Supporting Information

General Chemoselective Hindered Amide Coupling Enabled by TCFH-Catalytic Oxyma and Transient Imine Protection

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1. Procedures, Materials and Instrumentation

1.1 General Experiment Procedures

All reactions were carried out on the benchtop without special precautions towards air or moisture. Reported concentrations refer to solution volumes at room temperature. Concentration of organic solutions under reduced pressure was performed on a Büchi rotary evaporator using house vacuum (~ 40 mm Hg). Reactions were monitored by HPLC. Column chromatography (using an ISCO and visualizing at 210 nm and 254 nm) was performed with silica cartridges.

1.2 Materials

All commercially available reagents were purchased from Sigma–Aldrich, Alfa Aesar, Strem, Oakwood, Chem-Impex Int'l. Inc., or TCI and used without purification, unless otherwise indicated. Anhydrous solvents were used as received. Deuterated NMR solvents were purchased from Cambridge Isotope Laboratories.

1.3 Instrumentation

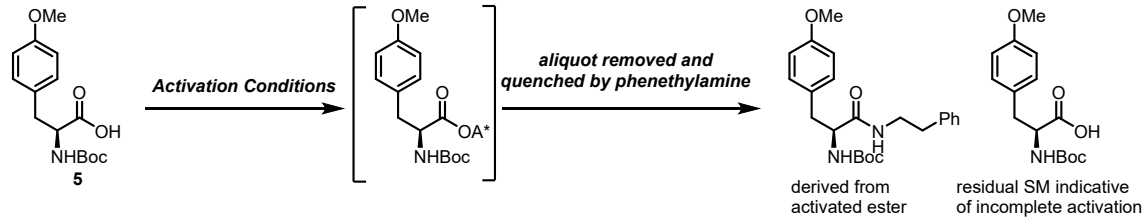
Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 25 °C (unless stated otherwise) on 400 or 500 MHz spectrometers. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual proton resonances of the NMR solvent. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent. The solvent peak was referenced to 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C for $CDCl_3$. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sp = septet, m = multiplet), coupling constants (J) in Hertz (Hz).

High-resolution mass spectrometric data was obtained by either ESI or CI with a TOF spectrometer in MeCN

2. Additional Reaction Optimization Data

2.1 Evaluation of Common Coupling Reagents for Challenging Amide Bond Formation

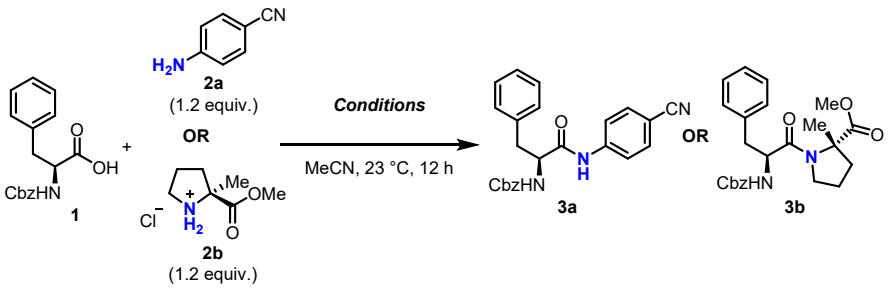
Before exploring conditions for chemoselectivity, we first evaluated a range of simple, inexpensive, and common coupling conditions to investigate their reactivity in the coupling of poorly reactive nucleophiles. We selected $SOCl_2$, CDI, EDC, PivCl, and ethyl chloroformate in our evaluation. Since all the reagents except EDC require preactivation of carboxylic acid to avoid undesired reaction between activators and nucleophiles, we evaluated the preactivation conditions in order to ensure high conversion of carboxylic acid to the activated species (acid chloride, mixed anhydride, acyl imidazole, etc). Since the activated species readily hydrolyze on LC, it is difficult to directly monitor the activation by tracking the activated species. Instead, we choose to aliquot the reaction and quench it with phenethylamine solution to analyze the phenethylamine-derived product and the residual starting material, which indirectly tells us the degree of activation.



Entry	Activation	**quenched pdt** (LC area %)	**SM** (LC area %)
1	$SOCl_2$ (1.2 eq), 4 eq. DIPEA, 0.1 eq. DMF	87%	10%
2	CDI (1.1 eq), 0.2 eq. imidazole-HCl	98%	2%
3	PivCl (1 eq.), 1 eq. NMM	96%	2%
4	ClC(O)OEt (1 eq), 1 eq. NMM	95%	2%

Figure S1. Screen of the activation conditions. Conversion was determined by HPLC analysis of the crude reaction mixture.

After screening, the most optimal activation conditions were shown in Figure S1. Base was found to be necessary to quench acid byproduct from $SOCl_2$ reaction to suppress Boc deprotection, although a small amount of deBoc impurity was still observed. The acid additive was found to promote acyl imidazole formation using CDI. Clean formation of activated ester was observed with PivCl and ethyl chloroformate using NMM as the base. After identifying the activation conditions, we decided to evaluate the coupling with the Cbz-protected substrate to avoid the issue with Boc deprotection under $SOCl_2$ conditions.



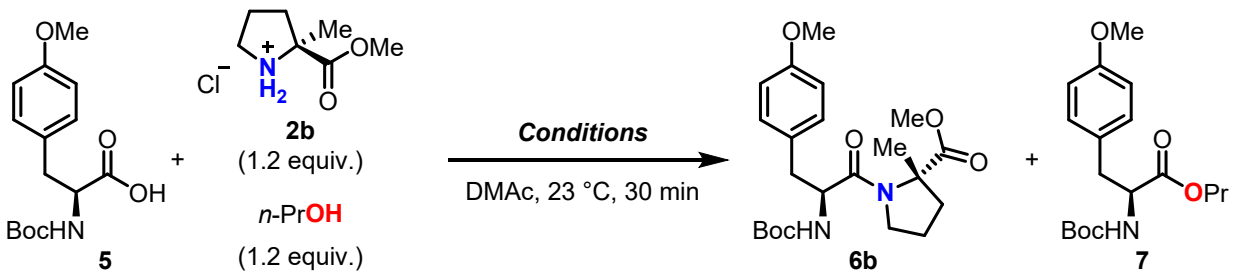
Entry	Activation	Coupling for **2a**	**3a** (LC area %)
1	$SOCl_2$ (1.2 eq), 4 eq. DIPEA, 0.1 eq. DMF	1.2 eq. **2a**	62%
2	CDI (1.1 eq), 0.2 eq. imidazole-HCl	1.2 eq. **2a**	32%
3	N/A	EDC (1.2 eq). 1.2 eq. **2a**	58%
4	PivCl (1 eq.), 1 eq. NMM	1.2 eq. **2a**	75%
5	ClC(O)OEt (1 eq), 1 eq. NMM	1.2 eq. **2a**	81%

Entry	Activation	Coupling for **2b**	**3b** (LC area %)
1	$SOCl_2$ (1.2 eq), 4 eq. DIPEA, 0.1 eq. DMF	1.2 eq. **2b**	15%
2	CDI (1.1 eq), 0.2 eq. imidazole-HCl	1 eq. DIPEA, 1.2 eq. **2b**	2%
3	N/A	EDC (1.2 eq). 1 eq. DIPEA, 1.2 eq. **2b**	66%
4	PivCl (1 eq.), 1 eq. NMM	1 eq. DIPEA, 1.2 eq. **2b**	54%
5	ClC(O)OEt (1 eq), 1 eq. NMM	1 eq. DIPEA, 1.2 eq. **2b**	61%

Figure S2. Evaluation of Common Coupling Reagents for Challenging Amide Bond Formation

We evaluated those reagents in the coupling of a phenylalanine derivative **1** with electronically deactivated aniline **2a** or sterically deactivated amine **2b**. Using the activation conditions which we know will provide >90% activation, we saw incomplete conversion of **1**. Several unidentified side products were observed with $SOCl_2$. While reaction was relatively clean with CDI, the coupling between amines and acyl imidazole was slow. N-acylurea formation was observed with EDC. Formation of carbamate side product resulting from amine attached the carbonate carbonyl carbon was observed with ethyl chloroformate.

2.2 Additional Coupling Reagent Screen for Coupling with A Secondary Amine Nucleophile (2b)



Entry	Activator	Additive	Base	Conversion	**6b**:**7**
1	TCFH	Oxyma (1 equiv)	DIPEA (4 equiv)	98%	>50:1
2	TCFH	HOPO (1 equiv)	DIPEA (4 equiv)	92%	>50:1
3	TCFH	NMI (1 equiv)	DIPEA (4 equiv)	98%	1.8:1
4	TCFH	DMAP (1 equiv)	DIPEA (4 equiv)	94%	1:10
5	TCFH	NMI (3.5 equiv)	-	92%	1:10
6	EDC	HOPO (1 equiv)	DIPEA (4 equiv)	38%	>50:1
7	EDC	DMAP (1 equiv)	DIPEA (4 equiv)	44%	1:40

Entry	Activator	Base	Conversion	**3a** (LC area %)	**3a**:**4**
8	PyClop	DIPEA (4 equiv)	87%	50%	>50:1
9	PFPDPP	DIPEA (4 equiv)	82%	69%	8.6:1
10	HSTU	DIPEA (4 equiv)	76%	49%	2.4:1
11	PyOxim	DIPEA (4 equiv)	99%	94%	31:1
12	PyBroP	DIPEA (4 equiv)	99%	88%	>50:1
13	DEPBT	DIPEA (4 equiv)	85%	78%	23:1
14	HBTU	DIPEA (4 equiv)	99%	72%	2.9:1
15	DPPA	DIPEA (4 equiv)	93%	49%	16:1
16	MNBA	DIPEA (4 equiv)	98%	90%	27:1
17	PFTU	DIPEA (4 equiv)	98%	83%	13:1
18	HATU	DIPEA (4 equiv)	98%	93%	47:1

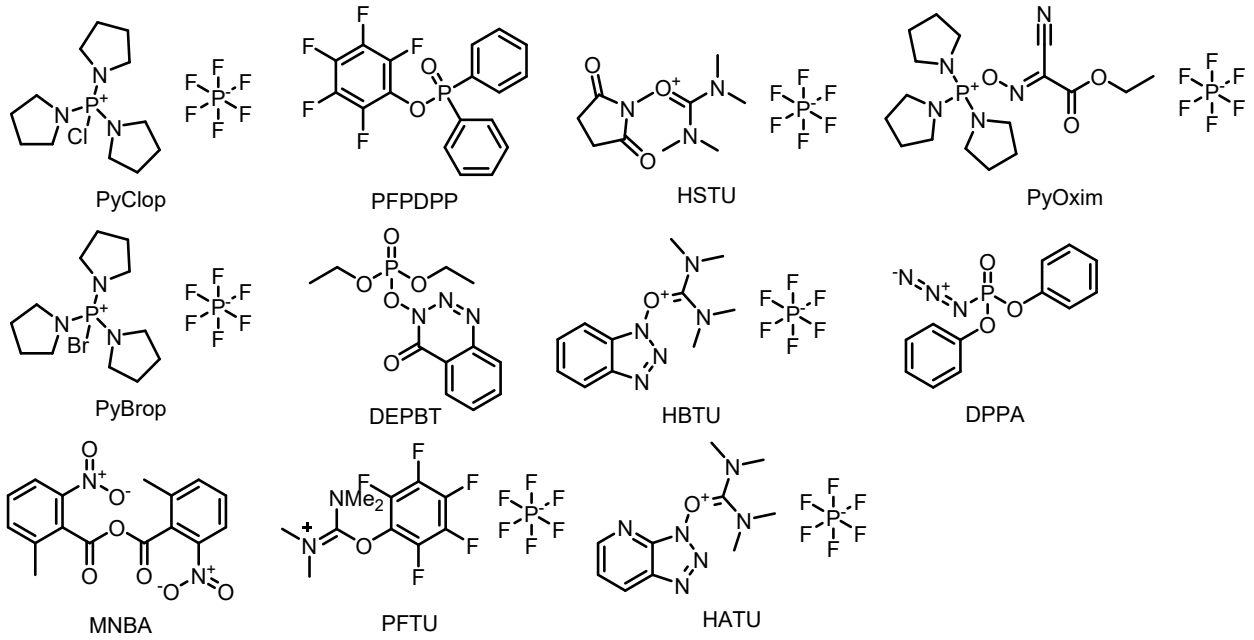
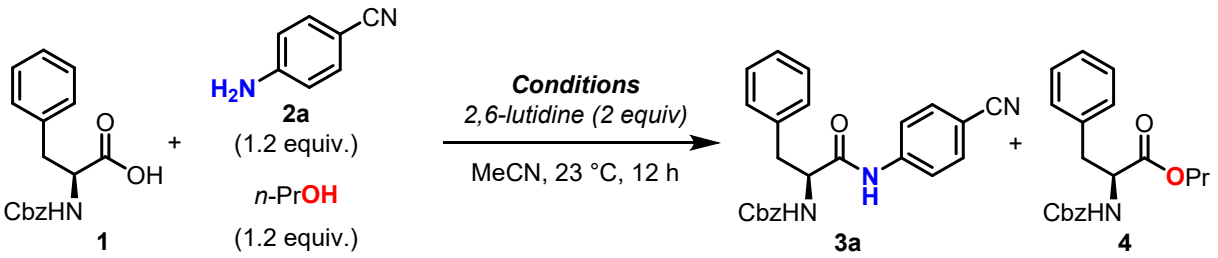


Figure S3. Additional coupling reagent screen for the coupling of **5** with **2b** and *n*-PrOH. Conversion and selectivity were determined by HPLC analysis of the crude reaction mixture.

The selectivity of coupling was found to be highly dependent on the identity of nucleophilic additives (Figure S1 entry 1–7). While *N*-oxide-based nucleophilic additives (HOPO and Oxyma) promoted coupling with high *N*-selectivity, reactions with nitrogen-heterocycle-based additives (NMI and DMAP) favor the formation of corresponding ester product **7**. The same trend was observed when EDC was used as the activator.

Among the additional commercial coupling reagents being screened (Figure S1 entry 8–17), several reagents (PyOxim, PyBrop, MNBA, and HATU) offered both high conversion and product ratio. These four reagents were tested in a different system shown below.

2.3 Additional Coupling Reagent Screen for Coupling with An Electron-Deficient Aniline (2a)

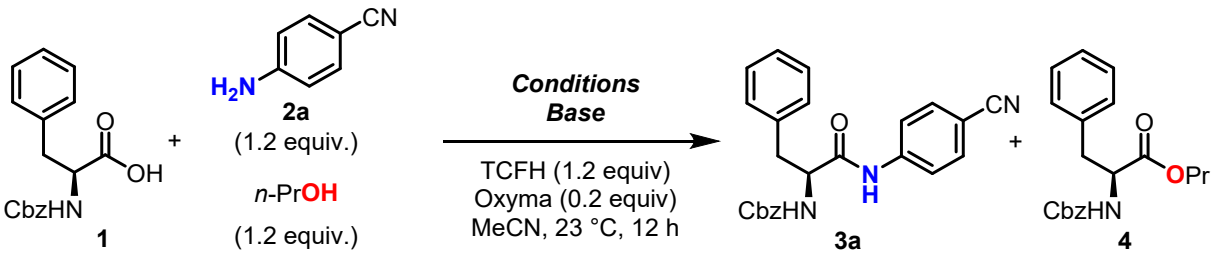


Entry	Activator	Conversion	**3a** (LC area %)	**3a**:**4**
1	HATU	73%	32%	1:1.2
2	PyBroP	48%	26%	2.2:1
3	PyOxim	41%	8%	1:3.8
4	MNBA	26%	0.5%	-

Figure S4. Additional coupling reagent screen for the coupling of **1** with **2a** and *n*-PrOH. Conversion and selectivity were determined by HPLC analysis of the crude reaction mixture.

Although the four coupling reagents showed promising results in Figure S1, lower conversion and selectivity were observed in coupling with 4-cyanoaniline.

2.4 Base Screen for Coupling with An Electron-Deficient Aniline (2a)

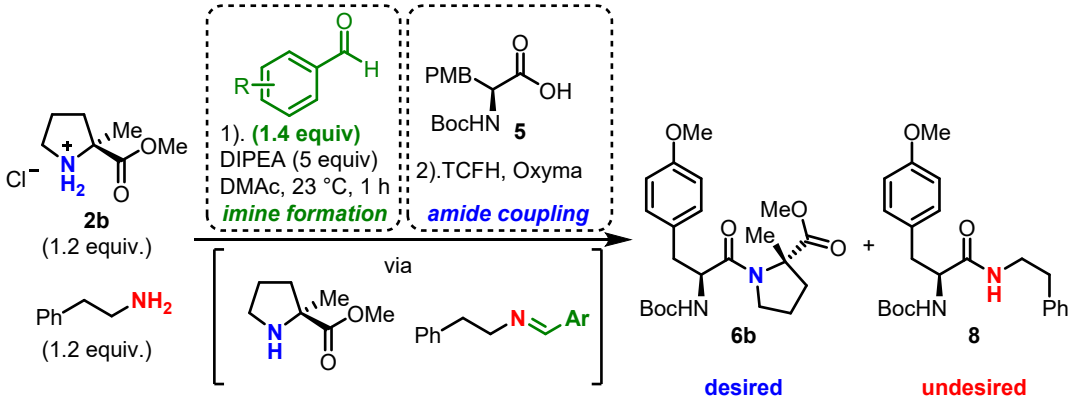


Entry	Base	**3a** (LC area %)	**3a**:**4**
1	2,6-lutidine (2 equiv)	96%	>50:1
2	2,6-lutidine (3 equiv)	95%	42:1
3	NMM (2 equiv)	93%	>50:1
4	NMM (3 equiv)	80%	9:1
5	DIPEA (2 equiv)	91%	>50:1
6	DIPEA (3 equiv)	65%	7.4:1

Figure S5. Base screen for the coupling of **1** with **2a** and *n*-PrOH. Conversion and selectivity were determined by HPLC analysis of the crude reaction mixture.

The basicity of the reaction mixture has strong impact on reaction performance. Stronger base and higher equivalency of base led to lower selectivity and less clean reaction. The optimal base was found to be weakly basic 2,6-lutidine (2 equiv).

2.5 Additional Aldehyde Screen



para and meta-substituted aldehydes

Entry	R	LCAP (**6b**)	**6b**:**8**	Entry	R	LCAP (**6b**)	**6b**:**8**
1	*no aldehyde*	ND	1:43	7	*m*-CF_3	74	10.1:1
2	*p*-OMe	57	2.7:1	8	*p*-CF_3	79	10.8:1
3	*p*-Me	56	3.2:1	9	*p*-CN	72	10.9:1
4	H	73	4.3:1	10	*m*-NO_2	81	11.3:1
5	*p*-Br	76	6.2:1	11	*p*-NO_2	75	12.3:1
6	*m*-Br	72	8.7:1				

ortho-substituted and miscellaneous aldehydes

Entry	R	LCAP (**6b**)	**6b**:**8**
12	*4-hydroxybenzaldehyde*	12	1:1.4
13	*3,5-dichlorosalicyaldehyde*	7	1:1.1
14	*3-hydroxybenzaldehyde*	25	2.4:1
15	2,4-dimethoxybenzaldehyde	56	2.7:1
16	*2-methoxybenzaldehyde*	68	3.5:1
17	*salicyaldehyde*	39	7.2:1
18	*isophthalaldehyde*	75	7.6:1
19	*terephthalaldehyde*	74	8.2:1
20	*2-fluorobenzaldehyde*	80	9.2:1
21	2-bromobenzaldehyde	73	12:1
22	*2-trifluoromethylbenzaldehyde*	79	15:1
23	*2-nitrobenzaldehyde*	77	16:1
24	*2-cyanobenzaldehyde*	42	17:1
25	*2-bromo-4-chlorobenzaldehyde*	86	22:1

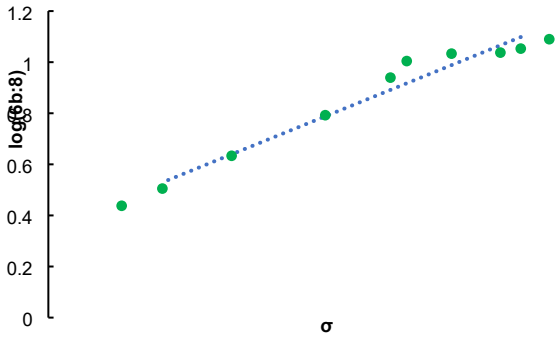


Figure S6. Additional aldehyde screen for the coupling of **5** with **2b** and phenethylamine and Hammett correlation between the electronics of aryl aldehydes and selectivity. Conversion and selectivity were determined by HPLC analysis of the crude reaction mixture.

As discussed in the main text, the selectivity increased as the aldehydes became more electron-deficient (entry 1-11). Aldehydes containing free phenols generally afforded complex reaction mixture with the formation of multiple side products (entry 12-14, 17), and the selectivity was poor. Ortho-substitution provides slightly enhanced selectivity comparing to substitution at meta or para-position. For example, 2-methoxybenzaldehyde (entry 16, 3.5:1) afforded higher selectivity than 4-methoxybenzaldehyde (entry 2, 2.7:1). The same trend also holds for bromo-, trifluoromethyl-, and nitrobenzaldehyde, and the highest selectivity is observed when the bromo, trifluoromethyl, and nitro group is at the ortho-position. 2-Bromo-4-chlorobenzaldehyde was found to be the most optimal one.

3. Safety Evaluation of TCFH and Oxyma

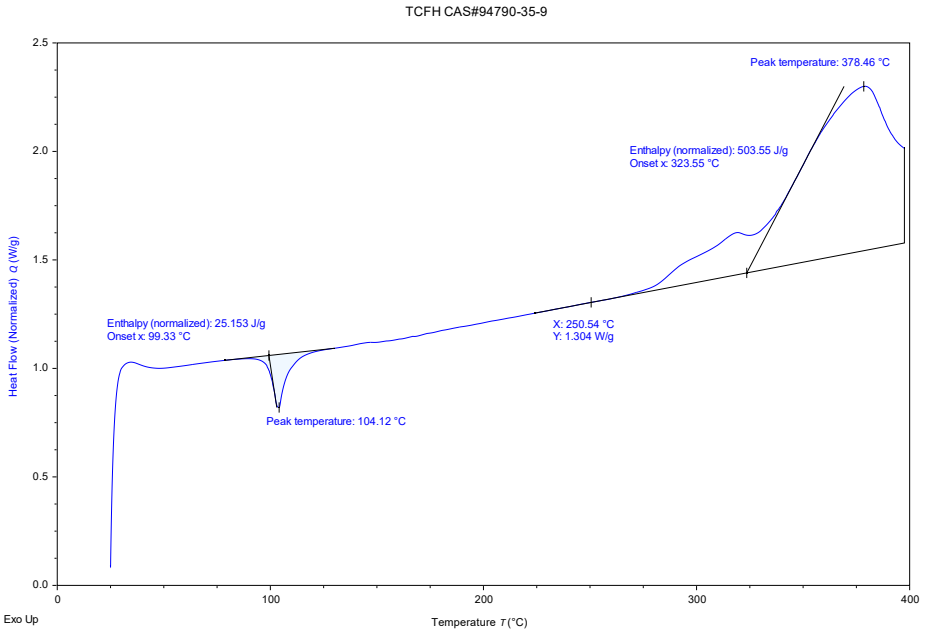


Figure S7. DSC for TCFH.

Melting point 95°C
Exotherm initiates at 250°C
TCFH is not expected to be shock sensitive based on Yoshida correlation

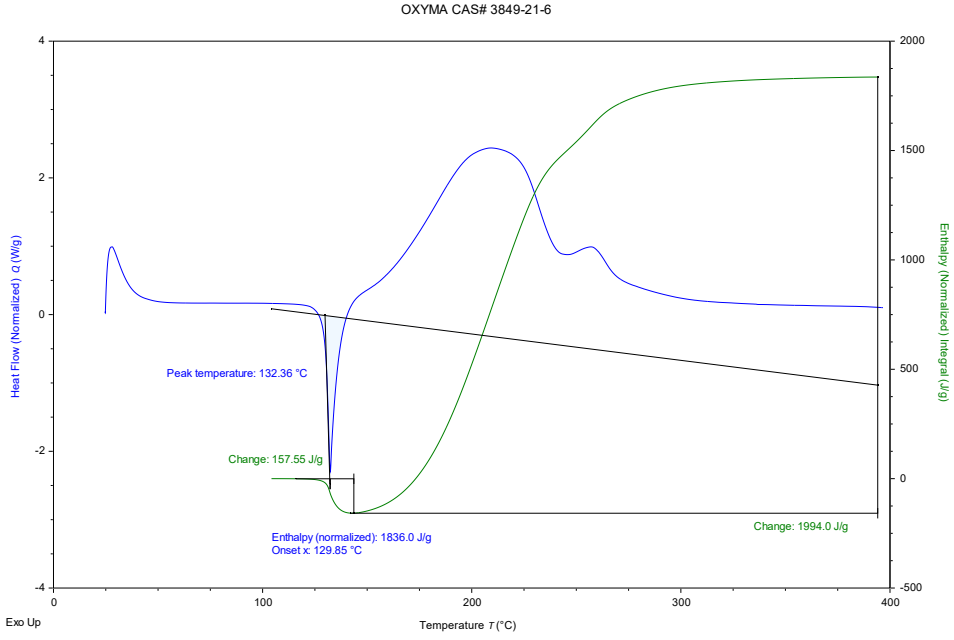


Figure S8. DSC for Oxyma.

Oxyma is highly energetic and Yoshida positive.
Melting Point: 130°C

No sign of decomposition or explosion was observed in drop weight experiments. Negative results for 3 of 3 experiments at 30N.
ARC and DSc isothermal ages showed no evidence of degradation at 70 °C (vs. operating temperature of 25 °C), therefore TCFH and Oxyma are safe to use on large scale.

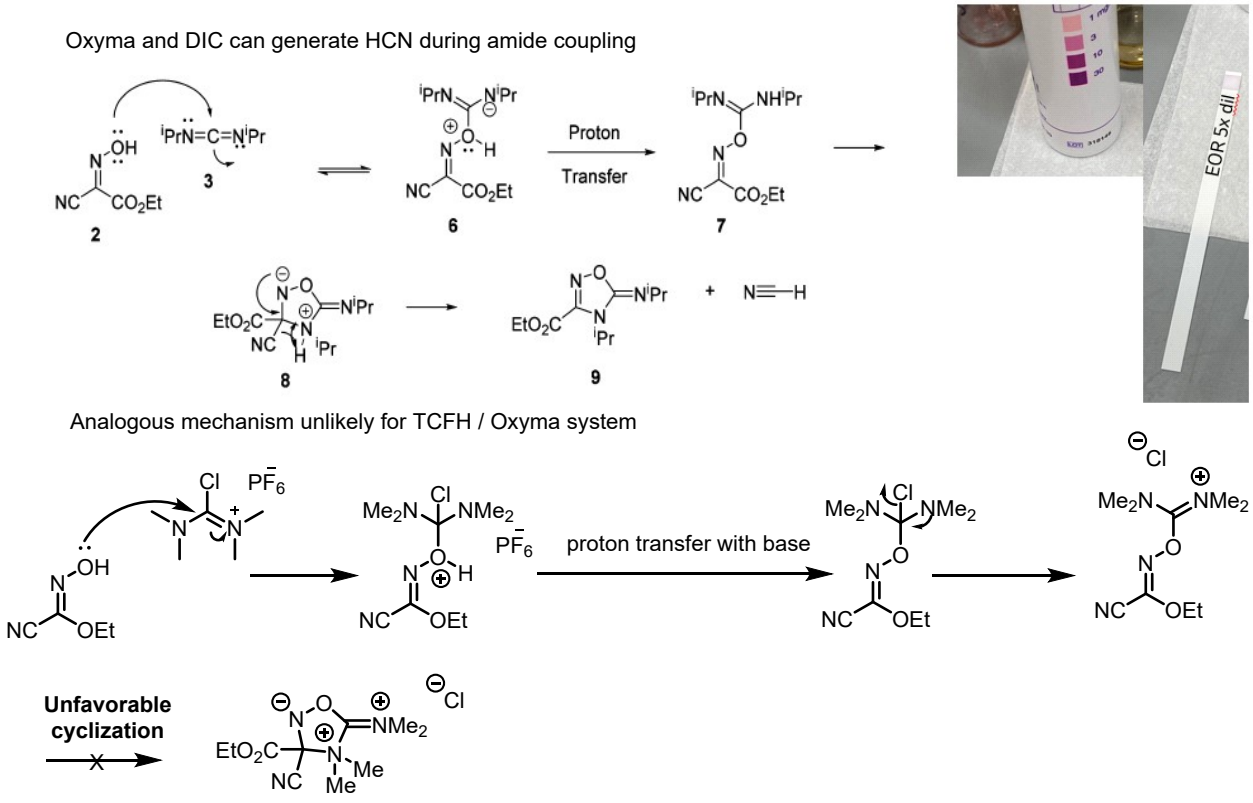
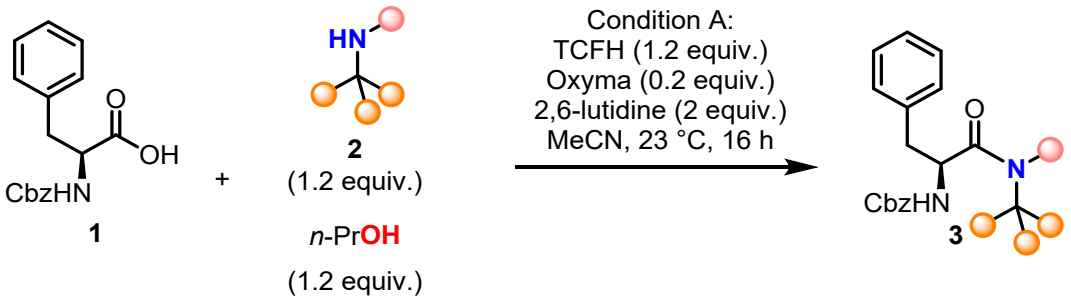


Figure S9. Pathway for possible HCN generation from Oxyma and CN^- testing strip result.

DIC and Oxyma have been reported to react and generate HCN in coupling reaction via a mechanism shown in **Figure S7**.[1] However, the analogous mechanism is unlikely for TCFH and Oxyma. Indeed, when CN^- testing strip was used to measure CN^- concentration in the reaction mixture, no CN^- was detected (limit of detection is 5 ppm).

4. Synthetic Procedures and Characterization Data

4.1 Synthesis and Characterization of Products



General Procedure A: General Procedure for Coupling of Cbz-Phe-OH (1) with anilines in the presence of *n*-PrOH

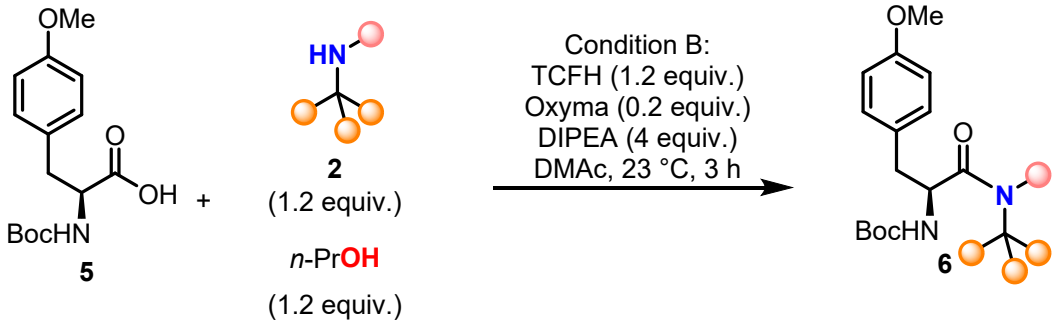
For product spotaneously crystallizing out during reaction:

To a 40 mL vial equipped with a stir bar was added **Cbz-Phe-OH (1)** (6.7 mmol, 1 equiv), MeCN (18 mL), 2,6-lutidine (13.4 mmol, 2 equiv), *n*-propanol (8.0 mmol, 1.2 equiv), and anilines (8.0 mmol, 1.2 equiv). To the reaction mixture was added Oxyma (1.3 mmol, 0.2 equiv). The solution was cooled to 0 ˚C in an ice bath. To the solution was added TCFH (7.4 mmol, 1.1 equiv). The reaction mixture was stirred at 0 ˚C for 10 min. The reaction was then warmed to 25 ˚C and stirred at 25 ˚C for 16 hours. Aliquot was diluted with MeOH:H2O (1:1), filtered, analyzed by HPLC to determine product ratio. The slurry was slowly transferred to 150 mL water to precipitate out all the product. The slurry was stirred at 25 ˚C for 30 min and filtered to afford the crude product. After the crude product was dried under vacuum, it was washed with 15 mL hexanes:MTBE (1:1) twice to remove impurities and afford clean product.

General Procedure B: General Procedure for Coupling of Cbz-Phe-OH (1) with anilines in the presence of *n*-PrOH

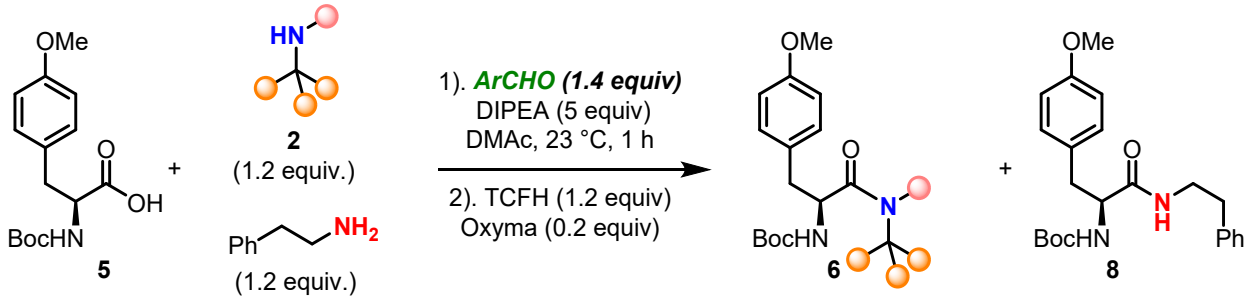
For product that remains soluble in reaction mixture:

To a 40 mL vial equipped with a stir bar was added **Cbz-Phe-OH (1)** (6.7 mmol, 1 equiv), MeCN (18 mL), 2,6-lutidine (13.4 mmol, 2 equiv), *n*-propanol (8.0 mmol, 1.2 equiv), and anilines (8.0 mmol, 1.2 equiv). To the reaction mixture was added Oxyma (1.3 mmol, 0.2 equiv). The solution was cooled to 0 ˚C in an ice bath. To the solution was added TCFH (7.4 mmol, 1.1 equiv). The reaction mixture was stirred at 0 ˚C for 10 min. The reaction was then warmed to 25 ˚C and stirred at 25 ˚C for 16 hours. Aliquot was diluted with MeOH:H2O (1:1), filtered, analyzed by HPLC to determine product ratio. The reaction mixture was transferred to a separatory funnel. To the sep funnel was added 100 mL EtOAc. The organic layer was washed with 30 mL 10 wt% citric acid, 30 mL sat. NaHCO3, and 30 mL sat. NaCl. The organic layer was dried over Na_2SO4 and concentrated *in vacuo*. The crude product was purified on a 120 g SiO_2 column (0-80% EtOAc/hexanes).



General Procedure C: General Procedure for Coupling of Boc-Tyr(Me)-OH (5) with amines in the presence of *n*-PrOH

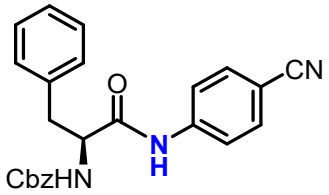
To a 40 mL vial equipped with a stir bar was added **Boc-Tyr(Me)-OH (5)** (8.2 mmol, 1 equiv), DMAc (12.5 mL), DIPEA (32.8 mmol, 4 equiv), *n*-propanol (9.9 mmol, 1.2 equiv), and amines (9.9 mmol, 1.2 equiv). To the reaction mixture was added Oxyma (1.64 mmol, 0.2 equiv). The solution was cooled to 0 ˚C in an ice bath. To the solution was added TCFH (9.9 mmol, 1.2 equiv). The reaction mixture was stirred at 0 ˚C for 30 min. The reaction was then warmed to 25 ˚C and stirred at 25 ˚C for 16 hours. Aliquot was diluted with MeCN:H2O (1:1), filtered, analyzed by HPLC to determine product ratio. The reaction mixture was transferred to a separatory funnel. To the sep funnel was added 100 mL EtOAc. The organic layer was washed with 30 mL 10 wt% citric acid, 30 mL sat. NaHCO3, and 30 mL sat. NaCl. The organic layer was dried over Na_2SO4 and concentrated *in vacuo*. The crude product was purified on a 120 g SiO_2 column (0-80% EtOAc/hexanes).



General Procedure D: General Procedure for Coupling of Boc-Tyr(Me)-OH (5) with amines in the presence of competing primary amines

To a 40 mL vial equipped with a stir bar was added, DMAc (12.5 mL), **amines (2)** (9.9 mmol, 1.2 equiv), DIPEA (41.1 mmol, 5 equiv), phenethylamine (9.9 mmol, 1.2 equiv), and benzaldehyde or 2-bromo-4-chlorobenzaldehyde (11.5 mmol, 1.4 equiv). The solution was stirred at 25 ˚C for 2 hours. To the reaction mixture was added Oxyma (1.64 mmol, 0.2 equiv) and **Boc-Tyr(Me)-OH (5)** (8.2 mmol, 1 equiv). The solution was cooled to 0 ˚C in an ice bath. To the solution was added TCFH (9.9 mmol, 1.2 equiv). The reaction mixture was stirred at 0 ˚C for 30 min. The reaction was then warmed to 25 ˚C and stirred at 25 ˚C for 16 hours. Aliquot was diluted with MeCN:H2O (1:1), filtered, analyzed by HPLC to determine product ratio. The reaction mixture was transferred to a separatory funnel. To the sep funnel was added 100 mL EtOAc. The organic layer was washed with 30 mL 10 wt% citric acid (x2), 30 mL sat. NaHCO3, and 30 mL sat. NaCl. The organic layer

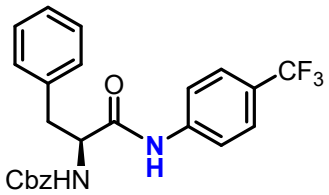
was dried over Na_2SO4 and concentrated *in vacuo*. The crude product was purified on a 120 g SiO_2 column (0-80% EtOAc/hexanes).



3a

Benzyl (S)-(1-((4-cyanophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (3a)

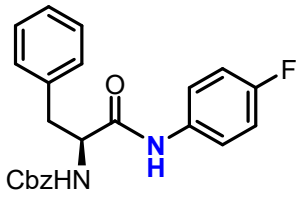
The compound was prepared using General Procedure A on 6.68 mmol scale with 87% isolated yield (2.33 g, 5.83 mmol) as a light brown solid.
Product selectivity: 15:1. (**3a**:**4**). HPLC retention time: **3a**: 6.39 min; **4**:6.82 min.
Enantiomeric excess of product: 100% (S)-**3a**: 5.32 min, (R)-**3a**: 6.92 min
^{1}H NMR (500 MHz, DMSO) δ 10.85 (s, 1H), 7.93 – 7.72 (m, 5H), 7.46 – 7.10 (m, 10H), 4.97 (s, 2H), 4.48 (td, *J* = 10.1, 4.7 Hz, 1H), 3.09 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.88 (dd, *J* = 13.4, 10.6 Hz, 1H).
^{13}C NMR (126 MHz, DMSO) δ 171.5, 156.0, 143.2, 137.6, 136.9, 133.2, 129.3, 128.3, 128.0, 127.7, 127.5, 126.4, 119.3, 119.0, 105.1, 65.4, 57.2, 37.2.
HRMS (ESI) m/z calculated for $C_{24}H_{22}N_3O_3$ [M+H]+: 400.1656; found: 400.1651.



3c

Benzyl (S)-(1-oxo-3-phenyl-1-((4-(trifluoromethyl)phenyl)amino)propan-2-yl)carbamate (3c)

The compound was prepared using General Procedure A on 6.68 mmol scale with 85% isolated yield (2.50 g, 5.65 mmol) as a light brown solid.
Product selectivity: 44:1. (**3c**:**4**). HPLC retention time: **3c**: 6.94 min; **4**:6.82 min.
Enantiomeric excess of product: 99.4% (S)-**3c**: 6.45 min, (R)-**3c**: 9.84 min
^{1}H NMR (500 MHz, DMSO) δ 10.53 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.42 – 7.06 (m, 10H), 4.98 (s, 2H), 4.46 (td, *J* = 9.8, 4.8 Hz, 1H), 3.06 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.89 (dd, *J* = 13.6, 10.3 Hz, 1H).
^{19}F NMR (471 MHz, DMSO) δ -60.35.
^{13}C NMR (126 MHz, DMSO) δ 171.2, 156.0, 142.4, 137.6, 136.9, 129.2, 128.3, 128.1, 127.7, 127.6, 126.4, 126.0 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 269.7 Hz), 123.4 (q, *J* = 32.0 Hz), 119.2, 65.4, 57.1, 37.3.
HRMS (ESI) m/z calculated for $C_{24}H_{22}F_3N_2O_3$ [M+H]+: 443.1577; found: 443.1576.



3d

Benzyl (S)-(1-((4-fluorophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (3d)

The compound was prepared using General Procedure A on 6.68 mmol scale with 83% isolated yield (2.18 g, 5.54 mmol) as a light red solid.

Product selectivity: >50:1. (**3d**:**4**). HPLC retention time: **3d**: 6.56 min; **4**:6.82 min.

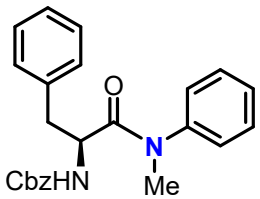
Enantiomeric excess of product: >99.9% (S)-**3d**: 4.34 min, (R)-**3d**: 3.83 min

^{1}H NMR (500 MHz, DMSO) δ 10.17 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.62 (dd, *J* = 8.9, 5.0 Hz, 2H), 7.38 – 7.25 (m, 9H), 7.24 – 7.12 (m, 4H), 4.98 (s, 2H), 4.42 (td, *J* = 9.7, 4.9 Hz, 1H), 3.04 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.87 (dd, *J* = 13.6, 10.2 Hz, 1H).

^{19}F NMR (471 MHz, DMSO) δ -119.18.

^{13}C NMR (126 MHz, DMSO) δ 170.4, 158.06 (d, *J* = 239.9 Hz), 156.0, 137.8, 136.9, 135.2, 135.2, 129.2, 128.3, 128.1, 127.7, 127.5, 126.4, 121.09 (d, *J* = 7.8 Hz), 115.27 (d, *J* = 22.2 Hz), 65.3, 56.9, 37.5.

HRMS (ESI) m/z calculated for $C_{23}H_{22}FN_2O_3$ [M+H]+: 393.1609; found: 393.1608.



3e

Benzyl (S)-(1-(methyl(phenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (3e)

The compound was prepared using General Procedure B on 8.35 mmol scale with 92% isolated yield (2.98 g, 7.67 mmol) as a light orange oil.

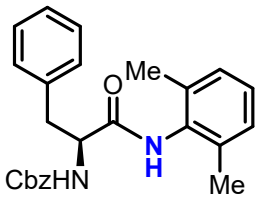
Product selectivity: >50:1. (**3e**:**4**). HPLC retention time: **3e**: 6.61 min; **4**: 6.85 min.

Enantiomeric excess of product: 100% (S)-**3e**: 7.17 min, (R)-**3e**: 7.68 min

^{1}H NMR (500 MHz, CD_3OD) δ 7.44 – 7.11 (m, 12H), 7.06 – 6.75 (m, 4H), 4.99 (s, 2H), 4.83 (s, 1H), 4.45 (t, *J* = 7.3 Hz, 1H), 3.18 (s, 3H), 2.92 (dd, *J* = 13.3, 6.8 Hz, 1H), 2.69 (dd, *J* = 13.3, 8.1 Hz, 1H).

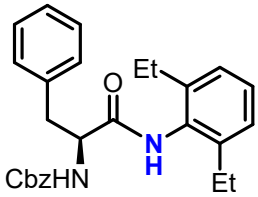
^{13}C NMR (126 MHz, CD_3OD) δ 173.7, 157.9, 144.0, 138.2, 138.1, 130.8, 130.2, 129.4, 129.3, 128.9, 128.7, 127.8, 67.5, 54.8, 39.4, 38.1.

HRMS (ESI) m/z calculated for $C_{24}H_{25}N_2O_3$ [M+H]+: 389.1860; found: 389.1858.



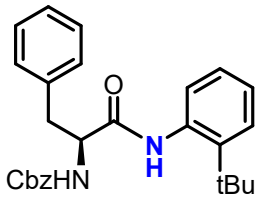
3f

Benzyl (S)-(1-((2,6-dimethylphenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (3f)
The compound was prepared using General Procedure A on 8.35 mmol scale with 90% isolated yield (3.03 g, 7.53 mmol) as a light yellow solid.
Product selectivity: >50:1. (**3f**:**4**). HPLC retention time: **3f**: 6.56 min; **4**: 6.85 min.
Enantiomeric excess of product: 99.9% (S)-**3f**: 8.42 min, (R)-**3f**: 7.14 min
^{1}H NMR (500 MHz, DMSO) δ 9.47 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.44 – 7.20 (m, 10H), 7.11 – 7.02 (m, 3H), 5.04 (d, *J* = 12.7 Hz, 1H), 4.97 (d, *J* = 12.7 Hz, 1H), 4.51 (td, *J* = 9.8, 5.1 Hz, 1H), 3.14 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.93 (dd, *J* = 13.5, 10.3 Hz, 1H), 2.07 (s, 6H).
^{13}C NMR (126 MHz, DMSO) δ 170.1, 156.0, 138.0, 137.1, 135.3, 134.8, 129.3, 128.2, 128.1, 127.7, 127.6, 127.5, 126.4, 126.3, 65.2, 56.5, 37.5, 17.9.
HRMS (ESI) m/z calculated for $C_{25}H_{27}N_2O_3$ [M+H]+: 403.2016; found: 403.2015.



3g

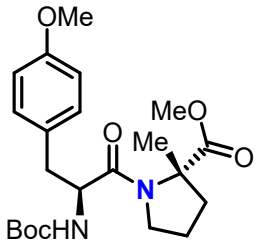
Benzyl (S)-(1-((2,6-diethylphenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (3g)
The compound was prepared using General Procedure A on 6.68 mmol scale with 80% isolated yield (2.31 g, 5.34 mmol) as a light yellow solid.
Product selectivity: 8.4:1. (**3g**:**4**). HPLC retention time: **3g**: 6.92 min; **4**: 6.84 min.
Enantiomeric excess of product: >99.9% (S)-**3g**: 5.08 min, (R)-**3g**: 4.87 min
^{1}H NMR (500 MHz, DMSO) δ 9.44 (s, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.37 – 7.22 (m, 8H), 7.20 – 7.14 (m, 1H), 7.08 (d, *J* = 7.6 Hz, 2H), 5.05 (d, *J* = 12.8 Hz, 1H), 4.96 (d, *J* = 12.8 Hz, 1H), 4.53 (td, *J* = 10.0, 4.9 Hz, 1H), 3.13 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.92 (dd, *J* = 13.5, 10.4 Hz, 1H), 2.47 – 2.33 (m, 4H), 1.05 (t, *J* = 7.5 Hz, 6H).
^{13}C NMR (126 MHz, DMSO) δ 171.0, 156.0, 141.6, 138.0, 137.1, 133.6, 129.2, 128.2, 128.1, 127.6, 127.4, 127.1, 126.3, 125.9, 65.2, 56.4, 37.3, 24.2, 14.6.
HRMS (ESI) m/z calculated for $C_{27}H_{31}N_2O_3$ [M+H]+: 431.2329; found: 431.2329.



3h

Benzyl (S)-(1-((2-(tert-butyl)phenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (3h)
The compound was prepared using General Procedure A on 6.68 mmol scale with 82% isolated yield (2.35 g, 5.46 mmol) as a light yellow solid.
Product selectivity: 8.6:1. (**3h**:**4**). HPLC retention time: **3h**: 6.98 min; **4**: 6.84 min.
Enantiomeric excess of product: >99.9% (S)-**3h**: 3.34 min, (R)-**3h**: 3.20 min
^{1}H NMR (500 MHz, DMSO) δ 9.31 (s, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.47 – 7.11 (m, 13H), 7.06 – 6.88 (m, 1H), 5.03 (d, *J* = 12.7 Hz, 1H), 4.97 (d, *J* = 12.7 Hz, 1H), 4.54 (td, *J* = 10.4, 4.5 Hz, 1H), 3.17 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.90 (dd, *J* = 13.5, 10.7 Hz, 1H), 1.29 (s, 9H).

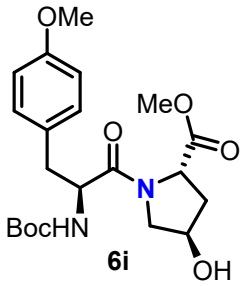
^{13}C NMR (126 MHz, DMSO) δ 171.2, 156.0, 146.0, 138.0, 137.0, 135.7, 130.8, 129.3, 128.2, 128.1, 127.7, 127.5, 126.7, 126.5, 126.3, 65.3, 56.6, 37.0, 34.5, 30.6.
HRMS (ESI) m/z calculated for $C_{27}H_{31}N_2O_3$ [M+H]+: 431.2329; found: 431.2331.



6b

Methyl (S)-1-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-2-methylpyrrolidine-2-carboxylate (6b)

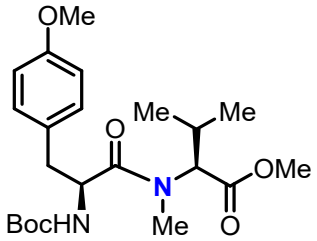
The compound was prepared using General Procedure C on 8.2 mmol scale with 97% isolated yield (3.34 g, 7.94 mmol) as an orange oil.
Product selectivity: >50:1. (**6b**:**7**). HPLC retention time: **6b**: 6.23 min; **7**: 6.77 min.
d.r. of product: >99:1 (S,S)-**6b**: 14.30 min, (R,S)-**6b**: 14.40 min
^{1}H NMR (500 MHz, CD_3OD) δ 7.18 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.47 (m, 0.5H, partially H/D exchange at NH), 4.50 – 4.34 (m, 1H), 3.89 – 3.80 (m, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 3.38 (m, 1H), 2.94 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.69 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.13 – 1.83 (m, 4H), 1.51 (s, 3H), 1.37 (s, 9H).
^{13}C NMR (126 MHz, CD_3OD) δ 175.6, 172.2, 160.0, 157.5, 131.6, 130.3, 114.8, 80.5, 67.6, 55.7, 55.5, 52.7, 39.3, 37.7, 28.6, 24.9, 21.4.
HRMS (ESI) m/z calculated for $C_{22}H_{33}N_2O_6$ [M+H]+: 421.2333; found: 421.2333.



6i

Methyl (2S,4R)-1-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-4-hydroxypyrrolidine-2-carboxylate (6i)

The compound was prepared using General Procedure C on 8.2 mmol scale with 91% isolated yield (3.15 g, 7.46 mmol) as a yellow oil.
Product selectivity: >50:1. (**6i**:**7**). HPLC retention time: **6i**: 5.31 min; **7**: 6.77 min.
d.r. of product: >99:1 (S,S)-**6i**: 5.31 min, (R,S)-**6i**: 5.25 min
^{1}H NMR (500 MHz, CD_3OD) δ 7.29 – 7.08 (m, 2H), 6.93 – 6.64 (m, 2H), 4.60 – 4.30 (m, 3H), 3.76 (s, 3H), 3.74 – 3.56 (m, 4H), 3.51 – 3.34 (m, 1H), 3.00 – 2.85 (m, 1H), 2.84 – 2.71 (m, 1H), 2.28 – 2.09 (m, 1H), 2.05 – 1.90 (m, 1H), 1.38 (s, 9H).
^{13}C NMR (126 MHz, CD_3OD) δ 173.9, 173.2, 160.1, 157.5, 131.7, 130.1, 114.8, 80.6, 70.9, 59.5, 56.1, 55.7, 55.3, 52.7, 38.3, 38.2, 28.7.
HRMS (ESI) m/z calculated for $C_{21}H_{31}N_2O_7$ [M+H]+: 423.2126; found: 423.2122.



6j

Methyl N-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-N-methyl-L-valinate (6j)

The compound was prepared using General Procedure C on 8.2 mmol scale with 84% isolated yield (2.90 g, 6.86 mmol) as a light orange solid.

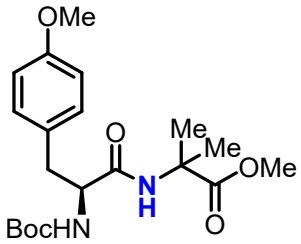
Product selectivity: 20:1. (**6j**:**7**). HPLC retention time: **6j**: 6.64 min; **7**: 6.74 min.

d.r. of product: >99:1 (S,S)-**6j**: 6.64 min, (R,S)-**6j**: 6.60 min

^{1}H NMR (500 MHz, CD_3OD) δ 7.12 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.76 (d, *J* = 10.7 Hz, 1H), 4.70 (t, *J* = 7.6 Hz, 1H), 3.76 (s, 3H), 3.70 – 3.63 (m, 3H), 2.97 – 2.73 (m, 5H), 2.23 – 2.06 (m, 1H), 1.38 (d, *J* = 5.2 Hz, 9H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.84 – 0.60 (m, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 175.5, 172.0, 160.1, 157.5, 131.5, 129.8, 114.9, 80.5, 63.2, 55.7, 53.6, 52.3, 38.4, 31.7, 28.6, 28.4, 20.0, 18.9.

HRMS (ESI) m/z calculated for $C_{22}H_{35}N_2O_6$ [M+H]+: 423.2126; found: 423.2122.



6k

Methyl (S)-2-(2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanamido)-2-methylpropanoate (6k)

The compound was prepared using General Procedure C on 8.2 mmol scale with 94% isolated yield (3.06 g, 7.76 mmol) as a light yellow solid.

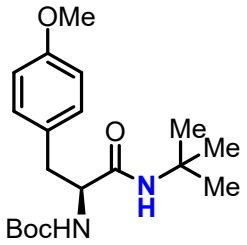
Product selectivity: >50:1. (**6k**:**7**). HPLC retention time: **6k**: 5.90 min; **7**: 6.74 min.

Enantiomeric excess of product: >99.9% (S)-**6k**: 3.26 min, (R)-**6k**: 3.14 min

^{1}H NMR (500 MHz, DMSO) δ 8.29 – 8.17 (m, 1H), 7.27 – 7.10 (m, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.72 – 6.20 (m, 1H), 4.19 – 3.91 (m, 1H), 3.71 (s, 3H), 3.55 (s, 3H), 2.84 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.64 (dd, *J* = 13.6, 9.9 Hz, 1H), 1.46 – 1.22 (m, 15H).

^{13}C NMR (126 MHz, DMSO) δ 174.3, 171.1, 157.8, 155.1, 130.2, 129.8, 113.4, 77.9, 55.5, 54.9, 54.9, 51.7, 36.7, 28.1, 24.8.

HRMS (ESI) m/z calculated for $C_{20}H_{31}N_2O_6$ [M+H]+: 395.2177; found: 395.2175.



6l

tert-Butyl (S)-(1-(tert-butylamino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)carbamate (6l)

The compound was prepared using General Procedure C on 8.2 mmol scale with 97% isolated yield (2.8 g, 7.99 mmol) as a light yellow solid.

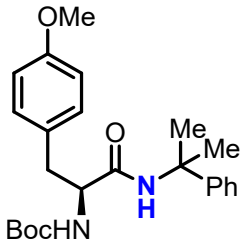
Product selectivity: >50:1. (**6l**:**7**). HPLC retention time: **6l**: 6.28 min; **7**: 6.74 min.

Enantiomeric excess of product: 97.1% (S)-**6l**: 3.11 min, (R)-**6l**: 3.33 min

^{1}H NMR (500 MHz, DMSO) δ 7.42 – 7.28 (m, 1H), 7.22 – 7.09 (m, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.67 – 6.15 (m, 1H), 4.13 – 3.87 (m, 1H), 3.70 (s, 3H), 2.85 – 2.72 (m, 1H), 2.70 – 2.56 (m, 1H), 1.31 (s, 9H), 1.22 (s, 9H).

^{13}C NMR (126 MHz, DMSO) δ 170.8, 157.7, 155.0, 130.2, 129.9, 113.3, 77.9, 56.1, 54.9, 50.0, 37.1, 28.4, 28.1.

HRMS (ESI) m/z calculated for $C_{19}H_{31}N_2O_4$ [M+H]+: 351.2279; found: 351.2275.



6m

tert-Butyl (S)-(3-(4-methoxyphenyl)-1-oxo-1-((2-phenylpropan-2-yl)amino)propan-2-yl)carbamate (6m)

The compound was prepared using General Procedure C on 8.2 mmol scale with 92% isolated yield (3.1 g, 7.51 mmol) as a light yellow solid.

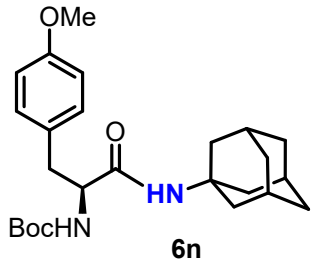
Product selectivity: >50:1. (**6m**:**7**). HPLC retention time: **6m**: 6.66 min; **7**: 6.74 min.

Enantiomeric excess of product: 99.6% (S)-**6m**: 5.14 min, (R)-**6m**: 4.83 min

^{1}H NMR (500 MHz, DMSO) δ 7.96 (s, 1H), 7.34 – 7.11 (m, 7H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.81 – 6.24 (m, 1H), 4.24 – 4.02 (m, 1H), 3.72 (s, 3H), 2.85 (dd, *J* = 13.6, 5.3 Hz, 1H), 2.74 – 2.58 (m, 1H), 1.51 (d, *J* = 28.7 Hz, 6H), 1.35 (s, 9H).

^{13}C NMR (126 MHz, DMSO) δ 170.7, 157.8, 155.3, 147.5, 130.3, 129.9, 127.7, 125.7, 124.7, 113.4, 77.9, 56.2, 54.9, 54.9, 36.5, 30.1, 28.7, 28.1.

HRMS (ESI) m/z calculated for $C_{24}H_{33}N_2O_4$ [M+H]+: 413.2435; found: 413.2434.



6n

tert-Butyl ((S)-1-(((3R,5R,7R)-adamantan-1-yl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)carbamate (6n)

The compound was prepared using General Procedure C on 8.2 mmol scale with 88% isolated yield (3.08 g, 7.19 mmol) as a light yellow solid.

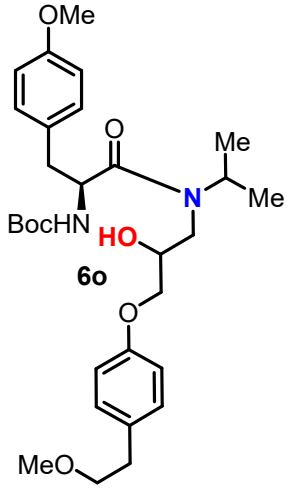
Product selectivity: >50:1. (**6n**:**7**). HPLC retention time: **6n**: 7.24 min; **7**: 6.74 min.

Enantiomeric excess of product: 96.7% (S)-**6n**: 8.57 min, (R)-**6n**: 7.75 min

^{1}H NMR (500 MHz, DMSO) δ 7.27 – 7.09 (m, 3H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.67 – 6.11 (m, 1H), 4.14 – 3.86 (m, 1H), 3.70 (s, 3H), 2.80 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.64 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.00 (s, 3H), 1.89 (s, 6H), 1.61 (s, 6H), 1.31 (s, 9H).

^{13}C NMR (126 MHz, DMSO) δ 170.6, 157.7, 155.0, 130.2, 129.9, 113.3, 77.9, 56.1, 54.9, 50.7, 40.9, 37.1, 36.0, 28.8, 28.1.

HRMS (ESI) m/z calculated for $C_{25}H_{37}N_2O_4$ [M+H]+: 429.2748; found: 429.2746.



6o

tert-Butyl ((2S)-1-((2-hydroxy-3-(4-(2-methoxyethyl)phenoxy)propyl)(isopropyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)carbamate (6o)

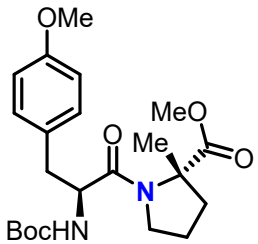
The compound was prepared using General Procedure C on 8.2 mmol scale with 74% isolated yield (3.31 g, 6.07 mmol) as an orange oil. The product is a mixture of diastereomers because the amine nucleophile is a racemic mixture (6.82 min and 6.89 min on achiral LC)

Enantiomeric ratio of product: (S,R)+(S,S)-**6o**: 96.2% (6.80 min and 7.29 min), (R,R)+(R,S)-**6o**: 3.8% (7.68 min and 9.17 min)

^{1}H NMR (500 MHz, MeOD) the product exists as a mixture of diastereomers and rotamers δ 7.21 – 7.07 (m, 4H), 6.94 – 6.72 (m, 4H), 4.95 – 4.84 (m, 1H), 4.39 – 3.98 (m, 2H), 4.00 – 3.78 (m, 2H), 3.78 – 3.45 (m, 6H), 3.43 – 3.33 (m, 1H), 3.28 – 3.15 (m, 1H), 3.06 – 2.66 (m, 4H), 1.53 – 1.30 (m, 9H), 1.29 – 0.70 (m, 6H).

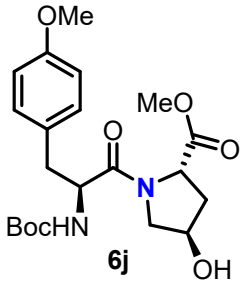
^{13}C NMR (126 MHz, MeOD) the product exists as a mixture of diastereomers and rotamers δ 175.6, 175.3, 175.2, 174.8, 160.2, 160.1, 160.1, 159.9, 158.7, 158.6, 158.5, 157.7, 157.4, 157.3,

132.8, 132.5, 131.6, 131.6, 131.5, 130.8, 130.0, 129.9, 115.6, 115.5, 115.5, 115.0, 115.0, 114.9, 114.7, 80.7, 80.6, 80.3, 74.9, 71.7, 71.4, 71.0, 70.8, 70.6, 70.6, 70.5, 58.7, 55.7, 55.6, 54.3, 54.2, 53.4, 53.3, 50.5, 50.4, 46.1, 46.0, 39.4, 39.2, 39.2, 38.9, 36.1, 28.7, 21.5, 21.4, 21.3, 20.8, 20.5, 20.4, 20.3, 20.2.
HRMS (ESI) m/z calculated for $C_{30}H_{45}N_2O_7$ [M+H]+: 545.3222; found: 545.3221.



6b

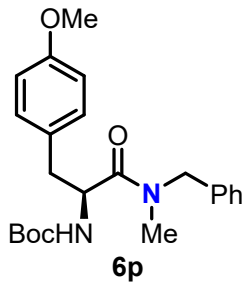
Methyl (S)-1-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-2-methylpyrrolidine-2-carboxylate (6b)
The compound was prepared using General Procedure D (using 2-bromo-4-chlorobenzaldehyde) on 8.2 mmol scale with 90% isolated yield (3.11 g, 7.39 mmol) as an orange oil.
Product selectivity: 22:1. (**6b**:**8**). HPLC retention time: **6b**: 11.16 min; **8**: 11.63 min.
d.r. of product: >99:1 (S,S)-**6b**: 14.30 min, (R,S)-**6b**: 14.40 min
^{1}H NMR (500 MHz, CD_3OD) δ 7.18 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.47 (m, 0.5H, partially H/D exchange at NH), 4.50 – 4.34 (m, 1H), 3.89 – 3.80 (m, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 3.38 (m, 1H), 2.94 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.69 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.13 – 1.83 (m, 4H), 1.51 (s, 3H), 1.37 (s, 9H).
^{13}C NMR (126 MHz, CD_3OD) δ 175.6, 172.2, 160.0, 157.5, 131.6, 130.3, 114.8, 80.5, 67.6, 55.7, 55.5, 52.7, 39.3, 37.7, 28.6, 24.9, 21.4.
HRMS (ESI) m/z calculated for $C_{22}H_{33}N_2O_6$ [M+H]+: 421.2333; found: 421.2333.



6j

Methyl (2S,4R)-1-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-4-hydroxypyrrolidine-2-carboxylate (6j)
The compound was prepared using General Procedure D (using 2-bromo-4-chlorobenzaldehyde) on 8.2 mmol scale with 92% isolated yield (3.19 g, 7.55 mmol) as a clear oil.
Product selectivity: 33:1. (**6j**:**8**). HPLC retention time: **6j**: 5.32 min; **8**: 6.37 min.
d.r. of product: >99:1 (S,S)-**6j**: 5.32 min, (R,S)-**6j**: 5.26 min
^{1}H NMR (500 MHz, CD_3OD) δ 7.29 – 7.08 (m, 2H), 6.93 – 6.64 (m, 2H), 4.60 – 4.30 (m, 3H), 3.76 (s, 3H), 3.74 – 3.56 (m, 4H), 3.51 – 3.34 (m, 1H), 3.00 – 2.85 (m, 1H), 2.84 – 2.71 (m, 1H), 2.28 – 2.09 (m, 1H), 2.05 – 1.90 (m, 1H), 1.38 (s, 9H).

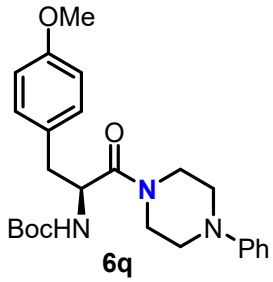
^{13}C NMR (126 MHz, CD_3OD) δ 173.9, 173.2, 160.1, 157.5, 131.7, 130.1, 114.8, 80.6, 70.9, 59.5, 56.1, 55.7, 55.3, 52.7, 38.3, 38.2, 28.7.
HRMS (ESI) m/z calculated for $C_{21}H_{31}N_2O_7$ [M+H]+: 423.2126; found: 423.2122.



6p

tert-Butyl (S)-(1-(benzyl(methyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)carbamate (6p)

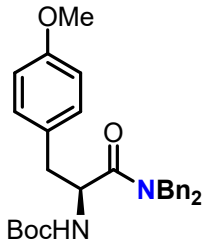
The compound was prepared using General Procedure D (using benzaldehyde) on 8.2 mmol scale with 94% isolated yield (3.07 g, 7.71 mmol) as a yellow oil.
Product selectivity: >50:1. (**6p**:**8**). HPLC retention time: **6p**: 6.77 min; **8**: 6.37 min.
Enantiomeric excess of product: >99.9% (S)-**6p**: 4.10 min, (R)-**6p**: 3.93 min
^{1}H NMR (500 MHz, CD_3OD, the product exists as 2.3:1 rotamer) δ 7.25 (q, *J* = 8.5 Hz, 3H), 7.17 – 6.99 (m, 4H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.77 (t, *J* = 7.5 Hz, 1H), 4.54 (t, *J* = 13.0 Hz, 1H), 4.50 – 4.39 (m, 1H), 3.75 (d, *J* = 3.4 Hz, 3H), 2.96 – 2.83 (m, 2H), 2.80 (d, *J* = 20.5 Hz, 3H), 1.39 (d, *J* = 33.7 Hz, 9H).
^{13}C NMR (126 MHz, CD_3OD, the product exists as 2.3:1 rotamer) δ 174.4, 160.1, 157.6, 137.9, 137.8, 131.5, 130.3, 129.9, 129.8, 129.5, 128.9, 128.6, 128.3, 128.0, 114.9, 80.6, 55.6, 54.1, 53.4, 53.3, 52.2, 39.1, 38.7, 35.3, 34.4, 28.7, 28.6.
HRMS (ESI) m/z calculated for $C_{23}H_{31}N_2O_4$ [M+H]+: 399.2279; found: 399.2276.



6q

tert-Butyl (S)-(3-(4-methoxyphenyl)-1-oxo-1-(4-phenylpiperazin-1-yl)propan-2-yl)carbamate (6q)

The compound was prepared using General Procedure D (using benzaldehyde) on 8.2 mmol scale with 93% isolated yield (3.66 g, 7.66 mmol) as a yellow oil.
Product selectivity: 38:1. (**6q**:**8**). HPLC retention time: **6q**: 6.59 min; **8**: 6.37 min.
Enantiomeric excess of product: >99.9% (S)-**6q**: 2.91 min, (R)-**6q**: 3.61 min
^{1}H NMR (500 MHz, CD_3OD) δ 7.25 – 7.08 (m, 4H), 6.84 (dd, *J* = 22.1, 8.4 Hz, 5H), 4.76 (t, *J* = 7.5 Hz, 1H), 3.91 – 3.74 (m, 1H), 3.64 (s, 3H), 3.59 – 3.36 (m, 3H), 3.17 – 3.05 (m, 1H), 3.05 – 2.76 (m, 4H), 2.38 – 2.18 (m, 1H), 1.41 (s, 9H).
13C NMR (126 MHz, CD_3OD) δ 172.4, 160.2, 157.4, 152.5, 131.7, 130.1, 129.9, 121.6, 117.9, 115.1, 80.6, 55.6, 52.7, 50.5, 50.4, 46.7, 43.2, 39.2, 28.7.
HRMS (ESI) m/z calculated for $C_{25}H_{34}N_3O_4$ [M+H]+: 440.2544; found: 440.2544.



6r

tert-Butyl (S)-(1-(dibenzylamino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)carbamate (6r)

The compound was prepared using General Procedure D (using benzaldehyde) on 8.2 mmol scale with 90% isolated yield (3.50 g, 7.38 mmol) as a light yellow solid.

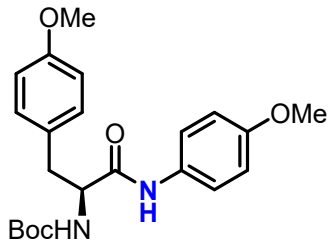
Product selectivity: 20:1. (**6r**:**8**). HPLC retention time: **6r**: 7.37 min; **8**: 6.37 min.

Enantiomeric excess of product: >99.9% (S)-**6r**: 4.96 min, (R)-**6r**: 4.76 min

^{1}H NMR (500 MHz, DMSO) δ 7.42 – 7.19 (m, 7H), 7.17 – 7.06 (m, 4H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 4.79 (d, *J* = 17.0 Hz, 1H), 4.68 (d, *J* = 15.2 Hz, 1H), 4.51 (q, *J* = 7.9 Hz, 1H), 4.43 (d, *J* = 17.1 Hz, 1H), 4.31 (d, *J* = 15.3 Hz, 1H), 3.70 (s, 3H), 2.82 – 2.67 (m, 2H), 1.46 – 0.97 (m, 9H).

13C NMR (126 MHz, DMSO) δ 172.6, 157.8, 155.5, 137.3, 137.2, 130.3, 129.6, 128.6, 128.2, 127.3, 127.2, 126.9, 126.7, 113.5, 78.2, 54.9, 52.2, 49.9, 48.3, 36.4, 28.1.

HRMS (ESI) m/z calculated for $C_{29}H_{35}N_2O_4$ [M+H]+: 475.2592; found: 475.2592.



6s

tert-Butyl (S)-(3-(4-methoxyphenyl)-1-((4-methoxyphenyl)amino)-1-oxopropan-2-yl)carbamate (6s)

The compound was prepared using General Procedure D (using 2-bromo-4-chlorobenzaldehyde) on 8.2 mmol scale with 71% isolated yield (2.32 g, 5.79 mmol) as a light pink solid.

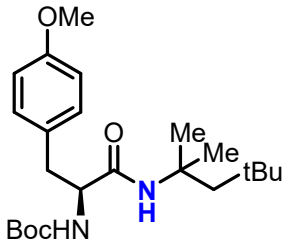
Product selectivity: 6.8:1. (**6s**:**8**). HPLC retention time: **6s**: 11.25 min; **8**: 11.62 min.

Enantiomeric excess of product: 99.2% (S)-**6s**: 3.04 min, (R)-**6s**: 2.86 min

^{1}H NMR (500 MHz, DMSO) δ 9.84 (s, 1H), 7.49 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 4.36 – 4.01 (m, 1H), 3.71 (d, *J* = 5.3 Hz, 6H), 2.92 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.83 – 2.71 (m, 1H), 1.33 (s, 9H).

^{13}C NMR (126 MHz, DMSO) δ 170.3, 157.8, 155.3, 155.2, 132.1, 130.2, 129.8, 120.8, 113.8, 113.5, 78.0, 56.7, 55.1, 54.9, 36.8, 28.1.

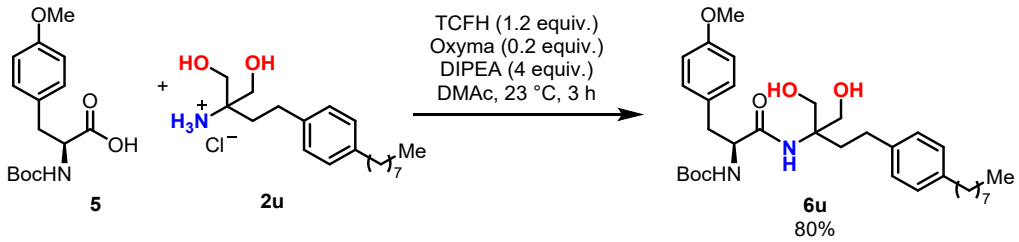
HRMS (ESI) m/z calculated for $C_{22}H_{28}N_2O_5Na$ [M+Na]+: 423.1896; found: 423.1890.



6t

tert-Butyl (S)-(3-(4-methoxyphenyl)-1-oxo-1-((2,4,4-trimethylpentan-2-yl)amino)propan-2-yl)carbamate (6t)

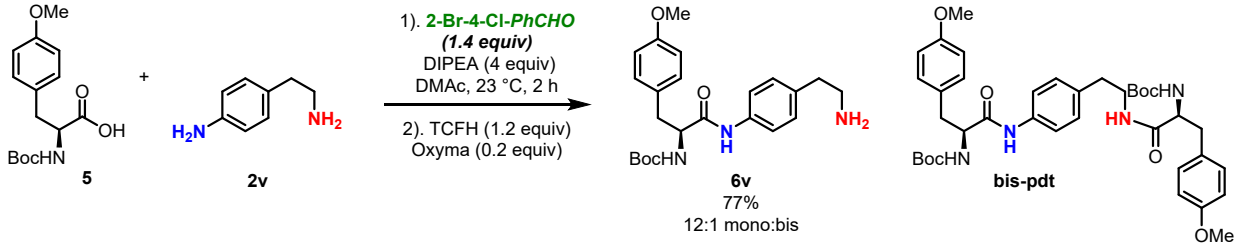
The compound was prepared using General Procedure D (using 2-bromo-4-chlorobenzaldehyde) on 8.2 mmol scale with 81% isolated yield (2.69 g, 6.62 mmol) as a light yellow solid.
Product selectivity: 6.3:1. (**6t**:**8**). HPLC retention time: **6t**: 7.23 min; **8**: 6.37 min.
Enantiomeric excess of product: 99.5% (S)-**6t**: 6.43 min, (R)-**6t**: 6.13 min
^{1}H NMR (500 MHz, DMSO) δ 7.25 – 7.08 (m, 3H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 1H), 4.12 – 3.92 (m, 1H), 3.70 (s, 3H), 2.82 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.63 (dd, *J* = 13.5, 10.1 Hz, 1H), 1.77 (d, *J* = 14.6 Hz, 1H), 1.58 (d, *J* = 14.6 Hz, 1H), 1.40 – 1.17 (m, 15H), 0.93 (s, 9H).
^{13}C NMR (126 MHz, DMSO) δ 170.6, 157.7, 155.1, 130.2, 130.0, 113.4, 77.9, 56.4, 54.9, 53.9, 50.3, 36.7, 31.2, 29.2, 28.7, 28.1.
HRMS (ESI) m/z calculated for $C_{23}H_{39}N_2O_4$ [M+H]+: 407.2905; found: 407.2902.



5 **2u** **6u**
80%

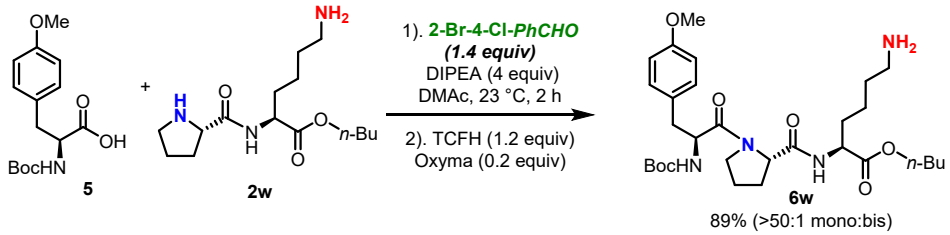
To a 40 mL vial equipped with a stir bar was added **Boc-Tyr(Me)-OH (5)** (1.25 g, 4.11 mmol, 1 equiv), DMAc (6.25 mL), DIPEA (2.87 mL, 16.4 mmol, 4 equiv), and fingolimod hydrochloride (1.59 g, 4.52 mmol, 1.1 equiv). To the reaction mixture was added Oxyma (0.117 g, 0.82 mmol, 0.2 equiv). The solution was cooled to 0 ˚C in an ice bath. To the solution was added TCFH (1.38 g, 4.93 mmol, 1.2 equiv). The reaction mixture was stirred at 0 ˚C for 30 min. The reaction was then warmed to 25 ˚C and stirred at 25 ˚C for 16 hours. Aliquot was diluted with MeCN:H2O (1:1), filtered, analyzed by HPLC to determine product ratio. The reaction mixture was transferred to a separatory funnel. To the sep funnel was added 100 mL EtOAc. The organic layer was washed with 30 mL 10 wt% citric acid, 30 mL sat. $NaHCO_3$, and 30 mL sat. NaCl. The organic layer was dried over Na_2SO4 and concentrated *in vacuo*. The crude product was purified on a 120 g SiO_2 column (0-80% EtOAc/hexanes) to afford a yellow oil with 80% isolated yield (1.93 g, 3.30 mmol).
Product selectivity: 23:1. (**6u**:**bis-pdt**). HPLC retention time: **6u**: 8.29 min; **bis-pdt**: 9.26 min.
^{1}H NMR (500 MHz, CD_3OD) δ 7.17 (d, *J* = 8.5 Hz, 2H), 7.11 – 6.99 (m, 4H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.23 (dd, *J* = 8.2, 6.9 Hz, 1H), 3.75 (d, *J* = 11.3 Hz, 1H), 3.72 – 3.65 (m, 4H), 3.60 (dd, *J* = 17.4, 11.3 Hz, 2H), 3.00 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.81 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.40 (dd, *J* = 10.5, 5.8 Hz, 2H), 1.92 (dd, *J* = 10.5, 6.3 Hz, 2H), 1.63 – 1.52 (m, 2H), 1.38 (s, 9H), 1.34 – 1.21 (m, 10H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 174.7, 160.0, 157.8, 141.2, 140.9, 131.4, 130.4, 129.3, 114.9, 80.8, 64.2, 64.1, 62.4, 58.3, 55.6, 38.2, 36.5, 34.5, 33.0, 32.8, 30.6, 30.4, 30.3, 29.9, 28.7, 23.7, 14.4.
HRMS (ESI) m/z calculated for $C_{34}H_{53}N_2O_6$ [M+H]+: 585.3898; found: 585.3900.



(S)-2-(4-(2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanamido)phenyl)ethan-1-aminium formate (6v)

To a 40 mL vial equipped with a stir bar was added, DMAc (10 mL), 2-(4-aminophenyl)ethylamine (1.04 mL, 7.88 mmol, 1.2 equiv), DIPEA (4.59 mL, 26.3 mmol, 4 equiv), and 2-bromo-4-chlorobenzaldehyde (2.02 g, 9.20 mmol, 1.4 equiv). The solution was stirred at 25 ˚C for 2 hours. To the reaction mixture was added Oxyma (0.187 g, 1.31 mmol, 0.2 equiv) and **Boc-Tyr(Me)-OH (5)** (2.0 g, 6.57 mmol, 1 equiv). The solution was cooled to 0 ˚C in an ice bath. To the solution was added TCFH (2.21 g, 7.88 mmol, 1.2 equiv). The reaction mixture was stirred at 0 ˚C for 10 min. The reaction was then warmed to 25 ˚C and stirred at 25 ˚C for 16 hours. Aliquot was diluted with MeCN:H2O (1:1), filtered, analyzed by HPLC to determine product ratio. The resulting slurry was slowly added to 120 mL water to precipitate out all the product. The solid was collected via filtration (no loss to liquor). The solid was transferred to a 250 mL flask. To the flask was added 120 mL 2-MeTHF and 30 mL 15 wt% NaHSO4 until a clear biphasic mixture was obtained. The aqueous layer was removed and was back-extracted with 30 mL 2-MeTHF. The two MeTHF layers were combined and dried over Na_2SO4. The crude product was purified on 80 g C18 column (100% H_2O w/ 0.1% formic acid to 50% H_2O w/ 0.1% formic acid/MeCN) to afford a white solid with 77% isolated yield (2.10 g, 5.08 mmol) as a white solid.
Product selectivity: 12:1. (**6v**:**bis-pdt**). HPLC retention time: **6v**: 4.64 min; **bis-pdt**: 6.75 min.
^{1}H NMR (500 MHz, DMSO) δ 10.11 (s, 1H), 8.46 (br, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 8.4 Hz, 2H), 4.39 – 4.06 (m, 1H), 3.69 (s, 3H), 3.19 – 2.71 (m, 6H), 1.30 (s, 9H).
^{13}C NMR (126 MHz, DMSO) δ 170.7, 165.7, 157.8, 155.4, 137.5, 132.7, 130.3, 129.8, 128.8, 119.5, 113.4, 78.0, 56.8, 54.9, 40.4, 36.6, 32.8, 28.1.
HRMS (ESI) m/z calculated for $C_{23}H_{32}N_3O_4$ [M+H]+: 414.2388; found: 414.2384.



Butyl ((S)-2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-prolyl-L-lysinate formate (6w)

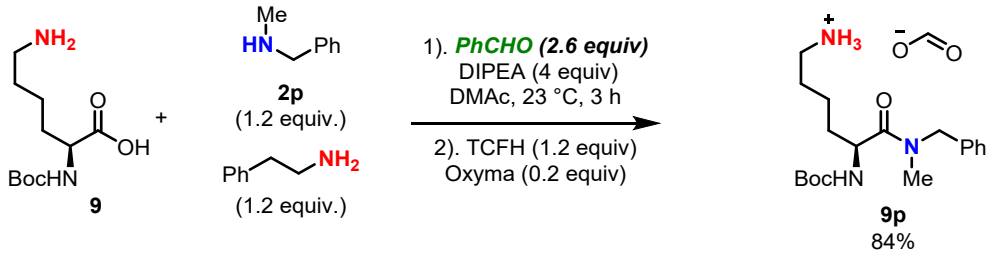
To a 40 mL vial equipped with a stir bar was added, DMAc (3.85 mL), **2w** (0.747 g, 1.99 mmol, 1.1 equiv), DIPEA (1.58 mL, 9.03 mmol, 5 equiv), and 2-bromo-4-chlorobenzaldehyde (0.56 g, 2.53 mmol, 1.4 equiv). The solution was stirred at 25 ˚C for 2 hours. To the reaction mixture was added Oxyma (0.051 g, 0.36 mmol, 0.2 equiv) and **Boc-Tyr(Me)-OH (5)** (0.55 g, 1.81 mmol, 1 equiv). The solution was cooled to 0 ˚C in an ice bath. To the solution was added TCFH (0.608 g, 2.17 mmol, 1.2 equiv). The reaction mixture was stirred at 0 ˚C for 10 min. The reaction was then warmed to 25 ˚C and stirred at 25 ˚C for 2 hours. Aliquot was diluted with MeCN:H2O (1:1), filtered, analyzed by HPLC to determine product ratio. The crude reaction mixture was directly loaded to a reverse phase column and purified on 80 g C18 column (100% H_2O w/ 0.1% formic acid to 50% H_2O w/ 0.1% formic acid/MeCN) to afford a white solid with 89% isolated yield (0.98 g, 1.61 mmol) as a white solid.

Product selectivity: >50:1. (**6v**:**bis-pdt**). HPLC retention time: **6v**: 5.05 min; **bis-pdt**: 7.12 min.

^{1}H NMR (500 MHz, CD_3OD) the product exists as 4:1 rotamer δ 8.51 (s, 1H), 7.27 – 7.10 (m, 2H), 6.99 – 6.76 (m, 2H), 4.54 – 4.25 (m, 3H), 4.22 – 3.99 (m, 2H), 3.84 – 3.66 (m, 4H), 3.59 – 3.38 (m, 1H), 3.07 – 2.81 (m, 3H), 2.73 (dd, J = 14.1, 9.0 Hz, 1H), 2.29 – 2.16 (m, 1H), 2.10 – 1.91 (m, 4H), 1.78 – 1.47 (m, 7H), 1.46 – 1.27 (m, 11H), 0.95 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, CD_3OD) only the major rotamer peaks are shown δ 174.4, 173.4, 173.1, 169.8, 160.0, 157.6, 131.5, 130.3, 115.3, 114.9, 80.6, 66.1, 61.5, 55.8, 55.7, 55.5, 53.1, 40.5, 37.6, 31.8, 30.5, 28.8, 28.7, 27.7, 26.0, 23.6, 20.1, 14.0.

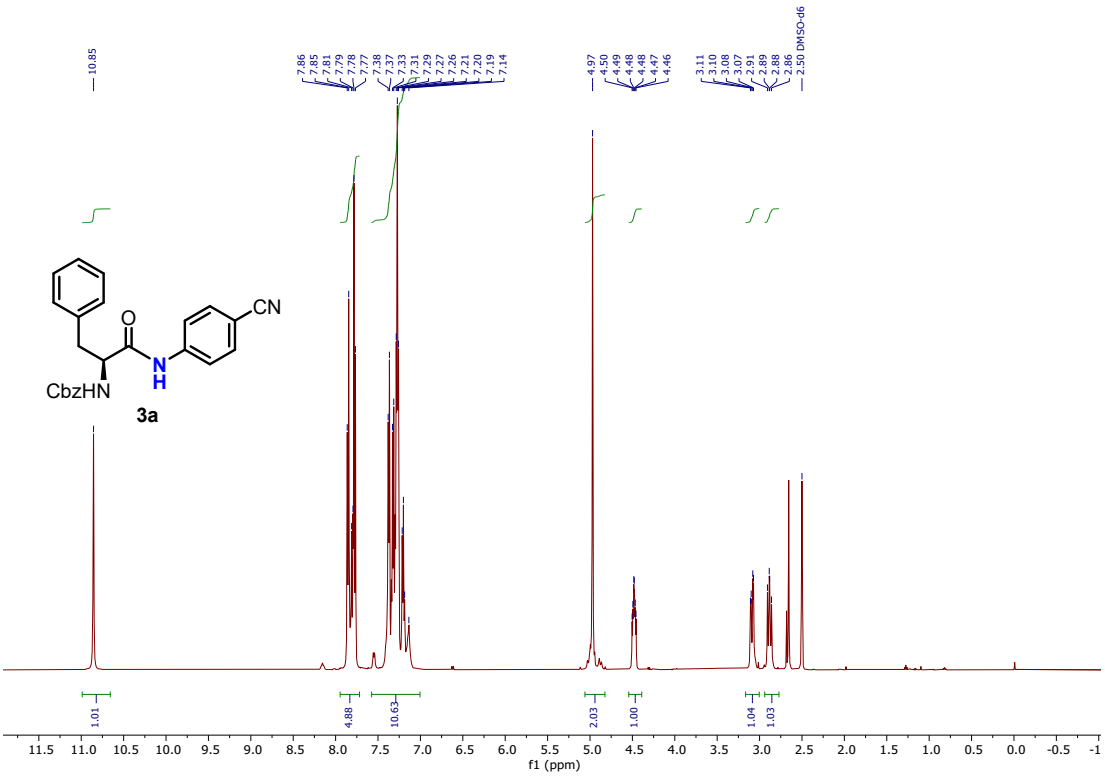
HRMS (ESI) m/z calculated for $C_{30}H_{49}N_4O_7$ [M+H]+: 577.3596; found: 577.3597.



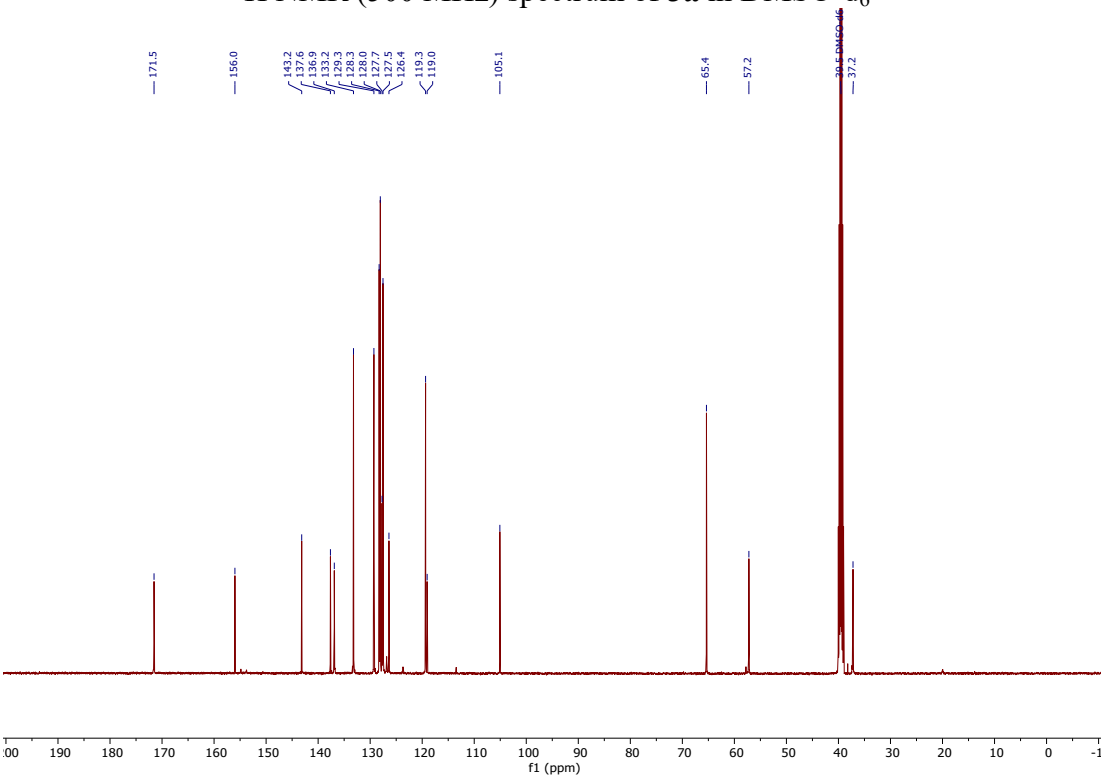
tert-Butyl (S)-(6-amino-1-(benzyl(methyl)amino)-1-oxohexan-2-yl)carbamate formate (9p).

To a 40 mL vial equipped with a stir bar was added DMAc (16 mL), *N*-methyl benzylamine (1.26 mL, 9.74 mmol, 1.2 equiv), Boc-Lys-OH (2 g, 8.12 mmol), phenethylamine (1.23 mL, 9.74 mmol, 1.2 equiv), DIPEA (5.67 mL, 32.5 mmol, 4 equiv), and benzaldehyde (2.14 mL, 21.11 mmol, 2.6 equiv). The solution was stirred at 25 ˚C for 3 hours to afford a nearly homogeneous solution. To the reaction mixture was added Oxyma (0.23 g, 1.62 mmol, 0.2 equiv). The solution was cooled to 0 ˚C in an ice bath. To the solution was added TCFH (2.73 g, 9.74 mmol, 1.2 equiv). The reaction mixture was stirred at 0 ˚C for 10 min. The reaction was then warmed to 25 ˚C and stirred at 25 ˚C for 3 hours. Aliquot was diluted with MeCN:H2O (1:1), filtered, analyzed by HPLC to determine product ratio. The crude reaction mixture was diluted with 200 mL EtOAc and washed with 10 wt% Na_2SO_4 (2x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified on a 150 g C18 column (100% H_2O w/ 0.1% formic acid to 30% H_2O w/ 0.1% formic acid/MeCN) to afford a white solid with 89% isolated yield (2.68 g, 6.83 mmol) as a white foamy solid.

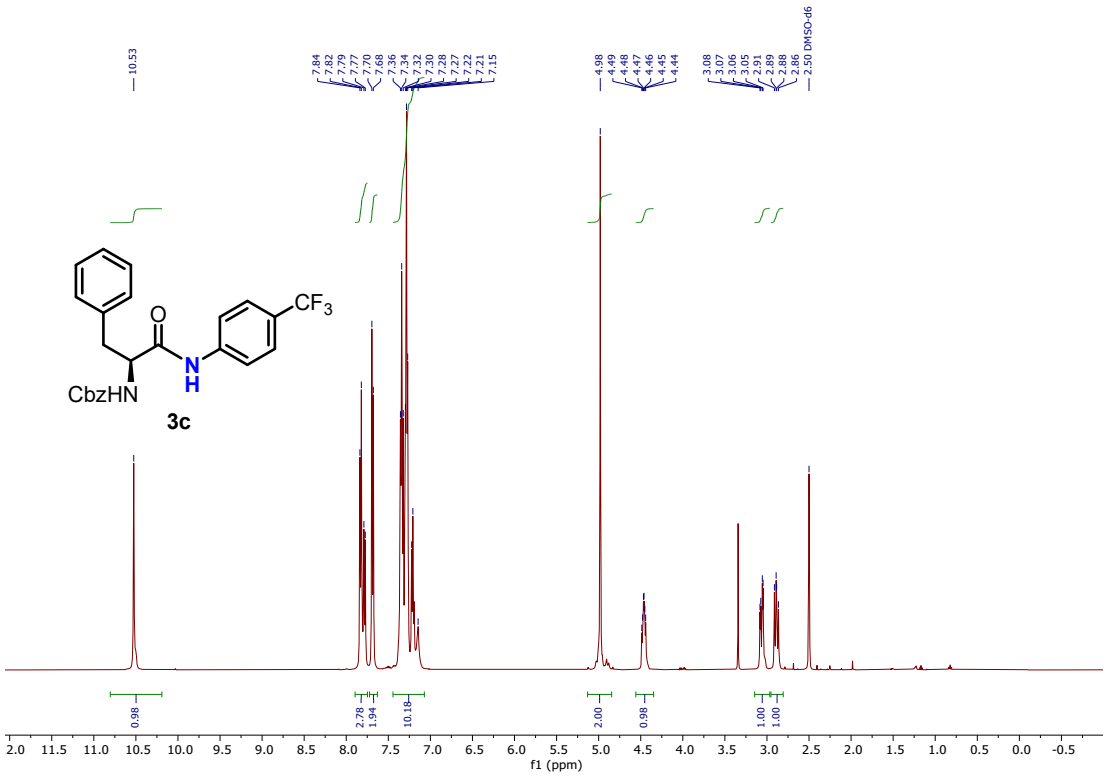
^{1}H NMR (500 MHz, D_2O) the product exists as 1:1 rotamer δ 8.47 (s, 1H), 7.56 – 7.17 (m, 5H), 4.75 – 4.43 (m, 2H), 3.39 – 3.07 (m, 2H), 3.07 – 2.82 (m, 3H), 1.84 – 1.65 (m, 2H), 1.64 – 1.51 (m, 2H), 1.44 (d, J = 31.1 Hz, 9H).
^{13}C NMR (126 MHz, CD_3OD) the product exists as 1:1 rotamer δ 174.7, 170.1, 163.7, 157.9, 157.7, 138.2, 138.1, 130.0, 129.9, 129.8, 129.7, 129.5, 128.8, 128.5, 128.2, 128.1, 80.6, 80.6, 54.1, 52.3, 51.8, 51.6, 41.9, 40.4, 40.4, 38.6, 36.4, 35.4, 34.7, 34.6, 32.9, 32.3, 28.7, 28.7, 28.2, 28.2, 23.7, 23.7.
HRMS (ESI) m/z calculated for $C_{19}H_{32}N_3O_3$ [M+H]+: 350.2438; found: 350.2436.



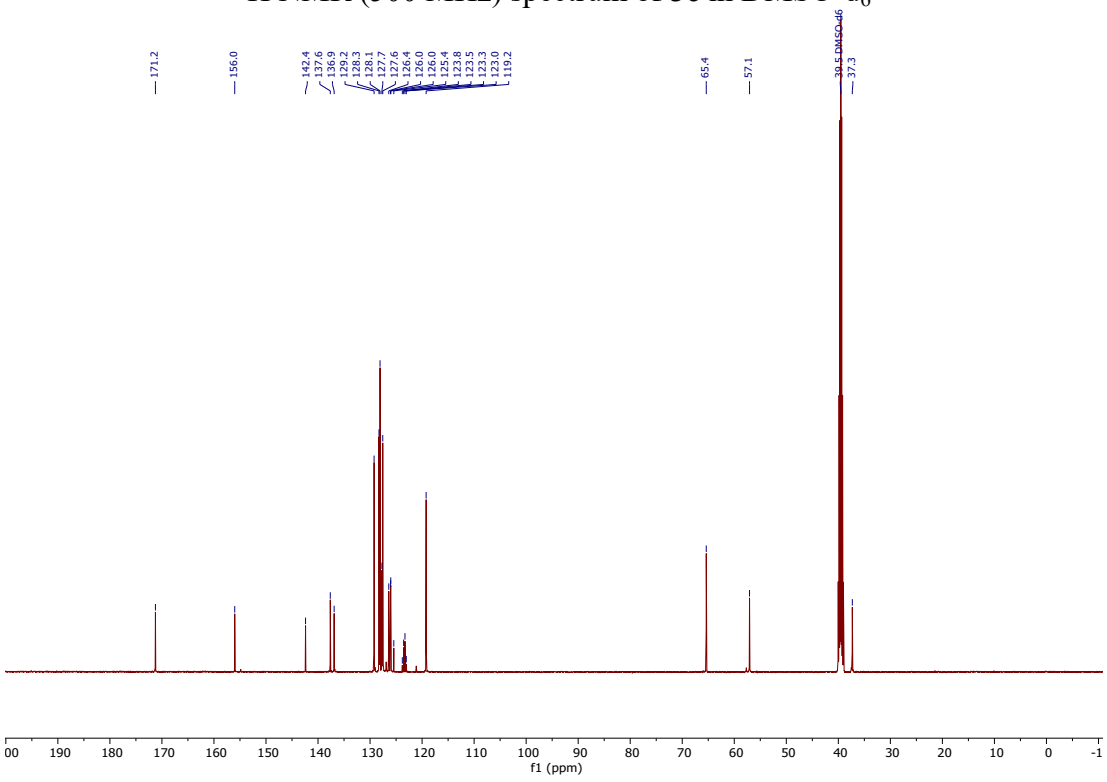
^{1}H NMR (500 MHz) spectrum of **3a** in DMSO-d_6



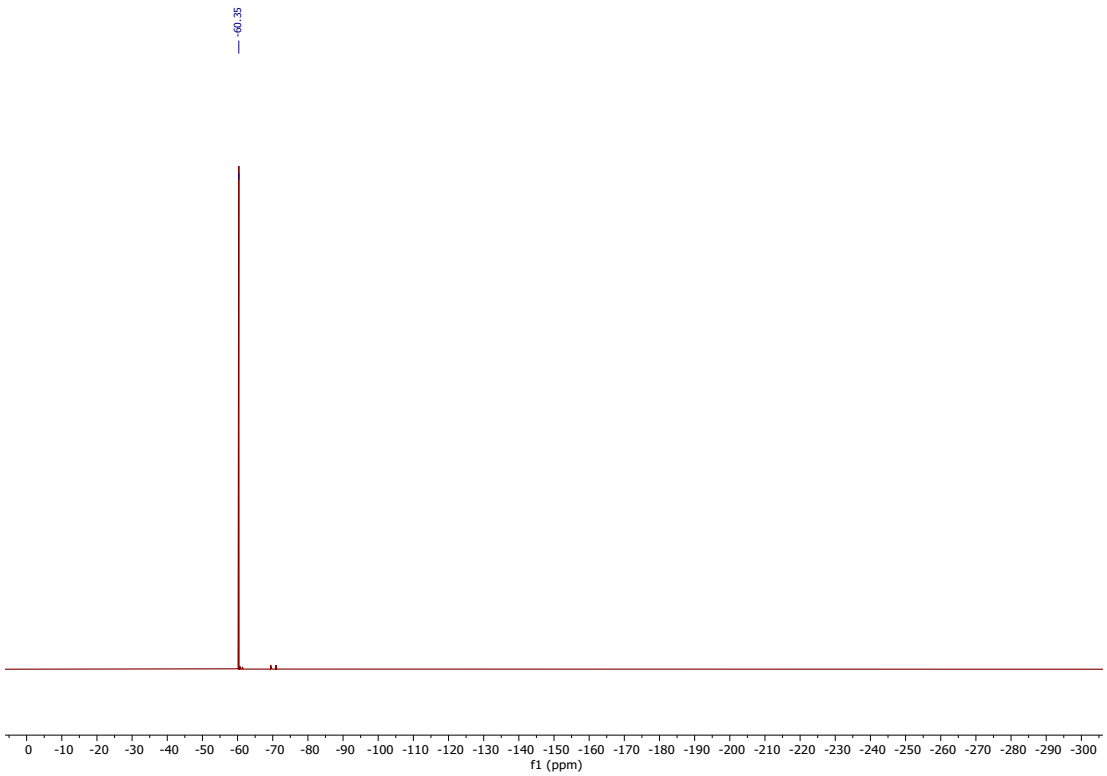
^{13}C NMR (126 MHz) spectrum of **3a** in DMSO-d_6



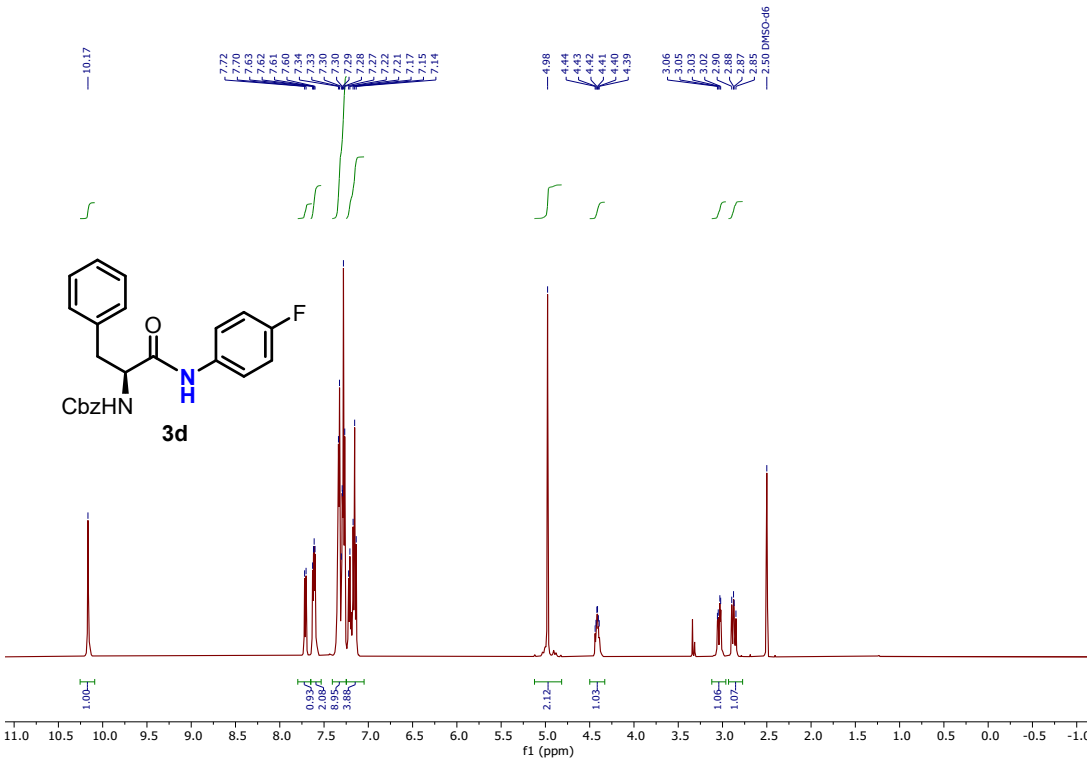
^{1}H NMR (500 MHz) spectrum of **3c** in DMSO-d_6



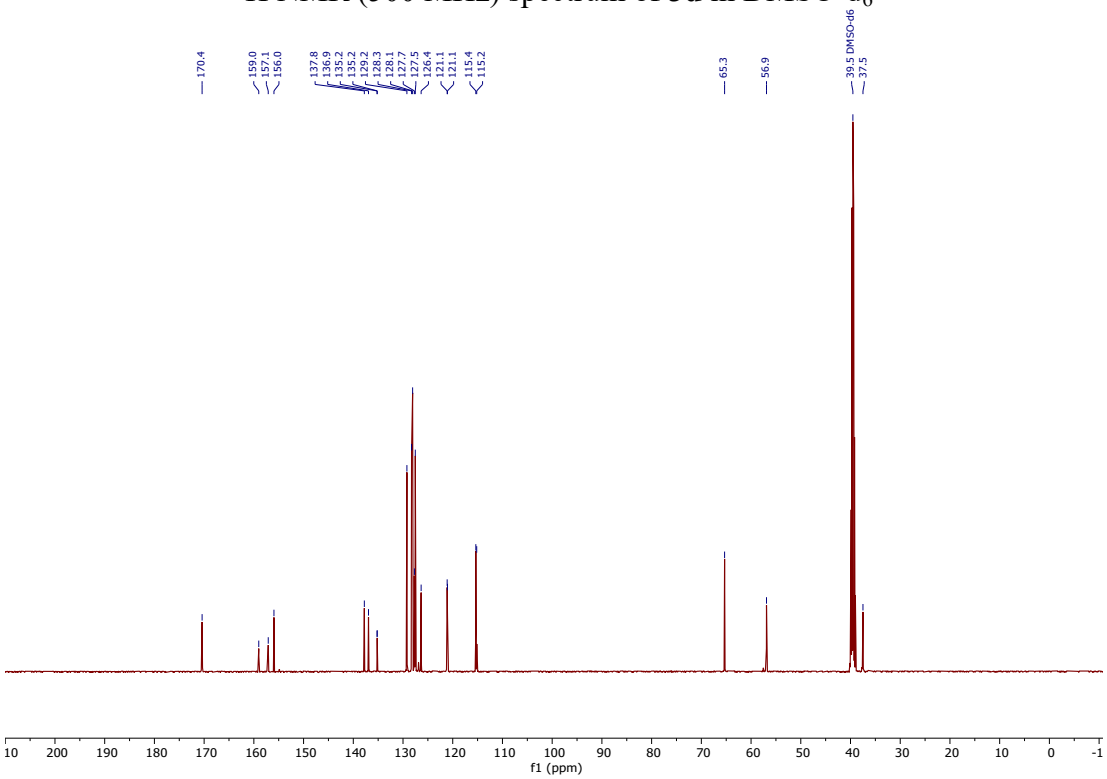
^{13}C NMR (126 MHz) spectrum of **3c** in DMSO-d_6



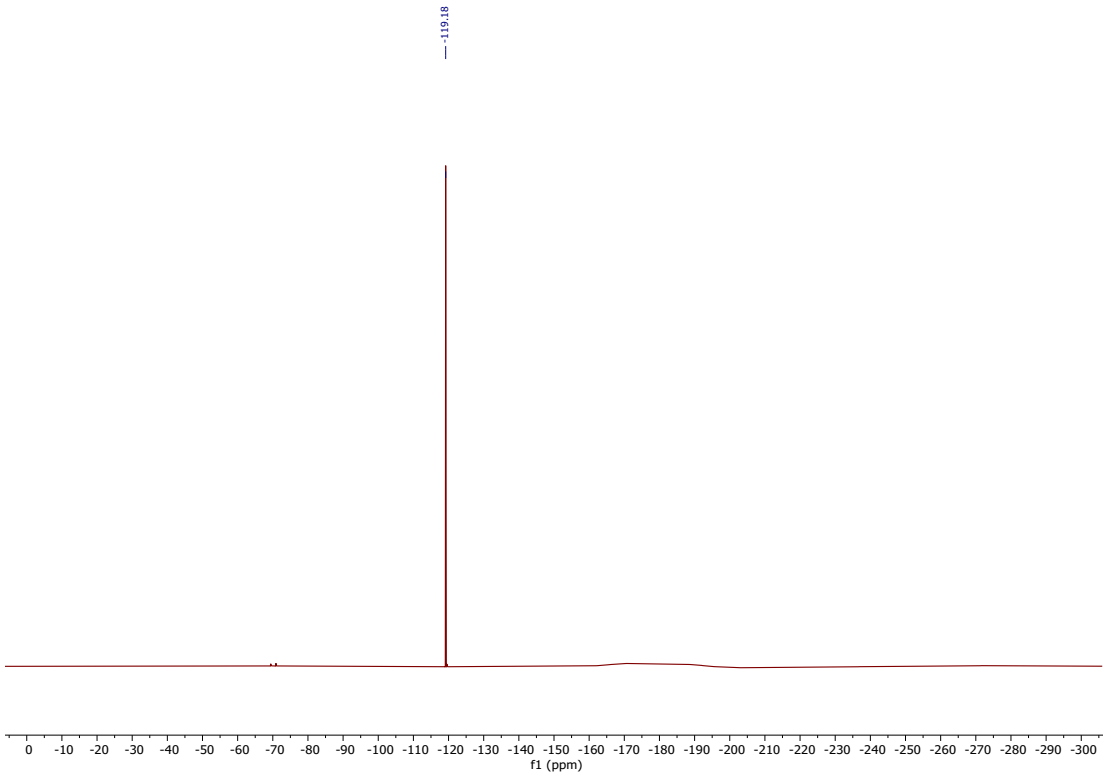
^{19}F NMR (471 MHz) spectrum of **3c** in DMSO-d_6



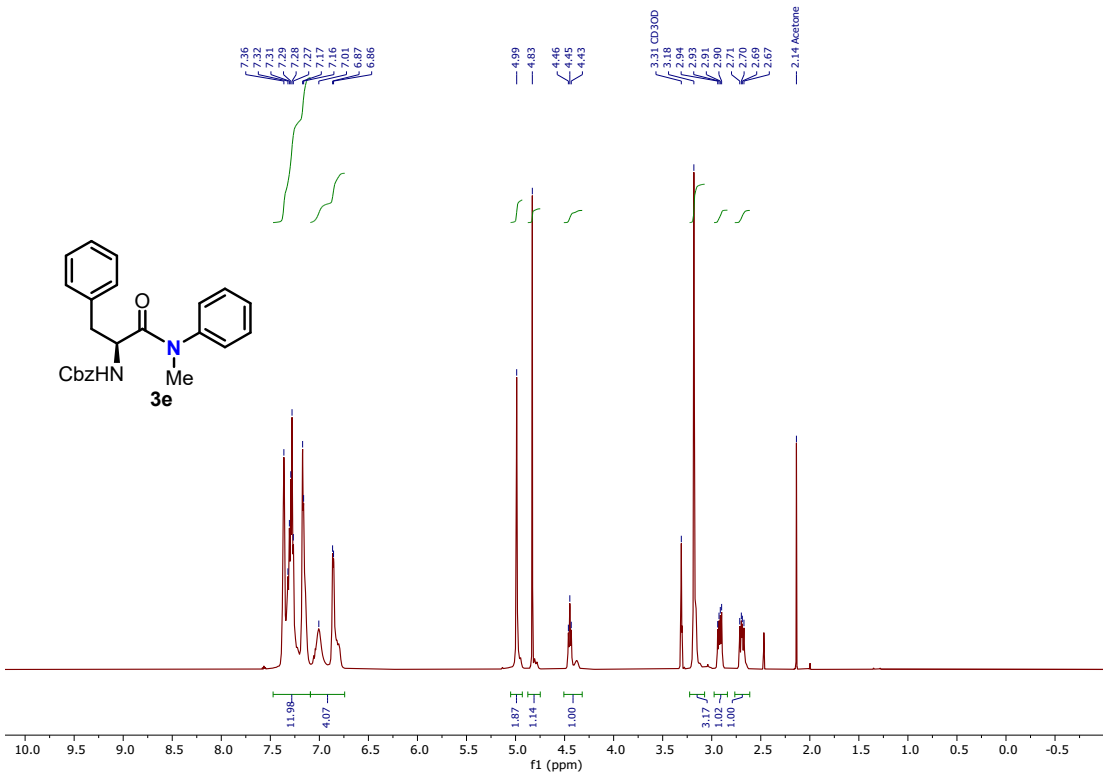
^{1}H NMR (500 MHz) spectrum of **3d** in DMSO-d_6



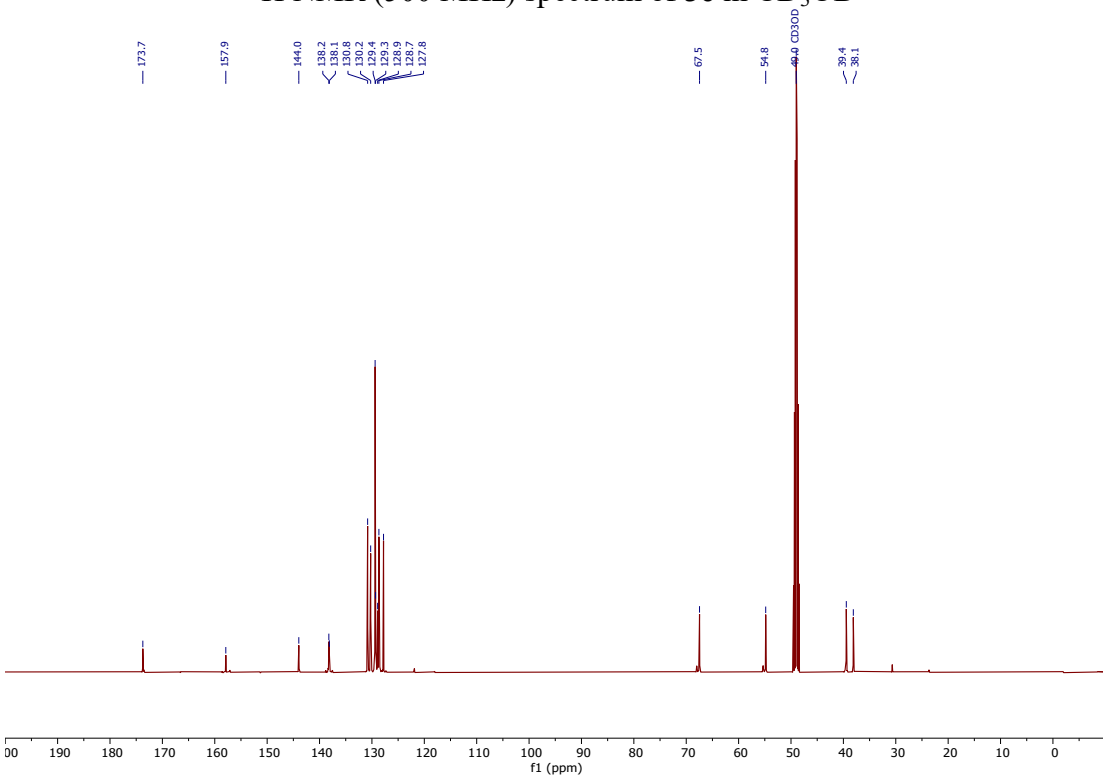
^{13}C NMR (126 MHz) spectrum of **3d** in DMSO-d_6



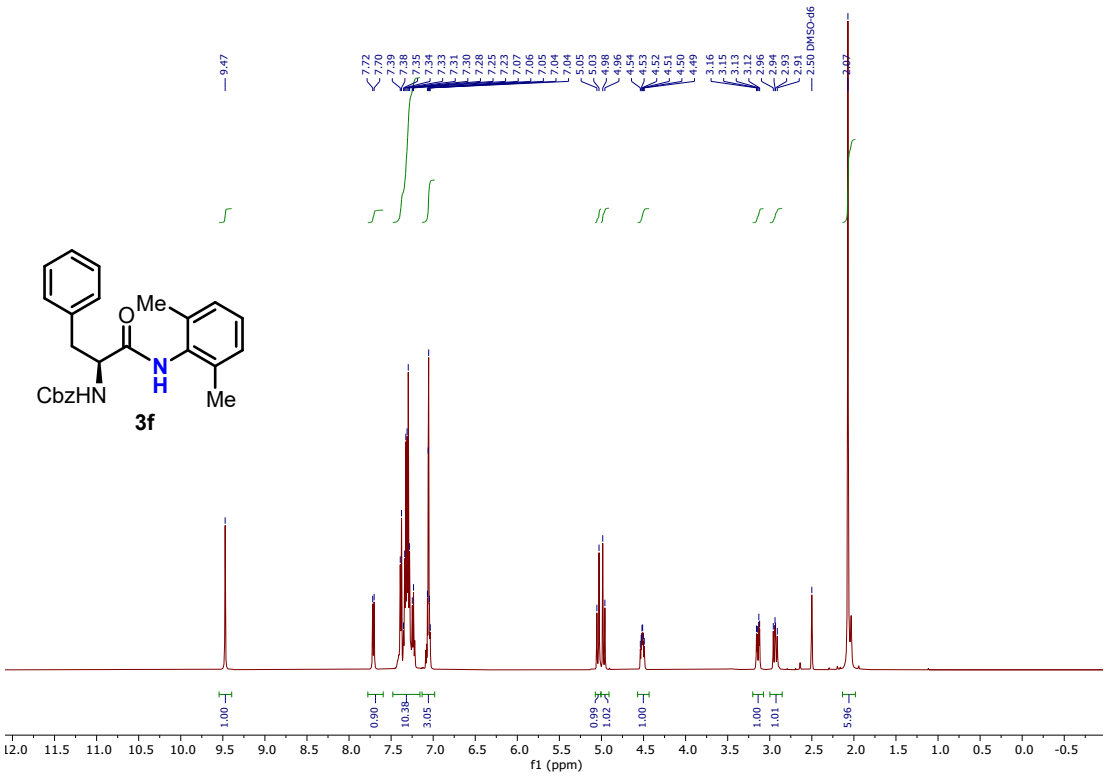
^{19}F NMR (471 MHz) spectrum of **3d** in DMSO-d_6



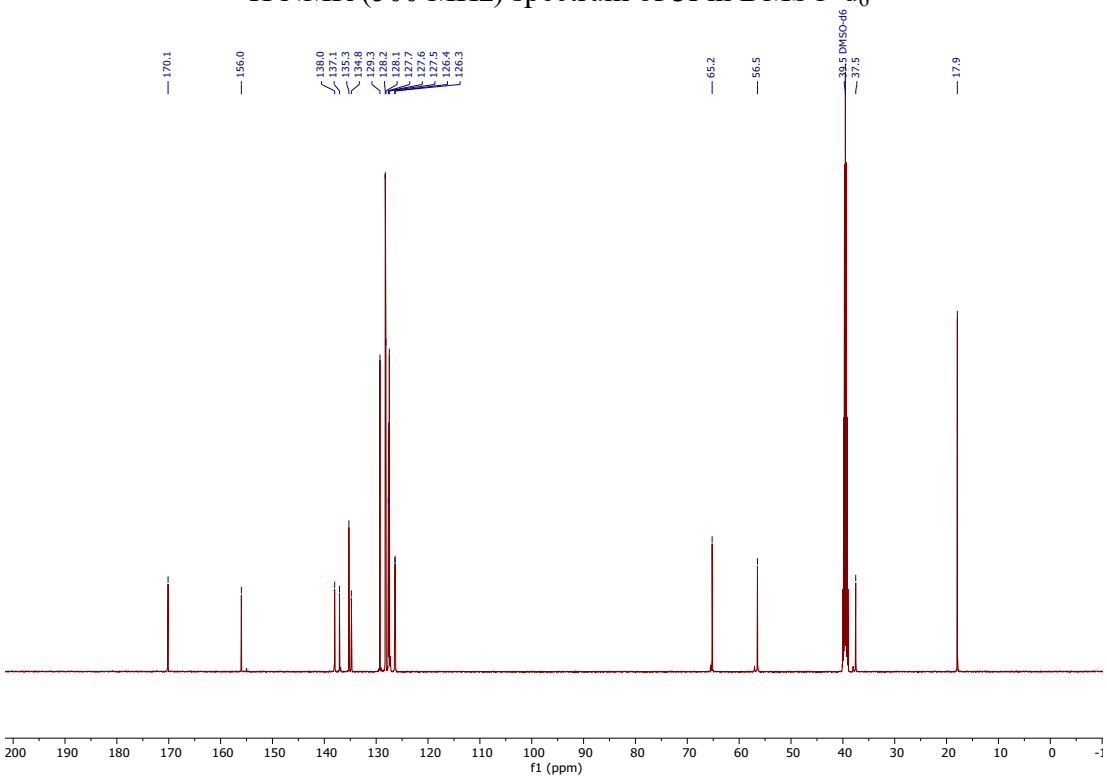
^{1}H NMR (500 MHz) spectrum of **3e** in CD_3OD



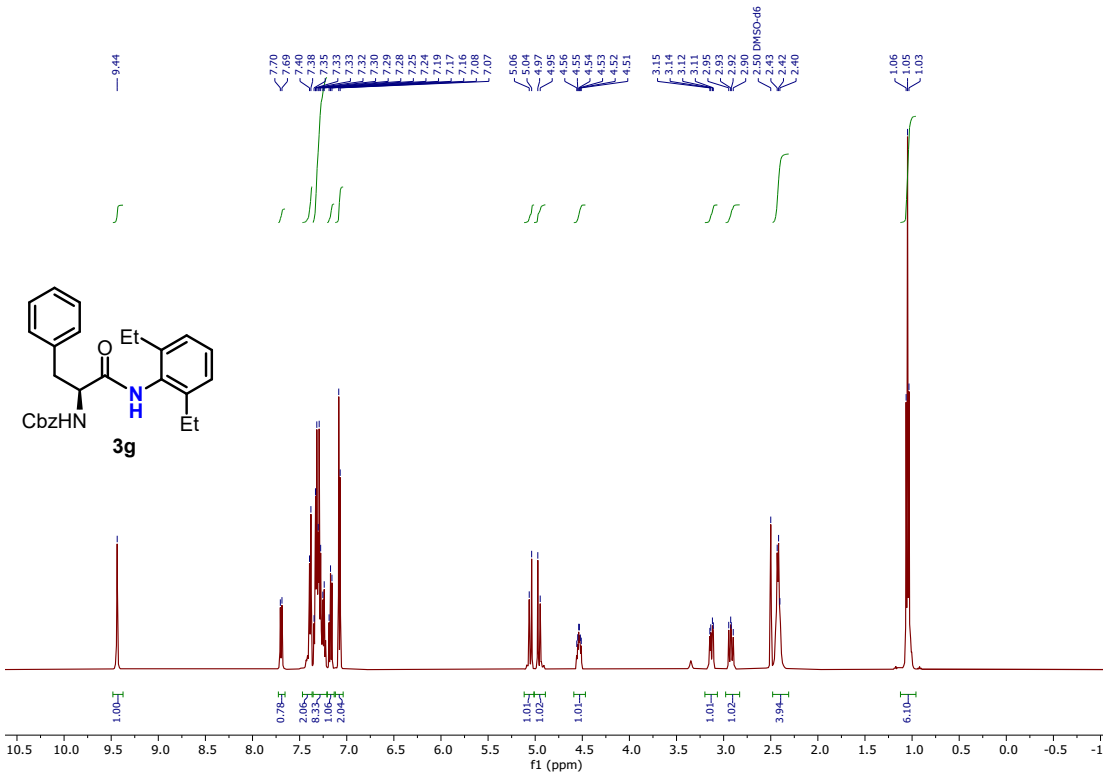
^{13}C NMR (126 MHz) spectrum of **3e** in CD_3OD



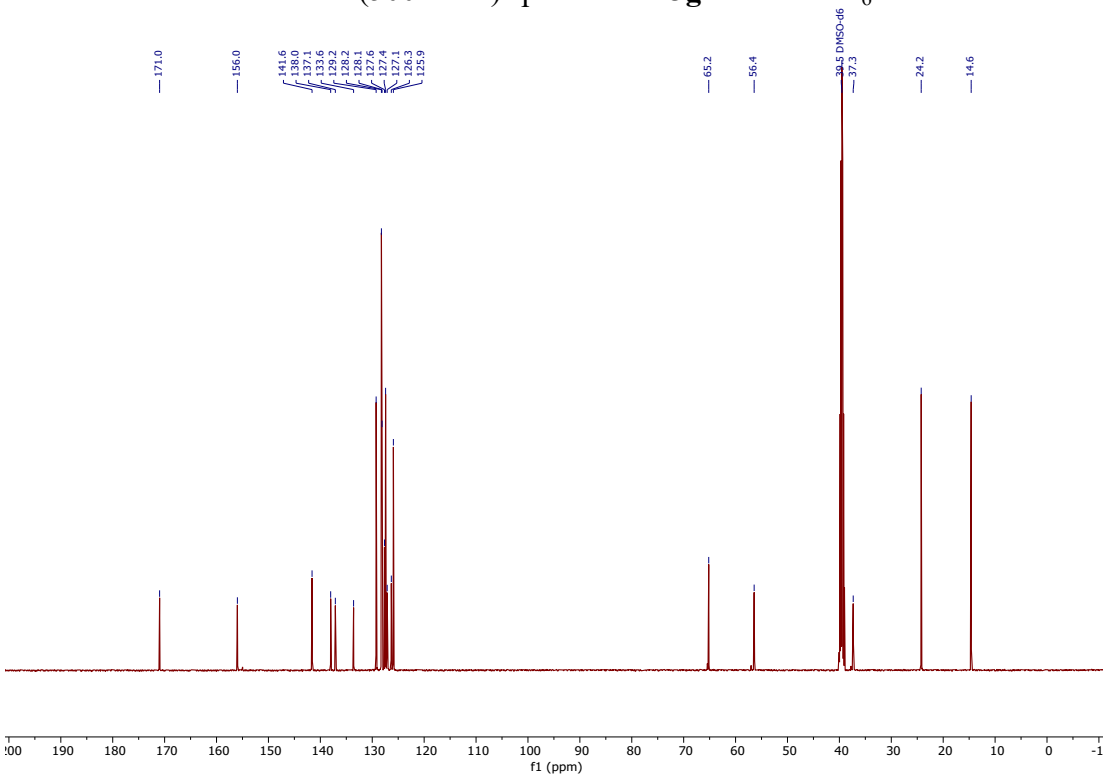
^{1}H NMR (500 MHz) spectrum of **3f** in DMSO-d_6



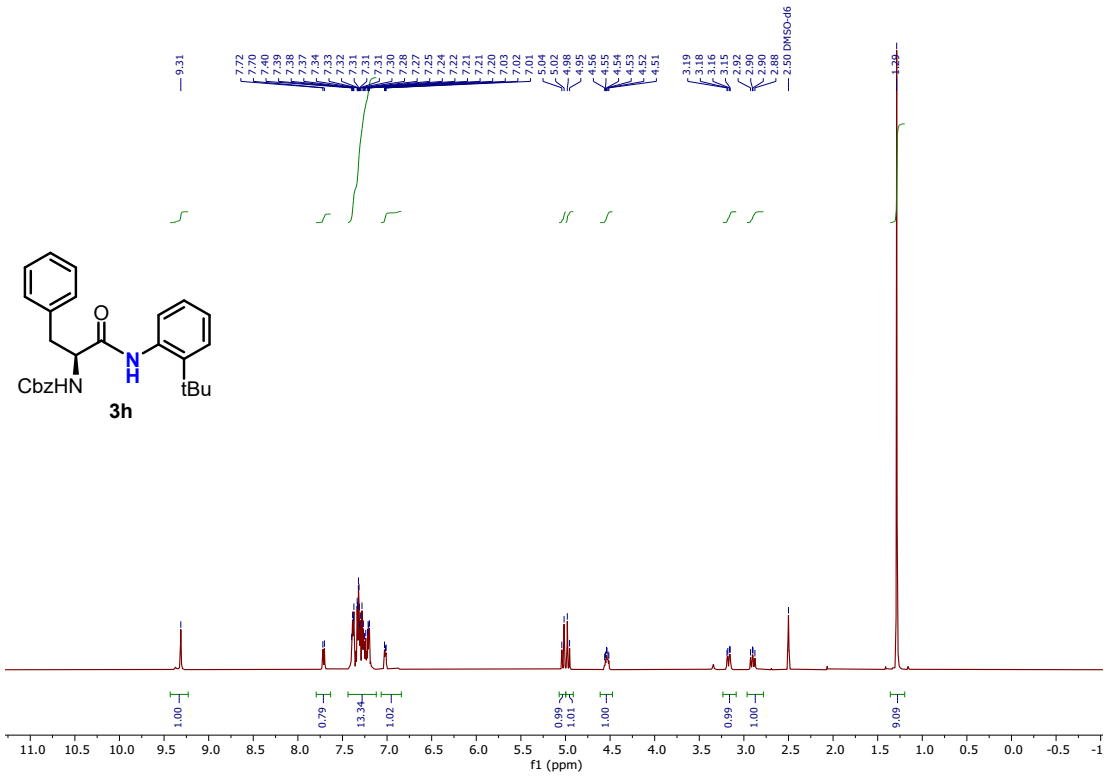
^{13}C NMR (126 MHz) spectrum of **3f** in DMSO-d_6



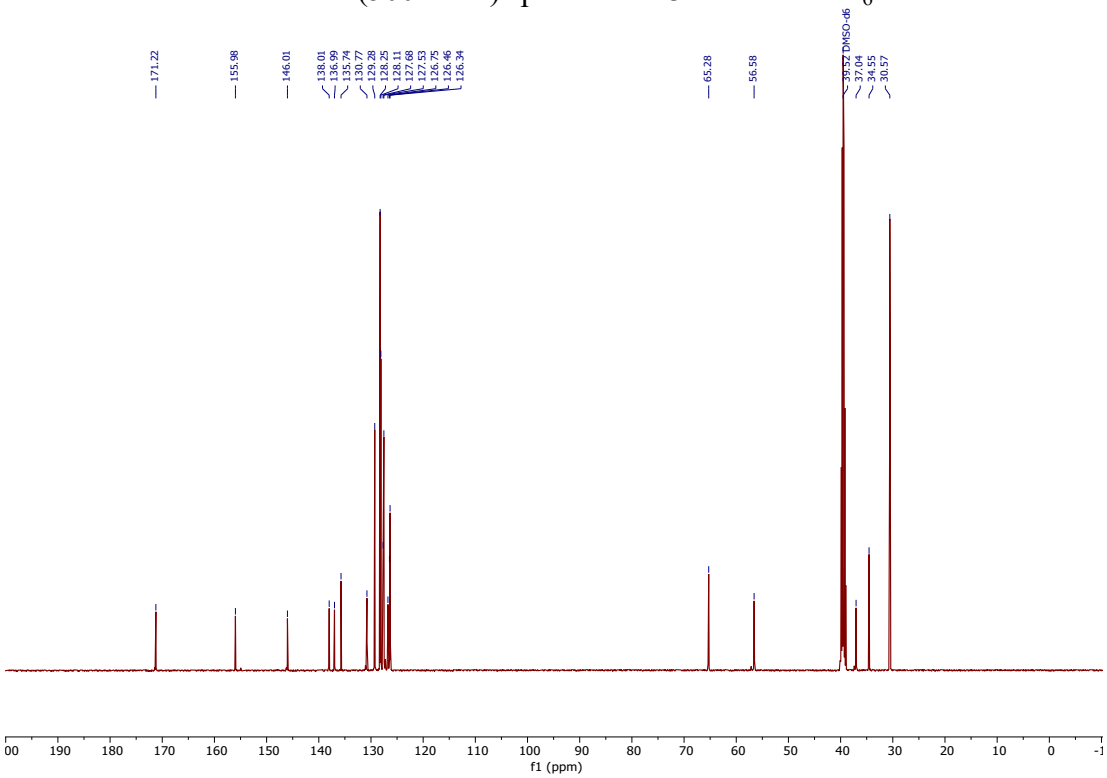
^{1}H NMR (500 MHz) spectrum of **3g** in DMSO-d_6



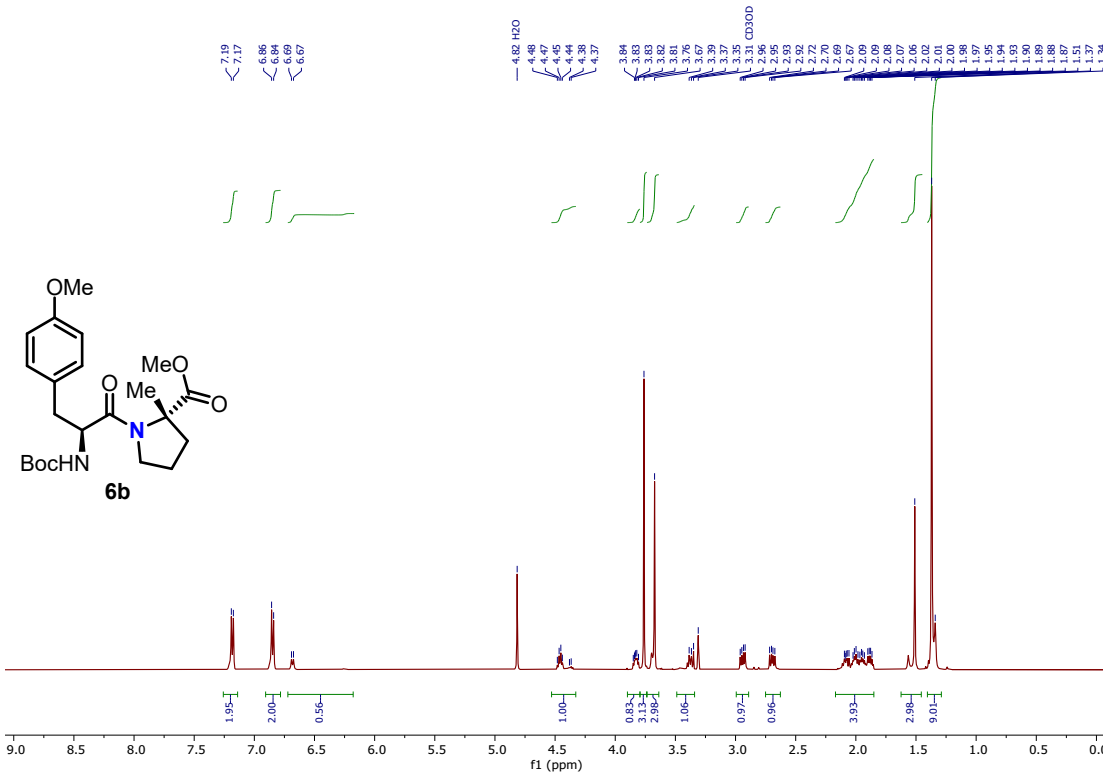
^{13}C NMR (126 MHz) spectrum of **3g** in DMSO-d_6



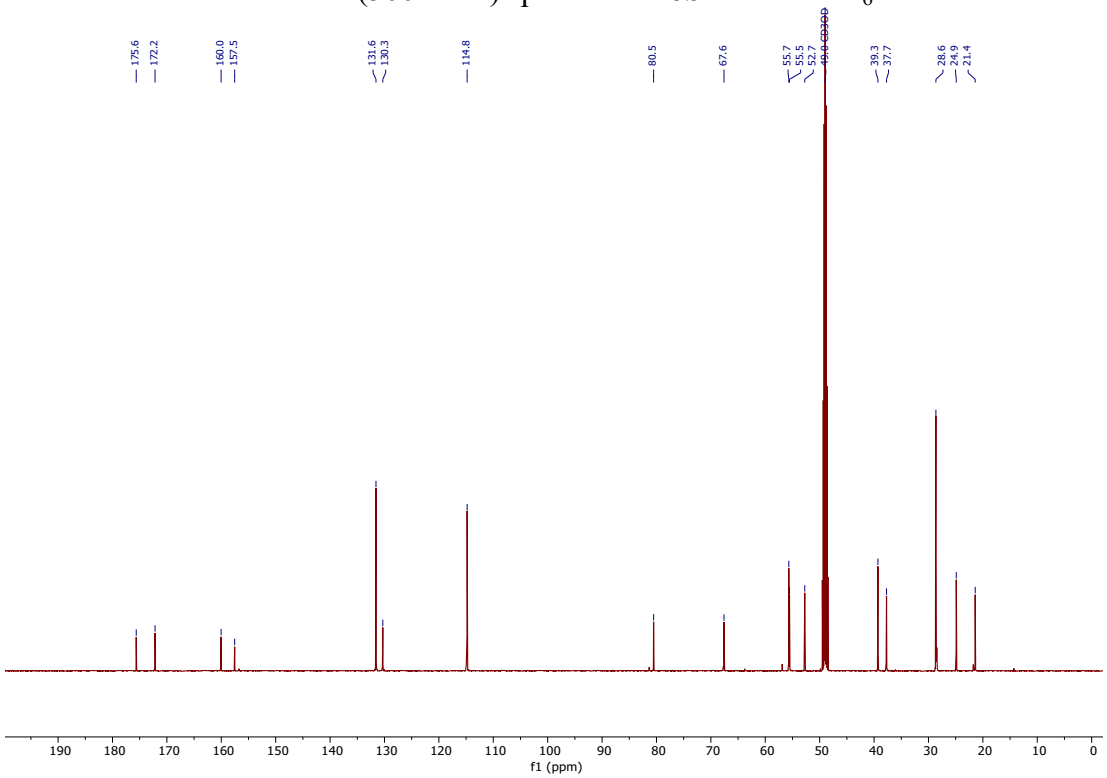
^{1}H NMR (500 MHz) spectrum of **3h** in DMSO-d_6



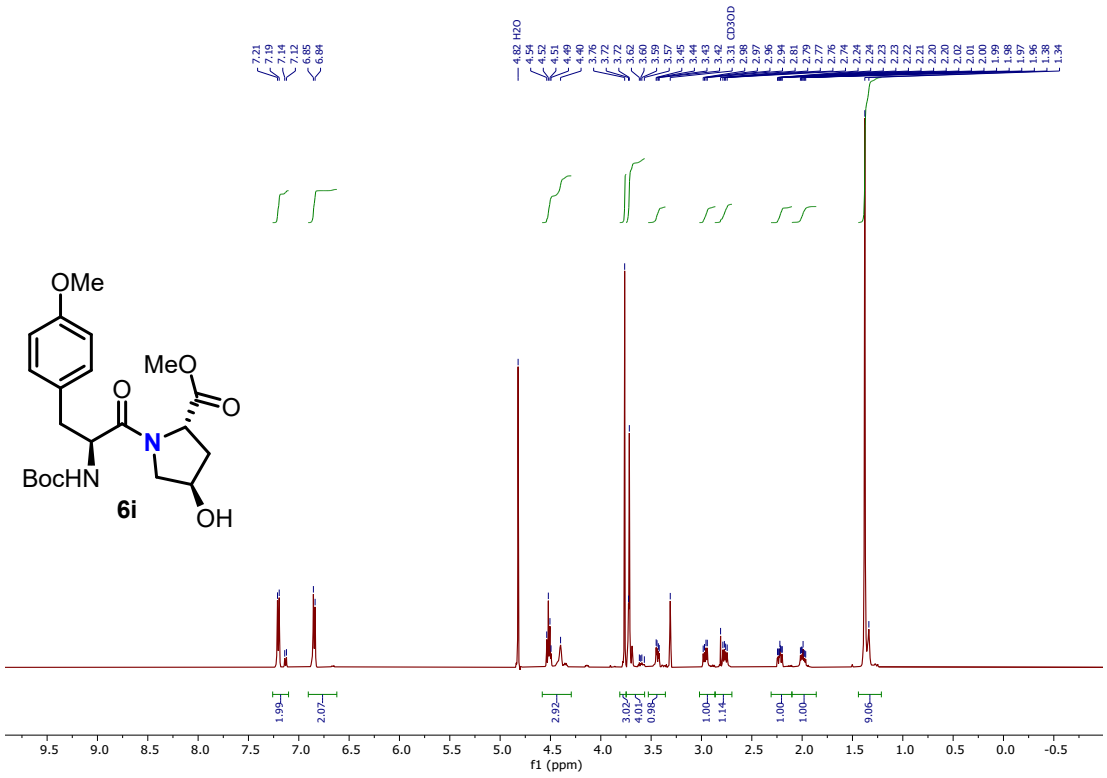
^{13}C NMR (126 MHz) spectrum of **3h** in DMSO-d_6



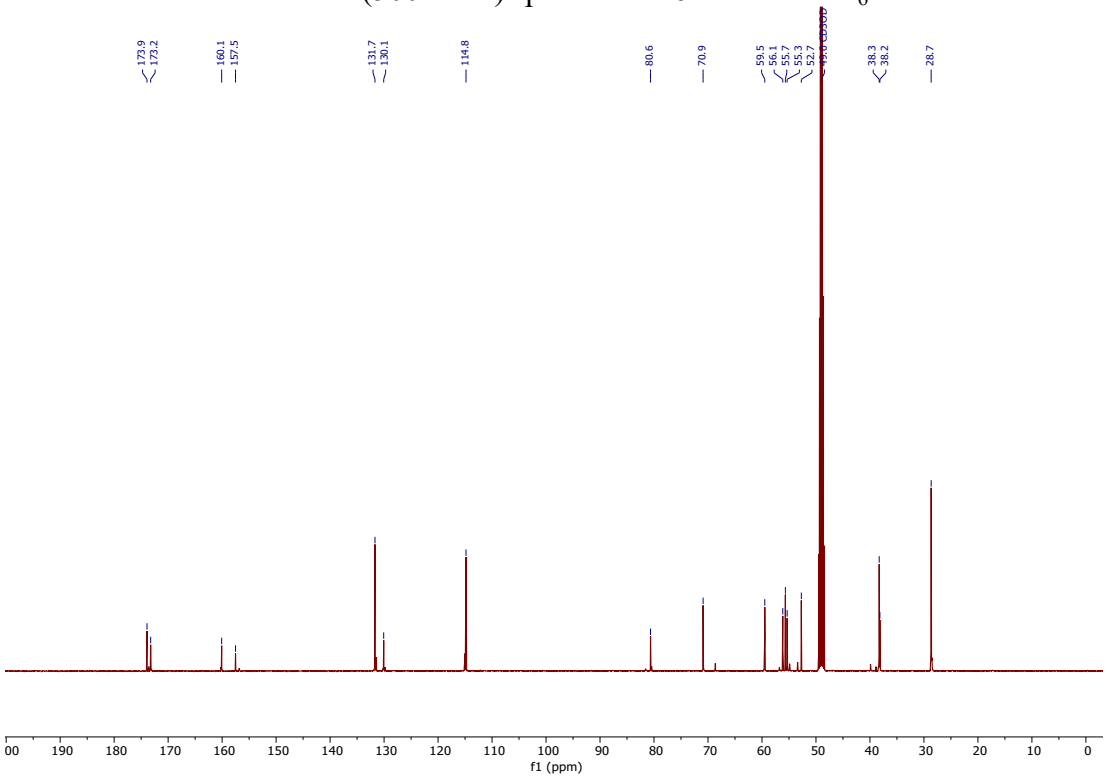
^{1}H NMR (500 MHz) spectrum of **6b** in DMSO-d_6



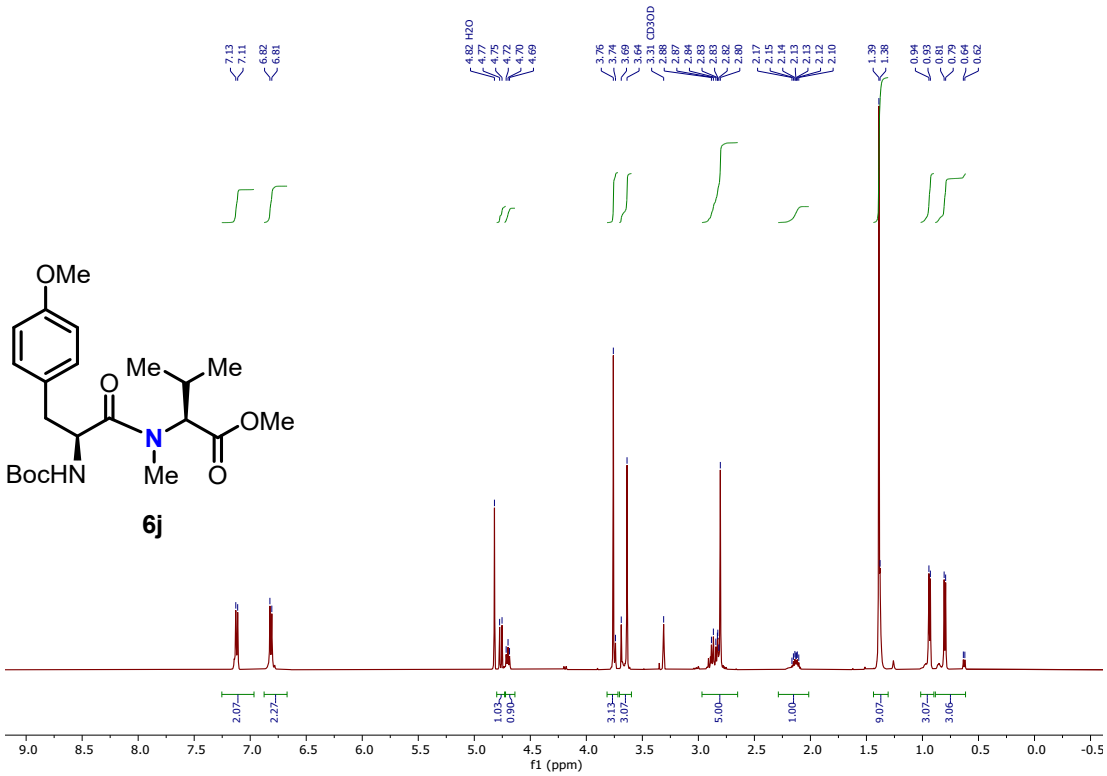
^{13}C NMR (126 MHz) spectrum of **6b** in DMSO-d_6



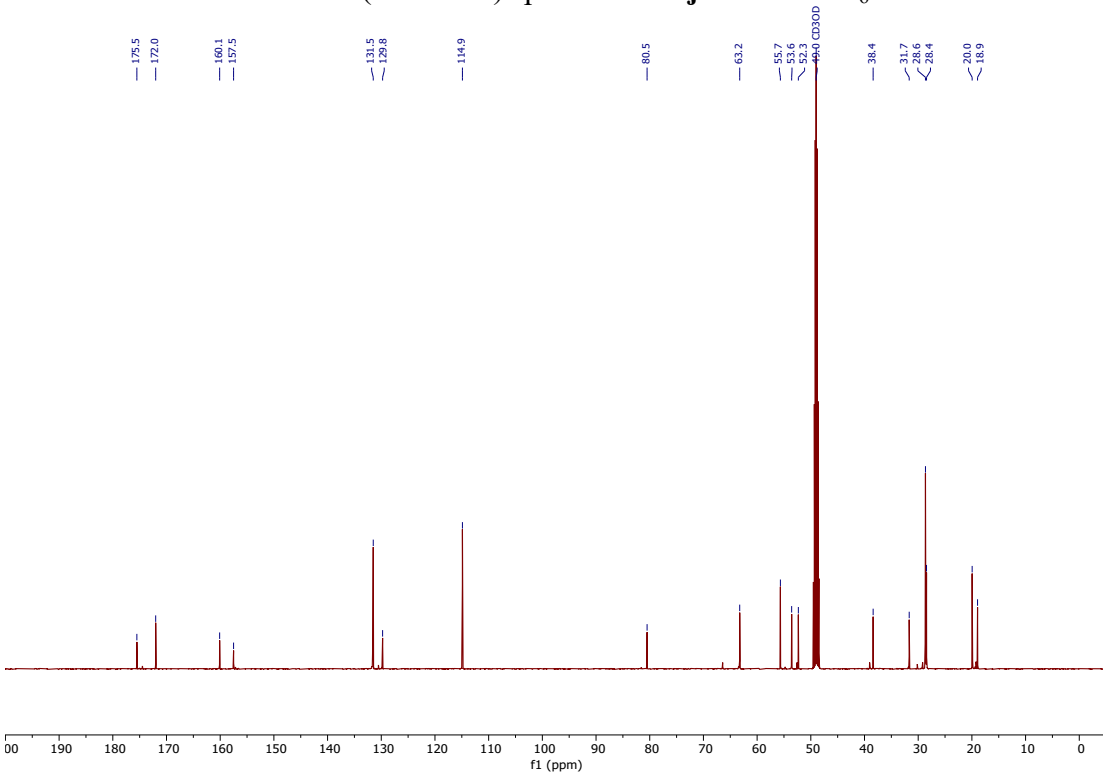
^{1}H NMR (500 MHz) spectrum of **6i** in DMSO-d_6



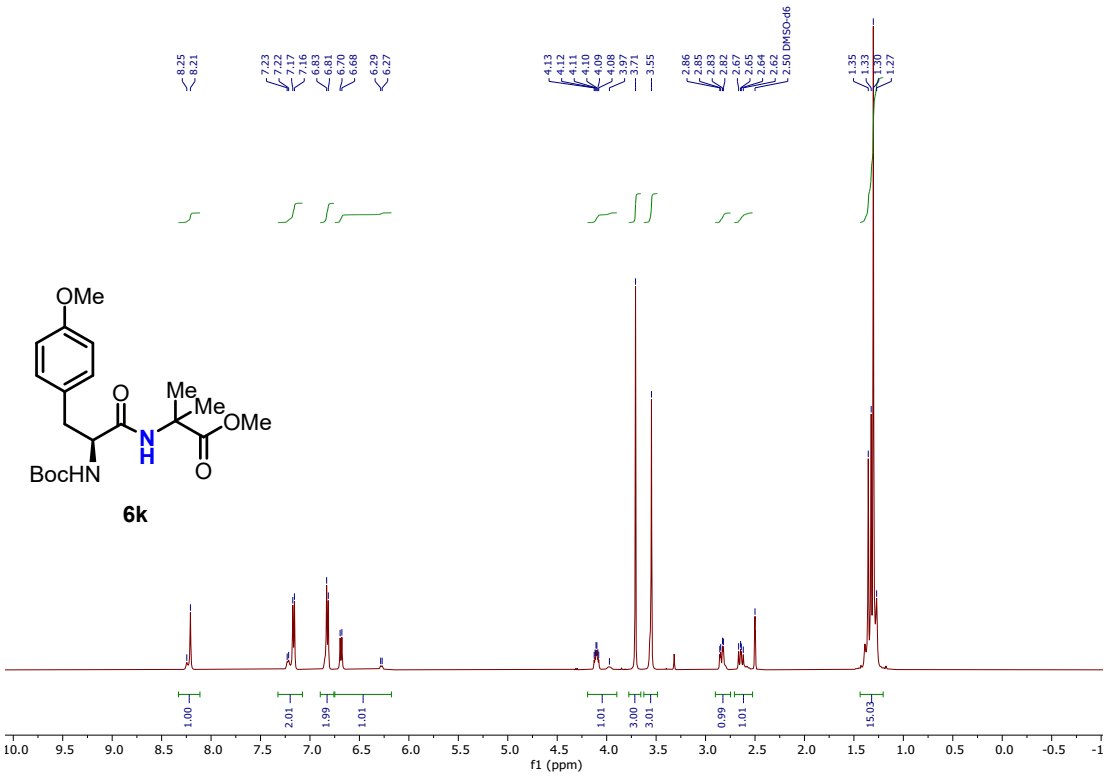
^{13}C NMR (126 MHz) spectrum of **6i** in DMSO-d_6



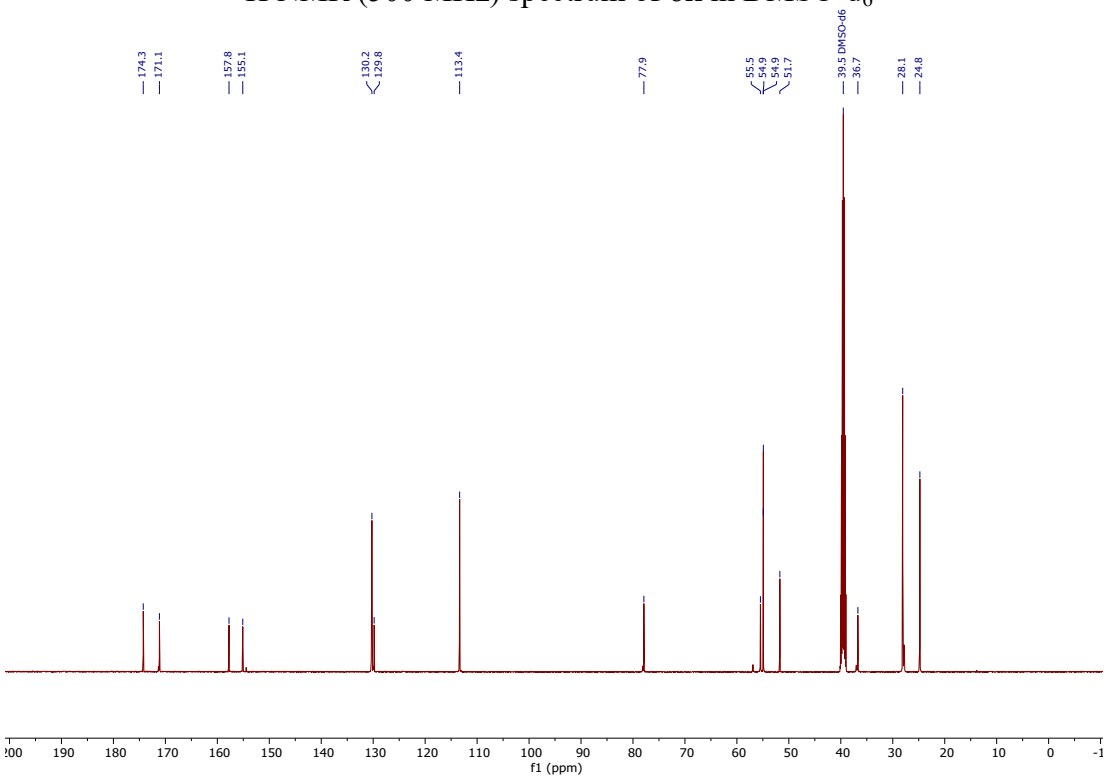
^{1}H NMR (500 MHz) spectrum of **6j** in DMSO-d_6



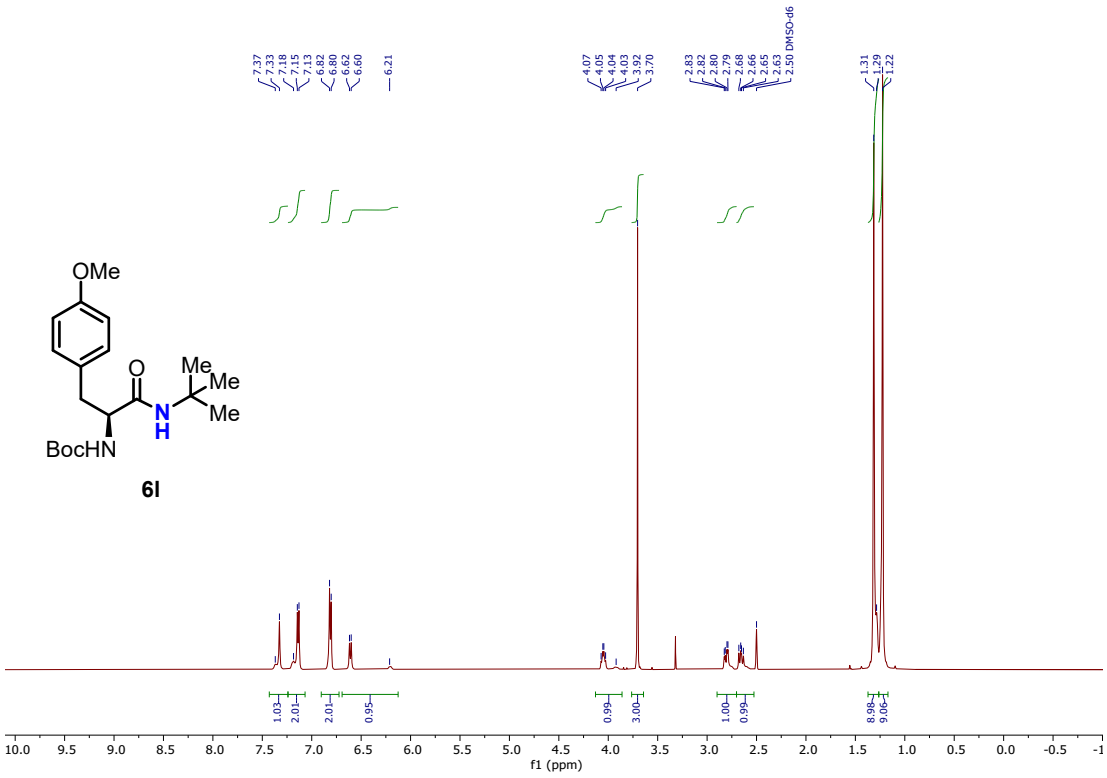
^{13}C NMR (126 MHz) spectrum of **6j** in DMSO-d_6



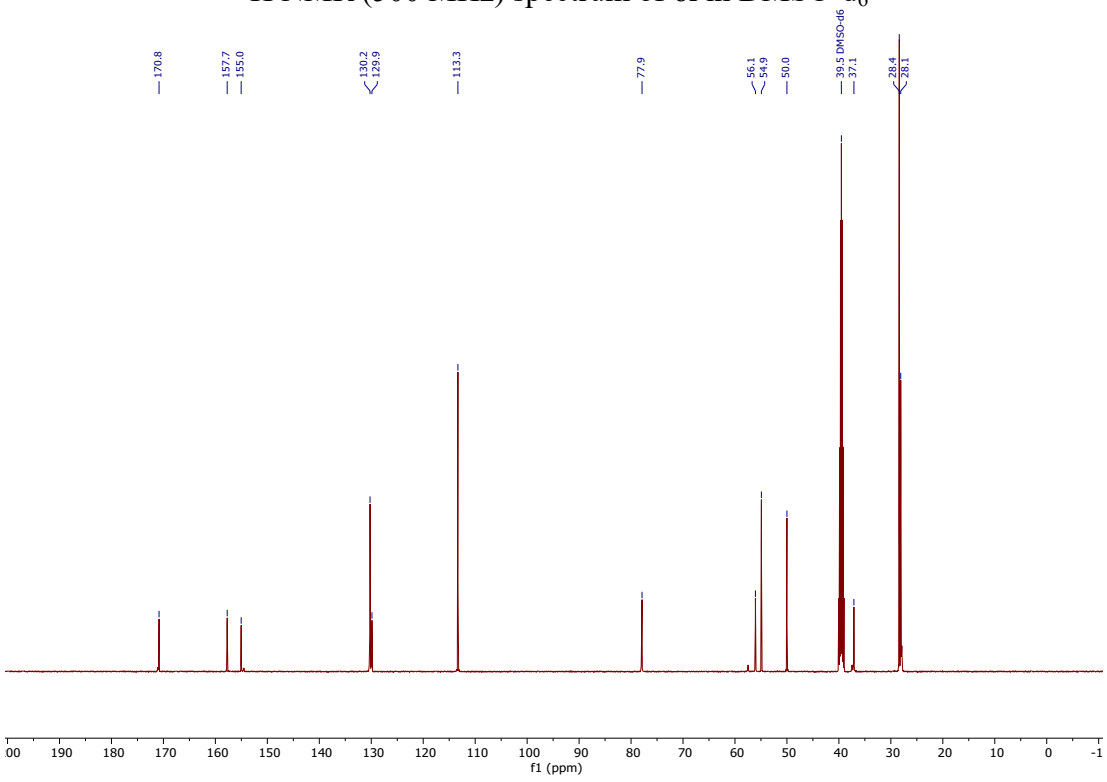
^{1}H NMR (500 MHz) spectrum of **6k** in DMSO-d_6



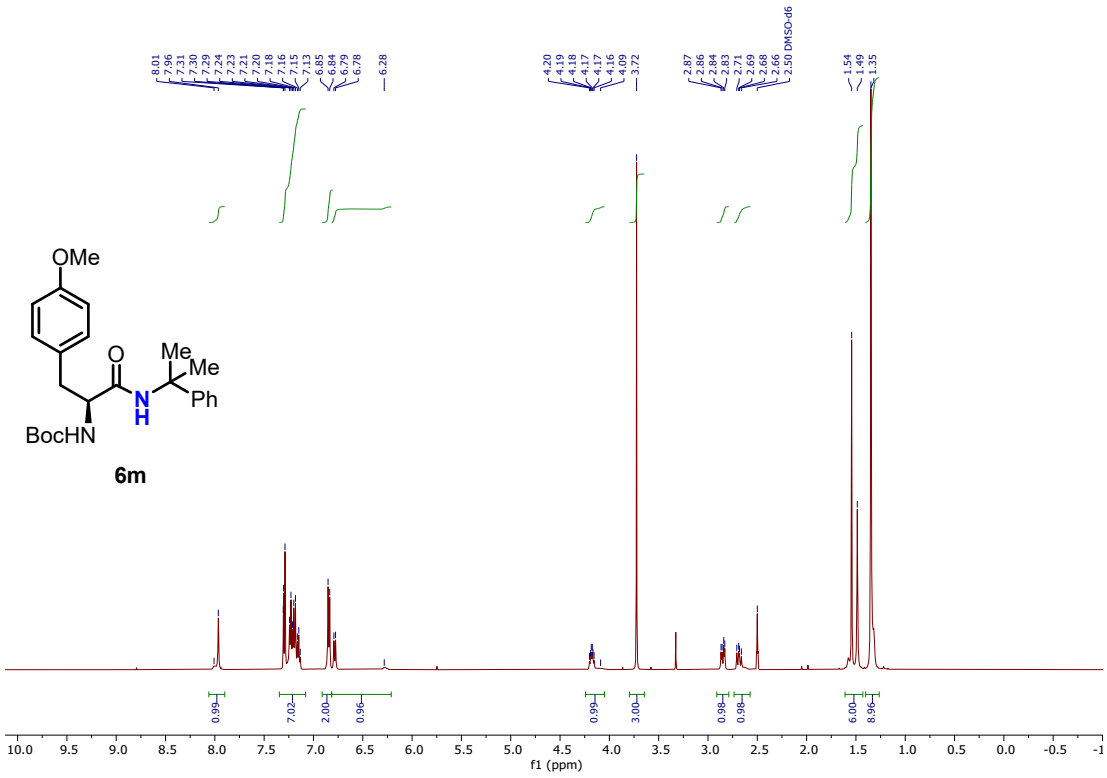
^{13}C NMR (126 MHz) spectrum of **6k** in DMSO-d_6



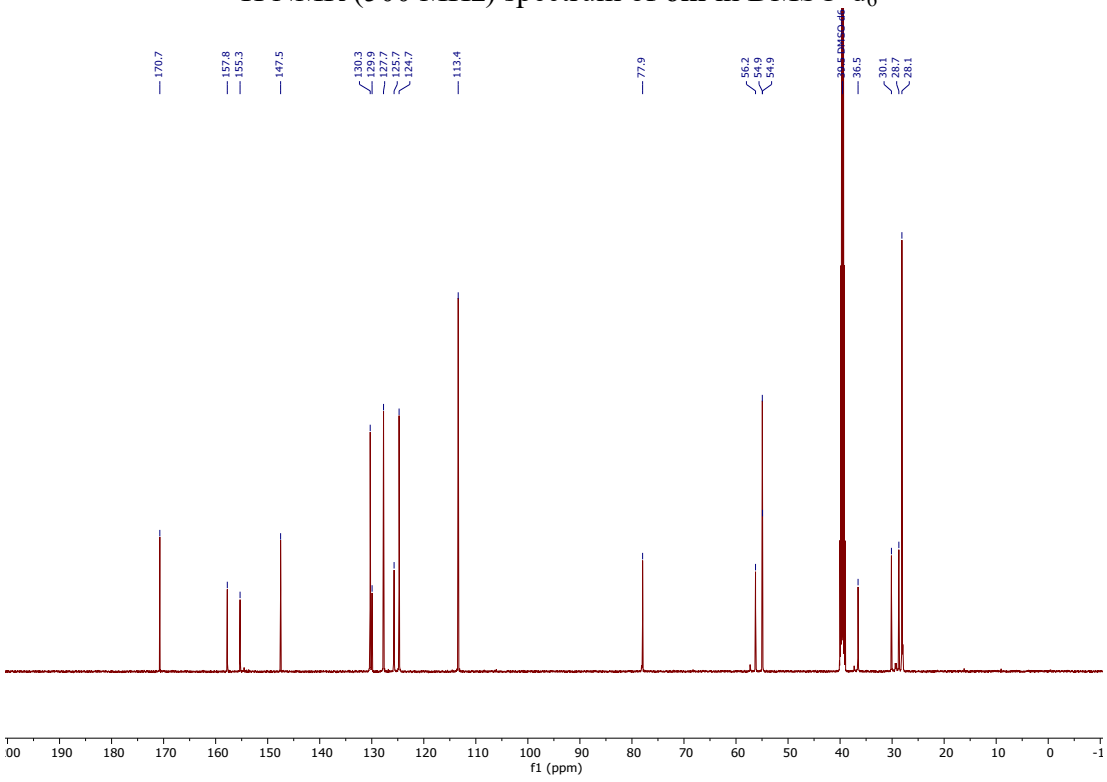
^{1}H NMR (500 MHz) spectrum of **6l** in DMSO-d_6



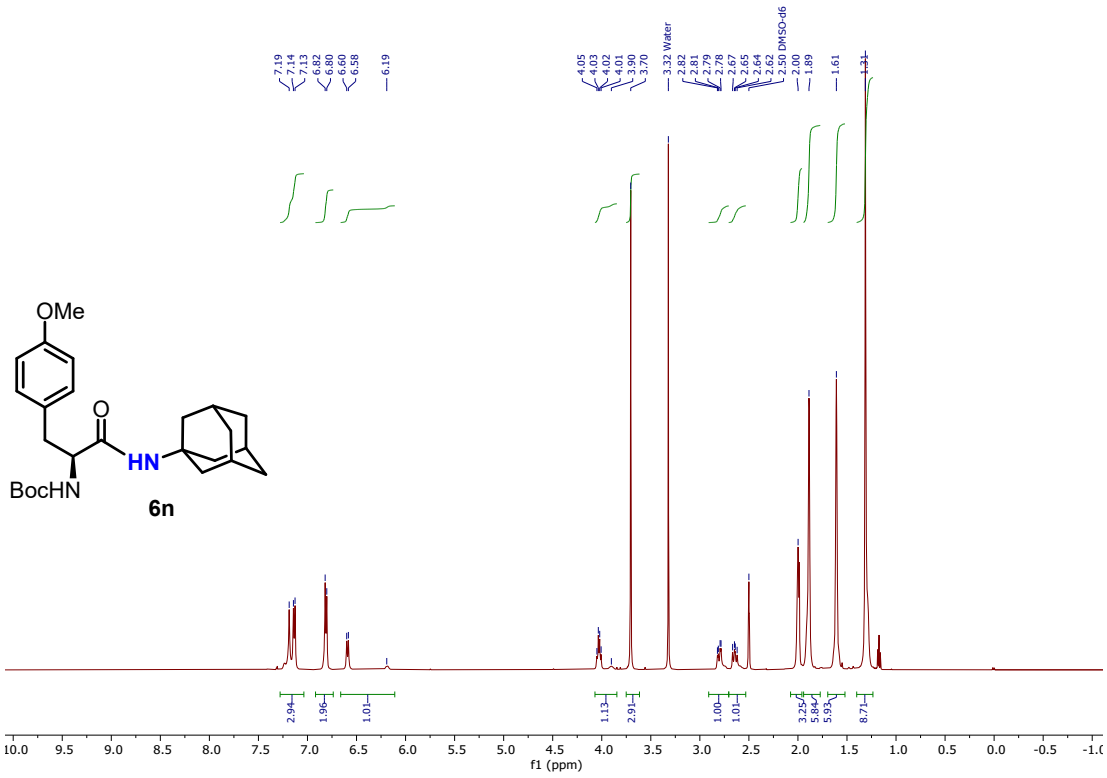
^{13}C NMR (126 MHz) spectrum of **6l** in DMSO-d_6



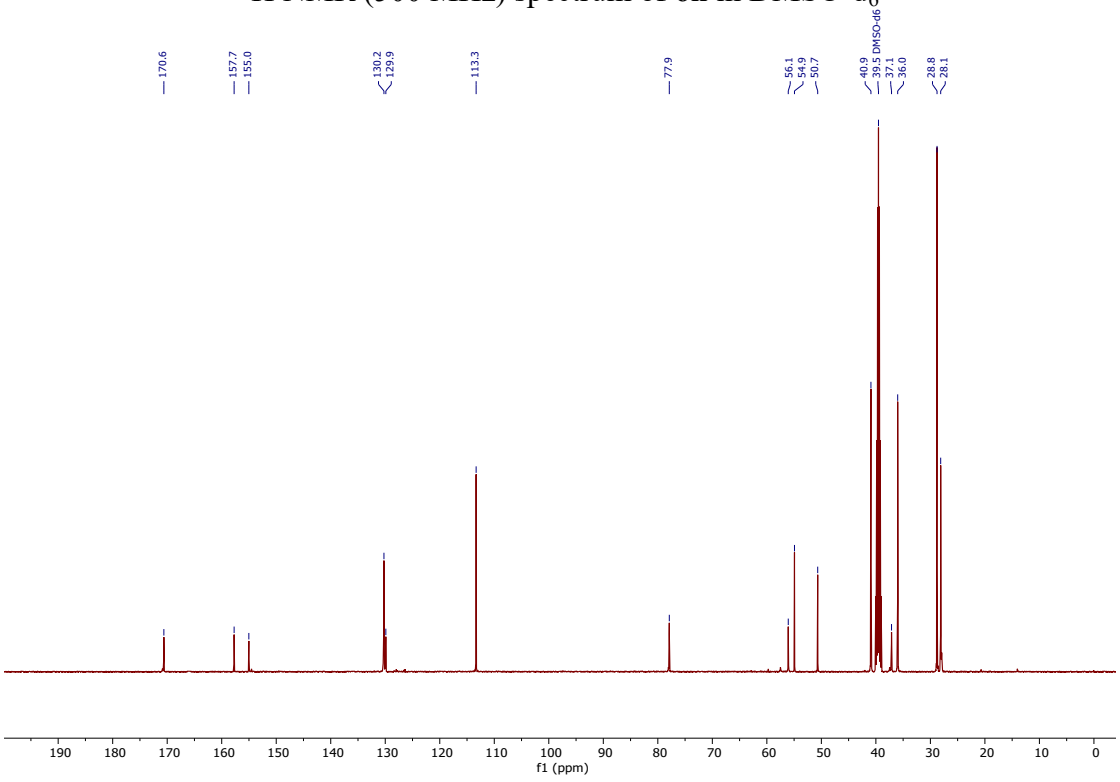
^{1}H NMR (500 MHz) spectrum of **6m** in DMSO-d_6



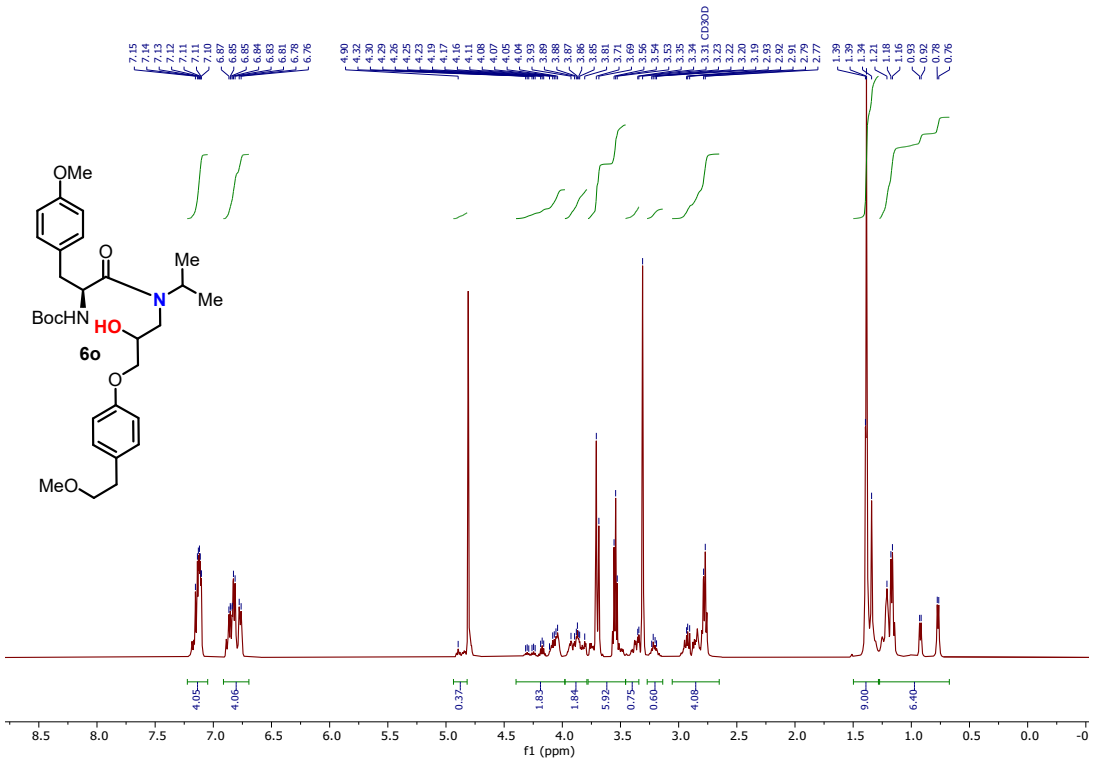
^{13}C NMR (126 MHz) spectrum of **6m** in DMSO-d_6



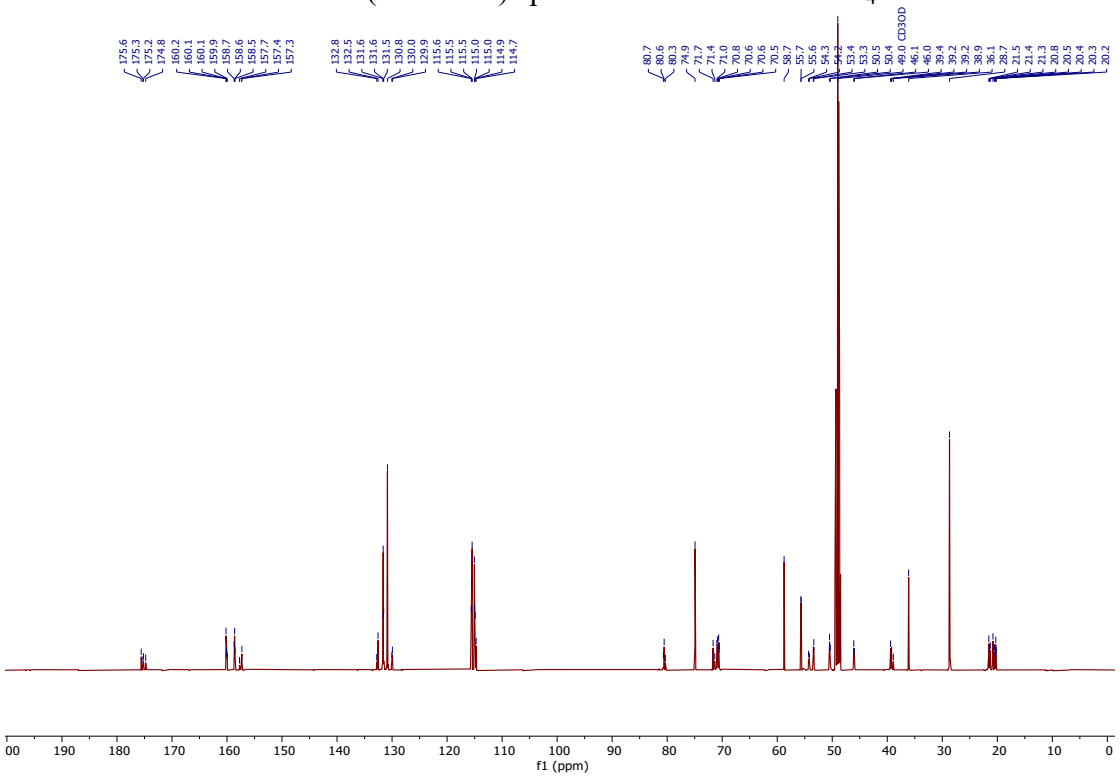
^{1}H NMR (500 MHz) spectrum of **6n** in DMSO-d_6



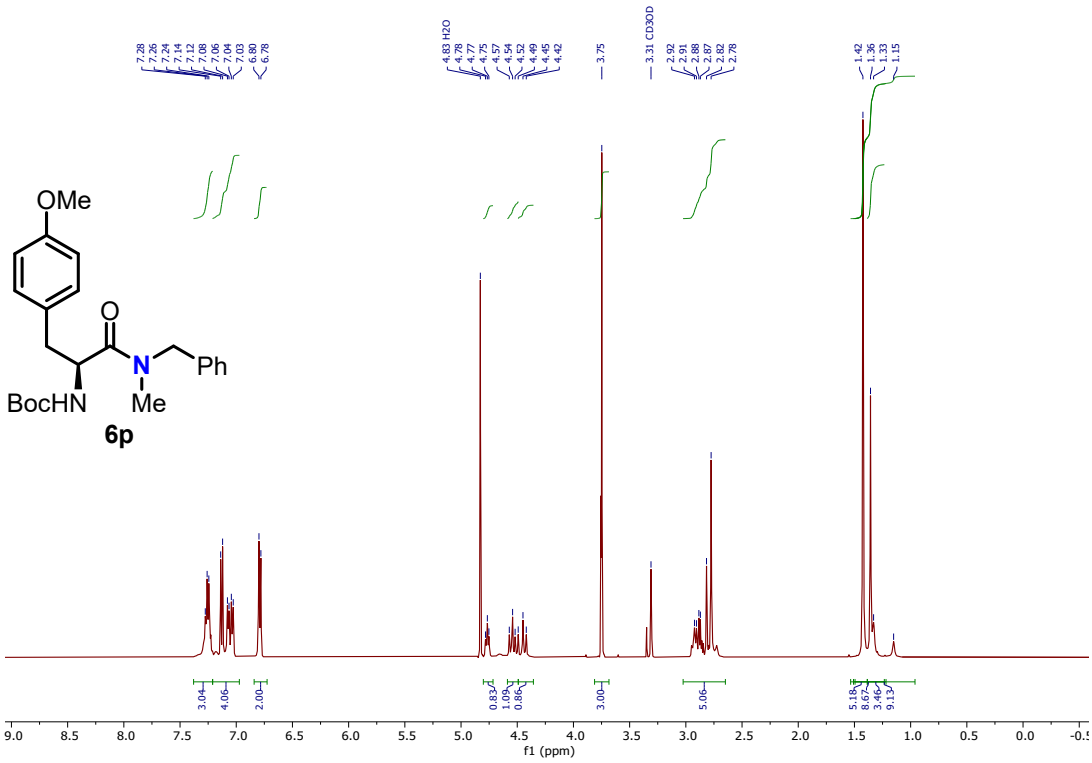
^{13}C NMR (126 MHz) spectrum of **6n** in DMSO-d_6



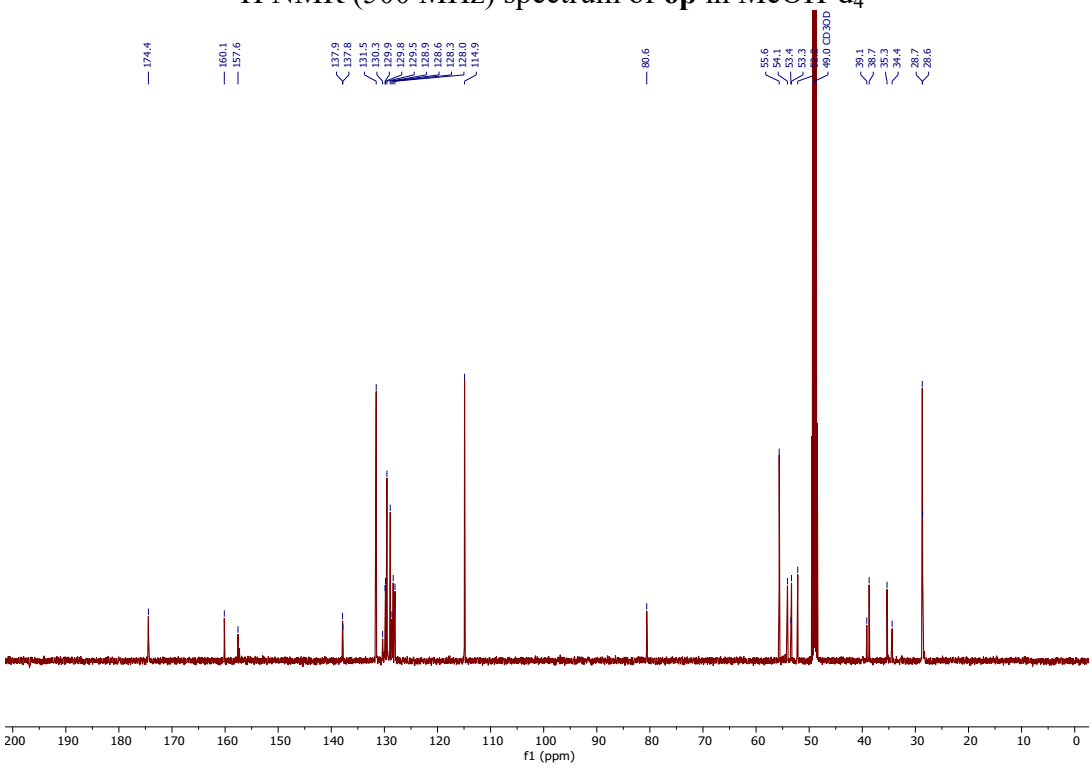
^{1}H NMR (500 MHz) spectrum of **6o** in MeOH-d_4



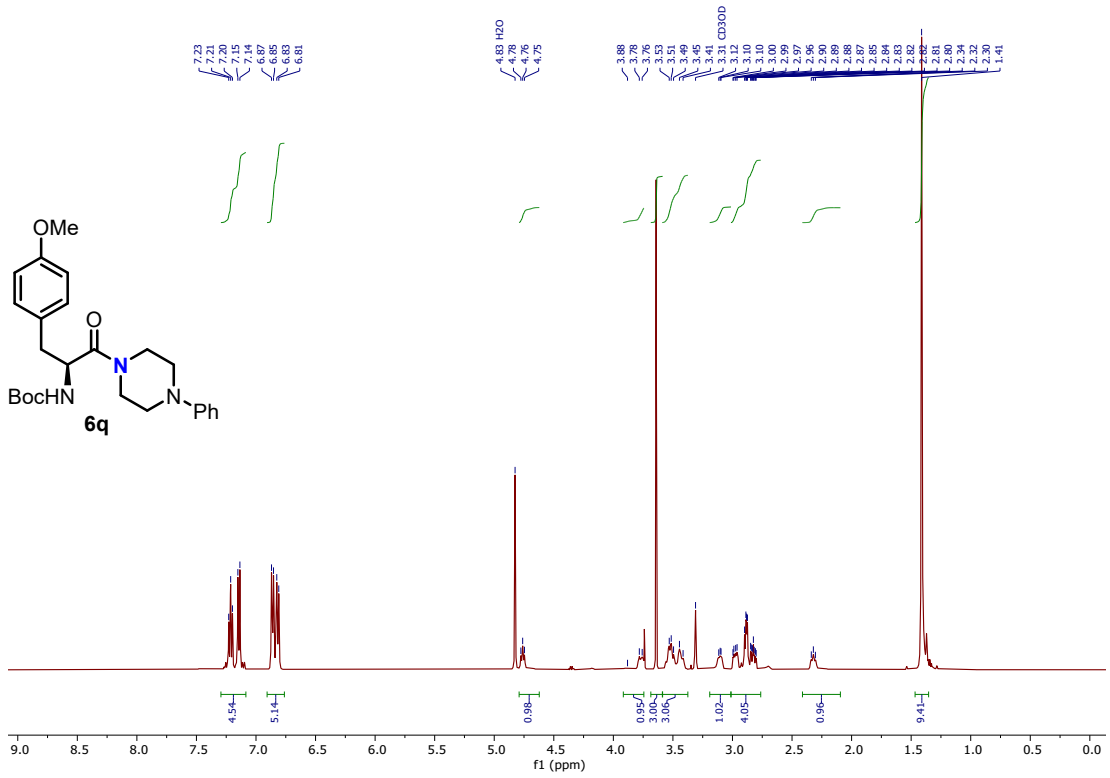
^{13}C NMR (126 MHz) spectrum of **6o** in MeOH-d_4



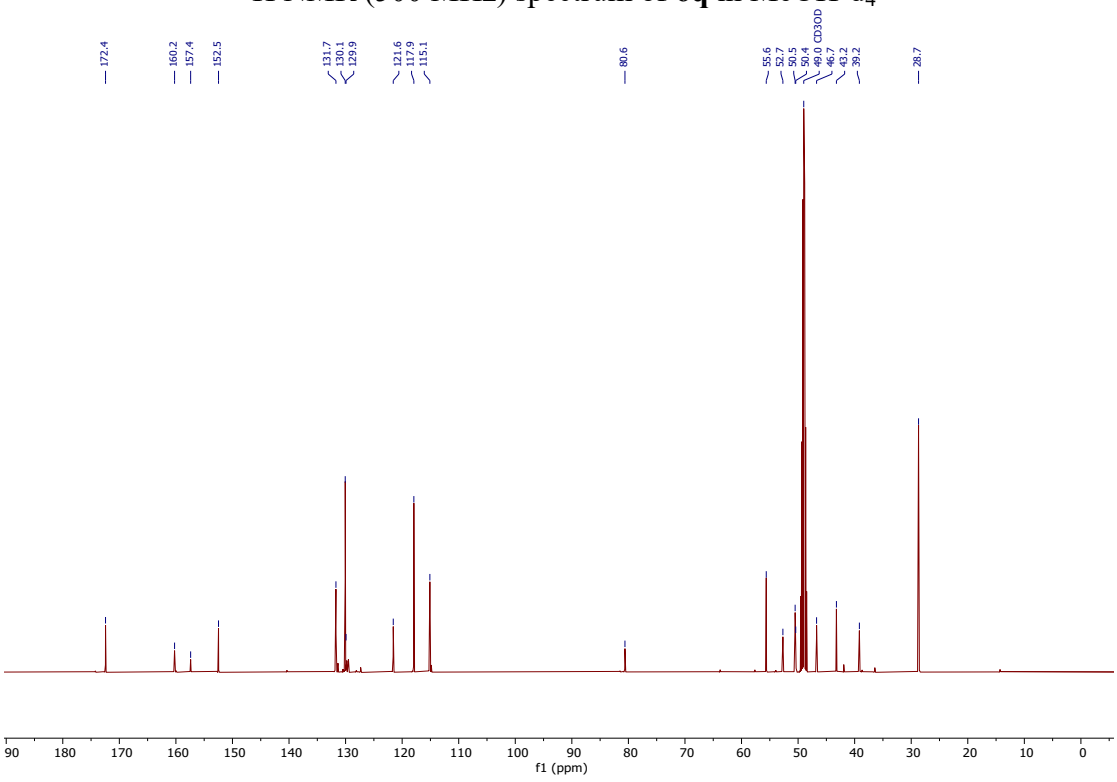
^{1}H NMR (500 MHz) spectrum of **6p** in MeOH-d_4



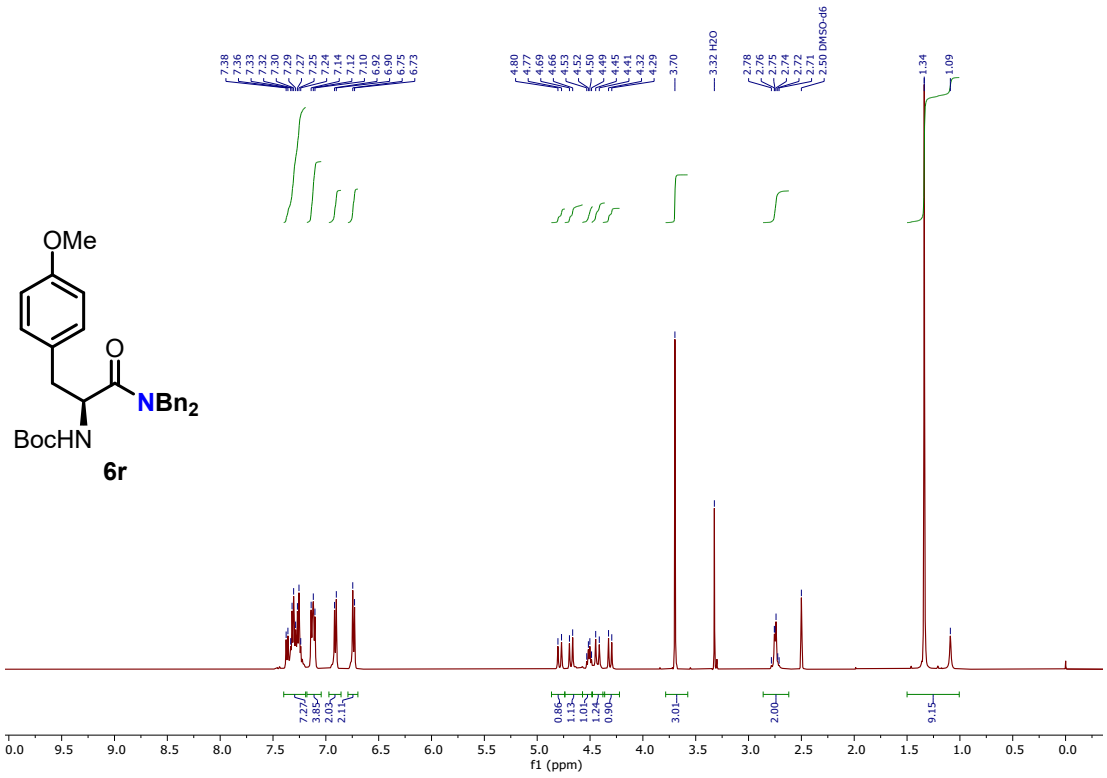
^{13}C NMR (126 MHz) spectrum of **6p** in MeOH-d_4



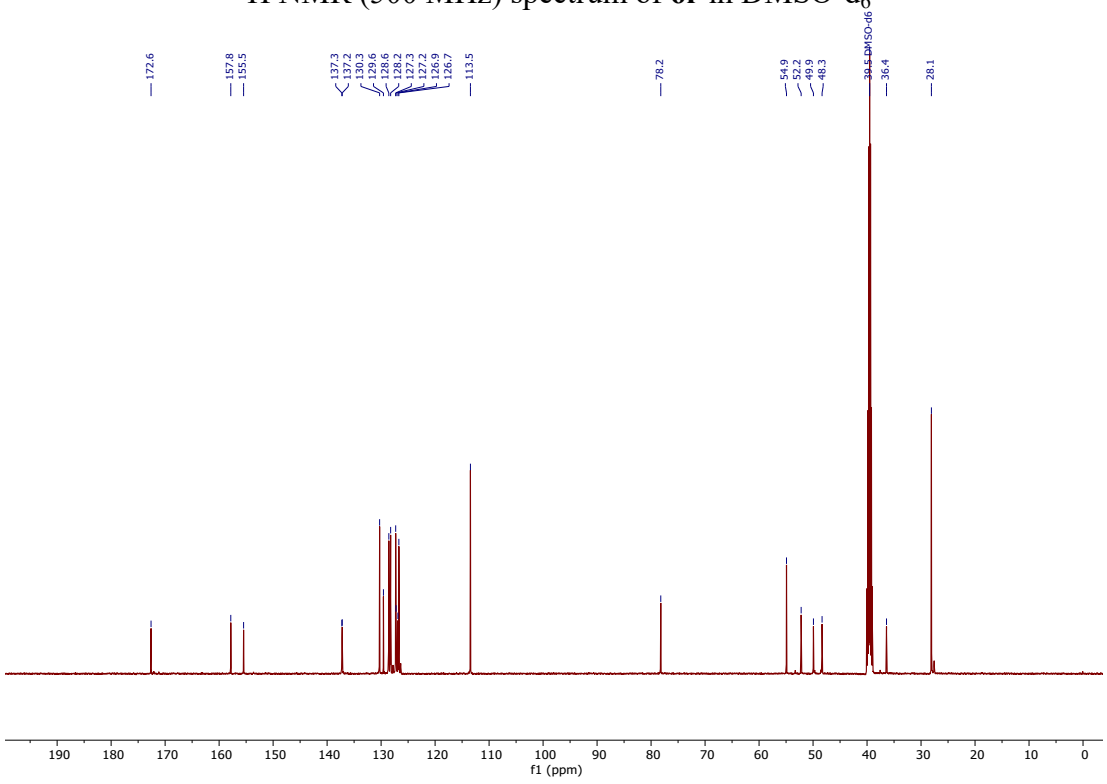
^{1}H NMR (500 MHz) spectrum of **6q** in MeOH-d_4



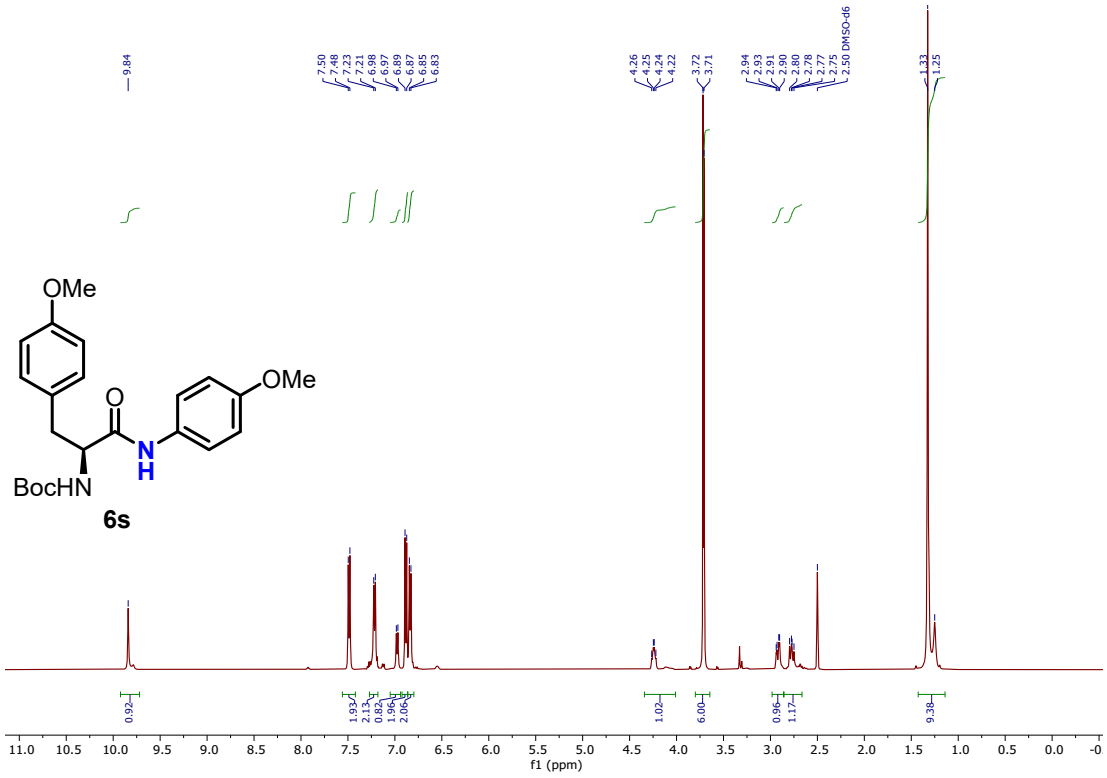
^{13}C NMR (126 MHz) spectrum of **6q** in MeOH-d_4



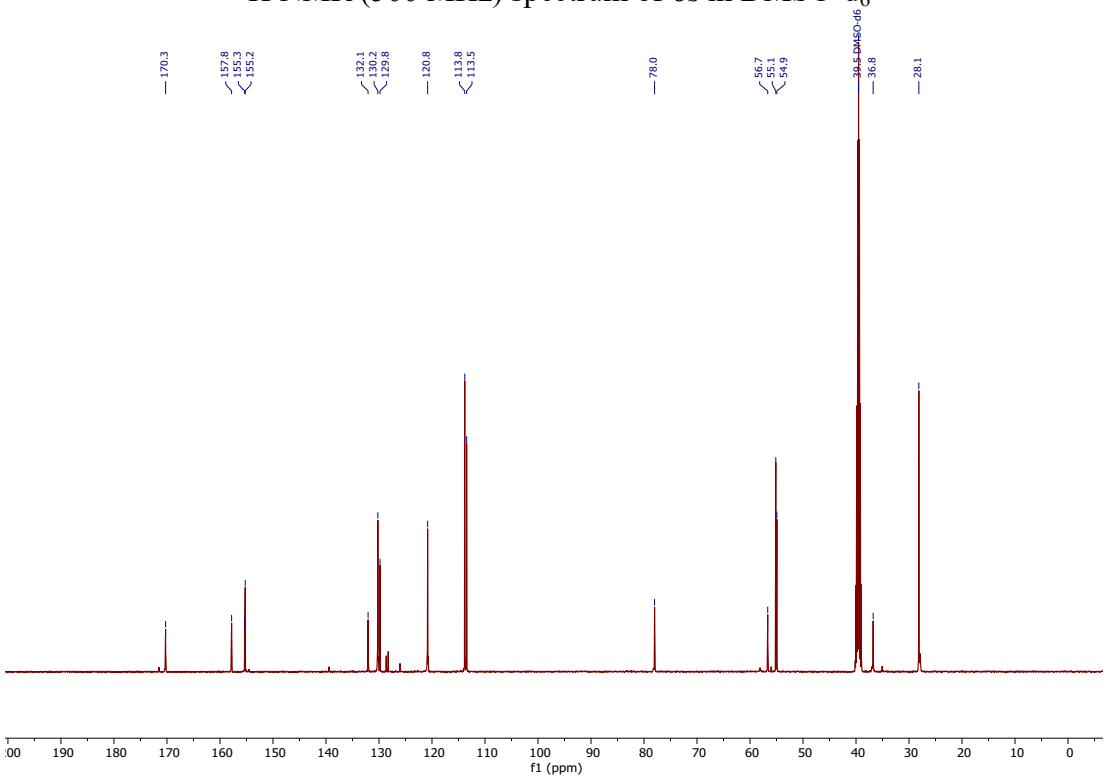
^{1}H NMR (500 MHz) spectrum of **6r** in DMSO-d_6



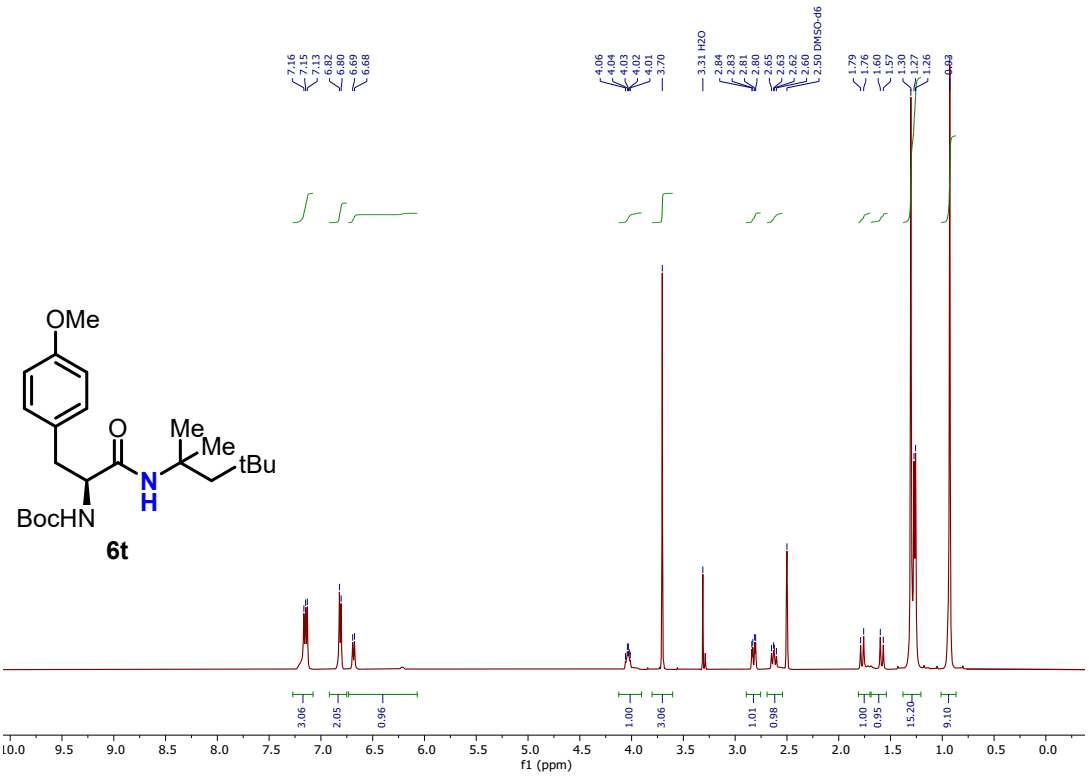
^{13}C NMR (126 MHz) spectrum of **6r** in DMSO-d_6



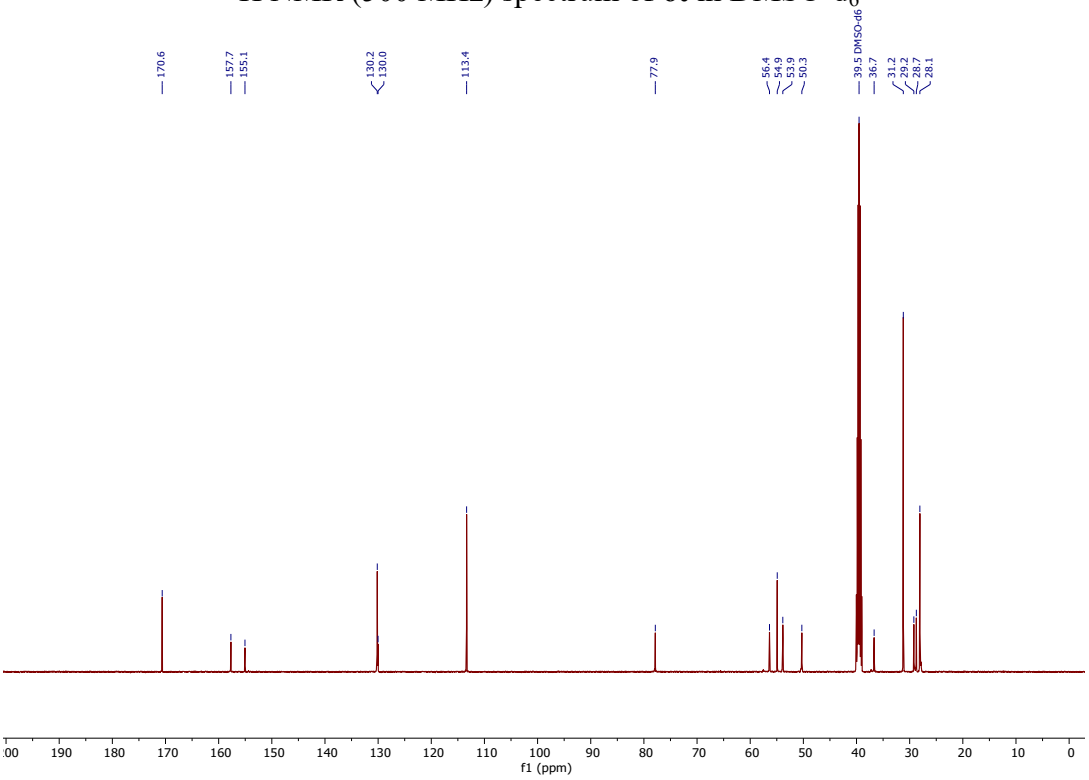
^{1}H NMR (500 MHz) spectrum of **6s** in DMSO-d$_6$



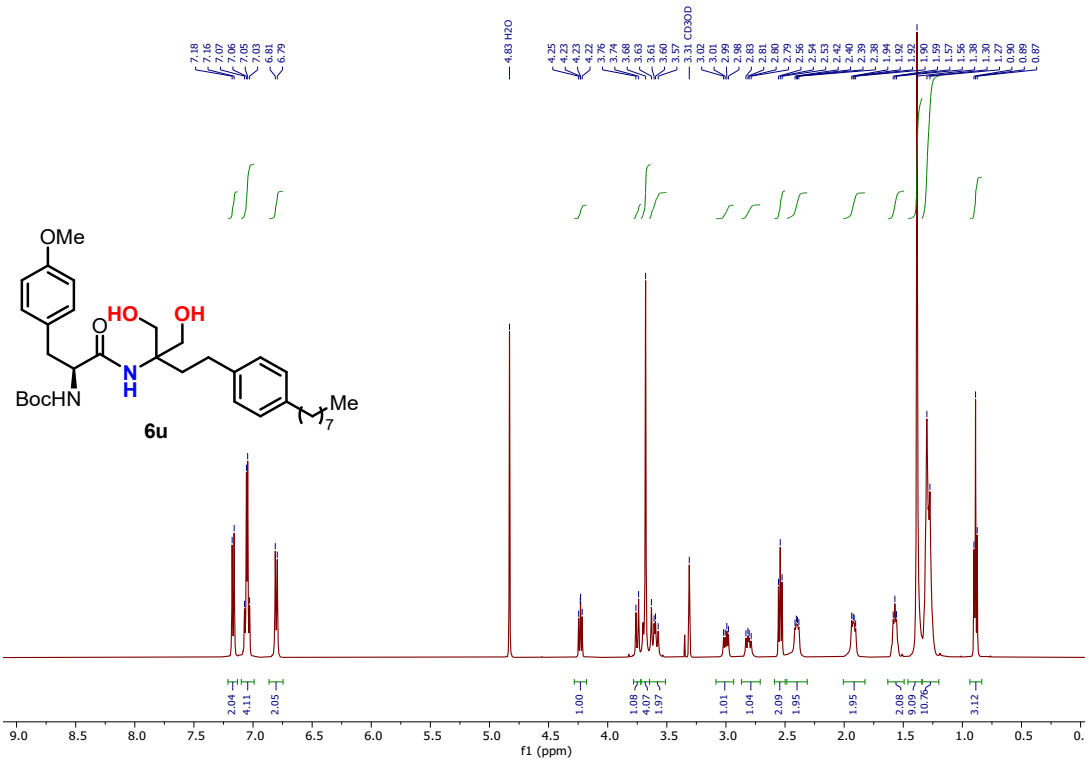
^{13}C NMR (126 MHz) spectrum of **6s** in DMSO-d$_6$



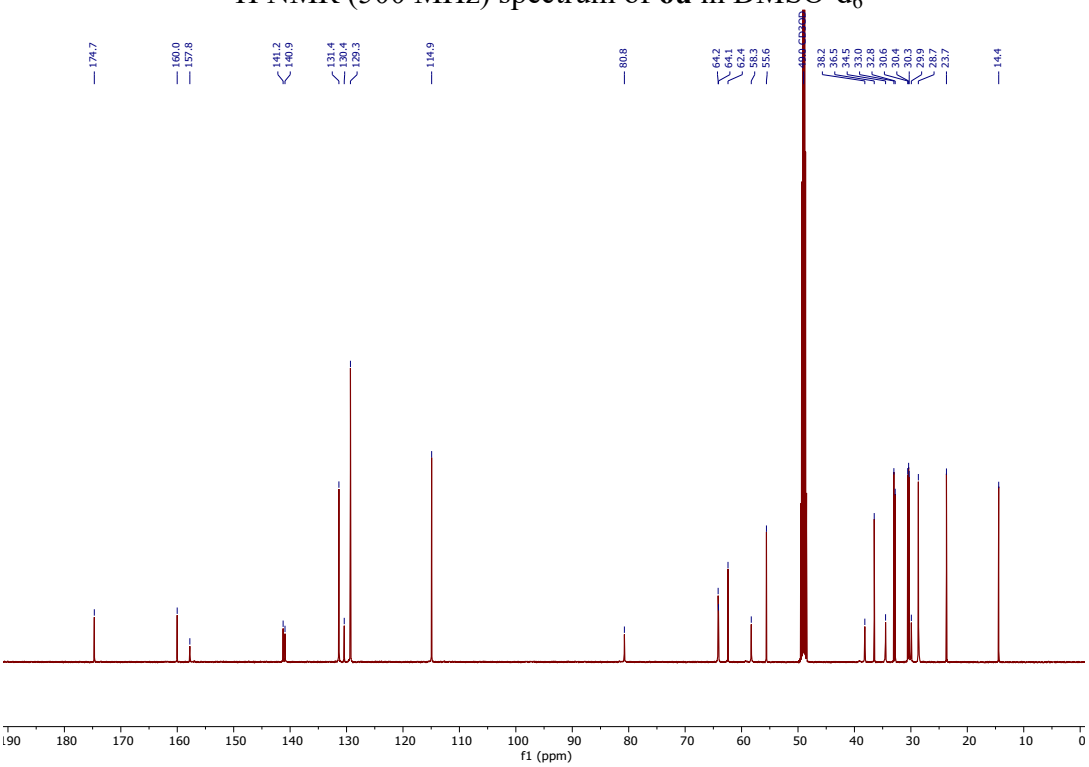
^{1}H NMR (500 MHz) spectrum of **6t** in DMSO-d_6



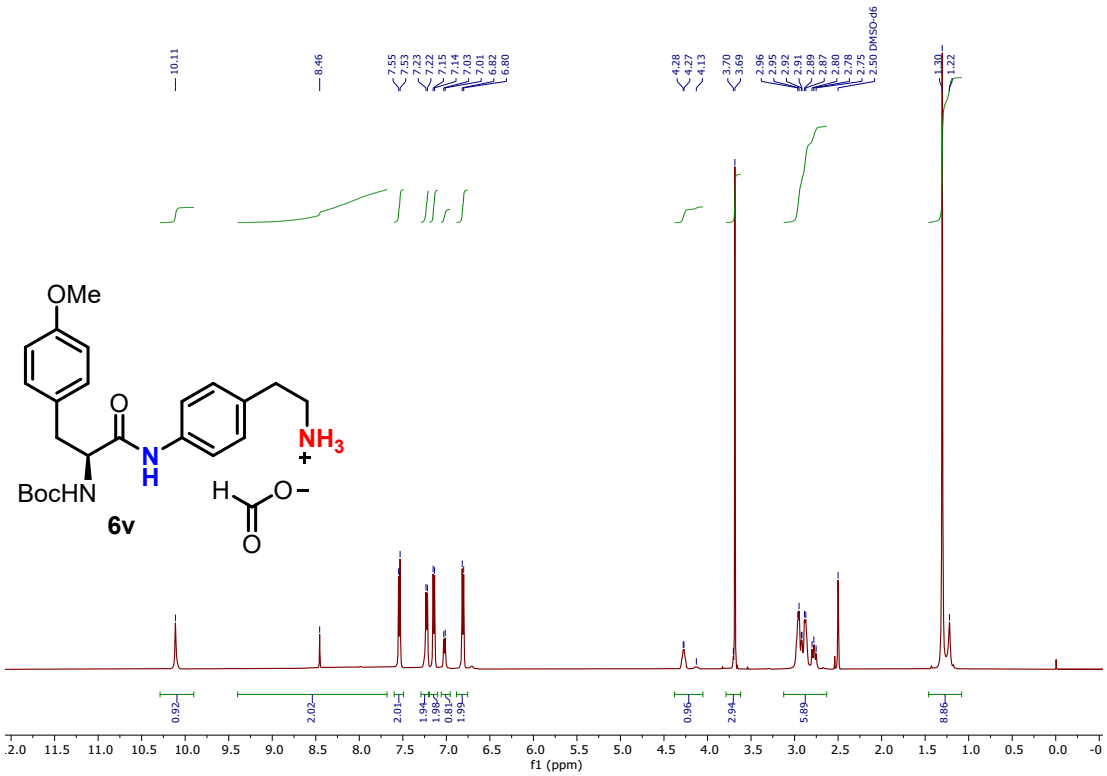
^{13}C NMR (126 MHz) spectrum of **6t** in DMSO-d_6



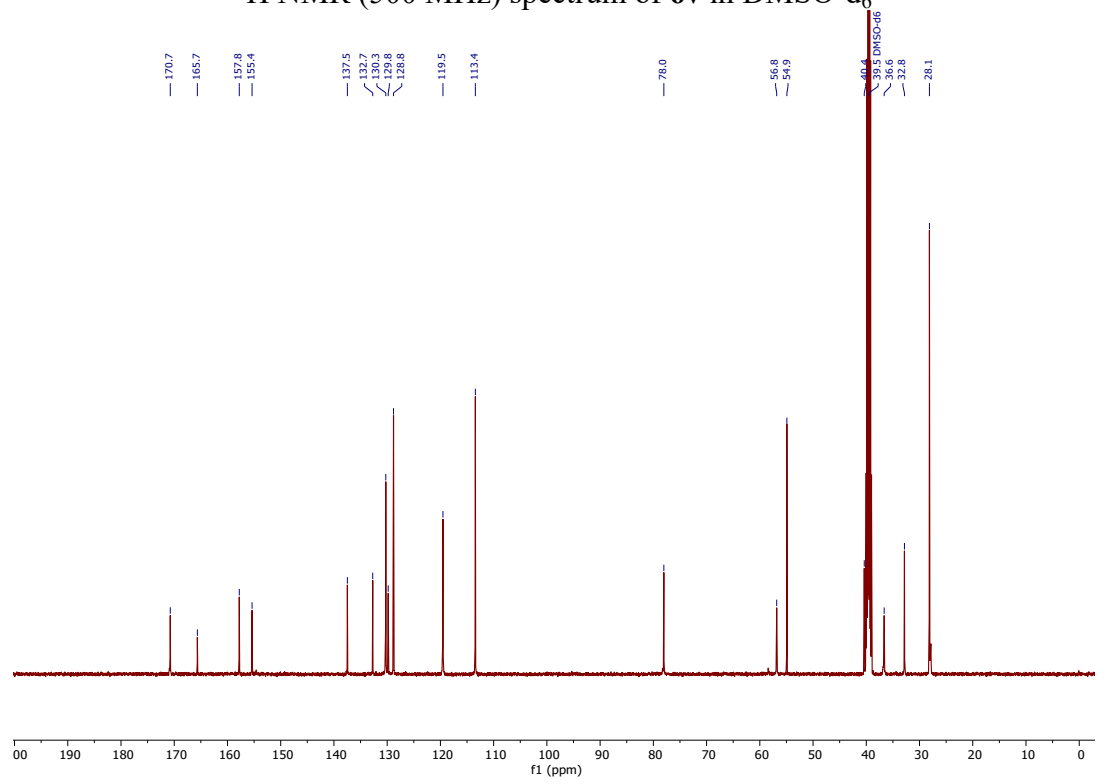
^{1}H NMR (500 MHz) spectrum of **6u** in DMSO-d$_6$



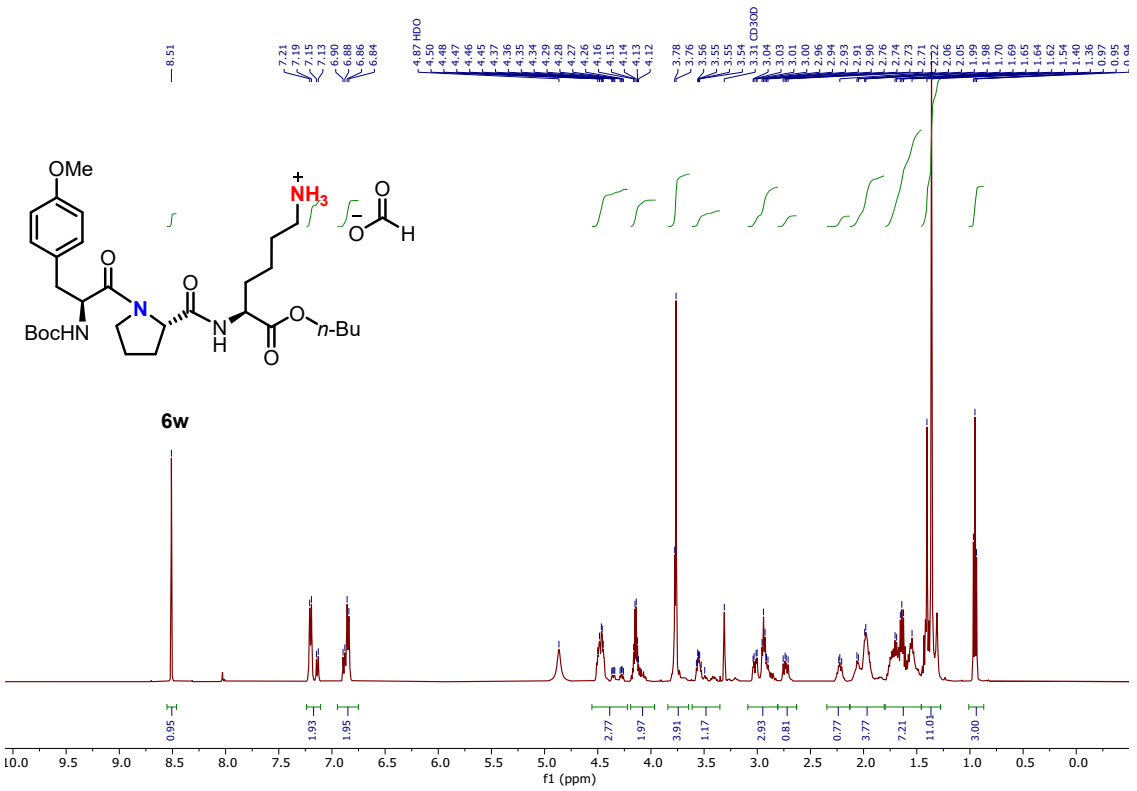
^{13}C NMR (126 MHz) spectrum of **6u** in DMSO-d$_6$



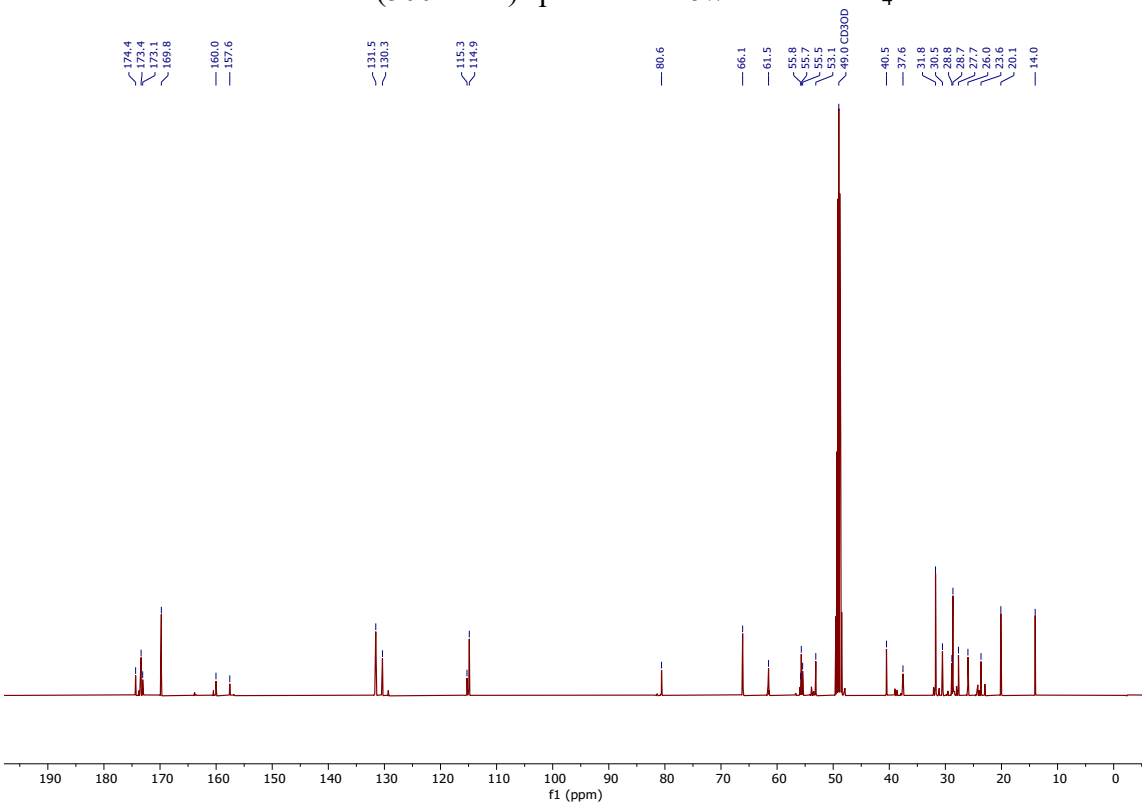
^{1}H NMR (500 MHz) spectrum of **6v** in DMSO-d_6



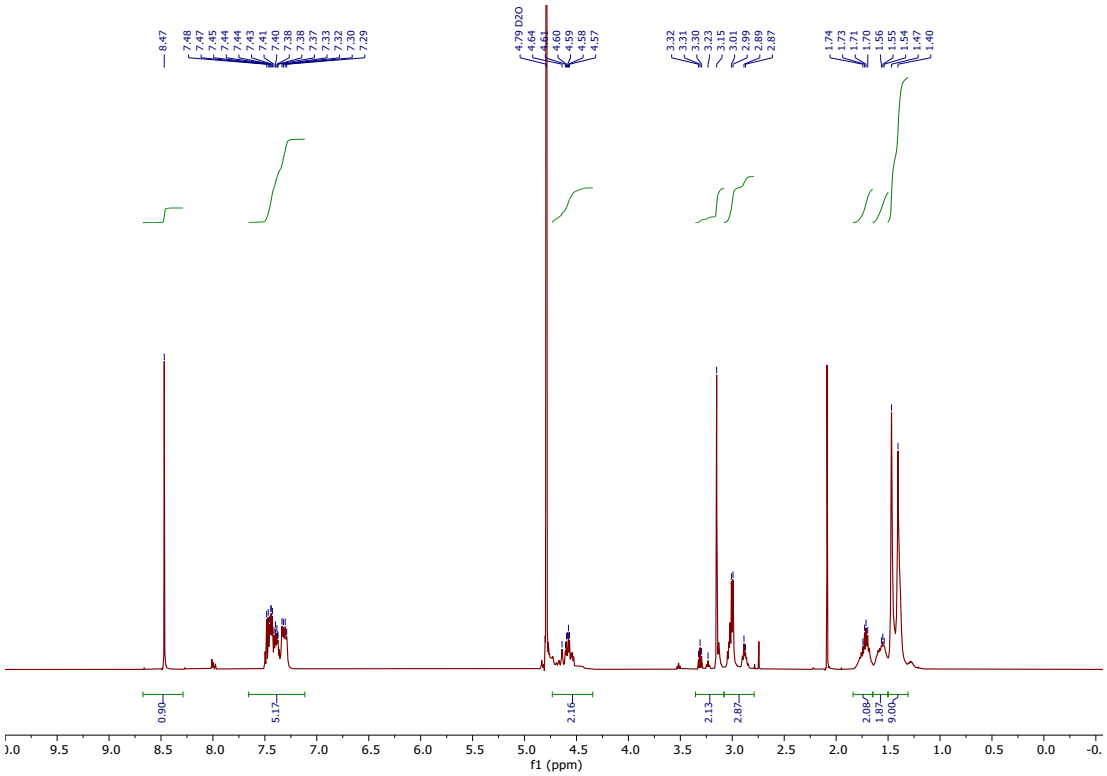
^{13}C NMR (126 MHz) spectrum of **6v** in DMSO-d_6



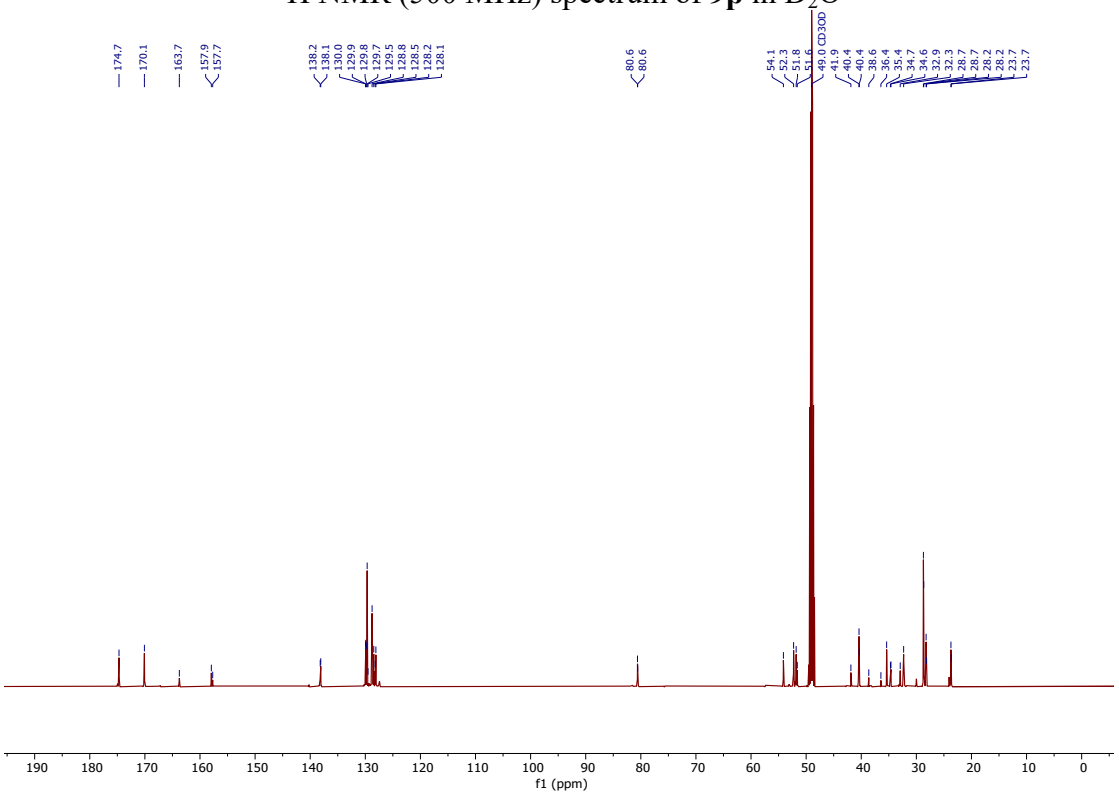
^{1}H NMR (500 MHz) spectrum of **6w** in MeOH-d_4



^{13}C NMR (126 MHz) spectrum of **6w** in MeOH-d_4

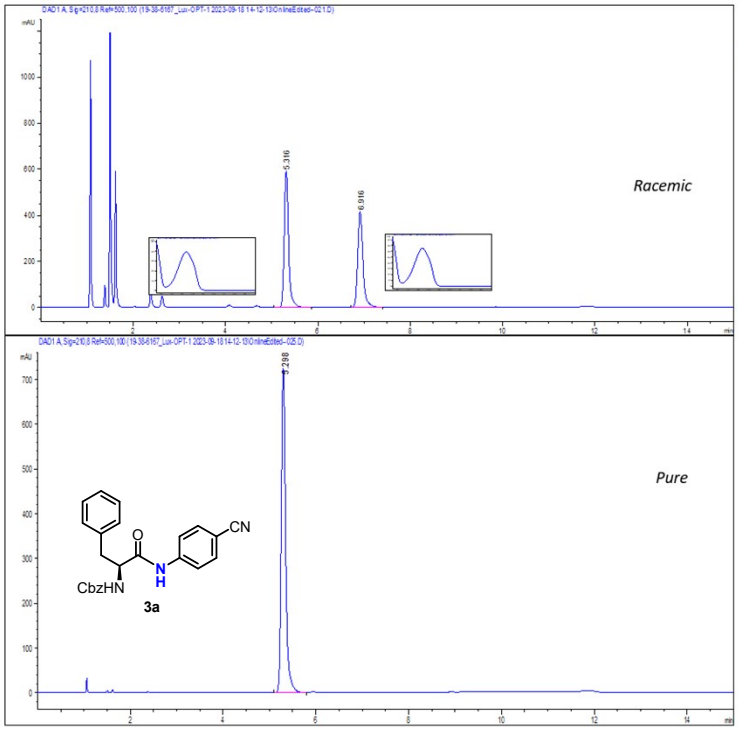


^{1}H NMR (500 MHz) spectrum of **9p** in D_2O



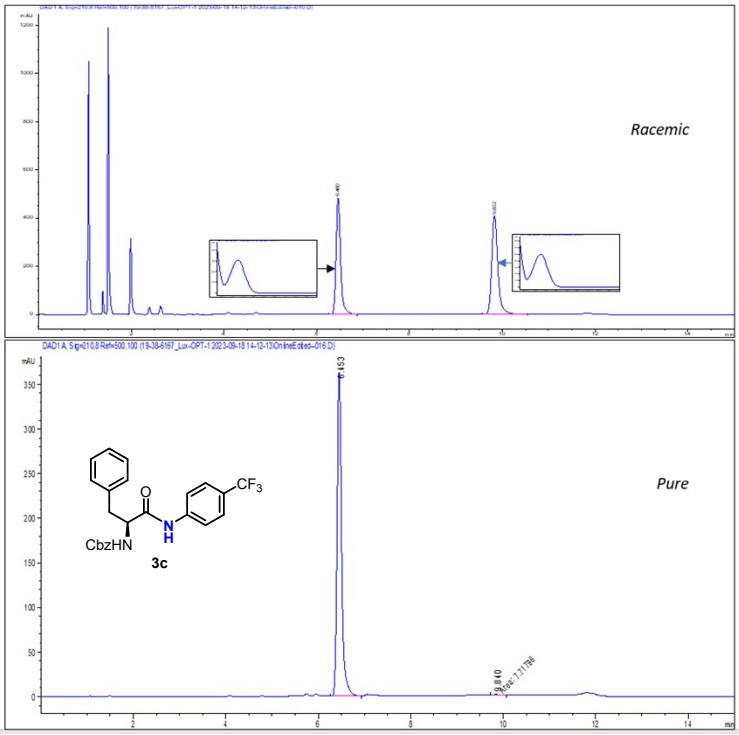
^{13}C NMR (126 MHz) spectrum of **9p** in MeOH-d_4

5. LC Chromatograms for Enantiomeric Purity Analysis



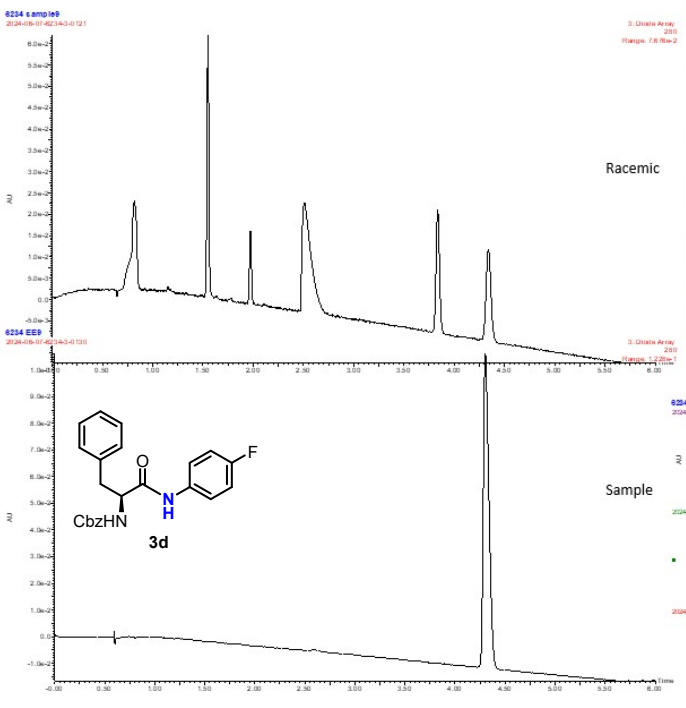
Method Parameters			
Column	LUX Cellulose 4; 4.6 x 150mm; 3µm (P/N: 00F-4490-E0)		
Mobile Phase A	0.1% H_3PO_4 (aq)		
Mobile Phase B	Acetonitirle		
Column Temp	25C		
Flow Rate	1.5 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	50	50
	10.00	30	70
	10.01	50	50
	15.00	50	50

	Major	Minor	EE
3a	100.00%	0.00%	***100.00%***



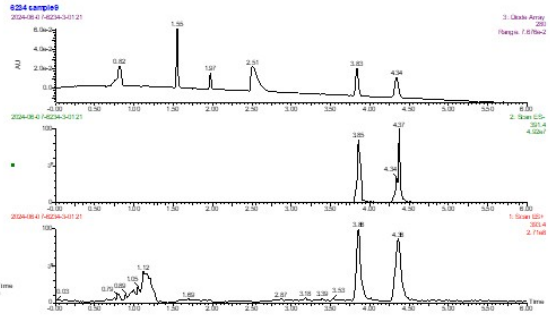
Method Parameters			
Column	LUX Cellulose 4; 4.6 x 150mm; 3µm (P/N: 00F-4490-E0)		
Mobile Phase A	0.1% H_3PO_4 (aq)		
Mobile Phase B	Acetonitirle		
Column Temp	25C		
Flow Rate	1.5 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	50	50
	10.00	30	70
	10.01	50	50
	15.00	50	50

	Major	Minor	EE
3c	99.69%	0.31%	***99.38%***

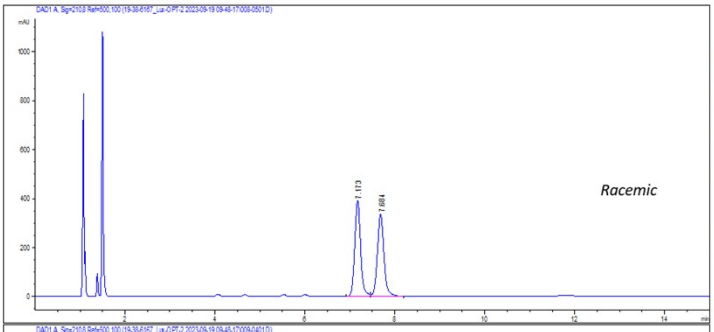


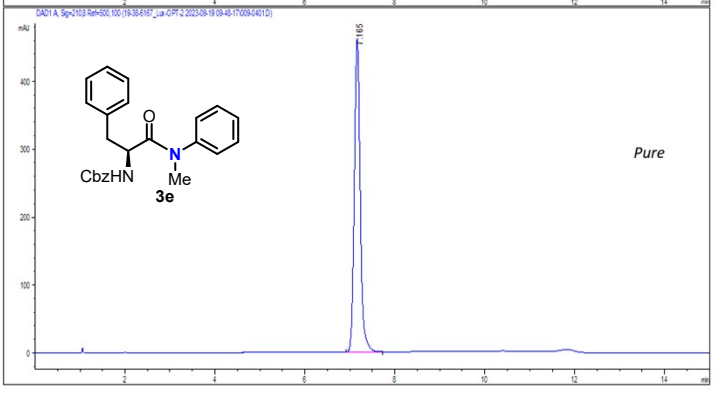
Method Parameters			
Column	Chiralcel OJ-3 – 4.6 x 150 mm; 3µm P/N: 17524		
Mobile Phase A	CO_2		
Mobile Phase B	25mM IBA in MeOH		
Column Temp	40C		
Flow Rate	3.0 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	99	1
	5.00	60	40
	6.00	60	40
Pressure	2900 psi		

	Major	Minor	EE
3d	100.00%	0.00%	100.00%



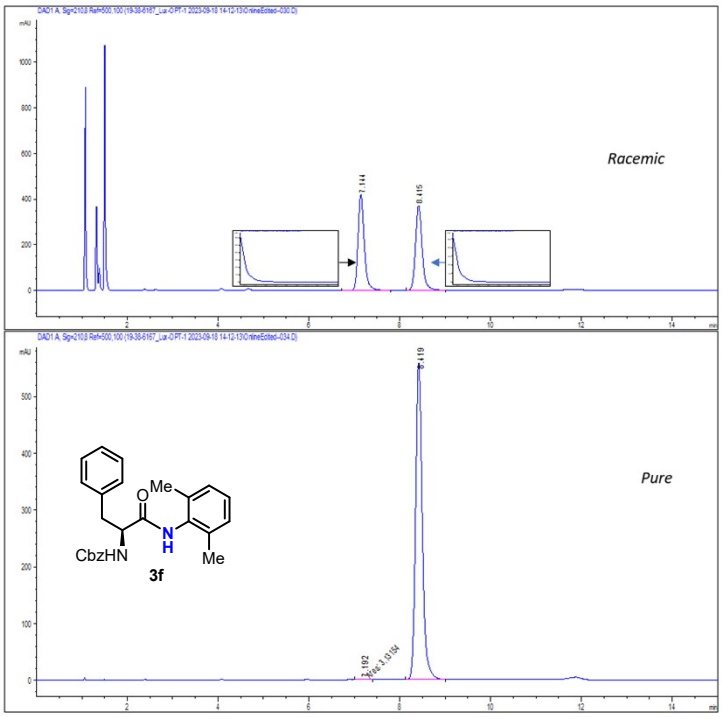
UV and Extracted MS (+) & MS (-)





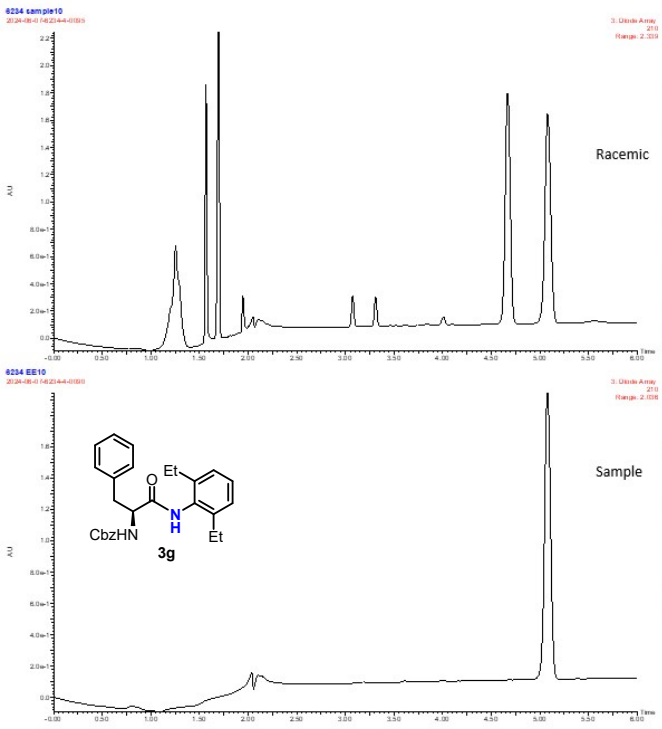
Method Parameters			
Column	LUX Cellulose 4; 4.6 x 150mm; 3µm (P/N: 00F-4490-E0)		
Mobile Phase A	0.1% H_3PO_4 (aq)		
Mobile Phase B	Acetonitrile		
Column Temp	25C		
Flow Rate	1.5 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	50	50
	10.00	30	70
	10.01	50	50
	15.00	50	50

	Major	Minor	EE
3e	100.00%	0.00%	100.00%



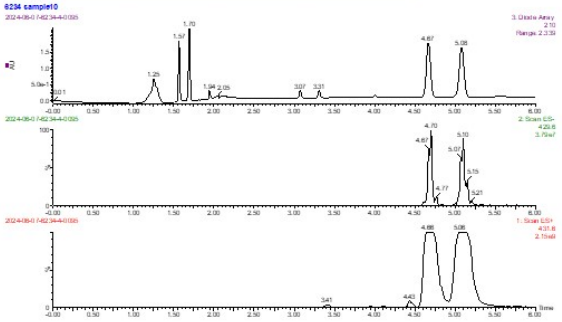
Method Parameters			
Column	LUX Cellulose 4; 4.6 x 150mm; 3µm (P/N: 00F-4490-E0)		
Mobile Phase A	0.1% H_3PO_4 (aq)		
Mobile Phase B	Acetonitirle		
Column Temp	25C		
Flow Rate	1.5 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	50	50
	10.00	30	70
	10.01	50	50
	15.00	50	50

	Major	Minor	EE
3f	99.95%	0.05%	***99.9%***

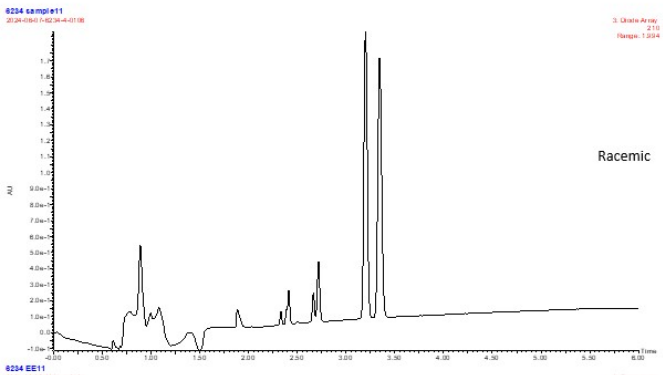


Method Parameters			
Column	Chiralpak AD-3 – 4.6 x 150 mm; 3µm P/N: 19524		
Mobile Phase A	CO_2		
Mobile Phase B	25mM IBA in EtOH		
Column Temp	40C		
Flow Rate	3.0 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	99	1
	5.00	60	40
	6.00	60	40
Pressure	2900 psi		

	Major	Minor	EE
3g	100.00%	0.00%	100.00%



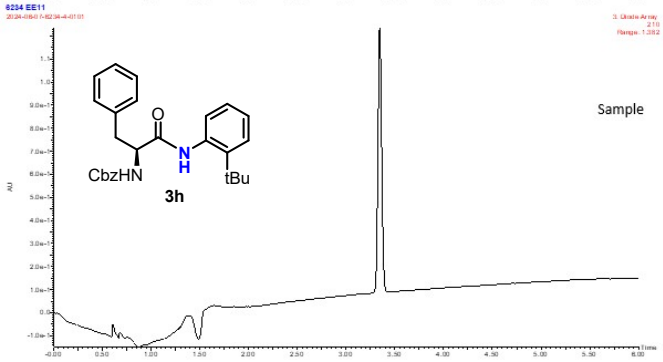
UV and Extracted MS (+) & MS (-)



Racemic

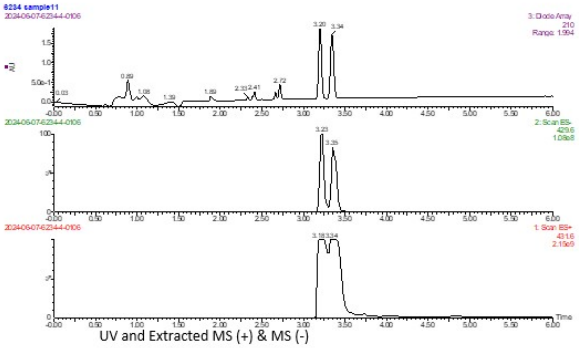
Method Parameters			
Column	Chiralcel OJ-3 – 4.6 x 150 mm; 3µm P/N: 17524		
Mobile Phase A	CO_2		
Mobile Phase B	25mM IBA in IPA		
Column Temp	40C		
Flow Rate	3.0 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	99	1
	5.00	60	40
	6.00	60	40
Pressure	2900 psi		

	Major	Minor	EE
3h	100.00%	0.00%	100.00%

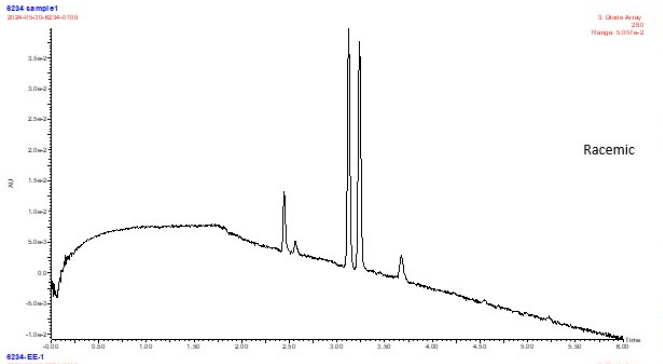


3h

Sample



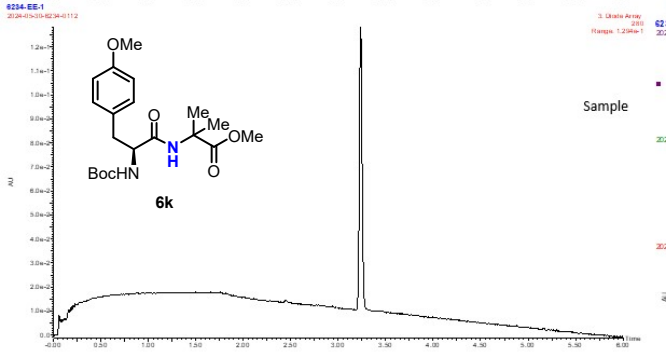
UV and Extracted MS (+) & MS (-)



Racemic

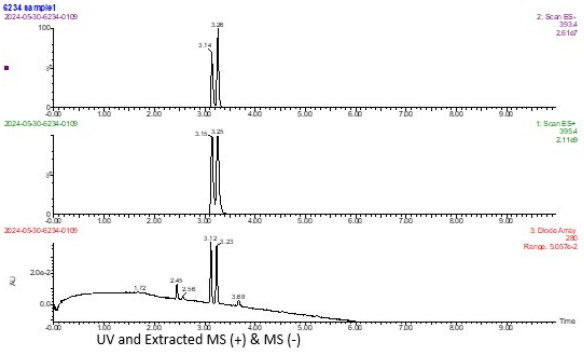
Method Parameters			
Column	Chiralpak IC – 4.6 x 150 mm; 3µm P/N: 83524		
Mobile Phase A	CO_2		
Mobile Phase B	2% H_2O + 0.2% NH_4OH in Methanol		
Column Temp	40C		
Flow Rate	2.0 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	99	1
	5.00	60	40
	6.00	60	40
Pressure	2900 psi		

	Major	Minor	EE
6k	100.00%	0.00%	100.00%

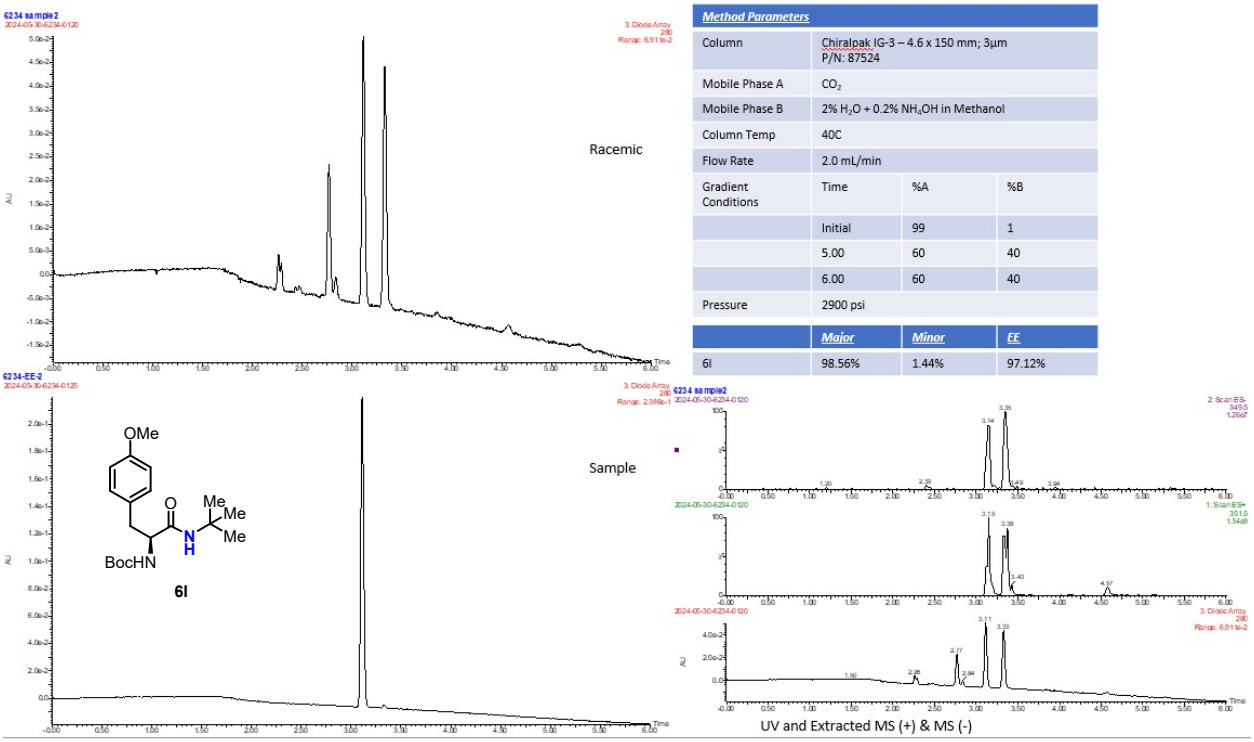


6k

Sample

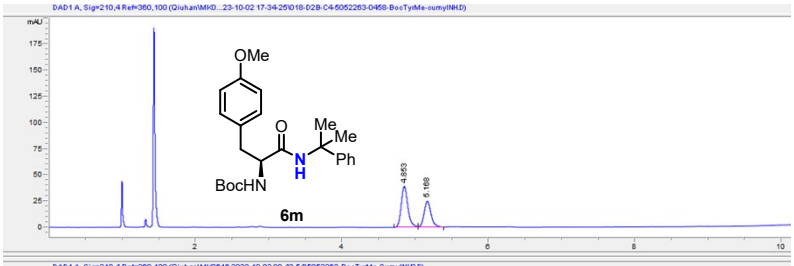


UV and Extracted MS (+) & MS (-)



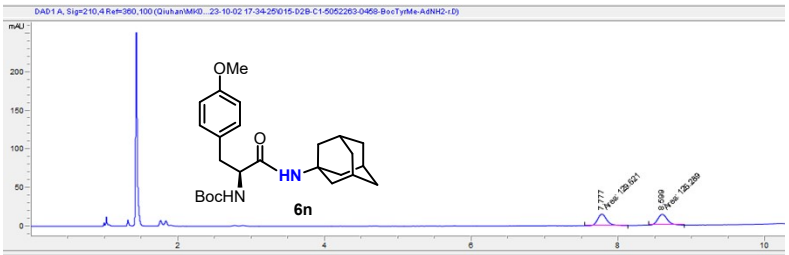
Method Parameters			
Column	Chiralpak IG-3 – 4.6 x 150 mm; 3µm P/N: 87524		
Mobile Phase A	CO_2		
Mobile Phase B	2% H_2O + 0.2% NH_4OH in Methanol		
Column Temp	40C		
Flow Rate	2.0 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	99	1
	5.00	60	40
	6.00	60	40
Pressure	2900 psi		

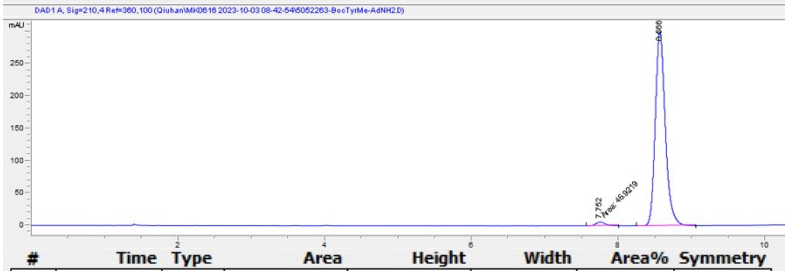
	Major	Minor	EE
6l	98.56%	1.44%	97.12%



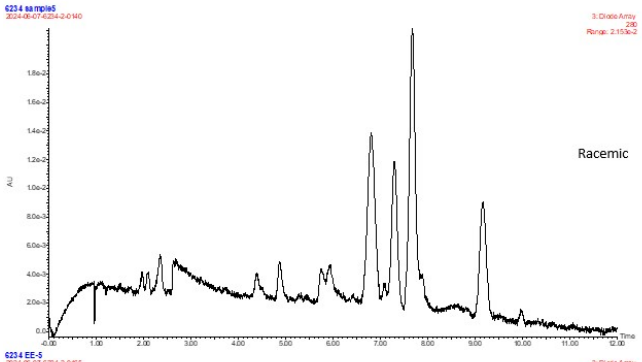
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.832	BB	10.1	1.6	0.0783	0.204	0.933
2	5.143	BB	4919.4	730.6	0.1026	99.796	0.756

```
LUX Cellulose 4; 4.6 x 150mm; 3µm
(P/N: 00F-4490-E0)
Mobile phase A: MeCN
Mobile phase C: H2O w/ 0.1% H3PO4
Column temp. = 25 °C, Flow rate = 1.5 mL/min, Post time = 0 min
Time / min   %A      %C
        0            50       50
       10            70       30
     10.1          50         50
       15           50     50
```



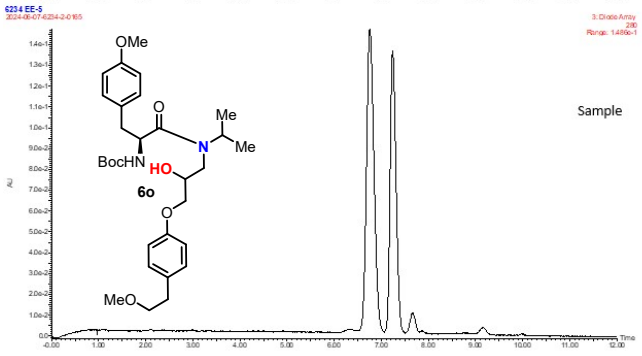


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.752	MM	46.9	5.6	0.1387	1.628	0.858
2	8.566	BB	2835.5	300.9	0.1439	98.372	0.784

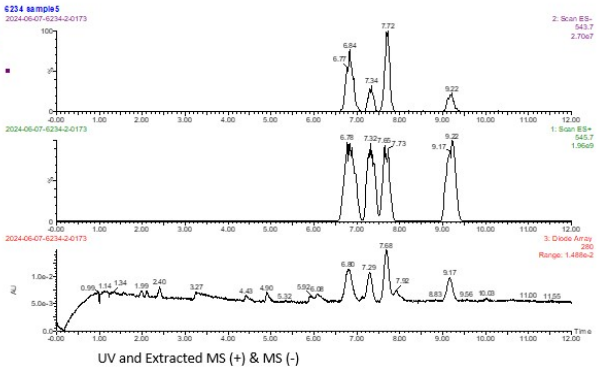


Racemic

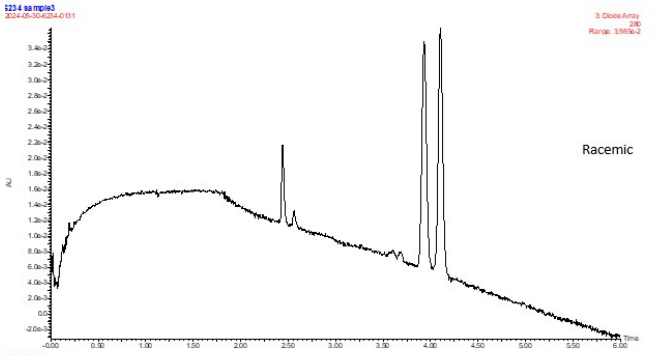
Method Parameters			
Column	Chiralcel OJ-3 – 4.6 x 150 mm; 3µm P/N: 17524		
Mobile Phase A	CO_2		
Mobile Phase B	2% H2O + 0.2% NH4OH in Methanol		
Column Temp	40C		
Flow Rate	2.0 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	99	1
	12.00	60	10
Pressure	2900 psi		



Sample



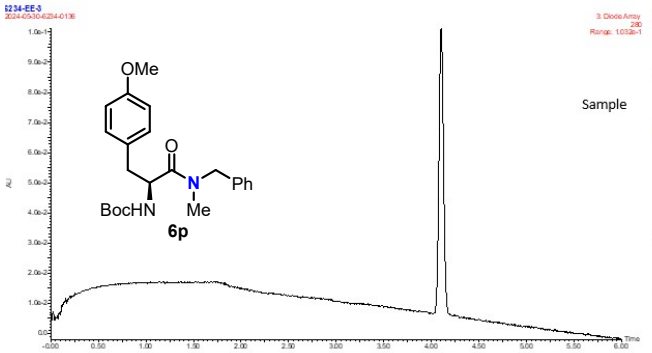
UV and Extracted MS (+) & MS (-)



Racemic

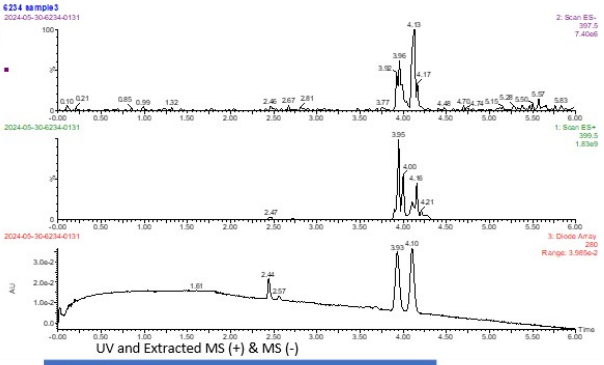
Method Parameters			
Column	Chiralpak IC – 4.6 x 150 mm; 3µm P/N: 83524		
Mobile Phase A	CO_2		
Mobile Phase B	2% H_2O + 0.2% NH_4OH in Methanol		
Column Temp	40C		
Flow Rate	2.0 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	99	1
	5.00	60	40
	6.00	60	40
Pressure	2900 psi		

	Major	Minor	EE
6p	100.00%	0.00%	100.00%

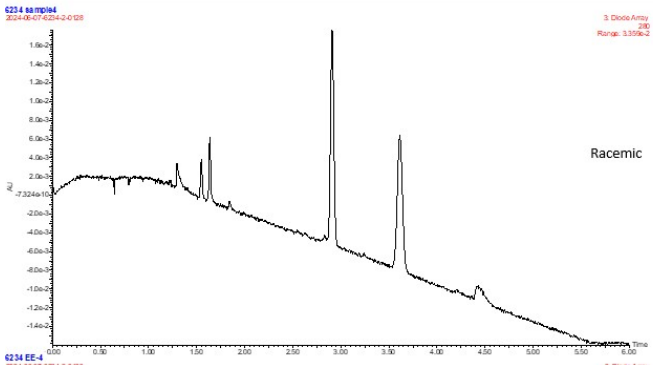


6p

Sample



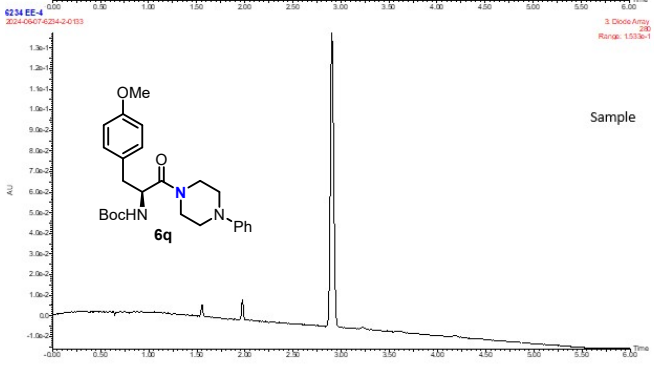
UV and Extracted MS (+) & MS (-)



Racemic

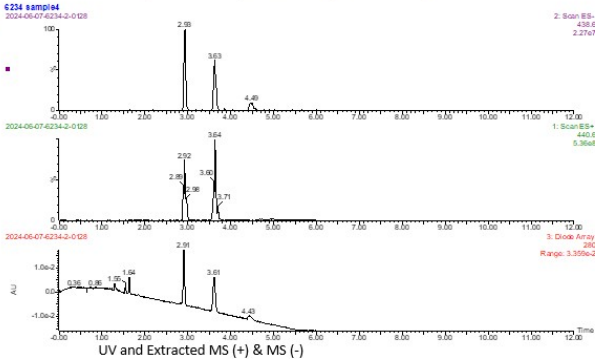
Method Parameters			
Column	Chiralcel OJ-3 – 4.6 x 150 mm; 3µm P/N: 17524		
Mobile Phase A	CO_2		
Mobile Phase B	25mM IBA in Methanol		
Column Temp	40C		
Flow Rate	3.0 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	99	1
	5.00	60	40
	6.00	60	40
Pressure	2900 psi		

	Major	Minor	EE
6q	100.00%	0.00%	100.00%

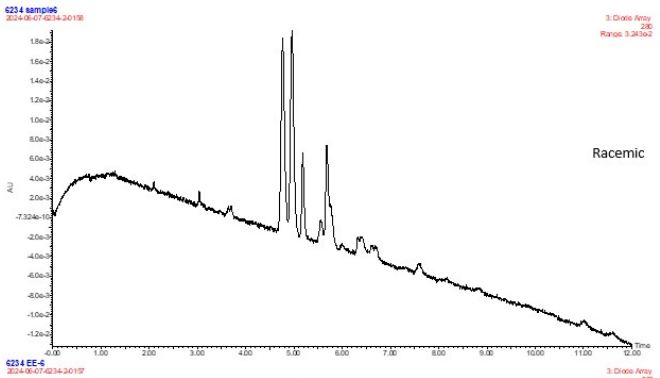


6q

Sample

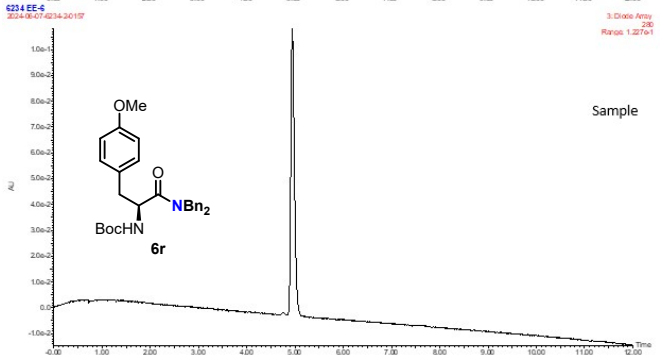


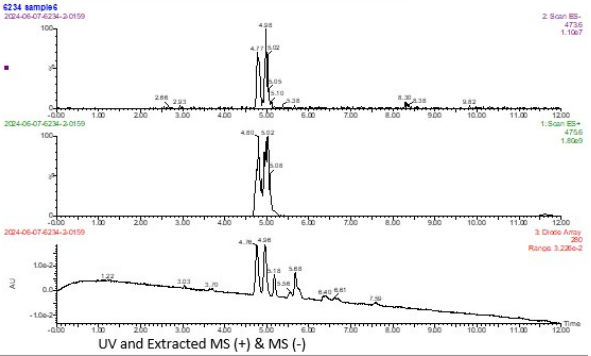
UV and Extracted MS (+) & MS (-)



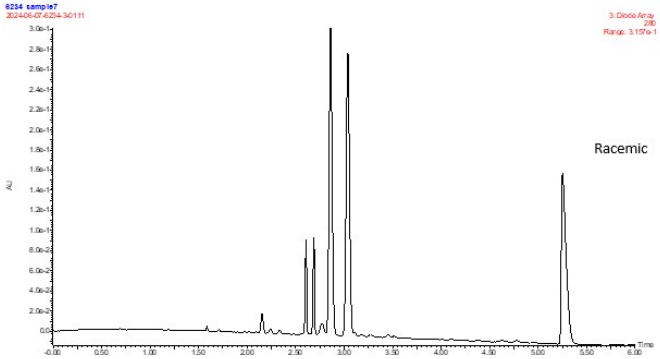
Method Parameters			
Column	Lux Cellulose 4 – 4.6 x 150 mm; 3µm P/N: 00F-4490-E0		
Mobile Phase A	CO_2		
Mobile Phase B	25 mM IBA in EtOH		
Column Temp	40C		
Flow Rate	3.0 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	99	1
	12.00	60	40
Pressure	2900 psi		

	Major	Minor	EE
6r	100.00%	0.00%	100.00%



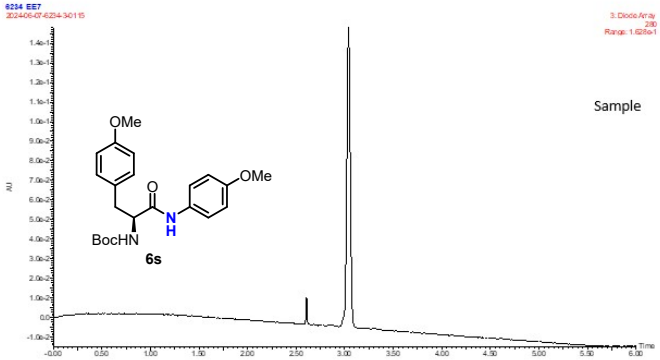


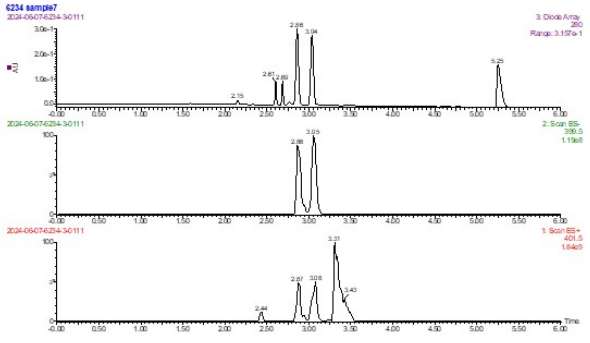
UV and Extracted MS (+) & MS (-)



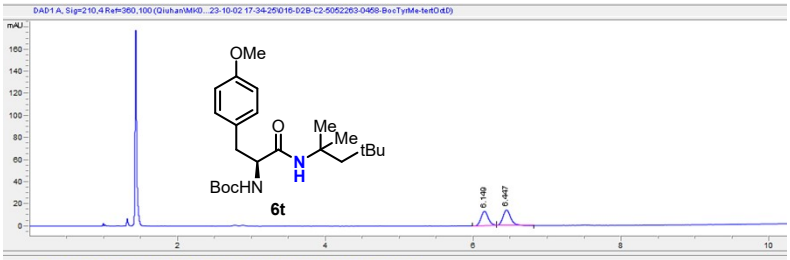
Method Parameters			
Column	Chiralcel OZ-3 – 4.6 x 150 mm; 3µm P/N: 45254		
Mobile Phase A	CO_2		
Mobile Phase B	25mM IBA in MeOH		
Column Temp	40C		
Flow Rate	3.0 mL/min		
Gradient Conditions	Time	%A	%B
	Initial	99	1
	5.00	60	40
	6.00	60	40
Pressure	2900 psi		

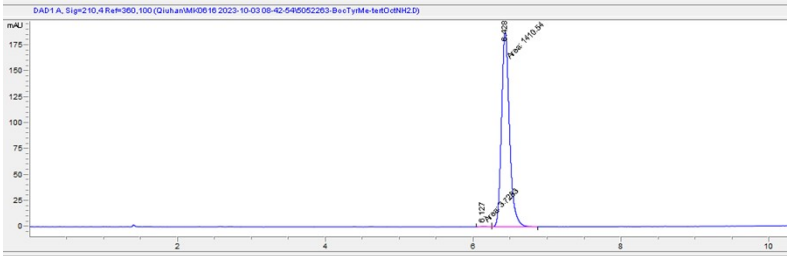
	Major	Minor	EE
CMPD-7	99.58%	0.42%	99.16%





UV and Extracted MS (+) & MS (-)





#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.127	MF	3.7	5.5E-1	0.1133	0.264	0.461
2	6.428	FM	1410.5	188.7	0.1246	99.736	0.771

6. References:

(1). It has been previously shown that Oxyma and DIC can react to generate HCN (M. Erny, M. Lundqvist, J. H. Rasmussen, O. Ludemann-Hombourger, F. Bihel, J. Pawlas, *Org. Process Res. Dev*. 2020, **24**, 1341–1349.). It was found that only carbodiimides bearing secondary alkyl substituents would undergo side reaction with Oxyma to produce CN^- (S. R. Manne, D. C. Akintayo, O. Luna, A. El-Faham, B. G. de la Torre, F. Albericio, *Org. Process Res. Dev*., 2022, **26**, 2894–2899).