Towards New Linchpin Reagents for the Direct Preparation of NCO-Containing Molecules

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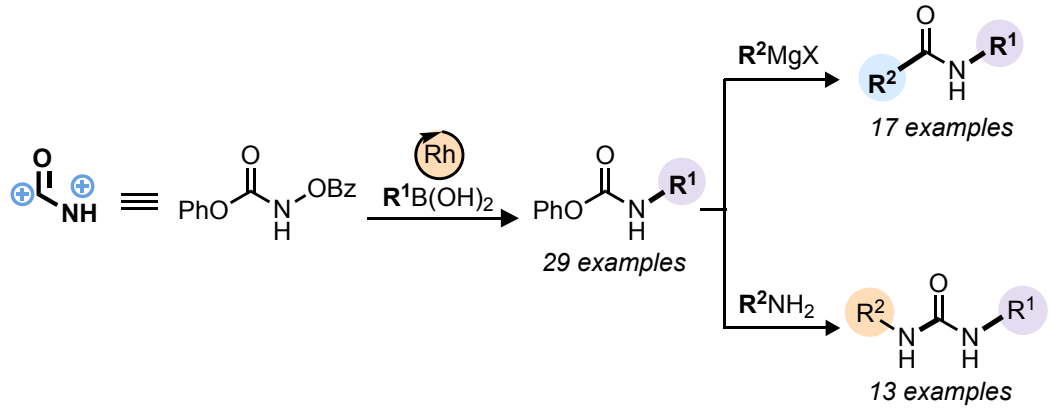
Abstract

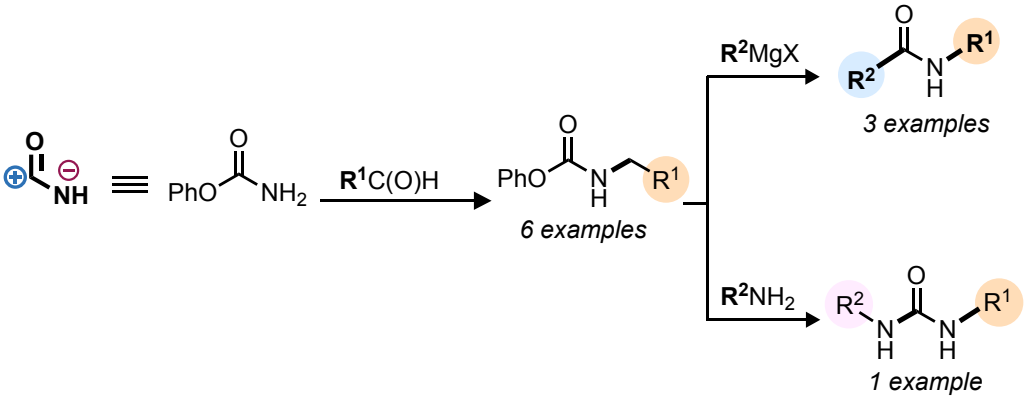
The development and application of reagents that serve as building blocks for the construction of molecules have resulted in significant advances to the scientific community. Among these, linchpins are small, strategically designed molecules that can be chemoselectively functionalized by sequential reactions, enabling the coupling of two or more reagents through a single, central scaffold. While there is literature precedent for olefin, ketone, and polyene-forming linchpins, no such linchpin exists for amide synthesis despite the ubiquitous nature of these and other NCO-containing subunits in pharmaceuticals and agrochemicals. This thesis focuses on the development of new linchpin reagents for NCO-containing products through the formation of C-N and C-X bonds.

Isocyanates are useful synthons and reactive intermediates. To control the exposure to these toxic reagents and their instability, blocked (or masked) isocyanates have been developed: an equilibrium generates the isocyanate in-situ, allowing for safer precursors and better control over the concentration of the reactive isocyanate. This strategy enables the development of new reactivity, particularly for heteroatom-substituted isocyanates. In Chapter 2, a bench-stable masked *O*-isocyanate with optimized leaving groups (OPh and OBz) is proven to indeed be an amide linchpin reagent, overcoming the limitations of traditional amide synthesis with a built-in N-C(=O) bond. The C(=O)-OPh and N-OBz bonds can undergo sequential reactions to functionalize the N-C=O subunit. The biselectrophilicity of the linchpin reagent imparts unique reactivity, making them attractive as linchpin molecules with high chemoselectivity. The linchpin reagent was first functionalized via rhodium-catalyzed electrophilic amination, followed by derivatization using Grignard reagents to provide hindered secondary amides and enamides. While this method was limited by its incompatibility with alkyl boronic acids, it provided a novel and effective route to

amide derivatives. Tertiary amides were also accessed by trapping of the magnesium amidate intermediate with an alkylating agent. Finally, extensions toward a general NCO linchpin were explored through the synthesis of lactams and unsymmetrical ureas.



In Chapter 3, a simpler, amphoteric linchpin is developed to overcome the limitations of the linchpin developed in Chapter 2. The simpler linchpin reagent was first functionalized via reductive amination, followed by derivatization with Grignard reagents to provide secondary amides or with amines to provide unsymmetrical ureas. While this method does give access to N-alkyl amides, it does not yet extend to ureas due to competing reaction pathways.



In summary, these studies show that linchpin-based methods can simplify the synthesis of NCO-containing molecules, offering chemists new tools for assembling complex structures with importance in agrochemical and pharmaceutical industries.

Acknowledgements

First and foremost, I would like to thank my research supervisor Prof. André Beauchemin for the opportunity, guidance, and support during my graduate studies. I am extremely fortunate for the support and understanding that you provided throughout the years. Your enthusiasm for chemistry and your ability to teach allowed me to have a deeper understanding of the concepts related to this project and great wisdom outside of it. Your mentorship played a major role in my development as a researcher and communicator.

I must also acknowledge my former mentor, Dr. Tony Durst for inspiring me to pursue graduate studies. Your patience and trust in me as an inexperienced undergraduate student gave me the tools and confidence to pursue higher education. I will forever cherish our conversations.

I am equally grateful for my lab manager, Dr. Monica Gill. Your ability to support and compassion in times of need helped endlessly. I am very grateful for the guidance provided throughout the years in the lab, and especially during the process of writing this thesis. Thank you and André for being the biggest believers in Team Linchpin.

I am also very thankful for my lab mates - my time within the Beauchemin group would not be the same without the group members, both past and present. I really enjoyed my time with all of you over the years and appreciated the support, encouragement and laughs, also all the cakes. To Bhavana, thank you for being the best part of Team Linchpin.

I thank my committee members, Prof. Newman and Prof. Gagosz, for their helpful suggestions, for reading my thesis, and offering useful feedback. I must also thank the NMR and mass spectroscopy facilities.

In addition, I would like to thank my family and friends who have provided me with continuous support and encouragement. I could not have completed this work without the love and support from them. From a young age, I believed that anything worth doing should be done with your whole heart. I want to thank my parents for instilling this value in me since my youth as it has gotten me to where I am in life. Thank you for teaching me hard work and sacrifice alongside this.

Thank you to my partner, Kieran, for inspiring me to truly follow my dreams. Changing programs to pursue a degree in education has not been a seamless transition and I doubt I could have done it without your constant love and support.

Un dernier coup de cœur.

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Statement of Contributions

Over the course of my time in the Beauchemin Group, I completed a CO-OP work term, an Honours project, then began graduate studies as a Master's student. Herein, I will lay out my contributions to the projects described in this Master's thesis.

In 2018, Dr. Qiang Wang obtained an initial hit on the electrophilic amination. This hit was crucial in supporting the feasibility of the development of an amide linchpin. Starting in 2022, I started in the Beauchemin Lab, being mentored by and working collaboratively with PhD candidate Bhavana Uppalapati (**BU**). My goal was to focus on one single type of reactivity, specifically the Rh-catalyzed electrophilic amination. These experiments were initiated during my CO-OP, advanced in my Honours project, expanded and ultimately finalized during my master's; this work is presented in Chapter 2 of this thesis, acknowledging, to the best of my ability, the collaborative contributions by **BU**. The results in Chapter 2 are part of a manuscript that was submitted in 2024. As a result of comments and feedback from reviewers, additional experiments were performed by both myself and **BU**, in a collaborative fashion, to ensure reviewers comments were addressed in a timely fashion. The next paragraph describes the specifics of the contributions.

A four solvent and three temperature optimization was performed during my CO-OP term. A small substrate scope of 13 compounds (**2.3.1-5, 2.3.7-8, 2.3.12-14, 2.3.17, 2.3.20, 2.3.22)** was accomplished by myself during my Honour's project. These compounds were resynthesized and recharacterized during my Master's degree.

In Chapter 2, I did the optimization in **Table 3** for the amination reactions while **BU** performed the optimization of **Table 1, Table 2** and **Table 4**. I performed the carbamate substrate scope (Section 2.2), with exception of the ene-carbamates (**2.3.27-29**), and carbamate **2.3.11**, synthesized by **BU**, and therefore not included in the supporting information of this thesis. BU performed the amide and lactam synthesis (**Section 2.3 and 2.4.1**). The urea synthesis (**Section 2.4.2**) was performed by myself (BU synthesized ene-urea **3.9.5**). **BU** and myself co-wrote the publication associated with this chapter.[1] All the work included in the experimental section of this thesis has been performed by me.

In Chapter 3, Bhavana Uppalapati initiated the work towards a simpler linchpin and obtained the initial hit for amination. I synthesized the entries for the substrate scope of the amination step and prepared the amides and ureas that illustrated the utility of the second step.

Dr. Monica Gill and Prof. André Beauchemin were consulted throughout the project, discussing results and possible new approaches that should be used.

All text, figures, schemes, and tables are original content. No artificial intelligence software was used to assist in the production or writing of this thesis.

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[1] B. Uppalapati‡, **M. A**. **Aubry**‡, Q. Wang, D. Abdelhamid, M. A. Gill, A. M. Beauchemin, Development and Applications of an Amide Linchpin Reagent. *Angew. Chem. Int. Ed.* **2024**, *64*, e202421258

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Abbreviations

^{13}C NMR	Carbon-13 nuclear magnetic resonance
^{1}H NMR	Proton nuclear magnetic resonance
Ar	Argon atmosphere
Bz	Benzoyl
$CDCl_3$	Deuterated chloroform
CH_2Cl_2	Dichloromethane
CsOAc	Cesium acetate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
dd	Doublet of doublets
Dioxane	1,4-Dioxane
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMPM	4,4-Dimethoxyphenylmethyl
DMSO	Dimethyl sulfoxide
dt	Doublet of triplets
eq. / equiv.	Equivalent(s)
Et	Ethyl
EtOAc	Ethyl acetate
g	Gram
Hz	Hertz
J	Coupling constant
Me	Methyl
MeOH	Methanol
m	Multiplet
mL	Millilitres
mmol	Millimoles
mins	Minutes
NCO	Isocyanate
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
OLG	Oxygen-leaving group
Ph	Phenyl
$PhCH_3$	Toluene
ppm	Parts per million
R	Generic substituent group

$RhCp^*Cl_2$	Pentamethylcyclopentadienyl rhodium(III) dichloride dimer
rt	Room temperature
s	Singlet
S_N1	Substitution Nucleophilic Unimolecular mechanism
S_N2	Substitution Nucleophilic Bimolecular mechanism
sp / sp^2 / sp^3	Orbital hybridization states
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TFA	Trifluoroacetic acid
TMB	1,3,5-Trimethoxybenzene
TMS	Triethylsilane

Chapter 1: Introduction

In this chapter, a review of linchpins in the literature is presented. The synthesis of isocyanates and heteroatom-based isocyanates is also reviewed. Building on this foundation, the concept of repurposing a masked O*-isocyanate reagent into an amide linchpin reagent is introduced.*

1.1Linchpin Reagents

1.1.1 Definition of a linchpin reagent

The development and application of new reagents to established chemistry have resulted in significant advances to the scientific community. Importantly, new reagents can enable different mechanistic pathways, sometimes forming the product through new bond disconnections. Linchpin reagents have been developed to facilitate the modular assembly of a variety of important substructures, such as ketones, alkenes, dienes, alkynes, arenes, acetates, and others. While the term 'linchpin' is used in the literature frequently, a set of well-defined criteria for application of the term has not emerged.

In this thesis, a 'linchpin' is defined as a small synthetic building block that enables modular synthesis by two or more selective functionalizations, such that the core of the linchpin (target functional group) remains in the product (**Figure 1**). The specific reactive sites on the core of the linchpin can be either biselectrophilic, bisnucleophilic or amphoteric in nature. Publications that refer to a building block as a linchpin, but do not fall within this definition, are not included in this literature review. Note that each scheme in this section will have the linchpin reagent and its respective synthon outlined in a blue box.

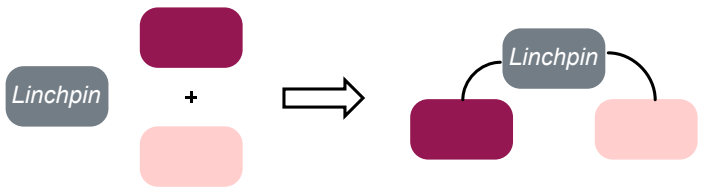

Figure 1: Linchpin concept

1.1.2 Linchpin reagents for alkenes and dienes

Metal-catalyzed cross-couplings have emerged as good reactions to construct olefin frameworks. Numerous syntheses of olefinic natural products rely on Stille, Negishi, Suzuki–Miyaura, Sonogashira or Heck cross-couplings.[2] To capitalize on this strategy, doubly functionalized olefinic building blocks (linchpins) have been designed.[3] This linchpin strategy exploits the orthogonal reactivity of distinct functional groups, enabling the selective formation of new carbon–carbon bonds under controlled conditions. By utilizing reagents and reaction conditions that interact specifically with one functional group while leaving others unreacted, this approach allows for stepwise bond construction without undesired side reactions. Such orthogonal reactivity is particularly advantageous in the synthesis of complex molecules, as it facilitates the efficient and modular assembly of molecules with high chemoselectivity.

While many of the cross-coupling strategies discussed in this section were developed prior to the introduction of the term "linchpin", they align with the definition employed in this work. Although not originally described as such, these reagents still qualify based on our definition, as they use a single reagent with two different reactive sites to form bonds in a controlled, stepwise manner.

The alkene linchpin was first introduced in 1992 with Pulido's development of a bisnucleophilic linchpin reagent, which was employed in the final step of Nicolaou's total synthesis of rapamycin in 1995.[3a,b] The macrocycle of rapamycin was closed using a remarkable double Stille coupling using the distannylethylene linchpin. (**Scheme 1**)

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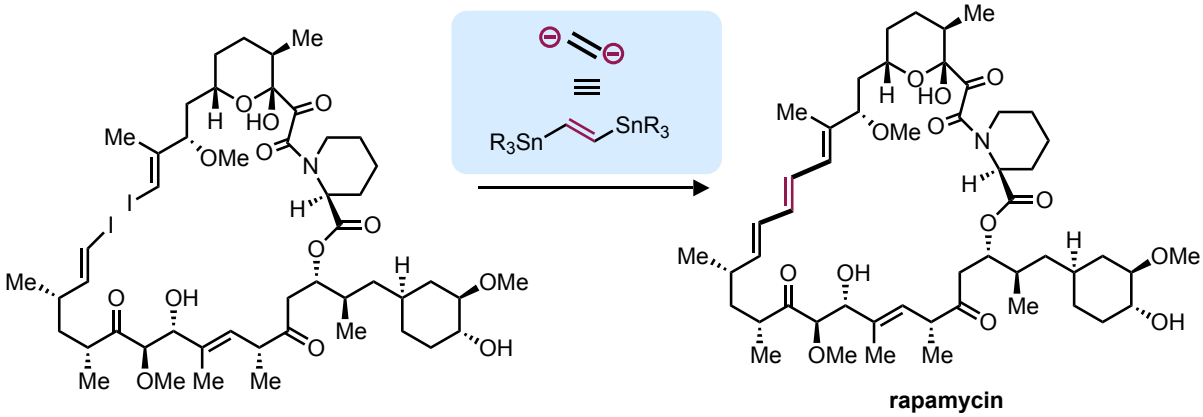
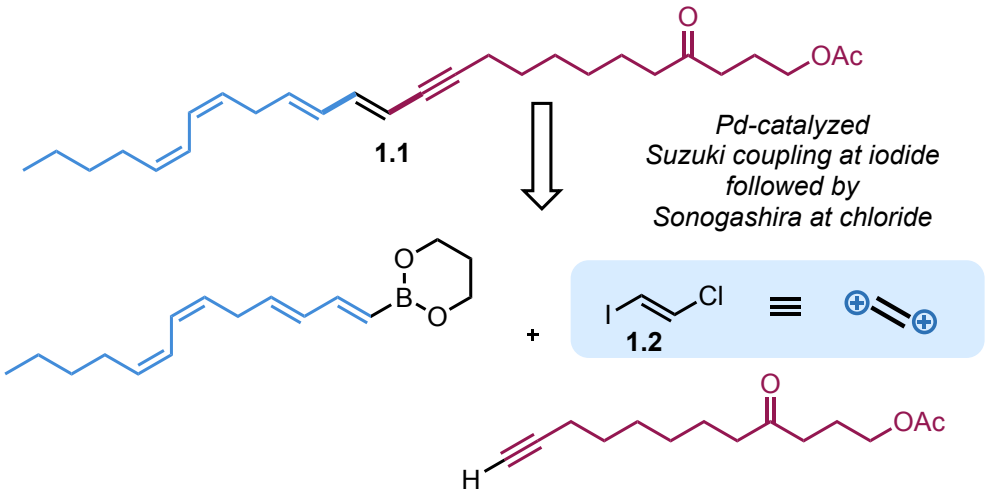
[2] M. R. Biscoe, J. Cornella, D. Kalyani, S. Neufeldt, *J. Org. Chem.* **2025**, *90*, 1234–1245.
[3] (a) A. Barbero, P. Cuadrado, I. Fleming, A. M. González, F. J. Pulido, *J. Chem. Soc., Chem. Commun.* **1992**, 351–353; (b) A. D. Piscopio, P. Bertinato, T. K. Chakraborty, N. Minowa, K. Koide, K. C. Nicolaou, *Chem. Eur. J.* **1995**, *1*, 318–333; (c) M. Alami, J.-F. Peyrat, J.-D. Brion, *Synthesis* **2000**, 1499–1515; (d) H. Ghasemi, C. Valente, M. G. Organ, *Tetrahedron* **2004**, *60*, 9453–9461.



Scheme 1: Pulido's bisnucleophilic linchpin in the synthesis of rapamycin

Later in 2004, the Organ group used a trans di-halogenated alkene under Suzuki, Sonogashira and Negishi cross-coupling conditions to obtain mono-coupled products.[3c,d] The group was interested in the effect of vicinyl olefinic halides on oxidative addition and subsequent coupling with a variety of organometallic partners. In their work for the synthesis of bupleurynol and its derivative **1.1**, they used alkene **1.2** as an alkene linchpin. (**Scheme 2**). In these reactions, other bifunctionalized alkenes did not appear to react at all and the dimer of the boronic ester was the only product isolated. This proves the utility of the linchpin approach.

A key advancement presented by this linchpin reagent is its demonstration of orthogonal reactivity, which was not observed in previous systems. For example, the bisnucleophilic tin linchpin reagent developed by Pulido lacked such reactivity, as both tin groups were chemically equivalent and therefore indistinguishable under standard coupling conditions. In contrast, Organ's linchpin contains two distinct coupling sites, enabling selective palladium-catalyzed cross-coupling reactions to occur under different reaction conditions.



Scheme 2: Organ's alkene linchpin for Pd-catalyzed cross coupling

It is important to note that the stereochemical information present in the linchpin is retained in the reaction sequence. Specifically, when a linchpin bearing the trans-alkene moiety, the reaction sequence yields the trans alkene product. At the time of writing this thesis, no linchpin for the synthesis of cis alkenes has emerged from the literature.

The use of linchpin reagents also allow a fast, modular and efficient access to polyenic chains (**Scheme 3**).[4] Various linchpin reagents exist for the synthesis of polyenes: silicon-silicon bifunctionalized dienes, boron-silicon bifunctionalized dienes, silicon-tin bifunctionalized dienes, tin-tin bifunctionalized dienes, boron-tin bifunctionalized dienes, halogen-boron bifunctionalized dienes, boron-boron bifunctionalized dienes, halogen-halogen bifunctionalized dienes, and miscellaneous other diene linchpin reagents.[5] Among these linchpins, metal-catalyzed cross-couplings emerged as reactions of choice.

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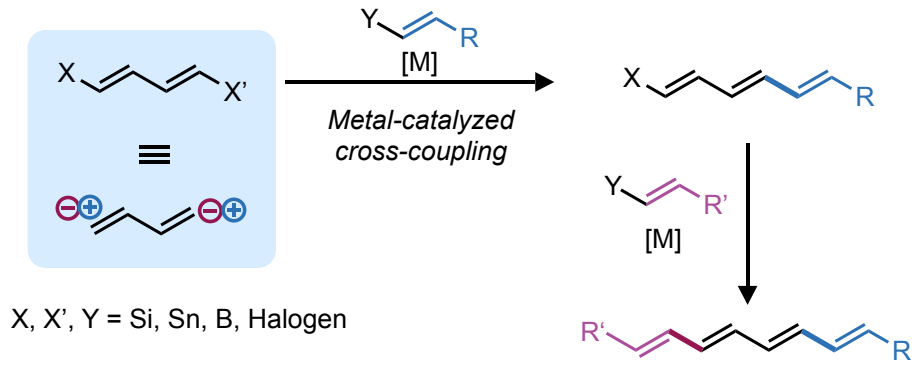
[4] B. M. Trost, H. Gholami, *J. Am. Chem. Soc.* **2018**, *140*, 11623–11626.
[5] For a review on polyene linchpins mentioned above, see: A. Rivas, A. Areal, P. Mora, R. Álvarez, A. R. de Lera, *Chem. Eur. J.* **2020**, *26*, 13543–13567 and references therein.

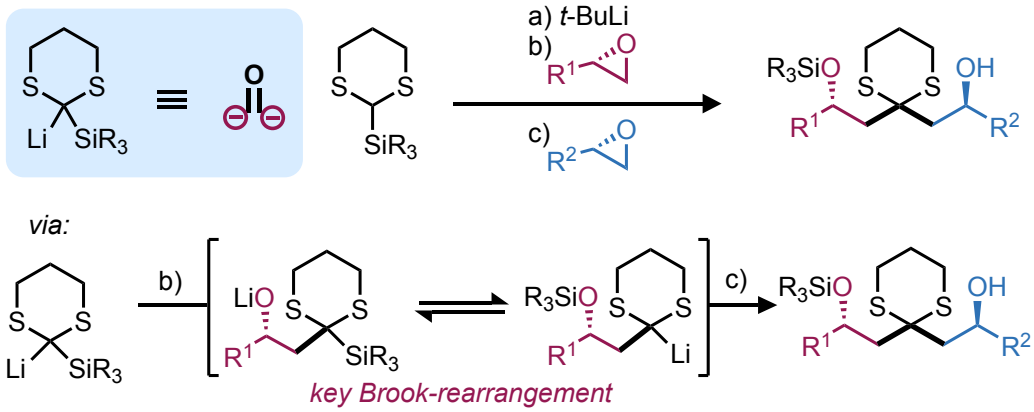


Scheme 3: Linchpin reagents in the synthesis of polyenic frameworks

1.1.3 Linchpin reagents for ketones

Ketone linchpins can either be biselectrophilic, bisnucleophilic or amphoteric in nature. For example, 1,3-dithianes can be used as linchpin reagents since these can act as masked acyl anion equivalents (bisnucleophilic). Smith's ketone linchpin describes the use of a dithiane linchpin to form various ketones by exploiting a solvent-controlled Brook rearrangement (**Scheme 4**).[6] Compatible electrophiles include terminal epoxides, epichlorohydrin, and vinyl epoxides. The advantages of this one-flask coupling protocol over the conventional stepwise addition of dithiane anions to electrophiles is the rapid, efficient, and stereo-controlled assembly of highly functionalized intermediates for complex molecule synthesis.

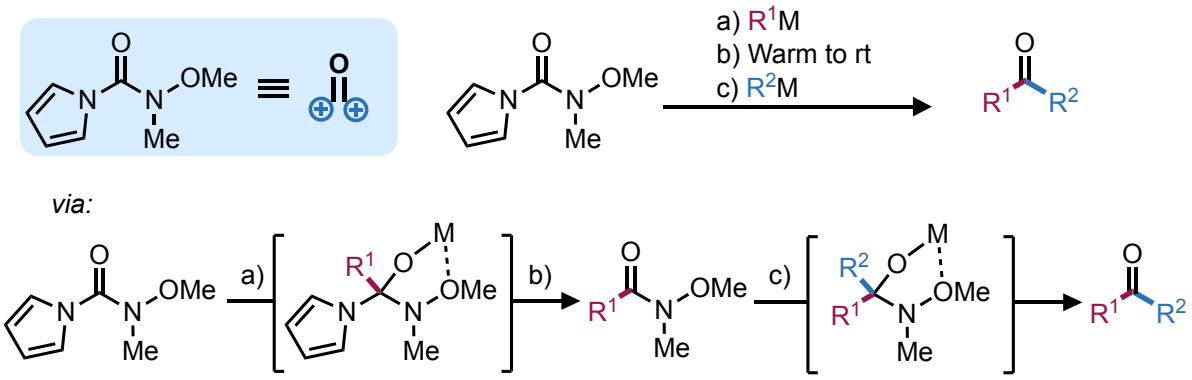
[6] (a) A. B. Smith, A. M. Boldi, *J. Am. Chem. Soc.* **1997**, *119*, 6925–6926; (b) A. B. Smith, S. M. Pitram, A. M. Boldi, M. J. Gaunt, C. Sfouggatakis, W. H. Moser, *J. Am. Chem. Soc.* **2003**, *125*, 14435–14445; (c) M. Farrell, B. Melillo, A. B. Smith III, *Angew. Chem. Int. Ed.* **2016**, *55*, 232–235.



Scheme 4: Smith's dithiane multicomponent linchpin

Alternatively, the ketone linchpin can be biselectrophilic and take advantage of the orthogonal reactivity of different leaving groups to selectively form new C-C bonds. Sarpong has developed a linchpin reagent that can generate ketones in a one-pot reaction through the use of a pyrrole-bearing carbonyl linchpin reagent (**Scheme 5**).[7] This biselectrophilic carbonyl linchpin must feature two leaving groups, each of which must generate differentially stable tetrahedral intermediates upon sequential addition of organometallic nucleophiles. Precisely, the initial reaction of the linchpin with the first nucleophile should give a tetrahedral intermediate that remains throughout the addition, but with a rate of collapse that can be modulated through reaction conditions. Following this controlled collapse, a new carbonyl electrophile (a Weinreb amide) is generated, ready for reaction with a second organometallic nucleophile. Due to the Weinreb amide chelate, persistence of the tetrahedral intermediate prevents double addition at the electrophilic carbon, conserving the ketone oxidation state and preventing the formation of a symmetrical ketone.

[7] S. T. Heller, J. N. Newton, T. Fu, R. Sarpong, *Angew. Chem. Int. Ed.* **2015**, *54*, 9839–9843.



Scheme 5: Sarpong's ketone linchpin

1.1.4 Other linchpins

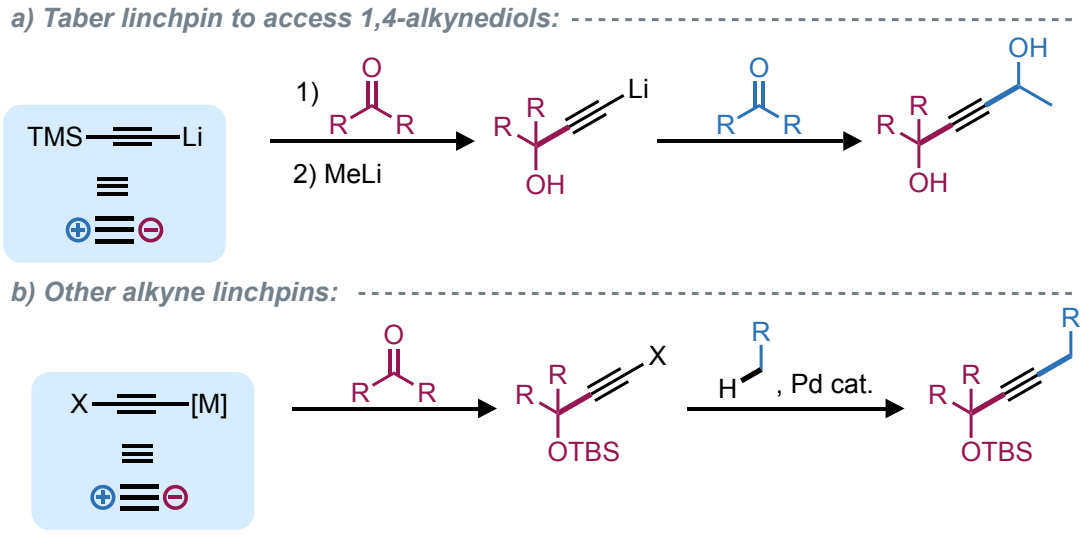
Numerous other linchpin strategies have been reported in the literature, reflecting the growing interest and rapid development in this area of synthetic chemistry. Notably, linchpins for alkyne synthesis have emerged as valuable tools, particularly for peptide–drug conjugation. Various methods are used to afford distinct alkyne motifs.

To access unsymmetrical 1,4-alkynediols, the Taber linchpin can be used by the coupling of trimethylsilylacetylene and two different aldehydes or ketones (**Scheme 6a**).[8] The dilithiated species is generated by the sequential addition of the first aldehyde or ketone to a solution of lithium trimethylsilylacetylide, followed by the addition of methyllithium, which removes the trimethylsilyl protecting group. Addition of the second aldehyde or ketone then leads to the unsymmetrical 1,4-alkynediol.

Building on this strategy, other alkyne motifs can be accessed. By covalently linking alkynes (linchpin) with ketones via a nucleophilic addition reaction then subsequently, subjecting

[8] D. F. Taber, P. H. Storck, *J. Org. Chem*. **2002**, *67*, 8273–8275.

the products to palladium-catalyzed C(sp^3)–H alkynylation (inverse Sonogashira coupling) the target alkyne products can be formed (**Scheme 6b**).[9]



Scheme 6: Alkyne linchpin strategy

Arene linchpins can be categorized as chemoselective cross coupling reagents,[10] reagents for aryne precursors[11] (**Figure 2**). The linchpins that consist of chemoselective cross coupling reagents are those with two different coupling groups that enable orthogonal reactivity. For example, there is the chemoselective cross-coupling via kinetic transmetallation[12] or haloselective reactions.[13]

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[9] (a) T. Liu, J. X. Qiao, M. A. Poss, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 10924–10927; (b) S. Porey, X. Zhang, S. Bhowmick, V. Kumar Singh, S. Guin, R. S. Paton, D. Maiti, *J. Am. Chem. Soc.* **2020**, *142*, 3762–3774.
[10] (a) J. W. B. Fyfe, N. J. Fazakerley, A. J. B. Watson, *Angew. Chem. Int. Ed.* **2017**, *56*, 1249–1253; (b) K. Lin, R. J. Wiles, C. B. Kelly, G. H. M. Davies, G. A. Molander, *ACS Catal.* **2017**, *7*, 5129–5133; (c) I. Kalvet, G. Magnin, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 1581–1585.
[11] (a) R. B. Krishna, S. H. Moncy, C. Mohan, *Org. Biomol. Chem.* **2023**, *21*, 479–488; (b) C. Arakawa, K. Kanemoto, K. Nakai, C. Wang, S. Morohashi, E. Kwon, S. Ito, N. Yoshikai, *J. Am. Chem. Soc.* **2024**, *146*, 3910–3919.
[12] W. B. Fyfe, N. J. Fazakerley, A. J. B. Watson, *Angew. Chem. Int. Ed.* **2017**, *56*, 1249–1253
[13] (a) K. Lin, R. J. Wiles, C. B. Kelly, G. H. M. Davies, G. A. Molander, *ACS Catal.* **2017**, *7*, 5129–5133; (b) I. Kalvet, G. Magnin, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 1581–1585.

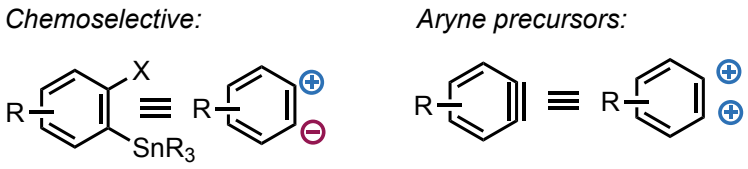

Figure 2: Arene linchpin strategies

Arynes are also effective and powerful synthetic tools for preparing functionalized arenes under mild reaction conditions. The syntheses have been classified based on the steps involved nucleophile-driven annulation reactions,[14] domino reactions,[15] and cycloaddition reactions.[16]

Arene linchpins for differing regioselectivity are also an area of interest. The Wang group utilizes site-selective C-H activation via thianthrenation to give ortho-substituted thianthrenium salts.[17] These salts can undergo various transformations such as thioetherification, sulfonation, methylation, Suzuki coupling, amination, thiocyanation, etherification, etc., giving access to a variety of substituted arenes. The linchpin developed by the Ritter group enables site-selective meta-dimethylation of the intermediate thianthrenium salt.[18]

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[14] (a) E. Yoshioka, M. Nishimura, T. Nakazawa, S. Kohtani, H. Miyabe, *J. Org. Chem*., **2015**, *80*, 8464–8469; (b) R. Samineni, P. Srihari, G. Mehta, *Org. Lett*., **2016**, *18*, 2832–2835; (c) S. Kallepu, K. Sanjeev, R. Chegondi, P. S. Mainkar, S. Chandrasekhar, *Org. Lett*., **2018**, *20*, 7121–7124; (d) Y. J. Hu, C. C. Gu, X. F. Wang, L. Min and C. C. Li, *J. Am. Chem. Soc.*, **2021**, *42*, 17862–17870; (e) B. Jiang, M. Dai, *Org. Lett.,* **2020**, *22*, 4176–4179; (f) Y.-Z. Xu, F. Sha and X.-Y. Wu, *Chem. Eur. J*., **2020**, *27*, 1066–1071; (g) A. Nilova, P. A. Sibbald, E. J. Valente, G. A. G. Montiel, H. C. Richardson, K. S. Brown, P. H. Cheong, D. R. Stuart, *Chem. Eur. J*., **2021**, *27*, 7168–7175.

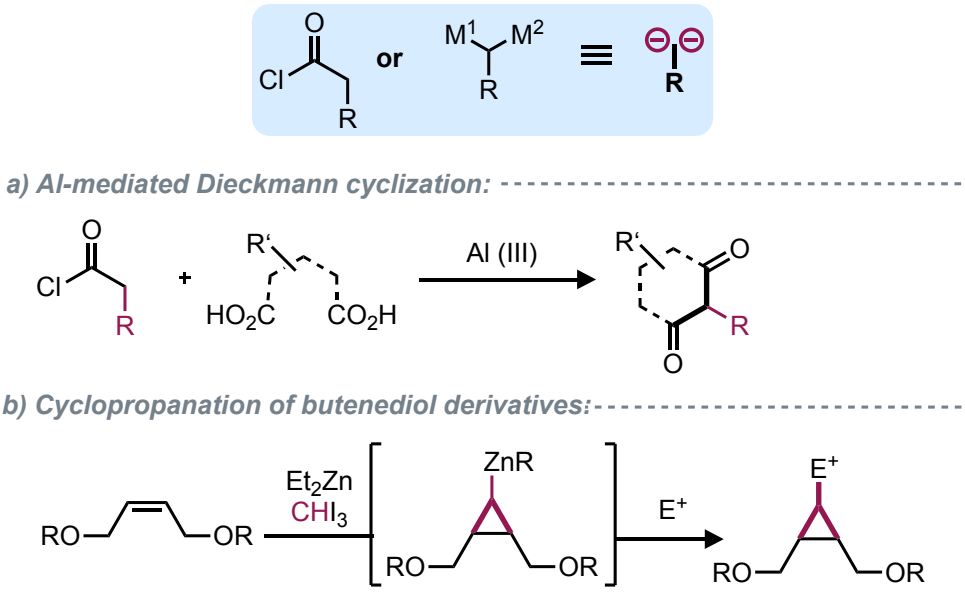
[15] (a) S. Singh, R. Samineni, P. Srihari,G. Mehta, *Tetrahedron*, **2019**, *75*, 2923–2932; (b) J. R. Hwu, A. Roy, A. Panja, W. C. Huang, Y. C. Hu, K. T. Tan, C. C. Lin, K. C. Hwang, M. H. Hsu, S. C. Tsay, *J. Org. Chem.,* **2020***, 85*, 9835–9843; (c) J. R. Hwu, A. Panja, N. K. Gupta, Y. C. Hu, K. T. Tan, C. C. Lin, K. C. Hwang, M. H. Hsu, W. C. Huang, S. C. Tsay, *Eur. J. Org. Chem*., **2020**, 683–693. (d) H. Hazarika, K. Chutia, B. Das, P. Gogoi, *New J. Chem*., **2022**, *46*, 86–96.

[16] (a) M. Neumeyer, J. Kopp, R. Brückner*, Chem. Eur. J.*, **2017**, *2017*, 2883–2915; (b) S. M. Anthony, V. Tona, Y. Zou, L. A. Morrill, J. M. Billingsley, M. Lim, Y. Tang, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.*, **2021**, *143*, 7471–7479; (c) S. Liu, P. Xie, L. Wu, J. Zhao, Z. Cai, L. He, *Org. Chem. Front*., **2022**, *9*, 1550–1555.

[17] X.-Y. Chen, Y.-N. Li, Y. Wu, J. Bai, Y. Guo, P. Wang, *J. Am. Chem. Soc.* **2023**, *145*, 10431–10440.

[18] A. Hamad, M. Mrozowicz, Y. Xie, T. Ritter, *Synlett* **2023**, *34*, A-E.

Other miscellaneous linchpins exist for a variety of uses.[19] Schindler and co-workers reported the use of acid chlorides as formal dianion linchpin reagents that enable access to cyclic 2-alkyl- and 2-acyl-1,3-alkanediones from dicarboxylic acids via an aluminum (III) mediated Dieckmann cyclization (**Scheme 7a**).[20] Alternatively, geminal dizinc carbenoids may be used as formal dianion linchpin reagents that enable the stereoselective synthesis of 1,2,3-substituted cyclopropanes (**Scheme 7b**).[21]



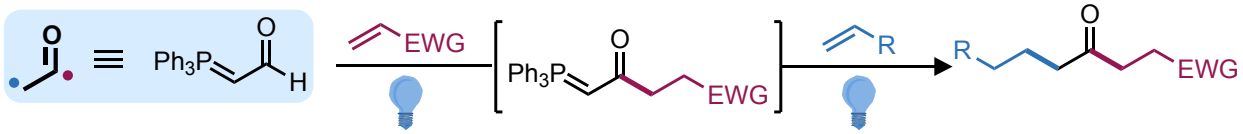
Scheme 7: Selected other linchpins

[19] Note that this is a non-exhaustive list of available linchpins and that linchpins exist for various other subunits: (a) T. Q. Davies, A. Hall, M. C. Willis, *Angew. Chem. Int. Ed.* **2017**, *56*, 14937–14941; (b) F. C. Sousa e Silva, K. Doktor, Q. Michaudel, *Org. Lett.* **2021**, *23*, 5271–5276; (c) H. D. Pickford, J. Nugent, B. Owen, J. Mousseau, R. C. Smith, E. A. Anderson, *J. Am. Chem. Soc.* **2021**, *143*, 9729–9736; (d) O. L. Garry, M. Heilmann, J. Chen, Y. Liang, X. Zhang, X. Ma, C. S. Yeung, D. J. Bennett, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2023**, *145*, 3092–3100; (e) C. R. Youshaw, M.-H. Yang, A. R. Gogoi, A. Rentería-Gómez, L. Liu, L. M. Morehead, O. Gutierrez, *Org. Lett.* **2023**, *25*, 8320–8325; (f) S. Samanta, P. Biswas, B. O'Bannon, D. C. Powers, *Angew. Chem. Int. Ed.* **2024**, e202406335; (g) N. Kranidiotis-Hisatomi, H. Yi, M. Oestreich, *Angew. Chem. Int. Ed.* **2021**, *60*, 13652–13655; (h) I. Marek, J. F. Normant, *Chem. Rev*. **1996**, *96*, 3241–3267; (i) J. D. St. Denis, Z. He, A. K. Yudin, *ACS Catal*. *2015*, *5*, 5373–5379.

[20] A. M. Armaly, S. Bar, C. S. Schindler, *Org. Lett*. **2017**, *19*, 3962-3965.

[21] A. B. Charette, A. Gagnon, J.-F. Fournier, *J. Am. Chem. Soc*. **2002**, *124*, 386– 387.

Another linchpin of note is the formyl-stabilized phosphonium ylide as a multifunctional linchpin under visible-light photoredox conditions (**Scheme 8**).[22] The method uses the ambiphilic character of the phosphonium ylide, which serves as both a nucleophilic and an electrophilic carbon-centered radical source. The stepwise and controllable generation of these radical intermediates allows sequential photocatalysis involving two mechanistically distinct radical additions, both of which are initiated by the same photocatalyst in one pot with high functional group tolerance. The methodology enables a bidirectional assembly of the linchpin with two electronically differentiated alkene fragments and thus offers rapid and modular access to 1,4-dicarbonyl compounds.



Scheme 8: Ambiphilic radical linchpin to access to 1,4-dicarbonyl compounds

While there exists a variety of linchpin reagents in the literature, there are some classes of molecules that do not have linchpin reagents for their synthesis, such as amides. To develop a new linchpin, a thorough understanding of the linchpin reagent itself must first be achieved. The following section focuses on isocyanate reagents, whose unique reactivity provides a foundation for exploring new linchpin strategies.

[22] A. Matsumoto, N. Maeda, K. Maruoka, *J. Am. Chem. Soc.* **2023**, *145*, 20344–20354.

1.2 Isocyanates

1.2.1 Carbon Isocyanates

Isocyanates are a class of molecules with a large variety of applications in the polymer, pharmaceutical, and agrochemical industries. Although isocyanates were first reported by Wurtz[23] in 1849, their widespread use did not begin until Bayer's 1937 discovery that they could undergo polymerization.[24] Since then, isocyanates have become important building blocks in several industrial scale applications such as coatings, paints, adhesives, sealants, and foams. In addition, isocyanates contribute to agrochemical and pharmaceutical industries via their use in urea, carbamate, amide, and heterocyclic syntheses (**Figure 3**).

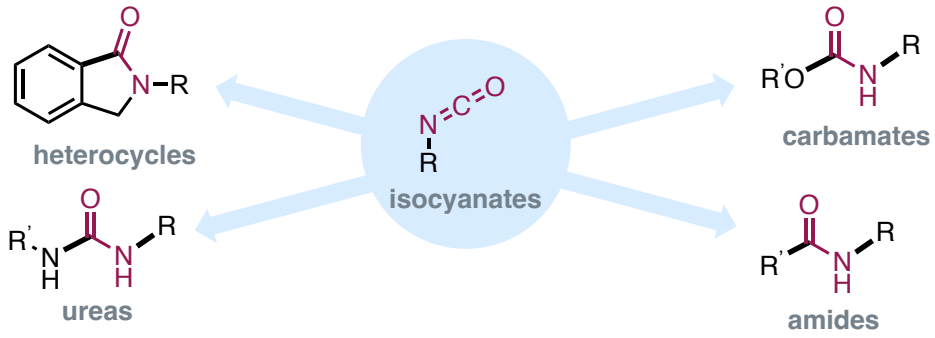


Figure 3: Isocyanate applications towards various classes of molecules

The prevalence of isocyanate reactions can be attributed to their high reactivity as electrophiles with various nucleophiles. Much of the electron density is located on the heteroatoms of the isocyanate, resulting in significant partial positive charge the carbon atom. (**Figure 4**)

[23] A. von Wurtz. *Justus Liebigs Ann. Chem.* **1849**, *71*, 326–342.
[24] O. Das. Bayer. *Angew. Chem.* **1947**, *59*, 257–272.

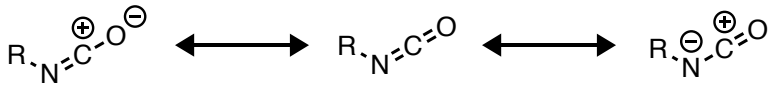
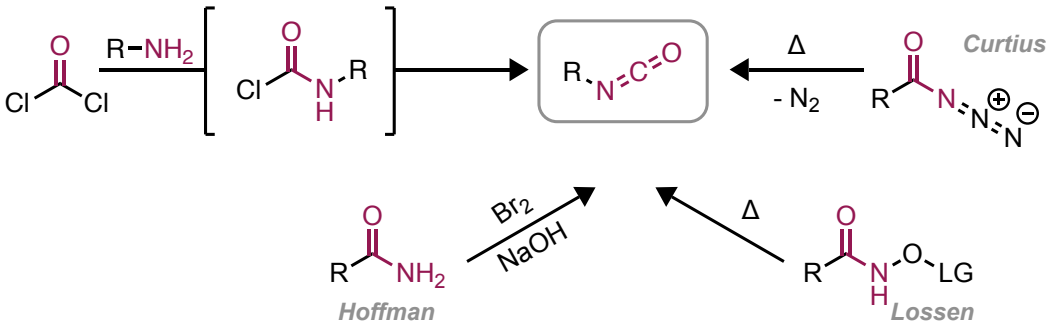


Figure 4: Isocyanate resonance structures

Various syntheses of isocyanates are reported in the literature, which can be classified according to the reaction involved. The most common method involves the reaction between an amine and phosgene and proceeds through a carbamoyl chloride intermediate. Curtius,[25] Hofmann,[26] or Lossen[27] rearrangements reactions have also been widely used. (**Scheme 9)**



Scheme 9: Common syntheses of isocyanates

The affinity of isocyanates for water, along with subsequent urea formation, require the use of anhydrous conditions.[28] Moreover, isocyanates of increasing reactivity are more prone to undergo dimerization. Aromatic isocyanates and diisocyanates can spontaneously dimerize, despite their storage at room temperature and in the absence of catalysts. Trimerization also easily occurs with both aromatic and aliphatic isocyanates, where six-membered isocyanurate structures are produced (**Scheme 10).**

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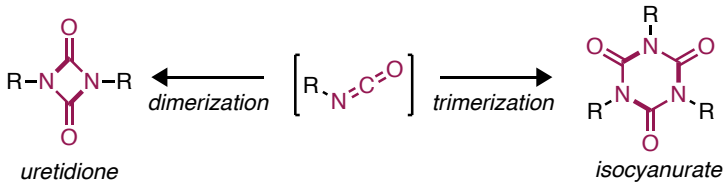
[25] A. K. Ghosh, A. Sarkar, M. Brindisi, *Org. Biomol. Chem*. **2018**, *16*, 2006–2027.
[26] E. S. Wallis, J. F. Lane*, Org. React*. **2011**, *3*, 267–306.
[27] M. Thomas, J. Alsarraf, N. Araji, I. Tranoy-Opalinski, B. Renoux, S. Papot, *Org. Biomol. Chem.* **2019***, 17*, 5420–5427.
[28] J. H. Saunders, *Chem. Rev*. **1948**, *43*, 203–218.



Scheme 10: Dimerization and trimerization of isocyanates

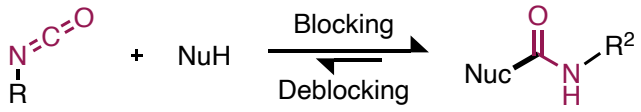
Isocyanates are also toxic reagents. Occupational exposure to methyl isocyanate, for example, can lead to asthma, acute lung damage, and bronchitis. The Bhopal disaster occurred in 1984 when approximately 45 tons of methyl isocyanate gas escaped from a plant in India, owned by a subsidiary of the U.S.-based Union Carbide Corporation, immediately killing at least 3,800 people and causing significant morbidity and premature death for many thousands more.[29] Investigations later established that substandard operating and safety procedures at the understaffed plant had led to the catastrophe.

1.2.2 Masked (Blocked) Isocyanates

Many of the issues associated with free isocyanates can be reduced with the use of masked (blocked) isocyanates. Masked isocyanates can release a free isocyanate *in situ* via a reversible deblocking reaction.[30] They can be prepared by reacting a free isocyanate with a nucleophile via a blocking reaction. Various blocking groups can be used, such as alcohols, amines and azoles. The rate of nucleophilic attack is determined by the identity of the nucleophile. For aliphatic nucleophiles with free isocyanates, the relative reaction rate is as follows, in decreasing order: primary amines, secondary amines, primary alcohols, secondary alcohols, and thiols.[31] The blocking and deblocking reactions are in equilibrium, with the equilibrium favouring the masked isocyanate (**Scheme 11**). The deblocking can be achieved using specific deblocking conditions,

[29] R. Varma, D. R. Varma, *Bull. Sci. Technol. Soc*. **2005**, *25*, 37–45.
[30] D. A. Wicks, Z. W. Wicks, *Prog. Org. Coat*. **1999**, *36*, 148–172.
[31] M. F. Sonnenschein, In Polyurethanes: Science, Technology, Markets, and Trends; *John Wiley & Sons, Inc*., **2020**.

often accomplished by heat or base, slowly releasing the free isocyanate *in situ*. It should be noted that each masked isocyanate has a specific deblocking temperature.



Scheme 11: Isocyanate blocking and deblocking equilibrium

1.2.3 Nitrogen Substituted Isocyanates

The isocyanates mentioned to date in this thesis possess a carbon substituent on the nitrogen atom, and extensive research has been conducted on these *C*-isocyanates (*C-NCO*).[32] However, nitrogen-substituted isocyanates (*N-NCO*) are much less common and have been researched much less in comparison. This gap in the literature gives the opportunity for investigation into the reactivity of free and blocked *N*-isocyanates. The *N-NCO* motif possessed by *N*-isocyanates leads to amphoteric reactivity, with an electrophilic carbon atom and a nucleophilic nitrogen atom. Due to their high reactivity, N-isocyanates are inherently unstable at room temperature and readily oligomerize at temperatures as low as –40 ºC, rendering them non-isolable and unavailable commercially.[33] Consequently, these intermediates cannot be used directly and must be generated in situ from more stable, blocked precursors. These reactive intermediates must therefore be formed *in situ* from more stable blocked precursors. In 2014, the Beauchemin group acquired spectroscopic evidence showing presence of the transient presence of an *N*-isocyanate from a masked *N*-isocyanate precursor.[34] The years of work achieved by the

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[32] J. H. Saunders, *Chem. Rev*. **1948**, *43*, 203–218.
[33] (a) R. Koch, C. Wentrup, *J. Org. Chem.* **2013**, *78*, 1802–1810; (b) M. Kurz, W. Reichen, *Tetrahedron Lett.* 1978, **19**, 1433–1436; (c) W. Reichen, *Chem. Rev.* 1978, **78**, 569–588; (d) J. F. Vincent-Rocan, A. M. Beauchemin, *Synthesis* **2016**, *48*, 3625–3645.
[34] A. Bongers, C. Clavette, W. Gan, S. I. Gorelsky, L. Betit, K. Lavergne, T. Markiewicz, P. J. Moon, N. Das Neves, N. K. Obhi, A. B. Toderian, A. M. Beauchemin, *J. Org. Chem.* **2017**, *82*, 1175–1194.

Beauchemin group[35] and various other groups[36] on *N*-isocyanates led to a significant expansion of their synthetic applicability, and warranted further exploration on oxygen-substituted isocyanates (*O-NCO*), which are even less known.

1.2.4 Oxygen Substituted Isocyanates

O-Isocyanates were first proposed in 1894 by Nef, where mercuric chloride and sodium isonitromethane were reacted to form the basic mercury salt of carbon dioxide oxime (*HO-N=C=O,* **Scheme 12a**).[37] Four years later, Jones revised the structure to a basic mercury salt of formhydroximic acid. He also reported that the reaction between ethyl ethoxycarbamate and phosphorus pentachloride resulted in the formation of the *O-Et* isocyanate, however this intermediate was not isolated and decomposed in the presence of water to give the *O*-ethylhydroxylamine hydrochloride (**Scheme 12b**).[38] Almost a decade later, more attempts were made to isolate *O*-isocyanates were made by Jones and Neuffer by enlarging the scope of the reaction to hydroxy urethanes and phosphorus pentachloride (**Scheme 12c**).[39] Various substrates

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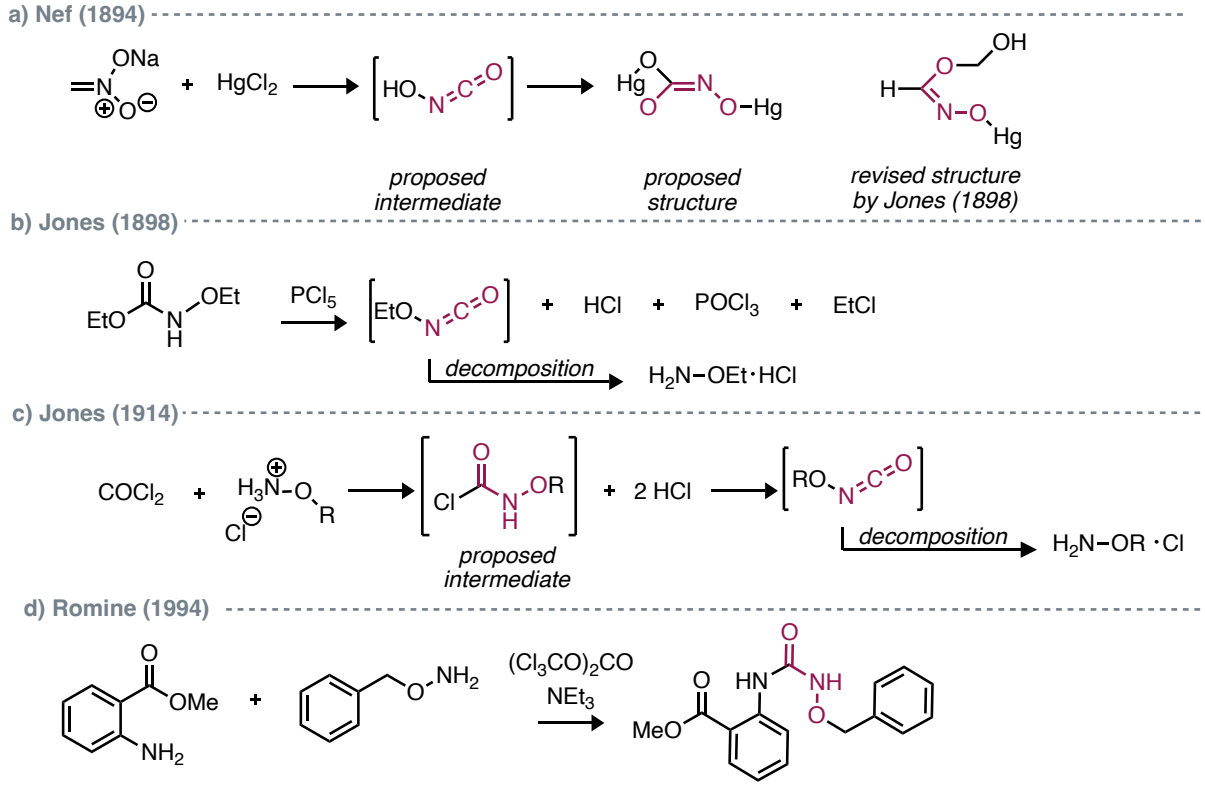
[35] J. F. Vincent-Rocan, A. M. Beauchemin*, Synthesis* **2016**, *48*, 3625–3645.
[36] (a) W. Lwowski, R. DeMauriac, T. W. Mattingly, E. Scheiffele, *Tetrahedron Lett* **1964***, 5,* 3285–3288; (b) R. Stollé, H. Nieland, M. J. Merkle, *Prakt. Chem.* **1927***, 117*, 185–210 ; (c) M. J. Busch, *J Chem Soc* **1901***, 80*, 488; (d) S. F. Acree, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3154–3158; (e) W. S. Wadsworth,; W. D. Emmons, *J. Org. Chem.* **1967***, 32*, 1279–1285.
[37] J. U. Nef, *Justus Liebigs Ann Chem* **1894**, *280*, 263–291.
[38] L. W. Jones, *J. Am. Chem. Soc*. **1898**, *20*, 1.
[39] L. W. Jones, L. Neuffer, *J. Am. Chem. Soc*. **1917**, 652.

were studied; however, all resulted in the hydrolysis of the isocyanate intermediate to the corresponding oxylamine hydrochlorides.



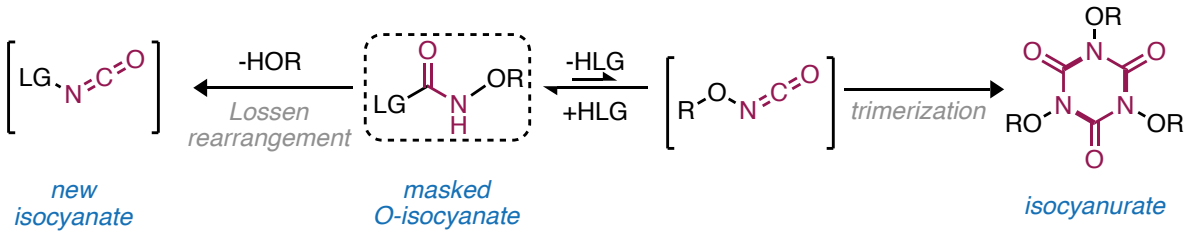
Scheme 12: First examples of *O*-isocyanates

In 1960, McKay attempted to react triethylamine, benzyloxylamine hydrochloride and phosgene to yield *O*-isocyanates, however, they only isolated the isocyanuric acid trimer, as well as a chlorination product.[40] In 1994, Romine was able to generate *N*-hydroxyureas accessed via a proposed *O*-isocyanate intermediate by revising these conditions.[41] An *O*-benzylhydroxylamine was treated with phosgene then added to a mixture of methylanthrilate and triethylamine. This method saw no evidence of trimerization or chlorination, suggesting that the reaction continued via a proposed *O*-isocyanate intermediate before reacting to give the target *N*-hydroxyurea

[40] A. F. McKay, D. L. Garmaise, G. Y. Paris, G. Gelblum, *Can. J. Chem.* **1960**, *38*, 343–358.
[41] S. W. Martin, N. A. Meanwell, J. R. Epperson, J. L. Romine, *Synthesis* **1994**, *8*, 846–850.

(**Scheme 12d**).[44] These are the first and only examples of accessing *O*-isocyanates and highlights the scarcity in their use. For years, the trimer formation was used as indirect evidence to support the formation of *O*-isocyanates. Despite the use of *O*-isocyanates to access hydroxyureas well over three decades ago, there has been little to no research on *O*-isocyanates due to their reactivity.

The *O-NCO* motif in *O*-isocyanates leads to amphoteric reactivity, with an electrophilic carbon atom and a weakly nucleophilic oxygen atom. This amphoteric character renders them more reactive than their carbon-substituted counterparts, making the use of masking groups essential for these substrates. The chemistry of *O*-isocyanates was mostly unexplored due to two known side reactions: the Lossen rearrangement of the masked isocyanate[42] and the trimerization of the free isocyanate.[43] Free *O*-isocyanates trimerize upon heating or under basic conditions to form the aromatic isocyanurate trimer, which is an irreversible process (**Scheme 13**).



Scheme 13: Side reactions of *O*-isocyanates

In contrast, masked *O*-isocyanates can also undergo the oxa-Lossen rearrangement due its weak *N-O* bond. The Lossen rearrangement (**Scheme 14a**) is characterized by the activation of an oxygen atom by an electron withdrawing group, which subsequently behaves as a leaving group. This prompts the migration of a carbon group (R) following N-H proton abstraction by a base,

[42] (a) S. Hanessian, S. J. Johnstone, *Org. Chem.* **1999**, *64*, 5896–5903; (b) S. Fioravanti, F. Marchetti, A. Morreale, L. Pellacani, P. A. Tardella, *Org. Lett.* **2003**, 5, 1019–1021; (c) J. G. Krause, B. D. Leskiw, M. L. Emery, M. E. McGahan, M. P. McCourt, R Priefer, *Tetrahedron Lett.* **2010**, 51, 3568–3570; (d) T. Baburaj, S. Thambidurai, *Tetrahedron Lett*. **2014**, *55*, 561–563; (e) T. Baburaj, S. Thambidurai, S. *Synlett* **2015**, *26*, 1137.

resulting in the formation of an isocyanate product.[43] This isocyanate product can subsequently react with any nucleophile in the system, resulting in the formation of many potential side-products.

Scheme 14: General reaction mechanism for the Lossen rearrangements

Heteroatom migration in Lossen rearrangements is relatively rare in the literature, however, has been reported as an undesired side reaction (**Scheme 14b**). Research groups have observed the unexpected formation of oxa-Lossen rearrangement products (oxygen-group migration) during attempts to perform electrophilic amination using bis-protected hydroxylamines.[45] In addition, the Beauchemin group recently conducted a study on the aza-Lossen rearrangement (nitrogen-group migration), using *N*-hydroxyureas as precursors.[44]

The strength of the N–O bond in masked *O*-isocyanates is closely tied to the leaving group ability of the oxygen substituent (OLG). As shown in **Figure 5**, when OLG is a poor leaving group (e.g., –OH or –OMe), the N–O bond is stronger, resulting in greater stability and reduced reactivity. Alternatively, when OLG is a good leaving group (e.g., –OBz or –OPiv), the N–O bond becomes weaker, increasing the compound's reactivity. The better leaving groups stabilize the negative

[43] (a) W. Lossen, *Liebigs Ann.* **1894**, 281, 169–305; (b) W. Lossen, *Liebigs Ann.* **1877**, 186, 1–74; (c) W. Lossen, *Liebigs Ann.* **1875**, 175, 271–304.
[44] D. E. Polat, D. D. Brzezinski, A. M. Beauchemin, *Org. Lett.* **2019**, *21*, 4849–4852.

charge upon departure more effectively, thereby weakening the adjacent N–O bond and facilitating rearrangement or cleavage processes.

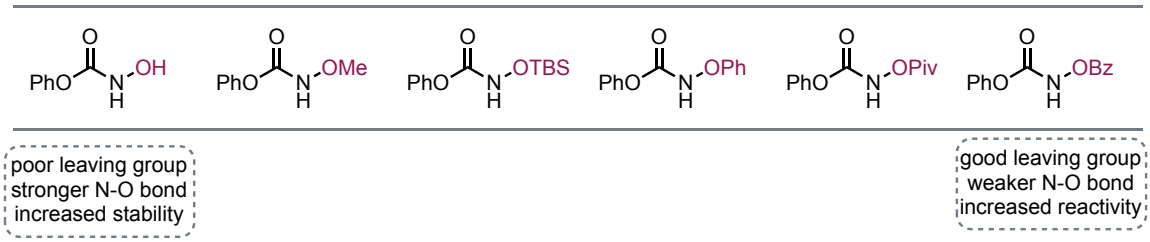


Figure 5: Various OLG groups for masked O-isocyanates

In synthetic work reported since 2017, the Beauchemin group demonstrated that *O*-isocyanates can be formed *in situ* from masked isocyanates, and used this approach in cascade reactions forming heterocycles,[45] and in alkene cycloaddition reactions.[46] The masked *O*-isocyanate molecule is a biselectrophile, with electrophilic centers at the carbonyl and the nitrogen of the molecule due to its weak *N-O* bond (**Figure 6**). These characteristics allow the molecule to have an opportunity for orthogonal reactivity.

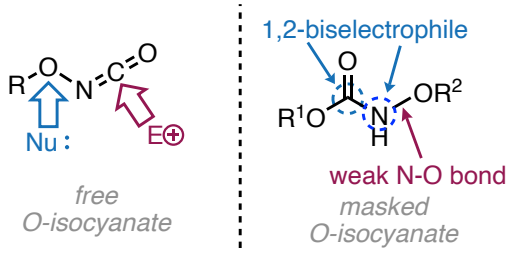


Figure 6: Amphoterism and biselectrophilicity of *O*-isocyanates

Armed with an understanding of the reactivity of isocyanates, the use of isocyanates in amide synthesis will now be presented, as well as a general overview on amide synthesis.

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[45] (a) R. A. Ivanovich, D. E. Polat, A. M. Beauchemin, *Adv. Synth. Catal.* **2017**, *359*, 4289–4293; (b) Q. Wang, J. An, H. Alper, W. J. Xiao, A. M. Beauchemin, *Chemical Communications* **2017**, *53*, 13055–13058; (c) M. A. Allen, R. A. Ivanovich, D. E. Polat, A. M. Beauchemin, *Org. Lett.* **2017**, *19*, 6574–6577.
[46] M. A. Allen, R. A. Ivanovich, A. M. Beauchemin, *Angew. Chem. Int. Ed.* **2020**, *59*, 23188–23197.

1.3 Amide Synthesis

1.3.1 Importance of Amides

Amide bond formation has been at the forefront of chemical synthesis for many decades, with amides being one of the most common subunits in pharmaceuticals and agrochemicals. The NCO subunit is ubiquitous in acyclic and cyclic bioactive molecules. Arguably, amides are the most important functional group containing this motif.[47] In fact, amides comprise ~38% of the top 200 small molecule drugs by retail sales.[48] Indeed, the frequency of amide bond construction in research facilities has doubled in the last 30 years and the reaction accounts for 1/6 reactions in pharmaceutical contexts.[49] Therefore, new reagents, reactions, and approaches to synthesize amides have steadily emerged to efficiently form a broad range of structures.[50] Among the reactions to form amides, C-C and C-N bond forming reactions account for approximately 30% of reactions in larger-scale drug candidate synthesis in the last 17 years.[51]

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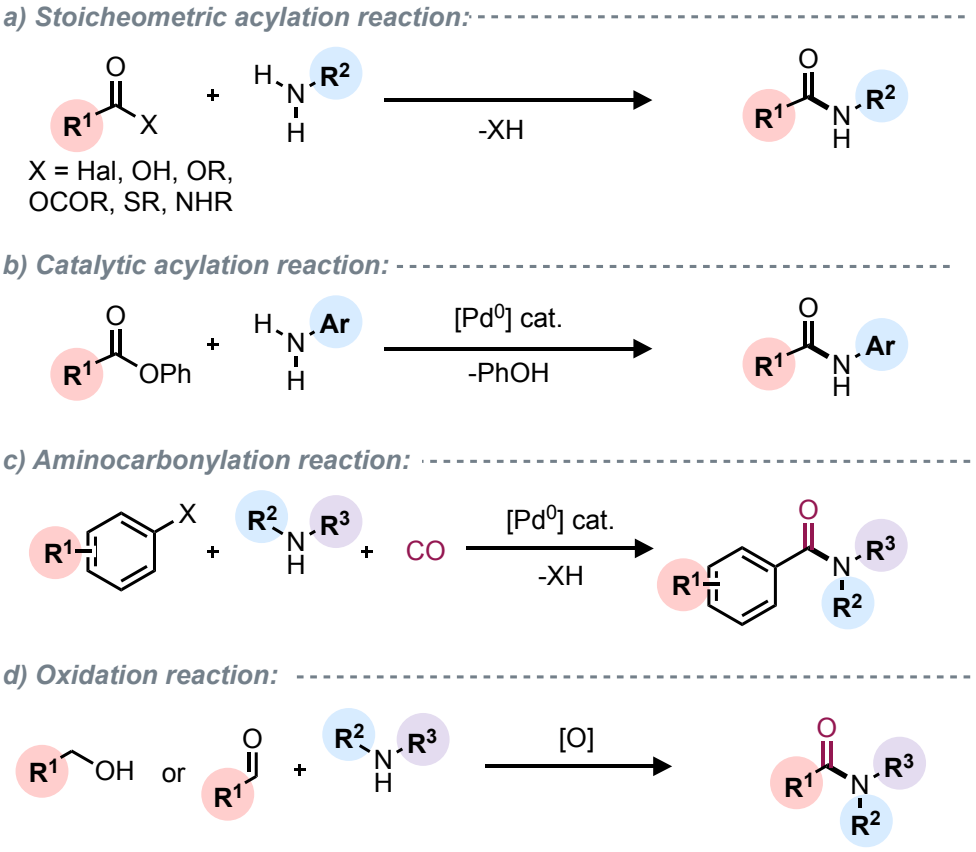
[47] (a) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; (b) D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443–4458.
[48] The number of amides was estimated building on studies of the top 200 small molecule drugs from 2018-2022. See N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Ed.* **2010**, *87*, 1348–1349.
[49] (a) D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443–4458; (b) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451–3479.
[50] (a) W. Muramatsu, T. Hattori, H. Yamamoto, *Chem. Commun.* **2021**, *57*, 6346–6359; (b) H. Lundberg, F. Tinnis, N. Selander, H. Adolfsson, *Chem. Soc. Rev.* **2014**, *43*, 2714–2742; (c) E. Massolo, M. Pirola, M. Benaglia, *Eur. J. Org. Chem.* **2020**, 4641–4651; (d) A. de la Torre, V. Tona, N. Maulide, *Angew. Chem. Int. Ed.* **2017**, *56*, 12416-12423.
[51] R. W. Dugger, J. A. Ragan, D. H. B. Ripin, *Org. Process Res. Dev.* **2005**, *9*, 253-258

1.3.2 Methods towards amide synthesis



Scheme 15: Approaches towards amide synthesis using C-N bond disconnection

The most common method towards amide synthesis uses the C-N bond disconnection, accessed via acylation chemistry (**Scheme 15a**).[52] Classic approaches utilize acid chlorides, acid anhydrides, and activated esters, as well as modern coupling reagents such as carbodiimides (DCC, EDC) or uronium salts (HATU, PyBOP). These methods rely on converting the carboxylic acid into a more reactive species that can efficiently condense with the nucleophilic amine. This transformation becomes problematic when synthesizing tertiary amides or hindered secondary amides due to weak nucleophilicity of the amine and/or steric hindrance at the electrophile. In

[52] (a) E. Serrano, R. Martin, *Eur. J. Org. Chem.* **2018**, *24*, 3051–3064; (b) T. Ben Halima, J. K. Vandavasi, M. Shkoor, S. G. Newman, *ACS Catal.* **2017**, *7*, 2176−2180.

recent years, several catalytic methods towards amides have been reported (**Scheme 15b**). One such method is the palladium catalyzed coupling of unactivated esters with anilines.[52b] Another approach involves aminocarbonylation, where amides are formed via transition metal-catalyzed carbonylation of aryl or alkyl halides in the presence of amines and carbon monoxide (**Scheme 15c**).[53] This approach is useful for assembling amides that are challenging to access through direct acylation, as it enables the incorporation of carbonyl groups into diverse molecular frameworks in a single step.

In addition, oxidative strategies have emerged as powerful alternatives to classical amide formation reactions. In these methods, aldehydes or alcohols react with amines to form imines or hemiaminals, which are subsequently oxidized to amides using mild oxidants such as TEMPO, TBHP, NBS, or transition metal catalysts.[54] These transformations allow for one-pot syntheses under relatively mild conditions and can avoid the need to pre-activate carboxylic acids. While many approaches for amide synthesis already exist, there is a continued demand for new synthetic methods, especially those forming amides without constructing the *N—C=O* amide bond.

The C-C bond disconnection is not as common when it comes to amide synthesis (**Scheme 16a**). In 2012, Bode and co-workers demonstrated that large and hindered amides could be formed from the addition of aryl and alkyl Grignard reagents to isocyanates using this disconnection.[55] Miura also showed that boronic acids could couple with isocyanates to form the new C-C bond via rhodium(I) catalysis.[56] These examples show the possibility of using blocked isocyanates as

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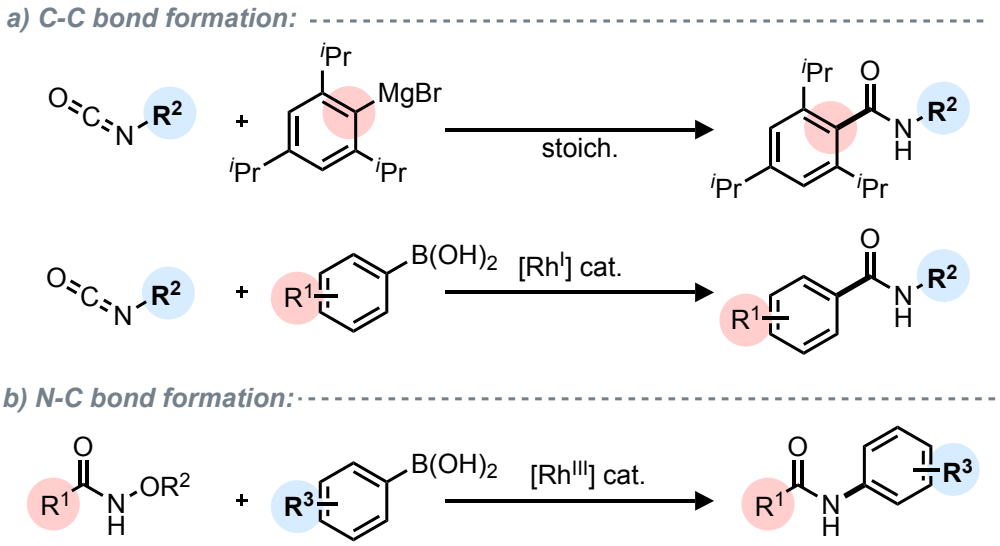
[53] A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114-4116.
[54] (a) S. B. Ghosh, J. S. Y. Ngiam, A. M. Seayad, D. T. Tuan, C. L. L. Chai, A. Chen, *J. Org. Chem.* **2012***, 77*, 8007–8015; (b) B. L. Ryland, S. S. Stahl, Angew. *Chem. Int. Ed.* **2014,** *53,* 8824-8838 and references therein.
[55] G. Schäfer, C. Matthey, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 9173–9175.
[56] T. Miura, Y. Takahashi, M. Murakami, *Chem. Comm.* **2007**, 3577-3579.

reagents towards amide synthesis. In a later publication, Miura developed conditions to achieve amides through N-C bond formation (**Scheme 16b**).[57] This transformation occurs from the rhodium(III) catalyzed amination of hydroxamic esters.



Scheme 16: Approaches towards amide synthesis using atypical bond construction

While the respective C-C and N-C bond forming reactions exist, to our knowledge, an amide linchpin reagent has not been reported among the potential building blocks that could enable amide synthesis. This absence presents a significant opportunity given the prevalence of amides in biologically active molecules, pharmaceuticals, and materials. The development of a linchpin that allows for the efficient and selective construction of amides would fill a clear gap in synthetic methodology. Such a reagent could streamline access to amide-containing structures and open new avenues for diversification in medicinal and synthetic chemistry.

While amides are the target products of an amide linchpin reagent, the focus of this work is not on the amides themselves, but rather on the design, reactivity, and utility of the linchpin

[57] T. Yasuhisa, K. Hirano, M. Miura, *Chem. Lett.* **2017**, *46*, 463–465.

reagents that enable their construction. By understanding and optimizing these reagents, this research aimed to create versatile and broadly applicable tools for synthetic chemistry, facilitating access to a wide range of NCO-containing molecules. This approach emphasizes the reagent as the key innovation, utilizing amide formation as a demonstration of the linchpin's potential rather than the primary target.

1.4 Research Hypotheses and Goals

We hypothesize that a masked *O*-isocyanate with optimized leaving groups (OR^1 and OR^2) could serve as an amide linchpin reagent. This approach could potentially overcome the limitations of traditional amide synthesis. For example, the use of alternative building blocks in which the C−N bond is already present can be a remarkably efficient alternative strategy.[58]

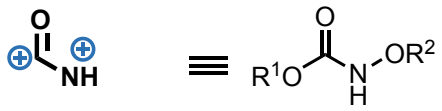
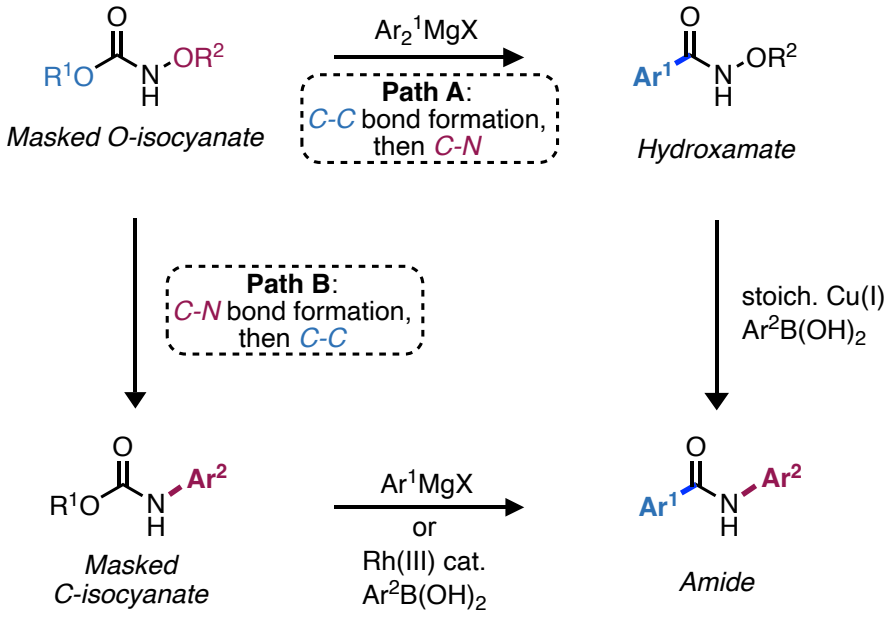


Figure 7: Masked *O*-isocyanate as linchpin contender

This hypothesis builds on previous work in the Beauchemin lab, with the development of bench-stable masked *O*-isocyanates, which allow for the slow release of free isocyanates *in situ*. It is anticipated that the *C(=O)-OR*^{1} and *N-OR*^{2} bonds can undergo sequential reactions to form various amides, provided chemoselectivity can be achieved. The biselectrophilicity of masked *O*-isocyanate reagents such as **1** imparts unique reactivity, making them attractive as linchpin contenders (**Figure 7**).

[58] R. M. De Figueiredo, J. S. Suppo, J. M. Campagne, *Chem. Rev.* **2016**, *116*, 12029–12122.



Scheme 17: Multi-pathway strategy towards functionalized amides

To develop appropriate orthogonal reactivity, the leaving groups must be optimized, then the chemoselectivity of the respective bond-forming reactions must be assessed. Having two suggested bond formation paths provides a risk minimization strategy to maximize applicability (**Scheme 17**).

Path A is the *C-O* bond functionalization reaction to form hydroxamates, followed by the *N-O* bond cleavage to form amides. This suggested route employed the use of Grignard reagents for the first reaction, followed by copper-mediated electrophilic amination.[59] This route, attempted by Dr. Alshimaa Mohammed and Ph.D candidate Bhavana Uppalapati, worked well for forming hydroxamates, but the subsequent amination reaction was not amenable to amide formation due to high reactivity of hydroxamates. Side reactions observed included urea hydrolysis, isocyanate trimerization, boronic acid homo-coupling and the Lossen rearrangement.

[59] Z. Zhang, L. S. Liebeskind, *Org. Lett*. **2008**, *10*, 3005-3008.

Wherein Path A suggested *C*-*O* bond cleavage followed by *N*-*O* bond cleavage, Path B suggested the reverse process. Various methods could enable the C-C bond formation step from masked *C*-isocyanate products.[60] Previous work within the Beauchemin lab had already achieved the C-C bond formation reaction through rhodium catalysis.[60a] Synthesis of amides was achieved through rhodium catalyzed coupling of boroxines with masked isocyanates. This reaction was made possible due to the ability to form both the isocyanate and the organorhodium intermediates *in situ* and at low concentration. Results demonstrated broad functional group tolerance, including protic nucleophilic groups such as amines, anilines, and alcohols. Alternatively, some literature reports showed the compatibility of isocyanates with Grignard reagents.[60b-j] Thus, only the *N*-*O* bond functionalization reaction had to be developed for Path B to synthesize amides. Upon starting my MSc with the Beauchemin group, my project focused on exploring the N-O bond functionalization for Path B.

Ultimately, the goal of the linchpin project was to find an appropriate amide linchpin reagent to synthesize large and hindered amides. To do this, the optimal linchpin and reaction conditions were determined. Subsequently, the orthogonal reactivity of the linchpin were evaluated in a one-pot synthesis. Different, inexpensive catalyst systems were also explored. If linear amide and lactam formation was successful, the substrate scope would be broadened to generalize the linchpin strategy towards other *NCO*-containing subunits. Limitations could be addressed in a second-generation amide linchpin reagent with different polarity synthons.

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[60] (a) J. S. Derasp, A. M. Beauchemin, *ACS Catal.* **2019**, *9*, 8104-8109; (b) G. Schäfer, C. Matthey, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 9173-9175; (c) H. M. Singleton, W. R. Edwards, Jr., *J. Am. Soc. Chem.* **1938**, *60*, 540-544; (d) L. Field, J. E. Lawson, J. W. McFarland, *J. Am. Chem. Soc.* **1956**, *78*, 4389-4394; (e) J. W. McFarland, R. L. Harris, *J. Org. Chem.* **1967**, *32,* 1273 -1274; (f) K. A. Parker, E. G. Gibbons, *Tetrahedron Lett.* **1975**, *16*, 981 – 984; (g) Y. Zhang, J. Jiang, Y. Chen, *Tetrahedron Lett.* **1987**, *28*, 3815-3816; (h) I. Stefanuti, S. A. Smith, R. J. K. Taylor, *Tetrahedron Lett.* **2000**, *41,* 3735-3738; (i) A. Padwa, K. R. Crawford, P. Rashatasakhon, M. Rose, *J. Org. Chem.* **2003**, *68*, 2609-2617; (j) M. I. Antczak, J. M. Ready, *Chem. Sci.* **2012**, *3*, 1450-1454.

Chapter 2: Developments and Applications of an NCO Linchpin

In Chapter 2, the development and validation of the first amide linchpin reagent and its use as a doubly electrophilic building block for the synthesis of a variety of NCO-containing molecules is demonstrated. This chapter is based on the manuscript published in Angewandte Chemie International Edition, in which Maxime Anna Aubry is the co-first author.

Citation: B. Uppalapati‡, **M. A**. **Aubry**‡, Q. Wang, D. Abdelhamid, M. A. Gill, A. M. Beauchemin, Development and Applications of an Amide Linchpin Reagent. *Angew. Chem. Int. Ed.* **2025**, *64*, e202421258.

‡Authors contributed equally.

The general context for the contributions presented in this Chapter is provided in the statement of contributions. Specifically, **MAA** performed most of the work on the amination reaction (section 2.2), including the optimization for **Table 3** in **Section 2.2**; while **BU** performed the optimizations for **Table 1, Table 2** and **Table 4**. **MAA** synthesized all substrates in **Section 2.2** with exception of the ene-carbamates (**2.3.27-29**) and carbamate **2.3.11**, which were synthesized by **BU**. **BU** work focusing on the C-C bond formation, forming amides and lactams is presented for context only. **BU** synthesized all products in **Section 2.3** and the lactam formation section (**Section 2.4.1**). **MAA** synthesized all urea products (**Section 2.4.2**), with exception of the ene-urea **2.9.5**, synthesized by **BU**. **MAA** and **BU** wrote the paper together.

2.1 Introduction

To our knowledge, an amide linchpin reagent had not been reported among the potential building blocks that could enable amide synthesis. This is surprising, as linchpin reagents have been developed to facilitate the modular assembly of a variety of important substructures, seen in the previous chapter.

Initially, we hypothesized that a suitable masked *O*-isocyanate linchpin reagent possessing the appropriate orthogonality for a chemoselective bond-forming sequence could be engineered (**Figure 8**). This reagent would require a finely tuned N-O bond to allow for efficient electrophilic amination reactions,[61] and a substituent on the carbonyl with sufficient leaving group ability to enable mild C-C bond formation.

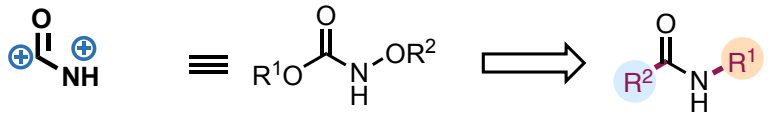

Figure 8: Use of masked O-isocyanate as amide linchpin reagent

As with other linchpin reagents, both the type of nucleophile and the order in which the linchpin is functionalized could impact the efficiency of the overall amide synthesis. Previous student Dr. Alshimaa Mohammed and PhD candidate Bhavana Uppalapati began with the evaluation of several potential reagents, varying the leaving groups at each electrophilic site. These research results provided key insights that ultimately led to the work presented in this thesis. For example, path A was challenging due to reactivity issues associated with both steps. In Step 1 of **Scheme 18a**, general lack of reactivity of the linchpin reagent was observed, typically requiring heating observe the desired C-C bond forming reactivity.[62] However, side reactions occur with weak N-O bond, requiring the use of more stable reagents. The use of a stronger N-O bond for Step 1, however, enabled difficulties in Step 2, where the amination step faces important limitations if stable OR^2 groups are used.

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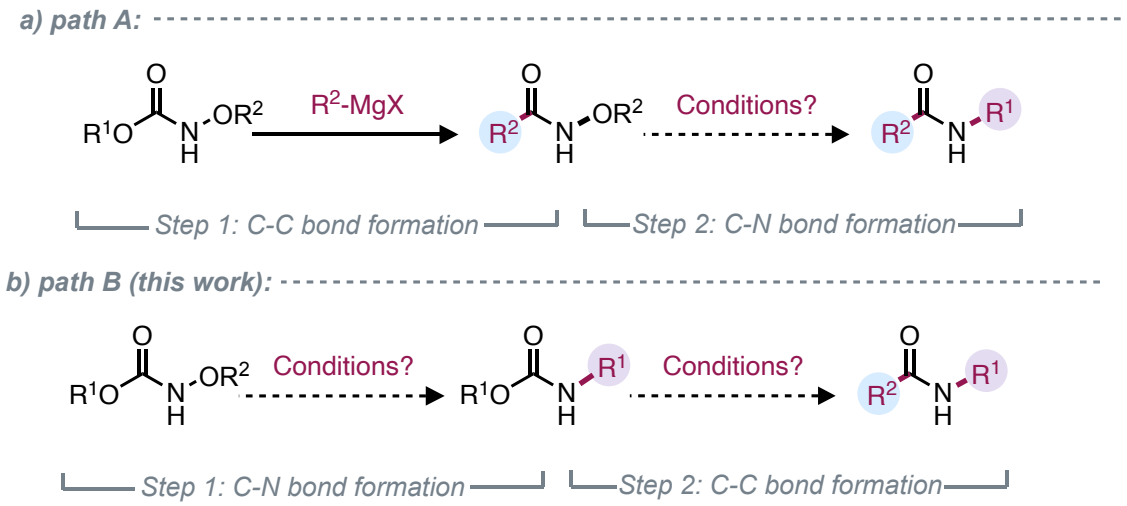
[61] (a) Z. Ma, Z. Zhou, L. Kürti, *Angew. Chem. Int. Ed.* **2017**, *129*, 10018–10022; (b) L. G. O'Neil, J. F. Bower, *Angew. Chem. Int. Ed.* **2021**, *60*, 25640–25666; (c) V. C. M. Gasser, S. Makai, B. Morandi, *Chem. Commun.* **2022**, *58*, 9991–10003. (d) K. Hirano, M. Miura, *J. Am. Chem. Soc.* **2022**, *144*, 648-661.

[62] A. Mohammed, New Reactivity of Masked Isocyanates with Organometallic Reagents. Ph.D. Dissertation, University of Ottawa, Ottawa, **2024**.

This work, along with the promising results obtained with catalytic amination reactions using N-O bond-containing reagents,[63] oriented the subsequent reagent and optimization efforts for the first step of the sequence (**Scheme 18b, Step 1**). A balance between stability and reactivity had to be established to ensure optimal amination reactivity (via N-O bond cleavage) while preventing undesired side reactions (e.g. isocyanate formation).

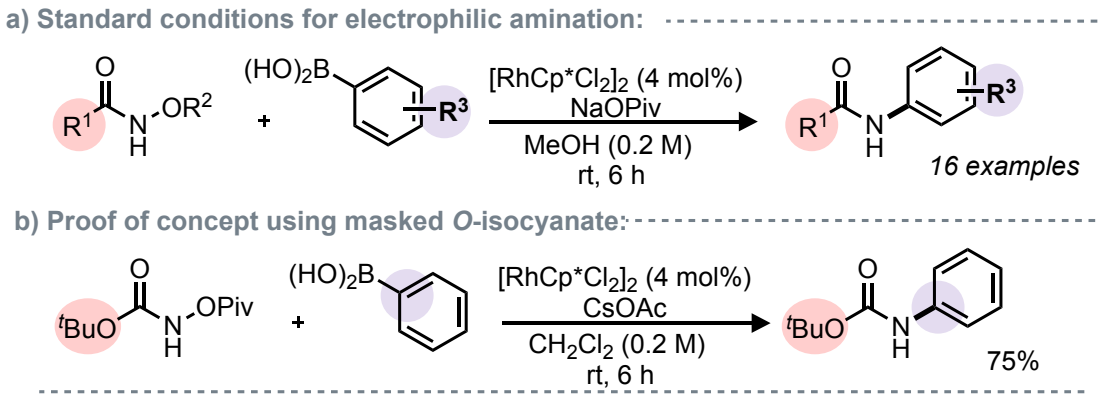


Scheme 18: Potential reaction sequences towards amides

2.2 C-N Bond Formation

Initial conditions were adapted from Hirano and Miura's electrophilic amination of boronic acids using more stable esters of hydroxamic acids (**Scheme 19a**).[57] In the paper, the scope of compatible hydroxylamines was briefly explored and one example is shown to demonstrate compatibility with masked *O*-isocyanates (**Scheme 19b**).

[63] X. Dong, Q. Liu, Y. Dong, H. Liu, *Chem. Eur. J.* **2017**, *23*, 2481–2511.



Scheme 19: Miura's amination conditions & proof of concept using masked *O*-isocyanates

To begin, the masked *O*-isocyanate reagent was optimized, with conditions using 2 mol% of commercially available $[RhCp^*Cl_2]_2$ and 1.0 equiv. of NaOAc in THF at 40 °C.

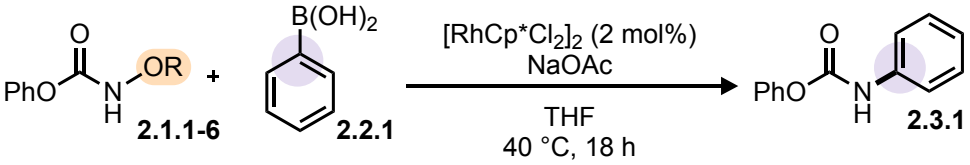


Table 1: Determination of amination reactivity of potential linchpin reagents

Entry	Linchpin Reagent	Yield of 2.3.1 (%)[b]
1	2.1.1: R = H	0
2	2.1.2: R = Me	0
3	2.1.3: R = TBS	0
4	2.1.4: R = Ph	0
5	2.1.5: R = Piv	99
6	**2.1.6: R = Bz**	**99**

[a] Reaction conditions: Masked *O*-isocyanate **2.1.6** (0.10 mmol, 1.00 equiv.), boronic acid **2.2.1** (0.12 mmol, 1.20 equiv.), $[RhCp^*Cl_2]_2$ (2 mol%), NaOAc (0.10 mmol, 1.20 equiv.), THF (0.5 mL, 0.2 M), Ar atmosphere, 18 h. [b] Yield of **2.3.1** was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard.

The weakness of the N-O bond is dependent on the leaving group ability of the O-LG group. A screen of leaving groups was performed by **B. Uppalapati** (**Table 1**). The entries in **Table 1** are ranked in order of increasing leaving group ability, where entries 1-4 did not show any reactivity under the reaction conditions. The leaving group ability in these entries are poor, resulting in a stronger N-O bond. In contrast, the more activated substrates in entries 5-6 afforded the desired product **2.3.1** in quantitative yields. The reagent **2.1.6** possessing a phenol blocking (masking) group and a benzoyl leaving group (entry 6) was obtained in a practical, cost-effective synthesis from hydroxylamine hydrochloride, and proved to be the most versatile and stable reagent. [64]

[64] A sample of linchpin reagent **2.1.6** has been stored on bench top under air at ambient temperature for >1 year with no observable degradation or change in quality as per NMR analysis.

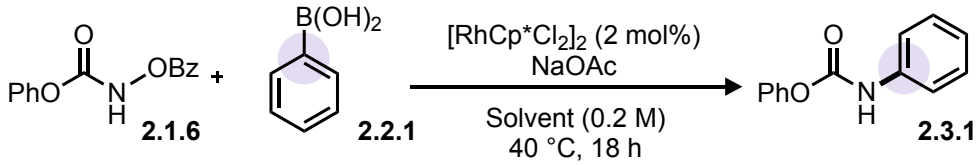


Table 2: Optimization of solvent

Entry	Solvent	Yield of 3a (%)[b]
1	CH_3OH	96
2	DMF	0
3	DMSO	0
4	CH_3CN	92
5	$PhCH_3$	99
6	Dioxane	82
7	**THF**	**99**
8	CH_2Cl_2	85

[a] Reaction conditions: Linchpin reagent **2.1.6** (0.10 mmol, 1.00 equiv.), boronic acid **2.2.1** (0.12 mmol, 1.20 equiv.), $[RhCp^*Cl_2]_2$ (2 mol%), NaOAc (0.10 mmol, 1.20 equiv.), solvent (0.5 mL, 0.2 M), 40 °C, Ar atmosphere, 18 h. [b] Yield of **2.3.1** was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard.

A screen of solvents was performed by **B. Uppalapati** (**Table 2**). The amination reaction generally proved efficient despite several changes to the optimal reaction conditions. A solvent screen determined that polar, nonpolar, and halogenated solvents performed well, with only DMF and DMSO resulting in a complete shutdown of the reactivity. Tetrahydrofuran was selected as the optimal solvent since it gave the highest yield and was easy to remove during purification.

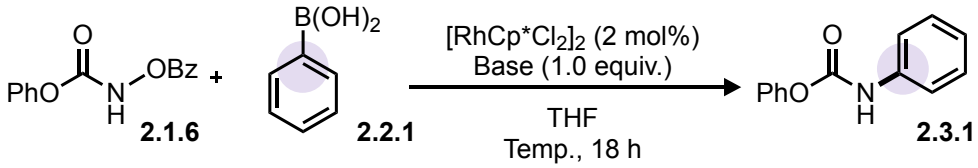


Table 3: Optimization of base, concentration and temperature

Entry	Base	Concentration (M)	Temperature (°C)	Yield of 3a (%)[b]
1	NaOAc	0.2	rt	99
2	NaOAc	0.2	40	99
3	NaOAc	0.2	66	97[d]
4	NaOBz	0.2	40	83
5	CsOAc	0.2	40	90
6	NEt_3	0.2	40	95
7	None	0.2	40	0
8	NaOAc	0.5	40	49[e]
9	NaOAc	0.1	40	92[c]
10	NaOAc	0.05	40	27[c]
11	NaOAc	0.2	40	96[d]

[a] Reaction conditions: Linchpin reagent **2.1.6** (0.10 mmol, 1.00 equiv.), boronic acid **2.2.1** (0.12 mmol, 1.20 equiv.), $[RhCp^*Cl_2]_2$ (2 mol%), base (0.10 mmol, 1.20 equiv.), THF, Ar atmosphere, 18 h. [b] Yield of **2.3.1** was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction time: 24 h, incomplete conversion of starting material. [d] Reaction done under air / without Ar atmosphere. [e] Reaction time: 2 h.

Table 3 shows an optimization of base, concentration and temperature. While the reaction with model substrate phenylboronic acid occurs at room temperature, when these conditions are used with derivatized boronic acids, reactivity is reduced, requiring the use of higher temperatures to observe reactivity (entries 1-2). The product does not degrade under higher temperatures (entry 3). Although different bases performed well (entries 4-6), sodium acetate emerged as the preferred base. The reaction did not proceed at all in the absence of base (entry 7). Concentrated conditions (entry 8) cause logistic issues with solubility giving a lower yield of product whereas the reaction

rates slow under dilute conditions (entry 9 and 10). The reaction also proceeds well under air (entry 11).

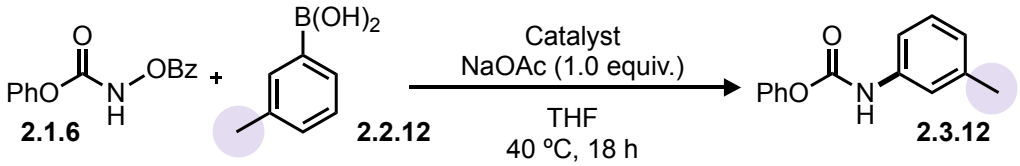
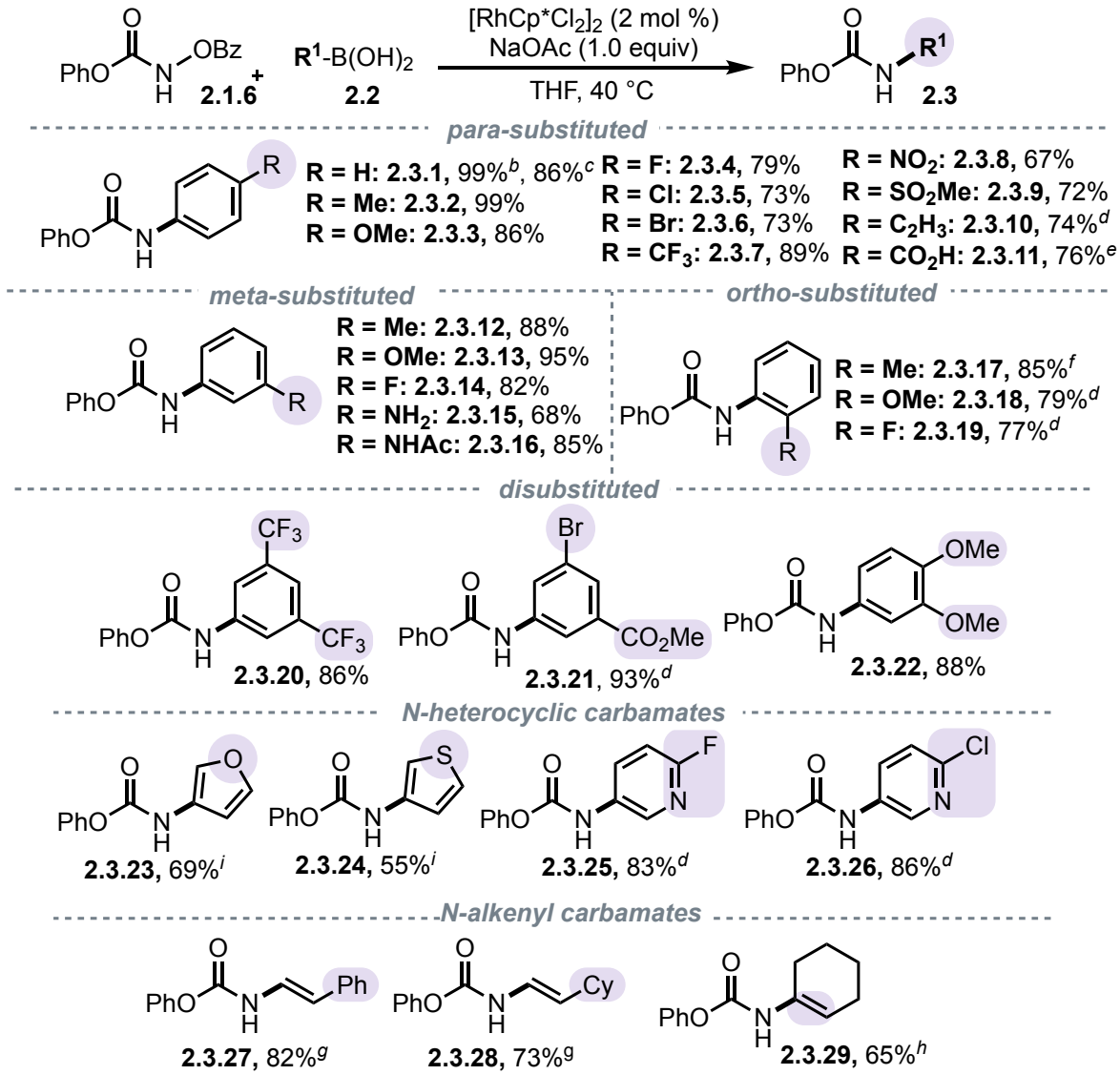


Table 4: Optimization of catalyst

Entry	Catalyst	Yield of 2.3.12(%)[b]
1	$FeCl_2$ (10 mol%)	0
2	$Rh((CH_3CN)_3Cp^*(SbF_6)$ (2 mol%)	82
3	$PdCl_2(PPh_3)_2$ (2 mol%)	0
4	$[IrCp^*Cl_2]_2$ (2 mol%)	0
5	$[Rh(OH)(cod)]_2$ (2 mol%)	0
6	Ru(*p*-cymene)Cl_2 (2 mol%)	0
7	$CuBr_2$ (10 mol%)	0
8	$Rh_2(OAc)_4$ (2 mol%)	0[c]
9	**$[RhCp^*Cl_2]_2$ (2 mol%)**	**92**
10	None	0

[a] Reaction conditions: Linchpin **2.1.6** (0.10 mmol, 1.00 equiv.), boronic acid **2.2.12** (0.12 mmol, 1.20 equiv.), $[RhCp^*Cl_2]_2$ (2 mol%), base (0.10 mmol, 1.20 equiv.), THF, Ar atmosphere, 18 h. [b] Yield of **2.3.12** was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction time: 24 h, incomplete conversion of starting material. [d] Reaction done under air / without Ar atmosphere. [e] Reaction time: 2 h.

A screen of catalysts was performed by **B. Uppalapati** (**Table 4**). The results from the screen showed that only rhodium (III) catalysts were compatible with N-O bond cleavage. A cationic rhodium (III) catalyst, $Rh((CH_3CN)_3Cp^*(SbF_6)$, was the only other catalyst that gave desired product, albeit in lower yield. With the optimal conditions in hand, the applicability of this transformation was thoroughly evaluated (**Scheme 20**).



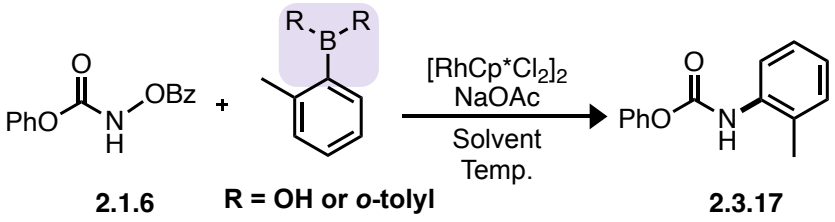
Scheme 20: Scope of Rh-catalyzed amination of linchpin reagent **2.1.6**

[a] Conditions: Linchpin **2.1.6** (0.10 - 0.50 mmol, 1.0 equiv.), $RB(OH)_2$ **2.2** (1.2 equiv.), NaOAc (1.0 equiv.), $[RhCp^*Cl_2]_2$ (2 mol%), under Ar, in THF (0.2 M), 40 °C, 18 h; [b] Reaction completed in 2 h; [c] 5.00 mmol scale; [d] Used 4 mol% catalyst and 3.6 equiv. of **2.2** instead; [e] Used 2.0 equiv. of NaOAc instead [f] Used 3.6 equiv. of **2.2** instead; [g] Used 1.5 equiv. of **2.2** in MeOH (0.2 M), 40 °C, 2 h; [h] Used 1.5 equiv. of **2.2** in THF (0.2 M), 66 °C, 2 h; [i] Used 4 mol% catalyst and 3.6 equiv. of **2.2** in THF (0.2 M), 66 °C, 48 h.

Pleasingly, most boronic acids were converted to the desired amination products in high yields. Electronics were explored on the aryl-boronic acid and found that they were well tolerated, showing slight decrease in yield with highly electron-withdrawing or donating substituents. Meta and para substitution on the boronic acid (**2.2.3-2.2.16**) generally gave excellent results, however,

the use of ortho-substituted boronic acids proved to be more challenging, leaving unreacted linchpin starting material.

Thus, conditions were re-optimized for the use of less reactive boronic acids. (**Table 5**) The use of higher temperatures did show slight increase in reactivity (entry 2), though the use of even higher temperatures led to degradation (entry 3). Increased catalyst loading yielded the target carbamate product in moderate yield (entry 4). It was found that boroxines are also compatible under the reaction conditions, affording the product in higher yield. Since one boroxine molecule contains three boron sources, the equivalencies were transferred to the boronic acid in entry 6, giving the target carbamate in high yield.



2.1.6 **R = OH or *o*-tolyl** **2.3.17**

Table 5: Re-optimization for ortho-substituted phenylboronic acids

Entry	Boron source	Catalyst loading (mol%)	Temperature (ºC)	Solvent (0.2 M)	Yield of 2.3.17 (%)
1[a]	Boronic acid (1.2 equiv.)	2	40	THF	14[c]
2[a]	Boronic acid (1.2 equiv.)	2	66	THF	21[c]
3[a]	Boronic acid (1.2 equiv.)	2	100	Dioxane	7[c]
4[b]	Boronic acid (1.2 equiv.)	4	40	THF	74[d]
5[b]	Boroxine (1.2 equiv.)	2	40	THF	76[d]
6[b]	Boronic acid (3.6 equiv.)	2	40	THF	85[d]

(a) Reaction time: 48 h (b) Reaction time: 18 h (c) ^{1}H-NMR yield using 1,3,5-trimethoxybenzene as an internal standard (d) Isolated yield

A gram-scale synthesis was successful, resulting in a negligible decrease in yield and enabling recrystallization of the product **2.3.1**. The phenyl carbamates containing a free amino group (**2.3.15**) or an N-H acetamide subunit (**2.1.16**) were also obtained reliably. Traditional Chan-

Lam amination conditions would not be suitable to achieve such chemoselectivity.[65] Styrenyl product **2.3.10** and several aryl halide-containing products were generated in moderate yields (**2.3.5-6, 2.3.21, 2.3.26**), which could then be functionalized through cross coupling chemistry. Gratifyingly, ortho-substituted phenyl carbamates **(2.3.17-19)** were obtained in excellent yields when modifications were made to the reaction conditions. Excess aryl boronic acid was necessary to obtain a high yield of product **2.3.17** (*o*-Me). In contrast, products **2.3.18** (*o*-OMe) and **2.3.19** (*o*-F) required both excess boronic acid and higher catalyst loading (4 mol%).

We then became interested in forming substrates less accessible by classic chemistry, notably, *N*-heterocyclic carbamates[66] and *N*-alkenyl carbamates.[67] The modified conditions also proved effective with heteroaryl boronic acids, enabling the synthesis of furyl (**2.3.23**), thienyl (**2.3.24**) and pyridyl carbamates (**2.3.25-26**). The halide substitution on the pyridylboronic acid provided the required attenuated basicity to react completely with reagent **1**. To our delight, *N*-alkenyl carbamates (**2.3.27-29**) were synthesized in moderate to excellent yields when conditions adapted from Feng and Loh were applied to the coupling of linchpin **2.1.6** with alkenylboronic acids.[68] These *N*-alkenyl carbamates were synthesized by **B. Uppalapati**.

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[65] (a) S. Liu, W. Zu, J. Zhang, L. Xu, *Org. Biomol. Chem.* **2017**, *15*, 9288–9292; (b) J.-Q. Chen, J.-H. Li, Z.-B. Dong, *Adv. Synth. Catal.* **2020**, *362*, 3311–3331; (c) M. J. West, J. W. B. Fyfe, J. C. Vantourout, A. J. B. Watson, *Chem. Rev.* **2019**, *119*, 12491-12523.

[66] (a) G. R. Ferguson, C. C. Alexander, *J. Agric. Food Chem.* **1953**, *1*, 888–889; (b) A. Padwa, M. A. Brodney, B. Liu, K. Satake, T. Wu, *J. Org. Chem.* **1999**, *64*, 3595–3607; (c) T. T. Pham, A. C. Lindsay, S.-W. Kim, L. Persello, X. Chen, N. Yan, J. Sperry, *ChemistrySelect* **2019**, *4*, 10097–10099; (d) R. Wouters, J. Tian, P. Herdewijn, S. De Jonghe, *ChemMedChem* **2019**, *14*, 237–254.

[67] (a) R. Matsubara, S. Kobayashi, *Acc. Chem. Res.* **2008**, *41*, 292–301; (b) K. Gopalaiah, H. B. Kagan, *Chem. Rev.* **2011**, *111*, 4599–4657; (c) T. Courant, G. Dagousset, G. Masson, *Synthesis* **2015**, *47*, 1799–1856; (d) K. C. Cartwright, S. B. Lang, J. A. Tunge, *J. Org. Chem.* **2019**, *84*, 2933–2940.

[68] For the reaction of *N*-pivaloyloxyamides with alkenylboronic acids, see: C. Feng, T.-P. Loh, *Org. Lett.* **2014**, *16*, 3444–3447.

Overall, the results presented in **Scheme 19** demonstrate that linchpin reagent **2.1.6** provides access to a variety of phenyl carbamates (**2.3.1-2.3.29**), which are masked (blocked) *C*-isocyanates. Such substrates are isocyanate precursors that reversibly form free isocyanates *in situ*, upon heating or in the presence of a catalyst.[69]

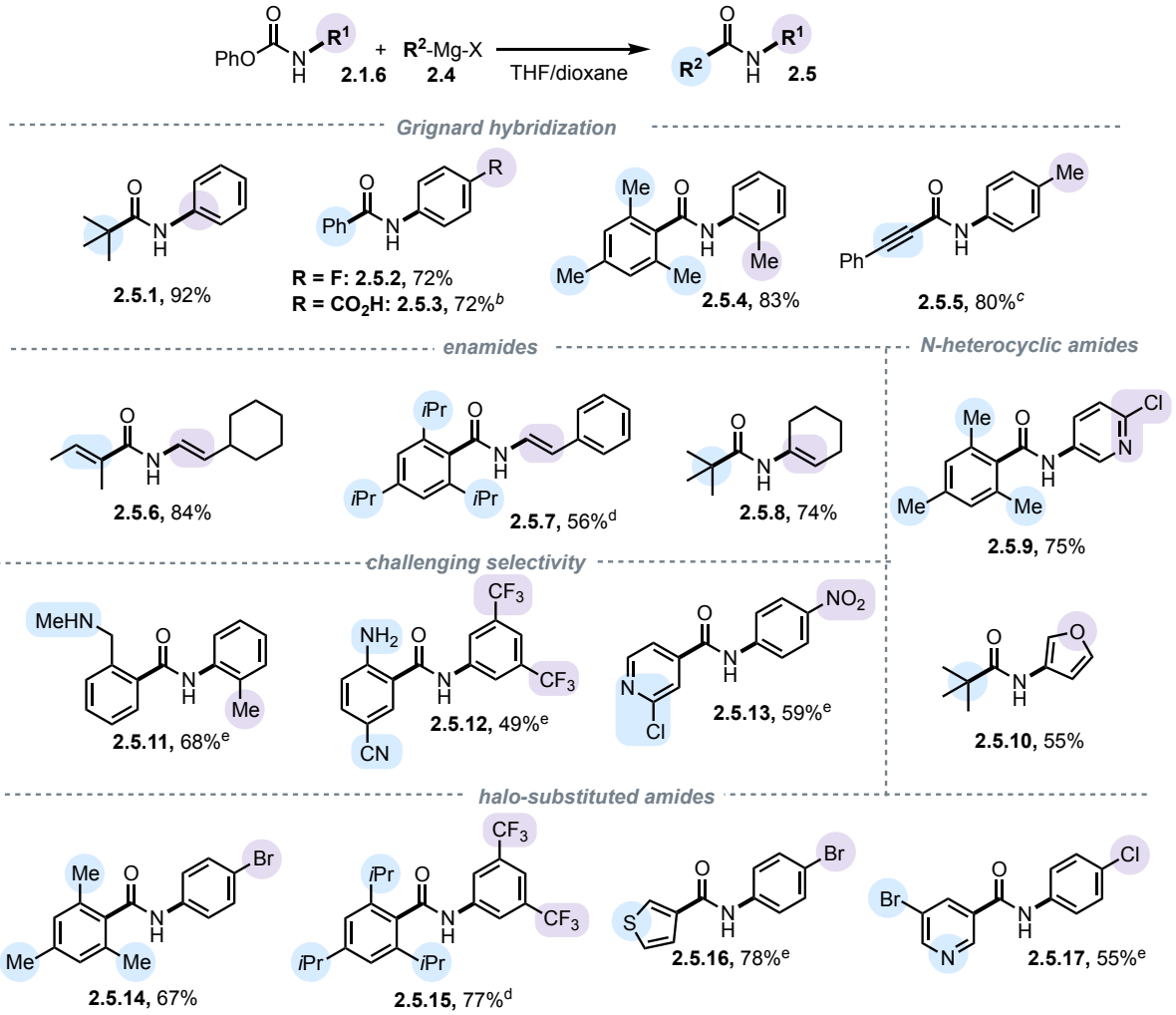
2.3 C-C Bond Formation

The C-C bond formation reaction (secondary and tertiary amide as well as lactam formation) was developed by PhD candidate Bhavana Uppalapati. Key results are included as essential context. The optimization towards this reaction will not be presented here but can be found in the Supplemental Information of the publication reporting this work. The text in this section (Section 2.3) is reproduced from the manuscript.[1]

As isocyanates are useful building blocks to form amides,[70] efforts then focused on identifying simple reactions that could convert the masked *C*-isocyanates **2.3** into useful amides. This would also validate the use of **2.1.6** as an amide linchpin reagent through a C-N, then C-C bond-forming reaction sequence. Encouragingly, Bode's synthesis of sterically hindered amides using isocyanates and Grignard reagents[55] could be adapted to use phenyl carbamates **2.3** as substrates to form the desired amide products (**Scheme 21**). First, Grignard reagents of various

[69] (a) P. Braunstein, D. Nobel, *Chem. Rev.* **1989**, *89*, 1927–1945; (b) E. Delebecq, J.-P. Pascault, B. Boutevin, F. Ganachaud, *Chem. Rev.* **2013**, *113*, 80–118.
[70] (a) K. Sasaki, D. Crich, *Org. Lett.* **2011**, *13*, 2256–2259; (b) V. Pace, S. Monticelli, K. de la Vega-Hernández, L. Castoldi, *Org. Biomol. Chem.* **2016**, *14*, 7848–7854; (c) J. D. Williams, W. J. Kerr, S. G. Leach, D. M. Lindsay, *Angew. Chem. Int. Ed.* **2018**, *57*, 12126–12130.

hybridizations (sp, sp^2 and sp^3) provided the desired amide products (**2.5.1-4**) at room temperature.



Scheme 21: Scope of amide formation from masked *C*-isocyanates **2.3**

[a] Conditions: Masked *C*-isocyanate **2.3** (0.20 mmol – 0.50 mmol, 1.0 equiv.), Grignard reagent **2.4** (4.0 equiv.), under Ar, in THF/dioxane, r.t., 30 minutes; [b] No dioxane added; [c] Grignard reagent prepared *in situ* from phenylacetylene [see Supporting Information]; [d] Masked *C*-isocyanate **2.3.27** added at 66 °C; [e] Grignard reagent prepared *in situ* from the corresponding (hetero)aryl halide [see Supporting Information].

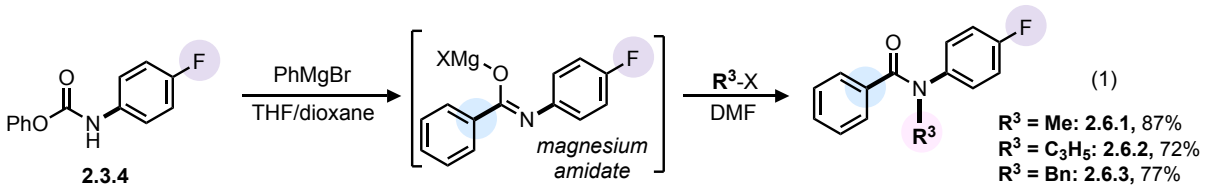
Several substrates were competent reaction partners, notably providing sterically hindered amides (**2.5.4, 2.5.7, 2.5.9, 2.5.15**) and products with strong electron-withdrawing groups (**2.5.12-13, 2.5.15**). These products are very difficult to form using conventional amide bond-forming

reactions either due to steric hindrance at the carbonyl group and / or due to the use of a deactivated nucleophile. Amides possessing heterocycles on either side of the NCO subunit (**2.5.9-10, 2.5.16-17**) were also formed in moderate to good yields (55-76% yield). Enamides constitute a class of amides that are typically not synthesized using traditional amide bond-forming reactions as the lability of enamines prevents them from being good reaction partners.[71] Remarkably, using the linchpin approach, enamides **2.5.6-8** were synthesized in good yields. The presence of free nitrogen or carboxylic acid substituents on either reaction partner is not tolerated in more traditional amide syntheses, due to chemoselectivity issues. Using Knochel's lithium-halogen exchange methodologies to prepare Grignard reagents in the presence of labile / reactive functional groups,[72] products containing a free amino (**2.5.12**), anilino (**2.5.11**) and nitro group (**2.5.13)** were prepared in good yield. We have previously reported the addition of carboxylic acids to isocyanates,[73] however, as illustrated in **2.5.3**, this reactivity is not observed, and the carboxylic acid is tolerated using this linchpin approach. Moreover, selective formation of the Grignard reagent in the presence of a second halide allowed formation of amide **2.5.17**.

Overall, the results in **Scheme 20** and **Scheme 21** highlight that amide linchpin reagent **2.1.6** provides access to a variety of secondary amides through an amination / Grignard addition sequence. Building on the previous results, it was hypothesized that tertiary amides could also be formed by alkylation of the magnesium amidate intermediate resulting from the Grignard addition

[71] (a) P. W. Hickmott, *Tetrahedron* **1982**, *38*, 3363–3446; (b) A. L. Campbell, G. R. Lenz, *Synthesis* **1987**, *1987*, 421–452; (c) G. Cook, Ed., *Enamines: Synthesis: Structure, and Reactions, Second Edition,* CRC Press, Boca Raton, **2020**.
[72] P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302-4320.
[73] J. Derasp, E. A. Barbera, N. R. Séguin, D. D. Brzezinski, A. M. Beauchemin, *Org. Lett.* **2020**, *22*, 7403–7407.

reaction. The results below confirm that tertiary amides can also be accessed via the linchpin strategy (*N*-alkyl, *N*-allyl, and *N*-benzyl) (**Equation 1**).[74]



Equation 1: Tertiary amide formation

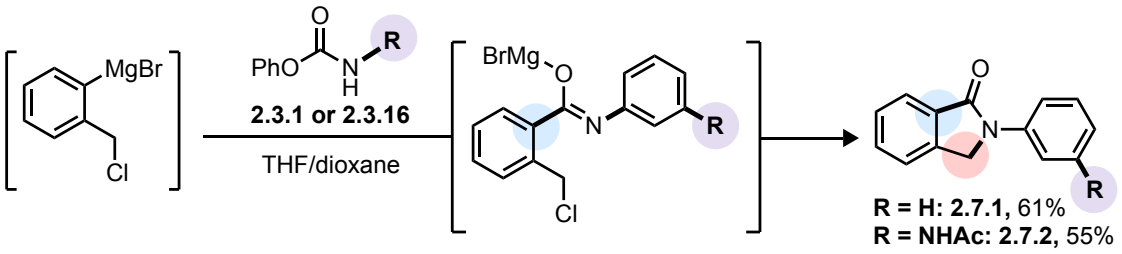
2.4 Linchpin reagent as an NCO building block

2.4.1: Lactam formation

*The lactam formation chemistry was performed by **B. Uppalapati**.*

While reagent **2.1.6** was shown to provide access to amides, this linchpin approach could have broader applicability as a general NCO building block, which can be employed to synthesize both cyclic and acyclic products. Given their importance in pharmaceuticals, lactams were selected as an NCO-containing cyclic target.[75] Recent work by Knochel, describing the reaction of a functionalized Grignard and a free isocyanate to afford a lactam, positioned us to feature the linchpin sequence in a C-N / C-C bond formation and subsequent cyclization event. Gratifyingly, both a simple and functionalized boronic acid were successful in forming the lactams **2.7.1** and **2.7.2** (**Equation 2**).

[74] The *N*-ethyl tertiary amide **6b** was obtained in 80% yield and corrected to 72% yield based on an unidentifiable impurity.
[75] F. I. Saldívar-González, E. Lenci, A. Trabocchi, J. L. Medina-Franco, *RSC Adv*. **2019**, *9*, 27105-27116.



Equation 2: Lactam formation

2.4.2: Urea formation

Ureas represent a versatile class of functional groups with broad applications in pharmaceuticals[76] and agrochemicals[77] (**Figure 9**). Structurally defined by the motif $R^1NH\text{-}CO\text{-}NR^2R^3$, they can be categorized as symmetrical ($R^1 = R^2$) or unsymmetrical ($R^1 \neq R^2$).

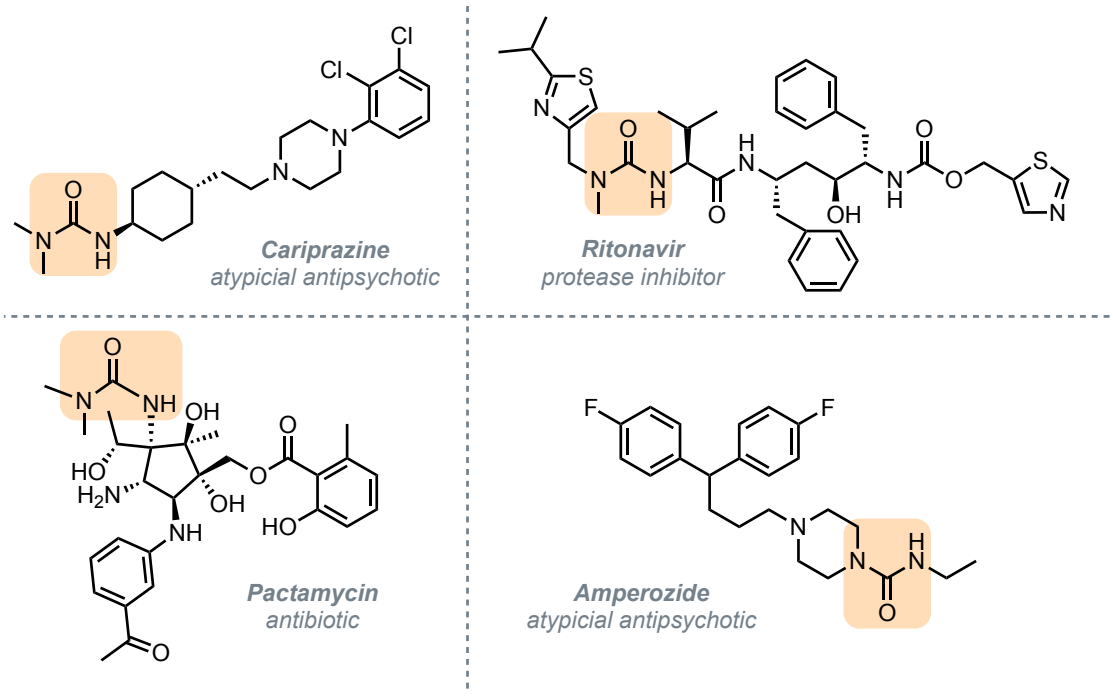


Figure 9: Representative urea-containing drugs

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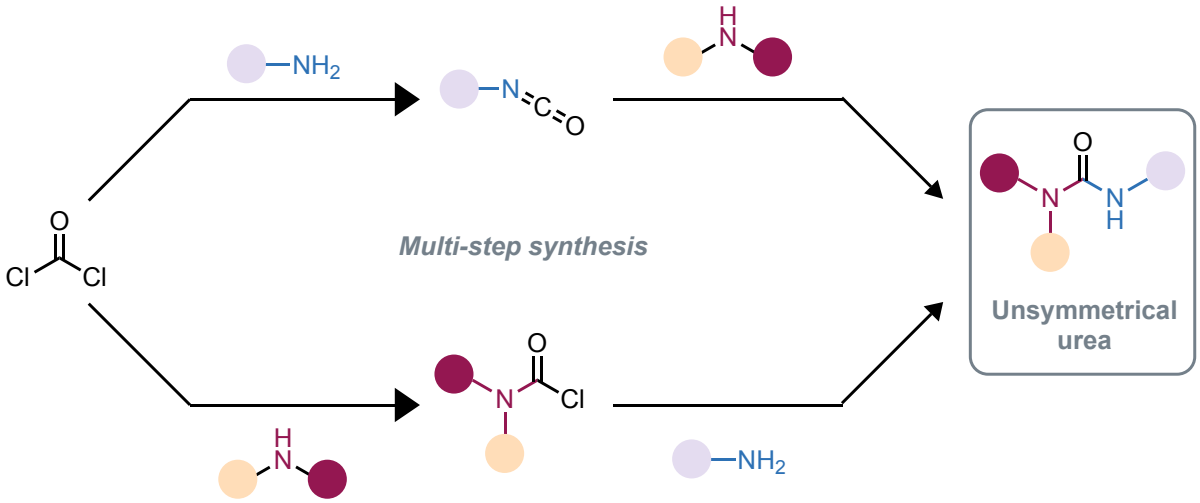
[76] (a) R. Ronchetti, G. Moroni, A. Carotti, A. Gioiello, E. Camaioni, *RSC Med. Chem.* **2021**, *12*, 1121-1143; (b) R. Listro, G. Rossino, F. Piaggi, F. F. Sonekan, D. Rossi, P. Linciano, S. Collina, *Front. Chem.* **2022**, *10*, 995351; (c) A. D. Jagtap, N. B. Kondekar, A. A. Sadani, J.-W. Chern, *Curr. Med. Chem.* **2017**, *24*, 622-651.
[77] (a) C. D. S. Tomlin, *The Pesticide Manual*, 14th ed., British Crop Production Council, Alton, UK, 2006; (b) A. O. Alli, M. O. Oose, *Br. J. Educ.* **2025**, *13*, 63-86.

Several synthetic strategies have been developed to access ureas, each offering distinct advantages depending on the desired substitution pattern and functional group compatibility. Classical approaches rely on the condensation of amines with phosgene or phosgene equivalents, such as triphosgene or carbonyldiimidazole (CDI), to access symmetrical or unsymmetrical ureas.[78] This method requires that one amine is added first to form a mono-substituted intermediate (isocyanate or carbamoyl derivative), followed by a second amine. Such reactions require careful monitoring and sequential addition to access unsymmetrical ureas (**Scheme 22**).



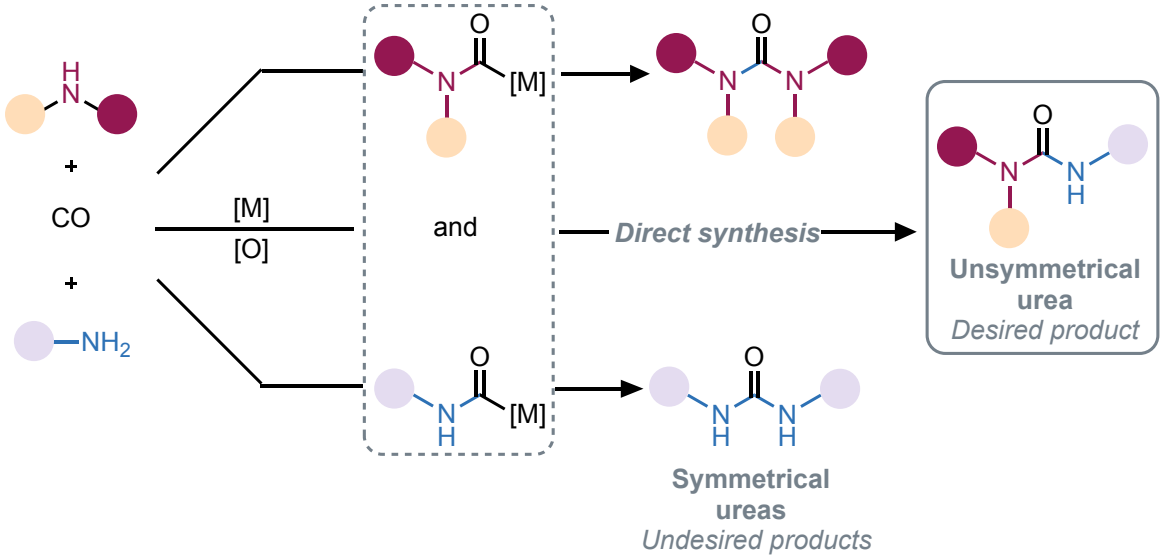
Scheme 22: Multistep approach towards unsymmetrical ureas.

Transition metal-catalyzed pathways have emerged, particularly those involving carbonyl insertion reactions or oxidative couplings of amines with alcohols or carbamates.[79] Such reactions

[78] (a) M. O. Ganiu, B. Nepal, J. P. Van Houten, R. Kartika, *Tetrahedron* **2020**, *76*, 131553; (b) F. Bigi, R. Maggi, G. Sartori, *Green Chem.* **2000**, *2*, 140–148.

[79] (a) M. Xu, A. R. Jupp, M. S. E. Ong, K. I. Burton, S. S. Chitnis, D. W. Stephan, *Angew. Chem. Int. Ed.* **2019,** *58*, 5707–5711; (b) C. Wu, H. Cheng, R. Liu, Q. Wang, Y. Hao, Y. Yu, F. Zhao, *Green Chem.* **2010,** *12*, 1811–1816; (c) B. Gabriele, G. Salerno, R. Mancuso, M. Costa, *J. Org. Chem.* **2004,** *69*, 4741–4750; (d) A. Ion, V. Parvulescu, P. Jacobs, D. D. Vos, *Green Chem.* **2007,** *9*, 158–161; (e) K. Orito, M. Miyazawa, T. Nakamura, A. Horibata, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, T. Yamazaki, M. Tokuda, *J. Org. Chem.* **2006,** *71*, 5951–5958; (f) M. Zhang, Z. Liu, Y. Wang, J. Wang, L. Zhang, *Science* **2024**, *384*, 1234-1238.

attempt to directly synthesize unsymmetrical ureas, however, selectivity issues can arise with these methods (**Scheme 23**).



Scheme 23: Direct synthesis of unsymmetrical ureas competing with symmetrical ureas

Despite these developments, the synthesis of unsymmetrical ureas continues to pose a significant challenge. The challenge lies with the chemoselective and regioselective differentiation of two distinct amines reacting with a carbonyl electrophile.[80] In the absence of control over the relative nucleophilicity or timing of amine addition, competitive or overreaction can lead to the formation of symmetrical byproducts or mixtures, complicating isolation and reducing overall yield.

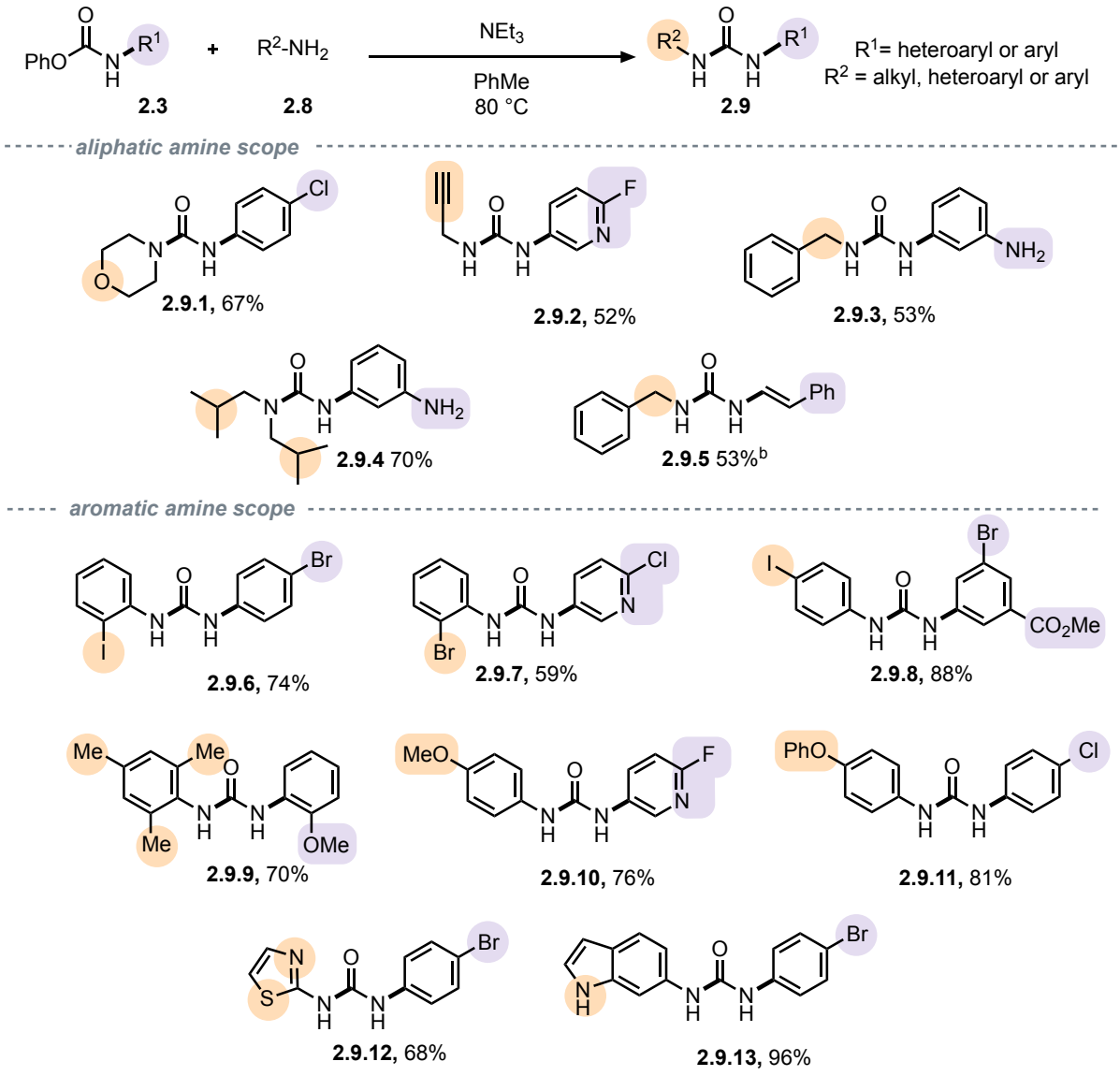
To overcome these issues, many modern strategies employ stepwise protocols. In the direct synthesis, careful optimization of reagent stoichiometry, order of addition, and electronic effects

[80] (a) F. Bigi, R. Maggi, G. Sartori, *Green Chem.* **2000**, *2*, 140–148; (b) K. Orito, M. Miyazawa, T. Nakamura, A. Horibata, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, T. Yamazaki, M. Tokuda, *J. Org. Chem.* **2006,** *71*, 5951–5958.

is critical. While significant progress has been made, the selective synthesis of unsymmetrical ureas remains an area of active investigation, particularly for applications in drug discovery.

Urea synthesis from isocyanate equivalents has gained significant interest in recent years.[81] The use of linchpin reagent **2.1.6** provides access to masked isocyanates **2.3**, which were converted to a range of unsymmetrical ureas (**2.9.1-13**) in good to excellent yields (**Scheme 24**). Aliphatic amines, including cyclic (**2.9.1**), acyclic (**2.9.4**), and activated, (**2.9.2-3, 2.9.5**), were successfully employed. Products **2.9.3**, **2.9.4**, and **2.9.13** were accessed chemoselectively, without requiring protection of the free nitrogen group. Sterically hindered aniline (**2.9.9**), electron-rich anilines (**2.9.10-11**), and amino-heterocycles (**2.9.12-13**) were competent nucleophiles. *N*-Alkenyl urea **2.9.5**, synthesized by BU, was obtained through a one-pot approach from **1** in 53% yield. These one-pot conditions were attempted on other substrates, notably **2.9.9** and **2.9.5**, but did not give consistent results. Therefore, the more reliable two-step conditions were employed for these substrates.

[81] (a) E. V. Vinogradova, B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 11132–11135; (b) Y. Ren, S. A. L. Rousseaux, *J. Org. Chem.* **2018**, *83*, 913–920; (c) J. Bruffaerts, N. von Wolff, Y. Diskin-Posner, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2019**, *141*, 16486–16493; (d) A. K. Ghosh, M. Brindisi, *J. Med. Chem.* **2020**, *63*, 2751–2788; (e) S. O. Kasatkina, K. K. Geyl, S. V. Baykov, M. S. Novikov, V. P. Boyarskiy, *Adv. Synth. Catal.* **2022**, *364*, 1295–1304.

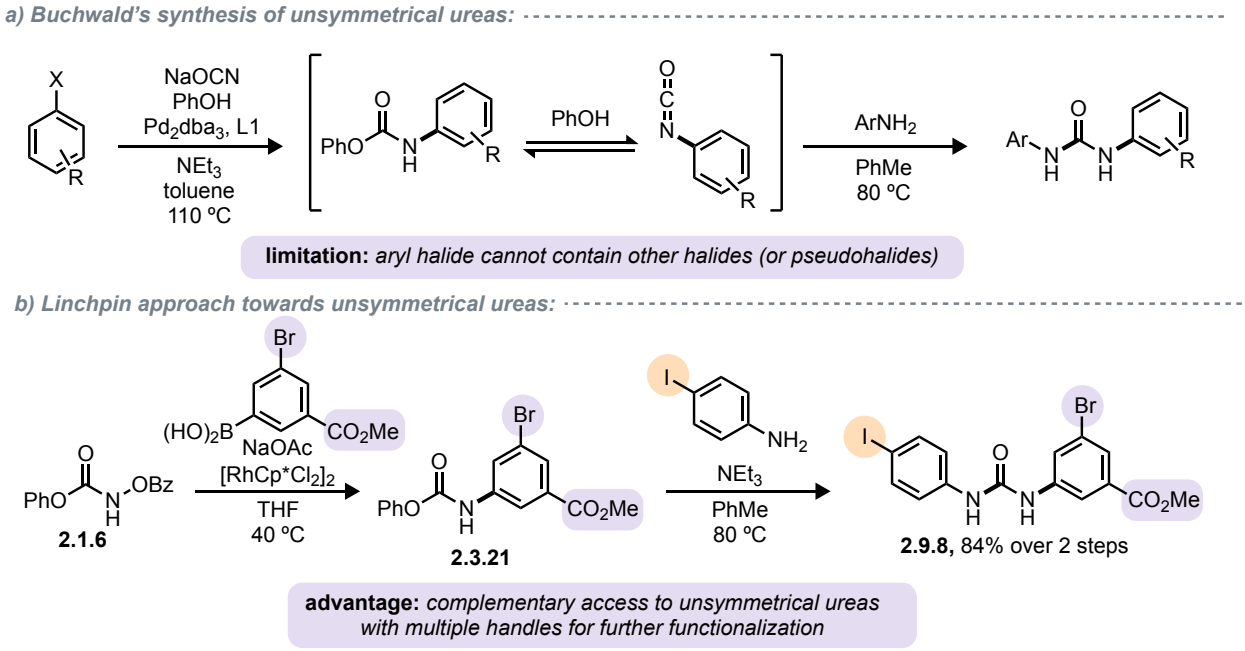


Scheme 24: Scope of urea formation from phenyl carbamates (masked *C*-isocyanates) **2.3**

[a] Conditions: Masked *C*-isocyanate **2.3** (0.20 mmol – 0.50 mmol, 1.0 equiv.), amine reagent **2.8** (1.2 equiv.) and NEt_3 (0.25 equiv.), under Ar, in toluene, 80 ºC, 16 h; [b] Synthesized in one-pot conditions from linchpin reagent **2.1.6**, (0.50 mmol, 1.0 equiv.) and (*E*)-styrylboronic acid (0.75 mmol, 1.5 equiv.), followed by benzylamine addition (2.50 mmol, 5.0 equiv.), under Ar in CH_3OH, 40 ºC.

Notably, the urea formation step is compatible with existing halogens on the masked isocyanate **2.3**, facilitating the formation of multiple polyhalogenated unsymmetrical ureas (**2.9.6-8**); these substrates could be further elaborated using the aryl halogen handles (**Scheme 25b**). This

provides complementarity to Buchwald's synthesis of unsymmetrical ureas via palladium-catalyzed coupling of aryl halides with NaOCN followed by subsequent nucleophilic addition of an amine (**Scheme 25a**).[81a]



Scheme 25: Complementary method for urea formation from phenyl carbamates

This method is compatible with a variety of amine nucleophiles and does not have any competing side reactions. The urea product can be precipitated from ether, allowing for simple and rapid purification. The results in **Scheme 20** and **Scheme 24** highlight that amide linchpin reagent **2.1.6** provides access to a variety of complex ureas.

2.5: Conclusion

In summary, a new doubly electrophilic linchpin reagent **2.1.6** was developed, enabling the synthesis of secondary amides through a rhodium-catalyzed electrophilic amination / Grignard addition sequence. Tertiary amides were also accessed by *in situ* alkylation of the magnesium amidate intermediate. The potential of **2.1.6** as an NCO linchpin reagent was further demonstrated

with the formation of lactams and unsymmetrical ureas. This strategy has immediate applicability to the synthesis of functional groups that are common in pharmaceuticals and agrochemicals, and efforts to expand this approach to other substrate classes will be reported in due course.

2.6: Appendix

2.6.1: Catalytic cycle

Based on the above findings and literature information, a plausible reaction mechanism is shown below.[57] First, the catalyst is converted to an active rhodium acetate species **2.a** with the aid of the base used in the reaction. Then, transmetallation with the boronic acid occurs to form **2.b** followed by an acetate ligand promoted proton abstraction from the masked *O*-isocyanate to form **2.c** and HOAc. This process is supported by the unsuccessful results with *N*-substituted hydroxamate esters in the Miura paper.[57] Two potential routes can be taken from **2.c**. First, there is the concerted *C*-*N* formation/*N*-*O* cleavage seen in **2.d** to give **2.f**. Alternatively, the reductive elimination to construct the C-N bond can occur, leaving the Rh(I) catalyst weakly coordinated to the carbonyl of the OBz leaving group (**2.e)**.[82] Subsequent oxidative addition into the N-O bond to regenerate the Rh(III) species can occur (**2.f**).[83] Due to the presence of the OBz leaving group, this route appears to be most supported via literature and DFT calculations, however, with current experimental data, these pathways cannot be distinguished at this time. Both routes will then release product, **2.3**, upon protonolysis with HOAc and regenerate the starting rhodium catalyst, **2.a**, completing the catalytic cycle.

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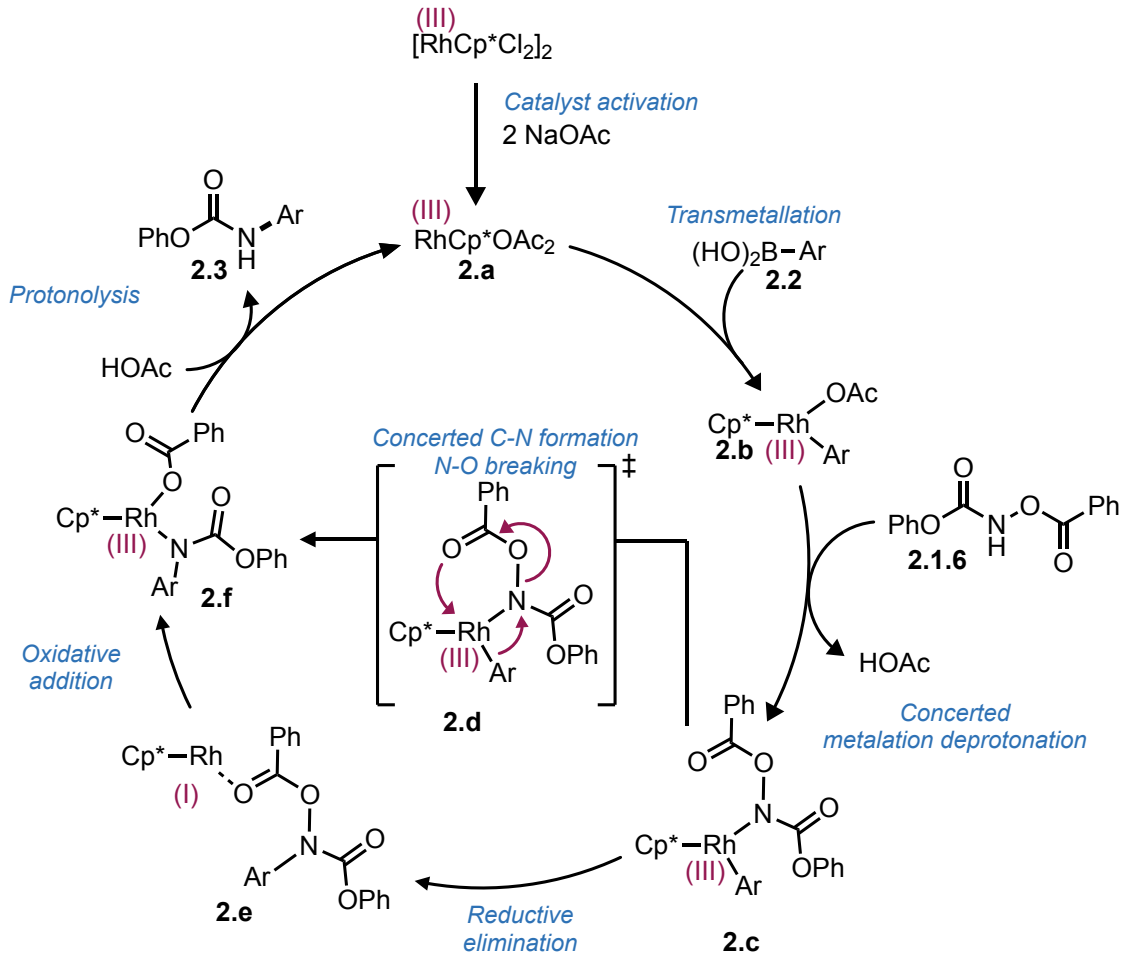
[82] L. Xu, Q. Zhu, G. Huang, B. Cheng, Y. Xia, *J. Org. Chem.* **2012***, 77*, 3017–3024.
[83] N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011***, 133, 16*, 6449–6457.



Scheme 26: Proposed catalytic cycle for Rh-catalyzed electrophilic amination

2.6.2: Substrates that failed to react

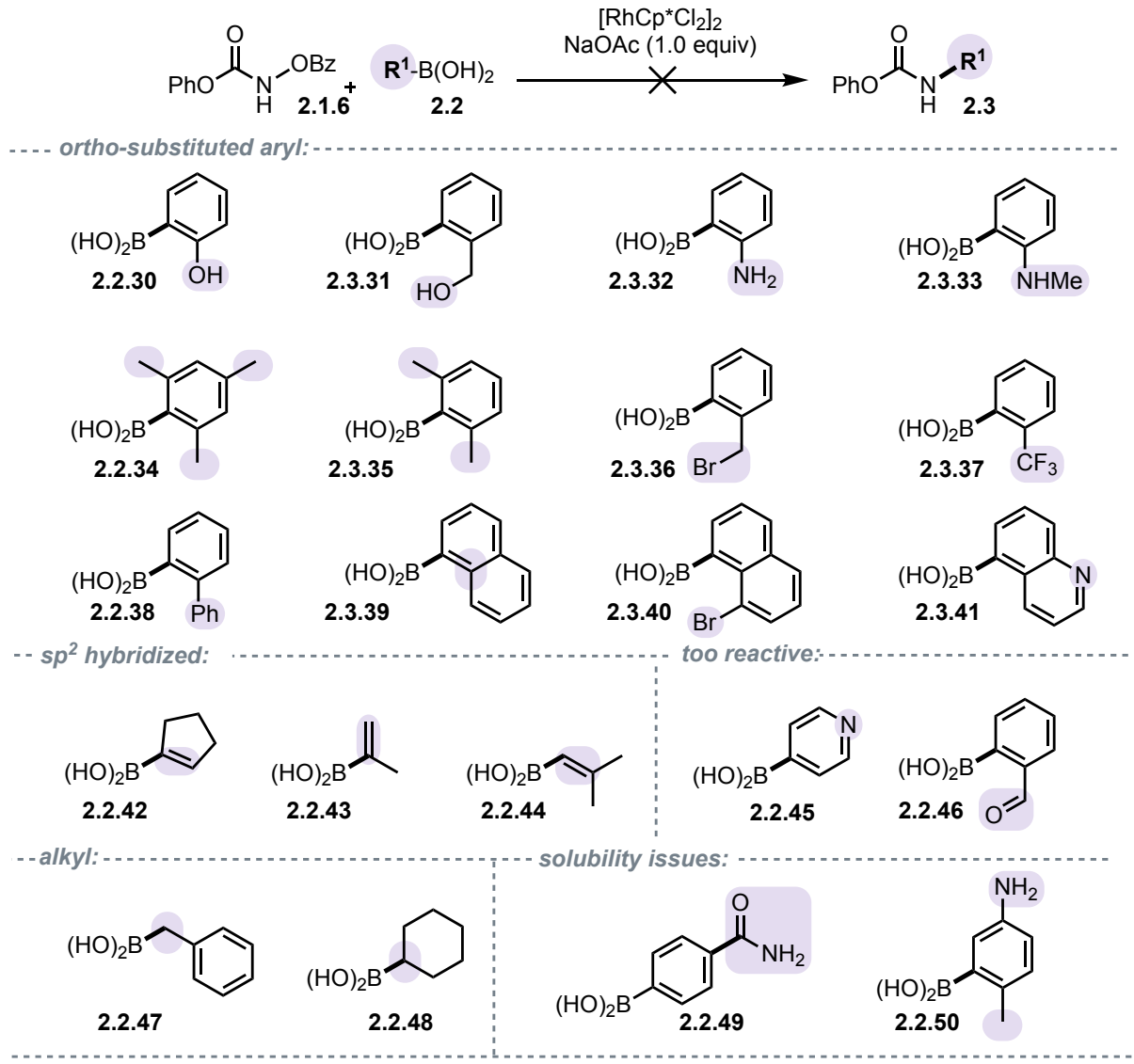
Many substrates were attempted that were not successful. The experiments contributed in ***Scheme 27*** *were divided approximately equally between myself and* ***B. Uppalapati****.*

The amination conditions developed in **Section 2.2** were amenable to a variety of boronic acid coupling partners. However, one of the early limitations of the method was the use of sterically hindered boronic acids, such as ortho-substituted aryl boronic acids. These limitations were eventually overcome for the *o*-tolyl substrate **2.3.7** via the use of additional boronic acid, and for the *o*-methoxy (**2.3.8**) and *o*-fluoro (**2.3.9**) substrates through the use of additional boronic acid

and catalyst (**Table 5**). It is hypothesized that with these substrates, steric hindrance at the B-C bond slowed transmetallation. This was overcome by using an increased concentration of boronic acid (3.6 equivalents rather than 1.2 equivalents). Additional catalyst loading also enabled the use of sterically hindered boronic acids. Similar strategies were used with heteroaryl boronic acids such as the furanyl (**2.3.23**), thienyl (**2.3.24**) and pyridyl (**2.3.25-26**) substrates. However, this optimization was employed on a case-by-case basis and did not provide a fix for all substrates attempted.

Scheme 27 shows the series of failed substrates, categorized by boronic acid-type. Only a selection of failed reactions will be discussed, specifically those that revealed useful information about the limitations of the reaction conditions or substrate compatibility.

The first category is comprised of ortho-substituted aryl boronic acids (**2.2.30-41**). These substrates did not have sufficient reactivity to react under the optimized reaction conditions and yielded unreacted linchpin starting material and boronic acid. Increasing the reaction temperature to reflux resulted in a complex mixture of products, mostly appearing to be degradation products of reagents as per NMR analysis. The subsequent sp^2-hybridized (**2.2.42-44**) and alkyl (**2.2.47-48**) categories also did not yield product due to lack of reactivity under the reaction conditions. These boronic acids often protodeborylated under the reaction conditions, likely due to their weaker C-B bond.



Scheme 27: Failed substrates using rhodium-catalyzed amination conditions

The pyridyl substrate **2.2.45** was too reactive and gave a complex mixture of a large number of products. It was hypothesized that the desired carbamate product was deblocking under the reaction conditions, releasing the free isocyanate in situ, which could further react with a variety of nucleophiles in the system to give a mixture of products. It was attempted to trap this free isocyanate using an amine nucleophile such as morpholine, however, this did not eliminate the mixture of side products. Using a halogenated pyridyl substrate **2.2.25** and **2.2.26** gave attenuated Lewis basicity, giving for more controlled reaction and less side products. The aldehyde substrate

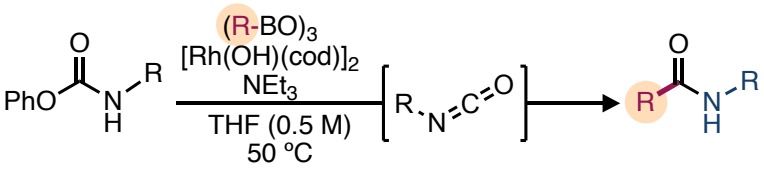
2.2.46 was also too reactive, yielding only 22% yield among many spots on the TLC. Due to off target reactivity, this substrate could not further be optimized.

Two boronic acids were not soluble in THF both at room temperature after extensive sonification and heating. The amide substrate **2.2.49** was not soluble in any organic solvent other than DMSO, which was not a compatible solvent under the amination reaction conditions (**Table 2, entry 3**). The amino methyl substrate **2.2.50** was soluble in methanol, toluene and acetonitrile, which were all solvents compatible with the amination conditions. However, protodeborylation occurred under the reaction conditions using methanol as solvent: ~20% of boronic acid is protodeborylated, ~20% of linchpin is converted to product, the rest remains unreacted. When refluxing the reaction in toluene and acetonitrile, the reaction goes to completion, however, the above yields for protodeborylation and product conversion remain the same.

2.6.3: Attempts towards one-pot amide formation from linchpin reagent 2.1.6

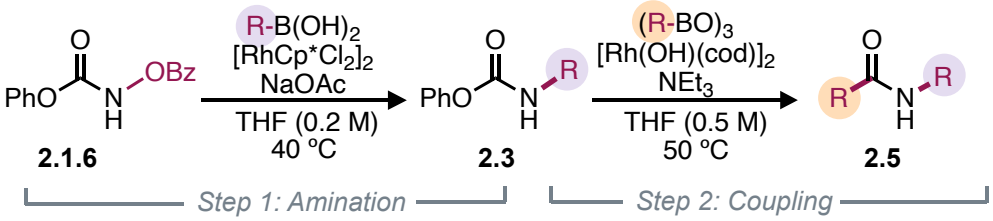
An alternate linchpin strategy focused on the synthesis of amides using a one-pot, dual-catalytic sequence. By integrating two distinct rhodium-catalyzed transformations, this strategy could enable the one-pot linchpin approach.

The *C-C* bond formation reaction using rhodium (I) catalysis had previously been achieved in 2019 (**Scheme 28**).[60a] Synthesis of amides was achieved through rhodium catalyzed coupling of boroxines with masked isocyanates. This reaction was made possible due to the ability to form both the isocyanate and the organorhodium intermediates *in situ* and in low concentration. Results showed broad functional group tolerance, including protic nucleophilic groups such as amines, anilines, and alcohols.



Scheme 28: Rhodium (I) catalyzed coupling of boroxines with masked isocyanates

With these results in hand, we attempted to generate amides from a one-pot sequence of rhodium (III) catalyzed electrophilic amination followed by rhodium (I) catalyzed coupling of carbamates and boroxines (**Scheme 29**).



Scheme 29: General scheme for the one-pot reaction amination-coupling sequence

The amination step with phenylboronic acid was straightforward and generally gave 99% yield of **2.3.1** upon purification. In this case, the crude reaction mixture was not worked up and instead subjected to the next reaction step. To do this, the method of addition posed an issue for the second step of the reaction. The procedure for the coupling step describes the addition of the masked isocyanate to a solution of catalyst and boroxine. The reaction rates were highly dependent on concentration and rhodium and catalyst loading. The masked isocyanate in the crude mixture from step 1 was already dissolved in THF, but at a lower concentration than required for the second step. As a result, some optimization of the method of addition was necessary. (**Table 6**).

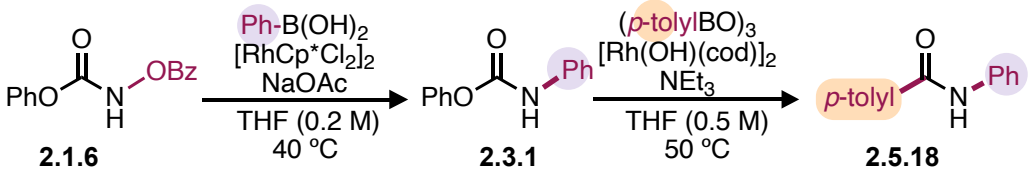


Table 6: Optimization of one-pot amide linchpin conditions

Entry	Method of addition	Eq. boroxine	Catalyst loading for second step (mol%)	Concentration in second step (M)	Yield of 2.5.18 (%)[b]
1	Neat crude to cat./boroxine solution	1.6	1	0.5	30[c]
2	Crude solution to cat./boroxine solution	1.6	1	0.167	n.d[d]
3	Neat cat./boroxine to crude solution	3.3	2.5	0.2	31
4	Neat cat./boroxine to crude solution	3.3	2.5	0.1	47
5	Cat./boroxine solution to crude solution	3.3	2.5	0.1	25

(a) Reaction time: 18 h (b) ^{1}H-NMR yield using 1,3,5-trimethoxybenzene as an internal standard (c) Isolated yield (d) Not determined - incomplete consumption of starting material

By concentrating the crude reaction mixture and transferring the residual solid to a solution of catalyst and boroxine in THF gave a 30% yield (entry 1). This method was not optimal because since the reaction scale was so small, a large amount of crude was left on the walls of the reaction vessel. Despite this, 30% yield of product was isolated, which could be further optimized. Addition of the crude solution in THF (0.2 M) to a solution of catalyst and boroxine, also in THF, led to more dilute reaction conditions (entry 2). Consequently, the reaction did not go to completion. It was not possible to determine an NMR yield due to the complexity of the NMR spectrum. Entries 3-5 employ alternate conditions (high boroxine equivalents, high catalyst loading, low

concentration) in an attempt to increase the reactivity. By addition of neat catalyst and boroxine to the crude reaction, a 31% NMR yield was obtained (entry 3). When decreasing the concentration by half (entry 4), the NMR yield increased to 47%. When changing the addition of catalyst and boroxine to a solution rather than neat, the NMR yield decreased to 25% (entry 5). Given these inconclusive results, efforts were focused on the individual amide formation reaction (**Table 7**).

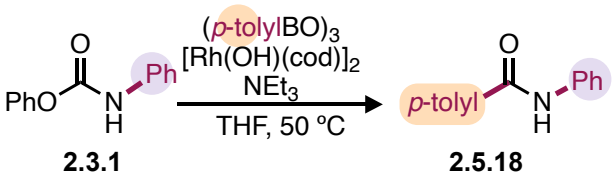


Table 7: Attempts to replicate rhodium (I) amide formation chemistry

Entry	Equiv. of boroxine	Catalyst loading (mol%)	Concentration (M)	Yield of 2.5.18(%)[b]
1	1.6	1.0	0.5	89[c]
2[d]	1.6	1.0	0.5	86
3[d]	1.6	2.5	0.2	99
4[d]	1.6	2.5	0.1	48
5[e]	3.3	2.5	0.133	50
6[e]	0.5	2.5	0.5	64
7[e]	1.6	2.5	0.5	54
8[e]	1.6	2.5	0.2	57
9[d]	1.6	2.5	0.2	92

(a) Reaction time: 18 h (b) ^{1}H-NMR yield using 1,3,5-trimethoxybenzene as an internal standard (c) Isolated yield, literature result[60a] (d) Carbamate purified via column chromatography (e) Carbamate purified via recrystallization

To begin, entry 1 describes the reported yield of the paper using *N*-phenyl phenyl carbamate **2.3.1** made from acylation chemistry under the standard high concentration, low catalyst and low boronic acid loading. When this chemistry was repeated using **2.3.1** made from the rhodium amination chemistry (purified via column chromatography), the yield was comparable (entry 2).

By lowering the concentration to 0.2 M, the yield was near quantitative (entry 3), however, by lowering it further to 0.1 M (entry 4), the yield reduced significantly.

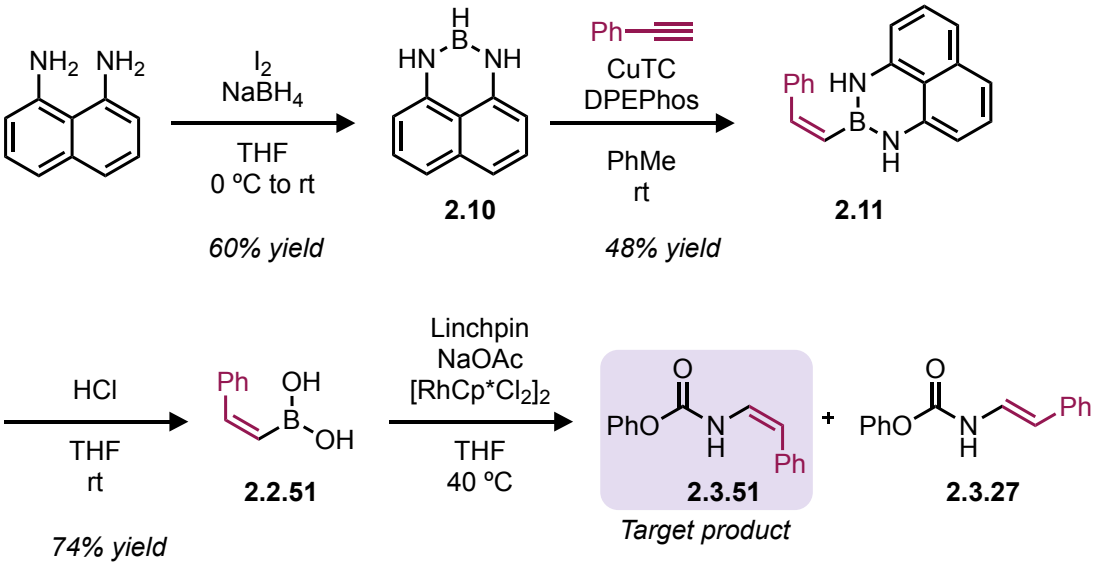
After these initial reactions, the gram scale reaction of **2.3.1** had been achieved and the product was purified via recrystallization. The NMR (seen in the Supplemental Information section) is pure and shows only product peaks. The characterization for the recrystallized product was the same as the product purified via column chromatography, thus, was used for a series of subsequent rhodium (I) experiments.

The alternative conditions for more challenging substrates (high boroxine equivalents, high catalyst loading, low concentration, entries 5-7) were employed and gave reduced reactivity. A test reaction to reproduce the yield from entry 2 was attempted, but the results were significantly lowered from 86% yield to 57% (entry 8). This suggested catalyst decomposition, however, upon attempting the reaction with carbamate **2.3.1** purified via column chromatography, the reactivity was restored (entry 9). This evidence suggests that purification via column chromatography removes an impurity that is not seen via NMR/IR and does not change the physical appearance of the material that recrystallization does not. This impurity does not interfere with the urea reaction formation but does compromise reactivity for the coupling reaction. It is hypothesized that the presence of this rhodium (III) impurity poisons the rhodium (I) catalyst, lowering the yield significantly. Due to the above results, the plan to pursue a one-pot reaction was postponed to focus on more feasible, higher priority tasks.

2.6.4: Attempts towards a cis alkene boronic acid

It was questioned whether the amination reaction would generate a cis-alkene carbamate or isomerize to the trans-alkene carbamate if reacted with a cis-alkene boronic acid. At the time of

working on this project, such boronic acid was not available from any commercial suppliers.[84] Since the boronic acid was not available, we needed to synthesize it, however, this synthesis was not trivial (**Scheme 30**).



Scheme 30: Attempted route towards *N*-cis-alkene carbamate

The first step was the generation of HB(dan) **2.10** from the iodine catalyzed reaction between sodium borohydride and diaminonaphthalene.[85] This was achieved in 60% yield and was relatively straightforward. The second step involved the copper-catalyzed Z-stereoselective hydroboration of alkynes with HB(dan) **2.10**.[86] This transformation is stereoselective for the cis isomer due to the formation of the DPEphos-ligated copper catalysts. It is hypothesized that this catalyst allows for stereoselectivity since the HB(dan) prefers the conformation of the intermediate with the phenyl group cis to the Cu to avoid steric interactions between the approaching dan group

[84] At the time of writing this thesis, boronic acid **2.2.51** is currently being sold under special inquiry for 750$ USD for a gram from Ambeed and needs to be stored under inert atmosphere at -20 °C.
[85] T. Tani, Y. Sawatsugawa, Y. Sano, Y. Hirataka, N. Takahashi, S. Hashimoto, T. Sugiura, T. Tsuchimoto, *Adv. Synth. Catal.* **2019**, *361*, 1815-1834.
[86] W. J. Woo, L. Lee, J. H. Moon, J. Y. Lee, J. Yun, *Org. Lett.* **2016**, *18*, 1390-1393.

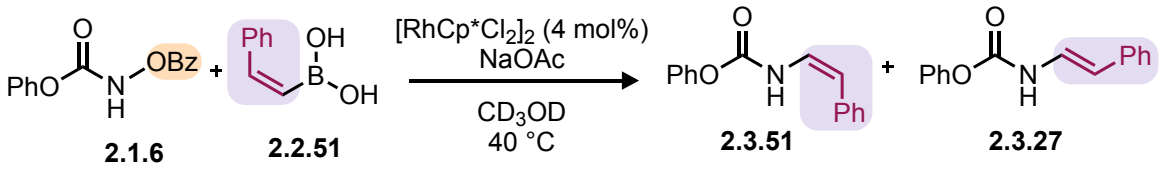
and the phenyl in the σ-bond metathesis step. This reaction gave a 48% yield of the cis isomer **2.11**.

The removal of the dan group from **2.11** to give the boronic acid **2.2.51** appeared to be straightforward in the literature.[87] Literature procedures suggested that this deprotection occurs with 4 equivalents of 5 M HCl in four hours. However, when attempting this transformation, the mixture was stirred at room temperature for 16 h, which led to the formation of a precipitate. The reaction was followed by TLC and did not proceed to completion during this time. Thus, 12 M HCl was added dropwise in 0.4 mL portions every two hours over the course of 8 hours until full consumption of starting material was observed. The suspension (dan) was filtered, and the solution was dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product **2.2.51**, which was purified via silica-gel flash column chromatography. This product rapidly degraded upon exposure to air, making purification column chromatography challenging.

In addition, the boronic acid **2.2.51** appears to undergo protodeborylation to styrene upon solvation in methanol-d_4 (observed by TLC, confirmed by NMR). Due to this rapid degradation, the reaction was performed in methanol-d_4 in order to take aliquots of the reaction mixture at distinct time intervals for NMR analysis. Analysis at 5 minutes reaction time suggests formation of the cis product **2.3.51** (J = 10.9 Hz, consistent with cis ene-carbamates).[88] Analysis at 20 minutes and 1 hour shows further formation of **2.3.51** along with the trans product **2.3.27**. After 10 hours of reaction time, the boronic acid **2.2.51** is fully consumed: the major product is the cis isomer

[87] J. Brals, T. M. McGuire, A. J. B. Watson, *Angew. Chem. Int. Ed.* **2023**, *62*, e202310462.
[88] (a) Y. Liang, F. Strieth-Kalthoff, P. Bellotti, F. Glorius, *Chem Catal.* **2021**, *7*, 1427-1436. (b) R. M. Moriarty, C. J. I. Chany, R. K. Vaid, O. Prakash, S. M. Tuladhar, *J. Org. Chem.* **1993**, *58*, 2478-2482.

2.3.51, however the ratio of trans product **2.3.27** to cis product **2.3.51** has increased. The ratio continues to increase upon 16 hours of reaction time. Unreacted starting linchpin material **2.1.6** remains present after 16 hours reaction time. Evidence strongly suggested that the cis product **2.3.51** isomerizes to the trans product **2.3.27** under the reaction conditions and that the ratio continues to increase even after work-up (see stacked spectra in **Figure 10** and **Table 8**).



2.1.6 **2.2.51** **2.3.51** **2.3.27**

Table 8: Attempted synthesis of **2.3.51**: Cis:trans ratio in the crude mixture at given intervals

Time	Cis : trans ratio
5 min	1 : 0.00
20 min	1 : 0.29
1 h	1 : 0.32
10 h	1 : 0.50
16 h	1 : 0.71
72 h (post-workup)	1 : 3.36
96 h (post-workup)	1 : 5.80

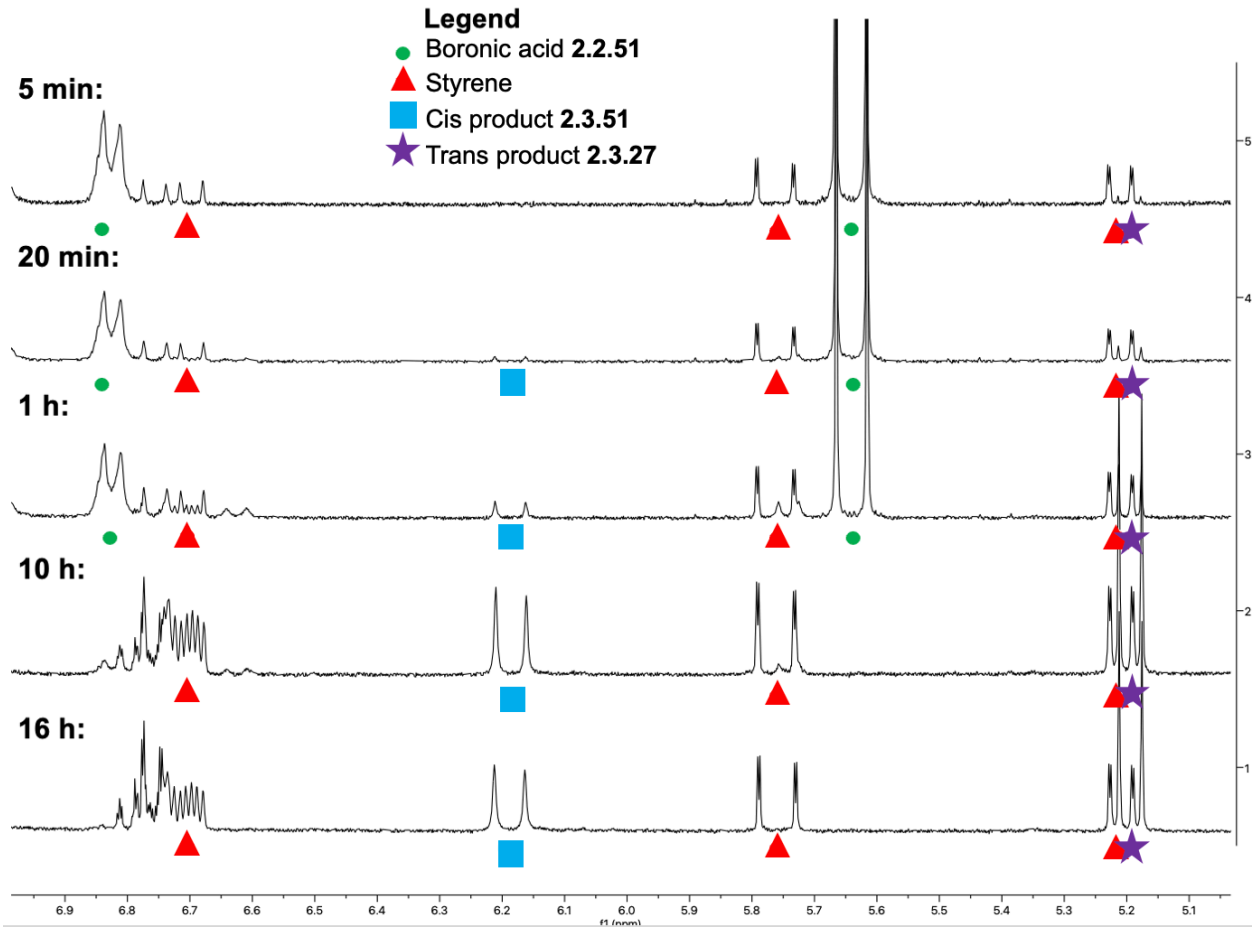


Figure 10: Attempted synthesis of **2.3.51**: ^{1}H NMR of Crude Mixture at Given Intervals

Due to the above constraints, the purification of this cis-alkene carbamate was abandoned, and efforts were focused on more fruitful aspects of the linchpin project.

Chapter 3: A Second-Generation NCO-Linchpin Reagent

In this chapter, a second-generation amide linchpin reagent with a reverse polarity synthon is presented. The use of this reagent for the synthesis of secondary amides through reductive amination / Grignard addition sequence is reported. Optimization towards unsymmetrical ureas is also reported. The proof of concept of N-alkylation on the simpler linchpin, demonstrated in this chapter, was obtained by B. Uppalapati (Scheme 35).

3.1: A second-generation linchpin

In the first-generation linchpin reagent, the amination step was limited to aryl and alkenyl boronic acids, with alkyl boronic acids proving incompatible. This posed a significant limitation, as many small molecule drugs containing amides and ureas feature alkyl chains on the nitrogen.[51] To overcome this, we aimed to develop a second-generation linchpin reagent by modifying the amination step to accommodate the formation of N-C(sp^3) bonds.

As demonstrated in Chapter 2, linchpin reagent **1** was biselectrophilic in nature. However, as alternative linchpin reagents were considered, we envisioned a linchpin reagent with inverted polarity at the nitrogen (**Figure 11**). This new reagent is simpler and more atom economical since it does not contain a benzoyl leaving group. As a result, this linchpin reagent would minimize waste and improve overall reaction efficiency; this makes the reagent more appealing for sustainable synthesis. However, a specific concern remains: the potential formation of free isocyanate under the reaction conditions, either from the starting material or the alkylated product. This possibility raises reactivity considerations that must be accounted for during reaction development. With a new linchpin reagent comes new opportunity, but also new, unprecedented reactivity. As with the previous linchpin, the functionalization reactions had to be optimized to achieve good orthogonal reactivity.

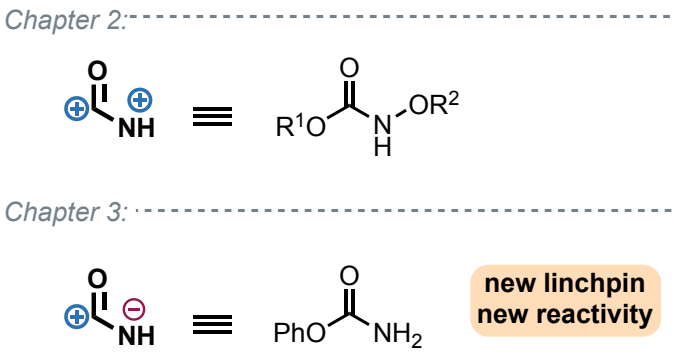


Figure 11: Amide linchpin synthons

Literature reports indicate that N–C bond formation via a nucleophilic nitrogen is possible, though such reactions have been limited in scope. In particular, N–C bond formation leading to carbamates remains relatively uncommon.[89] As a result, the following section will mostly focus on surveying examples of amide formation, which are more broadly represented in the literature. However, as demonstrated by the rhodium-catalyzed amination step discussed in Chapter 2, the strategies developed for amide synthesis could, in principle, be adapted for the formation of carbamates.

For one, amide arylation reactions have been extensively studied, with metal catalyzed processes being highly prevalent in the literature.[90] On the other hand, amide alkylation remains largely unexplored due to the fact that it is often only achievable by superstoicheometric amounts of strong base in polar solvents (**Scheme 31**).[91] Such reactions proceed via S_N1 or S_N2 type mechanisms, where the amide nucleophile adds to the alkyl halide.

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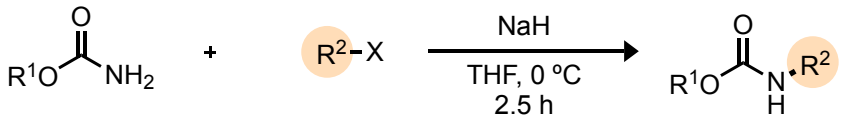
[89] (a) D. Dubé, A. A. Scholte, *Tetrahedron Lett.* **1999**, *40,* 2295–2298; (b) J. P. Hibbard, J. G. Yam, E. B. Alsalek, A. Bahamonde, *J. Org. Chem.* **2022**, *87*, 12036–12040; (c) S. Haubenreisser, M. Niggemann, *Adv. Synth. Catal.* **2011**, *353*, 469–474.
[90] (a) R. Dorel, C. P. Grugel, A. M. Haydl, *Angew. Chem., Int. Ed.* **2019**, *58*, 17118−17129. (b) A. Klapars, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc*. **2002**, *124*, 7421−7428. (c) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27−50.
[91] (a) A. L. J. Beckwith, in *Amides* (Ed.: J. Zabicky), Wiley, New York, 1970, pp. 73–185; (b) W. S. Fones, *J. Org. Chem.* **1949**, *14*, 1099−1102. (c) R. A. W. Johnstone, M. E. Rose, *Tetrahedron* **1979**, *35*, 2169−2173. (d) N. R. Ayyangar, A. R. Choudhary, U. R. Kalkote, A. A. Natu, *Synth. Commun.* **1988**, *18,* 2011−2016.



Scheme 31: Deprotonation and substitution reaction to give alkylated carbamates

To facilitate amide deprotonation and subsequent nucleophile attack, microwave irradiation and phase transfer catalysts are often employed.[92] To avoid the use of strong base and/or high temperatures, procedures have been developed using organometallic complexes, which allow the use of milder bases such as carbonates or phosphates.[93] A potassium phosphate tribasic mediated amide alkylation method emerged in the literature in which primary alkyl chlorides and bromides are coupled with amides (**Scheme 32**).[94] The K_3PO_4 acts as a phase transfer catalyst to facilitate this transformation. This reaction is limited to primary alkyl halides, which restricts its use to the formation of secondary amides. The use of more hindered alkyl halides, such as secondary or tertiary, typically results in reduced reactivity or unwanted side reactions like elimination. Additionally, the reaction is compatible with secondary amides, allowing for the formation of tertiary amides through further alkylation. While this expands the scope of accessible products, it also introduces the risk of over-alkylation, where uncontrolled or repeated alkylation leads to undesired tertiary amide formation or mixed products. As such, careful control of stoichiometry and reaction conditions is necessary to ensure selective monoalkylation when targeting secondary amides.

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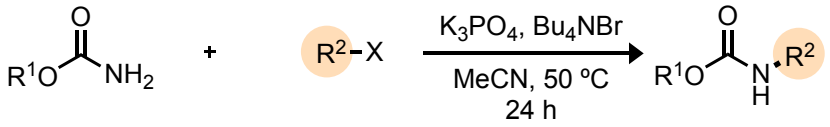
[92] (a) D. Bogdal, *Molecules* **1999**, *4*, 333−337. (b) I. Greiner, F. D. Sypaseuth, A. Grun, E. Karsai, G. Keglevich, *Lett. Org. Chem.* **2009**, *6,* 529−534.

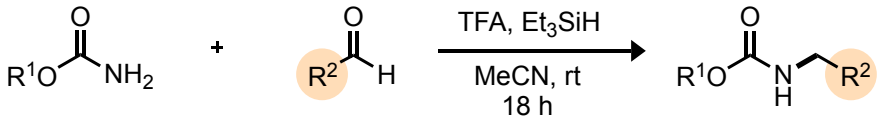
[93] a) C. Chen, J. C. Peters, G. C. Fu, *Nature* **2021**, *596*, 250−256; (b) X. Dai, F. Shi, *Org. Biomol. Chem.* **2019**, *17*, 2044−2054; (c) H.-Q. Do, S. Bachman, A. C. Bissember, J.C. Peters, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 2162−2167. (d) A. K. K. Fung, L.-J. Yu, M. S. Sherburn, M. L. Coote, *J. Org. Chem.* **2021**, *86,* 9723−9732; (e) G. Kumaraswamy, A. Pitchaiah, G. Ramakrishna, D. S. Ramakrishna, K. Sadaiah, *Tetrahedron Lett.* **2006**, *47,* 2013−2015; (f) J. Das, D. Banerjee, *J. Org. Chem.* **2018**, *83*, 3378−3384; (g) J.-P. Wan, Y. Jing, *J. Org. Chem.* **2015**, *11*, 2209−2222; (h) M. Rovira, M. Soler, I. Güell, M.-Z. Wang, L. Gómez, X. Ribas, *J. Org. Chem.* **2016**, *81,* 7315−7325.

[94] J. P. Hibbard, J. G. Yam, E. B. Alsalek, A. Bahamonde, *J. Org. Chem.* **2022**, *87*, 12036–12040.



Scheme 32: Phase transfer catalyzed substitution reaction to give alkylated carbamates[94]

Another route to N-C bond formation is the reductive amination of aldehydes (**Scheme 33**).[95] This work presents mono *N*-alkylation of primary amides, thioamides, carbamates and ureas using aromatic and aliphatic aldehydes as alkylating agents. While the method does result in high yields for the substrates shown, the optimization and scope are limited. The method is also only compatible with aldehydes, meaning only secondary amides are accessible using this method.



Scheme 33: Reductive amination of aldehydes to give alkylated carbamates

Amination of alcohols has been an emerging method towards N-C bond formation since 2002, with many transition metals proven to catalyze this transformation.[96] However, this generally requires harsh reaction conditions and extended reaction times, which limits the applicability of this approach. The Niggemann group recently reported a new calcium-based, highly Lewis acidic system that catalyzes the direct amination of secondary and tertiary benzylic, allylic and tertiary propargylic alcohols with nitrogen nucleophiles under very mild reaction conditions (**Scheme 34**).[97] This presents a viable route to access secondary and tertiary amides.

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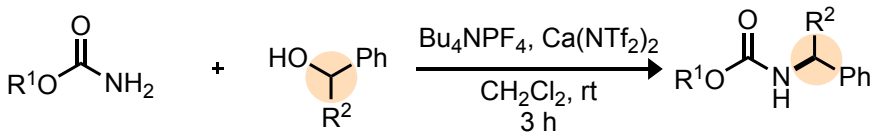
[95] D. Dubé, A. A. Scholte, *Tetrahedron Letters,* **1999**, *40, 2295–2298.*
[96] (a) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami, M. Yoshifuji, *J. Am. Chem. Soc.* **2002**, *124*, 10968- 10969; (b) Y. Kayaki, T. Koda, T. Ikariya, J. Org. Chem. 2004, 69, 2595-2597; (c) H. Kinoshita, H. Shinokubo, K. Oshima, *Org. Lett.* **2004**, *6,* 4085-4088; (d) J. Muzart, *Eur. J. Org. Chem.* **2007**, 3077-3089; (e) T. Nishikata, B. H. Lipshutz, *Org. Lett.* **2009**, *11*, 2377-2379; (f) O. Piechaczyk, C. Thoumazet, Y. Jean, P. le Floch, *J. Am. Chem. Soc.* **2006**, *128*, 14306-14317; (g) I. Usui, S. Schmidt, M. Keller, B. Breit, *Org. Lett.* **2008**, *10*, 1207-1210.
[97] S. Haubenreisser, M. Niggemann, *Adv. Synth. Catal.* **2011**, *353*, 469–474.



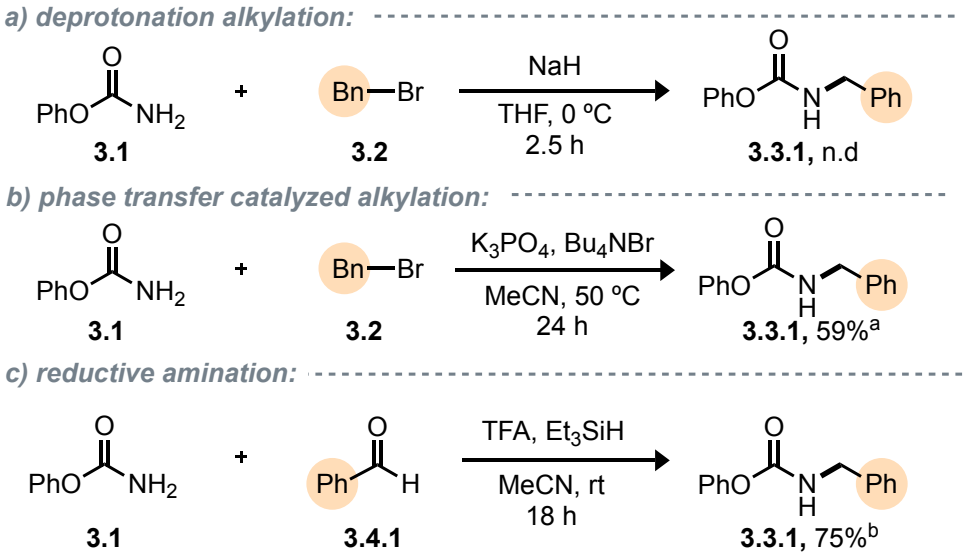
Scheme 34: Calcium-catalyzed direct amination of secondary and tertiary benzylic alcohols with nitrogen nucleophiles

All methods above were worth evaluating since once established, the subsequent reaction C-C bond forming reaction would already have a good leaving group ready to engage in established chemistry. Herein, proof of principle of the use of reagent **3.1** as a new, simpler linchpin reagent with different polarity to the linchpin presented in Chapter 2 is presented. This chapter will demonstrate the utility of the alternate linchpin to access motifs inaccessible using the chemistry established in the previous chapter.

3.2: N-C Bond formation towards masked *C*-isocyanates

The initial hits reported in this section (Scheme 35) were obtained by B. Uppalapati.

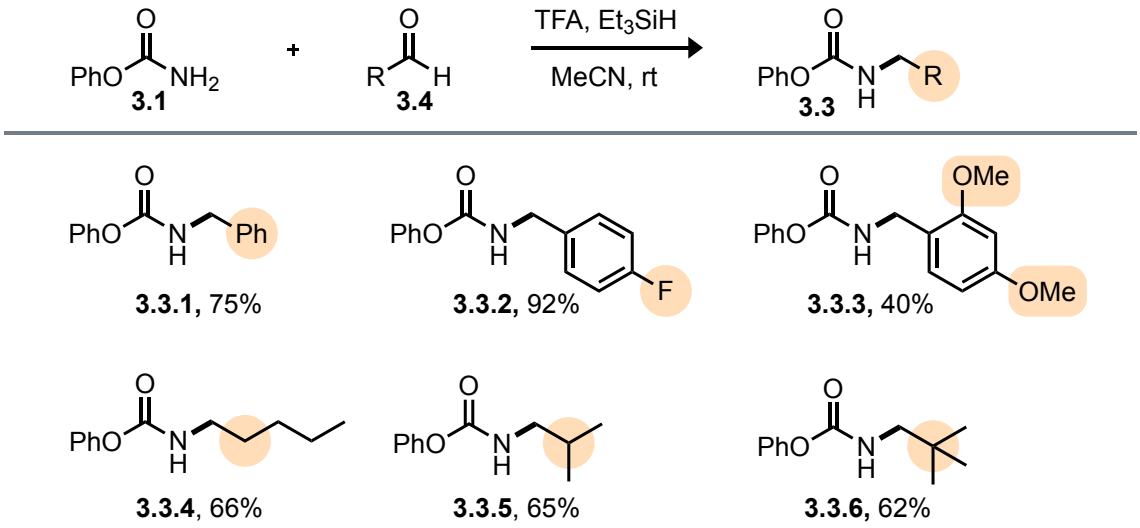
Several approaches were investigated to identify the most practical and efficient route to the target compound (**Scheme 35**). Experiments using the deprotonation–alkylation conditions deemed the route impractical due to the high reactivity of sodium hydride under the reaction conditions. Alternatively, phase-transfer catalyzed alkylation[94] with benzyl bromide afforded the desired product **3.3.1** in a promising 59% NMR yield (**Scheme 35b**). However, the reductive amination[95] with benzaldehyde proved more effective, delivering the target product **3.3.1** in a 75% isolated yield (**Scheme 35c**).



Scheme 35: Routes towards *N*-benyzlphenylcarbamate

[a] ^{1}H NMR yield [b] Isolated yield

Among the synthetic approaches explored for accessing carbamates, reductive amination of aldehydes emerged as the most efficient and reliable method. Conditions used phenyl carbamate **3.1**, trifluoroacetic acid and triethylsilane to provide the desired functionalized phenyl carbamate products **3.3**. With these conditions in hand, a preliminary substrate scope towards alkyl carbamates was attempted (**Scheme 36**).

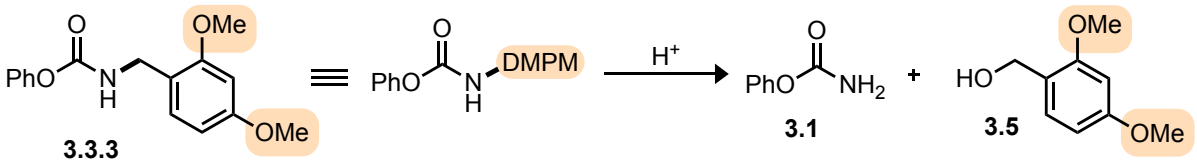


Scheme 36: Preliminary substrate scope towards alkyl carbamates

[a] Conditions: Linchpin reagent **3.1** (3.0 equiv.), aldehyde **3.4** (1.00 mmol, 1.0 equiv.), TFA (2.9 equiv.), Et_3SiH (3.0 equiv.) under Ar, in MeCN, rt, 18 hours.

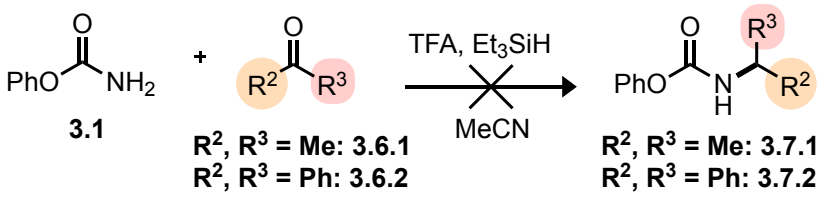
Most aldehydes **3.4** were converted to the desired amination products **3.3** in good yields (**Scheme 30**). The use of benzaldehydes (**3.3.1-3**) and alkyl aldehydes (**3.3.4-6**) gives similar yields. A reduction in yield was observed with **3.3.3** due to degradation of product under the acidic conditions. This target product contains what is known as a DMPM protected nitrogen. This motif is a common protecting group for amines and is readily removed under acidic conditions (**Scheme 37**).[98] Deprotection of this motif under acidic conditions would regenerate the starting carbamate **3.1** and the alcohol **3.5**. Since the carbamate is in excess, this degradation of product must be observed via formation of the alcohol, which was potentially formed according to NMR analysis (extra methoxy peaks and benzyl peaks which did not correspond to the aldehyde nor product). Despite this degradation, the target product **3.3.3** was acquired in 40% yield.

[98] (a) J. L. Marco, J. A. Hueso-Rodríguez, *Tetrahedron Lett.* **1988**, *29*, 2459–2462; (b) K. Horita, R. Abe, O. Yonemitsu, *Tetrahedron Lett.* **1988**, *29*, 4139–4142; (c) K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, O. Yonemitsu, *Tetrahedron* **1986**, *42*, 3021–3028.



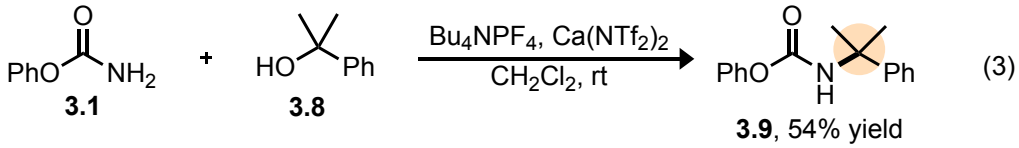
Scheme 37: DMPM deprotection under acidic conditions

This method was not amenable to all substrates attempted. The method was attempted with ketones **3.6** in order to give substituted products **3.7**, however, the starting materials did not react despite extensive reaction time (48 h) and prolonged heating (rt to 80 ºC) (**Scheme 38**). Thus, optimization of this reaction or a different method would need to be employed in order to access secondary and tertiary products.



Scheme 38: Limitation of reductive amination towards carbamates

To access such products, a calcium-catalyzed amination of π-activated alcohols with nitrogen nucleophiles were used.[97] The reaction between reagent **3.1** and the tertiary alcohol **3.8** yielded target product **3.9** in moderate yield (**Equation 3**). This entry provided proof of concept that this linchpin reagent can react to give tertiary alkyl carbamates. The procedure also suggested that it was possible to react with secondary alcohols and propargylic alcohols, though this has yet to be attempted using linchpin reagent **3.1** and is part of the future work associated with this project.

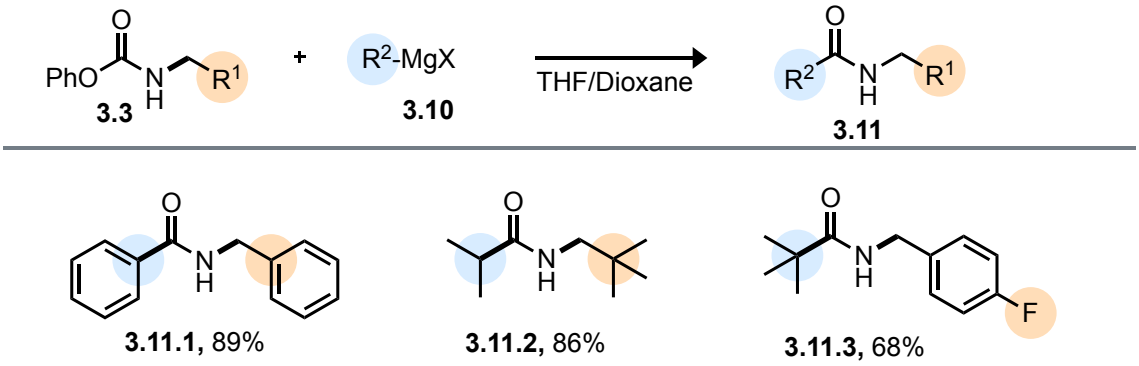


Equation 3: Preliminary access to tertiary alkyl carbamate products

The results presented in **Scheme 36** and **Equation 3** demonstrated that the new, simple linchpin reagent **3.1** provides access to a variety of alkyl carbamates (**3.3.1-6 and 3.9**), which are masked *C*-isocyanates that were inaccessible using linchpin reagent **2.1.6**.

3.3: C-C bond formation towards amide synthesis

Chapter 2 demonstrated the use of phenyl carbamates **2.3** as substrates for the formation of amide products. Building on this, the same chemistry was applied to alkyl carbamates **3.3** and **3.9** to evaluate their reactivity. Success in this reaction would validate the use of the simple reagent **3.1** as an alternative amide linchpin reagent.



Scheme 39: Preliminary substrate scope towards amides using alkyl carbamates

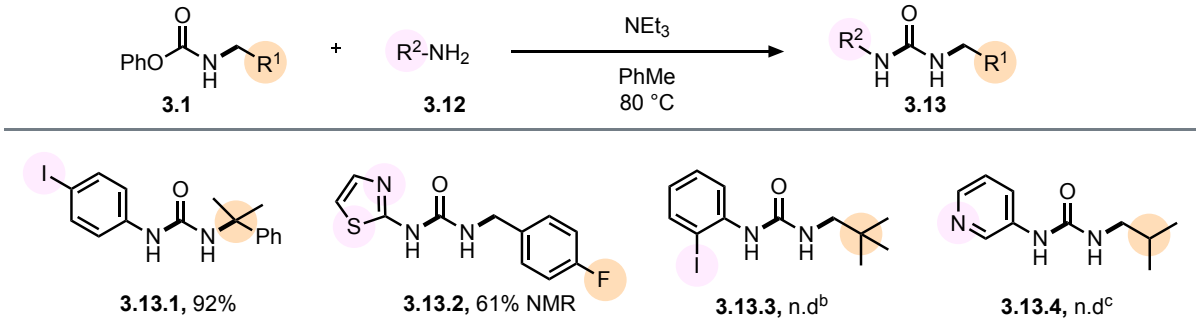
[a] Conditions: Masked *C*-isocyanate **3.3** (0.20 mmol, 1.0 equiv.), Grignard reagent **3.10** (4.0 equiv.), under Ar, in THF/dioxane, rt, 30 minutes.

Scheme 39 shows a preliminary substrate scope towards amides using alkyl carbamates. The target amide products **3.11.1** and **3.11.2** were achieved in high yield, whereas amide **3.11.3** is obtained in moderate yield.

The results in **Scheme 36** and **Scheme 39** highlight that amide linchpin reagent **3.1** provides access to a variety of secondary amides through a reductive amination / Grignard addition sequence and holds potential for broad applicability. Additional work remains needed to determine the full scope associated with this new linchpin reagent.

3.4: C-N bond formation towards urea synthesis

The use of linchpin reagent **3.1** provides access to alkyl carbamates **3.3** and **3.9**, which were attempted to be converted to unsymmetrical ureas (**3.13)** (**Scheme 40**). The only isolated entry in this substrate scope is unsymmetrical urea **3.13.1**, which was synthesized from the tertiary alkyl carbamate **3.9**. From these preliminary experiments, it appears that the primary alkyl carbamates **3.3** behave differently compared to tertiary alkyl carbamates under the reaction conditions. Substrates **3.13.2, 3.13.3** and **3.13.4** reacted to give a mixture of urea products. For substrates **3.13.3** and **3.13.4**, no internal standard was added to the NMR samples, thus no yield analysis could be performed. The reaction to synthesize **3.13.3** did not go to completion, with alkyl carbamate starting material **3.3.5** present via TLC and NMR analysis. Despite this, the reaction mixture contained a ratio of 0.11:1 for the unsymmetrical urea **3.13.3** and its symmetrical counterpart. The reaction to synthesize **3.13.4** did go to completion according to TLC and NMR analysis, however, the reaction mixture contained a ratio of 0.76:1 for the unsymmetrical urea **3.13.3** and its symmetrical counterpart.



Scheme 40: Preliminary substrate scope towards ureas using alkyl carbamates

[a] Conditions: Masked *C*-isocyanate **3.3** (0.20 mmol, 1.0 equiv.), amine reagent **3.12** (1.2 equiv.) and NEt_3 (0.25 equiv.), under Ar, in toluene, 80 ºC, 16 h; [b] Reaction did not go to completion, ratio of 0.11:1 for the unsymmetrical urea **3.13.3** and its symmetrical counterpart; [c] Reaction did go to completion, ratio of 0.76:1 for the unsymmetrical urea **3.13.4** and its symmetrical counterpart.

Primary alkyl carbamates are less electrophilic than their aryl carbamate counterparts. This lower electrophilicity may render them less reactive with nitrogen nucleophiles and more susceptible to side reactions with stronger nucleophiles. As a result, reactions involving these primary carbamates yield mixtures of unsymmetrical and symmetrical ureas, making isolation challenging. On the other hand, tertiary alkyl carbamate is sterically hindered, potentially contributing to the faster formation of the target product.

In contrast, the reactions with tertiary carbamate **3.9** or aryl carbamates **2.3** discussed in Chapter 2 proceed with greater selectivity and less side-reactions. To investigate this issue further, substrate **3.3.2** was used to model the reactivity of primary alkyl carbamates (**Table 9**).

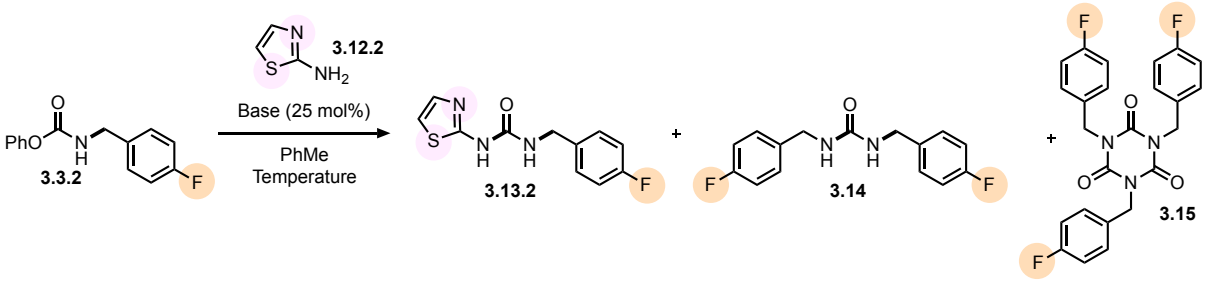


Table 9: Optimization for urea formation with alkyl carbamates

Entry[a]	Temperature (ºC)	Base (25 mol%)	Yield of **3.13.2** (%)[b]	Yield of **3.14** (%)[b]	Yield of **3.15** (%)[b,c]
1	80	NEt_3	61	15	0
2	rt	NEt_3	0	0	0
3[d]	80	NEt_3	47	19	12
4	80	DMAP	29	6	57
5	110	NEt_3	52	19	10
6	110	DMAP	38	2	60

[a] Conditions: Masked *C*-isocyanate **3.3.2** (0.20 mmol, 1.0 equiv.), amine reagent **3.12.2** (1.2 equiv.) and NEt_3 (0.25 equiv.), under Ar, in toluene, 80 ºC., 16 h; [b] ^{1}H-NMR yield using 1,3,5-trimethoxybenzene as an internal standard; [c] It is hypothesized that this product could be the trimerized isocyanate product, however, isolation and characterization would be required in order to confirm this; [d] Standard conditions were modified to add 1.00 equiv. of distilled H_2O.

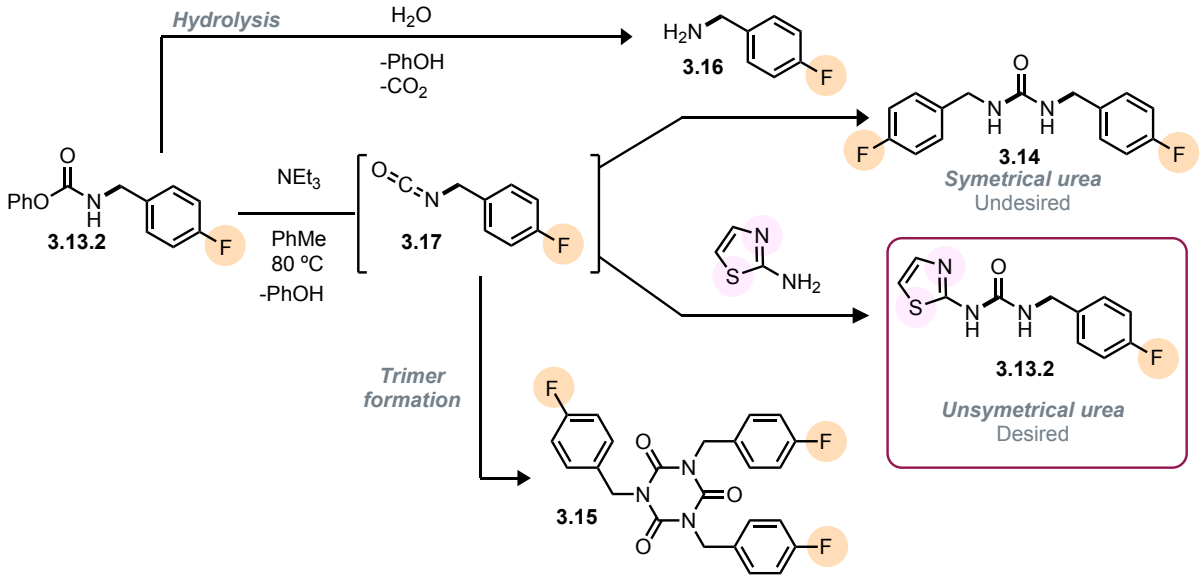
Using the standard urea conditions (entry 1), the unsymmetrical urea **3.13.2** product was obtained in a mixture with the symmetrical urea **3.14**. These products were observed as two separate spots on the TLC with a ΔR_f of 0.2 in 10% EtOAc/Hexanes, thus, the product was attempted to be purified via recrystallization with dichloromethane, and silica-gel flash column chromatography (100% hexanes to 10% EtOAc/hexanes) and silica-gel flash column chromatography (100% CH_2Cl_2 to 2% MeOH/ CH_2Cl). The purification always yielded an inseparable mixture of the unsymmetrical and symmetrical ureas. Despite the inseparable mixture, the unsymmetrical urea **3.13.2** was obtained in a 61% ^{1}H NMR yield and the symmetrical urea **3.14** was obtained in a 15% ^{1}H NMR yield.

It was then of interest to suppress the side-reaction pathway that lead to the formation of symmetrical urea (**Scheme 41**). First, the reaction temperature was lowered to stop degradation of the carbamate, however, this was not conducive to product formation of any kind. It was then hypothesized that the product was decomposing due to reaction with water. Hydrolysis of the carbamate would lead to the decarboxylation yielding the free amine **3.16**.[99] This free amine could react with a molecule of free isocyanate **3.17**, generating the symmetrical urea **3.14** (**Scheme 41**). This hypothesis was evaluated with entry 3, where an equivalent of water is added. The results of this reaction did not enable the formation of the symmetrical urea, however, the yield of unsymmetrical urea **3.13.2** decreased and a third unknown product **3.15** appeared.

This third product does not correspond to the free amine **3.16** nor the carboxylic acid resulting from the hydrolysis reaction prior to decarboxylation. It was hypothesized that this product could be the trimerized isocyanate product **3.15**, however, it was not possible to isolate and characterize this compound. This trimer would form from the trimerization of three molecules

[99] L. W. Dittert, T Higuchi*, J. Pharm. Sci.* **1963***, 52*, 852.

of free isocyanate.[44,100] This is a known process that occurs when the concentration of free isocyanate *in situ* is high and a base is present to catalyze the reaction.



Scheme 41: Proposed side-reactions occurring under the urea reaction conditions

Increasing the temperature from 80 ºC to 110 ºC (entry 5) shows the formation of this third product **3.15**, as well as a slight decrease in unsymmetrical urea yield. This would provide potential further evidence for the formation of the trimer **3.15**, since higher temperatures enable faster deblocking reaction rates, potentially leading to more free isocyanate *in situ*.

To further confirm this, a different base was used. By using a DMAP, a nucleophilic catalyst base, the deblocking reaction would be expected to be faster, potentially generating a larger concentration of free isocyanate *in situ.* In varying the base to DMAP (entries 4 and 6), this third side-product **3.15** was observed in even larger quantities. The formation of the unsymmetric and symmetric urea was suppressed. If the hypothesis that the third product is the trimer is correct, then increasing the base loading should further enhance the yield of this product.

[100] A. Al Nabulsi, D. Cozzula, T. Hagen, W. Leitner, T. E. Müller, *Polym. Chem.* **2018**, *9*, 4891–4899.

In the report from Beauchemin on base-catalyzed aminocarbonylation of O-Ph derived carbazates (masked *N*-isocyanates), the following trends were noted.[101] When loadings of base were increased or when stronger bases were used, the amount of dimerization byproduct increased; however, when the loadings of base were decreased starting material remained. This was expected, since increased base loadings or the use of stronger bases would increase the concentration of isocyanates *in situ*, resulting in increased isocyanate dimerization. While it is important to note that this study does deal with masked *N*-isocyanates rather than masked *C*-isocyanates, there is potential that these trends translate to the carbon-based system and thus will be investigated in due time. It should also be noted that 2-aminothiazole is a relatively weak nucleophile, and that this could favor byproduct formation over the desired product.

Further reactions and optimization are required to expand this method towards a broadly applicable urea synthesis. If the hypothesis that the trimer **3.15** is formed is confirmed, then efforts can be focused on suppressing this side-reaction while increasing reactivity towards unsymmetrical urea formation. Specifically, a bulky base, such as DBU, could be used to slow the deblocking reaction to hopefully promote unsymmetrical urea formation. Alternatively, deprotonated nitrogen nucleophiles, are of interest. Reverse addition could also be used to reduce to concentration of free isocyanate *in situ*.

3.5: Conclusion and Future Work

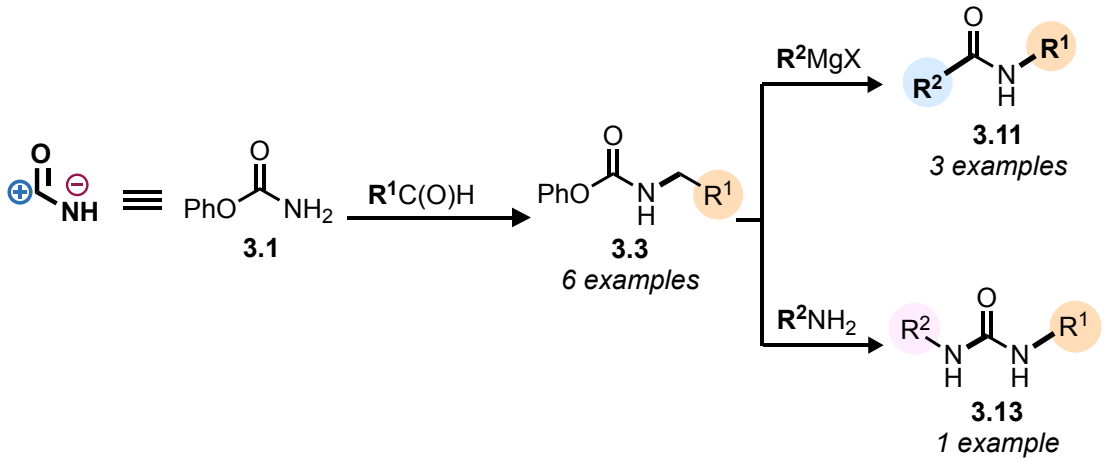
This chapter reports proof of principle of the use of reagent **3.1** as a new, simpler linchpin with different polarity to the linchpin presented in Chapter 2. This chapter shows the utility of the alternate linchpin to access motifs inaccessible using the chemistry established in the previous

[101] R. A. Ivanovich, J. Q. Quartus, N. Das Neves, F. Loiseau, M. Raymond, A. M. Beauchemin, *J. Org. Chem.* **2019**, *84*, 9792–9800.

chapter (**Scheme 42**). The new amination substrates **3.3** readily react with Grignard reagents to access a variety of amides **3.11**. However, the amination substrates show different reactivity than the aryl carbamates shown in Chapter 2 when reacting with amines and anilines to access unsymmetrical ureas **3.13**.

The preliminary investigation into the synthesis of unsymmetrical ureas from alkyl carbamates revealed key limitations that must be addressed for this strategy to be broadly applicable for urea synthesis. While the use of a tertiary alkyl carbamate **3.9** successfully yielded the desired unsymmetrical urea **3.13.1**, attempts to generalize this method to primary alkyl carbamates **3.3** led to significant challenges, including inseparable mixtures of unsymmetrical and symmetrical ureas and the formation of unidentified side products. The contrasting reactivity observed between the tertiary and primary alkyl carbamates suggests that steric and/or electronic factors play a critical role in determining the success of the transformation. These results highlight the need for further optimization of reaction conditions or structural modifications to improve the efficiency and scope of urea formation from primary alkyl carbamates. Future work will focus on expanding the scope of alkyl carbamates and exploring alternative bases, to enhance the selectivity and efficiency of unsymmetrical urea formation.

Future work will also be focused on the use of simpler linchpin reagent **3.1** to synthesize a variety of lactams and cyclic NCO-containing molecules.

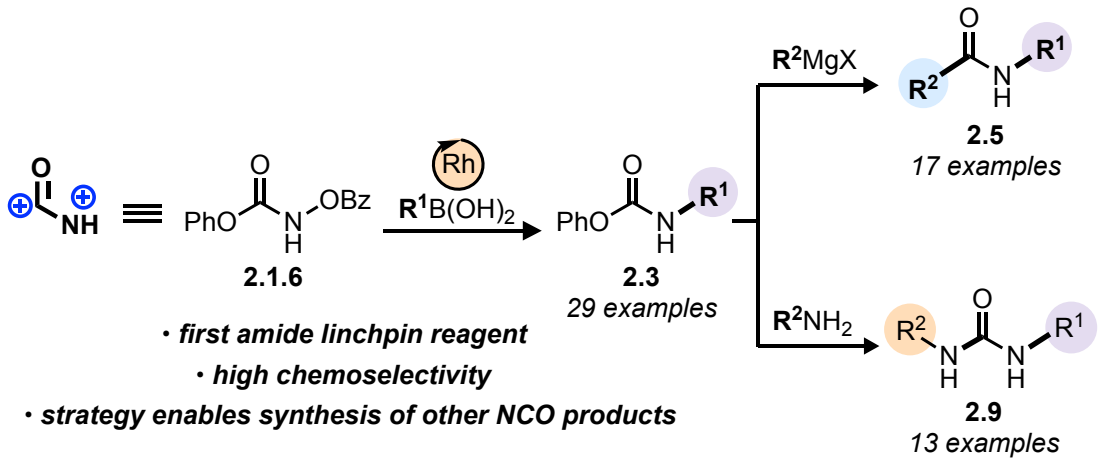


Scheme 42: Use of amphoteric linchpin towards the synthesis of amides and ureas

Chapter 4: Conclusions and Future Work

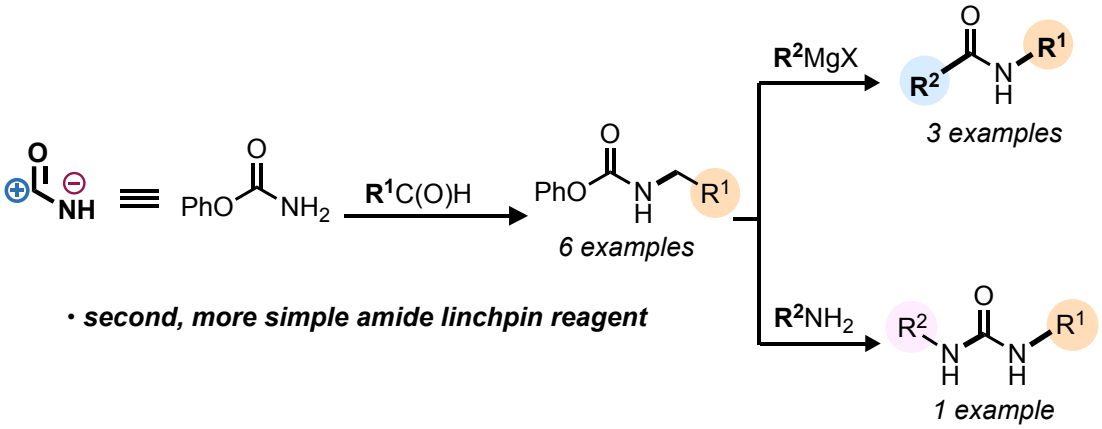
In conclusion, linchpin reagents for the synthesis of NCO-containing molecules have been developed. Indeed, the work presented here demonstrates that control of the in-situ formation of highly reactive intermediates, e.g. *O*-isocyanates and *C*-isocyanates, allows for selective reactions for the formation of C-N and C-C bonds.

First, a masked *O*-isocyanate reagent **2.1.6** with optimized leaving groups (OPh and OBz) was shown to function as an effective amide linchpin reagent, overcoming the limitations of traditional amide syntheses by incorporating a built-in N–C(=O) bond. The amide linchpin reagent was initially functionalized via rhodium-catalyzed electrophilic amination, followed by derivatization using Grignard reagents to yield hindered secondary amides and enamides **2.5 (Scheme 43)**. Tertiary amides **2.6** were also accessed by trapping the magnesium amidate intermediate with an alkylating agent. Finally, extensions toward a general NCO linchpin were explored through the synthesis of lactams **2.7** and unsymmetrical ureas **2.9**. However, limitations of the amination method remained: substrates derived from alkyl boronic acids could not be accessed, as these boronic acids were not suitable coupling partners. Despite this, the C–N bond formation strategy proved useful for generating a variety of masked isocyanate derivatives.



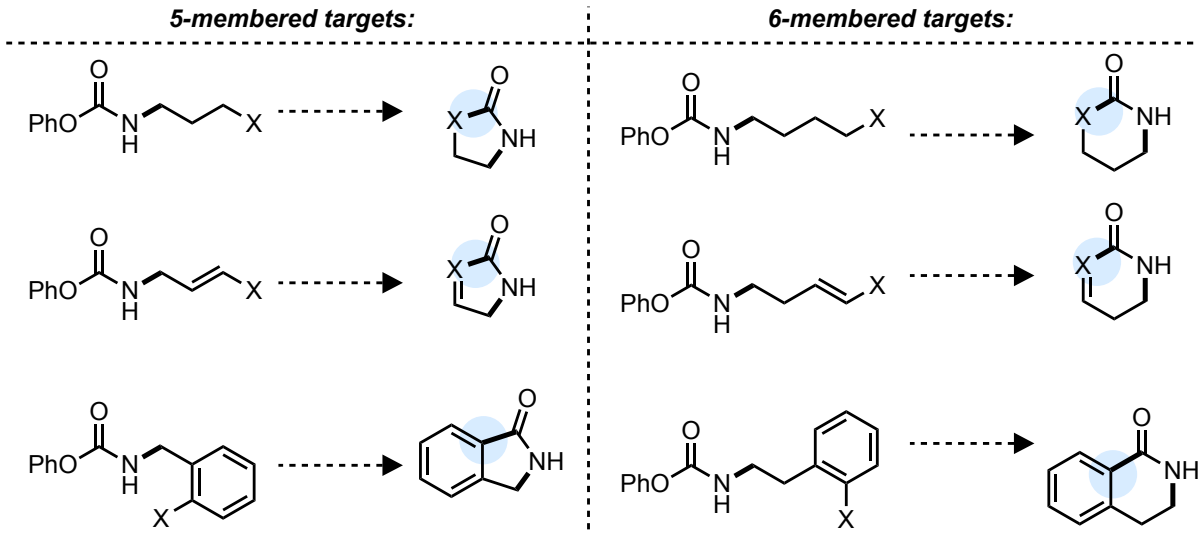
Scheme 43: Use of the first linchpin towards the synthesis of amides and ureas

Then, a second-generation, simpler linchpin reagent **3.1** was developed. The nature of this reagent was amphoteric in nature, enabling different reactivity to the first linchpin reagent. This addresses the above limitations (**Scheme 44**). The linchpin reagent was first functionalized via reductive amination, followed by derivatization using Grignard reagents to provide secondary amides **3.10** or using amines to provide unsymmetrical ureas **3.13**. While this method does give access to amides with alkyl chains on the nitrogen of the amide, this method does not yet extend to readily access ureas due competing reaction pathways.



Scheme 44: Use of amphoteric linchpin towards the synthesis of amides and ureas

Future work involves improving the applicability of this new reagent in synthesis, including the use of this amphoteric linchpin reagent to access a variety of biologically important targets, using intermolecular reactions. In addition, products formed by intramolecular reactivity are equally of interest. The approach of intramolecular cyclization by applying halogen-metal exchange for the formation of organometallic/heteroatom-isocyanate intermediate has significant potential to form interesting heterocycles in an efficient manner using the linchpin approach (**Scheme 43**). A variety of NCO containing molecules, such as lactams and molecules containing the ONCO motif as well as the NNCO motif are of interest.



Scheme 45: Target cyclic products using simpler linchpin reagent **3.1**

Chapter 5: Supplementary Information

General Experimental Details

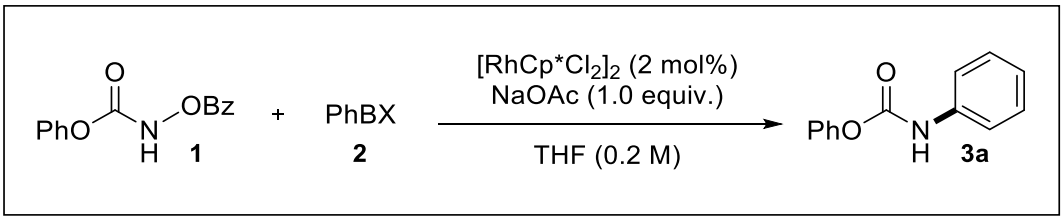
All reactions were carried out under argon atmosphere unless otherwise noted. Reaction heating was accomplished via an oil bath. Purification by column chromatography was performed using SiliCycle SiliFlash F60 230-400 mesh silica gel. Analytical thin layer chromatography (TLC) was performed on aluminum backed plates (EMC Chemicals, TLC Silica Gel 60 F_{254}), cut to size. Visualization was accomplished with UV light (254 nm – fixed wavelength), followed by staining with cerium ammonium molybdate (CAM) solution and heating. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 MHz, 400 MHz, 500 MHz, or 600 MHz spectrometer at ambient temperature.^{19}F NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer at ambient temperature. Spectral data are reported in ppm using solvent as the reference (chloroform-*d* at 7.26 ppm, dimethylsulfoxide-d_6 at 2.50 ppm, acetone-d_6 at 2.05 ppm or methanol-d_4 at 3.31 ppm for ^{1}H NMR; chloroform-*d* at 77.16 ppm, dimethylsulfoxide-d_6 at 39.52, acetone-d_6 at 29.84 or methanol-d_4 at 49.00 ppm for ^{13}C NMR, and trifluorotoluene at –63.72 ppm for ^{19}F NMR). ^{1}H NMR data are reported as: multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant(s) in Hz. Melting point (M.p.) temperatures were obtained using a Gallenkamp Melting Point Apparatus. Infrared (IR) spectra were obtained were recorded on an Attenuated Total Reflectance Fourier Transform Infrared spectrometer (ATR-FTIR). High-resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70 eV (EI) or Micromass Q-TOF I - Time of flight Electrospray Ionisation mass spectrometer (ESI). Unless otherwise noted, all starting materials and catalysts were purchased from commercial sources and used without further purification. Commercial Grignard reagents were titrated with salicylaldehyde phenylhydrazone prior to usage. Alkylating agents were passed through pipette columns containing basic alumina to remove impurities prior to usage. Tetrahydrofuran and dichloromethane were passed through a solvent purification system prior to usage. Dimethylformamide and 1,4-dioxane were stored over activated 3Å sieves for at least 3 days prior to usage.

Reaction Optimization

General Procedure for the Optimization of Rhodium-Catalyzed Amination of Reagent 1 with Aromatic Boronic Acids (Table S1)

To a microwave vial charged with a stir bar was added linchpin reagent 2.1.6 (1.00 equiv.), boron reagent **2** (1.20 equiv.), base (1.00 equiv.) and $[RhCp^*Cl_2]_2$ (2 mol%). The microwave vial was sealed and purged with argon for 5 minutes. Then, the appropriate solvent (0.2 M) was added via syringe and the reaction mixture was heated and stirred until the reaction was assessed complete by TLC. The reaction was removed from heat, quenched with water, and extracted with CH_2Cl_2 (3 x 5 mL on a 0.1 mmol scale). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was analyzed by NMR using 1,3,5-trimethoxybenzene as an internal standard. The conditions of Hirano and Miura, reported for the rhodium-catalyzed electrophilic amination of aryl boronic acids with secondary hydroxylamines, served as a starting point for the optimization of our conditions with masked *O*-isocyanate **1**.[57]

Table S1. Optimization of Boron Coupling Reagent[a]



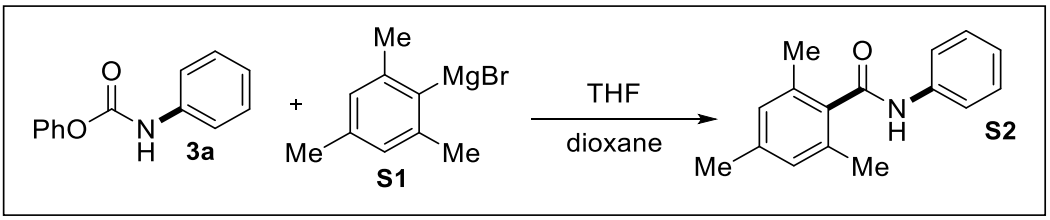
Entry	Boron Reagent	Yield of 3a (%)[b]
1	$Ph(BO)_3$[c]	99
2	$PhBF_3K$	0
3	**$PhB(OH)_2$**	**99**
4	PhBpin	0

[a] Reaction conditions: Linchpin reagent 2.1.6 (0.10 mmol, 1.00 equiv.), boron reagent **2** (0.12 mmol, 1.20 equiv.), $[RhCp^*Cl_2]_2$ (2 mol%), NaOAc (0.10 mmol, 1.20 equiv.), THF (0.5 mL, 0.2 M), Ar atmosphere, 18 h. [b] Yield of **3a** was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] 1.20 equiv. of $Ph(BO)_3$ refers to the equivalents of the entire boroxine unit.

General Procedure for the Optimization of Grignard Addition to Masked *C*-Isocyanates

An oven-dried microwave vial equipped with a stir bar was cooled under argon and charged with Grignard reagent **4** (4.00 equiv.) and dioxane. A separate 5-mL oven-dried round-bottom flask was cooled under argon, charged with masked *C*-isocyanate **3** (1.00 equiv.) and dissolved in THF. Order of addition and specific details are mentioned below the table. The reaction was stirred at appropriate temperature until assessed complete by TLC. The reaction was quenched with saturated aqueous ammonium chloride and extracted with EtOAc (3 x 5mL). The organic layers were combined, dried with sodium sulfate, and concentrated *in vacuo* to obtain the crude product, which was analyzed by NMR using 1,3,5-trimethoxybenzene as an internal standard. The conditions of Schafer and Bode, reported for the addition of Grignard reagents to isocyanates, served as a starting point for the optimization of our conditions with masked *C*-isocyanate **3**.[55]

Table S2. Partial Optimization of Grignard Addition to Masked *C*-Isocyanates[a]

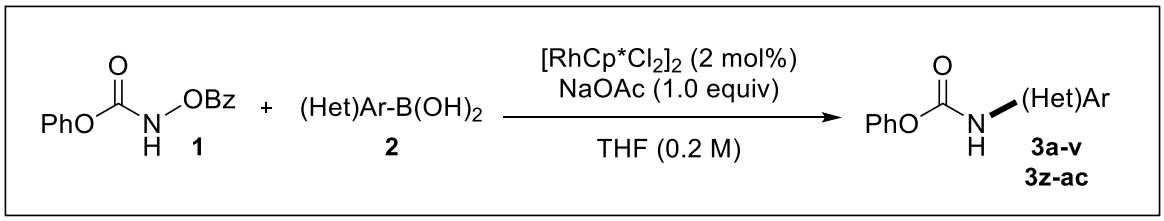


Entry	Conditions	Yield (%)[b]
1	1.00 equiv. Grignard, [*C*-isocyanate] = 0.20 M	55%[c]
2	2.00 equiv. Grignard, [*C*-isocyanate] = 0.17 M	50%[d]
3	4.00 equiv. Grignard, [*C*-isocyanate] = 0.12 M	37%[e]
4	4.00 equiv. Grignard, [*C*-isocyanate] = 0.075 M	80%[f]
5	4.00 equiv. Grignard with dioxane, [*C*-isocyanate] = 0.075 M	50%[g]
6	**4.00 equiv. Grignard with dioxane, [*C*-isocyanate] = 0.075 M**	**80%[h]**

[a] Conditions: Masked isocyanate **3a** (0.50 mmol, 1.00 equiv.), Grignard **S1**, THF, 0 °C to r.t., under Ar, 30 min. [b] Yield of **S2** was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] **S1** (0.63 mL, 0.50 mmol, 1.00 equiv., 0.80 M in THF) added dropwise to **3a** (0.50 mmol, 1.00 equiv.) in THF (2.00 mL, 0.25 M). [d] **S1** (1.25 mL, 1.00 mmol, 2.00 equiv., 0.80 M in THF) added dropwise to **3a** (0.50 mmol, 1.00 equiv.) in THF (2.00 mL, 0.25 M). [e] **S1** (2.50 mL, 2.00 mmol, 4.00 equiv., 0.80 M in THF) added dropwise to **3a** (0.50 mmol, 1.00 equiv.) in THF (2.00 mL, 0.25 M). [f] **3a** (0.20 mmol, 1.00 equiv.) in THF (1.75 mL) added dropwise to **S1** (0.91 mL, 0.80 mmol, 4.00 equiv., 0.80 M in THF). [g] **S1** (2.50 mL, 2.00 mmol, 4.00 equiv., 0.80 M in THF) added in three portions to **3a** (0.50 mmol, 1.00 equiv.) in THF (2.80 mL) and dioxane (1.40 mL) to achieve [**3a**] = 0.075 M. [h] **3a** (0.50 mmol, 1.00 equiv.) in THF (2.80 mL) and dioxane (1.40 mL) added dropwise to **S1** (2.50 mL, 0.80 mmol, 4.00 equiv., 0.80 M in THF).

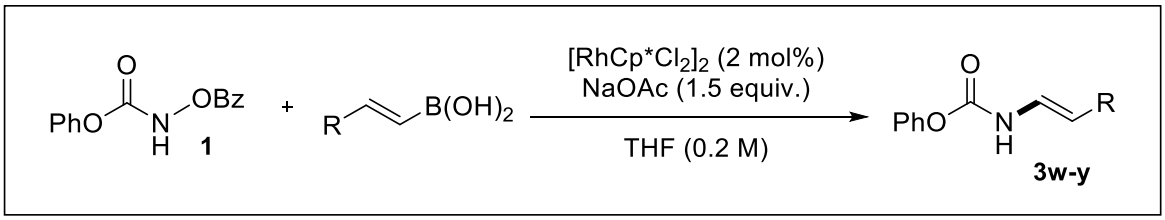
General Procedures

General Procedure A: Amination of Reagent 1 with (Hetero)Aromatic Boronic Acids



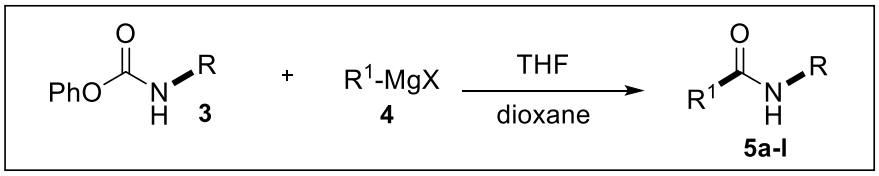
To a microwave vial charged with a stir bar was added masked *O*-isocyanate **1a** (1.00 equiv.), boronic acid (1.20 equiv.), sodium acetate (1.00 equiv.) and $[RhCp^*Cl_2]_2$ (2 mol%). The microwave vial was sealed and purged with argon for 5 minutes. Then, THF (0.2 M) was added via syringe and the reaction mixture was stirred at 40 ºC until the reaction was assessed complete by TLC. The reaction was removed from heat, quenched with water, and extracted with CH_2Cl_2 (3 x 5 mL on a 0.1 mmol scale). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified via silica-gel flash column chromatography. (Note: It was noted after method development that washing the combined organic phases with aqueous sodium bicarbonate usually removes most of the benzoic acid by-product).

General Procedure B: Amination of Reagent 1 with Alkenyl Boronic Acids



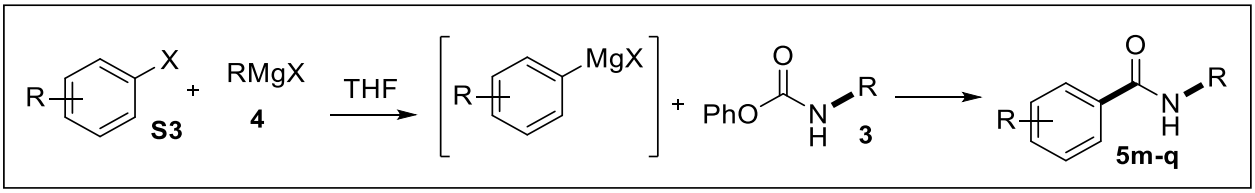
To a microwave vial charged with a stir bar was added masked *O*-isocyanate **1a** (1.00 equiv.), boronic acid (1.50 equiv.), sodium acetate (1.00 equiv.) and $[RhCp^*Cl_2]_2$ (2 mol%). The microwave vial was sealed and purged with argon for 5 minutes. Then, CH_3OH (0.2 M) was added via syringe and the reaction mixture was stirred at 40 ºC until the reaction was assessed complete by TLC. The reaction was removed from heat, quenched with water, and extracted with CH_2Cl_2 (3 x 5 mL on a 0.1 mmol scale). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified via silica-gel flash column chromatography. The conditions of Feng and Loh, reported for the rhodium-catalyzed cross-coupling of alkenylboronic acids with *N*-pivaloyloxyamides, served as a starting point for the optimization of our conditions with masked *O*-isocyanate **1**.[68]

General Procedure C: Synthesis of Amides from Masked *C*-Isocyanates 3 using Commercial Grignard Reagents



An oven-dried microwave vial equipped with a stir bar was cooled under argon and charged with a solution of the Grignard reagent (4.00 equiv.). Dioxane was added to this microwave vial. A separate 5-mL oven-dried round-bottom flask was cooled under argon, charged with masked *C*-isocyanate **3** (1.00 equiv.) prepared from General Procedure A or B, and dissolved in THF. This solution was added dropwise to the microwave vial and stirred at the appropriate temperature until consumption of starting material was observed by TLC. Individual volumes of reagents and solvents are listed for each reaction based on the concentration of commercially available Grignard reagent, such that [**3**] = 0.075M.

General Procedure D: Synthesis of Amides from Masked *C*-Isocyanates 3 using Prepared Grignard Reagents

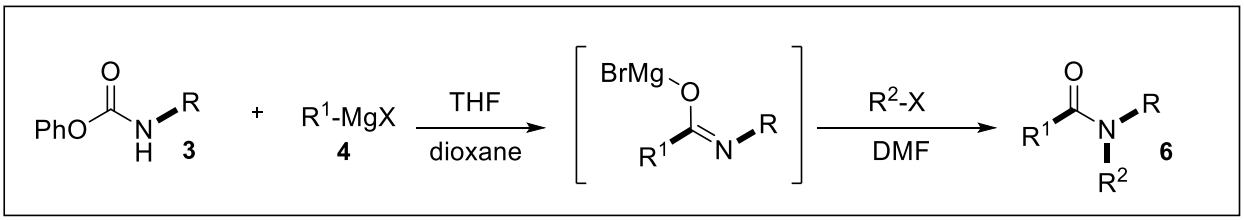


An oven-dried microwave vial equipped with a stir bar was cooled under argon and charged with a (hetero)aryl halide and cooled to the desired temperature. A Grignard reagent or a Turbo-Grignard reagent (*i*-PrMgBr, PhMgBr, or *i*-PrMgCl·LiCl) were added to the vial to allow for halide/magnesium exchange. A separate 5-mL oven-dried round-bottom flask was cooled under argon, charged with masked *C*-isocyanate **3** (1.00 equiv.) prepared from General Procedure A or B, and dissolved in THF. This solution was added dropwise to the microwave vial and stirred at the appropriate temperature until consumption of starting material was observed by TLC. The conditions of Knochel, reported for addition of various electrophiles to Grignard reagents prepared *in situ*, served as a starting point for the optimization of our conditions with masked *C*-isocyanate **3**.[102] It was found that a 1.00 equiv. excess of hetero(aryl) halide was required relative to the amount of Grignard reagent used to prevent undesired addition products from the Grignard

[102] (a) G. Varchi, C. Kofink, D. M. Lindsay, A. Ricci, P. Knochel, *Chem. Commun.* **2003**, 396-397; (b) M. Abarbri, J. Thibonnet, L. Bérillon, F. Dehmel, M. Rottlander, P. Knochel, *J. Org. Chem.* **2000**, *65*, 4618-4634; (c) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333-3336; (d) T. Delacroix, L. Bérillon, G. Cahiez, P. Knochel, *J. Org. Chem.* **2000**, *65*, 8108-8110.

reagents used for halogen/magnesium exchange (addition of *i*-Pr or Ph onto the isocyanate). Individual proportions of reagents and solvents are listed for each reaction.

General Procedure E: *N*-Alkylation of Grignard Amidates

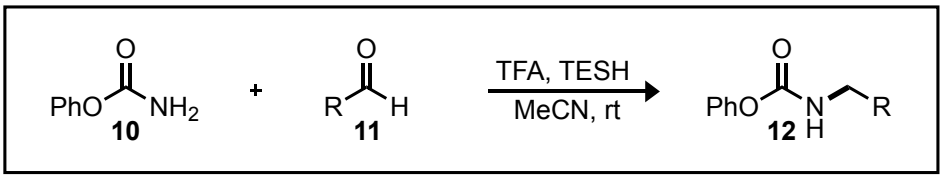


Intermediate amide **5** was prepared according to General Procedure C, followed by removal of the solvents *in vacuo*, and addition of DMF (0.1 M). The corresponding alkyl halide (5.0 or 10.0 equiv.) was added, followed by stirring at room temperature until consumption of starting material was observed by TLC. The reaction mixture was transferred to a round-bottom flask, rinsed with ethyl acetate (10 mL), quenched with 1 M HCl (10 mL), stirred for 5 minutes, neutralized with saturated sodium bicarbonate (10 mL), and transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic layer was collected and washed with saturated sodium bicarbonate (2 x 10 mL), and brine (2 x 10 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford the crude product, which was purified via silica-gel flash column chromatography.

General Procedure F: Synthesis of Ureas from Masked *C*-Isocyanates 3

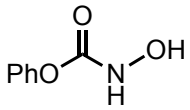
An oven-dried microwave vial equipped with a stir bar was cooled under argon and charged with masked *C*-isocyanate **3** (1.00 equiv.) prepared from General Procedure A or B. Toluene was added to this microwave vial. Triethylamine (0.25 equiv.) and amine reagent (1.20 equiv.) were added and stirred at the appropriate temperature until consumption of starting material was observed by TLC. Cold Et_2O was added to the reaction mixture upon completion of the reaction to give the product as a precipitate that was filtered off, washed with additional cold ether, and dried under high vacuum.

General Procedure G: Synthesis of Masked *C*-Isocyanates from Commercial Reagents



To a microwave vial charged with a stir bar was added phenylcarbamate **10** (3.00 equiv.) and acetonitrile (0.25 M). Then, TFA (2.90 equiv.) is added dropwise over 5 minutes. The aldehyde (1.00 equiv.) was then added, followed by triethylsilane (3.00 equiv.). The reaction mixture was stirred at room temperature until the reaction was assessed complete by TLC. The reaction was quenched with $NaHCO_3$ and extracted with ethyl acetate (3 x 10 mL on a 0.2 mmol scale). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product, which was purified via silica-gel flash column chromatography. The conditions of Dubé, reported for the reductive amination of aldehydes to generate amides was used.[95]

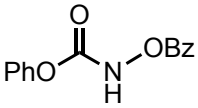
Characterization Data:



Phenyl *N*-hydroxycarbamate (S1): A round bottom flask equipped with a stir bar was charged with K_2CO_3 (7.60 g, 55.0 mmol, 1.10 equiv.) and NH_2OH•HCl (4.52 g, 65.0 mmol, 1.30 equiv.) in Et_2O (45 mL) and water (0.75 mL, 1.10 M total concentration). The solution was stirred at room temperature for 30 minutes, then cooled in an ice bath to 0 ºC. Phenylchloroformate (6.3 mL, 50.0 mmol, 1.00 equiv.) was added in three portions at 0 ºC, then allowed to warm to room temperature. The reaction mixture was stirred for 3 hours, at which time the solids were filtered, and the filtrate was concentrated *in vacuo* to obtain a white solid. This solid was triturated with petroleum ether (3 x 20 mL) and dried to obtain **S4** as a white solid (6.11 g, 80% yield).

S4: The spectral and physical properties of the product match those reported in the literature.[103]

TLC R_f: 0.20 in 20% EtOAc/hexanes**; ^{1}H NMR (400 MHz, Dimethylsulfoxide-d_6) δ** 10.34 (brs, 1H, NH/OH), 9.08 (s, 1H, NH/OH), 7.43 – 7.34 (m, 2H, Ar-H), 7.26 – 7.17 (m, 1H, Ar-H), 7.13 – 7.06 (m, 1H, Ar-H); **^{13}C NMR (101 MHz, Dimethylsulfoxide-d_6) δ** 155.5 (C), 150.7 (C), 129.4 (CH), 125.2 (CH), 121.6 (CH).



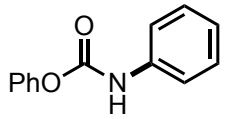
Phenyl *N*-benzoyloxycarbamate (2.1.6): A round-bottom flask equipped with a stir bar was charged with phenyl *N*-hydroxycarbamate (7.74 g, 50.5 mmol, 1.00 equiv.), and CH_2Cl_2 (169 mL, 0.3 M). This mixture was allowed to stir while being cooled to 0 °C in an ice bath. When most of the starting material had dissolved, Et_3N was added (7.0 mL, 50 mmol, 1.0 equiv.) followed by dropwise addition of benzoyl chloride (5.9 mL, 50 mmol, 1.0 equiv.). The ice bath was removed, and the reaction was allowed to warm to room temperature for 30 minutes. After consumption of starting material, as assessed by TLC, the reaction was quenched with water and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were subsequently washed with a saturated $NaHCO_3$ solution (10 mL) and with brine (10 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford **2.1.6** as a white solid (8.79 g, 68% yield).

2.1.6: The spectral and physical properties of the product match those reported in the literature.[104]

TLC R_f: 0.53 in 20% EtOAc/hexanes; **^{1}H NMR (500 MHz, Acetone-d_6) δ** 8.14 – 8.11 (m, 2H, Ar-H), 7.76 – 7.71 (m, 2H, Ar-H), 7.62 – 7.57 (m, 2H, Ar-H), 7.45 – 7.41 (m, 1H, Ar-H), 7.27 (t,

[103] A. O. Stewart, D. W. Brooks, *J. Org. Chem.* **1992**, *57*, 5020–5023.
[104] M. A. Allen, R. A. Ivanovich, D. E. Polat, A. M. Beauchemin, *Org. Lett.* **2017**, *19*, 6574–6577.

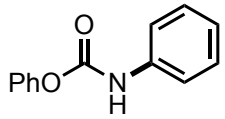
J = 7.4 Hz, 2H, Ar-H), 7.22 (d, *J* = 8.3 Hz, 1H, Ar-H), 6.95 (s, 1H, NH); **^{13}C NMR (126 MHz, Acetone-d_6) δ** 166.1 (C), 155.7 (C), 151.6 (C), 135.2 (CH), 130.5 (CH), 130.3 (CH), 129.9 (CH), 128.0 (C), 126.7 (CH), 122.2 (CH).



Phenyl *N*-phenylcarbamate (2.3.1): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0257 g, 0.100 mmol, 1.00 equiv.), phenylboronic acid (0.0145 g, 0.120 mmol, 1.20 equiv.) in THF (0.5 mL, 0.2 M) at 40 °C for 2 h. The product was purified by silica-gel flash column chromatography (100% CH_2Cl_2) to afford **2.3.1** as a white solid (0.021 g, 99%).

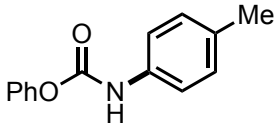
2.3.1: The spectral and physical properties of the product match those reported in the literature.[105]

TLC R*f*: 0.53 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.45 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.43 – 7.38 (m, 2H, Ar-H), 7.37 – 7.32 (m, 2H, Ar-H), 7.25 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.20 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.11 (t, *J* = 7.4 Hz, 1H, Ar-H), 6.95 (brs, 1H, NH); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 151.7 (C), 150.7 (C), 137.5 (C), 129.6 (CH), 129.3 (CH), 125.9 (CH), 124.1 (CH), 121.8 (CH), 118.9 (CH).



Phenyl *N*-phenylcarbamate (2.3.1 - gram scale synthesis): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (1.29 g, 5.00 mmol, 1.00 equiv.), phenylboronic acid (0.731 g, 6.00 mmol, 1.20 equiv.) in THF (25 mL, 0.2 M) at 40 °C for 2 h. The product was purified by recrystallization (CH_2Cl_2/hexanes) to afford **2.3.1** as a white solid (0.910 g, 86% yield).

2.3.1: The spectral and physical properties of the product match those reported in the literature.[105]



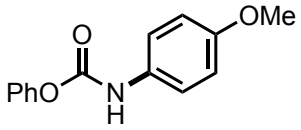
Phenyl *p*-tolylcarbamate (2.3.2): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 4-methylphenylboronic acid (0.0326 g, 0.240 mmol, 1.20 equiv.) in THF (1.0 mL, 0.2 M) at 40 °C

[105] A. B. Shivarkar, S. P. Gupte, R. V. Chaudhari, *J. Mol. Catal. Chem.* **2004**, *223*, 85–92.

for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.2** as a white solid (0.045 g, 99% yield).

2.3.2: The spectral and physical properties of the product match those reported in the literature.[105]

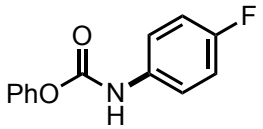
TLC R_f: 0.63 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.45 (dd, *J* = 8.4, 7.4 Hz, 2H, Ar-H), 7.38 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.30 (d, *J* = 6.7 Hz, 1H, Ar-H), 7.26 (m, 2H, Ar-H), 7.19 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.03 (brs, 1H, NH), 2.38 (s, 3H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 151.8 (C), 150.7 (C), 134.9 (C), 133.6 (C), 129.8 (CH), 129.5 (CH), 125.7 (CH), 121.8 (CH), 119.0 (CH), 20.9 (CH_3).



Phenyl (4-methoxyphenyl)carbamate (2.3.3): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 4-methoxyphenylboronic acid (0.0365 g, 0.240 mmol, 1.20 equiv.) in THF (1.0 mL, 0.2 M) at 40 °C for 18 h. The product was purified by recrystallization (CH_2Cl_2/hexanes) to afford **2.3.3** as a white solid (0.042 g, 86% yield).

2.3.3: The spectral and physical properties of the product match those reported in the literature.[106]

TLC R_f: 0.51 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.40 (m, 2H, Ar-H), 7.36 (m, 1H, Ar-H), 7.26 – 7.16 (m, 3H, Ar-H), 6.90 – 6.85 (m, 3H, Ar-H), 3.80 (s, 3H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 156.4 (C), 152.1 (C), 150.8 (C), 130.5 (C), 129.5 (CH), 125.8 (CH), 121.8 (CH), 120.8 (CH), 114.5 (CH), 55.6 (CH_3).



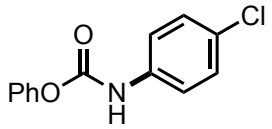
Phenyl (4-fluorophenyl)carbamate (2.3.4): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 4-fluorophenylboronic acid (0.0336 g, 0.240 mmol, 1.20 equiv.) in THF (1.0 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.4** as a white solid (0.036 g, 79% yield).

2.3.4: The spectral and physical properties of the product match those reported in the literature.[107]

TLC R_f: 0.57 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.47 – 7.35 (m, 4H, Ar-H), 7.30 – 7.23 (m, 1H, Ar-H), 7.20 (dd, *J* = 8.6, 1.2 Hz, 2H, Ar-H), 7.09 – 6.95 (m, 3H,

[106] H. Yasuda, J.-C. Choi, S.-C. Lee, T. Sakakura, *J. Organomet. Chem.* **2002**, *659*, 133–141.
[107] A. Velavan, S. Sumathi, K. K. Balasubramanian, *Eur. J. Org. Chem.* **2013**, *2013*, 3148–3157.

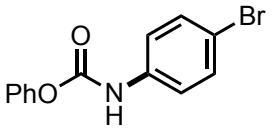
Ar-H); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 159.4 (d, $^{1}J_{C\text{-}F}$ = 242.5 Hz) (C), 152.0 (C), 150.6 (C), 133.5 (CH), 129.6 (CH), 125.9 (CH), 121.8 (CH), 120.7 (CH), 115.9 (d, $^{2}J_{C\text{-}F}$ = 22.7 Hz) (CH); **^{19}F NMR (283 MHz, Chloroform-*d*) δ** -118.8.



Phenyl *N*-(4-chlorophenyl)carbamate (2.3.5): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 4-chlorophenylboronic acid (0.0375 g, 0.240 mmol, 1.20 equiv.) in THF (1.0 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (15% EtOAc/hexanes) to afford **2.3.5** as a white solid (0.036 g, 73% yield).

2.3.5: The spectral and physical properties of the product match those reported in the literature.[108]

TLC R*f*: 0.62 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.43 – 7.29 (m, 4H, Ar-H), 7.29 – 7.20 (m, 3H, Ar-H), 7.20 – 7.14 (m, 2H, Ar-H), 7.09 (s, 1H, NH); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 151.8 (C), 150.5 (C), 136.1 (C), 129.6 (CH), 129.2 (CH), 129.0 (C), 126.0 (CH), 121.7 (CH), 120.1 (CH).



Phenyl *N*-(4-bromophenyl)carbamate (2.3.6): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0257 g, 0.10 mmol, 1.00 equiv.), 4-bromophenylboronic acid (0.0241 g, 0.12 mmol, 1.20 equiv.) in THF (0.5 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (5% EtOAc/hexanes) to afford **2.3.6** as a white solid (0.021 g, 73% yield).

2.3.6: The spectral and physical properties of the product match those reported in the literature.[60a]

TLC R*f*: 0.58 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.45 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.40 (dd, *J* = 7.6, 7.4 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.26 (m, 1H, Ar-H), 7.18 (dd, *J* = 8.6, 1.2 Hz, 2H, Ar-H), 6.95 (brs, 1H, NH); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 151.6 (C), 150.5 (C), 136.6 (C), 132.3 (CH), 129.6 (CH), 126.0 (CH), 121.7 (CH), 120.4 (CH), 116.7 (C).

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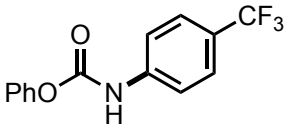
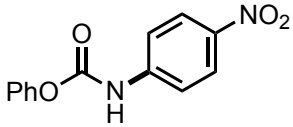
[108] H. Huang, W. Wang, X. Xu, C. Zhu, Y. Wang, J. Liu, W. Li, W. Fu, *Eur. J. Med. Chem.* **2020**, *189*, 112070.



Phenyl (4-(trifluoromethyl)phenyl)carbamate (2.3.7): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 4-trifluorophenylboronic acid (0.0400 g, 0.240 mmol, 1.20 equiv.) in THF (1.0 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.7** as a white solid (0.050 g, 89% yield).

2.3.7: The spectral and physical properties of the product match those reported in the literature.[109]

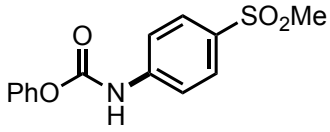
TLC R_f: 0.69 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.59 – 7.53 (m, 4H, Ar-H), 7.44 – 7.38 (m, 2H, Ar-H), 7.29 – 7.23 (m, 1H, NH), 7.24 – 7.17 (m, 3H, Ar-H); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 151.8 (C), 150.4 (C), 140.7 (C), 129.7 (CH), 126.6 (q, $^2J_{C\text{-}F}$ = 4 Hz) (C), 126.1 (CH), 124.1 (q, $^1J_{C\text{-}F}$ = 271 Hz) (C), 121.6 (CH), 118.3 (CH); **^{19}F NMR (283 MHz, Chloroform-*d*) δ** -62.2.



Phenyl (4-nitrophenyl)carbamate (2.3.8): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 4-nitrophenylboronic acid (0.0334 g, 0.240 mmol, 1.20 equiv.) in THF (1.0 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.8** as a white solid (0.035 g, 67% yield).

2.3.8: The spectral and physical properties of the product match those reported in the literature.[110]

TLC R_f: 0.50 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 8.22 (d, *J* = 9.1, 2H, Ar-H), 7.60 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.47 – 7.35 (m, 3H, Ar-H/NH), 7.33 – 7.24 (m, 1H, Ar-H), 7.24 – 7.16 (m, 2H, Ar-H); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 151.3 (C), 150.2 (C), 143.6 (C), 143.5 (C), 129.8 (CH), 126.4 (CH), 125.4 (CH), 121.6 (CH), 118.2 (CH).



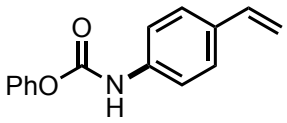
Phenyl (4-(methylsulfonyl)phenyl) carbamate (2.3.9): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0257 g, 0.100 mmol, 1.00 equiv.),

[109] S. Jaiswal, G. Gupta, S. R. Ayyannan, *Arch. Pharm.* **2022**, *355*, 2200081.
[110] L. Zhang, W. Xia, B. Wang, Y. Luo, W. Lu, *Synth. Commun.* **2011**, *41*, 3140–3146.

(4-(methylsulfonyl)phenyl)boronic acid (0.0152 g, 0.120 mmol, 1.20 equiv.) in THF (0.5 mL, 0.2 M) at 40 ºC for 18 h. The product was purified by single-solvent recrystallization in chloroform to afford **2.3.9** as a white solid (0.042 g, 72% yield).

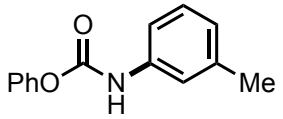
2.3.9: The spectral and physical properties of the product match those reported in the literature.[111] Note that this compound begins to degrade upon dissolution in Dimethylsulfoxide-d_6.

TLC R_f: 0.41 in 50% EtOAc/hexanes; **^{1}H NMR (400 MHz, Dimethylsulfoxide-d_6) δ** 10.77 (s, 1H, NH), 7.89 (d, J = 8.5 Hz, 2H, Ar-H), 7.75 (d, J = 8.6 Hz, 2H, Ar-H), 7.45 (dd, J = 7.7, 7.7 Hz, 2H, Ar-H), 7.28 (m, 3H, Ar-H), 3.17 (s, 3H, CH_3). **^{13}C NMR (101 MHz, Dimethylsulfoxide-d_6)** δ 151.6 (C), 150.3 (C), 143.4 (C), 134.5 (C), 129.5 (CH), 128.4 (CH), 125.8 (CH), 121.9 (CH), 118.2 (CH), 43.8 (CH_3).



Phenyl (4-vinylphenyl)carbamate (2.3.10): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 4-vinylphenylboronic acid (0.107 g, 0.720 mmol, 3.60 equiv.) and $[RhCp^*Cl_2]_2$ (0.005 g, 0.008 mmol, 4 mol%) in THF (1.0 mL, 0.2 M) at 40 ºC for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.10** as a white solid (0.035 g, 74% yield).

TLC R_f: 0.65 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.48 – 7.35 (m, 6H, Ar-H), 7.29 – 7.24 (m, 1H, Ar-H), 7.23 – 7.18 (m, 2H, Ar-H), 7.04 (brs, 1H, NH), 6.69 (dd, J = 17.6, 10.9 Hz, 1H, CH), 5.70 (dd, J = 17.5, 0.9 Hz, 1H, CH), 5.22 (dd, J = 10.9, 0.9 Hz, 1H, CH); **^{13}C NMR (101 MHz, Chloroform-d) δ** 151.6 (C), 150.5 (C), 136.9 (C), 136.1 (CH), 133.4 (C), 129.5 (CH), 127.0 (CH), 125.8 (CH), 121.7 (CH), 118.7 (CH), 113.0 (CH_2); **IR (neat):** $\tilde{\nu}$ = 3316 (w), 2924 (w), 1715 (s) cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{15}H_{13}NO_2$: 239.0946 $[M]^+$; found: 239.0934.



Phenyl *m*-tolylcarbamate (2.3.12): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 3-methylphenylboronic acid (0.0326 g, 0.240 mmol, 1.20 equiv.) in THF (1.0 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.12** as a white solid (0.040 g, 88% yield).

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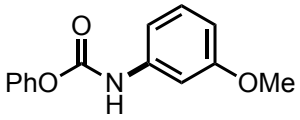
[111] C. B. Mishra, S. Kumari, A. Prakash, R. Yadav, A. K. Tiwari, P. Pandey, M. Tiwari, *Eur. J. Med. Chem.* **2018**, *151*, 520–532.

2.3.12: The spectral and physical properties of the product match those reported in the literature.[112]

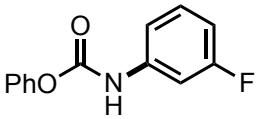
TLC R_f: 0.61 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.40 (dd, *J* = 7.9, 7.7 Hz, 2H, Ar-H), 7.30 (brs, 1H, NH), 7.22 (m, 5H, Ar-H), 6.95 (m, 2H, Ar-H), 2.34 (s, 3H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 151.7 (C), 150.6 (C), 139.1 (C), 137.3 (C), 129.4 (CH), 129.0 (CH), 125.7 (CH), 124.8 (CH), 121.7 (CH), 119.5 (CH), 115.9 (CH), 21.5 (CH_3).



***O*-Phenyl *N*-(3-methoxyphenyl)carbamate (2.3.13):** The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 3-methoxyphenylboronic acid (0.0365 g, 0.240 mmol, 1.20 equiv.) in THF (1.0 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (50% CH_2Cl_2/hexanes) to afford **2.3.13** as a white solid (0.046 g, 95% yield).

2.3.13: The spectral and physical properties of the product match those reported in the literature.[113]

TLC R_f: 0.53 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Methanol-d_4) δ** 7.45 – 7.35 (m, 2H, Ar-H), 7.23 (dddd, *J* = 8.0, 7.4, 1.1, 1.1 Hz, 1H, Ar-H), 7.20 - 7.12 (m, 4H, Ar-H), 7.02 (ddd, *J* = 8.1, 2.0, 0.9 Hz, 1H, Ar-H), 6.64 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H, Ar-H), 3.77 (s, 3H, CH_3); **^{13}C NMR (101 MHz, Methanol-d_4) δ** 161.7 (C), 154.1 (C), 152.3 (C), 141.0 (C), 130.7 (CH), 130.4 (CH), 126.6 (CH), 122.9 (CH), 112.2 (CH), 109.9 (CH), 105.8 (CH), 55.6 (CH_3).



Phenyl *N*-(3-fluorophenyl)carbamate (2.3.14): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0257 g, 0.100 mmol, 1.00 equiv.), 3-fluorophenylboronic acid (0.0336 g, 0.120 mmol, 1.20 equiv.) in THF (0.5 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.14** as a white solid (0.038 g, 82% yield).

2.3.14: The spectral and physical properties of the product match those reported in the literature.[108]

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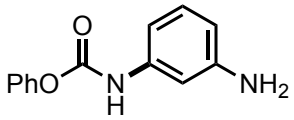
[112] M. S. Yadav, S. K. Singh, A. K. Agrahari, A. S. Singh, V. K. Tiwari, *Synthesis* **2021**, *53*, 2494–2502.
[113] M. A. Abbasi, A. Sonia, K. M. Khan, M. Ashraf, I. Afzal, N. Ambreen, M. Shahid, M. Abbas, *J. Chem. Soc. Pak.* **2013**, *35*, 385–390.

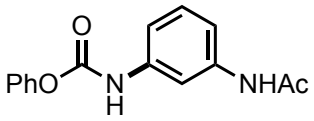
TLC R_f: 0.50 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.45 – 7.32 (m, 3H, Ar-H), 7.29 – 7.22 (m, 2H, Ar-H), 7.21 – 7.16 (m, 2H, Ar-H), 7.16 – 7.12 (m, 1H, NH), 7.11 – 7.05 (m, 1H, Ar-H), 6.80 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H, Ar-H). **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 163.2 (d, $^1J_{C\text{-}F}$ = 245 Hz) (C), 151.6 (C), 150.5 (C), 139.1 (d, $^3J_{C\text{-}F}$ = 11 Hz) (C), 130.3 (d, $^3J_{C\text{-}F}$ = 9 Hz) (CH), 129.6 (CH), 126.0 (CH), 121.7 (CH), 114.2 (CH), 110.7 (d, $^2J_{C\text{-}F}$ = 21 Hz) (CH), 106.4 (d, $^2J_{C\text{-}F}$ = 26 Hz) (CH); **^{19}F NMR (283 MHz, Chloroform-*d*) δ** -111.4.



Phenyl (3-aminophenyl)carbamate (2.3.15): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 3-aminophenylboronic acid (0.0328 g, 0.240 mmol, 1.20 equiv.) in THF (1.0 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (40% EtOAc/hexanes with 1 mL NEt_3) to afford **2.3.15** as a white solid (0.035 g, 68% yield).

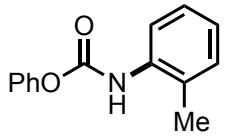
2.3.15: The spectral and physical properties of the product match those reported in the literature.[60a]

TLC R_f: 0.36 in 1% NEt_3 in 50% EtOAc/hexanes; **^{1}H NMR (600 MHz, Acetone-d_6) δ** 8.87 (s, 1H, NH), 7.40 (m, 2H, Ar-H), 7.23 (ddd, J = 7.4, 1.1, 1.0 Hz, 1H, Ar-H), 7.21 – 7.16 (m, 2H, Ar-H), 7.03 – 6.94 (m, 2H, Ar-H/NH), 6.79 (ddd, J = 8.1, 2.0, 0.9 Hz, 1H, Ar-H), 6.39 (ddd, J = 8.0, 2.2, 0.9 Hz, 1H, Ar-H), 4.66 (s, 2H, NH_2). **^{13}C NMR (151 MHz, Acetone-d_6) δ** 152.4 (C), 152.2 (C), 150.1 (C), 140.5 (C), 130.2 (CH), 130.1 (CH), 126.0 (CH), 122.7 (CH), 110.5 (CH), 108.1 (CH), 105.4 (CH).



Phenyl (3-acetamidophenyl)carbamate (2.3.16): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 3-acetamidophenylboronic acid (0.129 g, 0.720 mmol, 3.60 equiv.) and $[RhCp^*Cl_2]_2$ (0.005 g, 0.008 mmol, 4 mol%) in THF (1.0 mL, 0.2 M) at 40 ºC for 2 h. The product was purified by silica-gel flash column chromatography (40% EtOAc/hexanes) to afford **2.3.16** as a white solid (0.046 g, 85% yield).

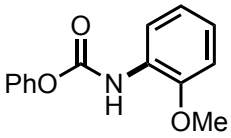
TLC R_f: 0.11 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Methanol-d_4) δ** 7.80 (d, J = 1.7 Hz, 1H, Ar-H), 7.44 – 7.35 (m, 2H, Ar-H), 7.31 – 7.19 (m, 4H, Ar-H), 7.18 (dd, J = 7.6, 1.2 Hz, 2H, Ar-H), 2.11 (s, 3H, CH_3); **^{13}C NMR (101 MHz, Methanol-d_4) δ** 170.3 (C), 152.7 (C), 150.9 (C), 139.1 (C), 138.9 (C), 129.0 (CH), 128.8 (CH), 125.2 (CH), 121.5 (CH), 114.9 (CH), 114.3 (CH), 110.5 (CH), 22.4 (CH_3); **IR (neat):** $\tilde{\nu}$ = 3383 (w), 3067 (w), 1671 (s), 1668 (s) cm^{-1}; **HRMS (EI):** *m/z* calcd for $C_{15}H_{14}N_2O_3$: 270.1004 $[M]^+$; found: 270.0982.



Phenyl *o*-tolylcarbamate (2.3.17): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0257 g, 0.100 mmol, 1.00 equiv.), 2-methylphenylboronic acid (0.0489 g, 0.360 mmol, 3.60 equiv.) in THF (0.5 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.17** as a white solid (0.019 g, 85% yield).

2.3.17: The spectral and physical properties of the product match those reported in the literature.[60a]

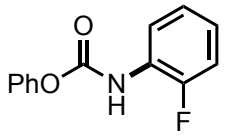
TLC R*f*: 0.74 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.87 (brs, 1H, NH), 7.45 – 7.35 (m, 2H, Ar-H), 7.32 – 7.17 (m, 5H, Ar-H), 7.08 (dd, *J* = 7.6, 7.6 Hz, 1H, Ar-H), 6.74 (brs, 1H, Ar-H), 2.34 (s, 3H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 152.0 (C), 150.7 (C), 135.4 (C), 130.5 (CH), 129.6 (C), 129.4 (CH), 127.0 (CH), 125.7 (CH), 124.5 (CH), 121.6 (CH), 120.9 (C), 17.7 (CH_3).



Phenyl (2-methoxyphenyl)carbamate (2.3.18): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0257 g, 0.100 mmol, 1.00 equiv.), 2-methoxyphenyl boronic acid (0.0547 g, 0.360 mmol, 3.60 equiv.) and $[RhCp^*Cl_2]_2$ (0.050 g, 0.0080 mmol, 4 mol%) in THF (0.5 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (3% EtOAc/hexanes) to afford **2.3.18** as a white solid (0.019 g, 79% yield).

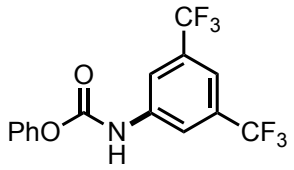
2.3.18: The spectral and physical properties of the product match those reported in the literature.[113]

TLC R*f*: 0.66 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Methanol-d_4) δ** 7.85 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.45 – 7.35 (m, 2H, Ar-H), 7.24 (dddd, *J* = 7.3, 7.3, 1.1, 1.1 Hz, 1H, Ar-H), 7.21 – 7.17 (m, 2H, Ar-H), 7.08 (ddd, *J* = 8.8, 7.4, 1.6 Hz, 1H, Ar-H), 7.02 (dd, *J* = 8.2, 1.5 Hz, 1H, Ar-H), 6.92 (ddd, *J* = 8.0, 7.3, 1.5 Hz, 1H, Ar-H), 3.91 (s, 3H, CH_3); **^{13}C NMR (101 MHz, Methanol-d_4) δ** 154.3 (C), 152.4 (C), 151.1 (C), 130.4 (CH), 128.1 (C), 126.6 (CH), 125.5 (CH), 122.9 (CH), 121.6 (CH), 121.5 (CH), 111.8 (CH), 56.3 (CH_3).



Phenyl (2-fluorophenyl)carbamate (2.3.19): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 2-fluorophenylboronic acid (0.101 g, 0.720 mmol, 3.60 equiv.) and $[RhCp^*Cl_2]_2$ (0.050 g, 0.0080 mmol, 4 mol%) in THF (1.0 mL, 0.2 M) at 40 ºC for 18 h. The product was purified by silica-gel flash column chromatography (2% EtOAc/hexanes) to afford **2.3.19** as a white solid (0.036 g, 77% yield).

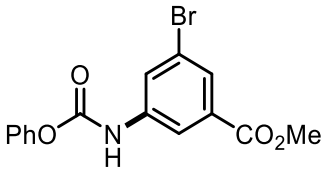
TLC R_f: 0.51 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 8.13 (br s, 1H, NH), 7.46 – 7.36 (m, 2H, Ar-H), 7.32 – 7.19 (m, 4H, Ar-H), 7.18 – 7.11 (m, 2H, Ar-H), 7.11 – 6.99 (m, 1H, Ar-H); **^{13}C NMR (151 MHz, Chloroform-*d*) δ** 153.2 (C), 151.5 (C), 150.6 (C), 129.6 (CH), 126.1 (C), 126.0 (CH), 124.9 (d, $^3J_{C\text{-}F}$ = 3.8 Hz) (CH), 124.0 (CH) , 121.7 (CH), 120.3 (C), 115.1 (d, $^2J_{C\text{-}F}$ = 19.1 Hz) (CH); **IR (neat):** $\tilde{\nu}$ = 3288 (w), 2917 (m), 1641 (m) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{13}H_{10}FNO_2$: 231.0696 $[M]^+$; found: 231.0672. **^{19}F NMR (471 MHz, Chloroform-*d*) δ** -132.5.



Phenyl (3,5-bis(trifluoromethyl)phenyl)carbamate (2.3.20): The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0257 g, 0.100 mmol, 1.00 equiv.), 3,5-bis(trifluoromethyl)phenylboronic acid (0.309 g, 0.120 mmol, 1.20 equiv.) in THF (0.5 mL, 0.2 M) at 40 °C for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.20** as a white solid (0.030 g, 86% yield).

2.3.20: The spectral and physical properties of the product match those reported in the literature.[114]

TLC R_f: 0.64 in 20% EtOAc/hexanes; **^{1}H NMR (600 MHz, Chloroform-*d*) δ** 7.96 (s, 2H, Ar-H), 7.61 (s, 1H, NH), 7.46 – 7.38 (m, 2H, Ar-H), 7.34 – 7.24 (m, 2H, Ar-H), 7.24 – 7.15 (m, 2H, Ar-H); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 151.4 (C), 150.1 (C), 139.0 (C), 132.8 (q, $^2J_{C\text{-}F}$ = 33 Hz) (C) (CH), 129.6 (CH), 126.3 (CH), 123.2 (q, $^1J_{C\text{-}F}$ = 272 Hz) (C), 121.6 (CH), 118.5 (CH), 117.3 (CH); **^{19}F NMR (471 MHz, Chloroform-*d*) δ** -63.2.

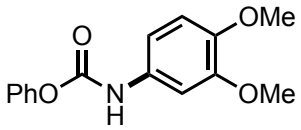


Phenyl (3-bromo-5-(methoxycarbonyl)phenyl)carbamate (2.3.21): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0514 g, 0.200

[114] V. Dašková, D. Padín, B. L. Feringa, *J. Am. Chem. Soc.* **2022**, *144*, 23603–23613.

mmol, 1.00 equiv.), 3-bromo-5-(methoxycarbonyl) phenylboronic acid (0.186 g, 0.720 mmol, 3.60 equiv.) and $[RhCp^*Cl_2]_2$ (0.005 g, 0.008 mmol, 4 mol%) in THF (1.0 mL, 0.2 M) at 40 ºC for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.21** as a white solid (0.065 g, 93% yield).

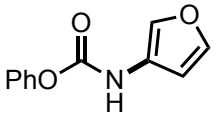
TLC R_f: 0.51 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 8.03 (s, 1H, Ar-H), 7.92 (dd, *J*=2.2, 1.4 Hz, 1H, Ar-H), 7.89 (dd, *J*=1.6, 1.6 Hz, 1H, Ar-H), 7.44 – 7.35 (m, 2H, Ar-H), 7.28 – 7.21 (m, 1H, Ar-H), 7.20 – 7.14 (m, 2H, Ar-H), 7.11 (s, 1H, NH), 3.90 (s, 3H, CH_3).**^{13}C NMR (101 MHz, Chloroform-*d*) δ** 165.5 (C), 151.5 (C), 150.4 (C), 139.0 (C), 132.6 (C), 129.7 (CH), 128.0 (CH), 126.2 (CH), 125.9 (CH), 123.2 (C), 121.7 (CH), 118.4 (CH), 52.7 (CH_3); **IR (neat):** ṽ = 3321 (br), 2924 (w), 1754 (m), 1706 (s) cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{15}H_{12}O_4NBr+Na^+$: 371.9847 $[M+Na]^+$; found: 371.9850.



***N*-(3,4-Dimethoxyphenyl)-*O*-phenylcarbamate (2.3.22):** The title compound was synthesized according to General Procedure A using linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 3,4-dimethoxyphenylboronic acid (0.0437 g, 0.240 mmol, 1.20 equiv.) in THF (1.0 mL, 0.2 M) at 40 °C for 2 h. The product was purified by recrystallization (CH_2Cl_2/hexanes) to afford **2.3.22** as a white solid (0.048 g, 88% yield).

2.3.22: The spectral and physical properties of the product match those reported in the literature.[60a]

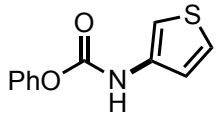
TLC R_f: 0.50 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.40 (t, *J* = 7.8, 2.3 Hz, 2H, Ar-H), 7.31 (brs, 1H, NH), 7.24 (m, 1H, Ar-H), 7.19 (m, 2H, Ar-H), 6.92 (brs, 1H, Ar-H), 6.85 – 6.76 (m, 1H, Ar-H), 3.86 (d, *J* = 1.4 Hz, 6H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 152.1 (C), 150.7 (C), 149.4 (C), 145.7 (C), 131.1 (C), 129.6 (CH), 125.9 (CH), 121.8 (CH), 111.6 (CH), 110.7 (CH), 103.9 (CH), 56.3 (CH_3), 56.0 (CH_3).



Phenyl furan-3-ylcarbamate (2.3.23): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0257 g, 0.100 mmol, 1.00 equiv.), 3-furanylboronic acid (0.403 g, 0.360 mmol, 3.60 equiv.) and $[RhCp^*Cl_2]_2$ (0.025 g, 0.0040 mmol, 4 mol%) in THF (0.5 mL, 0.2 M) at 66 ºC for 48 h. The product was purified by silica-gel flash column chromatography (5% EtOAc/hexanes) to afford **2.3.23** as a yellow solid (0.014 g, 69% yield).

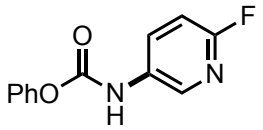
TLC R_f: 0.51 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.76 (s, 1H, Ar-H), 7.44 – 7.34 (m, 2H, Ar-H), 7.31 (dd, *J* = 1.9, 1.9 Hz, 1H, Ar-H), 7.28 – 7.22 (m, 1H, Ar-H), 7.20 – 7.15 (m, 2H, Ar-H), 6.80 (s, 1H, NH), 6.36 (d, J = 1.1 Hz, 1H, Ar-H); **^{13}C NMR (151 MHz,**

Chloroform-*d*) δ 151.6 (C), 150.6 (C), 136.6 (C), 132.3 (CH), 129.6 (CH), 126.0 (CH), 121.7 (CH), 120.4 (CH), 116.6 (C); **IR (neat):** ṽ = 3332 (w), 2920 (w), 1709 (s), 1651 (m), 1557 (m), 1489 (m) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{11}H_9NO_3$: 203.0582 $[M]^+$; found: 203.0554.



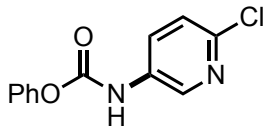
Phenyl thiophen-3-ylcarbamate (2.3.24): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 3-thienylboronic acid (0.128 g, 0.720 mmol, 3.60 equiv.) and $[RhCp^*Cl_2]_2$ (0.050 g, 0.0080 mmol, 4 mol%) in THF (1.0 mL, 0.2 M) at 66 ºC for 48 h. The product was purified by silica-gel flash column chromatography (5% EtOAc/hexanes). Product co-eluted with phenol, which was removed via extraction with K_2CO_3 (5 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford **2.3.24** as a white solid (0.025 g, 55% yield).

TLC R_f: 0.57 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.46 – 7.36 (m, 2H, Ar-H), 7.32 (brs, 1H, NH), 7.27 (dd, *J* = 5.3, 3.2 Hz, 2H, Ar-H), 7.25 – 7.16 (m, 3H, Ar-H), 7.02 (dd, *J* = 5.2, 1.5 Hz, 1H, Ar-H); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 151.9 (C), 150.7 (C), 135.2 (C), 129.6 (CH), 125.9 (CH), 125.3 (CH), 121.7 (CH), 120.7 (CH), 108.8 (CH); **IR (neat)**: ṽ = 3306 (br), 2917 (w), 1708 (s), 1549 (m) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{11}H_9NO_2S$: 219.0354 $[M]^+$; found: 219.0344.



Phenyl (6-fluoropyridin-3-yl)carbamate (2.3.25): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 6-fluoro-3-pyridinylboronic acid (0.101 g, 0.720 mmol, 3.60 equiv.) and $[RhCp^*Cl_2]_2$ (0.005 g, 0.008 mmol, 4 mol%) in THF (1.0 mL, 0.2 M) at 40 ºC for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.25** as a white solid (0.039 g, 83% yield).

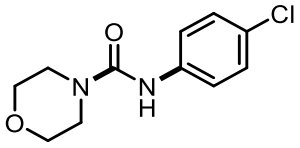
TLC R_f: 0.24 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Acetone-d_6) δ** 9.48 (s, 1H, NH), 8.40 (d, *J* = 2.9 Hz, 1H, Ar-H), 8.25 – 8.14 (m, 1H, Ar-H), 7.52 – 7.36 (m, 2H, Ar-H), 7.36 – 7.19 (m, 3H, Ar-H), 7.09 (dd, *J* = 8.9, 3.2 Hz, 1H, Ar-H). **^{13}C NMR (101 MHz, Acetone-d_6) δ** 160.3 (d, $^2J_{C\text{-}F}$ = 232.5 Hz) (C), 152.9 (C), 151.8 (C), 138.2 (C), 134.7 (CH), 132.7 (CH), 130.2 (CH), 126.4 (CH), 122.6 (CH), 110.0 (d, $^3J_{C\text{-}F}$ = 39.6 Hz) (CH); **IR (neat)**: ṽ = 3262 (w), 2922 (m), 2361 (w), 1749 (s) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{12}H_9FN_2O_2Na^+$: 255.0546 $[M+Na]^+$; found: 255.0540. **^{19}F NMR (471 MHz, Acetone-d_6) δ** -75.4.



Phenyl (6-chloropyridin-3-yl)carbamate (2.3.26): The title compound was synthesized by modifying General Procedure A to use linchpin reagent **2.1.6** (0.0514 g, 0.200 mmol, 1.00 equiv.), 6-chloro-3-pyridinylboronic acid (0.113 g, 0.720 mmol, 3.60 equiv.) and $[RhCp^*Cl_2]_2$ (0.005 g, 0.008 mmol, 4 mol%) in THF (1.0 mL, 0.2 M) at 40 ºC for 18 h. The product was purified by silica-gel flash column chromatography (10% EtOAc/hexanes) to afford **2.3.26** as a white solid (0.043 g, 86% yield).

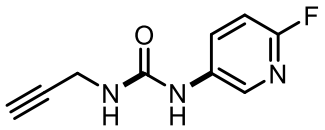
2.3.26: The spectral and physical properties of the product match those reported in the literature.[60a]

TLC R*f*: 0.33 in 20% EtOAc/hexanes; **^{1}H NMR (600 MHz, Acetone-*d*$_6$) δ** 9.53 (s, 1H, N-H), 8.60 (d, *J* = 2.8 Hz, 1H, Ar-H), 8.11 (dd, *J* = 8.7, 2.8 Hz, 1H, Ar-H), 7.43 (ddd, *J* = 7.7, 6.3, 1.8 Hz, 3H, Ar-H), 7.30 – 7.08 (m, 3H, Ar-H); **^{13}C NMR (151 MHz, Acetone-*d*$_6$) δ** = 152.7 (C), 151.7 (C), 145.3 (C), 140.8 (CH), 136.1 (C), 130.2 (CH), 129.7 (CH), 126.5 (CH), 125.0 (CH), 122.6 (CH).



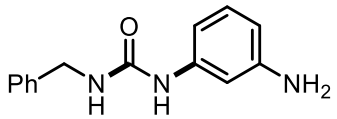
***N*-(4-Chlorophenyl)morpholine-4-carboxamide (2.9.1):** The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.5** (0.0495 g, 0.200 mmol, 1.00 equiv.) and morpholine (0.0207 mL, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.1** as a white powder (0.032 g, 67% yield).

TLC R*f*: 0.16 in 50% EtOAc/hexanes; **^{1}H NMR (400 MHz, Acetone-*d*$_6$) δ** 8.06 (brs, 1H, NH) 7.59 – 7.52 (m, 2H, Ar-H), 7.28 – 7.20 (m, 2H, Ar-H), 3.67 – 3.60 (m, 4H, CH_2), 3.51 – 3.41 (m, 4H, CH_2); **^{13}C NMR (101 MHz, Acetone-*d*$_6$) δ** 155.8 (C), 140.5 (C), 129.1 (CH), 127.1 (C), 121.6 (CH), 67.2 (CH_2), 45.2 (CH_2); **IR (neat)**: $\tilde{\nu}$ = 3280 (br), 2846 (w), 1633 (s), 1495 (s), 1246 (s), 1112 (s) cm^{-1}; **HRMS (ESI):** *m/z* calcd $C_{11}H_{13}ClN_2O_2$ [*M*+]: 240.0666; found: 240.06747.



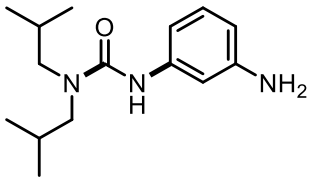
1-(6-Fluoropyridin-3-yl)-3-(prop-2-yn-1-yl)urea (2.9.2): The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.25** (0.0464 g, 0.200 mmol, 1.00 equiv.) and propargylamine (0.0152 mL, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.2** as a beige powder (0.020 g, 52% yield).

TLC R_f: 0.22 in 50% EtOAc/hexanes; **^{1}H NMR (600 MHz, Dimethylsulfoxide-d_6) δ** 8.85 (s, 1H, NH), 8.21 – 8.18 (m, 1H, NH), 8.00 (ddd, *J*=8.8, 7.3, 2.9, 1H, Ar-H), 7.07 (dd, *J*=8.8, 3.3, 1H, Ar-H), 6.67 (t, *J*=5.7, 1H, Ar-H), 3.88 (dd, *J*=5.7, 2.5, 2H, CH_2), 3.10 (t, *J*=2.5, 1H, C_{sp}-H); **^{13}C NMR (151 MHz, Dimethylsulfoxide-d_6) δ** 157.7 (d, $^2J_{C\text{-}F}$ = 230.2 Hz, C), 154.7 (C), 136.2 (d, $^4J_{C\text{-}F}$ = 15.3 Hz,), 135.2 (d, $^4J_{C\text{-}F}$ = 4.1 Hz), 131.5 (d, $^4J_{C\text{-}F}$ = 7.2 Hz ,CH), 109.0 (d, $^3J_{C\text{-}F}$ = 39.4 Hz, CH), 81.9 (C), 72.9 (CH), 28.9 (CH_2); **^{19}F NMR (283 MHz, Dimethylsulfoxide-d_6) δ** -77.95; **IR (neat)**: ṽ = 3298 (w), 3268 (w), 2898 (w), 1668 (s), 1482 (s), 1379 (s) cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_9H_8N_3OF+Na^+$ [*M*+Na]$^+$: 216.0549; found: 216.0551.



1-(3-Aminophenyl)-3-benzylurea (2.9.3): The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.15** (0.0457 g, 0.200 mmol, 1.00 equiv.) and benzylamine (0.135 mL, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.3** as a beige powder (0.027 g, 53% yield).

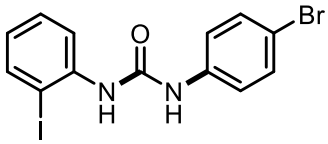
TLC R_f: 0.16 in 50% EtOAc/hexanes; **^{1}H NMR (400 MHz, Acetone-d_6) δ** 7.72 (s, 1H, NH), 7.36 – 7.27 (m, 4H, Ar-H), 7.26 – 7.18 (m, 1H, Ar-H), 6.97 (t, *J*=2.1, 1H, Ar-H), 6.88 (t, *J*=8.0, 1H, Ar-H), 6.61 (ddd, *J*=8.0, 2.1, 1.0, 1H, Ar-H), 6.25 (ddd, *J*=7.9, 2.2, 0.9, 1H, Ar-H), 6.10 (s, 1H, NH), 4.50 (s, 2H, NH_2), 4.38 (d, *J*=6.0, 2H, CH_2); **^{13}C NMR (101 MHz, Acetone-d_6) δ** 156.1 (C), 149.8 (C), 142.3 (C), 141.6 (C), 129.8 (CH), 129.2 (CH), 128.2 (CH), 127.6 (CH), 109.0 (CH), 107.9 (CH), 105.2 (CH), 44.1 (CH_2). **IR (neat)**: ṽ = 3309 (br) 3295 (br), 2872 (w), 1634 (s), 1558 (s), 1450 (s), 1232 (s) cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{15}H_{19}N_3O+Na^+$ [*M*+Na]$^+$: 264.1113; found: 264.1109.



3-(3-Aminophenyl)-1,1-diisobutylurea (2.9.4): The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.15** (0.0457 g, 0.200 mmol, 1.00 equiv.) and diisobutylamine (0.042 mL, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.4** as a beige powder (0.039 g, 70% yield).

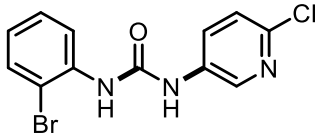
TLC R_f: 0.22 in 50% EtOAc/hexanes**; ^{1}H NMR (600 MHz, Chloroform-*d*) δ** 7.08 (d, *J* = 2.3, 1H, Ar-H), 7.02 (dd, *J* = 7.9, 7.9 Hz, 1H, Ar-H), 6.60 – 6.45 (m, 1H, Ar-H), 6.39 – 6.29 (m, 1H, Ar-H), 6.21 (brs, 1H, NH), 3.65 (brs, 2H, NH_2), 3.13 (d, *J* = 7.5 Hz, 4H, CH_2), 2.02 (m, 2H, CH), 0.94 (dd, *J* = 6.7, 1.0, 12H, CH_3); **^{13}C NMR (151 MHz, Chloroform-*d*) δ** 155.4 (C), 147.4 (C), 140.4 (C), 129.6 (CH), 109.8 (CH), 109.5 (CH), 106.5 (CH), 56.2 (CH_2), 28.0 (CH), 20.5 (CH_3);

IR (neat): $\tilde{\nu}$ = 3303 (br), 2953 (w), 2866 (w), 1626 (s), 1533 (s), 1451 (s) cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{15}H_{26}N_3O+H^+$ $[M+H]^+$: 264.2076; found: 264.2093.



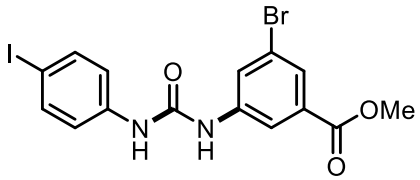
***N*-(4-Bromo-phenyl)-*N*'-(2-iodo-phenyl)-urea (2.9.6):** The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.6** (0.0584 g, 0.200 mmol, 1.00 equiv.) and 2-iodoaniline (0.0438 g, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.6** as a white powder (0.062 g, 74% yield).

TLC R_f: 0.83 in 50% EtOAc/hexanes; **^{1}H NMR (400 MHz, Acetone-d_6) δ** 8.97 (s, 1H, NH), 8.06 (dt, *J* = 8.3, 1.8 Hz, 1H, Ar-H), 7.84 (dd, *J* = 7.9, 1.5, 1H, Ar-H), 7.56 – 7.51 (m, 2H, Ar-H), 7.51 – 7.41 (m, 3H, Ar-H), 7.38 (ddd, *J* = 8.5, 7.3, 1.5, 1H, Ar-H), 6.86 (td, *J* = 7.6, 1.6, 1H, Ar-H); **^{13}C NMR (101 MHz, Acetone-d_6) δ** 152.9 (C), 150.3 (C), 140.0 (CH), 132.5 (CH), 129.7 (CH), 125.9 (CH), 123.6 (C), 121.3 (CH), 121.2 (CH), 115.0 (C), 90.7 (C); **IR (neat)**: $\tilde{\nu}$ = 3255 (br), 3020 (w), 1644 (s), 1542 (s), 1487 (s), 1279 (s) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{13}H_{10}ON_2BrI$: 415.9021 $[M]^+$; found: 415.9040.



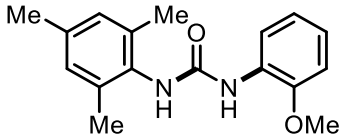
1-(2-Bromophenyl)-3-(6-chloropyridin-3-yl)urea (2.9.7): The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.26** (0.0497 g, 0.200 mmol, 1.00 equiv.) and 2-bromoaniline (0.0412 g, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.7** as a white powder (0.038 g, 59% yield).

TLC R_f: 0.56 in 50% EtOAc/hexanes; **^{1}H NMR (400 MHz, Methanol-d_4) δ** 8.47 (d, *J* = 2.8 Hz, 1H, Ar-H), 8.09 – 8.00 (m, 2H, Ar-H), 7.59 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-H), 7.39 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.33 (ddd, *J* = 8.5, 7.3, 1.5 Hz, 1H, Ar-H), 7.04 – 6.96 (m, 1H, Ar-H); **^{13}C NMR (101 MHz, Methanol-d_4) δ** 154.4 (C), 144.9 (C), 140.7 (CH), 137.8 (C), 137.3 (C), 133.7 (CH), 130.7 (CH), 129.2 (CH), 126.0 (CH), 125.5 (CH), 124.0 (CH), 115.2 (C); **IR (neat)**: $\tilde{\nu}$ = 3381 (br), 3047 (w), 1712 (s), 1525 (s), 1520 (s), 1462 (s) cm^{-1}; **HRMS (ESI):** *m/z* calcd $C_{12}H_9N_3OBrCl+Na^+$ $[M+Na]^+$: 347.9515; found: 347.9514.



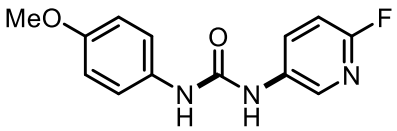
***N*-(3-Bromo-5-(methoxycarbonyl)phenyl)-*N′*-(4-iodo-phenyl)-urea (2.9.8):** The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.21** (0.144 g, 0.411 mmol, 1.00 equiv.) and 4-iodoaniline (0.108 g, 0.493 mmol, 1.20 equiv.) in toluene (0.8 mL, 0.5 M) at 80 ºC for 5 h. The reaction mixture was concentrated *in vacuo* to afford the crude product, which was purified via silica-gel flash column chromatography (10% acetone/hexanes to 100% acetone) to afford **2.9.8** as a beige amorphous solid (0.171 g, 88% yield).

TLC R_f: 0.15 in 20% EtOAc/hexanes; **^{1}H NMR (600 MHz, Dimethylsulfoxide-d_6) δ** 9.20 (s, 1H, NH), 8.97 (s, 1H, NH), 8.06 – 8.02 (m, 1H, Ar-H), 7.98 (dd, *J* = 2.0, 2.0 Hz, 1H, Ar-H), 7.61 (d, *J* = 8.7, 3H, Ar-H), 7.39 – 7.13 (m, 2H, Ar-H), 3.86 (s, 3H, CH_3); **^{13}C NMR (151 MHz, Dimethylsulfoxide-d_6) δ** 164.9 (C), 152.2 (C), 141.6 (C), 139.2 (C), 137.3 (CH), 132.0 (C), 124.6 (CH), 124.5 (CH), 121.8 (C), 120.9 (CH), 117.7 (CH), 85.3 (C), 52.6 (CH_3); **IR (neat)**: $\tilde{\nu}$ = 3295 (br), 2920 (w), 1731 (s), 1640 (s), 1576 (s), 1275 (s) cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{15}H_{12}BrIN_2O_3$+Na^+ $[M+Na]^+$: 496.8963; found: 496.8974.



1-Mesityl-3-(2-methoxyphenyl)urea (2.9.9): The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.18** (0.0487 g, 0.200 mmol, 1.00 equiv.) and 2,4,6-trimethylaniline (0.034 mL, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.9** as a white fluffy solid (0.040 g, 70% yield).

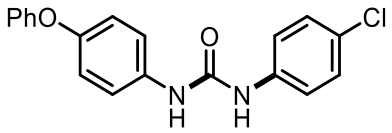
TLC R_f: 0.37 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Dimethylsulfoxide-d_6) δ** 8.26 (br s, 2H, NH), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar-H), 6.99 (dd, *J* = 8.0, 1.8, 1H, Ar-H), 6.95 – 6.79 (m, 4H, Ar-H), 3.87 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.15 (s, 6H, CH_3).; **^{13}C NMR (101 MHz, Dimethylsulfoxide-d_6) δ** 153.1 (C), 147.3 (C), 135.1, 132.6, 129.3, 128.3, 121.2, 120.5, 117.8, 110.6, 55.7 (CH_3), 20.5 (CH_3), 18.2 (CH_3) ; **IR (neat)**: $\tilde{\nu}$ = 3312 (w), 3296 (w), 1645 (m), 1539 (s), 1216 (s) cm^{-1}; **HRMS (ESI):** *m/z* calcd for $C_{17}H_{20}N_2O_2$+Na^+ $[M+Na]^+$: 307.1422; found: 307.1427.



1-(6-Fluoropyridin-3-yl)-3-(4-methoxyphenyl)urea (2.9.10): The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.25** (0.0464 g, 0.200 mmol, 1.00 equiv.) and *p*-anisidine (0.0295 g, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.10** as a grey powder (0.040 g, 76% yield).

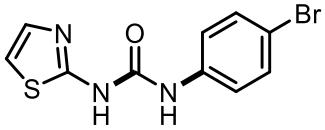
TLC R_f: 0.22 in 50% EtOAc/hexanes; **^{1}H NMR (600 MHz, Dimethylsulfoxide-d_6) δ** 8.81 (s, 1H, NH), 8.63 (s, 1H, NH), 8.24 (dd, *J* = 3.0, 1.4 Hz, 1H, Ar-H), 8.05 (ddd, *J* = 8.7, 7.3, 2.8 Hz, 1H,

Ar-H), 7.35 (d, J = 9.0 Hz, 1H, Ar-H), 7.11 (dd, J = 8.8, 3.2 Hz, 1H, Ar-H), 6.93 – 6.78 (m, 2H, Ar-H), 3.72 (s, 3H, CH_3); **^{13}C NMR (151 MHz, Dimethylsulfoxide-d_6) δ** 158.6 (C), 157.1 (C), 152.8 (d, $^2J_{C-F}$ = 285.0 Hz, C), 136.6 (d, $^4J_{C-F}$ = 15.3 Hz, CH), 134.9 (C), 132.4 (C), 131.9 (d, $^4J_{C-F}$ = 7.5 Hz), 120.4 (CH), 114.0 (CH), 109.1 (d, $^3J_{C-F}$ = 39.3 Hz, CH), 55.2 (CH_3); **^{19}F NMR (283 MHz, Dimethylsulfoxide-d_6) δ** -77.61; **IR (neat)**: ṽ = 3290 (br), 2840 (w), 1635 (s),1560 (s), 1484 (s), 1238 (s) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{13}H_{12}O_2N_3F$: 261.0914 $[M]^+$; found: 261.0891.



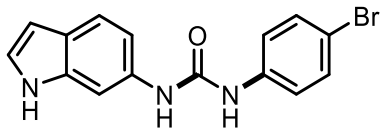
1-(4-Chlorophenyl)-3-(4-phenoxyphenyl)urea (2.9.11): The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.5** (0.0495 g, 0.200 mmol, 1.00 equiv.) and 4-phenoxyaniline (0.0444 g, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.11** as a grey powder (0.055 g, 81% yield).

TLC R$_f$: 0.67 in 50% EtOAc/hexanes; **^{1}H NMR (400 MHz, Acetone-d_6) δ** 8.20 (d, J = 29.2 Hz, 1H, NH), 7.60 – 7.50 (m, 4H, Ar-H), 7.35 (m, 2H, Ar-H), 7.31 – 7.25 (m, 2H, Ar-H), 7.12 – 7.05 (m, 1H, Ar-H), 7.01 – 6.89 (m, 4H, Ar-H); **^{13}C NMR (101 MHz, Acetone-d_6) δ** 159.1 (C), 153.3 (C), 152.7 (C), 139.9 (C), 136.6 (C), 130.6 (CH), 129.5 (CH), 127.2 (C), 123.6 (CH), 121.3 (CH), 121.2 (CH), 120.8 (CH), 120.7 (CH), 120.6 (CH), 118.7 (CH); **IR (neat)**: ṽ = 3296 (br), 3039 (w), 1635 (s), 1558 (s), 1487 (s) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{19}H_{15}O_2N_2Cl$: 338.0822 $[M]^+$; found: 338.08310.



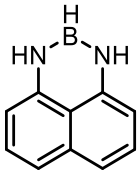
1-(4-Bromophenyl)-3-(thiazol-2-yl)urea (2.9.12): The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.6** (0.0584 g, 0.200 mmol, 1.00 equiv.) and 2-aminothiazole (0.0240 g, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.12** as a white powder (0.041 g, 68% yield).

TLC R$_f$: 0.27 in 50% EtOAc/hexanes; **^{1}H NMR (400 MHz, Dimethylsulfoxide-d_6) δ** 10.62 (brs, 1H, NH), 9.12 (s, 1H, NH), 7.51 – 7.43 (m, 4H, Ar-H), 7.37 (d, J = 3.7 Hz, 1H, HetAr-H), 7.11 (d, J = 3.7 Hz, 1H, HetAr-H); **^{13}C NMR (151 MHz, Dimethylsulfoxide-d_6) δ** = 159.6 (C), 151.8 (C), 138.2 (C), 131.6 (CH), 136.8 (CH), 120.5 (CH), 114.1 (C), 112.4 (CH). **IR (neat)**: ṽ = 3417 (br), 3300 (w), 3294 (w), 1638 (s), 1539 (s), 1222 (s) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{10}H_8ON_3BrS$: 296.9571 $[M]^+$; found: 296.9558.



1-(4-Bromophenyl)-3-(*1H*-indol-6-yl)urea (2.9.13): The title compound was synthesized according to General Procedure F using masked isocyanate **2.3.6** (0.0584 g, 0.200 mmol, 1.00 equiv.) and 5-aminoindole (0.317 g, 0.240 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified to afford **2.9.13** as a light purple powder (0.063 g, 96% yield).

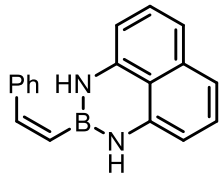
TLC R*f*: 0.33 in 50% EtOAc/hexanes; **^{1}H NMR (400 MHz, Dimethylsulfoxide-*d*$_6$) δ** 10.96 (s, 1H, NH), 8.73 (s, 1H, NH), 8.44 (s, 1H, NH), 7.66 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.43 (s, 4H, Ar-H), 7.33 – 7.27 (m, 2H, Ar-H), 7.07 (dd, *J* = 8.7, 2.1 Hz, 1H, Ar-H), 6.35 (td, *J* = 2.0, 1.0 Hz, 1H, Ar-H); **^{13}C NMR (101 MHz, Dimethylsulfoxide-*d*$_6$) δ** 152.9 (C), 139.6 (C), 132.4 (C), 131.5 (CH), 131.1 (C), 127.7 (C), 125.8 (CH), 119.9 (CH), 114.8 (CH), 112.7 (C), 111.3 (CH), 110.2 (CH), 100.9 (CH); **IR (neat)**: $\tilde{\nu}$ = 3287 (br), 3052 (w), 1721 (s), 1554 (s), 1448 (s), 1192 (s) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{15}H_{12}ON_3Br$: 329.0164 $[M]^+$; found: 329.0191.



2,3-Dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine (2.10): The title compound was synthesized using a literature procedure.[85] Under an argon atmosphere, 1,8-diaminonaphthalene (1.81 g, 11.5 mmol, 1.00 equiv.), $NaBH_4$ (0.870 g, 23.0 mmol, 2.00 equiv.) and THF (5.9 mL, 1.95 M) were placed in a round-bottom flask. To this was added a THF (5.9 mL, 1.95 M) solution of iodine (2.92 g, 11.5 mmol, 1.00 equiv.) dropwise over 30 min at 0 ºC. The resulting mixture was allowed to warm to room temperature and stirred for 2 h at the same temperature. Water (10 mL) was added to the mixture, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the crude product, which was purified via silica-gel flash column chromatography (100% Hexanes to 10% EtOAc) to afford **2.10** as a pale pink solid (1.17 g, 60% yield).

2.10: The spectral and physical properties of the product match those reported in the literature.[85]

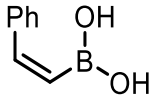
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.10 (dd, *J* = 8.3, 7.2 Hz, 2H, Ar-H), 7.02 (dd, *J* = 8.4, 1.2 Hz, 2H, Ar-H), 6.30 (dd, *J* = 7.2, 1.2 Hz, 2H, Ar-H), 5.85 (brs, 2H, NH); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 140.7 (C), 136.5 (C), 127.7 (CH), 120.6 (CH), 118.0 (C), 105.9 (CH).



(*Z*)-2-Styryl-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.11): The title compound was synthesized using a literature procedure.[86] A mixture of CuTC (0.0636 g, 0.33 mmol, 6 mol %), DPEphos (0.1664 g, 0.309 mmol, 5.5 mol %) and HB(dan) (0.935 g, 5.62 mmol, 1.00 equiv.) in anhydrous toluene (33 mL, 0.167 M) were stirred for 15 min in a round-bottom flask under an atmosphere of argon. Phenylacetylene (0.740 mL, 6.74 mmol, 1.20 equiv.) was added to the reaction mixture with the use of toluene (33 mL, 0.167 M) and the reaction mixture was stirred at room temperature and monitored by TLC. Upon completion of the reaction, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to afford the crude product, which was purified via silica-gel flash column chromatography (100% hexanes to 10% EtOAc) to afford **2.11** as a white solid (0.731 g, 48% yield).

2.11: The spectral and physical properties of the product match those reported in the literature.[86]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.42 (m, 2H, Ar-H), 7.37 – 7.29 (m, 3H, Ar-H), 7.21 (d, *J* = 14.6 Hz, 1H, CH), 7.08 (dd, *J* = 8.3, 7.2 Hz, 2H, Ar-H), 7.01 (dd, *J* = 8.3, 1.2 Hz, 2H, Ar-H), 6.18 (dd, *J* = 7.1, 1.1 Hz, 2H, Ar-H), 5.77 (d, *J* = 14.6 Hz, 1H, CH), 5.60 (s, 2H, NH); **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 145.3 (CH), 141.1 (C), 138.8 (C), 136.4 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 126.0 (C), 119.8 (C), 117.7 (CH), 105.9 (CH).



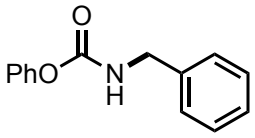
(Z)-Styrylboronic acid (2.2.51): To a solution of (Z)-2-styryl-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (0.7305 g, 2.70 mmol, 1 equiv.) in THF (21.6 mL, 0.125 M) was added HCl (5 M, 1.8 mmol, 4.00 equiv.) at room temperature. The mixture was stirred at room temperature for 16 h, leading to the formation of precipitation. Reaction was followed by TLC and 12 M HCl was added dropwise over the course of 8 hours until consumption of starting material was observed. The suspension was filtered, and the solution was dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product, which was purified via silica-gel flash column chromatography (100% hexanes to 10% EtOAc/hexanes) to afford **2.2.51** as a white solid (0.731 g, 48% yield).

Note: This product rapidly degrades upon exposure to air. Degradation to styrene occurs upon solution in MeOH.

2.2.51: The spectral and physical properties of the product match those reported in the literature.[87]

^{1}H NMR (300 MHz, Acetone-d_6) δ 7.60 – 7.45 (m, 1H), 7.45 – 7.36 (m, 1H), 7.36 – 7.14 (m, 3H), 7.05 – 6.82 (m, 2H), 5.68 (d, *J* = 15.0, 1H).

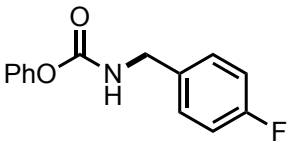
^{1}H NMR (300 MHz, Methanol-d_4) δ 7.45 – 7.31 (m, 2H), 7.29 – 7.15 (m, 2H), 7.08 (d, J = 14.8 Hz, 1H), 5.64 (d, J = 14.8 Hz, 1H).



Phenyl benzylcarbamate (3.3.1): The title compound was synthesized according to General Procedure G using benzaldehyde (102 μL, 1.00 mmol, 1.00 equiv.) in acetonitrile (4 mL, 0.25 M) at room temperature for 18 h. The product was purified via silica-gel flash column chromatography (2% EtOAc/hexanes to 20% EtOAc/hexanes) to afford **3.3.1** as a white powder (0.170 g, 75% yield).

3.3.1: The spectral and physical properties of the product match those reported in the literature.[115]

TLC R_f: 0.38 in 20% EtOAc/hexanes; **^{1}H NMR (600 MHz, Chloroform-*d*) δ** 7.38 – 7.35 (m, 6H, Ar-H), 7.32 (td, *J* = 6.3, 2.6 Hz, 1H, Ar-H), 7.22 – 7.19 (m, 1H, Ar-H), 7.17 – 7.14 (m, 2H, Ar-H), 5.31 (s, 1H, NH), 4.47 (d, *J*=5.9, 2H, CH_2); **^{13}C NMR (151 MHz, Chloroform-*d*) δ** 154.8 (C), 151.2 (C), 138.1 (C), 129.4 (CH), 128.9 (CH), 127.9 (CH), 125.5 (CH), 121.7 (CH), 45.5 (CH_2).



Phenyl *N*-(4-Fluorobenzyl)carbamate (3.3.2): The title compound was synthesized according to General Procedure G using 4-fluorobenzaldehyde (212 μL, 2.00 mmol, 1.00 equiv.) in acetonitrile (8.00 mL, 0.25 M) at room temperature for 18 h. The product was purified via silica-gel flash column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes) to afford **3.3.2** as a white powder (0.455 g, 92% yield).

3.3.2: The spectral and physical properties of the product match those reported in the literature.[116]

TLC R_f: 0.60 in 20% EtOAc/hexanes; **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 7.46 – 7.37 (m, 2H, Ar-H), 7.36 – 7.26 (m, 3H, Ar-H), 7.22 – 7.15 (m, 2H, Ar-H), 7.11 – 7.03 (m, 2H, Ar-H), 5.70 (s, 1H, NH), 4.40 (d, *J* = 6.1 Hz, 2H, CH_2); **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 162.3 (d, $^2J_{C\text{-}F}$ = 245.6 Hz, C) , 154.9 (C), 151.0 (C), 134.0 (d, $^5J_{C\text{-}F}$ = 3.2 Hz, C), 129.5 (CH), 129.4 (d, $^4J_{C\text{-}F}$ = 8.0 Hz, CH), 125.4 (CH), 121.6 (CH), 115.5 (d, $^3J_{C\text{-}F}$ = 21.4 Hz, CH), 44.5 (CH_2); **^{19}F NMR (283 MHz, Chloroform-*d*) δ** -64.01.

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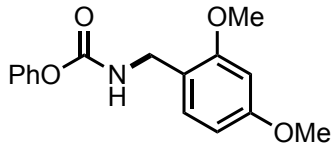
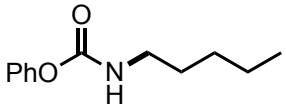
[115] A. Roy, N. Haque, R. Chatterjee, S. Biswas, A. Bhaumik, M. Sarkar, S. M. Islam, *New J. Chem.* **2023**, *47*, 6673-6684.

[116] W. Shaojie, P. Liangsheng, **2017**, Tartaric acid pimavanserin impurities and preparation method thereof, CN107216271A, 2017-09-29.



Phenyl *N*-[(2,4-Dimethoxyphenyl)methyl]carbamate (3.3.3): The title compound was synthesized according to General Procedure G using 2,4-dimethoxybenzaldehyde (0.332 g, 2.00 mmol, 1.00 equiv.) in acetonitrile (8.00 mL, 0.25 M) at room temperature for 18 h. The product was purified via silica-gel flash column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes) to afford **3.3.3** as a white powder (0.227 g, 40% yield).

TLC R*f*: 0.35 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.39 – 7.29 (m, 2H, Ar-H), 7.23 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.22 – 7.13 (m, 1H, Ar-H), 7.11 (dd, *J* = 8.6, 1.2 Hz, 2H, Ar-H), 6.53 – 6.39 (m, 2H, Ar-H), 5.52 (s, 1H, NH), 4.37 (d, *J* = 6.0 Hz, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.81 (s, 3H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 160.8 (C), 158.7 (C), 154.6 (C), 151.3 (C), 130.7 (CH), 129.3 (CH), 125.3 (CH), 121.8 (CH), 118.9 (C), 104.0 (CH), 98.8 (CH), 55.6 (CH_3), 55.5 (CH_3), 41.0 (CH_2); **IR (neat)**: $\tilde{\nu}$ = 3322 (br), 2917 (w), 1706 (s), 1613 (s), 1489 (s), 1206 (s) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{16}H_{17}O_4N$: 287.1158 $[M]^+$; found: 287.1168

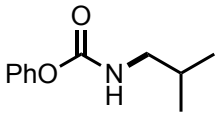


Phenyl pentylcarbamate (3.3.4): The title compound was synthesized according to General Procedure G using valderaldehyde (106 µL, 1.00 mmol, 1.00 equiv.) in acetonitrile (4.00 mL, 0.25 M) at room temperature for 18 h. The product was purified via silica-gel flash column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes) to afford **3.3.4** as a white wax (0.136 g, 66% yield).

3.3.4: The spectral and physical properties of the product match those reported in the literature.[117]

TLC R*f*: 0.77 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.43 – 7.29 (m, 2H, Ar-H), 7.22 – 7.15 (m, 1H, Ar-H), 7.15 – 7.07 (m, 2H, Ar-H), 5.23 (d, *J* = 6.0 Hz, 1H, NH), 3.23 (td, *J* = 7.2, 5.9 Hz, 2H, CH_2), 1.54 (p, *J* = 7.4 Hz, 2H, CH_2), 1.34 (m, 4H, CH_2), 0.94 – 0.89 (t, *J* = 6.8 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** = 154.7 (C), 151.2 (C), 129.3 (CH), 125.2 (CH), 121.7 (CH), 41.3 (CH_2), 29.5 (CH_2), 28.9 (CH_2), 22.4 (CH_2), 14.0 (CH_3).

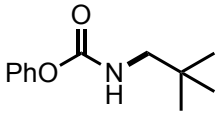
[117] R. D. Healey, E. M. Saied, X. Cong, G. Karsai, L. Gabellier, J. Saint-Paul, E. Del Nero, S. Jeannot, M. Drapeau, S. Fontanel, D. Maurel, S. Basu, C. Leyrat, J. Golebiowski, G. Bossis, C. Bechara, T. Hornemann, C. Arenz, S. Granier, *Angew. Chem. Int. Ed*. **2022**, *61*, e202109967.



Isobutyl-carbamic acid phenyl ester (3.3.5): The title compound was synthesized according to General Procedure G using isobutyraldehyde (183 µL, 2.00 mmol, 1.00 equiv.) in acetonitrile (8.00 mL, 0.25 M) at room temperature for 18 h. The product was purified via silica-gel flash column chromatography (2% EtOAc/hexanes to 5% EtOAc/hexanes) to afford **3.3.5** as a white wax (0.127 g, 65% yield).

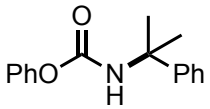
3.3.5: The spectral and physical properties of the product match those reported in the literature.[118]

TLC R_f: 0.84 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.35 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.19 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.14 (d, *J* = 8.0 Hz, 2H, Ar-H), 5.21 (s, 1H, NH), 3.08 (t, *J* = 6.5 Hz, 2H, CH_2), 1.82 (m, 1H, CH), 0.95 (d, *J* = 6.8 Hz, 6H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 154.9 (C), 151.2 (C), 129.3 (CH), 125.2 (CH), 121.6 (CH), 48.6 (CH_2), 28.7 (CH), 20.0 (CH_3).



Phenyl-*N*-neopentylcarbamate (3.3.6): The title compound was synthesized according to General Procedure G using pivaldehyde (217 µL, 2.00 mmol, 1.00 equiv.) in acetonitrile (8.00 mL, 0.25 M) at room temperature for 18 h. The product was purified via silica-gel flash column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes) to afford **3.3.6** as a white wax (0.128 g, 62% yield).

TLC R_f: 0.64 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.33 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.17 (t, *J* = 7.4, 1H, Ar-H), 7.12 (d, *J* = 7.8 Hz, 2H, Ar-H), 3.04 (d, *J* = 6.5, 2H, CH_2), 0.93 (s, 9H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 155.1 (C), 151.2 (C), 129.3 (CH), 125.2 (CH), 121.6 (CH), 52.7 (CH_2), 32.1 (C), 27.1 (CH_3); **IR (neat)**: $\tilde{\nu}$ = 3353 (br), 2952 (w), 2865 (w), 1737 (s), 1735 (s), 1526 (s), 1488 (s) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{12}H_{17}O_2N$: 207.1259 $[M]^+$; found: 207.1272



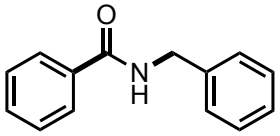
Phenyl (2-Phenylpropan-2-yl)carbamate (3.9): The title compound was synthesized using a literature procedure.[97] To an oven-dried microwave vial was added 2-phenylpropan-2-ol (0.5 mmol) and linchpin reagent **3.1** (0.75 mmol). The reagents are dissolved in 1.5 mL of dichloromethane (0.33 M). Then, Bu_4NPF_6 (5 mol%) and $Ca(NTf_2)_2$ (5 mol%) are stirred until

[118] T. Patonay, E. Patonay-Peli, F. Mogyoródi, *Synth. Commun*. **1990**, *20*, 2865–2885.

conversion of the alcohol is complete (monitored by TLC). For the isolation of the product, 5 mL of saturated $NaHCO_3$ solution is added, the aqueous phase extracted with dichloromethane, the combined organic phases dried over Na_2SO_4 and concentrated in vacuo. The product was purified via silica-gel flash column chromatography (10% EtOAc/hexanes to 20% EtOAc/hexanes) to afford **3.9** as a white powder (0.138 g, 54% yield).

3.9: The spectral and physical properties of the product match those reported in the literature.[97]

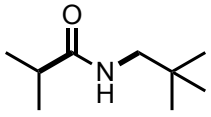
TLC R_f: 0.46 in 25% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.51 – 7.43 (m, 2H, Ar-H), 7.40 – 7.21 (m, 5H, Ar-H), 7.19 – 7.07 (m, 3H, Ar-H), 5.47 (s, 1H, NH), 1.74 (s, 6H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 152.7 (C), 151.0 (C), 146.7 (C), 129.3 (CH), 128.6 (CH), 127.0 (CH), 125.2 (CH), 124.9 (CH), 121.7 (CH), 55.8 (C), 31.0 (CH_3), 29.8 (CH_3).



***N*-Benzyl benzamide (3.11.1):** The title compound was synthesized according to General Procedure C using phenyl magnesium bromide (1.00 mL, 0.800 mmol, 0.8 M in THF, 4.00 equiv.). The Grignard was diluted with 0.66 mL of dioxane, then a solution of masked isocyanate **3.3.1** (0.045 g, 0.200 mmol, 1.00 equiv.) in 1.00 mL of THF was added dropwise. After 30 minutes at room temperature, the reaction mixture was transferred to a round-bottom flask, rinsed with ethyl acetate (10 mL), quenched with 1 M HCl (10 mL), stirred for 5 minutes, neutralized with saturated sodium bicarbonate (10 mL), and transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 10mL). The organic layer was collected and washed with saturated sodium bicarbonate (2 x 10 mL), and brine (2 x 10 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford the crude product, which was purified via silica-gel flash column chromatography (20% EtOAc/hexanes to 50% EtOAc/hexanes) to afford **3.11.1** as a white crystalline solid (0.037 g, 89% yield).

3.11.1: The spectral and physical properties of the product match those reported in the literature.[119]

TLC R_f: 0.5 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.82 – 7.72 (m, 2H, Ar-H), 7.53 – 7.46 (m, 1H, Ar-H), 7.41 (t, J = 7.2 Hz, 2H, Ar-H), 7.38 – 7.22 (m, 5H, Ar-H), 6.42 (s, 1H, NH), 4.63 (d, J = 5.6 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 167.5 (C), 138.3 (C), 134.5 (C), 131.7 (CH), 128.9 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.1 (CH), 44.3 (CH_2).

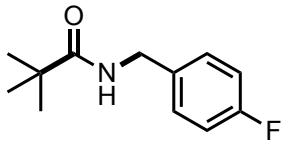


***N*-Beopentylisobutyramide (3.11.2):** The title compound was synthesized according to General Procedure C using isopropyl magnesium chloride (1.00 mL, 0.800 mmol, 0.8 M in THF, 4.00 equiv.). The Grignard was diluted with 0.65 mL of dioxane, then a solution of masked isocyanate

[119] J. B. Gualtierotti, X. Schumacher, P. Fontaine, G. Masson, Q. Wang, J. Zhu, *Chem. Eur. J.* **2012**, *18*, 14812– 14819.

3.3.6 (0.039 g, 0.200 mmol, 1.00 equiv.) in 1.00 mL of THF was added dropwise. After 30 minutes at room temperature, the reaction mixture was transferred to a separatory funnel, quenched with 1 M HCl (10 mL), stirred for 5 minutes. The aqueous layer was extracted with ethyl acetate (3 x 10mL). The organic layer was collected and washed with 1 M NaOH (2 x 10 mL), and brine (2 x 10 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to **3.11.2** as a clear waxy solid (0.028 g, 86% yield).

TLC R*f*: 0.9 in 10% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 5.45 (s, 1H, NH), 3.05 (d, *J* = 6.2 Hz, 1H, CH_2), 2.35 (ddd, *J* = 11.2, 8.6, 5.7 Hz, 1H, CH), 1.19 – 1.08 (d, 6H, CH_3), 0.89 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.9 (C), 50.2 (CH_2), 36.0 (CH), 31.9 (CH), 27.2 (CH_3), 19.8 (CH_3); **HRMS (EI)**: *m/z* calcd for $C_9H_{19}NO$: 157.1457 $[M]^+$; found: 157.1440.

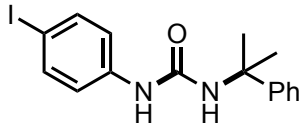


***N*-(4-Fluorobenzyl)pivalamide (3.11.3):** The title compound was synthesized according to General Procedure C using tertbutyl magnesium chloride (0.500 mL, 0.800 mmol, 1.6 M in ether, 4.00 equiv.). The Grignard was diluted with 0.65 mL of dioxane, then a solution of masked isocyanate **3.3.2** (0.049 g, 0.200 mmol, 1.00 equiv.) in 1.50 mL of THF was added dropwise. After 30 minutes at room temperature, the reaction mixture was transferred to a separatory funnel, quenched with 1 M HCl (10 mL), stirred for 5 minutes. The aqueous layer was extracted with ethyl acetate (3 x 10mL). The organic layer was collected and washed with 1 M NaOH (2 x 10 mL), and brine (2 x 10 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford the crude product, which was purified via silica-gel flash column chromatography (5% EtOAc/hexanes to 30% EtOAc/hexanes) to afford **3.11.3** as a white waxy solid (0.030 g, 68% yield).

3.11.3: The spectral and physical properties of the product match those reported in the literature.[120]

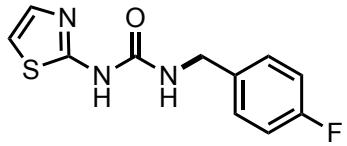
TLC R*f*: 0.43 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.28 – 7.18 (m, 2H, Ar-H), 7.01 (dd, J = 8.7, 8.7 Hz, 2H, Ar-H), 5.91 (s, 1H, NH), 4.40 (d, J = 5.6 Hz, 2H, CH_2), 1.22 (s, 9H, CH_3); **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 178.3 (C), 162.2 (d, $^1J_{C\text{-}F}$ = 245.5 Hz, C), 160.9 (C), 134.5 (C), 129.3 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, CH), 115.6 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, CH), 42.9 (CH_2), 38.7 (C), 27.6 (CH_3); **^{19}F NMR (300 MHz, Chloroform-*d*) δ** -117.2.

[120] R. Zhao, W. Lu, *Org. Lett.* **2017** *19*, 1768-1771.



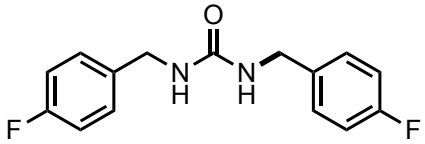
(4-Iodophenyl)-3-(2-phenylpropan-2-yl)urea (3.13.1): The title compound was synthesized according to General Procedure F using masked isocyanate **3.9** (0.0510 g, 0.200 mmol, 1.00 equiv.) and 4-iodoaniline (0.108 g, 0.493 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was purified via recrystallization with ether to afford **3.13.1** as a white powder (0.070 g, 92% yield).

TLC R*f*: 0.37 in 20% EtOAc/hexanes; **^{1}H NMR (400 MHz, Dimethylsulfoxide-*d*$_6$) δ** 8.51 (s, 1H, NH), 7.51 – 7.41 (m, 2H, Ar-H), 7.40 – 7.33 (m, 2H, Ar-H), 7.30 – 7.26 (m, 2H, Ar-H), 7.19 – 7.12 (m, 3H, Ar-H), 6.61 (s, 1H, NH), 1.56 (s, 6H, CH_3); **^{13}C NMR (101 MHz, Dimethylsulfoxide-*d*$_6$)** δ 153.7 (C), 148.3 (C), 140.4 (C), 137.1 (CH), 128.0 (CH), 125.9 (CH), 124.7 (CH), 119.7 (CH), 83.3 (C) 54.3 (C), 29.6 (CH_3); **IR (neat)**: $\tilde{\nu}$ = 3325 (br), 2980 (w), 1650 (s), 1545 (s), 1486 (s), 1307 (s) cm^{-1}; **HRMS (EI)**: *m/z* calcd for $C_{16}H_{17}ON_2I$: 380.0386 $[M]^+$; found: 380.0392.



1-(4-Fluorobenzyl)-3-(thiazol-2-yl)urea (3.13.2): The title compound was synthesized according to General Procedure F using masked isocyanate **3.3.2** (0.0490 g, 0.200 mmol, 1.00 equiv.) and 4-iodoaniline (0.108 g, 0.493 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was attempted to be purified via recrystallization with dichloromethane and silica-gel flash column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes) and silica-gel flash column chromatography (100% $CH_2Cl_2$to 2% MeOH/CH_2Cl_2). The purification yielded an inseparable mixture of the unsymmetric urea **3.13.2** and the symmetric urea **3.14** as a beige powder (0.039 g, 61% yield of **3.13.2** and 15% yield of **3.14**).

TLC R*f*: 0.49 in 20% EtOAc/hexanes; **^{1}H NMR (600 MHz, Dimethylsulfoxide-d$_6$)** δ 7.33 (dd, *J*=8.5, 5.6 Hz, 2H, Ar-H), 7.29 – 7.26 (m, 1H, Ar-H), 7.19 – 7.09 (m, 3H, Ar-H), 4.32 (d, *J* = 6.0 Hz, 2H, CH_2); **^{13}C NMR (151 MHz, Dimethylsulfoxide-d$_6$) δ** 160.6 (d, $^1J_{C\text{-}F}$ = 242.3 Hz, Ar-H), 159.4 (C), 153.3 (C), 136.7 (CH), 136.5 (d, $^4J_{C\text{-}F}$ =3.0 Hz, C), 128.6 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 114.5 (d, $^2J_{C\text{-}F}$ = 21.3 Hz, CH), 111.3 (CH), 41.6 (CH_2); **^{19}F NMR (300 MHz, Dimethylsulfoxide-d$_6$) δ** -118.1.



1,3-Bis(4-fluorobenzyl)urea (3.14): The title compound was a side product in the synthesis of **3.13.2**, synthesized according to General Procedure F using masked isocyanate **3.3.2** (0.0490 g, 0.200 mmol, 1.00 equiv.) and 4-iodoaniline (0.108 g, 0.493 mmol, 1.20 equiv.) in toluene (0.4 mL, 0.5 M) at 80 ºC for 18 h. The product was attempted to be purified via recrystallization with dichloromethane and silica-gel flash column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes) and silica-gel flash column chromatography (100% $CH_2Cl_2$to 2% MeOH/CH_2Cl_2). The purification yielded an inseparable mixture of the unsymmetric urea **3.13.2** and the symmetric urea **3.14** as a beige powder (0.039 g, 61% yield of **3.13.2** and 15% yield of **3.14**).

3.14: The spectral and physical properties of the product match those reported in the literature.[121]

TLC R_f: 0.55 in 20% EtOAc/hexanes; **^{1}H NMR (600 MHz, Dimethylsulfoxide-d_6) δ** 7.30 (d, *J* = 3.6 Hz, 4H, Ar-H), 7.02 (d, *J* = 3.6 Hz, 4H, Ar-H), 4.20 (d, *J* = 6.0 Hz, 4H, CH_2); **^{13}C NMR (151 MHz, Dimethylsulfoxide-d_6) δ** 160.4 (d, $^1J_{C\text{-}F}$ = 241.7 Hz, C), 157.4 (C), 135.3 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, C), 128.3 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, CH), 114.3 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 41.5 (CH_2); **^{19}F NMR (300 MHz, Dimethylsulfoxide-d_6) δ** -118.6.

[121] M. Xu, A. R. Jupp, M. S. E. Ong, K. I. Burton, S. S. Chitnis, D. W. Stephan, *Angew. Chem. Int. Ed*. **2019**, *58*, 5707-5711.

Publications and Presentations from this work

Publications

1. B. Uppalapati‡, **M. A. Aubry**‡, Q. Wang, D. Abdelhamid, M. A. Gill, A. M. Beauchemin, Development and Applications of an Amide Linchpin Reagent. *Angew. Chem. Int. Ed.* **2024**, *64*, e202421258.

2. **Simpler Linchpins**. Manuscript in preparation.

Poster Presentations (indicates presenter)*

1. **Development of a New Linchpin Reagent Towards the Modular Synthesis of Amides.** Uppalapati, B*; Mohamed, A. M.; Aubry, M. A.; Beauchemin, A. M. QOMSBOC. October 14-16, 2022.
2. **Development of a Linchpin Reagent for Direct Preparation of Amides.** Aubry, M. A*.; Uppalapati, B.; Beauchemin, A. M. QOMSBOC. November 10-12, 2023.
3. **Development and Applications of an NCO Linchpin Reagent.** Uppalapati, B.*; Aubry, M. A.; Beauchemin, A. M. QOMSBOC. November 8-10, 2024.

Oral Presentations (indicates presenter)*

1. **Development and Applications of an Amide Linchpin Reagent.** Uppalapati, B.*; Aubry, M. A.; Beauchemin, A. M. OCCI. May 24, 2024.
2. **Development and Applications of a Linchpin Reagent: Amides and Beyond.** Aubry, M. A*.; Uppalapati, B.; Beauchemin, A. M. Paraza Symposium. September 6, 2024. (Awarded best 15 minute presentation, $500 prize)
3. **Development and Applications of an NCO Linchpin Reagent.** Uppalapati, B.*; Aubry, M. A.; Beauchemin, A. M. EWOC Virtual Symposium. 2024.

Claims to Original Research

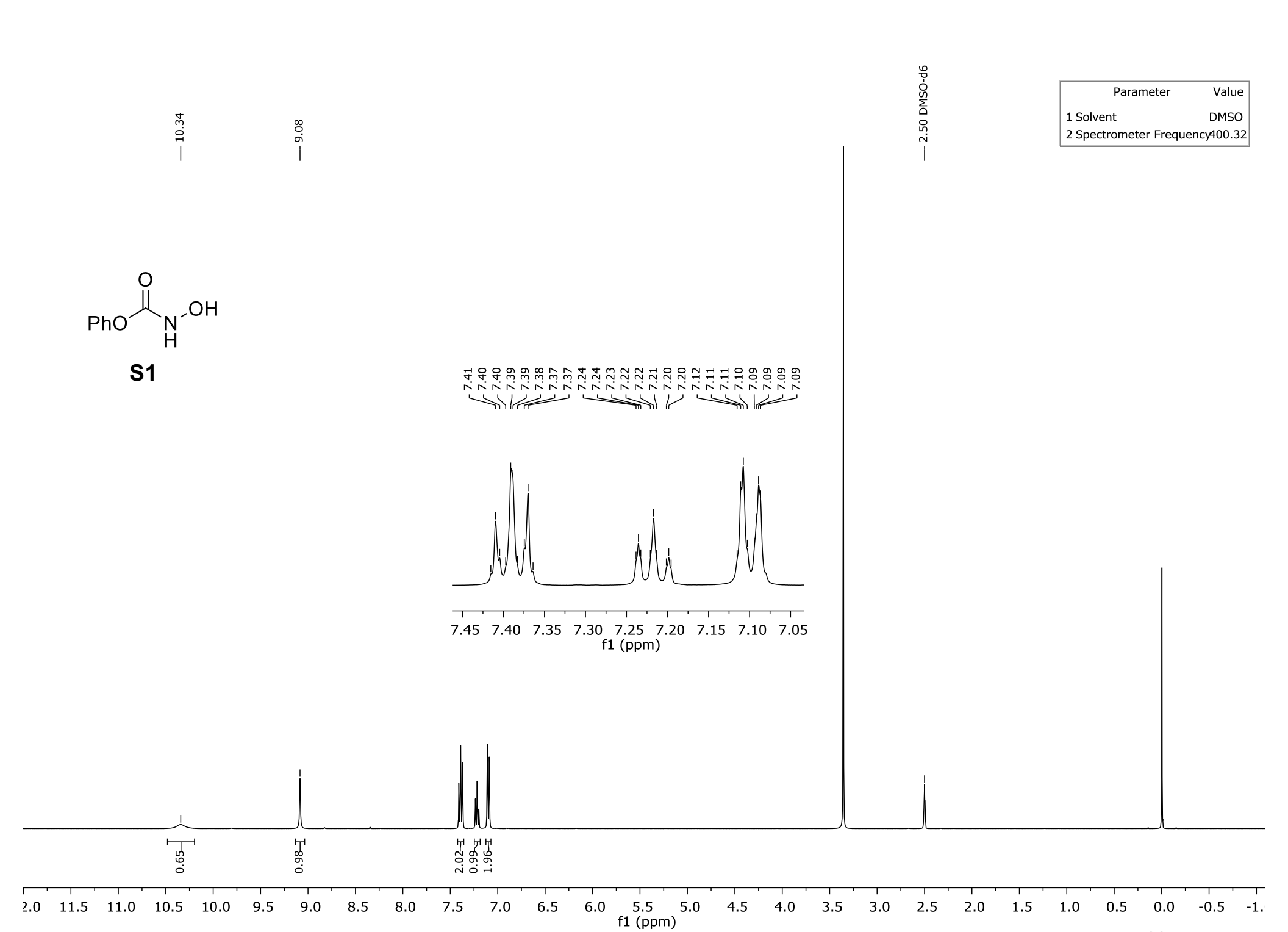
1. A masked *O*-isocyanate reagent **2.1.6** has been developed to be the first amide / NCO linchpin reagent.

2. The rhodium-catalyzed amination of masked *O*-isocyanate **2.1.6** with aryl boronic acids **2.2** to form a new C-N bond was discovered, optimized and the substrate scope of the reaction was determined.

3. The products of the rhodium-catalyzed amination of masked *O*-isocyanates **2.3** may be further functionalized using Grignard reagents to yield amides **2.5**, and nitrogen nucleophiles such as amines, to yield unsymmetrical ureas **2.9**.

4. The use of phenyl carbamate **3.1** can be used as a simpler linchpin reagent via a reductive amination/Grignard sequence to form amides **3.3**.

Spectra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9.08
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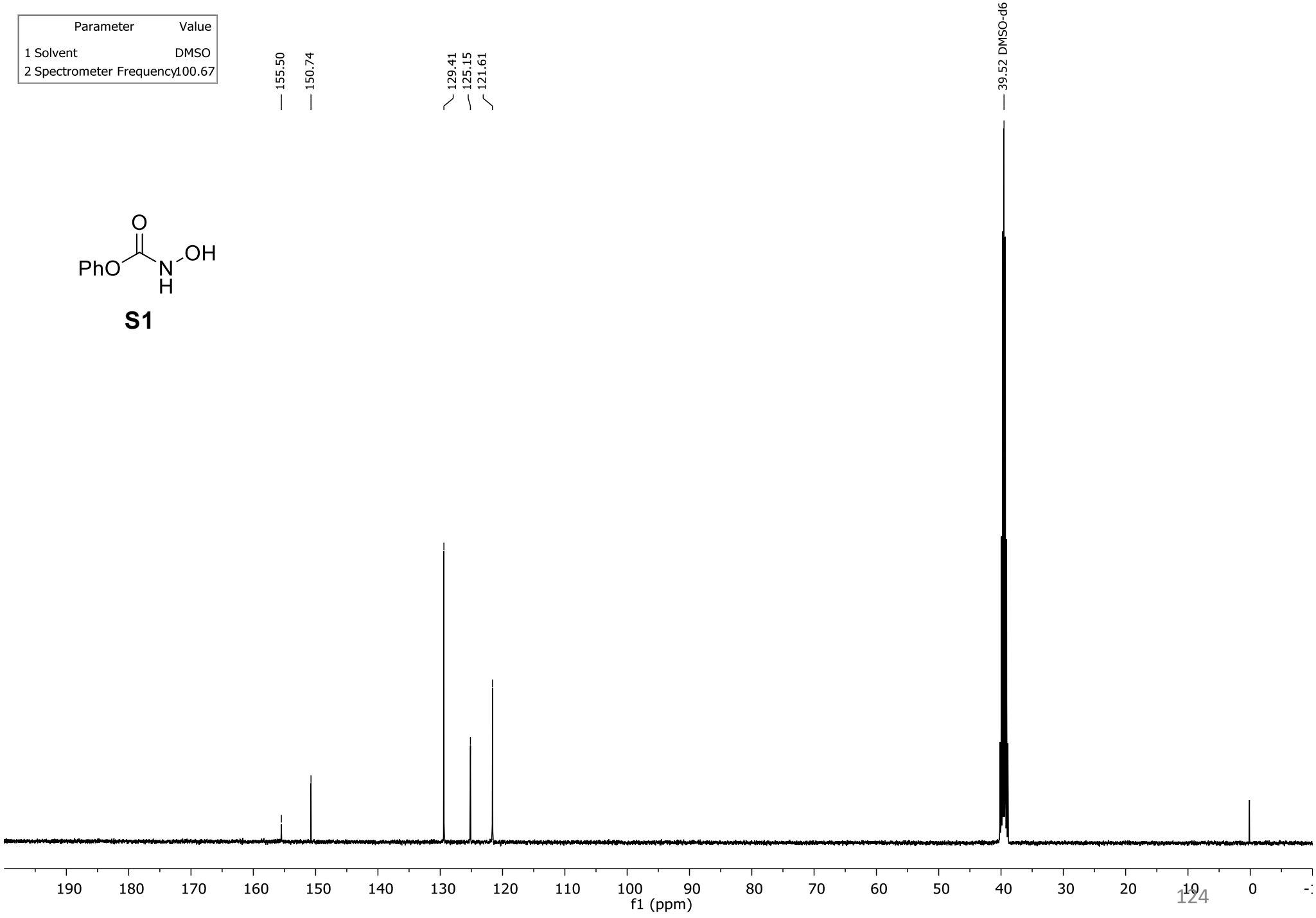
O
N
H
OH
S1
7.41 7.40 7.40 7.39 7.39 7.38 7.37 7.24 7.24 7.23 7.22 7.22 7.21 7.20 7.20 7.12 7.11 7.11 7.10 7.09 7.09 7.09 7.09
7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05
f1 (ppm)
0.65
0.98
2.02
0.99
1.96
f1 (ppm)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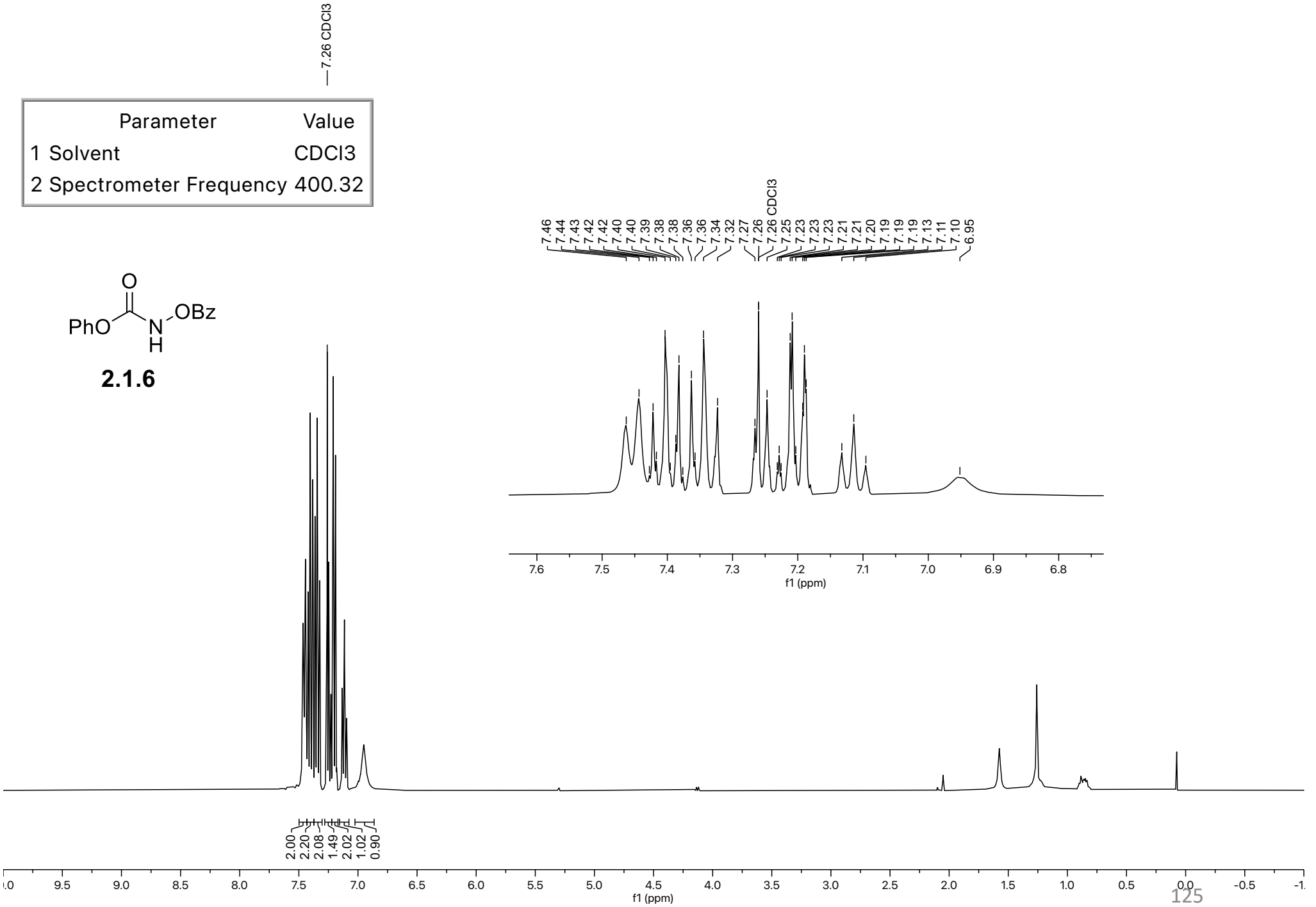
f1 (ppm)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N
H
OBz
2.1.6
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7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8
f1 (ppm)
2.00 2.20 2.08 1.49 2.02 1.02 0.90
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	125.80

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130.32
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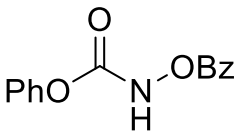
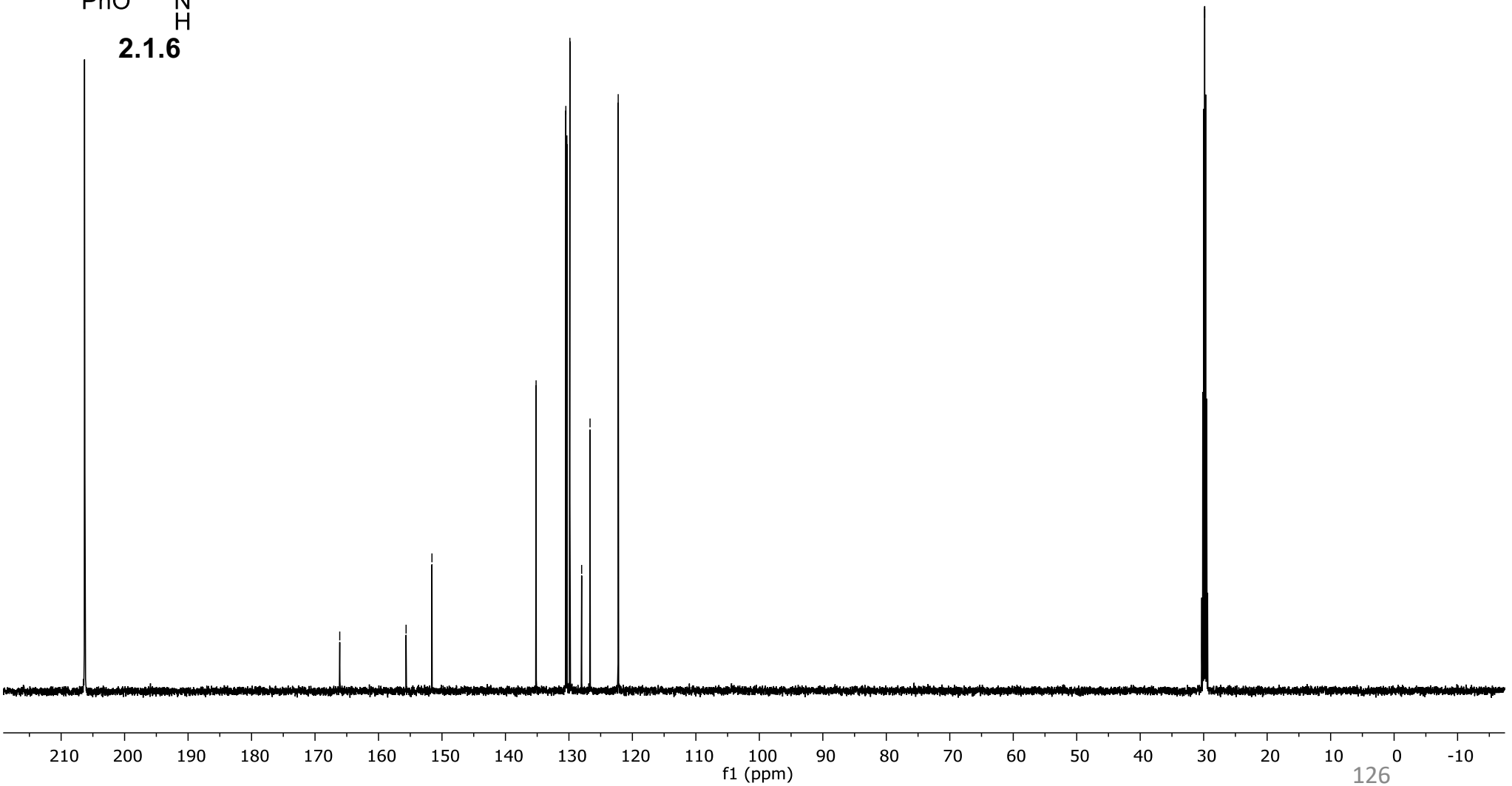
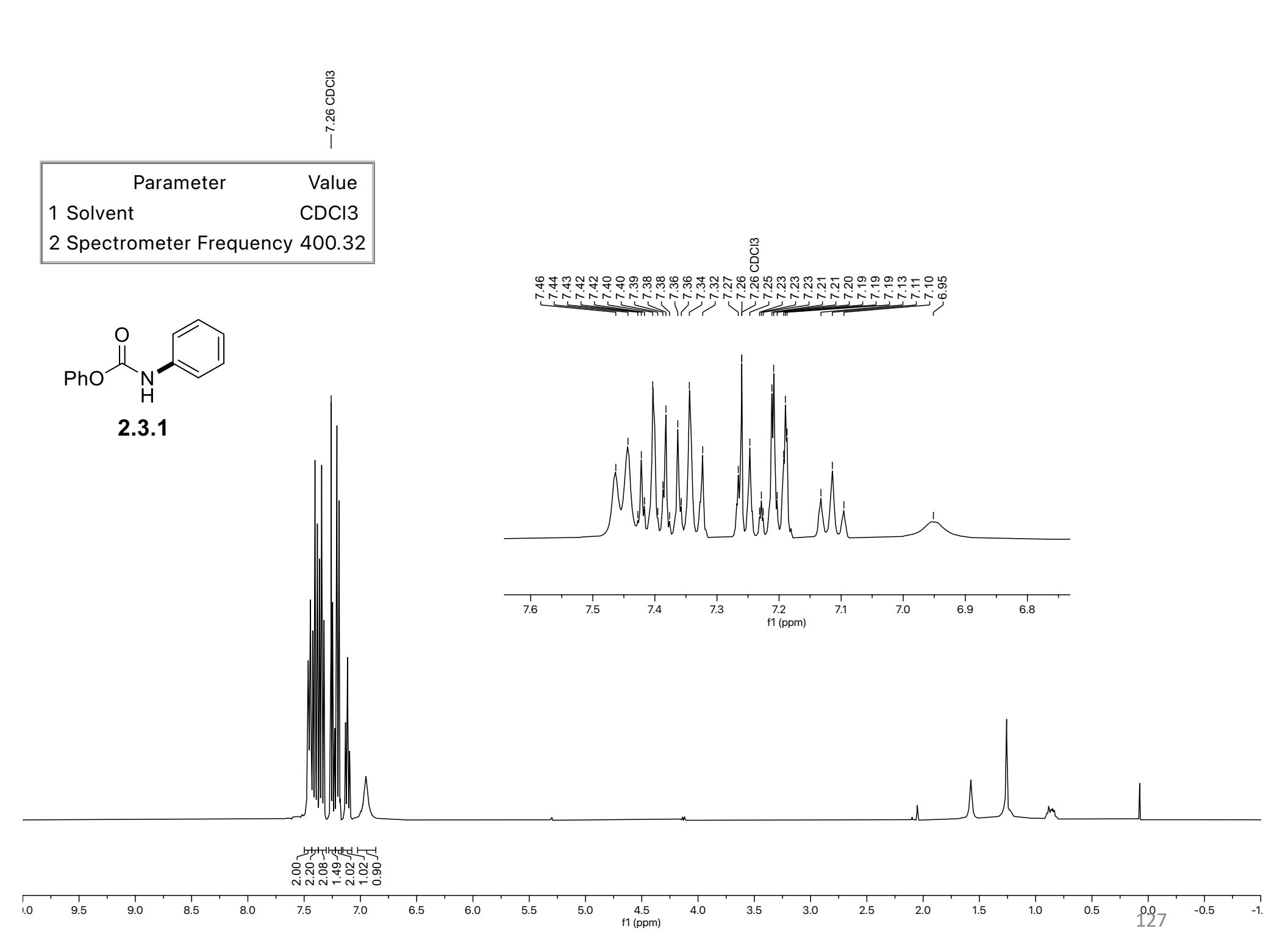
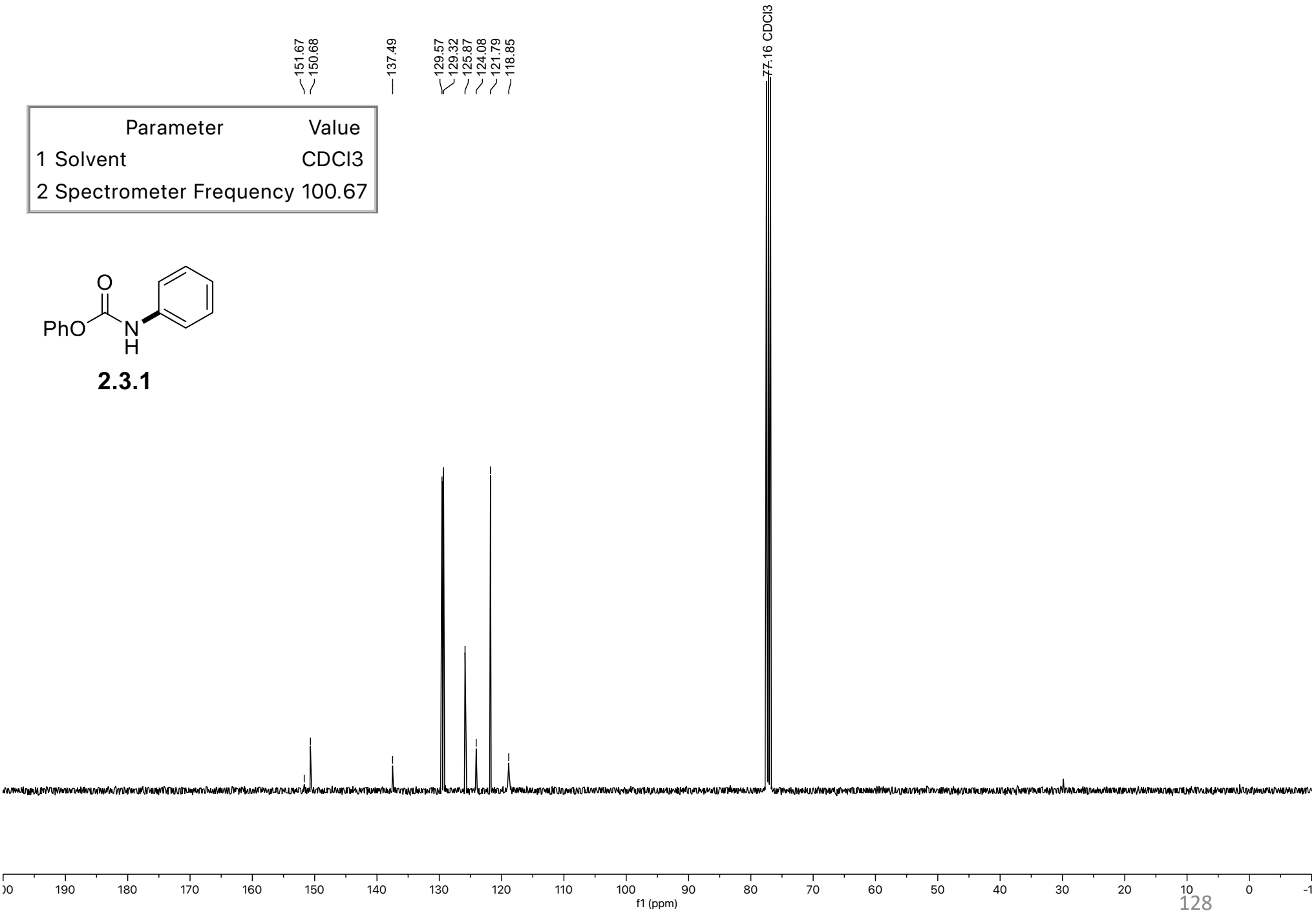
29.84 (CD3)2CO

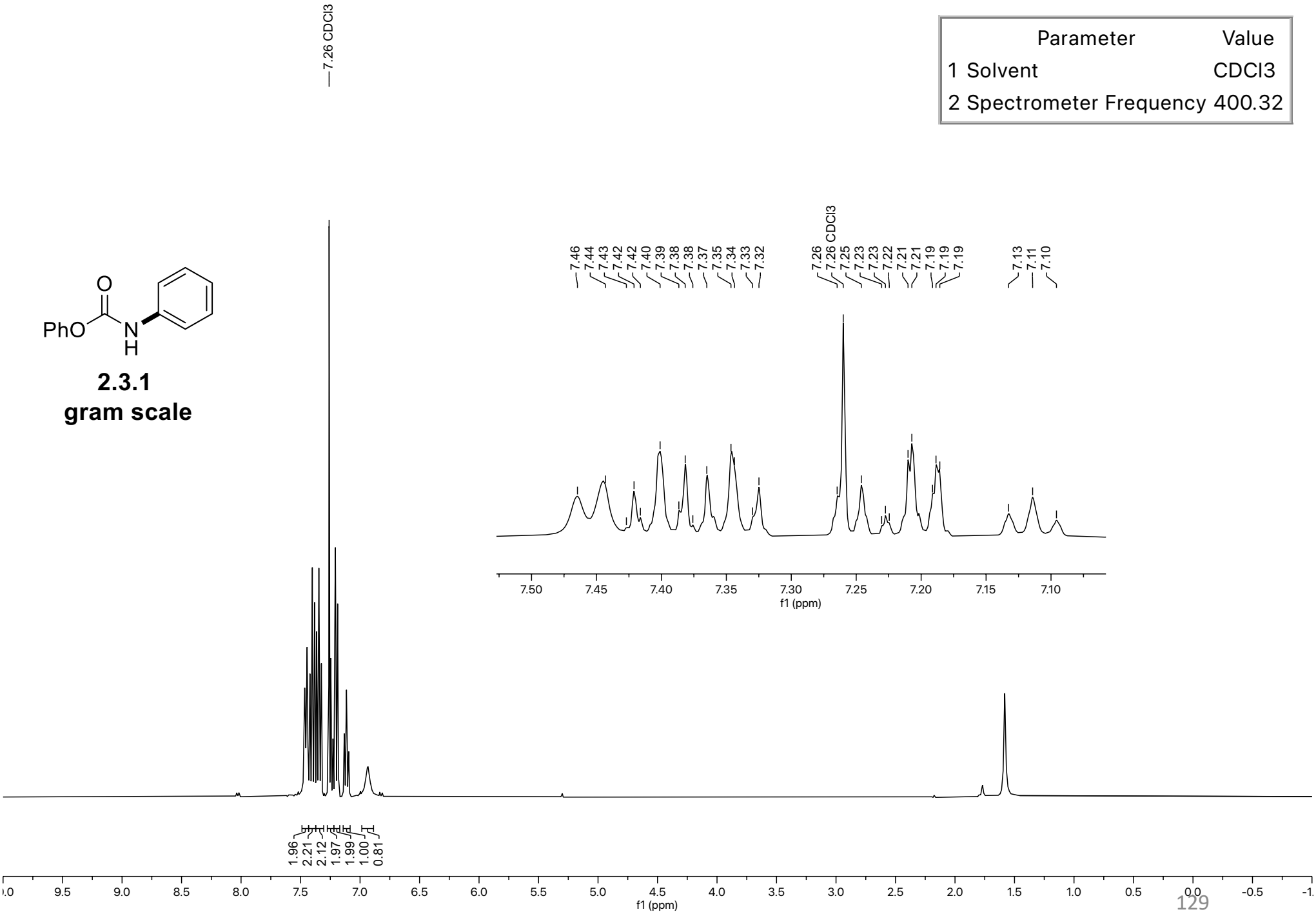


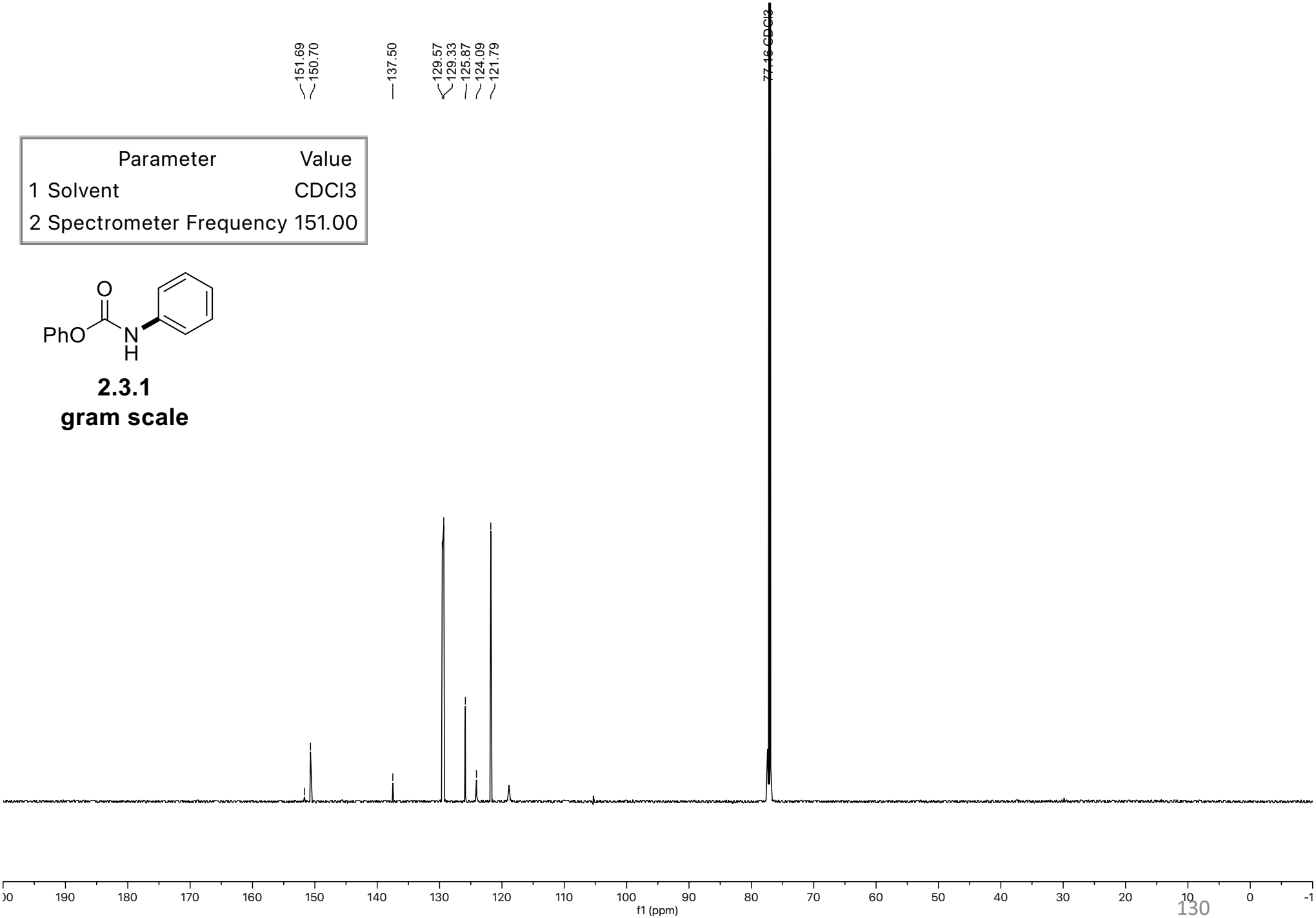
2.1.6



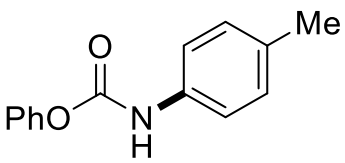

7.26 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
PhO
O
N
H
2.3.1
7.46
7.44
7.43
7.42
7.42
7.40
7.40
7.39
7.38
7.38
7.36
7.36
7.34
7.32
7.27
7.26
7.26 CDCl3
7.25
7.23
7.23
7.23
7.21
7.21
7.20
7.19
7.19
7.19
7.13
7.11
7.10
6.95
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
f1 (ppm)
2.00
2.20
2.08
1.49
2.02
1.02
0.90
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
f1 (ppm)


151.67
150.68
137.49
129.57
129.32
125.87
124.08
121.79
118.85
77.16 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
PhO
O
N
H
2.3.1
f1 (ppm)

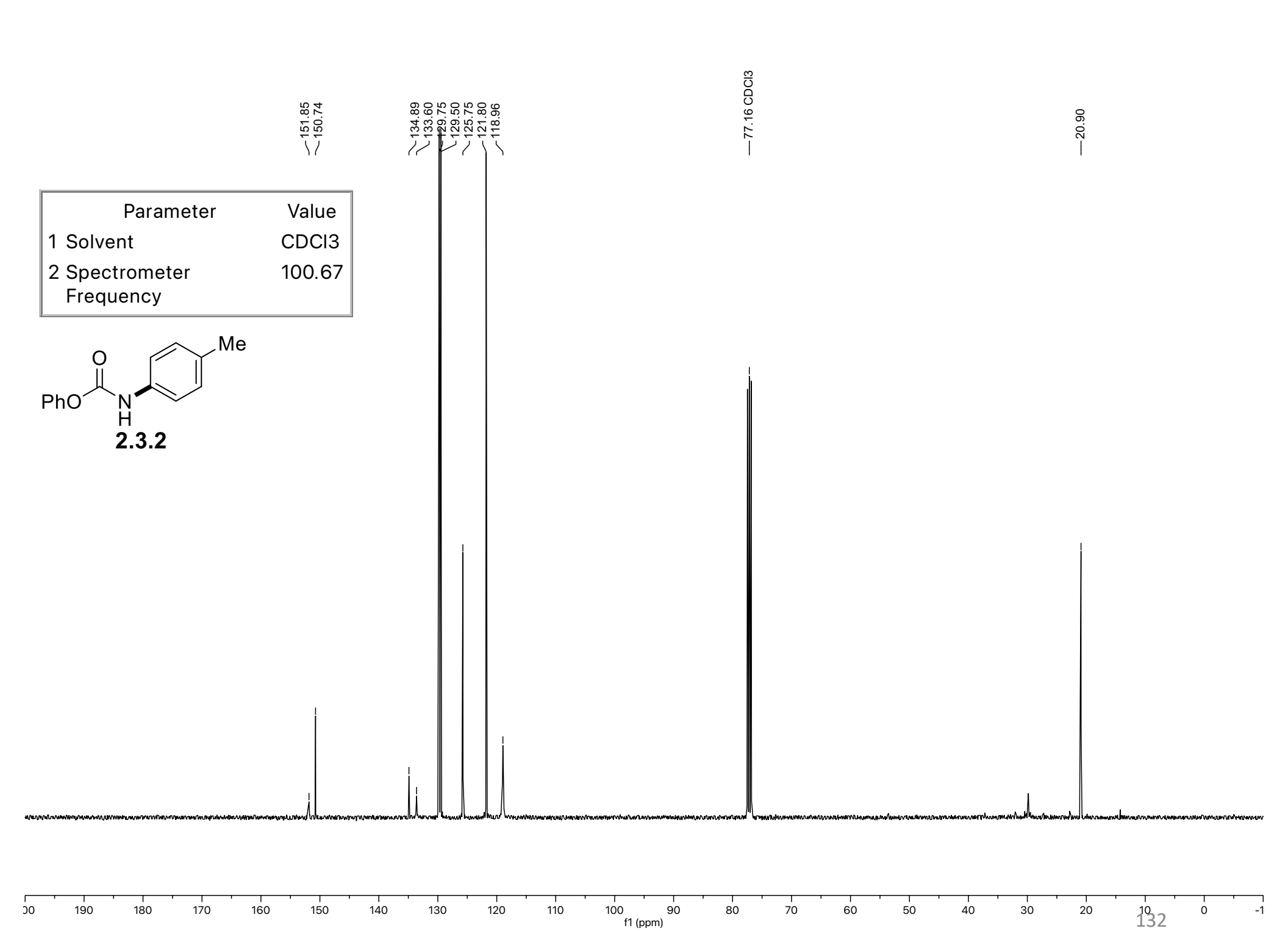

7.26 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
PhO
N
H
2.3.1
gram scale
7.46 7.44 7.43 7.42 7.42 7.40 7.39 7.38 7.38 7.37 7.35 7.34 7.33 7.32
7.26 CDCl3 7.25 7.23 7.23 7.22 7.21 7.21 7.19 7.19 7.19
7.13 7.11 7.10
7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10
f1 (ppm)
1.96 2.21 2.12 1.97 1.99 1.00 0.81
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
f1 (ppm)


151.69
150.70
137.50
129.57
129.33
125.87
124.09
121.79
77.16 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 151.00
PhO
O
N
H
2.3.1
gram scale
f1 (ppm)

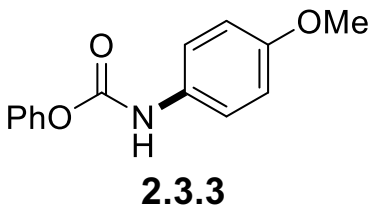
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



2.3.2

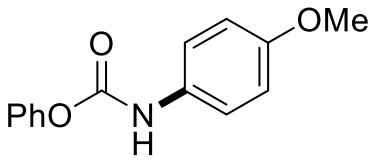

151.85
150.74
134.89
133.60
129.75
129.50
125.75
121.80
118.96
77.16 CDCl3
20.90
Parameter
Value
1 Solvent
CDCl3
2 Spectrometer Frequency
100.67
Me
O
PhO
N
H
2.3.2
f1 (ppm)

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32

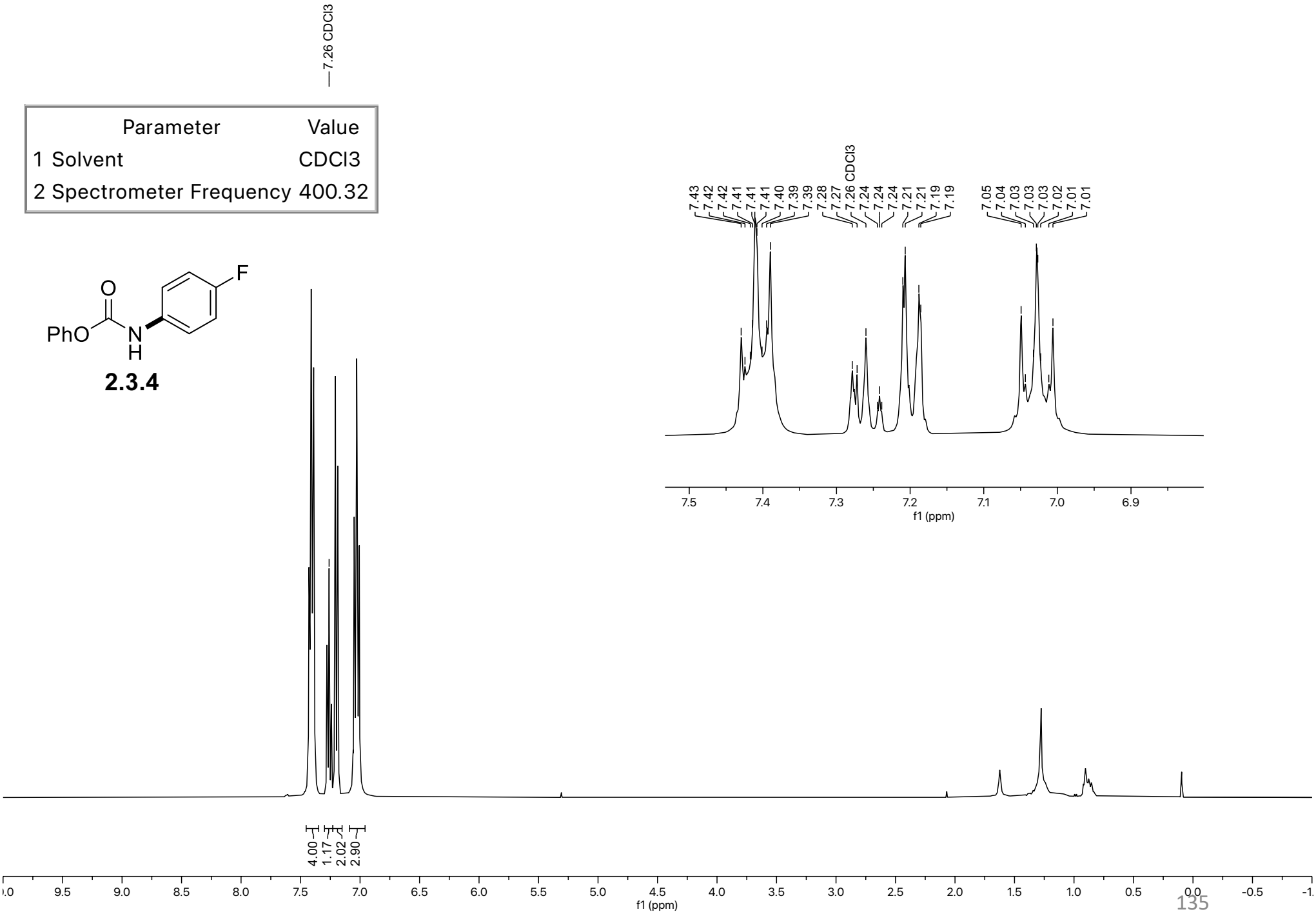


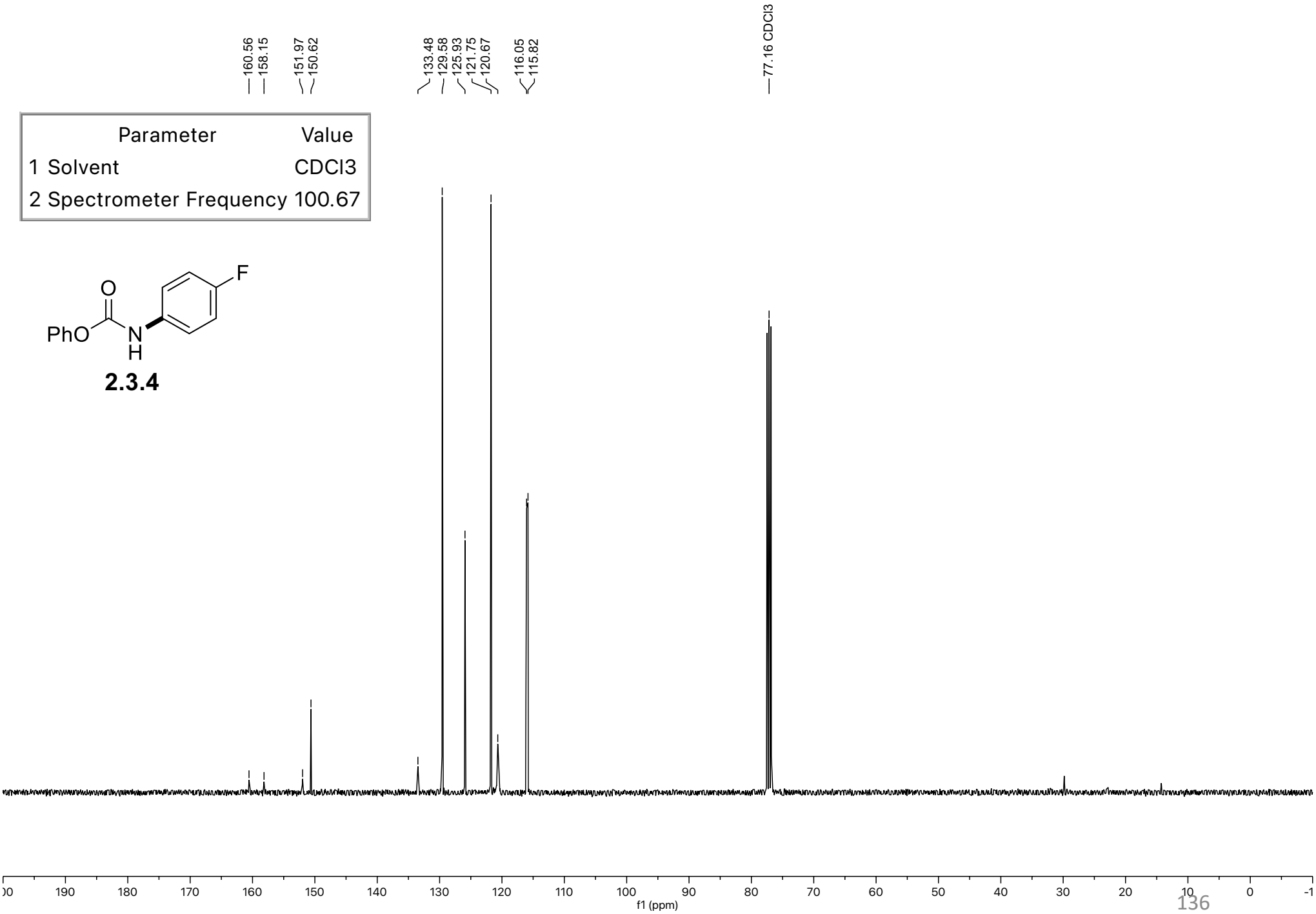
2.3.3

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67

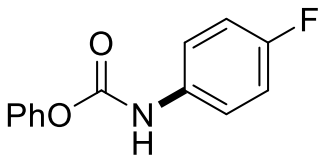


2.3.3

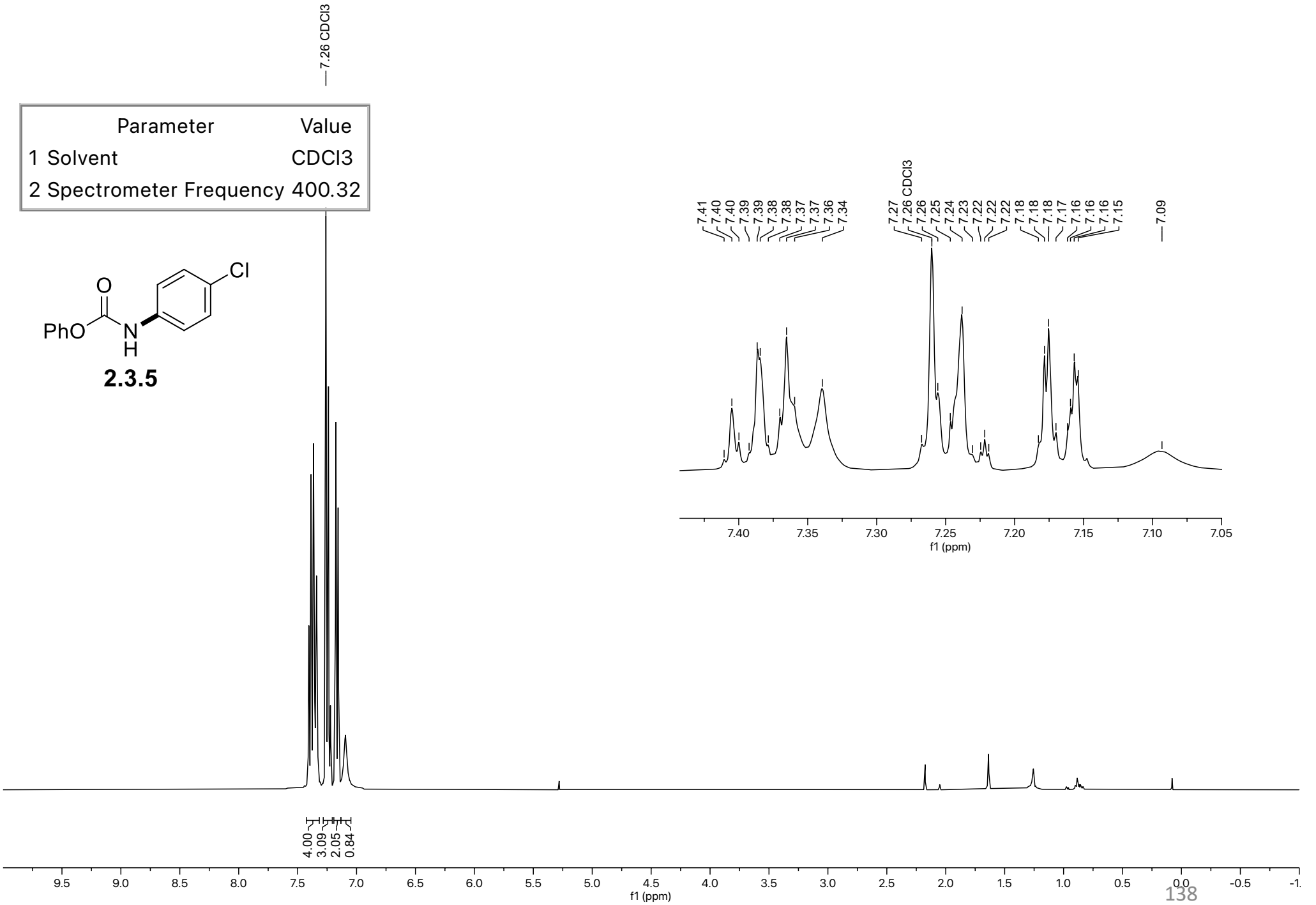

7.26 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
PhO
O
N
H
F
2.3.4
7.43 7.42 7.42 7.41 7.41 7.41 7.40 7.39 7.39 7.28 7.27 7.26 CDCl3 7.24 7.24 7.24 7.21 7.21 7.19 7.19 7.05 7.04 7.03 7.03 7.03 7.02 7.01 7.01
7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
4.00 1.17 2.02 2.90
9.5 9.0 8.5 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
f1 (ppm)

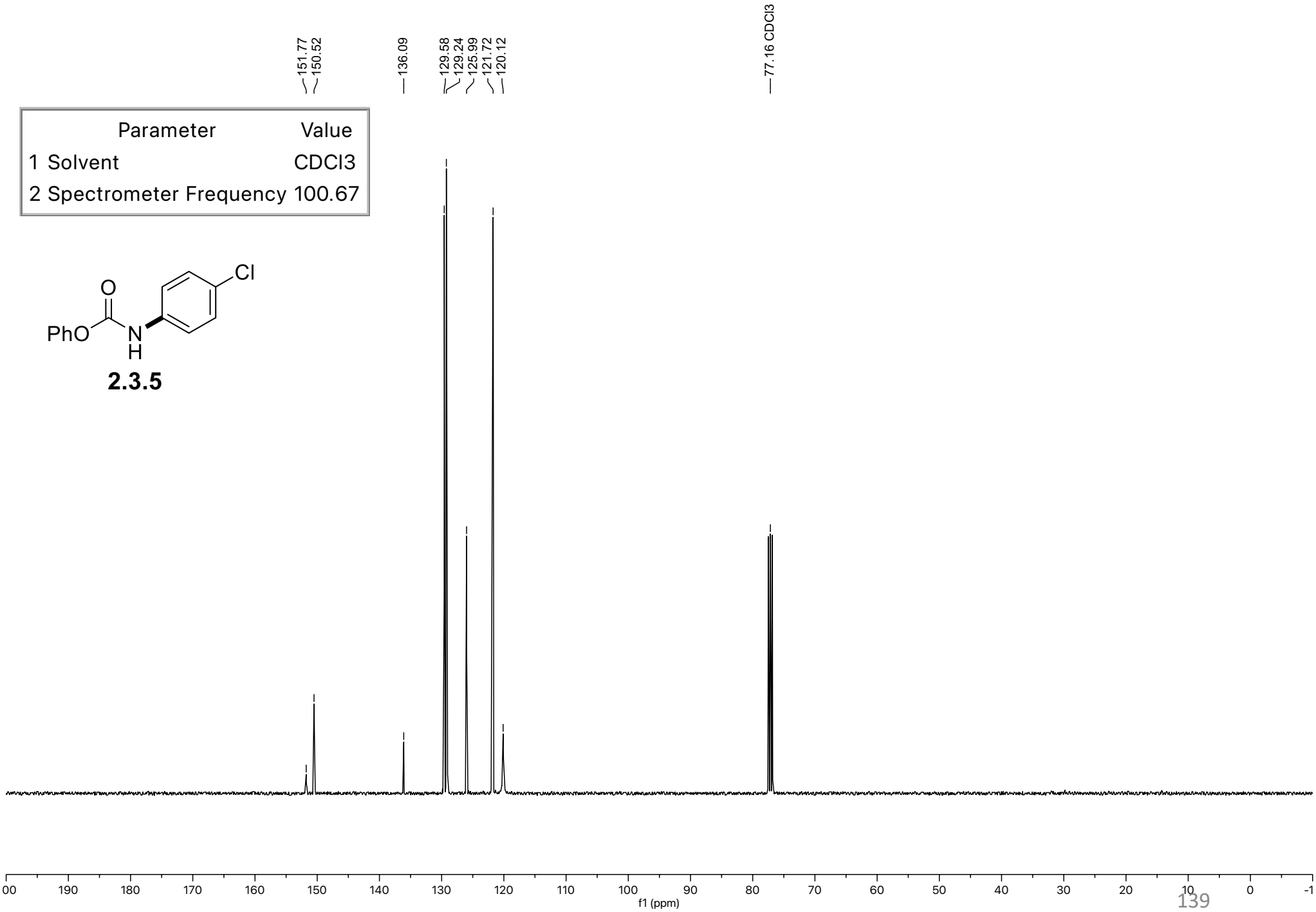

160.56
158.15
151.97
150.62
133.48
129.58
125.93
121.75
120.67
116.05
115.82
77.16 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
O
PhO
N
H
F
2.3.4
f1 (ppm)

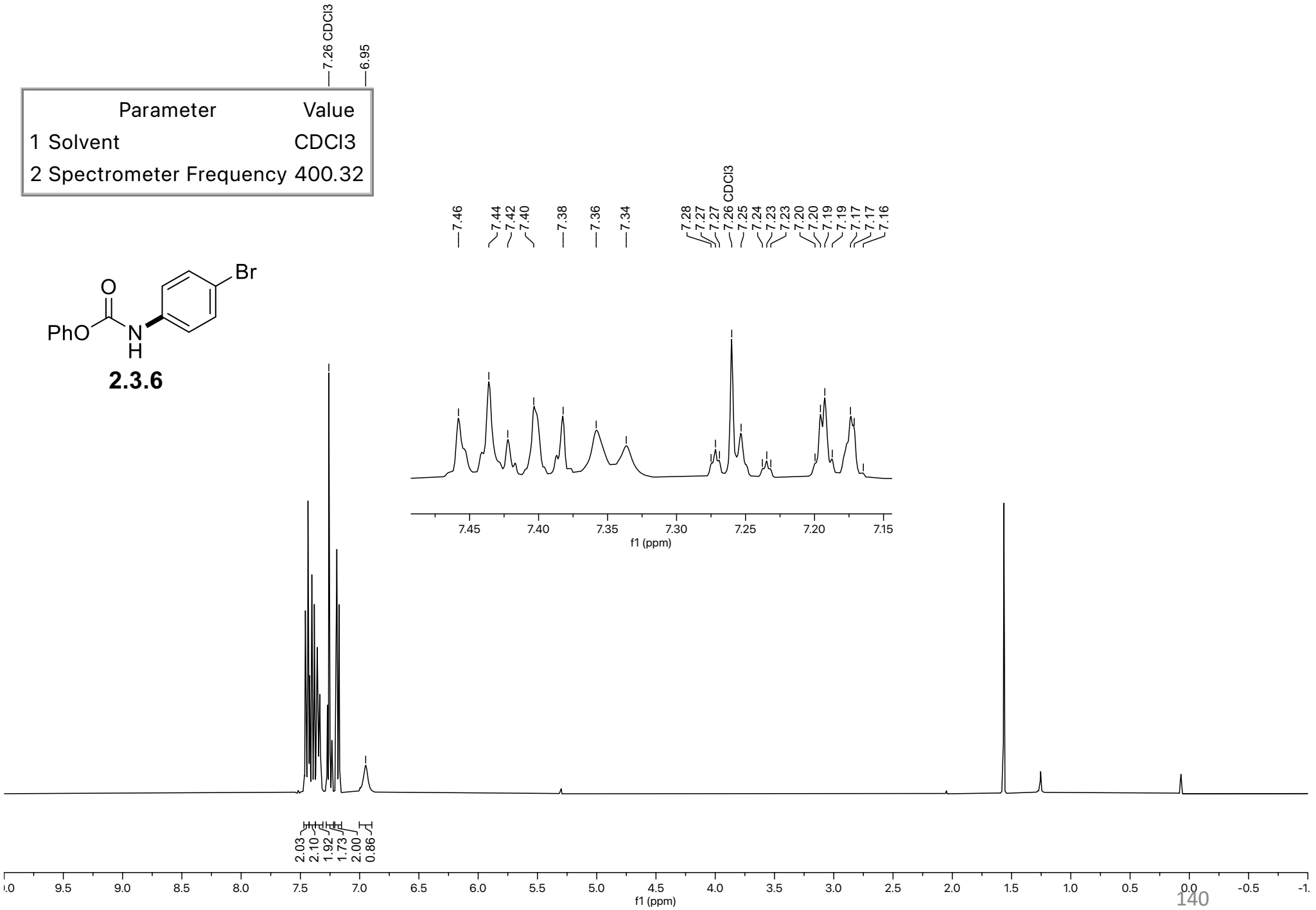
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	282.56

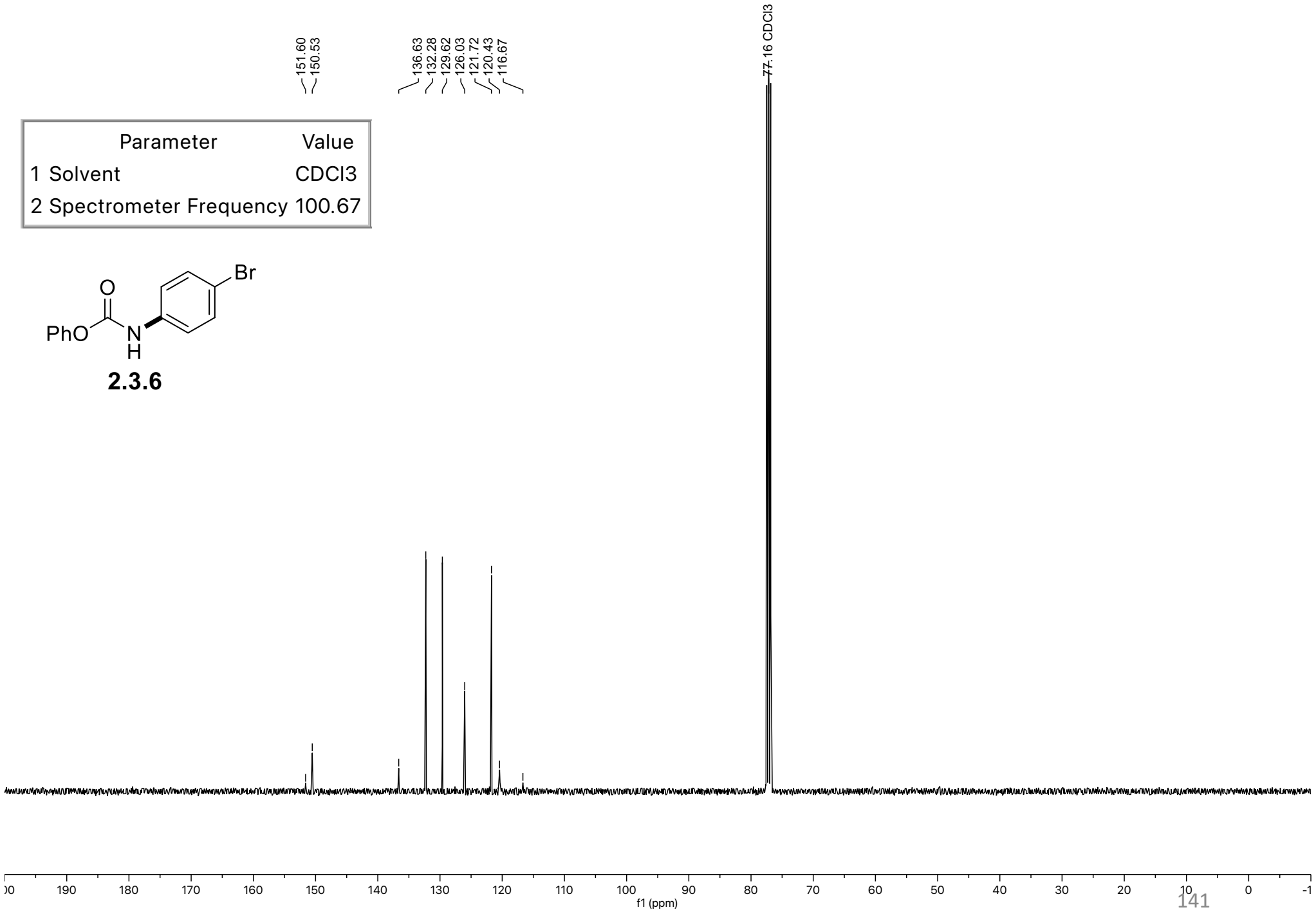


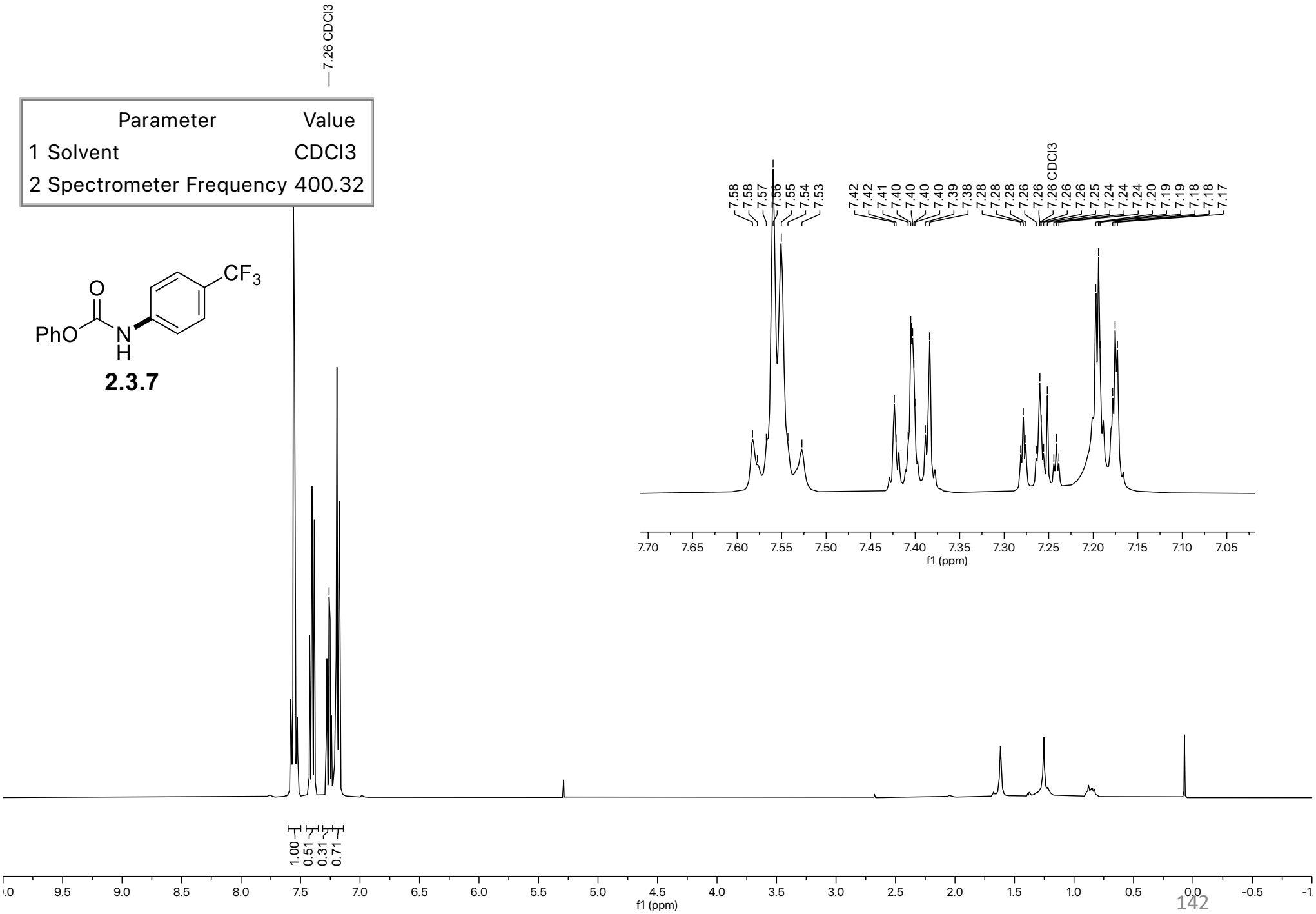
2.3.4

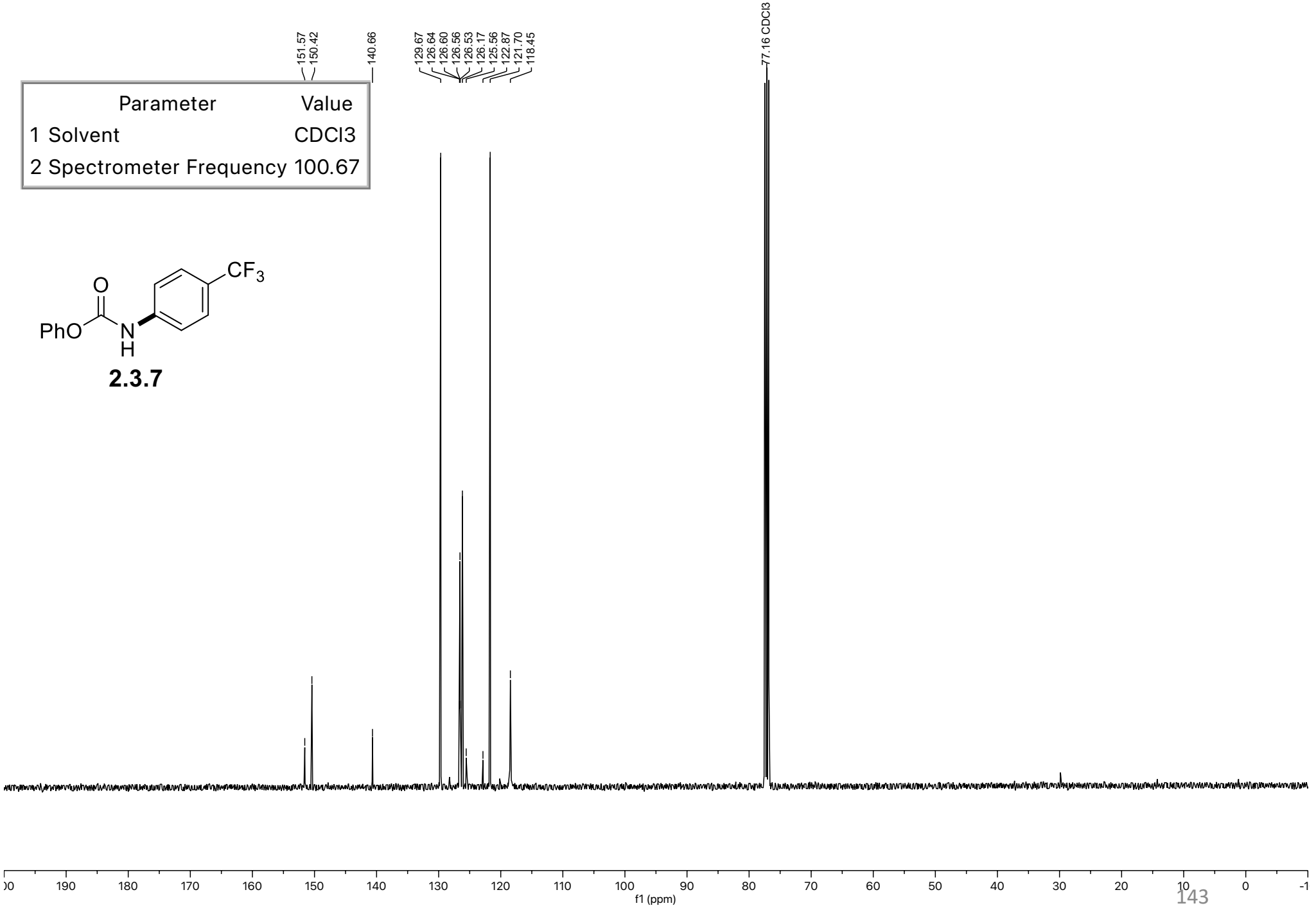

7.26 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
Cl
O
PhO
N
H
2.3.5
7.41 7.40 7.40 7.39 7.39 7.38 7.38 7.37 7.37 7.36 7.34
7.27 7.26 CDCl3 7.26 7.25 7.24 7.23 7.22 7.22 7.22 7.18 7.18 7.18 7.17 7.16 7.16 7.16 7.15
7.09
7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05
f1 (ppm)
4.00 3.09 2.05 0.84
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
f1 (ppm)


151.77
150.52
136.09
129.58
129.24
125.99
121.72
120.12
77.16 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
Cl
O
PhO
N
H
2.3.5
f1 (ppm)

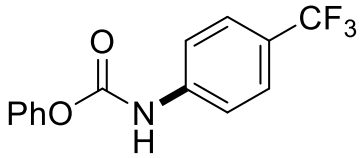

7.26 CDCl3
6.95
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
7.46
7.44
7.42
7.40
7.38
7.36
7.34
7.28
7.27
7.27
7.26 CDCl3
7.25
7.24
7.23
7.23
7.20
7.20
7.19
7.19
7.17
7.17
7.16
Br
O
PhO
N
H
2.3.6
7.45
7.40
7.35
7.30
7.25
7.20
7.15
f1 (ppm)
2.03
2.10
1.92
1.73
2.00
0.86
f1 (ppm)


151.60
150.53
136.63
132.28
129.62
126.03
121.72
120.43
116.67
77.16 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
Br
O
PhO
N
H
2.3.6
f1 (ppm)

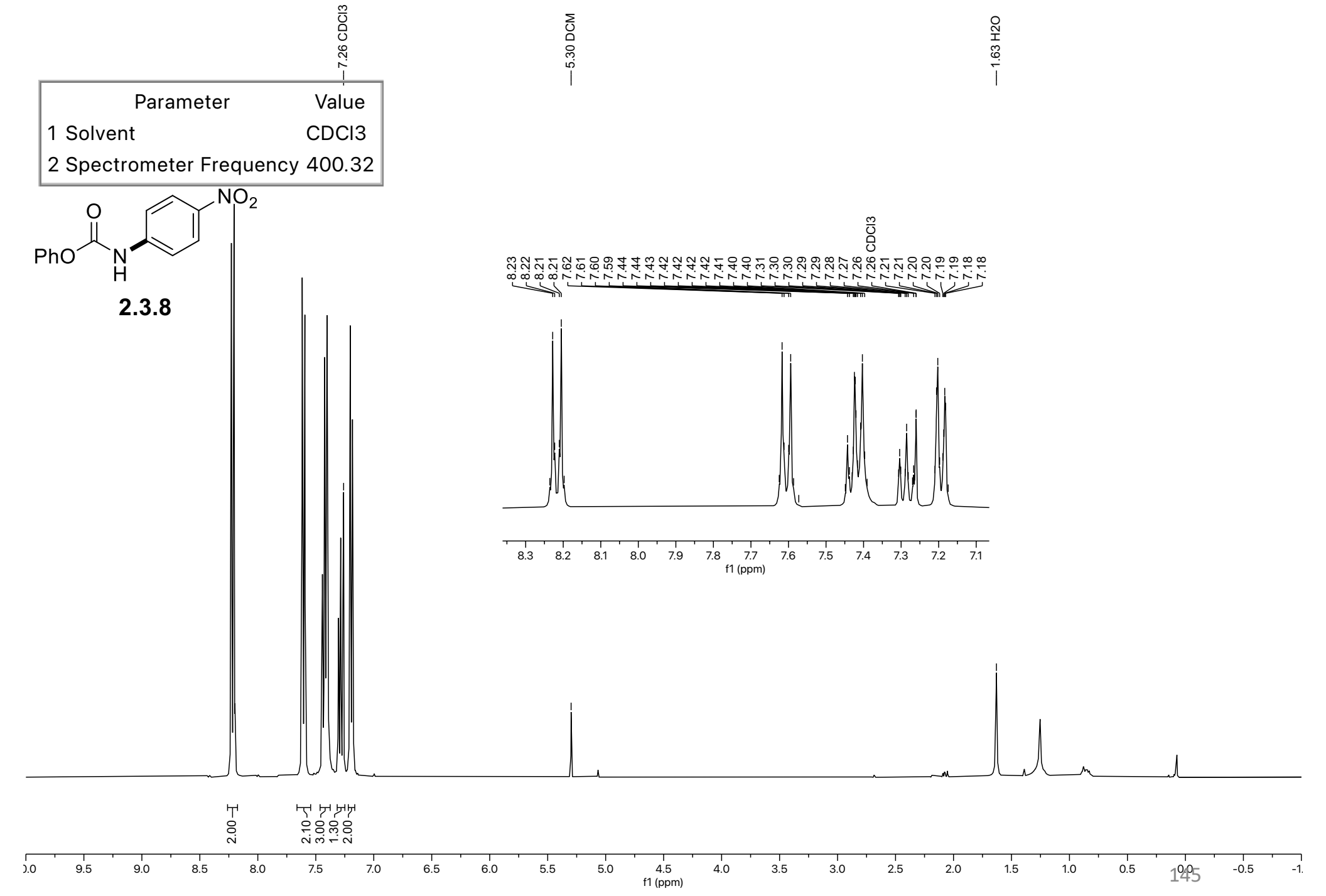

7.26 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
CF3
O
PhO
N
H
2.3.7
7.58 7.58 7.57 7.56 7.55 7.54 7.53
7.42 7.42 7.41 7.40 7.40 7.40 7.40 7.39 7.38
7.28 7.28 7.28 7.26 7.26 7.26 CDCl3 7.26 7.26 7.25 7.24 7.24 7.24 7.20 7.19 7.19 7.18 7.18 7.17
7.70 7.65 7.60 7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05
f1 (ppm)
1.00 0.51 0.31 0.71
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
f1 (ppm)

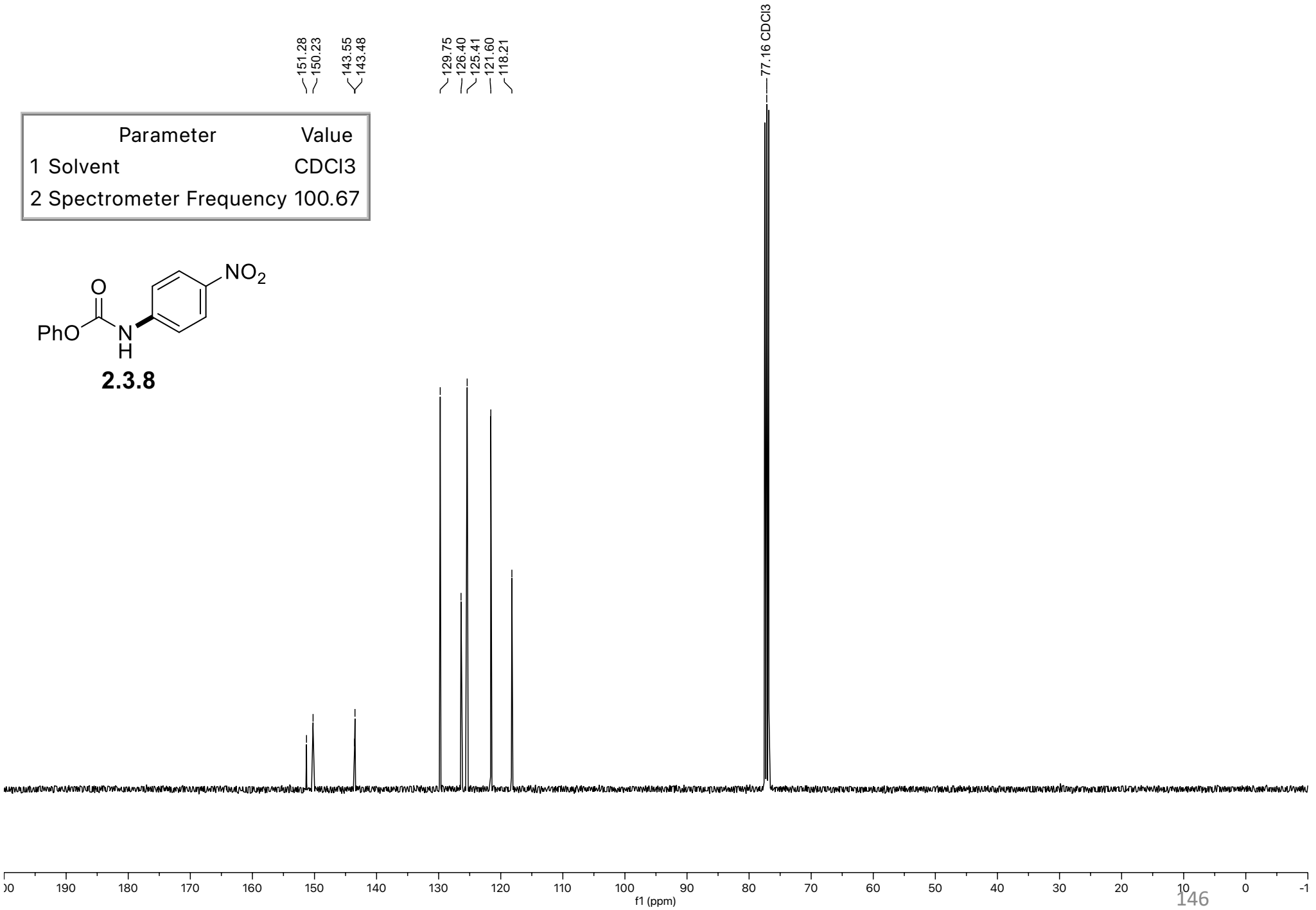

151.57
150.42
140.66
129.67
126.64
126.60
126.56
126.53
126.17
125.56
122.87
121.70
118.45
77.16 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
PhO
O
N
H
CF3
2.3.7
f1 (ppm)

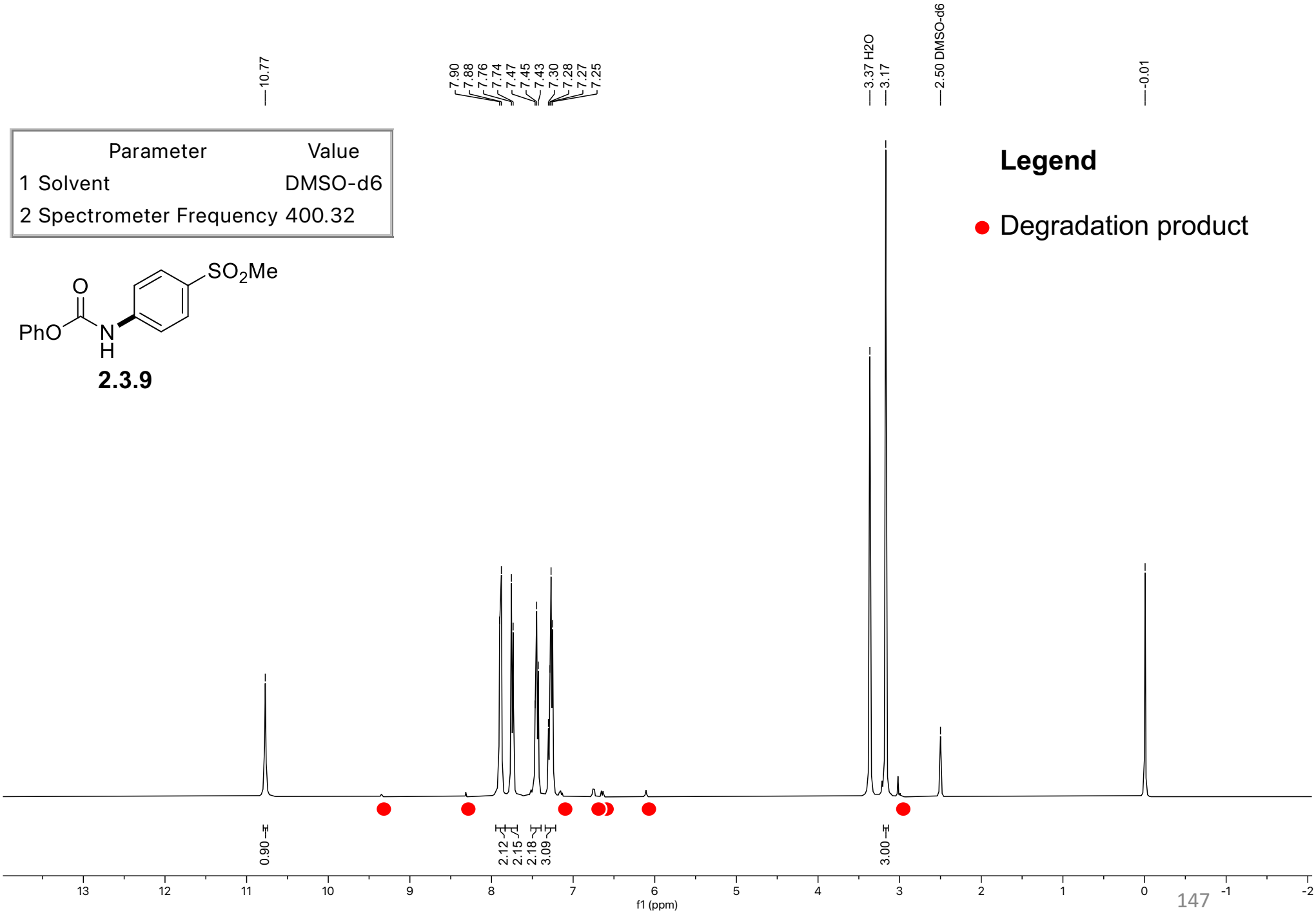
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	282.56

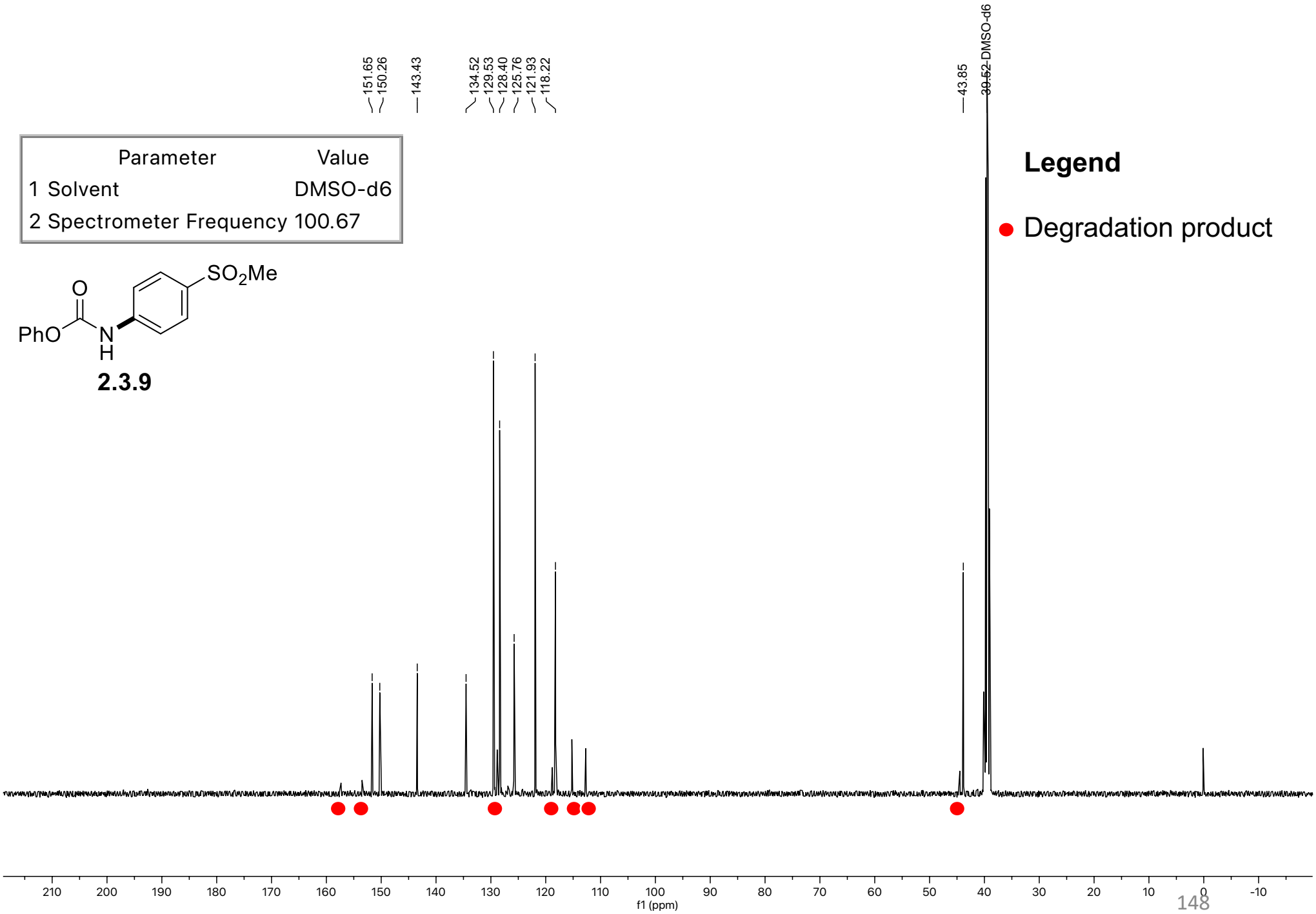


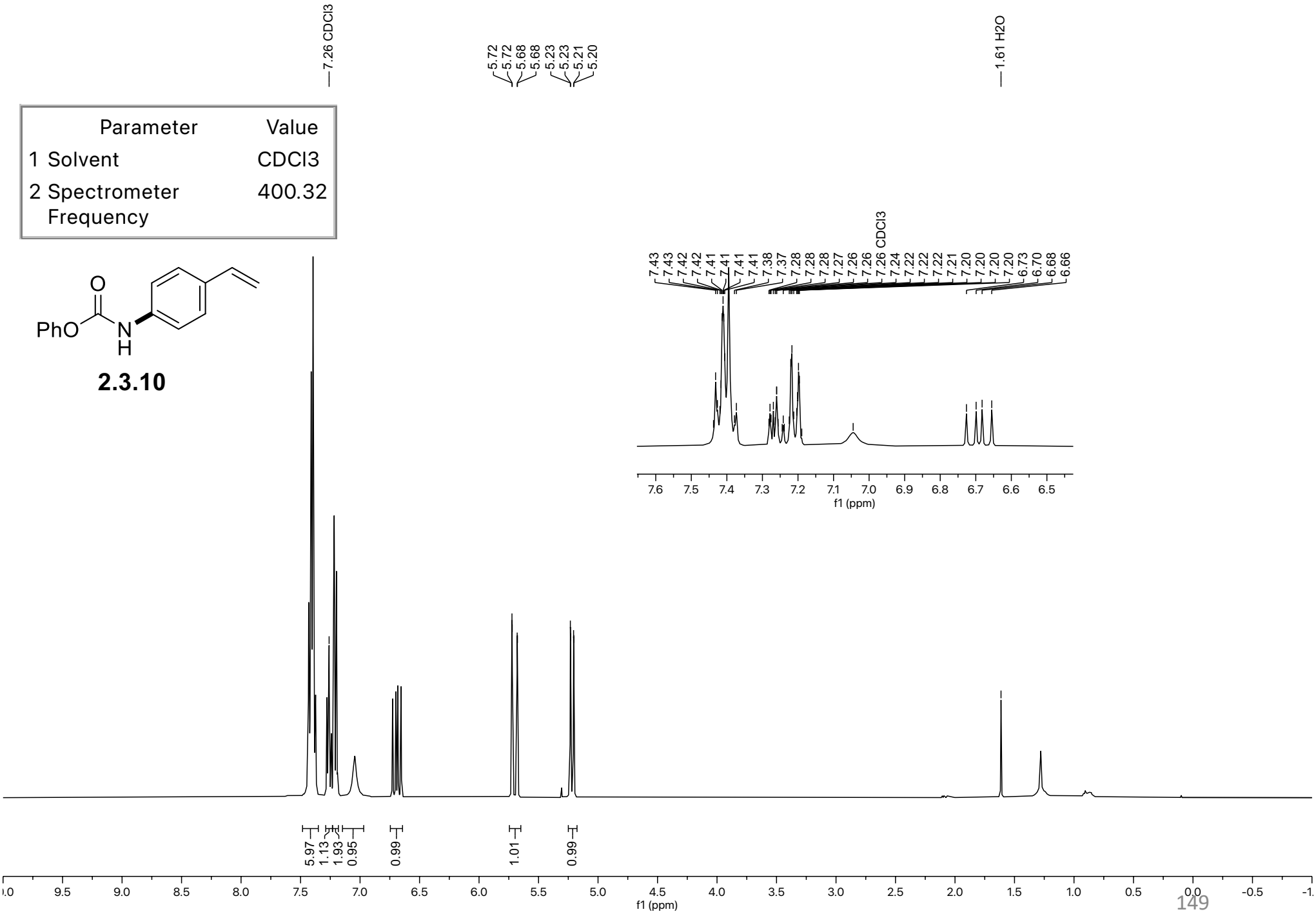
2.3.7


7.26 CDCl3
5.30 DCM
1.63 H2O
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
NO2
O
PhO
N
H
2.3.8
8.23 8.22 8.21 8.21 7.62 7.61 7.60 7.59 7.44 7.44 7.43 7.42 7.42 7.42 7.42 7.41 7.40 7.40 7.31 7.30 7.30 7.29 7.29 7.28 7.27 7.26 CDCl3 7.26 7.21 7.21 7.20 7.20 7.19 7.19 7.18 7.18
8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1
f1 (ppm)
2.00 2.10 3.00 1.30 2.00
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
f1 (ppm)


151.28
150.23
143.55
143.48
129.75
126.40
125.41
121.60
118.21
77.16 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
NO2
O
PhO
N
H
2.3.8
f1 (ppm)

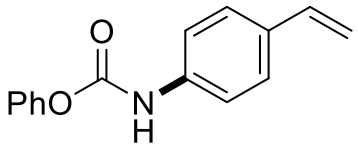

10.77
7.90
7.88
7.76
7.74
7.47
7.45
7.43
7.30
7.28
7.27
7.25
3.37 H2O
3.17
2.50 DMSO-d6
0.01
Parameter Value
1 Solvent DMSO-d6
2 Spectrometer Frequency 400.32
SO2Me
O
PhO
N
H
2.3.9
Legend
Degradation product
0.90
2.12
2.15
2.18
3.09
3.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


151.65
150.26
143.43
134.52
129.53
128.40
125.76
121.93
118.22
43.85
39.52
DMSO-d6
Parameter Value
1 Solvent DMSO-d6
2 Spectrometer Frequency 100.67
SO2Me
O
PhO
N
H
2.3.9
Legend
Degradation product
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26 CDCl3
5.72
5.72
5.68
5.68
5.23
5.23
5.21
5.20
1.61 H2O
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
O
PhO
N
H
2.3.10
7.43
7.43
7.42
7.42
7.41
7.41
7.41
7.41
7.38
7.37
7.28
7.28
7.28
7.27
7.26
7.26
CDCl3
7.24
7.22
7.22
7.22
7.21
7.20
7.20
7.20
7.20
6.73
6.70
6.68
6.66
7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5
f1 (ppm)
5.97
1.13
1.93
0.95
0.99
1.01
0.99
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
f1 (ppm)

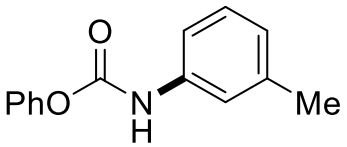
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67

151.58
150.55
136.92
136.06
133.42
129.46
127.02
125.78
121.68
118.73
113.02
77.38 CDCl3
77.06 CDCl3
76.75 CDCl3



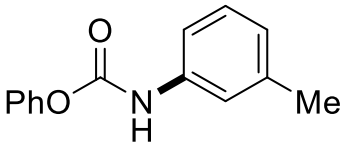
2.3.10

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



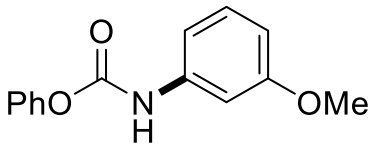
2.3.12

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67

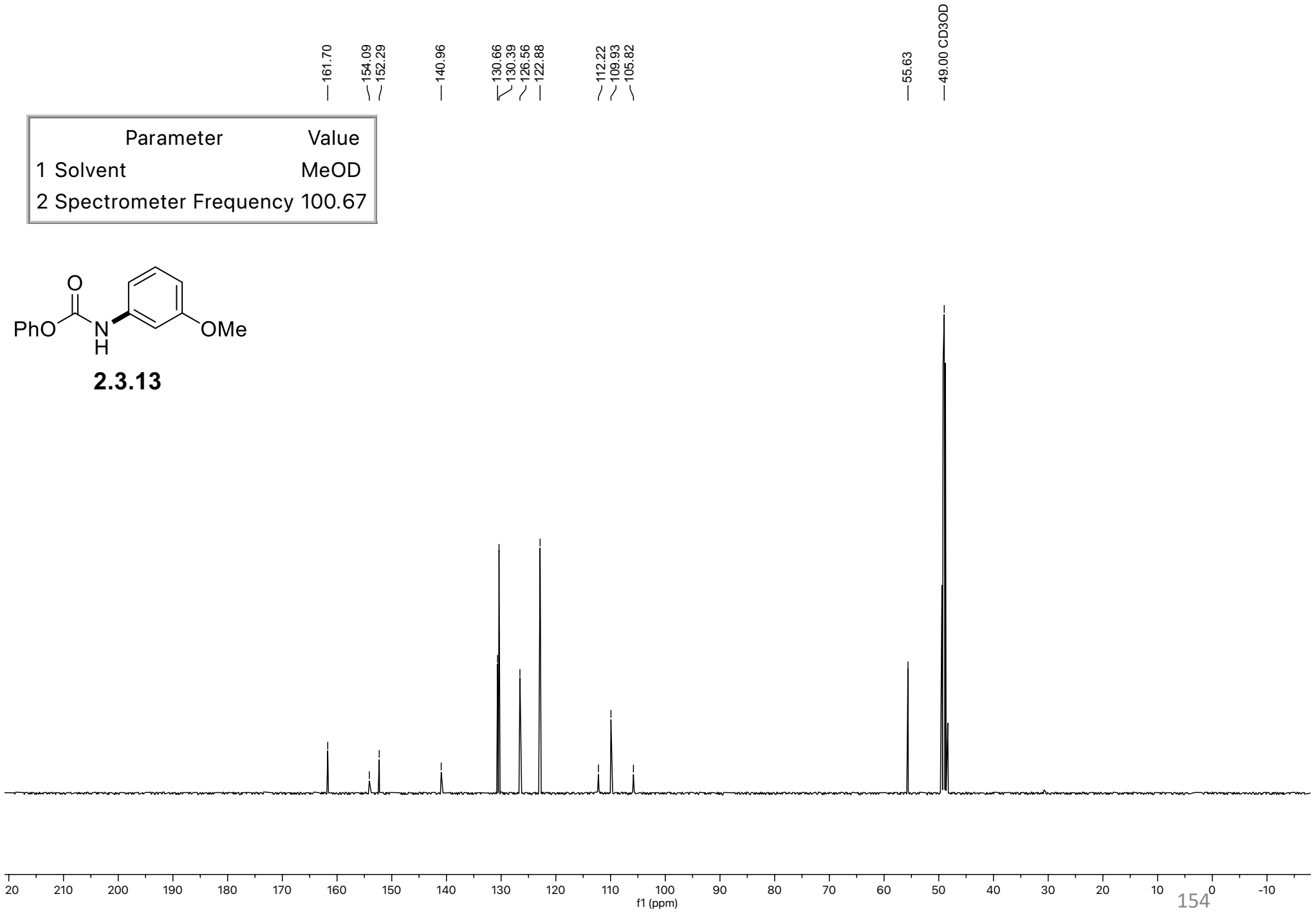


2.3.12

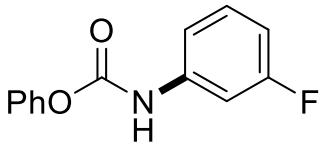
Parameter	Value
1 Solvent	MeOD
2 Spectrometer Frequency	400.32



2.3.13

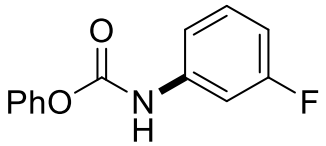

161.70
154.09
152.29
140.96
130.66
130.39
126.56
122.88
112.22
109.93
105.82
55.63
49.00 CD3OD
Parameter Value
1 Solvent MeOD
2 Spectrometer Frequency 100.67
PhO
O
N
H
OMe
2.3.13
f1 (ppm)

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



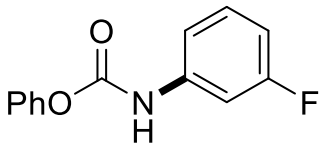
2.3.14

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67

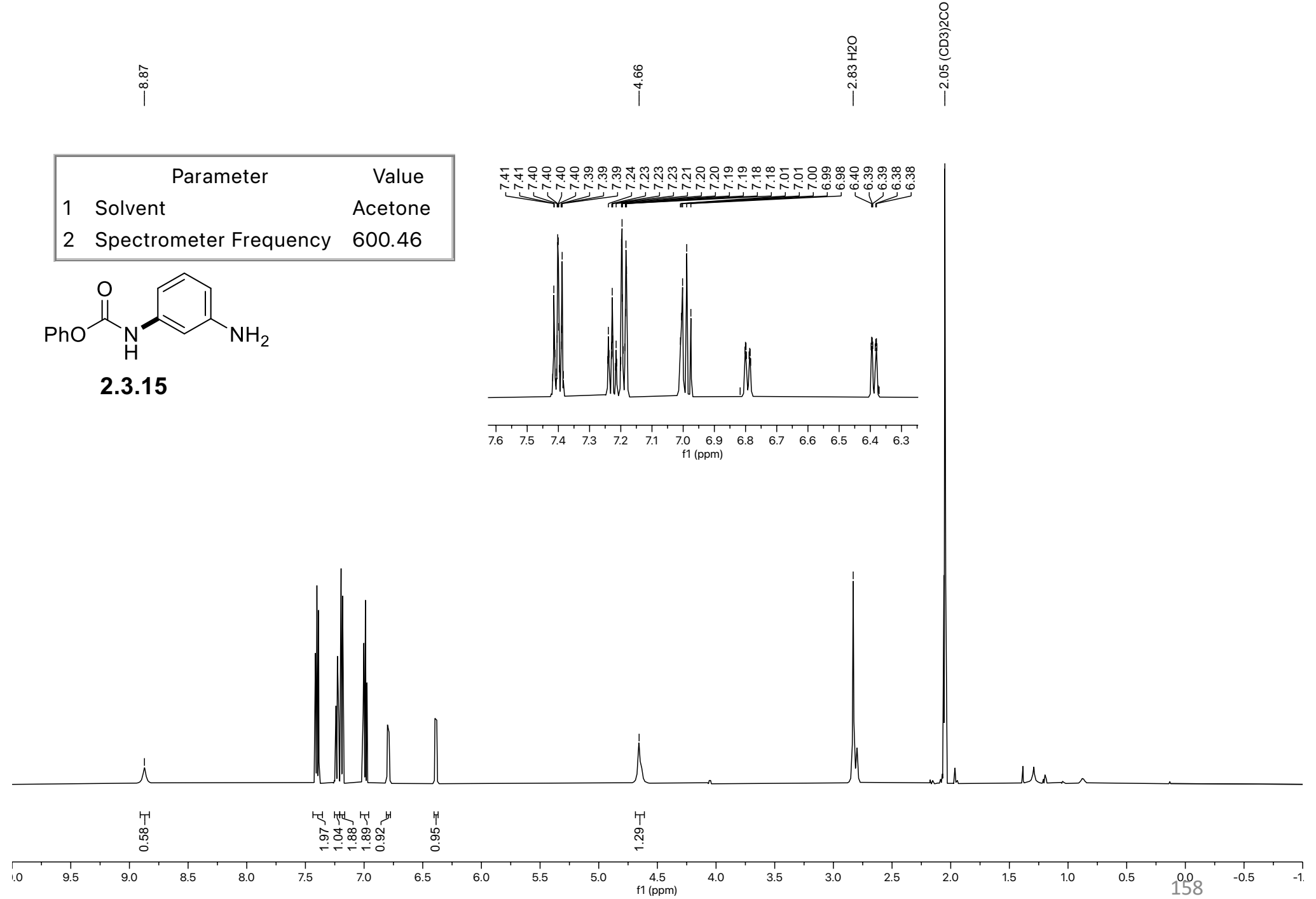


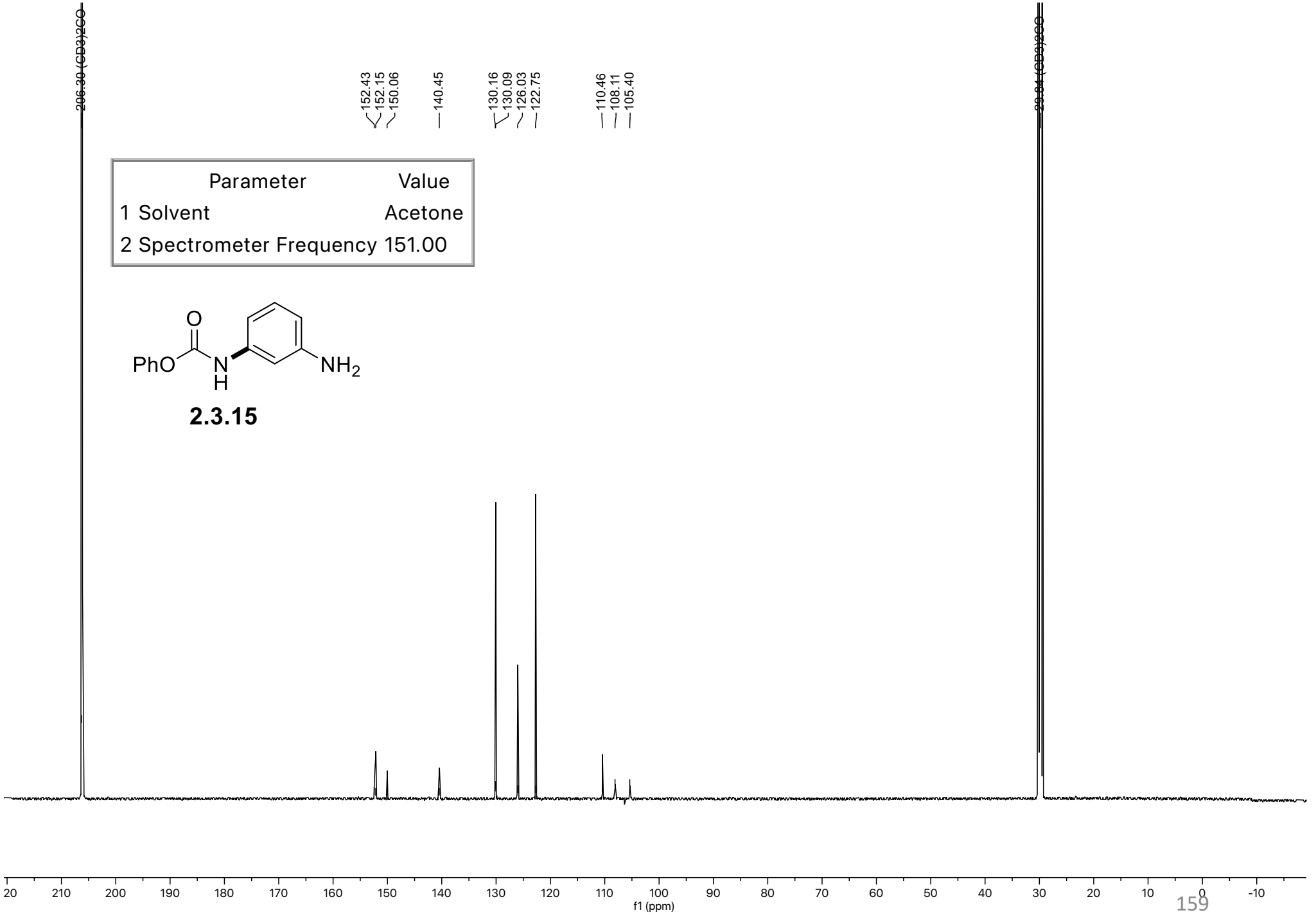
2.3.14

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	282.56

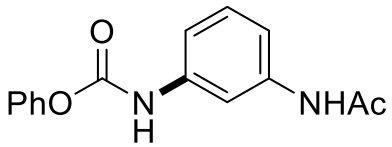


2.3.14

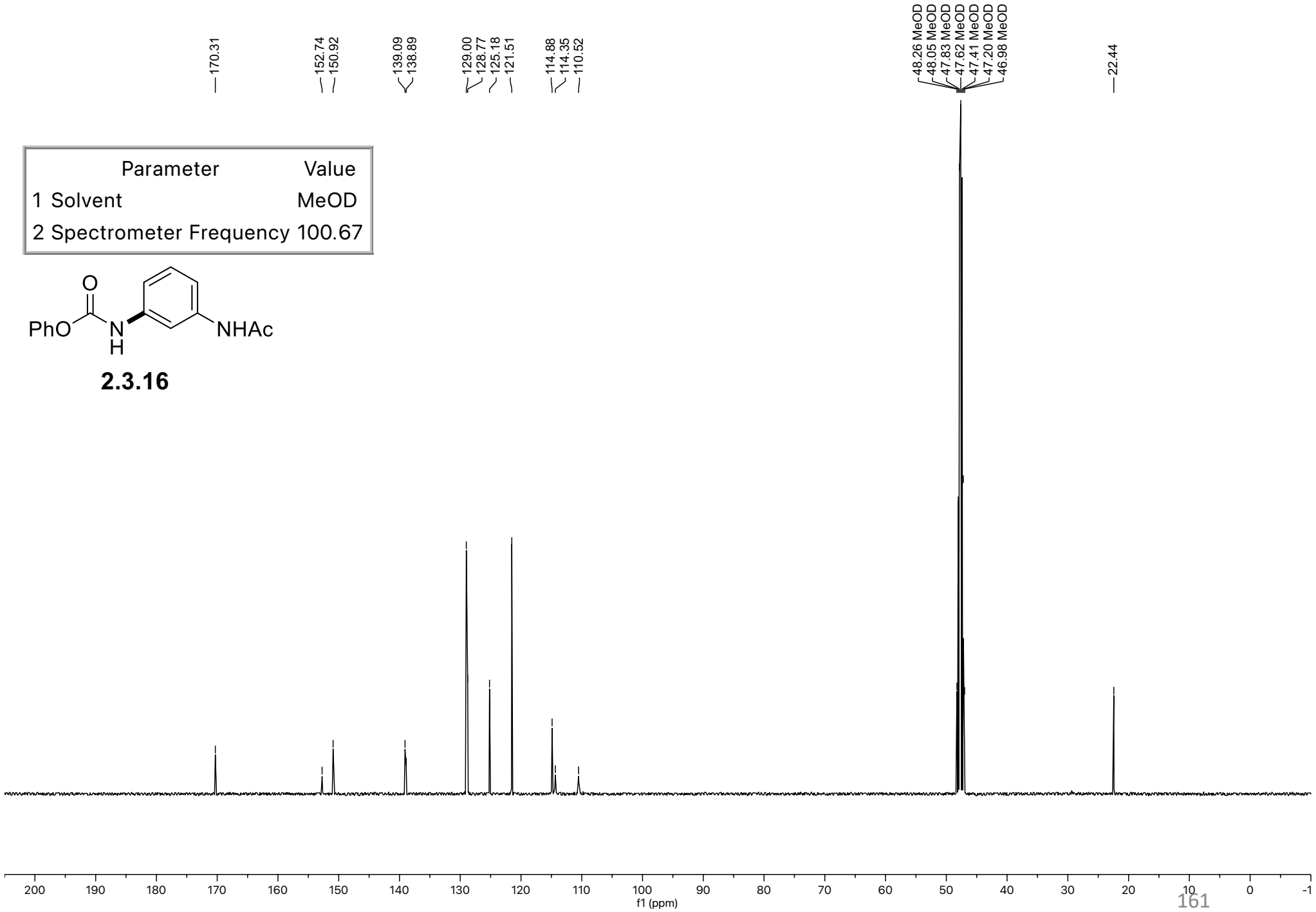

8.87
4.66
2.83 H2O
2.05 (CD3)2CO
Parameter Value
1 Solvent Acetone
2 Spectrometer Frequency 600.46
PhO
O
N
H
NH2
2.3.15
7.41 7.41 7.40 7.40 7.40 7.40 7.39 7.39 7.39 7.24 7.23 7.23 7.23 7.21 7.20 7.20 7.19 7.19 7.18 7.18 7.01 7.01 7.00 6.99 6.98 6.40 6.39 6.39 6.38 6.38
7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3
f1 (ppm)
0.58
1.97
1.04
1.88
1.89
0.92
0.95
1.29
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
f1 (ppm)

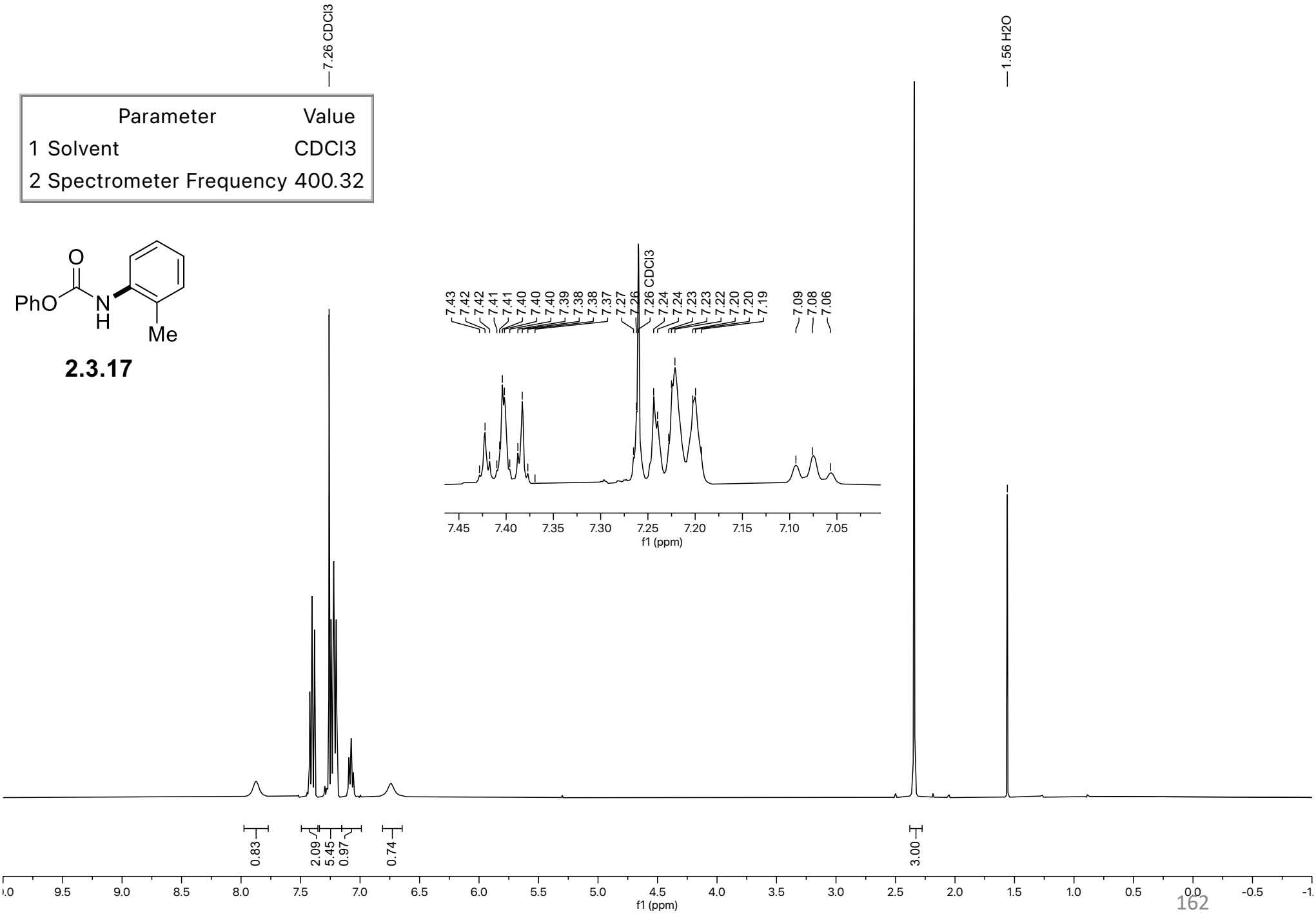

206.30 (CD3)2CO
152.43
152.15
150.06
140.45
130.16
130.09
126.03
122.75
110.46
108.11
105.40
29.84 (CD3)2CO
Parameter Value
1 Solvent Acetone
2 Spectrometer Frequency 151.00
PhO
O
N
H
NH2
2.3.15
f1 (ppm)

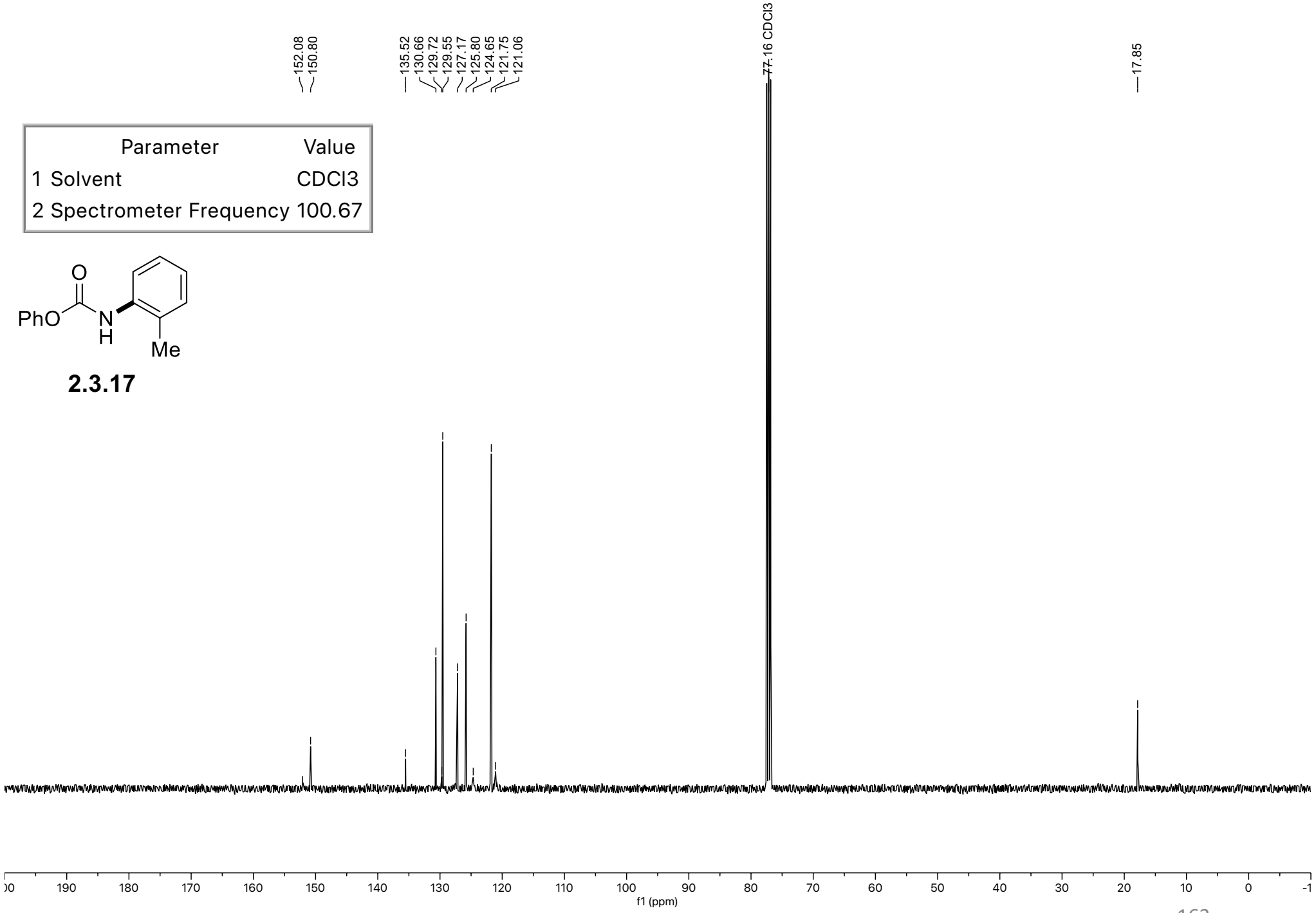
Parameter	Value
1 Solvent	MeOD
2 Spectrometer Frequency	400.32



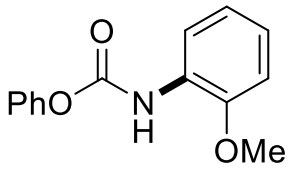
2.3.16


170.31
152.74
150.92
139.09
138.89
129.00
128.77
125.18
121.51
114.88
114.35
110.52
48.26 MeOD
48.05 MeOD
47.83 MeOD
47.62 MeOD
47.41 MeOD
47.20 MeOD
46.98 MeOD
22.44
Parameter Value
1 Solvent MeOD
2 Spectrometer Frequency 100.67
PhO
O
N
H
NHAc
2.3.16
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

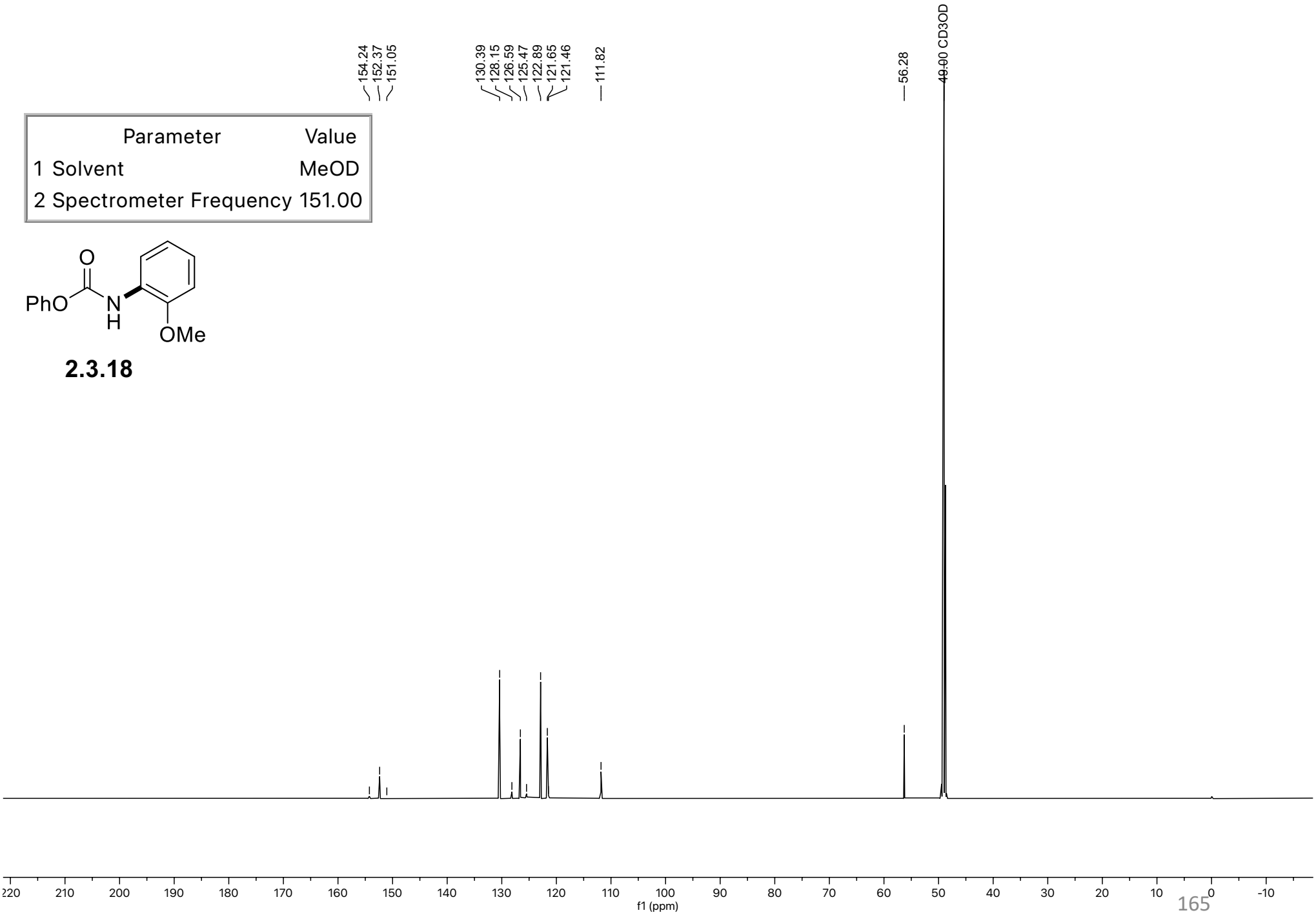

7.26 CDCl3
1.56 H2O
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
PhO
O
N
H
Me
2.3.17
7.43 7.42 7.42 7.41 7.41 7.40 7.40 7.39 7.38 7.38 7.37 7.27 7.26 7.26 CDCl3 7.24 7.24 7.23 7.23 7.22 7.20 7.20 7.19 7.09 7.08 7.06
7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05
f1 (ppm)
0.83 2.09 5.45 0.97 0.74 3.00
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
f1 (ppm)

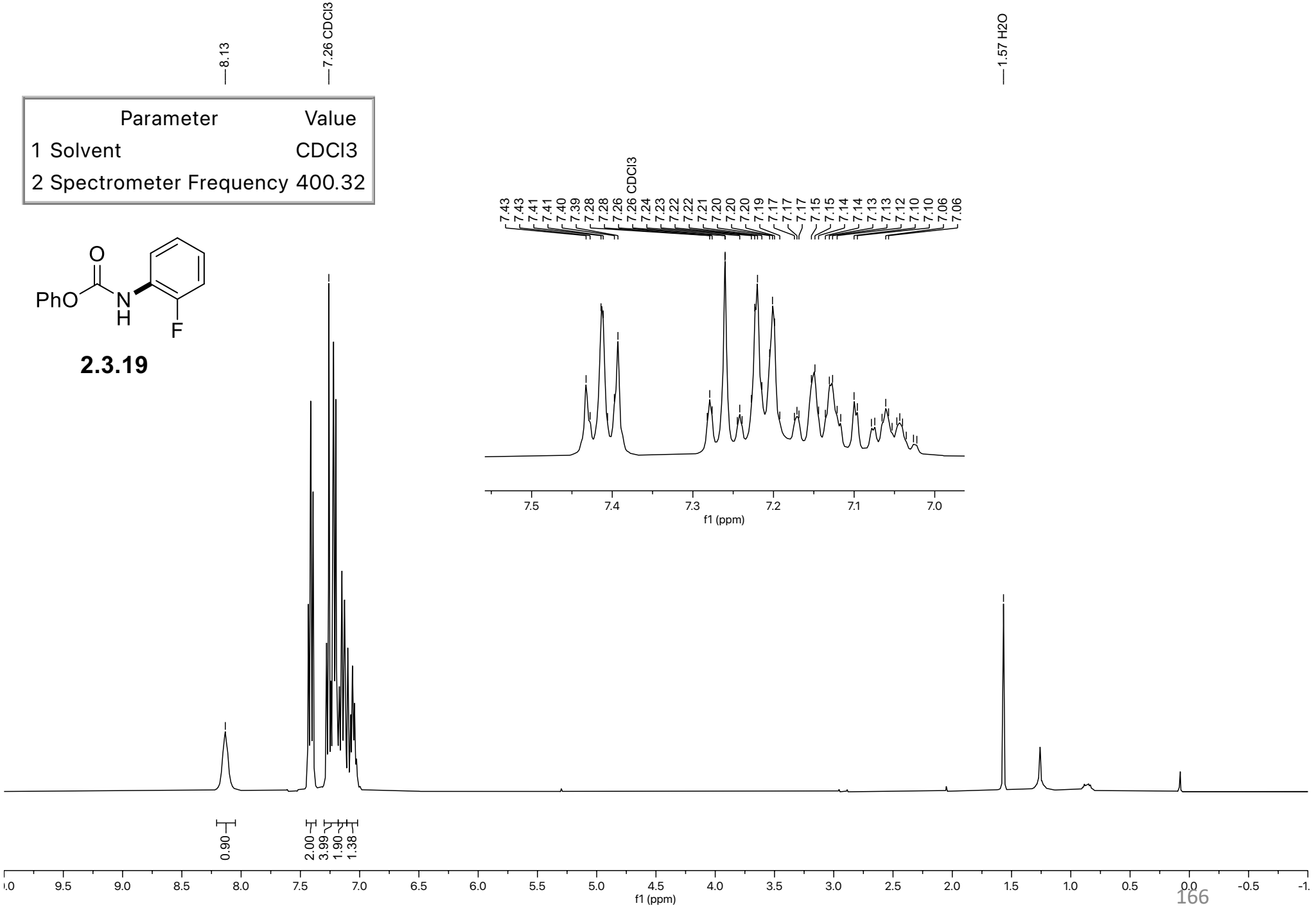

152.08
150.80
135.52
130.66
129.72
129.55
127.17
125.80
124.65
121.75
121.06
77.16 CDCl3
17.85
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
PhO
O
N
H
Me
2.3.17
f1 (ppm)

Parameter	Value
1 Solvent	MeOD
2 Spectrometer Frequency	600.46

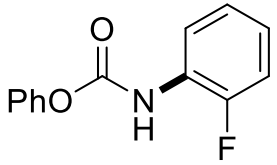


2.3.18


154.24
152.37
151.05
130.39
128.15
126.59
125.47
122.89
121.65
121.46
111.82
56.28
49.00 CD3OD
Parameter Value
1 Solvent MeOD
2 Spectrometer Frequency 151.00
PhO
O
N
H
OMe
2.3.18
f1 (ppm)

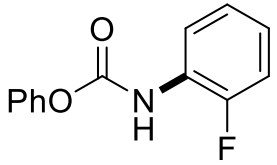

8.13
7.26 CDCl3
1.57 H2O
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
PhO
O
N
H
F
2.3.19
7.43 7.43 7.41 7.41 7.40 7.39 7.28 7.28 7.26 CDCl3 7.24 7.23 7.22 7.22 7.21 7.20 7.20 7.20 7.19 7.17 7.17 7.17 7.15 7.15 7.14 7.14 7.13 7.13 7.12 7.10 7.10 7.06 7.06
7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
0.90 2.00 3.99 1.90 1.38
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
f1 (ppm)

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67



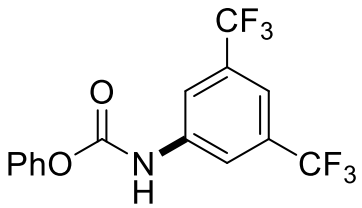
2.3.19

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	282.38



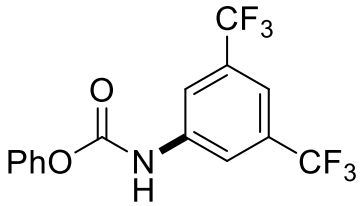
2.3.19

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	600.46



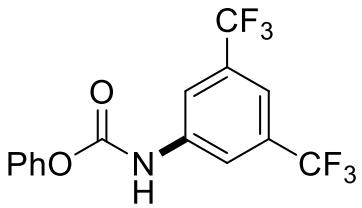
2.3.20

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	151.00



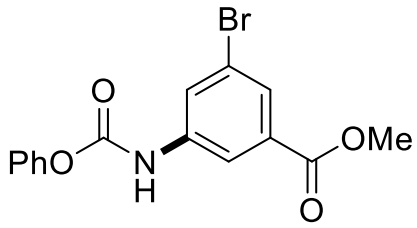
2.3.20

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	282.56



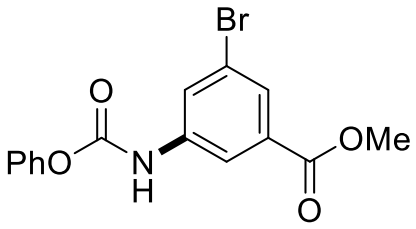
2.3.20

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32

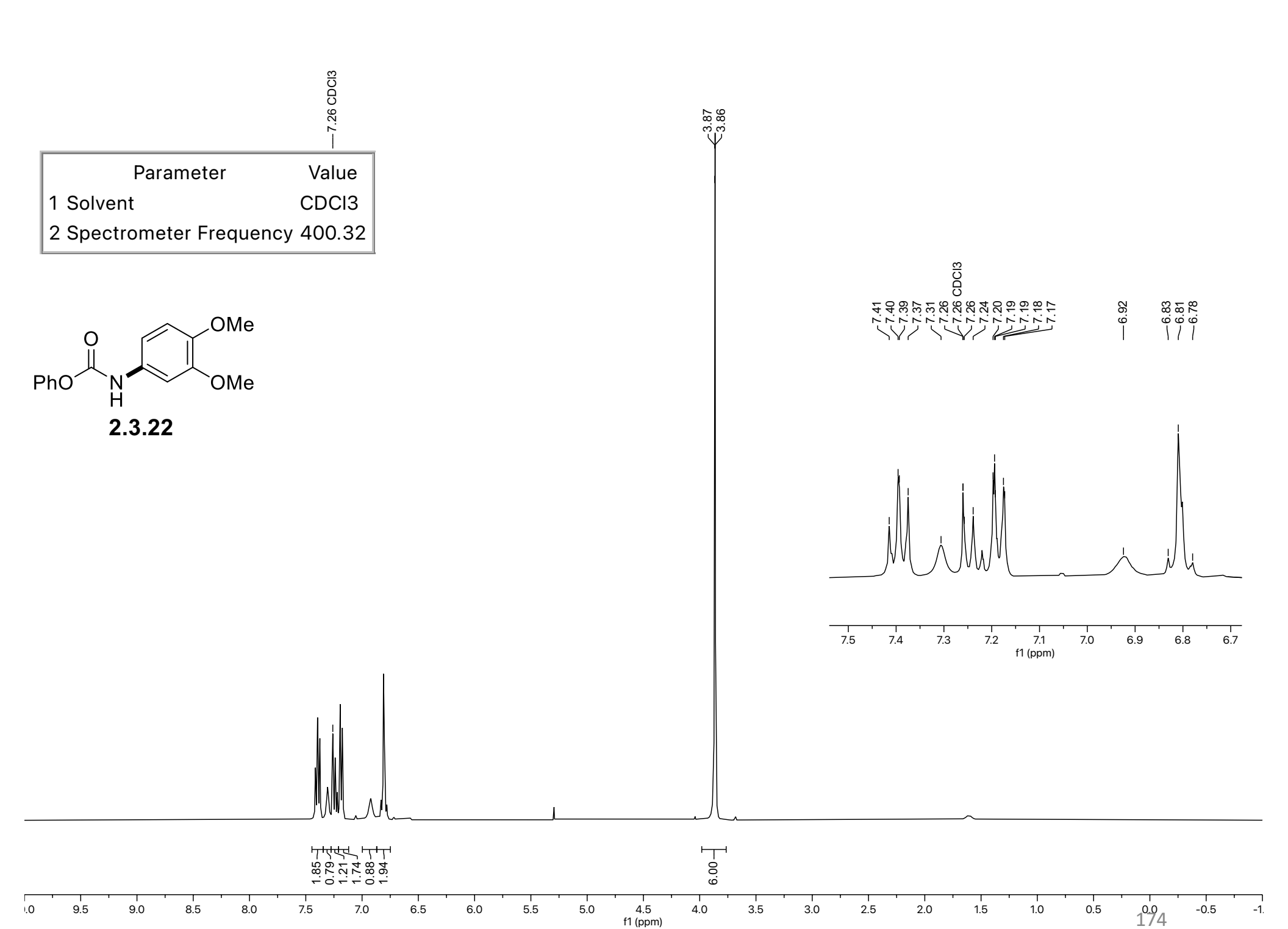


2.3.21

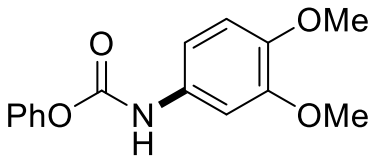
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67



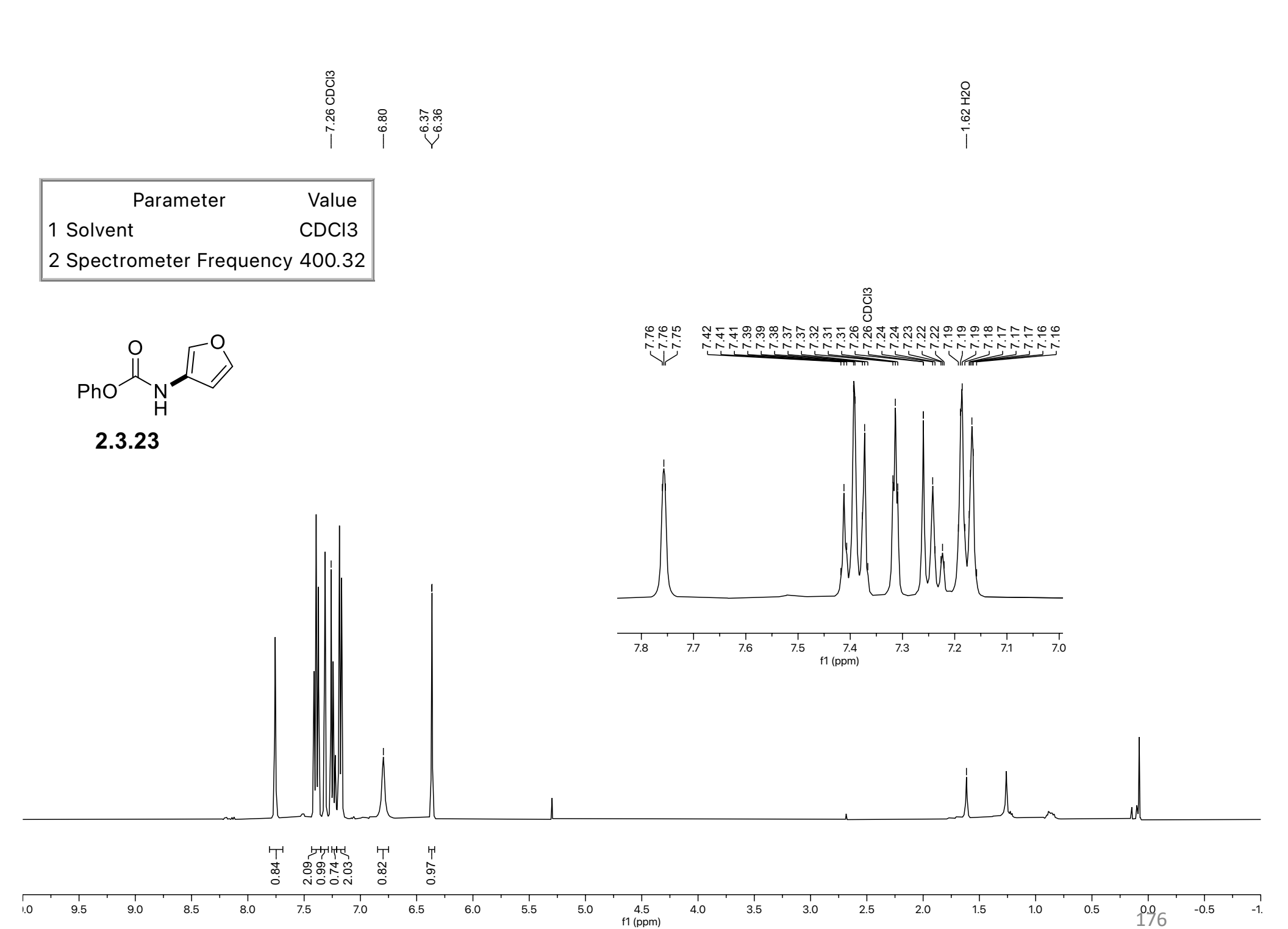
2.3.21


7.26 CDCl3
3.87
3.86
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
OMe
O
PhO
N
H
OMe
2.3.22
7.41
7.40
7.39
7.37
7.31
7.26 CDCl3
7.26
7.24
7.20
7.19
7.18
7.17
6.92
6.83
6.81
6.78
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
f1 (ppm)
1.85
0.79
1.21
1.74
0.88
1.94
6.00
f1 (ppm)

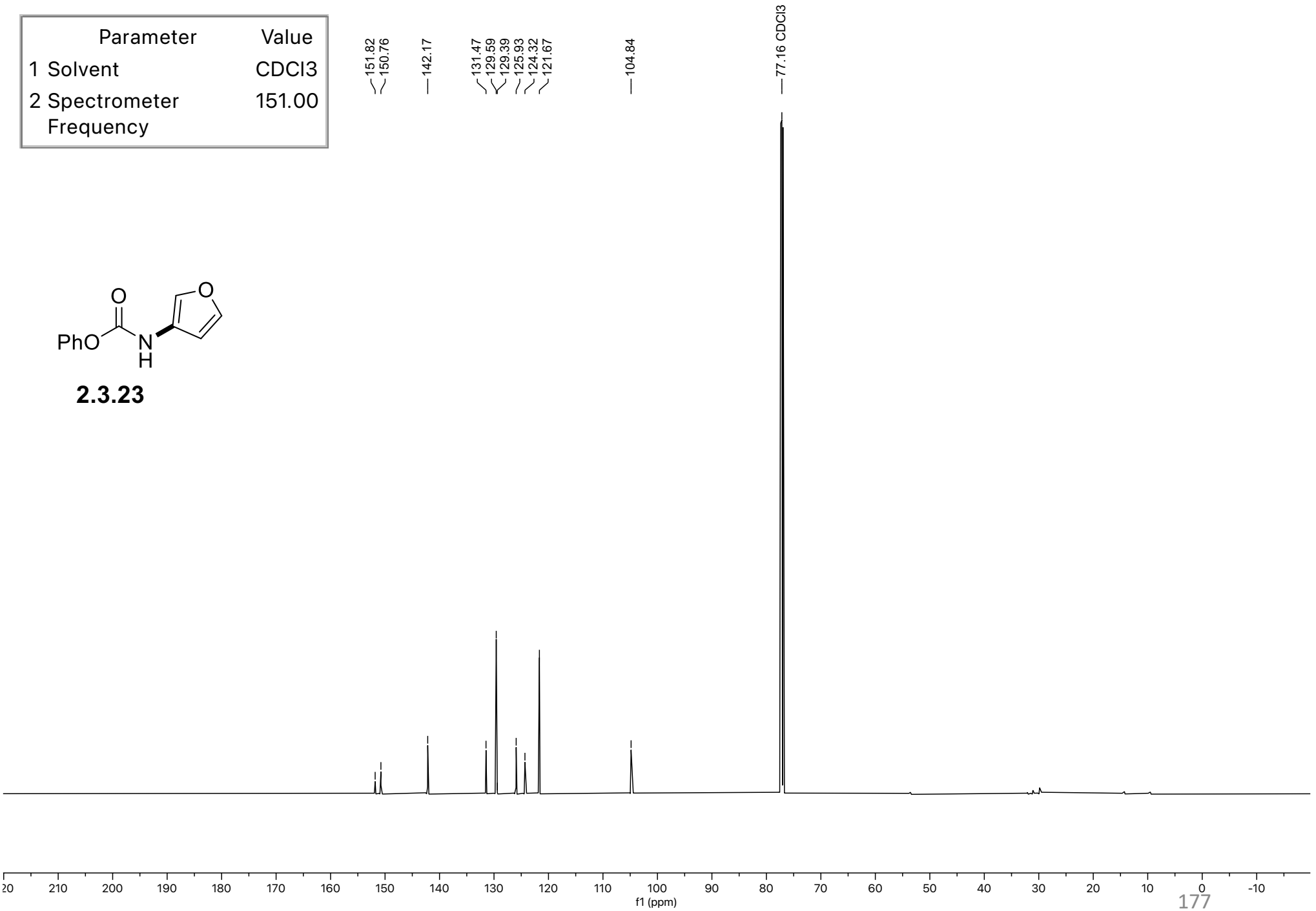
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67



2.3.22

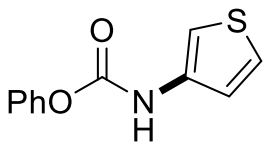

7.26 CDCl3
6.80
6.37
6.36
1.62 H2O
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
PhO
N
H
O
O
2.3.23
7.76
7.76
7.75
7.42
7.41
7.41
7.39
7.39
7.38
7.37
7.37
7.32
7.31
7.26 CDCl3
7.24
7.24
7.23
7.22
7.22
7.19
7.19
7.19
7.18
7.17
7.17
7.17
7.16
7.16
f1 (ppm)
0.84
2.09
0.99
0.74
2.03
0.82
0.97
f1 (ppm)

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	151.00



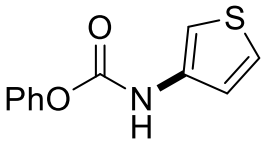
2.3.23

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



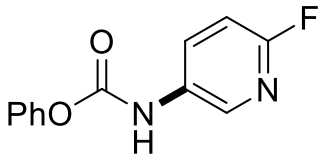
2.3.24

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67

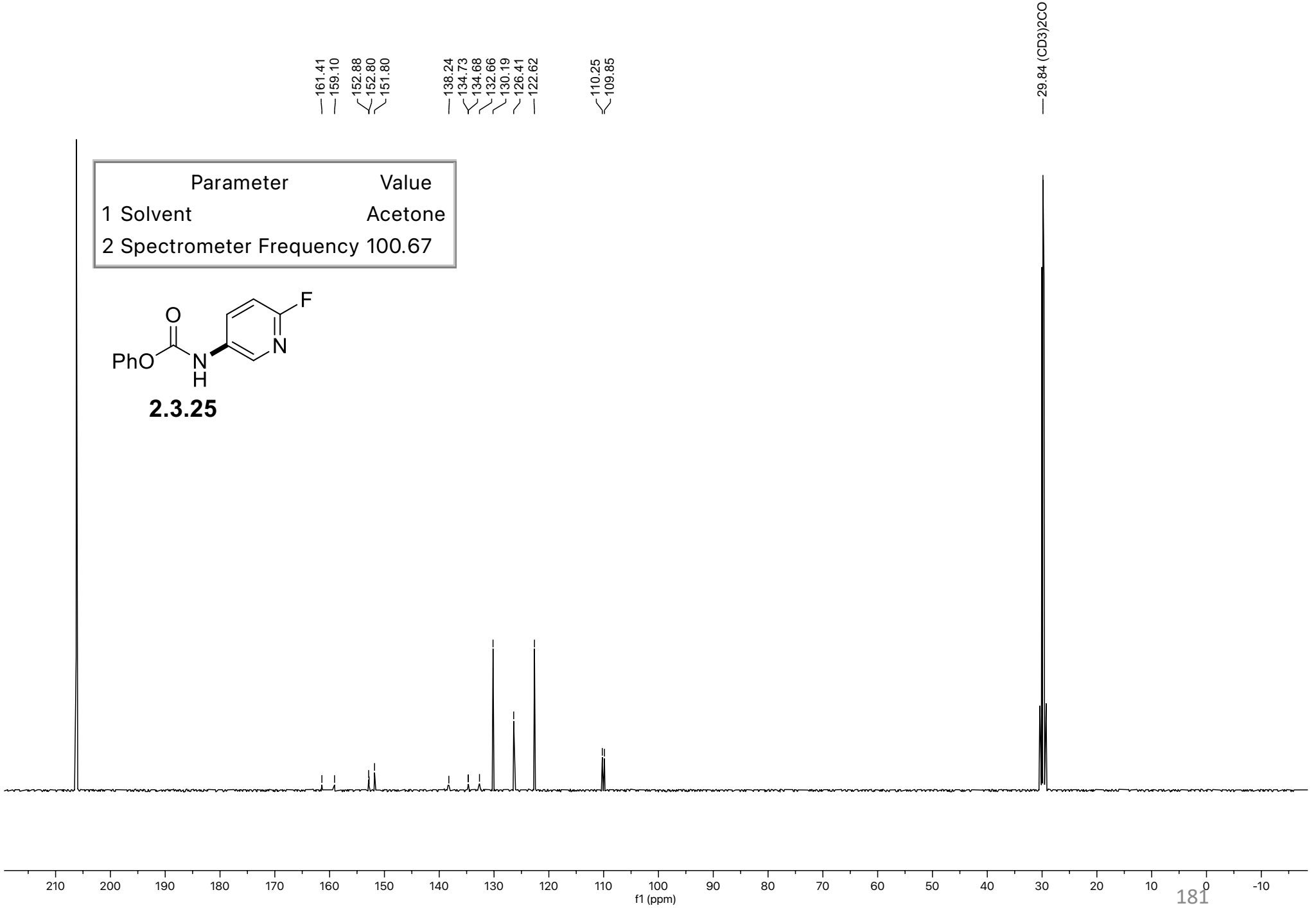


2.3.24

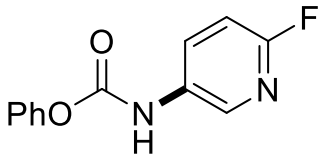
Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	400.32



2.3.25

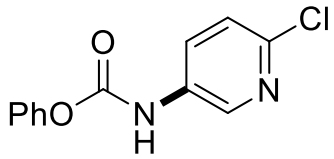

161.41
159.10
152.88
152.80
151.80
138.24
134.73
134.68
132.66
130.19
126.41
122.62
110.25
109.85
29.84 (CD3)2CO
Parameter Value
1 Solvent Acetone
2 Spectrometer Frequency 100.67
O
PhO
N
H
F
N
2.3.25
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	282.56

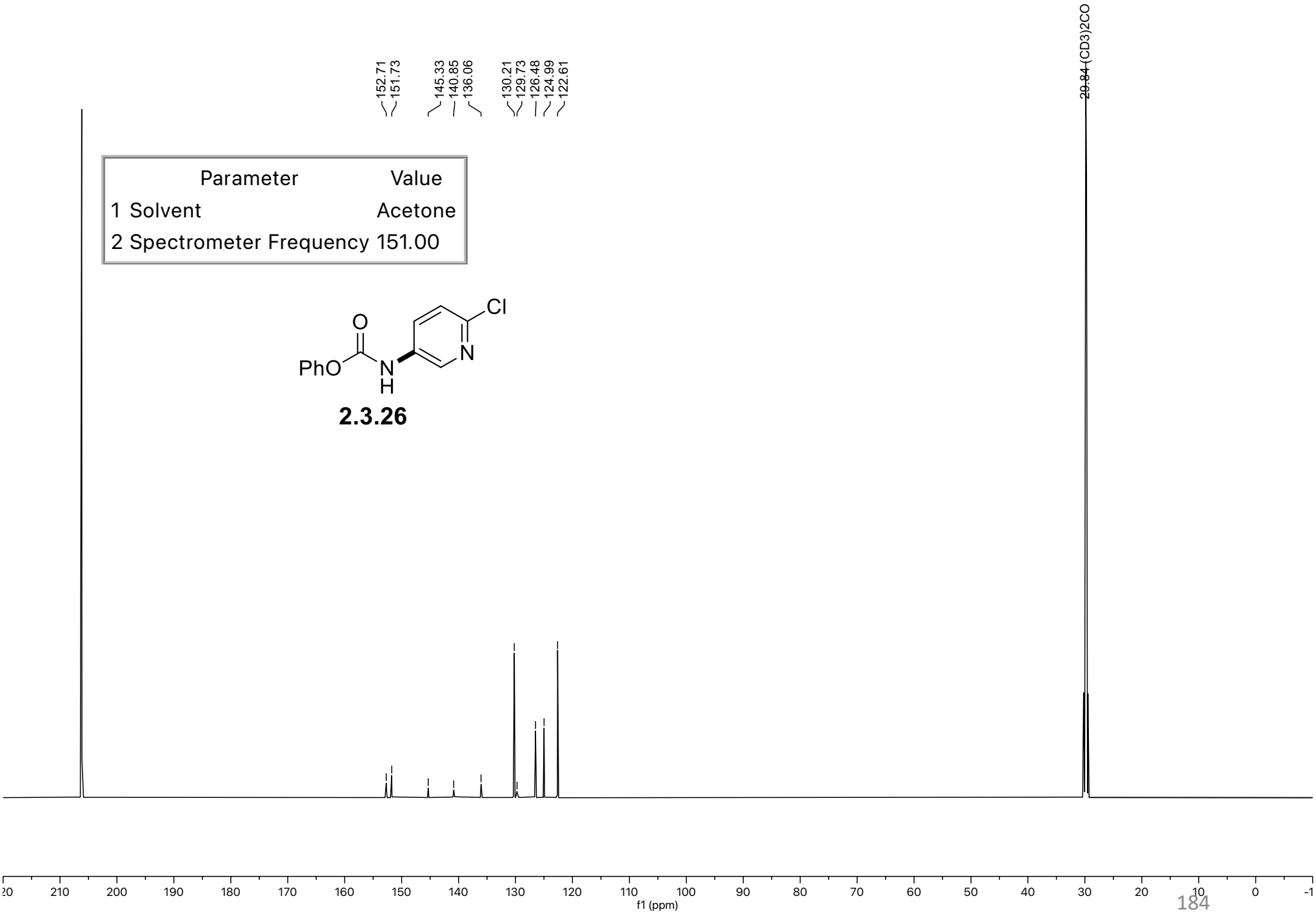


2.3.25

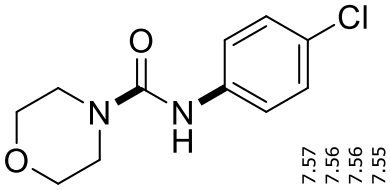
Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	600.46



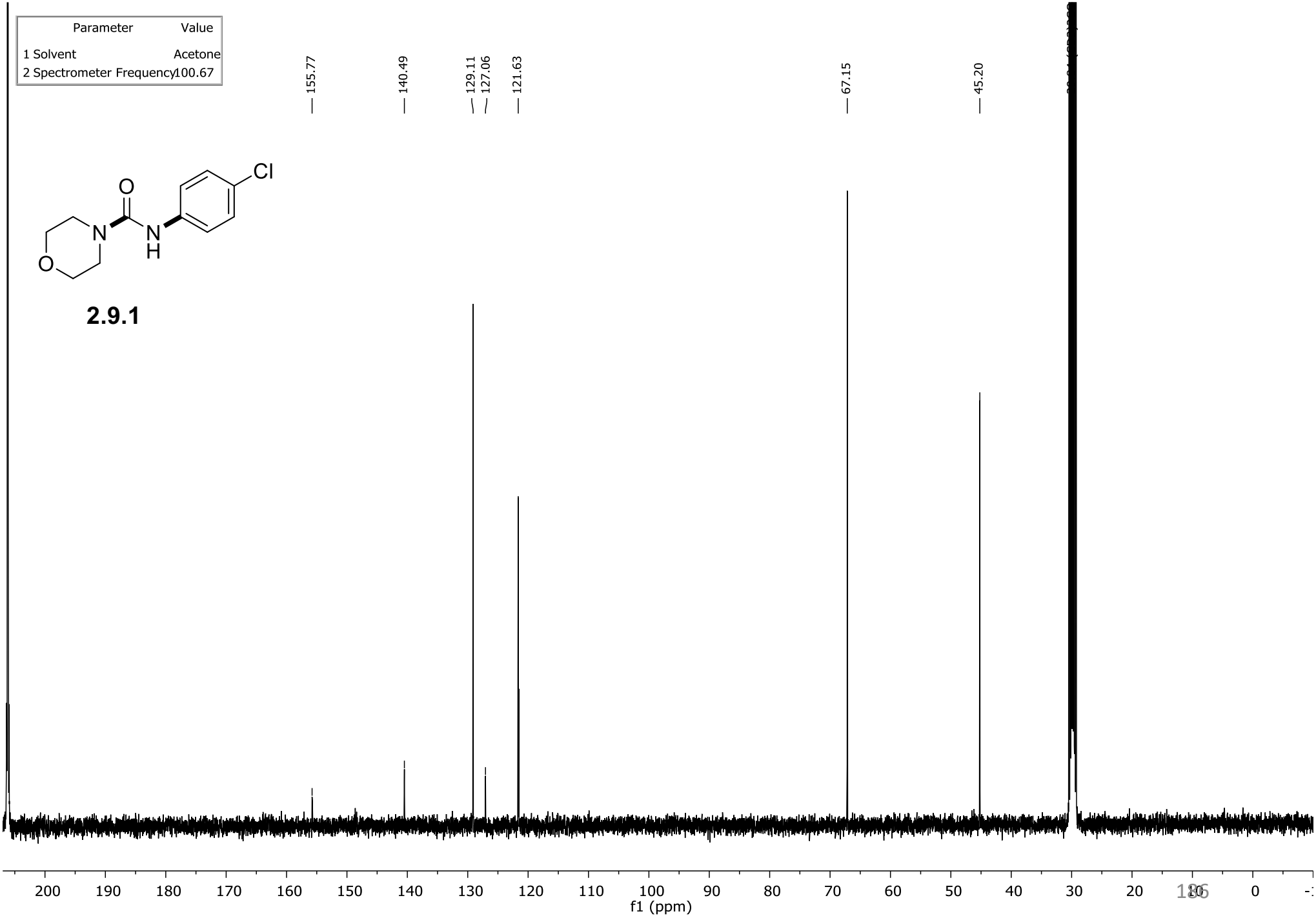
2.3.26


152.71
151.73
145.33
140.85
136.06
130.21
129.73
126.48
124.99
122.61
29.84 (CD3)2CO
Parameter Value
1 Solvent Acetone
2 Spectrometer Frequency 151.00
O
PhO
N
H
Cl
N
2.3.26
f1 (ppm)

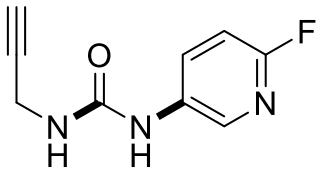
Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	400.32



2.9.1

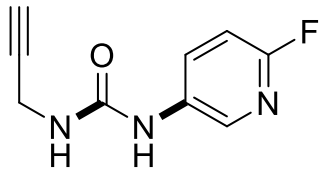

Parameter Value
1 Solvent Acetone
2 Spectrometer Frequency 100.67
155.77
140.49
129.11
127.06
121.63
67.15
45.20
Cl
O
N
N
H
O
2.9.1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Parameter	Value
1 Solvent	DMSO
2 Spectrometer Frequency	600.46



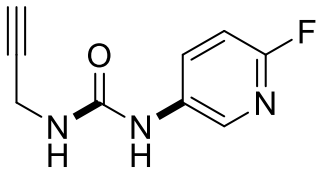
2.9.2

Parameter	Value
1 Solvent	DMSO
2 Spectrometer Frequency	151.00



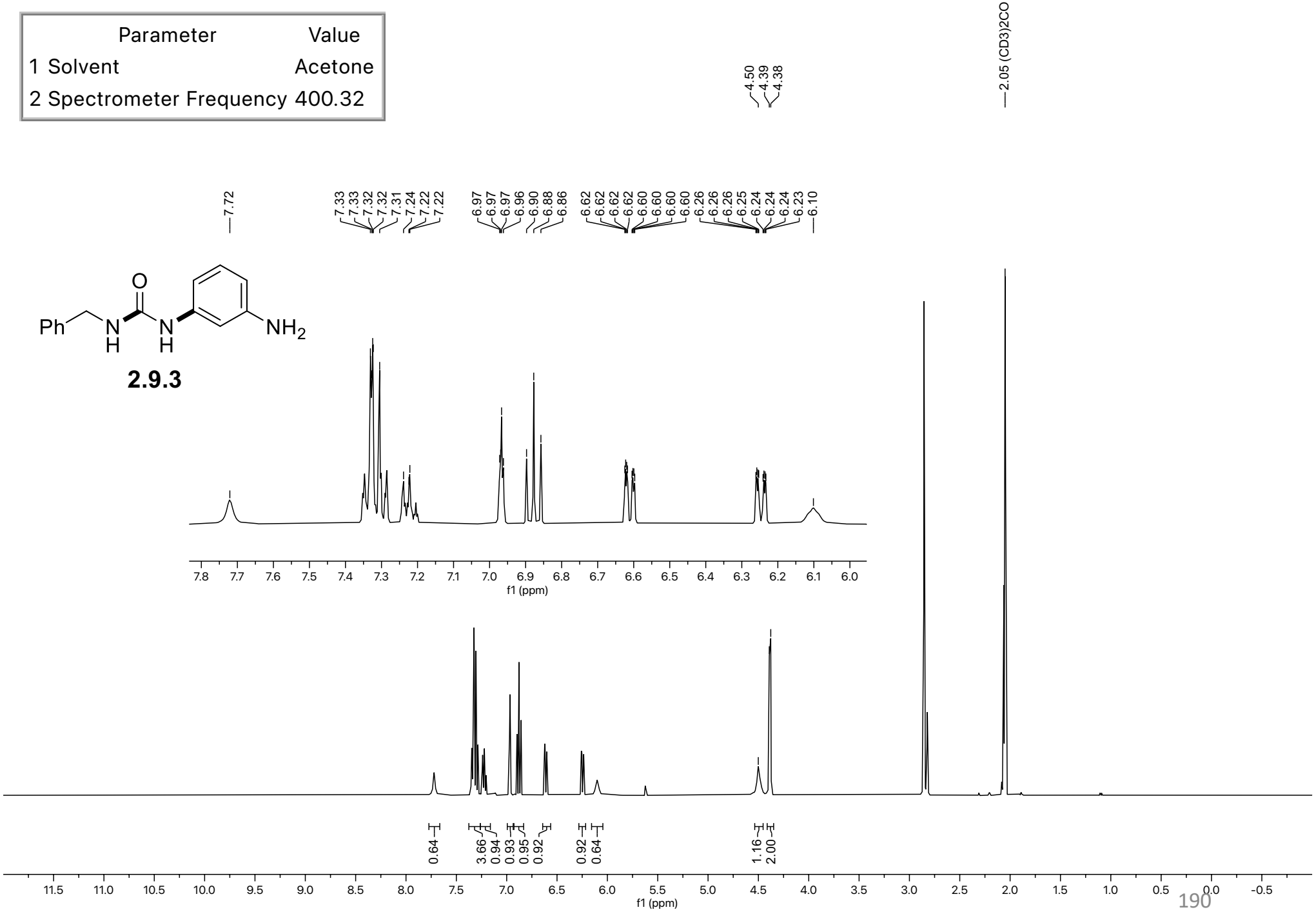
2.9.2

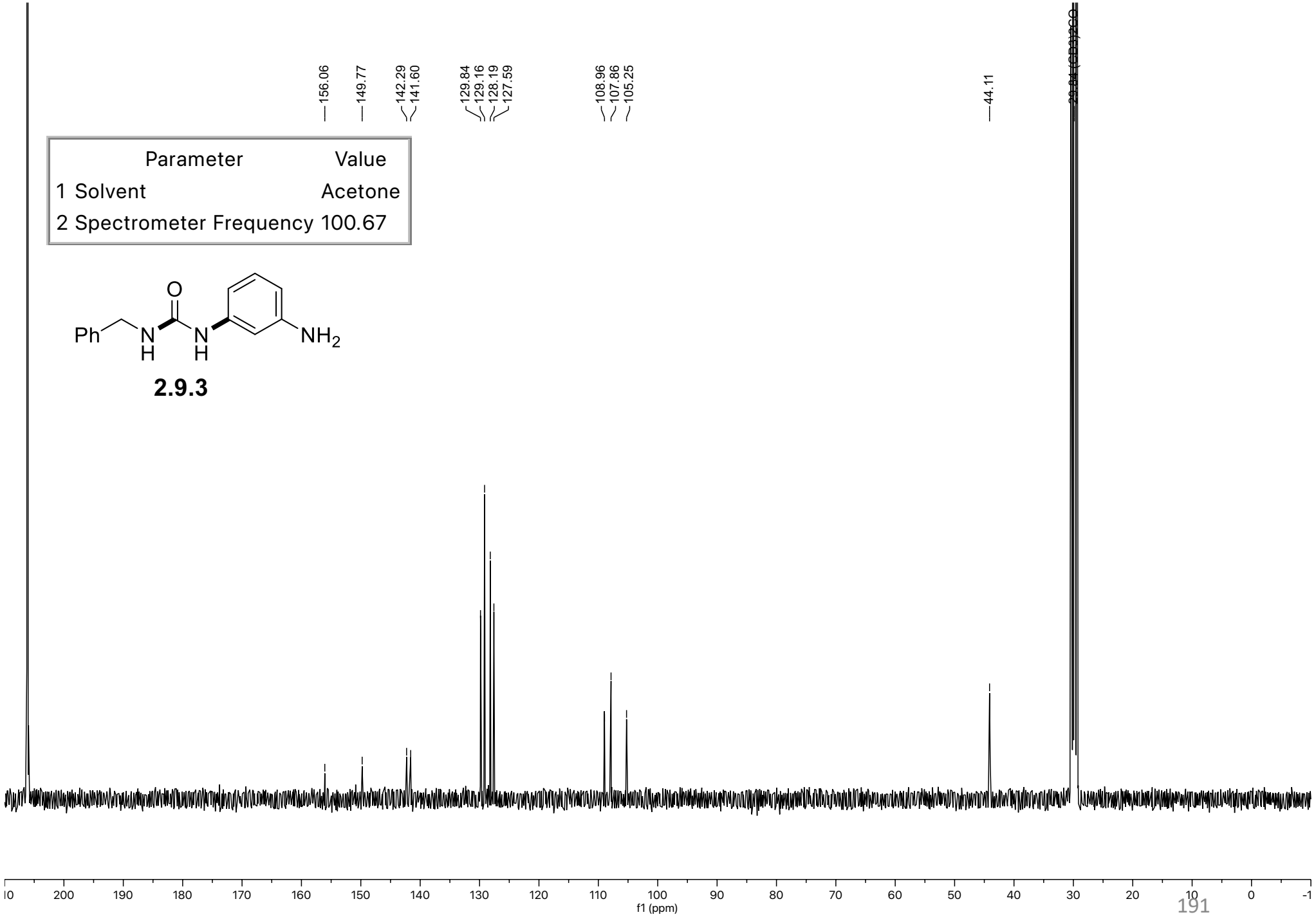
Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	282.56



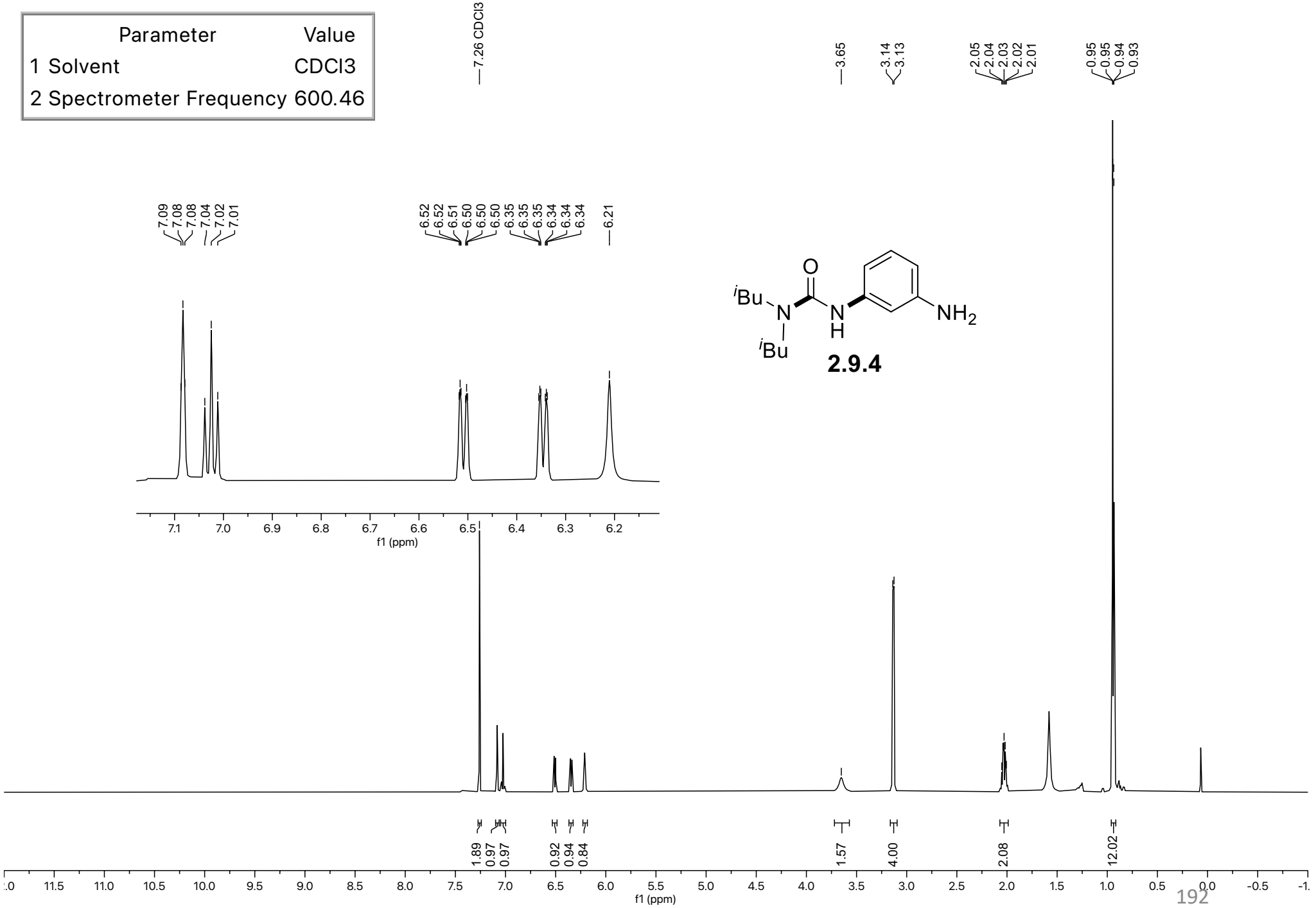
2.9.2

Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	400.32

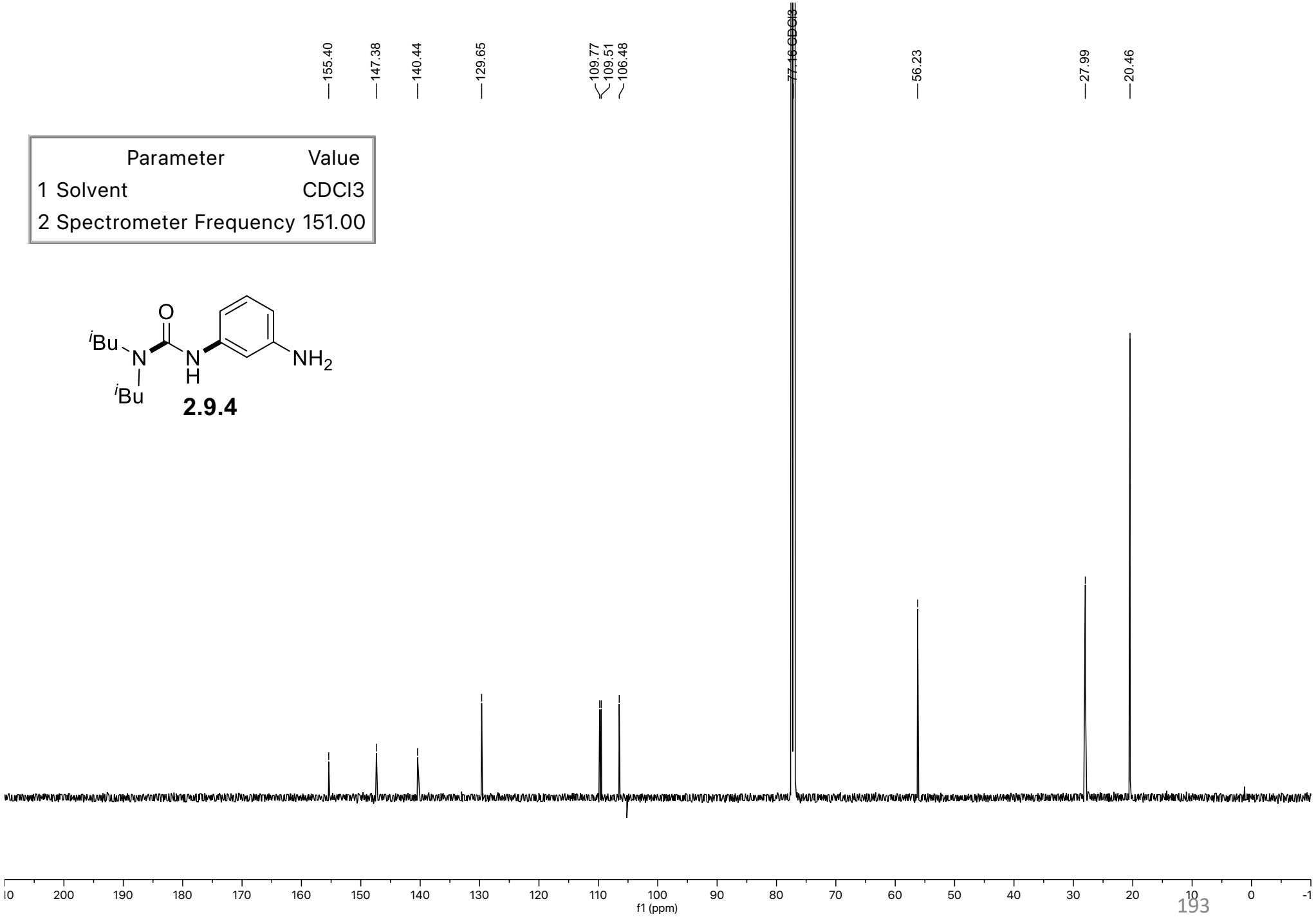



156.06
149.77
142.29
141.60
129.84
129.16
128.19
127.59
108.96
107.86
105.25
44.11
Parameter Value
1 Solvent Acetone
2 Spectrometer Frequency 100.67
Ph
N
H
O
N
H
NH2
2.9.3
f1 (ppm)

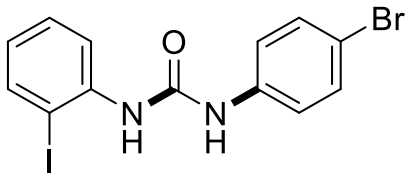
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	600.46



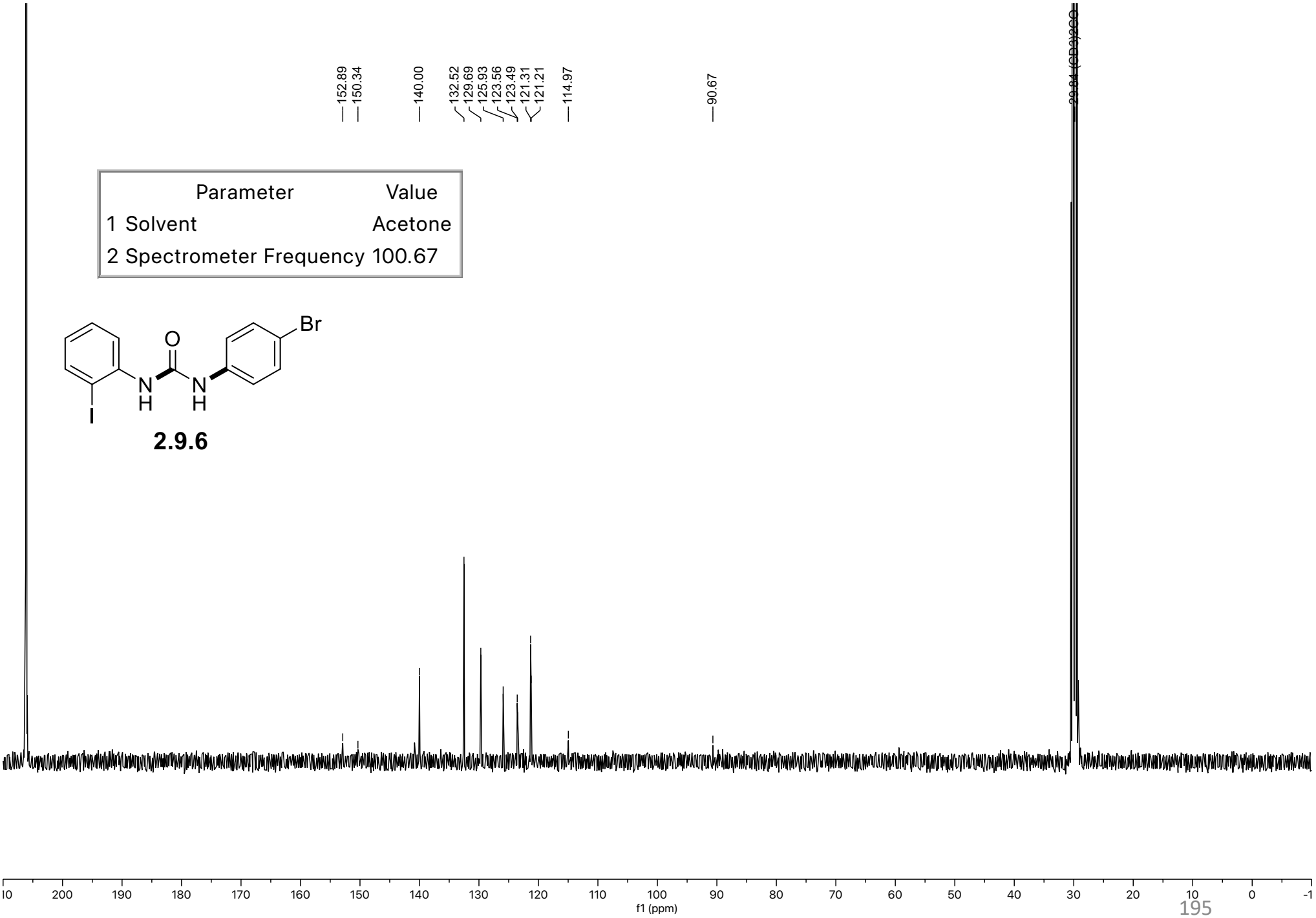
2.9.4


155.40
147.38
140.44
129.65
109.77
109.51
106.48
77.16 CDCl3
56.23
27.99
20.46
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 151.00
iBu
N
iBu
O
N
H
NH2
2.9.4
f1 (ppm)

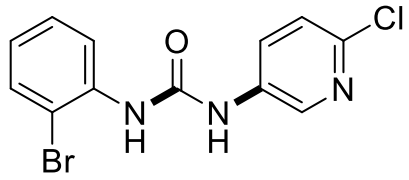
Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	400.32



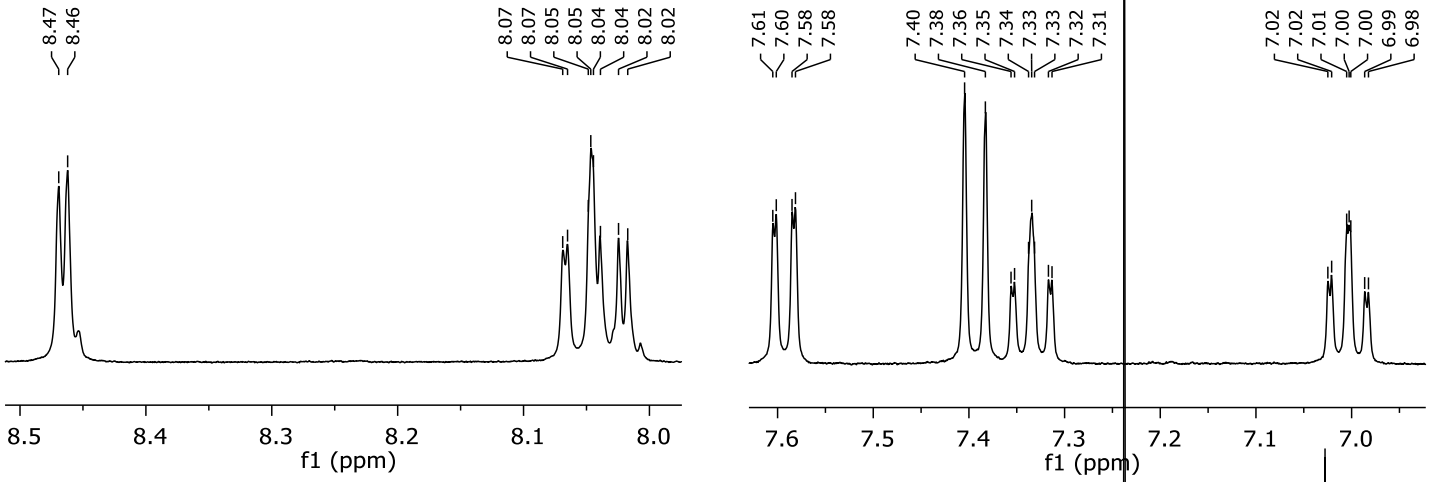
2.9.6


152.89
150.34
140.00
132.52
129.69
125.93
123.56
123.49
121.31
121.21
114.97
90.67
29.84 (CD3)2CO
Parameter Value
1 Solvent Acetone
2 Spectrometer Frequency 100.67
Br
O
N
H
N
H
I
2.9.6
f1 (ppm)

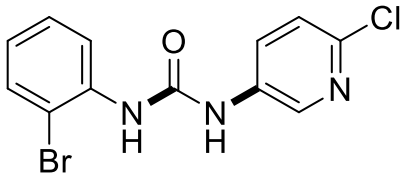
Parameter	Value
1 Solvent	MeOD
2 Spectrometer Frequency	400.32



2.9.7

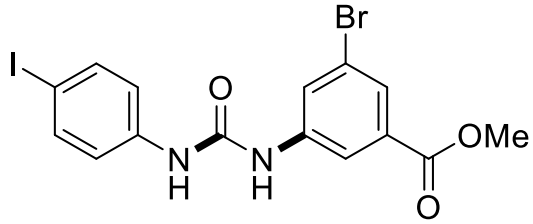


Parameter	Value
1 Solvent	MeOD
2 Spectrometer Frequency	100.67

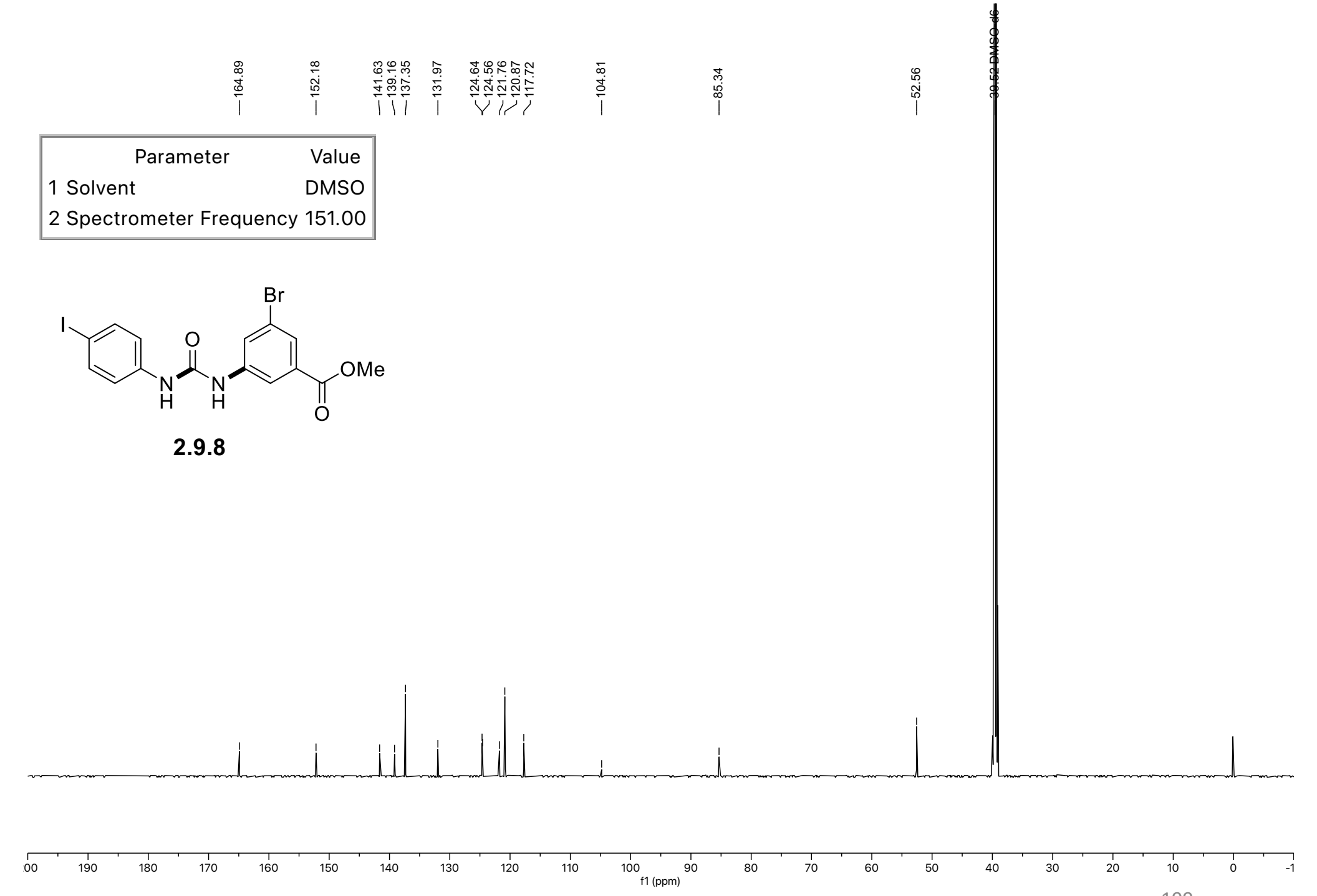


2.9.7

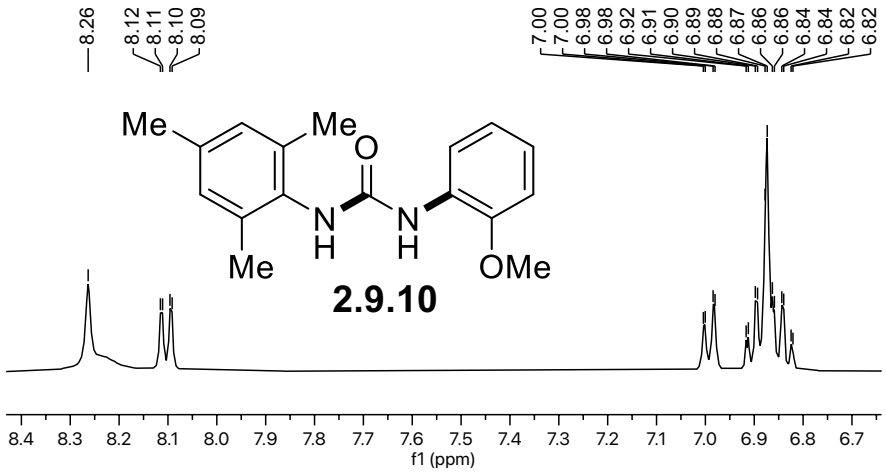
Parameter	Value
1 Solvent	DMSO
2 Spectrometer Frequency	600.46

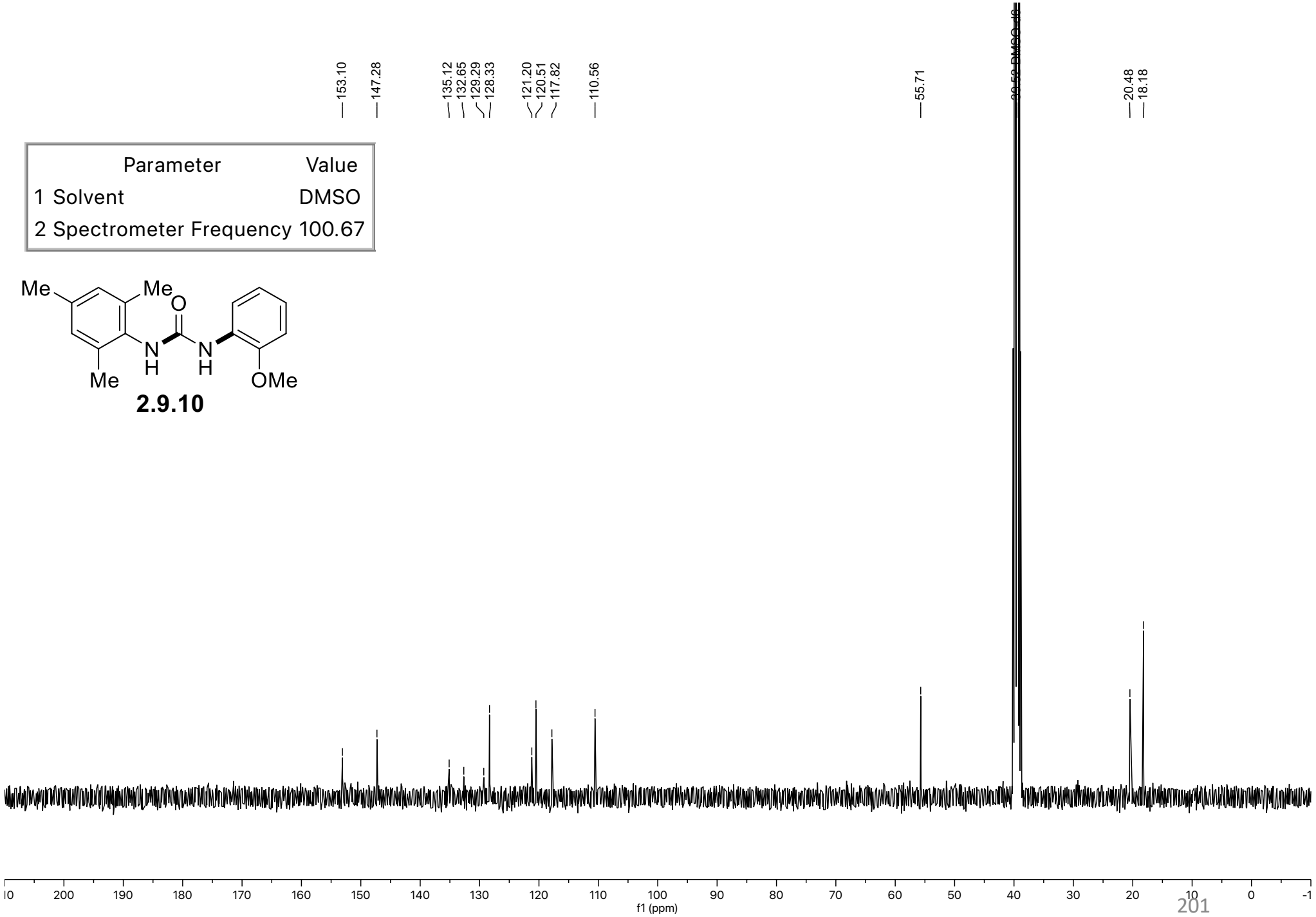


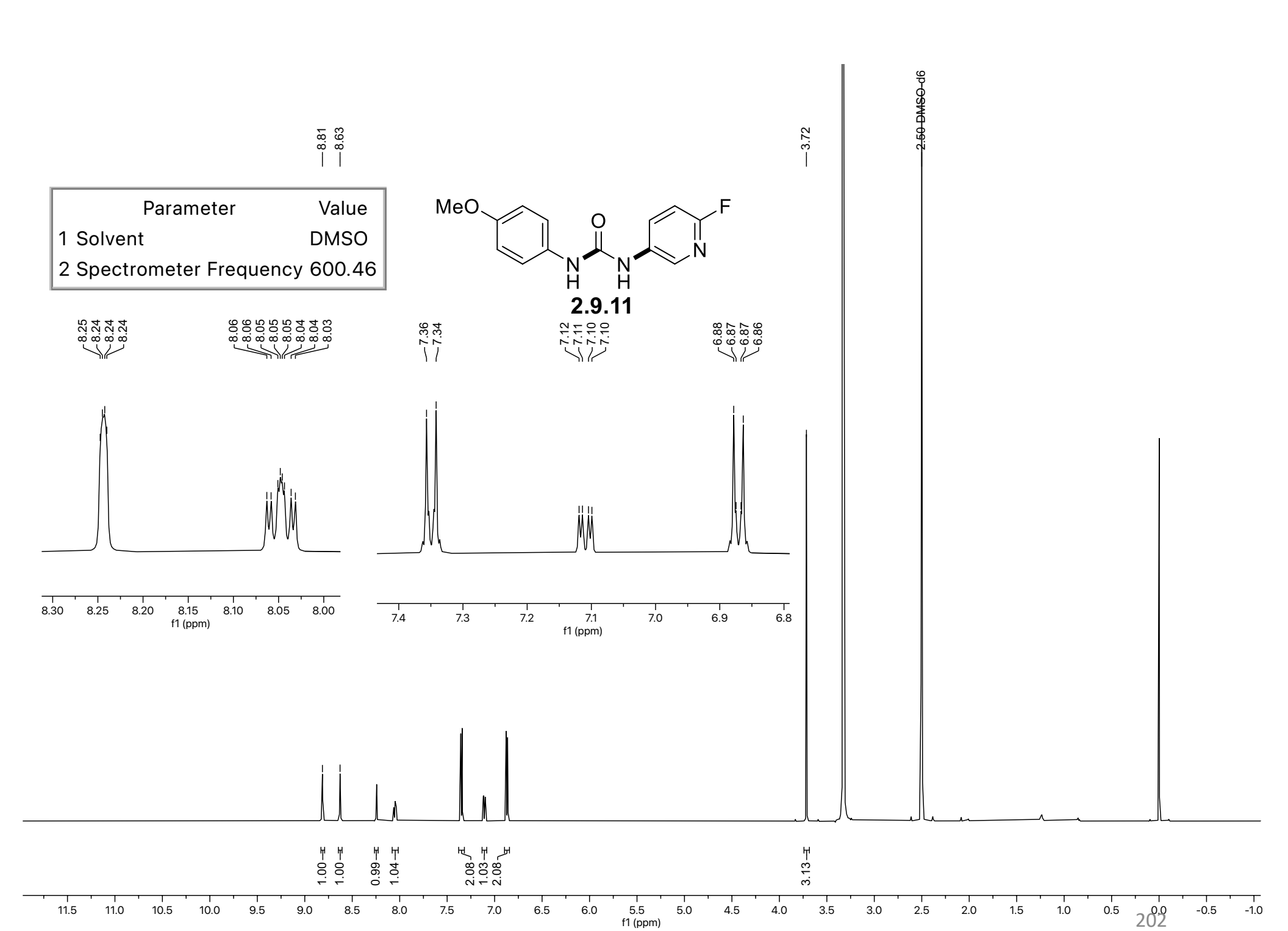
2.9.8


164.89
152.18
141.63
139.16
137.35
131.97
124.64
124.56
121.76
120.87
117.72
104.81
85.34
52.56
39.52 DMSO-d6
Parameter Value
1 Solvent DMSO
2 Spectrometer Frequency 151.00
Br
I
O
N
H
N
H
OMe
O
2.9.8
f1 (ppm)

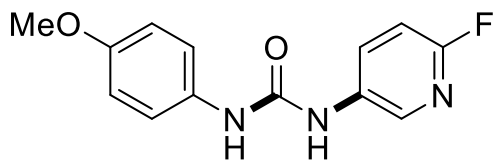
Parameter	Value
1 Solvent	DMSO
2 Spectrometer Frequency	400.32




153.10
147.28
135.12
132.65
129.29
128.33
121.20
120.51
117.82
110.56
55.71
20.48
18.18
Parameter Value
1 Solvent DMSO
2 Spectrometer Frequency 100.67
Me
Me
O
N
H
N
H
Me
OMe
2.9.10
f1 (ppm)

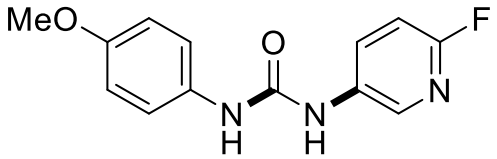

Parameter Value
1 Solvent DMSO
2 Spectrometer Frequency 600.46
MeO
O
F
N
N H
N H
2.9.11
8.81
8.63
3.72
2.50 DMSO-d6
8.25 8.24 8.24 8.24
8.06 8.06 8.05 8.05 8.05 8.04 8.04 8.03
7.36 7.34
7.12 7.11 7.10 7.10
6.88 6.87 6.87 6.86
8.30 8.25 8.20 8.15 8.10 8.05 8.00
f1 (ppm)
7.4 7.3 7.2 7.1 7.0 6.9 6.8
f1 (ppm)
1.00 1.00 0.99 1.04 2.08 1.03 2.08 3.13
11.5 11.0 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 -0.5 -1.0
f1 (ppm)

Parameter	Value
1 Solvent	DMSO
2 Spectrometer Frequency	151.00

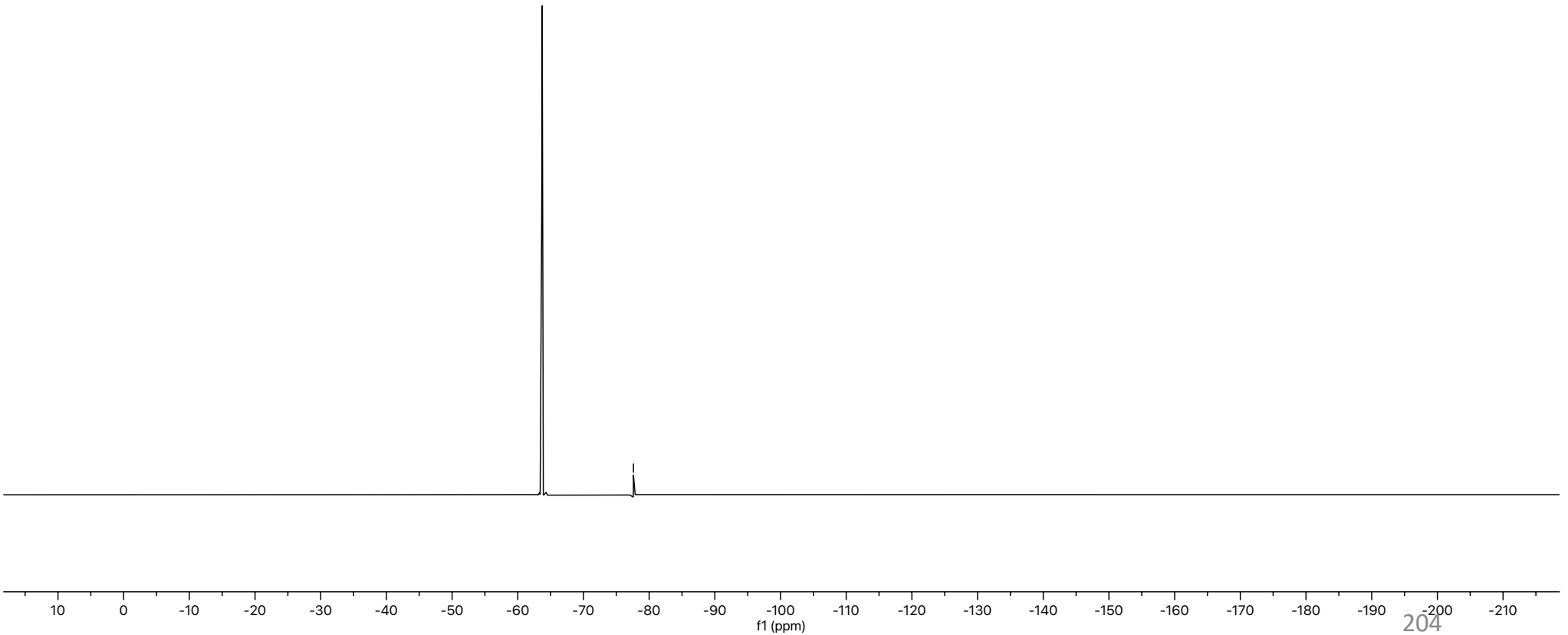


2.9.11

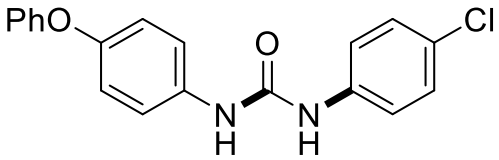
Parameter	Value
1 Solvent	DMSO
2 Spectrometer Frequency	282.56



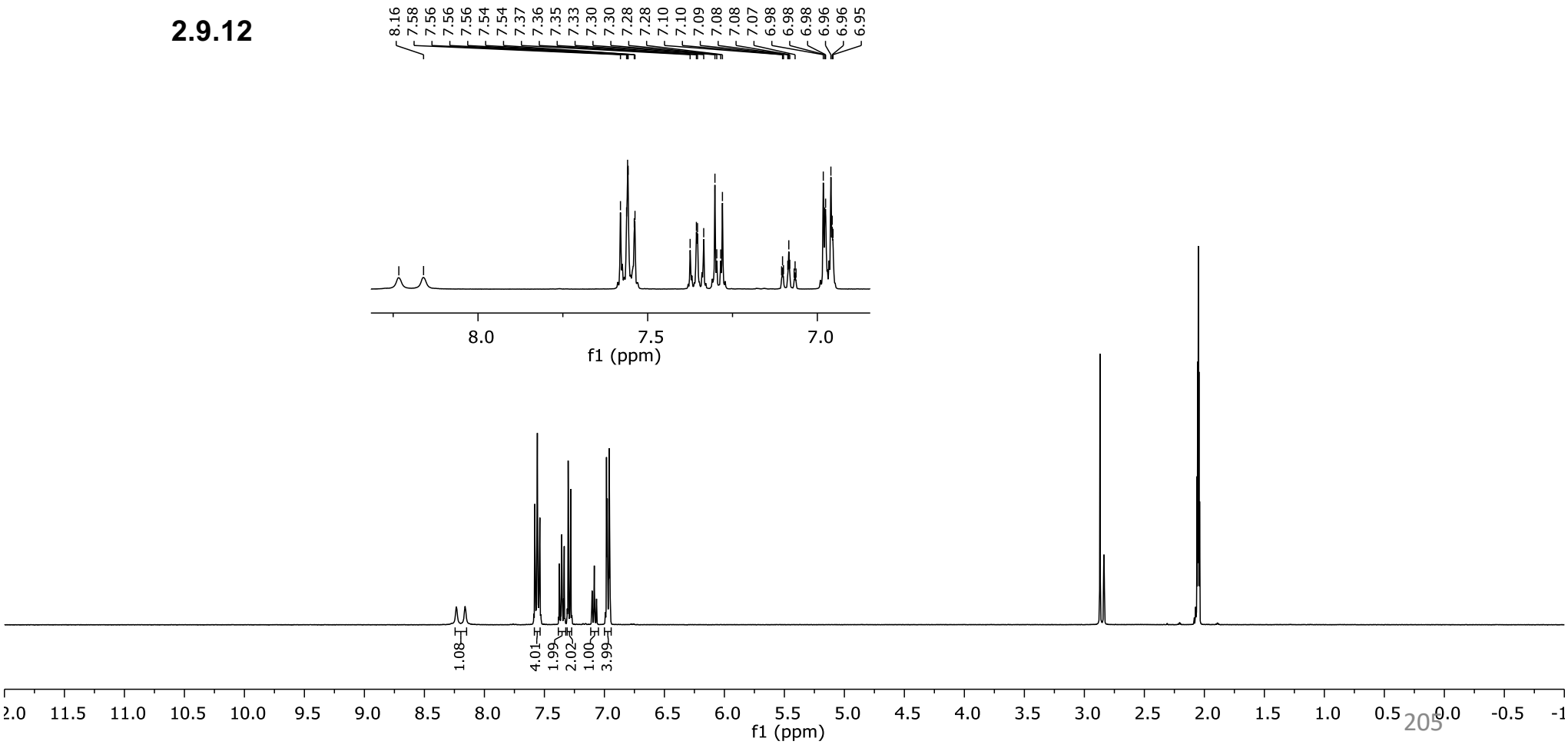
2.9.11

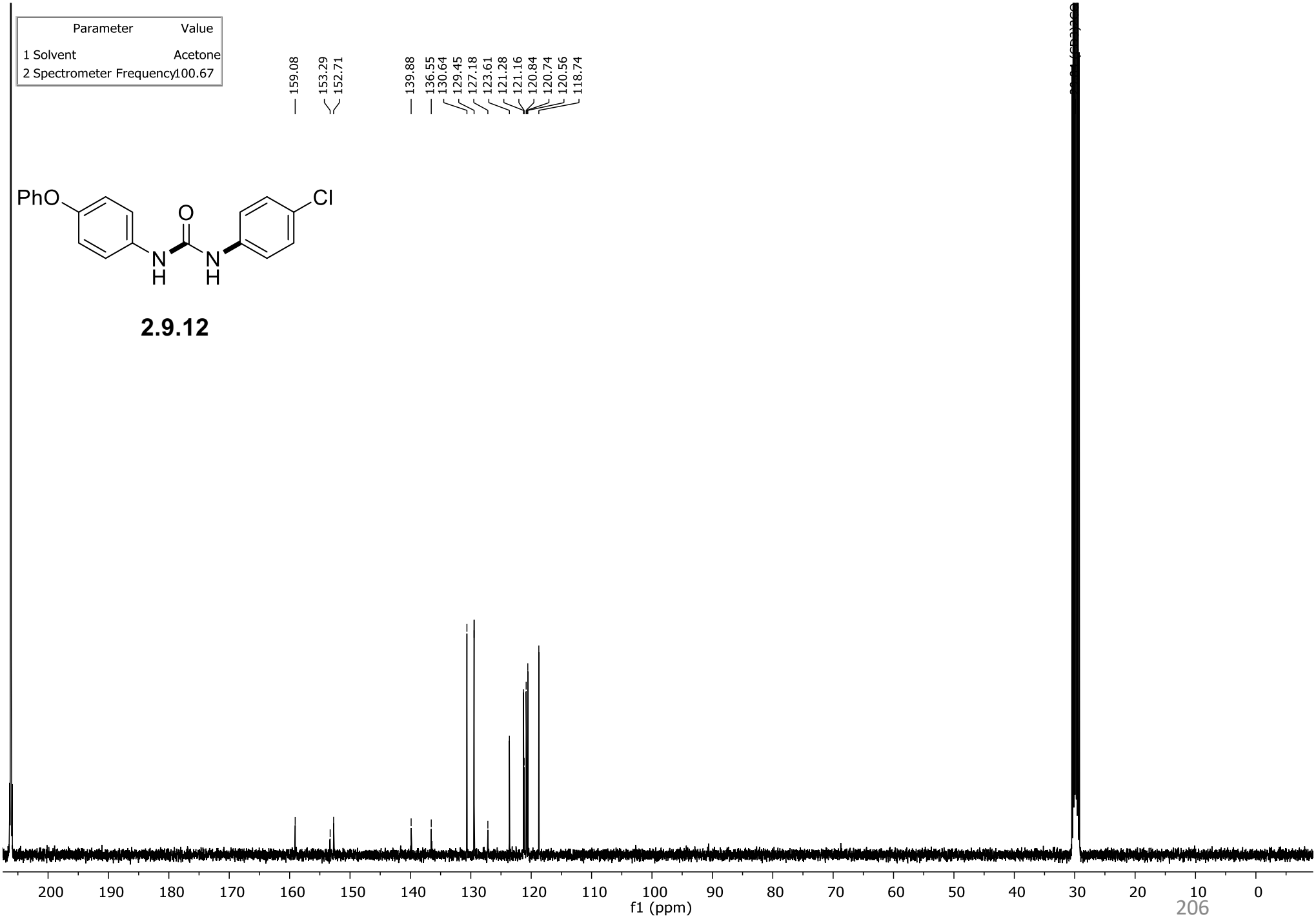


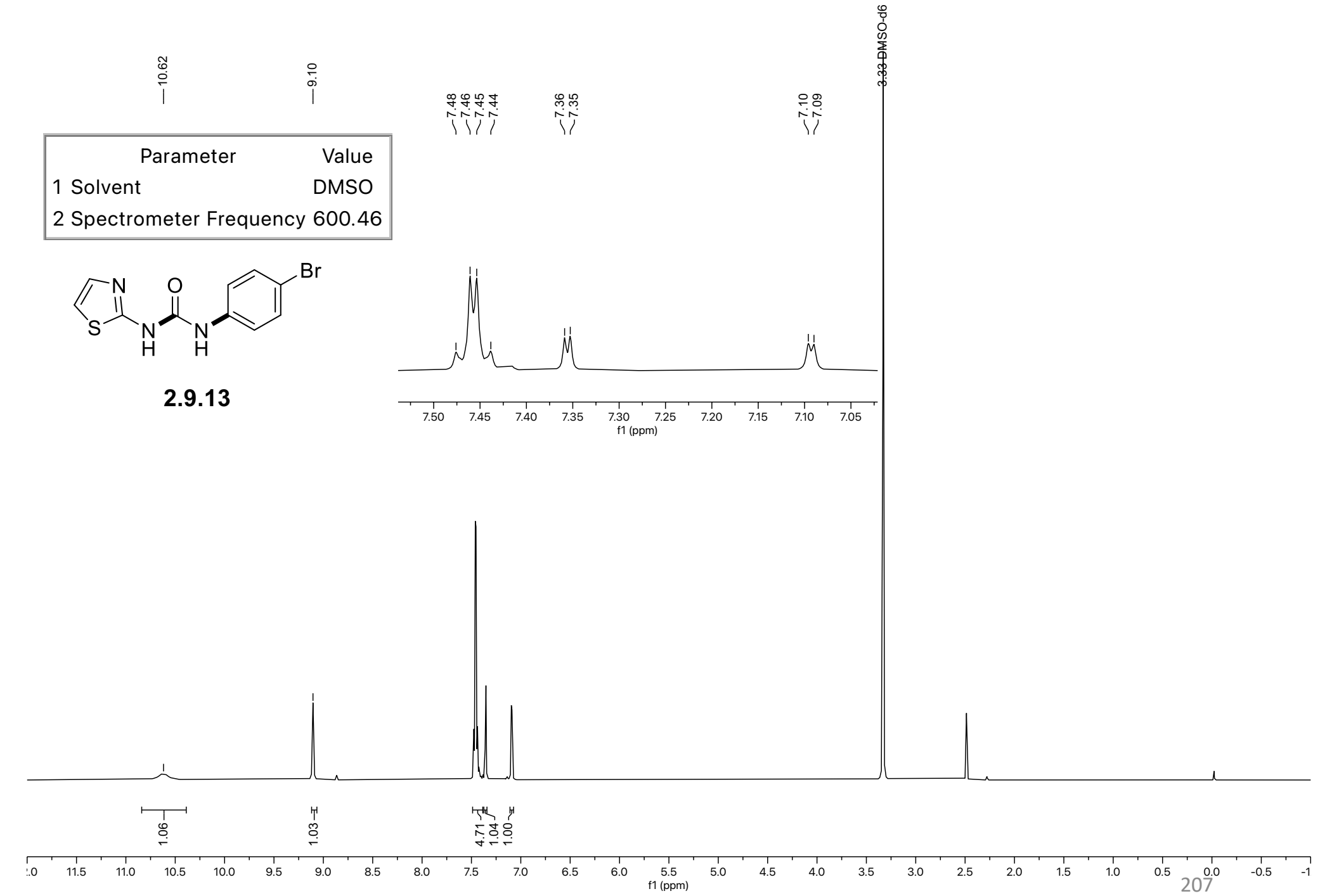
Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	400.32

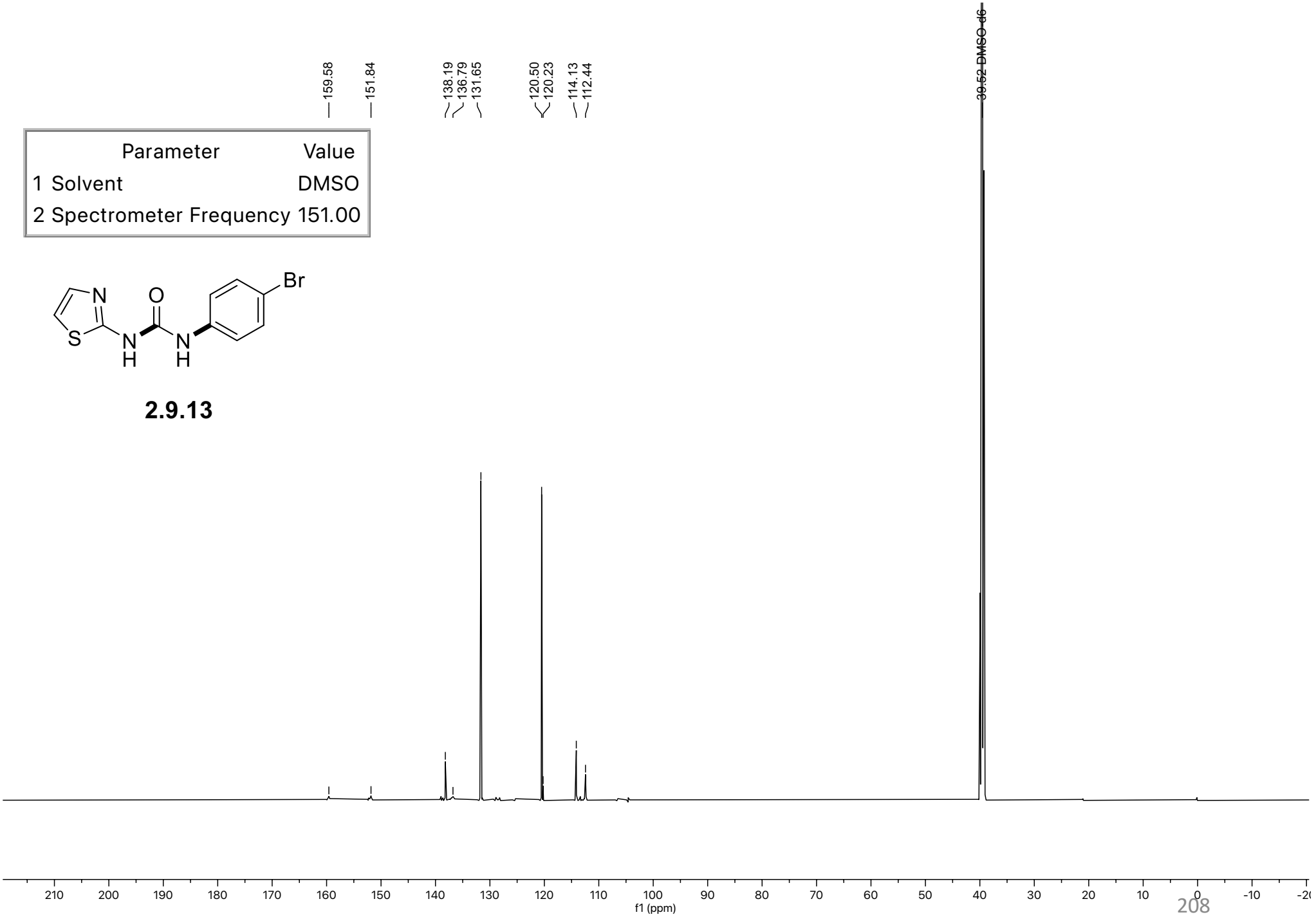


2.9.12

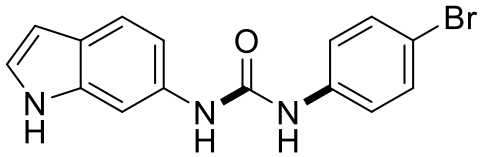



Parameter Value
1 Solvent Acetone
2 Spectrometer Frequency 100.67
159.08
153.29
152.71
139.88
136.55
130.64
129.45
127.18
123.61
121.28
121.16
120.84
120.74
120.56
118.74
PhO
O
N
H
N
H
Cl
2.9.12
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


10.62
9.10
7.48
7.46
7.45
7.44
7.36
7.35
7.10
7.09
3.33 DMSO-d6
Parameter Value
1 Solvent DMSO
2 Spectrometer Frequency 600.46
Br
N
O
S
N
H
N
H
2.9.13
7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05
f1 (ppm)
1.06
1.03
4.71
1.04
1.00
11.5 11.0 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 -0.5 -1
f1 (ppm)

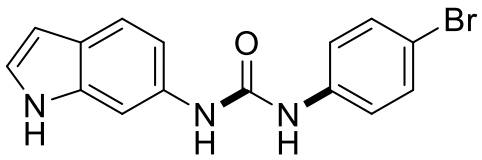

159.58
151.84
138.19
136.79
131.65
120.50
120.23
114.13
112.44
39.52 DMSO-d6
Parameter Value
1 Solvent DMSO
2 Spectrometer Frequency 151.00
N
O
S
N
H
N
H
Br
2.9.13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Parameter	Value
1 Solvent	DMSO
2 Spectrometer Frequency	400.32



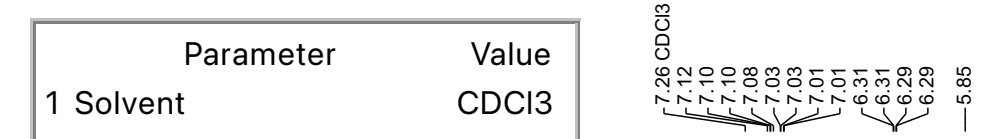
2.9.13

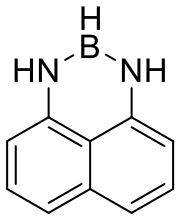
Parameter	Value
1 Solvent	DMSO
2 Spectrometer Frequency	100.67



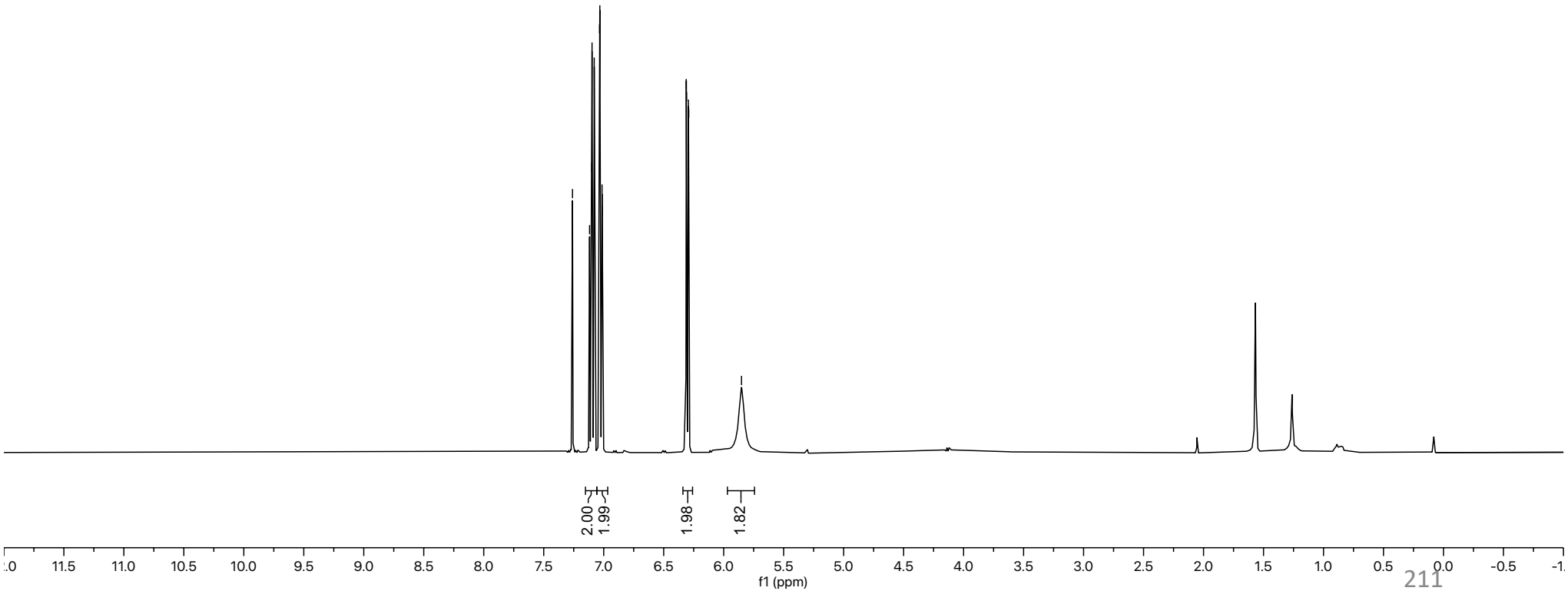
2.9.13

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32

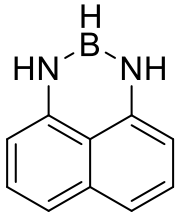




2.10

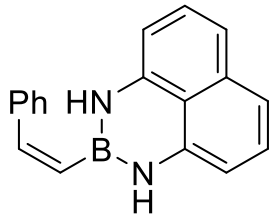


Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67



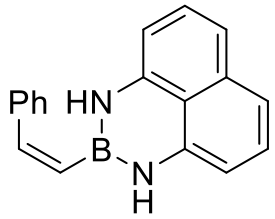
2.10

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



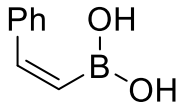
2.11

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67

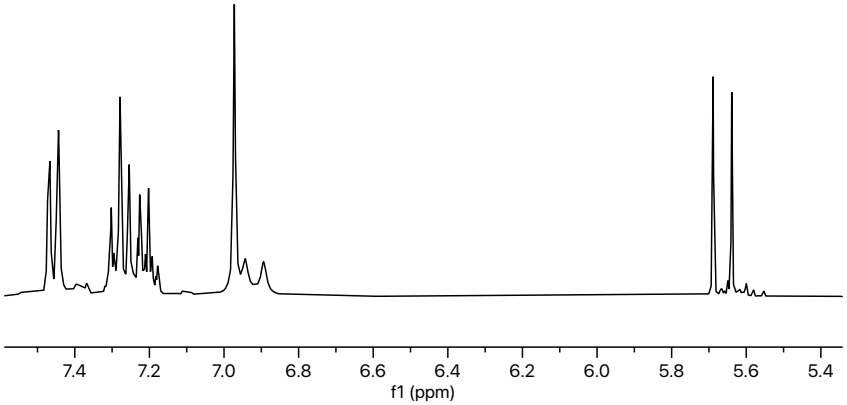


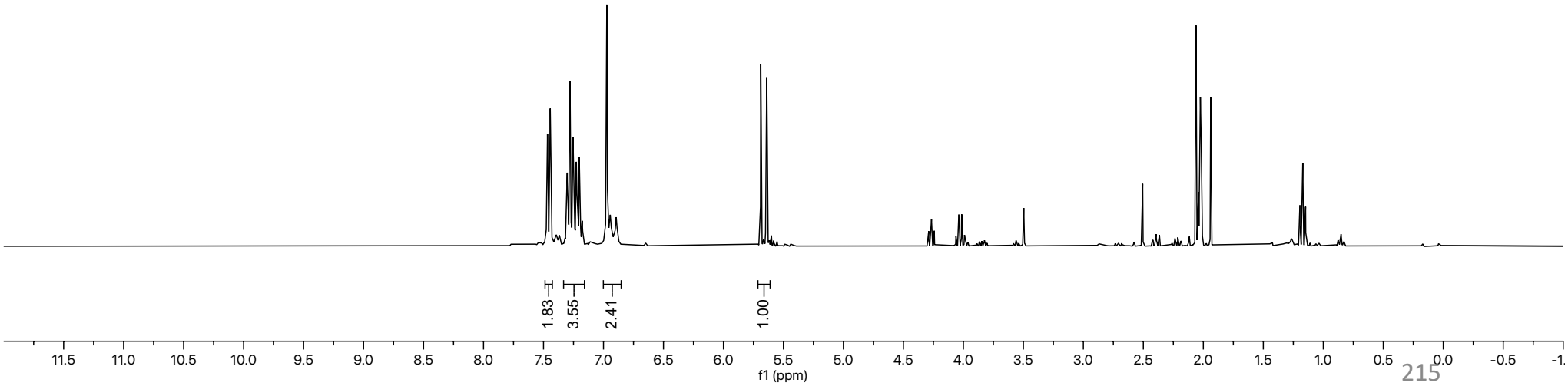
2.11

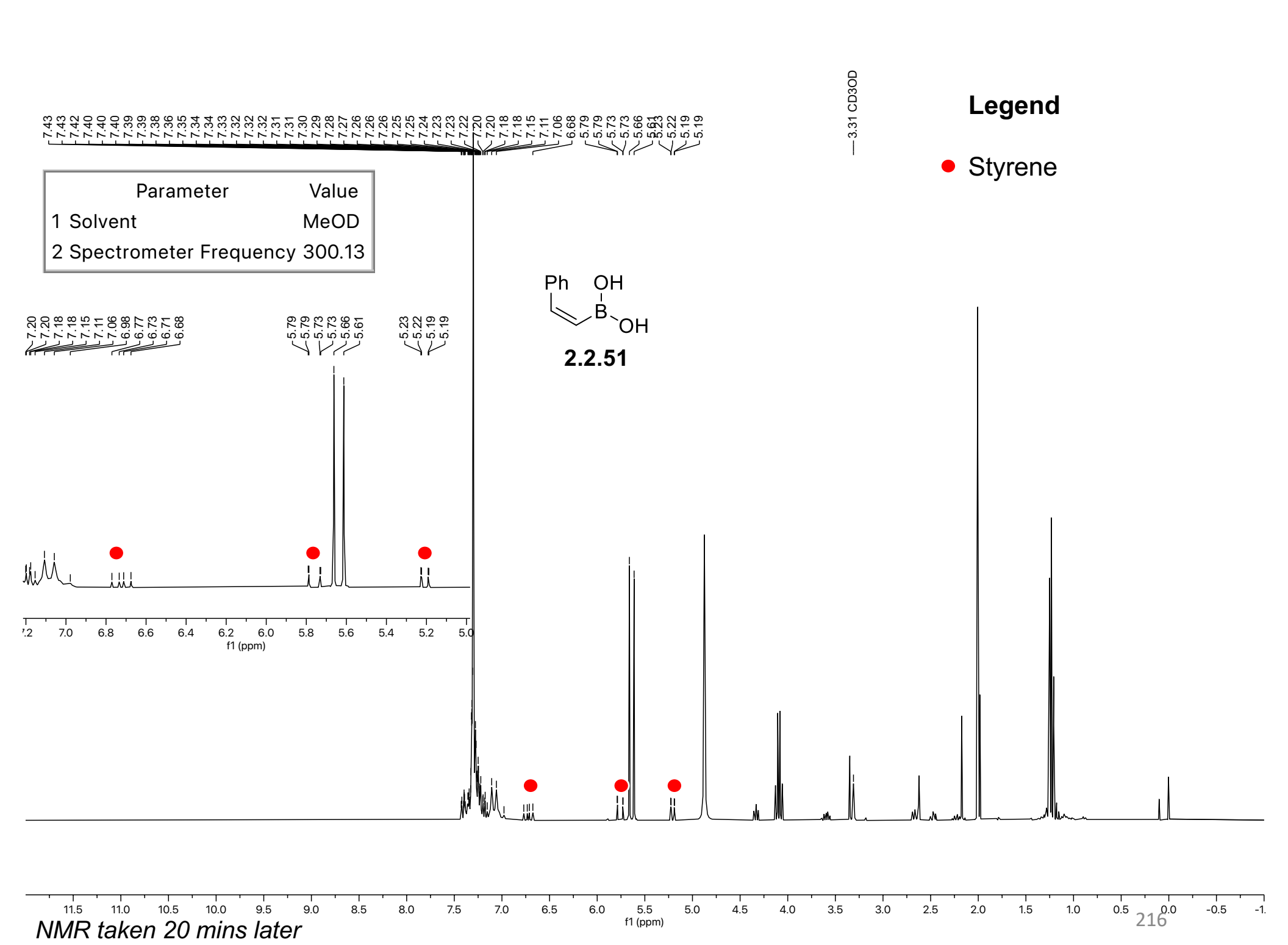
Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	300.13



2.2.51

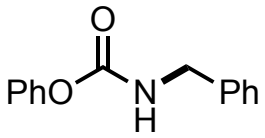




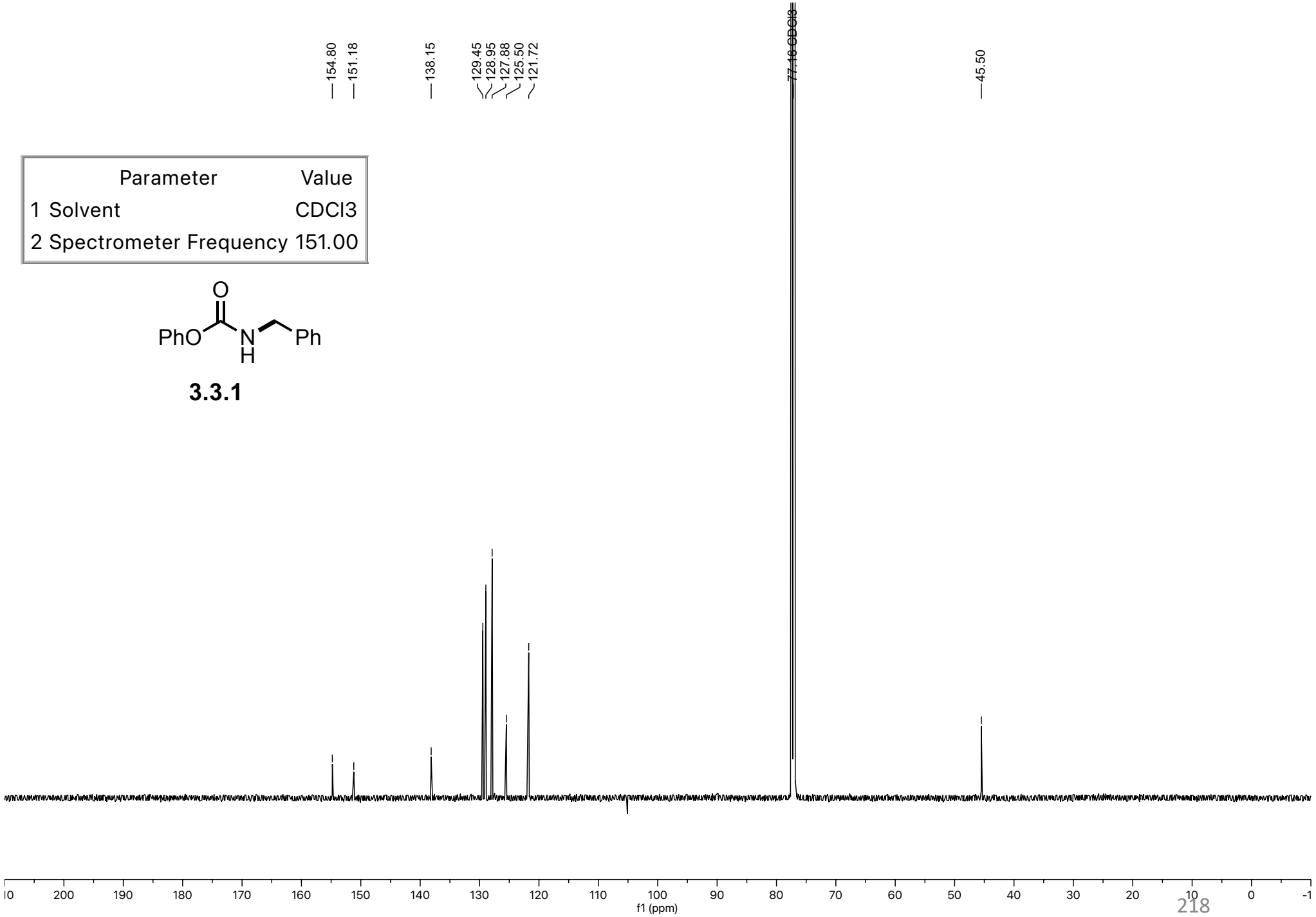


NMR taken 20 mins later

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	600.46



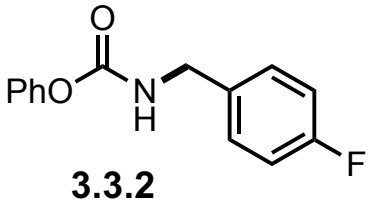
3.3.1



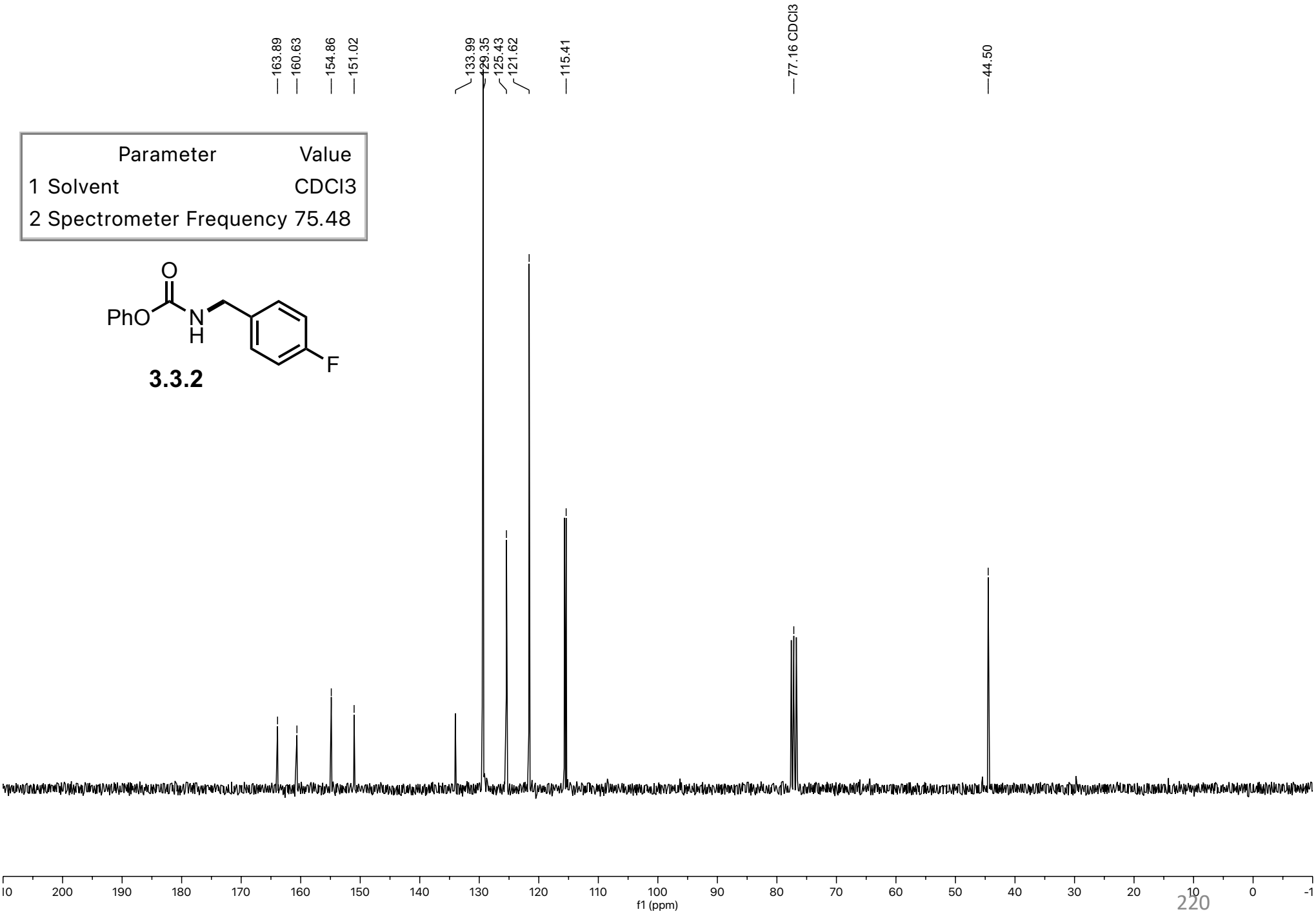
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	151.00

3.3.1

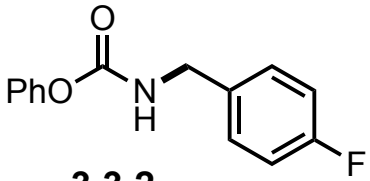
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	300.13



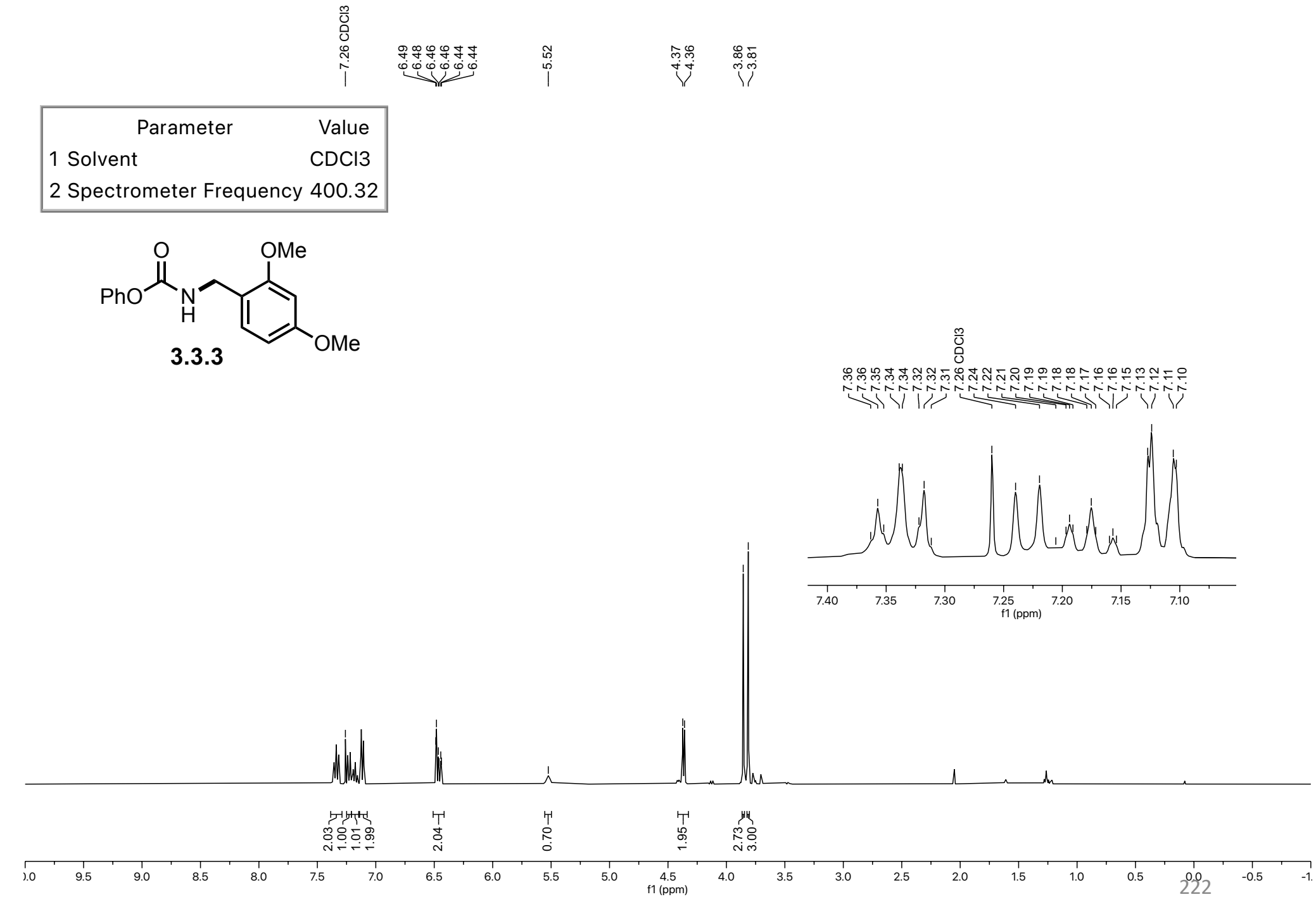
3.3.2

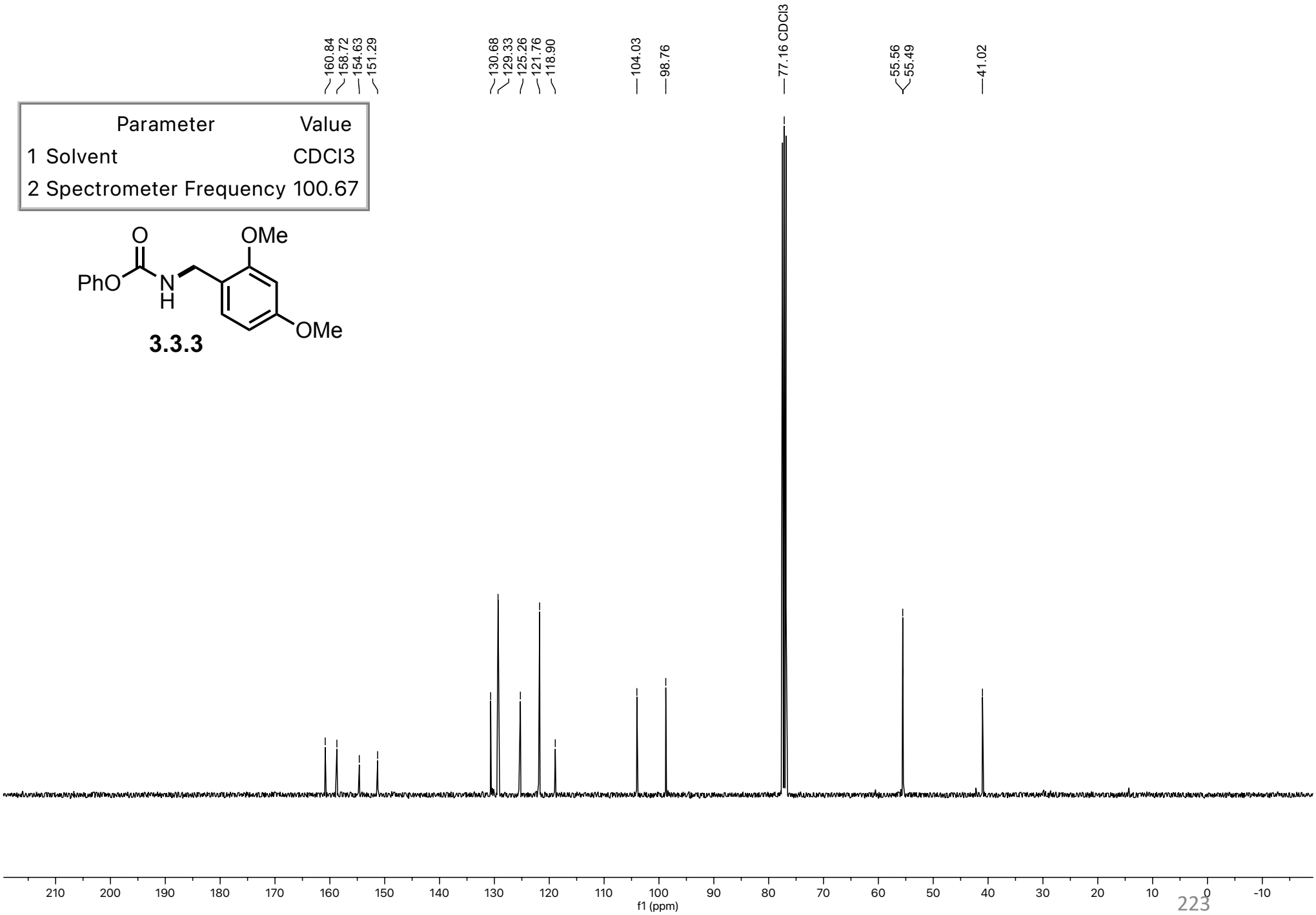

163.89
160.63
154.86
151.02
133.99
129.35
125.43
121.62
115.41
77.16 CDCl3
44.50
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 75.48
O
PhO
N
H
F
3.3.2
f1 (ppm)

Parameter	Value
1 Solvent	CDCl3f
2 Spectrometer Frequency	282.56

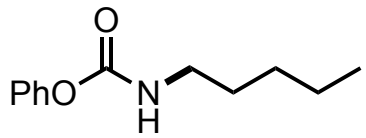


3.3.2

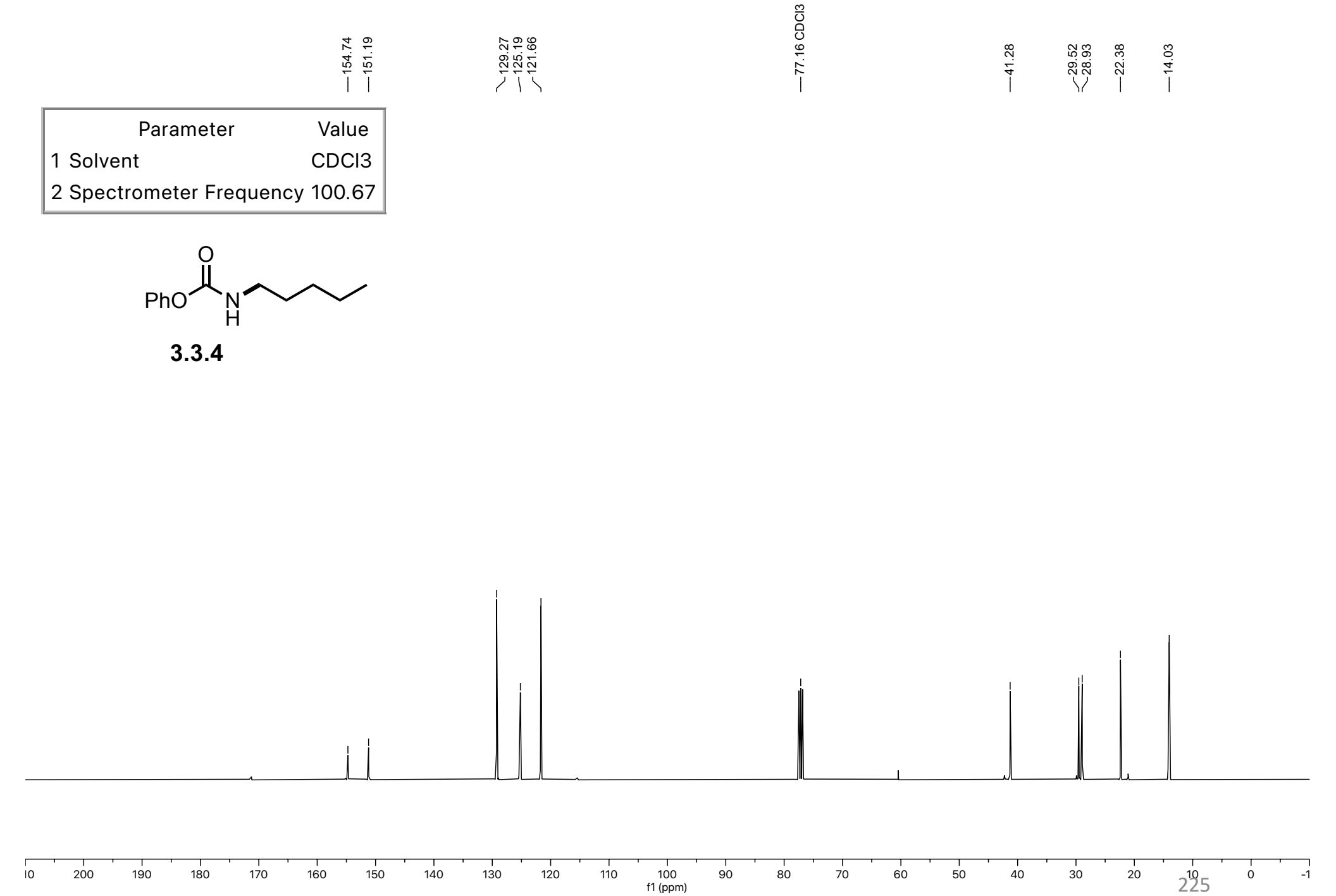

7.26 CDCl3
6.49
6.48
6.46
6.46
6.44
6.44
5.52
4.37
4.36
3.86
3.81
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.32
O
OMe
PhO
N
H
OMe
3.3.3
7.36
7.36
7.35
7.34
7.34
7.32
7.32
7.31
7.26 CDCl3
7.24
7.22
7.21
7.20
7.19
7.19
7.18
7.18
7.17
7.16
7.16
7.15
7.13
7.12
7.11
7.10
7.40
7.35
7.30
7.25
7.20
7.15
7.10
f1 (ppm)
2.03
1.00
1.01
1.99
2.04
0.70
1.95
2.73
3.00
f1 (ppm)


160.84
158.72
154.63
151.29
130.68
129.33
125.26
121.76
118.90
104.03
98.76
77.16 CDCl3
55.56
55.49
41.02
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
O
OMe
PhO
N
H
OMe
3.3.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

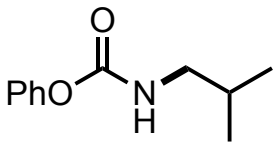
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



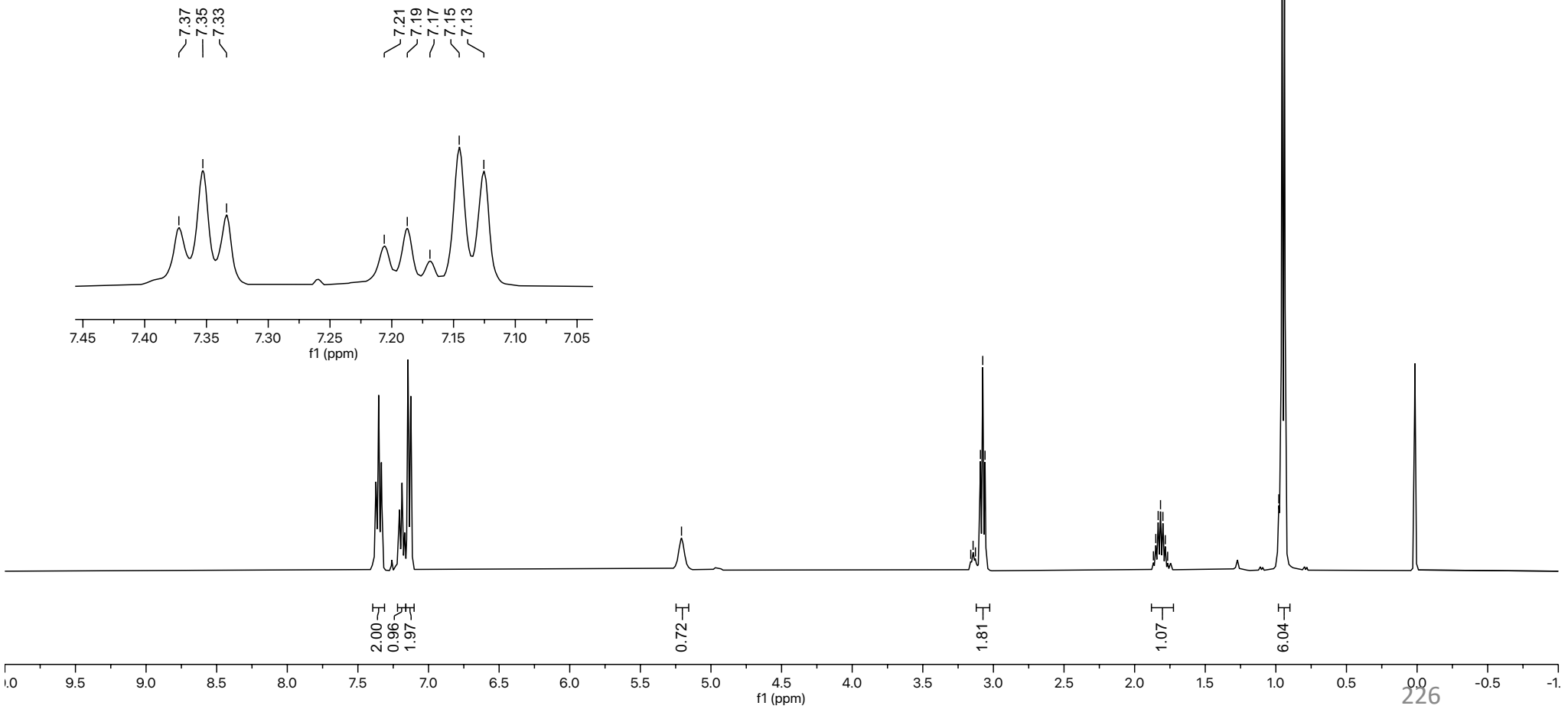
3.3.4

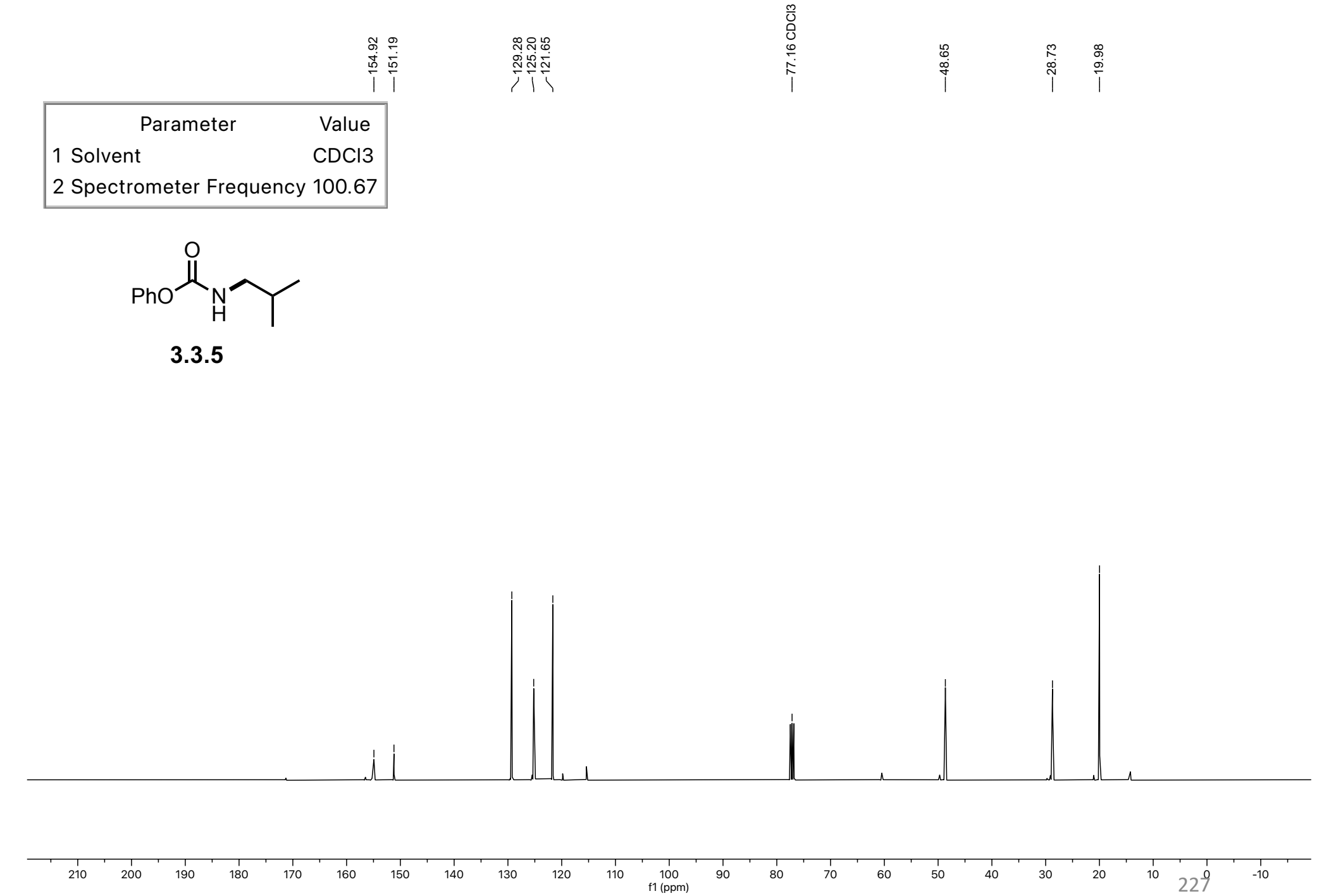

154.74
151.19
129.27
125.19
121.66
77.16 CDCl3
41.28
29.52
28.93
22.38
14.03
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
O
PhO
N
H
3.3.4
f1 (ppm)

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32

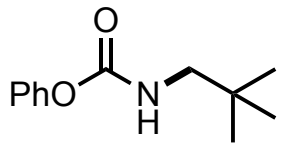


3.3.5

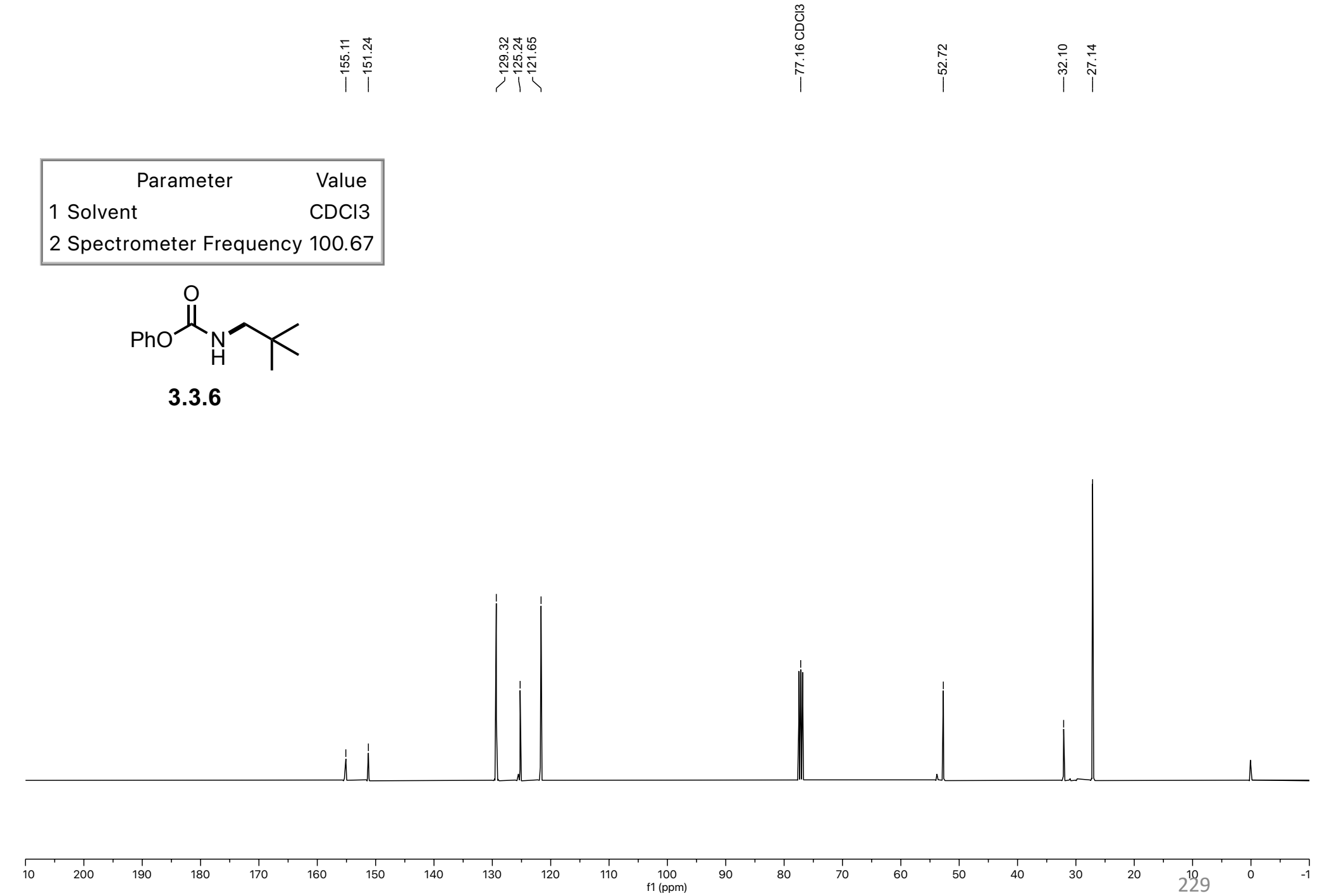



154.92
151.19
129.28
125.20
121.65
77.16 CDCl3
48.65
28.73
19.98
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
O
PhO
N
H
3.3.5
f1 (ppm)

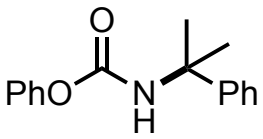
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



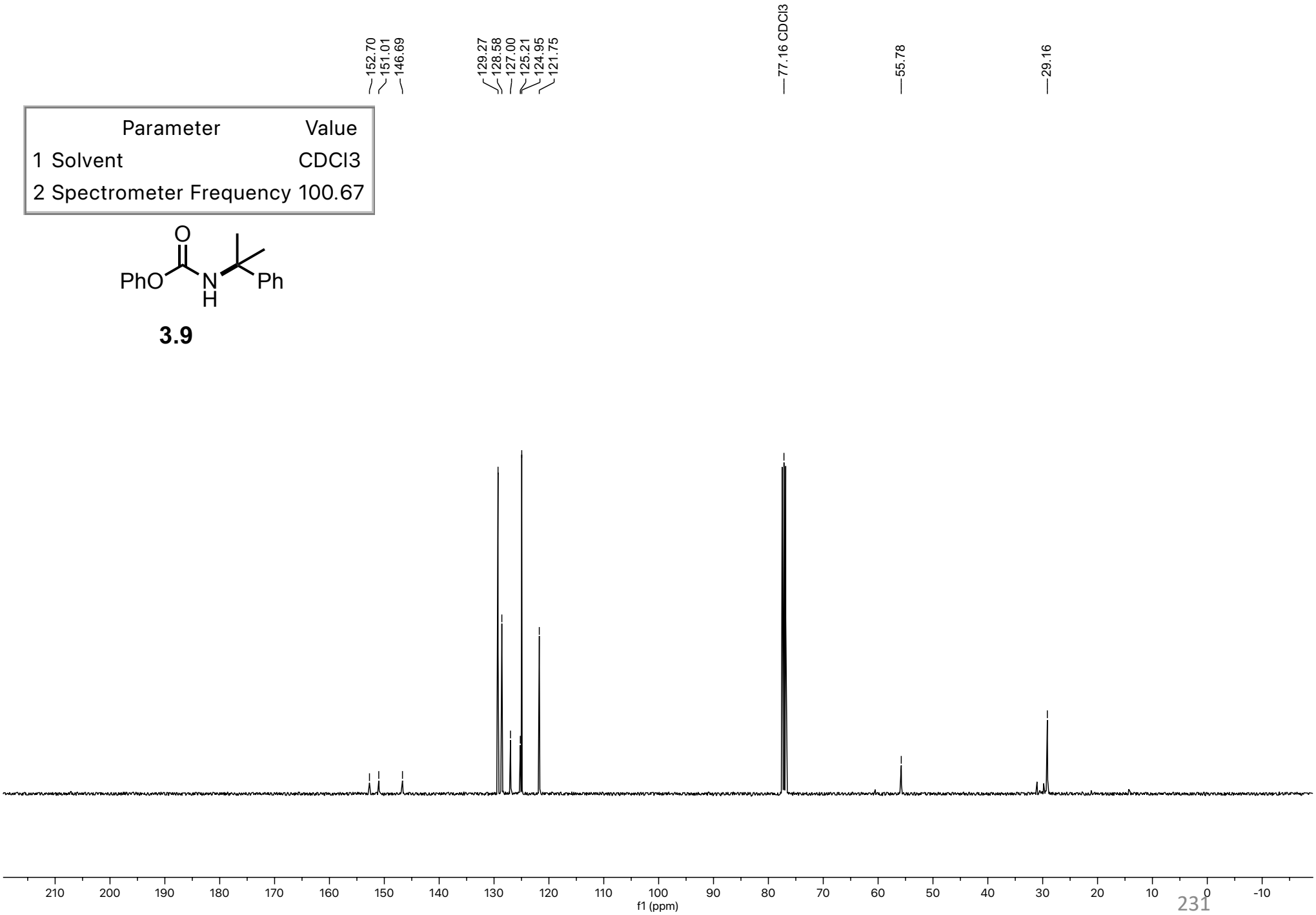
3.3.6


155.11
151.24
129.32
125.24
121.65
77.16 CDCl3
52.72
32.10
27.14
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
O
PhO
N
H
3.3.6
f1 (ppm)

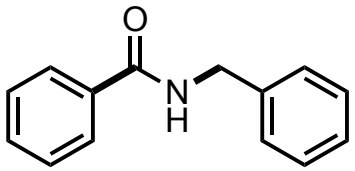
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



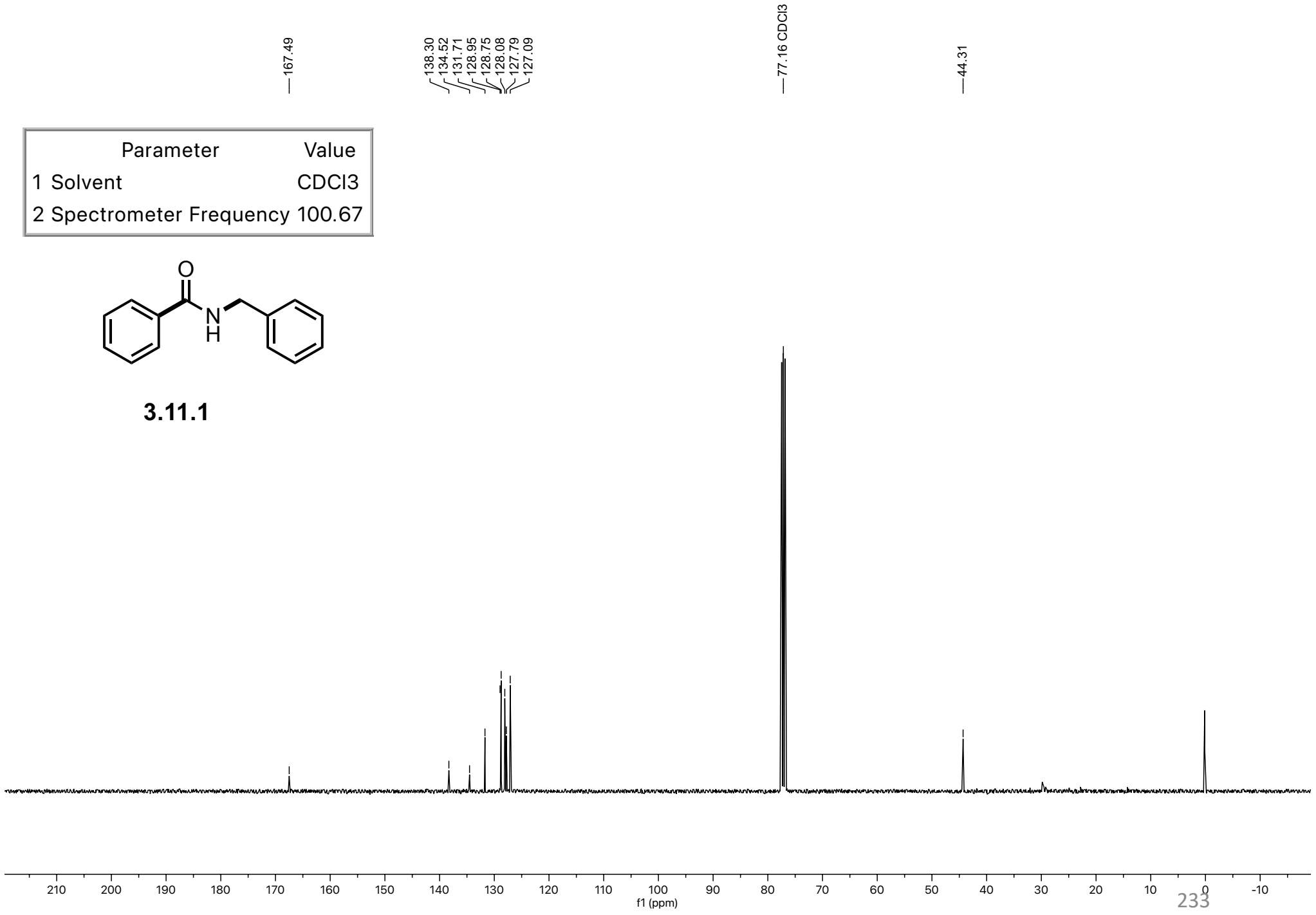
3.9


152.70
151.01
146.69
129.27
128.58
127.00
125.21
124.95
121.75
77.16 CDCl3
55.78
29.16
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
PhO
O
N
H
Ph
3.9
f1 (ppm)

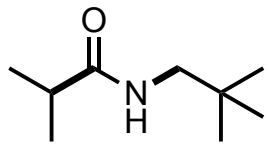
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



3.11.1


167.49
138.30
134.52
131.71
128.95
128.75
128.08
127.79
127.09
77.16 CDCl3
44.31
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
O
N
H
3.11.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



3.11.2

177.05

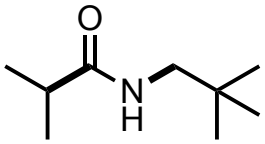
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	100.67

77.16 CDCl3

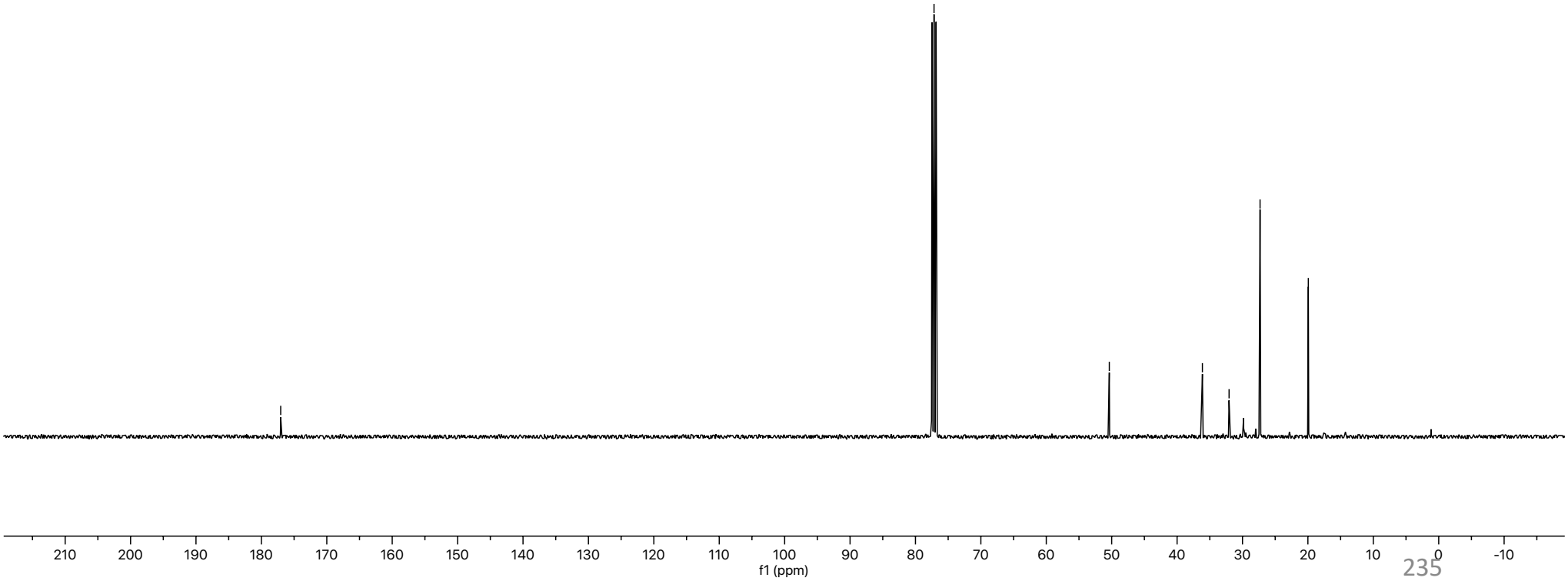
50.36

36.13
32.05
27.31

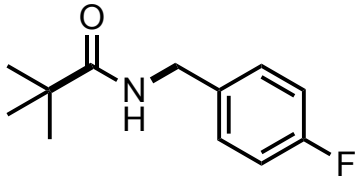
19.94



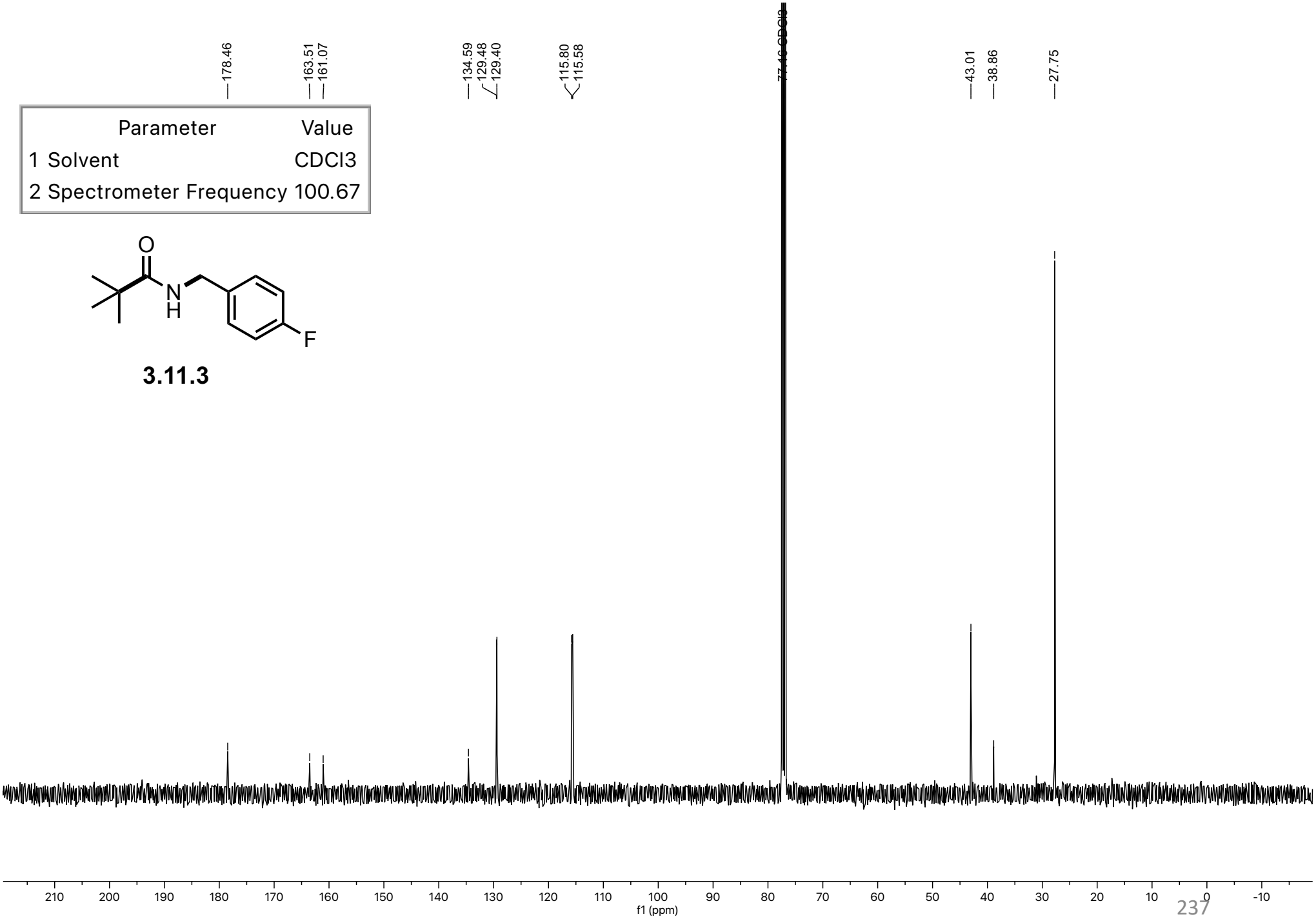
3.11.2



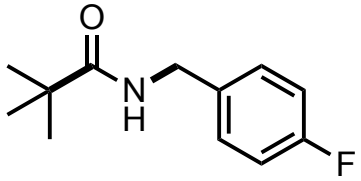
Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	400.32



3.11.3

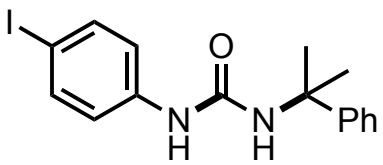

178.46
163.51
161.07
134.59
129.48
129.40
115.80
115.58
77.16 CDCl3
43.01
38.86
27.75
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 100.67
O
N
H
F
3.11.3
f1 (ppm)

Parameter	Value
1 Solvent	CDCl3
2 Spectrometer Frequency	282.56

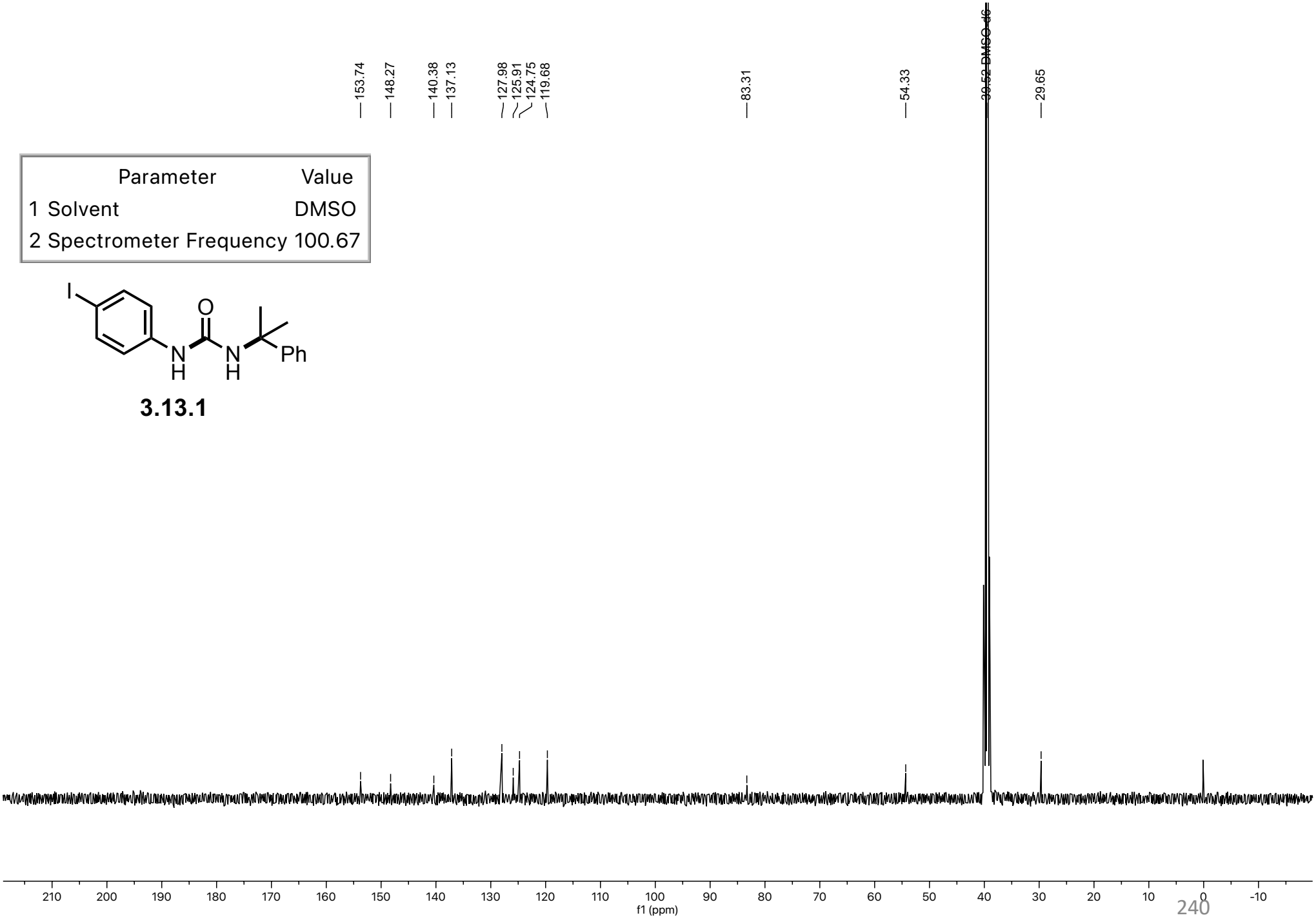


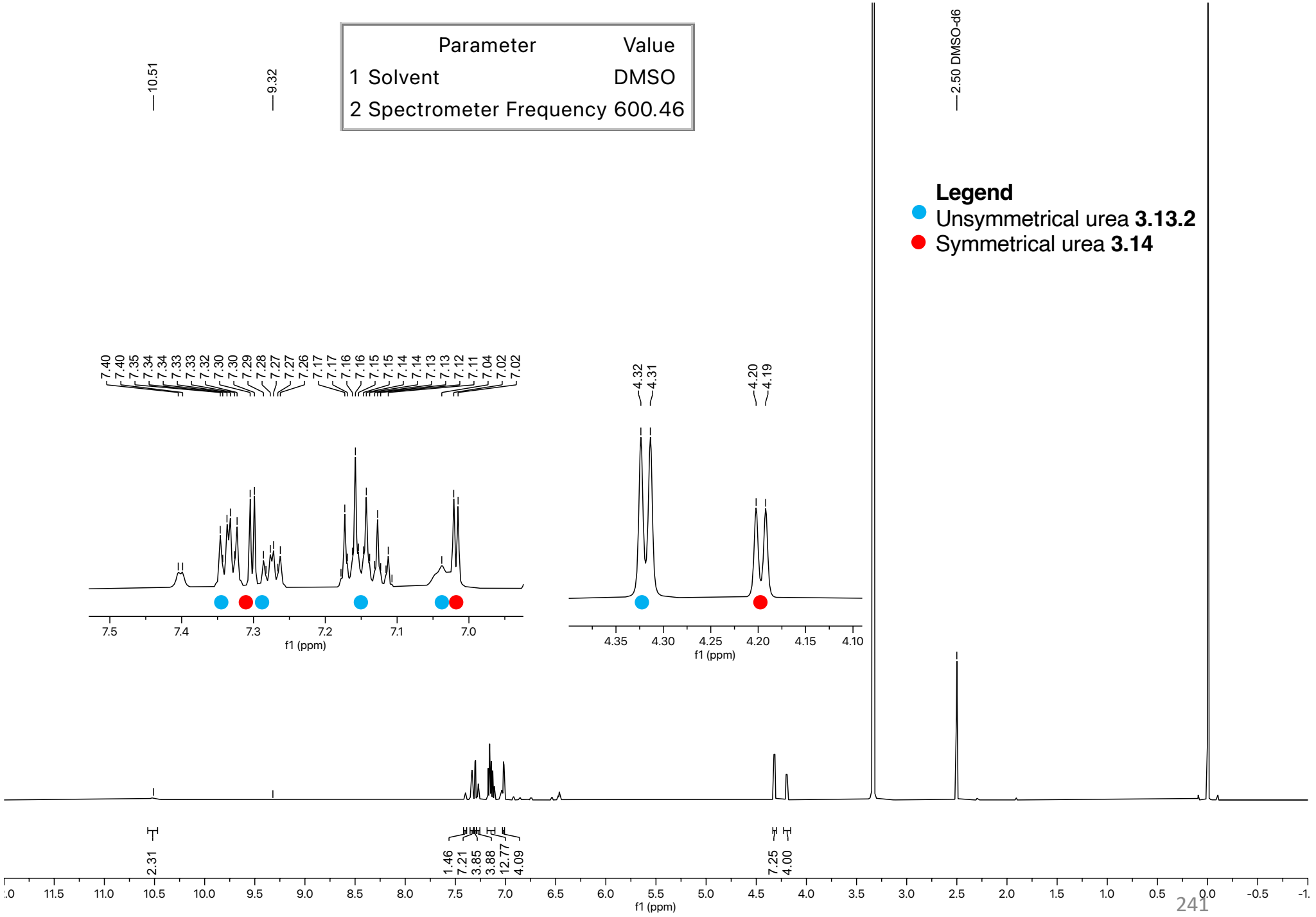
3.11.3

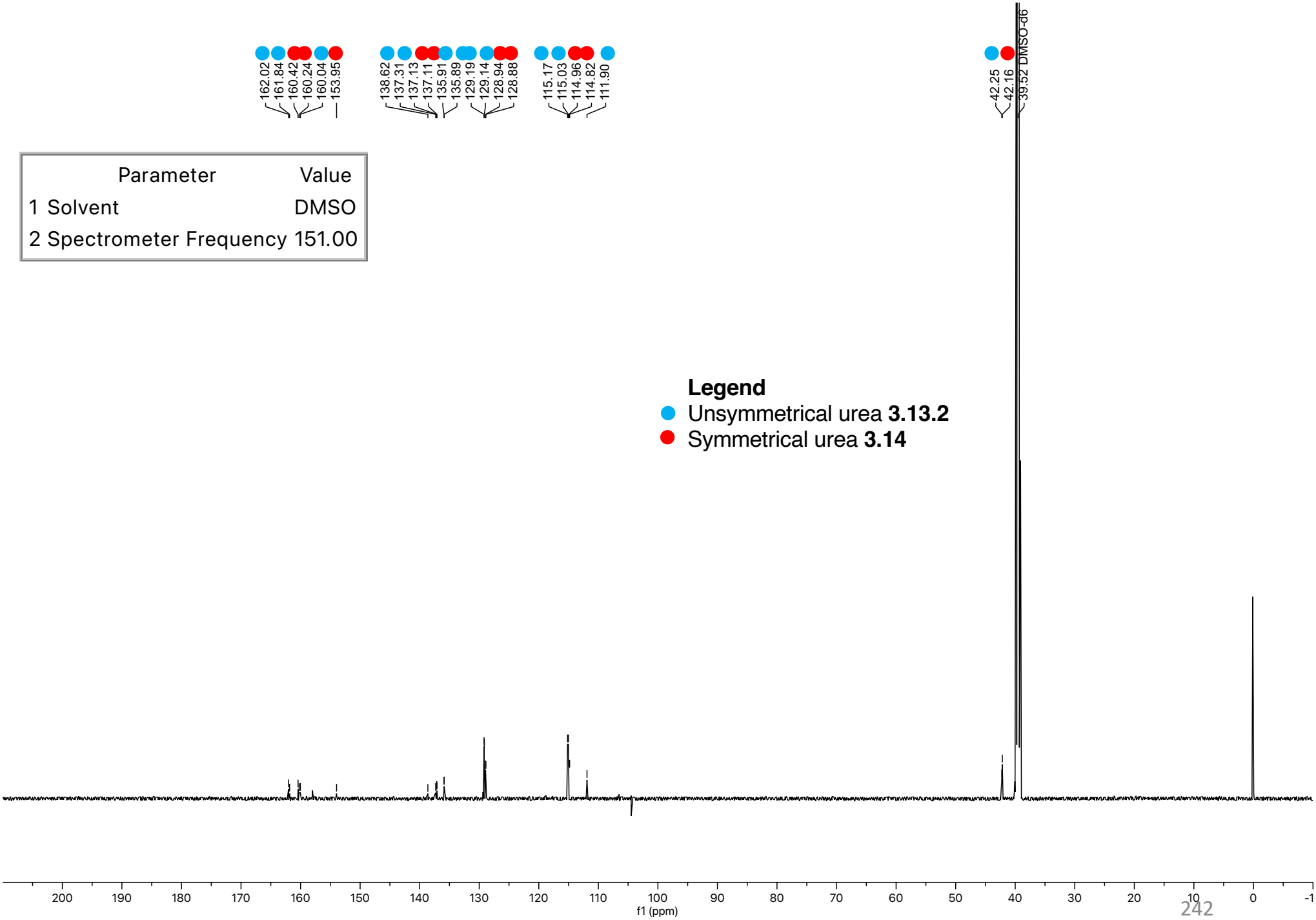
Parameter	Value
1 Solvent	DMSO
2 Spectrometer Frequency	400.32



3.13.1

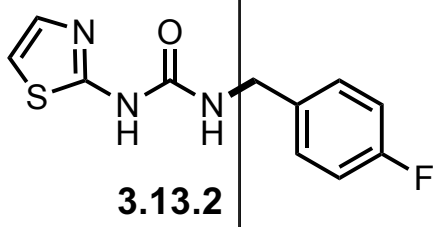

153.74
148.27
140.38
137.13
127.98
125.91
124.75
119.68
83.31
54.33
39.52 DMSO-d6
29.65
Parameter Value
1 Solvent DMSO
2 Spectrometer Frequency 100.67
I
O
N H
N H
Ph
3.13.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Parameter Value
1 Solvent DMSO
2 Spectrometer Frequency 600.46
Legend
Unsymmetrical urea 3.13.2
Symmetrical urea 3.14
10.51
9.32
2.50 DMSO-d6
7.40 7.40 7.35 7.34 7.34 7.33 7.33 7.32 7.30 7.30 7.29 7.28 7.27 7.27 7.26 7.17 7.17 7.16 7.16 7.15 7.15 7.14 7.14 7.13 7.13 7.12 7.11 7.04 7.02 7.02
4.32 4.31 4.20 4.19
f1 (ppm)
2.31 1.46 7.21 3.85 3.88 12.77 4.09 7.25 4.00
f1 (ppm)



	Parameter	Value
1	Solvent	DMSO
2	Spectrometer Frequency	151.00

Parameter	Value
1 Solvent	Acetone
2 Spectrometer Frequency	282.56



3.13.2

-118.01
-118.59

Legend
- Unsymmetrical urea **3.13.2**
- Symmetrical urea **3.14**