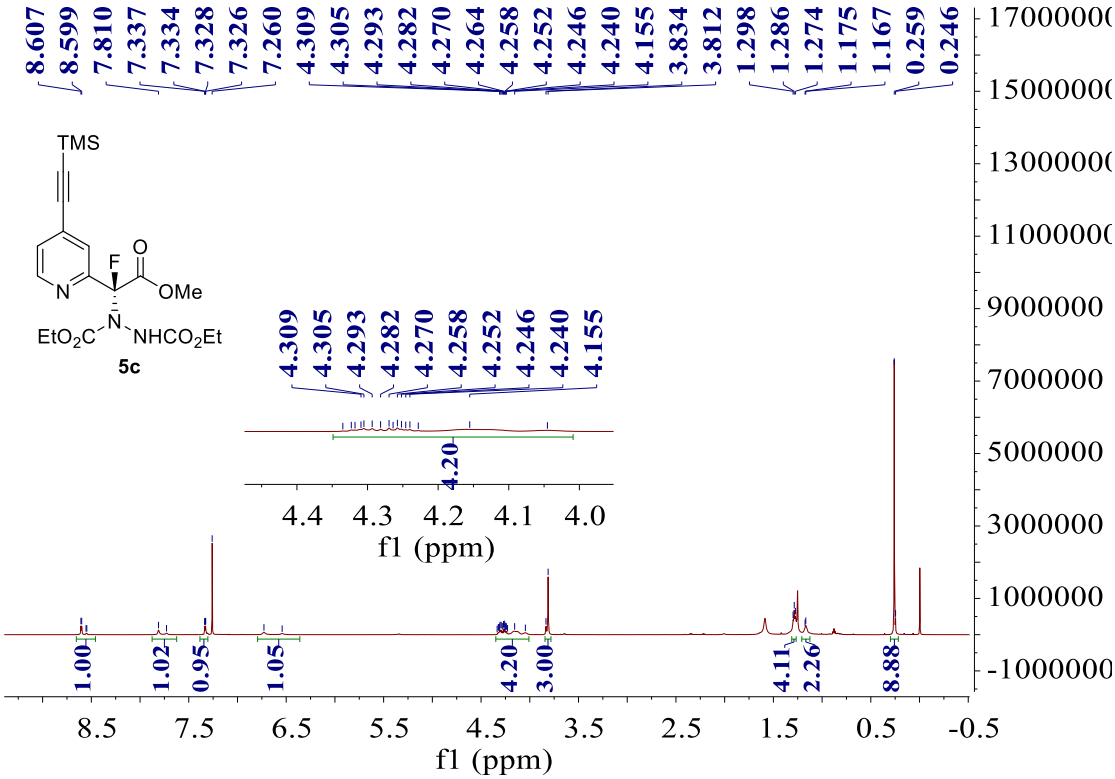
^{13}C{^{1}H} NMR Spectrum of **4c** (100 MHz, $CDCl_3$, rt)



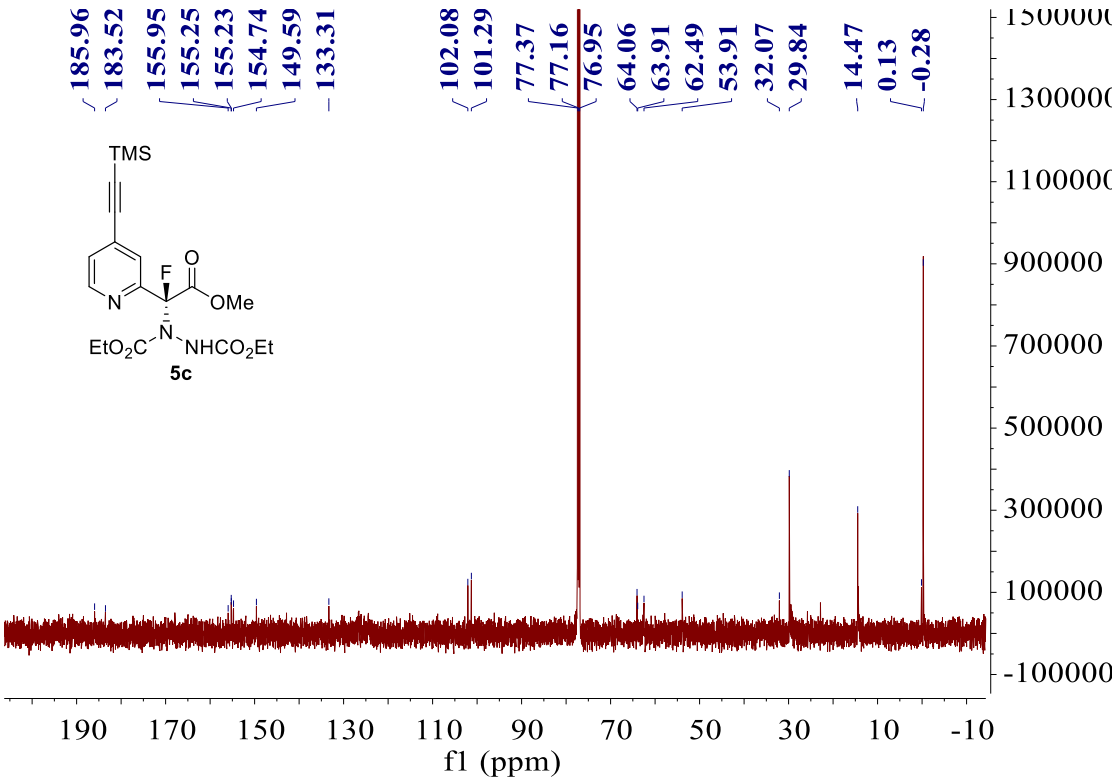
$^{19}F\{^{1}H\}$ NMR Spectrum of **4c** (376 MHz, $CDCl_3$, rt)



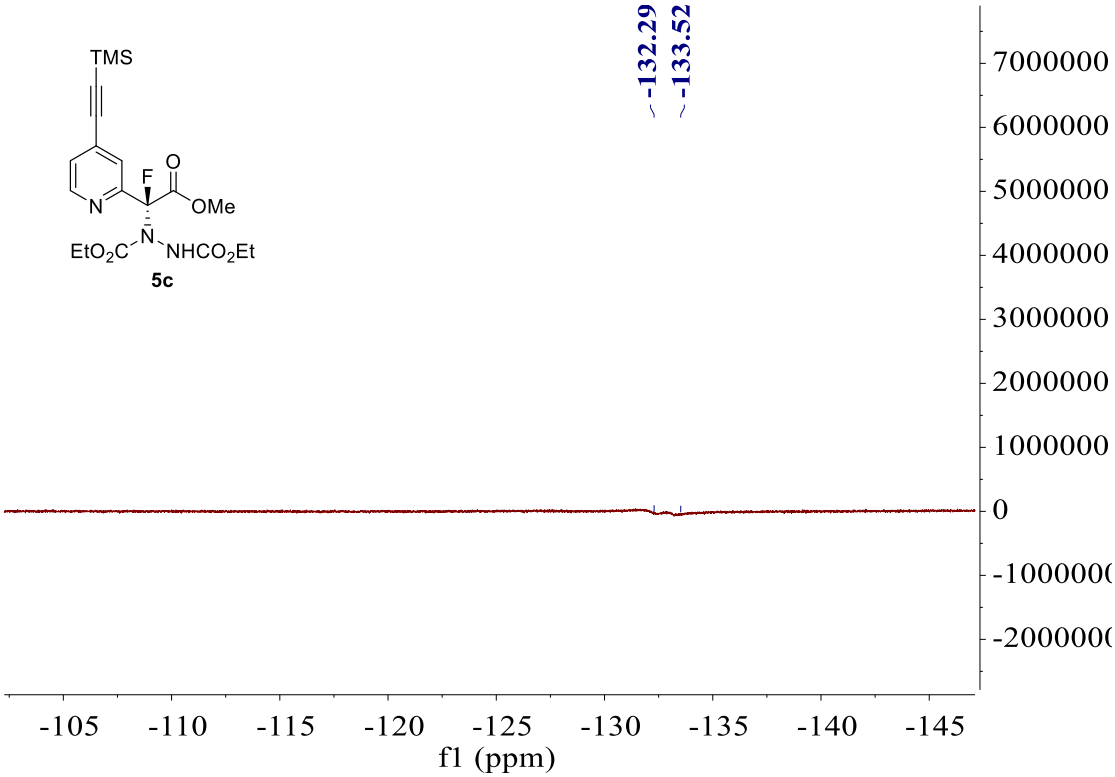
^{1}H NMR Spectrum of **5c** (600 MHz, $CDCl_3$, rt)



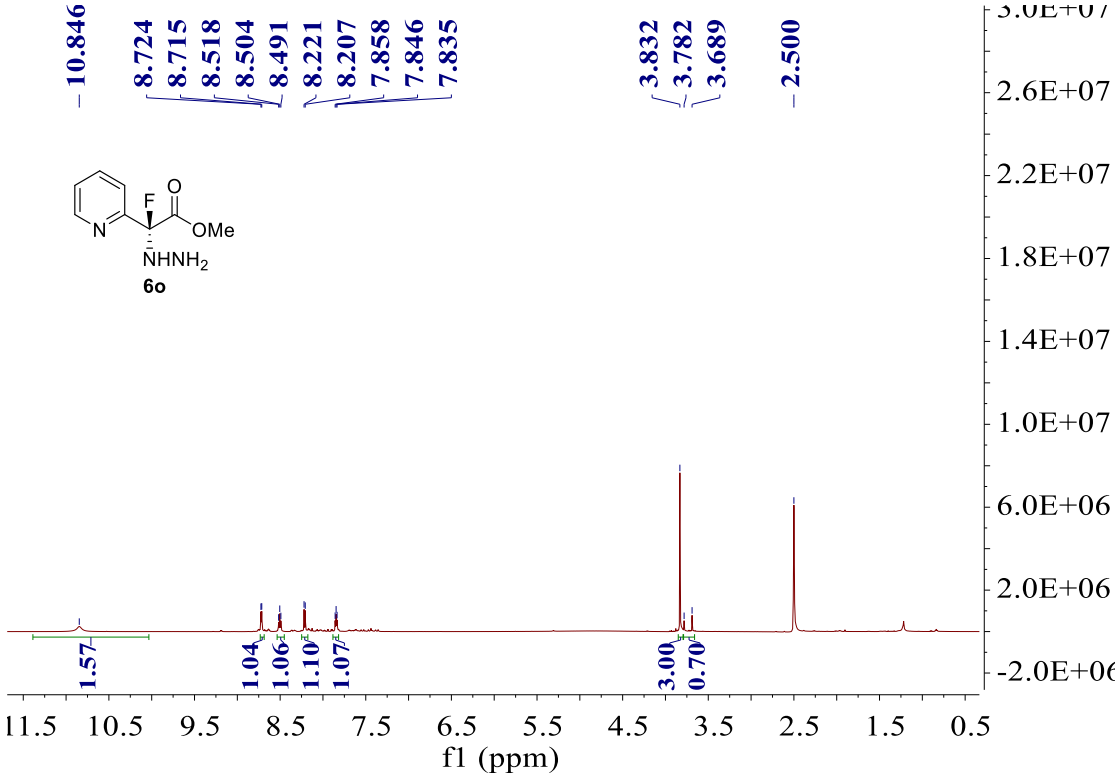
^{13}C{^{1}H} NMR Spectrum of **5c** (150 MHz, $CDCl_3$, rt)



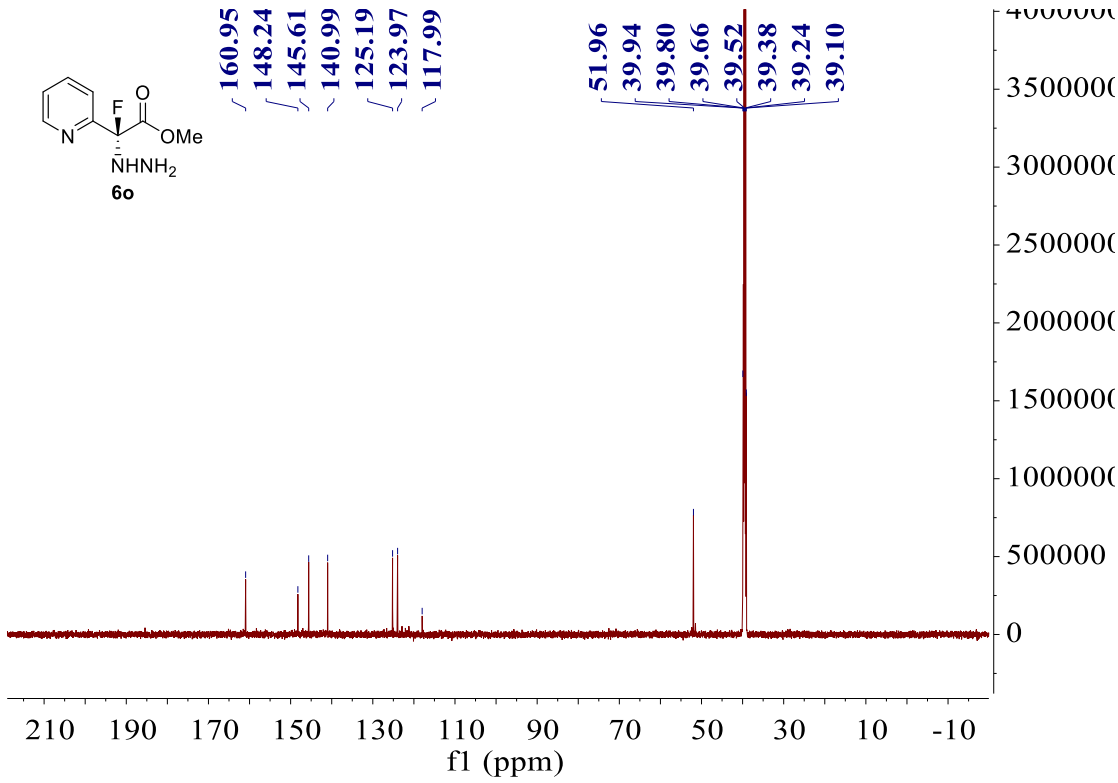
$^{19}F\{^{1}H\}$ NMR Spectrum of **5c** (565 MHz, $CDCl_3$, rt)



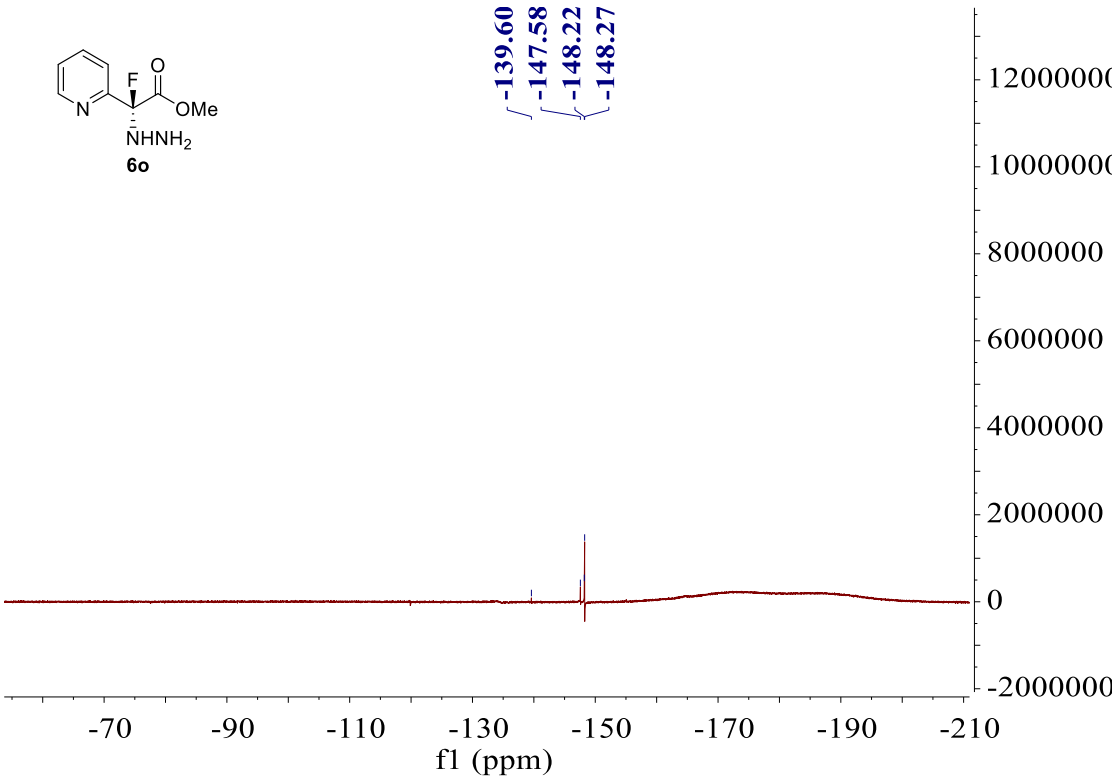
^{1}H NMR Spectrum of **6o** (600 MHz, DMSO-d^6, rt)



^{13}C{^{1}H} NMR Spectrum of **6o** (150 MHz, DMSO-d^6, rt)

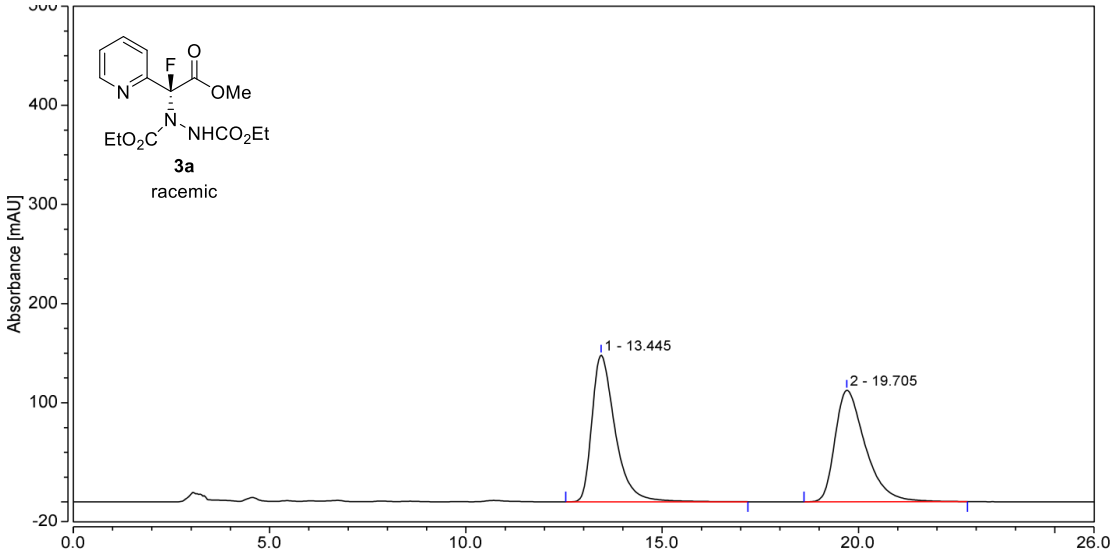


$^{19}F\{^{1}H\}$ NMR Spectrum of **6o** (565 MHz, DMSO-d^6, rt)



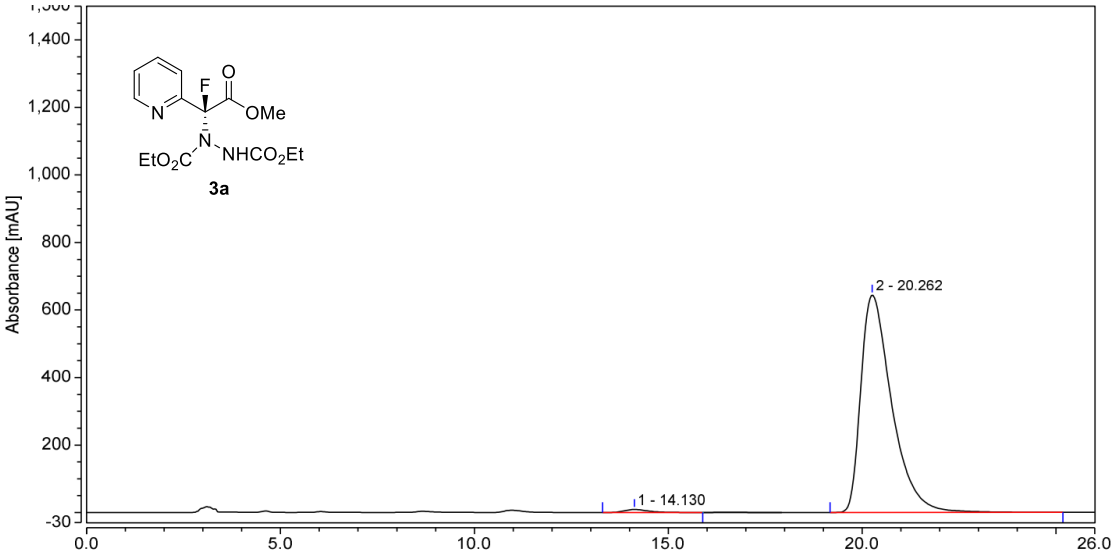
HPLC spectra

HPLC Spectrum of **3a**



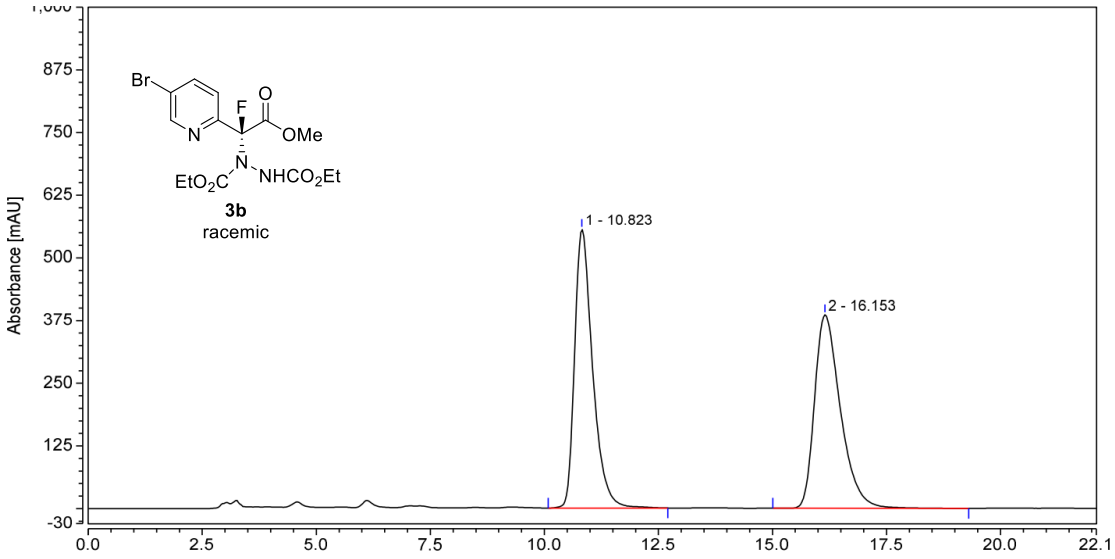
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	13.445	101.402	147.973	50.18	56.82
2	19.705	100.670	112.447	49.82	43.18
Total		**202.072**	**260.421**	**100.00**	**100.00**

HPLC Spectrum of **3a**



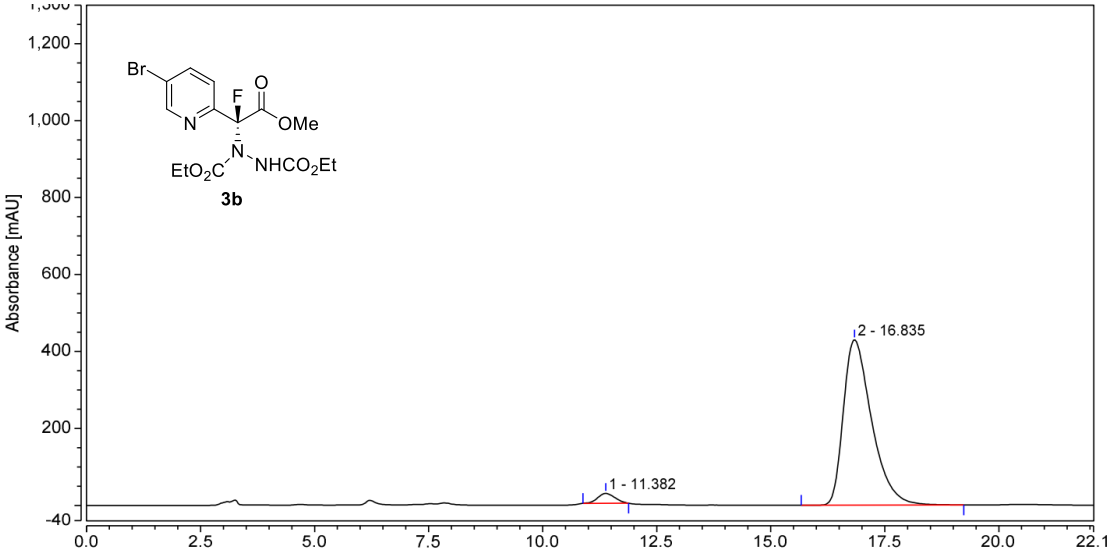
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	14.130	6.603	9.055	1.10	1.39
2	20.262	595.819	644.175	98.90	98.61
Total:		**602.423**	**653.229**	**100.00**	**100.00**

HPLC Spectrum of **3b**



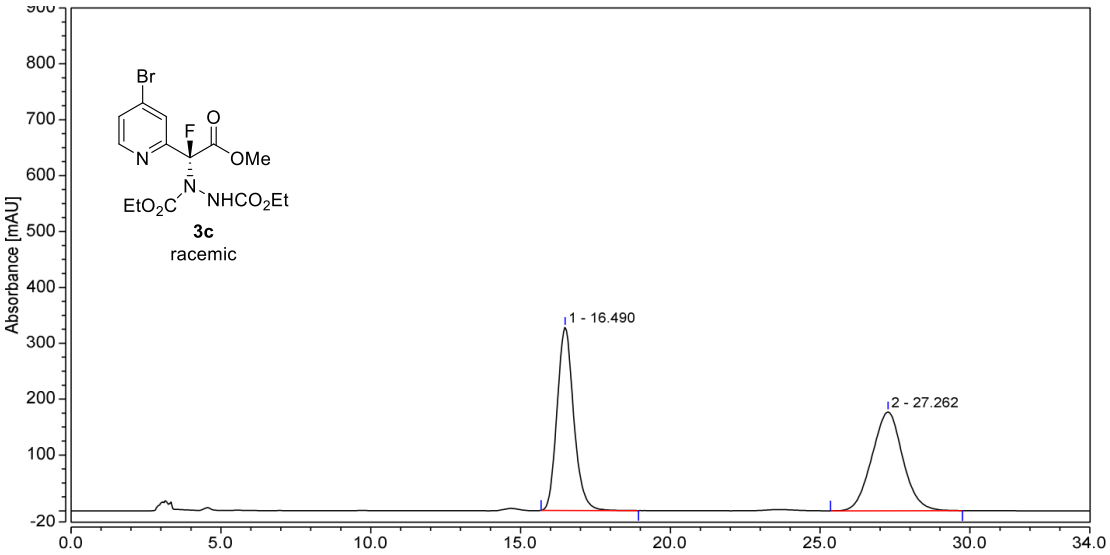
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	10.823	254.575	555.668	50.17	59.04
2	16.153	252.831	385.560	49.83	40.96
Total		**507.406**	**941.228**	**100.00**	**100.00**

HPLC Spectrum of **3b**



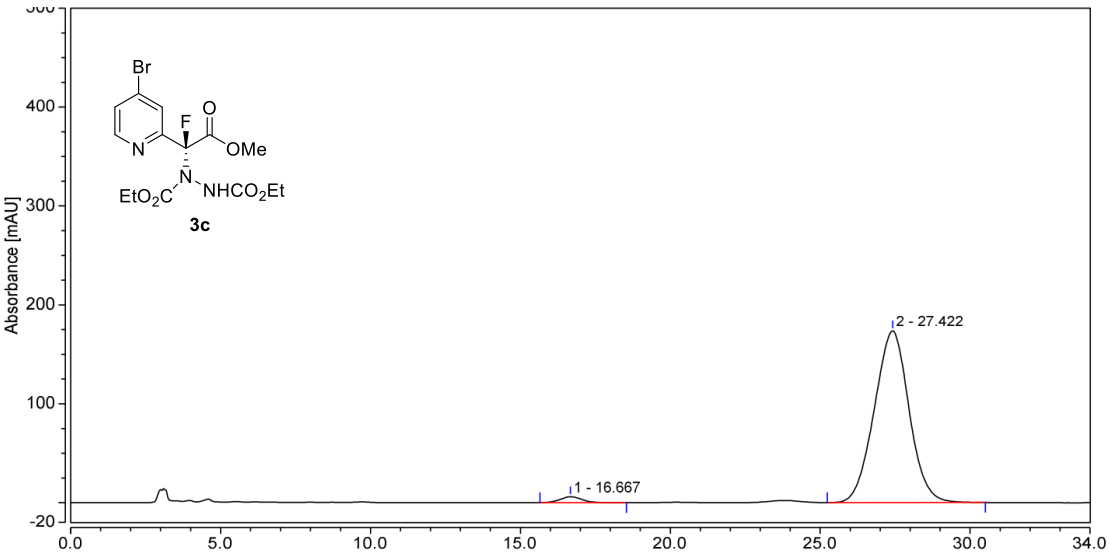
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	11.382	11.189	25.562	3.49	5.61
2	16.835	309.805	429.692	96.51	94.39
Total		**320.993**	**455.253**	**100.00**	**100.00**

HPLC Spectrum of **3c**



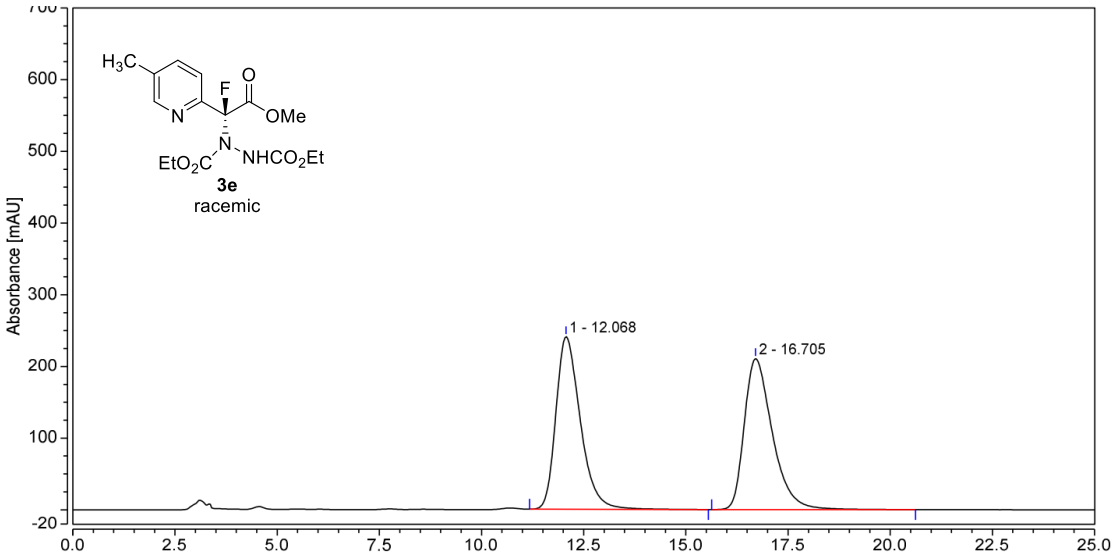
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	16.490	210.744	327.780	49.89	64.96
2	27.262	211.671	176.797	50.11	35.04
Total		**422.415**	**504.577**	**100.00**	**100.00**

HPLC Spectrum of **3c**



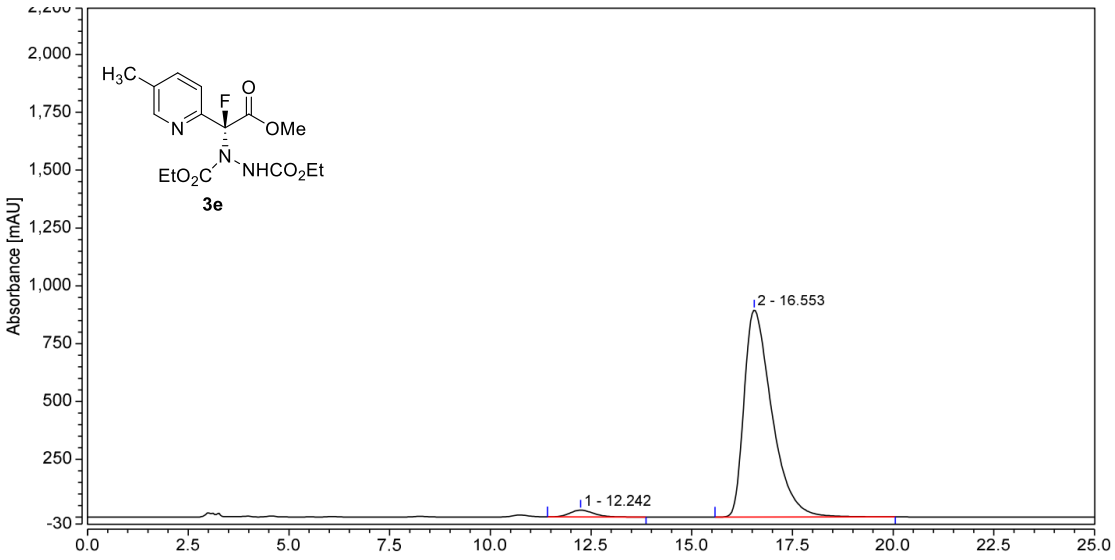
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	16.667	5.119	6.080	2.14	3.38
2	27.422	234.284	173.787	97.86	96.62
Total		**239.403**	**179.867**	**100.00**	**100.00**

HPLC Spectrum of **3e**



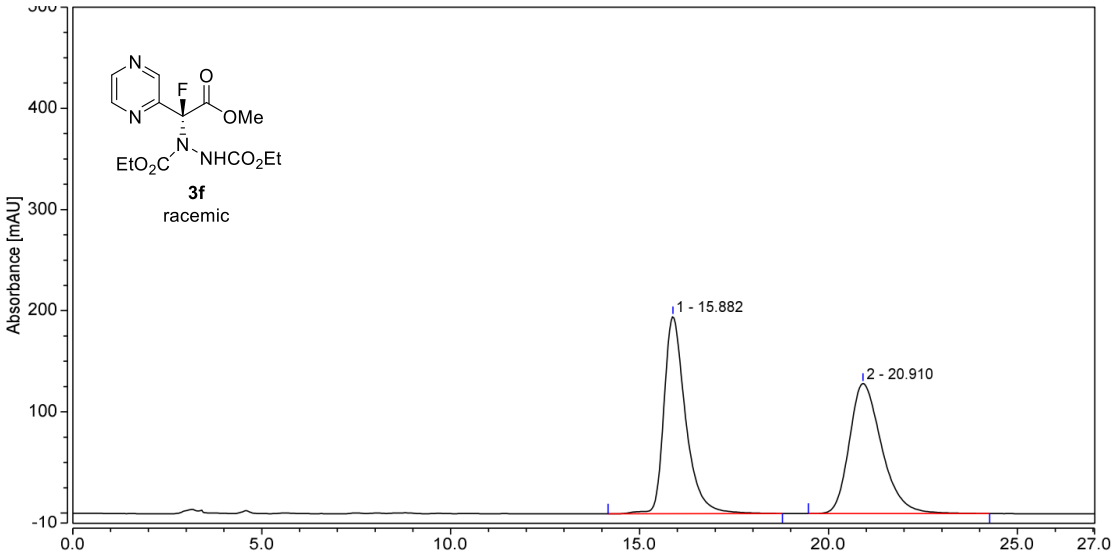
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	12.068	167.201	240.900	49.84	53.35
2	16.705	168.299	210.612	50.16	46.65
Total		**335.500**	**451.513**	**100.00**	**100.00**

HPLC Spectrum of **3e**



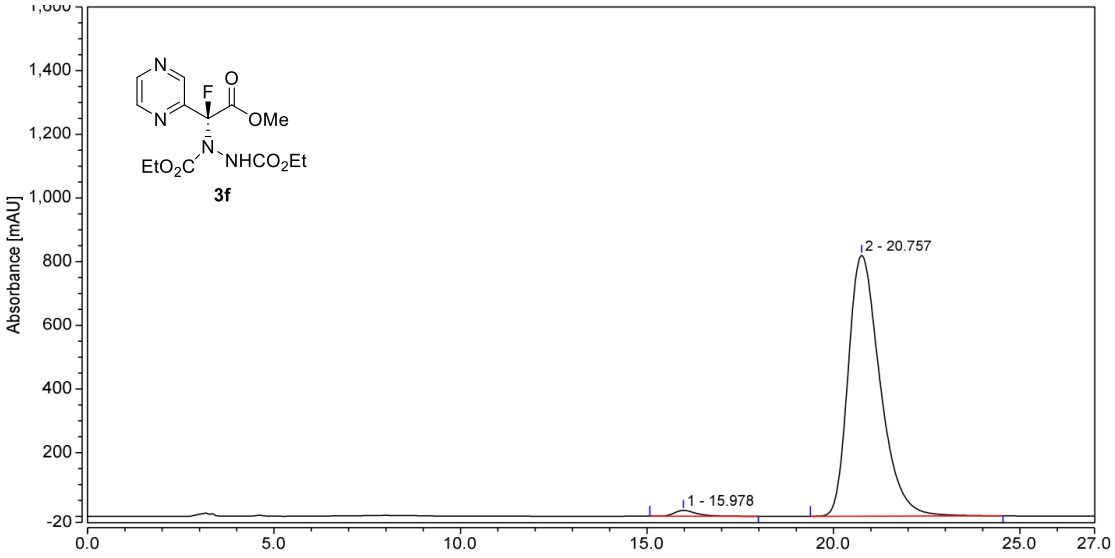
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	12.242	20.483	29.809	2.78	3.22
2	16.553	716.116	894.872	97.22	96.78
Total		**736.600**	**924.681**	**100.00**	**100.00**

HPLC Spectrum of **3f**



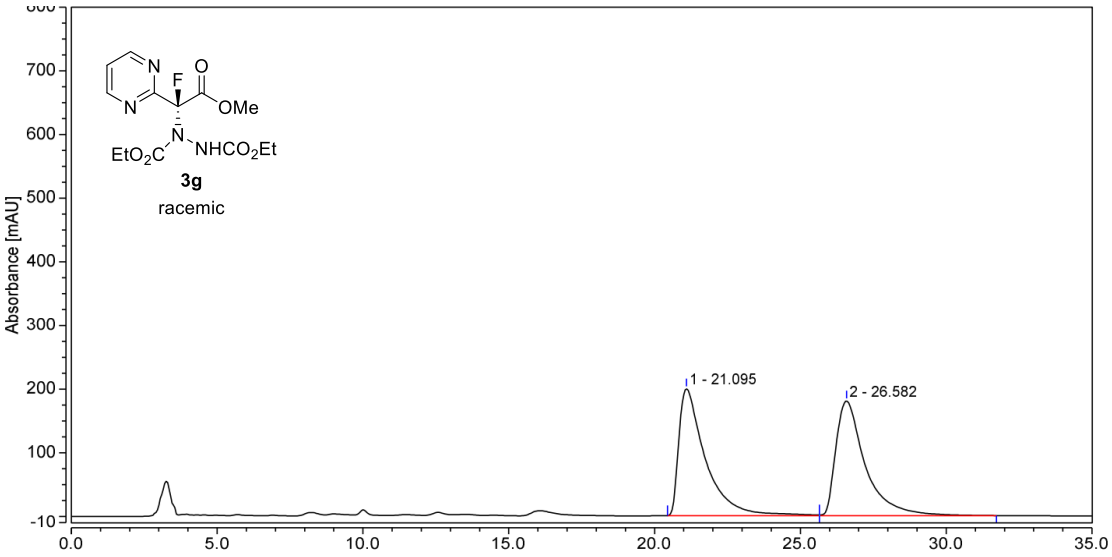
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	15.882	129.770	194.853	50.39	60.24
2	20.910	127.737	128.585	49.61	39.76
Total		**257.506**	**323.438**	**100.00**	**100.00**

HPLC Spectrum of **3f**



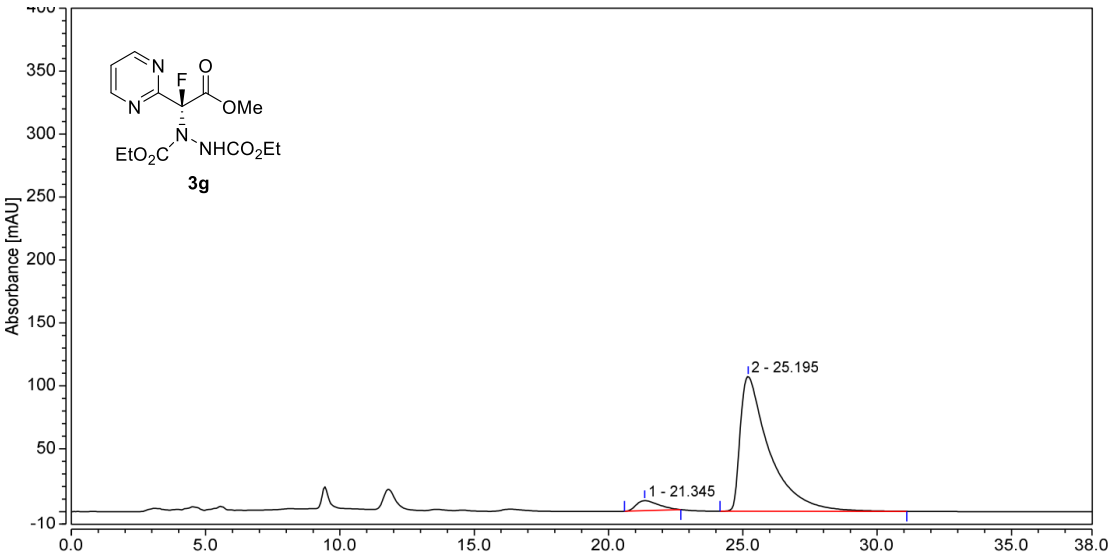
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	15.978	12.266	18.297	1.49	2.18
2	20.757	810.751	819.619	98.51	97.82
Total		**823.017**	**837.916**	**100.00**	**100.00**

HPLC Spectrum of **3g**



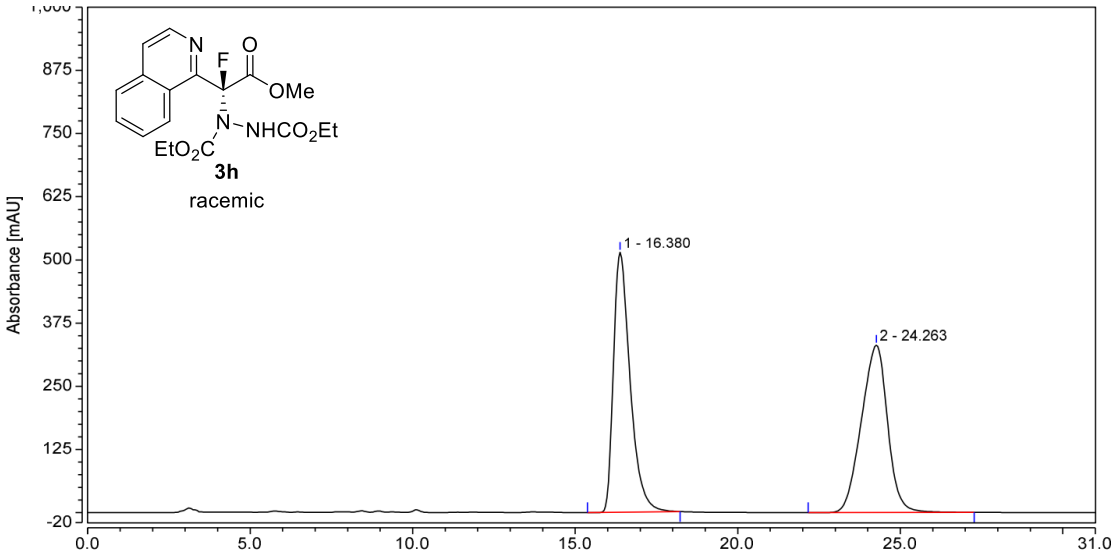
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	21.095	210.772	199.076	50.11	52.52
2	26.582	209.819	179.986	49.89	47.48
Total:		**420.592**	**379.063**	**100.00**	**100.00**

HPLC Spectrum of **3g**



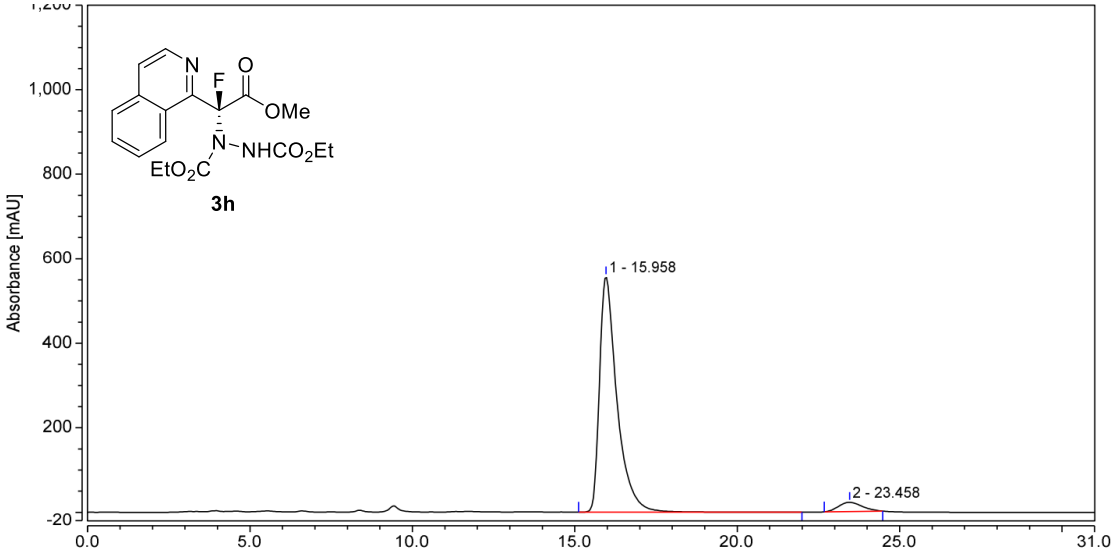
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	21.345	7.764	7.965	5.43	6.92
2	25.195	135.250	107.083	94.57	93.08
Total:		**143.015**	**115.048**	**100.00**	**100.00**

HPLC Spectrum of **3h**



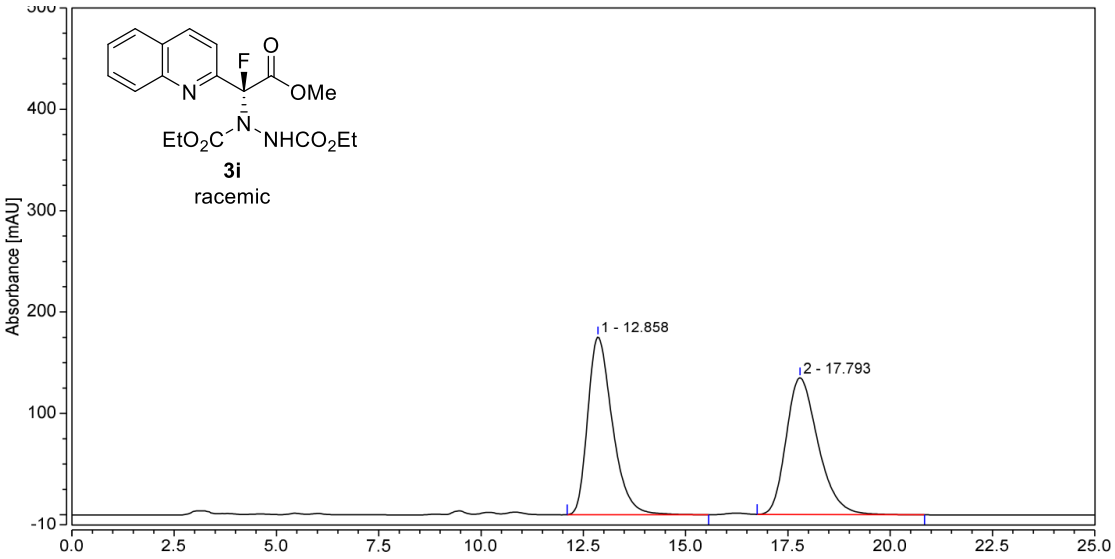
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	16.380	305.483	513.979	49.68	60.82
2	24.263	309.364	331.111	50.32	39.18
Total:		**614.847**	**845.090**	**100.00**	**100.00**

HPLC Spectrum of **3h**



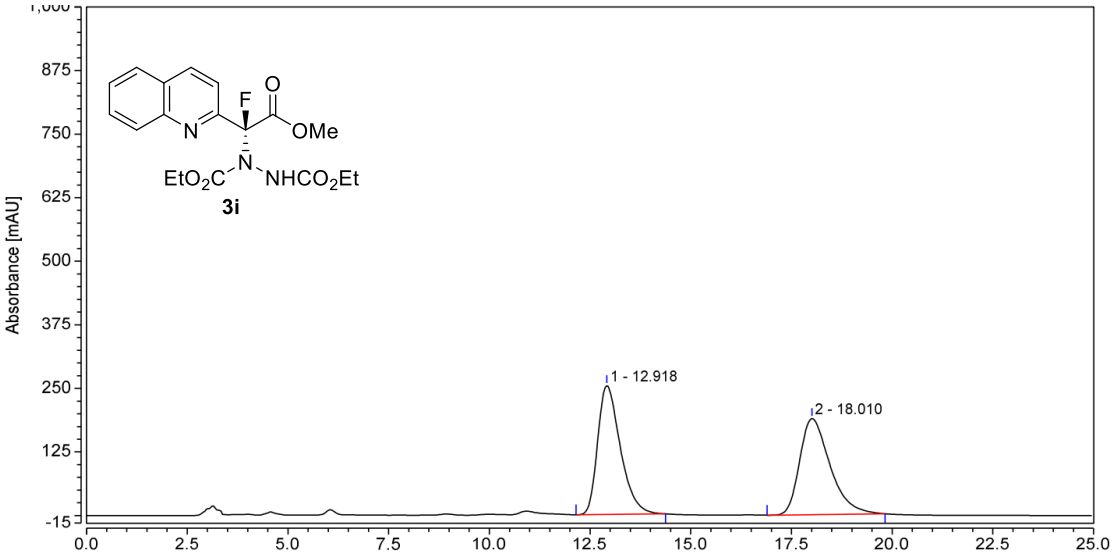
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	15.958	348.552	557.456	95.08	96.27
2	23.458	18.054	21.618	4.92	3.73
Total:		**366.606**	**579.074**	**100.00**	**100.00**

HPLC Spectrum of **3i**



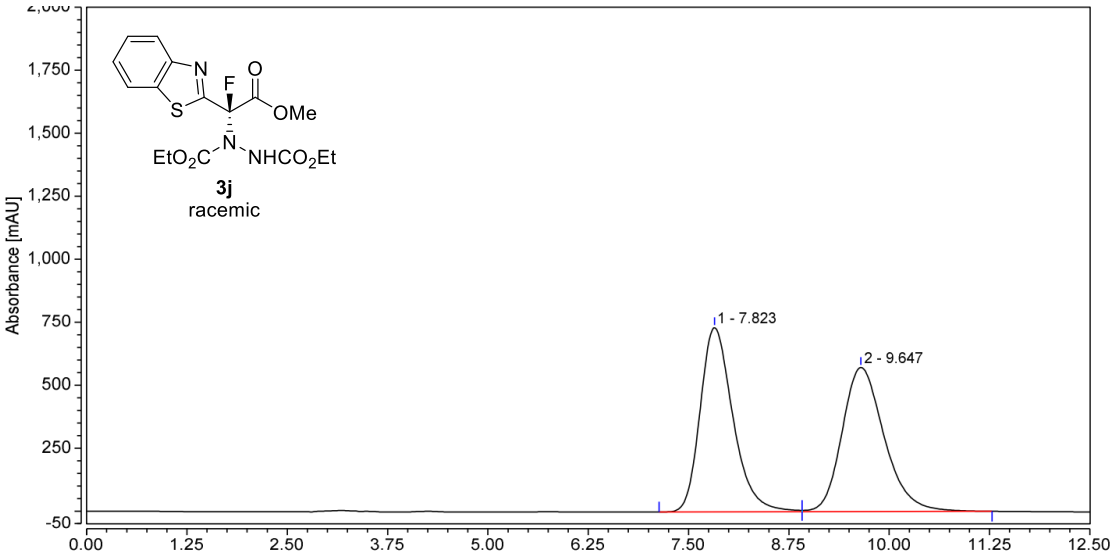
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	12.858	122.769	175.406	50.11	56.54
2	17.793	122.246	134.820	49.89	43.46
Total:		**245.016**	**310.226**	**100.00**	**100.00**

HPLC Spectrum of **3i**



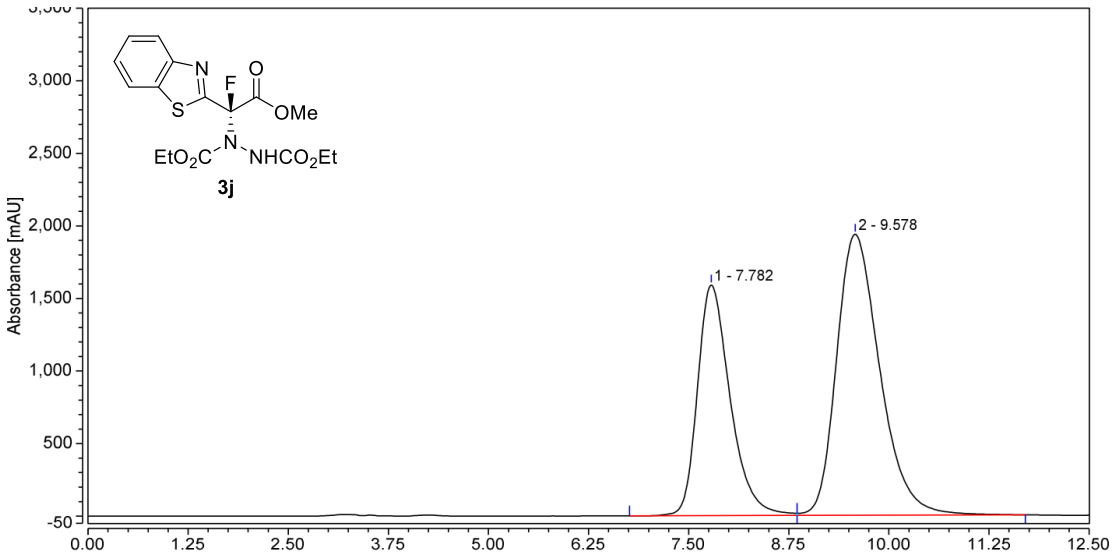
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	12.918	165.846	253.330	50.13	57.26
2	18.010	164.996	189.079	49.87	42.74
Total:		**330.843**	**442.409**	**100.00**	**100.00**

HPLC Spectrum of **3j**



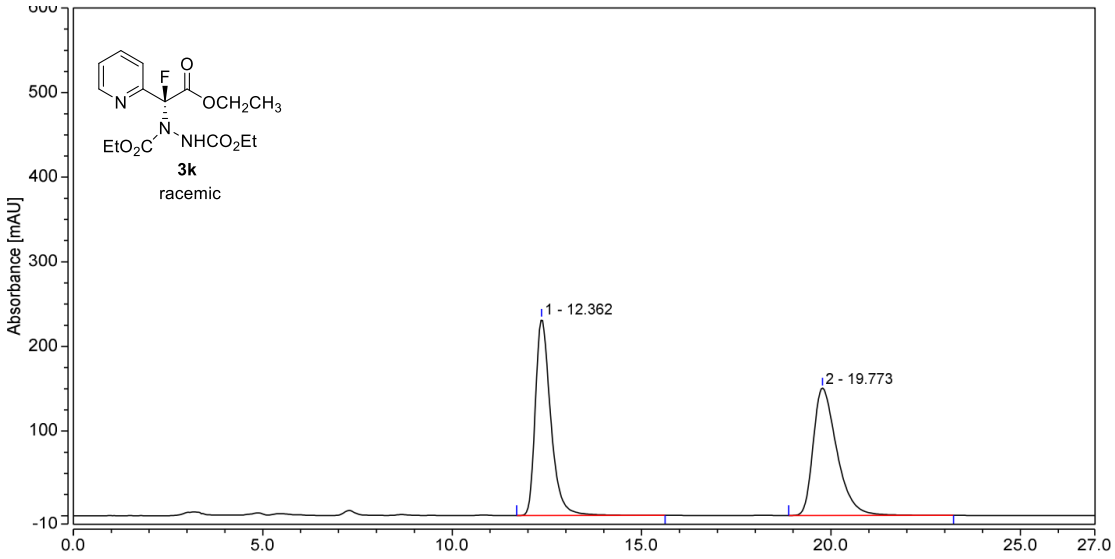
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	7.823	347.134	731.260	49.92	56.11
2	9.647	348.230	571.918	50.08	43.89
Total		**695.364**	**1303.178**	**100.00**	**100.00**

HPLC Spectrum of **3j**



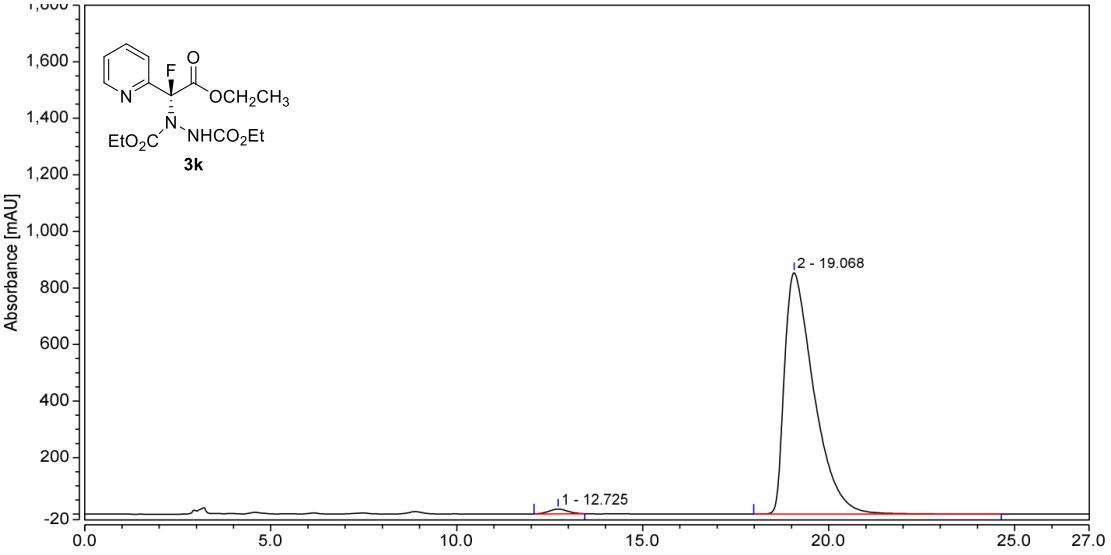
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	7.782	752.349	1589.575	38.32	45.07
2	9.578	1210.898	1937.137	61.68	54.93
Total		**1963.247**	**3526.712**	**100.00**	**100.00**

HPLC Spectrum of **3k**



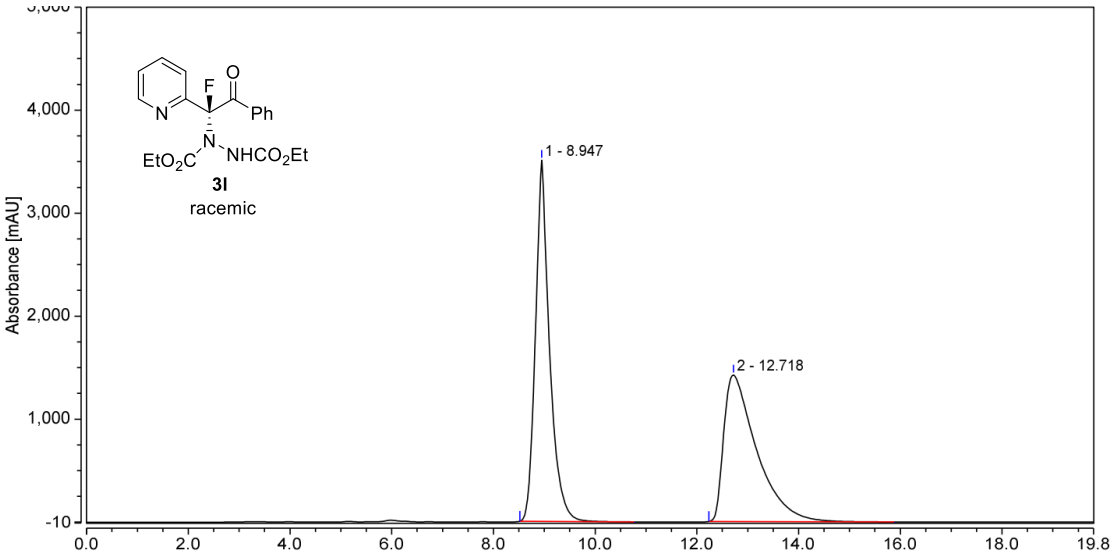
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	12.362	109.244	232.023	50.02	60.63
2	19.773	109.168	150.656	49.98	39.37
Total		**218.412**	**382.679**	**100.00**	**100.00**

HPLC Spectrum of **3k**



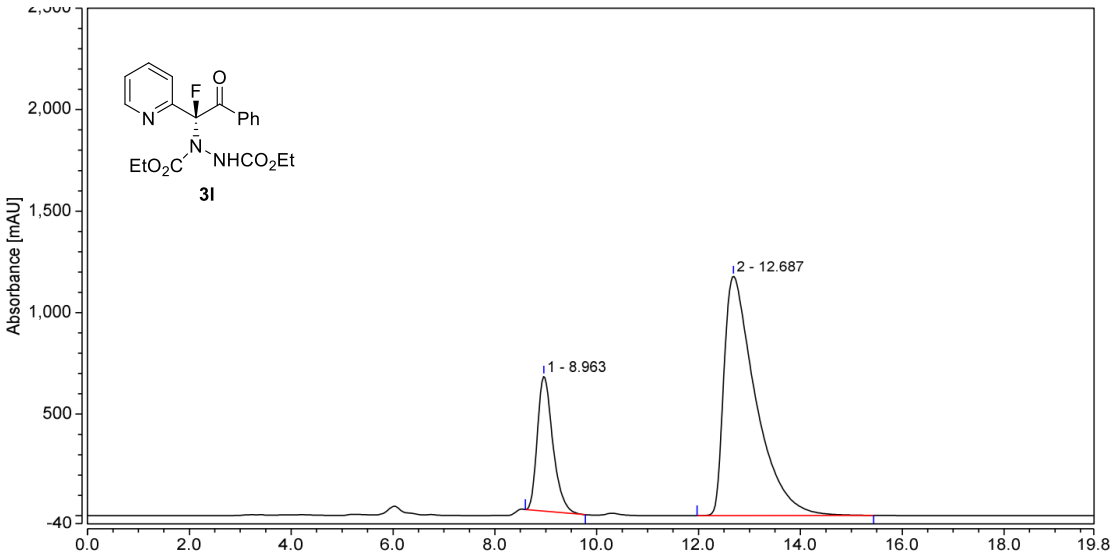
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	12.725	9.873	16.758	1.24	1.92
2	19.068	784.077	854.007	98.76	98.08
Total		**793.950**	**870.765**	**100.00**	**100.00**

HPLC Spectrum of **3l**



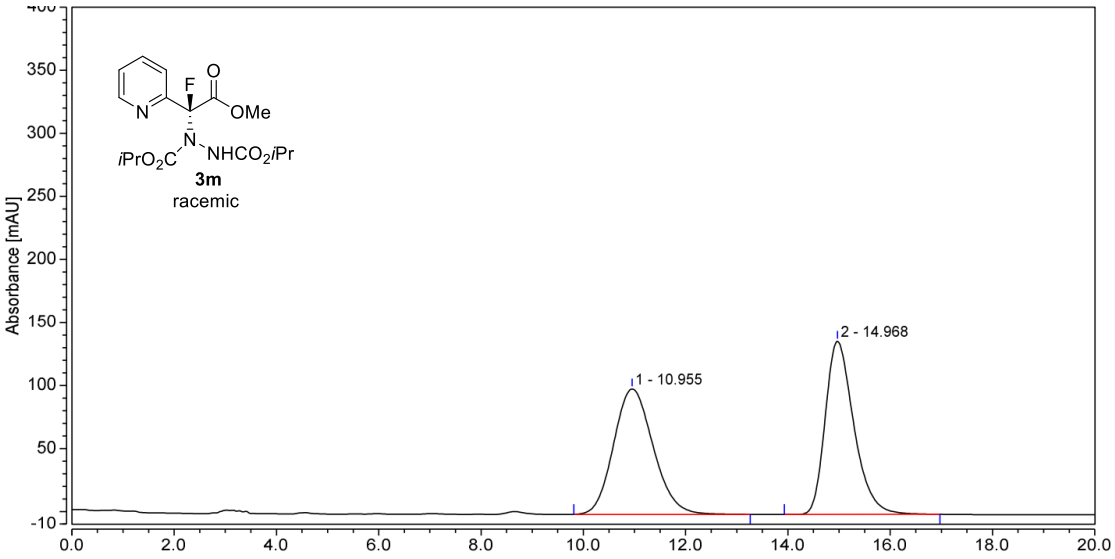
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	8.947	1122.538	3505.941	51.31	71.15
2	12.718	1065.269	1421.853	48.69	28.85
Total		**2187.806**	**4927.793**	**100.00**	**100.00**

HPLC Spectrum of **3l**



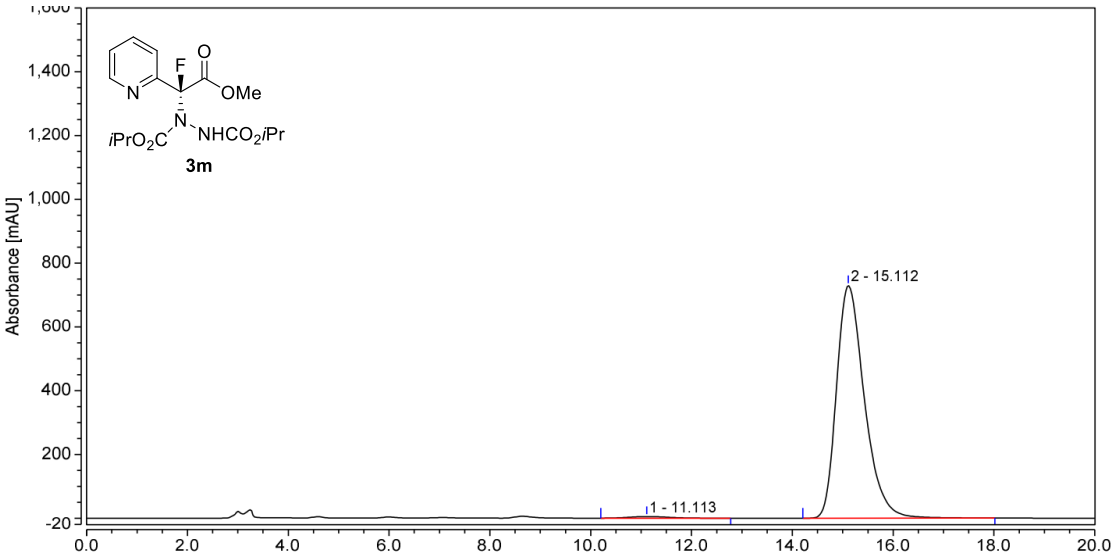
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	8.963	234.307	665.115	21.59	36.05
2	12.687	850.850	1179.833	78.41	63.95
Total		**1085.157**	**1844.948**	**100.00**	**100.00**

HPLC Spectrum of **3m**



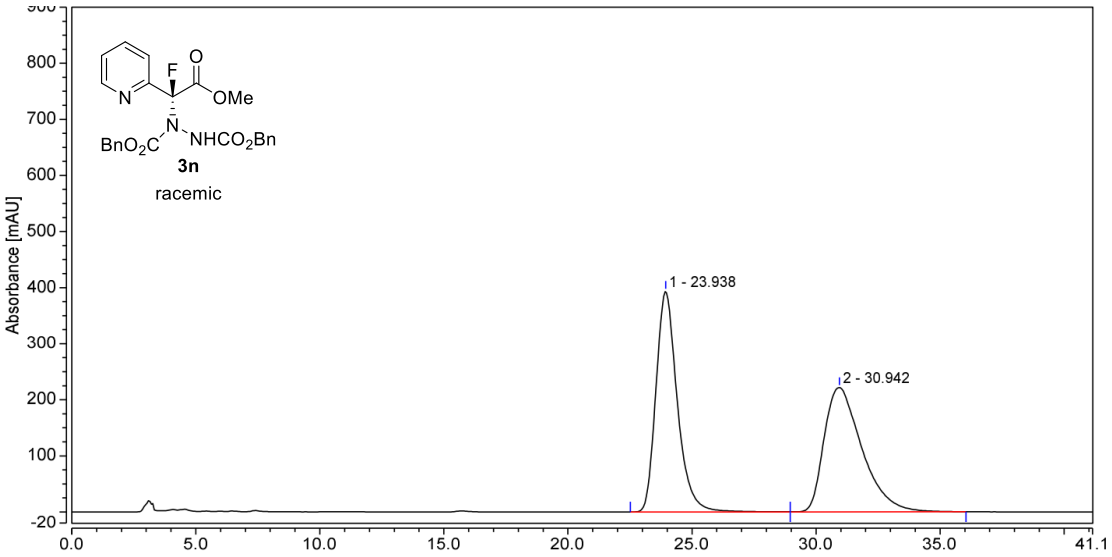
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	10.955	89.340	99.512	50.03	42.01
2	14.968	89.244	137.356	49.97	57.99
Total:		**178.584**	**236.869**	**100.00**	**100.00**

HPLC Spectrum of **3m**



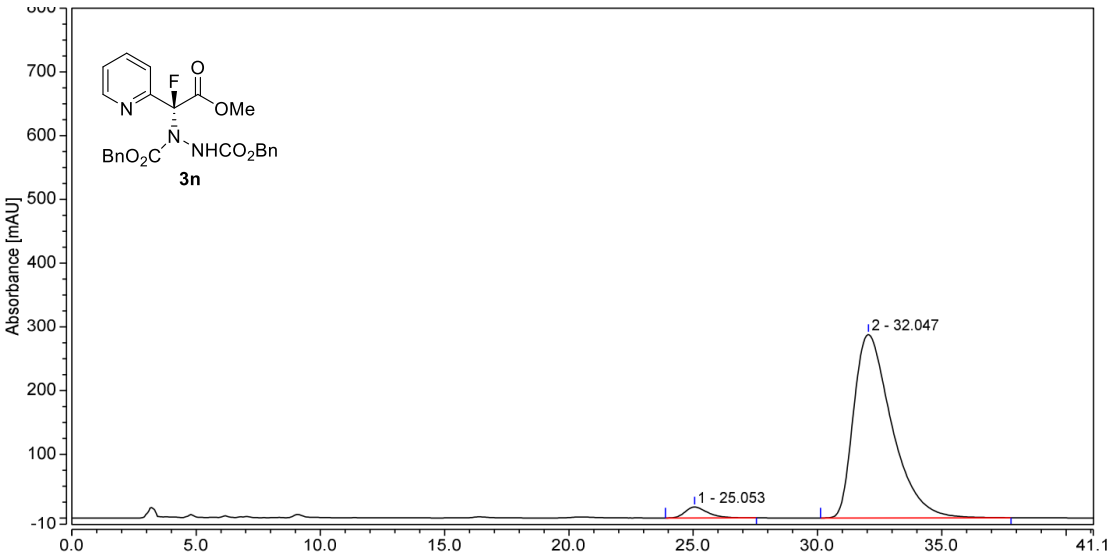
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	11.113	4.574	4.959	0.97	0.68
2	15.112	467.313	729.245	99.03	99.32
Total		**471.887**	**734.205**	**100.00**	**100.00**

HPLC Spectrum of **3n**



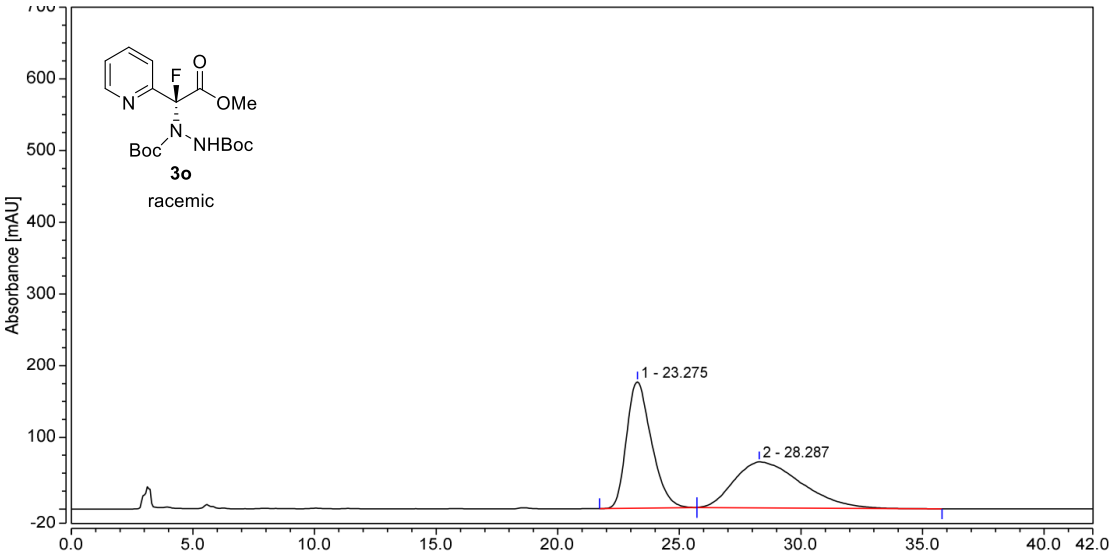
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	23.938	392.650	393.526	50.11	63.98
2	30.942	390.889	221.598	49.89	36.02
Total		**783.539**	**615.125**	**100.00**	**100.00**

HPLC Spectrum of **3n**



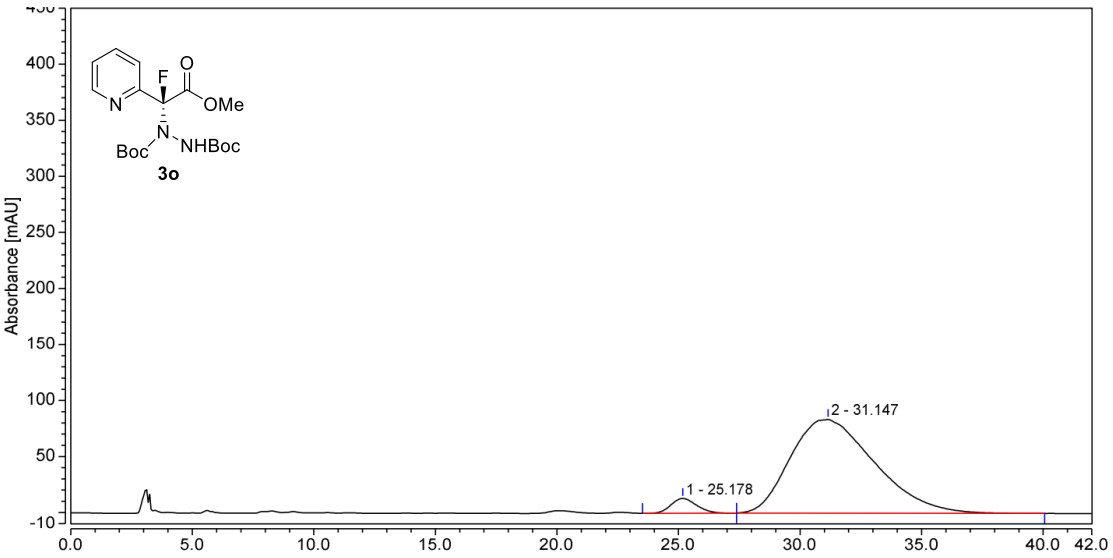
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	25.053	18.004	17.051	3.40	5.59
2	32.047	511.446	287.961	96.60	94.41
Total:		**529.450**	**305.012**	**100.00**	**100.00**

HPLC Spectrum of **3o**



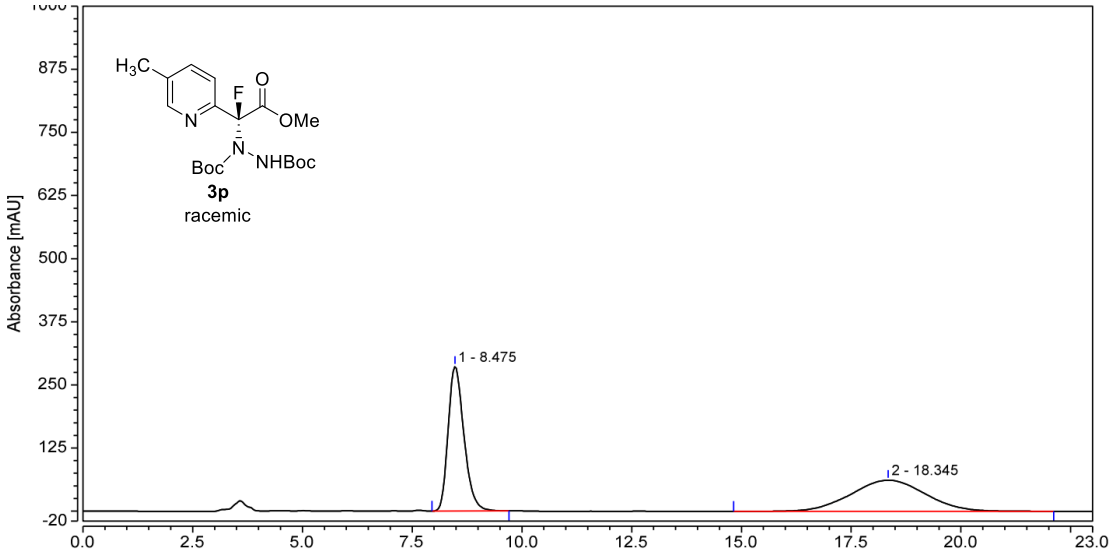
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	23.275	208.285	176.118	50.42	73.31
2	28.287	204.852	64.107	49.58	26.69
Total		**413.137**	**240.225**	**100.00**	**100.00**

HPLC Spectrum of **3o**



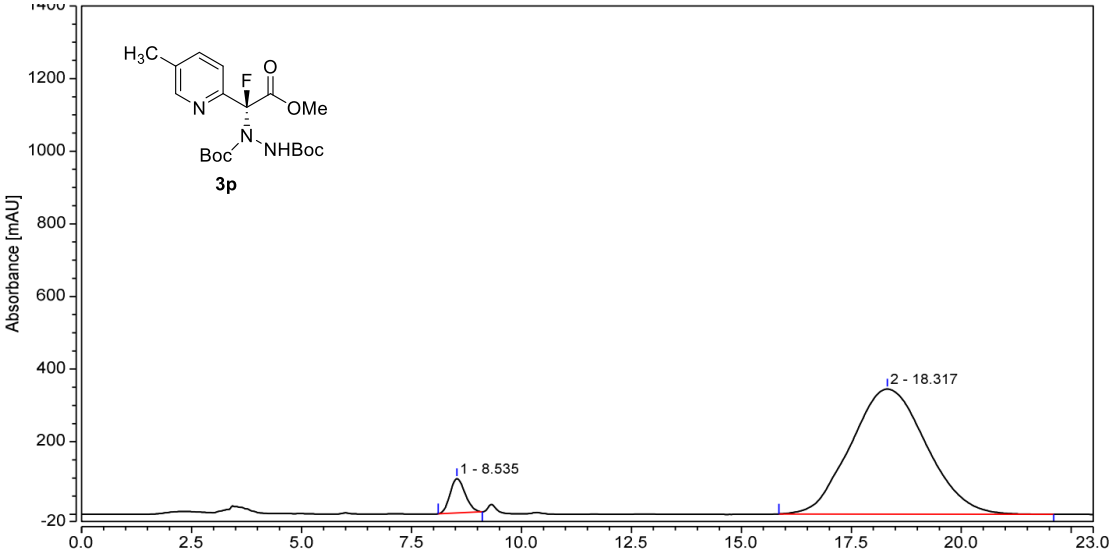
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	25.178	15.822	13.071	4.50	13.52
2	31.147	336.116	83.572	95.50	86.48
Total:		**351.938**	**96.643**	**100.00**	**100.00**

HPLC Spectrum of **3p**



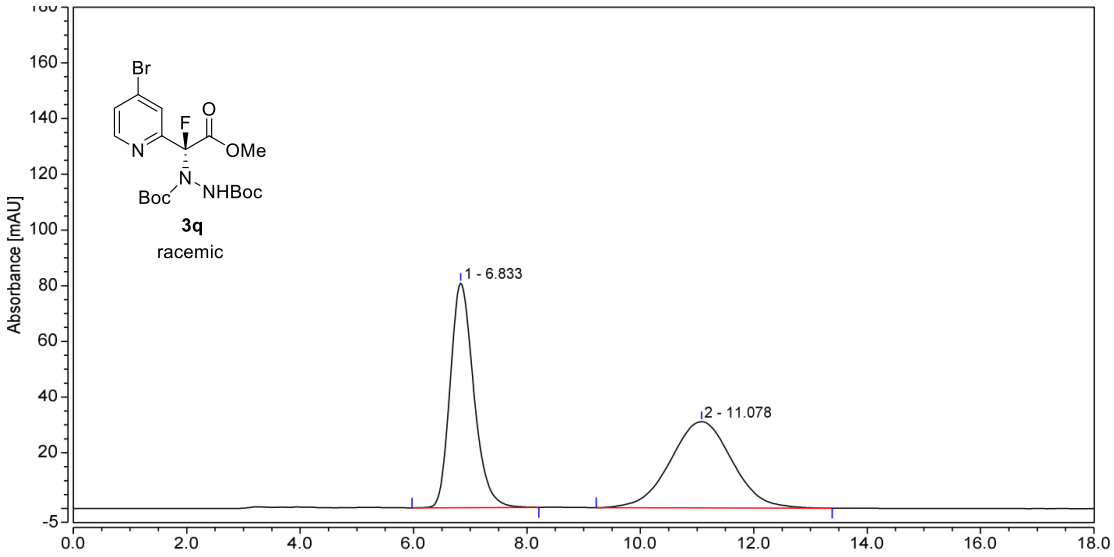
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	8.475	119.864	286.338	49.73	82.30
2	18.345	121.155	61.586	50.27	17.70
Total:		**241.019**	**347.925**	**100.00**	**100.00**

HPLC Spectrum of **3p**



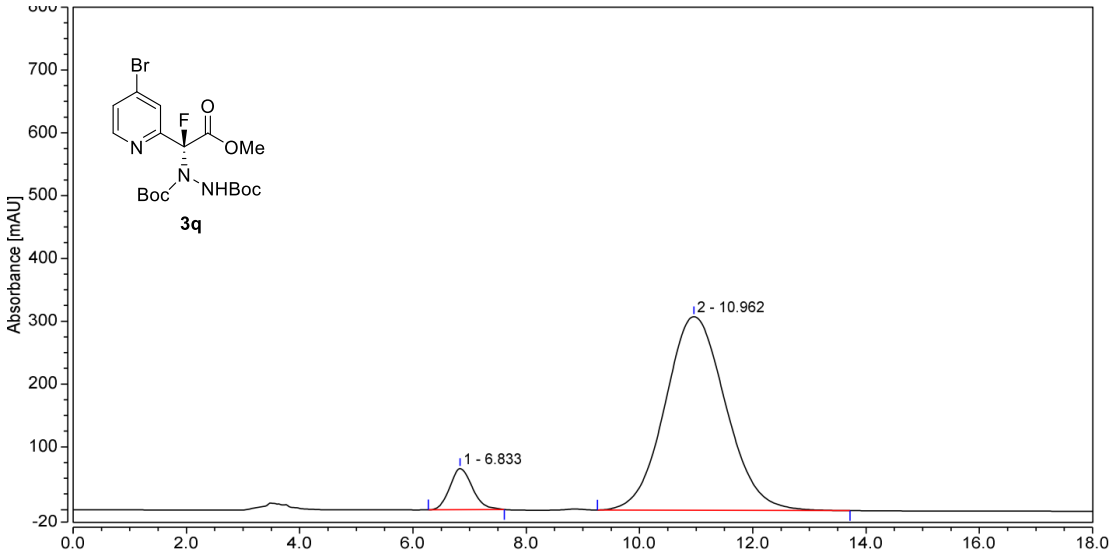
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	8.535	37.652	94.383	5.20	21.51
2	18.317	687.108	344.474	94.80	78.49
Total:		**724.760**	**438.857**	**100.00**	**100.00**

HPLC Spectrum of **3q**



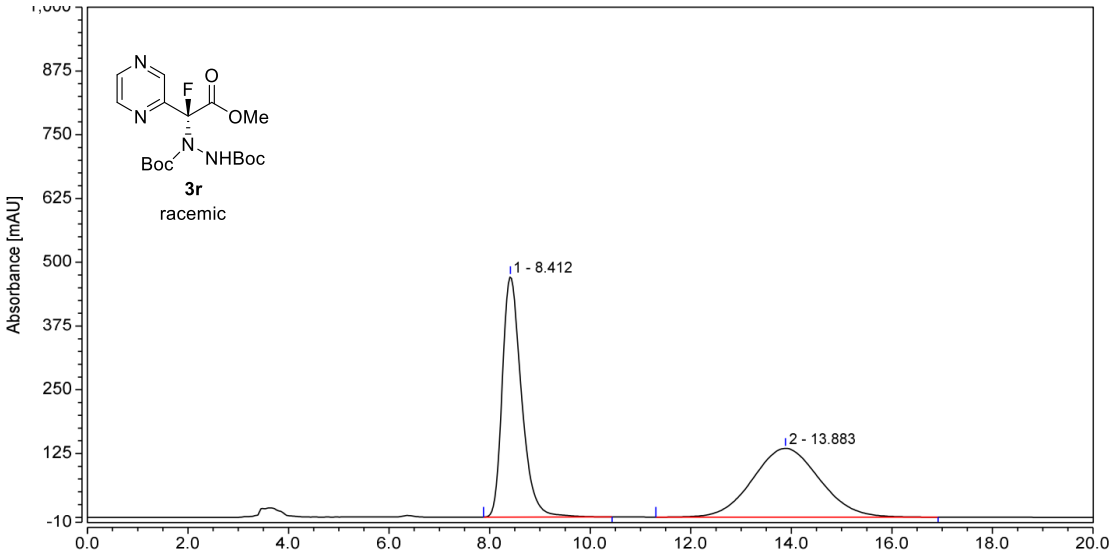
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	6.833	38.797	80.573	49.82	72.25
2	11.078	39.072	30.953	50.18	27.75
Total:		**77.868**	**111.526**	**100.00**	**100.00**

HPLC Spectrum of **3q**



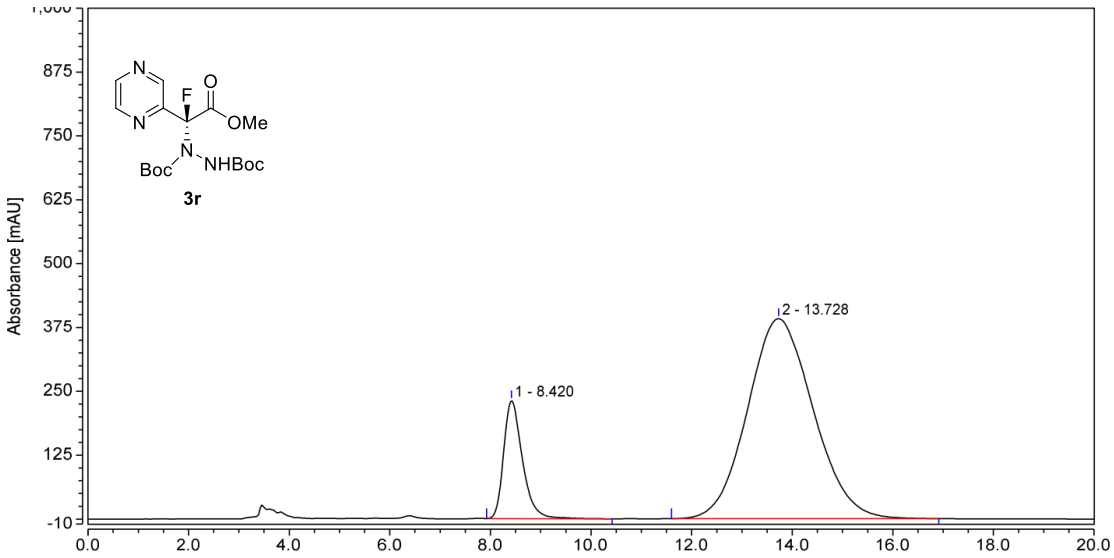
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	6.833	30.265	65.445	7.34	17.52
2	10.962	382.309	308.058	92.66	82.48
Total:		**412.574**	**373.503**	**100.00**	**100.00**

HPLC Spectrum of **3r**



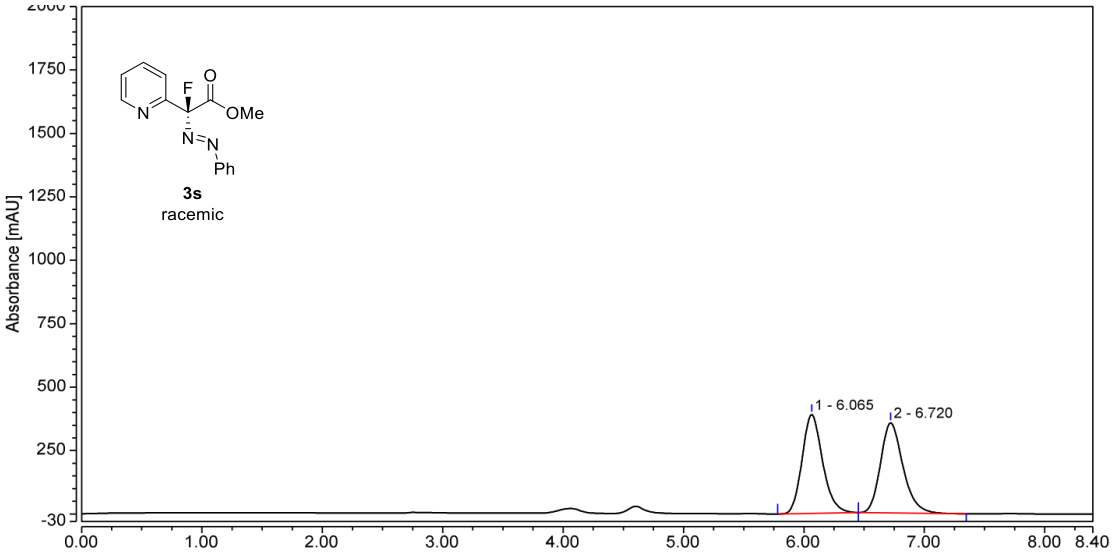
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	8.412	208.078	471.310	49.91	77.75
2	13.883	208.816	134.857	50.09	22.25
Total:		**416.894**	**606.167**	**100.00**	**100.00**

HPLC Spectrum of **3r**



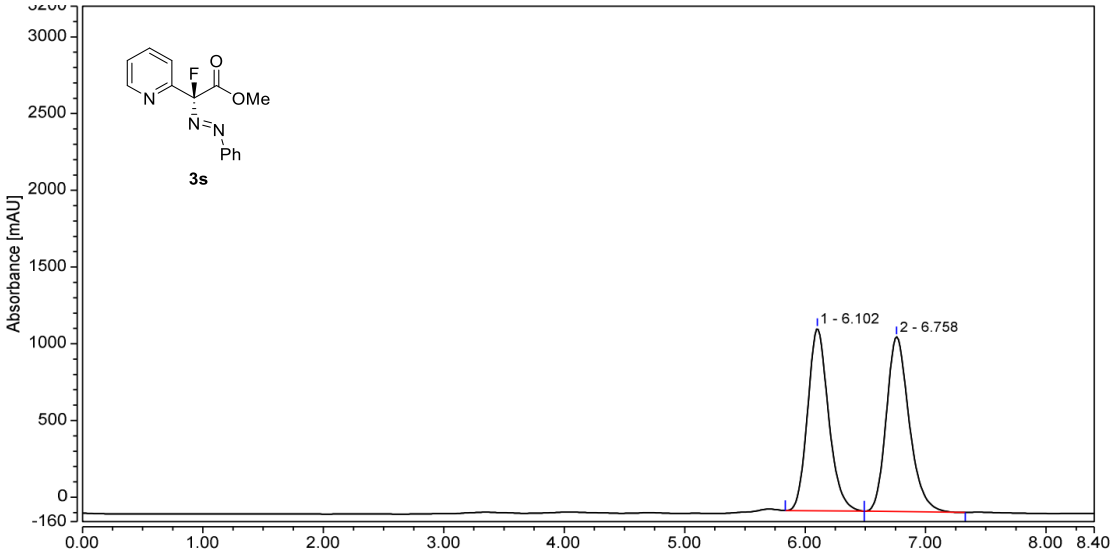
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	8.420	99.875	230.762	14.46	37.08
2	13.728	591.018	391.565	85.54	62.92
Total:		**690.893**	**622.327**	**100.00**	**100.00**

HPLC Spectrum of **3s**



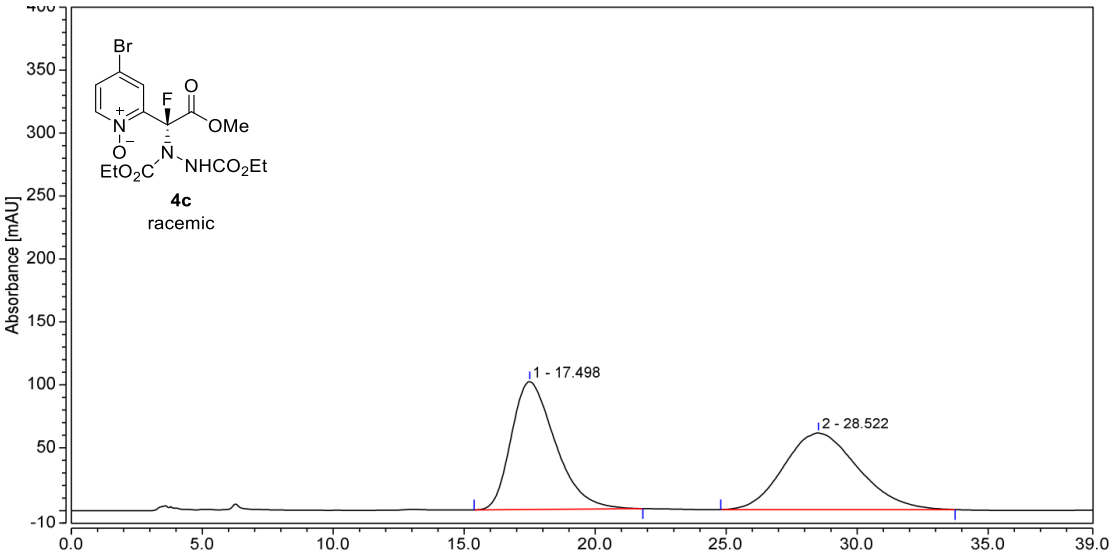
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	6.065	77.136	390.062	50.02	52.34
2	6.720	77.082	355.209	49.98	47.66
Total:		**154.218**	**745.271**	**100.00**	**100.00**

HPLC Spectrum of **3s**



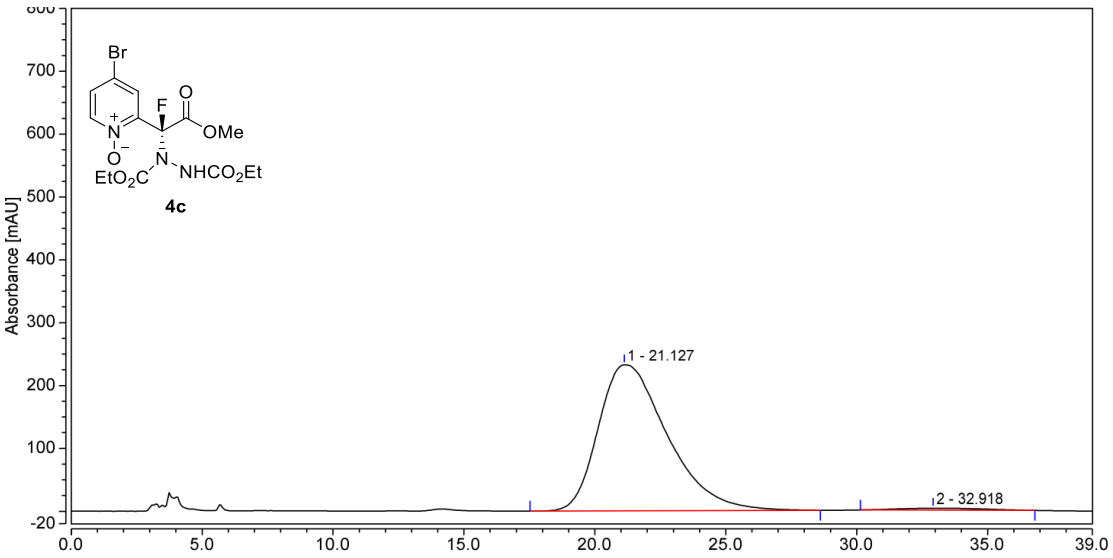
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	6.102	239.389	1187.239	48.88	51.03
2	6.758	250.387	1139.131	51.12	48.97
Total:		**489.776**	**2326.370**	**100.00**	**100.00**

HPLC Spectrum of **4c**



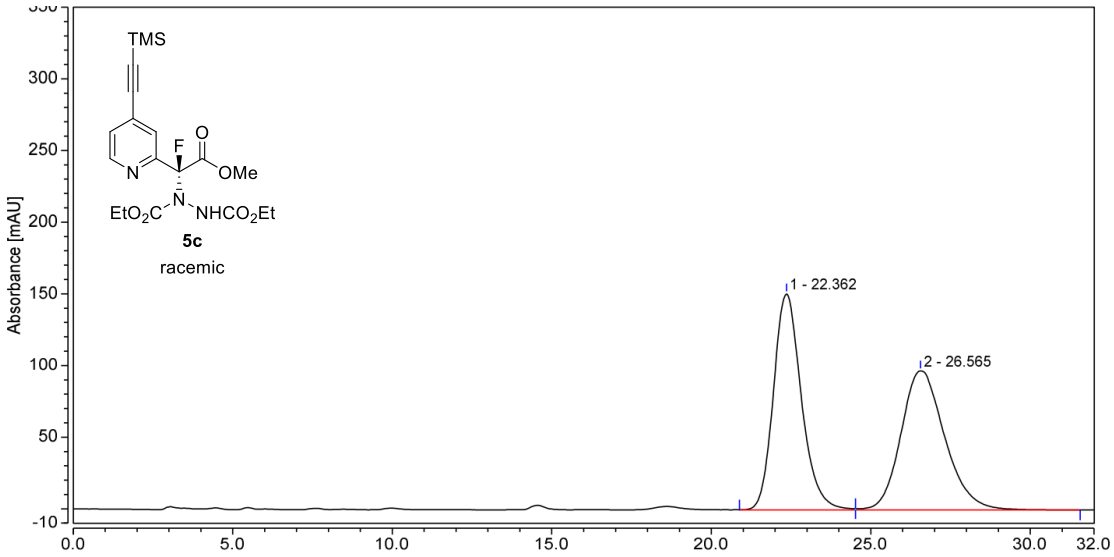
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	17.498	198.392	101.634	49.72	62.51
2	28.522	200.602	60.944	50.28	37.49
Total		**398.994**	**162.578**	**100.00**	**100.00**

HPLC Spectrum of **4c**



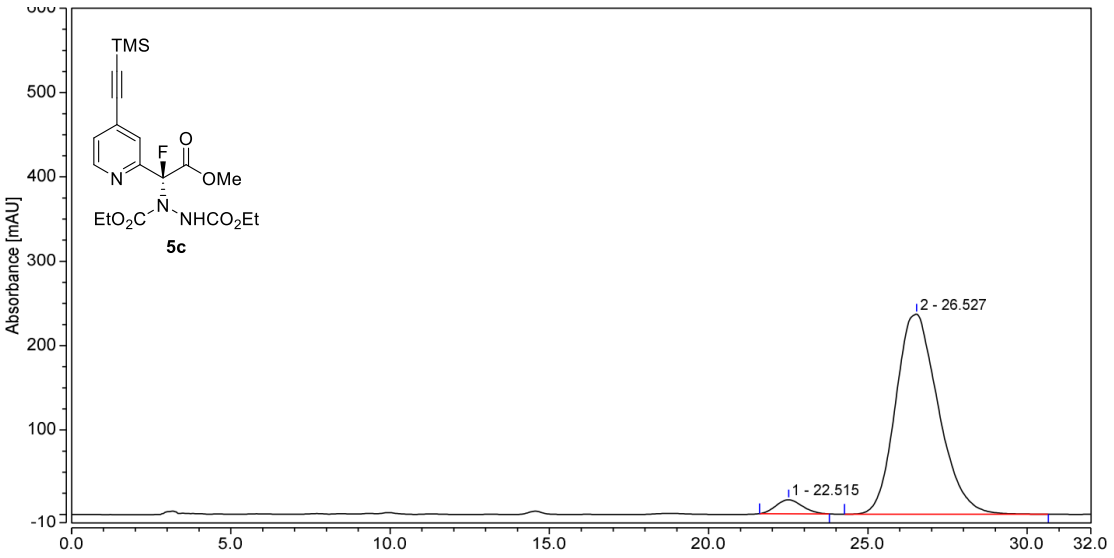
Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	21.127	709.554	232.437	98.37	98.67
2	32.918	11.766	3.129	1.63	1.33
Total		**721.320**	**235.567**	**100.00**	**100.00**

HPLC Spectrum of **5c**



Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	22.362	152.717	150.735	49.72	60.84
2	26.565	154.413	97.029	50.28	39.16
Total		**307.129**	**247.763**	**100.00**	**100.00**

HPLC Spectrum of **5c**



Peak	Retention Time min	Area mAU*min	Height mAU	Area %	Height %
1	22.515	15.837	16.484	4.12	6.50
2	26.527	368.570	237.136	95.88	93.50
Total		**384.407**	**253.620**	**100.00**	**100.00**

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