Supporting Information

Two-Component Redox Organocatalyst for Peptide Bond Formation

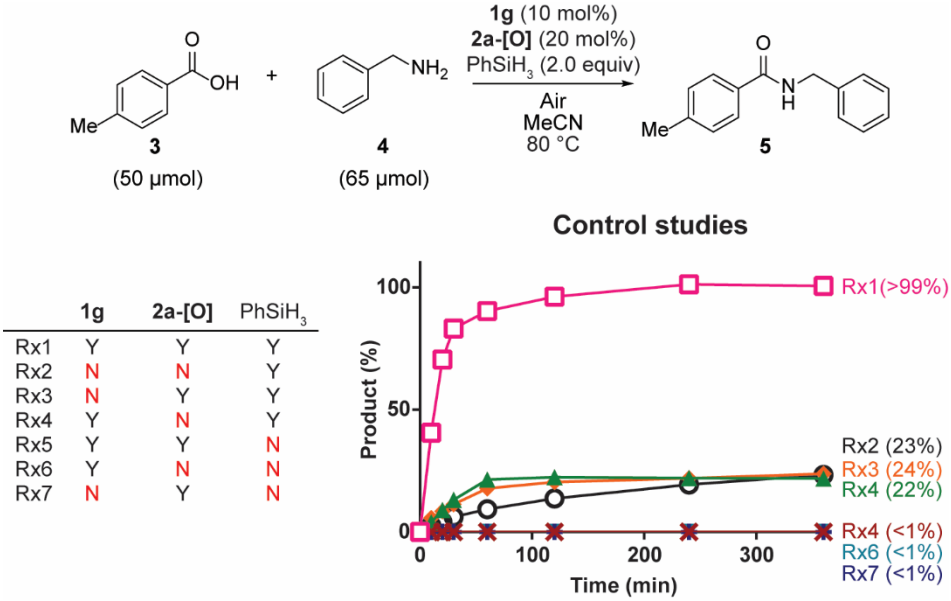
Handoko‡, Nihar R. Panigrahi‡, and Paramjit S. Arora*

Department of Chemistry, New York University, 100 Washington Square East, New York, NY 10003

Table of Contents

1 Supporting Figures and Tables

1.1. Control Studies



	1g	2a-[O]	$PhSiH_3$
Rx1	Y	Y	Y
Rx2	N	N	Y
Rx3	N	Y	Y
Rx4	Y	N	Y
Rx5	Y	Y	N
Rx6	Y	N	N
Rx7	N	Y	N

Figure S 1. Results of the control studies to probe reaction dependence on each reaction component. Reaction condition: toluic acid **3** (50 µmol), benzylamine **4** (65 µmol), **1g** (10 mol %, 5 µmol), **2a-[O]** (20 mol %, 10 µmol), $PhSiH_3$ (2 equiv., 100 µmol) in MeCN (1 mL) at 80 °C under open air.

To confirm whether the product formation observed was due to phenylsilane alone or in combination with either one or both catalysts (**1g** and **2a-[O]**), we conducted control studies (**Figure S 1** reaction Rx1 to Rx7) where each of these reaction components are removed. When phenylsilane is used alone under (reaction Rx2), the reaction rate slows down dramatically with only 23% product formation within six hours of reaction, in contrast to that of reaction Rx1 (where all the reaction components are present). To probe whether phenylsilane interacts with only one of the catalysts (**1g** or **2a-[O]**) in the catalysis, we tested condition in reaction Rx3 (without **1g**) and Rx4 (without **2a-[O]**). The results from both are virtually similar to that of reaction Rx2. The results indicate the existence of a cooperative mechanism between phenylsilane, diselenide **1g**, and phosphine oxide **2a-[O]** in promoting amide bond formation.

1.2. Catalyst Loading Studies

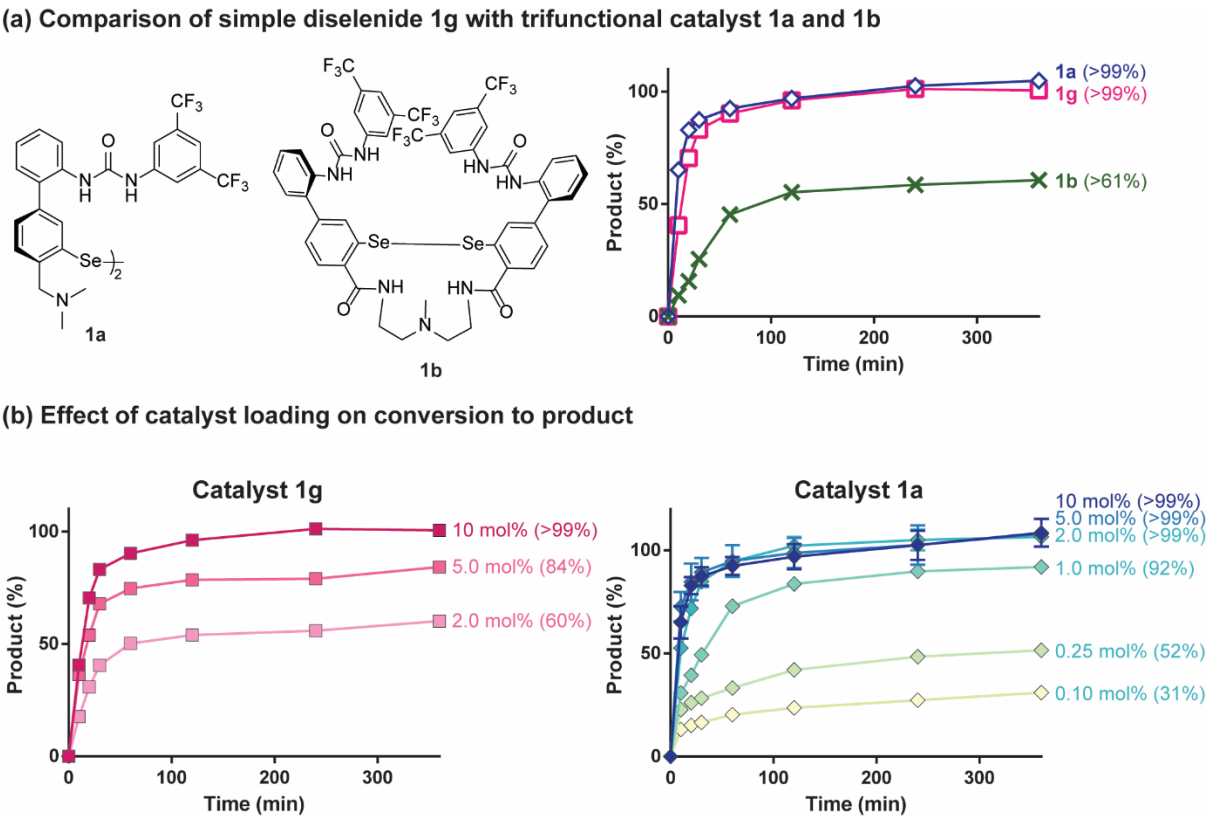
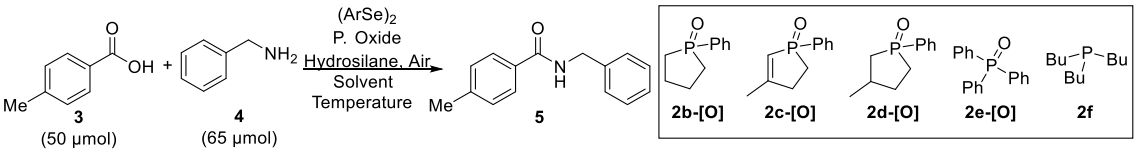


Figure S 2. (a) Comparison among diselenide catalyst **1a**, **1b**, and **1g** in promoting amide bond coupling. The reaction condition is similar to that found in **Figure S 1**. (b) Results from catalyst loading experiments. Datapoints for catalyst **1a** for 10 mol %, 5.0 mol %, and 2.0 mol % were obtained in triplicate; error bars represent standard deviation.

1.3. Optimization of Reaction Conditions

Table S 1. Optimization of Reaction Conditions

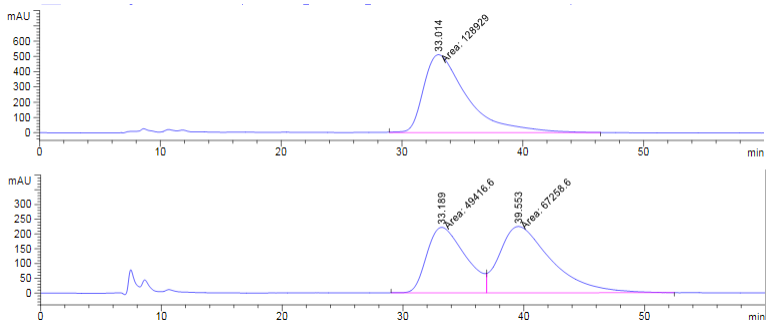


	Diselenide	P.Oxide	Hydrosilanes	Solvents	Temperature	Conversion (Time)[a]
1	**1a** (10 mol %)	**2a-[O]** (20 mol %)	$PhSiH_3$ (2.0 equiv)	MeCN	80 °C	>99% (2 h)
2		**2b-[O]** (20 mol %)				78% (4 h)
3		**2c-[O]** (20 mol %)				83% (4 h)
4		**2d-[O]** (20 mol %)				70% (4 h)
5		**2e-[O]** (20 mol %)				23% (1 h)
6		**2f** (20 mol %)				27% (2 h)
7	**1a** (2.0 mol %)	**2a-[O]** (10 mol %)	$PhSiH_3$ (2.0 equiv)	MeCN	80 °C	99% (2 h)
8		**2a-[O]** (5.0 mol %)				97% (4 h)
9		**2a-[O]** (2.0 mol %)				89% (6 h)
10		**2a-[O]** (1.0 mol %)				71% (6 h)
11	**1a** (2.0 mol %)	**2a-[O]** (10 mol %)	Ph_2SiH_2 (2.0 equiv)	MeCN	80 °C	>14% (2 h)
12			Et_3SiH (2.0 equiv)			<1% (6 h)
13			TMDS[b] (2.0 equiv)			<1% (6 h)
14	**1a** (2.0 mol %)	**2a-[O]** (10 mol %)	$PhSiH_3$ (1.5 equiv)	MeCN	80 °C	89% (2 h)
15			$PhSiH_3$ (1.0 equiv)			60% (2 h)
16			$PhSiH_3$ (0.5 equiv)			22% (2 h)
17			$PhSiH_3$ (0.3 equiv)			3% (2 h)
18	**1a** (2.0 mol %)	**2a-[O]** (10 mol %)	$PhSiH_3$ (3 x 0.5 equiv)	MeCN	80 °C	>99% (2 h)
19			PhSiH3 (3 x 0.33 equiv)			84% (4 h)
20	**1a** (2.0 mol %)	**2a-[O]** (10 mol %)	$PhSiH_3$ (2.0 equiv)	Toluene	80 °C	55% (2 h)
21				Dioxane		71% (6 h)
22				DMF		37% (4 h)
23				DMSO		40% (1 h)
24	**1a** (2.0 mol %)	**2a-[O]** (10 mol %)	$PhSiH_3$ (2.0 equiv)	MeCN	60 °C	87% (4 h)
25					40 °C	71% (6 h)
26					20 °C	<1 % (6 h)

[a]Conversions were monitored by HPLC using biphenyl as the internal standard. The time to reach maximum conversion for each condition is provided in parentheses. [b]TMDS = Tetramethyldisiloxane ($(Me_2SiH)_2O$).

1.4. Diastereomeric Ratio Data

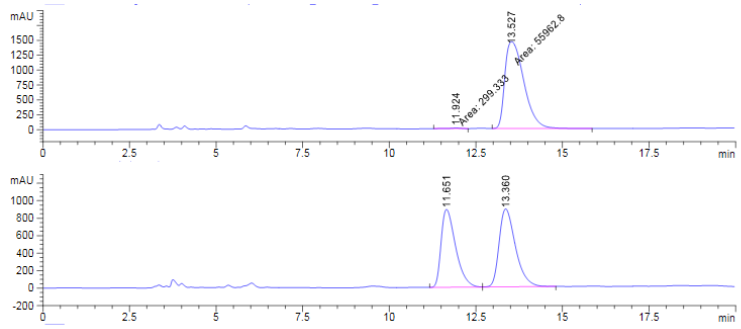
BocAla-TrpNH$_2$




```
Signal 3: DAD1 E, Sig=280,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  33.014 MM    4.2096 1.28929e5   510.45566 100.0000

Totals :                  1.28929e5   510.45566


Signal 3: DAD1 E, Sig=280,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  33.189 MF    3.7040 4.94166e4   222.35880  42.3540
   2  39.553 FM    4.9819 6.72586e4   225.01030  57.6460

Totals :                  1.16675e5   447.36909
```

Figure S 3. (Top) Chromatogram (280 nm) of BocAla-TrpNH$_2$ obtained from the catalytic reaction. (Bottom) Chromatogram (280 nm) of diastereomeric LL/DL mixture of BocAla-TrpNH$_2$ standard. HPLC condition: Chiralcel AD-H; isocratic elution of hexanes : isopropanol = 86 : 14; flow rate = 0.75 mL/min.

BocPhe-AlaO^{t}Bu




```
Signal 3: DAD1 D, Sig=214,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.924 MM    0.4206  299.33264   11.86100   0.5320
   2  13.527 MM    0.6383 5.59628e4  1461.19788  99.4680

Totals :                  5.62622e4  1473.05888


Signal 3: DAD1 D, Sig=214,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.651 VV    0.4522 2.60163e4   892.21204  46.8961
   2  13.360 VB    0.5089 2.94601e4   893.01044  53.1039

Totals :                  5.54764e4  1785.22247
```

Figure S 4. (Top) Chromatogram (214 nm) of BocPhe-AlaO^{t}Bu obtained from the catalytic reaction. (Bottom) Chromatogram (214 nm) of diastereomeric LL/DL mixture of BocPhe-AlaO^{t}Bu standard. HPLC condition: Chiralcel OD; isocratic elution of hexanes : isopropanol = 97 : 3; flow rate = 1.0 mL/min.

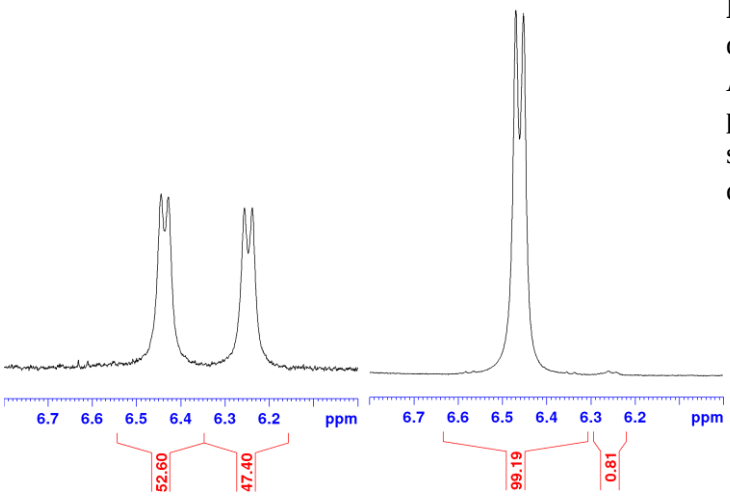


Figure S 5. (Left) Cropped ^{1}H NMR spectrum of diastereomeric LL/DL mixture of BocPhe-AlaO^{t}Bu standard. Peaks correspond to the amide proton of each isomer. (Right) Cropped ^{1}H NMR spectrum of BocPhe-AlaO^{t}Bu obtained from the catalytic reaction.

BocVal-AlaO^{t}Bu

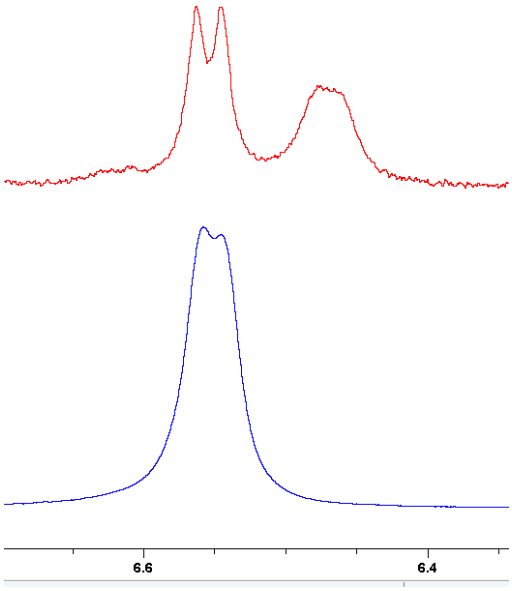


Figure S 6. (Top) Cropped ^{1}H NMR spectrum of diastereomeric LL/DL mixture of BocVal-AlaO^{t}Bu standard. Peaks correspond to the amide proton of each isomer. (Bottom) Cropped ^{1}H NMR spectrum of BocVal-AlaO^{t}Bu obtained from the catalytic reaction.

2. Mechanistic Studies

In the control studies using catalyst **1a** (**Figure S 1**), we have shown that the amidation reaction proceeds appreciably only when the diselenide catalyst (**1a**), phosphine oxide catalyst (**2a-[O]**), and $PhSiH_3$ are present, suggesting a cooperative mechanism involving the three. We envisioned the involvement of a key selenophosphonium intermediate, formed from the reaction of diselenide **1a** with reduced phosphine **2a**, that activates carboxylic acids to form amides, in analogy to the established mechanism for phosphonium-based activating reagents.

To probe the mechanism of the catalysis, we studied the coupling of 4-fluorobenzoic acid (**6**) and benzylamine (**4**) using a combination of ^{19}F, ^{31}P, and ^{77}Se NMR spectroscopic methods to identify any intermediates formed during the reaction. Diselenide catalyst **1g** was used instead of **1a** due to its better solubility at high concentration in acetonitrile, allowing for fast detection of selenium intermediate in ^{77}Se NMR spectra.

As shown in reaction Rx2 in **Figure S 1**, $PhSiH_3$ alone has the capacity to promote amide bond formation, albeit very slowly. Reaction Rx2 can therefore be viewed as the uncatalyzed background reaction and any intermediate formed in reaction Rx2 may potentially interact with **1g** and **2a-[O]** in the catalysis. We thus begin our studies by identifying intermediates formed where $PhSiH_3$ alone is used to promote the coupling of **6** and **4** (**Figure S 7**). When **6** (^{19}F δ −108.2 ppm) and **4** were mixed together, formation of the expected ammonium carboxylate ensued (^{19}F δ −111.4 ppm). Upon addition of $PhSiH_3$ to this mixture, evolution of gas was noted (presumably hydrogen gas) and the ^{19}F NMR spectrum of the reaction mixture showed signals for complex intermediate **Int-1** (^{19}F δ −106 to −108 ppm) that decreased over time and product **7** (^{19}F δ −110.9 ppm) that increased over time. This observation is consistent with mechanistic studies conducted by Denton *et al*., in which the group attributed **Int-1** as complex mixtures of silyl esters.[1-2] As previously shown, formation of amide product **7** was slow, with only 23% conversion within six hours of reaction. When the reaction was added with water (0.1% TFA), **Int-1** quickly hydrolyzed back into the starting material.

We next investigated the same reaction in the presence of 10 mol % **1g** and 20 mol % **2a-[O]** (**Figure S 8**). Similarly, we observed the formation of **Int-1** and product **7** in the ^{19}F NMR spectrum. Unlike the uncatalyzed reaction, formation of product **7** was rapid and the reaction was completed within two hours. By ^{31}P NMR spectroscopy, we observed that reduced phosphine **2a** (^{31}P δ 29.2 ppm)[3] was the only major phosphorus species present within the first two to 15 minutes of the reaction, when conversion to product was the fastest. This observation indicates that the reduction of phosphine **2a-[O]** by hydrosilanes ($PhSiH_3$ or possibly **Int-1**) is rapid and the reduced **2a** is the resting state of the catalyst at high concentration of reductant. Beyond 15 minutes, **2a-[O]** reappeared, coinciding with the diminishing of **2a** and **Int-1**. New chemical species at 66.6 ppm (**Int-2**) was also observed (which was later confirmed to be a selenophosphonium intermediate). After quenching with water, **Int-2** converted readily into **2a-[O].**

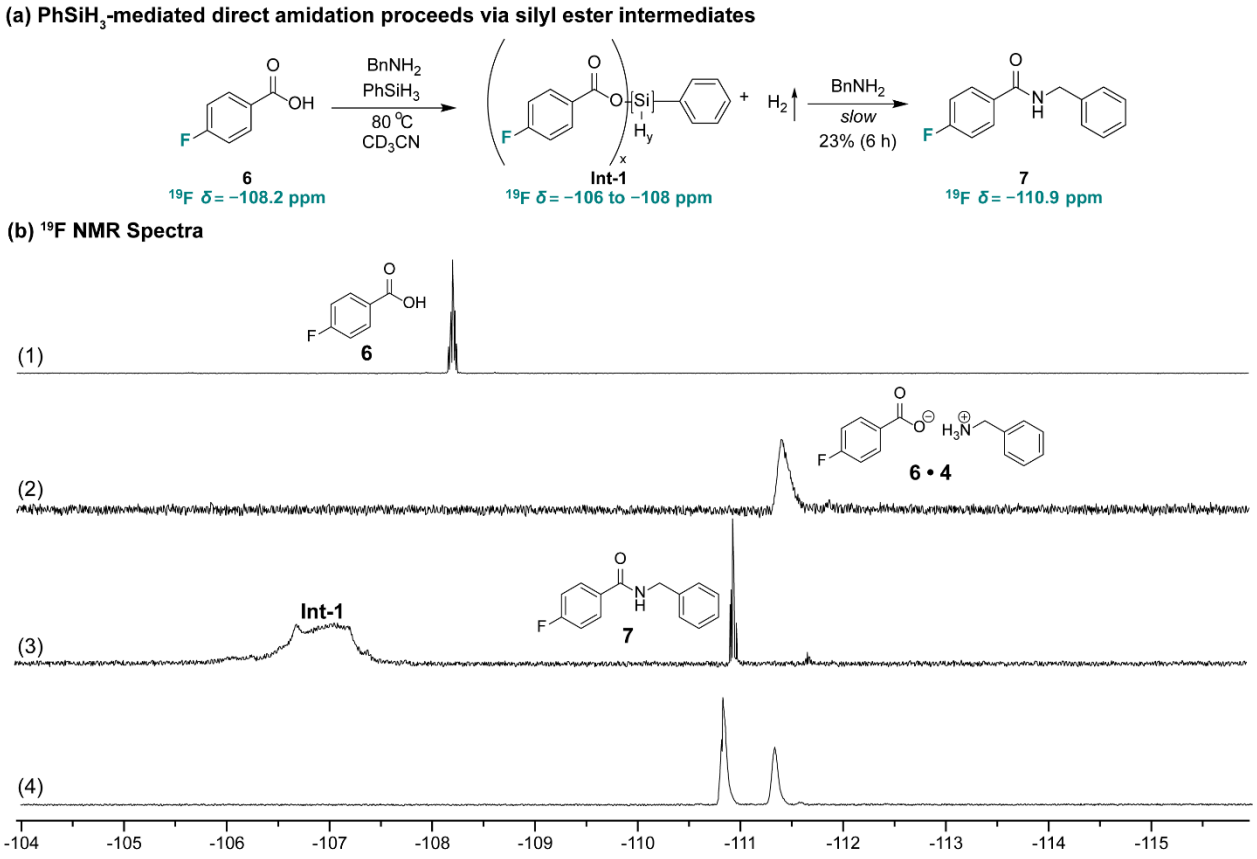


Figure S 7.(a) Upon mixing of carboxylic acid **6** (50 µmol), benzylamine **4** (60 µmol), and $PhSiH_3$ (150 µmol) in CD_3CN (1 mL) at 80°C, silyl esters **Int-1** was formed concomitant with the release of hydrogen gas. The formation of amide **7** from **Int-1** proceeded slowly. (b) Evolution of the ^{19}F NMR spectra during the coupling: (1) 4-fluorobenzoic acid **6** starting material, (2) after addition of benzylamine **4**, (3) after addition in $PhSiH_3$ (after one hour), and (4) after quenching with water (0.1% TFA).

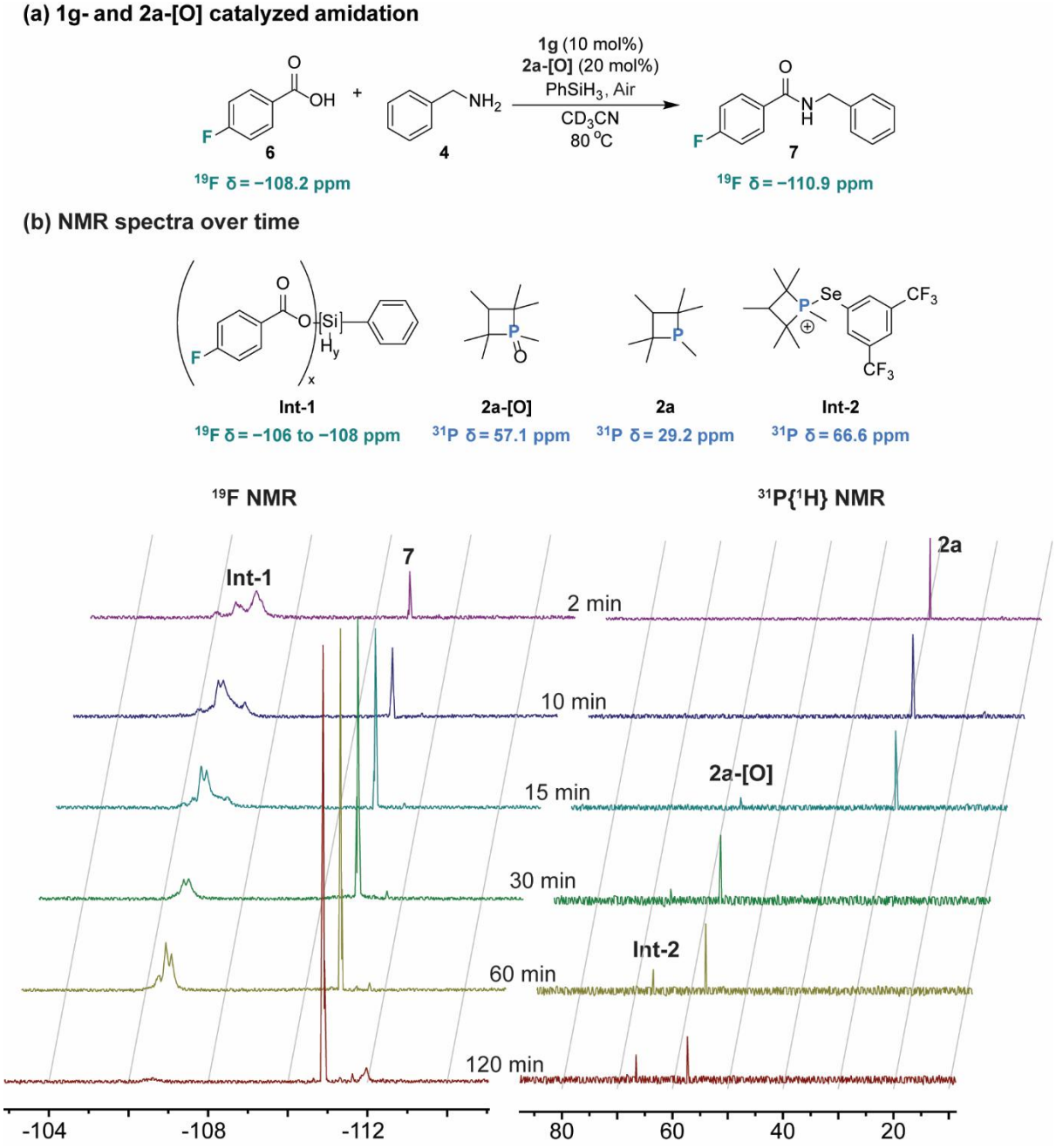


Figure S 8. (a) Reaction condition: carboxylic acid **6** (50 µmol), benzylamine **4** (60 µmol), $PhSiH_3$ (150 µmol), **1g** (10 mol %), **2a-[O]** (20 mol %) in CD_3CN (1 mL) at 80°C under open air. (b) ^{19}F and ^{31}P NMR spectra of the catalyzed reactions. The identity for **Int-2** (^{31}P δ 66.6 ppm) was later confirmed in subsequent studies.

Based on the results of the above experiments, we hypothesized that reduced phosphine **2a** reacts with diselenide **1g** to form an active intermediate **Int-2**, presumably selenophosphonium intermediate, that rapidly promotes amide bond formation from **Int-1**. To probe how **Int-1** transforms into product **7**, we pre-formed **Int-1** with excess $PhSiH_3$ and reacted it with stoichiometric amount (one equivalent each) of **1g** and **2a-[O]** (Figure S **9**). Upon addition of both catalysts, product **7** rapidly formed within ten minutes, and a transient new species of **Int-3** (^{19}F δ −104.4 ppm) (which was later confirmed to be a selenoester intermediate) was detected in the ^{19}F NMR spectroscopy. Small amount of carboxylic acid **6** (^{19}F δ −108.2 ppm) was also transiently detected along the reaction. In the ^{31}P NMR spectrum, we similarly observed rapid reduction of **2a-[O]** into **2a** and formation of **Int-2**.

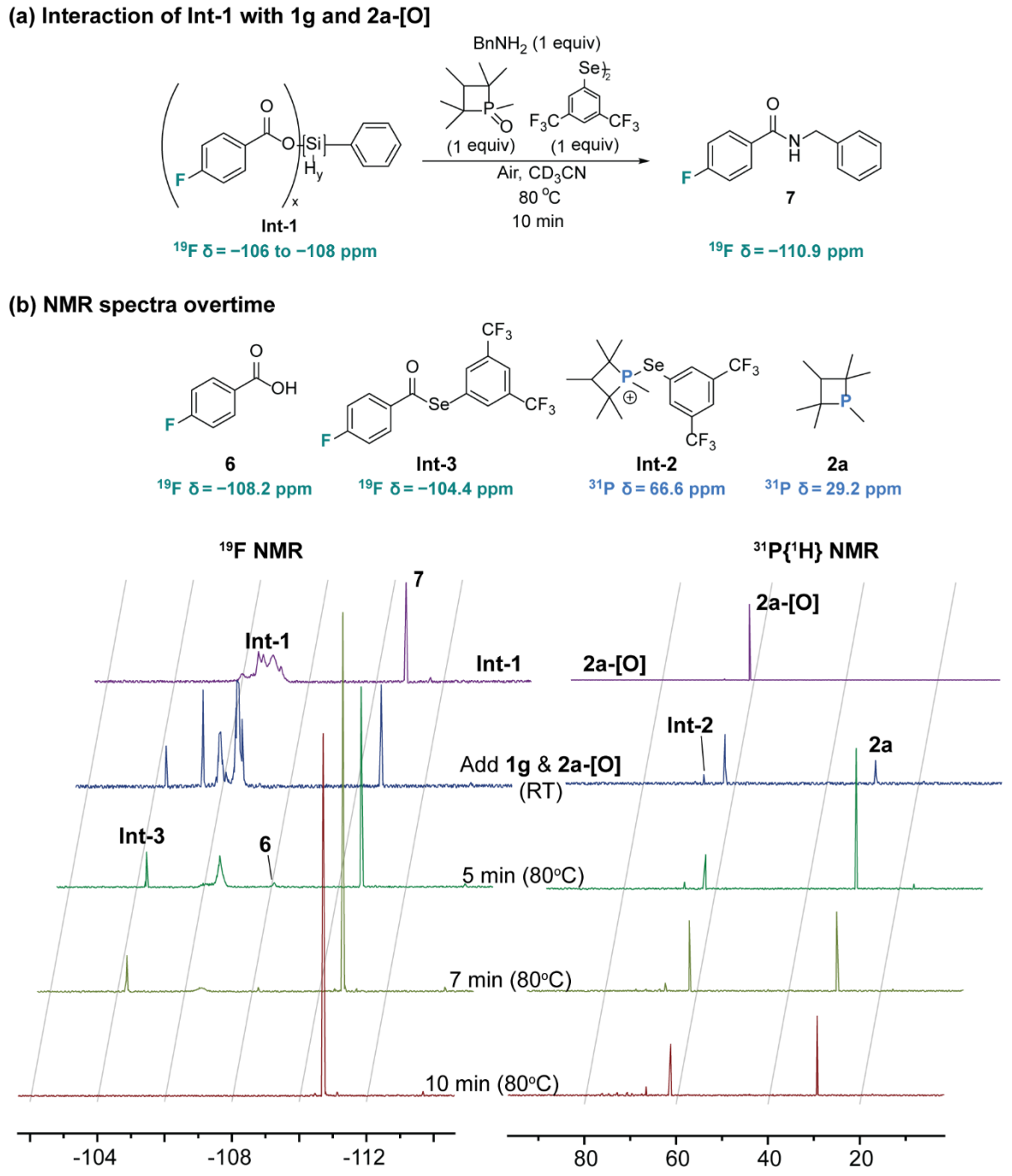


Figure S 9. (a) Interaction of pre-formed **Int-1** with stoichiometric amount of **1g** (50 μmol) and **2a-[O]** (50 μmol). (b) ^{19}F and ^{31}P NMR spectra of the reaction over time. Structures for **Int-2** and **Int-3** were confirmed in subsequent studies.

We hypothesize that the detected **Int-3** is a selenoester intermediate, formed by the reaction of carboxylic acid **6** (hydrolyzed from **Int-1**) with **Int-2** (hypothesized to be selenophosphonium intermediate). To confirm the identity of these intermediates, **Int-2** and **Int-3** were generated exclusively from their presumed precursors and characterized by NMR spectroscopy and HRMS.

Int-2 is hypothesized to be a selenophosphonium intermediate. Therefore, we reacted catalyst **1g** and **2a-[O]** with excess $PhSiH_3$ (three equivalents) at 80°C (**Figure S 10**). Within five minutes of reaction, we observed complete reduction of **2a-[O]** to **2a**, consistent with our previous observation in **Figure S 8**. **Int-2** (^{31}P δ 66.6 ppm; ^{77}Se δ −344.5 ppm) formed only gradually (complete formation within four hours), suggesting that selenophosphonium formation is the slower step in the phosphorus cycle. This observation is in agreement with **2a** being a less nucleophilic phosphine.[4] Evidence of **Int-2** being a selenophosphonium species was deduced from the identical *J*-coupling magnitude (−733 Hz) of its signals in ^{31}P and ^{77}Se NMR spectra, indicating a direct P−Se bond. Further confirmation was obtained from high-resolution mass spectrometry of the reaction mixture, where the mass-to-charge ratio corresponding to that of [**Int-2**•H_2O]$^+$ adduct was detected.

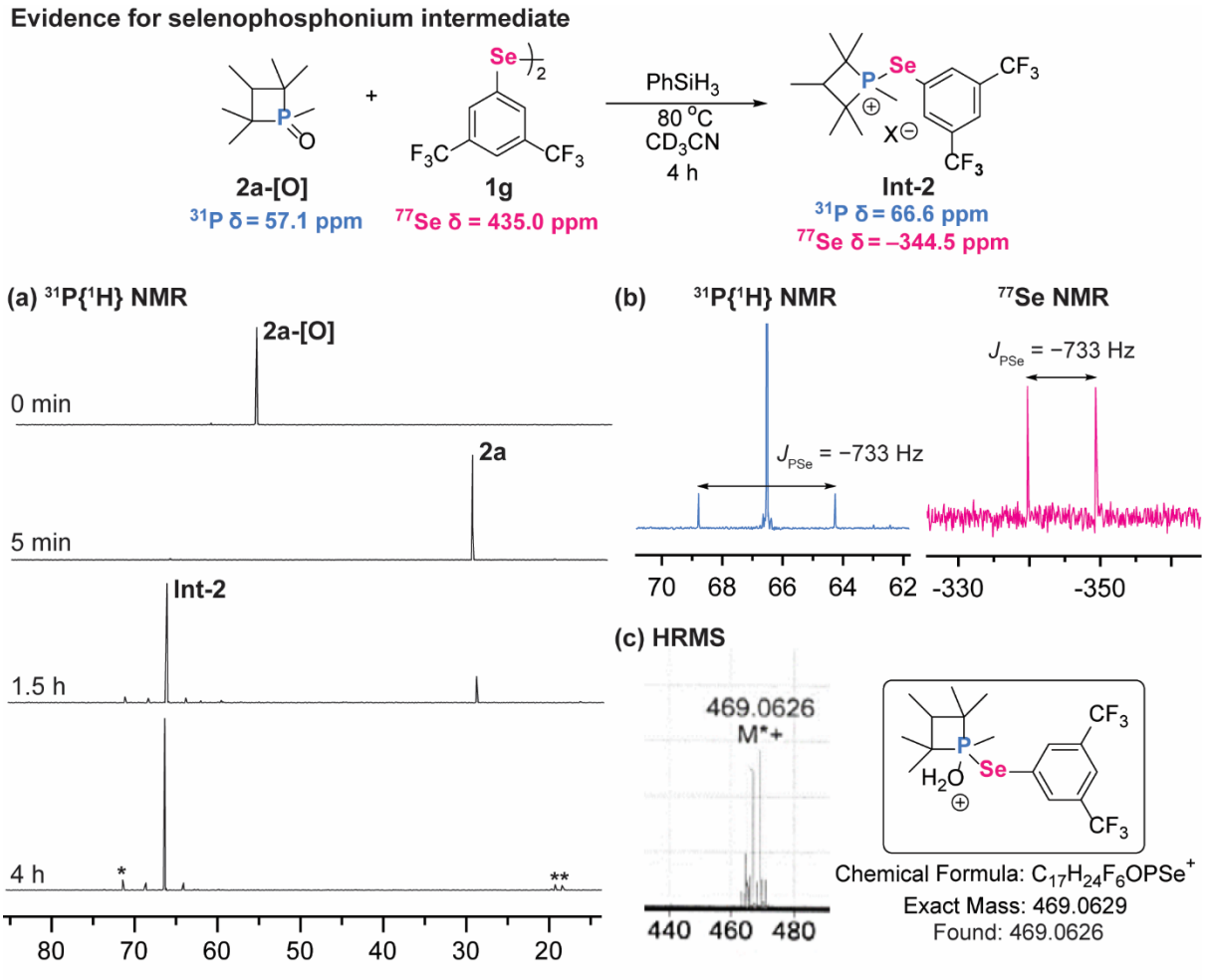


Figure S 10. Reaction condition: **1g** (50 µmol), **2a-[O]** (50 µmol) and $PhSiH_3$ (150 µmol) in CD_3CN (1 mL) at 80 °C. (a) ^{31}P NMR spectra of the reaction over time. (*) Presumably diastereomer of **Int-2**. (**) Unidentifiable peaks. (b) *J* coupling of **Int-2** in ^{31}P and ^{77}Se NMR spectra indicates a species with direct P–Se bond. (c) Detection of [**Int-2**•H_2O]$^+$ adduct in HRMS.

Having identified **Int-2**, we next treated it with carboxylic acid **6** and amine **4** at room temperature to see whether it can promote the formation of amide bond (**Figure S 11**). Indeed, upon addition, product **7** along with **Int-3** were detected in ^{19}F NMR spectroscopy. Concurrently, in ^{31}P NMR spectroscopy, selenophosphonium **Int-2** quickly converted into **2a-[O]**, indicating the successful activation of carboxylic acid **6**. When heat (80 °C) was applied to the reaction, formation of product **7** was accelerated concurrent with the diminishing of **Int-3**, while **2a-[O]** was reduced back to **2a** (from residual excess $PhSiH_3$), signifying the importance of heat to promote the reduction of **2a-[O]** to ensure turnover of the catalysis.

Int-3 is hypothesized to be a selenoester intermediate formed from the activation of carboxylic acid **6** with **Int-2**. Therefore, we performed an experiment where pre-formed **Int-2** was treated with **6** in the absence of benzylamine **4** (**Figure S 12**). As expected, carboxylic acid **6** converted fully into **Int-3** within 15 minutes as detected by ^{19}F NMR spectroscopy. ^{77}Se NMR spectra of **Int-3** showed chemical shifts at δ 649.1 ppm, which is within the reported range for selenoesters.[5] Addition of benzylamine **4** to **Int-3** at room temperature quickly transformed it into product **7**. Due to the low sensitivity of ^{77}Se NMR, only **1g** was detected at the end of the NMR acquisition (two hours). It is most likely that 3,5-bis(trifluoromethyl)benzeneselenolate was released and oxidized by air rapidly into **1g**.

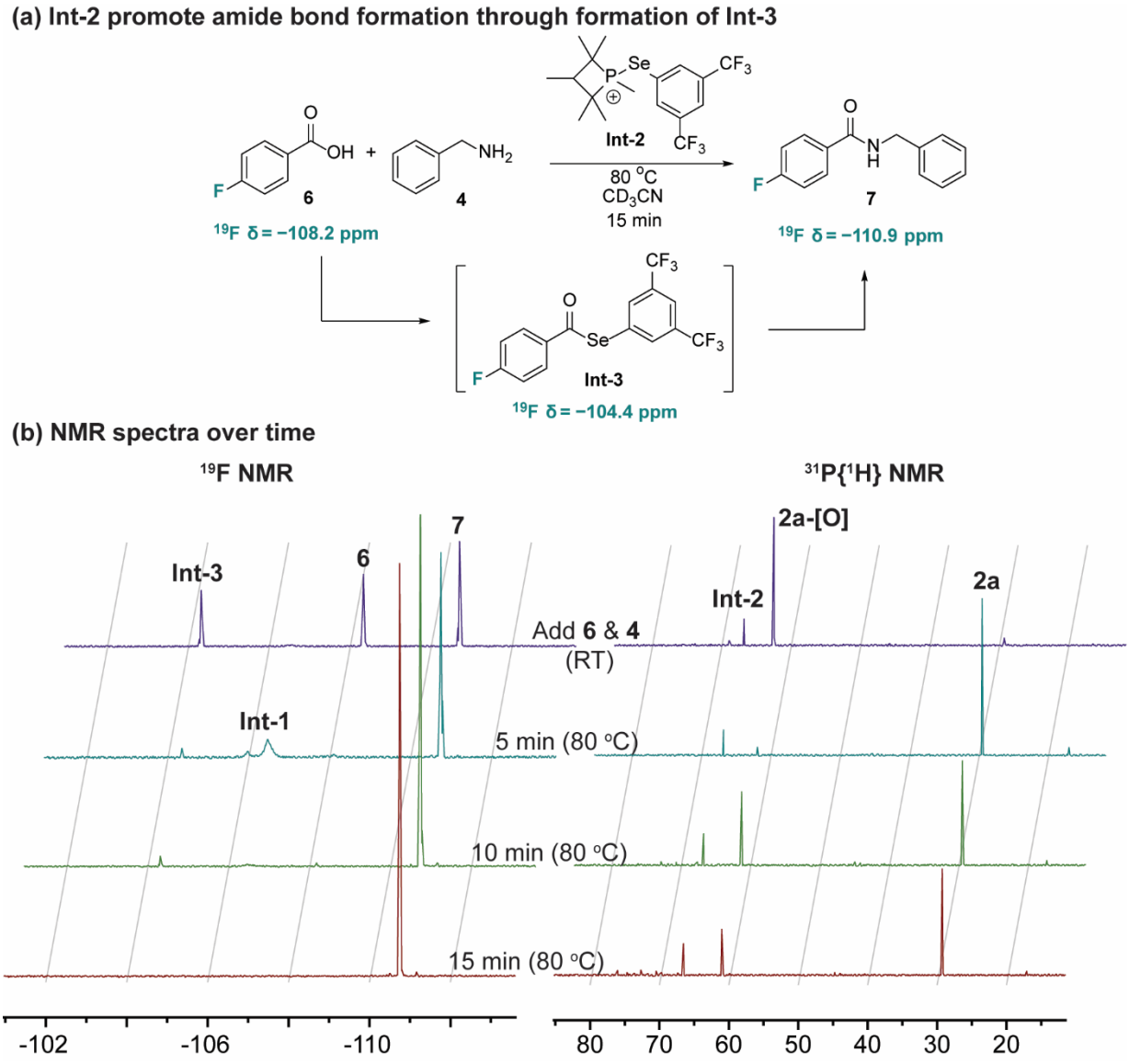


Figure S 11. (a) The addition of carboxylic acid **6** (50 μmol) and **4** (60 μmol) to **Int-2** (from Figure S **10**) led to rapid product formation within 15 minutes. (b) ^{19}F and ^{31}P NMR spectra of the reaction mixture over time. Transient **Int-3** was detected upon addition of **6** and **4** to **Int-2** at room temperature.

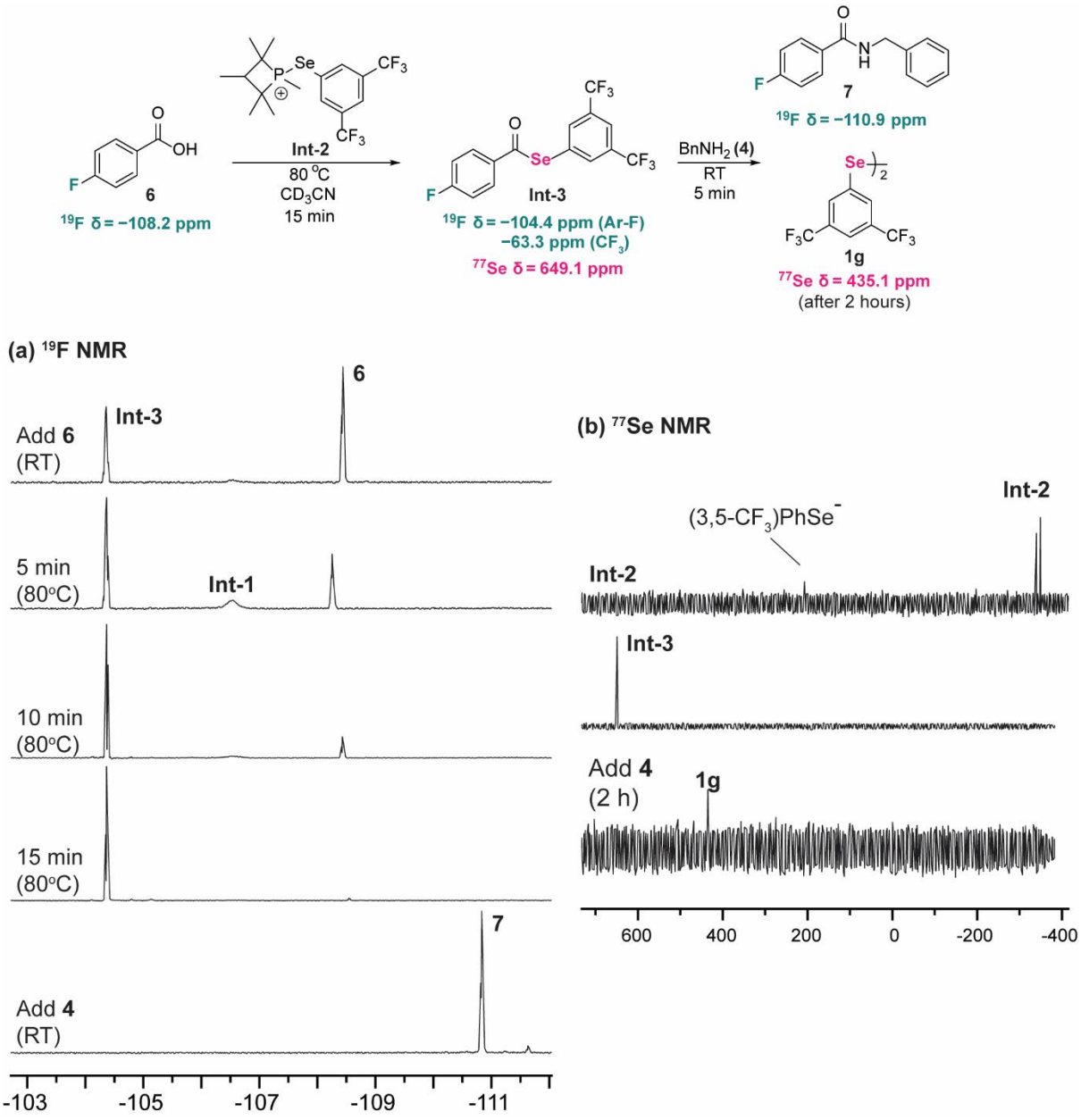


Figure S 12. Activation of carboxylic acid **6** (50 μmol) into selenoester **Int-3** by selenophosphonium **Int-2**. Addition of benzylamine **4** (50 μmol) led to product formation. (a) ^{19}F NMR spectra of the reaction over time. (b) ^{77}Se NMR spectra of key intermediate **Int-2**, **Int-3**, and **1g**. The chemical shift for **Int-3** is within the reported range for selenoester species.

Aside from the diselenide catalyst, phosphine oxide catalyst, and phenylsilane reductant, another key component of the catalysis is oxygen (from air). To confirm that the catalysis proceeds in accordance with our hypothesized dual catalytic system, we conducted additional control experiments where the rates of product conversion in the presence and absence of air were compared. As seen in **Figure S 13**, formation of product **7** when the reaction was conducted under argon was slower, comparable to that with reaction Rx2. Upon continuous bubbling of the reaction mixture with air (after 100 min), formation of product **7** was accelerated, indicative of the involvement of air (presumably oxygen) in the catalysis.

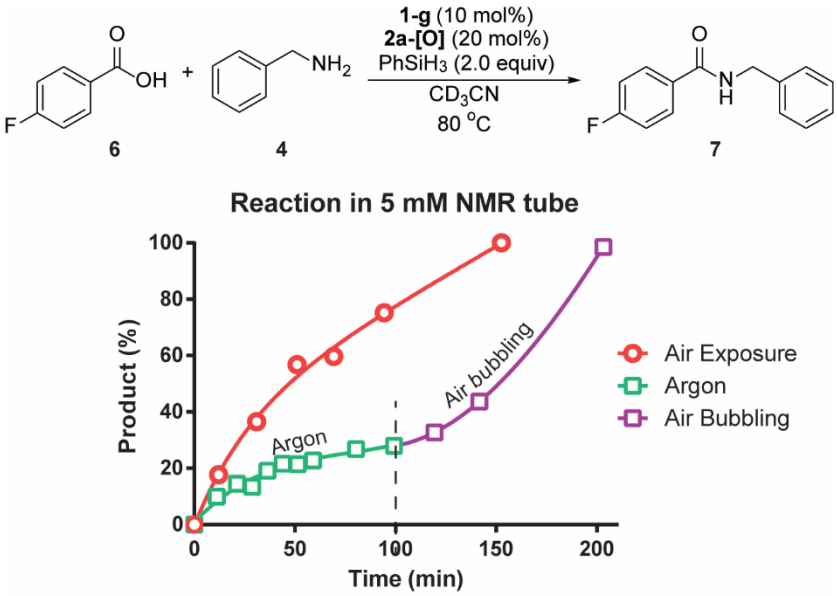


Figure S 13. Probing the dependence of the dual catalytic reaction on air. Reaction condition: **6** (50 µmol), **4** (60 µmol), **1g** (10 mol %), **2a-[O]** (20 mol %) and $PhSiH_3$ (2.0 equivalent) in CD_3CN (1 mL) at 80 °C. Reactions were conducted inside 5 mm NMR tubes. Percent conversion was determined by ^{19}F NMR.

3. Experimental Procedures and Data

3.1 Synthesis and Source of the Catalysts

Catalyst **1c**–**1h** used in this report are from the same batch used in reference 6 of this supporting information, while catalyst **1a** and **1b** are from the same batch used in reference 7. Detailed procedures for synthesis of each catalyst can be found in the supporting information of the respective references. Catalyst **2a-[O]** was obtained by courtesy of Prof. Radosevich (MIT).[8] Catalyst **2b-[O]**, **2c-[O]**, **2d-[O]**, **2e-[O]**, **2f** were obtained from commercial sources.

3.2 Catalyst Screening and Reaction Progress Monitoring

Representative general procedure

Into a 5 mL vial was added *p*-toluic acid **3** (6.81 mg, 50 μmol), benzylamine **4** (7.11 μL, 65 μmol), diselenide catalyst **1** (10 mol %, 5 μmol), phosphine oxide catalyst **2** (20 mol %, 10 μmol), biphenyl (7.71 mg, 50 μmol, as the internal standard for HPLC), and dry MeCN (1.0 mol). $PhSiH_3$ (12.30 μL, 100 μmol) was then added to the solution. The vial was put in a heating block at 80 °C. The reaction progress was then monitored periodically by analytical HPLC (no active exclusion of moisture from the air was necessary and the reaction was exposed to open air during sample acquisition for HPLC analyses).

Reaction progress monitoring

From the reaction mixture, 5.0 μL of aliquot was transferred and quenched into a small LCMS vial containing 195 μL of MeCN (5% Water + 0.1% TFA). Ten microliters of the diluted solution was then injected into HPLC column (Poroshell 120 EC-C18 4.6 × 100 mm 2.7 μm column). HPLC condition: 0.1% TFA (v/v) in water (solvent A): acetonitrile (solvent B); gradient 45–100% (solvent B) in 6 min, flow rate = 1.5 mL/min, detection wavelength = 254 nm.

Reaction conversion at any time point was determined through interpolation from a standard curve (**Figure S 14**) correlating the ratio of product/biphenyl concentration to that of product/biphenyl peak area:

$$\%Product = \frac{A_p}{A_{is}} \times \frac{C_{is}}{0.4482} \times \frac{1}{C_{sm}} \times 100\% \quad (1)$$

Where A_p is the peak area of the product, A_{is} is the peak area of the internal standard (biphenyl), C_{is} is the concentration of the internal standard, and C_{sm} is the concentration of the starting material (toluic acid).

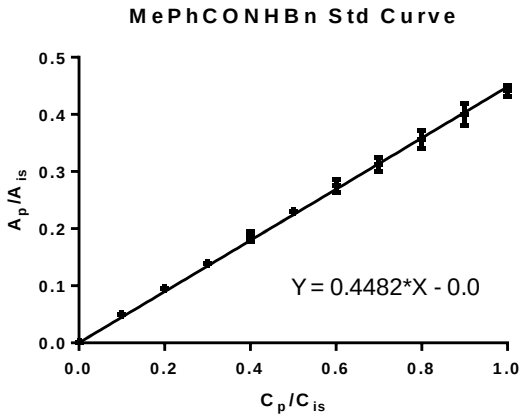


Figure S 14. Standard curve for *N*-benzyl-4-methylbenzamide (**5**) showing a linear correlation between the ratio of product/biphenyl concentration (C_p/C_{is}) and product/biphenyl peak area (A_p/A_{is}). All data points were obtained in triplicate.

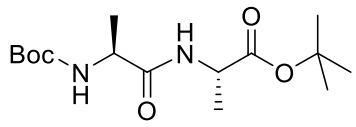
3.3 Solution-Phase Synthesis of Dipeptides

General procedure

In a 10 mL vial equipped with a stir bar was charged with 2.5 mL of dry acetonitrile followed by the addition of Boc-Xaa-OH (50 mmol), HCl•H-Xaa-O^{t}Bu or HCl•H-Xaa-NH_2 (55 mmol), DIEA (55 mmol), catalyst **1g** (4 mol %), and **2a-[O]** (10 mol %). The vial was then placed in a heat block at 80 °C and $PhSiH_3$ was added in portion every 30 minutes (3× or 4× 50 mmol). Progress of the reaction was monitored by TLC. Starting materials were generally consumed after two to three hours. After completion of the reaction, acetonitrile was evaporated under vacuum and 2.0 mL of CH_2Cl_2 was added. The solution was then loaded directly into a chromatographic column for purification to yield Boc-protected dipeptides.

Product Characterization

***tert*-butyl (*tert*-butoxycarbonyl)-L-alanyl-L-alaninate**



Purified by flash column chromatography using gradient elution of 10% to 50% EtOAc in hexanes.

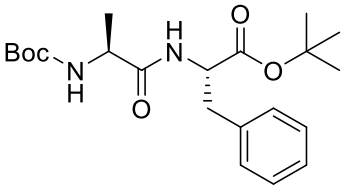
White foam (94%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ.6.58 (d, J = 7.0 Hz, 1H), 5.05 (br, 1 H), 4.42 (dq, J = 7.1, 7.0 Hz, 1H), 4.25–4.05 (m, 1H), 1.45 (s, 9H), 1.44 (s, 9H), 1.36 (d, J = 7.1 Hz, 3H), 1.35 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0, 171.9, 82.00, 77.23 48.7, 28.3, 27.9, 18.55, 18.51. (Note: 2 quaternary carbons are missing possibly due to overlapping signals)

HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{28}N_2NaO_5^+$ 339.1890; Found 339.1886.

***tert*-butyl (*tert*-butoxycarbonyl)-L-alanyl-L-phenylalaninate**



Purified by flash column chromatography using gradient elution of 10% to 30% EtOAc in hexanes.

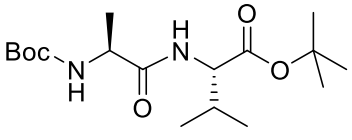
White foam (84%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ. 7.30–7.18 (m, 3H), 7.17–7.11 (m, 2H), 6.57 (d, J = 7.6 Hz, 1H), 5.16–4.98 (m, 1H), 4.70 (dt, J = 7.4, 6.2 Hz, 1H), 4.28–4.01 (m, 1H), 3.15–3.00 (m, 2H), 1.43 (s, 9H), 1.38 (s, 9H), 1.31 (d, J =7.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0, 170.2, 155.2, 136.1, 129.5, 128.3, 126.9, 82.3, 79.9, 53.5, 50.1, 38.0, 28.2, 27.9, 18.4.

HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{32}N_2NaO_5^+$ 415.2203; Found 415.2204.

***tert*-butyl (*tert*-butoxycarbonyl)-L-alanyl-L-valinate**



Purified by flash column chromatography using gradient elution of 10% to 40% EtOAc in hexanes.

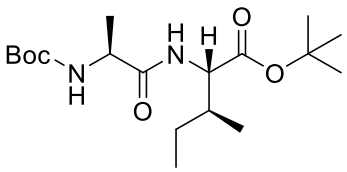
Colorless oil (154 mg, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ.6.61 (d, J = 8.6 Hz, 1H), 5.10 (d, J = 7.5 Hz, 1H), 4.39 (dd, J = 8.8, 4.6 Hz, 1H), 4.29–4.01 (m, 1H), 2.20–2.05 (m, 1H), 1.44 (s, 9H), 1.42 (s, 9H), 1.33 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 170.8, 155.5, 81.9, 80.0, 57.3, 50.1, 31.4, 28.3, 28.0, 18.9, 18.0, 17.5.

HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{32}N_2NaO_5^+$ 368.2235; Found 368.2248.

tert-butyl (*tert*-butoxycarbonyl)-L-alanyl-L-isoleucinate



Purified by flash column chromatography using gradient elution of 10% to 50% EtOAc in hexanes.

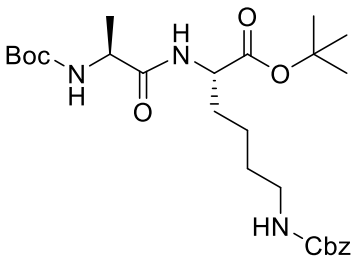
White foam (172 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, J = 8.1 Hz, 1H), 5.17 (d, J = 7.3 Hz, 1H), 4.40 (dd, J = 8.6, 4.6 Hz, 1H), 4.15 (brs, 1H), 1.84 – 1.79 (m, 1H), 1.41(s, 9H), 1.39 (s, 9H), 1.30 (d, J = 7.0 Hz, 3H), 1.18 – 1.08 (m, 1H), 0.89 – 0.84 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.40, 170.76, 155.54, 81.92, 79.94, 77.16, 56.82, 50.09, 38.15, 28.35, 28.09, 25.21, 18.08, 15.35, 11.73.

HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for. $C_{18}H_{34}N_2NaO_5^+$ 381.2365; Found 381.2381

tert-butyl N^6-((benzyloxy)carbonyl)-N^2-((*tert*-butoxycarbonyl)-L-alanyl)-L-lysinate



Purified by flash column chromatography using gradient elution of 20% to 60% EtOAc in hexanes.

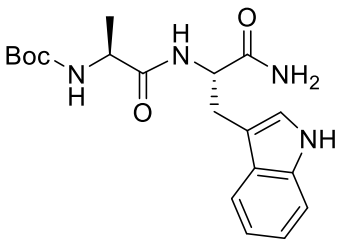
White foam (95%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ. 7.37–7.27 (m, 5H), 6.77 (d, J = 7.1 Hz, 1H), 5.34–4.97 (m, 4H), 4.49–4.36 (m, 1H), 4.30–4.05 (m, 1H), 3.26–3.03 (m, 2H), 1.87–1.71 (m, 1H), 1.69–1.46 (m, 3H), 1.43 (s, 9H), 1.41 (s, 9H), 1.29 (d, J = 7.0, 3H), 1.36–1.22 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6, 171.1, 156.4, 155.4, 136.6, 128.4, 128.1, 128.0, 82.0, 79.9, 66.5, 52.3, 49.9, 40.5, 31.9, 29.1, 28.2, 27.9, 22.0, 18.2

HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{42}N_3O_7^+$ 508.3017; Found 508.3012.

***tert*-butyl ((S)-1-(((S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)carbamate**



Purified by flash column chromatography using gradient elution of 0% to 10% MeOH in CH_2Cl_2.

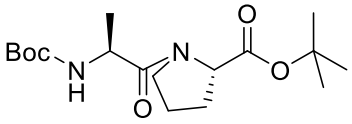
White foam (85%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ.8.85 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.21–7.05 (m, 2H), 7.05–6.96 (m, 2H), 6.51 (s, 1H), 5.85 (s, 1H), 5.20 (br, 1H), 4.80–4.66 (m, 1H), 4.09–3.96 (m, 1H), 3.45–3.25 (m. 1H), 3.16 (dd, J = 14.6, 6,4 Hz, 1H), 1.37–1.16 (m, 12 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.2, 172.8, 155.8, 136.2, 127.4, 123.6, 122.1, 119.5, 118.5, 111.5, 109.6, 80.5, 53.3, 51.1, 28.0, 27.2, 17.8.

HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calcd for $C_{19}H_{26}N_4NaO_4^+$ 397.1846; Found 397.1861.

***tert*-butyl (*tert*-butoxycarbonyl)-L-alanyl-L-prolinate**



Purified by flash column chromatography using gradient elution of 10% to 60% EtOAc in hexanes.

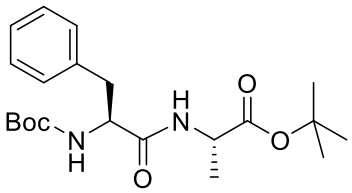
White foam (161 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (d, J = 7.9 Hz, 1H), 4.42 – 4.33 (m, 2H), 3.61-3.57 (m, 1H), 3.48-3.46 (m, 1H), 2.13-2.08 (m, 2H), 1.96 – 1.87 (m, 3H), 1.41 (s, 9H), 1.39 (s, 9H), 1.29 (d, J = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.43, 171.09, 155.34, 81.37, 79.57, 59.65, 47.74, 46.77, 41.22, 28.99, 28.46, 28.39, 28.11, 28.08, 27.97, 27.83, 24.84, 24.04, 18.38.

HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calcd for $C_{17}H_{30}N_2NaO_5^+$ 365.2047; Found 365.2078.

***tert*-butyl (*tert*-butoxycarbonyl)-L-phenylalanyl-L-alaninate**



Purified by flash column chromatography using gradient elution of 10% to 60% EtOAc in hexanes.

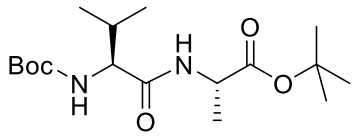
White foam (187 mg, 95%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ.7.31–7.25 (m, 2H), 7.25–7.15 (m, 2H), 6.46 (d, J = 6.9 Hz, 1H), 5.01 (br, 1H), 4.33–4.26 (m, 2H), 3.14–2.98 (m, 2H), 1.43 (s, 9H), 1.40 (s, 9H), 1.31 (d, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6, 170.5, 155.3, 136.5, 129.3, 128.6, 126.9, 82.0, 80.1, 55.6, 48.7, 38.4, 28.2, 27.9, 18.6.

HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calcd for $C_{21}H_{32}N_2NaO_5^+$ 415.2203; Found 415.2219.

***tert*-butyl (*tert*-butoxycarbonyl)-L-valyl-L-alaninate**



Purified by flash column chromatography using gradient elution of 10% to 40% EtOAc in hexanes.

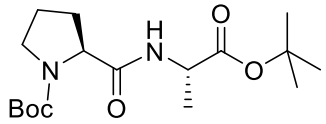
White foam (189 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (d, *J* = 5.0 Hz, 1H), 5.15 (d, *J* = 7.2 Hz, 1H), 4.42 (p, *J* = 7.1 Hz, 1H), 3.93 (br t, 7.0 Hz, 1H), 2.11-2.09 (m, 1H), 1.44 (s, 9H), 1.42 (s, 9H) 1.34 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.00, 171.12, 155.96, 82.03, 79.87, 59.89, 48.77, 36.78, 31.19, 28.41, 28.04, 24.81, 19.33, 18.55, 17.82.

HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{33}N_2O_5^+$ 345.2384; Found 345.2387.

***tert*-butyl (S)-2-(((S)-1-(*tert*-butoxy)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate**



Purified by flash column chromatography using gradient elution of 20% to 60% EtOAc in hexanes.

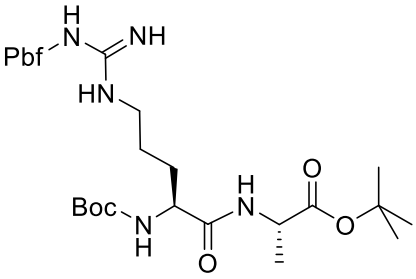
White foam (153 mg, 90%).

^{1}H NMR ($CDCl_3$/CD_3OD, 400 MHz): *δ*.8.36–8.08 (m, 1H), 4.37–4.09 (m, 2H), 3.58–3.46 (m, 2H), 3.46–3.35 (m, 2H), 2.34–2.09 (m, 1H), 2.08–1.77 (m, 3H), 1.50–1.39 (m, 18H), 1.36 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 175.4, 173.4, 173.2, 156.3, 155.9, 82.5, 81.4, 81.1, 79.5, 61.4, 61.0, 50.3, 50.2, 48.2, 47.9, 32.3, 31.4, 28.7, 28.6, 28.2, 25.3, 24.6, 17.5, 17.4. (Mixture of rotamers)

HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{31}N_2O_5^+$ 343.2227; Found 343.2222.

***tert*-butyl N^2-(*tert*-butoxycarbonyl)-N^ω-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-L-arginyl-L-alaninate**



Purified by flash column chromatography using gradient elution of 80% to 100% EtOAc in hexanes.

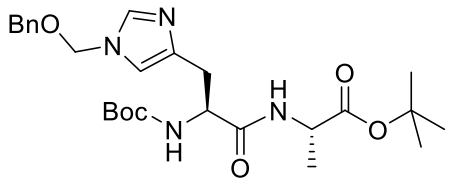
White foam (203 mg, 62%).

^{1}H NMR ($CDCl_3$/CD_3OD, 400 MHz): *δ*. 4.03 (q, *J* = 7.2 Hz, 1H), 3.84–3.70 (m, 1H), 2.98–2.84 (m, 2H), 2.75–2.57 (m, 3H), 2.29 (s, 3H), 2.23 (s, 3H), 1.81 (s, 3H), 1.38–1.22 (m, 3H), 1.20–1.13 (m, 24 H), 1.08 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 155 MHz): *δ* 172.1, 169.6, 162.5, 158.7, 156.3, 155.9, 138.3, 132.2, 124.5, 117.4, 86.3, 81.7, 79.7, 48.9, 48.6, 43.2, 36.4, 28.5, 28.2, 27.9, 25.2, 19.2, 18.5, 17.9, 17.6, 12.4.

HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $C_{31}H_{52}N_5O_8S^+$ 654.3531; Found 654.3571.

***tert*-butyl N^{τ}-((benzyloxy)methyl)-N^{α}-(*tert*-butoxycarbonyl)-L-histidyl-L-alaninate**



Purified by flash column chromatography using gradient elution of 0% to 10% MeOH in CH_2Cl_2.

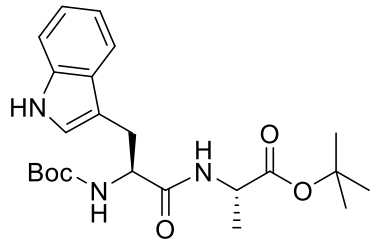
White foam (187 mg, 76%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ.7.49 (s, 1H), 7.40–7.28 (m, 5H), 6.90 (s, 1H), 6.68 (d, J = 7.2 Hz, 1H), 5.41–5.24 (m, 3H), 4.51 (s, 2H), 4.43–4.26 (m, 2H), 3.19–2.98 (m, 2H), 1.44 (s, 9H), 1.41 (s, 9H), 1.27 (d, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 170.1, 155.3, 138.3, 136.0, 129.3, 128.7, 128.3, 128.1, 128.0, 82.0, 80.2, 73.1, 69.9, 53.8, 48.7, 28.2, 27.9, 26.8, 18.4

HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{39}N_4O_6^+$ 503.2864; Found 503.2869.

***tert*-butyl (*tert*-butoxycarbonyl)-L-tryptophyl-L-alaninate**



Purified by flash column chromatography using gradient elution of 30% to 70% EtOAc in hexanes.

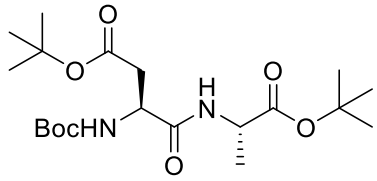
White foam (129 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.03 (s, 1H), 6.53 (d, J = 7.0 Hz, 1H), 5.19 (s, 1H), 4.46 (s, 1H), 4.40 – 4.27 (m, 1H), 3.29 – 3.17 (m, 2H), 1.41 (s, 18H), 1.24 (d, J = 7.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.76, 171.29, 155.55, 136.39, 134.14, 127.67, 123.42, 122.19, 119.64, 118.93, 111.32, 110.46, 81.97, 80.11, 60.49, 55.24, 48.89, 28.36, 27.99, 21.11, 18.55, 14.27.

HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calcd for $C_{23}H_{33}N_3NaO_5^+$ 454.2313; Found 454.2310.

***tert*-butyl (S)-4-(((S)-1-(*tert*-butoxy)-1-oxopropan-2-yl)amino)-3-((*tert*-butoxycarbonyl)amino)-4-oxobutanoate**



Purified by flash column chromatography using gradient elution of 20% to 60% EtOAc in hexanes.

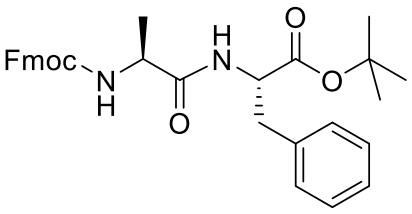
White foam (135 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J = 7.1 Hz, 1H), 5.70 (d, J = 8.1 Hz, 1H), 4.43-4.36 (m, 2H), 2.82-2.77 (m 1H), 2.65-2.60 (m, 1H), 1.42-1.40 (m, 27H), 1.31 (d, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.17, 170.45, 169.50, 155.78, 82.14, 82.02, 79.67, 51.02, 48.75, 38.14, 28.40, 28.01, 27.98, 18.69.

HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{36}N_2NaO_7^+$ 439.2415; Found 439.2422.

tert-butyl (((9_H_-fluoren-9-yl)methoxy)carbonyl)-L-alanyl-L-phenylalaninate



Purified by flash column chromatography using gradient elution of 10% to 50% EtOAc in hexanes.

White foam (57%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ. 7.77 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.3 Hz, 2H), 7.44–7.34 (m, 2H), 7.36–7.28 (m, 2H), 7.26–7.16 (m, 3H), 7.16–7.10 (m, 2H), 6.44 (d, J = 7.2 Hz, 1H), 5.39 (d, J = 6.0 Hz, 1H), 4.73 (dt, J = 7.7, 6.1 Hz, 1H), 4.46–4.31 (m, 2H), 4.31–4.16 (m, 2H), 3.17–3.01 (m, 2H), 1.48–1.31 (m, 12H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6, 170.2, 155.8, 143.8, 141.3, 135.9, 129.4. 128.3, 127.7, 127.1, 127.0, 125.1, 119.9, 82.5, 67.1, 53.6, 50.4, 47.1, 37.9, 27.9, 18.7.

HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{31}H_{34}N_2NaO_5^+$ 537.2360; Found 537.2383.

3.4 Catalytic Solid-Phase Peptide Synthesis

Pentapeptides (Fmoc-AA_4-AA_3-AA_2-AA_1-Gly-OH) were synthesized using Tentagel S-RAM resin (0.05 mmol, 208 mg, 0.24 mol/g) preloaded with Fmoc-glycine. Reaction solution consisting of catalyst **1a** (5 mol %, 0.0025 mmol) and **2a-[O]** (10 mol %, 0.005 mmol) in 500 μL of dry acetonitrile was prepared at the beginning of SPPS.

Fmoc deprotection: To a properly washed resin in a glass syringe equipped with a stir bar and frit was added 2 mL of 20% piperidine in DMF solution. One mililiter of tetrabutylammonium fluoride (1.0 M in THF) was also added during the deprotection step to scavenge any silane polymers formed after the coupling reactions. Afterward, the deprotection solution was drained and the resin was washed with dry DMF and acetonitrile (3×).

Amino acid coupling: Fmoc-Xaa-OH (0.075 mmol) was added to the washed resin along with 500 μL of solution consisting of catalyst **1a** and **2a-[O]** in acetonitrile (prepared at the beginning of SPPS). Subsequently, $PhSiH_3$ (one equivalent, 0.05 mmol) was added, and the reaction mixture was stirred at 80 °C. Additional one equivalent of $PHSiH_3$ was added after every 30 minutes until a total of four equivalents of $PhSiH_3$ was added. After two hours of reaction (calculated from the first addition of $PhSiH_3$), the solution was then drained, and the resin was washed with DMF, CH_2Cl_2, and dry acetonitrile (3x). Completion of the coupling was assessed using Kaiser test or chloranil test (for proline). If necessary, the coupling was repeated to ensure the completion of the reaction.

Global deprotection: After all amino acids were coupled, the resin was treated with a cocktail mixture consisting of TFA/Triisopropylsilane/Water (95:2.5:2.5) for one hour. Subsequently, the resin was filtered. The collected TFA solution was then evaporated, and the resulting residue was precipitated with cold diethyl ether. The precipitate was then triturated with cold diethyl ether 3× to give the crude peptide as white powder. It was then directly analyzed with HPLC and HRMS.

3.5 NMR Spectroscopy Studies

Procedure for Air Dependence Studies

A solution of carboxylic acid **6** (7.00 mg, 50 μmol), catalyst **1g** (2.92 mg, 10 mol %), catalyst **2a-[O]** (1.74 mg, 20 mol %) in CD_3CN (1 mL) was prepared and transferred into 5 mm NMR tube. The tube was then flushed with argon. Under constant and gentle argon flushing, benzylamine **4** (7.11 μL, 60 μmol) and $PhSiH_3$ (12.30 μL, 100 μmol) were quickly added into the tube. The tube was sealed and inverted 3× to ensure proper mixing. The tube was then put into the NMR spectrometer (temperature set to 80 °C) for data acquisition. After 100 minutes, the tube was opened (high pressure!) and put into hot sand bath (80 °C). Using a syringe connected to a long needle, air was bubbled into the reaction mixture periodically.

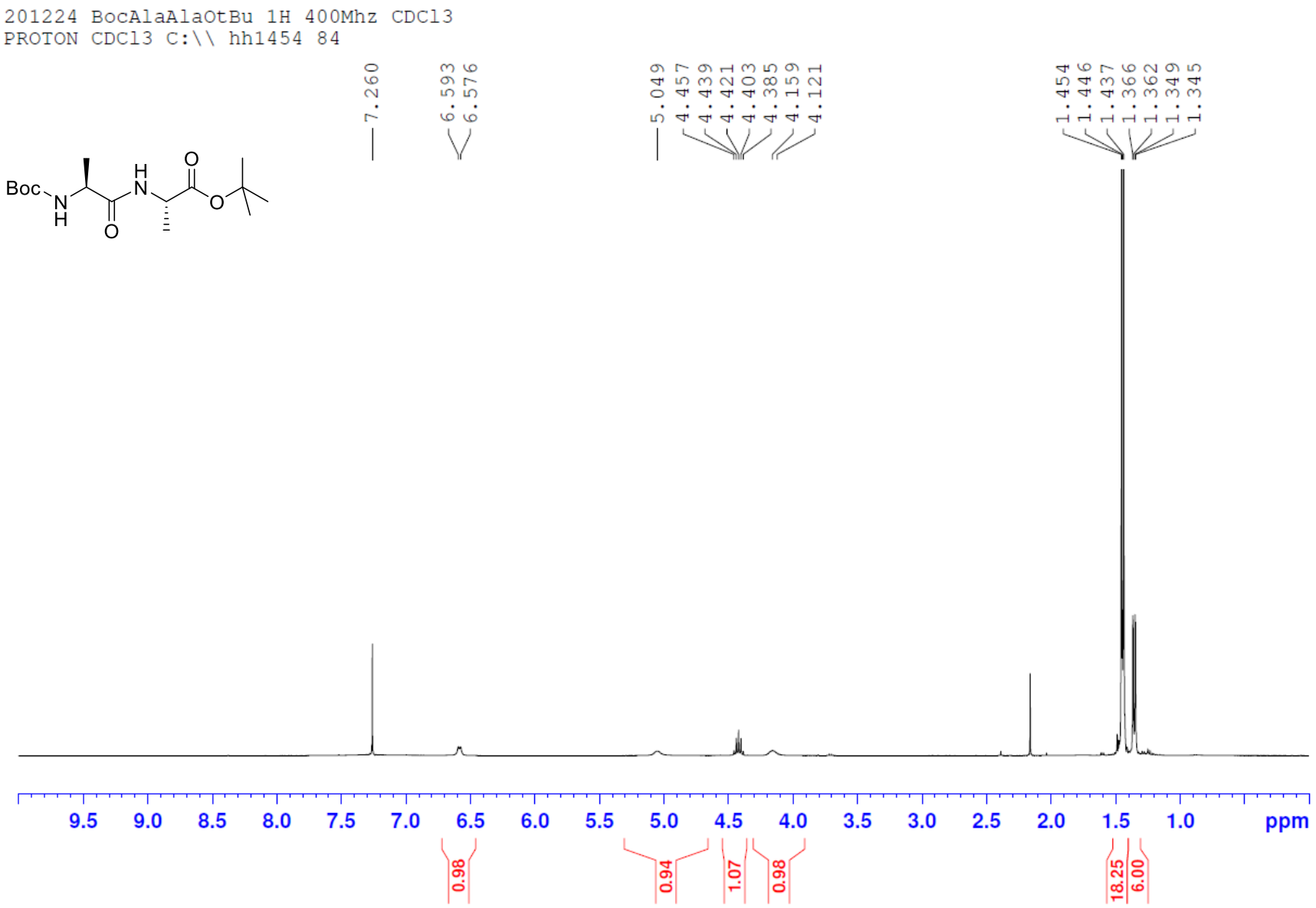
For control reaction (air exposure), a similar procedure was followed, except that a hole was punched into the NMR tube cap and no argon was flushed into the NMR tube.

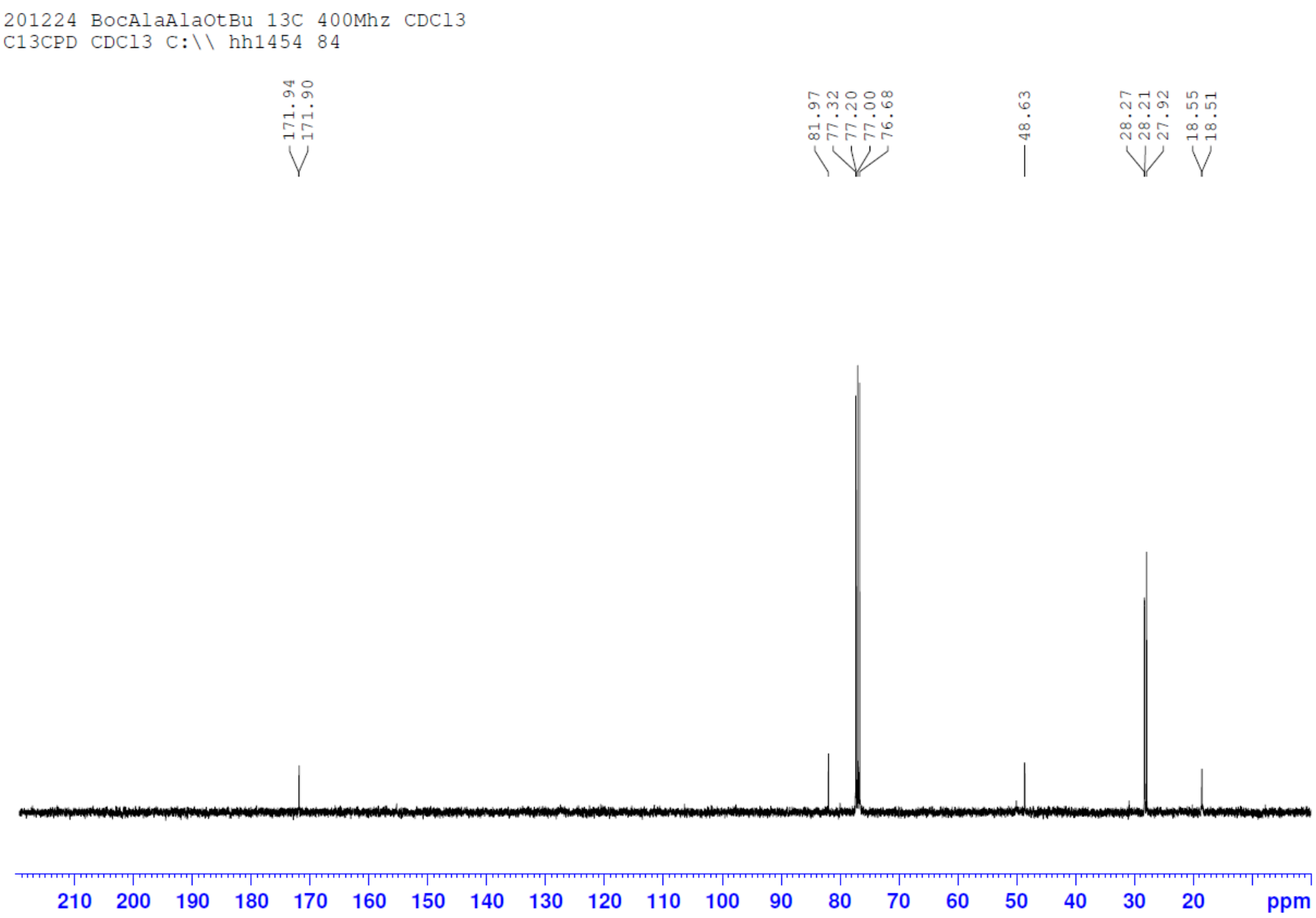
4. References

1. Andrews, K. G.; Faizova, R.; Denton, R. M., A practical and catalyst-free trifluoroethylation reaction of amines using trifluoroacetic acid. *Nat. Commun.* **2017,** *8* (1), 15913.
2. Stoll, E. L.; Tongue, T.; Andrews, K. G.; Valette, D.; Hirst, D. J.; Denton, R. M., A practical catalytic reductive amination of carboxylic acids. *Chem. Sci.* **2020,** *11* (35), 9494-9500.
3. Lecomte, M.; Lipshultz, J. M.; Kim-Lee, S.-H.; Li, G.; Radosevich, A. T., Driving Recursive Dehydration by PIII/PV Catalysis: Annulation of Amines and Carboxylic Acids by Sequential C–N and C–C Bond Formation. *J. Am. Chem. Soc* **2019,** *141* (32), 12507-12512.
4. Zhang, K.; Cai, L.; Yang, Z.; Houk, K. N.; Kwon, O., Bridged [2.2.1] bicyclic phosphine oxide facilitates catalytic γ-umpolung addition–Wittig olefination. *Chem. Sci.* **2018,** *9* (7), 1867-1872.
5. Duddeck, H., Selenium-77 nuclear magnetic resonance spectroscopy. *Prog. Nucl. Magn. Reson. Spectrosc.* **1995,** *27* (1), 1-323.
6. Handoko; Benslimane, Z.; Arora, P. S., Diselenide-Mediated Catalytic Functionalization of Hydrophosphoryl Compounds. *Org. Lett.* **2020,** *22* (15), 5811-5816.
7. Handoko; Satishkumar, S.; Panigrahi, N. R.; Arora, P. S., Rational Design of an Organocatalyst for Peptide Bond Formation. *J. Am. Chem. Soc* **2019,** *141* (40), 15977-15985.
8. Nykaza, T. V.; Cooper, J. C.; Radosevich, A. T., anti-1, 2, 2, 3, 4, 4-Hexamethylphosphetane 1-Oxide. *Org. Synth.* **2019,** *96*, 418-435.

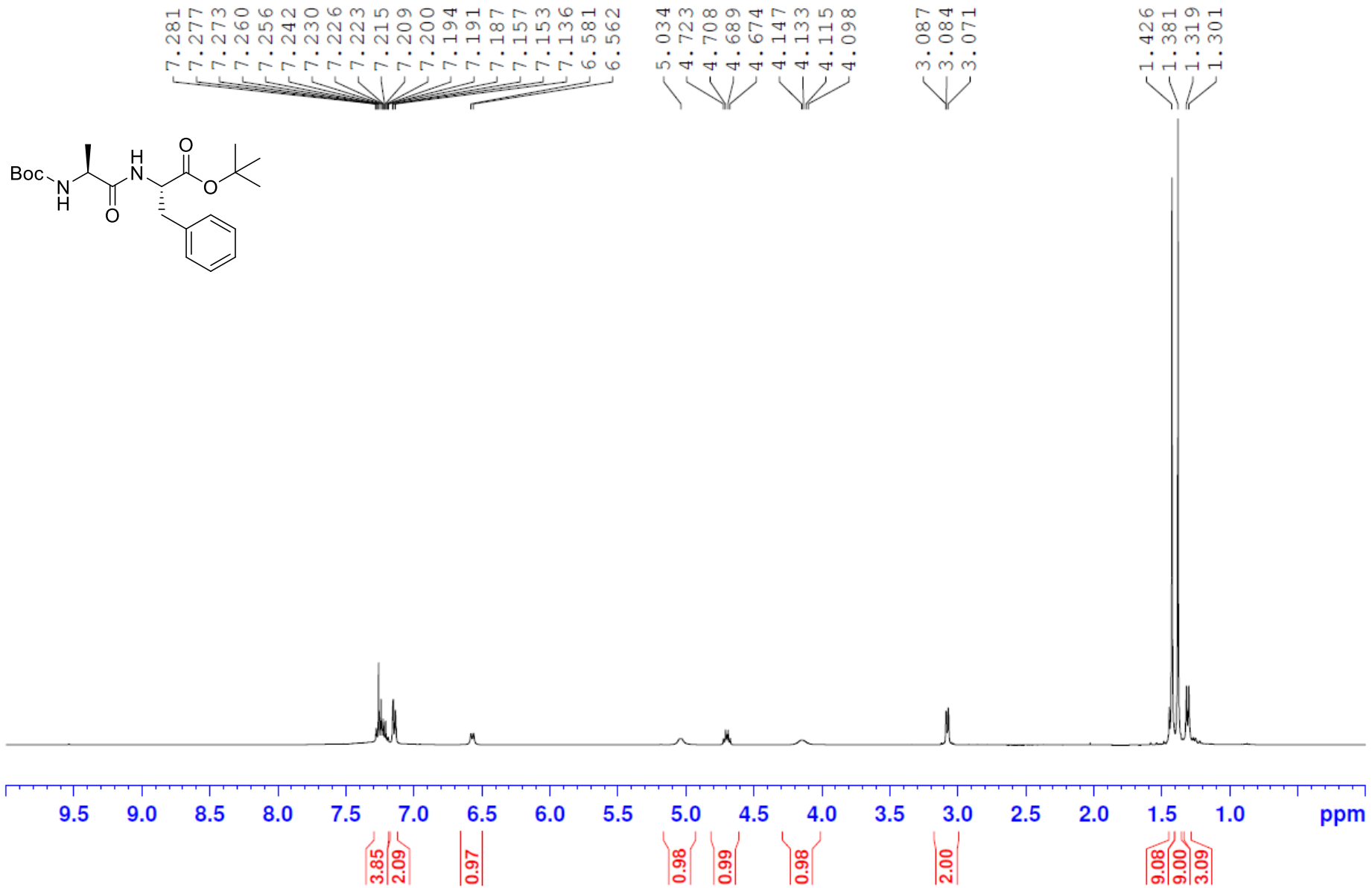
5. NMR Spectra

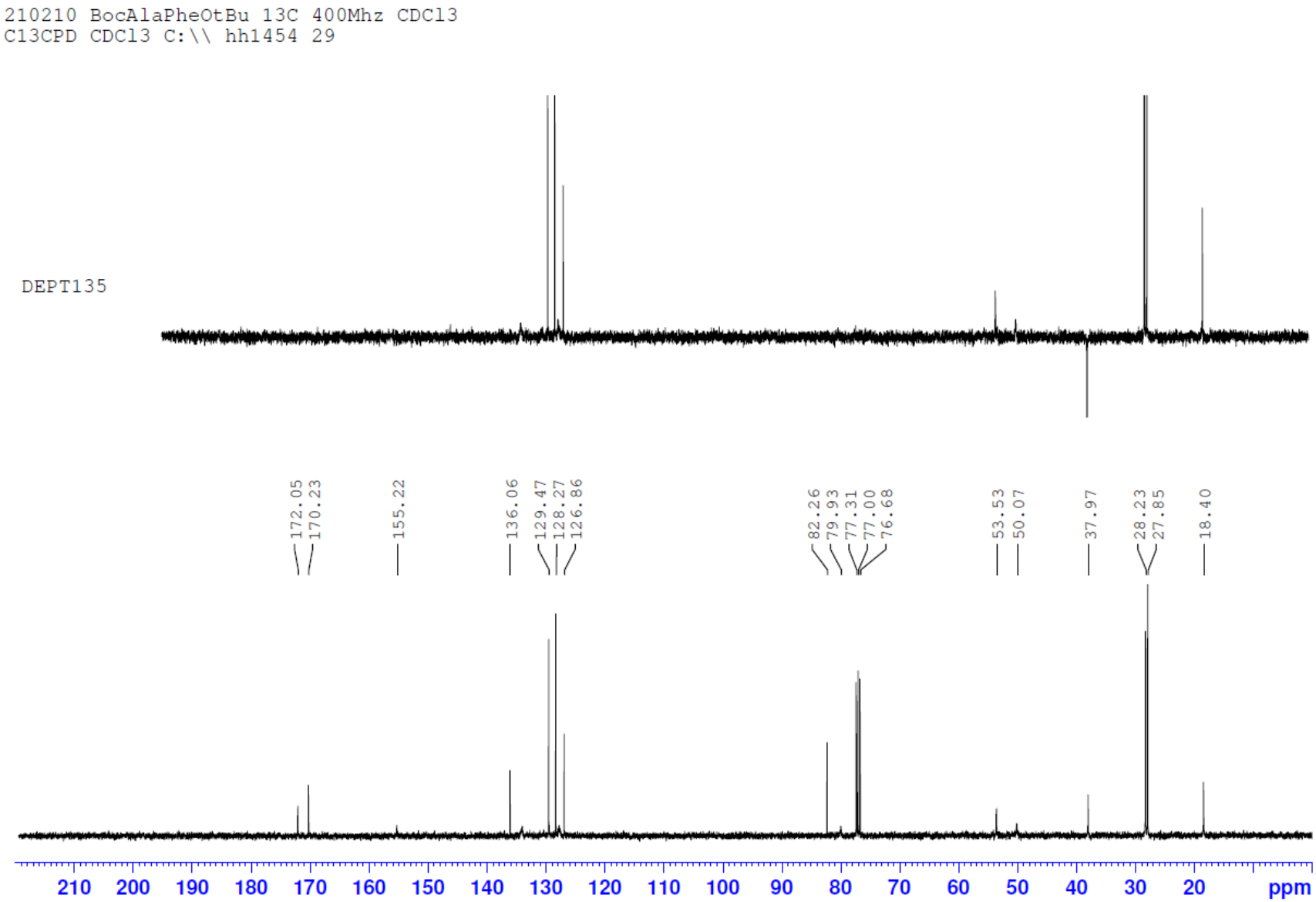
(Next Page)


201224 BocAlaAlaOtBu 1H 400Mhz CDCl3
PROTON CDCl3 C:\\ hh1454 84
7.260
6.593
6.576
5.049
4.457
4.439
4.421
4.403
4.385
4.159
4.121
1.454
1.446
1.437
1.366
1.362
1.349
1.345
Boc
N
H
H
N
O
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.98
0.94
1.07
0.98
18.25
6.00

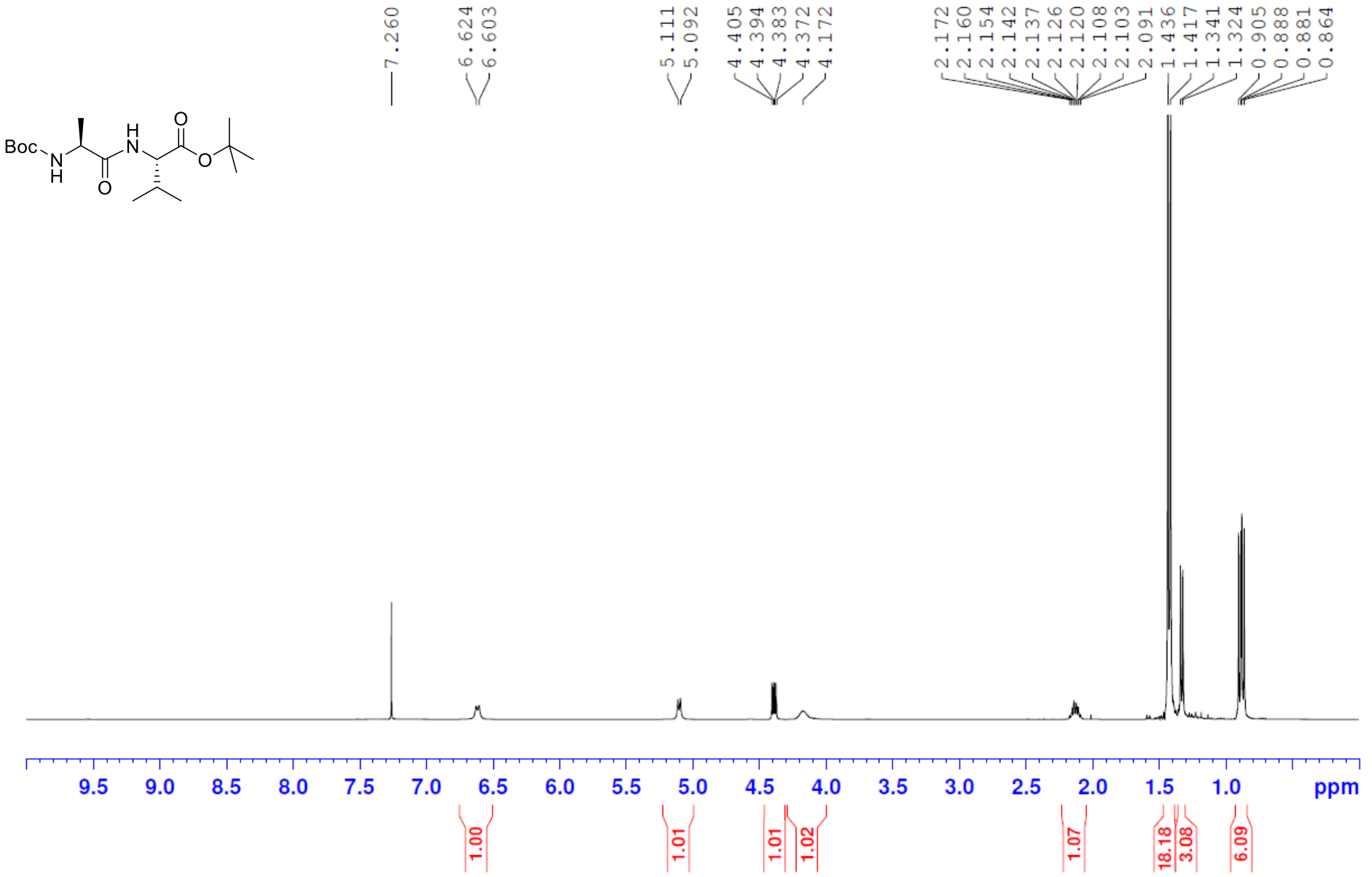

201224 BocAlaAlaOtBu 13C 400Mhz CDCl3
C13CPD CDCl3 C:\\ hh1454 84
171.94
171.90
81.97
77.32
77.20
77.00
76.68
48.63
28.27
28.21
27.92
18.55
18.51
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

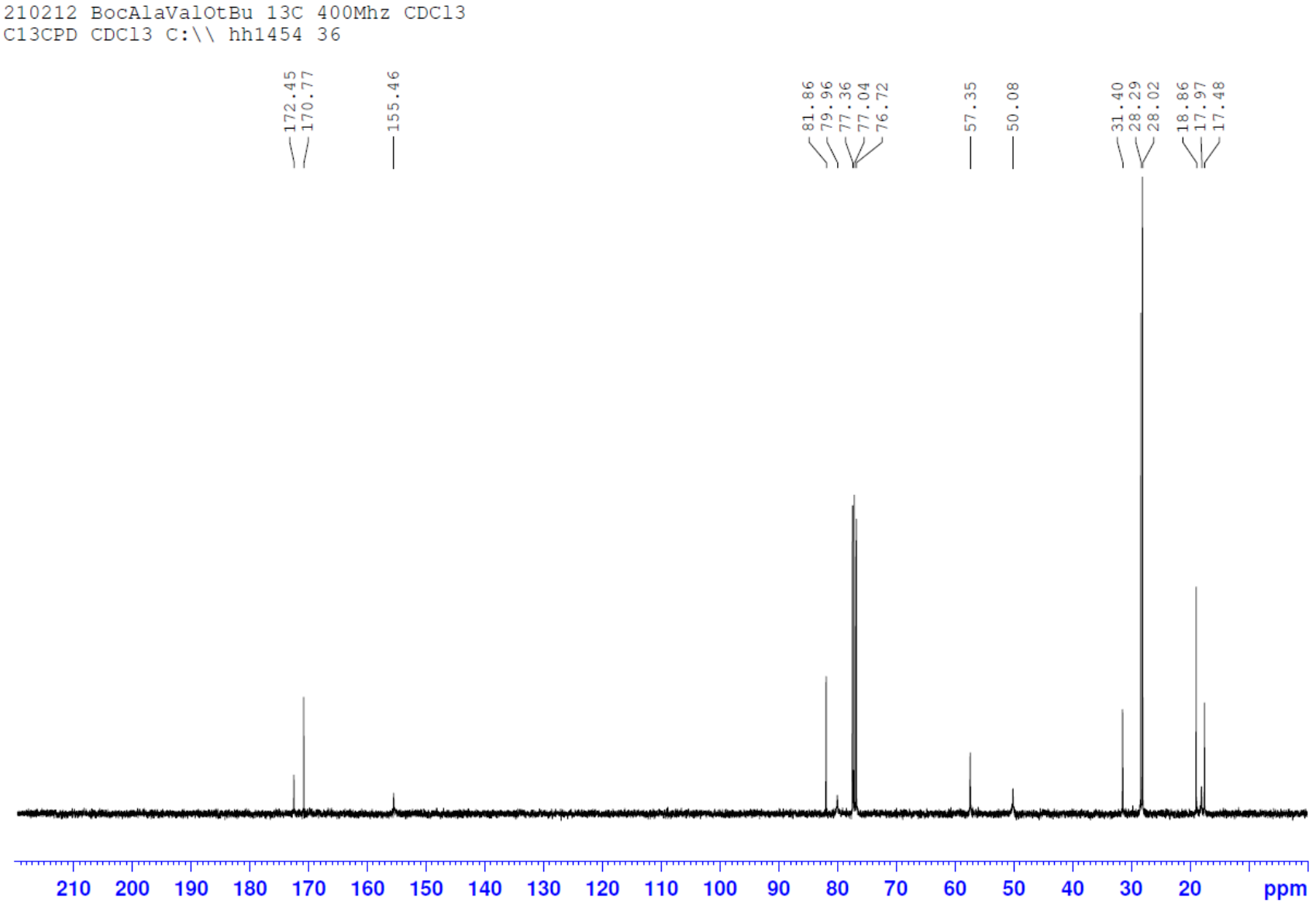
210210 BocAlaPheOtBu 1H 400Mhz CDCl3
PROTON CDCl3 C:\\ hh1454 29

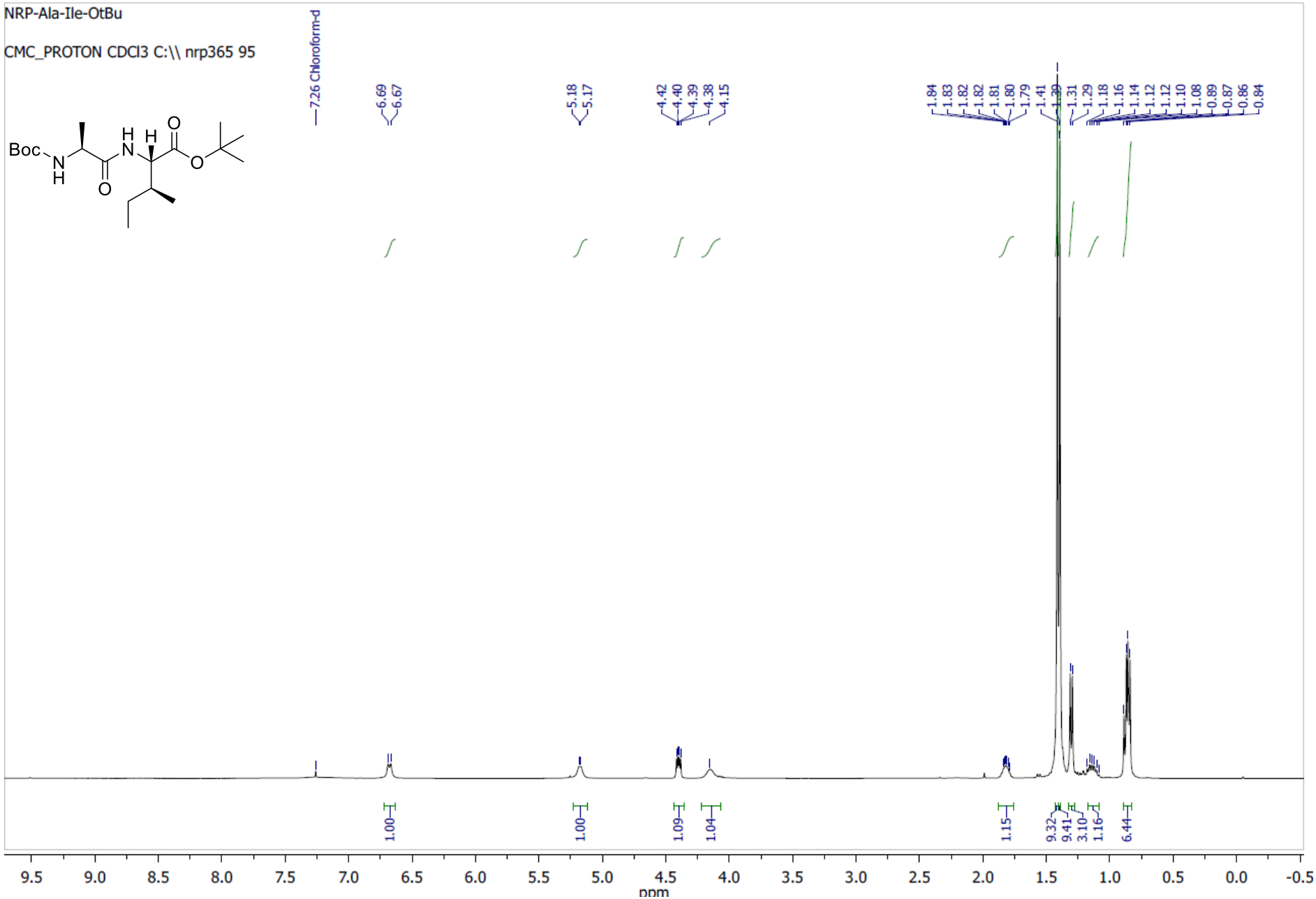


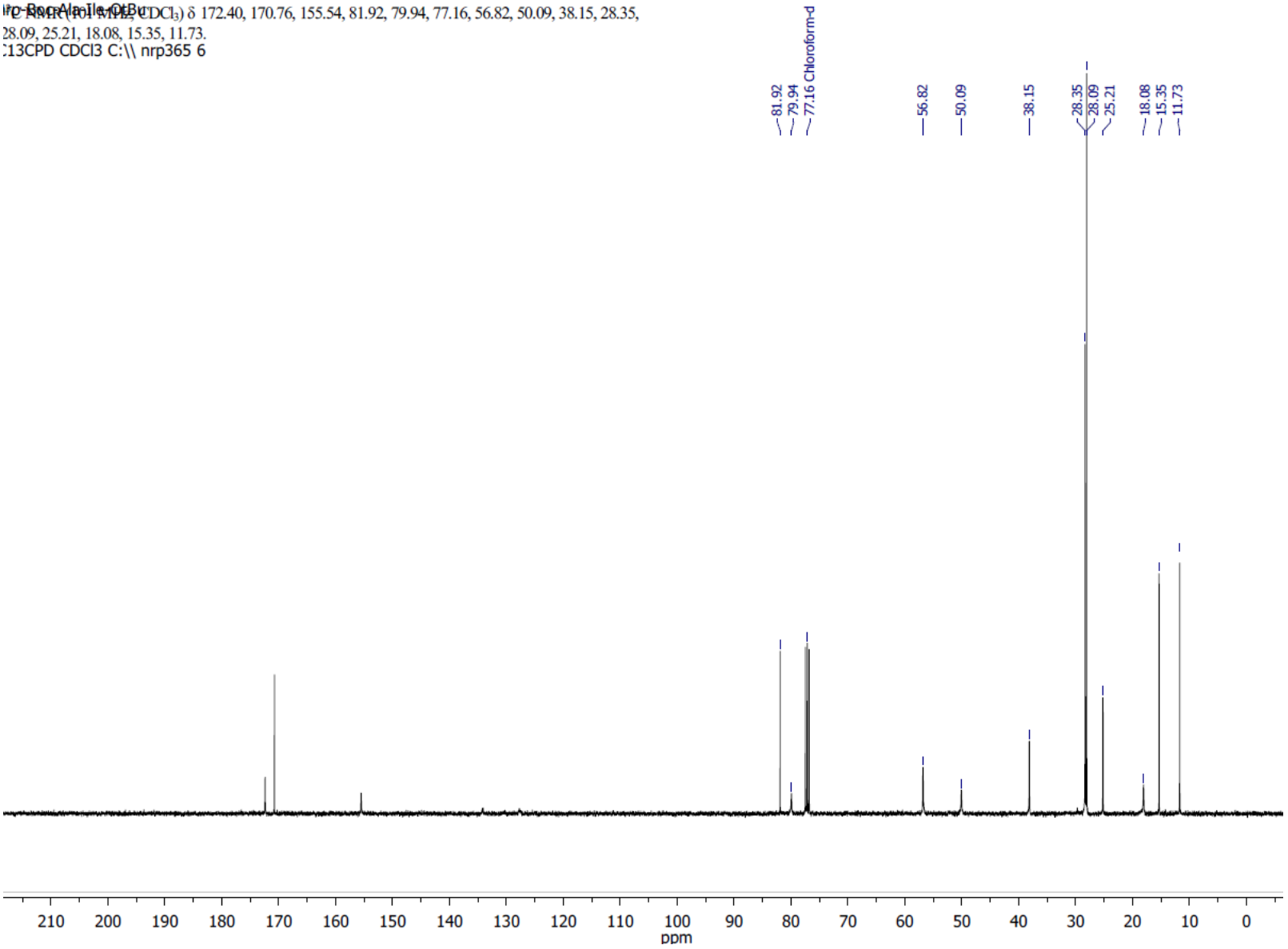

210210 BocAlaPheOtBu 13C 400Mhz CDCl3
C13CPD CDCl3 C:\\ hh1454 29
DEPT135
172.05
170.23
155.22
136.06
129.47
128.27
126.86
82.26
79.93
77.31
77.00
76.68
53.53
50.07
37.97
28.23
27.85
18.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

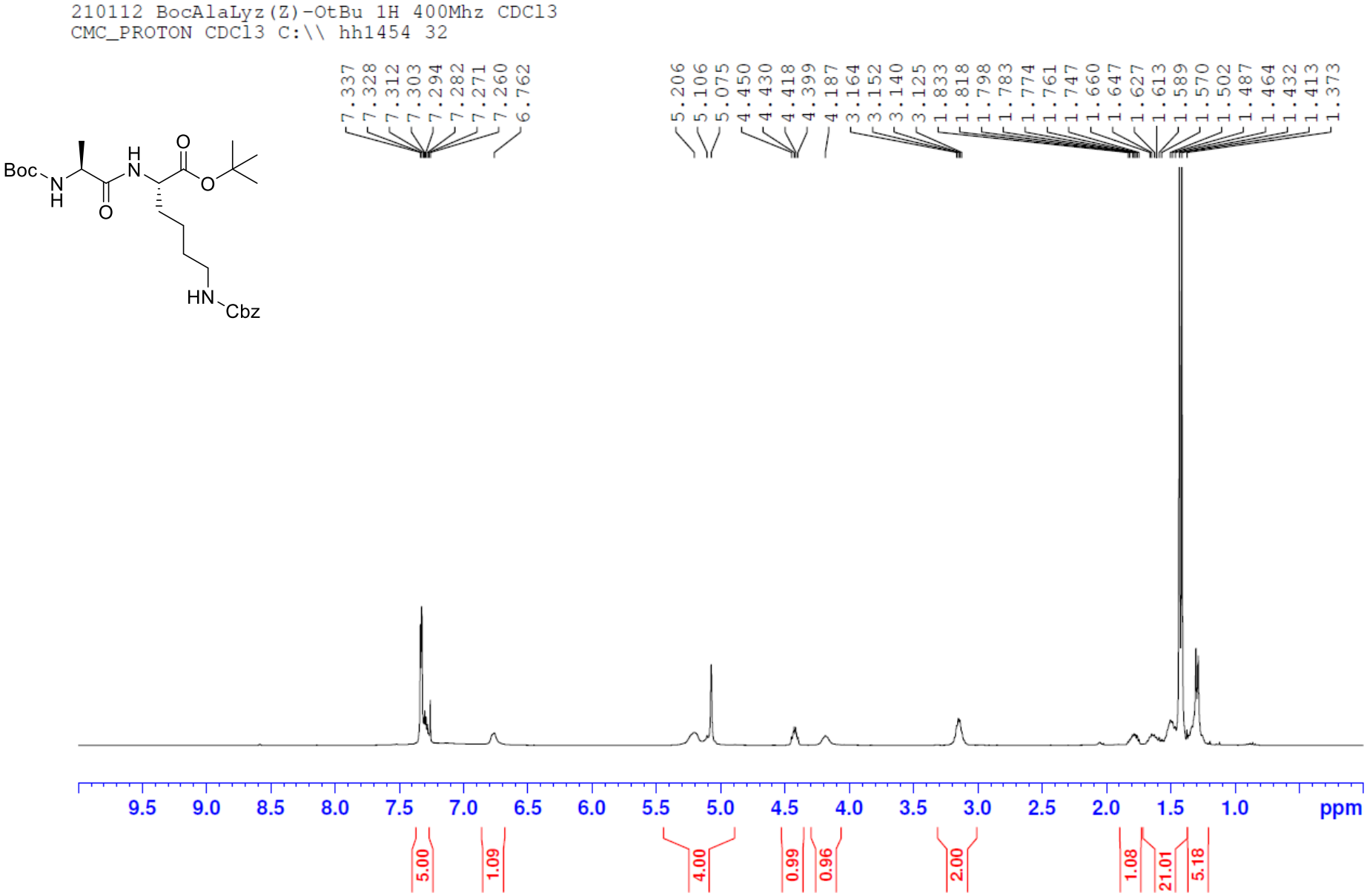
210212 BocAlaValOtBu 1H 400Mhz CDCl3
PROTON CDCl3 C:\\ hh1454 36

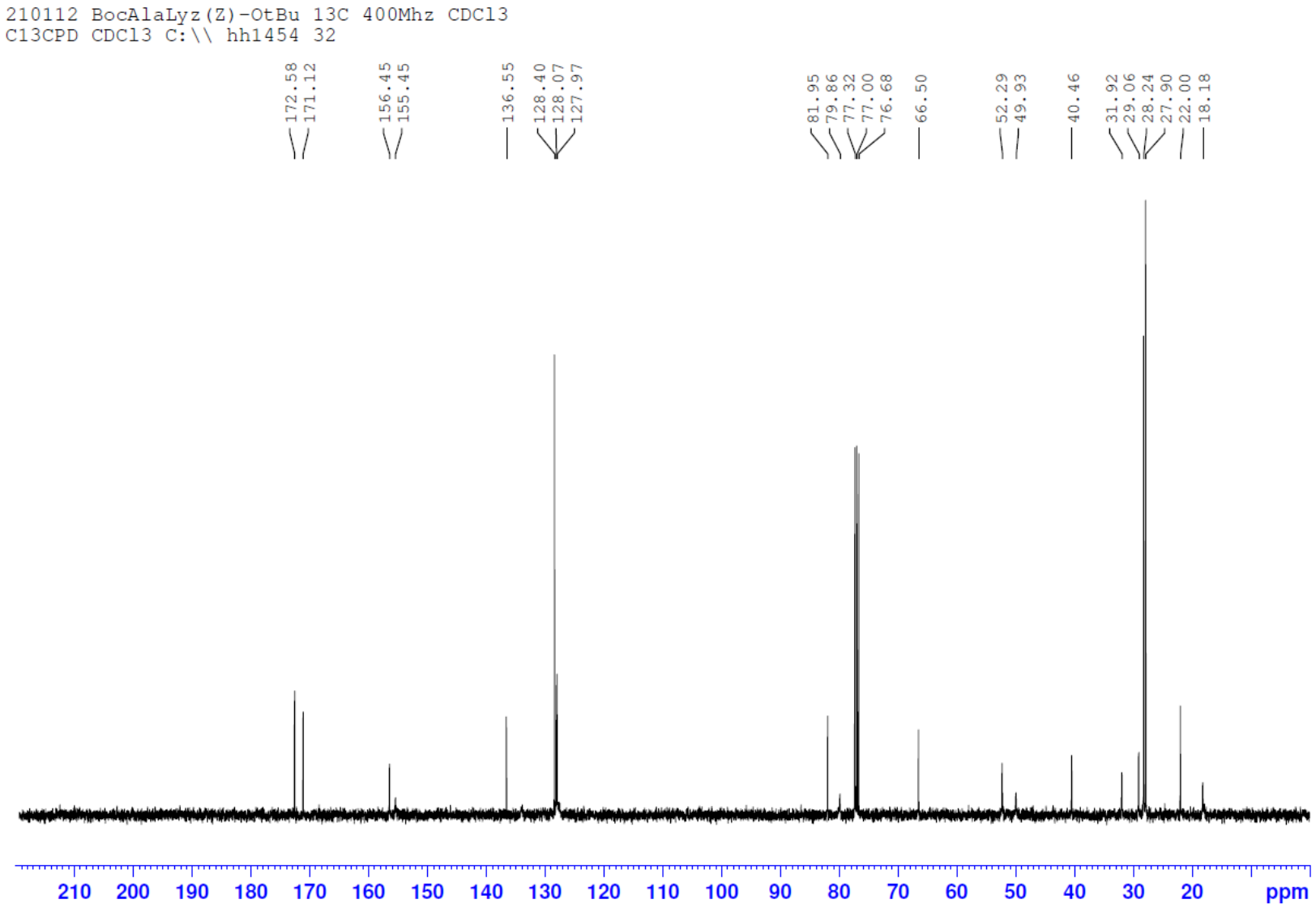


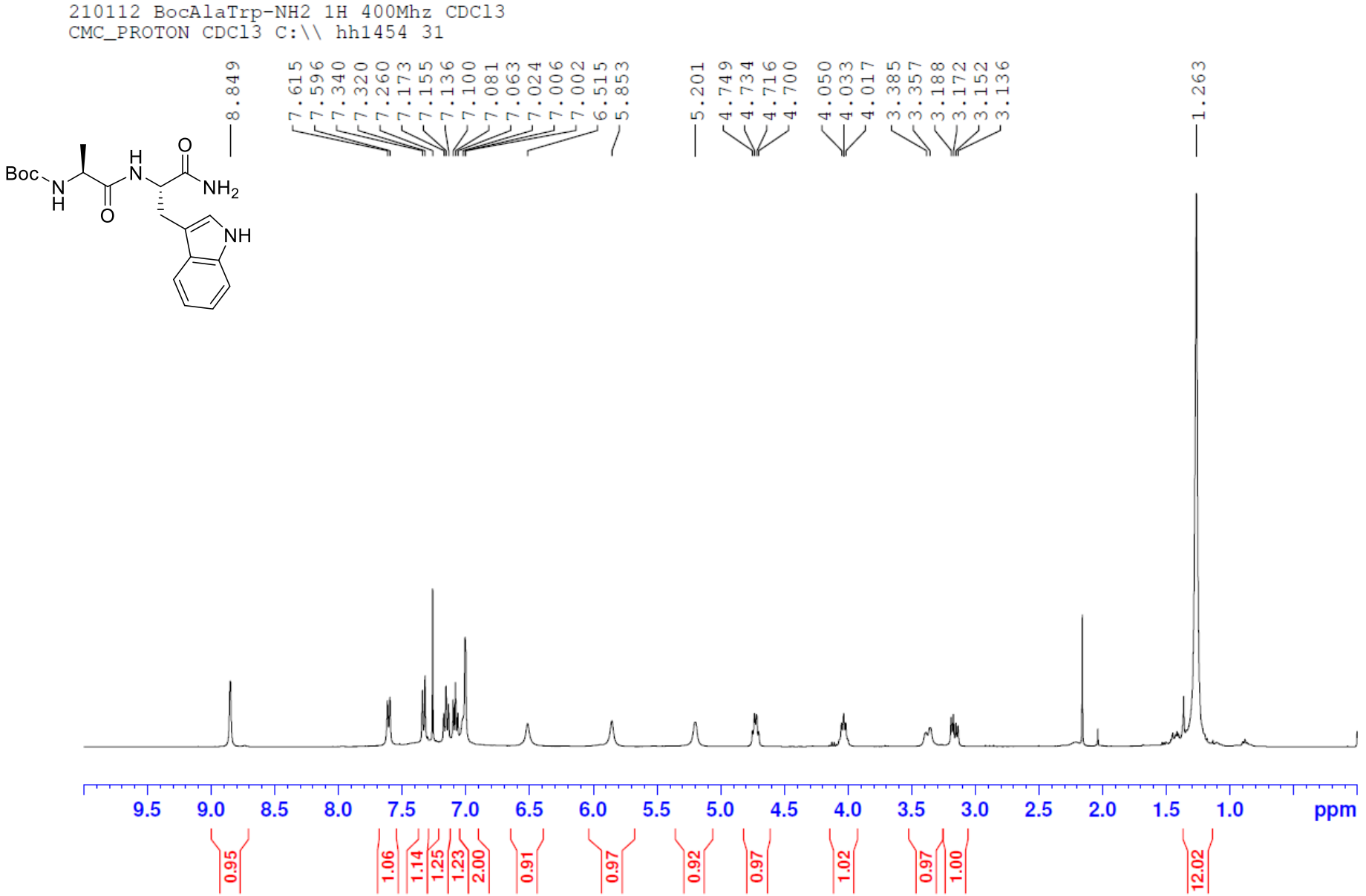

210212 BocAlaValOtBu 13C 400Mhz CDCl3
C13CPD CDCl3 C:\\ hh1454 36
172.45
170.77
155.46
81.86
79.96
77.36
77.04
76.72
57.35
50.08
31.40
28.29
28.02
18.86
17.97
17.48
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

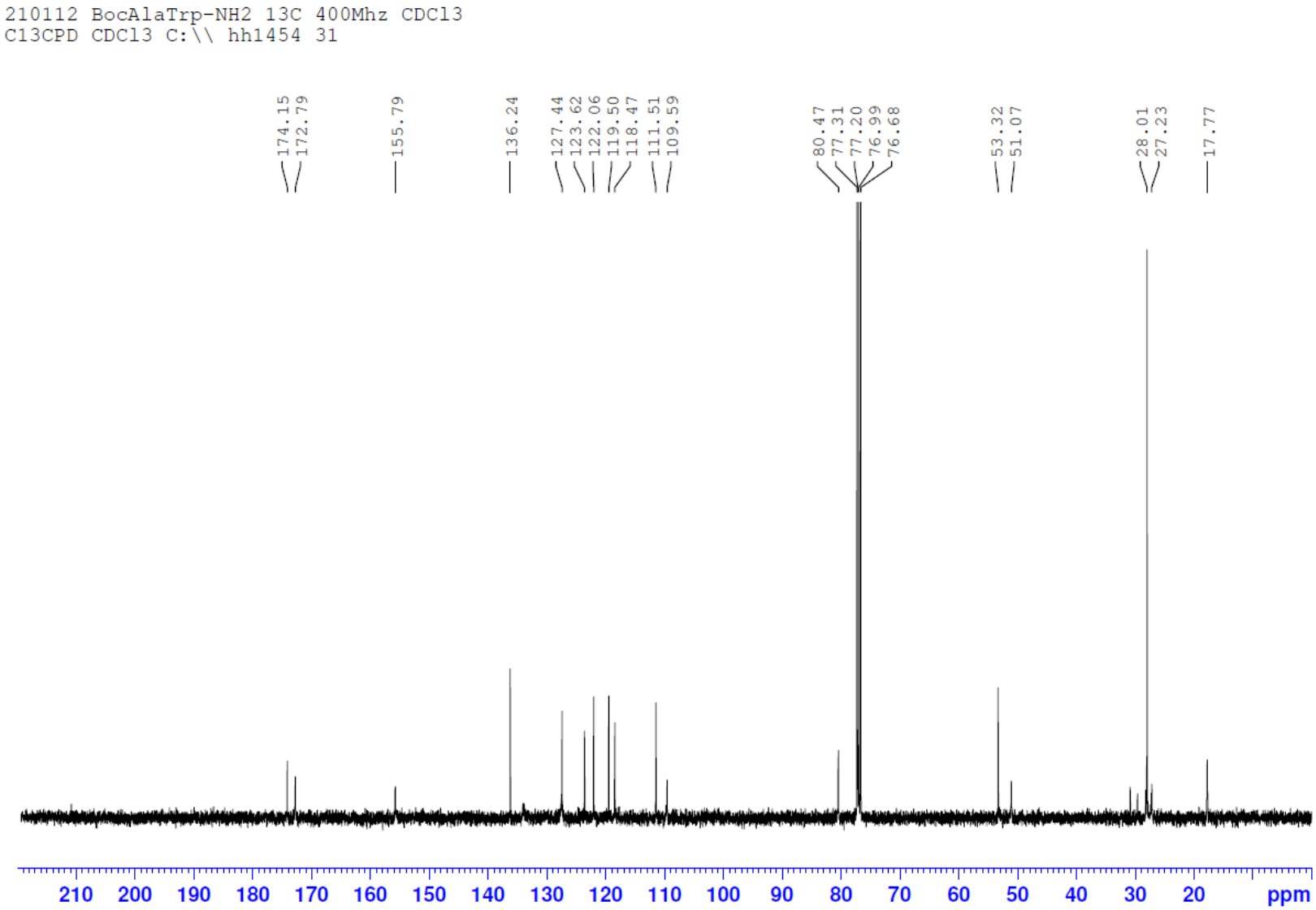

NRP-Ala-Ile-OtBu
CMC_PROTON CDCl3 C:\\ nrp365 95
Boc
N
H
O
H
N
H
O
O
7.26 Chloroform-d
6.69
6.67
5.18
5.17
4.42
4.40
4.39
4.38
4.15
1.84
1.83
1.82
1.82
1.81
1.80
1.79
1.41
1.39
1.31
1.29
1.18
1.16
1.14
1.12
1.12
1.10
1.08
0.89
0.87
0.86
0.84
1.00
1.00
1.09
1.04
1.15
9.32
9.41
3.10
1.16
6.44
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

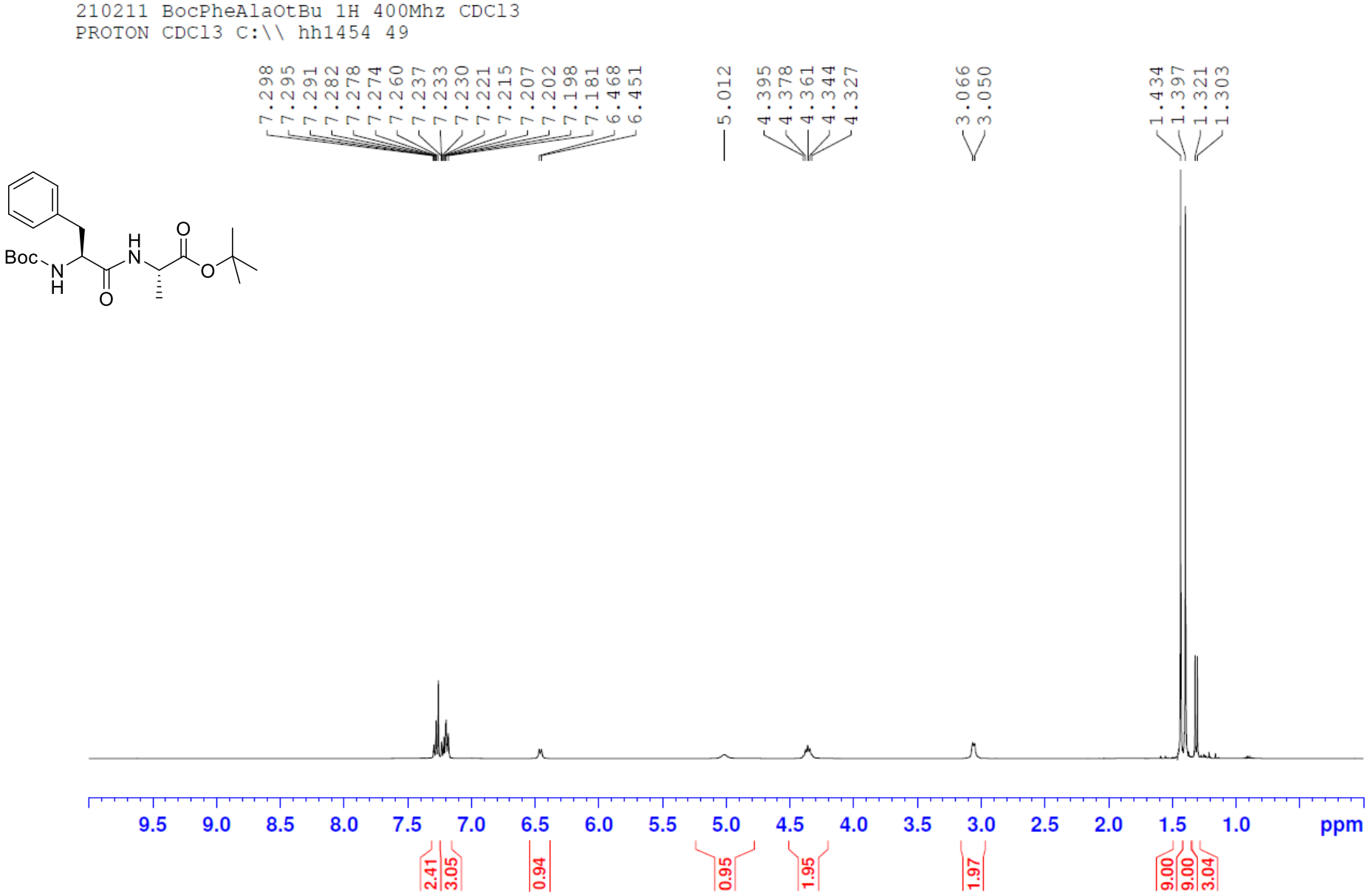

13C NMR (101 MHz, $CDCl_3$) δ 172.40, 170.76, 155.54, 81.92, 79.94, 77.16, 56.82, 50.09, 38.15, 28.35, 28.09, 25.21, 18.08, 15.35, 11.73.
C13CPD CDCl3 C:\\ nrp365 6
81.92
79.94
77.16 Chloroform-d
56.82
50.09
38.15
28.35
28.09
25.21
18.08
15.35
11.73
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

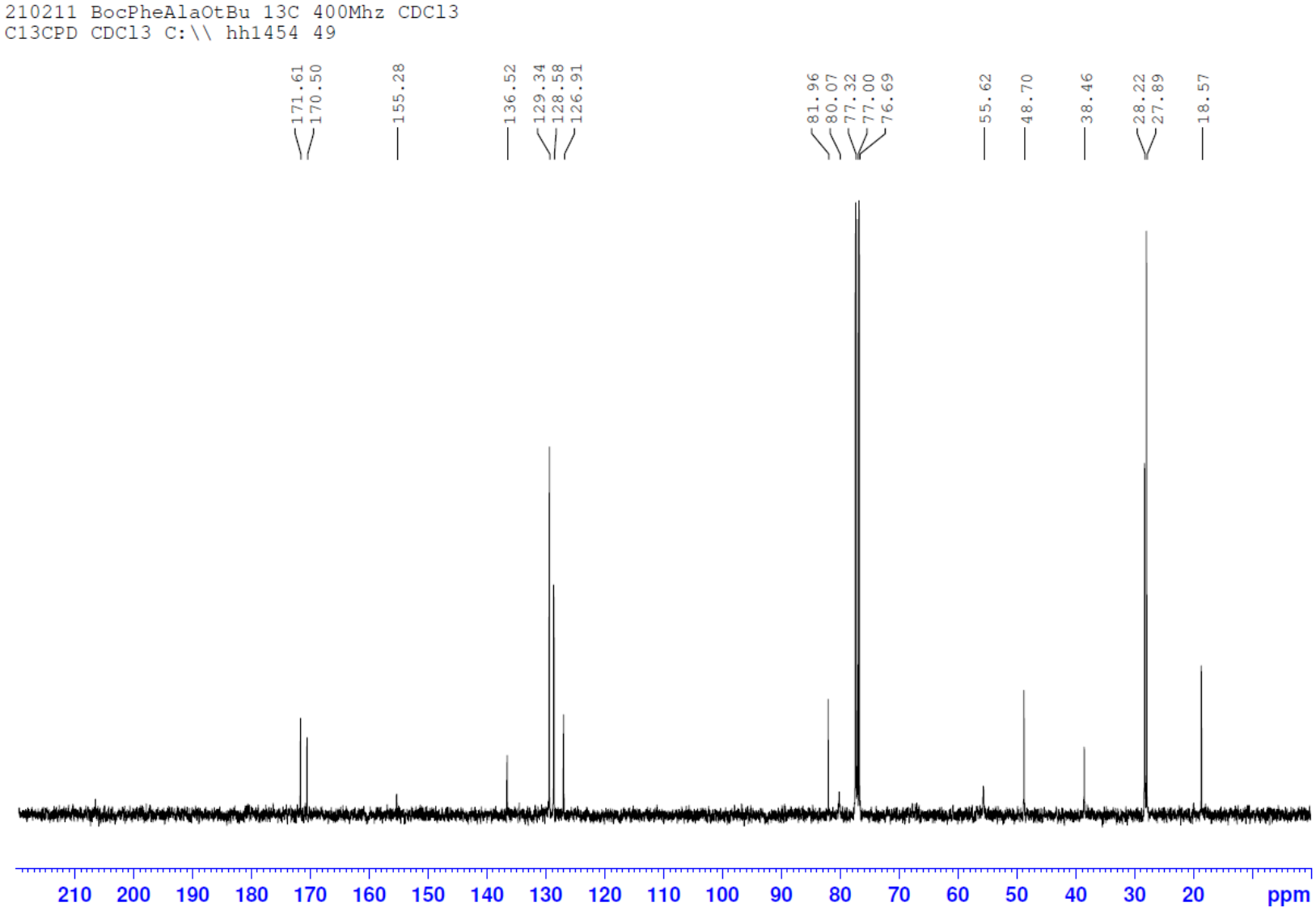

210112 BocAlaLyz(Z)-OtBu 1H 400Mhz CDCl3
CMC_PROTON CDCl3 C:\\ hh1454 32
7.337
7.328
7.312
7.303
7.294
7.282
7.271
7.260
6.762
5.206
5.106
5.075
4.450
4.430
4.418
4.399
4.187
3.164
3.152
3.140
3.125
1.833
1.818
1.798
1.783
1.774
1.761
1.747
1.660
1.647
1.627
1.613
1.589
1.570
1.502
1.487
1.464
1.432
1.413
1.373
Boc
N
H
O
H
N
O
O
HN
Cbz
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
5.00
1.09
4.00
0.99
0.96
2.00
1.08
21.01
5.18

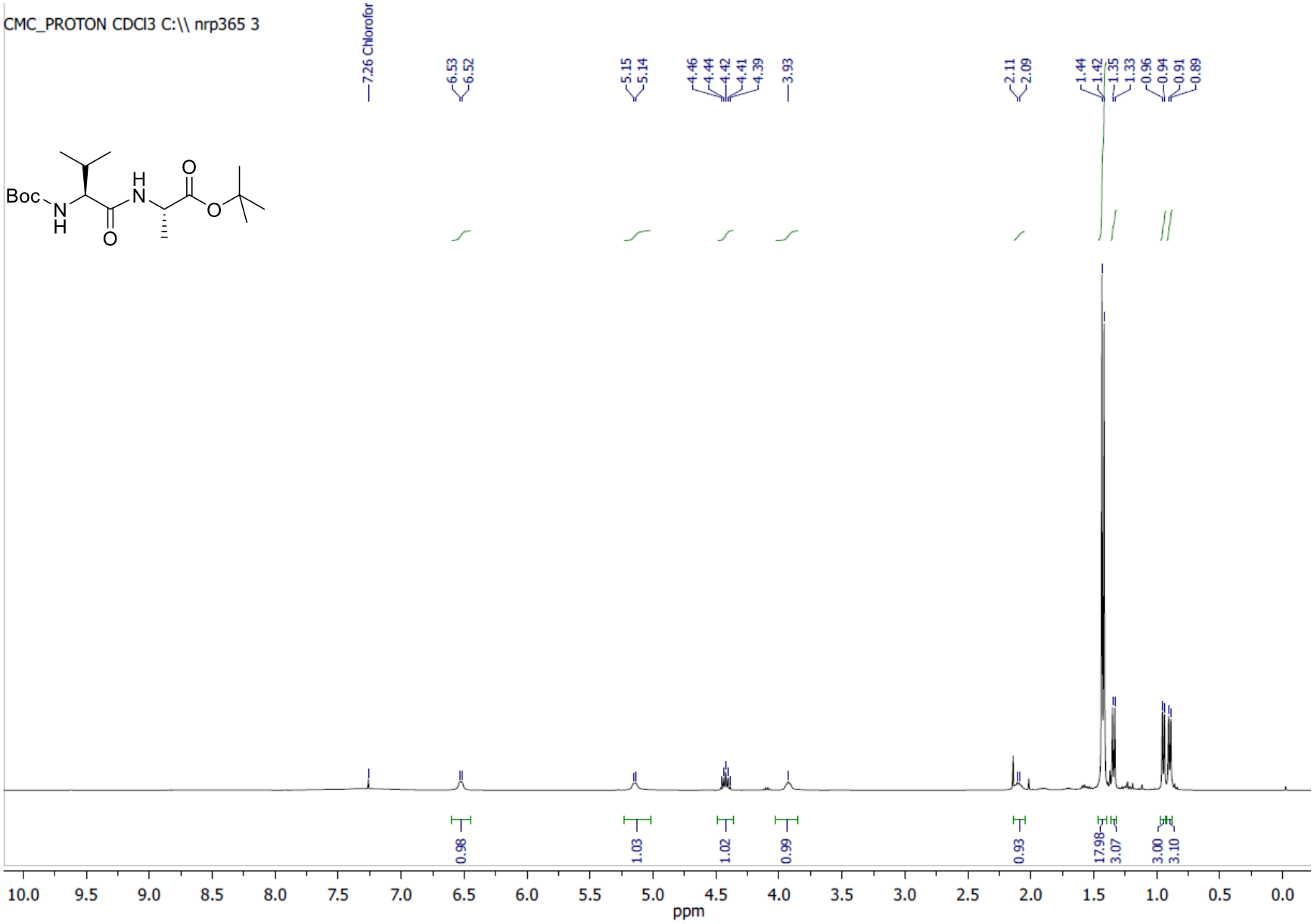

210112 BocAlaLyz(Z)-OtBu 13C 400Mhz CDCl3
C13CPD CDCl3 C:\\ hh1454 32
172.58
171.12
156.45
155.45
136.55
128.40
128.07
127.97
81.95
79.86
77.32
77.00
76.68
66.50
52.29
49.93
40.46
31.92
29.06
28.24
27.90
22.00
18.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

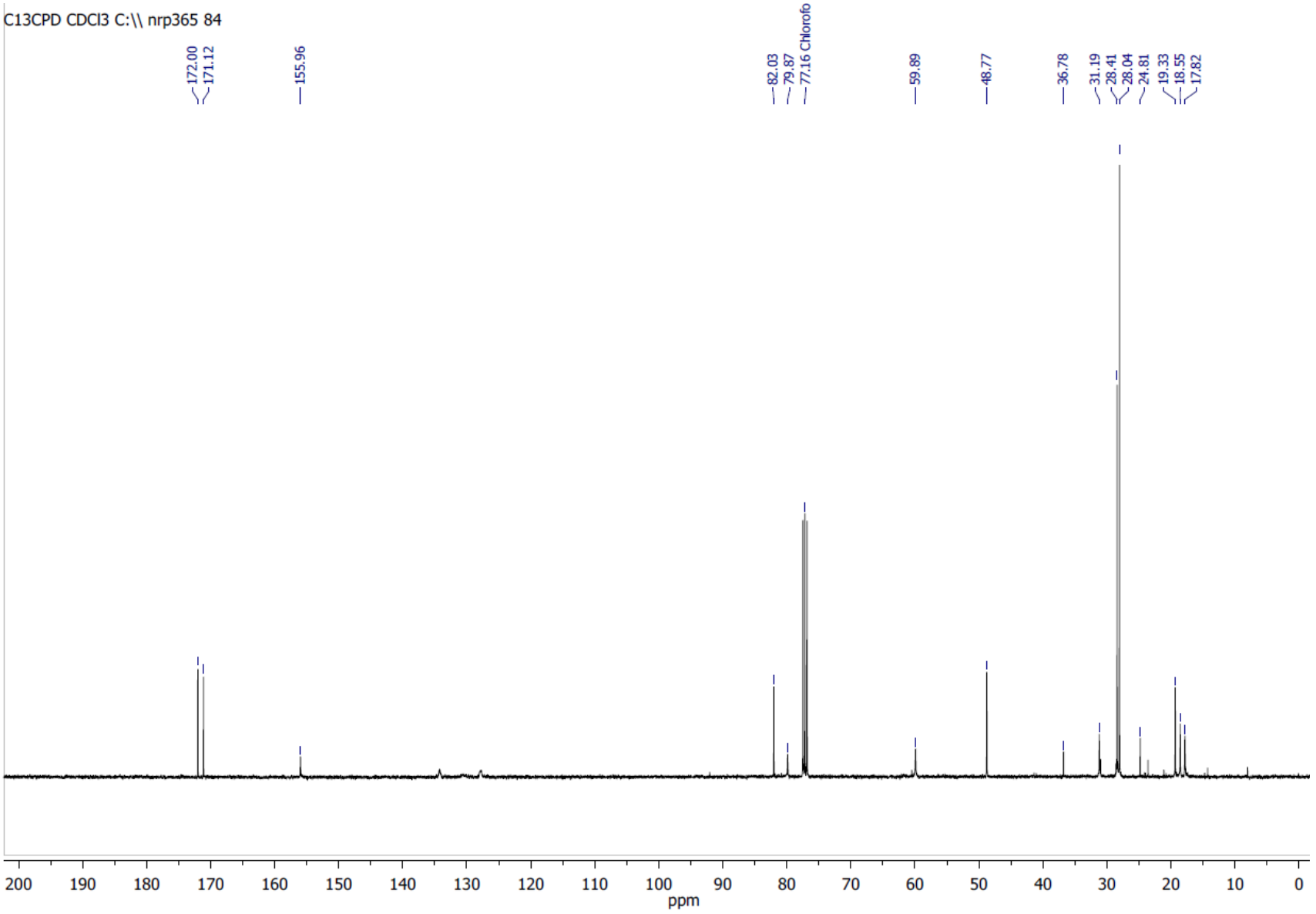

210112 BocAlaTrp-NH2 1H 400Mhz CDCl3
CMC_PROTON CDCl3 C:\\ hh1454 31
8.849
7.615
7.596
7.340
7.320
7.260
7.173
7.155
7.136
7.100
7.081
7.063
7.024
7.006
7.002
6.515
5.853
5.201
4.749
4.734
4.716
4.700
4.050
4.033
4.017
3.385
3.357
3.188
3.172
3.152
3.136
1.263
Boc
NH
O
NH
O
NH2
NH
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.95
1.06
1.14
1.25
1.23
2.00
0.91
0.97
0.92
0.97
1.02
0.97
1.00
12.02

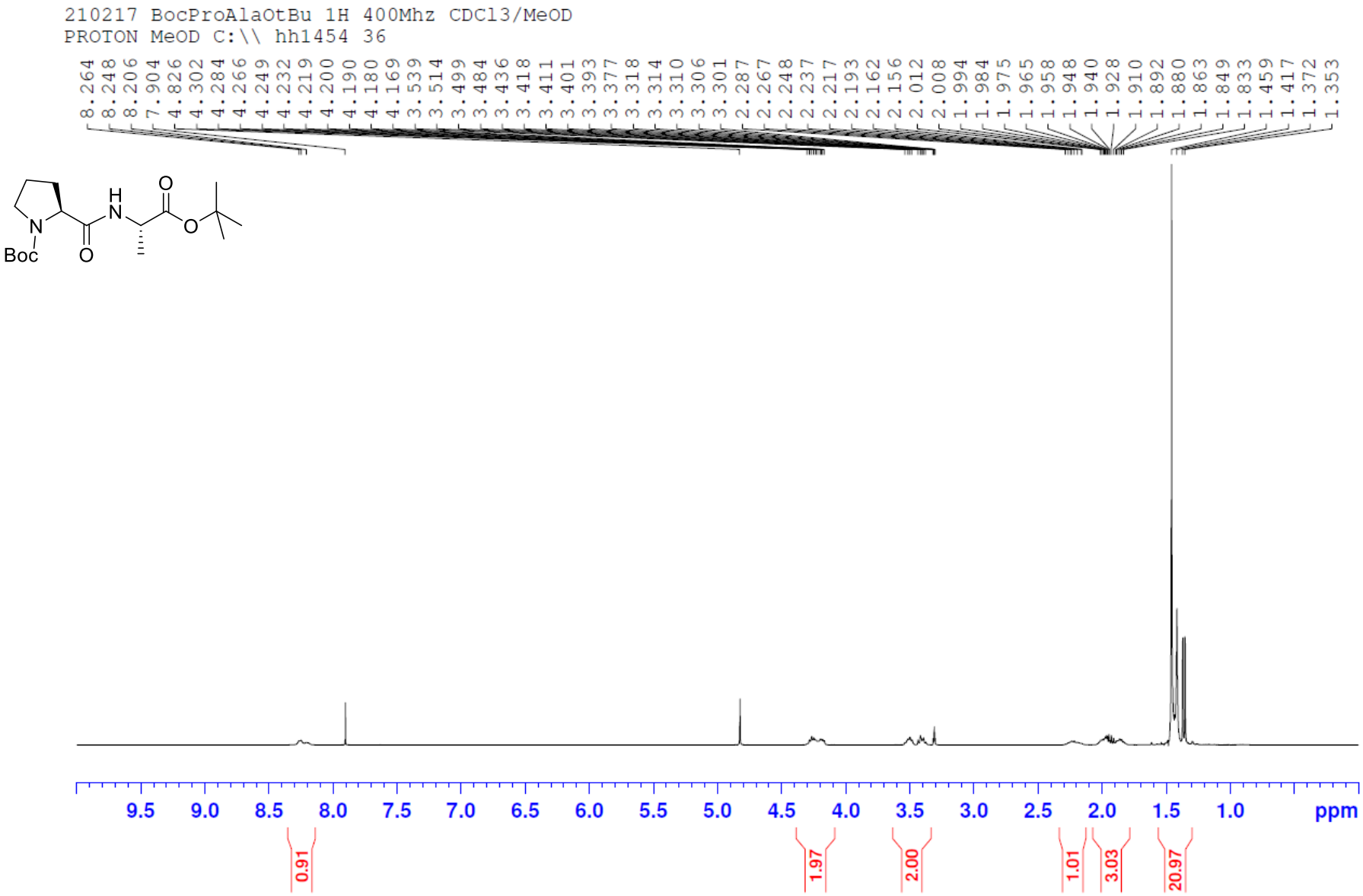

210112 BocAlaTrp-NH2 13C 400Mhz CDCl3
C13CPD CDCl3 C:\\ hh1454 31
174.15
172.79
155.79
136.24
127.44
123.62
122.06
119.50
118.47
111.51
109.59
80.47
77.31
77.20
76.99
76.68
53.32
51.07
28.01
27.23
17.77
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

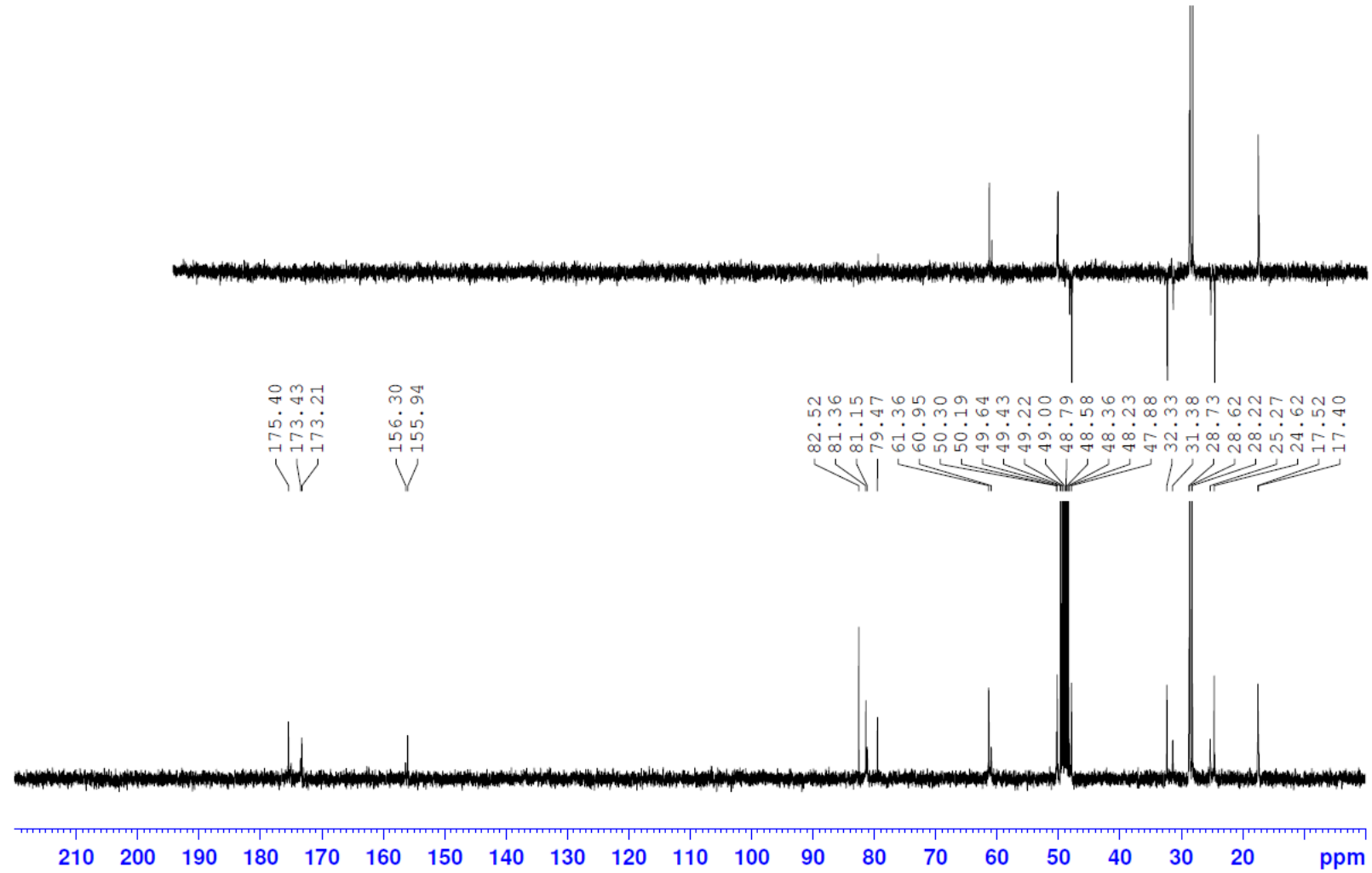

210211 BocPheAlaOtBu 1H 400Mhz CDCl3
PROTON CDCl3 C:\\ hh1454 49
7.298
7.295
7.291
7.282
7.278
7.274
7.260
7.237
7.233
7.230
7.221
7.215
7.207
7.202
7.198
7.181
6.468
6.451
5.012
4.395
4.378
4.361
4.344
4.327
3.066
3.050
1.434
1.397
1.321
1.303
Boc
N
H
H
N
O
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.41
3.05
0.94
0.95
1.95
1.97
9.00
9.00
3.04


210211 BocPheAlaOtBu 13C 400Mhz CDCl3
C13CPD CDCl3 C:\\ hh1454 49
171.61
170.50
155.28
136.52
129.34
128.58
126.91
81.96
80.07
77.32
77.00
76.69
55.62
48.70
38.46
28.22
27.89
18.57
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

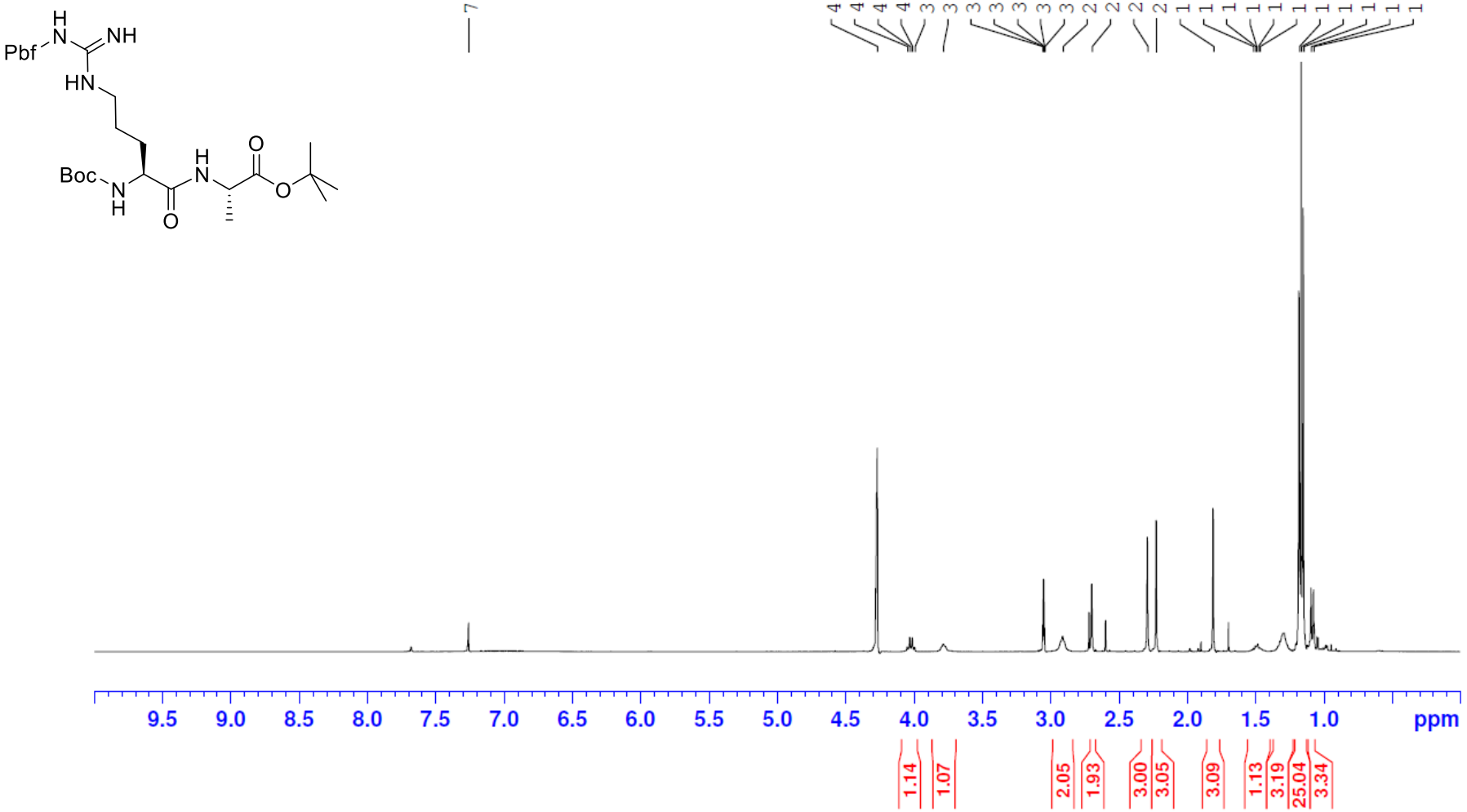

CMC_PROTON CDCl3 C:\\ nrp365 3
7.26 Chloroform
6.53
6.52
5.15
5.14
4.46
4.44
4.42
4.41
4.39
3.93
2.11
2.09
1.44
1.42
1.35
1.33
0.96
0.94
0.91
0.89
Boc
N
H
O
H
N
O
O
0.98
1.03
1.02
0.99
0.93
17.98
3.07
3.00
3.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

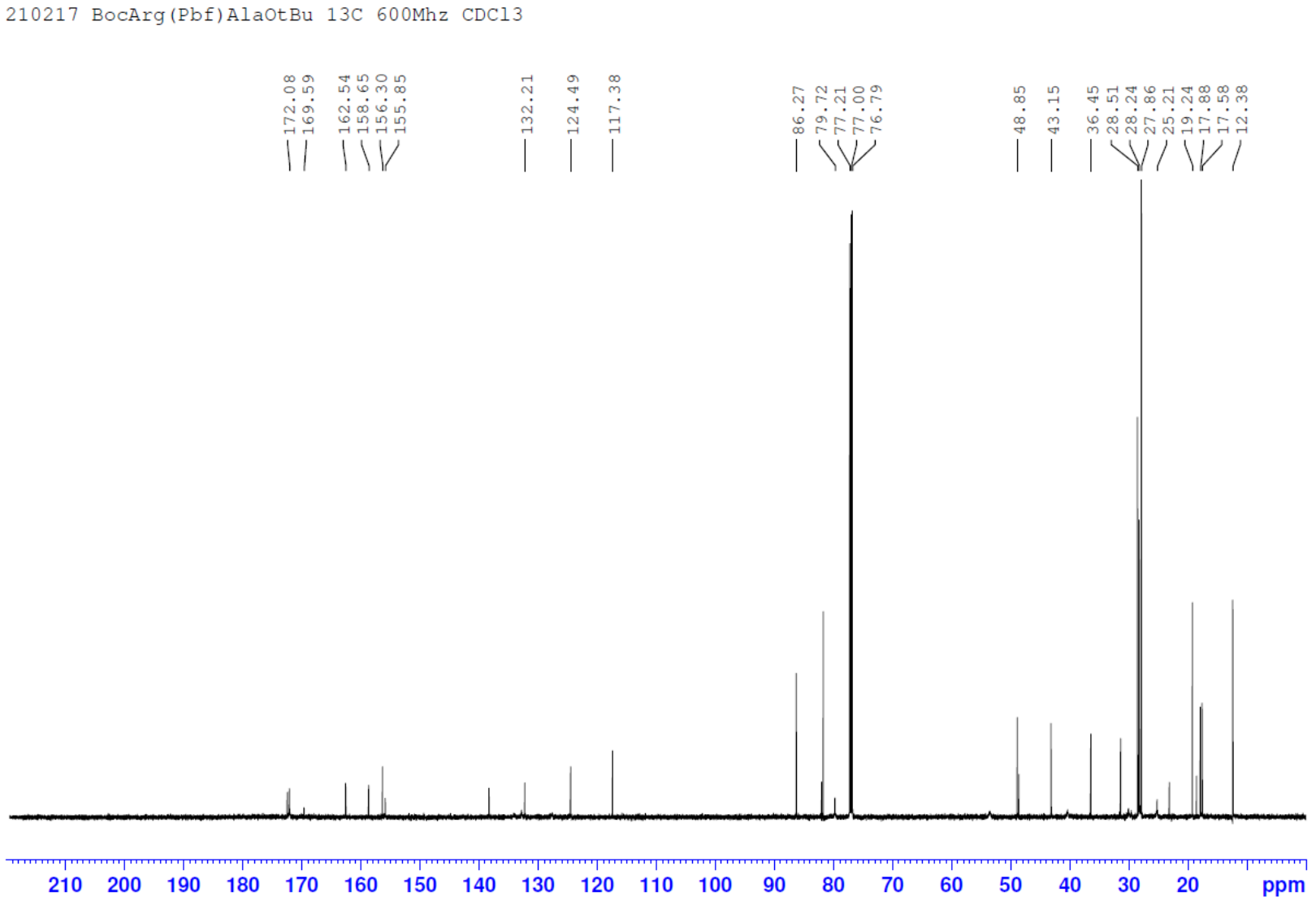

C13CPD CDCl3 C:\\ nrp365 84
172.00
171.12
155.96
82.03
79.87
77.16 Chlorofo
59.89
48.77
36.78
31.19
28.41
28.04
24.81
19.33
18.55
17.82
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

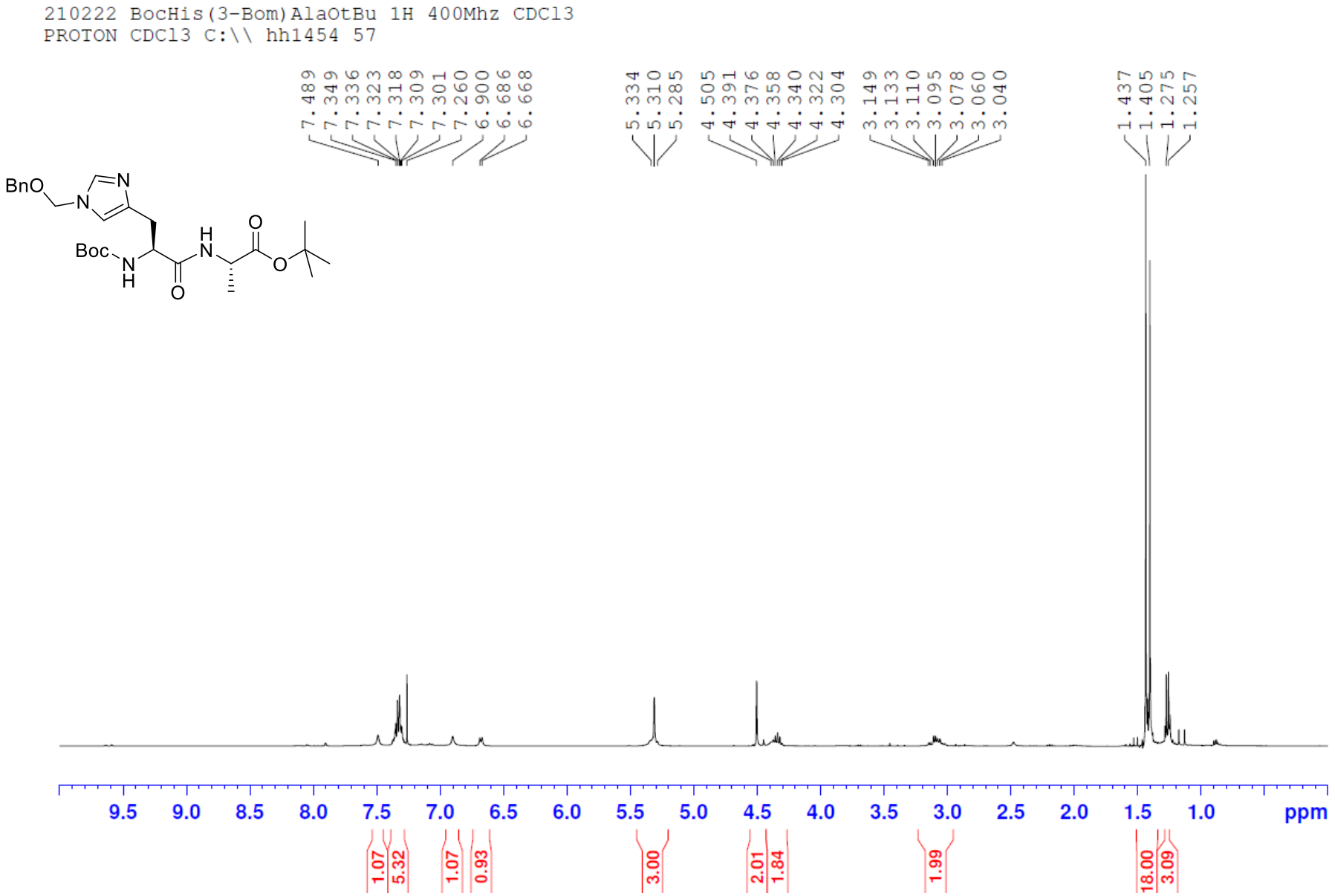

210217 BocProAlaOtBu 1H 400Mhz CDCl3/MeOD
PROTON MeOD C:\\ hh1454 36
8.264
8.248
8.206
7.904
4.826
4.302
4.284
4.266
4.249
4.232
4.219
4.200
4.190
4.180
4.169
3.539
3.514
3.499
3.484
3.436
3.418
3.411
3.401
3.393
3.377
3.318
3.314
3.310
3.306
3.301
2.287
2.267
2.248
2.237
2.217
2.193
2.162
2.156
2.012
2.008
1.994
1.984
1.975
1.965
1.958
1.948
1.940
1.928
1.910
1.892
1.880
1.863
1.849
1.833
1.459
1.417
1.372
1.353
Boc
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.91
1.97
2.00
1.01
3.03
20.97

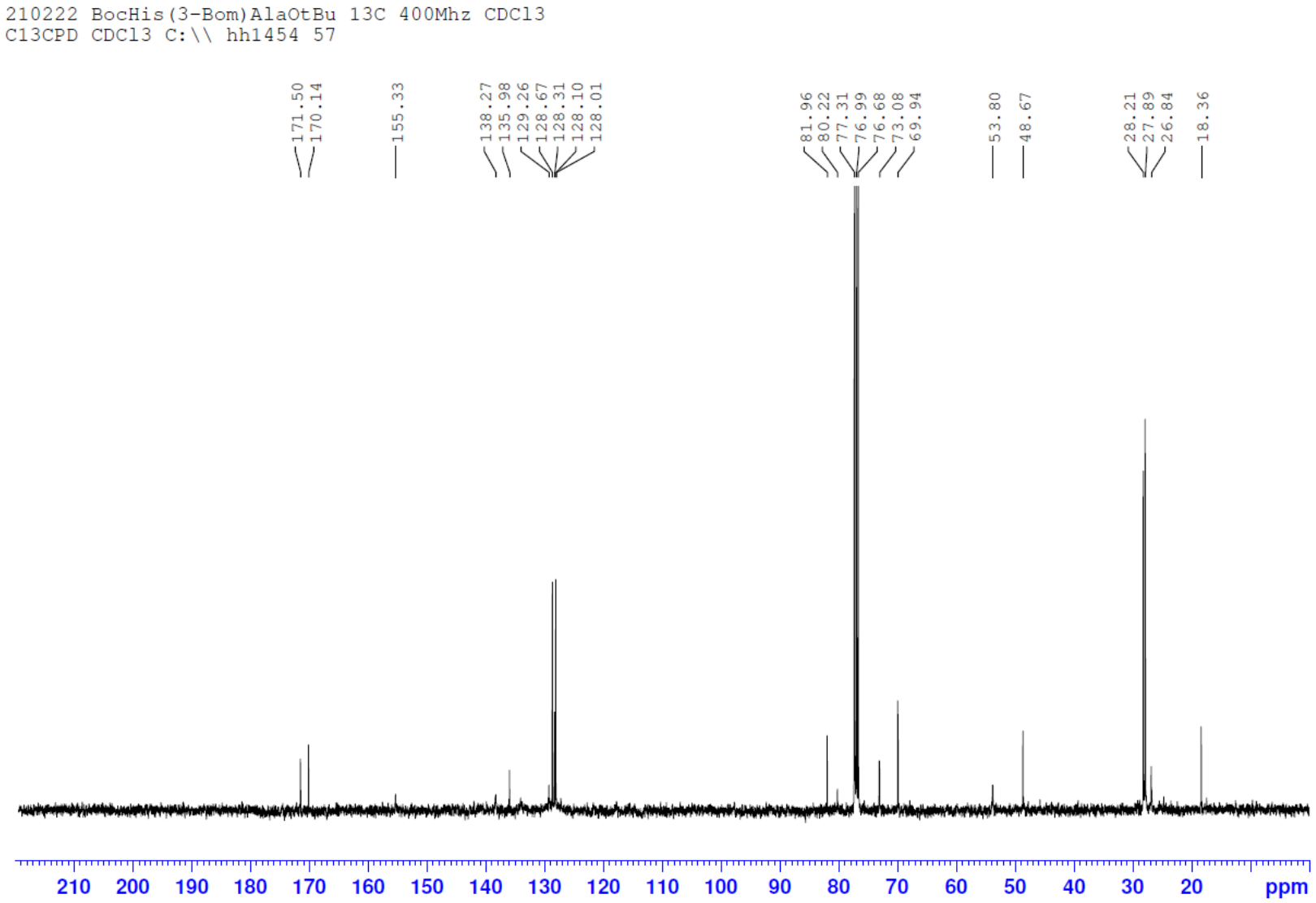

210217 BocProAlaOtBu 13C 400Mhz CDCl3/MeOD
C13CPD MeOD C:\\ hh1454 36
175.40
173.43
173.21
156.30
155.94
82.52
81.36
81.15
79.47
61.36
60.95
50.30
50.19
49.64
49.43
49.22
49.00
48.79
48.58
48.36
48.23
47.88
32.33
31.38
28.73
28.62
28.22
25.27
24.62
17.52
17.40
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

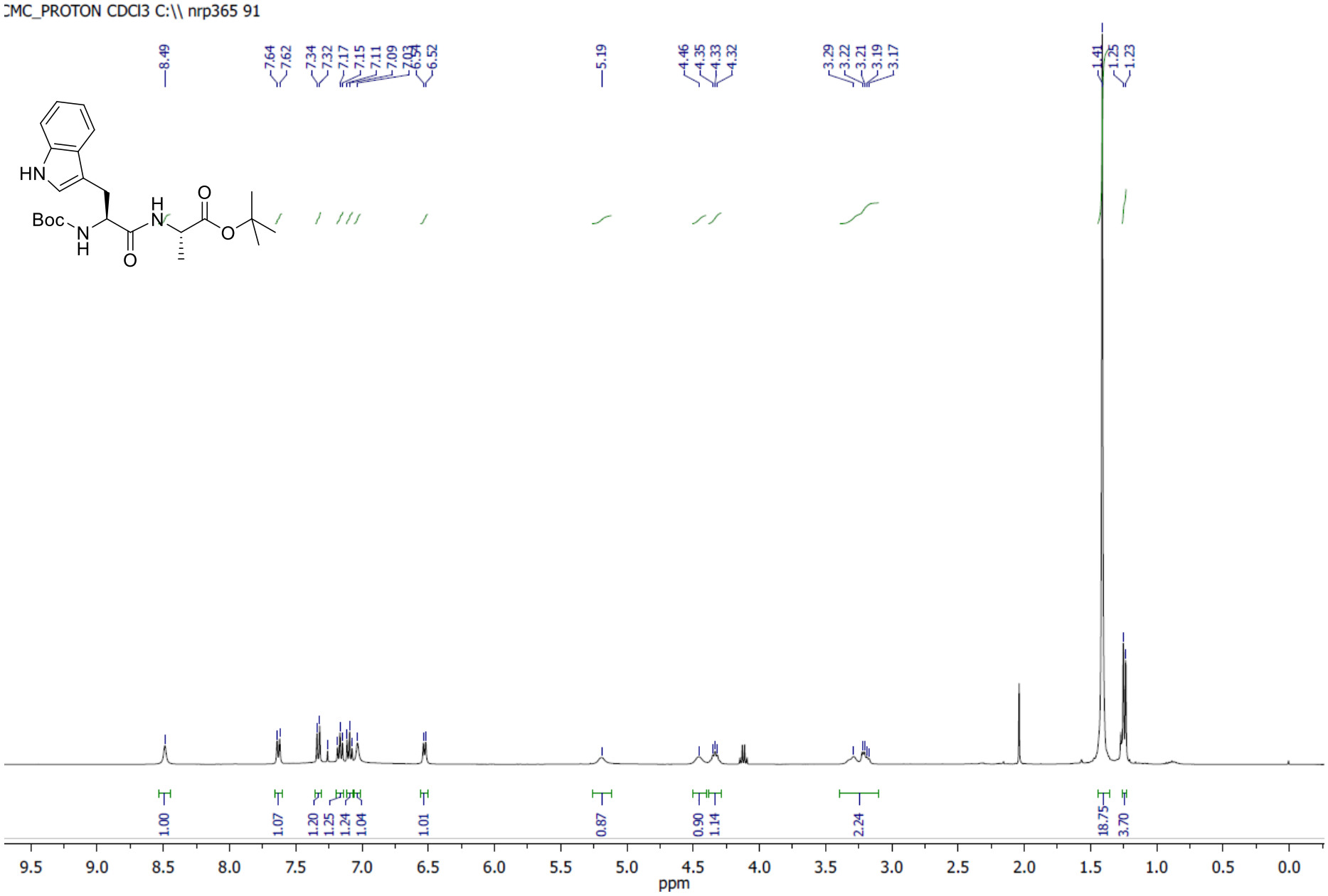
210222 BocArg(Pbf)AlaOtBu 1H 400Mhz CDCl3/MeOD
PROTON CDCl3 C:\\ hh1454 56

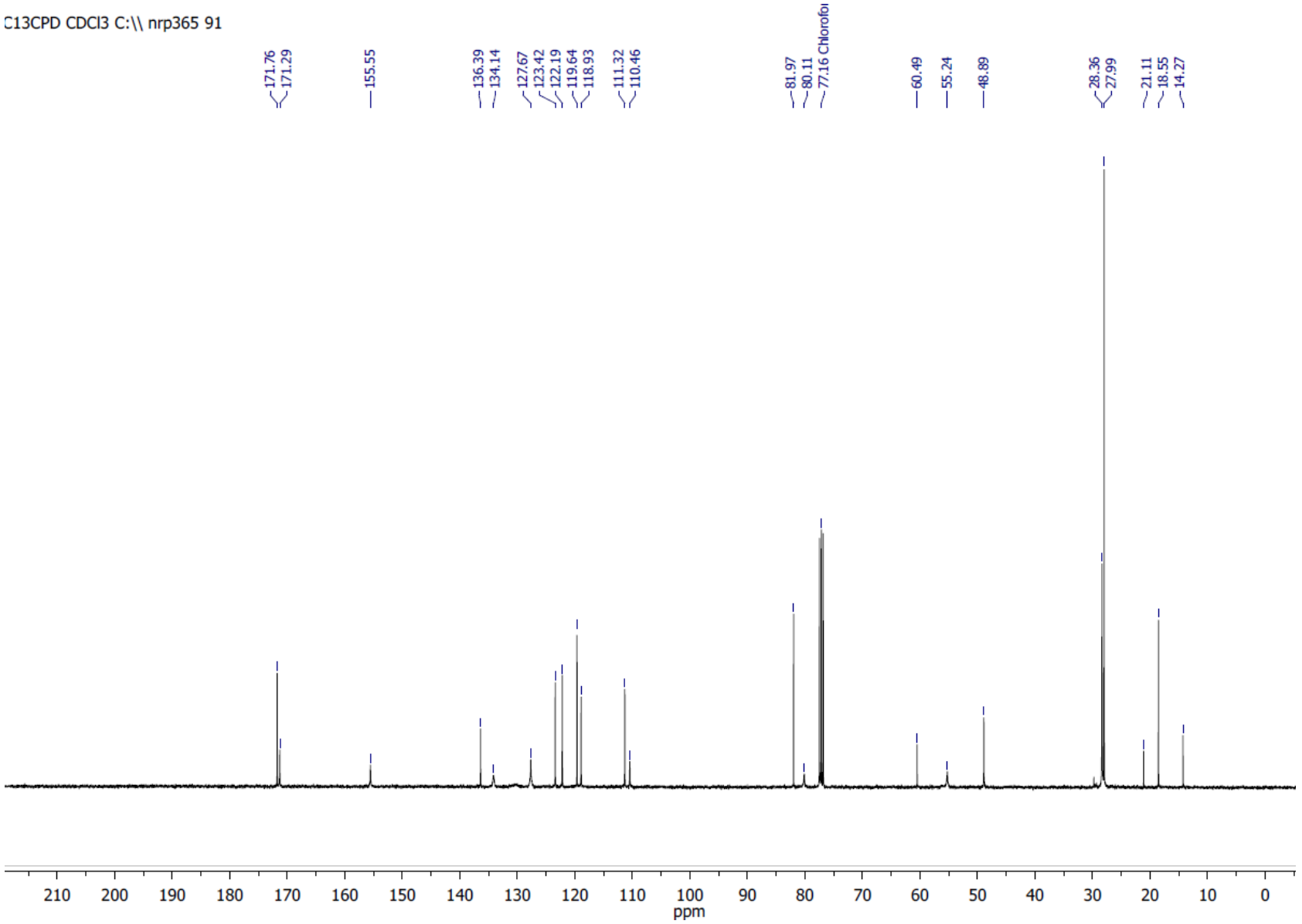


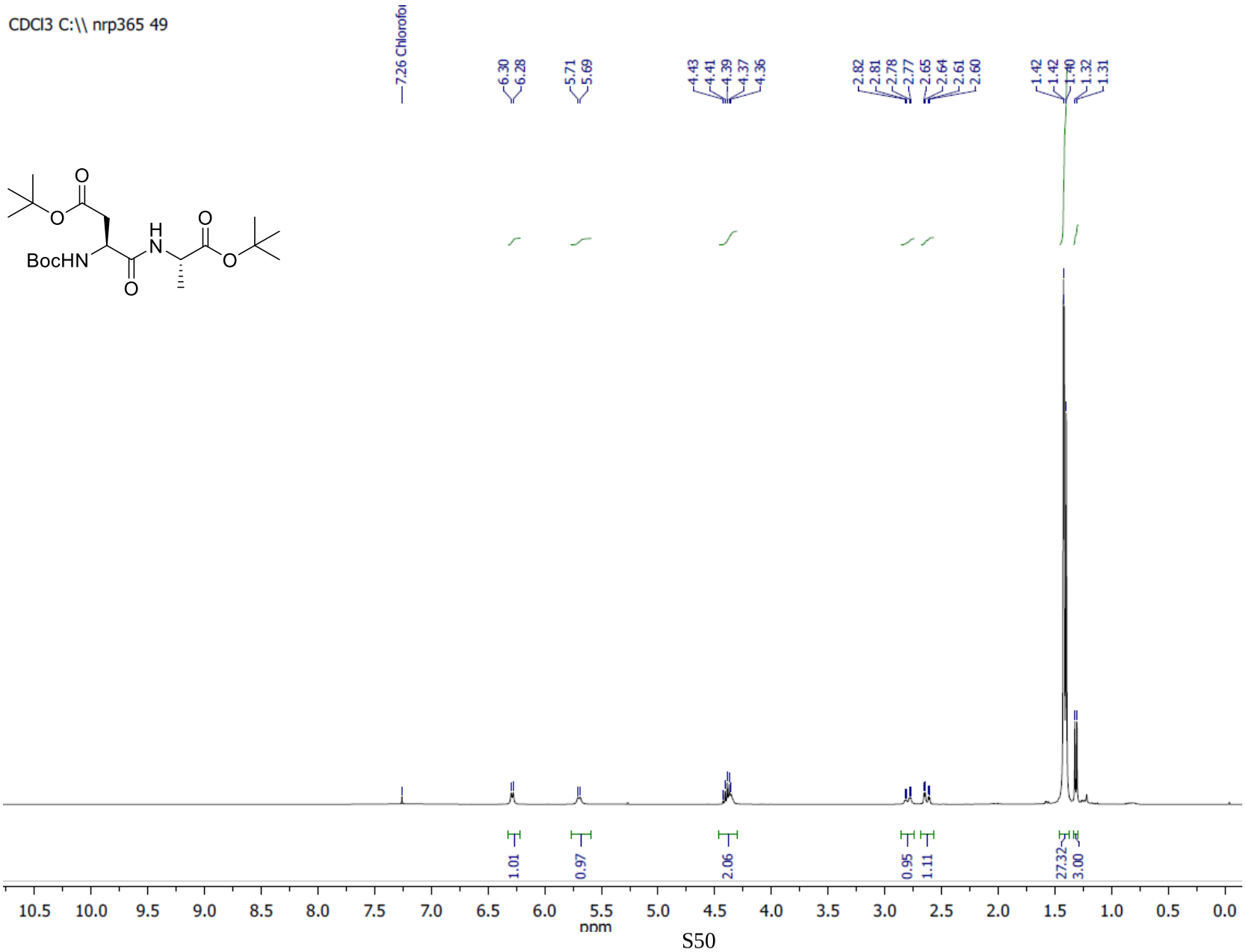

210217 BocArg(Pbf)AlaOtBu 13C 600Mhz CDCl3
172.08
169.59
162.54
158.65
156.30
155.85
132.21
124.49
117.38
86.27
79.72
77.21
77.00
76.79
48.85
43.15
36.45
28.51
28.24
27.86
25.21
19.24
17.88
17.58
12.38
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

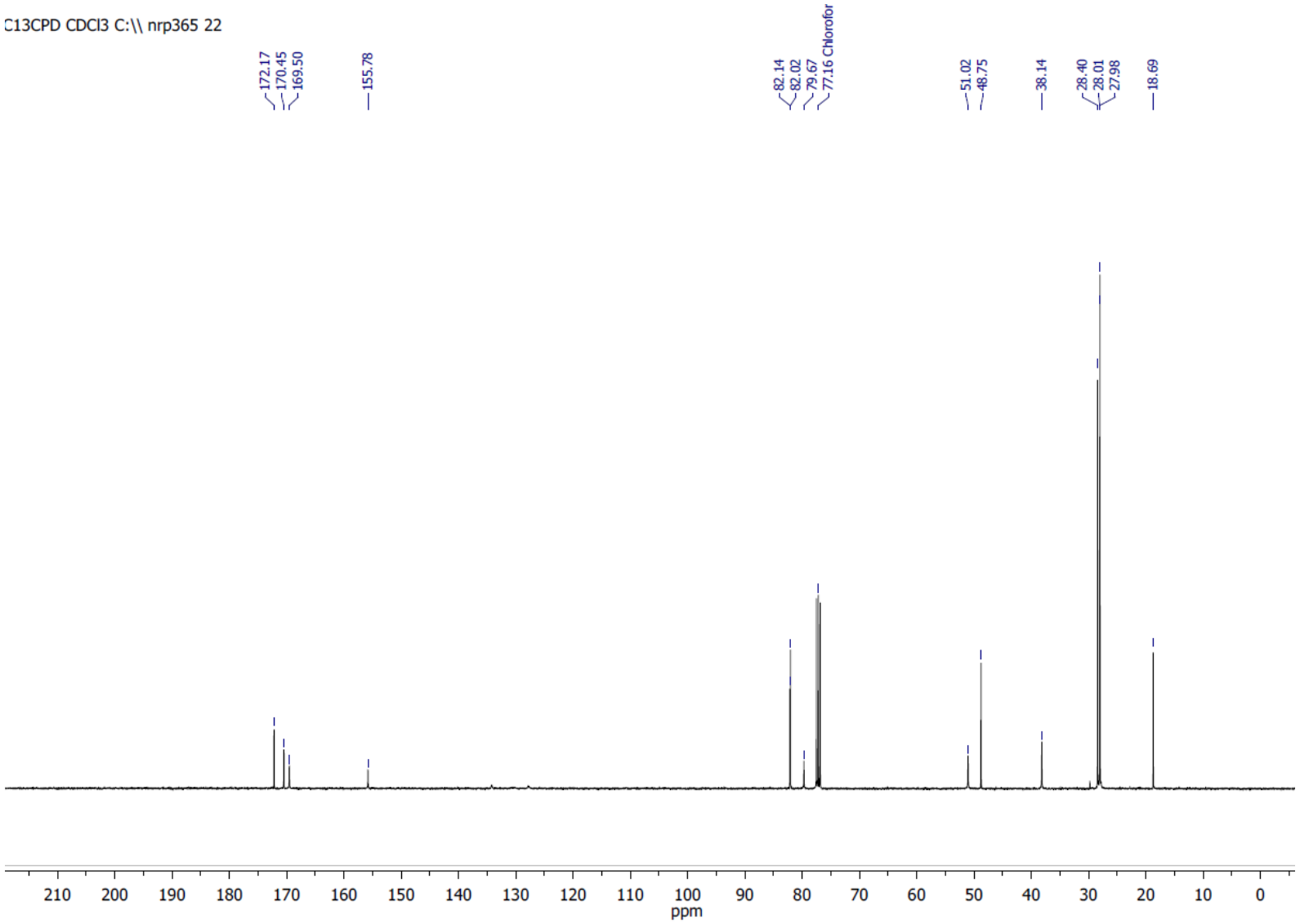

210222 BocHis(3-Bom)AlaOtBu 1H 400Mhz CDCl3
PROTON CDCl3 C:\\ hh1454 57
7.489
7.349
7.336
7.323
7.318
7.309
7.301
7.260
6.900
6.686
6.668
5.334
5.310
5.285
4.505
4.391
4.376
4.358
4.340
4.322
4.304
3.149
3.133
3.110
3.095
3.078
3.060
3.040
1.437
1.405
1.275
1.257
BnO
N
N
Boc
N
H
H
N
O
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.07
5.32
1.07
0.93
3.00
2.01
1.84
1.99
18.00
3.09

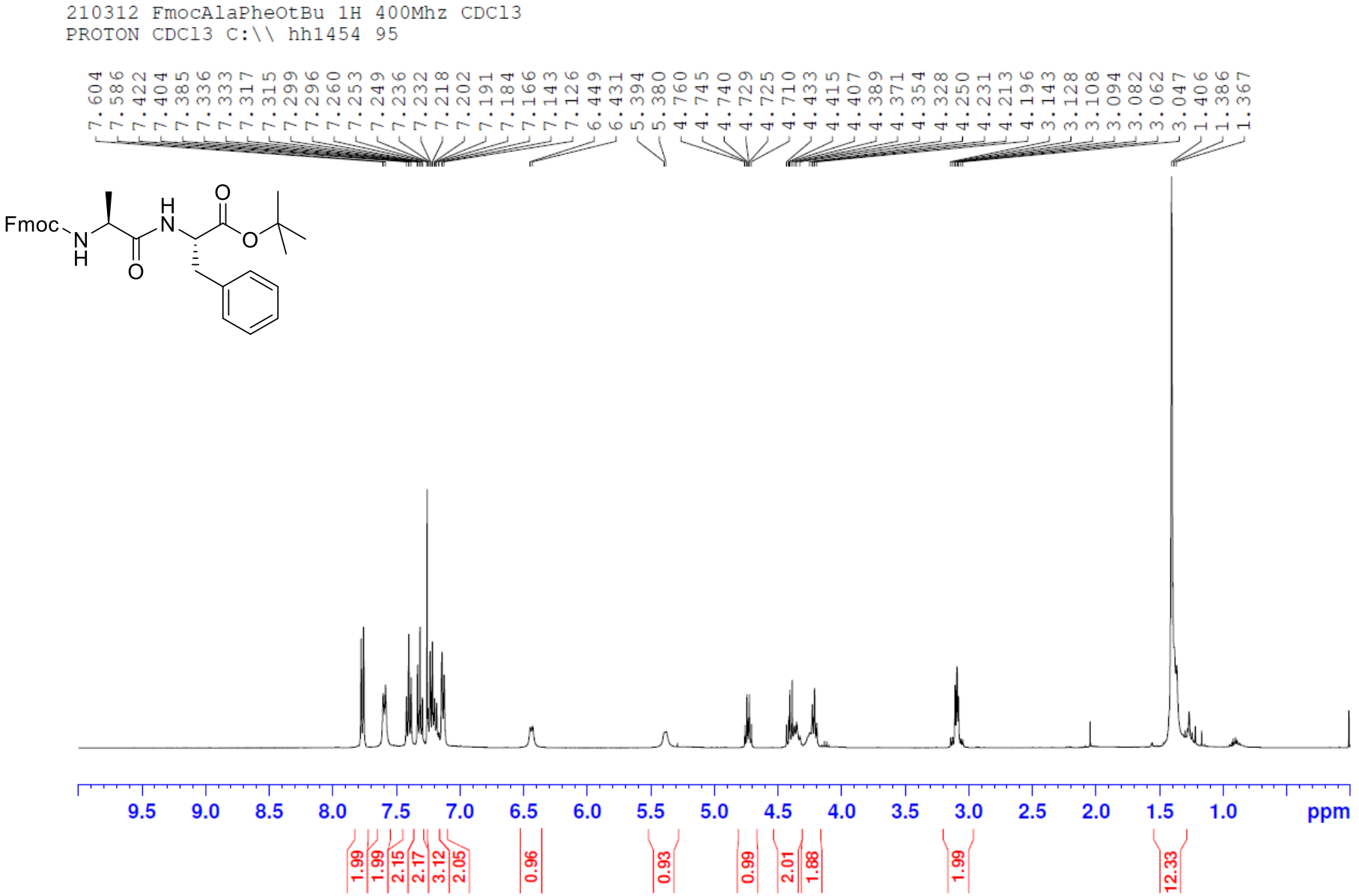

210222 BocHis(3-Bom)AlaOtBu 13C 400Mhz CDCl3
C13CPD CDCl3 C:\\ hh1454 57
171.50
170.14
155.33
138.27
135.98
129.26
128.67
128.31
128.10
128.01
81.96
80.22
77.31
76.99
76.68
73.08
69.94
53.80
48.67
28.21
27.89
26.84
18.36
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

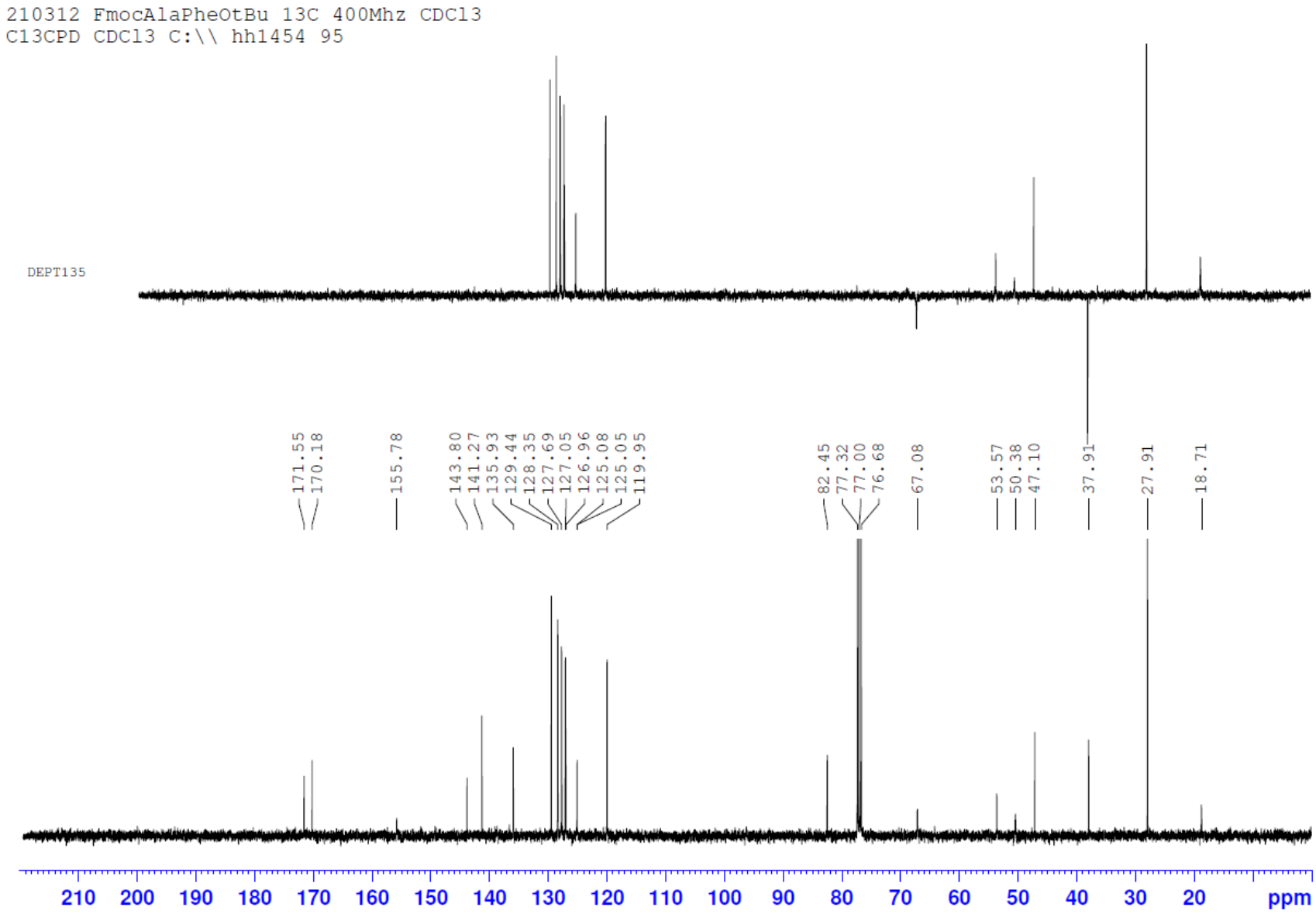

CMC_PROTON CDCl3 C:\\ nrp365 91
8.49
7.64
7.62
7.34
7.32
7.17
7.15
7.11
7.09
7.03
6.94
6.52
5.19
4.46
4.35
4.33
4.32
3.29
3.22
3.21
3.19
3.17
1.41
1.25
1.23
HN
Boc
N
H
H
N
O
O
O
1.00
1.07
1.20
1.25
1.24
1.04
1.01
0.87
0.90
1.14
2.24
18.75
3.70
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


C13CPD CDCl3 C:\\ nrp365 91
171.76
171.29
155.55
136.39
134.14
127.67
123.42
122.19
119.64
118.93
111.32
110.46
81.97
80.11
77.16 Chlorofo
60.49
55.24
48.89
28.36
27.99
21.11
18.55
14.27
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


CDCl3 C:\\ nrp365 49
7.26 Chlorofo
6.30
6.28
5.71
5.69
4.43
4.41
4.39
4.37
4.36
2.82
2.81
2.78
2.77
2.65
2.64
2.61
2.60
1.42
1.42
1.40
1.32
1.31
BocHN
O
O
H
N
O
O
O
1.01
0.97
2.06
0.95
1.11
27.32
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


C13CPD CDCl3 C:\\ nrp365 22
172.17
170.45
169.50
155.78
82.14
82.02
79.67
77.16 Chlorofor
51.02
48.75
38.14
28.40
28.01
27.98
18.69
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


210312 FmocAlaPheOtBu 1H 400Mhz CDCl3
PROTON CDCl3 C:\\ hh1454 95
7.604
7.586
7.422
7.404
7.385
7.336
7.333
7.317
7.315
7.299
7.296
7.260
7.253
7.249
7.236
7.232
7.218
7.202
7.191
7.184
7.166
7.143
7.126
6.449
6.431
5.394
5.380
4.760
4.745
4.740
4.729
4.725
4.710
4.433
4.415
4.407
4.389
4.371
4.354
4.328
4.250
4.231
4.213
4.196
3.143
3.128
3.108
3.094
3.082
3.062
3.047
1.406
1.386
1.367
Fmoc
N
H
O
H
N
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.99
1.99
2.15
2.17
3.12
2.05
0.96
0.93
0.99
2.01
1.88
1.99
12.33


210312 FmocAlaPheOtBu 13C 400Mhz CDCl3
C13CPD CDCl3 C:\\ hh1454 95
DEPT135
171.55
170.18
155.78
143.80
141.27
135.93
129.44
128.35
127.69
127.05
126.96
125.08
125.05
119.95
82.45
77.32
77.00
76.68
67.08
53.57
50.38
47.10
37.91
27.91
18.71
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm