Electrochemical oxidative heterodifunctionalization of dehydroalanine: Access to unnatural α, α-disubstituted amino esters

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Supporting Information

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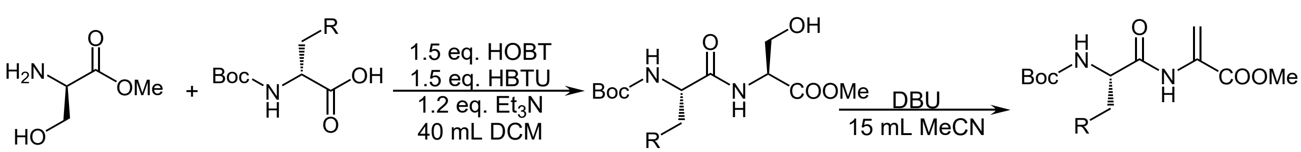
1. General Information

Unless otherwise stated, analytical grade solvents and commercially available reagents were used without further purification. All solvents were analytical reagent or better and were degassed prior to use. The instrument for electrolysis was dual display potentiostat (DJS-292B) (made in China). The anode electrode is carbon rod electrodes (Φ 6mm) and the cathode electrode is platinum plate electrodes (15 mm×15 mm×0.3 mm). Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 200-300 mesh silica gel in petroleum (boiling point is between 60-90°C). Gradient flash chromatography was conducted eluting with a continuous gradient from petroleum to the indicated solvent, and they are listed as volume/volume ratios. High resolution mass spectra (HRMS) for molecular were measured with an Agilent 6224 instrument and accurate masses were reported for the molecular ion + Hydrogen (M+H) or molecular ion + Sodium (M+Na). The ^{1}H, ^{13}C NMR spectra were recorded on a Bruker Advance III (400 MHz) spectrometers with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. For ^{1}H NMR, chemical shifts (δ) were given in ppm relatives to internal standard (TMS at 0 ppm, $CDCl_3$ at 7.26 ppm). For ^{13}C-NMR, chemical shifts (δ) were reported in ppm using solvent as internal standard ($CDCl_3$ at 77.00 ppm).

2. General Experimental Procedures

2.1 Detailed Experimental Procedures for Dehydroalanine Derivatives[1][2][3]

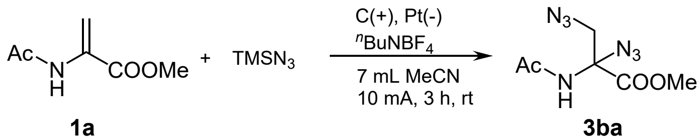


A 2.0 mmol   **B** 2.0 mmol   **C**   Dipeptides **1aa-3ai**

To a solution of Boc-L-serine **A** (410 mg, 2.0 mmol, 1.0 equiv.) in 40 mL CH_2Cl_2 was added HOBT (1-hydroxybenzotriazole) (3.0 mmol), HBTU (O-benzotriazole-N, N, N', N'-tetramethyluronium-hexafluorophosphate) (3.0 mmol) and triethylamine (2.4 mmol). The mixture was stirred for 30 min at room temperature, and then, peptide **B** (2.0 mmol) was added to the solution. The reaction was stirred overnight. After regular workup, the reaction mixture washed by saturated $NaHCO_3$ solution (40 mL x 3), 2 M hydrochloric acid solution (40 mL x 3) and H_2O (40 mL x 3). The organic layers were combined, dried over Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (DCM/MeOH) to afford corresponding dipeptides **C**. To a solution of **C** (2.0 mmol, 1.0 equiv.) in 15 mL MeCN was added DBU (10 mmol, 5 equiv) ,and the resulting mixture was stirred for an additional 8 hours.

2.2 Optimization of reaction conditions

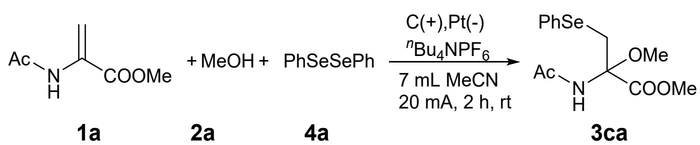
Table S1 Optimization of the reaction conditions



Entry	Variaton from the standard conditions[a]	yield
1	none	46
2	Without electric current	N.D.
3	$^{n}Bu_4NI$	N.D.
4	$^{n}Bu_4NF$	N.D.
5	$^{n}Bu_4NPF_6$	27
6	$^{n}Bu_4NClO_4$	20
7	$LiClO_4$	Trace
8	5 mA	29
9	15 mA	36

[a]Reaction conditions: undivided cell, carbon rod anode, Pt cathode, **1a** (0.2 mmol), $TMSN_3$ (1 mmol), $^{n}Bu_4NBF_4$ (0.2 mmol), MeCN (7mL), air, rt, 10 mA, 3 h. yield of isolated products. N.D = Not Detected

Table S2 Optimization of the reaction conditions

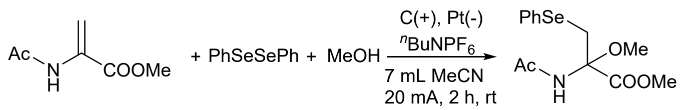


Entry	Variaton from the standard conditions[a]	yield
1	none	92
2	Without electric current	N.D.
3	C(+), Zn(-)	70
4	C(+), Ni(-)	82
5	C(+), Fe(-)	59
6	Pt(+), Pt(-)	42
7	10 mA, 4 h	83
8	15 mA,4 h	73
9	$^{n}Bu_4NClO_4$	66
10	$^{n}Bu_4NBF_4$	53
11	$^{n}Bu_4NI$	N.D.
12	2eq of **2a**	67
13	6eq of **2a**	78

[a]Reaction conditions: undivided cell, carbon rod anode, Pt cathode, **1a** (0.2 mmol), **2a** (0.8 mmol),

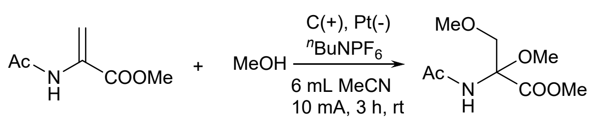
$^{n}Bu_4NPF_6$ (0.2 mmol), **4a** (0.2 mmol), MeCN (7 mL), air, rt, 20 mA, 2 h. yield of isolated products. N.D = Not Detected

2.3 Methyl 2-acetamido-2-methoxy-3-(phenylselanyl)propanoate (3ca) Synthesis



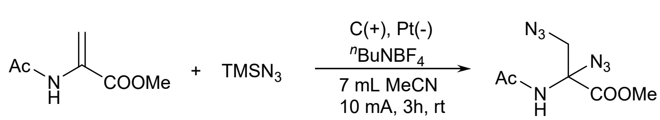
In an oven-dried undivided three-necked bottle (10 mL) equipped with a stir bar, **1a** (0.2 mmol), **4a** (0.2 mmol),**2a** (0.8 mmol) and $^{n}Bu_4NPF_6$ (0.2 mmol) were combined and added. Under the air, CH_3CN (7 mL) were injected respectively into the tubes via syringes. The bottle was equipped with carbon rod (ϕ 6 mm, about 10 mm immersion depth in solution) as the anode and platinum plate (15 mm×15 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolyzed at a constant current of 20 mA under room temperature for 1.5 h. After completion of the reaction, as indicated by TLC, the pure product (yield: 92%, 60.72 mg) was obtained by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate= 1.5:1).

2.4 Methyl 2-acetamido-2,3-dimethoxypropanoate (3aa) Synthesis



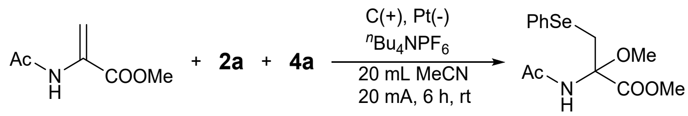
In an oven-dried undivided three-necked bottle (10 mL) equipped with a stir bar, **1a** (0.2 mmol), ,**2a** (1 mL) and $^{n}Bu_4NPF_6$ (0.2 mmol) were combined and added. Under the air, CH_3CN (6 mL) were injected respectively into the tubes via syringes. The bottle was equipped with carbon rod (ϕ 6 mm, about 10 mm immersion depth in solution) as the anode and platinum plate (15 mm×15 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolyzed at a constant current of 10 mA under room temperature for 3 h. After completion of the reaction, as indicated by TLC, the pure product (yield: 85%, 34.88 mg) was obtained by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate= 1.5:1).

2.5 Methyl 2-acetamido-2,3-diazidopropanoate (4ba) Synthesis



In an oven-dried undivided three-necked bottle (10 mL) equipped with a stir bar, **1a** (0.2 mmol), $TMSN_3$ (1 mol) and $^{n}Bu_4NBF_4$ (0.2 mmol) were combined and added. Under the air, CH_3CN (7 mL) were injected respectively into the tubes via syringes. The bottle was equipped with carbon rod (ϕ 6 mm, about 10 mm immersion depth in solution) as the anode and platinum plate (15 mm×15 mm×0.3 mm) as the cathode. The reaction mixture was stirred and electrolyzed at a constant current of 10 mA under room temperature for 3 h. After completion of the reaction, as indicated by TLC, the pure product (yield: 46%, 20.90 mg) was obtained by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate= 1.5:1).

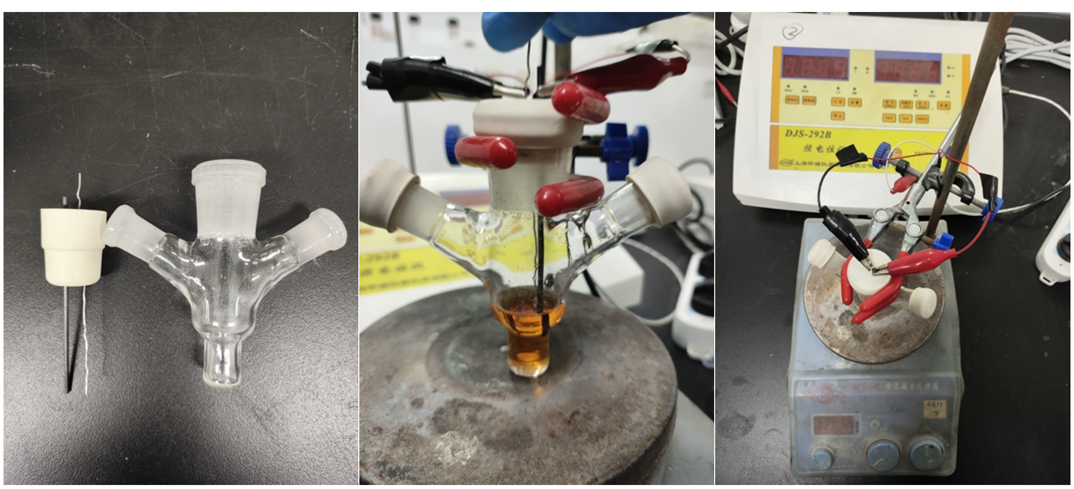
2.6 Gram-scale synthesis of 1a at 3 mmol scale

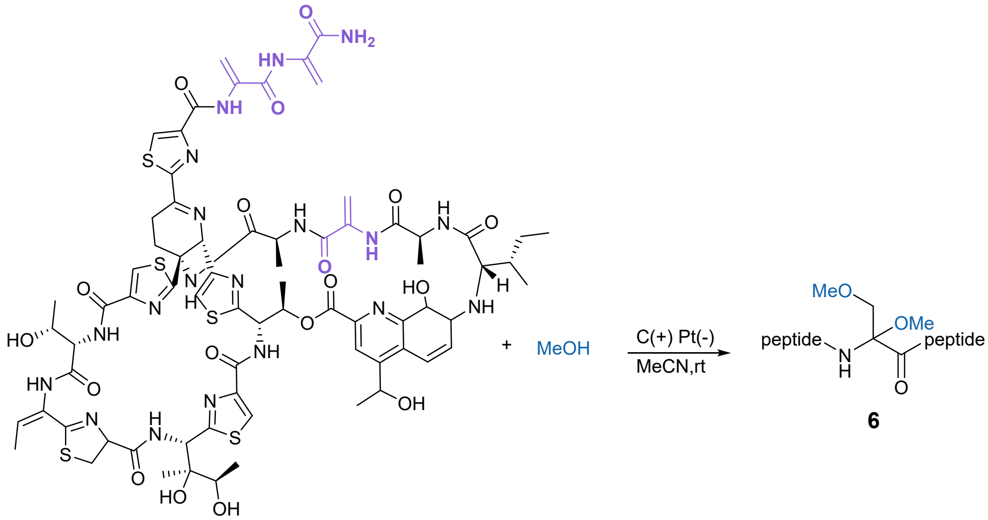


[a] Reaction conditions: **1a** (3.0 mmol), **2a** (3.0 mmol), **4a** (12.0 mmol),$^{n}Bu_4NPF_6$ (3.0 mmol), CH_3CN (20 mL), carbon rod (ϕ 6 mm, about 10 mm immersion depth in solution) as the anode and platinum plate (15 mm×15 mm×0.3 mm) as the cathode, 20 mA,6 h, rt, undivided cell.[b]Isolated yields.

2.7 Thiostrepton functionalization

In an oven-dried undivided three-necked bottle (5 mL) equipped with a stir bar, thiostrepton (10 mg), MeOH (20 μL), $^{n}Bu_4NPF_6$ (10 mg), CH_3CN (2 mL) were combined and added. The bottle was equipped carbon paper (Φ 1mm) as the anode and platinum wire (Φ 0.4mm) as the cathode. The reaction mixture was stirred and electrolysis at constant current of 10 mA under room temperature for 15 min.The reaction mixture was diluted with 5 mL ethyl acetate and 5 mL H_2O, the phases were washed with brine dried over $MgSO_4$ and the solvent was removed under vacuum. The sample was analyzed by MALDI-TOF with DHB as matrix.For determination of the product distribution, the areas of all the [M]+ -peaks of the products were summed up and divided by the area of the corresponding product.

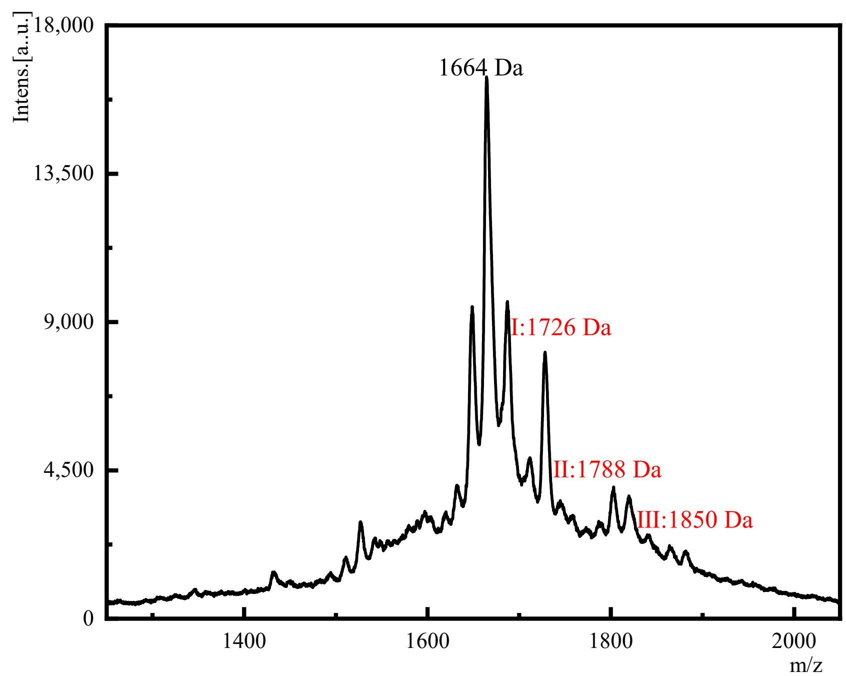




Thiostrepton (**5**)

Product	m/z [M]+	t = 10 min	t = 30 min
Starting material	1664	58	35
Mono	1726	27	37
Product	m/z [M]+	t = 10 min	t = 30 min
Di	1788	10	14
Tri	1850	5	14

t=10 min



t=30 min

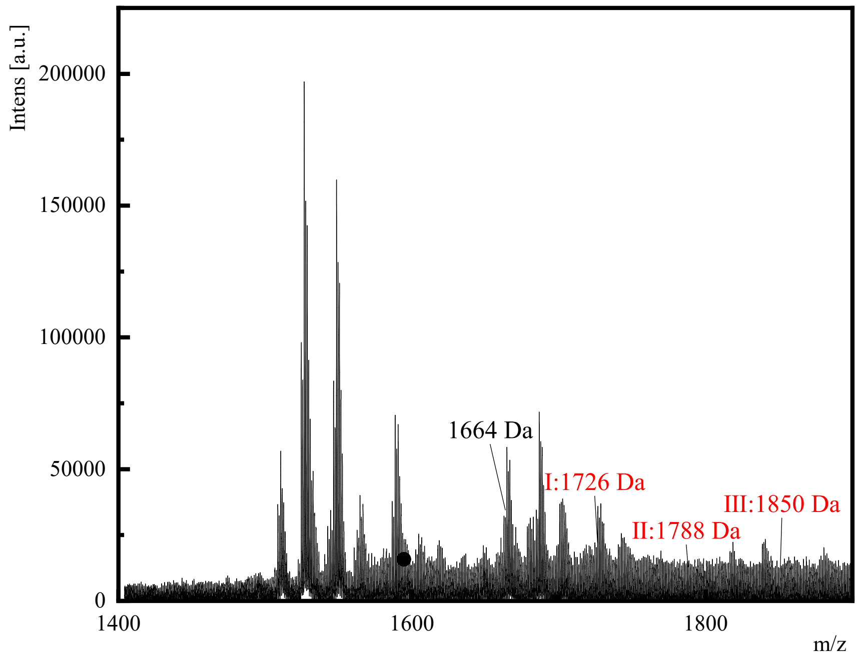
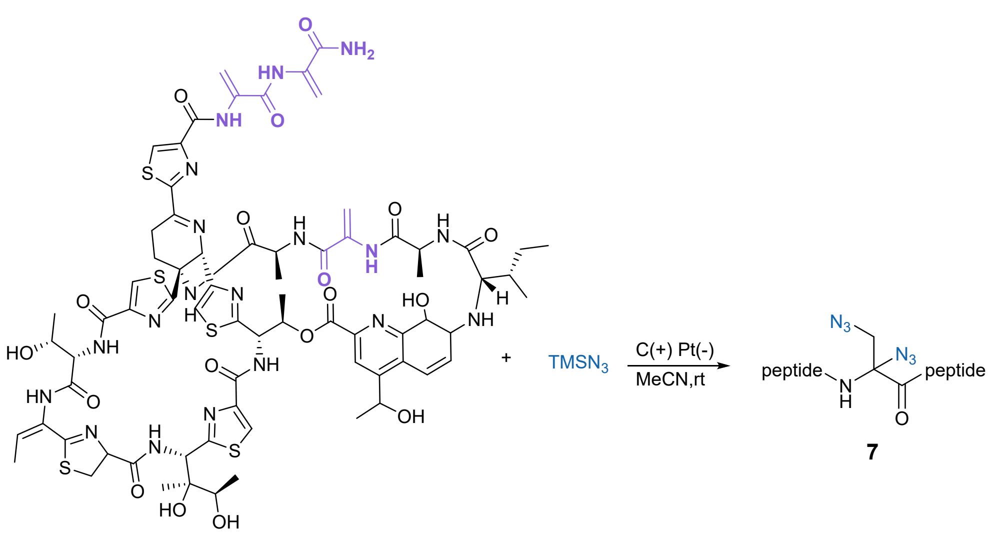


Figure S1. MALDI-TOF measurement of the crude product of the electrochemical modification of thiostrepton with MeOH

Thiostrepton functionalization

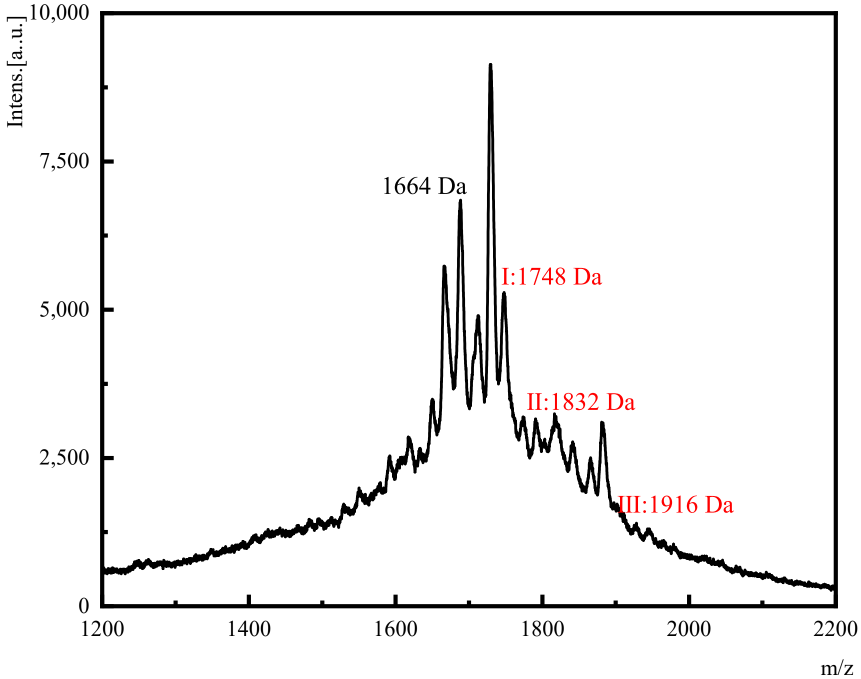
In an oven-dried undivided three-necked bottle (5 mL) equipped with a stir bar, thiostrepton (10 mg), $TMSN_3$ (20 μL), $^nBu_4NBF_4$ (10 mg), CH_3CN (3 mL) were combined and added. The bottle was equipped carbon paper (Φ 1mm) as the anode and platinum wire (Φ 0.4mm) as the cathode. The reaction mixture was stirred and electrolysis at constant current of 10 mA under room temperature for 15 min.The reaction mixture was diluted with 5 mL ethyl acetate and 5 mL H_2O, the phases were washed with brine dried over $MgSO_4$ and the solvent was removed under vacuum. The sample was analyzed by MALDI-TOF with DHB as matrix. For determination of the product distribution, the areas of all the [M]+ -peaks of the products were summed up and divided by the area of the corresponding product.



Thiostrepton (**5**)

Product	m/z [M]+	t = 10 min	t = 30 min
Starting material	1664	39	20
Mono	1748	32	38
Di	1832	21	31
Tri	1916	8	11

t=10 min



t=30 min

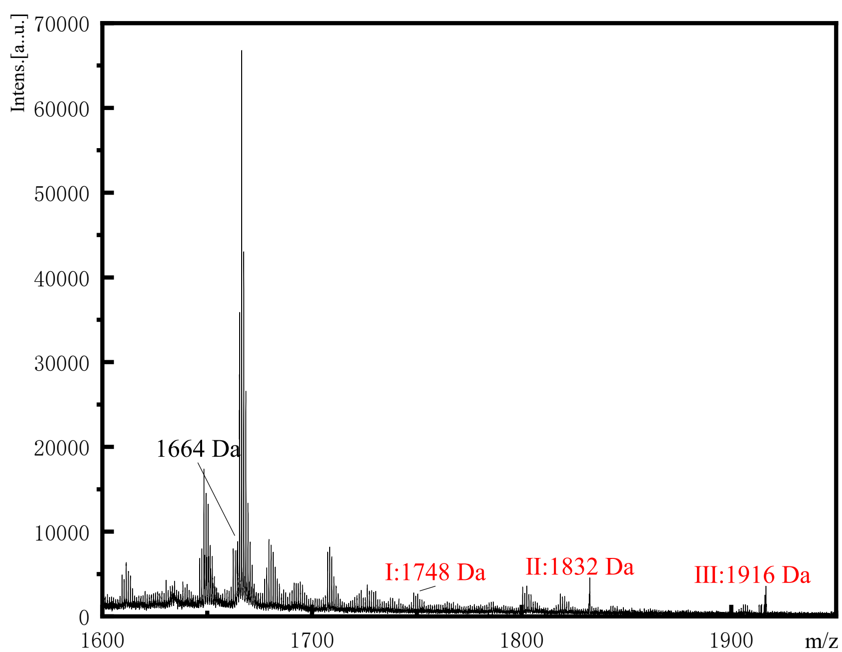
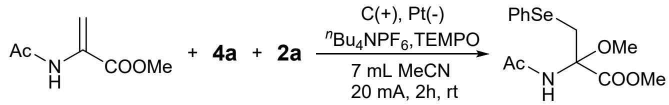


Figure S2. MALDI-TOF measurement of the crude product of the electrochemical modification of thiostrepton with $TMSN_3$

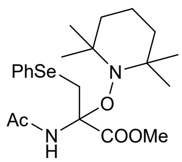
3. Mechanistic Experiments

3.1 Radical trapping experiments



1a
0.2 mmol 0.2 mmol 0.8 mmol n.d.

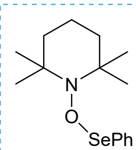
[a] Reaction conditions: **1a** (0.2 mmol), **4a** (0.2 mmol), **2a** (0.8 mmol), $^{n}Bu_4NPF_6$ (0.2 mmol), CH_3CN (7 mL), carbon rod (ϕ 6 mm, about 10 mm immersion depth in solution) as the anode and platinum plate (15 mm×15 mm×0.3 mm) as the cathode, 2 h, rt, undivided cell.



b'

Detected by HRMS of **b′** calcd for $C_{15}H_{23}NOSe$
$[M+H]^+$: 451.1659; Found: 451.1650

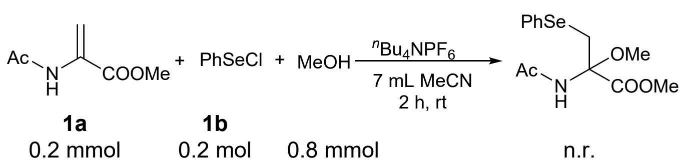
Figure S3. The HRMS spectra of compound **b'**



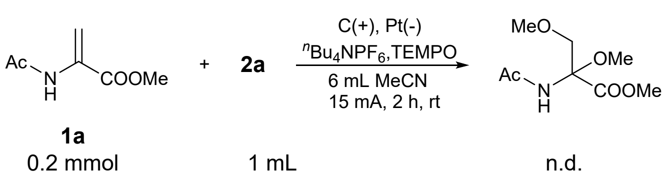
c'

Detected by HRMS of **c′** calcd for $C_{15}H_{23}NOSe$
$[M+H]^+$: 308.1077; Found: 308.1035

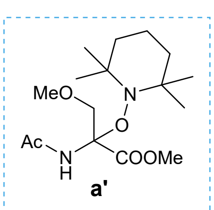
Figure S4. The HRMS spectra of compound **c'**



[a] Reaction conditions: **1a** (0.2 mmol), **6a** (0.2 mmol), **6a** (0.8 mmol),${}^{n}Bu_4NPF_6$ (0.2 mmol), TEMPO (0.6 mmol), CH_3CN (7 mL), carbon rod (ϕ 6 mm, about 10 mm immersion depth in solution) as the anode and platinum plate (15 mm×15 mm×0.3 mm) as the cathode, 20 mA, 6 h, rt, undivided cell.



[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1 mL), ${}^{n}Bu_4NPF_6$ (0.2 mmol), TEMPO (0.6 mmol), CH_3CN (6 mL), carbon rod (ϕ 6 mm, about 10 mm immersion depth in solution) as the anode and platinum plate (15 mm×15 mm×0.3 mm) as the cathode, 15 mA, 5 h, rt, undivided cell.



Detected by HRMS of **a′** calcd for $C_{16}H_{30}N_2O_5$

$[M+Na]^+$: 353.20469; Found: 353.20473

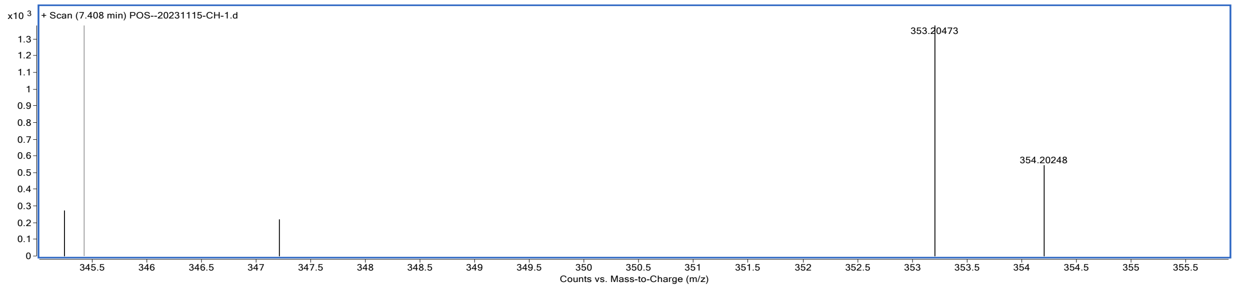


Figure S5. The HRMS spectra of compound **a'**

3.2 Cyclic voltammetry experiments

Cyclic voltammetry was performed in a three-electrode cell connected to a schlenk line at room temperature. The working electrode was a steady glassy carbon disk electrode, the counter electrode was a platinum wire. The reference was an Ag/AgCl electrode submerged in saturated aqueous KCl solution and separated from a reaction by a salt bridge.8 mL of CH_3CN containing 0.02 M ^{n}Bu_4NPF_6 were poured into the electrochemical cell in all experiments. The scan rate is 0.1 V/s. The positive scan range was from 0 V to 3.0 V and 0 V to -3.0 V.

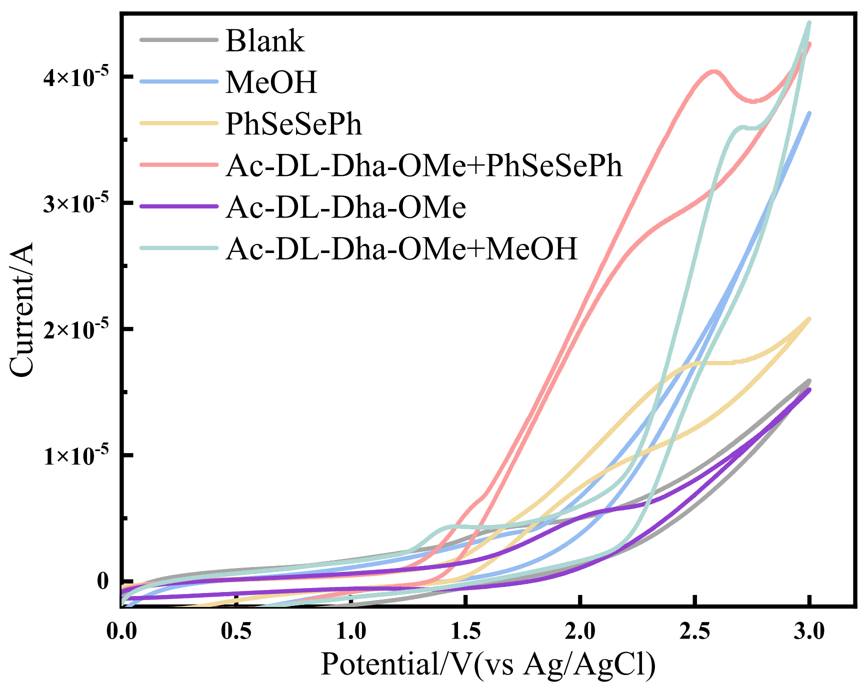


Figure S5. Cyclic voltammograms of substrate **1a**, **4a**, MeOH, **1a**+**4a**, **1a**+MeOH (0.02 M) 0-3 V

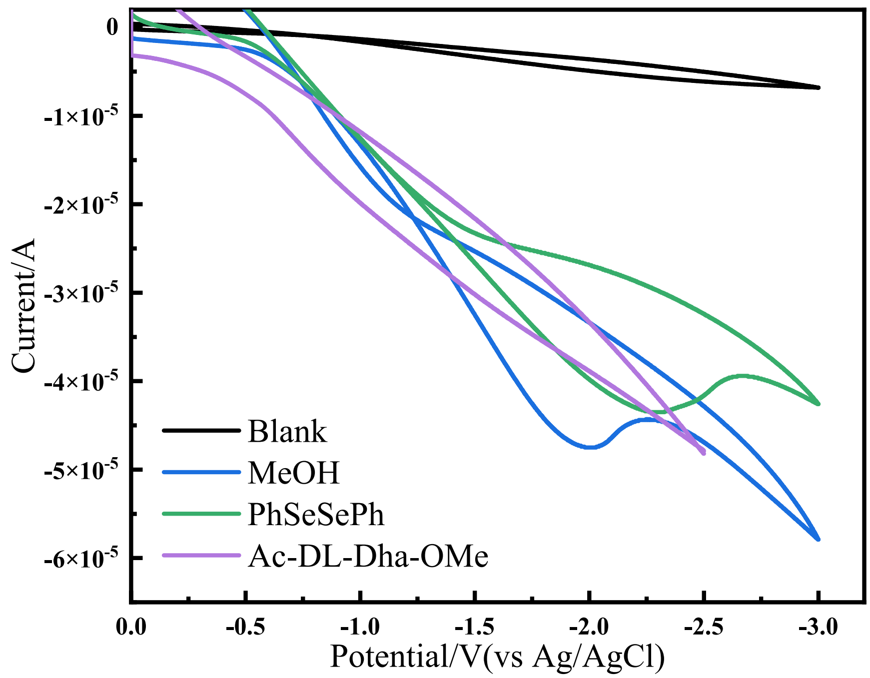


Figure S6. Cyclic voltammograms of substrate **1a**, **4a**, MeOH (0.02 M) -3-0 V

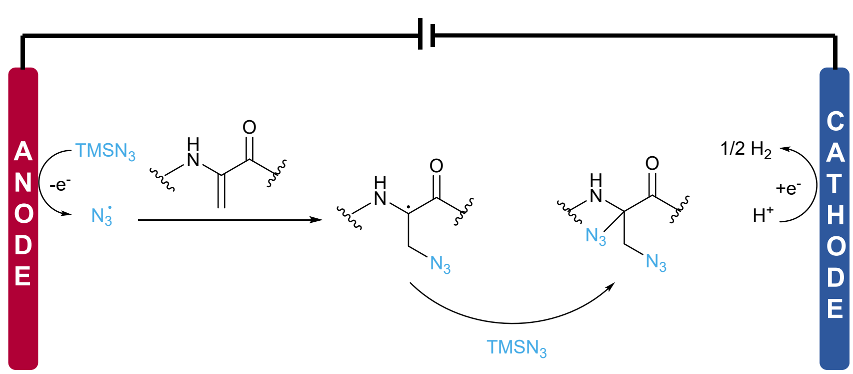
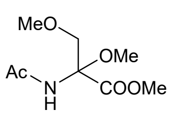


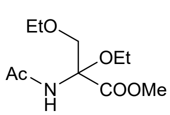
Figure S7： Proposed mechanism of diazidation

4. Detailed descriptions for products:



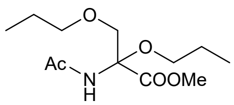
Methyl 2-acetamido-2,3-dimethoxypropanoate (3aa):

White solid (Yield: 90 %, 36.89 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.78 (s, 1H), 4.01 (d, J = 9.4 Hz, 1H), 3.80 (s, 3H), 3.67 (d, J = 9.4 Hz, 1H), 3.35 (s, 3H), 3.27 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.94, 169.51, 86.35, 73.44, 59.71, 53.24, 51.93, 23.71. HRMS (ESI) cald. For (M+Na)+ $C_8H_{15}NO_5$: 228.0842, found, 228.0842



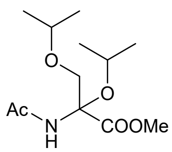
Methyl 2-acetamido-2,3-diethoxypropanoate (3ab):

White solid (Yield: 70 %, 32.65 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.83 (s, 1H), 4.15 (d, J = 9.6 Hz, 1H), 3.82 (s, 3H), 3.73 (d, J = 9.6 Hz, 1H), 3.65 – 3.41 (m, 4H), 2.08 (s, 3H), 1.18 (dt, J = 16.8, 7.0 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.05, 169.75, 86.36, 71.31, 67.38, 60.04, 53.13, 23.82, 14.95. HRMS (ESI) cald. For (M+Na)+ $C_{10}H_{19}NO_5$: 256.1155, found, 256.1155.



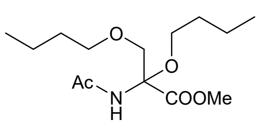
Methyl 2-acetamido-2,3-dipropoxypropanoate (3ac):

White solid (Yield: 61 %, 31.88 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.79 (s, 1H), 4.17 (d, J = 9.5 Hz, 1H), 3.80 (s, 3H), 3.71 (d, J = 9.5 Hz, 1H), 3.51 – 3.33 (m, 3H), 3.28 (dt, J = 8.7, 6.7 Hz, 1H), 2.05 (s, 3H), 1.64 – 1.43 (m, 4H), 0.86 (dt, J = 9.9, 7.4 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.18, 169,66.60, 86.53, 73.59, 71.25, 66.05, 53.06, 23.91, 22.82, 22.59, 10.52. HRMS (ESI) cald. For (M+Na)+ $C_{12}H_{23}NO_5$: 284.1468, found, 284.1462.



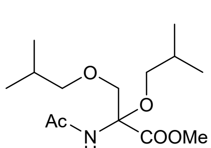
Methyl 2-acetamido-2,3-diisopropoxypropanoate (3ad):

White solid (Yield: 56 %, 36.45mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.88 (s, 1H), 4.28 (d, J = 9.3 Hz, 1H), 3.89 (p, J = 6.2 Hz, 1H), 3.81 (s, 3H), 3.66 (d, J = 9.3 Hz, 1H), 3.59 (p, J = 6.1 Hz, 1H), 2.06 (s, 3H), 1.15 – 1.03 (m, 12H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.15, 169.69, 86.51, 72.74, 68.69, 67.65, 52.97, 24.21, 23.74, 22.90, 22.07, 21.85. HRMS (ESI) cald. For (M+Na)+ $C_{12}H_{23}NO_5$: 284.1468, found, 284.1468.



Methyl 2-acetamido-2,3-dibutoxypropanoate (3ae)

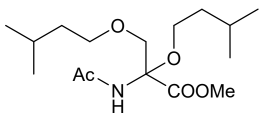
Yellow oil (Yield: 56 %, 32.41mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.74 (s, 1H), 4.14 (d, J = 9.6 Hz, 1H), 3.78 (s, 3H), 3.69 (d, J = 9.6 Hz, 1H), 3.52 – 3.37 (m, 3H), 3.31 (dt, J = 9.0, 6.6 Hz, 1H), 2.02 (s, 3H), 1.55 – 1.42 (m, 4H), 1.30 (dq, J = 14.8, 7.4 Hz, 4H), 0.86 (td, J = 7.4, 3.1 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.12, 169.42, 86.56, 71.69, 71.34, 64.01, 52.88, 31.63, 31.45, 23.79, 19.12, 19.10, 13.72, 13.68. HRMS (ESI) cald. For (M+Na)+ $C_{14}H_{27}NO_5$: 312.1781, found, 312.1785.



Methyl 2-acetamido-2,3-diisobutoxypropanoate (3af)

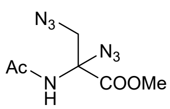
Colorless oil (Yield: 56 %, 32.40mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.76 (s, 1H), 4.18 (d, J = 9.5 Hz, 1H), 3.78 (s, 3H), 3.71 (d, J = 9.5 Hz, 1H), 3.28 – 3.13 (m, 3H), 3.05 (dd, J = 8.6, 6.7

Hz, 1H), 2.03 (s, 3H), 1.79 (dqd, J = 13.4, 6.6, 2.2 Hz, 2H), 0.88 – 0.79 (m, 12H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.17, 169.55, 169.44, 169.01, 86.60, 78.70, 71.36, 70.87, 52.85, 28.36, 28.17, 23.83, 19.30, 19.22, 19.07, 19.04, 18.86. HRMS (ESI) cald. For (M+Na)+ $C_{14}H_{27}NO_5$: 312.1781, found, 312.1796.



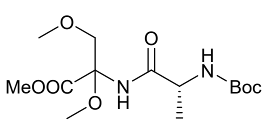
Methyl 2-acetamido-2,3-bis(isopentyloxy)propanoate (3ag)

Colorless oil (Yield: 40 %, 25.39mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.77 (s, 1H), 4.18 (d, J = 9.4 Hz, 1H), 3.81 (s, 3H), 3.72 (d, J = 9.6 Hz, 1H), 3.60 – 3.42 (m, 3H), 3.39 – 3.29 (m, 1H), 2.06 (s, 3H), 1.67 (ddt, J = 30.3, 13.4, 6.7 Hz, 2H), 1.50 – 1.36 (m, 4H), 0.87 (dd, J = 6.7, 2.9 Hz, 12H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.21, 169.65, 86.55, 71.28, 70.38, 62.62, 53.07, 38.34, 38.12, 25.99, 24.94, 24.71, 23.91, 22.56, 22.53, 22.49, 22.39. HRMS (ESI) cald. For (M+Na)+ $C_{16}H_{31}NO_5$: 340.2094, found, 340.2108.



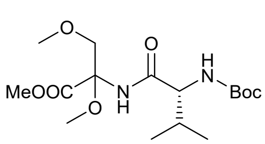
Methyl 2-acetamido-2,3-diazidopropanoate (3ba):

Colorless oil (Yield: 46 %, 20.90 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.05 (s, 1H), 4.00 (d, J = 12.6 Hz, 1H), 3.90 (s, 3H), 3.53 (d, J = 12.5 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.74, 167.17, 75.35, 53.98, 53.79, 22.89. HRMS (ESI) cald. For (M+Na)+ $C_6H_9N_7O_3$: 250.0659, found, 250.0658.



Methyl 2-((R)-2-((tert-butoxycarbonyl)amino)propanamido)-2,3-dimethoxypropanoate (3ah):

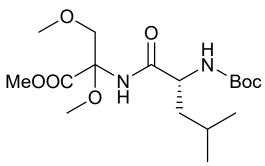
Colorless oil (Yield: 85 %, 56.84 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.40 (d, J = 43.1 Hz, 1H), 5.06 (s, 1H), 4.22 (s, 1H), 4.04 (d, J = 9.6 Hz, 1H), 3.84 (s, 3H), 3.72 (d, J = 13.1 Hz, 1H), 3.33 (d, J = 32.6 Hz, 6H), 1.45 (s, 9H), 1.39 (d, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.62, 172.57, 169.31, 155.50, 86.52, 86.38, 80.30, 73.48, 73.31, 59.73, 53.21, 53.19, 51.88, 51.84, 50.48, 28.23, 17.93. HRMS (ESI) cald. For (M+Na)+ $C_{14}H_{26}N_2O_7$: 357.1632, found, 357.1630.



Methyl 2-((R)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-2,3-

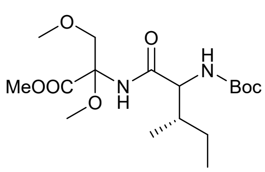
dimethoxypropanoate (3ai):

Colorless oil (Yield: 66%, 47.84 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.18 (d, J = 27.4 Hz, 1H), 5.02 (s, 1H), 4.02 (d, J = 9.5 Hz, 1H), 3.84 (d, J = 5.7 Hz, 3H), 3.72 (d, J = 9.5 Hz, 1H), 3.54 – 3.12 (m, 6H), 2.29 – 2.05 (m, 1H), 1.77 (s, 1H), 1.46 (s, 9H), 1.07 – 0.88 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.67, 169.61, 167.25, 154.00, 84.75, 84.30, 78.21, 71.83, 58.35, 57.82, 57.66, 51.36, 51.23, 50.18, 50.09, 28.73, 28.53, 26.34, 17.28, 15.60. HRMS (ESI) cald. For (M+Na)+ $C_{16}H_{30}N_2O_7$: 385.1945, found, 385.1941.



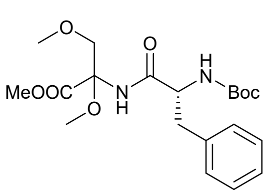
Methyl 2-((R)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-2,3-dimethoxypropanoate (3aj):

Colorless oil (Yield: 60%, 45.15 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.42 (s, 1H), 5.11 – 4.84 (m, 1H), 4.14 (s, 1H), 4.03 (dd, J = 23.5, 9.5 Hz, 1H), 3.83 (d, J = 3.4 Hz, 3H), 3.72 (d, J = 9.7 Hz, 1H), 3.34 (dd, J = 30.6, 3.3 Hz, 6H), 1.71 (s, 2H), 1.45 (s, 10H), 0.95 (t, J = 5.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.46, 169.33, 169.21, 155.72, 86.57, 86.25, 80.27, 73.68, 73.25, 59.75, 59.66, 53.19, 53.12, 51.92, 40.79, 40.64, 28.22, 24.73, 24.69, 22.92, 22.87, 21.84. HRMS (ESI) cald. For (M+Na)+ $C_{17}H_{32}N_2O_7$: 399.2101, found, 399.2102.



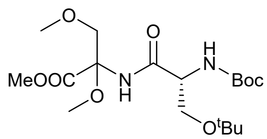
Methyl 2-((3S)-2-((tert-butoxycarbonyl)amino)-3-methylpentanamido)-2,3-dimethoxypropanoate (3ak):

Colorless oil (Yield: 50%, 37.65 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.18 (d, J = 33.0 Hz, 1H), 5.05 (dd, J = 22.7, 8.3 Hz, 1H), 4.02 (dd, J = 44.9, 9.2 Hz, 2H), 3.80 (d, J = 5.9 Hz, 3H), 3.68 (d, J = 9.4 Hz, 1H), 3.45 – 3.15 (m, 6H), 1.98 (s, 2H), 1.88 (ddq, J = 13.4, 6.9, 4.3, 3.6 Hz, 1H), 1.42 (s, 9H), 1.00 – 0.84 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.68, 167.25, 153.94, 84.26, 78.19, 71.84, 71.04, 57.81, 51.35, 50.16, 35.15, 26.35, 22.77, 13.54, 9.59. HRMS (ESI) cald. For (M+Na)+ $C_{17}H_{32}N_2O_7$: 399.2101, found, 399.2109.



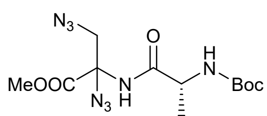
Methyl 2-((R)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-2,3-dimethoxypropanoate (3ai):

Colorless oil (Yield: 67%, 55.01 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.34 – 7.07 (m, 6H), 5.04 (s, 1H), 4.42 (s, 1H), 3.98 (dd, J = 15.2, 9.5 Hz, 1H), 3.82 (d, J = 4.5 Hz, 3H), 3.64 (dd, J = 36.8, 9.6 Hz, 1H), 3.32 (d, J = 6.4 Hz, 3H), 3.20 (d, J = 8.7 Hz, 3H), 3.10 (d, J = 6.1 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.13, 171.09, 169.14, 169.03, 155.43, 136.44, 136.35, 129.42, 128.68, 127.02, 86.53, 86.26, 73.57, 73.38, 59.68, 59.64, 56.00, 53.18, 53.13, 51.99, 37.90, 37.64, 28.21. HRMS (ESI) cald. For (M+Na)+ $C_{20}H_{30}N_2O_7$: 433.1945, found, 433.1940.



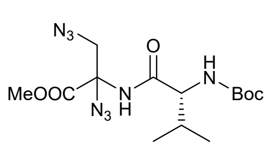
Methyl 2-((R)-3-(tert-butoxy)-2-((tert-butoxycarbonyl)amino)propanamido)-2,3-dimethoxypropanoate (3am):

Colorless oil (Yield: 64%, 52.03 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.91 (d, J = 24.1 Hz, 1H), 5.48 (s, 1H), 4.23 (s, 1H), 4.04 (d, J = 9.4 Hz, 1H), 3.94 – 3.71 (m, 5H), 3.43 (s, 1H), 3.38 (s, 3H), 3.30 (s, 3H), 1.47 (s, 9H), 1.22 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ170.50, 170.38, 169.12, 169.05, 155.29, 86.57, 85.95, 79.90, 74.03, 73.96, 73.55, 61.69, 61.52, 59.60, 54.51, 54.33, 52.99, 51.80, 28.18, 27.25, 27.18. HRMS (ESI) cald. For (M+K)+ $C_{18}H_{34}N_2O_8$: 429.1997, found, 429.1999.



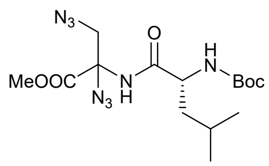
Methyl (S)-2,3-diazido-2-((R)-2-((tert-butoxycarbonyl)amino)propanamido)propanoate (3bb):

yellow oil (Yield: 43%, 30.65 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.90 (d, J = 21.5 Hz, 1H), 5.03 (s, 1H), 4.24 (s, 1H), 3.99 – 3.92 (m, 1H), 3.87 (s, 3H), 3.53 (dd, J = 12.5, 7.8 Hz, 1H), 1.45 (s, 9H), 1.36 (dd, J = 7.0, 2.2 Hz, 3H).^{13}C NMR (101 MHz, Chloroform-d) δ 171.63, 165.10, 165.07, 154.03, 79.00, 73.38, 52.29, 52.06, 51.96, 47.91, 26.32, 15.33. HRMS (ESI) cald. For (M+Na)+ $C_{12}H_{20}N_8O_5$: 379.1448, found, 379.1442.



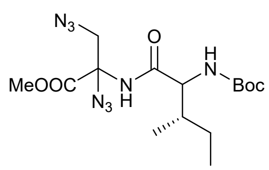
Methyl (S)-2,3-diazido-2-((R)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)propanoate (3bc):

Colorless liquid (Yield: 36%, 27.68 mg).^{1}H NMR (400 MHz, Chloroform-d) δ 7.43 (s, 1H), 4.97 (s, 1H), 3.88 (s, 3H), 3.64 – 3.49 (m, 1H), 2.18 (tt, J = 13.3, 6.7 Hz, 1H), 1.67 (s, 1H), 1.46 (s, 9H), 1.25 (s, 1H), 1.02 – 0.94 (m, 6H).^{3}C NMR (101 MHz, Chloroform-d) δ 172.70, 172.58, 166.93, 156.17, 80.54, 75.29, 59.74, 53.85, 30.24, 30.14, 28.22, 19.18, 19.10, 17.82, 17.73. HRMS (ESI) cald. For (M+Na)+ $C_{14}H_{24}N_8O_5$: 407.1761, found, 407.1765.



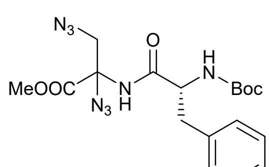
Methyl (S)-2,3-diazido-2-((R)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)propanoate (3bd):

Yellow oil (Yield: 44%, 35.06 mg).^{1}H NMR (400 MHz, Chloroform-d) δ 7.93 (s, 1H), 4.95 (s, 1H), 4.19 (s, 1H), 3.95 (d, J = 12.5 Hz, 1H), 3.88 (s, 3H), 3.54 (dd, J = 12.4, 9.0 Hz, 1H), 1.74 – 1.64 (m, 2H), 1.46 (d, J = 4.9 Hz, 10H), 0.99 – 0.91 (m, 6H).^{13}C NMR (101 MHz, Chloroform-d) δ 173.74, 166.89, 156.12, 80.54, 75.26, 60.40, 53.75, 52.64, 40.36, 28.17, 24.61, 22.72. HRMS (ESI) cald. For (M+Na)+ $C_{15}H_{26}N_8O_5$: 421.1918, found, 421.1918.



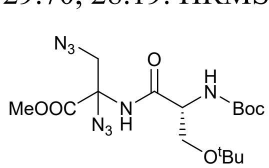
Methyl 2,3-diazido-2-((3S)-2-((tert-butoxycarbonyl)amino)-3-methylpentanamido)propanoate (3be):

Yellow oil (Yield: 36%, 28.69 mg).^{1}H NMR (400 MHz, Chloroform-d) δ 7.67 (s, 1H), 5.10 (s, 1H), 3.99 (s, 1H), 3.86 (s, 4H), 3.54 (d, J = 12.5 Hz, 1H), 1.87 (s, 1H), 1.44 (s, 10H), 1.13 (s, 1H), 0.93 (dt, J = 21.4, 7.1 Hz, 6H).^{13}C NMR (101 MHz, Chloroform-d) δ 172.67, 172.55, 166.88, 156.05, 80.56, 75.27, 59.14, 54.43, 53.85, 36.44, 28.23, 24.72, 24.69, 15.44, 15.37, 11.22. HRMS (ESI) cald. For (M+Na)+ $C_{15}H_{26}N_8O_5$: 421.1918, found, 421.1917.



Methyl (S)-2,3-diazido-2-((R)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)propanoate (3bf):

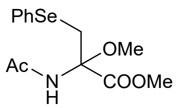
Yellow oil (Yield: 40%, 34.60 mg).^{1}H NMR (400 MHz, Chloroform-d) δ 7.47 – 7.16 (m, 6H), 5.05 (d, J = 7.7 Hz, 1H), 4.52 – 4.29 (m, 1H), 3.96 – 3.73 (m, 4H), 3.54 – 3.30 (m, 1H), 3.08 (s, 2H), 1.43 (s, 9H).^{13}C NMR (101 MHz, Chloroform-d) δ 172.21, 172.14, 166.81, 166.76, 155.71, 136.17, 136.08, 129.33, 129.27, 128.84, 128.76, 127.18, 127.14, 80.87, 75.28, 75.23, 55.60, 54.09, 37.62, 29.70, 28.19. HRMS (ESI) cald. For (M+Na)+ $C_{18}H_{24}N_8O_5$: 455.1761, found, 455.1768.



**Methyl (S)-2,3-diazido-2-((R)-3-(tert-butoxy)-2-((tert-

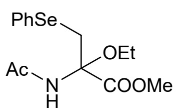
butoxycarbonyl)amino)propanamido)propanoate (3bg):

Yellow oil (Yield: 38%, 32.56 mg).^{1}H NMR (400 MHz, Chloroform-d) δ8.22 (s, 1H), 5.43 (s, 1H), 4.27 (s, 1H), 4.07 – 3.94 (m, 1H), 3.93 – 3.85 (m, 3H), 3.81 (s, 1H), 3.54 (t, J = 12.6 Hz, 1H), 3.40 (t, J = 7.9 Hz, 1H), 1.46 (s, 9H), 1.31 – 1.20 (m, 9H).^{13}C NMR (101 MHz, Chloroform-d) δ 171.51, 166.89, 166.83, 155.31, 80.16, 75.43, 75.31, 74.60, 74.52, 61.58, 61.43, 54.14, 53.94, 53.62, 28.23, 27.27, 27.21.HRMS (ESI) cald. For (M+Na)+ $C_{16}H_{28}N_8O_6$: 451.2024, found, 451.2023.



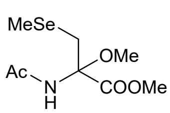
Methyl 2-acetamido-2-methoxy-3-(phenylselanyl)propanoate (3ca):

White solid (Yield: 92 %, 60.72 mg).^{1}H NMR (400 MHz, Chloroform-d) δ 7.50 (dd, J = 6.5, 3.1 Hz, 2H), 7.28 – 7.16 (m, 3H), 6.73 (s, 1H), 4.19 (d, J = 12.9 Hz, 1H), 3.58 (s, 3H), 3.26 (d, J = 13.0 Hz, 1H), 3.17 (s, 3H), 1.76 (s, 3H).^{13}C NMR (101 MHz, Chloroform-d) δ 169.69, 169.46, 133.89, 129.13, 128.62, 127.63, 88.26, 53.07, 52.24, 31.69, 23.58. HRMS (ESI) cald. For (M+Na)+ $C_{13}H_{17}NO_4Se$: 348.0274, found, 348.0277.



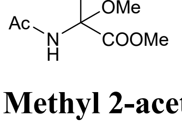
Methyl 2-acetamido-2-ethoxy-3-(phenylselanyl)propanoate (3cb):

White solid (Yield: 70 %, 48.20 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.52 (dd, J = 6.5, 3.0 Hz, 2H), 7.30 – 7.16 (m, 3H), 6.75 (s, 1H), 4.24 (d, J = 13.0 Hz, 1H), 3.59 (s, 3H), 3.52 – 3.40 (m, 1H), 3.32 – 3.20 (m, 2H), 1.77 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.78, 169.46, 133.76, 129.06, 128.82, 127.50, 87.62, 60.46, 52.93, 32.17, 23.60, 15.04. HRMS (ESI) cald. For (M+Na)+ $C_{14}H_{19}NO_4Se$: 362.0431, found, 362.0437.



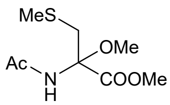
Methyl 2-acetamido-2-methoxy-3-(methylselanyl)propanoate (3cc):

White solid (Yield: 58 %, 31.11 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.88 (s, 1H), 3.79 (s, 3H), 3.62 (d, J = 13.0 Hz, 1H), 3.24 (s, 3H), 2.92 (d, J = 12.9 Hz, 1H), 2.05 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.77, 169.63, 87.46, 53.18, 52.35, 30.56, 23.77, 5.78. HRMS (ESI) cald. For (M+Na)+ $C_8H_{15}NO_4Se$: 286.0118, found, 286.0114.



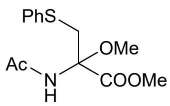
Methyl 2-acetamido-3-(benzylselanyl)-2-methoxypropanoate (3cd):

White solid (Yield: 51 %, 35.12 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.30 (d, J = 6.2 Hz, 4H), 7.22 (td, J = 6.0, 2.6 Hz, 1H), 6.70 (s, 1H), 3.81 (s, 2H), 3.77 (s, 3H), 3.59 (d, J = 12.8 Hz, 1H), 3.30 (s, 3H), 2.91 (d, J = 12.8 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.74, 169.49, 138.95, 129.03, 128.89, 128.67, 128.45, 127.04, 86.58, 53.14, 52.52, 30.29, 28.49, 23.59. HRMS (ESI) cald. For (M+Na)+ $C_{14}H_{19}NO_4Se$: 362.0431, found, 362.0450.



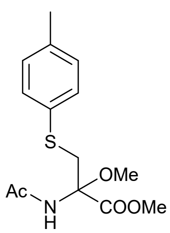
Methyl 2-acetamido-2-methoxy-3-(methylthio)propanoate (3ce):

White solid (Yield: 40 %, 17.69 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.91 (s, 1H), 3.79 (s, 3H), 3.53 (d, J = 14.0 Hz, 1H), 3.24 (s, 3H), 2.93 (d, J = 14.0 Hz, 1H), 2.10 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.83, 169.79, 87.54, 53.19, 52.13, 39.35, 23.72, 16.87. HRMS (ESI) cald. For (M+Na)+ $C_8H_{15}NO_4S$: 244.0614, found, 244.0614.



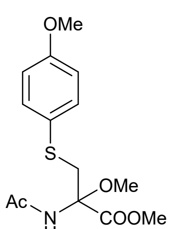
Methyl 2-acetamido-2-methoxy-3-(phenylthio)propanoate (3cf):

White solid (Yield: 45 %, 25.50 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.33 (m, 2H), 7.28 – 7.12 (m, 3H), 6.66 (s, 1H), 4.26 (d, J = 14.1 Hz, 1H), 3.63 (s, 3H), 3.29 (d, J = 14.1 Hz, 1H), 3.13 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.73, 169.61, 134.35, 131.64, 128.98, 127.19, 88.53, 53.19, 51.93, 37.87, 23.59. HRMS (ESI) cald. For (M+Na)+ $C_{13}H_{17}NO_4S$: 306.0770, found, 306.0778.



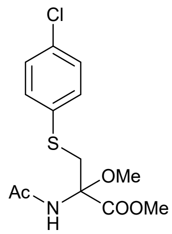
Methyl 2-acetamido-2-methoxy-3-(p-tolylthio)propanoate (3cg):

White solid (Yield: 50 %, 29.74 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.30 (d, J = 7.9 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 6.70 (s, 1H), 4.24 (d, J = 14.1 Hz, 1H), 3.68 (s, 3H), 3.28 (d, J = 14.1 Hz, 1H), 3.17 (s, 3H), 2.30 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.69, 169.64, 137.33, 132.09, 130.69, 129.70, 88.53, 53.15, 51.89, 38.36, 23.54, 21.02. HRMS (ESI) cald. For (M+Na)+ $C_{14}H_{19}NO_4S$: 320.0927, found, 320.0921.



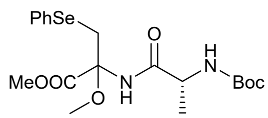
Methyl 2-acetamido-2-methoxy-3-((4-methoxyphenyl)thio)propanoate (3ch):

White solid (Yield: 56 %, 35.10 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.33 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.71 (s, 1H), 4.17 (d, J = 14.1 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.19 (d, J = 14.1 Hz, 1H), 3.13 (s, 3H), 1.74 (s, 3H).^{13}C NMR (101 MHz, Chloroform-d) δ 169.68, 169.66, 159.40, 134.45, 124.68, 114.54, 88.55, 55.37, 53.18, 51.82, 38.97, 23.62. HRMS (ESI) cald. For (M+Na)+ $C_{14}H_{19}NO_5S$: 336.0876, found, 336.0873.



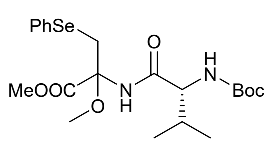
Methyl 2-acetamido-3-((4-chlorophenyl)thio)-2-methoxypropanoate (3ci):

White solid (Yield: 40 %, 25.42 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.38 – 7.34 (m, 2H), 7.31 – 7.24 (m, 2H), 6.72 (s, 1H), 4.32 (d, J = 14.1 Hz, 1H), 3.73 (s, 3H), 3.33 (d, J = 14.1 Hz, 1H), 3.19 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.70, 169.52, 133.30, 132.93, 132.90, 129.03, 88.48, 53.28, 51.94, 37.96, 23.62. HRMS (ESI) cald. For (M+Na)+ $C_{14}H_{16}NO_4SCl$: 352.0380, found, 352.0389.



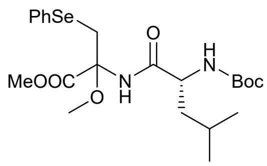
Methyl 2-((R)-2-((tert-butoxycarbonyl)amino)propanamido)-2-methoxy-3-(phenylselanyl)propanoate (3cj):

Yellow oil (Yield: 76 %, 69.83 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 – 7.45 (m, 3H), 7.28 – 7.20 (m, 3H), 4.92 (dd, J = 69.1, 7.3 Hz, 1H), 4.18 (dd, J = 24.8, 12.9 Hz, 1H), 3.57 (d, J = 13.6 Hz, 3H), 3.34 (t, J = 12.7 Hz, 1H), 3.20 (d, J = 4.8 Hz, 3H), 1.46 (d, J = 8.4 Hz, 9H), 1.24 (dd, J = 7.3, 2.0 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.31, 172.12, 169.14, 169.04, 155.44, 133.71, 133.67, 129.05, 128.93, 128.87, 127.53, 88.12, 87.76, 80.21, 52.98, 52.92, 52.26, 52.23, 50.40, 32.42, 31.95, 28.30, 28.28, 17.64, 17.47. HRMS (ESI) cald. For (M+Na)+ $C_{19}H_{28}N_2O_6Se$: 477.1064, found, 477.1062.



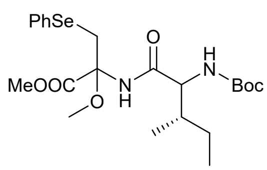
Methyl 2-((R)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-2-methoxy-3-(phenylselanyl)propanoate (3ck):

Yellow oil (Yield: 58 %, 56.55 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 – 7.49 (m, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.31 – 7.25 (m, 3H), 5.02 (t, J = 9.1 Hz, 1H), 4.12 (dd, J = 12.8, 7.5 Hz, 1H), 4.02 – 3.85 (m, 1H), 3.54 (d, J = 14.6 Hz, 3H), 3.39 (dd, J = 12.8, 9.0 Hz, 1H), 3.26 (s, 3H), 2.23 – 2.10 (m, 1H), 1.49 (s, 9H), 1.06 – 0.87 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.44, 171.36, 169.04, 155.84, 133.62, 133.54, 129.16, 129.11, 128.98, 127.65, 127.57, 87.26, 80.11, 60.30, 60.10, 52.85, 52.83, 52.47, 52.41, 33.39, 33.29, 30.35, 30.24, 29.69, 29.35, 28.30, 19.46, 19.37, 17.53. HRMS (ESI) cald. For (M+Na)+ $C_{21}H_{32}N_2O_6Se$: 505.1377, found, 505.1377.



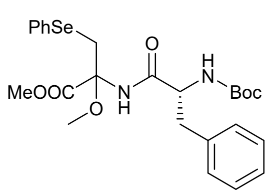
Methyl 2-((R)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-2-methoxy-3-(phenylselanyl)propanoate (3cl):

White solid (Yield: 90 %, 90.27 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.51 (ddt, J = 6.6, 4.5, 2.9 Hz, 2H), 7.42 (s, 1H), 7.27 – 7.20 (m, 3H), 4.72 (dd, J = 42.9, 7.8 Hz, 1H), 4.15 (t, J = 12.5 Hz, 1H), 4.02 (d, J = 9.1 Hz, 1H), 3.54 (d, J = 8.0 Hz, 3H), 3.33 (t, J = 12.9 Hz, 1H), 3.20 (d, J = 4.3 Hz, 3H), 1.73 – 1.52 (m, 2H), 1.44 (d, J = 7.1 Hz, 9H), 1.37 – 1.22 (m, 1H), 0.95 – 0.87 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.28, 172.16, 169.14, 169.07, 155.66, 133.60, 133.57, 129.07, 127.52, 87.73, 87.58, 80.21, 53.47, 52.91, 52.36, 52.31, 40.32, 32.72, 32.50, 28.28, 24.78, 24.69, 23.04, 22.99. HRMS (ESI) cald. For (M+Na)+ $C_{22}H_{34}N_2O_6Se$: 519.1533, found, 519.1533.



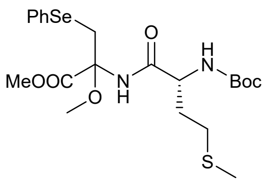
Methyl 2-((3S)-2-((tert-butoxycarbonyl)amino)-3-methylpentanamido)-2-methoxy-3-(phenylselanyl)propanoate (3cm):

White solid (Yield: 63 %, 63.19 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 – 7.44 (m, 2H), 7.36 (s, 1H), 7.23 (ddq, J = 5.9, 4.2, 1.8 Hz, 3H), 5.04 (t, J = 9.0 Hz, 1H), 4.06 (dd, J = 25.0, 12.8 Hz, 1H), 3.98 – 3.82 (m, 1H), 3.49 (d, J = 20.2 Hz, 3H), 3.35 (dd, J = 12.8, 6.3 Hz, 1H), 3.22 (s, 3H), 1.89 – 1.78 (m, 1H), 1.51 (d, J = 3.6 Hz, 1H), 1.44 (s, 9H), 1.11 (ddt, J = 14.0, 9.5, 7.0 Hz, 1H), 0.91 (ddd, J = 16.4, 14.0, 7.1 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.45, 171.38, 168.99, 155.76, 133.63, 133.58, 133.52, 129.17, 129.09, 129.02, 127.62, 127.55, 87.15, 87.11, 80.03, 59.68, 59.52, 52.79, 52.43, 52.34, 36.82, 36.70, 33.39, 28.29, 24.71, 24.62, 15.71, 15.52, 11.49, 11.45. HRMS (ESI) cald. For (M+Na)+ $C_{22}H_{34}N_2O_6Se$: 519.1533, found, 519.1539.



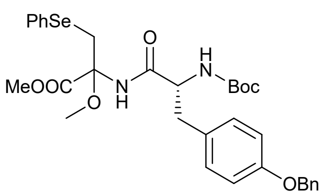
Methyl 2-((R)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-2-methoxy-3-(phenylselanyl)propanoate (3cn):

White solid (Yield: 75 %, 80.33 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.43 (m, 2H), 7.38 (s, 1H), 7.30 – 7.12 (m, 9H), 4.78 (d, J = 7.2 Hz, 1H), 4.22 – 3.99 (m, 2H), 3.50 (d, J = 8.1 Hz, 3H), 3.24 (dd, J = 28.5, 12.9 Hz, 1H), 3.07 (d, J = 32.6 Hz, 3H), 2.94 (d, J = 6.9 Hz, 1H), 1.37 (d, J = 2.0 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.08, 170.88, 168.97, 168.96, 155.39, 136.56, 136.46, 133.66, 133.65, 129.36, 129.27, 129.08, 128.95, 128.74, 127.59, 127.55, 127.02, 127.00, 87.82, 87.44, 80.40, 55.90, 52.91, 52.41, 52.34, 37.64, 37.03, 32.98, 32.48, 29.71, 28.26, 28.24. HRMS (ESI) cald. For (M+Na)+ $C_{25}H_{32}N_2O_6Se$: 553.1377, found, 553.1375.



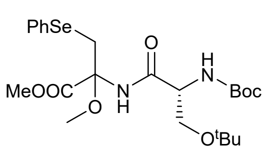
Methyl 2-((R)-2-((tert-butoxycarbonyl)amino)-4-(methylthio)butanamido)-2-methoxy-3-(phenylselanyl)propanoate (3co):

Colorless oil (Yield: 65 %, 67.54 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 – 7.45 (m, 3H), 7.24 (h, J = 2.3 Hz, 3H), 5.04 (dd, J = 56.6, 8.0 Hz, 1H), 4.20 – 4.08 (m, 2H), 3.53 (d, J = 25.8 Hz, 3H), 3.33 (dd, J = 19.1, 12.9 Hz, 1H), 3.19 (s, 3H), 2.55 (tt, J = 14.0, 6.8 Hz, 2H), 2.09 (d, J = 12.0 Hz, 3H), 2.02 – 1.67 (m, 2H), 1.44 (d, J = 9.4 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.31, 171.15, 169.02, 168.96, 155.55, 133.72, 129.09, 128.86, 127.62, 87.90, 87.85, 80.31, 53.86, 52.99, 52.95, 52.39, 52.38, 32.46, 32.40, 30.87, 30.23, 30.21, 28.31, 28.28, 15.36, 15.32. HRMS (ESI) cald. For (M+Na)+ $C_{21}H_{32}N_2O_6SSe$: 537.1098, found, 537.1098.



Methyl 2-((R)-3-(4-(benzyloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanamido)-2-methoxy-3-(phenylselanyl)propanoate (3cp):

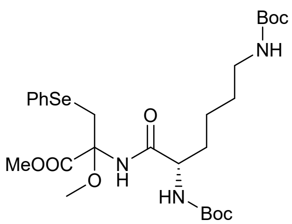
Yellow oil (Yield: 43 %, 55.18 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.49 (dtd, J = 4.8, 4.0, 2.4 Hz, 2H), 7.43 – 7.29 (m, 6H), 7.27 – 7.20 (m, 3H), 7.15 – 7.09 (m, 2H), 6.93 – 6.89 (m, 2H), 5.03 (s, 2H), 4.84 (d, J = 6.4 Hz, 1H), 4.24 – 4.00 (m, 2H), 3.54 (d, J = 9.9 Hz, 3H), 3.29 (dd, J = 18.8, 12.9 Hz, 1H), 3.12 (d, J = 30.1 Hz, 3H), 2.99 – 2.90 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.20, 171.00, 168.99, 157.87, 157.84, 155.42, 136.98, 133.68, 133.64, 130.45, 130.37, 129.10, 128.97, 128.75, 128.61, 128.00, 127.60, 127.56, 127.46, 127.45, 115.12, 115.11, 87.78, 87.34, 80.38, 70.01, 56.02, 52.91, 52.44, 52.35, 36.76, 36.22, 33.13, 32.58, 29.72, 28.29, 28.28. HRMS (ESI) cald. For (M+Na)+ $C_{32}H_{38}N_2O_7Se$: 659.1796, found, 659.1700.



Methyl 2-((R)-3-(tert-butoxy)-2-((tert-butoxycarbonyl)amino)propanamido)-2-methoxy-3-

(phenylselanyl)propanoate (3cq):

Yellow oil (Yield: 40 %, 42.52 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.97 (d, J = 54.0 Hz, 1H), 7.48 (ddd, J = 5.6, 3.7, 2.0 Hz, 2H), 7.24 – 7.19 (m, 3H), 5.34 (t, J = 6.2 Hz, 1H), 4.25 – 4.10 (m, 1H), 3.73 (ddd, J = 17.0, 10.0, 3.7 Hz, 2H), 3.52 (d, J = 35.7 Hz, 3H), 3.37 – 3.23 (m, 2H), 3.17 (d, J = 15.3 Hz, 3H), 1.45 (d, J = 6.4 Hz, 9H), 1.19 (d, J = 3.0 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.50, 170.18, 168.98, 168.96, 155.25, 133.91, 133.48, 129.14, 129.02, 128.95, 128.67, 127.65, 127.45, 88.54, 87.69, 80.05, 79.85, 74.17, 74.11, 61.60, 54.57, 54.43, 52.90, 52.79, 52.36, 52.22, 32.86, 31.56, 28.32, 27.41, 27.39. HRMS (ESI) cald. For (M+Na)+ $C_{23}H_{36}N_2O_7Se$: 519.1533, found, 519.1530.



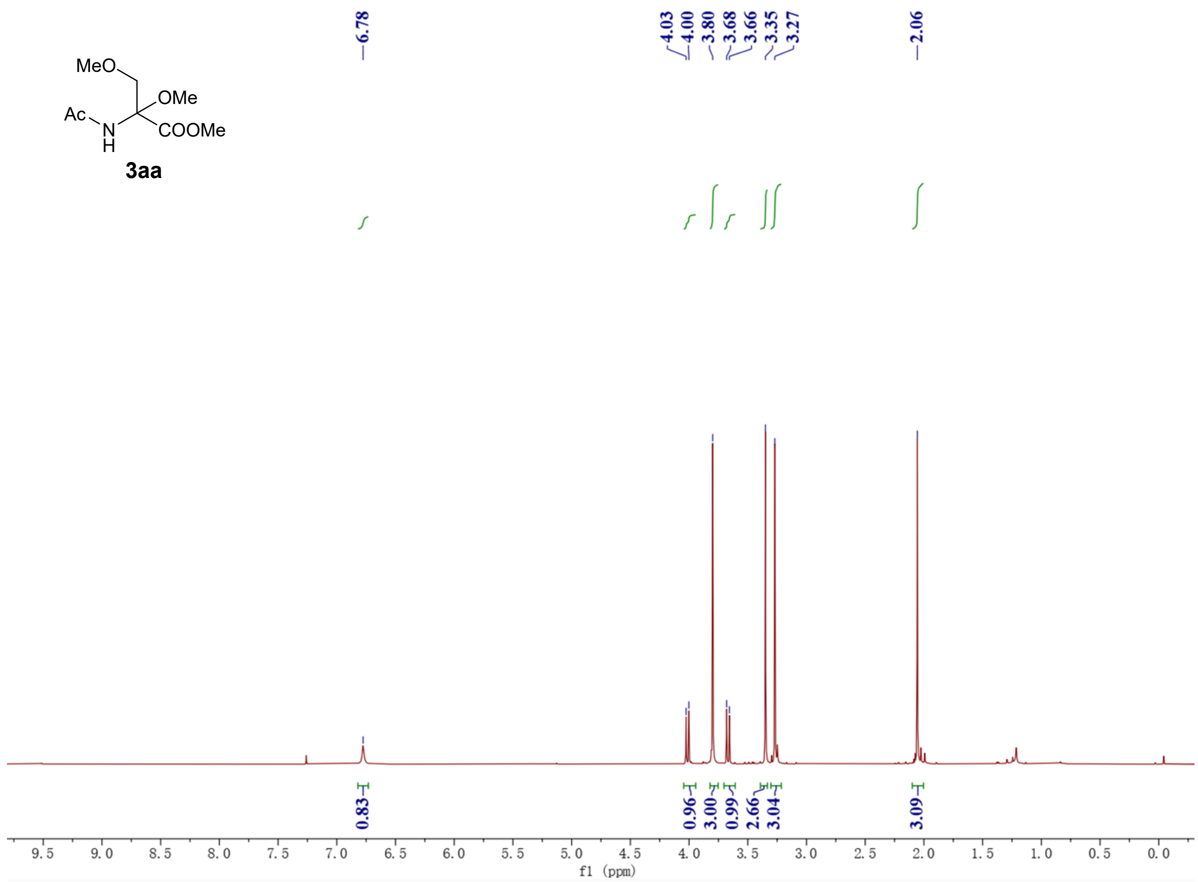
Methyl 2-((S)-2,6-bis((tert-butoxycarbonyl)amino)hexanamido)-2-methoxy-3-(phenylselanyl)propanoate (3cr):

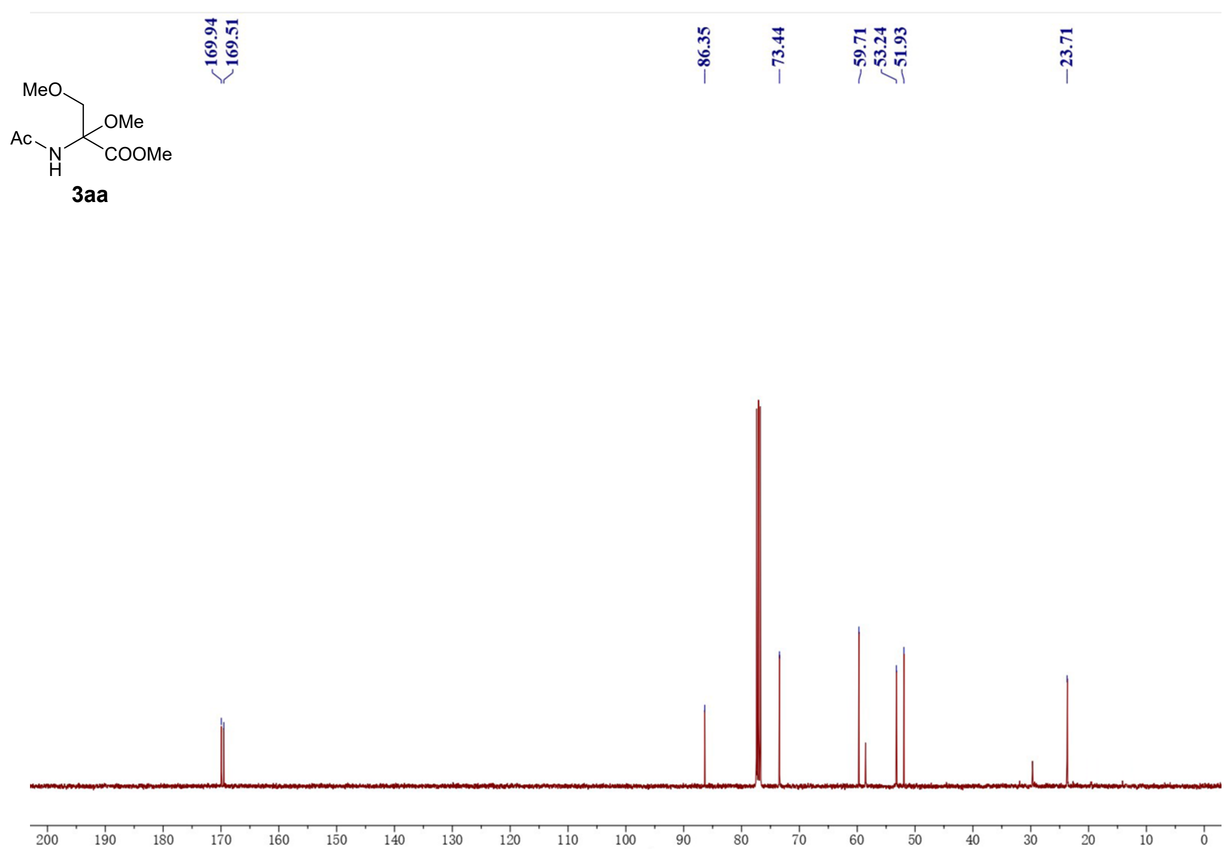
Colorless liquid; (Yield: 40 %, 49.33 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.55 – 7.44 (m, 3H), 7.22 (td, J = 3.6, 1.8 Hz, 3H), 5.09 (dd, J = 25.9, 7.4 Hz, 1H), 4.65 (d, J = 6.0 Hz, 1H), 4.11 (dd, J = 21.7, 12.9 Hz, 1H), 3.93 (qd, J = 8.6, 5.8, 4.3 Hz, 1H), 3.52 (d, J = 10.0 Hz, 3H), 3.32 (dd, J = 12.8, 6.4 Hz, 1H), 3.19 (d, J = 6.1 Hz, 3H), 3.08 (p, J = 6.5 Hz, 2H), 1.42 (dd, J = 7.3, 3.7 Hz, 24H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.90, 171.76, 169.07, 169.03, 156.23, 156.21, 155.79, 133.66, 133.61, 129.08, 129.03, 127.54, 87.78, 87.41, 80.20, 79.14, 54.88, 52.93, 52.90, 52.37, 52.31, 39.80, 32.96, 32.40, 31.06, 29.70, 29.68, 28.44, 28.30, 22.56. HRMS (ESI) cald. For (M+Na)+ $C_{27}H_{32}N_3O_8Se$: 634.2167, found, 634.2169.

[1] R. A. Serwa, J.-M. Swiecicki, D. Homann, C. P. R. Hackenberger, Phosphoramidate-peptide synthesis by solution- and solid-phase Staudinger-phosphite reactions. *J. Pept. Sci.* **2010**, 16, 563–567.
[2] Alam J, Keller T H, Loh T P. Functionalization of peptides and proteins by Mukaiyama aldol reaction. *J. Am. Chem. Soc*. **2010**, 132, 9546-9548.
[3] R. A. Aycock, D. B. Vogt and N. T. Jui, A practical and scalable system for heteroaryl amino acid synthesis.*Chem. Sci.*, **2017**,8, 7998-8003

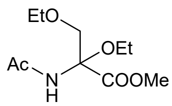
5. NMR spectra of all products

^{1}H and ^{13}C NMR spectra of **3aa**

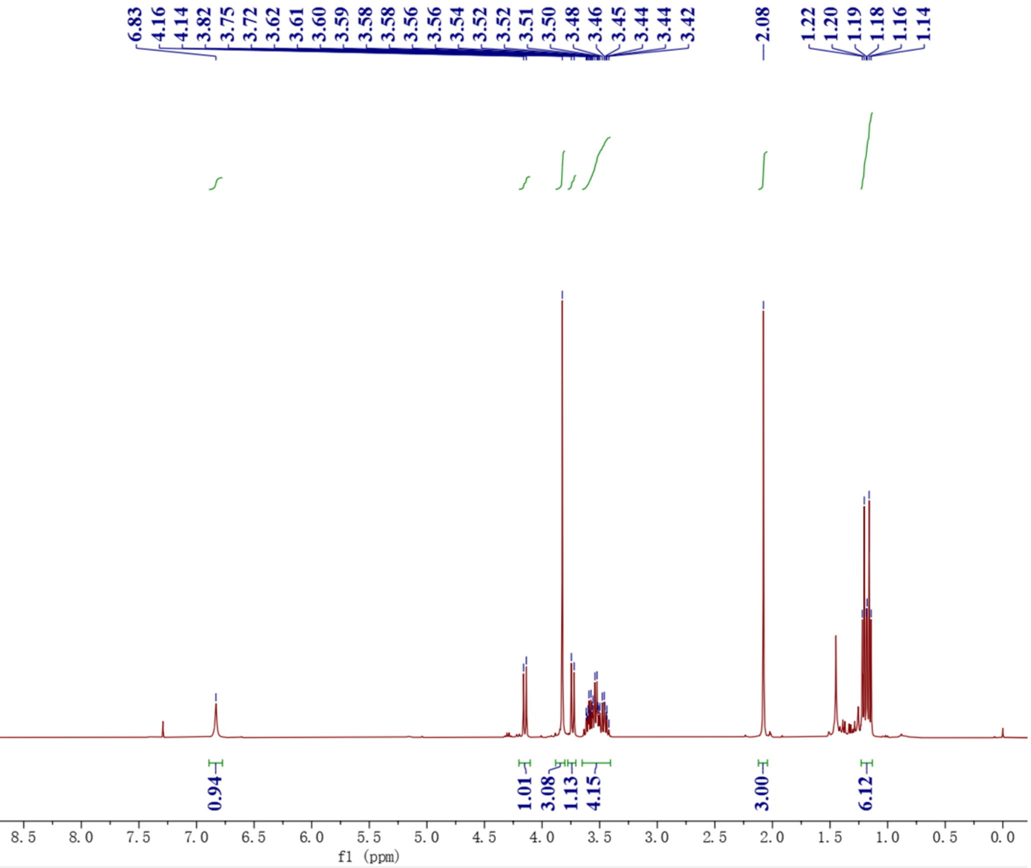


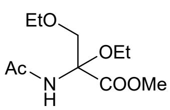


^{1}H and ^{13}C NMR spectra of **3ab**



3ab





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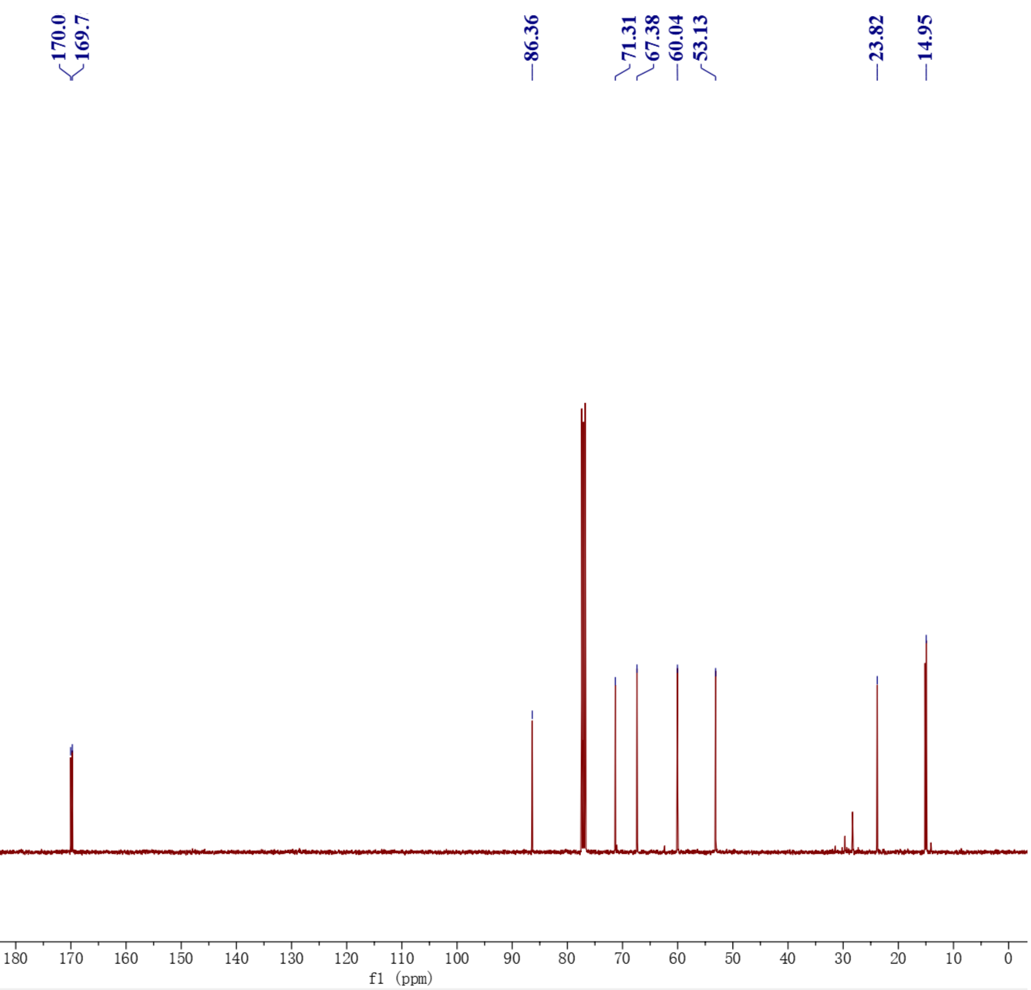
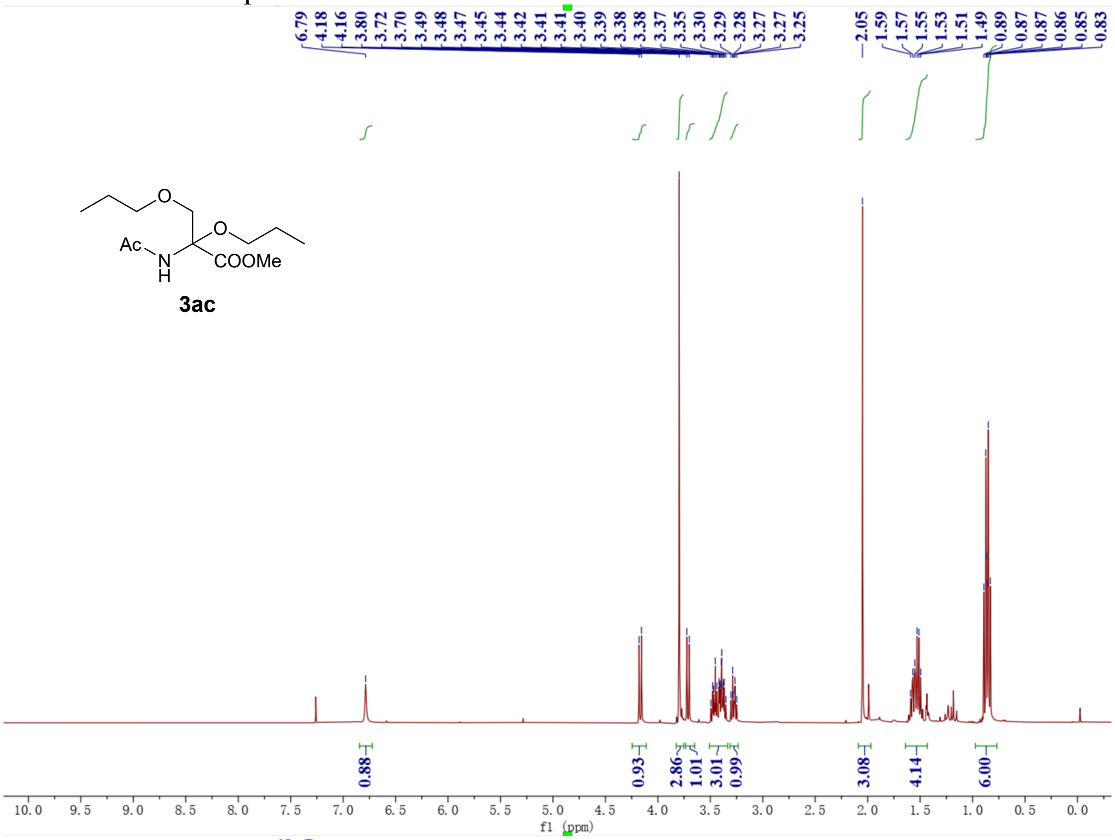
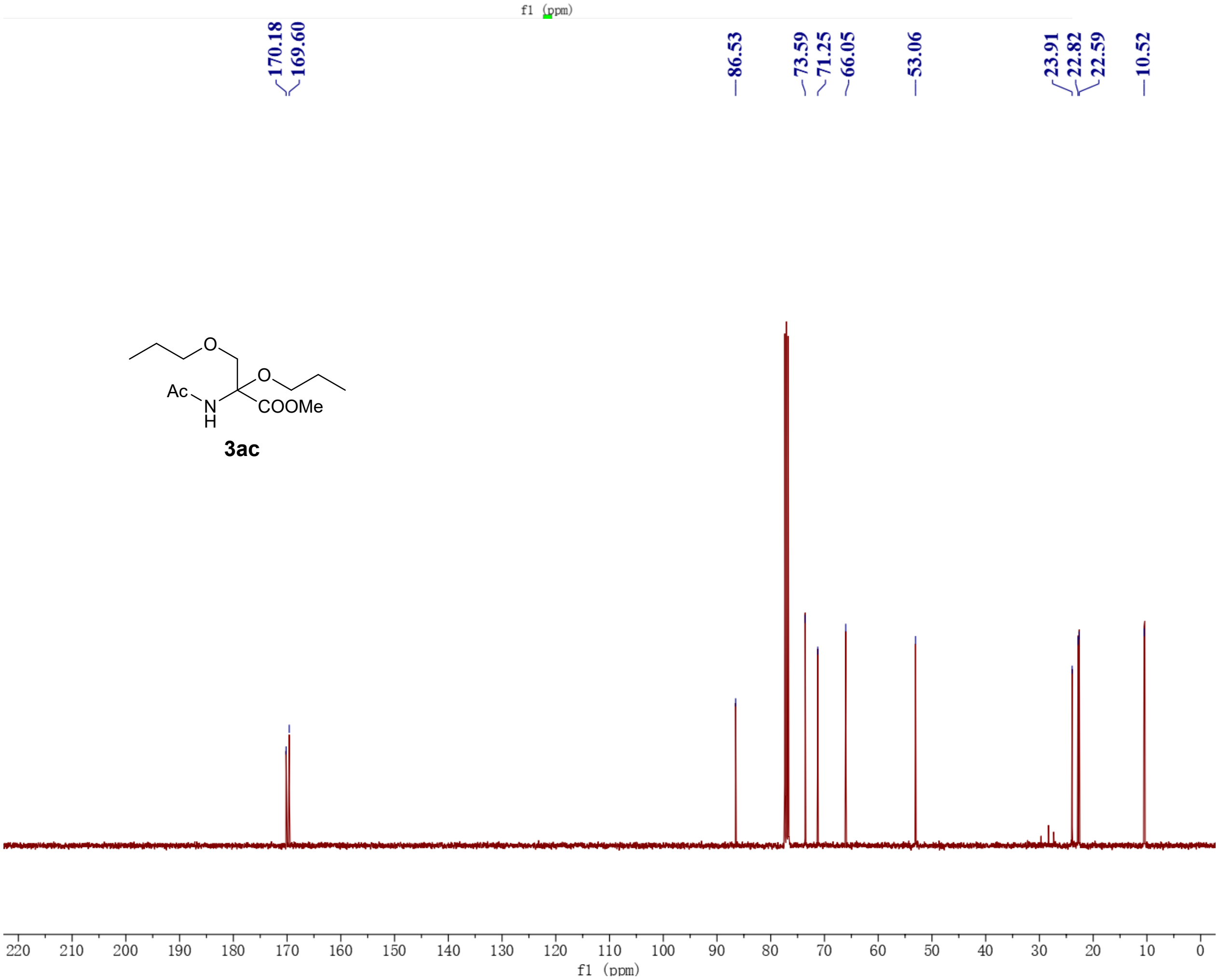
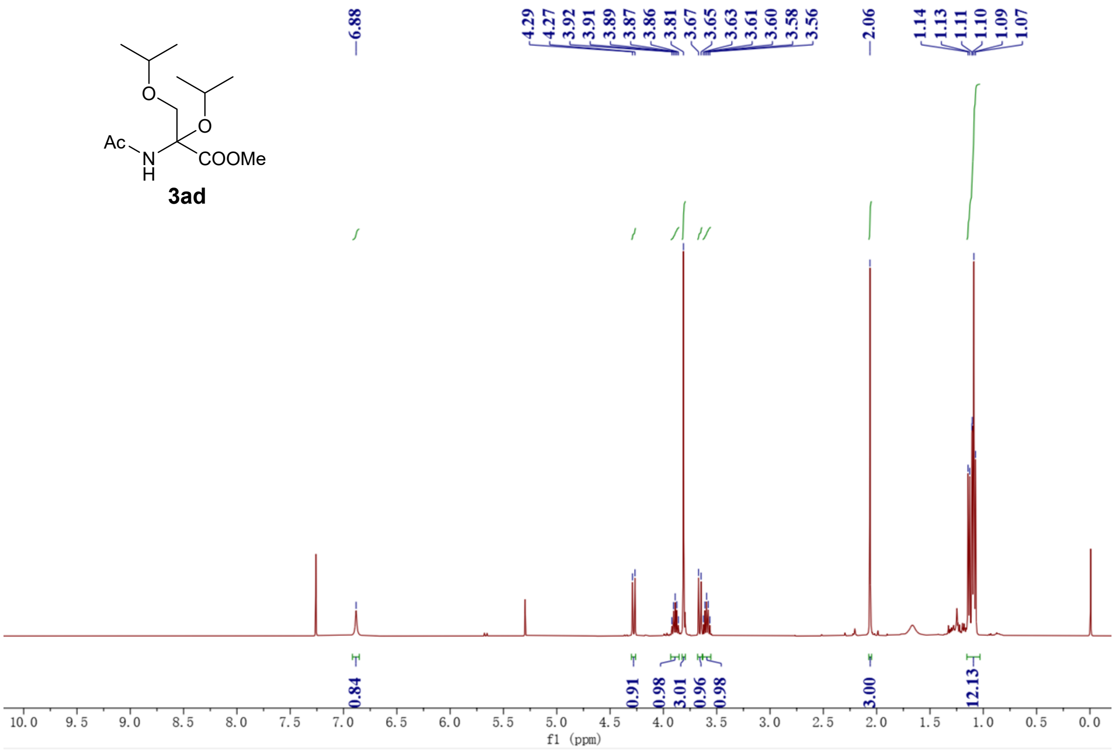


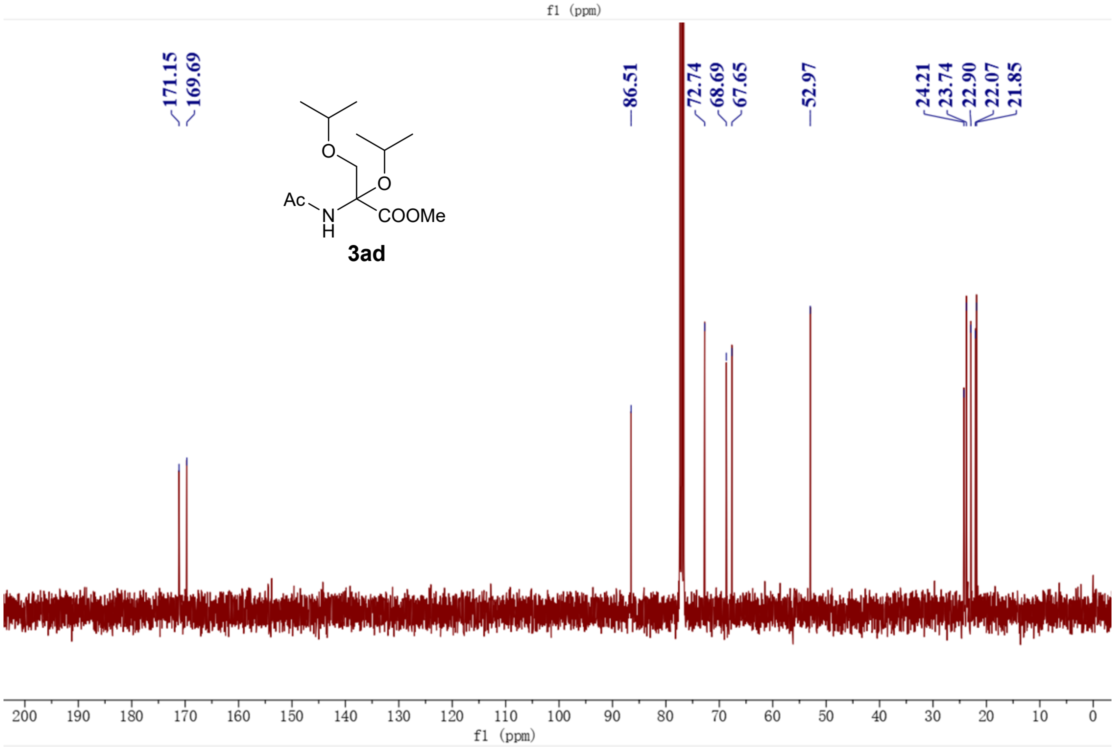
^{1}H and ^{13}C NMR spectra of **3ac**



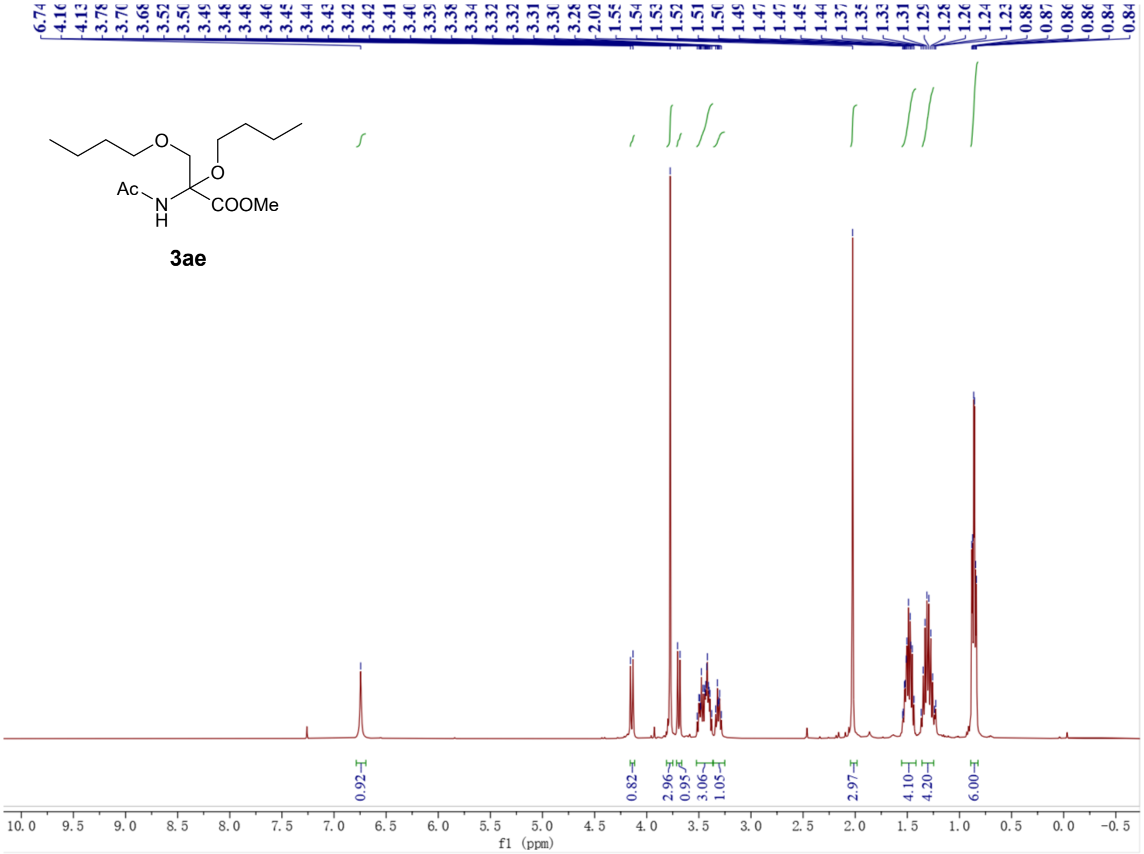


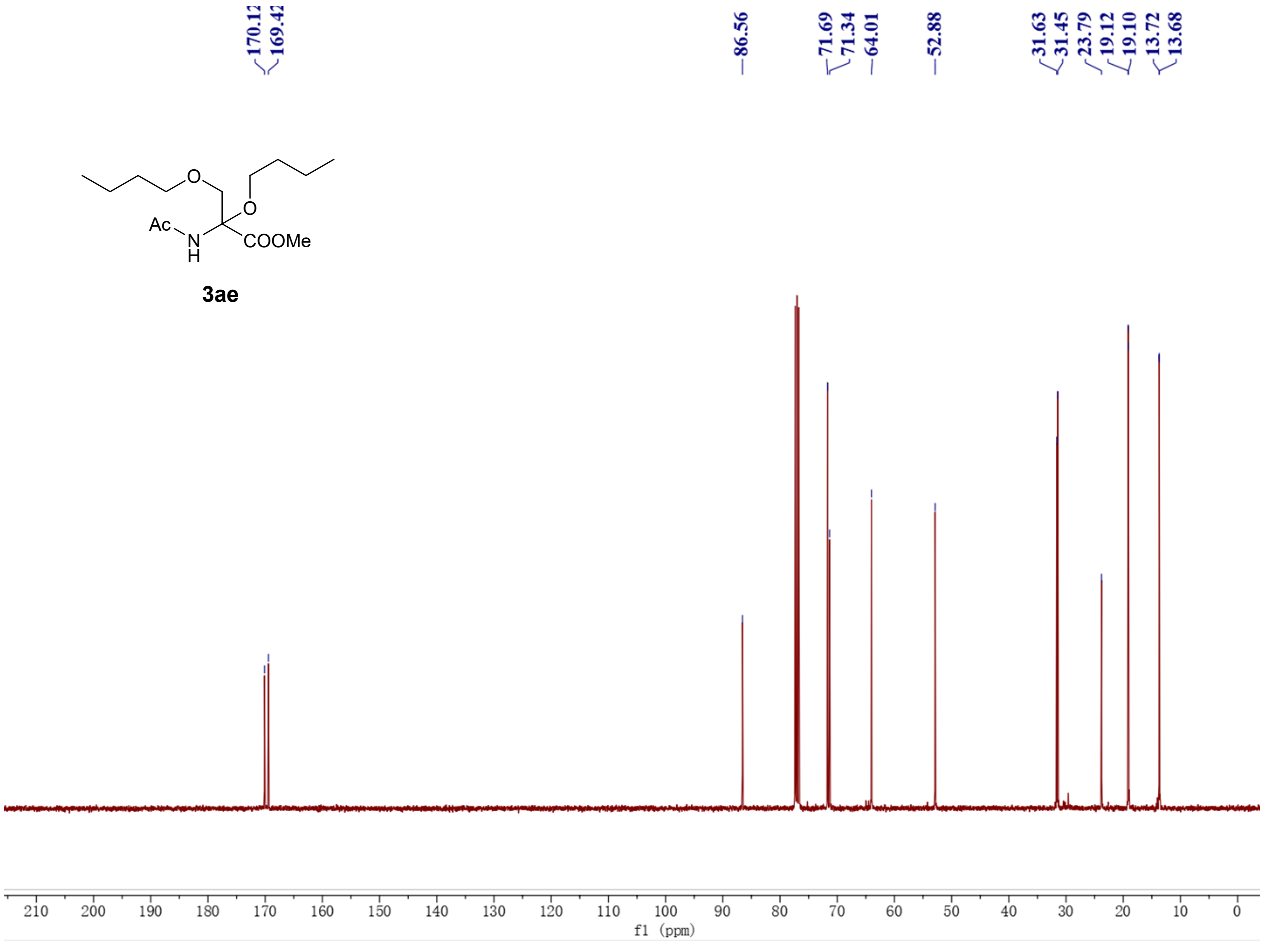
^{1}H and ^{13}C NMR spectra of **3ad**



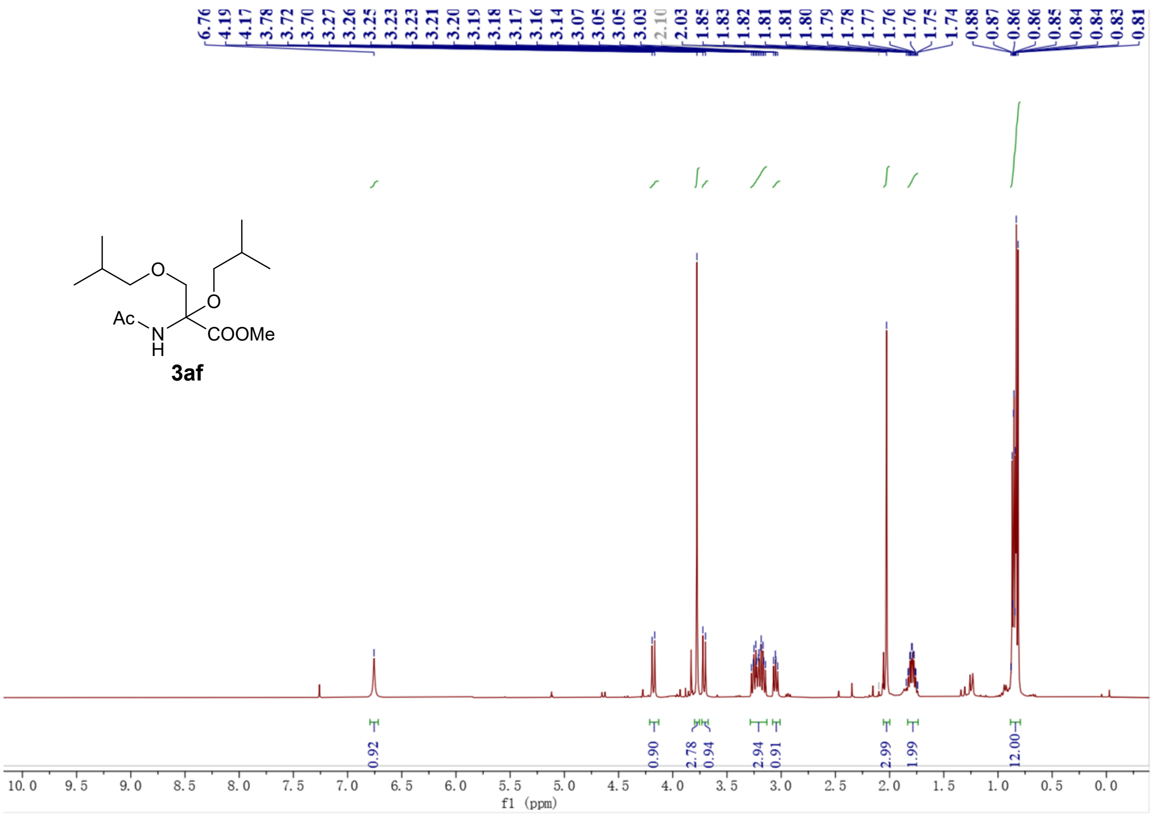


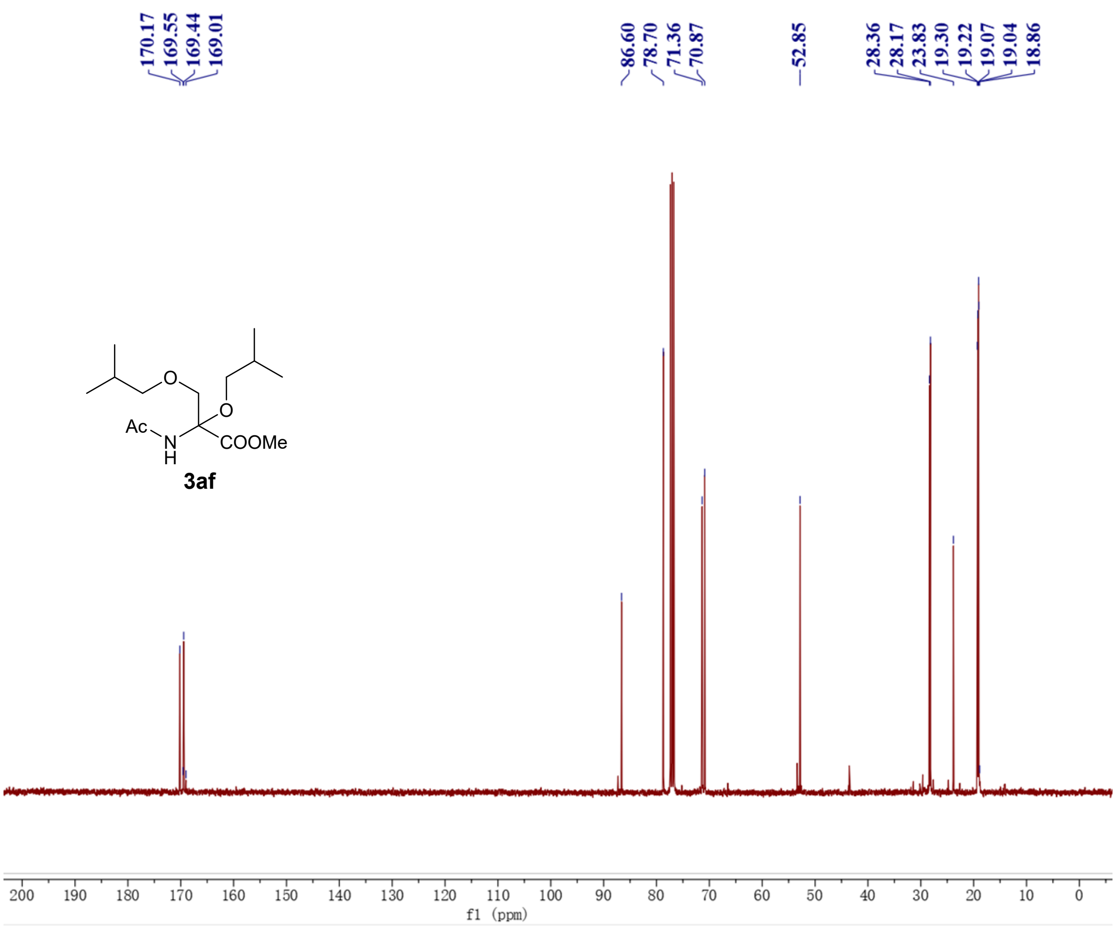
[1]H and [13]C NMR spectra of **3ae**



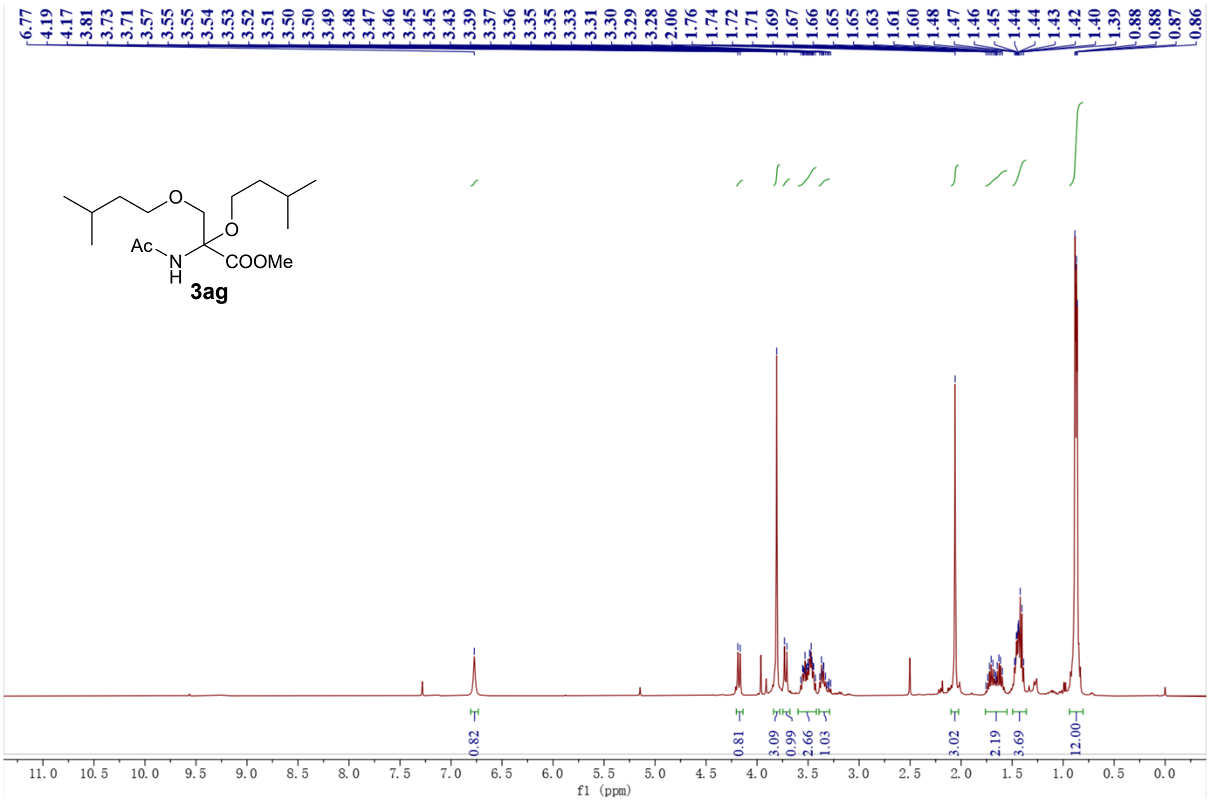


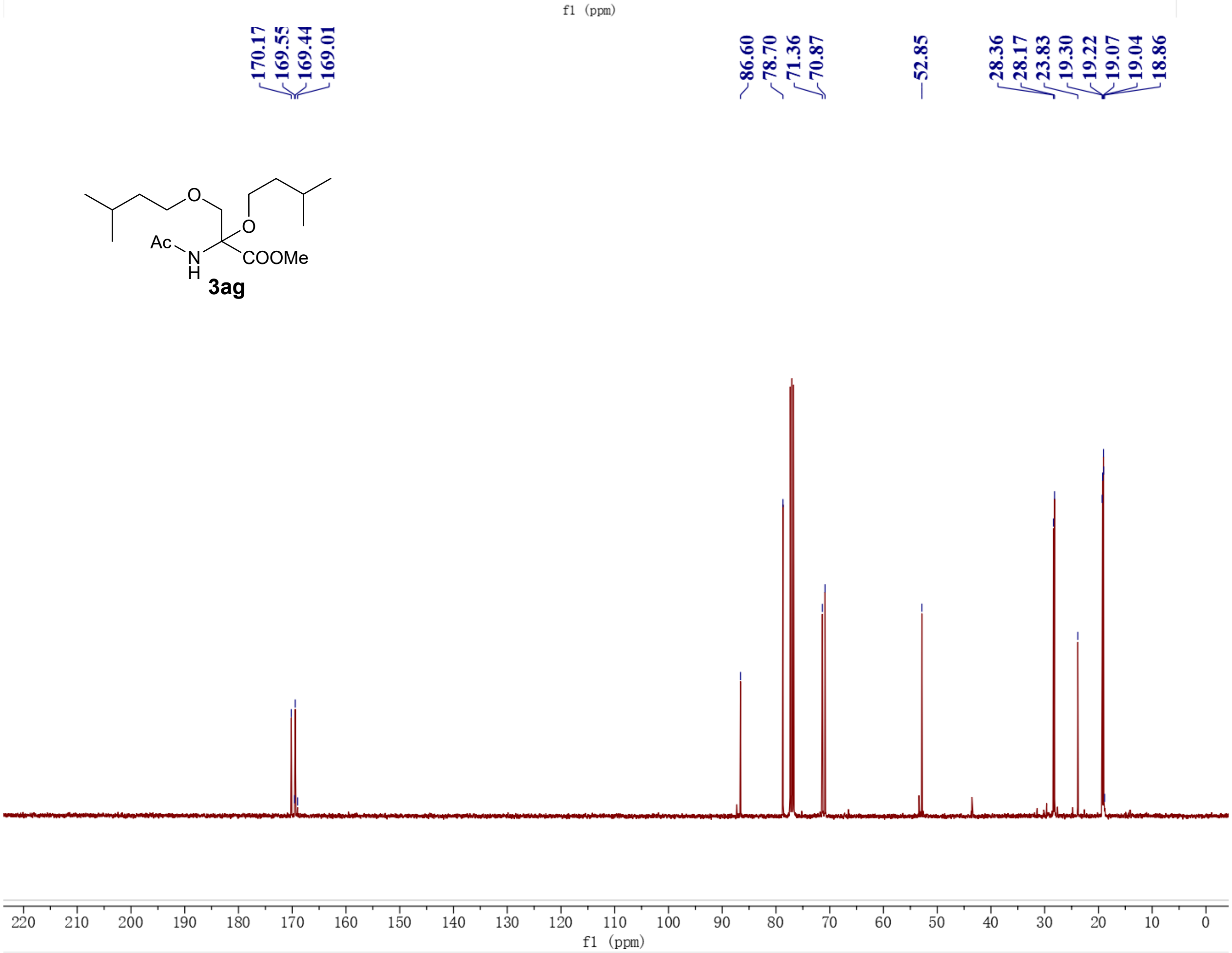
[1]H and [13]C NMR spectra of **3af**



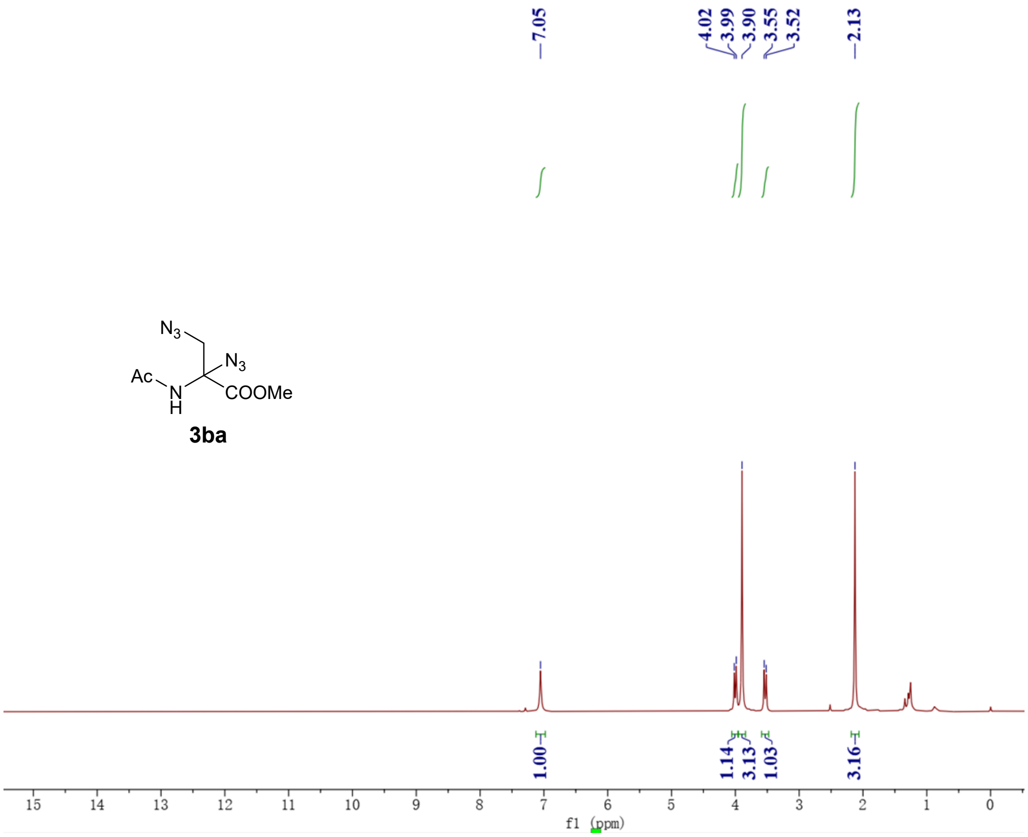


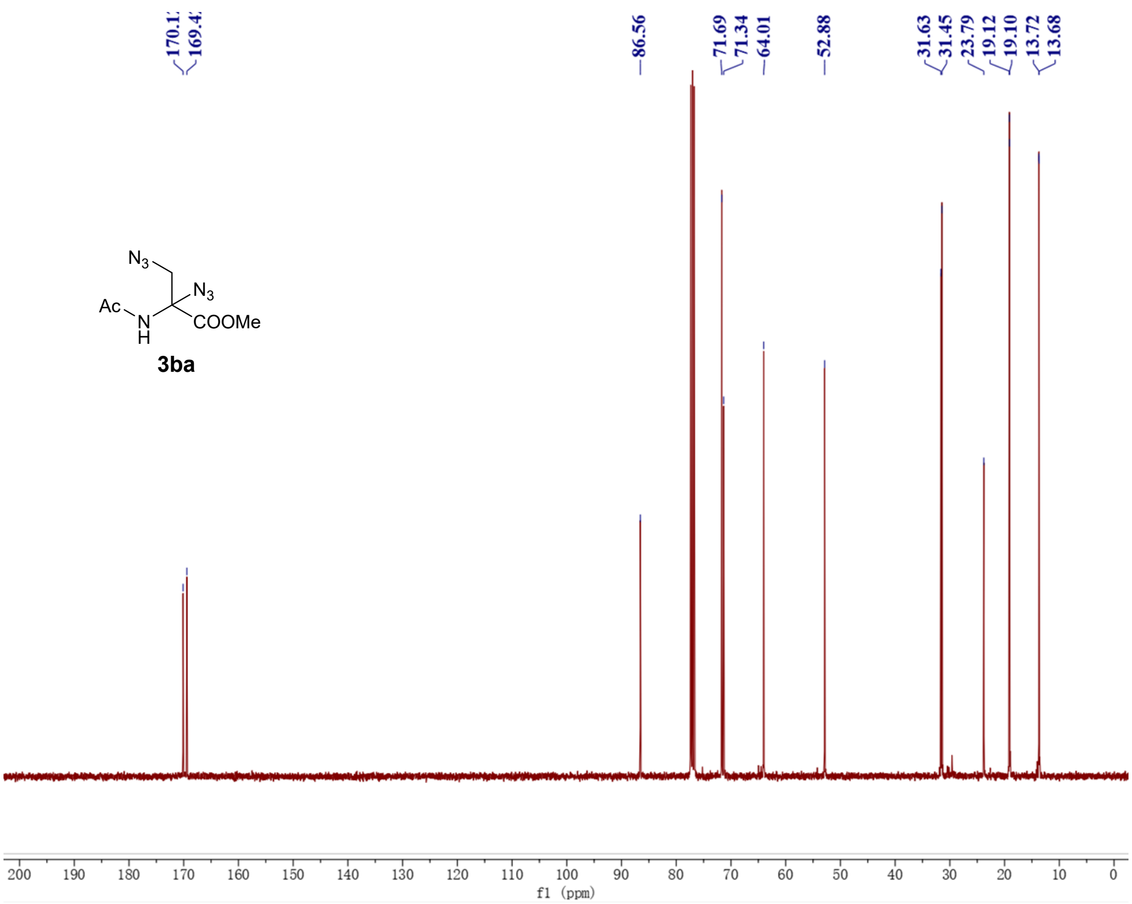
[1]H and [13]C NMR spectra of **3af**



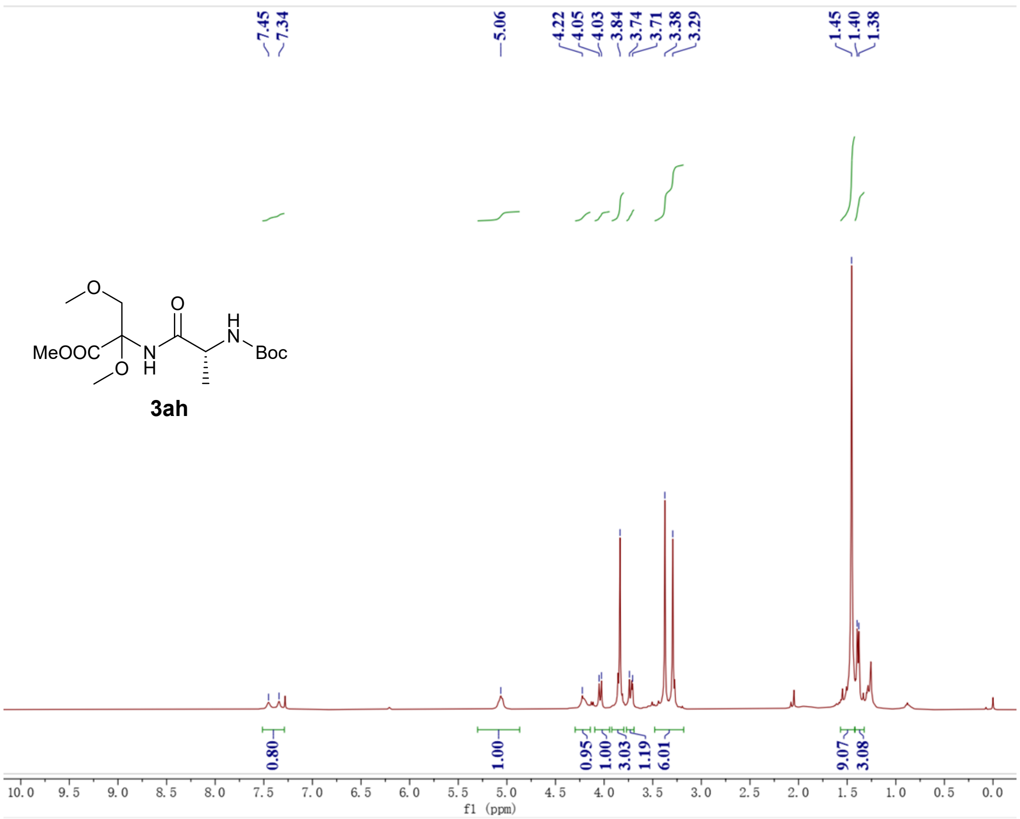


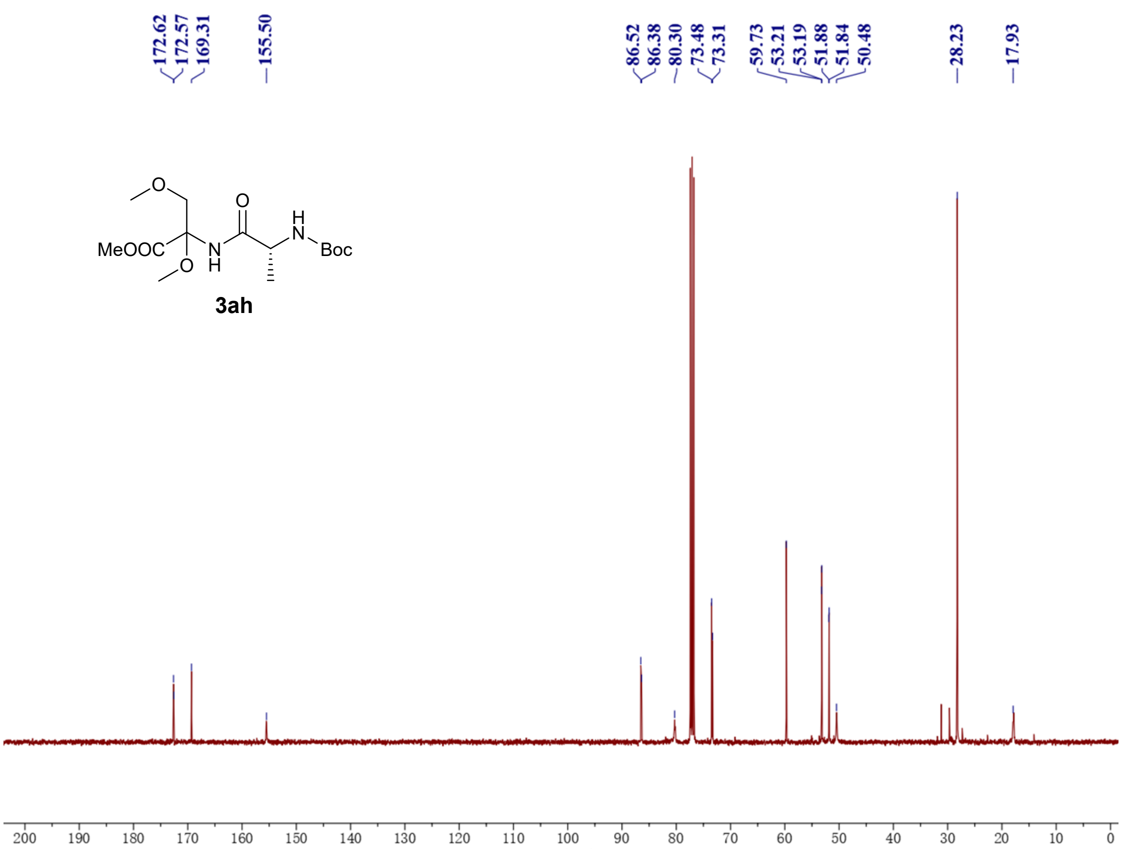
[1]H and [13]C NMR spectra of **3ba**



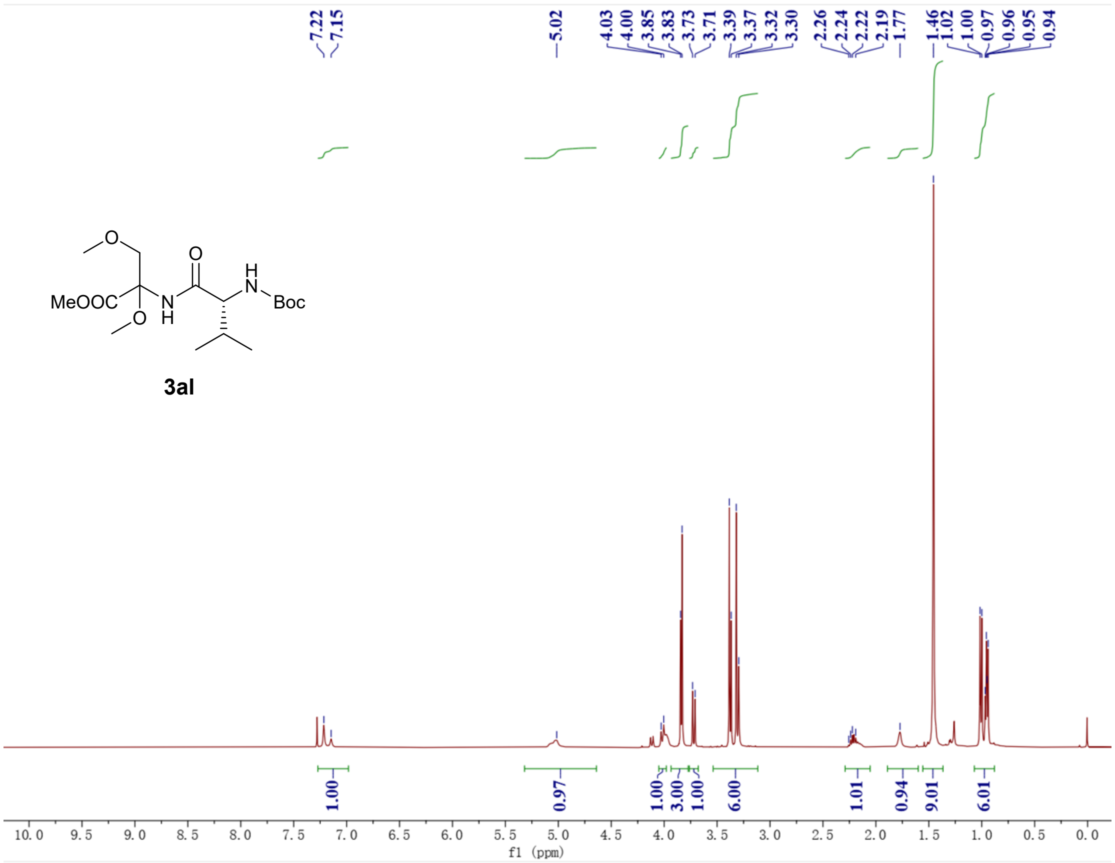


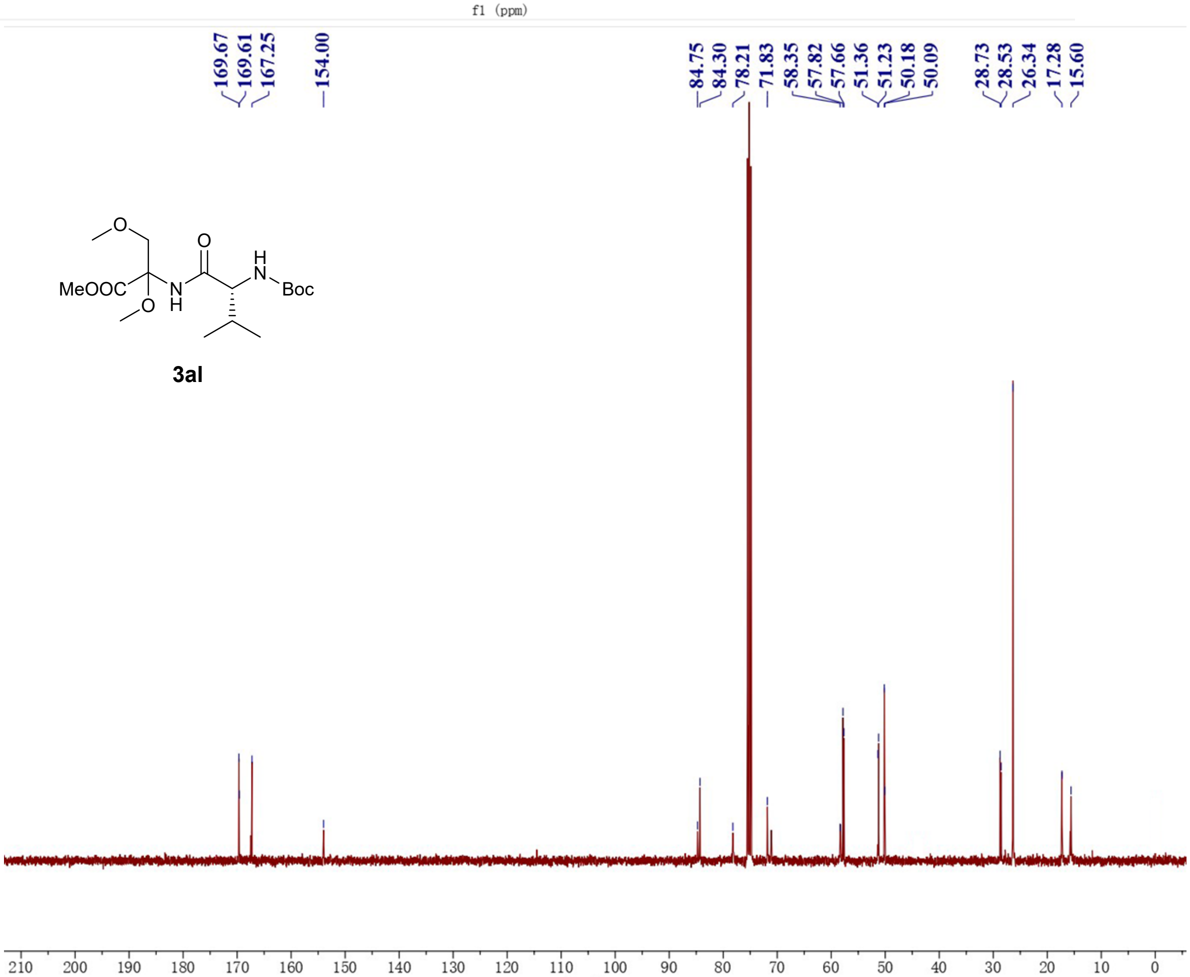
[1]H and [13]C NMR spectra of **3ah**



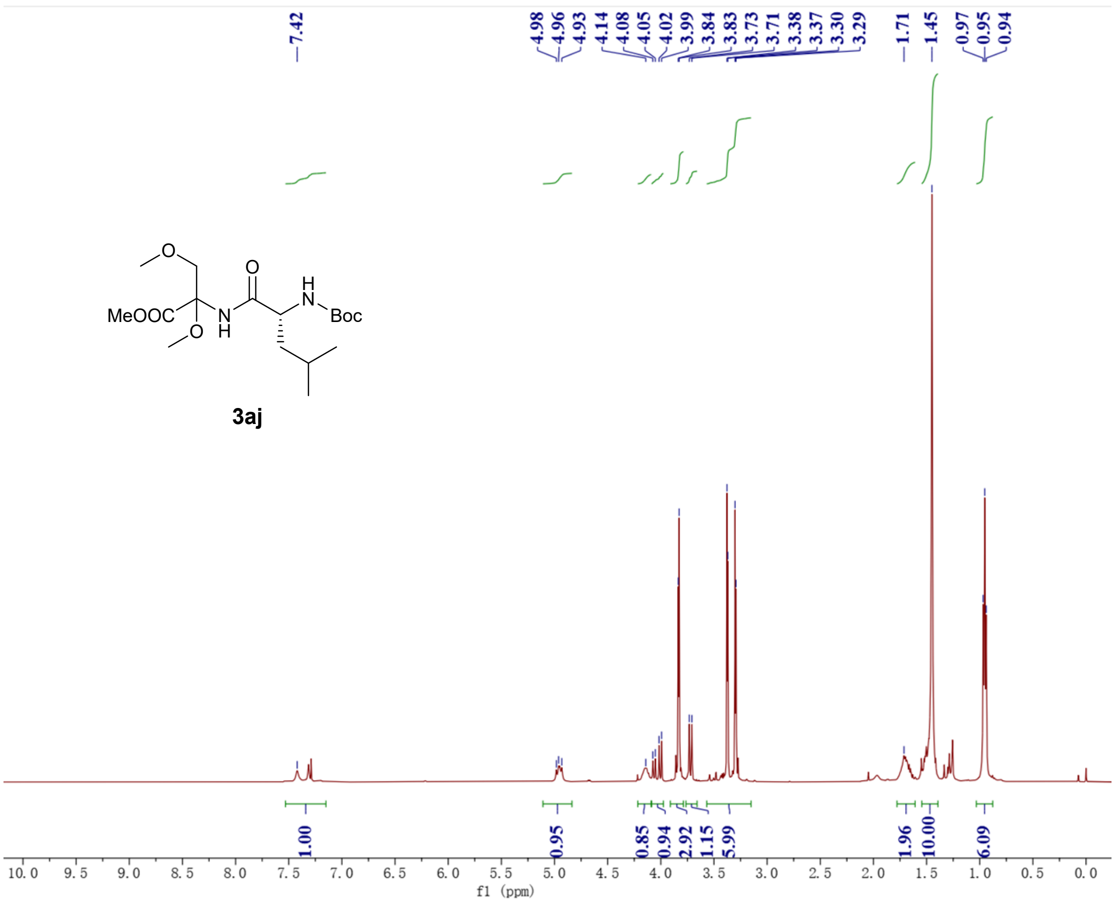


[1]H and [13]C NMR spectra of **3al**

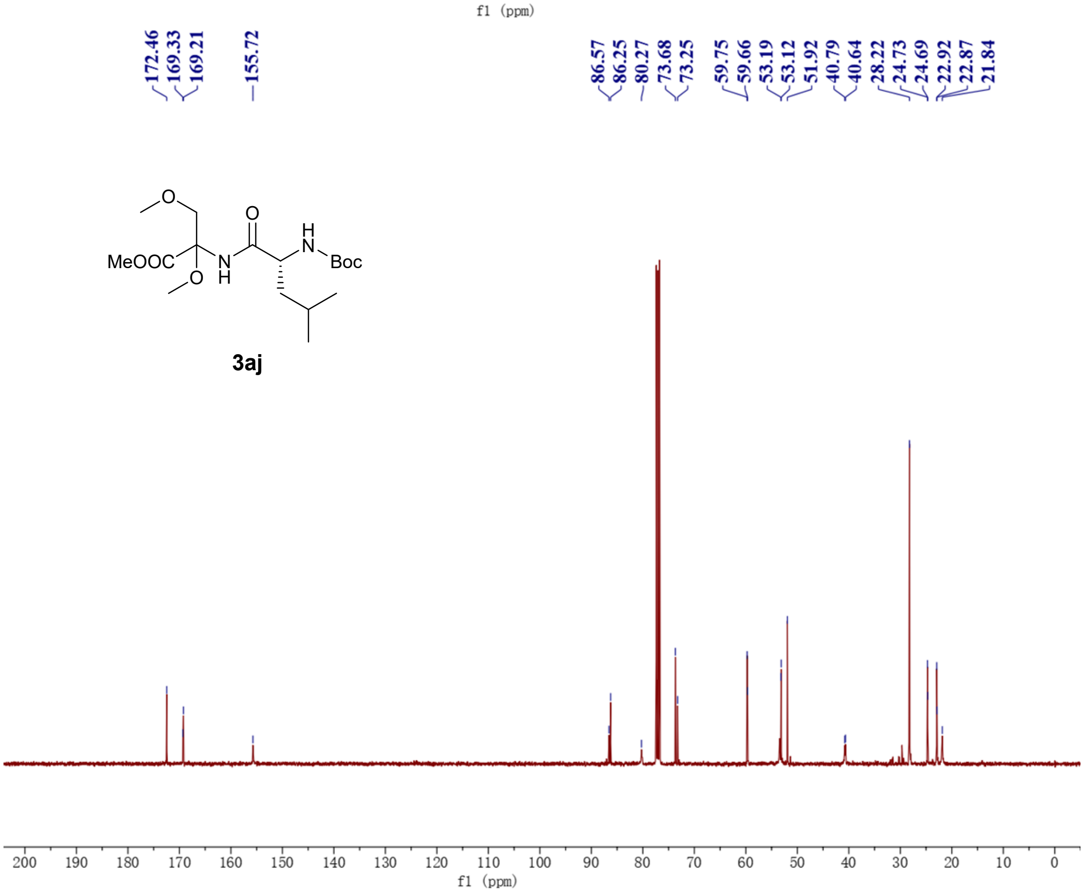




^{1}H and ^{13}C NMR spectra of **3aj**

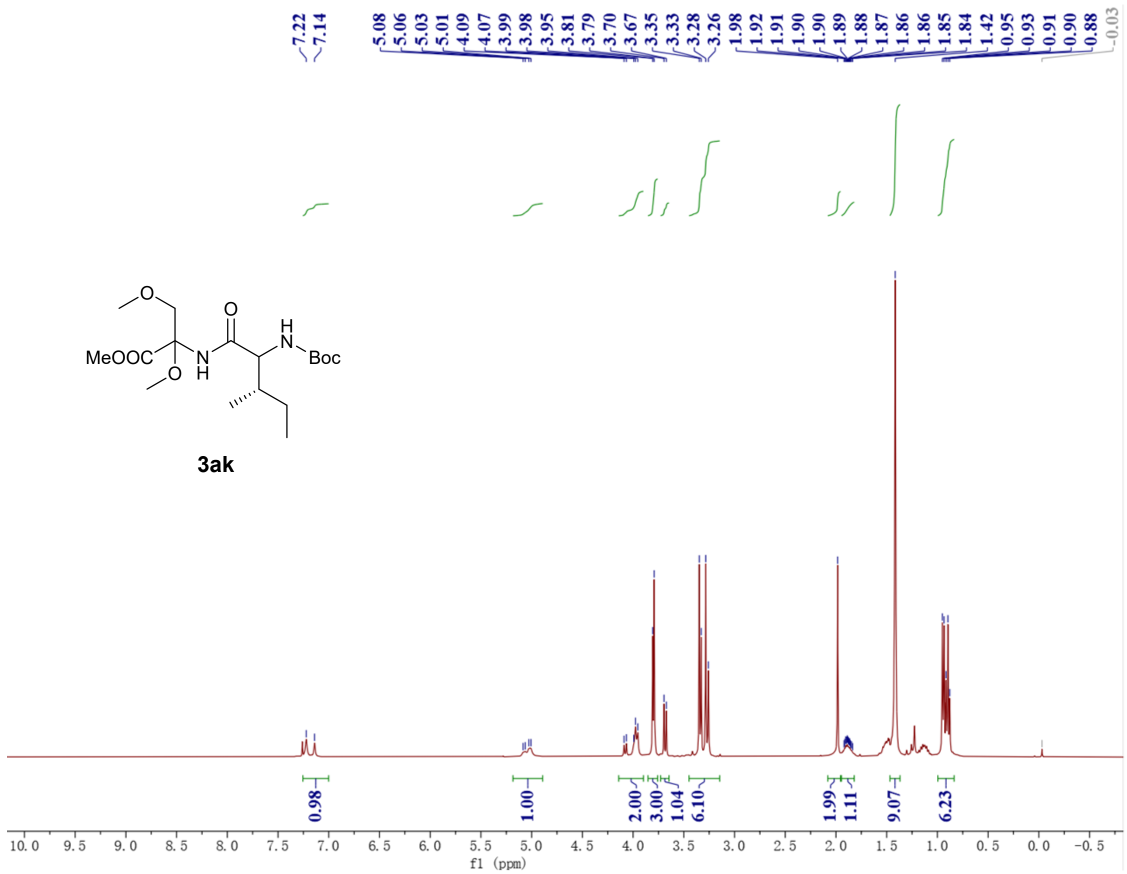


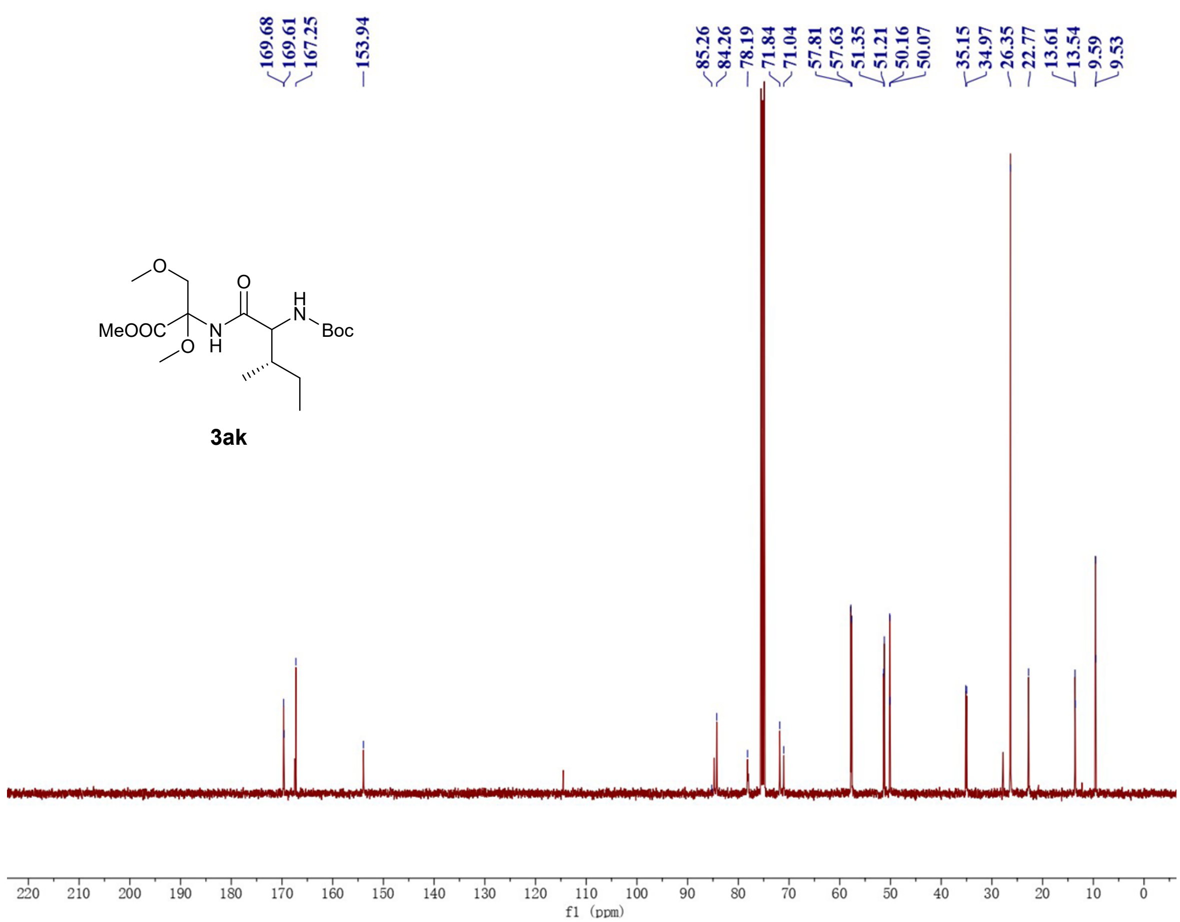
3aj



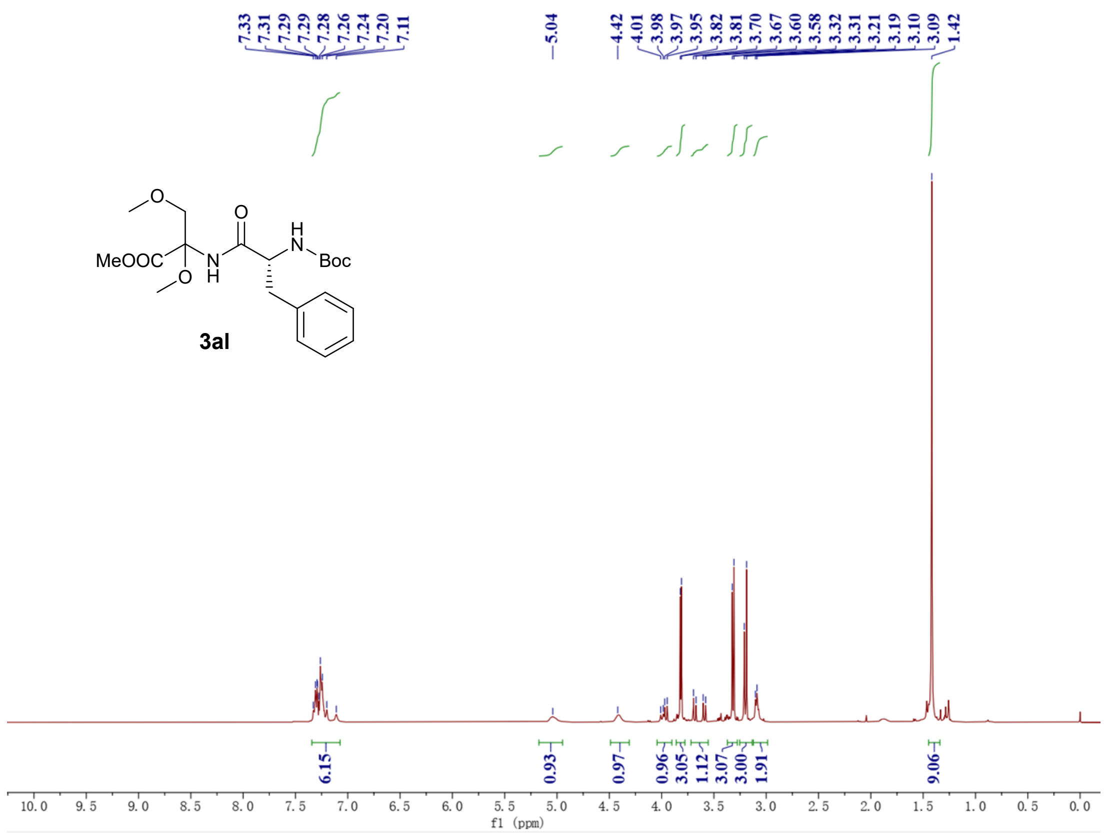
3aj

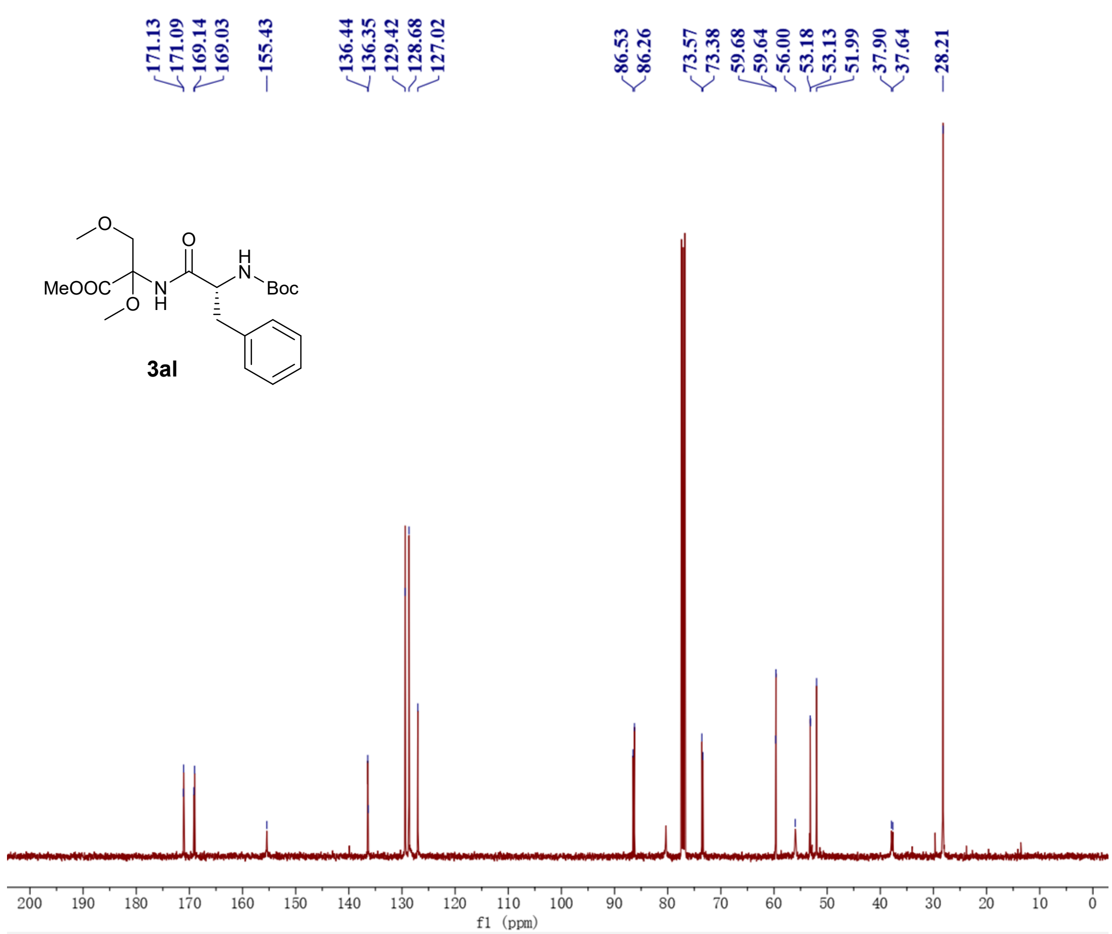
^{1}H and ^{13}C NMR spectra of **3ak**



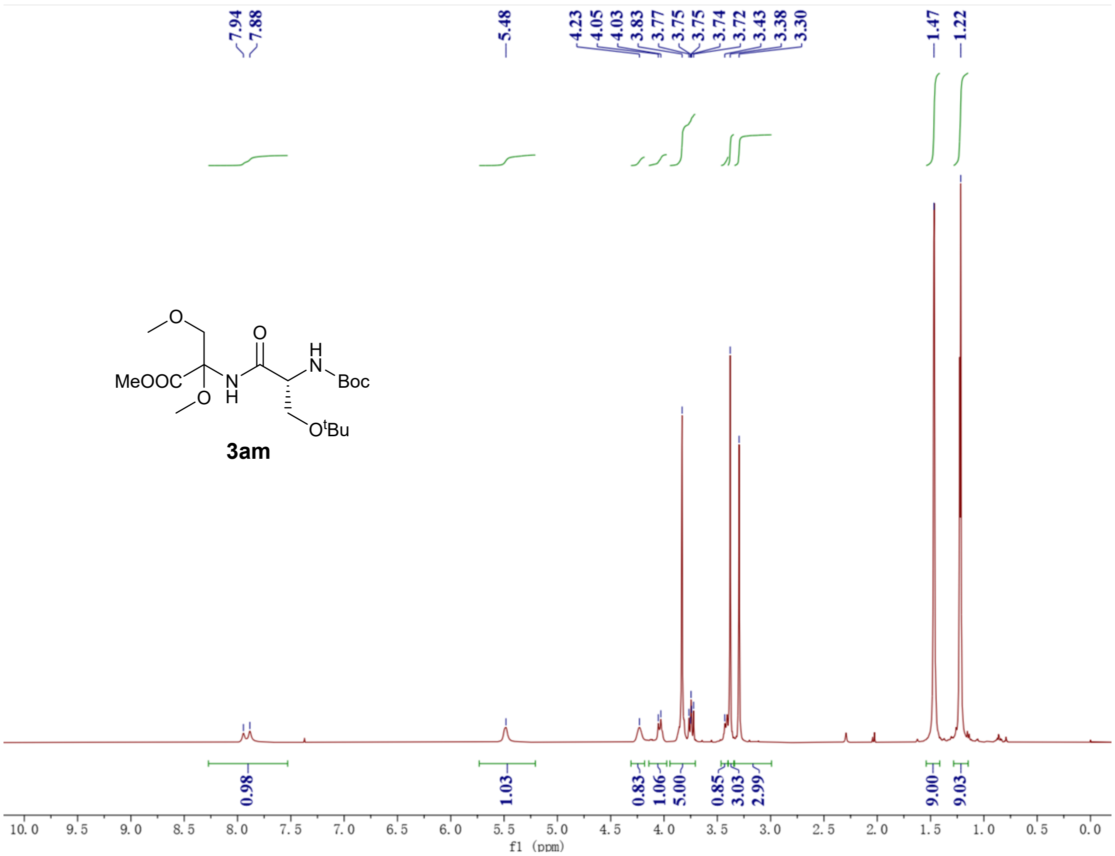


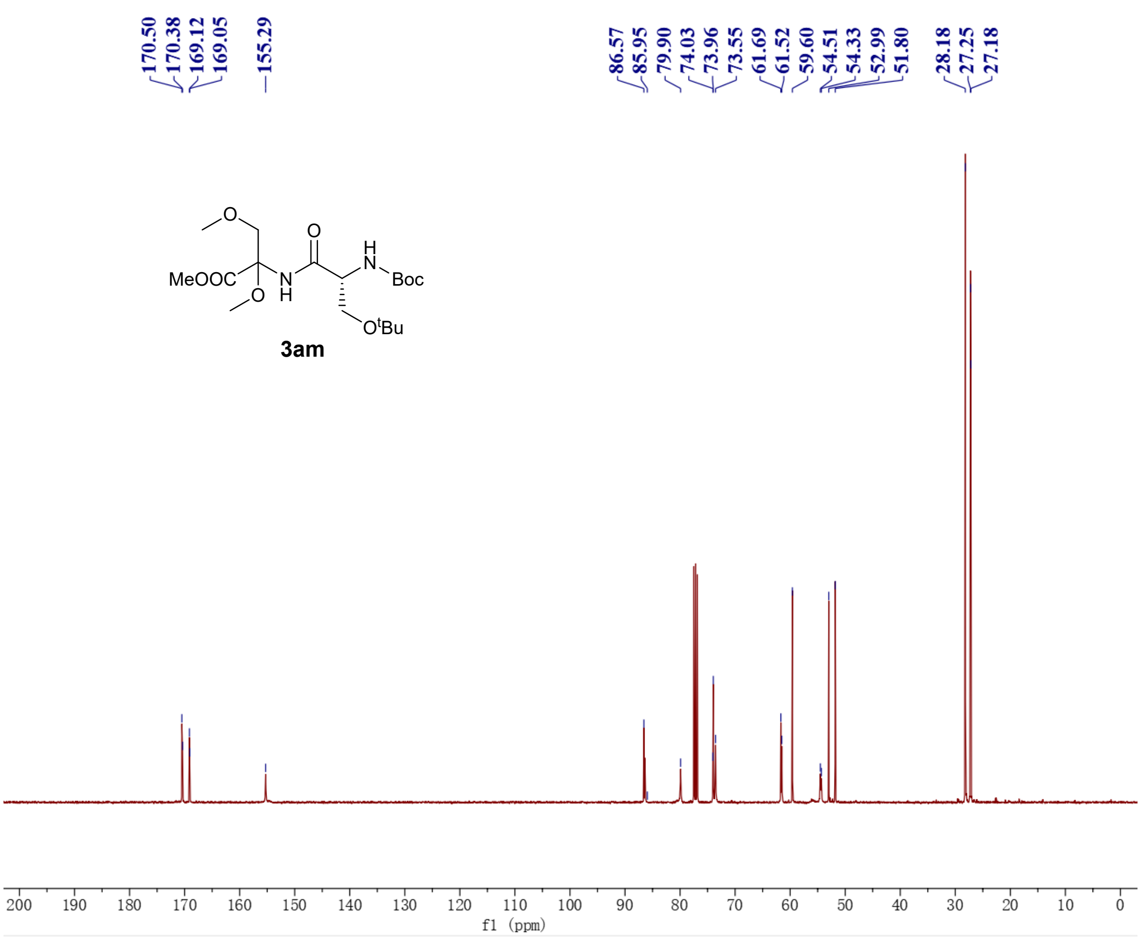
[1]H and [13]C NMR spectra of **3al**



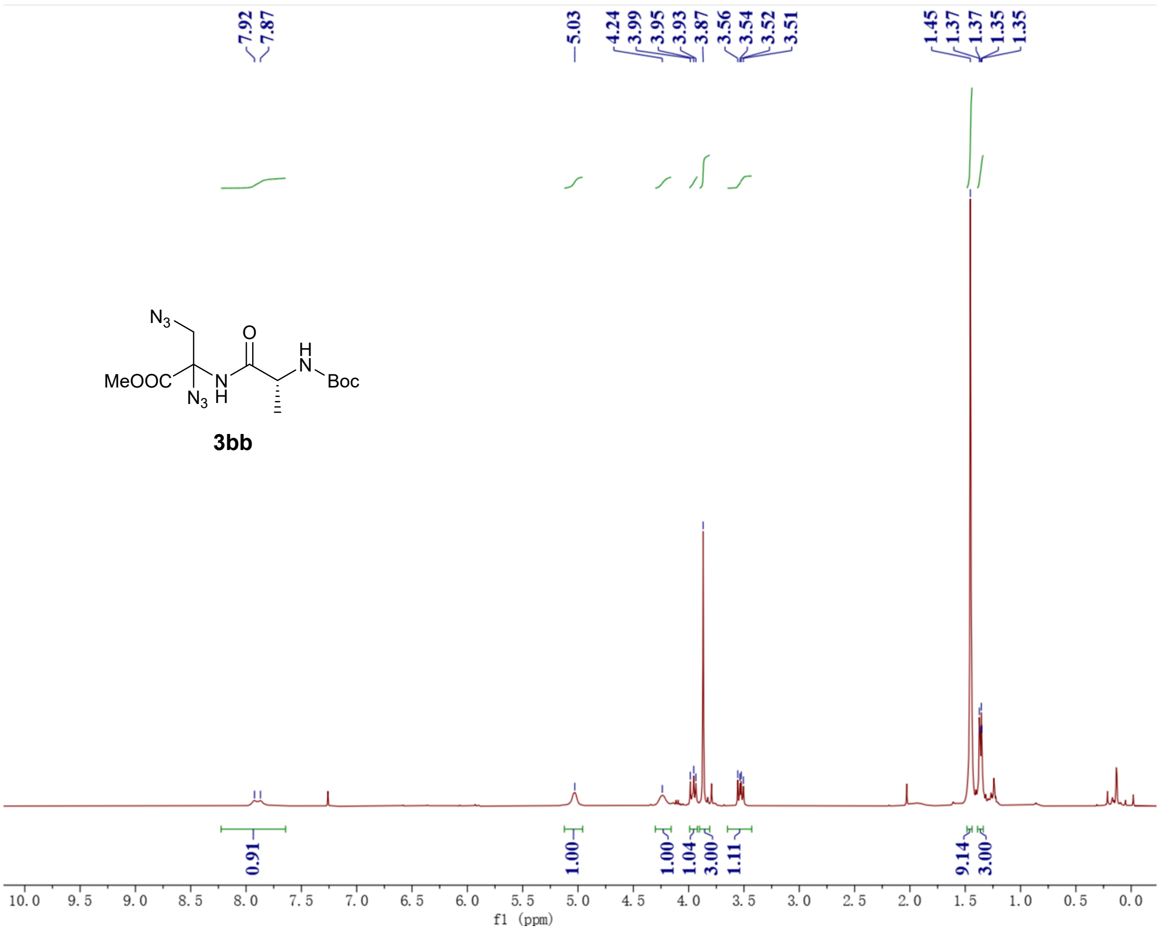


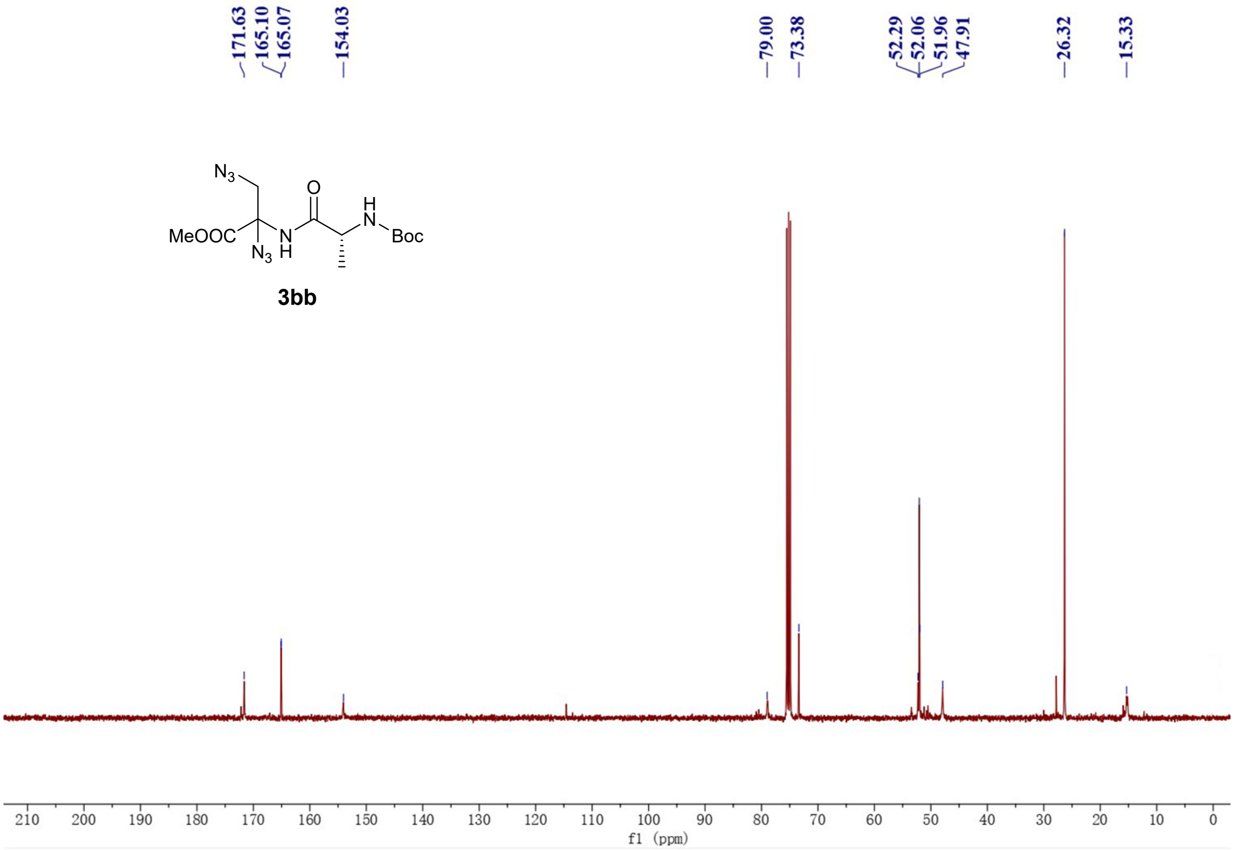
^{1}H and ^{13}C NMR spectra of **3am**



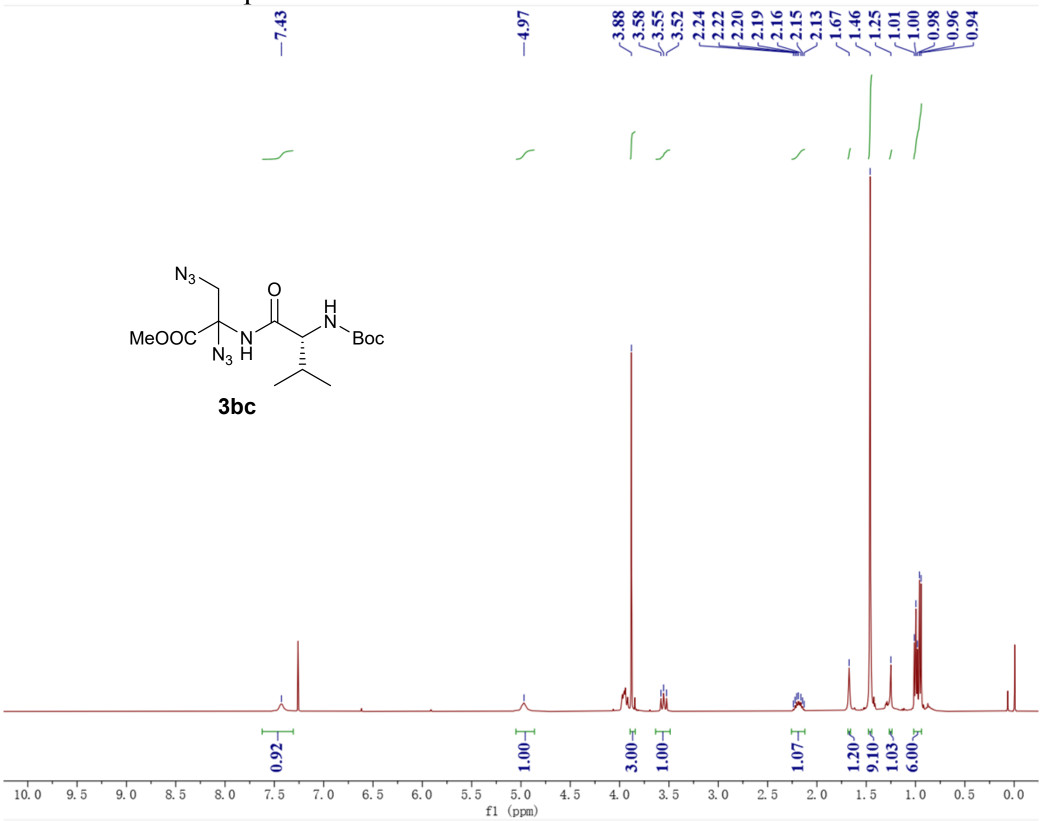


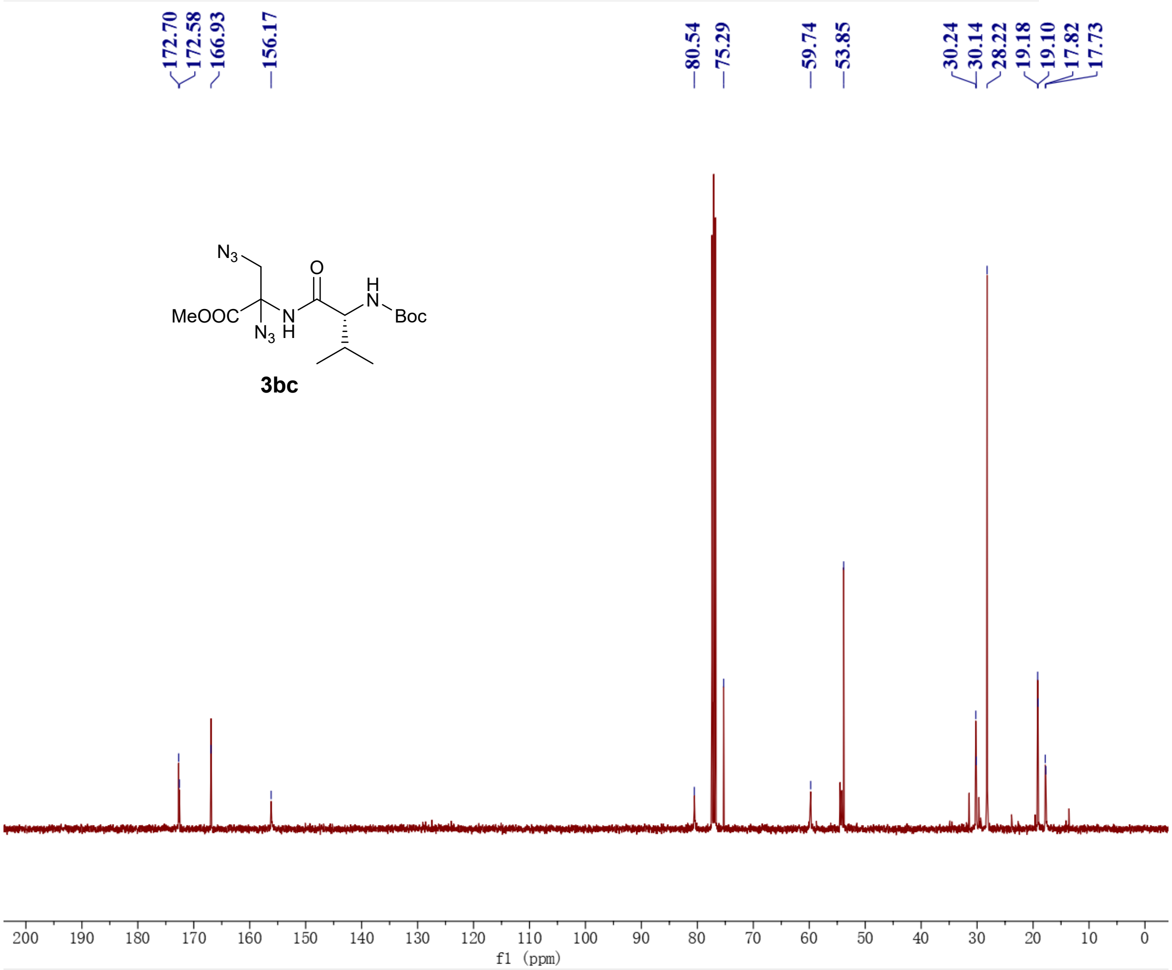
^{1}H and ^{13}C NMR spectra of **3bb**



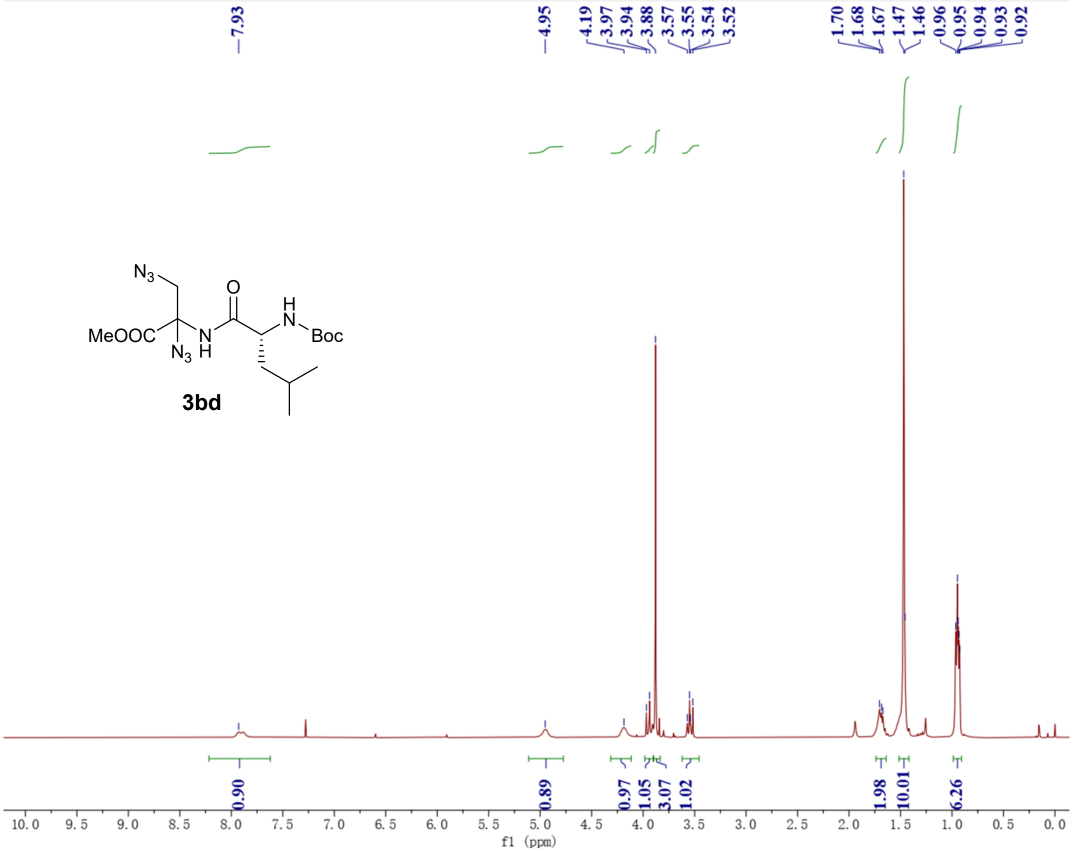


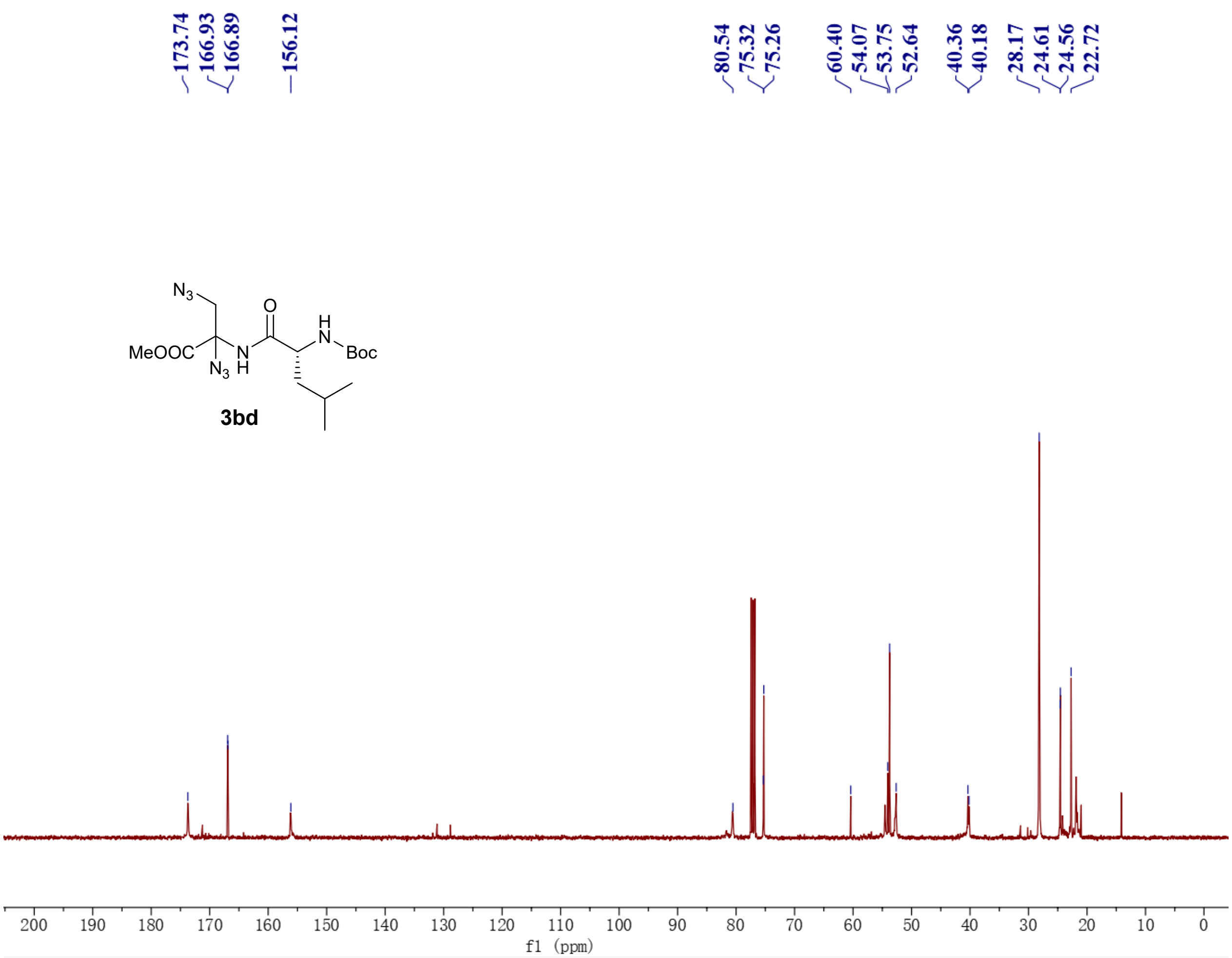
^{1}H and ^{13}C NMR spectra of **3bc**



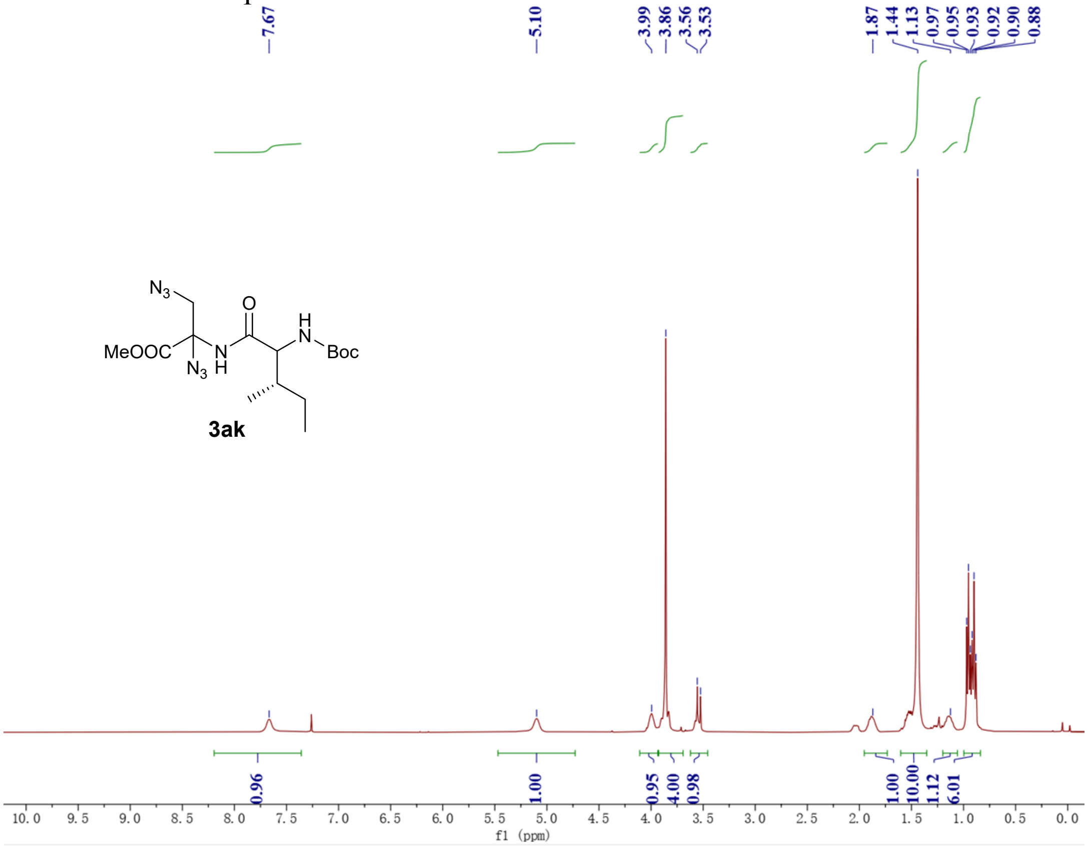


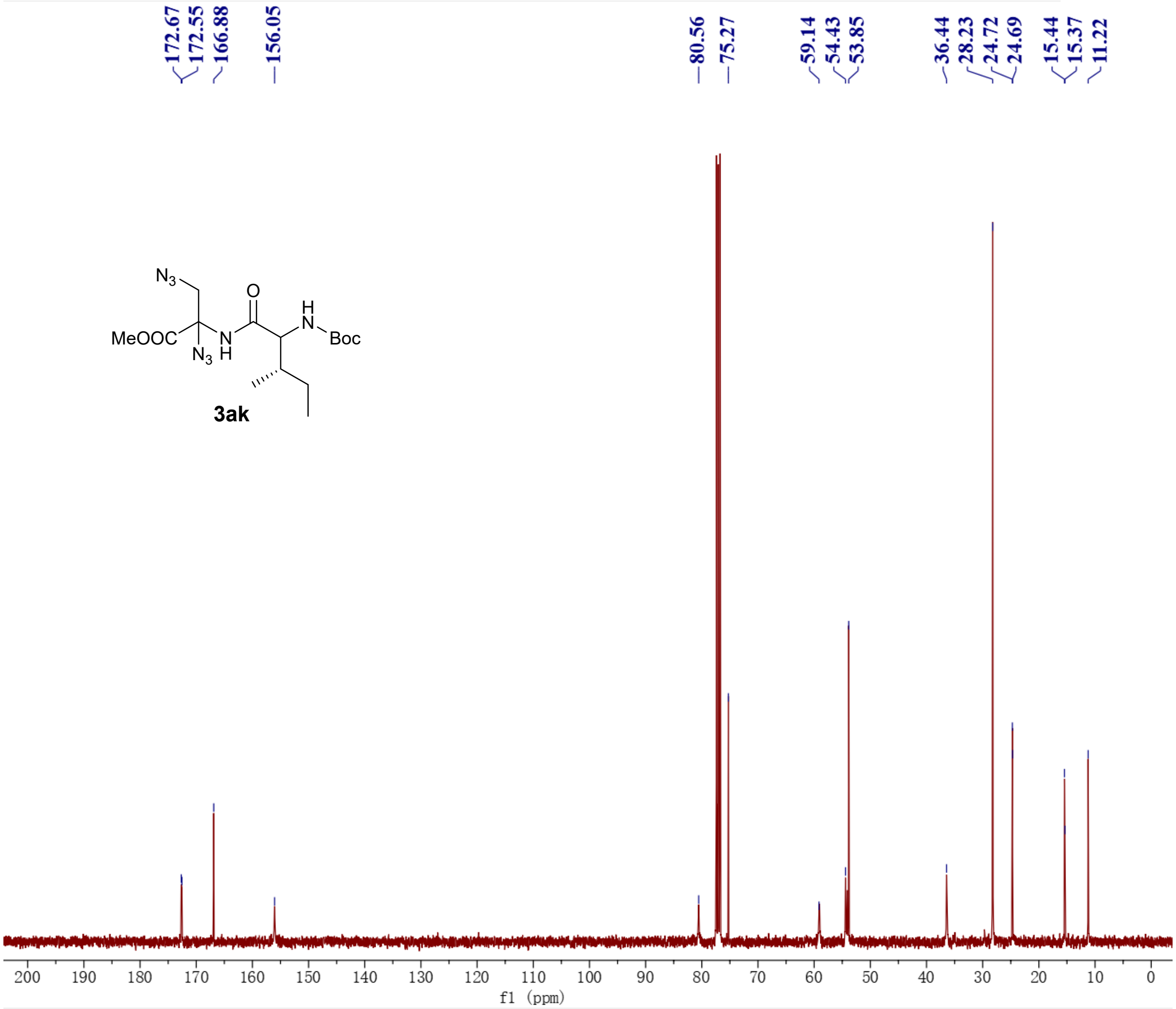
^{1}H and ^{13}C NMR spectra of **3bd**



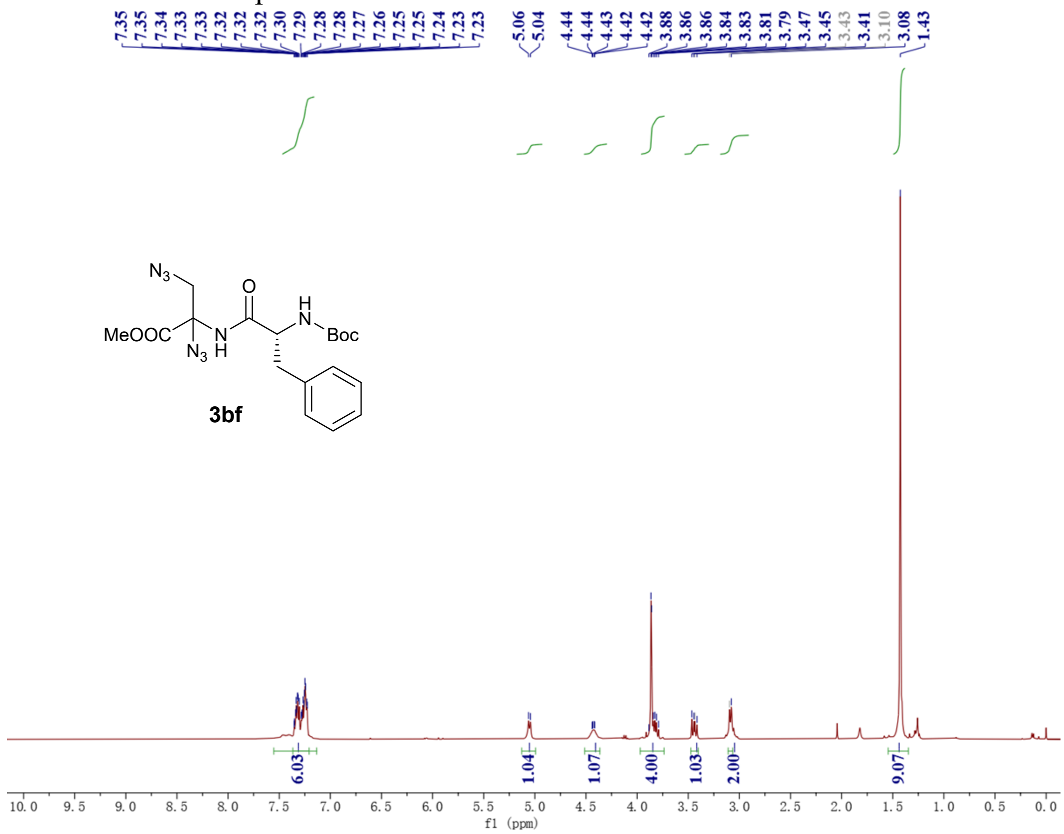


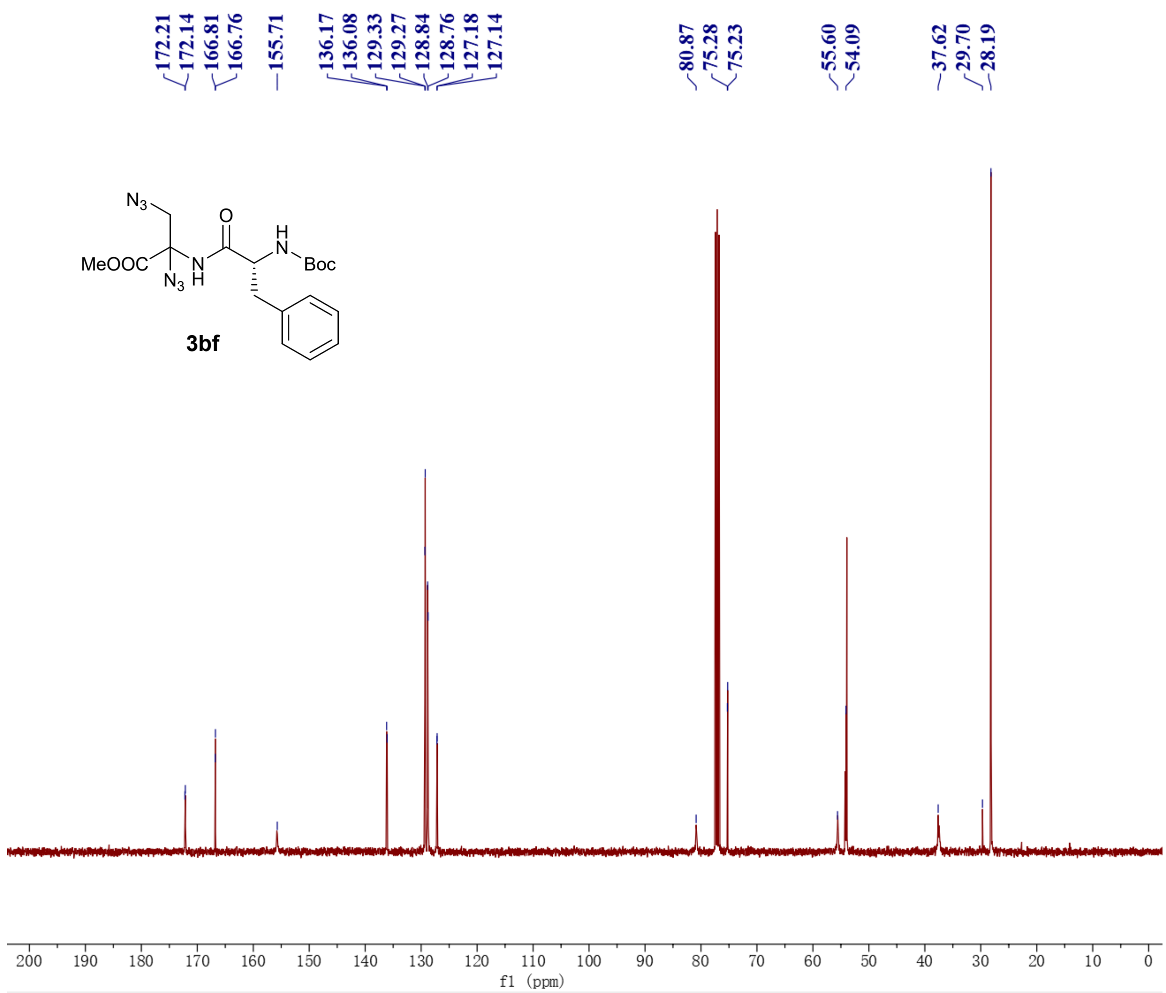
[1]H and [13]C NMR spectra of **3ak**



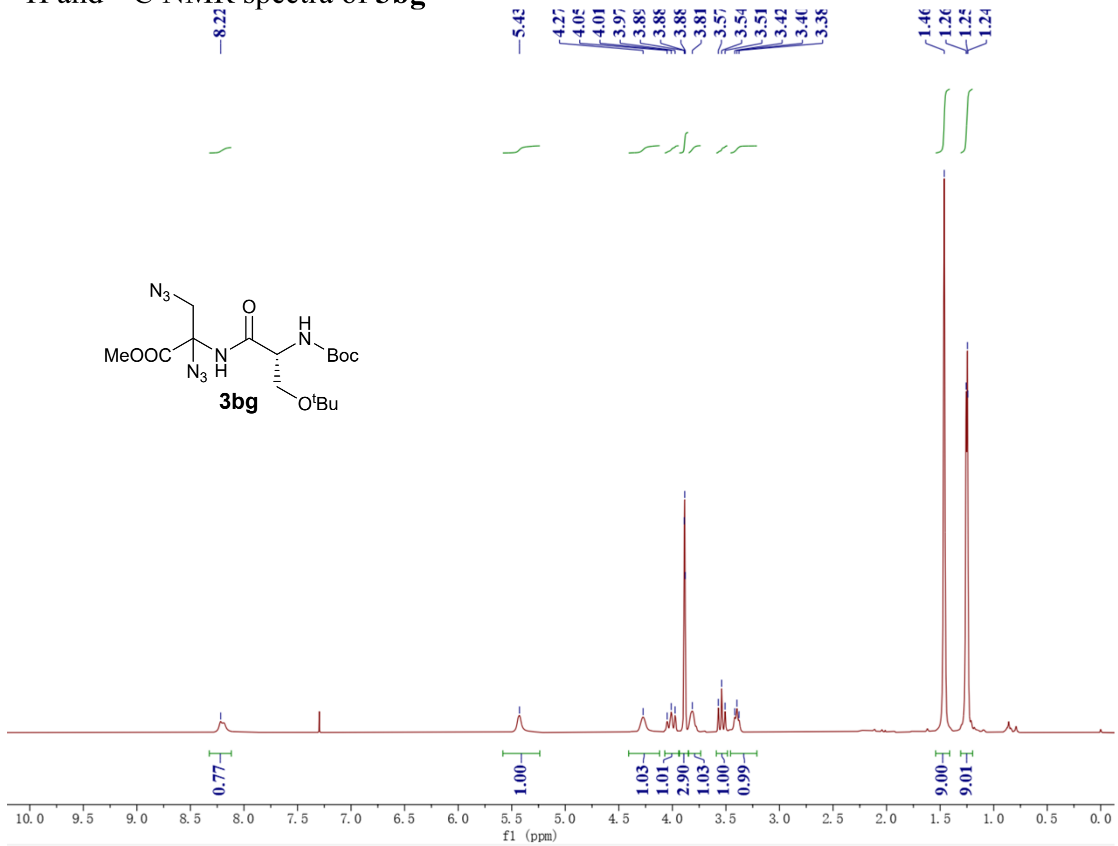


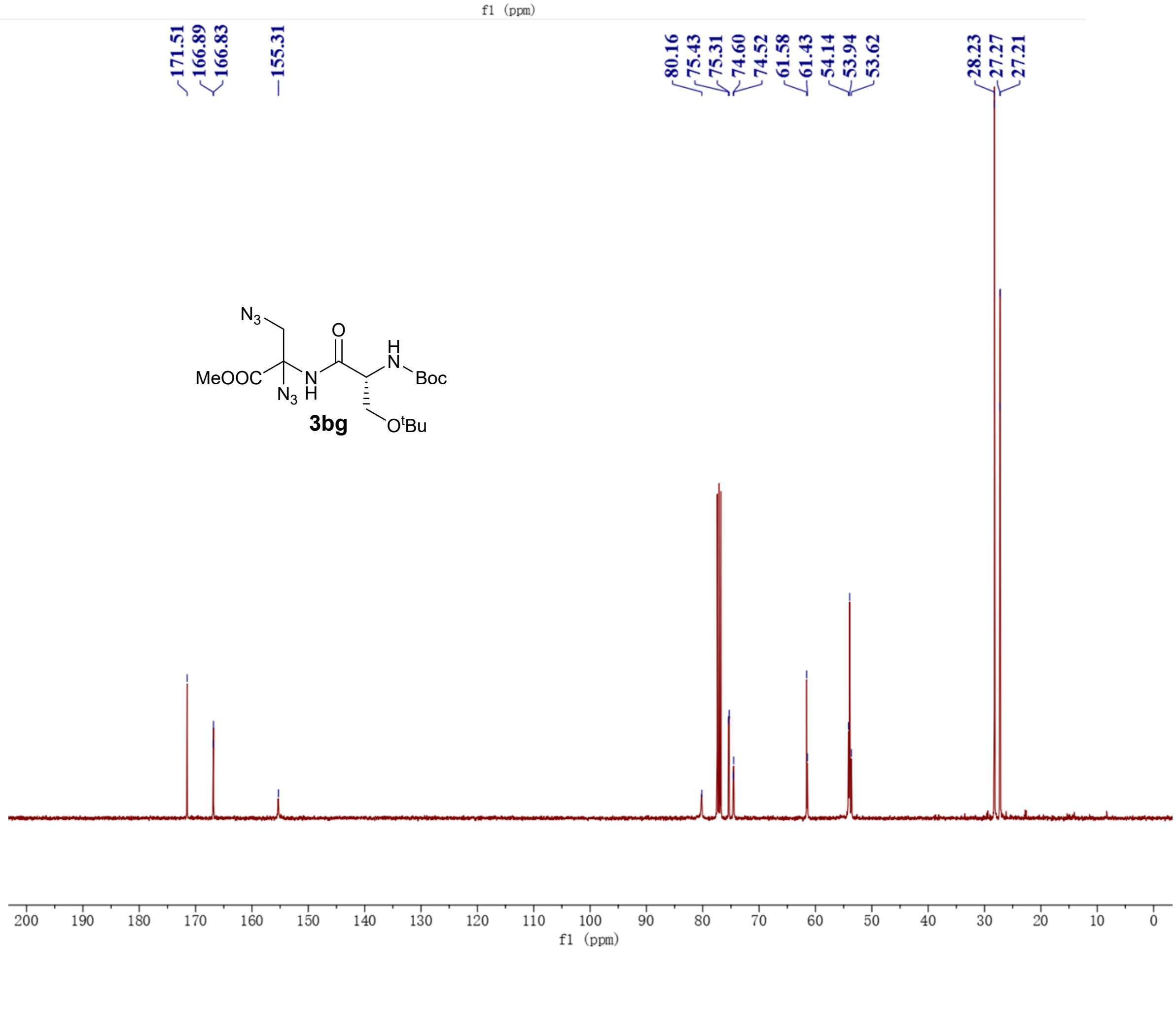
^{1}H and ^{13}C NMR spectra of **3bf**



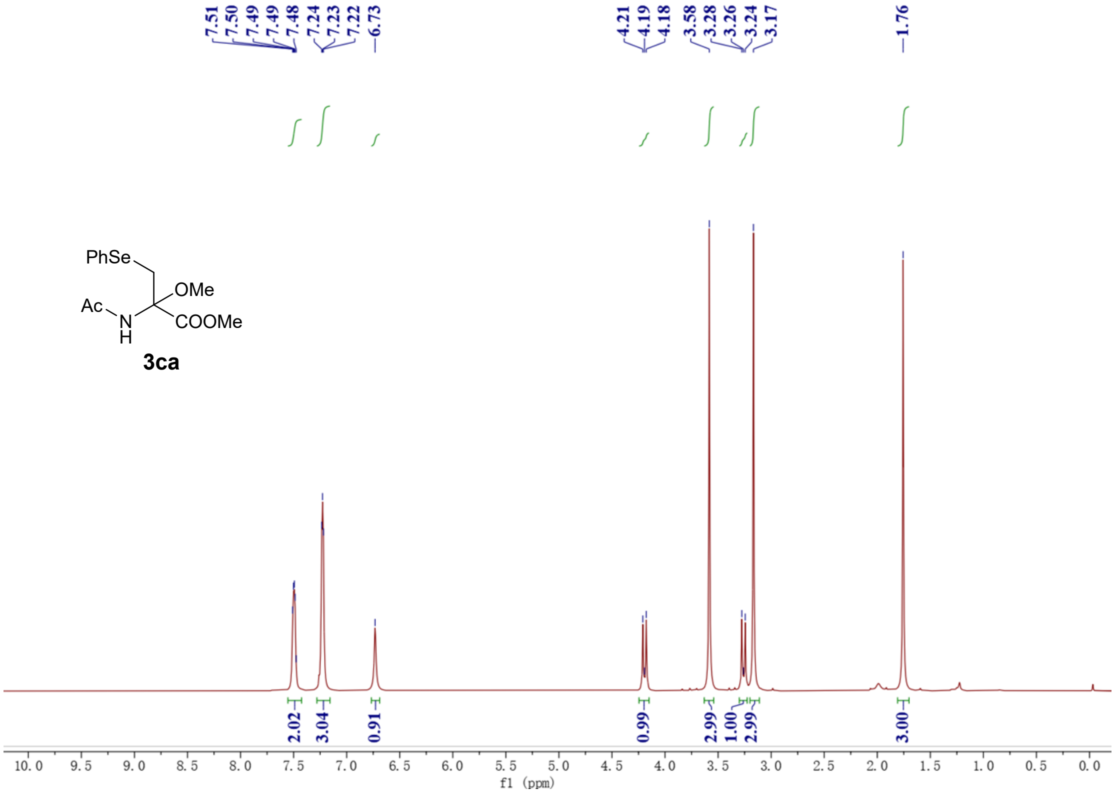


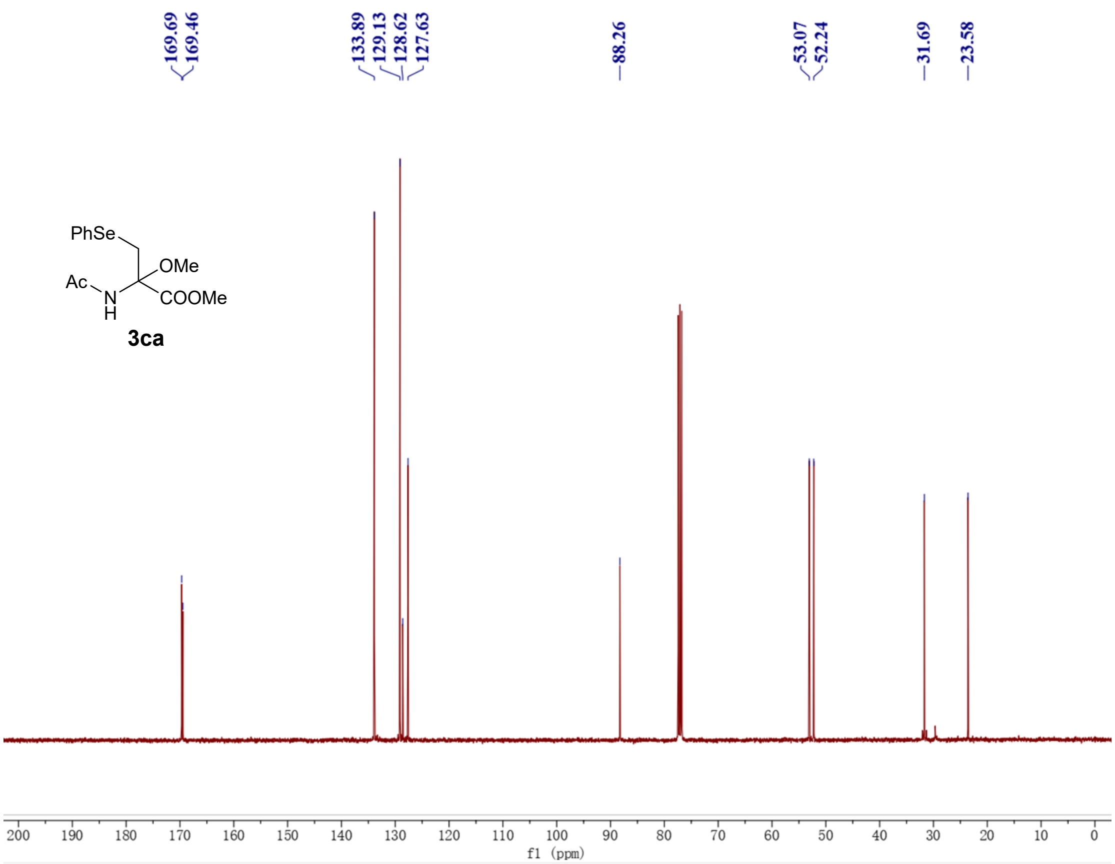
^{1}H and ^{13}C NMR spectra of **3bg**



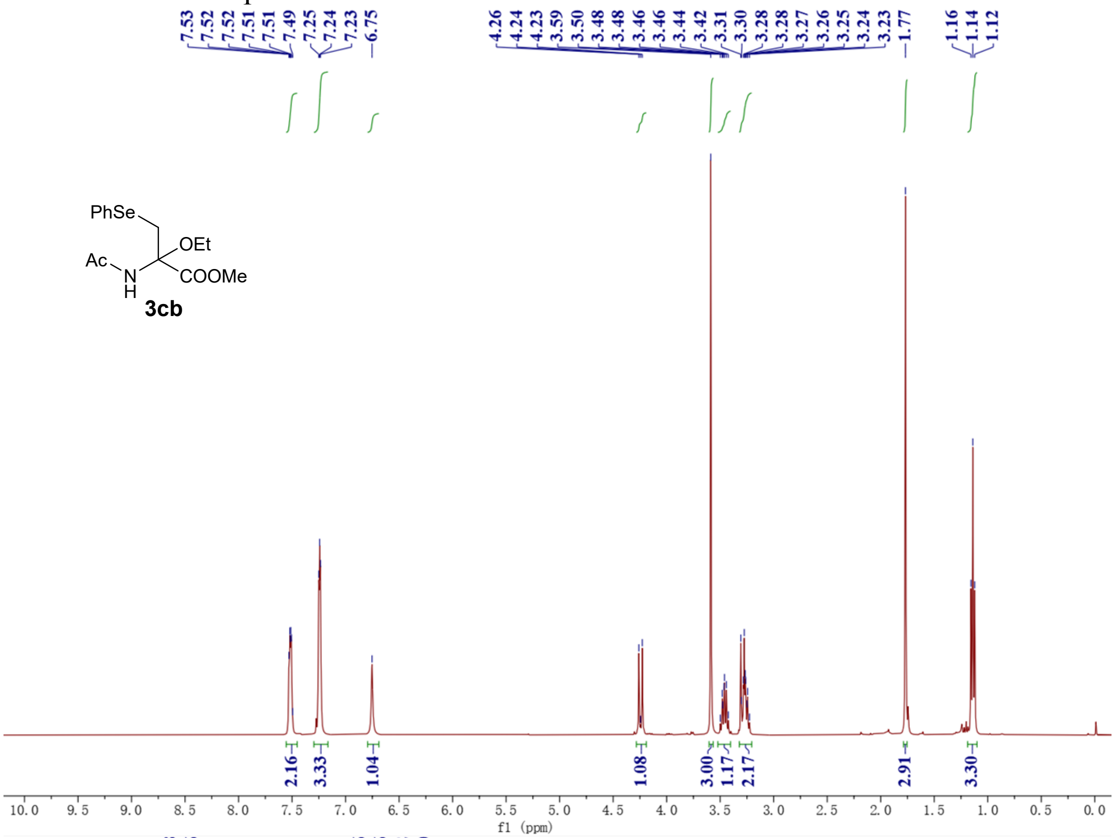


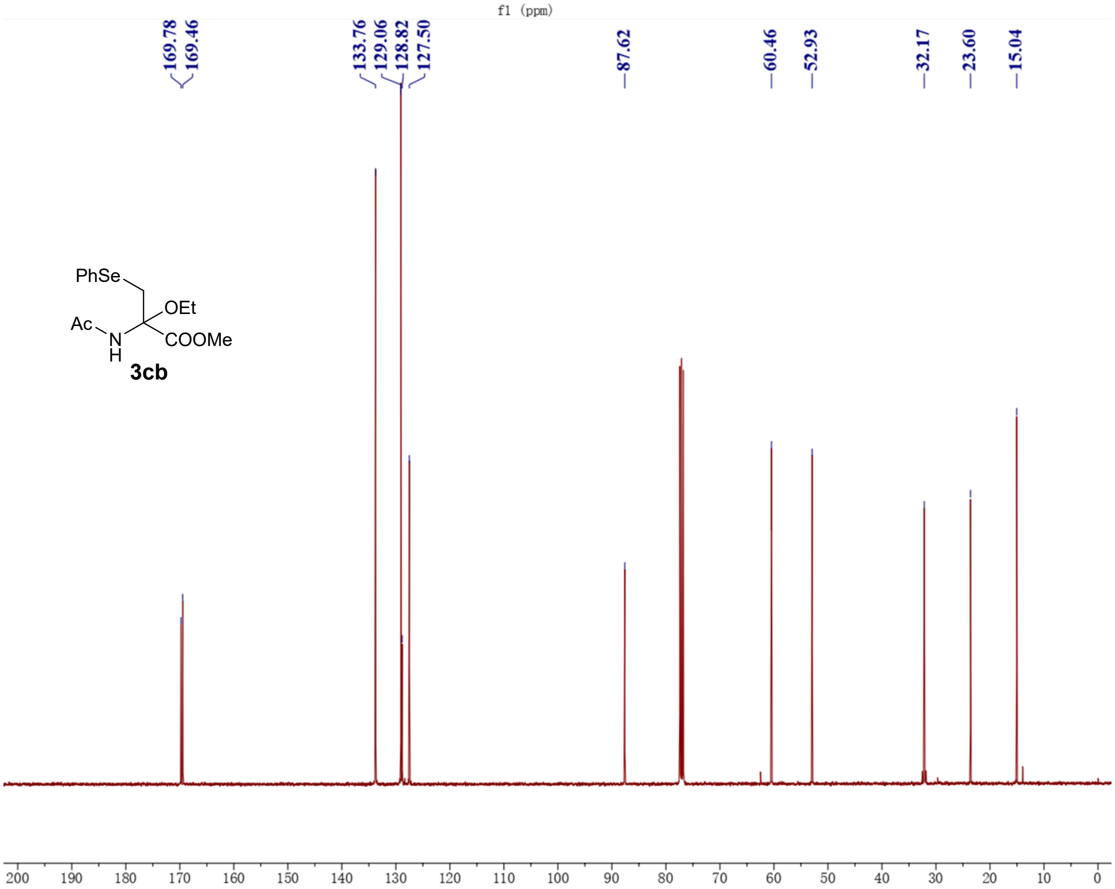
^{1}H and ^{13}C NMR spectra of **3ca**



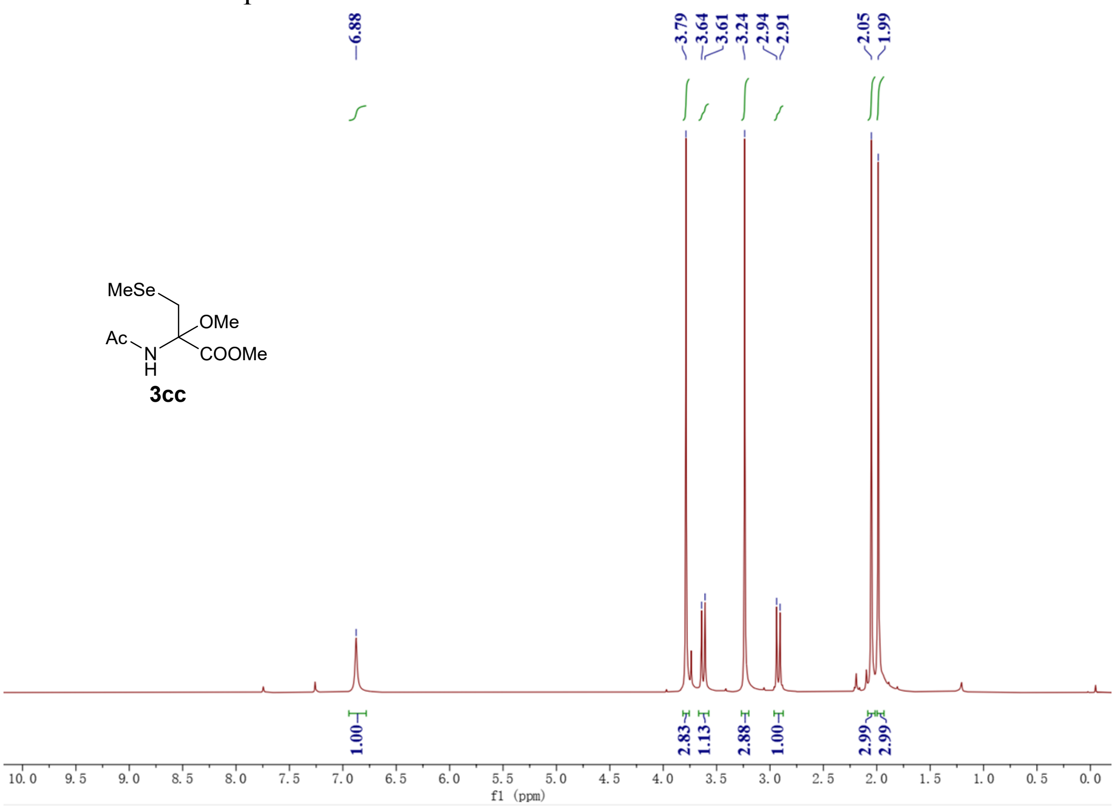


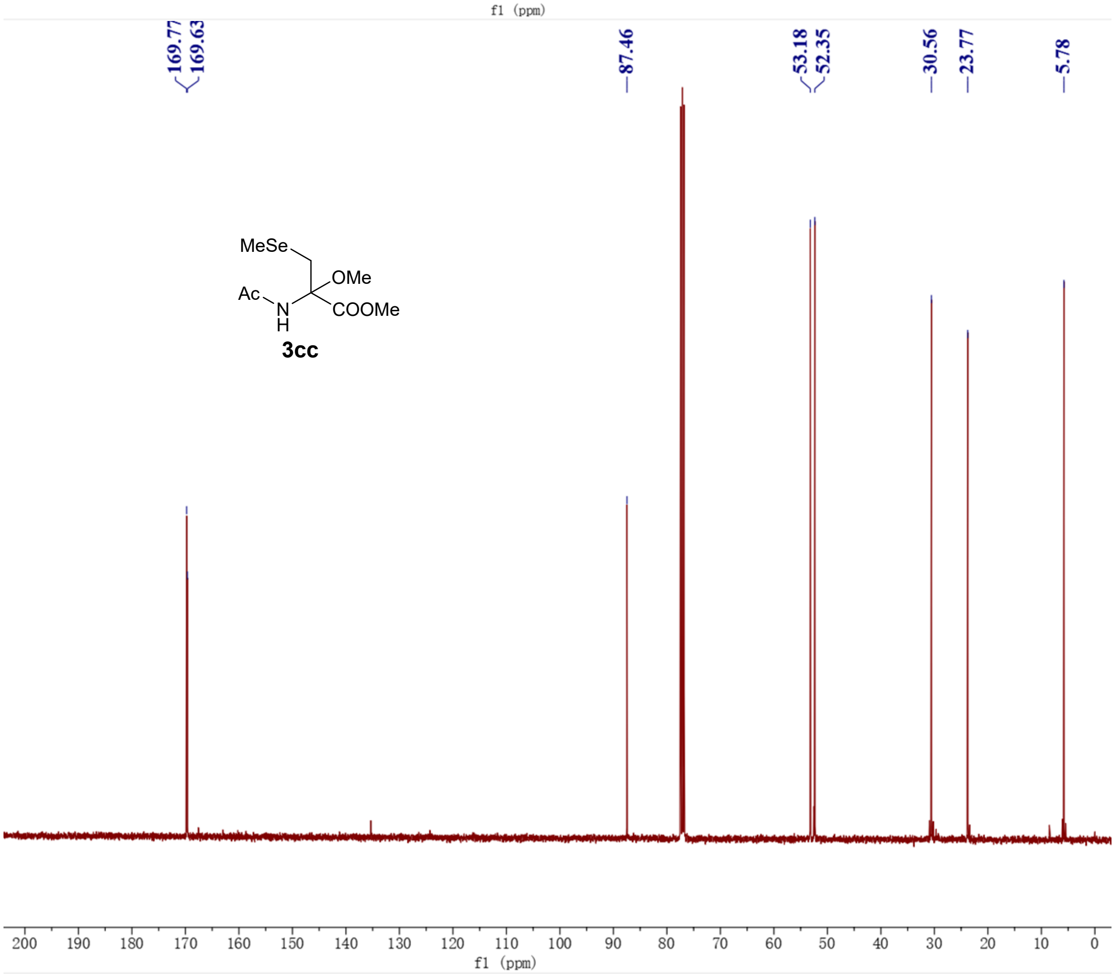
^{1}H and ^{13}C NMR spectra of **3cb**



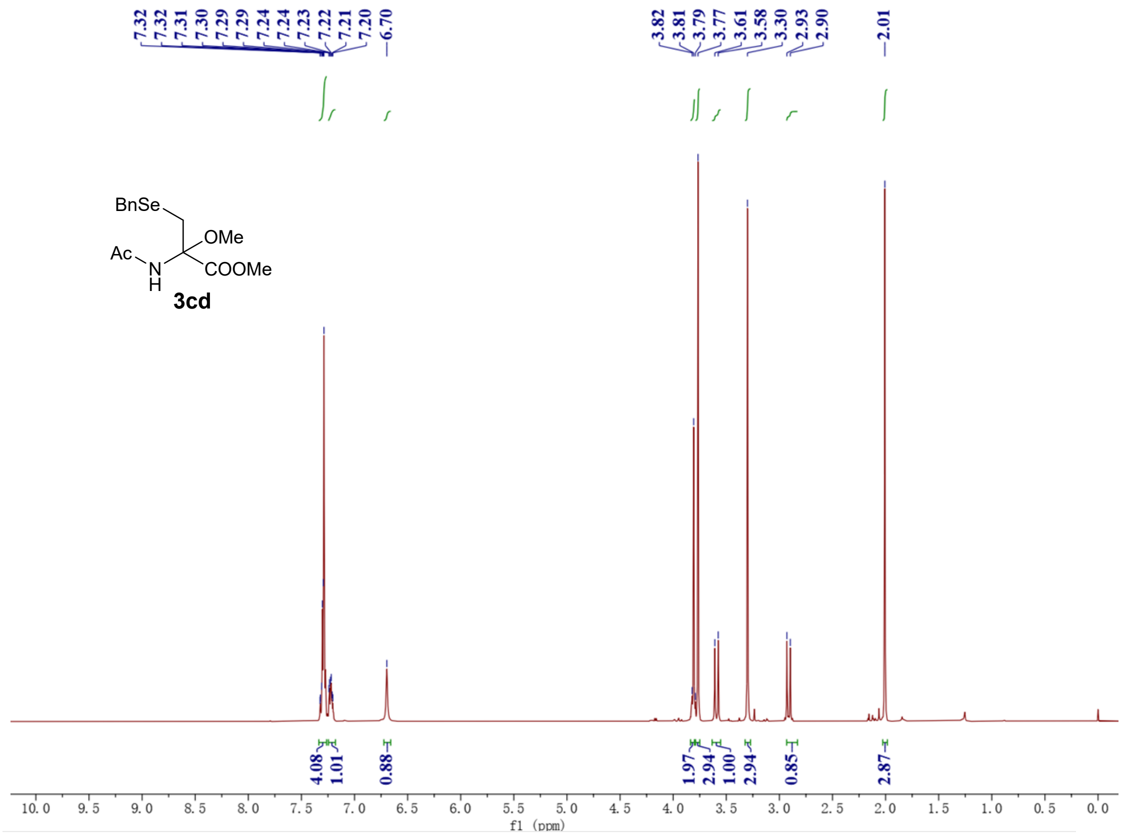


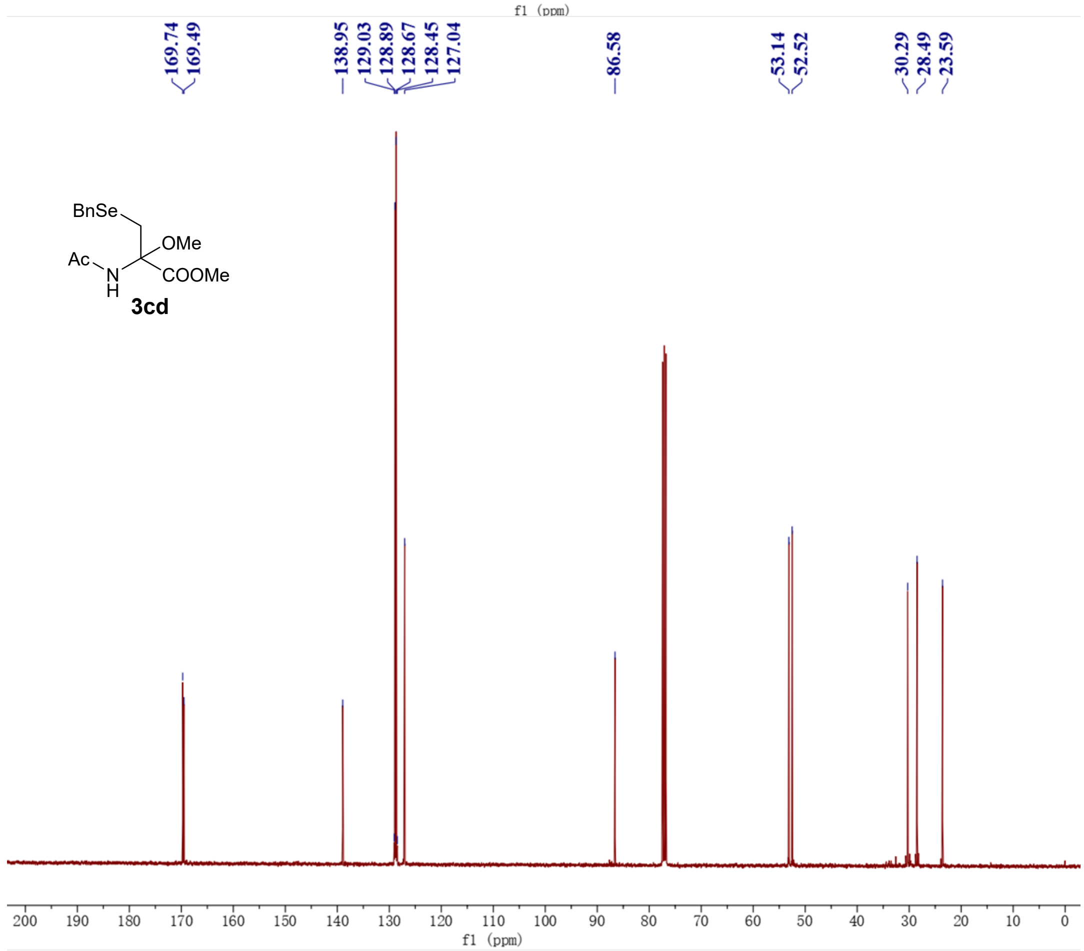
^{1}H and ^{13}C NMR spectra of **3cc**



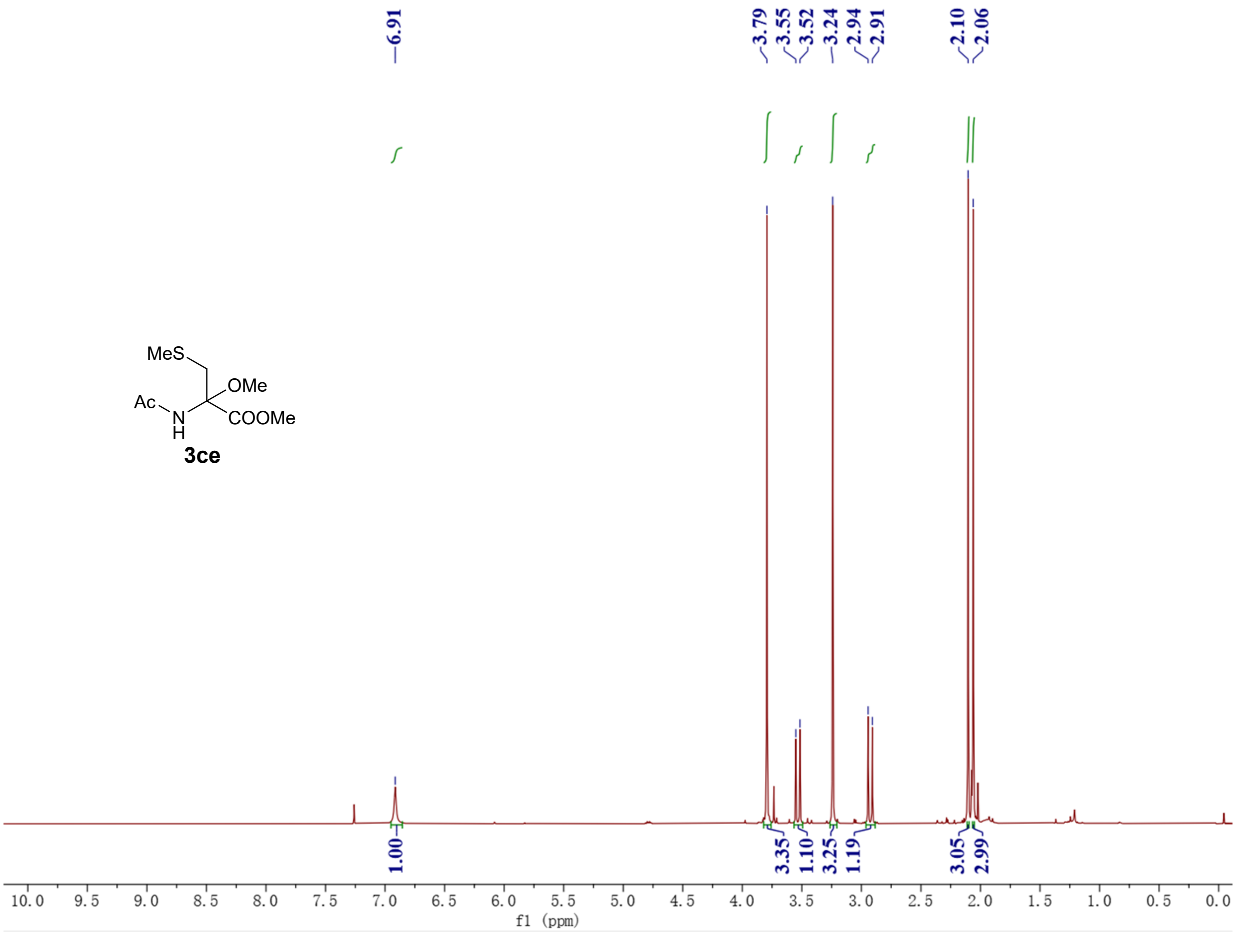


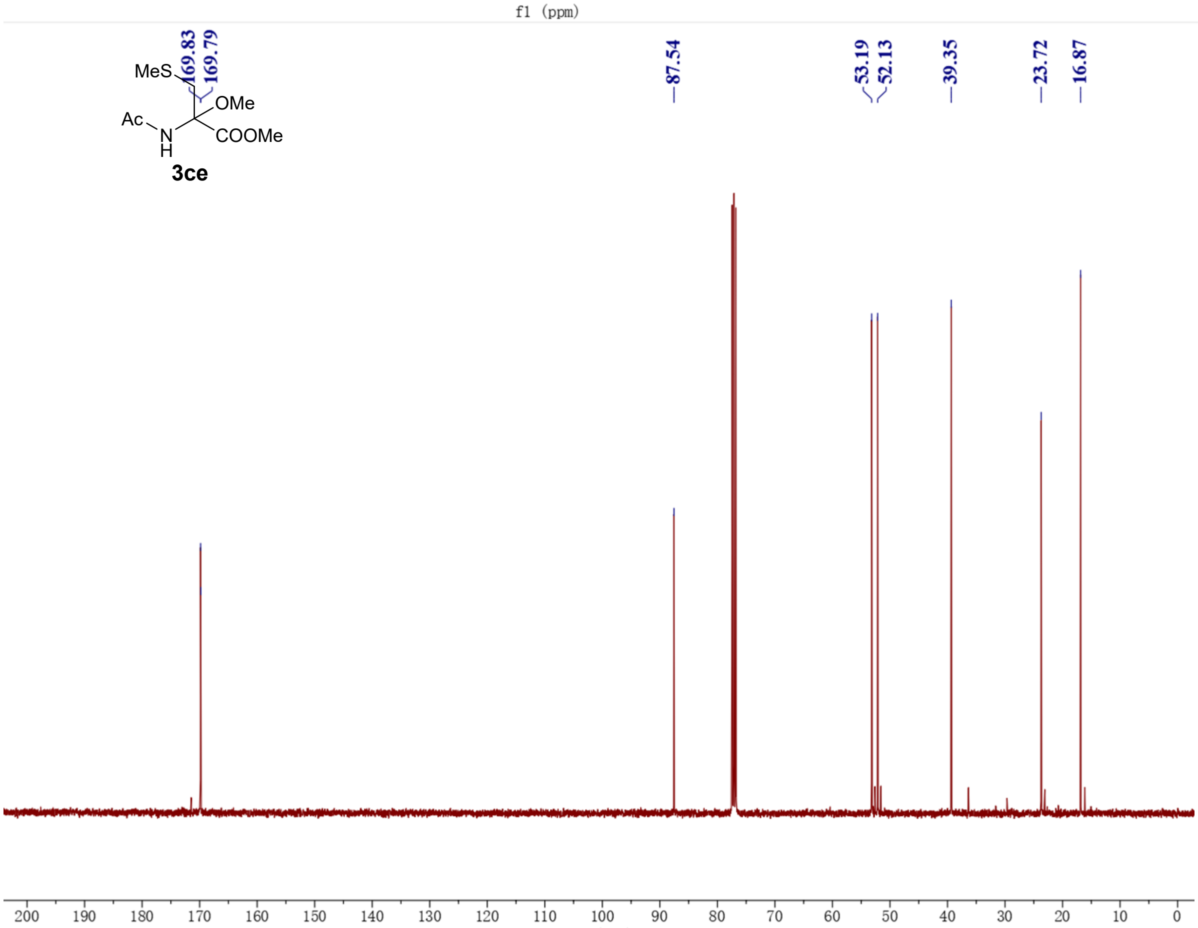
^{1}H and ^{13}C NMR spectra of **3cd**



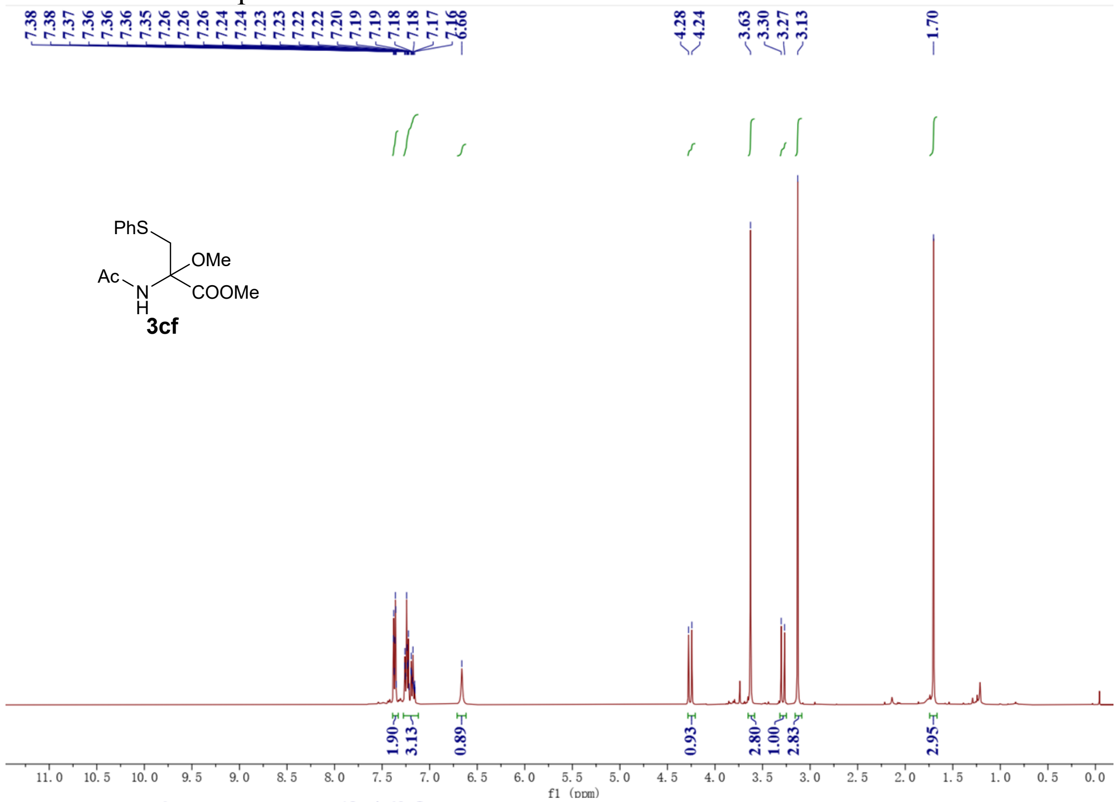


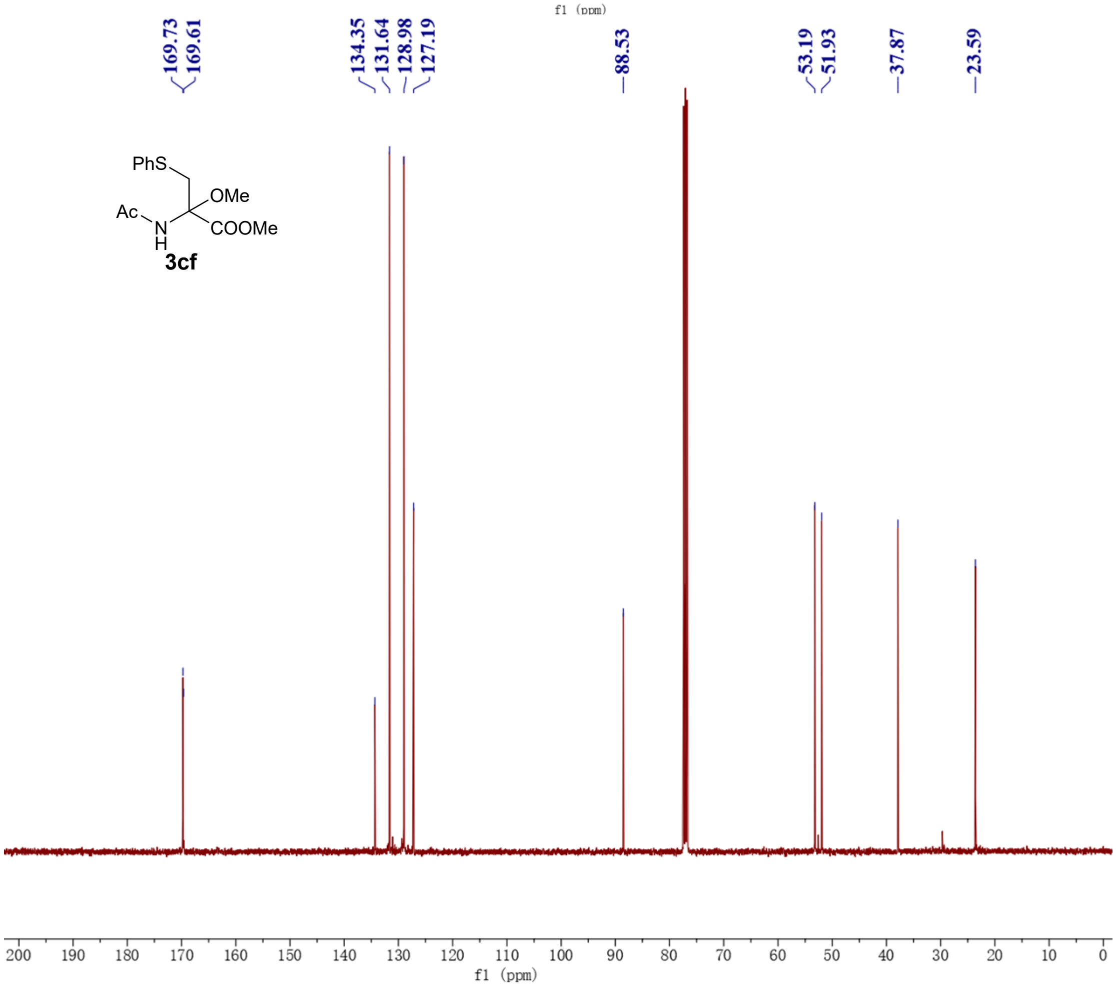
^{1}H and ^{13}C NMR spectra of **3ce**



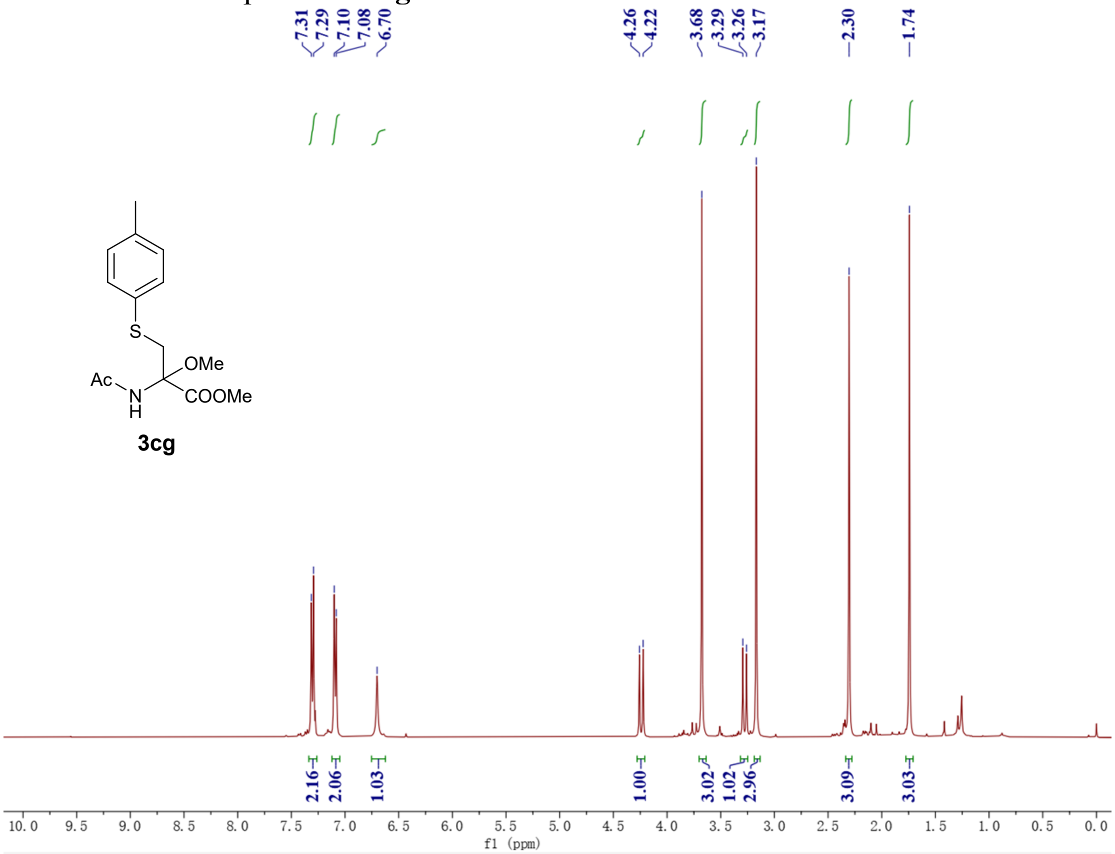


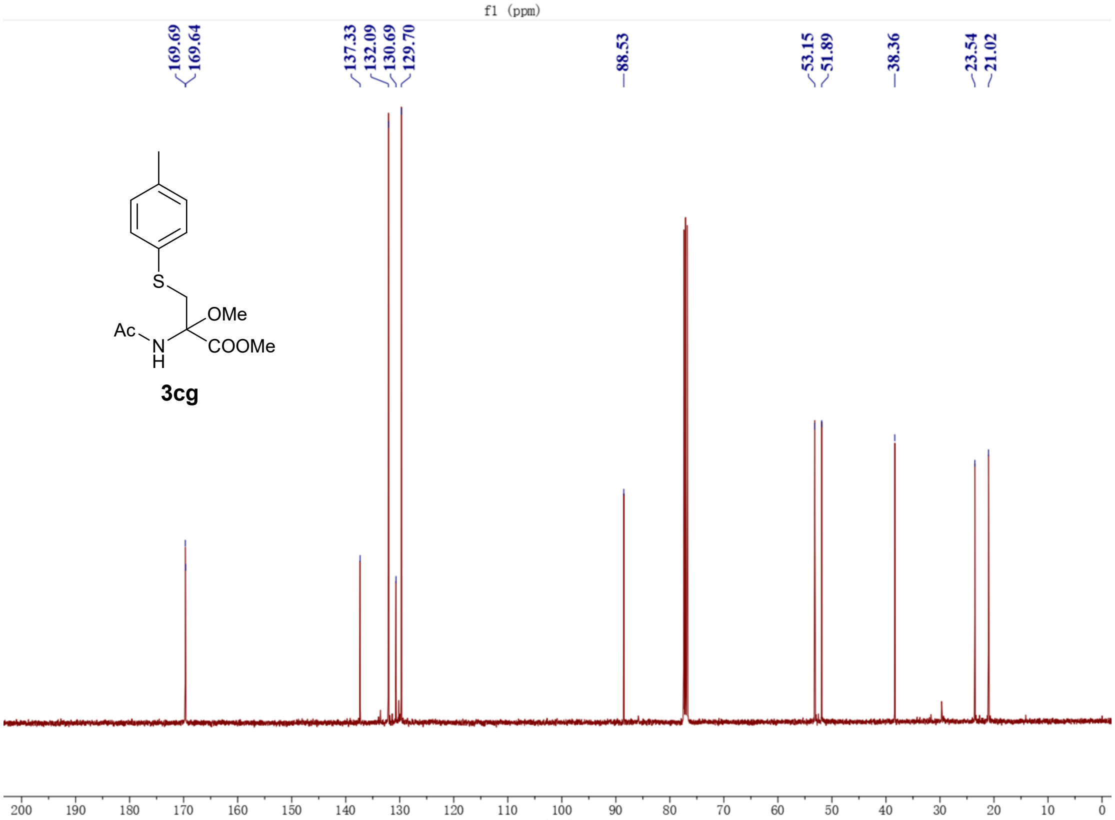
^1H and ^{13}C NMR spectra of **3cf**



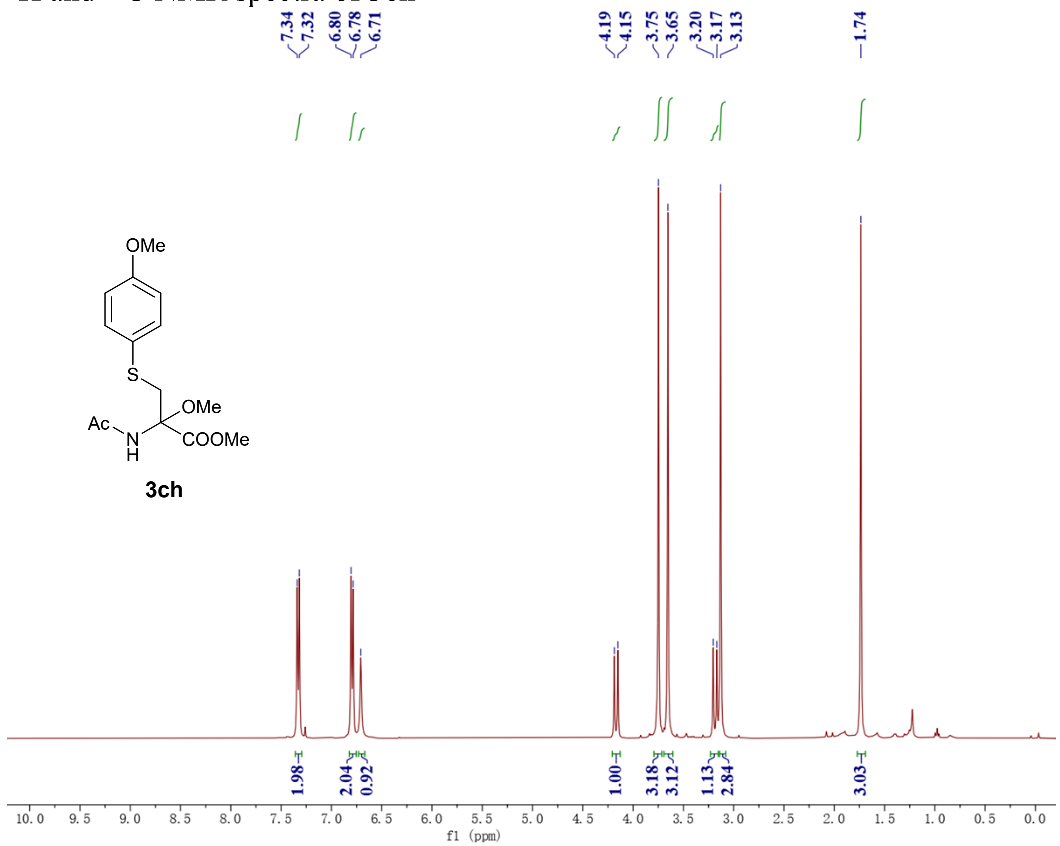


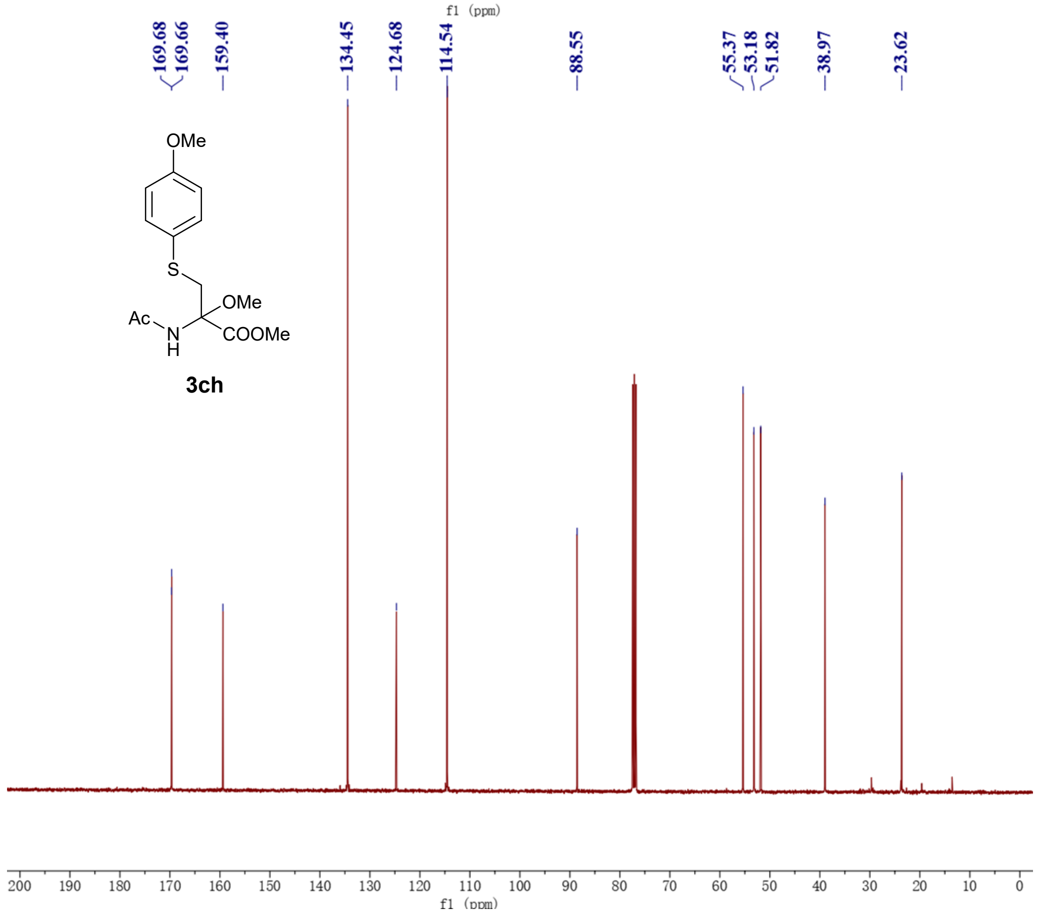
[1]H and [13]C NMR spectra of **3cg**



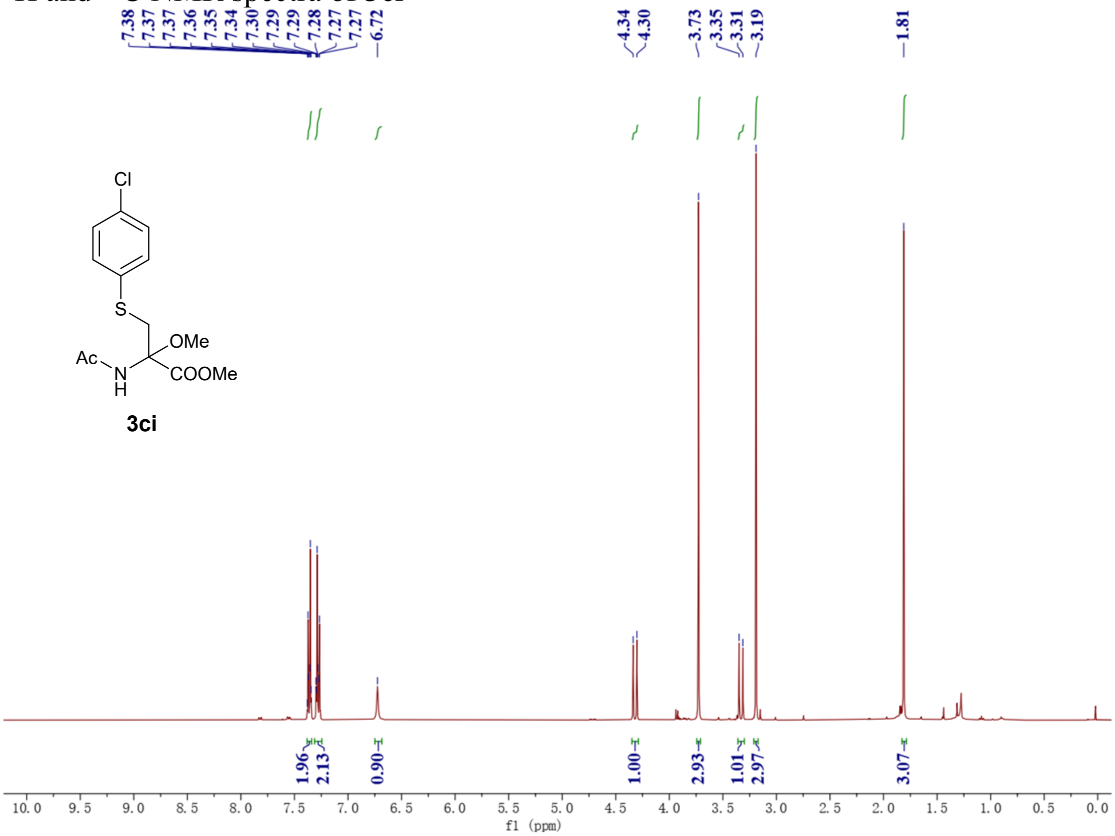


^{1}H and ^{13}C NMR spectra of **3ch**

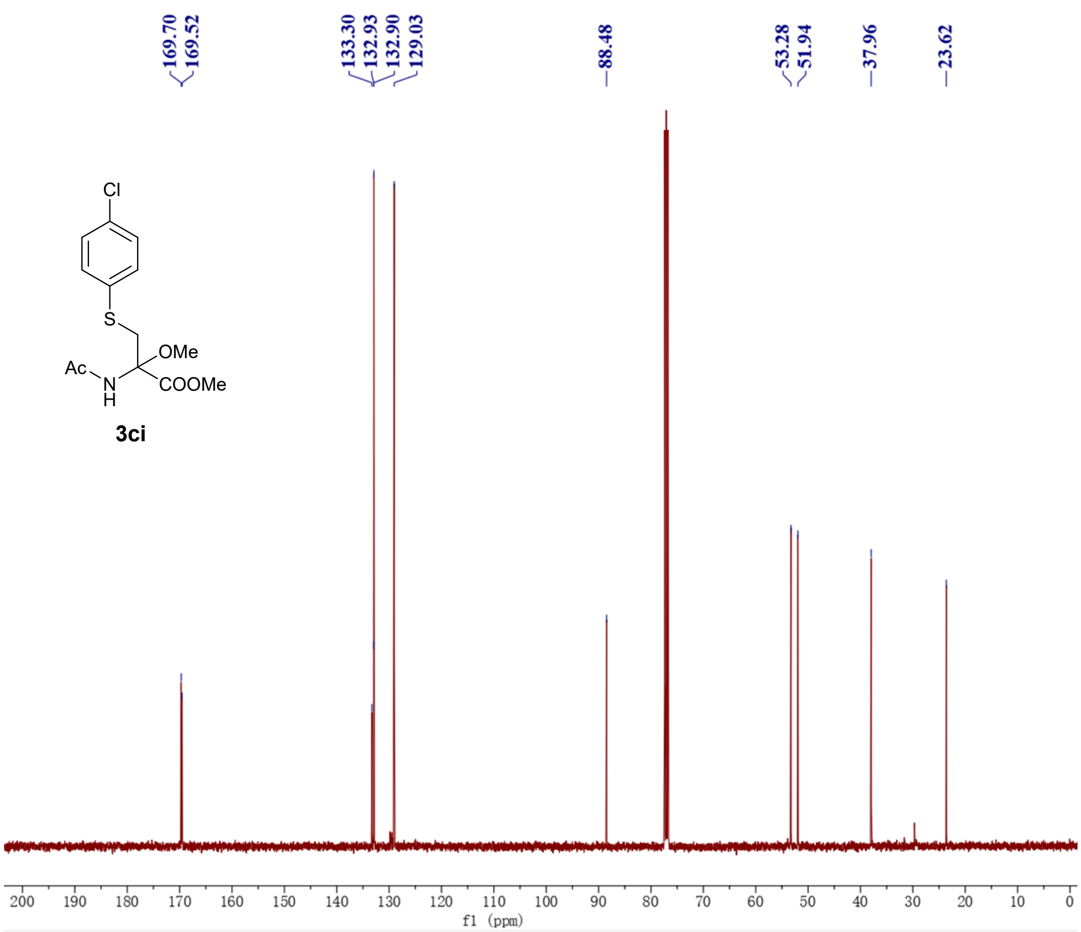




[1]H and [13]C NMR spectra of **3ci**

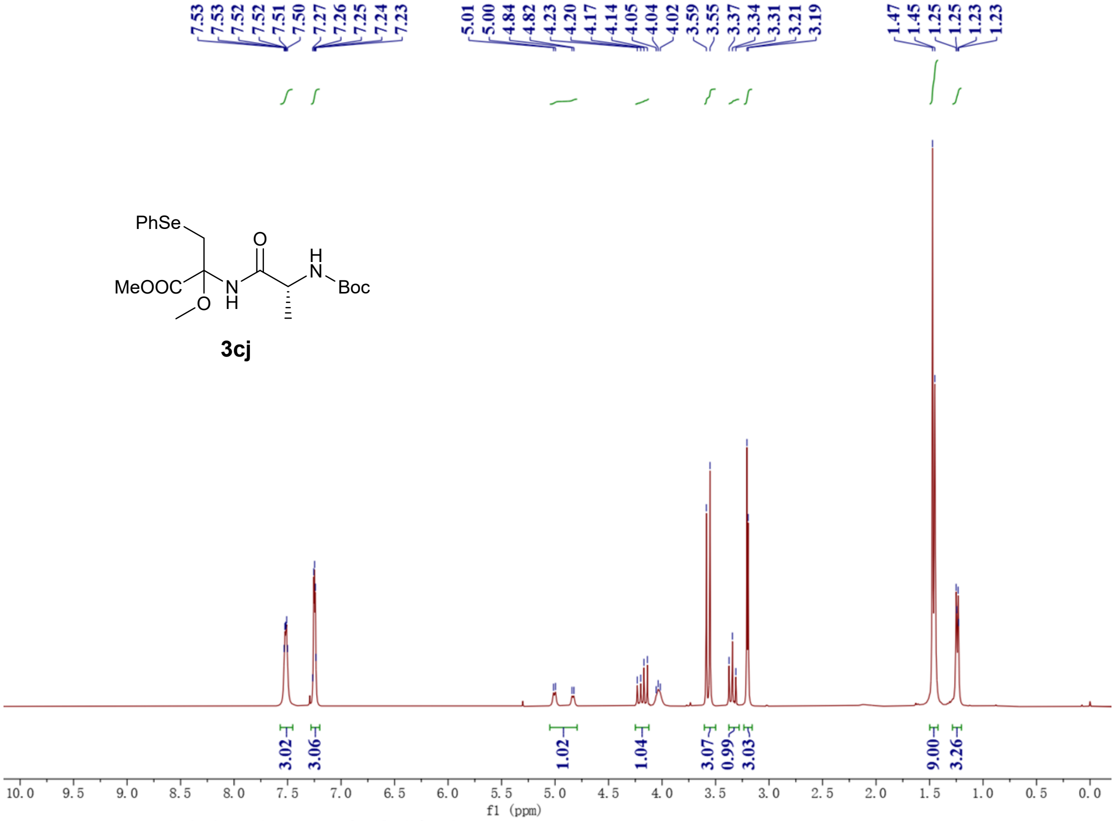


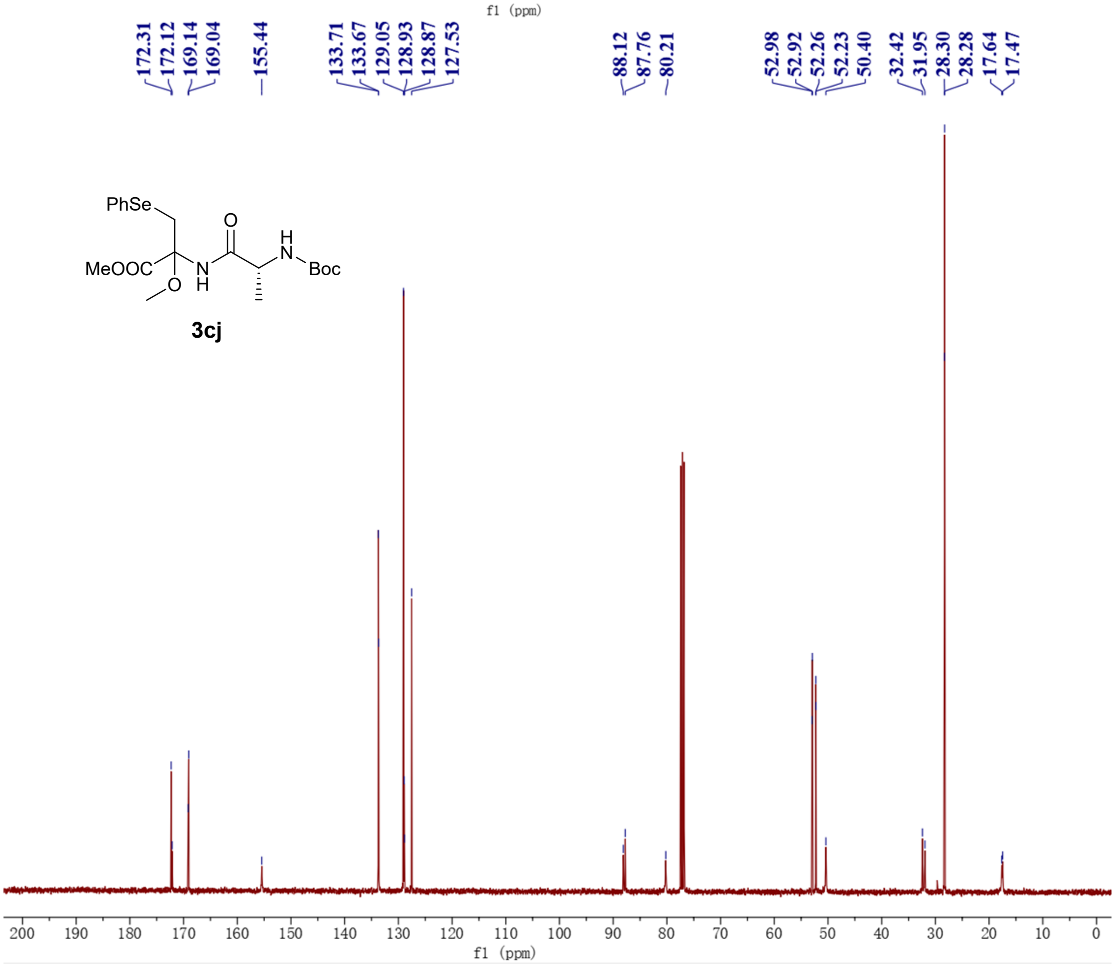
3ci



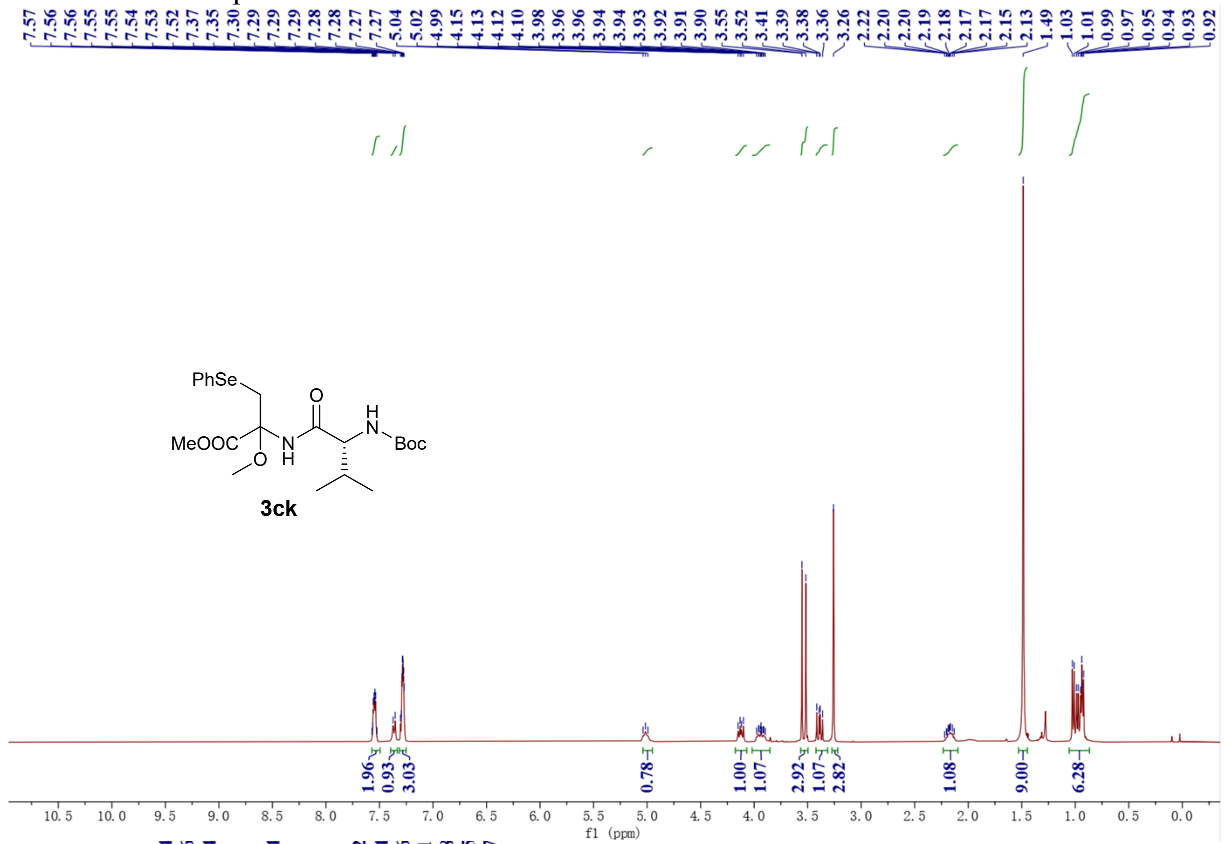
3ci

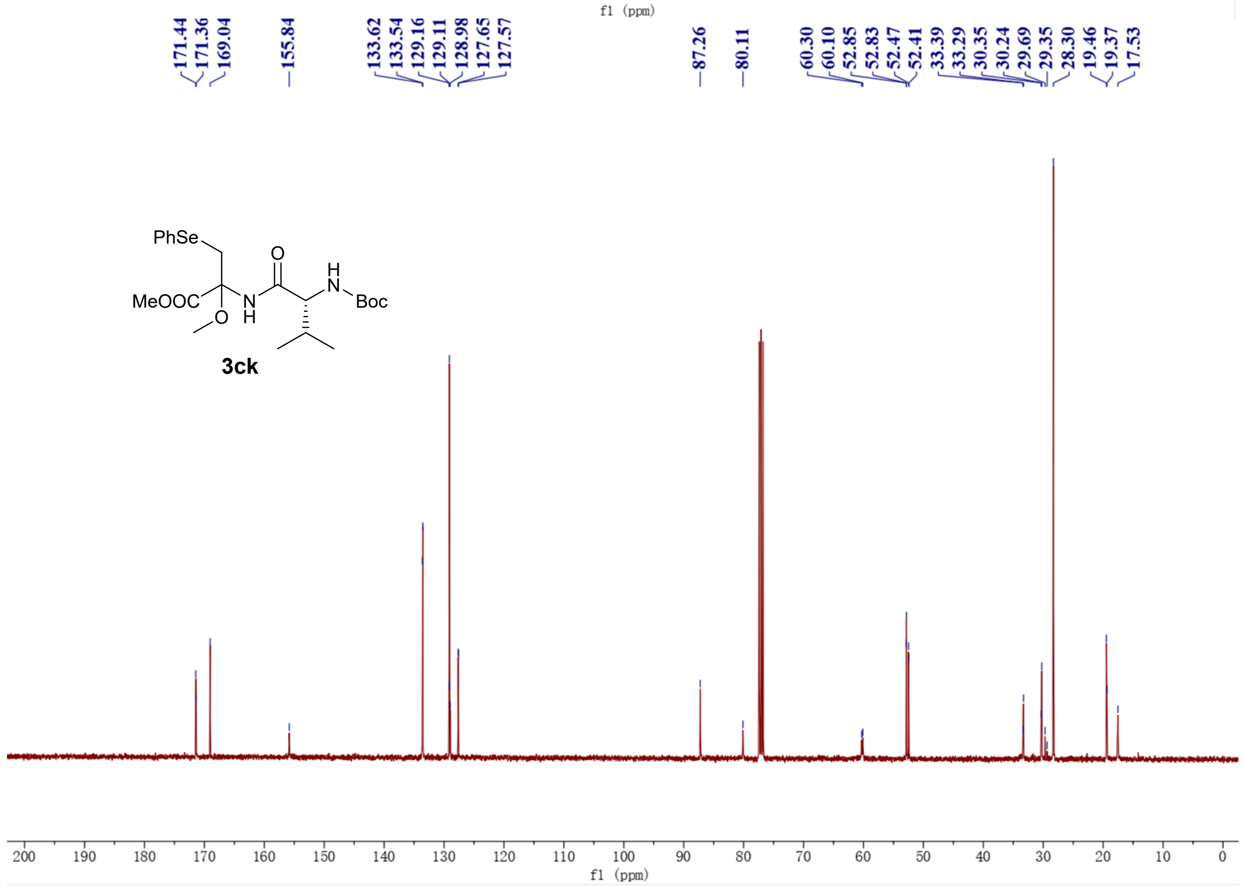
[1]H and [13]C NMR spectra of **3cj**



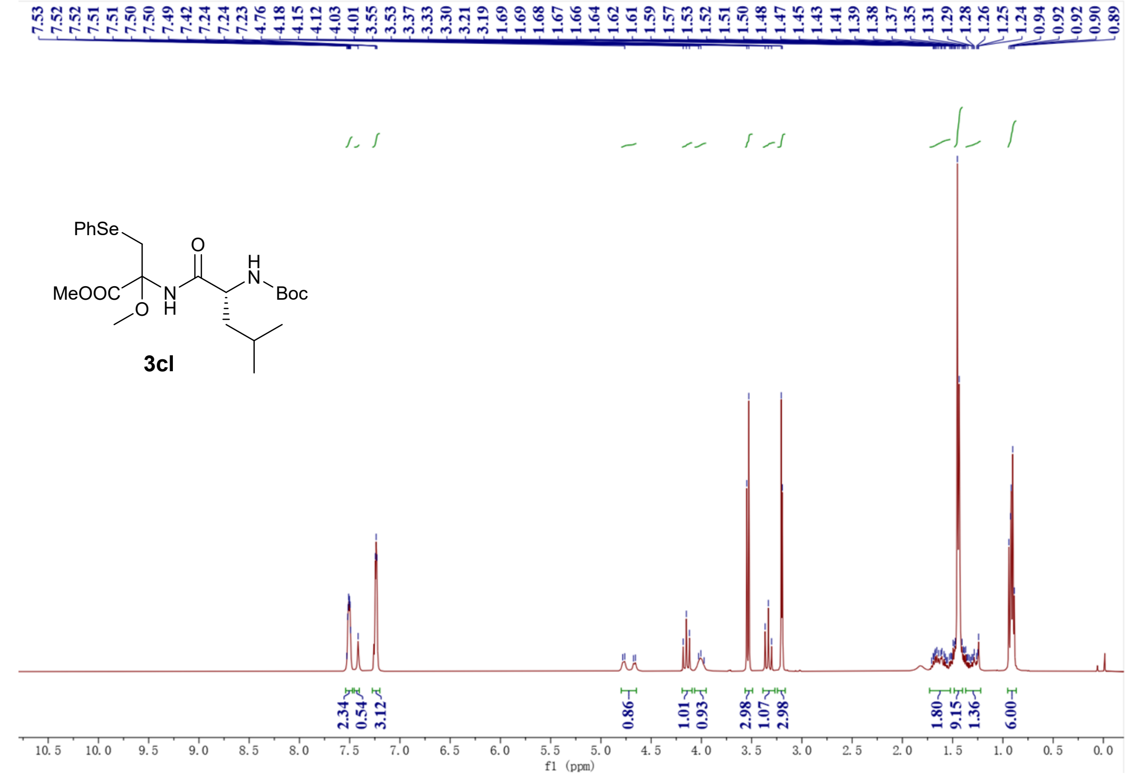


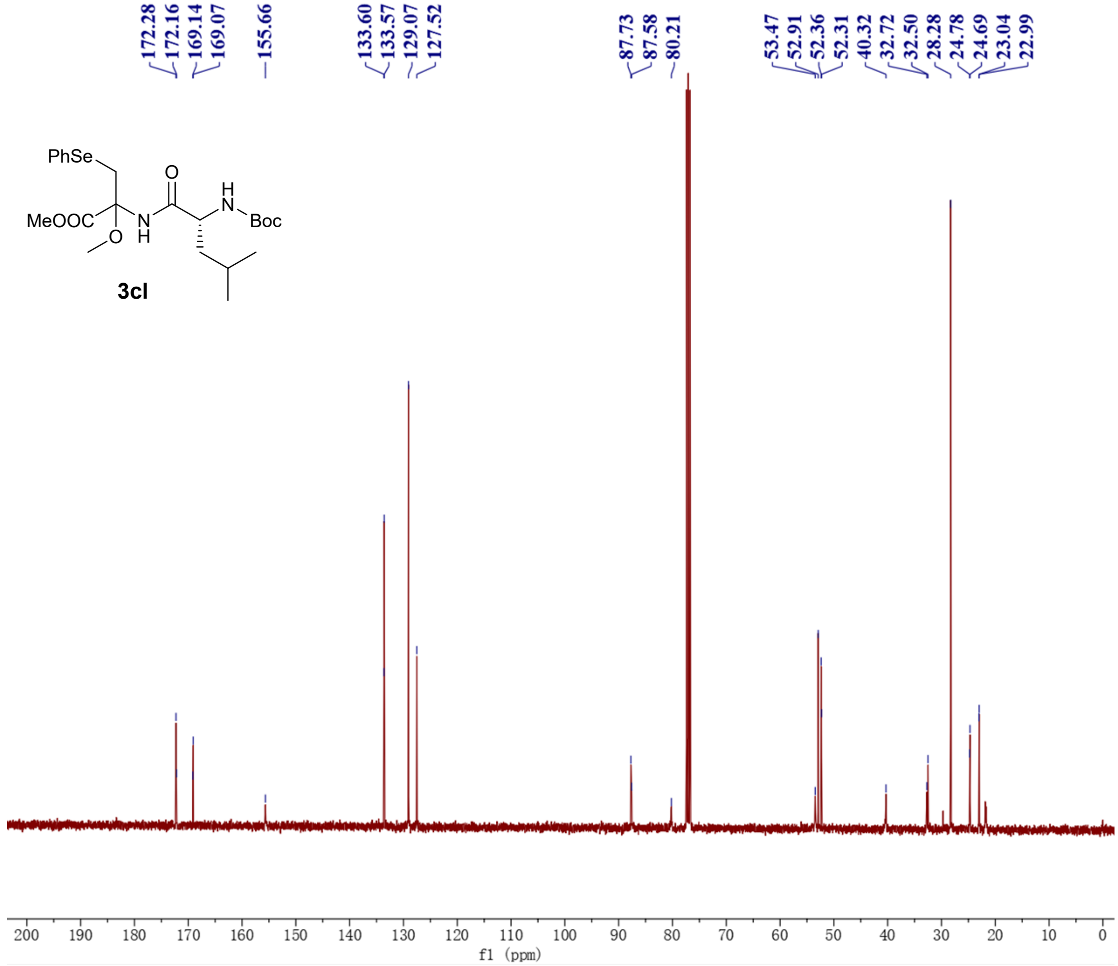
^{1}H and ^{13}C NMR spectra of **3ck**



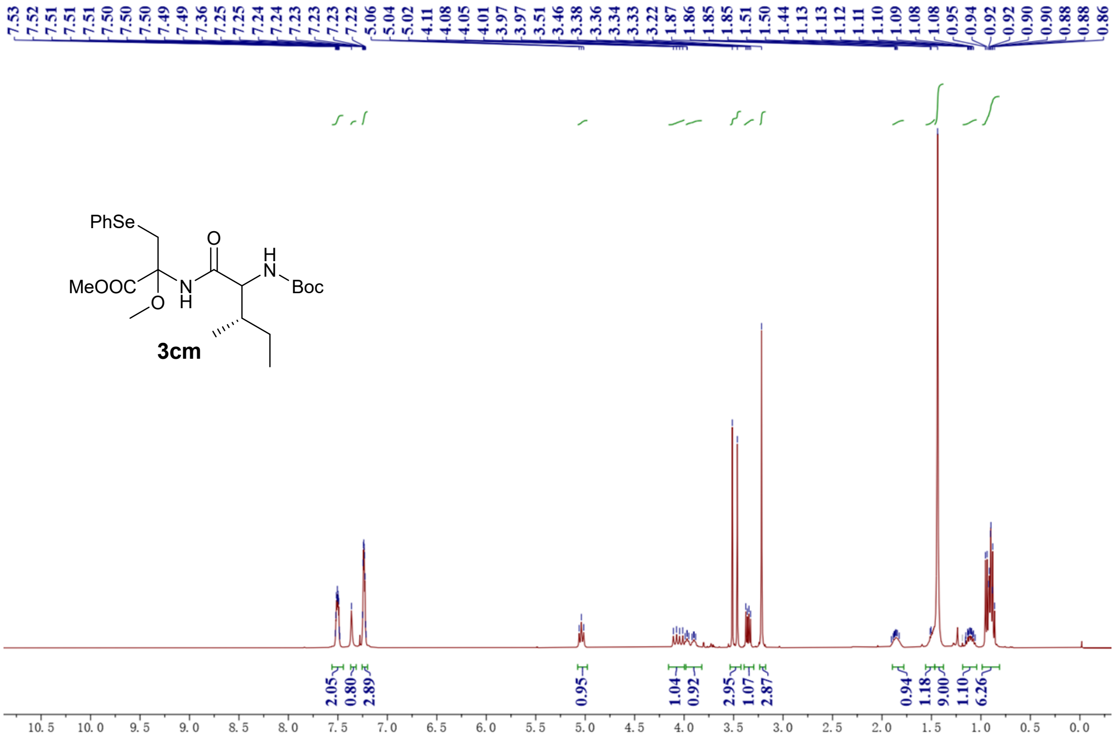


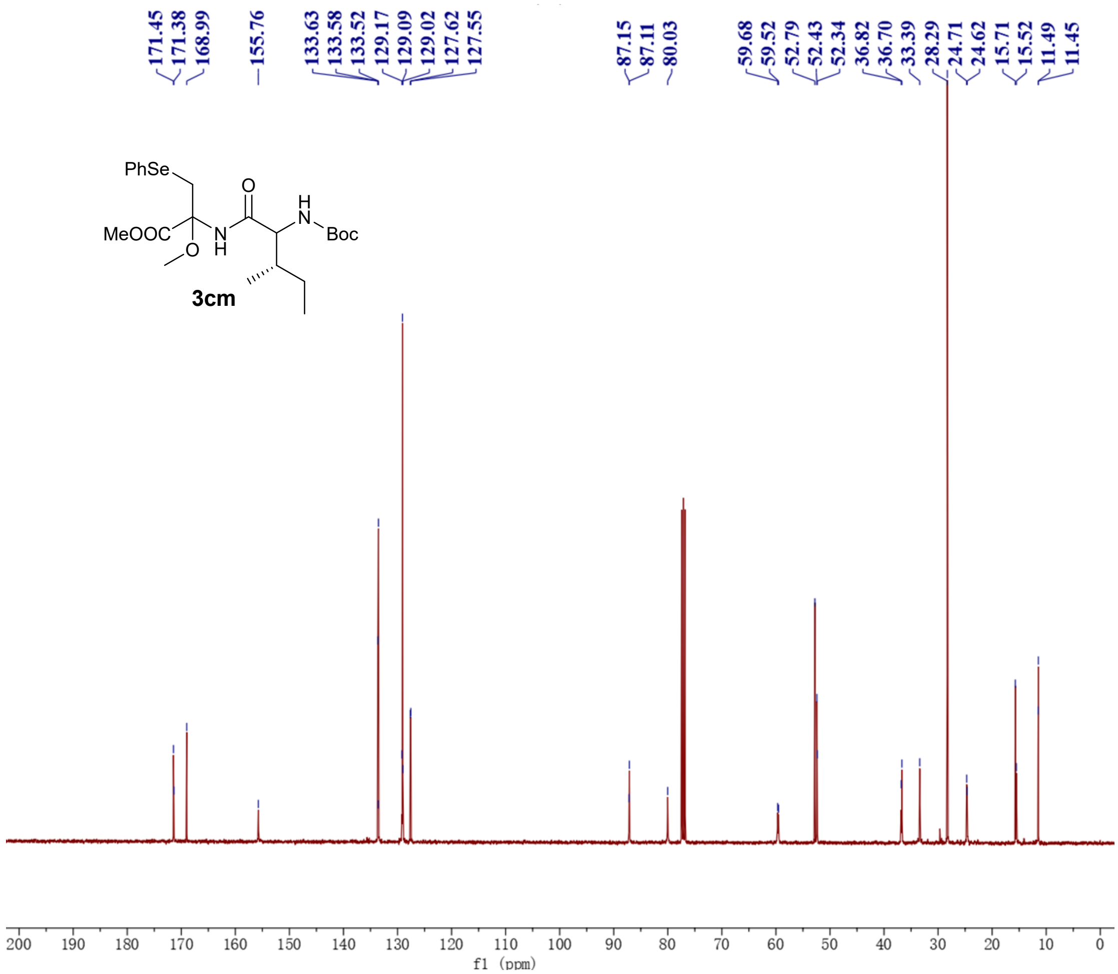
[1]H and [13]C NMR spectra of **3cl**



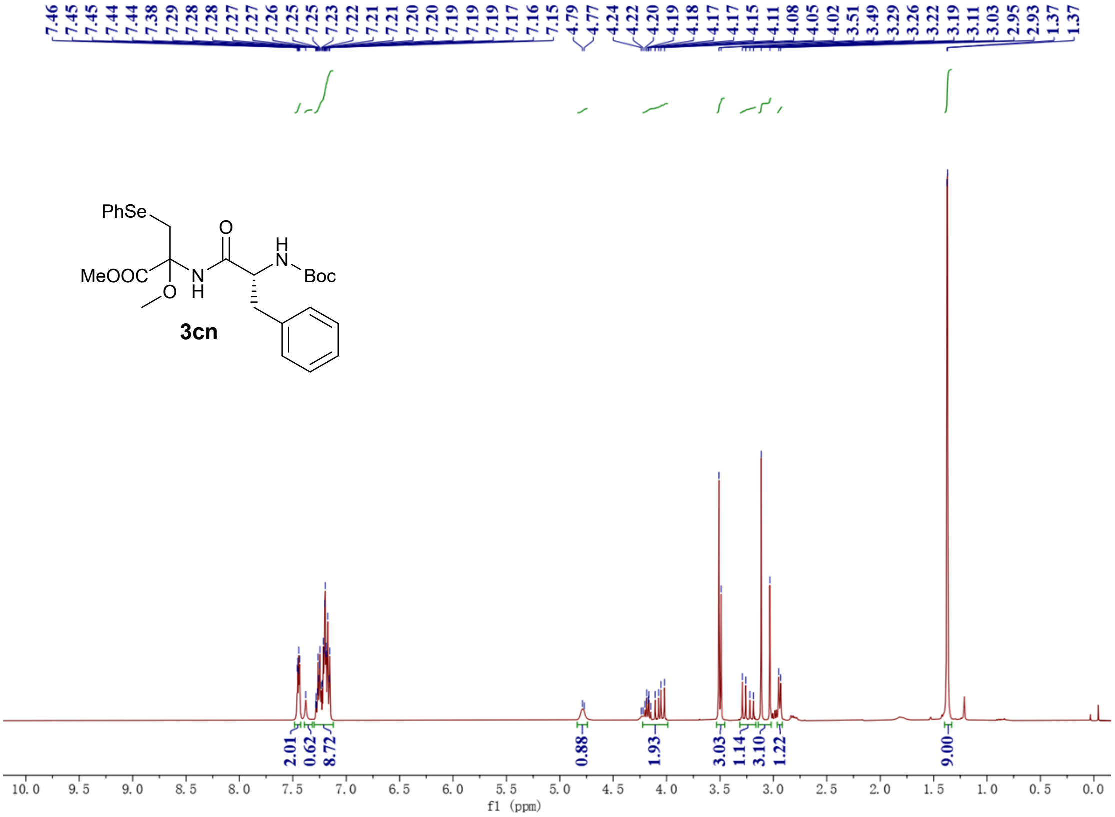


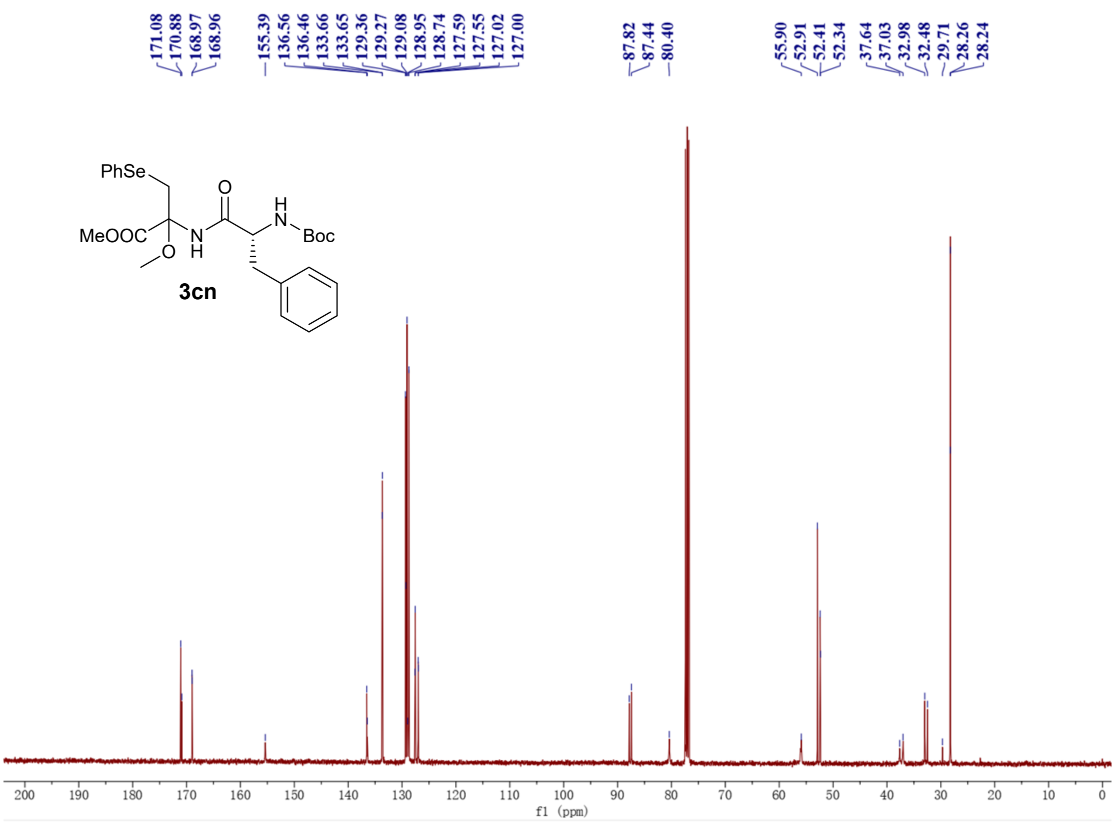
[1]H and [13]C NMR spectra of **3cm**



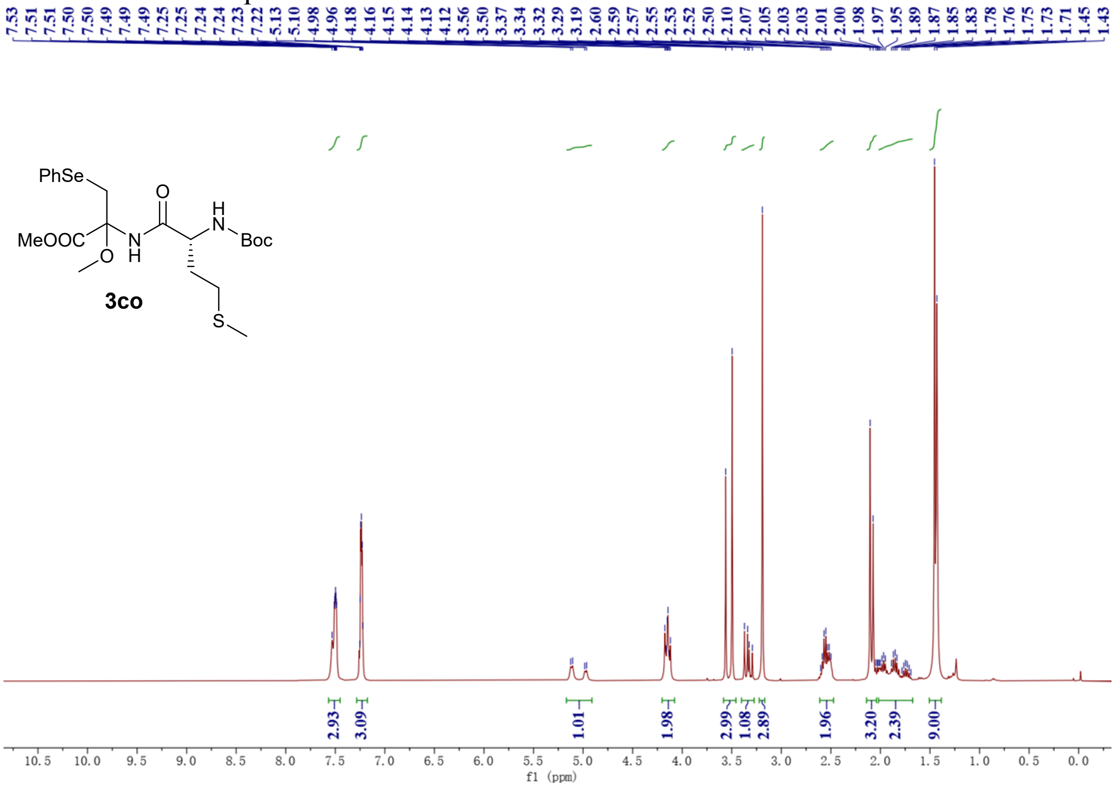


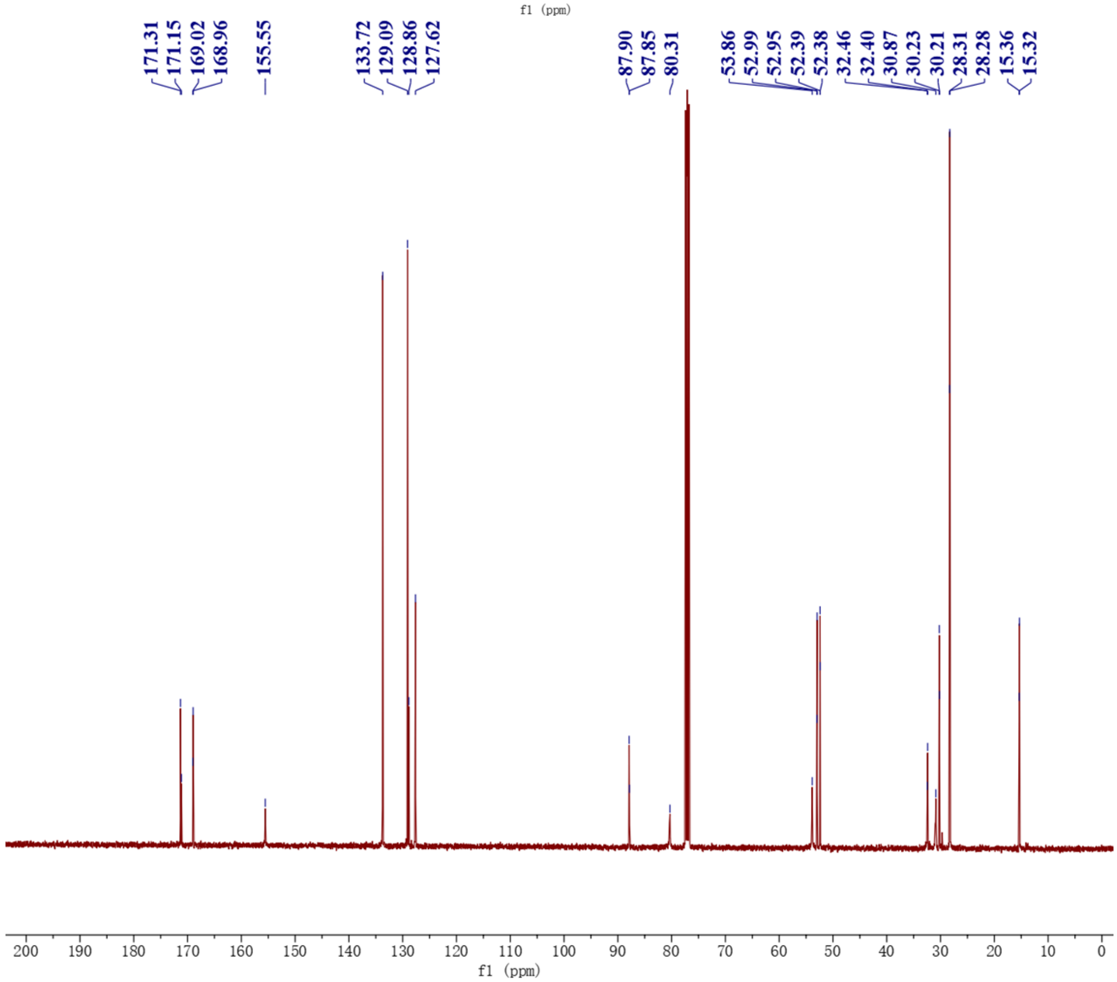
^{1}H and ^{13}C NMR spectra of **3cn**



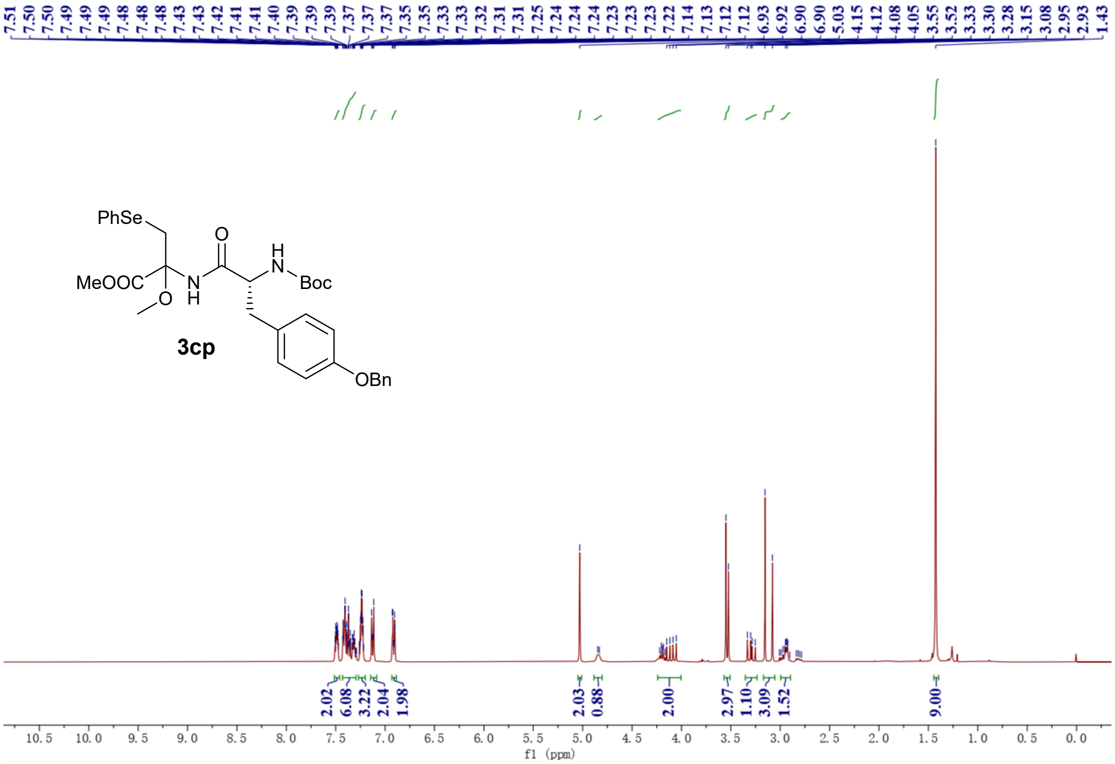


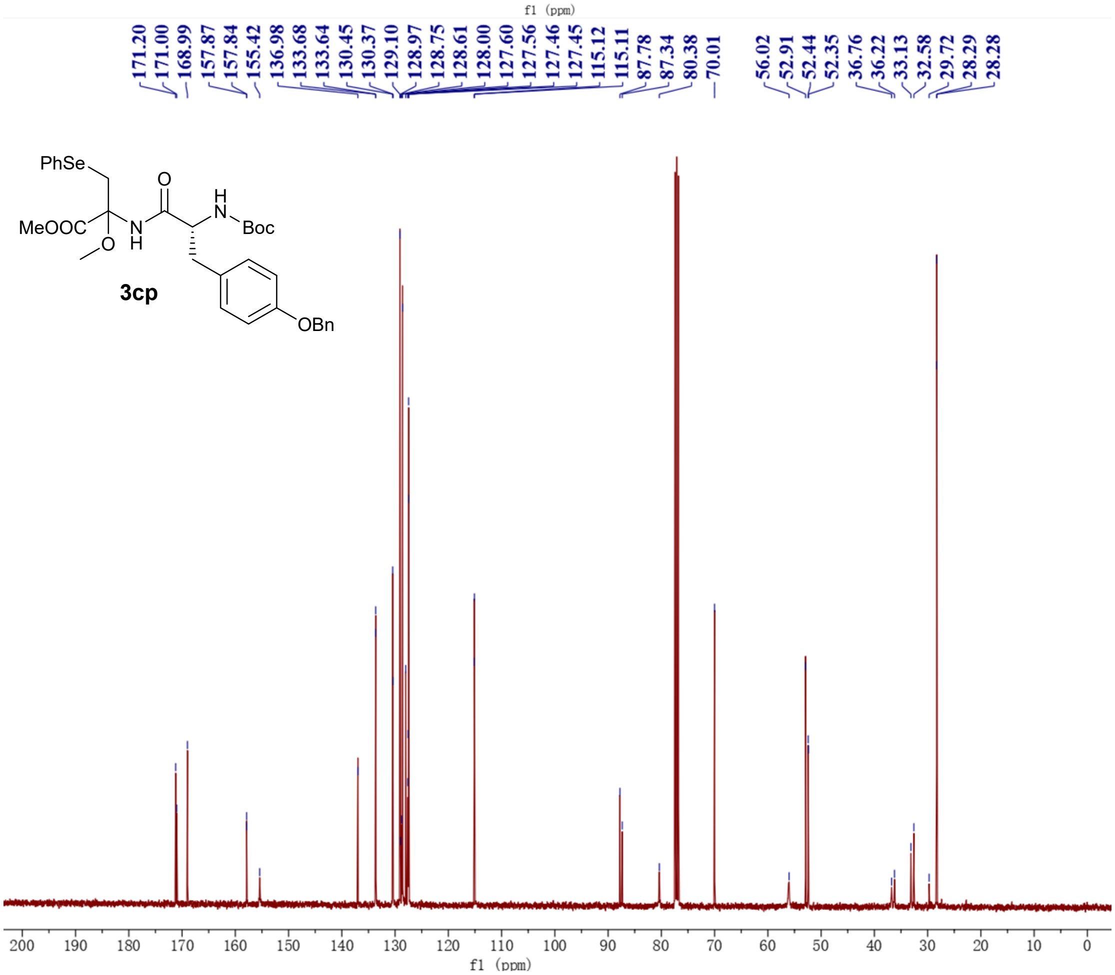
^{1}H and ^{13}C NMR spectra of **3co**



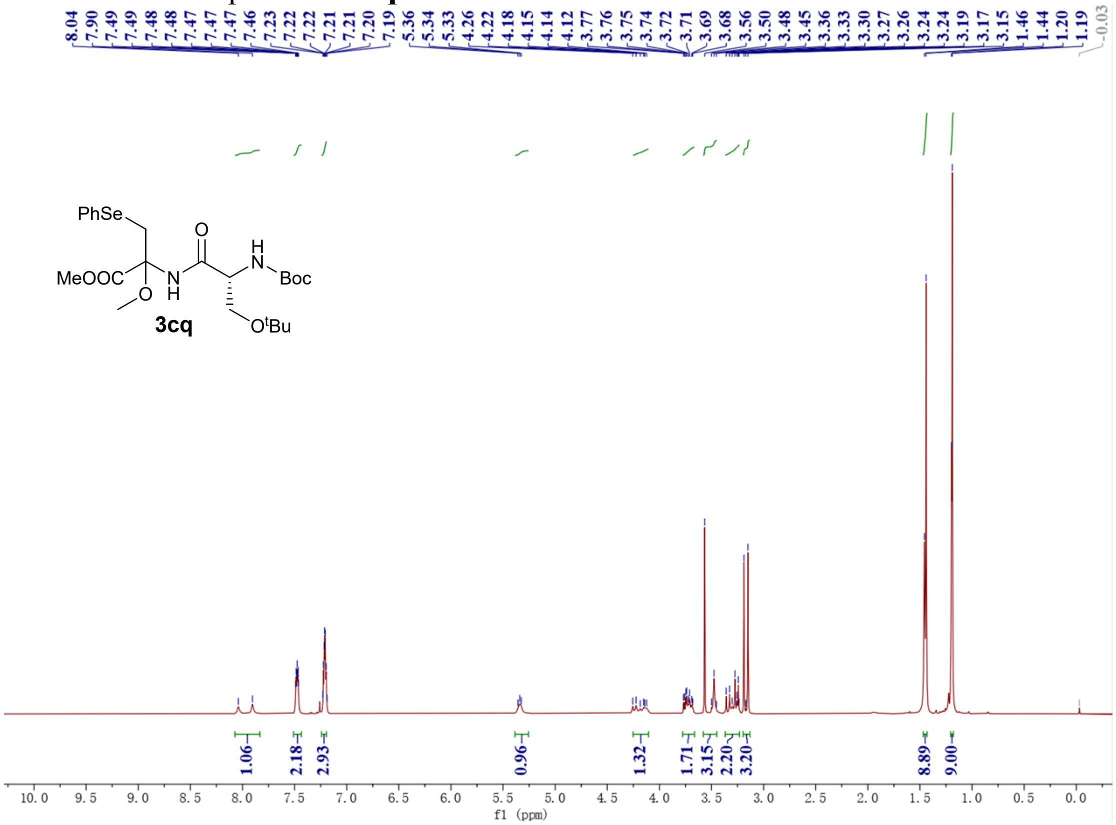


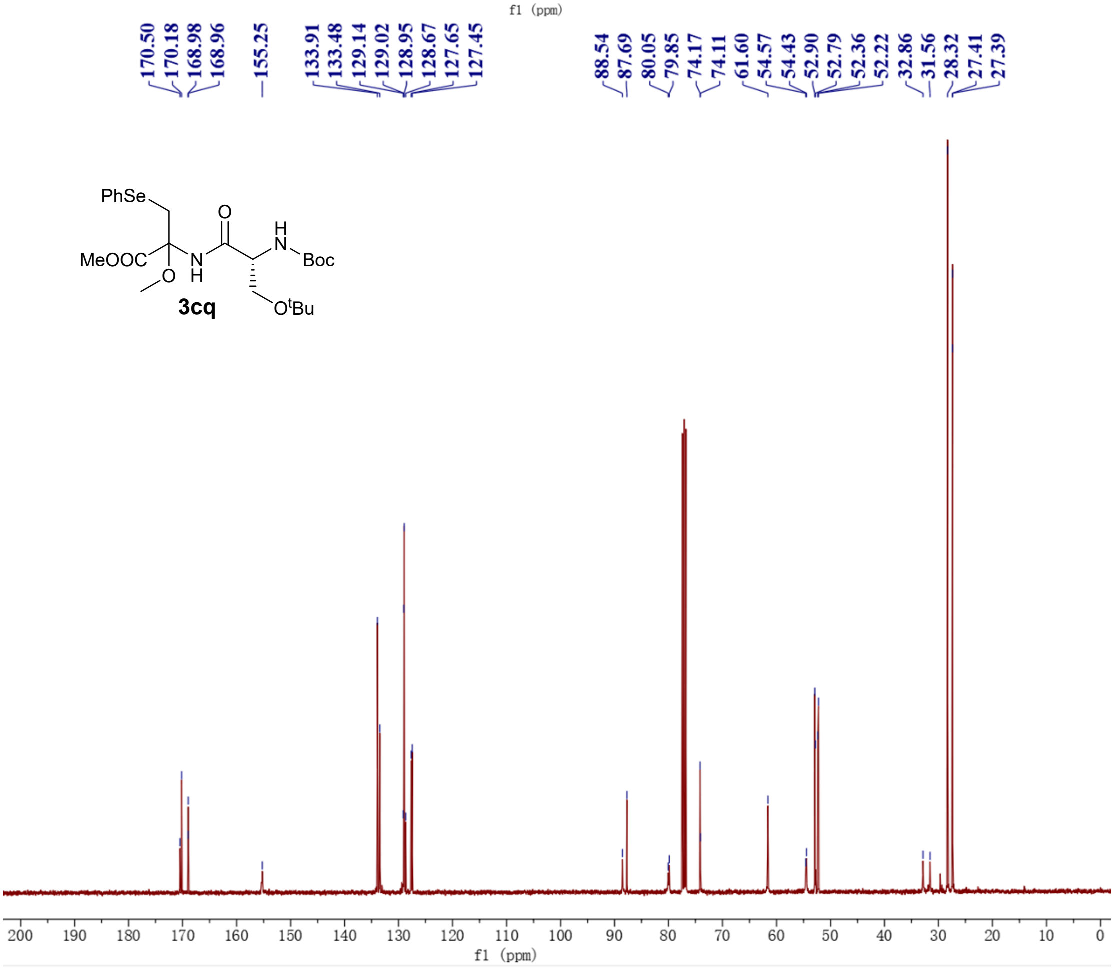
[1]H and [13]C NMR spectra of **3cp**



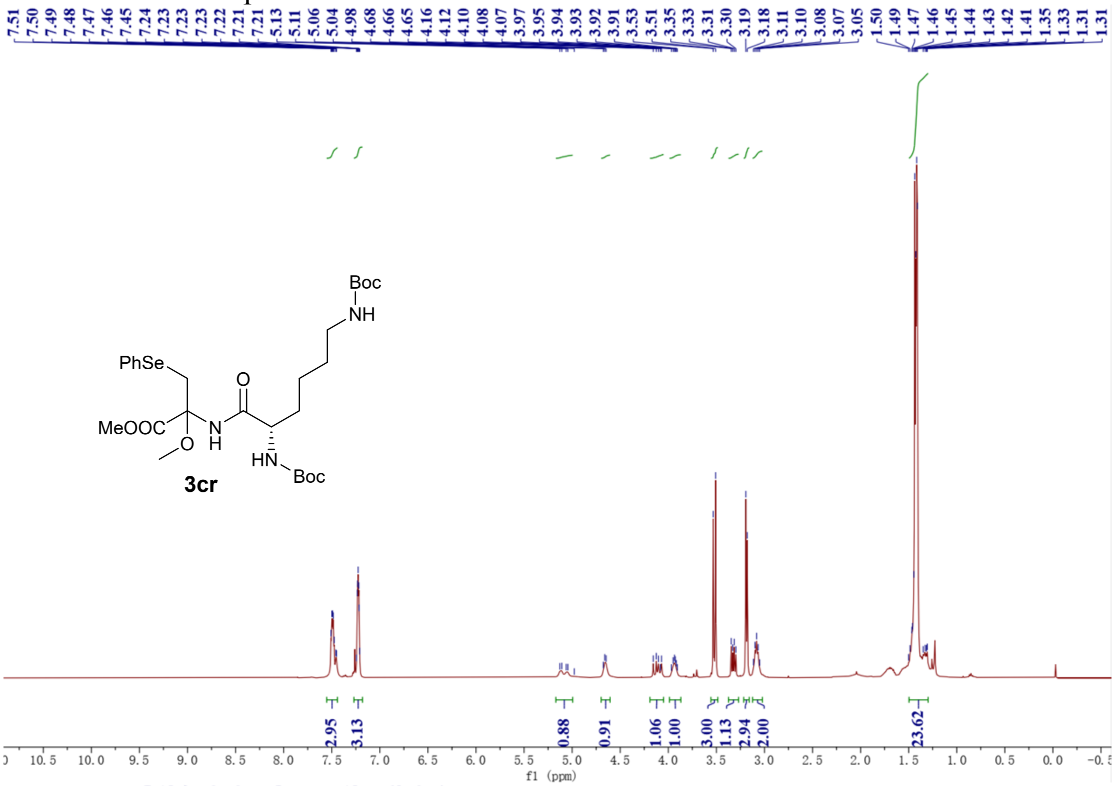


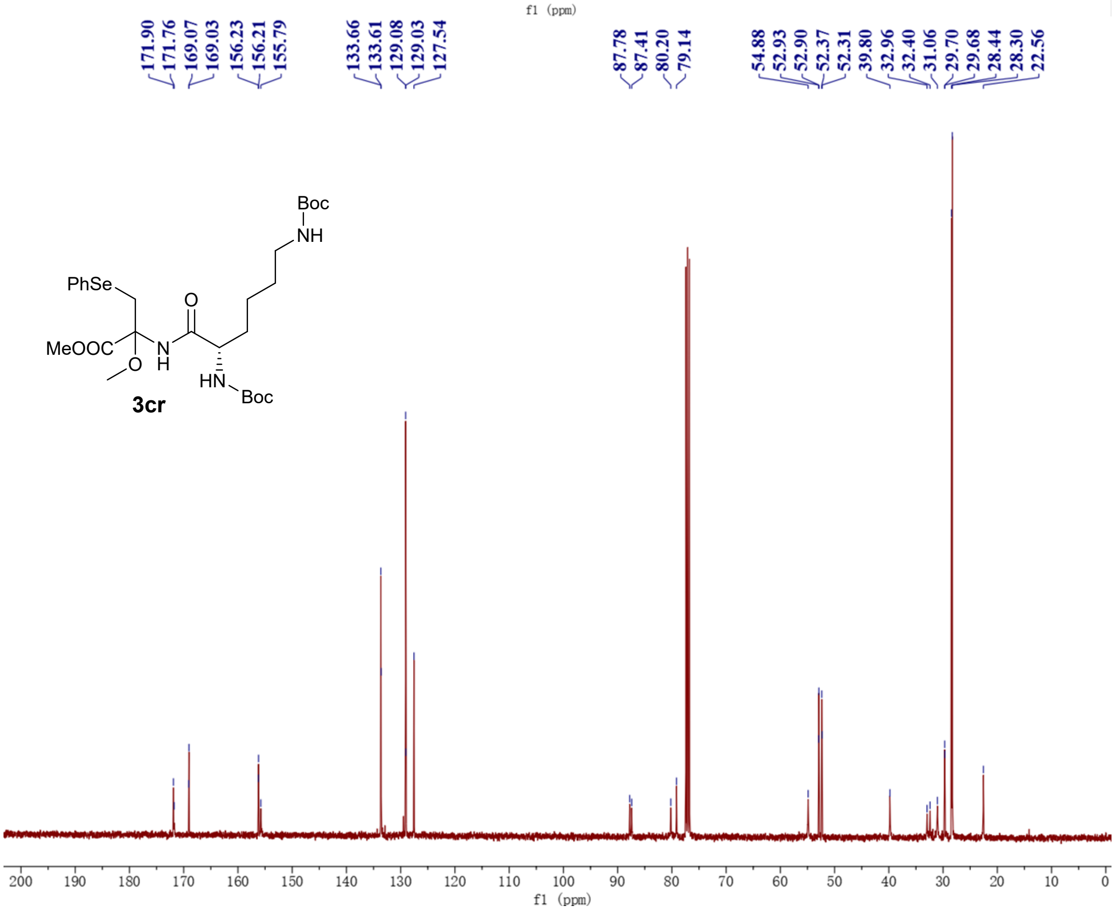
[1]H and [13]C NMR spectra of **3cq**

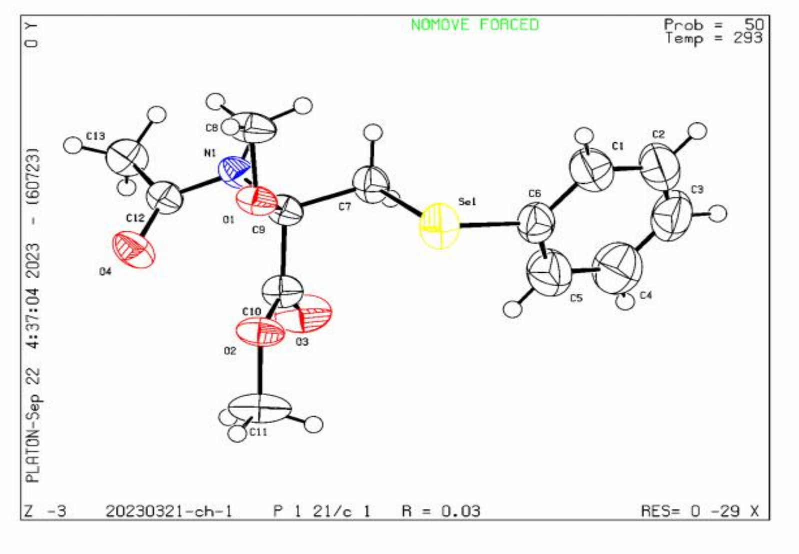


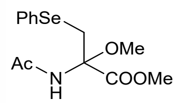


[1]H and [13]C NMR spectra of **3cr**









3ca

6. X-ray single-crystal data

Datablock:

Bond precision:	C-C = 0.0047 A		Wavelength=1.54184
Cell:	a=12.5578(3)	b=12.4264(3)	c=9.7765(2)
	alpha=90	beta=105.148(2)	gamma=90
Temperature:	293 K		

	Calculated	Reported
Volume	1472.60(6)	1472.60(6)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C13 H17 N O4 Se	C13 H17 N O4 Se
Sum formula	C13 H17 N O4 Se	C13 H17 N O4 Se
Mr	330.24	330.23
Dx,g cm-3	1.490	1.490
Z	4	4
Mu (mm-1)	3.550	3.550
F000	672.0	672.0
F000’	670.58	
h,k,lmax	15,15,12	15,15,11
Nref	3100	2939
Tmin,Tmax	0.639,0.653	0.777,1.000
Tmin’	0.579	

Correction method= # Reported T Limits: Tmin=0.777 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.948 Theta(max)= 76.573

R(reflections)= 0.0320(2466) wR2(reflections)= 0.0868(2939)

S = 1.057 Npar= 175

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

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a Alert level C

PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L= 0.600 5 Report

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a Alert level G

PLAT007_ALERT_5_G	Number of Unrefined Donor-H Atoms		1 Report
PLAT199_ALERT_1_G	Reported _cell_measurement_temperature	(K)	293 Check
PLAT200_ALERT_1_G	Reported _diffrn_ambient_temperature	(K)	293 Check
PLAT912_ALERT_4_G	Missing # of FCF Reflections Above STh/L=	0.600	133 Note
PLAT941_ALERT_3_G	Average HKL Measurement Multiplicity		3.8 Low
PLAT978_ALERT_2_G	Number C-C Bonds with Positive Residual Density.		1 Info

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0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
1 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
6 **ALERT level G** = General information/check it is not something unexpected

2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
1 ALERT type 2 Indicator that the structure model may be wrong or deficient
2 ALERT type 3 Indicator that the structure quality may be low
1 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check
