Supplementary Information

A Practical Approach for Oligopeptide Synthesis via Synergistic Photoredox, Cobaloxime, and Organophosphorus Triple Catalysis

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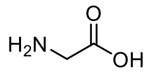
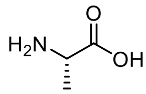
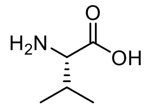
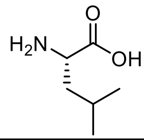
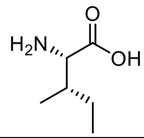
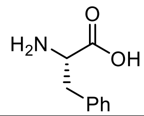
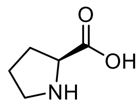
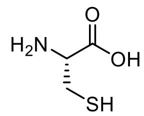
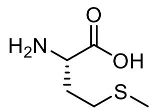
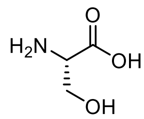
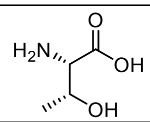
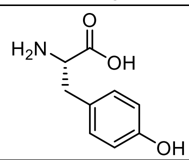
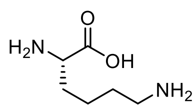
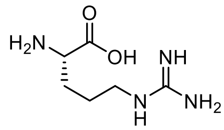
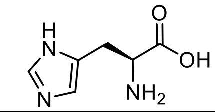
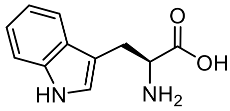
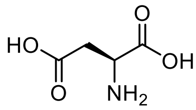
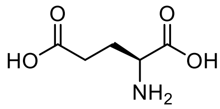
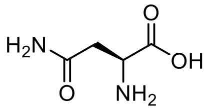
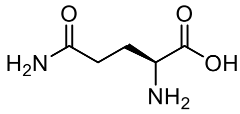
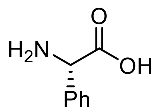
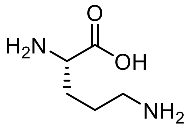
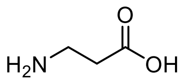
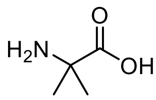
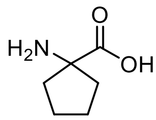
1. General Information

All reactions were performed in dry solvents under a N_2 atmosphere and anhydrous conditions. Acetonitrile (MeCN) was freshly distilled over CaH_2 prior to use. All other reagents were used as received from commercial sources. Pd/C was 10% palladium on carbon (wetted with ca. 55% water). Reactions were monitored through thin layer chromatography (TLC) on 0.25-mm silica gel plates and visualized with UV light (254 nm) and w.t.10% phosphomolybdic acid in ethanol solution. Flash column chromatography (FCC) was performed using silica gel. NMR spectra were recorded using Bruker Magnet System 400 Ascend instruments, calibrated to $CD(H)Cl_3$, DMSO-d_6, CD_3OD as the internal reference (7.26, 2.50, 3.31 and 77.0, 39.5, 49.0 ppm for ^1H and ^{13}C NMR spectra, respectively). ^1H NMR spectral data are reported in terms of chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectral data are reported in terms of chemical shift (δ, ppm). The following abbreviations indicate the multiplicities: s, singlet. d, doublet. t, triplet. q, quartet. m, multiplet. High-resolution mass spectra were obtained using Thermo Fisher Scientific Q Exactive Plus mass spectrometer with electrospray ionization (ESI) probe operating in positive ion mode or Thermo Fisher Scientific Exactive GC high-resolution orbitrap GC mass using electron impact. Gas chromatography (GC) was performed on a Techcomp GC 7900 instrument. High Performance Liquid Chromatography were obtained from SHIMADZU LC-2030 Plus. The photocatalysts $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$[1] and the cobaloximes $Co(dmgH)(dmgH_2)Cl$[2] were prepared according to previous reports.

The abbreviations and structures for all amino acids in the manuscript were shown below:

entry	abbreviation	amino acid	structure
1	Gly	glycine	
2	Ala	*L*-alanine	
3	Val	*L*-valine	
4	Leu	*L*-leucine	
5	Ile	*L*-isoleucine	
6	Phe	*L*-phenylalanine	
7	Pro	*L*-proline	
8	Cys	*L*-cysteine	
9	Met	*L*-methionine	
10	Ser	*L*-serine	
11	Thr	*L*-threonine	
12	Tyr	*L*-tyrosine	
13	Lys	*L*-lysine	

14	Arg	*L*-arginine	
15	His	*L*-histidine	
16	Trp	*L*-tryptophan	
17	Asp	*L*-aspartic acid	
18	Glu	*L*-glutamic acid	
19	Asn	*L*-asparagine	
20	Gln	*L*-glutamine	
21	Phg	*L*-phenylglycine	
22	Orn	*L*-ornithine	
23	β-Ala	β-alanine	
24	Aib	2-aminoisobutyric acid	
25	A_{c5c}	1-aminocyclopentane-1-carboxylic acid	

2. Reaction Optimization

2.1 Reaction setup

All the reactions were performed with an RLH-18 octet photocatalytic parallel reaction system (Figure S1), which was purchased from Beijing Roger tech Ltd. The reaction system was equipped with eight 456 nm 10 W blue light LEDs (Figure S2) and placed on a magnetic hotplate stirrer (DLAB MS-H-Pro[A]) to keep the reaction temperature at 65 °C.

Figure S1. Integrated photoreactor and associated equipment

Beijing Rogertech Ltd
http://www.rogertech.cn
Tel: +86(10)62966884
Fax:

RLH-18 10WLED Test report

Product Mark

Model: 1-455nm(456.7)@10W | Manufacture: Beijing Rogertech Ltd

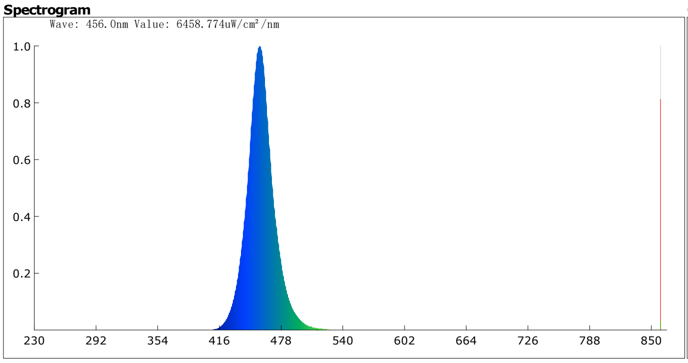
Temperature: 20°C | Humidity: 65%

Tester: Wu | Test Date: 2022-06-21,15:34:31

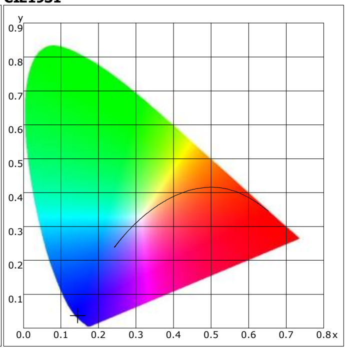
Parameter

Name	Value	Name	Value	Name	Value	Name	Value
ESuv(mW/cm²)	0.0000	CIE u,v	0.1839,0.0693	CIE1931 Y	130873.648		
Euvc(mW/cm²)	0.0000	CIE u',v'	0.1839,0.1039	CIE1931 Z	2949318.500		
Euvb(mW/cm²)	0.0000	SDCM	100.00	TLCI-2012	1		
Euva(mW/cm²)	0.0000	Ra	-63.7	Integral Time(ms)	0.1		
Euv(mW/cm²)	0.00	Ee(mW/cm²)	194.23262	Peak Signal	53258		
Eb(mW/cm²)	190.91	S/P	20.108	Dark Signal	2045		
Eg(mW/cm²)	1.67	Dominant(nm)	461.30	Compensate level	2878		
Er(mW/cm²)	0.00	Purity(%)	98.5				
Eir(mW/cm²)	0.00	HalfWidth(nm)	25.2				
E(lx)	89386.70	Peak(nm)	456.7				
Candle E(fc)	8304.23	Center(nm)	457.4				
CCT(K)	100000	Centroid(nm)	458.5				
Duv	-0.05186	Color Ratio(RGB)	0.0,12.1,87.9				
CIE x,y	0.1446,0.0363	CIE1931 X	520893.188				

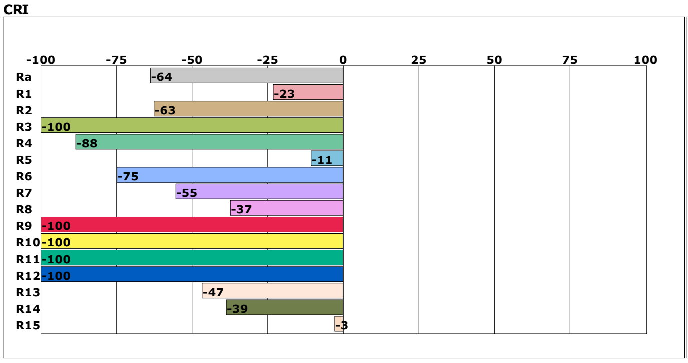
Spectrogram

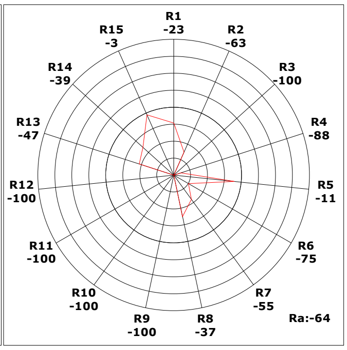


CIE1931



CRI





Instrument Status

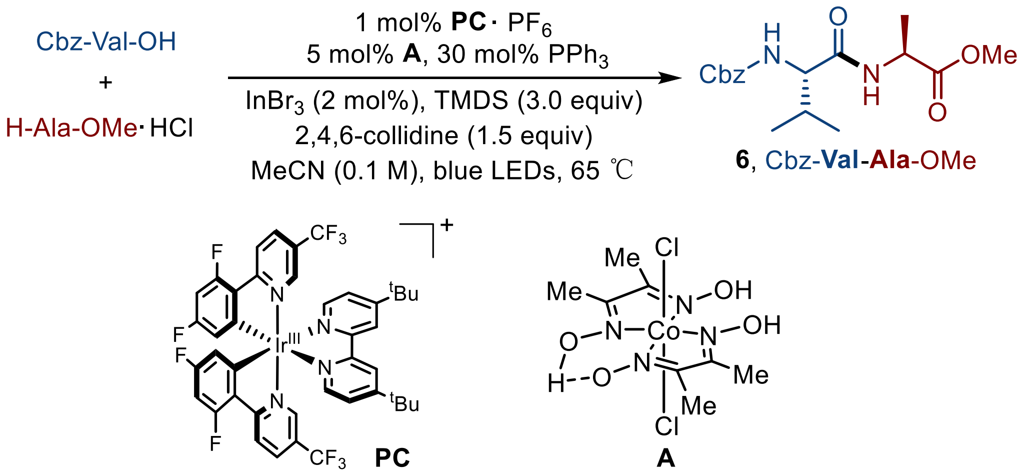
Type: OHSP-350UV | SN: 0 | Scan Range: 230-850nm

Integral Time: 0.077ms | VPeak: 53258 | VDark: 2045

Remark:

Figure S2. RLH-18 10W LED Test Report

2.2 General procedure

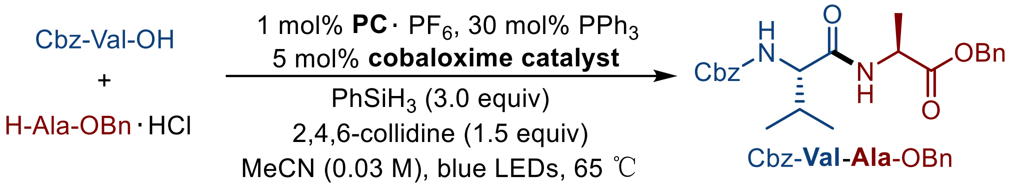


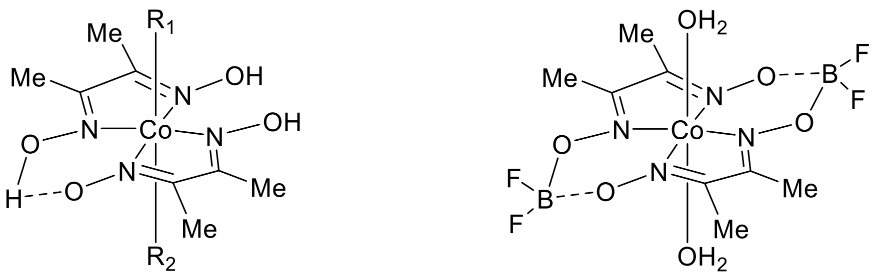
$Ir(dF(CF_3)ppy)_2(dtbbpy)^+$ cobaloxime

To an oven-dried reaction tube equipped with a stir bar was added Cbz-*L*-Val-OH (0.2 mmol, 1.0 equiv.), *L*-Ala-OMe·HCl (0.3 mmol, 1.5 equiv.), PPh_3 (0.06 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The tube was sealed and placed under nitrogen before MeCN (2 mL), TMDS (0.6 mmol, 3.0 equiv.) and 2,4,6-collidine (0.3 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 12 h. Upon complete consumption of the starting material, the reaction mixture was concentrated and purified through column chromatography to afford the desired peptide product.

2.3 Optimization details

Table S1. Screening of cobaloxime catalysts





Co^III-A; R_1 = R_2 = Cl; $Co(dmgH)(dmgH_2)Cl_2$

Co^III-B; R_1 = Cl; R_2 = Py; $Co(dmgH)_2PyCl$

Co^III-C; R_1 = Cl; R_2 = 4-OMePy; $Co(dmgH)_2$(4-OMePy)Cl

Co^III-D; R_1 = Cl; R_2 = 4-NMe_2Py; $Co(dmgH)_2$(4-NMe_2Py)Cl

Co^III-E; R_1 = Cl; R_2 = 4-CNPy; $Co(dmgH)_2$(4-CNPy)Cl

Co^III-F; R_1 = Cl; R_2 = 4-COMePy; $Co(dmgH)_2$(4-COMePy)Cl

Co^III-G; R_1 = Cl; R_2 = 4-COOMePy; $Co(dmgH)_2$(4-COOMePy)Cl

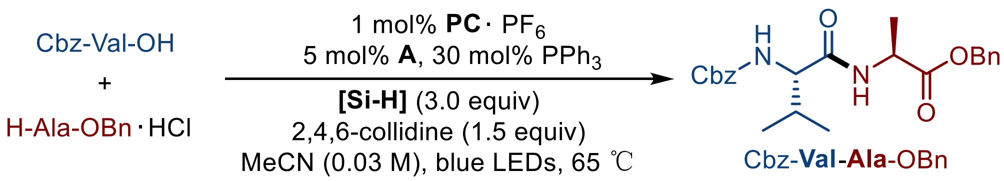
Co^III-H; R_1 = R_2 = Py; $Co(dmgH)(dmgH_2)Py_2$

Co^II-I; $Co(dmgBF_2)_2(H_2O)_2$

entry	**cobaloxime catalyst**	yield(%)[a]
1	**A**	49
2	**B**	43
3	**C**	42
4	**D**	42
5	**E**	40
6	**F**	45
7	**G**	38
8	**H**	46
9	**I**	trace

[a]Yields of isolated products.

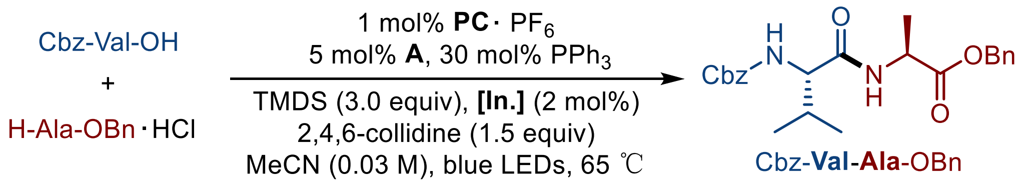
Table S2. Screening of hydrosilanes



entry	[Si-H]	yield(%)[a]
1	$PhSiH_3$	49
2[b]	$PhSiH_3$	55
3[c]	$PhSiH_3$	39
4	Ph_2SiH_2	35
5	Ph_3SiH	30
6[d]	$(EtO)_2MeSiH$	22
7[b]	$(EtO)_3SiH$	44
8[b]	Et_3SiH	60
9[d]	PMHS	25
10	TMDS	46
11[b]	TMDS	77
12[c]	TMDS	37

[a]Yields of isolated products. [b]$InBr_3$ (2 mol%) was added. [c]$Ti(O^iPr)_4$ (10 mol%) was added. [d]bis-(4-nitrophenyl)phosphate (15 mol%) was added.

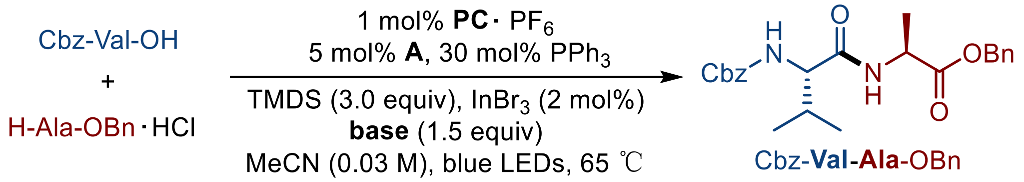
Table S3. Screening of additives



entry	[In.]	yield(%)[a]
1	$InCl_3$	38
2	InI_3	63
3	$In_2(SO_4)_3$	37
4	$In(OTf)_3$	36
5	$In(acac)_3$	35
6	$InAc_3{\cdot}6H_2O$	37
7	$In(NO_3)_3{\cdot}xH_2O$	32
8	$InBr_3$	77
9	$InBr_3$	66
10	$InBr_3$	71
11	$InBr_3$	65

[a]Yields of isolated products. [b]$InBr_3$ (1 mol%) was added. [c]$InBr_3$ (5 mol%) was added. [d]$InBr_3$ (10 mol%) was added.

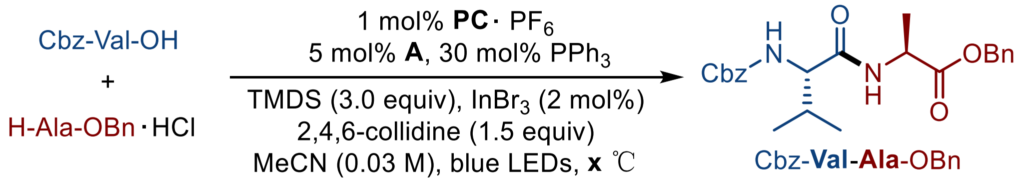
Table S4. Screening of bases



entry	**base**	yield(%)[a]
1	2,4,6-collidine	77
2	2,6-lutidine	66
3	DBU	67
4	K_2HPO_4	63
5	Na_2HPO_4	60
6	$NaHCO_3$	67

[a]Yields of isolated products.

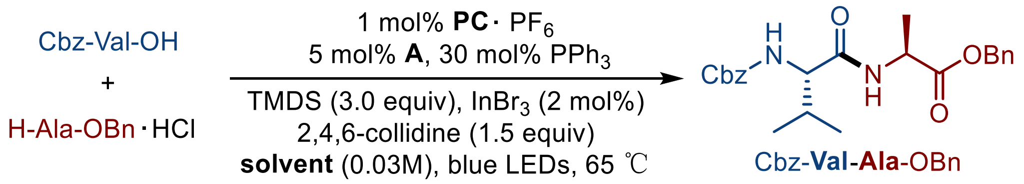
Table S5. Screening of temperature



entry	**x** °C	yield(%)[a]
1	25	41
2	50	40
3	65	77
4	80	68

[a]Yields of isolated products.

Table S6. Screening of solvent

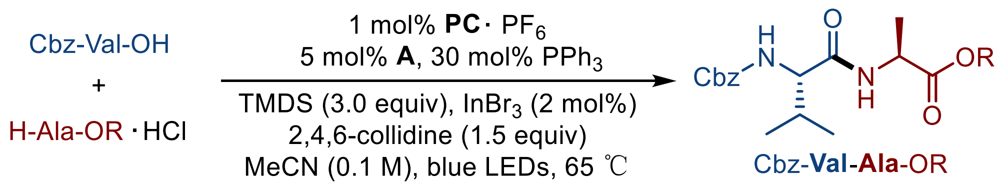


entry	**solvent**	yield(%)[a]
1	DCE	62
2	THF	trace
3	1,4-dioxane	N.D.
4	DMF	N.D.

5	DMSO	N.P.
6	MeCN	77
7[b]	MeCN	65
8[c]	MeCN	81
9[d]	MeCN	71

[a]Yields of isolated products. [b]MeCN (0.05M). [c]MeCN (0.1M). [d]MeCN (0.2M).

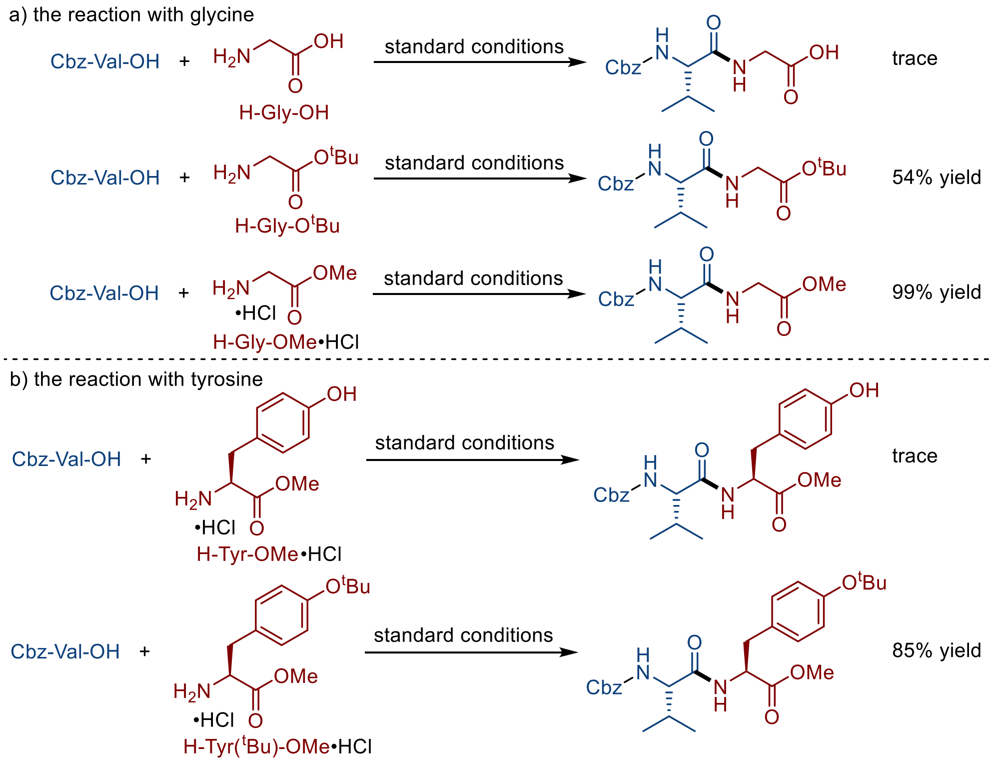
Table S7. Screening of protecting groups

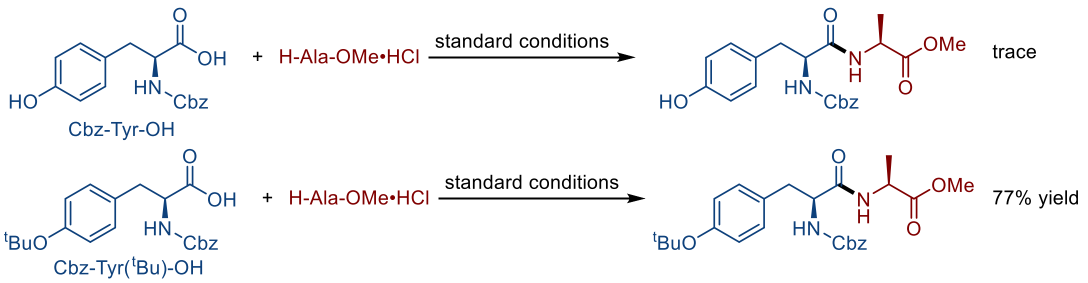


entry	R	yield(%)[a]
1	Bzl	81
2	^{t}Bu	83
3	Et	77
4	Me	86

[a]Yields of isolated products.

Meanwhile, a series of unprotected amino acids were investigated. As shown in Figure S3, the reaction with unprotected tyrosine (Tyr) and arginine (Arg) led to a complicated mixture, and the yields of the target dipeptides were significantly reduced.





c) the reaction with arginice

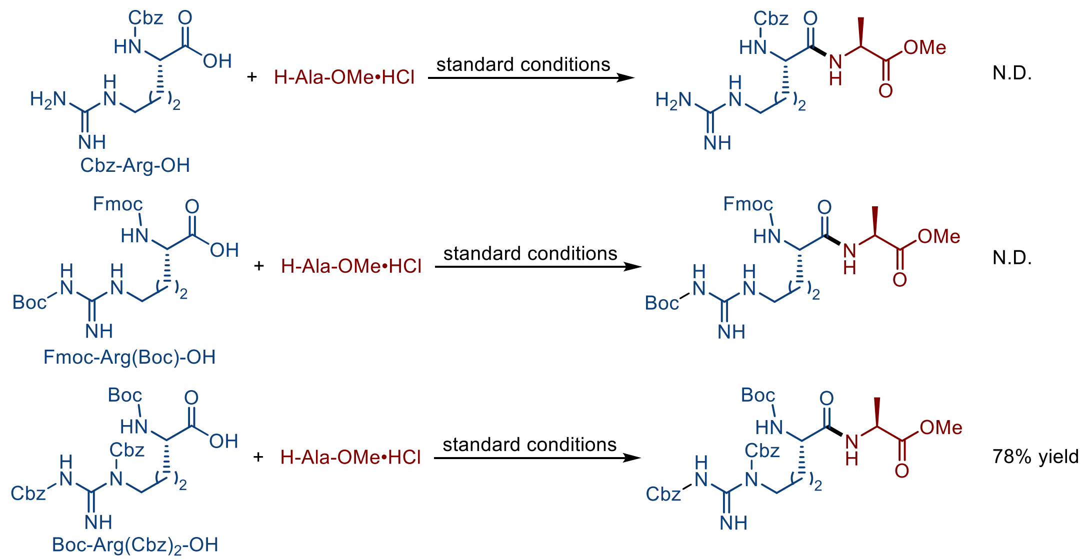
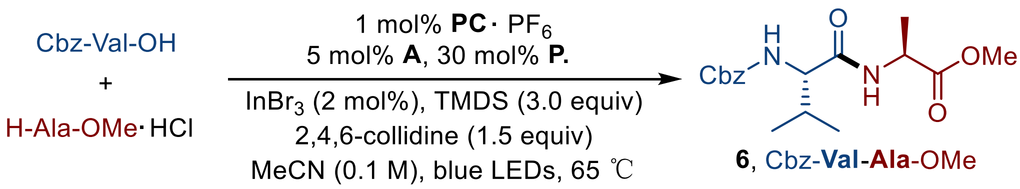
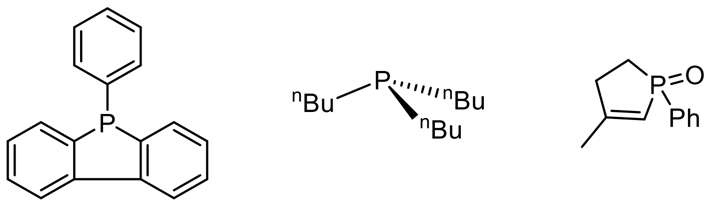


Figure S3. The reactions with unprotected amino acids

Table S8. Screening of phosphines



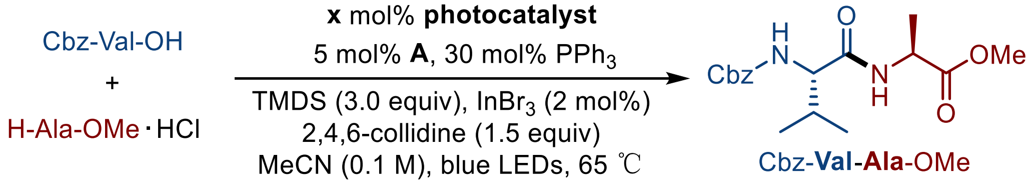


P-1 **P-2** **P-3**

entry	P.	yield(%)[a]
1	PPh_3	86
2	$Ph_3P=O$	53
3	**P-1**	57
4	**P-2**	45
5	**P-3**	trace

[a]Yields of isolated products.

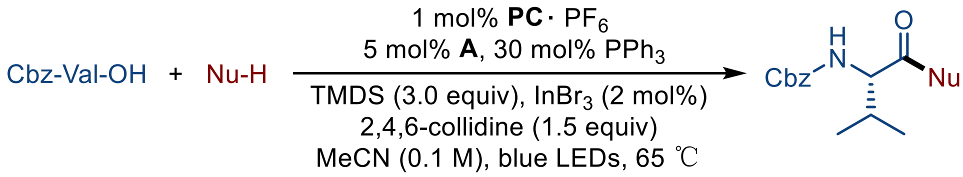
Table S9. Screening of photocatalysts

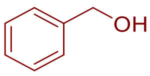
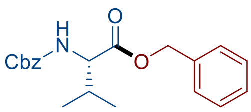
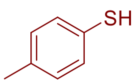
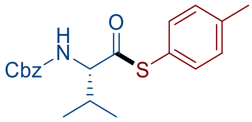
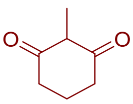
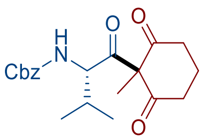


entry	**photocatalyst**	**x**	yield (%)[a]
1	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	1	86
2	$Ir(ppy)_3$	1	trace
3	$[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$	1	55
4	$Ru(bpy)_3{\cdot}6H_2O$	1	trace
5	$Ru(bpz)_3(PF_6)_2$	1	trace
6	4-CzIPN	5	23
7	$Mes\text{-}Acr^+BF_4^-$	5	20
8[b]	EosinY-2Na	5	16

[a]Yields of isolated products. [b]Irradiated by green LED lamps.

Table S10. Studying of nucleophiles



entry	Nu-H	product	yield (%)[a]
1			89
2			15
3			38

[a]Yields of isolated products.

2.4 Comparative experiments

In our previous work, we reported a photocatalytic strategy for the formation of acyloxyphosphonium ions that enabled direct amidation. Hence, comparative experiments were conducted in Figure S4. The yield of the reaction between sterically hindered Cbz-Val-OH and H-Ala-OMe•HCl improved from 41% to 86% with the triple catalytic system, indicating that the current process was more efficient.

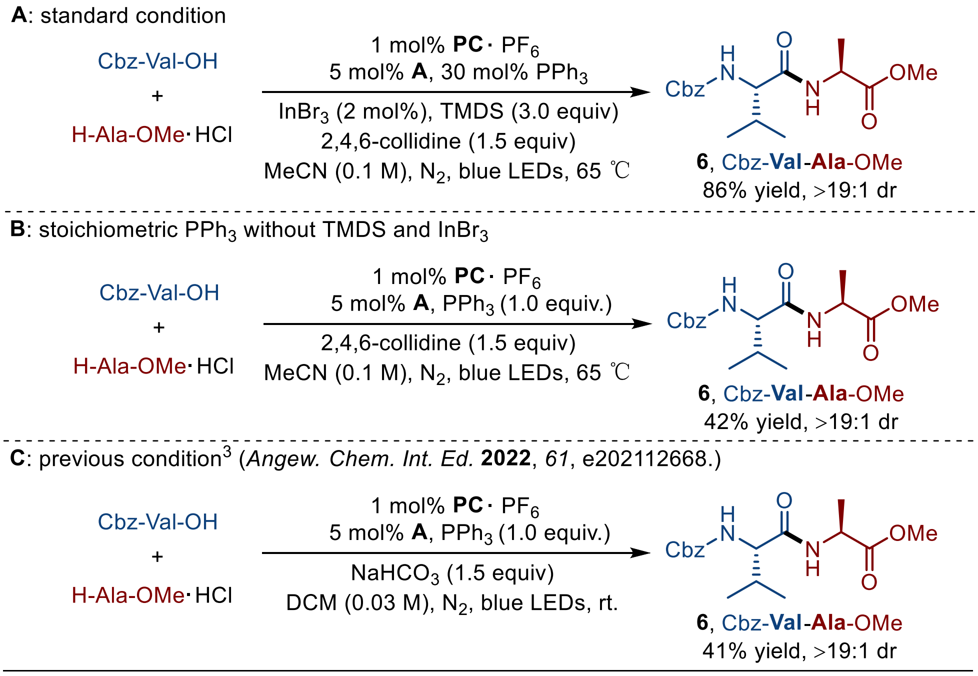
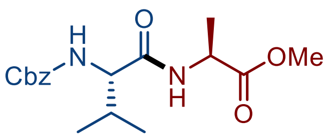


Figure S4. Comparative experiments

2.5 Characterization data

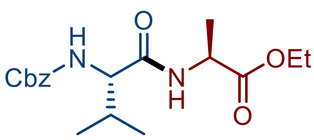
Cbz-Val-Ala-OMe



6

White solid, m.p.: 154 – 157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.09 (m, 5H), 6.76 (d, J = 4.0 Hz, 1H), 5.60 (d, J = 8.0 Hz, 1H), 5.25 – 4.98 (m, 2H), 4.74 – 4.44 (m, 1H), 4.20 – 3.97 (m, 1H), 3.73 (s, 3H), 2.21 – 2.00 (m, 1H), 1.38 (d, J = 8.0 Hz, 3H), 1.08 – 0.79 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 171.0, 156.4, 136.2, 128.5, 128.1, 128.0, 67.0, 60.1, 52.4, 48.0, 31.3, 19.0, 18.0, 17.8. HRMS-ESI: calcd for $C_{17}H_{25}N_2O_5^+$ ([M + H]$^+$) m/z 337.17580, found 337.17426.

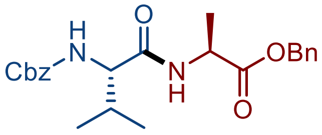
Cbz-Val-Ala-OEt



6a

White solid, m.p.: 162 – 163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.19 (m, 5H), 7.11 (d, J = 4.0 Hz, 1H), 5.86 (d, J = 8.0 Hz, 1H), 5.23 – 4.92 (m, 2H), 4.64 – 4.44 (m, 1H), 4.33 – 3.96 (m, 3H), 2.16 – 2.02 (m, 1H), 1.36 (d, J = 8.0 Hz, 3H), 1.25 (t, J = 8.0 Hz, 3H), 0.98 (d, J = 4.0 Hz, 3H), 0.94 (d, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.2, 156.5, 136.3, 128.4, 128.0, 127.9, 66.8, 61.3, 60.1, 48.0, 31.4, 19.1, 18.0, 17.9, 14.0. HRMS-ESI: calcd for $C_{18}H_{27}N_2O_5^+$ ([M + H]$^+$) m/z 351.19145, found 351.19000.

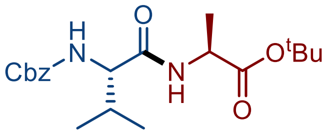
Cbz-Val-Ala-OBzl



6b

White solid, m.p.: 153 – 155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.13 (m, 10H), 7.01 (d, *J* = 8.0 Hz, 1H), 5.73 (d, *J* = 8.0 Hz, 1H), 5.30 – 4.89 (m, 4H), 4.62 (p, *J* = 8.0 Hz, 1H), 4.25 – 3.94 (m, 1H), 2.15 – 1.95 (m, 1H), 1.35 (d, *J* = 8.0 Hz, 3H), 0.94 (d, *J* = 8.0 Hz, 3H), 0.90 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 171.2, 156.5, 136.3, 135.3, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 67.1, 66.9, 60.1, 48.0, 31.4, 19.1, 18.0. HRMS-ESI: calcd for $C_{23}H_{29}N_2O_5^+$ ([M + H]$^+$) *m/z* 413.20710, found 413.20516.

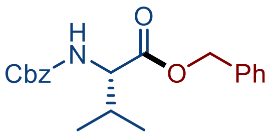
Cbz-Val-Ala-O^{t}Bu



6c

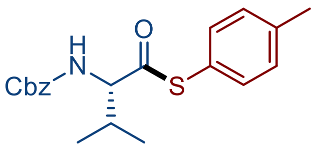
Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.15 (m, 5H), 7.03 (d, *J* = 8.0 Hz, 1H), 5.86 (d, *J* = 12.0 Hz, 1H), 5.26 – 4.87 (m, 2H), 4.46 (p, *J* = 8.0 Hz, 1H), 4.25 – 4.01 (m, 1H), 2.20 – 1.98 (m, 1H), 1.44 (s, 9H), 1.33 (d, *J* = 4.0 Hz, 3H), 0.98 (d, *J* = 4.0 Hz, 3H), 0.93 (d, *J* = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 171.0, 156.5, 136.4, 128.4, 128.0, 127.9, 81.7, 66.8, 60.1, 48.6, 31.4, 27.9, 19.2, 18.2, 17.9. HRMS-ESI: calcd for $C_{20}H_{31}N_2O_5^+$ ([M + H] $^+$) *m/z* 379.22275, found 379.22106.

benzyl ((benzyloxy)carbonyl)-L-valinate



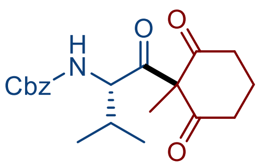
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.04 (m, 10H), 5.33 (d, *J* = 8.0 Hz, 1H), 5.22 – 4.97 (m, 4H), 4.36 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.29 – 1.98 (m, 1H), 0.94 (d, *J* = 8.0 Hz, 3H), 0.84 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 156.3, 136.3, 135.3, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 77.4, 77.3, 77.1, 76.8, 67.0, 59.0, 31.3, 19.0, 17.4. HRMS-ESI: calcd for $C_{19}H_{22}NO_4^+$ ([M + H]$^+$) *m/z* 342.16998, found 342.16962.

***S*-(*p*-tolyl) (*S*)-2-(((benzyloxy)carbonyl)amino)-3-methylbutanethioate**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.29 (m, 5H), 7.29 – 7.09 (m, 4H), 5.28 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 2H), 4.59 – 4.21 (m, 1H), 2.51 – 2.18 (m, 4H), 1.04 (d, *J* = 8.0 Hz, 3H), 0.92 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 156.2, 139.9, 136.1, 134.5, 130.1, 128.6, 128.3, 128.1, 123.4, 67.3, 65.6, 31.2, 21.3, 19.4, 16.8. HRMS-ESI: calcd for $C_{20}H_{23}NO_3SNa^+$ ([M + H]$^+$) *m/z* 380.12909, found 380.12903.

benzyl (*S*)-(3-methyl-1-(1-methyl-2,6-dioxocyclohexyl)-1-oxobutan-2-yl) carbamate

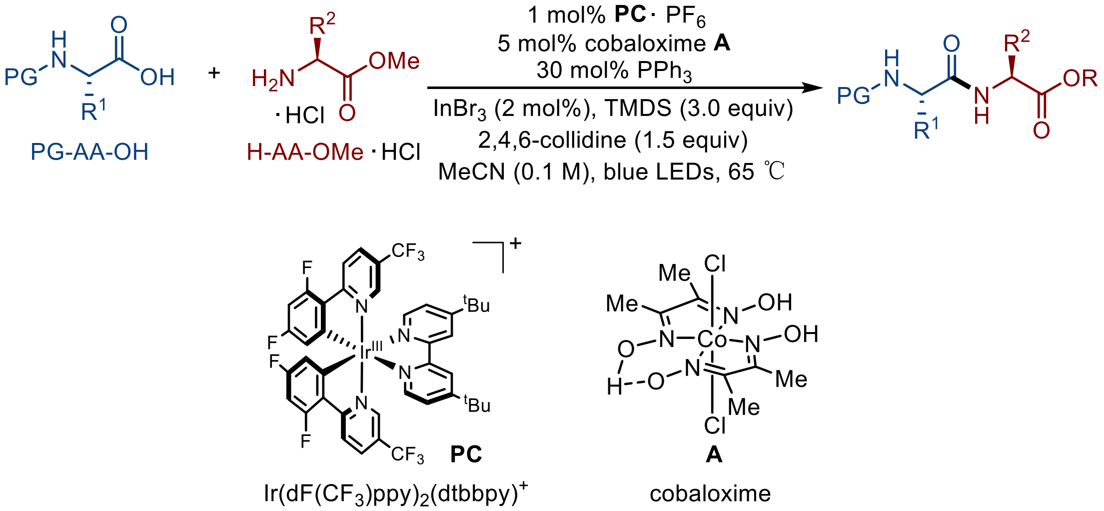


Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.22 (m, 5H), 5.25 (d, *J* = 8.0 Hz, 1H), 5.13 (s, 2H), 4.45 – 4.21 (m, 1H), 2.72 – 2.15 (m, 5H), 2.12 – 1.87 (m, 2H), 1.66 (s, 3H), 1.07 (d, *J* = 8.0 Hz, 3H), 0.98 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$)

δ 199.0, 169.0, 163.8, 156.2, 136.0, 128.6, 128.3, 128.2, 125.1, 67.3, 59.2, 36.9, 30.9, 28.4, 20.8, 19.2, 17.4, 8.4. HRMS-ESI: calcd for $C_{20}H_{25}NO_5Na^+$ ($[M + H]^+$) *m/z* 382.16249, found 382.16196.

3. Dipeptide Synthesis

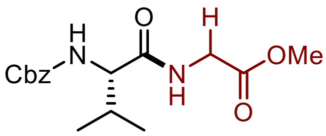
3.1 General procedure



To an oven-dried reaction tube equipped with a stir bar was added protected amino acid (0.5 mmol, 1.0 equiv.), amino acid ester hydrochloride (0.75 mmol, 1.5 equiv.), PPh_3 (0.15 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The tube was sealed and placed under nitrogen before MeCN (5 mL), TMDS (1.5 mmol, 3.0 equiv.) and 2,4,6-collidine (0.75 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 12 to 20 h. Upon complete consumption of the starting material, the reaction mixture was concentrated and purified through column chromatography to afford the desired dipeptide product.

3.2 Characterization data

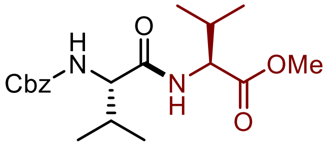
Cbz-Val-Gly-OMe



8

White solid, m.p.: 154 – 158 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.15 (m, 5H), 7.01 (s, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 5.22 – 4.95 (m, 2H), 4.28 – 4.09 (m, 1H), 4.10 – 3.85 (m, 2H), 3.71 (s, 3H), 2.27 – 1.99 (m, 1H), 1.07 – 0.77 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 170.1, 156.5, 136.2, 128.5, 128.1, 127.9, 67.0, 60.2, 52.2, 41.0, 31.1, 19.1, 17.8. HRMS-ESI: calcd for $C_{16}H_{23}N_2O_5^+$ ($[M + H]^+$) *m/z* 323.16015, found 323.15857.

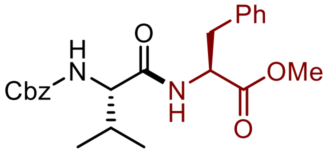
Cbz-Val-Val-OMe



9

White solid, m.p.: 104 – 106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.16 (m, 5H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.70 (d, *J* = 8.0 Hz, 1H), 5.26 – 4.96 (m, 2H), 4.55 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.37 – 4.02 (m, 1H), 3.71 (s, 3H), 2.29 – 1.92 (m, 2H), 1.18 – 0.55 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 171.6, 156.5, 136.4, 128.4, 128.0, 127.8, 66.9, 60.2, 57.1, 52.0, 31.2, 31.0, 19.1, 18.9, 18.0, 17.8. HRMS-ESI: calcd for $C_{19}H_{29}N_2O_5^+$ ($[M + H]^+$) *m*/*z* 365.20710, found 365.20552.

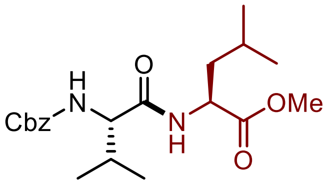
Cbz-Val-Phe-OMe



10

White solid, m.p.: 144 – 146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.27 (m, 5H), 7.27 – 7.16 (m, 3H), 7.08 (d, *J* = 4.0 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 5.52 (d, *J* = 8.0 Hz, 1H), 5.29 – 4.98 (m, 2H), 4.89 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.26 – 3.94 (m, 1H), 3.67 (s, 3H), 3.27 – 2.87 (m, 2H), 2.22 – 1.93 (m, 1H), 1.14 – 0.61 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.1, 156.3, 136.3, 135.7, 129.2, 128.6, 128.5, 128.1, 128.0, 127.1, 67.0, 60.2, 53.2, 52.3, 37.9, 31.2, 19.1, 17.8. HRMS-ESI: calcd for $C_{23}H_{29}N_2O_5^+$ ($[M + H]^+$) *m*/*z* 413.20710, found 413.20530.

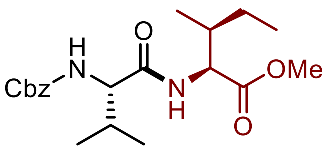
Cbz-Val-Leu-OMe



11

Light yellow solid, m.p.: 101 – 104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.12 (m, 5H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.60 (d, *J* = 8.0 Hz, 1H), 5.27 – 4.97 (m, 2H), 4.72 – 4.48 (m, 1H), 4.22 – 3.99 (m, 1H), 3.71 (s, 3H), 2.23 – 1.95 (m, 1H), 1.77 – 1.58 (m, 2H), 1.58 – 1.44 (m, 1H), 0.97 (d, *J* = 8.0 Hz, 3H), 0.95 – 0.74 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 171.2, 156.4, 136.3, 128.5, 128.1, 127.9, 66.9, 60.1, 52.2, 50.7, 41.2, 31.4, 24.8, 22.7, 21.8, 19.0, 17.9. HRMS-ESI: calcd for $C_{20}H_{31}N_2O_5^+$ ($[M + H]^+$) *m*/*z* 379.22275, found 379.22109.

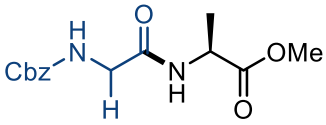
Cbz-Val-Ile-OMe



12

White solid, m.p.: 120 – 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.15 (m, 5H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.71 (d, *J* = 12.0 Hz, 1H), 5.27 – 4.95 (m, 2H), 4.59 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.29 – 3.99 (m, 1H), 3.71 (s, 3H), 2.19 – 1.99 (m, 1H), 1.96 – 1.79 (m, 1H), 1.51 – 1.32 (m, 1H), 1.24 – 1.09 (m, 1H), 1.05 – 0.69 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.4, 156.4, 136.3, 128.4, 128.0, 127.8, 66.9, 60.1, 56.4, 52.0, 37.6, 31.3, 25.1, 19.1, 17.9, 15.4, 11.5. HRMS-ESI: calcd for $C_{20}H_{31}N_2O_5^+$ ($[M + H]^+$) *m*/*z* 379.22275, found 379.22107.

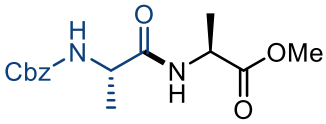
Cbz-Gly-Ala-OMe



13

Light yellow solid, m.p.: 89 – 92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.19 (m, 5H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.95 (s, 1H), 5.10 (s, 2H), 4.56 (p, *J* = 8.0 Hz, 1H), 3.89 (d, *J* = 4.0 Hz, 2H), 3.69 (s, 3H), 1.36 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 169.0, 156.7, 136.2, 128.5, 128.1, 128.0, 67.0, 52.4, 48.0, 44.3, 17.9. HRMS-ESI: calcd for $C_{14}H_{19}N_2O_5^+$ ([M + H]$^+$) *m/z* 295.12885, found 295.12753.

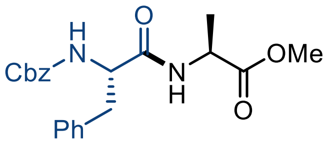
Cbz-Ala-Ala-OMe



14

White solid, m.p.: 90 – 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.17 (m, 5H), 7.06 (d, *J* = 4.0 Hz, 1H), 5.81 (d, *J* = 8.0 Hz, 1H), 5.21 – 4.98 (m, 2H), 4.55 (p, *J* = 8.0 Hz, 1H), 4.44 – 4.20 (m, 1H), 3.71 (s, 3H), 1.36 (t, *J* = 4.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.2, 156.0, 136.2, 128.5, 128.1, 127.9, 66.9, 52.4, 50.3, 48.0, 18.8, 18.0. HRMS-ESI: calcd for $C_{15}H_{21}N_2O_5^+$ ([M + H]$^+$) *m/z* 309.14450, found 309.14284.

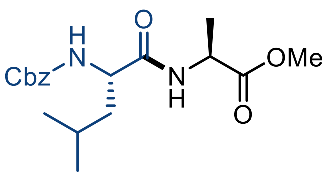
Cbz-Phe-Ala-OMe



15

White solid, m.p.: 128 – 131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.03 (m, 10H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.62 (d, *J* = 8.0 Hz, 1H), 5.16 – 4.95 (m, 2H), 4.65 – 4.37 (m, 2H), 3.68 (s, 3H), 3.15 – 2.93 (m, 2H), 1.31 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 170.8, 156.0, 136.3, 136.2, 129.3, 128.6, 128.5, 128.1, 127.9, 127.0, 67.0, 56.0, 52.4, 48.1, 38.6, 18.1. HRMS-ESI: calcd for $C_{21}H_{25}N_2O_5^+$ ([M + H]$^+$) *m/z* 385.17580, found 385.17407.

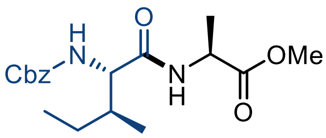
Cbz-Leu-Ala-OMe



16

White solid, m.p.: 93 – 95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.51 (d, *J* = 8.0 Hz, 1H), 5.26 – 4.99 (m, 2H), 4.56 (p, *J* = 8.0 Hz, 1H), 4.42 – 4.13 (m, 1H), 3.74 (s, 3H), 1.83 – 1.60 (m, 2H), 1.58 – 1.47 (m, 1H), 1.37 (d, *J* = 8.0 Hz, 3H), 1.07 – 0.75 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.0, 156.2, 136.2, 128.5, 128.1, 128.0, 66.9, 53.3, 52.4, 48.0, 41.6, 24.6, 22.9, 21.9, 18.0. HRMS-ESI: calcd for $C_{18}H_{27}N_2O_5^+$ ([M + H]$^+$) *m/z* 351.19145, found 351.18976.

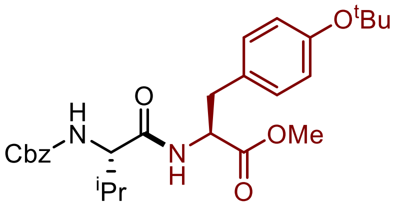
Cbz-Ile-Ala-OMe



17

White solid, m.p.: 119 –122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.17 (m, 5H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.80 (d, *J* = 8.0 Hz, 1H), 5.24 – 4.91 (m, 2H), 4.68 – 4.40 (m, 1H), 4.15 (t, *J* = 8.0 Hz, 1H), 3.71 (s, 3H), 1.95 – 1.72 (m, 1H), 1.64 – 1.46 (m, 1H), 1.36 (d, *J* = 8.0 Hz, 3H), 1.21 – 1.08 (m, 1H), 1.02 – 0.67 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 171.3, 156.4, 136.3, 128.4, 128.0, 127.9, 66.9, 59.4, 52.3, 47.9, 37.6, 24.7, 17.8, 15.2, 11.2. HRMS-ESI: calcd for $C_{18}H_{27}N_2O_5^+$ ($[M + H]^+$) *m*/*z* 351.19145, found 351.19052.

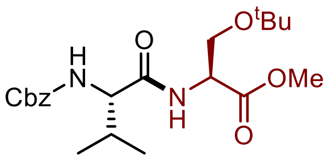
Cbz-Val-Tyr(^{t}Bu)-OMe



18

White solid, m.p.: 116 – 118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.16 (m, 5H), 7.01 (d, *J* = 8.0 Hz, 3H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.79 (d, *J* = 12.0 Hz, 1H), 5.29 – 4.93 (m, 2H), 4.84 (dd, *J* = 12.0, 8.0 Hz, 1H), 4.30 – 3.97 (m, 1H), 3.61 (s, 3H), 3.02 (d, *J* = 8.0 Hz, 2H), 2.17 – 1.95 (m, 1H), 1.30 (s, 9H), 1.02 – 0.69 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 171.2, 156.4, 154.4, 136.4, 130.6, 129.6, 128.4, 128.0, 127.9, 124.1, 78.2, 66.9, 60.2, 53.4, 52.1, 37.4, 31.2, 28.8, 19.0, 17.9. HRMS-ESI: calcd for $C_{27}H_{37}N_2O_6^+$ ($[M + H]^+$) *m*/*z* 485.26461, found 485.26261.

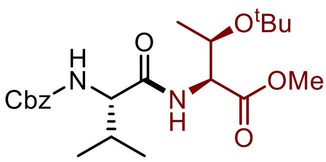
Cbz-Val-Ser(^{t}Bu)-OMe



19

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.17 (m, 5H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.62 (d, *J* = 8.0 Hz, 1H), 5.30 – 4.96 (m, 2H), 4.81 – 4.61 (m, 1H), 4.24 – 4.00 (m, 1H), 3.81 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.72 (s, 3H), 3.54 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.22 – 2.06 (m, 1H), 1.12 (s, 9H), 1.02 – 0.75 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.6, 156.3, 136.3, 128.4, 128.0, 127.9, 73.4, 66.9, 61.7, 60.0, 52.8, 52.3, 31.6, 27.2, 19.0, 17.6. HRMS-ESI: calcd for $C_{21}H_{33}N_2O_6^+$ ($[M + H]^+$) *m*/*z* 409.23331, found 409.23149.

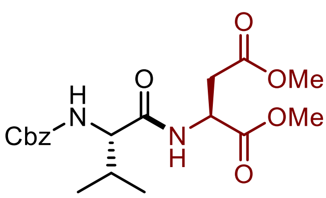
Cbz-Val-Thr(^{t}Bu)-OMe



20

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.23 (m, 5H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.52 (d, *J* = 8.0 Hz, 1H), 5.22 – 5.01 (m, 2H), 4.49 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.32 – 4.07 (m, 2H), 3.68 (s, 3H), 2.22 (dd, *J* = 12.0, 8.0 Hz, 1H), 1.16 (d, *J* = 4.0 Hz, 3H), 1.10 (s, 9H), 1.00 (d, *J* = 4.0 Hz, 3H), 0.95 (d, *J* = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.9, 156.2, 136.3, 128.5, 128.1, 128.0, 74.0, 67.2, 66.9, 60.2, 57.8, 52.1, 31.1, 28.2, 28.2, 21.0, 19.2, 17.4. HRMS-ESI: calcd for $C_{22}H_{35}N_2O_6^+$ ($[M + H]^+$) *m*/*z* 423.24896, found 423.24698.

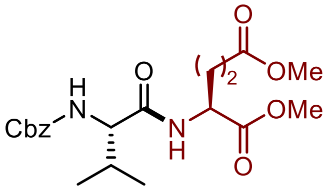
Cbz-Val-Asp(OMe)-OMe



21

White solid, m.p.: 135 – 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 6.94 (m, 6H), 5.78 (d, *J* = 12.0 Hz, 1H), 5.28 – 4.98 (m, 2H), 4.98 – 4.73 (m, 1H), 4.16 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.89 – 3.42 (m, 6H), 2.99 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.81 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.24 – 1.94 (m, 1H), 1.19 – 0.66 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 171.3, 171.0, 156.4, 136.3, 128.4, 128.0, 127.9, 66.8, 60.0, 52.7, 52.0, 48.3, 35.9, 31.5, 19.0, 17.7. HRMS-ESI: calcd for $C_{19}H_{27}N_2O_7^+$ ($[M + H]^+$) *m*/*z* 395.18128, found 395.17965.

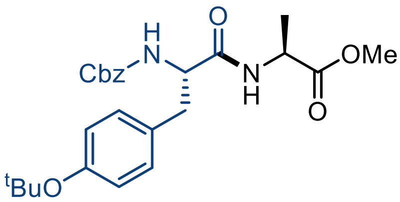
Cbz-Val-Glu(OMe)-OMe



22

White solid, m.p.: 124 – 128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.22 (m, 5H), 7.12 (d, *J* = 8.0 Hz, 1H), 5.70 (d, *J* = 8.0 Hz, 1H), 5.27 – 4.95 (m, 2H), 4.70 – 4.50 (m, 1H), 4.12 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.90 – 3.45 (m, 6H), 2.54 – 2.28 (m, 2H), 2.27 – 2.14 (m Hz, 1H), 2.14 – 2.04 (m, 1H), 2.04 – 1.90 (m, 1H), 1.08 – 0.76 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.0, 171.5, 156.4, 136.3, 128.4, 128.1, 127.9, 66.9, 60.1, 52.4, 51.8, 51.6, 31.3, 30.0, 26.9, 19.0, 17.8. HRMS-ESI: calcd for $C_{20}H_{29}N_2O_7^+$ ($[M + H]^+$) *m*/*z* 409.19693, found 409.19496.

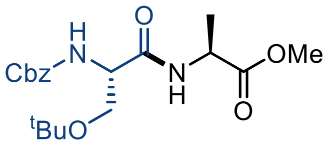
Cbz-Tyr(^{t}Bu)-Ala-OMe



23

White solid, m.p.: 115 – 118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.23 (m, 5H), 7.16 – 7.02 (m, 2H), 6.96 – 6.81 (m, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.58 (d, *J* = 8.0 Hz, 1H), 5.15 – 4.94 (m, 2H), 4.61 – 4.32 (m, 2H), 3.69 (s, 3H), 3.01 (d, *J* = 8.0 Hz, 2H), 1.45 – 1.18 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 170.6, 156.0, 154.3, 136.2, 131.1, 129.8, 128.5, 128.1, 128.0, 124.2, 78.3, 67.0, 56.0, 52.4, 48.1, 37.9, 28.8, 18.1. HRMS-ESI: calcd for $C_{25}H_{33}N_2O_6^+$ ($[M + H]^+$) *m*/*z* 457.23331, found 457.23108.

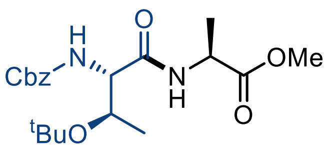
Cbz-Ser(^{t}Bu)-Ala-OMe



24

White oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 4.0 Hz, 1H), 7.38 – 7.09 (m, 5H), 5.86 (d, *J* = 4.0 Hz, 1H), 5.26 – 4.97 (m, 2H), 4.57 (p, *J* = 8.0 Hz, 1H), 4.26 (s, 1H), 3.79 (d, *J* = 4.0 Hz, 1H), 3.72 (s, 3H), 3.40 (t, *J* = 8.0 Hz, 1H), 1.39 (d, *J* = 8.0 Hz, 3H), 1.20 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 169.9, 156.0, 136.2, 128.4, 128.1, 128.0, 74.1, 66.9, 61.7, 54.3, 52.3, 48.1, 27.2, 18.3. HRMS-ESI: calcd for $C_{19}H_{29}N_2O_6^+$ ($[M + H]^+$) *m*/*z* 381.20201, found 381.20036.

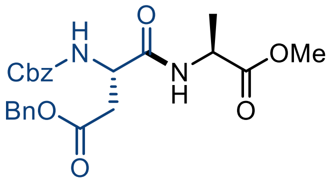
Cbz-Thr(^{t}Bu)-Ala-OMe



25

White oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.18 (m, 5H), 5.99 (d, *J* = 4.0 Hz, 1H), 5.27 – 4.99 (m, 2H), 4.52 (p, *J* = 4.0 Hz, 1H), 4.34 – 3.99 (m, 2H), 3.73 (s, 3H), 1.41 (d, *J* = 8.0 Hz, 3H), 1.36 – 0.87 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 169.0, 156.0, 136.3, 128.5, 128.0, 127.9, 75.3, 66.7, 58.5, 52.2, 48.2, 28.1, 18.2, 16.7. HRMS-ESI: calcd for $C_{20}H_{31}N_2O_6^+$ ($[M + H]^+$) *m*/*z* 395.21766, found 395.21660.

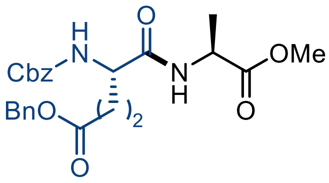
Cbz-Asp(OBzl)-Ala-OMe



26

White solid, m.p.: 127 – 129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.14 (m, 10H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 8.0 Hz, 1H), 5.34 – 4.87 (m, 4H), 4.75 – 4.57 (m, 1H), 4.57 – 4.42 (m, 1H), 3.69 (s, 3H), 3.04 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.75 (dd, *J* = 16.0, 4.0 Hz, 1H), 1.35 (d, *J* = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 171.6, 170.0, 156.0, 136.0, 135.3, 128.6, 128.6, 128.4, 128.3, 128.2, 67.3, 66.9, 52.4, 50.9, 48.3, 36.4, 18.0. HRMS-ESI: calcd for $C_{23}H_{27}N_2O_7^+$ ([M + H]$^+$) *m*/*z* 443.18128, found 443.17947.

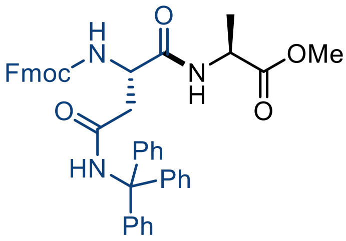
Cbz-Glu(OBzl)-Ala-OMe



27

White solid, m.p.: 127 – 128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.17 (m, 10H), 7.09 (d, *J* = 8.0 Hz, 1H), 5.92 (d, *J* = 8.0 Hz, 1H), 5.25 – 4.90 (m, 4H), 4.63 – 4.46 (m, 1H), 4.37 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.68 (s, 3H), 2.69 – 2.40 (m, 2H), 2.28 – 2.07 (m, 1H), 2.05 – 1.86 (m, 1H), 1.34 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 173.0, 171.0, 156.2, 136.2, 135.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 67.0, 66.5, 53.8, 52.4, 48.1, 30.2, 28.2, 17.8. HRMS-ESI: calcd for $C_{24}H_{29}N_2O_7^+$ ([M + H]$^+$) *m*/*z* 457.19693, found 457.19484.

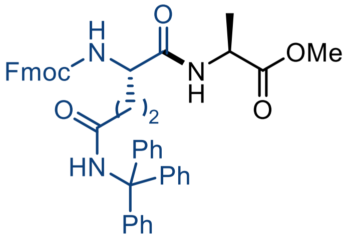
Fmoc-Asn(Trt)-Ala-OMe



28

White solid, m.p.: 207 – 209 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.40 – 7.29 (m, 3H), 7.27 – 7.01 (m, 18H), 6.63 (d, *J* = 8.0 Hz, 1H), 4.71 – 4.51 (m, 1H), 4.45 – 4.20 (m, 3H), 4.13 (t, *J* = 8.0 Hz, 1H), 3.63 (s, 3H), 3.04 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.65 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.28 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 171.1, 170.6, 156.3, 144.3, 143.9, 143.7, 141.3, 141.3, 128.8, 128.0, 127.8, 127.1, 127.1, 125.3, 120.0, 70.9, 67.3, 52.5, 51.3, 48.5, 47.1, 38.5, 17.6. HRMS-ESI: calcd for $C_{42}H_{40}N_3O_6^+$ ([M + H]$^+$) *m*/*z* 682.29116, found 682.29069.

Fmoc-Gln(Trt)-Ala-OMe

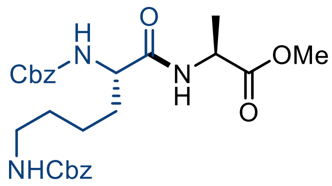


29

White solid, m.p.: 141 – 144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.29 (m, 3H), 7.25 – 6.92 (m, 18H), 6.10 (d, *J* = 8.0 Hz, 1H), 4.48 – 4.35 (m, 1H), 4.35 – 4.24 (m, 2H), 4.23 – 4.04 (m, 2H), 3.59 (s, 3H), 2.62 – 2.26 (m, 2H), 2.15 – 1.88 (m, 2H), 1.22 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.1, 171.3, 156.2, 144.6, 143.9, 143.8, 141.3, 141.3, 128.7, 128.0, 127.7, 127.1, 127.1, 125.2, 120.0, 70.6, 67.0, 53.6, 52.4, 48.2, 47.1, 33.2, 29.6, 17.4. HRMS-ESI:

calcd for $C_{43}H_{42}N_3O_6^+$ ([M + H]$^+$) *m/z* 696.30681, found 696.30354.

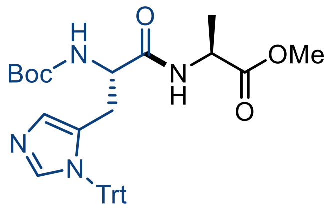
Cbz-Lys(Cbz)-Ala-OMe



30

White solid, m.p.: 145 – 148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.18 (m, 10H), 7.09 (d, *J* = 8.0 Hz, 1H), 5.89 (d, *J* = 4.0 Hz, 1H), 5.46 – 5.23 (m, 1H), 5.22 – 4.91 (m, 4H), 4.52 (p, *J* = 8.0 Hz, 1H), 4.33 – 4.12 (m, 1H), 3.65 (s, 3H), 3.15 (d, *J* = 4.0 Hz, 2H), 1.91 – 1.56 (m, 2H), 1.55 – 1.41 (m, 2H), 1.41 – 1.19 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 171.7, 156.7, 156.3, 136.6, 136.2, 128.5, 128.4, 128.1, 128.1, 128.0, 128.0, 66.9, 66.5, 54.4, 52.4, 48.0, 40.3, 32.2, 29.2, 22.0, 17.7. HRMS-ESI: calcd for $C_{26}H_{34}N_3O_7^+$ ([M + H]$^+$) *m/z* 500.23913, found 500.23712.

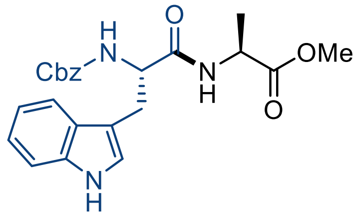
Boc-His(Trt)-Ala-OMe



31

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 1H), 7.34 – 7.23 (m, 9H), 7.19 – 7.02 (m, 6H), 6.67 (s, 1H), 6.50 (d, *J* = 4.0 Hz, 1H), 4.66 – 4.30 (m, 2H), 3.65 (s, 3H), 3.18 – 3.00 (m, 1H), 2.94 (dd, *J* = 16.0, 4.0 Hz, 1H), 1.44 (s, 9H), 1.29 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 171.3, 155.7, 142.3, 138.5, 136.7, 129.7, 128.0, 128.0, 119.5, 79.6, 75.2, 54.4, 52.2, 48.0, 30.2, 28.3, 18.3. HRMS-ESI: calcd for $C_{34}H_{39}N_4O_5^+$ ([M + H]$^+$) *m/z* 583.29150, found 583.28876.

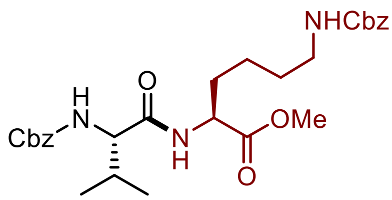
Cbz-Trp-Ala-OMe



32

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.18 (m, 6H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.73 (d, *J* = 8.0 Hz, 1H), 5.18 – 4.88 (m, 2H), 4.67 – 4.46 (m, 1H), 4.42 (p, *J* = 8.0 Hz, 1H), 3.57 (s, 3H), 3.26 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.16 (dd, *J* = 16.0, 4.0 Hz, 1H), 1.19 (d, *J* = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 171.3, 156.2, 136.3, 128.5, 128.2, 128.0, 127.5, 123.6, 122.0, 119.5, 118.7, 111.4, 109.9, 67.0, 55.5, 52.4, 48.2, 28.6, 18.0. HRMS-ESI: calcd for $C_{23}H_{26}N_3O_5^+$ ([M + H]$^+$) *m/z* 424.18670, found 424.18558.

Cbz-Val-Lys(Cbz)-OMe

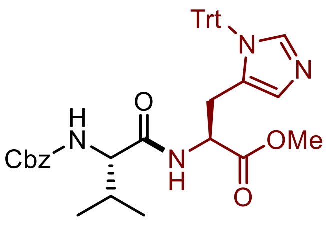


33

White solid, m.p.: 122 – 126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.20 (m, 10H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.02 – 5.51 (m, 2H), 5.22 – 4.88 (m, 4H), 4.64 – 4.38 (m, 1H), 4.33 – 4.09 (m, 1H), 3.69 (s, 3H), 3.33 – 2.91 (m, 2H), 2.16 – 1.95 (m, 1H), 1.81 – 1.53 (m, 2H), 1.51 – 1.37 (m, 2H), 1.33 – 1.24 (m, 2H), 0.93 (d, *J* = 8.0 Hz, 3H), 0.82 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 172.5, 172.0, 156.8, 156.7, 136.5, 136.2, 128.5, 128.5, 128.4, 128.1, 128.1, 67.1, 66.7, 59.9, 52.3, 40.3, 31.5, 31.4, 29.3, 22.5, 19.1, 17.5, 14.1. HRMS-ESI: calcd for $C_{28}H_{28}N_3O_7^+$ ($[M + H]^+$) *m/z* 528.27043, found 528.26819.

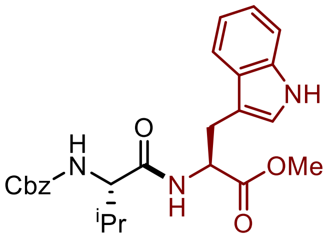
Cbz-Val-His(Trt)-OMe



34

Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.59 (m, 2H), 7.50 (s, 1H), 7.42 – 7.29 (m, 9H), 7.27 – 7.19 (m, 4H), 7.18 – 6.96 (m, 6H), 6.66 (s, 1H), 5.94 (d, *J* = 12.0 Hz, 1H), 5.19 – 4.90 (m, 2H), 4.89 – 4.74 (m, 1H), 4.25 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.60 (s, 3H), 3.07 (d, *J* = 4.0 Hz, 2H), 2.36 – 2.07 (m, 1H), 0.98 (d, *J* = 4.0 Hz, 3H), 0.89 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 171.2, 156.3, 143.2, 141.7, 138.0, 136.4, 135.3, 129.6, 128.4, 128.3, 128.2, 128.2, 127.9, 127.8, 126.2, 124.2, 120.0, 119.1, 110.1, 75.9, 66.7, 59.9, 52.6, 52.2, 31.4, 29.3, 19.1, 17.5. HRMS-ESI: calcd for $C_{39}H_{41}N_4O_5^+$ ($[M + H]^+$) *m/z* 645.30715, found 645.30408.

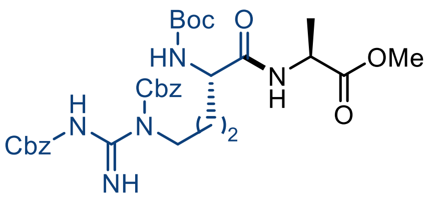
Cbz-Val-Trp-OMe



35

White solid, m.p.: 152 – 154 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.23 (m, 4H), 7.23 – 7.16 (m, 2H), 7.23 – 7.16 (m, 1H), 7.09 – 7.01 (m, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.87 – 6.76 (m, 1H), 5.59 (d, *J* = 12.0 Hz, 1H), 4.99 (d, *J* = 12.0 Hz, 1H), 4.93 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.29 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.61 (s, 3H), 3. 39 – 3.06 (m, 2H), 2.16 – 1.97 (m, 1H), 1.07 – 0.60 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 171.7, 156.6, 136.2, 136.1, 128.5, 128.1, 128.1, 127.3, 123.4, 122.1, 119.5, 118.3, 111.4, 109.1, 67.0, 59.8, 52.8, 52.4, 31.6, 27.6, 19.1, 17.5. HRMS-ESI: calcd for $C_{20}H_{30}N_3O_5^+$ ($[M + H]^+$) *m/z* 452.21800, found 452.21585.

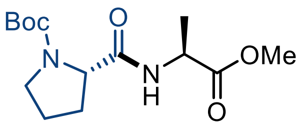
Boc-Arg(Cbz)₂-Ala-OMe



36

White solid, m.p.: 105 – 108 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 – 9.07 (m, 2H), 7.52 – 7.16 (m, 10H), 6.94 (s, 1H), 5.61 (d, *J* = 8.0 Hz, 1H), 5.33 – 5.21 (m, 2H), 5.21 – 5.05 (m, 2H), 4.45 (p, *J* = 8.0 Hz, 1H), 4.29 (d, *J* = 8.0 Hz, 1H), 4.07 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.97 – 3.81 (m, 1H), 3.65 (s, 3H), 1.86 – 1.57 (m, 4H), 1.43 (s, 9H), 1.19 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 171.7, 163.6, 160.8, 155.8, 155.6, 136.6, 134.6, 128.8, 128.8, 128.4, 128.3, 127.9, 127.8, 79.7, 68.9, 66.9, 53.6, 52.3, 48.0, 44.0, 28.8, 28.3, 24.6, 17.6. HRMS-ESI: calcd for $C_{31}H_{41}N_5O_9^+$ ($[M + H]^+$) *m/z* 628.29770, found 628.29673.

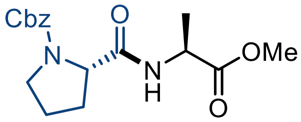
Boc-Pro-Ala-OMe



37a

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (s, 1H), 4.38 – 4.05 (m, 1H), 3.71 (s, 3H), 3.56 – 3.15 (m, 2H), 2.47 – 1.71 (m, 4H), 1.44 (s, 9H), 1.37 (d, J = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 172.1, 155.6, 80.3, 60.8, 59.7, 52.3, 47.9, 47.0, 30.9, 28.2, 24.4, 23.6, 18.1. HRMS-ESI: calcd for $C_{14}H_{25}N_2O_5^+$ ([M + H]$^+$) m/z 301.17580, found 301.17441.

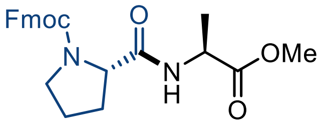
Cbz-Pro-Ala-OMe



37b

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.23 (m, 5H), 7.20 (s, 0.5H), 6.54 (s, 0.5H), 5.16 (s, 2H), 4.68 – 4.43 (m, 1H), 4.41 – 4.21 (m, 1H), 3.92 – 3.63 (m, 3H), 3.62 – 3.25 (m, 2H), 2.44 – 1.73 (m, 4H), 1.44 – 1.06 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 171.3, 155.9, 136.4, 128.4, 128.0, 127.8, 67.2, 60.3, 52.3, 48.1, 47.5, 46.9, 31.0, 28.4, 24.5, 23.6, 18.0. HRMS-ESI: calcd for $C_{17}H_{23}N_2O_5^+$ ([M + H]$^+$) m/z 335.16015, found 335.15856.

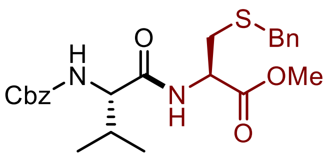
Fmoc-Pro-Ala-OMe



37c

White oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 2H), 7.66 – 7.47 (m, 2H), 7.46 – 7.33 (m, 2H), 7.33 – 7.22 (m, 2H), 7.14 (s, 0.6H), 6.53 (s, 0.4H), 4.68 – 4.48 (m, 1H), 4.47 – 4.04 (m, 4H), 3.85 – 3.28 (m, 5H), 2.44 – 1.73 (m, 4H), 1.54 – 1.17 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 171.3, 156.0, 143.8, 141.3, 127.7, 127.0, 125.1, 125.0, 120.0, 67.7, 60.8, 60.3, 52.3, 48.2, 47.5, 47.2, 47.0, 31.2, 28.5, 24.6, 23.5, 18.5, 18.1. HRMS-ESI: calcd for $C_{24}H_{27}N_2O_5^+$ ([M + H]$^+$) m/z 423.19145, found 423.19193.

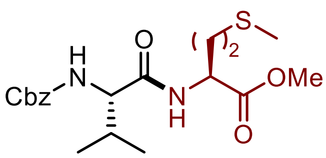
Cbz-Val-Cys(Bzl)-OMe



38

White solid, m.p.: 174 – 177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 6.92 (m, 10H), 6.56 (d, J = 4.0 Hz, 1H), 5.39 (d, J = 8.0 Hz, 1H), 5.23 – 4.99 (m, 2H), 4.89 – 4.66 (m, 1H), 4.19 – 3.92 (m, 1H), 3.89 – 3.41 (m, 5H), 2.87 (d, J = 4.0 Hz, 2H), 2.24 – 2.07 (m, 1H), 1.10 – 0.71 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.9, 156.3, 137.6, 136.2, 128.9, 128.6, 128.5, 128.2, 128.0, 127.3, 67.1, 60.1, 52.6, 51.6, 36.6, 33.1, 31.2, 19.1, 17.6. HRMS-ESI: calcd for $C_{24}H_{31}N_2O_5S^+$ ([M + H]$^+$) m/z 459.19482, found 459.19269.

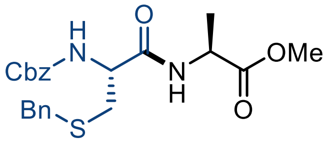
Cbz-Val-Met-OMe



39

Light yellow solid, m.p.: 122 – 124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.18 (m, 6H), 5.83 (d, J = 12.0 Hz, 1H), 5.24 – 4.98 (m, 2H), 4.73 (dd, J = 12.0, 8.0 Hz, 1H), 4.24 – 4.07 (m, 1H), 3.72 (s, 3H), 2.59 – 2.37 (m, 2H), 2.22 – 2.07 (m, 2H), 2.07 – 2.01 (m, 3H), 2.01 – 1.87 (m, 1H), 1.06 – 0.84 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.7, 156.5, 136.2, 128.5, 128.1, 127.9, 67.0, 60.3, 52.4, 51.5, 31.3, 29.9, 19.1, 18.0, 15.3. HRMS-ESI: calcd for $C_{19}H_{29}N_2O_5S^+$ ([M + H]$^+$) *m/z* 397.17917, found 397.17749.

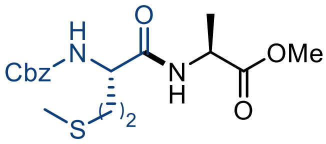
Cbz-Cys(Bzl)-Ala-OMe



40

White solid, m.p.: 138 – 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.13 (m, 10H), 6.89 (s, 1H), 5.69 (d, *J* = 8.0 Hz, 1H), 5.12 (s, 2H), 4.54 (p, *J* = 8.0 Hz, 1H), 4.44 – 4.18 (m, 1H), 3.86 – 3.50 (m, 5H), 2.87 (dd, *J* = 12.0, 4.9 Hz, 1H), 2.75 (dd, *J* = 16.0, 4.0 Hz, 1H), 1.38 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 169.9, 155.9, 137.9, 136.1, 129.0, 128.6, 128.5, 128.2, 128.1, 127.2, 67.2, 54.1, 52.5, 48.3, 36.6, 33.9, 18.2. HRMS-ESI: calcd for $C_{22}H_{27}N_2O_5S^+$ ([M + H]$^+$) *m/z* 431.16352, found 431.16162.

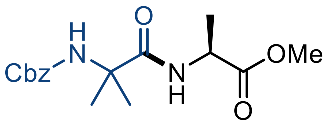
Cbz-Met-Ala-OMe



41

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.20 (m, 5H), 7.11 (d, *J* = 4.0 Hz, 1H), 5.95 (d, *J* = 12.0 Hz, 1H), 5.22 – 4.98 (m, 2H), 4.62 – 4.50 (m, 1H), 4.51 – 4.36 (m, 1H), 3.72 (s, 3H), 2.69 – 2.45 (m, 2H), 2.21 – 2.00 (m, 4H), 1.99 – 1.84 (m, 1H), 1.36 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 171.1, 156.1, 136.2, 128.5, 128.1, 128.0, 66.9, 53.6, 52.4, 48.0, 32.0, 29.8, 17.8, 15.1. HRMS-ESI: calcd for $C_{17}H_{25}N_2O_5S^+$ ([M + H]$^+$) *m/z* 369.14787, found 369.14649.

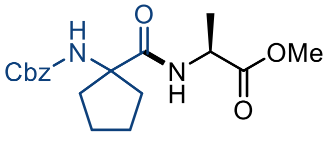
Cbz-Aib-Ala-OMe



42

Light yellow solid, m.p.: 67 – 70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.08 (m, 5H), 6.90 (d, *J* = 4.0 Hz, 1H), 5.64 (s, 1H), 5.08 (s, 2H), 4.74 – 4.29 (m, 1H), 3.70 (s, 3H), 1.84 – 1.43 (m, 6H), 1.34 (d, *J* = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 173.4, 155.1, 136.3, 128.5, 128.1, 128.0, 66.6, 56.8, 52.3, 48.2, 25.6, 25.1, 18.0. HRMS-ESI: calcd for $C_{16}H_{23}N_2O_5^+$ ([M + H]$^+$) *m/z* 323.16015, found 323.15987.

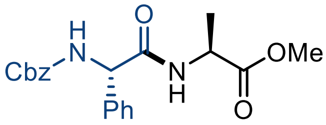
Cbz-Ac$_5$c-Ala-OMe



43

White solid, m.p.: 103 – 104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.19 (m, 5H), 7.07 (s, 1H), 5.35 (s, 1H), 5.10 (s, 2H), 4.53 (s, 1H), 3.70 (s, 3H), 2.43 – 2.15 (m, 2H), 2.06 – 1.85 (m, 2H), 1.82 – 1.57 (m, 4H), 1.49 – 1.09 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 173.5, 155.5, 136.3, 128.5, 128.2, 128.1, 67.2, 66.9, 52.3, 48.3, 37.2, 36.6, 24.1, 18.1. HRMS-ESI: calcd for $C_{18}H_{25}N_2O_5^+$ ([M + H]$^+$) *m/z* 349.17580, found 349.17597.

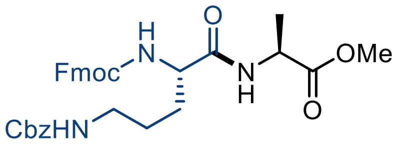
Cbz-Phg-Ala-OMe



44

White solid, m.p.: 179 – 181 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 6.98 (m, 10H), 6.54 (s, 1H), 6.16 (s, 1H), 5.30 (d, *J* = 8.0 Hz, 1H), 5.14 – 5.00 (m, 2H), 4.63 – 4.41 (m, 1H), 3.64 (s, 3H), 1.37 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 169.4, 155.7, 137.6, 136.2, 129.0, 128.5, 128.5, 128.1, 128.0, 127.3, 67.0, 58.6, 52.4, 48.4, 18.1. HRMS-ESI: calcd for $C_{20}H_{23}N_2O_5^+$ ([M + H]$^+$) *m/z* 371.16015, found 371.15925.

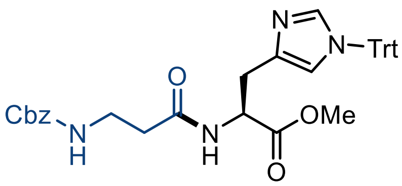
Fmoc-Orn(Cbz)-Ala-OMe



45

White solid, m.p.: 148 – 150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.63 – 7.46 (m, 2H), 7.44 – 7.13 (m, 9H), 5.91 (d, *J* = 8.0 Hz, 1H), 5.55 – 5.18 (m, 1H), 5.17 – 4.86 (m, 2H), 4.70 – 4.02 (m, 5H), 3.65 (s, 3H), 3.42 – 2.90 (m, 2H), 1.95 – 1.45 (m, 4H), 1.34 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 171.9, 157.1, 156.4, 143.9, 143.7, 141.3, 136.5, 128.5, 128.1, 128.0, 127.7, 127.1, 125.1, 120.0, 67.1, 66.7, 53.4, 52.3, 48.0, 47.1, 39.7, 30.3, 25.9, 17.7. HRMS-ESI: calcd for $C_{32}H_{36}N_3O_7^+$ ([M + H]$^+$) *m/z* 574.25478, found 574.25383.

Cbz-β-Ala-His(Trt)-OMe



46

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.17 (m, 16H), 7.16 – 6.97 (m, 6H), 6.73 – 6.38 (m, 2H), 5.01 (s, 2H), 4.87 – 4.70 (m, 1H), 3.74 – 3.28 (m, 5H), 3.16 – 2.93 (m, 2H), 2.56 – 2.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 171.4, 156.5, 142.2, 138.9, 136.9, 136.3, 129.7, 128.4, 128.1, 127.8, 127.7, 119.6, 75.3, 66.2, 52.8, 52.1, 37.6, 36.6, 29.4. HRMS-ESI: calcd for $C_{37}H_{37}N_4O_5^+$ ([M + H]$^+$) *m/z* 617.27585, found 617.27503.

4. Gram-scale Synthesis in Continuous-flow

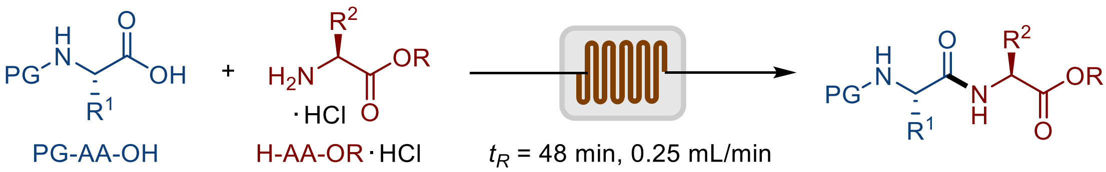
4.1 Flow reactor setup.

The outline diagram of the assembled flow photoreactor was shown in Figure S5. The flow photoreactor was mainly consisted of a peristaltic pump (RBT100-15L), an RLH-18 octet photocatalytic parallel reaction system with eight 10W blue LEDs, and a cylindrical coil continuous-flow reaction system (RLR-18CF, Figure S6), which were purchased from Beijing Roger tech Ltd. FEP tubing (1 mm inner diameter) was selected, and the calculated residence volume of the tubing was about 12 mL. The continuous-flow reaction system was placed on a magnetic hotplate stirrer (DLAB MS-H-Pro^{A}) to keep the reaction temperature at 60 °C.

Figure S5. Picture of the Flow Photoreactor

Figure S6. Pictures of the cylindrical coil

4.2 General procedure



A 200 mL reaction bottle equipped with a PTFE valve was charged with protected amino acid (4.0 mmol, 1.0 equiv.), amino acid ester hydrochloride (4.8 mmol, 1.2 equiv.), PPh_3 (1.2 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The bottle was evacuated and purged with nitrogen three times. The valve was closed after MeCN (32 mL), DMF (8 mL), TMDS (12.0 mmol, 3.0 equiv.) and 2,4,6-collidine (6.0 mmol, 1.5 equiv.) were added under nitrogen. The mixture solution was sonicated for 15 min, then pumped *via* peristatic pump to pass through the flow photoredox system with a flow rate of 0.25 mL/min at 60 °C. The outlet solution was collected, concentrated, and purified through column chromatography to afford the desired dipeptide product.

4.3 General procedure for the deprotection of the Cbz-group

The Cbz-group protected peptide in absolute methanol (0.1M) was performed in the presence of Pd/C (w.t. 15%) at room temperature. The reaction was allowed to stir in an atmosphere of hydrogen (balloon, 1 atm) overnight, then the mixture was filtrated over celite, and the organic solvent was evaporated to afford desired product without further purification. And the crude product was used directly for the next step.

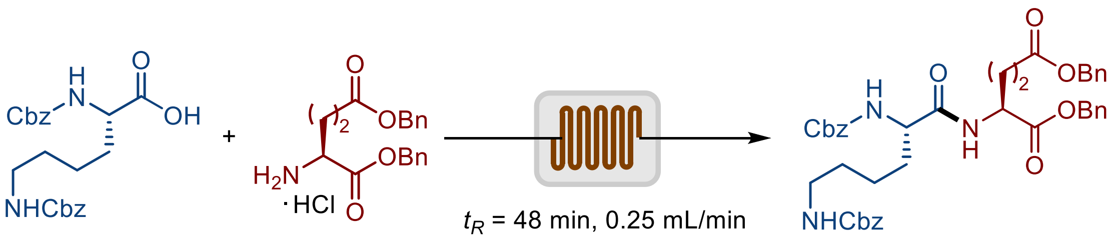
4.4 General procedure for the deprotection of the Boc-group

The Boc-group protected peptide was dissolved in a minimal amount of EtOAc at 0 °C. The HCl/EA solution (0.5M) was added to the flask slowly and the reaction was stirred at 0 °C. Upon complete consumption of the starting material, the reaction mixture was concentrated, and the crude was diluted with H_2O. The aqueous layer was then adjusted to pH ≈ 8 with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic solvent was dried over sodium sulfate and concentrated to afford the desired product without further purification. And the crude product was used directly for the next step.

4.5 General procedure for hydrolysis of methyl esters

To a solution of the peptide methyl ester in THF (0.25M) was added 0.25N NaOH (1.05 equiv.). Upon complete consumption of the starting material, the reaction mixture was diluted with H_2O and the aqueous layer was washed with EtOAc. The aqueous layer was then adjusted to pH ≈ 2 with 1N HCl and extracted with EtOAc twice. The combined extracts were dried over sodium sulfate and concentrated to afford the desired product without further purification. And the crude product was used directly for the next step.

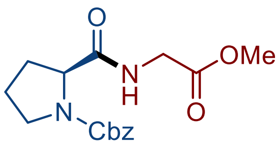
4.6 General procedure for multigram synthesis



A 200 mL reaction bottle equipped with a PTFE valve was charged with Cbz-*L*-Lys(Cbz)-OH (10.0 mmol, 1.0 equiv.), *L*-Glu(OBzl)-OBzl·HCl (12 mmol, 1.2 equiv.), PPh_3 (3.0 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The bottle was evacuated and purged with nitrogen three times. The valve was closed after MeCN (80 mL), DMF (20 mL), TMDS (30.0 mmol, 3.0 equiv.) and 2,4,6-collidine (15 mmol, 1.5 equiv.) were added under nitrogen. The mixture solution was sonicated for 15 min, then pumped *via* peristatic pump to pass through the flow photoredox system with a flow rate of 0.25 mL/min at 60 °C. The outlet solution was collected and concentrated. The crude solid was dissolved in a minimal amount of CH_2Cl_2, followed by precipitation with petroleum ether, then filtered and washed with petroleum ether to afford crude product. The filtrate was collected and concentrated, then recrystallized with CH_2Cl_2 and petroleum ether for another time. The crude product was combined and washed with MeOH and petroleum ether, then dried with vacuum-oven to afford Cbz-Lys(Cbz)-Glu(OBzl)-OBzl as a white solid (5.17 g, 71% yield).

4.7 Characterization data

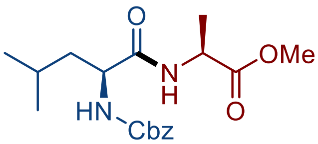
Cbz-Pro-Gly-OMe



47

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 6.77 (m, 6H), 5.54 – 4.76 (m, 2H), 4.56 – 4.22 (m, 1H), 4.21 – 3.79 (m, 2H), 3.79 – 2.97 (m, 5H), 2.47 – 1.56 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.4, 170.1, 155.7, 154.8, 136.4, 128.3, 127.9, 127.6, 67.0, 60.4, 52.0, 47.3, 46.9, 41.0, 31.1, 29.0, 24.3, 23.4. HRMS-ESI: calcd for $C_{16}H_{21}N_2O_5^+$ ([M + H]$^+$) *m/z* 321.14450, found 321.14406.

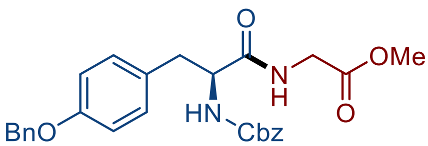
Cbz-Leu-Ala-OMe



48

White solid, m.p.: 93 – 95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.51 (d, *J* = 8.0 Hz, 1H), 5.26 – 4.99 (m, 2H), 4.56 (p, *J* = 8.0 Hz, 1H), 4.42 – 4.13 (m, 1H), 3.74 (s, 3H), 1.83 – 1.60 (m, 2H), 1.58 – 1.47 (m, 1H), 1.37 (d, *J* = 8.0 Hz, 3H), 1.07 – 0.75 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.0, 156.2, 136.2, 128.5, 128.1, 128.0, 66.9, 53.3, 52.4, 48.0, 41.6, 24.6, 22.9, 21.9, 18.0. HRMS-ESI: calcd for $C_{18}H_{27}N_2O_5^+$ ([M + H]$^+$) *m/z* 351.19145, found 351.18976.

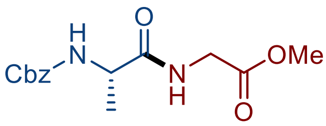
Cbz-Tyr(Bzl)-Gly-OMe



49

White solid, m.p.: 127 – 129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.22 (m, 10H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.83 – 6.60 (m, 1H), 5.62 (d, *J* = 8.0 Hz, 1H), 5.31 – 4.83 (m, 4H), 4.68 – 4.33 (m, 1H), 4.13 – 3.85 (m, 2H), 3.73 (s, 3H), 3.25 – 2.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.0, 157.8, 156.1, 136.9, 136.1, 130.4, 128.6, 128.5, 128.2, 128.0, 127.5, 115.0, 69.9, 67.0, 56.1, 52.3, 41.1, 37.6. HRMS-ESI: calcd for $C_{27}H_{29}N_2O_6^+$ ([M + H]$^+$) *m/z* 477.20201, found 477.19985.

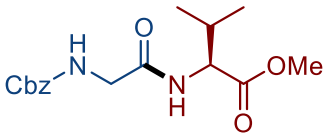
Cbz-Ala-Gly-OMe



50

White solid, m.p.: 98 – 101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.01 (m, 6H), 6.06 (d, *J* = 8.0 Hz, 1H), 5.28 – 4.87 (m, 2H), 4.53 – 4.16 (m, 1H), 4.08 – 3.81 (m, 2H), 3.67 (s, 3H), 1.36 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 170.3, 156.1, 136.2, 128.5, 128.1, 127.9, 66.8, 52.2, 50.4, 41.0, 18.5. HRMS-ESI: calcd for $C_{14}H_{19}N_2O_5^+$ ([M + H]$^+$) *m/z* 295.12885, found 295.12819.

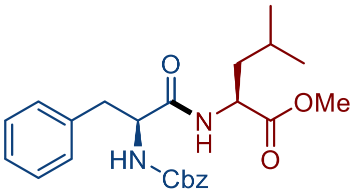
Cbz-Gly-Val-OMe



51

White solid, m.p.: 143 – 146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.22 (m, 5H), 7.10 (d, J = 8.0 Hz, 1H), 6.22 – 5.89 (m, 1H), 5.44 – 4.90 (m, 2H), 4.54 (dd, J = 8.0, 4.3 Hz, 1H), 3.94 (d, J = 4.0 Hz, 2H), 3.69 (s, 3H), 2.31 – 1.90 (m, 1H), 1.25 – 0.47 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 169.4, 156.7, 136.3, 128.5, 128.1, 128.0, 67.0, 57.2, 52.2, 44.3, 31.1, 18.9, 17.7. HRMS-ESI: calcd for $C_{16}H_{23}N_2O_5^+$ ($[M + H]^+$) m/z 323.16015, found 323.15988.

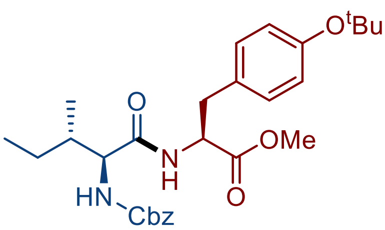
Cbz-Phe-Leu-OMe



52

White solid, m.p.: 108 – 112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 6.94 (m, 10H), 6.66 (d, J = 8.0 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 5.22 – 4.85 (m, 2H), 4.70 – 4.33 (m, 2H), 3.67 (s, 3H), 3.21 – 2.82 (m, 2H), 1.70 – 1.32 (m, 3H), 1.04 – 0.59 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 170.9, 156.0, 136.4, 136.2, 129.4, 128.5, 128.5, 128.1, 127.9, 126.9, 67.0, 56.0, 52.2, 50.8, 41.3, 38.5, 24.7, 22.7, 21.9. HRMS-ESI: calcd for $C_{24}H_{31}N_2O_5^+$ ($[M + H]^+$) m/z 427.22275, found 427.22095.

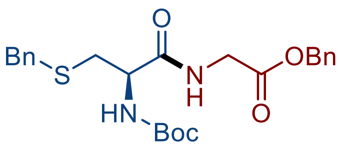
Cbz-Ile-Tyr(^{t}Bu)-OMe



53

White solid, m.p.: 110 – 111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.16 (m, 5H), 7.11 – 6.63 (m, 5H), 5.78 (d, J = 12.0 Hz, 1H), 5.25 – 4.93 (m, 2H), 4.83 (dd, J = 12.0, 8.0 Hz, 1H), 4.16 (t, J = 8.0 Hz, 1H), 3.62 (s, 3H), 3.02 (d, J = 6.2 Hz, 2H), 1.90 – 1.73 (m, 1H), 1.60 – 1.42 (m, 1H), 1.29 (s, 9H), 1.15 – 1.05 (m, 1H), 0.97 – 0.68 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.2, 156.3, 154.4, 136.4, 130.6, 129.6, 128.4, 128.0, 127.9, 124.1, 66.9, 59.5, 53.4, 52.1, 37.5, 37.3, 28.8, 24.7, 15.2, 11.3. HRMS-ESI: calcd for $C_{28}H_{39}N_2O_6^+$ ($[M + H]^+$) m/z 499.28026, found 499.28068.

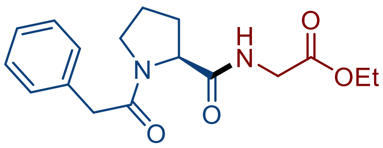
Boc-Cys(Bzl)-Gly-OBzl



54

White solid, m.p.: 75 – 77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 6.96 (m, 11H), 5.59 (d, J = 8.0 Hz, 1H), 5.12 (s, 2H), 4.39 (s, 1H), 4.15 – 3.89 (m, 2H), 3.79 – 3.58 (m, 2H), 2.80 (d, J = 8.0 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 169.5, 155.6, 138.0, 135.2, 129.1, 128.6, 128.6, 128.5, 128.4, 127.2, 80.3, 67.2, 53.6, 41.4, 36.4, 33.8, 28.3. HRMS-ESI: calcd for $C_{24}H_{31}N_2O_5S^+$ ($[M + H]^+$) m/z 459.19482, found 459.19263.

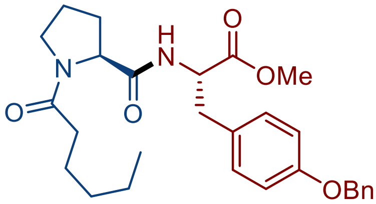
Noopept



55

White solid, m.p.: 90 – 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.44 (m, 1H), 7.40 – 7.09 (m, 5H), 4.72 – 4.30 (m, 1H), 4.27 – 4.03 (m, 2H), 4.02 – 3.81 (m, 2H), 3.78 – 3.37 (m, 4H), 2.43 – 1.69 (m, 4H), 1.41 – 1.04 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.7, 171.2, 171.0, 169.6, 169.6, 134.3, 134.2, 129.0, 128.6, 128.5, 126.9, 126.8, 61.3, 61.2, 61.1, 59.7, 47.6, 47.0, 41.8, 41.6, 41.2, 41.0, 32.0, 27.6, 24.8, 22.5, 14.1, 14.0. HRMS-ESI: calcd for $C_{17}H_{23}N_2O_4^+$ ([M + H]$^+$) *m*/*z* 319.16523, found 319.16382.

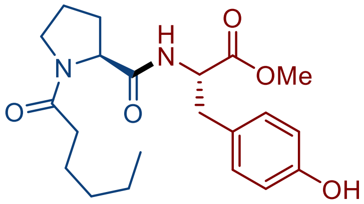
Methyl (*S*)-3-(4-(benzyloxy)phenyl)-2-((*S*)-1-pentanoylpyrrolidine-2-carboxamido)propanoate



56

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 0.8H), 7.47 – 7.23 (m, 5H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.95 – 6.74 (m, 2H), 6.64 (d, *J* = 8.0 Hz, 0.2H), 5.14 – 4.91 (m, 2H), 4.91 – 4.65 (m, 1H), 4.63 – 4.17 (m, 1H), 3.90 – 3.54 (m, 3H), 3.51 – 3.21 (m, 2H), 3.17 – 2.80 (m, 2H), 2.40 – 1.49 (m, 8H), 1.43 – 1.13 (m, 4H), 1.03 – 0.66 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 173.2, 171.9, 171.8, 171.5, 171.0, 157.9, 157.6, 137.0, 136.8, 130.2, 129.9, 128.5, 128.5, 128.1, 127.9, 127.4, 115.0, 114.5, 69.8, 69.8, 61.2, 59.3, 53.3, 52.9, 52.4, 52.2, 47.2, 46.6, 37.0, 36.5, 34.5, 34.3, 31.8, 31.6, 31.5, 27.0, 24.8, 24.4, 24.3, 22.5, 22.2, 14.0, 14.0. HRMS-ESI: calcd for $C_{28}H_{37}N_2O_5^+$ ([M + H]$^+$) *m*/*z* 481.26970, found 481.26864.

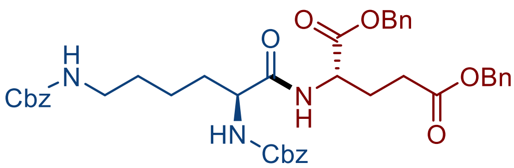
Dilept



56'

White solid, m.p.: 115 – 117 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, *J* = 12.0 Hz, 1H), 8.72 – 7.83 (m, 1H), 7.00 (t, *J* = 8.0 Hz, 2H), 6.82 – 6.43 (m, 2H), 4.64 – 4.11 (m, 2H), 3.89 – 3.48 (m, 3H), 3.48 – 3.20 (m, 2H), 3.12 – 2.69 (m, 2H), 2.23 (t, *J* = 8.0 Hz, 1H), 2.16 – 1.56 (m, 5H), 1.56 – 1.35 (m, 2H), 1.36 – 1.02 (m, 4H), 0.97 – 0.68 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 172.4, 172.3, 171.5, 171.5, 156.5, 156.4, 130.4, 130.3, 127.7, 127.4, 115.4, 115.3, 59.9, 59.2, 54.3, 53.8, 52.3, 52.1, 47.1, 46.7, 36.3, 35.8, 34.0, 33.6, 32.0, 31.4, 31.4, 29.2, 24.5, 24.3, 22.5, 14.3. HRMS-ESI: calcd for $C_{21}H_{31}N_2O_5^+$ ([M + H]$^+$) *m*/*z* 391.22275, found 391.22096.

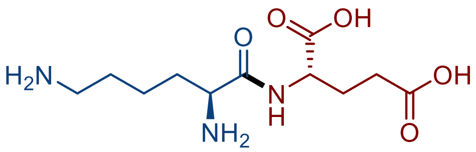
Cbz-Lys(Cbz)-Glu(OBzl)-OBzl



57

White solid, m.p.: 124 – 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.39 – 6.93 (m, 20H), 6.00 (d, *J* = 8.0 Hz, 1H), 5.59 – 5.29 (m, 1H), 5.22 – 4.87 (m, 8H), 4.69 – 4.53 (m, 1H), 4.41 – 4.10 (m, 1H), 3.07 (s, 2H), 2.45 – 2.24 (m, 2H), 2.21 – 2.07 (m, 1H), 2.03 – 1.87 (m, 1H), 1.82 – 1.67 (m, 1H), 1.67 – 1.51 (m, 1H), 1.48 – 1.18 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 172.3, 171.6, 156.7, 156.4, 136.7, 136.3, 135.7, 135.2, 128.6, 128.6, 128.5, 128.5, 128.3, 128.3, 128.1, 128.0, 67.3, 66.9, 66.5, 54.6, 51.8, 40.3, 32.2, 30.2, 29.2, 26.8, 22.2. HRMS-ESI: calcd for $C_{41}H_{46}N_3O_9^+$ ([M + H]$^+$) *m*/*z* 724.32286, found 724.32260.

Vilon

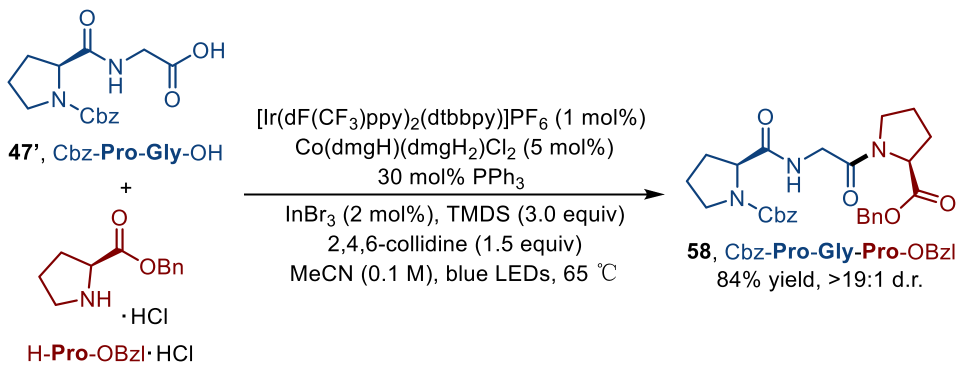


57'

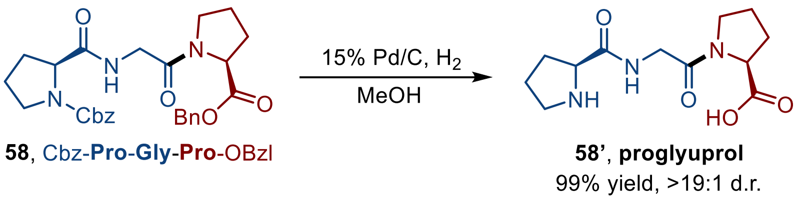
White solid, m.p.: 194 – 196 °C. ^{1}H NMR (400 MHz, D_2O) δ 4.24 – 3.79 (m, 2H), 3.10 – 2.79 (m, 2H), 2.35 – 2.09 (m, 2H), 2.09 – 1.73 (m, 4H), 1.73 – 1.56 (m, 2H), 1.54 – 1.18 (m, 2H). ^{13}C NMR (100 MHz, D_2O) δ 182.0, 178.1, 169.4, 55.4, 52.9, 38.9, 33.9, 30.3, 28.0, 26.2, 20.9. HRMS-ESI: calcd for $C_{11}H_{22}N_3O_5^+$ ([M + H]$^+$) *m*/*z* 276.15540, found 276.15411.

5. Peptide fragment condensation

5.1 Synthesis of proglyuprol

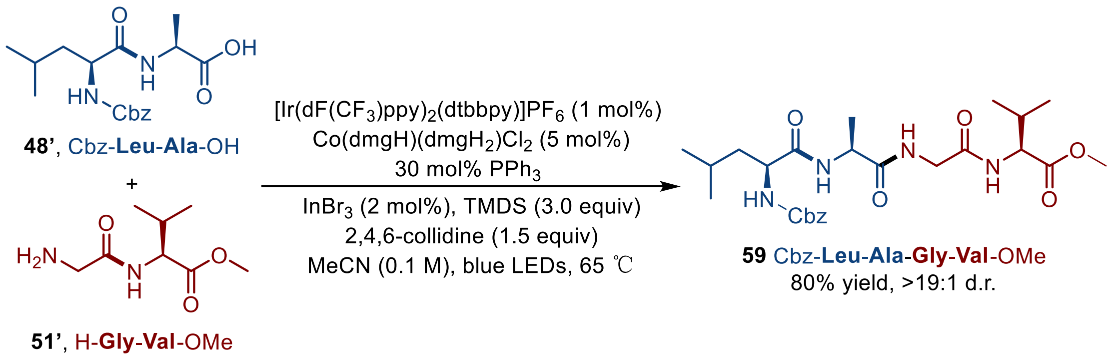


To an oven-dried reaction tube equipped with a stir bar was added Cbz-Pro-Gly-OH (1.0 mmol, 1.0 equiv.), *L*-Pro-OBzl ·HCl (1.5 mmol, 1.5 equiv.), PPh_3 (0.3 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The tube was sealed and placed under nitrogen before MeCN (10 mL), TMDS (3.0 mmol, 3.0 equiv.) and 2,4,6-collidine (1.5 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 16 h. Upon complete consumption of the starting material, the reaction mixture was concentrated and purified through column chromatography to afford Cbz-Pro-Gly-Pro-OBzl **58** as colorless oil (414.6 mg, 84% yield).

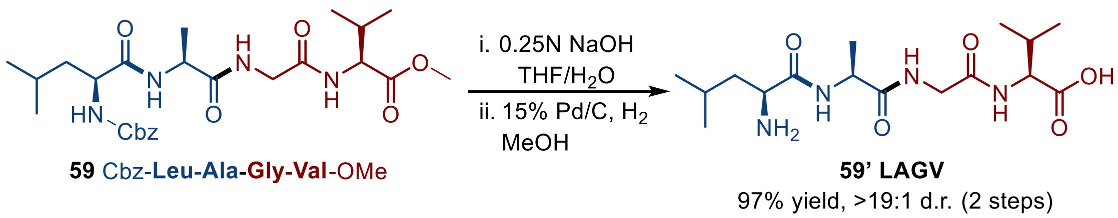


Cbz-Pro-Gly-Pro-OBzl (394.8 mg, 0.8 mmol, 1.0 equiv.) in absolute methanol (8 mL) was performed in the presence of Pd/C (107.7 mg) at room temperature. The reaction was allowed to stir in an atmosphere of hydrogen (balloon, 1 atm) overnight, then the mixture was filtrated over celite, and the organic solvent was evaporated to afford proglyuprol **58’** as a colorless oil (213.3 mg, 99% yield).

5.2 Synthesis of LAGV in batch



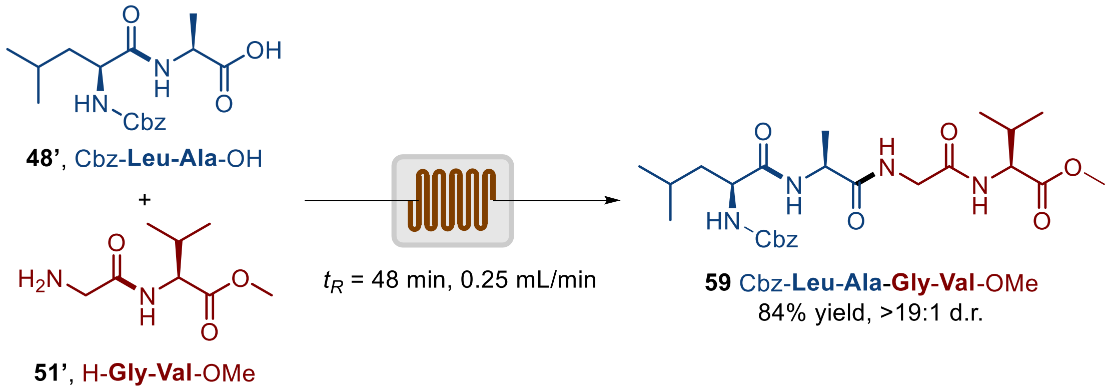
To an oven-dried reaction tube equipped with a stir bar was added Cbz-Leu-Ala-OH (0.8 mmol, 1.0 equiv.), H-Gly-Val-OMe (0.8 mmol, 1.0 equiv.), PPh_3 (0.24 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The tube was sealed and placed under nitrogen before MeCN (8 mL), TMDS (2.4 mmol, 3.0 equiv.) and 2,4,6-collidine (1.2 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 12 h. Upon complete consumption of the starting material, the reaction mixture was concentrated and purified through column chromatography to afford Cbz-Leu-Ala-Gly-Val-OMe **59** as a white solid (324.2 mg, 80% yield).



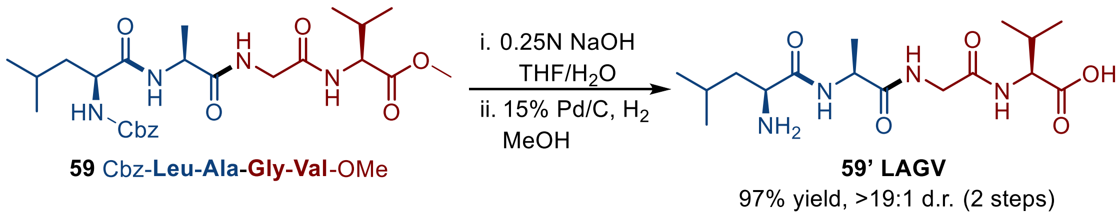
To a solution of Cbz-Leu-Ala-Gly-Val-OMe (324.2 mg, 0.64 mmol, 1.0 equiv.) in THF (2.5 mL) was added 0.25N NaOH (0.67 mmol, 1.05 equiv.). The mixture was stirred for 30 min at room temperature. Upon complete consumption of the starting material, the reaction mixture was diluted with H_2O and the aqueous layer washed with EtOAc. The aqueous layer was then adjusted to pH ≈ 2 with 1N HCl and extracted with EtOAc twice. The combined extracts were dried over sodium sulfate and concentrated to afford Cbz-Leu-Ala-Gly-Val-OH without further purified (308.9 mg, 98% yield).

Cbz-Leu-Ala-Gly-Val-OH (308.9 mg, 0.63 mmol, 1.0 equiv.) in absolute methanol (6 mL) was performed in the presence of Pd/C (84.2 mg) at room temperature. The reaction was allowed to stir in an atmosphere of hydrogen (balloon, 1 atm) overnight, then the mixture was filtrated over celite, and washed with water. The aqueous solution was dried with vacuum-oven to afford LAGV **59'** as a white solid (222.5 mg, 99% yield).

5.3 Synthesis of LAGV in continuous-flow

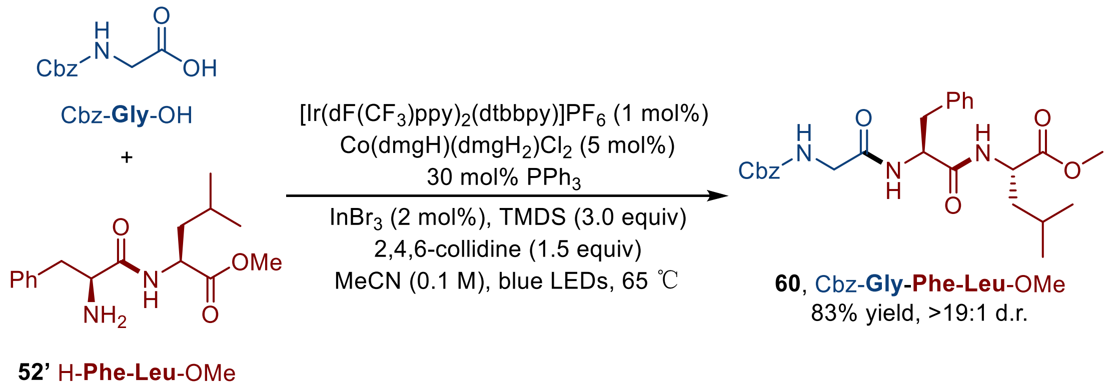


A 200 mL reaction bottle equipped with a PTFE valve was charged with protected amino acid (3.6 mmol, 1.0 equiv.), amino acid ester hydrochloride (3.6 mmol, 1.0 equiv.), PPh_3 (1.08 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The bottle was evacuated and purged with nitrogen three times. The valve was closed after MeCN (28.8 mL), DMF (7.2 mL), TMDS (10.8 mmol, 3.0 equiv.) and 2,4,6-collidine (5.4 mmol, 1.5 equiv.) were added under nitrogen. The mixture was sonicated for 15 min, then pumped *via* a peristatic pump to pass through the flow photoredox system with a flow rate of 0.25 mL/min at 60 °C. The outlet solution was collected, concentrated and purified through column chromatography to afford Cbz-Leu-Ala-Gly-Val-OMe **59** as a white solid (1.5320 g, 84% yield).

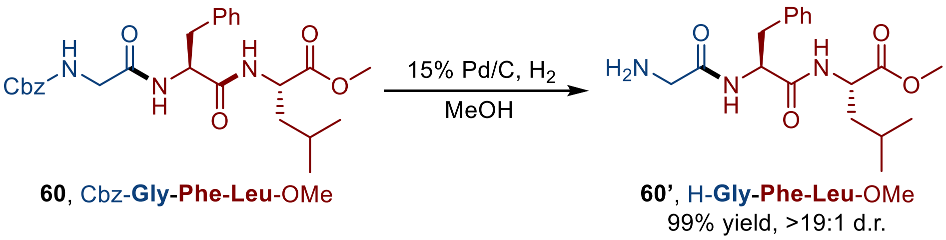


To a solution of Cbz-Leu-Ala-Gly-Val-OMe (1.5320 g, 3.0 mmol, 1.0 equiv.) in THF (12.0 mL) was added 0.25N NaOH (3.15 mmol, 1.05 equiv.). The mixture was stirred for 30 min at room temperature. Upon complete consumption of the starting material, the reaction mixture was diluted with H_2O and the aqueous layer was washed with EtOAc. The aqueous layer was then adjusted to pH ≈ 2 with 1N HCl and extracted with EtOAc twice. The combined extracts were dried over sodium sulfate and concentrated to afford Cbz-Leu-Ala-Gly-Val-OH without further purified (1.4482 g, 98% yield).
Cbz-Leu-Ala-Gly-Val-OH (1.4482 g, 2.94 mmol, 1.0 equiv.) in absolute methanol (30 mL) was performed in the presence of Pd/C (395.0 mg) at room temperature. The reaction was allowed to stir in an atmosphere of hydrogen (balloon, 1 atm) overnight, then the mixture was filtrated over celite, and washed with water. The aqueous solution was dried with vacuum-oven to afford LAGV **59'** as a white solid (1.0431 g, 99% yield).

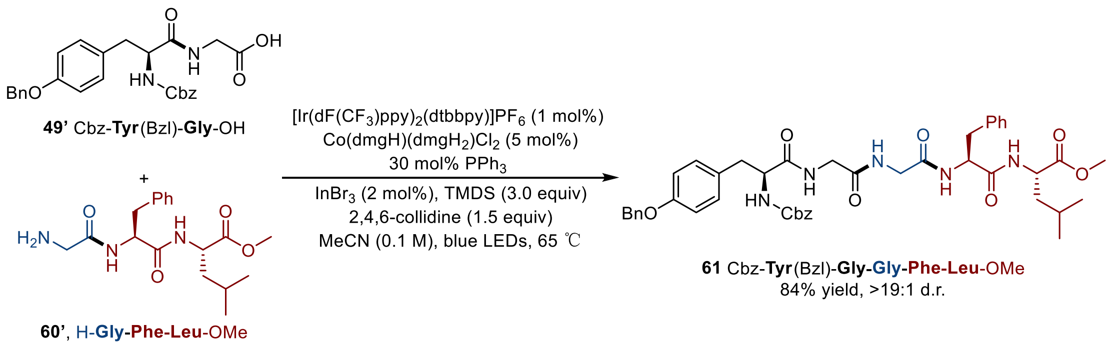
5.4 Synthesis of leu-enkephalin



To an oven-dried reaction tube equipped with a stir bar was added Cbz-Gly-OH (1.0 mmol, 1.0 equiv.), H-Phe-Leu-OMe (1.5 mmol, 1.5 equiv.), PPh_3 (0.3 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The tube was sealed and placed under nitrogen before MeCN (10 mL), TMDS (3.0 mmol, 3.0 equiv.) and 2,4,6-collidine (1.5 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 16 h. Upon complete consumption of the starting material, the reaction mixture was concentrated and purified through column chromatography to afford Cbz-Gly-Phe-Leu-OMe **60** as a white solid (406.2 mg, 84% yield).

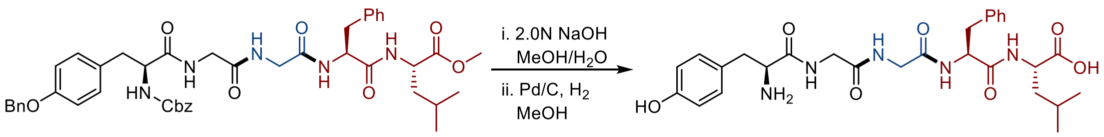


Cbz-Gly-Phe-Leu-OMe (406.2 mg, 0.84 mmol, 1.0 equiv.) in absolute methanol (8.5 mL) was performed in the presence of Pd/C (110.8 mg) at room temperature. The reaction was allowed to stir in an atmosphere of hydrogen (balloon, 1 atm) overnight, then the mixture was filtrated over celite, and the organic solvent was evaporated to afford H-Gly-Phe-Leu-OMe **60'** as a white solid without further purified (290.6 mg, 99% yield).



To an oven-dried reaction tube equipped with a stir bar was added Cbz-Tyr(Bzl)-Gly-

OH (0.8 mmol, 1.0 equiv.), H-Gly-Phe-Leu-OMe (0.8 mmol, 1.0 equiv.), PPh_3 (0.24 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The tube was sealed and placed under nitrogen before MeCN (8 mL), TMDS (2.4 mmol, 3.0 equiv.) and 2,4,6-collidine (1.2 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 20 h. Upon complete consumption of the starting material, the reaction mixture was concentrated and purified through column chromatography to afford Cbz-Tyr(Bzl)-Gly-Gly-Phe-Leu-OMe **61** as a white solid (533.5 mg, 84% yield).

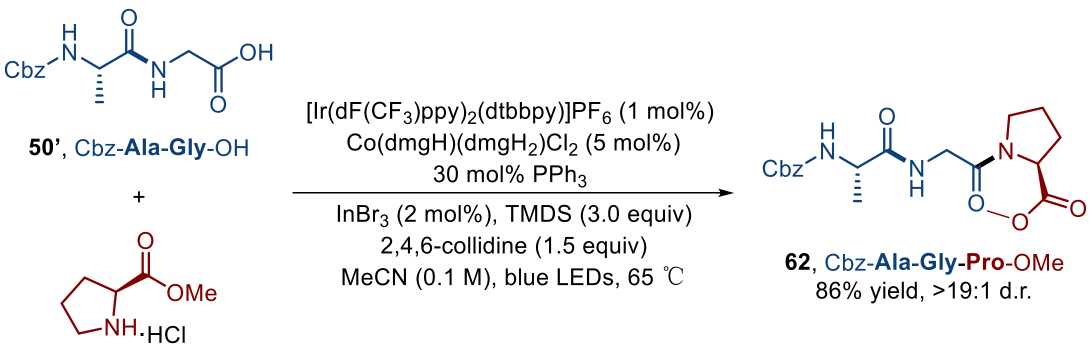


61 Cbz-**Tyr**(Bzl)-**Gly**-**Gly**-**Phe**-**Leu**-OMe

61', **leu-enkephalin**
97% yield, >19:1 d.r. (2 steps)

To a solution of Cbz-Tyr(Bzl)-Gly-Gly-Phe-Leu-OMe (476.4 mg, 0.6 mmol, 1.0 equiv.) in methanol (45 mL) was added 2M NaOH (9 mL) at 0 °C for 30 min. Upon complete consumption of the starting material, the reaction mixture was neutralized with 2N HCl to pH ≈ 7.0 and evaporated to remove methanol. The residue was acidified with 2N HCl to pH ≈ 1.0. The precipitates were collected by filtration to afford Cbz-Tyr-Gly-Gly-Phe-Leu-OH as a white solid without further purified (406.3 mg, 98% yield).
Cbz-Tyr-Gly-Gly-Phe-Leu-OH (406.3 mg, 0.59 mmol, 1.0 equiv.) in absolute methanol (6.0 mL) was performed in the presence of Pd/C (110.8 mg) at room temperature. The reaction was allowed to stir in an atmosphere of hydrogen (balloon, 1 atm) overnight, then the mixture was filtrated over celite, and the organic solvent was evaporated to afford leu-enkephalin **61'** as a white solid (324.5 mg, 99% yield).

5.5 Synthesis of (^{t}Bu)-fanlizhicyclopeptide B



50', Cbz-**Ala**-**Gly**-OH

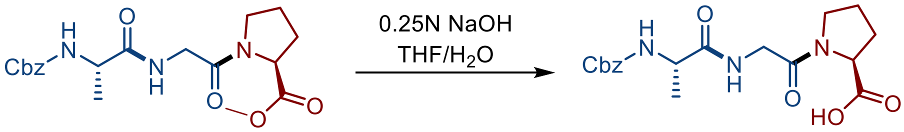
\+

H-**Pro**-OMe · HCl

62, Cbz-**Ala**-**Gly**-**Pro**-OMe
86% yield, >19:1 d.r.

To an oven-dried reaction tube equipped with a stir bar was added Cbz-Ala-Gly-OH (1.0 mmol, 1.0 equiv.), *L*-Pro-OMe·HCl (1.5 mmol, 1.5 equiv.), PPh_3 (0.3 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The tube was sealed and placed under nitrogen before MeCN (10 mL), TMDS (3.0 mmol, 3.0 equiv.) and 2,4,6-collidine (1.5 mmol, 1.5

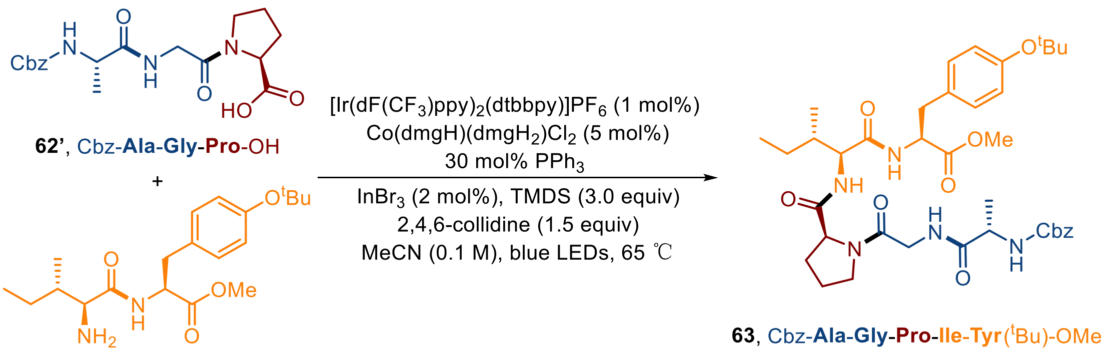
equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 16 h. Upon complete consumption of the starting material, the reaction mixture was concentrated and purified through column chromatography to afford Cbz-Ala-Gly-Pro-OMe **62** as a white oil (336.6 mg, 86% yield).



62, Cbz-**Ala**-**Gly**-**Pro**-OMe

62', Cbz-**Ala**-**Gly**-**Pro**-OH
91% yield, >19:1 d.r.

To a solution of Cbz-Ala-Gly-Pro-OMe (336.6 mg, 0.86 mmol, 1.0 equiv.) in THF (3.5 mL) was added 0.25N NaOH (0.90 mmol, 1.05 equiv.). The mixture was stirred for 30 min at room temperature. Upon complete consumption of the starting material, the reaction mixture was diluted with H_2O and the aqueous layer was washed with EtOAc. The aqueous layer was then adjusted to pH ≈ 2 with 1N HCl and extracted with EtOAc twice. The combined extracts were dried over sodium sulfate and concentrated to afford Cbz-Ala-Gly-Pro-OH **62'** as a white solid without further purified (295.4 mg, 91% yield).

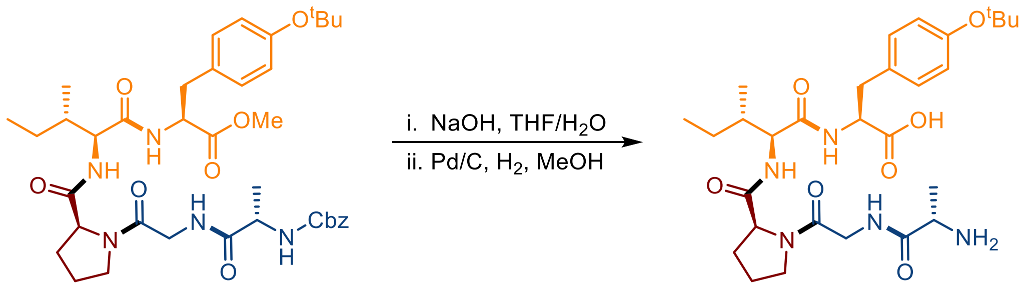


62', Cbz-**Ala**-**Gly**-**Pro**-OH

53', H-**Ile**-**Tyr**(**t**Bu)-OMe

63, Cbz-**Ala**-**Gly**-**Pro**-**Ile**-**Tyr**(^{t}Bu)-OMe
92% yield, >19:1 d.r.

To an oven-dried reaction tube equipped with a stir bar was added Cbz-Ala-Gly-Pro-OH (0.75 mmol, 1.0 equiv.), H-Ile-Tyr(^{t}Bu)-OMe (1.125 mmol, 1.5 equiv.), PPh_3 (0.225 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%). The tube was sealed and placed under nitrogen before MeCN (7.5 mL), TMDS (2.25 mmol, 3.0 equiv.) and 2,4,6-collidine (1.125 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 24 h. Upon complete consumption of the starting material, the reaction mixture was concentrated and purified through column chromatography to afford Cbz-Ala-Gly-Pro-Ile-Tyr(^{t}Bu)-OMe **63** as a white solid (499.5 mg, 92% yield).



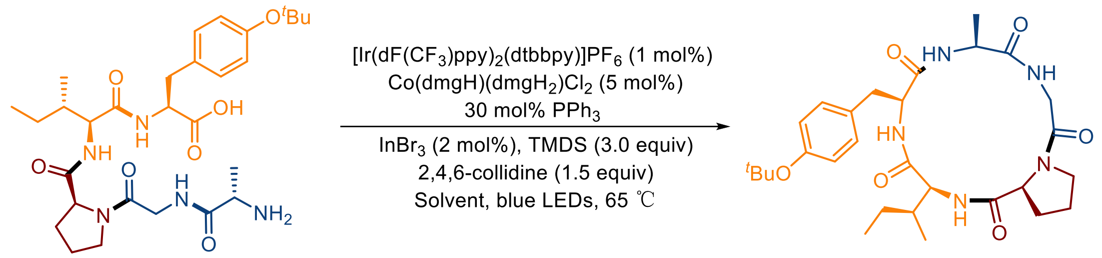
63, Cbz-**Ala**-**Gly**-**Pro**-**Ile**-**Tyr**(^{t}Bu)-OMe

63', H-**Ala**-**Gly**-**Pro**-**Ile**-**Tyr**(^{t}Bu)-OH
91% yield, >19:1 d.r. (2 steps)

To a solution of Cbz-Ala-Gly-Pro-Ile-Tyr(^{t}Bu)-OMe (499.5 mg, 0.69 mmol, 1.0 equiv.) in THF (2.8 mL) was added 0.25N NaOH (0.73 mmol, 1.05 equiv.). The mixture was stirred for 30 min at room temperature. Upon complete consumption of the starting material, the reaction mixture was diluted with H_2O and the aqueous layer washed with EtOAc. The aqueous layer was then adjusted to pH ≈ 2 with 1N HCl and extracted with EtOAc twice. The combined extracts were dried over sodium sulfate and concentrated to afford Cbz-Ala-Gly-Pro-Ile-Tyr(^{t}Bu)-OH as a white solid without further purified (450.6 mg, 92% yield).

Cbz-Ala-Gly-Pro-Ile-Tyr(^{t}Bu)-OH (450.6 mg, 0.63 mmol, 1.0 equiv.) in absolute methanol (6.3 mL) was performed in the presence of Pd/C (122.9 mg) at room temperature. The reaction was allowed to stir in an atmosphere of hydrogen (balloon, 1 atm) overnight, then the mixture was filtrated over celite, and the organic solvent was evaporated to afford H-Ala-Gly-Pro-Ile-Tyr(^{t}Bu)-OH **63'** as a white solid without further purified (359.1 mg, 99% yield).

Table S10. Optimization of cyclic peptide synthesis



63', H-**Ala**-**Gly**-**Pro**-**Ile**-**Tyr**(^{t}Bu)-OH

64, **(^{t}Bu)-fanlizhicyclopeptide B**

entry[a]	solvent	concentration (M)	yield(%)[b]
1	MeCN	0.1	15
2	MeCN	0.05	15
3	MeCN	0.03	19
4	MeCN/DMF (4:1)	0.03	39
5	MeCN/DMA (4:1)	0.03	33
6	MeCN/DMSO (4:1)	0.03	13
7[c]	MeCN/DMF (4:1)	0.03	25
8[d]	MeCN/DMF (4:1)	0.03	36

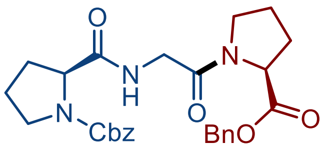
9[e]	MeCN/DMF (4:1)	0.03	36

[a]H-Ala-Gly-Pro-Ile-Tyr(^{t}Bu)-OH **63'** (0.2 mmol, 1.0 equiv.). [b]Yields of isolated products. [c][Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 (2 mol%) and Co(dmgH)(dmgH$_2$)Cl_2 (10 mol%). [d]PPh_3 (50 mol%). [e]HOBt (0.2 mmol, 1.0 equiv.) was added.

To an oven-dried reaction tube equipped with a stir bar was added H-Ala-Gly-Pro-Ile-Tyr(^{t}Bu)-OH (0.2 mmol, 1.0 equiv.), PPh_3 (0.06 mmol, 30 mol%), $InBr_3$ (2 mol%), [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 (1 mol%) and Co(dmgH)(dmgH$_2$)Cl_2 (5 mol%). The tube was sealed and placed under nitrogen before MeCN (4.8 mL), DMF (1.2 mL), TMDS (0.6 mmol, 3.0 equiv.) and 2,4,6-collidine (0.3 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 24 h. Then the reaction mixture was concentrated and purified through column chromatography to afford (^{t}Bu)-fanlizhicyclopeptide B **64** as a white solid (43.1 mg, 39% yield).

5.6 Characterization data

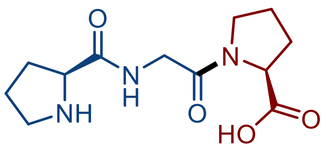
Cbz-Pro-Gly-Pro-OBzl



58

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 6.62 (m, 11H), 5.34 – 4.90 (m, 4H), 4.78 – 4.24 (m, 2H), 4.24 – 3.65 (m, 2H), 3.63 – 3.25 (m, 4H), 2.33 – 1.63 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.4, 166.6, 155.4, 136.4, 135.4, 128.5, 128.3, 128.2, 128.1, 127.8, 127.6, 66.9, 66.6, 60.6, 58.7, 46.8, 45.7, 41.8, 31.1, 28.7, 24.3, 21.9. HRMS-ESI: calcd for $C_{27}H_{32}N_3O_6^+$ ($[M + H]^+$) m/z 494.22856, found 494.22822.

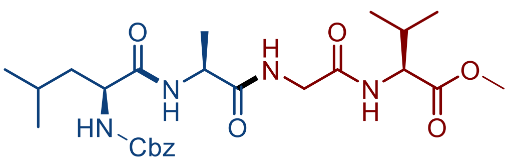
Proglyuprol



58'

Colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 4.55 – 4.29 (m, 2H), 4.23 – 3.93 (m, 2H), 3.74 – 3.37 (m, 4H), 2.59 – 1.71 (m, 8H). ^{13}C NMR (100 MHz, CD_3OD) δ 176.2, 169.3, 167.4, 60.5, 59.7, 46.2, 41.6, 31.4, 29.9, 24.4, 23.8, 22.2. HRMS-ESI: calcd for $C_{12}H_{20}N_3O_4^+$ ($[M + H]^+$) m/z 270.14483, found 270.14443.

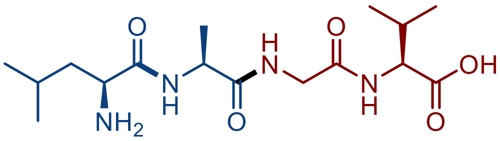
Cbz-Leu-Ala-Gly-Val-OMe



59

White solid, m.p.: 129 – 131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.57 (m, 2H), 7.44 (d, J = 8.0 Hz, 1H), 7.38 – 7.24 (m, 5H), 5.96 (d, J = 12.0 Hz, 1H), 5.24 – 4.94 (m, 2H), 4.85 – 4.64 (m, 1H), 4.61 – 4.51 (m, 1H), 4.50 – 4.32 (m, 1H), 4.24 – 3.98 (m, 2H), 3.69 (s, 3H), 2.18 – 2.10 (m, 1H), 1.76 – 1.48 (m, 3H), 1.35 (t, J = 4.0 Hz, 3H), 1.08 – 0.70 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.5, 172.3, 168.9, 156.4, 136.3, 128.5, 128.1, 127.9, 66.9, 57.3, 53.5, 52.1, 48.9, 43.1, 42.1, 31.2, 24.6, 22.9, 22.0, 18.9, 17.9. HRMS-ESI: calcd for $C_{25}H_{39}N_4O_7^+$ ([M + H]$^+$) *m/z* 507.28133, found 507.28172.

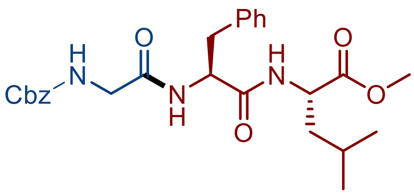
LAGV



59’

White solid, m.p.: 143 – 145 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 4.34 – 4.18 (m, 2H), 4.12 – 3.99 (m, 1H), 3.96 – 3.83 (m, 1H), 3.80 – 3.69 (m, 1H), 3.34 (s, 1H), 2.26 – 2.12 (m, 1H), 1.83 – 1.59 (m, 3H), 1.51 – 1.34 (m, 3H), 1.16 – 0.97 (m, 6H), 0.97 – 0.84 (m Hz, 6H). ^{13}C NMR (100 MHz, CD_3OD) δ 175.8, 173.5, 173.4, 169.7, 59.3, 51.6, 49.7, 42.3, 40.1, 30.8, 24.0, 21.8, 21.0, 18.7, 17.4, 16.2. HRMS-ESI: calcd for $C_{16}H_{31}N_4O_5^+$ ([M + H]$^+$) *m/z* 359.22890, found 359.22902.

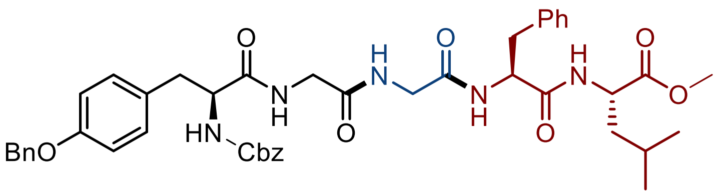
Cbz-Gly-Phe-Leu-OMe



60

White solid, m.p.: 114 – 117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.26 (m, 5H), 7.25 – 7.00 (m, 6H), 6.06 (s, 1H), 5.07 (s, 2H), 4.95 – 4.78 (m Hz, 1H), 4.63 – 4.44 (m, 1H), 3.86 (d, *J* = 4.0 Hz, 2H), 3.63 (s, 3H), 3.18 – 2.82 (m, 2H), 1.69 – 1.35 (m, 3H), 1.03 – 0.62 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 171.0, 169.3, 156.7, 136.4, 136.3, 129.4, 128.5, 128.4, 128.1, 128.0, 126.8, 67.0, 54.3, 52.2, 50.9, 44.2, 41.1, 38.6, 24.7, 22.6, 21.9. HRMS-ESI: calcd for $C_{26}H_{34}N_3O_6^+$ ([M + H]$^+$) *m/z* 484.24421, found 484.24340.

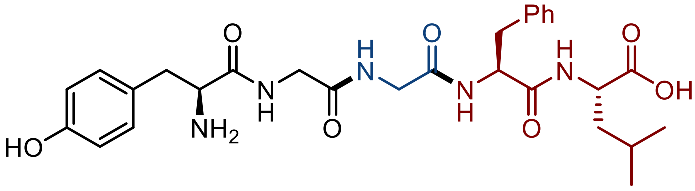
Cbz-Tyr(Bzl)-Gly-Gly-Phe-Leu-OMe



61

White solid, m.p.: 102 – 105 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 – 7.32 (m, 5H), 7.31 – 7.15 (m, 10H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.10 – 4.93 (m, 4H), 4.71 – 4.65 (m, 1H), 4.49 – 4.40 (m, 1H), 4.38 – 4.23 (m, 1H), 3.97 – 3.71 (m, 4H), 3.97 – 3.71 (m, 3H), 3.23 – 3.02 (m, 2H), 2.00 – 2.72 (m, 2H), 1.75 – 1.48 (m, 3H), 1.02 – 0.72 (m, 6H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.5, 172.9, 172.0, 170.7, 169.8, 157.7, 157.1, 137.3, 136.9, 136.7, 130.0, 129.2, 129.0, 128.1, 128.0, 128.0, 127.6, 127.4, 127.3, 127.1, 126.3, 114.5, 69.5, 66.3, 56.9, 54.4, 51.3, 50.8, 42.5, 41.9, 39.9, 37.4, 36.5, 24.4, 21.9, 20.5. HRMS-ESI: calcd for $C_{44}H_{52}N_5O_9^+$ ([M + H]$^+$) *m/z* 794.37595, found 794.37262.

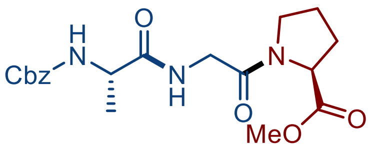
Leu-enkephalin



61'

White solid, m.p.: 148 – 151 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 – 7.11 (m, 5H), 7.10 – 6.95 (m, 2H), 6.77 – 6.58 (m, 2H), 4.70 – 4.60 (m, 1H), 4.56 – 4.46 (m, 1H), 4.46 – 4.31 (m, 1H), 3.88 – 3.63 (m, 4H), 3.20 (dt, *J* = 12.0, 4.0 Hz, 1H), 3.04 (dt, *J* = 12.0, 4.0 Hz, 1H), 3.00 – 2.83 (m, 2H), 1.79 – 1.55 (m, 3H), 1.06 – 0.73 (m, 6H). ^{13}C NMR (100 MHz, CD_3OD) δ 175.0, 174.6, 172.4, 172.1, 170.1, 159.0, 155.9, 137.1, 130.1, 128.9, 128.9, 128.0, 128.0, 127.6, 126.3, 126.3, 114.8, 54.6, 51.0, 43.3, 42.0, 40.3, 37.1, 36.9, 24.5, 22.0, 20.5. HRMS-ESI: calcd for $C_{28}H_{38}N_5O_7^+$ ($[M + H]^+$) *m*/*z* 556.27658, found 556.27601.

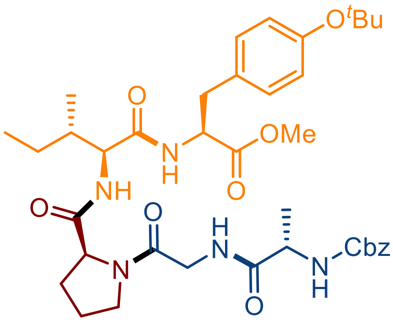
Cbz-Ala-Gly-Pro-OMe



62

White oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 6.86 (m, 6H), 6.17 – 5.88 (m, 1H), 5.24 – 4.91 (m, 2H), 4.62 – 4.43 (m, 1H), 4.43 – 4.19 (m, 1H), 4.19 – 3.76 (m, 2H), 3.69 (s, 3H), 3.63 – 3.28 (m, 2H), 2.30 – 1.71 (m, 4H), 1.51 – 1.19 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 172.2, 166.9, 155.9, 136.4, 128.4, 128.0, 66.7, 58.8, 52.3, 50.5, 45.9, 41.8, 28.9, 24.5, 18.8. HRMS-ESI: calcd for $C_{19}H_{26}N_3O_6^+$ ($[M + H]^+$) *m*/*z* 392.18161, found 392.18082.

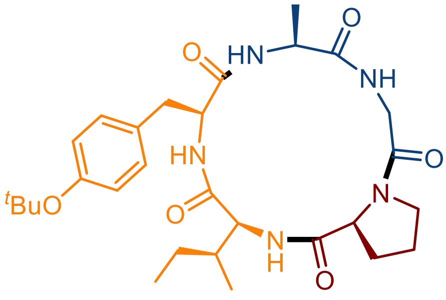
Cbz-Ala-Gly-Pro-Ile-Tyr(^{t}Bu)-OMe



63

White solid, m.p.: 189 – 191 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.37 – 7.27 (m, 5H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.93 (d, *J* = 8.0 Hz, 1H), 5.22 – 4.97 (m, 2H), 4.77 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.65 – 4.33 (m, 2H), 4.31 – 3.90 (m, 3H), 3.74 – 3.56 (m, 4H), 3.52 – 3.36 (m, 1H), 3.02 (d, *J* = 8.0 Hz, 2H), 2.24 – 1.71 (m, 5H), 1.48 – 1.39 (m, 1H), 1.36 (d, *J* = 8.0 Hz, 3H), 1.33 – 1.24 (m, 9H), 1.12 – 1.01 (m, 1H), 0.92 – 0.72 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 171.8, 171.3, 170.8, 167.8, 156.0, 154.4, 136.3, 130.6, 129.7, 128.5, 128.1, 128.0, 124.2, 78.4, 66.9, 60.2, 57.9, 53.4, 52.1, 50.3, 46.6, 42.1, 37.2, 36.7, 28.8, 28.7, 24.8, 24.7, 19.1, 15.3, 11.2. HRMS-ESI: calcd for $C_{38}H_{54}N_5O_9^+$ ($[M + H]^+$) *m*/*z* 724.39160, found 724.39071.

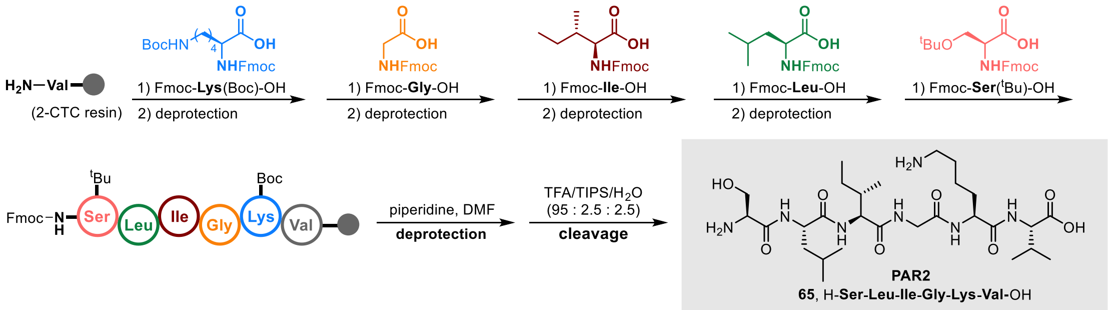
(^{t}Bu)-fanlizhicyclopeptide B



64

White solid, m.p.: 224 – 226 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.83 (s, 1H), 7.57 (d, *J* = 4.0 Hz, 1H), 7.24 – 6.99 (m, 3H), 6.86 (d, *J* = 8.0 Hz, 2H), 4.72 (s, 1H), 4.47 – 4.27 (m, 2H), 4.26 – 4.08 (m, 2H), 4.04 – 3.90 (m, 1H), 3.66 – 3.55 (m, 1H), 3.53 – 3.41 (m, 1H), 3.31 – 3.00 (m, 3H), 2.37 – 2.22 (m, 1H), 2.20 – 2.06 (m, 1H), 2.05 – 1.92 (m, 2H), 1.91 – 1.79 (m, 1H), 1.49 – 1.39 (m, 1H), 1.39 – 1.31 (m, 3H), 1.30 (s, 9H), 1.06 – 0.97 (m, 1H), 1.06 – 0.97 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 172.3, 172.2, 172.1, 168.5, 154.2, 131.6, 129.9, 124.2, 78.3, 62.6, 58.9, 56.9, 49.7, 47.0, 42.2, 36.6, 35.9, 29.7, 28.9, 25.2, 25.1, 15.9, 15.4, 10.9. HRMS-ESI: calcd for $C_{29}H_{44}N_5O_6^+$ ([M + H]$^+$) *m*/*z* 558.32861, found 558.32790.

6. Solid phase peptide synthesis (SPPS) of PAR2



Incorporating the First Amino Acid on the Solid Support

2-Chlorotrityl Chloride resin (330 mg) with a loading of 0.8-1.5 mmol/g was placed in an oven-dried reaction tube. The resin was swollen in 5 mL CH_2Cl_2 for 30 min, then filtered, and added to a solution of Fmoc-*L*-Val-OH (169.7 mg, 0.5 mmol, 1.0 equiv.), *N*, *N*-diisopropylethylamine (DIPEA, 129.3 mg, 1.0 mmol, 2.0 equiv.) in DMF/CH_2Cl_2 (1:1, v/v, 5 mL). The loading reaction was stirring for 2 h at room temperature. Then, the resin was filtered and washed with DMF (3 × 5.0 mL) and CH_2Cl_2 (3 × 5.0 mL).

Removing Fmoc-Protection

A solution of 20% piperidine in DMF (5 mL) was added to the tube with Fmoc-Val-resin and stirred for 30 min. The reaction progress was monitored by ninhydrin ethanolic solution. Then, the resin was filtered and washed with DMF (3 × 5.0 mL) and CH_2Cl_2 (3 × 5.0 mL).

Peptide Elongation

To an oven-dried reaction tube equipped with a stir bar was added Fmoc amino acid (0.5 mmol, 1.0 equiv.), PPh_3 (0.15 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%), $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%) and the resin. The tube was sealed and placed under nitrogen before MeCN (5 mL), TMDS (1.5 mmol, 3.0 equiv.) and 2,4,6-collidine (0.75 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 12 h. The reaction progress was monitored by ninhydrin ethanolic solution. Then, the resin was filtered and washed with DMF and CH_2Cl_2.

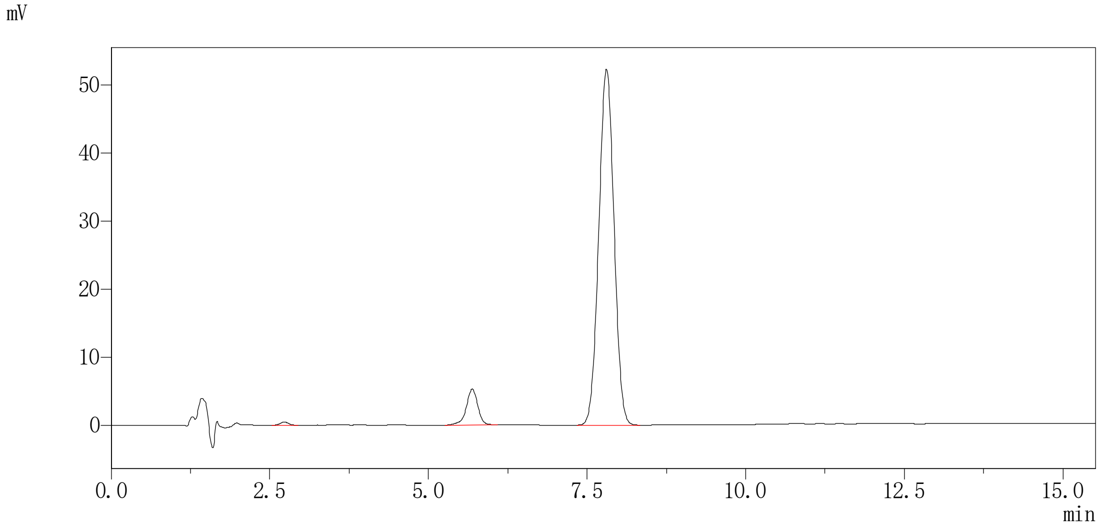
Resin Cleavage

Cleavage was then performed with 2.0 mL of a freshly prepared TFA/TIS/H_2O (95:2.5:2.5, v/v/v) solution for 2 h. The resin was then filtered and washed with pure TFA (3 × 1 mL). The collected TFA solution was evaporated, and the residue was washed by petroleum ether (4 × 5.0 mL) to afford crude product as a beige solid. The precipitate then was dissolved in MeOH for HPLC/MS analysis.

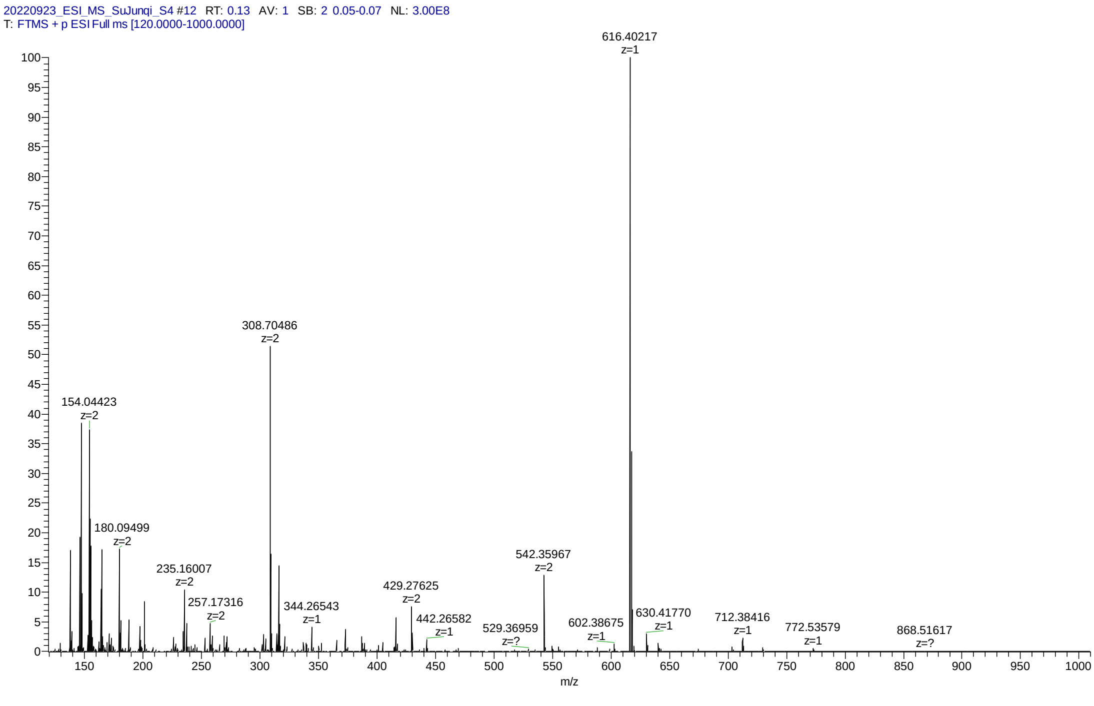
HPLC Analysis

HPLC analysis was performed using Shim-pack GIST C18 5 μm analytical column, 4.6

I.D. × 150 mm, 215 nm UV detection. The mobile phase consisted of DDI water with 0.1% (v/v) HPLC grade formic acid (solvent A), and HPLC grade acetonitrile (solvent B). Isocratic elution with 40% solvent B at a flow rate of 1.0 mL/min over 15 min gave the target peptide, t_R = 7.8 min. HRMS-ESI: calcd for $C_{28}H_{54}N_7O_8^+$ ($[M + H]^+$) *m/z* 616.40284, found: 616.40217, calcd for ($[M + 2H]^{2+}$) *m/z* 308.70505, found: 308.70486.

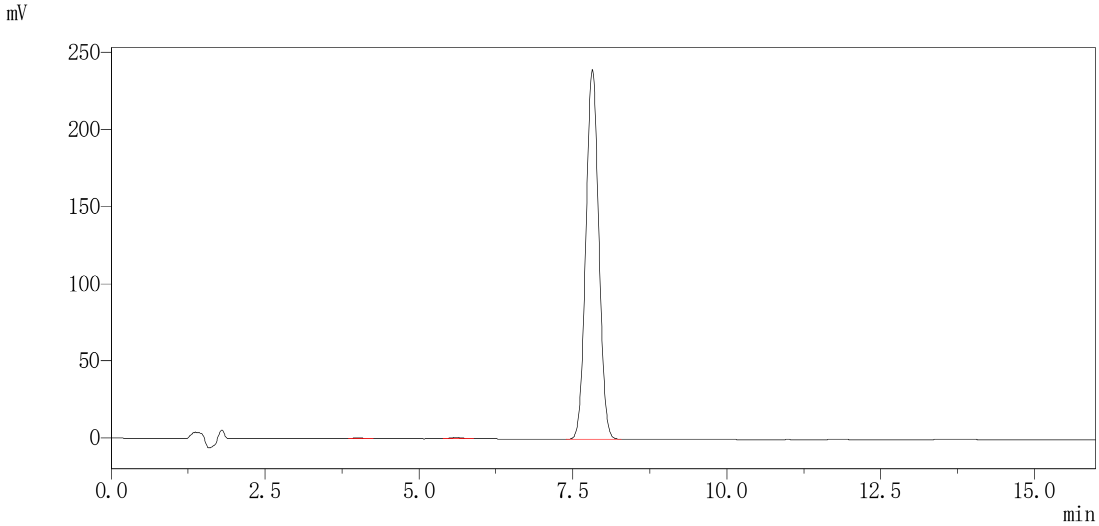


Peak	RetTime (min)	Area (μV*s)	Heigth (μV)	Area %
1	2.729	4381	467	0.463
2	5.690	66717	5289	7.056
3	7.806	874447	52340	92.481



Further purification

The crude product was dissolved in MeOH and THF, followed by precipitation with petroleum ether, then filtered and washed with petroleum ether to afford desired peptide as an off-white solid. The product was dissolved in MeOH for HPLC/MS analysis.

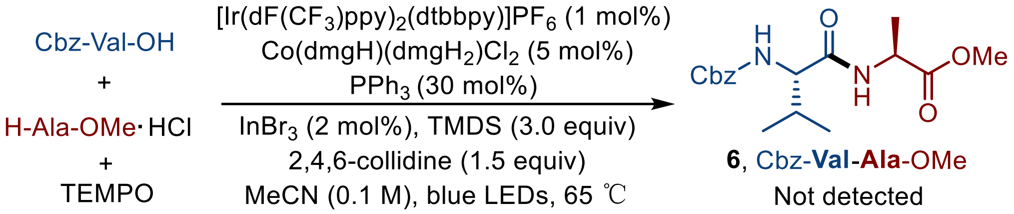


Peak	RetTime (min)	Area (µV*s)	Heigth (µV)	Area %
1	4.000	5354	549	0.152
2	5.605	11682	914	0.333
3	7.815	3493963	239700	99.515

7. Control experiments

7.1 Radical quenching experiment

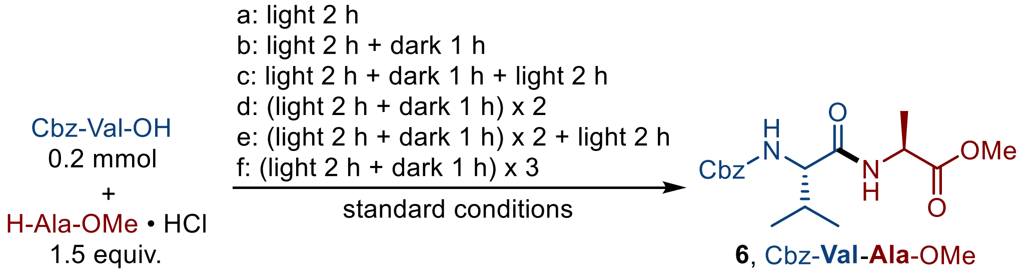
Radical quenching experiment was performed as indicated in the following. Upon addition of TEMPO (1.0 equiv.) into the reaction mixture, the coupling was completely inhibited. This result indicated the radical nature of this transformation.



Procedure: To an oven-dried reaction tube equipped with a stir bar was added Cbz-*L*-Val-OH (0.2 mmol, 1.0 equiv.), *L*-Ala-OMe·HCl (0.3 mmol, 1.5 equiv.), 2,2,6,6-tetramethylpiperidinooxy (TEMPO, 0.2 mmol, 1.0 equiv.), PPh_3 (0.06 mmol, 30 mol%), $InBr_3$ (2 mol%), [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 (1 mol%) and Co(dmgH)(dmgH_2)Cl_2 (5 mol%). The tube was sealed and placed under nitrogen before MeCN (2 mL), TMDS (0.6 mmol, 3.0 equiv.) and 2,4,6-collidine (0.3 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 12 h. No desired dipeptide product was detected.

7.2 Light ON/OFF experiments

To examine the impact of light, we conducted experiments under alternating periods of irradiation and darkness. This resulted in an interruption of the reaction progress in the absence of light and recuperation of reactivity on further illumination, which allowed precise temporal control over the entire reaction period. These results demonstrated that light is a necessary component of the reaction.



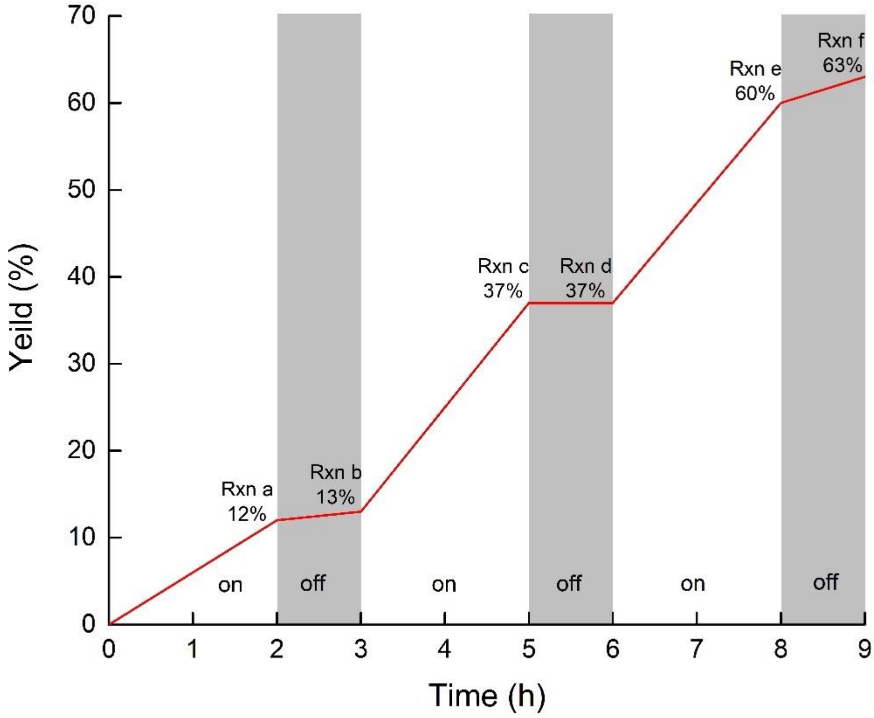
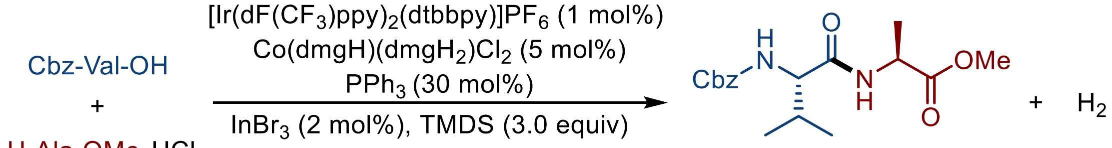


Figure S7. Light on/off expriments

7.3 Detection of hydrogen

In order to verify the evolution of H_2 during the reaction, the gas phase in the headspace of the reaction vessel was analyzed by gas chromatography after reaction for 12 h. As shown in figure S8, 0.48 mmol H_2 was detected by GC analysis using pure helium as an internal standard (Table S11 and Eq. S1). The control experiments (Table S12) indicated that a maximum amount of H_2 was detected under standard conditions. Only 0.04 mmol H_2 was detected in the absence of TMDS and $InBr_3$ (Table S12, entry 6). These results demonstrated that H_2 was generated from both Co^{III}-H and TMDS (Table S12).[4]



6, Cbz-**Val**-**Ala**-OMe

According to the general procedure (section S2.2), Cbz-*L*-Val-OH (0.2 mmol, 1.0 equiv.), *L*-Ala-OMe·HCl (0.3 mmol, 1.5 equiv.), PPh_3 (0.06 mmol, 30 mol%), $InBr_3$ (2 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1 mol%) and $Co(dmgH)(dmgH_2)Cl_2$ (5 mol%)

were added to an oven-dried reaction tube equipped with a stir bar. The tube was sealed and placed under nitrogen before MeCN (2 mL), TMDS (0.6 mmol, 3.0 equiv.) and 2,4,6-collidine (0.3 mmol, 1.5 equiv.) were added. Then the system was stirred under the irradiation of blue LED lamps at 65 °C for 12 h. Then 5 mL helium was injected into the reaction tube and spread evenly for five minutes. 100 μL mixture gas from the reaction tube was injected into the gas chromatography, and hydrogen was detected in 0.48 mmol. Then the reaction mixture was concentrated and purified through column chromatography to afford dipeptide **6** in 86% yield.

7.3.1 Data analysis

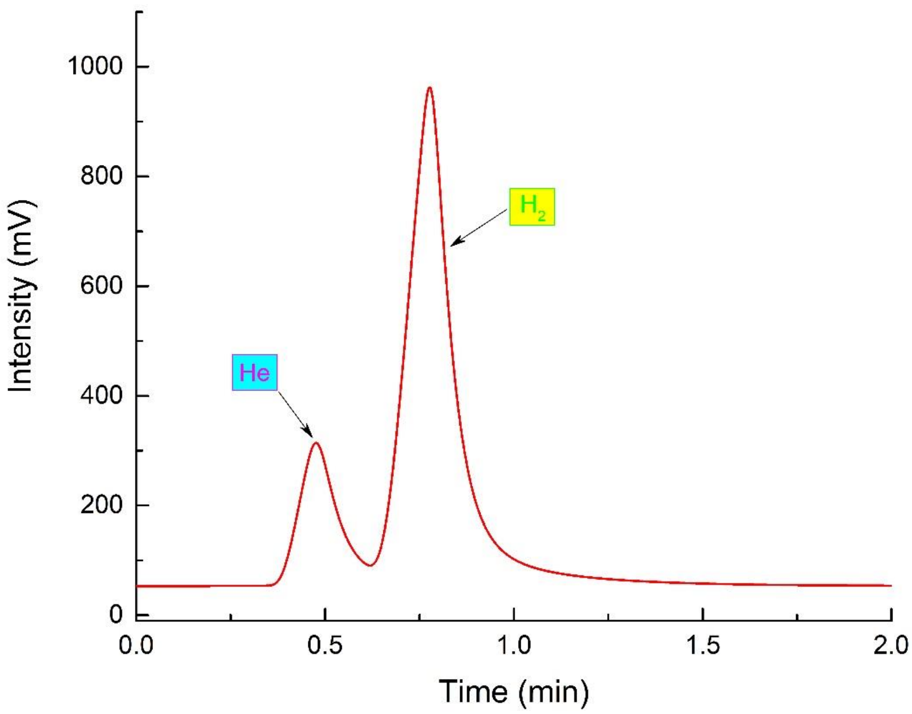


Figure S8. Monitoring of H_2 by GC.

Table S11. Data of GC

Entry	RetTime (min)	Heigth (μV)	Area
1	0.4760	261163	1889000
2	0.7773	909639	8293107

The conversion between the area and the amount of H_2 was calculated by equation S1.[5]

$$n_{H_2} = \frac{\frac{A_{H_2}}{A_{He}} \cdot f \cdot V_{He}}{V_m} \quad \text{(Eq. S1)}$$

n_{H_2} , The amount of H_2, mmol

A_{H_2} , The measured peak area of H_2,

A_{He} , The measured peak area of He,

V_{He} , The volume of injected He, mL

f = 0.5392, Response factor, [3]

V_m = 24.5 mL·mmol^{-1}, molar volume (298.15 K, 101.325 kPa).

7.3.2 Control experiments

Table S12. Detection of H_2

Entry	Variation from standard conditions	amount of H_2 (mmol)^a
1	none	0.48
2	without PPh_3	0.40
3	without **PC**·PF_6	0.43
4	without cobaloxime **A**	0.42
5	without light	0.38
6	without TMDS and $InBr_3$	0.04

^{a}Determined by GC using pure He as an internal standard.

7.4 Amidation promoted by hydrosilanes

In view of the fact that hydrosilanes have been reported as coupling agents for amide bond formation,[6] we also examined the posibility of TMDS-promoted amidation. As shown in Table S13 and Figure S9, both the control experiments and NMR analysis indicated that TMDS was not a suitable coupling reagent for the amidation.

7.4.1 Control experiments

In the presence of 3.0 equiv. of $PhSiH_3$, Cbz-Gly-OH coupled with glycine methyl ester to afford the desired dipeptide in 43% yield (Table S13, entry 1).[7] However, sterically hindered Cbz-Val-OH and H-Ala-OMe were not compatible with the conditions, only trace amount of the desired dipeptide was formed (Table S13, entry 2). These results were consistent with Charette's study.[8] In contrast, no product was detected when TMDS was utilized instead of $PhSiH_3$ (entry 3–6).

Table S13. The coupling of amino acids with **[Si-H]**

Cbz-AA_1-OH (0.2 mmol, 1.0 equiv.) + H-AA_2-OMe•HCl (1.5 equiv.) → Cbz-AA_1–AA_2-OMe

Conditions: **[Si-H]** (3.0 equiv.), 2,4,6-collidine (1.5 equiv.), MeCN (0.1 M), 65 ℃, N_2, blue LEDs

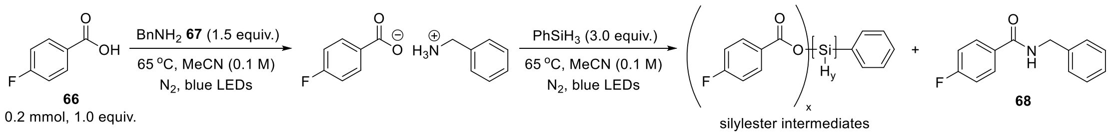
entry	AA_1	AA_2	[Si-H]	Yield[a]
1	Gly	Gly	$PhSiH_3$	43%
2	Val	Ala	$PhSiH_3$	trace
3	Gly	Gly	TMDS	N.R.
4	Val	Ala	TMDS	N.R.
5[b]	Gly	Gly	TMDS	N.R.
6[b]	Val	Ala	TMDS	N.R.

[a]Yields of isolated products. [b]$InBr_3$ (2 mol%) was added.

7.4.2 NMR analysis

Related studies by Denton[9] and Arora[3b] have demonstrated that phenylsilylester is the key intermediate for the hydrosilane-promoted amidation. To probe the mechanism, several control experiments and ^{19}F NMR spectroscopic were conducted to identify the silylester intermediate.

Firstly, we tried to detect the proposed silylester intermediates through the $PhSiH_3$ promoted amidation (Figure S9). As shown in Figure S9b, when 4-fluorobenzoic acid **66** (^{19}F δ −108.3 ppm) and benzylamine **67** were mixed in MeCN at 65 °C, the expected ammonium carboxylate was formed at δ −112.7 ppm. After addition of $PhSiH_3$ to the mixture for 5 h, we detected the formation of the desired amide **68** (δ −111.4 ppm). Furthermore, other new multiple signals were appeared at δ −106 to −108 ppm, which were assigned to the silylester intermediates. When water (0.1% TFA) was added to the reaction, the multiple signals quickly hydrolyzed back into the ammonium carboxylate and the reaction gave the product **68** in 44% yield within 12 h.



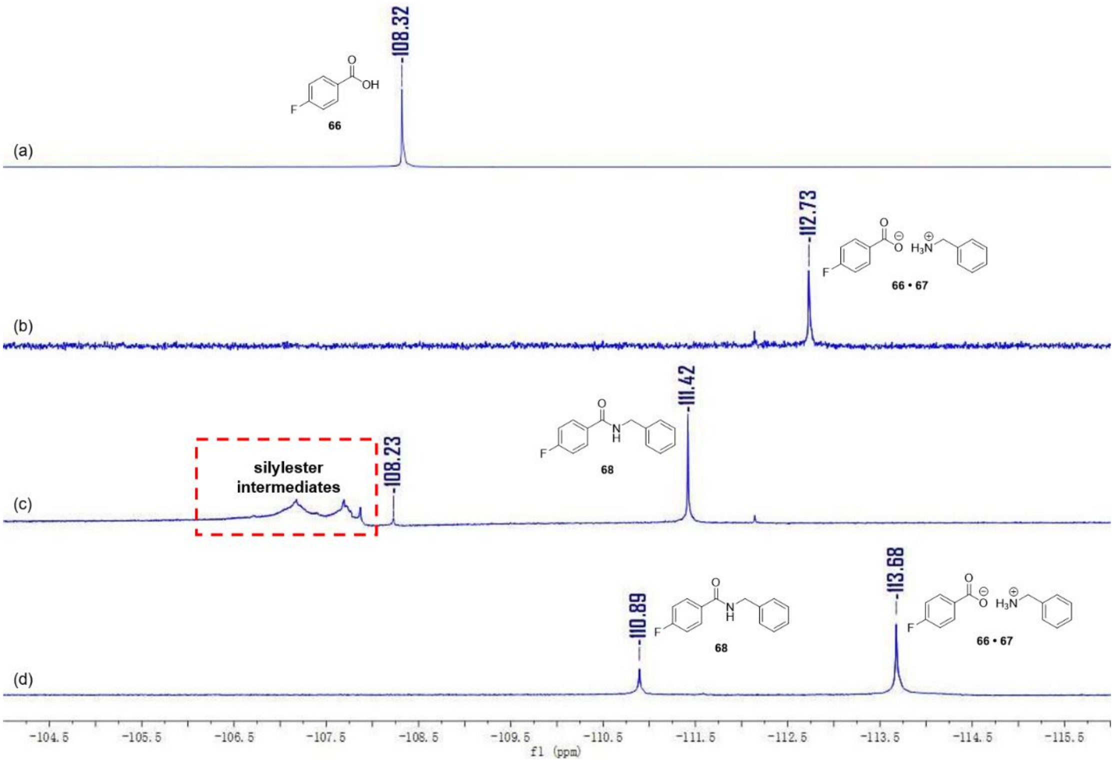
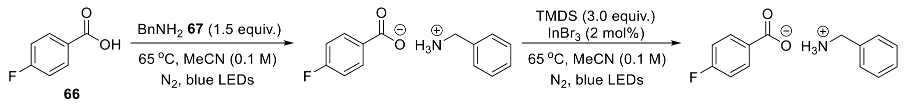


Figure S9. Evolution of the ${}^{19}F$ NMR spectra during the reaction (chemcail shift was calibrated by hexafluorobenzene at δ −164.9 ppm). (a) 4-fluorobenzoic acid **66**, (b) a mixture of 4-fluorobenzoic acid **66** and benzylamine **67**, (c) after addition of $PhSiH_3$ for 5 h, and (d) after quenching with water (0.1% TFA).

Then TMDS and $InBr_3$ were utilized to repeat above studies. As shown in Figure S10c, when TMDS and $InBr_3$ were added to the mixture of 4-fluorobenzoic acid and benzylamine, no other signals appeared in the ^{19}F NMR spectrum, indicating that the silylester intermediates and products were not formed.



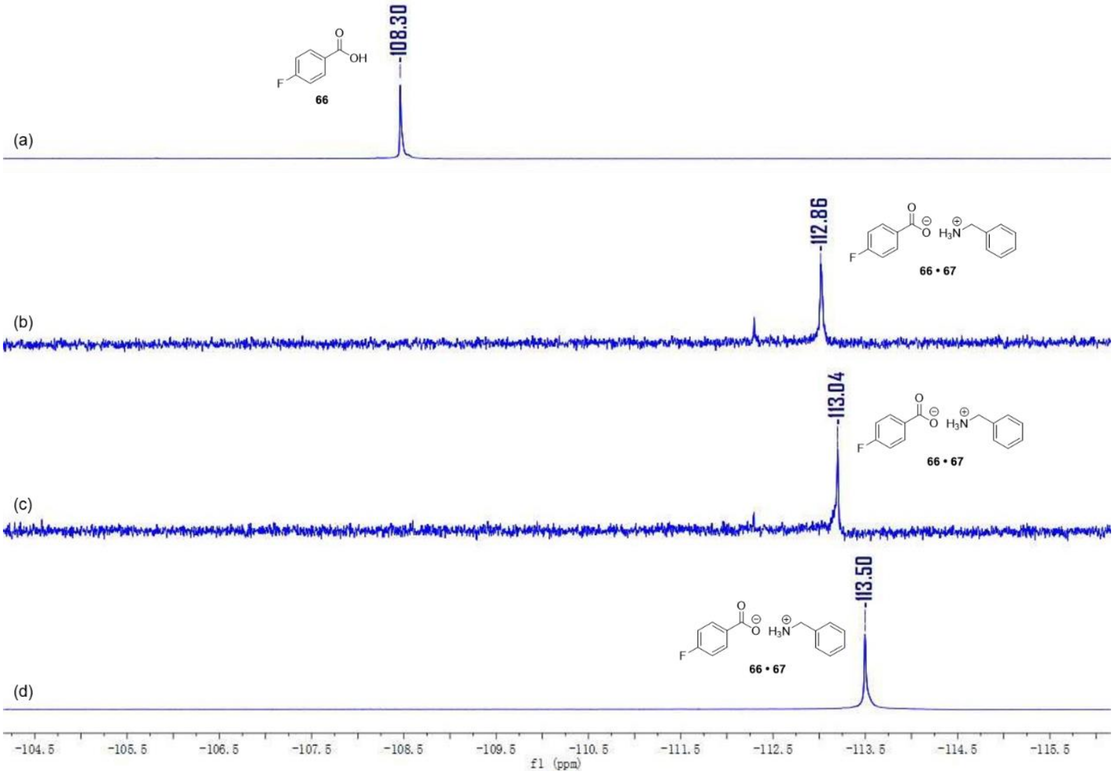
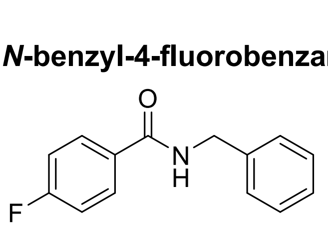


Figure S10. Evolution of the ^{19}F NMR spectra during the reaction (chemcail shift was calibrated by hexafluorobenzene at δ -164.9 ppm). (a) 4-fluorobenzoic acid **66**, (b) a mixture of 4-fluorobenzoic acid **66** and benzylamine **67**, (c) after addition of TMDS and $InBr_3$ for 5 h, and (4) after quenching with water (0.1% TFA).

***N*-benzyl-4-fluorobenzamide**

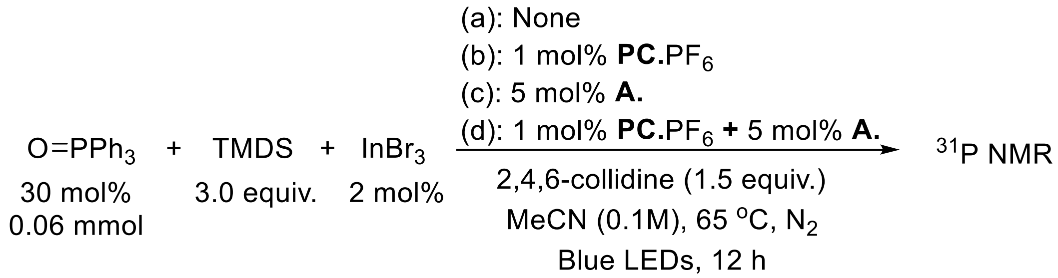


68

White solid, m.p.: 146 – 149 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.67 (m, 2H), 7.46 – 7.26 (m, 5H), 7.15 – 6.99 (m, 2H), 6.46 (s, 1H), 4.61 (d, *J* = 4.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (d, *J* = 31.0 Hz), 163.6, 138.1, 130.6 (d, *J* = 3.0 Hz), 129.4 (d, *J* = 9.0 Hz), 128.9, 128.0, 127.8, 115.7 (d, *J* = 22.0 Hz), 44.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.2. HRMS-ESI: calcd for $C_{14}H_{13}NOF^+$ ($[M + H]^+$) *m/z* 230.09757, found 230.09735.

7.5 Reduction of $Ph_3P{=}O$ to PPh_3

As shown in Figure S11, several control experiments were conducted to confirm the reduction of $Ph_3P{=}O$. Initially, a mixture of $Ph_3P{=}O$, TMDS, $InBr_3$ and 2,4,6-collidine was irradiated by blue LEDs at 65 °C. After 12 h, only one signal at δ −27.65 ppm was detected by ^{31}P NMR analysis of the mixture, which corresponds to $Ph_3P{=}O$ (Figure S11a). Similar results were obtained, when **PC**·PF_6 or cobaloxime **A** was added to the reaction mixture (Figure S11b and c). However, when **PC**·PF_6 and cobaloxime **A** were added to the reaction at the same time, a new signal appeared at δ −5.11 ppm (Figure S11d), which was assigned to PPh_3. The formation of PPh_3 was also confirmed by GCMS analysis (Figure S12), indicating that $Ph_3P{=}O$ could be reducted to PPh_3 in our condition. Further study to confirm the photoredox and cobaloxime promoted $P^{III}/P^{V}{=}O$ catalysis is currently underway in our laboratory.



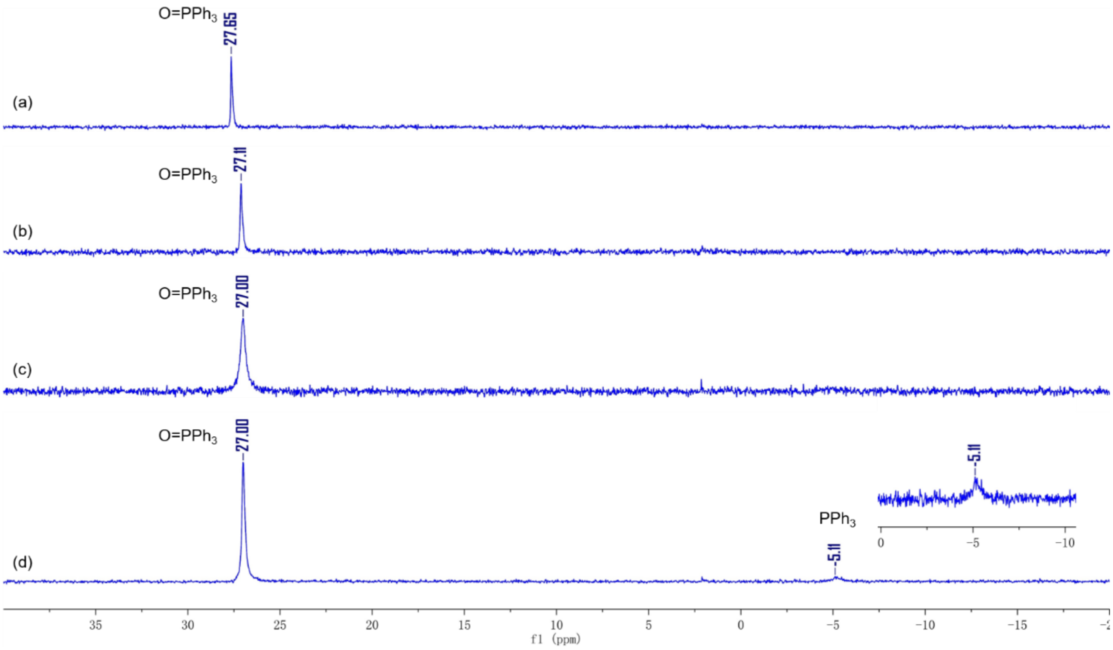


Figure S11. The ^{31}P NMR spectra for the reduction of $Ph_3P{=}O$ to PPh_3 (chemcail shift was calibrated by triphenyl phosphite at δ -127.7 ppm).

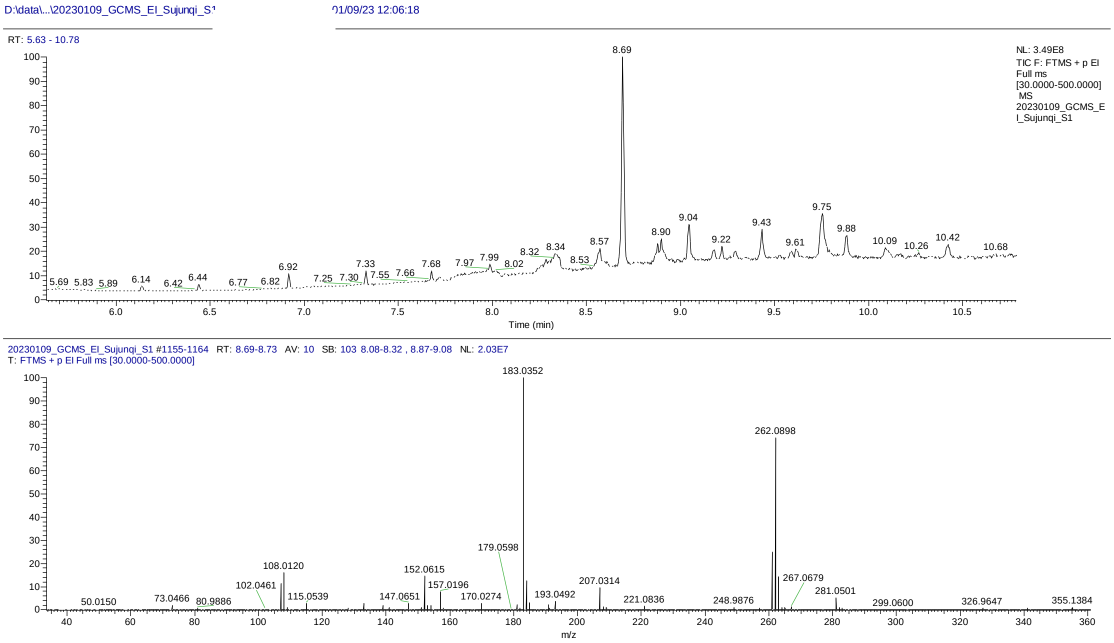


Figure S12. The GCMS spectra for the detection of PPh_3.

8. References

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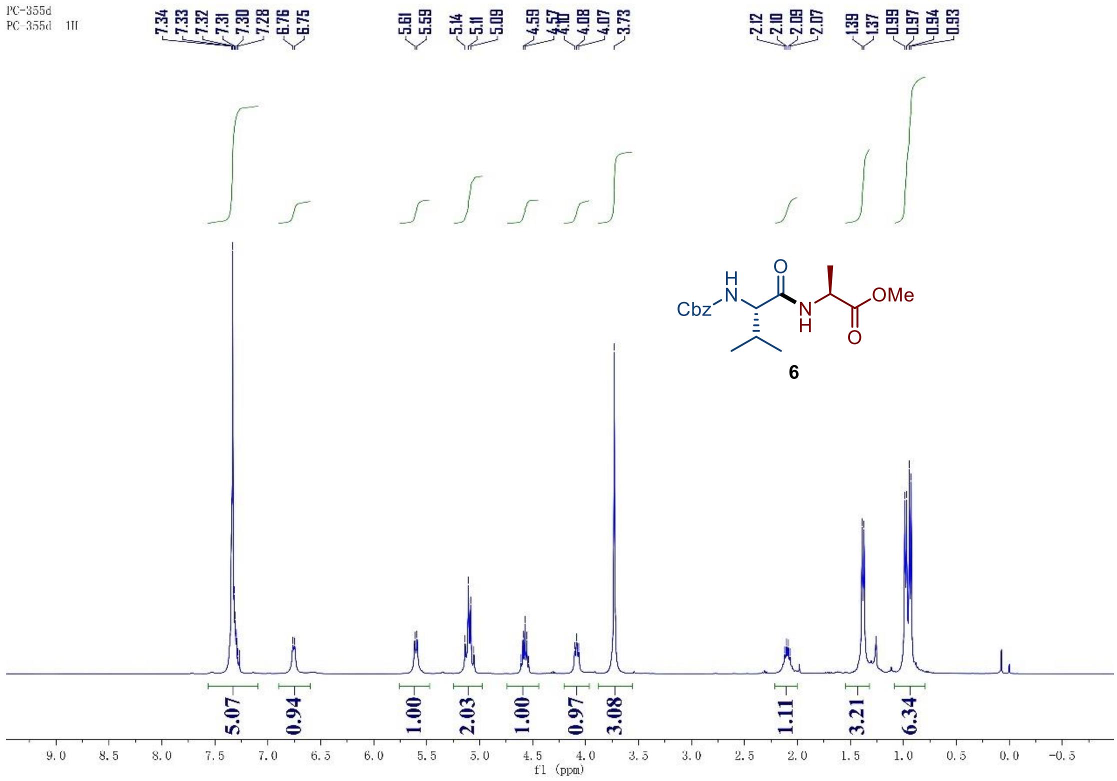
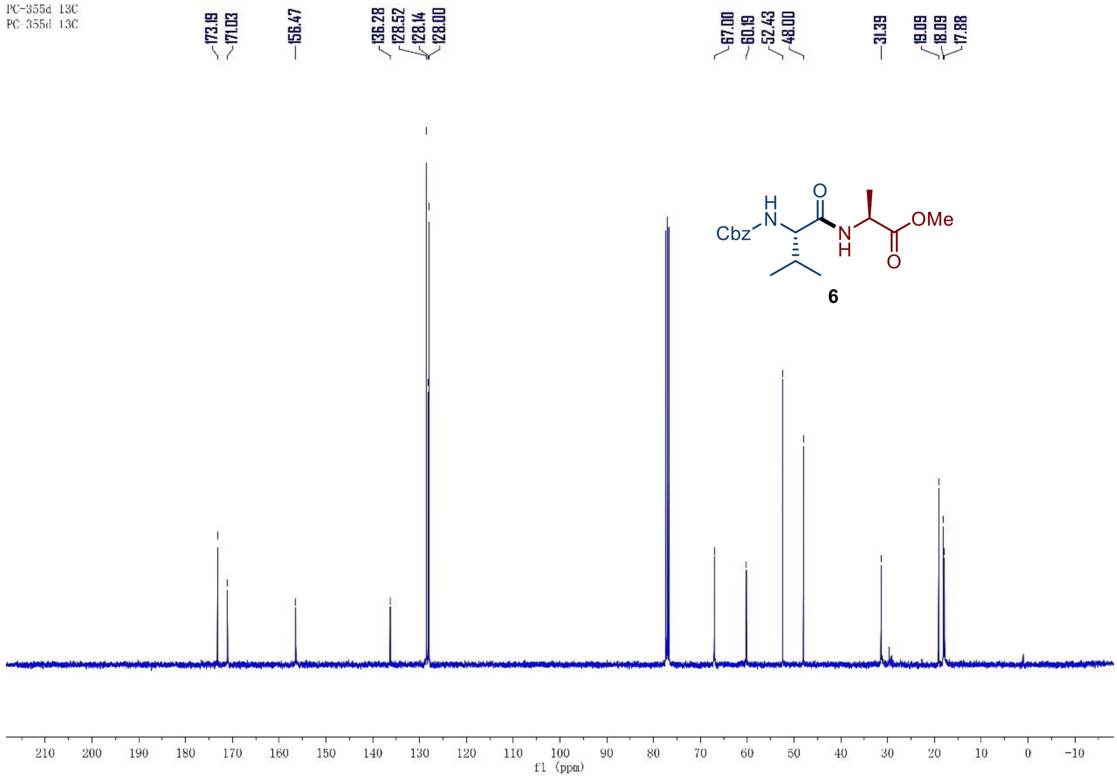
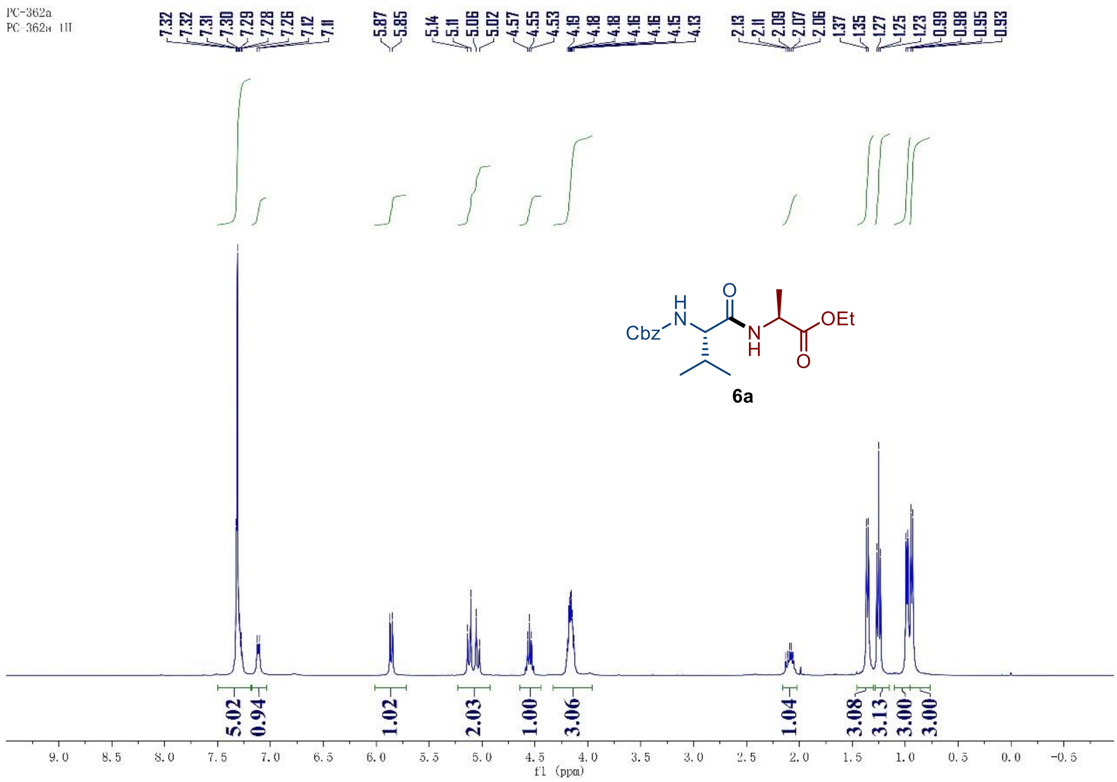
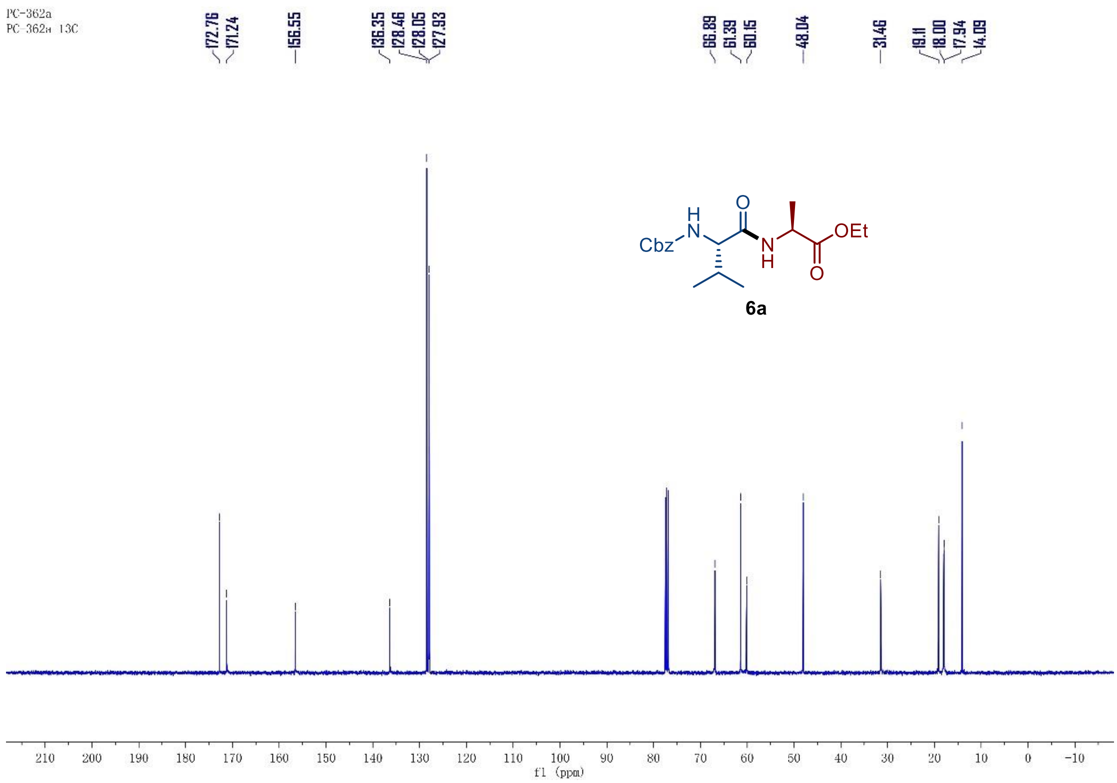
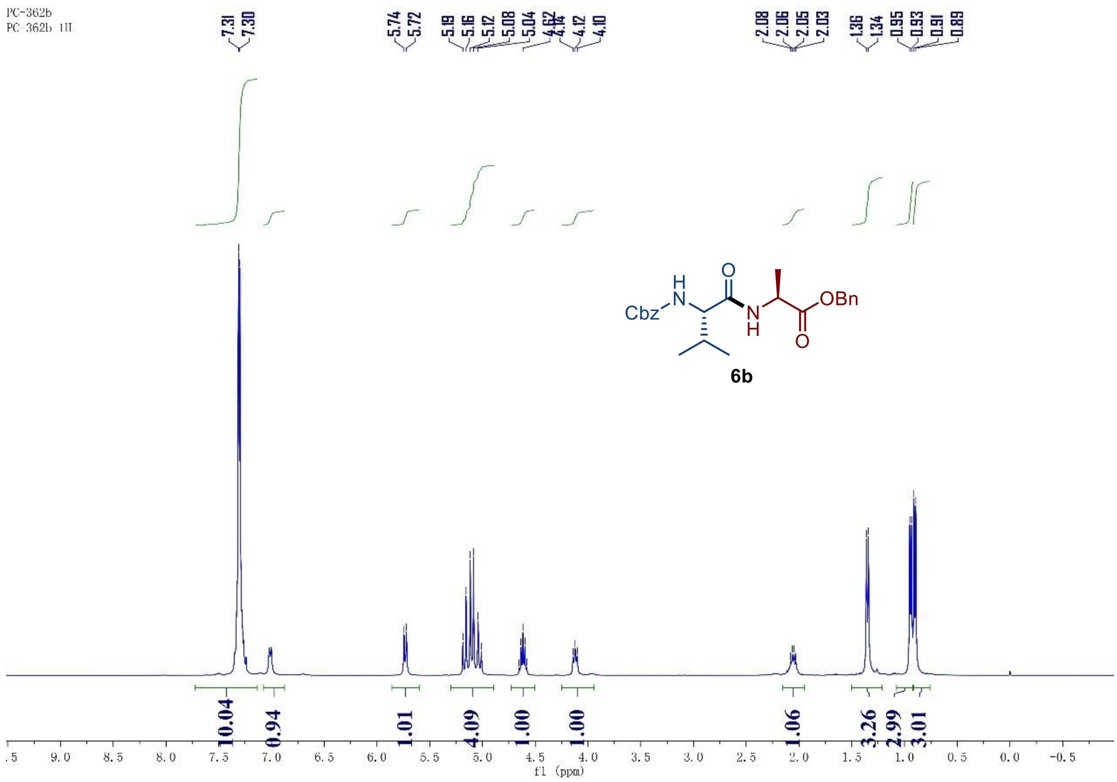
9. Copy of ^{1}H NMR and ^{13}C NMR spectra

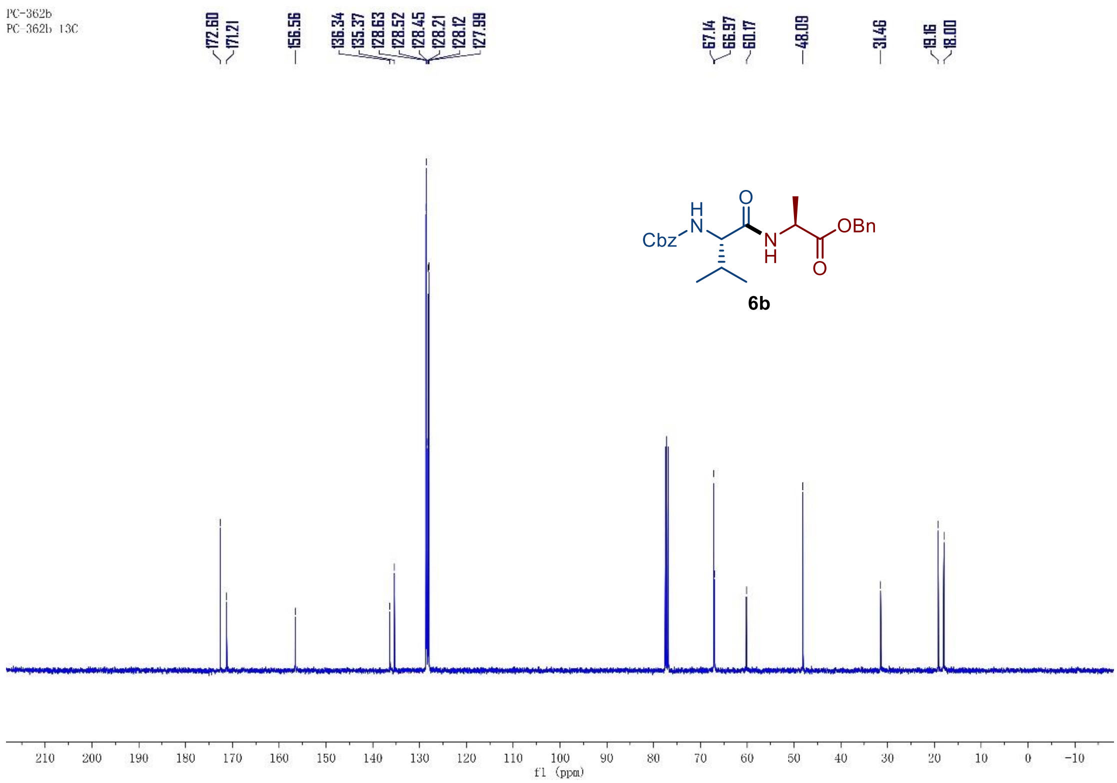


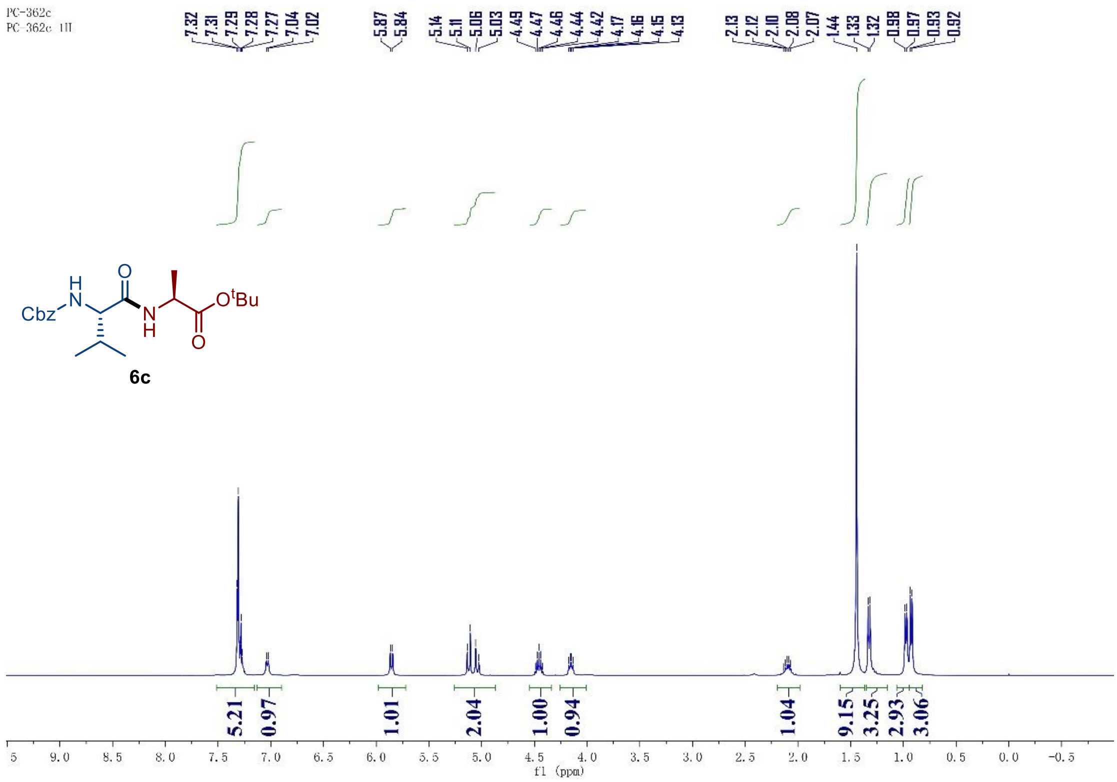


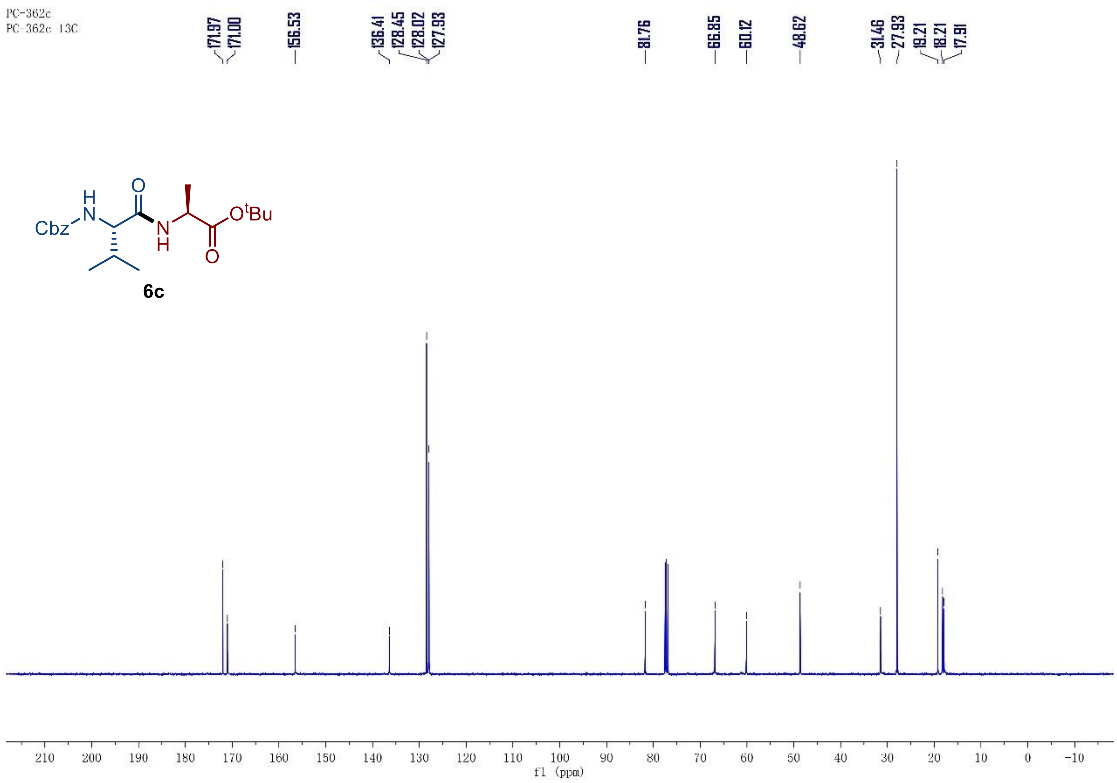

PC-362a
PC-362a 1H
7.32 7.32 7.31 7.30 7.29 7.28 7.26 7.12 7.11
5.87 5.85
5.14 5.11 5.06 5.02 4.57 4.55 4.53 4.19 4.18 4.18 4.16 4.16 4.15 4.13
2.13 2.11 2.09 2.07 2.06 1.37 1.35 1.27 1.25 1.23 0.99 0.98 0.95 0.93
Cbz
N
H
O
N
H
OEt
O
6a
5.02 0.94 1.02 2.03 1.00 3.06 1.04 3.08 3.13 3.00 3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

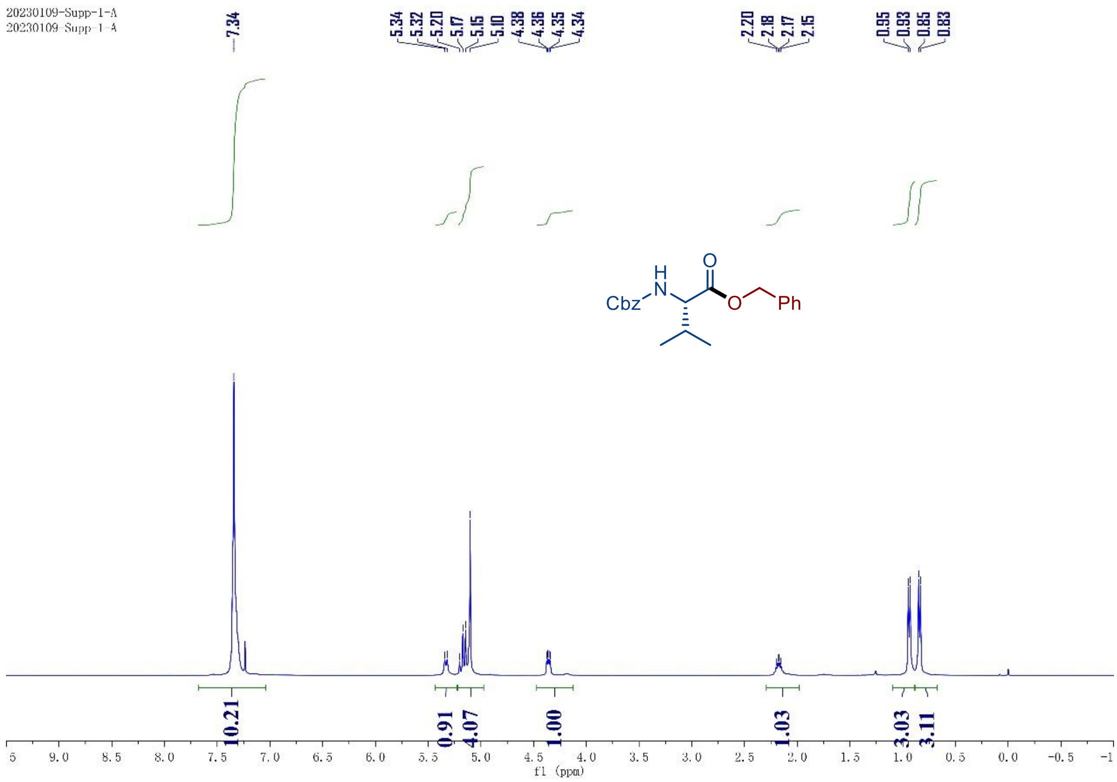

PC-362a
PC-362a 13C
172.76 171.24
156.55
136.35 128.46 128.05 127.93
66.89 61.39 60.15
48.04
31.46
19.11 18.00 17.94 14.09
Cbz
N
H
O
N
H
OEt
O
6a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

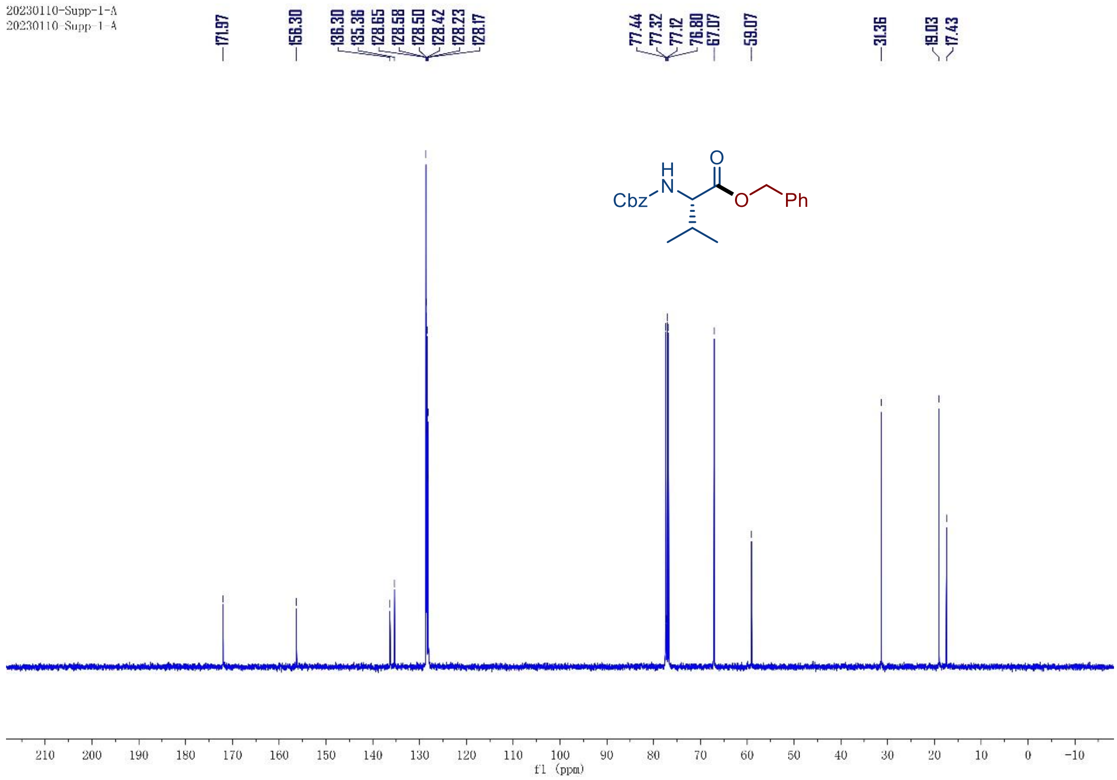

PC-362b
PC-362b 1H
7.31
7.30
5.74
5.72
5.19
5.16
5.12
5.08
5.04
4.62
4.14
4.12
4.10
2.08
2.06
2.05
2.03
1.36
1.34
0.95
0.93
0.91
0.89
Cbz
N
H
O
N
H
OBn
O
6b
10.04
0.94
1.01
4.09
1.00
1.00
1.06
3.26
2.99
3.01
f1 (ppm)

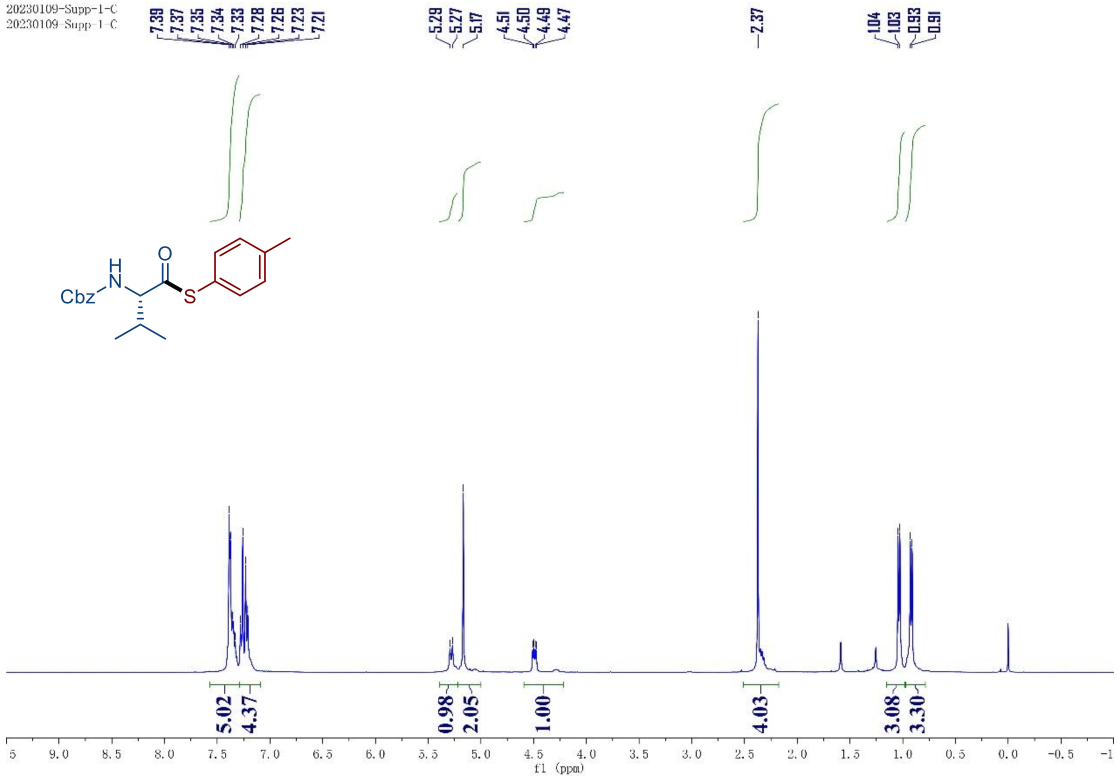

PC-362b
PC-362b 13C
172.60
171.21
156.56
136.34
135.37
128.63
128.52
128.45
128.21
128.12
127.99
67.14
66.97
60.17
48.09
31.46
19.16
18.00
Cbz
N
H
O
N
H
OBn
O
6b
f1 (ppm)

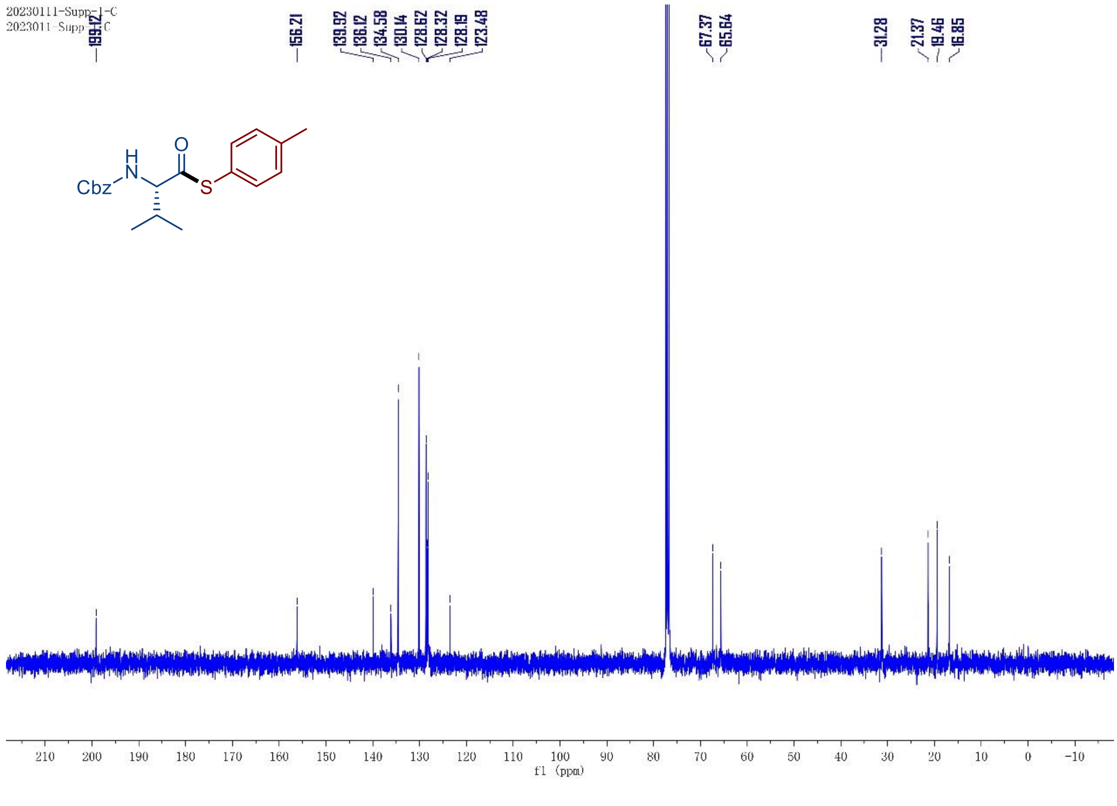


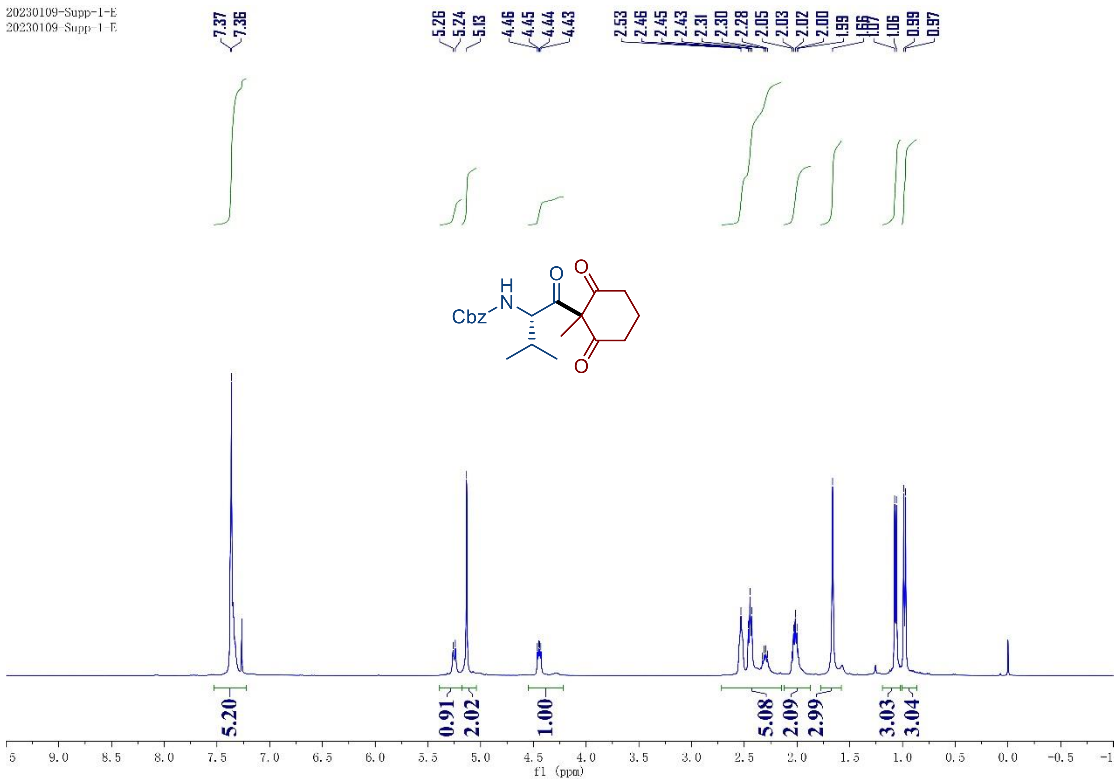


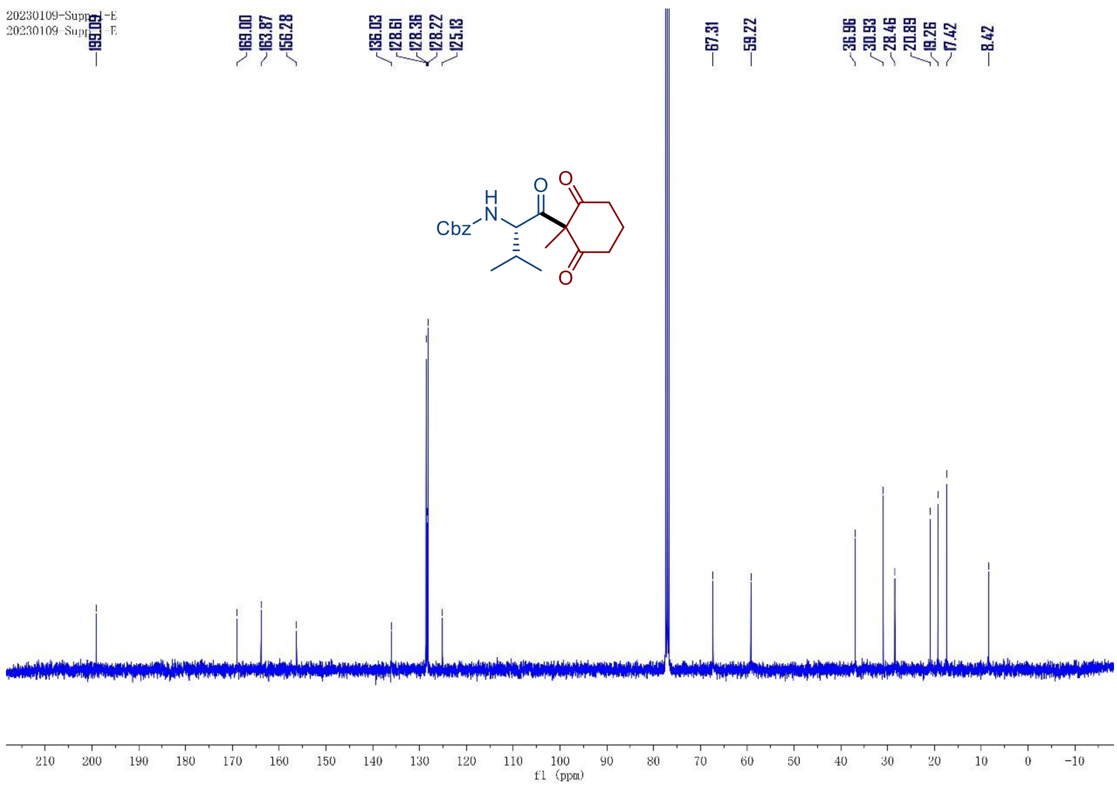

20230109-Supp-1-A
20230109-Supp-1-A
7.34
5.34 5.32 5.20 5.17 5.15 5.10 4.38 4.36 4.35 4.34
2.20 2.18 2.17 2.15
0.95 0.93 0.85 0.83
Cbz
H
N
O
O
Ph
10.21
0.91
4.07
1.00
1.03
3.03
3.11
f1 (ppm)

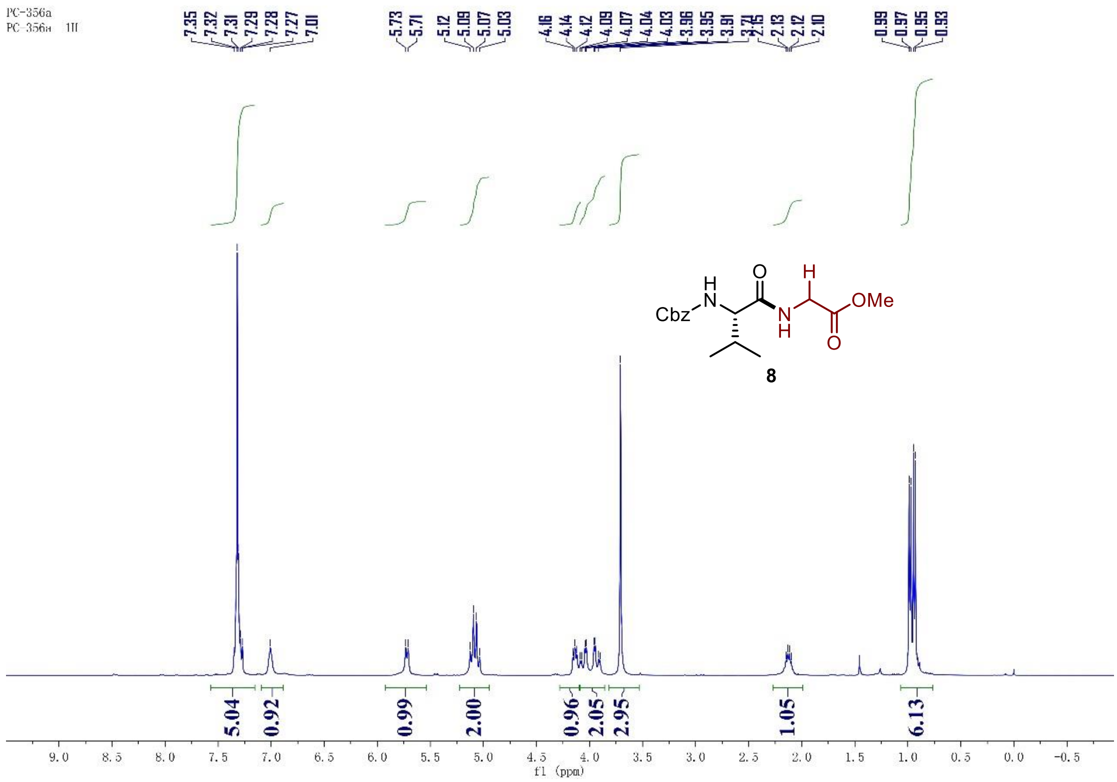

20230110-Supp-1-A
20230110-Supp-1-A
171.97
156.30
136.30 135.36 128.65 128.58 128.50 128.42 128.23 128.17
77.44 77.32 77.12 76.80 67.07
59.07
31.36
19.03 17.43
Cbz
H
N
O
O
Ph
f1 (ppm)

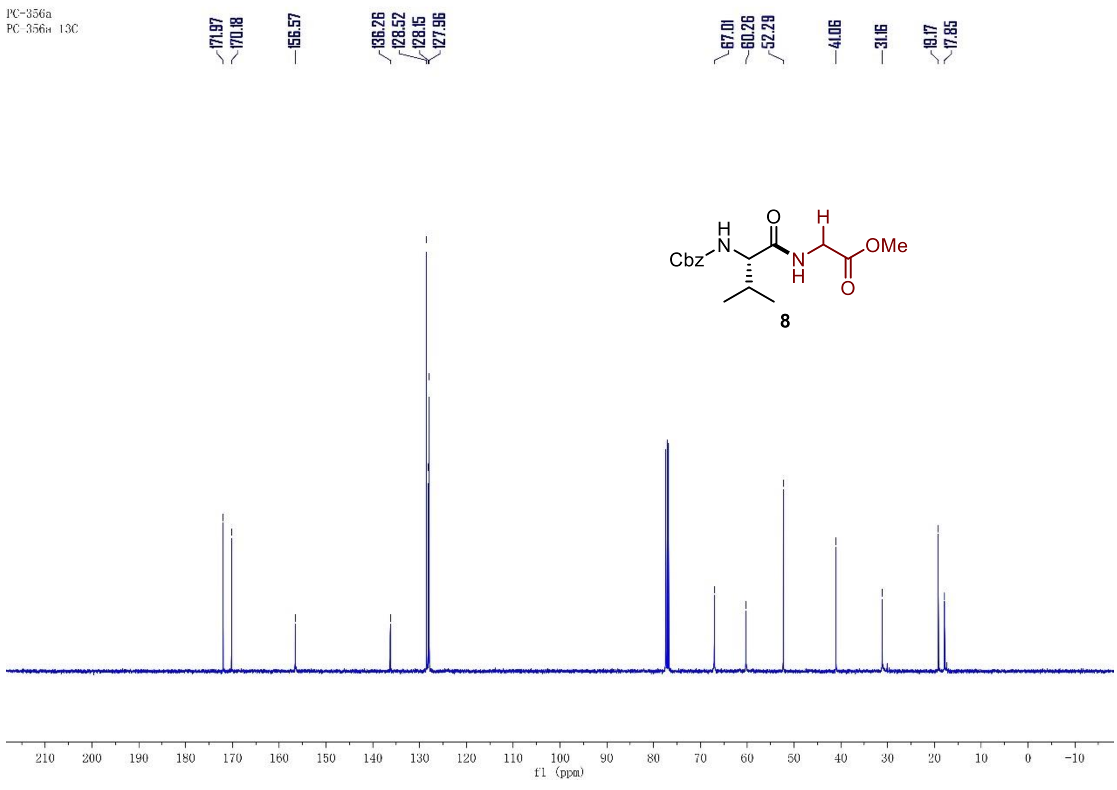

20230109-Supp-1-C
20230109-Supp-1-C
7.39
7.37
7.35
7.34
7.33
7.28
7.26
7.23
7.21
5.29
5.27
5.17
4.51
4.50
4.49
4.47
2.37
1.04
1.03
0.93
0.91
Cbz
N
H
O
S
5.02
4.37
0.98
2.05
1.00
4.03
3.08
3.30
f1 (ppm)

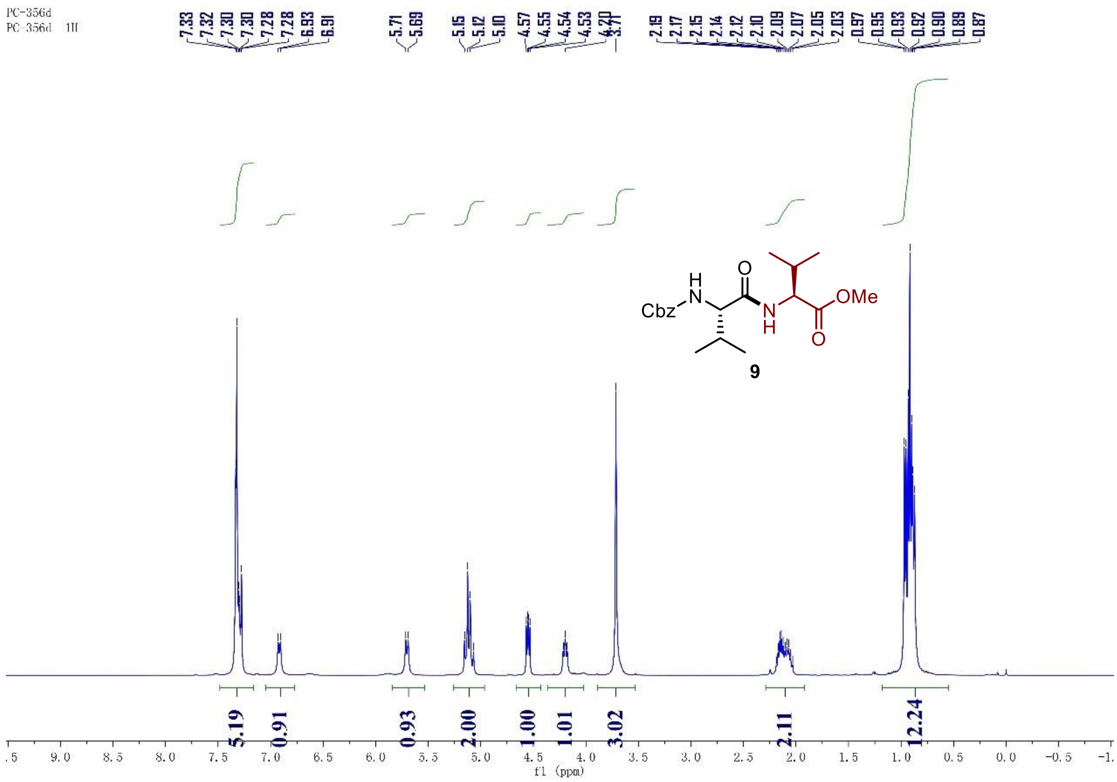

20230111-Supp-1-C
20230111-Supp-1-C
199.12
156.21
139.92
136.12
134.58
130.14
128.62
128.32
128.19
123.48
67.37
65.64
31.28
21.37
19.46
16.85
Cbz
N
H
O
S
f1 (ppm)

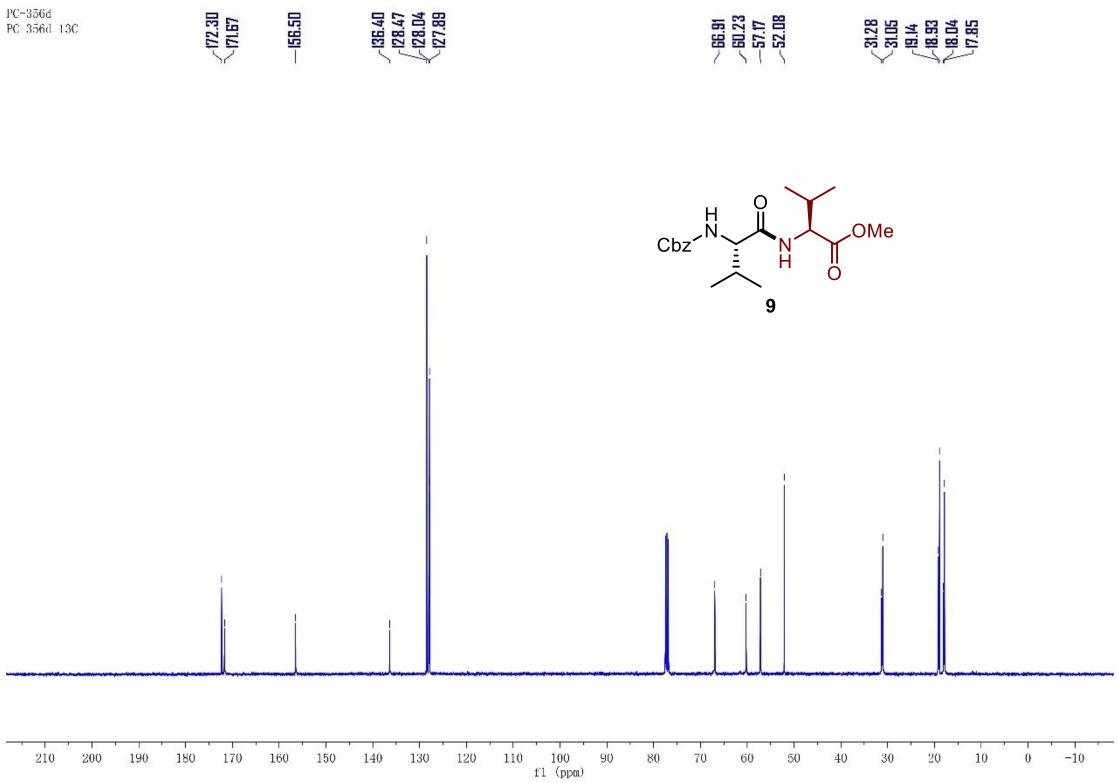

20230109-Supp-1-E
20230109-Supp-1-E
7.37
7.36
5.26
5.24
5.13
4.46
4.45
4.44
4.43
2.53
2.46
2.45
2.43
2.31
2.30
2.28
2.05
2.03
2.02
2.00
1.99
1.66
1.07
1.06
0.99
0.97
Cbz
H
N
O
O
O
5.20
0.91
2.02
1.00
5.08
2.09
2.99
3.03
3.04
f1 (ppm)

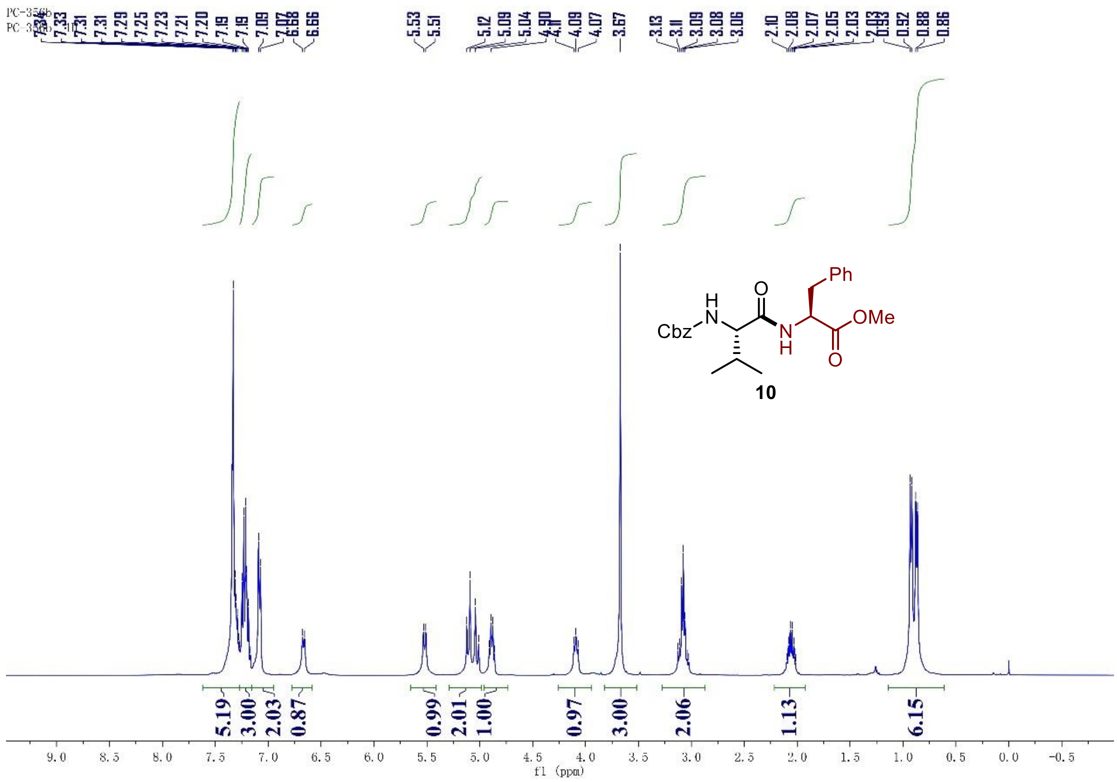

20230109-Supp-1-E
20230109-Supp-1-E
169.00
163.87
156.28
136.03
128.61
128.36
128.22
125.13
67.31
59.22
36.96
30.93
28.46
20.89
19.26
17.42
8.42
Cbz
H
N
O
O
O
f1 (ppm)

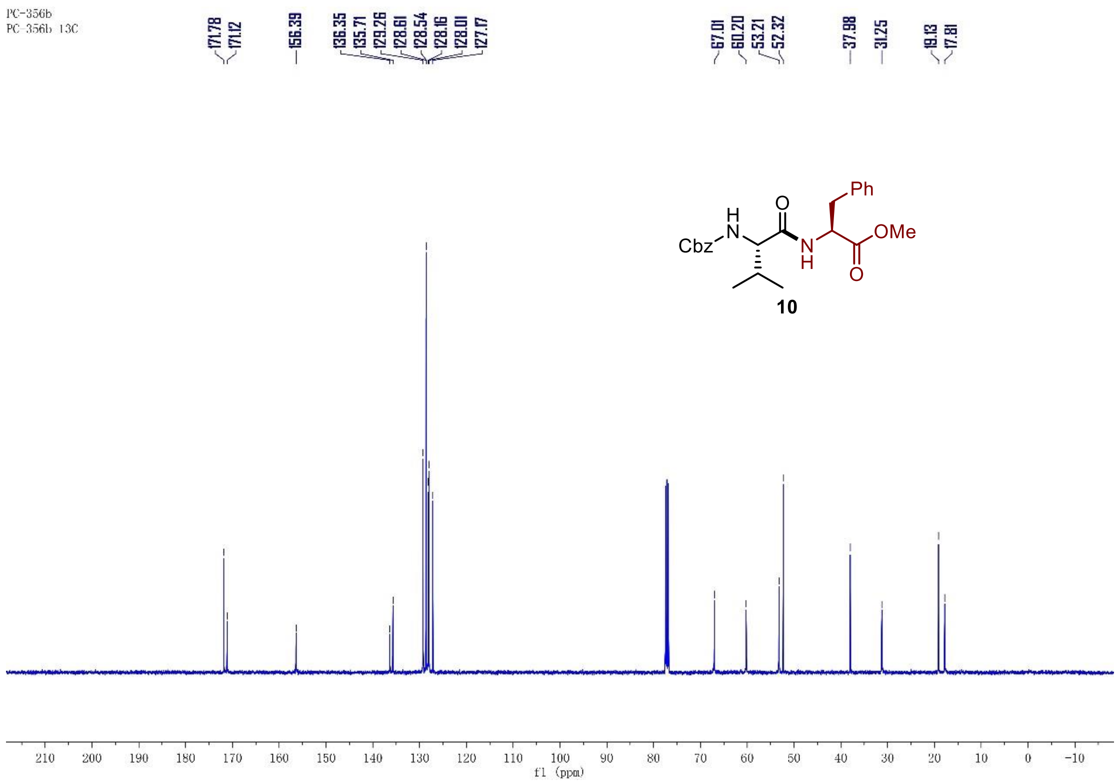

PC-356a
PC-356a 1H
7.35 7.32 7.31 7.29 7.28 7.27 7.01
5.73 5.71 5.12 5.09 5.07 5.03
4.16 4.14 4.12 4.09 4.07 4.04 4.03 3.96 3.95 3.91 3.71 2.15 2.13 2.12 2.10
0.99 0.97 0.95 0.93
Cbz
OMe
8
5.04 0.92 0.99 2.00 0.96 2.05 2.95 1.05 6.13
f1 (ppm)

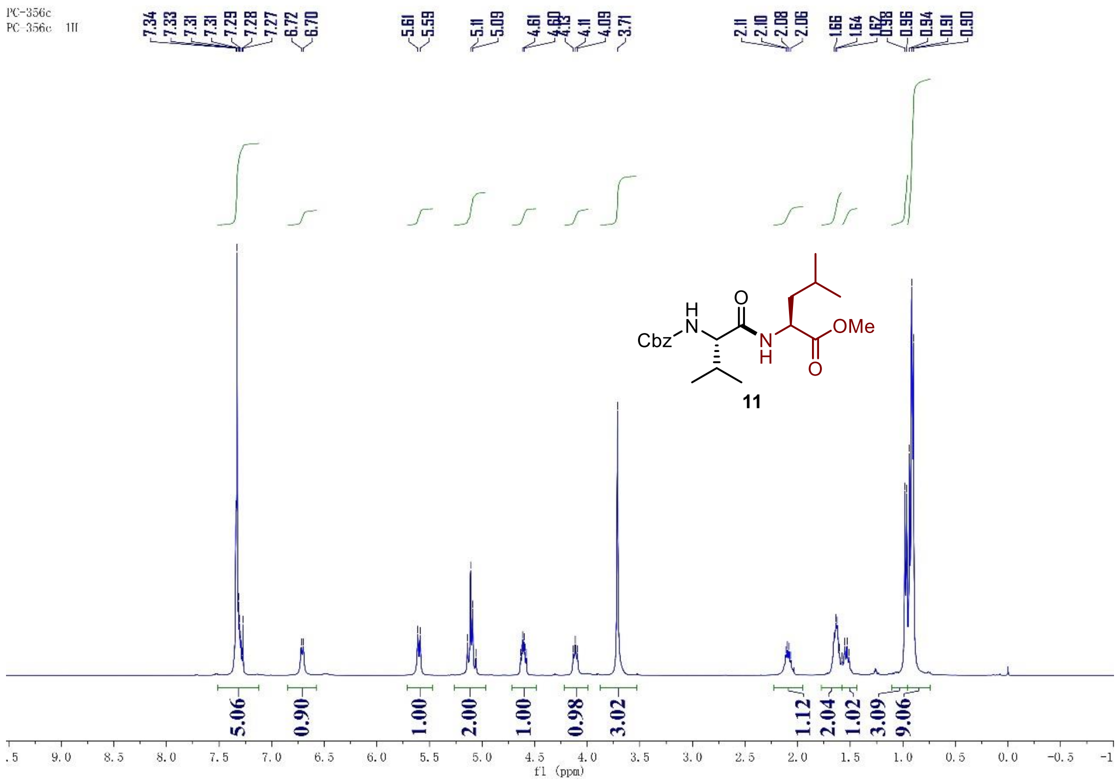

PC-356a
PC-356a 13C
171.97 170.18 156.57 136.26 128.52 128.15 127.96
67.01 60.26 52.29 41.06 31.16 19.17 17.85
Cbz
OMe
8
f1 (ppm)

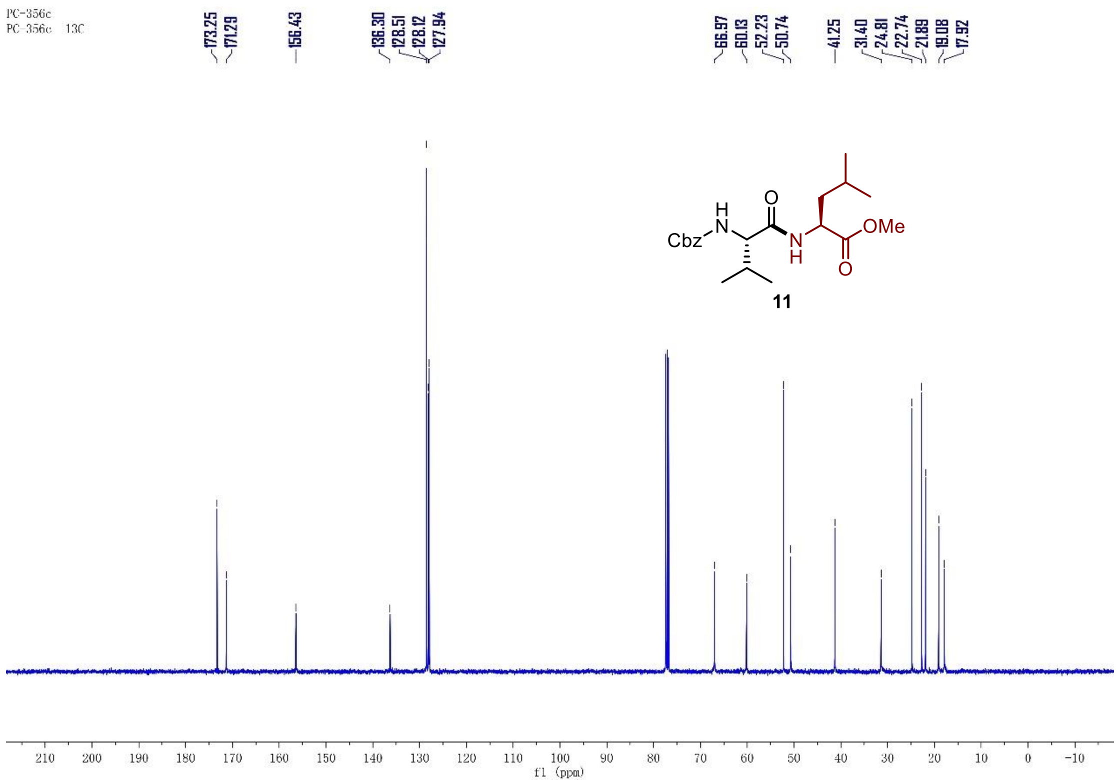

PC-356d
PC-356d 1H
7.33
7.32
7.30
7.30
7.28
7.28
6.93
6.91
5.71
5.69
5.15
5.12
5.10
4.57
4.55
4.54
4.53
4.20
3.71
2.19
2.17
2.15
2.14
2.12
2.10
2.09
2.07
2.05
2.03
0.97
0.95
0.93
0.92
0.90
0.89
0.87
Cbz
N
H
O
N
H
OMe
O
9
5.19
0.91
0.93
2.00
1.00
1.01
3.02
2.11
12.24
f1 (ppm)

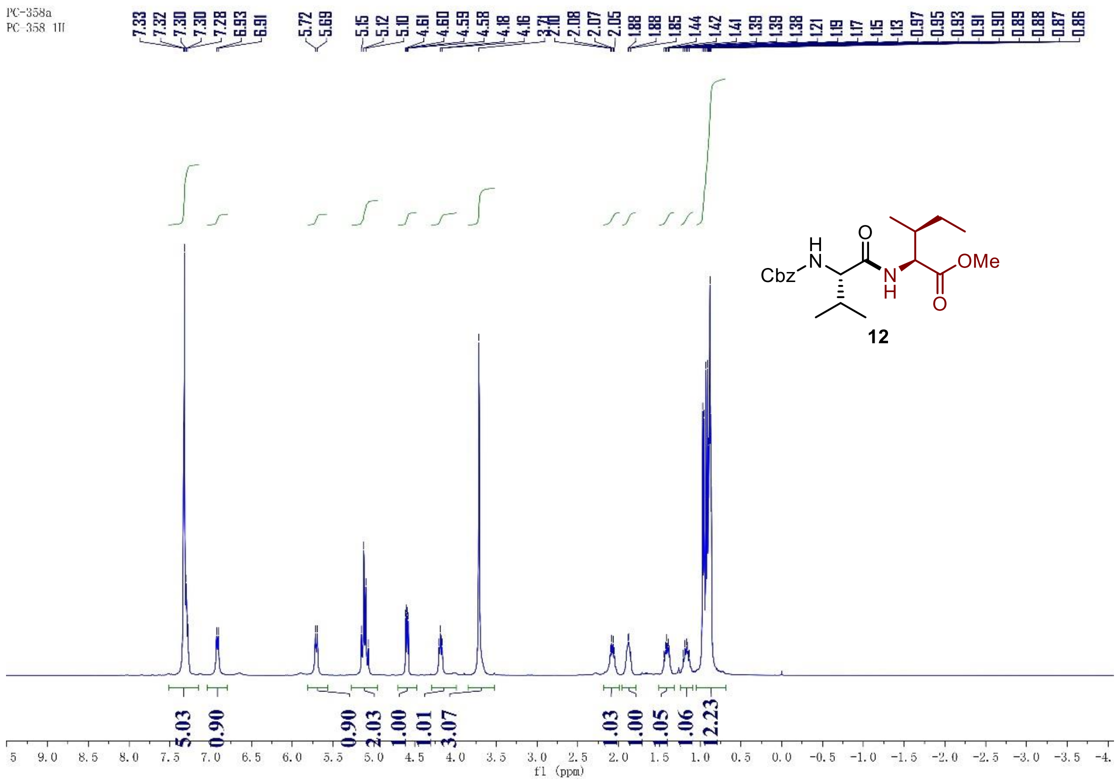

PC-356d
PC-356d 13C
172.30
171.67
156.50
136.40
128.47
128.04
127.89
66.91
60.23
57.17
52.08
31.28
31.05
19.14
18.93
18.04
17.85
Cbz
N
H
O
N
H
OMe
O
9
f1 (ppm)

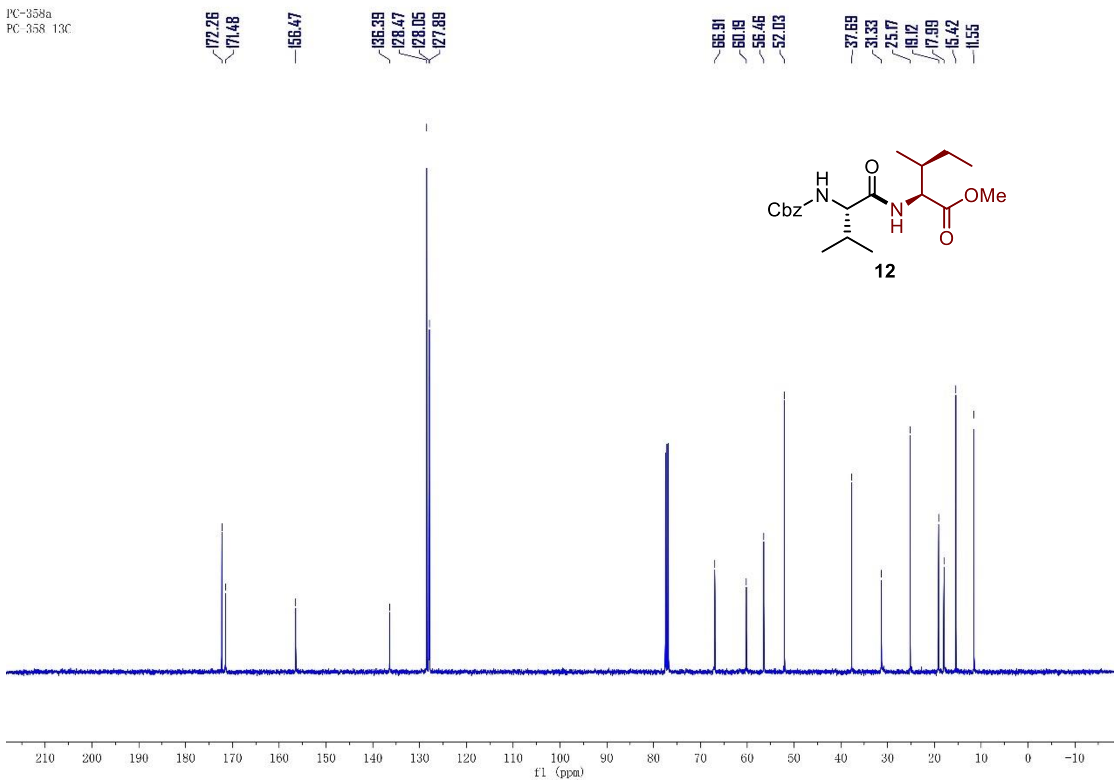

PC-356b
7.33
7.31
7.29
7.25
7.23
7.21
7.20
7.19
7.19
7.09
6.66
5.53
5.51
5.12
5.09
5.04
4.09
4.07
3.67
3.13
3.11
3.09
3.08
3.06
2.10
2.08
2.07
2.05
2.03
0.92
0.88
0.86
Cbz
H
N
O
N
H
Ph
OMe
O
10
5.19
3.00
2.03
0.87
0.99
2.01
1.00
0.97
3.00
2.06
1.13
6.15
f1 (ppm)

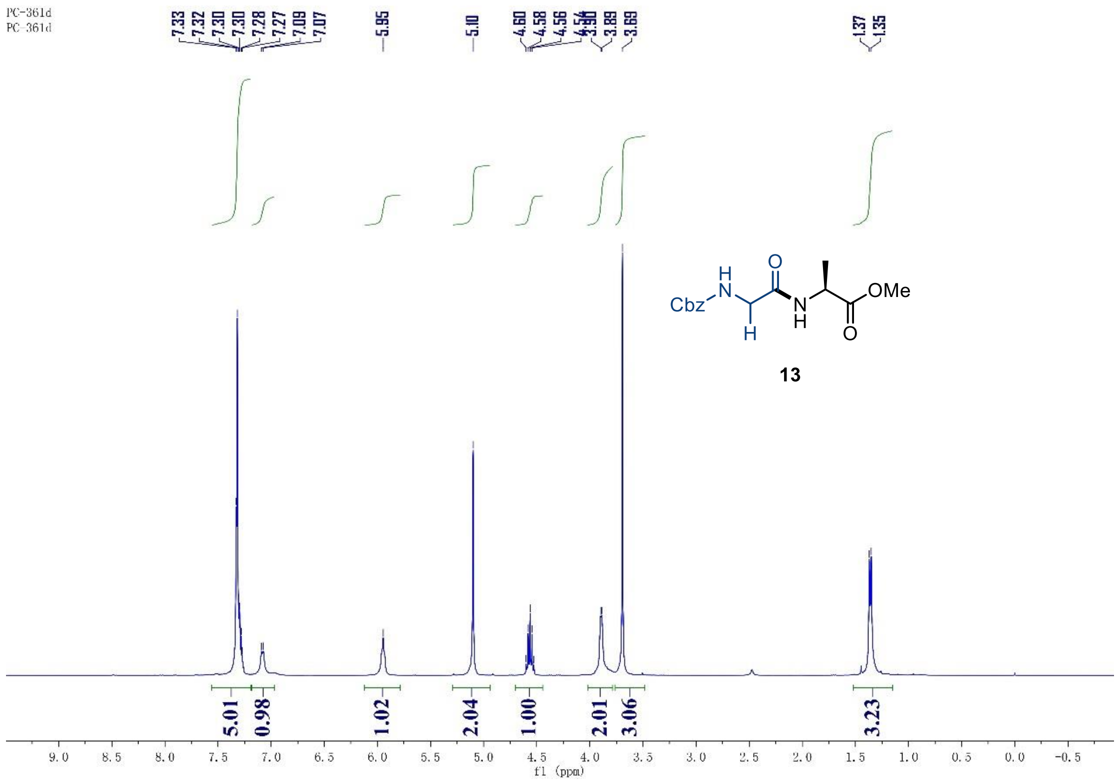

PC-356b
PC-356b 13C
171.78
171.12
156.39
136.35
135.71
129.26
128.61
128.54
128.16
128.01
127.17
67.01
60.20
53.21
52.32
37.98
31.25
19.13
17.81
Cbz
H
N
O
N
H
Ph
OMe
O
10
f1 (ppm)


PC-356c
PC-356c 1H
7.34
7.33
7.31
7.31
7.29
7.28
7.27
6.72
6.70
5.61
5.59
5.11
5.09
4.61
4.13
4.11
4.09
3.71
2.11
2.10
2.08
2.06
1.66
1.64
0.96
0.94
0.91
0.90
Cbz
N
H
O
N
H
OMe
O
11
5.06
0.90
1.00
2.00
1.00
0.98
3.02
1.12
2.04
1.02
3.09
9.06
f1 (ppm)

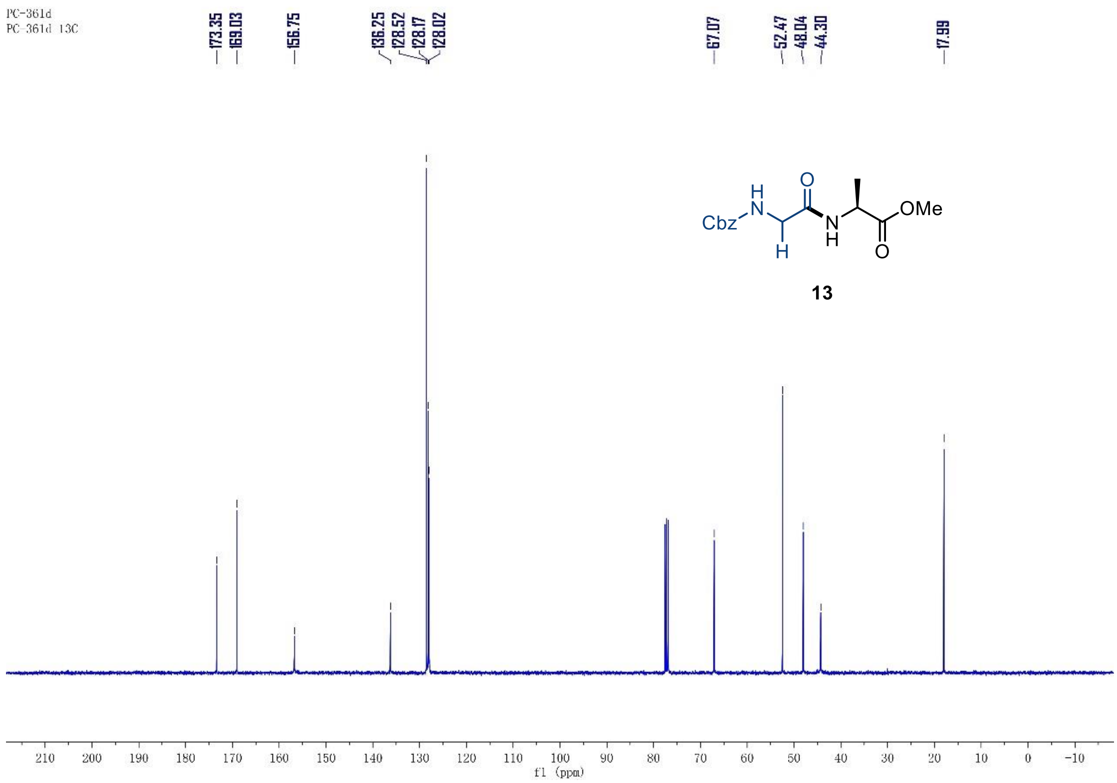

PC-356c
PC-356c 13C
173.25
171.29
156.43
136.30
128.51
128.12
127.94
66.97
60.13
52.23
50.74
41.25
31.40
24.81
22.74
21.89
19.08
17.92
Cbz
N
H
O
N
H
OMe
O
11
f1 (ppm)


PC-358a
PC-358 1H
Cbz
H
N
O
N
H
OMe
O
12
f1 (ppm)

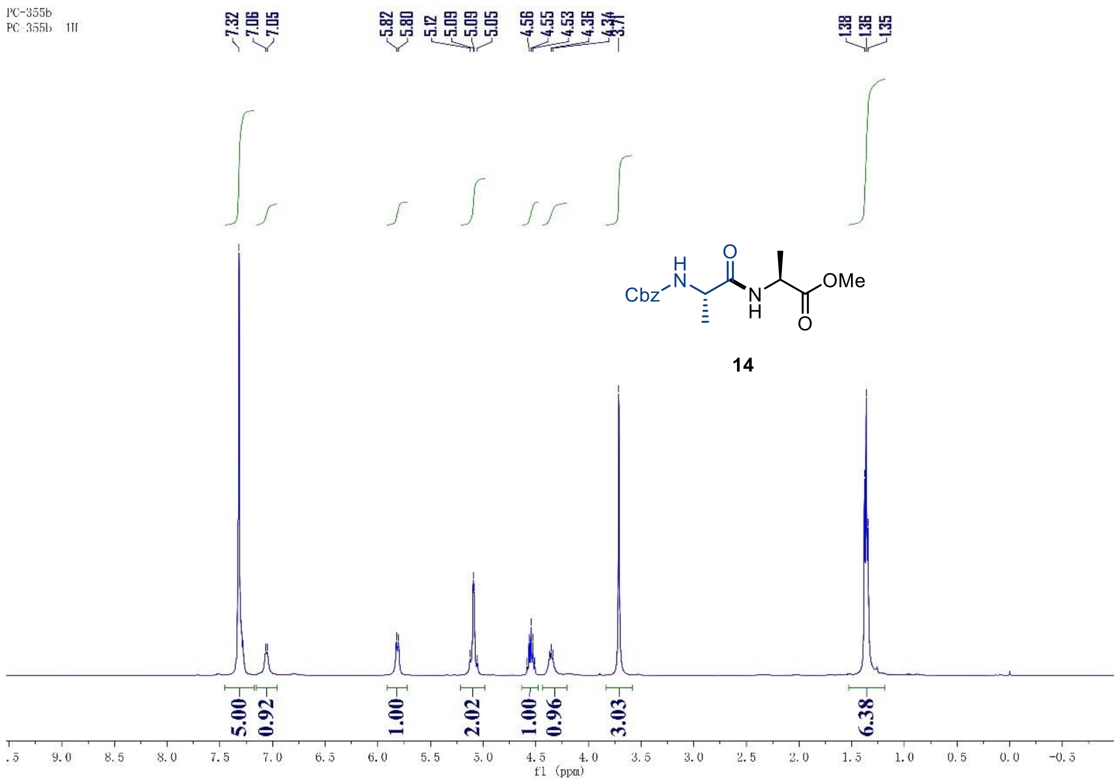

PC-358a
PC-358 13C
Cbz
H
N
O
N
H
OMe
O
12
f1 (ppm)


PC-361d
PC-361d
7.33 7.32 7.30 7.30 7.28 7.27 7.09 7.07
5.95
5.10
4.60 4.58 4.56 4.54
3.90 3.89
3.69
1.37 1.35
Cbz N H H O N H OMe O
5.01 0.98 1.02 2.04 1.00 2.01 3.06 3.23
f1 (ppm)

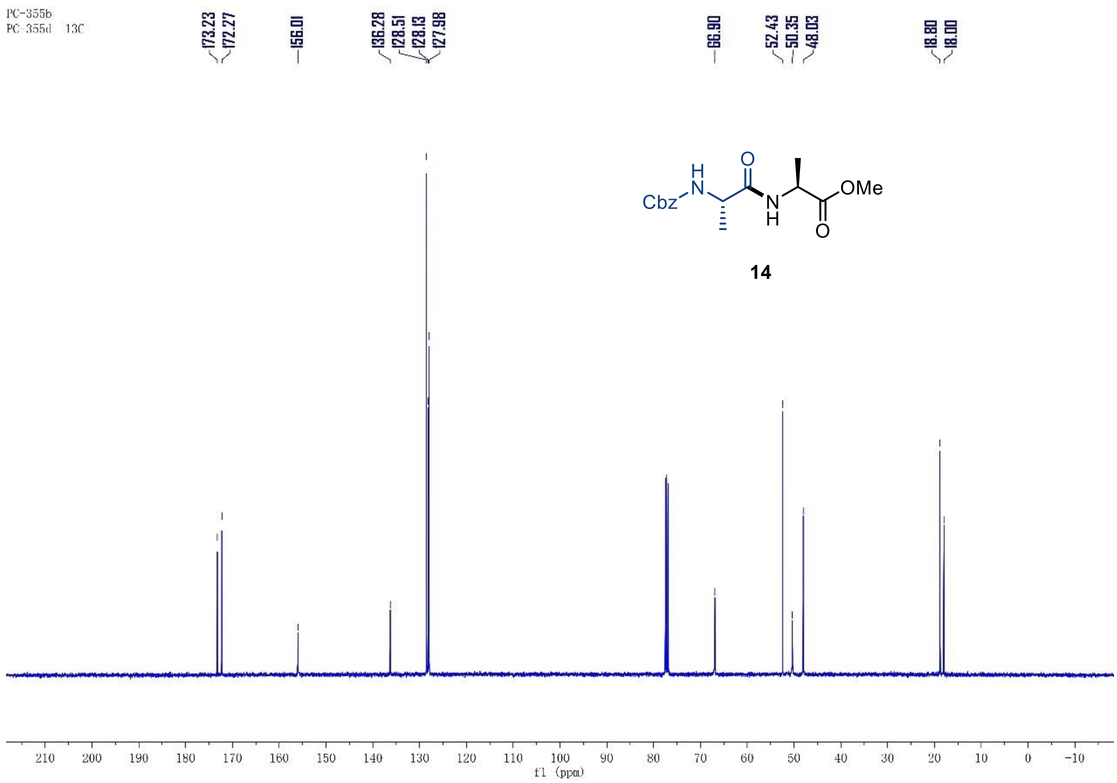
13


PC-361d
PC-361d 13C
173.35 169.03 156.75 136.25 128.52 128.17 128.02 67.07 52.47 48.04 44.30 17.99
Cbz N H H O N H OMe O
f1 (ppm)

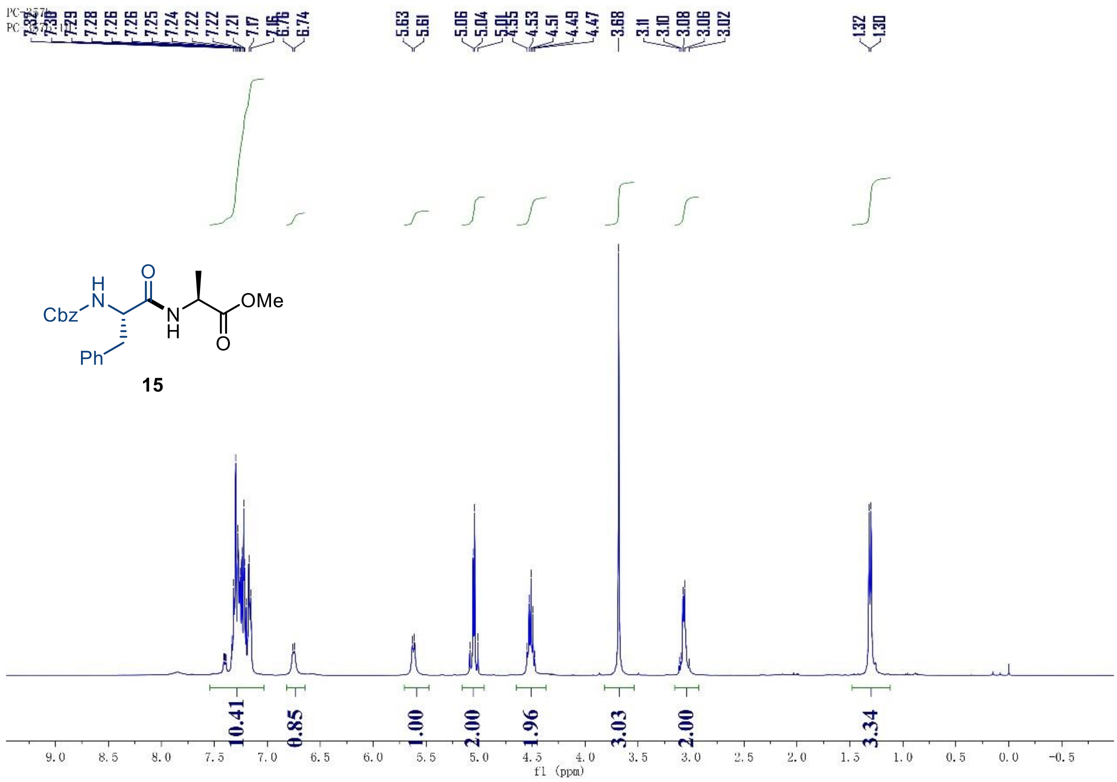
13

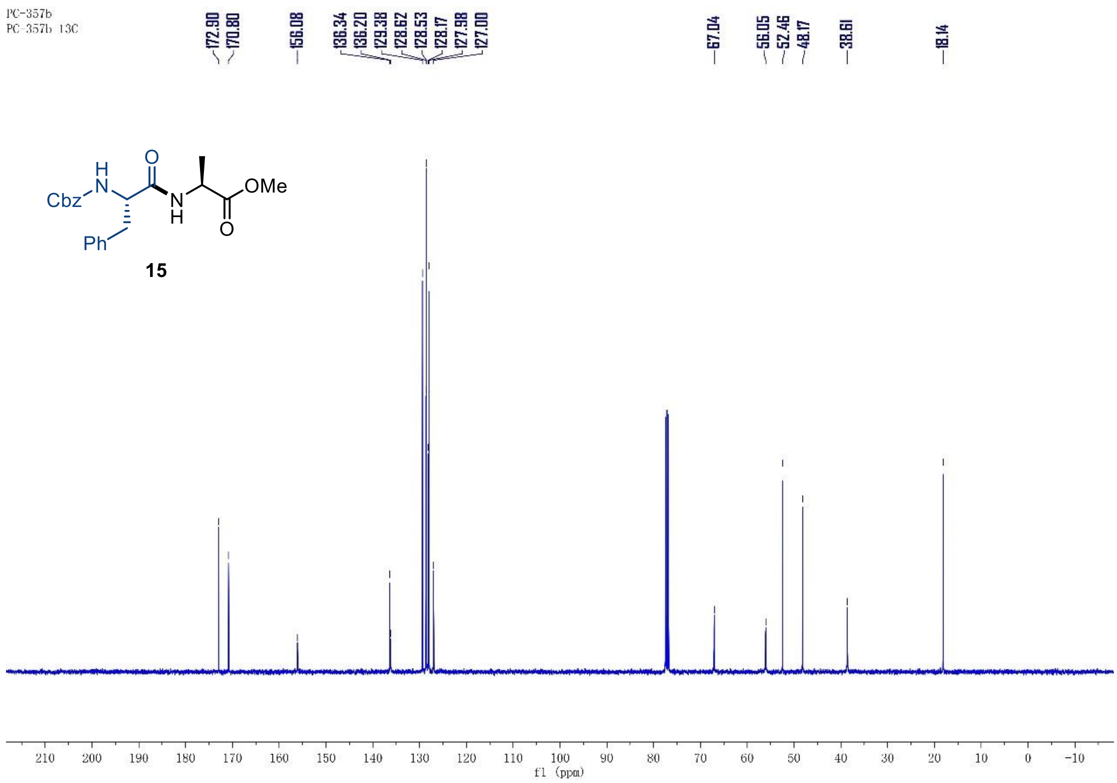


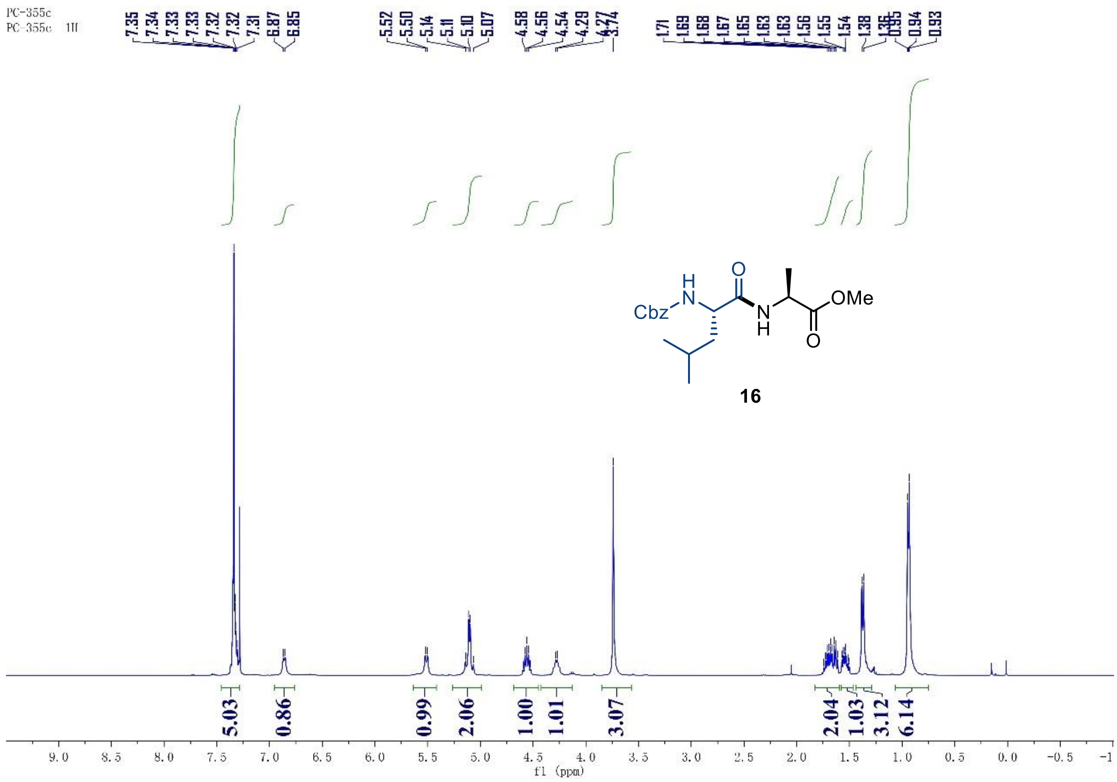
PC-355b
PC-355b 1H
7.32
7.06
7.05
5.82
5.80
5.12
5.09
5.09
5.05
4.56
4.55
4.53
4.36
4.34
3.71
1.38
1.36
1.35
Cbz
N
H
O
N
H
OMe
O
14
5.00
0.92
1.00
2.02
1.00
0.96
3.03
6.38
f1 (ppm)

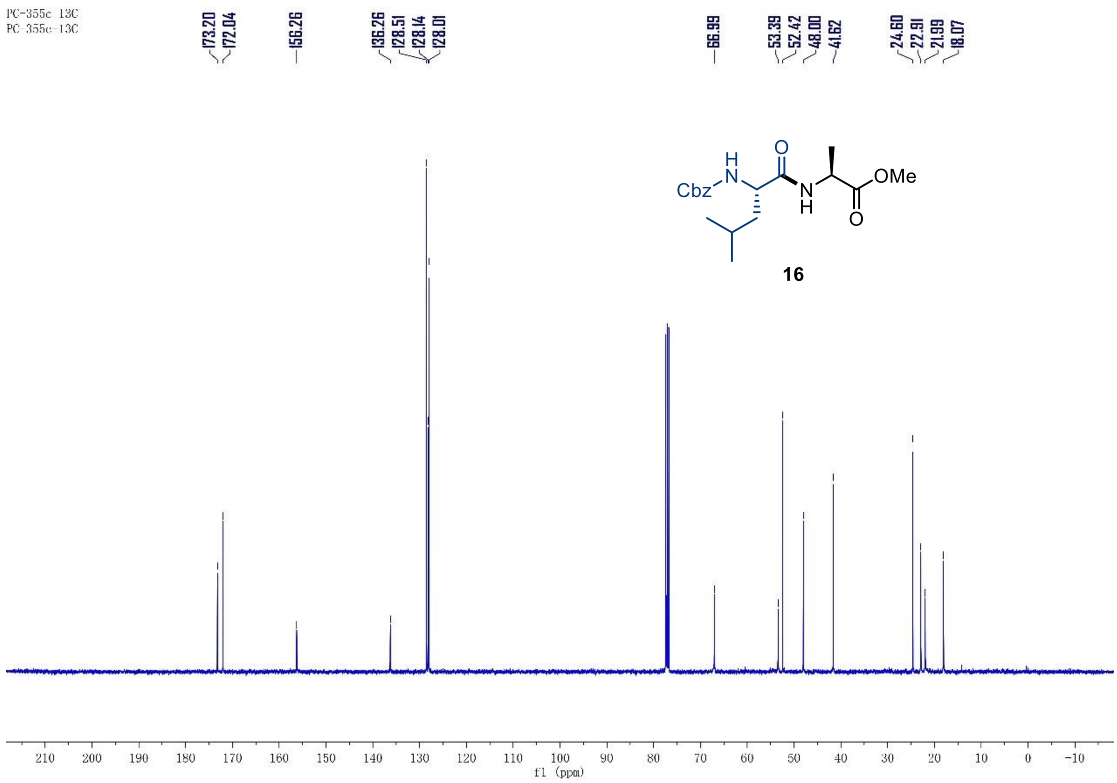


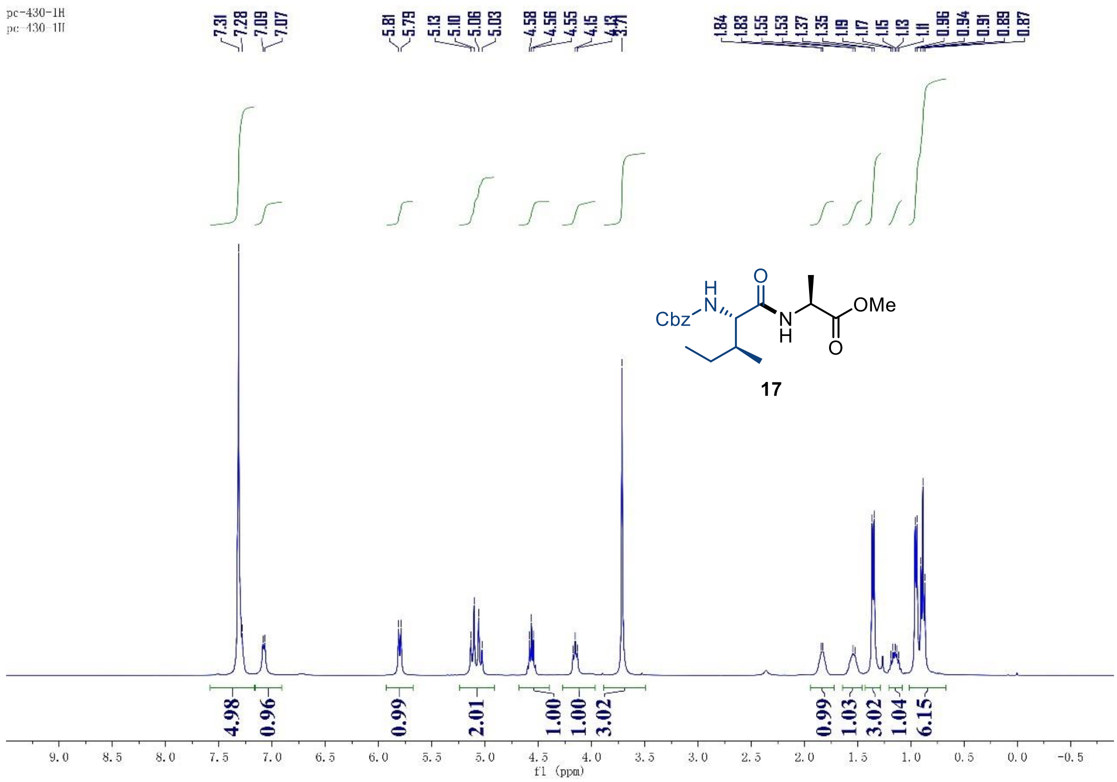
PC-355b
PC-355d 13C
173.23
172.27
156.01
136.28
128.51
128.13
127.98
66.90
52.43
50.35
48.03
18.80
18.00
Cbz
N
H
O
N
H
OMe
O
14
f1 (ppm)


7.32
7.30
7.29
7.28
7.26
7.26
7.25
7.24
7.22
7.22
7.21
7.17
7.16
6.75
6.74
5.63
5.61
5.06
5.04
5.01
4.55
4.53
4.51
4.49
4.47
3.68
3.11
3.10
3.08
3.06
3.02
1.32
1.30
Cbz
H
N
O
N
H
OMe
O
Ph
15
10.41
0.85
1.00
2.00
1.96
3.03
2.00
3.34
f1 (ppm)

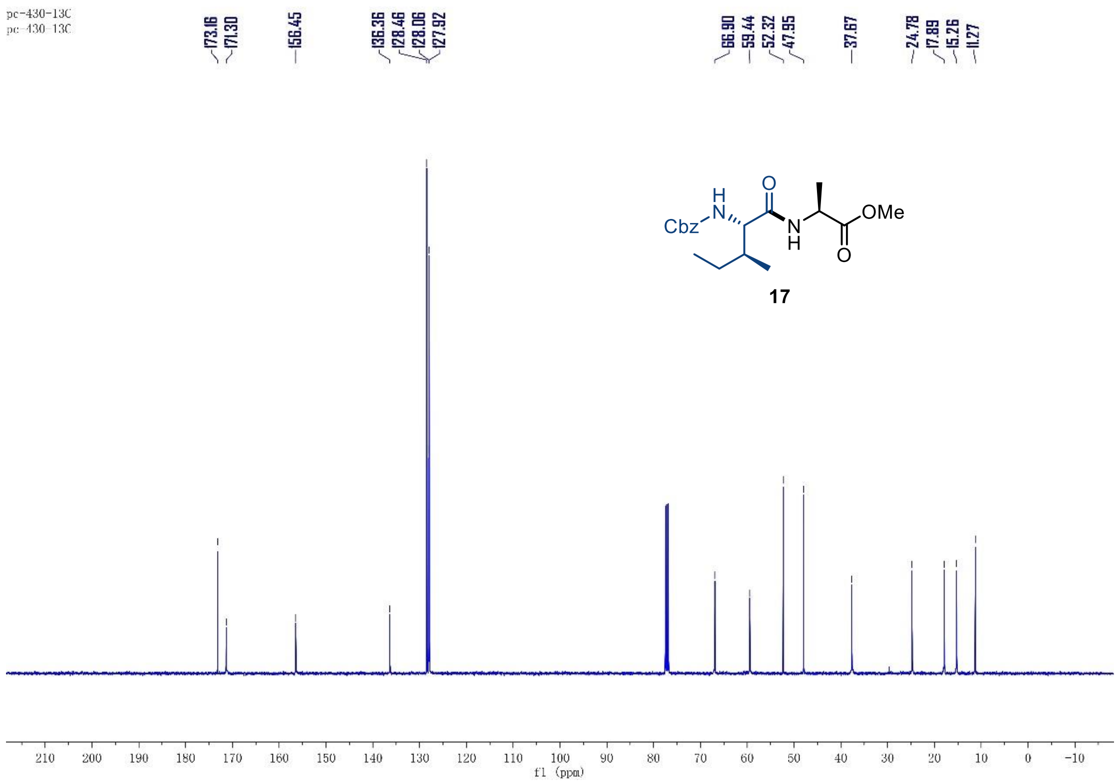

PC-357b
PC-357b 13C
172.90
170.80
156.08
136.34
136.20
129.38
128.62
128.53
128.17
127.98
127.00
67.04
56.05
52.46
48.17
38.61
18.14
Cbz
H
N
O
N
H
OMe
O
Ph
15
f1 (ppm)


PC-355c
PC-355c 1H
7.35 7.34 7.33 7.33 7.32 7.32 7.31 6.87 6.85
5.52 5.50 5.14 5.11 5.10 5.07 4.58 4.56 4.54 4.29 4.27 3.74
1.71 1.69 1.68 1.67 1.65 1.63 1.63 1.56 1.55 1.54 1.38 1.36 0.95 0.94 0.93
Cbz
H
N
O
N
H
OMe
O
16
5.03
0.86
0.99
2.06
1.00
1.01
3.07
2.04
1.03
3.12
6.14
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

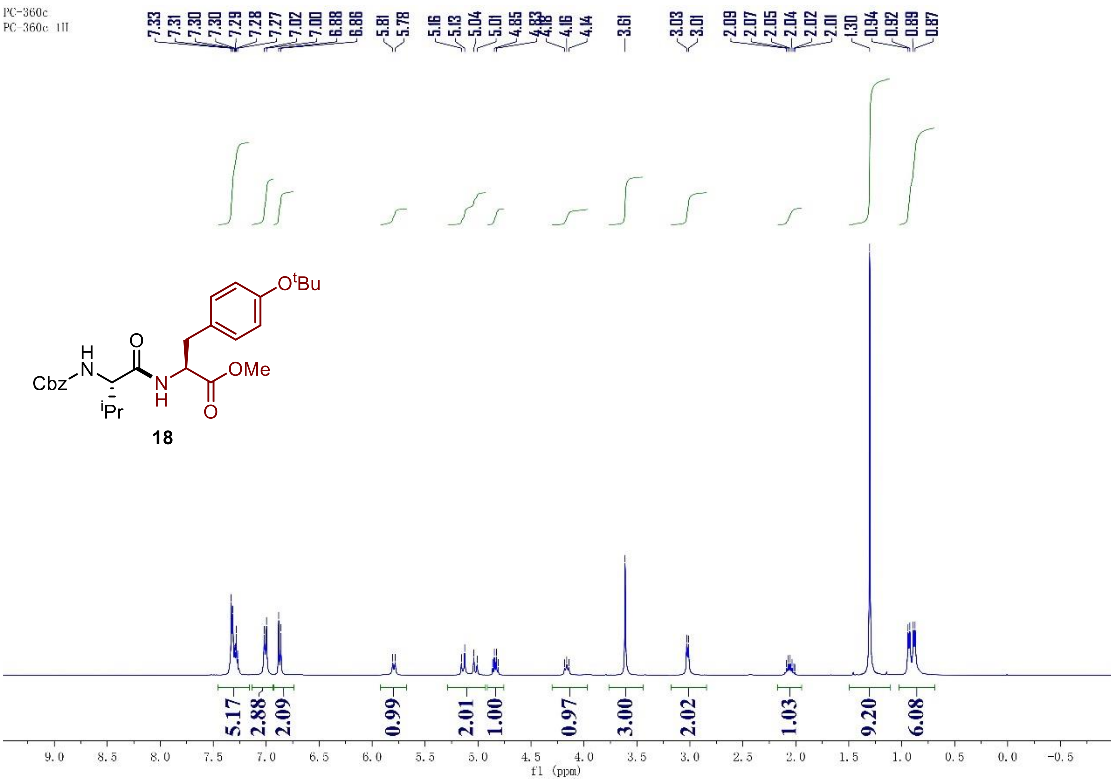

PC-355c 13C
PC-355c 13C
173.20 172.04 156.26 136.26 128.51 128.14 128.01
66.99 53.39 52.42 48.00 41.62 24.60 22.91 21.99 18.07
Cbz
H
N
O
N
H
OMe
O
16
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

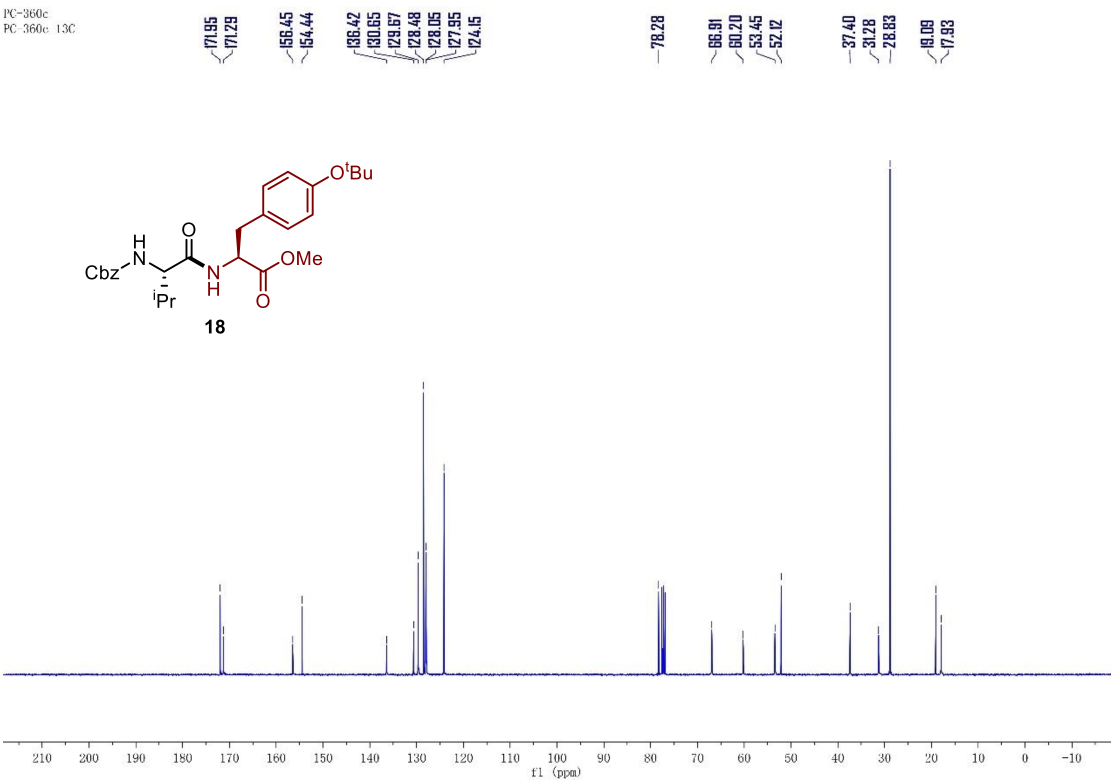

pc-430-1H
pc-430-1H
7.31
7.28
7.09
7.07
5.81
5.79
5.13
5.10
5.06
5.03
4.58
4.56
4.55
4.15
4.13
3.71
1.84
1.83
1.55
1.53
1.37
1.35
1.19
1.17
1.15
1.13
1.11
0.96
0.94
0.91
0.89
0.87
Cbz
OMe
4.98
0.96
0.99
2.01
1.00
1.00
3.02
0.99
1.03
3.02
1.04
6.15
f1 (ppm)

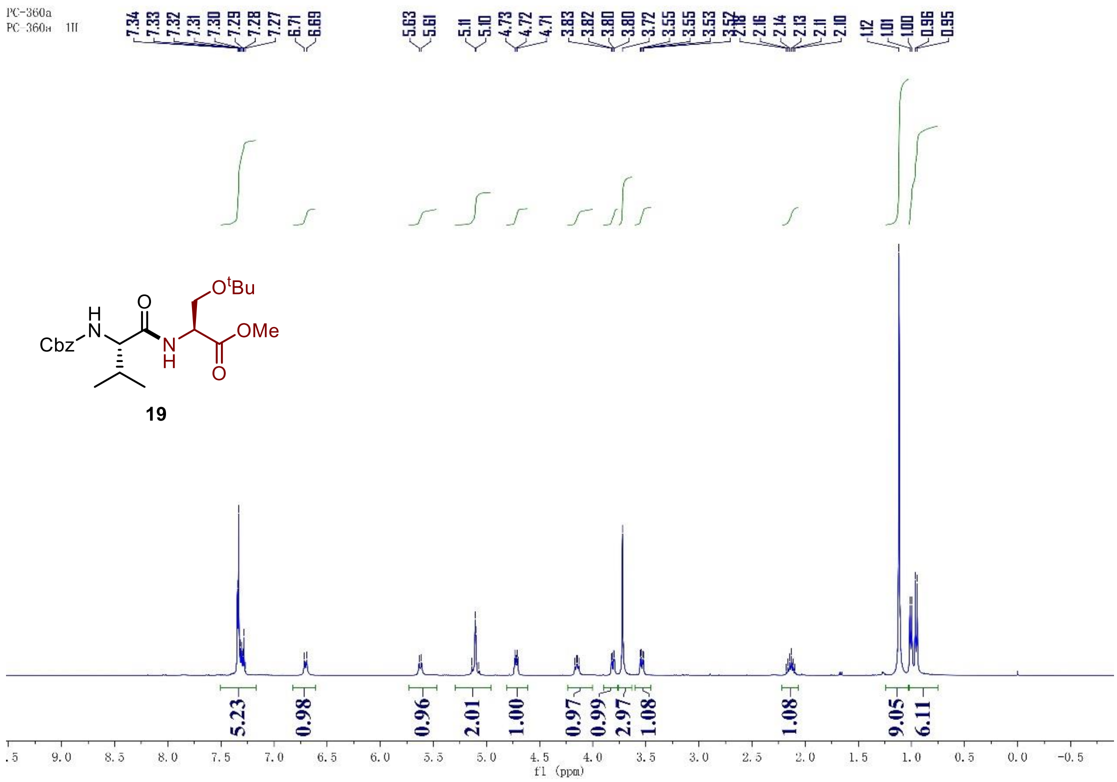
17

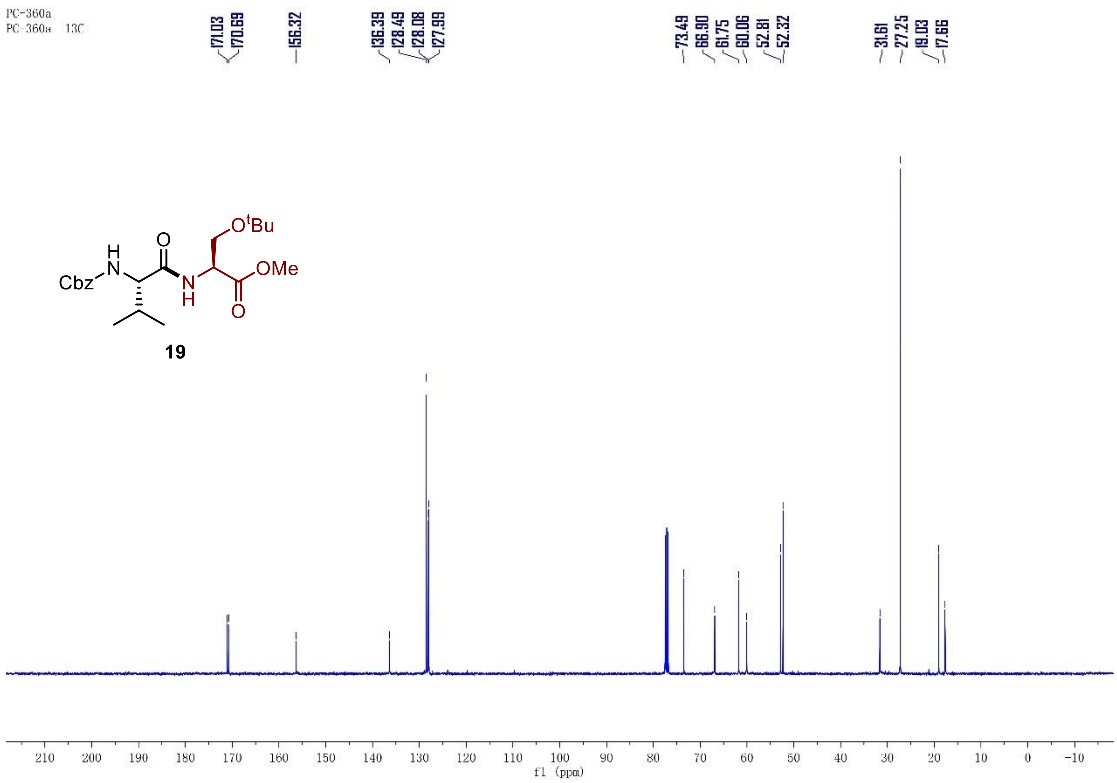

pc-430-13C
pc-430-13C
173.16
171.30
156.45
136.36
128.46
128.06
127.92
66.90
59.44
52.32
47.95
37.67
24.78
17.89
15.26
11.27
Cbz
OMe
f1 (ppm)

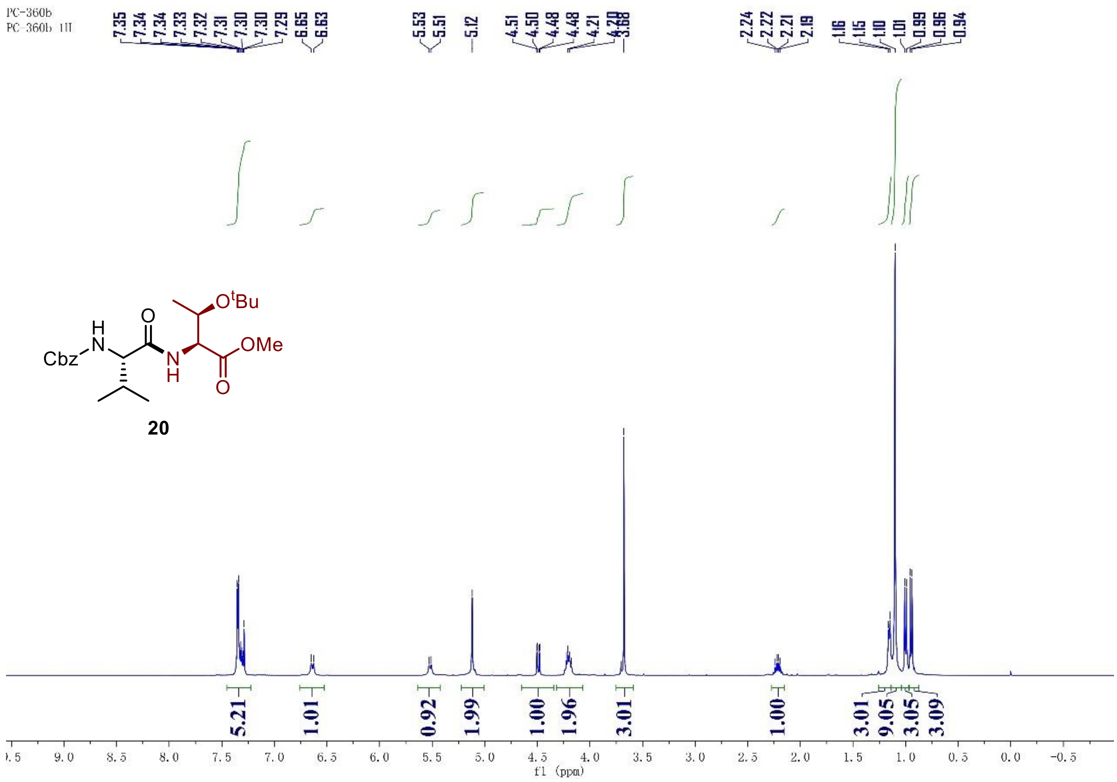
17

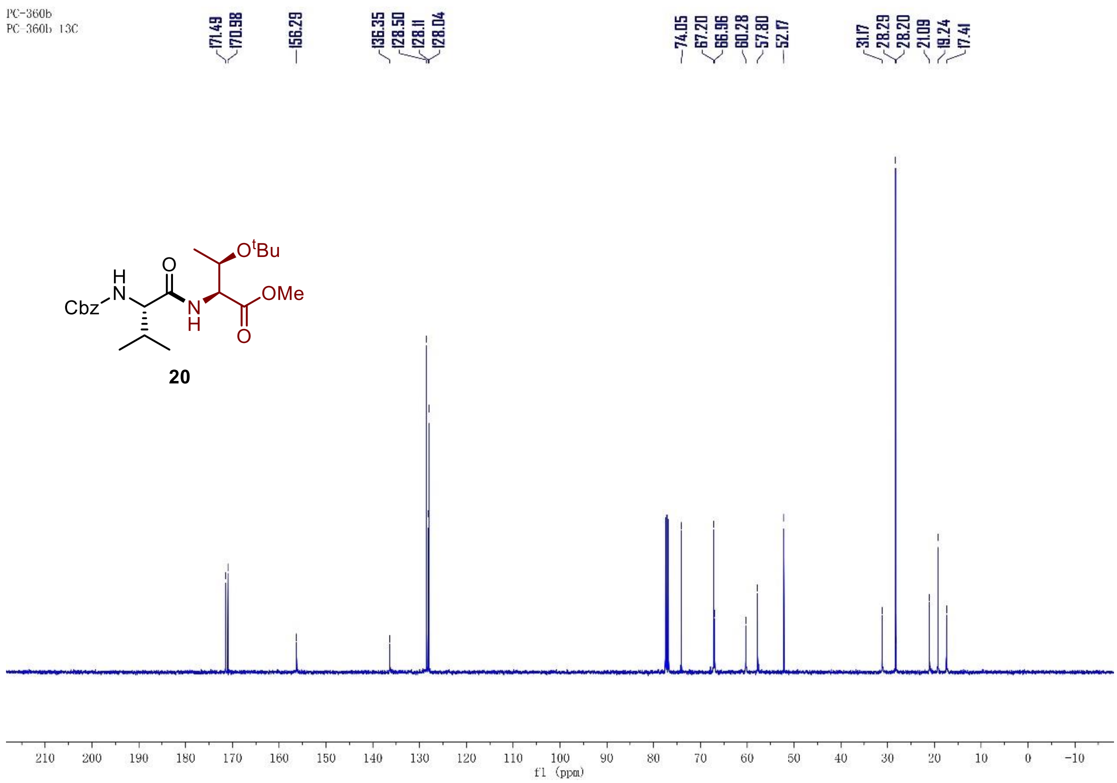

PC-360c
PC-360c 1H
7.33 7.31 7.30 7.29 7.28 7.27 7.02 7.00 6.88 6.86 5.81 5.78 5.16 5.13 5.04 5.01 4.85 4.83 4.18 4.16 4.14 3.61 3.03 3.01 2.09 2.07 2.05 2.04 2.02 2.01 1.30 0.94 0.92 0.89 0.87
OtBu
OMe
Cbz
N
H
O
iPr
18
5.17 2.88 2.09 0.99 2.01 1.00 0.97 3.00 2.02 1.03 9.20 6.08
f1 (ppm)

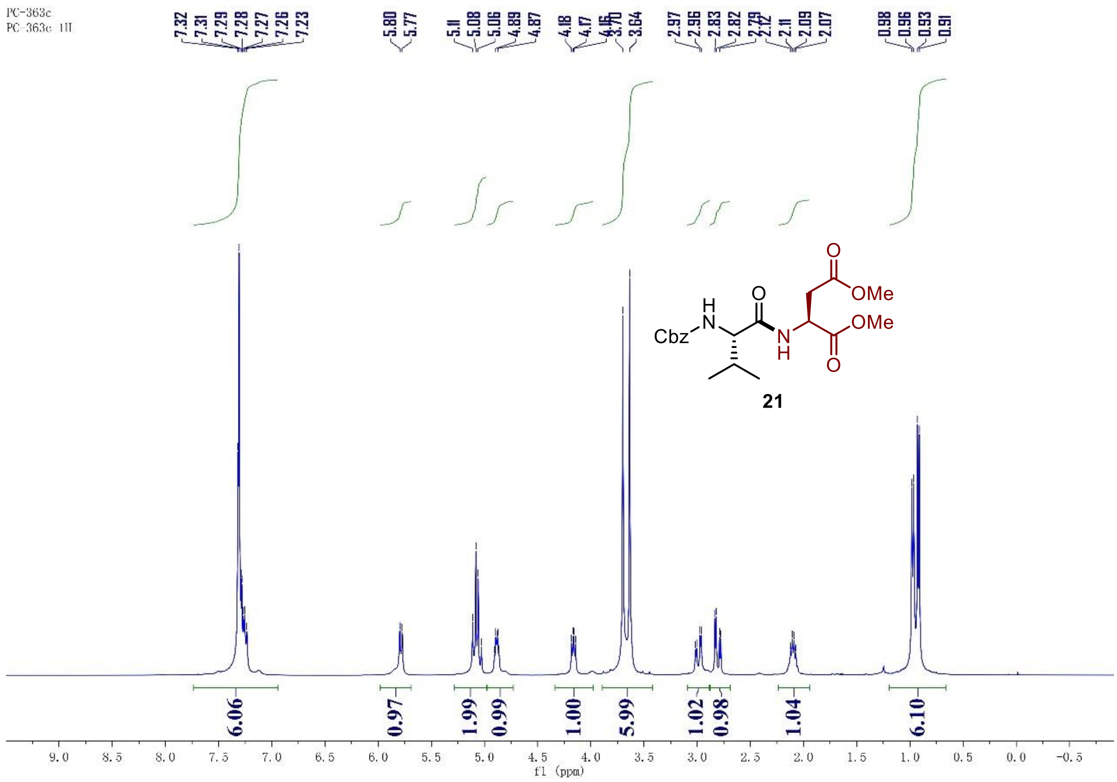

PC-360c
PC-360c 13C
171.95 171.29 156.45 154.44 136.42 130.65 129.67 128.48 128.05 127.95 124.15 78.28 66.91 60.20 53.45 52.12 37.40 31.28 28.83 19.09 17.93
OtBu
OMe
Cbz
N
H
O
iPr
18
f1 (ppm)

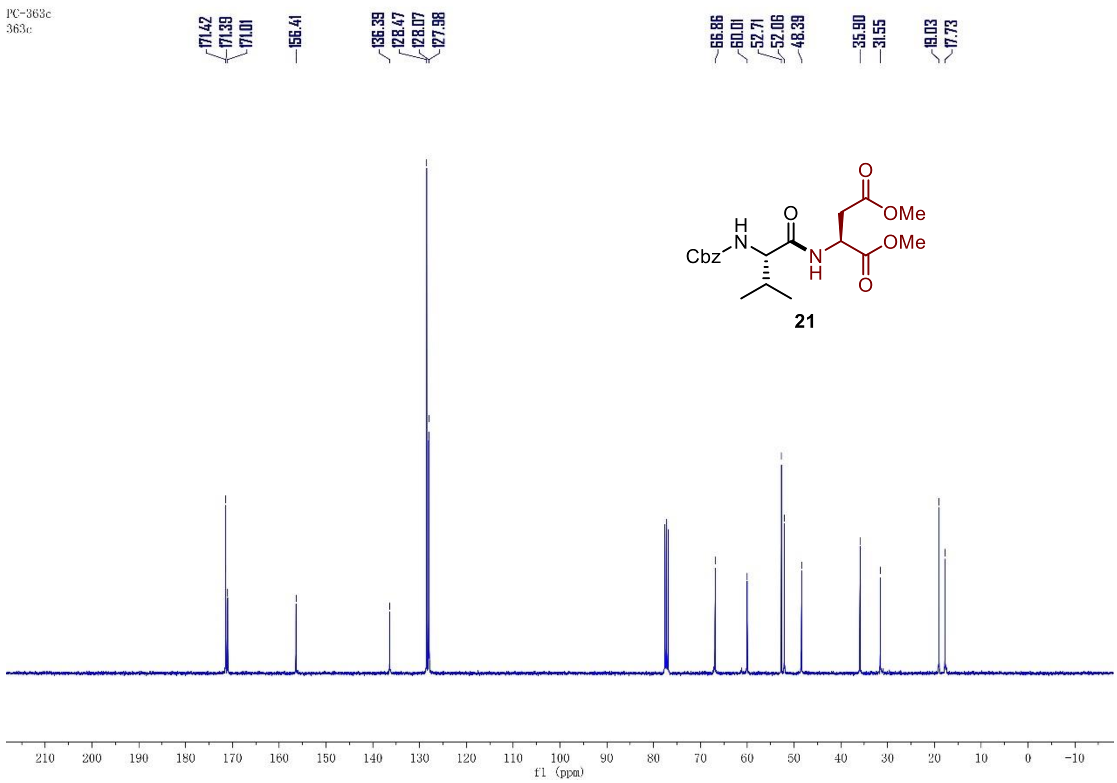

PC-360a
PC-360a 1H
7.34 7.33 7.32 7.31 7.30 7.29 7.28 7.27 6.71 6.69 5.63 5.61 5.11 5.10 4.73 4.72 4.71 3.83 3.82 3.80 3.80 3.72 3.55 3.55 3.53 3.52 2.18 2.16 2.14 2.13 2.11 2.10 1.12 1.01 1.00 0.96 0.95
O^tBu
Cbz
N
H
O
OMe
19
5.23 0.98 0.96 2.01 1.00 0.97 0.99 2.97 1.08 1.08 9.05 6.11
f1 (ppm)

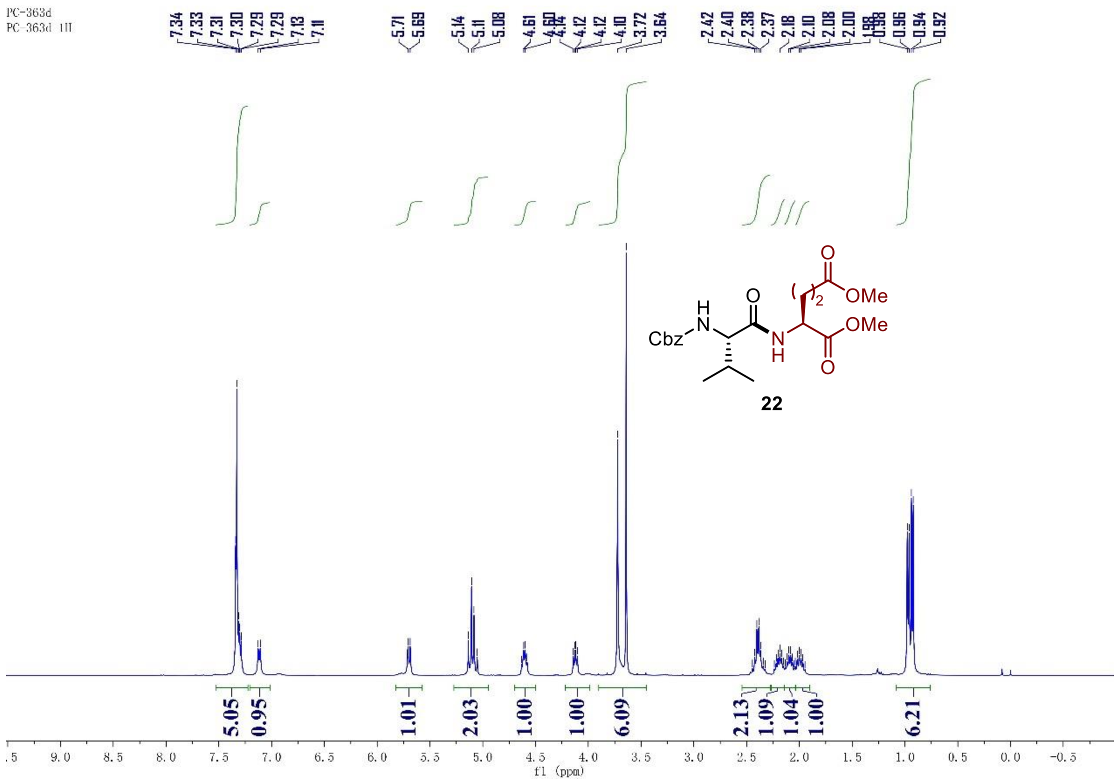

PC-360a
PC-360a 13C
171.03 170.69 156.32 136.39 128.49 128.08 127.99 73.49 66.90 61.75 60.06 52.81 52.32 31.61 27.25 19.03 17.66
O^tBu
Cbz
N
H
O
OMe
19
f1 (ppm)

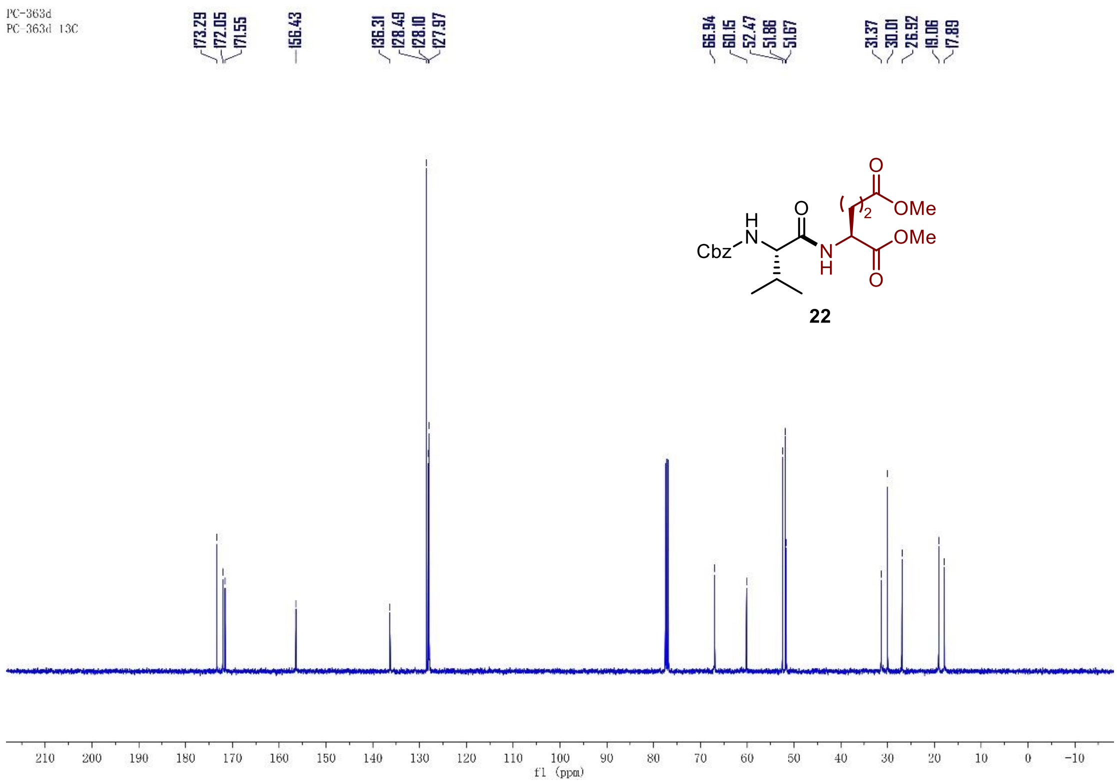

PC-360b
PC-360b 1H
7.35 7.34 7.34 7.33 7.32 7.31 7.30 7.30 7.29 6.65 6.63
5.53 5.51 5.12
4.51 4.50 4.48 4.48 4.21 4.20 3.69
2.24 2.22 2.21 2.19
1.16 1.15 1.10 1.01 0.99 0.96 0.94
OtBu
Cbz
N
H
O
OMe
20
5.21 1.01 0.92 1.99 1.00 1.96 3.01 1.00 3.01 9.05 3.05 3.09
f1 (ppm)

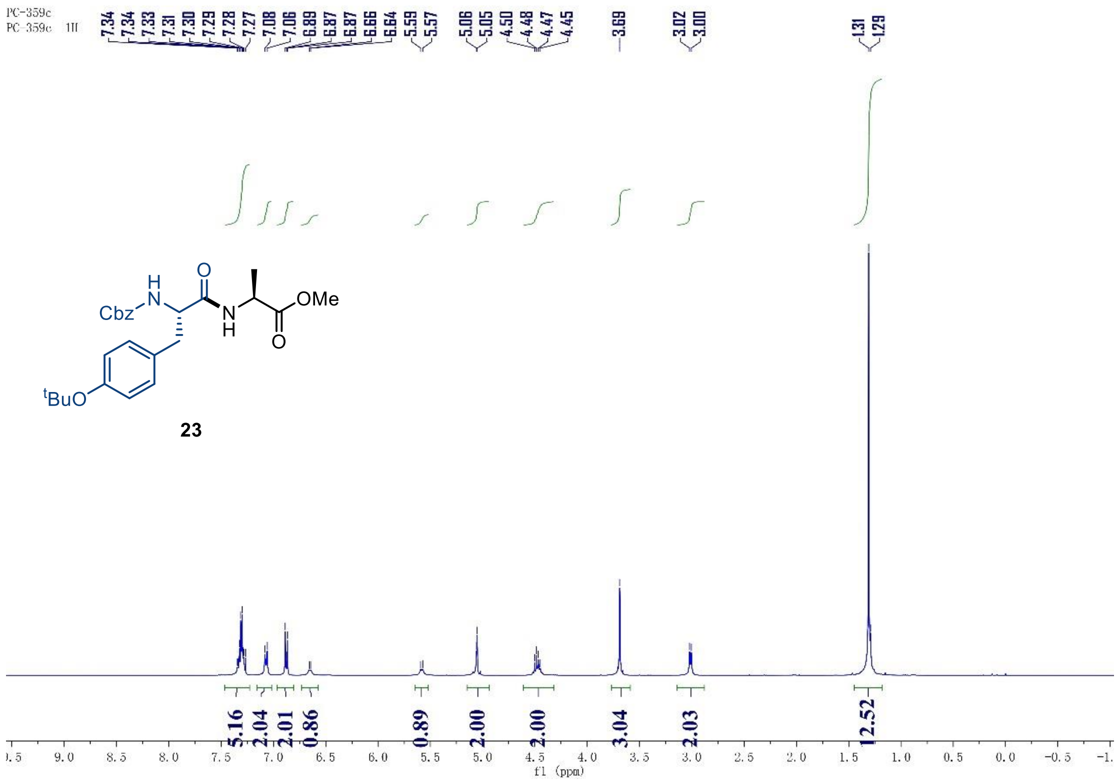

PC-360b
PC-360b 13C
171.49 170.98 156.29
136.35 128.50 128.11 128.04
74.05 67.20 66.96 60.28 57.80 52.17
31.17 28.29 28.20 21.09 19.24 17.41
OtBu
Cbz
N
H
O
OMe
20
f1 (ppm)

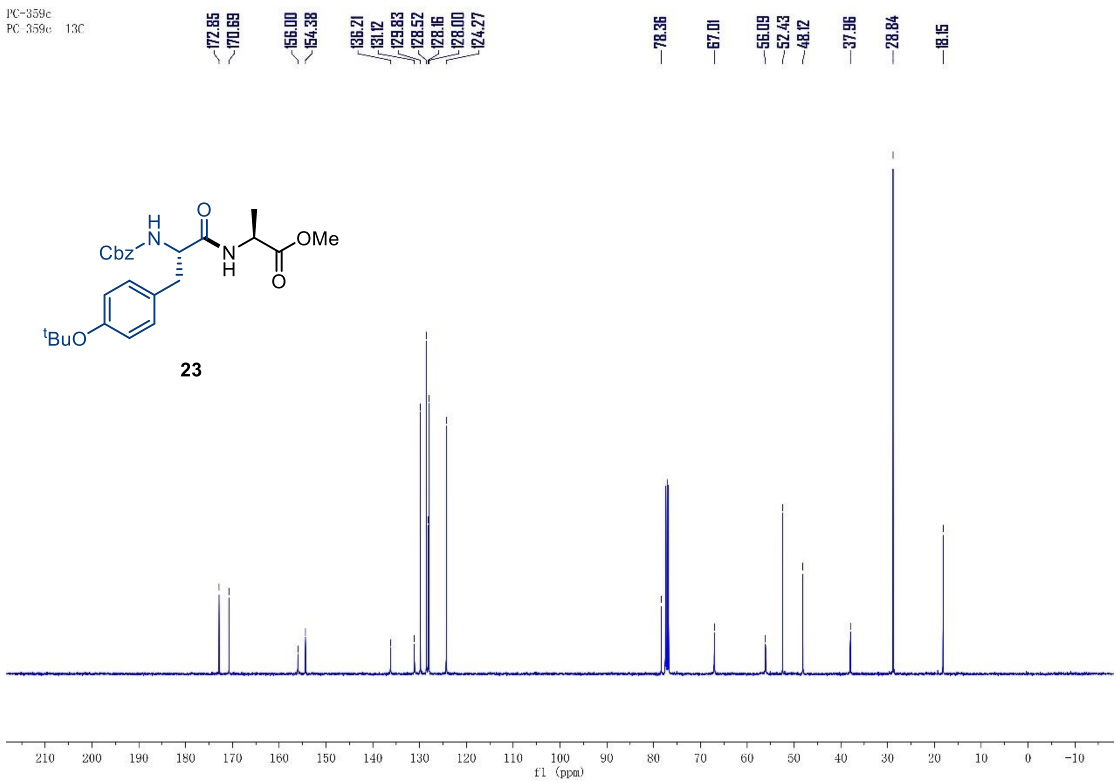

PC-363c
PC-363c 1H
Cbz
N
H
O
N
H
O
OMe
OMe
O
21
f1 (ppm)

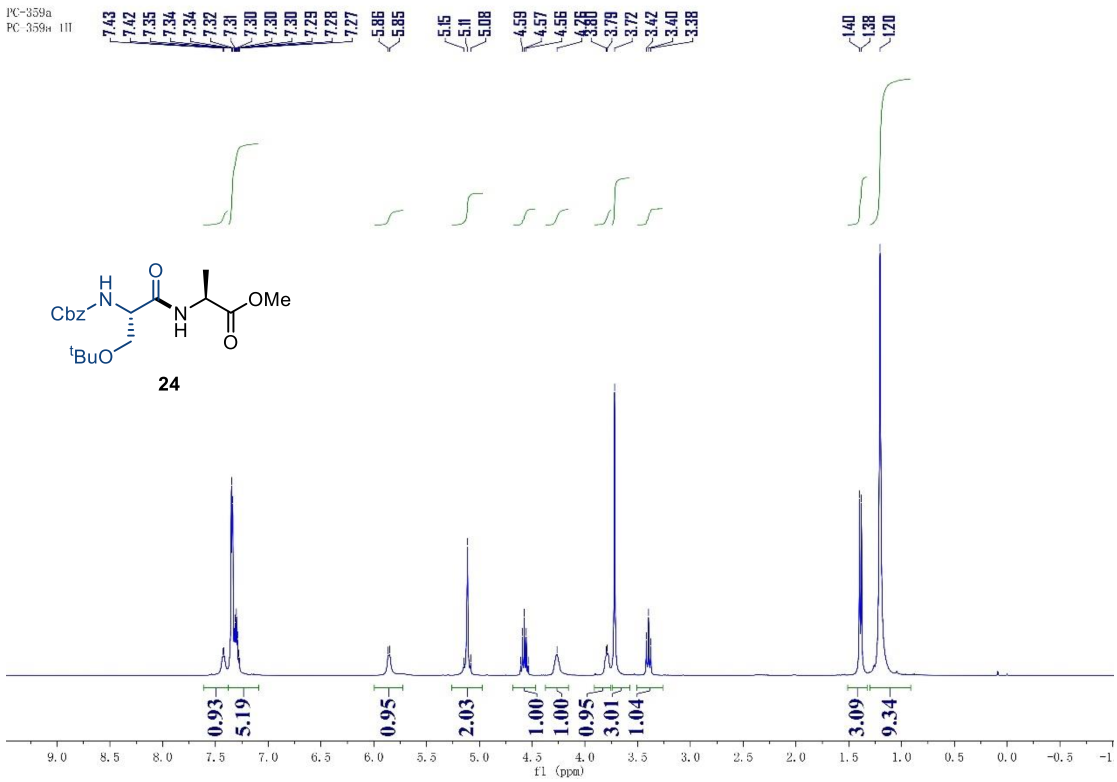

PC-363c
363c
Cbz
N
H
O
N
H
O
OMe
OMe
O
21
f1 (ppm)

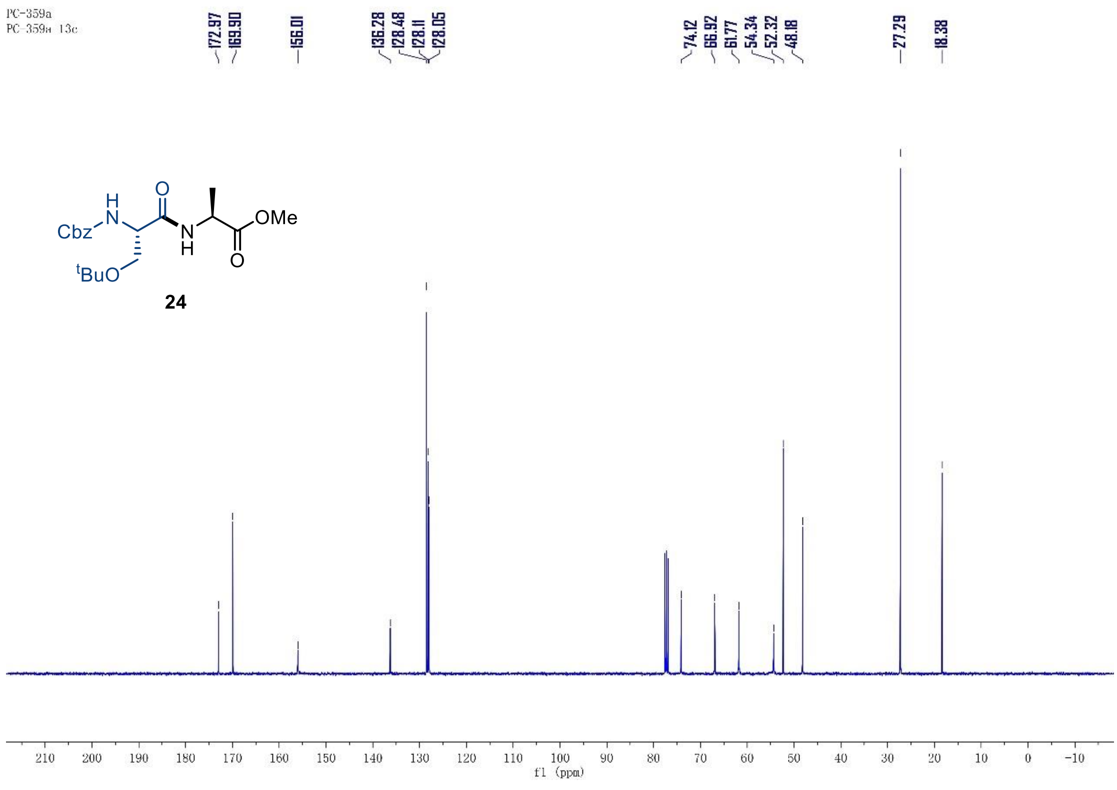

PC-363d
PC-363d 1H
7.34 7.33 7.31 7.30 7.29 7.29 7.13 7.11 5.71 5.69 5.14 5.11 5.08 4.61 4.60 4.14 4.12 4.12 4.10 3.72 3.64 2.42 2.40 2.38 2.37 2.18 2.10 2.08 2.00 1.98 1.98 0.96 0.94 0.92
Cbz
N
H
O
N
H
O
OMe
O
OMe
2
22
5.05 0.95 1.01 2.03 1.00 1.00 6.09 2.13 1.09 1.04 1.00 6.21
f1 (ppm)

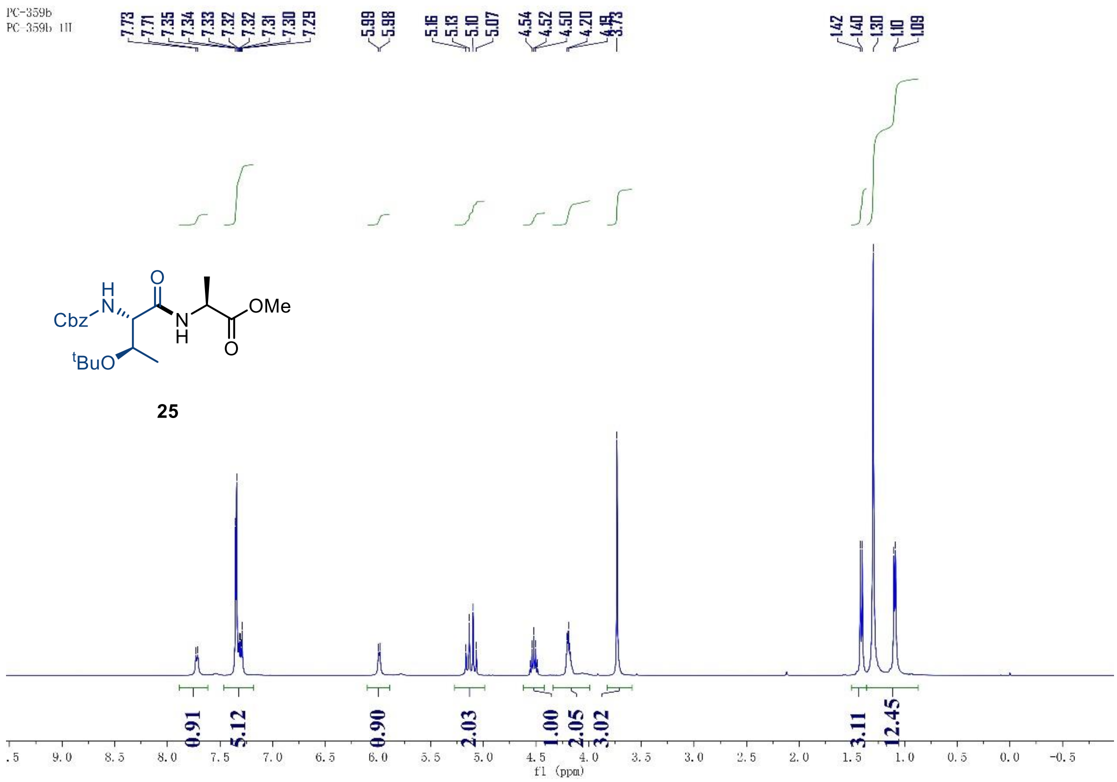

PC-363d
PC-363d 13C
173.29 172.05 171.55 156.43 136.31 128.49 128.10 127.97 66.94 60.15 52.47 51.86 51.67 31.37 30.01 26.92 19.06 17.89
Cbz
N
H
O
N
H
O
OMe
O
OMe
2
22
f1 (ppm)

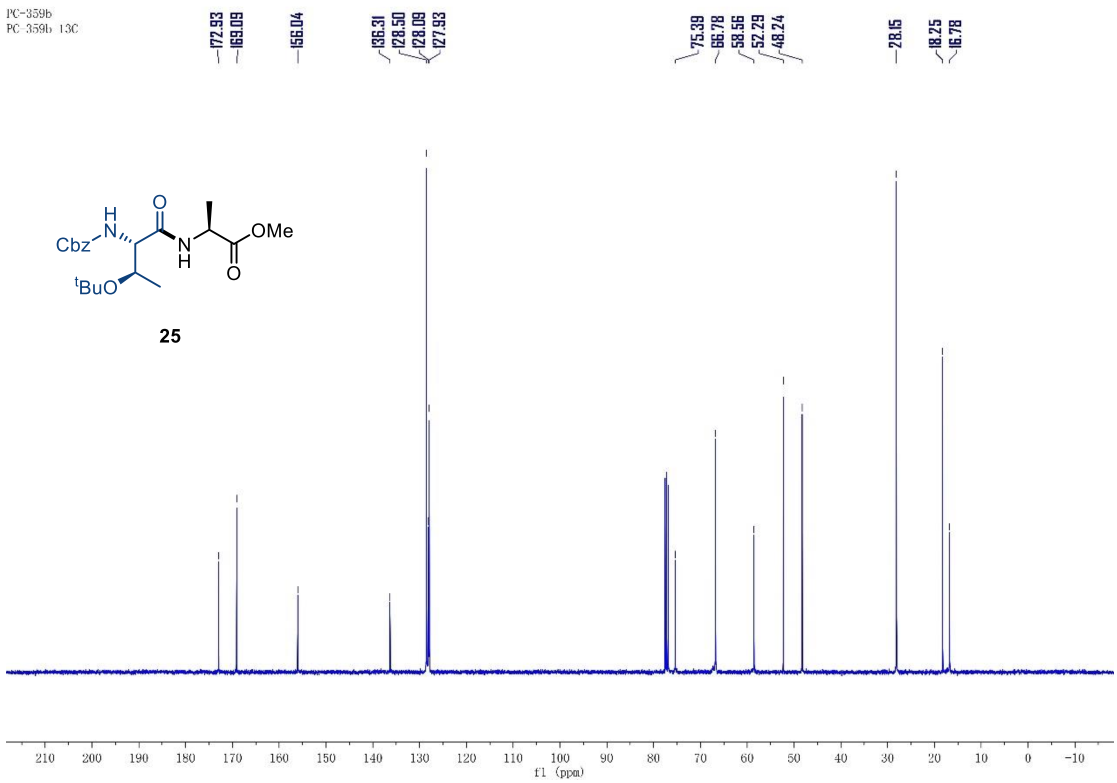


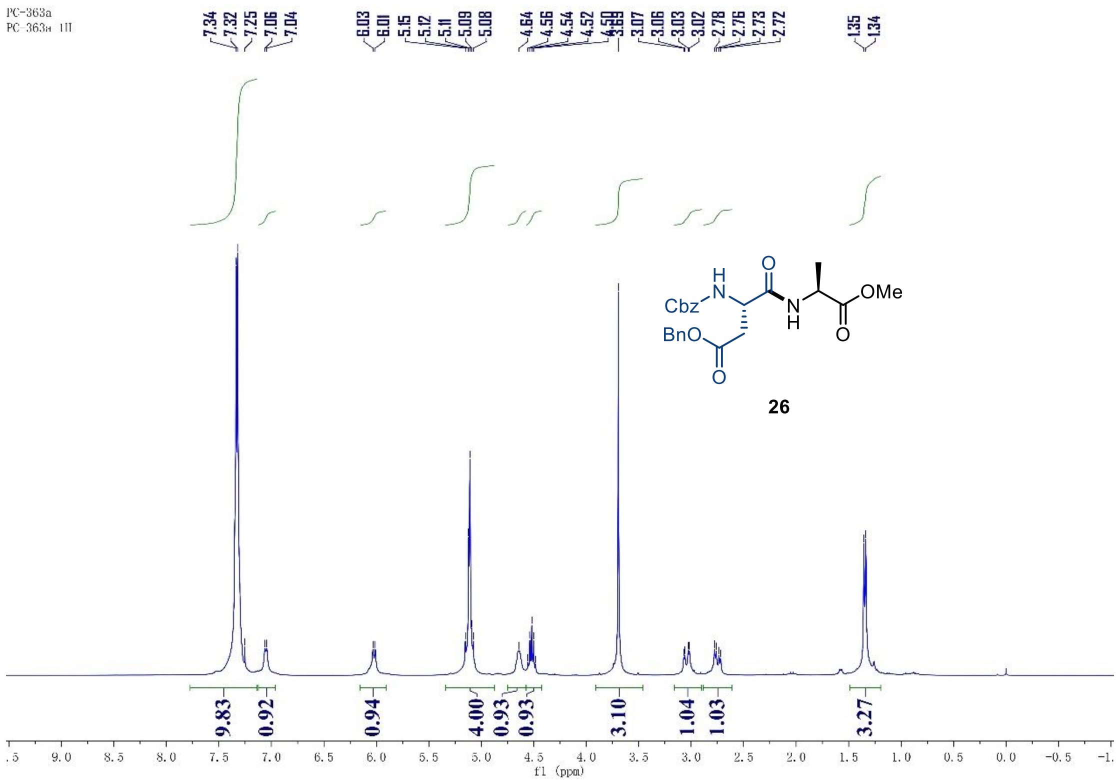


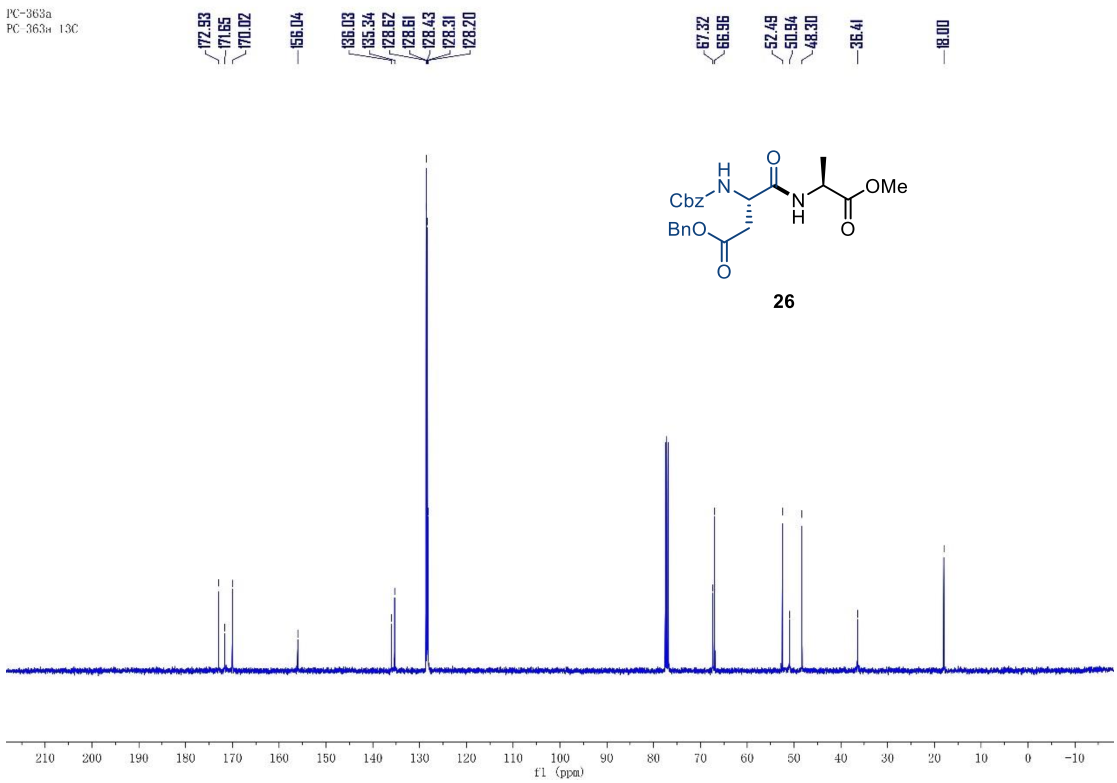


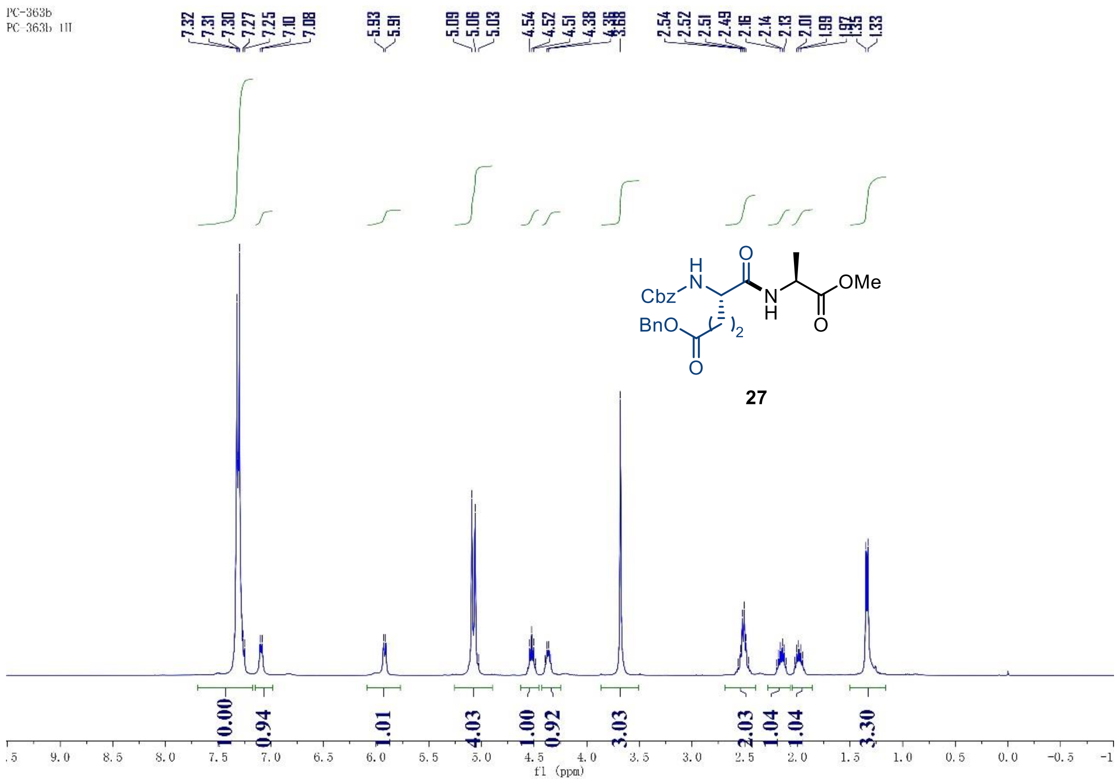



PC-359b
PC-359b 1H
7.73 7.71 7.35 7.34 7.33 7.32 7.32 7.31 7.30 7.29
5.99 5.98
5.16 5.13 5.10 5.07
4.54 4.52 4.50 4.20 4.15 3.73
1.42 1.40 1.30 1.10 1.09
Cbz
N
H
O
N
H
OMe
O
tBuO
25
0.91 5.12 0.90 2.03 1.00 2.05 3.02 3.11 12.45
.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

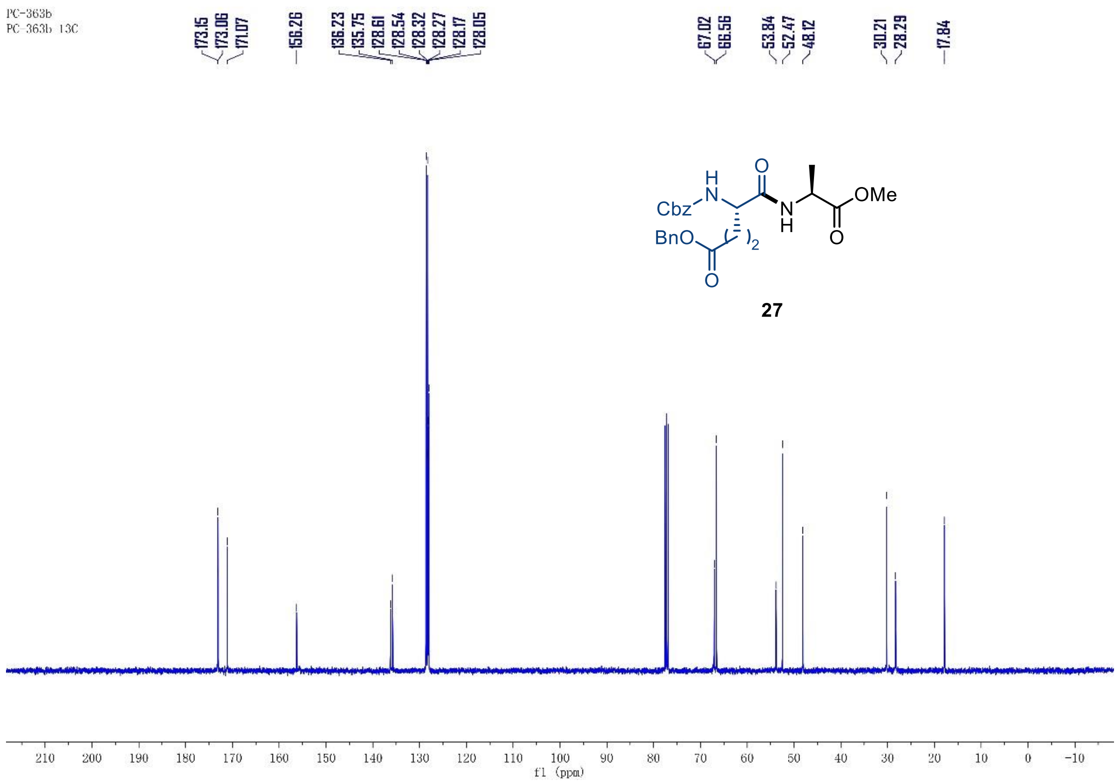

PC-359b
PC-359b 13C
172.93 169.09
156.04
136.31 128.50 128.09 127.93
75.39 66.78 58.56 52.29 48.24
28.15
18.25 16.78
Cbz
N
H
O
N
H
OMe
O
tBuO
25
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


PC-363a
PC-363a 1H
7.34
7.32
7.25
7.06
7.04
6.03
6.01
5.15
5.12
5.11
5.09
5.08
4.64
4.56
4.54
4.52
4.50
3.69
3.07
3.06
3.03
3.02
2.78
2.76
2.73
2.72
1.35
1.34
9.83
0.92
0.94
4.00
0.93
0.93
3.10
1.04
1.03
3.27
f1 (ppm)
Cbz
H
N
O
N
H
OMe
O
BnO
O
26

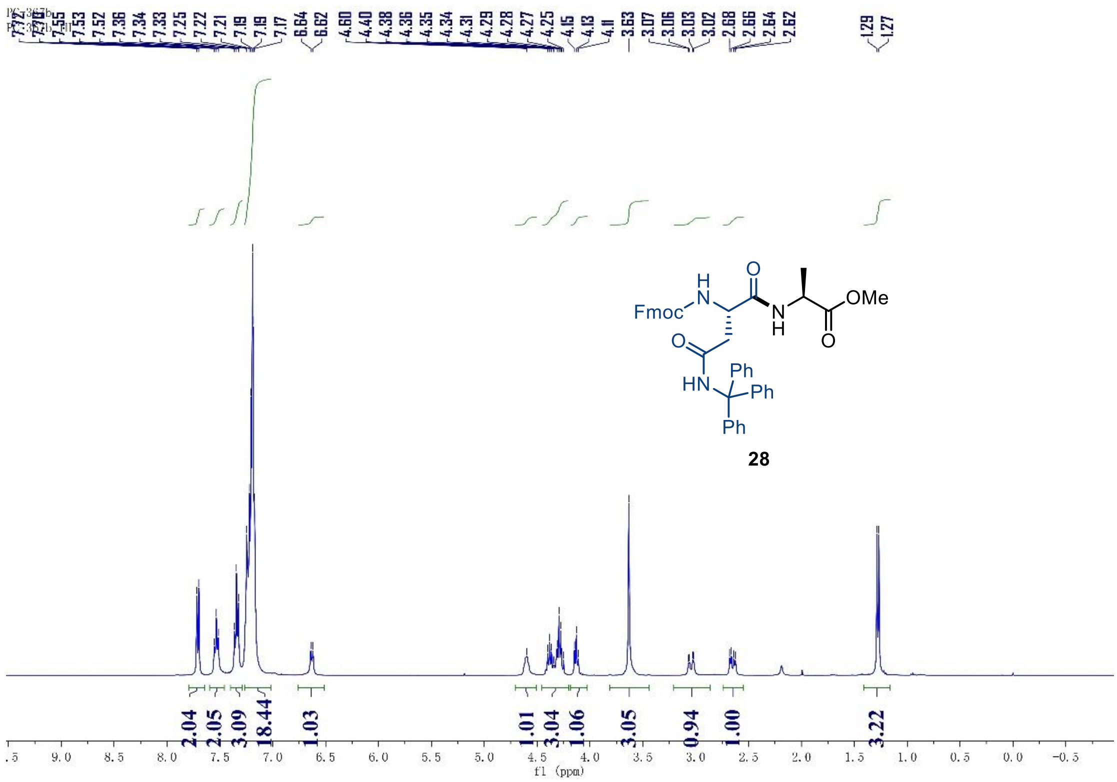

PC-363a
PC-363a 13C
172.93
171.65
170.02
156.04
136.03
135.34
128.62
128.61
128.43
128.31
128.20
67.32
66.96
52.49
50.94
48.30
36.41
18.00
f1 (ppm)
Cbz
H
N
O
N
H
OMe
O
BnO
O
26

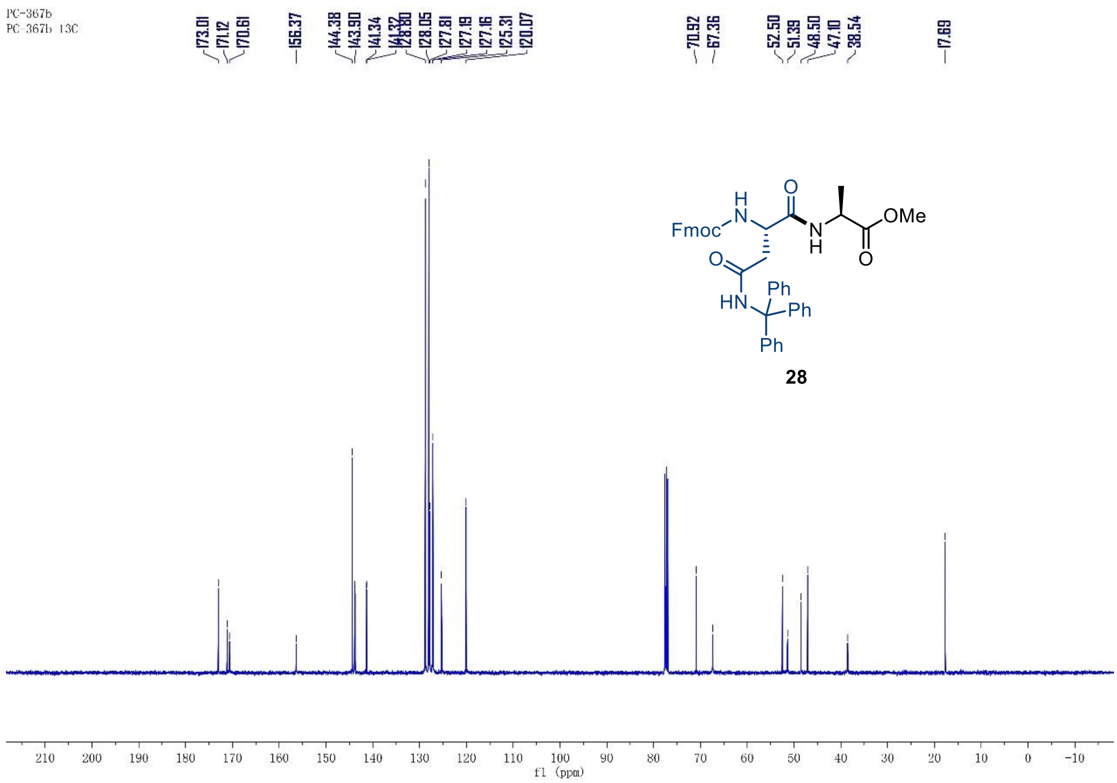

PC-363b
PC-363b 1H
7.32 7.31 7.30 7.27 7.25 7.10 7.08
5.93 5.91
5.09 5.06 5.03
4.54 4.52 4.51 4.38 4.36 3.68
2.54 2.52 2.51 2.49 2.16 2.14 2.13 2.01 1.99 1.97 1.35 1.33
Cbz
H
N
O
N
H
OMe
O
BnO
)2
O
10.00
0.94
1.01
4.03
1.00
0.92
3.03
2.03
1.04
1.04
3.30
f1 (ppm)

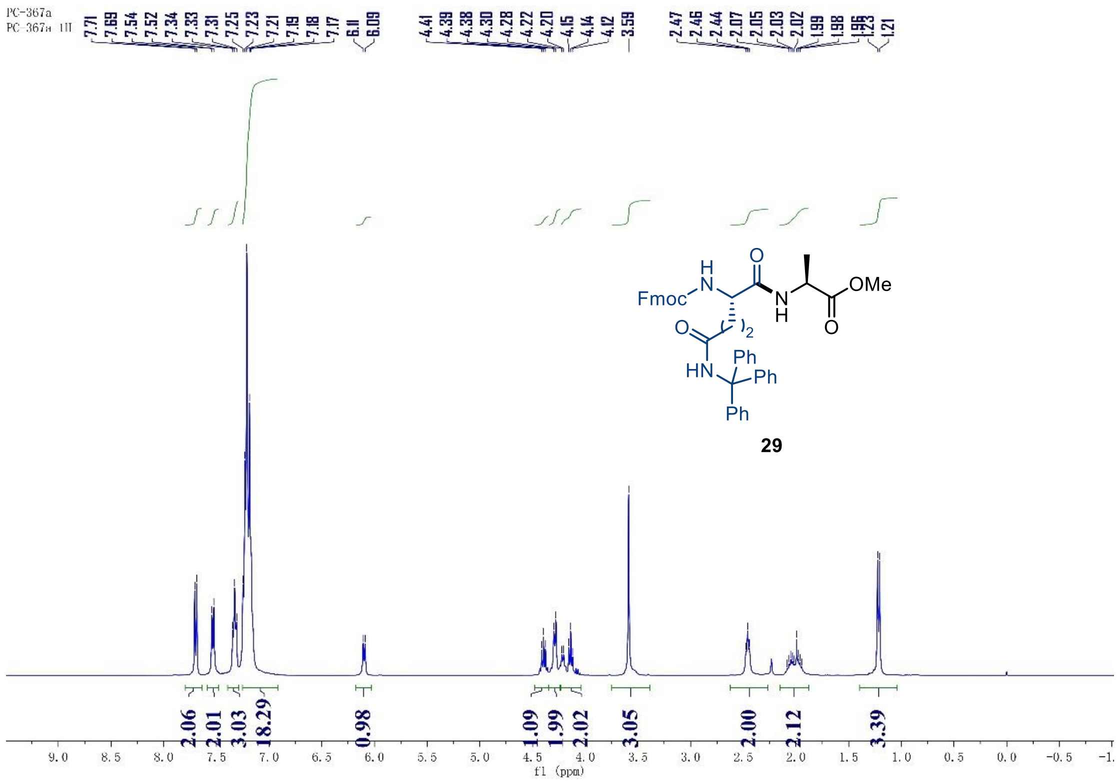
27

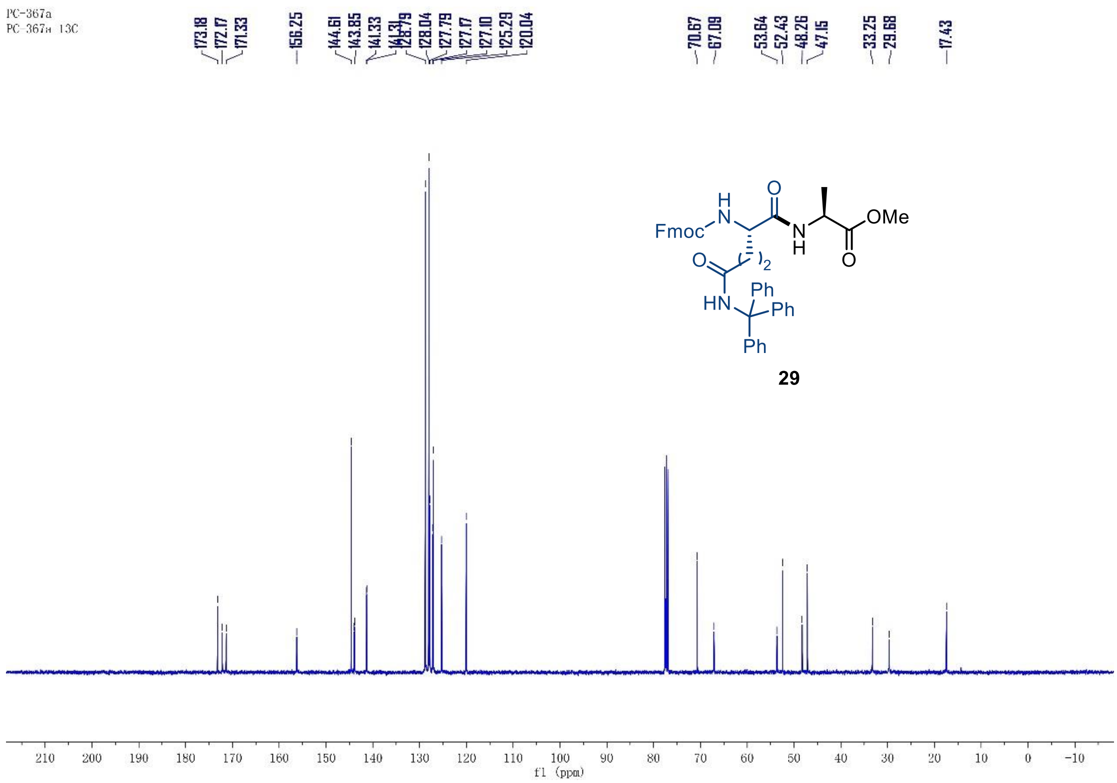

PC-363b
PC-363b 13C
173.15 173.06 171.07
156.26
136.23 135.75 128.61 128.54 128.32 128.27 128.17 128.05
67.02 66.56
53.84 52.47 48.12
30.21 28.29
17.84
Cbz
H
N
O
N
H
OMe
O
BnO
)2
O
f1 (ppm)

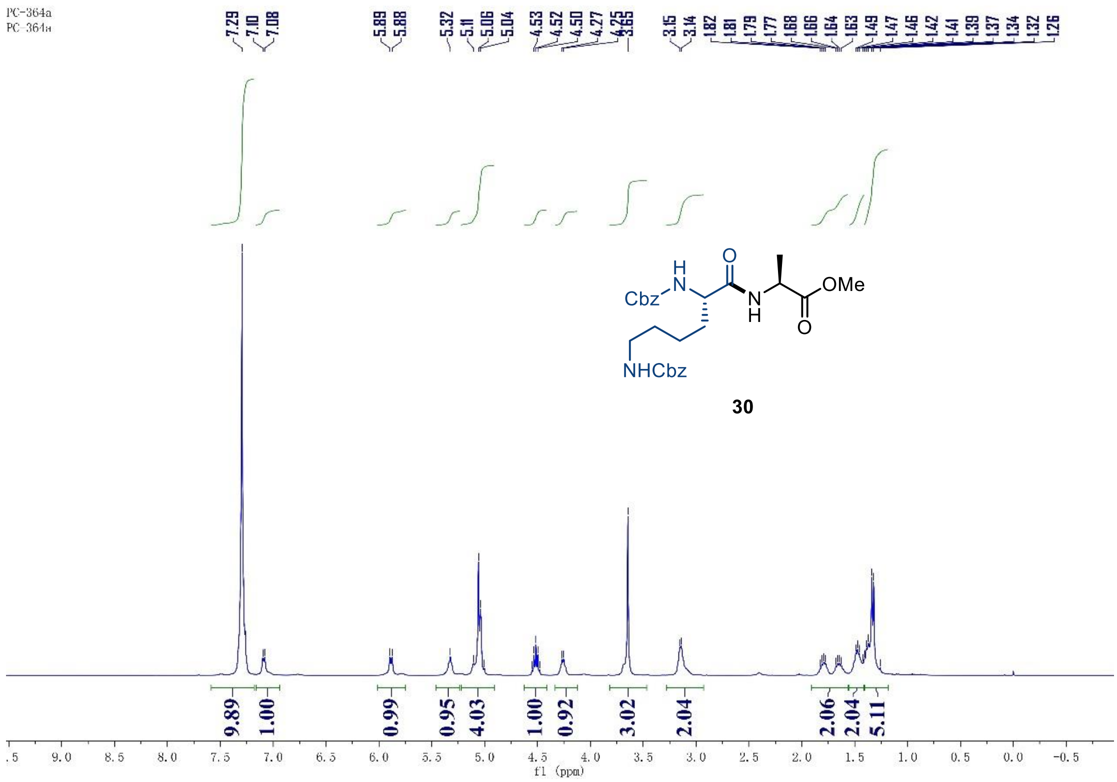
27

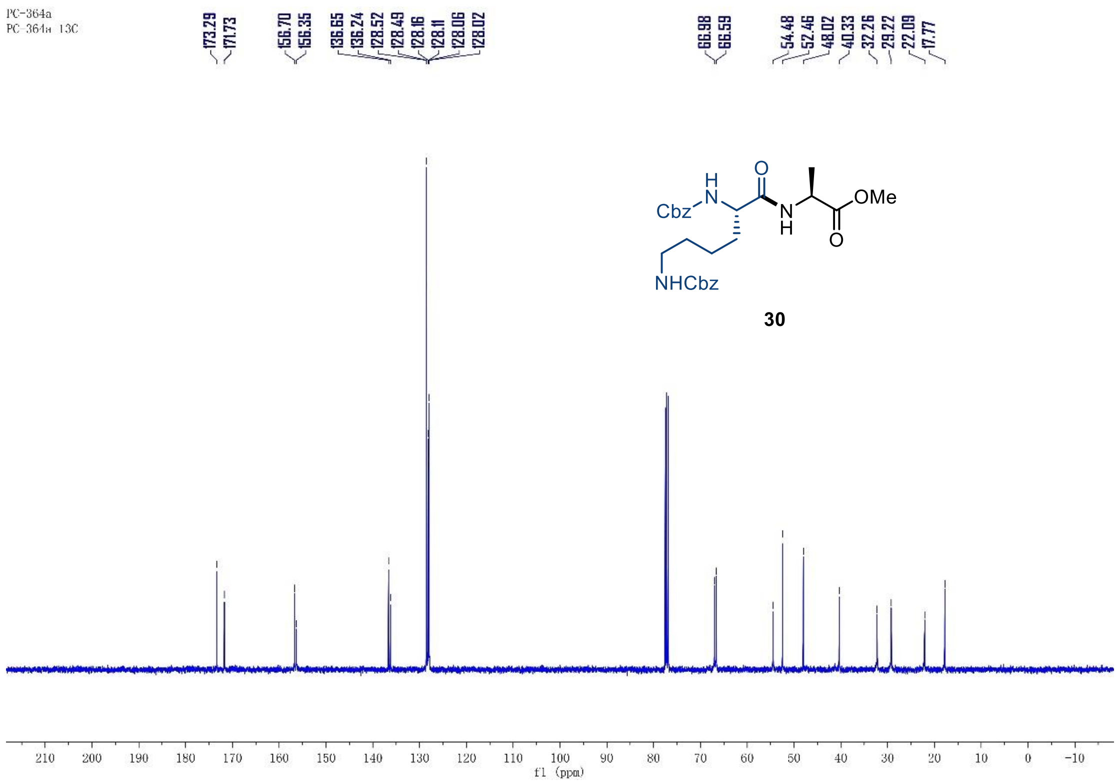


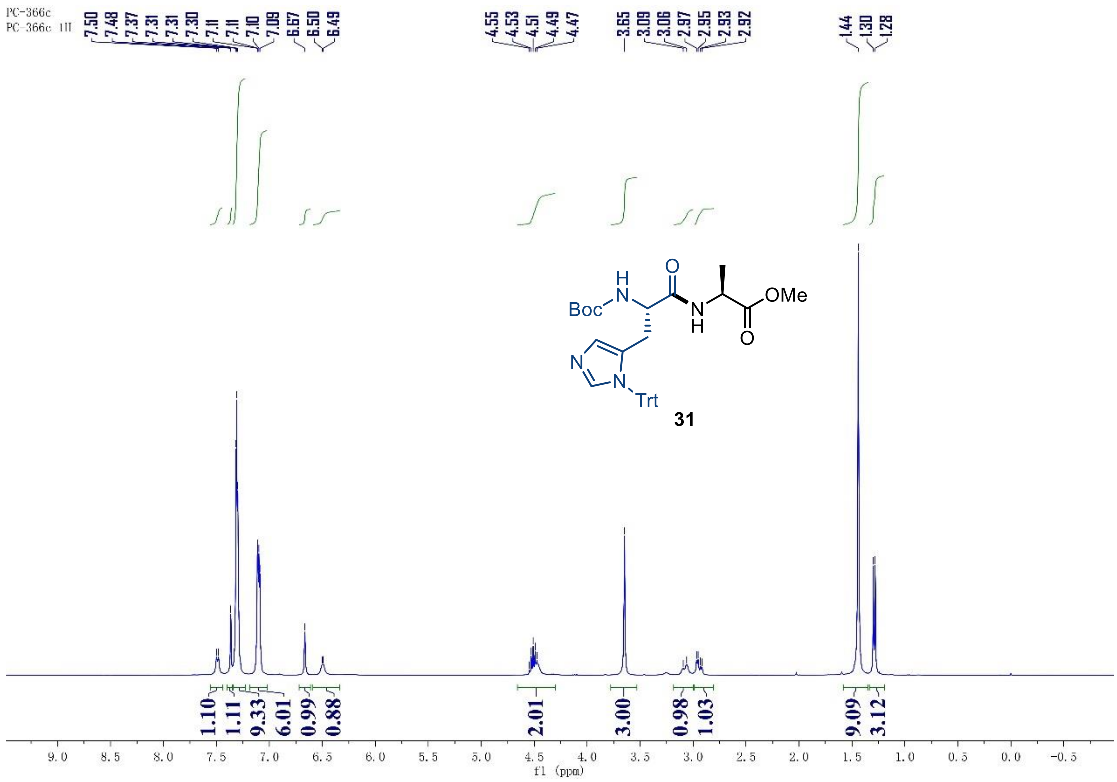



PC-367a
PC-367a 1H
7.71 7.69 7.54 7.52 7.34 7.33 7.31 7.25 7.23 7.21 7.19 7.18 7.17 6.11 6.09
4.41 4.39 4.38 4.30 4.28 4.22 4.20 4.15 4.14 4.12 3.59
2.47 2.46 2.44 2.07 2.05 2.03 2.02 1.99 1.98 1.96 1.23 1.21
Fmoc
H
N
O
N
H
OMe
O
O
)2
HN
Ph
Ph
Ph
29
2.06
2.01
3.03
18.29
0.98
1.09
1.99
2.02
3.05
2.00
2.12
3.39
f1 (ppm)

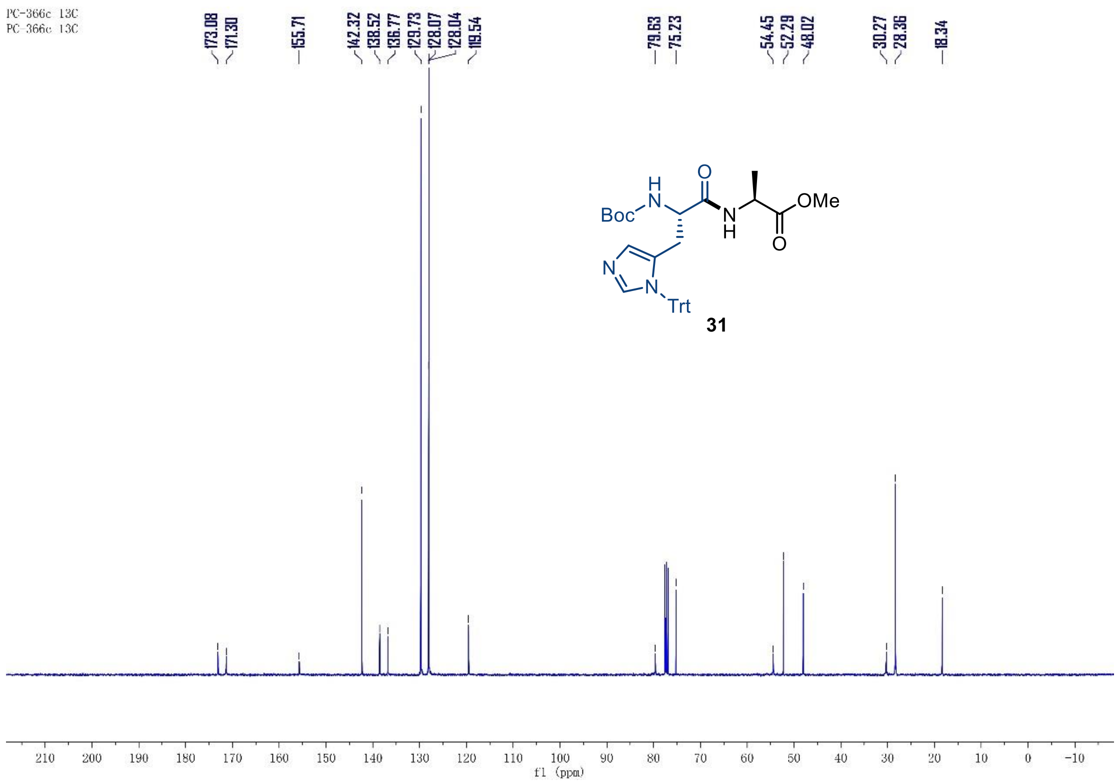

PC-367a
PC-367a 13C
173.18 172.17 171.33 156.25 144.61 143.85 141.33 141.31 128.79 128.04 127.79 127.17 127.10 125.29 120.04
70.67 67.09 53.64 52.43 48.26 47.15 33.25 29.68 17.43
Fmoc
H
N
O
N
H
OMe
O
O
)2
HN
Ph
Ph
Ph
29
f1 (ppm)


PC-364a
PC-364H
7.29 7.10 7.08 5.89 5.88 5.32 5.11 5.06 5.04 4.53 4.52 4.50 4.27 4.25 3.65 3.15 3.14 1.82 1.81 1.79 1.77 1.68 1.66 1.64 1.63 1.49 1.47 1.46 1.42 1.41 1.39 1.37 1.34 1.32 1.26
Cbz
NHCbz
OMe
30
9.89 1.00 0.99 0.95 4.03 1.00 0.92 3.02 2.04 2.06 2.04 5.11
f1 (ppm)

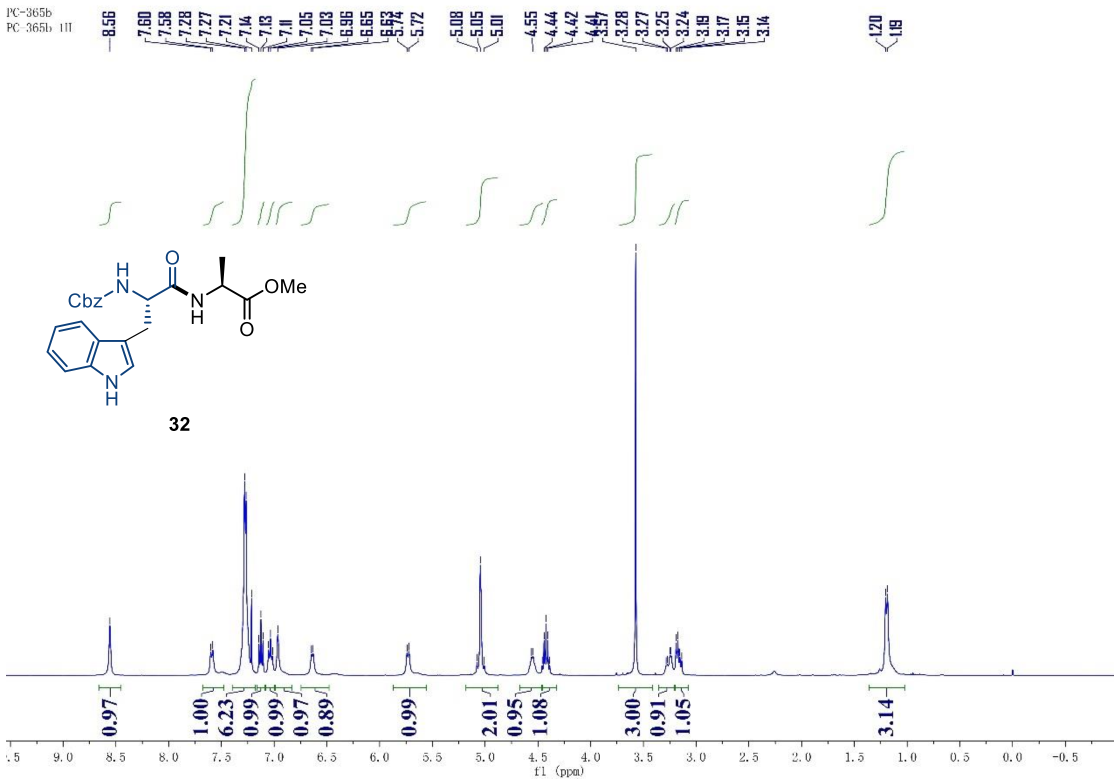

PC-364a
PC-364H 13C
173.29 171.73 156.70 156.35 136.65 136.24 128.52 128.49 128.16 128.11 128.06 128.02 66.98 66.59 54.48 52.46 48.02 40.33 32.26 29.22 22.09 17.77
Cbz
NHCbz
OMe
30
f1 (ppm)

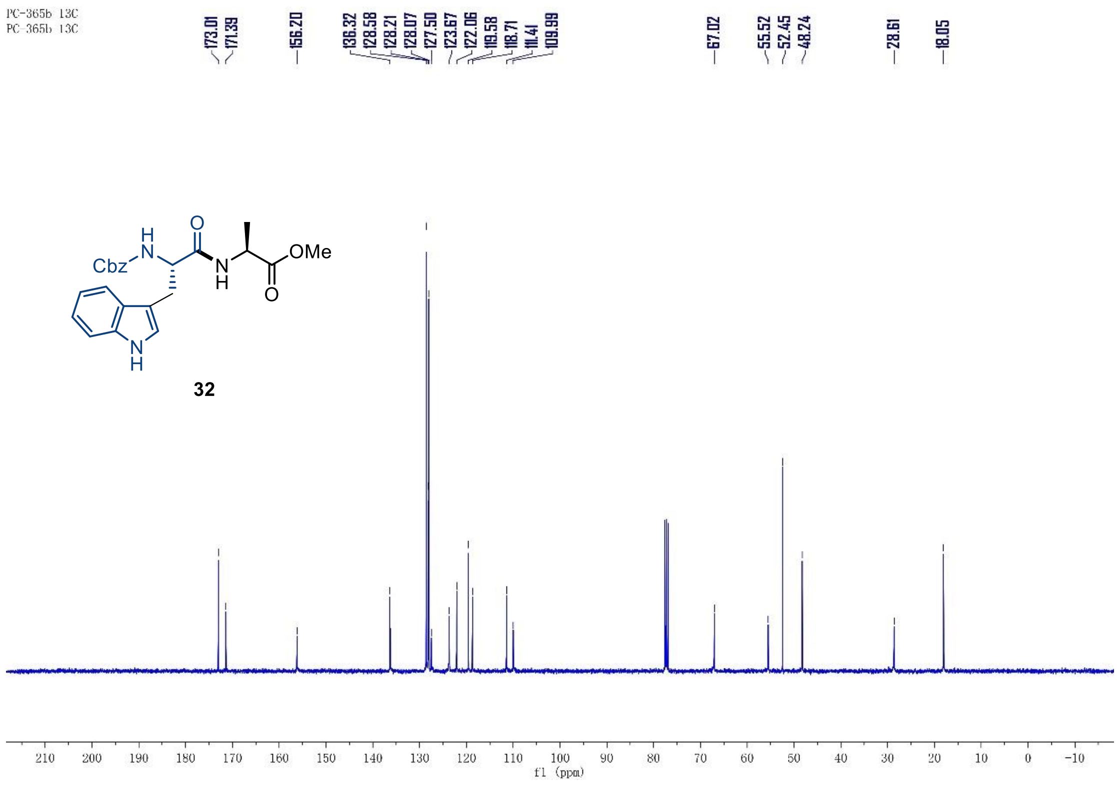


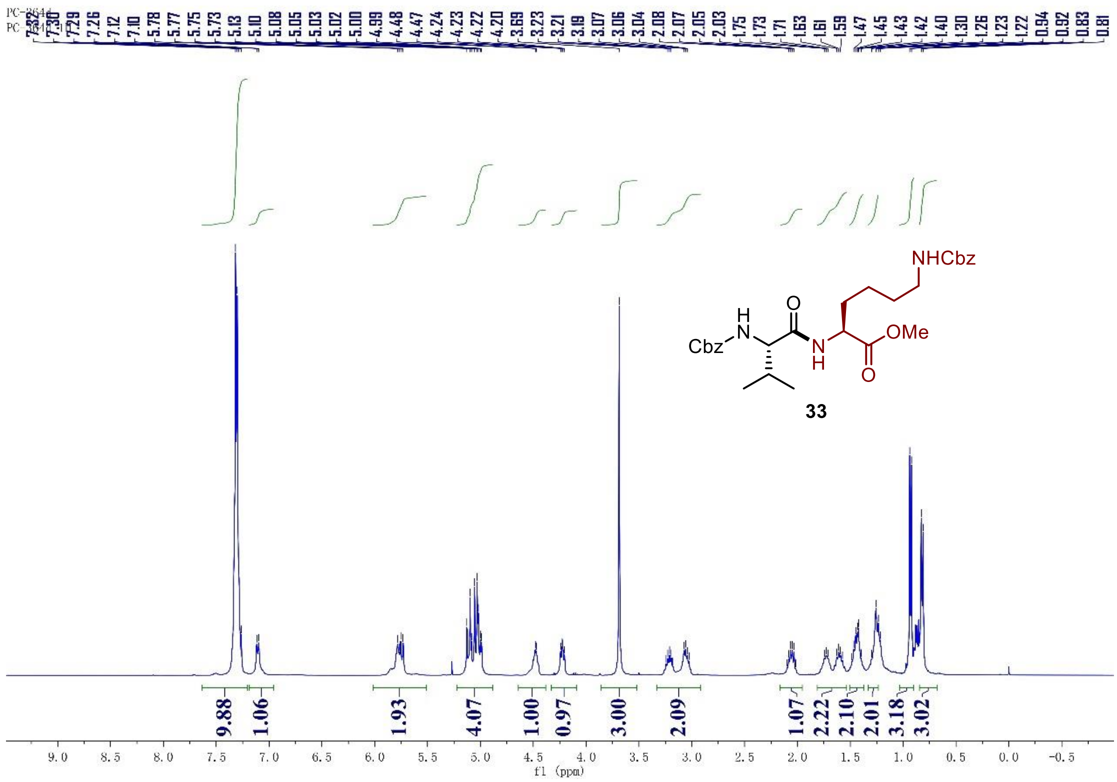
PC-366c
PC-366c 1H
7.50 7.48 7.37 7.31 7.31 7.31 7.30 7.11 7.11 7.10 7.09 6.67 6.50 6.49
4.55 4.53 4.51 4.49 4.47
3.65 3.09 3.06 2.97 2.95 2.93 2.92
1.44 1.30 1.28
1.10 1.11 9.33 6.01 0.99 0.88 2.01 3.00 0.98 1.03 9.09 3.12
Boc
H
N
O
N
H
OMe
O
N
N
Trt
31
f1 (ppm)

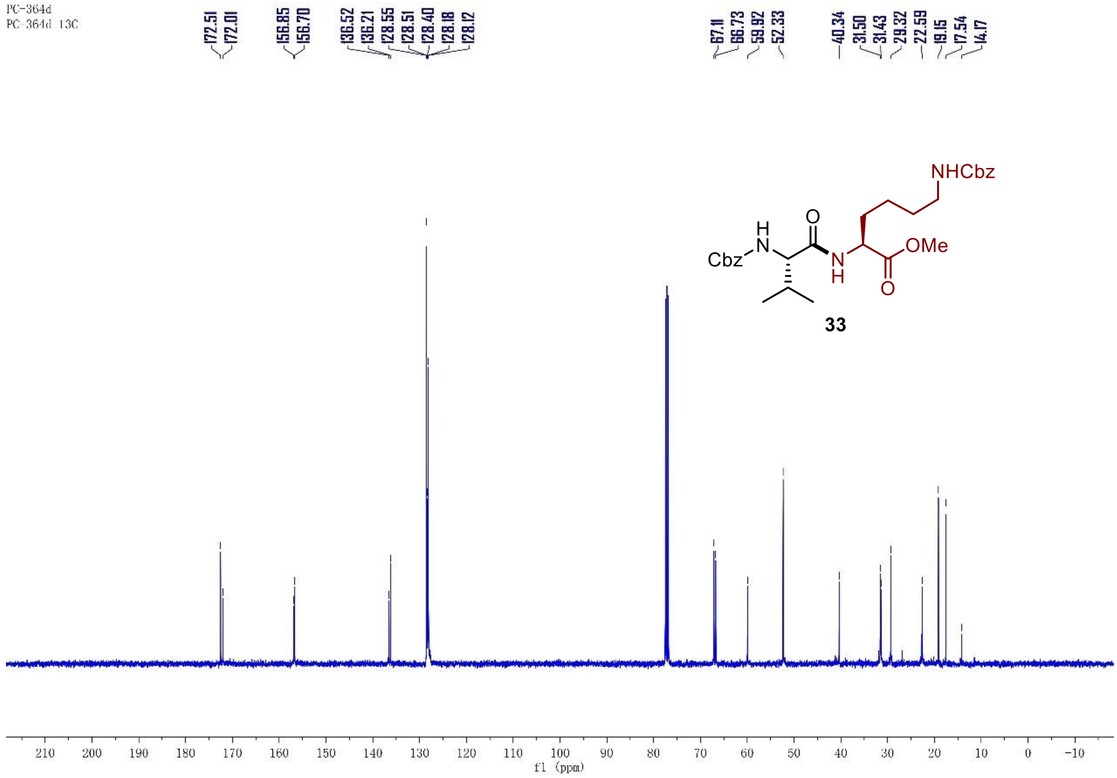


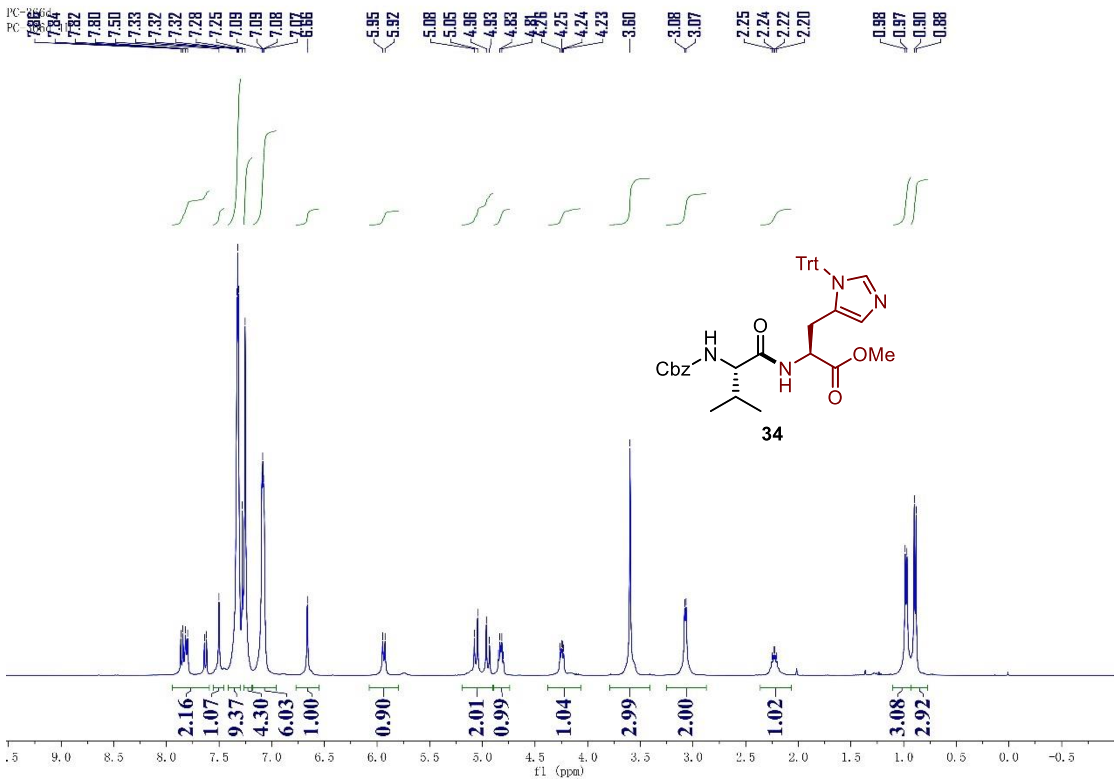
PC-366c 13C
PC-366c 13C
173.08 171.30 155.71 142.32 138.52 136.77 129.73 128.07 128.04 119.54
79.63 75.23 54.45 52.29 48.02 30.27 28.36 18.34
Boc
H
N
O
N
H
OMe
O
N
N
Trt
31
f1 (ppm)

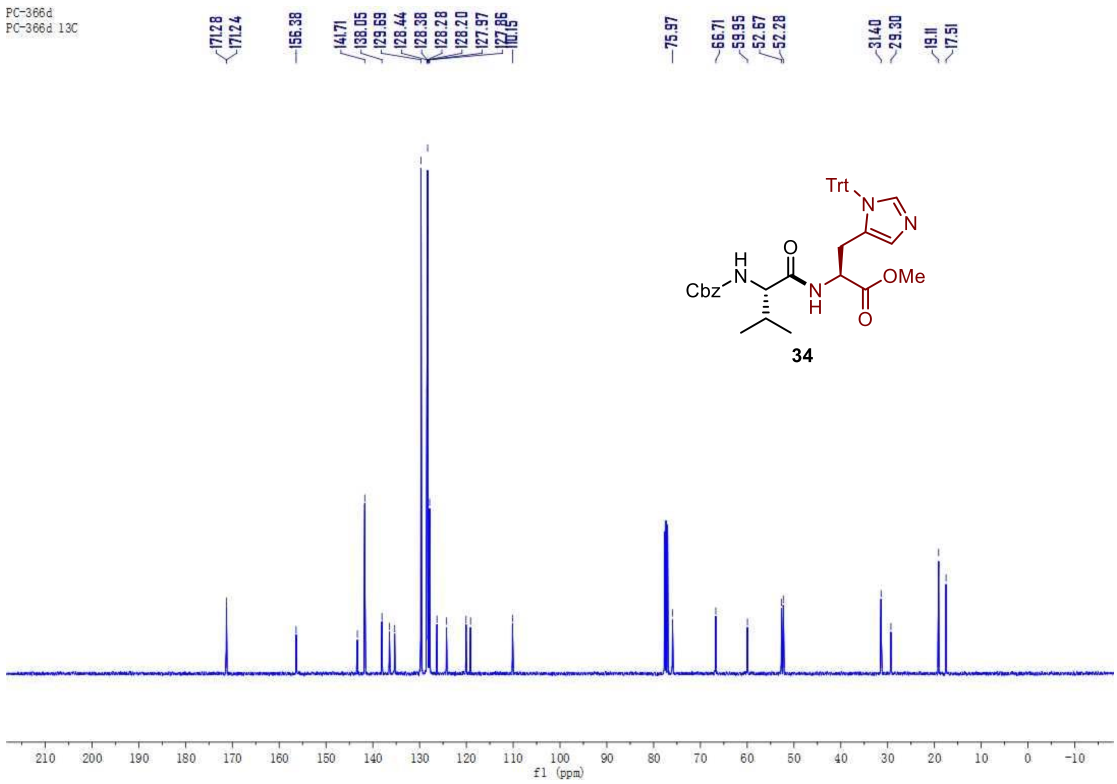

PC-365b
PC-365b 1H
8.56 7.60 7.58 7.28 7.27 7.21 7.14 7.13 7.11 7.05 7.03 6.96 6.65 6.63 5.74 5.72 5.08 5.05 5.01 4.55 4.44 4.42 4.41 3.57 3.28 3.27 3.25 3.24 3.19 3.17 3.15 3.14 1.20 1.19
Cbz
N
H
O
OMe
32
0.97 1.00 6.23 0.99 0.99 0.97 0.89 0.99 2.01 0.95 1.08 3.00 0.91 1.05 3.14
f1 (ppm)

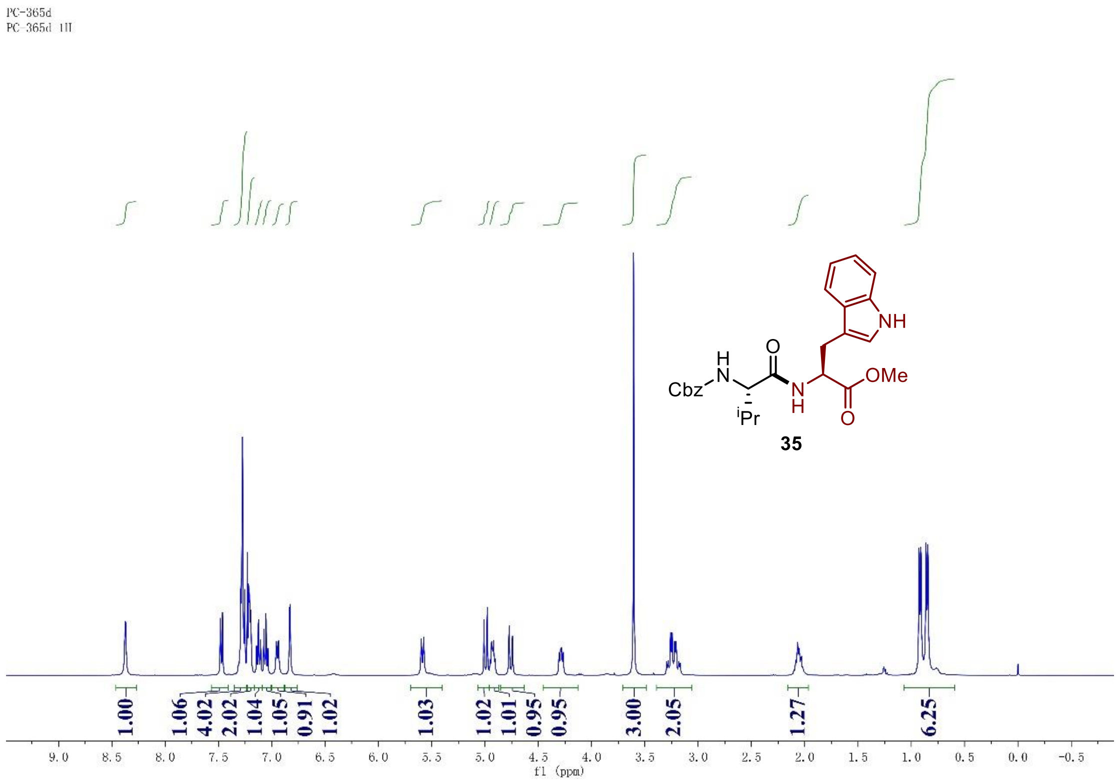

PC-365b 13C
PC-365b 13C
173.01 171.39 156.20 136.32 128.58 128.21 128.07 127.50 123.67 122.06 119.58 118.71 111.41 109.99 67.02 55.52 52.45 48.24 28.61 18.05
Cbz
N
H
O
OMe
32
f1 (ppm)


PC-364d
9.88
1.06
1.93
4.07
1.00
0.97
3.00
2.09
1.07
2.22
2.10
2.01
3.18
3.02
f1 (ppm)
NHCbz
Cbz
OMe
33

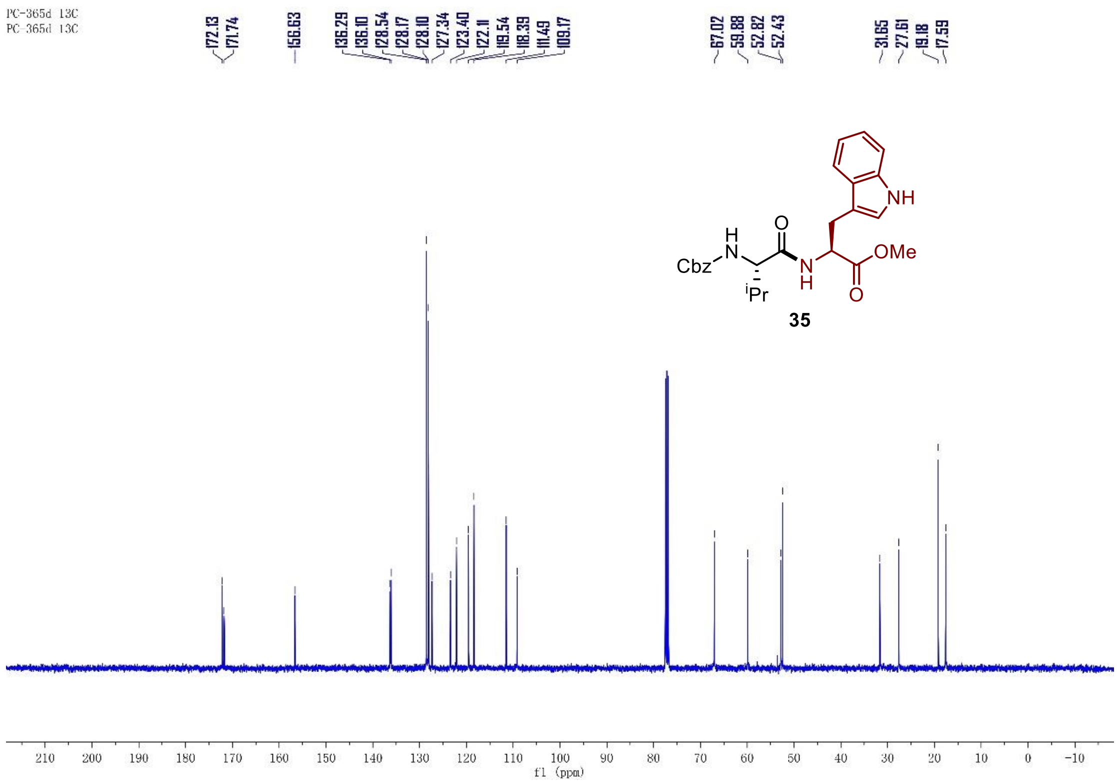

PC-364d
PC-364d 13C
172.51
172.01
156.85
156.70
136.52
136.21
128.55
128.51
128.40
128.18
128.12
67.11
66.73
59.92
52.33
40.34
31.50
31.43
29.32
22.59
19.15
17.54
14.17
f1 (ppm)
NHCbz
Cbz
OMe
33


Trt
N
N
O
H
N
Cbz
N
H
OMe
O
34
f1 (ppm)

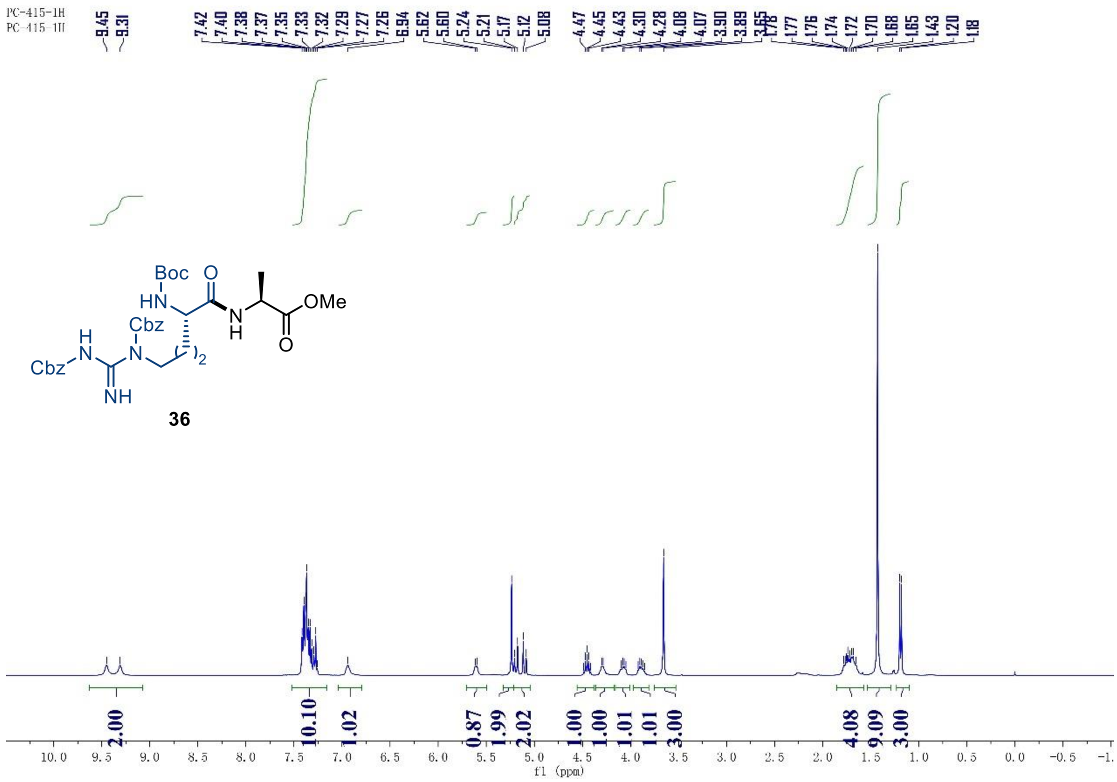

PC-366d
PC-366d 13C
Trt
N
N
O
H
N
Cbz
N
H
OMe
O
34
f1 (ppm)

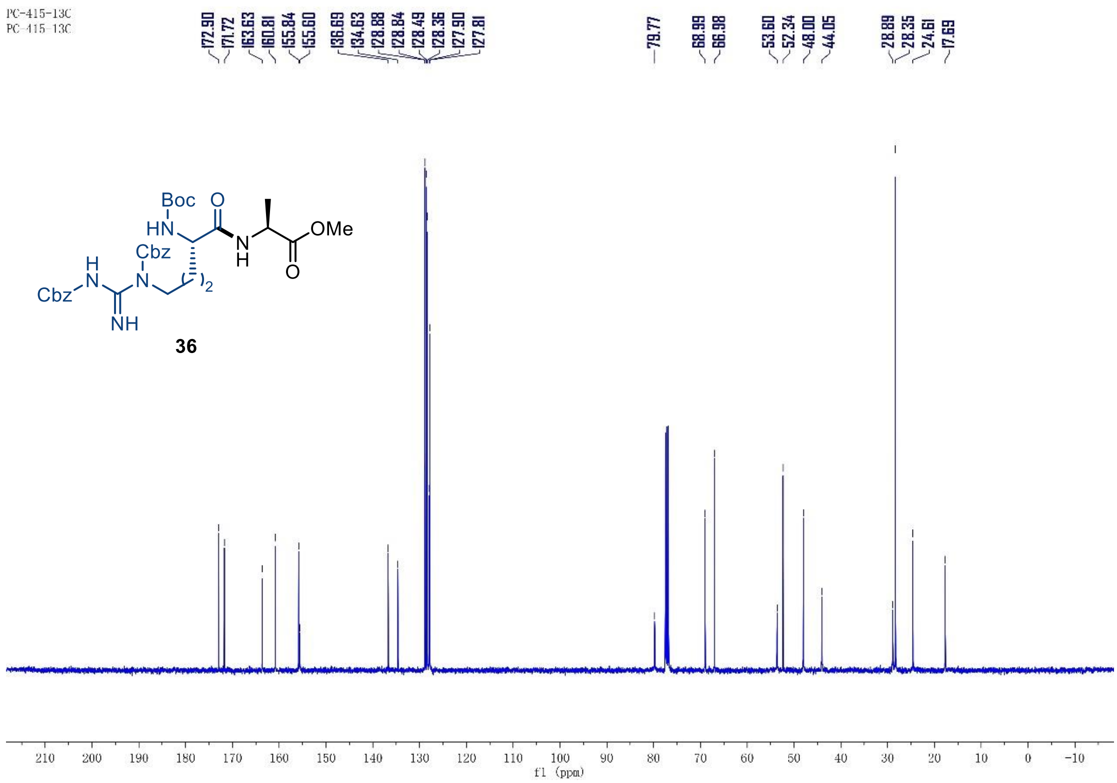


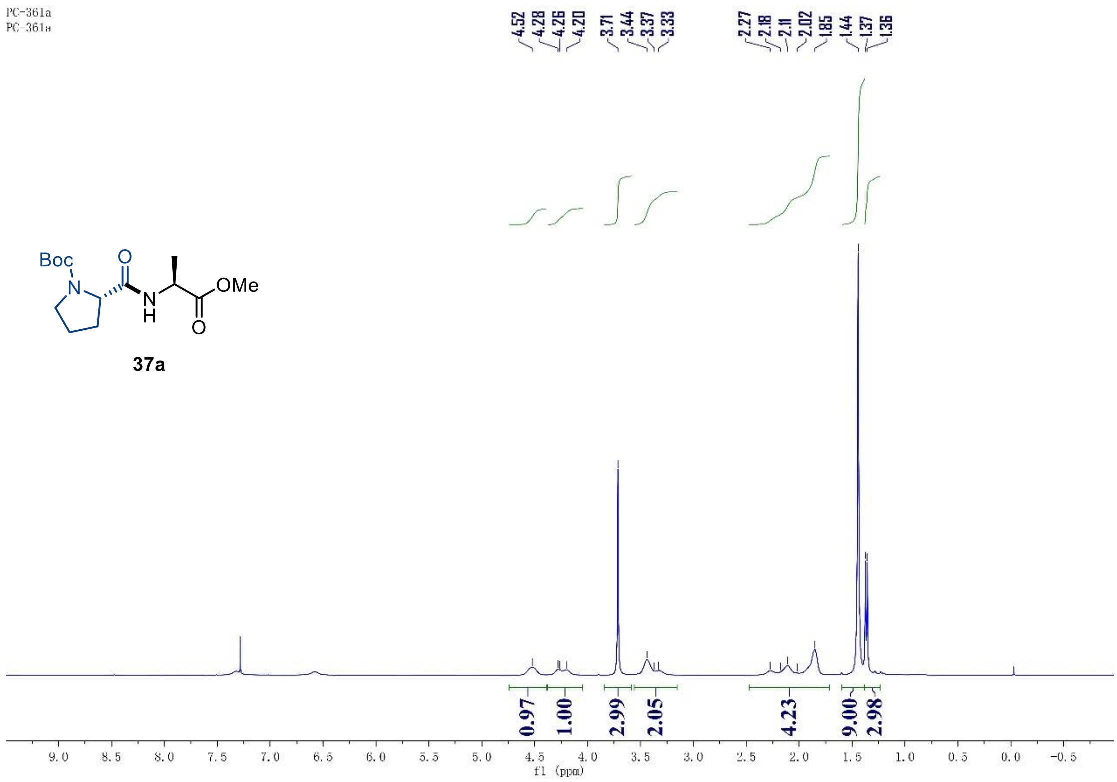
PC-365d
PC-365d 1H
1.00
1.06
4.02
2.02
1.04
1.05
0.91
1.02
1.03
1.02
1.01
0.95
0.95
3.00
2.05
1.27
6.25
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
Cbz
N
H
O
iPr
N
H
NH
OMe
O
35

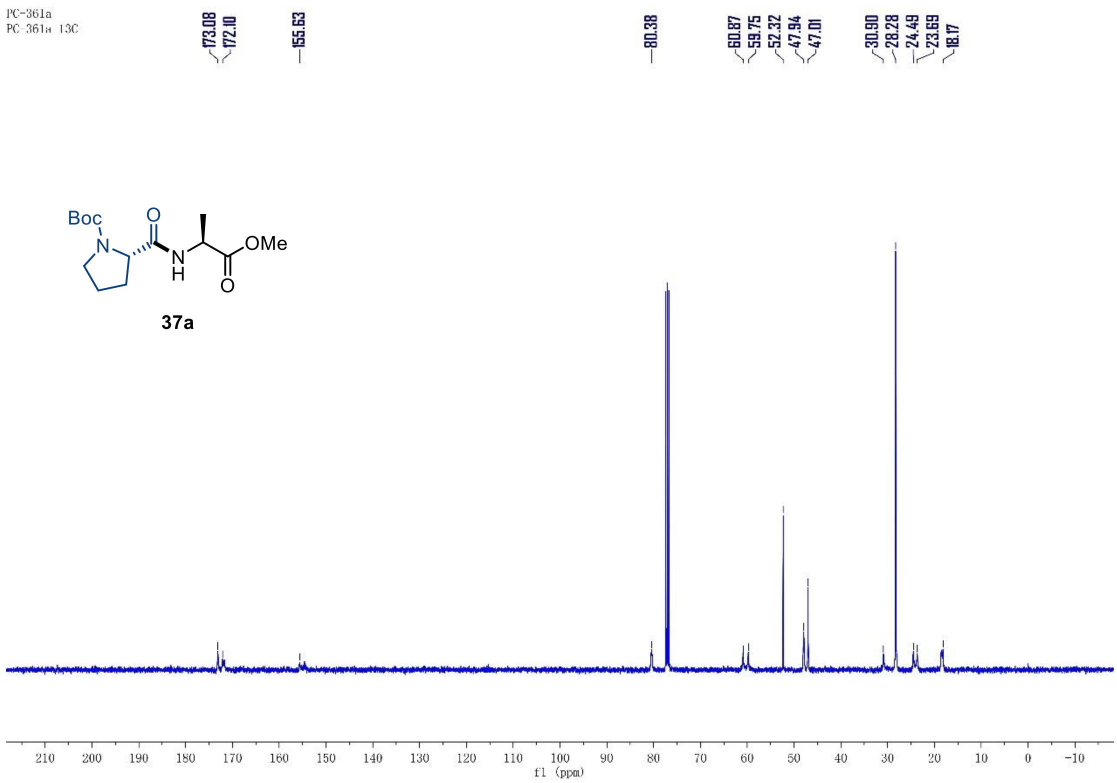


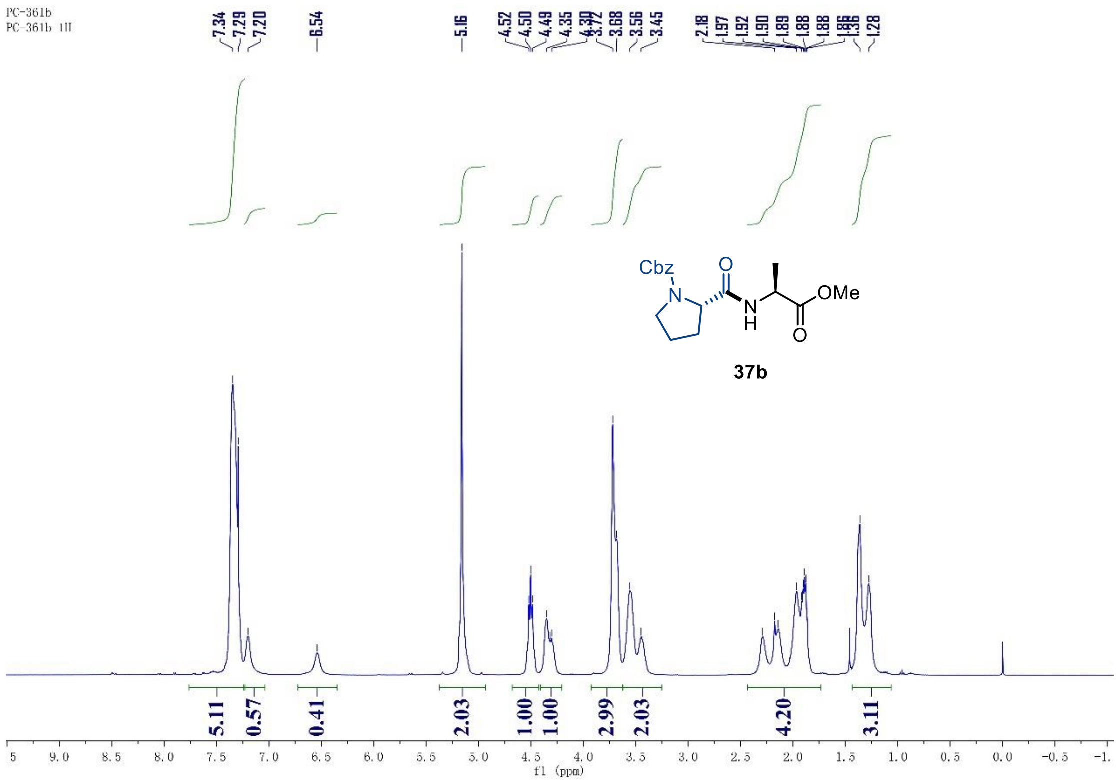
PC-365d 13C
PC-365d 13C
172.13
171.74
156.63
136.29
136.10
128.54
128.17
128.10
127.34
123.40
122.11
119.54
118.39
111.49
109.17
67.02
59.88
52.82
52.43
31.65
27.61
19.18
17.59
Cbz
N
H
O
iPr
N
H
NH
OMe
O
35
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

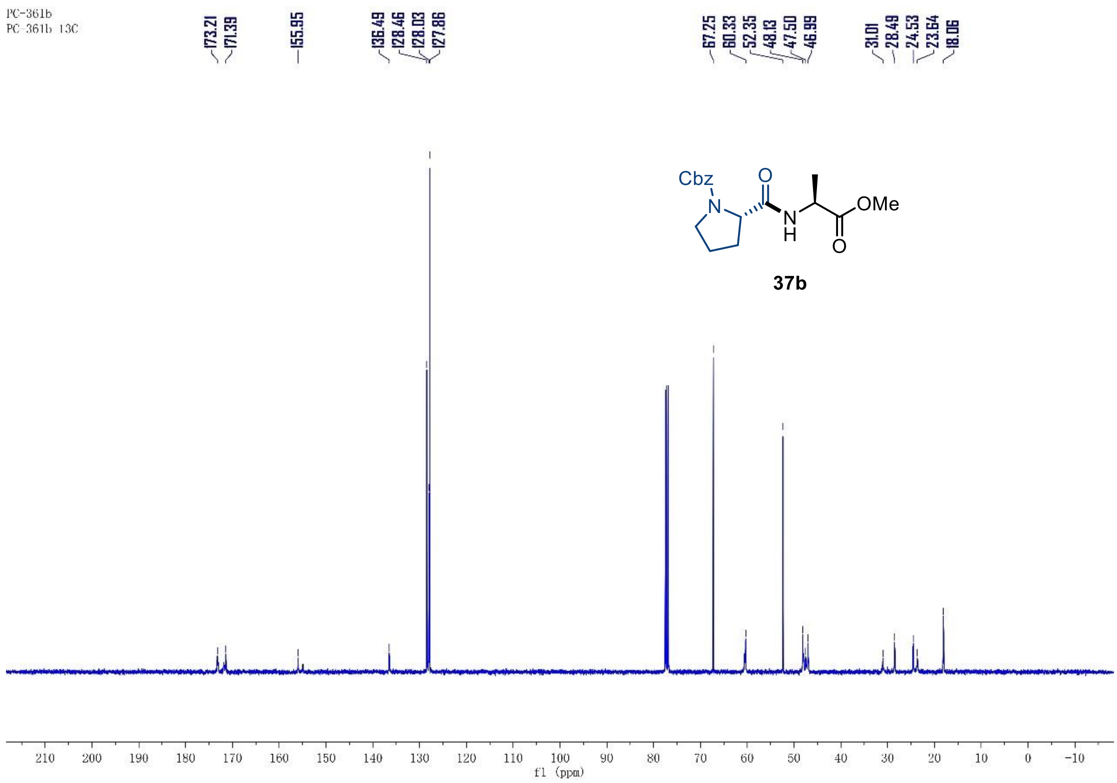

PC-415-1H
9.45
9.31
7.42
7.40
7.38
7.37
7.35
7.33
7.32
7.29
7.27
7.26
6.94
5.62
5.60
5.24
5.21
5.17
5.12
5.08
4.47
4.45
4.43
4.30
4.28
4.08
4.07
3.90
3.89
3.65
1.78
1.77
1.76
1.74
1.72
1.70
1.68
1.65
1.43
1.20
1.18
Boc
HN
O
N
H
OMe
O
Cbz
H
N
N
Cbz
NH
36
2.00
10.10
1.02
0.87
1.99
2.02
1.00
1.00
1.01
1.01
3.00
4.08
9.09
3.00
f1 (ppm)

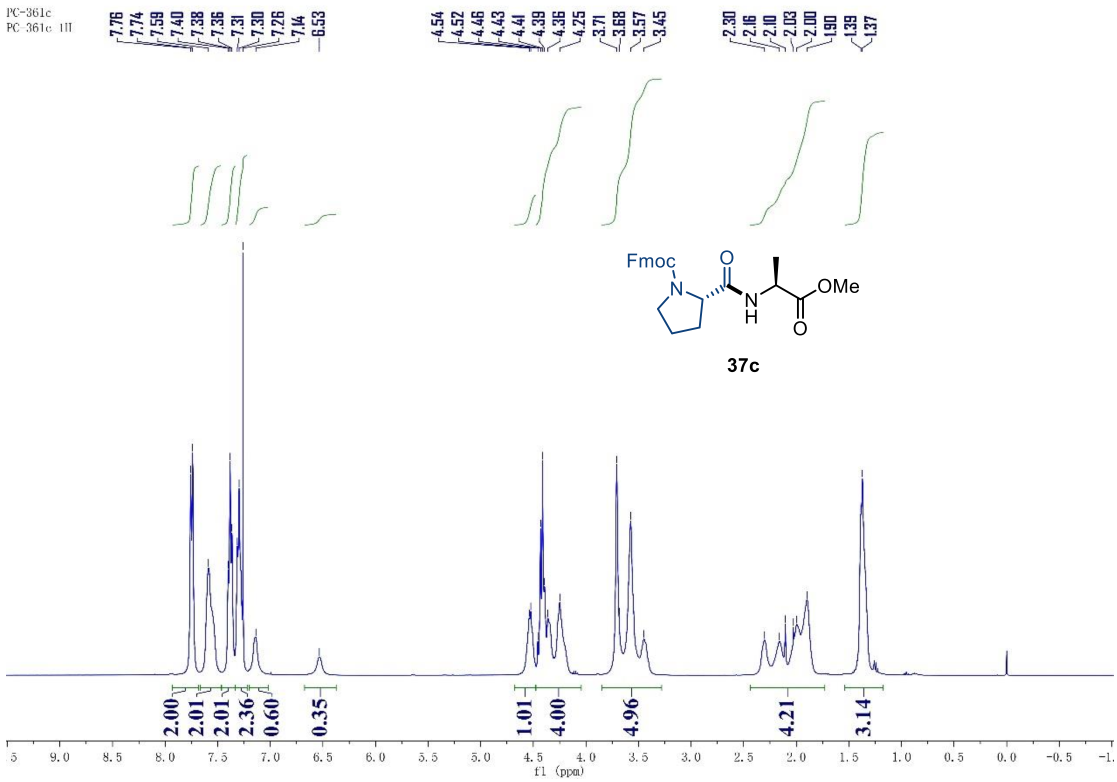

PC-415-13C
172.90
171.72
163.63
160.81
155.84
155.60
136.69
134.63
128.88
128.84
128.49
128.36
127.90
127.81
79.77
68.99
66.98
53.60
52.34
48.00
44.05
28.89
28.35
24.61
17.69
Boc
HN
O
N
H
OMe
O
Cbz
H
N
N
Cbz
NH
36
f1 (ppm)

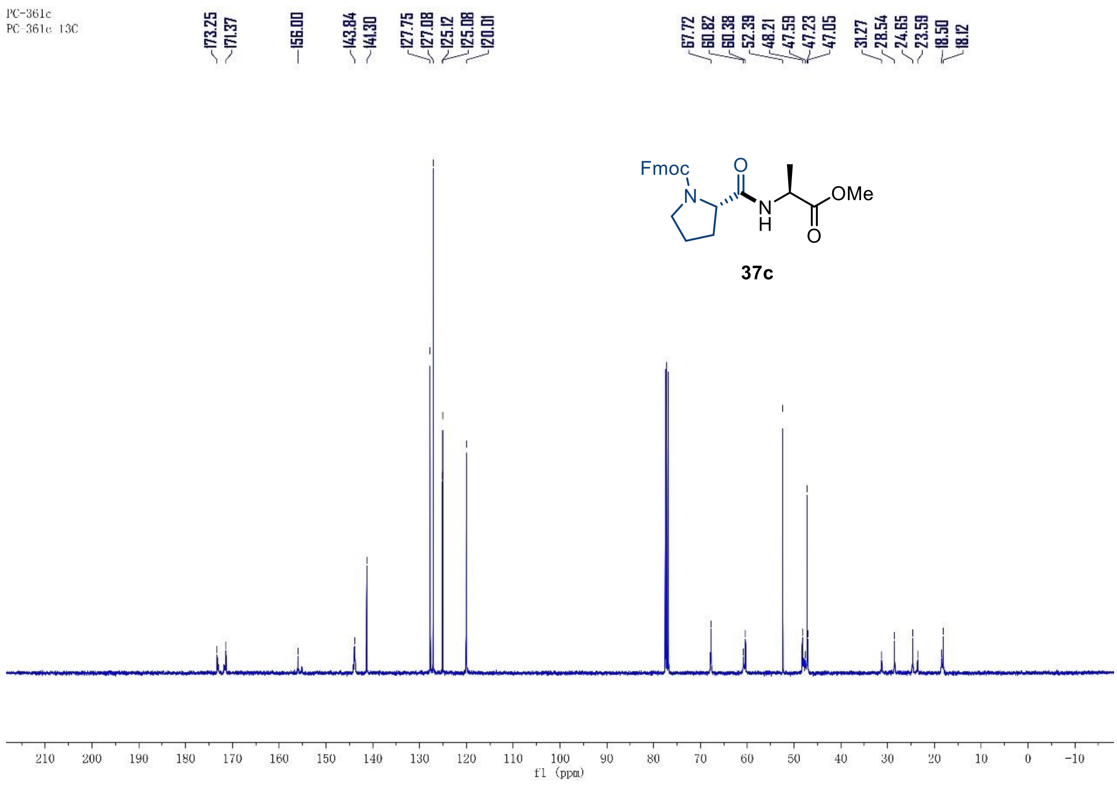

PC-361a
PC-361H
4.52 4.28 4.26 4.20 3.71 3.44 3.37 3.33 2.27 2.18 2.11 2.02 1.85 1.44 1.37 1.36
Boc
N
O
N
H
OMe
O
37a
0.97 1.00 2.99 2.05 4.23 9.00 2.98
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

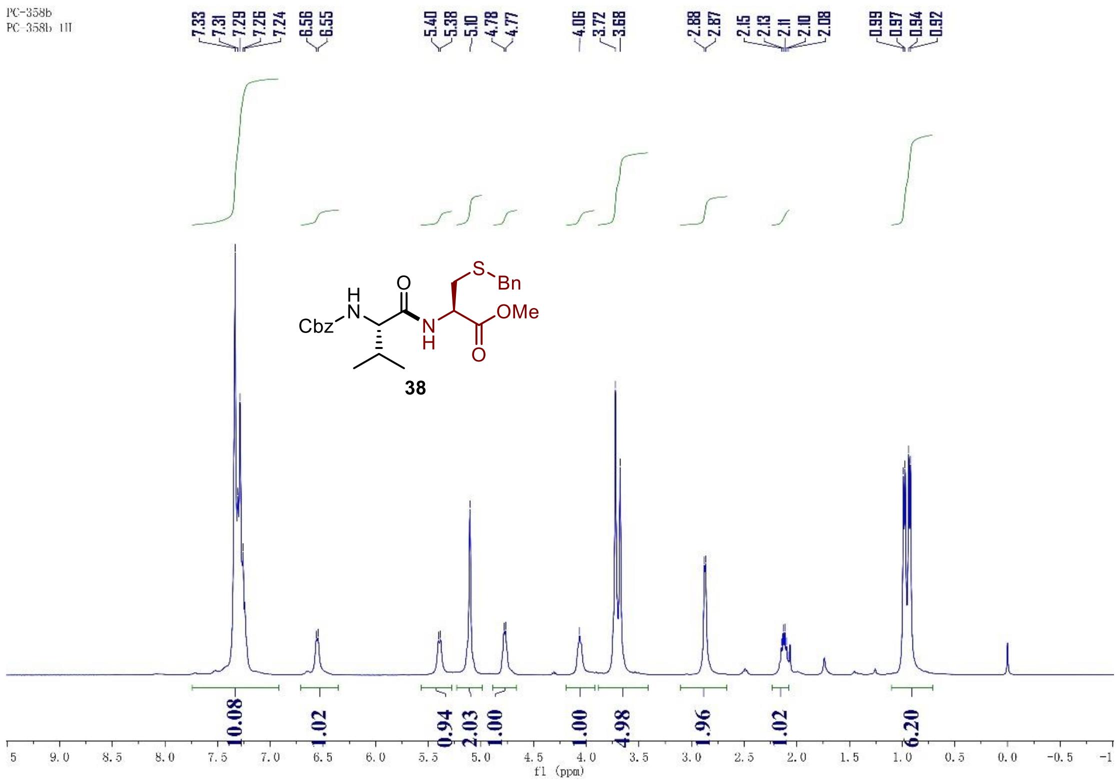

PC-361a
PC-361H 13C
173.08 172.10 155.63 80.38 60.87 59.75 52.32 47.94 47.01 30.90 28.28 24.49 23.69 18.17
Boc
N
O
N
H
OMe
O
37a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

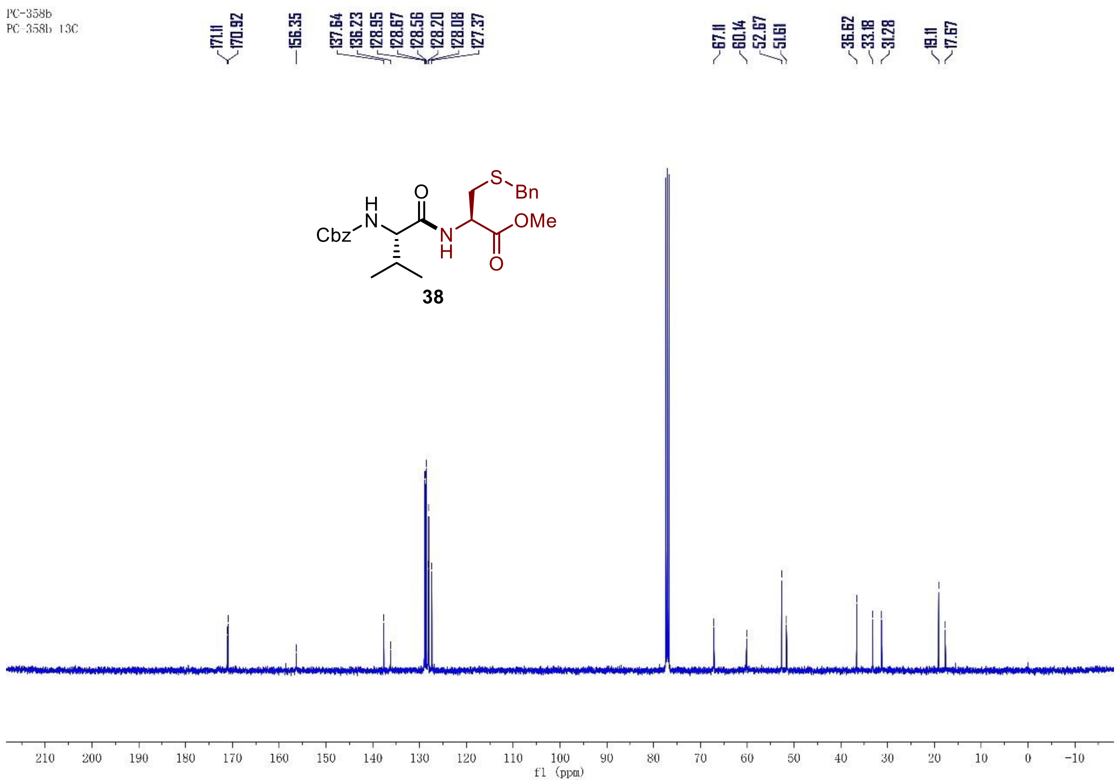

PC-361b
PC-361b 1H
7.34
7.29
7.20
6.54
5.16
4.52
4.50
4.49
4.35
4.30
3.72
3.68
3.56
3.45
2.18
1.97
1.92
1.90
1.89
1.88
1.88
1.86
1.36
1.28
Cbz
N
O
N
H
OMe
O
37b
5.11
0.57
0.41
2.03
1.00
1.00
2.99
2.03
4.20
3.11
f1 (ppm)

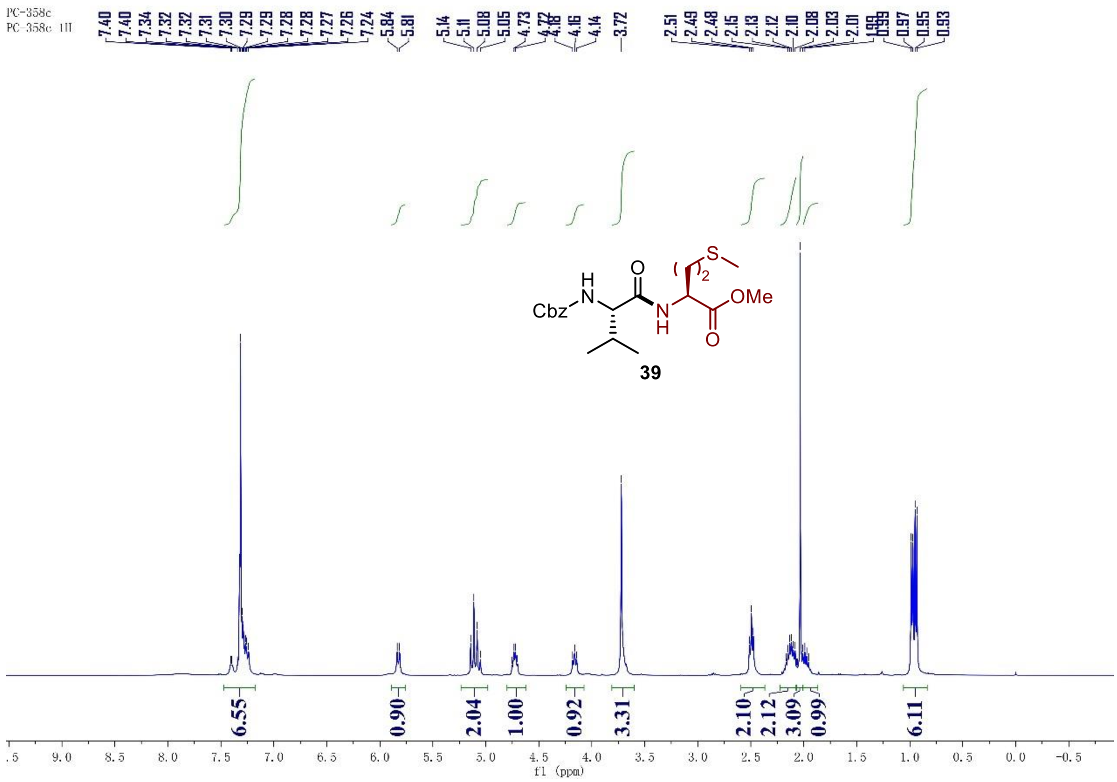

PC-361b
PC-361b 13C
173.21
171.39
155.95
136.49
128.46
128.03
127.86
67.25
60.33
52.35
48.13
47.50
46.99
31.01
28.49
24.53
23.64
18.06
Cbz
N
O
N
H
OMe
O
37b
f1 (ppm)

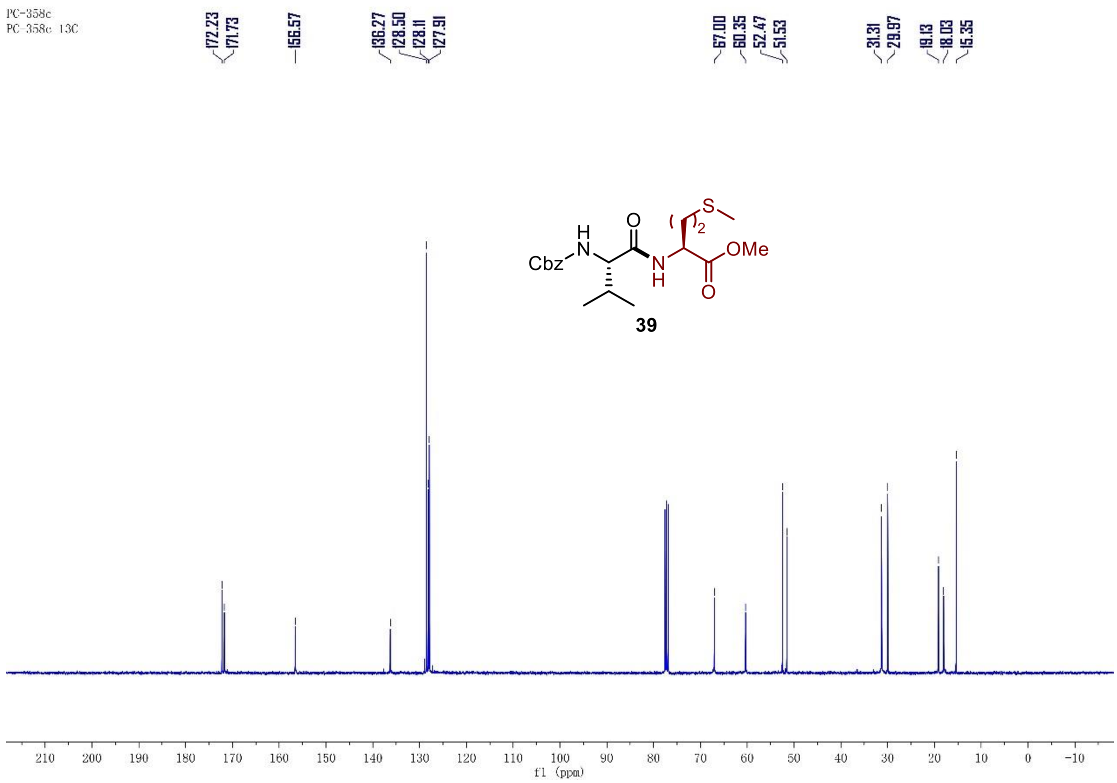

PC-361c
PC-361c 1H
7.76
7.74
7.59
7.40
7.38
7.36
7.31
7.30
7.26
7.14
6.53
4.54
4.52
4.46
4.43
4.41
4.39
4.36
4.25
3.71
3.68
3.57
3.45
2.30
2.16
2.10
2.03
2.00
1.90
1.39
1.37
Fmoc
N
O
N
H
OMe
O
37c
2.00
2.01
2.01
2.36
0.60
0.35
1.01
4.00
4.96
4.21
3.14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

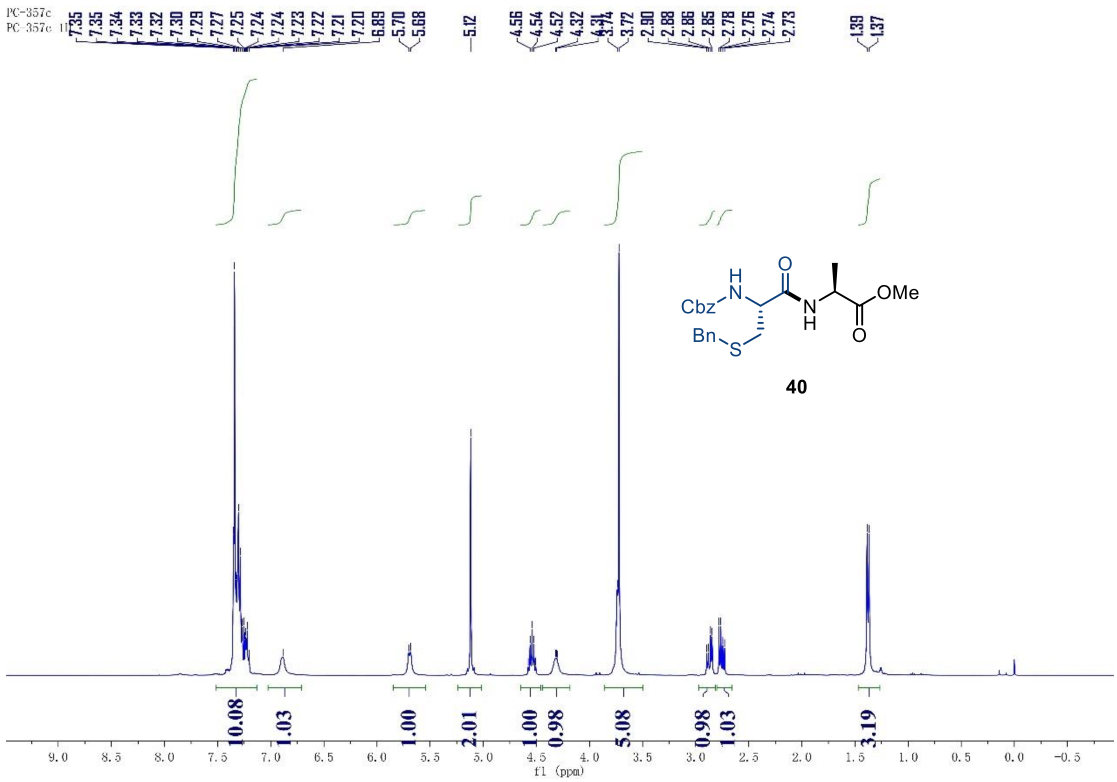

PC-361c
PC-361c 13C
173.25
171.37
156.00
143.84
141.30
127.75
127.08
125.12
125.08
120.01
67.72
60.82
60.38
52.39
48.21
47.59
47.23
47.05
31.27
28.54
24.65
23.59
18.50
18.12
Fmoc
N
O
N
H
OMe
O
37c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


PC-358b
PC-358b 1H
7.33 7.31 7.29 7.26 7.24 6.56 6.55 5.40 5.38 5.10 4.78 4.77 4.06 3.72 3.68 2.88 2.87 2.15 2.13 2.11 2.10 2.08 0.99 0.97 0.94 0.92
Cbz
H
N
O
S
Bn
OMe
38
10.08 1.02 0.94 2.03 1.00 1.00 4.98 1.96 1.02 6.20
f1 (ppm)

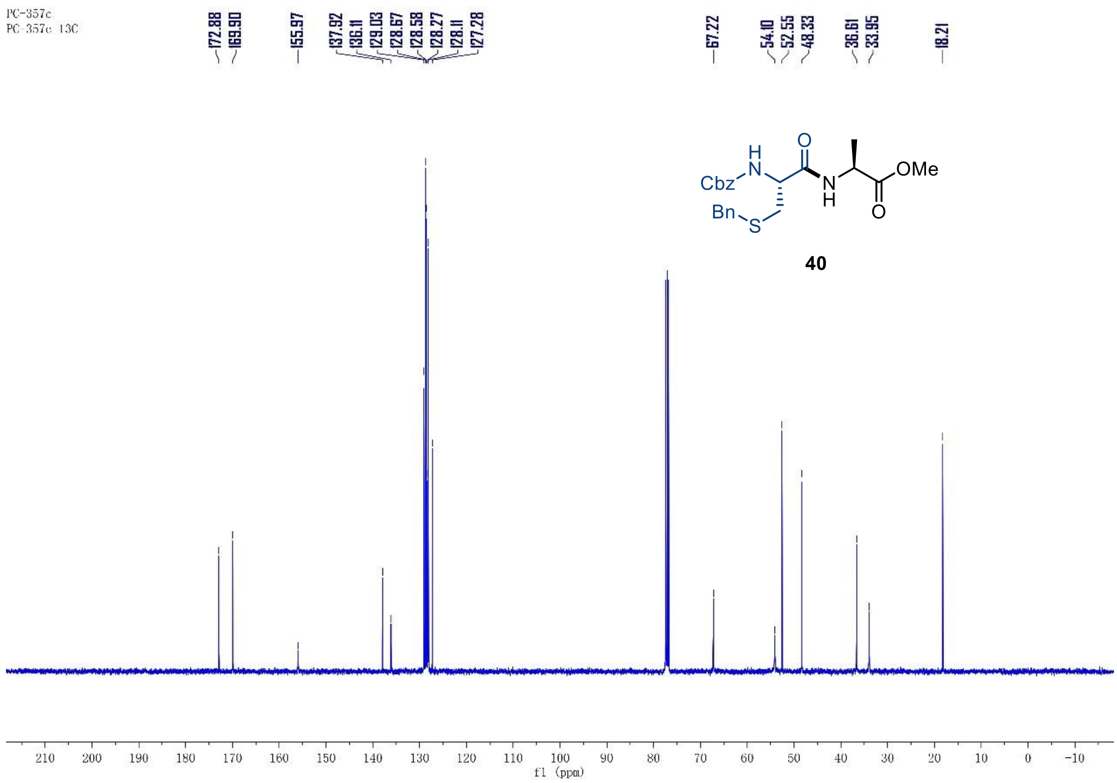

PC-358b
PC-358b 13C
171.11 170.92 156.35 137.64 136.23 128.95 128.67 128.56 128.20 128.08 127.37 67.11 60.14 52.67 51.61 36.62 33.18 31.28 19.11 17.67
Cbz
H
N
O
S
Bn
OMe
38
f1 (ppm)



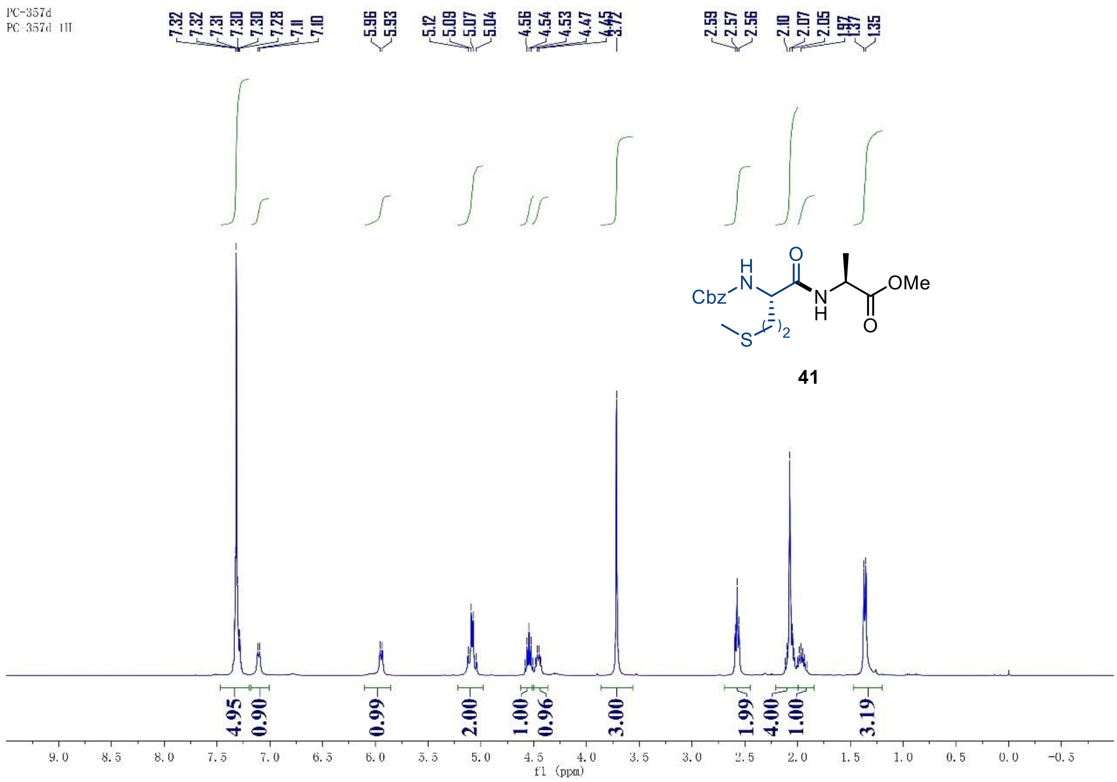


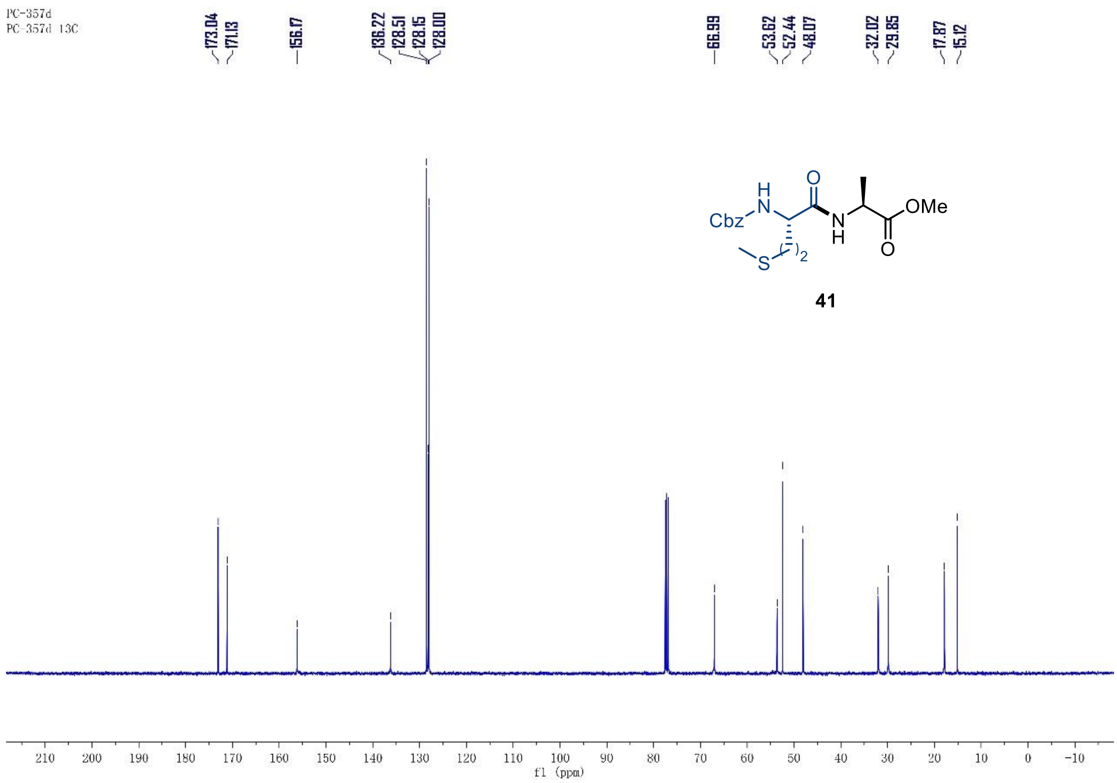

PC-357c
7.35 7.35 7.34 7.33 7.32 7.30 7.29 7.27 7.25 7.24 7.24 7.23 7.22 7.21 7.20 6.89 5.70 5.68 5.12 4.56 4.54 4.52 4.32 4.31 3.74 3.72 2.90 2.88 2.86 2.85 2.78 2.76 2.74 2.73 1.39 1.37
Cbz
N
H
O
N
H
OMe
O
Bn
S
10.08 1.03 1.00 2.01 1.00 0.98 5.08 0.98 1.03 3.19
f1 (ppm)

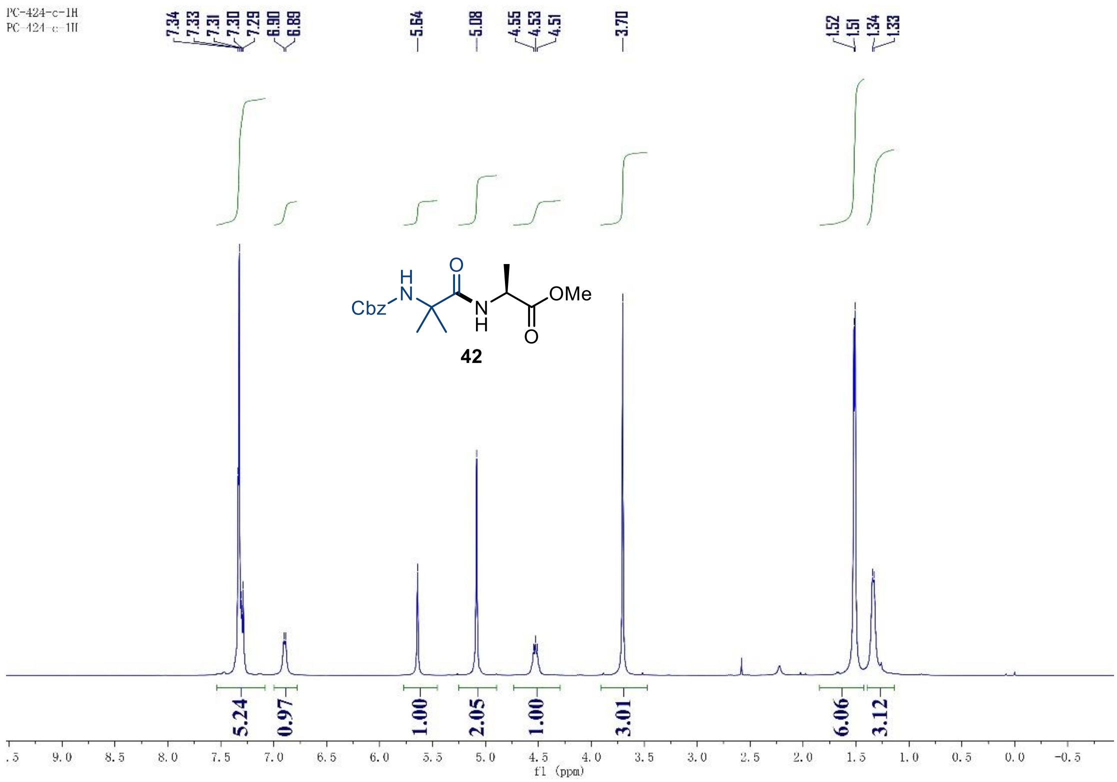
40

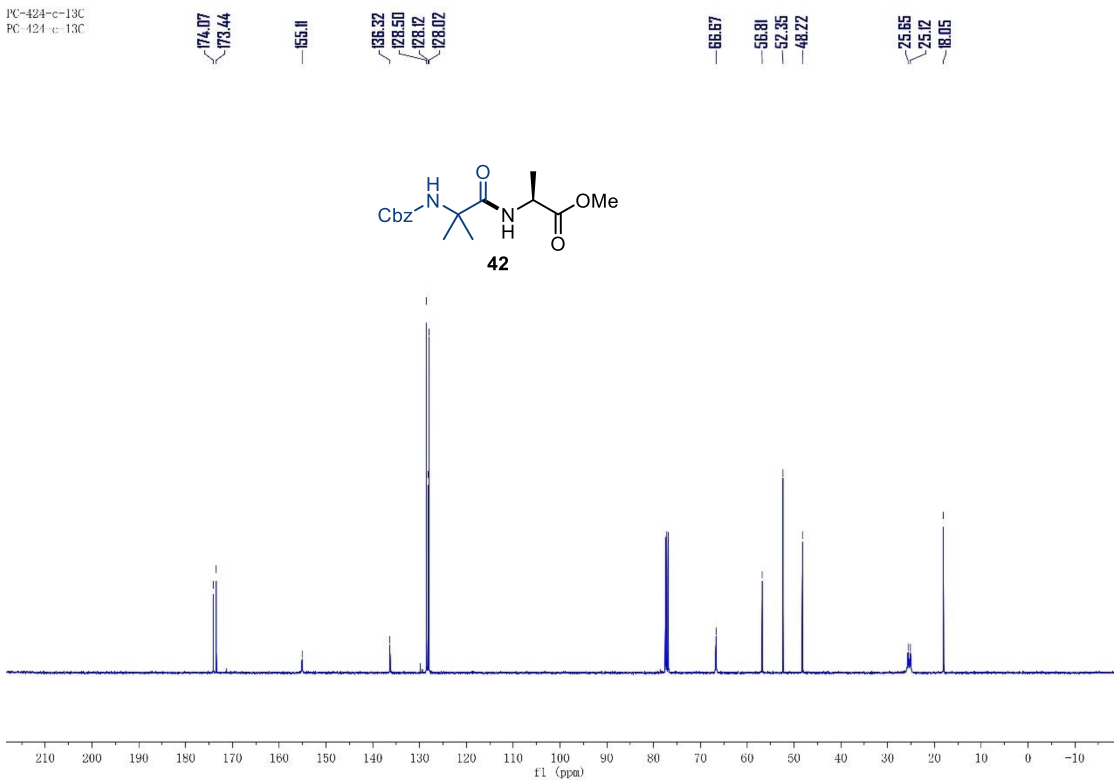

PC-357c
PC-357c 13C
172.88 169.90 155.97 137.92 136.11 129.03 128.67 128.58 128.27 128.11 127.28 67.22 54.10 52.55 48.33 36.61 33.95 18.21
Cbz
N
H
O
N
H
OMe
O
Bn
S
f1 (ppm)

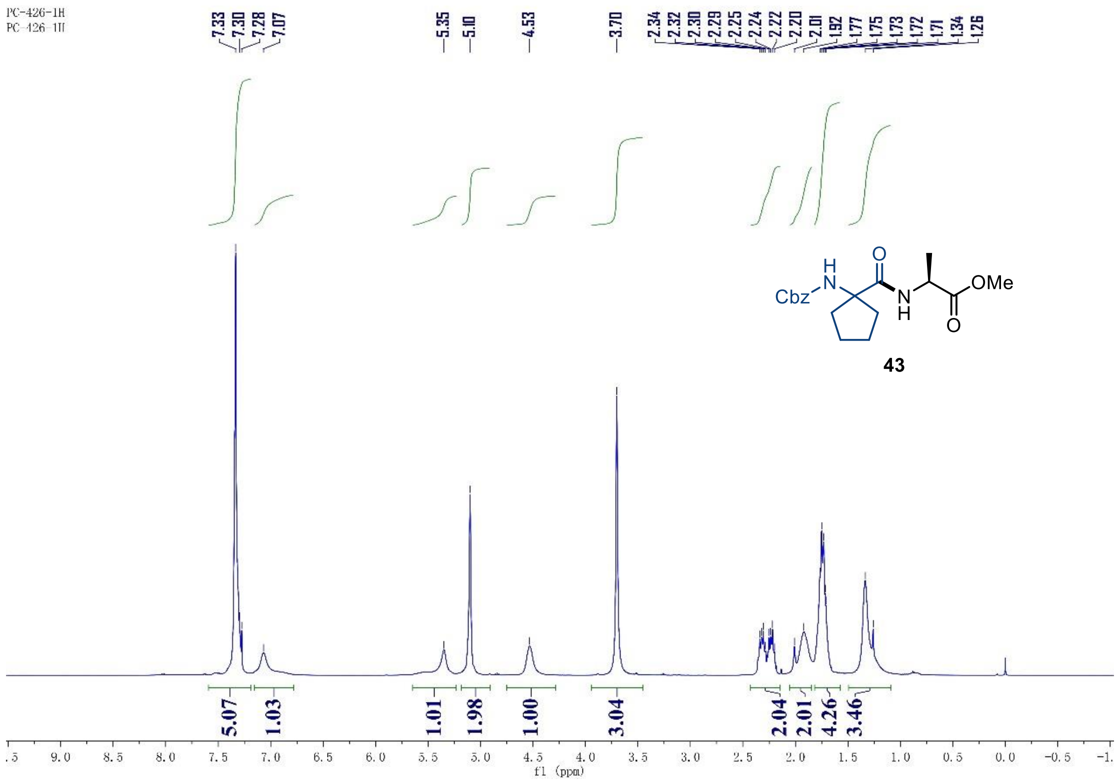
40

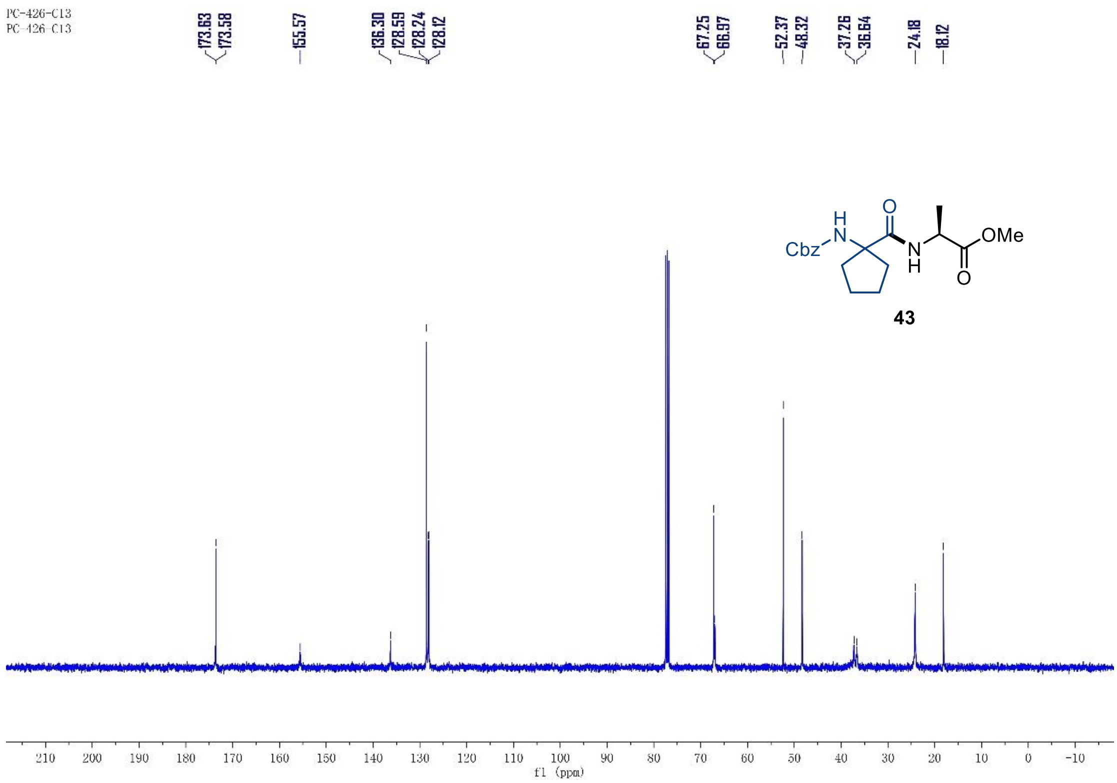

PC-357d
PC-357d 1H
Cbz
N
H
O
N
H
OMe
O
S
2
41
f1 (ppm)

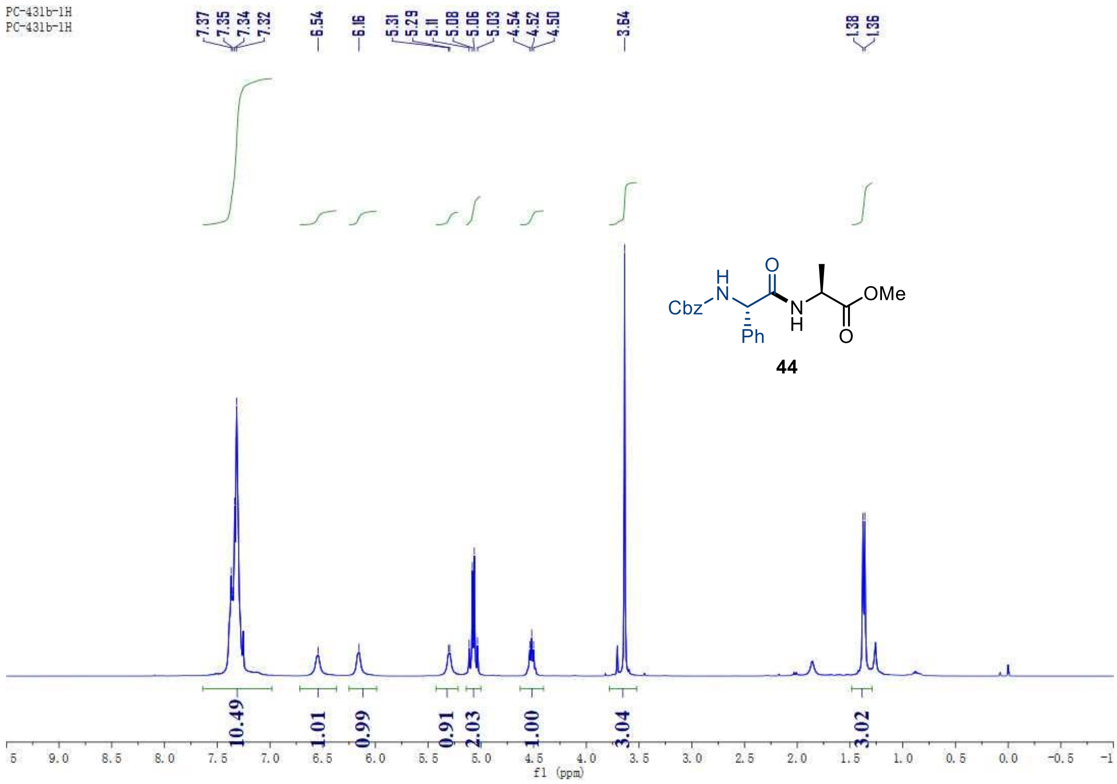

PC-357d
PC-357d 13C
173.04
171.13
156.17
136.22
128.51
128.15
128.00
66.99
53.62
52.44
48.07
32.02
29.85
17.87
15.12
Cbz
N
H
O
N
H
OMe
O
S
2
41
f1 (ppm)

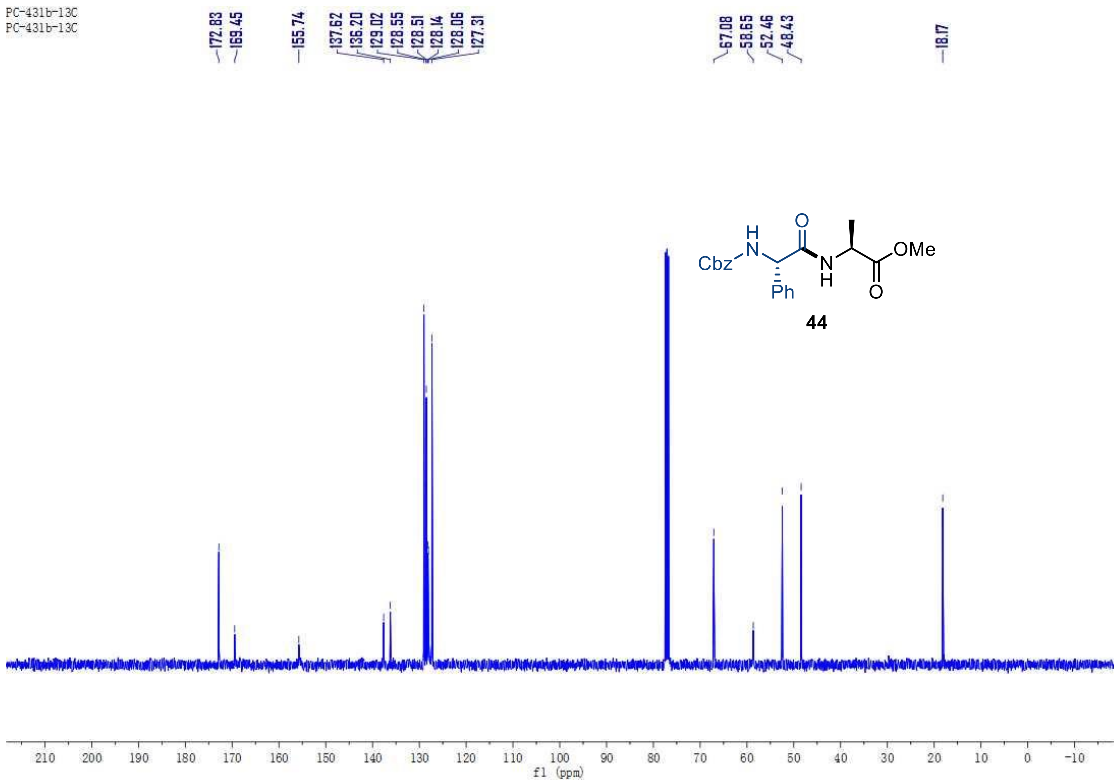

PC-424-c-1H
7.34 7.33 7.31 7.30 7.29 6.90 6.89 5.64 5.08 4.55 4.53 4.51 3.70 1.52 1.51 1.34 1.33
Cbz N H O N H OMe O
42
5.24 0.97 1.00 2.05 1.00 3.01 6.06 3.12
f1 (ppm)

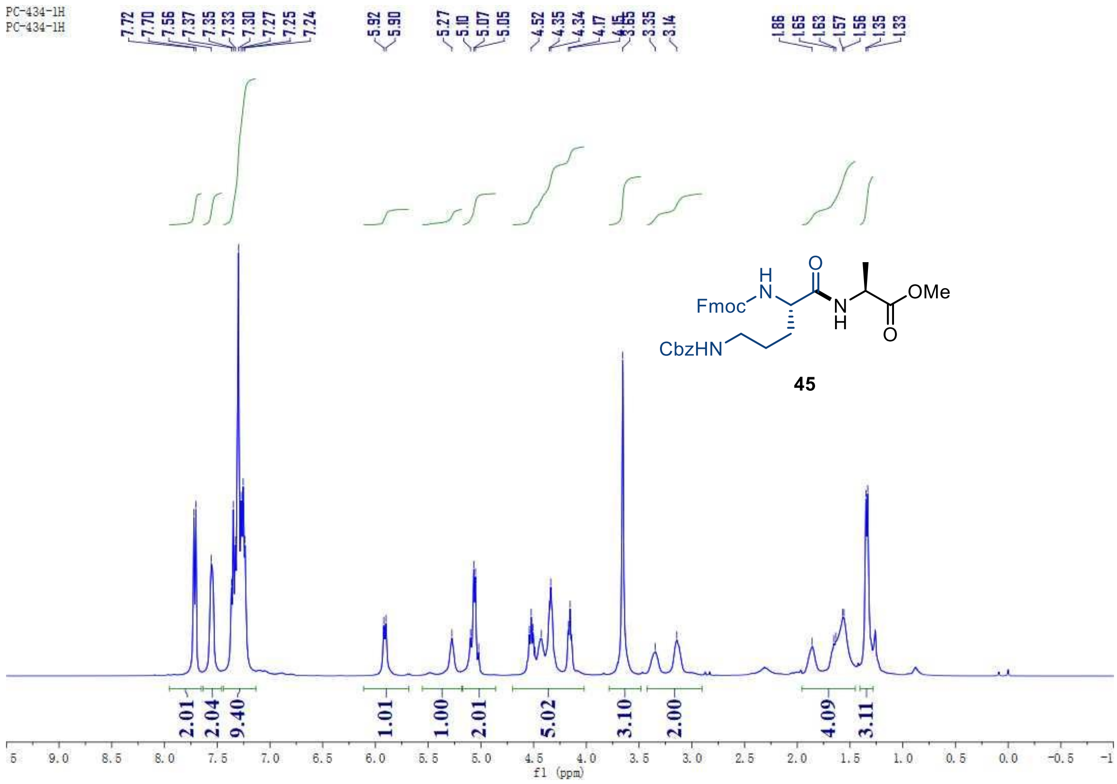

PC-424-c-13C
174.07 173.44 155.11 136.32 128.50 128.12 128.02 66.67 56.81 52.35 48.22 25.65 25.12 18.05
Cbz N H O N H OMe O
42
f1 (ppm)

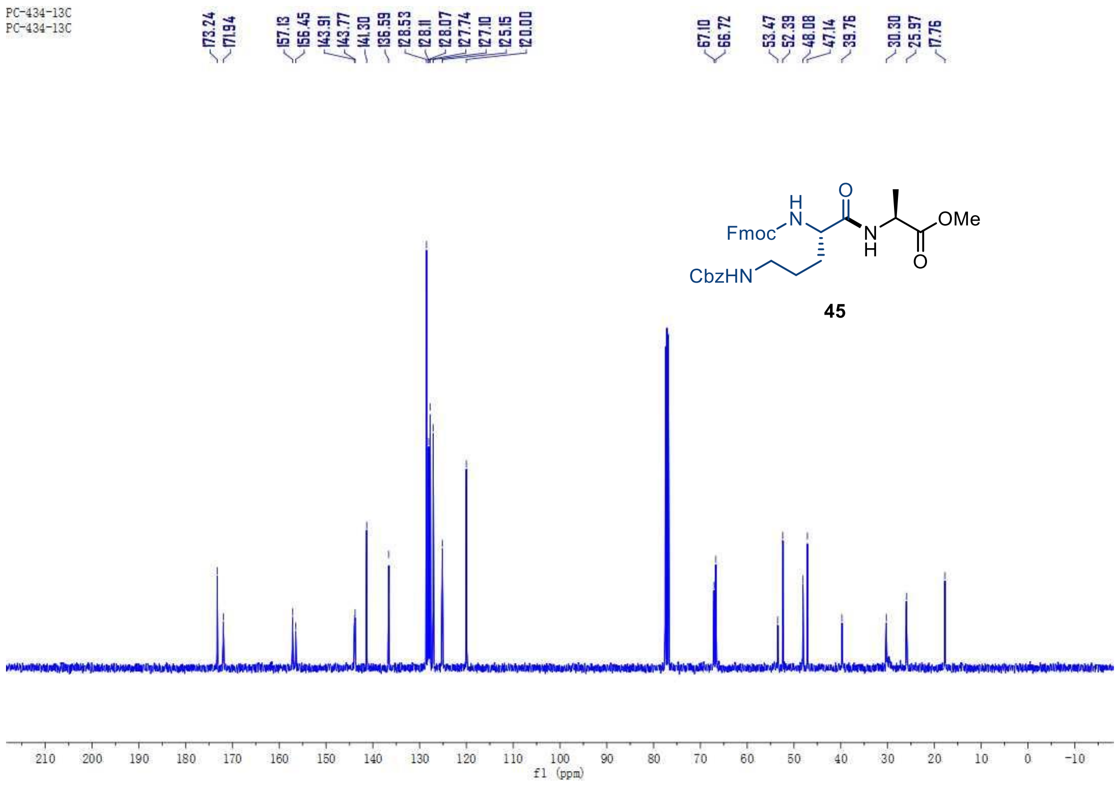

PC-426-1H
7.33
7.30
7.28
7.07
5.35
5.10
4.53
3.70
2.34
2.32
2.30
2.29
2.25
2.24
2.22
2.20
2.01
1.92
1.77
1.75
1.73
1.72
1.71
1.34
1.26
5.07
1.03
1.01
1.98
1.00
3.04
2.04
2.01
4.26
3.46
Cbz
OMe
43
f1 (ppm)


PC-426-C13
173.63
173.58
155.57
136.30
128.59
128.24
128.12
67.25
66.97
52.37
48.32
37.26
36.64
24.18
18.12
Cbz
OMe
43
f1 (ppm)


PC-431b-1H
PC-431b-1H
7.37
7.35
7.34
7.32
6.54
6.16
5.31
5.29
5.11
5.08
5.06
5.03
4.54
4.52
4.50
3.64
1.38
1.36
Cbz
N
H
O
N
H
OMe
O
Ph
44
10.49
1.01
0.99
0.91
2.03
1.00
3.04
3.02
f1 (ppm)


PC-431b-13C
PC-431b-13C
172.83
169.45
155.74
137.62
136.20
129.02
128.55
128.51
128.14
128.06
127.31
67.08
58.65
52.46
48.43
18.17
Cbz
N
H
O
N
H
OMe
O
Ph
44
f1 (ppm)


PC-434-1H
PC-434-1H
7.72
7.70
7.56
7.37
7.35
7.33
7.30
7.27
7.25
7.24
5.92
5.90
5.27
5.10
5.07
5.05
4.52
4.35
4.34
4.17
4.15
3.65
3.35
3.14
1.86
1.65
1.63
1.57
1.56
1.35
1.33
Fmoc
N
H
O
N
H
OMe
O
CbzHN
45
2.01
2.04
9.40
1.01
1.00
2.01
5.02
3.10
2.00
4.09
3.11
f1 (ppm)


PC-434-13C
PC-434-13C
173.24
171.94
157.13
156.45
143.91
143.77
141.30
136.59
128.53
128.11
128.07
127.74
127.10
125.15
120.00
67.10
66.72
53.47
52.39
48.08
47.14
39.76
30.30
25.97
17.76
Fmoc
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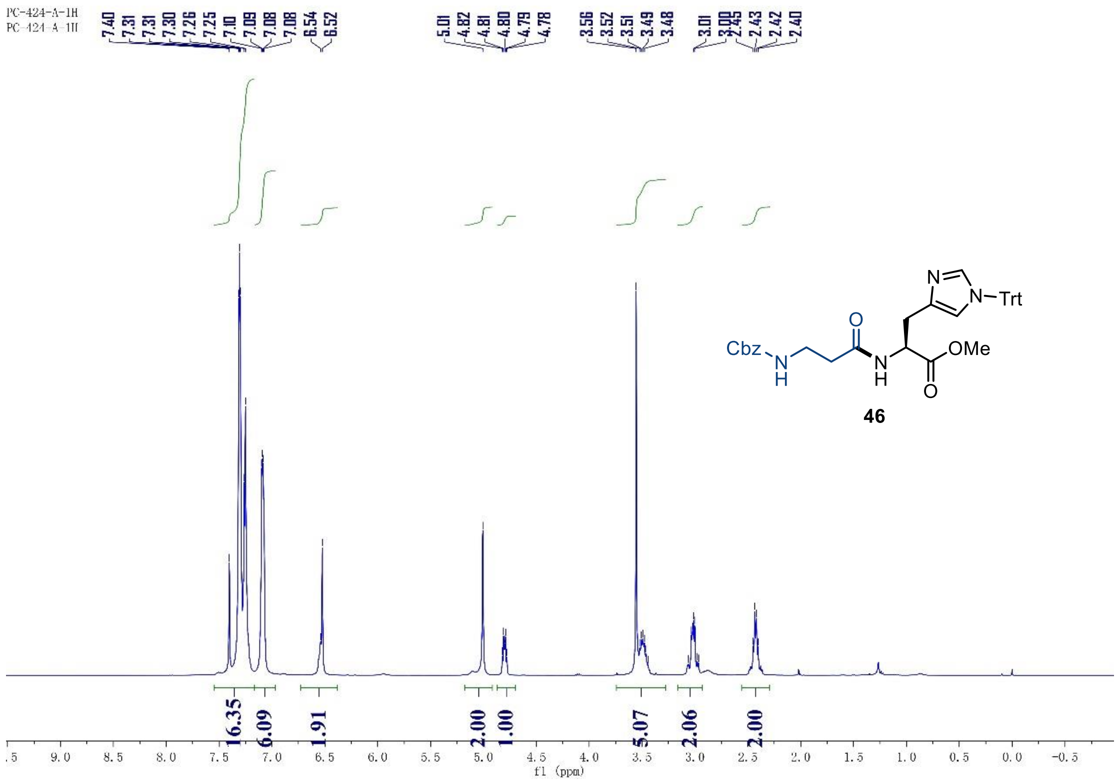
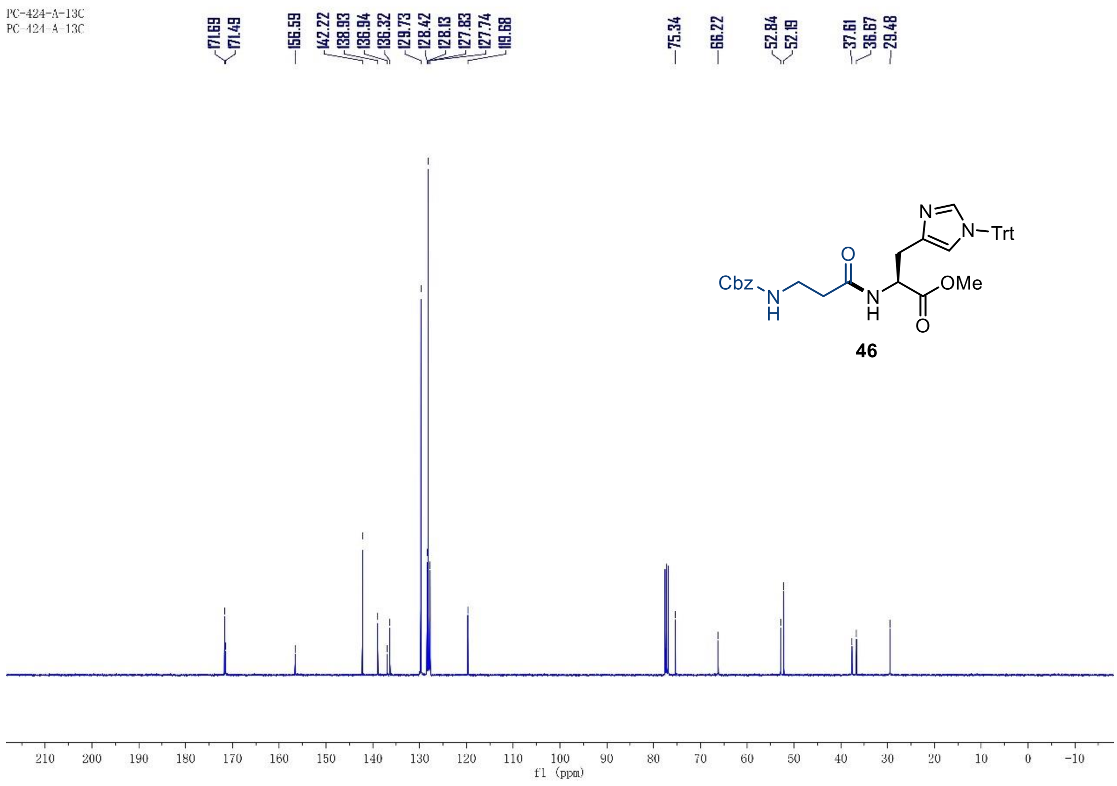
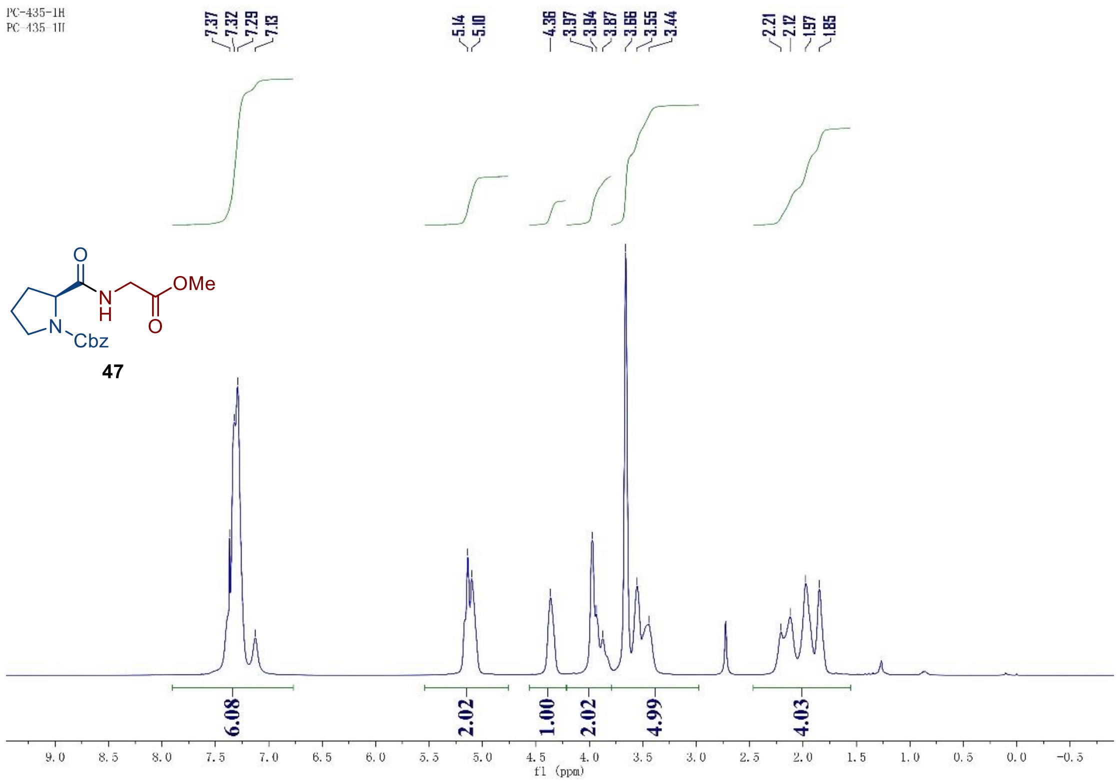
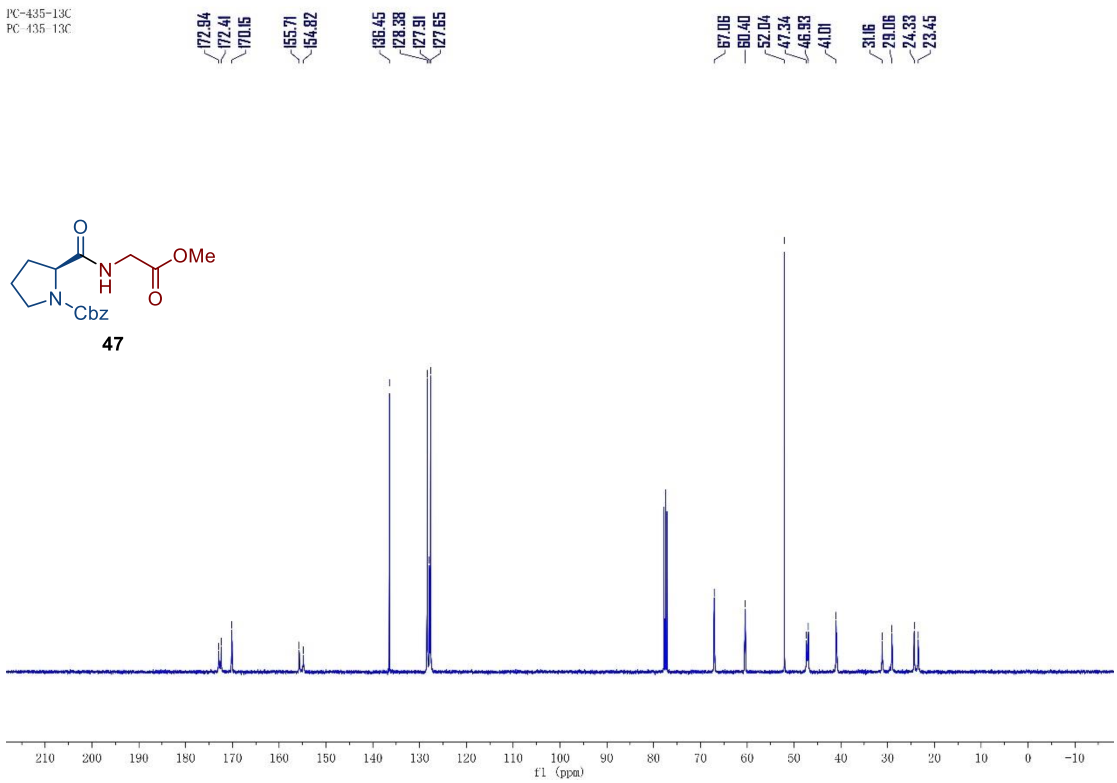
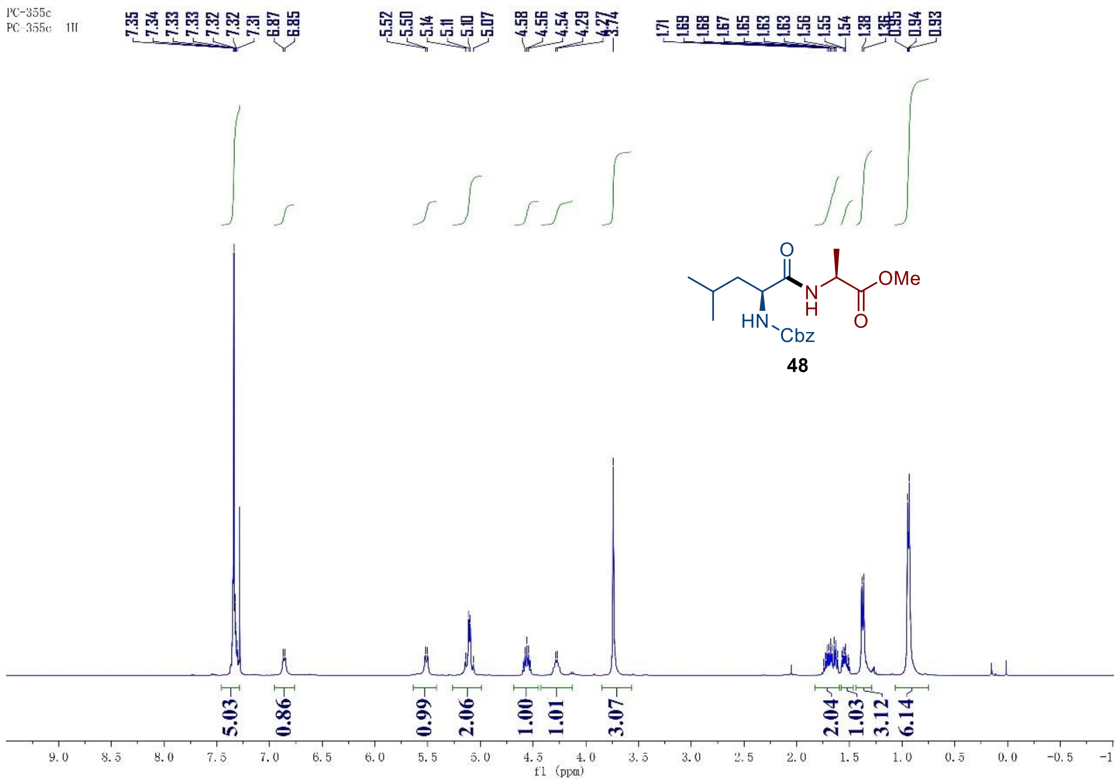
H
OMe
O
CbzHN
45
f1 (ppm)

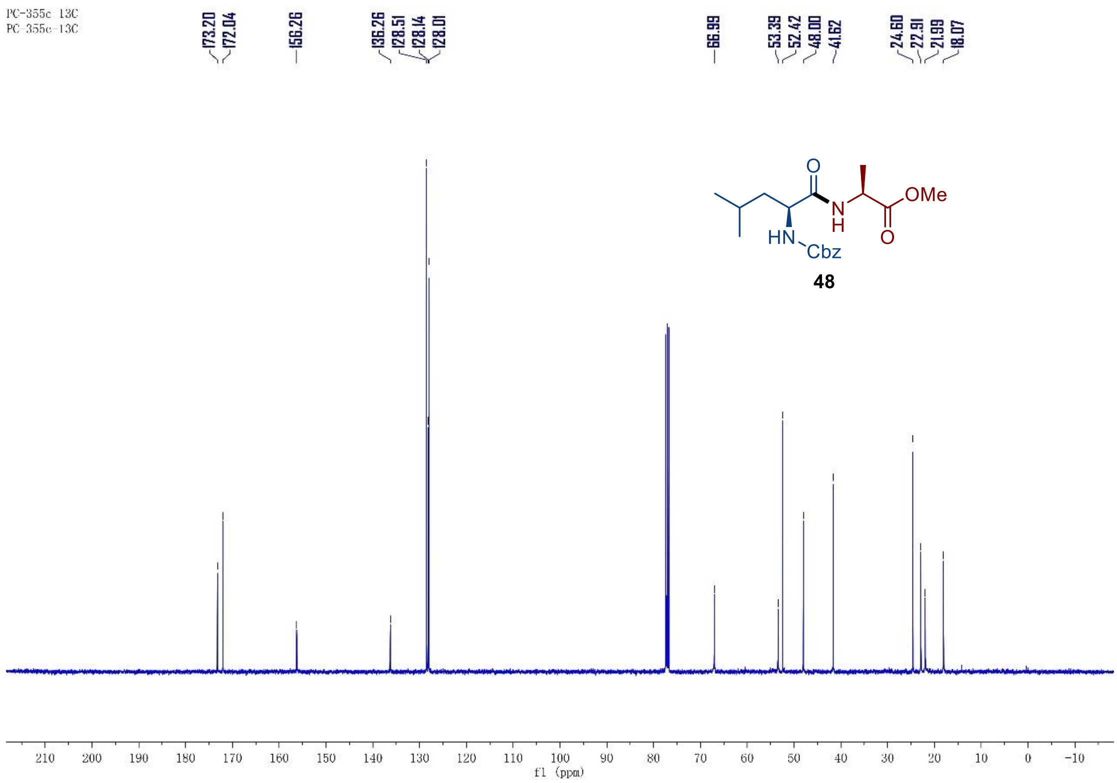


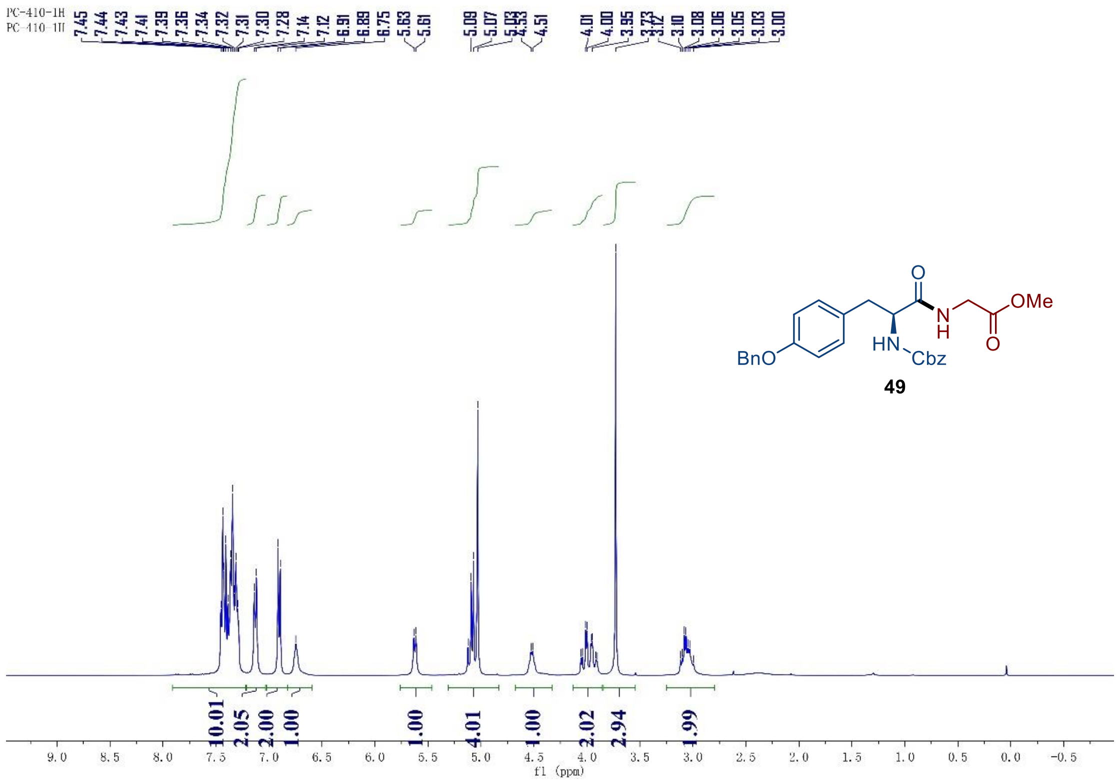



PC-435-1H
PC-435-1H
7.37
7.32
7.29
7.13
5.14
5.10
4.36
3.97
3.94
3.87
3.66
3.55
3.44
2.21
2.12
1.97
1.85
OMe
N
H
O
O
N
Cbz
47
6.08
2.02
1.00
2.02
4.99
4.03
f1 (ppm)

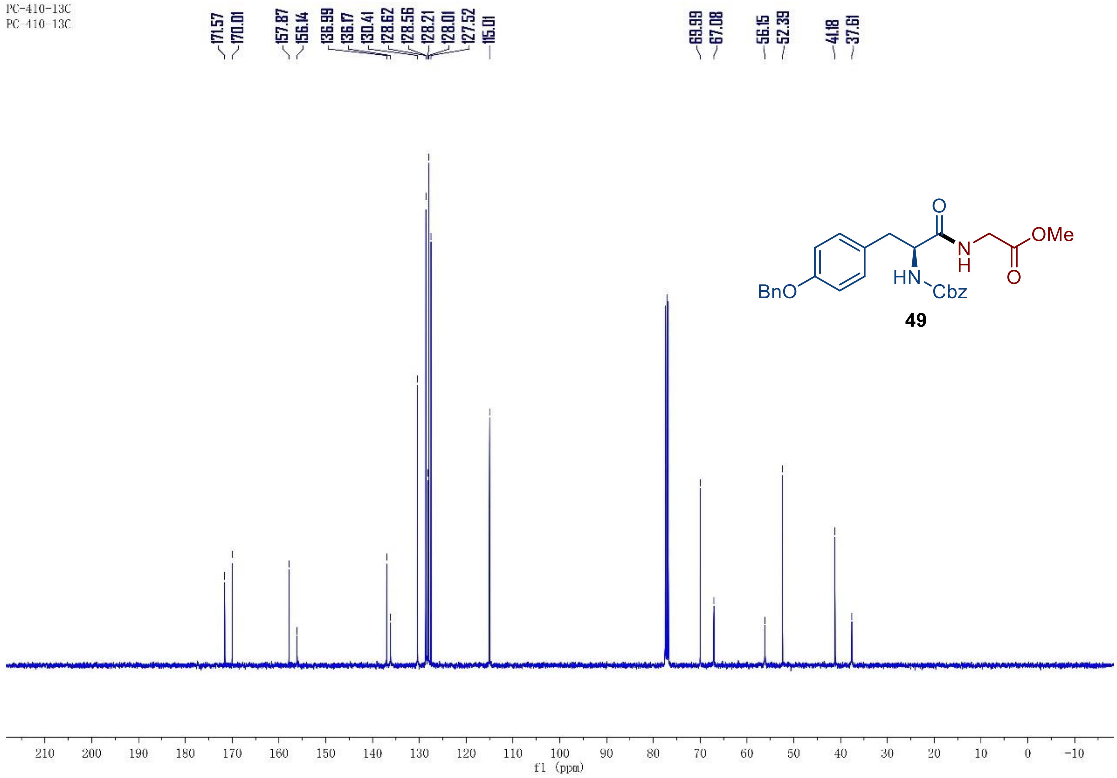

PC-435-13C
PC-435-13C
172.94
172.41
170.15
155.71
154.82
136.45
128.38
127.91
127.65
67.06
60.40
52.04
47.34
46.93
41.01
31.16
29.06
24.33
23.45
OMe
N
H
O
O
N
Cbz
47
f1 (ppm)


PC-355c
PC-355c 1H
7.35 7.34 7.33 7.33 7.32 7.32 7.31 6.87 6.85
5.52 5.50 5.14 5.11 5.10 5.07
4.58 4.56 4.54 4.29 4.27 3.74
1.71 1.69 1.68 1.67 1.65 1.63 1.63 1.56 1.55 1.54 1.38 1.36 0.95 0.94 0.93
O
N
H
OMe
O
HN
Cbz
48
5.03 0.86 0.99 2.06 1.00 1.01 3.07 2.04 1.03 3.12 6.14
f1 (ppm)

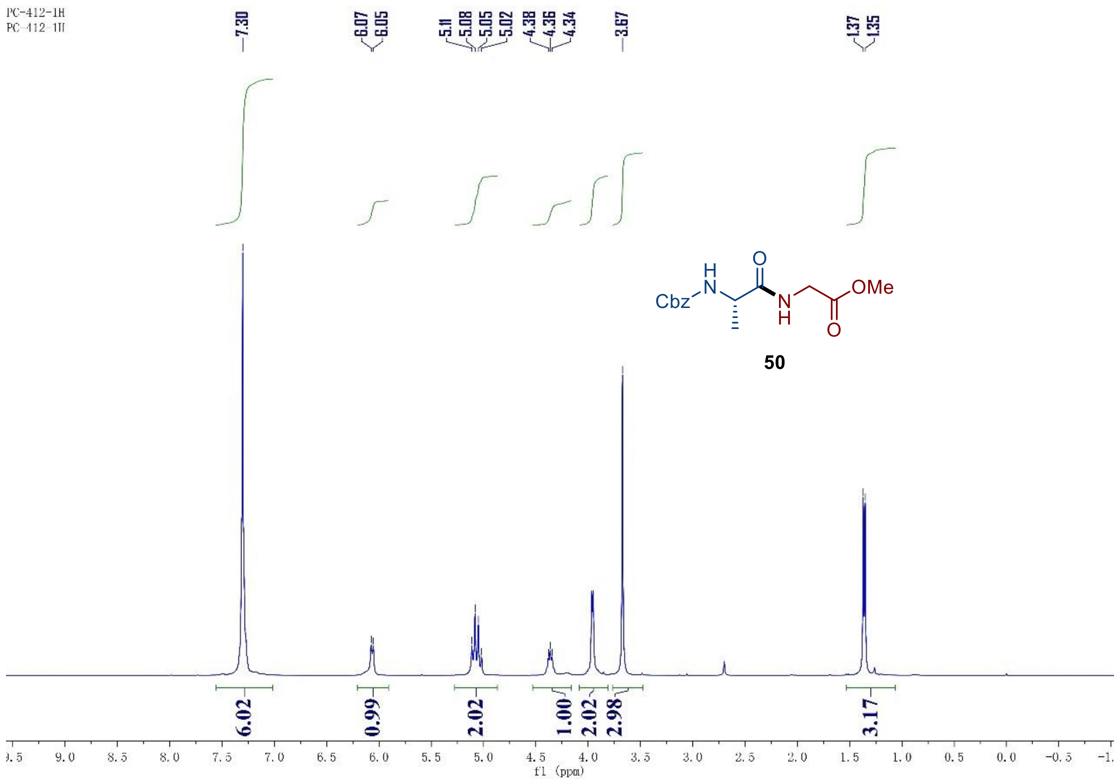

PC-355c 13C
PC-355c 13C
173.20 172.04
156.26
136.26 128.51 128.14 128.01
66.99
53.39 52.42 48.00 41.62
24.60 22.91 21.99 18.07
O
N
H
OMe
O
HN
Cbz
48
f1 (ppm)

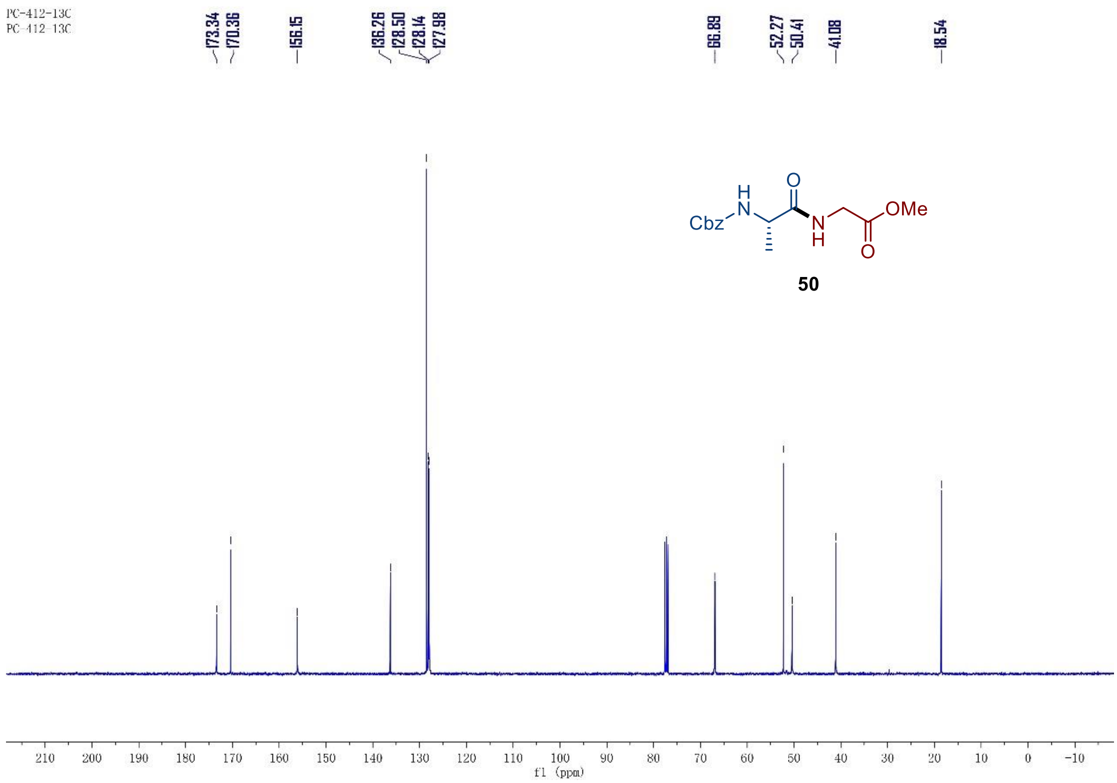

PC-410-1H
7.45 7.44 7.43 7.41 7.39 7.36 7.34 7.32 7.31 7.30 7.28 7.14 7.12 6.91 6.89 6.75 5.63 5.61 5.09 5.07 5.03 4.53 4.51 4.01 4.00 3.95 3.73 3.72 3.10 3.08 3.06 3.05 3.03 3.00
BnO
HN
Cbz
O
N
H
OMe
O
10.01
2.05
2.00
1.00
1.00
4.01
1.00
2.02
2.94
1.99
f1 (ppm)

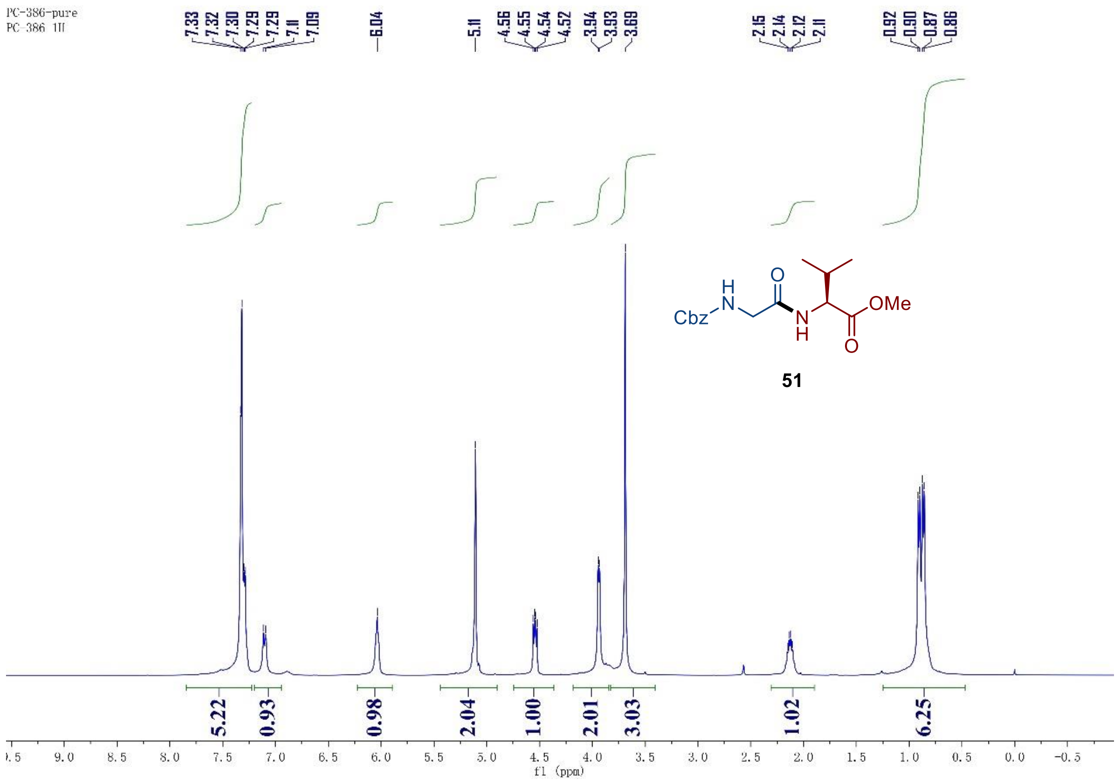
49

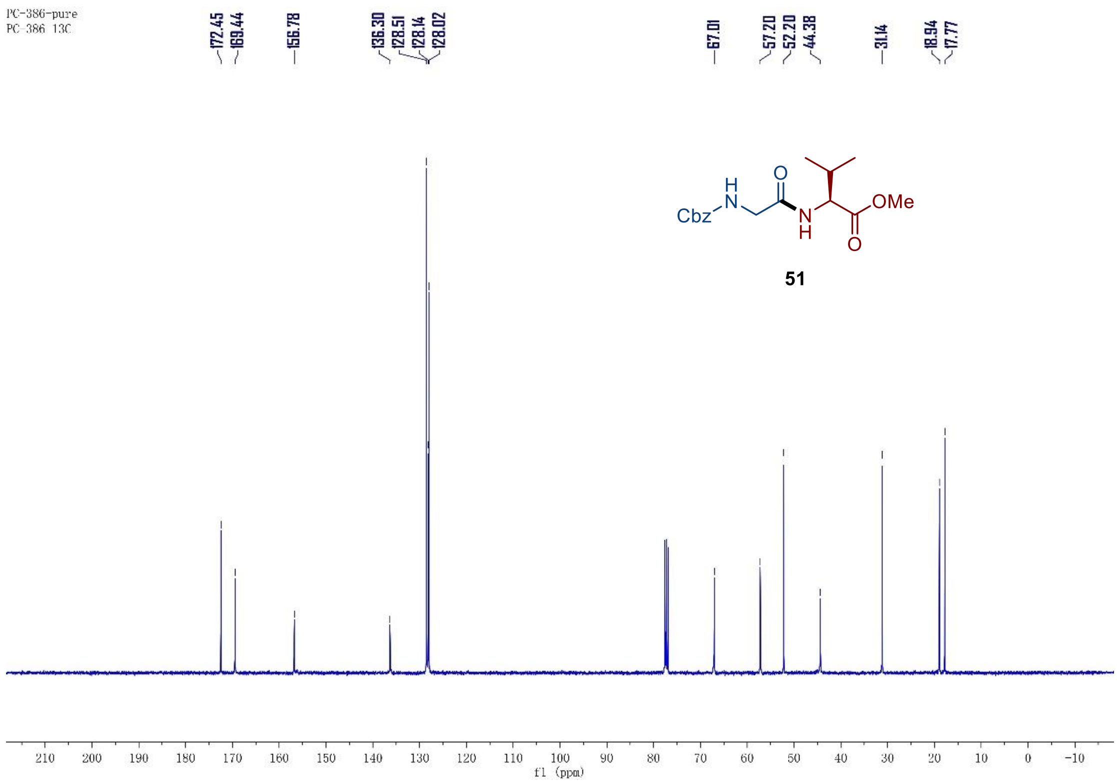

PC-410-13C
171.57 170.01 157.87 156.14 136.99 136.17 130.41 128.62 128.56 128.21 128.01 127.52 115.01 69.99 67.08 56.15 52.39 41.18 37.61
BnO
HN
Cbz
O
N
H
OMe
O
f1 (ppm)

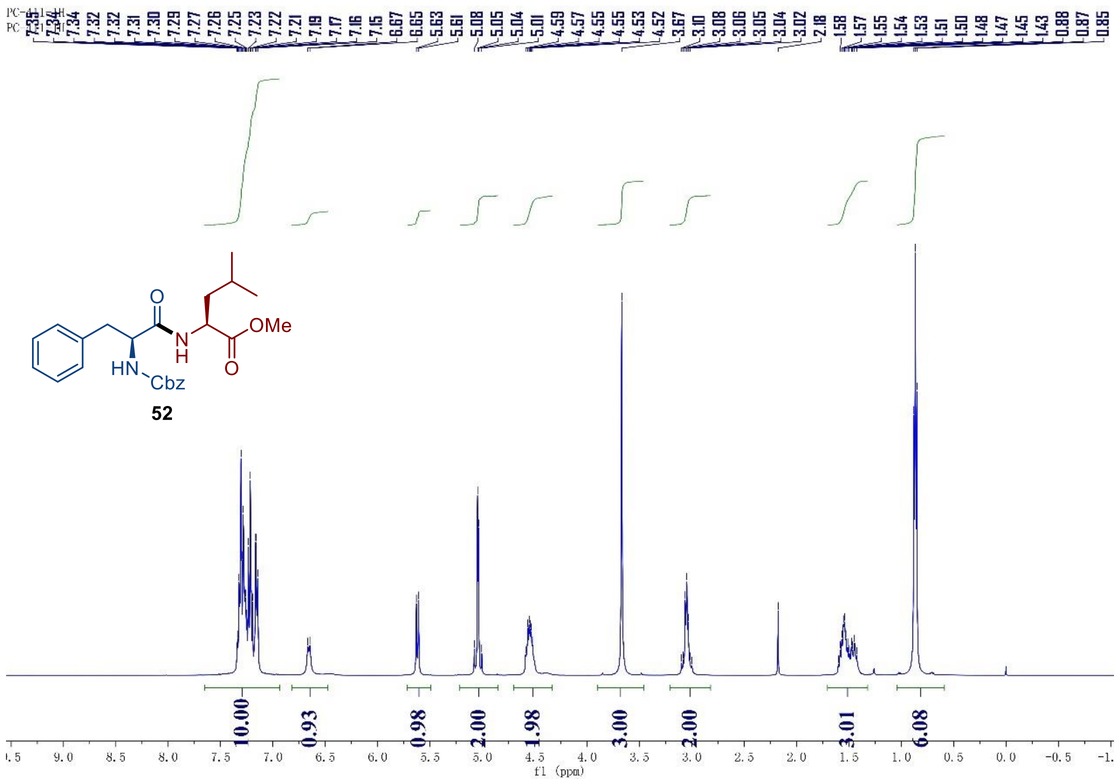
49


PC-412-1H
PC-412-1H
7.30
6.07
6.05
5.11
5.08
5.05
5.02
4.38
4.36
4.34
3.67
1.37
1.35
Cbz
H
N
O
N
H
OMe
O
50
6.02
0.99
2.02
1.00
2.02
2.98
3.17
f1 (ppm)

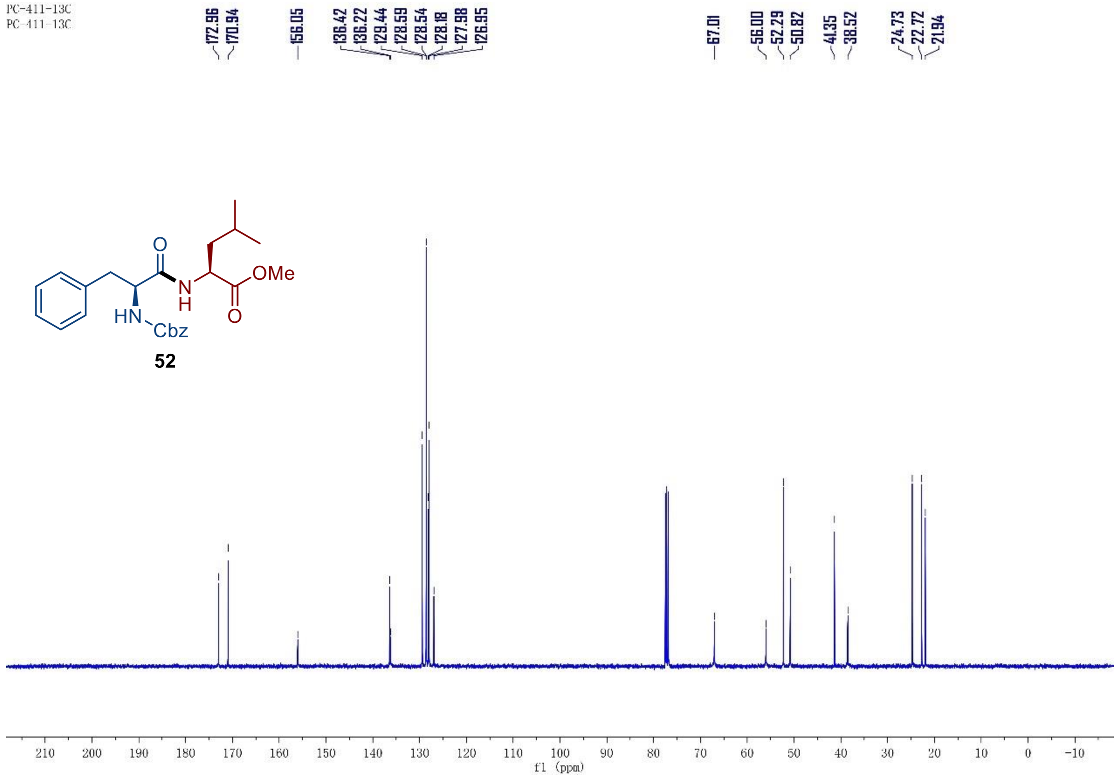

PC-412-13C
PC-412-13C
173.34
170.36
156.15
136.26
128.50
128.14
127.98
66.89
52.27
50.41
41.08
18.54
Cbz
H
N
O
N
H
OMe
O
50
f1 (ppm)


PC-386-pure
PC-386 1H
7.33 7.32 7.30 7.29 7.29 7.11 7.09
6.04
5.11 4.56 4.55 4.54 4.52 3.94 3.93 3.69
2.15 2.14 2.12 2.11
0.92 0.90 0.87 0.86
Cbz
N
H
O
N
H
OMe
O
51
5.22
0.93
0.98
2.04
1.00
2.01
3.03
1.02
6.25
f1 (ppm)

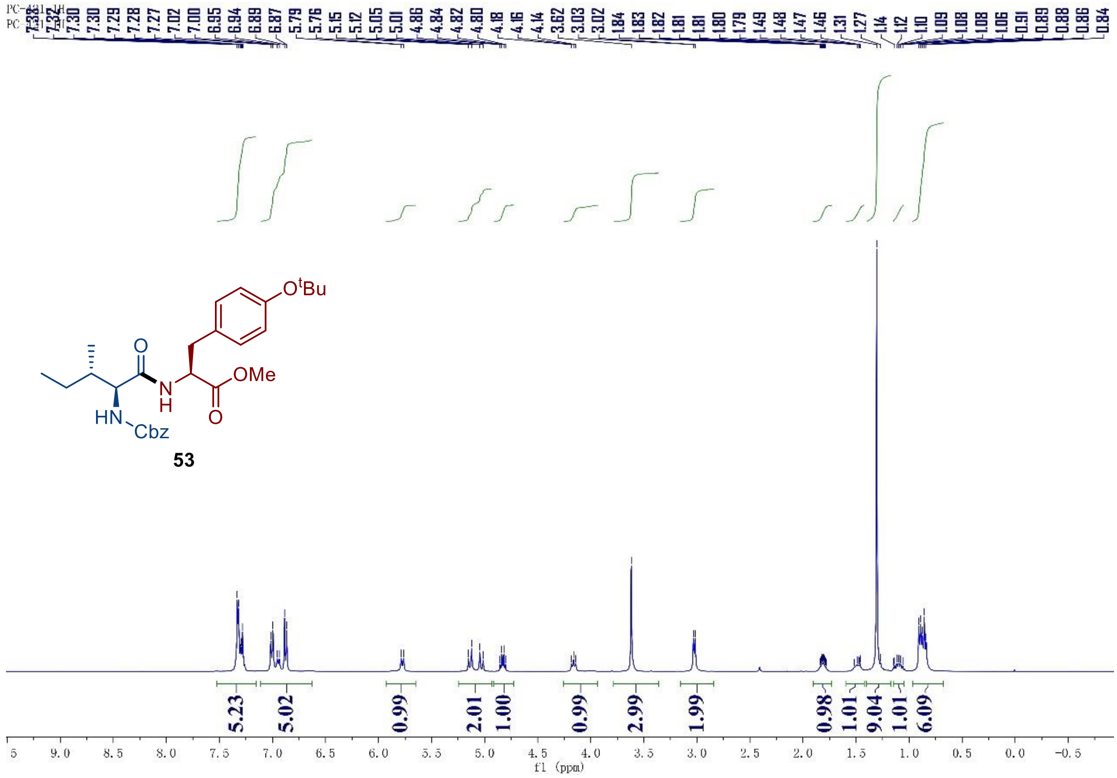

PC-386-pure
PC-386 13C
172.45 169.44
156.78
136.30 128.51 128.14 128.02
67.01
57.20 52.20 44.38
31.14
18.94 17.77
Cbz
N
H
O
N
H
OMe
O
51
f1 (ppm)

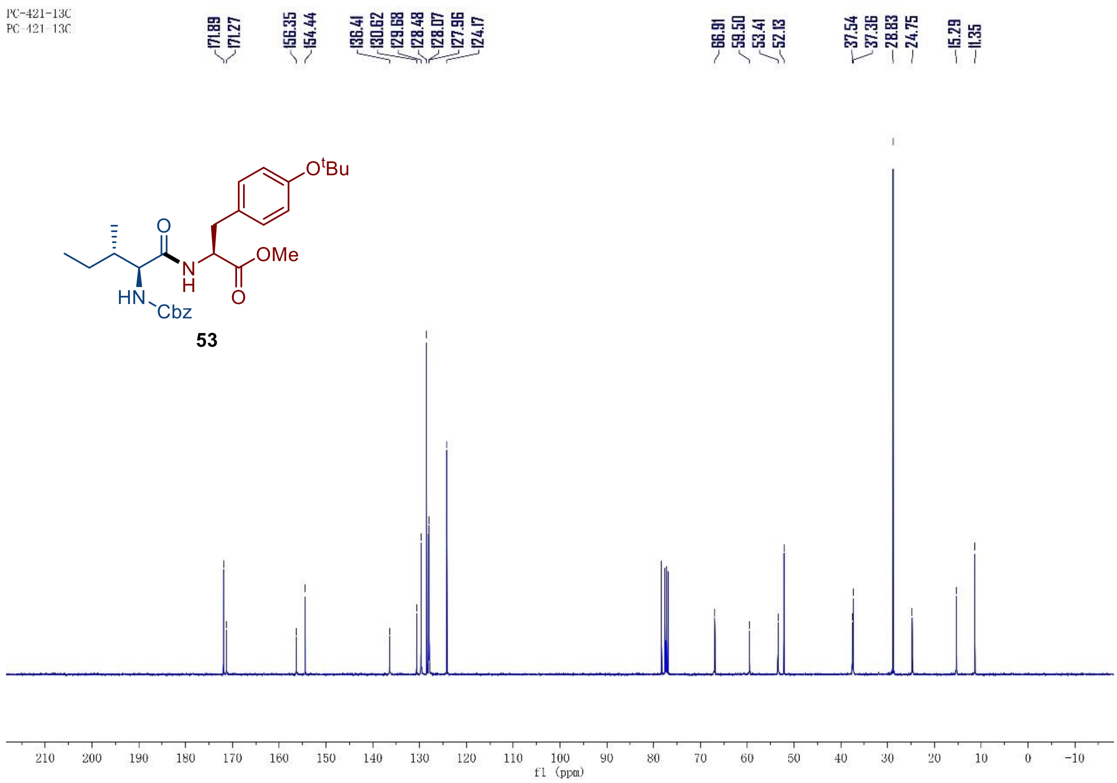


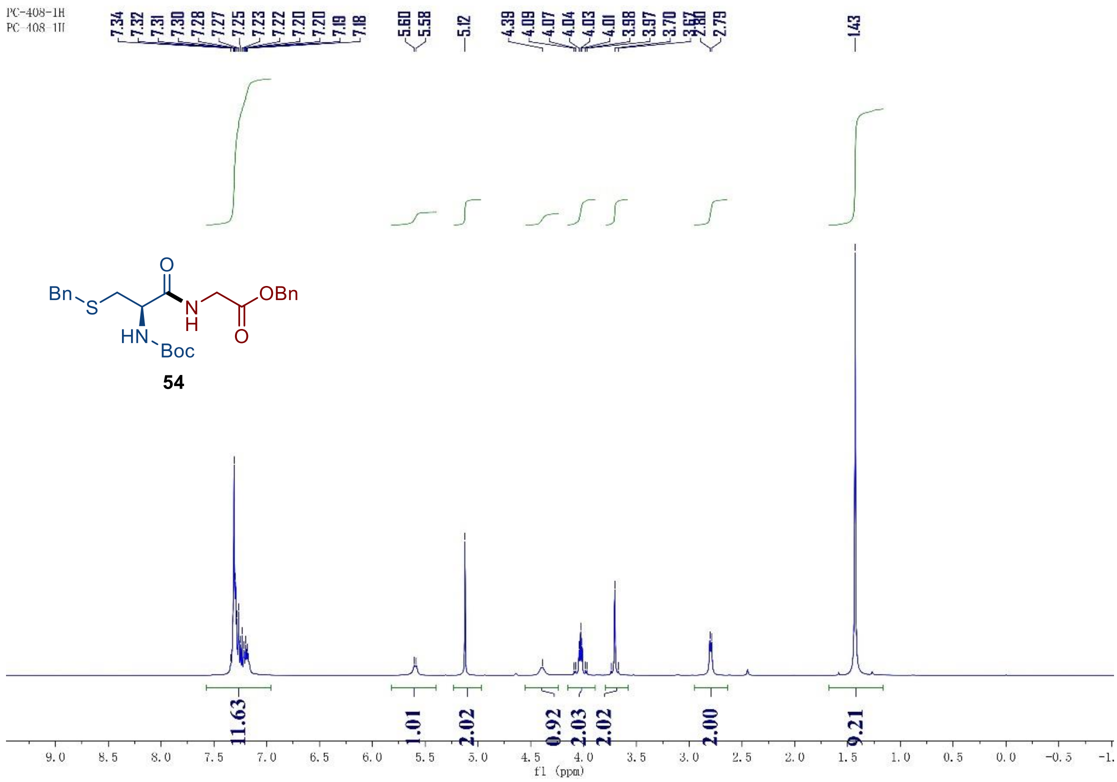
OMe
HN
Cbz
52
f1 (ppm)

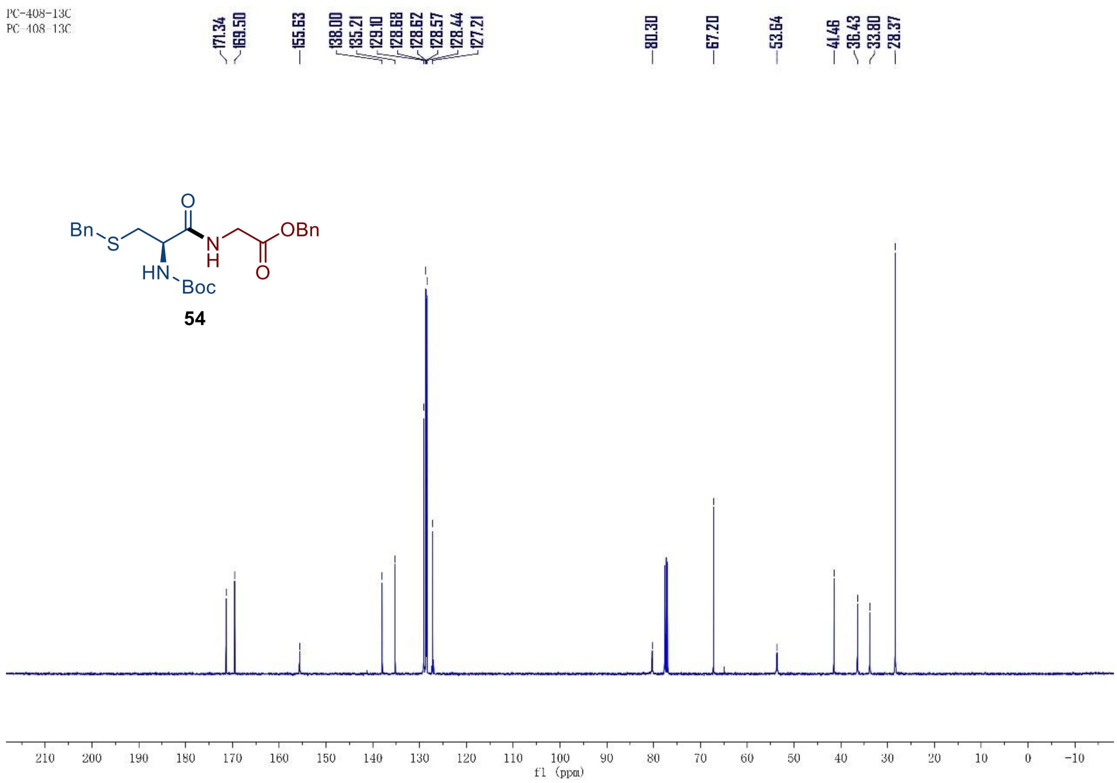


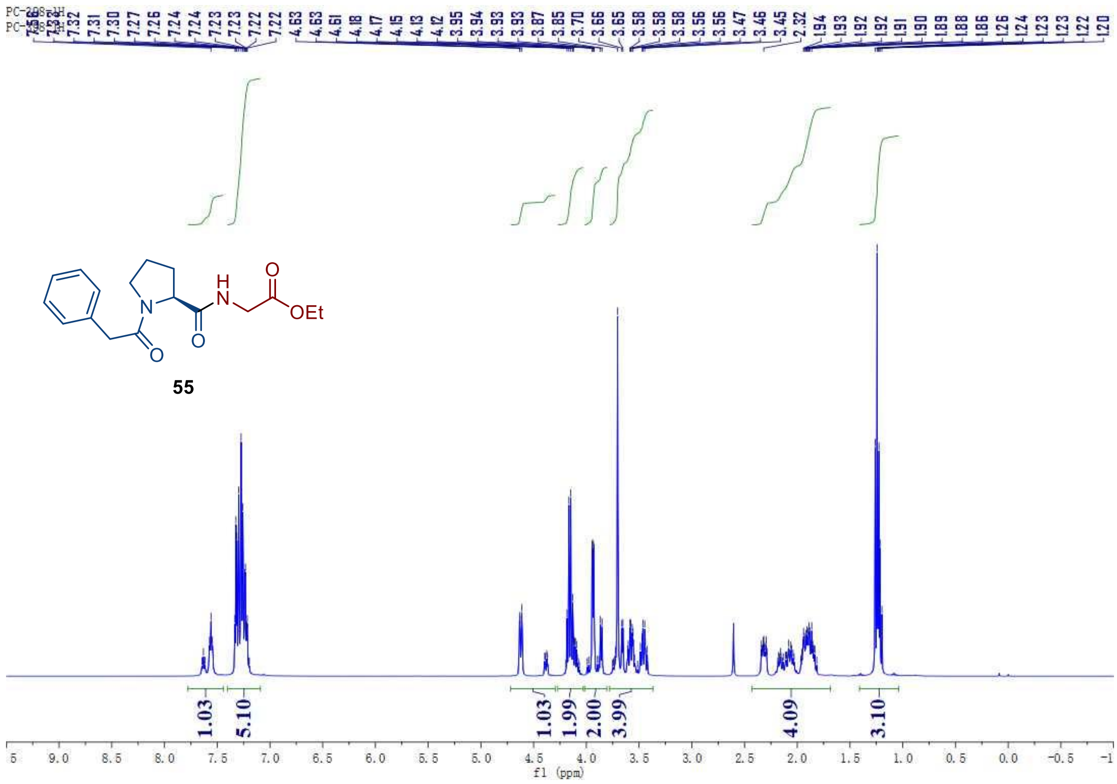
PC-411-13C
OMe
HN
Cbz
52
f1 (ppm)


PC-421-1H
7.33 7.32 7.30 7.30 7.29 7.28 7.27 7.02 7.00 6.95 6.94 6.89 6.87 5.79 5.76 5.15 5.12 5.05 5.01 4.86 4.84 4.82 4.80 4.18 4.16 4.14 3.62 3.03 3.02 1.84 1.83 1.82 1.81 1.81 1.80 1.79 1.49 1.48 1.47 1.46 1.31 1.27 1.14 1.12 1.10 1.09 1.08 1.08 1.06 0.91 0.89 0.88 0.86 0.84
O^tBu
O
OMe
N
H
HN
Cbz
O
53
5.23
5.02
0.99
2.01
1.00
0.99
2.99
1.99
0.98
1.01
9.04
1.01
6.09
f1 (ppm)

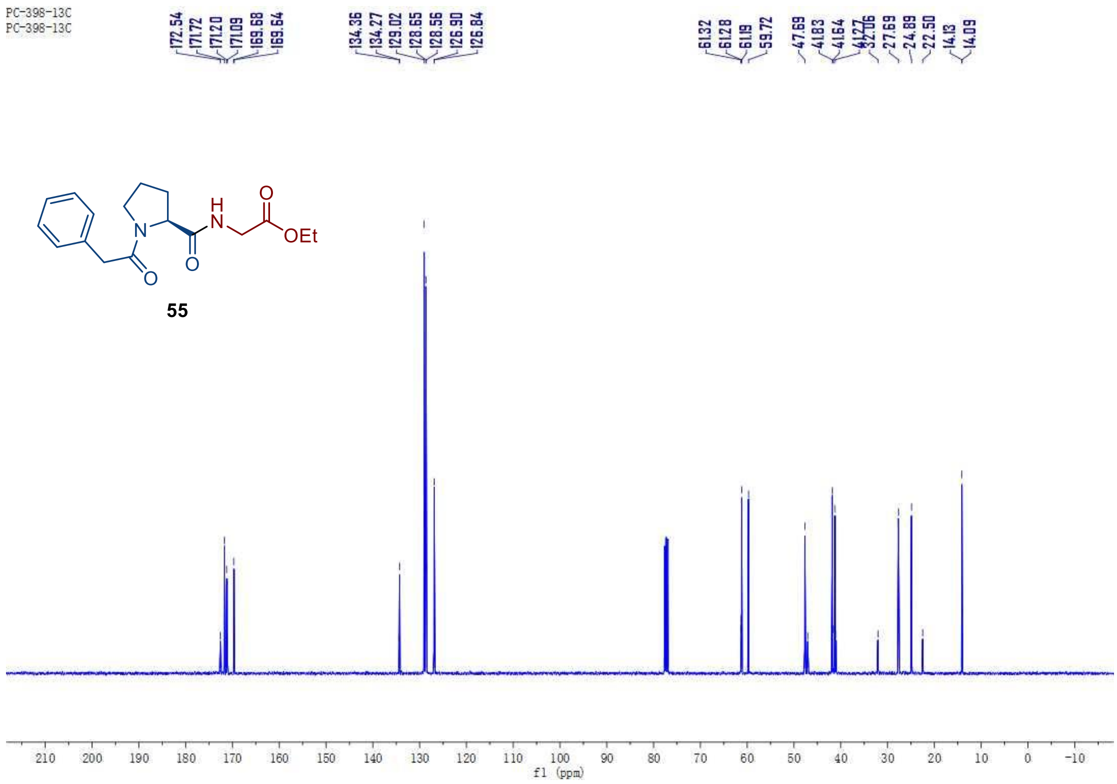

PC-421-13C
171.89 171.27 156.35 154.44 136.41 130.62 129.68 128.48 128.07 127.96 124.17 66.91 59.50 53.41 52.13 37.54 37.36 28.83 24.75 15.29 11.35
O^tBu
O
OMe
N
H
HN
Cbz
O
53
f1 (ppm)


PC-408-1H
7.34 7.32 7.31 7.30 7.28 7.27 7.25 7.23 7.22 7.20 7.20 7.19 7.18
5.60 5.58
5.12
4.39 4.09 4.07 4.04 4.03 4.01 3.98 3.97 3.70 3.67 2.80 2.79
1.43
Bn S O N H OBn O HN Boc
54
11.63 1.01 2.02 0.92 2.03 2.02 2.00 9.21
f1 (ppm)

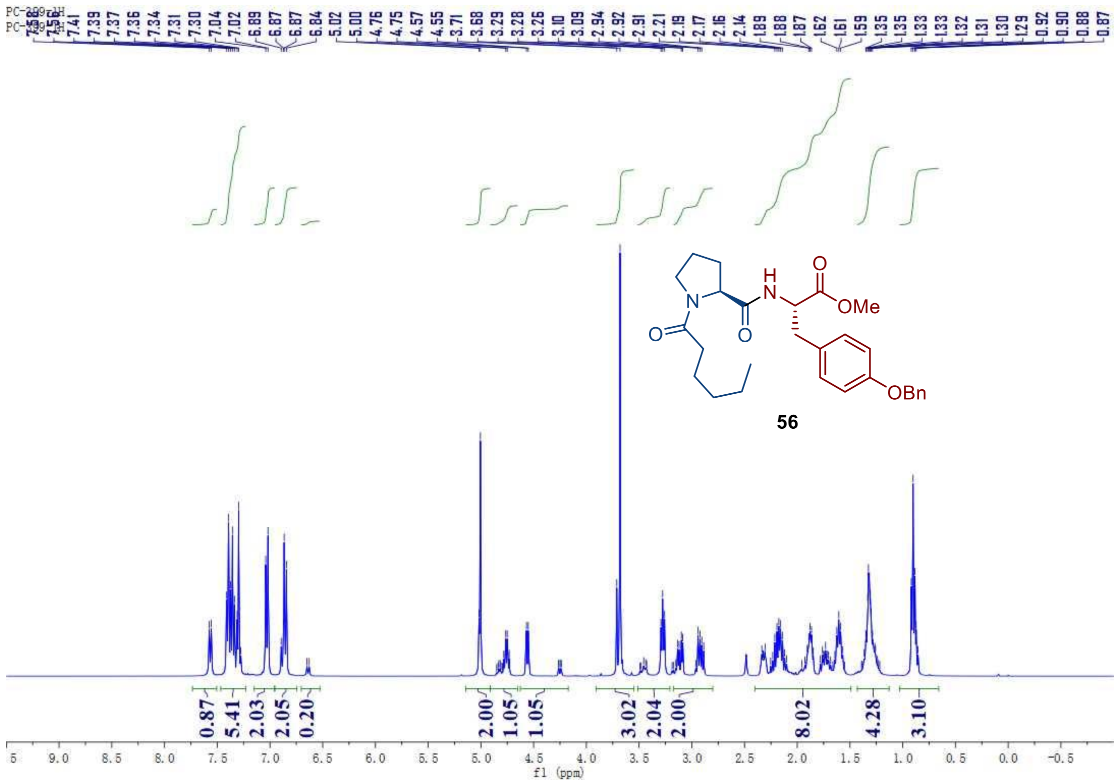

PC-408-13C
171.34 169.50
155.63
138.00 135.21 129.10 128.68 128.62 128.57 128.44 127.21
80.30
67.20
53.64
41.46 36.43 33.80 28.37
Bn S O N H OBn O HN Boc
54
f1 (ppm)

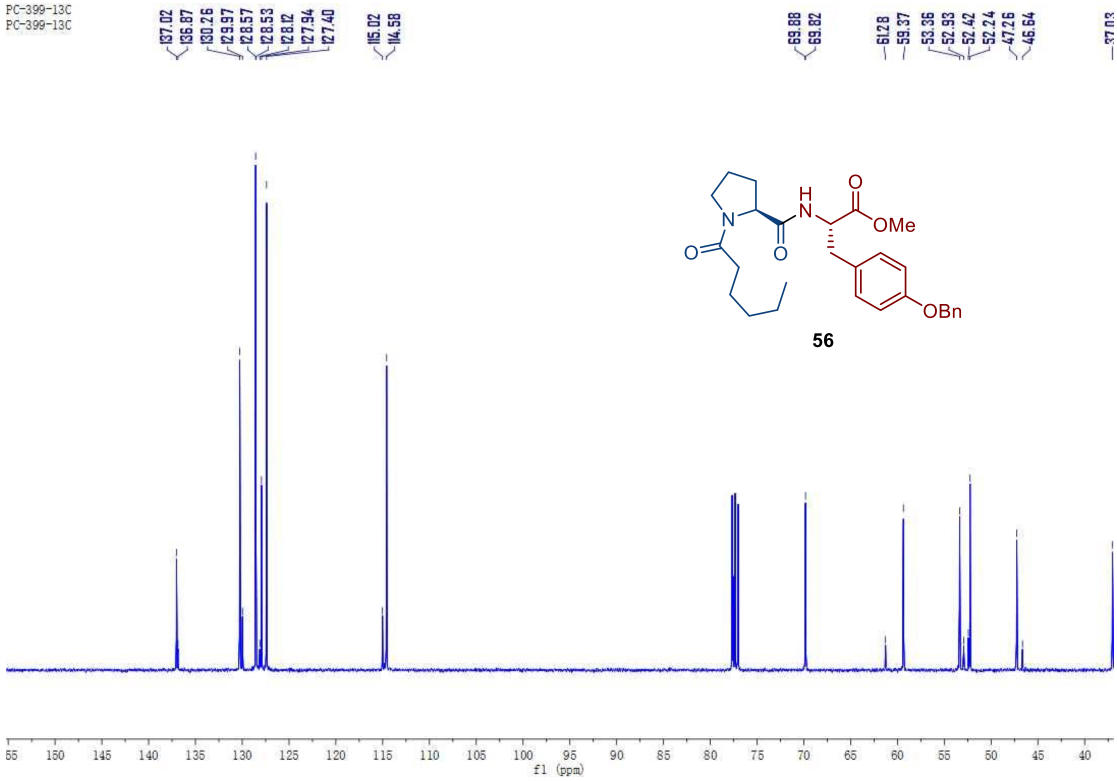


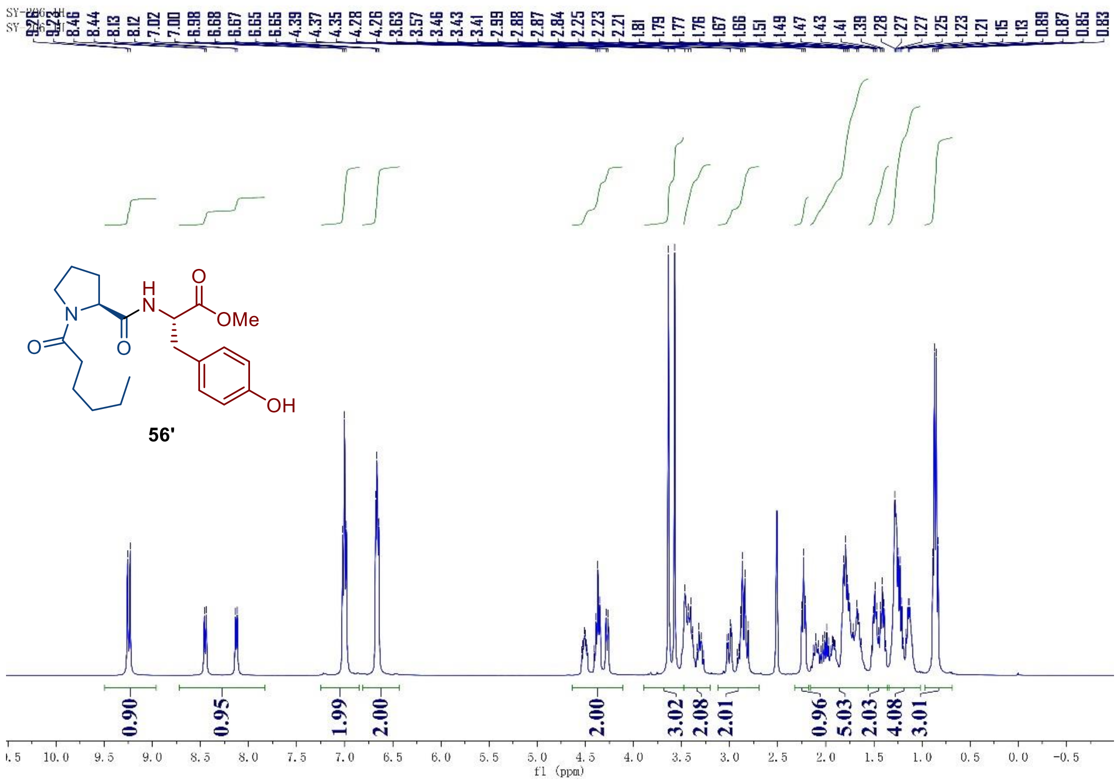
55

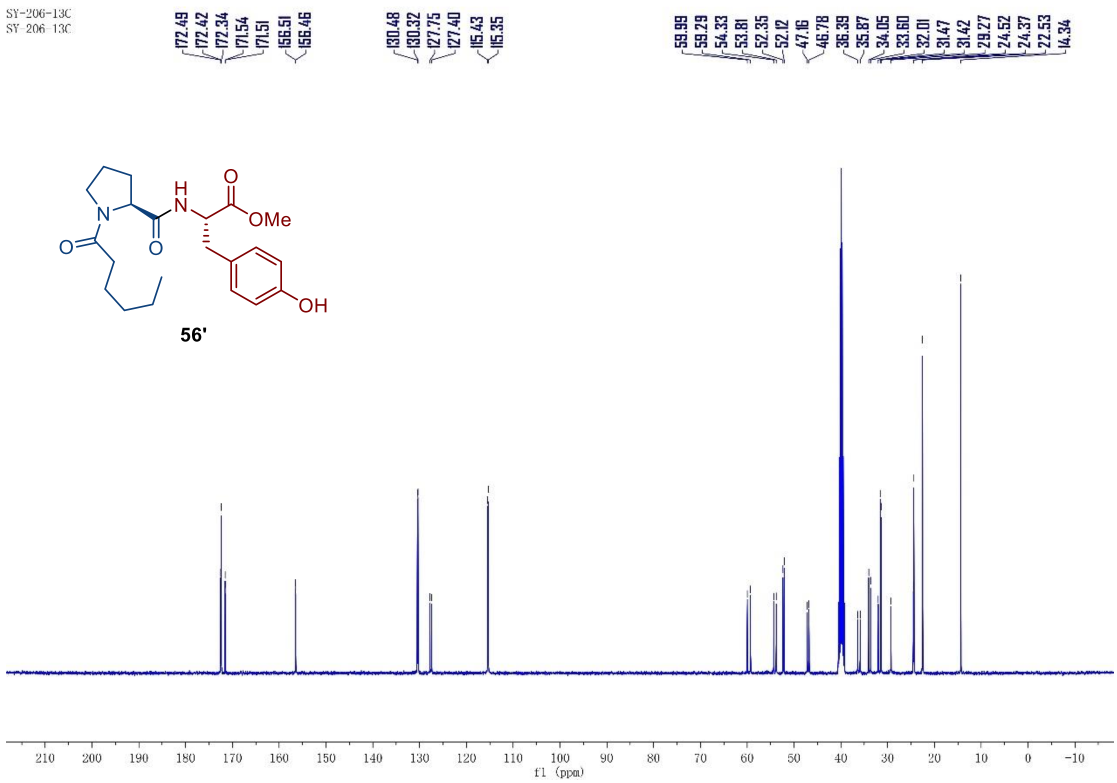


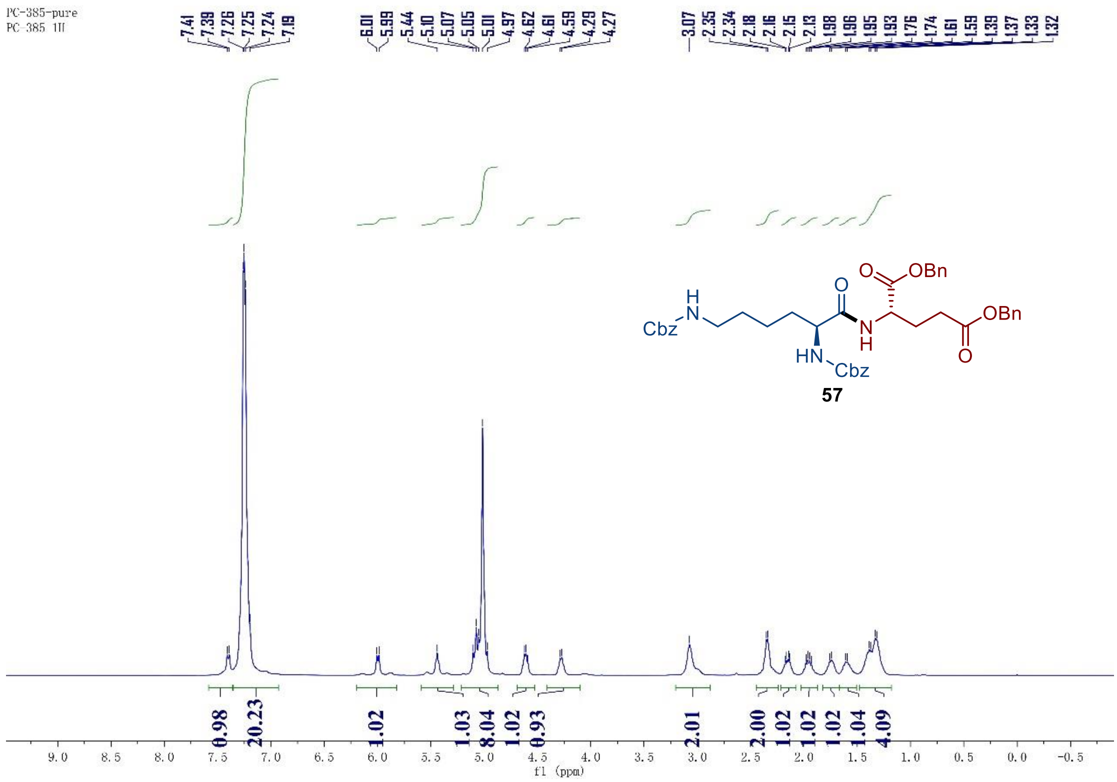
55

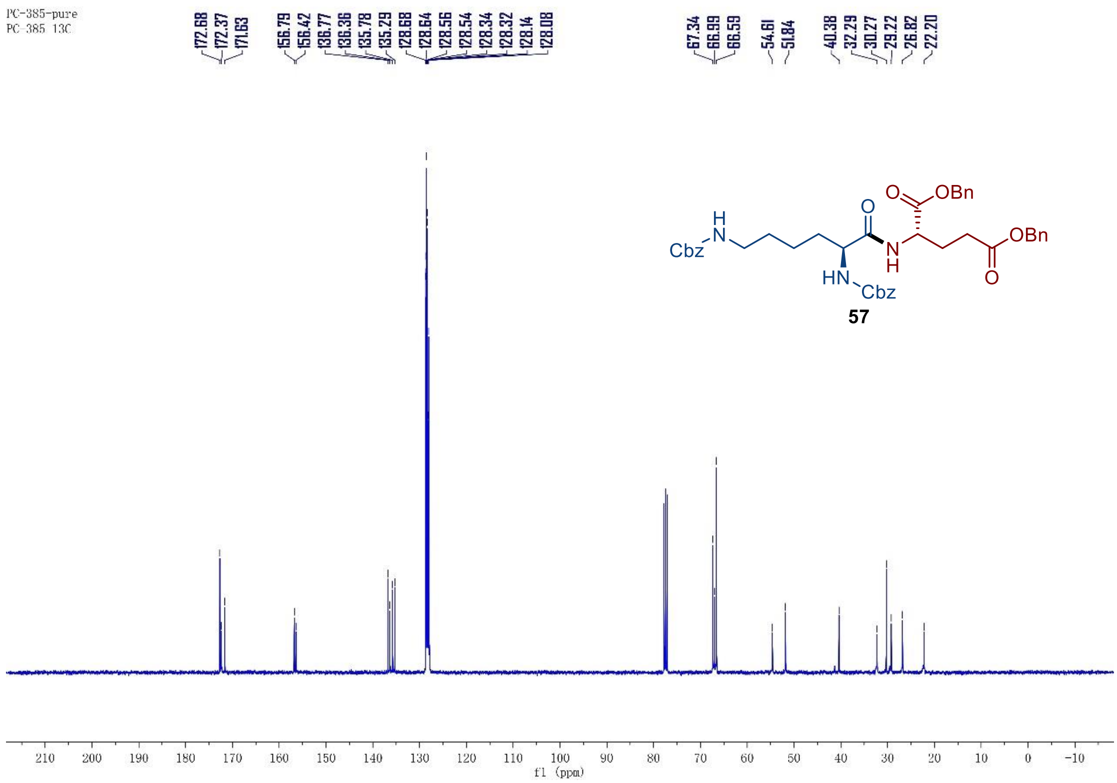


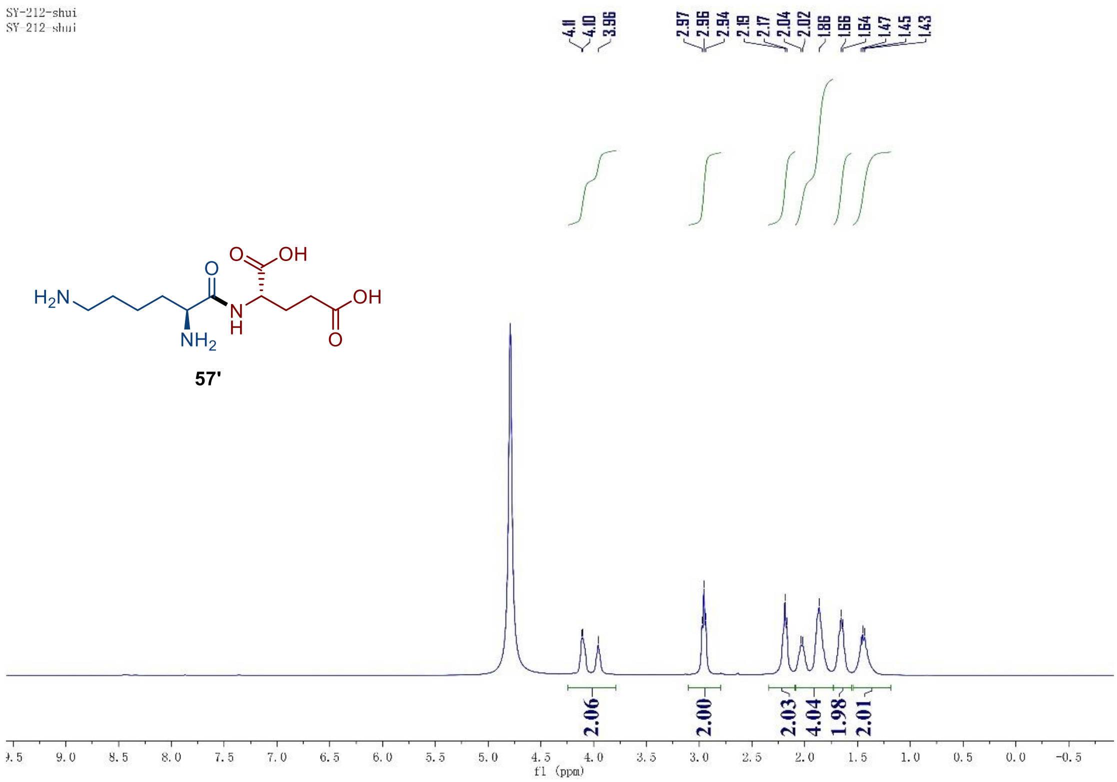


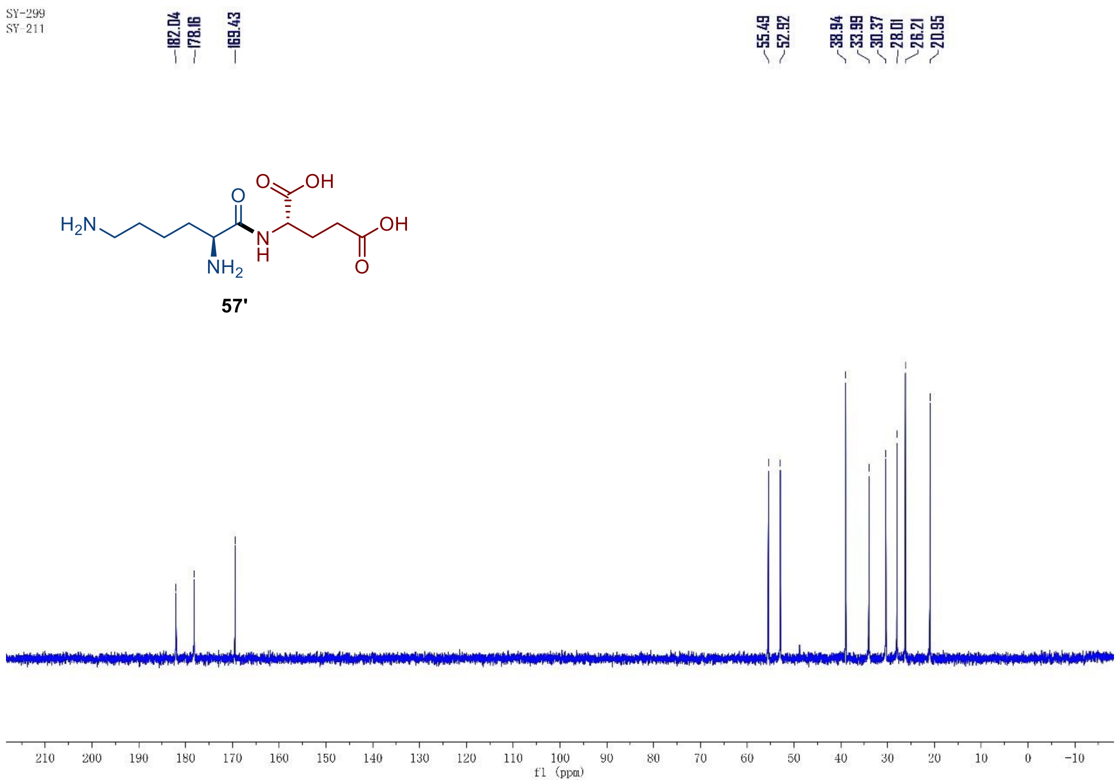

8.46
8.44
8.13
8.12
7.02
7.00
6.98
6.68
6.67
6.65
6.65
4.39
4.37
4.35
4.28
4.26
3.63
3.57
3.46
3.43
3.41
2.99
2.88
2.87
2.84
2.25
2.23
2.21
1.81
1.79
1.77
1.76
1.67
1.66
1.51
1.49
1.47
1.43
1.41
1.39
1.28
1.27
1.27
1.25
1.23
1.21
1.15
1.13
0.89
0.87
0.85
0.83
H
N
O
OMe
N
O
O
OH
56'
0.90
0.95
1.99
2.00
2.00
3.02
2.08
2.01
0.96
5.03
2.03
4.08
3.01
f1 (ppm)

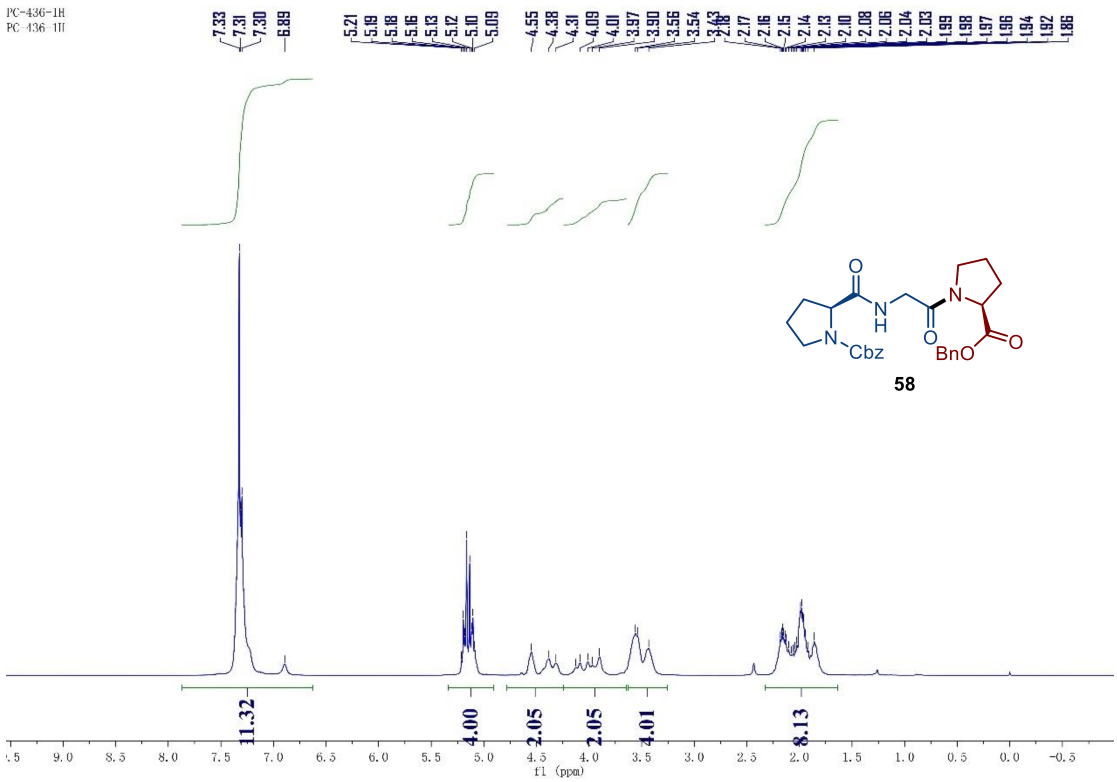

SY-206-13C
SY-206-13C
172.49
172.42
172.34
171.54
171.51
156.51
156.46
130.48
130.32
127.75
127.40
115.43
115.35
59.99
59.29
54.33
53.81
52.35
52.12
47.16
46.78
36.39
35.87
34.05
33.60
32.01
31.47
31.42
29.27
24.52
24.37
22.53
14.34
H
N
O
OMe
N
O
O
OH
56'
f1 (ppm)

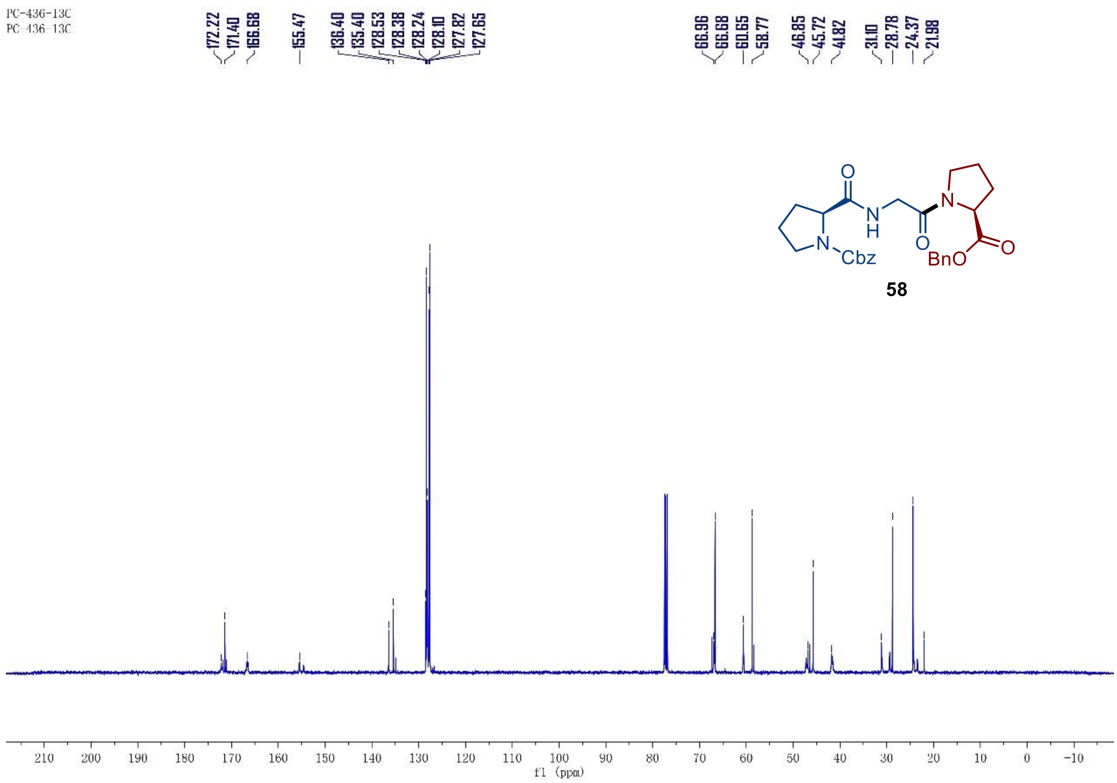

PC-385-pure
PC-385 1H
7.41 7.39 7.26 7.25 7.24 7.19
6.01 5.99 5.44 5.10 5.07 5.05 5.01 4.97 4.62 4.61 4.59 4.29 4.27
3.07 2.35 2.34 2.18 2.16 2.15 2.13 1.98 1.96 1.95 1.93 1.76 1.74 1.61 1.59 1.39 1.37 1.33 1.32
0.98 20.23 1.02 1.03 8.04 1.02 0.93 2.01 2.00 1.02 1.02 1.02 1.04 4.09
f1 (ppm)
Cbz
OBn
HN
Cbz
57

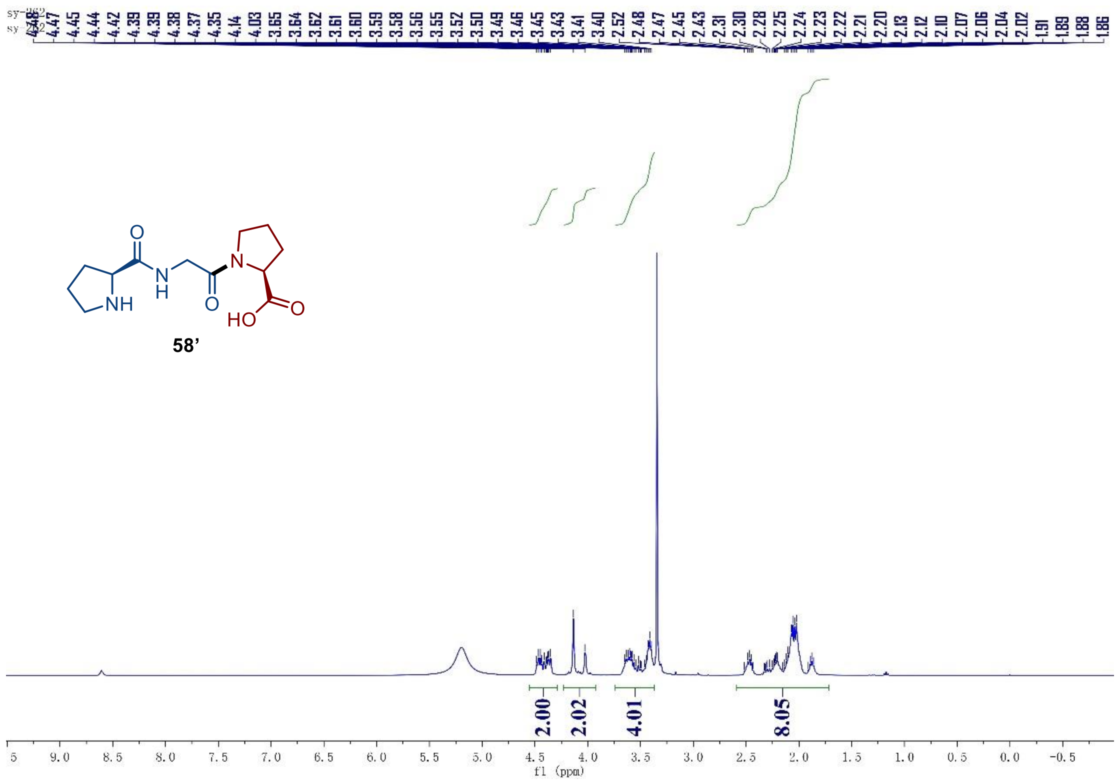

PC-385-pure
PC-385 13C
172.68 172.37 171.63 156.79 156.42 136.77 136.36 135.78 135.29 128.68 128.64 128.56 128.54 128.34 128.32 128.14 128.08
67.34 66.99 66.59 54.61 51.84 40.38 32.29 30.27 29.22 26.82 22.20
f1 (ppm)
Cbz
OBn
HN
Cbz
57

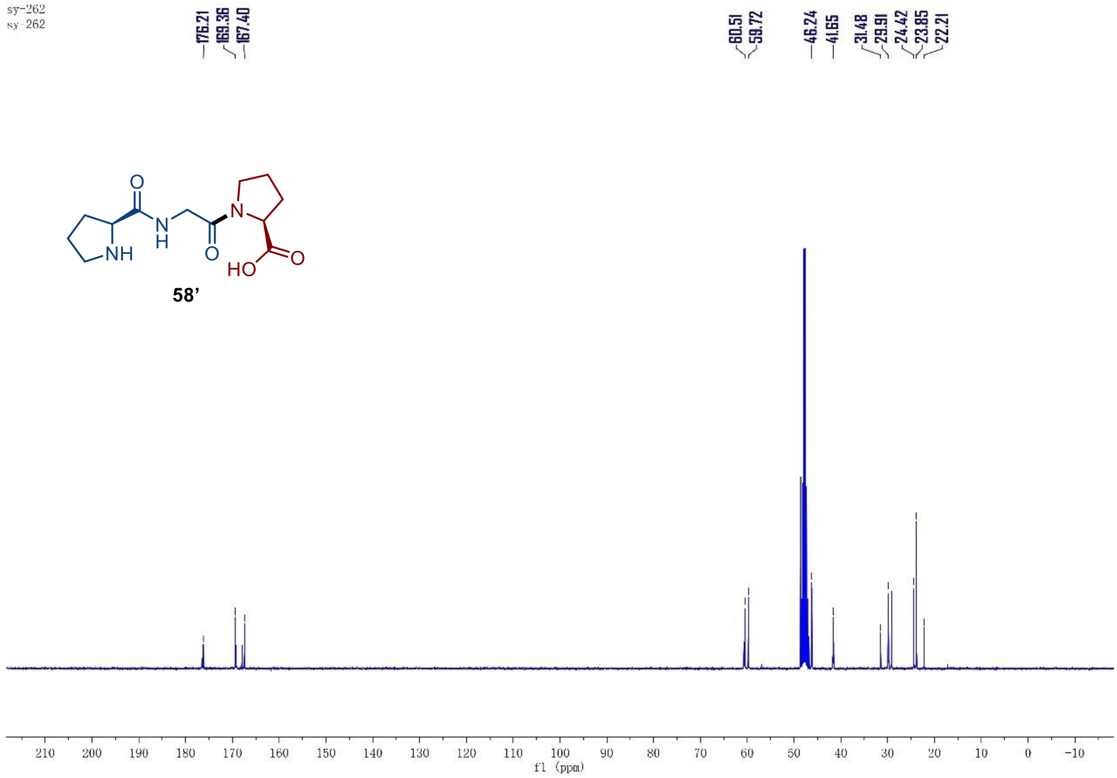

SY-212-shui
SY-212-shui
4.11
4.10
3.96
2.97
2.96
2.94
2.19
2.17
2.04
2.02
1.86
1.66
1.64
1.47
1.45
1.43
H2N
NH2
O
N
H
O
OH
OH
O
57'
2.06
2.00
2.03
4.04
1.98
2.01
f1 (ppm)

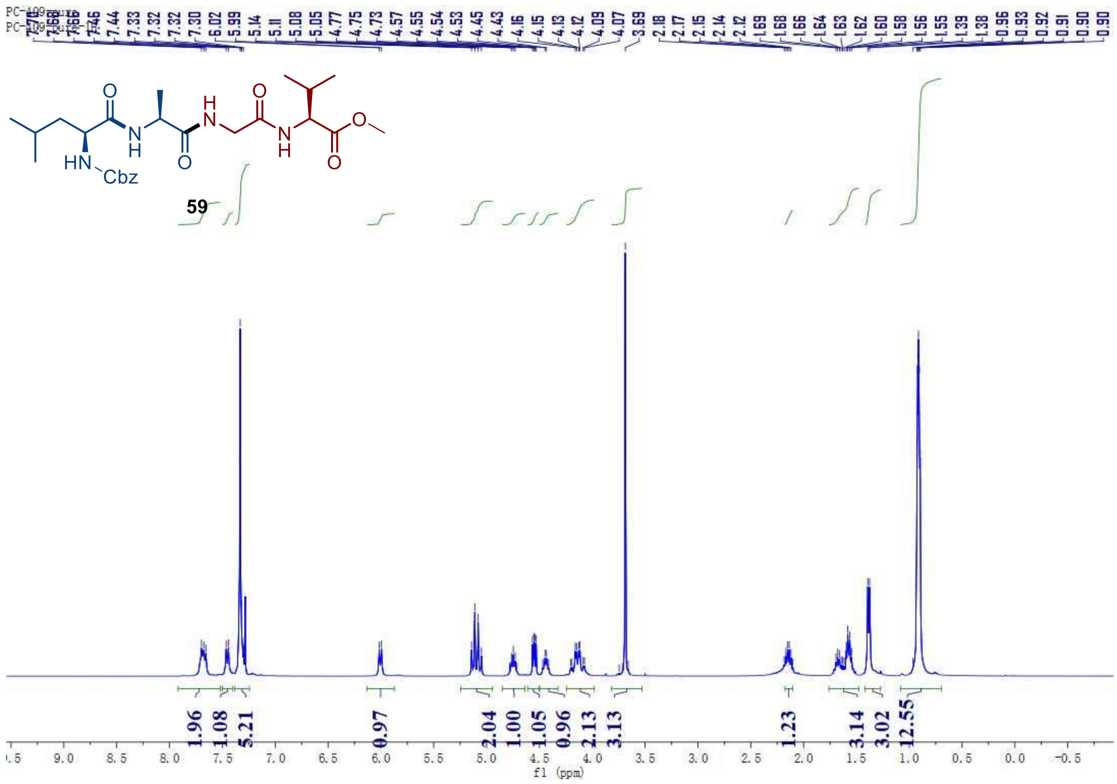

SY-299
SY-211
182.04
178.16
169.43
55.49
52.92
38.94
33.99
30.37
28.01
26.21
20.95
H2N
NH2
O
N
H
O
OH
OH
O
57'
f1 (ppm)

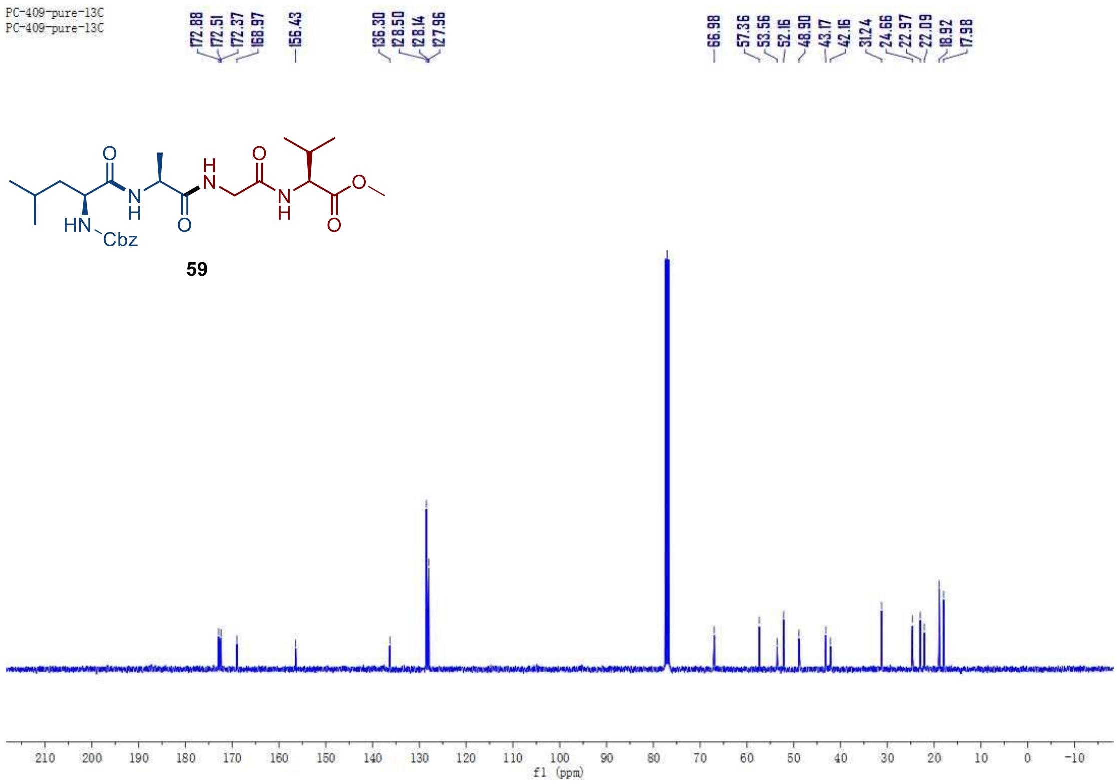

PC-436-1H
PC-436-1H
7.33
7.31
7.30
6.89
5.21
5.19
5.18
5.16
5.13
5.12
5.10
5.09
4.55
4.38
4.31
4.09
4.01
3.97
3.90
3.56
3.54
3.43
3.18
2.17
2.16
2.15
2.14
2.13
2.10
2.08
2.06
2.04
2.03
1.99
1.98
1.97
1.96
1.94
1.92
1.86
O
N
H
O
N
N
Cbz
BnO
O
58
11.32
4.00
2.05
2.05
4.01
8.13
f1 (ppm)

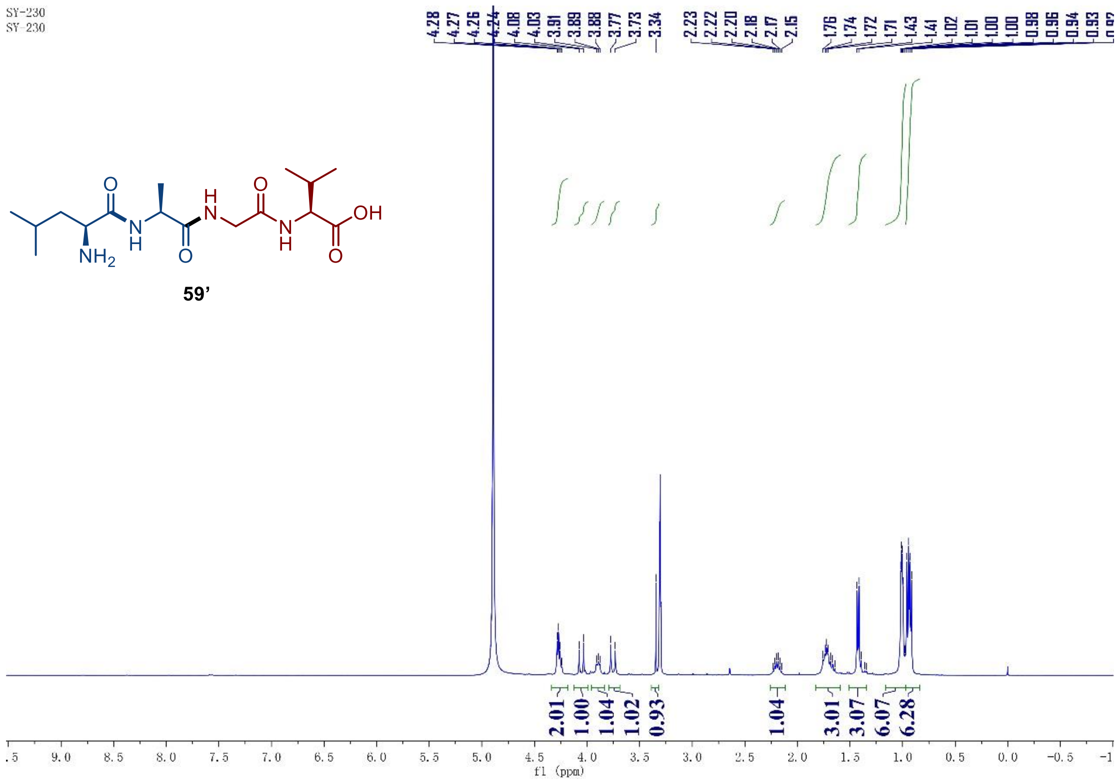

PC-436-13C
PC-436-13C
172.22
171.40
166.68
155.47
136.40
135.40
128.53
128.38
128.24
128.10
127.82
127.65
66.96
66.68
60.65
58.77
46.85
45.72
41.82
31.10
28.78
24.37
21.98
O
N
H
O
N
N
Cbz
BnO
O
58
f1 (ppm)

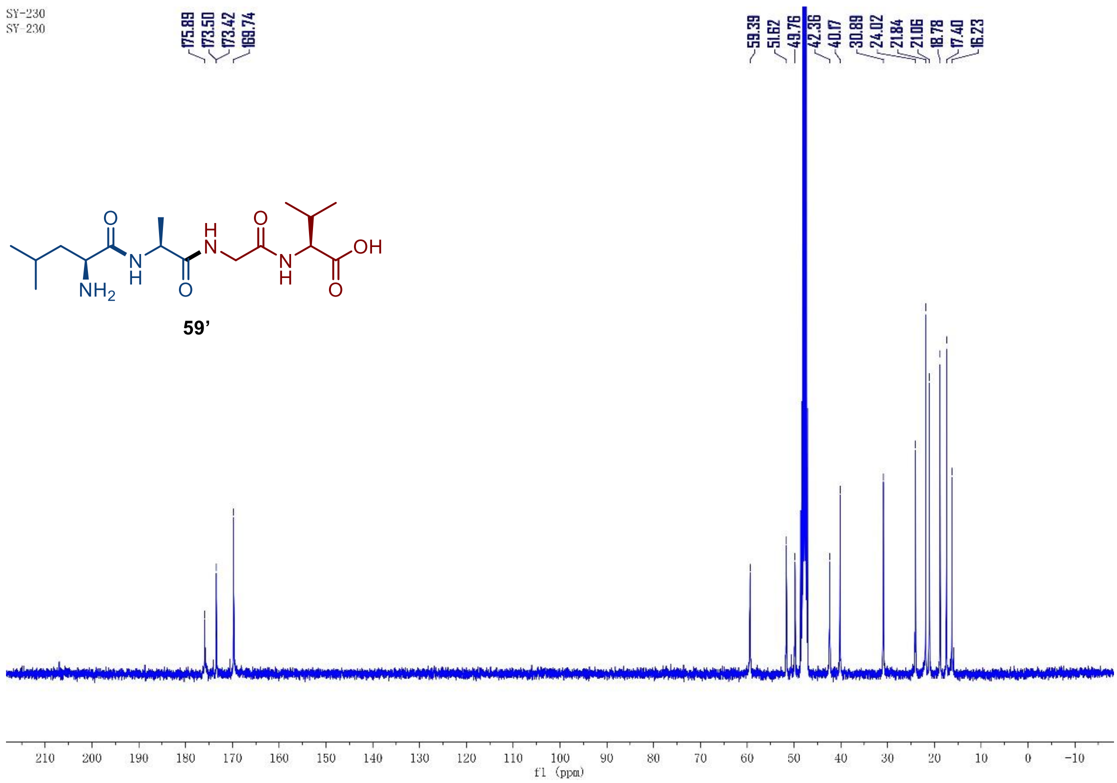

sy-262
4.48 4.47 4.45 4.44 4.42 4.39 4.39 4.38 4.37 4.35 4.14 4.03 3.65 3.64 3.62 3.61 3.60 3.59 3.58 3.56 3.55 3.52 3.50 3.49 3.46 3.45 3.43 3.41 3.40 2.52 2.48 2.47 2.45 2.43 2.31 2.30 2.28 2.25 2.24 2.23 2.22 2.21 2.20 2.13 2.12 2.10 2.07 2.06 2.04 2.02 1.91 1.89 1.88 1.86
O
N
H
NH
HO
O
N
58'
2.00
2.02
4.01
8.05
f1 (ppm)

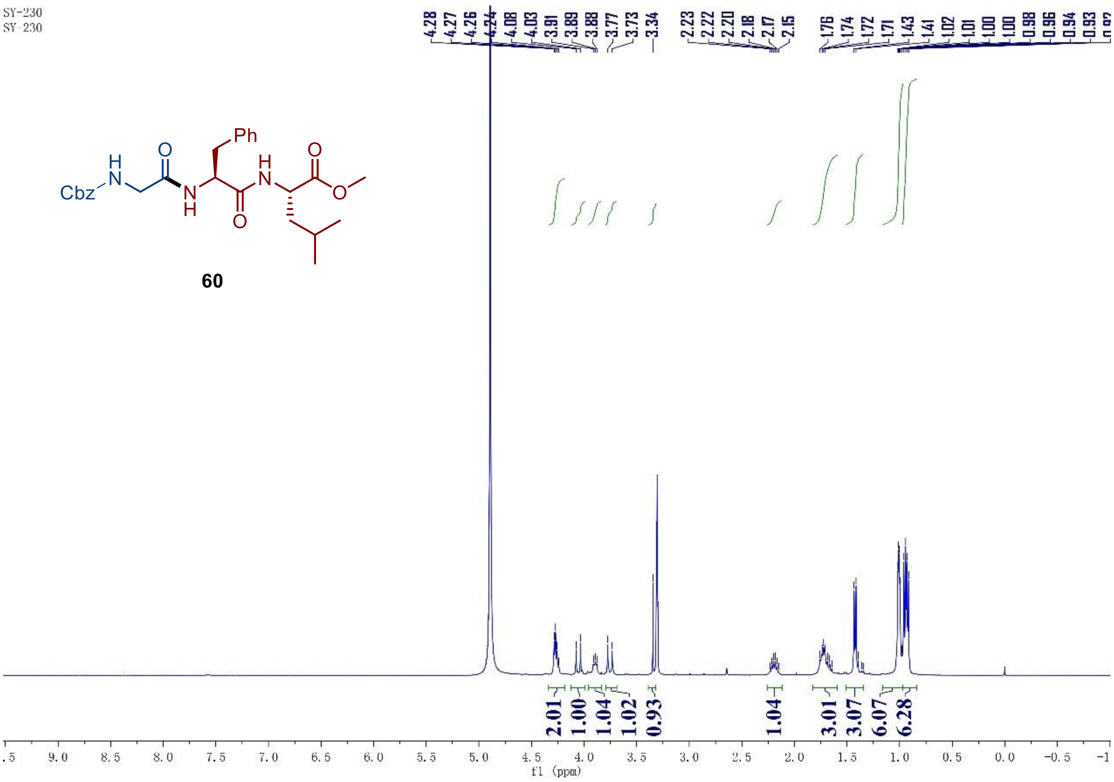

sy-262
176.21 169.36 167.40
60.51 59.72
46.24 41.65 31.48 29.91 24.42 23.85 22.21
O
N
H
NH
HO
O
N
58'
f1 (ppm)


PC-409-pure
7.44
7.33
7.32
7.32
7.30
6.02
5.99
5.14
5.11
5.08
5.05
4.77
4.75
4.73
4.57
4.55
4.54
4.53
4.45
4.43
4.16
4.15
4.13
4.12
4.09
4.07
3.69
2.18
2.17
2.15
2.14
2.12
1.69
1.68
1.66
1.64
1.63
1.62
1.60
1.58
1.56
1.55
1.39
1.38
0.96
0.93
0.92
0.91
0.90
0.90
HN
Cbz
59
1.96
1.08
5.21
0.97
2.04
1.00
1.05
0.96
2.13
3.13
1.23
3.14
3.02
12.55
f1 (ppm)

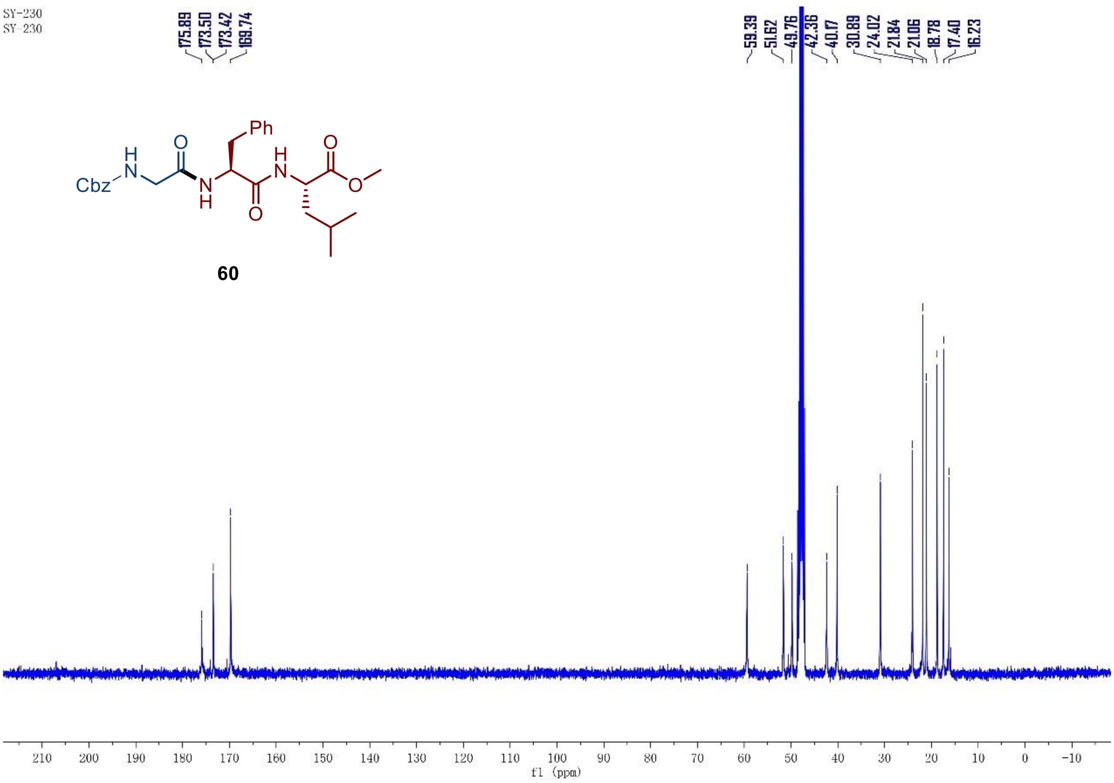

PC-409-pure-13C
PC-409-pure-13C
172.88
172.51
172.37
168.97
156.43
136.30
128.50
128.14
127.96
66.98
57.36
53.56
52.16
48.90
43.17
42.16
31.24
24.66
22.97
22.09
18.92
17.98
HN
Cbz
59
f1 (ppm)


SY-230
SY-230
4.28
4.27
4.26
4.24
4.08
4.03
3.91
3.89
3.88
3.77
3.73
3.34
2.23
2.22
2.20
2.18
2.17
2.15
1.76
1.74
1.72
1.71
1.43
1.41
1.02
1.01
1.00
0.98
0.96
0.94
0.93
59'
2.01
1.00
1.04
1.02
0.93
1.04
3.01
3.07
6.07
6.28
f1 (ppm)

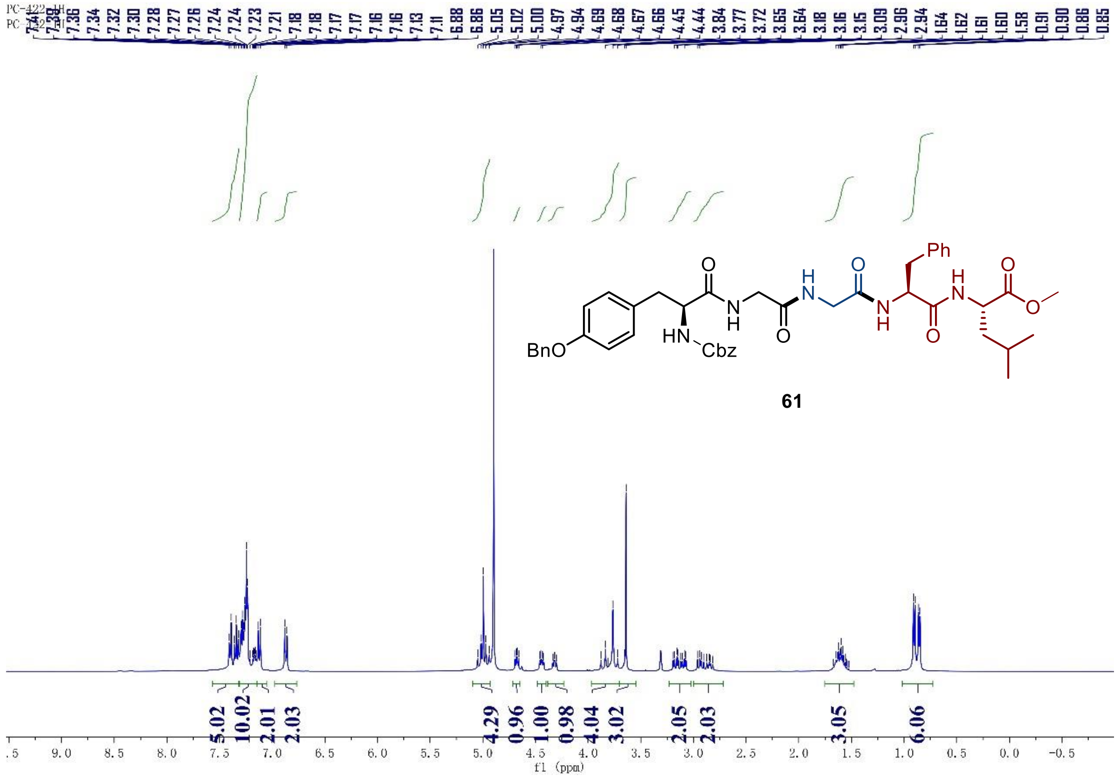

SY-230
SY-230
175.89
173.50
173.42
169.74
59.39
51.62
49.76
42.36
40.17
30.89
24.02
21.84
21.06
18.78
17.40
16.23
59'
f1 (ppm)


SY-230
SY-230
4.28
4.27
4.26
4.24
4.08
4.03
3.91
3.89
3.88
3.77
3.73
3.34
2.23
2.22
2.20
2.18
2.17
2.15
1.76
1.74
1.72
1.71
1.43
1.41
1.02
1.01
1.00
0.98
0.96
0.94
0.93
2.01
1.00
1.04
1.02
0.93
1.04
3.01
3.07
6.07
6.28
f1 (ppm)

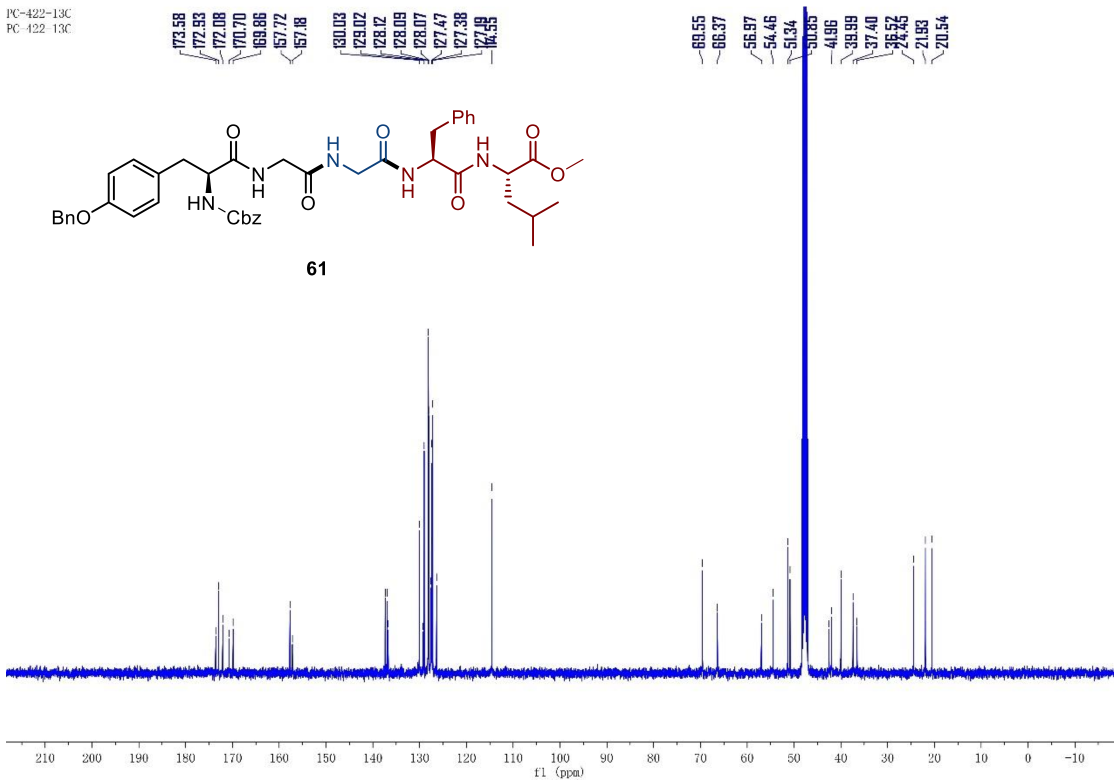
60


SY-230
SY-230
175.89
173.50
173.42
169.74
59.39
51.62
49.76
42.36
40.17
30.89
24.02
21.84
21.06
18.78
17.40
16.23
f1 (ppm)

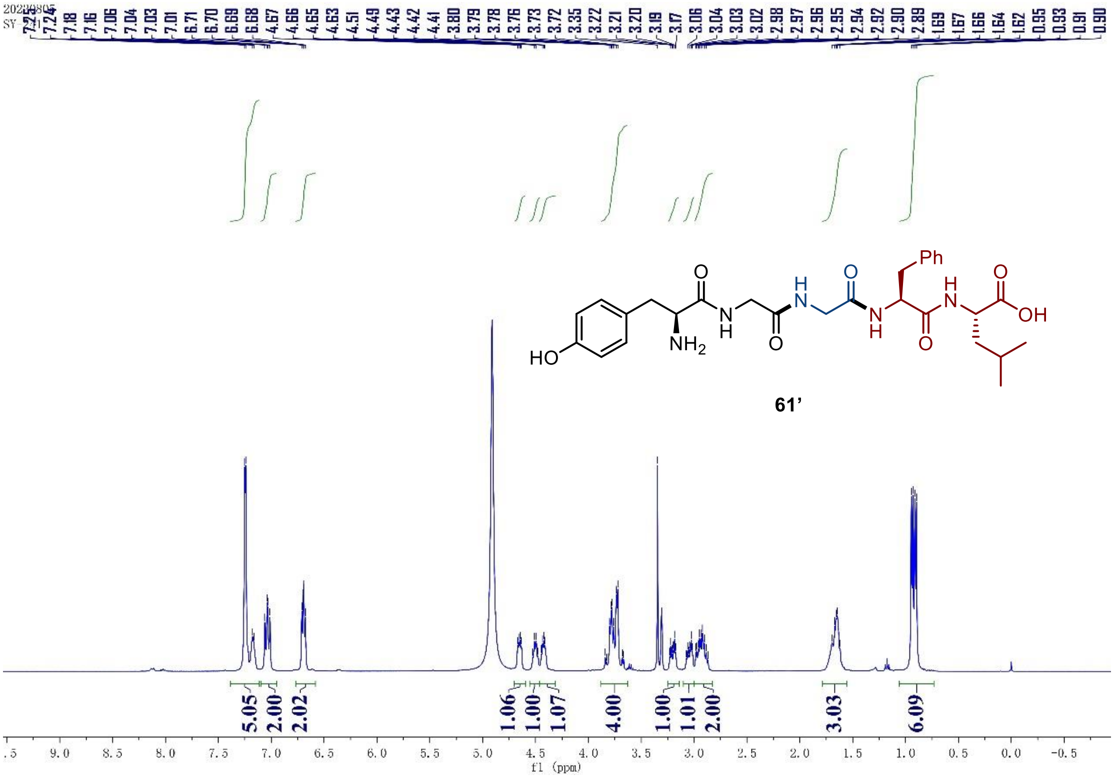
60

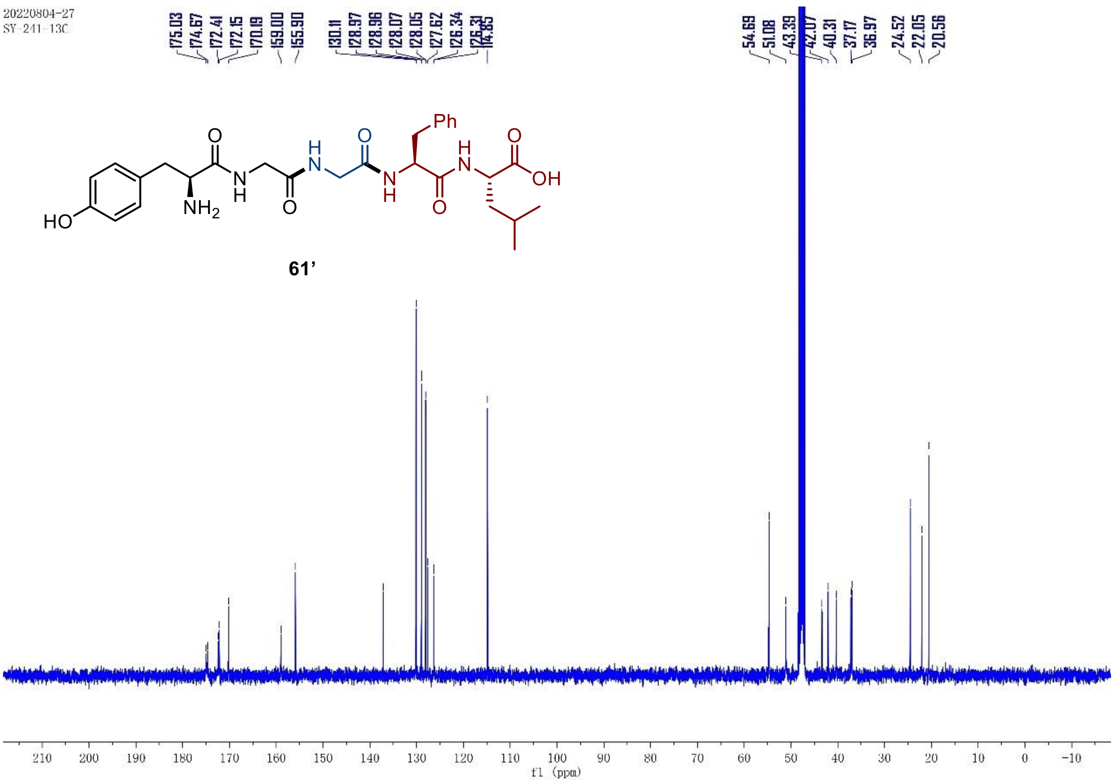


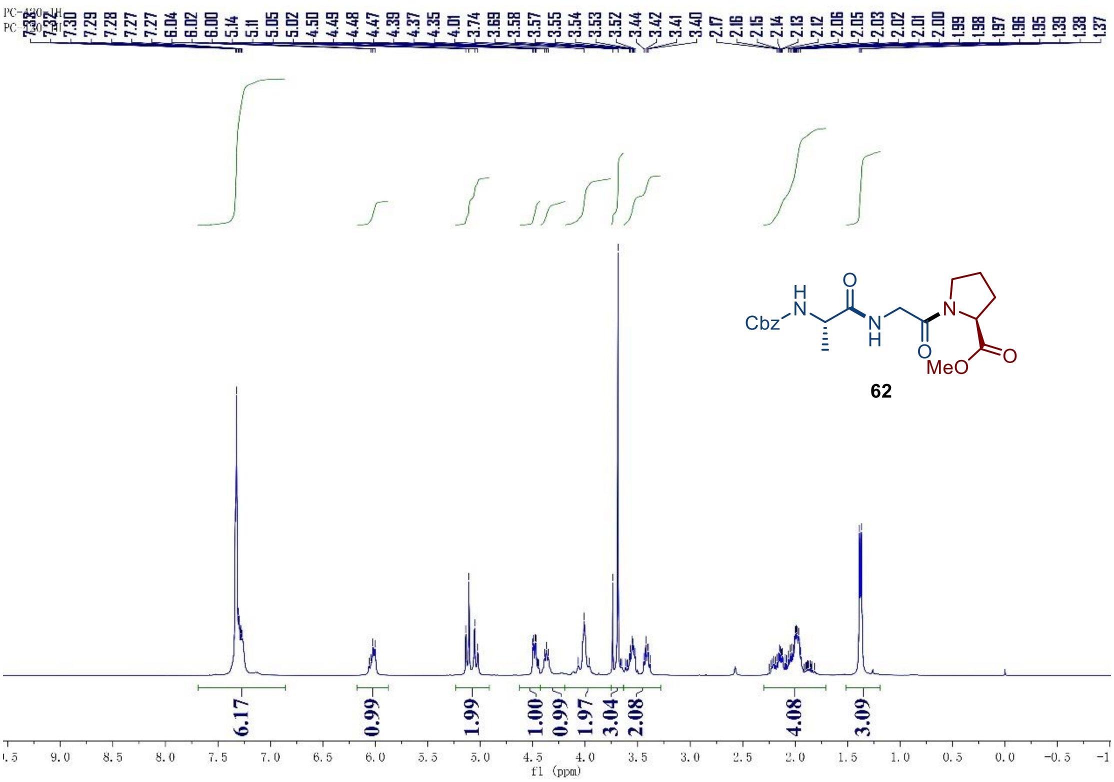
BnO
HN
Cbz
Ph
61
f1 (ppm)



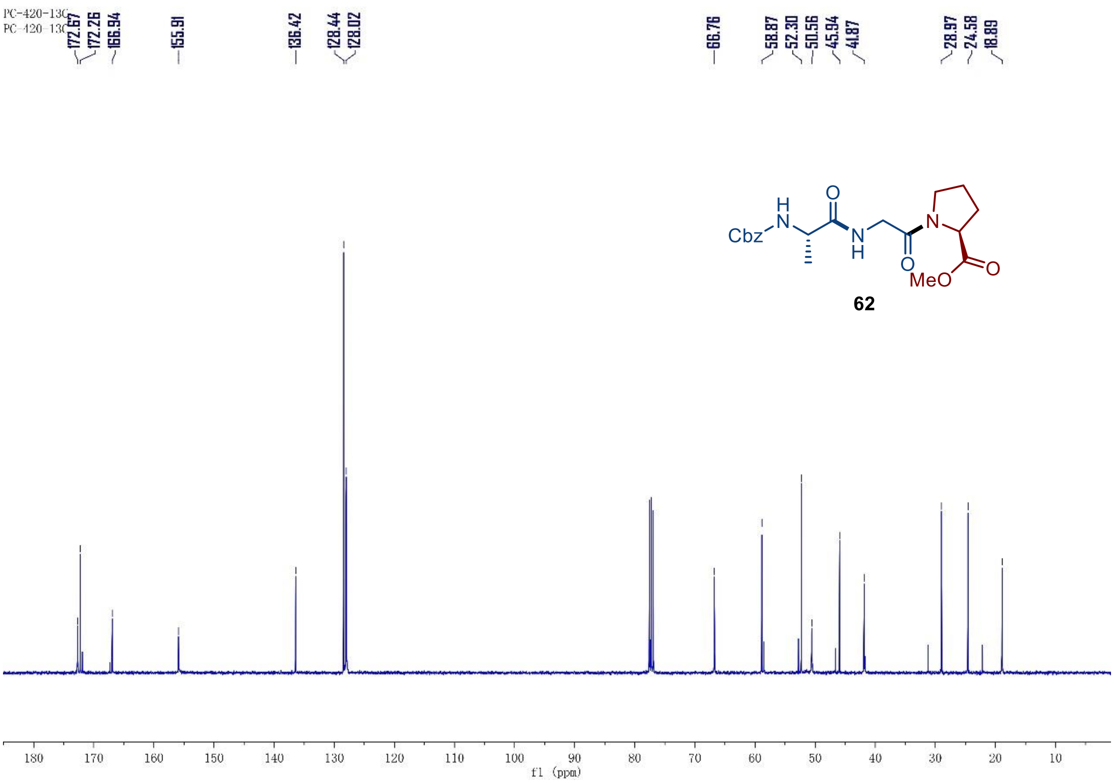
PC-422-13C
BnO
HN
Cbz
Ph
61
f1 (ppm)


61’
f1 (ppm)

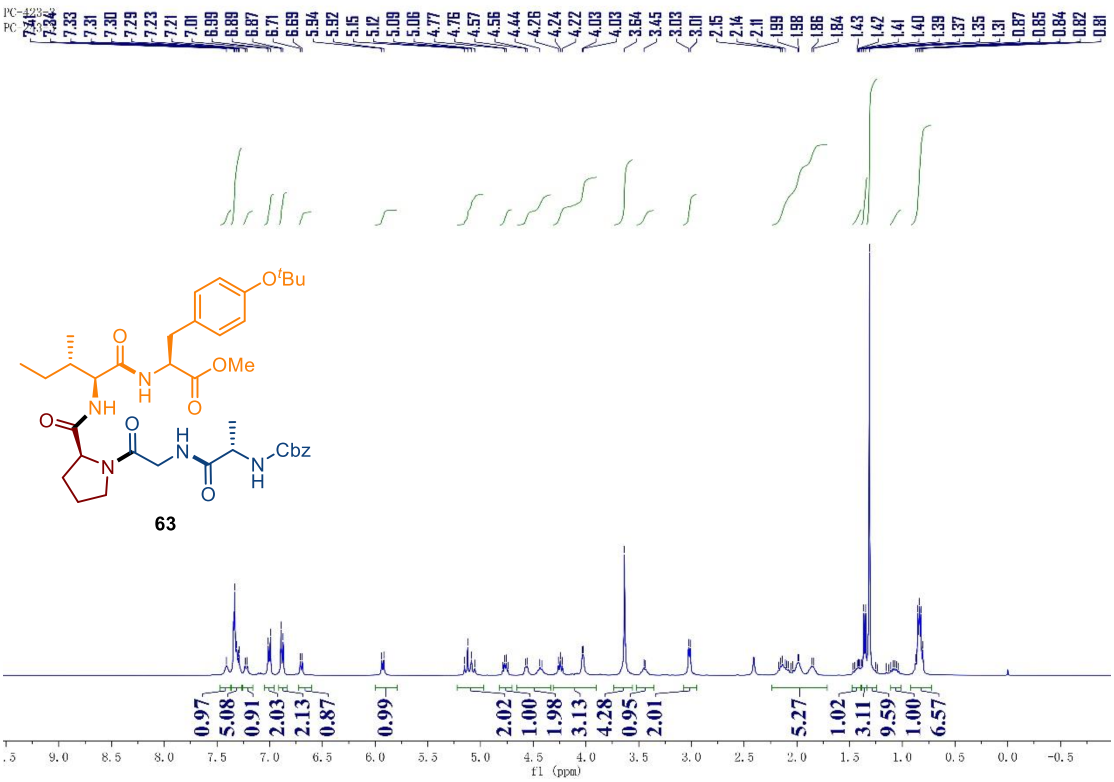

20220804-27
SY-241-13C
61’
f1 (ppm)



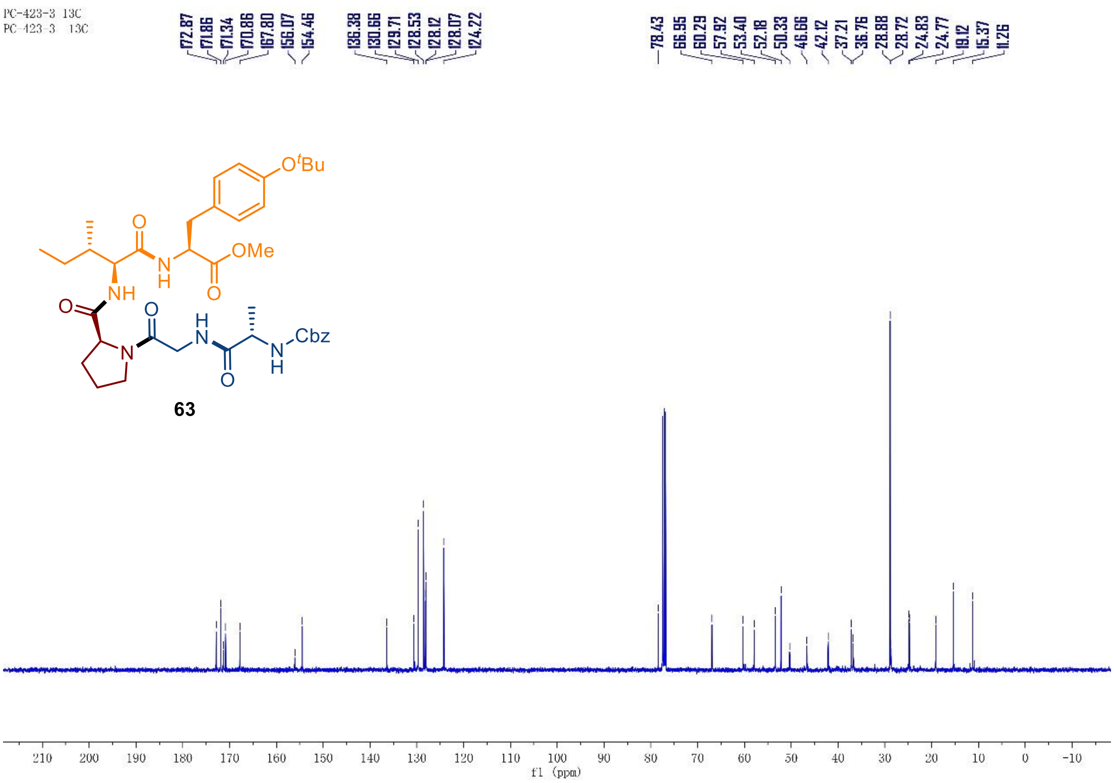
Cbz
MeO
62
6.17
0.99
1.99
1.00
0.99
1.97
3.04
2.08
4.08
3.09
f1 (ppm)



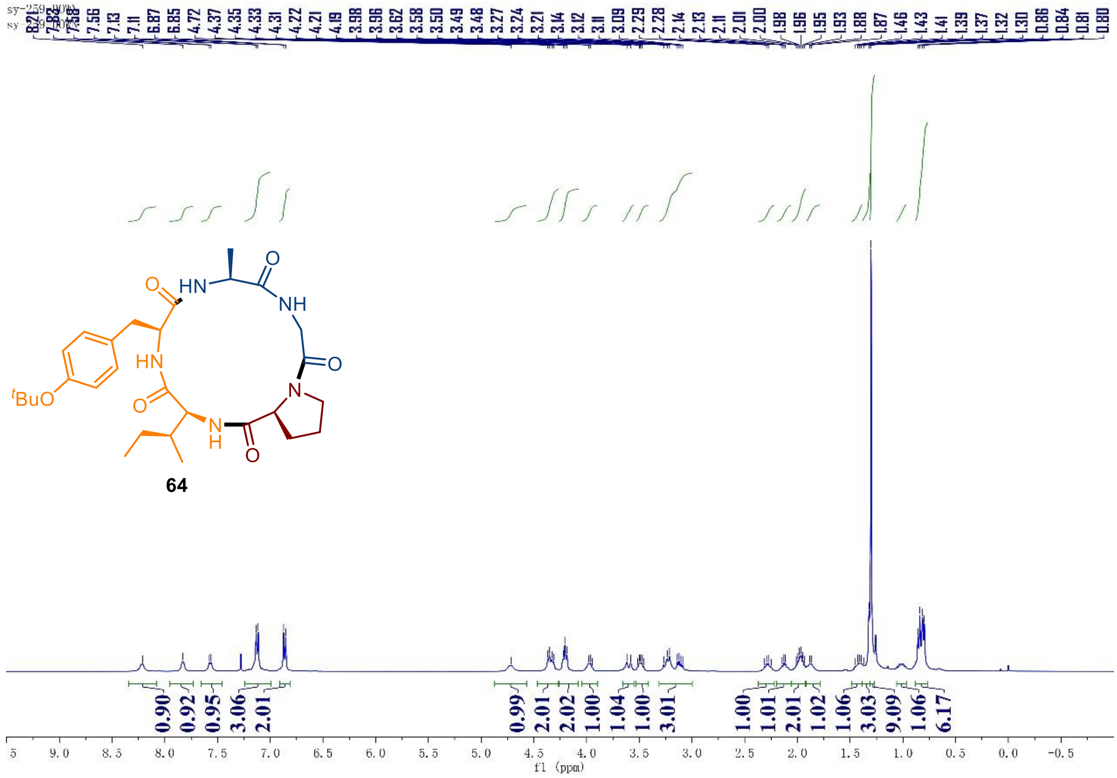
PC-420-13C
172.67
172.26
166.94
155.91
136.42
128.44
128.02
66.76
58.87
52.30
50.56
45.94
41.87
28.97
24.58
18.89
Cbz
MeO
62
f1 (ppm)

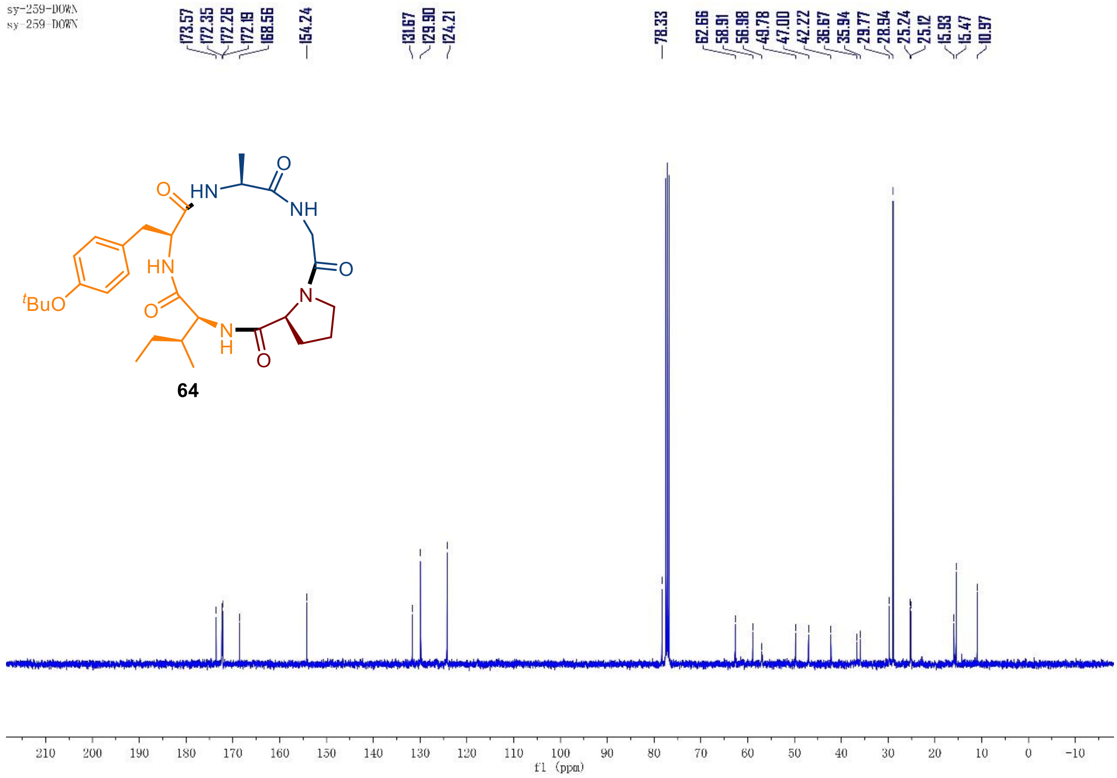


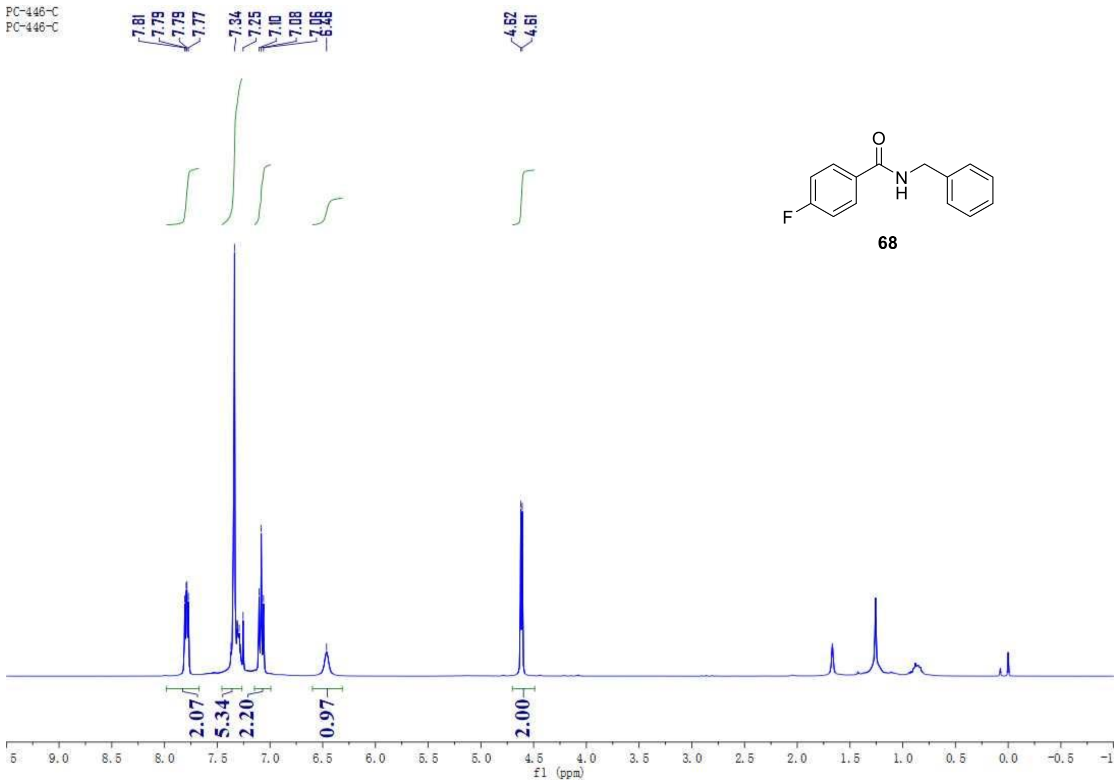
63

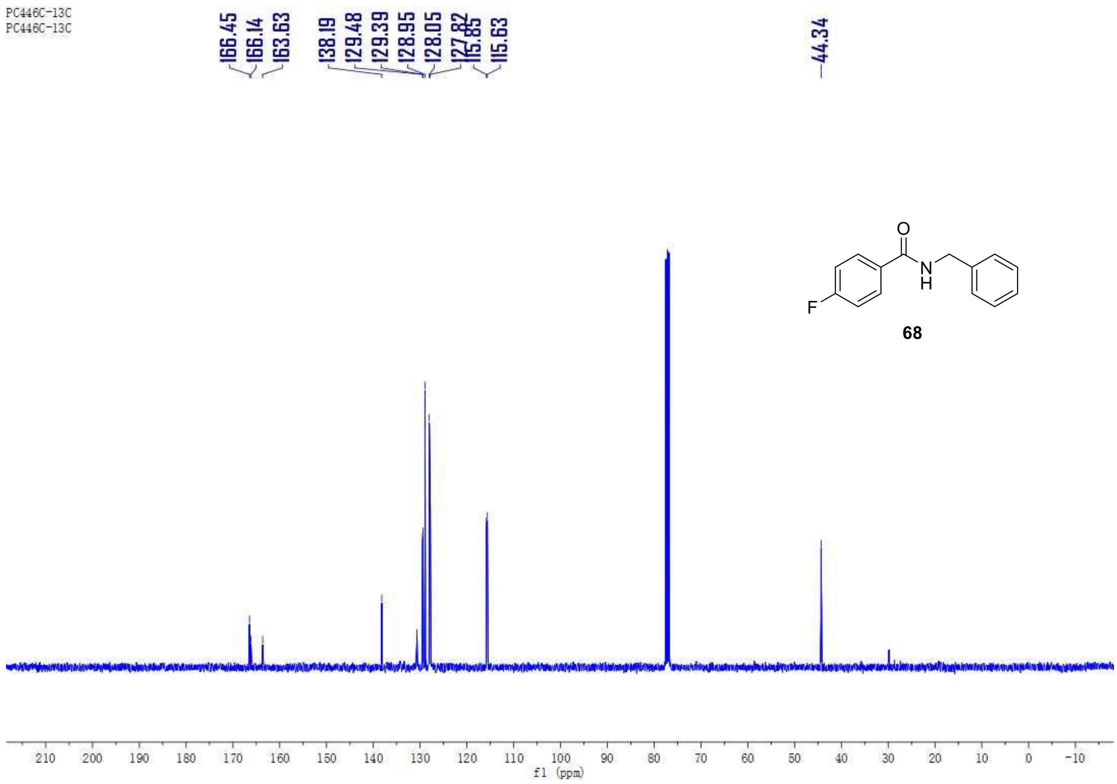


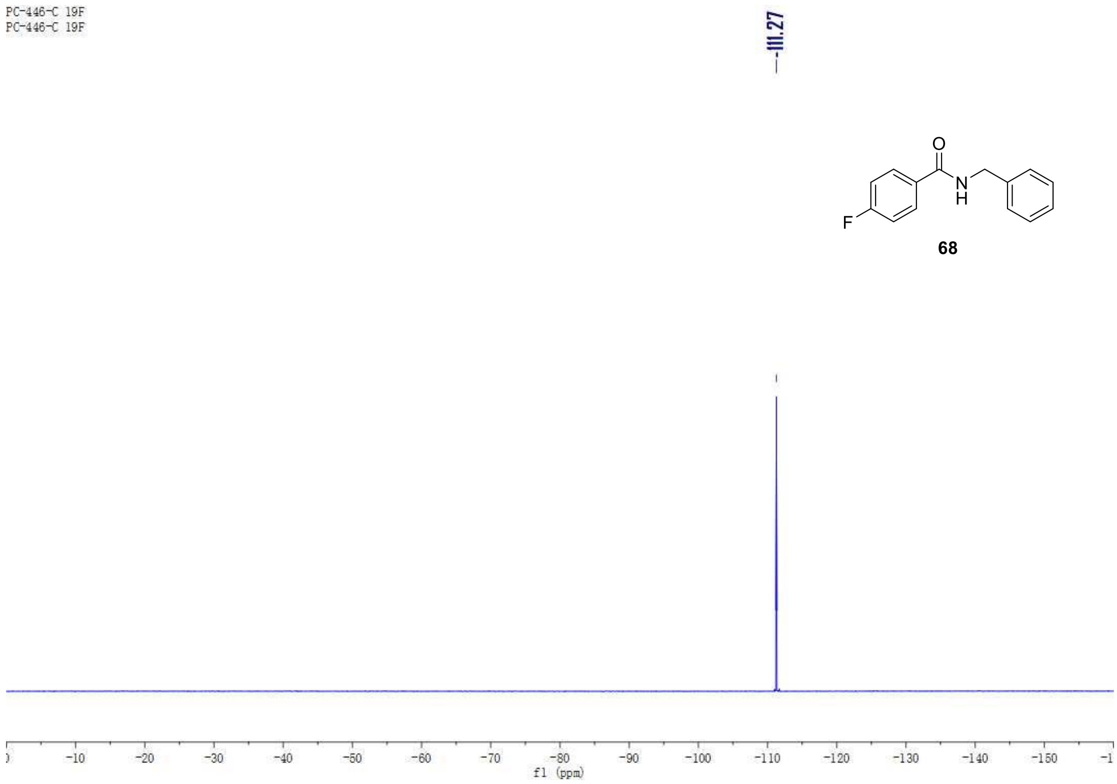
63


sy-259-D0%N
8.21
7.82
7.58
7.56
7.13
7.11
6.87
6.85
4.72
4.37
4.35
4.33
4.31
4.22
4.21
4.19
3.98
3.96
3.62
3.58
3.50
3.49
3.48
3.27
3.24
3.21
3.14
3.12
3.11
3.09
2.29
2.28
2.14
2.13
2.11
2.01
2.00
1.98
1.96
1.95
1.93
1.88
1.87
1.46
1.43
1.41
1.39
1.37
1.32
1.30
0.86
0.84
0.81
0.80
HN
O
NH
O
O
HN
N
tBuO
O
N
H
O
64
0.90
0.92
0.95
3.06
2.01
0.99
2.01
2.02
1.00
1.04
1.00
3.01
1.00
1.01
2.01
1.02
1.06
3.03
9.09
1.06
6.17
f1 (ppm)


sy-259-D0%N
173.57
172.35
172.26
172.19
168.56
154.24
131.67
129.90
124.21
78.33
62.66
58.91
56.98
49.78
47.00
42.22
36.67
35.94
29.77
28.94
25.24
25.12
15.93
15.47
10.97
64
f1 (ppm)


PC-446-C
PC-446-C
7.81
7.79
7.79
7.77
7.34
7.25
7.10
7.08
7.06
6.46
4.62
4.61
O
N
H
F
68
2.07
5.34
2.20
0.97
2.00
f1 (ppm)


PC446C-13C
PC446C-13C
166.45
166.14
163.63
138.19
129.48
129.39
128.95
128.05
127.82
115.85
115.63
44.34
O
N
H
F
68
f1 (ppm)


PC-446-C 19F
PC-446-C 19F
-111.27
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)
O
N
H
F

68