

Addition of carbon nucleophiles to hemiaminals promoted by a Lewis acidic polyoxotungstate

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1. General remarks

Reagents and chemicals were purchased from commercial sources and used as received. The Hf substituted polyoxotungstate (POM/Hf), *N*-Boc-2-hydroxypyrrolidine¹ and *N*-Boc-2-hydroxypiperidine¹ were prepared as described previously. Unless otherwise noted, reactions were carried out under argon atmosphere with magnetic stirring in redistilled solvents when necessary. Solvents were purified and dried by standard procedures. Merck 60F254 silica gel was used for thin-layer chromatography (TLC) and Merck Geduran SI 60 Å silica gel 60 (40-63 µM) was used for flash column chromatography.

Melting points were measured on a Stuart Scientific Melting Point SMP3 apparatus in open capillaries. IR spectra were recorded from a Bruker Tensor 27 ATR diamond PIKE spectrophotometer. NMR ¹H, ³¹P, ¹³C spectra were recorded at 400, 162, and 100 MHz, respectively, using a Bruker AVANCE 400 spectrometer equipped with a BBFO probe. Some ¹³C NMR spectra were recorded at 50 MHz using a Bruker AVANCE 200. Chemical shifts are reported in ppm, using, for ¹H and ¹³C, solvent residual peak as internal standard references and external H₃PO₄ for ³¹P. Coupling constants (*J*) are given in Hertz (Hz), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

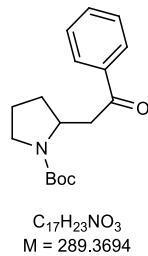
Mass spectrometry experiments have been carried out at the Institut Parisien de Chimie Moléculaire (FR2769) on an electrospray-ion trap instrument

2. General Procedures

General Procedure 1 (GP1). POM/Hf catalyzed addition of Carbon Nucleophiles to hemiaminal 1. To a solution of POM/Hf (1 mol%, 0.004 mmol) in CH₃CN (1 mL) were added *N*-Boc-2-hydroxypyrrolidine **1a** (0.4 mmol, 1 equiv.), the silyl enol ether **2** (ketene-acetals) (0.4 mmol, 1 equiv.), 1,3-dicarbonyl compounds **6** (0.4 mmol, 1 equiv.) allytrimethylsilane (2 mmol, 5 equiv.). After completion, 2 mL of a solution of acetone/ethanol (1/1) were added, followed by 20 mL of diethyl ether. The white precipitate (catalyst) was recovered by filtration or by centrifugation and the remaining organic solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/Pentane) to afford the desired product.

3. Descriptions

2-(2-Oxo-2-phenyl-ethyl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (**3a**)

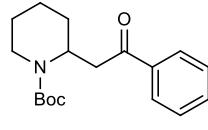


$C_{17}H_{23}NO_3$
M = 289.3694

Following **GP1**, from N-Boc-2-hydroxypyrrolidine **1a** (30 mg, 0.16 mmol), 1-phenylvinyl trimethylsilyl ether **2a** (34 μ L, 0.16 mmol) and POM/Hf (1 mol%, 0.0016 mmol), to give the desired product **3a** as a clear oil (33 mg, 0.12 mmol, 72% yield). Spectral data correspond to those described in the literature.² [*Tetrahedron*, 1996, 52, 2629-2646]

IR ν max (neat) / cm^{-1} 1677, 1391; ^1H NMR (400 MHz, CDCl_3) δ 1.39 (s, 9H, *t*-Bu), 1.64–1.72 (m, 1H, *CHH*), 1.73 –1.87 (m, 2H, CH_2), 1.99 (ddd, J = 16.7, 12.4, 7.6 Hz, 1H, *CHH*), 2.77 (dd, J = 15.4, 9.9 Hz, 1H, *COCHH*), 3.30 (t, J = 6.5 Hz, 2H, NCH_2), 3.57 (bs, 1H, *COCHH*), 4.26 (ddt, J = 10.8, 7.6, 3.2 Hz, 1H, *NCH*), 7.37 –7.41 (td, J = 7.0, 1.5 Hz, 2H, Harom), 7.47 –7.50 (t, J = 7.4 Hz, 1H, Harom), 7.93 (d, J = 7.4 Hz, 2H, Harom); ^{13}C NMR (100 MHz, CDCl_3) δ 23.2 (CH_2), 28.5 (CH_3 , *t*-Bu), 30.7 (CH_2), 43.4 (CH_2), 46.5 (CH_2), 54.3 (CH), 79.5 (*Ct*-Bu), 128.3 (CHarom), 128.6 (CHarom), 133.1 (CHarom), 136.9 (Carom), 154.4 (CO₂), 198.9 (CO).

2-(2-oxo-2-phenylethyl) -piperidine-1-carboxylic acid *tert*-Butyl ester (**3b**)

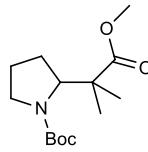


$C_{18}H_{25}NO_3$
M = 303.40

Following **GP1** from *N*-Boc-2-hydroxypiperidine **1a** (40.8 mg, 0.20 mmol), 1-phenylvinyl trimethylsilyl ether **2a** (42 μ L 0.20 mmol) and POM/Hf (1 mol %, 0.002 mmol), to give the desired product **3b** as a clear oil (10 mg, 0.03 mmol, 16% yield). Spectral data correspond to those described in the literature.³ [*Journal of the American Chemical Society*, 2008, 130, 13745-13754]

IR ν max (neat) / cm^{-1} 1684, 1669, 1409. ^1H NMR (400 MHz, CDCl_3) δ 1.39 (s, 9H, *t*-Bu), 1.44 – 1.71 (m, 6H, 3 CH_2), 2.91 (td, J = 13.2, 2.7 Hz, 1H, *NCHH*), 3.11 (ddd, J = 20.5, 14.4, 7.3 Hz, 2H, CH_2Ph), 4.07 (d, J = 13.5 Hz, 1H, *NCHH*), 4.75 – 4.94 (m, 1H, *NCH*), 7.50 (t, J = 7.4 Hz, 2H, Harom), 7.59 (t, J = 7.3 Hz, 2H, Harom), 8.02 (t, J = 7.2 Hz, 1H, Harom). ^{13}C NMR (100 MHz, CDCl_3) δ 18.9 (CH_2), 25.3 (CH_2), 28.2 (CH_2), 28.3 (CH_3 , *t*-Bu), 39.2 (CH_2), 39.4 (CH_2), 48.2 (CH), 79.6 (*Ct*-Bu), 128.3 (CHarom), 128.6 (CHarom), 133.1 (CHarom), 136.9 (Carom), 154.7 (CO₂), 198.4 (CO).

2-(1-methoxy-2-methyl-1-oxopropan-2-yl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (**3c**)

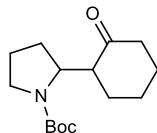


$C_{14}H_{25}NO_4$
M = 271.3526

Following **GP1** with *N*-Boc-2-hydroxypyrrolidine **1a** (34 mg, 0.18 mmol), 1-Methoxy-2-methyl-1-(trimethylsiloxy)propene **2b** (39 μ L, 0.18 mmol), and POM/Hf (10 mol%, 0.018 mmol), to give the desired product **3c** as a clear oil (28 mg, 0.10 mmol, 58% yield).⁴ [*Tetrahedron Lett.* 2006, 47, 7853-7856. *Tetrahedron Lett.* 2006, 47, 1669–1672.]

IR ν max (neat) / cm^{-1} 1692, 1377, 1365. ^1H NMR (400 MHz, CDCl_3) δ 1.06 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.39 (s, 9H, $t\text{-Bu}$), 1.59 – 1.79 (m, 3H, CH_2CHH), 1.80 – 1.96 (m, 1H, CHH), 3.11 (dt, $J = 11.2, 6.9$ Hz, 1H, NCHH), 3.47 – 3.67 (m, 4H, $\text{COOCH}_3 + \text{NCHH}$), 4.18 (dd, $J = 8.6, 3.0$ Hz, 1H, NCH). ^{13}C NMR (63 MHz, CDCl_3) δ 21.2 (CH_3), 24.1 (CH_2), 27.5 (CH_2), 28.4 ($\text{CH}_3, t\text{-Bu}$), 47.8 (CH_2), 51.9 (CO_2CH_3), 62.9 (CH), 79.5 (Ct-Bu), 155.8 (CO_2), 177.3 (CO).

2-(2-oxocyclohexyl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (3e)

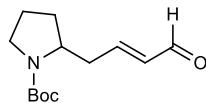


$\text{C}_{15}\text{H}_{25}\text{NO}_3$
M = 267.3639

Following **GP1** with *N*-Boc-2-hydroxypyrrrolidine **1b** (30 mg, 0.16 mmol), 1-(trimethylsiloxy) cyclohexene **2c** (32 μL , 0.16 mmol), and POM/Hf (1 mol %, 0.0016 mmol), to give the desired product **3e** as a 30/70 mixture of diastereomers (27 mg, 0.10 mmol, 63% yield). With 10 mol% POM/Hf, (42 mg, 0.16 mmol, 98% yield).

IR ν max (neat) / cm^{-1} 1686, 1388. ^1H NMR (250 MHz, CDCl_3 , mixture of diastereomers) δ [1.41] (s, 3.4 H, $t\text{-Bu}$, 1 *dia. mino*), 1.42 (s, 5.6 H, $t\text{-Bu}$, 1 *dia.*), 1.51 – 2.20 (m, 10H, 5 CH_2), 2.20 – 2.45 (m, 2 H, CH_2), 3.15 – 3.28 (m, 2 H, $\text{CHH} + \text{CH}$), 3.43 (bs, 1H, CHH), [4.12] (bs, 0.3H, NCH , 1 *dia. mino*), 4.26 (bs, 0.69 H, NCH , 1 *dia.*). ^{13}C NMR (101 MHz, CDCl_3) δ 24.4 (CH_2 , 1 *dia.*), [24.9] (CH_2 , 1 *dia.*), 26.7 (CH_2 , 1 *dia.*), [27.1] (CH_2 , 1 *dia.*), 27.6 (CH_2 , 1 *dia.*), [28.0] (CH_2 , 1 *dia.*), 28.5 ($\text{CH}_3, t\text{-Bu}$), 31.0 (CH_2), 42.0 (CH_2), 42.7 (CH_2), 45.9 (CH_2 , 1 *dia.*), [47.2] (CH_2 , 1 *dia.*), 52.1(CH, 1 *dia.*), [53.5] (CH, 1 *dia.*), 56.01 (NCH , 1 *dia.*), [56.7] (NCH , 1 *dia.*), 79.2 (Ct-Bu), 154.5 (CO_2 , 1 *dia.*), [155.1] (CO_2 , 1 *dia.*), 211.9 (CO). HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_3$ ($M + \text{Na}$) $^+$ 290.1727, found 290.1730.

2-(1-oxobut-3-en-2-yl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (3g)

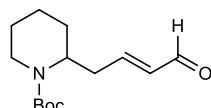


$\text{C}_{13}\text{H}_{21}\text{NO}_3$
M = 239.3107

Following **GP1** with *N*-Boc-2-hydroxypyrrrolidine **1a** (96.4 mg, 0.51 mmol), 1-(trimethylsiloxy)-1,3-butadiene **2d** (98 μL , 0.55 mmol), and POM/Hf (1 mol%, 0.005 mmol), to give the desired product **3g** as a clear oil (83 mg, 0.35 mmol, 69% yield).

IR ν max (neat) / cm^{-1} 1683. ^1H NMR (400 MHz, CDCl_3) δ 1.39 (s, 9H, $t\text{-Bu}$), 1.59 (bs, 1H, CHH), 1.71 – 1.84 (m, 2H, CH_2), 1.86 – 2.00 (m, 1H, CHH), 2.38 – 2.42 (m, 1H, CHHCH=CH), 2.68 (bs, 1H, CHHCH=CH), 3.24 – 3.33 (m, 2H, NCH_2), 3.91 (bs, 1H, NCH), 6.02 – 6.09(m, 1H, CHCHO), 6.75 (dt, $J = 15.0, 7.0$ Hz, 1H, CH=CHCHO), 9.44 (d, $J = 7.0$ Hz, 1H, CHO). ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers) δ 22.9 (CH_2), [23.6] (CH_2), 28.5 ($\text{CH}_3, t\text{-Bu}$), 30.0 (CH_2), [30.7] (CH_2), 37.7 ($\text{CH}_2\text{CH=CH}$), [38.1] ($\text{CH}_2\text{CH=CH}$), 46.4 (NCH_2), [46.6] (NCH_2), 56.0 (NCH), 79.4 (Ct-Bu), [79.6] (Ct-Bu), 134.5 (CHCHO), 154.5 ($\text{CH=CHCHO} + \text{CO}_2$), [155.0] ($\text{CH=CHCHO} + \text{CO}_2$), 193.6 (CHO), [193.8] (CHO). HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_3$ ($M + \text{Na}$) $^+$ 262.1414, found 262.1416.

2-(1-oxobut-3-en-2-yl)-piperidine-1-carboxylic acid *tert*-Butyl ester (3h**)**

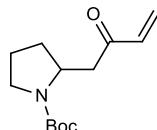


C₁₄H₂₃NO₃
M = 253.34

Following **GP1** with *N*-Boc-2-hydroxypiperidine **1b** (98.7 mg, 0.49 mmol), 1-(trimethylsiloxy)-1,3-butadiene **2d** (96 µL, 0.54 mmol) and POM/Hf (114 mg, 4 mol%, 0.02 mmol), to give the desired product **3h** as a clear oil (30 mg, 0.12 mmol, 24% yield).

IR ν max (neat) / cm⁻¹ 1684. ¹H NMR (400 MHz, CDCl₃) δ 1.36 (s, 9H, *t*-Bu), 1.40 – 1.67 (m, 6H, 3CH₂), 2.45 (dd, *J* = 14.5, 7.3, 6.2, 1.4 Hz, 1H, CHHCH=CH), 2.69 – 2.84 (m, 2H, CHHCH=CH+NCHH), 4.00 (d, *J* = 13.1 Hz, 1H, NCHH), 4.49 (bs, 1H, NCH), 6.13 (dd, *J* = 15.5, 7.9 Hz, 1H, CHCHO), 6.81 (dt, *J* = 15.5, 7.4 Hz, 1H, CH=CHCHO), 9.49 (d, *J* = 7.9 Hz, 1H, CHO). ¹³C NMR (100 MHz, CDCl₃) δ 18.8 (CH₂), 25.3 (CH₂), 28.3 (CH₂), 28.4 (CH₃, *t*-Bu), 33.7 (CH₂CH=CH), 39.0 (NCH₂), 49.4 (NCH), 79.6 (Ct-Bu), 134.3 (CHCHO), 154.9 (CO₂), 155.1 (CH=CHCHO), 193.7 (CHO). HRMS (ESI) m/z calcd for C₁₄H₂₃NO₃ (M + Na)⁺ 276.1570, found 276.1574

2-(2-oxobut-3-en-1-yl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (3i**)**

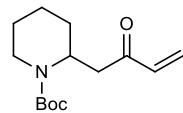


C₁₃H₂₁NO₃
M = 239.31

Following **GP1** with *N*-Boc-2-hydroxypyrrrolidine **1a** (123.2 mg, 0.66 mmol), 2-trimethylsiloxy-1,3-butadiene **2e** (178 µL, 0.99 mmol), and POM/Hf (10 mol%, 0.066 mmol), to give the desired product **3i** as a clear oil (71 mg, 0.30 mmol, 45% yield).

IR ν max (neat) / cm⁻¹ 1684, 1391. ¹H NMR (400 MHz, CDCl₃) δ 1.45 (s, 9H, *t*-Bu), 1.61 – 1.73 (m, 1H, CHH), 1.74 – 1.89 (m, 2H, CH₂), 1.94 – 2.10 (m, 1H, CHH), 2.52 (bs, 1H, CHHCO), 3.03 – 3.53 (m, 3H, NCH₂+CHHCO), 4.17 (ddt, *J* = 11.0, 7.6, 3.2 Hz, 1H, NCH), 5.82 – 5.91 (m, 1H, CH=CHH_{cis}), 6.31 (bs, 2H, CH=CHH_{trans}). ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers) δ 22.8 (CH₂), [23.5] (CH₂), 28.5 (CH₃, *t*-Bu), 30.3 (CH₂), [31.3] (CH₂), 43.7 (CH₂), [44.5] (CH₂), 46.2 (CH₂), [46.5] (CH₂), 53.8 (CH), [54.1] (CH), 79.2 (C, *t*-Bu), [79.6] (Ct-Bu), 128.6 (CH₂), [128.9] (CH₂), 136.8 (CH), 154.3 (CO₂), 199.2 (CO), [199.7] (CO). HRMS (ESI) m/z calcd for C₁₃H₂₁NO₃ (M + Na)⁺ 262.1414, found 262.1412.

2-(2-oxobut-3-en-1-yl)-piperidine-1-carboxylic acid *tert*-Butyl ester (3j**)**



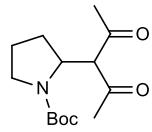
C₁₄H₂₃NO₃
M = 253.34

Following **GP1** with *N*-Boc-2-hydroxypiperidine **1b** (104.7 mg, 0.52 mmol), 2-(trimethylsiloxy)-1,3-butadiene **2e** (140 µL, 0.78 mmol), and POM/Hf (10 mol%, 0.052 mmol), to give the desired product **3j** as a clear oil (13 mg, 0.05 mmol, 10% yield).

IR ν max (neat) / cm⁻¹ 1687. ¹H NMR (400 MHz, CDCl₃) δ 1.44 (s, 9H, *t*-Bu), 1.53 – 1.69 (m, 6H, 3CH₂), 2.74 – 2.87 (m, 3H, NCHH + CH₂CO), 3.99 (m, 1H, NCHH), 4.71 (dd, *J* = 12.2, 5.6 Hz, 1H, NCH), 5.85 (dd, *J* = 10.3, 1.2 Hz, 1H, CH=CHH_{cis}), 6.26 (dd, *J* = 13.0, 1.2 Hz, 1H, CH=CHH_{trans}), 6.38 (dd, *J* = 13.0, 10.3 Hz, 1H, COCH=CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 18.8 (CH₂), 25.3 (CH₂), 28.2 (CH₂), 28.4 (CH₃, *t*-Bu), 39.5 (NCH₂), 40.3 (CH₂CO), 47.8 (NCH), 79.7

(C_t-Bu), 128.6 (CH=CH₂), 136.5 (CH=CH₂), 154.7 (CO₂), 198.9 (CO). HRMS (ESI) m/z calcd for C₁₄H₂₃NO₃ (M + Na)⁺ 276.1570, found 276.1573.

2-(2,4-dioxophentane-3-yl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (7a)

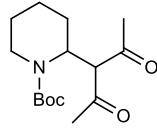


C₁₄H₂₃NO₄
M = 269.3367

Following **GP1** with *N*-Boc-2-hydroxypyrrolidine **1a** (39mg, 0.21 mmol), 2,4-pentanedione **6a** (21.4 μ L, 0.21 mmol), and POM/Hf (10 mol%, 0.021 mmol), to give the desired product **7a** as a clear oil (35 mg, 0.13 mmol, 63% yield). Spectral data correspond to those described in the literature.⁶ [Journal of Organic Chemistry, 1983, 48, 4058-4067.]

IR ν max (neat) / cm⁻¹ 1686, 1389, 1364. ¹H NMR (400 MHz, C₆D₆) δ 1.12 – 1.23 (m, 1H, CHH), 1.24 – 1.33 (m, 1H, CHH), 1.42 (s, 9H, *t*-Bu), 1.70 (bs, 2H, CH₂), 1.84 (s, 3H, COCH₃), 1.88 (s, 3H, COCH₃), 2.94 – 3.25 (m, 2H, NCH₂), 4.41 – 4.45 (m, 2H, 2CH). ¹³C NMR (101 MHz, C₆D₆) δ 22.3 (CH₂), 27.0 (CH₂ + CH₃, *t*-Bu), 27.8 (CH₃), 30.3 (CH₃), 45.5 (CH₂), 55.9 (NCH), 67.4 (CH), 77.9 (C_t-Bu), 153.1 (CO₂), 200.5 (CO), 203.3 (CO).

2-(2,4-dioxopentan-3-yl)-piperidine-1-carboxylic acid *tert*-Butyl ester (7b)

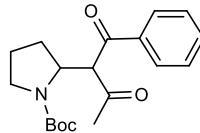


C₁₅H₂₅NO₄
M = 283.36

Following **GP1** with *N*-Boc-2-hydroxypiperidine (78 mg, 0.39 mmol), 2,4-pentanedione (40 μ L, 0.39 mmol), and POM/Hf (10 mol%, 0.039 mmol), to give the desired product **7b** as a clear oil (63 mg, 0.22 mmol, 57% yield).

IR ν max (neat) / cm⁻¹ 1686. ¹H NMR (400 MHz, CDCl₃) δ 1.38 – 1.64 (m, 15H, *t*-Bu + 3CH₂), 2.07 (s, 3H, COCH₃), 2.14 (s, 3H, COCH₃), 2.67 (bs, 1H, NCHH), 3.88 (bd, *J* = 51.8 Hz, 1H, NCHH), 4.23 (d, *J* = 10.8 Hz, 1H, CH), 5.06 (bd, *J* = 48.8 Hz, 1H, NCH). ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers) δ 19.2 (CH₂), 25.1 (CH₂), 26.9 (COCH₃ + CH₂), 28.3 (CH₃, *t*-Bu), 31.0 (COCH₃), 39.0 (CH₂), [40.3] (CH₂), 49.8 (NCH), [51.1] (NCH), 68.9 (CH), 80.1 (C_t-Bu), 154.5 (CO₂), 202.2 (CO). HRMS (ESI) m/z calcd for C₁₅H₂₅NO₄ (M + Na)⁺ 306.1676, found 306.1667.

2-(1,3-dioxo-1-phenylbutan-2-yl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (7c)

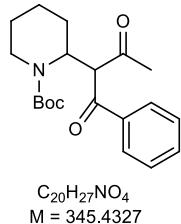


C₁₉H₂₅NO₄
M = 331.4061

Following **GP1** with *N*-Boc-2-hydroxypyrrolidine **1a** (39 mg, 0.21 mmol), 1-phenyl-1,3-butanedione **6b** (35 mg, 0.21 mmol), and POM/Hf (10 mol%, 0.021 mmol), to give the desired product **7c** as a clear oil (44.5 mg, 0.13 mmol, 64% yield).

IR ν max (neat) / cm^{-1} 1681, 1389. ^1H NMR (400 MHz, CDCl_3 , mixture of rotamers and diastereomers) δ 1.20 – 1.73 (m, 11H, $\text{CH}_2 + t\text{-Bu}$), 1.74 – 2.19 (m, 5H, $\text{COCH}_3 + \text{CH}_2$), 2.70 – 3.53 (m, 2H, NCH_2), 4.24 – 4.69 (m, 1H, NCH), 4.77 – 5.54 (m, 1H, CH), 7.46 – 7.51 (m, 2H, Harom), 7.57 – 7.64 (m, 1H, Harom), 7.98 (d, $J = 6.9$ Hz, 2H, Harom). ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers and diastereomers) δ 22.7 (CH_2), [23.6] (CH_2), 28.2 (CH_2), 28.3 ($\text{CH}_3, t\text{-Bu}$), [28.4] ($\text{CH}_3, t\text{-Bu}$), 29.2 (COCH_3), [31.3] (COCH_3), 46.4 (CH_2), 57.6 (NCH), 63.0 (CH), [63.7] (CH), 79.6 ($Ct\text{-Bu}$), [80.3] ($Ct\text{-Bu}$), 128.7 (CHarom), [128.8] (CHarom), 133.5 (CHarom), [133.8] (CHarom), 136.7 (Carom), [137.4] (Carom), 154.7 (CO_2), 198.0 (CO), 202.9 (CO). HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_4$ ($M + \text{Na}$) $^+$ 354.1676, found 354.1674.

2-(1,3-dioxo-1-phenylbutan-2-yl)-piperidine-1-carboxylic acid *tert*-Butyl ester (7d)

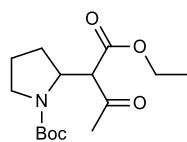


$\text{C}_{20}\text{H}_{27}\text{NO}_4$
 $M = 345.4327$

Following **GP1** with *N*-Boc-2-hydroxypiperidine **1b** (75.6 mg, 0.38 mmol), and 1-phenyl-1,3-butanedione **6b** (61.5 mg, 0.38 mmol) and POM/Hf (10 mol%, 0.04 mmol), to give the desired product **7d** as a white solid, one diastereomer was separated in 8% (11 mg), the other one was obtained as a mixture with impurities (9.5 mg of product was expected from the ^1H NMR).

IR ν max (neat) / cm^{-1} 1687, 1159. ^1H NMR (400 MHz, CDCl_3) δ 1.38 (s, 9H, *t*-Bu), 1.55 – 1.74 (m, 6H, 3CH_2), 2.25 (s, 3H, COCH_3), 2.65 (bs, 1H, NCHH), 3.89 (bs, 1H, NCHH), 5.08 (d, $J = 11.1$ Hz, 1H, CH), 5.33 (d, $J = 9.8$ Hz, 1H, NCH), 7.48 (t, $J = 7.6$ Hz, 2H, Harom), 7.59 (t, $J = 7.4$ Hz, 1H, Harom), 7.97 (d, $J = 8.6$ Hz, 2H, Harom). ^{13}C NMR (100 MHz, CDCl_3) δ 19.3 (CH_2), 25.2 (CH_2), 27.2 (CH_2), 28.2 ($\text{CH}_3, t\text{-Bu}$), 28.5 (COCH_3), 39.2 (CH_2), 51.3 (NCH), 63.8 (CH), 79.8 ($Ct\text{-Bu}$), 128.6 (CHarom), 128.8 (CHarom), 133.5 (CHarom), 136.9 (Carom), 154.2 (CO_2), 193.9 (CO), 202.8 (CO). HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_4$ ($M + \text{Na}$) $^+$ 368.1832, found 368.1831.

2-(1-ethoxy-1,3-dioxobutan-2-yl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (7e)

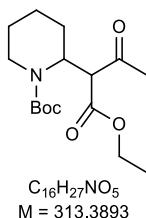


$\text{C}_{15}\text{H}_{25}\text{NO}_5$
 $M = 299.3627$

Following **GP1** with *N*-Boc-2-hydroxypyrrolidine **1a** (51.4 mg, 0.28 mmol), ethyl acetoacetate **6c** (35 μL , 0.28 mmol), and POM/Hf (10 mol%, 0.028 mmol), to give the desired product **7e** as a 58/42 mixture of diastereomers (46 mg, 0.15 mmol, 55% yield).

IR ν max (neat) / cm^{-1} 1688, 1390, 1366, 1157. ^1H NMR (400 MHz, CDCl_3 , mixture of diastereomers) δ 1.15 – 1.27 (m, 3H, CH_2CH_3), 1.39 (s, 5.2H, *t*-Bu, 1 dia.), [1.40] (s, 3.7H, *t*-Bu, 1 dia. mino), 1.64 – 1.81 (m, 2H, CH_2), 1.82 – 2.09 (m, 2H, CH_2), 2.16 (s, 3H, COCH_3), 3.12 – 3.23 (m, 2H, NCHH), 3.36 (bs, 1H, NCHH), 4.03 – 4.19 (m, 3H, $\text{CH} + \text{CH}_2\text{CH}_3$), 4.21 – 4.39 (m, 1H, NCH). ^{13}C NMR (100 MHz, CDCl_3 , mixture of diastereomers) δ 14.0 ($\text{CH}_3, 1$ dia.), [14.1] ($\text{CH}_3, 1$ dia.), 23.6 (CH_2), 28.5 ($\text{CH}_3, t\text{-Bu}$), 29.2 (CH_2), 30.9 ($\text{COCH}_3, 1$ dia.), [31.8] ($\text{COCH}_3, 1$ dia.), 46.7 ($\text{CH}_2, 1$ dia.), [47.0] ($\text{CH}_2, 1$ dia.), 56.4 ($\text{NCH}, 1$ dia.), [57.0] ($\text{NCH}, 1$ dia.), 61.2 (CH_2), 61.5 (CH), 79.7 ($Ct\text{-Bu}$), 154.5 (CO_2), 168.5 (CO), [169.0] (CO, 1 dia.), 201.9 (CO, 1 dia.), [203.9] (CO, 1 dia.). HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_5$ ($M + \text{Na}$) $^+$ 322.1625, found 322.1617.

2-(1-ethoxy-1,3-dioxobutan-2-yl)-piperidine-1-carboxylic acid *tert*-Butyl ester (7f)

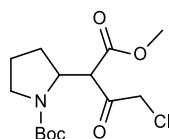


C₁₆H₂₇NO₅
M = 313.3893

Following **GP1** with *N*-Boc-2-hydroxypiperidine **1b** (77.5 mg, 0.39 mmol), ethyl acetoacetate **6c** (50 μL, 0.39 mmol), and POM/Hf (10 mol%, 0.039 mmol), to give the desired product **7f** as a colorless oil, only one diastereomer was successfully separated in 35% yield (42.4 mg).

IR ν max (neat) / cm⁻¹ 1685, 1156. ¹H NMR (400 MHz, CDCl₃) δ 1.25 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 1.38 – 1.54 (m, 12H, CH₂ + CHH + *t*-Bu), 1.59 – 1.69 (m, 3H, CH₂ + CHH), 2.28 (s, 3H, COCH₃), 2.85 (bs, 1H, NCHH), 3.83 – 4.28 (m, 4H, CH₂ + NCHH + CH), 5.02 (bs, 1H, NCH). ¹³C NMR (100 MHz, CDCl₃, mixture of rotamers) δ 13.9 (CH₂CH₃), 19.0 (CH₂), 25.1 (CH₂), 27.1 (CH₂), 28.3 (CH₃, *t*-Bu), 28.9 (COCH₃), 38.9 (CH₂), [40.4] (CH₂), 49.5 (NCH), [50.3] (NCH), 59.5 (CH), 61.4 (CH₂), 79.7 (*Ct*-Bu), 154.4 (CO₂), 167.6 (CO), [168.4] (CO), 201.4 (CO). HRMS (ESI) m/z calcd for C₁₆H₂₇NO₅ (M + Na)⁺ 336.1781, found 336.1788.

2-(4-chloro-1-methoxy-1,3-dioxobutan-2-yl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (7g)

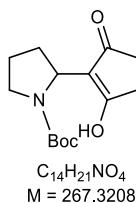


C₁₄H₂₂ClNO₅
M = 319.7812

Following **GP1** with Boc-2-hydroxypyrrrolidine **1a** (37 mg, 0.20 mmol), Methyl 4-chloroacetoacetate **6d** (24 μL, 0.20 mmol), and POM/Hf (10 mol%, 0.02 mmol), to give the desired product **7g** as a 56/44 mixture of diastereomers (31 mg, 0.10 mmol, 49% yield).

IR ν max (neat) / cm⁻¹ 1684, 1391, 1158. ¹H NMR (400 MHz, CDCl₃, mixture of diastereomers) δ 1.41 (s, 5H, *t*-Bu, 1 *dia.*), [1.42] (s, 4H, *t*-Bu, 1 *dia.*), 1.68 – 1.89 (m, 2.6H, CH₂ + CHH (1 *dia.*)), 1.96 – 2.06 (m, 0.6 H, CHH, 1 *dia.*), 2.06 – 2.16 (m, 1H, CHH, 2 *dias.*), 3.18 – 3.28 (m, 1H, NCHH), 3.37 (bs, 1H, NCHH), 3.68 (s, 1.3H, COOCH₃, 1 *dia.*), [3.70] (s, 1.7 H, COOCH₃, 1 *dia.*), 4.06 – 4.63 (m, 4H, NCH + CH + CH₂Cl). ¹³C NMR (100 MHz, CDCl₃, mixture of diastereomers) δ 23.5 (CH₂), 28.3 (CH₃, *t*-Bu), 28.5 (CH₂, 1 *dia.*), [29.21 *dia.*] (CH₂), 46.5 (CH₂, 1 *dia.*), [46.9] (CH₂, 1 *dia.*), 47.7 (CH₂, 1 *dia.*), [49.2] (CH₂, 1 *dia.*), 52.5 (COOCH₃, 1 *dia.*), [52.5] (COOCH₃, 1 *dia.*), 55.9 (NCH), 56.8 (CH, 1 *dia.*), [57.0] (CH, 1 *dia.*), 79.9 (*Ct*-Bu), 154.4 (CO₂), 167.9 (CO, 1 *dia.*), [168.5] (CO, 1 *dia.*), 195.7 (COCH₂, 1 *dia.*), [196.9] (COCH₂, 1 *dia.*). HRMS (ESI) m/z calcd for C₁₄H₂₂ClNO₅ (M + Na)⁺ 342.1079, found 342.1082.

2-(2,5-dioxocyclopentyl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (**7i**)



Following **GP1** with *N*-Boc-2-hydroxypyrrolidine **1a** (39 mg, 0.21 mmol), 1,3-cyclopentanedione **6e** (21 mg, 0.21 mmol) and POM/Hf (12 mg, 1 mol%, 0.002 mmol), to give the desired product **7i** as a white solid (54 mg, 0.20 mmol, 95% yield), which is mainly in its enol form.

IR ν max (neat) / cm^{-1} 1625, 1388, 1160. ^1H NMR (400 MHz, CDCl_3) δ 1.38 (s, 9H, *t*-Bu), 1.72 – 1.89 (m, 2H, 2CHH), 2.27 (bs, 1H, CHH), 2.34 (bs, 4H, 2CH₂), 2.56 (bs, 1H, CHH), 3.19 – 3.38 (m, 2H, NCH₂), 4.46 – 4.56 (m, 1H, NCH). ^{13}C NMR (100 MHz, C_6D_6) δ 25.7 (CH₂), 27.4 (CH₂), 28.2 (CH₃, *t*-Bu), 30.0 (2CH₂), 46.7 (CH₂), 52.3 (CH), 80.9 (*Ct*-Bu), 116.5 (C), 157.7 (CO₂), 195.9 (CO + COH). HRMS (ESI) m/z calcd for $C_{14}H_{21}NO_4$ ($M + \text{Na}^+$) 290.1363, found 290.1365.

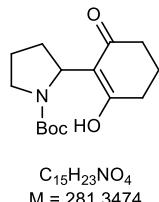
2-(2,5-dioxocyclopentyl)-piperidine-1-carboxylic acid *tert*-Butyl ester (**7j**)



Following **GP1** with *N*-Boc-2-hydroxypiperidine **1b** (58.4 mg, 0.29 mmol), 1,3-cyclopentanedione **6e** (29.2 mg, 0.29 mmol) and POM/Hf (1 mol%, 0.003 mmol), to give the desired product **7j** as a white solid (67.7 mg, 0.24 mmol, 83% yield), which is mainly in its enol form. ⁷[*Tetrahedron Letters*, 2004, 45, 2821-2823]

IR ν max (neat) / cm^{-1} 1690, 1581, 1401, 1371. ^1H NMR (400 MHz, CDCl_3 , mixture of rotamers) δ 1.36 – 1.58 (m, 10H, *t*-Bu + CHH), 1.58 – 1.77 (m, 3H, 2CHH + CHH), 2.23 – 2.37 (m, 2H, 2CHH), 2.49 (m, 4H, 2CH₂), 2.75 (t, $J = 11.9$ Hz, 1H, NCHH), 3.87 (d, $J = 12.3$ Hz, 1H, NCHH), 4.88 (d, $J = 6.4$ Hz, 1H, CH). ^{13}C NMR (100 MHz, CDCl_3) δ 21.4 (CH₂), 24.7 (CH₂), 25.3 (CH₂), 28.4 (CH₃, *t*-Bu), 41.4 (CH₂), 46.2 (CH), 81.7 (*Ct*-Bu), 117.2 (C), 158.1 (CO₂). HRMS (ESI) m/z calcd for $C_{15}H_{23}NO_4$ ($M + \text{Na}^+$) 304.1519, found 304.1518.

2-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-pyrrolidine-1-carboxylic acid *tert*-Butyl ester (**7k**)



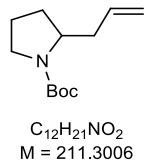
Following **GP1** with *N*-Boc-2-hydroxypyrrolidine **1a** (115 mg, 0.61 mmol), 1,3-Cyclohexanenedione **6f** (71 μL , 0.61 mmol) and POM/Hf (34 mg, 1 mol%, 0.006 mmol), to give the desired product **7k** as a white solid (146 mg, 0.52 mmol, 85% yield), which is mainly in its enol form.

IR ν max (neat) / cm^{-1} 1633, 1383. ^1H NMR (400 MHz, C_6D_6) δ 1.20 – 1.49 (m, 12H, CH₂ + CHH + *t*-Bu), 1.69 – 1.89 (m, 2H, 2CHH), 2.01 – 2.25 (m, 4H, CH₂ + 2CHH), 2.29 – 2.38 (m, 1H, CHH), 3.44 – 3.60 (m, 1H, NCHH), 3.60 – 3.67 (m, 1H, NCHH), 4.79 (dd, $J = 9.3, 5.4$ Hz, 1H, CH), 11.47 (s, 1H, OH). ^{13}C NMR (100 MHz, C_6D_6) δ 19.8 (CH₂), 25.5 (CH₂),

28.3 (CH₃, *t*-Bu), 29.4 (CH₂), 30.2 (CH₂), 37.6 (CH₂), 47.5 (NCH₂), 53.2 (CH), 80.4 (C*t*-Bu), 117.2 (C), 156.9 (CO₂), 175.9 (COH), 196.3 (CO). HRMS (ESI) m/z calcd for C₁₅H₂₃NO₄ (M + Na)⁺ 304.1519, found 304.1527.

4. Allylation Reaction.

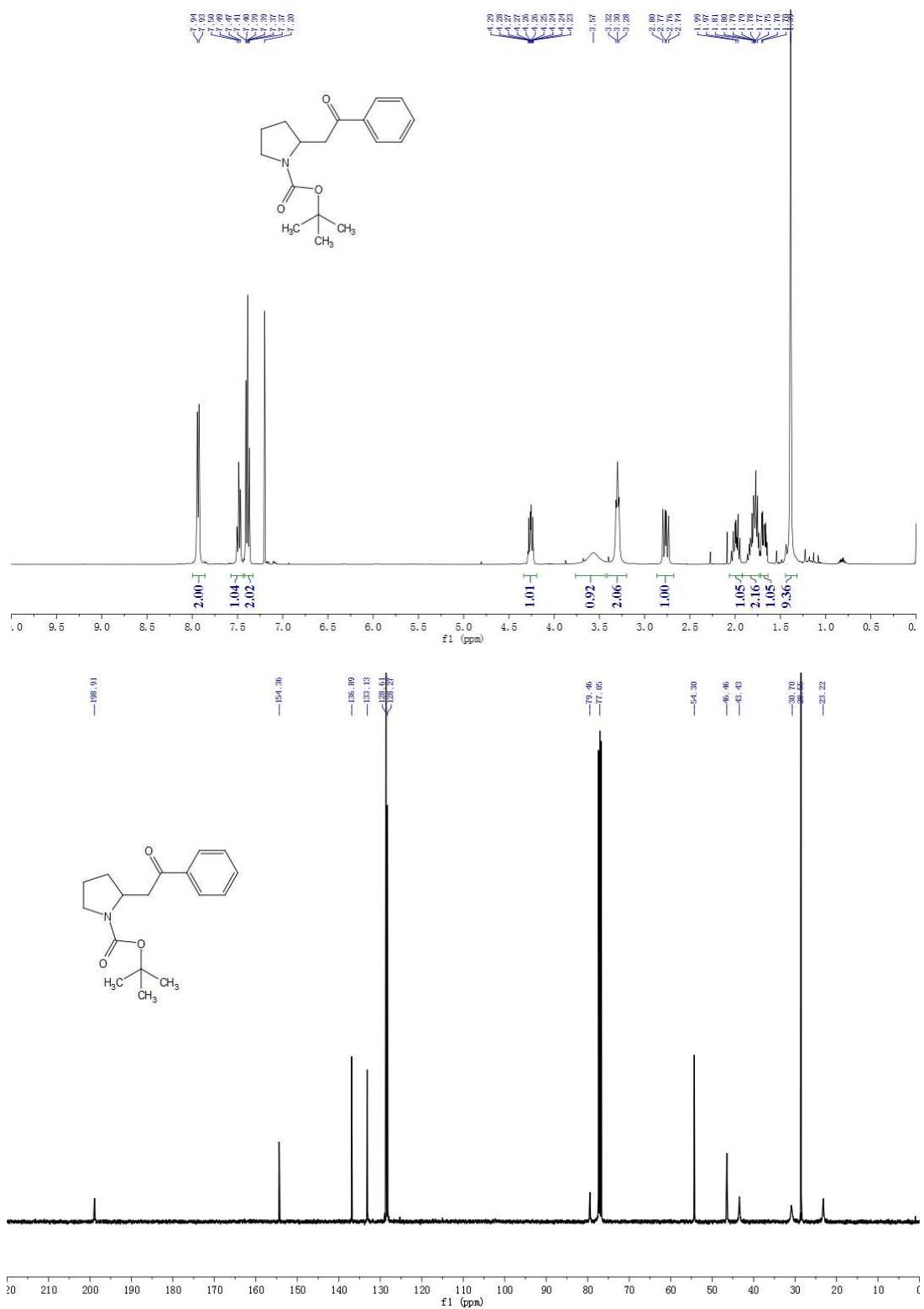
2-Allylpyrrolidine-1-carboxylic acid *tert*-butyl ester (**8a**)



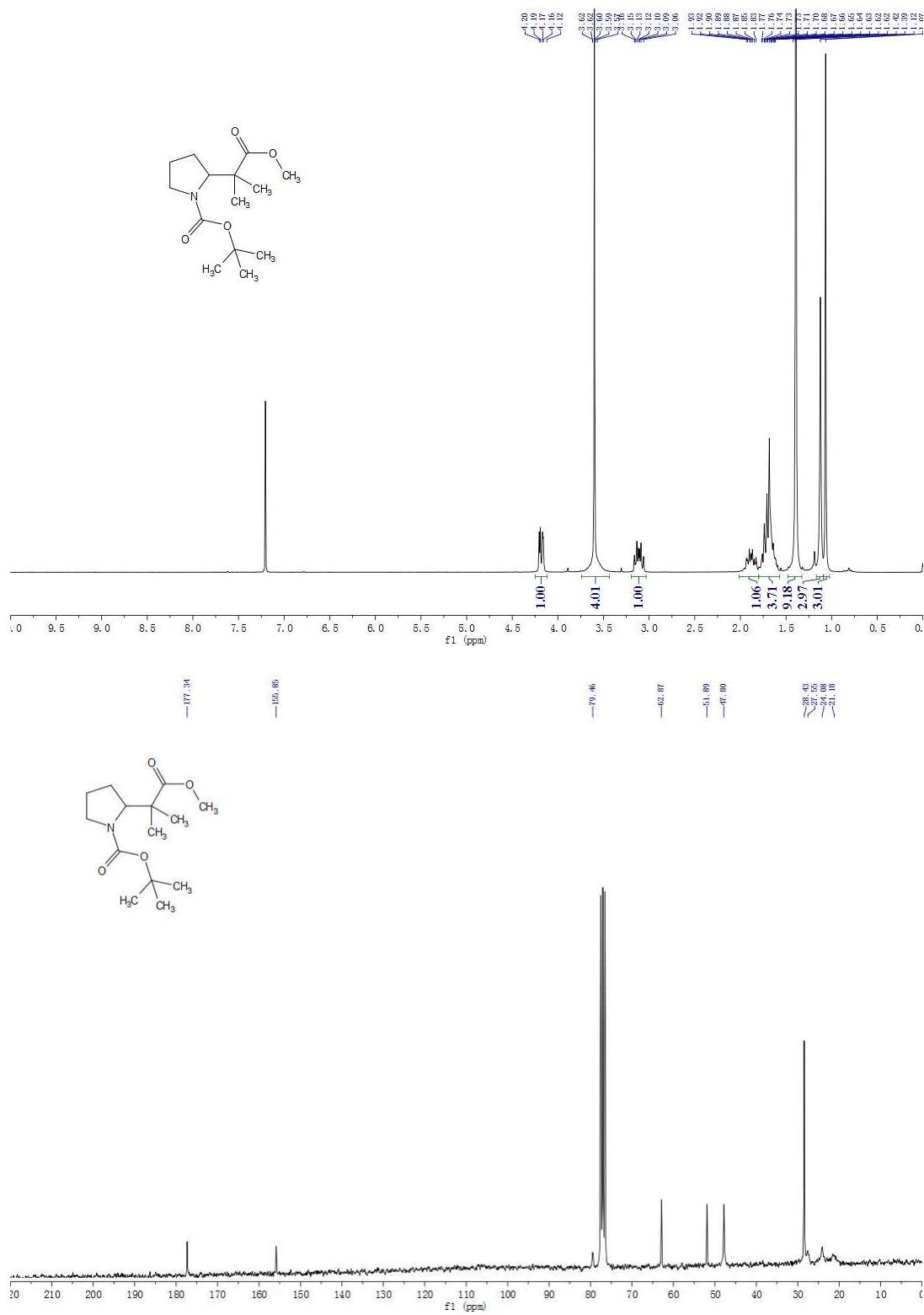
Following **GP1** with *N*-Boc-2-hydroxypyrrolidine **1a** (116.2 mg, 0.62 mmol), allyltrimethylsilane (0.5 mL, 3.1 mmol) and POM/Hf (702 mg, 20 mol%, 0.12 mmol), to give the desired product **8a** as a clear oil (22.7 mg, 0.11 mmol, 17% yield).
⁸[*Org. Lett.*, 2010, 12, 4176–4179]

¹H NMR (400 MHz, CDCl₃) δ 1.49 (s, 9H, *t*-Bu), 1.63 – 1.99 (m, 4H, 2CH₂), 2.06 – 2.23 (m, 1H, CH/CH=CH₂), 2.42 – 2.59 (m, 1H, CH/CH=CH₂), 3.25 – 3.47 (m, 2H, NCH₂), 3.76 – 3.90 (m, 1H, NCH), 5.00 – 5.14 (m, 2H, CH=CH₂), 5.67 – 5.87 (m, 1H, CH=CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 23.2 (CH₂), 28.5 (CH₃, *t*-Bu), 29.7 (CH₂), 38.7 (CH₂), 46.5 (NCH₂), 56.8 (NCH), 79.0 (C*t*-Bu), 116.9 (CH=CH₂), 135.3 (CH=CH₂), 154.5 (CO₂).

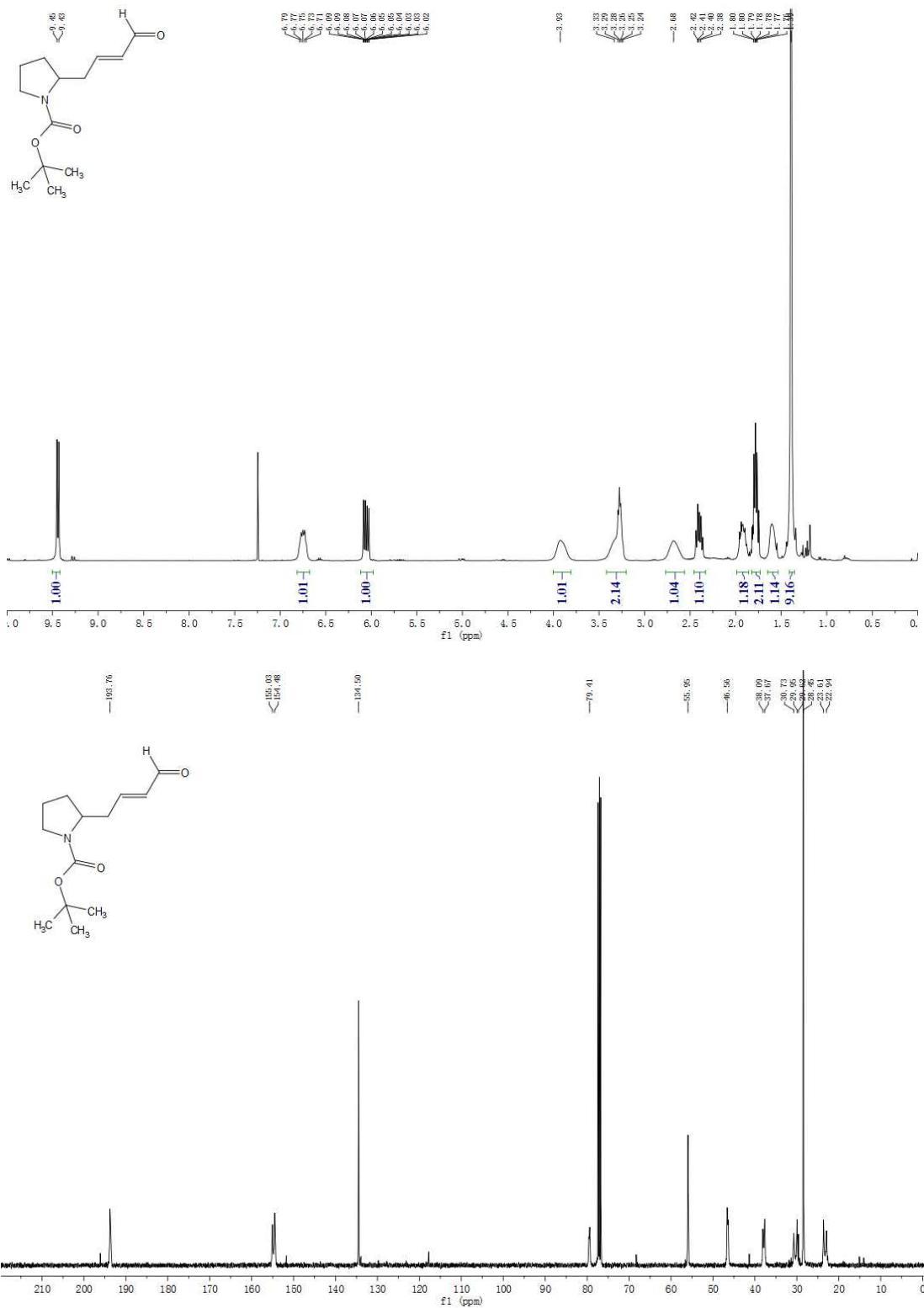
¹H and ¹³C NMR Spectra of **3a**



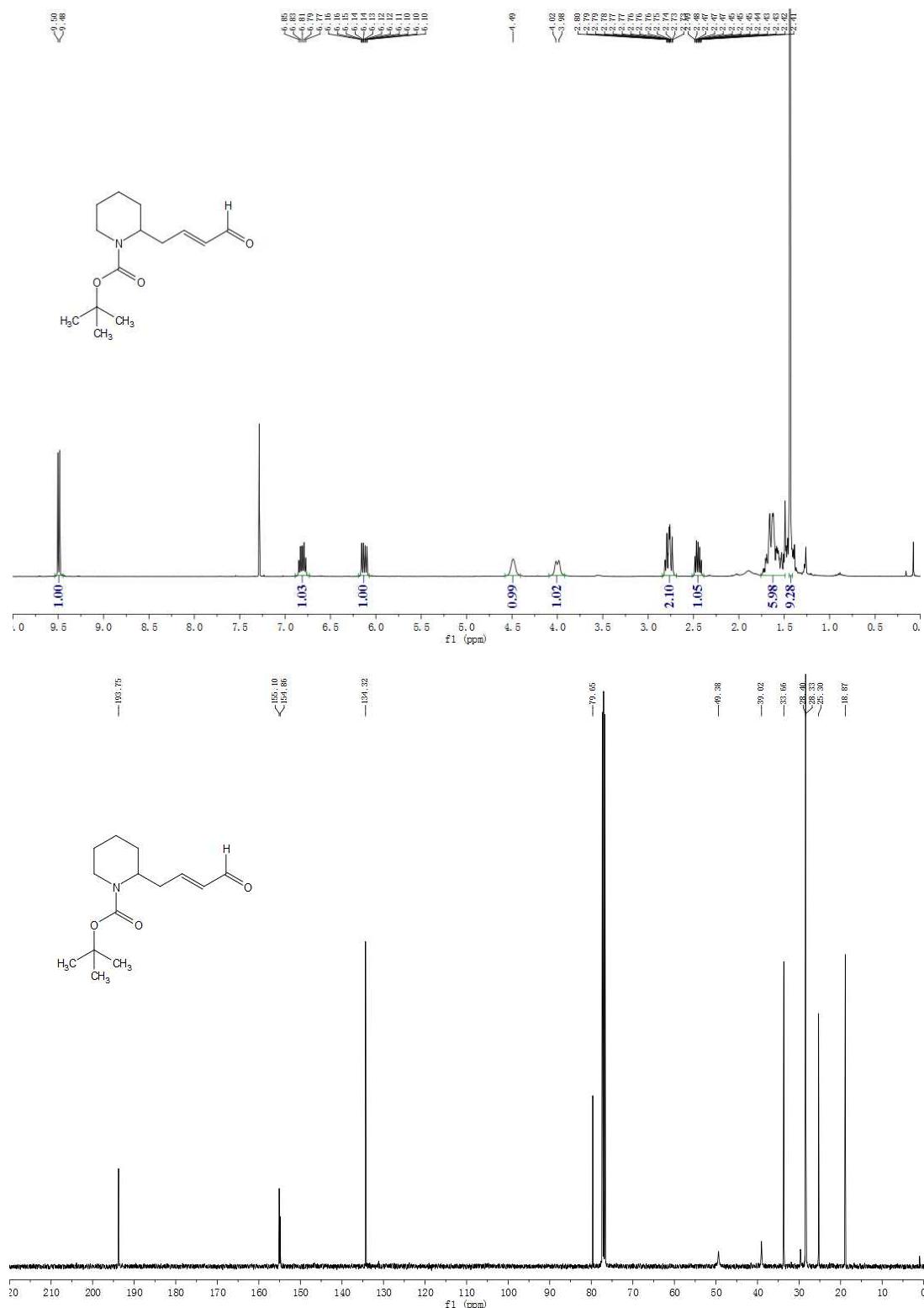
¹H and ¹³C NMR Spectra of **3c**



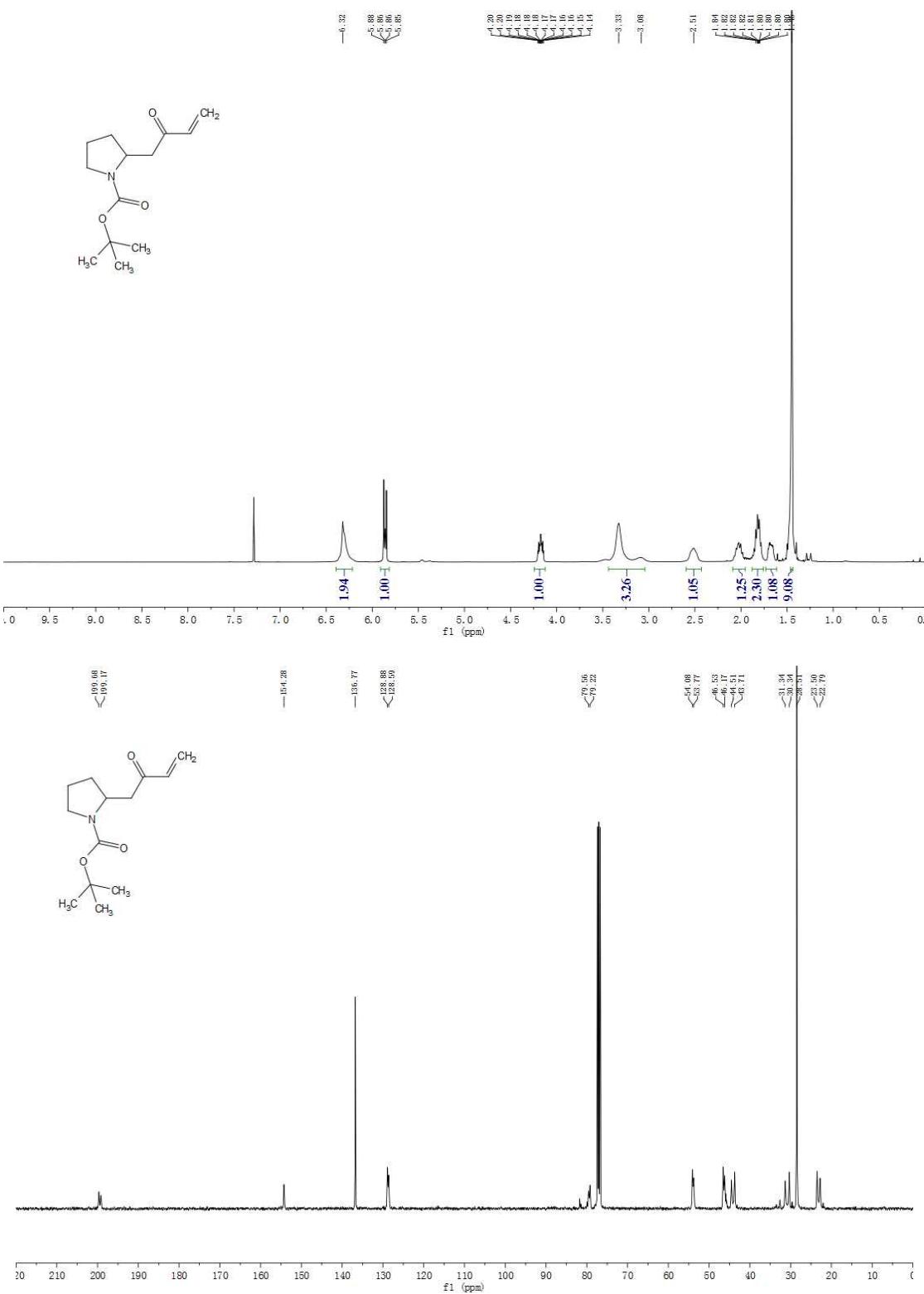
¹H and ¹³C NMR Spectra of 3g



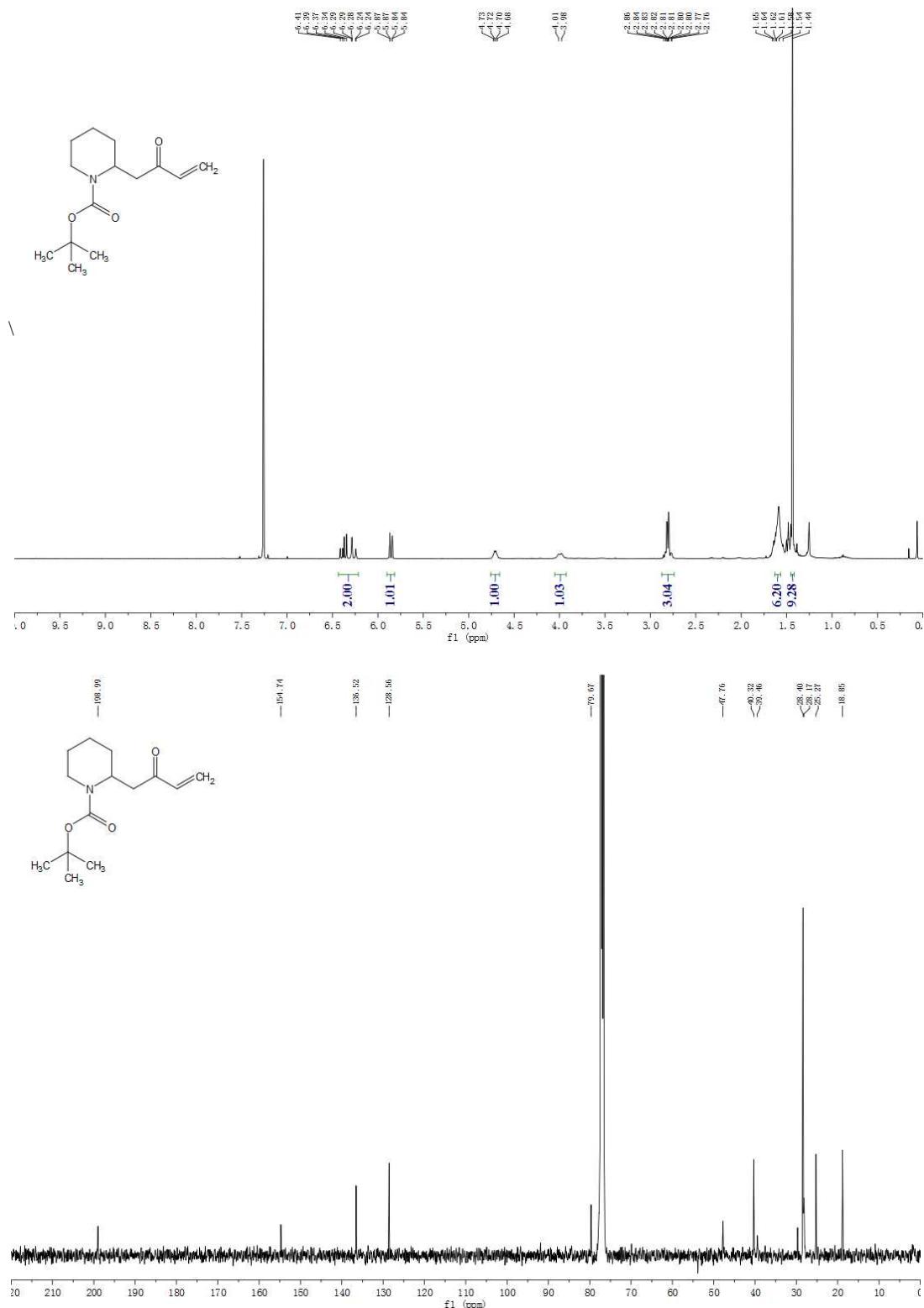
¹H and ¹³C NMR Spectra of **3h**



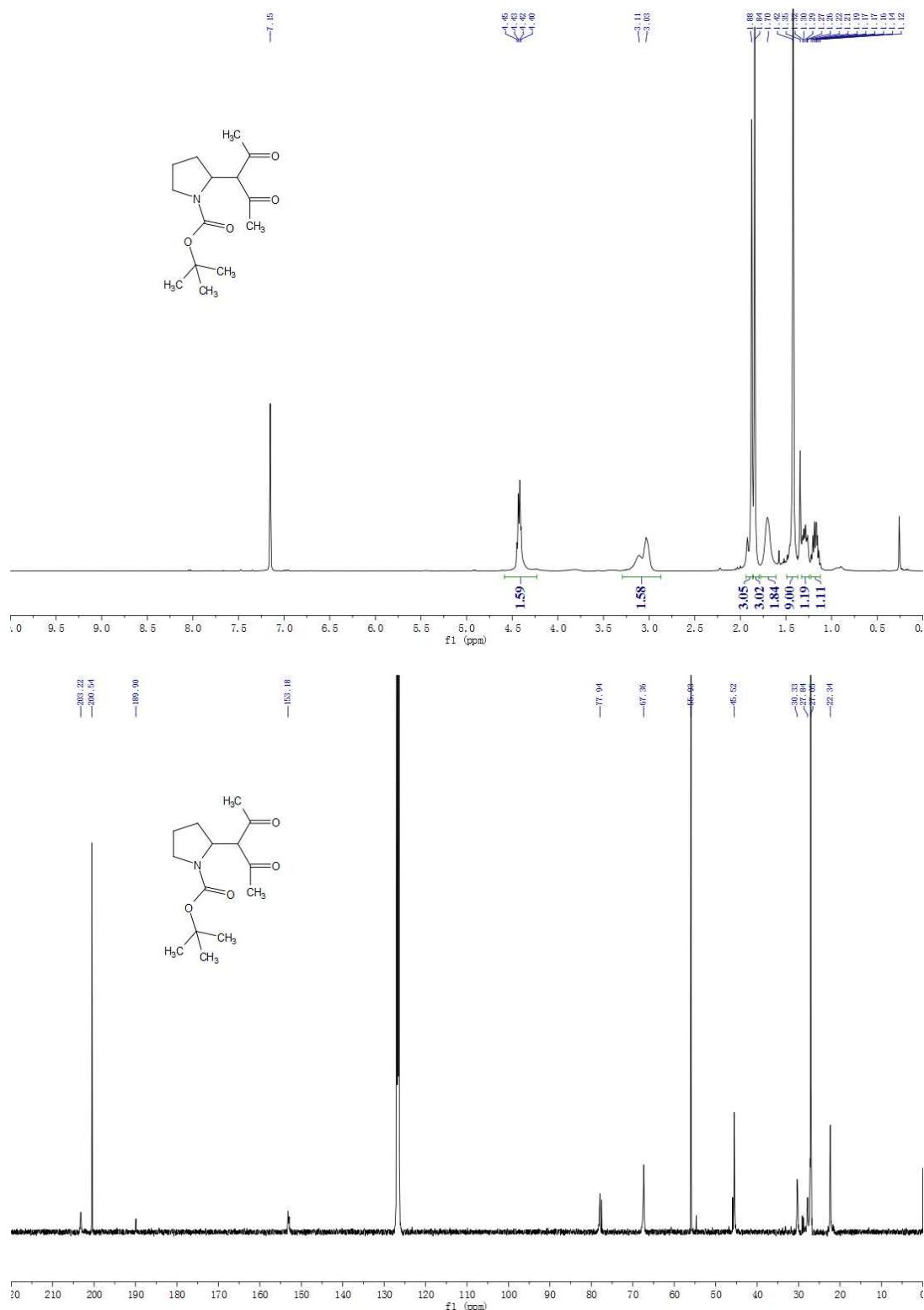
¹H and ¹³C NMR Spectra of **3i**



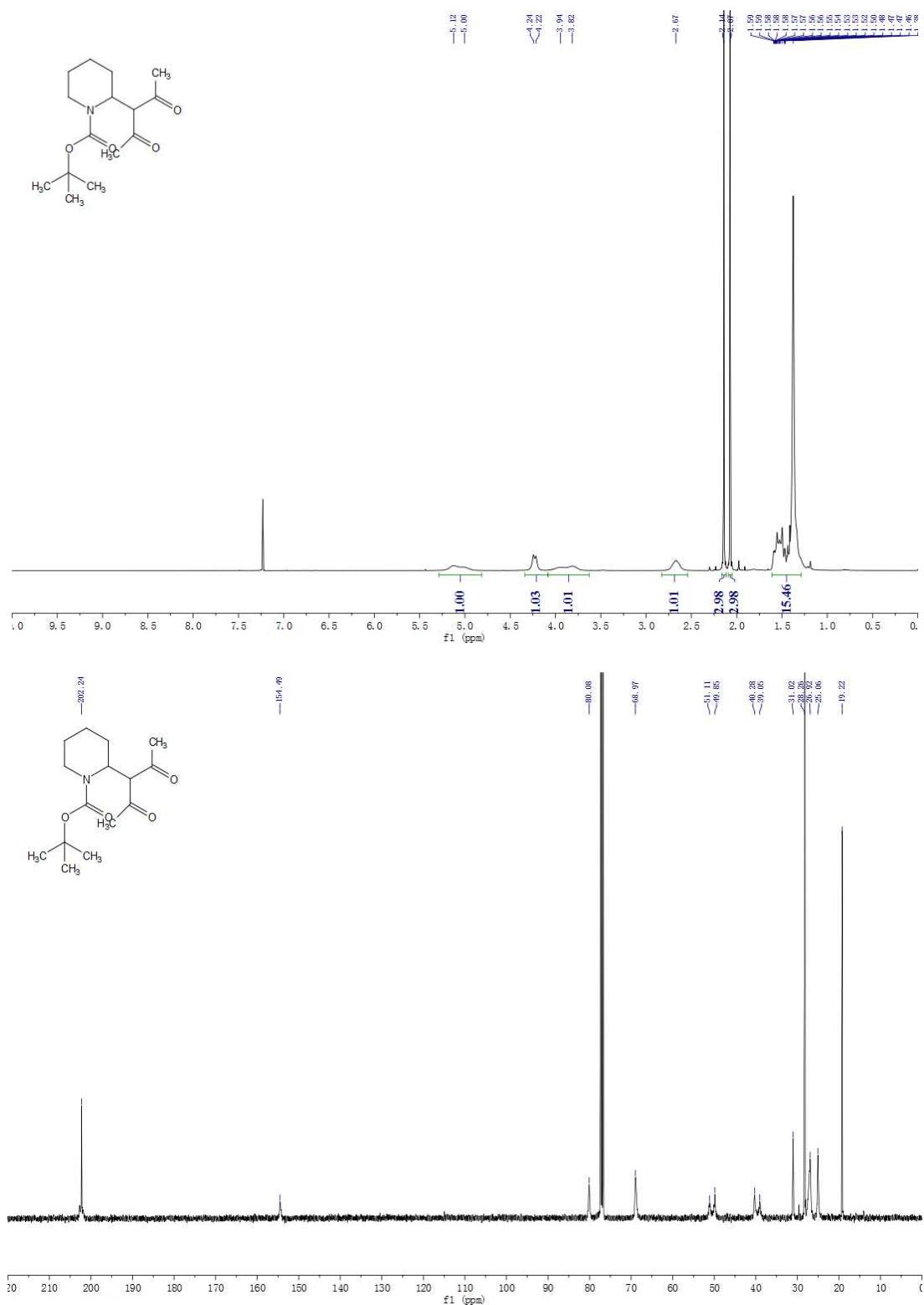
¹H and ¹³C NMR Spectra of **3j**



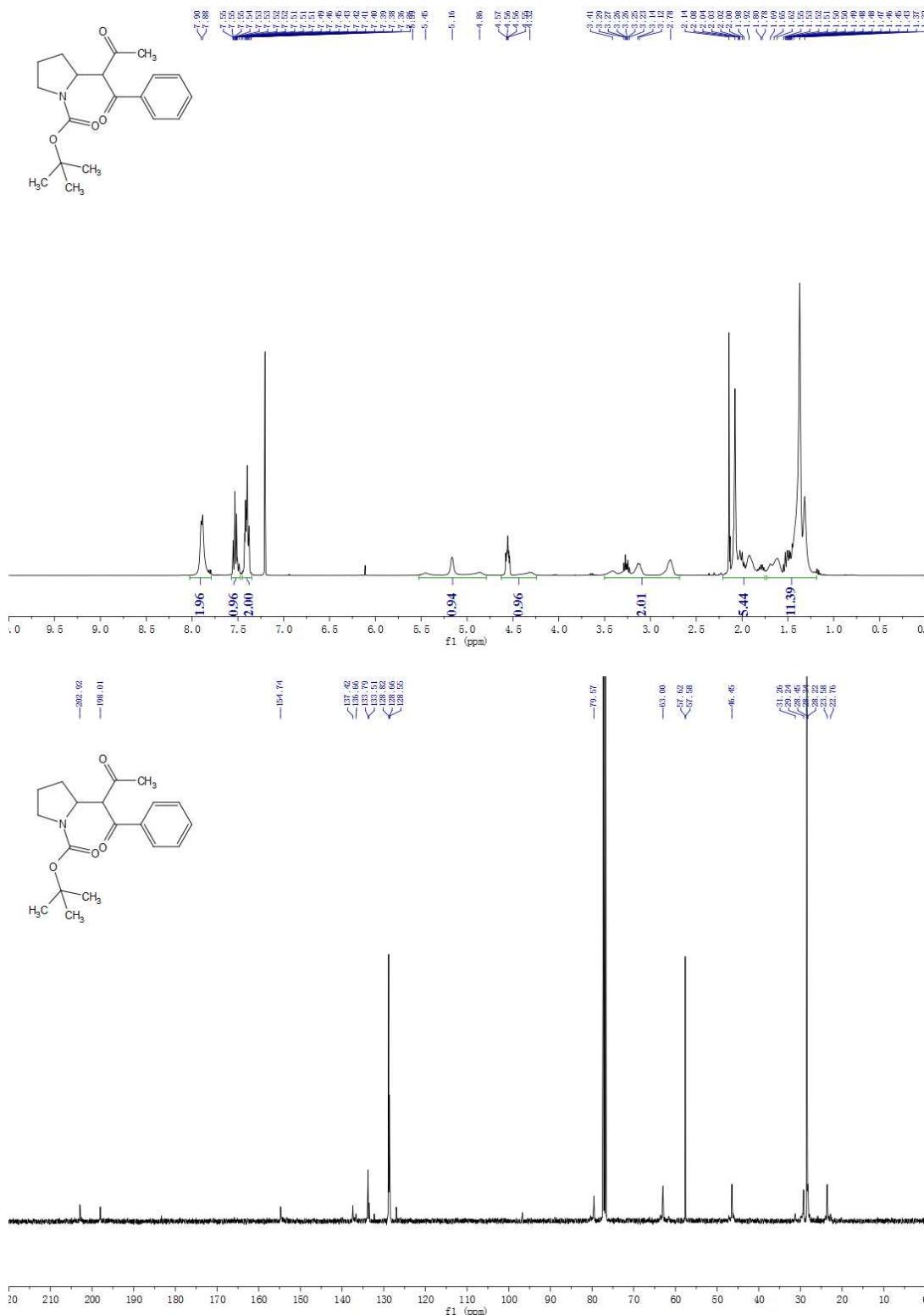
¹H and ¹³C NMR Spectra of 7a



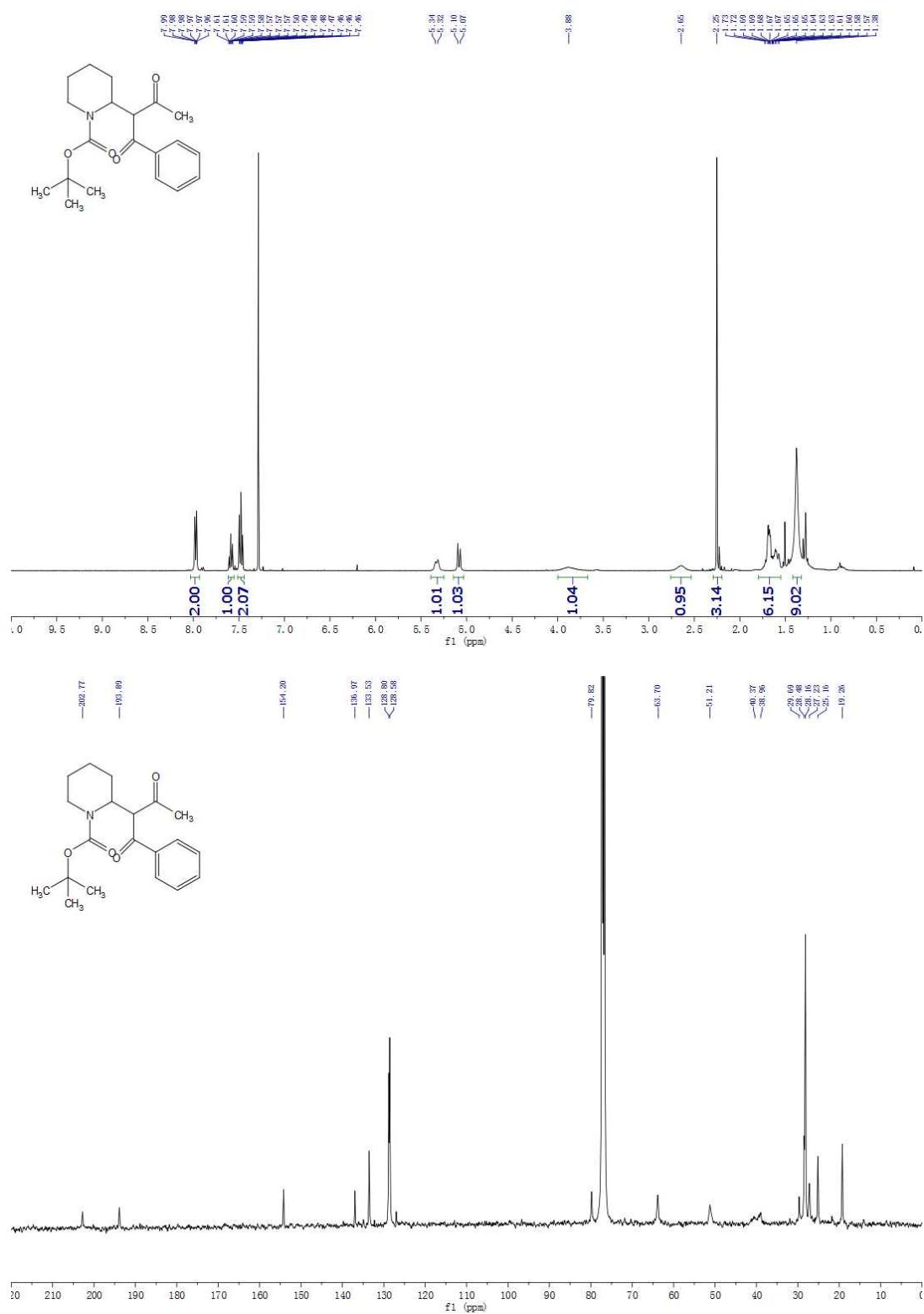
¹H and ¹³C NMR Spectra of 7b



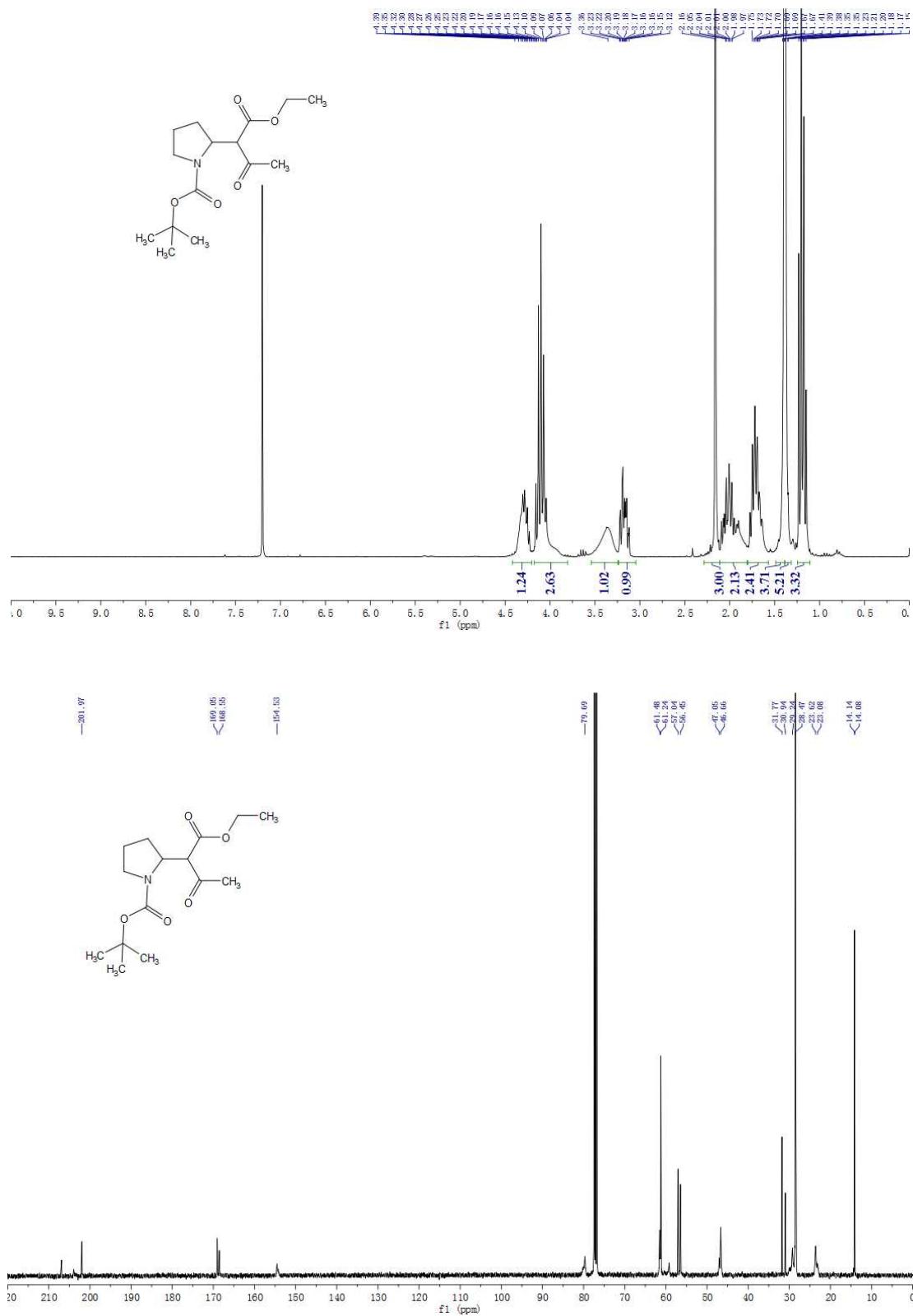
¹H and ¹³C NMR Spectra of 7c



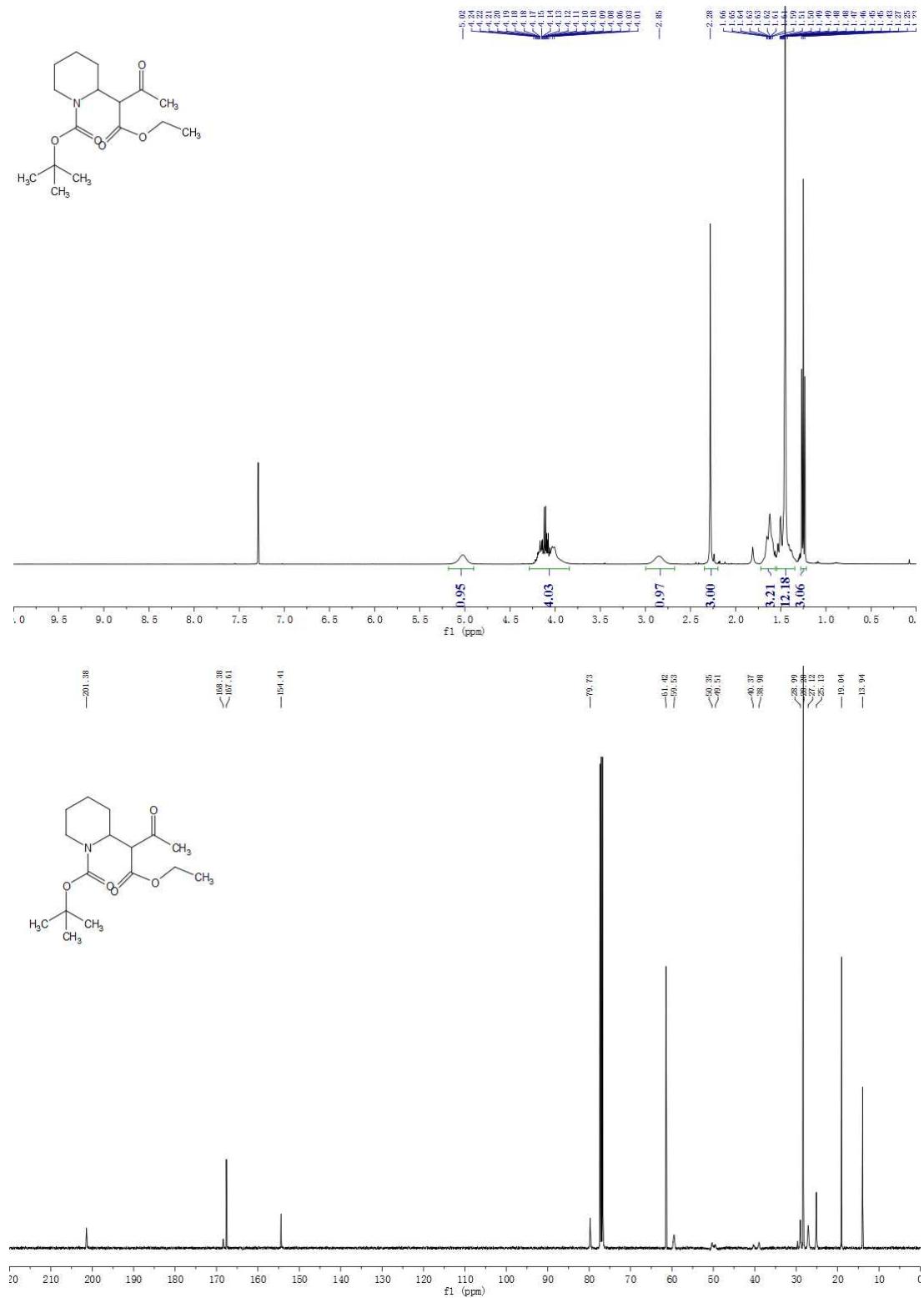
¹H and ¹³C NMR Spectra of 7d



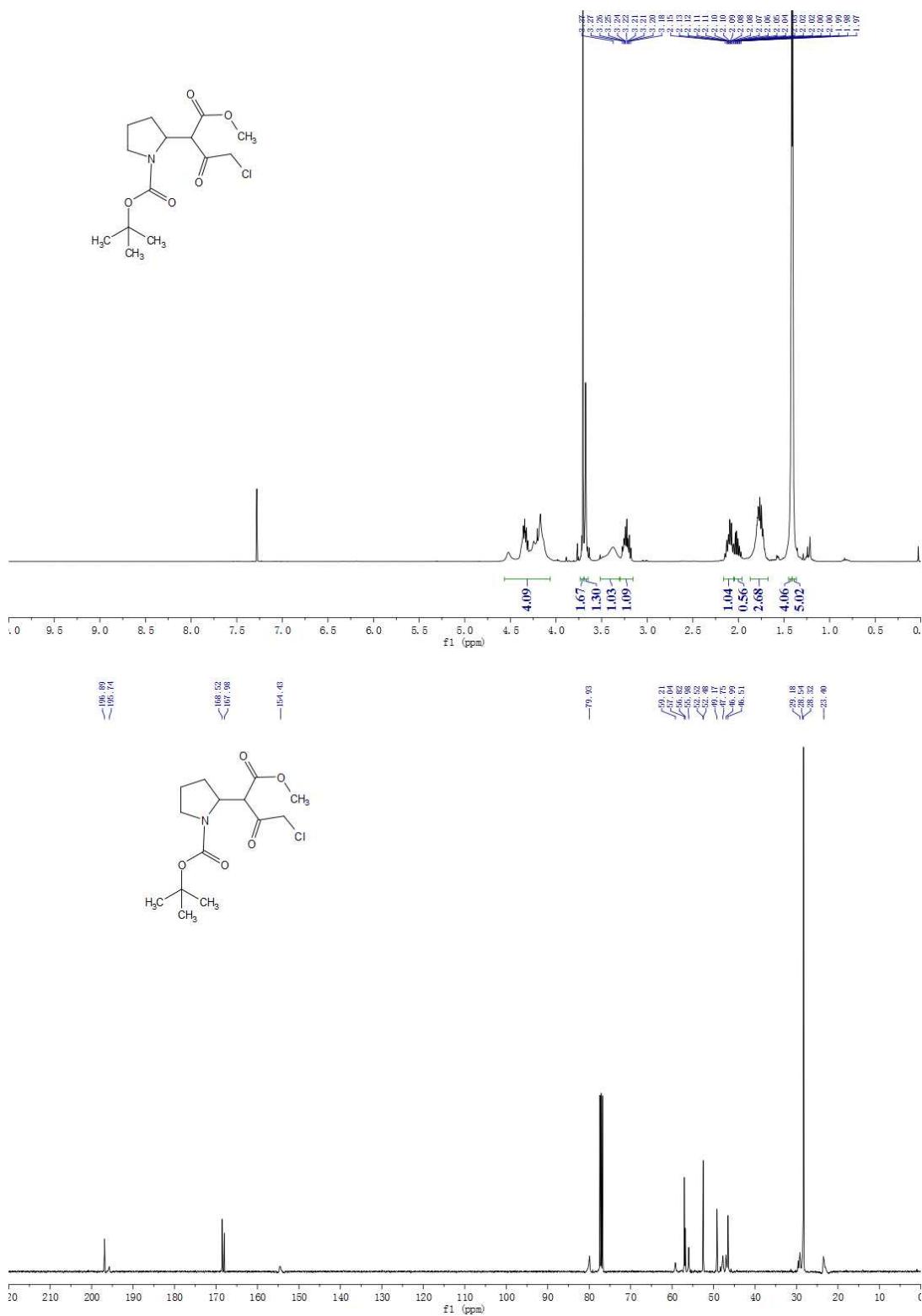
¹H and ¹³C NMR Spectra of 7e



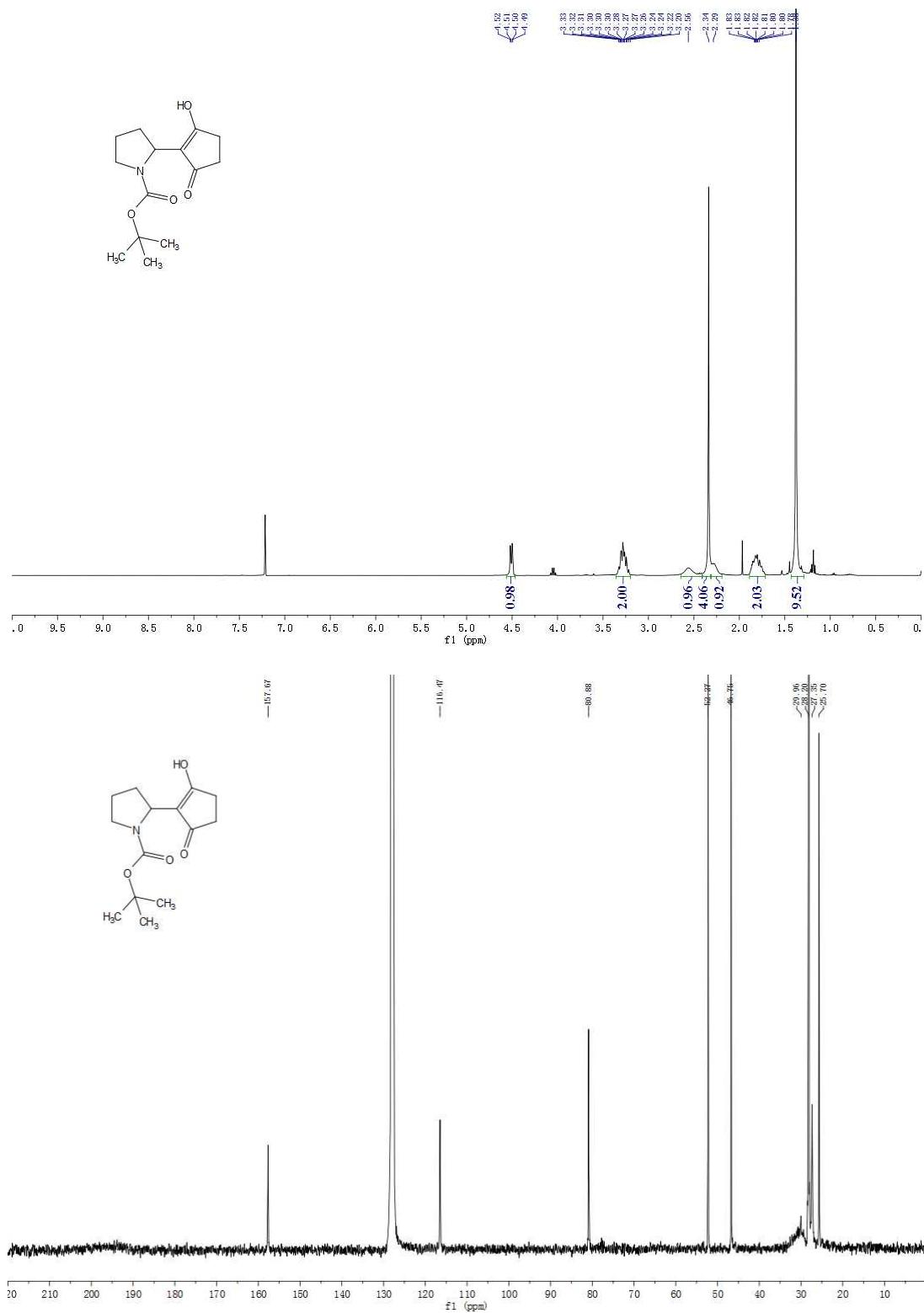
¹H and ¹³C NMR Spectra of 7f



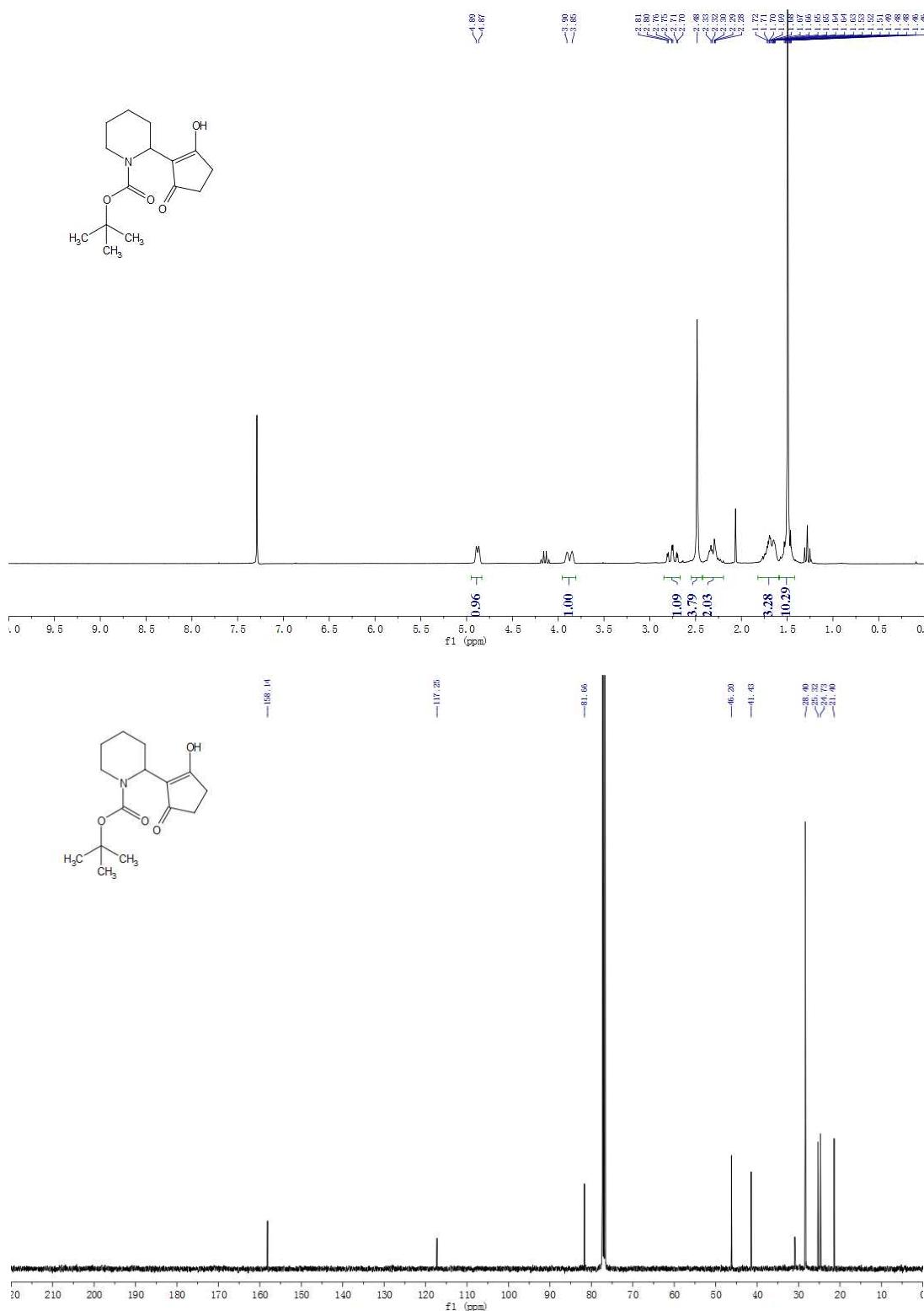
¹H and ¹³C NMR Spectra of 7g



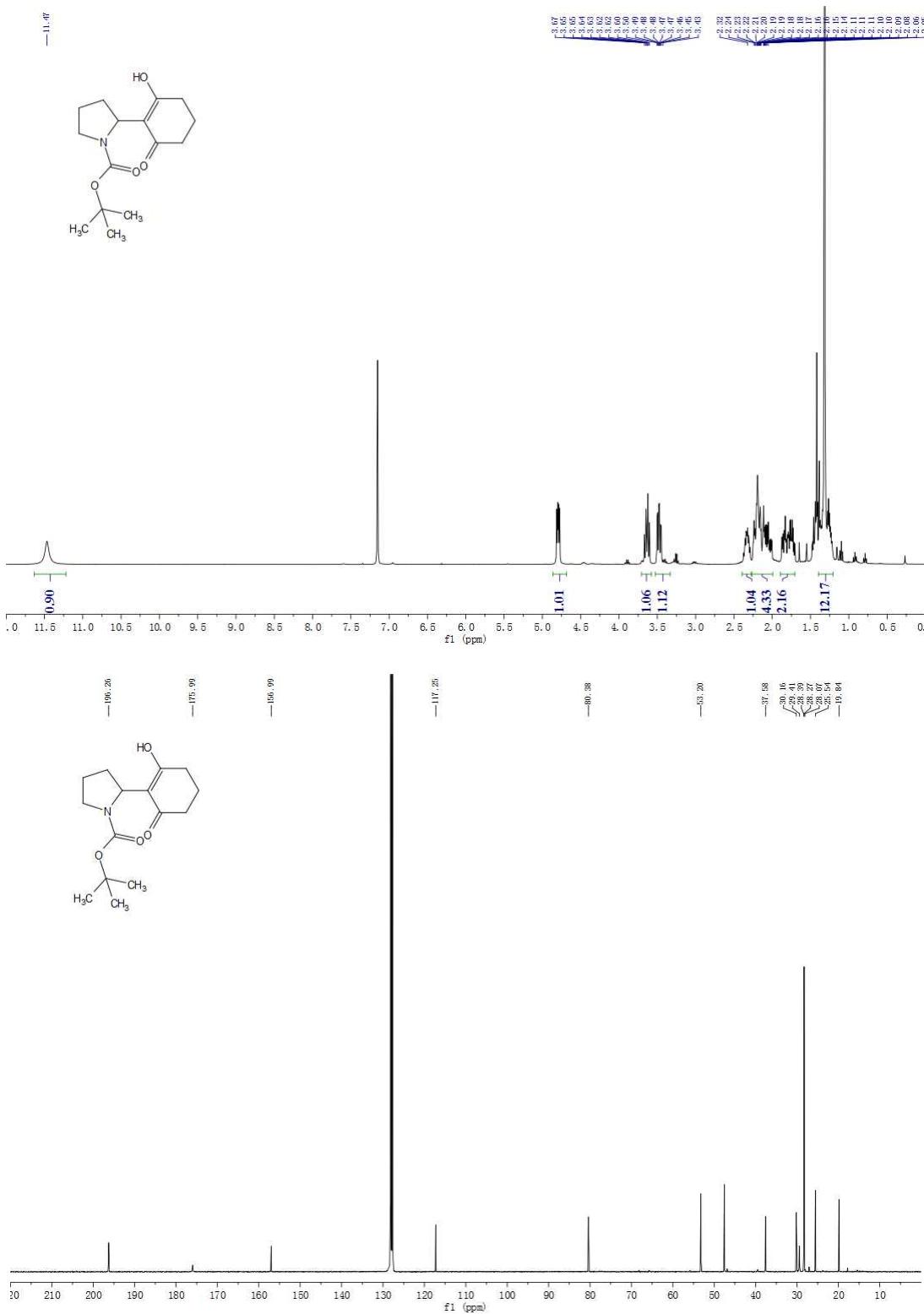
¹H and ¹³C NMR Spectra of **7i**



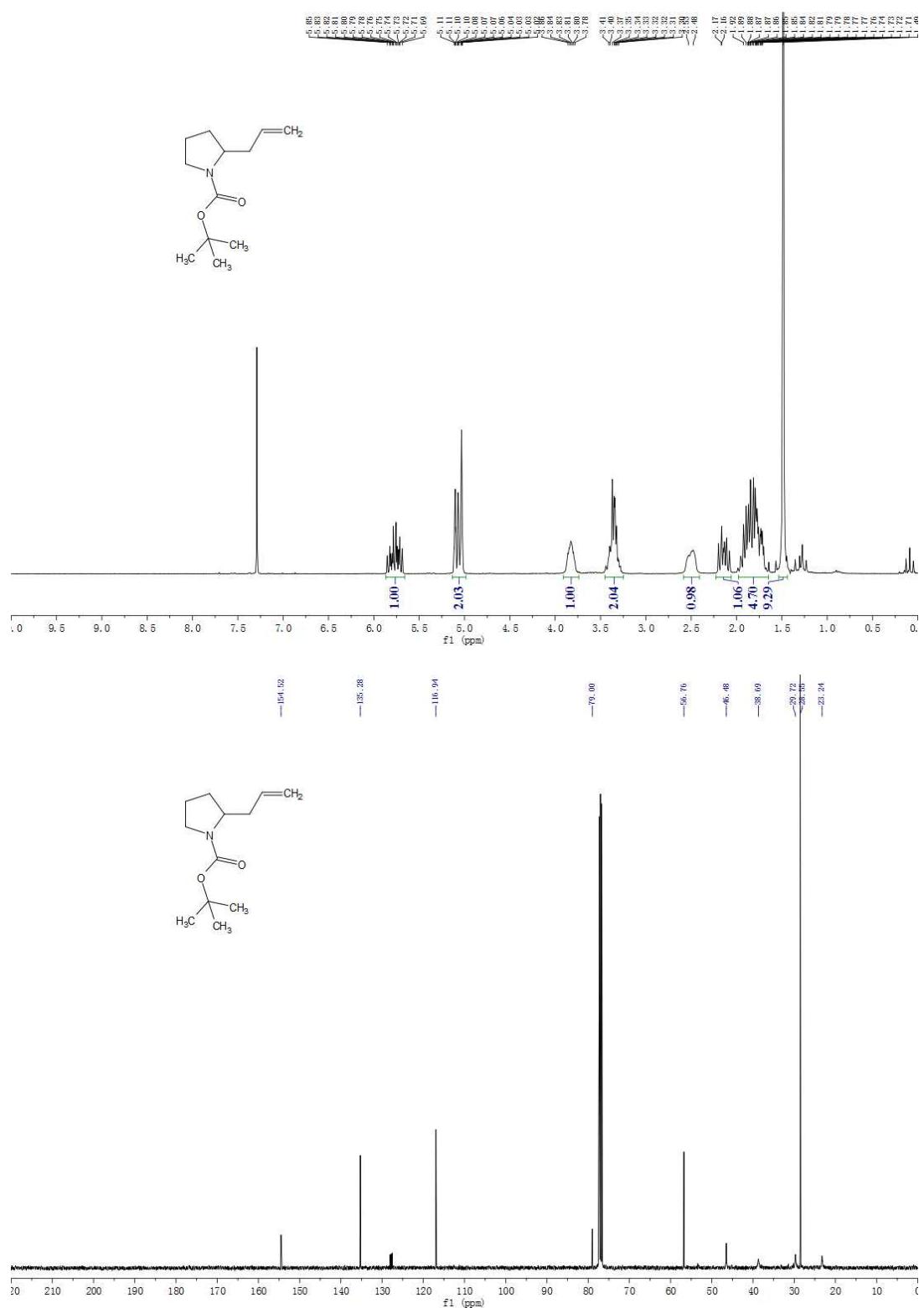
¹H and ¹³C NMR Spectra of 7j



¹H and ¹³C NMR Spectra of **7k**



¹H and ¹³C NMR Spectra of **8a**



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