Novel Palladium Precatalysts and their Application in Cross-Coupling Reactions and Copper-Catalyzed Enantioselective Ring Formation

By

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B.A. Chemistry
St. Mary's College of Maryland, 2010

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Abstract

Chapters 1 - 3

A series of easily prepared, phosphine-ligated palladium precatalysts based on the 2-aminobiphenyl scaffold have been prepared. The role of the precatalyst-associated labile halide (or pseudohalide) in the formation and stability of the palladacycle has been examined. It was found that replacing the chloride in the previous version of the precatalyst with a mesylate leads to a new class of precatalysts with improved solution stability and that are readily prepared from a wider range of phosphine ligands, including the bulky, electron-rich di-*tert*-butylphosphino biaryl ligands. Additionally, *N*-methyl- and *N*-phenyl analogues have been prepared. These efficacy of these precatalysts were examined in a broad range of C-C, C-N, and C-O bond-forming reactions.

Chapter 4

The intramolecular hydroalkylation of di- and trisubstituted alkenes bearing a pendant alkyl bromide to form stereodefined (hetero)carbocycles is reported. The system is highly regio- and stereoselective and employs a Cu-DTBM-SEGPHOS catalyst and (dimethoxy)methylsilane as the stoichiometric reductant. This intramolecular hydroalkylation reaction provides facile access to a multitude of ring systems and its utility is further demonstrated in the enantioselective synthesis of paroxetine.

Acknowledgements

First and foremost, I would like to thank my parents, Joe Bruno and Sue Kownacki for everything they have done for me. For as long as I can remember they have encouraged me to explore the world in every way I possibly can and did everything in their power to give me a chance to succeed (a special shoutout to my dad for having me computer-literate since 1989). Also a huge thanks to the rest of my family—you guys are one of the most loving and supportive bunch of people in existence.

I would also like to thank Dr. Andy Koch, my undergraduate advisor. I worked with him from 2004, as a junior in high school, until 2010, when I graduated from college. I can say with 100% certainty that I would not be here without his guidance. He instilled a passionate curiosity for science that has not waned and taught me so much more than just science. He is one of the greatest humans this world has to offer.

I would like to thank Prof. Steve Buchwald a thousand times for taking a chance on me that fateful day in January, 2010. Through my time at MIT he has completely changed the way that I think about and approach science. He gave me tremendous amounts of freedom to explore and was the catalyst (see what I did there?) for huge changes in my life. Also, a big thanks to my thesis committee, Prof. Tim Swager and Prof. Tim Jamison for always being willing to chat and being very supportive.

A very special thanks to Prof. Tom Maimone, Prof. Nate Jui, and Dr. Aaron Sather for a whole lot of patience in teaching me how to be a good science writer.

Also, I am very grateful to Dr. Yong Zhang for telling me my idea was dumb in order to motivate me to go do it ASAP. This lead to quite a fruitful start to my PhD. Additionally, a huge thanks to Dr. Yiming Wang. In working with him on copper hydride catalysis, I rediscovered how much I love my job.

I would like to thank every graduate student of the Buchwald lab that I have worked with over the course of the last 5 years—Brett, Todd, Georgiy (a great gym bud and great friend), Pedro, Yang, Spencer, Yuxuan. I'd also like to thank the fantastic group of 8 that I came in with—Phill, Mingjuan, Katya, Nathan, Nootaree, Jim, and Rong. It has been a true pleasure to grow with you guys for the last 5 years. I would also like to thank Paula, one of the best friends I have had in my life. Thank you to everyone I have had the pleasure of working with.

Everyone that I grew up with—Erin, Matt, Cory, Scott, Deirdra, Stephanie, Jesse—friends from college—Taylor, Neil, Anita, Liam, Brim, Julia, Sam. Shane: even you! An Erlenmeyer of biodiesel from the first experiment I ever ran as a scientist is the best gift I have ever received. All of you are fantastic and made me the person I am today. Thank you so much for being supportive and still loving me even though I mostly fell off the face of the earth for the last 5 years. I look forward to seeing all of you this summer.

Lastly, I would like to thank the best 3 roommates a young man could possibly have. John, Brittany, and Amanda, you guys are seriously the greatest. I'm so fond of you all, I honestly don't even know what to write. It really feels like I live with family.

In the most agnostic way possible, I am truly blessed. I love you all.

Preface

This thesis has been adapted from the following published articles co-written by the author:

Bruno, N. C.; Tudge, M.T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4,* 916–920.

Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876–2879.

Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161–4166.

Respective Contributions

Chapter 1 describes the synthesis of 2-aminobiphenylpalladium methanesulfonate precatalysts and their applications in cross-coupling reactions. Dr. Matthew Tudge (Merck) performed the experiments illustrated in Figure 3. Dr. Peter Mueller solved the crystal structures depicted in Figure 4, Figure 5, and Figure 6.

Chapter 2 describes the synthesis of 2-aminobiphenylpalladium methanesulfonate precatalysts bearing extremely bulky di-*tert*-butylphosphino biaryl ligands and their applications in cross-coupling reactions. The author performed all of the experiments and Dr. Peter Mueller solved the crystal structure depicted in Figure 1.

Chapter 3 describes the synthesis of 2-aminobiphenylpalladium methonatesulfonate precatalysts bearing methyl and phenyl substitution on the nitrogen of 2-aminobiphenyl. Nootaree Niljianskul synthesized compounds **6a**, **6c, 7c,** and **6d** in the compounds in Scheme 5. Dr. Peter Mueller solved the crystal structures in Figure 1.

Chapter 4 describes the copper hydride-catalyzed intramolecular hydroalkylation of alkenes in collaboration with Dr. Yiming Wang. Dr. Yiming Wang synthesized compounds **5a, 5b, 5c,** and **5h** in Table 1, **7a, 7b, 7g,** and **7h** in Table 3, compound **10-NTs** in Scheme 2, and performed the optimization reactions in Table 2.

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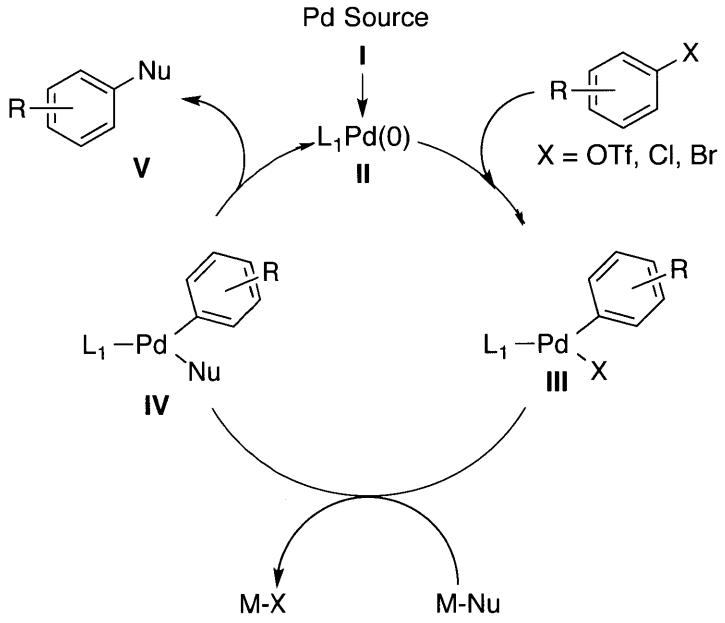
Introduction

Part 1

Palladium-catalyzed cross-coupling reactions have become common tools for C-C and C-X bond formation in academic and industrial settings. A typical catalytic cycle (Scheme 1) begins with oxidative addition into **II**, to form oxidative addition complex **III**. This is followed by transmetallation with a nucleophile to form **IV** and subsequent reductive elimination give product **V** and regenerates **II**.

Scheme 1. Typical catalytic cycle of palladium-catalyzed cross-coupling.



Privileged ligand scaffolds have emerged that can effectively support a vast range of transformations. However, as more complex cross-coupling reactions are developed, the method for generation of the catalytically active $L_nPd(0)$ (**I** to **II** in Scheme 1) is often pivotal to the success of a cross-coupling reaction.

Many traditional palladium sources can have significant problems in generating active catalysts. Stable Pd(0) sources such as $Pd_n(dba)_m$ contain dibenzylideneacetone (dba) ligands that can impede the catalytic cycle. Additionally, common Pd(II) sources such as $Pd(OAc)_2$ and $PdCl_2$ need to be reduced to Pd(0) in situ before entering a Pd(0)-Pd(II) cross- coupling cycle. Other Pd sources such as allyl and $[(cinnamyl)PdCl]_2$ dimers and $Pd(PPh_3)_4$ are thermally unstable.

An increasingly popular solution to the issue of palladium activation is through the use of palladium precatalysts. Precatalysts are generally pre-formed Pd(II) and Pd(0) species such as palladacycles and $Pd[P(tBu)_3]_2$ that exhibit air and moisture stability. Precatalysts activate under general reaction conditions or with external additives to provide the necessary $L_nPd(0)$ species to enter the catalytic cycle.

Part 2

Ligated copper hydride species are powerful catalytic intermediates capable of a wide range of transformations centered on the reduction of π systems. These reactions generally begin with the hydrocupration of the unsaturated species followed by trapping the organocopper intermediate with an electrophile to provide product (Figure 1).

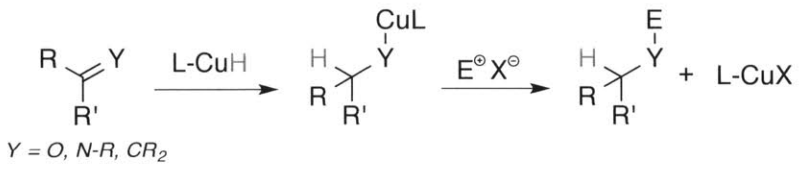


Figure 1. General mode of CuH reactivity.

First reported in 1988, Stryker's Reagent ($[(Ph_3P)CuH]_6$ showed remarkable selectivity in the conjugate reductions of a range of carbonyl derivatives, including unsaturated aldehydes, ketones, and esters. Following these seminal publications, with the proper use of chiral ligands, a number of copper hydride-catalyzed reductions have been performed stereoselectively, e.g. conjugate reductions, the reduction of ketones to alcohols, imines to amines, and the hydroamination of alkynes and alkenes.

The work presented herein is divided into two distinct parts. Chapter 1 – 3 explore the development of 2-aminobiphenylpalladium methanesulfonate precatalysts and their applications in a broad range of cross couplings. Chapter 4 explores the development of the intramolecular, asymmetric hydroalkylation of alkenes to form stereodefined (hetero)carbocycles.

Chapter 1: Design and Preparation of New Palladium Precatalysts for C-C and C-N Cross-Coupling Reactions

1.1: Introduction

Over the past thirty years palladium-catalyzed coupling reactions have become powerful tools for generating carbon–carbon and carbon–heteroatom bonds.[1,2] Key to the success of such couplings is the efficient generation of a phosphine-ligated Pd(0) species to enter into the catalytic cycle. Common commercially available Pd(0) sources such as $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ contain ligands that can interfere with the reaction.[3] Commercial $Pd_2(dba)_3$ has also recently been shown to contain varying amounts of Pd nanoparticles and free dba.[4] To avoid this problem, Pd(II) sources, such as $Pd(OAc)_2$ and $PdCl_2$, are sometimes used, though these must be reduced in situ. Often the efficiency of these reductions is inadequate for a wide range of coupling reactions.

Recently, solutions to the problem of catalyst activation have taken the form of readily activated palladium precatalysts. Many such systems have been reported, including the pyridine-stabilized NHC precatalysts (PEPPSI),[5] ligated allylpalladium chloride precatalysts,[6] imine-derived precatalysts,[7] and the palladacycle-based precatalysts **1** and **2** previously reported by our group (Figure 1).[8,9] Each of these species is a pre-ligated air and moisture stable Pd(II) source, which forms a ligated Pd(0) species in situ when exposed to base.

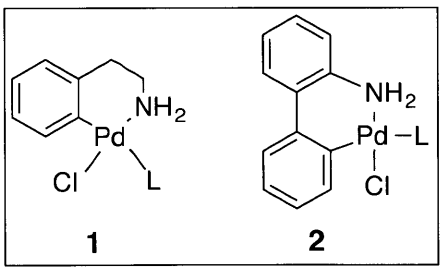


Figure 1. Related precatalysts[8,9] reported by our group.

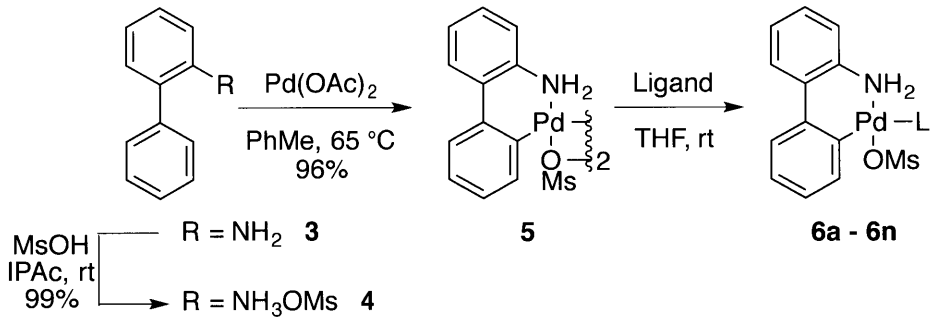
While both we and the Merck Process Group have successfully employed palladacyclic precatalysts in various transformations, those previously reported versions still suffer from drawbacks. For example, the first reported synthesis of **1** required three steps and involved the handling of organometallic intermediates. Recently, Vicente *et al.* reported a deft alternative procedure for the synthesis of **1**, which involved a C–H activation/cyclopalladation sequence starting from $Pd(OAc)_2$.[10–12] However this procedure also required the use of triflic acid and an additional ion exchange step.

In 2010 we developed a class of biarylamine-derived precatalysts **2** as a more convenient alternative to **1**. A similar C–H activation/cyclopalladation sequence, as discovered by Albert *et al.*,[13,14] also provides access to precatalyst **2** in a one-pot procedure from $Pd(OAc)_2$ which does not require the handling of any organometallic intermediates. Precatalysts of type **2**, however, cannot be generated with larger ligands such as *t*BuXPhos and BrettPhos. Additionally, these precatalysts are not stable in solution for extended periods of time. Thus, access to a precatalyst system with enhanced stability and broader range of ligands would be highly desirable. Herein we report the development of a series of novel precatalysts based on a cyclopalladated 2-aminobiphenylmesylate backbone.

1.2: Results and Discussion

We postulated that precatalysts related to **2** that incorporated larger ligands might be accessible by rendering the Pd(II) center more electron-poor *via* replacement of the

chloride with a more electron-withdrawing species. Additionally, we thought that a non-coordinating anion could allow for the incorporation of larger ligands by making the palladium center less sterically encumbered. After evaluating a variety of halides and pseudohalides, it was ultimately found that palladium precatalysts analogous to **2** with the chloride replaced by a methanesulfonate group (Scheme 1, **6a–6n**) could be readily prepared with both BrettPhos and *t*BuXPhos. Moreover, this new class of precatalyst allowed us to meet our secondary goal: to retain the ease of preparation and stability of precatalysts of general structure **2**. As detailed in Scheme 1, μ-OMs dimer **5** is generated in high yield from commercially available 2-aminobiphenyl **3** *via* a sequence involving mesylate salt formation and cyclopalladation. To demonstrate the practicality of this process, the reaction was performed with 315 g of mesylate salt **4** to afford 417 g μ-OMs **5** (96% yield) after isolation directly from the reaction mixture. Reactions of a wide array of synthetically important ligands with μ-OMs **5** in THF or dichloromethane proceed smoothly (15–45 minutes) to afford the desired palladacycle precatalyst **6**.



Scheme 1. Preparation of palladium methanesulfonate precatalysts.

Because of their versatility and broad applicability as ligands for palladium-catalyzed reactions, **L1–L14** (Figure 2) were selected as an ideal set of ligands to test for compatibility with our mesylate precatalyst structure **6**. We found that all of the ligands in combination with **5** afforded precatalysts **6a–6n** in excellent yields with short reaction times. In fact, due to their high solubility and fast rate of formation, precatalysts **6a–6n** can also be prepared and used in situ, directly from μ-OMs dimer **5**. This operationally facile process should allow for rapid testing of an array of ligands for a desired chemical transformation using a single palladium precursor.

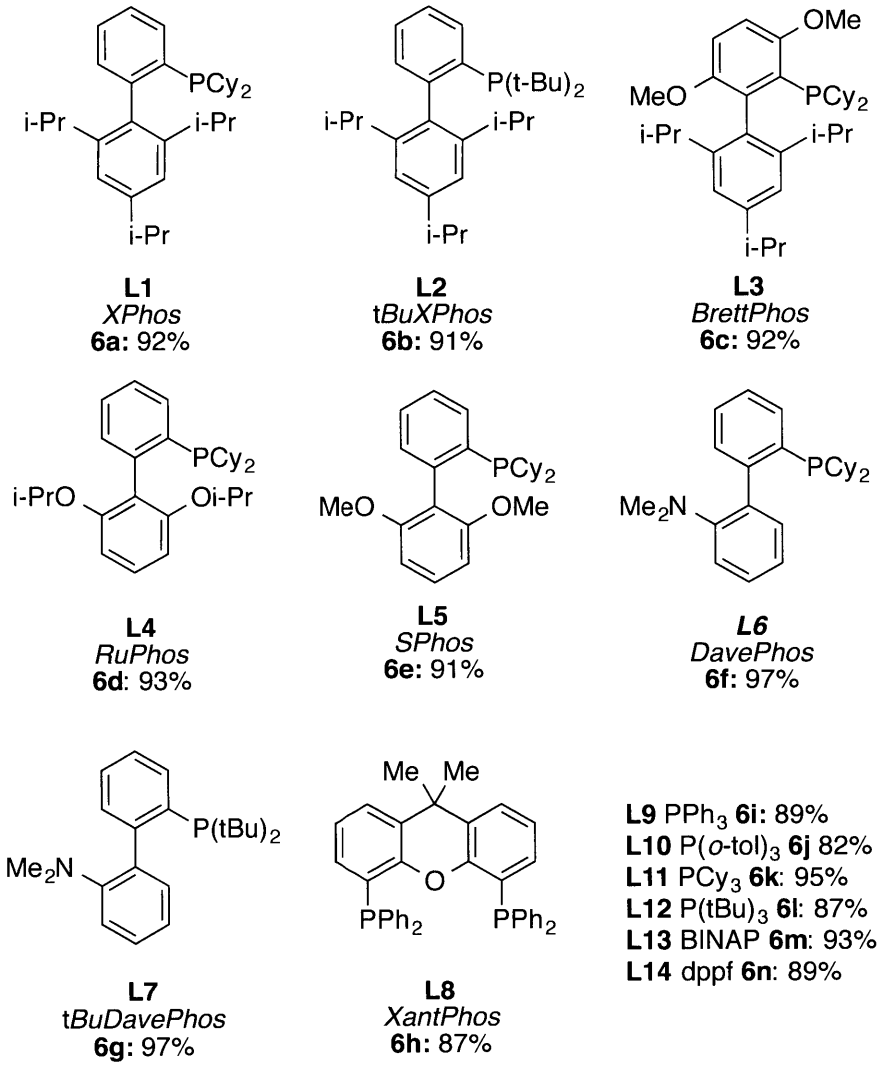


Figure 2. Ligands from which precatalyst **6** was prepared and isolated yields of precatalysts.

In order to investigate the role of the mesylate anion leading to the broader scope of ligands that can be incorporated into precatalysts **6**, we carried out ^{1}H NMR studies of d^5-pyridine complexes derived from μ-dimers **5** and **7**. As shown in Figure 3, treatment of 0.05 mmol samples of μ-dimers **5** and **7** with 10 μL of d^5-pyridine in 0.75 mL CD_2Cl_2 afforded the d^5-pyridine complexes **8** and **9** in situ. The resonance for the NH_2 group of complex **9** is shifted downfield by 0.76 ppm units relative to that of complex **8**, suggesting a more electron deficient palladium center is present in **9**.

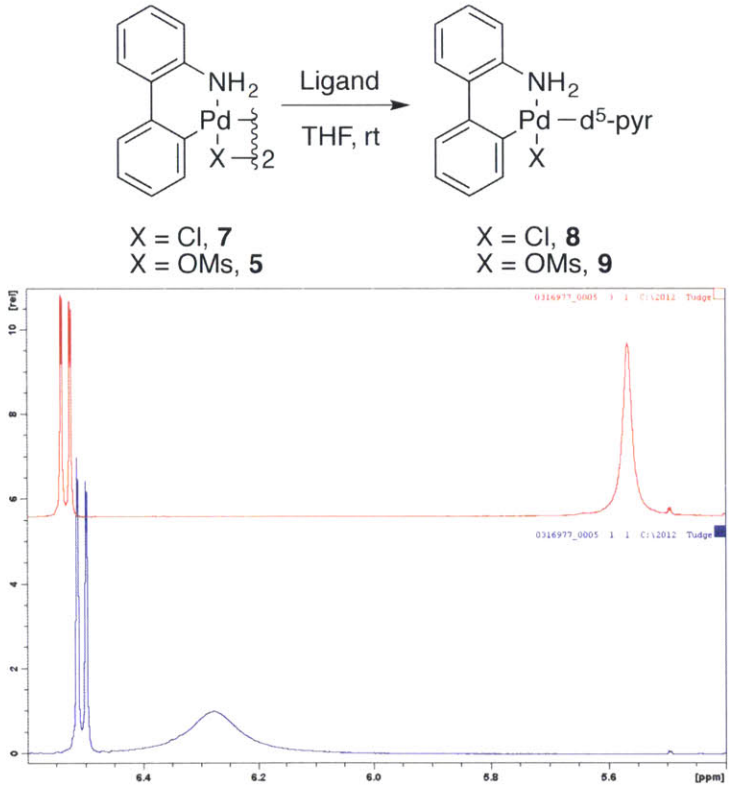


Figure 3. ^{1}H spectra of in situ generated **8** and **9** showing a downfield shift of the amine protons of 0.76 ppm for **9** relative to **8**.

Single crystal X-ray crystal structures of precatalyst **2** with **L1** as the supporting ligand, **2·L1**, **2** with BINAP as the supporting ligand, **2·L13**, and precatalysts **6a**, **6b**, **6c**

and **6m** provide additional structural evidence suggesting enhanced electrophilicity of the palladium mesylate center. All of these complexes feature a tetracoordinate palladium(II) center with slightly distorted square planar geometries. In the case of **2·L1**, **6a**, **6b**, and **6c** the 2-aminobiphenyl ligand chelates the palladium center and in each species the phosphine ligand is in the *cis* conformation relative to the aryl moiety of the 2-aminobiphenyl carbon bound to palladium. It is also worth noting that in each of these species the corresponding Pd–P, Pd–N and Pd–C bond lengths are nearly identical to each other between the four complexes. In **2·L1** and **6a** the chloride and mesylate anions are bound to palladium with bond lengths of 2.412 Å and 2.184 Å respectively (Figure 4). While the two species are structurally very similar, preliminary *in silico* studies indicate that the palladium center in **6a** is a more electron deficient species.[15]

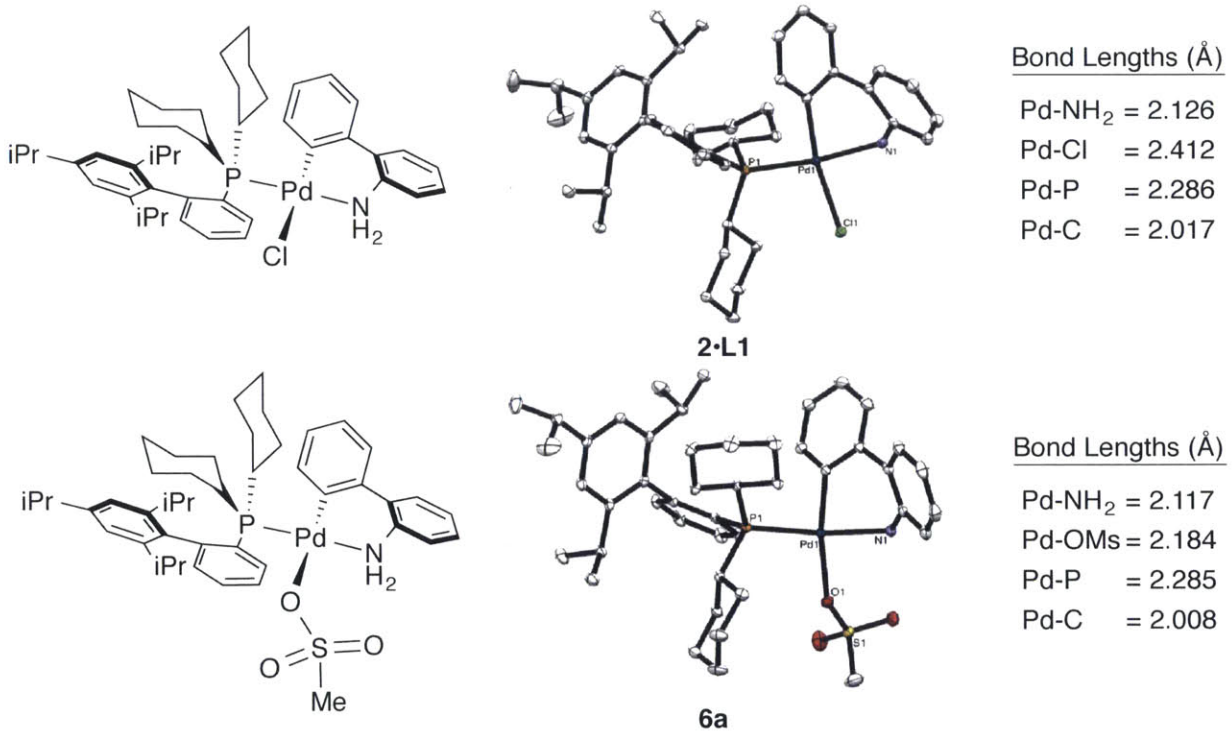


Figure 4. Crystallographically-determined X-ray structure representations of **6a** and **2·L1** and relevant bond lengths (thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted)

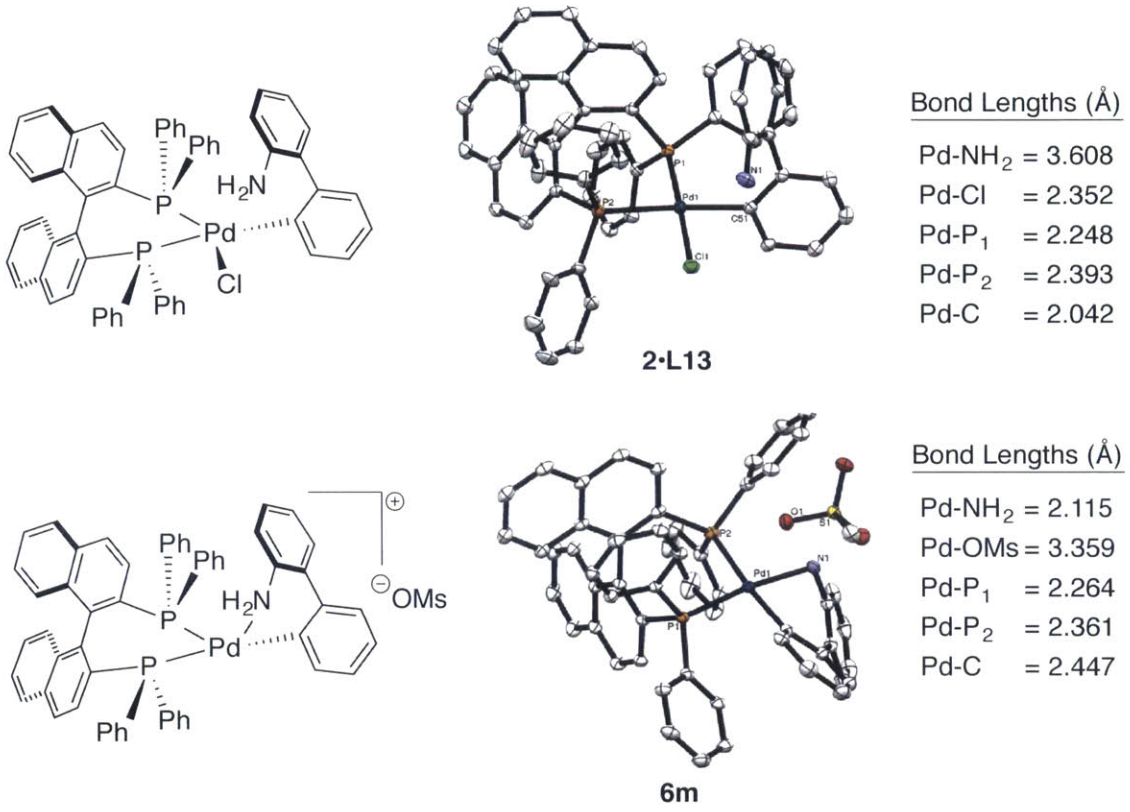


Figure 5. Crystallographically determined X-ray structure representations of **2·L13** and **6m** and relevant bond lengths (thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted.)

The differences between **2** and **6** are pronounced in chelating bis-phosphines. In **6m** both phosphines of the BINAP ligand are coordinated to the palladium center with the mesylate anion dissociated (Pd–O bond distance = 3.359 Å) (Figure 5). This is in contrast to **2·L13**, where chloride ligand does not dissociate and remains bound to the palladium center, while the amine moiety of the 2-aminobiphenyl ligand is displaced by one of the phosphine groups of the BINAP ligand. That one of the phosphines of BINAP and the 2-amino group are hemilabile in **2·L13** is seen in its ^{31}P NMR spectrum in chloroform, where two rapidly exchanging species (one sharp doublet at 15 ppm (J_{P-P} = 15.3) and a broad singlet at 36 ppm) are observed.

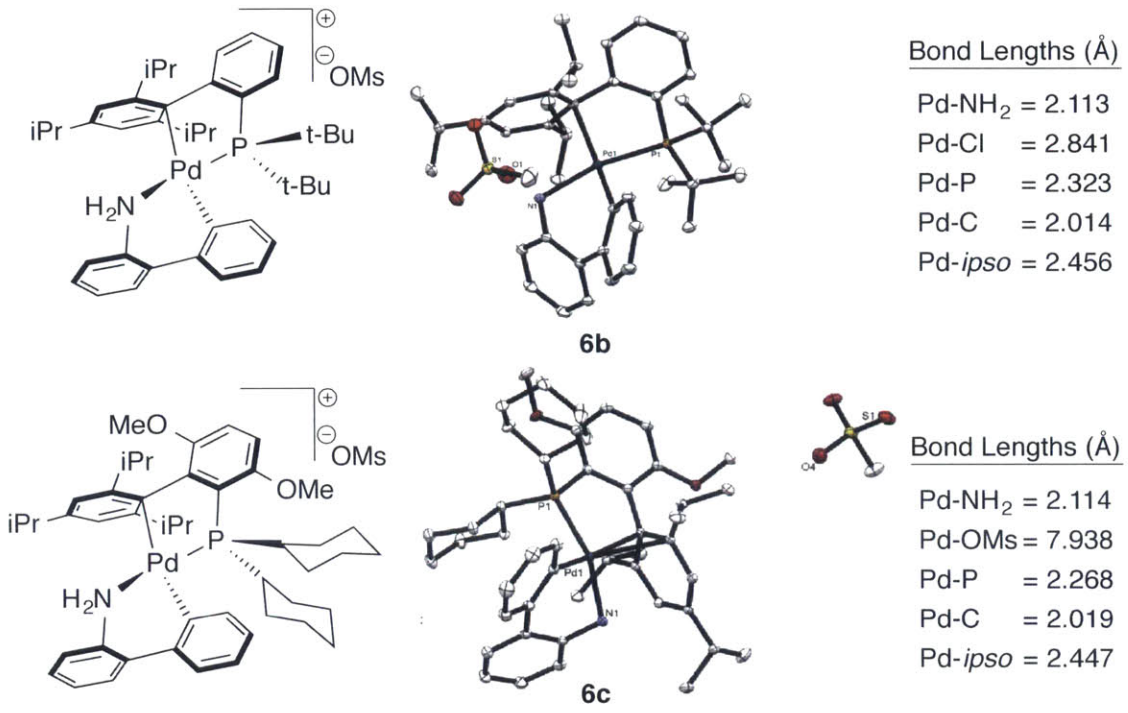


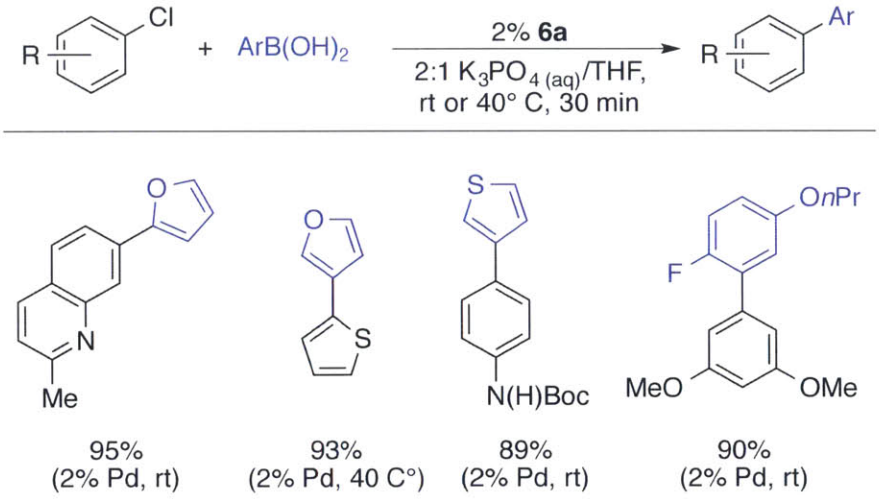
Figure 6. Crystallographically determined X-ray structure representations of **6b** and **6c** and relevant bond lengths (thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted.)

Examining the structures of **6b** and **6c**, precatalysts of which the analogous **2** cannot be made (Figure 6), the mesylate anion dissociates from palladium, allowing the palladium center to accommodate the very bulky ligands **L2** and **L3**. To occupy the fourth coordination site left vacant by the dissociated mesylate the palladium coordinates to the *ipso* carbon of the of the triisopropylphenyl ring. It is likely that **6** can accommodate these larger ligands while **2** cannot due to the inability of the chloride to dissociate from the palladium center while the mesylate anion can.

With a series of mesylate precatalysts **6** in hand, we examined their efficiency in various cross-coupling reactions. Biaryl phosphine ligand **L1** (XPhos) has seen application in a broad range of transition metal-catalyzed C–C and C–N bond forming processes.[16–18] To test the utility of XPhos precatalyst **6a**, we evaluated its performance

in the Suzuki–Miyaura coupling of unstable boronic acids that are extremely prone to protodeboronation.[9] The success of this coupling process, as reported, was dependent on the extremely fast activation of the XPhos precatalyst of type **2** at room temperature in conjunction with its high level of catalytic activity. With the analogous XPhos-derived mesylate precatalyst **6e**, unstable boronic acids could be coupled with electron-rich, sterically hindered, and heteroaryl chlorides under mild conditions (rt → 40° C) with short reaction times (30 minutes) and in high yields similar to the previously reported results (Table 1).

Table 1. Suzuki-Miyaura coupling of boronic acids prone to rapid protodeboronation with **6a**[a]

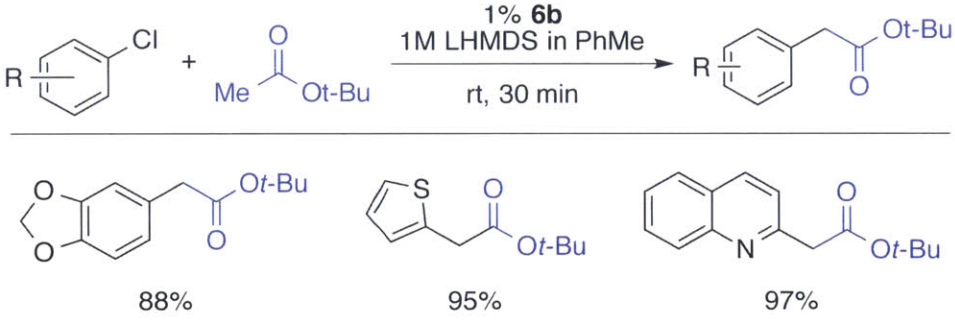


[a] Aryl chloride (1 mmol), boronic acid (1.5 mmol), precatalyst **6a** (2%), THF (2 mL) 0.5 M aq. K_3PO_4 (4 mL); average isolated yield of two runs.

The *t*-butyl-substituted version of **L1**, **L2** (*t*BuXPhos), has also been utilized in a range of transformations including vinyl trifluoromethylations,[19] α-arylations,[20] the amination of heteroaryl halides,[21] and arylation of sulfonamides.[22] In 2008 the α-

arylation of *t*-butyl acetate with aryl halides in the presence of LHMDS and precatalyst **1** with *t*BuXPhos as the ligand was reported. Using precatalyst **6b** the α-arylation of *t*-butyl acetate could be achieved in excellent yields employing both aryl and heteroaryl chlorides (Table 2).

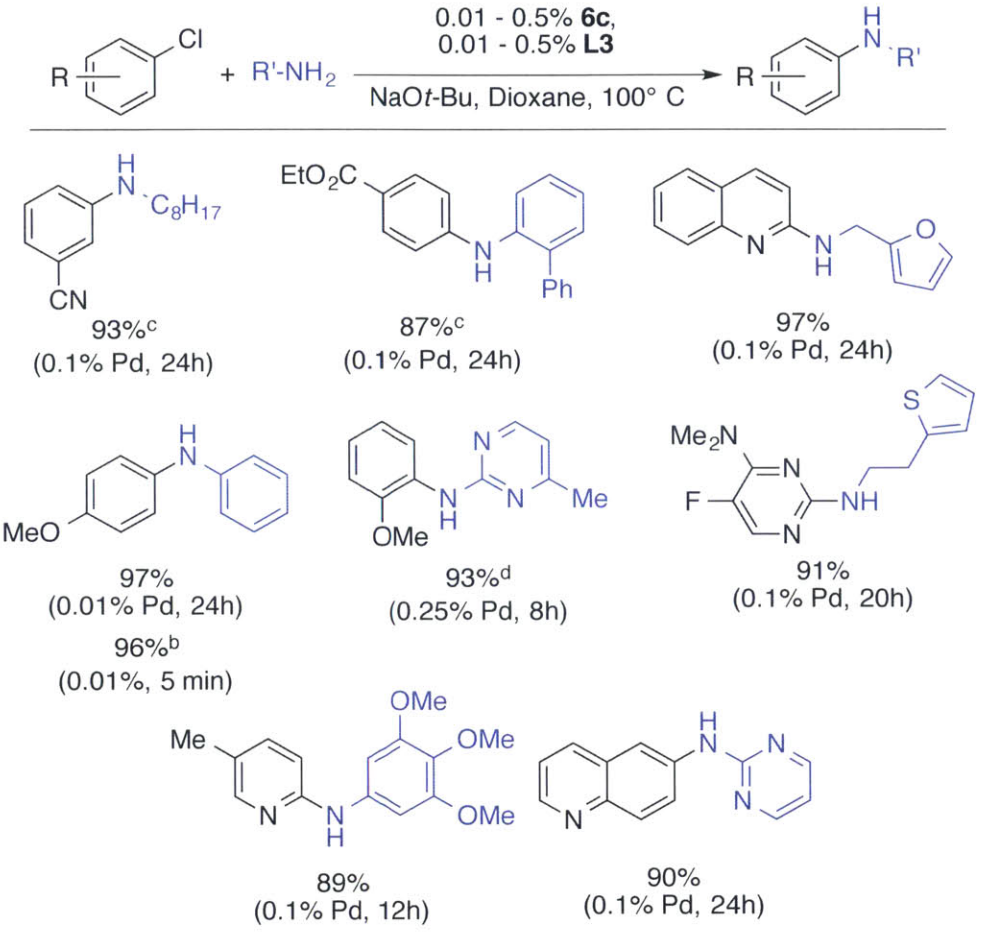
Table 2. Arylation of *tert*-butyl acetate catalyzed by **6b** at room temperature[a]



[a] Aryl chloride (0.5 mmol), *t*BuOAc (0.75 mmol), 1M LHMDS (1.5 mL), **6b** (1 mol%); average isolated yield of two runs.

Palladium-catalyzed C–N coupling reactions are powerful tools in both industry and academia. Recent work by our group has shown **L3** and **L4** to be highly efficient supporting ligands for Pd in the coupling of primary amines and secondary amines, respectively.[23–25] Novel palladacycle precatalysts **6c** and **6d** are also extremely effective in the coupling of primary (Table 3) and secondary (Table 4) amines with aryl halides, even at very low catalyst loadings, and display activity comparable to that of the previous generation precatalysts of type **1** and **2** (for **L4**).

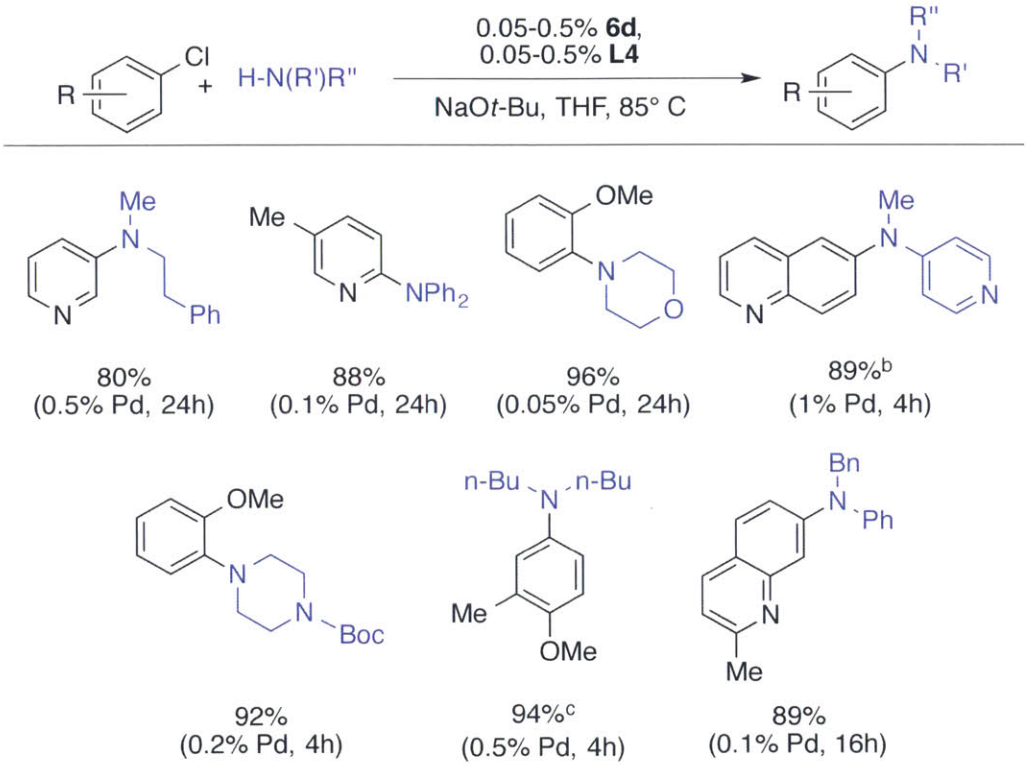
Table 3. Arylation of primary amines with **6c**/**L3**



[a] Aryl chloride (1 mmol), amine (1.2 mmol), NaO*t*-Bu, (1.2 mmol), **6c** (0.01–0.5%), **L3** (0.01–0.5%), dioxane (1 mL) 100 °C. [b] Aryl iodide (1 mmol), amine (1.4 mmol), NaO*t*-Bu, (1.4 mmol), toluene (1 mL) 100 °C. [c] Cs_2CO_3 was used as the base. [d] *t*-BuOH was used as the solvent; average isolated yields of two runs.

$Pd_2(dba)_3$ as palladium sources. Vials of palladium source and ligand were aged for ten minutes in 1 mL of THF and directly added to a reaction tube containing the aryl halide and boronic acid, followed by the addition of base. The results of this study clearly indicate that XPhos is the optimal ligand for this transformation, with the catalyst based on RuPhos also showing moderate activity. The μ-OMs dimer is optimal as the palladium source, with the chloride and acetate dimers showing some activity. The use of $Pd(OAc)_2$ and $Pd_2(dba)_3$ under these conditions provided little product.

Table 4. Arylation of secondary amines with **6d**/**L4**

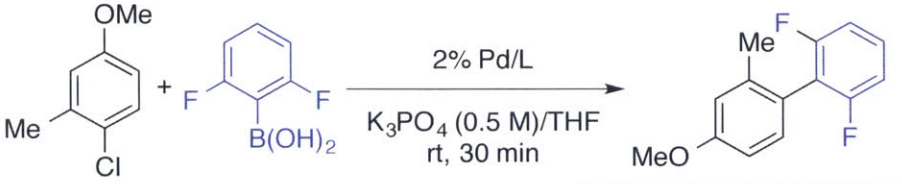


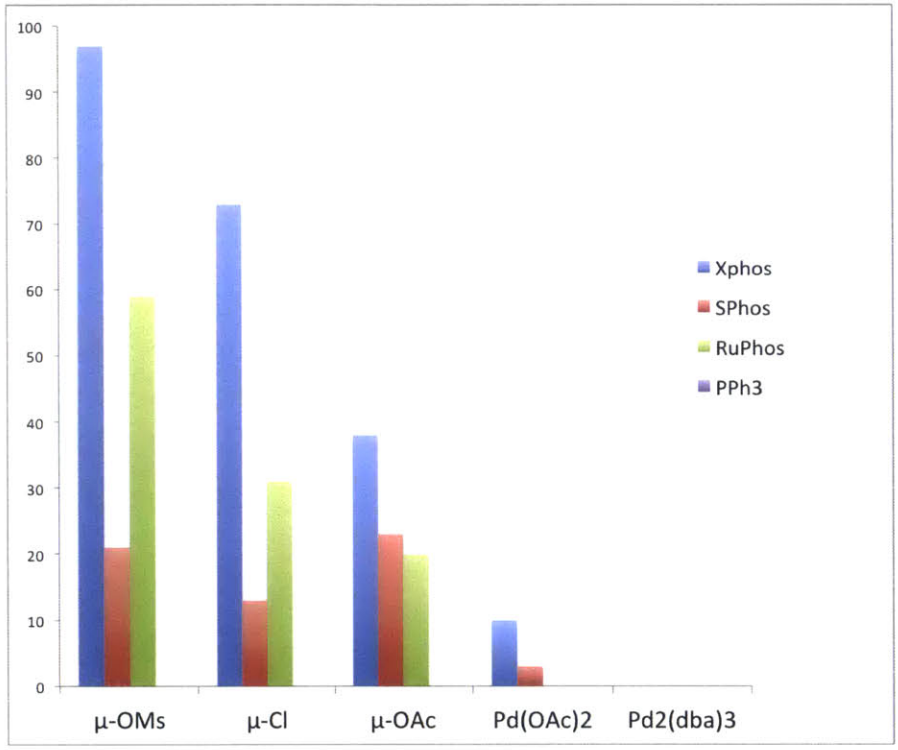
[a] Aryl chloride (1 mmol), amine (1.2 mmol), NaO*t*Bu (1.2 mmol), THF (1 mL), 85 °C. [b] **6a**/**L1** is used. [c] ArBr is used; average isolated yield of two runs.

1.3: Conclusions

In conclusion we have developed a new series of palladium precatalysts based on the 2-aminobiphenyl mesylate palladacycle **5**. These precatalysts can be prepared with a broad range of phosphine ligands in a facile and straightforward way and can be activated under mild conditions to generate the desired LPd(0) species. These precatalysts are all obtained in high yields from common intermediate **5**, which can be

Table 5. Screening of ligands and palladium sources for in situ precatalyst generation in the Suzuki-Miyarua coupling of a boronic acid prone to rapid protodeboronation.





[a] 1 mol% Pd, 1 mol% ligand aged 10 min in 1 mL THF, then ArCl (0.50 mmol), boronic acid (0.75 mmol), $K_3PO_{4\,(aq)}$ (1.0 mmol, 0.5 M), rt, 30 min. Yields determined by ^1H NMR using 1, 3, 5-trimethoxybenzene as an internal standard.

synthesized from readily available starting materials in a three-step process, which avoids rigorous Schlenk techniques. We anticipate that these precatalysts will considerably improve the scope of palladium-catalyzed cross-coupling reactions.

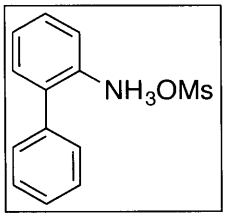
1.4: Experimental

General: Reagent Information THF, Et_2O, CH_2Cl_2, and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF and Et_2O) or through neutral alumina and copper (II) oxide (for toluene and CH_2Cl_2). All reagents and solvents were purchased and used as received unless otherwise noted. The 0.5 M K_3PO_4 solution was prepared by dissolving K_3PO_4 (10.6 g, 50 mmol) in deionized water (100 mL) and degassed by performing several evacuation/argon refill cycles under sonication prior to use. 2-Aminobiphenyl (97%) was purchased from Aldrich Chemical Co. Methanesulfonic acid (98%) was purchased from Fluka Chemicals. 2-Furanylboronic acid and 3-thienylboronic acid were purchased from Aldrich Chemical Co. Palladium acetate was received a gift from BASF and Strem. XPhos was received as a gift from Saltigo. t-ButylXPhos was received as a gift from Strem. (±)-BINAP was received as a gift from Rhodia. RuPhos, SPhos and XantPhos were purchased from Aldrich Chemical Co. BrettPhos was received as a gift from Aldrich Chemical Co. Aryl halides, amines, and arylboronic acids were purchased from Aldrich Chemical Co, Alfa Aesar, Acros Organics, Frontier Scientific, or TCI America and used as received. Anhydrous cesium carbonate was purchased from Strem. Sodium t-butoxide was purchased from Aldrich Chemical Company. The bases were stored in a nitrogen- filled glovebox and were taken out in small quantities and stored in a desiccator on the bench top for up to two weeks. Flash chromatography was performed with SiliCycle SiliaFlash® F60 silica gel.

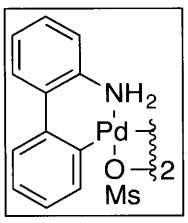
General: Analytical Information. Compounds were characterized by ^1H NMR, ^{13}C NMR, and ^{31}P NMR (where applicable). Copies of the ^1H, ^{13}C, and ^{31}P NMR spectra can be found at the end of the Supporting Information. Proton and carbon Nuclear Magnetic Resonance spectra were recorded on a Varian 500 MHz instrument. Phosphorus Nuclear Magnetic Resonance spectra were recorded on a Varian 300 MHz instrument. All ^1H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm), methanol (3.31 ppm), or acetonitrile (1.94 ppm)

in the deuterated solvent. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), methanol (49.00 ppm) or acetonitrile (118.26 ppm) and all were obtained with ^{1}H decoupling. All ^{31}P NMR spectra are reported in ppm relative to 85% aq. phosphoric acid (0.00 ppm). All GC analyses were performed on an Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column.

General: Procedural Information



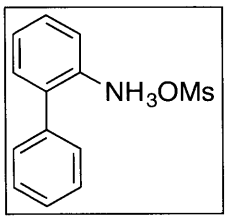
2-Ammoniumbiphenyl methanesulfonate: A 300 mL round-bottomed flask equipped with a magnetic stir bar was charged with 2-aminobiphenyl (5.07 g, 30.0 mmol, 1.0 equiv) and diethyl ether (100 mL). A solution of methanesulfonic acid (1.94 mL, 30.0 mmol, 1.0 equiv) in diethyl ether (15 mL) was added slowly and the mixture was stirred for 30 min. The reaction mixture was then filtered, washed with diethyl ether (3x15 mL) and dried under vacuum to provide the title compound as a white solid. **Yield**: 7.81 g, 97%. **^{1}H NMR** (300 MHz, CD_3OD) δ 7.64 - 7.40 (m, 9H), 4.93 (s, 2H), 2.68 (s, 3H) ppm. **^{13}C NMR** (126 MHz, CD_3OD) δ 137.35, 136.48, 131.80, 129.46, 129.18, 129.14, 129.02, 128.70, 127.88, 123.91, 38.36 ppm. **IR** (neat, cm^{-1}): 3033, 1482, 1229, 1126, 774, 763, 701.



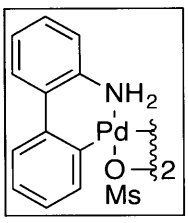
μ-OMs Dimer 5: A 300 mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum was charged with 2-ammoniumbiphenyl mesylate (7.89 g, 30.0 mmol, 1.00 equiv) and palladium acetate (6.72 g, 30.0 mmol, 1.00 equiv). After ensuring the solids were finely divided, toluene (120 mL) was added. The mixture was stirred at 50 °C for 45 min or until it became milky and off-white in appearance. After being allowed to cool to room temperature the suspension was diluted with diethyl ether, filtered, washed with toluene (25 mL) and diethyl ether (3x25 mL), and dried under vacuum for 24 hours to provide the title compound as an off-white to tan solid. **Yield**: 10.2 g, 92%. **^{1}H NMR** (500 MHz, CD_3CN) δ 7.63 - 7.59 (m, 1H), 7.47 (dd, J = 7.6, 1.6 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.32 - 7.25 (m, 2H), 7.22 (dd, J = 7.8, 1.1 Hz, 1H), 7.17 (td, J = 7.4, 1.2 Hz, 1H), 7.08 (td, J = 7.5, 1.6 Hz, 1H), 6.49 (bs, 2H), 2.56 (s, 3H) ppm. **^{13}C NMR** (126 MHz,

CD_3CN) δ 139.53, 139.09, 137.08, 136.70, 135.94, 128.13, 128.09, 127.39, 126.49, 126.32, 125.44, 120.83, 39.33 ppm. **IR** (neat, cm^{-1}): 3259, 3210, 1571, 1497, 1425, 1233, 1104, 1023, 760, 739, 590. Anal. Calcd. for $C_{13}H_{13}NO_3PdS$: C, 42.23; H, 3.54. Found: C, 42.51; H, 3.63.

Procedure for large-scale preparation of *μ*-OMs dimer

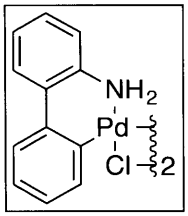


2-Ammoniumbiphenyl mesylate: To a 3- necked round-bottomed flask fitted with a mechanical stirrer, nitrogen inlet and addition funnel was added isopropyl acetate (2.5 L) and 2-aminobiphenyl (500 g, 3 mol 1 equiv). The reaction was aged for 30 minutes until the 2-aminobiphenyl was almost completely dissolved. The reaction was then cooled to 10 °C and methanesulfonic acid added (192 mL, 3 mol, 1 equiv) over 30 minutes. The reaction was aged for 2 h after which time the resultant white solid was collected by filtration and washed with isopropyl acetate (2 x 150 mL). The solid was dried by pulling N_2 through the cake for 24 h with intermittent agitation of the solid. **Yield**: 779 g, 99%. **^{1}H NMR** (500 MHz, CD_3CN) δ 7.62 - 7.56 (1H, m), 7.45 (1H, dd, *J* = 7.5, 1.6), 7.38-7.36 (1H, m), 7.30-7.25 (2H, m), 7.20-7.15 (2H, m), 7.07 (1H, td, *J* = 7.5, 1.6), 6.1 (2H, br s), 2.53 (3H, s).



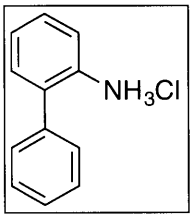
μ-OMs Dimer 5: To a nitrogen flushed 3-necked round-bottomed flask fitted with a thermocouple and mechanical stirrer was added toluene (2.1 L). The toluene was sparged with N_2 for 30 minutes before adding 2-ammoniumbiphenyl mesylate (315 g, 1.186 mol, 1.01 equiv) and palladium acetate (264 g, 1.175 mol, 1.00 equiv) under a gentle flow of N_2. The dark orange slurry was heated to 65 °C for 1.75 h after which time the slurry changed from brown to light yellow in color. The reaction was cooled to 18 °C and treated with methyl *t*-butyl ether (0.5 L). The resultant solid was collected via filtration and the cake washed with 500 mL of 1:1 toluene / methyl *t*-butyl ether. The solid was dried by pulling N_2 through the cake for 24 h with intermittent agitation of the solid . **Yield**: 417 g, 96%. **^{1}H NMR** (500 MHz, CD_2Cl_2 / d^5-pyr) δ 7.62 (1H, dd, *J* = 7.6, 1.3), 7.46 (1H, dd, *J* = 7.6, 1.5), 7.34 (1H, dd, *J* = 7.6, 1.3), 7.27 (1H, td, *J* = 7.5, 1.3), 7.21 (1H, td, *J* = 7.5, 1.3), 7.11 (1H, td, *J* = 7.5, 1.2), 6.87 (1H, td, *J* = 7.6, 1.5), 6.51 (1H, td, *J* = 7.6, 1.2), 6.28 (2H, br. s), 2.58

(3H, s) ppm.

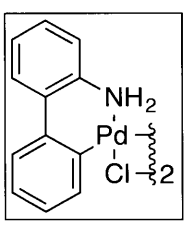


μ-Cl Dimer 7: A 24 mL test tube equipped with a magnetic stir bar and fitted with a Teflon septum was charged with 2-ammoniumbiphenyl chloride (205 mg, 1.00 mmol, 1.00 equiv) and palladium acetate (224 mg, 1.00 mmol, 1.00 equiv). The tube was evacuated and backfilled with argon, after which anhydrous acetonitrile (5 mL) was added. The mixture was stirred at 40 °C overnight, until becoming a milky suspension. After cooling to room temperature the reaction mixture was diluted with diethyl ether (20 mL) and pentane (10 mL), filtered, and washed with diethyl ether (2x10 mL). It was then dried under vacuum for 24 hours to provide the title compound as an off-white solid. **Yield**: 272 mg, 88%. **^{1}H NMR** (500 MHz, DMSO-d^6) δ 7.55 (dd, *J* = 13.9, 9.9 Hz, 1H), 7.49 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.46 - 7.35 (m, 2H), 7.22 - 7.08 (m, 4H), 6.37 (s, 1H) ppm. **^{13}C NMR** (126 MHz, DMSO-d^6) δ 148.71, 141.33, 139.70, 138.16, 137.30, 136.17, 128.17, 128.11, 126.38, 125.81, 125.57, 121.59 ppm. **IR** (neat, cm^{-1}): 3255, 3115, 1568, 1495, 1416, 1113, 1029, 940, 776, 698.

Procedure for large-scale preparation μ-Cl dimer



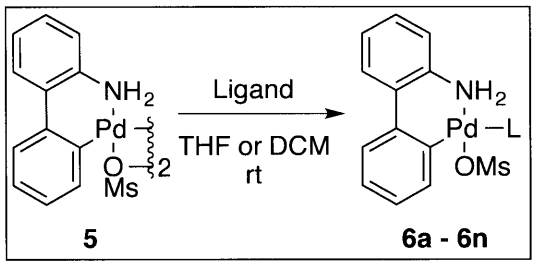
2-Ammoniumbiphenyl chloride: Isopropyl acetate (600 mL) was added to a 1 L 3-necked, round-bottomed flask fitted with a mechanical stirrer, N_2 inlet, and thermocouple. To this was added methanol (35.9 mL, 0.866 mol) followed by trimethylsilyl chloride (85 mL, 0.665 mol). The solution was aged at 22 °C for 1 h before adding 2-aminobiphenyl (75 g, 0.443 mol). The 2-aminobiphenyl hydrochloride formed a thick slurry which was stirred continuously for 3 h. The solid was collected by filtration, washed with IPAc (3 x 100 mL) and dried via pulling N_2 through the cake for 24 h. **Yield**: 90 g, 99%. **^{1}H NMR** (500 MHz, CD_3CN) δ 7.59 - 7.54 (1H, m), 7.46-7.37 (1H, m), 7.32-7.20 (4H, m), 7.15-7.02 (2H, m), 5.55-5.39 (2H, br d) ppm.



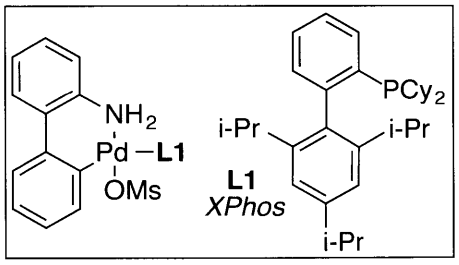
μ-Cl Dimer 7: To a 3-necked round-bottomed flask fitted with an overhead stirrer, N_2

inlet and thermocouple was added 2-aminobiphenyl hydrochloride (99.9 g, 0.486 mol) and THF (1000 mL). The solution was sparged with N_2 for 10 minutes before adding palladium acetate (109 g, 0.486 mol). The slurry was heated to 60 °C for 75 minutes before cooling to 20 °C at which point a thick precipitate formed. Heptane (500 mL) was added over 5 minutes and the slurry was aged for 15 minutes. The solid was collected by filtration and washed with 2:1 THF / heptane (2 x 500 mL) then MeOH (500 mL). The pale yellow solid was then dried for 24 h by pulling N_2 through the cake. **Yield**: 149 g, 94%. **^{1}H NMR** (500 MHz, CD_2Cl_2 / d^5-pyr) δ 7.64 (1H, dd, J = 7.6, 1.4), 7.50 (1H, dd, J = 7.7, 1.5), 7.30 (2H, m), 7.23 (1H, td, J = 7.5, 1.6), 7.13 (1H, td, J = 7.4, 1.2), 6.86 (1H, td, J = 7.7, 1.6), 6.53 (1H, dd, J = 7.6, 1.2), 5.57 (2H, br. s) ppm.

General Procedure A: Precatalyst preparation

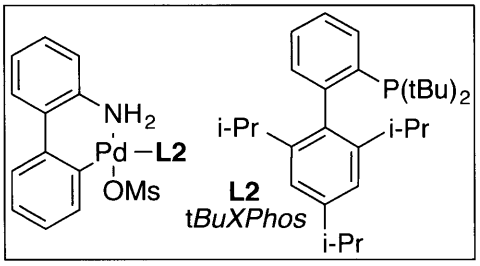


A screw-top test tube, equipped with a magnetic stir bar and fitted with a Teflon screw-cap, was charged with μ-OMs dimer **5** (370 mg, 0.50 mmol, 0.50 equiv) and ligand (1.00 mmol, 1.00 equiv). THF or DCM (5 mL) was added and the reaction was stirred for 15 min to 1 h. The reaction progress was monitored by ^{31}P NMR, observing the disappearance of free ligand signal and appearance of the precatalyst signal downfield. After completion, the reaction mixture was transferred to a scintillation vial and the solvent was removed under vacuum at room temperature until ~10% remained. The residue was then precipitated and triturated with pentane. The resulting solid was isolated via filtration and further dried under vacuum.

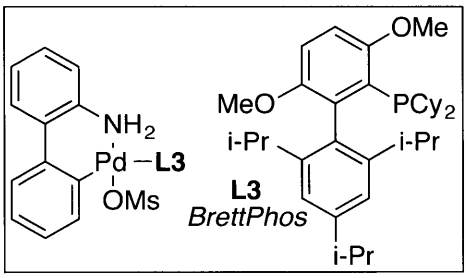


Precatalyst 6a: General procedure A was followed using, XPhos (477 mg, 1.00 mmol, 1.00 equiv) and THF. Off-white solid. **Yield**: 740 mg (88%). **^{1}H NMR** (500 MHz, CD_3OD) δ 7.97

(ddt, J = 8.0, 6.9, 3.2 Hz, 1H), 7.65 - 7.49 (m, 5H), 7.32 (dd, J = 7.3, 1.9 Hz, 1H), 7.29 - 7.19 (m, 4H), 7.17 - 7.08 (m, 1H), 7.04 - 6.91 (m, 2H), 3.37 (h, J = 6.9 Hz, 1H), 2.93 (hept, J = 6.7 Hz, 1H), 2.69 (s, 3H), 2.55 (tdt, J = 12.3, 7.1, 2.4 Hz, 1H), 2.33 (ddt, J = 23.8, 20.8, 10.3 Hz, 2H), 2.20 - 2.06 (m, 1H), 2.06 - 1.75 (m, 9H), 1.71 - 1.49 (m, 7H), 1.49 - 0.98 (m, 11H), 0.97 - 0.72 (m, 7H), 0.17 (qdd, J = 13.7, 6.1, 4.1 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, CD_3OD) δ 156.26, 155.25, 150.83, 144.91, 140.63, 139.91, 139.51, 135.18, 133.96, 133.19, 133.10, 132.88, 131.76, 128.57, 128.54, 128.15, 127.30, 127.21, 127.10, 125.98, 124.79, 123.60, 121.19, 67.69, 38.40, 35.83, 35.59, 34.48, 34.17, 32.77, 31.99, 31.80, 31.41, 29.97, 29.62, 27.81, 27.53, 27.45, 26.25, 26.13, 26.03, 25.67, 25.35, 24.86, 24.53, 24.34, 23.33, 23.15, 22.95, 22.26, 13.29 ppm (observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 65.21, 35.86 ppm. **IR** (neat, cm^{-1}): 2958, 2932, 2852, 1461, 1239, 1138, 1030, 1002, 877, 748, 736.

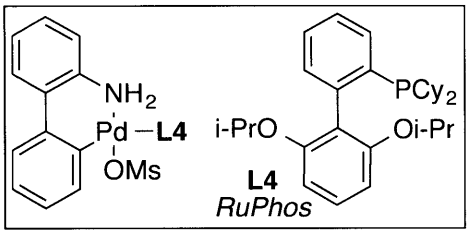


Precatalyst 6b: General procedure A was followed using *t*-BuXPhos (424 mg, 1.00 mmol, 1.00 equiv) and DCM. Yellow solid. **Yield**: 780 mg (94%) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96 (dd, J = 9.3, 6.4 Hz, 1H), 7.62 (d, J = 1.6 Hz, 1H), 7.51 ∂ 7.42 (m, 3H), 7.40 ∂ 7.32 (m, 2H), 7.16 ∂ 7.00 (m, 5H), 6.88 (dt, J = 5.1, 3.5 Hz, 1H), 6.79 ∂ 6.67 (m, 2H), 3.39 (dt, J = 13.7, 7.0 Hz, 1H), 2.95 (dd, J = 13.6, 6.8 Hz, 1H), 2.32 (d, J = 17.3 Hz, 3H), 2.05 ∂ 1.80 (m, 4H), 1.61 ∂ 1.40 (m, 15H), 1.34 ∂ 1.02 (m, 12H), 1.02 ∂ 0.77 (m, 10H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.13, 156.41, 152.01, 140.58, 139.24, 139.17, 137.39, 136.60, 135.43, 134.13, 131.00, 128.19, 127.96, 127.38, 127.17, 127.05, 126.78, 125.93, 125.42, 123.79, 120.73, 39.31, 39.16, 39.02, 38.88, 38.76, 34.38, 33.32, 32.10, 32.07, 31.36, 30.77, 30.73, 26.70, 25.99, 24.80, 24.47, 24.44, 24.10 ppm. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 57.17 ppm.

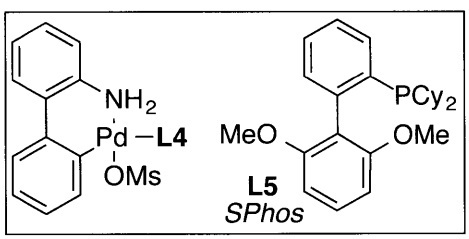


Precatalyst 6c: General procedure A was followed using BrettPhos (537 mg, 1.00 mmol, 1.00 equiv) and DCM. Yellow solid. **Yield**: 838 mg (94%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 -

7.34 (m, 2H), 7.25 (d, J = 1.8 Hz, 1H), 7.20 - 6.89 (m, 8H), 6.83 - 6.74 (m, 1H), 5.74 - 5.61 (m, 1H), 3.83 (s, 3H), 3.79 (s, 0H), 3.40 (s, 3H), 3.30 (hept, J = 7.8, 7.4 Hz, 1H), 2.82 (h, J = 6.7 Hz, 1H), 2.76 - 2.61 (m, 2H), 2.05 (d, J = 10.4 Hz, 1H), 1.66 - 1.54 (m, 1H), 1.54 - 1.09 (m, 11H), 1.10 - 0.60 (m, 12H), 0.28 (qdd, J = 12.8, 6.4, 3.4 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.33, 155.52, 155.00, 154.63, 151.84, 143.68, 140.41, 139.85, 136.40, 135.33, 134.80, 128.72, 128.25, 126.95, 126.73, 125.97, 124.44, 123.26, 120.89, 118.64, 115.30, 112.47, 55.58, 54.94, 39.37, 34.36, 34.19, 33.96, 33.02, 32.86, 30.89, 29.86, 29.49, 28.31, 27.96, 27.08, 26.78, 26.30, 25.93, 24.89, 24.84, 24.69, 24.46 ppm (Observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 43.33 ppm. **IR** (neat, cm^{-1}): 2922, 2852, 1577, 1462, 1443, 1254, 1224, 1183, 1034, 1008, 892, 926, 768, 724.

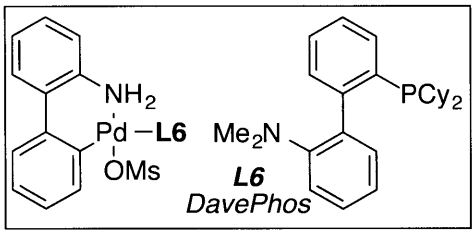


Precatalyst 6d: General procedure A was followed using RuPhos (466 mg, 1.00 mmol, 1.00 equiv) and THF. White powder. **Yield**: 780 mg (91%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.40 (t, J = 8.4 Hz, 1H), 7.57 - 7.49 (m, 1H), 7.46 - 7.30 (m, 5H), 7.23 - 6.97 (m, 7H), 6.96 - 6.87 (m, 2H), 6.76 - 6.70 (m, 1H), 5.08 (d, J = 10.6 Hz, 1H), 4.77 (hept, J = 6.1 Hz, 1H), 4.43 (hept, J = 6.0 Hz, 1H), 3.73 (dddd, J = 7.0, 4.8, 2.4, 1.2 Hz, 1H), 3.35 (d, J = 11.1 Hz, 1H), 2.68 (s, 3H), 2.36 - 2.23 (m, 2H), 1.98 - 1.74 (m, 4H), 1.63 - 1.40 (m, 7H), 1.38 - 1.25 (m, 2H), 1.27 - 0.75 (m, 12H), 0.67 (d, J = 6.0 Hz, 3H), -0.10 (d, J = 11.3 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.51, 161.59, 145.11, 142.35, 140.34, 138.55, 137.77, 136.09, 132.22, 131.58, 128.96, 128.69, 127.71, 127.32, 127.17, 125.65, 121.57, 107.54, 106.12, 100.50, 72.56, 71.99, 40.18, 36.02, 35.78, 31.09, 29.93, 28.06, 27.79, 27.67, 27.33, 26.78, 26.40, 26.02, 22.73, 22.47, 22.40, 21.74, 21.64 ppm (observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 41.57 ppm. **IR** (neat, cm^{-1}): 2926, 1569, 1455, 1215, 1184, 1106, 1032, 779, 761, 613.

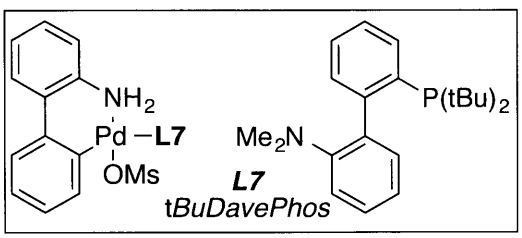


Precatalyst 6e: General procedure A was followed using SPhos (410 mg, 1.00 mmol, 1.00 equiv) and THF. White

powder. **Yield**: 712 mg (92%) **^{1}H NMR** (500 MHz, CD_3OD) δ 8.08 (t, 1H), 7.81 (t, 1H), 7.57 (dd, 1H), 7.55 - 7.44 (m, 2H), 7.34 (dd, 1H), 7.32 - 7.22 (m, 4H), 7.13 (d, 1H), 7.08 (dd, 1H), 6.97 (d, 1H), 3.95 (s, 3H), 3.42 (s, 3H), 2.69 (s, 3H), 2.47 (m, 1H), 2.31 - 2.11 (m, 2H), 2.10 - 1.47 (m, 8H), 1.46 - 0.78 (m, 12H), -0.07 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.35, 166.00, 146.89, 146.74, 145.46, 144.05, 143.93, 140.95, 139.50, 139.45, 139.30, 139.24, 136.01, 135.28, 135.19, 132.18, 131.17, 130.87, 130.75, 129.53, 124.35, 109.97, 109.09, 108.61, 59.58, 59.07, 42.25, 39.27, 39.02, 34.58, 34.37, 33.03, 32.99, 31.53, 31.50, 31.47, 31.38, 31.21, 31.14, 30.25, 30.22, 30.12, 30.05, 29.67, 29.50 ppm (observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 43.18 ppm. **IR** (neat, cm^{-1}): 2929, 1586, 1470, 1427, 1243, 1139, 1108, 1034, 1002, 768, 749, 728.

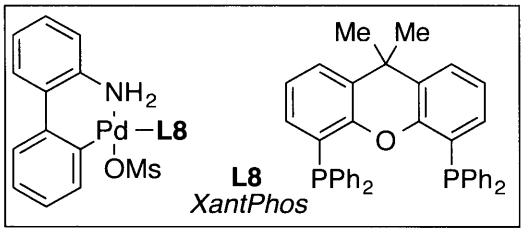


Precatalyst 6f: General procedure A was followed using DavePhos (394 mg, 1.00 mmol, 1.00 equiv) and THF. Bright yellow powder. **Yield**: 735 mg (97%) **^{1}H NMR** (500 MHz, CD_3OD) δ 7.86 (td, *J* = 7.7, 1.4 Hz, 1H), 7.72 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H), 7.53 - 7.40 (m, 4H), 7.36 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.30 (dt, *J* = 7.1, 1.4 Hz, 1H), 7.28 - 7.14 (m, 5H), 7.11 (td, *J* = 7.3, 0.9 Hz, 1H), 6.93 (dd, *J* = 7.8, 1.2 Hz, 1H), 2.83 - 2.71 (m, 1H), 2.69 (s, 3H), 2.59 (s, 7H), 2.32 (dddd, *J* = 25.1, 12.8, 9.1, 2.1 Hz, 1H), 2.24 - 2.09 (m, 2H), 2.01 - 1.90 (m, 1H), 1.90 - 1.79 (m, 1H), 1.77 - 1.42 (m, 5H), 1.42 - 1.23 (m, 2H), 1.11 - 0.65 (m, 5H), - 0.12 - -0.25 (m, 1H) ppm. **^{13}C NMR** (126 MHz, CD_3OD) δ 156.57, 143.89, 140.24, 139.87, 136.42, 134.15, 133.48, 131.99, 130.84, 128.26, 127.85, 127.82, 127.57, 127.22, 126.92, 125.37, 121.08, 120.36, 118.43, 115.72, 42.34, 38.32, 36.12, 32.88, 32.48, 28.49, 27.92, 27.66, 27.03, 26.48, 26.14, 25.97, 25.52 ppm (Observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 38.99 ppm. **IR** (neat, cm^{-1}) 2927, 2854, 1578, 1493, 1420, 1213, 1187, 1028, 1020, 748, 740, 615.

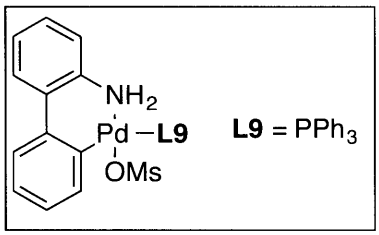


Precatalyst 6g: General procedure A was followed using *t*BuDavePhos (341 mg, 1.00 mmol, 1.00 equiv) and THF.

Bright yellow solid. **Yield**: 690 mg (97%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H), 7.84 (ddd, *J* = 7.9, 6.4, 1.3 Hz, 1H), 7.52 (ddd, *J* = 7.5, 3.8, 1.3 Hz, 1H), 7.49 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.40 - 7.33 (m, 1H), 7.33 - 7.25 (m, 2H), 7.23 (dt, *J* = 7.2, 1.6 Hz, 1H), 7.19 - 7.10 (m, 4H), 7.10 - 7.01 (m, 4H), 5.23 - 5.15 (m, 1H), 3.03 (d, *J* = 11.1 Hz, 1H), 2.65 (s, 6H), 2.59 (s, 3H), 1.69 (d, *J* = 14.2 Hz, 9H), 0.84 (d, *J* = 14.8 Hz, 9H) ppm. **^{13}C NMR** (126 MHz, CD_3OD) δ 156.85, 144.47, 139.41, 137.83, 136.98, 134.41, 131.70, 131.29, 131.22, 129.95, 128.19, 127.47, 127.27, 126.78, 126.47, 126.42, 125.51, 121.94, 120.18, 118.28, 115.49, 114.42, 67.69, 42.38, 39.31, 39.17, 39.02, 38.91, 38.35, 32.04, 32.00, 29.36, 29.32, 25.34 ppm (Observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 58.60 ppm.

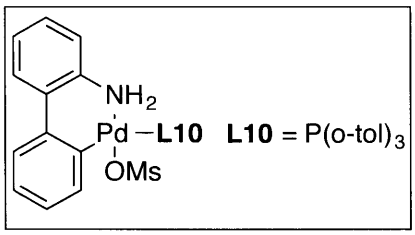


Precatalyst 6h: General procedure A was followed using XantPhos (578 mg, 1.00 mmol, 1.00 equiv) and DCM Yellow powder. **Yield**: 820 mg (87%) **^{1}H NMR** (500 MHz, CD_3OD) δ 7.88 (d, *J* = 6.9 Hz, 2H), 7.58 - 7.49 (m, 3H), 7.44 (dd, *J* = 18.0, 8.1 Hz, 4H), 7.38 - 7.11 (m, 13H), 7.10 - 6.92 (m, 7H), 6.82 (t, *J* = 7.1 Hz, 2H), 6.69 (dt, *J* = 19.3, 8.3 Hz, 4H), 6.16 (d, *J* = 7.7 Hz, 1H), 2.68 (s, 3H), 1.76 (d, *J* = 5.3 Hz, 6H) ppm. **^{13}C NMR**: A suitable spectrum could not be obtained. **^{31}P NMR** (121 MHz, CD_2Cl_2) δ 41.38 , 23.49 , 16.31 (d, *J* = 28.9 Hz), 2.23 (d, *J* = 24.7 Hz) ppm. **IR** (neat, cm^{-1}): 2927, 1570, 1481, 1435, 1408, 1183, 1094, 1036, 1000, 739, 707, 616.

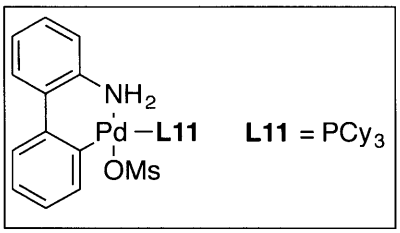


Precatalyst 6i: General procedure A was followed using triphenylphosphine (262 mg, 1.00 mmol, 1.00 equiv) and THF. White powder. **Yield** 562 mg, 88%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 - 7.52 (m, 1H), 7.50 - 7.38 (m, 10H), 7.34 - 7.23 (m, 10H), 6.95 - 6.88 (m, 1H), 6.46 (dddd, *J* = 7.8, 7.0, 1.6, 0.8 Hz, 1H), 6.42 (ddd, *J* = 7.7, 5.9, 1.3 Hz, 1H), 4.54 (s, 1H), 2.36 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.96, 138.34, 138.31, 134.95, 134.86, 130.94, 130.92, 129.67, 129.28, 128.62, 128.53, 128.51, 127.79, 127.44, 126.50, 125.84, 125.64, 121.16, 77.54, 77.28, 77.03, 39.27 ppm (observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 34.40. **IR** (neat, cm^{-}

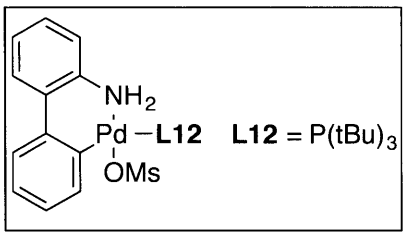
^{1}): 3270, 1571, 1491, 1481, 1435, 1249, 1136, 1098, 1033, 1001, 744, 727, 707, 691.



Precatalyst 6j: General procedure A was followed using tri(*o*-tolyl)phosphine (304 mg, 1.00 mmol, 1.00 equiv) and THF. White powder. **Yield**: 552 mg, 84%. Complex NMR spectra likely due to rapid exchange in solution. **IR** (neat, cm^{-1}): 3047, 1590, 1495, 1448, 1223, 1134, 1045, 1019, 1002, 804, 717, 676.

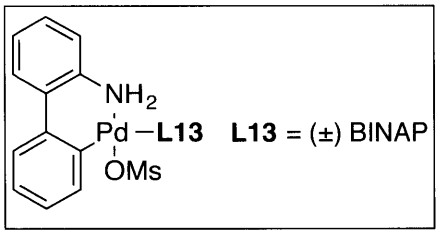


Precatalyst 6k: In a nitrogen glove box, general procedure A was followed using tricyclohexylphosphine (280 mg, 1.00 mmol, 1.00 equiv) and THF. White powder. **Yield**: 620 mg, 95%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 - 7.35 (m, 2H), 7.30 - 7.25 (m, 1H), 7.25 - 7.13 (m, 4H), 7.07 (td, *J* = 7.3, 1.2 Hz, 1H), 7.00 (td, *J* = 7.4, 1.6 Hz, 1H), 4.23 - 4.12 (m, 1H), 2.79 (s, 3H), 1.97 - 0.81 (m, 33H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.28, 140.10, 137.59, 137.54, 136.59, 128.40, 127.67, 127.31, 125.93, 125.60, 125.13, 120.60, 40.01, 32.84, 32.67, 30.14, 29.12, 27.94, 27.85, 27.79, 27.71, 26.51 ppm (observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 38.60 ppm. **IR** (neat, cm^{-1}): 3137, 2925, 2850, 1613, 1491, 1440, 1236, 1152, 1070, 1032, 1002, 889, 850, 798, 735.

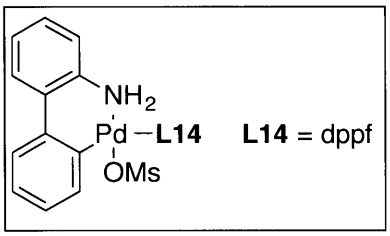


Precatalyst 6l: In a nitrogen glove-box, general procedure A was followed using P(*t*Bu)$_3$ (1.00 mL, 1 M in PhMe, 1.00 mmol, 1.00 equiv) and THF. Brown solid. **Yield**: 498 mg, 87% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 6.3 Hz, 1H), 7.40 (m, *J* = 7.7, 3.4, 1.0 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.23 (td, *J* = 7.6, 1.4 Hz, 1H), 7.16 (qd, *J* = 7.4, 1.3 Hz, 2H), 7.04 (td, *J* = 7.3, 0.9 Hz, 1H), 6.96 (td, *J* = 7.5, 1.6 Hz, 1H), 4.01 - 3.94 (m, 1H), 2.81 (s, 3H), 1.28 (d, *J* = 12.5 Hz, 27H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.83, 139.11, 138.48, 138.44, 128.64, 127.02, 126.38, 126.07, 125.66, 124.78, 119.68, 77.53, 40.41, 40.07, 40.01, 32.49, 32.47 ppm (Observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 72.00 ppm. **IR** (neat, cm^{-1}): 3105, 1594, 1488, 1418, 1392,

1369, 1243, 1137, 1011, 1000, 935, 773.



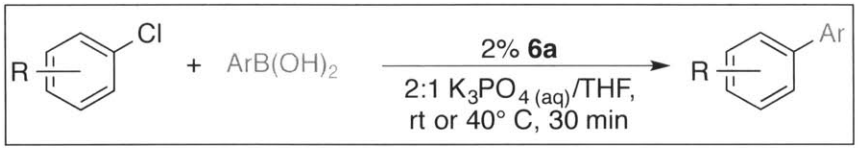
Precatalyst 6m: General procedure A was followed using *(±)*-BINAP (622 mg, 1.00 mmol, 1.00 equiv) and THF. Beige solid. **Yield**: 936 mg (95%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 - 7.89 (m, 3H), 7.84 - 7.77 (m, 2H), 7.66 - 7.51 (m, 4H), 7.47 - 7.33 (m, 4H), 7.32 - 6.92 (m, 16H), 6.91 - 6.76 (m, 3H), 6.74 - 6.66 (m, 2H), 6.58 - 6.46 (m, 4H), 6.29 (tt, *J* = 7.4, 1.8 Hz, 1H), 6.21 (d, *J* = 7.6 Hz, 1H), 2.27 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.34, 140.32, 139.49, 139.46, 139.40, 139.39, 139.36, 139.27, 139.22, 139.19, 139.18, 139.15, 139.12, 137.85, 136.64, 136.62, 135.86, 135.77, 134.89, 134.77, 134.48, 134.46, 134.33, 134.32, 133.99, 133.92, 132.78, 131.32, 131.24, 131.10, 130.79, 130.04, 129.98, 129.59, 129.51, 129.10, 129.06, 128.92, 128.79, 128.75, 128.68, 128.49, 128.41, 128.37, 128.33, 128.16, 128.13, 128.04, 127.93, 127.83, 127.64, 127.56, 127.34, 127.26, 127.14, 127.05, 126.85, 126.48, 126.31, 126.24, 126.19, 124.64, 124.30, 122.80, 122.38, 120.47, 39.64 ppm (Observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 36.37 (d, *J* = 42.2 Hz), 15.68 (d, *J* = 42.3 Hz) ppm. **IR** (neat, cm^{-1}): 3048, 1571, 1493, 1435, 1309, 1183, 1096, 1035, 816, 737, 721, 606.



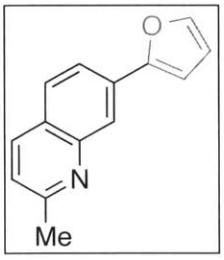
Precatalyst 6n: General procedure A was followed using 1,1'-bis(diphenylphosphino)ferrocene (554 mg, 1.00 mmol, 1.00 equiv) and THF. Orange powder. **Yield**: 822 mg, 89%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 - 7.97 (m, 2H), 7.61 - 7.42 (m, 12H), 7.34 - 7.21 (m, 7H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.04 (dt, *J* = 18.9, 5.6 Hz, 2H), 7.01 - 6.92 (m, 2H), 6.72 (dt, *J* = 13.9, 7.5 Hz, 2H), 6.47 (t, *J* = 7.3 Hz, 1H), 5.70 (d, *J* = 7.7 Hz, 1H), 4.37 (t, *J* = 13.3 Hz, 4H), 4.26 (d, *J* = 18.1 Hz, 2H), 3.96 (s, 1H), 3.84 (s, 1H), 2.33 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.09, 137.70, 136.09, 135.98, 135.09, 134.99, 133.71, 133.61, 133.08, 132.98, 132.35, 131.90, 131.57, 131.21, 130.89, 130.31, 130.25, 129.96, 129.89, 128.83, 128.75, 128.28, 128.19, 127.64, 127.45, 125.91, 125.49, 120.27, 76.43, 75.84, 74.52, 74.04, 73.49, 73.15, 71.13, 68.20, 39.34, 25.84 ppm (Observed complexity due to P-C splitting). **^{31}P NMR** (121 MHz, CD_3OD) δ 32.37 (d, *J* = 33.7 Hz), 11.22 (d, *J* = 33.7 Hz) ppm. **IR** (neat, cm^{-1}): 3041,

1569, 1482, 1435, 1307, 1223, 1179, 1096, 1035, 825, 748, 733, 701, 629, 565.

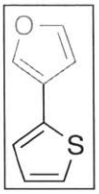
General Procedure B: Suzuki-Miyura Coupling of Unstable Boronic Acids



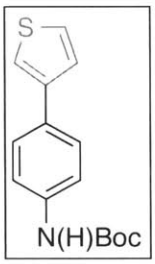
A screw-top test tube equipped with a magnetic stir bar and Teflon septum was charged with aryl halide, if solid, (1 mmol, 1 equiv), boronic acid (1.5 mmol, 1.5 equiv), and precatalyst **6a** (2 mol%),. The tube was then evacuated and backfilled with argon (this sequence was performed a total of three times). Then the aryl halide, if liquid, was added followed by THF (2 mL) and degassed 0.5 M K_3PO_4 solution (4 mL, 2 mmol, 2 equiv). The reaction mixture was then stirred at rt or 40 °C for 30 min. After being allowed to cooll to room temperature the reaction mixture was diluted with water (10 mL) and diethyl ether (10 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3x10mL). The combined organic phases were dried over magnesium sulfate, concentrated under vacuum, and purified via flash chromatography.



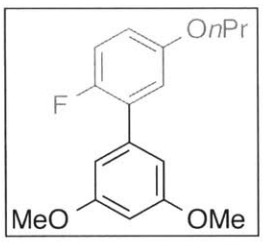
7-(furan-2-yl)-2-methylquinoline: General procedure B was followed using 7-chloro-2- methylquinoline (177 mg, 1.00 mmol, 1.00 equiv), and 2-furylboronic acid (168 mg, 1.50 mmol, 1.50 equiv) at rt. The crude product was purified by flash chromatography, eluting with with 30% ethyl acetate in hexanes, to provide the title compound as an orange solid. **Yield**: 198 mg, 95%. **mp** = 40 – 42° C. **^{1}H NMR** (500 MHz, CD_3OD) δ ∂ 8.09 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.73 (s, 2H), 7.62 (d, *J* = 1.1 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 3.4 Hz, 1H), 6.55 (dd, *J* = 3.3, 1.7 Hz, 1H), 2.62 (s, 3H) ppm. **^{13}C NMR** (126 MHz, CD_3OD) δ 159.82, 153.18, 147.38, 143.29, 136.86, 132.19, 128.22, 125.95, 122.12, 121.91, 120.49, 111.94, 107.08, 23.48 ppm. **IR** (neat, cm^{-1}): 1623, 1512, 1219, 1156, 1011, 885, 842, 735, 594. Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.26; H, 5.30. Found: C, 79.86; H, 5.41.



3-(thiophen-2-yl)furan: General procedure B was followed using 2-chlorothiophene (92 µL, 1.00 mmol, 1.00 equiv) and 3-furylboronic acid (168 mg, 1.50 mmol, 1.50 equiv), at 40 °C. The crude product was purified by flash chromatography, eluting with 10% ethyl acetate in hexanes, to provide the title compound as a light brown oil. **Yield**: 140 mg, 93%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.50 (t, *J* = 1.7 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.17 (dd, *J* = 3.5, 1.1 Hz, 1H), 7.09 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.69 (dd, *J* = 1.9, 0.9 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.85, 138.46, 135.15, 127.87, 123.89, 123.67, 120.90, 109.72 ppm. **IR** (neat, cm^{-1}): 2924, 2851, 1602, 1451, 1327, 1260, 1238, 999, 800, 747, 721.



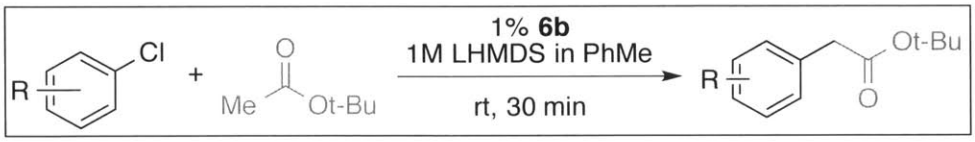
***t*-butyl 4-(4-(thiophen-3-yl)phenyl)piperazine-1-carboxylate:** General procedure B was followed using *t*-butyl (4-chlorophenyl)carbamate (228 mg, 1.00 mmol, 1.00 equiv), and 3-thiophenylboronic acid (192 mg, 1.50 mmol, 1.50 equiv), at 40 °. The crude product was purified by flash chromatography, eluting with 20% ethyl acetate in hexanes, to provide the title compound as a white solid. **Yield**: 275 mg, 89%. **mp** = 151 – 153° C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.0 Hz, 1H), 7.53 (d, *J* = 2.1 Hz, 1H), 7.42 - 7.38 (m, 3H), 7.38 - 7.35 (m, 2H), 6.55 (s, 1H), 1.54 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.96, 142.08, 137.63, 131.01, 127.21, 126.41, 126.38, 119.64, 119.00, 28.60 ppm. **IR** (neat, cm^{-1}): 3372, 1704, 1512, 1235, 1165, 778.



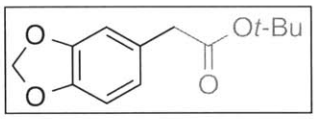
2-fluoro-5-isopropoxy-3',5'-dimethoxy-1,1'-biphenyl: General procedure B was followed using 3,5- dimethoxychlorobenzene (172 mg, 1.00 mmol, 1.00 equiv), and 2-fluoro-5-isopropoxyboronic acid (297 mg, 1.50 mmol, 1.50 equiv), **6a** (18.4 mg, 0.02 mmol, 2%) at rt. The crude product was purified by flash chromatography, eluting with 20% ethyl acetate in hexanes, to provide the title compound as an orange solid. **Yield**: 261 mg, 90%. **mp** = 70 – 71° C. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.12 - 7.06 (m, 1H), 6.99 (dd, *J* = 6.3, 3.1 Hz, 1H), 6.86 (dt, *J* = 8.9, 3.5 Hz, 1H), 6.73 - 6.70 (m, 2H), 6.52 (t, *J* = 2.3 Hz, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 3.85 (s, 6H), 1.88 - 1.78 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 160.98, 155.60, 155.59, 155.06, 153.15, 137.98, 129.65, 129.53, 116.77, 116.57, 116.24, 116.22, 114.83,

114.77, 107.33, 107.30, 99.90, 70.41, 55.59, 22.86, 10.48 ppm. **IR** (neat, cm^{-1}): 2960, 1593, 1456, 1406, 1251, 1212, 1193, 1148, 1057, 1019, 838, 809, 771, 690, 631.

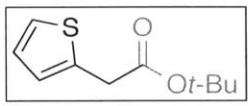
General Procedure for the a-Arylation of *t*-Butyl Acetate



General Procedure C: An oven-dried, screw-top test tube equipped with a stir bar and a Teflon septum was charged with aryl halide, if solid, (0.5 mmol, 1 equiv) and precatalyst **6b** (4 mg, 1 mol%). The tube was evacuated and backfilled with argon (this procedure was repeated a total of three times). To this tube was then added *t*-butyl acetate (101 µL, 0.75 mmol, 1.5 equiv), aryl halide, if liquid, and LHMDS (1 M in toluene, 1.5 mmol, 1.5 mL). The reaction was stirred at room temperature for 30 min then shaken vigorously with saturated ammonium chloride (2 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x5mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude products were purified by flash chromatography on silica gel and dried under vacuum.

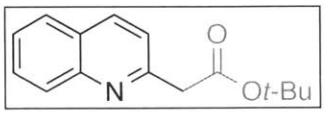


***t*-butyl 2-(benzo[*d*][1,3]dioxol-5-yl)acetate:** General procedure C was followed using 5-chloro benzo[*d*][1,3]dioxole (59 µL mg, 0.5 mmol). The crude product was purified by flash chromatography, eluting with 10% ethyl acetate in hexanes to provide the title compound as a light yellow oil. **Yield**: 108 mg, 91%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.80 - 6.74 (m, 2H), 6.73 - 6.69 (m, 1H), 5.94 (s, 2H), 3.44 (s, 2H), 1.45 (d, J = 4.2 Hz, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.29, 147.85, 146.71, 128.53, 122.56, 109.91, 108.44, 101.17, 81.08, 42.45, 28.28 ppm. **IR** (neat, cm^{-1}): 1713, 1634, 1434, 1317, 1286, 1269, 1193, 1149, 1052, 976, 758, 736.



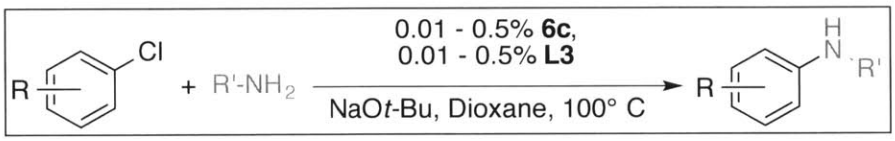
***t*-butyl 2-(thiophen-2-yl)acetate:** General procedure C was followed using 2-chlorothiophene (46 µL, 0.5 mmol, 1.0 equiv). The crude product was purified by

column chromatography, eluting with 10% diethyl ether in hexanes, to provide the title compound as a dark yellow oil. **Yield**: 93 mg, 95% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (d, J = 5.1 Hz, 1H), 6.98 - 6.94 (m, 1H), 6.93 (s, 1H), 3.76 (s, 2H), 1.49 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.95, 136.10, 126.88, 126.72, 125.08, 81.62, 37.08, 28.25 ppm. **IR** (neat, cm^{-1}): 1732, 1684, 1662, 1593, 1522, 1514, 1436, 1412, 1208, 1032, 834, 803, 753, 609.



***t*-butyl 2-(quinolin-2-yl)acetate:** General procedure C was followed using 2-methylquinoline (82 mg, 0.5 mmol, 1.0 equiv). The crude product was purified by flash chromatography, eluting with 20% ethyl acetate in hexanes, to provide the title compound as a bright orange/yellow oil. **Yield**: 117 mg, 97%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (dd, J = 13.6, 8.5 Hz, 2H), 7.74 (dd, J = 8.1, 1.3 Hz, 1H), 7.65 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.46 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 3.94 (s, 2H), 1.43 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.70, 155.30, 147.75, 136.32, 129.40, 128.96, 127.44, 126.90, 126.18, 121.74, 81.24, 45.93, 28.00 ppm. **IR** (neat, cm^{-1}): 1723, 1597, 1366, 1268, 1257, 1128, 1116, 952, 839, 807, 782, 761, 602.

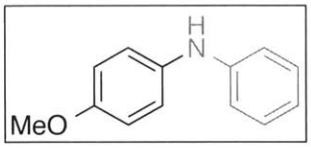
General Procedures D – F: C-N Cross Coupling Reaction of Primary Amines



General Procedure D: An oven-dried, screw-top test tube equipped with a magnetic stir bar and Teflon septum was charged with, aryl halide, if solid, (1 mmol, 1 equiv), amine, if solid, (1.2 mmol, 1.2 equiv), NaO*t*-Bu (115 mg, 1.2 mmol, 1.2 equiv), and precatalyst **6c** (0.01 – 1 mol). The tube was evacuated and backfilled with argon (this sequence was repeated a total of three times). The aryl halide and amine were then added if liquid, followed by dioxane (1 mL). The reaction was heated at 100 °C and monitored by thin-layer chromatography or gas chromatography, observing the disappearance of aryl halide. After completion the reaction was cooled to room temperature, diluted with ethyl acetate, and filtered through a plug of Celite. The crude mixture was concentrated then purified by flash chromatography.

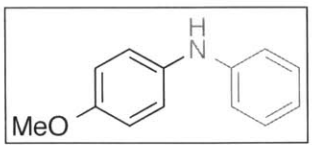
General Procedure E: An oven-dried screw-top test tube equipped with a stir bar and Teflon septum was charged with aryl iodide, if solid, (1 mmol, 1 equiv), amine, if solid, (1.4 mmol, 1.4 equiv), NaO*t*-Bu (135 mg, 1.40 mmol, 1.40 equiv) and precatalyst **6c** (0.01 – 1 mol%). The tube was evacuated and backfilled with argon (this sequence was repeated a total of three times). Then the aryl halide and amine was added if they are liquid, followed by toluene (1 mL). The reaction was stirred at 100 °C and monitored by thin-layer chromatography or gas chromatography, observing the disappearance of aryl iodide. After completion the reaction was allowed to cool to room temperature, diluted with ethyl acetate, and filtered through a plug of Celite. The crude product was concentrated then purified by column chromatography.

General Procedure F: An oven-dried screw-top test tube equipped with a stir bar and Teflon septum was charged with aryl halide, if solid, (1 mmol, 1 equiv), amine, if solid, (1.2 mmol, 1.2 equiv), Cs_2CO_3 (391 mg, 1.20 mmol, 1.20 equiv), and precatalyst **6c** (0.01 – 1 mol. The tube was evacuated and backfilled with argon (this sequence was repeated a total of three times). Then the aryl halide and amine were added if they are liquid followed by tBuOH (1 mL). The reaction was stirred at 100° C and monitored by thin-layer chromatography or gas chromatography, observing the disappearance of aryl halide. After completion the reaction was allowed to cool to room temperature, diluted with ethyl acetate, and filtered through a plug of Celite. The crude product was concentrated then purified by flash chromatography.

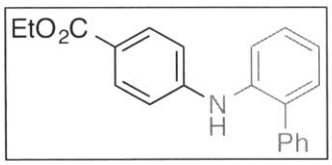


4-Methoxy-*N*-Phenylaniline: Following general procedure D, a mixture of 4-chloroanisole (123 µL, 1.00 mmol, 1.00 equiv), aniline (110 µL, 1.20 mmol, 1.20 equiv), NaO*t*-Bu (115 mg, 1.20 mmol, 1.20 equiv), **6c** and **L3** (10 µL, 0.01 M in THF, 0.01 mol%) and dioxane (1 mL) was stirred at 100 °C for 24 h. The crude product was purified by flash chromatography, eluting with 10% ethyl acetate in hexanes, to provide the title compound as an off-white solid. **Yield**: 193 mg, 97%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 15.2, 7.0 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.91 - 6.83 (m, 3H), 5.51 (s, 1H), 3.82 (s, 3H) ppm **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.49, 145.90, 145.39, 135.93, 129.56, 122.45, 119.80, 115.86, 114.90, 55.83

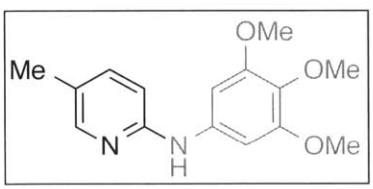
ppm. **IR** (neat, cm^{-1}): 2904, 1587, 1521, 1309, 1110, 808, 745.



4-Methoxy-*N*-Phenylaniline: Following general procedure E, a mixture of 4-iodoanisole (234 mg, 1.00 mmol, 1.00 equiv), aniline (110 µL, 1.20 mmol, 1.20 equiv), NaO*t*-Bu (115 mg, 1.20 mmol, 1.20 equiv), **6c** and **L3** (10 µL, 0.01 M in THF, 0.01 mol%) and THF (1 mL) was stirred at 100 °C for 5 min. The crude product was purified by flash chromatography, eluting with 10% ethyl acetate in hexanes, to provide the title compound as an off-white solid. **Yield**: 190 mg, 96%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 15.2, 7.0 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.91 - 6.83 (m, 3H), 5.51 (s, 1H), 3.82 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.49, 145.90, 145.39, 135.93, 129.56, 122.45, 119.80, 115.86, 114.90, 55.83 ppm.

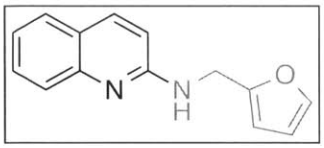


Ethyl 4-([1,1'-biphenyl]-2-ylamino)benzoate: Following general procedure F, a mixture of ethyl-4- chlorobenzoate (155 µL, 1.00 mmol, 1.00 equiv), 2-aminobiphenyl (177 mg, 1.05 mmol, 1.05 equiv) Cs_2CO_3 (391 mg, 1.2 mmol, 1.2 equiv) **6c** (0.9 mg, 0.1 mol%) and *t*BuOH (1 mL) was stirred at 100 °C for 24 h. The crude product was purified by column chromatography, eluting with 20% ethyl acetate in hexanes, to provide the title compound as an off-white solid. **Yield**: 288 mg, 88%. **mp** = 115 – 116° C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.51 - 7.32 (m, 7H), 7.16 (td, *J* = 7.5, 1.3 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 2H), 5.82 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.73, 148.57, 138.82, 138.14, 134.18, 131.67, 131.36, 129.45, 129.11, 128.54, 127.91, 123.67, 121.74, 121.18, 114.93, 60.69, 14.70 ppm. **IR** (neat, cm^{-1}): 1704, 1609, 1518, 1275, 1173, 1104, 745, 700.

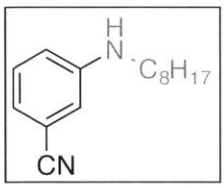


5-methyl-*N*-(3,4,5-trimethoxyphenyl)pyridin-2-amine: Following general procedure D, a mixture of 2- chloro-*5*-methylpyridine (135 µL, 1.00 mmol, 1.00 equiv), 3,4,5-trimethoxyaniline (220 mg, 1.20 mmol, 1.20 equiv), NaO*t*-Bu (115 mg, 1.20 mmol, 1.20 equiv), **6c** (0.9 mg, 0.1%) and dioxane (1 mL) was stirred

at 100 °C for 12 h. The crude product was purified by flash chromatography, eluting with ethyl acetate, to provide the title compound as a white solid. **Yield**: 245 mg, 89%. **mp** = 132 – 134° C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.4 Hz, 1H), 7.31 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.83 (s, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.57 (s, 2H), 3.82 (s, 6H), 2.21 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.62, 153.82, 148.15, 138.87, 137.45, 133.71, 124.03, 108.51, 98.21, 61.23, 56.27, 17.76 ppm. **IR** (neat, cm^{-1}): 1602, 1496, 1414, 1296, 1228, 1127, 1010, 818. Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61. Found: C, 65.95; H, 6.56.

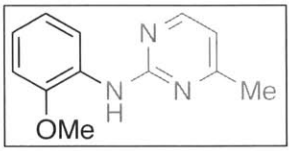


***N*-(furan-2-ylmethyl)quinolin-2-amine:** Following general procedure D, a mixture of 2-chloroquinoline (166 mg, 1.00 mmol, 1.00 equiv), furfurylamine (96 µL, 1.2 mmol, 1.2 equiv) NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv) **6c** (0.9 mg, 0.1 mol%) and dioxane (1 mL) was stirred at 100 C° for 20 h. The crude product was purified by column chromatography, eluting with 50% ethyl acetate in hexanes, to provide the title compound as a light yellow solid. **Yield**: 217 mg, 97%. **mp** = 152 – 153° C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.9 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.65 - 7.53 (m, 2H), 7.39 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.28 - 7.21 (m, 1H), 6.65 (d, *J* = 8.9 Hz, 1H), 6.32 (ddd, *J* = 16.4, 3.2, 1.3 Hz, 2H), 5.12 (s, 1H), 4.75 (d, *J* = 5.5 Hz, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.52, 152.85, 148.09, 142.20, 137.60, 129.82, 127.71, 126.56, 123.86, 122.56, 111.88, 110.70, 107.49, 39.05 ppm. **IR** (neat, cm^{-1}): 3251, 1620, 1538, 1403, 1185, 1145, 1014, 911, 815, 755, 738. Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39. Found: C,7 75.14; H, 5.55.

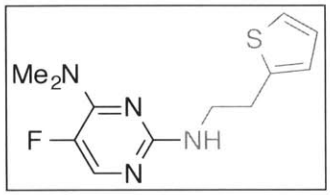


3-Cyano-*N*-(*n*-octyl)aniline: Following general procedure F, a mixture of 3-chlorobenzonitrile (137 mg, 1.00 mmol, 1.00 equiv), *n*-octylamine (202 µL, 1.20 mmol, 1.20 equiv), Cs_2CO_3 (391 mg, 1.10 mmol, 1.20 equiv), **6c** (2.5 mg, 0.25 mol%), and *t*BuOH (1 mL) was stirred at 100 °C for 24 h. The crude product was purified by column chromatography, eluting with 10% ethyl acetate in hexanes, to provide the title compound as a yellow oil. **Yield**: 213 mg, 93%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 - 7.17 (m, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.80 - 6.72 (m, 2H), 3.94 (s, 1H), 3.08 (dd, *J* = 12.0, 7.0 Hz, 2H), 1.68 - 1.56 (m, 2H), 1.45 - 1.21 (m, 10H), 0.90

(dt, J = 13.9, 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.95, 130.05, 120.39, 119.90, 117.32, 114.79, 112.99, 43.81, 32.06, 29.61, 29.49, 29.42, 27.33, 22.91, 14.37 ppm. **IR** (neat, cm^{-1}): 2924, 2187, 1602, 1581, 1334, 843, 777, 680.

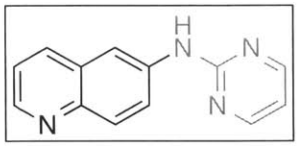


***N*-(2-methoxyphenyl)-4-methylpyrimidin-2-amine**: Following general procedure D, a mixture of 2- chloroanisole (123 µL, 1.00 mmol, 1.00 equiv), 2-amino-4-methylpyrimidine (131 mg, 1.20 mmol, 1.20 equiv) NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv), **6c** (0.9 mg, 0.1 mol%) and *t*BuOH (1 mL) was stirred at 100 C° for 12 hours. The crude product was purified by flash chromatography, eluting with 50% ethyl acetate in hexanes, to provide the title compound as an off-white solid. **Yield**: 200 mg, 93%. **mp** = 61 – 62° C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.61 (dd, J = 7.9, 1.7 Hz, 1H), 8.27 (d, J = 5.0 Hz, 1H), 7.77 (s, 1H), 7.01 (td, J = 7.7, 1.5 Hz, 1H), 6.96 (td, J = 7.7, 1.7 Hz, 1H), 6.86 (dd, J = 8.0, 1.5 Hz, 1H), 6.54 (d, J = 5.0 Hz, 1H), 3.85 (s, 3H), 2.40 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.15, 160.10, 157.61, 147.97, 129.67, 121.69, 121.09, 118.55, 112.28, 110.07, 55.83, 24.41 ppm. **IR** (neat, cm^{-1}): 3423, 1528, 1446, 1238, 1117, 1023, 787, 749, 618. Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09. Found: C, 66.98; H, 6.20.



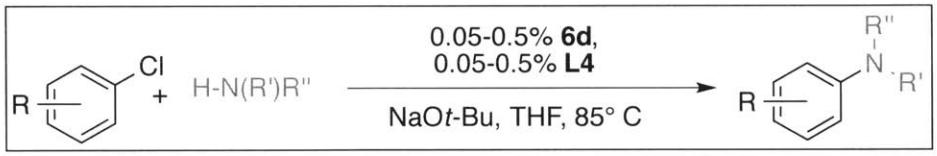
5-fluoro-*N*^{4},*N*^{4}-dimethyl-*N*^{2}-(2-(thiophen-2-yl)ethyl)pyrimidine-2,4-diamine: Following general procedure D, a mixture of 2-chloro-5-fluoro-*N*,*N*-dimethylpyrimidin-4-amine (175 mg, 1.00 mmol, 1.00 equiv), 2-thiopheneethylamine (140 µL, 1.20 mmol, 1.20 equiv) NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv) **6c** (0.9 mg, 0.1 mol%) and dioxane (1 mL) was stirred at 100 C° for 20 h. The crude product was purified by flash chromatography, eluting with 50% ethyl acetate in hexanes, to provide the title compound as a light yellow, crystalline solid. **Yield**: 242 mg, 91%. **mp** = 73° C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 (d, J = 6.9 Hz, 1H), 7.13 (dd, J = 5.1, 1.2 Hz, 1H), 6.92 (dd, J = 5.1, 3.4 Hz, 1H), 6.85 - 6.81 (m, 1H), 5.13 (s, 1H), 3.59 (q, J = 6.8 Hz, 2H), 3.15 (d, J = 2.2 Hz, 6H), 3.09 (t, J = 6.9 Hz, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.11, 158.09, 152.74, 152.69, 142.63, 142.42, 142.36, 140.75, 127.14, 125.32, 123.83, 77.62, 77.37, 77.11, 43.84, 38.94, 38.88, 30.44 ppm. ^{19}F NMR (282 MHz, $CDCl_3$)

δ -162.97 ppm. **IR** (neat, cm^{-1}): 3242, 1599, 1540, 1446, 1420, 1401, 1216, 1112, 770, 692. Anal. Calcd. for $C_{12}H_{15}FN_4S$: C, 54.11; H, 5.68. Found: C, 54.20; H, 5.64.

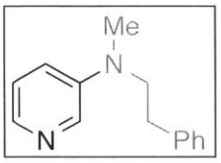


***N*-(pyrimidin-2-yl)quinolin-6-amine:** Following general procedure D, a mixture of 6-chloroquinoline (166 mg, 1.00 mmol, 1.00 equiv), 2-aminopyrimidine (115 mg, 1.20 mmol, 1.20 equiv), NaOtBu (115 mg, 1.20 mmol, 1.20 equiv) **6c** (0.9 mg, 0.1 mol%) and dioxane (1 mL) was stirred at 100 C° for 24 hours. The crude product was purified by column chromatography, eluting with 50% ethyl acetate in hexanes, to provide the title compound as a light yellow solid. **Yield**: 200 mg, 90%. **mp** = 149 – 150° C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.49 (d, *J* = 4.8 Hz, 2H), 8.43 - 8.35 (m, 2H), 8.13 - 8.07 (m, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.72 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.33 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.77 (t, *J* = 4.8 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.30, 158.25, 148.77, 145.11, 137.83, 135.70, 130.18, 129.34, 124.10, 121.67, 114.48, 113.27 ppm. **IR** (neat, cm^{-1}): 1566, 1534, 1450, 1024, 787, 751, 620.

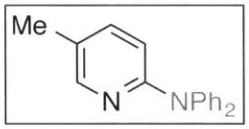
General Procedure G: C-N Cross Coupling Reaction of Secondary Amines



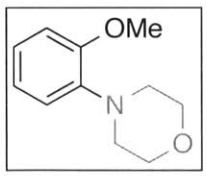
An oven-dried screw-top test tube equipped with a stir bar and Teflon septum was charged with aryl halide, if solid, (1 mmol, 1 equiv), amine, if solid, (1.2 mmol, 1.20 equiv), NaO*t*Bu (115 mg, 1.2 mmol, 1.2 equiv), and precatalyst **6d** (0.01 – 1 mol%). The tube was evacuated and backfilled with argon (this sequence was repeated a total of three times). The aryl halide and amine were then added, if liquid, followed by THF (1 mL). The reaction was stirred at 85° C and monitored by thin-layer chromatography or gas chromatography, observing the disappearance of aryl halide. After completion the reaction was allowed to cool to room temperature, diluted with ethyl acetate, and filtered through a plug of Celite. The crude product was concentrated then purified by flash chromatography.



***N*-methyl-*N*-phenethylpyridin-3-amine**: Following general procedure G, a mixture of 3-chloropyridine (96 µL, 1.00 mmol, 1.00 equiv), N-methylphenethyl amine (174 µL, 1.20 mmol, 1.20 equiv) NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv), **L4** (2.3 mg, 0.5 mol%), **6d** (4.1 mg, 0.5 mol %) and THF (1 mL) was stirred at 85 °C for 24 h. The crude product was purified by flash chromatography, eluting with 30% ethyl acetate in hexanes, to provide the title compound as a yellow oil. **Yield**: 170 mg, 80% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (t, *J* = 5.8 Hz, 1H), 7.97 (dd, *J* = 4.6, 1.2 Hz, 1H), 7.35 - 7.28 (m, 2H), 7.25 - 7.17 (m, 3H), 7.17 - 7.11 (m, 1H), 6.96 (ddd, *J* = 8.5, 3.1, 1.3 Hz, 1H), 3.62 - 3.56 (m, 2H), 2.90 (s, 3H), 2.89 - 2.83 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.77, 139.43, 137.56, 134.80, 129.03, 128.86, 126.64, 123.84, 118.50, 54.50, 39.83, 38.43, 33.08 ppm. **IR** (neat, cm^{-1}): 1581, 1492, 1356, 1182, 791, 745.

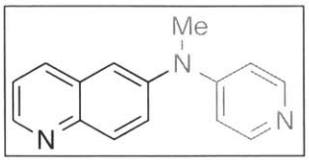


5-methyl-*N*,*N*-diphenylpyridin-2-amine: Following general procedure G, a mixture of 2-chloro-5- methylpyridine (110 µL, 1.00 mmol, 1.00 equiv), diphenylamine (203 mg, 1.20 mmol, 1.20 equiv) NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv), **L4** (0.5 mg, 0.1 mol %), **6d** (0.8 mg, 0.1 mol %) and THF (1 mL) was stirred at 85 °C for 24 h. The crude product was purified by flash chromatography, eluting with 20% ethyl acetate in hexanes, to provide the title compound as an off-white solid. **Yield**: 228 mg, 88%. mp = 82 – 83° C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.4 Hz, 1H), 7.38 - 7.29 (m, 5H), 7.24 - 7.16 (m, 4H), 7.13 (tt, *J* = 7.3, 1.3 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 2.28 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.42, 148.53, 146.74, 138.56, 129.59, 126.05, 125.97, 124.28, 114.83, 17.97 ppm. **IR** (neat, cm^{-1}): 1588, 1475, 1381, 1316, 1263, 1022, 820, 760, 692, 623. Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19. Found: C, 82.75; H, 6.36.

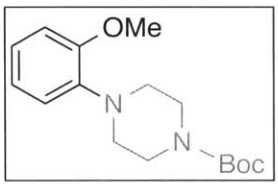


4-(2-methoxyphenyl)morpholine: Following general procedure G, a mixture of 2-chloroanisole (122 µL, 1.00 mmol, 1.00 equiv), morpholine (104 µL, 1.20 mmol, 1.20 equiv), NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv), **L4** and **6d** (50µL ,0.01 M in THF, 0.05 mol%), and THF (1mL) was stirred at 85 °C for 24 h. The crude product was purified by flash chromatography, eluting with 10% ethyl acetate in hexanes, to provide the title compound as a light yellow

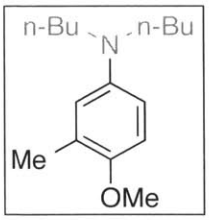
oil. Yield: 185 mg, 96%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.03 (tt, *J* = 8.5, 4.2 Hz, 1H), 6.95 (d, *J* = 4.1 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 3.93 - 3.89 (m, 5H), 3.88 (s, 3H), 3.11 - 3.06 (m, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.45, 141.30, 123.40, 121.26, 118.22, 111.46, 67.45, 55.59, 51.40 ppm. **IR** (neat, cm^{-1}): 1581, 1493, 1356, 1113, 791, 745.



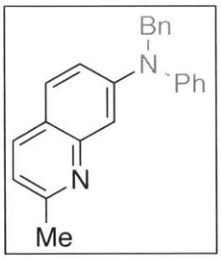
***N*-methyl-*N*-(pyridin-4-yl)quinolin-6-amine:** Following general procedure G, a mixture of 6- chloroquinoline (164 mg, 1.00 mmol, 1.00 equiv), N-methyl-4-aminopyridine (130 mg, 1.20 mmol, 1.20 equiv) NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv), **L1** (4.7 mg, 1.00 mol %), **6a** (9.2 mg, 1 mol%) and toluene (1 mL) was stirred at 110 °C for 4 h. The crude product was purified by flash chromatography, eluting with a 95:5:1 mixture of dichlormethane:methanol:triethylamine, to provide the title compound as a viscous yellow oil. **Yield**: 209 mg, 89%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.94 - 8.88 (m, 1H), 8.26 (d, *J* = 6.1 Hz, 2H), 8.13 (dd, *J* = 19.8, 8.6 Hz, 2H), 7.64 (s, 1H), 7.59 (dd, *J* = 9.0, 1.9 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.66 (d, *J* = 6.1 Hz, 2H), 3.44 (d, *J* = 5.5 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.73, 150.57, 150.21, 146.66, 144.35, 135.75, 131.55, 129.31, 128.85, 123.53, 121.90, 109.22, 77.74, 77.31, 76.89 ppm. **IR** (neat, cm^{-1}): 1593, 1544, 1496, 1379, 1355, 1335, 1224, 1118, 1071, 996, 922, 845, 803, 624.



***t*-butyl 4-(2-methoxyphenyl)piperazine-1-carboxylate:** Following general procedure G, a mixture of 2- chloroanisole (122 µL, 1.00 mmol, 1.00 equiv), *t*-butyl piperazine-1-carboxylate (223 mg, 1.20 mmol, 1.20 equiv) NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv), **L4** (0.9 mg, 0.2 mol %), **6d** (1.7 mg, 0.2 mol %) and THF (1 mL) was stirred at 85 °C for 4 h. The crude product was purified by flash chromatography, eluting with 20% ethyl acetate in hexanes, to provide the title compound as a light yellow solid. **Yield**: 268 mg, 92%. **mp** = 69 – 70° C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.05 - 6.99 (m, 1H), 6.94 - 6.90 (m, 2H), 6.88 (d, *J* = 8.2 Hz, 1H), 3.87 (s, 3H), 3.67 - 3.55 (m, 4H), 3.01 (d, *J* = 4.1 Hz, 4H), 1.49 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.04, 152.45, 141.31, 123.54, 121.22, 118.57, 111.42, 79.91, 55.62, 50.93, 28.70 ppm. **IR** (neat, cm^{-1}): 2975, 1697, 1502, 1421, 1242, 1173, 1122, 1030, 923, 747.



***N,N*-dibutyl-4-methoxy-3-methylaniline:** Following general procedure G, a mixture of 4-bromo-2- methylanisole (201 mg, 1.00 mmol, 1.00 equiv), di-*n*-butylamine (202 µL, 1.20 mmol, 1.20 equiv) NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv), **L4** (2.3 mg, 0.5 mol %), **6d** (4.1 mg, 0.5 mol %) and THF (1 mL) was stirred at 85 °C for 4 h. The crude product was purified by flash chromatography, eluting with 20% ethyl acetate in hexanes, to provide the title compound as a light yellow oil. **Yield**: 234 mg, 94% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.84 (d, *J* = 8.8 Hz, 1H), 6.67 (d, *J* = 3.0 Hz, 1H), 6.61 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.86 (s, 3H), 3.33 - 3.23 (m, 5H), 2.33 (s, 3H), 1.70 - 1.58 (m, 4H), 1.45 (dq, *J* = 14.7, 7.4 Hz, 5H), 1.05 (t, *J* = 7.4 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.82, 143.36, 127.59, 117.02, 111.98, 111.59, 56.31, 52.00, 29.87, 20.78, 17.05, 14.38 ppm. **IR** (neat, cm^{-1}): 2957, 2872, 1615, 1510, 1465, 1369, 1246, 1187, 1040, 842, 790, 754, 692. Anal. Calcd. for $C_{16}H_{27}NO$: C, 77.06; H, 10.91. Found: C, 76.89; H, 10.67.



***N*-benzyl-2-methyl-*N*-phenylquinolin-7-amine:** Following general procedure G, a mixture of 7-chloro-2- methylquinoline (177 mg, 1.00 mmol, 1.00 equiv), N-benzylaniline (220 mg, 1.20 mmol, 1.20 equiv) NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv), **L4** (0.5 mg, 0.1 mol %), **6d** (0.8 mg, 0.1 mol %) and THF (1 mL) was stirred at 85 °C for 24 h. The crude product was purified by flash chromatography, eluting with 20% ethyl acetate in hexanes, to provide the title compound as a vibrant yellow solid. **Yield**: 288 mg, 89%. **mp** = 111 – 112° C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.45 (s, 1H), 7.41 - 7.26 (m, 8H), 7.25 - 7.18 (m, 2H), 7.11 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 5.15 (s, 2H), 2.65 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.41, 149.78, 149.34, 147.60, 138.69, 135.86, 129.95, 128.88, 128.14, 127.16, 126.82, 124.57, 124.31, 121.22, 119.47, 119.41, 112.49, 56.66, 25.62 ppm. **IR** (neat, cm^{-1}): 1618, 1594, 1492, 1384, 1350, 1327, 1223, 1153, 1060, 1029, 942, 833, 772, 272, 709, 667.

Precatalyst Solution: A 7 mL scintillation vial equipped with a Teflon septum was charged with palladium source (0.01 mmol, 1.00 equiv) and ligand (0.01 mmol, 1.00 equiv). The vial was evacuated and refilled

with argon. This was repeated twice. THF (1 mL) was then added and the solution was allowed to age for ten minutes, with occasional swirling, before use in a coupling reaction.

Screening: Suzuki-Miyaura Coupling of 4-Chloro-3-Methylanisole with 2, 6-Difluorophenylboronic Acid: A screw-top test tube equipped with a magnetic stir bar and Teflon septum was charged with 2,6-difluorophenylboronic acid (119 mg, 0.75 mmol, 1.50 equiv). It was then evacuated and refilled with argon. This was repeated three times. Then 4-chloro-3-methylanisole (70 µL, 0.50 mmol, 1.00 equiv) was added by syringe, followed by the aged precatalyst solution in THF (1 mL, 2 mol% Pd) and aqueous K_3PO_4 (0.5 M, 2.00 mL, 1.00 mmol, 2.00 equiv). The reaction was stirred at room temperature for half an hour, after which it was opened to air, diluted with diethyl ether and 1, 3, 5-trimethoxybenzene (250 µL, 1 M in diethyl ether) was added as an internal standard. The solvent was removed under vacuum and the yield was determined by ^{1}H NMR.

X-Ray Structure Determination

Low-temperature diffraction data (**ϕ**-and **ω**-scans) were collected on a Siemens Platform three-circle diffractometer coupled to a Bruker-AXS Smart Apex CCD detector with graphite-monochromated Mo K**α** radiation (**λ** = 0.71073 Å) for the structure of compound 6a and on a Bruker-AXS X8 Kappa Duo diffractometer coupled to a Smart Apex2 CCD detector with Mo K**α** radiation (**λ** = 0.71073 Å) from an I**µ**S micro-source for the structure of compounds **2•L1**, **6b**, **6c**, **6n** and **2•L13**. All structures were solved by direct methods using SHELXS[26] and refined against F^2 on all data by full-matrix least squares with SHELXL-97[27] using established refinement techniques.[28] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl groups). All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3-distances and displacement parameters as well as rigid bond restraints for anisotropic displacement parameters unless otherwise noted below.

Compound **6a** crystallizes in the triclinic space group *P-1* with one molecule in the asymmetric unit.

Compound **2•L1** crystallizes in the triclinic space group P-1 with one molecule in the asymmetric unit. There is evidence of slight disorder of the C41,C41,C42 iPr group (namely elongated thermal ellipsoids of those atoms and residual electron density around them), however all attempts to parameterize this disorder failed (ratio refined to 95:5, thermal ellipsoids of minor component were poor, etc.).

Compound **6b** crystallizes in the triclinic space group P-1 with one molecule in the asymmetric unit. Coordinates for the nitrogen bound hydrogen atoms were taken from the difference Fourier Synthesis. The hydrogen atoms in question were subsequently refined semi-freely with the help of distance restraints while constraining their U_{iso} to 1.2 times the value of the U_{eq} of the nitrogen atom to which they bind.

Compound **6c** crystallizes in the monoclinic space group *$P2_1/n$* with one molecule in the asymmetric unit. Coordinates for the nitrogen bound hydrogen atoms were taken from the difference Fourier Synthesis. The hydrogen atoms in question were subsequently refined semi-freely with the help of distance restraints while constraining their U_{iso} to 1.2 times the value of the U_{eq} of the nitrogen atom to which they bind. Compound 6n crystallizes in the triclinic space group P-1 with two molecules in the asymmetric unit. There is a fairly complex solvent disorder (all CH_2Cl_2), which was refined with the help of extensive restraints and some equal-ADP constraints. The asymmetric unit contains two $C_{56}H_{42}NP_2Pd$ target molecules with two CH_3SO_3 counter ions as well as seven CH_2Cl_2 solvent molecules. Six of those solvent molecules are fully occupied, the seventh one is located in the asymmetric unit in form of two half occupied molecules, located near crystallographic inversion centers. Three of the solvent molecules are not disordered, three are disordered over two positions. The two half occupied solvent molecules are highly disordered, one over four (two independent) and the other one over six (three independent) positions.

Compound **2•L13** crystallizes in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit.

Table 1. Crystal data and structure refinement for **6a**

Identification code	12044
Empirical formula	C50 H72 N O4 P Pd S
Formula weight	920.52
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 12.3071(10) Å a= 102.4550(10)°.
	b = 13.5653(11) Å b= 94.4810(10)°.
	c = 14.7831(12) Å g = 98.6540(10)°.
Volume	2366.8(3) $Å^3$
Z	2
Density (calculated)	1.292 mg/m^3
Absorption coefficient	0.513 mm^{-1}
F(000)	976
Crystal size	0.33 x 0.30 x 0.14 mm^3
Theta range for data collection	1.42 to 30.51°.
Index ranges	-17<=h<=17, -19<=k<=19, -21<=l<=21
Reflections collected	68495
Independent reflections	14378 [R(int) = 0.0449]
Completeness to theta = 30.51°	99.5 %
Absorption correction	Semi-empirical from equivalents

Max. and min. transmission	0.9316 and 0.8489
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	14378 / 269 / 599
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0313, wR2 = 0.0757
R indices (all data)	R1 = 0.0370, wR2 = 0.0795
Largest diff. peak and hole	1.102 and -0.488 e.$Å^{-3}$

Table 2. Crystal data and structure refinement for **2·L1.**

Identification code	x12053
Empirical formula	C45 H59 Cl N P Pd
Formula weight	786.75
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.1656(13) Å a= 97.346(3)°.
	b = 13.4105(18) Å b= 101.171(3)°.
	c = 15.503(2) Å g = 101.772(3)°.
Volume	1998.7(5) $Å^3$
Z	2
Density (calculated)	1.307 mg/m^3
Absorption coefficient	0.603 mm^{-1}
F(000)	828
Crystal size	0.20 x 0.12 x 0.03 mm^3
Theta range for data collection	1.36 to 30.51°.

Index ranges	-14<=h<=14, -19<=k<=19, -22<=l<=22
Reflections collected	126595
Independent reflections	12138 [R(int) = 0.0293]
Completeness to theta = 30.51°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9821 and 0.8890
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12138 / 2 / 454
Goodness-of-fit on F^2	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0201, wR2 = 0.0533
R indices (all data)	R1 = 0.0217, wR2 = 0.0544
Largest diff. peak and hole	0.850 and -0.386 e.$Å^{-3}$

Table 3. Crystal data and structure refinement for **6b**.

Identification code	x12064
Empirical formula	C44 H62 Cl4 N O3 P Pd S
Formula weight	964.18
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.8288(9) Å a= 110.420(2)°.
	b = 13.3096(11) Å b= 93.341(2)°.
	c = 17.3470(15) Å g = 103.421(2)°.
Volume	2252.3(3) $Å^3$
Z	2

Density (calculated)	1.422 mg/m^3
Absorption coefficient	0.770 mm^{-1}
F(000)	1004
Crystal size	0.25 x 0.24 x 0.23 mm^3
Theta range for data collection	1.27 to 31.30°.
Index ranges	-15<=h<=15, -19<=k<=19, -25<=l<=25
Reflections collected	221977
Independent reflections	14723 [R(int) = 0.0322]
Completeness to theta = 31.30°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8427 and 0.8307
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	14723 / 15 / 515
Goodness-of-fit on F^2	1.053
Final R indices [I>2sigma(I)]	R1 = 0.0236, wR2 = 0.0603
R indices (all data)	R1 = 0.0253, wR2 = 0.0612
Largest diff. peak and hole	0.903 and -0.883 $e.Å^{-3}$

Table 4. Crystal data and structure refinement for **6c**.

Identification code	x12062
Empirical formula	C48 H66 N O5 P Pd S
Formula weight	906.45
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n

Unit cell dimensions	a = 15.5569(6) Å a= 90°.
	b = 17.0797(7) Å b= 94.2220(10)°.
	c = 16.7243(6) Å g = 90°.
Volume	4431.7(3) $Å^3$
Z	4
Density (calculated)	1.359 mg/m^3
Absorption coefficient	0.549 mm^{-1}
F(000)	1912
Crystal size	0.30 x 0.20 x 0.13 mm^3
Theta range for data collection	1.71 to 31.00°.
Index ranges	-22<=h<=22, -24<=k<=24, -21<=l<=24
Reflections collected	211874
Independent reflections	14118 [R(int) = 0.0474]
Completeness to theta = 31.00°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9321 and 0.8527
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	14118 / 2 / 529
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0248, wR2 = 0.0595
R indices (all data)	R1 = 0.0323, wR2 = 0.0637
Largest diff. peak and hole	0.567 and -0.363 $e.Å^{-3}$

Table 5. Crystal data and structure refinement for **6n.**

Identification code	x12061
Empirical formula	C60.50 H52 Cl7 N O3 P2 Pd S

Formula weight	1289.58
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 13.9763(14) Å a= 75.424(2)°.
	b = 20.426(2) Å b= 85.472(2)°.
	c = 21.290(2) Å g = 76.307(2)°.
Volume	5713.9(10) $Å^3$
Z	4
Density (calculated)	1.499 Mg/m^3
Absorption coefficient	0.791 mm^{-1}
F(000)	2628
Crystal size	0.30 x 0.25 x 0.05 mm^3
Theta range for data collection	1.06 to 31.00°.
Index ranges	-20<=h<=20, -29<=k<=29, -30<=l<=30
Reflections collected	370048
Independent reflections	36383 [R(int) = 0.0485]
Completeness to theta = 31.00°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9615 and 0.7972
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	36383 / 828 / 1552
Goodness-of-fit on F^2	1.087
Final R indices [I>2sigma(I)]	R1 = 0.0407, wR2 = 0.1032
R indices (all data)	R1 = 0.0536, wR2 = 0.1108
Largest diff. peak and hole	1.593 and -1.092 $e.Å^{-3}$

Table 6. Crystal data and structure refinement for **2·L13.**

Identification code	x12094
Empirical formula	C57.50 H45 Cl4 N P2 Pd
Formula weight	1060.08
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 14.5500(18) Å a= 90°.
	b = 13.7601(17) Å b= 94.469(3)°.
	c = 23.806(3) Å g = 90°.
Volume	4751.8(10) $Å^3$
Z	4
Density (calculated)	1.482 mg/m^3
Absorption coefficient	0.724 mm^{-1}
F(000)	2164
Crystal size	0.40 x 0.35 x 0.25 mm^3
Theta range for data collection	1.59 to 32.03°.
Index ranges	-21<=h<=21, -20<=k<=20, -35<=l<=35
Reflections collected	420406
Independent reflections	16548 [R(int) = 0.0491]
Completeness to theta = 32.03°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8397 and 0.7605
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	16548 / 1187 / 838

Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0307, wR2 = 0.0798
R indices (all data)	R1 = 0.0382, wR2 = 0.0856
Largest diff. peak and hole	0.944 and -0.843 e.$Å^{-3}$

Computational Methods

All calculations were carried out with Q-Chem suite of computational programs.[29] Ground state geometry optimizations were evaluated using the B3LYP[30] density functional method. For C, H, N, P, S and Cl atoms, the 6-31G(d) basis set was used; while LANL2DZ effective core potentials of Hay and Wadt[31-33] with double- ζ basis sets were used for Pd atom. Frequency calculations were performed on all optimized structures to verify that they have no negative frequencies. Gibbs free energies were calculated at 298.18 K and 1 atm. All charges were evaluated using Natural Bond Orbital version 5.0 (NBO 5.0) population analysis as implemented in Q-Chem.[34]

Comparison of Natural Charges on Pd:

6a: 0.52891

2•L1: 0.47961

Net Positive Charge on **6a** Complex: 0.0493

6a

Pd 2.36008 -0.02901 0.37054
O 3.16060 1.94661 -0.25936
S 4.06845 2.64750 0.75821
O 3.36105 2.95328 2.01791
O 5.37242 1.93548 0.89665
C 4.44707 4.21274 -0.05186
H 5.12407 4.76918 0.59957
H 3.51951 4.76934 -0.19751
H 4.92658 4.00527 -1.01000
P 0.10401 0.49247 -0.17389
C -0.10200 2.08728 -1.16079
H -1.15625 2.09028 -1.46995
C 0.78134 2.07839 -2.43002
H 1.83172 2.01947 -2.12740
H 0.57157 1.19632 -3.04474
C 0.55921 3.34706 -3.27192
H 1.21679 3.32091 -4.15029
H -0.47302 3.36070 -3.65387
C 0.81232 4.61686 -2.44950
H 1.87359 4.65422 -2.16559
H 0.61496 5.51117 -3.05452
C -0.05376 4.62892 -1.18292
H -1.11221 4.70862 -1.47274
H 0.16884 5.51469 -0.57400
C 0.14809 3.36348 -0.32946
H -0.52663 3.39697 0.53217
H 1.16730 3.34036 0.06699
C -0.72103 -0.85218 -1.22425
H -1.15224 -1.53561 -0.48349
C -1.84660 -0.37857 -2.17114
H -2.62346 0.15602 -1.62242
H -1.43112 0.31930 -2.90941
C -2.47973 -1.55923 -2.93013
H -2.98555 -2.21965 -2.21307
H -3.25831 -1.17653 -3.60298
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H 0.39128 2.15048 4.36850

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H 6.29053 -0.53321 -1.16459

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C 0.83332 -3.42003 2.60107

H 0.10822 -3.57174 3.39720

C 1.01559 -2.13878 2.06553

H 0.42778 -1.31898 2.46422

C 1.94235 -1.89706 1.04535

2·L1

Cl 3.34312 -2.98791 0.60605

Pd 2.61141 -0.61475 0.66251

P 0.33161 -0.83905 0.06666

C -0.17837 0.44306 -1.23295

H -0.48471 1.31107 -0.63695

C 1.03833 0.87322 -2.09120

H 1.86327 1.18495 -1.44924

H 1.40191 0.01561 -2.67297

C 0.67198 2.01548 -3.05364

H 0.41532 2.91055 -2.46759

H 1.55245 2.27843 -3.65374

C -0.50827 1.64605 -3.96059

H -0.78260 2.49491 -4.60023

H -0.20625 0.83005 -4.63385

C -1.71190 1.19474 -3.12435

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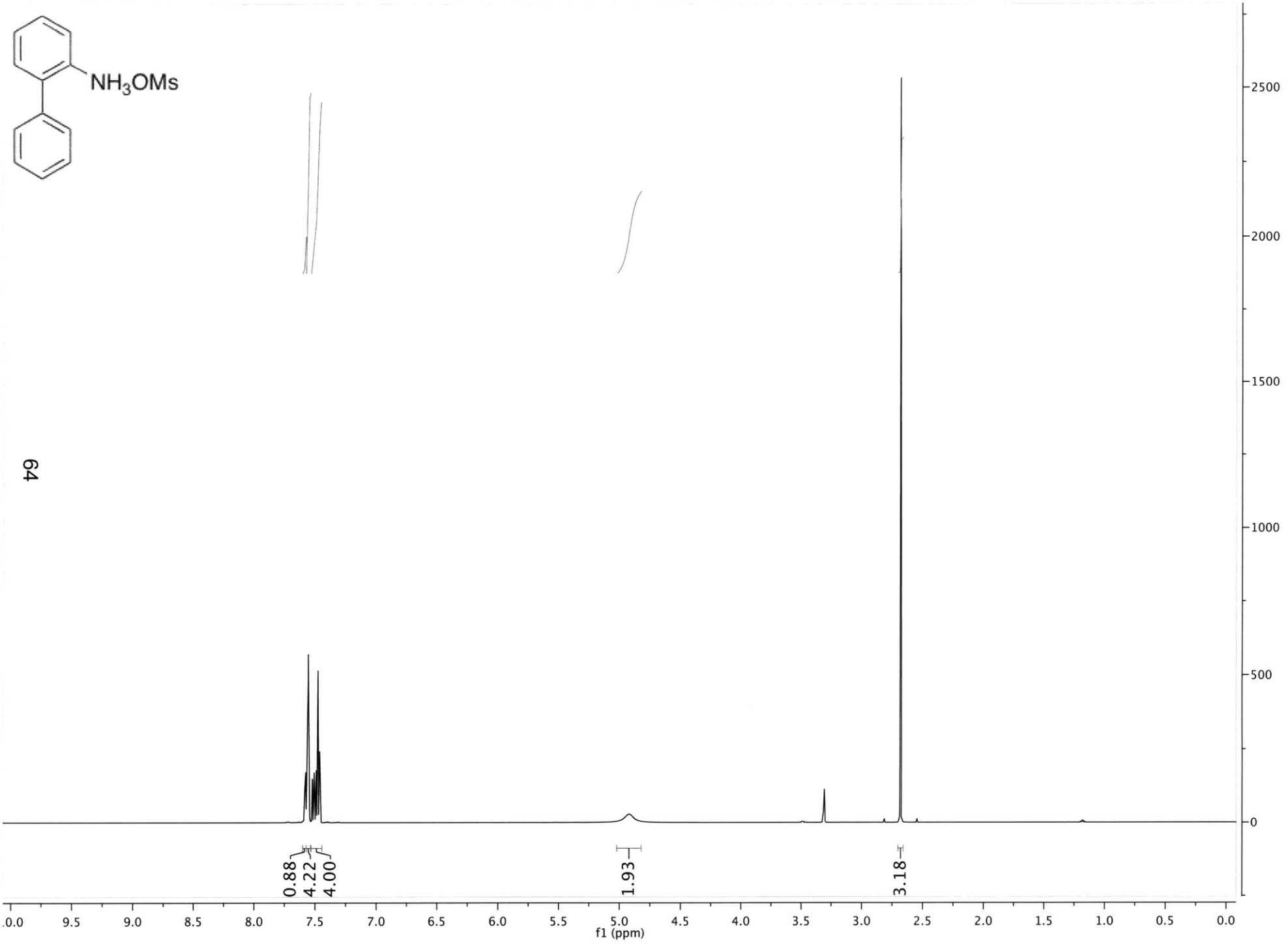
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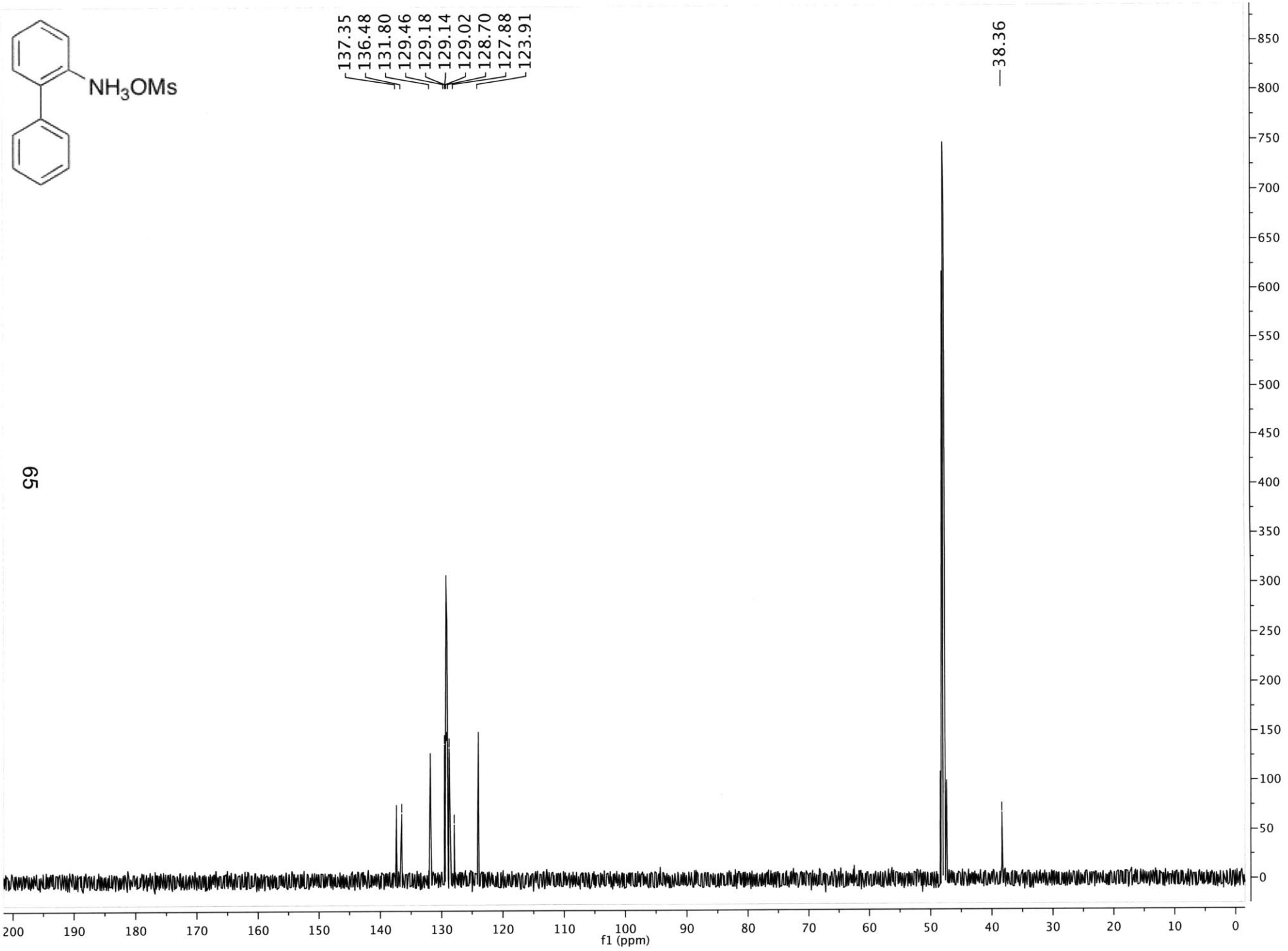
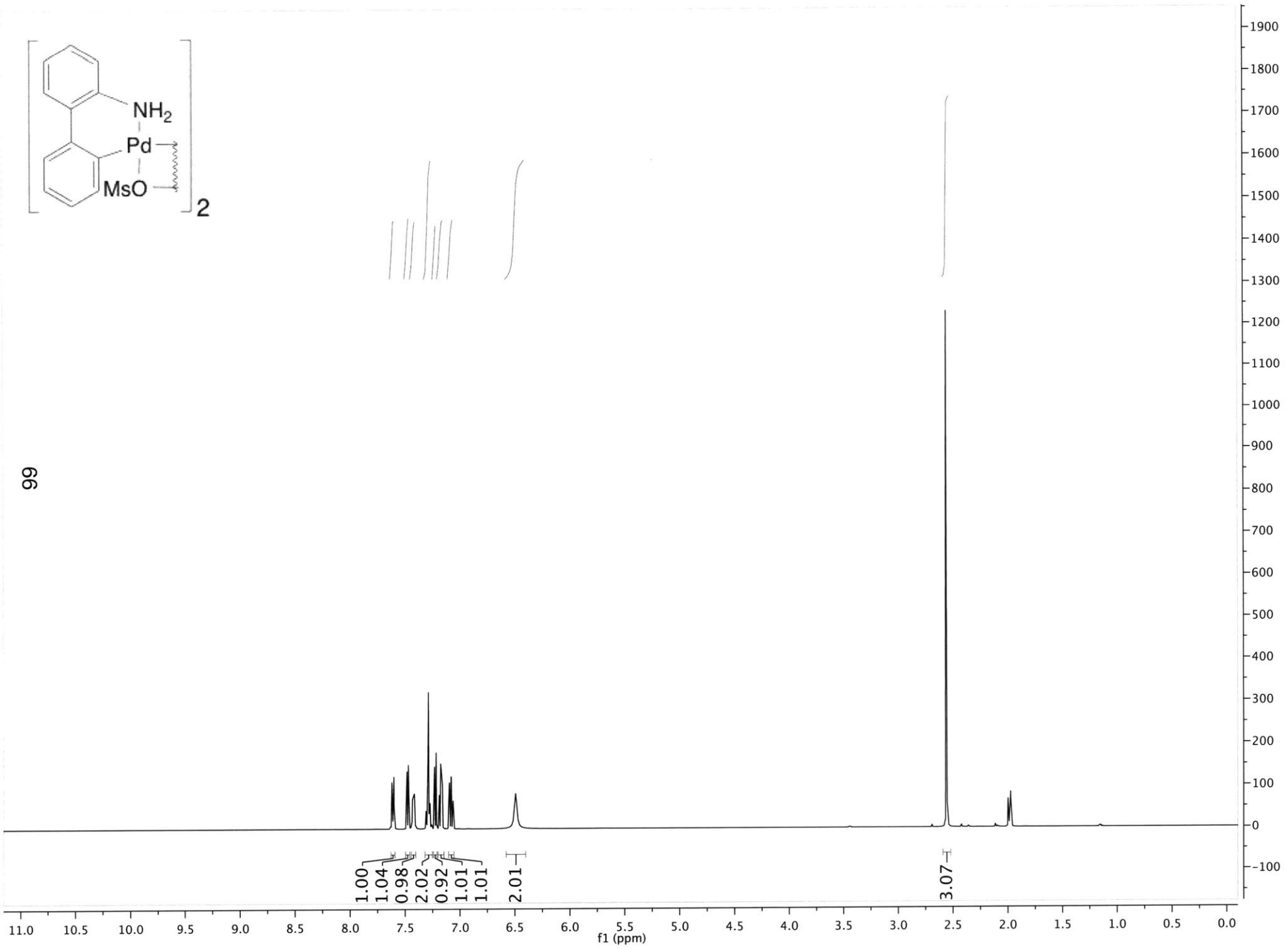
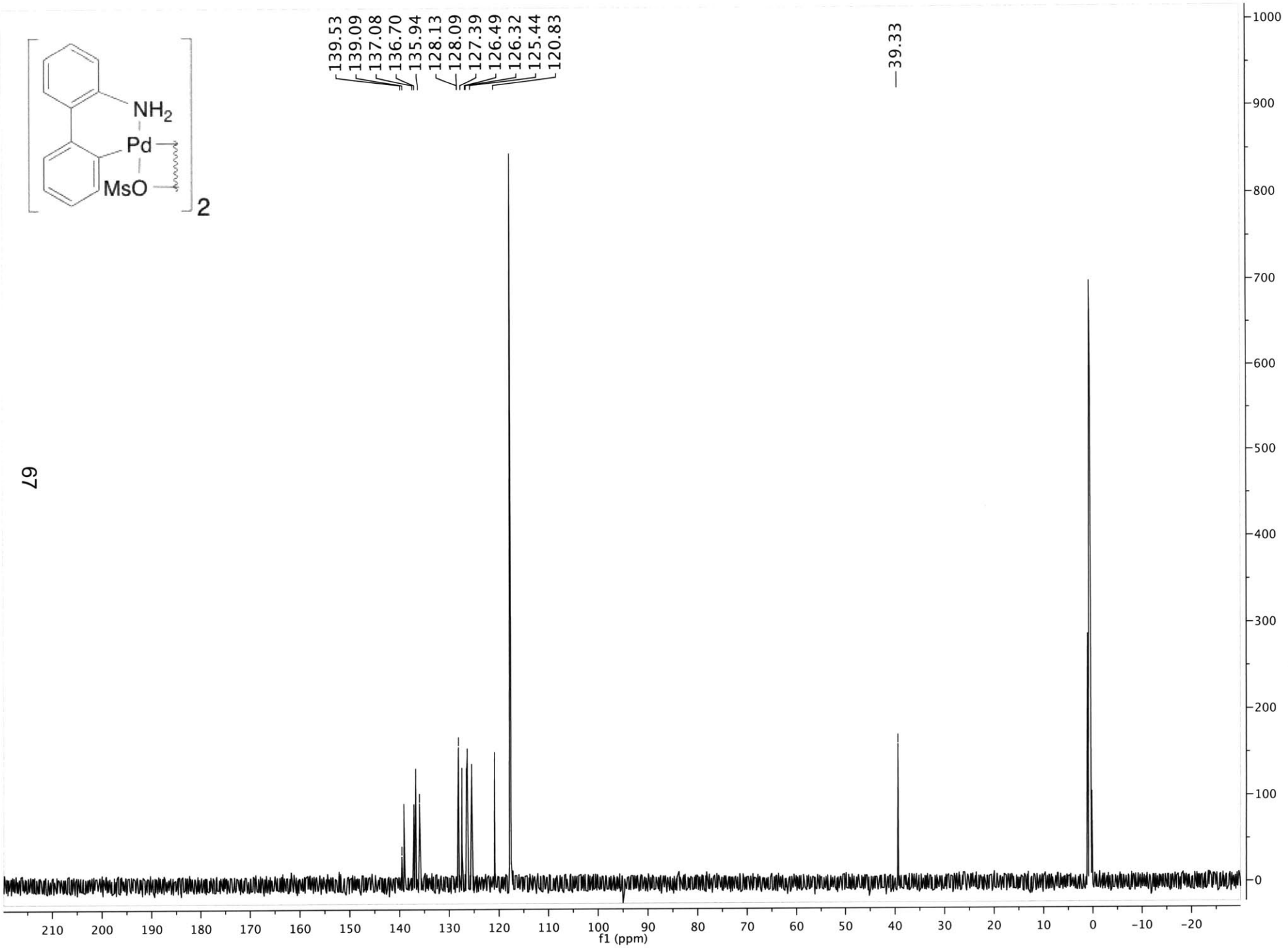
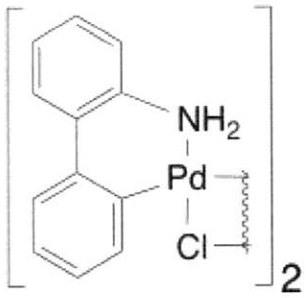
1.93
3.18
f1 (ppm)


NH3OMs
137.35
136.48
131.80
129.46
129.18
129.14
129.02
128.70
127.88
123.91
38.36
f1 (ppm)

65


NH2
Pd
MsO
2
99
1.00
1.04
0.98
2.02
0.92
1.01
1.01
2.01
3.07
f1 (ppm)

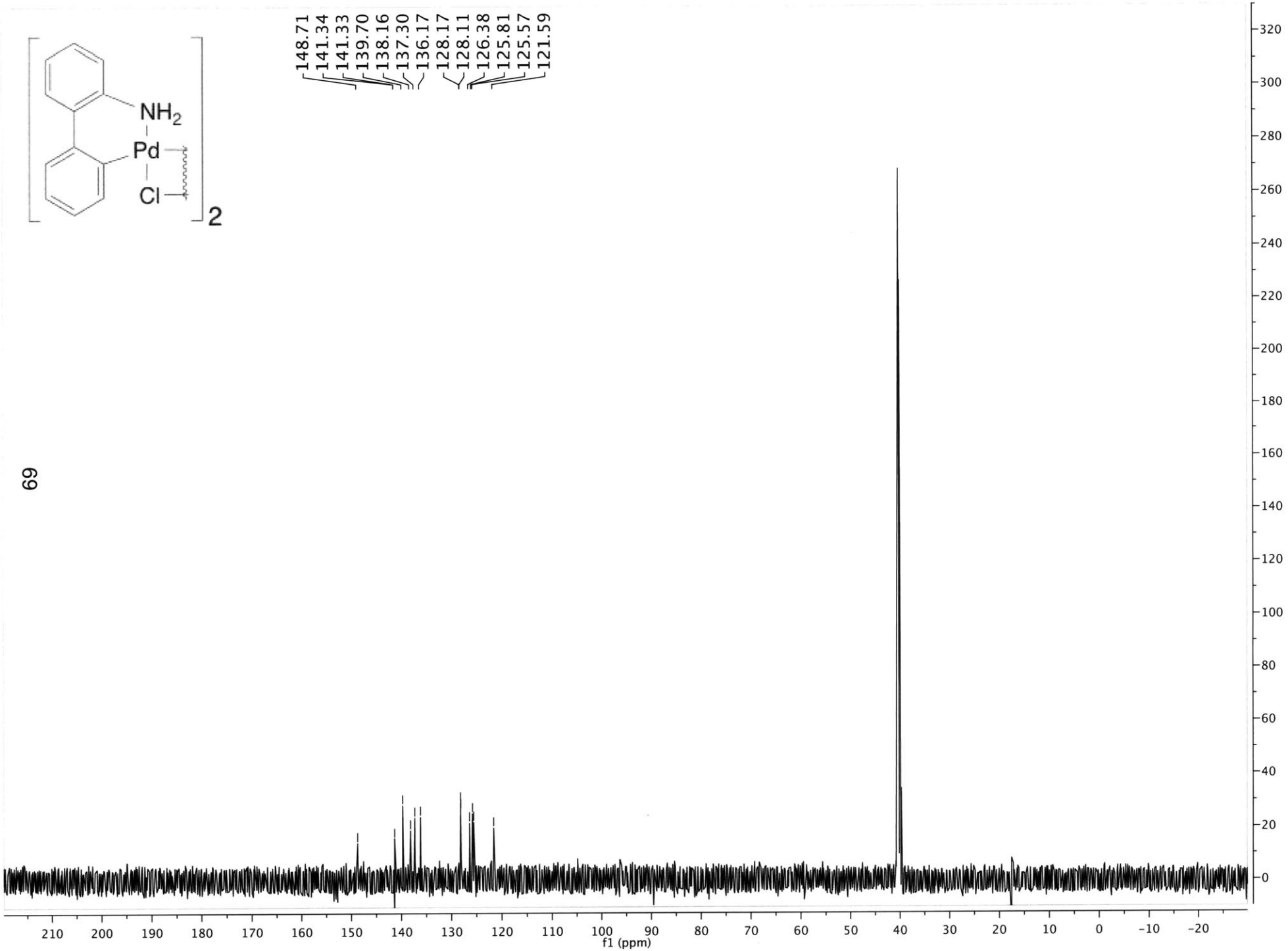

NH2
Pd
MsO
2
139.53
139.09
137.08
136.70
135.94
128.13
128.09
127.39
126.49
126.32
125.44
120.83
39.33
67
f1 (ppm)

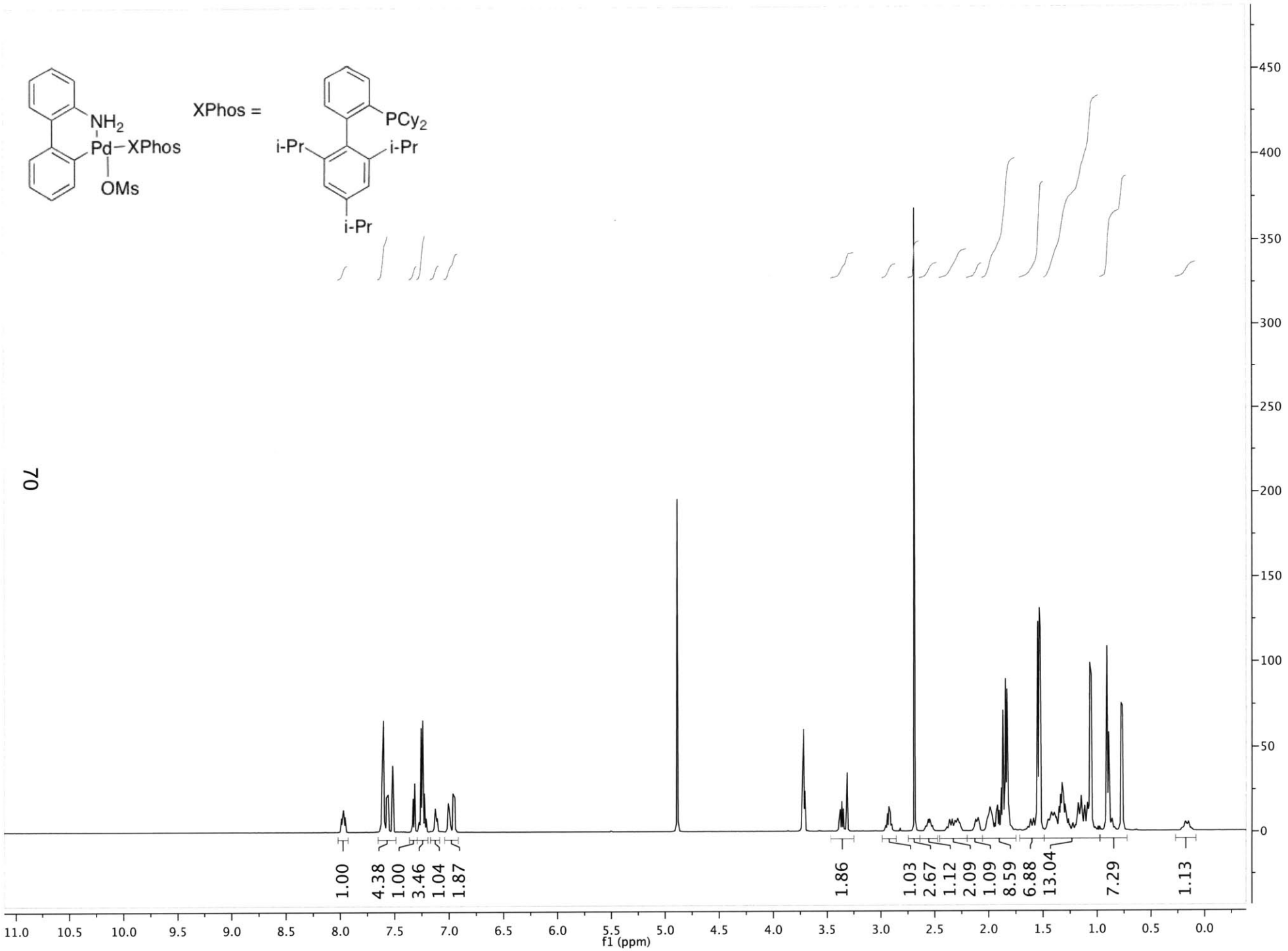


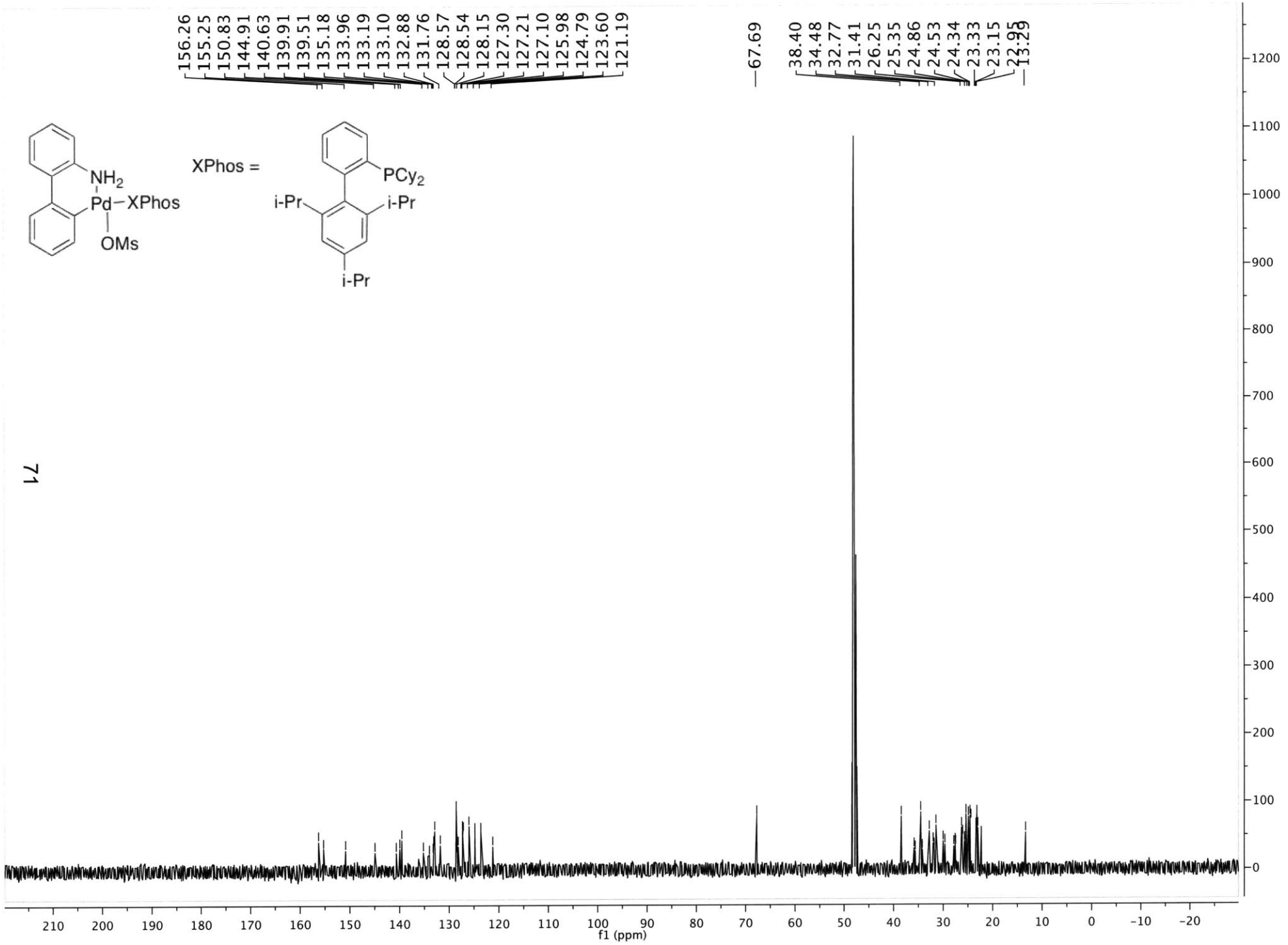
68

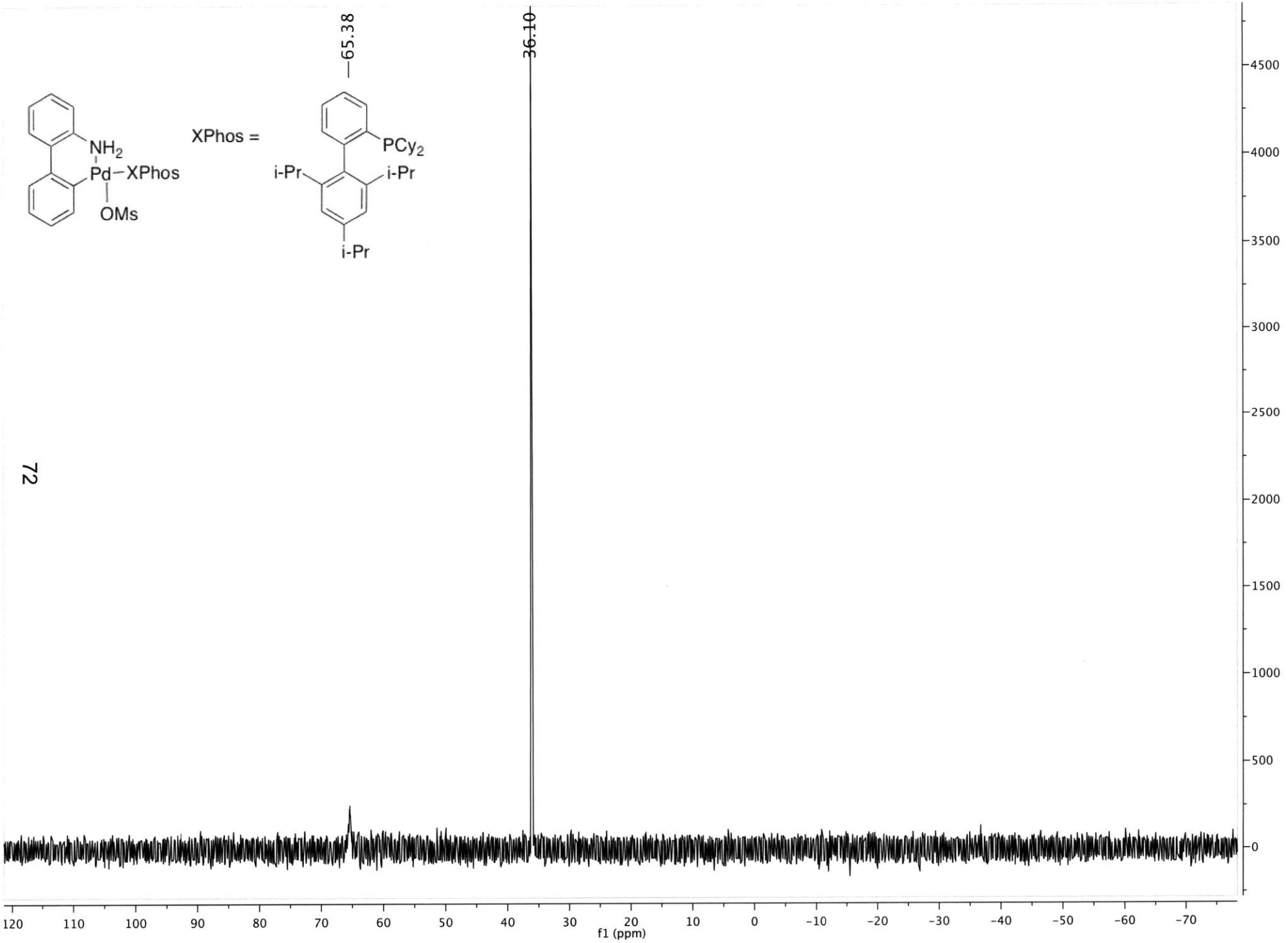
1.00
0.94
2.05
3.96
0.95

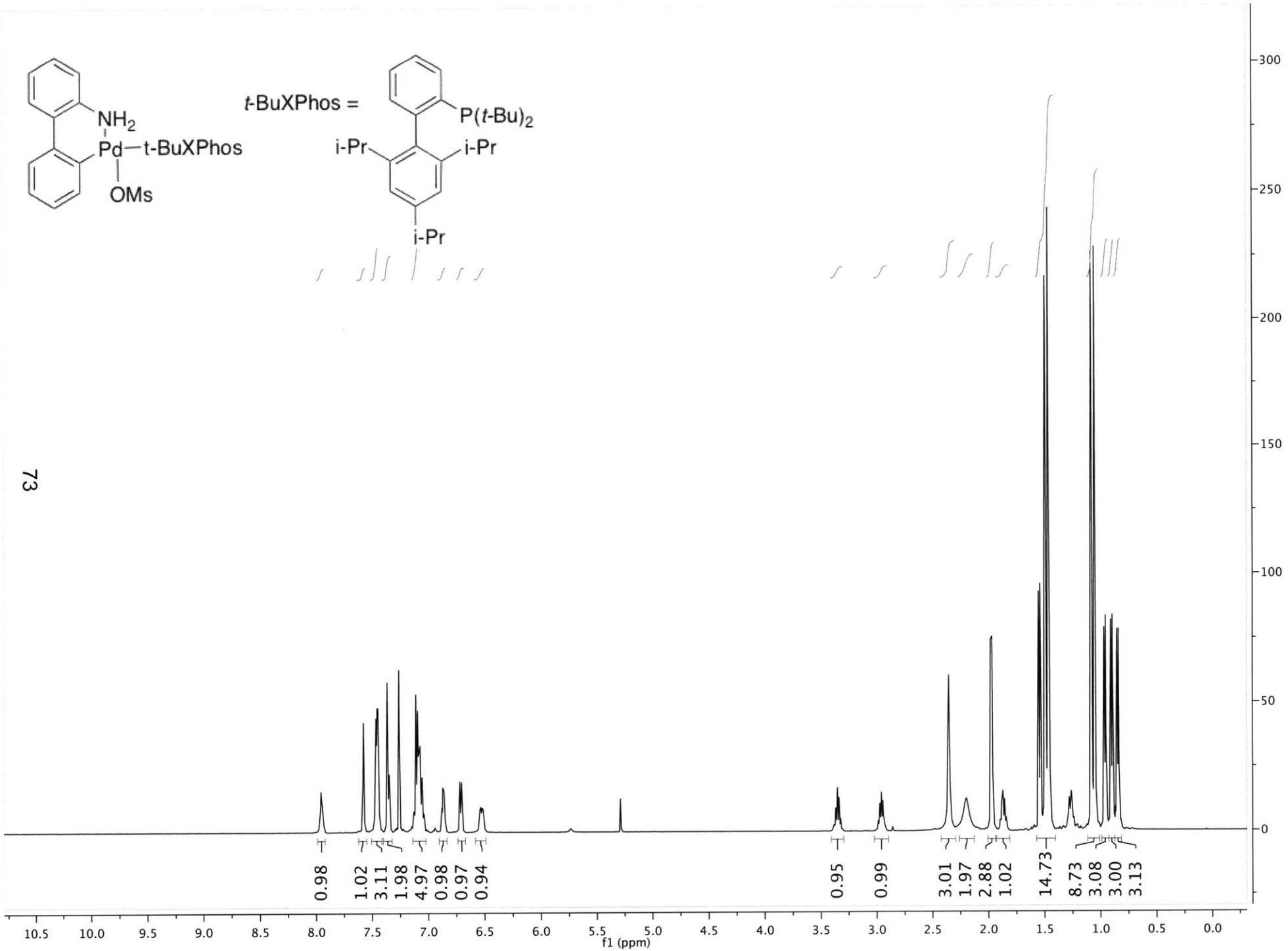
f1 (ppm)

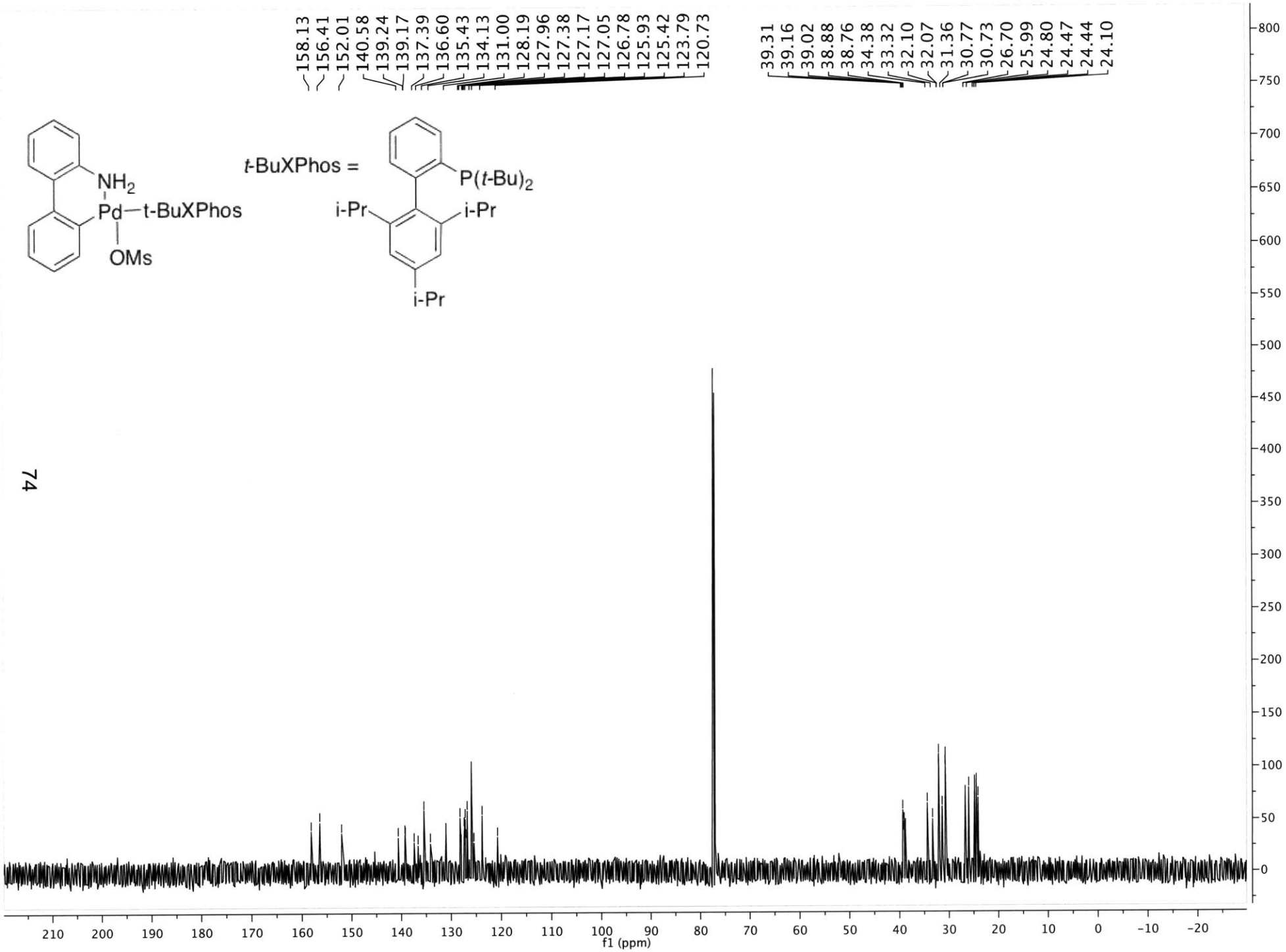

148.71
141.34
141.33
139.70
138.16
137.30
136.17
128.17
128.11
126.38
125.81
125.57
121.59
NH2
Pd
Cl
2
69
f1 (ppm)

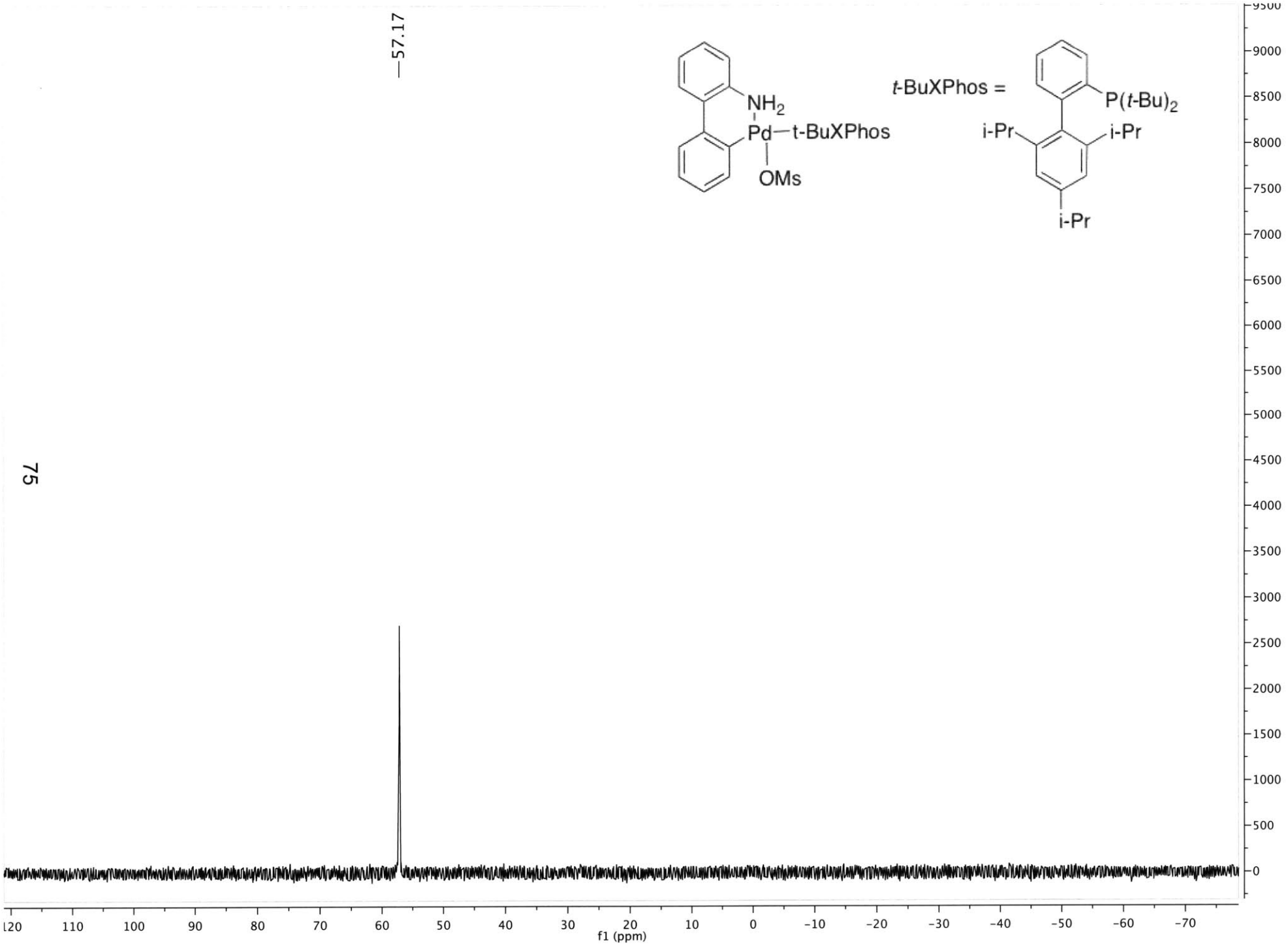

NH2
Pd–XPhos
OMs
XPhos =
PCy2
i-Pr
i-Pr
i-Pr
70
1.00
4.38
1.00
3.46
1.04
1.87
1.86
1.03
2.67
1.12
2.09
1.09
8.59
6.88
13.04
7.29
1.13
f1 (ppm)

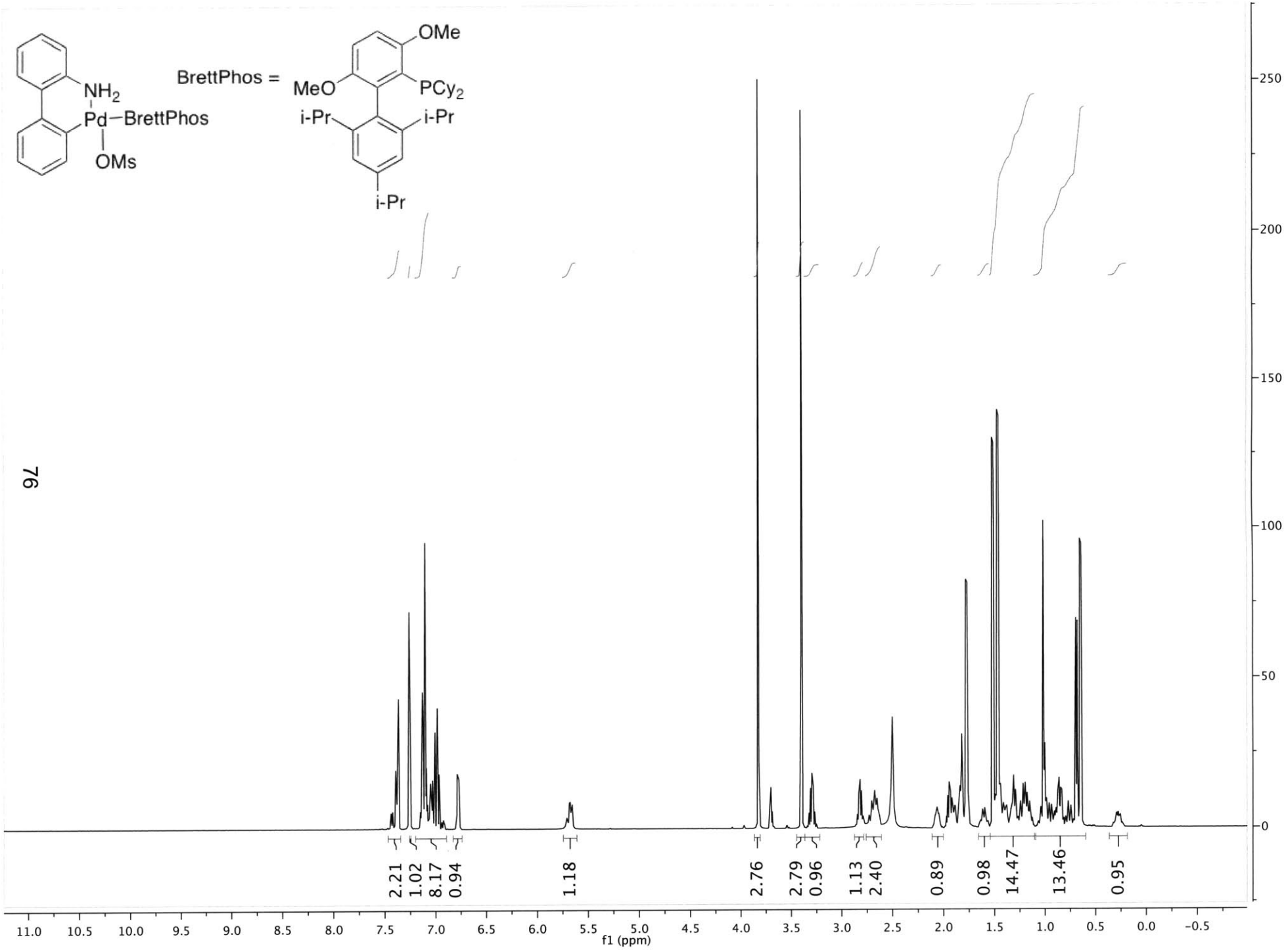

156.26
155.25
150.83
144.91
140.63
139.91
139.51
135.18
133.96
133.19
133.10
132.88
131.76
128.57
128.54
128.15
127.30
127.21
127.10
125.98
124.79
123.60
121.19
67.69
38.40
34.48
32.77
31.41
26.25
25.35
24.86
24.53
24.34
23.33
23.15
22.95
13.29
NH2
Pd—XPhos
OMs
XPhos =
PCy2
i-Pr
i-Pr
i-Pr
71
f1 (ppm)

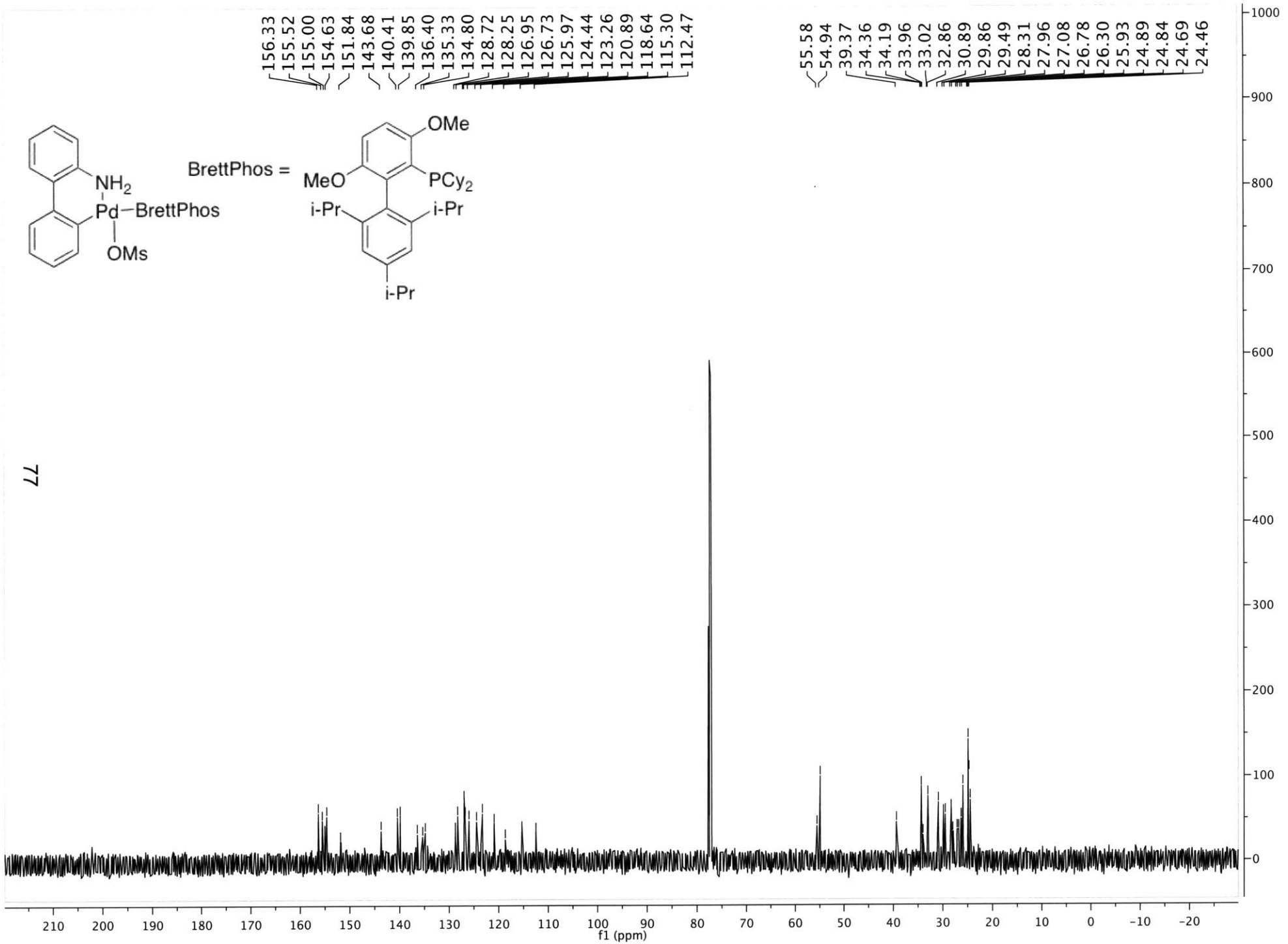

65.38
36.10
NH2
Pd—XPhos
OMs
XPhos =
PCy2
i-Pr
i-Pr
i-Pr
72
4500
4000
3500
3000
2500
2000
1500
1000
500
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

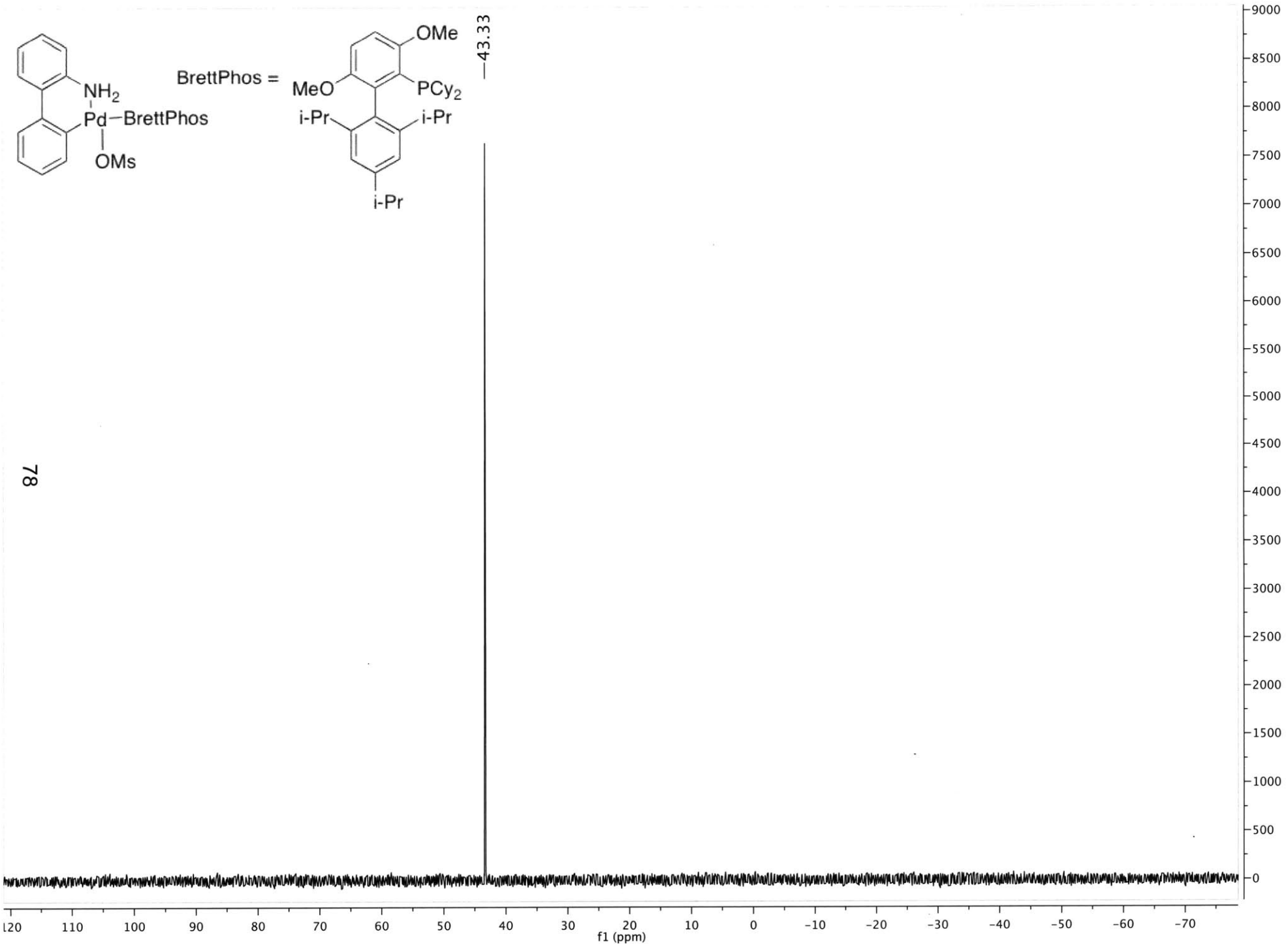

NH2
Pd—t-BuXPhos
OMs
t-BuXPhos =
P(t-Bu)2
i-Pr
i-Pr
i-Pr
0.98
1.02
3.11
1.98
4.97
0.98
0.97
0.94
0.95
0.99
3.01
1.97
2.88
1.02
14.73
8.73
3.08
3.00
3.13
f1 (ppm)

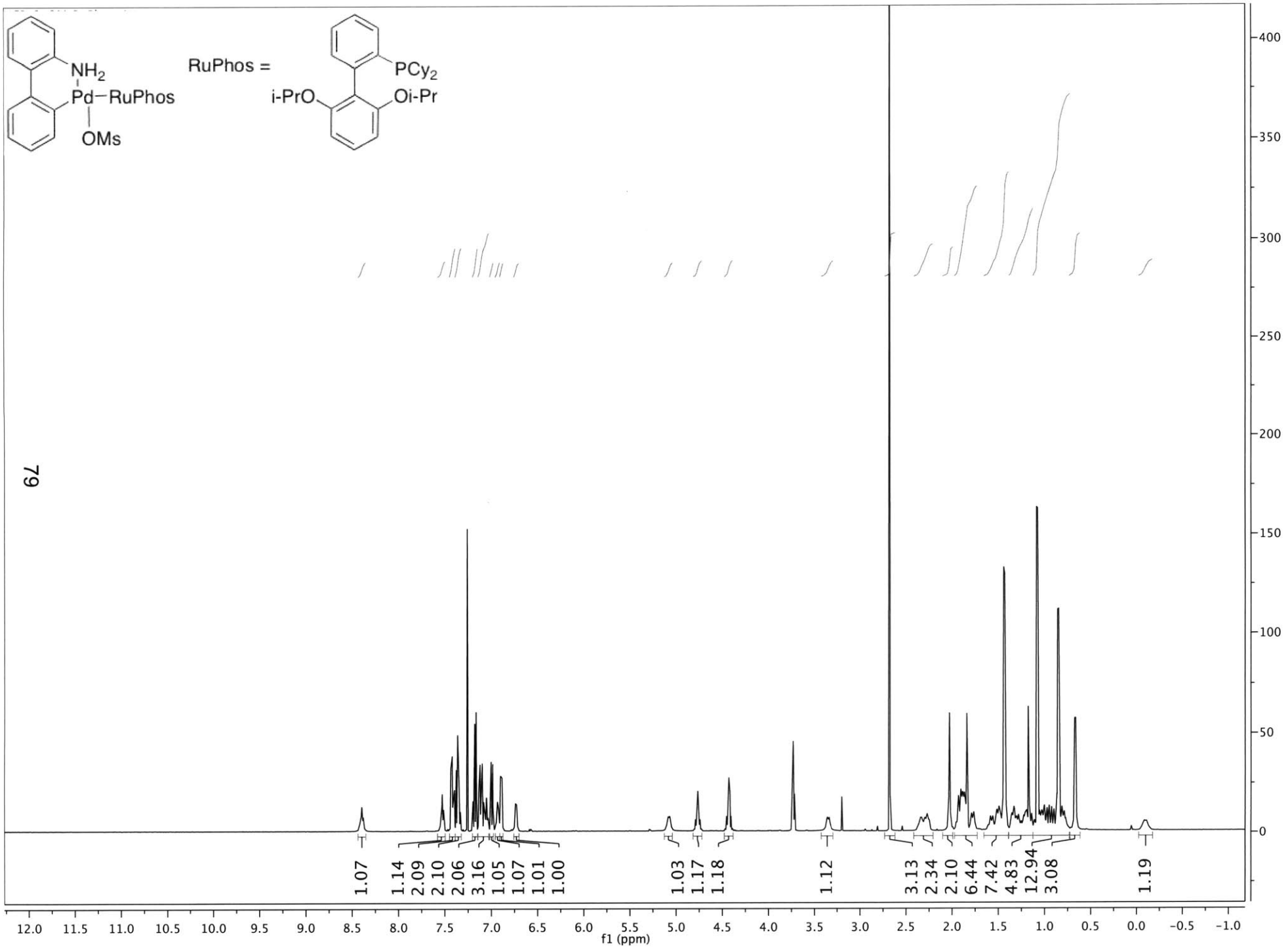

158.13
156.41
152.01
140.58
139.24
139.17
137.39
136.60
135.43
134.13
131.00
128.19
127.96
127.38
127.17
127.05
126.78
125.93
125.42
123.79
120.73
39.31
39.16
39.02
38.88
38.76
34.38
33.32
32.10
32.07
31.36
30.77
30.73
26.70
25.99
24.80
24.47
24.44
24.10
NH2
Pd
t-BuXPhos
OMs
t-BuXPhos =
P(t-Bu)2
i-Pr
i-Pr
i-Pr
f1 (ppm)

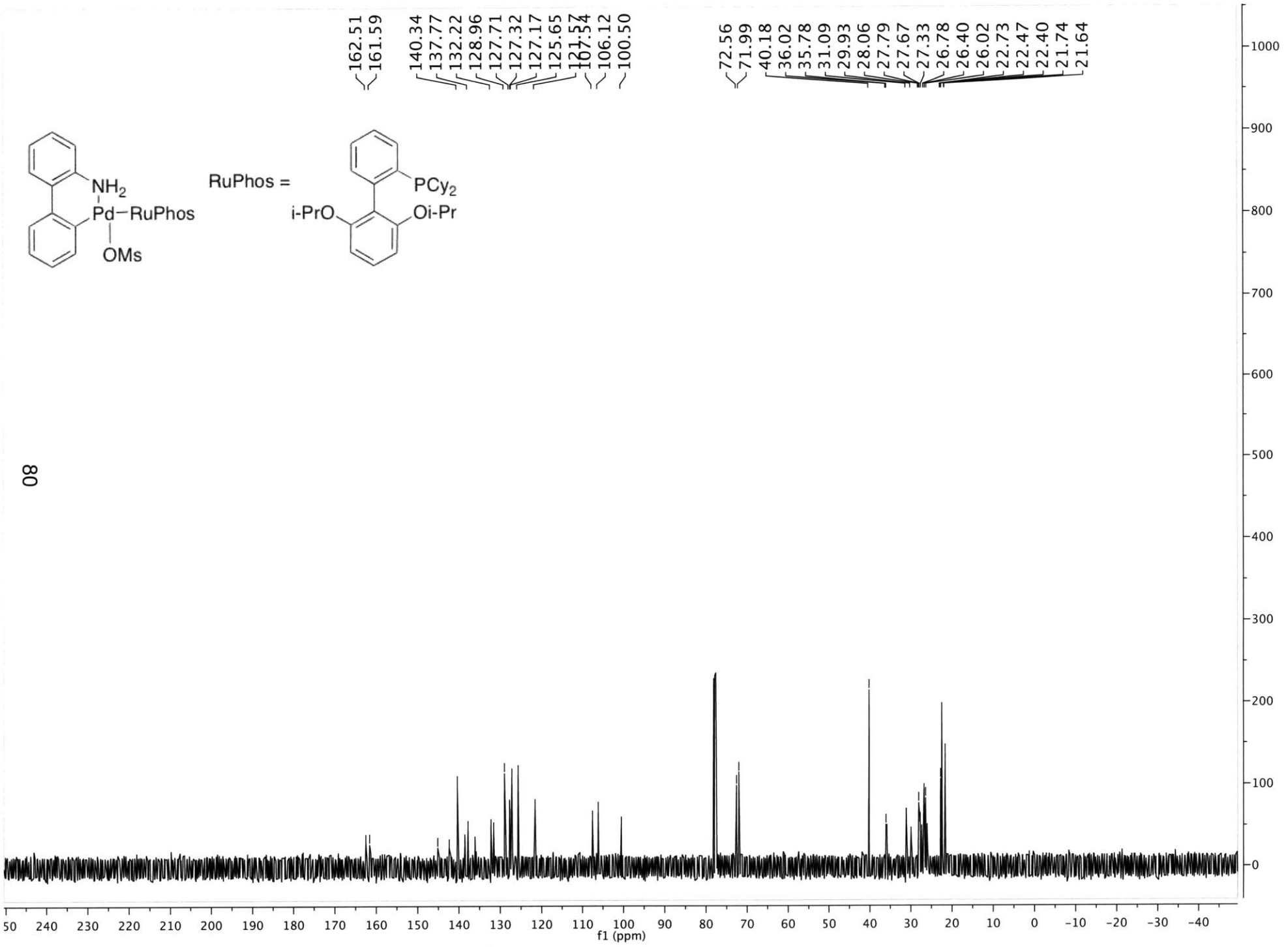

—57.17
NH2
Pd—t-BuXPhos
OMs
t-BuXPhos =
P(t-Bu)2
i-Pr
i-Pr
i-Pr
76
f1 (ppm)

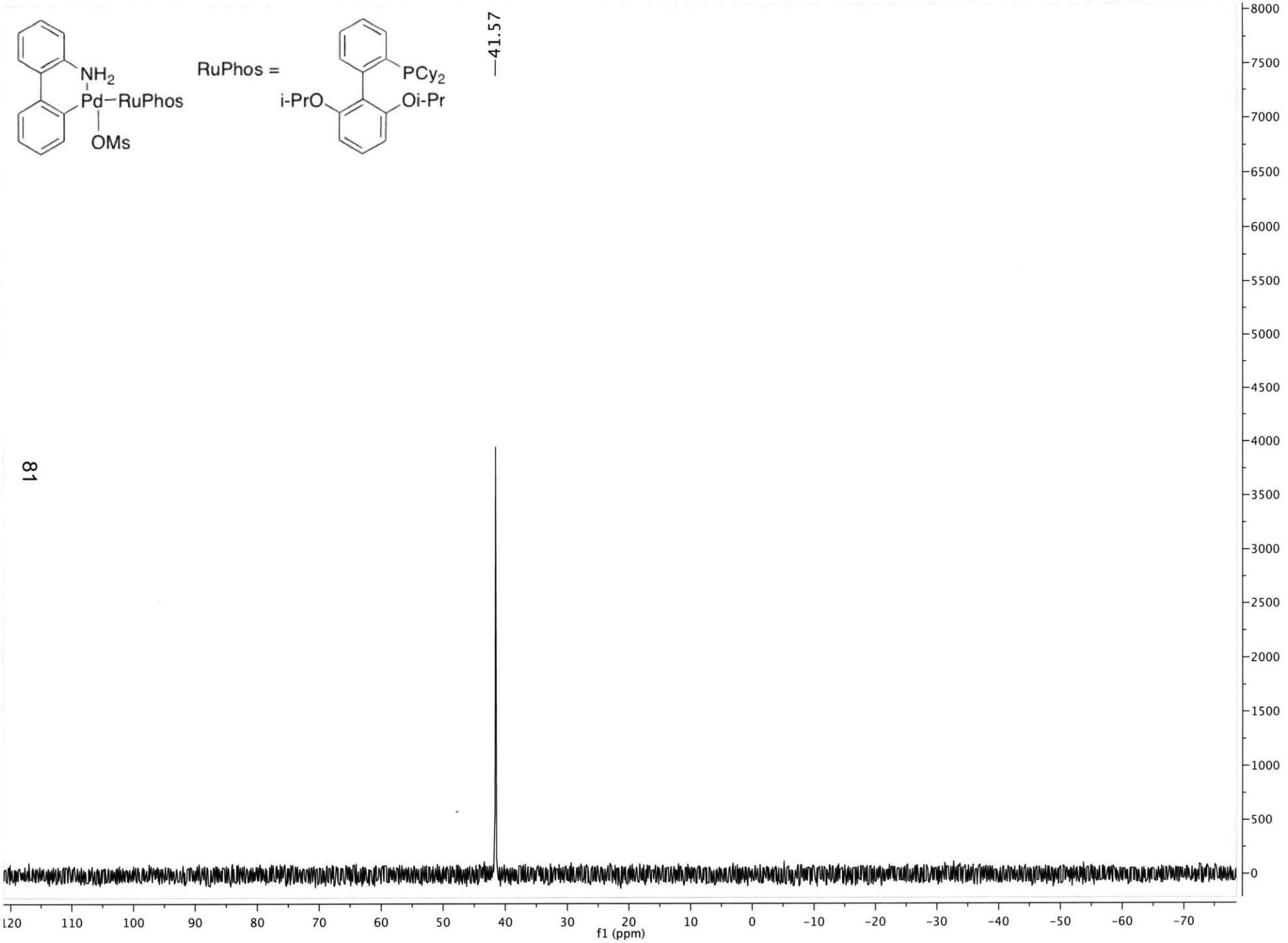

NH2
Pd–BrettPhos
OMs
BrettPhos =
OMe
MeO
PCy2
i-Pr
i-Pr
i-Pr
76
2.21
1.02
8.17
0.94
1.18
2.76
2.79
0.96
1.13
2.40
0.89
0.98
14.47
13.46
0.95
f1 (ppm)

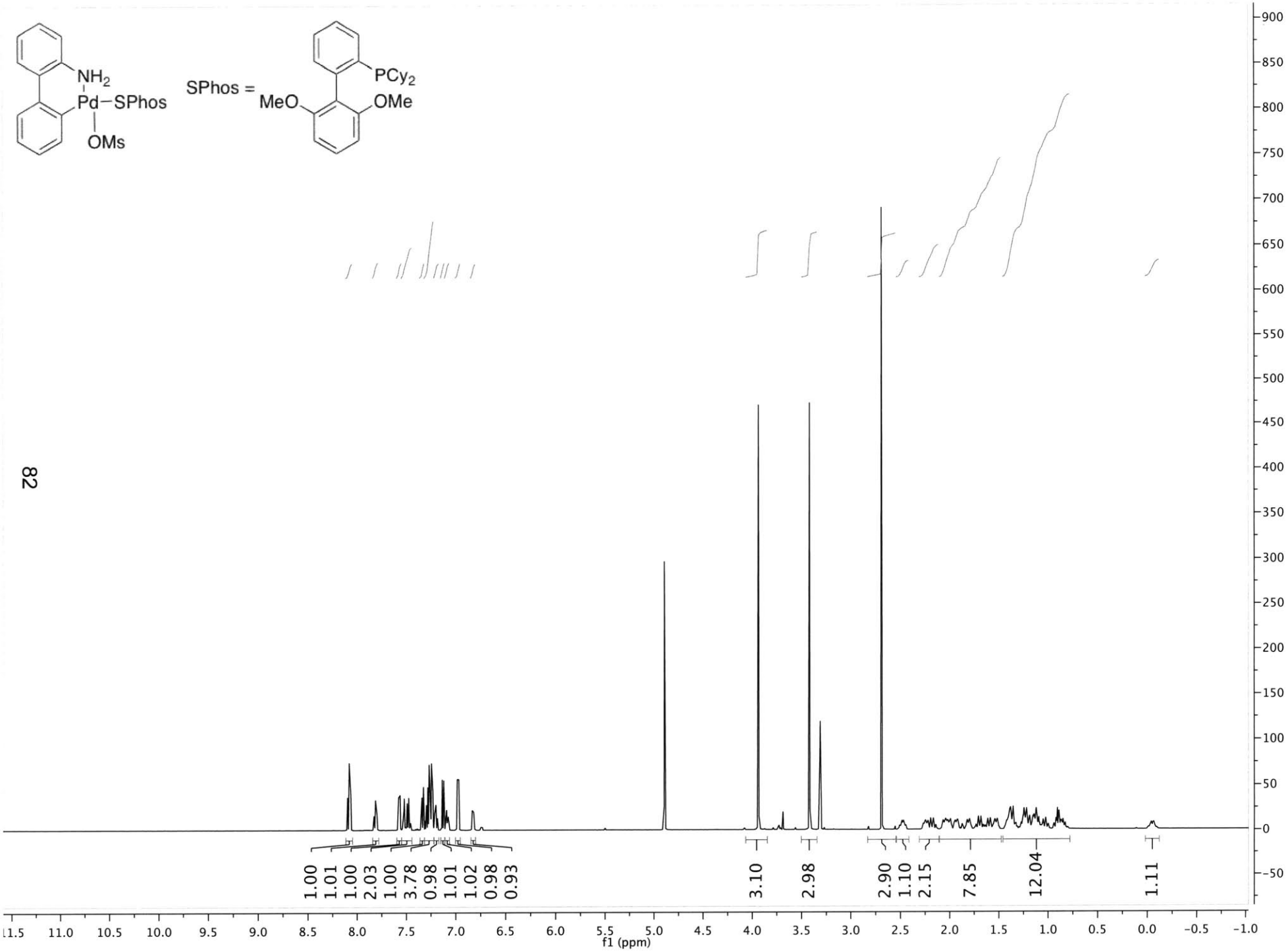

156.33
155.52
155.00
154.63
151.84
143.68
140.41
139.85
136.40
135.33
134.80
128.72
128.25
126.95
126.73
125.97
124.44
123.26
120.89
118.64
115.30
112.47
55.58
54.94
39.37
34.36
34.19
33.96
33.02
32.86
30.89
29.86
29.49
28.31
27.96
27.08
26.78
26.30
25.93
24.89
24.84
24.69
24.46
NH2
Pd–BrettPhos
OMs
BrettPhos =
OMe
MeO
PCy2
i-Pr
i-Pr
i-Pr
77
1000
900
800
700
600
500
400
300
200
100
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

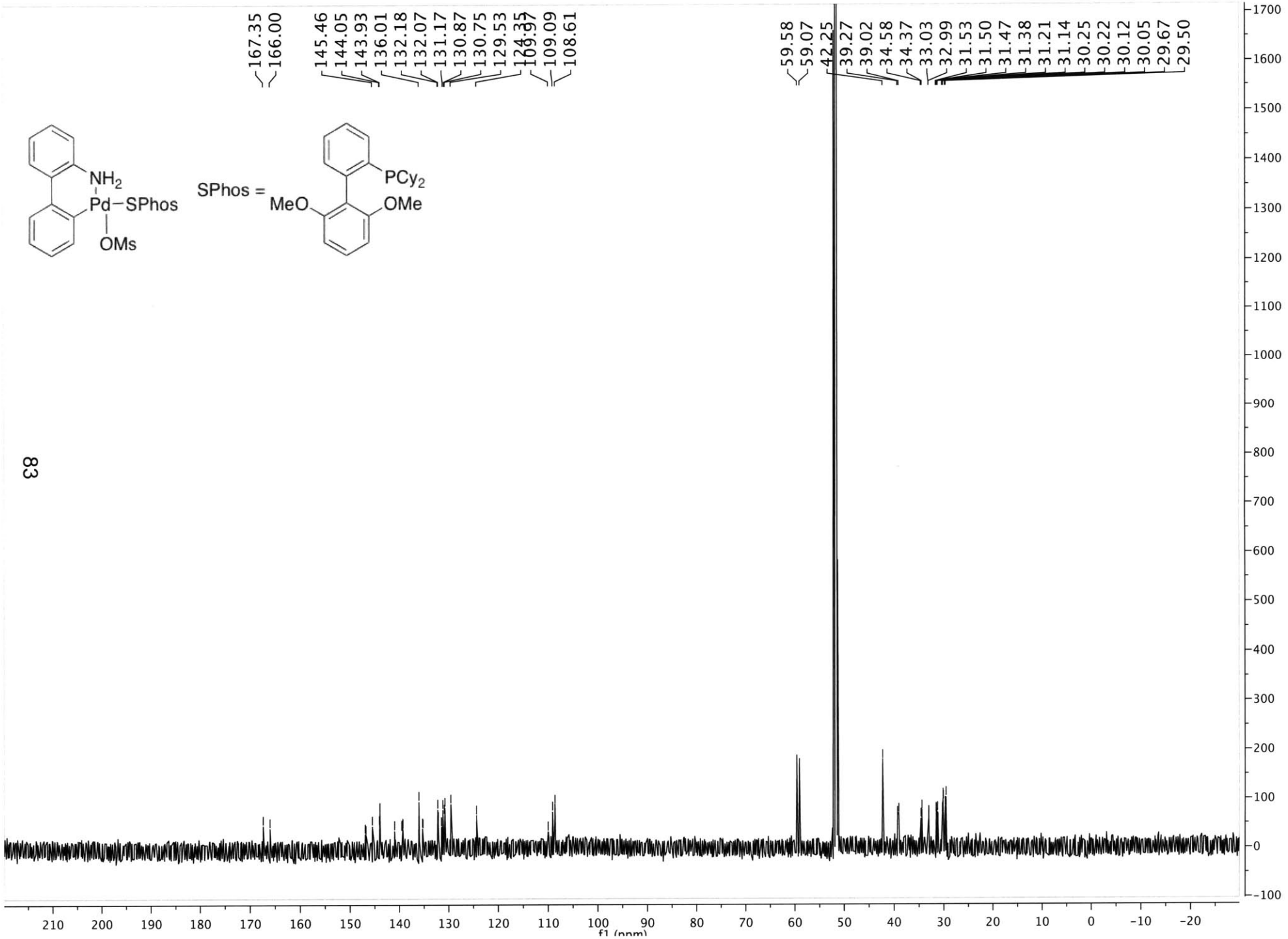

NH2
Pd–BrettPhos
OMs
BrettPhos =
OMe
MeO
PCy2
i-Pr
i-Pr
i-Pr
43.33
78
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

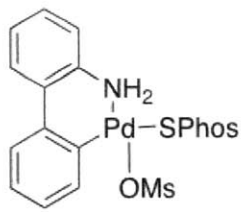

NH2
Pd—RuPhos
OMs
RuPhos =
PCy2
i-PrO
Oi-Pr
79
1.07
1.14
2.09
2.10
2.06
3.16
1.05
1.07
1.01
1.00
1.03
1.17
1.18
1.12
3.13
2.34
2.10
6.44
7.42
4.83
12.94
3.08
1.19
f1 (ppm)


162.51
161.59
140.34
137.77
132.22
128.96
127.71
127.32
127.17
125.65
121.57
107.54
106.12
100.50
72.56
71.99
40.18
36.02
35.78
31.09
29.93
28.06
27.79
27.67
27.33
26.78
26.40
26.02
22.73
22.47
22.40
21.74
21.64
NH2
Pd–RuPhos
OMs
RuPhos =
PCy2
i-PrO
Oi-Pr
80
1000
900
800
700
600
500
400
300
200
100
0
f1 (ppm)

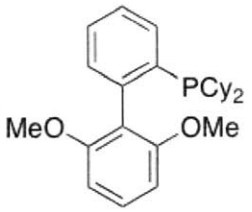

NH2
Pd—RuPhos
OMs
RuPhos =
PCy2
i-PrO
Oi-Pr
41.57
81
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)


NH2
Pd–SPhos
OMs
SPhos =
PCy2
MeO
OMe
82
1.00
1.01
1.00
2.03
1.00
3.78
0.98
1.01
1.02
0.98
0.93
3.10
2.98
2.90
1.10
2.15
7.85
12.04
1.11
f1 (ppm)


167.35
166.00
145.46
144.05
143.93
136.01
132.18
132.07
131.17
130.87
130.75
129.53
124.35
109.97
109.09
108.61
59.58
59.07
42.25
39.27
39.02
34.58
34.37
33.03
32.99
31.53
31.50
31.47
31.38
31.21
31.14
30.25
30.22
30.12
30.05
29.67
29.50
NH2
Pd–SPhos
OMs
SPhos =
MeO
PCy2
OMe
f1 (ppm)

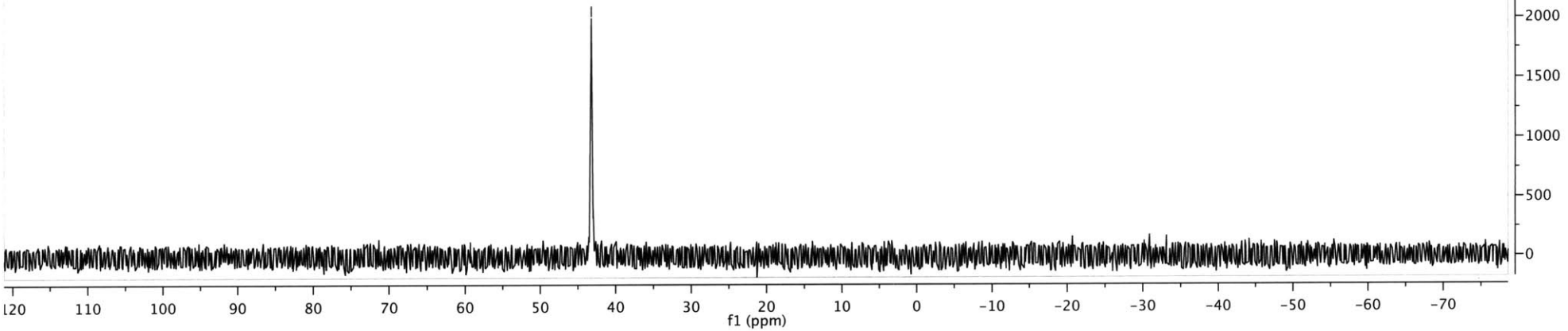


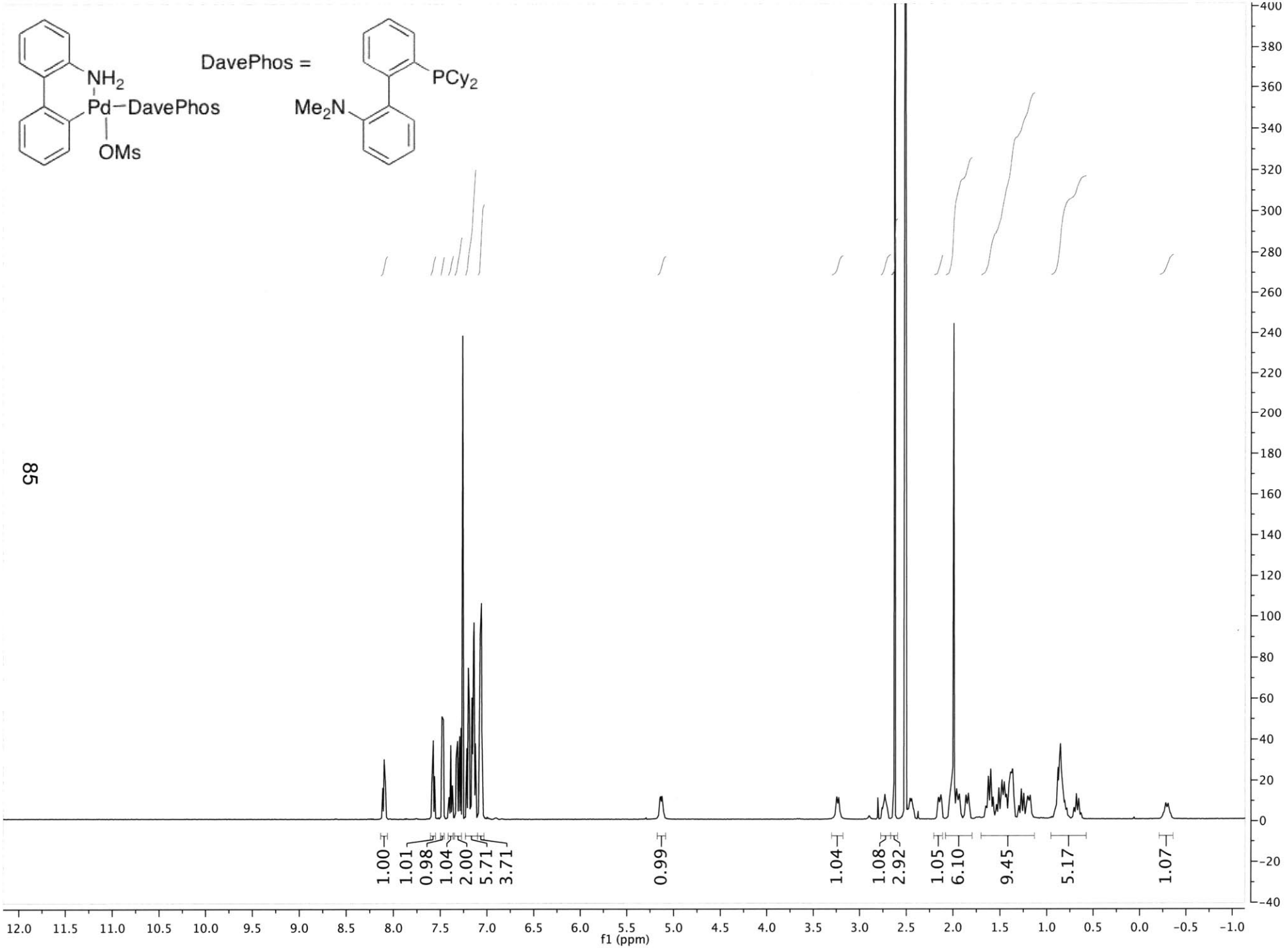
SPhos =

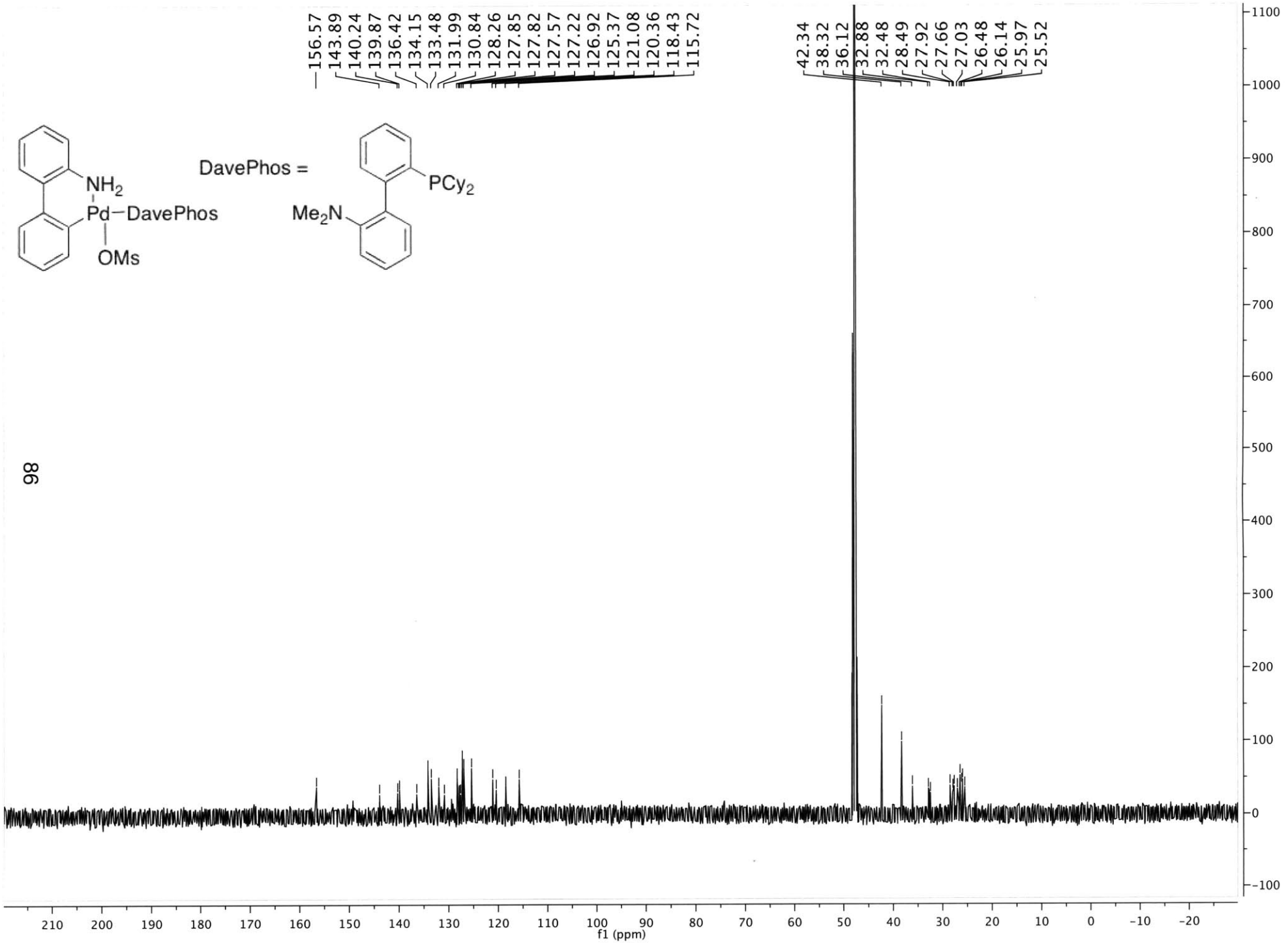


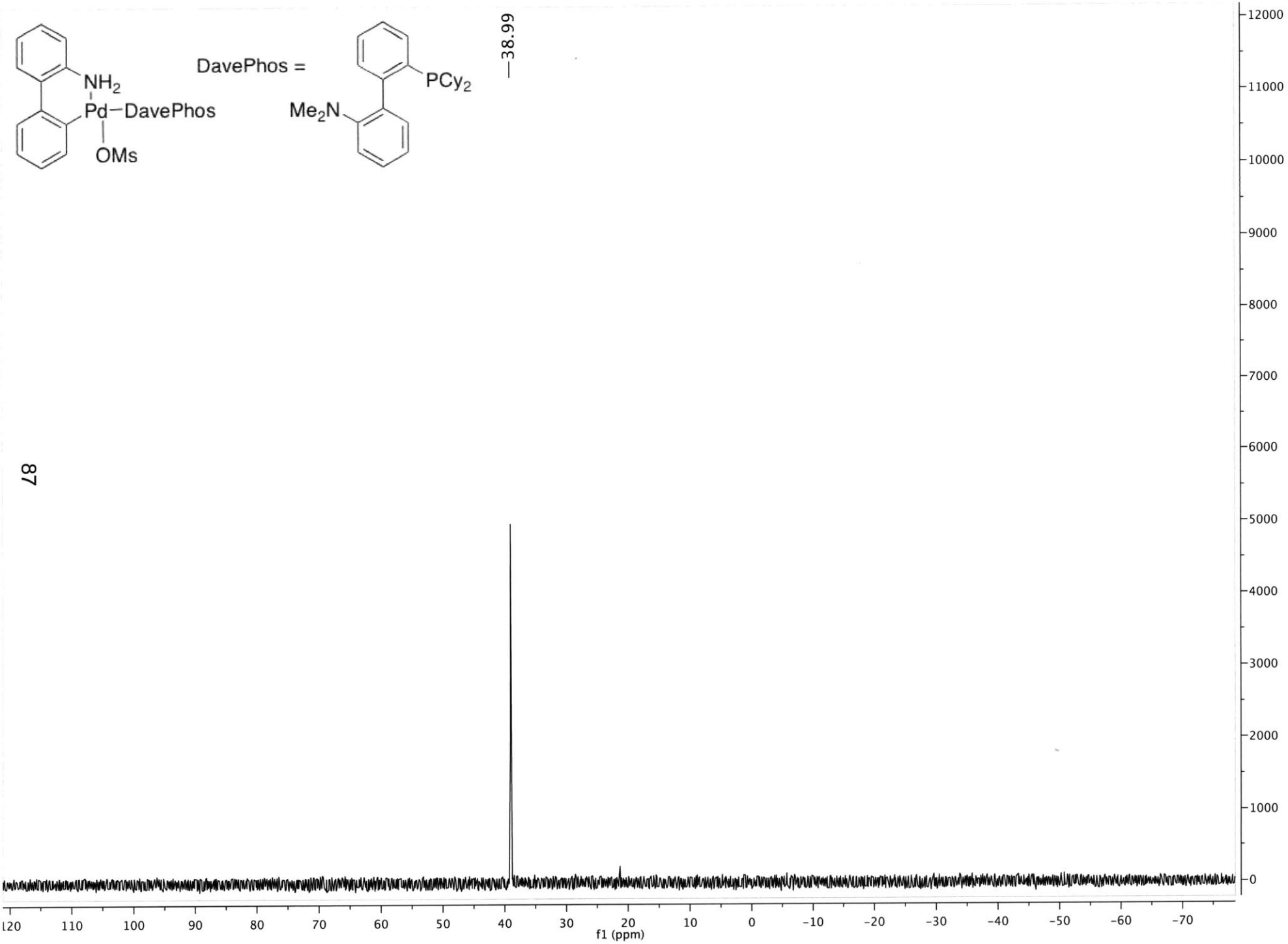
43.18

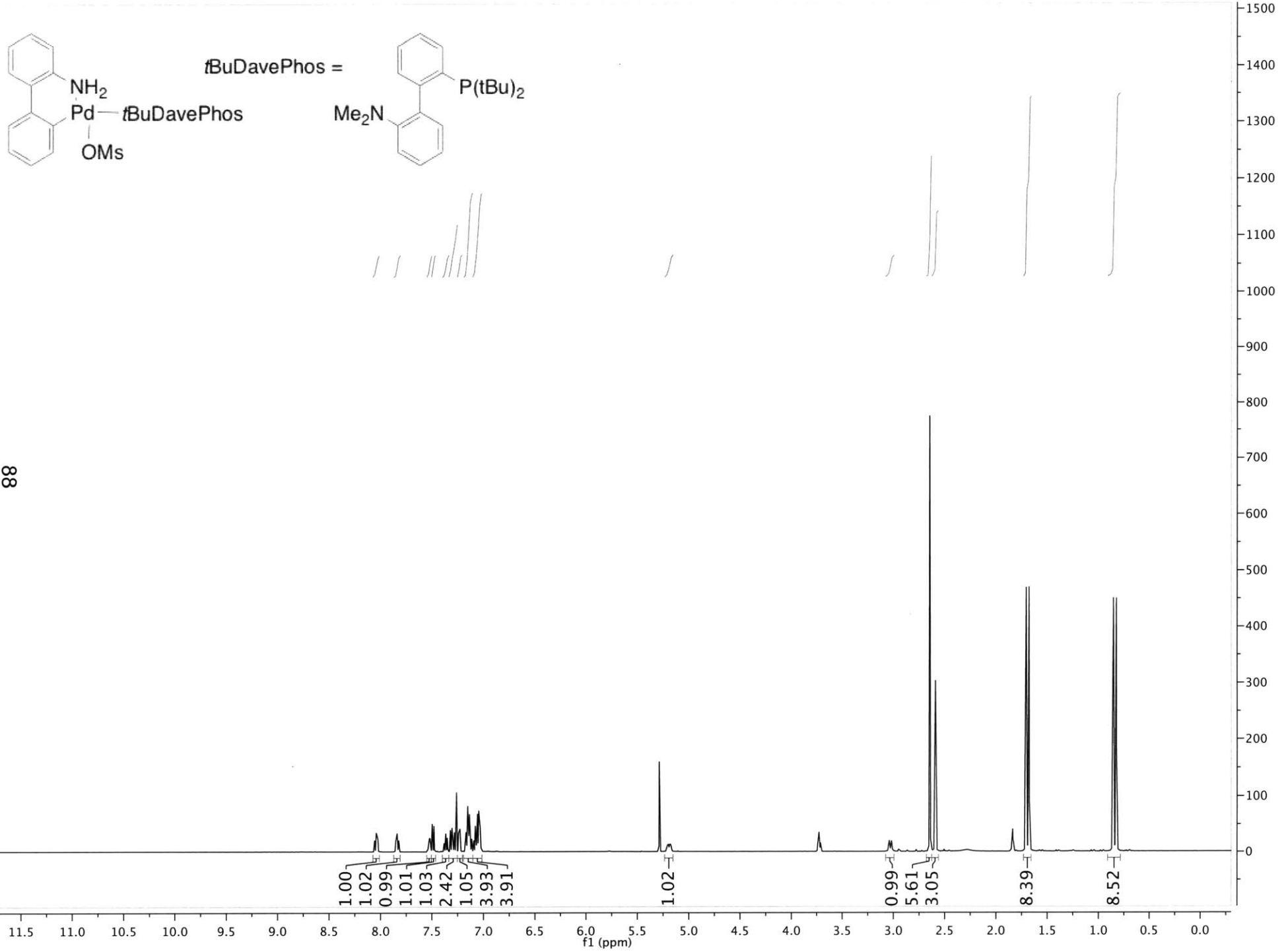
84

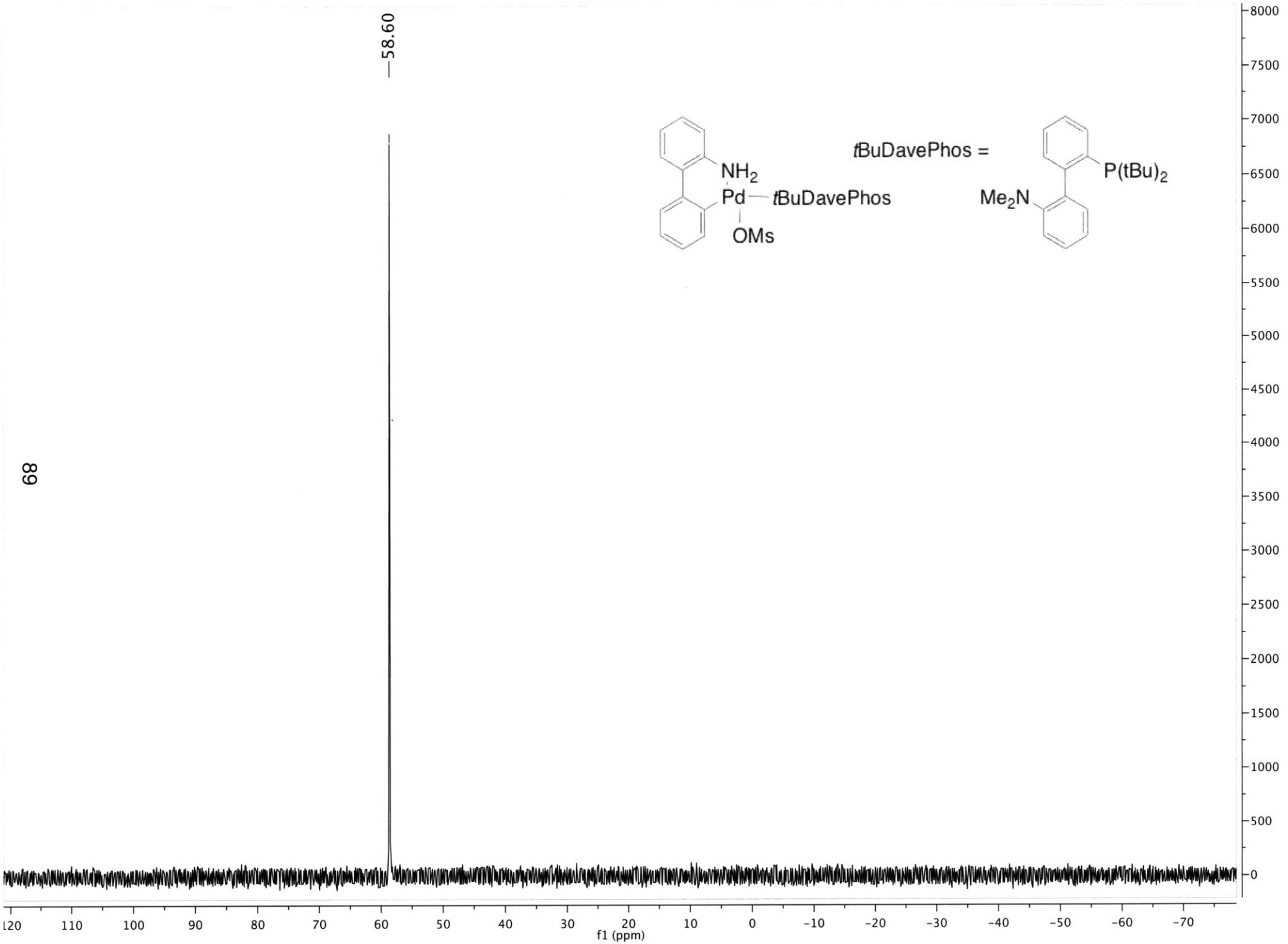


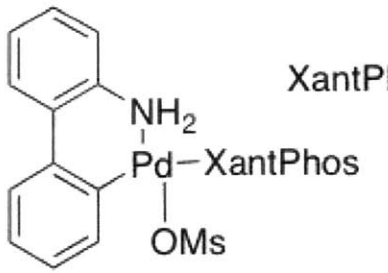

NH2
Pd–DavePhos
OMs
DavePhos =
PCy2
Me2N
85
1.00
1.01
0.98
1.04
2.00
5.71
3.71
0.99
1.04
1.08
2.92
1.05
6.10
9.45
5.17
1.07
f1 (ppm)


156.57
143.89
140.24
139.87
136.42
134.15
133.48
131.99
130.84
128.26
127.85
127.82
127.57
127.22
126.92
125.37
121.08
120.36
118.43
115.72
42.34
38.32
36.12
32.88
32.48
28.49
27.92
27.66
27.03
26.48
26.14
25.97
25.52
NH2
Pd—DavePhos
OMs
DavePhos =
PCy2
Me2N
98
f1 (ppm)

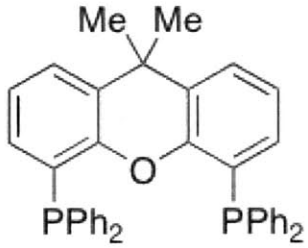

NH2
Pd—DavePhos
OMs
DavePhos =
PCy2
Me2N
38.99
87
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)


NH2
Pd
tBuDavePhos
OMs
tBuDavePhos =
P(tBu)2
Me2N
1.00
1.02
0.99
1.01
1.03
2.42
1.05
3.93
3.91
1.02
0.99
5.61
3.05
8.39
8.52
f1 (ppm)

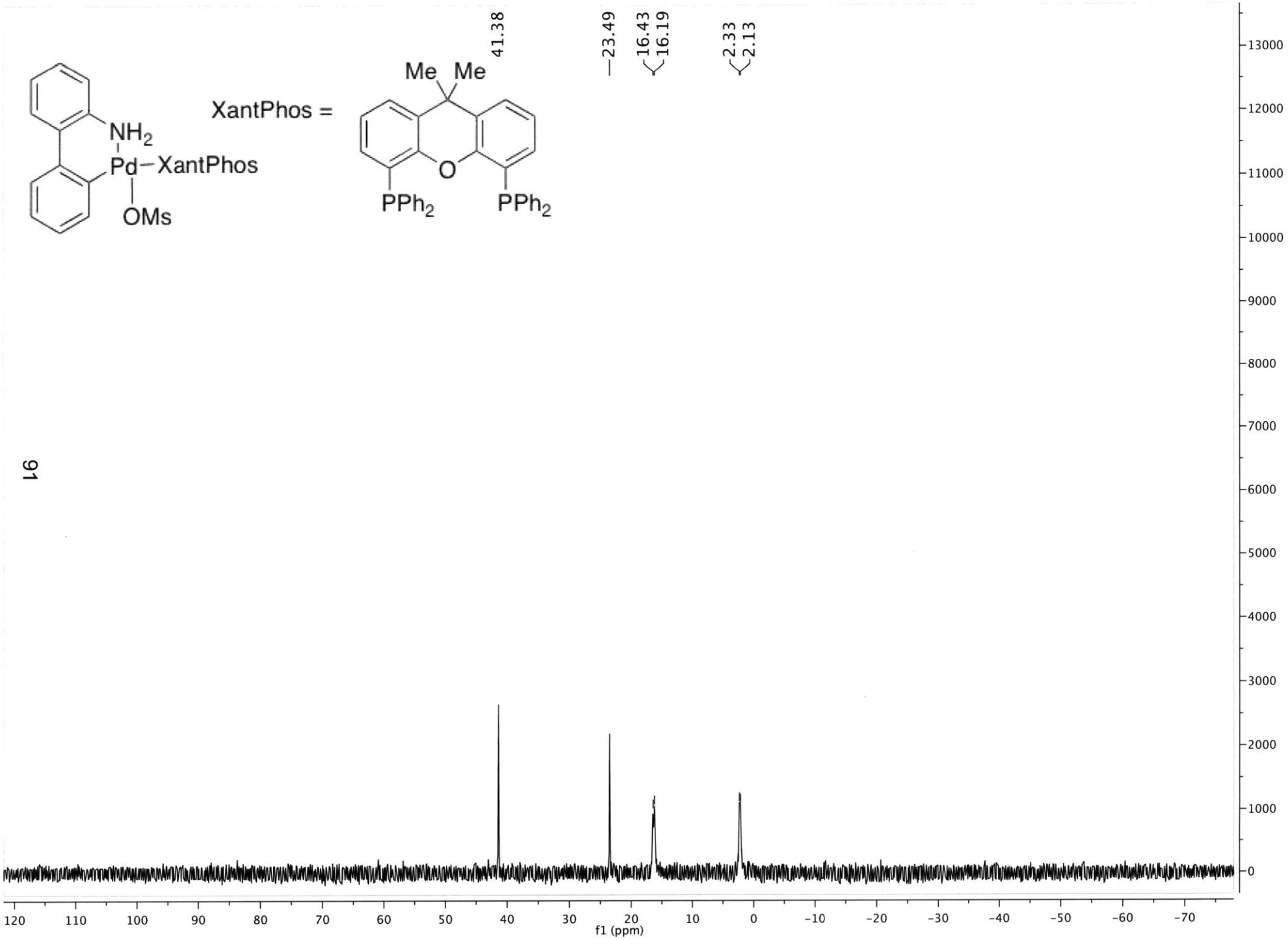

58.60
NH2
Pd
tBuDavePhos
OMs
tBuDavePhos =
P(tBu)2
Me2N
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

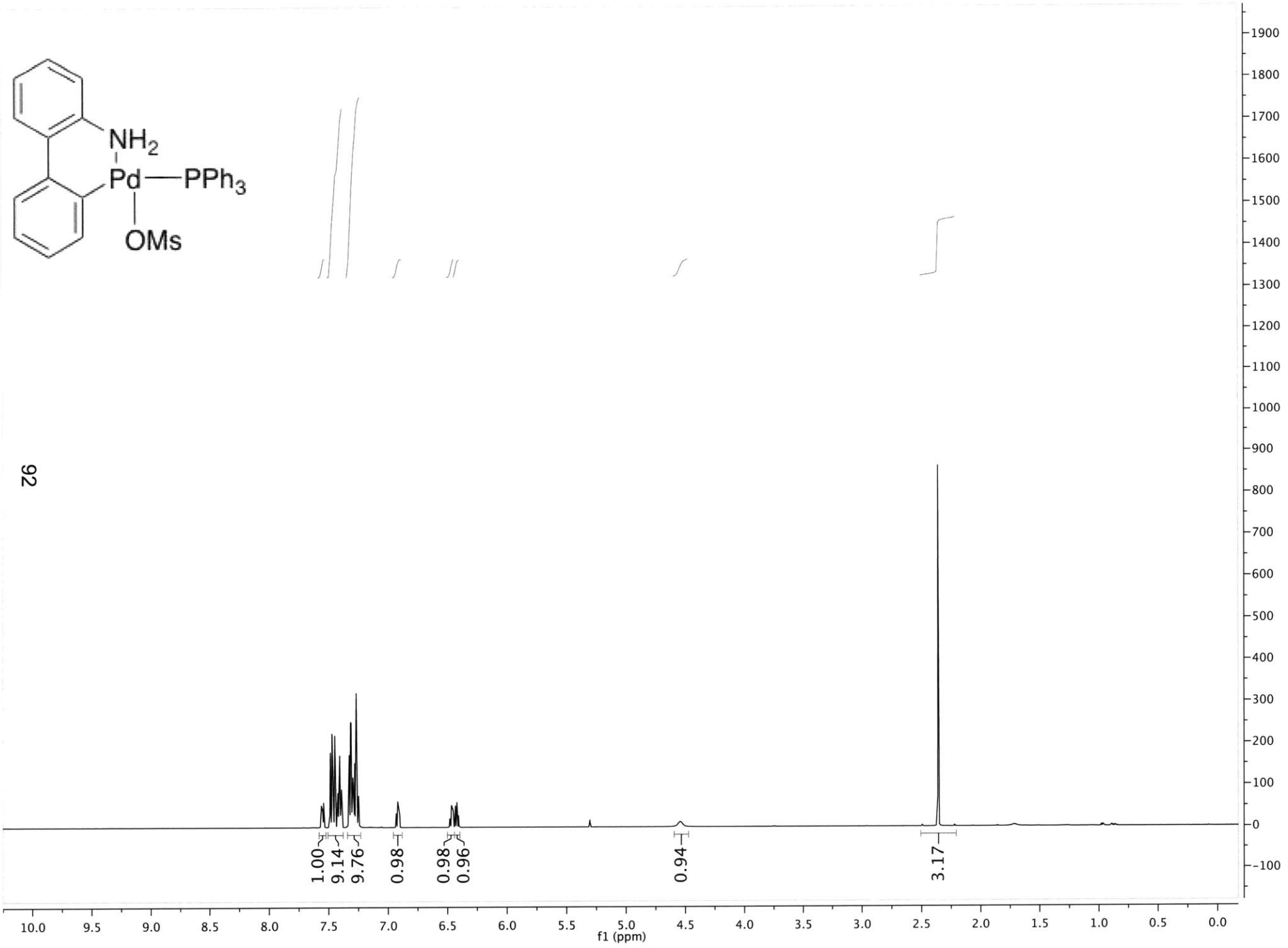

NH2
Pd–XantPhos
OMs

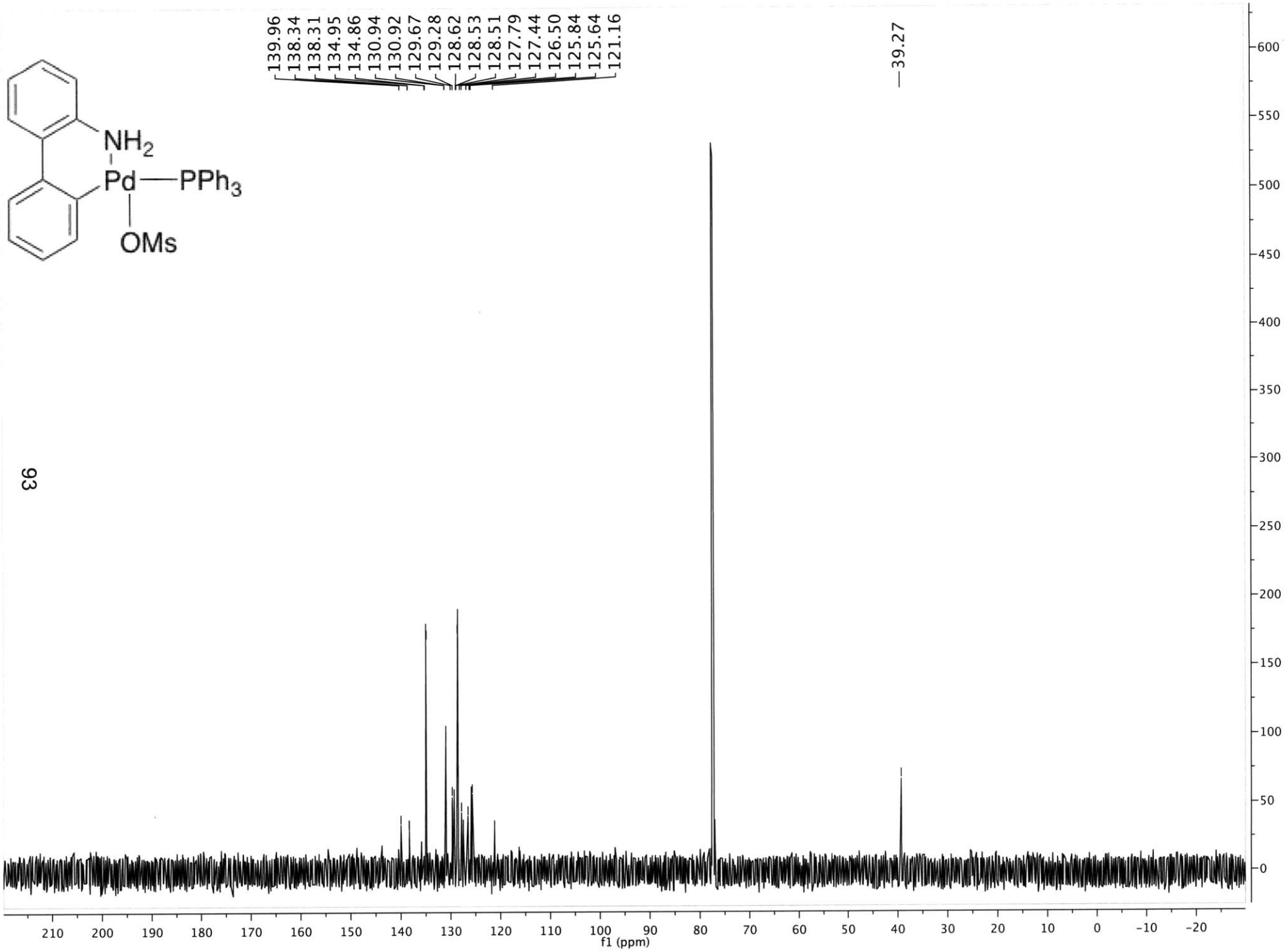
XantPhos =

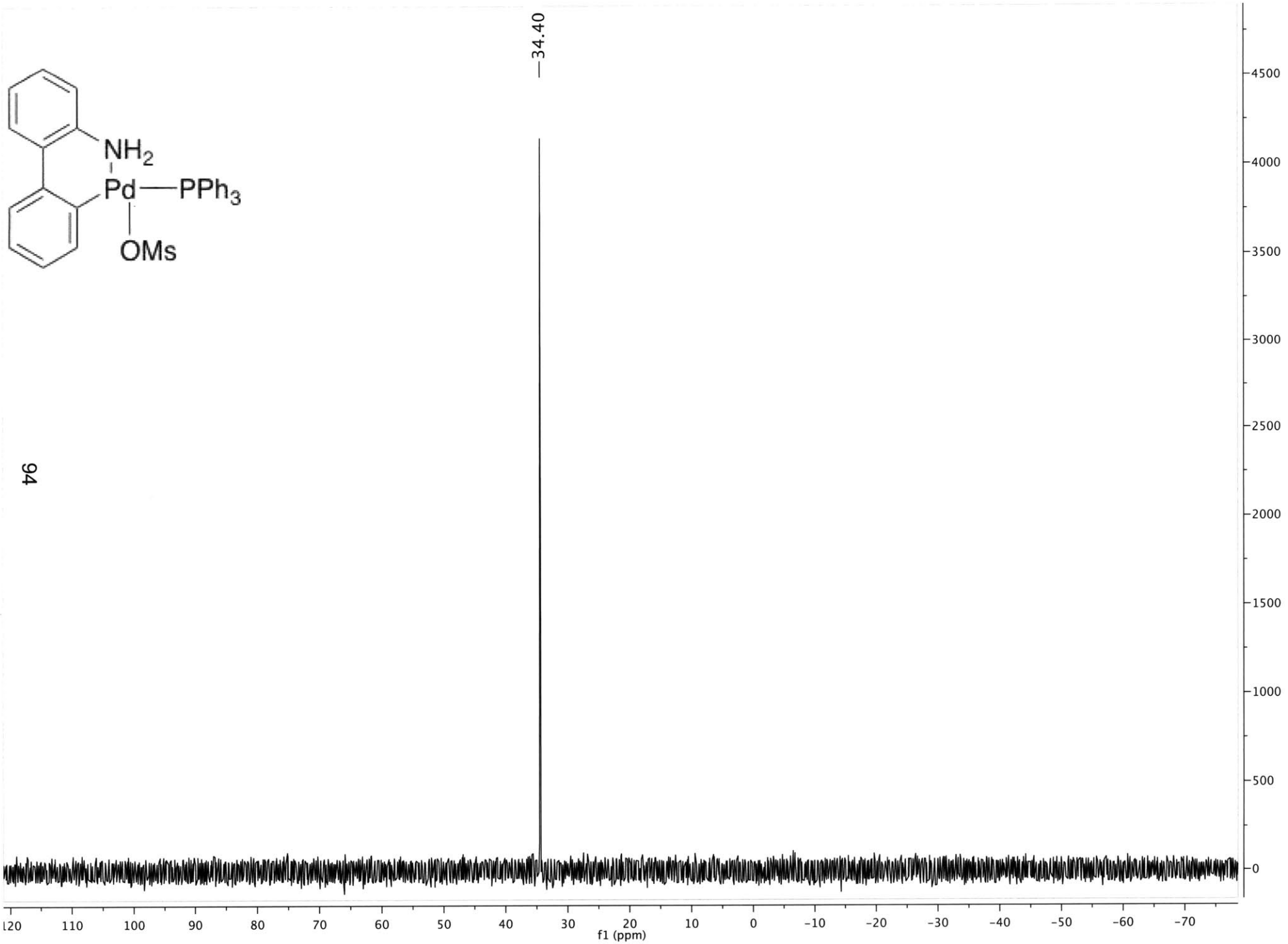

Me Me
O
PPh2
PPh2

06
2.01
3.21
4.18
13.33
6.77
2.11
4.23
1.01
2.87
6.00
f1 (ppm)

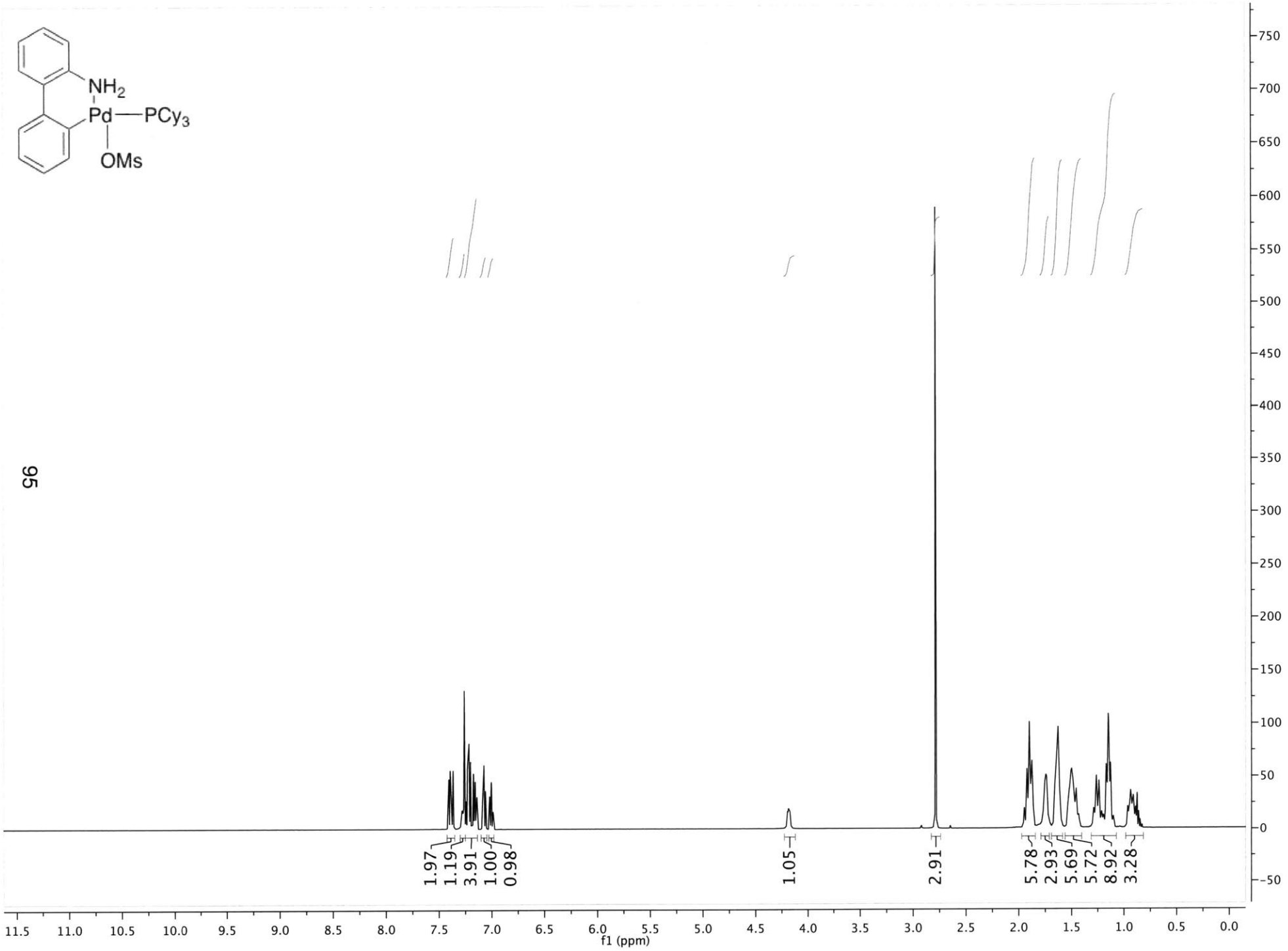

NH2
Pd–XantPhos
OMs
XantPhos =
Me Me
O
PPh2
PPh2
41.38
23.49
16.43
16.19
2.33
2.13
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

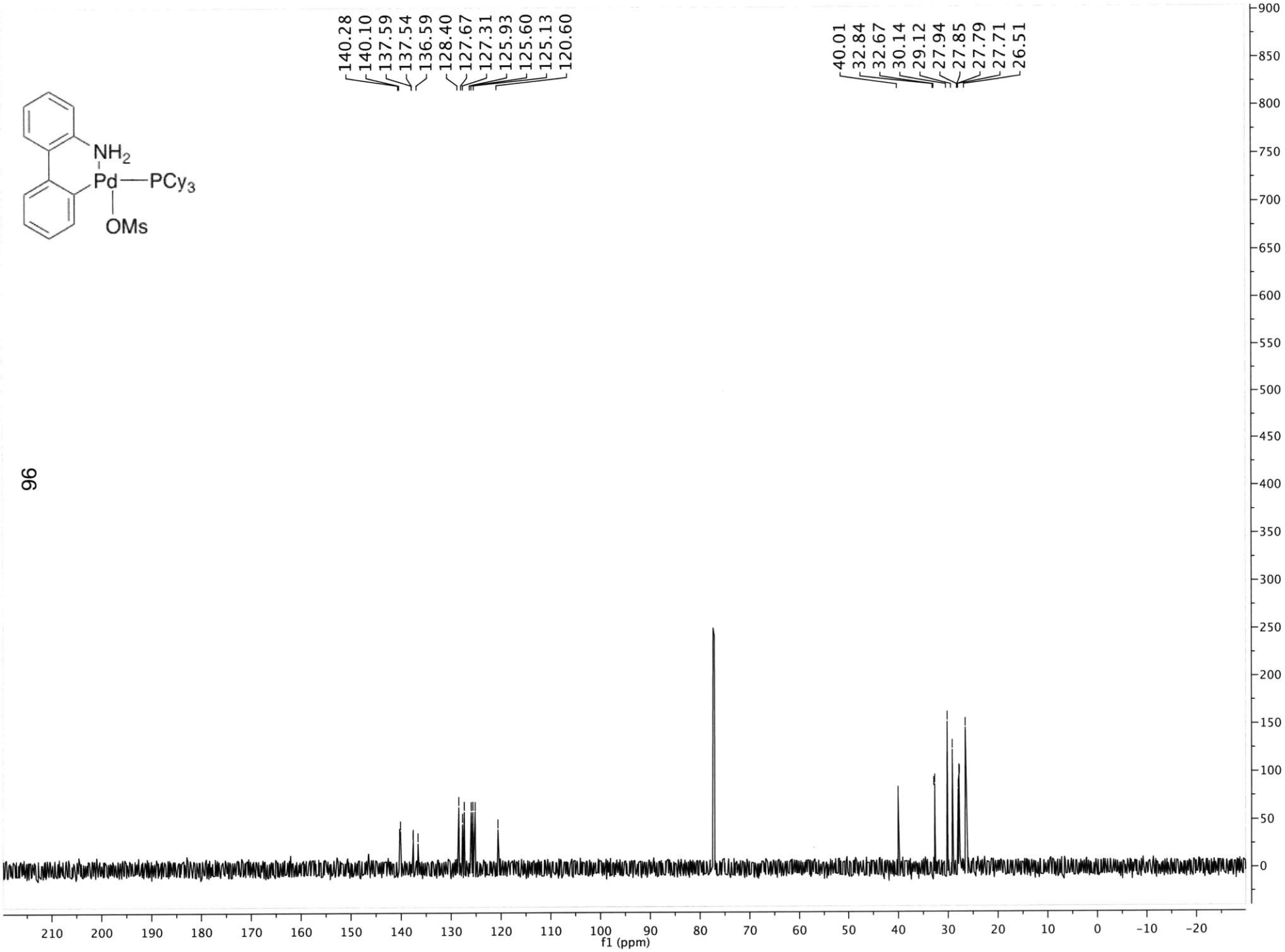

NH2
Pd
PPh3
OMs
92
1.00
9.14
9.76
0.98
0.98
0.96
0.94
3.17
f1 (ppm)

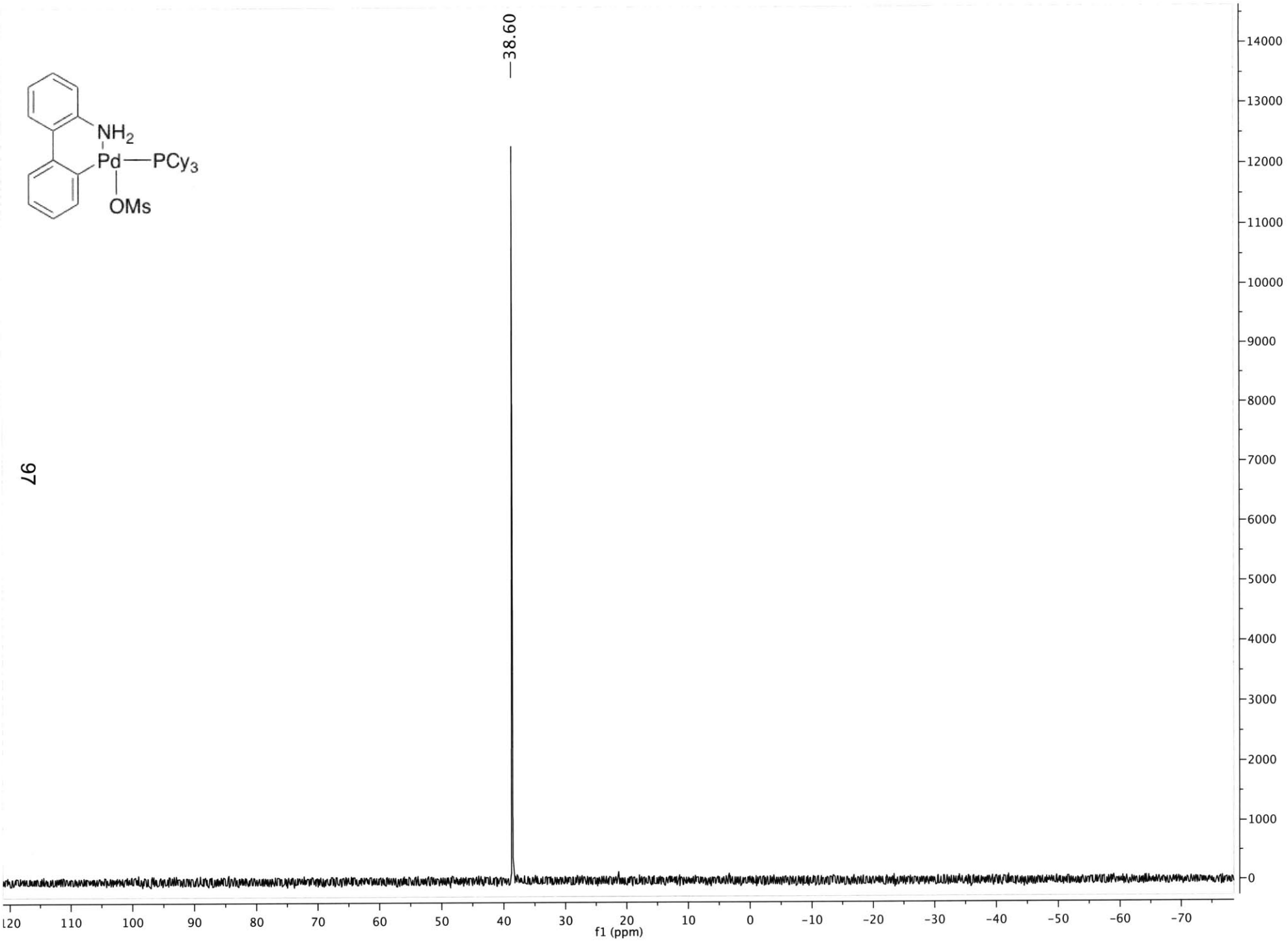

139.96
138.34
138.31
134.95
134.86
130.94
130.92
129.67
129.28
128.62
128.53
128.51
127.79
127.44
126.50
125.84
125.64
121.16
39.27
NH2
Pd
PPh3
OMs
93
f1 (ppm)

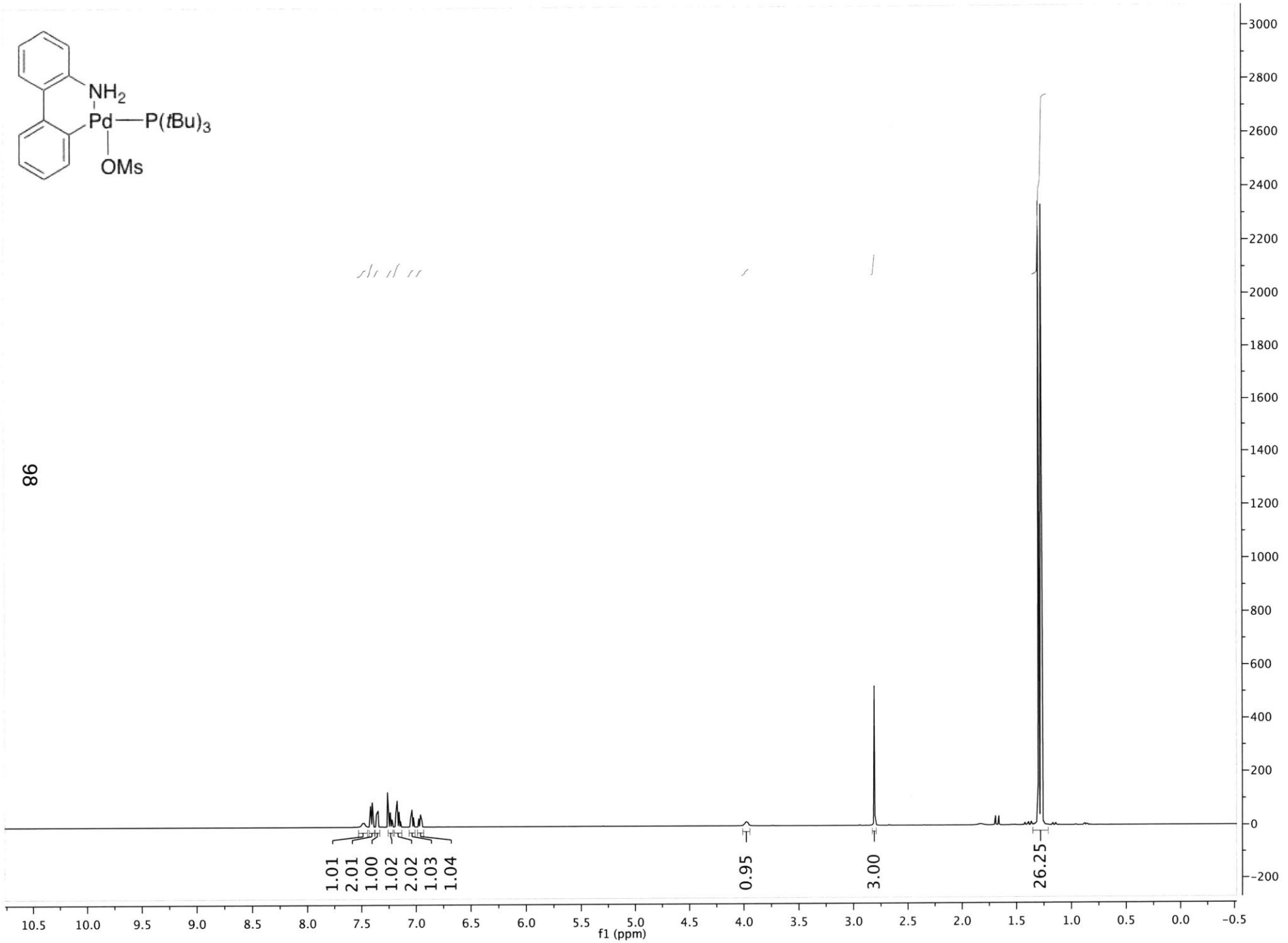

NH2
Pd
PPh3
OMs
34.40
4500
4000
3500
3000
2500
2000
1500
1000
500
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

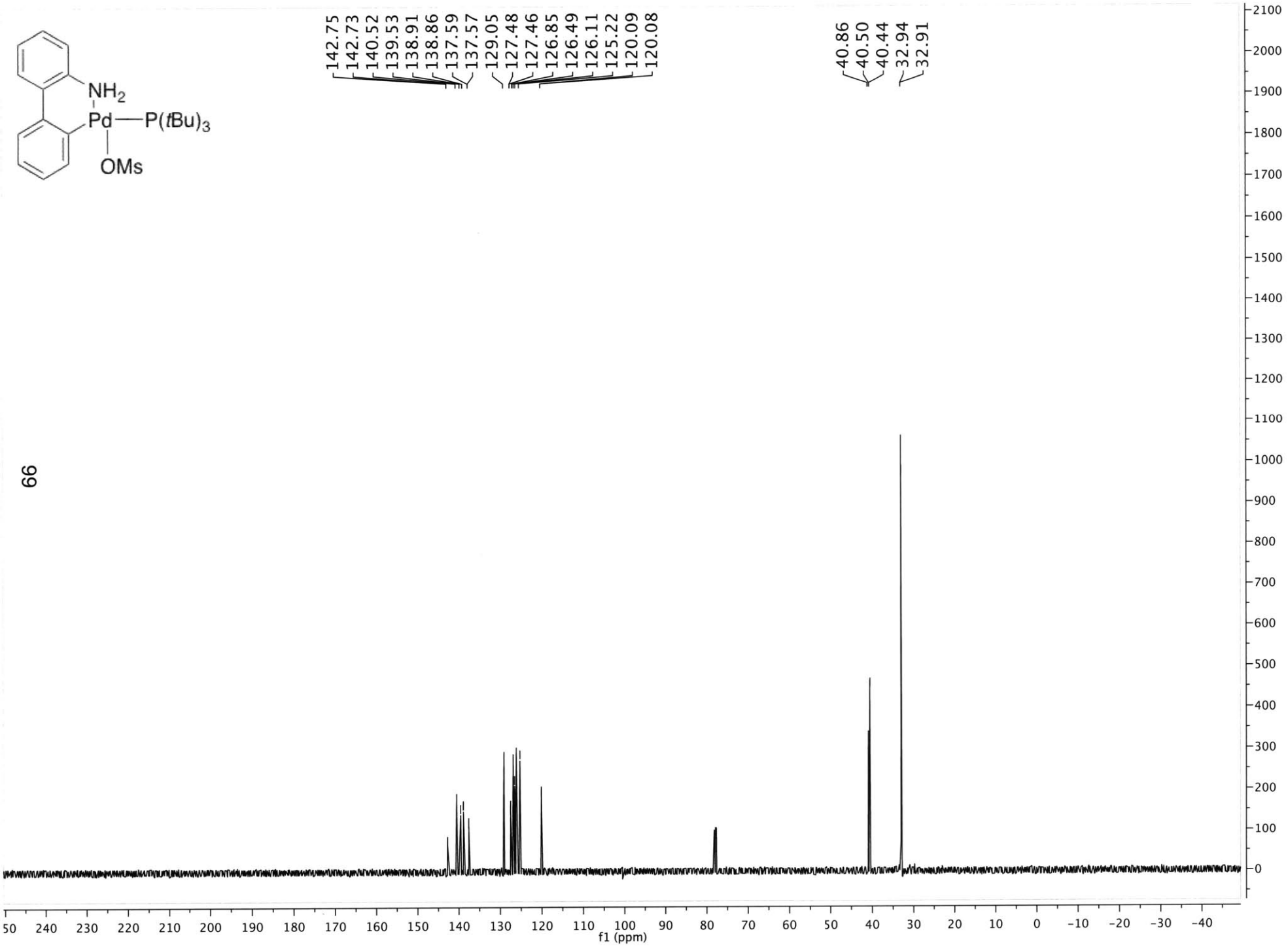
94

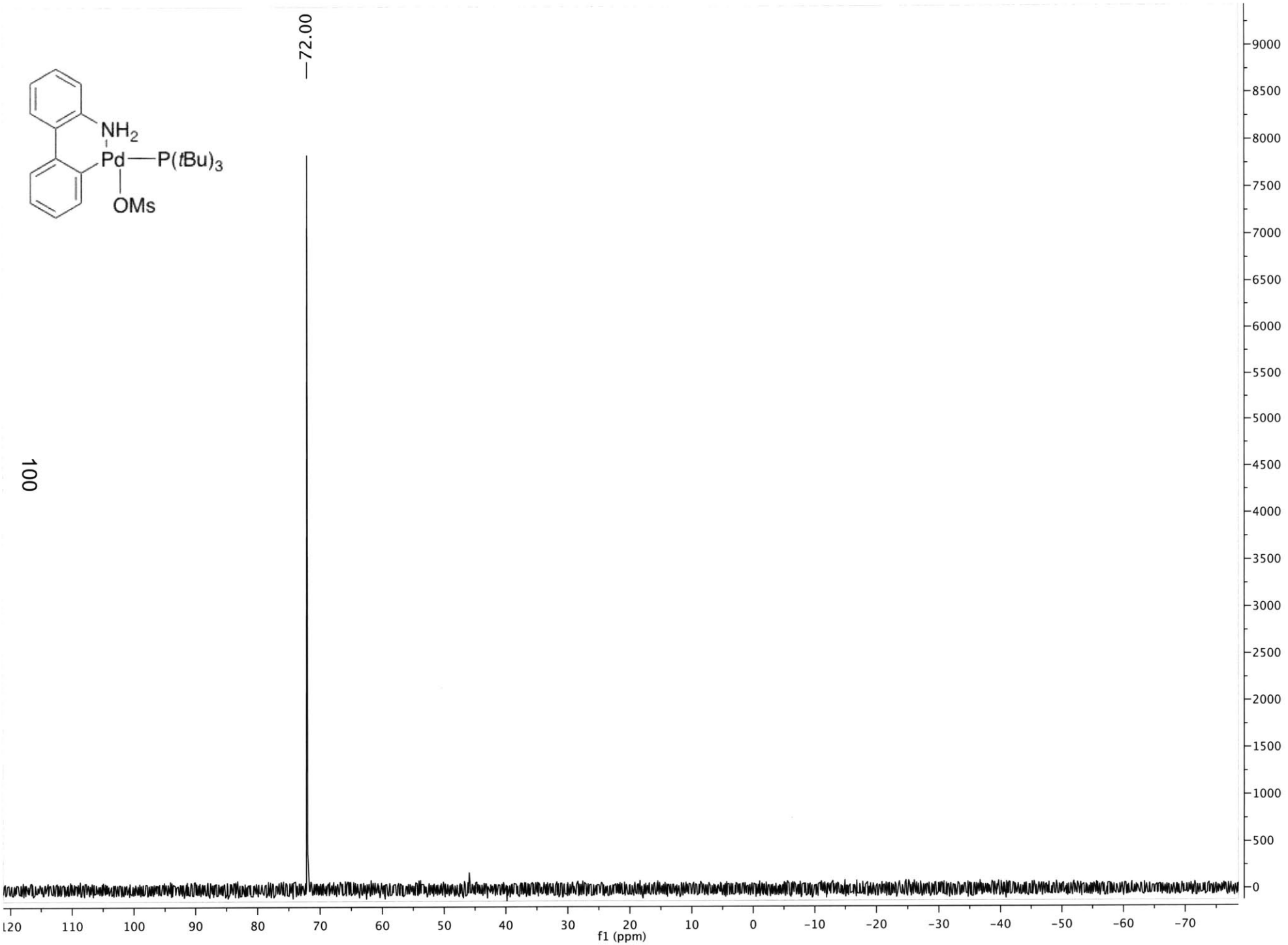

NH2
Pd—PCy3
OMs
95
1.97
1.19
3.91
1.00
0.98
1.05
2.91
5.78
2.93
5.69
5.72
8.92
3.28
f1 (ppm)

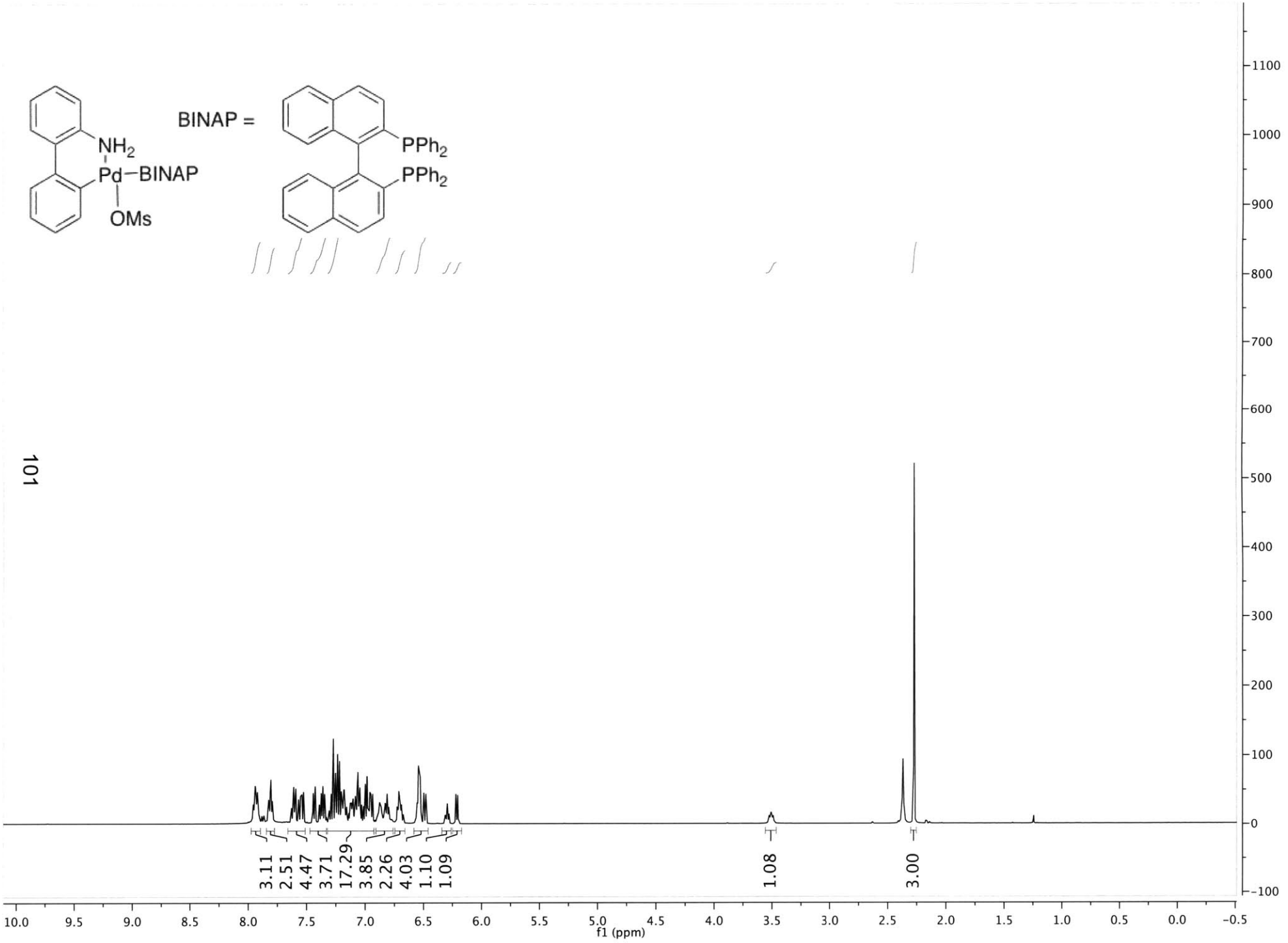

140.28
140.10
137.59
137.54
136.59
128.40
127.67
127.31
125.93
125.60
125.13
120.60
40.01
32.84
32.67
30.14
29.12
27.94
27.85
27.79
27.71
26.51
NH2
Pd
PCy3
OMs
96
f1 (ppm)

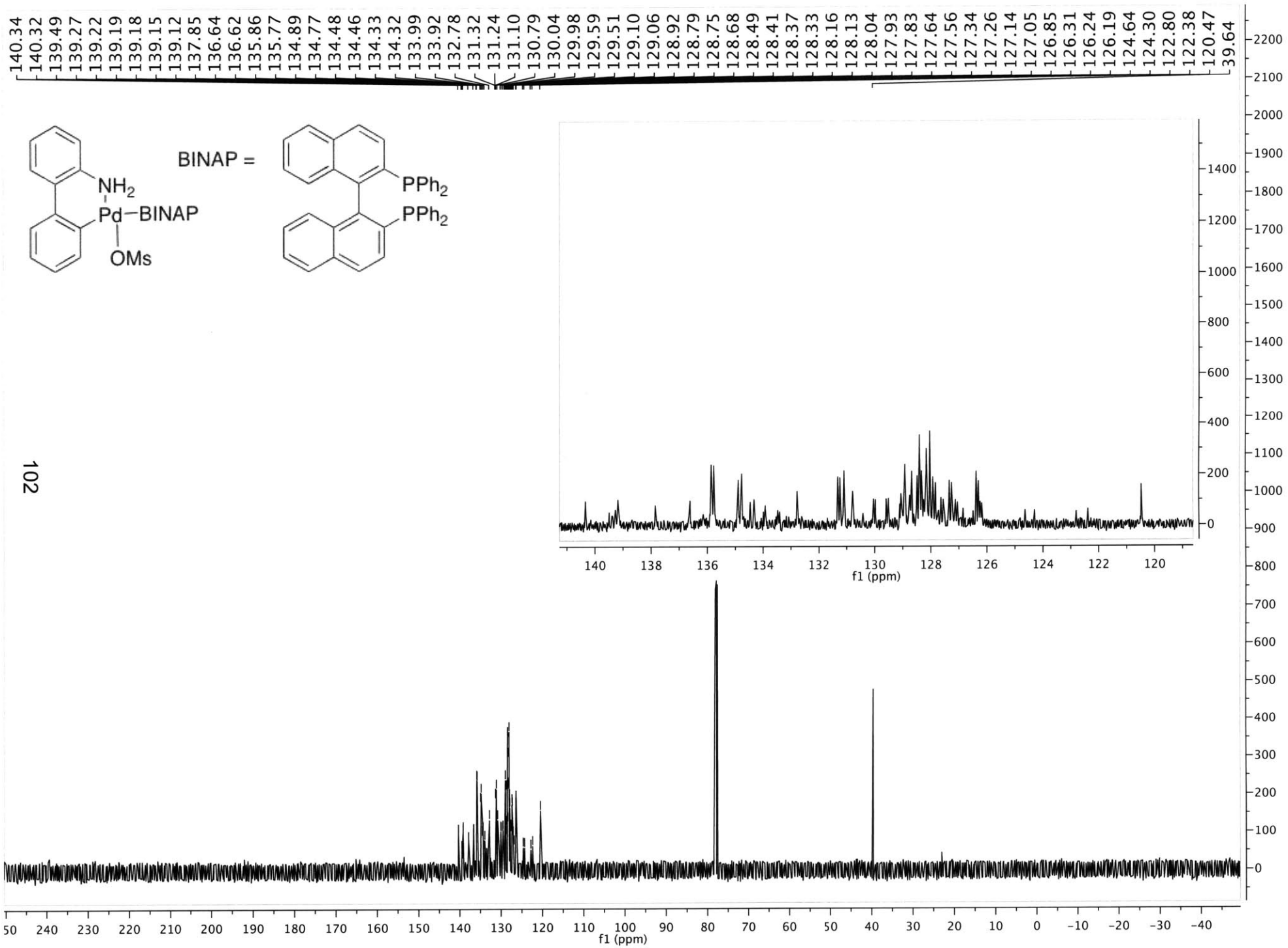

38.60
NH2
Pd
PCy3
OMs
97
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

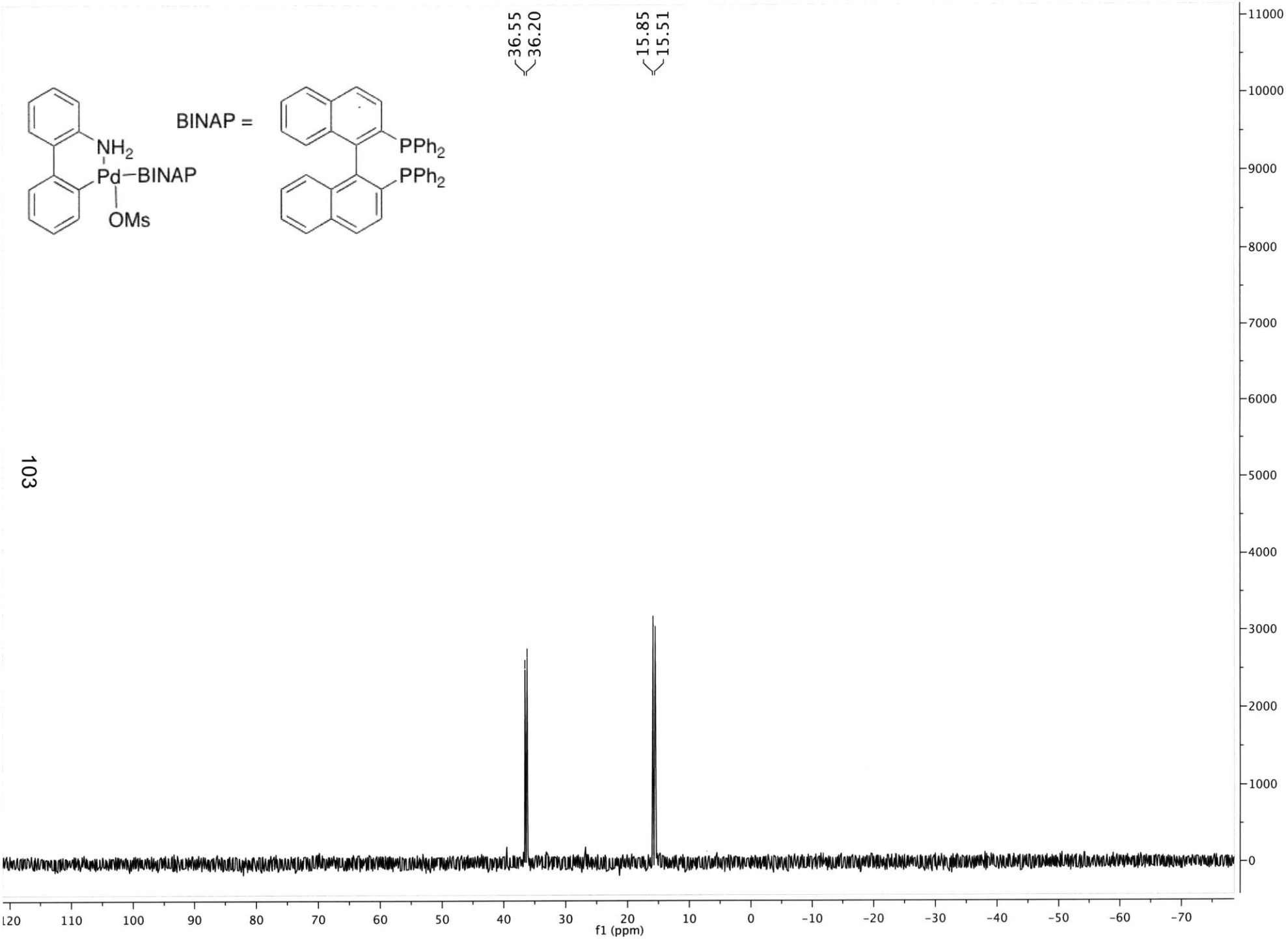

NH2
Pd—P(tBu)3
OMs
98
1.01
2.01
1.00
1.02
2.02
1.03
1.04
0.95
3.00
26.25
f1 (ppm)


NH2
Pd—P(tBu)3
OMs
142.75
142.73
140.52
139.53
138.91
138.86
137.59
137.57
129.05
127.48
127.46
126.85
126.49
126.11
125.22
120.09
120.08
40.86
40.50
40.44
32.94
32.91
66
f1 (ppm)

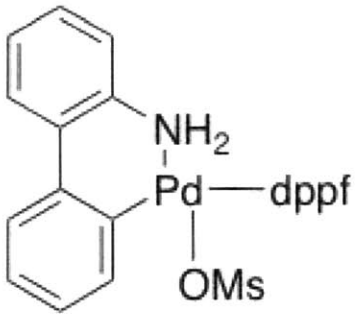

72.00
NH2
Pd—P(tBu)3
OMs
100
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

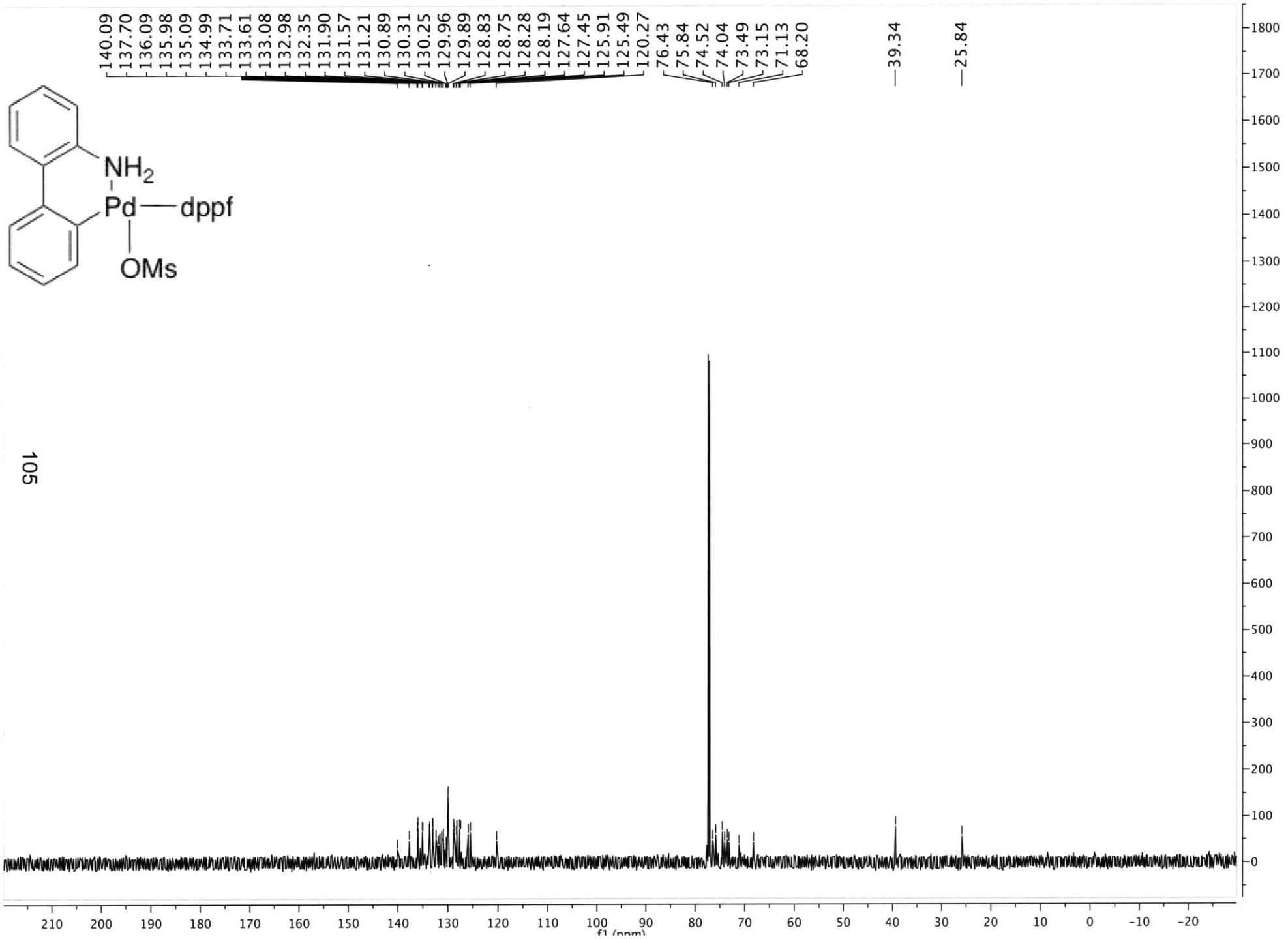

NH2
Pd–BINAP
OMs
BINAP =
PPh2
PPh2
101
3.11
2.51
4.47
3.71
17.29
3.85
2.26
4.03
1.10
1.09
1.08
3.00
f1 (ppm)

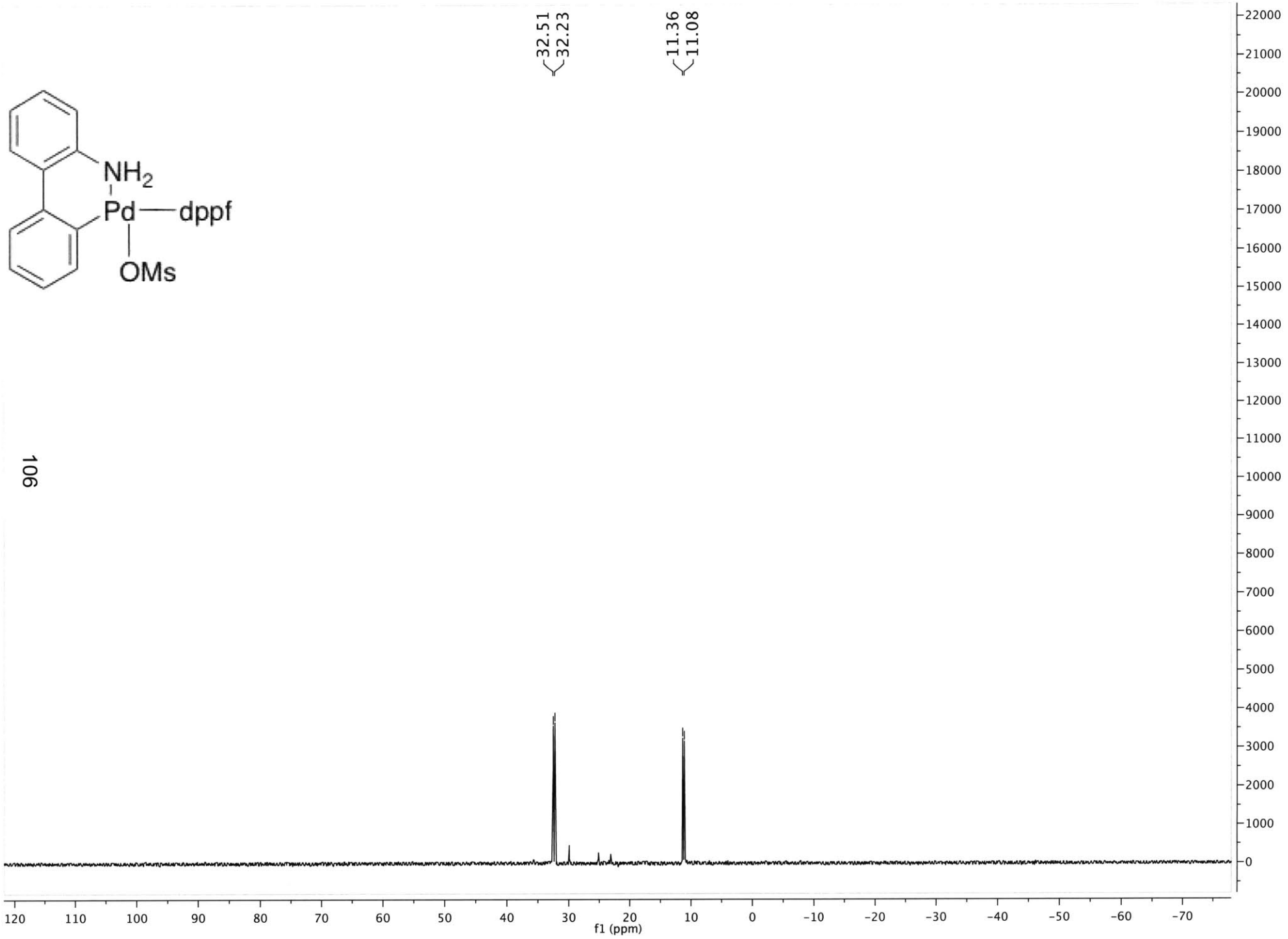

140.34
140.32
139.49
139.27
139.22
139.19
139.18
139.15
139.12
137.85
136.64
136.62
135.86
135.77
134.89
134.77
134.48
134.46
134.33
134.32
133.99
133.92
132.78
131.32
131.24
131.10
130.79
130.04
129.98
129.59
129.51
129.10
129.06
128.92
128.79
128.75
128.68
128.49
128.41
128.37
128.33
128.16
128.13
128.04
127.93
127.83
127.64
127.56
127.34
127.26
127.14
127.05
126.85
126.31
126.24
126.19
124.64
124.30
122.80
122.38
120.47
39.64
BINAP =
NH2
Pd–BINAP
OMs
PPh2
PPh2
102
f1 (ppm)
f1 (ppm)

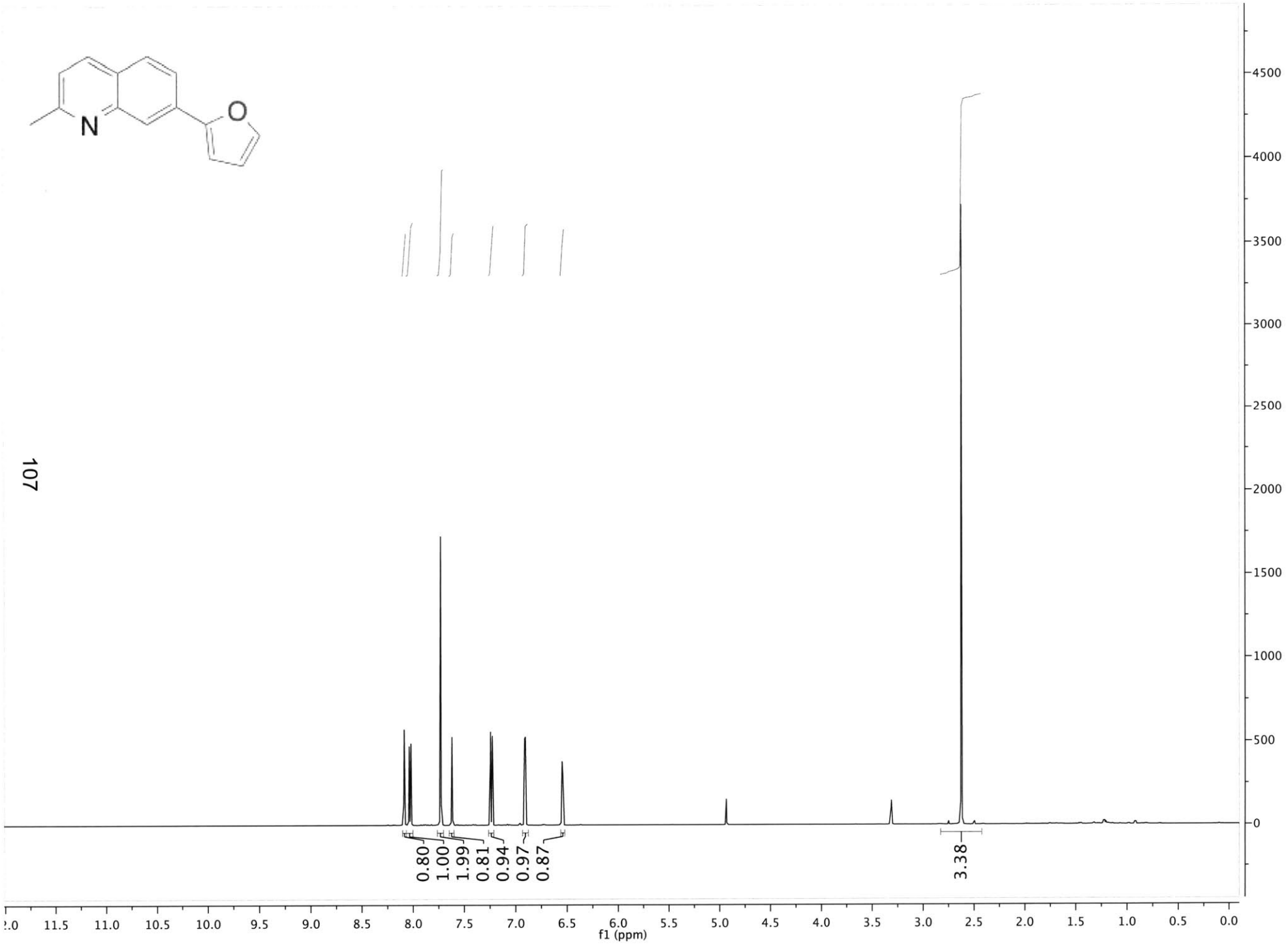

36.55
36.20
15.85
15.51
NH2
Pd–BINAP
OMs
BINAP =
PPh2
PPh2
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

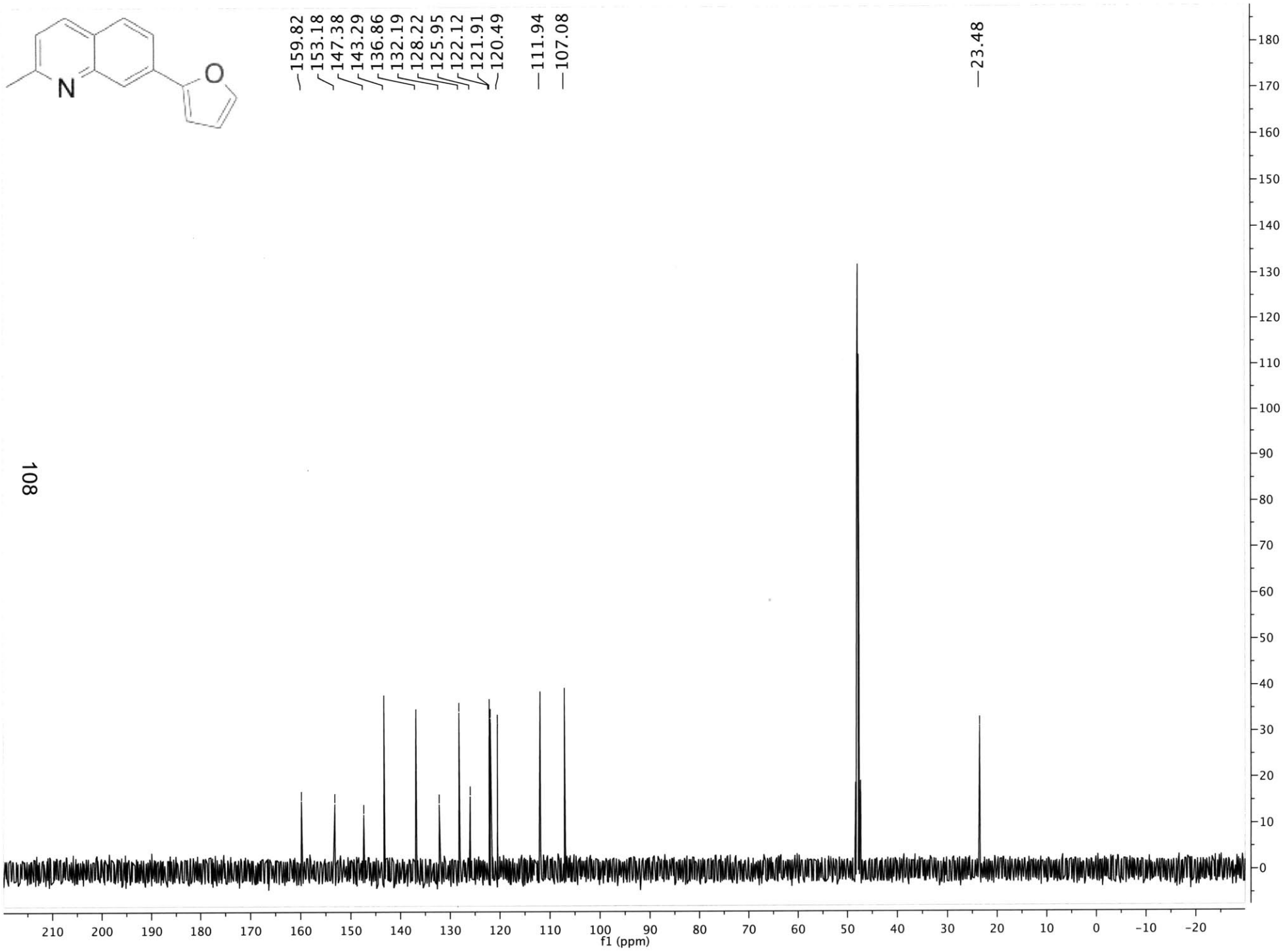
NCB-3-OMsdppf-1H
STANDARD PROTON PARAMETERS

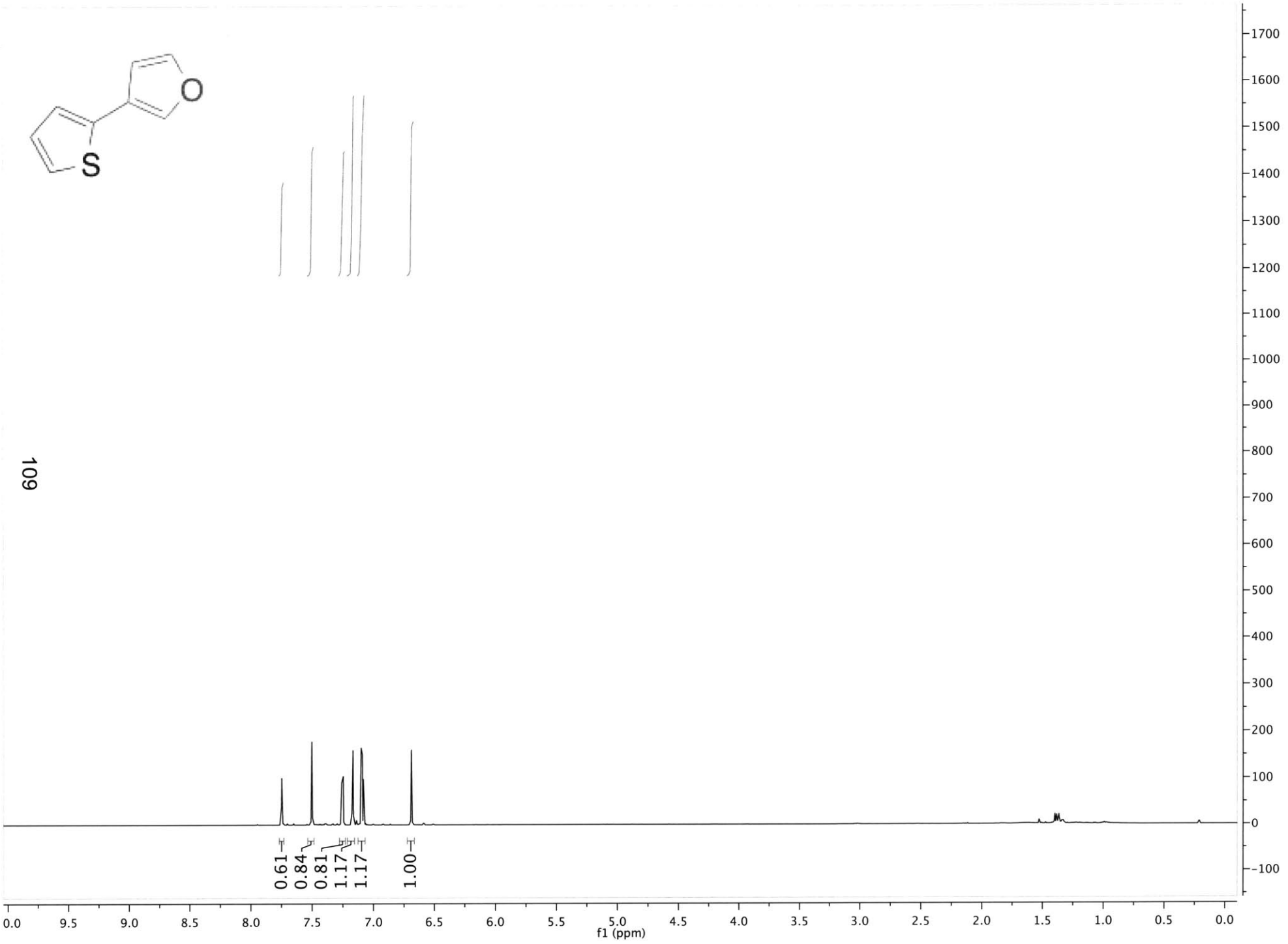


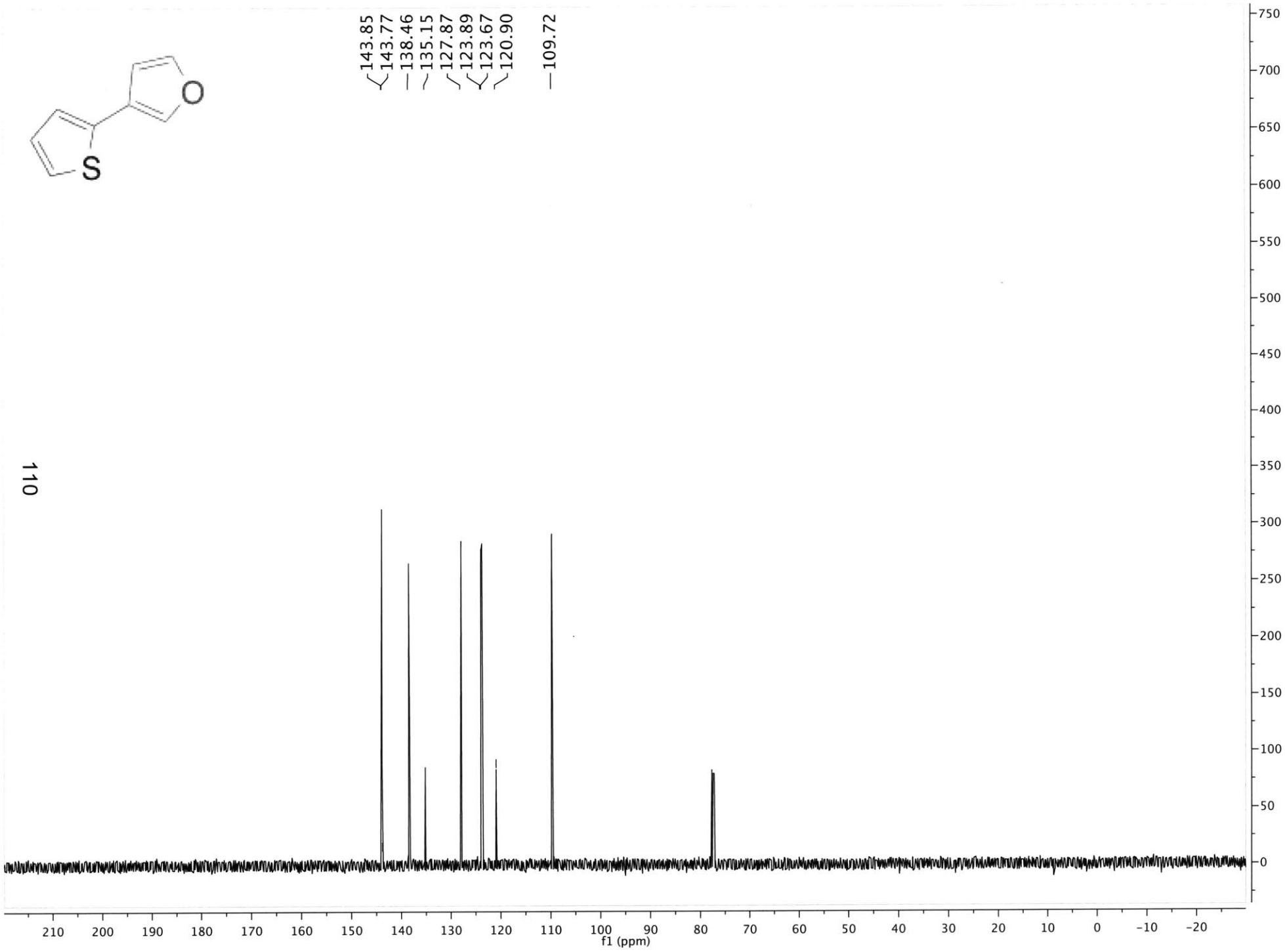

140.09
137.70
136.09
135.98
135.09
134.99
133.71
133.61
133.08
132.98
132.35
131.90
131.57
131.21
130.89
130.31
130.25
129.96
129.89
128.83
128.75
128.28
128.19
127.64
127.45
125.91
125.49
120.27
76.43
75.84
74.52
74.04
73.49
73.15
71.13
68.20
39.34
25.84
NH2
Pd
dppf
OMs
105
f1 (ppm)

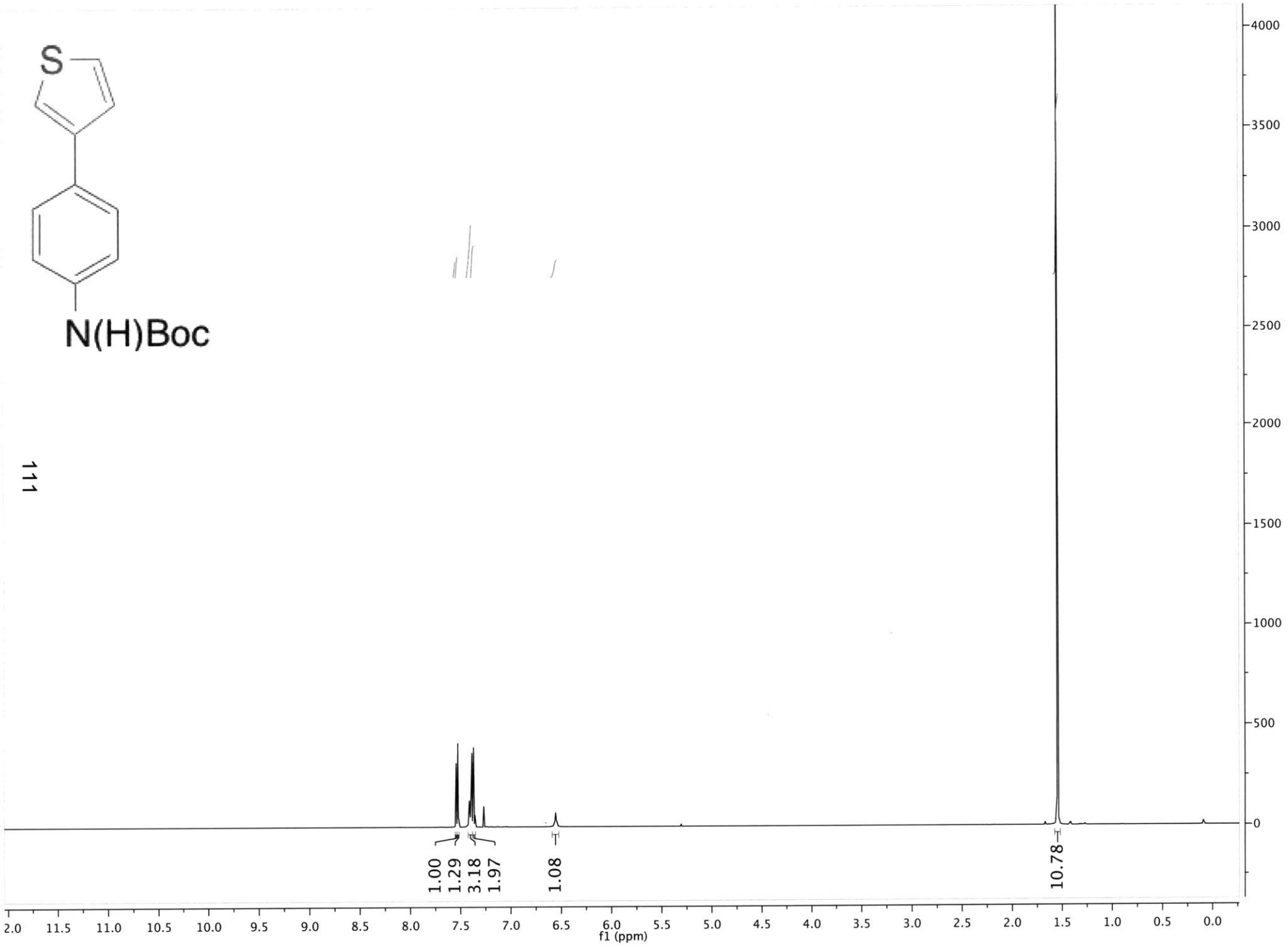

32.51
32.23
11.36
11.08
NH2
Pd
dppf
OMs
106
f1 (ppm)

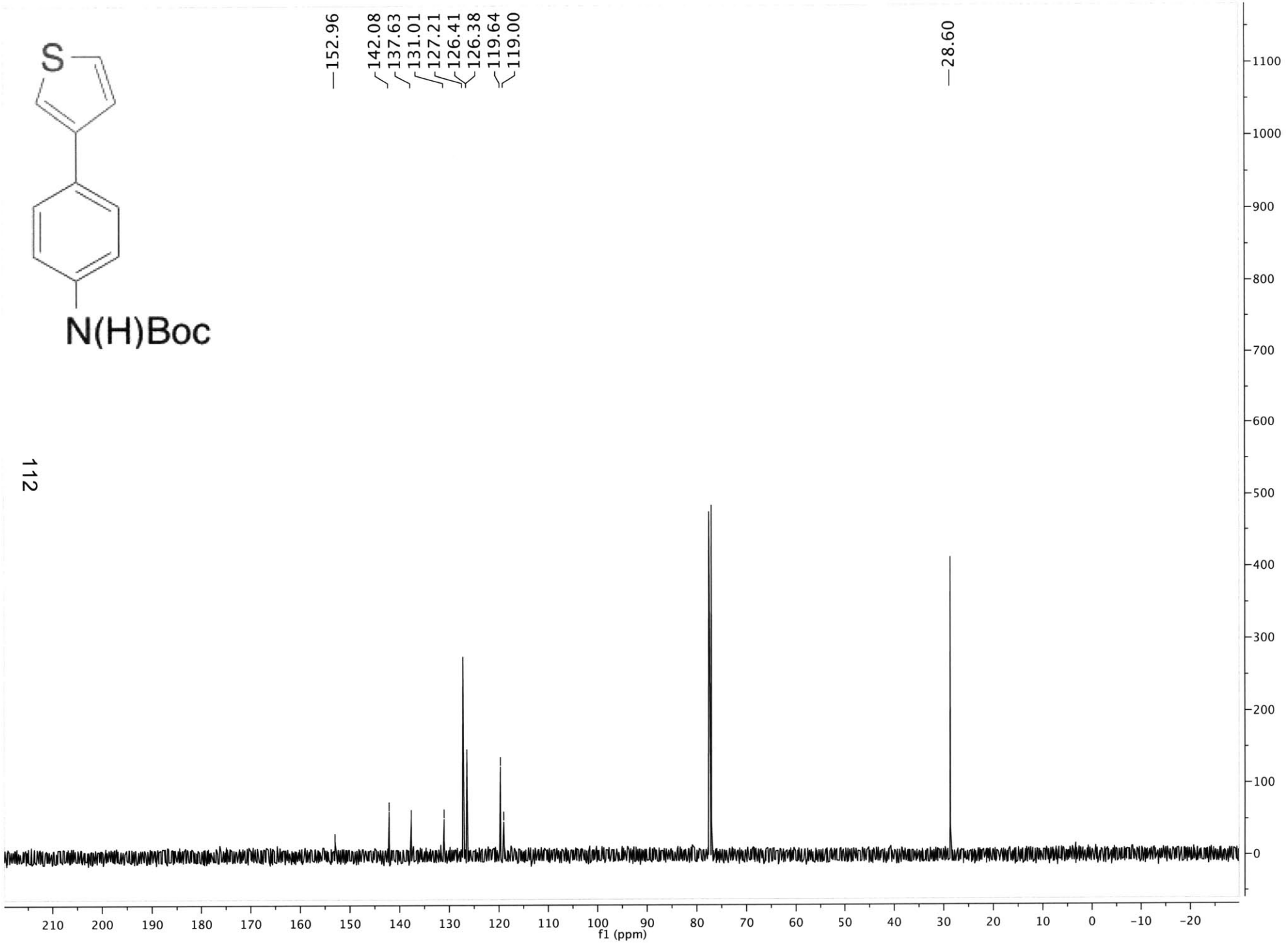

N
O
107
0.80
1.00
1.99
0.81
0.94
0.97
0.87
3.38
f1 (ppm)

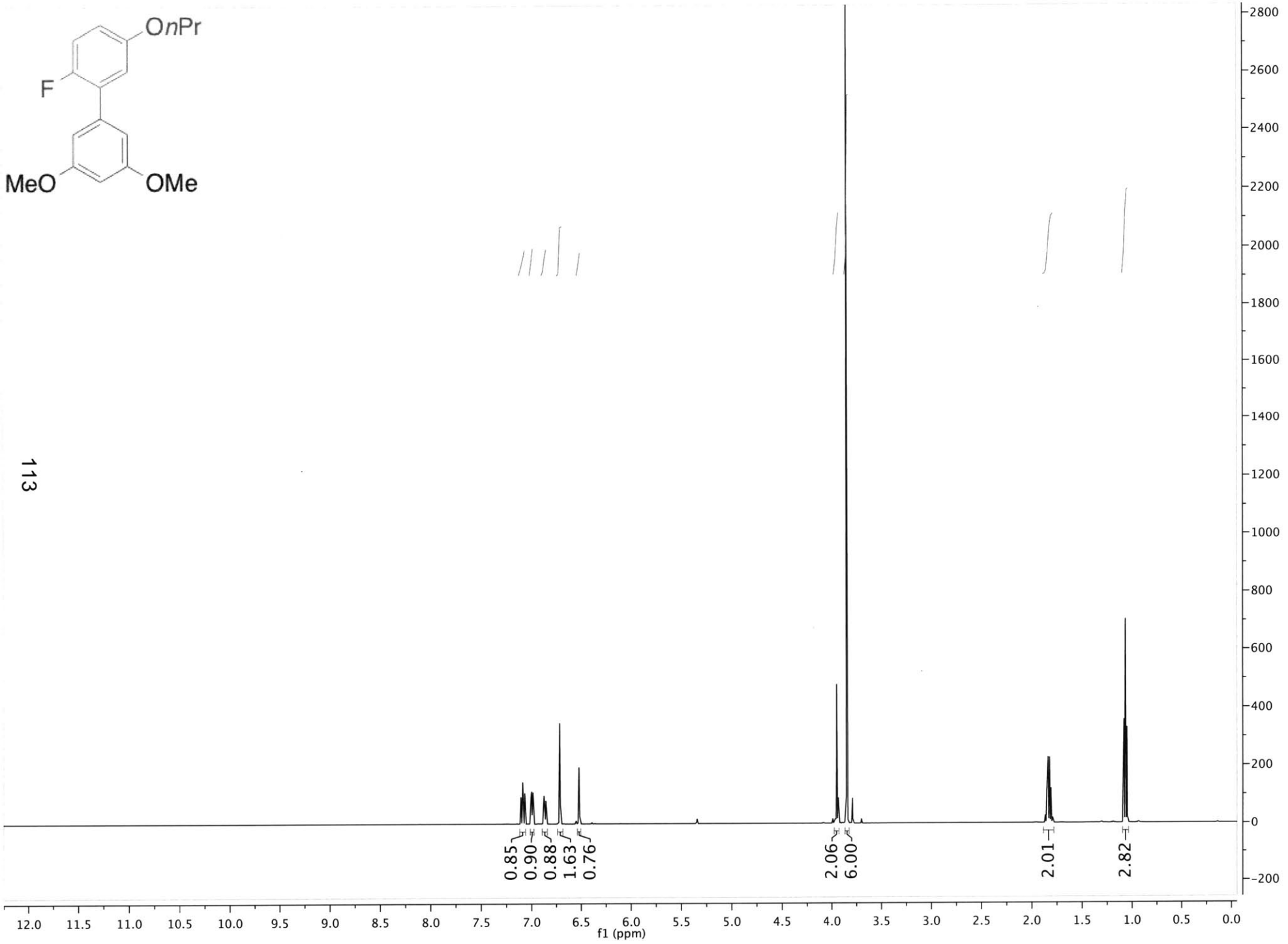

N
O
159.82
153.18
147.38
143.29
136.86
132.19
128.22
125.95
122.12
121.91
120.49
111.94
107.08
23.48
108
f1 (ppm)

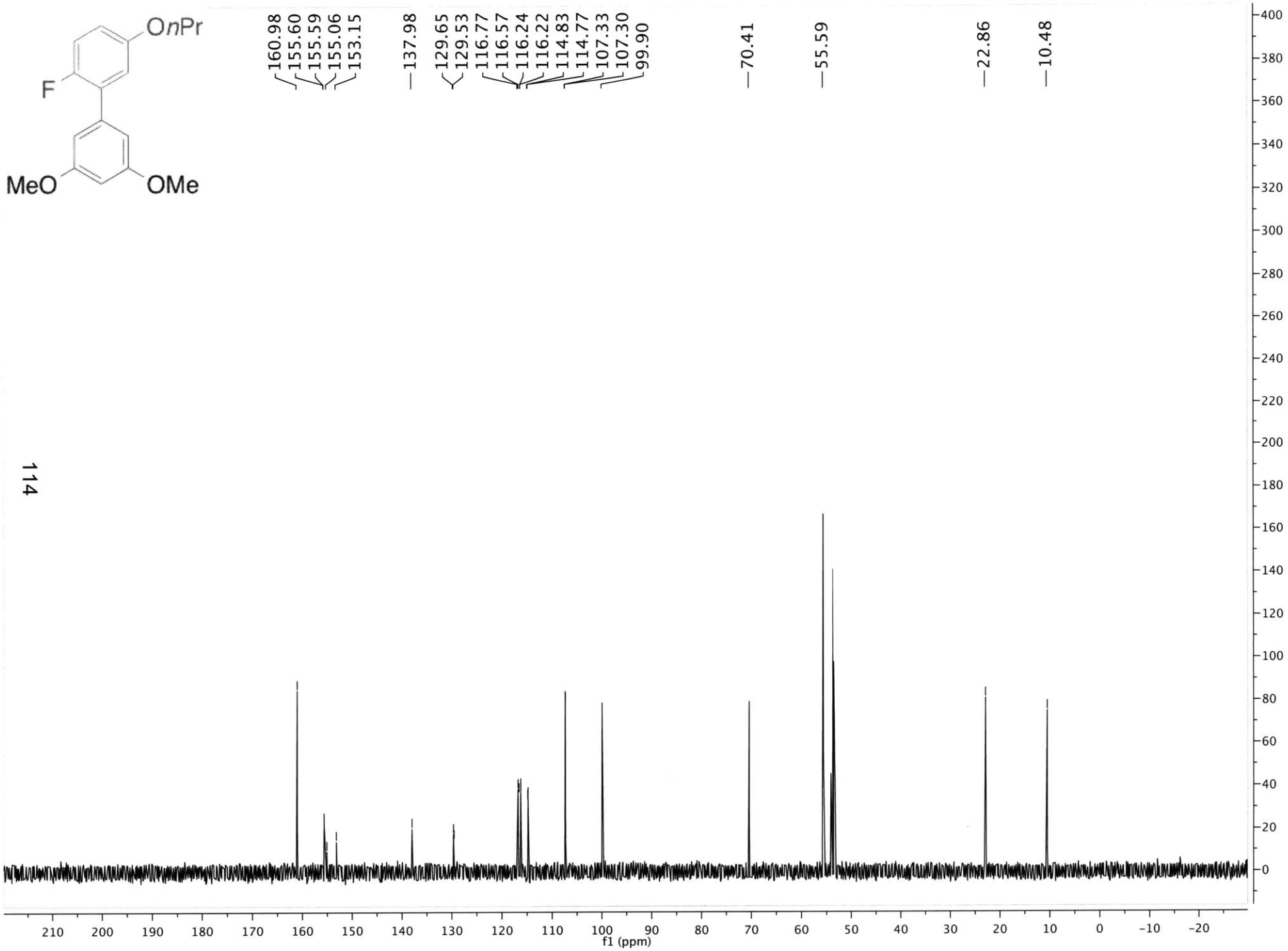

O
S
109
0.61
0.84
0.81
1.17
1.17
1.00
f1 (ppm)

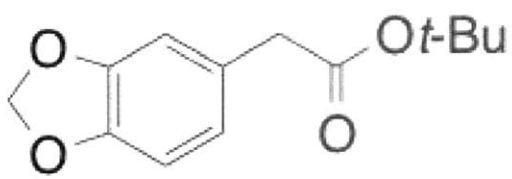

143.85
143.77
138.46
135.15
127.87
123.89
123.67
120.90
109.72
O
S
110
f1 (ppm)


S
N(H)Boc
111
1.00
1.29
3.18
1.97
1.08
10.78
f1 (ppm)

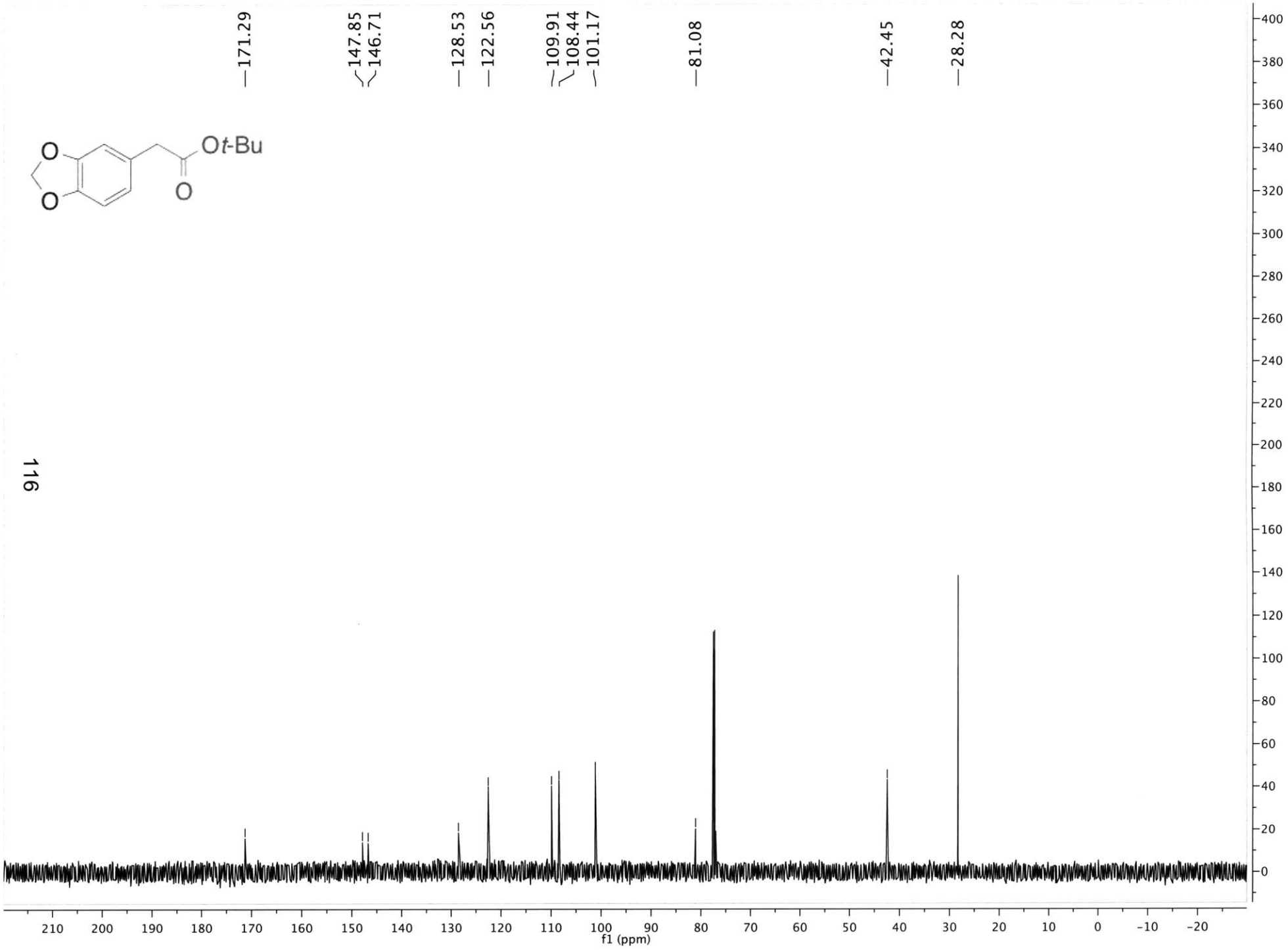

S
N(H)Boc
152.96
142.08
137.63
131.01
127.21
126.41
126.38
119.64
119.00
28.60
112
f1 (ppm)

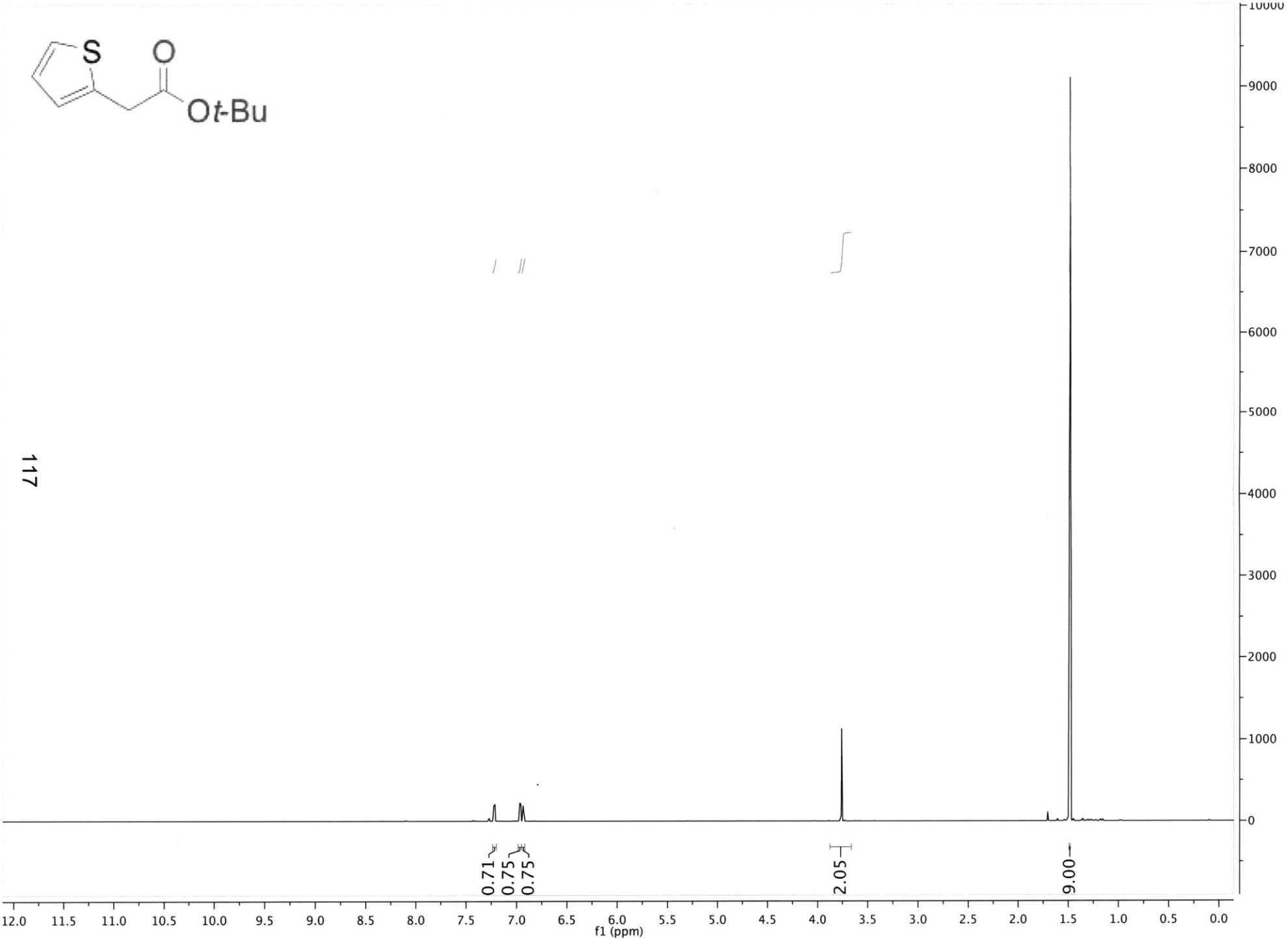

OnPr
F
MeO
OMe
113
0.85
0.90
0.88
1.63
0.76
2.06
6.00
2.01
2.82
f1 (ppm)

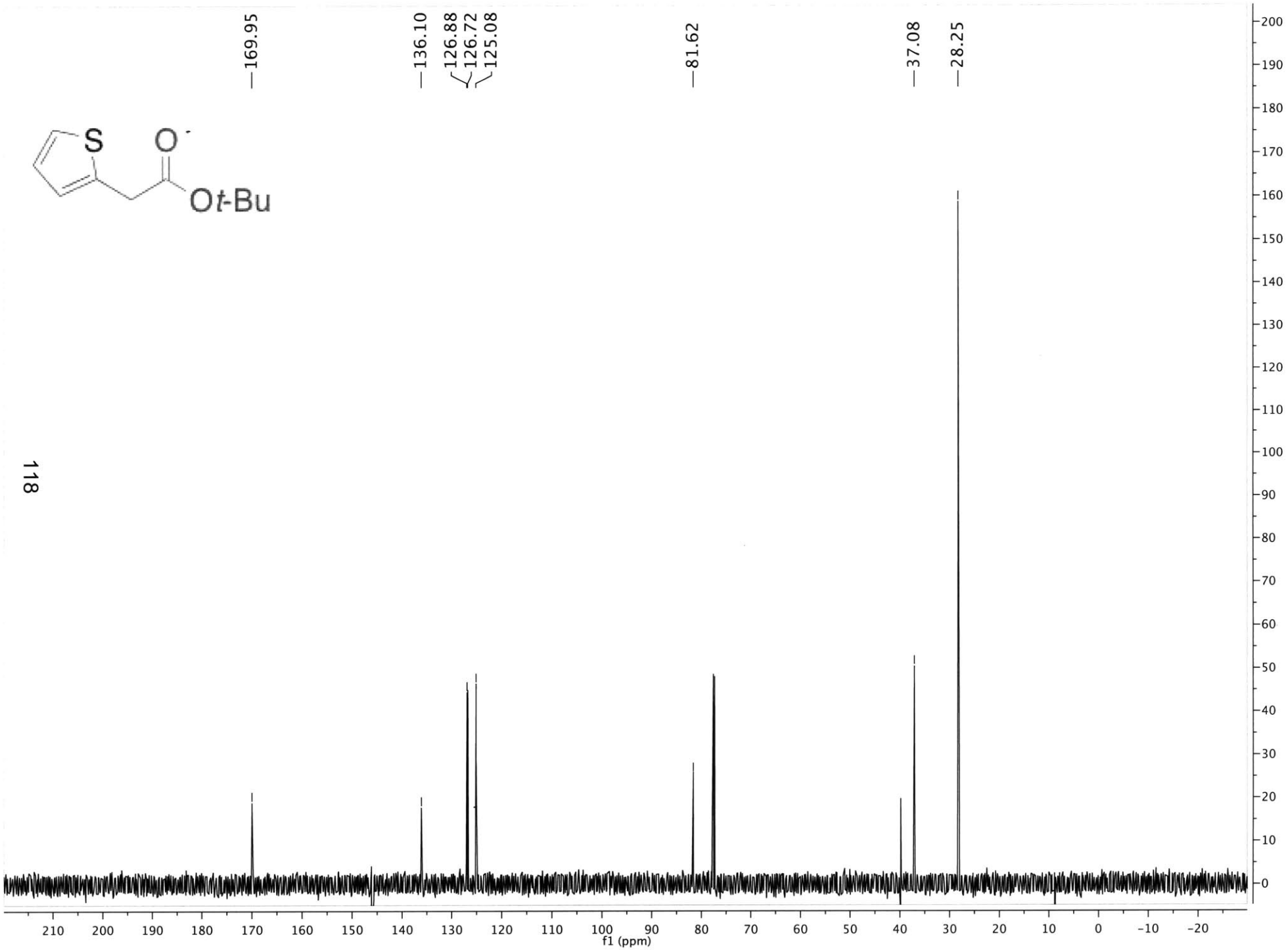

OnPr
F
MeO
OMe
160.98
155.60
155.59
155.06
153.15
137.98
129.65
129.53
116.77
116.57
116.24
116.22
114.83
114.77
107.33
107.30
99.90
70.41
55.59
22.86
10.48
114
f1 (ppm)

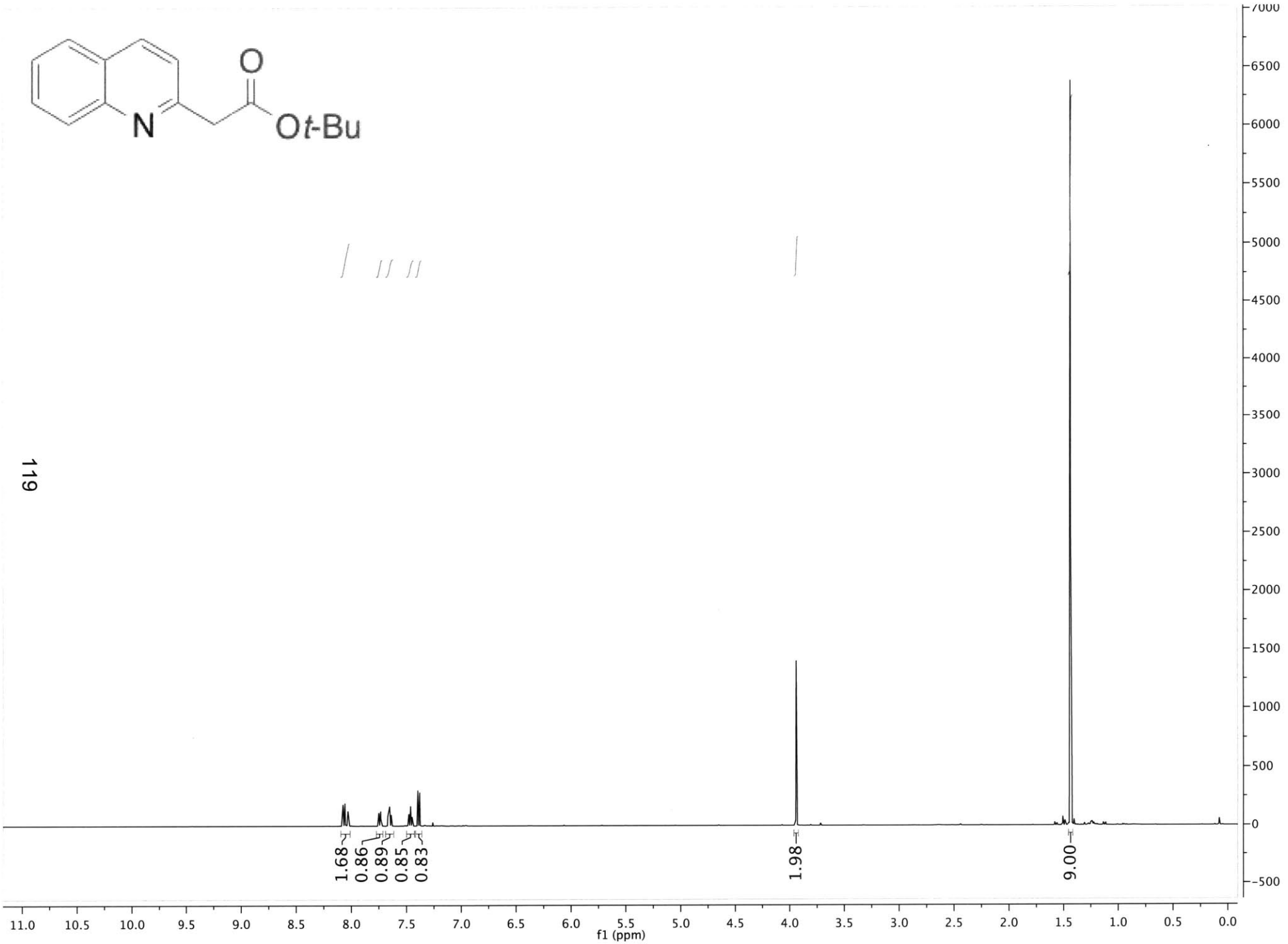


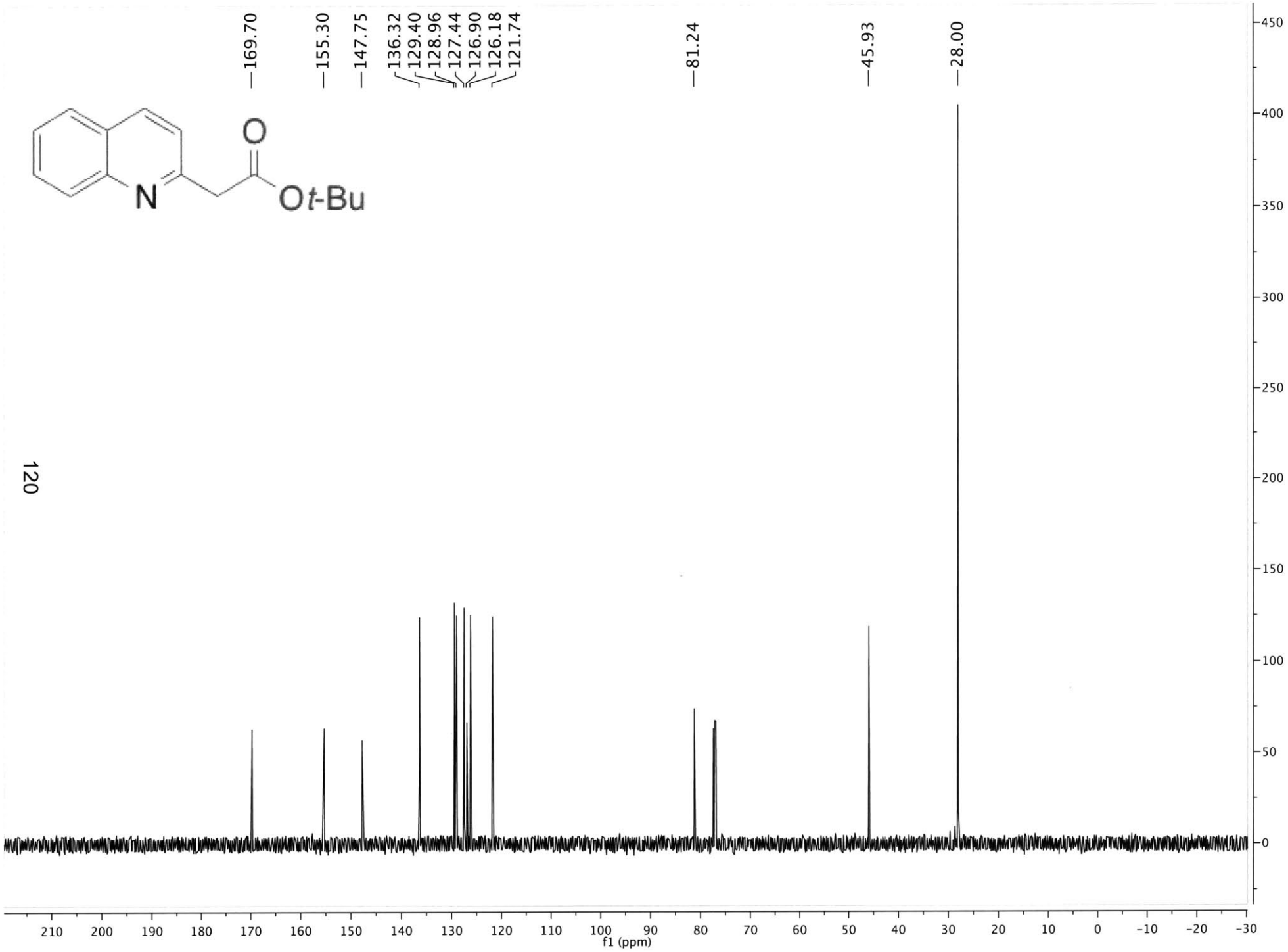
115


171.29
147.85
146.71
128.53
122.56
109.91
108.44
101.17
81.08
42.45
28.28
Ot-Bu
O
O
O
f1 (ppm)

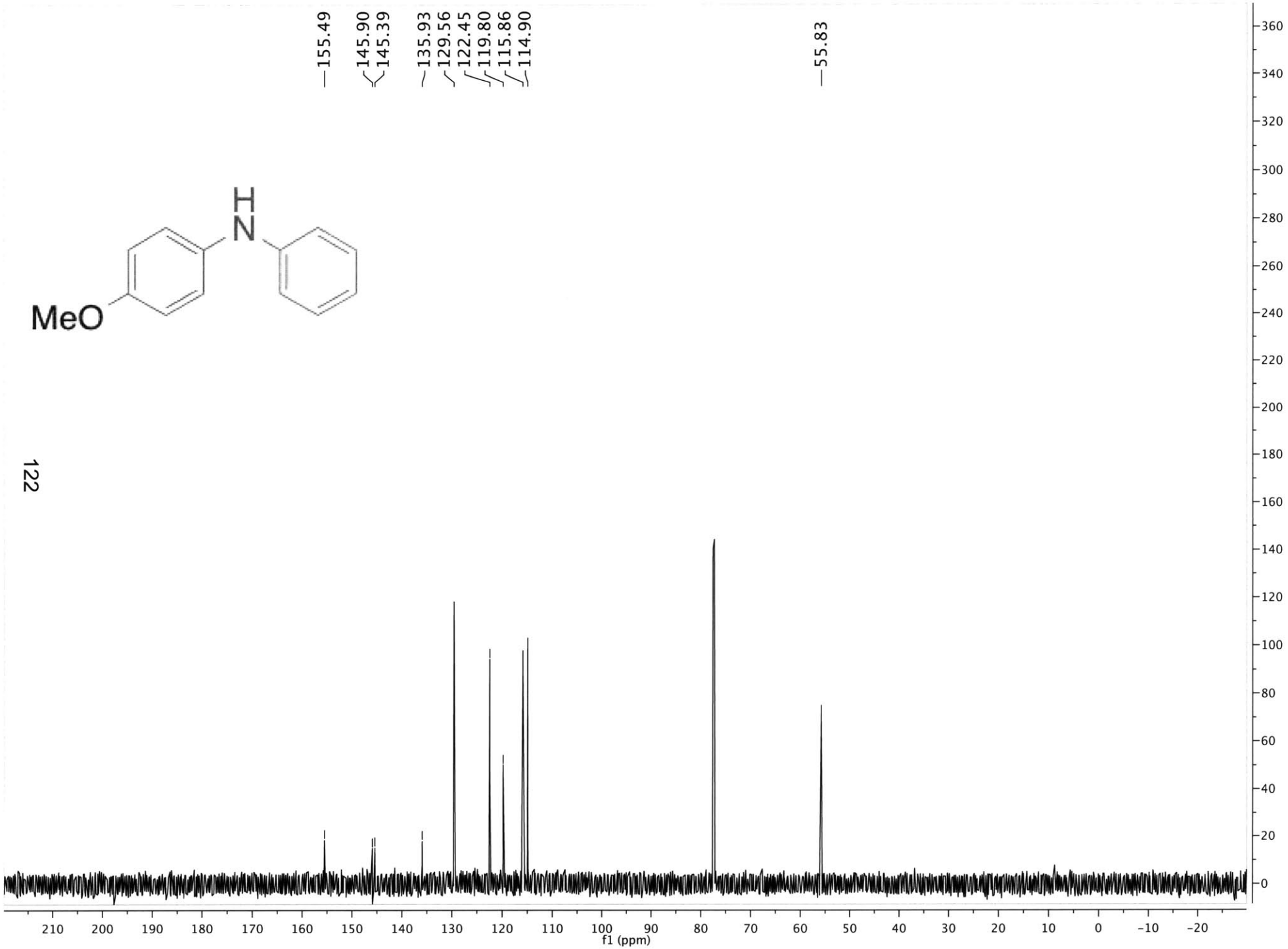

S
O
Ot-Bu
0.71
0.75
0.75
2.05
9.00
f1 (ppm)

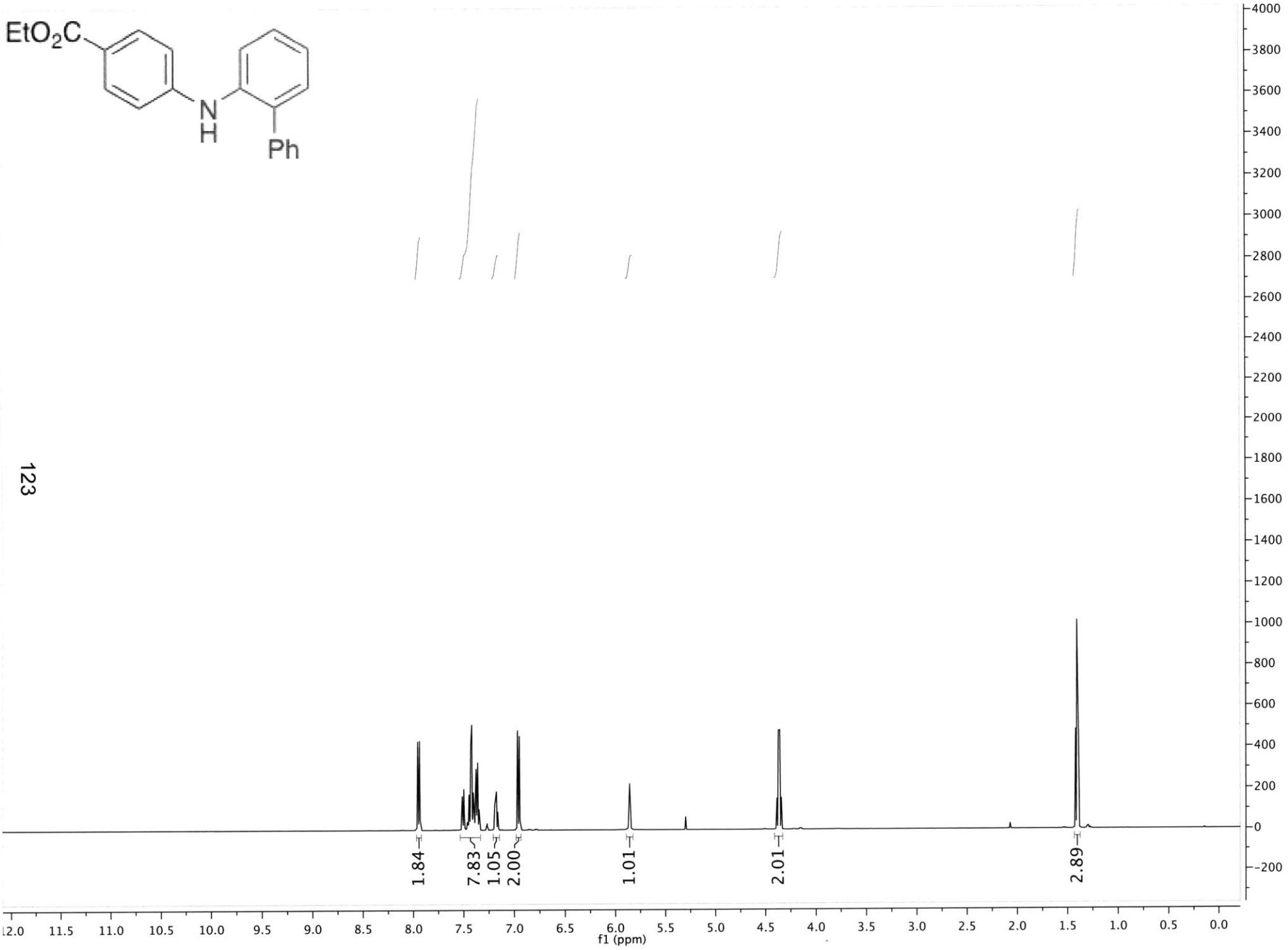

169.95
136.10
126.88
126.72
125.08
81.62
37.08
28.25
S
O
Ot-Bu
f1 (ppm)


O
N
Ot-Bu
1.68
0.86
0.89
0.85
0.83
1.98
9.00
f1 (ppm)


169.70
155.30
147.75
136.32
129.40
128.96
127.44
126.90
126.18
121.74
81.24
45.93
28.00
O
N
Ot-Bu
120
450
400
350
300
250
200
150
100
50
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)


MeO
H
N
121
2.10
2.00
2.03
3.00
1.01
3.35
f1 (ppm)


155.49
145.90
145.39
135.93
129.56
122.45
119.80
115.86
114.90
55.83
MeO
H
N
f1 (ppm)


EtO2C
N
H
Ph
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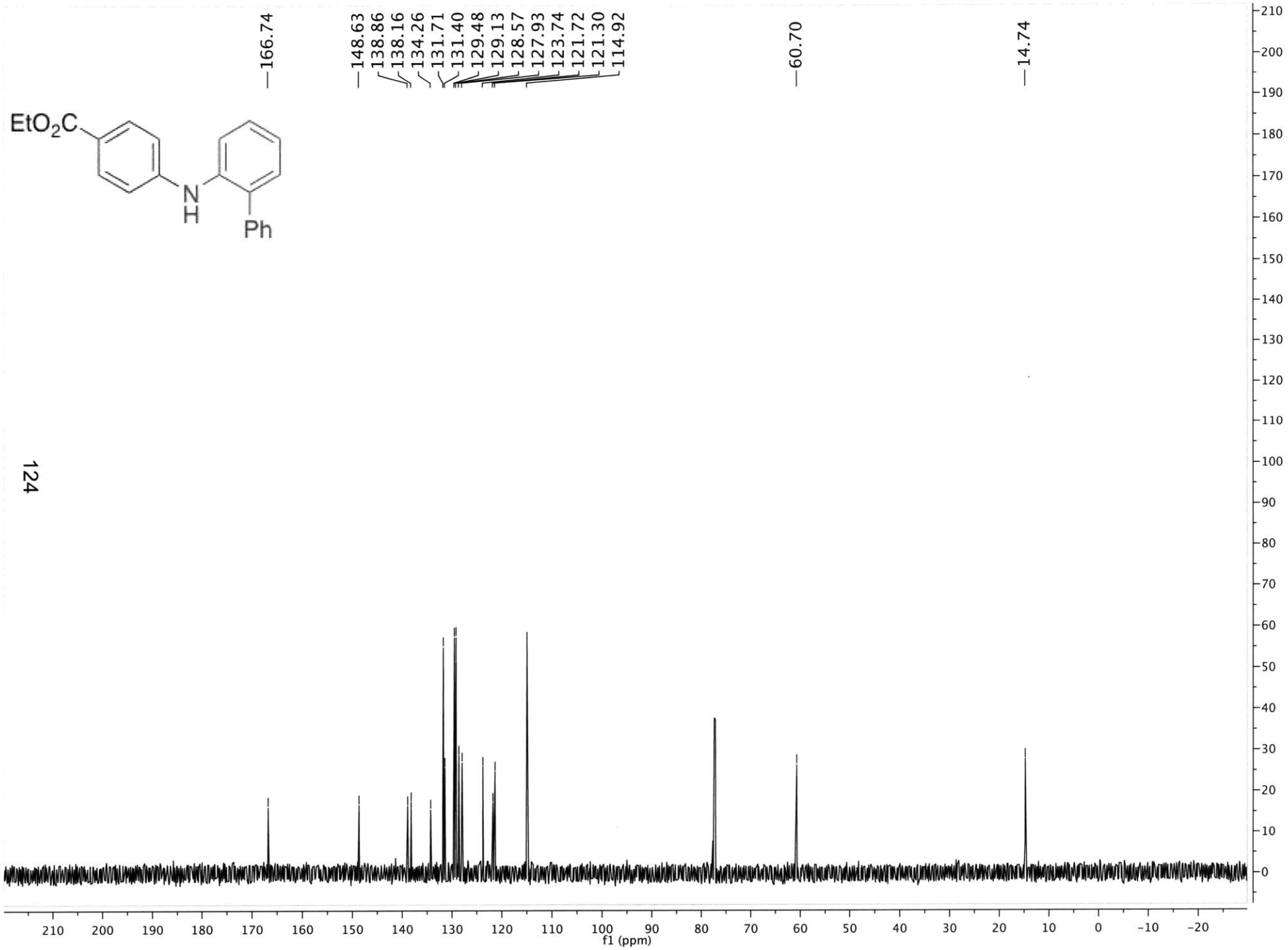
7.83
1.05
2.00
1.01
2.01
2.89
f1 (ppm)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138.86
138.16
134.26
131.71
131.40
129.48
129.13
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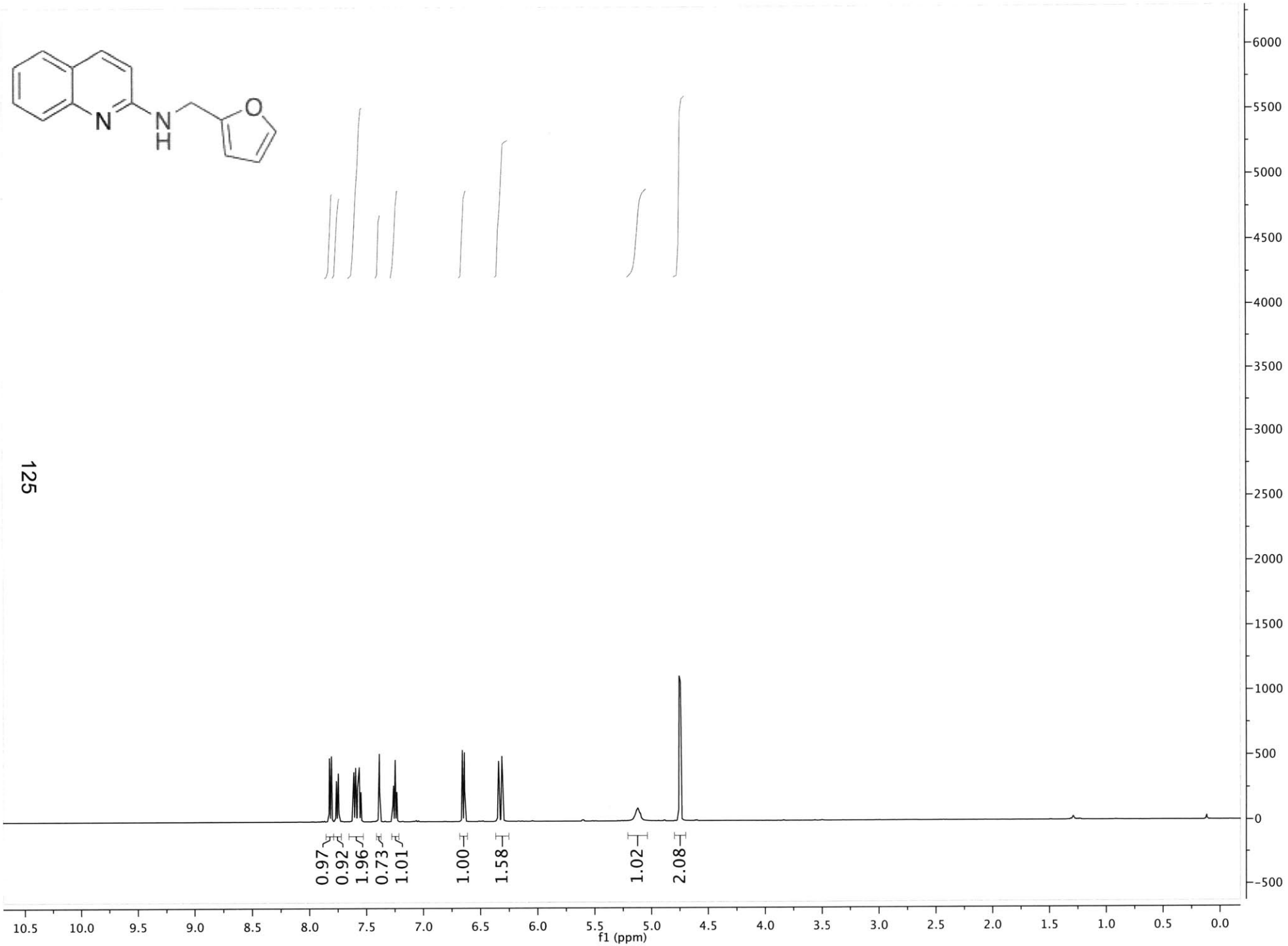
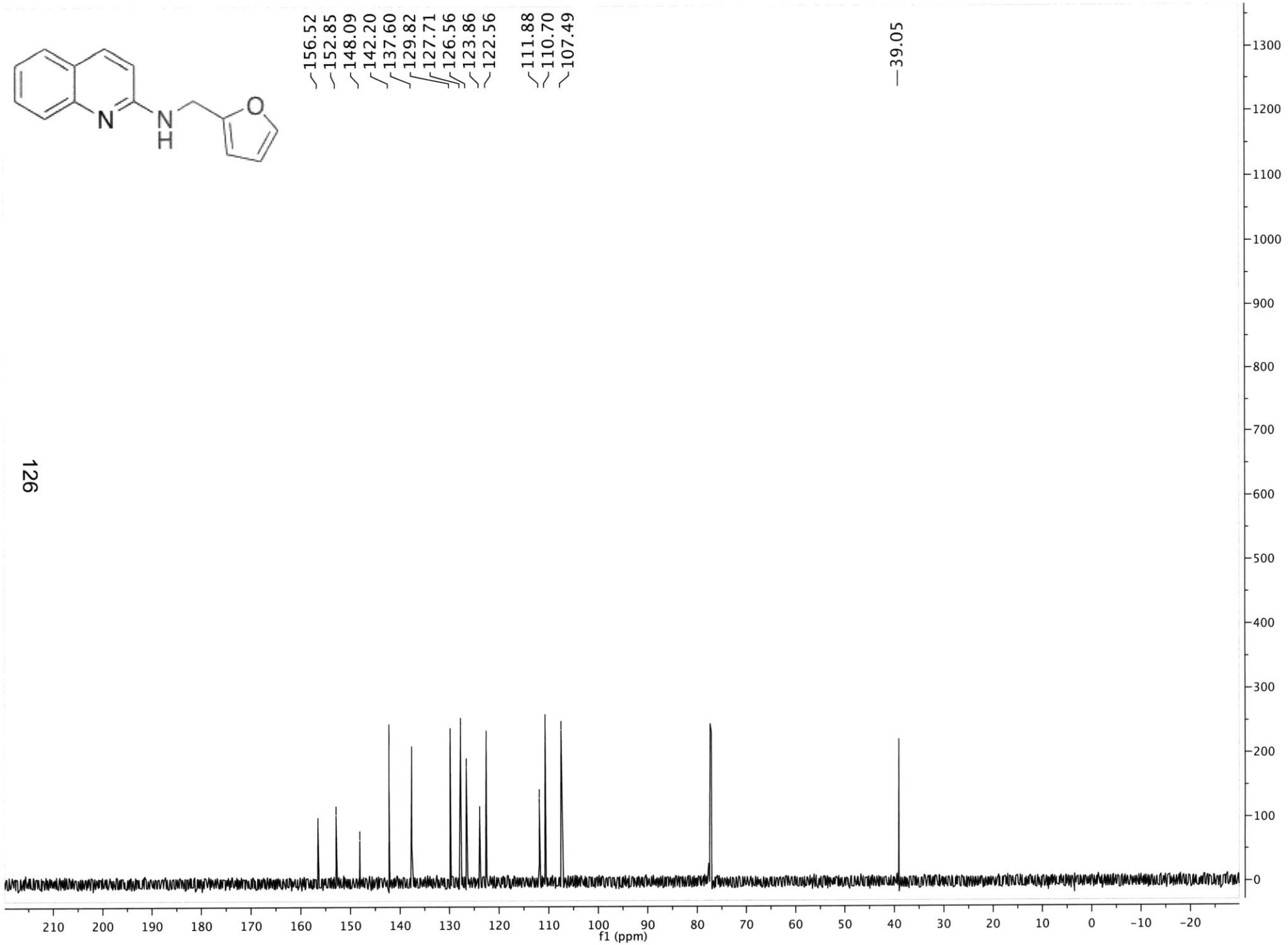
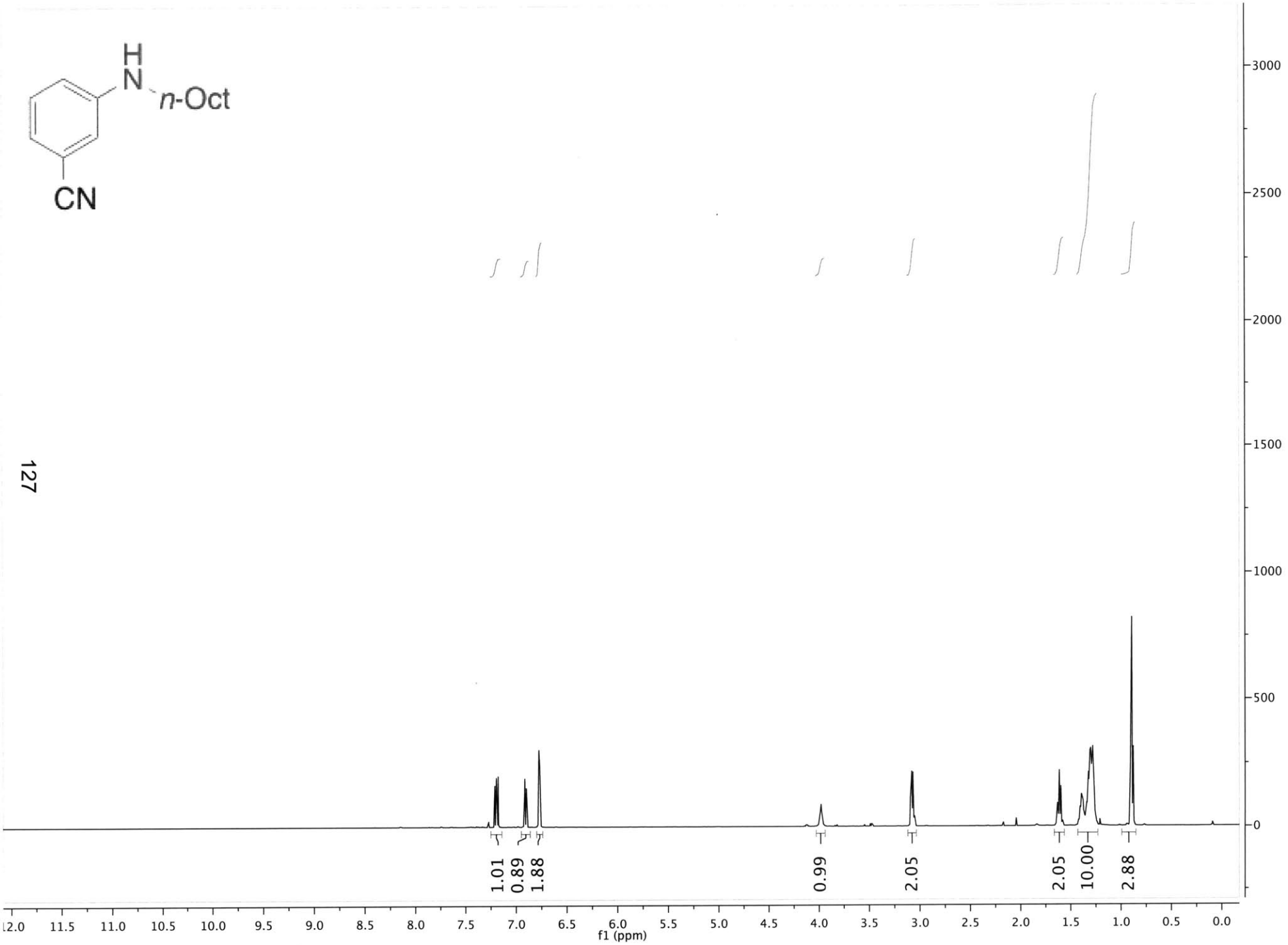
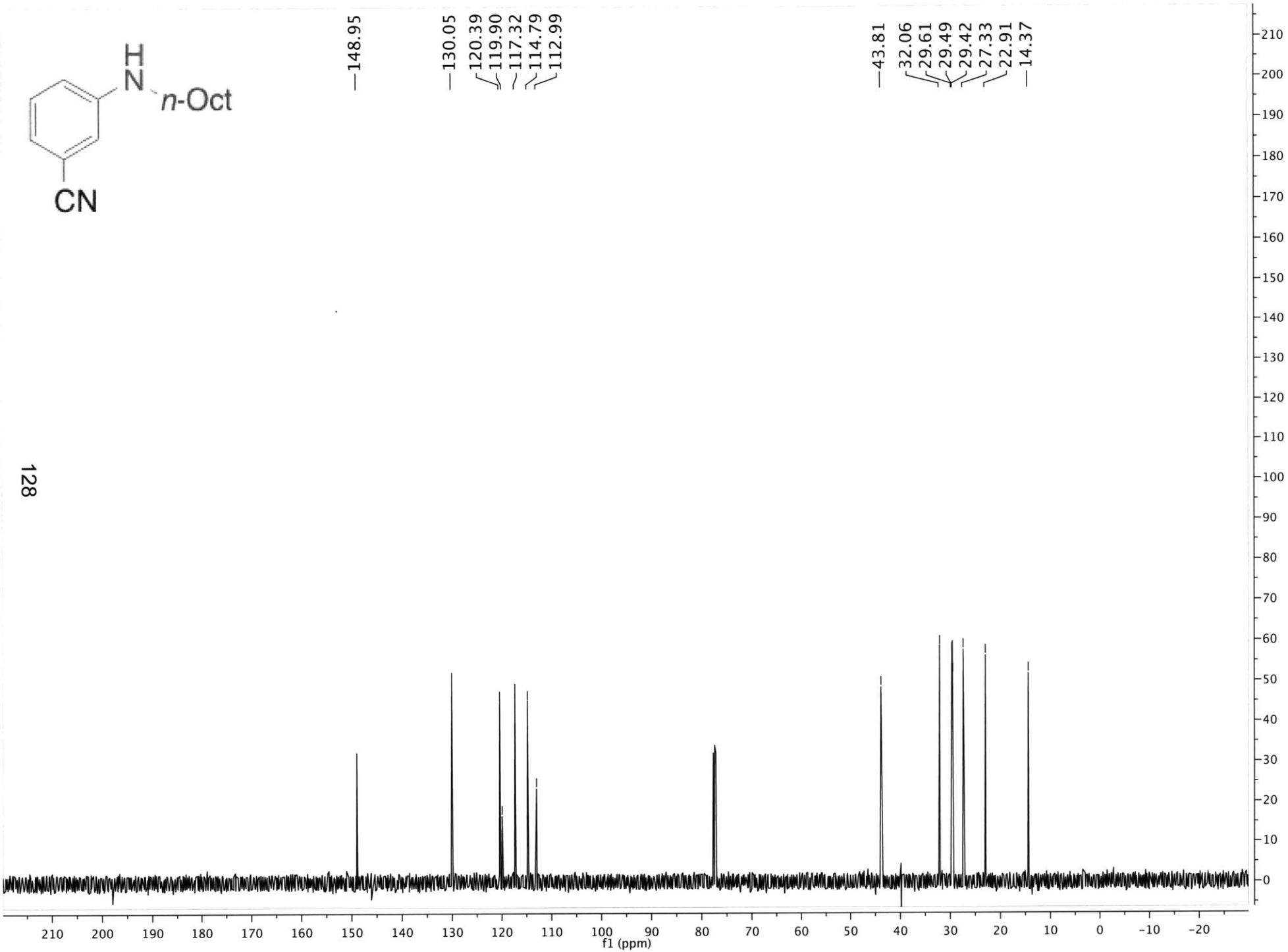
127.93
123.74
121.72
121.30
114.92
60.70
14.74
EtO2C
N
H
Ph
f1 (ppm)

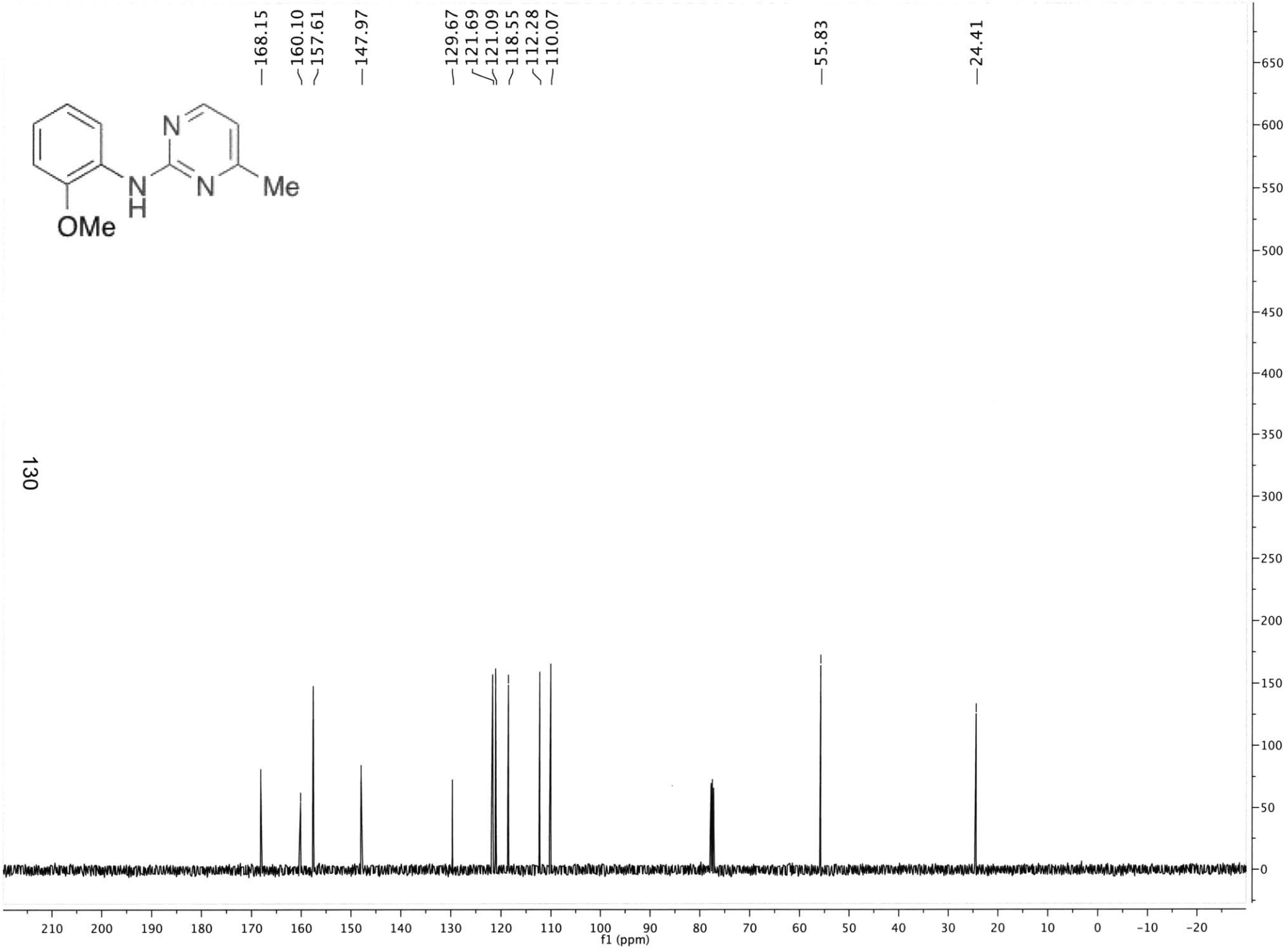

N
N
H
O
125
0.97
0.92
1.96
0.73
1.01
1.00
1.58
1.02
2.08
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

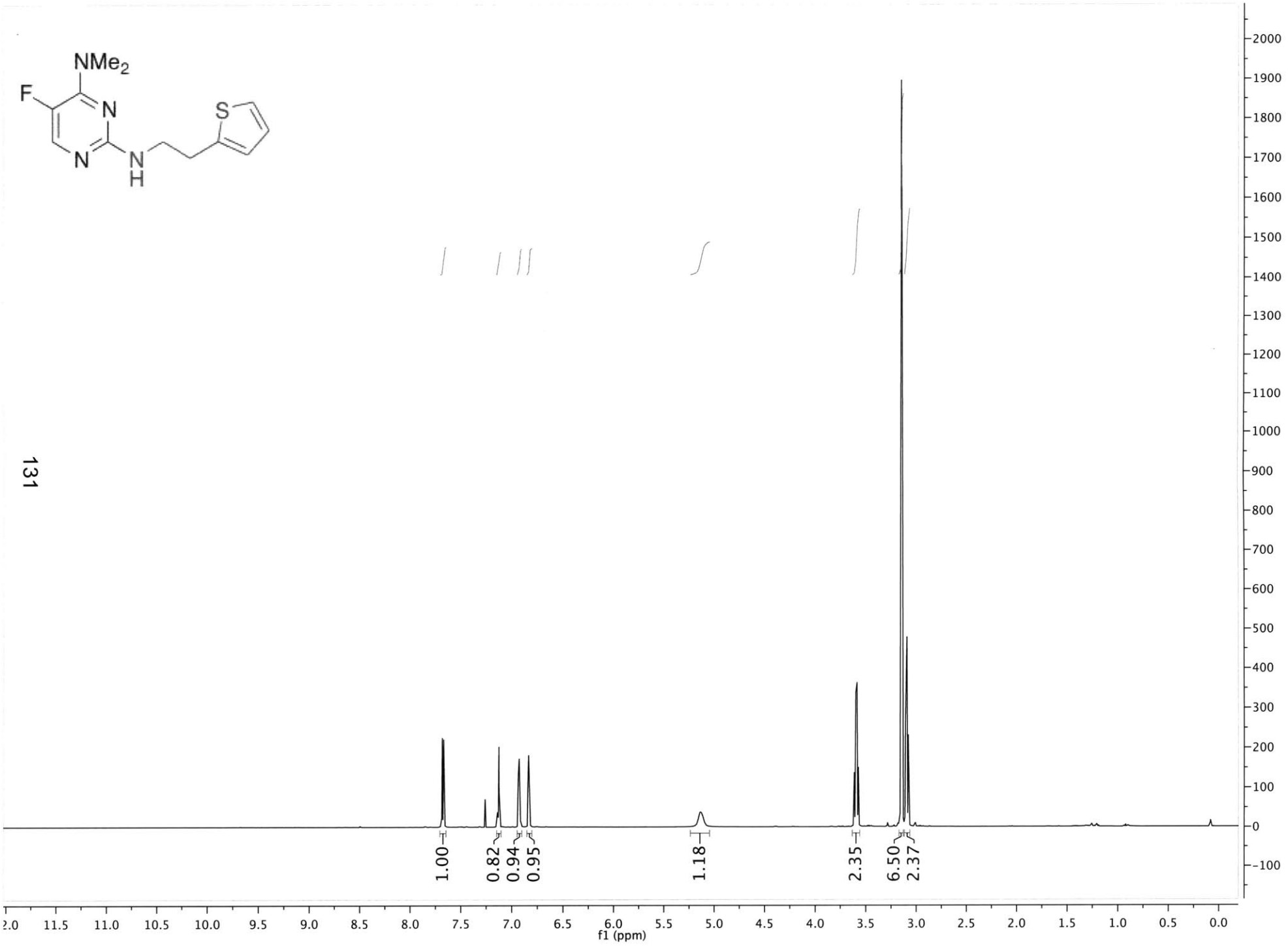

156.52
152.85
148.09
142.20
137.60
129.82
127.71
126.56
123.86
122.56
111.88
110.70
107.49
39.05
N
N
H
O
f1 (ppm)

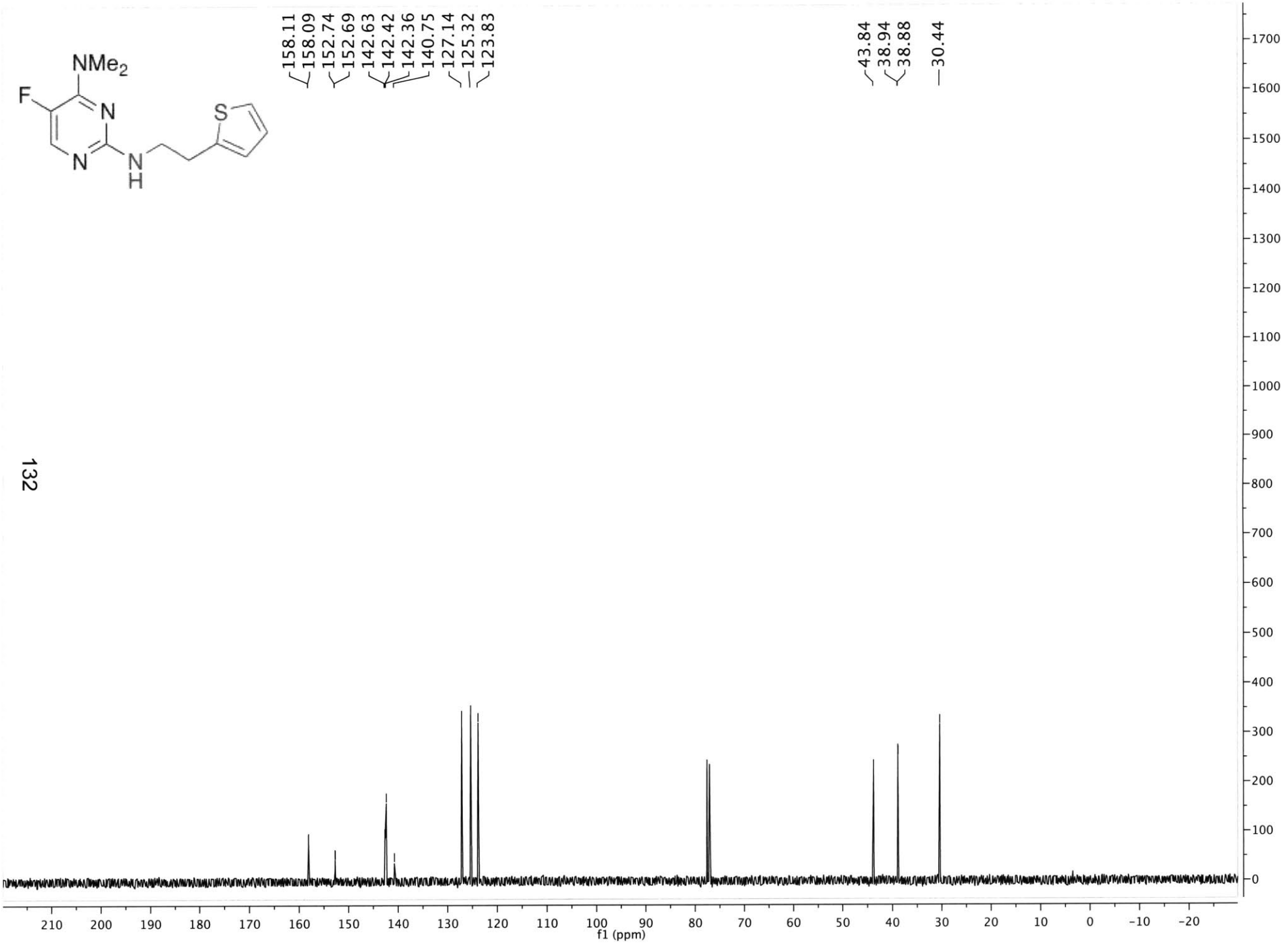

H
N
n-Oct
CN
127
1.01
0.89
1.88
0.99
2.05
2.05
10.00
2.88
f1 (ppm)


148.95
130.05
120.39
119.90
117.32
114.79
112.99
43.81
32.06
29.61
29.49
29.42
27.33
22.91
14.37
H
N
n-Oct
CN
f1 (ppm)

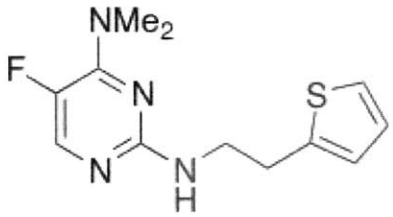

N
N
H
N
Me
OMe
129
0.97
0.96
1.00
1.08
1.05
1.05
1.00
3.49
3.31
f1 (ppm)

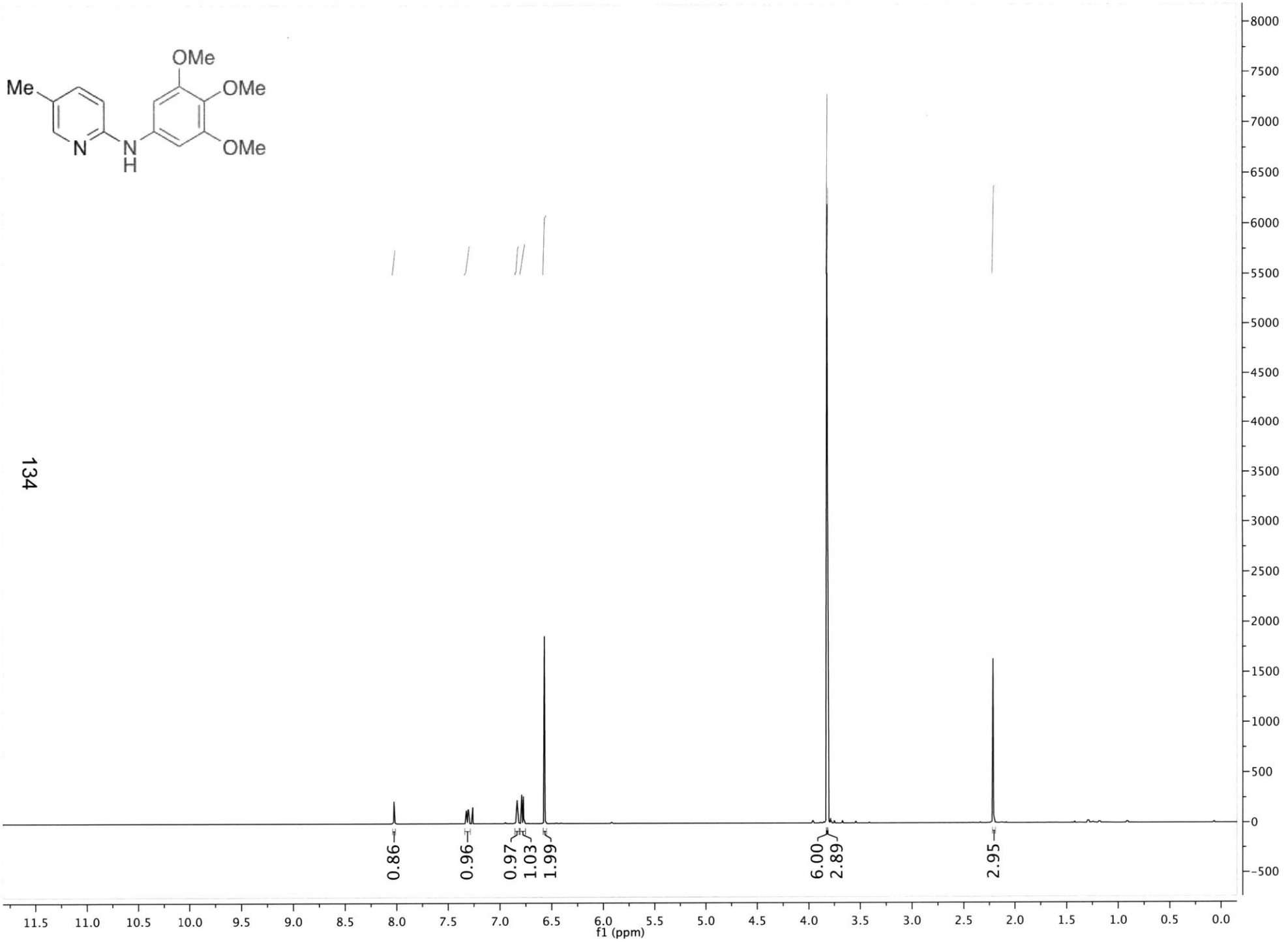

168.15
160.10
157.61
147.97
129.67
121.69
121.09
118.55
112.28
110.07
55.83
24.41
N
N
N
H
Me
OMe
130
f1 (ppm)

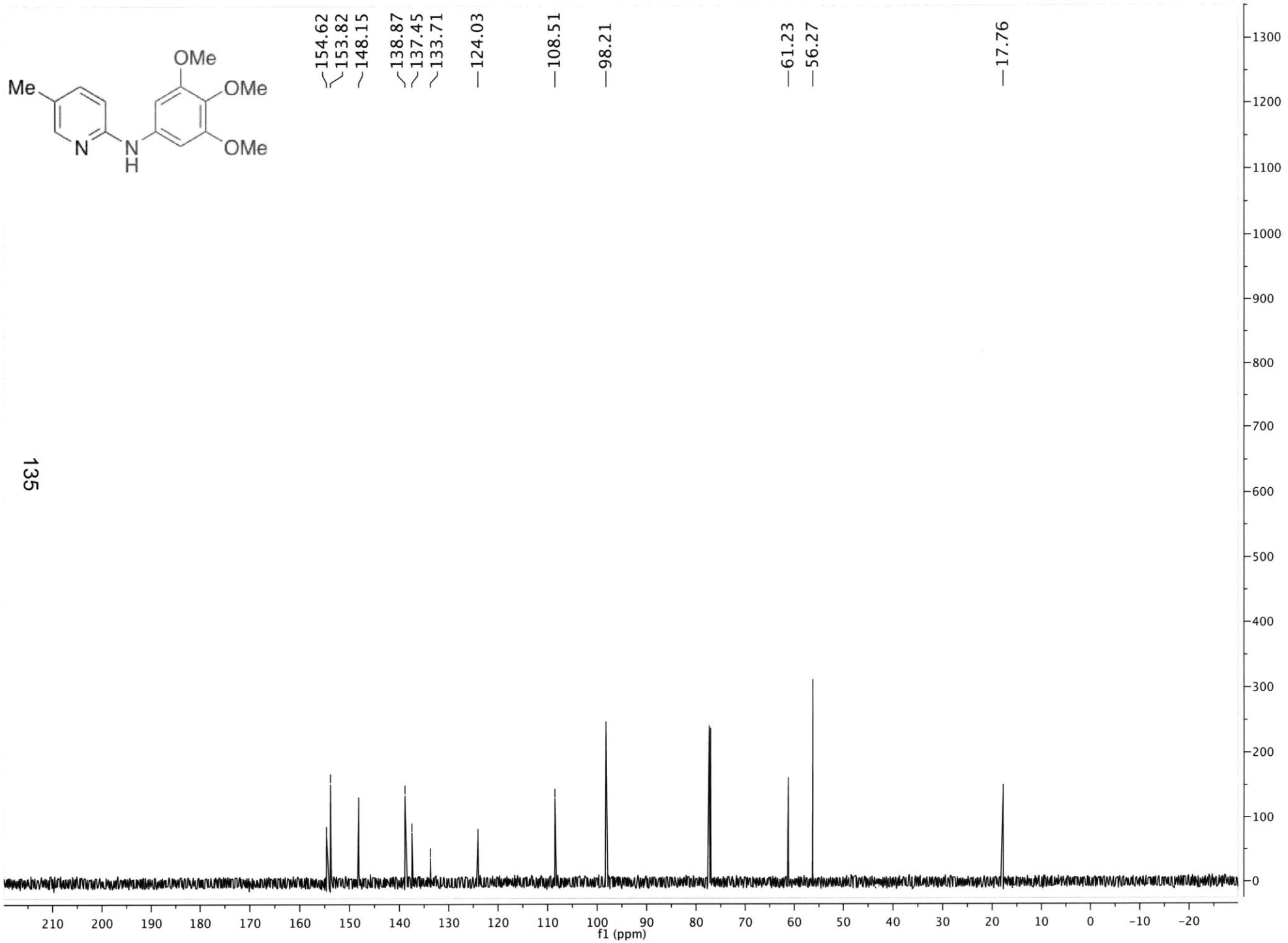

NMe2
F
N
S
N
N
H
131
1.00
0.82
0.94
0.95
1.18
2.35
6.50
2.37
f1 (ppm)


NMe2
F
N
S
N
N
H
158.11
158.09
152.74
152.69
142.63
142.42
142.36
140.75
127.14
125.32
123.83
43.84
38.94
38.88
30.44
f1 (ppm)

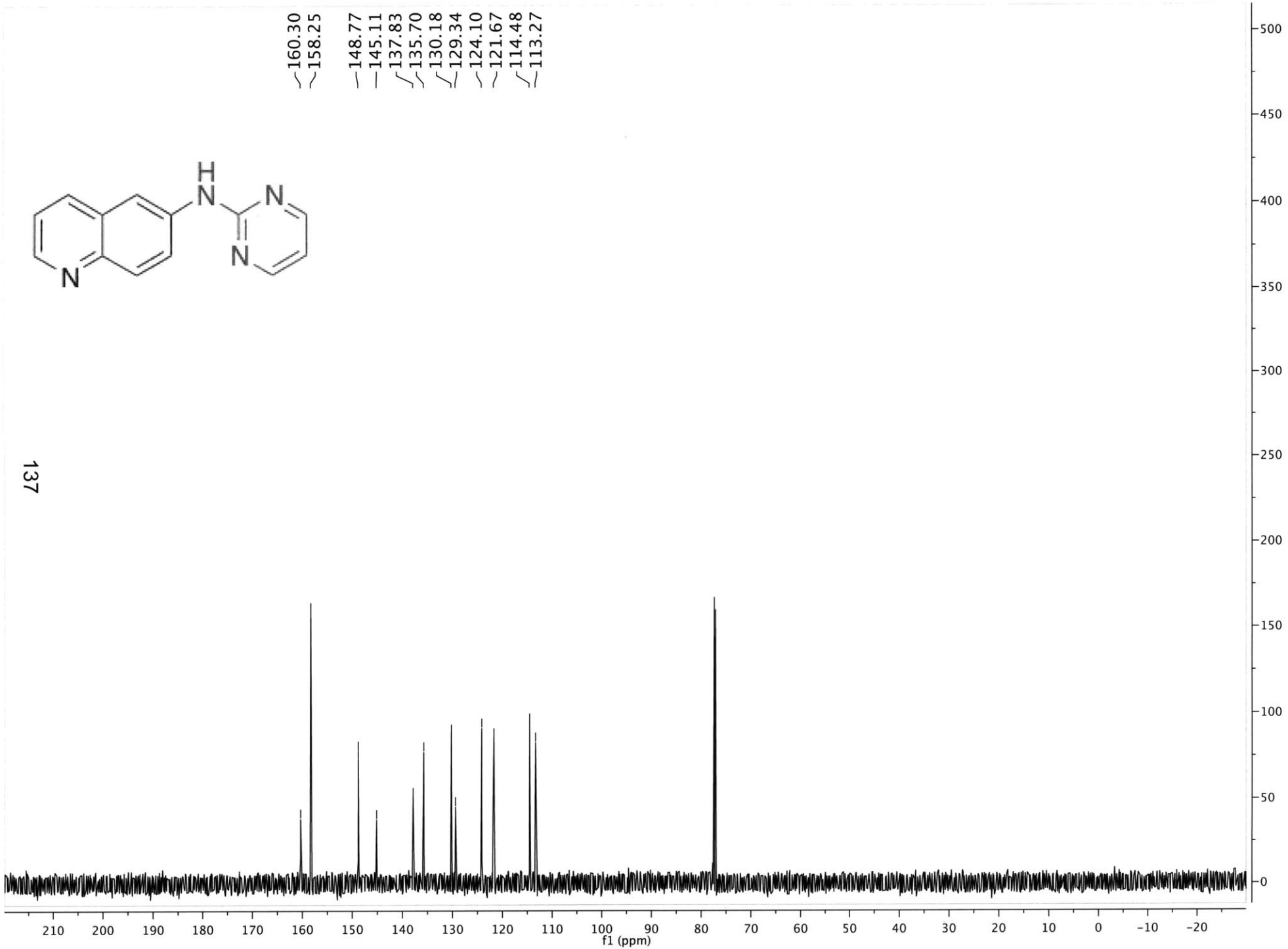
NCB-2-108-19F
19F OBSERVE
STANDARD PARAMETERS

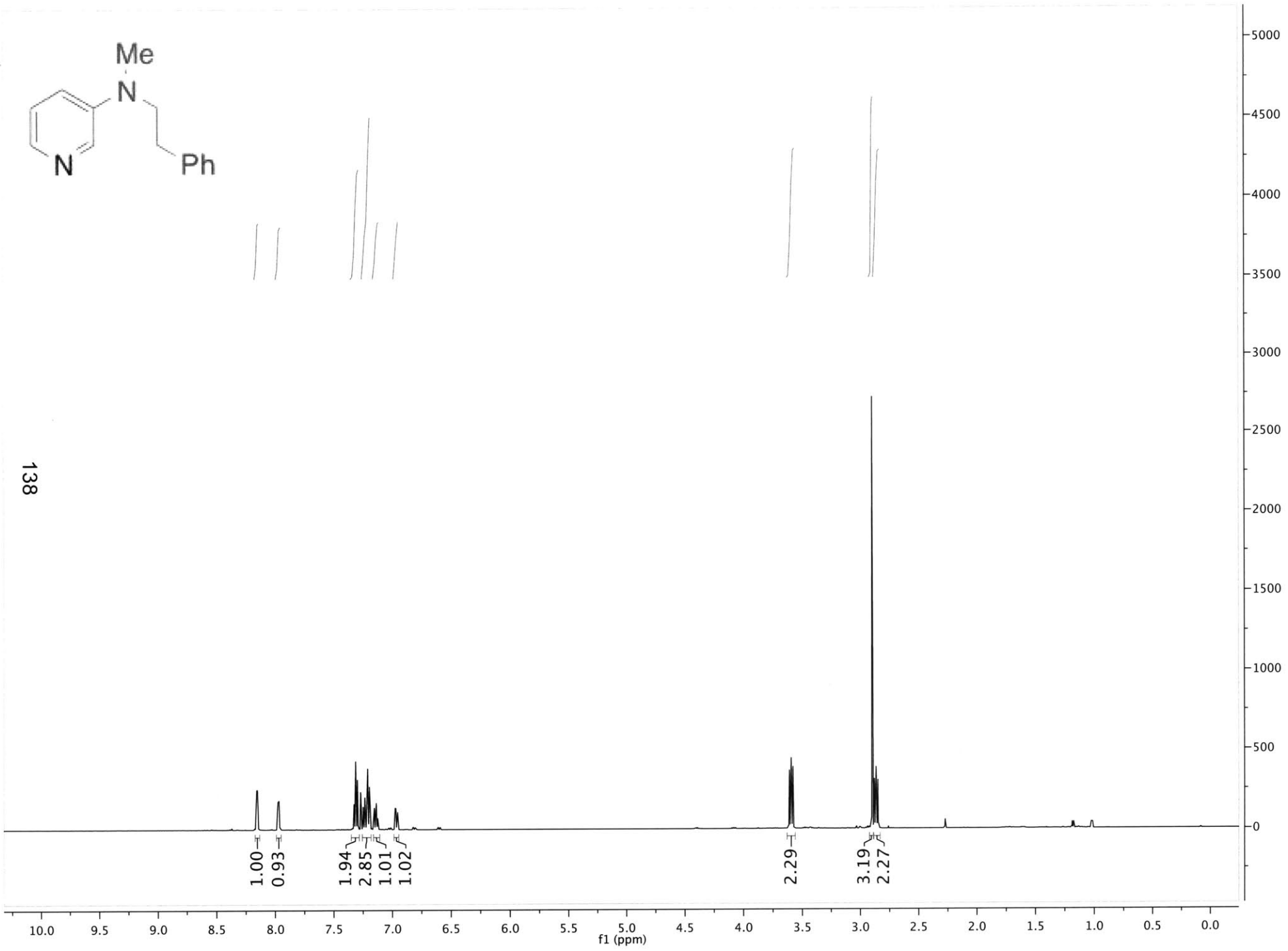


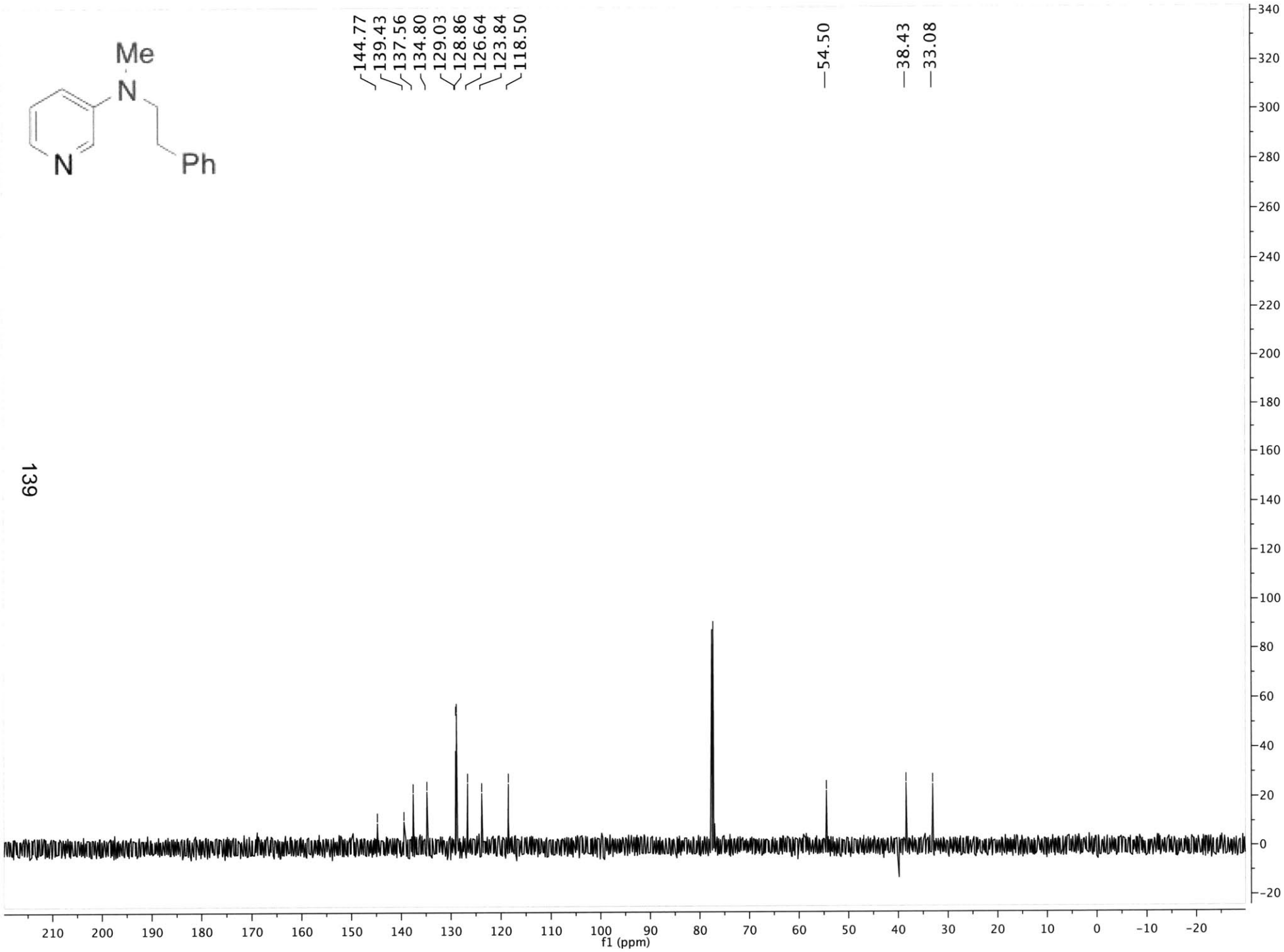

OMe
Me
OMe
N
N
H
OMe
134
0.86
0.96
0.97
1.03
1.99
6.00
2.89
2.95
f1 (ppm)

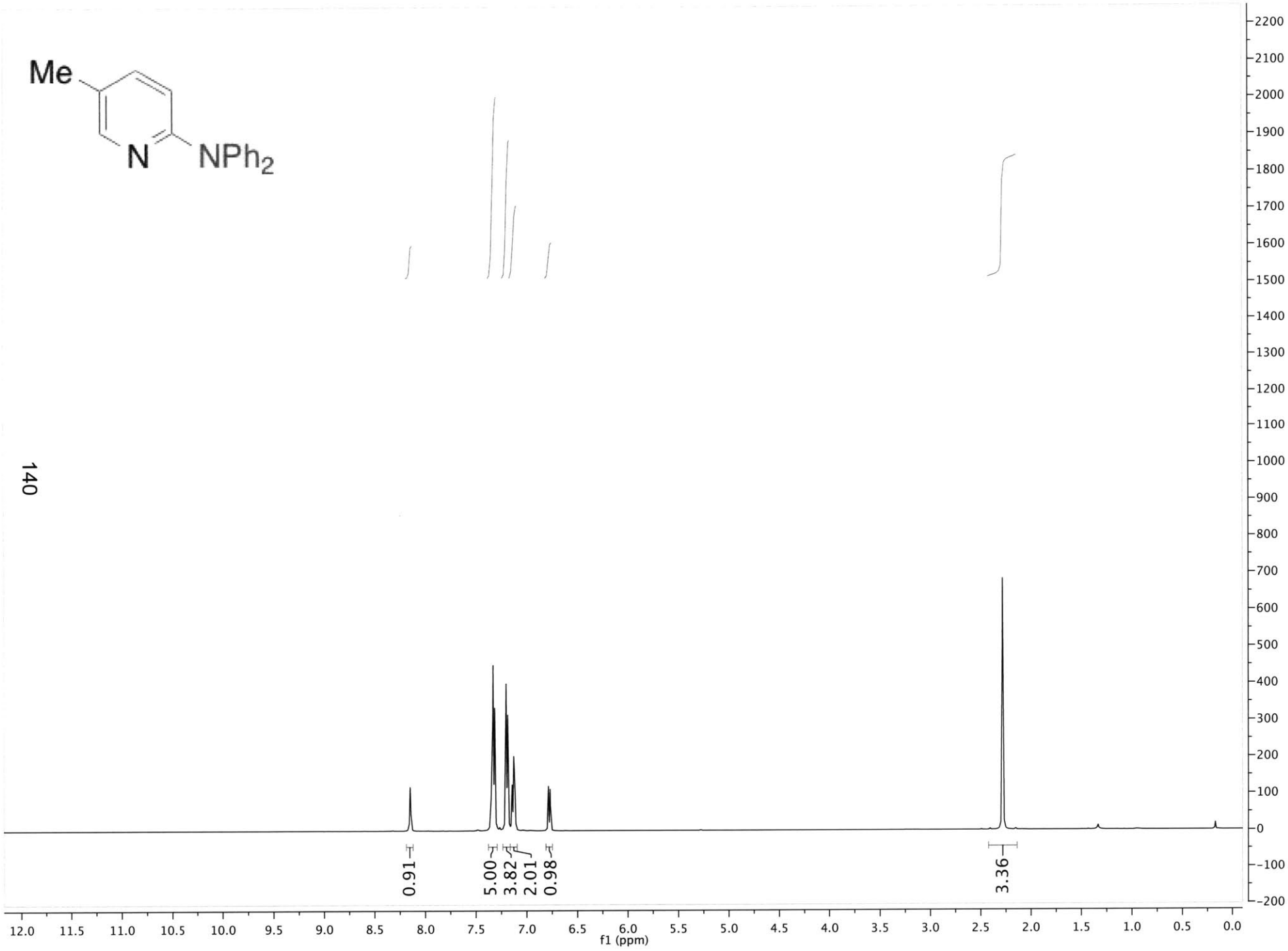

Me
OMe
OMe
OMe
N
N
H
154.62
153.82
148.15
138.87
137.45
133.71
124.03
108.51
98.21
61.23
56.27
17.76
f1 (ppm)

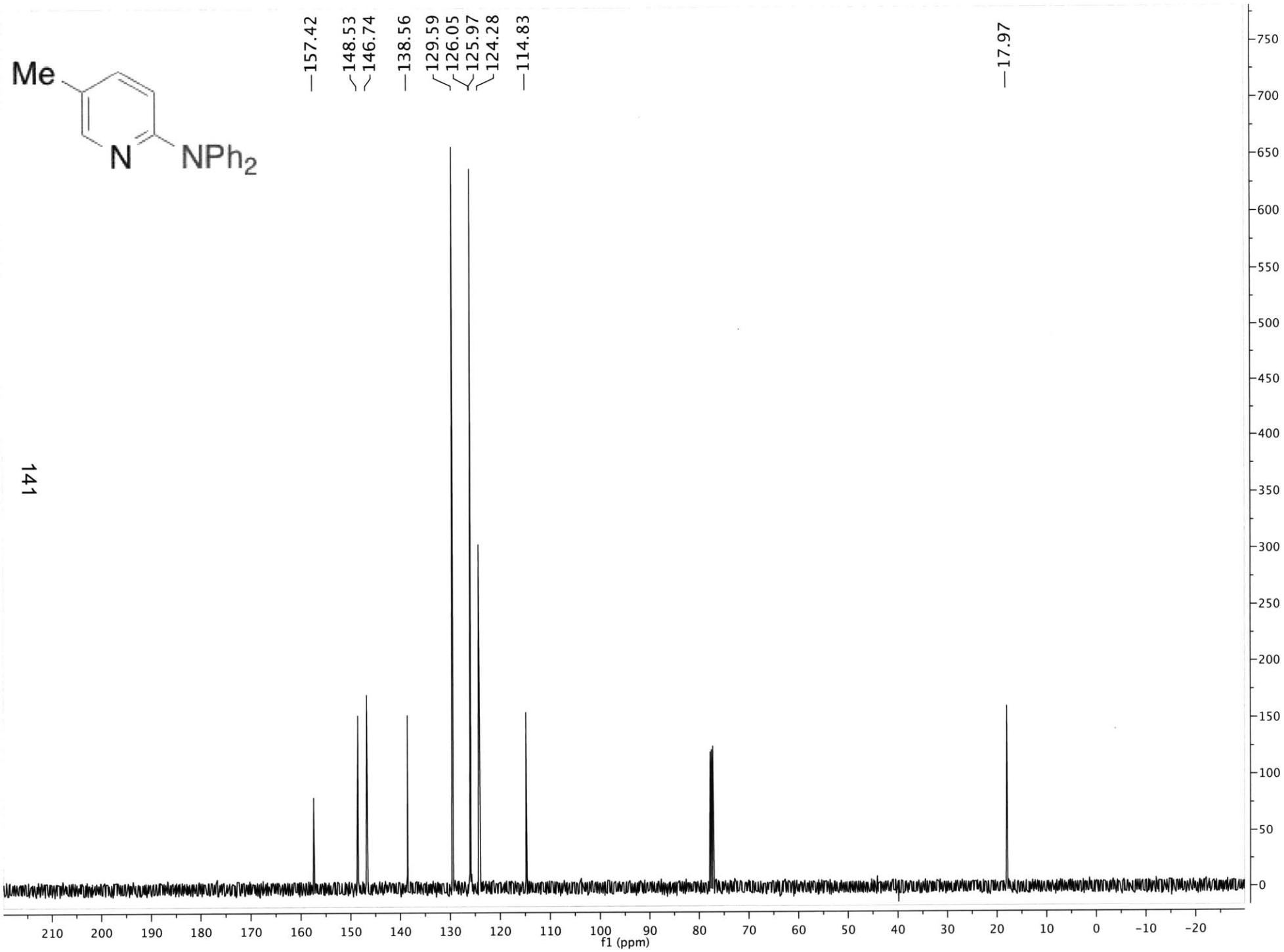

136
1.00
2.07
2.11
1.12
1.02
1.14
1.09
1.09
f1 (ppm)

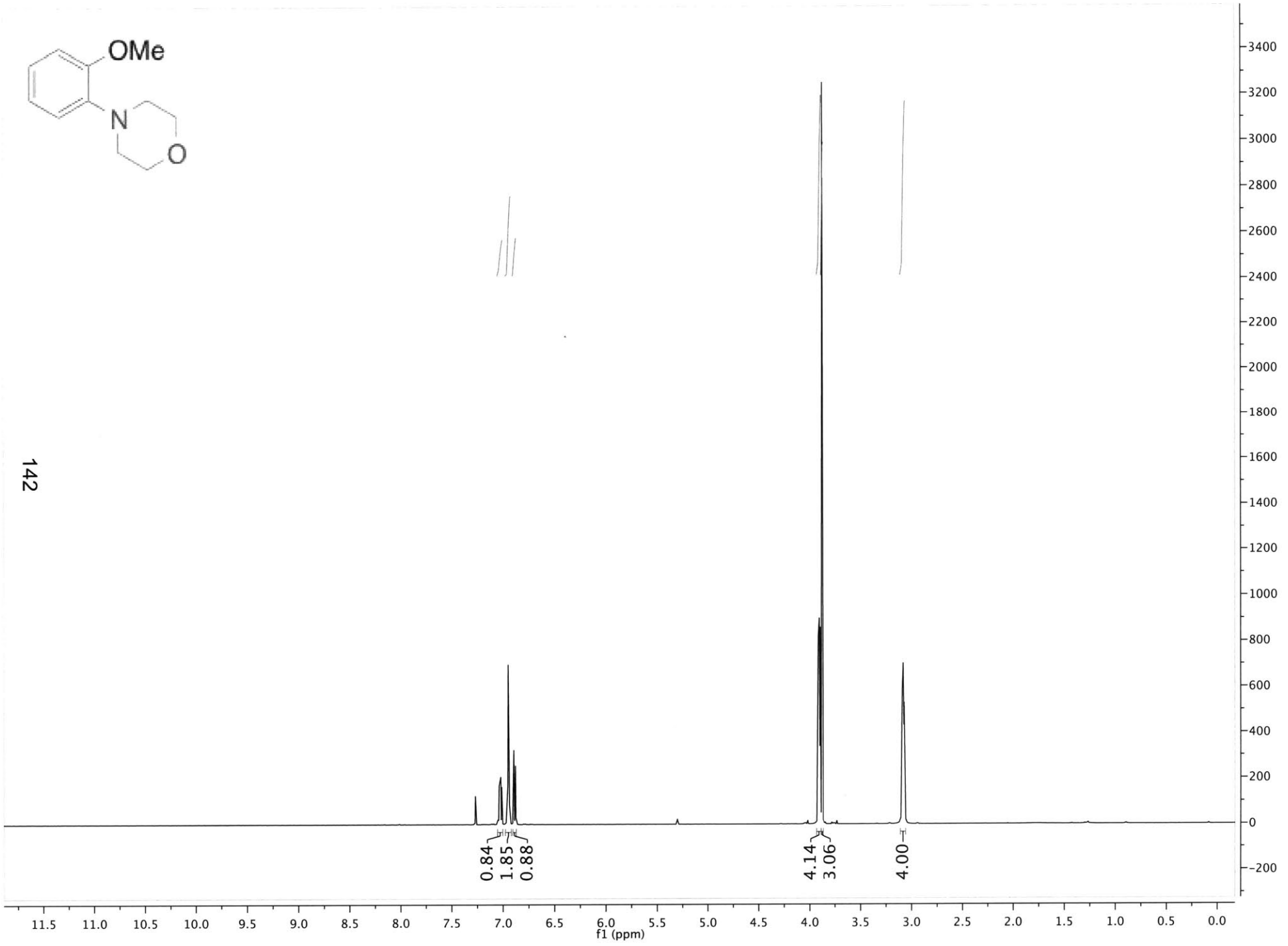

160.30
158.25
148.77
145.11
137.83
135.70
130.18
129.34
124.10
121.67
114.48
113.27
H
N
N
N
N
137
f1 (ppm)

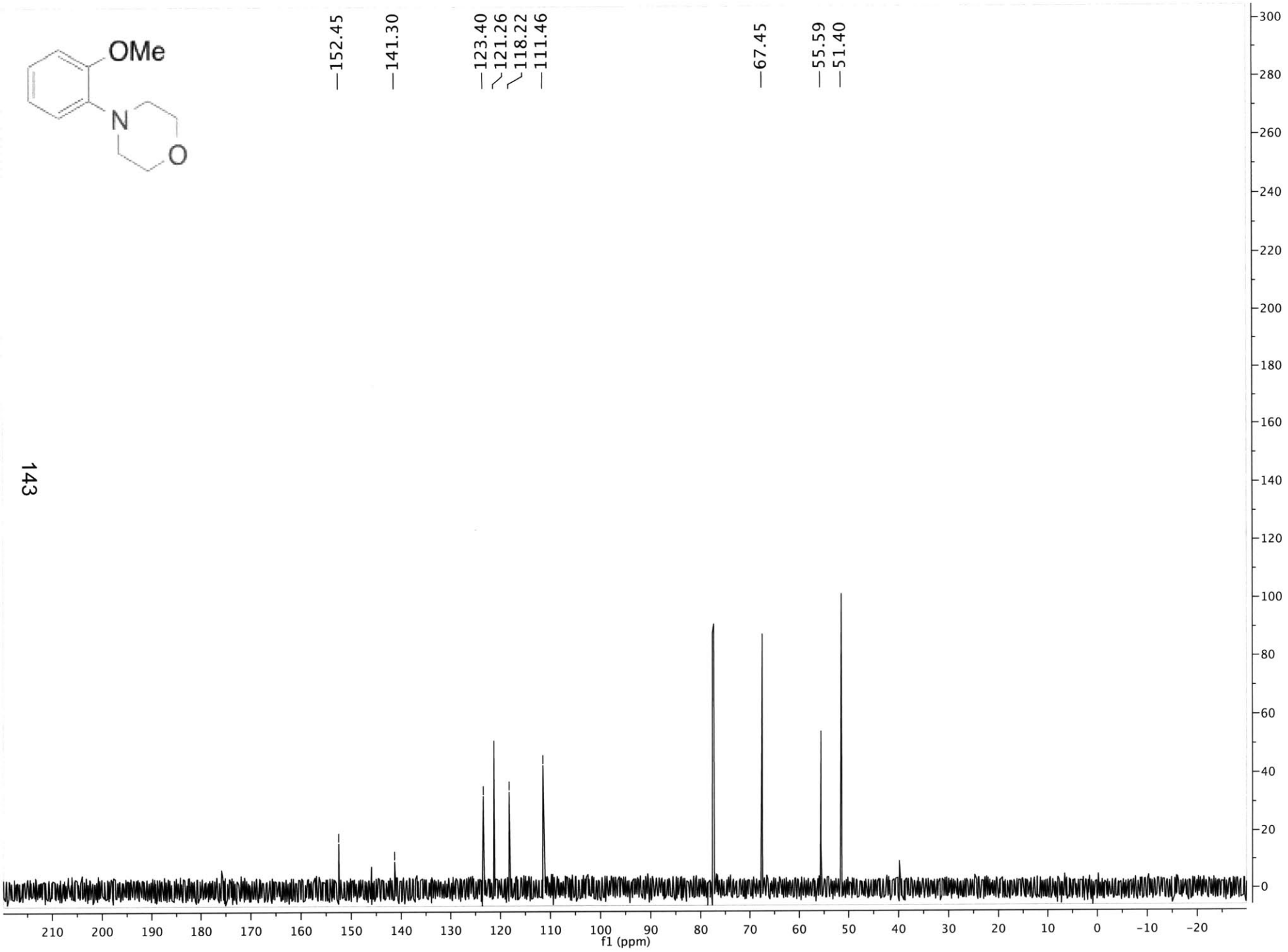

Me
N
N
Ph
138
1.00
0.93
1.94
2.85
1.01
1.02
2.29
3.19
2.27
f1 (ppm)

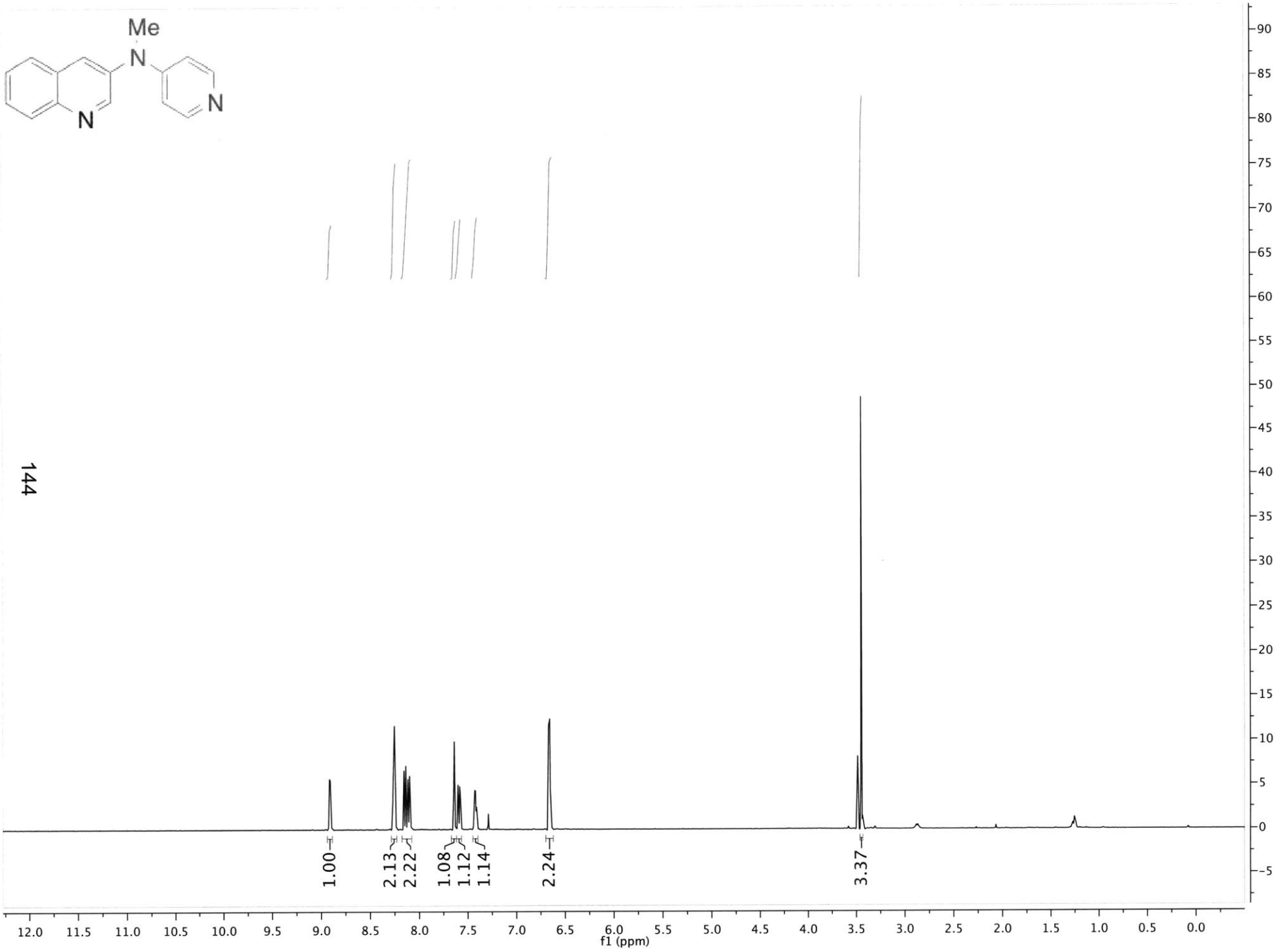

Me
N
N
Ph
144.77
139.43
137.56
134.80
129.03
128.86
126.64
123.84
118.50
54.50
38.43
33.08
f1 (ppm)

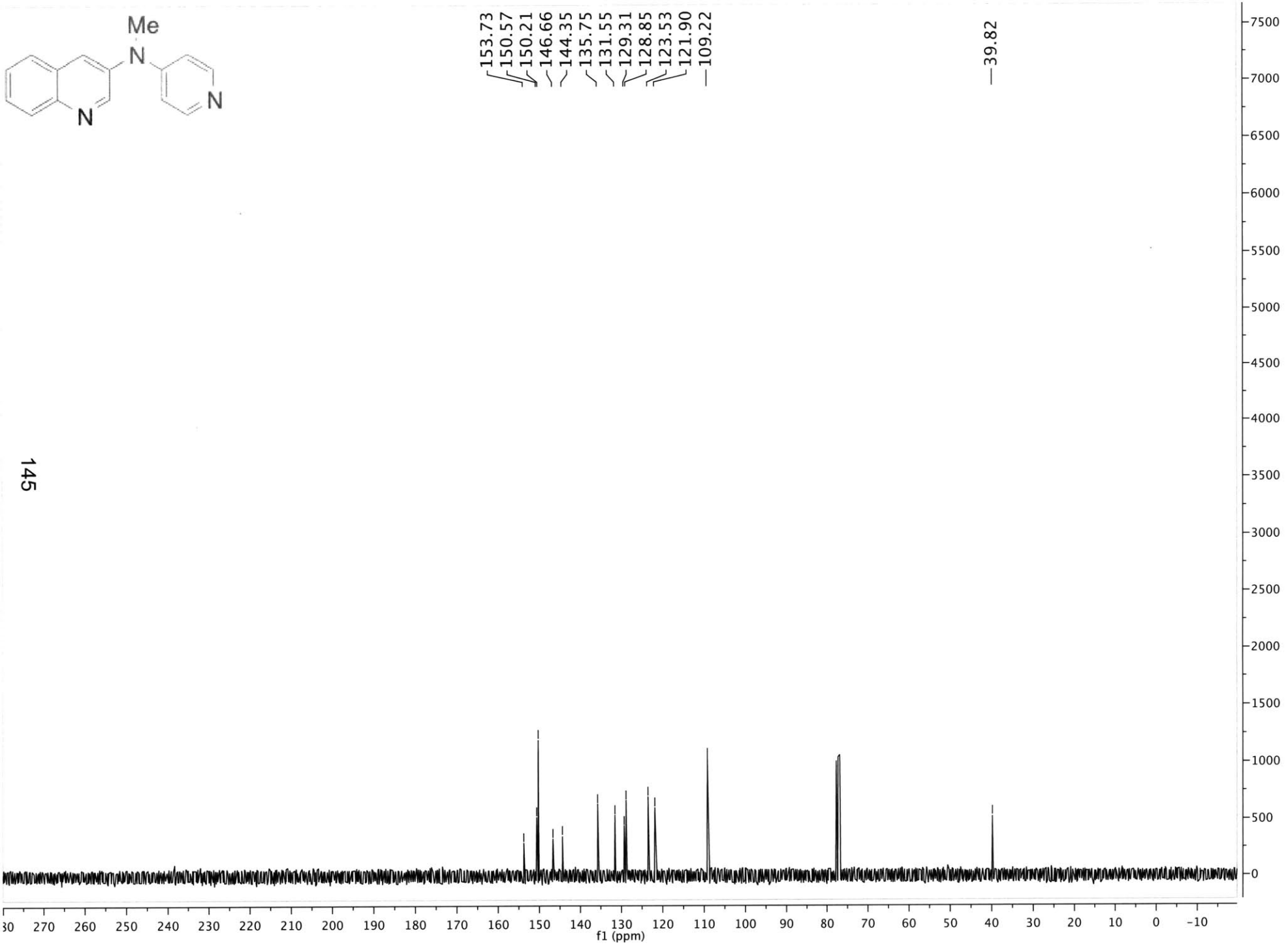

Me
N
NPh2
140
0.91
5.00
3.82
2.01
0.98
3.36
f1 (ppm)

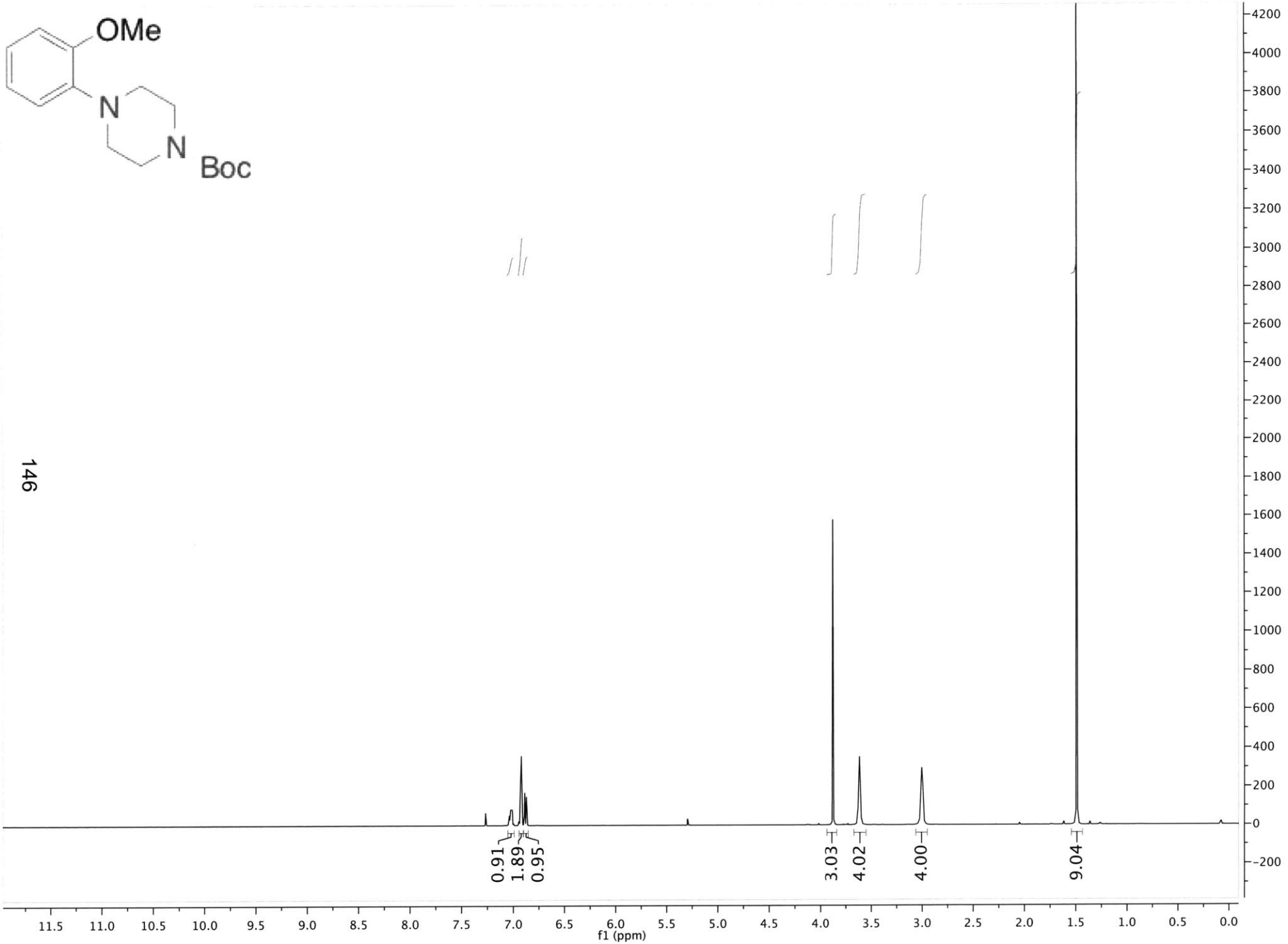

Me
N
NPh2
157.42
148.53
146.74
138.56
129.59
126.05
125.97
124.28
114.83
17.97
141
f1 (ppm)

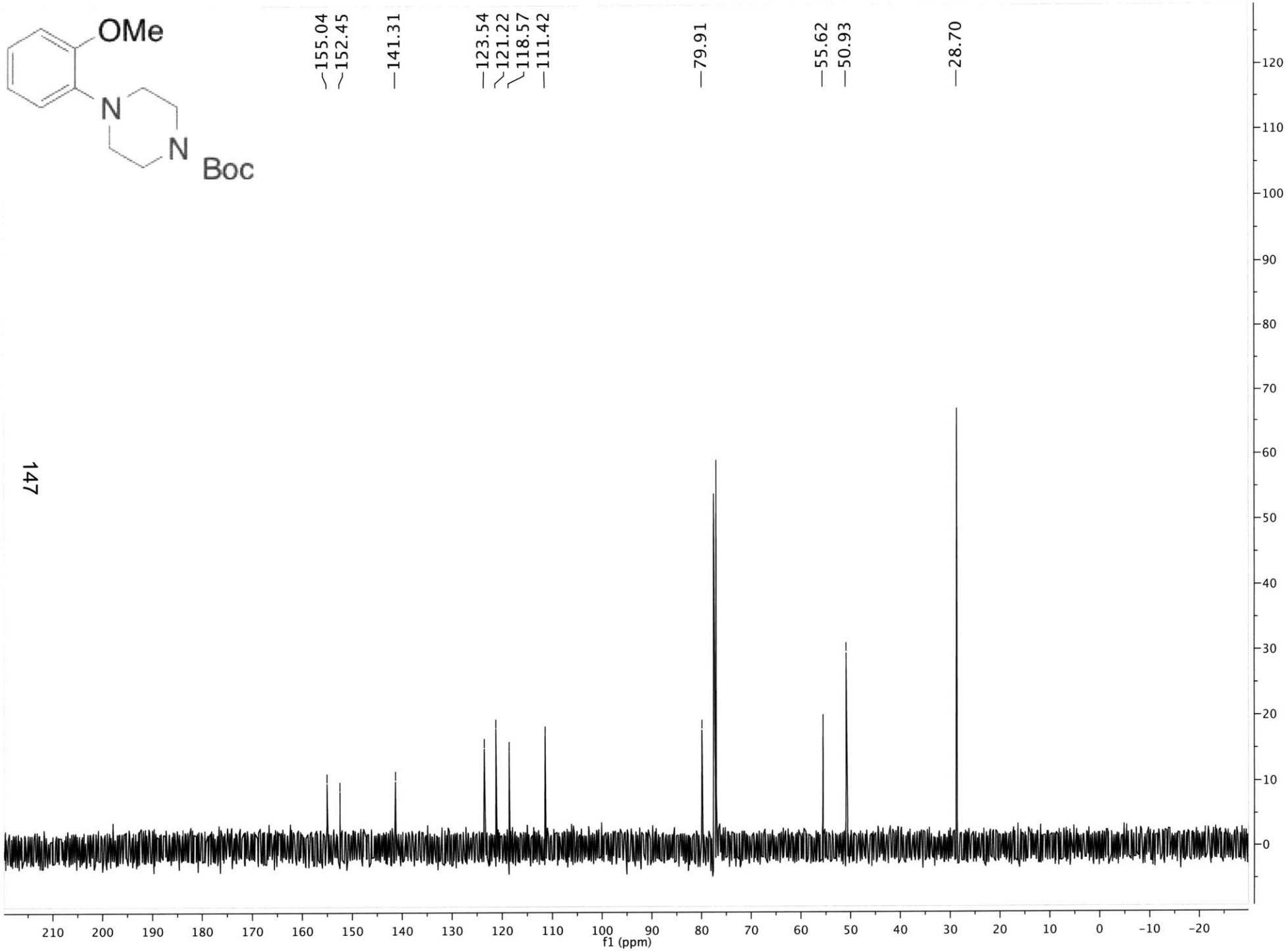

OMe
N
O
142
0.84
1.85
0.88
4.14
3.06
4.00
f1 (ppm)

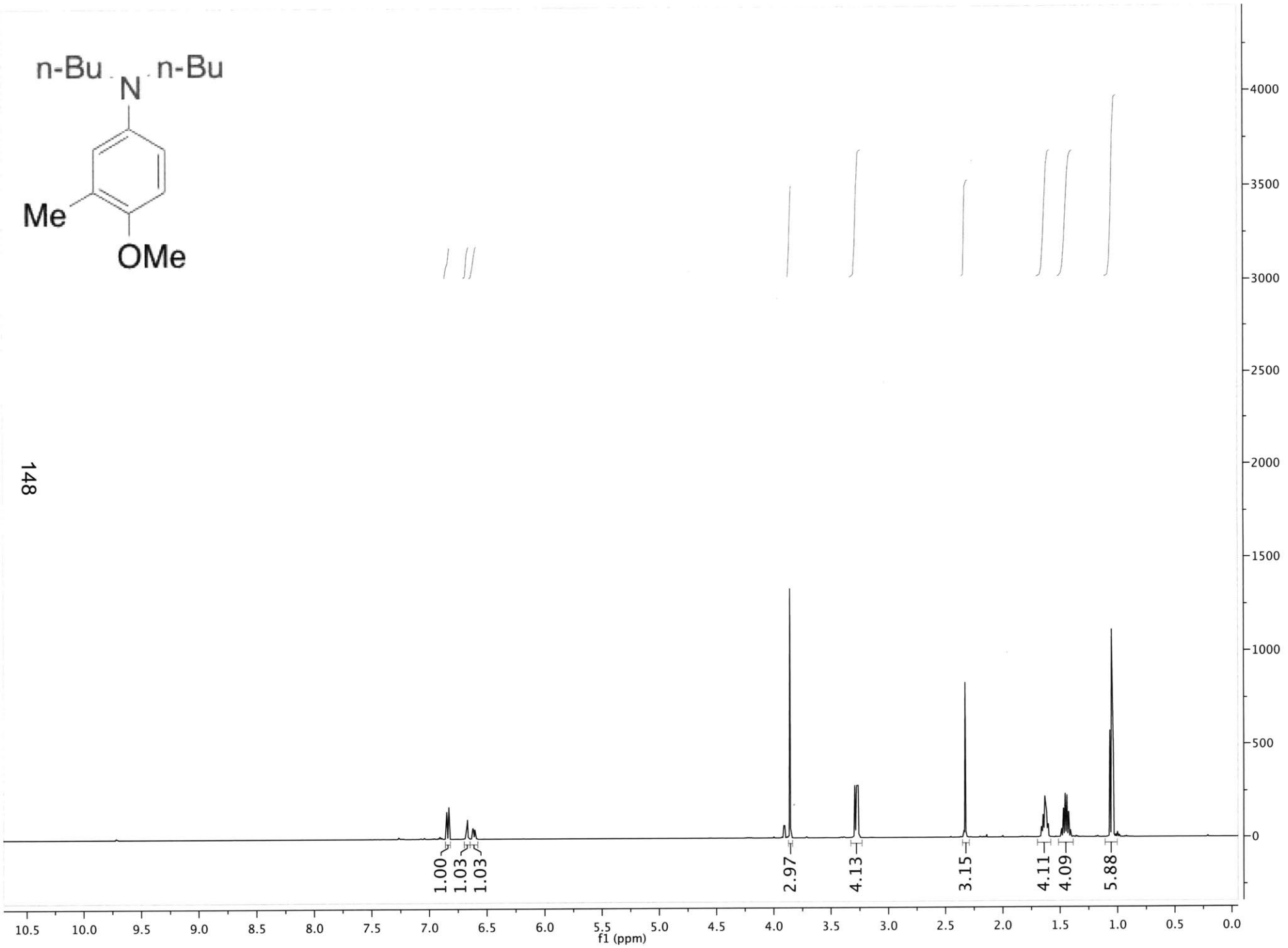

OMe
N
O
152.45
141.30
123.40
121.26
118.22
111.46
67.45
55.59
51.40
f1 (ppm)

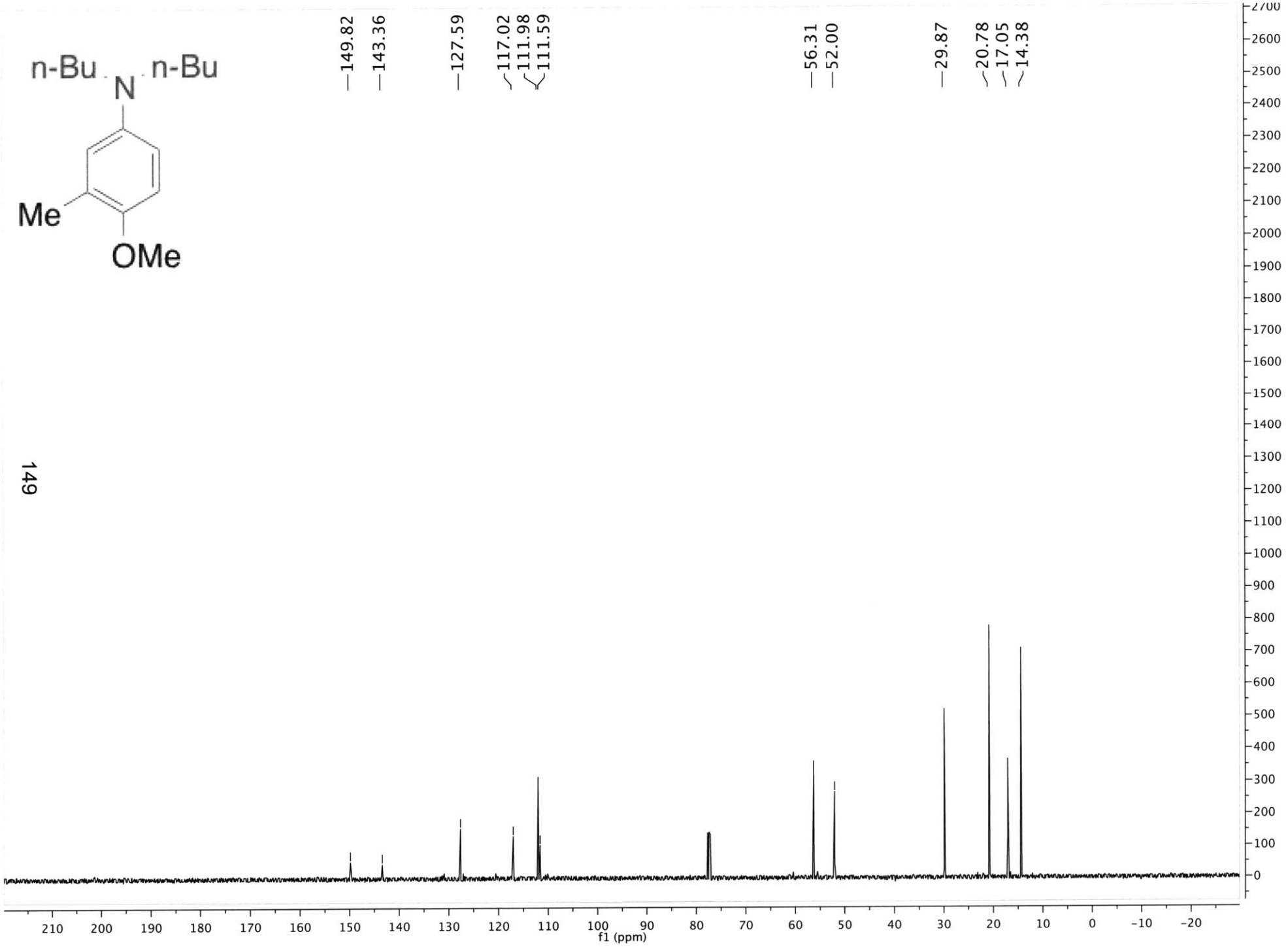

Me
N
N
N
144
1.00
2.13
2.22
1.08
1.12
1.14
2.24
3.37
f1 (ppm)

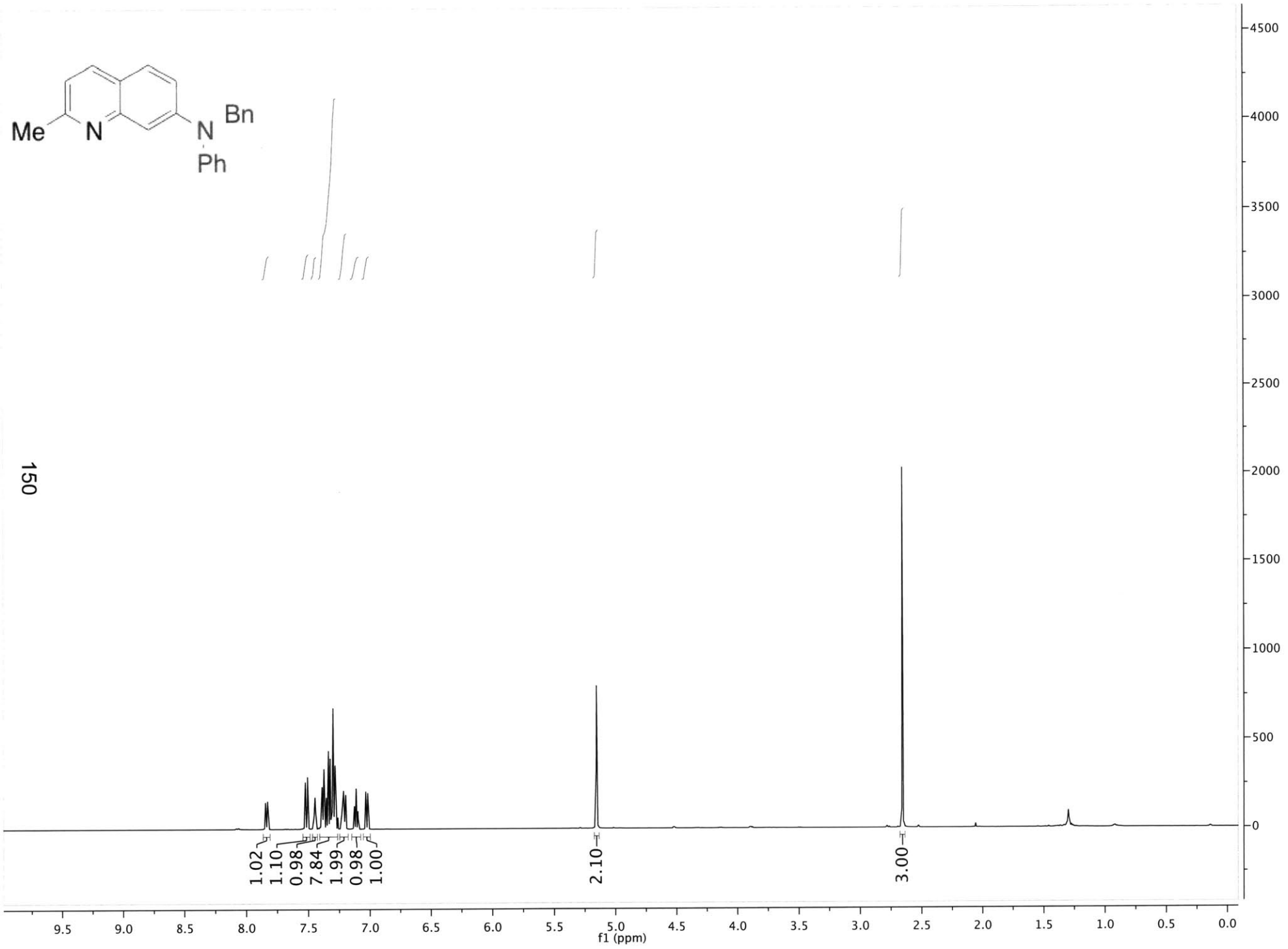

Me
N
N
N
153.73
150.57
150.21
146.66
144.35
135.75
131.55
129.31
128.85
123.53
121.90
109.22
39.82
145
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

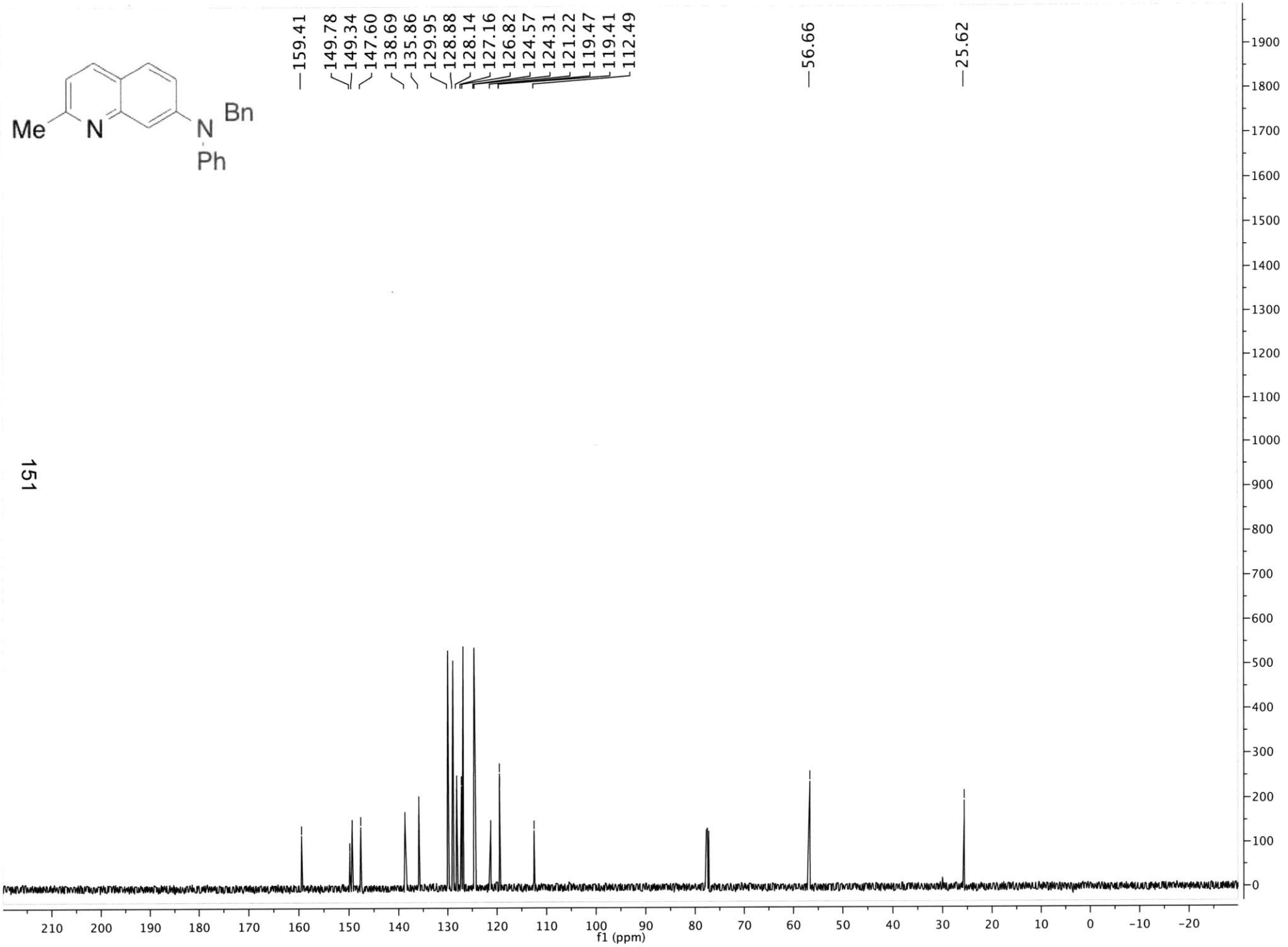

OMe
N
N
Boc
146
0.91
1.89
0.95
3.03
4.02
4.00
9.04
f1 (ppm)


OMe
N
N
Boc
155.04
152.45
141.31
123.54
121.22
118.57
111.42
79.91
55.62
50.93
28.70
147
f1 (ppm)


n-Bu
N
n-Bu
Me
OMe
148
1.00
1.03
1.03
2.97
4.13
3.15
4.11
4.09
5.88
f1 (ppm)


n-Bu
N
n-Bu
Me
OMe
149.82
143.36
127.59
117.02
111.98
111.59
56.31
52.00
29.87
20.78
17.05
14.38
f1 (ppm)


Me
N
N
Bn
Ph
150
1.02
1.10
0.98
7.84
1.99
0.98
1.00
2.10
3.00
f1 (ppm)


159.41
149.78
149.34
147.60
138.69
135.86
129.95
128.88
128.14
127.16
126.82
124.57
124.31
121.22
119.47
119.41
112.49
56.66
25.62
Me
N
N
Bn
Ph
f1 (ppm)

1.5: References

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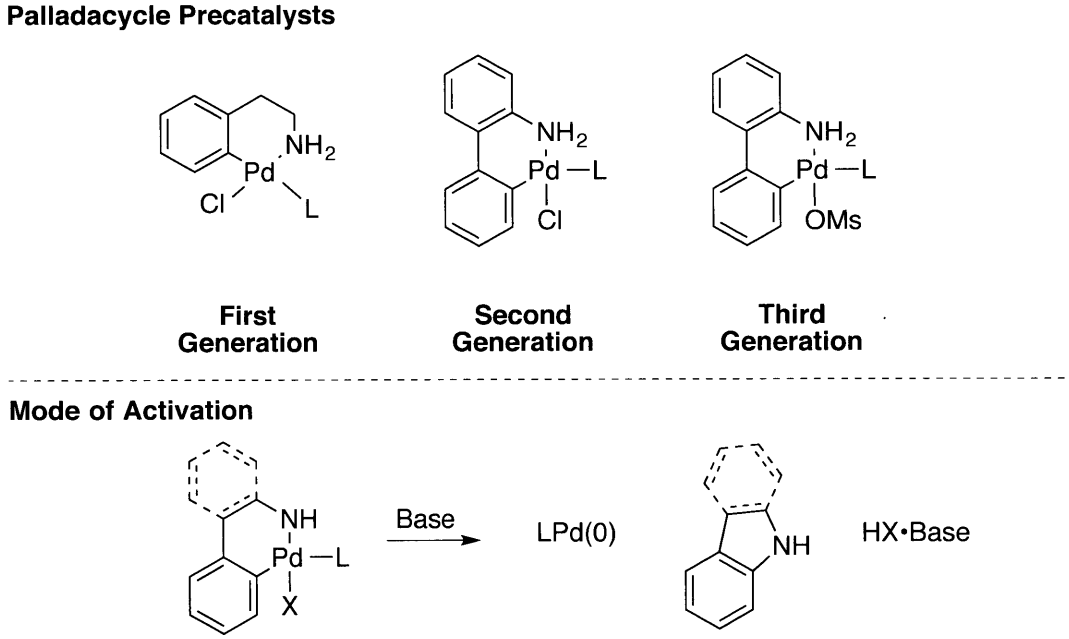
Chapter 2: Synthesis and Application of Palladium Precatalysts that Accommodate Extremely Bulky Di-*tert*-butylphosphino Biaryl Ligands

2.1: Introduction

Dialkylphosphino biaryl compounds have emerged as privileged ligands for a wide range of palladium-catalyzed cross-coupling processes. Di-*tert*-butylphosphino biaryls represent a subset of this ligand class with catalysts based upon them having demonstrated a unique ability to efficiently induce extremely challenging and important processes, including the construction of CC,[1] CN,[2-6] CO,[7-9] and CF bonds.[10] In general, structural features of these ligands facilitate difficult reductive eliminations, thus contributing to their overall effectiveness. The formation of the catalytically active LPd(0) species, however, is less efficient when using these ligands. Two common methods have been utilized to overcome this issue: (1) water-mediated reduction of Pd(II) precursors[11] and (2) ligand and $Pd_2(dba)_3$ premixing.[12] Neither approach is ideal, as they both require an extra equivalent of ligand, and more importantly, the catalyst activation step involves an additional operation conducted in a second reaction vessel. Thus, we sought a simple, general approach to generating active catalysts based on these ligands.

Addressing the difficulty of efficient formation of active catalytic species, in Chapter 1 we described the development of a family of air- and moisture-stable palladacycles, shown in Scheme 1, that allow for quantitative formation of the desired monoligated Pd(0) species.[13-15] These precatalysts are easily prepared using standard techniques and provide highly active catalysts for use in a broad array of synthetic applications. Under the basic conditions commonly employed in cross-coupling reactions, these

complexes undergo deprotonation and reductive elimination to generate LPd(0) along with relatively inert indoline (generation 1) or carbazole (generation 2 and 3). While precatalysts based on a number of important ligands (including R_3P, Ar_3P, BINAP, XantPhos, and dialkylphosphino biaryls) can be prepared, a means to access precatalysts based on di-*tert*-butylphosphino biaryl ligands has remained elusive. Herein, we report a general method for the synthesis of precatalysts based on these ligands and demonstrate the high catalytic efficiency of these complexes in several challenging cross-coupling reactions.



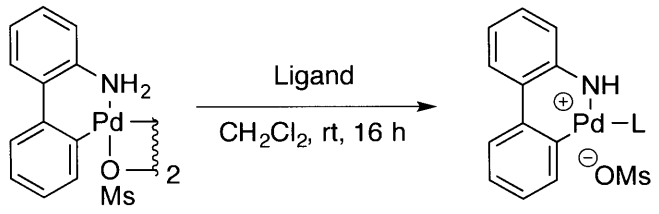
Scheme 1. Palladacyclic precatalysts previously developed in our laboratory and their general mode of activation

2.2: Results and Discussion

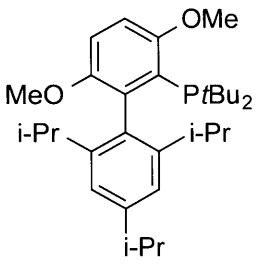
We recently reported the third-generation precatalysts wherein dimeric 2-aminobiphenylpalladium methanesulfonate complex **1** can be treated with a range of phosphine ligands to provide methanesulfonate precatalysts, **2**. These palladium sources are particularly useful; they allow for the direct incorporation of a range of ligands from a single intermediate and are efficiently converted to the active catalysts under very mild conditions.[15] Initially the re- ported conditions for 2 were not successful for the formation of precatalysts with ligands **L1** – **L5**. As a result, we investigated a series of palladacyclic triflate precatalysts for these ligands.[16]

However, after reexamining the reaction conditions for preparing **2** we found that the use of chlorinated solvents (CH_2Cl_2 or $CHCl_3$) could be used for the incorporation of **L1** – **L5**.[17] Thus, stirring μ-OMs dimer **1** with *t*-BuBrettPhos (**L1**) in CH_2Cl_2 for 12 h at room temperature, followed by trituration of the crude material with diethyl ether, cleanly afforded the desired precatalyst in 90% yield. Additionally, this protocol could be used to form precatalyst **2** bearing **L2** – **L5** in uniformly high yields (Table 1). The structure of **2a** was confirmed by X-ray crystallography and is shown in Figure 1. As previously described,[15] the palladium center is cationic with the fourth coordination site being occupied through coordinating to the *ipso* carbon of triisopropyl ring of the ligand.

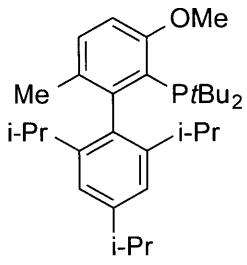
Table 1. Preparation of Methanesulfonate Precatalysts with **L1**–**L5**



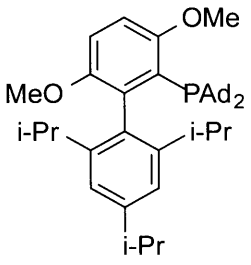
1 **2**



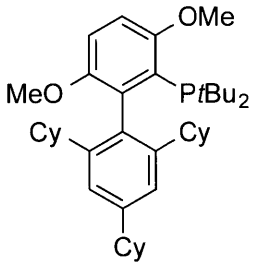
L1
tBuBrettPhos
2a: 90%



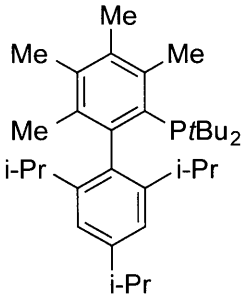
L2
RockPhos
2b: 91%



L3
AdBrettPhos
2c: 94%



L4
2d: 88%



L5
Me4tBuPhos
2e: 89%

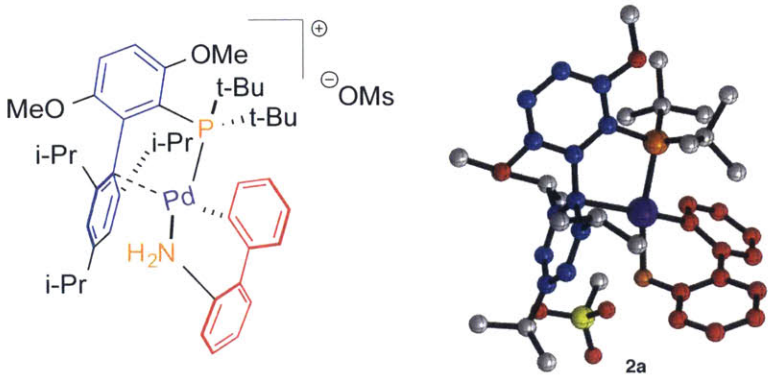
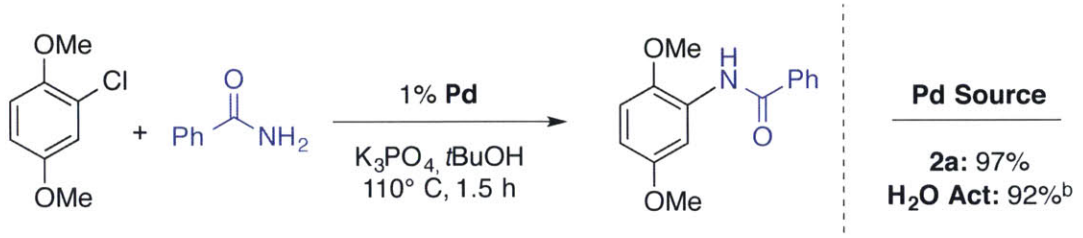


Figure 1. Crystallographically determined X-ray structure of 2a (thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted for clarity).

Our reported procedure for the palladium-catalyzed amidation reaction of aryl chlorides employed a catalyst based on **L1**.[5] The procedure was efficient, requiring only 1 mol% palladium and relatively short reaction times; however, use of the water-mediated preactivation method was necessary to generate the active catalyst. To evaluate the efficacy of **2a**, we utilized 1 mol% of **2a** in the reaction of benzamide with 2-chloro-1,4-dimethoxybenzene (Scheme 2). Under otherwise identical conditions, the secondary amide product was obtained in slightly higher yield than previously obtained when using **2a**.

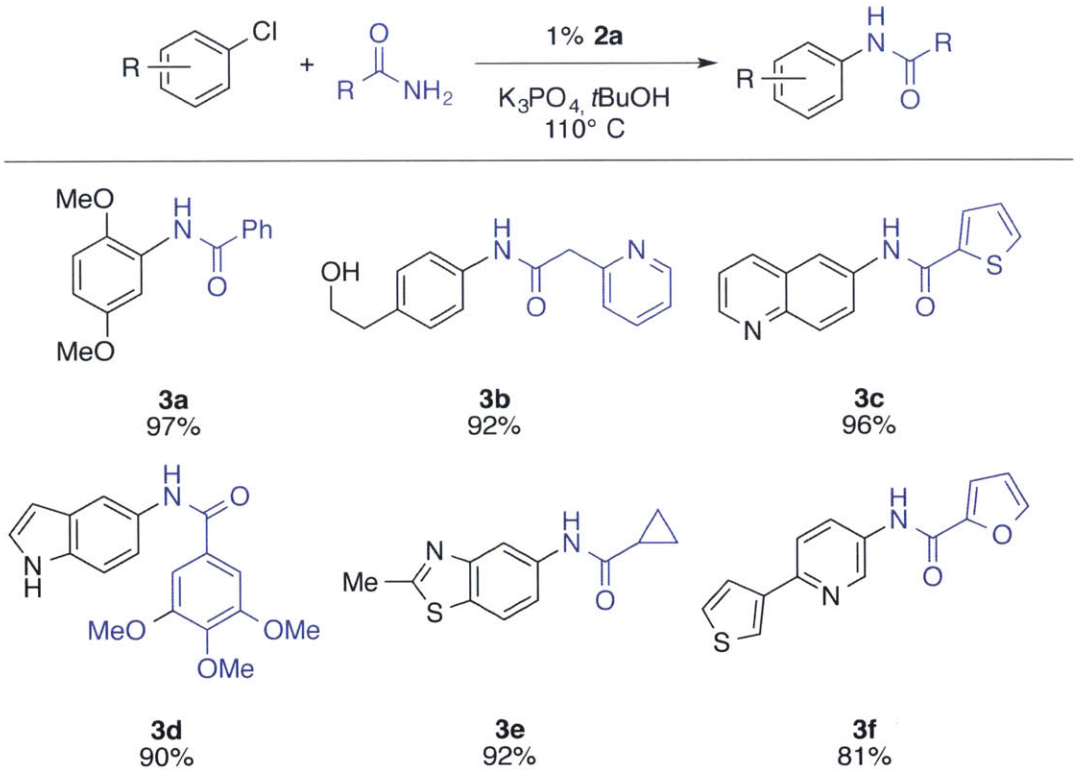
Scheme 2. Comparison of catalytic activities of **2a** and water activation in the arylation of a primary amide[a]



[a] General Conditions: ArCl (1 mmol), amide (1.05 – 1.2 mmol), K_3PO_4 (1.4 mmol), 2a (1 mol%), *t*BuOH (2 mL), 110 °C, 1.5 h, isolated yields. [b] Previously reported yield.[5]

As shown in Table 2, we further evaluated the efficiency of **2a** toward more functionalized aryl chlorides and primary amides. In general, the use of **2a** exhibited good functional group tolerance; we observed no competitive CO bond formation or N-arylation of indole in the cases of **3b** and **3d**, respectively.

Table 2. Arylation of primary amides with **2a**[a]

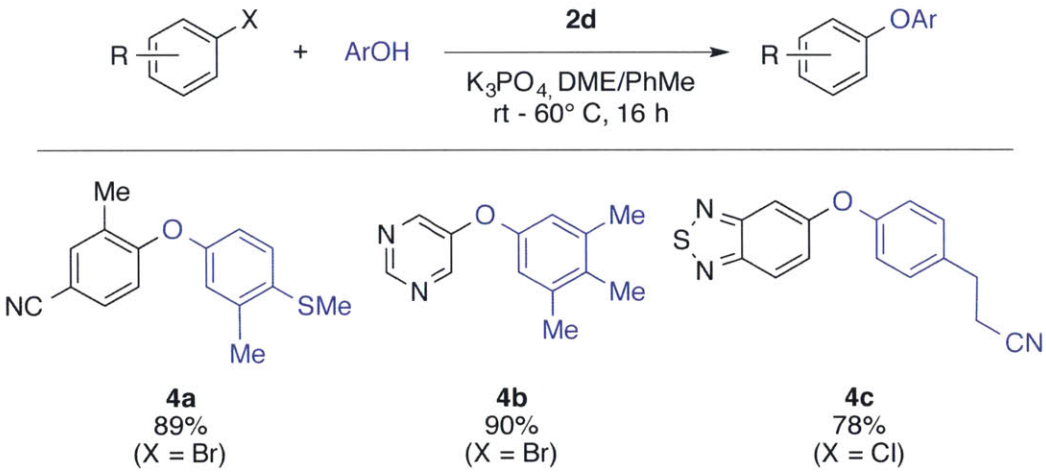


[a] Aryl chloride (1 mmol), amide (1.05 – 1.2 mmol), K_3PO_4 (1.4 mmol), **2a** (1 mol%), *t*BuOH (2 mL), 110 °C, 1.5 h; isolated yields, average of two runs.

We were also interested in assessing the performance of the new precatalysts in Pd-catalyzed CO bond-forming reactions. We previously demonstrated the coupling of aryl halides and phenols using a [(cinnamyl)PdCl]$_2$/**L4** catalyst system.[7] This original procedure involved the use of 0.25 – 3 mol% of Pd, excess **L4**, at between ambient

temperature and 100 °C. However, when **2d** was used in place of [(cinnamyl)PdCl]$_2$/L4 (Table 3), the diaryl ether products were formed in good yields, under mild reaction conditions (ambient to 60 °C, 1.5 – 2 mol% of Pd) and without the need to add excess ligand. Similarly, utilizing a precatalysts (**2b**) derived from RockPhos (**L2**), which was previously described to be an excellent supporting ligand for the Pd-catalyzed arylation of aliphatic alcohols,[8] we were able to couple a variety of primary alcohols with aryl halides (Table 4). Aryl alkyl ethers were obtained in good to excellent yields, comparable to our previously described results.[18]

Table 3. Arylation of phenols with **2d**[a]



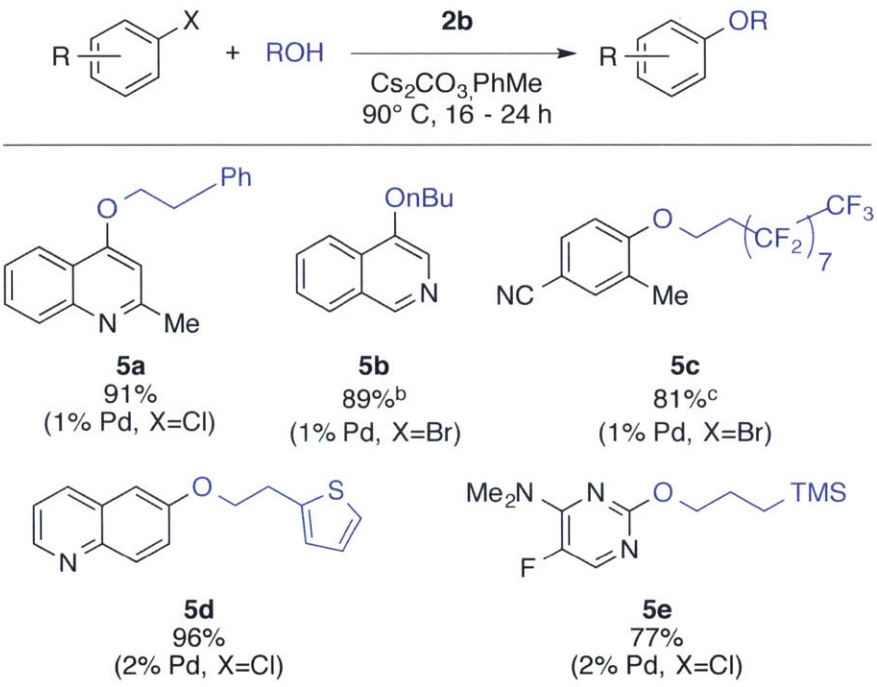
4a
89%
(X = Br)

4b
90%
(X = Br)

4c
78%
(X = Cl)

[a] Aryl halide (1 mmol), phenol (1.5 mmol), K_3PO_4 (1.5 mmol), **3d** (1.5 – 2 mol %) 3:2 PhMe/DME (1 mL), rt – 60 °C, 16 h; isolated yields, average of two runs.

Table 4. Arylation of aliphatic alcohols with **2b**[a]



[a] Aryl halide (1 mmol), alcohol (1.5 mmol), Cs_2CO_3 (2 mmol), **2b** (1 – 2 mol %) PhMe (1 mL), 90 °C, 24 h; isolated yields, average of two runs. [b] 3 equiv of alcohol. [c] 1.05 equiv of alcohol.

2.3: Conclusions

In summary, we have developed a series of ligated palladium precatalysts that incorporate extremely bulky ligands (**L1** – **L5**). The use of these precatalysts address a number of issues in catalyst activation. They are significantly more convenient to use and obviate the need to use excess ligand to generate active LPd(0) species. These precatalysts are bench stable and easily synthesized on a large scale (10 g for **2a**). We expect that their use will expand the scope of known transformations and facilitate the discovery of new Pd-catalyzed processes.

2.4: Experimental

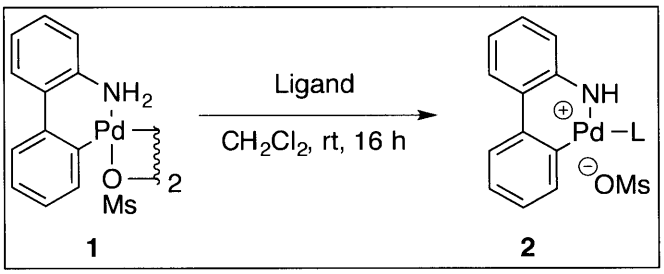
General: Reagent Information. THF and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing it under argon pressure through two packed columns of neutral alumina (for THF) or through neutral alumina and copper (II) oxide (for toluene). Anhydrous tribasic potassium phosphate was purchased from Acros Organics, stored in a nitrogen-filled glovebox and removed in small quantities. It was stored on the bench in a desiccator for up to two weeks. Cesium carbonate was purchased from Aldrich Chemical Co., stored in a nitrogen-filled glovebox and ground in a coffee grinder before use. Small quantities were stored on the bench in a desiccator for up to two weeks. Anhydrous *t*BuOH was purchased from Aldrich Chemical Co. in Sure-Seal™ bottles and used as received. $Pd(OAc)_2$ was purchased from Strem Chemicals Inc. or Johnson Matthey. The ligands tBuBrettPhos (**L1**)[19], RockPhos (**L2**)[19], AdBrettPhos (**L3**)[3], DinoPhos (**L4**)[7] and Me_4tBuXPhos (**L5**)[20] were prepared according to literature procedures. Palladium complexes **1** and **6** were synthesized according to a literature procedure.[15] All other reagents were purchased from Aldrich Chemical Co., Strem Chemicals, Acros Organics, Alfa Aesar, or TCI America and used as received. Flash chromatography was performed with SiliCycle SiliaFlash® F60 silica gel.

General Analytical Information: Compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F and ^{31}P NMR (where applicable). Copies of the ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra can be found at the end of the Supporting Information. ^{1}H and ^{13}C Nuclear Magnetic Resonance spectra were recorded on a Varian 500 MHz instrument. Fluorine and phosphorus Nuclear Magnetic Resonance spectra were recorded on a Varian 300 MHz instrument. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual deuterochloroform (7.26 ppm), CD_2Cl_2 (5.32 ppm), or DMSO-d^6 (2.50 ppm) in the deuterated solvent. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), CD_2Cl_2 (53.84 ppm) or DMSO-d^6 (39.52 ppm) and all were obtained with ^{1}H decoupling. All ^{19}F NMR spectra are reported in ppm relative to $CFCl_3$ (0.00 ppm). All ^{31}P NMR spectra

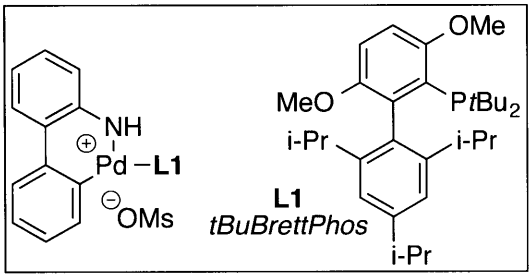
are reported in ppm relative to 85% aq. phosphoric acid (0.00 ppm). All GC analyses were performed on an Agilent 7850A gas chromatograph with an FID detector using a J & W DB-1 column.

General: Procedural Information

General Procedure A: Precatalyst Synthesis

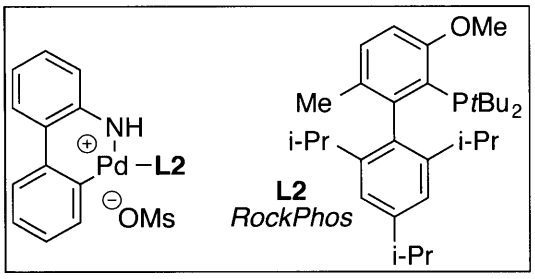


A 24 mL test tube equipped with a magnetic stir bar was charged with 2-aminobiphenylpalladium methanesulfonate dimer **1** (370 mg, 0.50 mmol, 0.50 equiv) and ligand (1.00 mmol, 1.00 equiv). Dichloromethane (5 mL) was added from a squirt bottle and the tube was capped. The mixture was stirred overnight at ambient temperature, at which time it became dark red in appearance. The reaction progress was monitored by observing the disappearance of free-ligand and appearance of a new signal at ~45 ppm in the 31P NMR spectrum. After the reaction was complete, the solvent was removed with the aid of a rotary evaporator until a red solid remained and diethyl ether (25 mL) was added. The mixture was triturated with the aid of sonication until a dark powder resulted. The solid was isolated by filtration and dried under vacuum.

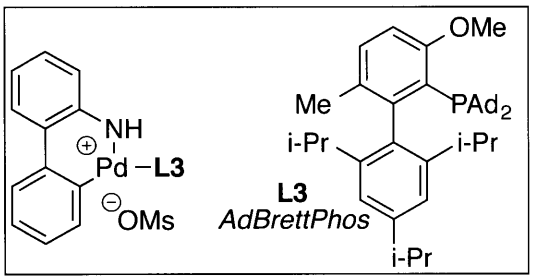


OMs tBuBrettPhos Precatalyst 2a – Large Scale: A 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with 1 (4.07 g, 5.5 mmol, 0.50 equiv) and L1 (5.33 g, 11.0 mmol, 1.00 equiv). Dichloromethane (55 mL) was added by syringe and the flask was sealed with a rubber septum. The mixture was stirred at room temperature overnight at which time it became

dark red in appearance. The solvent was removed with the aid of a rotary evaporator and diethyl ether (150 mL) was added. The resulting slurry was triturated with the aid of sonication until a dark orange powder resulted. The solid was isolated by filtration and dried under vacuum to afford the title compound. **Yield**: 7.87 g, 90%. **^{1}H NMR** (500 MHz, CD_2Cl_2) Complex Spectrum – See Attached. **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 157.74, 147.97, 142.08, 140.84, 138.01, 128.72, 127.38, 126.84, 126.07, 124.37, 122.34, 120.45, 119.18, 111.99, 66.35, 57.13, 55.92, 55.27, 54.78, 35.18, 32.92, 32.87, 32.38, 32.34, 32.01, 31.04, 29.88, 29.86, 28.70, 26.93, 26.26, 25.12, 25.09, 24.89, 24.65, 24.32, 23.97, 23.52 ppm (Observed complexity due to C-P splitting). **^{31}P NMR** (121 MHz, CD_2Cl_2) δ 77.22, 42.72 ppm. **IR** (neat, cm^{-1}): 1456, 1423, 1223, 1173, 1037, 761.

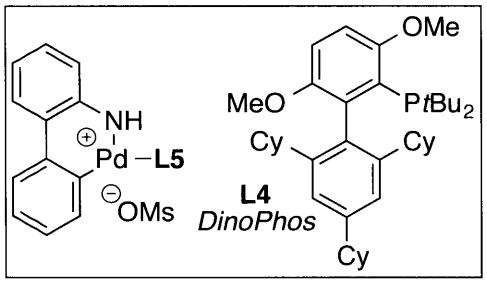


OMs RockPhos Precatalyst 2a: General procedure A was followed using RockPhos. (468 mg, 1.00 mmol, 1.00 equiv). Brown powder. **Yield**: 762 mg, 91%. **^{1}H NMR** (500 MHz, CD_2Cl_2) Complex Spectrum – See Attached. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 160.4, 151.3, 146.7, 146.1, 139.8, 134.3, 134.3, 130.4, 122.6, 122.6, 122.2, 119.7, 111.4, 105.3, 104.7, 56.7, 37.6 37.3, 34.3, 32.6, 32.5, 31.2, 30.9, 29.7, 26.0, 25.8, 25.3, 24.5, 24.2, 22.6, 22.4, 14.3 ppm (observed complexity is due to C-P splitting). **^{31}P NMR** (121 MHz, CD_2Cl_2) δ 79.06, 75.86, 44.44 ppm. **IR** (neat, cm-1): 2959, 1569, 1455, 1262, 1147, 1030, 755, 637.

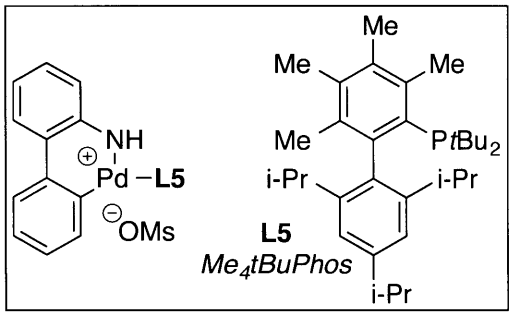


OMs AdBrettPhos Precatalyst: General procedure A was followed using, AdBrettPhos (641 mg, 1.00 mmol, 1.00 equiv) Dark red to brown powder. **Yield**: 950 mg, 94%. **^{1}H NMR** (500 MHz, CD_2Cl_2) Complex Spectrum – See Attached. **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 155.86, 151.32, 148.10, 140.90, 126.03, 122.21, 120.42, 119.46, 119.12, 112.19, 112.05, 57.17, 55.83, 43.00, 42.75, 40.63, 40.61, 40.15, 38.22, 37.48, 36.08, 36.07, 34.82, 32.00, 31.79, 29.44, 29.36, 29.07, 28.99,

26.30, 25.82, 24.34, 23.83, 14.54 ppm (observed complexity is due to C- P). **^{31}P NMR** (121 MHz, CD_2Cl_2) δ 83.25, 79.70, 41.11 ppm. **IR** (neat, cm^{-1}): 2907, 1456, 1283, 1149, 1030, 738, 636.

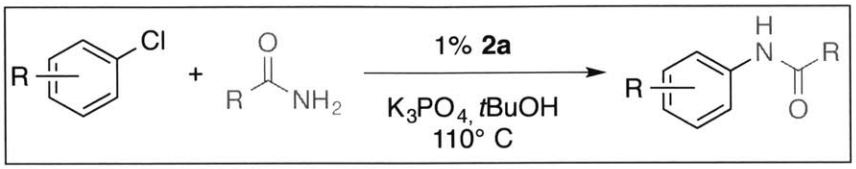


OMs DinoPhos Precatalyst 2d: General procedure A was followed using DinoPhos **(L4)** (628 mg, 1.00 mmol, 1.00 equiv). Reddish-brown powder. **Yield**: 860 mg, 88%. **^{1}H NMR** (500 MHz, CD_2Cl_2) Complex Spectrum – See Attached. **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 159.34, 159.19, 156.43, 154.78, 142.65, 141.40, 140.12, 137.85, 135.88, 128.60, 128.17, 127.61, 127.46, 127.35, 126.89, 126.02, 125.77, 125.74, 123.40, 120.82, 120.40, 119.10, 115.59, 112.62, 112.03, 100.50, 45.42, 43.45, 43.37, 41.41, 40.00, 39.91, 39.80, 39.67, 37.46, 36.53, 36.15, 35.84, 35.68, 35.43, 35.14, 35.05, 32.97, 32.92, 32.40, 32.36, 29.94, 29.92, 28.78, 27.81, 27.59, 27.44, 27.37, 27.34, 27.27, 27.06, 26.71, 26.58, 26.51, 26.28, 26.23, 26.02 ppm (Observed complexity due to C-P coupling). **^{31}P NMR** (121 MHz, CD_2Cl_2) δ 76.89, 43.29 ppm. **IR** (neat, cm^{-1}): 2923, 1451, 1253, 1222, 1148, 1030, 738, 636.

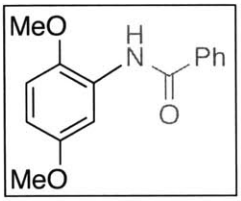


OMs Me_4tBuXPhos Precatalyst 2e: General procedure A was followed using Me_4tBuXPhos (481 mg, 1.00 mmol, 1.00 equiv). Brown powder. **Yield**: 755 mg, 86%. **^{1}H NMR** (500 MHz, CD_2Cl_2) Complex Spectrum – See Attached. **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 151.94, 147.64, 146.20, 145.31, 140.87, 137.94, 126.06, 123.22, 120.85, 120.44, 119.17, 112.03, 40.18, 39.07, 38.84, 34.94, 34.58, 31.57, 30.73, 30.72, 29.89, 28.19, 28.14, 26.09, 25.55, 25.25, 24.88, 24.59, 24.41, 22.88, 22.87, 21.28, 18.22, 17.13, 17.12 ppm (observed complexity is due to C-P coupling). **^{31}P NMR** (121 MHz, CD_2Cl_2) δ 62.32, 47.37 ppm. **IR** (neat, cm-1): 2962, 1456, 1262, 1151, 1029, 738, 639.

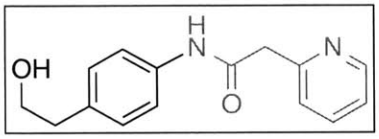
General Procedure B: Arylation of Primary Amides



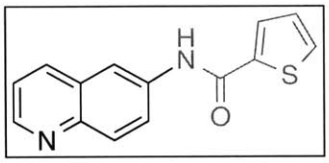
A 24 mL screw-top test tube equipped with a stir bar and Teflon septum was charged with aryl chloride, if solid (1.00 mmol, 1.00 equiv), amide (1.05 – 1.20 mmol, 1.05 – 1.20 equiv), **2a** (8.5 mg, 0.01 mmol, 1 mol%), and tribasic potassium phosphate (297 mg, 1.40 mmol, 1.40 equiv). The tube was evacuated and backfilled with argon (this sequence was repeated a total of three times.) Then the aryl halide was added by syringe if a liquid, followed by tBuOH (2 mL). Under positive pressure of argon, the Teflon septum was replaced with an unpunctured one and the reaction was placed in a preheated oil bath at 110 °C and stirred for 1.5 h. The reaction was monitored by thin layer chromatography. After completion the reaction was cooled to room temperature and diluted with ethyl acetate (5 mL) and water (5 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3x5 mL). The combined organic phases were dried over magnesium sulfate, concentrated with the aid of a rotary evaporator and purified by flash chromatography.



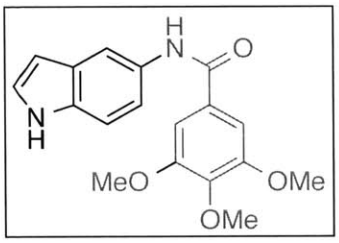
***N*-(2,5-dimethoxyphenyl)benzamide 3a:**[5] Following general procedure B, a mixture of 2-chloro-1, 4-dimethoxybenzene (143 µL, 1.00 mmol, 1.00 equiv), benzamide (145 mg, 1.20 mmol, 1.20 equiv) K_3PO_4 (297 mg, 1.40 mmol, 1.40 equiv) **2a** (8.5 mg, 1 mol%), and *t*BuOH (2 mL) was stirred at 110 °C for 1.5 h. The crude product was purified via flash chromatography eluting with 20% EtOAc in hexanes to provide the title compound as a light-yellow solid. **Yield**: 249 mg, 97%. **mp** = 83 – 84 °C. **^{1}H NMR** (500 MHz, DMSO-d^6) δ 9.37 (s, 1H), 8.01 - 7.92 (m, 2H), 7.62 - 7.55 (m, 2H), 7.52 (tt, J = 6.5, 1.4 Hz, 2H), 7.00 (d, J = 9.0 Hz, 1H), 6.73 (dd, J = 8.9, 3.1 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H) ppm. **^{13}C NMR** (126 MHz, DMSO-d^6) δ 166.05, 154.01, 146.29, 135.58, 132.87, 129.70, 128.79, 128.58, 113.16, 111.14, 110.60, 57.39, 56.56 ppm. **IR** (neat, cm^{-1}): 3325, 1652, 1535, 1485, 1445, 1420, 1224, 1046, 860, 810, 694, 674.



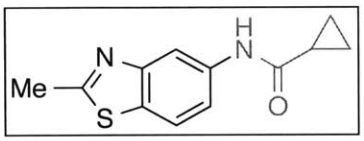
***N*-(4-(2-hydroxyethyl)phenyl)-2-(pyridin-2-yl)acetamide 3b:** Following general procedure B, a mixture of 4-chlorophenethyl alcohol (157 mg, 1.00 mmol, 1.00 equiv), 2-(pyridin-2-yl)acetamide (143 mg, 1.05 mmol, 1.05 equiv), K_3PO_4 (297 mg, 1.40 mmol, 1.40 equiv) **2a** (8.5 mg, 1 mol%), and tBuOH (2 mL) was stirred at 110 °C for 1.5 h. The crude product was purified via flash chromatography eluting with a gradient of 0 – 5 % methanol in dichloromethane to provide the title compound as an off-white solid. **Yield**: 228 mg, 92 %. **mp** = 96 – 97 °C. **^{1}H NMR** (500 MHz, DMSO-d^6) δ 10.15 (s, 1H), 8.53 - 8.44 (m, 1H), 7.74 (td, J = 7.7, 1.9 Hz, 1H), 7.53 - 7.45 (m, 2H), 7.37 (dd, J = 7.8, 1.2 Hz, 1H), 3.86 - 3.76 (m, 2H), 7.30 - 7.20 (m, 1H), 7.17 - 7.06 (m, 2H), 4.60 (t, J = 5.2 Hz, 1H), 3.54 (td, J = 7.1, 5.2 Hz, 2H), 2.64 (t, J = 7.1 Hz, 2H) ppm. **^{13}C NMR** (126 MHz, DMSO-d^6) δ 169.08, 157.28, 150.12, 138.27, 137.70, 135.49, 130.21, 125.11, 123.05, 120.17, 46.99, 39.65 ppm. **IR** (neat, cm^{-1}): 3258, 2924, 1695, 1606, 1538, 1439, 1171, 1064, 1003, 811, 755, 700. Anal. Calcd. for $C_{15}H_{15}N_2O_2$: C, 70.29; H, 6.29. Found: C, 69.89; H, 6.18.



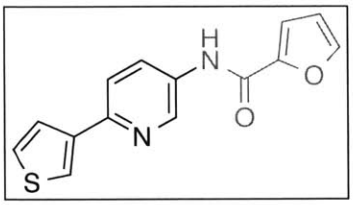
N-(quinolin-6-yl)thiophene-2-carboxamide 3c: Following general procedure B, a mixture of 6-chloroquinoline (163 mg, 1.00 mmol, 1.00 equiv), thiophene-2-carboxamide (134 mg, 1.05 mmol, 1.05 equiv), K_3PO_4 (297 mg, 1.40 mmol, 1.40 equiv) **2a** (8.5 mg, 1 mol%), and tBuOH (2 mL) was stirred at 110 °C for 2 h. The crude product was purified via flash chromatography eluting with 70% ethyl acetate in hexanes to provide the title compound as a yellow solid. **Yield**: 244 mg, 96%. **mp** = 185 °C. **^{1}H NMR** (500 MHz, DMSO-d^6) δ 10.55 (s, 1H), 8.80 (dd, J = 4.2, 1.7 Hz, 1H), 8.50 - 8.42 (m, 1H), 8.31 (dd, J = 8.3, 1.7 Hz, 1H), 8.10 (dd, J = 3.8, 1.2 Hz, 1H), 8.06 - 7.99 (m, 2H), 7.89 (dd, J = 5.0, 1.1 Hz, 1H), 7.48 (dd, J = 8.3, 4.2 Hz, 1H), 7.25 (dd, J = 5.0, 3.7 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, DMSO-d^6) δ 161.37, 150.43, 146.04, 140.93, 137.86, 136.74, 133.39, 130.61, 130.56, 129.36, 129.33, 125.33, 122.95, 117.52 ppm. **IR** (neat, cm^{-1}): 3272, 1657, 1549, 1419, 1367, 1277, 1221, 887, 826, 793, 721, 615. Anal. Calcd. for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96. Found: C, 65.83; H, 4.12.



***N*-(1*H*-indol-5-yl)-3,4,5-trimethoxybenzamide 3d:** Following general procedure B, a mixture of 5-chloroindole (152 mg, 1.00 mmol, 1.00 equiv), 3,4,5-trimethoxybenzamide (254 mg, 1.20 mmol, 1.20 equiv), K_3PO_4 (297 mg, 1.40 mmol, 1.40 equiv) **2a** (8.5 mg, 1 mol%), and *t*BuOH (2 mL) was stirred at 110 °C for 1.5 h. The crude product was purified via flash chromatography eluting with 80% ethyl acetate in hexanes to provide the title compound as a beige solid. **Yield**: 295 mg, 90%. **mp** = 190 – 191 °C. **^{1}H NMR** (500 MHz, DMSO-d^6) δ 11.07 (s, 1H), 10.01 (s, 1H), 7.95 - 7.92 (s, 1H), 7.37 (m, 2H), 7.36 - 7.31 (m, 3H), 6.44 - 6.40 (m, 1H), 3.88 (s, 6H), 3.73 (s, 3H) ppm. **^{13}C NMR** (126 MHz, DMSO-d^6) δ 165.17, 153.27, 140.60, 133.76, 131.40, 131.23, 128.11, 126.62, 117.16, 113.36, 111.72, 105.75, 101.83, 60.79, 56.72 ppm. **IR** (neat, cm^{-1}): 3281, 1623, 1583, 1505, 1414, 1330, 1231, 1123, 1003, 763, 726. Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56. Found: C, 65.99; H, 5.74.

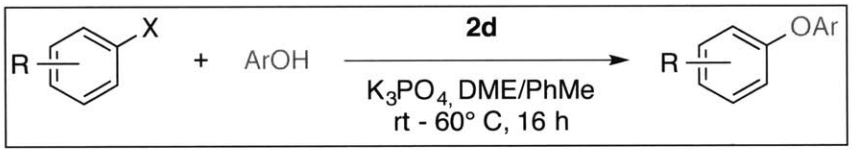


***N*-(2-methylbenzo[*d*]thiazol-5-yl)cyclopropanecarboxamide 3e:** Following general procedure B, a mixture of 5-chloro-2-methylbenzothiazole (183 mg, 1.00 mmol, 1.00 equiv), cyclopropylamide (90 mg, 1.05 mmol, 1.05 equiv), K_3PO_4 (297 mg, 1.40 mmol, 1.40 equiv) **2a** (8.5 mg, 1 mol%), and *t*BuOH (2 mL) was stirred at 110 °C for 1.5 h. The crude product was purified via flash chromatography eluting with ethyl acetate to provide the title compound as a light-yellow, crystalline solid. **Yield**: 214 mg, 92%. **mp** = 183 – 184 °C. **^{1}H NMR** (500 MHz, DMSO-d^6) δ 10.38 (s, 1H), 8.27 (d, J = 2.0 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.53 (dd, J = 8.7, 2.1 Hz, 1H), 2.75 (s, 3H), 1.80 (tt, J = 7.7, 4.7 Hz, 1H), 0.90 - 0.76 (m, 4H) ppm. **^{13}C NMR** (126 MHz, DMSO-d^6) δ 172.71, 168.73, 154.43, 138.80, 130.09, 122.67, 117.87, 112.72, 20.74, 15.62, 8.21 ppm. **IR** (neat, cm^{-1}): 3284, 1658, 1576, 1516, 1464, 1400, 1324, 1224, 1179, 908, 799, 656, 649. Anal. Calcd. for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21. Found: C, 61.89; H, 4.99.

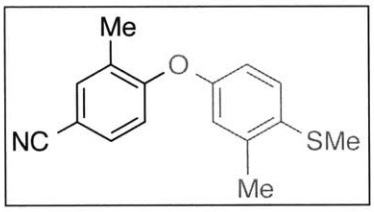


***N*-(6-(thiophen-3-yl)pyridin-3-yl)furan-2-carboxamide 3f:** Following general procedure B, a mixture of 5-chloro-2-(thiophen-3-yl)pyridine (195 mg, 1.00 mmol, 1.00 equiv), 2-furamide (117 mg, 1.05 mmol, 1.05 equiv), K_3PO_4 (297 mg, 1.40 mmol, 1.40 equiv) **2a** (8.5 mg, 1 mol%), and *t*BuOH (2 mL) was stirred at 110 °C for 1.5 h. The crude reaction mixture was loaded directly onto a silica gel column and the product was purified via flash chromatography, eluting with 80% ethyl acetate in hexanes, to provide the title compound as a yellow solid. **Yield**: 217 mg, 81%. **mp** = 161 – 163 °C. **^{1}H NMR** (500 MHz, DMSO-d^6) δ 10.50 (s, 1H), 8.94 (d, J = 2.5 Hz, 1H), 8.22 (dd, J = 8.6, 2.6 Hz, 1H), 8.09 (dd, J = 3.0, 1.3 Hz, 1H), 8.03 - 7.92 (m, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.81 - 7.69 (m, 1H), 7.67 - 7.58 (m, 1H), 7.43 - 7.33 (m, 1H), 6.77 - 6.68 (m, 1H) ppm. **^{13}C NMR** (126 MHz, DMSO-d^6) - 157.56, 149.29, 148.31, 147.18, 142.76, 142.67, 134.96, 129.27, 128.12, 127.31, 124.20, 121.14, 116.47, 113.49 ppm. **IR** (neat, cm^{-1}): 3281, 1656, 1585, 1473, 1390, 1301, 1162, 798, 746, 607

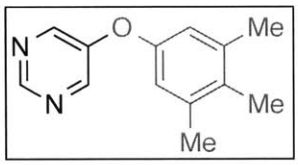
General Procedure C: Arylation of Phenols



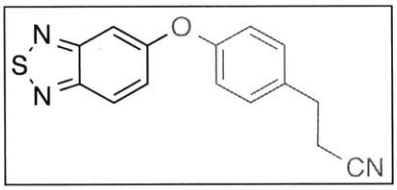
A screw-top test tube equipped with a magnetic stir bar and fitted with a Teflon screw cap was charged with aryl halide (1.00 mmol, 1.00 equiv), phenol (1.50 mmol, 1.50 equiv), K_3PO_4 (318 mg, 1.50 mmol, 1.50 equiv) and **2d** (1 – 2 mol%). The tube was sealed and evacuated and backfilled with argon (this sequence was repeated a total of three times). Then toluene (0.6 mL) and 1,2-dimethoxyethane (0.4 mL) were added by syringe. The reaction mixture was stirred at room temperature or 60° for 16 – 24 h. After completion the reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (5 mL) and eluted through a plug of silica with additional diethyl ether. The crude reaction mixture was concentrated with the aid of a rotary evaporator and purified by flash chromatography.



3-methyl-4-(3-methyl-4-(methylthio)phenoxy)benzonitrile 4a: Following general procedure C, a mixture of 4-bromo-3-methylbenzonitrile (196 mg, 1.00 mmol, 1.00 equiv), 3-methyl-4-(methylthio)phenol (231 mg, 1.50 mmol, 1.50 equiv), K_3PO_4 (318 mg, 1.50 mmol, 1.50 equiv), **2d** (20 mg, 0.02 mmol, 2 mol%), toluene (0.6 mL) and 1, 2-dimethoxyethane (0.4 mL) was stirred at room temperature for 16 h. The crude reaction mixture was purified by flash chromatography, eluting with 0 – 5% diethyl ether in hexanes to provide the title compound as a yellow solid. **Yield**: 239 mg, 89%. **mp** = 54 – 56 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (dd, J = 2.1, 0.9 Hz, 1H), 7.42 - 7.38 (m, 1H), 7.21 - 7.18 (m, 1H), 6.87 - 6.83 (m, 2H), 6.76 (d, J = 8.5 Hz, 1H), 2.47 (s, 3H), 2.34 (m, J = 2.7 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.01, 153.07, 138.70, 135.17, 133.72, 131.75, 129.93, 127.33, 121.56, 119.29, 118.03, 116.88, 106.01, 20.43, 16.35, 16.22 ppm. **IR** (neat, cm^{-1}): 2224, 1603, 1493, 1471, 1268, 1248, 1153, 1125, 1059, 955, 873, 819, 789, 689.

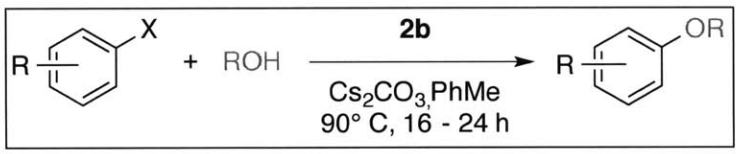


5-(3,4,5-trimethylphenoxy)pyrimidine 4b: Following general procedure C, a mixture of 5-bromopyrimidine (159 mg, 1.00 mmol, 1.00 equiv), 3,4,5-trimethylphenol (204 mg, 1.50 mmol, 1.50 eq,) K_3PO_4 (318 mg, 1.50 mmol, 1.50 equiv), **2d** (15 mg, 0.015 mmol, 1.5 mol%), toluene (0.6 mL) and 1, 2- dimethoxyethane (0.4 mL) was stirred at 60 °C for 16 h. The crude reaction mixture was purified by flash chromatography, eluting with a gradient of 10 – 25 % ethyl acetate in hexanes to provide the title compound as a yellow, crystalline solid. **Yield**: 195 mg, 91%. **mp** = 89 – 91 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (dd, J = 2.1, 0.9 Hz, 1H), 7.40 (ddd, J = 8.5, 2.2, 0.7 Hz, 1H), 7.21 - 7.17 (m, 1H), 6.87 - 6.83 (m, 2H), 6.76 (d, J = 8.5 Hz, 1H), 2.47 (s, 3H), 2.36 - 2.33 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.57, 153.34, 152.83, 147.19, 139.39, 132.72, 118.91, 21.47, 15.63 ppm. **IR** (neat, cm^{-1}): 1566, 1534, 1450, 1024, 787, 751, 620. Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59. Found: C, 73.08; H, 6.74.

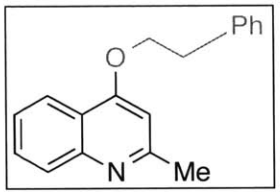


3-(4-(benzo[*c*][1,2,5]thiadiazol-5-yloxy)phenyl)propanenitrile 4c: Following general procedure C, a mixture of 5-chloro-2, 1, 3-benzothiadiazole (170 mg, 1.00 mmol, 1.00 equiv), 3-(4-hydroxyphenyl)propionitrile (221 mg, 1.50 mmol, 1.50 equiv), 2d (20 mg, 0.02 mmol, 2 mol%), toluene (0.6 mL) and 1, 2- dimethoxyethane (0.4 mL) was stirred at 60 °C for 24 h. The crude reaction mixture was purified by flash chromatography, eluting with 0 – 30 % ethyl acetate in hexanes to provide the title compound as a yellow solid. **Yield**: 281 mg, 78%. **mp** = 76 – 77 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (dd, J = 9.4, 0.7 Hz, 1H), 7.46 (ddd, J = 9.5, 2.4, 0.9 Hz, 1H), 7.31 (d, J = 6.6 Hz, 1H), 7.22 (dd, J = 2.4, 0.7 Hz, 1H), 7.13 - 7.10 (m, 2H), 3.00 (t, J = 7.3 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.41, 156.24, 155.08, 152.41, 135.45, 130.82, 125.55, 122.84, 121.48, 119.70, 105.25, 31.65, 20.23 ppm. **IR** (neat, cm^{-1}): 2232, 1606, 1508, 1483, 1423, 1270, 1219, 1175, 849, 816, 756.

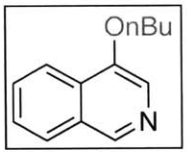
General Procedure D: Arylation of Alkyl Alcohols



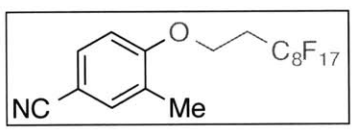
A screw-top test tube equipped with a magnetic stir bar and fitted with a Teflon septum screw cap was charged with aryl halide (1.00 mmol, 1.00 equiv), alcohol, if solid, (1.50 mmol, 1.50 equiv), Cs_2CO_3 (652 mg, 2.00 mmol, 2.00 equiv) and **2b** (1 – 2 mol%). The tube was sealed and evacuated and backfilled with argon (this sequence was repeated a total of three times). Then the alcohol, if liquid, was added by syringe, followed by toluene (1 mL). The reaction mixture was stirred at 90 °C for 16 – 24 h. After completion the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (5 mL) and filtered through a pad of celite. The crude reaction mixture was concentrated with the aid of a rotary evaporator and purified by flash chromatography.



2-Methyl-4-phenethoxyquinoline (5a):[18] Following general prodecure D, a mixture of 4-chloro-2-methylquinoline (164 mg, 1.00 mmol, 1.00 equiv), phenethyl alcohol (180 µL, 1.50 mmol, 1.50 equiv), Cs_2CO_3 (652 mg, 2.00 mmol, 2.00 equiv), **2b** (9 mg, 0.01 mmol, 1 mol%) and toluene (1 mL) was stirred at 90 °C for 16 h. The crude product mixture was purified by flash chromatography, eluting with 40% ethyl acetate in hexanes to provide the title compound as a light yellow solid. **Yield**: 240 mg, 91%. **mp** = 83 – 85 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (dd, J = 8.3, 1.5 Hz, 1H), 7.98 - 7.93 (m, 1H), 7.65 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.44 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.36 (s, 1H), 7.30 - 7.25 (m, 1H), 6.58 (s, 1H), 4.35 (t, J = 6.9 Hz, 2H), 3.24 (t, J = 6.9 Hz, 2H), 2.67 (s, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.11, 160.75, 138.51, 130.47, 129.75, 129.35, 128.77, 127.46, 125.48, 122.41, 120.54, 101.85, 69.65, 36.25, 26.67 ppm. **IR** (neat, cm^{-1}): 1598, 1567, 1510, 1423, 1345, 1251, 1184, 1114, 1023, 751, 701, 653.

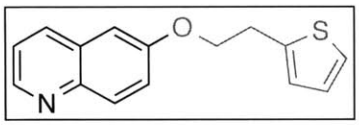


4-Butoxyisoquinoline (5b):[8] Following general prodecure D, a mixture of 4-bromoisoquinoline (207 mg, 1.00 mmol, 1.00 equiv), n-butanol (312 µL, 3.00 mmol, 3.00 equiv), Cs_2CO_3 (652 mg, 2.00 mmol, 2.00 equiv), **2b** (9 mg, 0.01 mmol, 1 mol%) and toluene (1 mL) was stirred at 90 °C for 16 h. The crude product mixture was purified by flash chromatography, eluting with 50% ethyl acetate in hexanes to provide the title compound as a yellow oil. Yield: 178 mg, 89%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.23 (dt, J = 8.4, 1.4 Hz, 1H), 8.07 (d, J = 1.4 Hz, 1H), 7.96 - 7.88 (m, 1H), 7.68 (dddt, J = 8.2, 6.7, 2.4, 1.2 Hz, 1H), 7.61 (dddd, J = 9.4, 6.8, 2.9, 1.6 Hz, 1H), 4.22 (dtd, J = 6.3, 4.0, 2.0 Hz, 2H), 1.92 (tdd, J = 9.1, 6.5, 4.6 Hz, 2H), 1.68 - 1.54 (m, 2H), 1.04 (td, J = 7.4, 1.9 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.73, 145.58, 130.13, 129.81, 129.01, 128.24, 127.54, 124.32, 121.89, 69.03, 32.05, 20.09, 14.61 ppm. **IR** (neat, cm^{-1}): 2957, 1578, 1502, 1458, 1399, 1279, 1156, 1121, 1091, 851, 779, 751, 619.

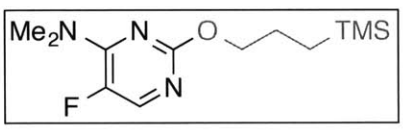


4-(1H, 1H, 2H, 2H-perfluorodecyloxy)-3-methylbenzonitrile 5c: Following general prodecure D, a mixture of 4-bromo-3-

methylbenzonitrile (207 mg, 1.00 mmol, 1.00 equiv), 1H,1H,2H,2H-perfluorodecanol (487 mg, 1.05 mmol, 1.05 equiv), Cs_2CO_3 (652 mg, 2.00 mmol, 2.00 equiv), **2b** (9 mg, 0.01 mmol, 1 mol%) and toluene (1 mL) was stirred at 90 °C for 16 h. The crude product mixture was purified by column chromatography, eluting with a gradient of 0 - 10% ethyl acetate in hexanes to provide the title compound as an light yellow solid. **Yield**: 469 mg, 81%. **mp** = 34 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.5, 2.1 Hz, 1H), 7.43 (dd, J = 2.1, 1.0 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 4.33 (t, J = 6.4 Hz, 2H), 2.68 (tt, J = 18.1, 6.4 Hz, 2H), 2.24 - 2.18 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.18, 136.17, 134.89, 132.59, 119.89, 118.85, 111.33, 60.98, 31.83 (t, J = 21.8 Hz), 16.56 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -81.23 (t, J = 9.9 Hz), -113.66 (p, J = 16.7 Hz), -121.03 - -122.83 (m), -122.83 – -123.53 (m), -123.89 (t, J = 13.9 Hz), -126.56 (t, J = 13.7 Hz). **IR** (neat, cm^{-1}): 2224, 1500, 1247, 1198, 1131, 808, 654.



6-(2-(thiophen-2-yl)ethoxy)quinoline 5d: Following general prodecure E, a mixture of 6-chloroquinoline (167 mg, 1.00 mmol, 1.00 equiv), 2-thiopheneethanol (167 µL, 1.50 mmol, 1.50 equiv), Cs_2CO_3 (652 mg, 2.00 mmol, 2.00 equiv), **2b** (18 mg, 0.02 mmol, 2 mol%) and toluene (1 mL) was stirred at 90 °C for 16 h. The crude product mixture was purified by flash chromatography, eluting with a gradient of 0 - 20% ethyl acetate in hexanes to provide the title compound as an off-white solid. **Yield**: 245 mg, 96%. **mp** = 52 – 54 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.77 (dd, J = 4.2, 1.6 Hz, 1H), 8.01 (dd, J = 8.8, 2.5 Hz, 2H), 7.40 (dd, J = 9.2, 2.8 Hz, 1H), 7.33 (dd, J = 8.3, 4.2 Hz, 1H), 7.19 (dd, J = 5.0, 1.3 Hz, 1H), 7.06 (d, J = 2.8 Hz, 1H), 7.02 - 6.90 (m, 2H), 4.30 (t, J = 6.7 Hz, 2H), 3.45 - 3.31 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.44, 148.73, 145.15, 140.83, 135.51, 131.63, 129.96, 127.60, 126.36, 124.81, 123.19, 122.09, 106.79, 69.36, 30.63 ppm. **IR** (neat, cm^{-1}): 1622, 1500, 1380, 1227, 1171, 1111, 1034, 927, 847, 828, 782, 768, 740, 701, 620.



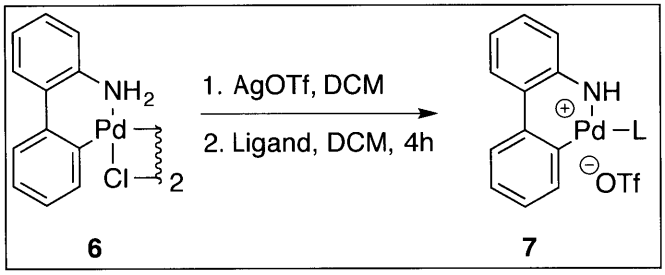
5-fluoro-N,N-dimethyl-2-(3-(trimethylsilyl)propoxy)pyrimidin-4-amine 5e: Following general prodecure D, a mixture of 2-chloro-5-

fluoro-N,N-dimethylpyrimidin-4-amine (176 mg, 1.00 mmol, 1.00 equiv), 3-(trimethylsilyl)propan-1-ol (198 mg, 1.50 mmol, 1.50 equiv), Cs_2CO_3 (652 mg, 2.00 mmol, 2.00 equiv), **2b** (18 mg, 0.02 mmol, 2 mol%) and toluene (1 mL) was stirred at 90 °C for 16 h. The crude product mixture was purified by column chromatography, eluting with 50% ethyl acetate in hexanes to provide the title compound as a yellow oil. **Yield**: 209 mg, 77%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, J = 6.3 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 3.17 (d, J = 2.3 Hz, 6H), 1.80 - 1.68 (m, 2H), 0.61 - 0.50 (m, 2H), -0.07 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.92 , 153.98 (d, J = 6.6 Hz), 144.92, 143.26 (d, J = 26.9 Hz), 70.84 , 39.55 (d, J = 7.2 Hz), 24.18 , 13.13 , -1.07 ppm. **IR** (neat, cm^{-1}): 2952, 1605, 1419, 1340, 1246, 1224, 1051, 855, 830, 769, 750. Anal. Calcd. for $C_{12}H_{22}FN_3OSi$: C, 53.10; H, 8.17. Found: C, 53.39; H, 8.02.

Triflate Palladacycle Precatalysts

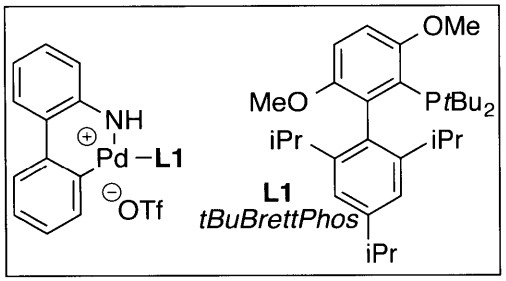
Initially we were unable to prepare palladium methanesulfonate precatalysts of L1 – L5, and instead prepared the triflate analogues. Upon synthesizing **2a – 2e**, however, we compared the reactivities of **7a** and **2a** and found no significant differences.

General Procedure E: 2-Aminobiphenylpalladium Triflate Precatalysts



A 24 mL test tube equipped with a magnetic stir bar was charged with 2-aminobiphenylpalladium chloride dimer **6** (310 mg, 0.50 mmol, 0.50 equiv) and AgOTf (257 mg, 1.00 mmol, 1.00 equiv). Dichloromethane (10 mL) was added from a squirt bottle, the tube was sealed with a Teflon screw-top septum, and wrapped in aluminum foil. The mixture was stirred at ambient temperature for 30 minutes, at which time a grey slurry formed. The slurry was filtered through a pad of celite into a 50 mL round-bottomed flask containing a magnetic stir bar and ligand (1.00 mmol, 1.00 eq). The pad of celite was further washed with

additional dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 1 – 4 h and the reaction progress was monitored by observing the disappearance of free-ligand and appearance of a new signal at ~45 ppm in the ^{31}P NMR spectrum. After completion, the solvent was removed with the aid of a rotary evaporator and pentane (25 mL) was added. The mixture was triturated with the aid of sonication until a dark powder resulted. The solid was isolated by filtration and dried under vacuum.



OTf tBuBrettPhos Precatalyst – Large Scale: A 250 mL round-bottomed flask equipped with a stir bar and wrapped in aluminum foil was charged with μ-Cl dimer (3.41 g, 5.5 mmol, 0.50 equiv) and AgOTf (2.82 g, 11.0 mmol, 1.00 equiv). Dichloromethane (100 mL) was added and the mixture was stirred at room temperature for 30 min. The mixture was then eluted through a plug of celite into a 500 mL round bottom flask equipped with a stir bar and tBuBrettPhos (5.33 g, 11.0 mmol, 1.00 equiv). The pad of celite was washed with additional dichloromethane (50 mL). The mixture was stirred at room temperature overnight and became dark red in appearance. At this time, the solvent was removed with the aid of a rotary evaporator and pentane (150 mL) was added. The mixture was sonicated and triturated until a dark orange powder resulted. The solid was filtered and dried under vacuum to afford the title compound. **Yield**: 9.59 g, 96%. **^{1}H NMR** (500 MHz, $CDCl_3$) Complex Spectrum – See Attached **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.81, 159.52, 157.16, 155.20, 154.23, 154.04, 153.94, 151.68, 151.56, 150.85, 147.38, 141.30, 140.90, 139.41, 137.43, 136.21, 136.17, 135.27, 135.25, 135.15, 135.01, 128.24, 127.54, 126.83, 125.94, 125.76, 124.02, 123.89, 122.35, 121.76, 121.62, 120.28, 119.80, 117.64, 117.61, 117.25, 106.28, 105.70, 56.61, 55.37, 55.30, 54.94, 54.89, 54.49, 54.38, 39.80, 39.67, 39.49, 39.37, 37.24, 36.98, 34.58, 34.51, 34.30, 32.57, 32.52, 32.00, 31.49, 30.56, 29.51, 29.46, 26.50, 26.04, 26.02, 25.16, 24.94, 24.86, 24.61, 24.55, 24.11, 23.22, 22.53 ppm (observed complexity due to C-P and C-F splitting). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 78.53, 44.12 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -78.03 ppm. **IR** (neat, cm^{-1}): 2957, 1578, 1456, 1422, 1252, 1149, 1031, 755, 636.

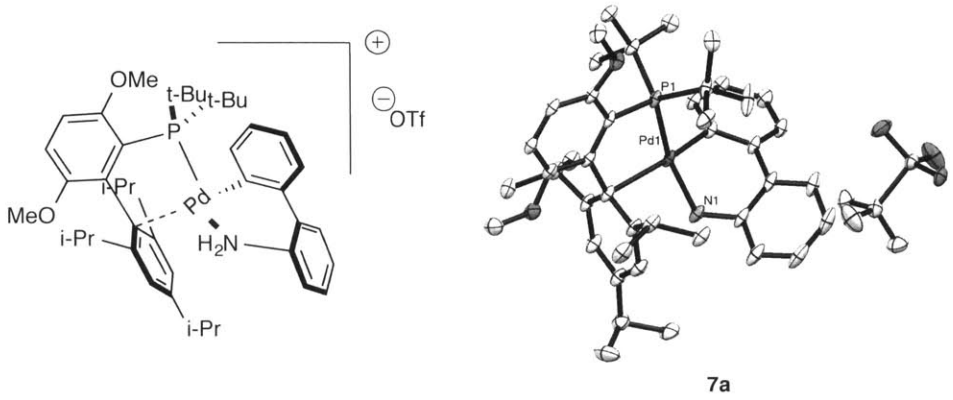
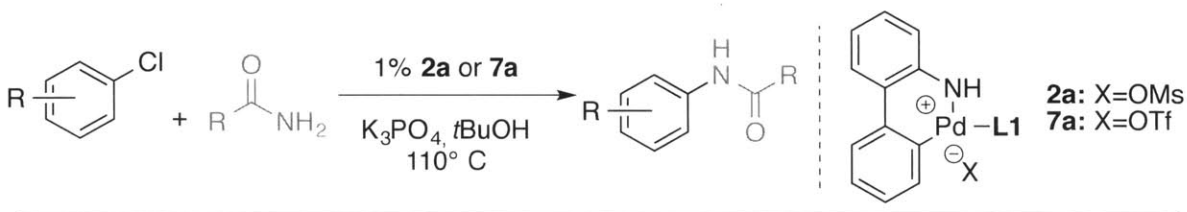
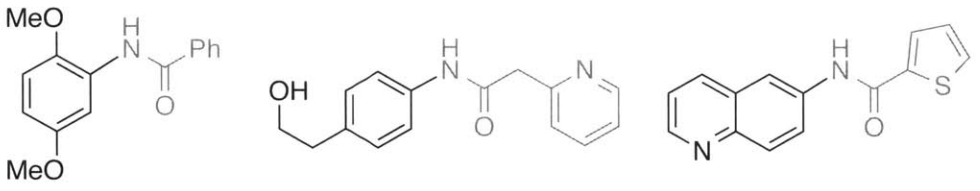


Figure 1. Crystallographically-determined X-ray structure of **7a** (thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted for clarity).

Table 1. Arylation of Primary Amides with **2a** and **7a** comparing the reactivities of each[a,*]

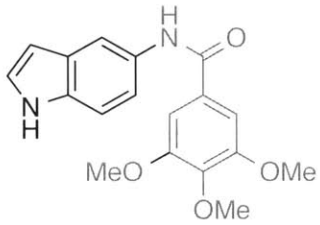




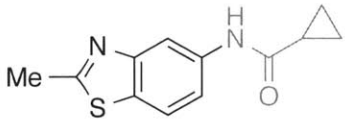
2a: 97%
7a: 96%

2a: 92%
7a: 92%

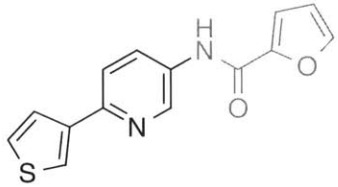
2a: 96%
7a: 97%



2a: 90%
7a: 77%



2a: 92%
7a: 86%



2a: 81%
7a: 88%

[a] ArCl (1 mmol), amide (1.05 – 1.2 mmol), K3PO4 (1.4 mmol), 2a (1 mol%), tBuOH (2 mL), 110 °C, 1.5 h; isolated yields, average of two runs.

*No significant difference in reactivities was observed between methanesulfonate precatalyst **2a** and trifluoromenthanesulfonate precatalyst **7a** in the arylation of primary amides.

X-Ray Structure Determination

Low-temperature diffraction data (ϕ-and ω-scans) were collected on a Bruker-AXS X8 Kappa Duo diffractometer coupled to a Smart Apex2 CCD detector with Mo Kα radiation (λ = 0.71073 Å) from an IμS micro-source for the structure of compounds **2a** and **5a**. All structures were solved by direct methods using SHELXS[21] and refined against F^2 on all data by full-matrix least squares with SHELXL-97[22] using established refinement techniques.[23] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl groups). All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3-distances and displacement parameters as well as rigid bond restraints for anisotropic displacement parameters unless otherwise noted below.

Compound **2a** crystallizes in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit.

Compound **7a** crystallizes in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit. The hydrogen atoms on N1 correspond to the two highest residual density maxima. The nitrogen containing ligand (N1 to C52) shows higher than average motion. Attempts to refine a disorder failed.

Table 2. Crystal data and structure refinement for **2a** .

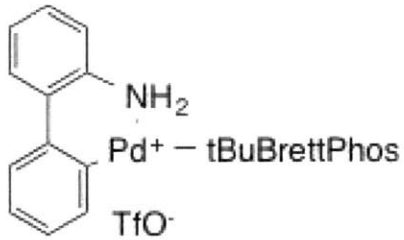
Identification code	x12164
Empirical formula	C44 H62 N O5 P Pd S
Formula weight	854.38
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 15.5444(13) Å a= 90°.

	b = 16.3387(14) Å b= 96.6810(10)°.
	c = 16.8546(14) Å g = 90°.
Volume	4251.6(6) $Å^3$
Z	4
Density (calculated)	1.335 mg/m^3
Absorption coefficient	0.567 mm^{-1}
F(000)	1800
Crystal size	0.16 x 0.15 x 0.12 mm^3
Theta range for data collection	1.69 to 31.00°.
Index ranges	-22<=h<=22, -23<=k<=23, -24<=l<=24
Reflections collected	77171
Independent reflections	13547 [R(int) = 0.0361]
Completeness to theta = 31.00°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9351 and 0.9147
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	13547 / 2 / 499
Goodness-of-fit on F2	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0299, wR2 = 0.0737
R indices (all data)	R1 = 0.0435, wR2 = 0.0824
Largest diff. peak and hole	0.888 and -1.127 $e.Å^{-3}$

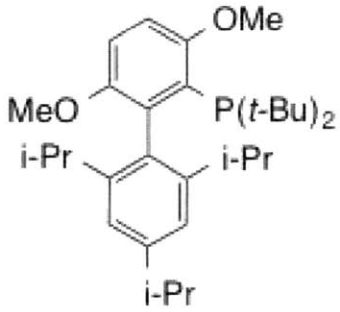
Table 3. Crystal data and structure refinement for **7a**.

Identification code	x12124
Empirical formula	C44 H59 F3 N O5 P Pd S
Formula weight	908.35
Temperature	100(2) K

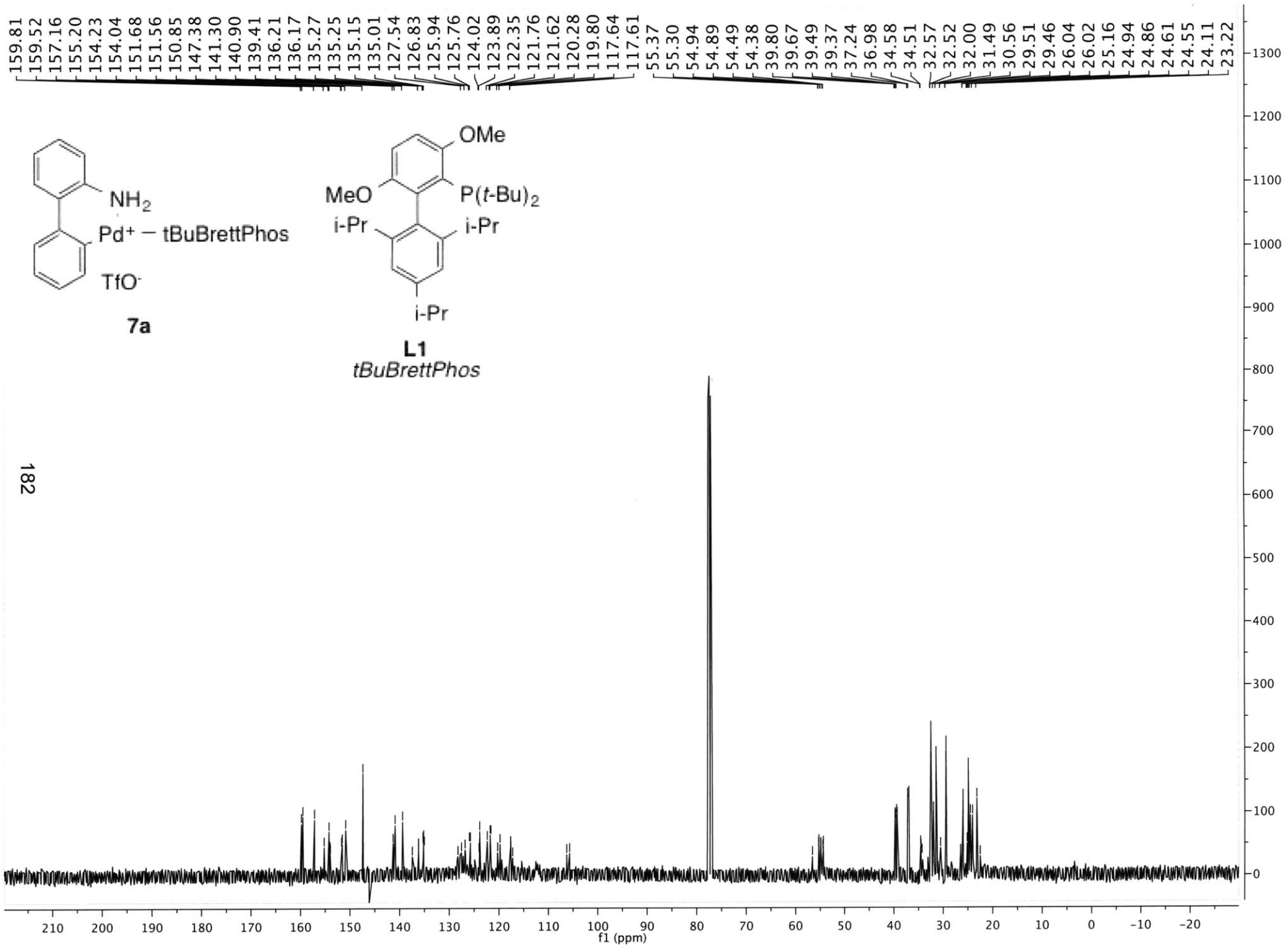
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 11.4497(5) Å a= 90°.
	b = 22.2598(9) Å b= 102.1430(10)°.
	c = 17.1180(7) Å g = 90°.
Volume	4265.2(3) $Å^3$
Z	4
Density (calculated)	1.415 mg/m^3
Absorption coefficient	0.580 mm^{-1}
F(000)	1896
Crystal size	0.40 x 0.30 x 0.15 mm^3
Theta range for data collection	1.52 to 31.51°.
Index ranges	-16<=h<=16, -32<=k<=32, -25<=l<=24
Reflections collected	145732
Independent reflections	14208 [R(int) = 0.0539]
Completeness to theta = 31.51°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9181 and 0.8012
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	14208 / 494 / 617
Goodness-of-fit on F2	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0315, wR2 = 0.0739
R indices (all data)	R1 = 0.0447, wR2 = 0.0826
Largest diff. peak and hole	0.691 and -1.009 $e.Å^{-3}$



7a



L1
tBuBrettPhos


159.81
159.52
157.16
155.20
154.23
154.04
151.68
151.56
150.85
147.38
141.30
140.90
139.41
136.21
136.17
135.27
135.25
135.15
135.01
127.54
126.83
125.94
125.76
124.02
123.89
122.35
121.76
121.62
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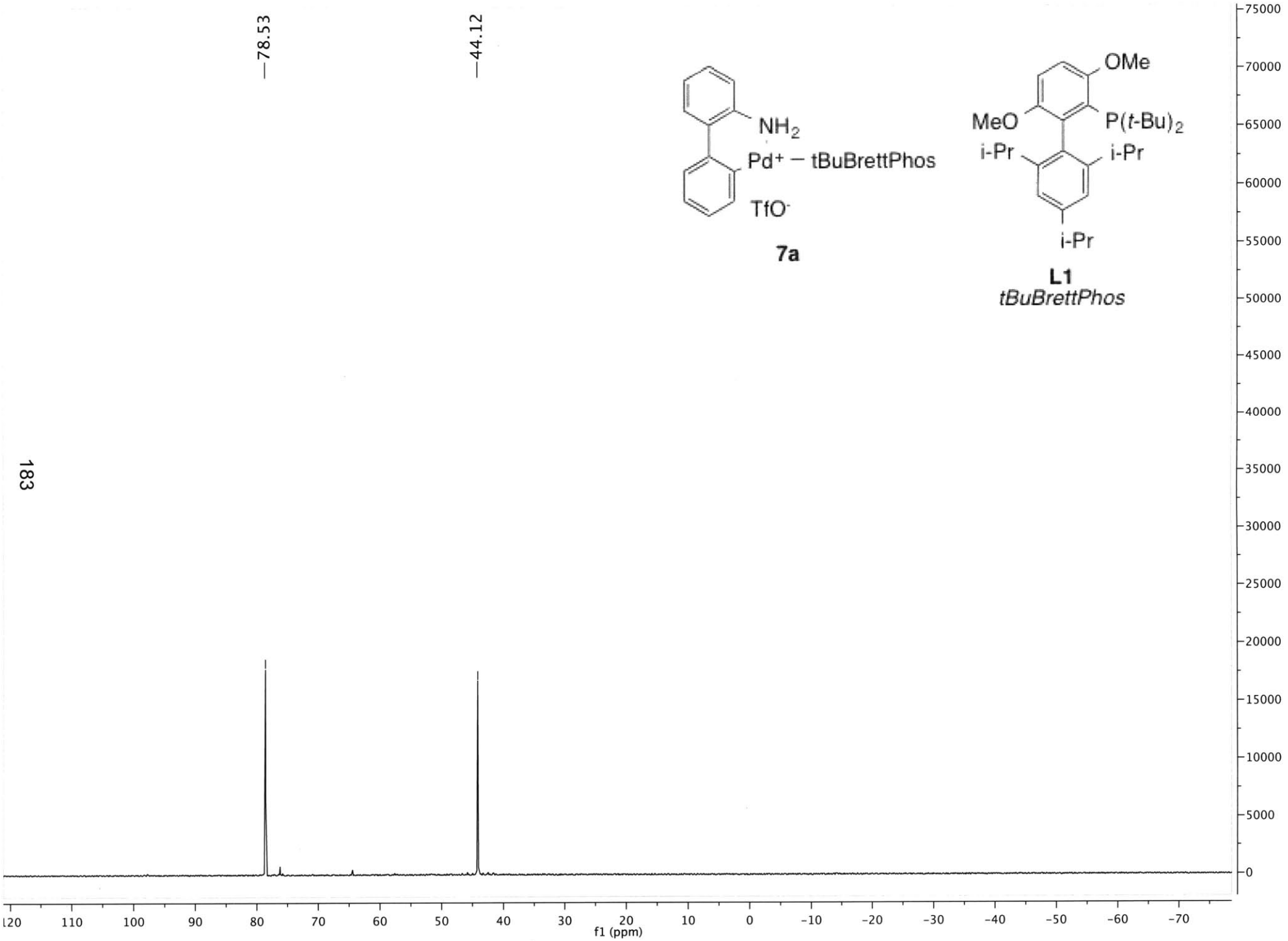
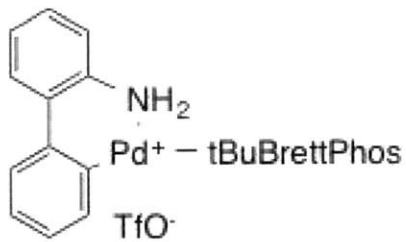
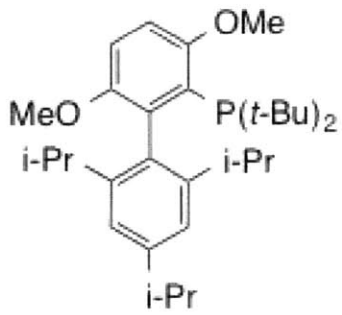
119.80
117.64
117.61
55.37
55.30
54.94
54.89
54.49
54.38
39.80
39.67
39.49
39.37
37.24
36.98
34.58
34.51
32.57
32.52
32.00
31.49
30.56
29.51
29.46
26.04
26.02
25.16
24.94
24.86
24.61
24.55
24.11
23.22
NH2
Pd+ – tBuBrettPhos
TfO-
7a
OMe
MeO
P(t-Bu)2
i-Pr
i-Pr
i-Pr
L1
tBuBrettPhos
182
f1 (ppm)

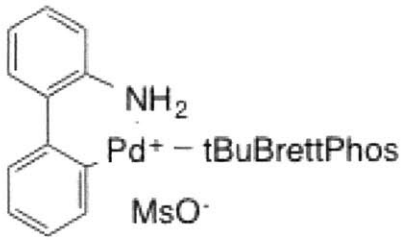

78.53
44.12
NH2
Pd+ – tBuBrettPhos
TfO-
7a
OMe
MeO
P(t-Bu)2
i-Pr
i-Pr
i-Pr
L1
tBuBrettPhos
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

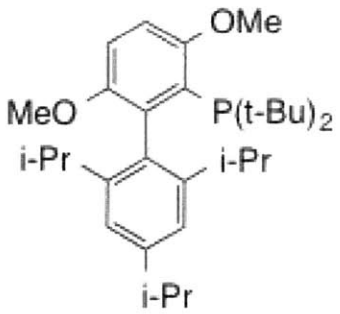


7a



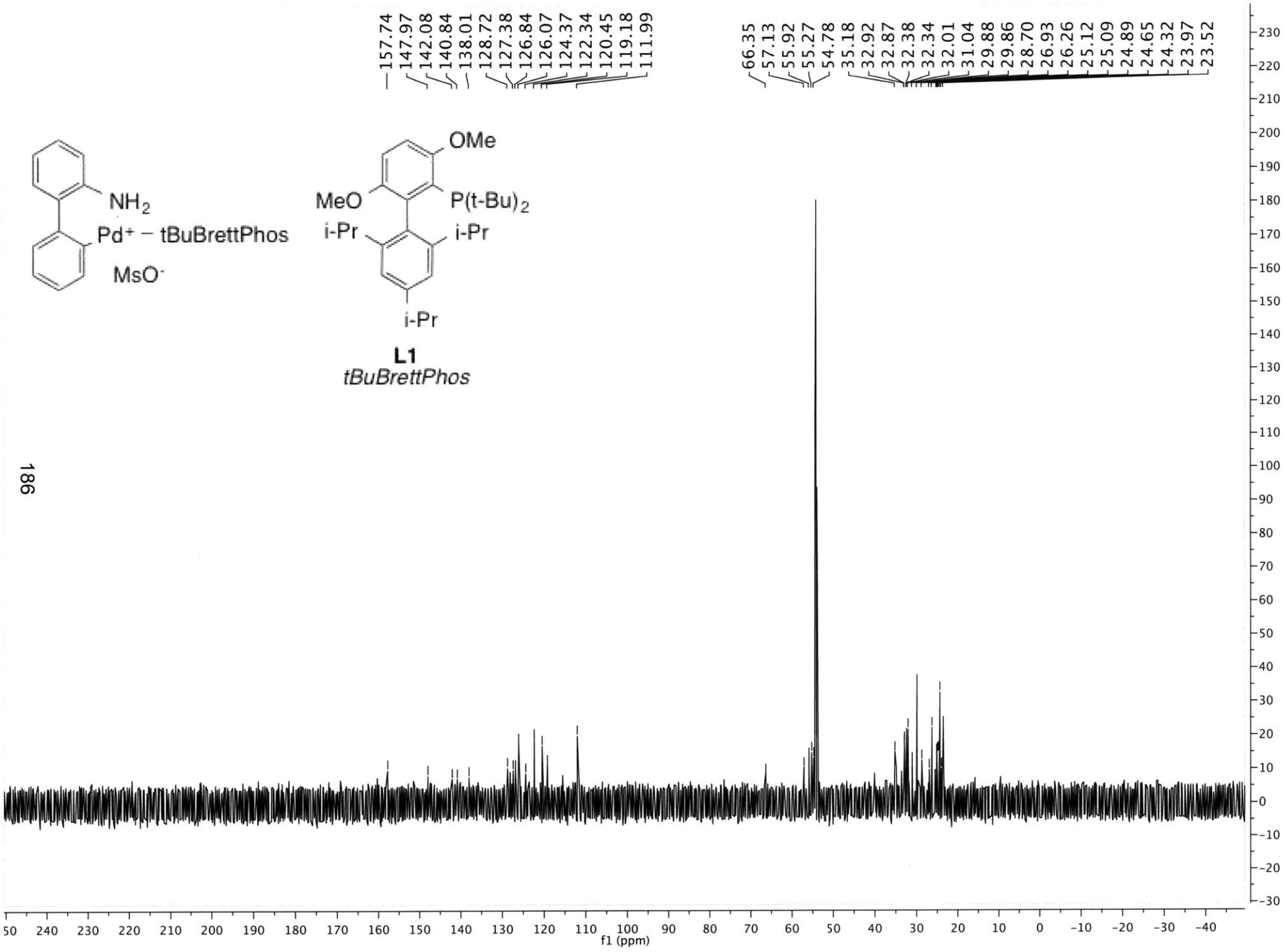
L1
tBuBrettPhos

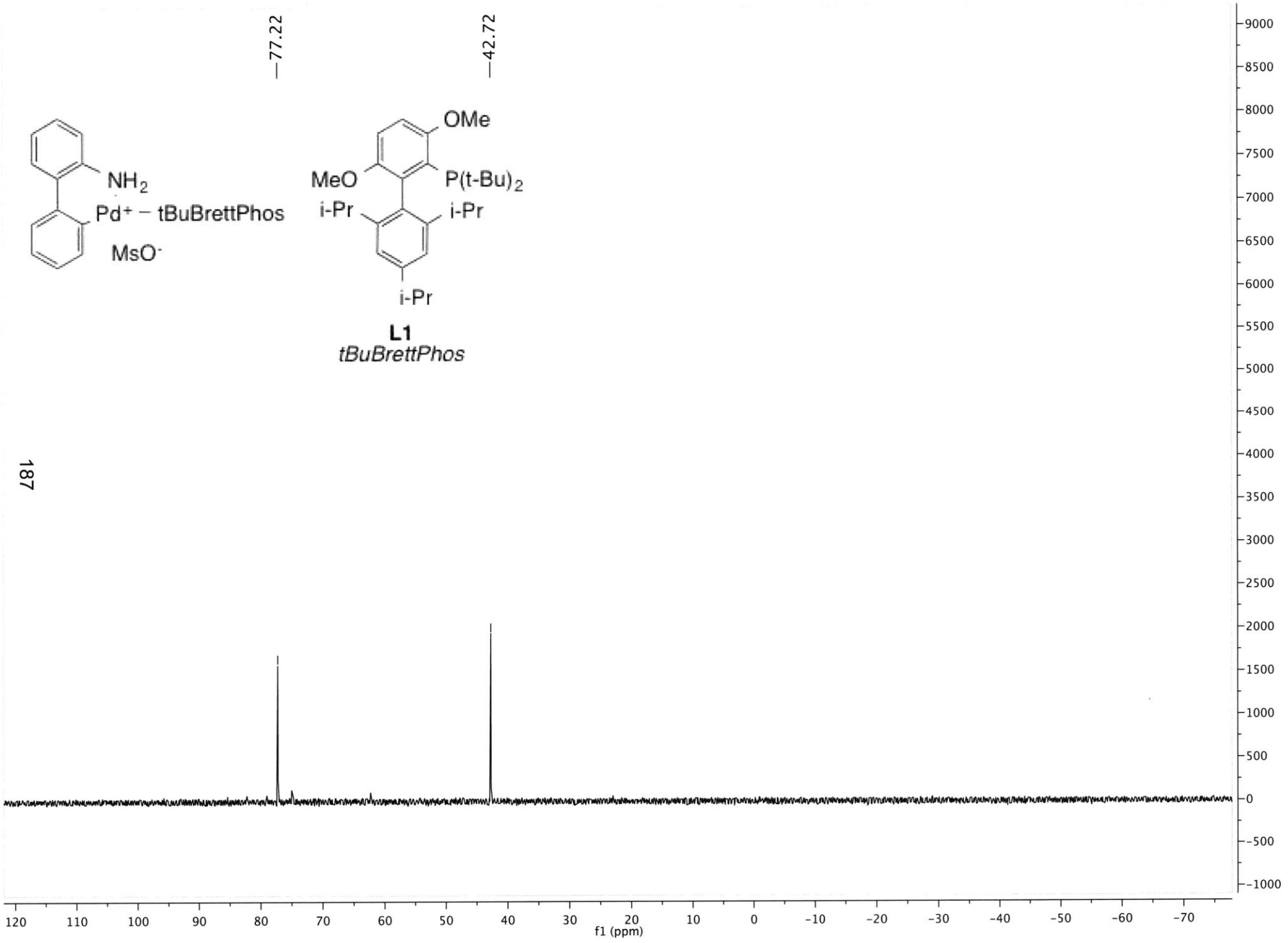


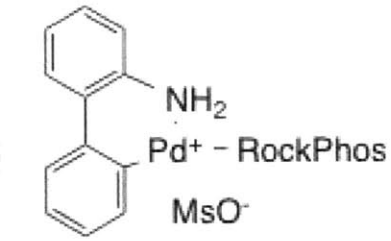


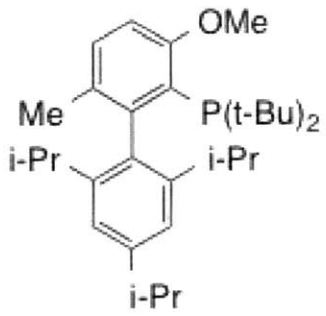
L1
tBuBrettPhos

185


157.74
147.97
142.08
140.84
138.01
128.72
127.38
126.84
126.07
124.37
122.34
120.45
119.18
111.99
66.35
57.13
55.92
55.27
54.78
35.18
32.92
32.87
32.38
32.34
32.01
31.04
29.88
29.86
28.70
26.93
26.26
25.12
25.09
24.89
24.65
24.32
23.97
23.52
NH2
Pd+ – tBuBrettPhos
MsO-
OMe
MeO
P(t-Bu)2
i-Pr
i-Pr
i-Pr
L1
tBuBrettPhos
f1 (ppm)

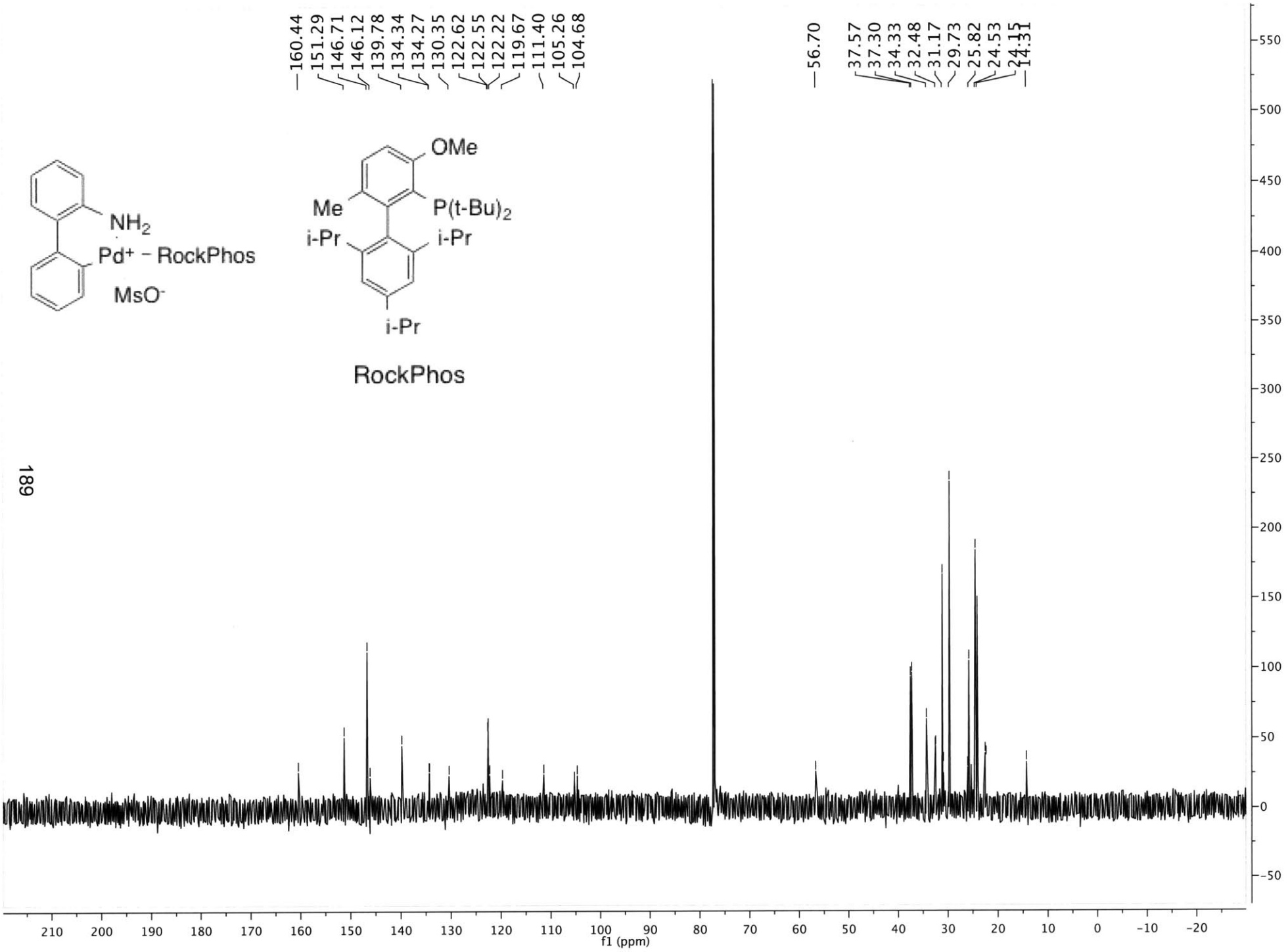

77.22
42.72
NH2
Pd+ – tBuBrettPhos
MsO-
OMe
MeO
P(t-Bu)2
i-Pr
i-Pr
i-Pr
L1
tBuBrettPhos
187
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

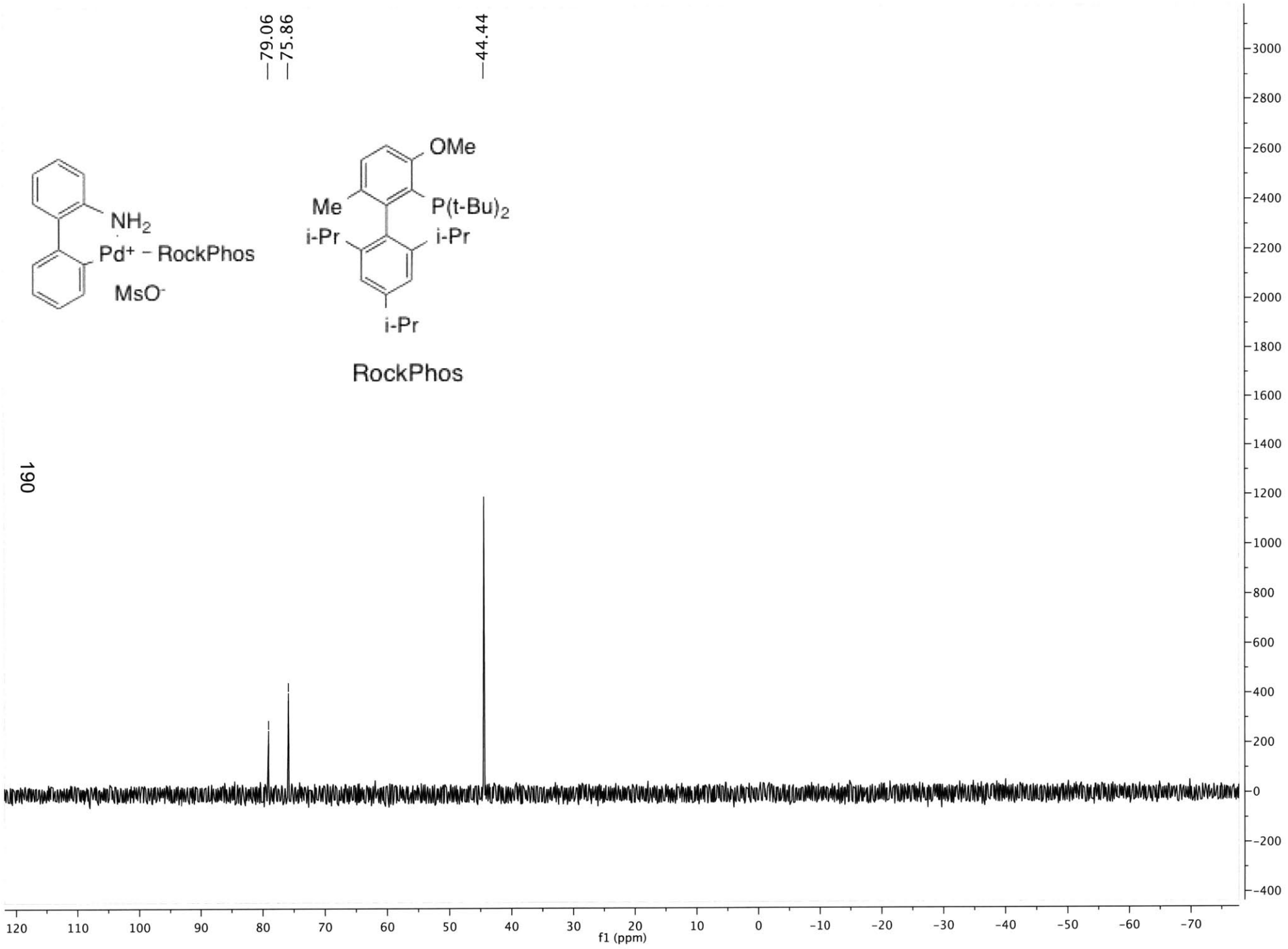


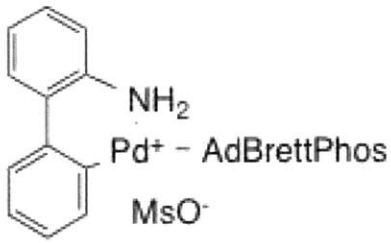


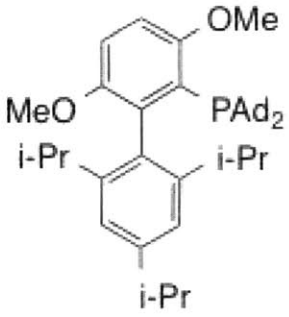
RockPhos

f1 (ppm)


160.44
151.29
146.71
146.12
139.78
134.34
134.27
130.35
122.62
122.55
122.22
119.67
111.40
105.26
104.68
56.70
37.57
37.30
34.33
32.48
31.17
29.73
25.82
24.53
24.15
14.31
NH2
Pd+ – RockPhos
MsO-
OMe
Me
P(t-Bu)2
i-Pr
i-Pr
i-Pr
RockPhos
f1 (ppm)

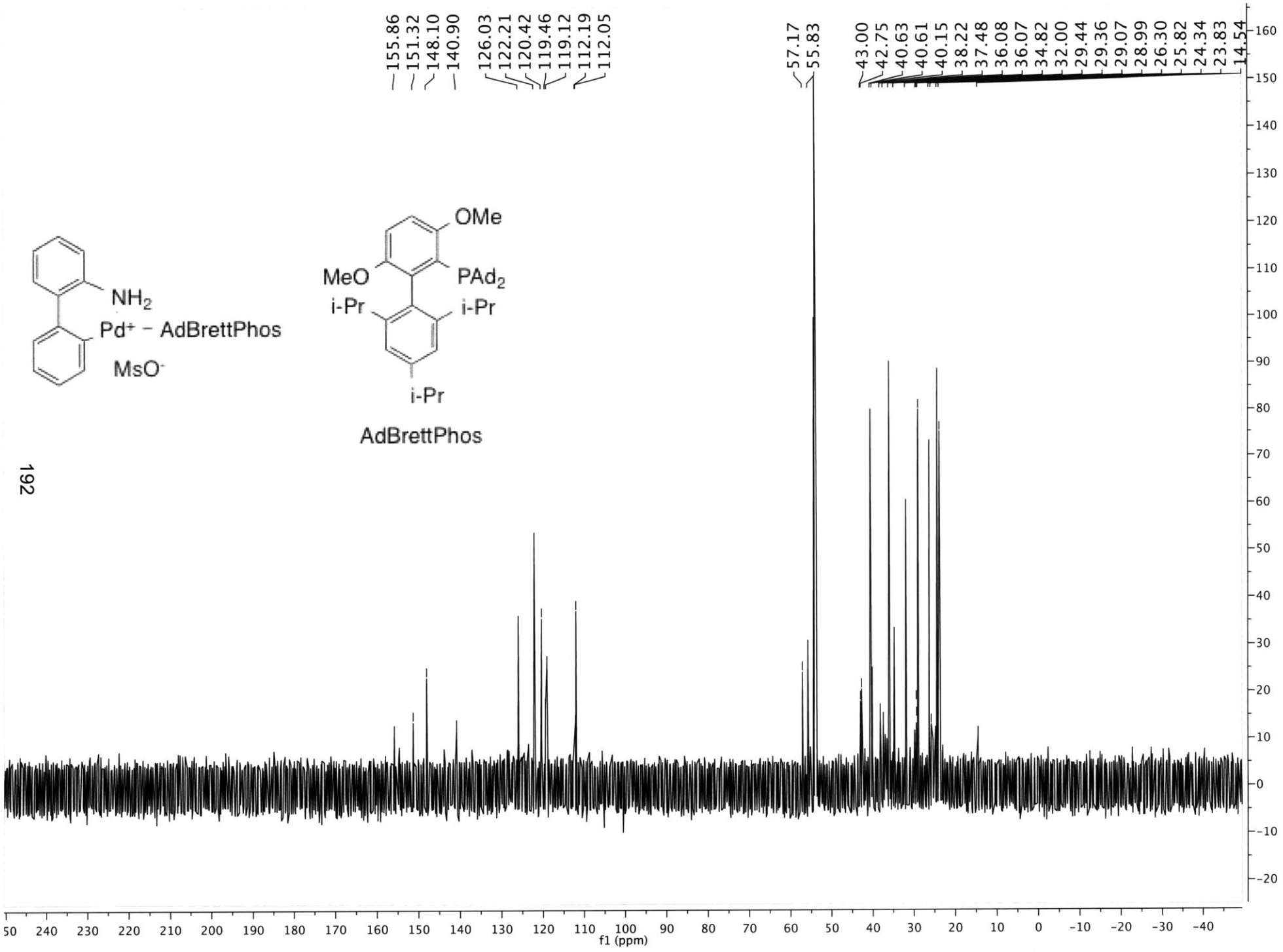

79.06
75.86
44.44
NH2
Pd+ – RockPhos
MsO-
OMe
Me
P(t-Bu)2
i-Pr
i-Pr
i-Pr
RockPhos
190
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)



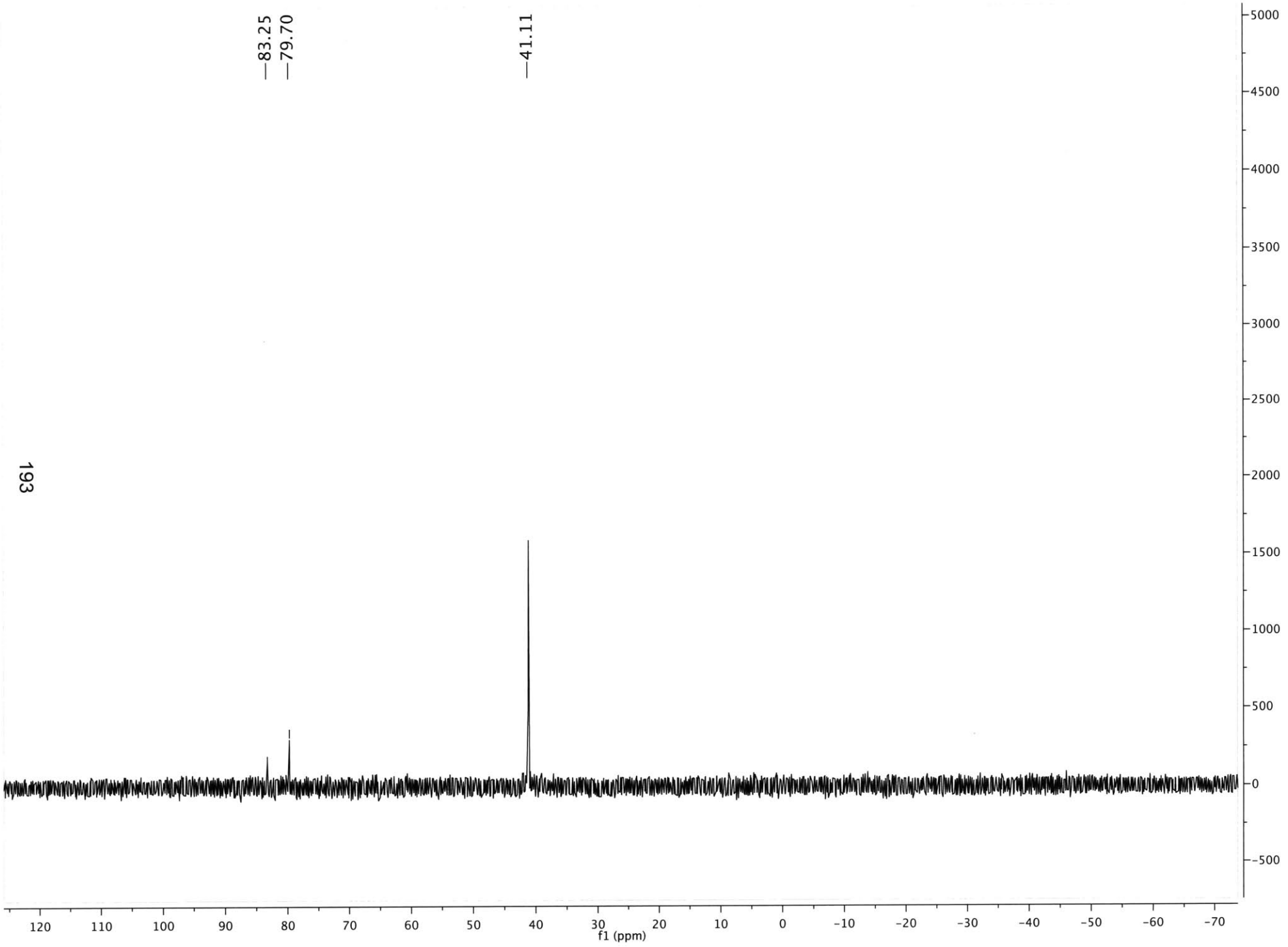


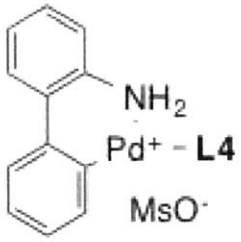
AdBrettPhos

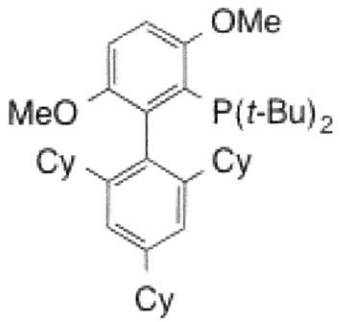
191


155.86
151.32
148.10
140.90
126.03
122.21
120.42
119.46
119.12
112.19
112.05
57.17
55.83
43.00
42.75
40.63
40.61
40.15
38.22
37.48
36.08
36.07
34.82
32.00
29.44
29.36
29.07
28.99
26.30
25.82
24.34
23.83
14.54
NH2
Pd+ − AdBrettPhos
MsO-
OMe
MeO
PAd2
i-Pr
i-Pr
i-Pr
AdBrettPhos
f1 (ppm)

192

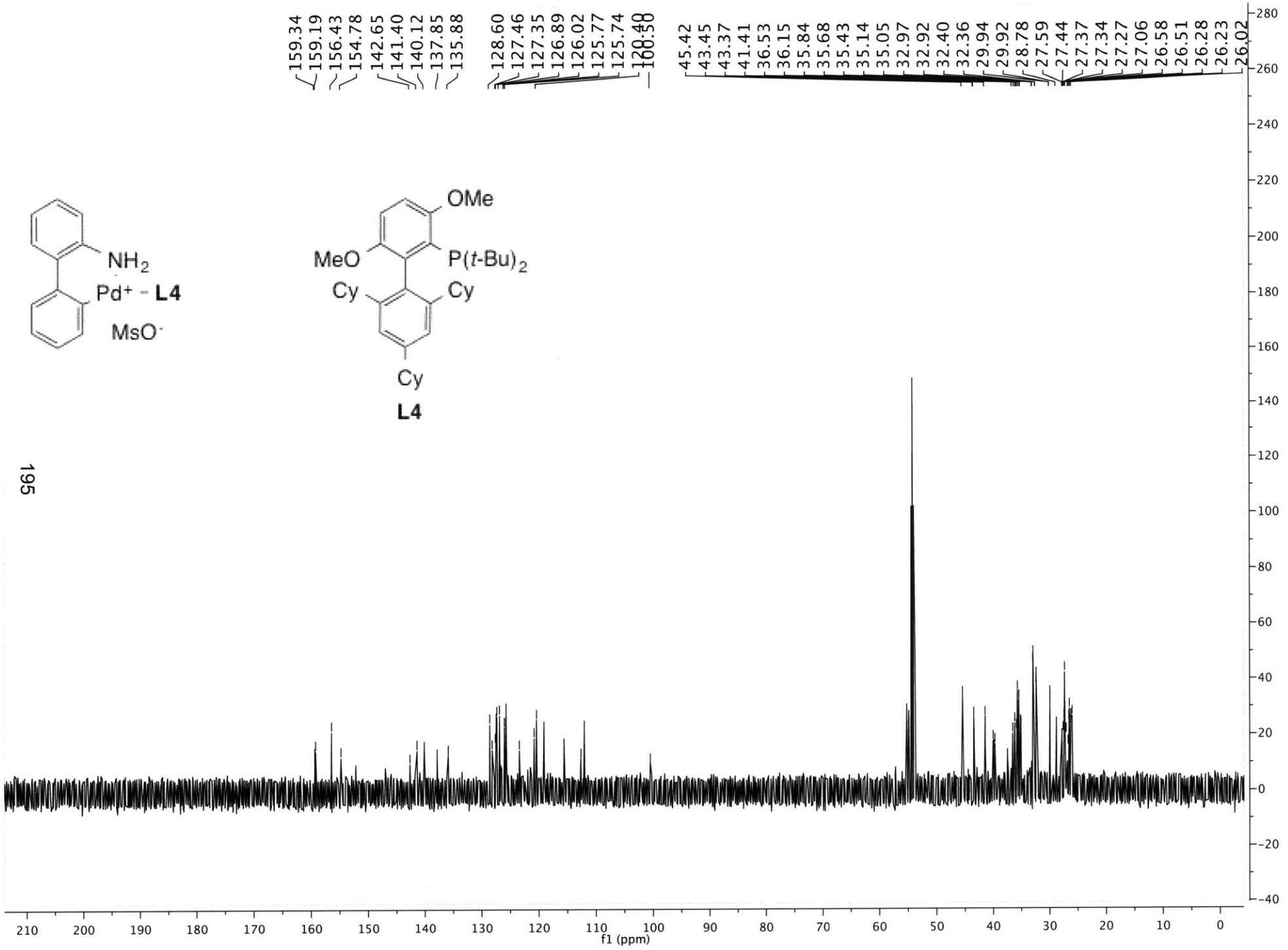

83.25
79.70
41.11
193
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

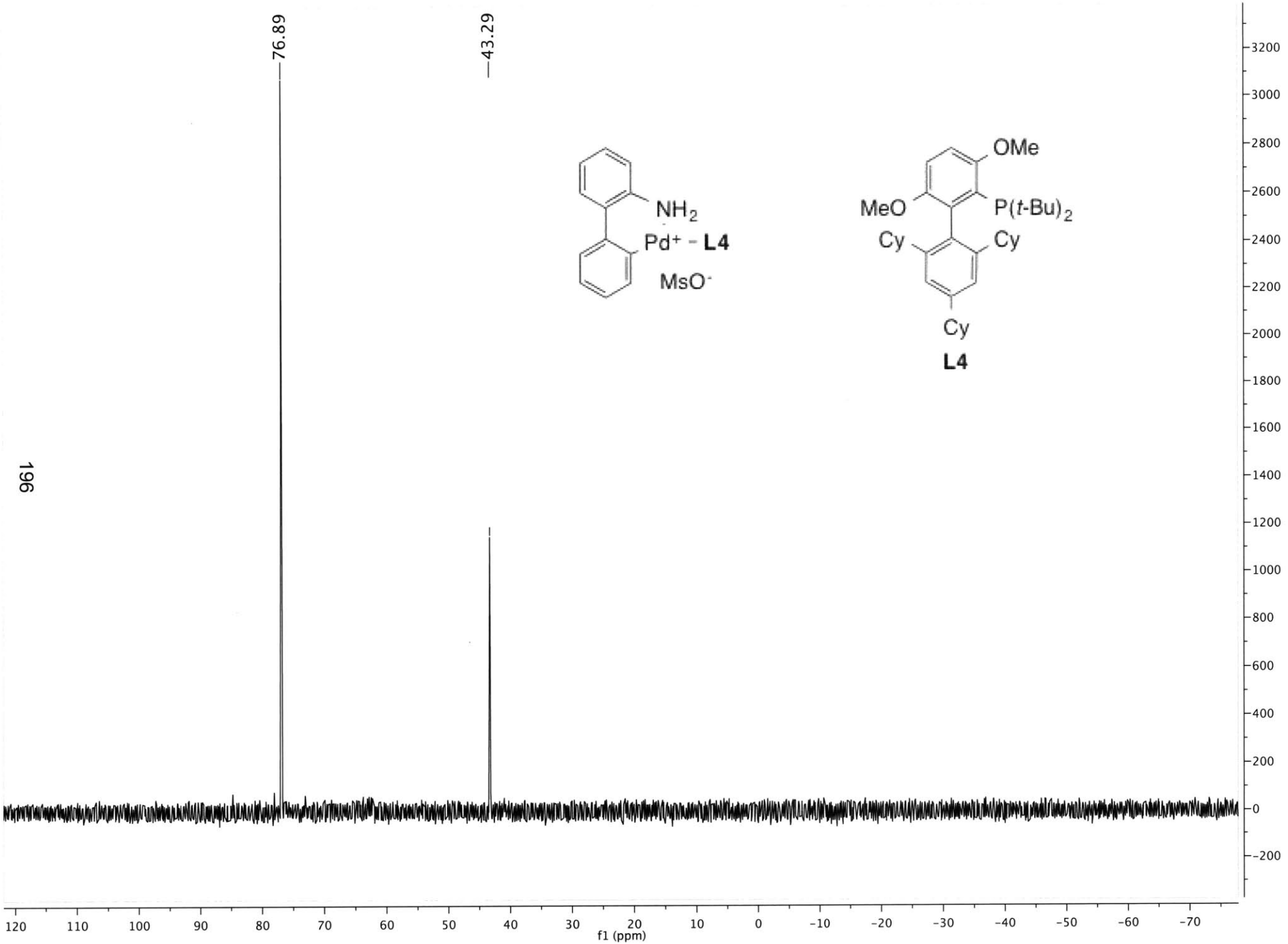

NH2
Pd+ - L4
MsO-

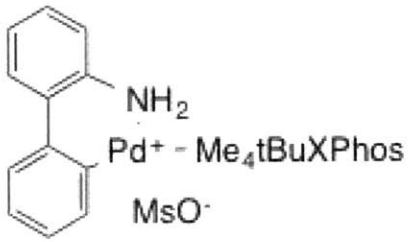

OMe
MeO
P(t-Bu)2
Cy
Cy
Cy

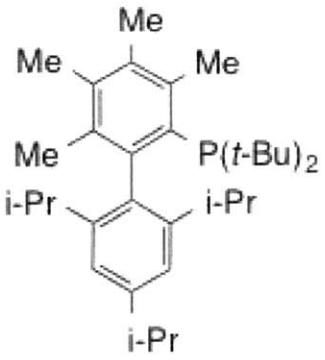
L4

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
12.0
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
f1 (ppm)


159.34
159.19
156.43
154.78
142.65
141.40
140.12
137.85
135.88
128.60
127.46
127.35
126.89
126.02
125.77
125.74
120.40
100.50
45.42
43.45
43.37
41.41
36.53
36.15
35.84
35.68
35.43
35.14
35.05
32.97
32.92
32.40
32.36
29.94
29.92
28.78
27.59
27.44
27.37
27.34
27.27
27.06
26.58
26.51
26.28
26.23
26.02
NH2
Pd+ - L4
MsO-
OMe
MeO
P(t-Bu)2
Cy
Cy
Cy
L4
195
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

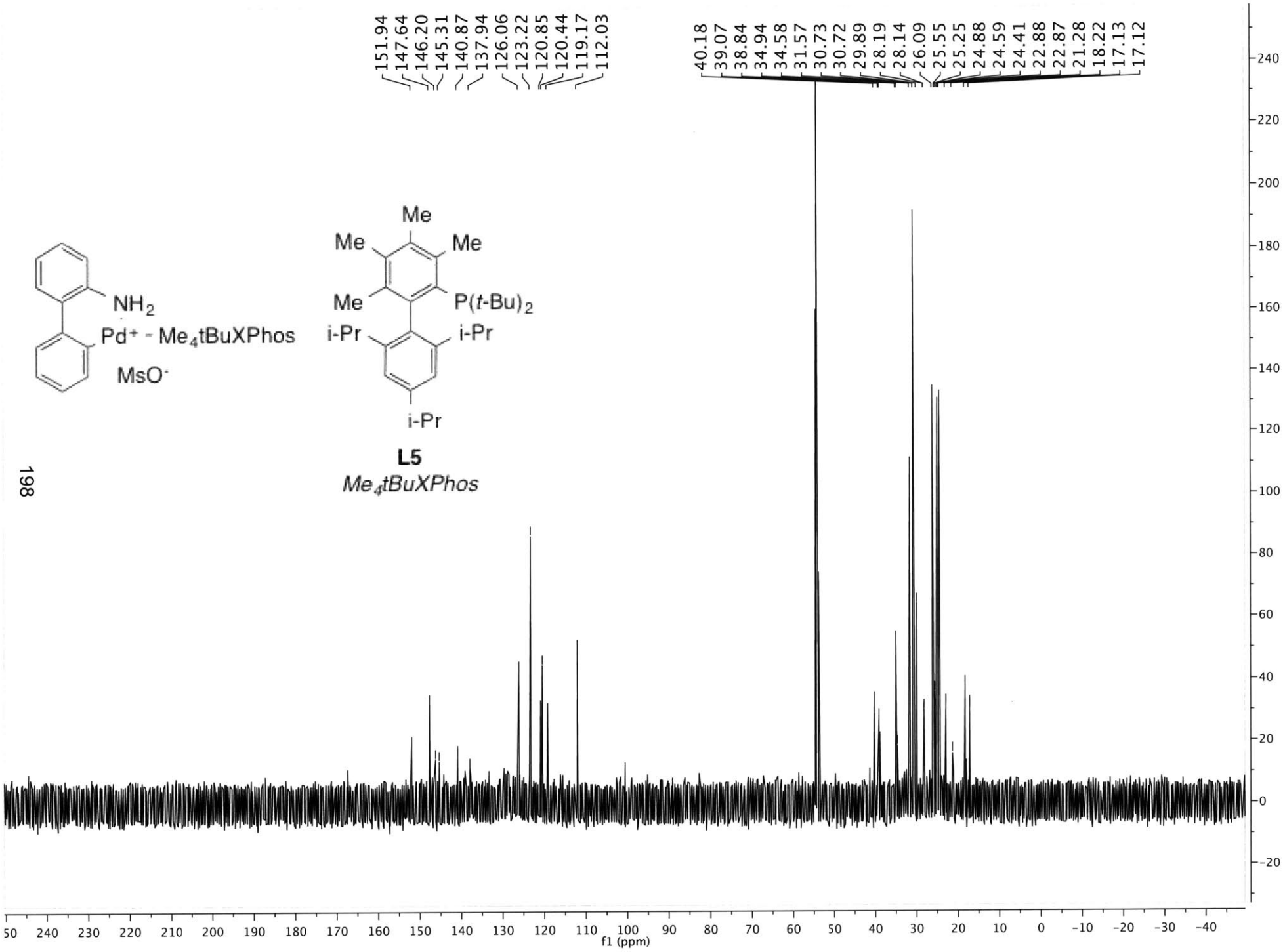

76.89
43.29
NH2
Pd+ - L4
MsO-
OMe
MeO
P(t-Bu)2
Cy
Cy
Cy
L4
196
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)





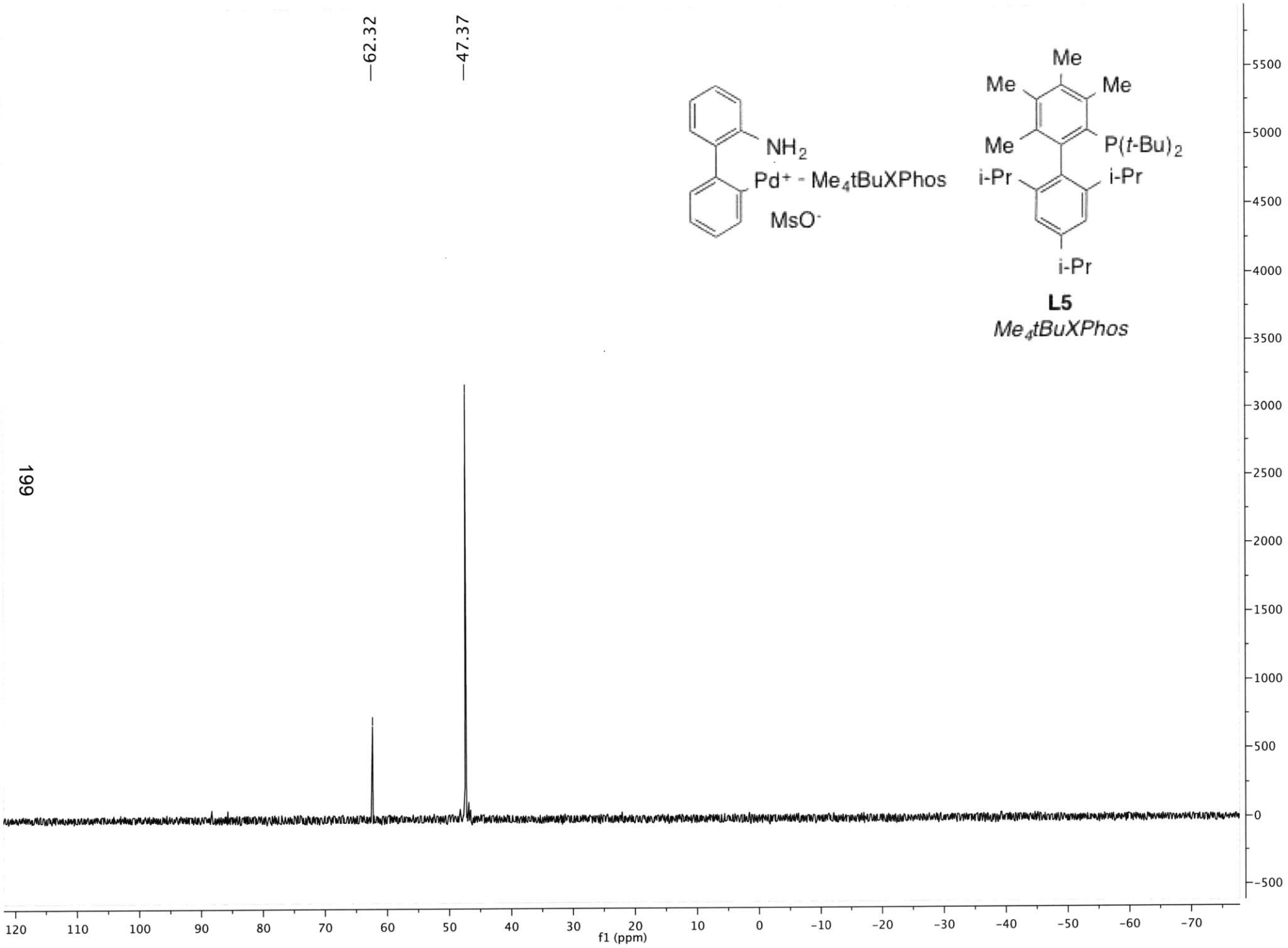
L5

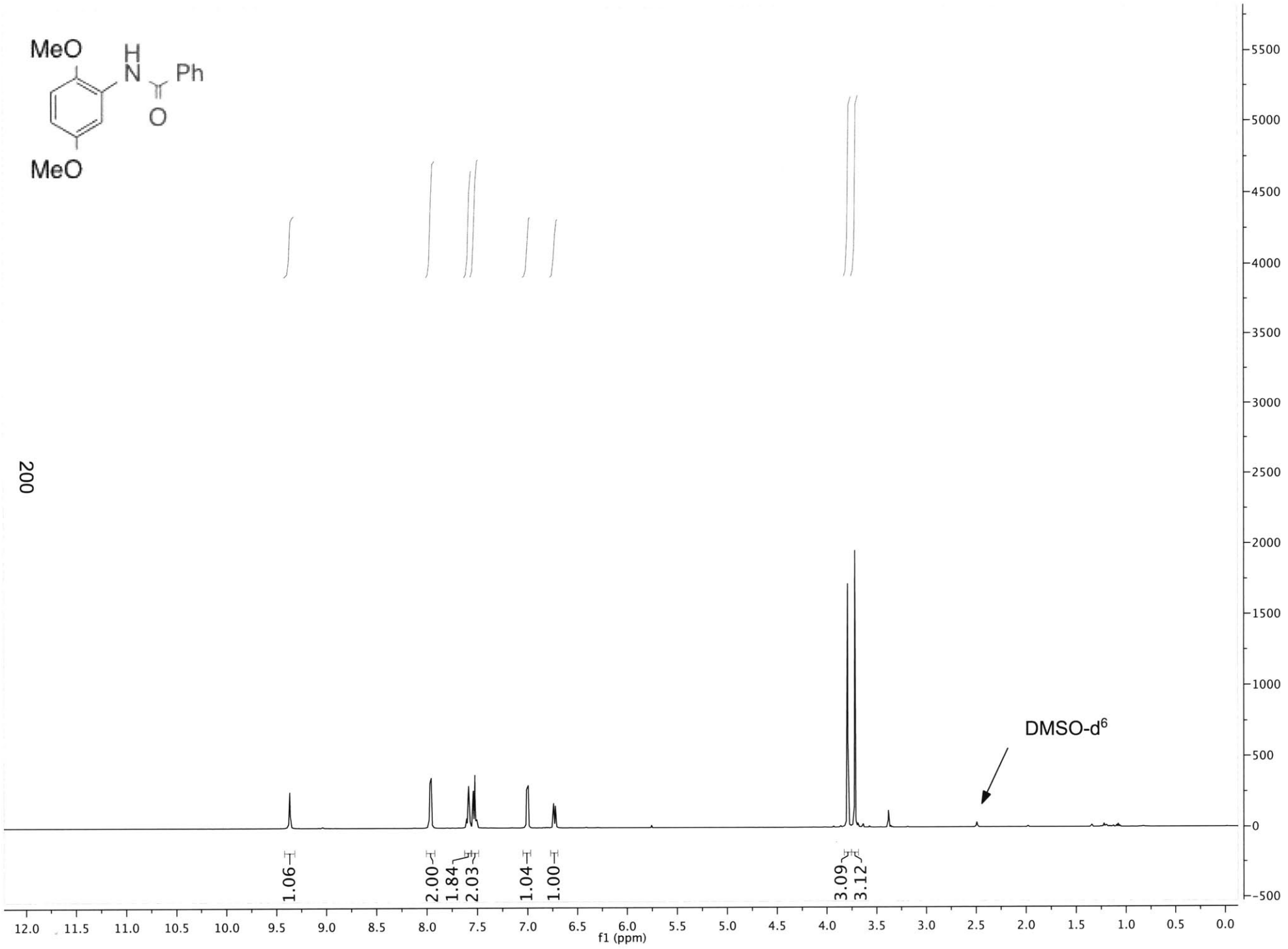
Me_4tBuXPhos

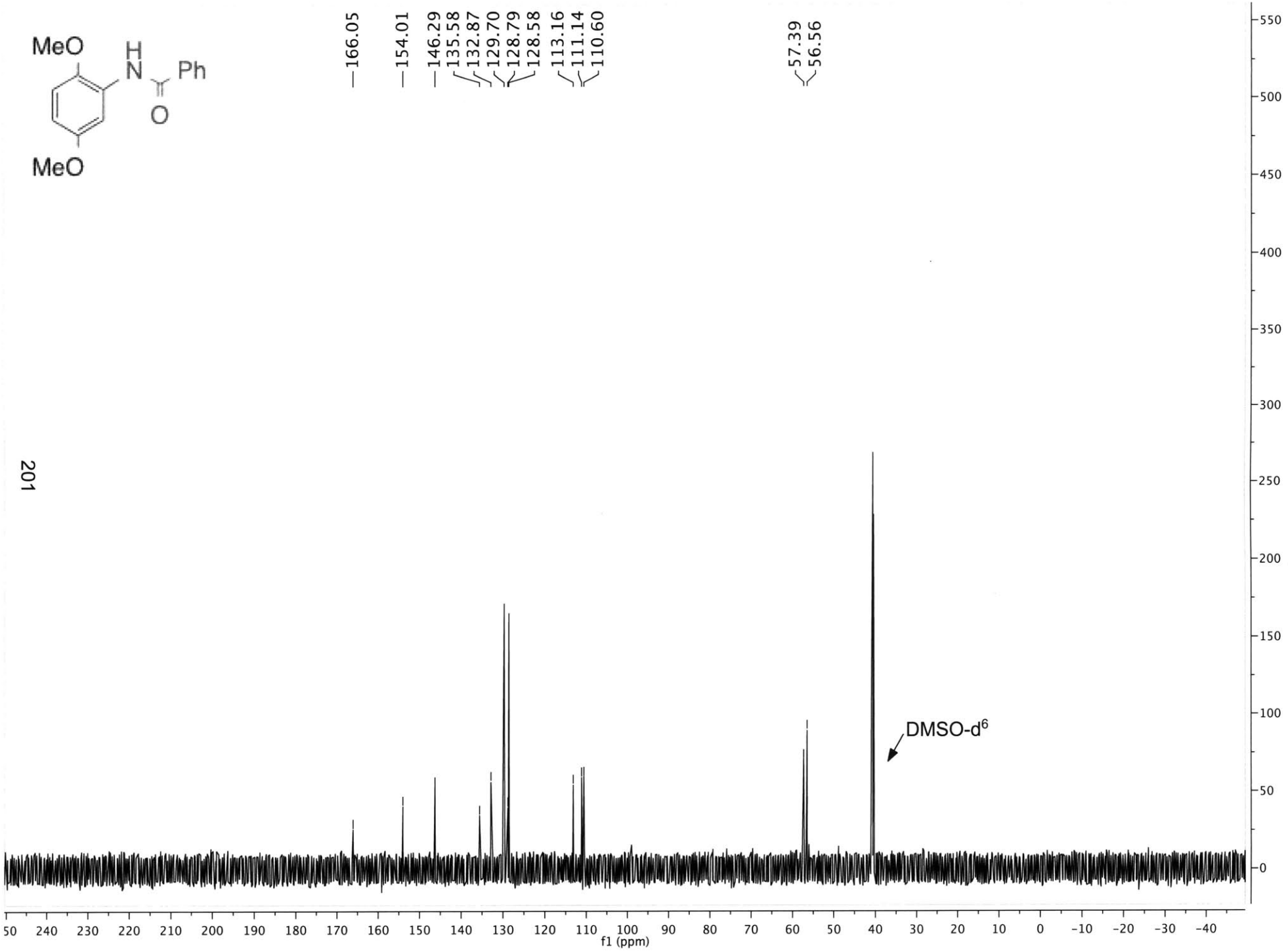


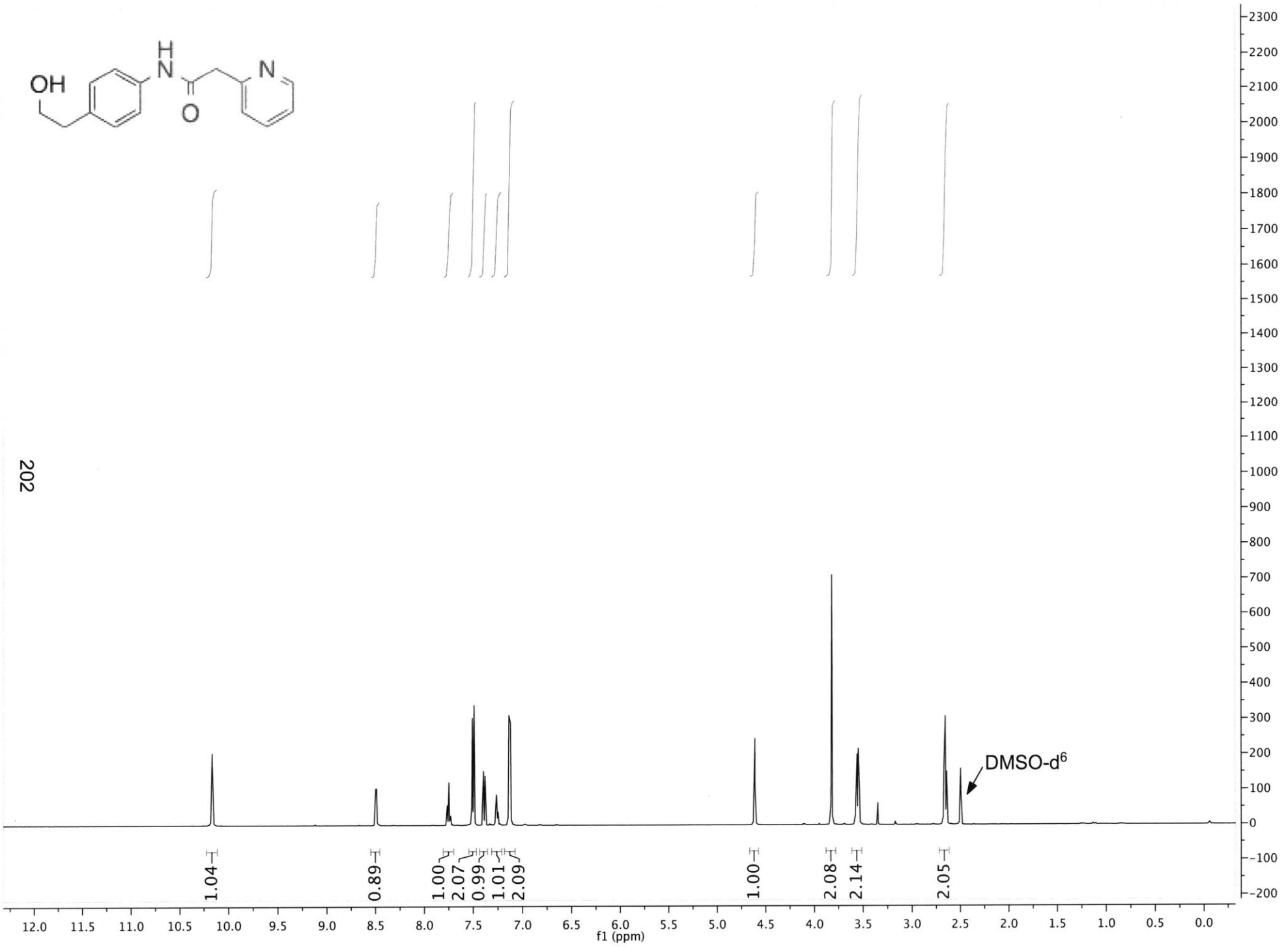
L5

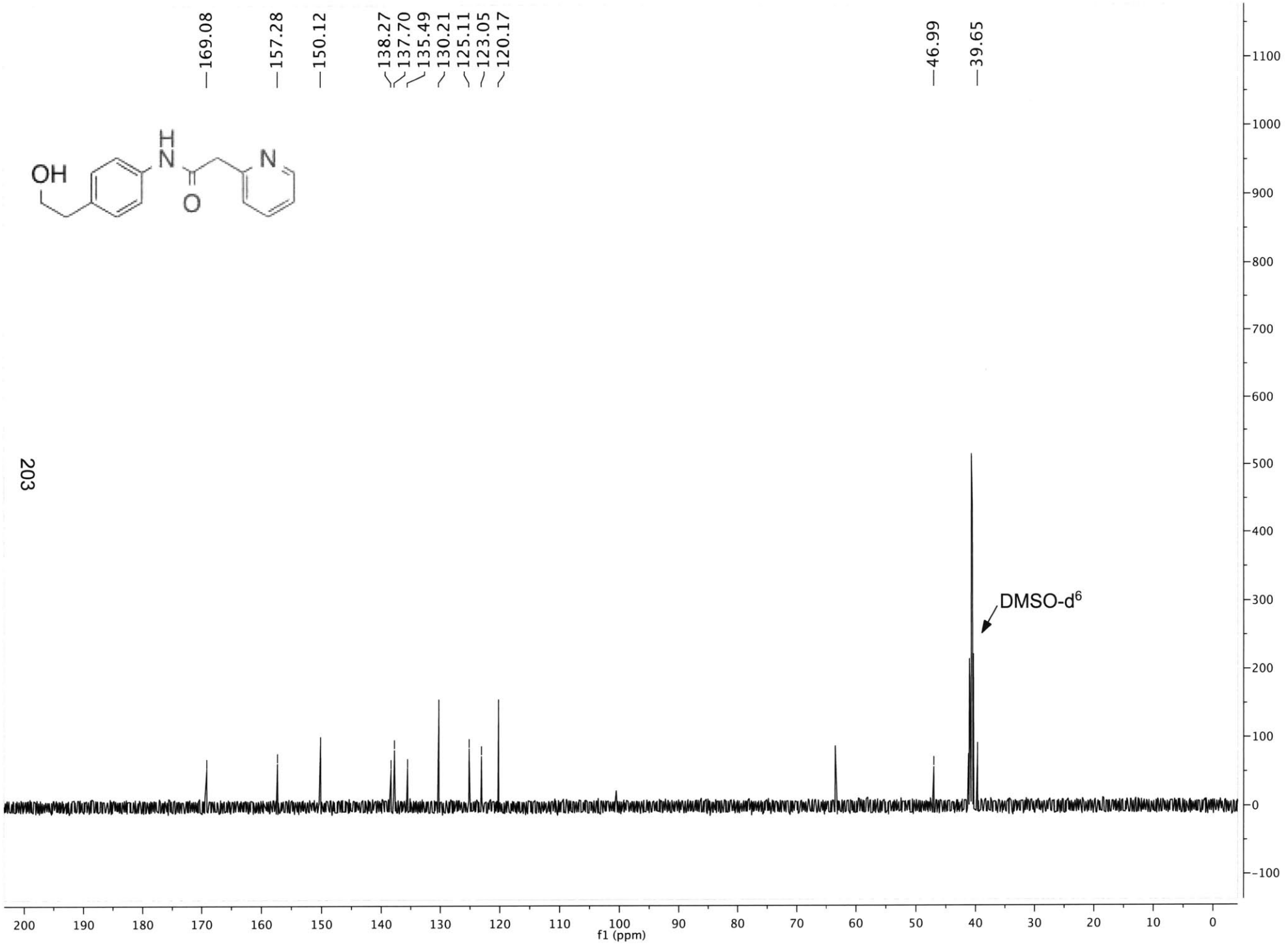
Me_4tBuXPhos

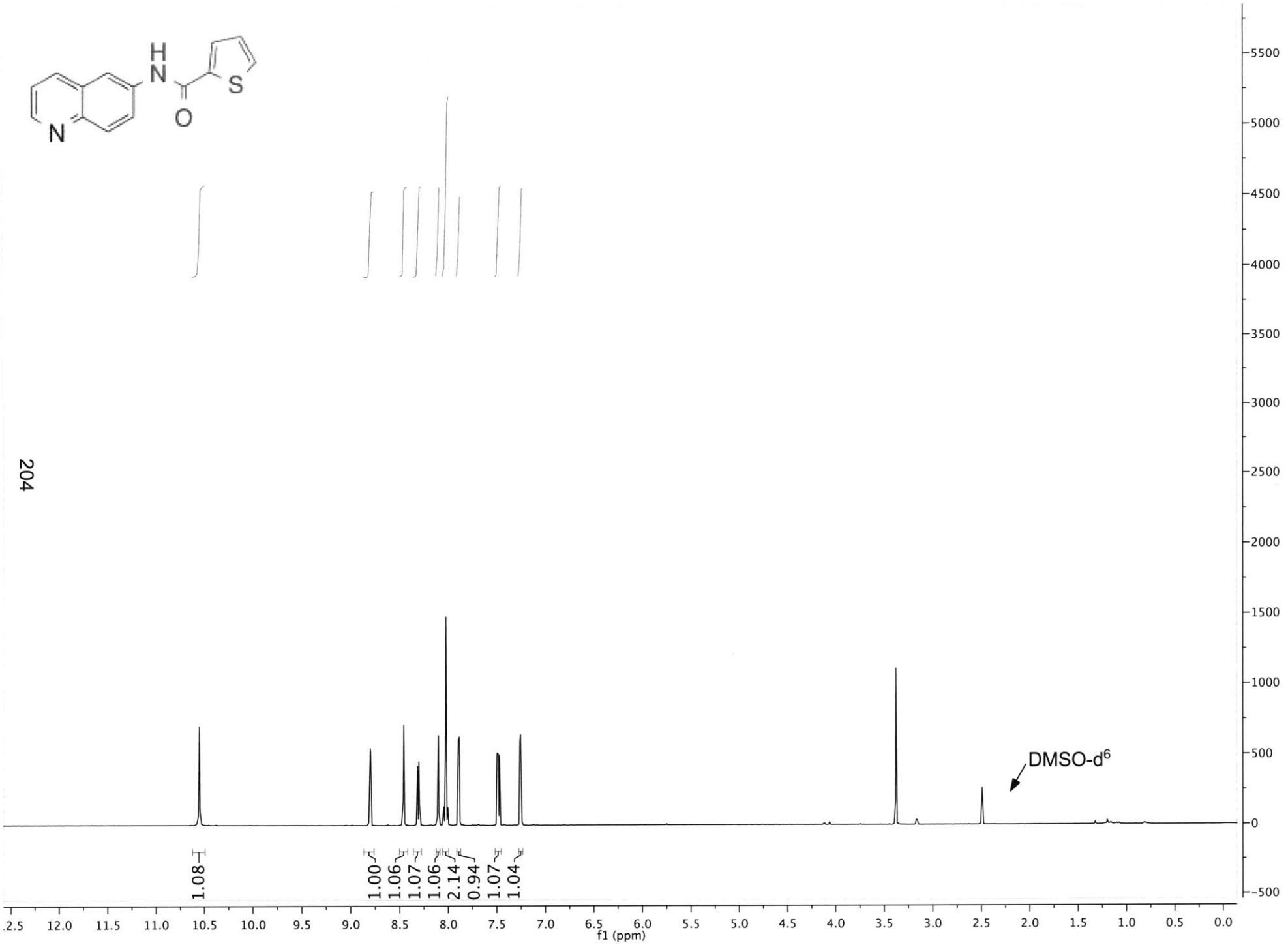

62.32
47.37
NH2
Pd+ - Me4tBuXPhos
MsO-
Me
Me
Me
Me
P(t-Bu)2
i-Pr
i-Pr
i-Pr
L5
Me4tBuXPhos
199
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

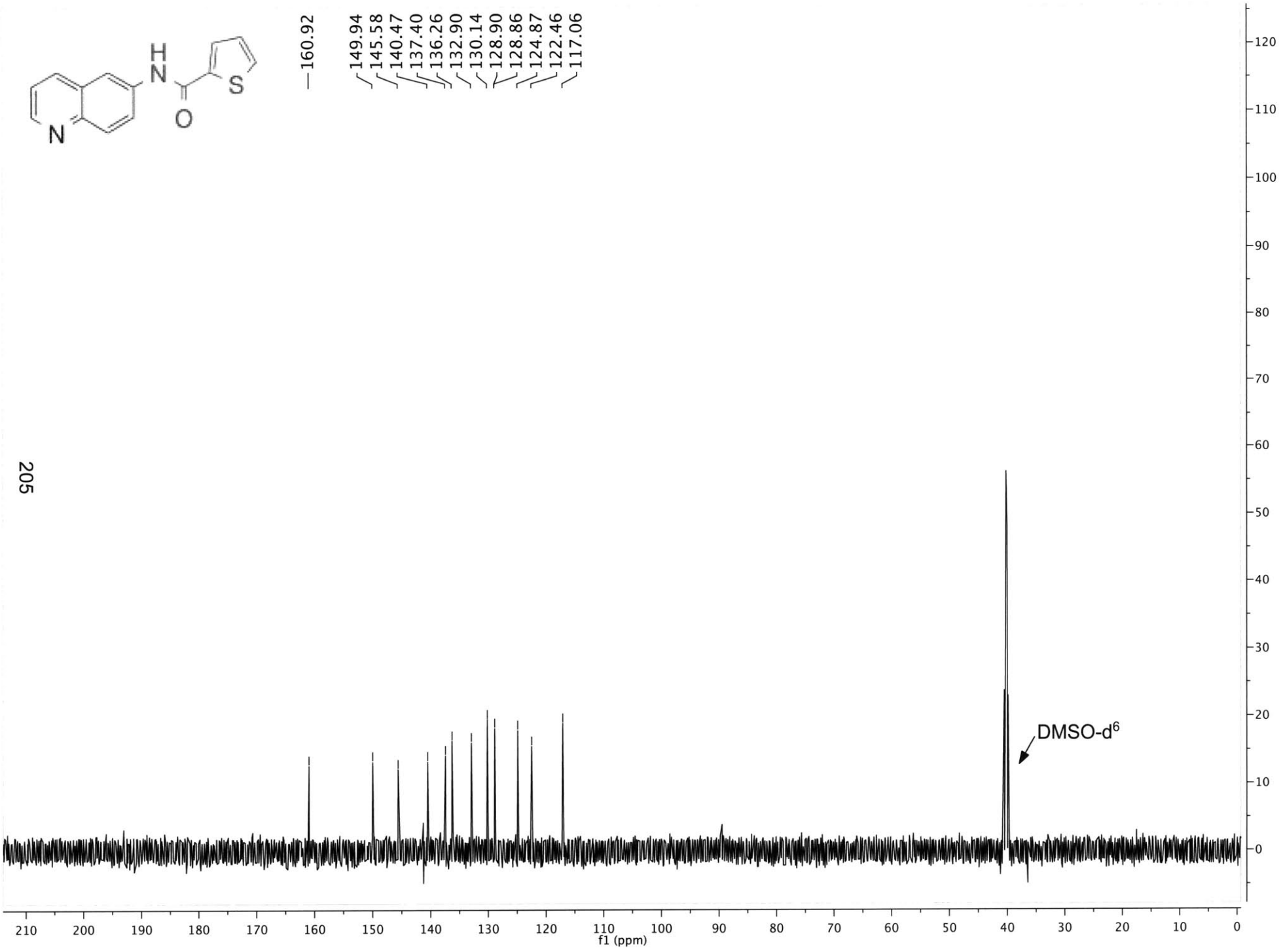

MeO
H
N
Ph
O
MeO
200
DMSO-d6
1.06
2.00
1.84
2.03
1.04
1.00
3.09
3.12
f1 (ppm)

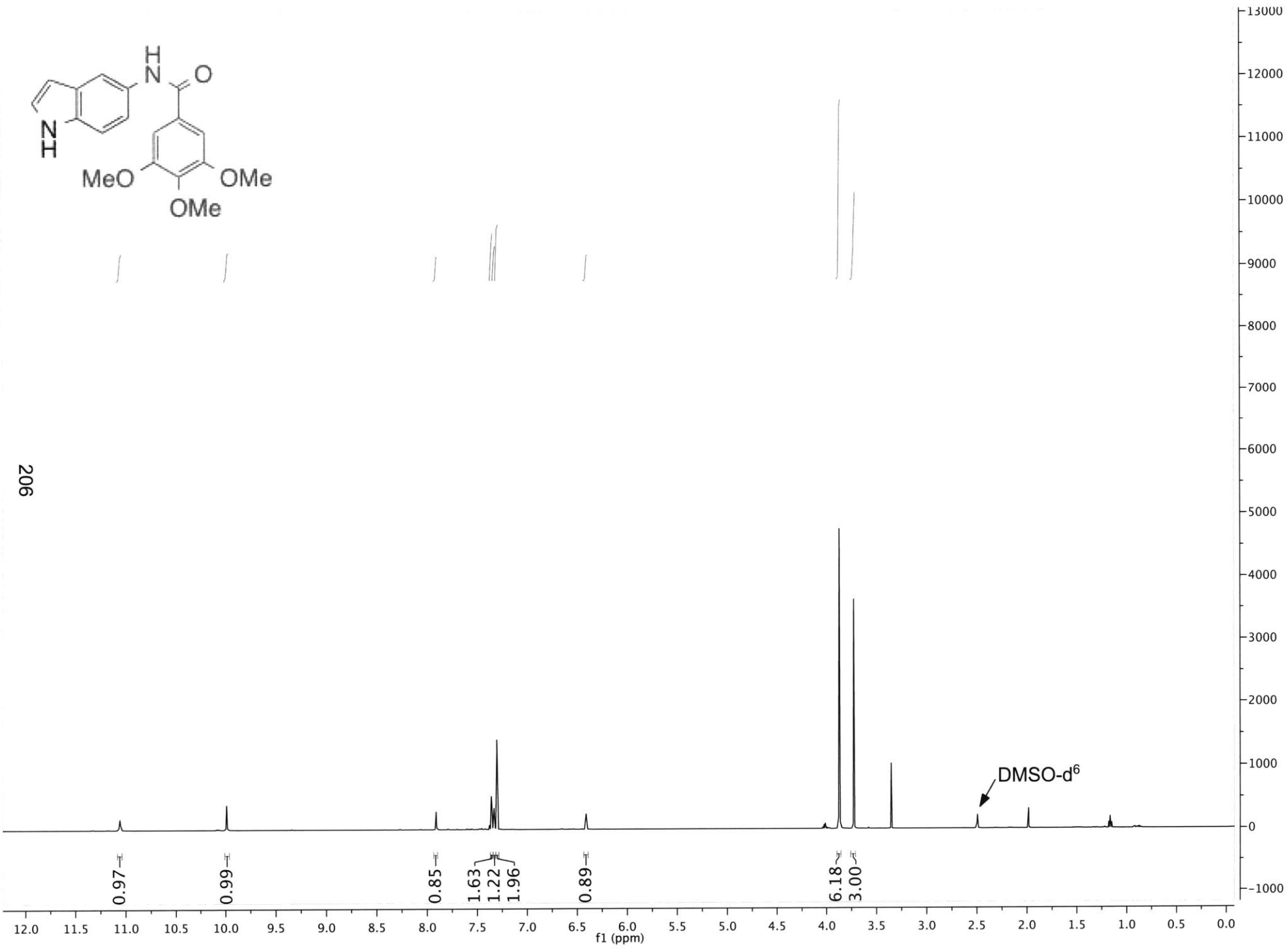

MeO
H
N
Ph
O
MeO
166.05
154.01
146.29
135.58
132.87
129.70
128.79
128.58
113.16
111.14
110.60
57.39
56.56
201
DMSO-d6
f1 (ppm)

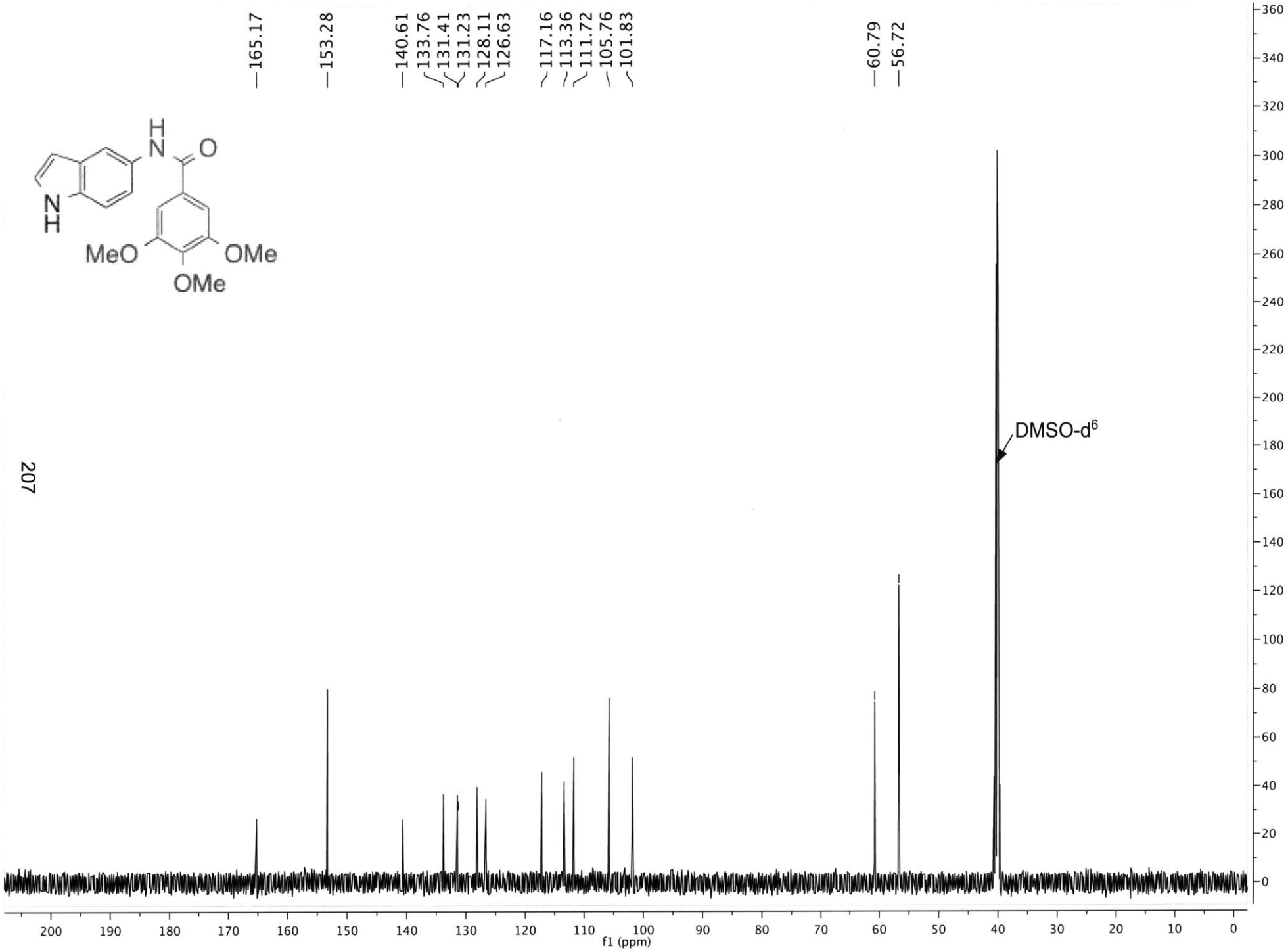

OH
HN
O
N
202
DMSO-d6
1.04
0.89
1.00
2.07
0.99
1.01
2.09
1.00
2.08
2.14
2.05
f1 (ppm)

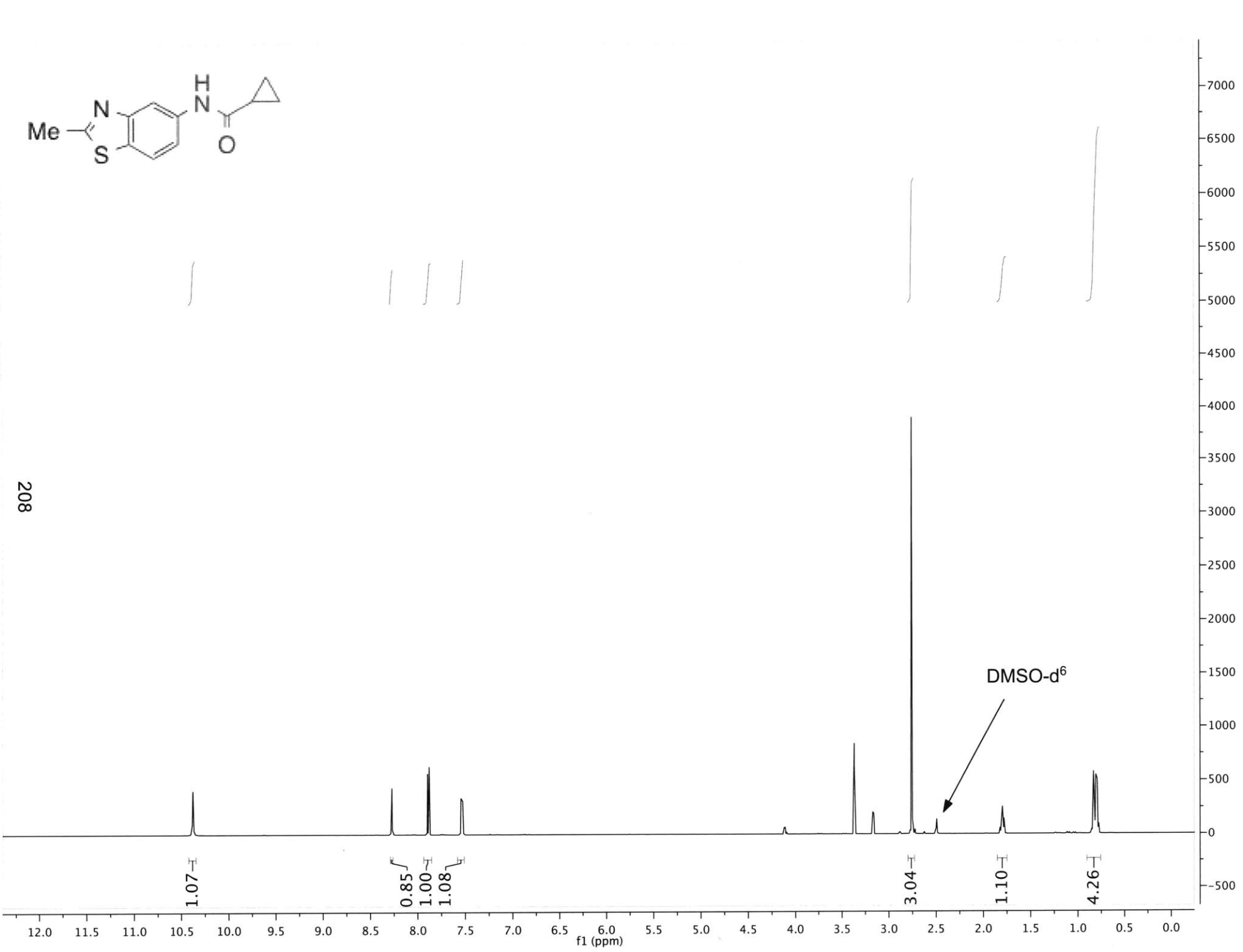

169.08
157.28
150.12
138.27
137.70
135.49
130.21
125.11
123.05
120.17
46.99
39.65
OH
H
N
N
O
203
DMSO-d6
f1 (ppm)


H
N
S
O
N
204
DMSO-d6
1.08
1.00
1.06
1.07
1.06
2.14
0.94
1.07
1.04
f1 (ppm)


160.92
149.94
145.58
140.47
137.40
136.26
132.90
130.14
128.90
128.86
124.87
122.46
117.06
H
N
O
S
N
205
DMSO-d6
f1 (ppm)


206
DMSO-d6
0.97
0.99
0.85
1.63
1.22
1.96
0.89
6.18
3.00
f1 (ppm)


165.17
153.28
140.61
133.76
131.41
131.23
128.11
126.63
117.16
113.36
111.72
105.76
101.83
60.79
56.72
HN
O
NH
MeO
OMe
OMe
DMSO-d6
207
f1 (ppm)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N
S
H
N
O
208
DMSO-d6
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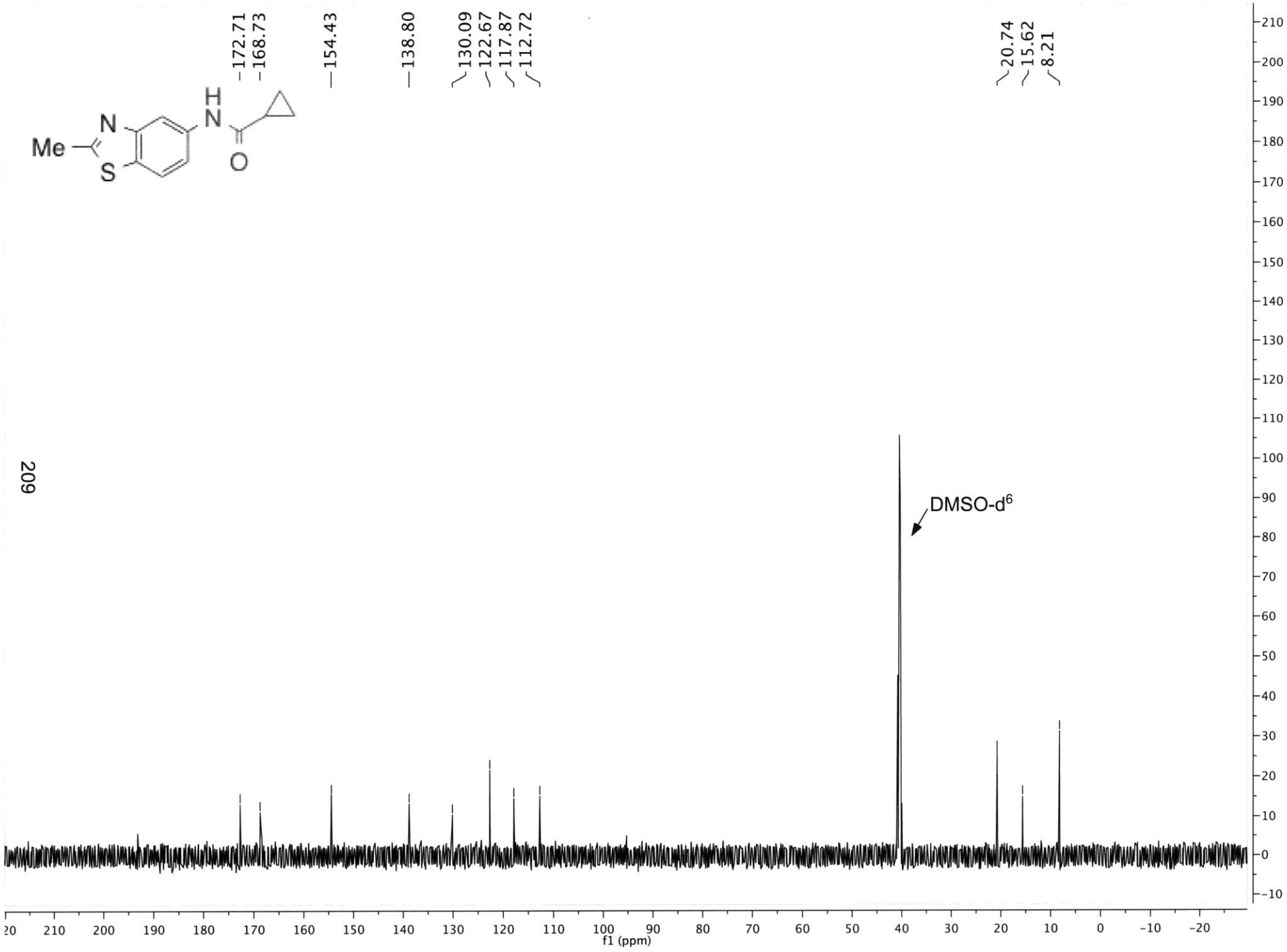
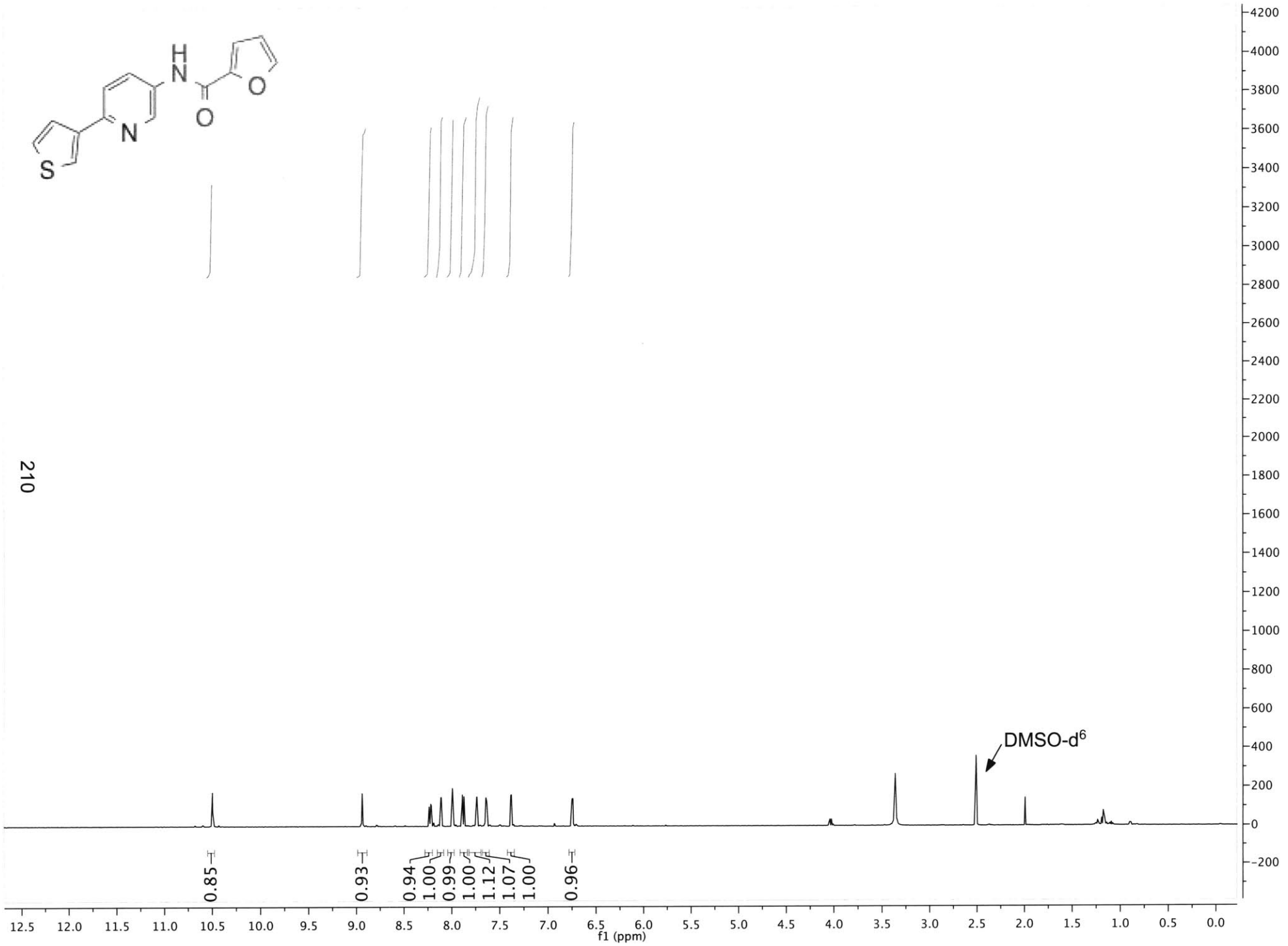
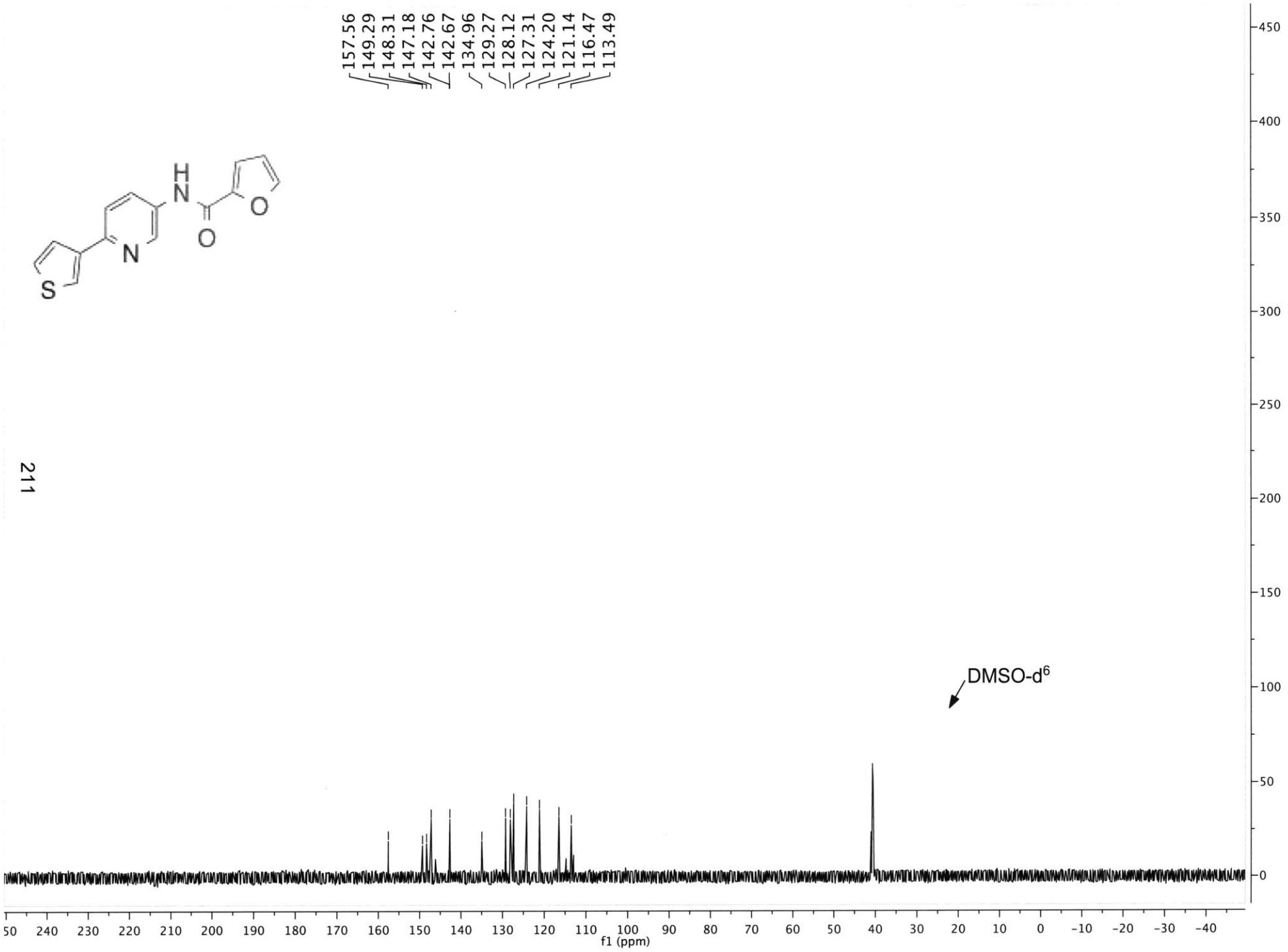
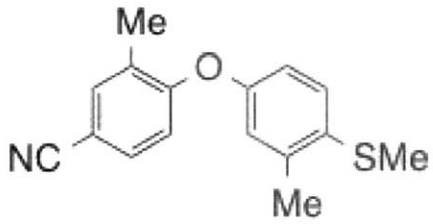
0.85
1.00
1.08
3.04
1.10
4.26
f1 (ppm)


172.71
168.73
154.43
138.80
130.09
122.67
117.87
112.72
20.74
15.62
8.21
Me
N
S
H
N
O
209
DMSO-d6
f1 (ppm)

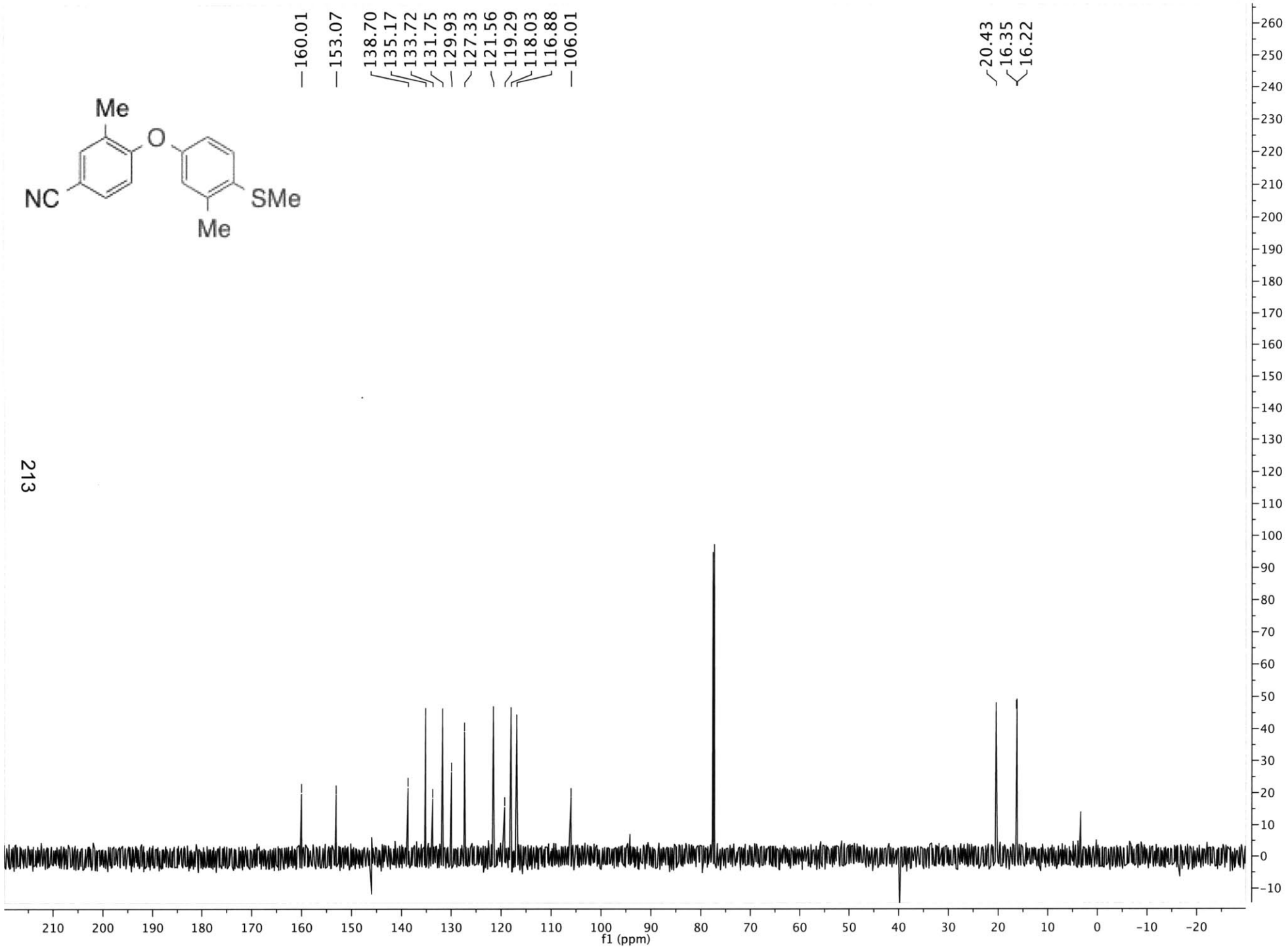

HN
O
O
N
S
210
DMSO-d6
0.85
0.93
0.94
1.00
0.99
1.00
1.12
1.07
1.00
0.96
f1 (ppm)


157.56
149.29
148.31
147.18
142.76
142.67
134.96
129.27
128.12
127.31
124.20
121.14
116.47
113.49
HN
O
O
N
S
DMSO-d6
f1 (ppm)

211



212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153.07
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133.72
131.75
129.93
127.33
121.56
119.29
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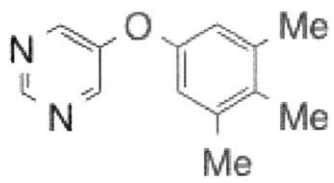
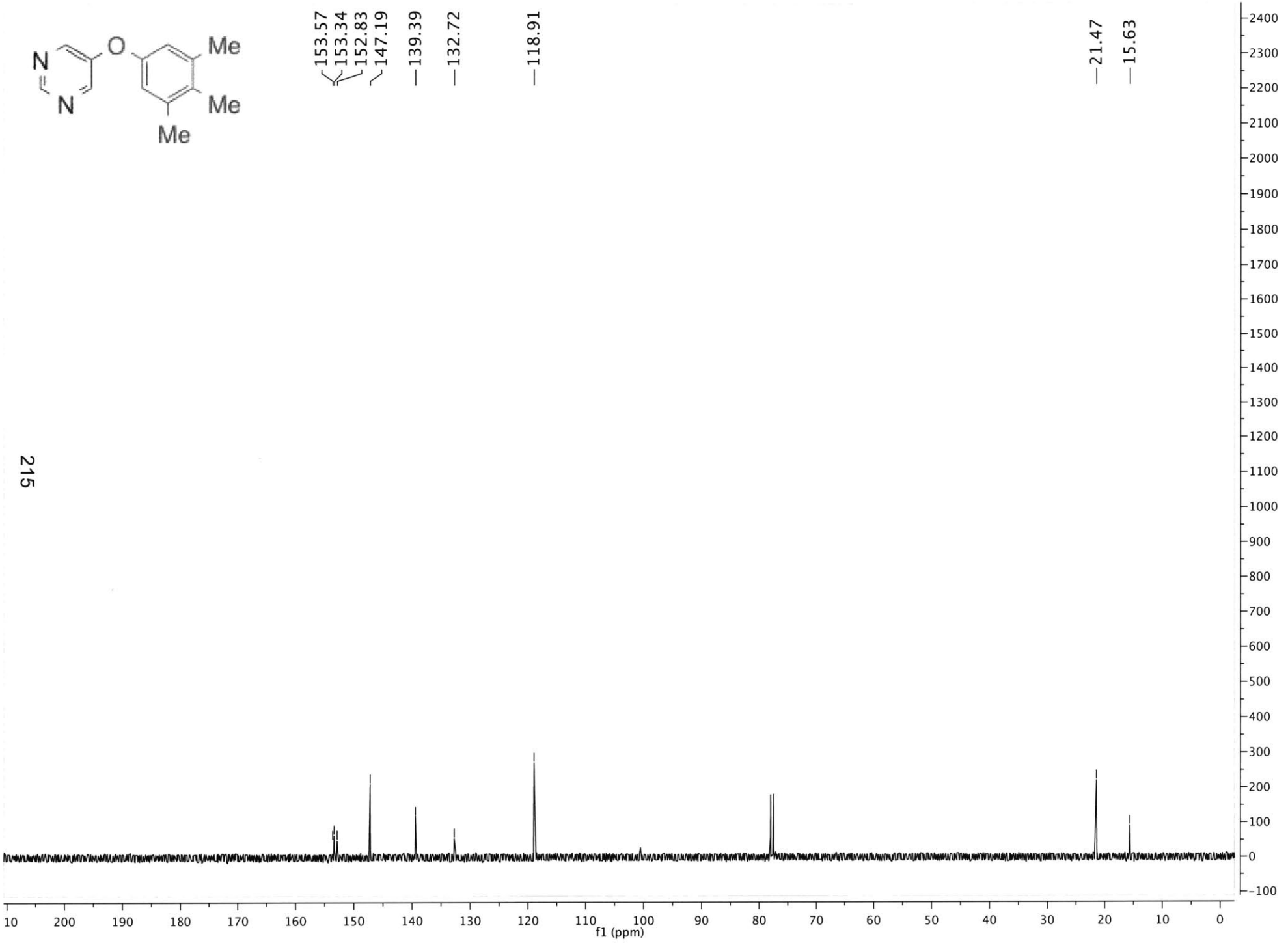
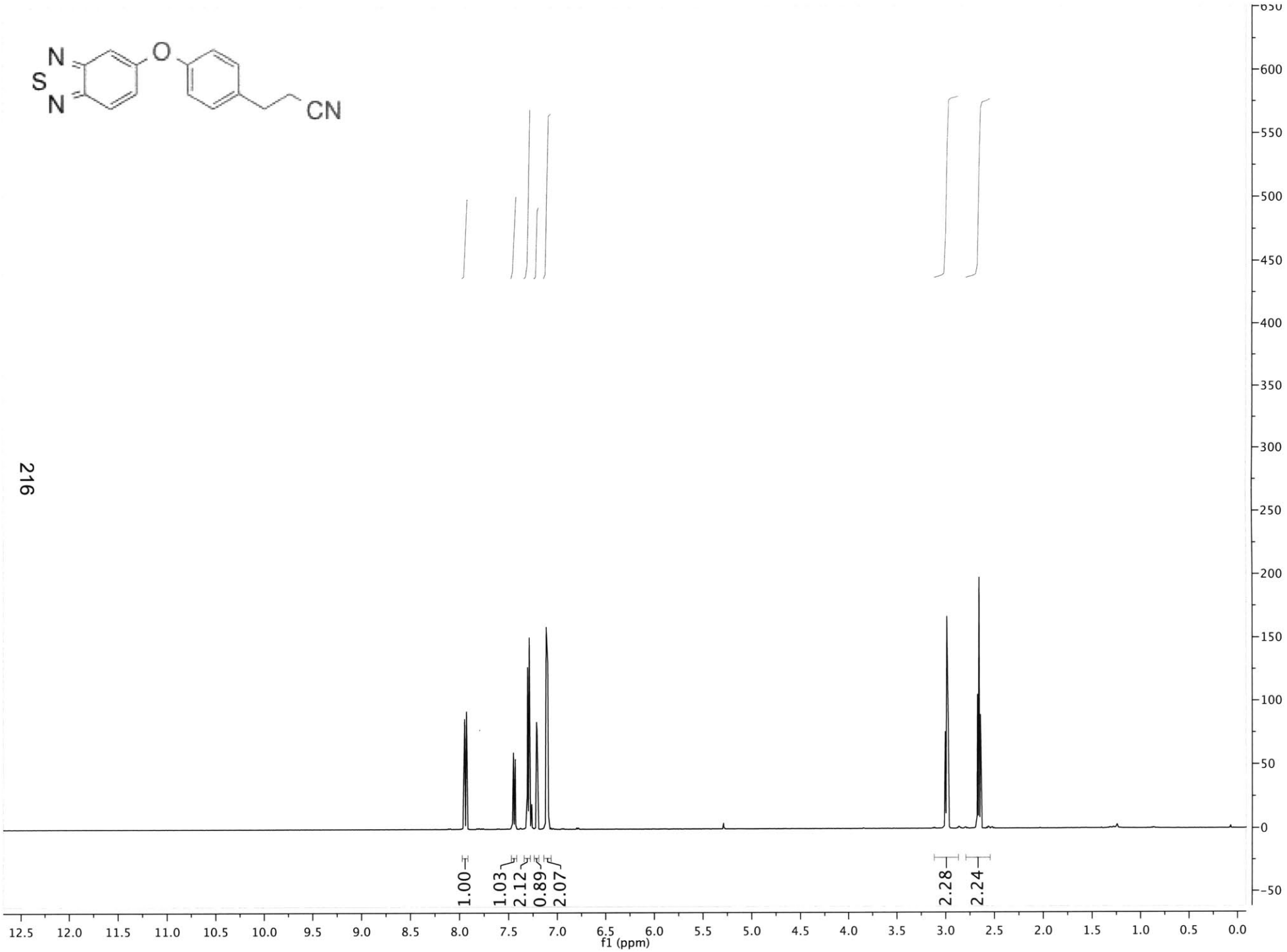
106.01
20.43
16.35
16.22
Me
O
NC
SMe
Me
213
f1 (ppm)



214


N
O
Me
N
Me
Me
153.57
153.34
152.83
147.19
139.39
132.72
118.91
21.47
15.63
215
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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S
N
O
CN
216
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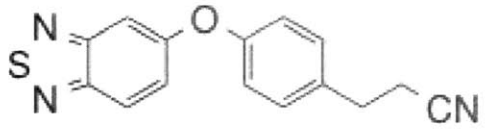
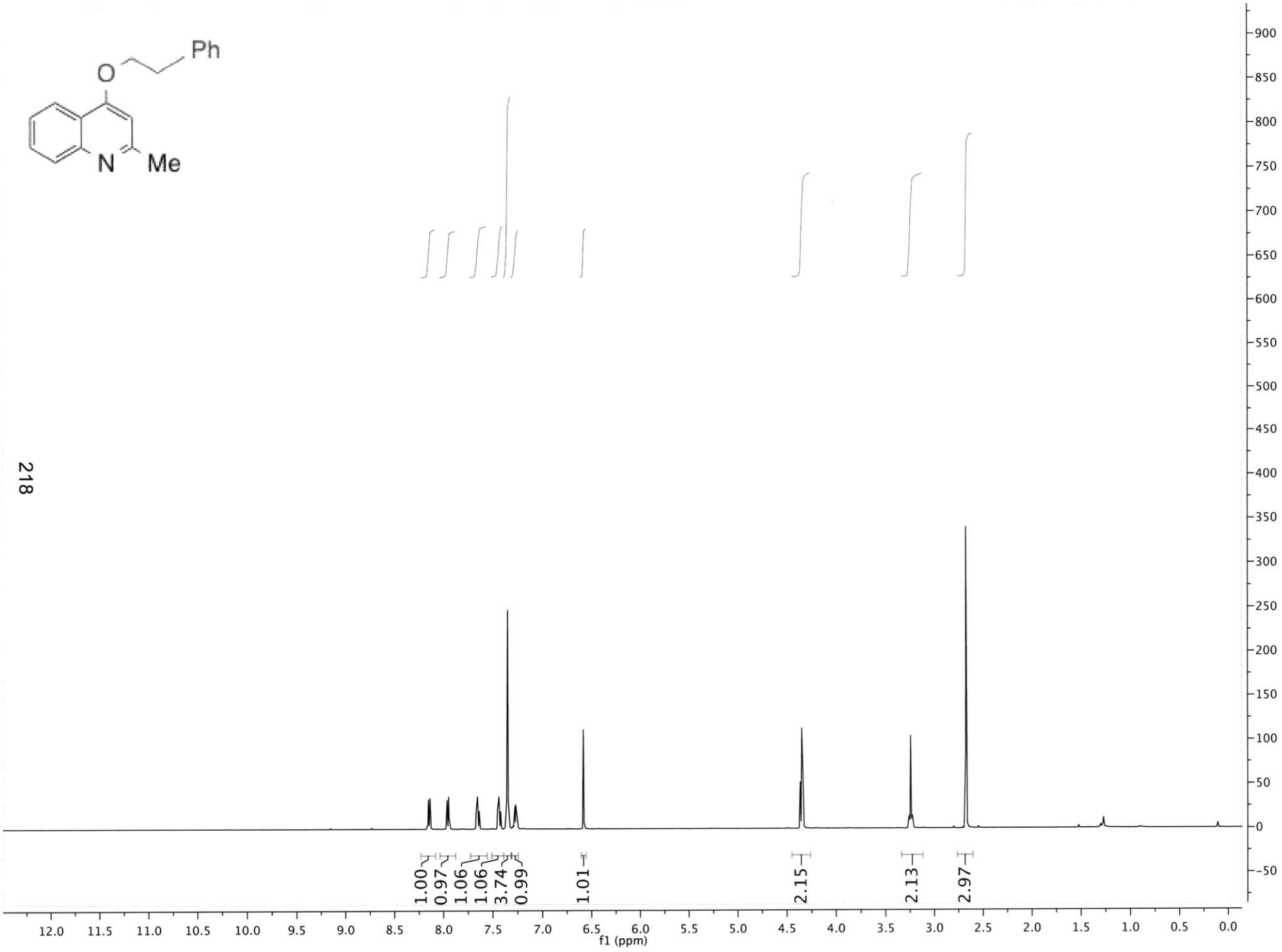
2.12
0.89
2.07
2.28
2.24
f1 (ppm)



160.41
156.24
155.08
152.41
135.45
130.82
125.55
122.84
121.48
119.70
105.25
31.65
20.23

217


Ph
O
N
Me
218
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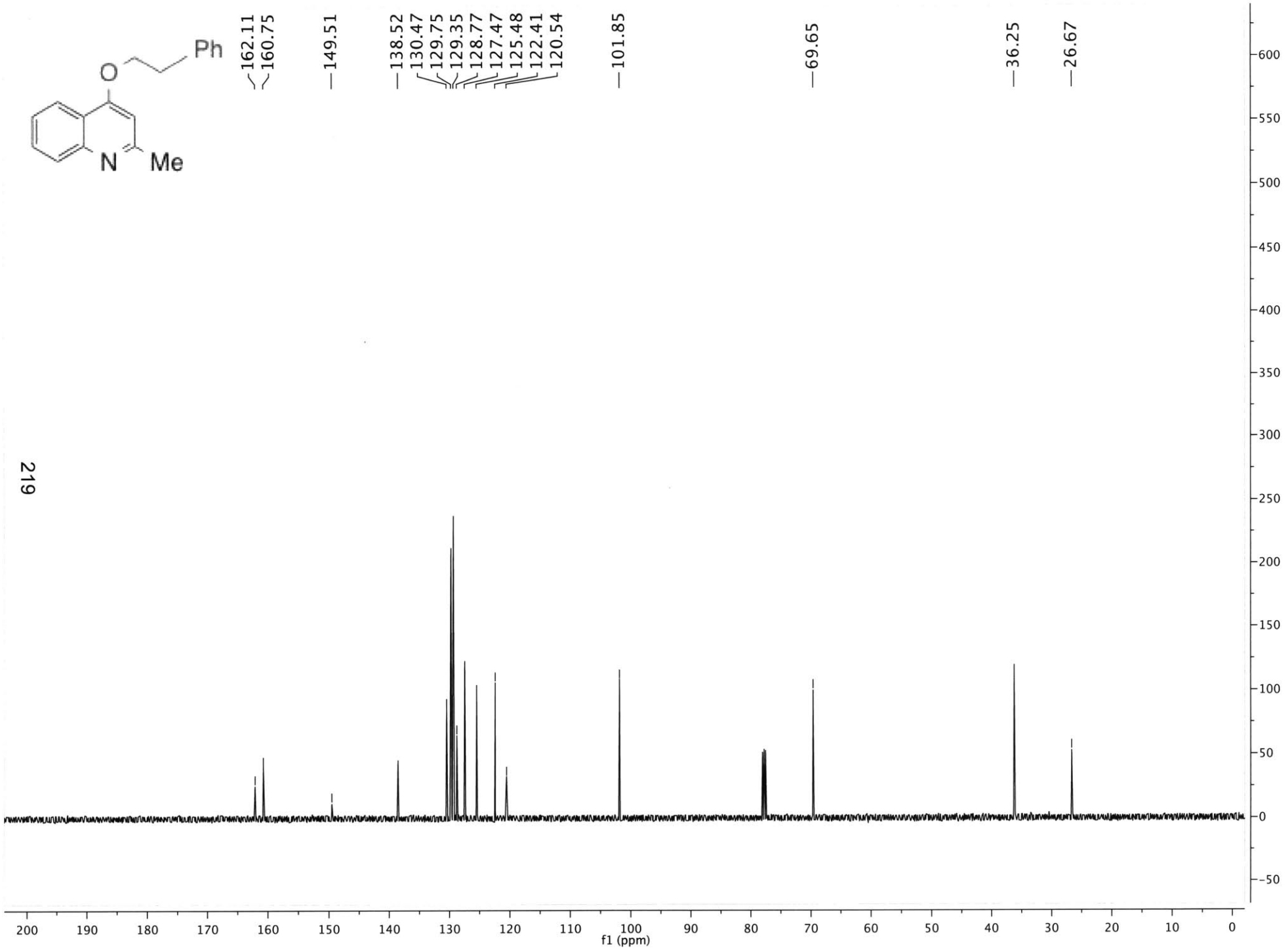
0.97
1.06
1.06
3.74
0.99
1.01
2.15
2.13
2.97
f1 (ppm)


Ph
O
N
Me
162.11
160.75
149.51
138.52
130.47
129.75
129.35
128.77
127.47
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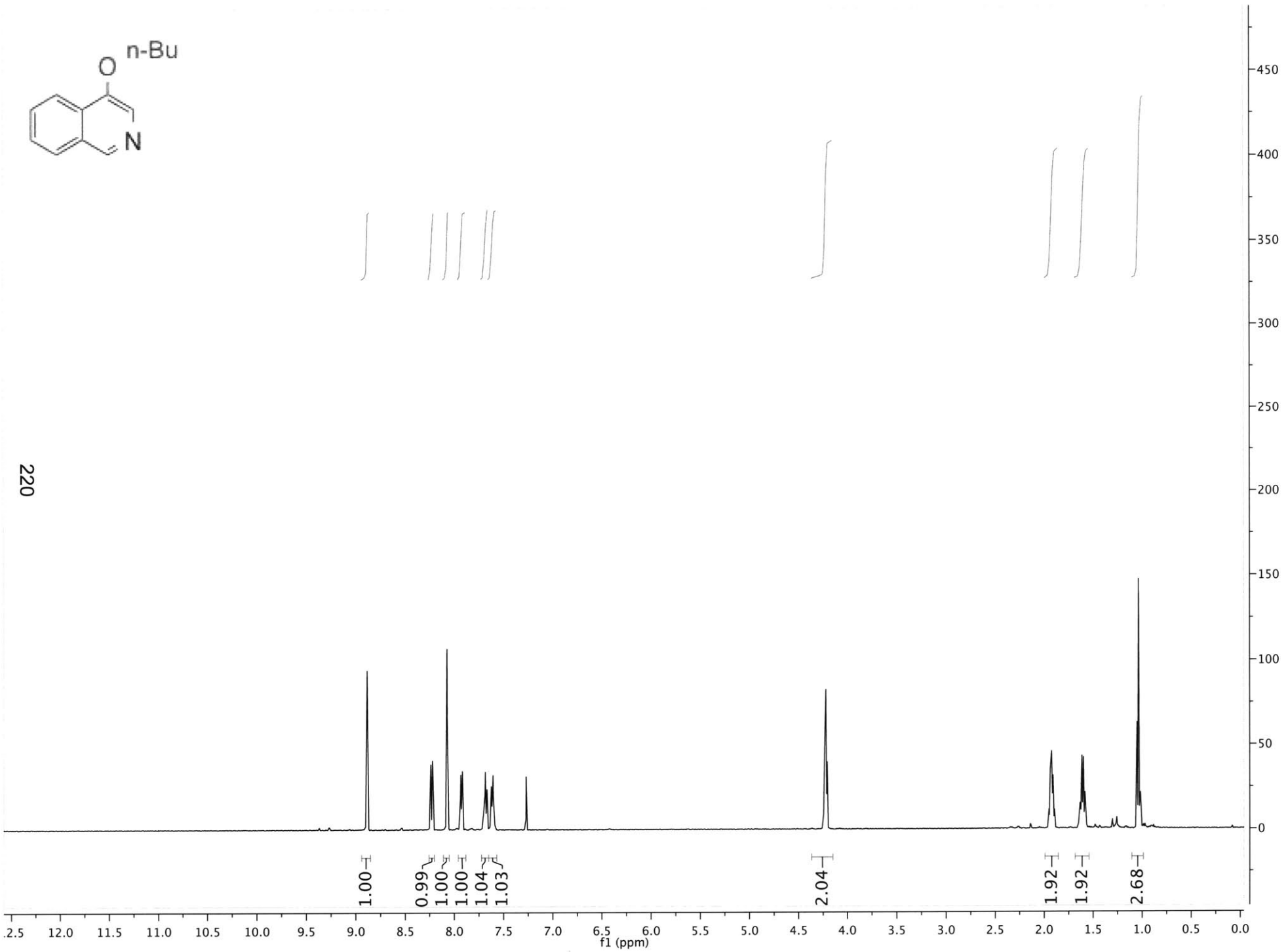
101.85
69.65
36.25
26.67
219
f1 (ppm)


n-Bu
O
N
220
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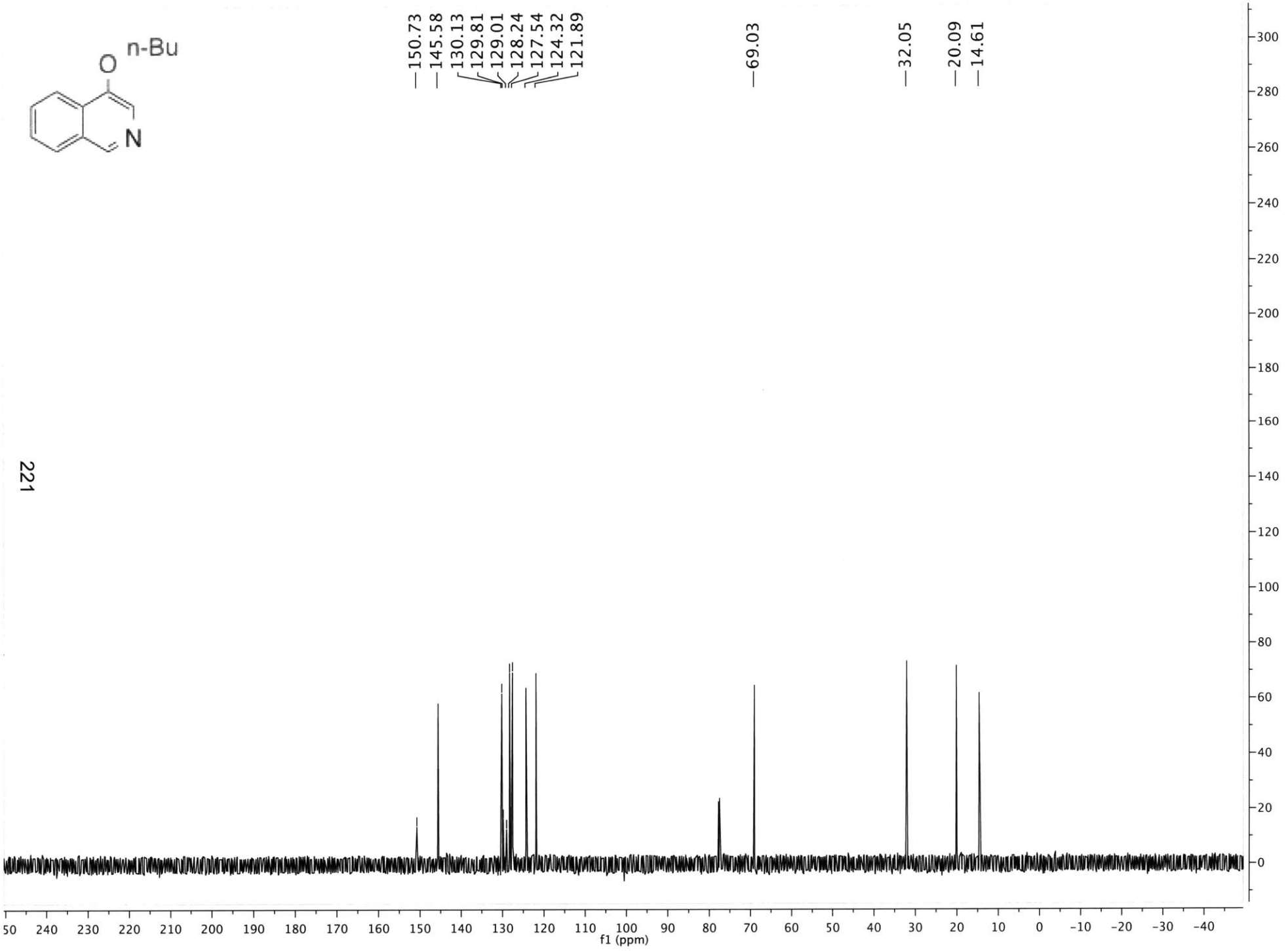
0.99
1.00
1.00
1.04
1.03
2.04
1.92
1.92
2.68
f1 (ppm)


n-Bu
O
N
150.73
145.58
130.13
129.81
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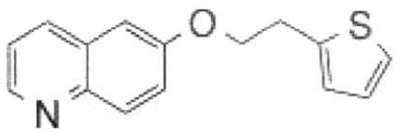
128.24
127.54
124.32
121.89
69.03
32.05
20.09
14.61
221
f1 (ppm)



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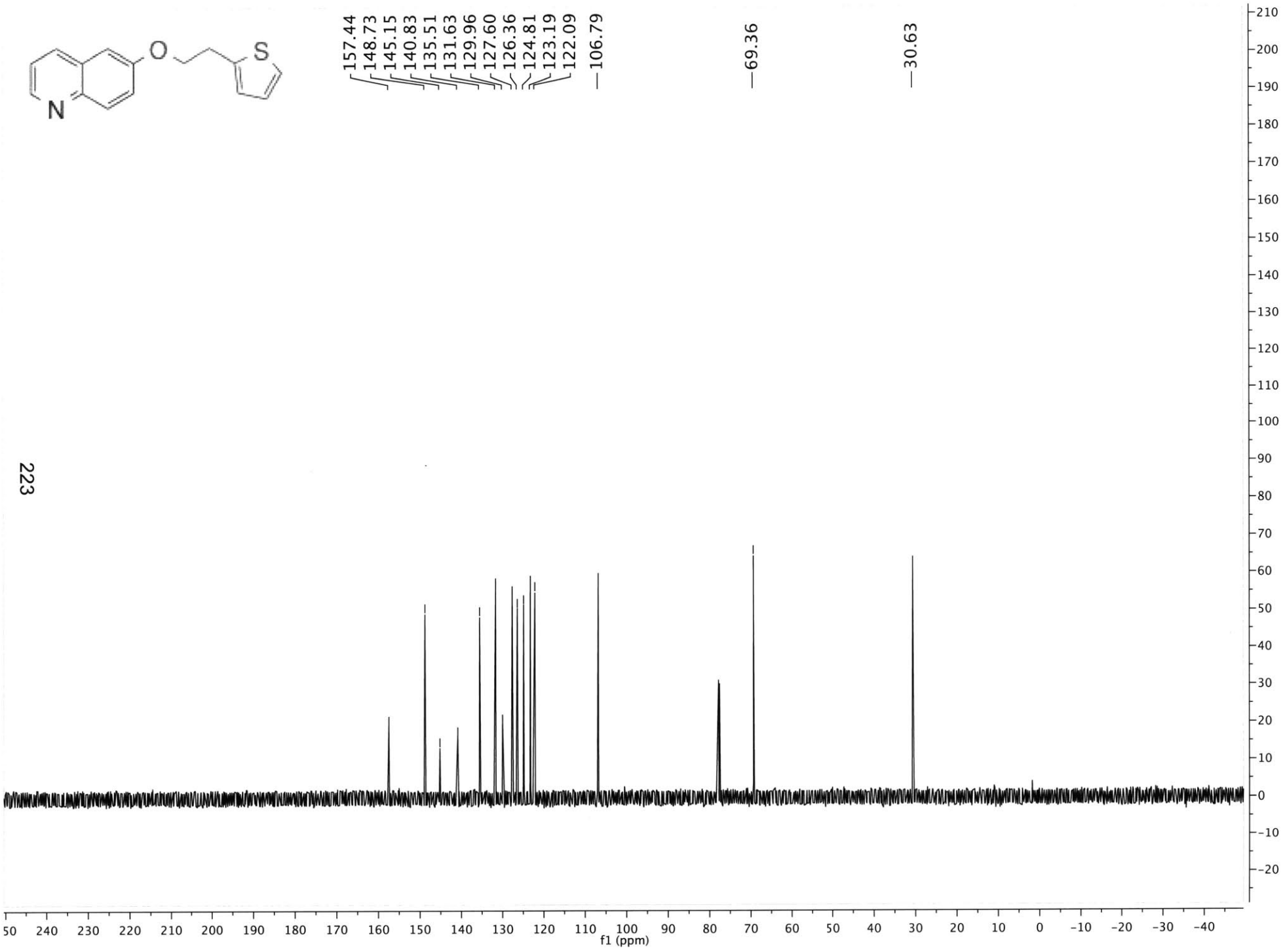
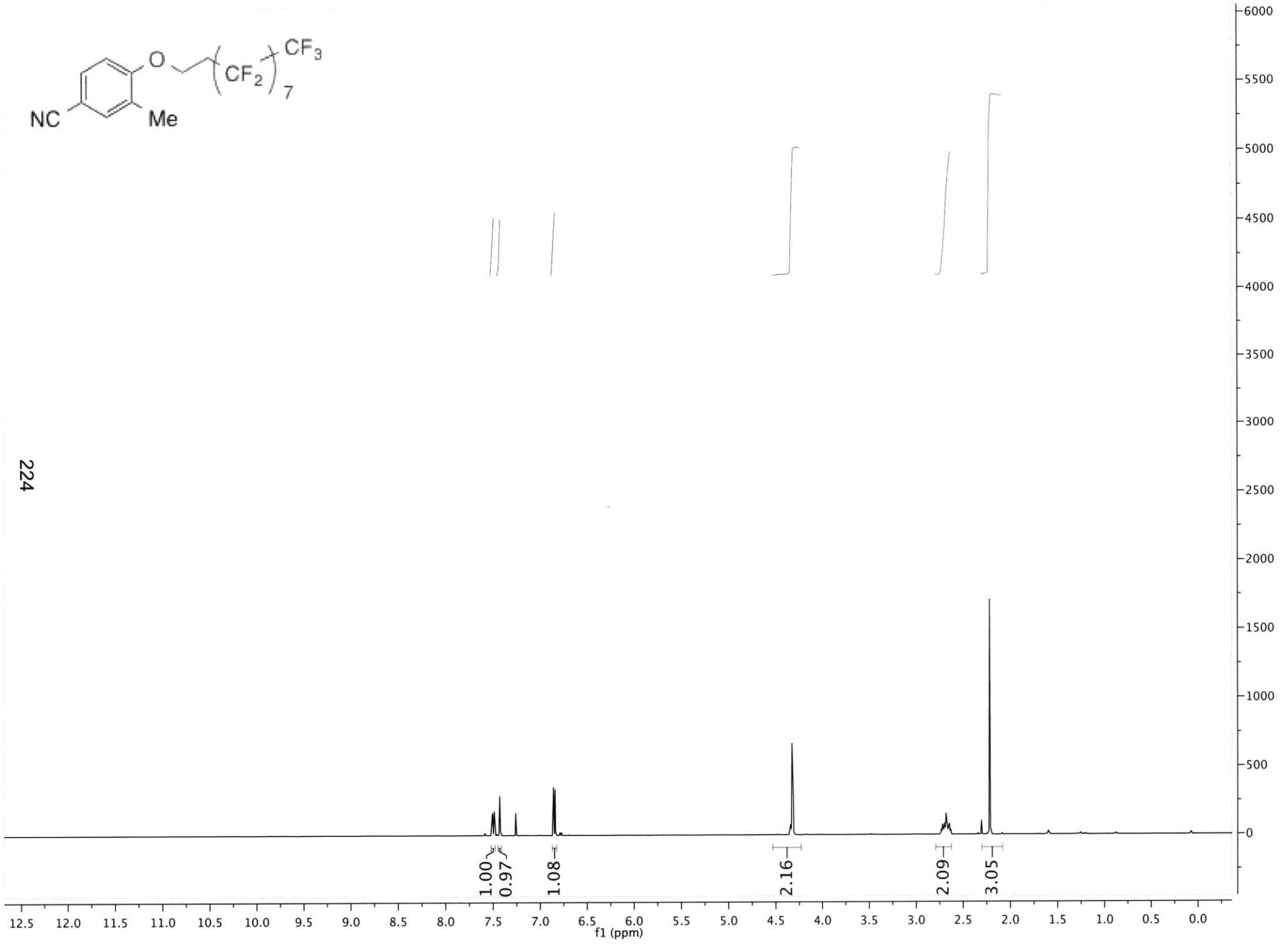
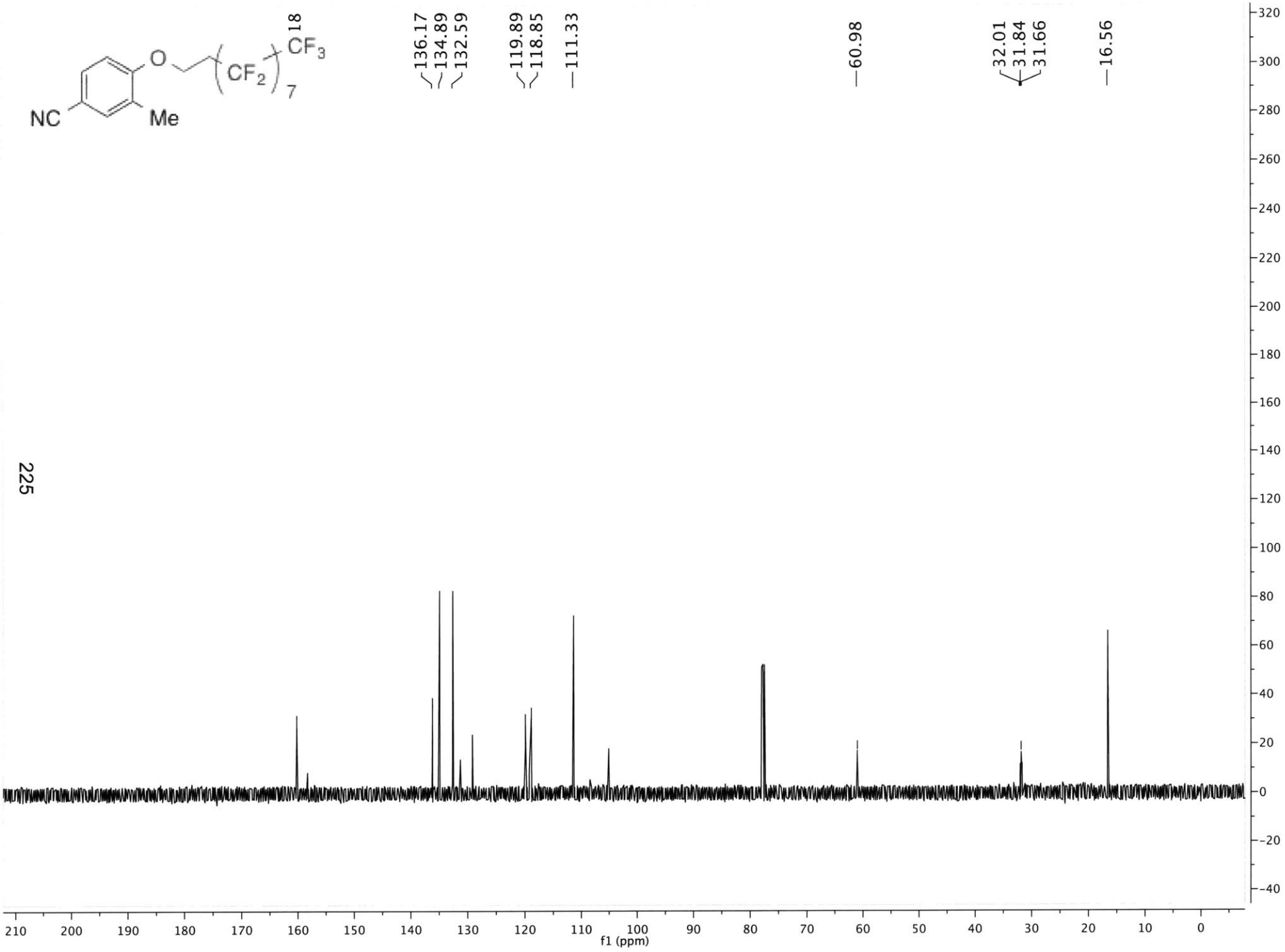
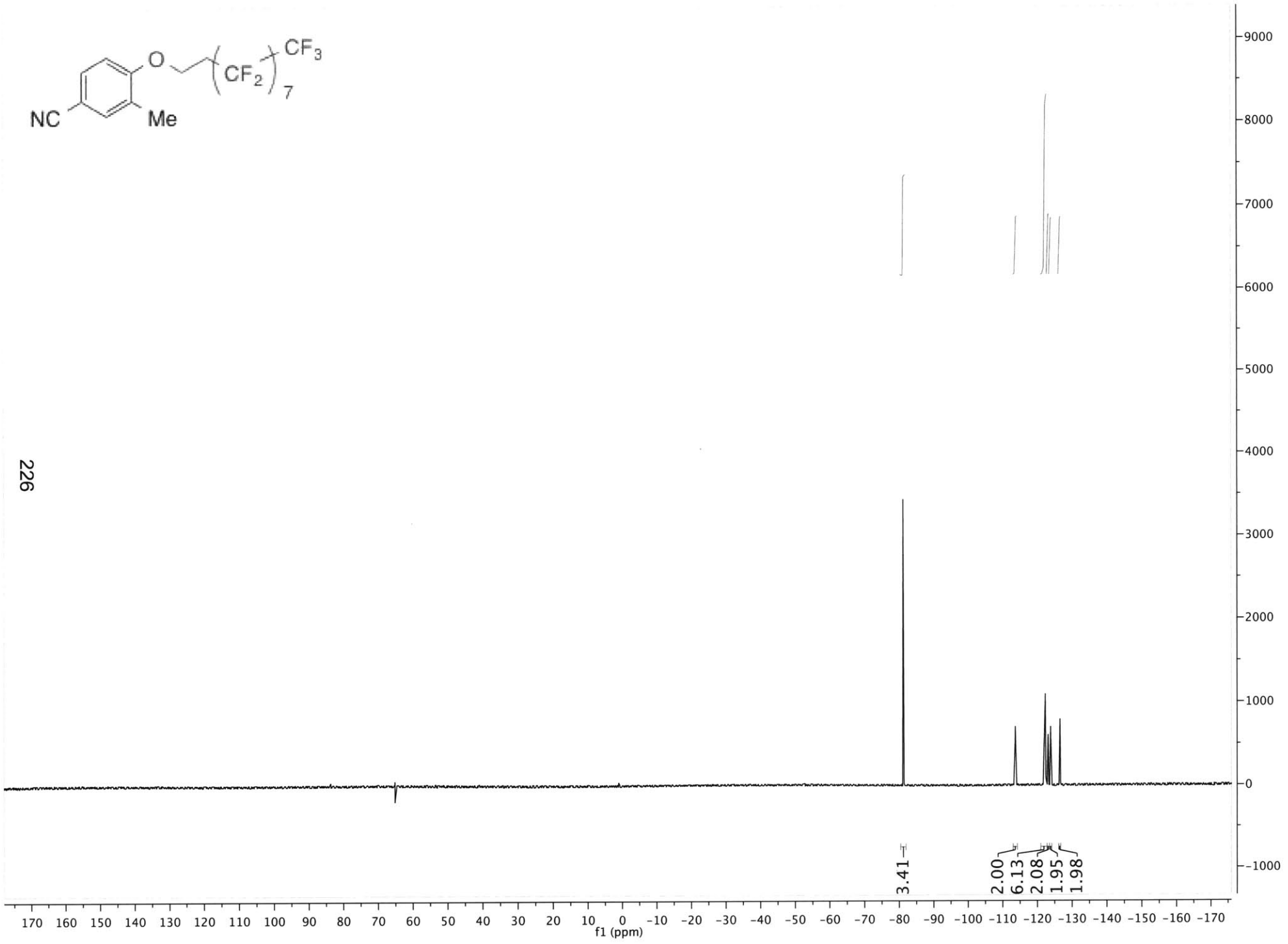
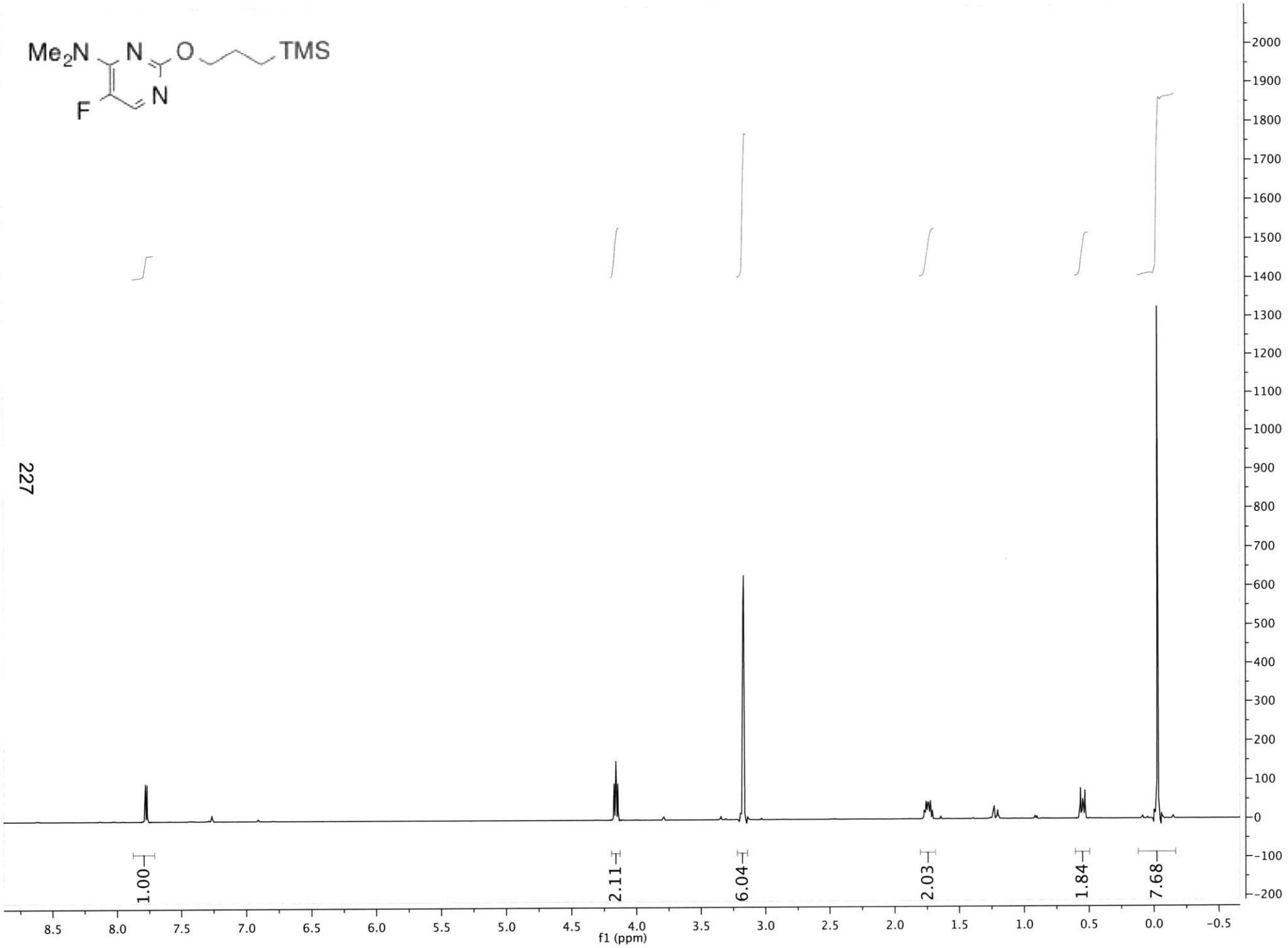
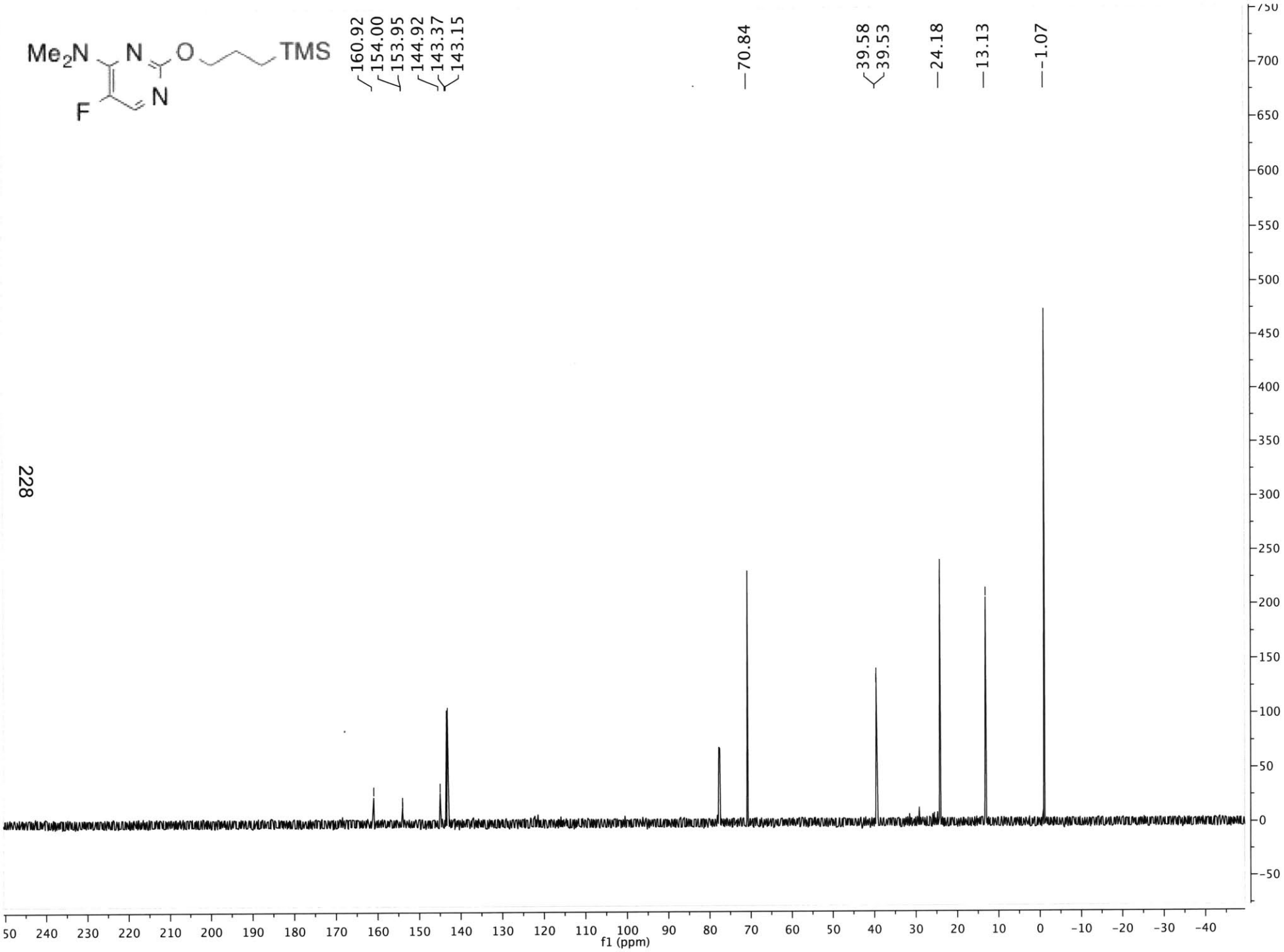

O
S
N
157.44
148.73
145.15
140.83
135.51
131.63
129.96
127.60
126.36
124.81
123.19
122.09
106.79
69.36
30.63
223
f1 (ppm)


NC
Me
O
CF2
7
CF3
224
1.00
0.97
1.08
2.16
2.09
3.05
f1 (ppm)


NC
Me
O
CF2
7
CF3
18
136.17
134.89
132.59
119.89
118.85
111.33
60.98
32.01
31.84
31.66
16.56
225
f1 (ppm)


NC
Me
O
CF2
7
CF3
226
3.41
2.00
6.13
2.08
1.95
1.98
f1 (ppm)


Me2N
N
O
TMS
F
N
227
1.00
2.11
6.04
2.03
1.84
7.68
f1 (ppm)


Me2N
N
O
TMS
F
N
160.92
154.00
153.95
144.92
143.37
143.15
70.84
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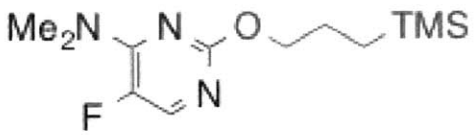
39.53
24.18
13.13
-1.07
228
f1 (ppm)


Me2N
N
O
TMS
N
F

-159.33
4400
4200
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

2.5: References

1. Strotman, N. A.; Chobanian, H. R.; Guo, Y.; He, J.; Wilson, J. E. *Org. Lett.* **2010**, *12*, 3578.
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4. Ueda, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 10364.
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11. Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505.
12. Ueda, S.; Su, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *132*, 700.
13. Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.
14. Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073.
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16. Palladacyclic triflate precatalyst analogues have also been prepared. They exhibit similar reactivity but silver triflate is necessary for their preparation, making them inferior. See the Supporting Information for details.
17. The formation of precatalysts **2a-e** only went to completion in chlorinated solvents (CH_2Cl_2 and $CHCl_3$).
18. Maligres, P. E.; Li, J.; Krska, S. W.; Schreier, J,. D.; Raheem, I, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 9071. This report notes that in difficult couplings, such as the formation of **5a**, **L2**/$Pd_2(dba)_3$ was only effective when the palladium and ligand were premixed and molecular sieves were used. The use of **2b** circumvents these issues and provides the desired product in comparable yields without molecular sieves or premixing.
19. Hoshiya, N.; Buchwald, S. L. *Adv. Syn. Catal.* **2012**, *354*, 2031–2037.
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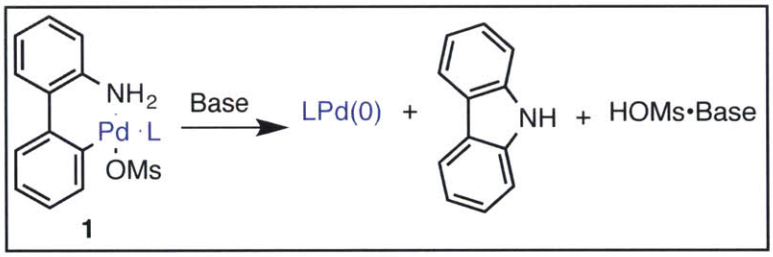
Chapter 3: *N*-Substituted 2-Aminobiphenylpalladium Methanesulfonate Precatalysts and their Use in C-C and C-N Cross-Couplings

3.1: Introduction

In Chapters 1 and 2 we described the development of palladium precatalysts based on a ligated 2-aminobiphenylpalladium methanesulfonate palladacycle (**1**, Scheme 1).[1,2] Precatalyst **1** activates through the deprotonation of the palladium-bound amine, to give a Pd-amido complex which then reductively eliminates to form carbazole, a methanesulfonate salt, and LPd(0). Precatalysts of type **1** can accommodate a variety of ligands and are applicable to numerous palladium-catalyzed transformations.[3-6]

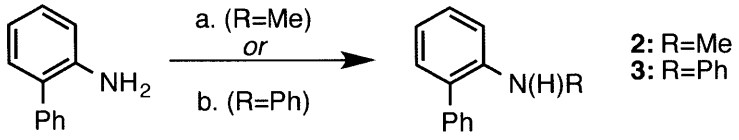
Scheme 1. Palladium methanesulfonate precatalysts and their generic mode of activation.



Despite the advantages of **1**, a few drawbacks limit their utility in some applications. These include: 1) The carbazole byproduct generated through the activation of **1** can be *N*-arylated, consuming valuable starting materials or potentially complicating workup/purification of the desired product[2] and 2) There is some concern regarding the presence of trace amounts of residual NH_2-aminobiphenyls in pharmaceutical samples due to potential health risks.[7,8] *N*-alkyl and *N*-aryl analogues of **1** would overcome these concerns and provide a useful alternative to **1**.

3.2: Results and Discussion

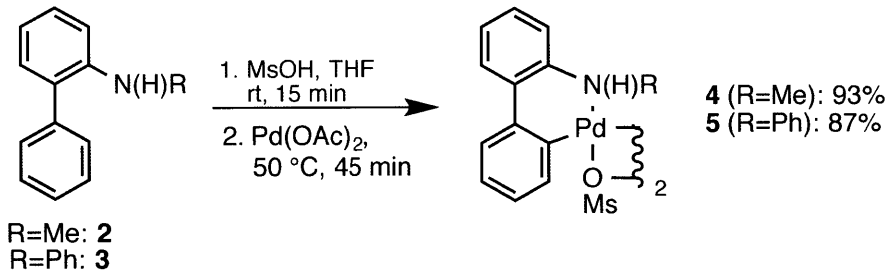
Scheme 2. Preparation of *N*-methyl and *N*-phenyl 2-aminobiphenyl derivatives



[a] i) nBuLi, THF, 0 °C, 30 min ii) MeI, 0 °C – rt, 30 min, quant. conv. [b] 1 mol% **1·L1**, PhCl, NaOtBu, dioxane, 100 °C, 30 min, 99%.

N-substituted 2-aminobiphenyls could be readily prepared on a 30 mmol scale via N-methylation and N-arylation as shown in scheme 2. The unpurified products[9] from these reactions can be directly used to prepare the corresponding palladacycles. Treatment of *N*-methyl-2-aminobiphenyl, **2**, and *N*-phenyl-2-aminobiphenyl, **3**, with methanesulfonic acid followed by heating the resulting salt solution with $Pd(OAc)_2$ provided the dimeric palladacycles **4** and **5**. These procedures were amenable to scale up, providing the desired palladium dimers in excellent yields at a 30 mmol scale (Scheme 3).

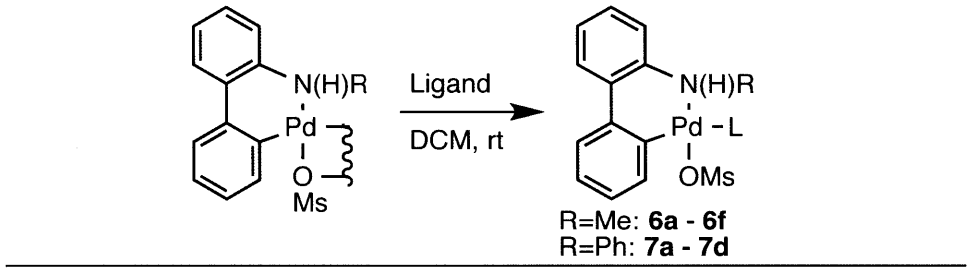
Scheme 3. Preparation of N-substituted μ-OMs palladium dimers



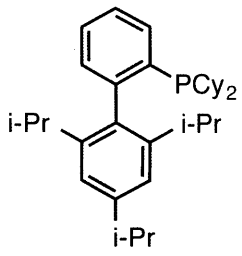
These were subsequently treated with phosphines at room temperature in dichloromethane to provide the N-substituted precatalysts (Table 1). Precatalysts that incorporated a variety of ligands could be prepared as shown in Table 1. In contrast,

however, to what we observed with **1**, we were unable to make precatalysts containing the largest of our ligands: attempts to incorporate *t*BuBrettPhos, RockPhos, and AdBrettPhos were unsuccessful.[10] Additionally, while we could prepare **6f** from (±)-BINAP, we were unable to obtain the corresponding *N*-phenyl analogue, **7f**.[11]

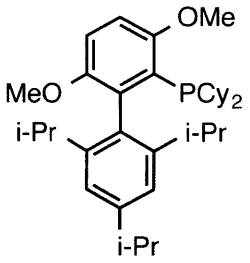
Table 1. Preparation of N-substituted palladium methanesulfonate precatalysts.



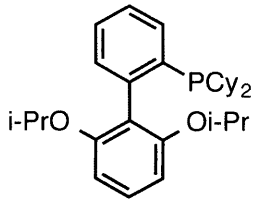
R=Me: **6a - 6f**
R=Ph: **7a - 7d**



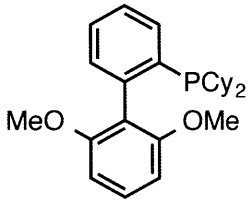
L1
XPhos
6a: 85%
7a: 99%



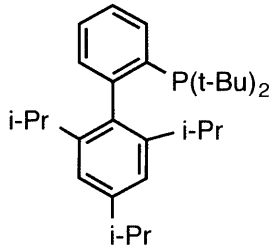
L2
BrettPhos
6b: 94% (10g scale)
7b: 86% (10g scale)



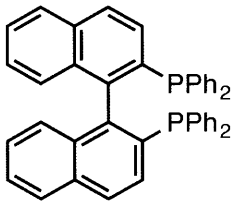
L3
RuPhos
6c: 96%
7c: 95%



L4
SPhos
6d: 86%
7d: 92%



L5
tBuXPhos
6e: 89%



L6
(±) BINAP
6f: 90%

The solid-state structures of **6a** and **7a** were determined by single crystal X-ray crystallography (Figure 1). Both possess a tetracoordinated Pd(II) center with a slightly

distorted square planar geometry. The phosphine is bound to the palladium center *cis* to the Pd-C bond. Additionally the methanesulfonate anion is directly bound to the palladium center. This is similar to what was previously observed for **1** (L=XPhos).

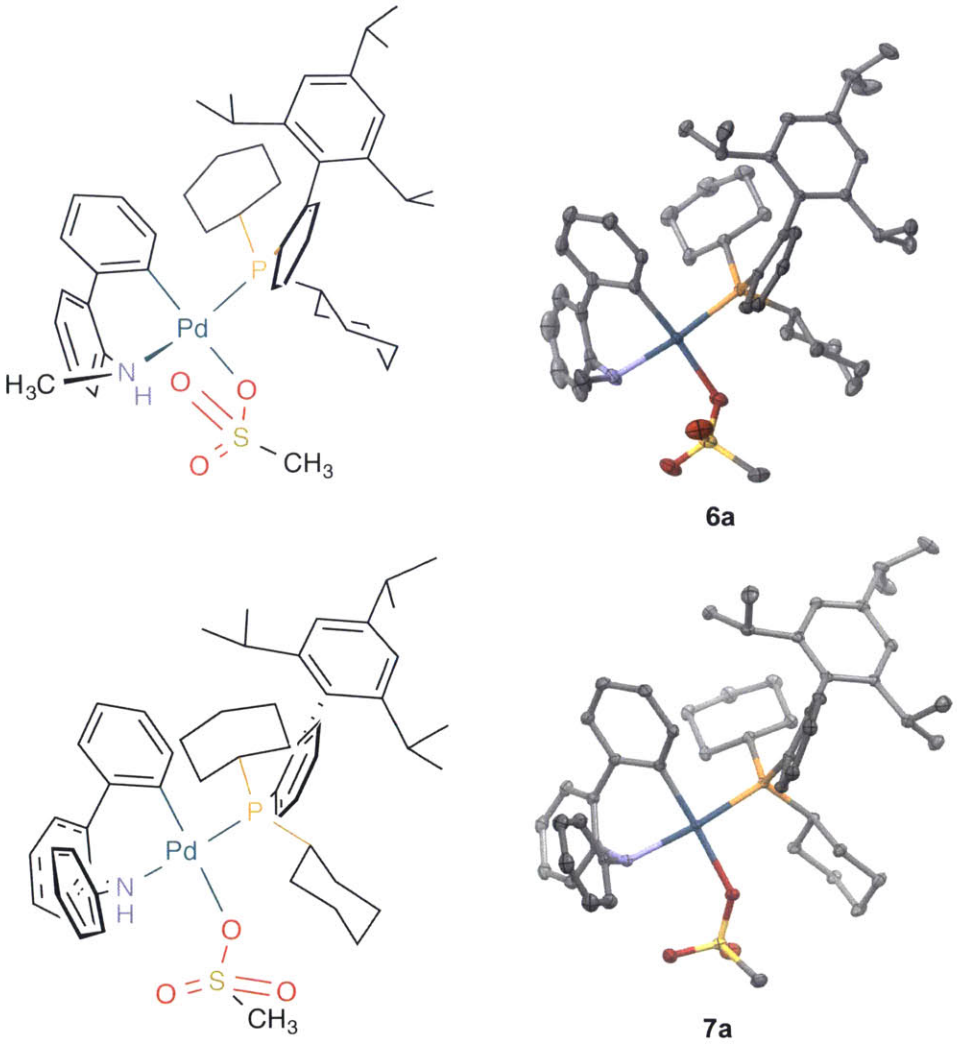
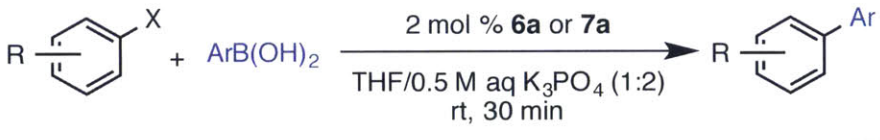


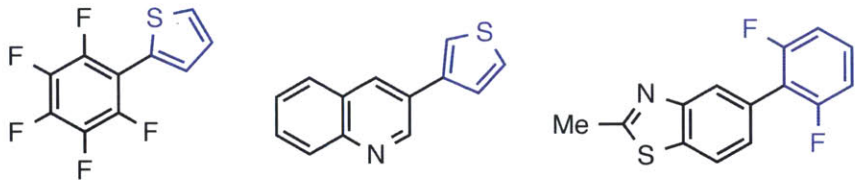
Figure 1. Crystallographically-determined X-ray structures of **6a** and **7a** (thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted for clarity).

To evaluate the reactivity of precatalysts **6** and **7** we first examined their efficacy in promoting the Suzuki-Miyaura coupling of aryl halides with arylboronic acids that are

prone to rapid protodeboronation under standard cross-coupling reaction conditions. As previously described, the rapid generation of a highly active LPd(0) is essential for success of these reactions.[12] These reactions allowed us to test whether **6** and **7** activate rapidly at room temperature. As shown in Table 2, both **6a** and **7a** were highly effective precatalysts in the coupling of (hetero)aryl halides and unstable boronic acids, providing the arylated products in uniformly good yields.

Table 2. Suzuki-Miyaura coupling of unstable boronic acids with precatalysts **6a** and **7a**[a]





6a: 87%
7a: 95%
(X=Cl)

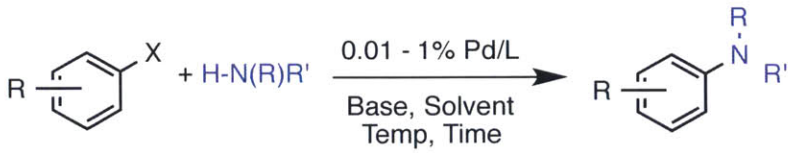
6a: 96%
7a: 99%
(X=Br)

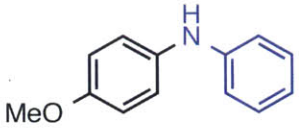
6a: 95%
7a: 99%
(X=Cl)

[a] General Conditions: ArX (1 mmol), Ar'B(OH)$_2$ (1.5 mmol), **6a** or **7a** (2 mol %), 0.5 M $K_3PO_{4(aq)}$ (4 mL), THF (2 mL), rt, 30 min, average of two isolated yields.

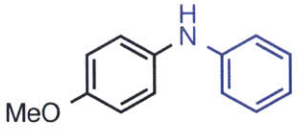
We also evaluated precatalysts of type **6** and **7** in C-N cross-coupling reactions. They were found to be effective in the arylation of primary amines, secondary amines, as well as primary amides (Table 3). The precatalyst was able to be employed at low catalyst loadings (0.01 mol %) for the arylation of aniline with 4-chloro and 4-iodoanisole.

Table 3. *N*-arylation of amines and amides with precatalysts **6** and **7**.





6b: 94%[a]
7b: 97%[a]
(5 min, X=I)
0.01 mol% Pd



6b: 96%[b]
7b: 90%[b]
(24 h, X=Cl)
0.01 mol% Pd

6c: 88%[c]
7c: 85%[c]
(24 h, X=Cl)
1 mol% Pd

[a] Aryl iodide (1 mmol), aniline (1.4 mmol), NaOtBu (1.4 mmol), **6b** or **7b** (10 μL, 0.01 M in THF), toluene (1 mL), 110 °C, 5 min. [b] Aryl chloride (1 mmol), aniline (1.2 mmol), NaOtBu (1.2 mmol), **6b** or **7b** (10 μL, 0.01 M in THF), dioxane (1 mL), 110 °C, 24 h. [c] Aryl chloride (1 mmol), aniline (1.2 mmol), NaOtBu (1.2 mmol), **6c** or **7c** (1 mol%), toluene (1 mL), 110 °C, 24 h.

3.3: Conclusions

In conclusion, we have developed a series of precatalysts based on the *N*-methyl and *N*-phenyl 2-aminobiphenylpalladium methanesulfonate scaffold. By utilizing *N*-substituted 2-aminobiphenyls, the chance of the trace contamination of reaction products with NH_2-aminobiphenyls is eliminated. Additionally, the *N*-substituted carbazole that results during precatalyst activation cannot be further arylated, preventing the waste of the aryl halide substrate. We believe that these precatalysts, like **1**, will find many applications in palladium-catalyzed cross-coupling chemistry in both academia and industry.

3.4: Experimental

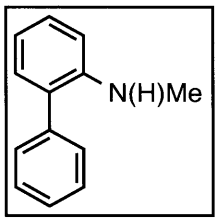
General: Reagent Information. THF and toluene were purchased in solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing it under argon pressure through two packed columns of neutral alumina (for THF) or through neutral alumina and copper (II) oxide (for toluene). Anhydrous tribasic potassium phosphate and sodium *t*-butoxide were purchased from commercial suppliers. These bases were stored in a nitrogen-filled glovebox and removed in small quantities. They were stored on the bench in a desiccator for up to two weeks. $Pd(OAc)_2$ was purchased from Johnson Matthey. All ligands were purchased from Strem Chemical Co. or Sigma Aldrich.. All other reagents were purchased from commercial suppliers and used as received. Aqueous 0.5 M K_3PO_4 solution was prepared by dissolving K_3PO_4 (1.06 g, 5 mmol) in deionized water (19 mL) and degassed by performing three sets of evacuation and argon refill cycles under sonication. Flash chromatography was performed with SiliCycle *SiliaFlash® F60* silica gel.

General: Analytical Information. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR (when applicable), ^{19}F NMR (when applicable), IR spectroscopy, melting point (when applicable), and elemental analysis or mass spectrometry. The ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra can be found in Section III of the supporting information. ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR were recorded on Varian 300 MHz, Varian 500 MHz, or Bruker 400 MHz spectrometers. The spectra were calibrated according to residual solvent peaks ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR; CD_2Cl_2: 5.32 ppm for ^{1}H NMR and 53.84 ppm for ^{13}C NMR; CD_3OD: 3.31 for ^{1}H NMR and 49.00 for ^{13}C NMR), an external reference (H_3PO_4: 0 ppm for ^{31}P; $CFCl_3$: 0 ppm for ^{19}F), or an internal reference (CF_3Ph: -63.7 ppm for ^{19}F). The ^{13}C, and ^{31}P NMR spectra were obtained with ^{1}H decoupling, and the ^{19}F NMR spectra were obtained without ^{1}H decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet, br = broad, app = apparent. Reactions were monitored by gas chromatography (GC) and thin-layer chromatography (TLC). GC analyses were performed on an Agilent 7890A gas chromatograph with an FID detector using a J & W DB-1 column. Thin- layer chromatography

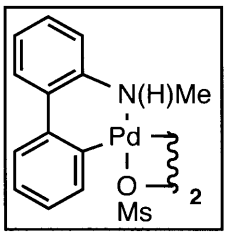
(TLC) was performed on Silicycle 250 μm silica gel plates. Compounds were visualized by irradiation with UV light or I_2. Yields refer to pure compounds, unless otherwise indicated.

General: Procedural Information

***N*- methyl-2-aminobiphenylpalladium methanesulfonate (4):**



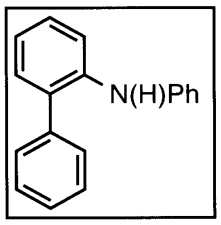
Step 1 – *N*-methyl-2-aminobiphenyl (2): A flame-dried 300 mL round-bottomed flask equipped with a magnetic stir bar was charged with 2-aminobiphenyl and capped with a rubber septum. The flask was evacuated and backfilled with argon, followed by the addition of THF (100 mL). The mixture was cooled to 0 °C in an ice bath. At 0 °C, nBuLi (2.5 M in hexanes, 12.6 mL, 31.5 mmol, 1.05 equiv) was added slowly. After the addition of nBuLi was complete the bright yellow reaction mixture was stirred for 1 h at 0 °C. Then iodomethane (1.89 mL, 30.3 mmol, 1.01 equiv) was added slowly, at which time the color faded to a dull yellow. The mixture was stirred for an additional 30 minutes at rt. Saturated $NaHCO_{3(aq)}$ (25 mL) and water (25 mL) were added and the aqueous layer was extracted with diethyl ether (3x50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to provide the title compound as a yellow oil as a 95:5 mixture of mono:dimethylated product, as determined by gas chromatography and ^{1}H NMR. The crude mixture was used directly in the next step without further purification. Yield: 5.45 g, 99%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 - 7.42 (m, 4H), 7.40 - 7.34 (m, 1H), 7.30 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H), 7.12 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.80 (td, *J* = 7.4, 1.1 Hz, 1H), 6.72 (dd, *J* = 8.2, 1.0 Hz, 1H), 3.98 (s, 1H), 2.82 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.40, 139.72, 130.27, 129.66, 129.11, 129.02, 127.79, 127.43, 117.03, 110.02, 31.03 ppm. **IR** (neat, cm^{-1}): 1613, 1603, 1509, 1490, 1435, 1284, 1008, 770, 746, 701, 615.



Step 2: Palladium Methanesulfonate Dimer (4): A 200 mL round-bottomed flask equipped with a magnetic stir bar was charged with N-methyl-2-aminobiphenyl (5.52 g, 30.0 mmol, 1.00 equiv, 95:5

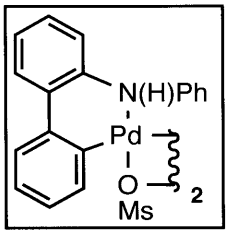
mono:dimethylated) and THF (60 mL). With stirring, methanesulfonic acid (1.84 mL, 28.5 mmol, 0.95 equiv [1 equiv relative to monomethylated amine]) was added slowly and the reaction mixture stirred for 15 min at room temperature. Palladium acetate (6.38 g, 28.5 mmol, 0.95 equiv) was added in one portion and rinsed off the walls of the flask with additional THF (15 mL). The flask was capped with a rubber septum and the deep red slurry was stirred at 50 °C for 45 min. After cooling to room temperature, the dark yellow solution was filtered through a plug of cotton to remove traces of palladium black and ~95% of the solvent was removed with the aid of a rotary evaporator. Diethyl ether (150 mL) was added to the flask and the mixture was sonicated to precipitate the product. The solid was isolated via vacuum filtration and dried under vacuum overnight to provide the title compound as a tan solid. Yield: 10.2 g, 93%. **^{1}H NMR** (500 MHz, CD_2Cl_2 + 10 μL pyridine-d^5) δ 7.70 (d, J = 7.7 Hz, 1H), 7.66 ? 7.56 (m, 1H), 7.52 ? 7.47 (m, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.7 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 6.94 ? 6.84 (m, 1H), 6.50 (d, J = 7.7 Hz, 1H), 2.70 (d, J = 5.6 Hz, 3H), 2.61 (s, 3H) ppm. **^{13}C NMR** (126 MHz, CD_3OD) δ 142.02, 140.71, 133.40, 128.89, 128.49, 127.19, 126.54, 125.24, 38.95 ppm. **IR** (neat, cm^{-1}): 3205, 1230, 1136, 1118, 1026, 735, 727 714, 589.

***N*-Phenyl-2-aminobiphenylpalladium methanesulfonate (5):**



Step 1 – *N*-Phenyl-2-aminobiphenyl (3): A 100 mL oven-dried round-bottomed flask equipped with a magnetic stir bar was charged with 2-aminobiphenyl (5.07 g, 30.0 mmol, 1.00 equiv) sodium *tert*-butoxide (3.07 g, 32.0 mmol, 1.07 equiv) and XPhos precatalyst **1•L1** (306 mg, 0.30 mmol, 1 mol %). The flask was capped with a rubber septum and subsequently evacuated and backfilled with argon (this procedure was repeated one additional time). Chlorobenzene (3.04 mL, 30.0 mmol, 1.00 equiv) was then added by syringe, followed by dioxane (30 mL). The reaction mixture was stirred at 100 °C for 30 minutes. It was then cooled to room temperature, diluted with ethyl acetate (50 mL) and filtered through a plug of silica gel layered on top of celite, eluting the mixture with additional ethyl acetate. The mixture was concentrated with the aid of a rotary evaporator

and the product was obtained as a dark yellow oil, containing traces of N, N-diphenyl-2-aminobiphenyl and 9-phenylcarbazole. It was used for the next step without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 - 7.46 (m, 4H), 7.46 - 7.38 (m, 2H), 7.34 - 7.27 (m, 4H), 7.12 - 7.02 (m, 3H), 6.97 (tt, *J* = 7.4, 1.1 Hz, 1H), 5.66 (bs, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.09, 140.88, 139.74, 132.23, 131.63, 130.08, 130.06, 129.64, 128.96, 128.20, 121.82, 121.79, 118.94, 118.18. **IR** (neat, cm^{-1}): 1611, 1500, 1479, 1434, 1008, 749, 721, 702.

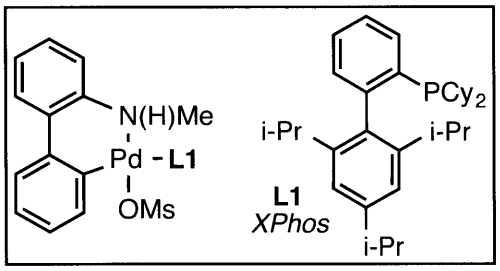


Step 2: Palladium Methanesulfonate Dimer (5):

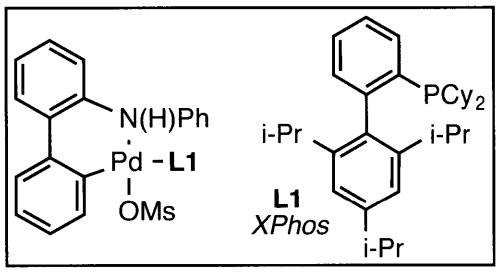
A 300 mL round-bottomed flask equipped with a magnetic stir bar was charged with *N*-phenyl-2-aminobiphenyl (7.35 g, 30.0 mmol, 1.00 equiv) and THF (50 mL). Methanesulfonic acid (1.95 mL, 30.0 mmol, 1.00 equiv) was added slowly with vigorous stirring. After stirring the reaction mixture for 15 minutes, palladium acetate (6.72 g, 30.0 mmol, 1.00 equiv) was added to the flask in one portion and rinsed off the walls of the flask with additional THF (25 mL). The flask was capped with a rubber septum and the deep red slurry was stirred at 50 °C for 45 min. Over the course of the reaction the deep red color dissipates and a tan slurry forms. The reaction mixture is cooled to room temperature and poured into an Erlenmeyer flask containing pentane (75 mL) and diethyl ether (75 mL). The solid was isolated via vacuum filtration and dried under vacuum overnight to afford the title compound as a tan powder. Yield: 12.1 g, 87%. **^{1}H NMR** (500 MHz, CD_3CN) δ 10.47 (s, 1H), 7.83 - 7.79 (m, 1H), 7.52 (ddd, *J* = 7.8, 6.9, 1.9 Hz, 1H), 7.47 - 7.39 (m, 3H), 7.20 - 7.13 (m, 2H), 7.13 - 7.09 (m, 2H), 7.09 - 7.03 (m, 2H), 7.00 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.89 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 2.75 (s, 3H). **^{13}C NMR** (126 MHz, CD_3OD) δ 142.02, 140.71, 133.40, 128.89, 128.49, 127.19, 126.54, 125.24, 38.95 ppm. **^{13}C NMR** (126 MHz, CD_3CN) ∂ 146.42, 142.43, 140.61, 137.54, 136.78, 136.48, 130.03, 129.80, 129.52, 129.28, 127.78, 127.09, 127.02, 126.65, 123.75, 122.10, 40.29 ppm. **IR** (neat, cm^{-1}): 3115, 1493, 1218, 1130, 1025, 762, 735, 716, 606.

General Procedure A: Precatalyst Synthesis: A 24 mL screw-top test tube equipped with a stir bar was charged with **4** (384 mg, 0.50 mmol, 0.50 equiv) or **5** (446 mg, 0.50mmol, 0.50 equiv),

and ligand (1.00 mmol, 1.00 equiv). Dichloromethane (5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed with the aid of rotary evaporation. Pentane (25 mL) was added to the residue to precipitate the precatalyst, which was then isolated via vacuum filtration and dried under vacuum overnight to provide the precatalyst.

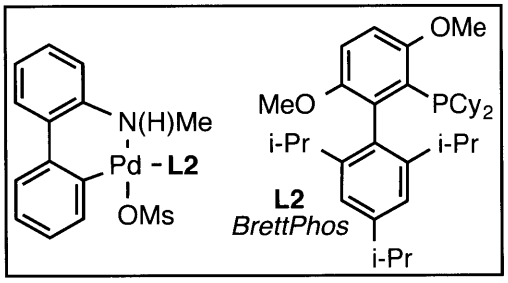


XPhos Precatalyst 6a: General procedure A was followed using XPhos (476 mg, 1.00 mmol, 1.00 equiv). Tan solid. Yield: 730 mg, 85%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.97 (ddd, *J* = 9.2, 4.9, 2.9 Hz, 1H), 7.65 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.63 - 7.57 (m, 3H), 7.41 - 7.23 (m, 5H), 7.16 - 7.10 (m, 1H), 7.04 - 6.94 (m, 2H), 3.39 (h, *J* = 6.9 Hz, 1H), 2.94 (hept, *J* = 6.8 Hz, 1H), 2.69 (s, 3H), 2.61 - 2.49 (m, 1H), 2.37 (qt, *J* = 12.4, 3.1 Hz, 1H), 2.29 (d, *J* = 10.9 Hz, 1H), 2.09 (dd, *J* = 6.0, 2.6 Hz, 4H), 1.98 (ddd, *J* = 13.4, 9.5, 5.0 Hz, 2H), 1.94 - 1.75 (m, 5H), 1.56 (dd, *J* = 6.9, 2.5 Hz, 7H), 1.51 - 1.23 (m, 7H), 1.22 - 1.06 (m, 6H), 0.94 - 0.83 (m, 4H), 0.67 (d, *J* = 6.8 Hz, 2H), 0.15 (ttd, *J* = 14.4, 8.3, 7.2, 4.6 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, CD_3OD) δ 157.50, 156.27, 151.51, 145.34, 145.20, 144.44, 135.62, 134.14, 133.12, 132.87, 131.81, 130.51, 130.44, 129.54, 129.13, 129.06, 128.59, 128.53, 128.23, 127.98, 127.77, 127.24, 126.88, 125.87, 124.60, 123.36, 122.12, 41.91, 40.81, 40.65, 39.68, 39.58, 38.51, 37.44, 35.83, 35.58, 34.52, 33.89, 33.25, 32.86, 32.43, 31.43, 30.35, 30.16, 28.44, 28.04, 26.78, 26.61, 25.59, 25.07, 24.59, 24.02, 23.16, 22.78 ppm (Observed complexity due to C-P splitting). **^{31}P NMR** (121 MHz, CD_3OD) δ 39.49 ppm. **IR** (neat, cm^{-1}): 2924, 1462, 1420, 1144, 1020, 1003, 876, 766, 738.



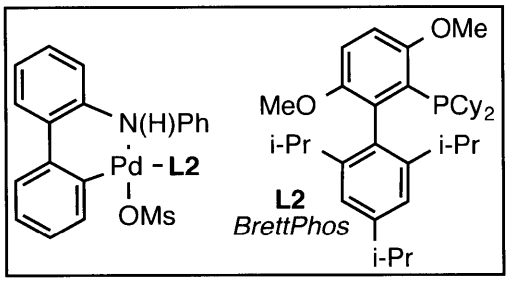
XPhos Precatalyst 7a: General procedure A was followed using XPhos (476 mg, 1.00 mmol, 1.00 equiv). Tan solid. Yield: 913 mg, 99%. **^{1}H NMR** (500 MHz, CD_3OD) δ 8.02 - 7.94 (m, 1H), 7.77 - 7.71 (m,

2H), 7.69 - 7.60 (m, 3H), 7.56 - 7.48 (m, 2H), 7.26 - 7.19 (m, 1H), 7.13 - 7.06 (m, 2H), 7.05 - 6.93 (m, 4H), 6.89 (tt, J = 7.4, 1.3 Hz, 1H), 6.79 - 6.73 (m, 1H), 6.65 (dd, J = 8.4, 1.4 Hz, 2H), 3.20 (hept, J = 6.9 Hz, 1H), 2.97 (hept, J = 6.8 Hz, 1H), 2.69 (s, 3H), 2.56 - 2.30 (m, 3H), 2.09 (d, J = 12.8 Hz, 1H), 2.05 - 1.86 (m, 4H), 1.86 - 1.68 (m, 2H), 1.64 - 1.37 (m, 3H), 1.37 - 1.20 (m, 6H), 1.20 - 1.05 (m, 6H), 0.97 (ddd, J = 16.6, 8.1, 3.7 Hz, 1H), 0.93 - 0.84 (m, 5H), 0.70 (d, J = 6.8 Hz, 2H), -0.09 (dh, J = 17.1, 4.7, 3.9 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, CD_3OD) δ 155.98, 155.02, 152.13, 145.47, 145.33, 143.35, 142.87, 141.96, 139.91, 137.51, 135.27, 135.22, 133.58, 133.42, 133.34, 132.42, 130.11, 129.14, 129.09, 129.03, 128.93, 128.84, 128.79, 128.50, 127.31, 126.60, 125.88, 125.33, 123.22, 38.86, 36.61, 36.36, 34.94, 34.64, 33.39, 32.79, 32.59, 32.14, 30.84, 30.01, 28.40, 28.34, 27.92, 27.82, 26.75, 26.66, 26.50, 26.43, 26.38, 26.31, 26.12, 25.51, 25.48, 24.48, 23.65, 22.85, 22.77, 22.72, 13.76 ppm (observed complexity due to C-P splitting). **^{31}P NMR** (121 MHz, CD_3OD) δ 40.59 ppm. **IR** (neat, cm^{-1}): 2923, 1422, 1254, 1145, 1024, 1002, 773, 760, 740, 691.

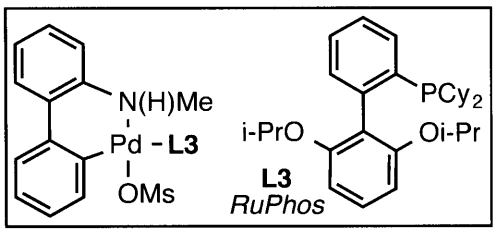


BrettPhos Precatalyst 6b (11 mmol scale): General procedure A was followed using BrettPhos (5.91 g, 11 mmol, 1.00 equiv), **4** (4.22 g, 5.5 mmol, 0.50 equiv), and dichloromethane (50 mL). Off-white solid. Yield: 9.59 g, 94%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.61 (dd, J = 7.5, 1.6 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.52 (d, J = 1.9 Hz, 1H), 7.36 (td, J = 7.5, 1.3 Hz, 1H), 7.32 (td, J = 7.6, 1.6 Hz, 1H), 7.28 - 7.22 (m, 3H), 7.17 (h, J = 2.6, 2.2 Hz, 3H), 6.99 (dd, J = 7.7, 1.3 Hz, 1H), 3.88 (s, 3H), 3.45 (s, 3H), 3.37 (dq, J = 13.9, 6.8 Hz, 1H), 2.99 (p, J = 6.7 Hz, 1H), 2.95 - 2.83 (m, 1H), 2.83 - 2.73 (m, 1H), 2.69 (s, 3H), 2.14 (d, J = 11.2 Hz, 1H), 2.08 - 1.93 (m, 6H), 1.90 (d, J = 10.1 Hz, 1H), 1.87 - 1.67 (m, 4H), 1.63 - 1.18 (m, 11H), 1.18 - 0.77 (m, 6H), 0.71 (dd, J = 9.2, 6.7 Hz, 5H), 0.41 (qdd, J = 12.8, 6.3, 3.5 Hz, 1H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 158.42, 156.44, 156.12, 155.72, 152.25, 152.13, 151.62, 147.07, 142.01, 141.25, 139.66, 135.33, 135.18, 134.58, 130.86, 129.46, 128.53, 127.97, 127.59, 124.16, 123.53,

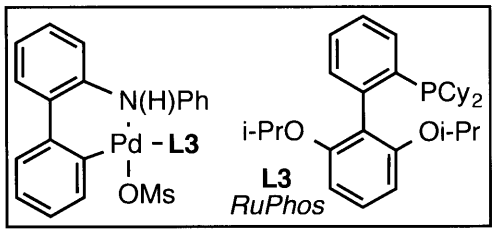
123.30, 122.14, 120.05, 116.08, 113.22, 55.99, 55.40, 40.72, 40.03, 35.21, 34.69, 34.46, 33.98, 33.78, 33.41, 31.42, 30.45, 30.24, 28.80, 28.69, 28.40, 28.29, 27.43, 27.33, 27.23, 26.75, 26.51, 26.06, 25.03, 24.99, 24.90, 24.46, 24.36 ppm. **^{31}P NMR** (121 MHz, CD_3OD) δ 41.61 ppm. **IR** (neat, cm^{-1}): 3236, 2925, 2849, 1422, 1252, 1215, 1201, 1173, 1041, 1011, 763, 747, 739, 727.



BrettPhos Precatalyst 7b (11 mmol scale): General procedure A was followed using BrettPhos (5.91 g, 11 mmol, 1.00 equiv), **5** (4.91 g, 5.5 mmol, 0.50 equiv), and dichloromethane (50 mL). Tan solid. Yield: 9.35 g, 86%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.73 - 7.66 (m, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.56 - 7.46 (m, 2H), 7.42 - 7.34 (m, 1H), 7.29 - 7.23 (m, 1H), 7.19 (d, *J* = 2.2 Hz, 2H), 7.13 - 7.06 (m, 1H), 7.06 - 6.96 (m, 4H), 6.96 - 6.91 (m, 2H), 6.90 - 6.78 (m, 3H), 6.65 - 6.58 (m, 2H), 3.88 (s, 3H), 3.47 (s, 3H), 3.12 (hept, *J* = 7.0 Hz, 1H), 3.07 - 2.89 (m, 2H), 2.71 (s, 4H), 2.24 (d, *J* = 11.2 Hz, 1H), 2.06 (p, *J* = 6.8 Hz, 1H), 2.02 - 1.97 (m, 3H), 1.98 - 1.83 (m, 2H), 1.83 - 1.46 (m, 5H), 1.46 - 1.21 (m, 5H), 1.20 - 0.80 (m, 9H), 0.75 (dd, *J* = 20.6, 6.7 Hz, 5H), 0.30 (dtd, *J* = 13.4, 10.8, 10.0, 6.3 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 156.72, 155.98, 155.64, 155.06, 151.92, 151.61, 144.55, 143.34, 143.27, 140.56, 137.85, 135.53, 135.38, 134.87, 134.82, 129.82, 129.40, 129.24, 128.97, 128.94, 128.88, 128.46, 128.36, 127.13, 126.63, 126.26, 125.43, 125.18, 124.93, 124.79, 123.51, 122.78, 122.00, 121.83, 116.13, 113.28, 56.02, 55.29, 40.24, 35.06, 34.84, 34.61, 34.27, 34.08, 33.44, 31.81, 30.84, 30.43, 30.37, 30.31, 28.73, 28.65, 28.47, 28.36, 28.15, 27.50, 27.45, 27.38, 27.34, 26.73, 26.47, 25.36, 25.22, 24.90, 24.38, 23.73, 23.03, 14.56 ppm (observed complexity due to C-P splitting). **^{31}P NMR** (121 MHz, CD_3OD) δ 45.87 ppm. **IR** (neat, cm^{-1}): 2926, 1418, 1255, 1144, 1124, 1039, 1012, 1002, 758, 739, 690.

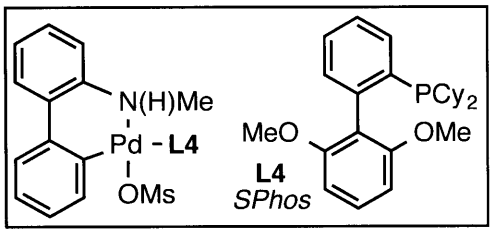


RuPhos Precatalyst 6c: General procedure A was followed using RuPhos (466 mg, 1.00 mmol, 1.00 equiv). White solid. Yield: 817 mg, 86%. **^{1}H NMR** (500 MHz, CD_3OD) δ 8.10 (t, *J* = 8.4 Hz, 1H), 7.85 - 7.77 (m, 1H), 7.66 - 7.59 (m, 1H), 7.53 (tt, *J* = 7.6, 1.5 Hz, 1H), 7.48 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.39 - 7.25 (m, 4H), 7.25 - 7.18 (m, 1H), 7.12 - 7.04 (m, 2H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.79 (ddd, *J* = 7.8, 3.0, 1.3 Hz, 1H), 0.17 - 0.02 (m, 1H), 4.87 - 4.79 (m, 1H), 4.54 (hept, *J* = 6.1 Hz, 1H), 2.70 (s, 3H), 2.45 (tdd, *J* = 12.6, 9.7, 5.1 Hz, 1H), 2.34 (t, *J* = 11.4 Hz, 1H), 2.28 - 2.09 (m, 5H), 2.09 - 1.88 (m, 1H), 1.82 (d, *J* = 13.3 Hz, 1H), 1.71 (qt, *J* = 12.4, 3.2 Hz, 1H), 1.66 - 1.48 (m, 4H), 1.48 - 0.96 (m, 8H), 0.94 - 0.68 (m, 6H) ppm. **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 163.25, 162.16, 151.60, 145.50, 142.43, 141.70, 140.22, 137.26, 135.48, 132.30, 130.86, 129.54, 128.89, 128.58, 127.77, 127.62, 127.31, 122.64, 106.58, 40.51, 40.50, 40.22, 35.91, 35.67, 31.05, 30.16, 28.01, 27.94, 27.71, 27.59, 27.23, 27.14, 26.77, 26.67, 26.56, 26.44, 22.44, 22.30, 21.47 ppm (observed complexity due to C-P splitting). **^{31}P NMR** (121 MHz, CD_3OD) δ 45.04. **IR** (neat, cm^{-1}): 3236, 2926, 2843, 1448, 1257, 1204, 1099, 1062, 1039, 786, 761.

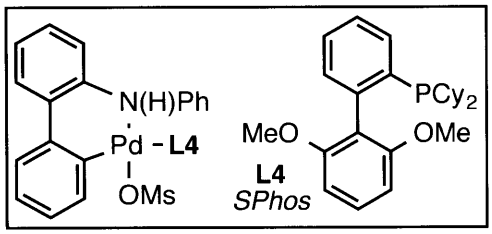


RuPhos Precatalyst 7c: General procedure A was followed using RuPhos (466 mg, 1.00 mmol, 1.00 equiv). Orange solid. Yield: 873 mg, 96%. **^{1}H NMR** (500 MHz, CD_3OD) ∂ 7.98 (t, *J* = 8.3 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.74 - 7.66 (m, 1H), 7.61 - 7.45 (m, 5H), 7.19 - 7.05 (m, 3H), 6.97 (dq, *J* = 31.7, 7.5 Hz, 4H), 6.88 - 6.78 (m, 2H), 6.72 (dd, *J* = 7.6, 3.7 Hz, 1H), 6.64 (d, *J* = 7.9 Hz, 2H), 4.93 (p, *J* = 6.0 Hz, 1H), 4.60 (p, *J* = 6.2 Hz, 1H), 2.69 (s, 4H), 2.41 (p, *J* = 11.8, 11.0 Hz, 2H), 2.23 (q, *J* = 12.8 Hz, 1H), 2.02 (dd, *J* = 21.8, 13.1 Hz, 3H), 1.96 - 1.48 (m, 9H), 1.46 - 0.83 (m, 14H), 0.72 (dd, *J* = 12.8, 5.9 Hz, 3H), -0.06 - -0.21 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) Complex Spectrum—See supporting information (significant peak broadening observed). **^{31}P NMR** (121 MHz, CD_3OD) δ

62.77, 46.93 ppm. **IR** (neat, cm^{-1}): 2926, 1459, 1245, 1136, 1111, 1064, 1028, 1000, 761, 756, 738, 690.

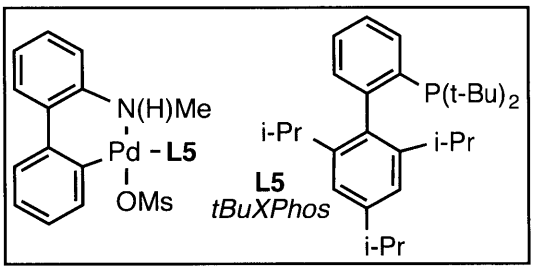


SPhos Precatalyst 6d: General procedure A was followed using SPhos (410 mg, 1.00 mmol, 1.00 equiv). White solid. Yield: 680 mg, 86%. **^{1}H NMR** (500 MHz, CD_3OD) δ 8.16 (t, *J* = 8.4 Hz, 1H), 7.87 - 7.78 (m, 1H), 7.68 - 7.61 (m, 1H), 7.56 - 7.44 (m, 2H), 7.41 - 7.25 (m, 5H), 7.26 - 7.19 (m, 1H), 7.14 - 7.05 (m, 3H), 6.84 (ddd, *J* = 7.7, 3.1, 1.4 Hz, 1H), 3.96 (s, 3H), 3.41 (s, 3H), 2.69 (s, 3H), 2.54 - 2.38 (m, 1H), 2.27 - 2.15 (m, 2H), 2.14 (dd, *J* = 5.9, 2.5 Hz, 3H), 2.04 (s, 4H), 1.94 (dd, *J* = 11.0, 7.1 Hz, 1H), 1.81 (d, *J* = 13.3 Hz, 1H), 1.70 (qt, *J* = 12.2, 3.1 Hz, 1H), 1.65 - 1.47 (m, 2H), 1.42 (d, *J* = 13.1 Hz, 1H), 1.36 (dt, *J* = 12.8, 3.3 Hz, 2H), 1.30 - 0.95 (m, 4H), 0.95 - 0.74 (m, 2H), 0.10 - -0.07 (m, 1H) ppm. **^{13}C NMR** (126 MHz, CD_2Cl_2) Complex Spectrum—See supporting information (significant peak broadening observed). **^{31}P NMR** (121 MHz, CD_3OD) δ 46.88 ppm. **IR** (neat, cm^{-1}): 1452, 1288, 1234, 1108, 1094, 1034, 1000, 888, 760, 719.

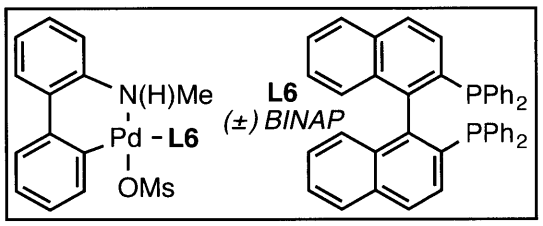


SPhos Precatalyst 7d: General procedure A was followed using SPhos (410 mg, 1.00 mmol, 1.00 equiv). Bright yellow solid. Yield: 788 mg, 92%. **^{1}H NMR** (500 MHz, CD_3OD) δ 8.05 (t, *J* = 8.4 Hz, 1H), 7.83 (td, *J* = 7.7, 1.6 Hz, 1H), 7.73 (dq, *J* = 5.3, 2.3 Hz, 1H), 7.61 - 7.46 (m, 5H), 7.18 (dd, *J* = 20.2, 8.3 Hz, 2H), 7.10 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.07 - 7.00 (m, 2H), 6.95 (dddd, *J* = 16.4, 7.8, 6.6, 0.9 Hz, 2H), 6.89 - 6.81 (m, 2H), 6.76 - 6.70 (m, 1H), 6.63 (dq, *J* = 7.1, 1.1 Hz, 2H), 4.09 (s, 3H), 4.04 - 3.91 (m, 1H), 3.40 (s, 3H), 2.69 (s, 3H), 2.43 (d, *J* = 9.8 Hz, 1H), 2.36 - 2.17 (m, 2H), 2.13 - 1.97 (m, 3H), 1.91 (d, *J* = 13.1 Hz, 1H), 1.79 (d, *J* = 13.3 Hz, 1H), 1.60 (ddt, *J* = 50.7, 13.1, 3.4 Hz, 3H), 1.49 - 1.14 (m, 4H), 1.16 - 0.83 (m, 5H), -0.17 (dd, *J* = 12.0, 6.3 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.15, 140.04, 139.52, 134.28, 129.41, 129.14, 128.78, 127.83,

127.42, 126.97, 125.79, 124.78, 121.29, 105.55, 56.48, 56.09, 40.56, 35.94, 35.78, 34.84, 32.01, 28.54, 28.46, 27.04, 23.07, 14.81 ppm (observed complexity due to C-P splitting).[31]**P NMR** (121 MHz, CD_3OD) δ 47.74 ppm. **IR** (neat, cm^{-1}): 1231, 1143, 1035, 1001, 763, 740, 571.



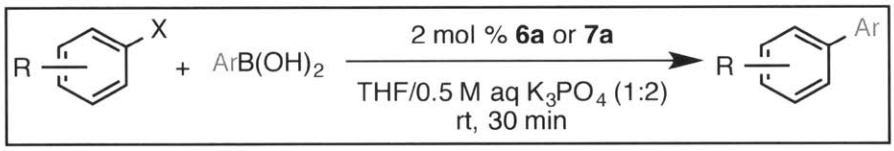
***t*BuXPhos Precatalyst 6e:** General procedure A was followed using tBuXPhos (424 mg, 1.00 mmol, 1.00 equiv). Light yellow solid. Yield: 720 mg, 89%. **^{1}H NMR** (500 MHz, CD_3OD) δ 8.15 (t, *J* = 6.8 Hz, 1H), 7.93 - 6.80 (m, 13H), 3.44 - 3.32 (m, 1H), 3.14 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.71 (m, 4H), 2.29 - 1.69 (m, 6H), 1.70 - 0.57 (m, 30H) ppm. **^{13}C NMR** (126 MHz, CD_3CN) δ 160.35, 157.50, 153.88, 145.45, 145.31, 143.70, 142.04, 141.30, 139.39, 137.43, 137.38, 136.73, 135.48, 135.25, 134.95, 134.87, 132.04, 132.03, 129.81, 129.08, 128.93, 128.90, 128.79, 128.66, 128.49, 128.00, 127.91, 127.86, 127.03, 126.84, 126.39, 125.40, 124.78, 122.59, 122.58, 121.77, 43.84, 40.72, 40.71, 39.95, 39.73, 39.59, 39.47, 39.35, 35.05, 33.73, 32.21, 32.19, 32.15, 32.06, 30.82, 30.78, 26.18, 25.41, 24.28, 24.08, 24.04, 23.81, 23.26, 14.35 ppm (observed complexity due to C-P splitting). **^{31}P NMR** (121 MHz, DMSO-d6) δ 56.13 ppm. **IR** (neat, cm^{-1}): 1247, 1143, 1031, 1018, 1001, 759, 747, 739, 729.



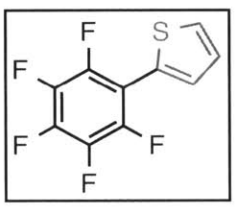
(±)-BINAP Precatalyst 6f: General procedure A was followed using (±)-BINAP (622 mg, 1.00 mmol, 1.00 equiv). Yellow solid. Yield: 903 mg, 90%. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.99 - 7.91 (m, 2H), 7.84 - 7.68 (m, 7H), 7.59 - 7.50 (m, 3H), 7.47 - 7.38 (m, 2H), 7.38 - 7.11 (m, 10H), 7.10 - 7.00 (m, 3H), 7.00 - 6.86 (m, 4H), 6.84 - 6.78 (m, 2H), 6.75 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.71 - 6.64 (m, 2H), 6.52 - 6.47 (m, 1H), 6.39 (tdd, *J* = 7.6, 6.7, 2.6, 1.3 Hz, 1H), 6.35 - 6.31 (m, 1H), 2.68 (s, 3H), 2.28 (d, *J* = 2.7 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 164.86, 164.00, 151.61, 141.05, 141.04, 140.80, 140.30, 138.83, 138.49, 138.41, 138.15, 135.77, 135.68, 135.07, 135.02,

134.97, 134.90, 134.71, 134.69, 134.56, 134.54, 134.06, 133.98, 133.73, 133.66, 133.08, 133.06, 131.75, 131.73, 131.58, 131.08, 131.01, 130.86, 130.24, 130.18, 130.00, 129.96, 129.88, 129.12, 129.04, 128.89, 128.87, 128.70, 128.57, 128.55, 128.26, 128.17, 127.90, 127.68, 127.60, 127.58, 127.54, 127.49, 127.45, 127.25, 126.67, 126.44, 126.38, 126.31, 123.73, 123.39, 122.52, 122.10, 121.51, 41.37, 40.11 ppm (observed complexity due to C-P splitting). **^{31}P NMR** (121 MHz, CD_3OD) δ 36.35 (d, J = 42.5 Hz), 35.18 (d, J = 43.6 Hz), 13.92 (d, J = 42.4 Hz), 12.42 (d, J = 43.7 Hz). **IR** (neat, cm^{-1}): 3202, 1225, 1193, 1037, 758, 734, 695, 670.

General Procedure B – Suzuki-Miyaura Coupling

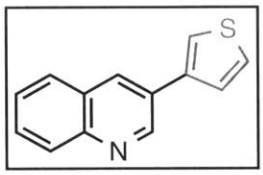


A screw-top test tube equipped with a magnetic stir bar was charged with **6a** or **7a** (0.02 mmol, 2 mol%), arylboronic acid (1.50 mmol, 1.50 equiv), aryl halide (if solid, 1.00 mmol, 1.00 equiv), and the tube was sealed with a Teflon screw-cap septum. The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and the aryl halide, if liquid (1.00 mmol, 1.00 equiv) was added at this time. Anhydrous THF (2 mL) and 0.5 M aq. K_3PO_4 solution (4 mL) were then added via syringe and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with EtOAc (10 mL) and H_2O (10 mL) and the layers separated. The aqueous layer was extracted with additional EtOAc (3x5mL). The combined organic layers were dried over Na_2SO_4 and filtered through a pad of celite. The filtrate was concentrated and the resulting residue was purified by flash chromatography using a Biotage Isolera Four system with a SNAP 25 g cartridge to afford the desired product.

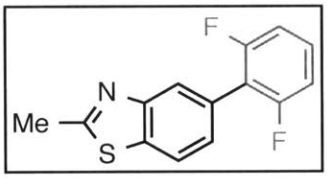


2-(Perfluorophenyl)thiophene: General procedure B was followed using 1-chloro-pentafluorobenzene (203 mg, 1.00 mmol, 1.00 equiv) and thienyl-2-boronic acid (192 mg, 1.50 mmol, 1.50 equiv). White solid. Yield with **6a**:

217 mg, 87%. Yield with **7a**: 238 mg, 95%. **mp** = 39.4-40.9 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.55 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.54 – 7.52 (dd, *J* = 3.8, 1.2, 1H), 7.21 – 7.18 (dd, *J* = 4.9, 3.8 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.3 (m), 142.7 (m), 141 (m), 139.2 – 138.6 (m), 136.7 (m), 130.2-130.1 (td, *J* = 5.5, 1 Hz), 128.3 – 128.2 (t, *J* = 3.8 Hz), 127.3, 126.3 (m), 110.0 (m) ppm. **^{19}F NMR** (282.4 MHz, $CDCl_3$) δ -141.2 (5F) ppm. **IR** (neat, cm^{-1}): 3110, 2923, 1531. 1477. 1468. 1420, 1391. 1378, 1347, 1222, 1073, 1060, 970, 819, 759, 740, 713, 690, 633. Anal. Calcd. for $C_{10}H_3F_5S$: C, 48.01; H, 1.21. Found: C, 48.19; H, 1.18.



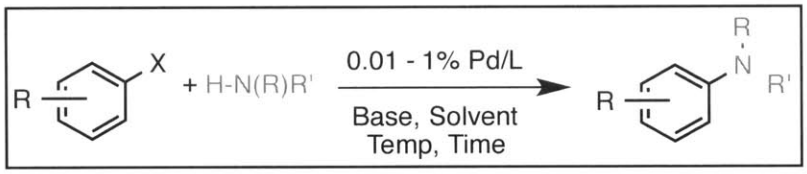
3-(Thiophen-3-yl)quinoline: General procedure B was followed using 3-bromoquinoline (208 mg, 1.00 mmol, 1.00 equiv) and thienyl-3-boronic acid (192 mg, 1.50 mmol, 1.50 equiv). White solid. **mp** = 88.5-89.0 °C. Yield with **6a:** 202 mg, 95%. Yield with **7a**: 210 mg, 99%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.22 – 9.21(d, *J* = 2.3 Hz, 1H), 8.32 – 8.31 (d, *J* = 2.2 Hz, 1H), 8.15 – 8.13 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.88 – 7.86 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.72 – 7.68 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.67 (dd, *J* = 2.9, 1.4 Hz, 1H), 7.58 – 7.54 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.53– 7.50 (m, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.35, 147.11, 138.78, 131.86, 129.18, 129.10, 128.62, 127.97, 127.77, 126.97, 126.95, 125.99, 121.54 ppm. **IR** (neat, cm^{-1}): 1599, 1570, 1488, 1124, 968, 951, 876, 859, 844, 693, 667, 647, 641, 616, 603, 600 . Anal. Calcd. for $C_{13}H_9NS$: C, 73.90; H, 4.29. Found: C, 73.77; H, 4.27.



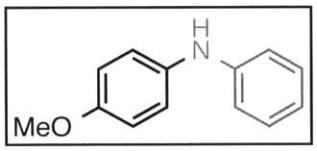
5-(2,6-Difluorophenyl)-2-methylbenzo-[*d*]thiazole: General procedure B was followed using 5-chloro-2-methylbenzothiazole (184 mg, 1.00 mmol, 1.00 equiv) and 2,6-difluorobenzeneboronic acid (237 mg, 1.50 mmol, 1.50 equiv). White solid. **mp** = 126 – 127 °C. Yield from **6a**: 248 mg, 95%. Yield from **7a**: 255 mg, 98%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (q, *J* = 1.4 Hz, 1H), 7.91 – 7.89 (d, *J* = 8.3 Hz, 1H), 7.47 – 7.43 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.35 – 7.28 (tt, *J* = 8.4, 6.3 Hz, 1H), 7.05 – 6.99 (m, 2H), 2.87 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.6, 161.4 – 158.9 (dd, *J*

= 53.3, 26.4 Hz, 2C), 135.6, 129.1 – 128.9 (t, J = 10.4 Hz), 126.9, 124.2 (dt, J = 253, 2.2 Hz, 2C), 121.1, 118.2 – 117.9 (t, J = 18.9 Hz), 111.8 – 111.6 (d, J = 26.3 Hz), 111.8 – 111.6 (d, J = 12.4 Hz), 20.2 ppm. **^{19}F NMR** (282.4 MHz, $CDCl_3$) δ -114.5 (t, J = 6.8 Hz, 2F) ppm. **IR** (neat, cm^{-1}): 1626, 1586, 1463, 1442, 1411, 1270, 1251,1174, 993, 819, 781, 770, 736, 667, 659, 650, 645, 636. Anal. Calcd. for $C_{14}H_9F_2NS$: C, 64.35; H, 3.47. Found: C, 64.17; H, 3.63.

General Procedure C – Arylation of Amines

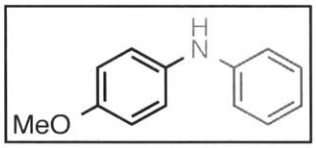


A screw-top test tube equipped with a magnetic stir bar was charged with NaOtBu (1.2 – 1.4 mmol, 1.2 – 1.4 equiv), aryl halide if solid (1.00 mmol, 1.00 equiv), precatalyst (0.01 – 1 mol%) and the tube was sealed with a Teflon screw-cap septum. The tube was evacuated and backfilled with argon (this procedure was performed a total of three times), after which aryl halide, if liquid, and amine (1.2 – 1.4 mmol, 1.2 – 1.4 equiv), and solvent (1 mL) were added by syringe. The reaction mixture was heated at 110 °C for 24 h, after which it was cooled to room temperature and diluted with ethyl acetate. The crude reaction mixture was then filtered through a pad of celite, concentrated with the aid of rotary evaporation, and purified by column chromatography.

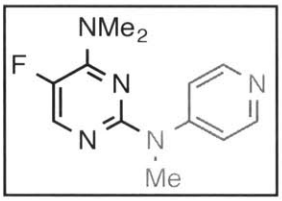


4-Methoxydiphenylamine (X=I): General procedure C was followed using 4-iodoanisole (234 mg, 1.00 mmol, 1.00 equiv), aniline (128 μL, 1.40 mmol, 1.40 equiv), NaO*t*Bu (134 mg, 1.40 mmol, 1.40 equiv), precatalyst solution (0.01 M in THF, 10 μL, 0.01 mol%), and toluene (1 mL) for 5 min. Off-white solid. Yield with **6b**: 191 mg, 94%. Yield with **7b**: 179 mg, 97%. **mp** = 101 – 102 °C. **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.32 - 7.18 (m, 2H), 7.14 - 7.05 (m, 2H), 6.99 - 6.91 (m, 2H), 6.91 - 6.80 (m, 3H), 5.51 (s, 1H), 3.82 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ

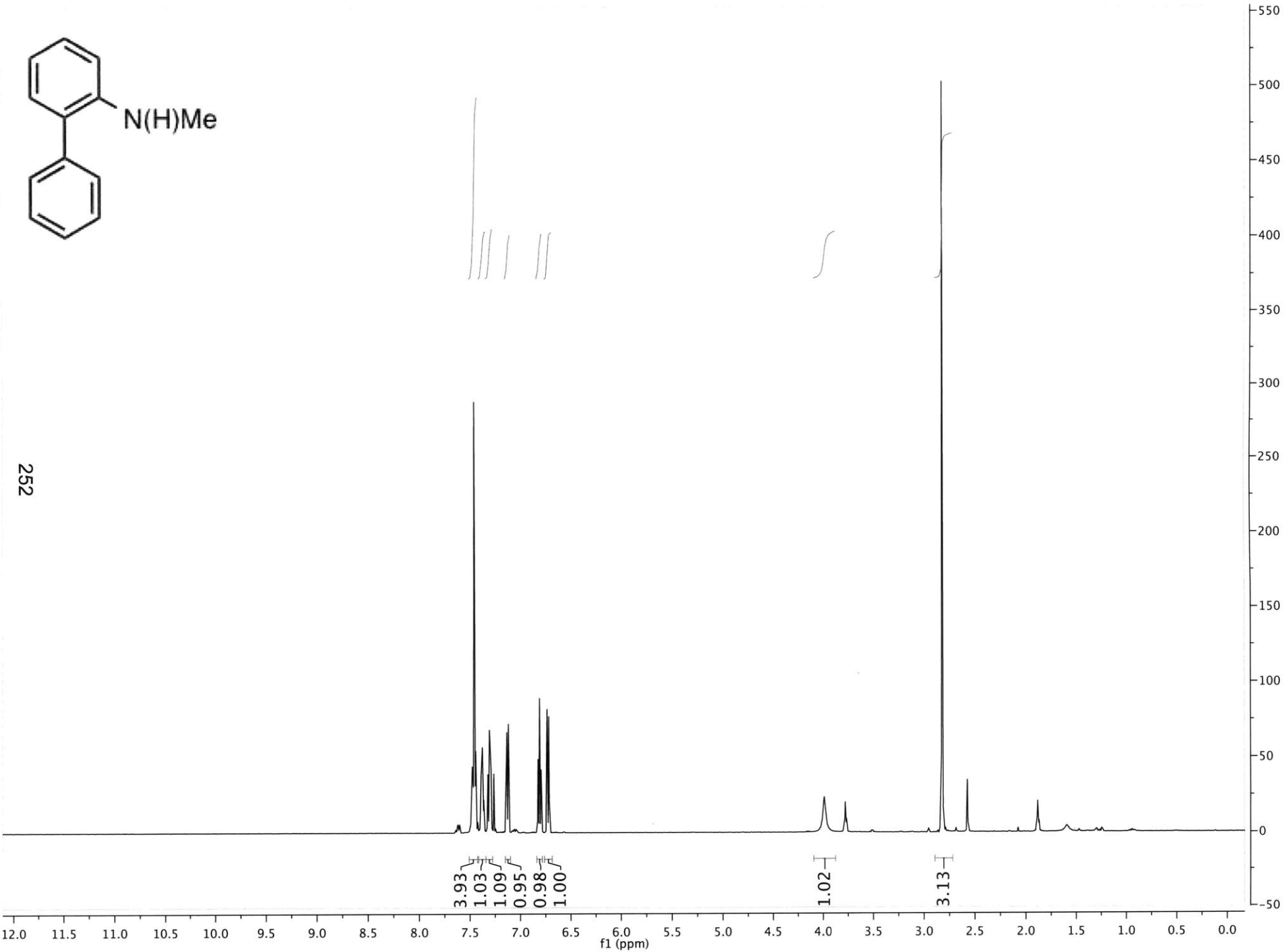
155.99, 145.90, 136.46, 130.05, 122.93, 120.29, 116.37, 115.40, 56.31 ppm. **IR** (neat, cm^{-1}): 3386, 1595, 1500, 1489, 1443, 1297, 1247, 1236, 1032, 749, 694.

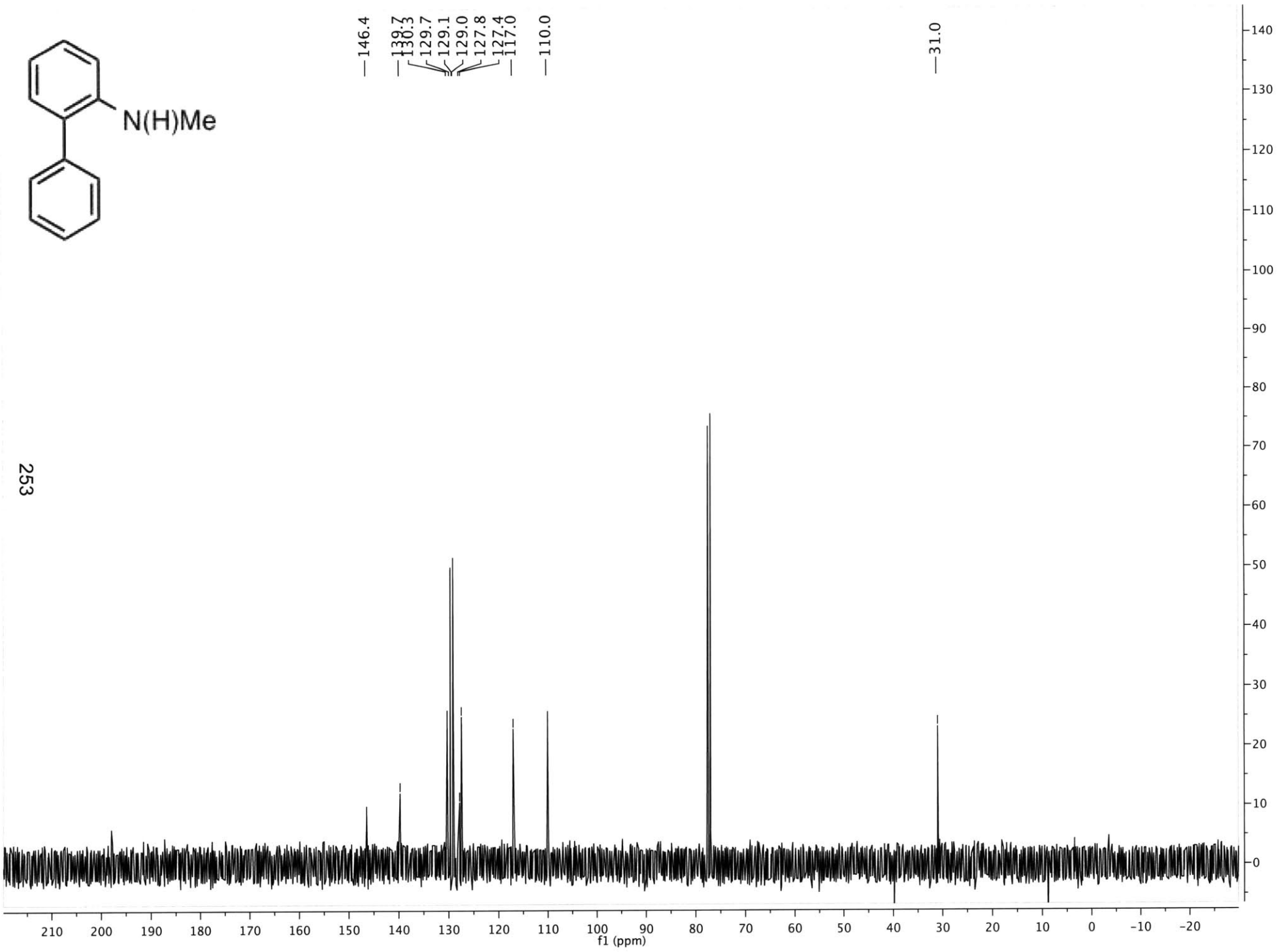


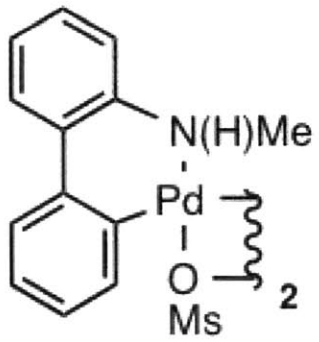
4-Methoxydiphenylamine (X=Cl): General procedure C was followed using 4-chloroanisole (123 μL, 1.00 mmol, 1.00 equiv), aniline (110 μL, 1.20 mmol, 1.20 equiv), NaO*t*Bu (115 mg, 1.20 mmol, 1.20 equiv), precatalyst solution (0.01 M in THF, 10 μL, 0.01 mol%), and dioxane (1 mL) for 24 h. Off-white solid. Yield with **6b**: 187 mg, 96%. Yield with **7b**: 193 mg, 90%. Characterization data consistent with above case where X=I.



5-Fluoro-N^2,N^4,N^4-trimethyl-N^2-(pyridin-4-yl)pyrimidine-2,4-diamine: General procedure C was followed using 2-chloro-5-fluoro-*N*,*N*-dimethylpyrimidin-4-amine (176 mg, 1.00 mmol, 1.00 equiv), *N*-methylpyridin-4-amine (130 mg, 1.20 mmol, 1.20 equiv), NaOtBu (115 mg, 1.20 mmol, 1.20 equiv), precatalyst (0.01 mmol), and PhMe (1 mL) for 24 h. Yellow, crystalline solid. Yield with **6c**: 217 mg, 88%. Yield with **7c**: 210 mg, 85%. **^{1}H NMR** (500 MHz, Chloroform-d) δ 8.48 - 8.38 (m, 2H), 7.82 (d, *J* = 6.4 Hz, 1H), 7.40 - 7.29 (m, 2H), 3.53 (s, 3H), 3.14 (d, *J* = 2.2 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, Chloroform-d) δ 156.59 , 153.06 , 152.56 (d, *J* = 6.1 Hz), 150.14, 144.18, 142.60 (d, *J* = 26.2 Hz), 142.21, 117.59, 39.48 (d, *J* = 7.0 Hz), 37.51 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -154.44 ppm. **IR** (neat, cm^{-1}): 1602, 1575, 1390, 1371, 1324, 1216, 844, 827, 768, 633, 596.


N(H)Me
252
3.93
1.03
1.09
0.95
0.98
1.00
1.02
3.13
f1 (ppm)


N(H)Me
146.4
139.7
130.3
129.7
129.1
129.0
127.8
127.4
117.0
110.0
31.0
f1 (ppm)

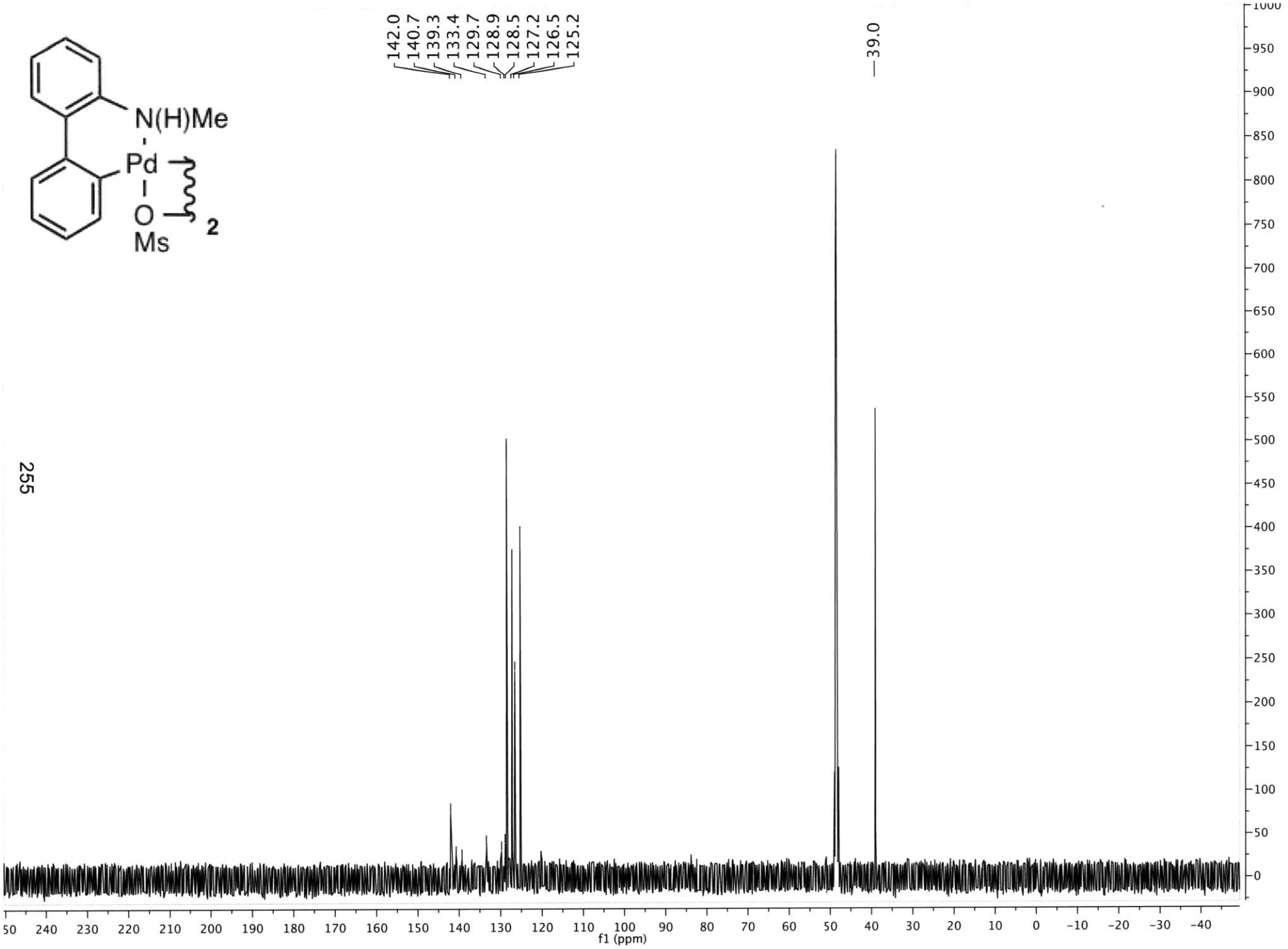


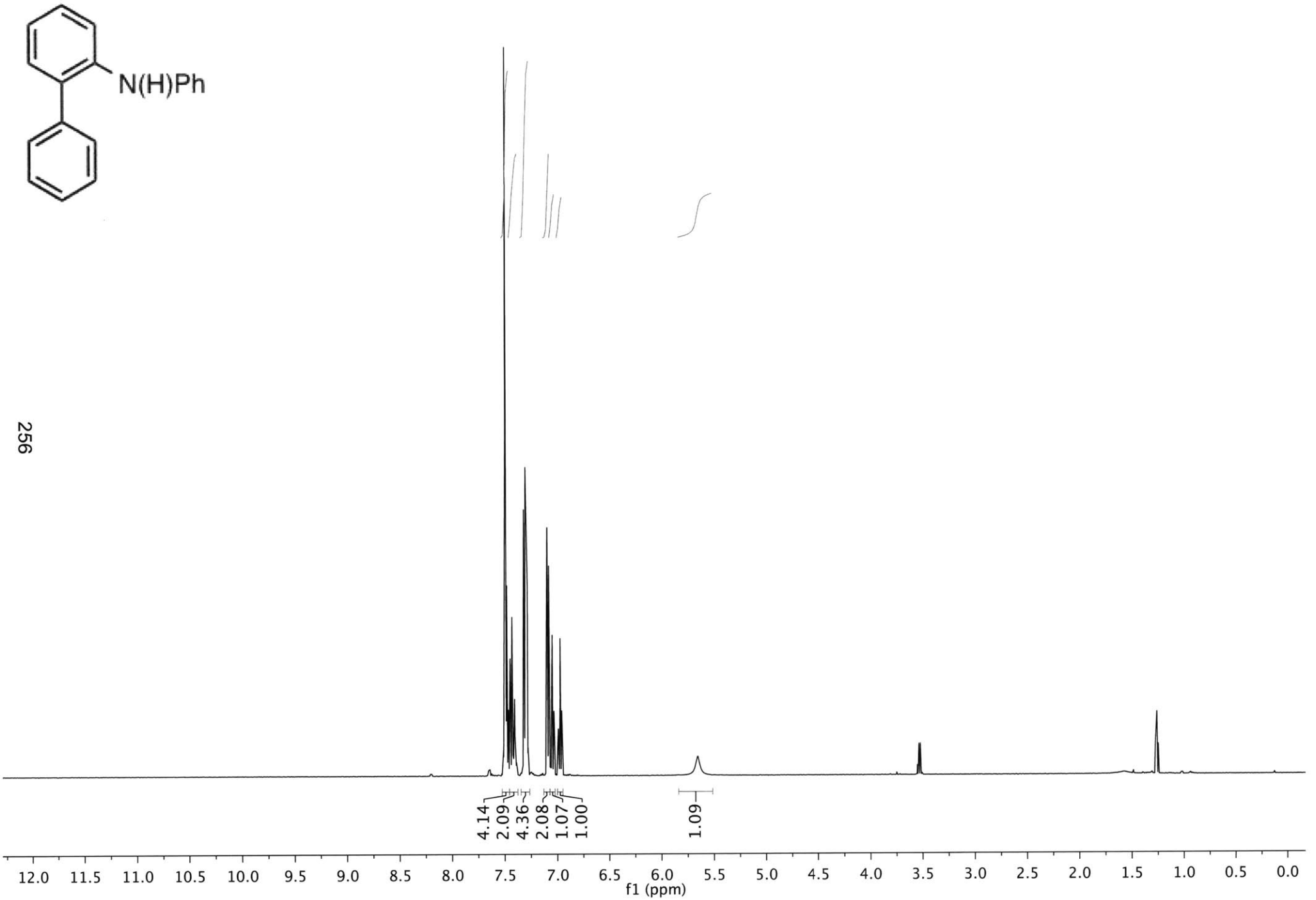
254

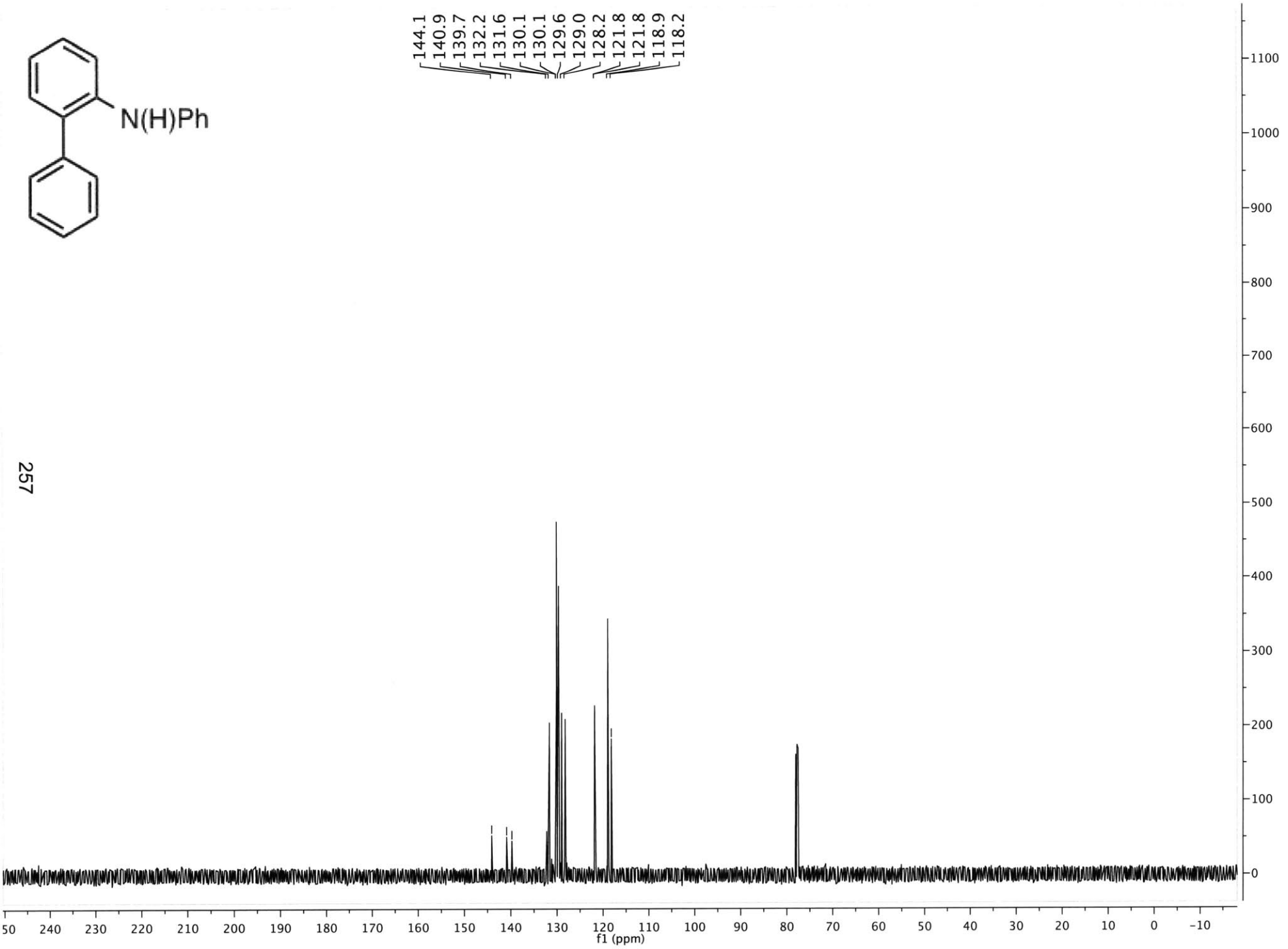
1.00 0.96 1.07 0.91 1.24 1.10 1.07 1.06 0.94

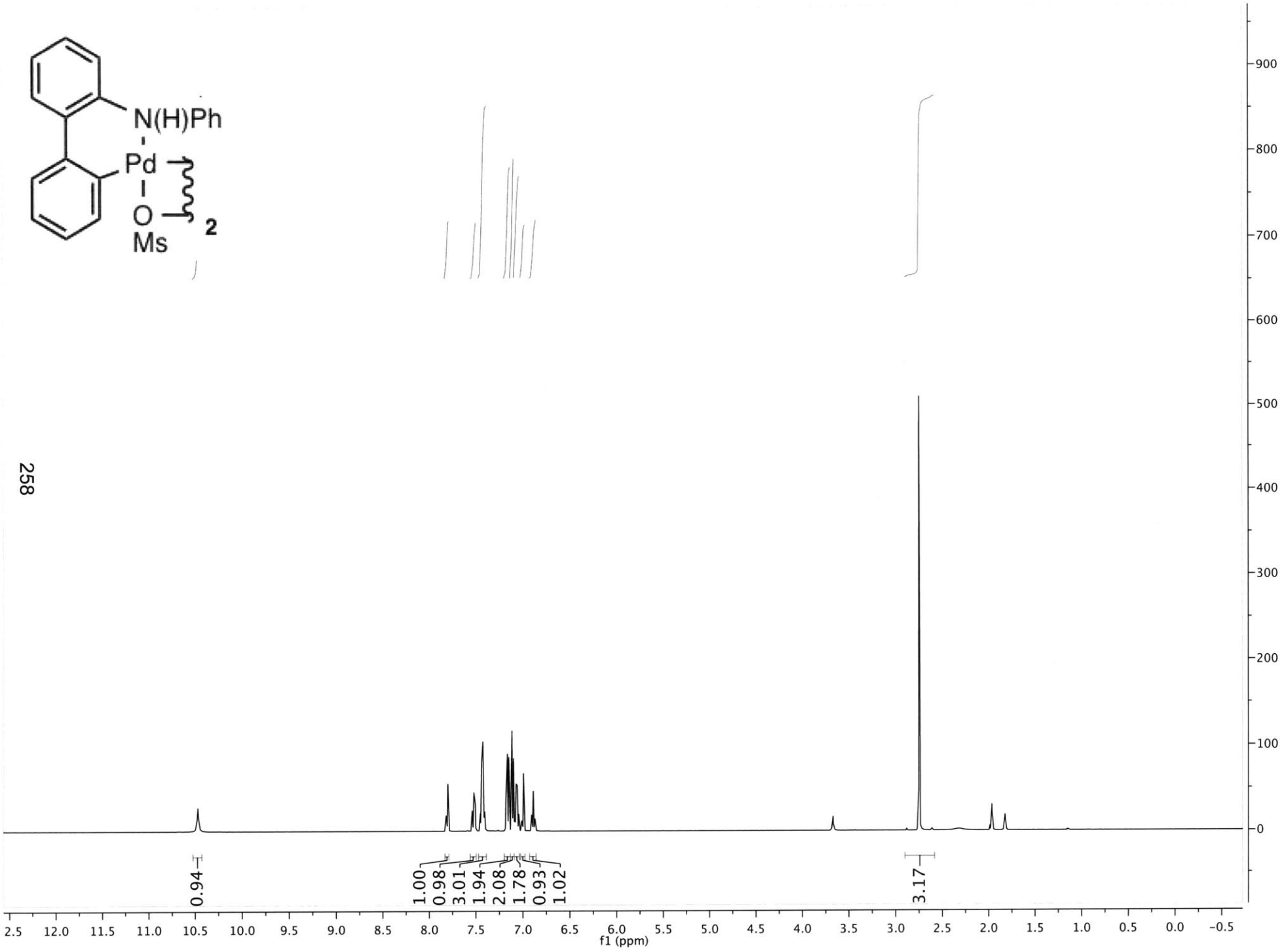
2.85 3.18

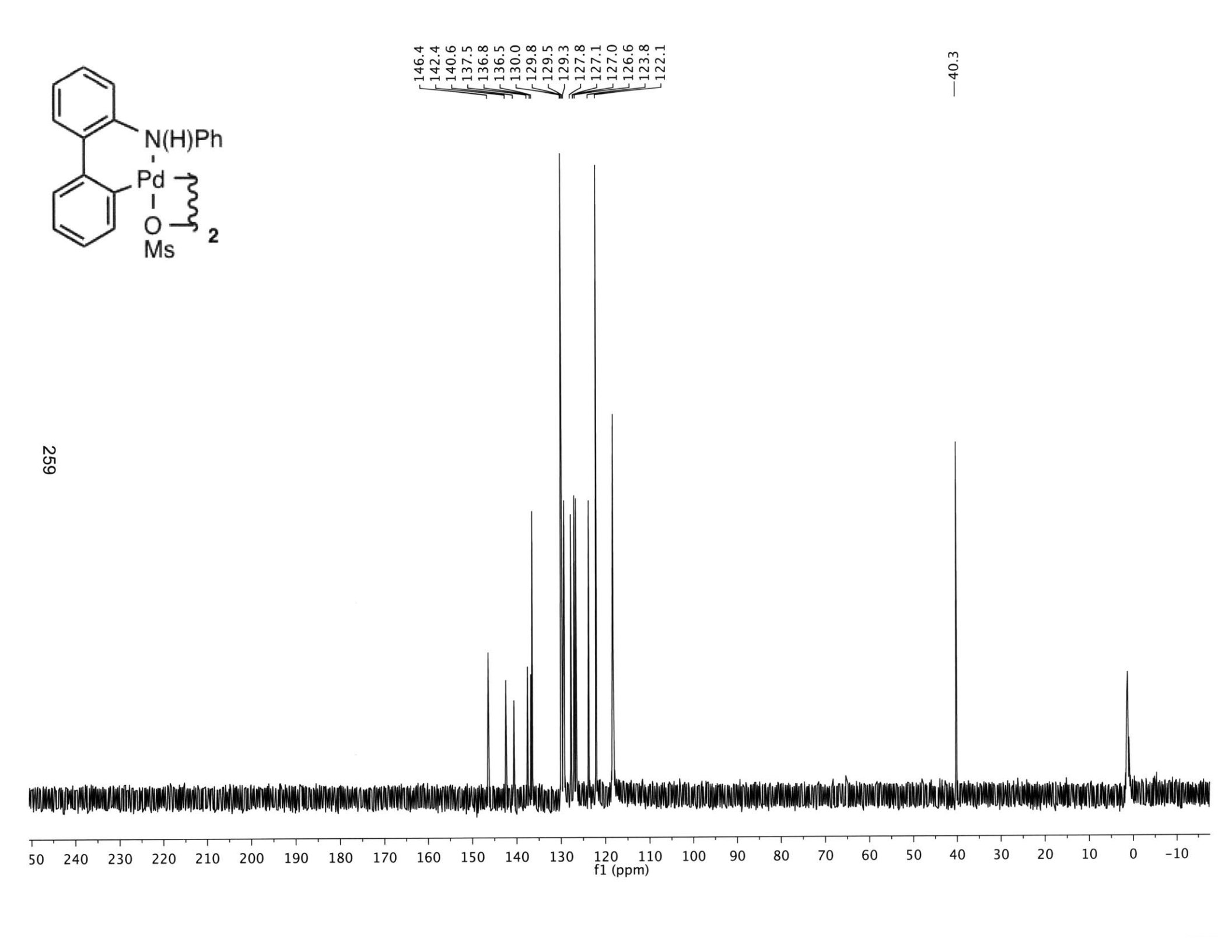
f1 (ppm)

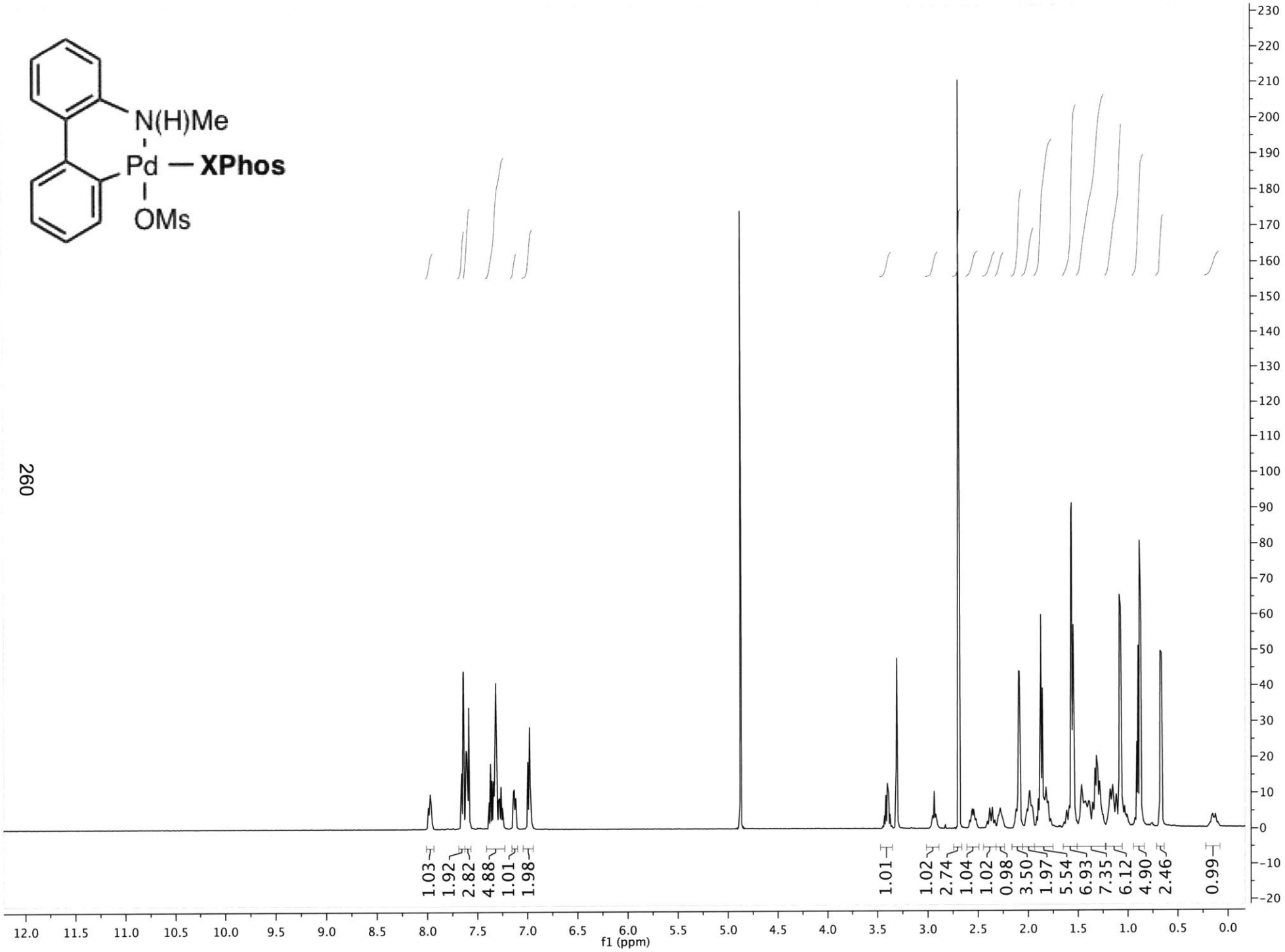

N(H)Me
Pd
O
Ms
2
142.0
140.7
139.3
133.4
129.7
128.9
128.5
127.2
126.5
125.2
39.0
255
f1 (ppm)

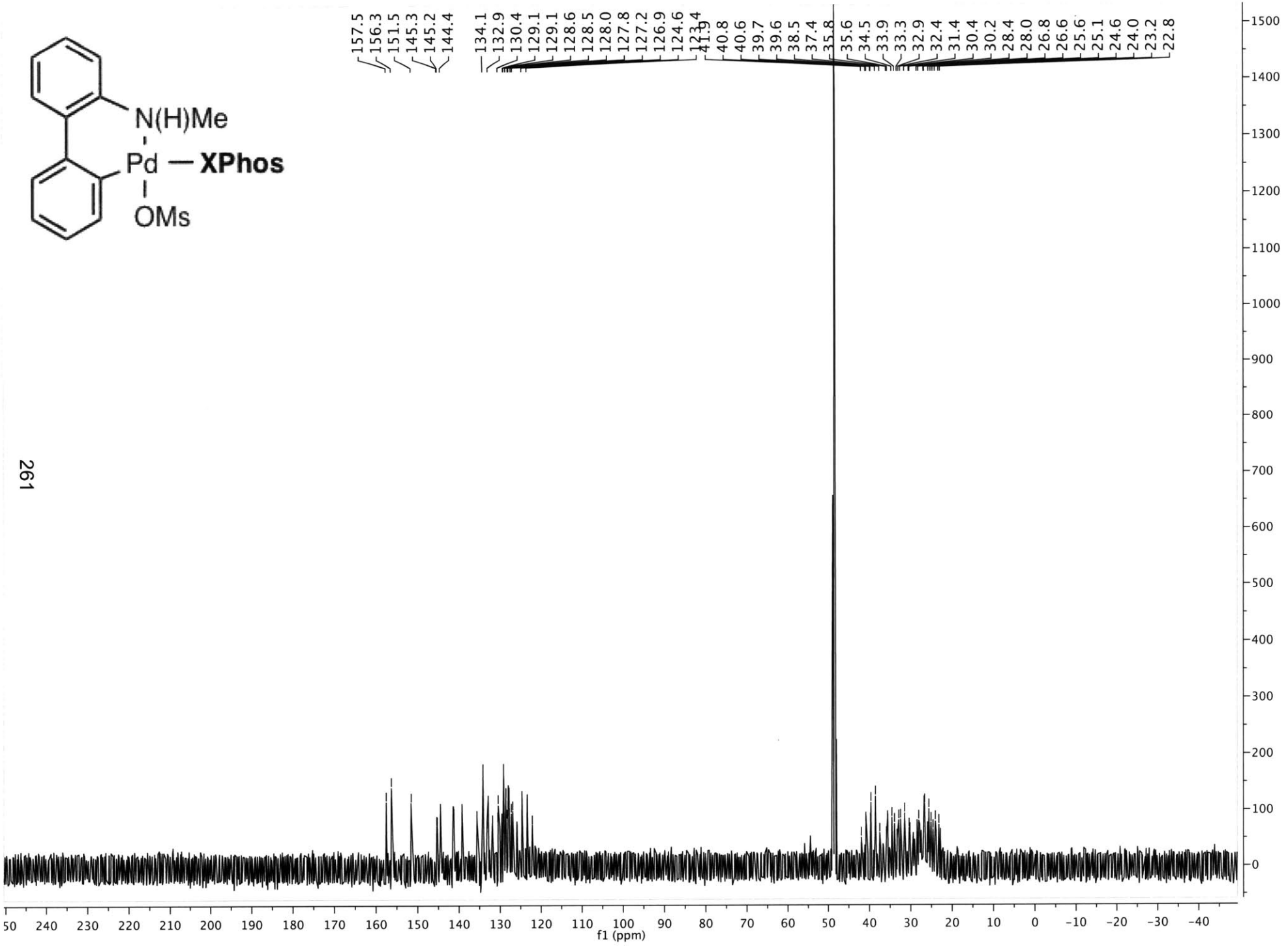

N(H)Ph
256
4.14
2.09
4.36
2.08
1.07
1.00
1.09
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


144.1
140.9
139.7
132.2
131.6
130.1
130.1
129.6
129.0
128.2
121.8
121.8
118.9
118.2
N(H)Ph
257
f1 (ppm)

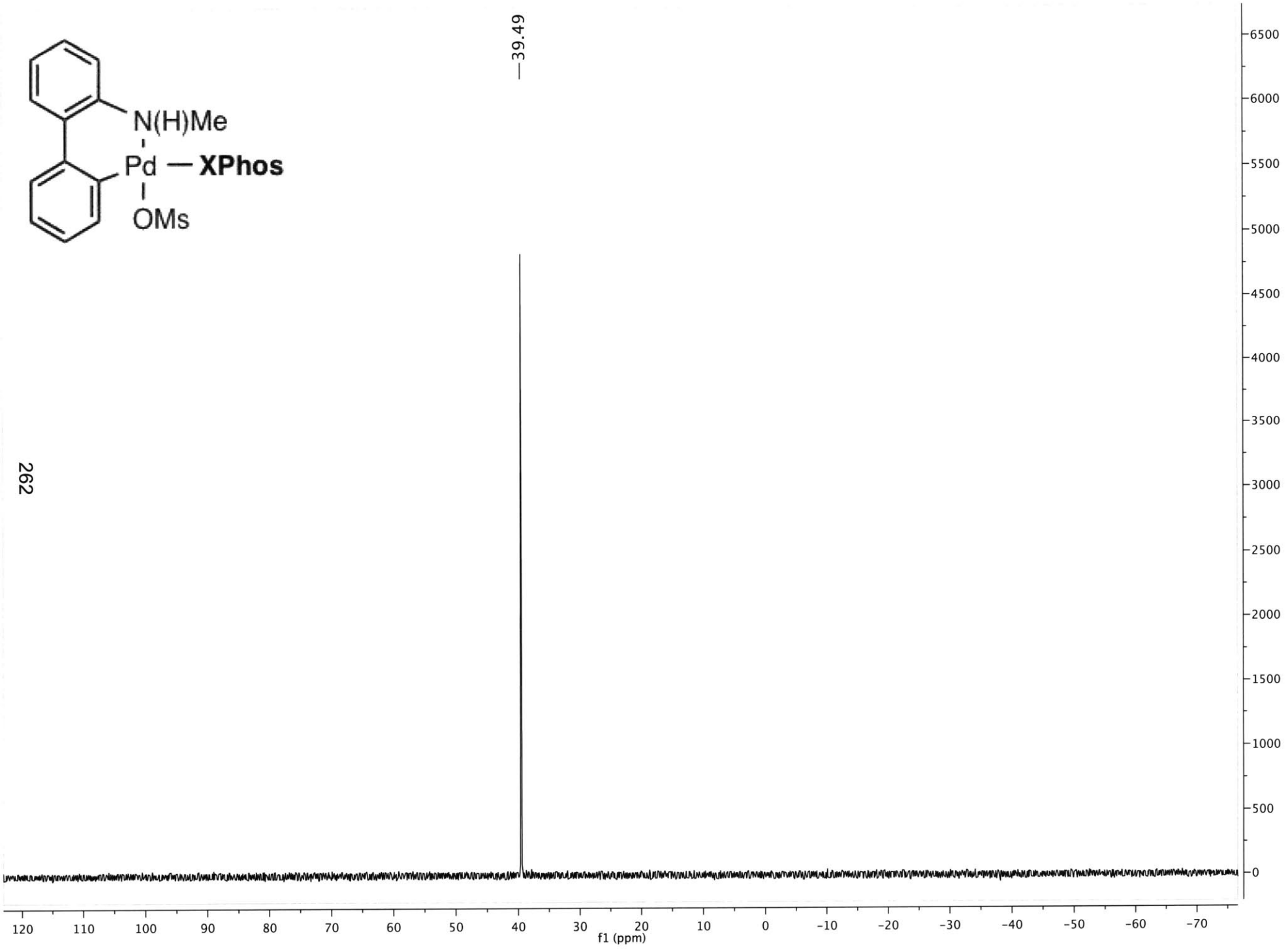

N(H)Ph
Pd
O
Ms
2
258
0.94
1.00
0.98
3.01
1.94
2.08
1.78
0.93
1.02
3.17
f1 (ppm)

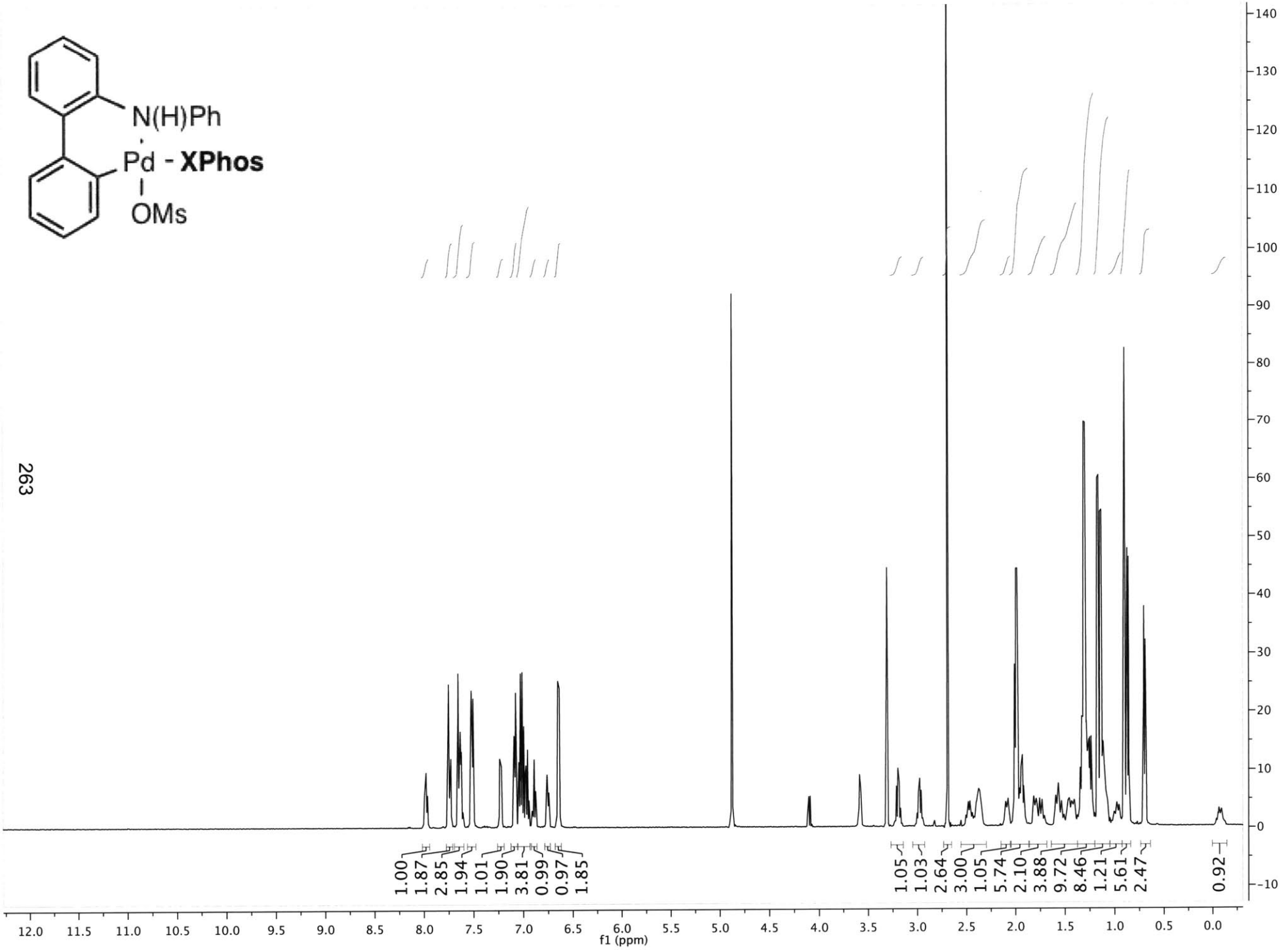

146.4
142.4
140.6
137.5
136.8
136.5
130.0
129.8
129.5
129.3
127.8
127.1
127.0
126.6
123.8
122.1
40.3
N(H)Ph
Pd
O
Ms
2
259
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

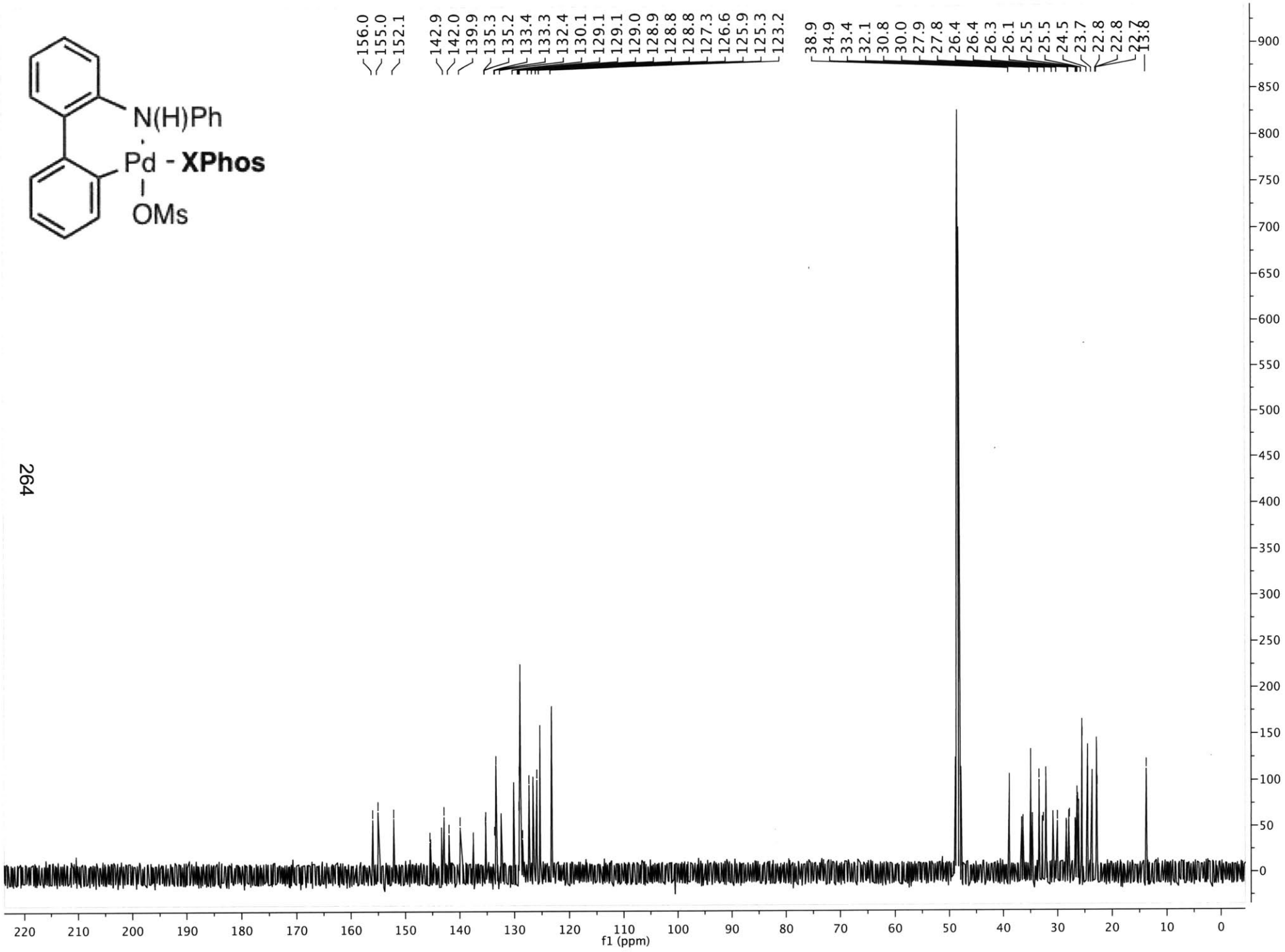

N(H)Me
Pd — XPhos
OMs
260
1.03
1.92
2.82
4.88
1.01
1.98
1.01
1.02
2.74
1.04
1.02
0.98
3.50
1.97
5.54
6.93
7.35
6.12
4.90
2.46
0.99
f1 (ppm)

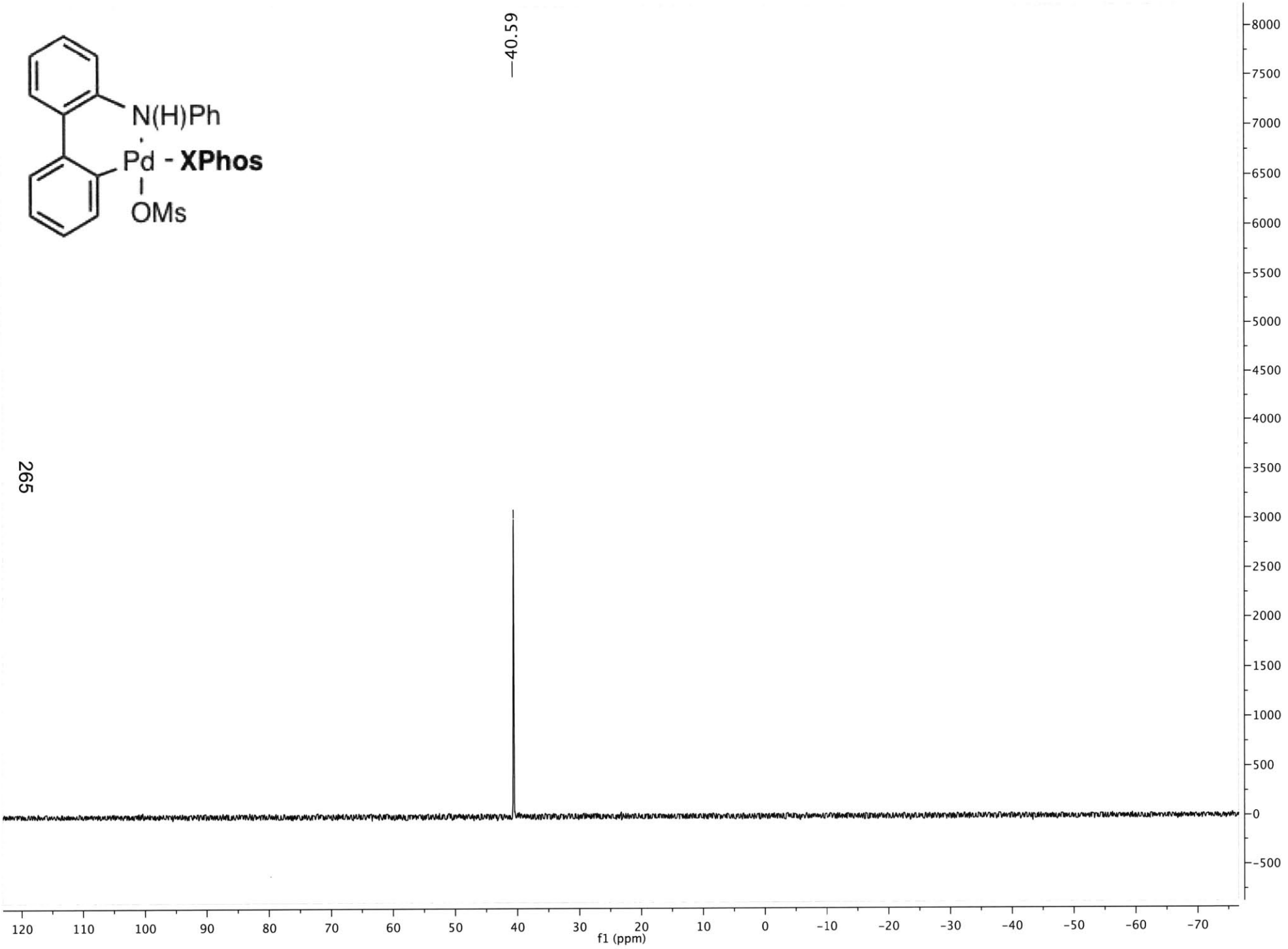

N(H)Me
Pd — XPhos
OMs
157.5
156.3
151.5
145.3
145.2
144.4
134.1
132.9
130.4
129.1
129.1
128.6
128.5
128.0
127.8
127.2
126.9
124.6
123.4
41.9
40.8
40.6
39.7
39.6
38.5
37.4
35.8
35.6
34.5
33.9
33.3
32.9
32.4
31.4
30.4
30.2
28.4
28.0
26.8
26.6
25.6
25.1
24.6
24.0
23.2
22.8
f1 (ppm)

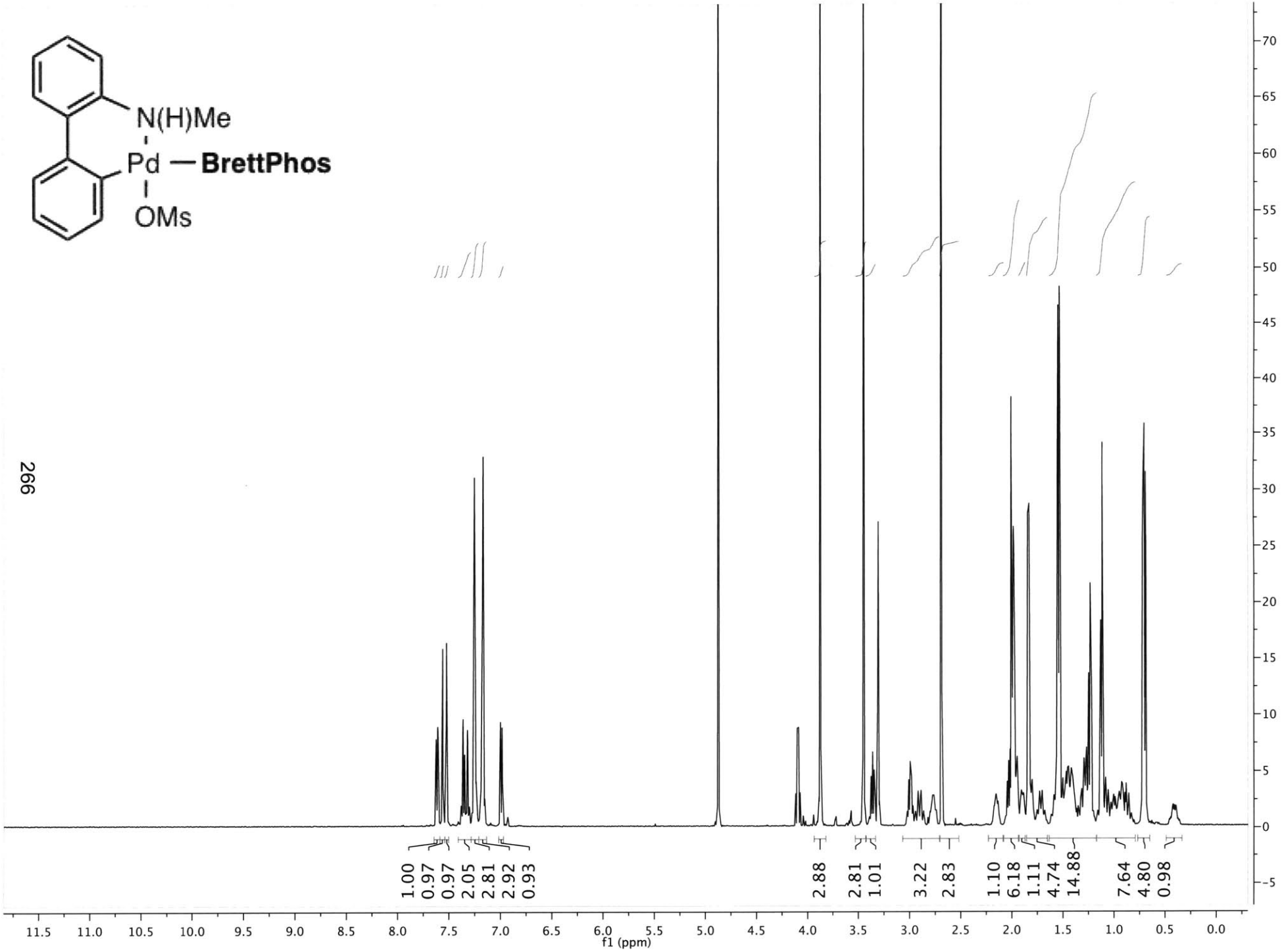
261


N(H)Me
Pd — XPhos
OMs
39.49
262
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)


N(H)Ph
Pd - XPhos
OMs
263
1.00
1.87
2.85
1.94
1.01
1.90
3.81
0.99
0.97
1.85
1.05
1.03
2.64
3.00
1.05
5.74
2.10
3.88
9.72
8.46
1.21
5.61
2.47
0.92
f1 (ppm)

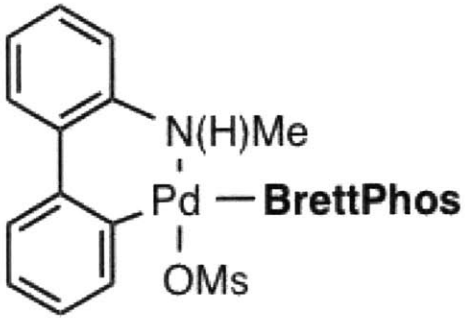

N(H)Ph
Pd - XPhos
OMs
156.0
155.0
152.1
142.9
142.0
139.9
135.3
135.2
133.4
133.3
132.4
130.1
129.1
129.1
129.0
128.9
128.8
128.8
127.3
126.6
125.9
125.3
123.2
38.9
34.9
33.4
32.1
30.8
30.0
27.9
27.8
26.4
26.4
26.3
26.1
25.5
25.5
24.5
23.7
22.8
22.8
22.7
13.8
f1 (ppm)

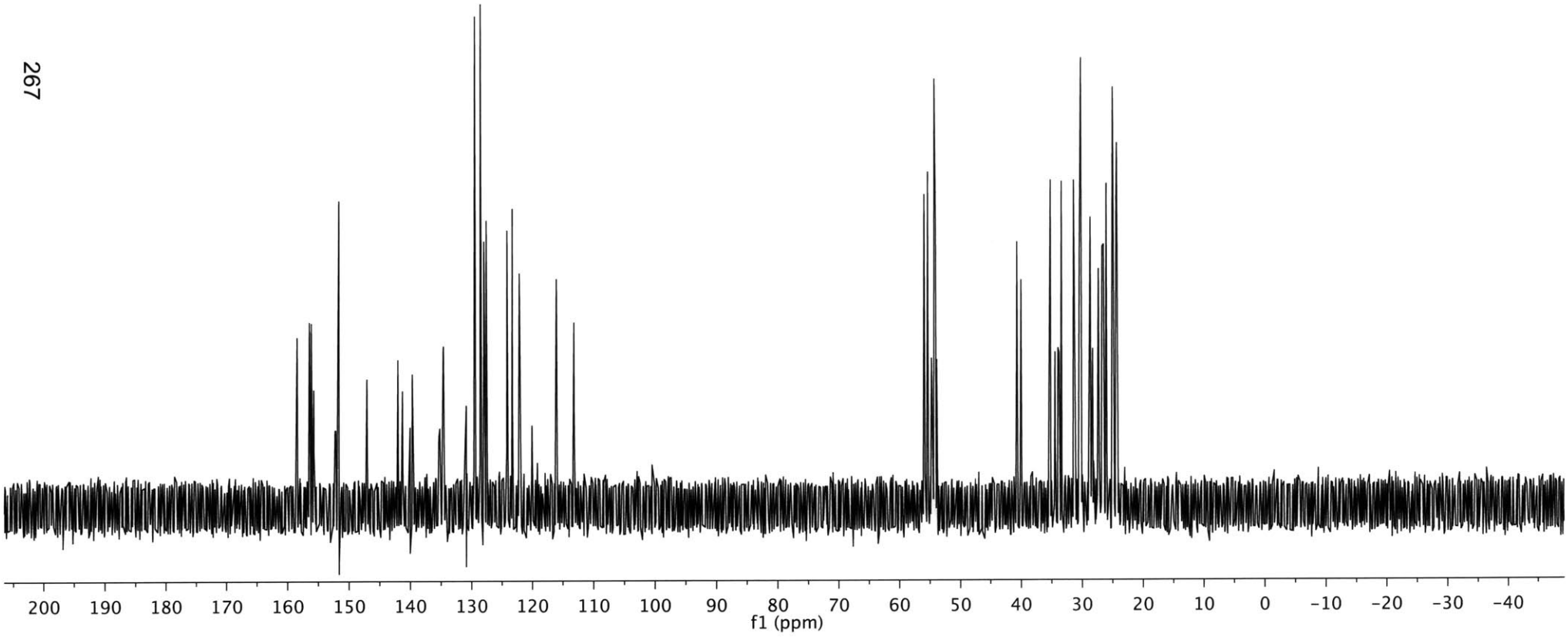

N(H)Ph
Pd - XPhos
OMs
40.59
265
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

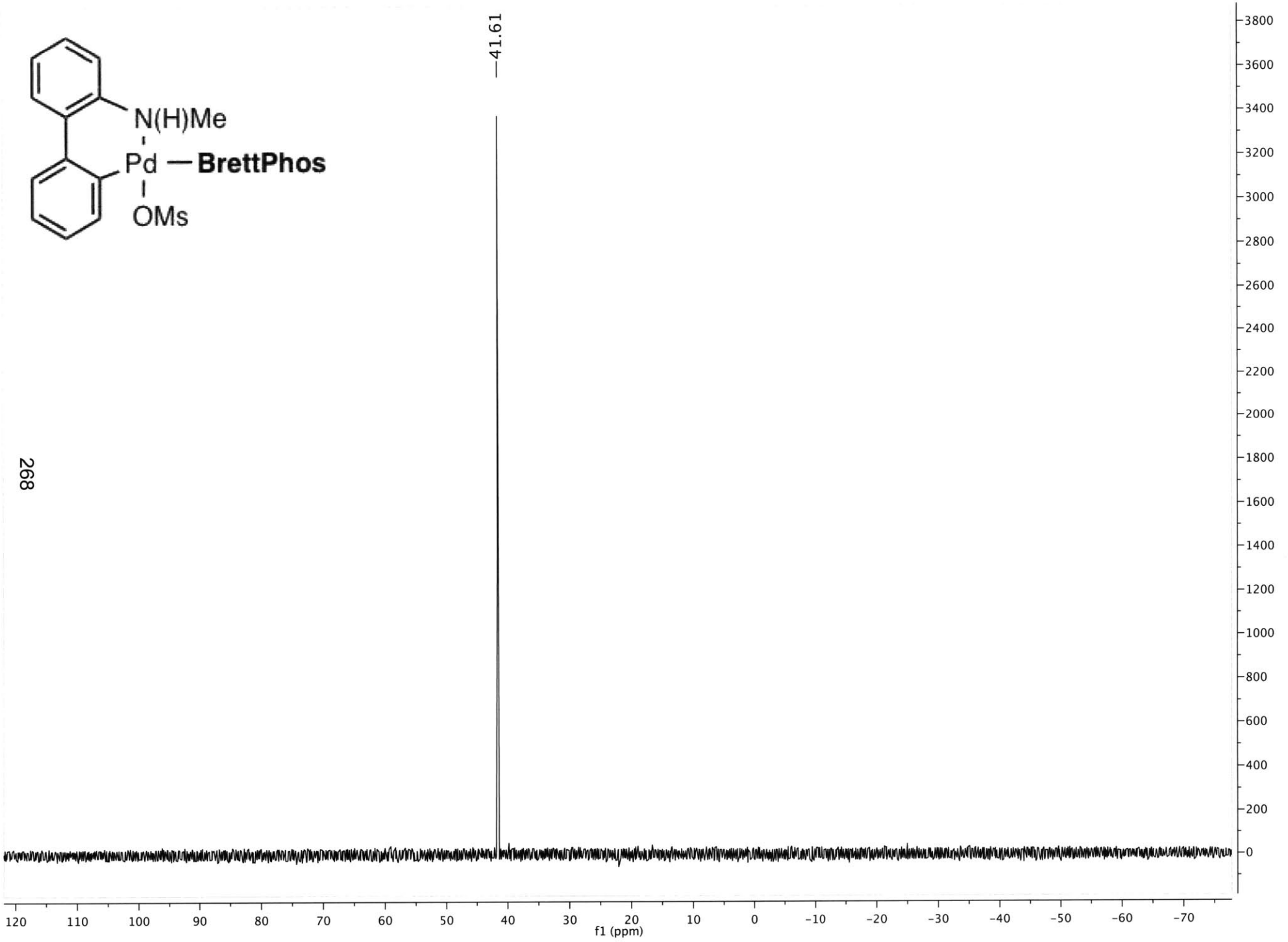

N(H)Me
Pd — BrettPhos
OMs
266
1.00
0.97
0.97
2.05
2.81
2.92
0.93
2.88
2.81
1.01
3.22
2.83
1.10
6.18
1.11
4.74
14.88
7.64
4.80
0.98
f1 (ppm)

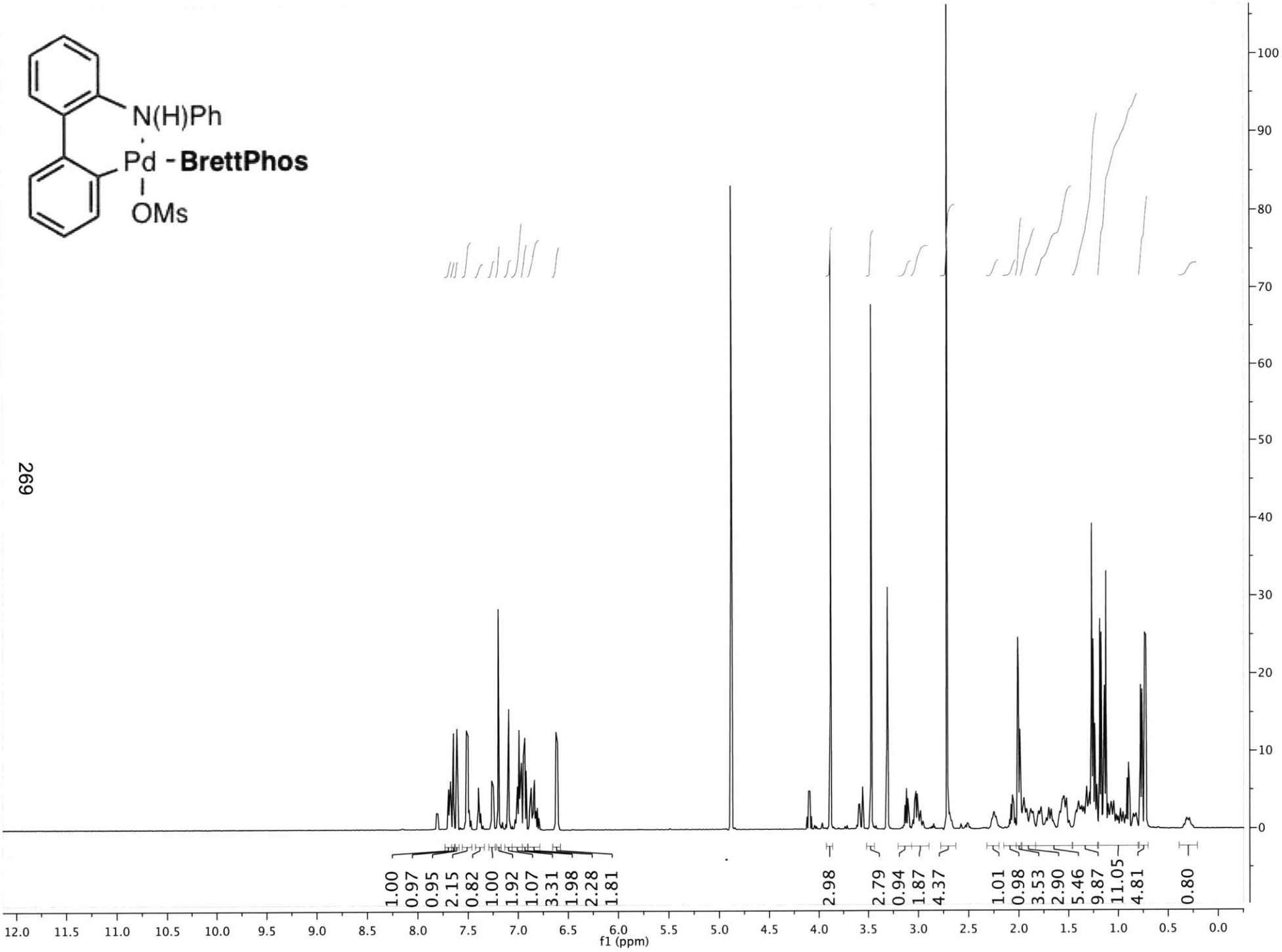
158.4
156.4
156.1
155.7
152.3
152.1
151.6
147.1
142.0
141.2
139.7
135.3
135.2
134.6
130.9
129.5
128.5
128.0
127.6
124.2
123.5
123.3
122.1
120.0
116.1
113.2

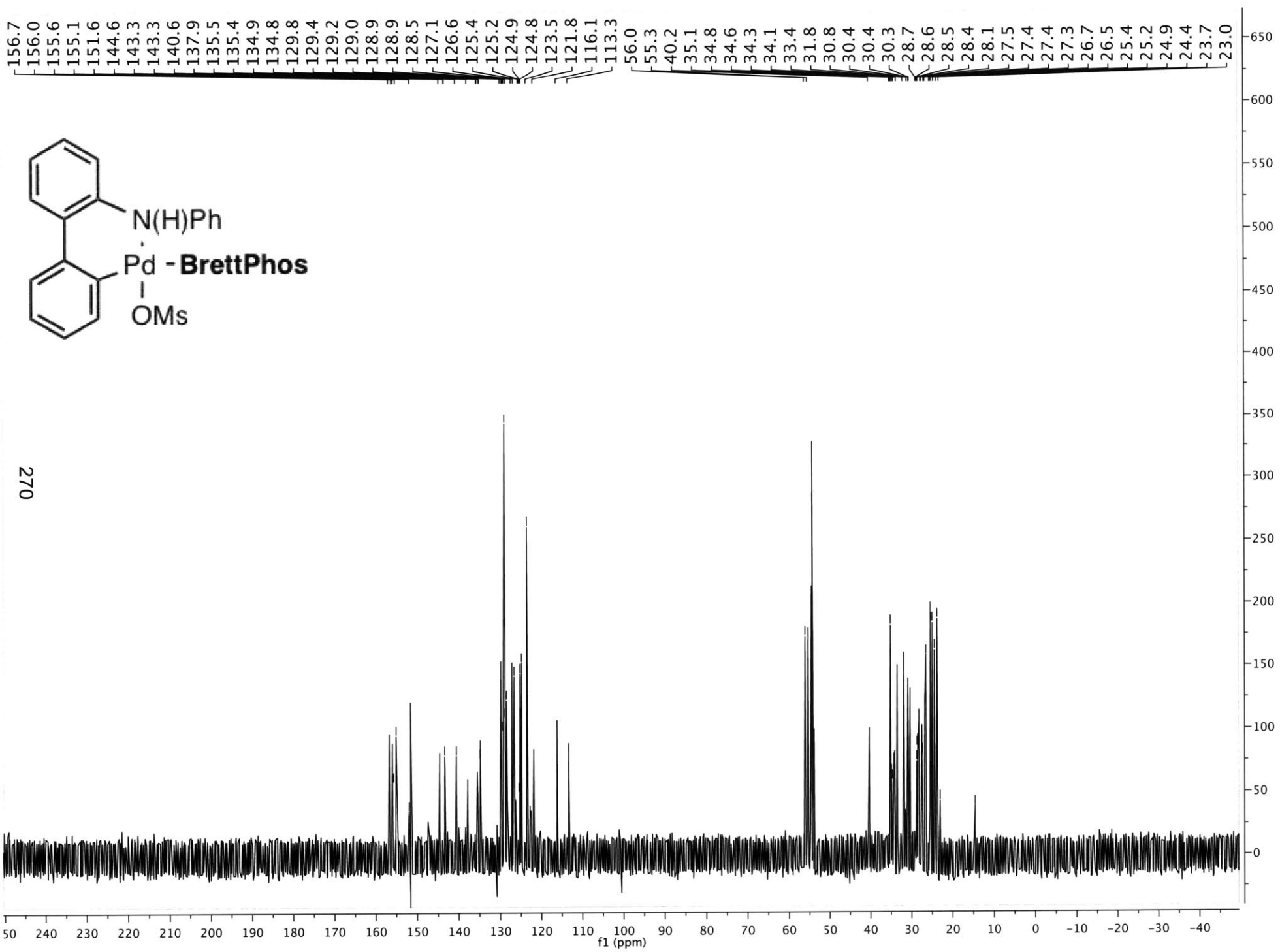
56.0
55.4
40.7
40.0
35.2
34.7
34.5
34.0
33.8
33.4
31.4
30.5
30.2
28.8
28.7
28.4
28.3
27.4
27.3
27.2
26.8
26.5
26.1
25.0
25.0
24.9
24.5
24.4

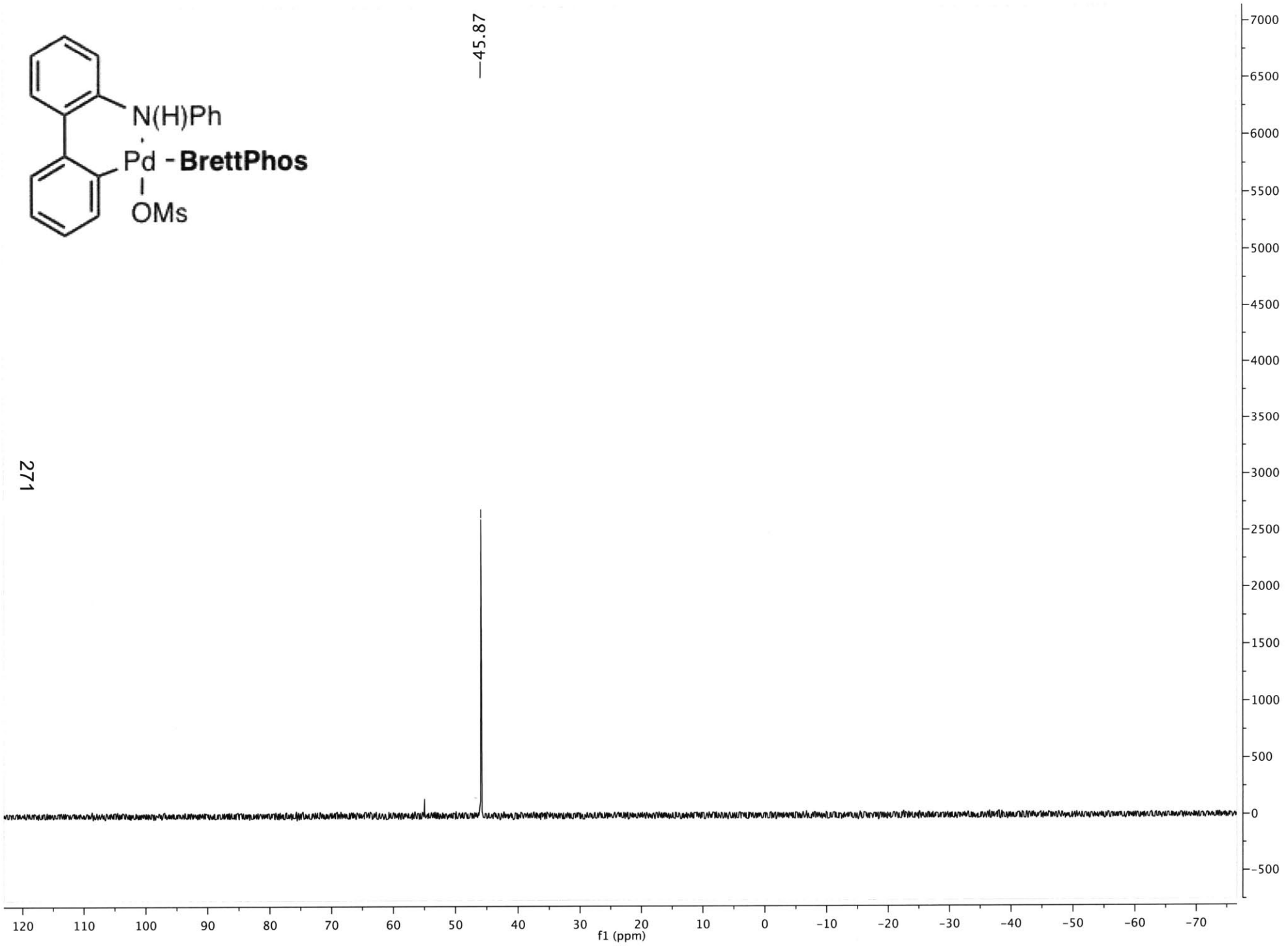


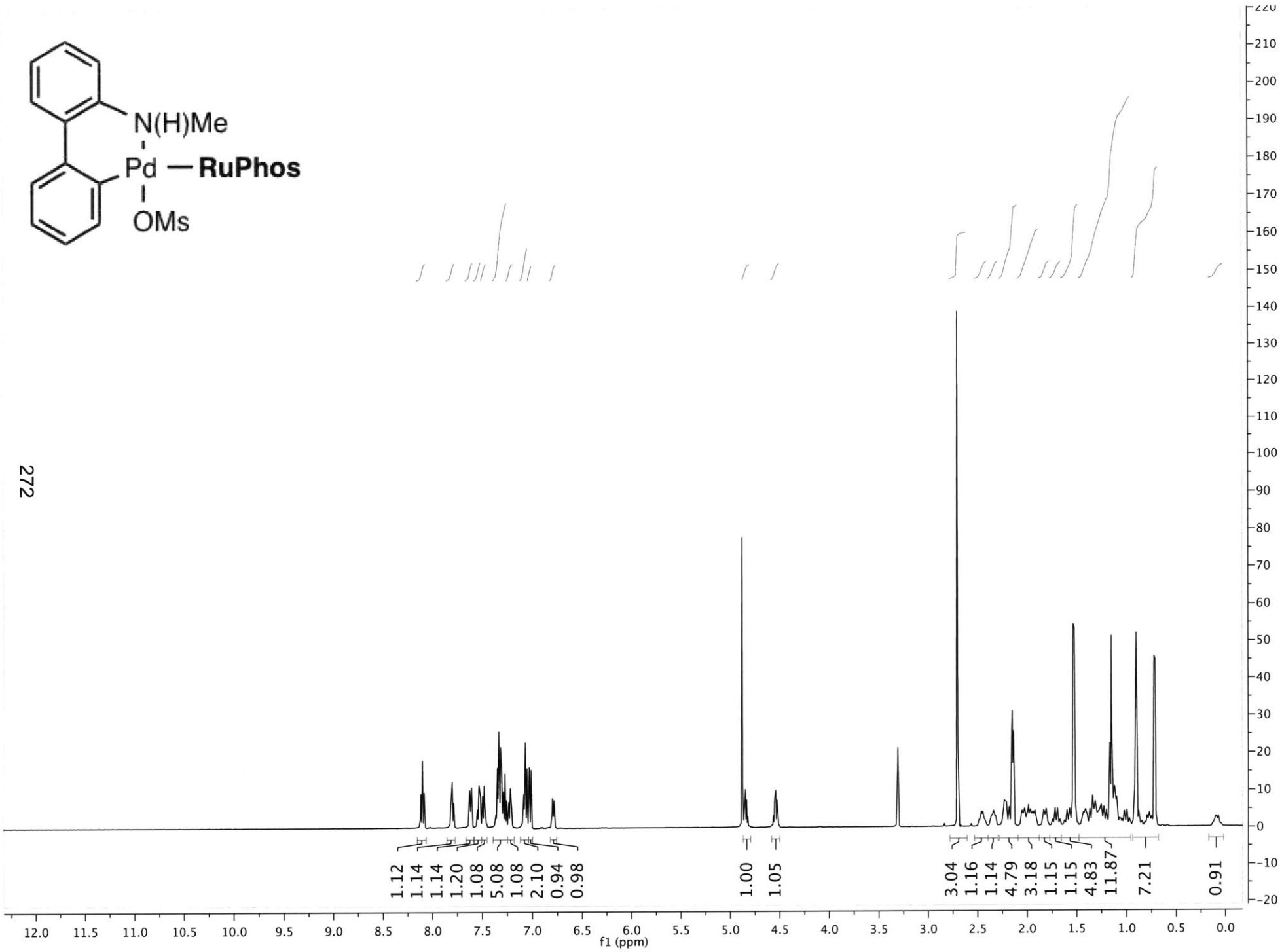


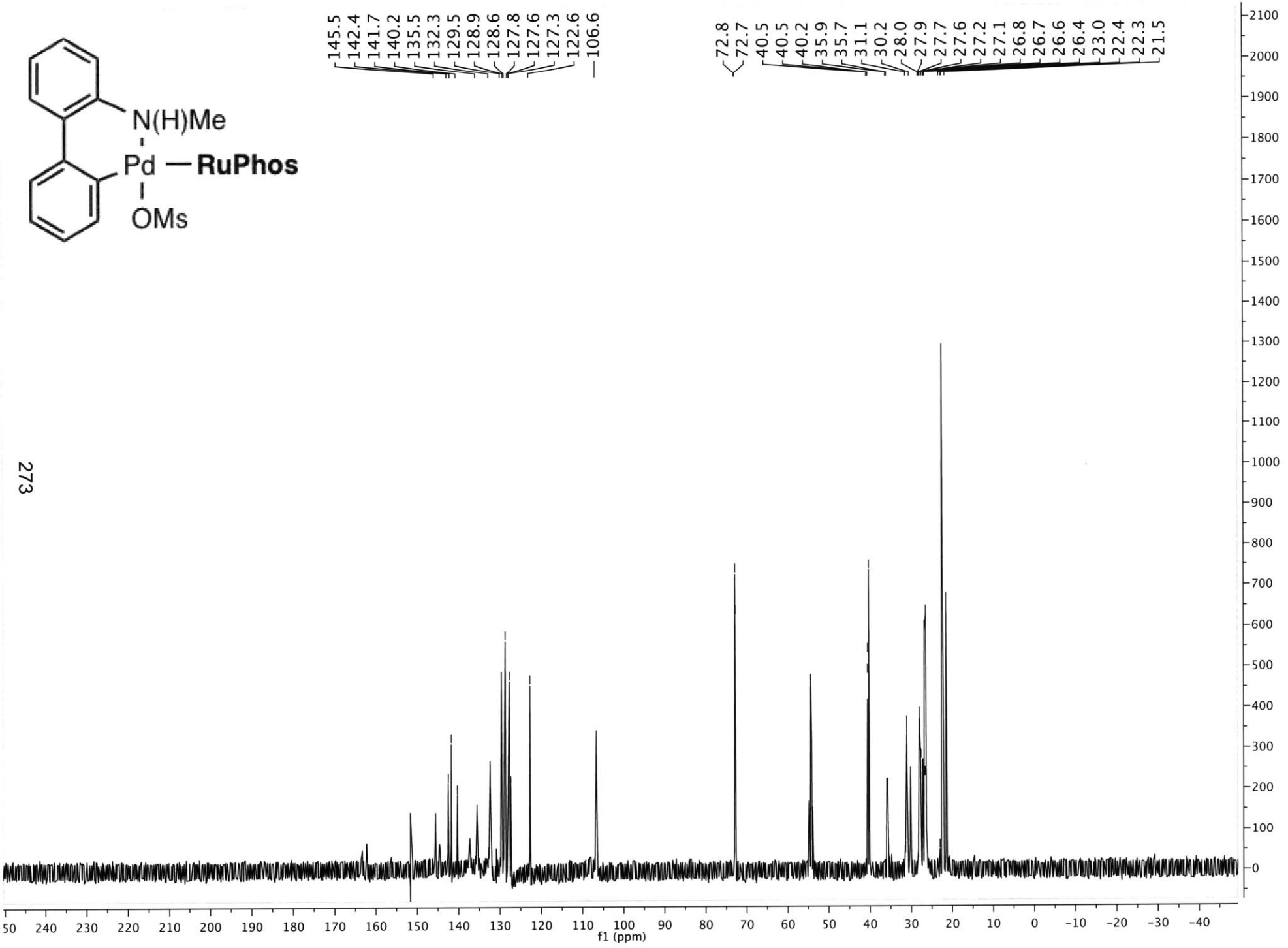

N(H)Me
Pd — BrettPhos
OMs
41.61
268
f1 (ppm)

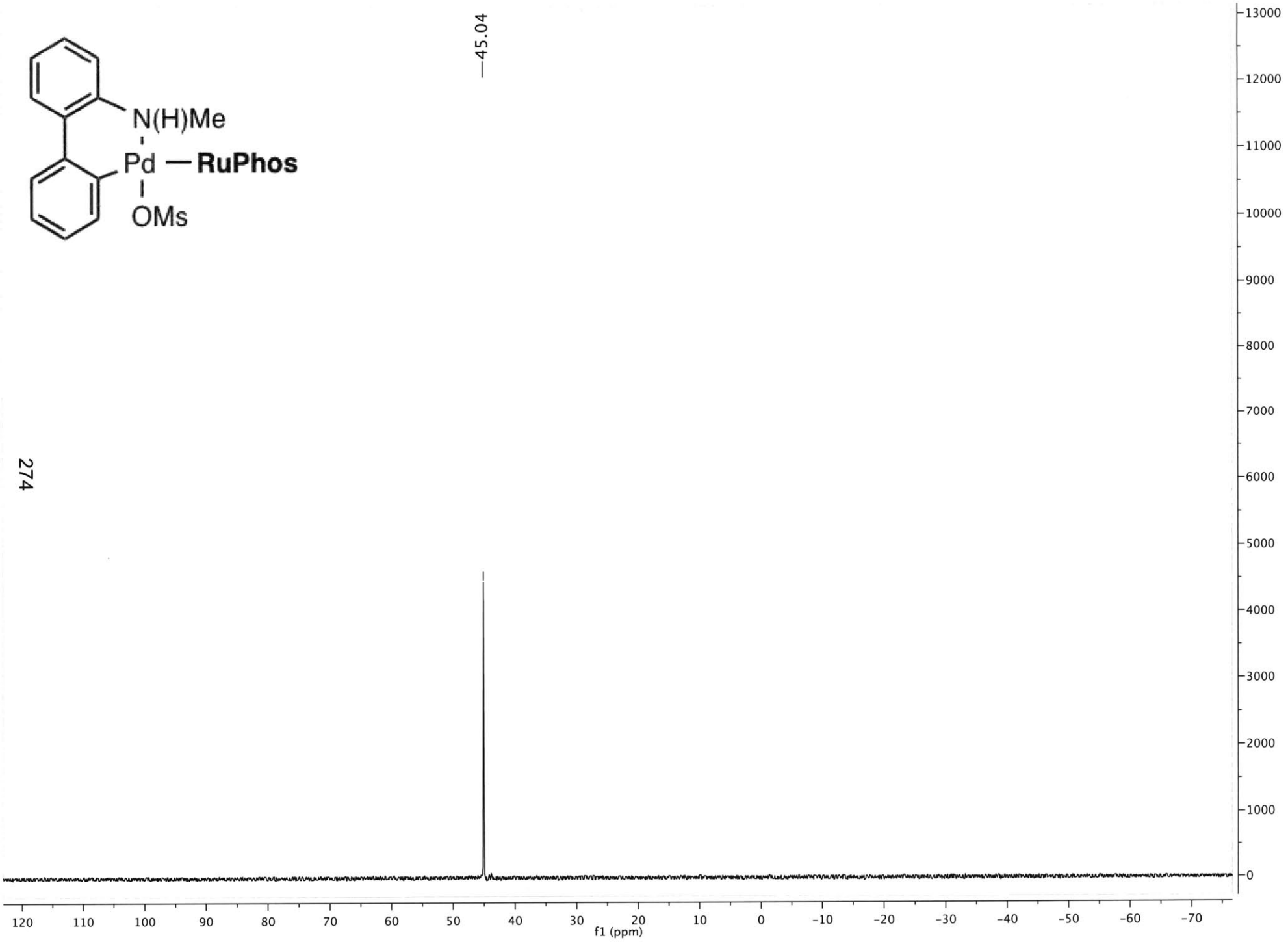

N(H)Ph
Pd - BrettPhos
OMs
269
1.00
0.97
0.95
2.15
0.82
1.00
1.92
1.07
3.31
1.98
2.28
1.81
2.98
2.79
0.94
1.87
4.37
1.01
0.98
3.53
2.90
5.46
9.87
11.05
4.81
0.80
f1 (ppm)

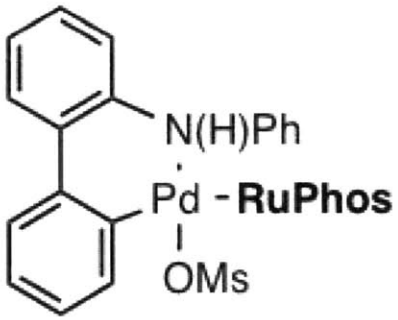

156.7
156.0
155.6
155.1
151.6
144.6
143.3
143.3
140.6
137.9
135.5
135.4
134.9
134.8
129.8
129.4
129.2
129.0
128.9
128.9
128.5
127.1
126.6
125.4
125.2
124.9
124.8
123.5
121.8
116.1
113.3
56.0
55.3
40.2
35.1
34.8
34.6
34.3
34.1
33.4
31.8
30.8
30.4
30.4
30.3
28.7
28.6
28.5
28.4
28.1
27.5
27.4
27.4
27.3
26.7
26.5
25.4
25.2
24.9
24.4
23.7
23.0
N(H)Ph
Pd - BrettPhos
OMs
270
650
600
550
500
450
400
350
300
250
200
150
100
50
0
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)


N(H)Ph
Pd - BrettPhos
OMs
45.87
271
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)


N(H)Me
Pd — RuPhos
OMs
272
1.12
1.14
1.14
1.20
1.08
5.08
1.08
2.10
0.94
0.98
1.00
1.05
3.04
1.16
1.14
4.79
3.18
1.15
1.15
4.83
11.87
7.21
0.91
f1 (ppm)


N(H)Me
Pd — RuPhos
OMs
145.5
142.4
141.7
140.2
135.5
132.3
129.5
128.9
128.6
127.8
127.6
127.3
122.6
106.6
72.8
72.7
40.5
40.5
40.2
35.9
35.7
31.1
30.2
28.0
27.9
27.7
27.6
27.2
27.1
26.8
26.7
26.6
26.4
23.0
22.4
22.3
21.5
273
f1 (ppm)

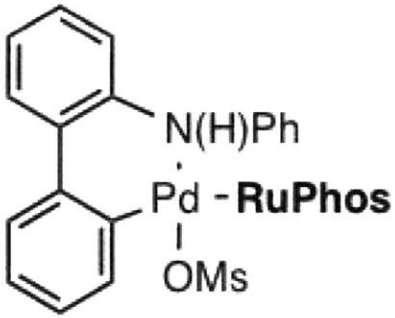

N(H)Me
Pd — RuPhos
OMs
45.04
274
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)



275

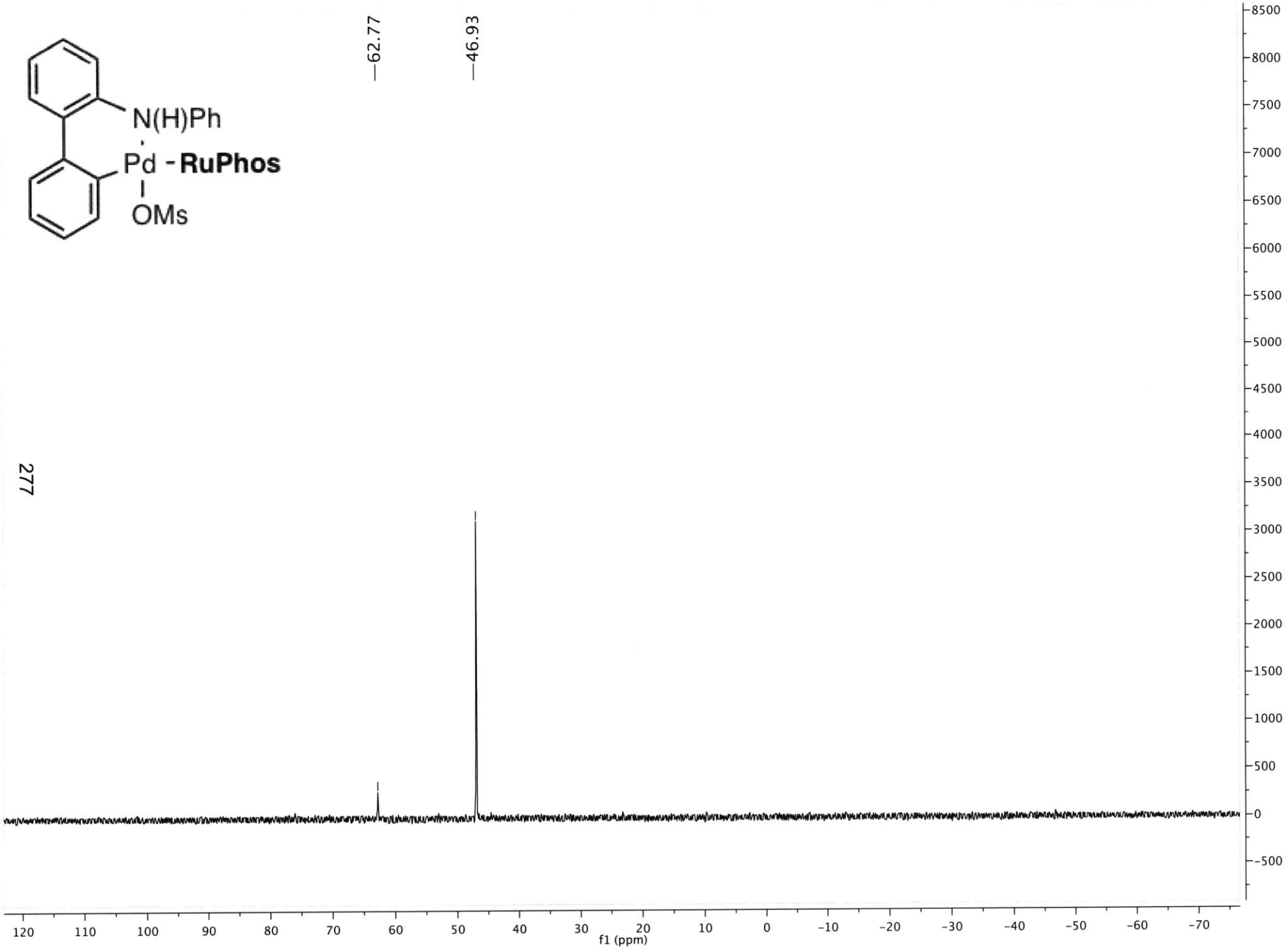
1.00 1.09 1.04 4.15 2.63 3.14 1.57 0.89 1.27 0.99 0.83 2.65 1.61 0.84 2.13 8.51 15.91 2.52 0.76

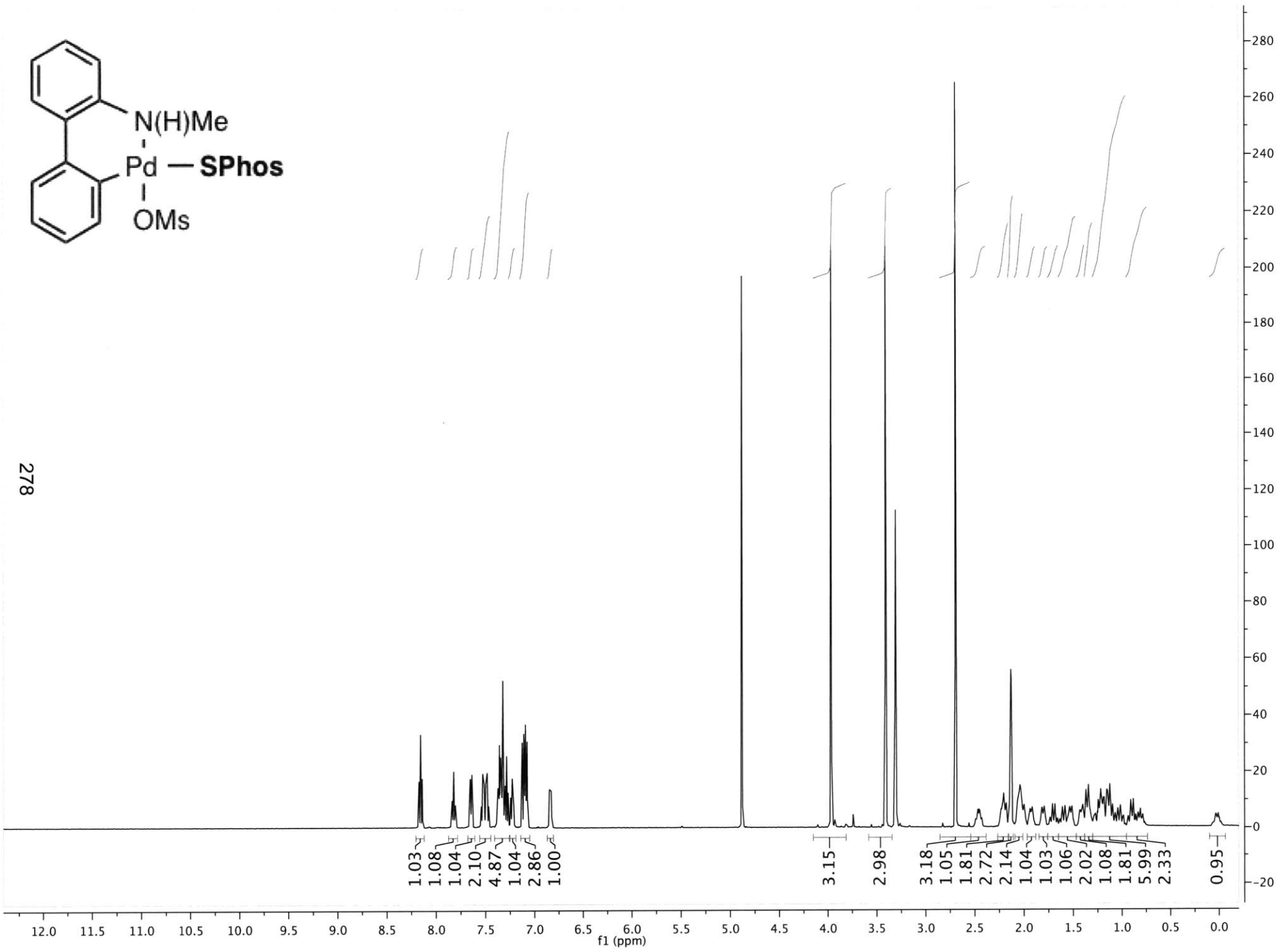
f1 (ppm)

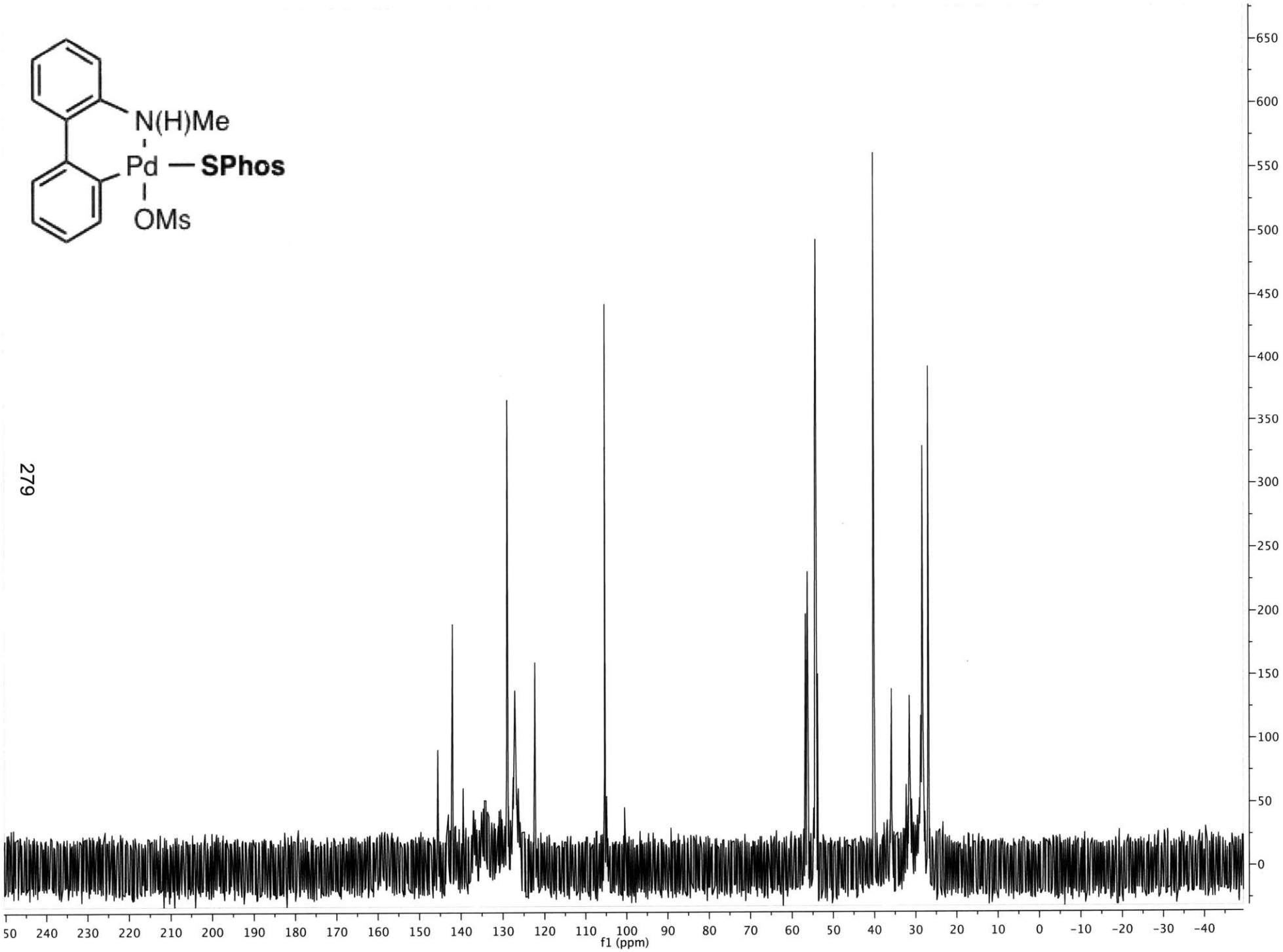


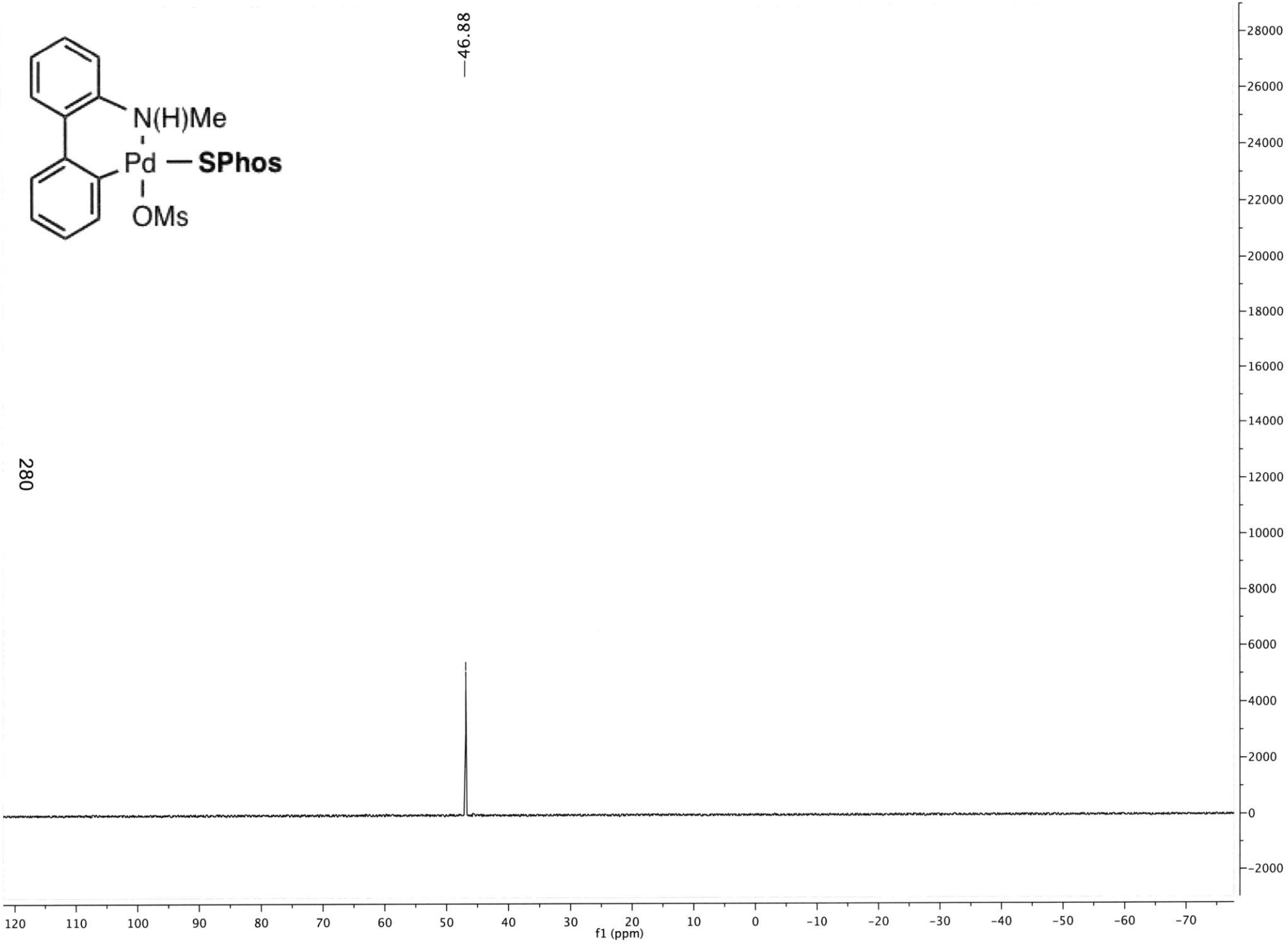
276

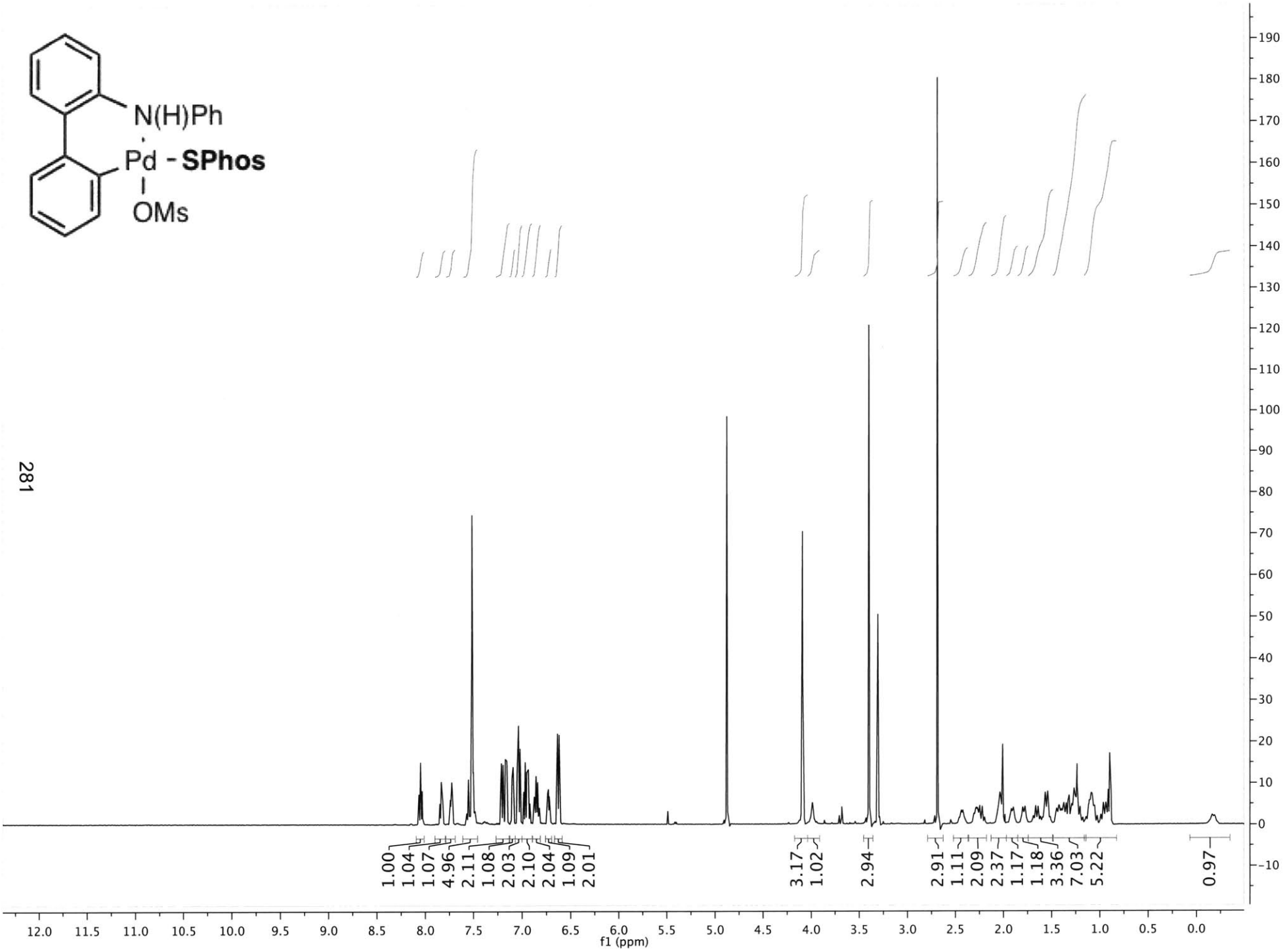
f1 (ppm)

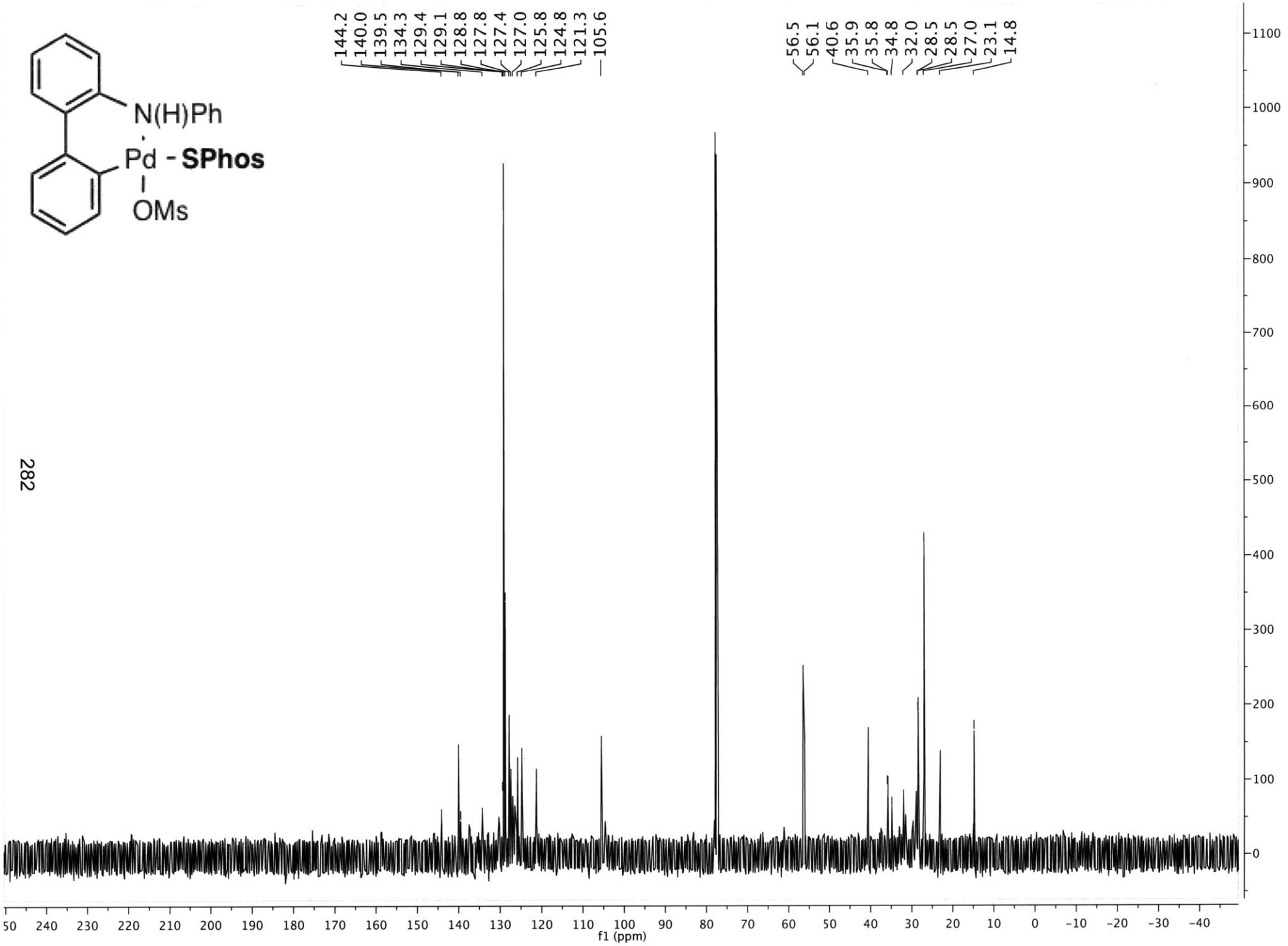

N(H)Ph
Pd - RuPhos
OMs
62.77
46.93
277
f1 (ppm)

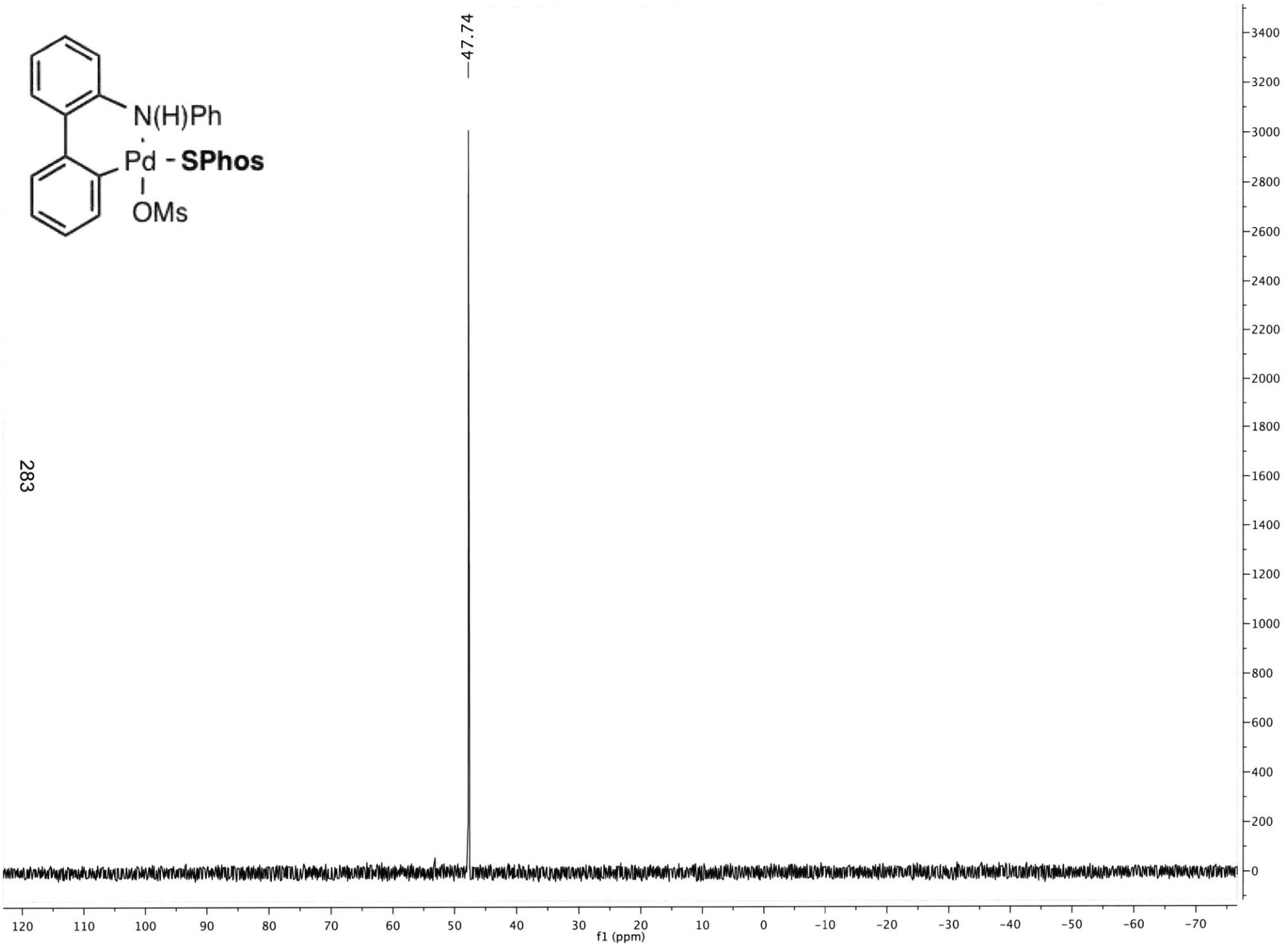

N(H)Me
Pd — SPhos
OMs
278
1.03
1.08
1.04
2.10
4.87
1.04
2.86
1.00
3.15
2.98
3.18
1.05
1.81
2.72
2.14
1.04
1.03
1.06
2.02
1.08
1.81
5.99
2.33
0.95
f1 (ppm)

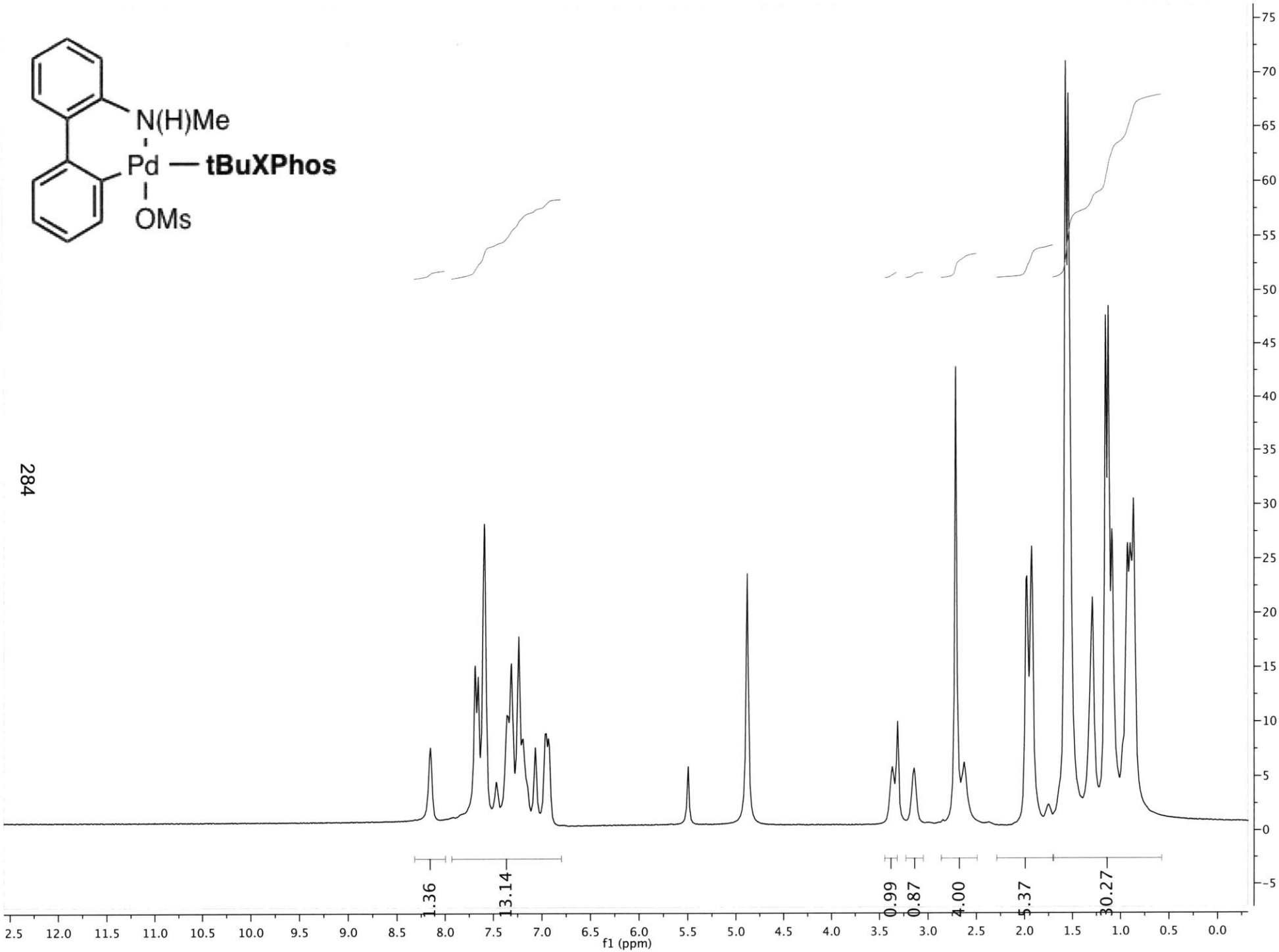

N(H)Me
Pd — SPhos
OMs
279
650
600
550
500
450
400
350
300
250
200
150
100
50
0
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

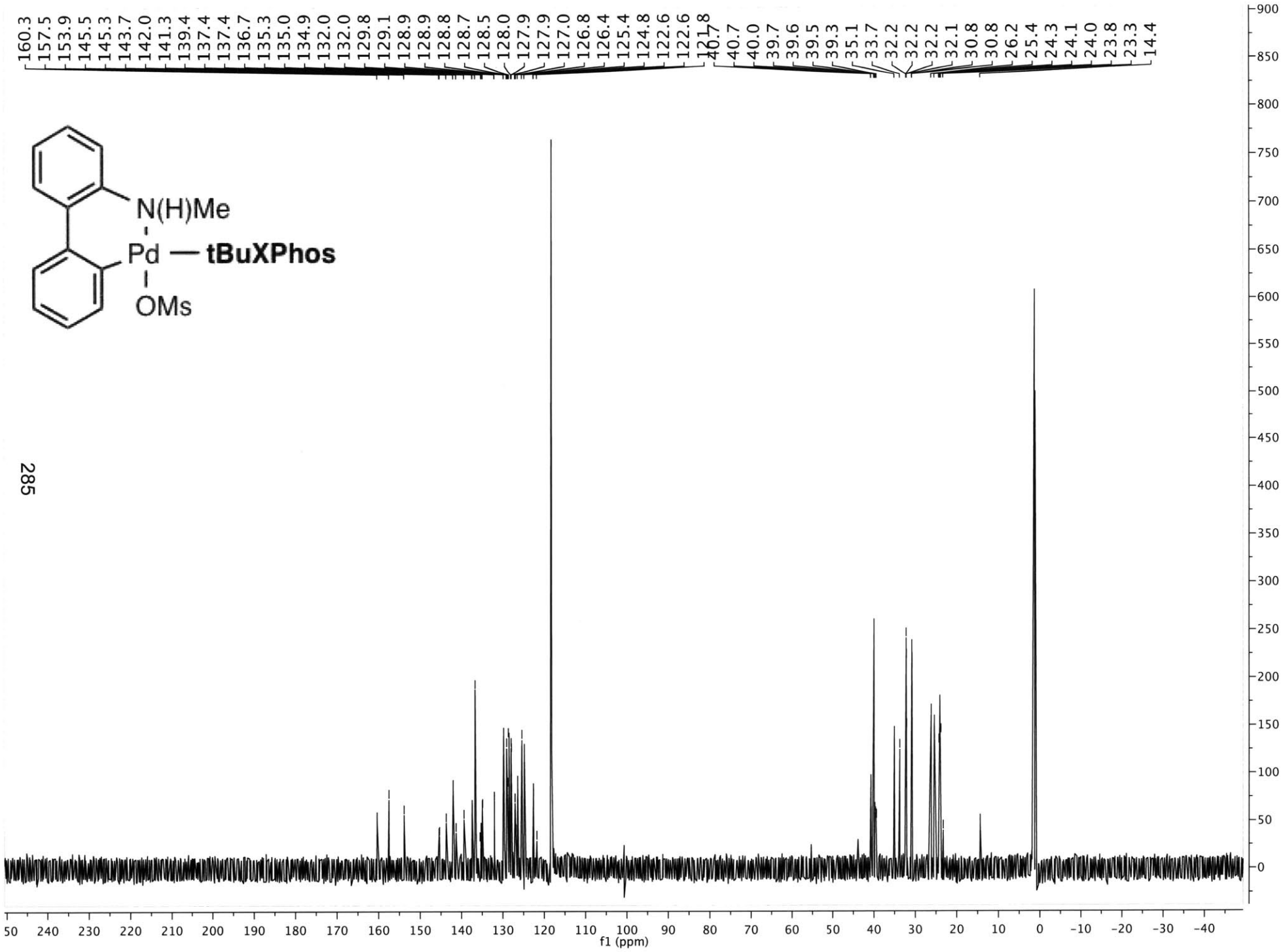

N(H)Me
Pd — SPhos
OMs
46.88
280
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

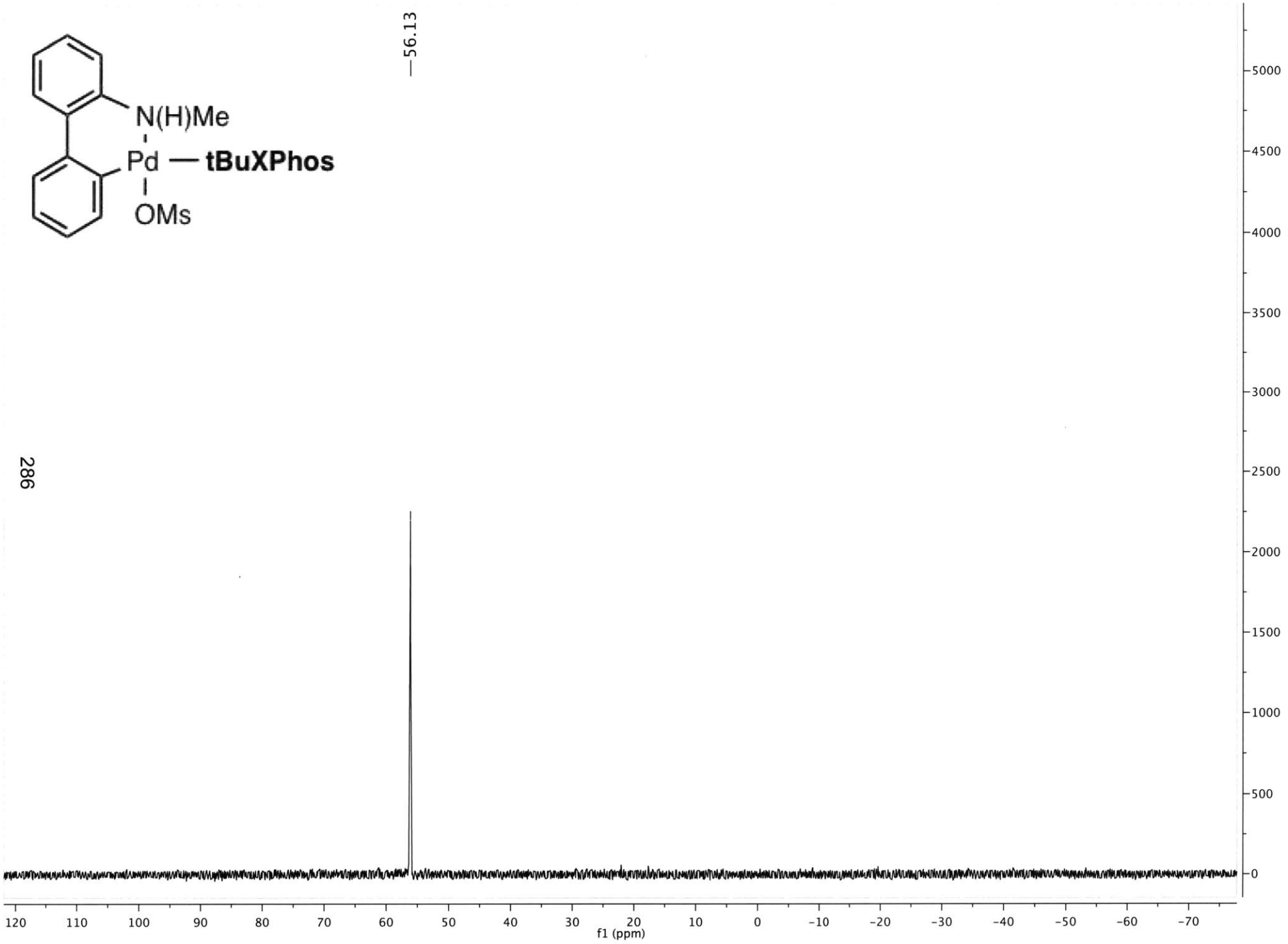

N(H)Ph
Pd - SPhos
OMs
281
1.00
1.04
1.07
4.96
2.11
1.08
2.03
2.10
2.04
1.09
2.01
3.17
1.02
2.94
2.91
1.11
2.09
2.37
1.17
1.18
3.36
7.03
5.22
0.97
f1 (ppm)

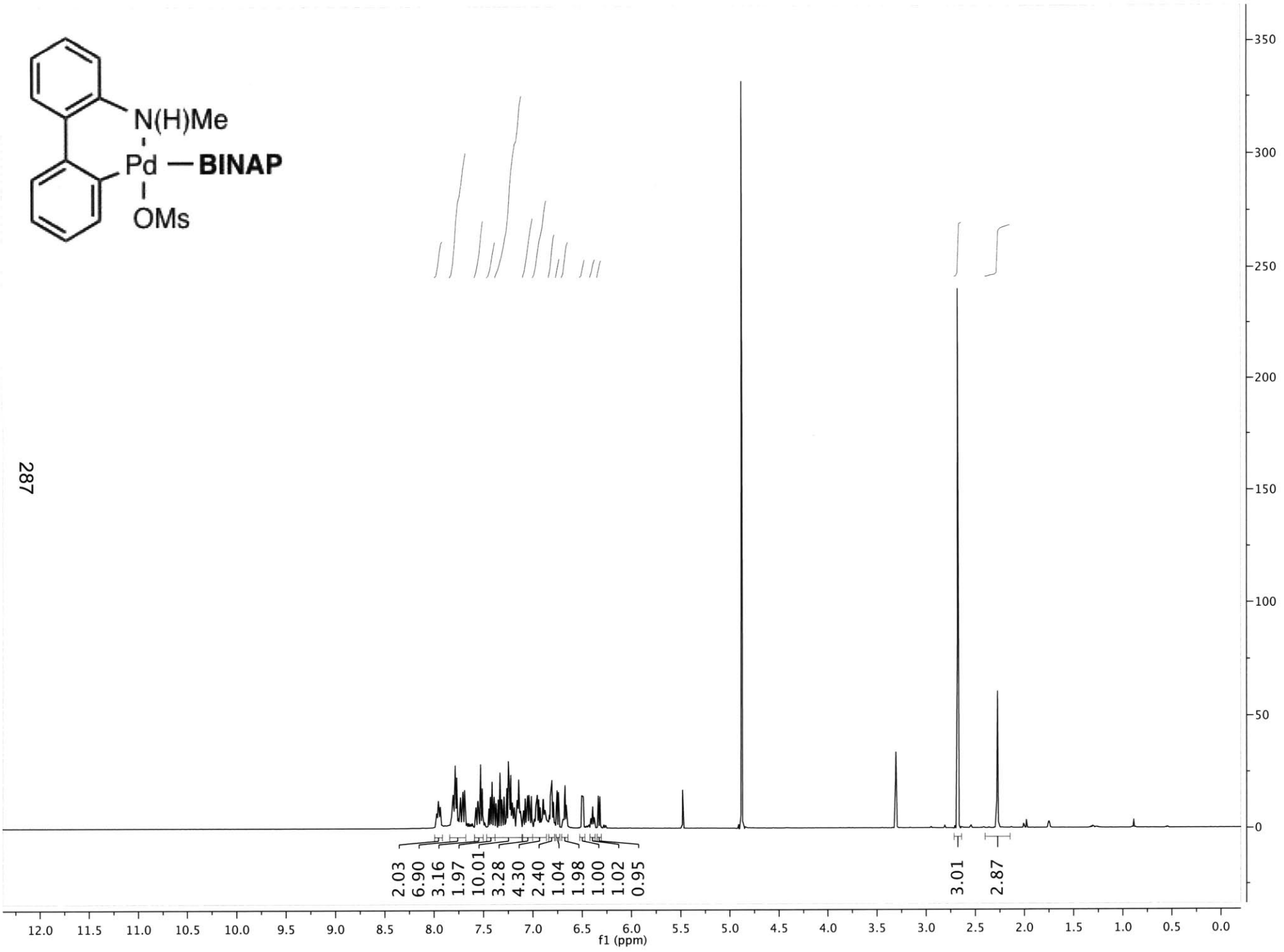

144.2
140.0
139.5
134.3
129.4
129.1
128.8
127.8
127.4
127.0
125.8
124.8
121.3
105.6
56.5
56.1
40.6
35.9
35.8
34.8
32.0
28.5
28.5
27.0
23.1
14.8
N(H)Ph
Pd - SPhos
OMs
282
f1 (ppm)

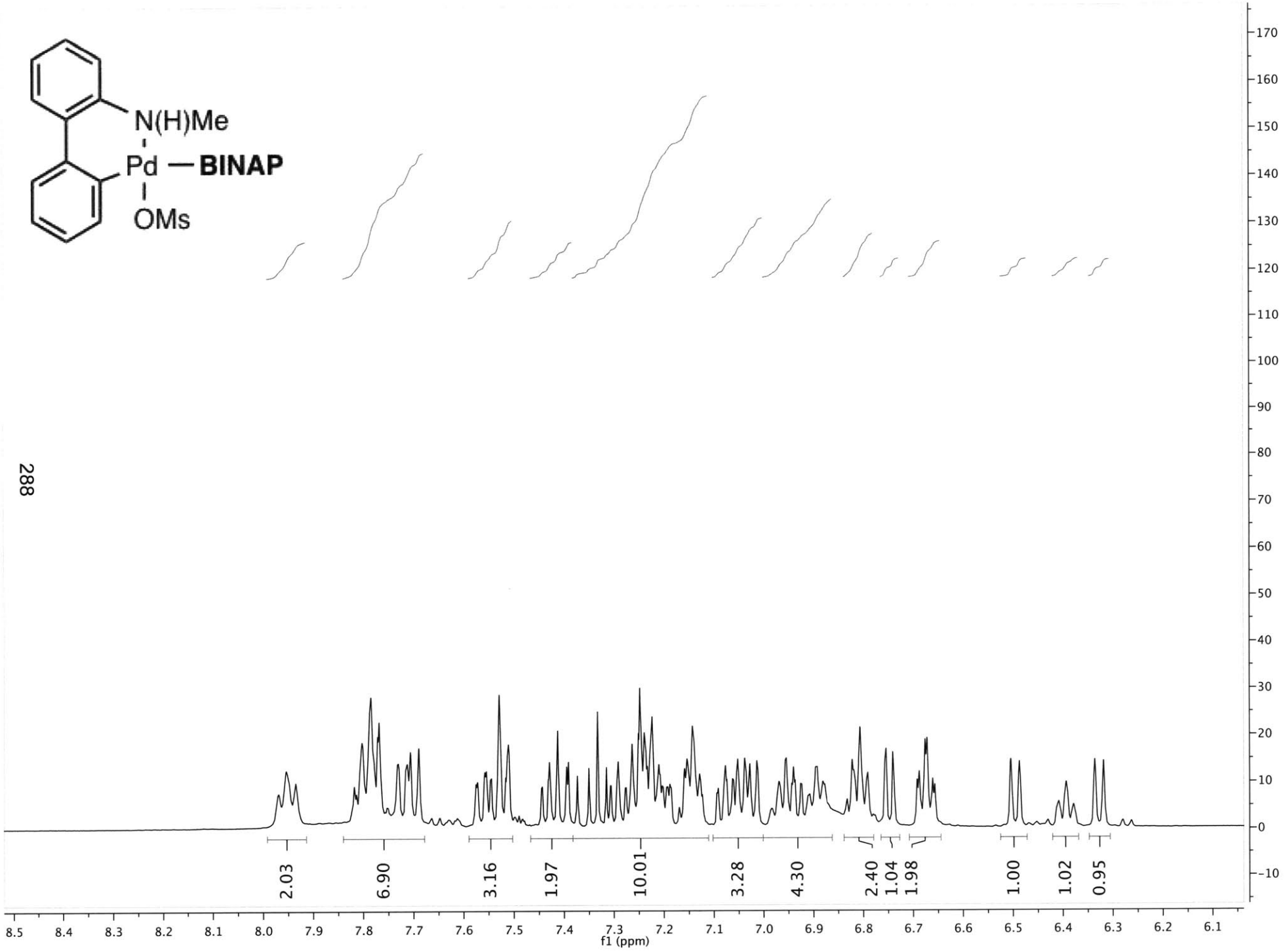

47.74
N(H)Ph
Pd - SPhos
OMs
283
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)

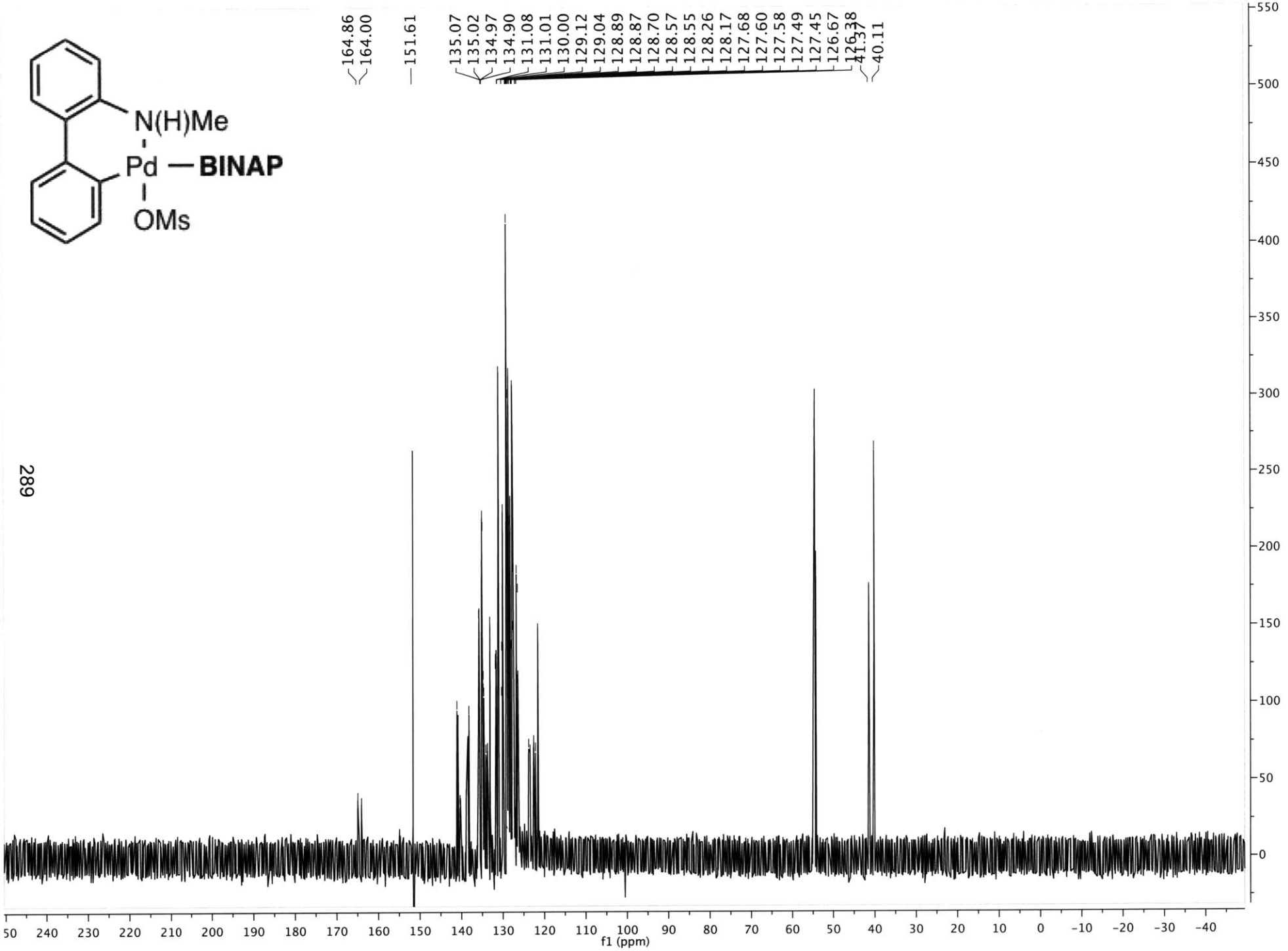

N(H)Me
Pd — tBuXPhos
OMs
284
1.36
13.14
0.99
0.87
4.00
5.37
30.27
f1 (ppm)

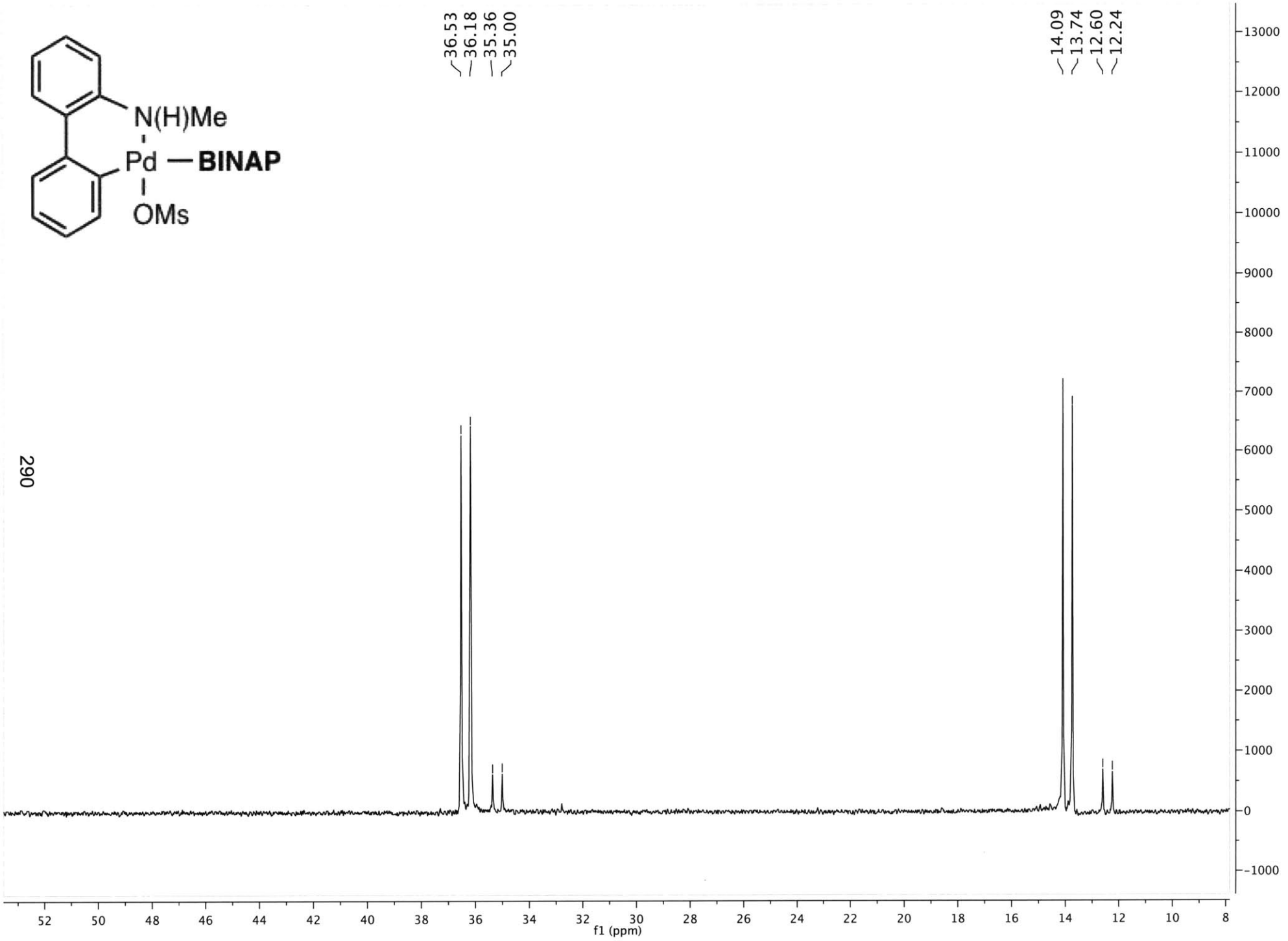

160.3
157.5
153.9
145.5
145.3
143.7
142.0
141.3
139.4
137.4
137.4
136.7
135.3
135.0
134.9
132.0
132.0
129.8
129.1
128.9
128.9
128.8
128.7
128.5
128.0
127.9
127.9
127.0
126.8
126.4
125.4
124.8
122.6
122.6
121.8
40.7
40.7
40.0
39.7
39.6
39.5
39.3
35.1
33.7
32.2
32.2
32.2
32.1
30.8
30.8
26.2
25.4
24.3
24.1
24.0
23.8
23.3
14.4
N(H)Me
Pd — tBuXPhos
OMs
285
f1 (ppm)

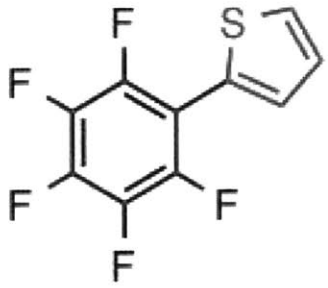

N(H)Me
Pd — tBuXPhos
OMs
56.13
286
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (ppm)


N(H)Me
Pd — BINAP
OMs
287
2.03
6.90
3.16
1.97
10.01
3.28
4.30
2.40
1.04
1.98
1.00
1.02
0.95
3.01
2.87
f1 (ppm)

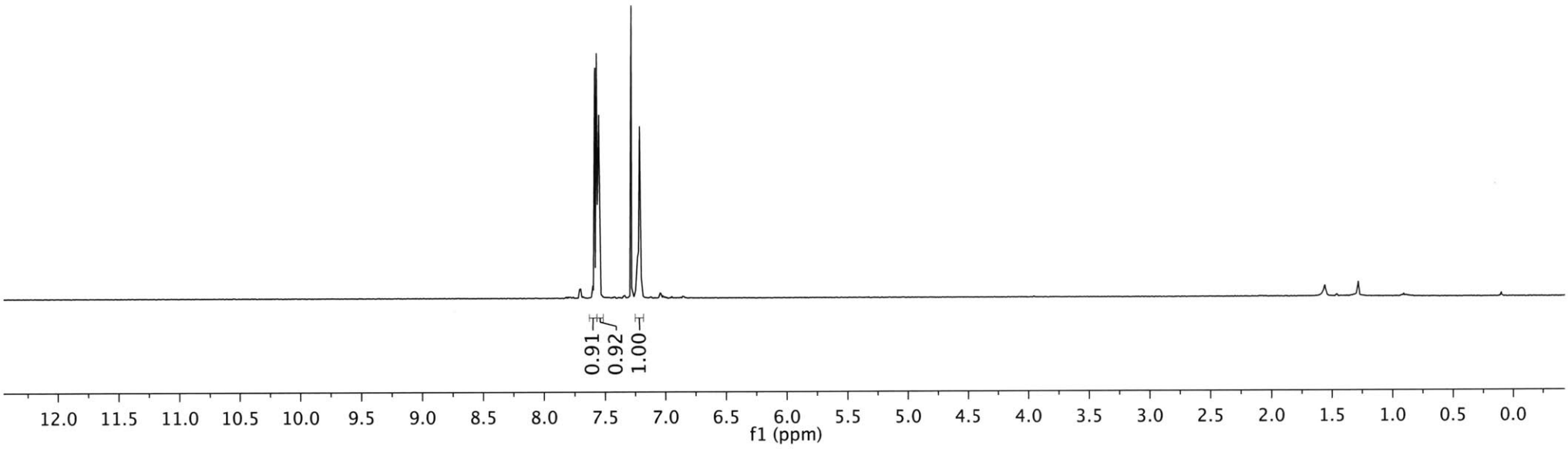

N(H)Me
Pd — BINAP
OMs
288
2.03
6.90
3.16
1.97
10.01
3.28
4.30
2.40
1.04
1.98
1.00
1.02
0.95
f1 (ppm)

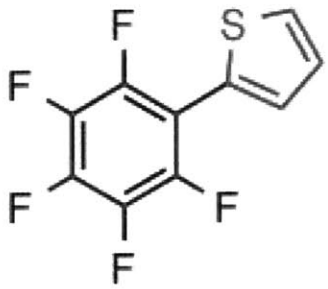

N(H)Me
Pd — BINAP
OMs
164.86
164.00
151.61
135.07
135.02
134.97
134.90
131.08
131.01
130.00
129.12
129.04
128.89
128.87
128.70
128.57
128.55
128.26
128.17
127.68
127.60
127.58
127.49
127.45
126.67
126.38
41.37
40.11
289
f1 (ppm)


N(H)Me
Pd — BINAP
OMs
36.53
36.18
35.36
35.00
14.09
13.74
12.60
12.24
290
f1 (ppm)


F
S
F
F
F
F

291


0.91
0.92
1.00
12.0
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
f1 (ppm)



145.3
142.7
138.6
136.8
130.2
130.1
130.1
128.3
128.3
128.2
127.3
126.3

292

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

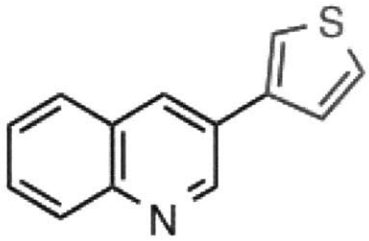
f1 (ppm)

F
S
F
F
F
F

—-140.894

293

7.5 -138.0 -138.5 -139.0 -139.5 -140.0 -140.5 -141.0 -141.5 -142.0 -142.5 -143.0 -143.5 -144.0 -144.5 -145.0 -145.5 -146.0 -146.5 -147.0 -147.5 -14
f1 (ppm)



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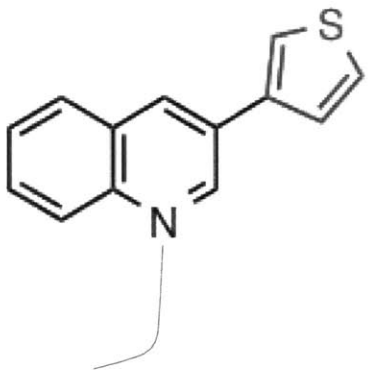
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N

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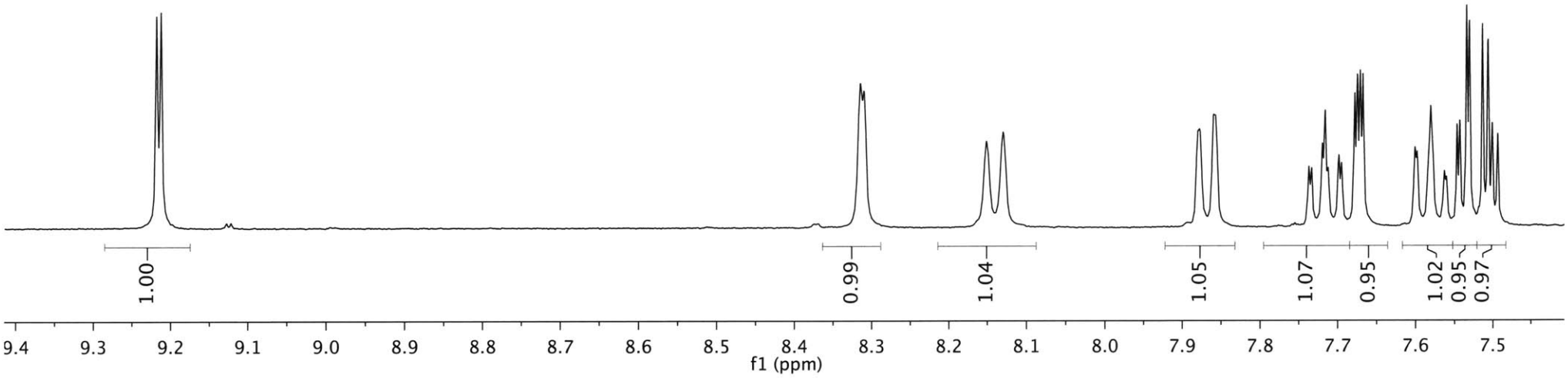
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9.0
8.9
8.8
8.7
8.6
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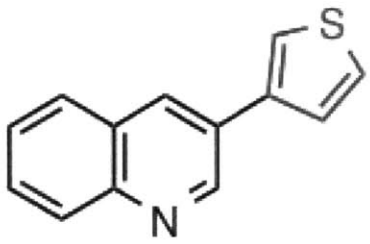
7.5
f1 (ppm)



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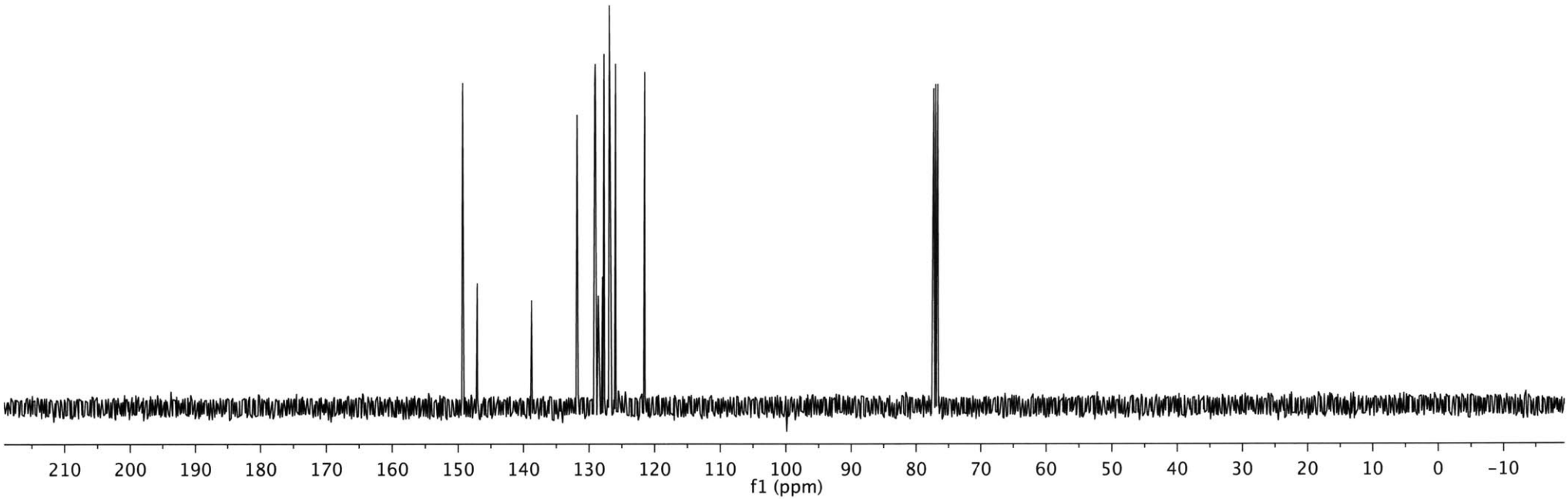
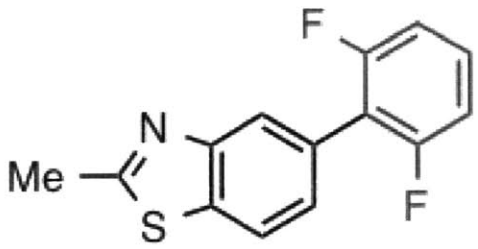
126.0
121.5

296





297

0.90
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0.95
0.98
1.89
3.00

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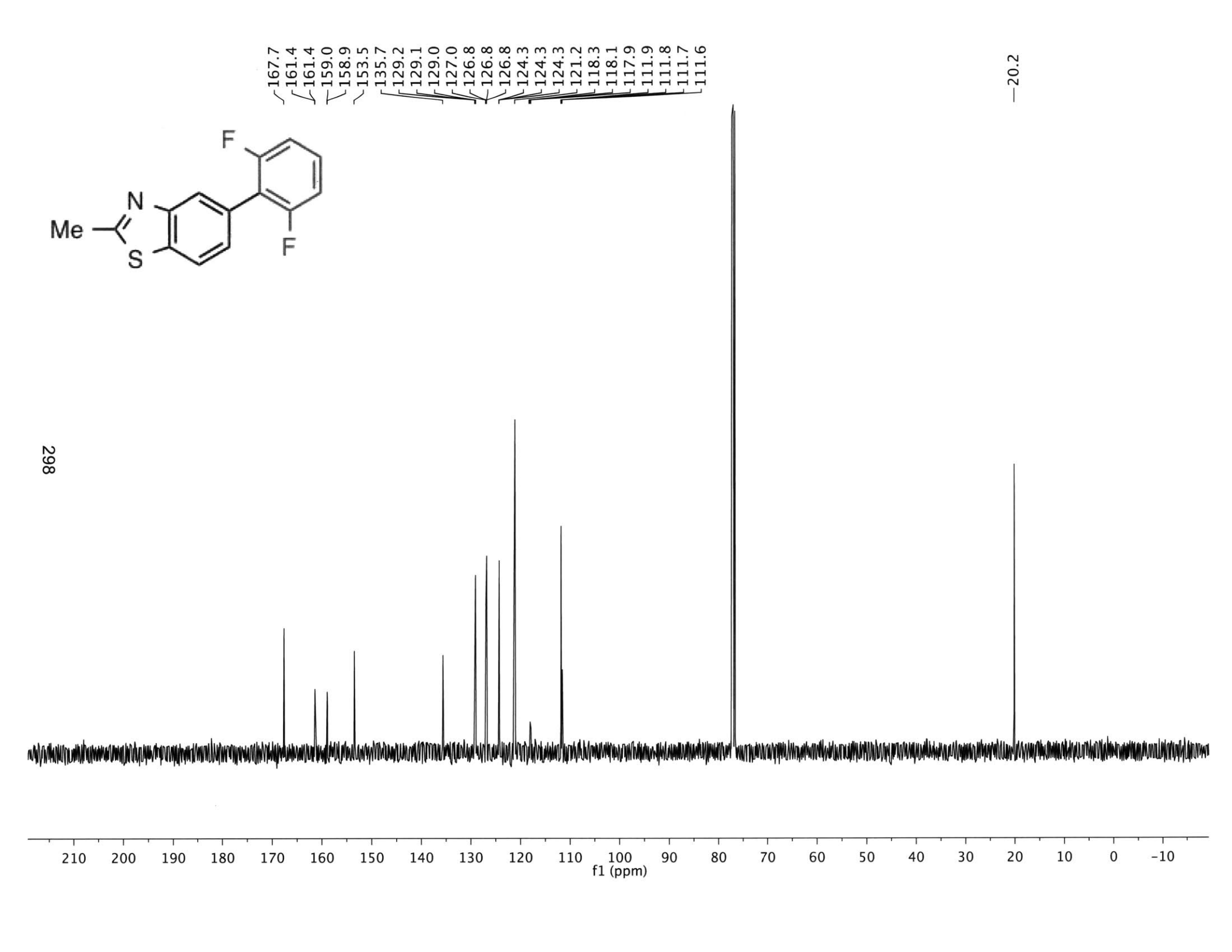
f1 (ppm)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129.2
129.1
129.0
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126.8
124.3
124.3
124.3
121.2
118.3
118.1
117.9
111.9
111.8
111.7
111.6
20.2
F
N
Me
S
F
298
210
200
190
180
170
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150
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100
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40
30
20
10
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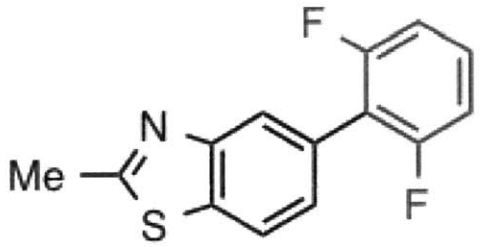
f1 (ppm)



-63.700

-114.473
-114.491
-114.508

299

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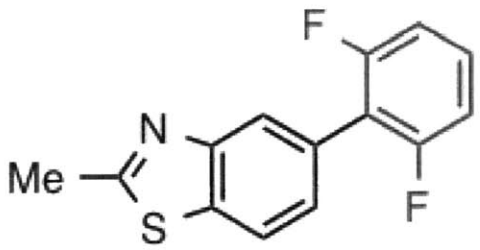

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-114.490
-114.509

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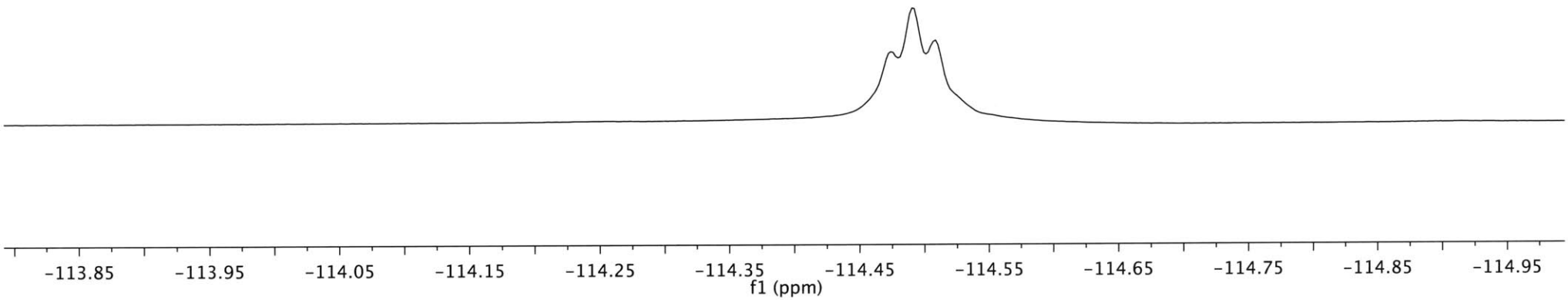

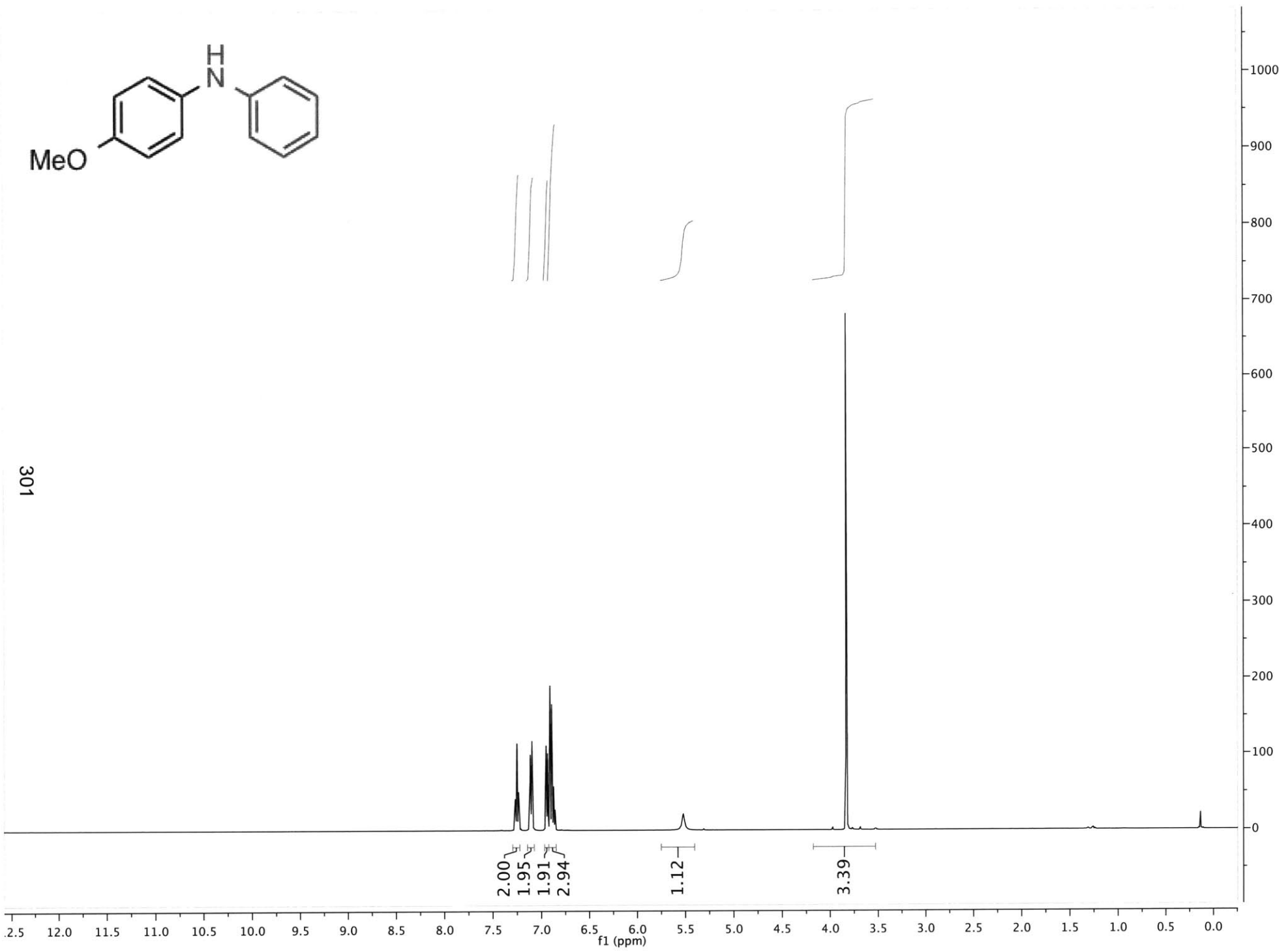
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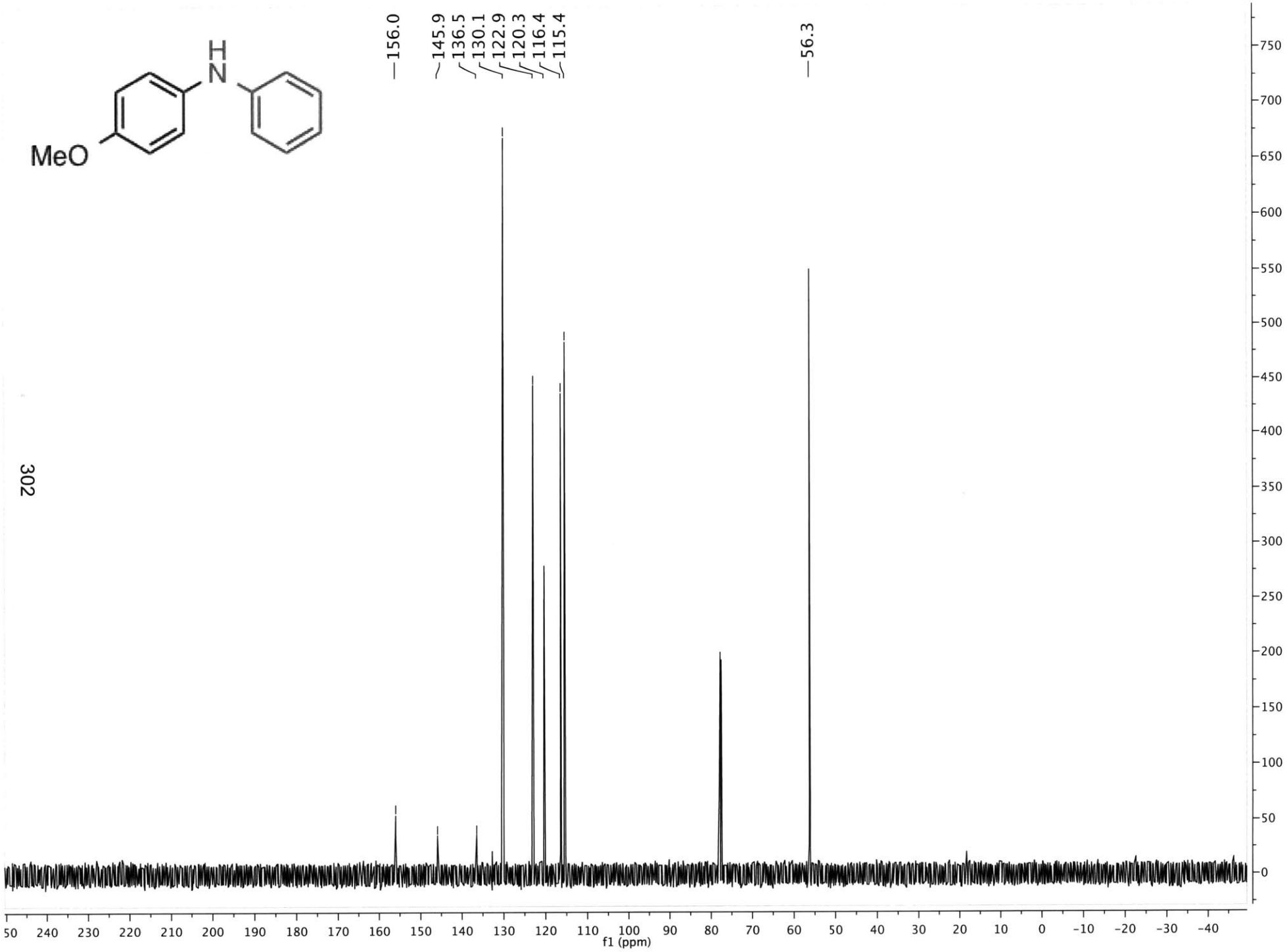
f1 (ppm)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H
N
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136.5
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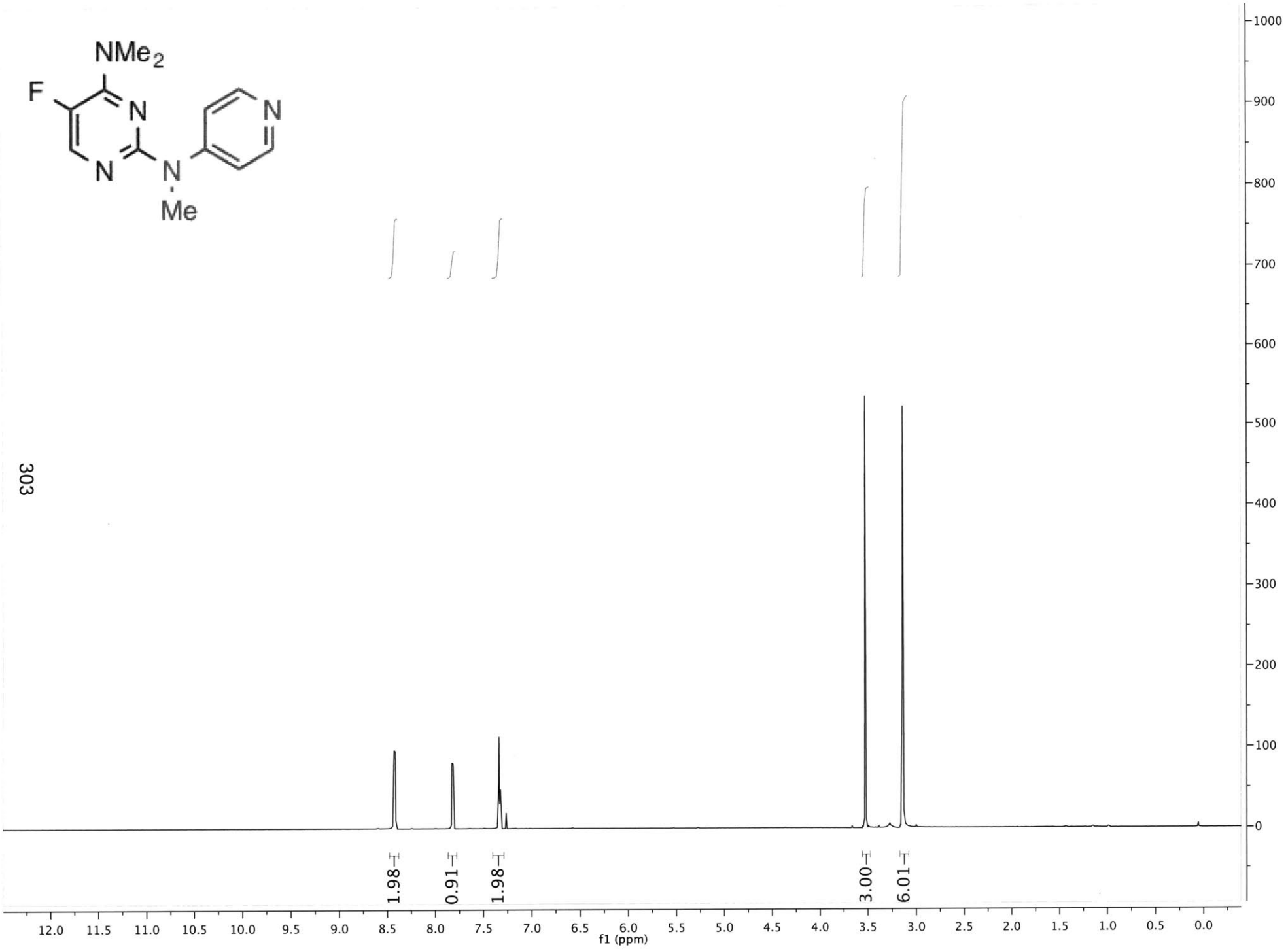
122.9
120.3
116.4
115.4
56.3
302
f1 (ppm)


NMe2
F
N
N
N
N
Me
303
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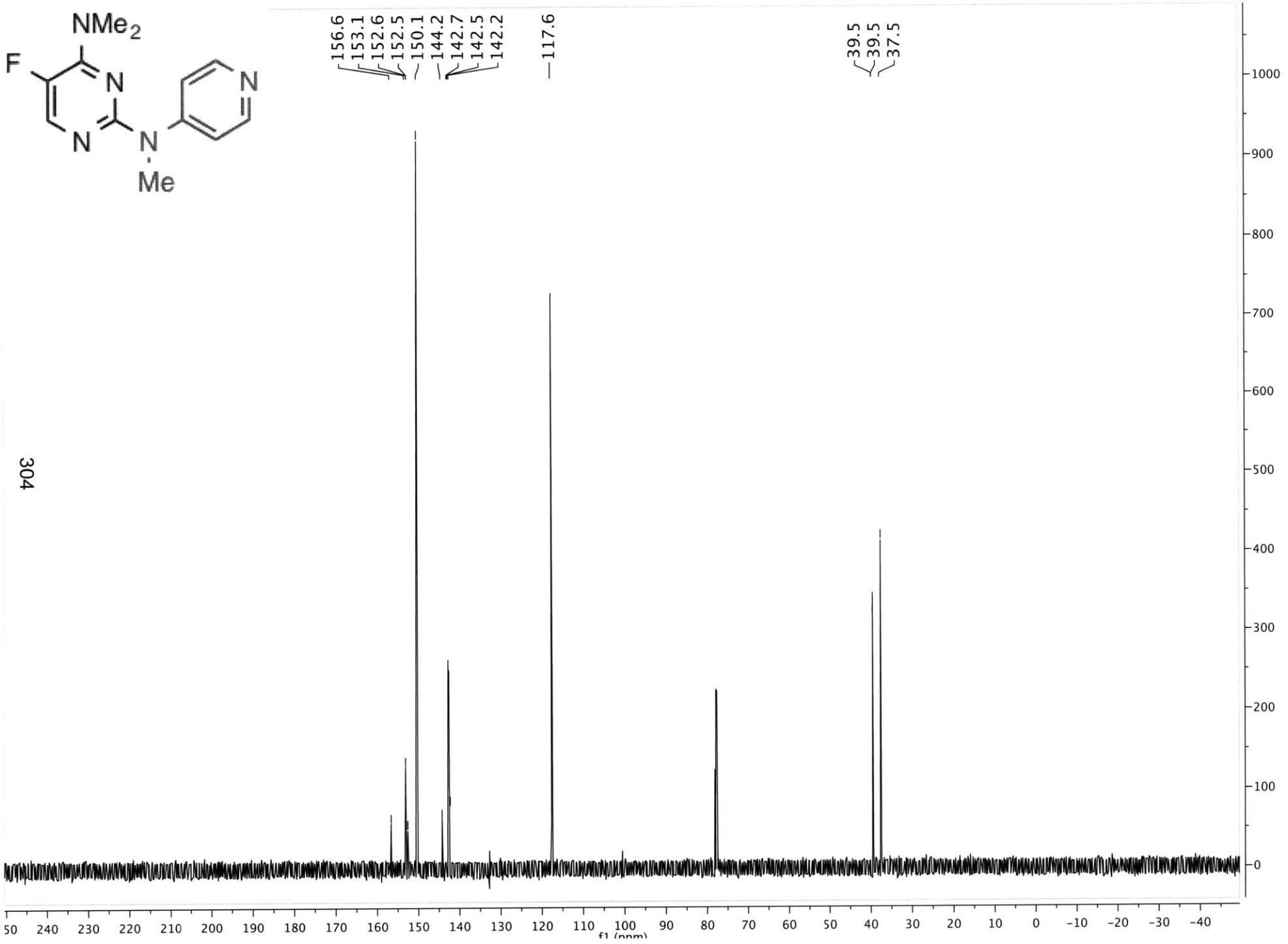
0.91
1.98
3.00
6.01
f1 (ppm)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F
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N
N
N
Me
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152.5
150.1
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142.7
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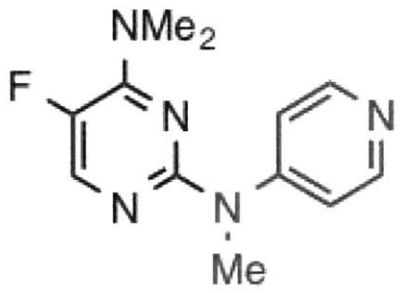
142.2
117.6
39.5
39.5
37.5
304
1000
900
800
700
600
500
400
300
200
100
0
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)


NMe2
F
N
N
N
N
Me

305

154.44
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170
f1 (ppm)

3.5: References

1. Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916–920.
2. For a different precatalyst recently developed in our laboratory based on ligated Pd(0)-1, 5-cod dimers, see: Lee, H. G.; Milner, P. J.; Buchwald, S.; L. *Org. Lett.* **2013**, *15*, 5602–5605.
3. Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876 – 2879.
4. Cheung, C. W.; Surry, D. S.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 3734–3737.
5. Senecal, T. D.; Shu, W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 10035 –10039.
6. Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 4190–4193.
7. We have never observed any aminobiphenyls in samples of precatalysts or in reaction mixtures and 2-aminobiphenyl is reported as being non-carcinogenic; Gorrod, J. W.; Kajbaf, M. *Eur. J. Drug Metab.* **1987**, *12*, 285 – 290.
8. However, 4-aminobiphenyl is known to cause bladder cancer in humans; Feng, Z.; Hu, W.; Rom, W. N.; Beland, F. A.; Tang, M-S. *Carcinogenesis.* **2002**, *23*, 1721–1727.
9. *N*-methyl-2-aminobiphenyl was isolated as a 95:5 mixture of the mono:dimethylated products, as confirmed by GC and NMR. The mixture was used directly, adjusting the equivalents of MsOH and $Pd(OAc)_2$ to 0.95. *N*-phenyl-2-aminobiphenyl contained traces of N-phenyl carbazole and diarylated product and was also used directly.
10. The reaction of these ligands and **4** only reach ~50% conversion. Their reaction with **7** produces a mixture of two species in equilibrium—the desired precatalyst and a related complex without the nitrogen bound to the Pd center.
11. When allowed to react with **7**, (±)-BINAP produces a mixture of two species in equilibrium—the desired precatalyst and the related complex without the nitrogen coordinated to the Pd center.
12. Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 11278–11287.

Chapter 4: Enantioselective Synthesis of (hetero)Carbocycles by the Intramolecular Copper-Catalyzed Hydroalkylation of Styrenes

4.1 Introduction

Ligated copper hydride species are powerful catalytic intermediates capable of a wide range of transformations centered on the reduction of π systems. These reactions generally begin with the hydrocupration of the unsaturated species followed by trapping the organocopper intermediate with an electrophile to provide product (Figure 1).[1]

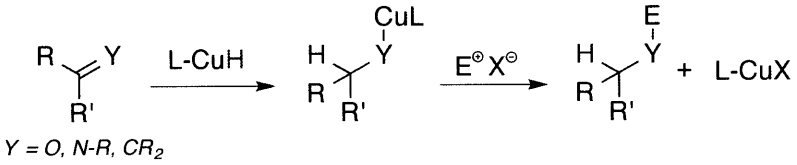


Figure 1. General mode of CuH reactivity.

With the proper choice of chiral ligand, copper hydride catalysis represents a versatile means of generating stereocenters with high levels of enantiomeric excess. Our lab has previously applied these catalyst systems to the conjugate reductions of α,β-unsaturated carbonyl compounds to produce enantioenriched beta-substituted esters,[2] alkyl cyclopentanones,[3,4] and beta-azaheterocyclic acid derivatives.[5] Others have reported elegant work in related areas, which include enantioselective hydroboration of styrenes,[6] reduction of ketones to alcohols,[7-9] imines to amines,[10] α,β-unsaturated ketones to allylic alcohols,[11] and activated alkenes to chiral alkanes.[12]

Recently, our lab reported the hydroamination of alkynes[13] and styrene derivatives[14] with high degrees of regio- and enantioselectivity (Scheme 2). This chemistry was achieved by the enantioselective hydrocupration of an alkene to form intermediate **II**. Subsequently, oxidative addition of an electrophilic amine (e.g. R_2NOBz) to **II** led to

intermediate **III**. This was followed by reductive elimination and reaction of the copper with silane to furnish an enantioenriched alkyl amine and regenerate the catalyst.

On the basis of this proposed mechanism, we speculated on the possibility of intercepting alkylcopper intermediate **II** with alkyl (pseudo)halide electrophiles. Such a process would result in a formal hydroalkylation of a carbon-carbon double bond. Furthermore, if the alkyl electrophile was tethered to the olefin, this could provide rapid access to stereodefined carbocycles and heterocycles.

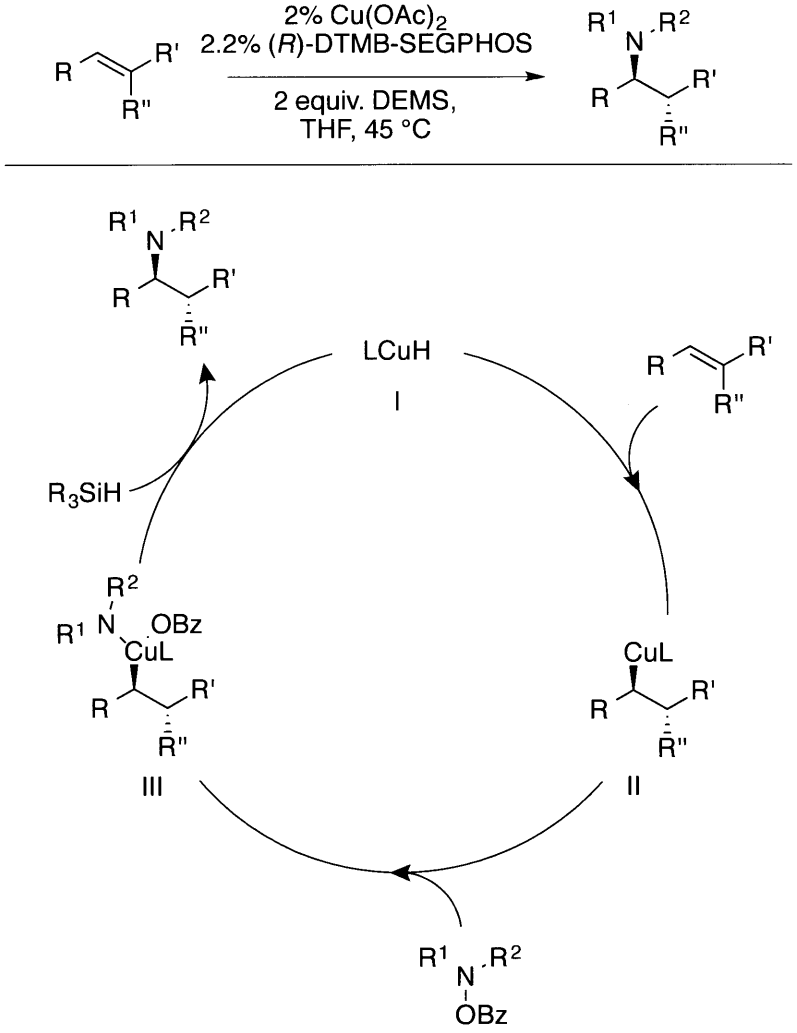


Figure 2. Previously reported hydroamination reaction and the proposed catalytic cycle.

Previously, Ito and coworkers reported an elegant enantioselective intramolecular boroalkylation of silyl alkenes with a pendant alkyl carbonate.[15] With (*R,R*)-quinoxP* as the chiral ligand, they were able to access 1,2-boron-silicon functionalized cyclopropanes in up to 98% yield and 99% ee. This method, however, was only applicable to 1-silyl allyl carbonates. Later they reported the intermolecular boroalkylation of homoallylic sulfonates to generate cyclobutylboronates and cyclopentylboronates in good to excellent yields.[16] This method represents an efficient means of accessing diasteromerically pure carbocycles. However, the reported process was racemic and was only applicable to 4- and 5-membered carbocycles. Additionally, in most cases, 1-silyl substitution of the alkene was necessary for the reaction to proceed in an efficient manner. Styrenes could be used to form cyclobutylboronates but provided lower yields.

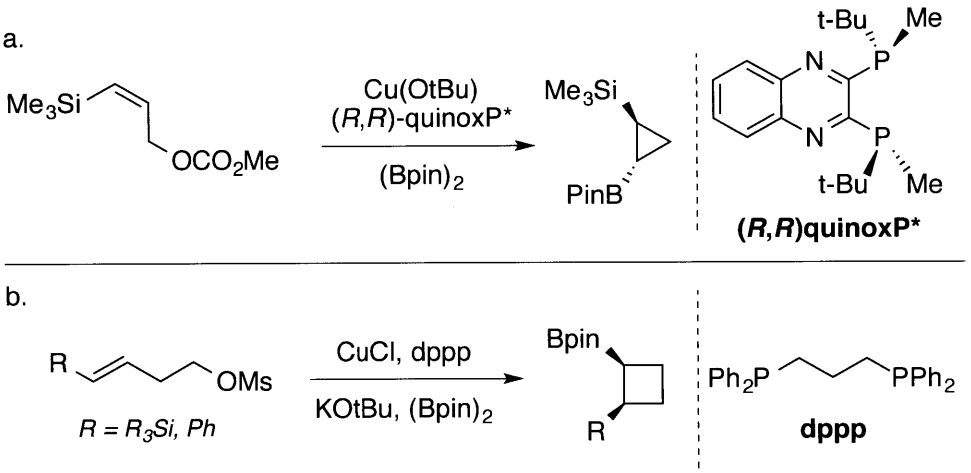


Figure 3. [a.] Enantioselective intramolecular borocyclopropanation and [b] diastereoselective intramolecular boroalkylation cyclizations reported by Ito.

Stereodefined carbocycles and heterocycles, e.g. piperidines, indanes, and tetralins, are commonly occuring motifs in natural products and pharmacologically-active

molecules (a small set of examples is shown in fig. 4).[17,18] Despite their overwhelming prevalence in nature and in pharmaceutical targets, there does not exist a unified strategy for the synthesis of a diverse range of enantiopure, densely-functionalized (hetero)carbocycles. Herein we present a copper hydride-catalyzed strategy to access a multitude of ring systems with a high degree of enantiomeric control.

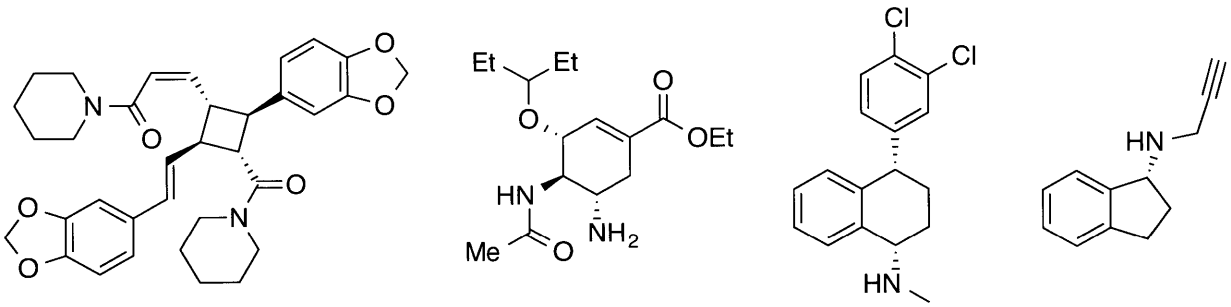


Figure 4. Examples of natural products and pharmaceutical drugs containing stereodefined (hetero)carbocycles.

4.2 Results and Discussion

Examining the synthetic disconnections to form (hetero)carbocycles, **1**, we envisioned that 4-, 5-, and 6-membered rings could be formed utilizing a trisubstituted olefin intermediate containing a tethered alkyl electrophile, **2** (Figure 5).

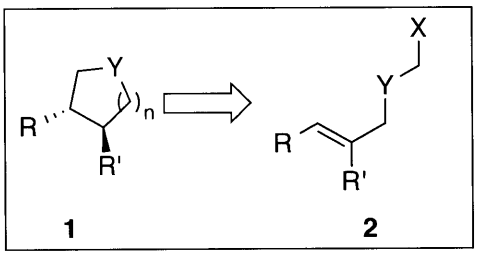
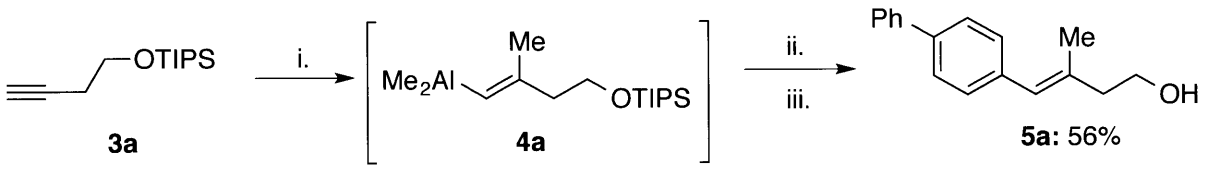


Figure 5. Retrosynthetic disconnection of stereodefined (hetero)carbocycles.

Investigating reported methods for the syntheses of trisubsituted olefins similar to **2**, we quickly realized that there are no broadly applicable means to access regio- and stereodefined trisubstituted olefins incorporating a tethered alkyl electrophile. Negishi,[19] Panek,[20] and Lipshutz[21] have reported tandem carboaluminations/cross coupling strategies with palladium and nickel, which demonstrate the feasibility of this strategy, albeit on a limited set of substrates. Building upon these methods with our laboratory's reported Negishi coupling methodology,[22] we were able to develop a 3-step, one-pot route to access diverse trisubstituted olefins with a pendant alkyl alcohol (Scheme 1).

Scheme 1. Synthesis of model olefin **5a** through tandem methylalumination/Negishi cross-coupling[a]



3a **4a** **5a:** 56%

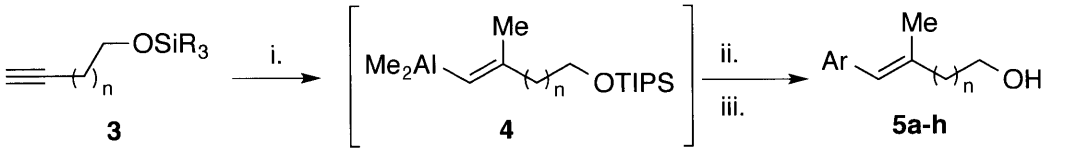
[a] i. Alkyne (10 mmol), Cp_2ZrCl_2 (10 mol%), H_2O (10 mol%), Me_3Al (15 mmol), DCE (5 mL), -20 °C – rt, 2 h; ii. 4-bromobiphenyl (9 mmol), OMsXPhos (2 mol%), XPhos (2 mol%), THF (10 mL), 0 °C – rt, 4 h; iii. TBAF (12 mmol), THF (50 mL), rt, 1 h.

First, the Cp_2ZrCl_2-catalyzed carboalumination of silyl-protected alkynyl alcohol **3** with Me_3Al, generated vinylalane **4**. Intermediate **4** was directly coupled with an aryl halide using OMsXPhos palladium precatalyst and deprotected in situ to provide the styrenyl alcohol, **5**, in 56% yield over three steps. Compound **5** was an ideal intermediate, as the alcohol could be converted into a variety of leaving groups, such as halides, phosphates, and sulfonates.

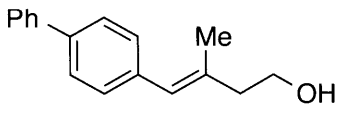
Having a robust method for the preparation of our model substrate, we explored the scope of the one-pot synthesis of more complex substrates. As shown in Table 1,

butynyl-, pentynyl-, and hexynyl-silyl ethers, heterocyclic aryl bromides, and electron poor aryl bromides were well tolerated to provide products **5a-h** in moderate to good yields over the one-pot, three-step sequence.

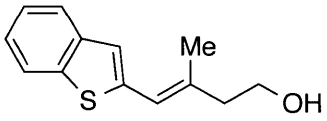
Table 1. Scope of trisubstituted olefins with a tethered alkyl alcohol[a]



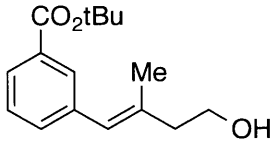
3 **4** **5a-h**



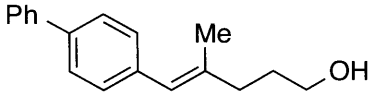
5a: 56%



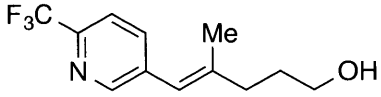
5b: 51%



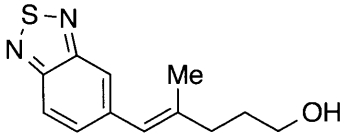
5c: 44%



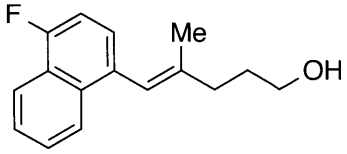
5d: 57%



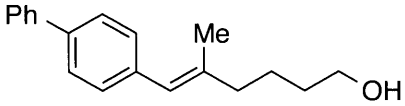
5e: 46%



5f: 38%



5g: 41%



5h: 52%

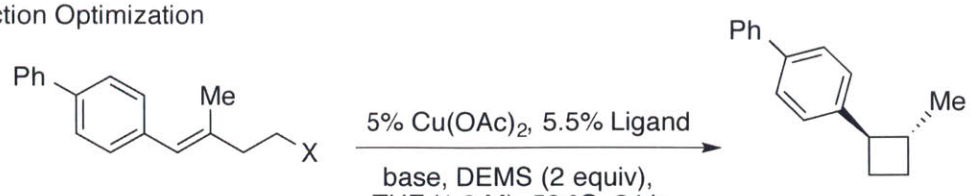
[a] i. Alkyne (10 mmol), Cp_2ZrCl_2 (1 mmol), H_2O (1 mmol), Me_3Al (15 mmol), DCE (5 mL), –20 °C to rt, 1 – 4 h; ii. Aryl halide (9 mmol), OMsXPhos precatalyst (2 mol%), XPhos (2 mol%), THF (10 mL), 0° C – rt, 0.5 – 16 h; iii. TBAF (12 mmol), THF (50 mL), rt, 1 h.

We then investigated the reactivity of the model substrate based on **5a** in intramolecular hydroalkylation, adapting the conditions reported in our previously reported hydroamination methodology. The results are summarized in Table 2.

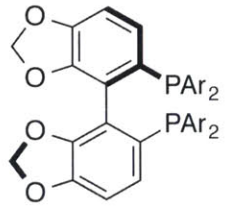
Stable, readily-available $Cu(OAc)_2$ was found to be an ideal copper precursor. LiOMe was the only base that furnished any product, as the use of other bases led to either substitution or E2 elimination. We speculate that LiOMe is effective due to its low nucleophilicity and poor solubility in THF, minimizing its direct reaction with **6** while still interacting with the copper intermediate to furnish a copper methoxide complex, thus facilitating catalyst turnover.[23] Additionally, DTBM-SEGPHOS and alkyl bromides were the only ligand and leaving group, respectively, that provided appreciable amounts of the desired product. Further optimization showed (dimethoxy)methylsilane to be superior in reactivity to (diethoxy)methylsilane as the stoichiometric in this transformation (Table 2, entry 13).

With optimized conditions in hand, we then explored the substrate scope with alkyl bromides **6a – h**. Our hydroalkylation tolerates a variety of substituents on the arene ring as well as heterocyclic arenes and efficiently generated 4- and 5-membered carbocycles as well as piperidines and tetrahydropyran ring systems with good yields and excellent stereocontrol.

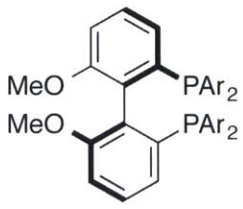
Table 2. Reaction Optimization



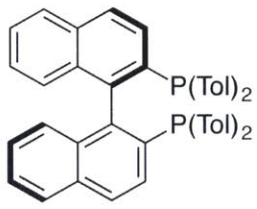
entry	X	ligand	base (equiv)	% yield[a] (% ee[b])
Effect of base				
1	OMs	**L1**	KO*t*-Bu (2.0)	0
2	OMs	**L1**	LiO*t*-Bu (2.0)	0
3	OMs	**L1**	LiOMe (2.0)	17 (96)
4	OMs	**L1**	NaOMe (2.0)	0
Effect of leaving group				
5	OTs	**L1**	LiOMe (2.0)	9
6	Br	**L1**	LiOMe (2.0)	16
7	Br	**L1**	LiOMe (4.0)	70 (97)
8	OMs	**L1**	LiOMe (4.0)	14
Effect of ligand				
9	Br	**L2**	LiOMe (4.0)	16
10	Br	**L3**	LiOMe (4.0)	0
11	Br	**L4**	LiOMe (4.0)	8
12	Br	**L5**	LiOMe (4.0)	5
Optimized Conditions				
13[c]	Br	**L1**	LiOMe (3.0)[d]	90[e]



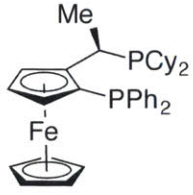
L1
(*R*)-DTBM-SEGPHOS
(Ar = 3,5-*t*-Bu_2-4-OMe-C_6H_2)



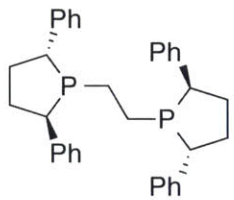
L2
(*R*)-DTBM-MeO-BIPHEP
(Ar = 3,5-*t*-Bu_2-4-OMe-C_6H_2)



L3
(*R*)-Tol-BINAP



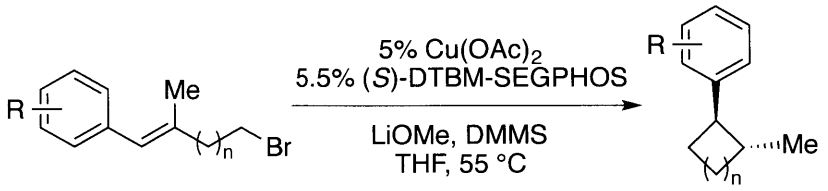
L4
(*R*)-(*S*)-JOSIPHOS



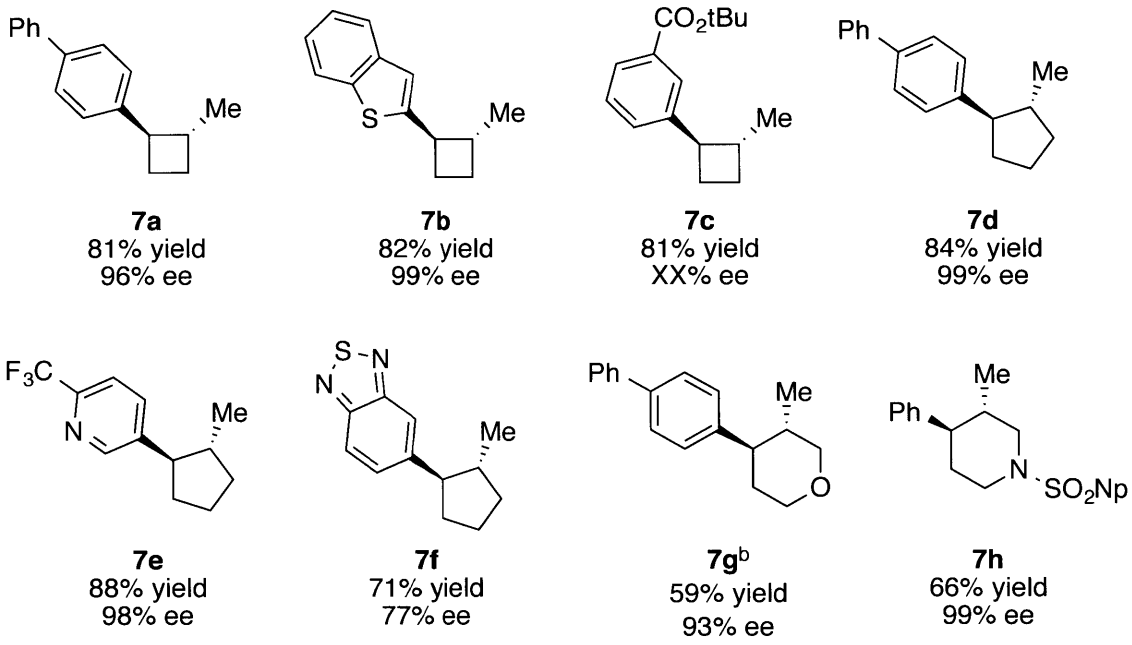
L5
(*R*,*R*)-Ph-BPE

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [b] ee determined by chiral HPLC. [c] On 0.5 mmol scale. [d] With 3.0 equiv (dimethoxy)methylsilane (DMMS) at 2.5 M in THF. [e] In 81% isolated yield and 96% ee.

Table 3. Scope of 4-, 5-, and 6-membered ring formation.[a]



6a-h **7a-h**



7a
81% yield
96% ee

7b
82% yield
99% ee

7c
81% yield
XX% ee

7d
84% yield
99% ee

7e
88% yield
98% ee

7f
71% yield
77% ee

7g[b]
59% yield
93% ee

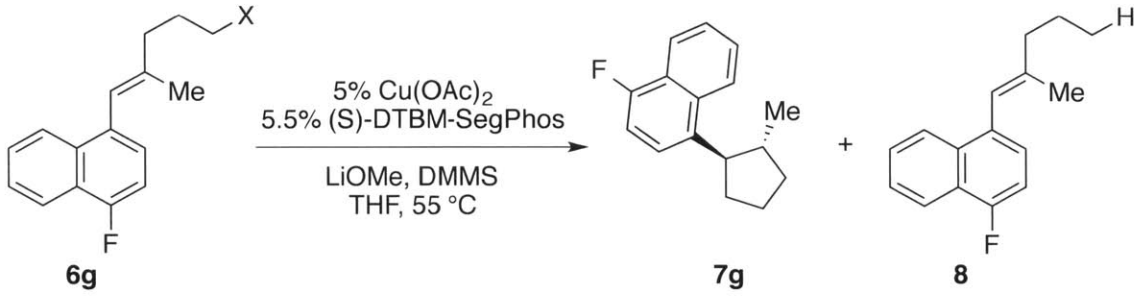
7h
66% yield
99% ee

[a] **6** (0.5 mmol), LiOMe (1.5 mmol), DMMS (1.5 mmol), $Cu(OAc)_2$ (5 mol%), (*S*)-DTBM-SEGPHOS (5.5 mol%), THF (2.5 M), 55 °C, 24 h. [b] 65 °C; Np = 2-naphthyl

While showing excellent reactivity with many substrates, we determined this hydroalkylation protocol was not fully compatible with substrates bearing extremely electron-rich or ortho-substituted arenes. These substrates gave mixtures of the desired product and the product of alkyl bromide reduction. We hypothesize that the presence of ortho-substituents or electron-rich arenes diminishes the rate of hydrocupration enough such that the rate of alkyl bromide reduction, a process known to be facile with CuH,[24] is

a competitive process. We thought that, perhaps, by changing the leaving group, we could slow the rate of reduction relative to hydrocupration. Investigation of a 4-fluoro-1-naphthyl substrate and bromide, chloride, methanesulfonate, and diethylphosphate as leaving groups (table 4) indicated that the bromide to still be optimal. The use of chloride gave trace conversion, while employing methanesulfonate or diethylphosphate gave complex mixtures of products.

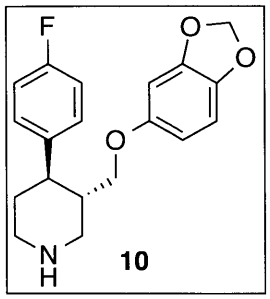
Table 4. Leaving group effect with a sterically-hindered substrate[a]



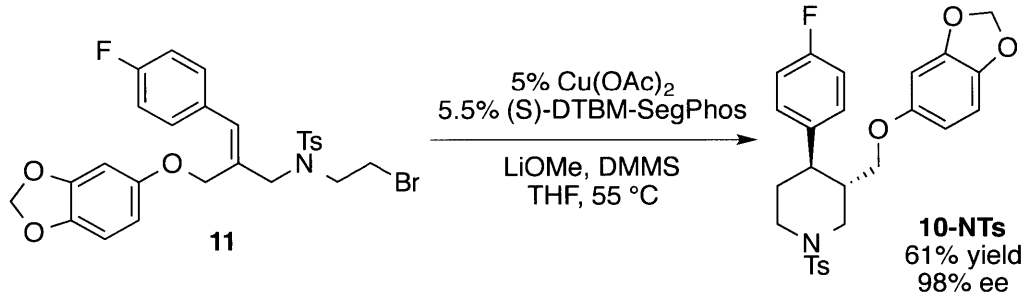
Entry	X	conv.	Yield **7g**	Yield **8**
1	Cl	trace	trace	0%
2	Br	100%	40%	60%
3	OMs	100%	~10%	~20%
4	$P(O)(OEt)_2$	100%	trace	trace

[a] **13** (0.1 mmol), LiOMe (0.4 mmol), DMMS (0.4 mmol), $Cu(OAc)_2$ (5 mol%), (*S*)-DTBM-SEGPHOS (5.5 mol%), THF (1 M), 55 °C, 24 h; yields determined by GC with dodecane as an internal standard.

To further illustrate the utility of our method, we developed a short synthesis of paroxetine, **10**, a widely prescribed SSRI-type antidepressant with a stereodefined piperidine core. The key intermediate, **11**, was synthesized in 6 steps from 4-fluorobenzaldehyde and sesamol. When **11** was submitted to our CuH cyclization conditions, paroxetine-N-tosylate was obtained in 61% yield with XX% ee (Scheme 2).



10



Scheme 2. Synthesis of Paroxetine

Having explored the scope of 4-, 5-, and 6-membered ring systems we next focused our efforts on their benzo-fused analogues. We envisioned that benzocyclobutenes, indanes, tetralins, and their heteroatom-containing analogues could be generated from 2-(bromoalkyl)styrenes.

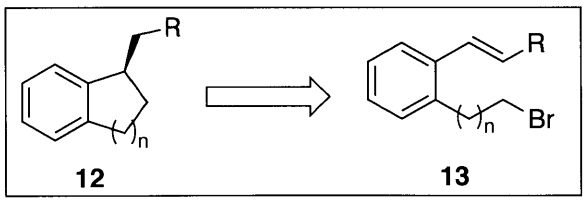
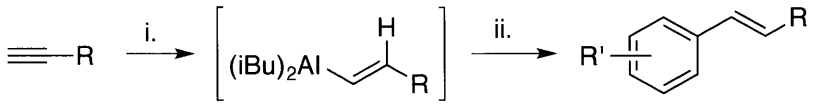


Figure 6. Retrosynthesis of benzo-fuzed ring systems.

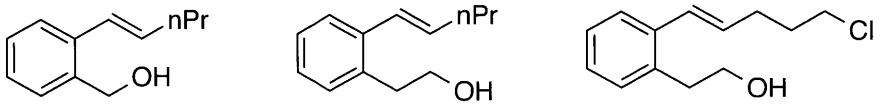
Investigating the synthesis of the requisite substrates, we again found no broadly-applicable methods existed to provide the desired styrenes with purely (*E*)-olefin geometry. Standard methods for olefin synthesis such as Wittig chemistry and the Horner-Wadsworth-Emmons reaction can provide (*E*)-olefins but with at least traces of the (*Z*)-isomer,[25] which, if inseparable, the could diminish the dr of the cyclization reaction. Additionally, Heck coupling of unactivated olefins could provide the desired styrenes, but often gives the (*E*)-isomer with the (*Z*)-isomer as well as branched coupling product as impurities.[26] Already having a method in hand for the alumino-Negishi coupling of vinylalanes, we were inspired by the work of Negishi,[19] Hoveyda,[27] and others[28-30] to synthesize (*E*)-styrenes from (*E*)-vinylalanes generated in situ.

It is well established that terminal alkynes can be stereo- and regioselectively hydroaluminated with diisobutylaluminum hydride (DIBAL-H), with a low degree of alkyne metallation (often ≤5%).[28] The resulting vinylalanes can be reacted with an alkyllithium to render the aluminum center more nucleophilic, followed by treatment with a range of electrophiles, with[27] or without[28] a metal catalyst. With the results from Table 1 we postulated that a vinylalane generated by hydroalumination could be readily cross-coupled with an aryl halide. This proved to be the case and provided the desired (E)-styrenes with no (Z) or branched isomers, and only traces (~5%) of the aryl alkyne, which could be removed by column chromatography. Our initial examination of the scope of the method is presented in Table 5.

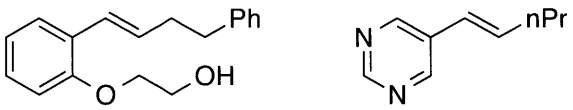
Table 5. Disubstituted (*E*)-styrene synthesis[a]



14 **15** **16a-e**

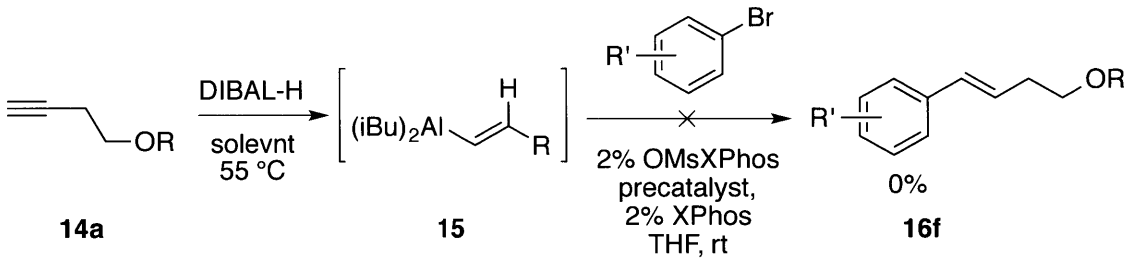


16a: 79%[b] **16b:** 84%[b] **16c:** 81%[b]



16d: 59%[b] **16e:** 89%[c]

[a] i. Alkyne (5 mmol), DIBAL-H (1 M in hexane, 5 mmol), 55 °C, 2 h. ii. aryl bromide (5 mmol), OMsXPhos precatalyst (0.1 mmol), XPhos (0.2 mmol), THF (5 mL), 0 °C – rt, 2 – 16 h. [b] Silyl ethers used, crude product stirred with TBAF (6 mmol) before purification. [c] Reaction performed at 1 mmol scale.



14a **15** **16f**

Scheme 5. Unsuccessful reaction of homopropargyl ethers

Interestingly, when the alkyne used contained a THP or silyl ether, this method provided none of the desired cross-coupling product. After confirming the hydroalumination was occurring, we found that raising the temperature of the cross-coupling step to 55 °C after 24 h at room temperature led to the formation of **16f** in ~20% yield, by GC analysis. Our current hypothesis is that complex **15a** or **15b**,

depending on the geometry of the hydroalumination product, is formed due to the Lewis bacisity of the oxygen in the ether-containing alkyne. The nucleophilicity of this complex is reduced, compared to that of **15**, rendering it far less reactive towards transmetallation of the vinyl fragment onto palladium. Efforts are currently underway to increase the nucleophilicity of these intermediates and render them reactive towards this methodology.

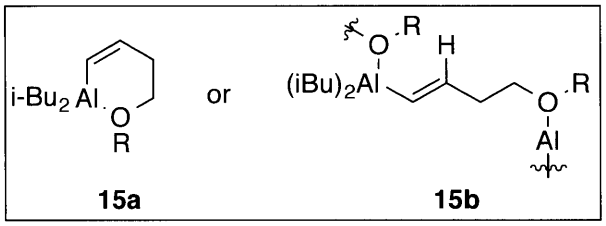
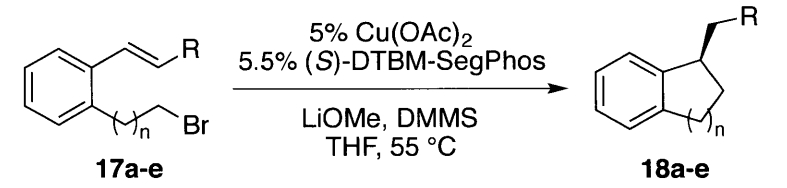


Figure 7. Proposed Inter- and Intramolecular aluminum-ether complexes

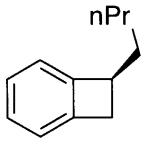
As shown in Table 6, 2-(bromoalkyl)styrenes **17a-e** were submitted to our hydroalkylation conditions. Indanes were formed with high yields and high ee's. Additionally, chromane **18e** was formed in good yield.

In contrast to the other substrates, **18a** formed in a modest yield of 41% with full conversion and no detectible reduction (Scheme 6). GC/MS analysis showed the desired product, dimeric product **19** and traces of 5 species with the mass of dimer **19** plus two hydrogen atoms (mwt=320). Benzylic bromides are much more reactive towards copper than unactivated alkyl bromides and benzocyclobutenes can also form xylylenes, which can undergo cycloaddition reactions. The reaction at room temperature provided ~5% product with the remaining material being starting material. We are currently investigating the optimization of this reaction.

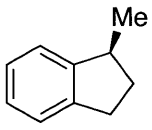
Table 6. Scope of benzo-fused ring formation[a]



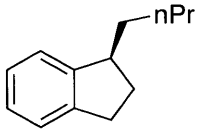
17a-e **18a-e**



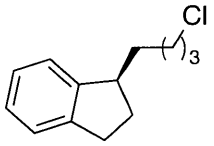
18a
41% yield
ee n.d.



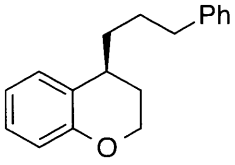
18b
94% yield
90% ee



18c
92% yield
85% ee

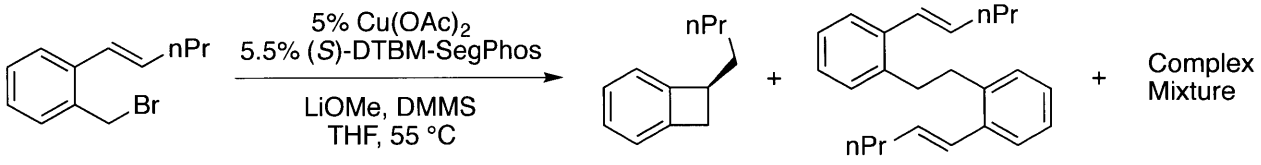


18d
82% yield
87% ee



18e[b]
79% yield
ee n.d.

[a] **17** (0.5 mmol), LiOMe (1.5 mmol), DMMS (1.5 mmol), $Cu(OAc)_2$ (5 mol%), (S)-DTBM-SEGPHOS (5.5 mol%), THF (2.5 M), 55 °C, 24 h. [b] 65 °C.



17a **18a:** 41% **19**

Scheme 6: Benzocyclobutane and byproduct formation

4.3 Conclusion

In summary, we have developed a methodology that provides unprecedented access to diverse sets of (hetero)carbocycles in good to excellent yields with a high degree of stereocontrol. The method's utility has been demonstrated in the synthesis of the SSRI paroxetine. Additionally, we have developed robust methodologies for the cross coupling of vinylalanes to provide (*E*)-di- and tri-substituted styrenes in moderate to excellent yields. We foresee that these methodologies will have implications in total synthesis and to have a great impact on further expanding the scope of CuH-catalyzed reactions.

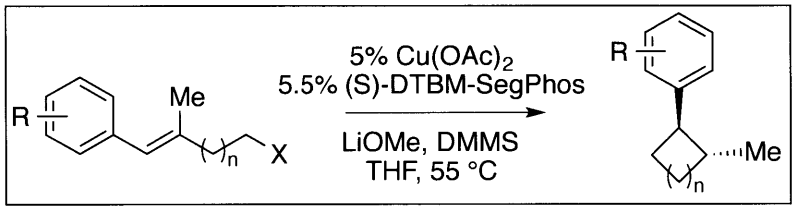
4.4: Experimental

General: Reagent Information. Anhydrous THF was purified by passing through two packed columns of neutral alumina and copper (II) oxide under a positive pressure of argon. $Cu(OAc)_2$ (99.999%, trace metal basis) was purchased from Sigma Aldrich and used as received. DTBM-SEGPHOS was purchased from Takasago International Co. and Strem Chemical Co. and used as received. (Dimethoxy)methylsilane was purchased from TCI and used as received, stored under nitrogen at -20 °C. TBAF (1 M in THF), Me_3Al (2 M in hexanes), and DIBAL-H (1 M in hexanes) were purchased in Sure/Seal® from Sigma Aldrich. LiOMe was purchased from Strem (LiOMe from other sources was found to be inferior in its reactivity). Alkynes were purchased from Oakwood, Alfa Aesar, and Sigma Aldrich and used as received. All other reagents and solvents were purchased from commercial sources and used as received. Flash chromatography was performed with SiliCycle *SiliaFlash® F60* silica gel.

General: Analytical Information. Compounds were characterized by ^1H NMR, ^{13}C NMR, and ^{19}F NMR (where applicable). Copies of the ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra can be found at the end of the Supporting Information. ^1H and ^{13}C NMR spectra were recorded on a Varian 500 MHz or a Bruker 400 MHz instrument. Fluorine NMR spectra were recorded on a Varian 300 MHz instrument. All ^1H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual deuterochloroform (7.26 ppm), CD_2Cl_2 (5.32 ppm), or DMSO-d^6 (2.50 ppm) in the deuterated solvent. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), CD_2Cl_2 (53.84 ppm) or DMSO-d^6 (39.52 ppm) and all were obtained with ^1H decoupling. Achiral gas chromatography (GC) analyses were performed on an Agilent 7890A gas chromatograph with an FID detector using a J & W DB-1 column. Thin- layer chromatography (TLC) was performed on Silicycle 250 μm silica gel plates. Compounds were visualized by irradiation with UV light or I_2. Yields refer to pure compounds, unless otherwise indicated. The enantiomeric excesses (ee) of the products were determined by high-performance liquid chromatography (HPLC) analysis performed on Agilent 1200 Series

chromatographs using a chiral column (25 cm) as noted for each compound or by GC on an Agilent 6850 gas chromatograph with an FID detector using a CP-Chirasil-Dex CB column.

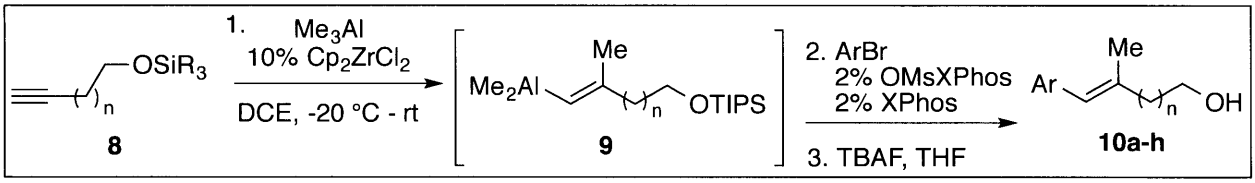
General Procedure A: Hydroalkylation



In a nitrogen-filled glovebox a small, oven-dried vial equipped with a magnetic stir bar was charged with $Cu(OAc)_2$ (4.6 mg, 0.025 mmol, 5 mol%), (S)-DTMB-SEGPHOS (32.6 mg, 0.0275 mmol, 5.5 mol%), and THF (0.2 mL). The vial was capped and stirred until a homogenous, dark green solution was obtained (~5 min). At this time, dimethoxy(methyl)silane (180 μL, 1.5 mmol, 3.0 equiv) was added, the vial was recapped, and stirred until a vibrant orange solution was obtained (~10 min)

While the L*CuH solution is stirring, an oven-dried screw-top reaction tube equipped with a magnetic stir bar and Teflon screw cap was charged with LiOMe (56 mg, 1.5 mmol, 3 equiv) and hydroalkylation substrate (0.5 mmol, 1.0 equiv). At this point the prepared L*CuH solution was added and the tube was capped and removed from the glovebox. The reaction mixture was placed in a preheated oil bath at 55 °C where it was stirred for 24 h. NOTE: It is vitally important that the stirring be vigorous. After completion, the reaction mixture was cooled to room temperature, diluted with hexanes (5 mL), and filtered through a plug of silica gel, eluting with dichloromethane. The crude mixture was concentrated and purified by column chromatography, eluting with a gradient of ethyl acetate in hexanes to provide the desired product. Enantiomeric excess was determined by comparing the sample against a racemic sample of the same compound utilizing either chiral HPLC or chiral GC techniquies.

General Procedure B: 3 Step, One-Pot Synthesis of Alkyl Alcohols.



Step 1: A 50 mL Schlenk flask, equipped with a magnetic stir bar and rubber septum, was charged with Cp_2ZrCl_2 (292 mg, 1.00 mmol, 10 mol%). The septum was held in place with copper wire and the flask was evacuated and backfilled with argon. Then dichloroethane (5 mL) was added by syringe. The flask was cooled to -20 °C in an ice/NaCl bath and Me_3Al (2.0 M in hexanes, 7.5 mL, 15 mmol, 1.50 equiv) was added slowly by syringe. Water (18 μL, 1 mmol, 0.1 equiv) was added CAREFULLY (vigorous reaction!) to the yellow solution, after which it was stirred for an additional 10 min at -20 °C. Then alkyne (10 mmol, 1.0 equiv) was added by syringe. The reaction mixture was allowed to warm to room temperature and allowed to stir for 1 - 4 h. The solvent and excess trimethylaluminum were removed under vacuum into an external trap cooled to -78 °C until a yellow paste remained.***

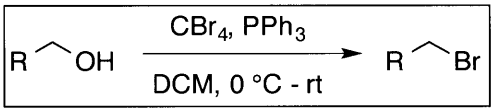
***NOTE**: At this point, the trap was removed from the vacuum line and allowed to warm to room temperature over the course of 24 h under air in the back of a fume hood. At the scale in which this reaction was run, this was enough to safely quench the excess Me_3Al. However, if repeating this reaction it is HIGHLY RECOMMENDED that the solution in the vacuum trap is carefully treated with sat. aq. Rochelle's salt to ensure that the Me_3Al is completely quenched.

Step 2: Under argon, the flask containing the yellow paste from **Step 1** was cooled in an ice bath and a solution of aryl halide (9 mmol, 0.9 equiv), OMsXPhos precatalyst (170 mg, 0.2 mmol, 2 mol%), XPhos (95 mg, 0.2 mmol, 2 mol%) in THF (10 mL), prepared under argon, was added slowly. The resulting yellow solution was allowed to warm to room temperature and stirred until judged to be complete by TLC. At this point the reaction mixture was transferred to a 250 mL Erlenmeyer flask, diluted with diethyl ether, cooled in an ice bath, and slowly quenched with a saturated aqueous solution of sodium-potassium

tartrate (Rochelle's salt) until gas evolution ceased. $MgSO_4$ was added to the solution and it was filtered. The crude mixture was concentrated with the aid of a rotary evaporator.

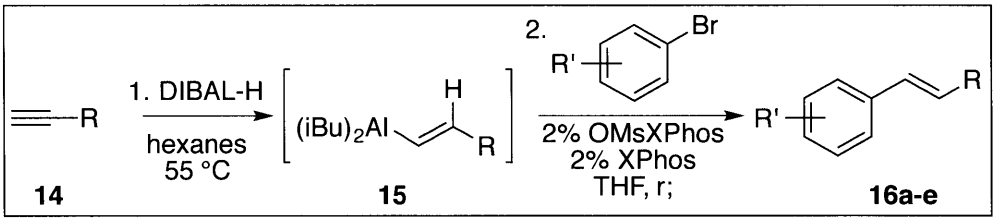
Step 3: With no precautions to exclude moisture or air, the residue from **Step** 2 was redissolved in THF (50 mL) and TBAF (1 M in THF, 12 mL, 1.2 equiv) was added. The flask was capped with a rubber septum and the dark-colored reaction mixture was stirred at room temperature until judged to be complete by TLC (generally ~1 h). The mixture was then diluted with water (50 mL) and extracted with diethyl ether (3x25 mL). The combined organic extracts were dried over $MgSO_4$, filtered through a pad of silica gel, and concentrated. The residue was then purified by column chromatography, eluting with a gradient of ethyl acetate in hexanes to provide the desired alkyl alcohol.

General Procedure C: Appel Reaction



A round-bottomed flask equipped with a magnetic stir bar was charged with alkyl alcohol (1 equiv), CBr_4 (1.1 – 1.2 equiv), and dichloromethane. The solution was cooled in an ice bath with stirring and PPh_3 (1.1 – 1.2 equiv) was added slowly. The reaction mixture was warmed to room temperature, capped, and stirred until judged to be complete by TLC. The reaction mixture was then filtered through a plug of silica gel, eluting with dichloromethane. The solution was concentrated and purified by column chromatography, first eluting with hexane to remove any PPh_3, CBr_4, and $CHBr_3$, then eluting with a gradient of ethyl acetate in hexanes to provide the desired alkyl bromide.

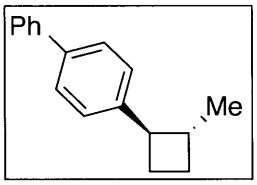
General procedure D: E-Styrene synthesis.



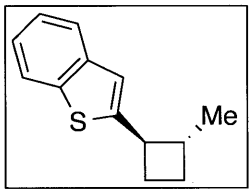
Step 1: A flame-dried screw-top reaction tube equipped with a magnetic stir bar and Teflon screw cap was charged with a solution of DIBAL-H (1 M in hexanes, 5 mL, 5 mmol, 1 equiv) by syringe. Under argon, the solution was cooled in an ice bath and terminal alkyne (5 mmol, 1 equiv) was added slowly by syringe. The reaction tube was removed from the ice bath, allowed to warm to room temperature, then stirred in a preheated oil bath at 55 °C for 2 h. The reaction mixture was then allowed to cool to room temperature.

Step 2. The tube containing the reaction mixture from **Step 1** was cooled in an ice bath under argon. A solution of aryl bromide (5 mmol, 1 equiv), OMsXPhos precatalyst (85 mg, 0.1 mmol, 2 mol%), and XPhos (48 mg, 0.1 mmol, 2 mol%) in THF (5 mL), prepared under argon, was added slowly by syringe. After the addition was complete, the reaction mixture was warmed to room temperature and stirred until judged to be complete by TLC (2 – 16 h). At this point the reaction mixture was transferred to a 250 mL Erlenmeyer flask and diluted with diethyl ether. A saturated solution of Rochelle's salt was added carefully until the precipitation of white solids stopped forming under further addition. Magnesium sulfate was then added and the solution was filtered, concentrated, and purified by column chromatography.

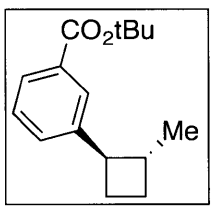
In the case of substrates bearing a silyl ether, the residue was then dissolved in THF (25 mL) and TBAF (1 M in THF, 6 mL, 6 mmol, 1.2 equiv) was added. The reaction mixture was stirred at room temperature until the process was judged to be complete by TLC (generally ~1 h). The mixture was then diluted with water (50 mL) and extracted with diethyl ether (3x25 mL). The combined organic extracts were dried over $MgSO_4$, filtered through a pad of silica gel, and concentrated. The residue was then purified by column chromatography, eluting with a gradient of ethyl acetate in hexanes to provide the desired styrene alcohol.



4-(trans-2-methylcyclobutyl)-1,1'-biphenyl: General procedure A was followed using (*E*)-4-(4-bromo-2-methylbut-1-en-1-yl)-1,1'-biphenyl (150 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 2% ethyl acetate in hexanes to provide the title compound as a white solid. **mp** = 50–52 °C. **Yield**: 90 mg, 81%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 2H), 7.55 (dd, *J* = 8.3, 1.9 Hz, 2H), 7.51 – 7.40 (m, 2H), 7.39 – 7.29 (m, 3H), 3.04 (q, *J* = 9.1 Hz, 1H), 2.54 – 2.37 (m, 1H), 2.24 (dt, *J* = 10.3, 7.5 Hz, 1H), 2.12 – 1.97 (m, 2H), 1.69 – 1.56 (m, 1H), 1.18 (d, *J* = 6.6 Hz, 3H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.52, 141.31, 138.93, 128.83, 127.15, 127.12, 127.10, 48.42, 39.54, 26.72, 25.91, 21.15 ppm. HPLC analysis indicated 96% ee.

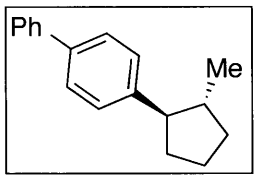


2-(trans-2-methylcyclobutyl)benzo[*b*]thiophene: General procedure A was followed using *tert*-butyl (*E*)-3-(4-bromo-2-methylbut-1-en-1-yl)benzoate (140 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 2% ethyl acetate in hexanes to provide the title compound as a clear oil. **Yield**: 83 mg, 82%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (ddt, *J* = 8.1, 2.8, 1.0 Hz, 1H), 7.68 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.31 (ddt, *J* = 8.1, 5.8, 1.5 Hz, 1H), 7.29 – 7.17 (m, 1H), 7.00 (dq, *J* = 1.9, 0.9 Hz, 1H), 3.30 – 3.17 (m, 1H), 2.62 – 2.42 (m, 1H), 2.34 (dtt, *J* = 10.5, 8.6, 1.7 Hz, 1H), 2.18 – 2.01 (m, 2H), 1.73 – 1.55 (m, 1H), 1.20 (dd, *J* = 6.6, 1.8 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.46, 140.33, 139.16, 124.19, 123.48, 122.90, 122.34, 118.68, 44.60, 40.97, 27.25, 26.67, 20.71 ppm. HPLC analysis indicated 99% ee.

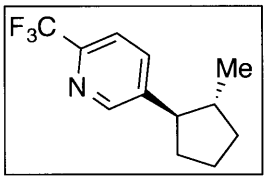


***tert*-butyl 3-(trans-2-methylcyclobutyl)benzoate**: General procedure A was followed using *tert*-butyl (*E*)-3-(4-bromo-2-methylbut-1-en-1-yl)benzoate (162 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 5% ethyl acetate in hexanes to provide the title compound as a pale yellow oil. **Yield**: 100 mg, 81%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.8 Hz, 1H), 7.81 (dt, *J* = 7.4, 1.6 Hz, 1H), 7.41 – 7.32 (m, 2H), 3.02 (q, *J* = 8.9 Hz, 1H), 2.48 – 2.37 (m, 1H), 2.26 – 2.18 (m, 1H),

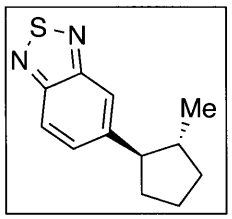
2.10 – 1.95 (m, 2H), 1.61 (m, 9+1H), 1.16 (d, J = 6.5 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.31, 145.57, 132.09, 130.97, 128.28, 127.71, 127.17, 81.09, 48.53, 39.53, 28.44, 26.77, 25.96, 21.18 ppm. GC analysis indicated XX% ee.



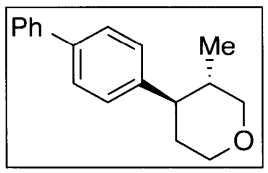
4-(trans-2-methylcyclobutyl)-1,1'-biphenyl: General procedure A was followed using (*E*)-4-(4-bromo-2-methylpent-1-en-1-yl)-1,1'-biphenyl (158 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 3% ethyl acetate in hexanes to provide the title compound as a clear oil. **Yield**: 99 mg, 84%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 2H), 7.58 – 7.53 (m, 2H), 7.49 – 7.42 (m, 2H), 7.38 – 7.33 (m, 1H), 7.33 – 7.29 (m, 2H), 2.49 (td, J = 9.7, 7.7 Hz, 1H), 2.18 – 2.10 (m, 1H), 2.10 – 2.00 (m, 1H), 2.00 – 1.91 (m, 1H), 1.88 – 1.72 (m, 3H), 1.43 – 1.29 (m, 1H), 0.99 (d, J = 6.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.87, 141.42, 138.99, 129.47, 128.93, 128.16, 127.25, 127.24, 127.18, 126.37, 54.44, 43.32, 35.67, 35.06, 24.17, 18.93 ppm. GC analysis indicated 99% ee.



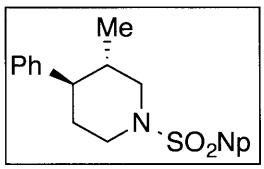
5-(trans-2-methylcyclopentyl)-2-(trifluoromethyl)pyridine: General procedure A was followed using (*E*)-5-(5-bromo-2-methylpent-1-en-1-yl)-2-(trifluoromethyl)pyridine (154 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 4% ethyl acetate in hexanes to provide the title compound as a clear oil. **Yield**: 99 mg, 84%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.57 (d, J = 2.0 Hz, 1H), 7.69 (dd, J = 8.0, 2.1 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 2.53 (td, J = 10.0, 7.9 Hz, 1H), 2.16 (dtd, J = 12.6, 8.1, 7.6, 4.4 Hz, 1H), 2.09 – 2.01 (m, 1H), 2.01 – 1.90 (m, 1H), 1.82 (dddd, J = 15.6, 14.4, 8.0, 4.4 Hz, 2H), 1.77 – 1.66 (m, 1H), 1.41 – 1.36 (m, 1H), 0.95 (dd, J = 6.4, 0.9 Hz, 3H) ppm. GC analysis indicated 98% ee.



5-(trans-2-methylcyclopentyl)benzo[*c*][1,2,5]thiadiazole: General procedure A was followed using (*E*)-5-(5-bromo-2-methylpent-1-en-1-yl)benzothiadiazole (149 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 1% ethyl acetate in hexanes to provide the title compound as a pale yellow oil. **Yield**: 77 mg, 71% yield. **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.92 (dd, *J* = 9.0, 0.7 Hz, 1H), 7.78 (dt, *J* = 1.6, 0.7 Hz, 1H), 7.50 (dd, *J* = 9.1, 1.6 Hz, 1H), 2.69 ? 2.57 (m, 1H), 2.25 ? 2.13 (m, 1H), 2.10 ? 1.97 (m, 2H), 1.88 ? 1.78 (m, 3 H), 1.45 ? 1.29 (m, 1H), 0.98 (d, *J* = 6.2 Hz, 3H) ppm. GC analysis indicated 77% ee.

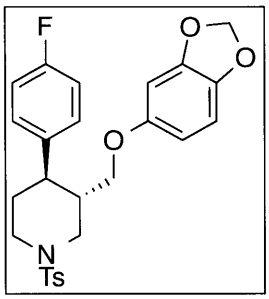


trans-4-([1,1'-biphenyl]-4-yl)-3-methyltetrahydro-2*H*-pyran: General procedure A was followed using (*E*)-4-(3-(2-bromoethoxy)-2-methylprop-1-en-1-yl)-1,1'-biphenyl (149 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 4% ethyl acetate in hexanes to provide the title compound as a clear oil. **Yield**: 74 mg, 59% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H), 7.55 (dd, *J* = 8.2, 2.0 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.37 – 7.31 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 4.14 – 4.06 (m, 1H), 4.00 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.53 (td, *J* = 11.9, 2.2 Hz, 1H), 3.14 (t, *J* = 11.1 Hz, 1H), 2.33 (td, *J* = 11.6, 3.9 Hz, 1H), 2.03 – 1.85 (m, 2H), 1.74 (ddt, *J* = 13.6, 3.8, 1.9 Hz, 1H), 0.66 (d, *J* = 6.6 Hz, 3H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.71, 141.08, 139.39, 128.86, 128.10, 127.32, 127.21, 127.12, 100.11, 74.71, 68.75, 49.58, 36.78, 34.90, 15.10 ppm. HPLC analysis indicated 93% ee.

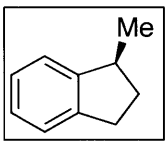


trans-3-methyl-1-(naphthalen-2-ylsulfonyl)-4-phenylpiperidine: General procedure A was followed using ((*E*)-*N*-(2-bromoethyl)-*N*-(2-methyl-3-phenylallyl)naphthalene-2-sulfonamide (222 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 5% ethyl acetate in hexanes to provide the title compound as a yellow oil. **Yield**: 119 mg, 66%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.46 – 8.37 (m, 1H), 8.04 (dd, *J* = 8.5, 2.5 Hz, 2H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.83 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.69 (dddd, *J* = 21.5, 8.2, 6.9, 1.3 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.15 – 7.06 (m,

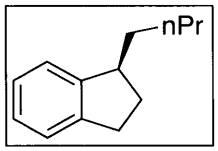
2H), 4.04 (ddt, *J* = 11.5, 4.2, 2.3 Hz, 1H), 4.01 – 3.95 (m, 1H), 2.40 (td, *J* = 11.7, 3.0 Hz, 1H), 2.10 – 2.00 (m, 2H), 1.94 (dddd, *J* = 23.3, 15.9, 11.8, 3.7 Hz, 2H), 1.85 (dq, *J* = 13.0, 3.3, 2.8 Hz, 1H), 0.67 (d, *J* = 5.7 Hz, 3H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.77, 135.00, 133.48, 132.38, 129.41, 129.31, 129.07, 128.92, 128.69, 128.08, 127.70, 127.56, 126.75, 123.21, 53.45, 49.92, 47.16, 36.30, 33.77, 17.06 ppm.



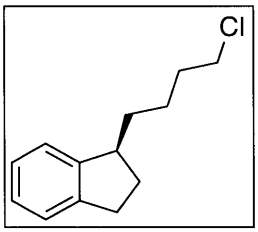
N-tosyl paroxetine: General procedure A was followed using (*Z*)-*N*-(2-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-3-(4-fluorophenyl)allyl)-*N*-(2-bromoethyl)-4-methylbenzenesulfonamide (281 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 10% ethyl acetate in hexanes to provide the title compound as a colorless oil. **Yield**: 148 mg, 61%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.14 – 7.03 (m, 2H), 7.03 – 6.89 (m, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.32 (d, *J* = 2.5 Hz, 1H), 6.10 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.88 (s, 2H), 4.12 (ddd, *J* = 11.4, 3.8, 1.9 Hz, 1H), 3.94 (ddt, *J* = 11.6, 4.3, 2.3 Hz, 1H), 3.58 (dd, *J* = 9.5, 2.7 Hz, 1H), 3.39 (dd, *J* = 9.5, 6.3 Hz, 1H), 2.45 (s, 4H), 2.41 – 2.28 (m, 2H), 2.23 (tdd, *J* = 11.0, 4.7, 1.6 Hz, 1H), 2.01 – 1.79 (m, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.02, 160.58, 154.12, 148.30, 143.72, 141.91, 138.46, 138.43, 133.24, 129.84, 128.87, 128.80, 127.89, 115.85, 115.64, 107.96, 105.60, 101.27, 98.07, 68.67, 49.65, 46.84, 43.26, 41.84, 33.41, 21.68 ppm.



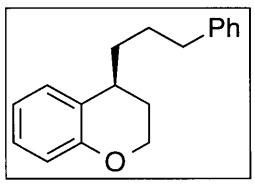
1-methylindane: General procedure A was followed using 2-(2-bromoethyl)styrene (106 mg, 0.5 mmol, 1.0 equiv). The crude residue was eluted through a short silica plug, eluting with pentane, concentrated, and eluted through a second short silica plug to give the title compound as a clear oil. **Yield**. 62 mg, 94%. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.24 – 7.10 (m, 4H), 3.26 – 3.15 (m, 1H), 2.96 – 2.79 (m, 2H), 2.32 (dtd, *J* = 12.3, 7.7, 3.8 Hz, 1H), 1.60 (dq, *J* = 12.3, 8.6 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 3H) ppm. GC analysis indicated 90% ee.



1-butyl-indane: General procedure A was followed using (*E*)-1-(2-bromoethyl)-2-(pent-1-en-1-yl)benzene (126 mg, 0.5 mmol, 1.0 equiv). The crude residue was eluted through a short silica plug, eluting with pentane, concentrated, and eluted through a second short silica plug to give the title compound as a clear oil. **Yield**: 80 mg, 92%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 1H), 7.21 – 7.13 (m, 2H), 3.12 (dq, *J* = 12.9, 7.7 Hz, 1H), 2.94 (ddd, *J* = 15.8, 8.6, 4.6 Hz, 1H), 2.85 (dt, *J* = 15.9, 8.1 Hz, 1H), 2.30 (dtd, *J* = 12.4, 8.0, 4.6 Hz, 1H), 1.95 – 1.81 (m, 1H), 1.69 (dq, *J* = 12.4, 7.9 Hz, 1H), 1.51 – 1.34 (m, 5H), 1.01 – 0.92 (m, 3H).

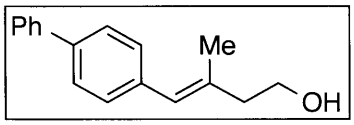


1-(4-chlorobutyl)-indane: General procedure A was followed using (*E*)-1-(2-bromoethyl)-2-(5-chloropent-1-en-1-yl)benzene (144 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with hexanes to provide the title compound as a pale yellow oil. **Yield**: 85 mg, 82%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.14 (m, 4H), 3.59 (td, *J* = 6.7, 1.3 Hz, 2H), 3.13 (qd, *J* = 7.7, 4.7 Hz, 1H), 2.95 (ddd, *J* = 15.8, 8.5, 4.6 Hz, 1H), 2.86 (dt, *J* = 15.9, 8.0 Hz, 1H), 2.31 (dtd, *J* = 12.5, 8.0, 4.7 Hz, 1H), 1.94 – 1.82 (m, 3H), 1.71 (dt, *J* = 12.5, 7.9 Hz, 1H), 1.64 – 1.54 (m, 2H), 1.50 – 1.41 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.04, 144.73, 127.03, 126.74, 125.18, 124.23, 45.81, 45.39, 34.98, 33.56, 32.80, 32.12, 25.71 ppm.

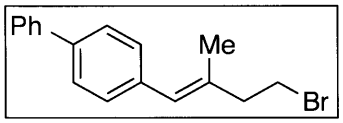


4-(3-phenylpropyl)chromane: General procedure A was followed using (*E*)-1-(2-bromoethoxy)-2-(4-phenylbut-1-en-1-yl)benzene (149 mg, 0.5 mmol, 1.0 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 3% ethyl acetate in hexanes to provide the title compound as a pale yellow oil. **Yield**: 99 mg, 79%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 8.1, 7.0 Hz, 2H), 7.26 – 7.19 (m, 3H), 7.15 – 7.08 (m, 2H), 6.87 (td, *J* = 7.5, 1.3 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.23 – 4.14 (m, 2H), 2.84 (dq, *J* = 10.3, 5.3 Hz, 1H), 2.69 (dddd, *J* = 28.9, 13.6, 8.7, 6.2 Hz, 2H), 2.09 (dddd, *J* = 13.6, 7.9, 5.7, 4.5 Hz, 1H), 1.93 – 1.70 (m, 4H), 1.62 (dtd, *J* = 12.6, 9.6, 4.2 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.70, 142.53, 129.33, 128.65, 128.60, 127.49, 126.76, 126.06, 120.32, 117.01, 63.75, 39.83, 36.27, 33.71, 29.11, 27.08 ppm.

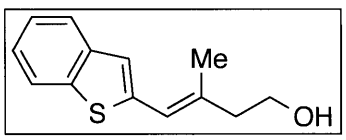
Substrate Syntheses



(*E*)-4-([1,1'-biphenyl]-4-yl)-3-methylbut-3-en-1-ol: General procedure B was followed, using (but-3-yn-1-yloxy)triisopropylsilane (2.26 g, 10 mmol, 1.0 equiv) and 4-bromobiphenyl (2.10 g, 9 mmol, 0.9 equiv). The crude reaction mixture was purified by column chromatography, eluting with a gradient of 0 – 40% ethyl acetate in hexanes to provide the title compound as a white, crystalline solid. **Yield**: 1.24 g, 58%. **mp** = 71–73 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.61 ? 7.57 (m, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.40 ? 7.34 (m, 3H), 6.43 (s, 1H), 3.85 (q, *J* = 6.2 Hz, 2H), 2.51 (td, *J* = 6.3, 1.0 Hz, 2H), 1.99 (d, *J* = 1.3 Hz, 3H), 1.47 (t, *J* = 5.8 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.51, 139.68, 137.62, 136.05, 129.98, 129.47, 128.06, 127.90, 127.67, 127.50, 61.21, 44.59, 18.54 ppm.

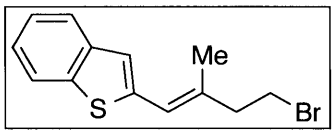


(*E*)-4-(4-bromo-2-methylbut-1-en-1-yl)-1,1'-biphenyl: Following general procedure C, a mixture of (*E*)-4-([1,1'-biphenyl]-4-yl)-3-methylbut-3-en-1-ol (477 mg, 2 mmol, 1 equiv), CBr_4 (794 mg, 2.4 mmol, 1.2 equiv), triphenylphosphine (630 g, 2.4 mmol, 1.2 equiv) and dichloromethane (25 mL) was stirred at room temperature for 1 h, when judged to be complete by TLC. The residue was purified by column chromatography, eluting with a gradient of 0 – 5% EtOAc in hexanes to provide the title compound as a crystalline, white solid. **Yield**: 602 mg, 97%. **mp** = 38–40 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.36 (dd, *J* = 8.0, 2.0 Hz, 3H), 3.60 (t, *J* = 7.4 Hz, 2H), 2.78 (td, *J* = 7.3, 1.1 Hz, 2H), 1.97 (d, *J* = 1.4 Hz, 3H) ppm.

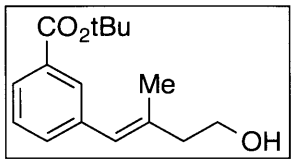


(*E*)-4-(benzo[*b*]thiophen-2-yl)-3-methylbut-3-en-1-ol: General procedure B was followed, using (but-3-yn-1-yloxy)triisopropylsilane (2.26 g, 10 mmol, 1.0 equiv) and 2-bromobenzothiophene (1.92 g, 9 mmol, 0.9 equiv). The crude reaction mixture was purified by column chromatography, eluting with a gradient of 0 – 40% ethyl acetate in hexanes to provide the title compound as a yellow oil. **Yield**: 1 g, 51%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 1H), 7.78 – 7.70 (m, 1H), 7.38 – 7.33 (m, 1H), 7.33 – 7.29 (m, 1H), 7.18

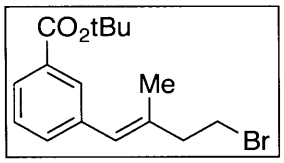
(s, 1H), 6.57 (q, J = 1.3 Hz, 1H), 3.86 (q, J = 6.1 Hz, 2H), 2.53 (t, J = 6.3 Hz, 2H), 2.13 (d, J = 1.3 Hz, 3H), 1.43 (td, J = 5.7, 2.2 Hz, 1H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 141.00, 139.69, 139.64, 136.88, 124.47, 124.14, 123.30, 123.13, 122.08, 121.44, 60.70, 44.36, 18.60 ppm.



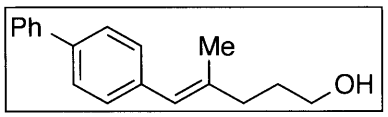
(*E*)-2-(4-bromo-2-methylbut-1-en-1-yl)benzo[*b*]thiophene: Following general procedure C a mixture of (*E*)-4-(benzo[*b*]thiophen-2-yl)-3-methylbut-3-en-1-ol (436 mg, 2 mmol, 1.2 equiv), CBr_4 (794 mg, 2.4 mmol, 1.2 equiv), triphenylphosphine (630 mg, 2.4 mmol, 1.2 equiv) and dichloromethane (25 mL) was stirred at room temperature for 2 h, when judged to be complete by TLC. The residue was purified by column chromatography, eluting with a gradient of 0 – 5% EtOAc in hexanes to provide the title compound as a light yellow oil. **Yield**: 440 mg, 78%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (dq, J = 7.6, 0.7 Hz, 1H), 7.75 – 7.69 (m, 1H), 7.36 – 7.31 (m, 1H), 7.29 (ddd, J = 8.5, 7.1, 1.5 Hz, 1H), 7.16 (s, 1H), 6.53 (h, J = 1.1 Hz, 1H), 3.55 (t, J = 7.4 Hz, 2H), 2.84 – 2.72 (m, 2H), 2.15 – 2.05 (m, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.79, 139.79, 139.63, 136.90, 124.50, 124.22, 123.42, 123.35, 122.09, 121.66, 44.27, 30.89, 18.26 ppm.



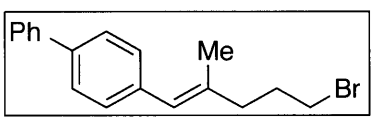
***tert*-butyl (*E*)-3-(4-hydroxy-2-methylbut-1-en-1-yl)benzoate:** General procedure B was followed, using (but-3-yn-1-yloxy)triisopropylsilane (2.26 g, 10 mmol, 1.0 equiv) and *tert*-butyl-3-bromobenzoate (2.31 g, 9 mmol, 0.9 equiv). The crude reaction mixture was purified by column chromatography, eluting with a gradient of 0 – 50% ethyl acetate in hexanes to provide the title compound as a dark yellow oil. **Yield**: 1.05 g, 45%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 – 7.87 (m, 1H), 7.83 (dt, J = 7.3, 1.7 Hz, 1H), 7.42 – 7.35 (m, 2H), 6.39 (d, J = 1.8 Hz, 1H), 3.82 (t, J = 6.4 Hz, 2H), 2.47 (td, J = 6.4, 1.1 Hz, 2H), 1.91 (d, J = 1.4 Hz, 3H), 1.60 (s, 9H), 1.06 (d, J = 1.1 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.07, 138.19, 136.46, 133.04, 132.08, 129.98, 128.23, 127.45, 127.08, 81.26, 60.73, 43.89, 28.43, 17.89 ppm.



***tert*-butyl (*E*)-3-(4-bromo-2-methylbut-1-en-1-yl)benzoate**: Following general procedure C, a mixture of *tert*-butyl (*E*)-3-(4-hydroxy-2-methylbut-1-en-1-yl)benzoate (877 mg, 3.35 mmol, 1 equiv), CBr_4 (1.33 g, 4.02 mmol, 1.2 equiv), triphenylphosphine (1.05 g, 4.02 mmol, 1.2 equiv) and dichloromethane (25 mL) was stirred at room temperature for 0.5 h, when judged to be complete by TLC. The residue was purified by column chromatography, eluting with a gradient of 0 – 5% EtOAc in hexanes to provide the title compound as a light yellow oil. **Yield**: 975 mg, 90%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 – 7.87 (m, 1H), 7.84 (dt, *J* = 7.0, 1.8 Hz, 1H), 7.44 – 7.35 (m, 2H), 6.40 – 6.36 (m, 1H), 3.56 (t, *J* = 7.4 Hz, 2H), 2.75 (td, *J* = 7.4, 1.2 Hz, 2H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.60 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.02, 138.04, 136.58, 133.03, 132.11, 129.98, 128.24, 127.57, 127.26, 81.25, 43.82, 31.31, 28.44, 17.58 ppm.

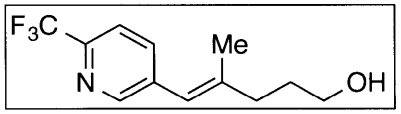


(*E*)-5-([1,1'-biphenyl]-4-yl)-4-methylpent-4-en-1-ol: General procedure B was followed, using *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (1.98 g, 10 mmol, 1.0 equiv) and 4-bromobiphenyl (2.10 g, 9 mmol, 0.9 equiv). In lieu of TBAF deprotection, after quenching the reaction mixture with Rochelle's salt, the crude reaction mixture was dissolved in methanol and a drop of conc. HCl was. The mixture was stirred for 2 hours, after which solid Na_2CO_3 and $MgSO_4$ was added. The mixture was filtered, concentrated, and purified by column chromatography, eluting with a gradient of 0 – 37.5% ethyl acetate in hexanes to provide the title compound as a white, crystalline solid. **mp** = 78–79 °C. **Yield**: 1.55 g, 68% (based on 4-bromobiphenyl). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 – 7.61 (m, 2H), 7.61 – 7.55 (m, 2H), 7.52 – 7.42 (m, 2H), 7.40 – 7.30 (m, 3H), 6.37 (d, *J* = 1.8 Hz, 1H), 3.74 (t, *J* = 6.5 Hz, 2H), 2.37 – 2.25 (m, 2H), 1.96 (d, *J* = 1.3 Hz, 3H), 1.90 – 1.79 (m, 2H), 1.58 (s, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.14, 139.12, 138.90, 137.67, 130.92, 129.47, 129.01, 127.38, 127.20, 127.00, 126.90, 125.08, 62.92, 37.36, 31.17, 18.20 ppm.

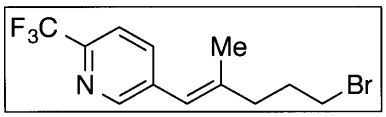


(*E*)-4-(5-bromo-2-methylpent-1-en-1-yl)-1,1'-biphenyl: Following general procedure C, a mixture of (*E*)-5-([1,1'-biphenyl]-4-yl)-4-methylpent-4-en-1-ol (1 g, 4 mmol, 1 equiv), CBr_4 (1.59 g, 4.8 mmol, 1.2 equiv), triphenylphosphine (1.26

g, 4.8 mmol, 1.2 equiv) and dichloromethane (25 mL) was stirred at room temperature for 0.5 h, when judged to be complete by TLC. The residue was purified by column chromatography, eluting with a gradient of 0 – 5% EtOAc in hexanes to provide the title compound as a crystalline, white solid. **Yield**: 1 g, 81%. **mp** = 48 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 – 7.61 (m, 2H), 7.61 – 7.56 (m, 2H), 7.53 – 7.42 (m, 2H), 7.40 – 7.31 (m, 3H), 6.38 (s, 1H), 3.49 (t, *J* = 6.7 Hz, 2H), 2.37 (ddd, *J* = 7.5, 6.6, 1.1 Hz, 2H), 2.18 – 2.08 (m, 2H), 1.94 (d, *J* = 1.3 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.11, 139.04, 137.51, 137.47, 129.48, 129.01, 127.41, 127.21, 127.02, 125.97, 39.82, 39.26, 33.58, 31.18, 18.12 ppm.

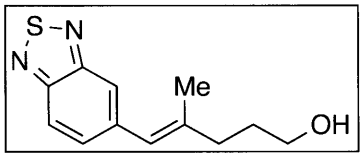


(*E*)-4-methyl-5-(6-(trifluoromethyl)pyridin-3-yl)pent-4-en-1-ol: General procedure B was followed, using *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (1.98 g, 10 mmol, 1.0 equiv) and 5-bromo-2-trifluoromethylpyridine (2 g, 9 mmol, 0.9 equiv). After quenching the aluminum with Rochelle's salt, the crude reaction mixture was dissolved in methanol and a drop of conc. HCl was added to cleave the TBS ether. The mixture was stirred for 2 hours, after which solid Na_2CO_3 and $MgSO_4$ was added. The mixture was filtered, concentrated, and purified by column chromatography, eluting with a gradient of 0 – 37.5% ethyl acetate in hexanes to provide the title compound as a yellow oil. **Yield**: 1.02 g, 46%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.62 – 8.55 (m, 1H), 7.69 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 6.29 (s, 1H), 3.73 (t, *J* = 6.4 Hz, 2H), 2.37 – 2.28 (m, 3H), 1.90 (d, *J* = 1.2 Hz, 3H), 1.87 – 1.78 (m, 3H), 1.64 – 1.50 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.32, 144.73, 144.18, 136.93, 120.66, 120.11, 62.57, 37.15, 30.96, 18.22 ppm.

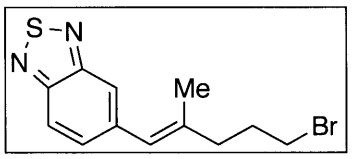


(*E*)-5-(5-bromo-2-methylpent-1-en-1-yl)-2-(trifluoromethyl) pyridine: Following general procedure C, a mixture of (*E*)-4-methyl-5-(6-(trifluoromethyl)pyridin-3-yl)pent-4-en-1-ol (929 mg, 3.79 mmol, 1.00 equiv), CBr_4 (1.38 g, 4.17 mmol, 1.1 equiv) and triphenylphosphine (1.09 g, 4.17 mmol, 262 mmol) was stirred overnight at room temperature. The crude residue was purified by column chromatography, eluting with a gradient of 0 – 5% ethyl acetate in hexanes to provide the title compound as a yellow oil that was stored at 4 °C. **Yield**: 920 mg, 79%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 2.0 Hz, 1H), 7.70 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.63 (dd, *J*

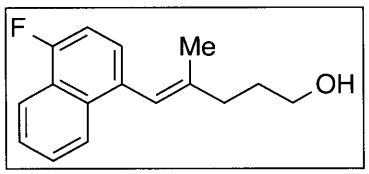
= 8.1, 0.8 Hz, 1H), 6.32 (s, 1H), 3.46 (t, J = 6.6 Hz, 2H), 2.44 – 2.34 (m, 2H), 2.15 – 2.07 (m, 2H), 1.89 (d, J = 1.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.32, 142.64, 136.97, 121.55, 120.13, 120.11, 120.09, 39.08, 33.20, 30.85, 18.14.



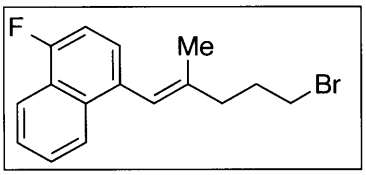
(*E*)-5-(benzo[*c*][1,2,5]thiadiazol-5-yl)-4-methylpent-4-en-1-ol: General procedure B was followed, using *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (1.98 g, 10 mmol, 1.0 equiv) and 5-bromobenzo[*c*][1,2,5]thiadiazole (1.93 g, 9 mmol, 0.9 equiv). The crude reaction mixture was purified by column chromatography, eluting with a gradient of 0 – 50% ethyl acetate in hexanes to provide the title compound as a yellow oil. **Yield**: 800 mg, 38%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (dd, J = 9.0, 0.8 Hz, 1H), 7.80 (dd, J = 1.7, 0.9 Hz, 1H), 7.46 (dd, J = 9.1, 1.6 Hz, 1H), 6.41 (p, J = 1.4 Hz, 1H), 3.74 (t, J = 6.4 Hz, 2H), 2.37 – 2.30 (m, 2H), 1.96 (d, J = 1.4 Hz, 3H), 1.90 – 1.80 (m, 2H), 1.71 – 1.58 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.46, 153.78, 142.28, 140.01, 132.57, 124.29, 120.77, 119.85, 62.71, 37.32, 31.10, 18.44 ppm.



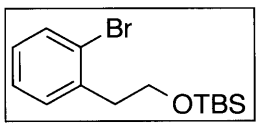
(*E*)-5-(5-bromo-2-methylpent-1-en-1-yl)benzo[*c*][1,2,5]thiadiazole: Following general procedure C a mixture of (*E*)-5-(benzo[*c*][1,2,5]thiadiazol-5-yl)-4-methylpent-4-en-1-ol (468 mg, 2 mmol, 1 equiv), CBr_4 (795 mg, 2.4 mmol, 1.2 equiv), triphenylphosphine (630 mg, 2.4 mmol, 1.2 equiv) and dichloromethane (25 mL) was stirred at room temperature for 0.5 h, when judged to be complete by TLC. The residue was purified by column chromatography, eluting with a gradient of 0 – 5% ethyl acetate in hexanes to provide the title compound as a yellow oil. While the starting material was geometrically pure, the product was a 5:1 mixture of (*E*):(*Z*) isomers. **Yield**: 554 mg, 93%. **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.96 – 7.89 (m, 1H), 7.82 (dt, J = 1.7, 0.9 Hz, 1H), 7.47 (dd, J = 9.1, 1.6 Hz, 1H), 6.45 (h, J = 1.4 Hz, 1H), 3.48 (t, J = 6.6 Hz, 2H), 2.41 (td, J = 7.3, 1.1 Hz, 2H), 2.19 – 2.10 (m, 2H), 1.97 – 1.96 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.43, 155.00, 140.70, 139.76, 132.47, 125.19, 120.86, 119.97, 39.23, 33.37, 31.00, 18.36 ppm.



(*E*)-5-(4-fluoronaphthalen-1-yl)-4-methylpent-4-en-1-ol: General procedure B was followed, using *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (1.98 g, 10 mmol, 1.0 equiv) and 1-bromo-4-fluoronaphthalene (2.03 g, 9 mmol, 0.9 equiv). The crude reaction mixture was purified by column chromatography, eluting with a gradient of 15 – 50% ethyl acetate in hexanes to provide the title compound as a dark yellow oil. **Yield**: 1.04 g, 47%. **^{1}H NMR** (500 MHz, Chloroform-d) δ 8.16 – 8.09 (m, 1H), 7.98 – 7.91 (m, 1H), 7.58 – 7.50 (m, 2H), 7.21 (ddd, *J* = 7.9, 5.6, 1.0 Hz, 1H), 7.11 (dd, *J* = 10.4, 7.9 Hz, 1H), 6.63 (p, *J* = 1.3 Hz, 1H), 3.80 (t, *J* = 6.5 Hz, 2H), 2.44 – 2.35 (m, 2H), 1.99 – 1.85 (m, 2H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.64 – 1.53 (m, 1H) ppm.

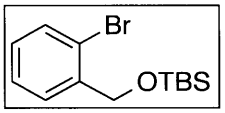


(*E*)-1-(5-bromo-2-methylpent-1-en-1-yl)-4-fluoronaphthalene: Following general procedure C, a mixture of (*E*)-5-(4-fluoronaphthalen-1-yl)-4-methylpent-4-en-1-ol (1 g, 4.1 mmol, 1 equiv), CBr_4 (1.49 g, 4.5 mmol, 1.1 equiv) triphenylphosphine (1.18 g, 4.5 mmol, 1.1 equiv) and dichloromethane (15 mL) was stirred at room temperature for 1 h, until judged to be complete by TLC. The residue was purified by column chromatography, eluting with a gradient of 0 – 10% ethyl acetate in hexanes to provide the title compound as a yellow oil. **Yield**: 1.12 g, 95%. **^{1}H NMR** (500 MHz, Chloroform-d) δ 8.20 – 8.07 (m, 1H), 7.95 (dt, *J* = 7.4, 2.3 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.21 (ddd, *J* = 7.8, 5.5, 0.9 Hz, 1H), 7.12 (dd, *J* = 10.4, 7.9 Hz, 1H), 6.67 (q, *J* = 1.4 Hz, 1H), 3.55 (t, *J* = 6.7 Hz, 2H), 2.47 (td, *J* = 7.3, 1.1 Hz, 2H), 2.18 (dq, *J* = 8.5, 6.7 Hz, 2H), 1.71 (d, *J* = 1.3 Hz, 3H) ppm.

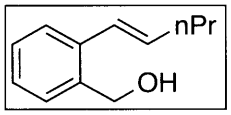


(2-bromophenethoxy)(*tert*-butyl)dimethylsilane: A 1 L round-bottomed flask equipped with a magnetic stir bar was charged with 2-(2-bromophenyl)ethanol (10 g, 50 mmol, 1 equiv.), imidazole (6.8 g, 100 mmol, 2 equiv) and dichloromethane (500 mL). After the mixture became homogeneous with stirring, (*tert*-butyl)dimethylchlorosilane (7.5 g, 50 mmol, 1 equiv) was added in one portion and the reaction mixture was stirred for 2 h, until judged to be complete by TLC. The

reaction mixture was washed with water, dried over $MgSO_4$ and filtered through a plug of silica gel, eluting with DCM. The solution was then concentrated to provide the title compound as a clear liquid. **Yield**: 15.6 g, 99%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.25 (m, 1H), 7.23 (td, *J* = 7.4, 1.2 Hz, 1H), 7.07 (ddd, *J* = 7.9, 7.2, 1.9 Hz, 1H), 3.84 (t, *J* = 7.0 Hz, 2H), 2.99 (t, *J* = 7.0 Hz, 2H), 0.88 (s, 9H), -0.01 (s, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.56, 132.89, 131.97, 128.15, 127.40, 124.83, 62.74, 39.86, 26.17, 18.57, -5.19 ppm.

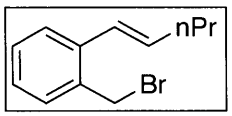


((2-bromobenzyl)oxy)(*tert*-butyl)dimethylsilane: A 1 L round-bottomed flask equipped with a magnetic stir bar was charged with 2-bromobenzyl alcohol (9.35 g, 50 mmol, 1 equiv.), imidazole (6.8 g, 100 mmol, 2 equiv) and dichloromethane (500 mL). After the mixture became homogeneous with stirring, (*tert*-butyl)dimethylchlorosilane (7.5 g, 50 mmol, 1 equiv) was added in one portion and the reaction mixture was stirred for 2 h, until judged to be complete by TLC. The reaction mixture was washed with water, dried over $MgSO_4$ and filtered through a plug of silica gel, eluting with DCM. The solution was then concentrated to provide the title compound as a clear liquid. **Yield**: 14.2 g, 95%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 – 7.10 (m, 1H), 7.57 (ddt, *J* = 7.7, 1.9, 1.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34 (td, *J* = 7.5, 1.2 Hz, 1H), 4.75 (d, *J* = 0.8 Hz, 2H), 0.98 (s, 9H), 0.15 (s, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.54, 132.23, 128.37, 127.75, 127.54, 121.23, 64.83, 26.19, 18.65, -5.09 ppm.

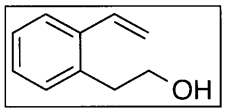


(*E*)-(2-(pent-1-en-1-yl)phenyl)methanol: General procedure D was followed using 1-pentyne (500 μL, 5 mmol, 1 equiv) and ((2-bromobenzyl)oxy)(*tert*-butyl)dimethylsilane (1.50 g, 5 mmol, 1 equiv). After TBAF deprotection and workup, the crude residue was purified by column chromatography, eluting with a gradient of 0 – 20% ethyl acetate in hexanes, to provide the title compound as a yellow oil. **Yield**: 740 mg, 84%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.31 – 7.25 (m, 1H), 7.23 (td, *J* = 7.4, 1.5 Hz, 1H), 6.76 – 6.60 (m, 1H), 6.16 (dt, *J* = 15.6, 7.0 Hz, 1H), 4.74 (s, 2H), 2.23 (qd, *J* = 7.1, 1.6 Hz, 2H), 1.79 – 1.65 (bs, 1H), 1.52

(h, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.28, 137.08, 134.09, 128.48, 128.31, 127.24, 126.76, 126.30, 63.73, 35.65, 22.81, 14.00 ppm.

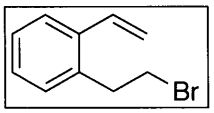


(*E*)-1-(bromomethyl)-2-(pent-1-en-1-yl)benzene: Following general procedure D, a mixture of (*E*)-(2-(pent-1-en-1-yl)phenyl)methanol (176 mg, 1 mmol, 1 equiv), CBr_4 (397 mg, 1.2 mmol, 1.2 equiv) and triphenylphosphine (315 mg, 1.2 mmol, 1.2 equiv) in DCM (5 mL) was stirred at rt for 30 min, until judge to be complete by TLC. The crude residue was purified by column chromatography, eluting with a gradient of 0 – 3% ethyl acetate in hexanes to provide the title compound as a light yellow oil. **Yield**: 191 mg, 80%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.8, 1.3 Hz, 1H), 7.29 (ddd, J = 17.4, 7.5, 1.4 Hz, 2H), 7.20 (td, J = 7.5, 1.3 Hz, 1H), 6.74 (dt, J = 15.7, 1.5 Hz, 1H), 6.22 (dt, J = 15.6, 7.0 Hz, 1H), 4.58 (s, 2H), 2.26 (qd, J = 7.1, 1.5 Hz, 2H), 1.55 (h, J = 7.4 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.83, 134.66, 134.22, 130.43, 129.30, 127.42, 126.78, 126.47, 35.70, 32.45, 22.72, 14.01 ppm.

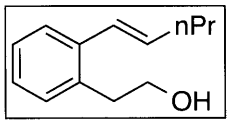


2-(2-vinylphenyl)ethan-1-ol: Following a modified literature procedure, a mixture of (2-bromophenethoxy)(*tert*-butyl)dimethylsilane (1.58 g, 5 mmol, 1 equiv), potassium vinyl tetrafluoroborate (670 mg, 5 mmol, 1 equiv), cesium carbonate (4.9 g, 15 mmol, 3 equiv), RuPhos-Pd-G3 (167 mg, 0.2 mmol, 4 mol%) and RuPhos (95 mg, 0.2 mmol, 4 mol%) in a 9:1 mixture of THF:degassed water was stirred at 85 °C for 24 h. The mixture was cooled to room temperature, diluted with diethyl ether, and the aqueous layer was separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The mixture was redissolved in THF (10 mL) and TBAF (1 M in THF, 6 mL, 6 mmol, 1.2 equiv) was added. The reaction mixture was stirred for 12 h, then diluted with diethyl ether, and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography, eluting with a gradient of 0 – 25% ethyl acetate in hexanes to provide the title compound as a light yellow oil. **Yield**: 720 mg, 97%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 – 7.47 (m, 1H), 7.29 – 7.18 (m, 3H), 7.02 (dd, J = 17.3, 10.9 Hz, 1H), 5.67 (dd, J = 17.3, 1.4 Hz, 1H), 5.33 (dd, J =

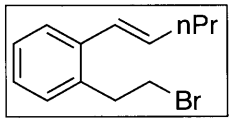
11.0, 1.4 Hz, 1H), 3.83 (t, J = 6.8 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H), 1.60 – 1.40 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.32, 135.82, 134.62, 130.56, 128.12, 127.20, 126.28, 116.28, 63.42, 36.65 ppm.



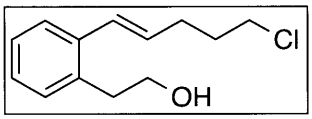
1-(2-bromoethyl)-2-vinylbenzene: Following general procedure B, a mixture of 2-(2-vinylphenyl)ethan-1-ol (446 mg, 3 mmol, 1 equiv), CBr_4 (1.1 g, 3.3 mmol, 1.1 equiv), and triphenylphosphine (865 mg, 3.3 mmol, 1.1 equiv) was stirred at room temperature overnight. The crude residue was purified by column chromatography, eluting with a gradient of 0 – 5% ethyl acetate in hexanes to provide the title compound as a clear oil. **Yield**: 440 mg, 70%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.2, 1.9 Hz, 1H), 7.35 – 7.22 (m, 2H), 7.22 – 7.16 (m, 1H), 6.97 (dd, J = 17.3, 11.0 Hz, 1H), 5.70 (dd, J = 17.3, 1.3 Hz, 1H), 5.38 (dd, J = 10.9, 1.3 Hz, 1H), 3.51 (dd, J = 8.8, 7.3 Hz, 2H), 3.26 (dd, J = 8.7, 7.3 Hz, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.01, 136.39, 134.08, 130.23, 128.25, 127.73, 126.45, 116.94, 37.28, 32.19 ppm.



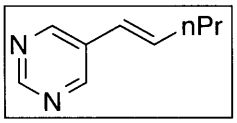
(*E*)-2-(2-(pent-1-en-1-yl)phenyl)ethan-1-ol: General procedure D was followed using 1-pentyne (500 μL, 5 mmol, 1 equiv) and (2-bromophenethoxy)(*tert*-butyl)dimethylsilane (1.58 g, 5 mmol, 1 equiv). After TBAF deprotection and workup, the crude residue was purified by column chromatography, eluting with a gradient of 0 – 20% ethyl acetate in hexanes, to provide the title compound as a yellow oil. (Note: the product contained 5% of the Sonogashira coupling product and was used without further purification.) **Yield**: 780 mg, 81%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 1H), 7.25 – 7.15 (m, 3H), 6.65 (dt, J = 15.7, 1.5 Hz, 1H), 6.11 (dt, J = 15.5, 7.0 Hz, 1H), 3.88 – 3.79 (m, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.22 (qd, J = 7.1, 1.5 Hz, 2H), 1.59 – 1.45 (m, 3H), 0.97 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) – 137.32, 135.82, 134.62, 130.56, 128.12, 127.20, 126.28, 116.28, 63.42, 36.65 ppm.



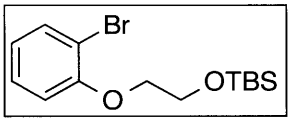
(*E*)-1-(2-bromoethyl)-2-(pent-1-en-1-yl)benzene: Following general procedure C, a mixture of (E)-2-(pent-1-en-1-yl)phenyl)ethan-1-ol (750 mg, 4 mmol, 1 equiv), CBr_4 (1.46g, 4.4 mmol, 1.1 equiv), and triphenylphosphine (1.15 g, 4.4 mmol, 1.1 equiv) was stirred overnight. The crude residue was purified by column chromatography, eluting with a gradient of 0 – 3% ethyl acetate in hexanes to provide the title compound as a light yellow oil. **Yield**: 760 mg, 77%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.24 (td, *J* = 7.4, 1.8 Hz, 1H), 7.21 – 7.14 (m, 2H), 6.59 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.14 (dt, *J* = 15.6, 7.0 Hz, 1H), 3.51 (dd, *J* = 8.8, 7.3 Hz, 2H), 3.24 (dd, *J* = 8.7, 7.3 Hz, 2H), 2.24 (qd, *J* = 7.1, 1.5 Hz, 2H), 1.52 (dt, *J* = 14.6, 7.3 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.25, 135.87, 134.17, 130.12, 127.61, 127.32, 126.92, 126.61, 37.42, 35.64, 32.26, 22.81, 13.99 ppm.



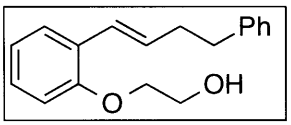
(*E*)-2-(2-(5-chloropent-1-en-1-yl)phenyl)ethan-1-ol: General procedure D was followed using a mixture of DIBAL-H (1 M in hexanes, 9.5 mL, 9.5 mmol, 1 equiv), 5-chloro-1-pentyne (970 mg, 9.5 mmol, 9.5 equiv) and (2-(2-bromophenyl)ethoxy)(*tert*-butyl)dimethylsilane (2.96 g, 9.5 mmol, 1 equiv). After quenching, the mixture was filtered through a plug of silica gel and concentrated, giving 3.2 g of a crude oil. Half the material (1.6 g) was dissolved in THF (10 mL) to which TBAF (1 M in THF, 6 mL, 6 mmol) was added. The mixture was stirred for 1 h, until judged to be complete by TLC. After workup, the residue was purified by column chromatography, eluting with 0 – 20% EtOAc in hexanes to provide the title compound as a yellow oil. (The mixture was isolated as a 3:1 mixture of desired product: 2-(2-bromophenyl)ethanol, and was used in the next step without further purification.) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 1H), 7.25 – 7.15 (m, 3H), 6.73 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.06 (dt, *J* = 15.5, 7.1 Hz, 1H), 3.82 (t, *J* = 6.8 Hz, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.96 (t, *J* = 6.8 Hz, 2H), 2.42 (qd, *J* = 7.1, 1.5 Hz, 2H), 2.02 – 1.92 (m, 2H), 1.55 – 1.48 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.08, 135.42, 131.11, 130.53, 128.94, 127.55, 127.16, 126.46, 63.38, 44.61, 36.73, 32.27, 30.56 ppm.



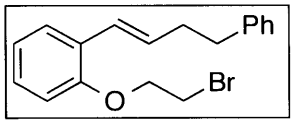
(*E*)-5-(pent-1-en-1-yl)pyrimidine: General procedure D was followed using 1-pentyne (100 μL, 1.00 mmol, 1.00 equiv) and 5-bromopyrimidine (157 mg, 1.00 mmol, 1.00 equiv). The crude residue was purified by column chromatography, eluting with a gradient of 0 – 20% ethyl acetate in hexanes to provide the title compound as a waxy, yellow solid. **Yield** 131 mg, 89%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.68 (s, 2H), 6.39 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.29 (dt, *J* = 16.1, 1.4 Hz, 1H), 2.27 – 2.19 (m, 2H), 1.52 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.32, 144.73, 144.18, 136.93, 120.66, 120.11, 62.57, 37.15, 30.96, 18.22 ppm.



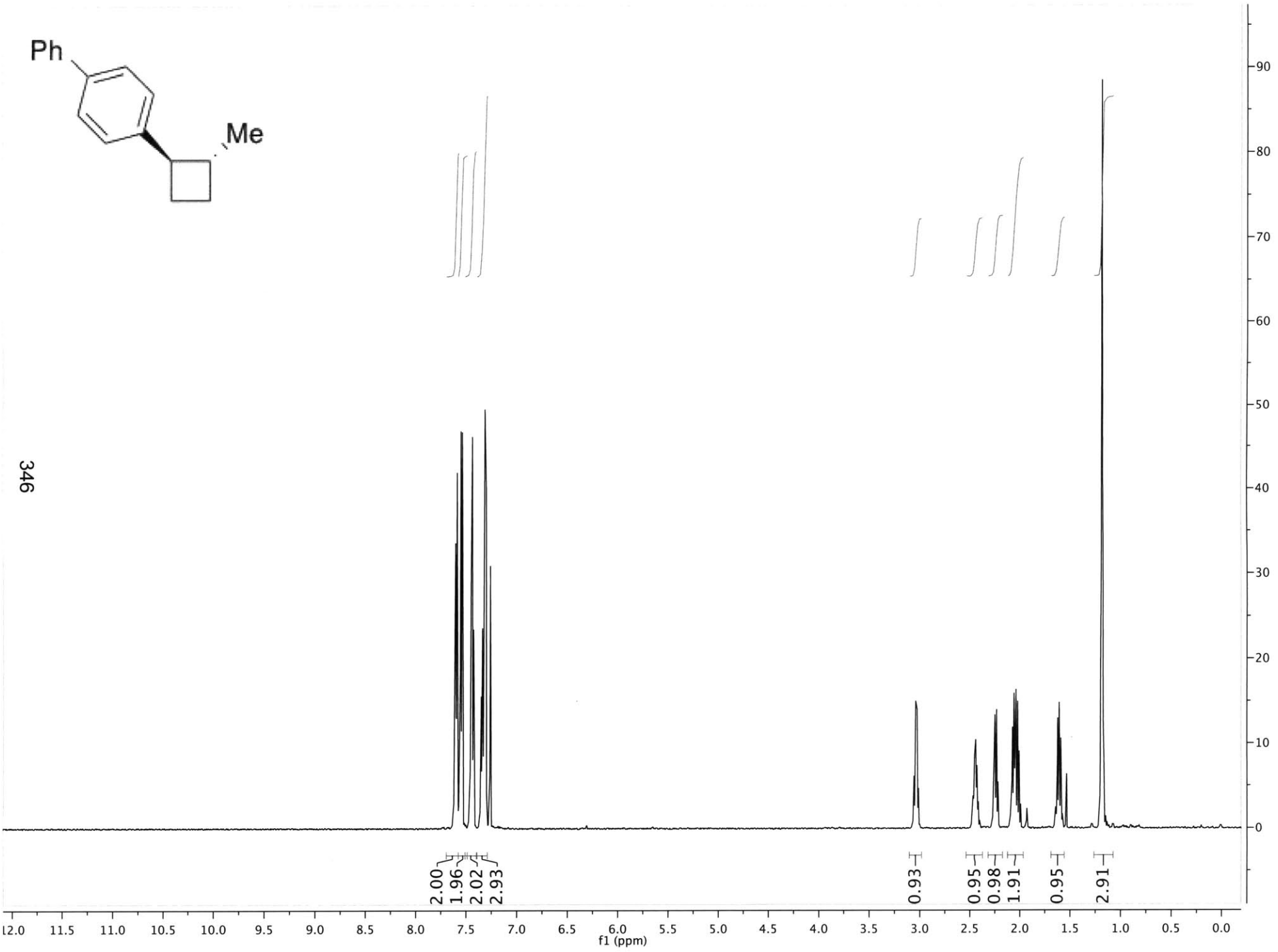
(2-(2-bromophenoxy)ethoxy)(*tert*-butyl)dimethylsilane: A 100 mL round-bottomed flask equipped with a magnetic stir bar and rubber septum was charged with 2-bromophenol (1.73 g, 10 mmol, 1 equiv), (2-bromoethoxy)(*tert*-butyl)dimethylsilane (2.87 g, 12 mmol, 1.2 equiv), potassium carbonate (2.76 g, 20 mmol, 2 equiv), and acetonitrile (30 mL). The reaction flask was capped and the mixture was stirred at 55 °C for 24 h. After cooling to room temperature the solvent was removed with the aid of a rotary evaporator. The crude residue was dissolved in hexane and filtered through a plug of silica gel, eluting with additional hexane. After removal of the solvent, the crude product was used directly in the next step without further purification.



(*E*)-2-(2-(4-phenylbut-1-en-1-yl)phenoxy)ethan-1-ol: General procedure D was followed using 4-phenyl-1-butyne (650 mg, 5 mmol, 5 equiv) and (2-(2-bromophenoxy)ethoxy)(*tert*-butyl)dimethylsilane (1.65 g, 5 mmol, 1 equiv). After TBAF deprotection and workup, the crude residue was purified by column chromatography, eluting with a gradient of 0 – 25% ethyl acetate in hexanes to provide the title compound as a light yellow oil. **Yield**: 788 mg, 59%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.15 (m, 4H), 6.95 (t d, *J* = 7.5, 1.0 Hz, 1H), 6.87 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.74 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.27 (dt, *J* = 15.9, 6.9 Hz, 1H), 4.10 (dd, *J* = 5.1, 3.9 Hz, 2H), 4.04 – 3.94 (m, 2H), 2.82 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.59 (dtd, *J* = 8.8, 6.9, 1.5 Hz, 2H), 2.01 (t, *J* = 6.2 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.52, 142.04, 131.17, 128.77, 128.57, 128.25, 127.37, 126.91, 126.10, 125.05, 121.53, 112.65, 70.05, 61.82, 36.16, 35.46 ppm.



(*E*)-1-(2-bromoethoxy)-2-(4-phenylbut-1-en-1-yl)benzene: Following general procedure C, a mixture of (*E*)-2-(2-(4-phenylbut-1-en-1-yl)phenoxy)ethan-1-ol (778 mg, 2.9 mmol, 1 equiv) CBr_4 (1.16 g, 3.5 mmol, 1.2 equiv), triphenylphosphine (917 mg, 3.5 mmol, 1.2 equiv), and dichloromethane (25 mL) was stirred at rt for 1 h, until judged to be complete by TLC. The crude residue was purified by column chromatography, eluting with a gradient of 0 – 5% EtOAc in hexanes to provide the title compound as a light yellow solid. **Yield**: 940 mg, 98%. **mp =** **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.28 – 7.24 (m, 2H), 7.24 – 7.16 (m, 2H), 6.96 (td, *J* = 7.5, 1.1 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.78 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.31 (dt, *J* = 16.0, 6.9 Hz, 1H), 4.30 (t, *J* = 6.2 Hz, 2H), 3.66 (t, *J* = 6.2 Hz, 2H), 2.83 (dd, *J* = 8.9, 6.7 Hz, 2H), 2.63 – 2.54 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.06, 142.12, 131.37, 128.75, 128.57, 128.15, 127.68, 127.00, 126.07, 124.97, 121.86, 112.94, 68.68, 36.15, 35.52, 29.59 ppm.


Ph
Me
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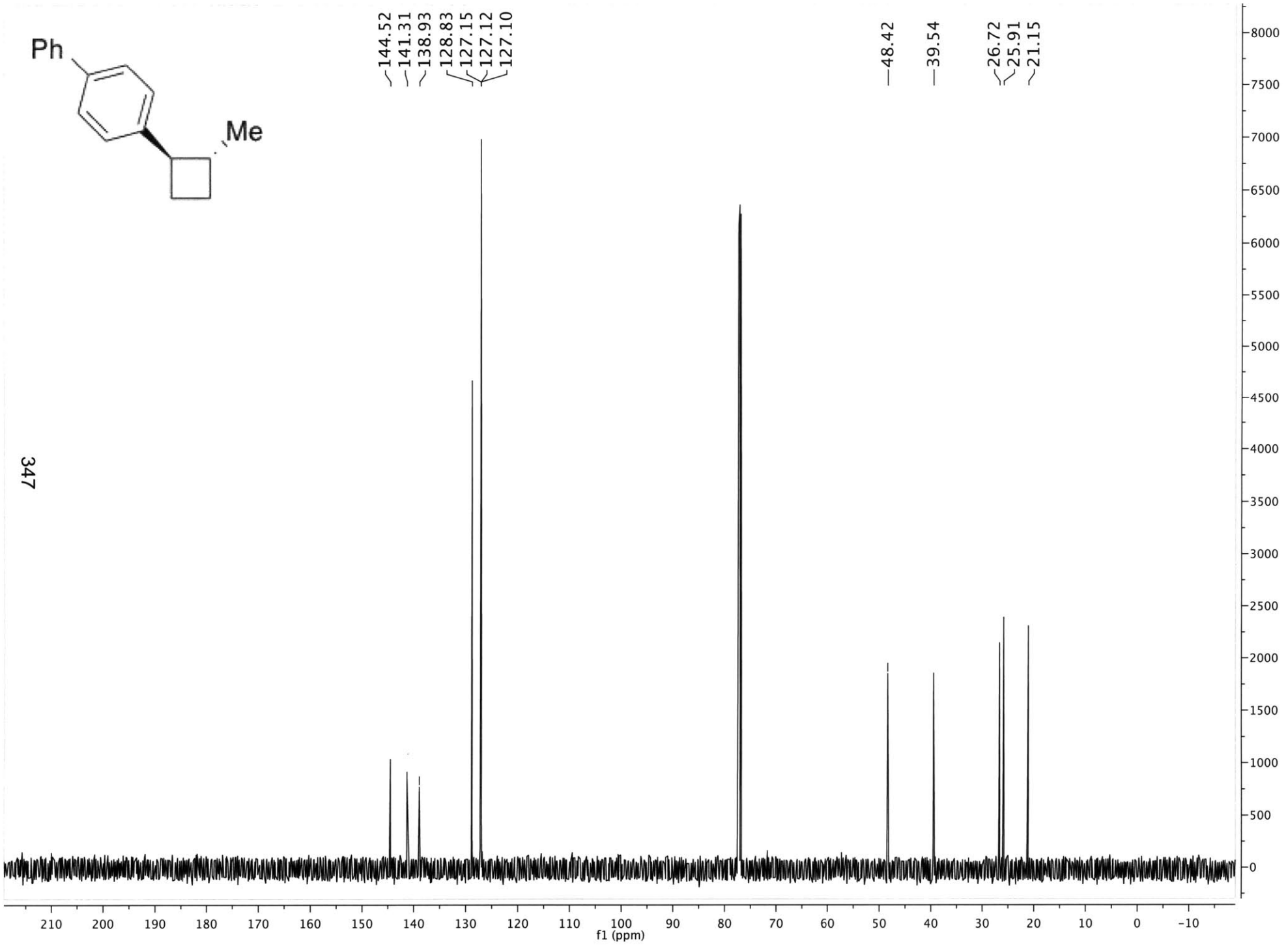
2.02
2.93
0.93
0.95
0.98
1.91
0.95
2.91
f1 (ppm)


Ph
Me
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127.10
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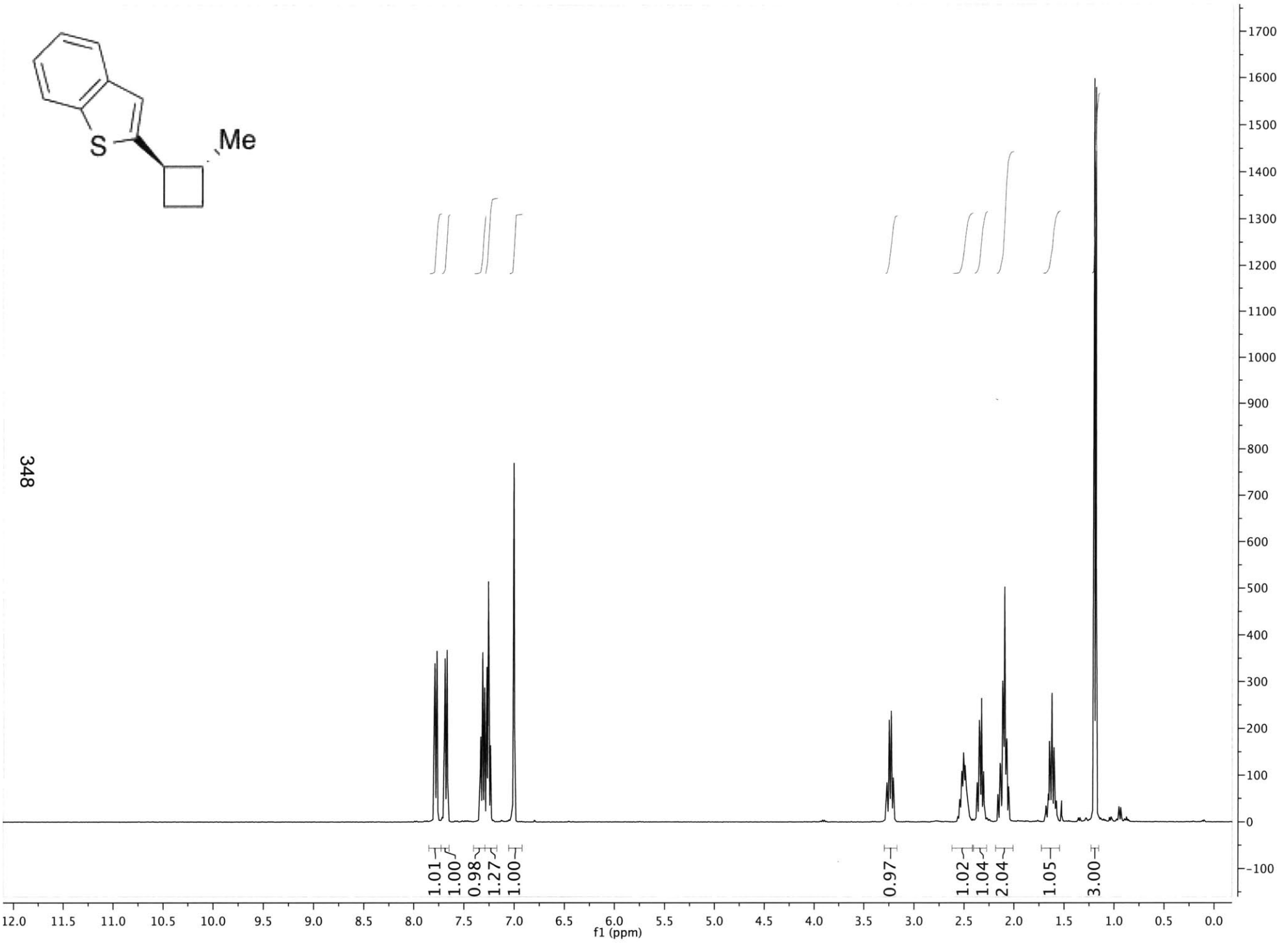
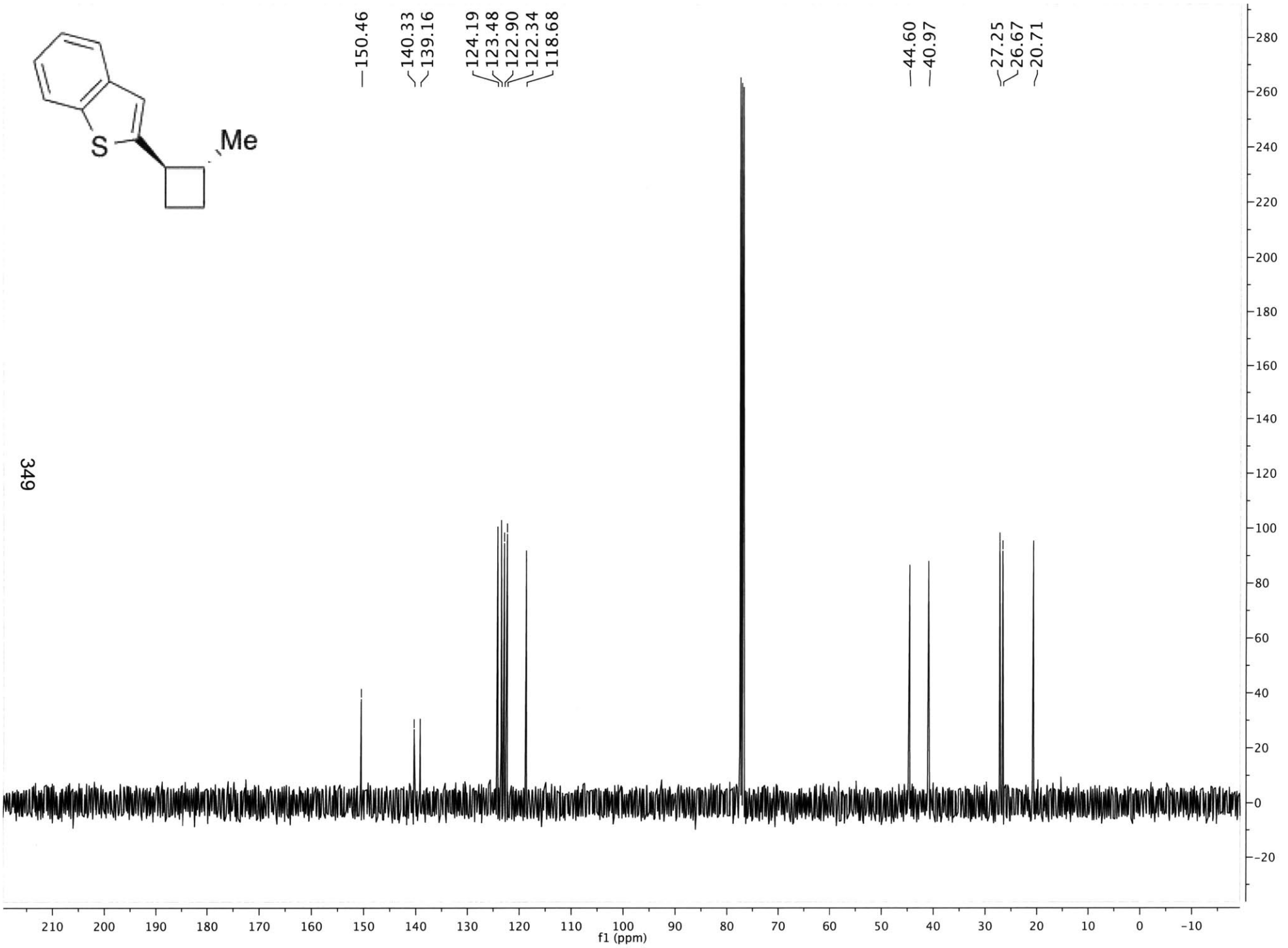
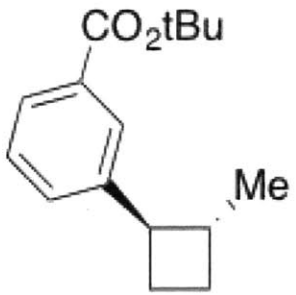
39.54
26.72
25.91
21.15
f1 (ppm)


S
Me
348
1.01
1.00
0.98
1.27
1.00
0.97
1.02
1.04
2.04
1.05
3.00
f1 (ppm)

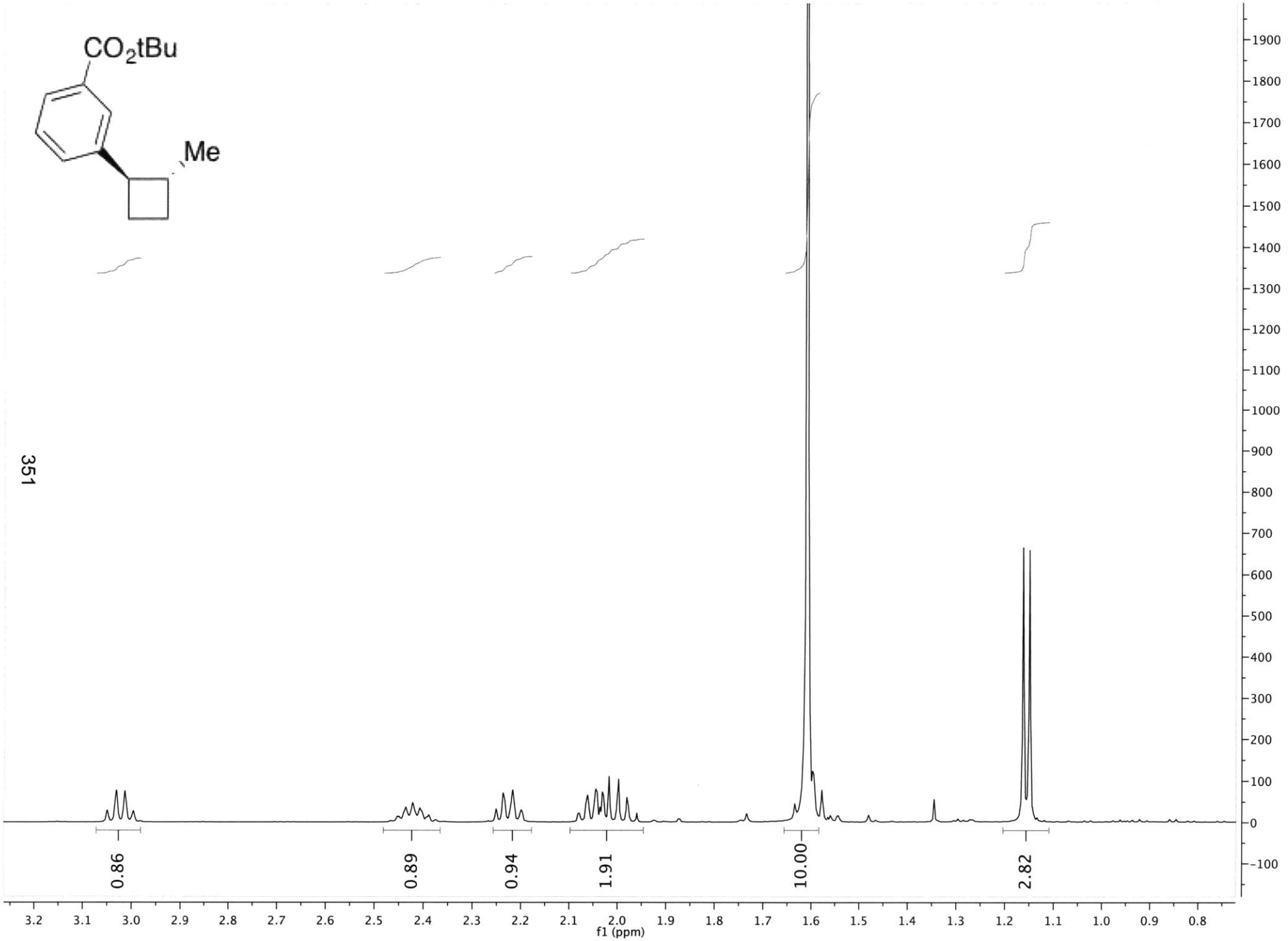

150.46
140.33
139.16
124.19
123.48
122.90
122.34
118.68
44.60
40.97
27.25
26.67
20.71
S
Me
f1 (ppm)



350

0.74
0.85
1.82
0.86
0.89
0.94
1.91
10.00
2.82

f1 (ppm)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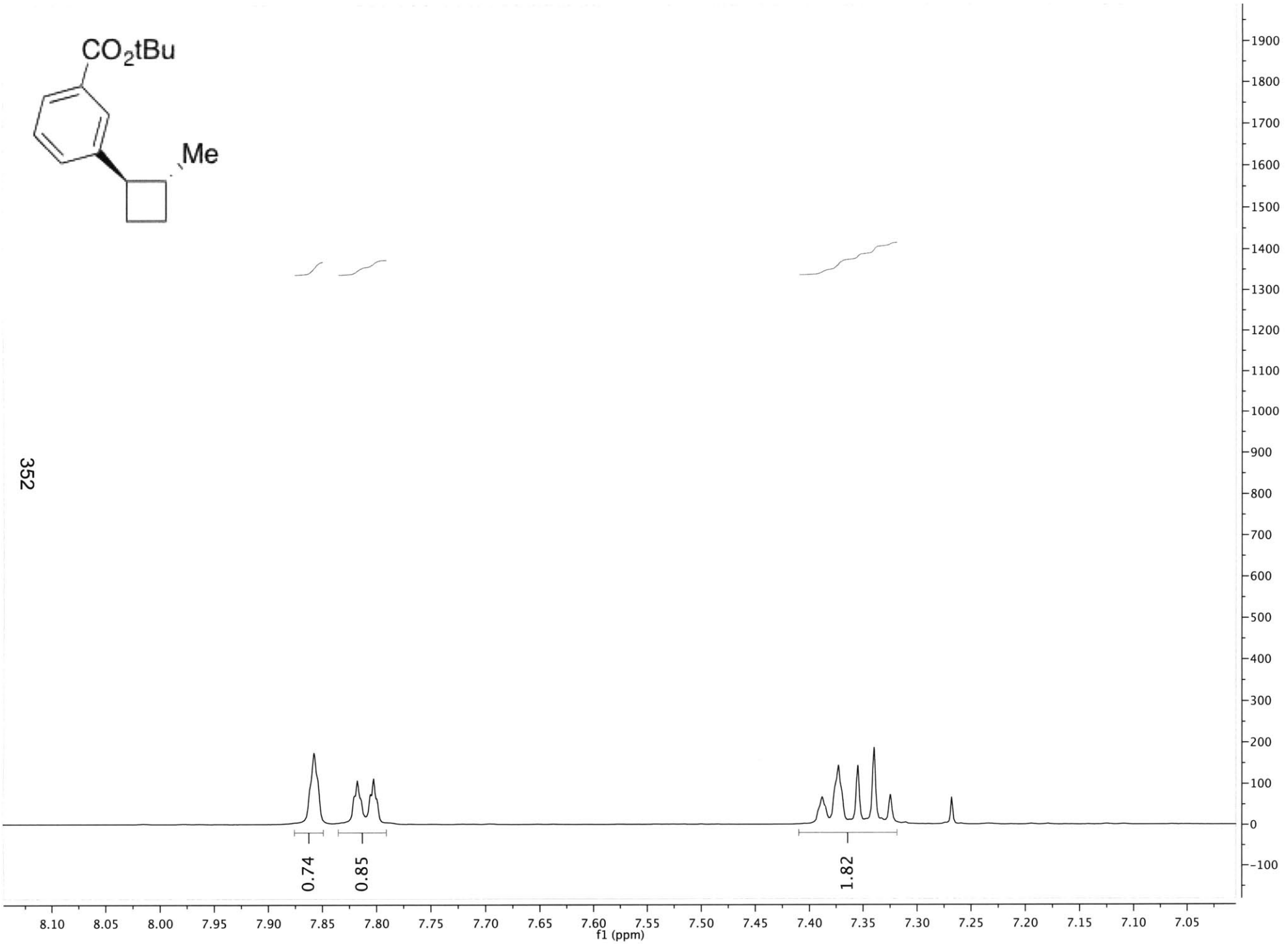
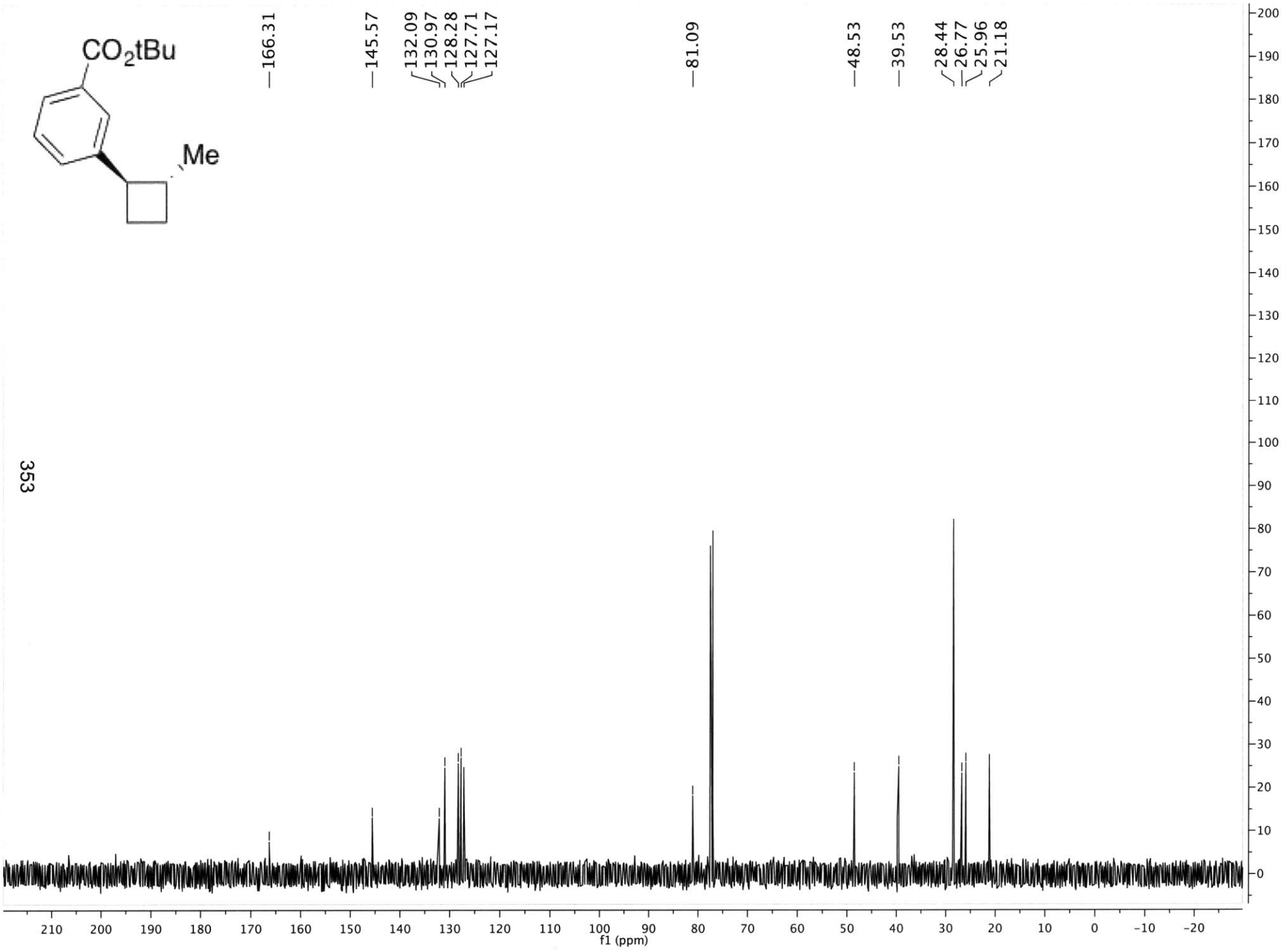
Me
351
0.86
0.89
0.94
1.91
10.00
2.82
f1 (ppm)


CO2tBu
Me
352
0.74
0.85
1.82
f1 (ppm)


CO2tBu
Me
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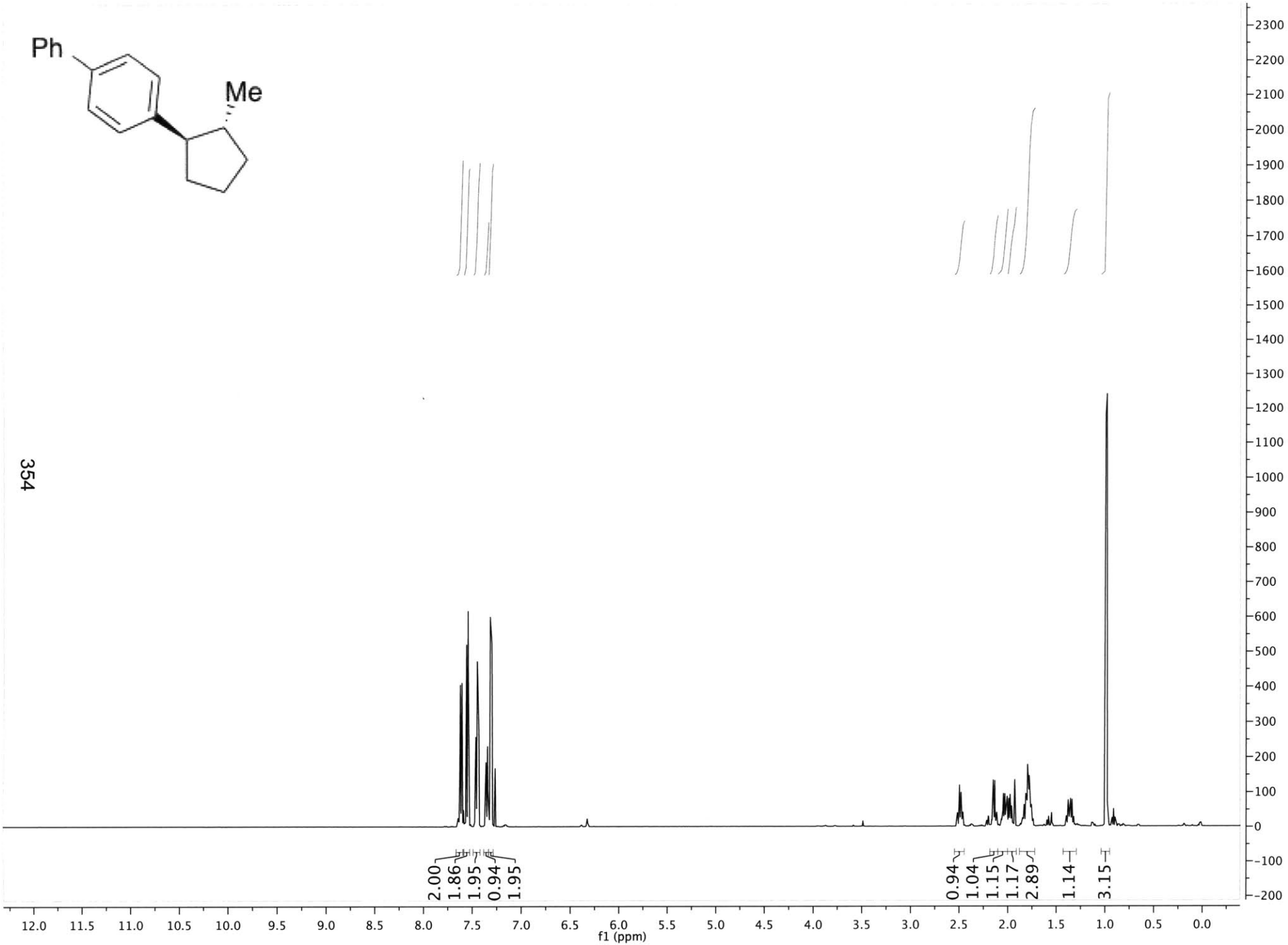
145.57
132.09
130.97
128.28
127.71
127.17
81.09
48.53
39.53
28.44
26.77
25.96
21.18
353
f1 (ppm)


Ph
Me
354
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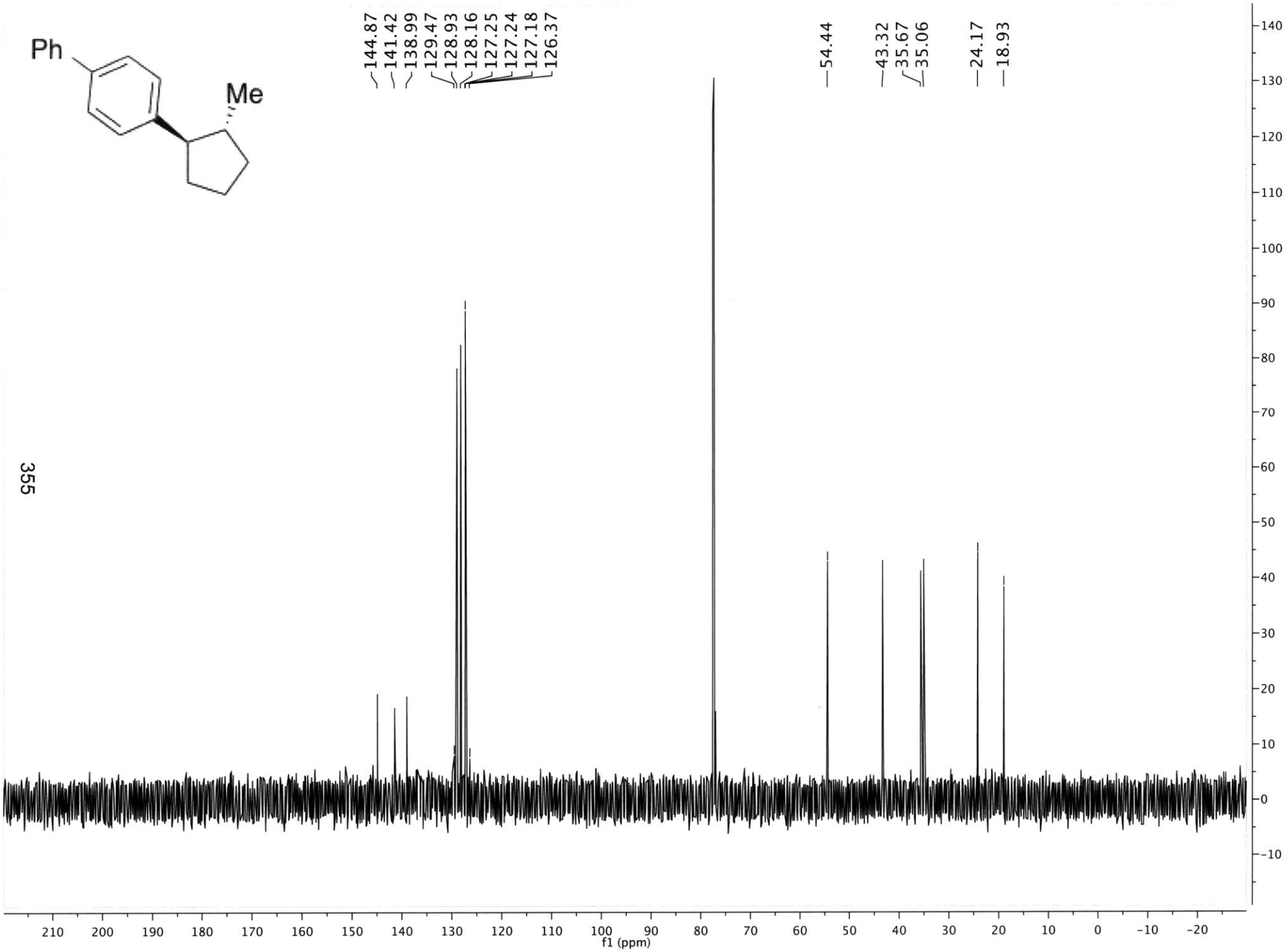
1.86
1.95
0.94
1.95
0.94
1.04
1.15
1.17
2.89
1.14
3.15
f1 (ppm)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Me
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128.16
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127.18
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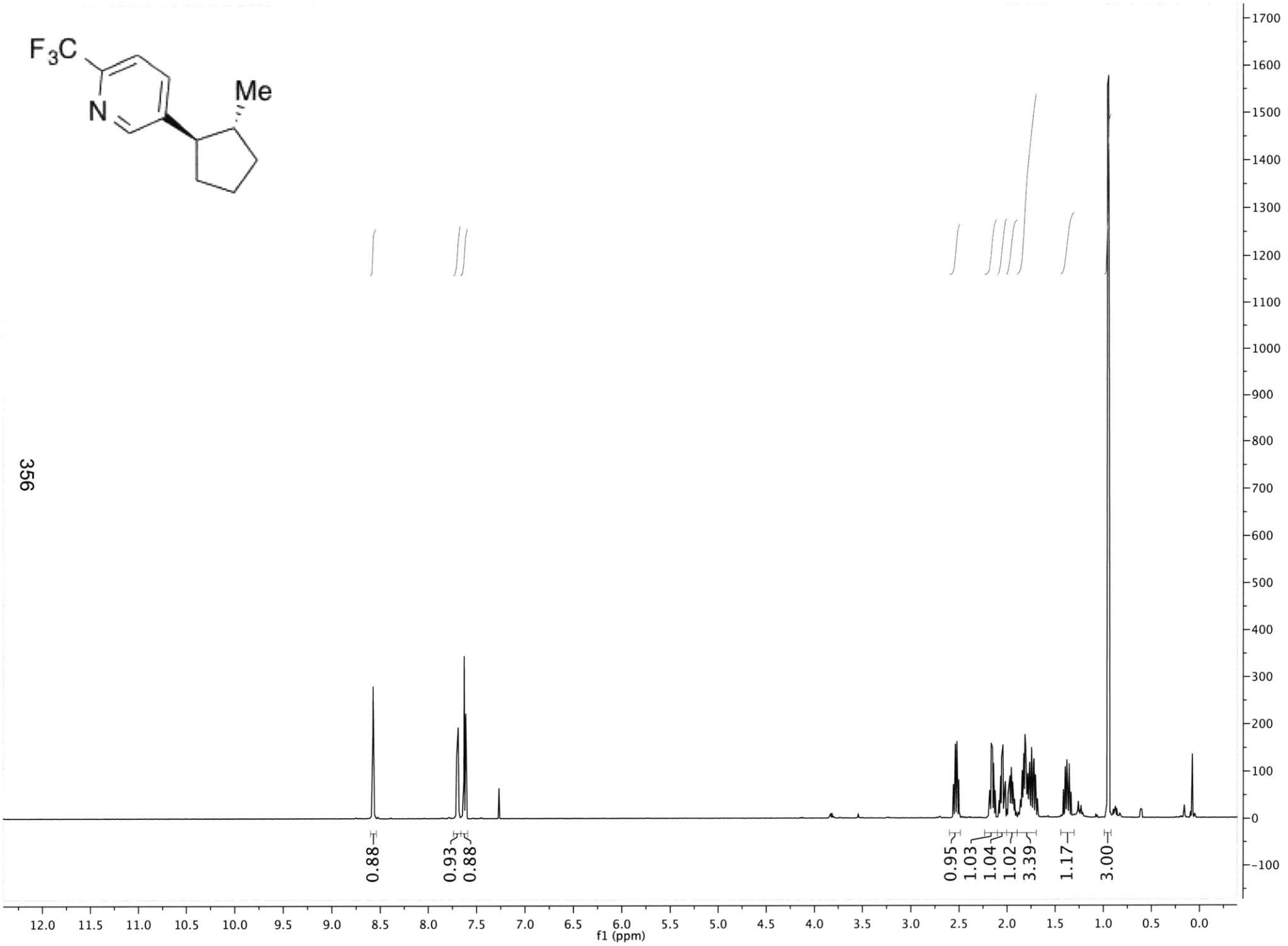
35.06
24.17
18.93
355
f1 (ppm)


F3C
N
Me
356
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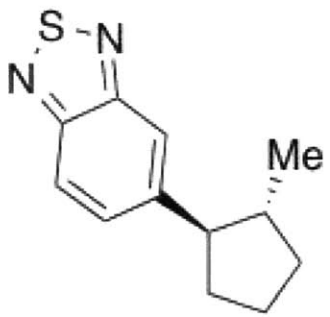
0.93
0.88
0.95
1.03
1.04
1.02
3.39
1.17
3.00
f1 (ppm)



357

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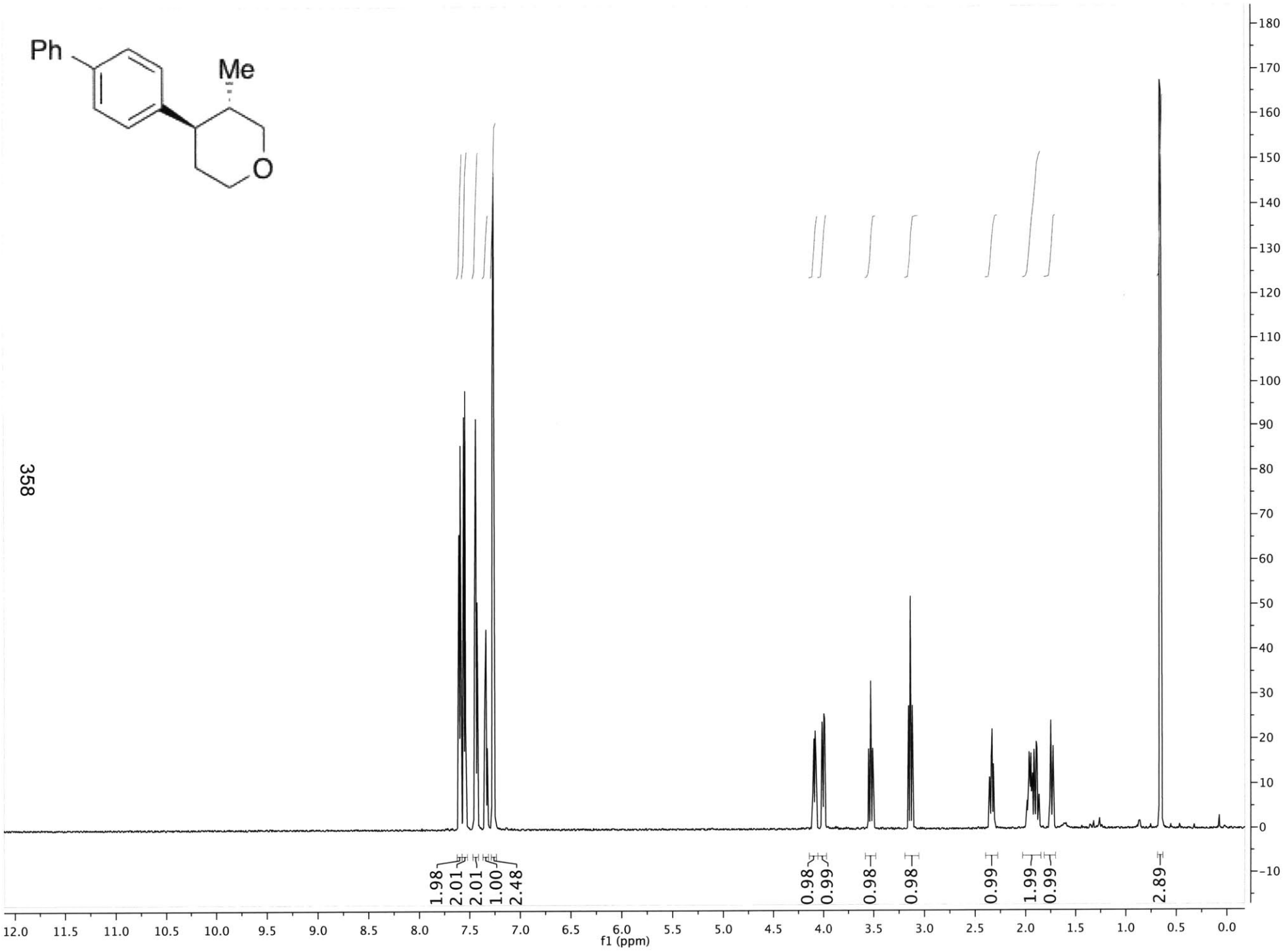
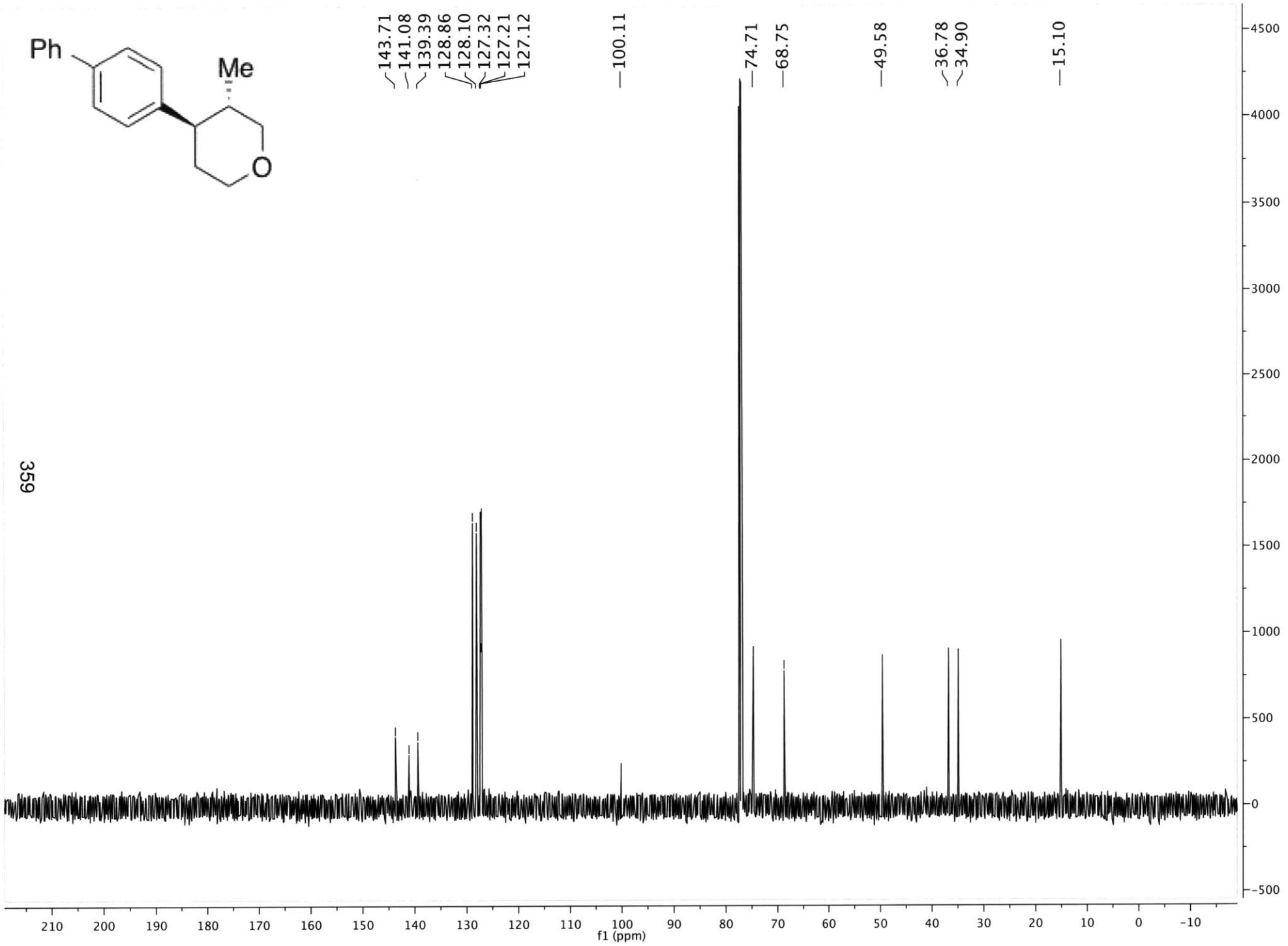
0.83
0.95
1.00
1.05
2.06
3.05
1.19
2.73

f1 (ppm)


Ph
Me
O
358
1.98
2.01
2.01
1.00
2.48
0.98
0.99
0.98
0.98
0.99
1.99
0.99
2.89
f1 (ppm)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128.86
128.10
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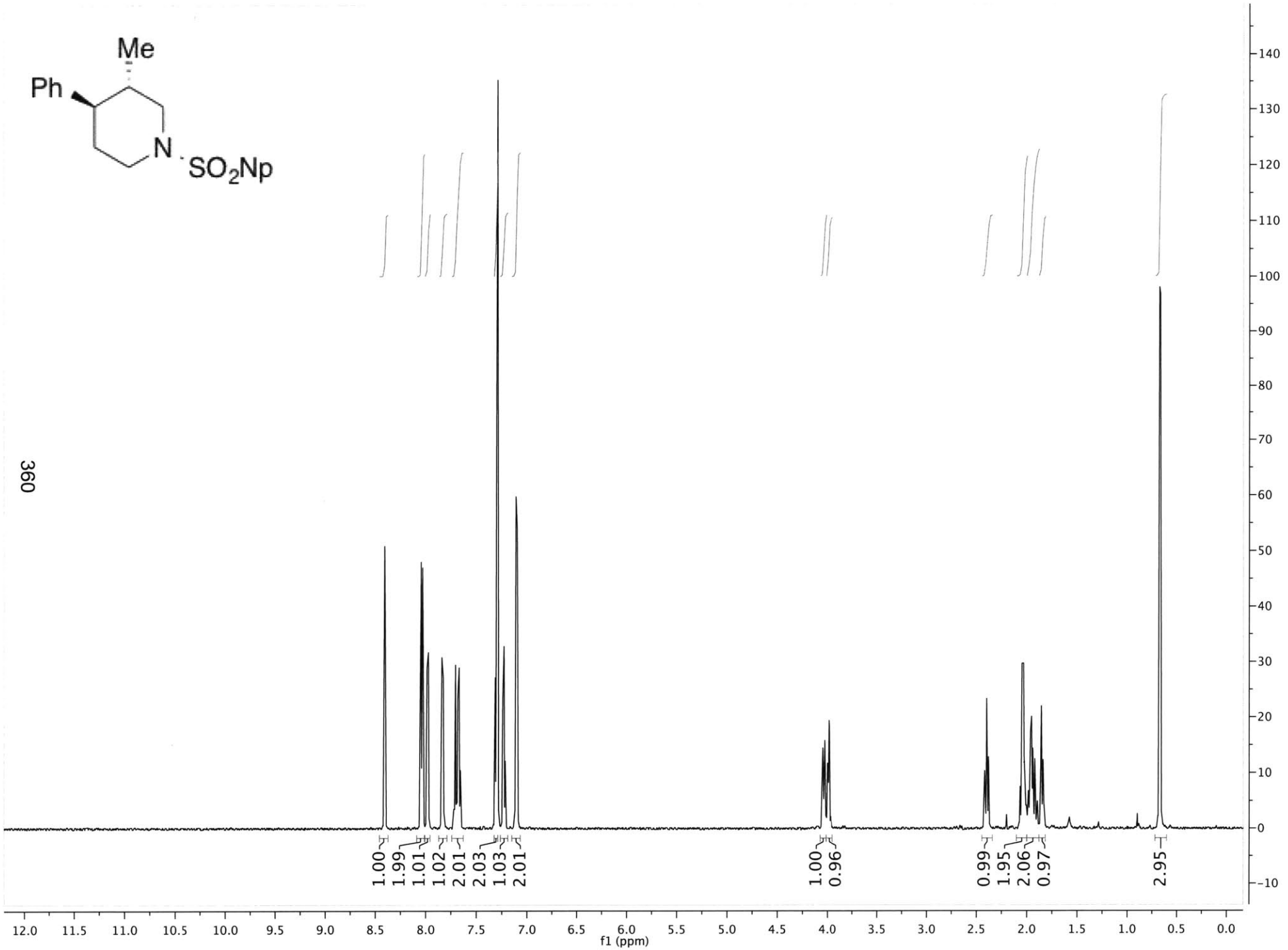
36.78
34.90
15.10
359
f1 (ppm)


Me
Ph
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SO2Np
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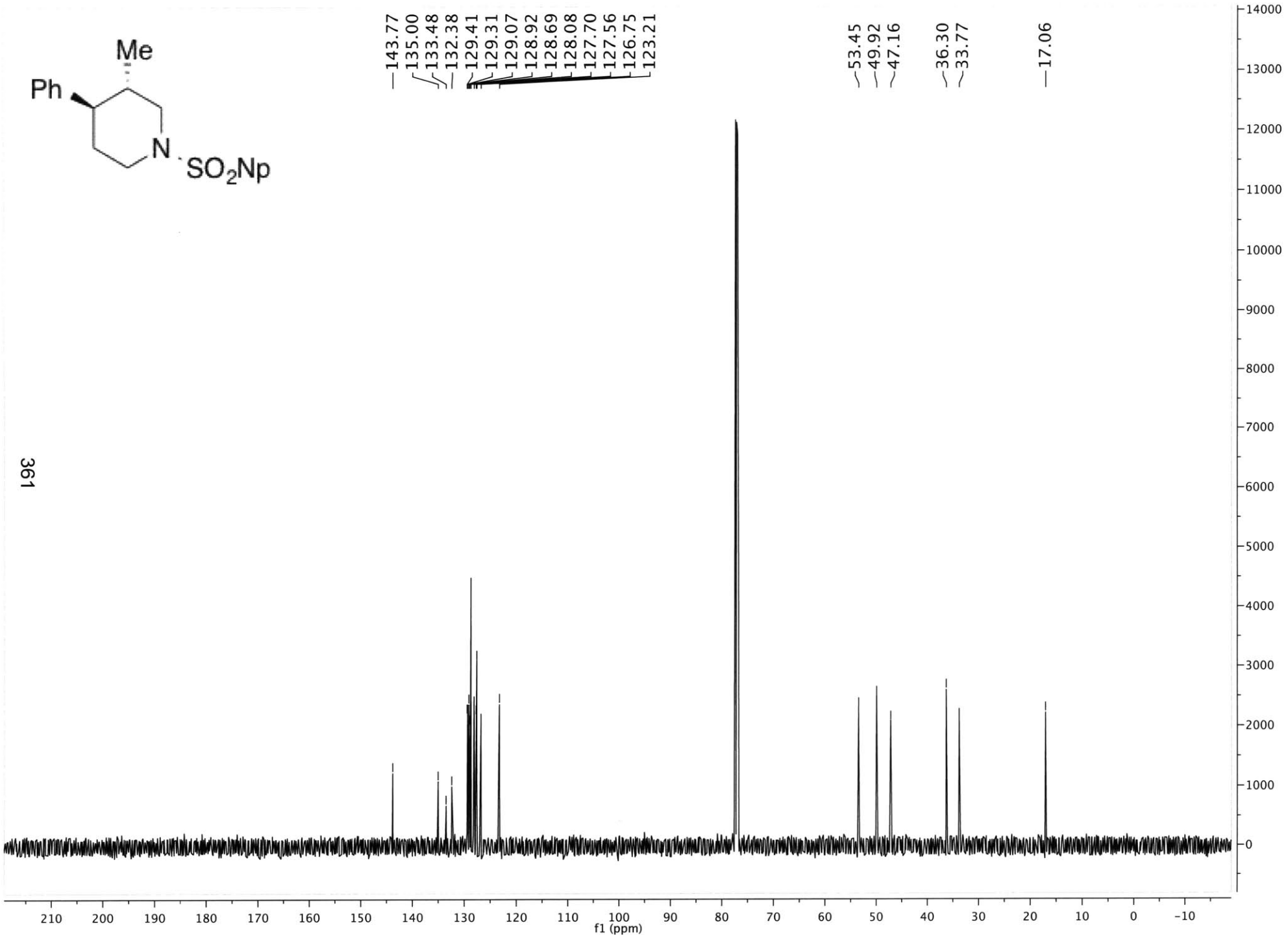
1.99
1.01
1.02
2.01
2.03
1.03
2.01
1.00
0.96
0.99
1.95
2.06
0.97
2.95
f1 (ppm)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Ph
N
SO2Np
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133.48
132.38
129.41
129.31
129.07
128.92
128.69
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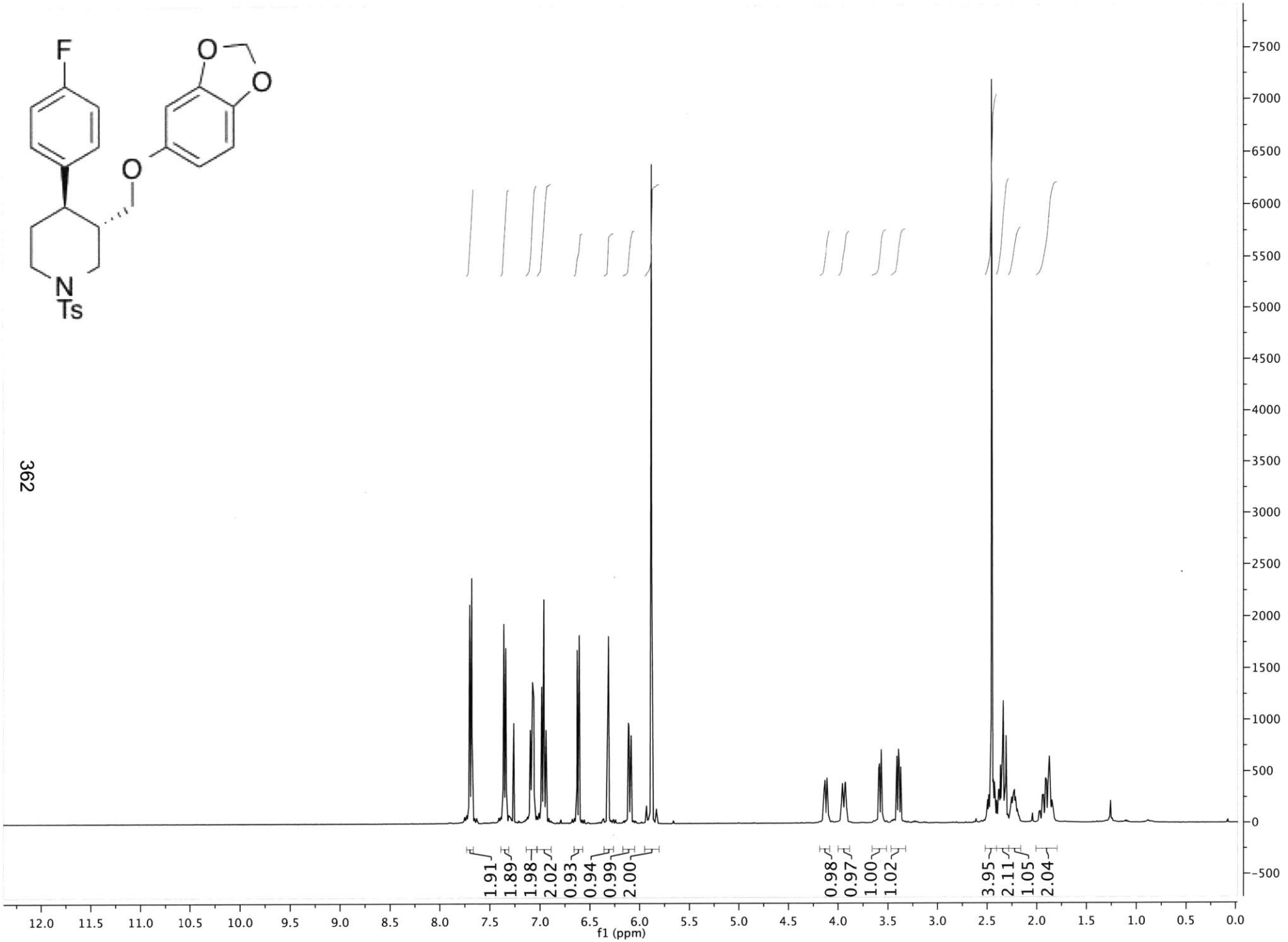
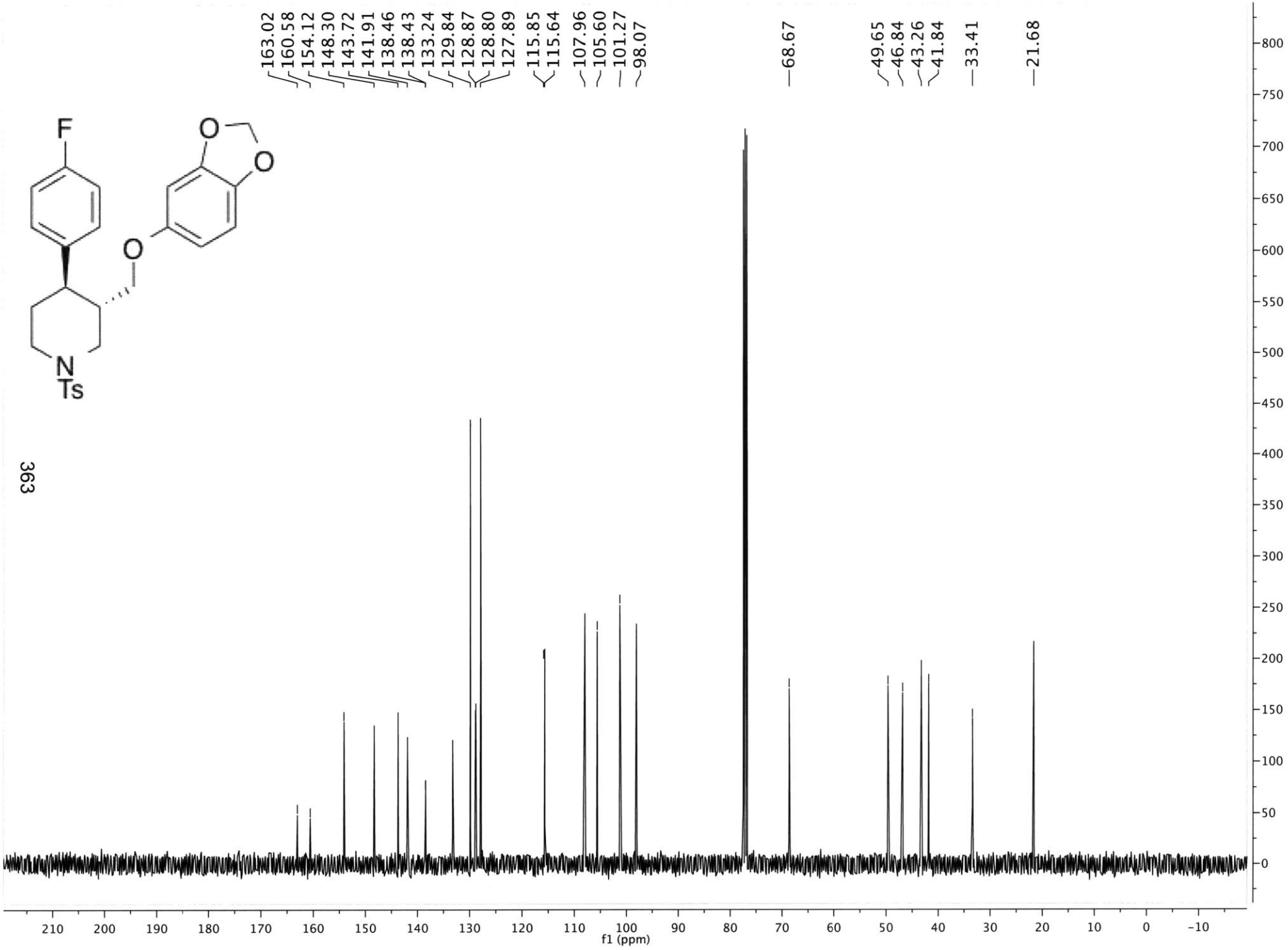
47.16
36.30
33.77
17.06
f1 (ppm)


F
O
O
O
N
Ts
362
1.91
1.89
1.98
2.02
0.93
0.94
0.99
2.00
0.98
0.97
1.00
1.02
3.95
2.11
1.05
2.04
f1 (ppm)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148.30
143.72
141.91
138.46
138.43
133.24
129.84
128.87
128.80
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115.85
115.64
107.96
105.60
101.27
98.07
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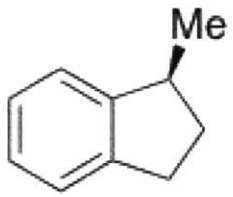
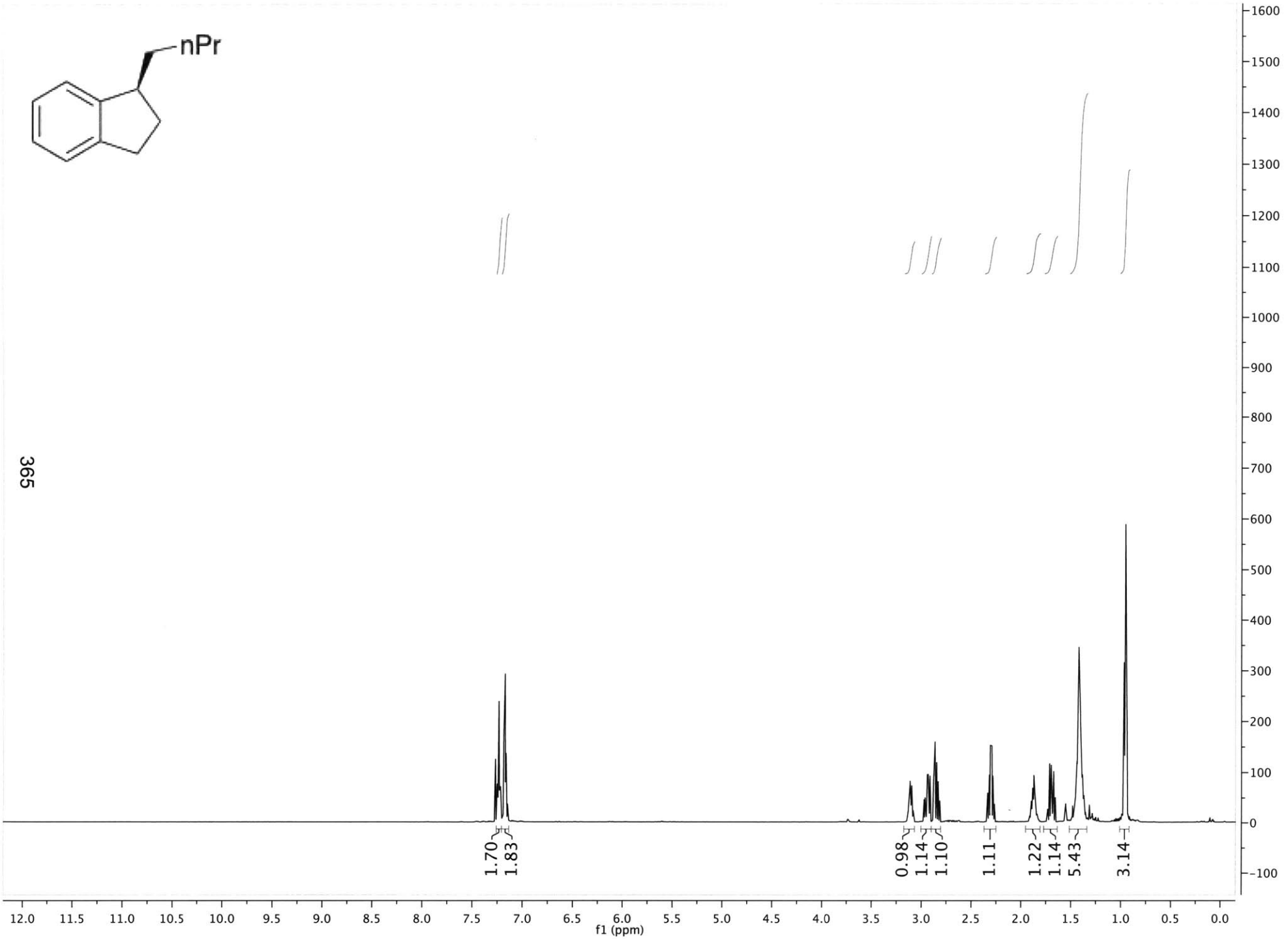
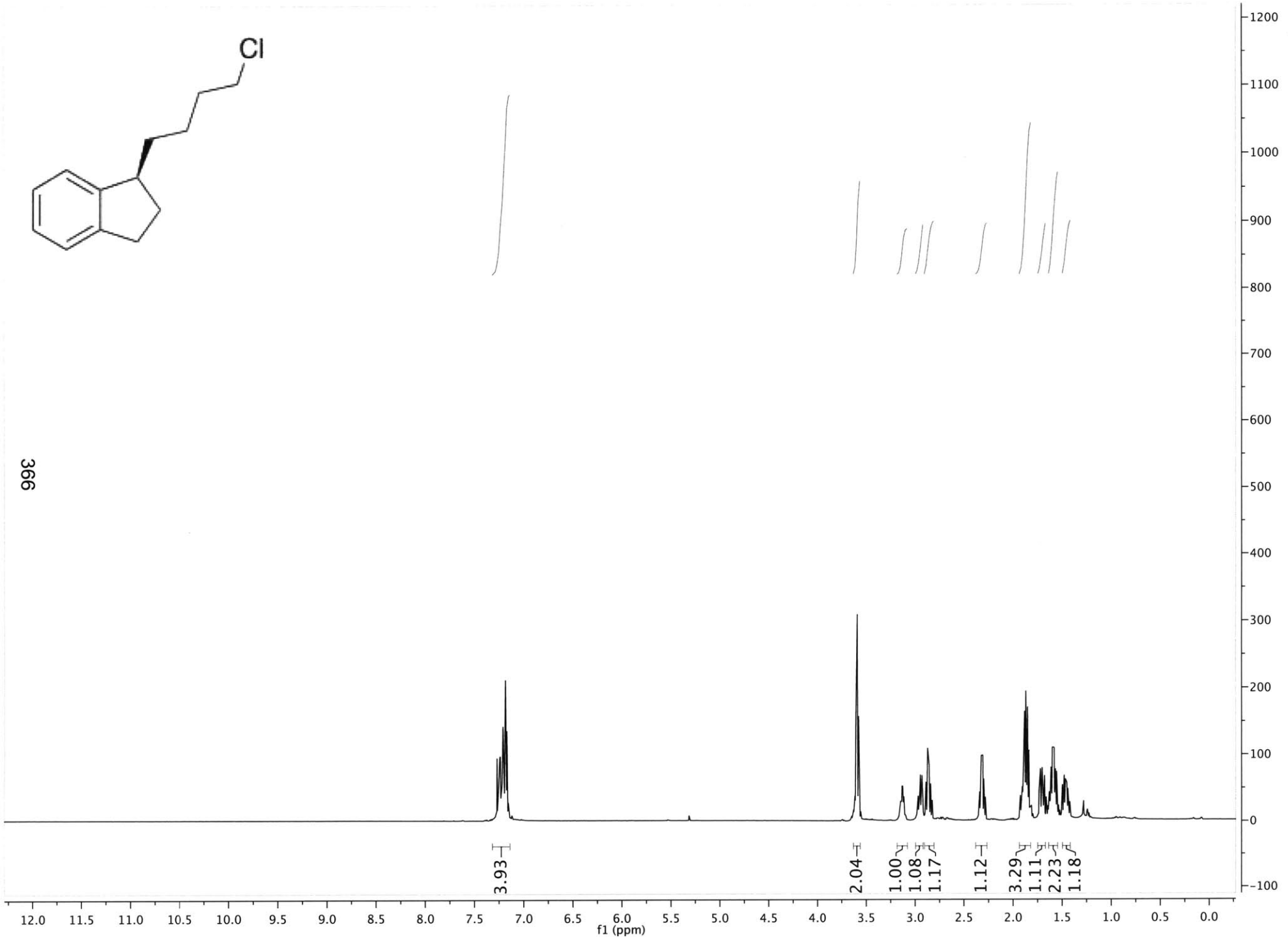
F
O
O
O
N
Ts
363
f1 (ppm)



364


nPr
365
1.70
1.83
0.98
1.14
1.10
1.11
1.22
1.14
5.43
3.14
f1 (ppm)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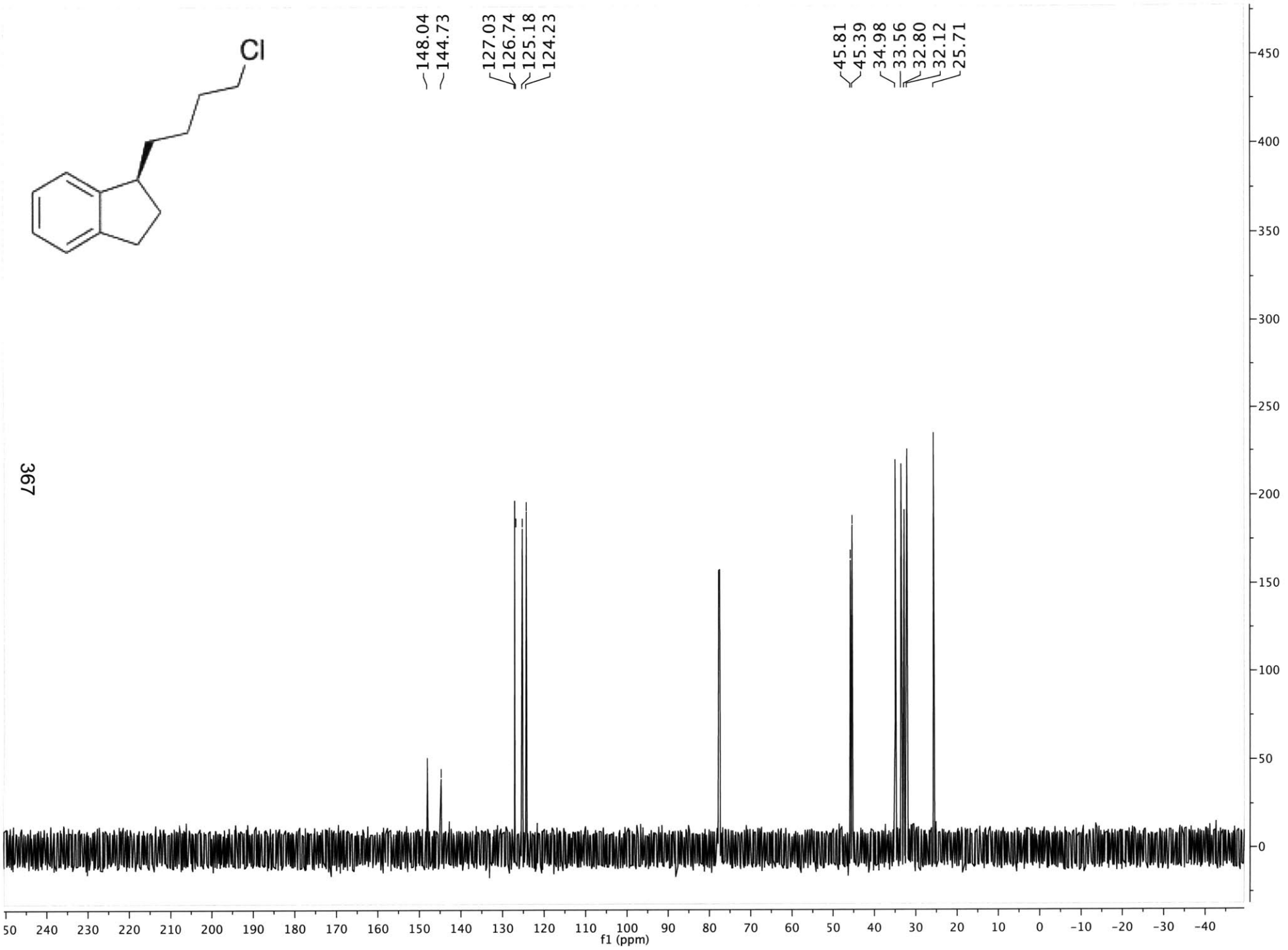
1.00
1.08
1.17
1.12
3.29
1.11
2.23
1.18
f1 (ppm)


Cl
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144.73
127.03
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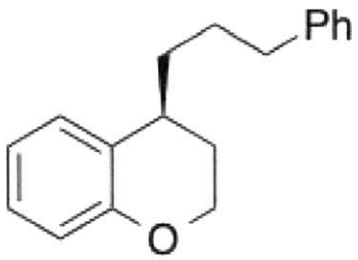
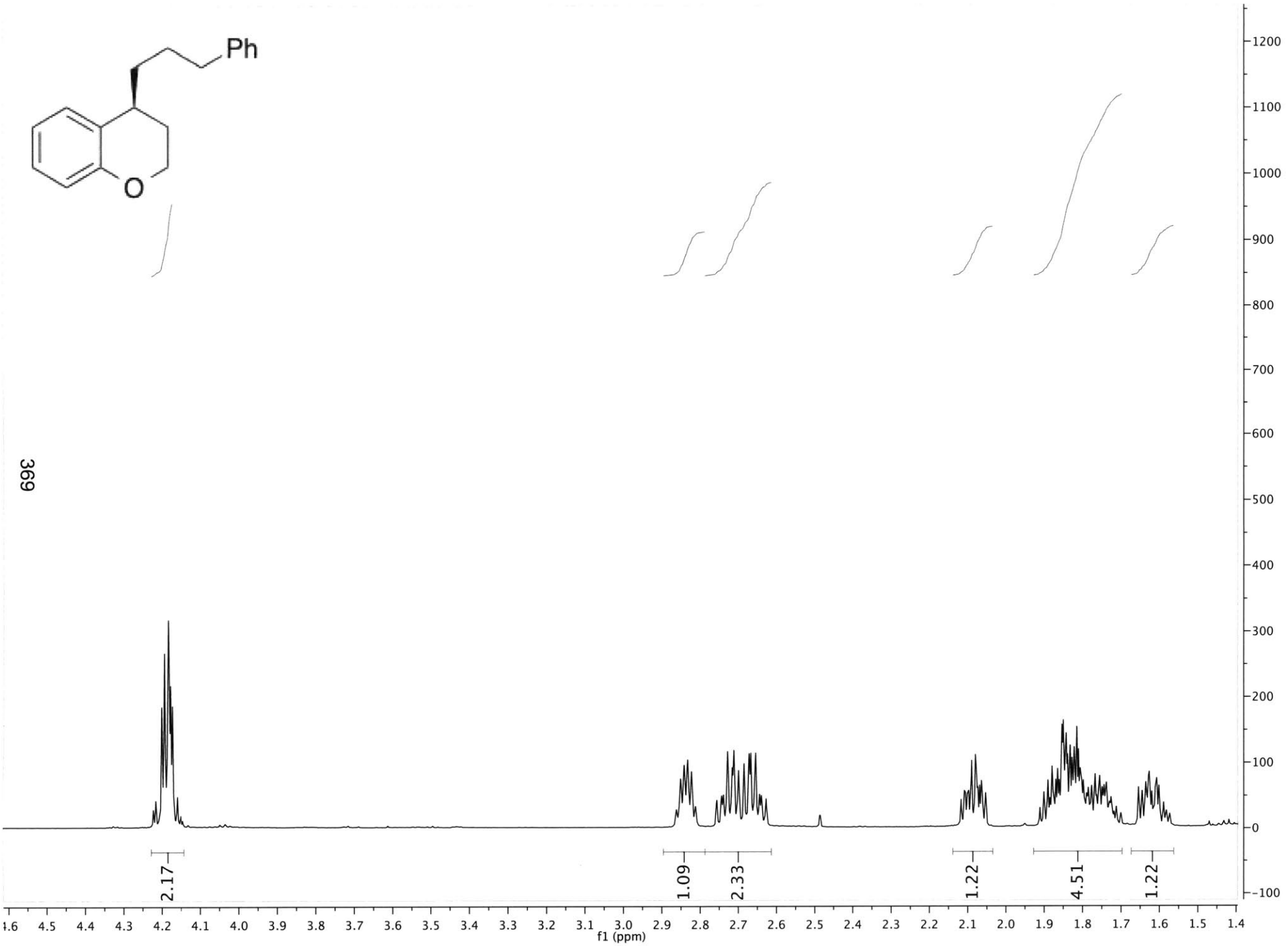
45.39
34.98
33.56
32.80
32.12
25.71
367
f1 (ppm)

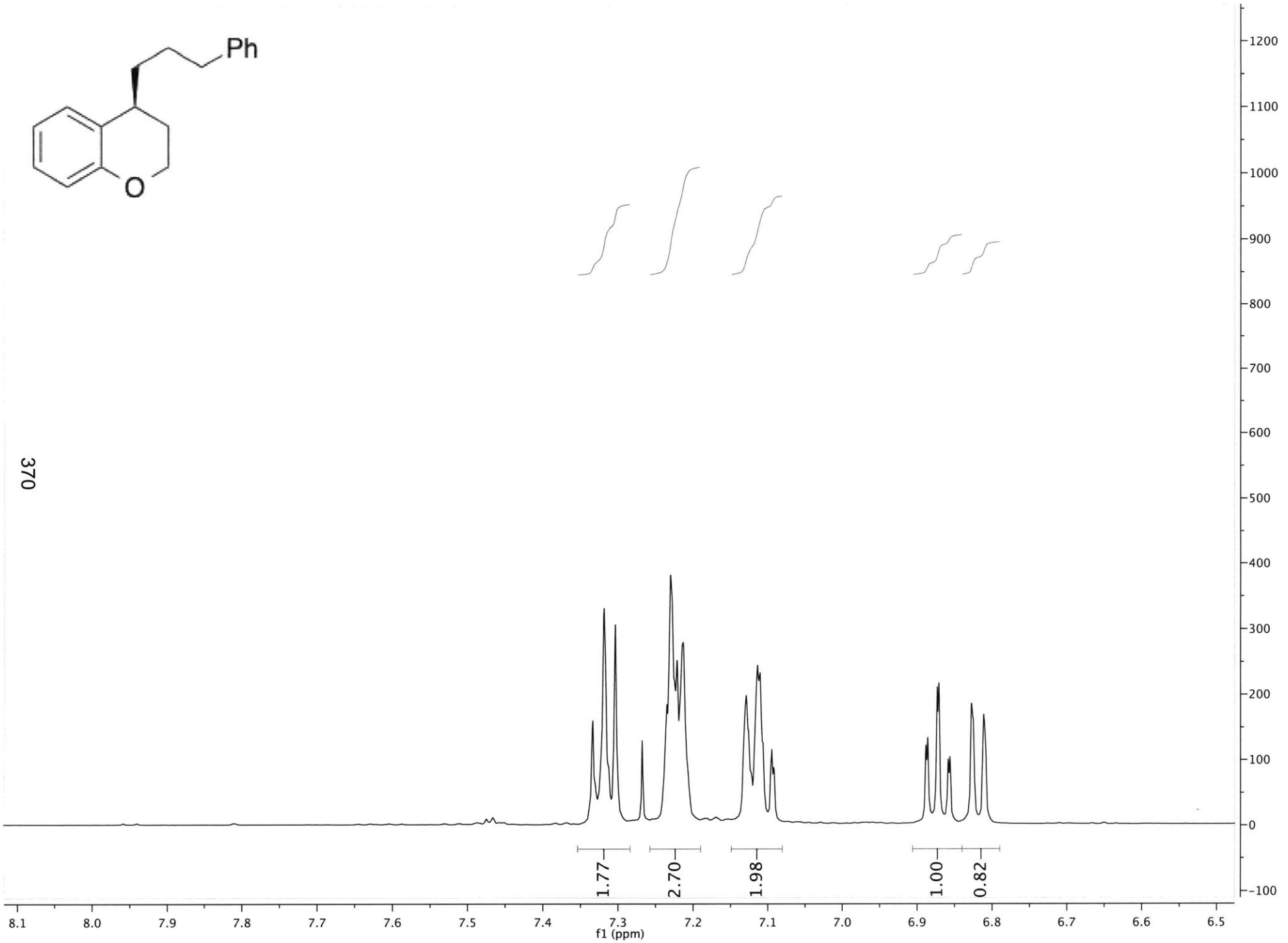


368

1.77
2.70
1.98
1.00
0.82
2.17
1.09
2.33
1.22
4.51
1.22

f1 (ppm)


Ph
O
369
2.17
1.09
2.33
1.22
4.51
1.22
f1 (ppm)


Ph
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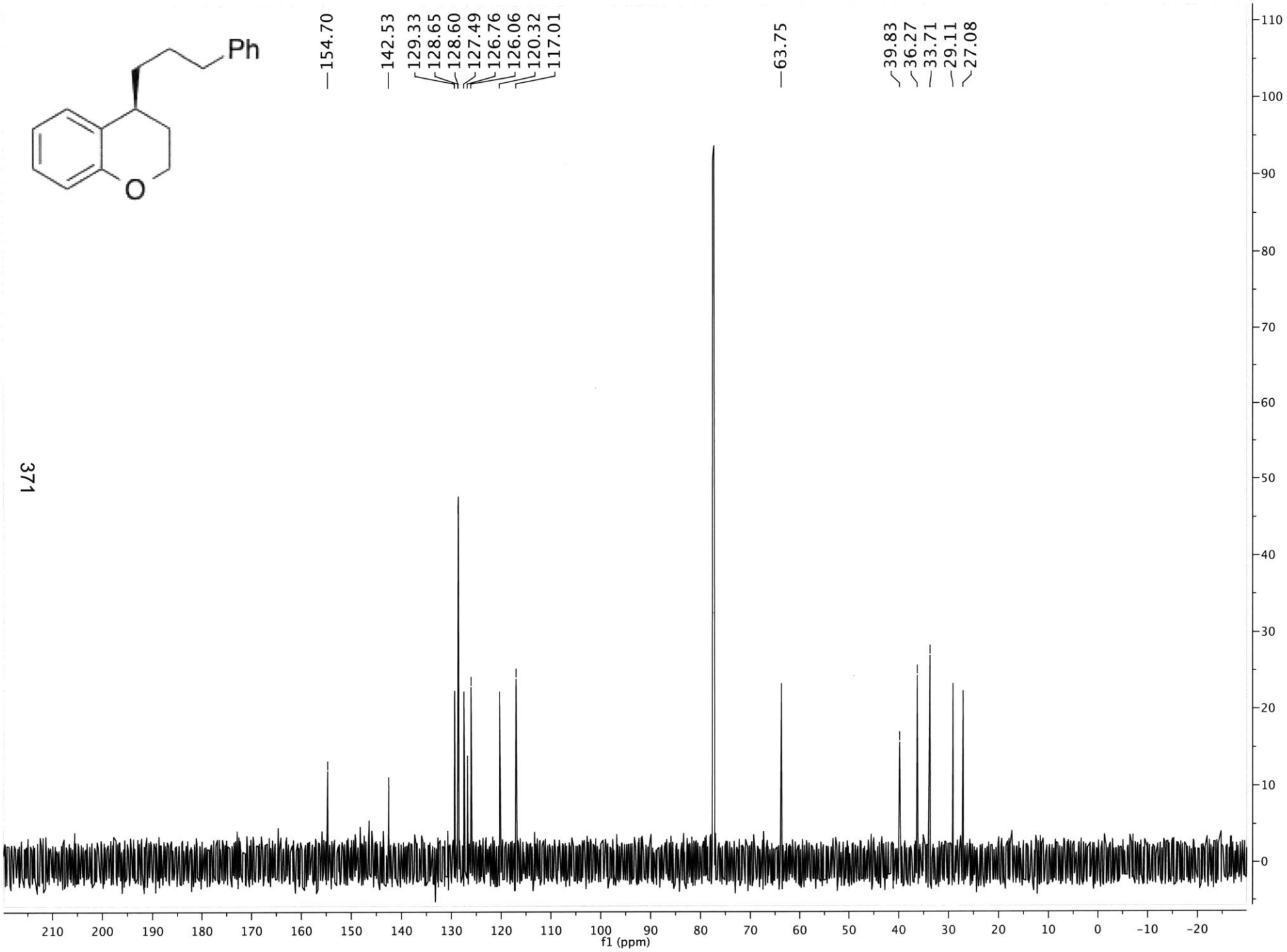
2.70
1.98
1.00
0.82
f1 (ppm)


Ph
O
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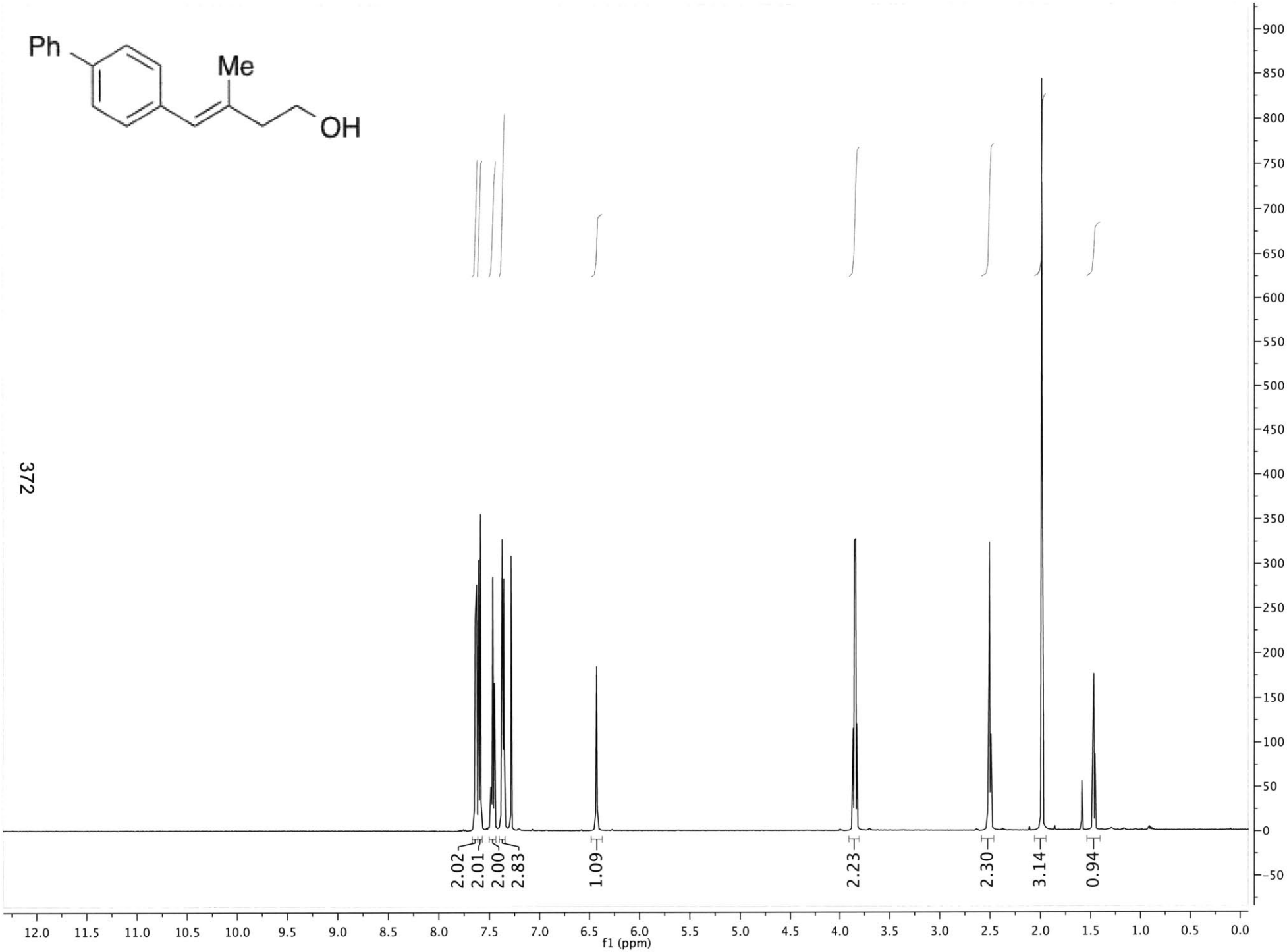
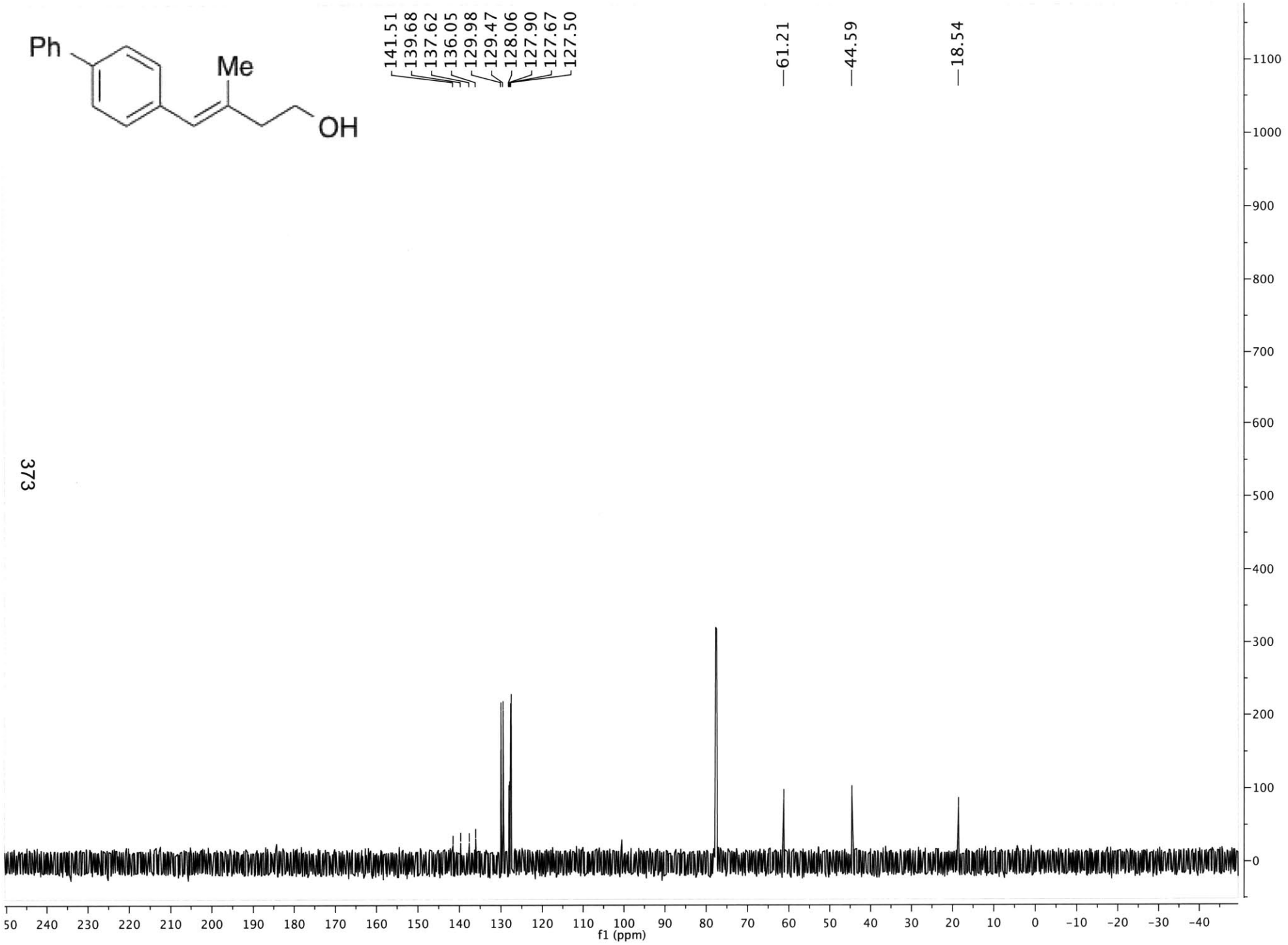
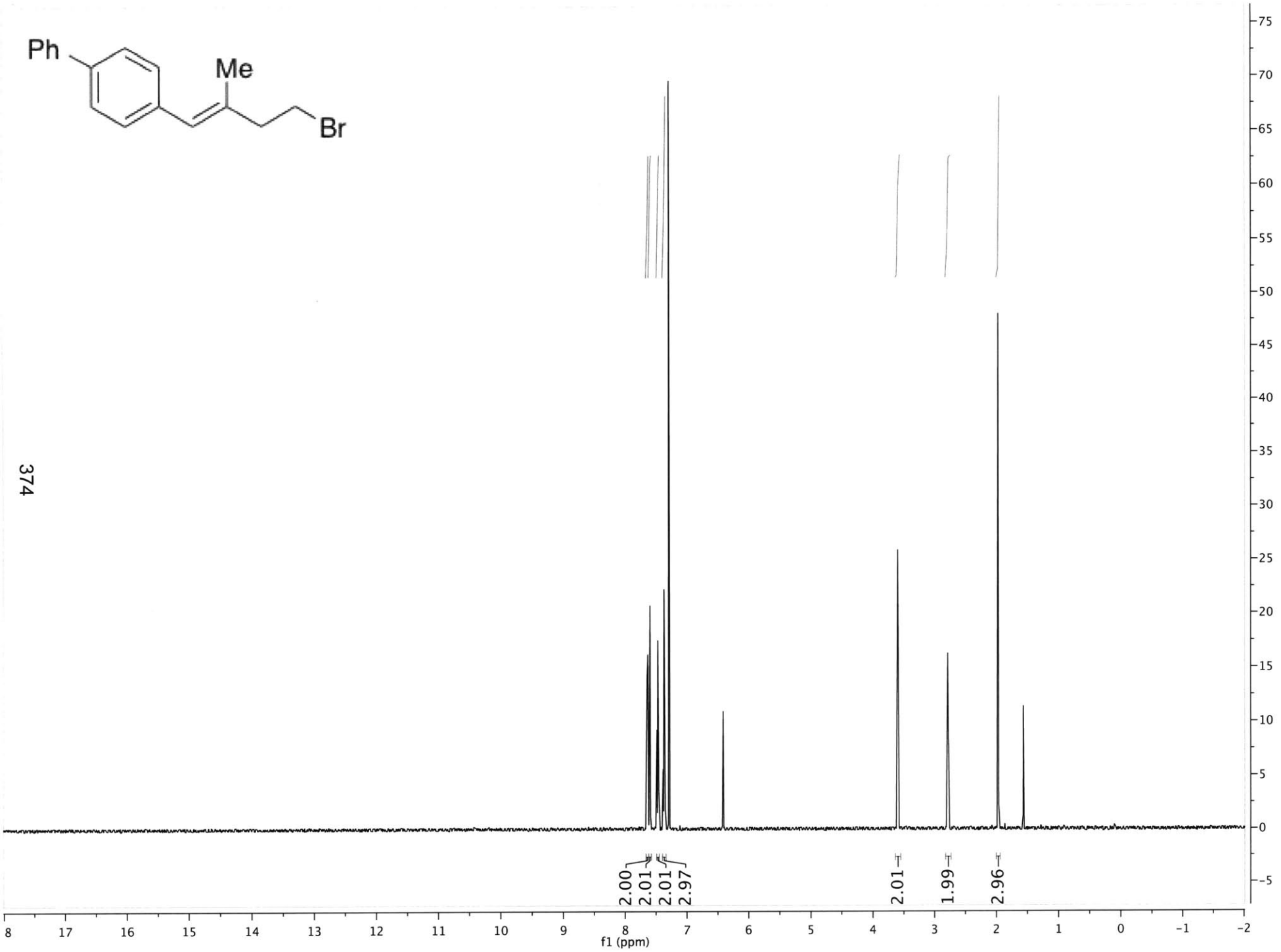
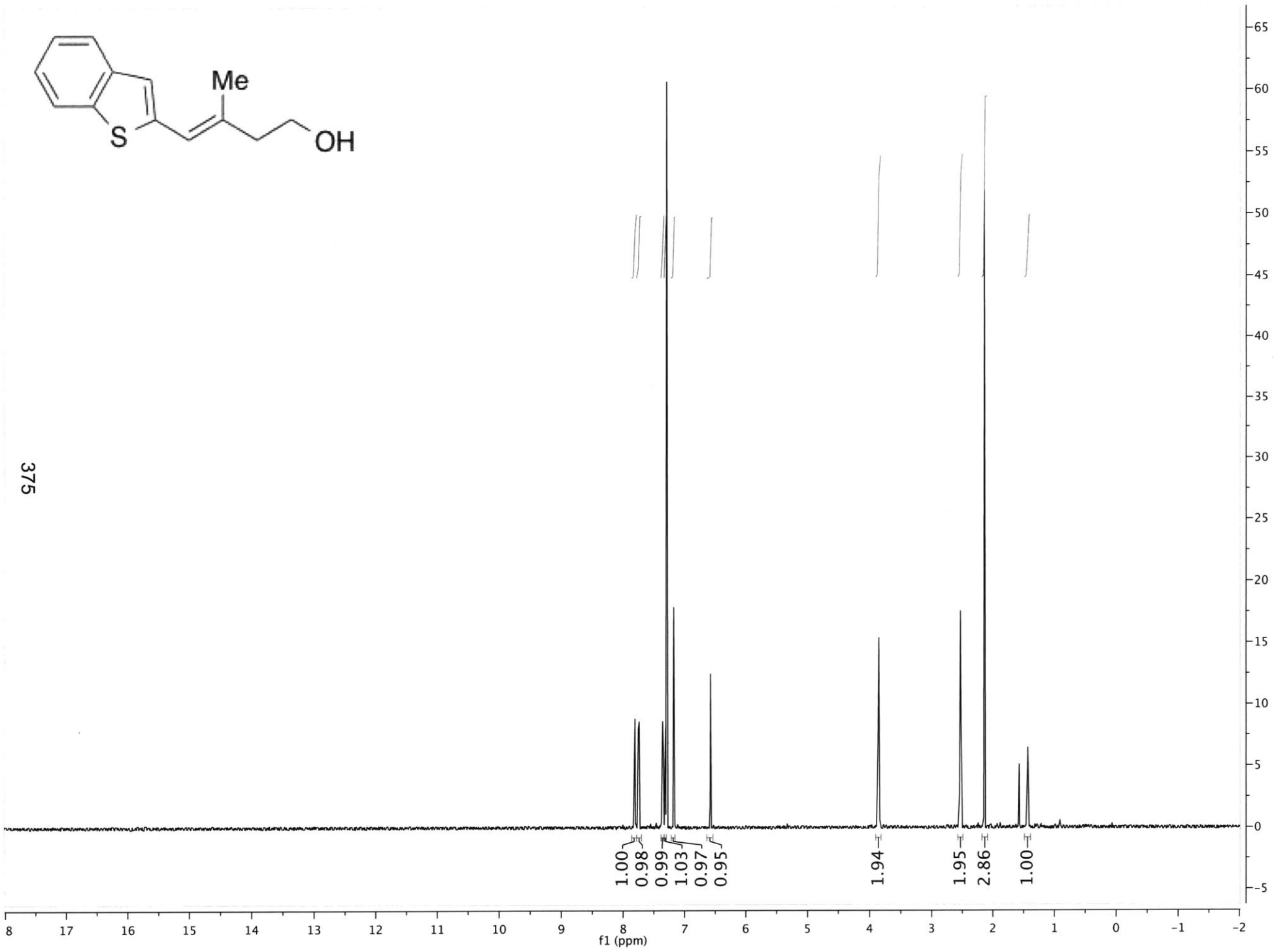
126.76
126.06
120.32
117.01
63.75
39.83
36.27
33.71
29.11
27.08
f1 (ppm)

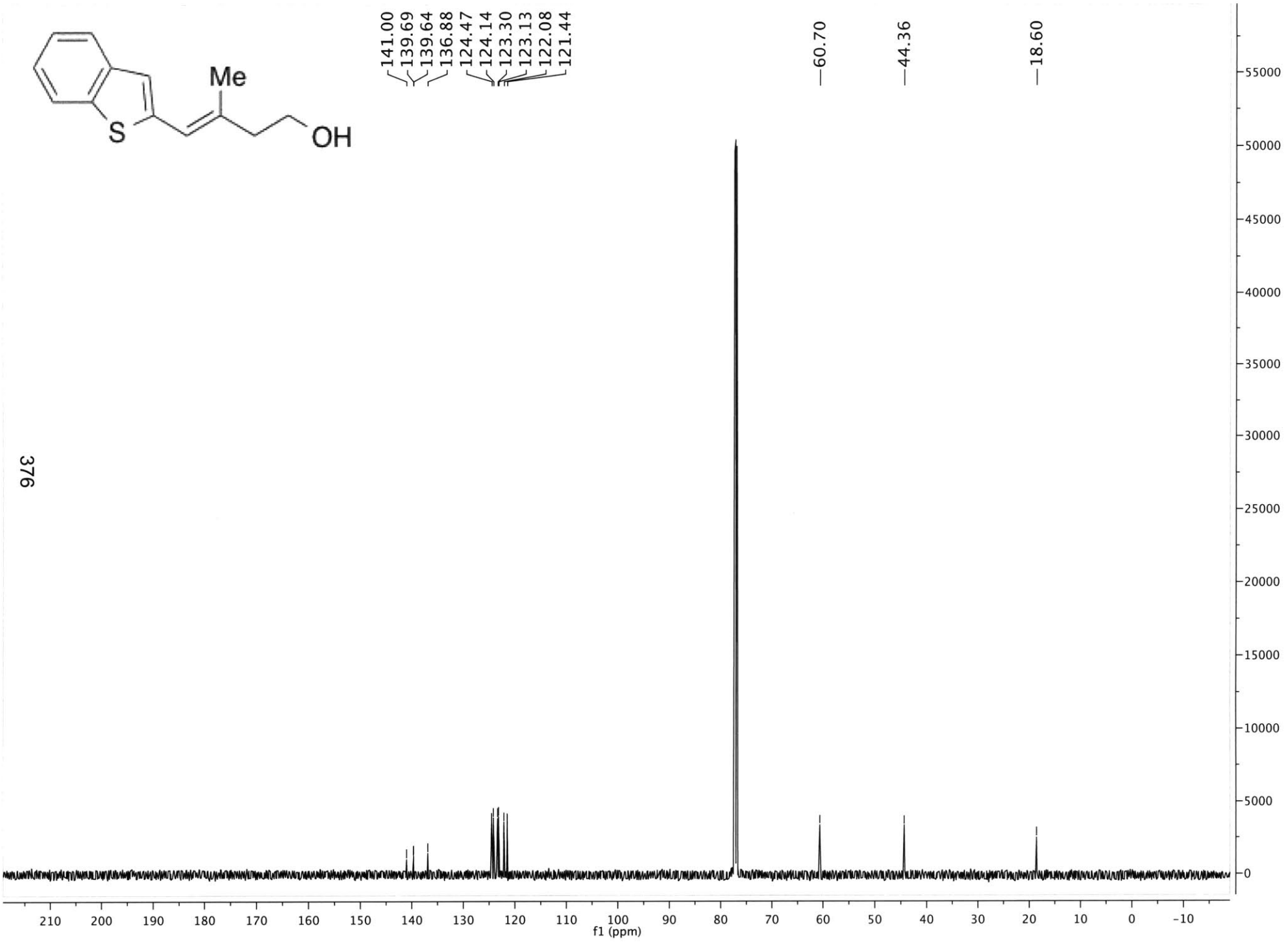

Ph
Me
OH
372
2.02
2.01
2.00
2.83
1.09
2.23
2.30
3.14
0.94
f1 (ppm)

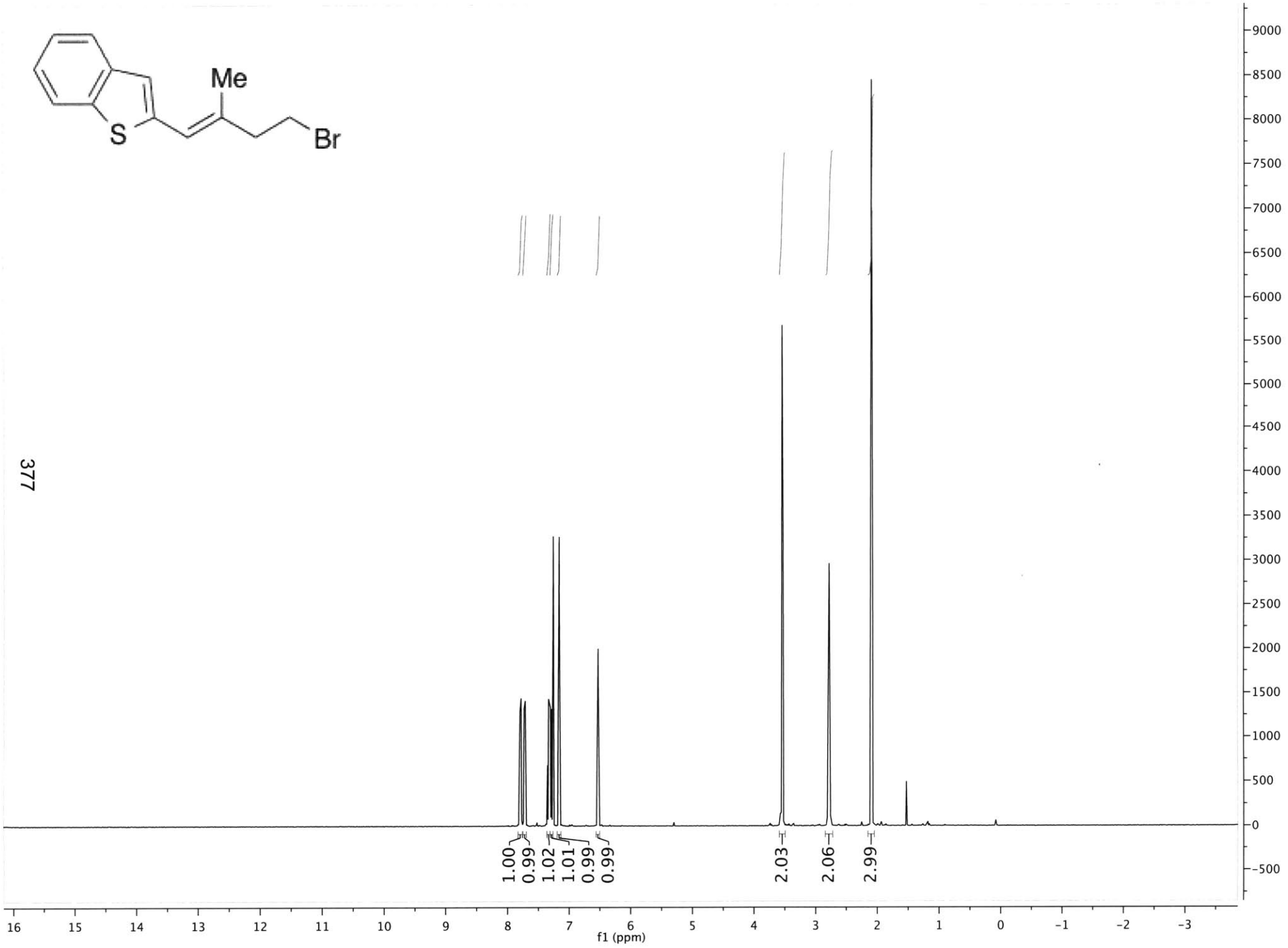

Ph
Me
OH
141.51
139.68
137.62
136.05
129.98
129.47
128.06
127.90
127.67
127.50
61.21
44.59
18.54
f1 (ppm)

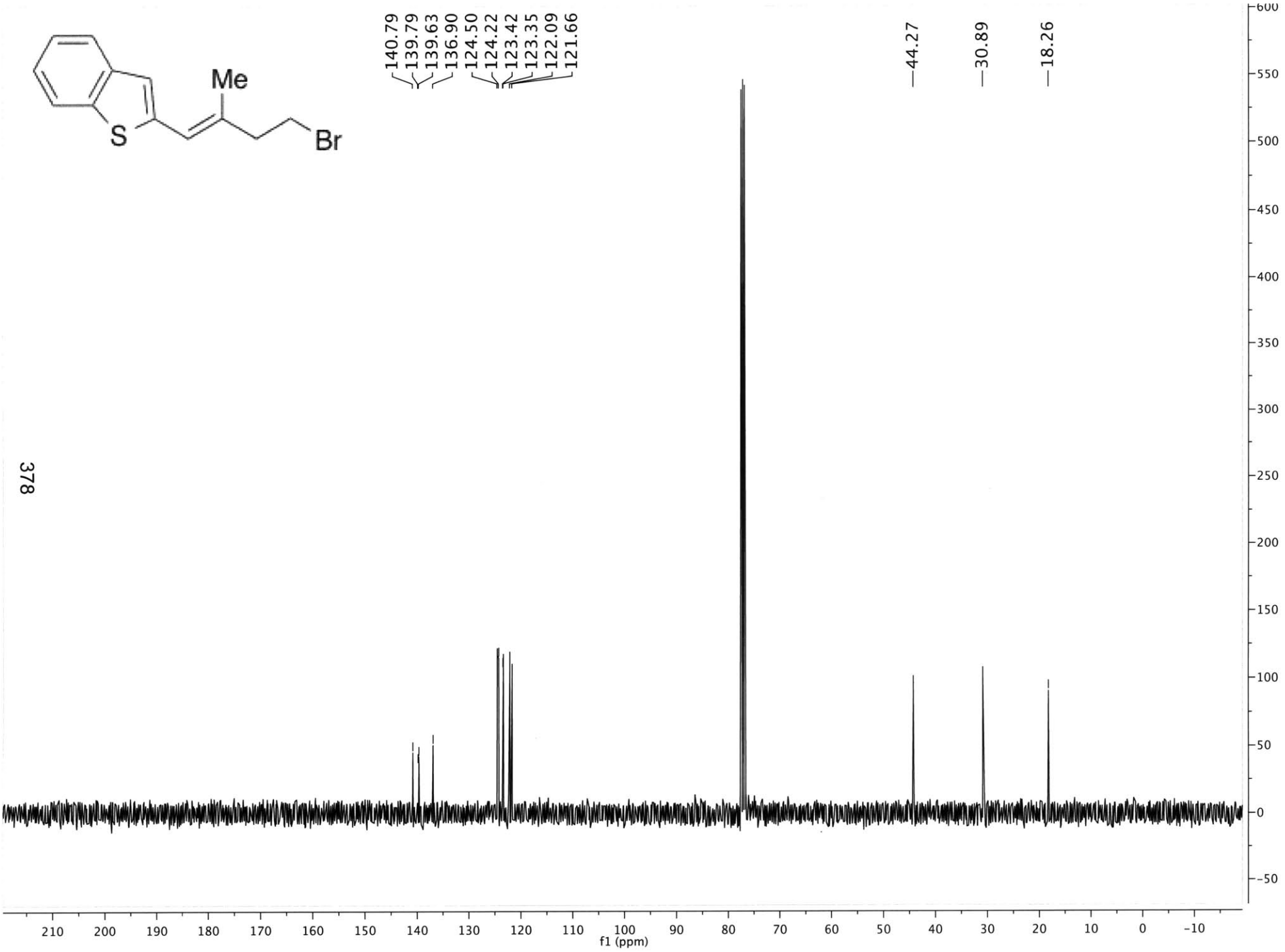

Ph
Me
Br
374
2.00
2.01
2.01
2.97
2.01
1.99
2.96
f1 (ppm)

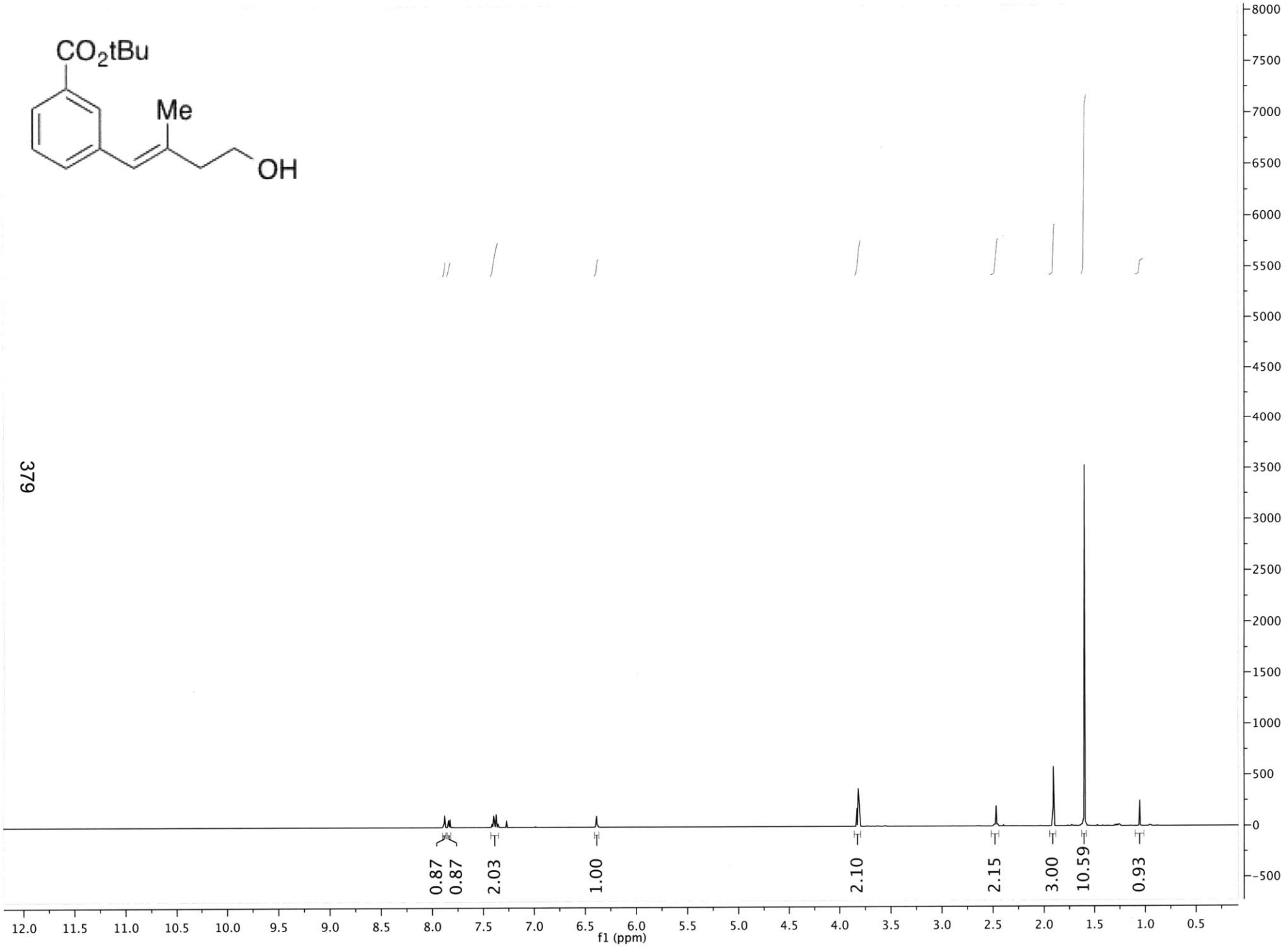


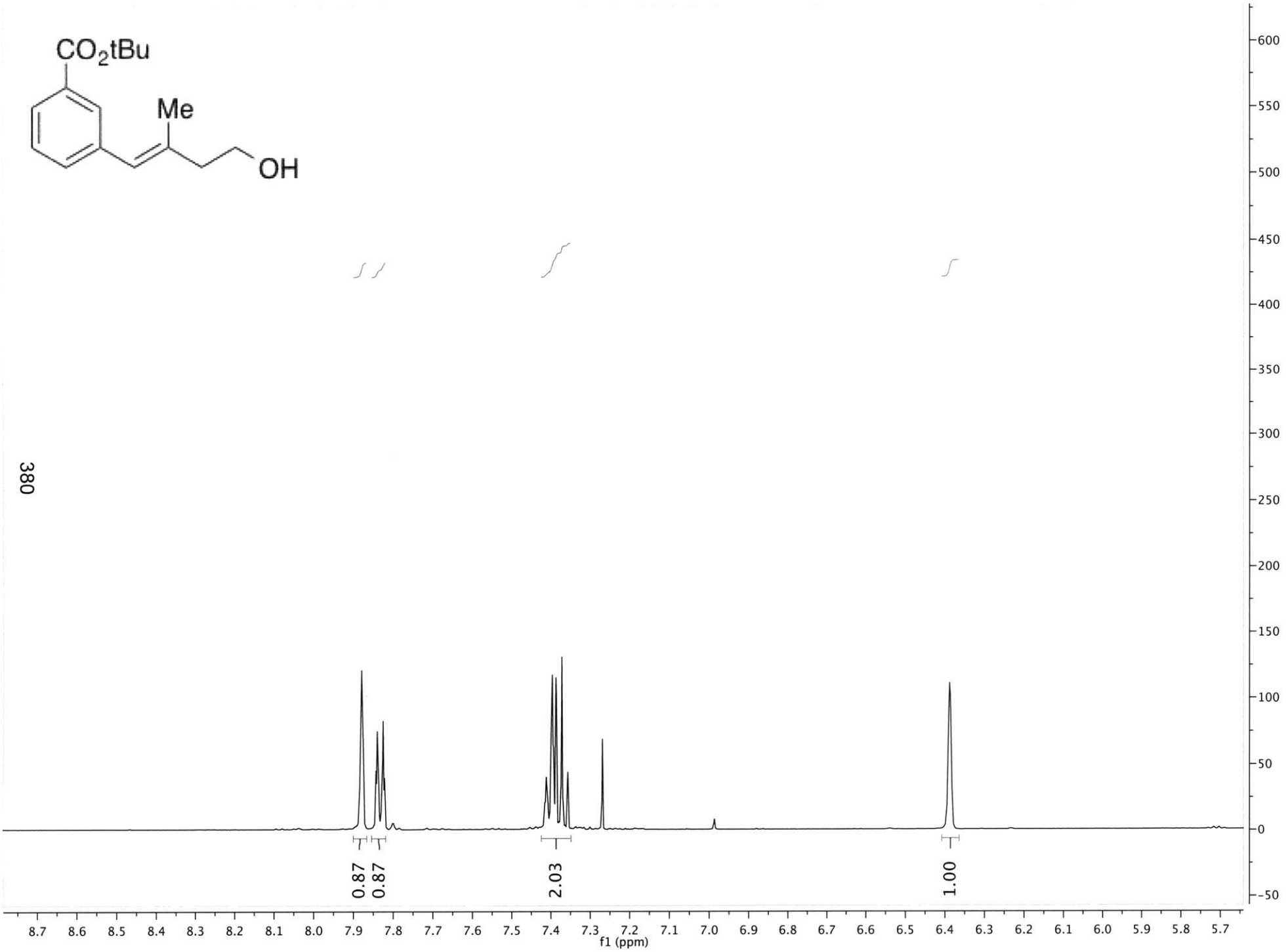
375

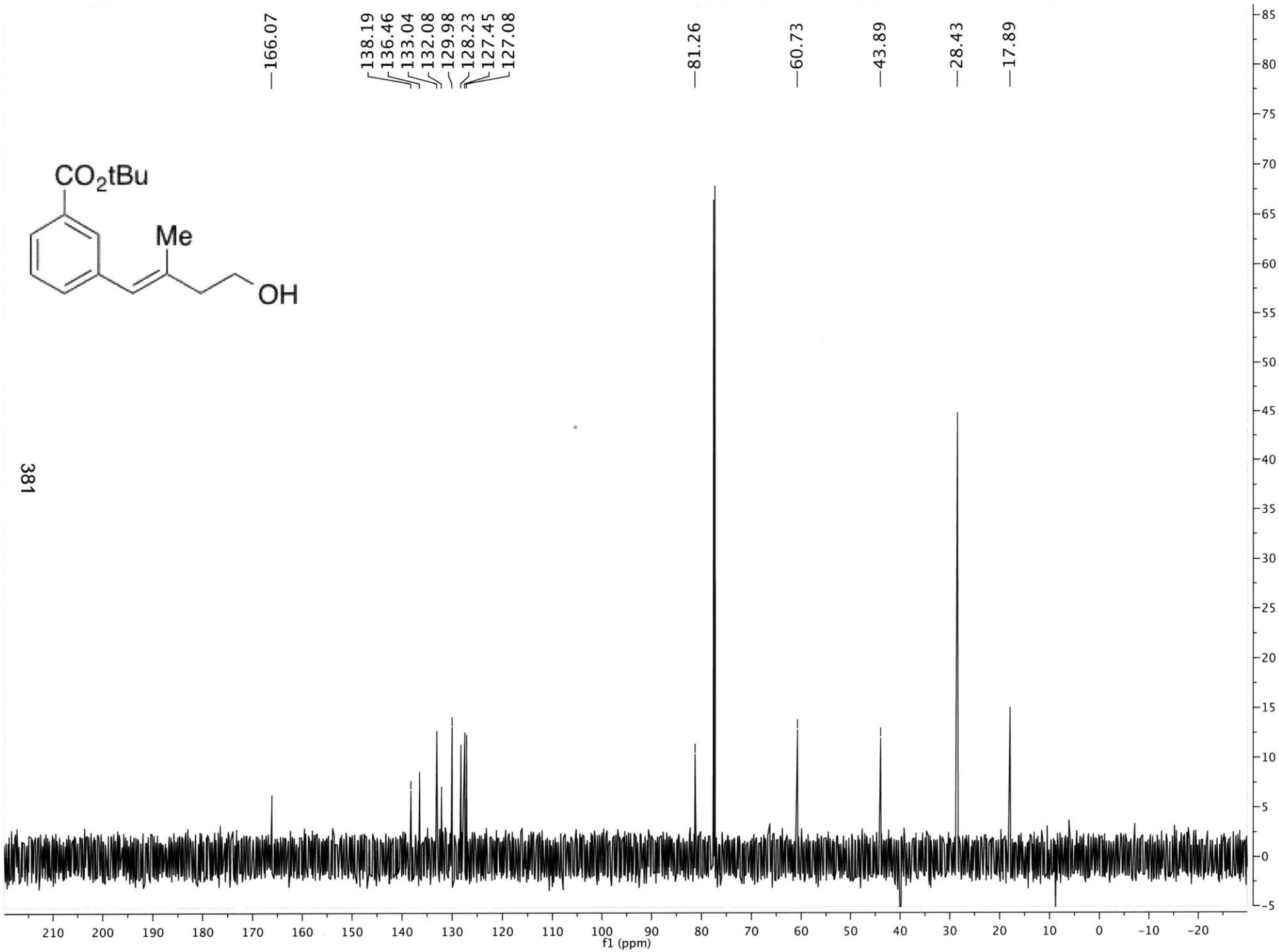

Me
S
OH
141.00
139.69
139.64
136.88
124.47
124.14
123.30
123.13
122.08
121.44
60.70
44.36
18.60
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

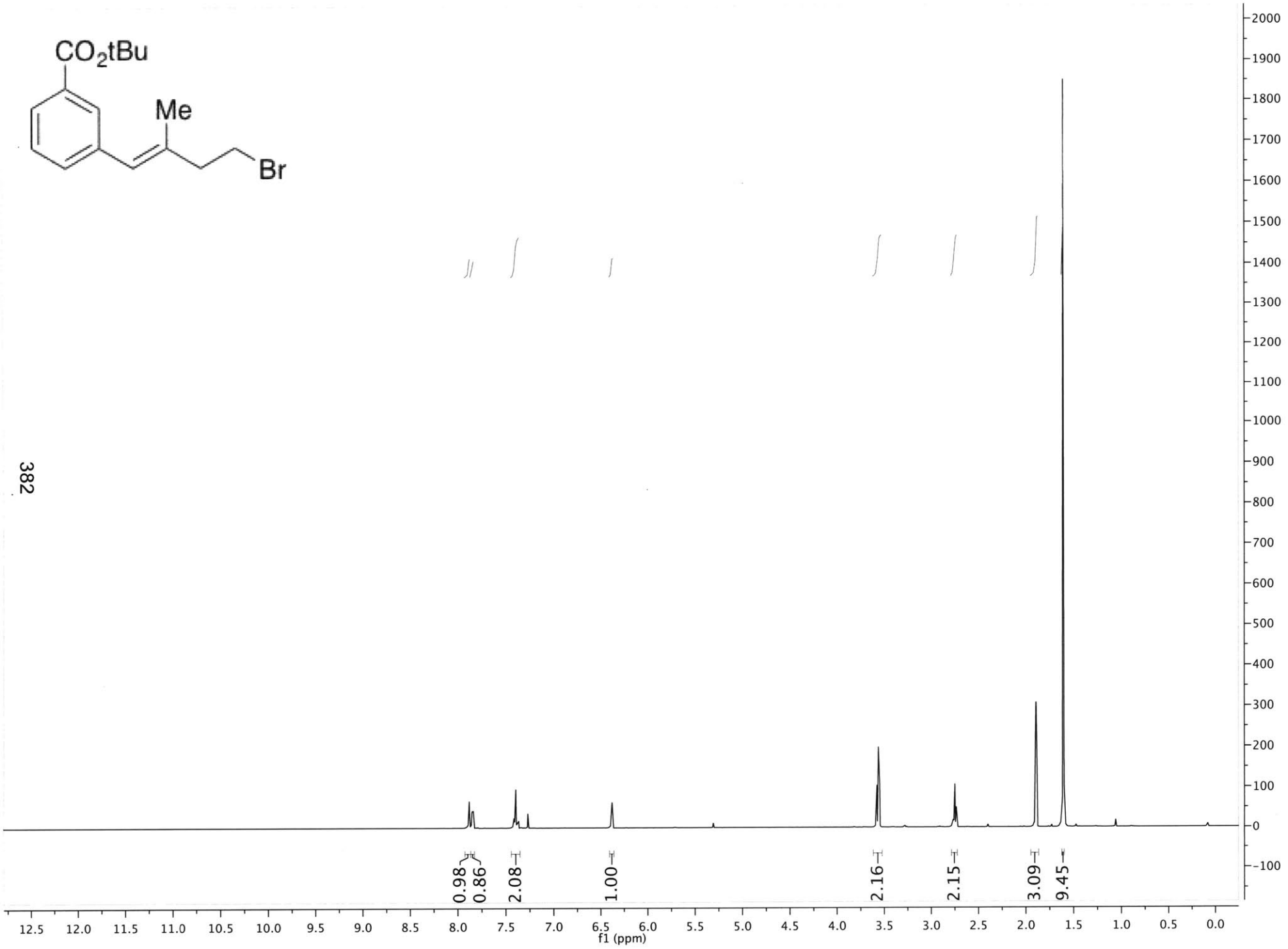

Me
S
Br
377
1.00
0.99
1.02
1.01
0.99
0.99
2.03
2.06
2.99
f1 (ppm)

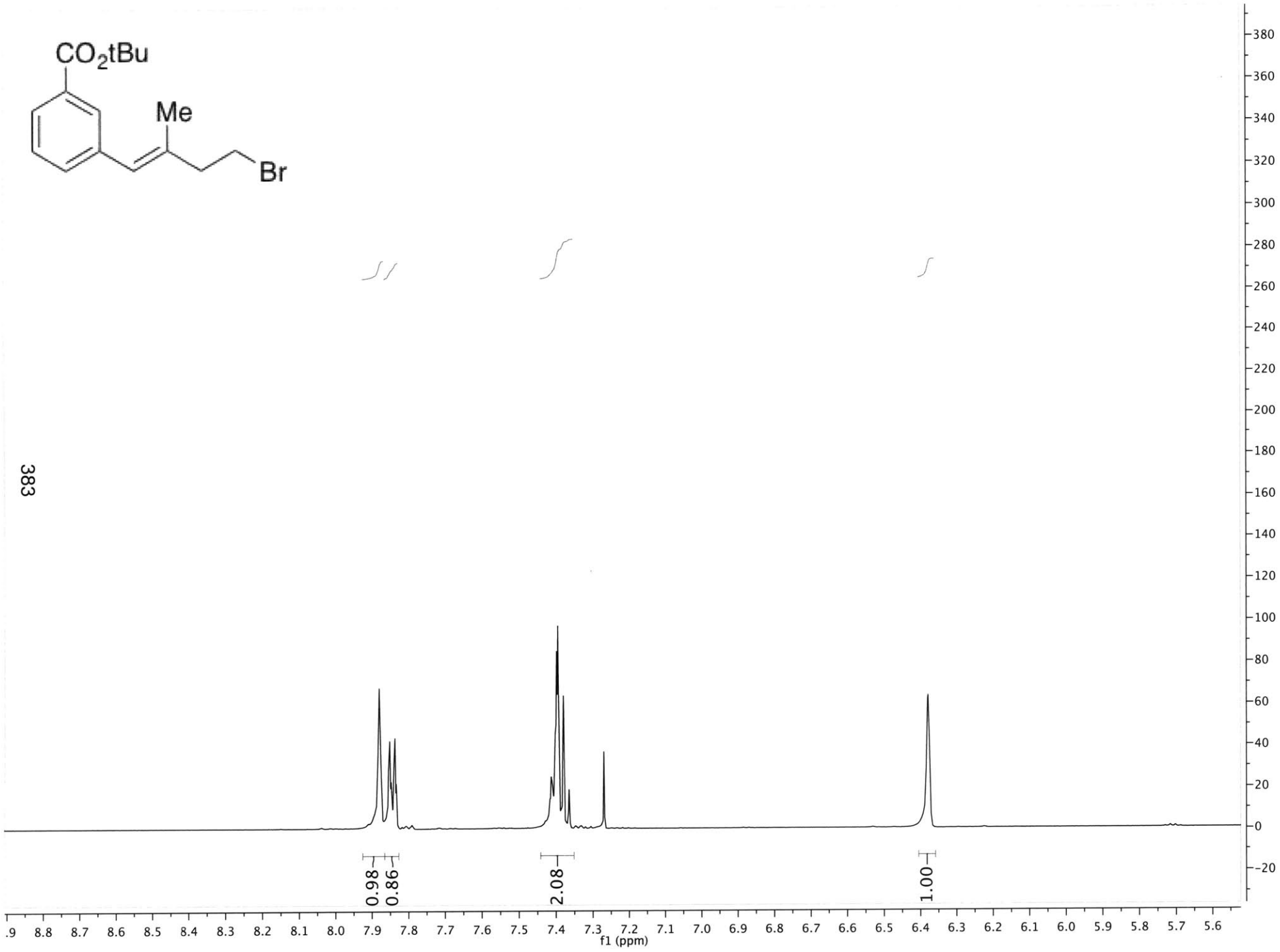

Me
S
Br
140.79
139.79
139.63
136.90
124.50
124.22
123.42
123.35
122.09
121.66
44.27
30.89
18.26
378
f1 (ppm)

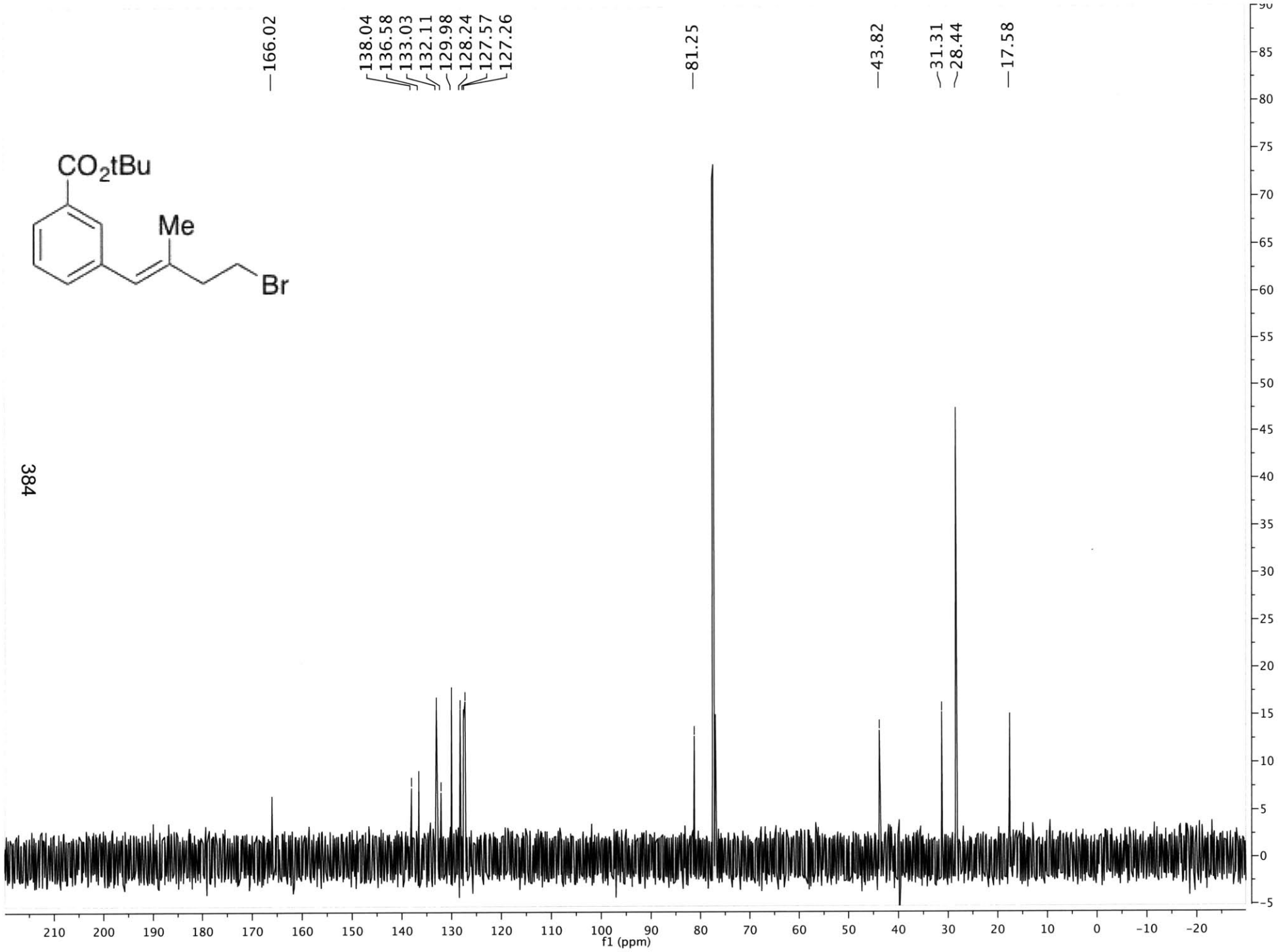

CO2tBu
Me
OH
379
0.87
0.87
2.03
1.00
2.10
2.15
3.00
10.59
0.93
f1 (ppm)

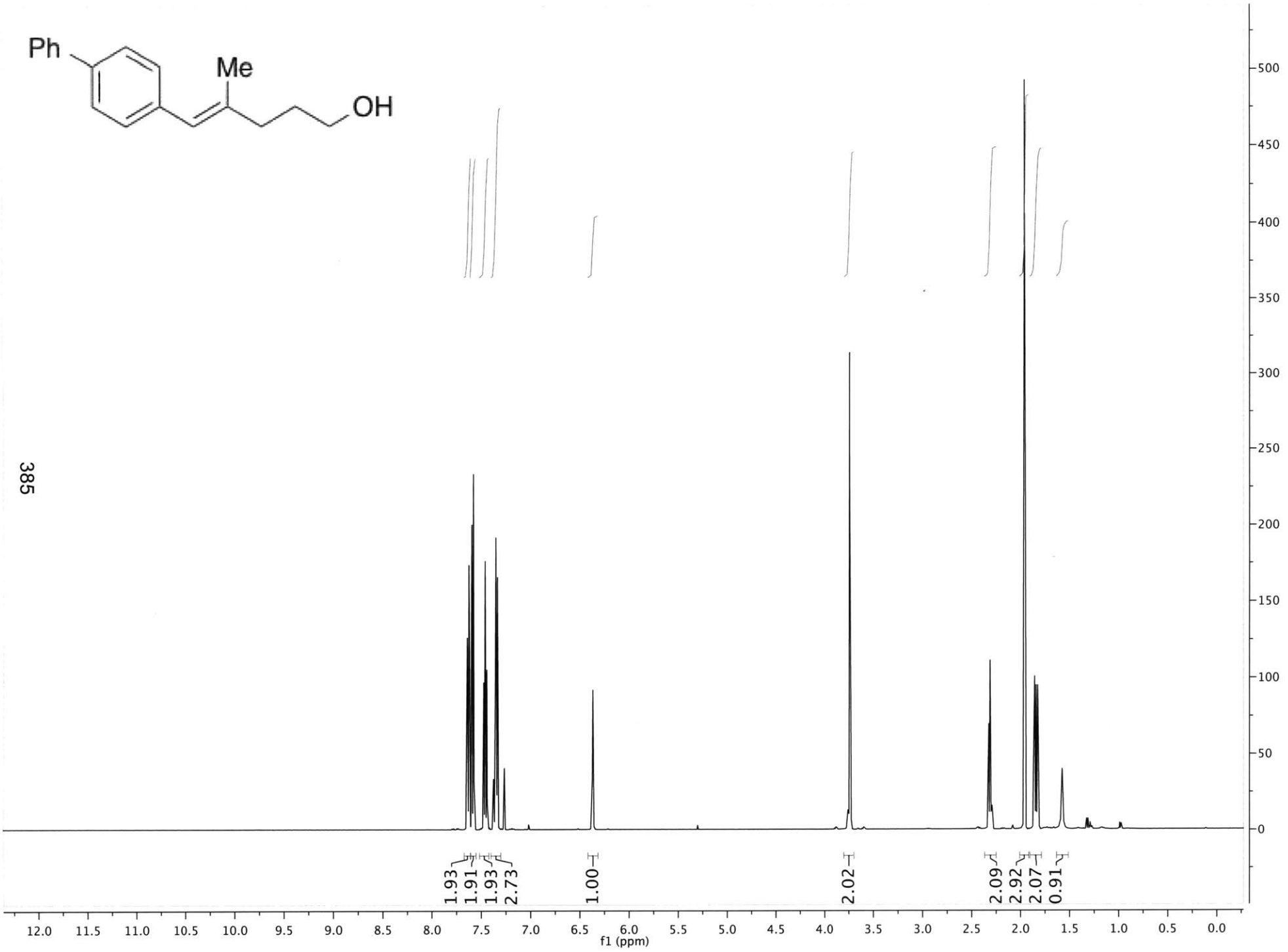

CO2tBu
Me
OH
380
0.87
0.87
2.03
1.00
f1 (ppm)

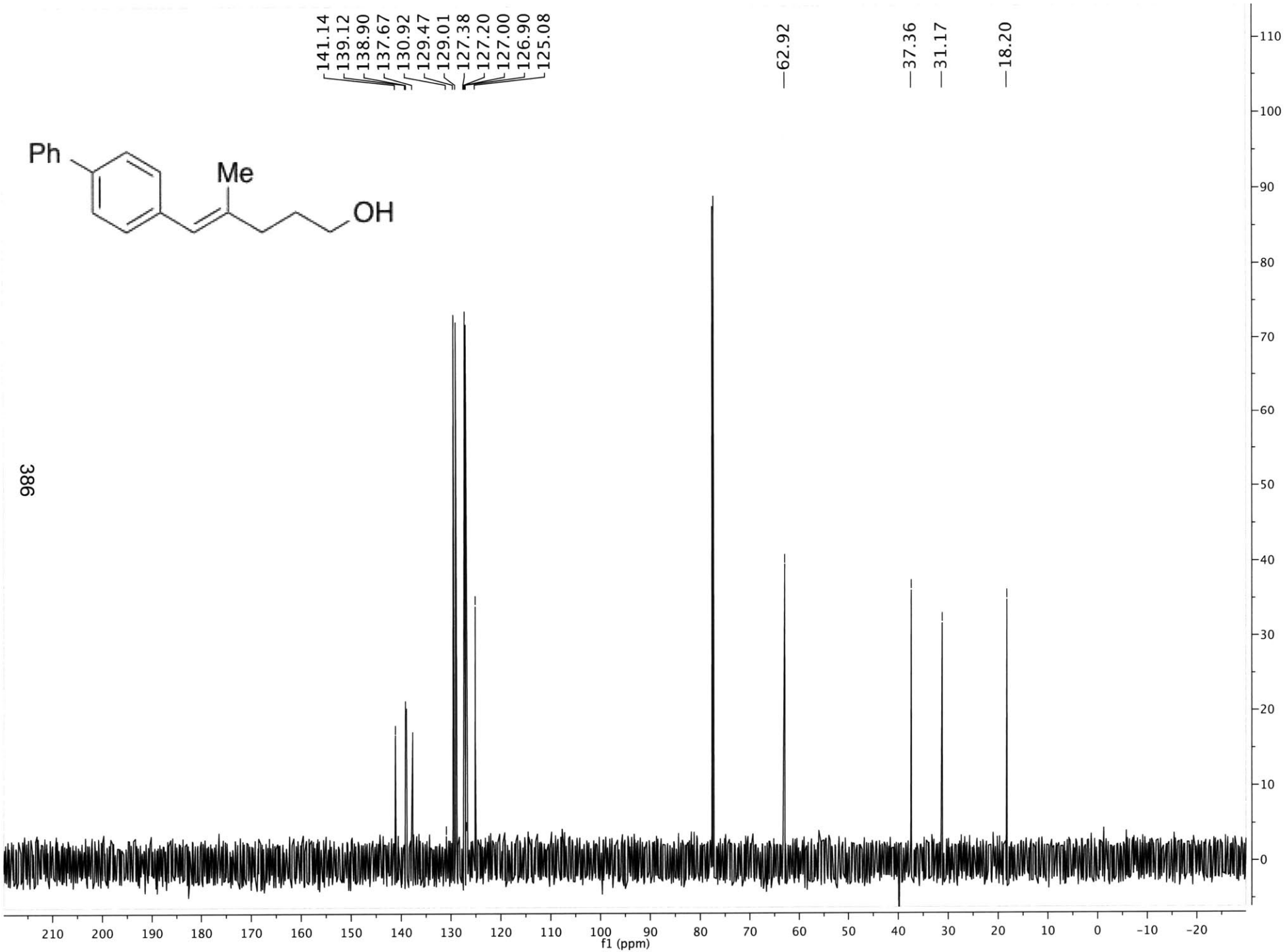

166.07
138.19
136.46
133.04
132.08
129.98
128.23
127.45
127.08
81.26
60.73
43.89
28.43
17.89
CO2tBu
Me
OH
381
f1 (ppm)

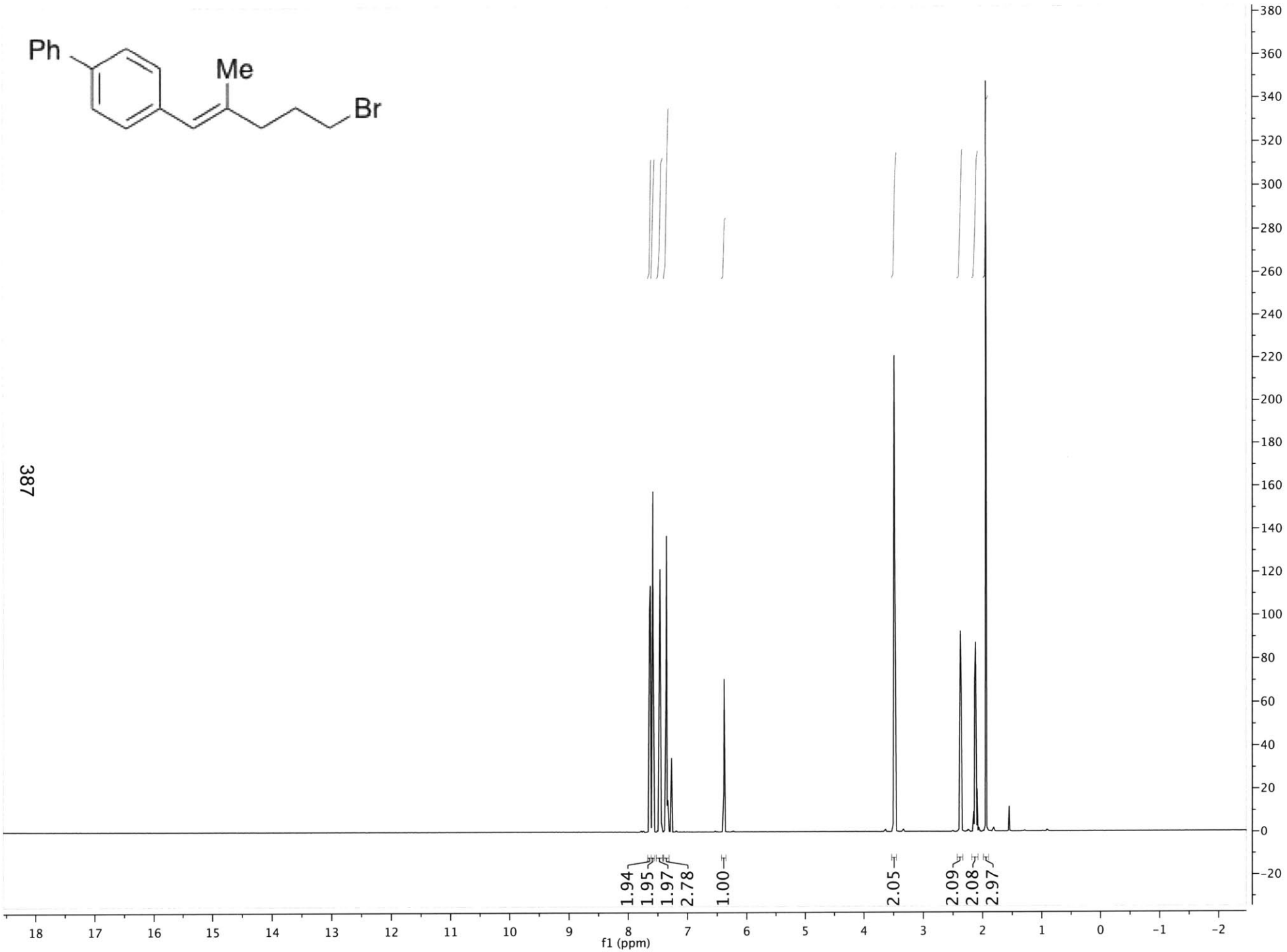

CO2tBu
Me
Br
382
0.98
0.86
2.08
1.00
2.16
2.15
3.09
9.45
f1 (ppm)

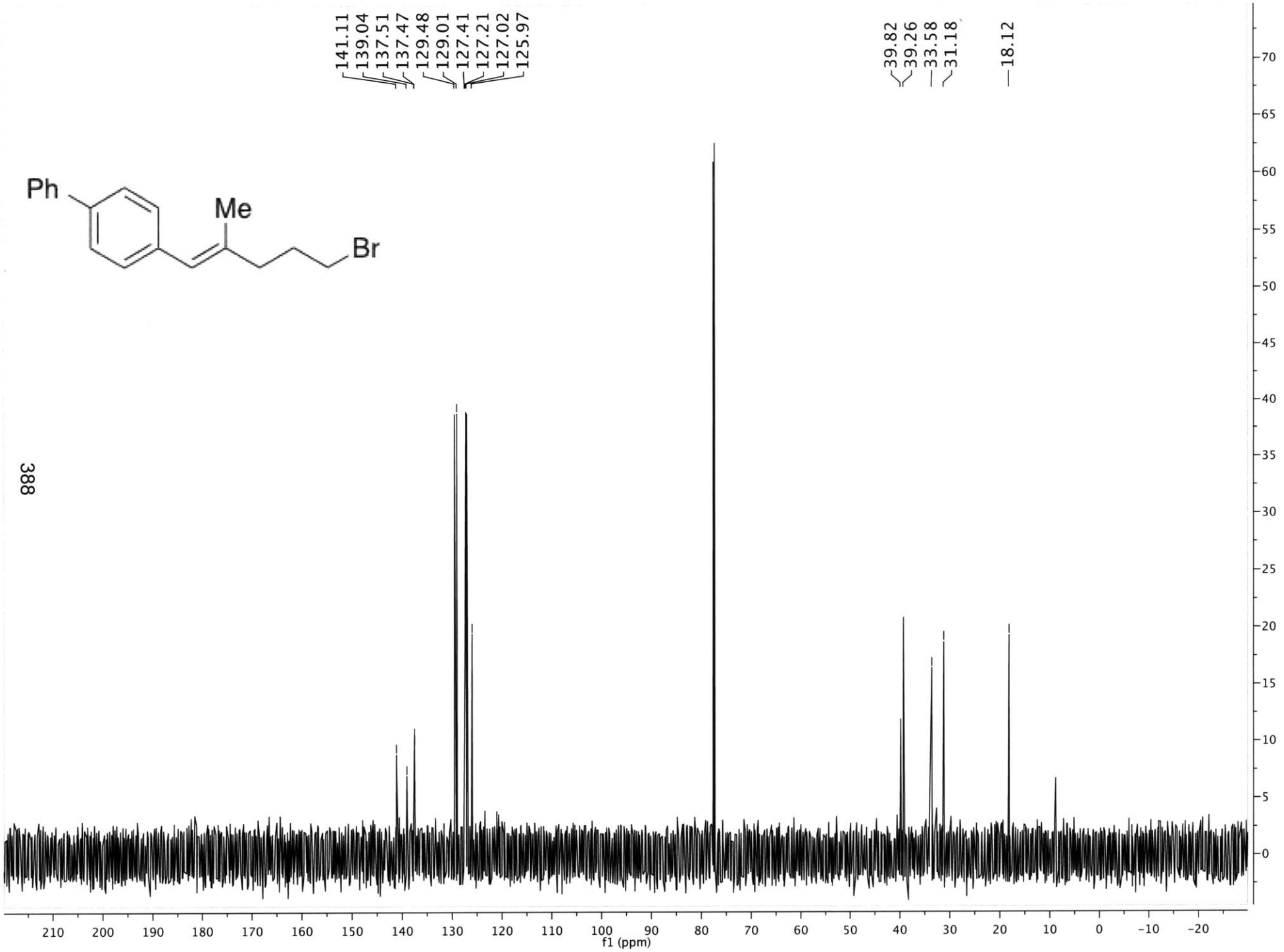

CO2tBu
Me
Br
383
0.98
0.86
2.08
1.00
f1 (ppm)

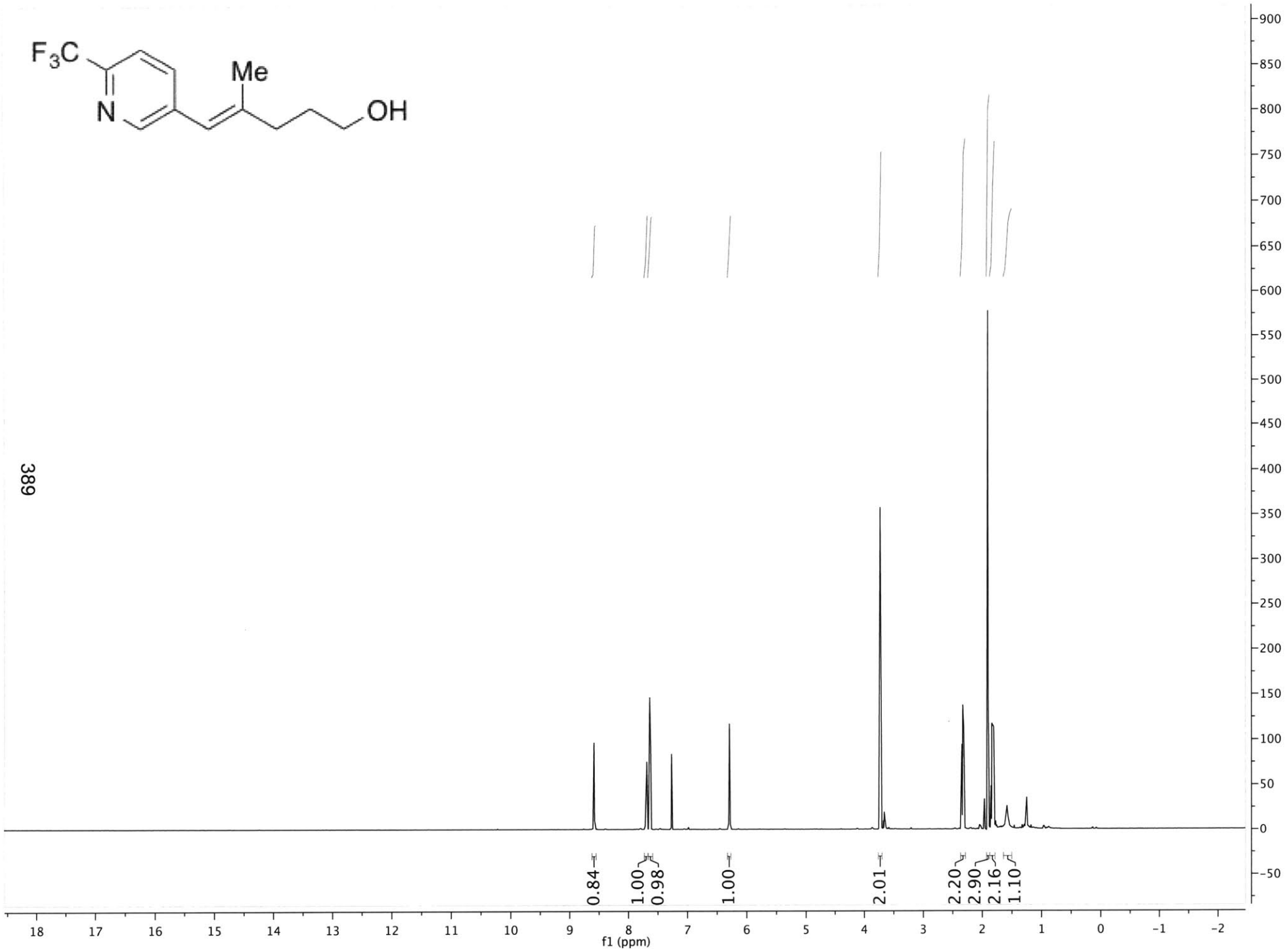

166.02
138.04
136.58
133.03
132.11
129.98
128.24
127.57
127.26
81.25
43.82
31.31
28.44
17.58
CO2tBu
Me
Br
384
f1 (ppm)

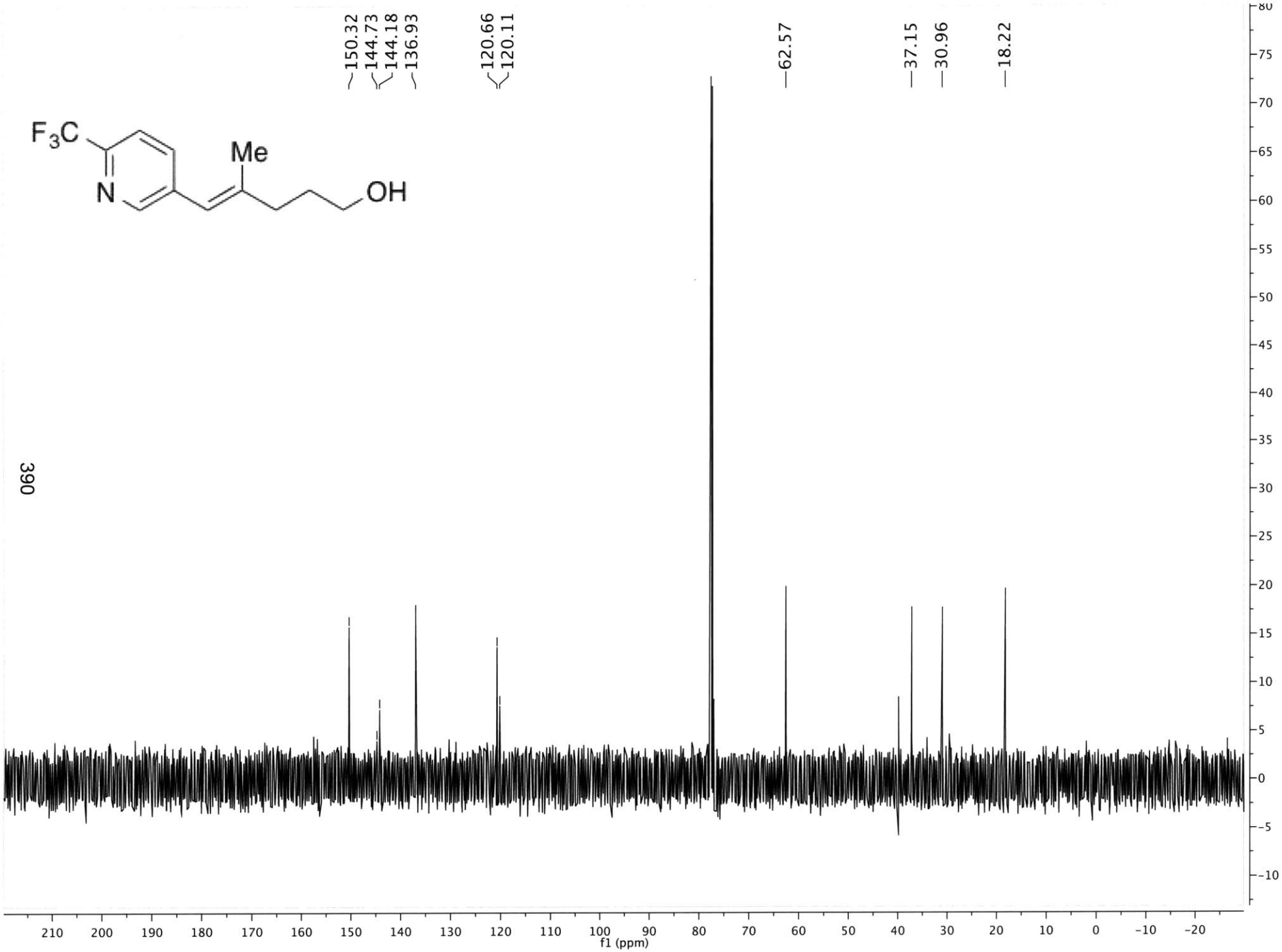

Ph
Me
OH
385
1.93
1.91
1.93
2.73
1.00
2.02
2.09
2.92
2.07
0.91
f1 (ppm)

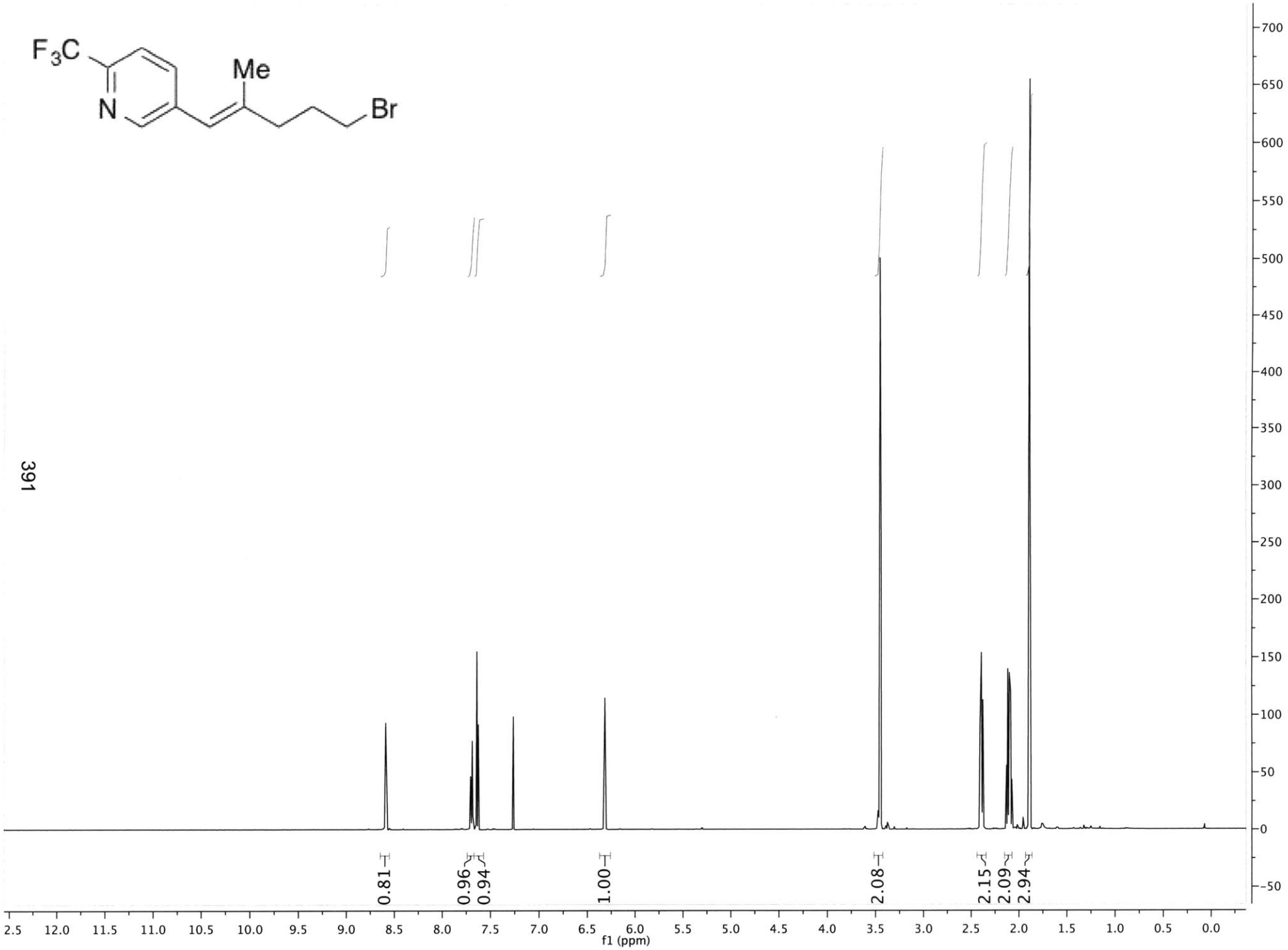

141.14
139.12
138.90
137.67
130.92
129.47
129.01
127.38
127.20
127.00
126.90
125.08
62.92
37.36
31.17
18.20
Ph
Me
OH
386
f1 (ppm)

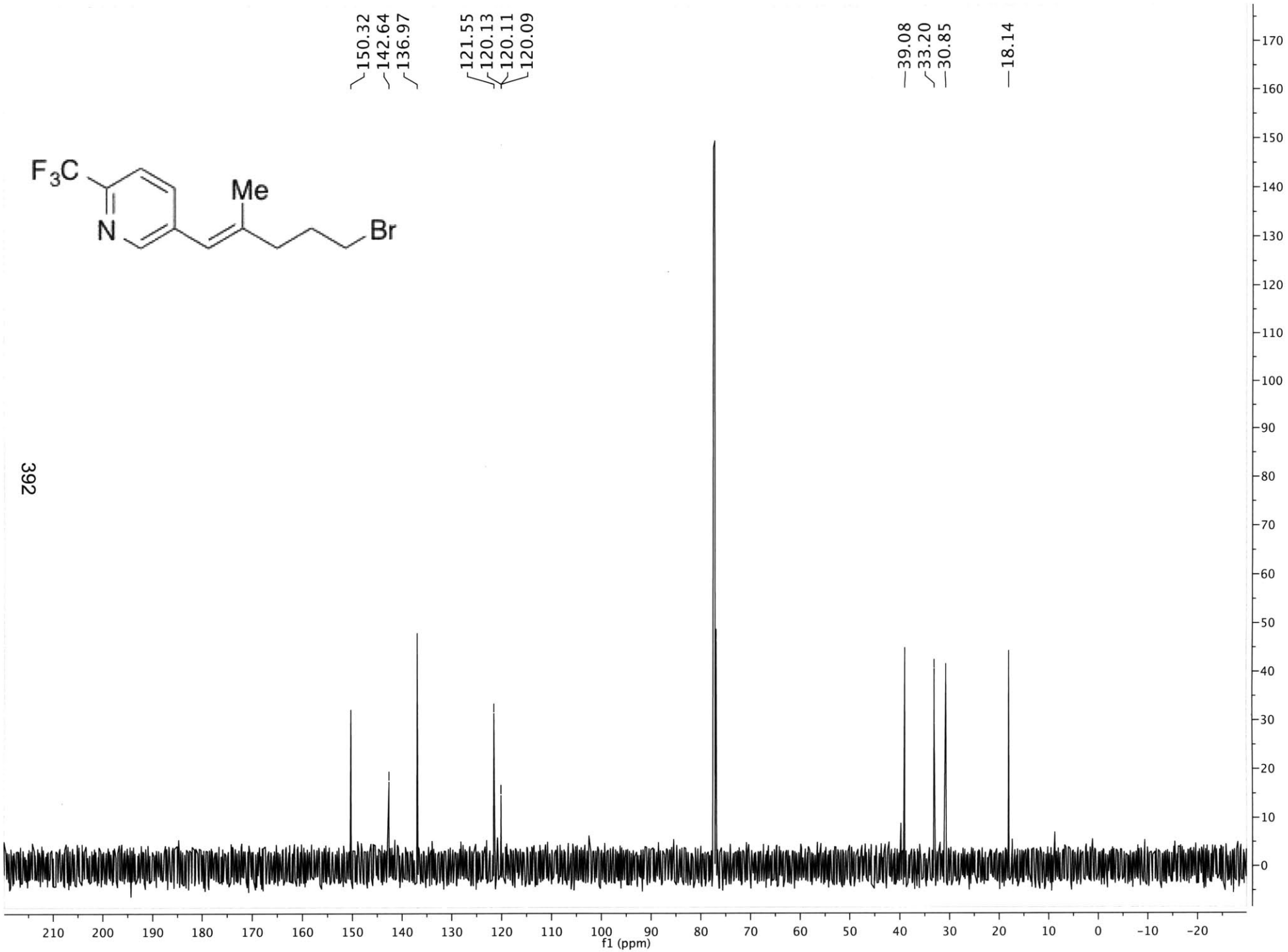

Ph
Me
Br
387
1.94
1.95
1.97
2.78
1.00
2.05
2.09
2.08
2.97
f1 (ppm)

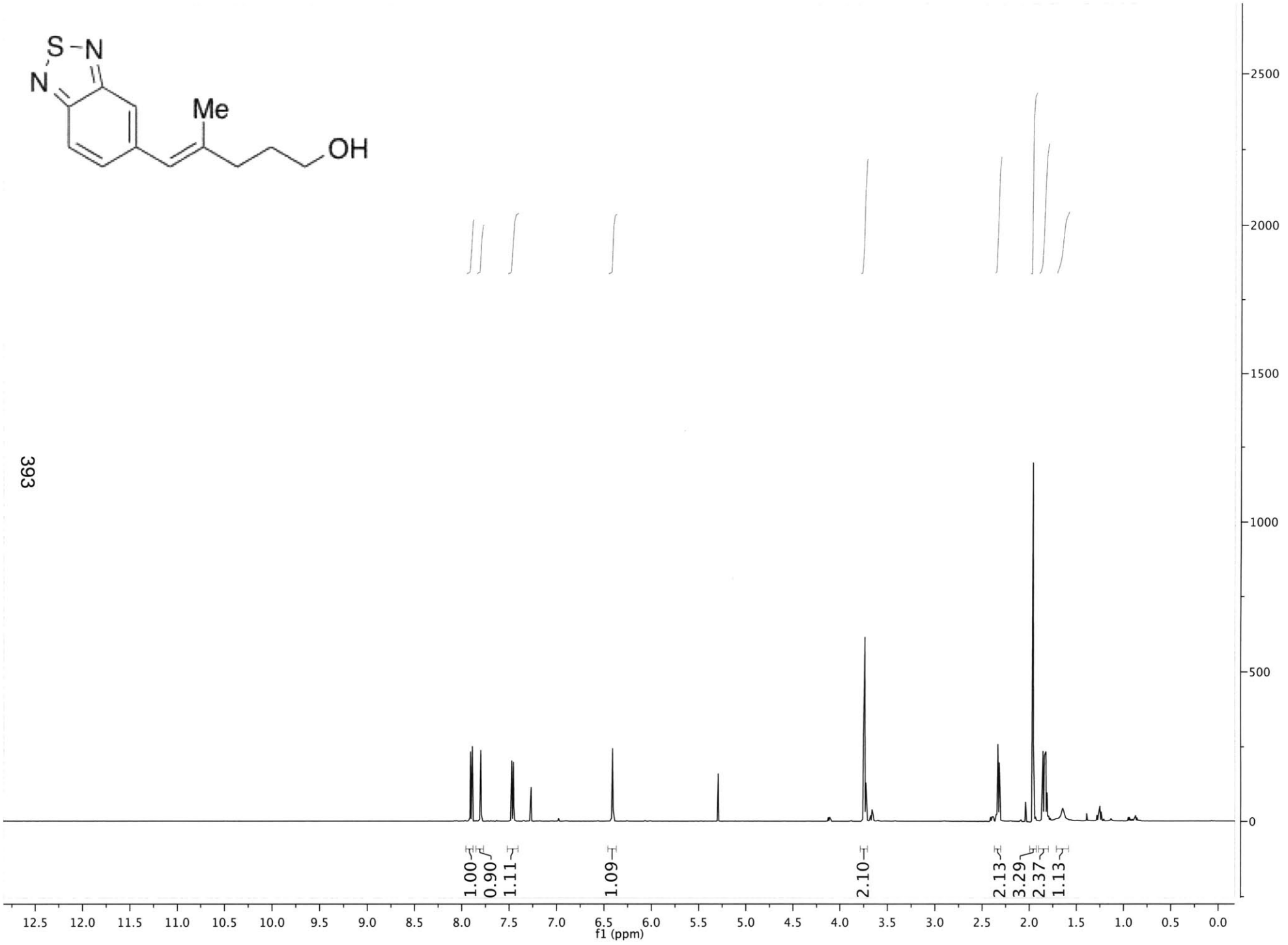

141.11
139.04
137.51
137.47
129.48
129.01
127.41
127.21
127.02
125.97
39.82
39.26
33.58
31.18
18.12
Ph
Me
Br
388
f1 (ppm)

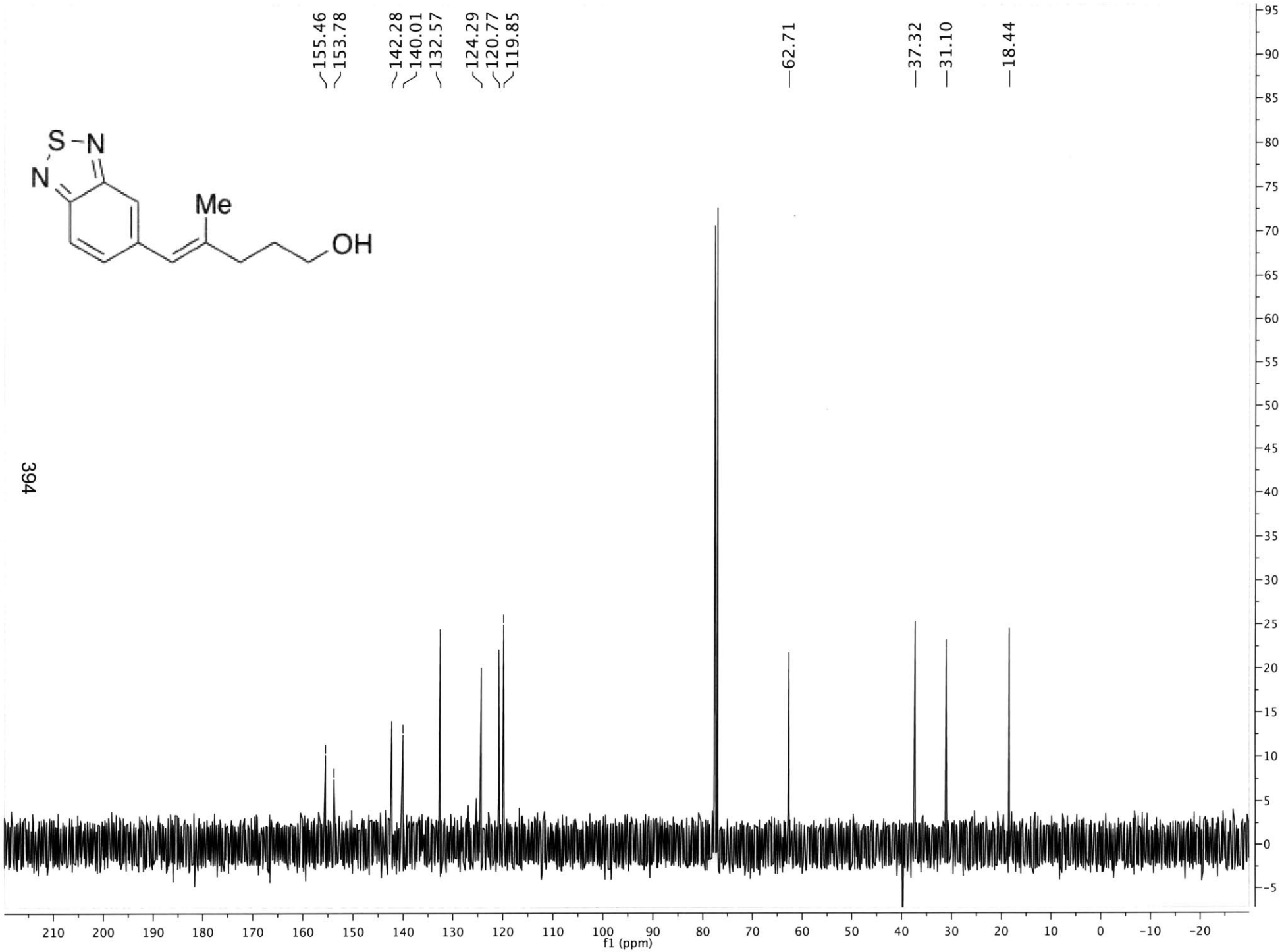

F3C
N
Me
OH
389
0.84
1.00
0.98
1.00
2.01
2.20
2.90
2.16
1.10
f1 (ppm)

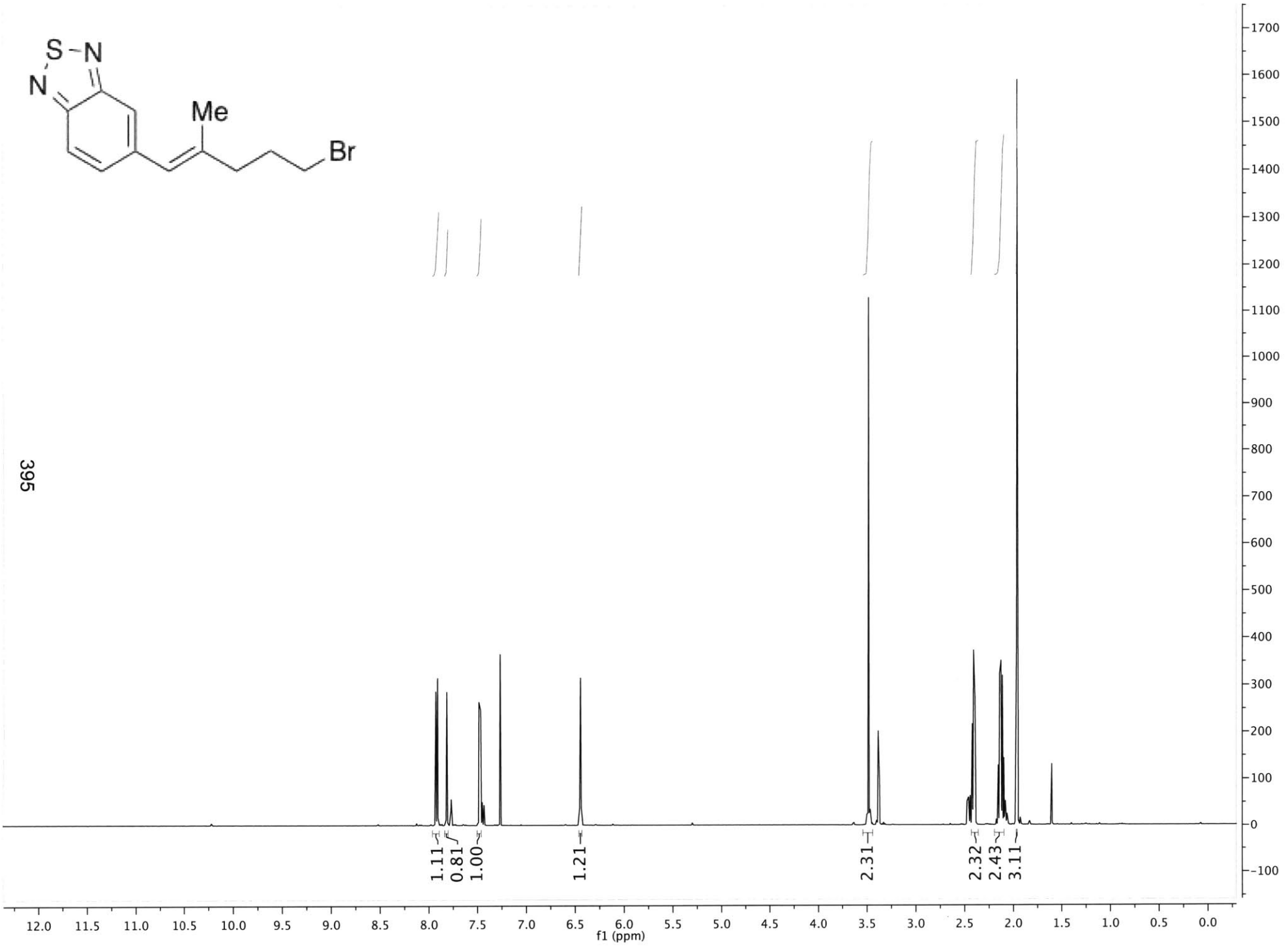

150.32
144.73
144.18
136.93
120.66
120.11
62.57
37.15
30.96
18.22
F3C
N
Me
OH
390
f1 (ppm)

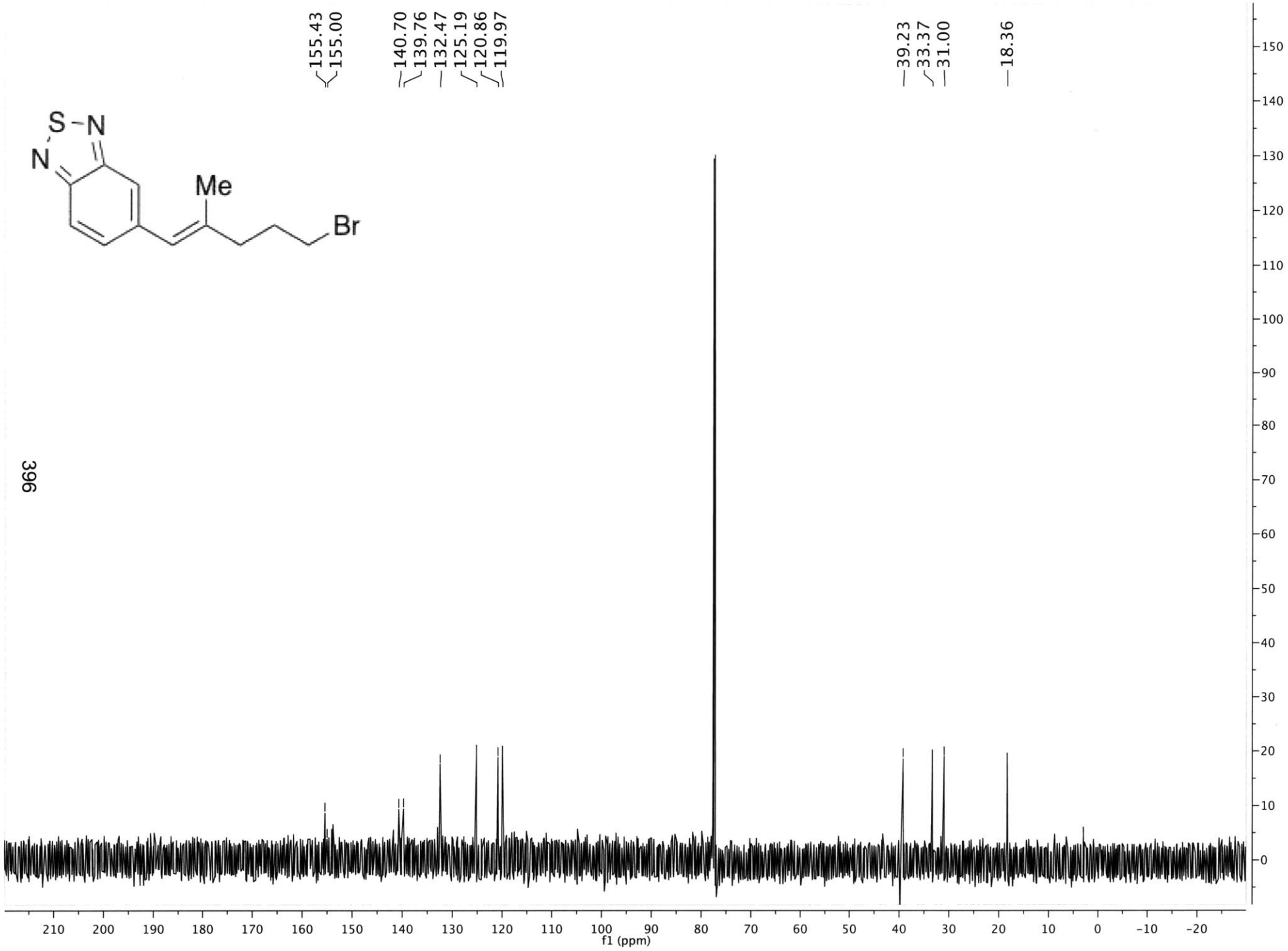

F3C
N
Me
Br
391
0.81
0.96
0.94
1.00
2.08
2.15
2.09
2.94
f1 (ppm)

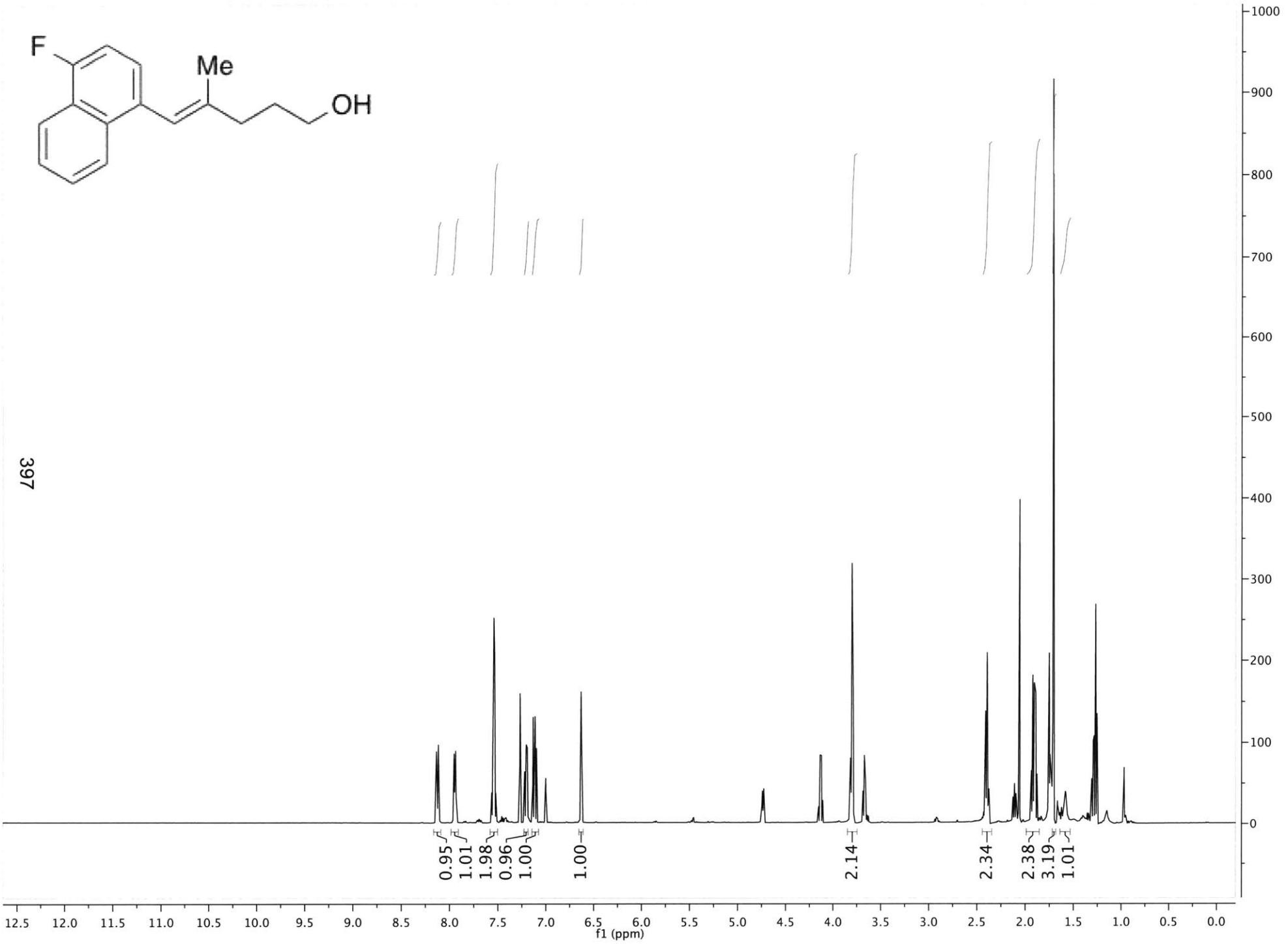

150.32
142.64
136.97
121.55
120.13
120.11
120.09
39.08
33.20
30.85
18.14
F3C
N
Me
Br
392
f1 (ppm)

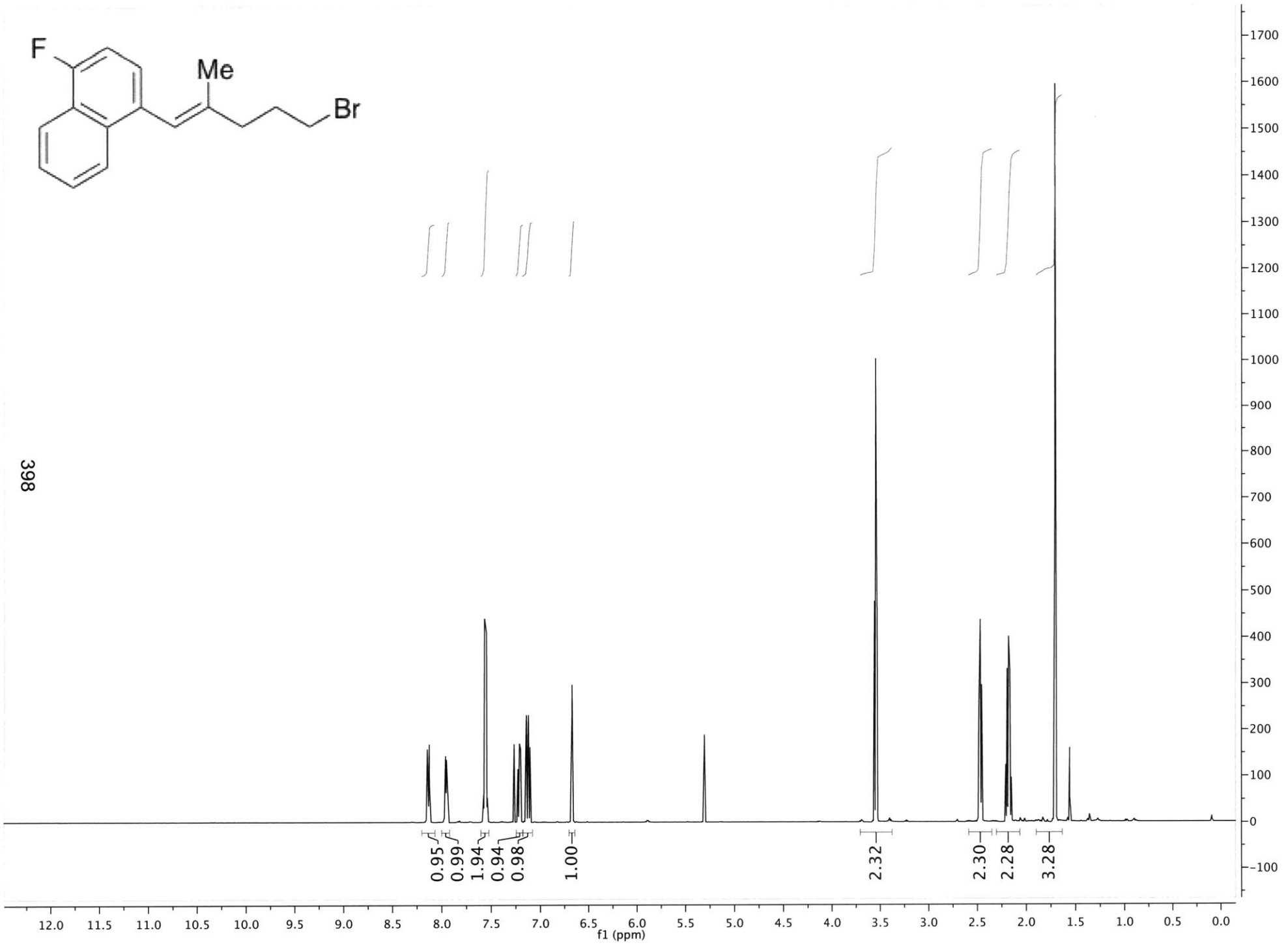

S
N
N
Me
OH
393
2500
2000
1500
1000
500
0
1.00
0.90
1.11
1.09
2.10
2.13
3.29
2.37
1.13
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

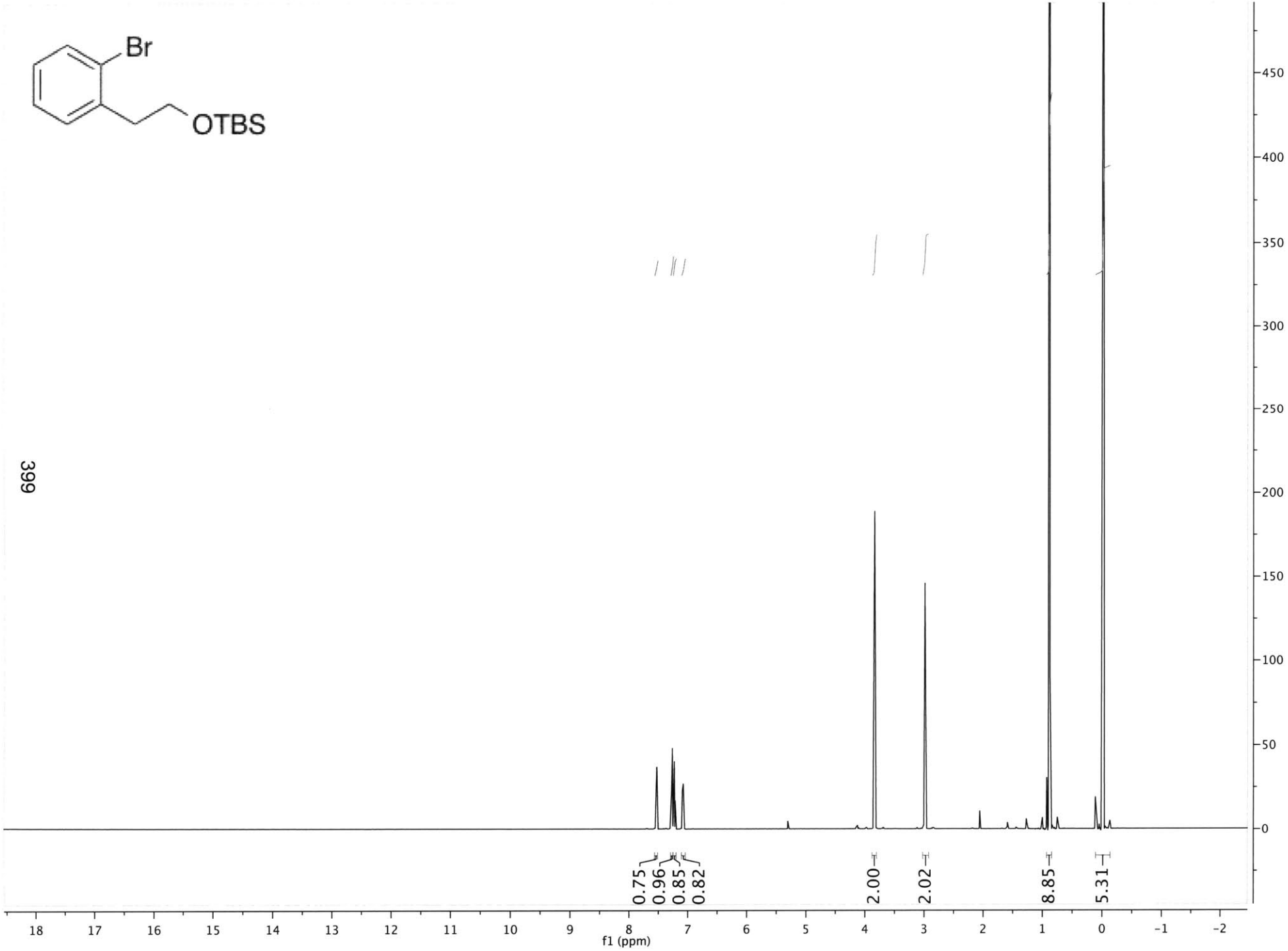

155.46
153.78
142.28
140.01
132.57
124.29
120.77
119.85
62.71
37.32
31.10
18.44
S
N
N
Me
OH
394
f1 (ppm)

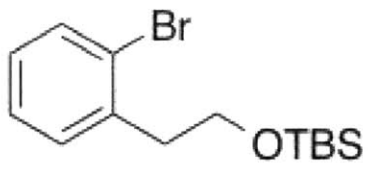

S
N
N
Me
Br
395
1.11
0.81
1.00
1.21
2.31
2.32
2.43
3.11
f1 (ppm)


155.43
155.00
140.70
139.76
132.47
125.19
120.86
119.97
39.23
33.37
31.00
18.36
S
N
N
Me
Br
396
f1 (ppm)


F
Me
OH
397
0.95
1.01
1.98
0.96
1.00
1.00
2.14
2.34
2.38
3.19
1.01
f1 (ppm)


F
Me
Br
398
0.95
0.99
1.94
0.94
0.98
1.00
2.32
2.30
2.28
3.28
f1 (ppm)


Br
OTBS
399
0.75
0.96
0.85
0.82
2.00
2.02
8.85
5.31
f1 (ppm)



400

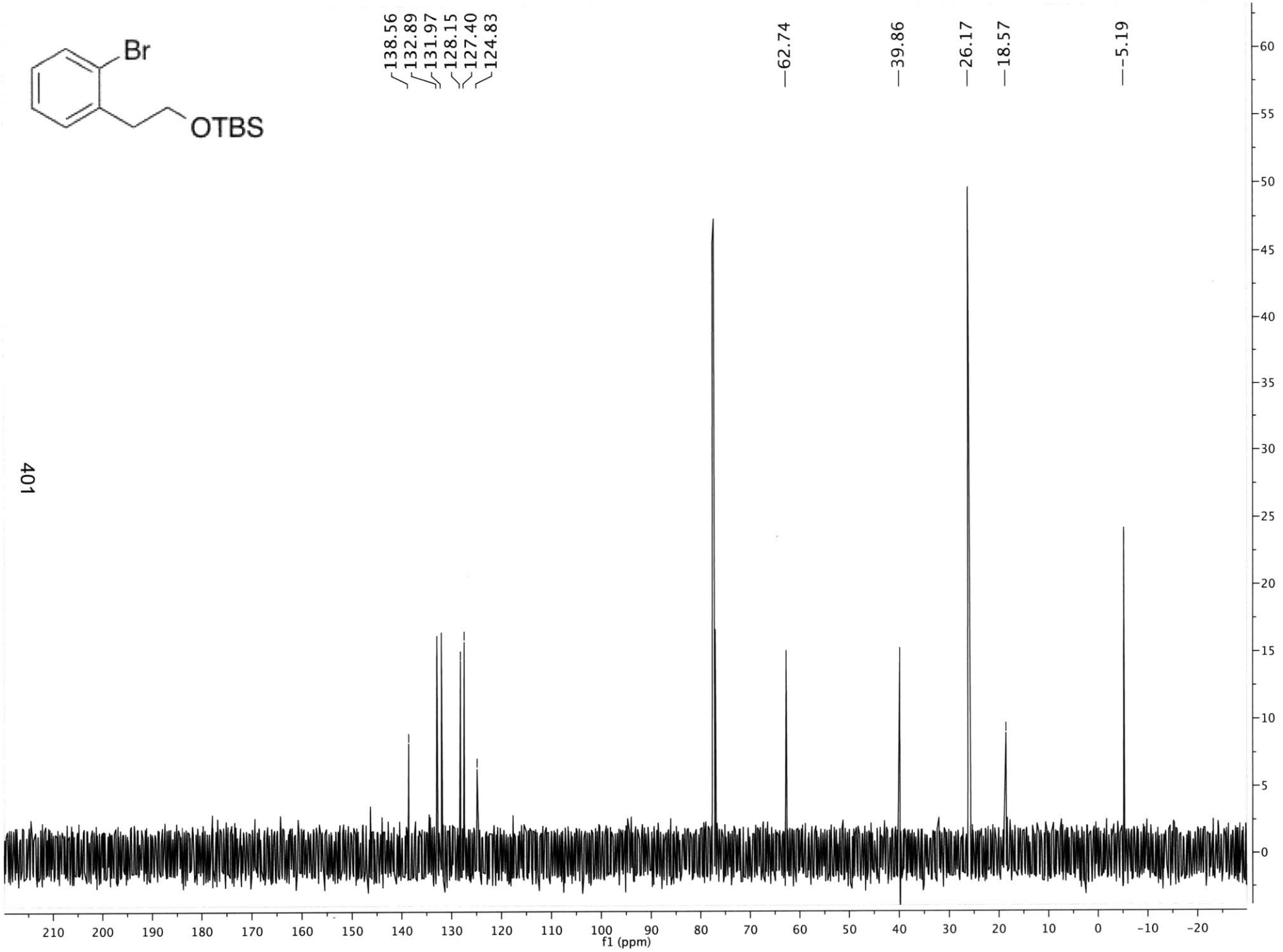
0.75

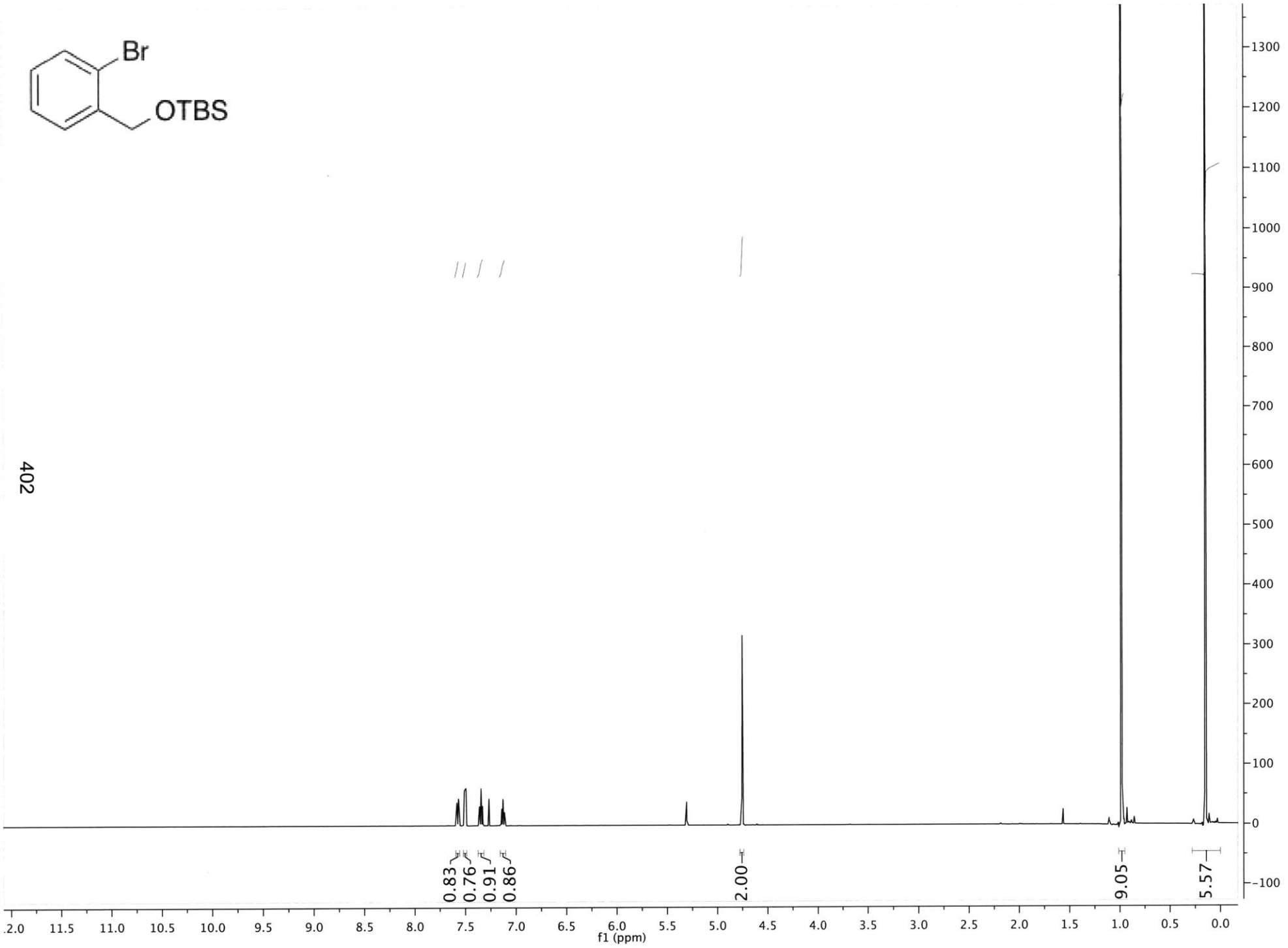
0.96

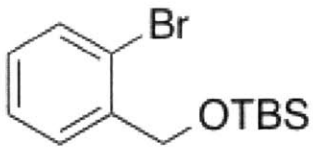
0.85

0.82

f1 (ppm)

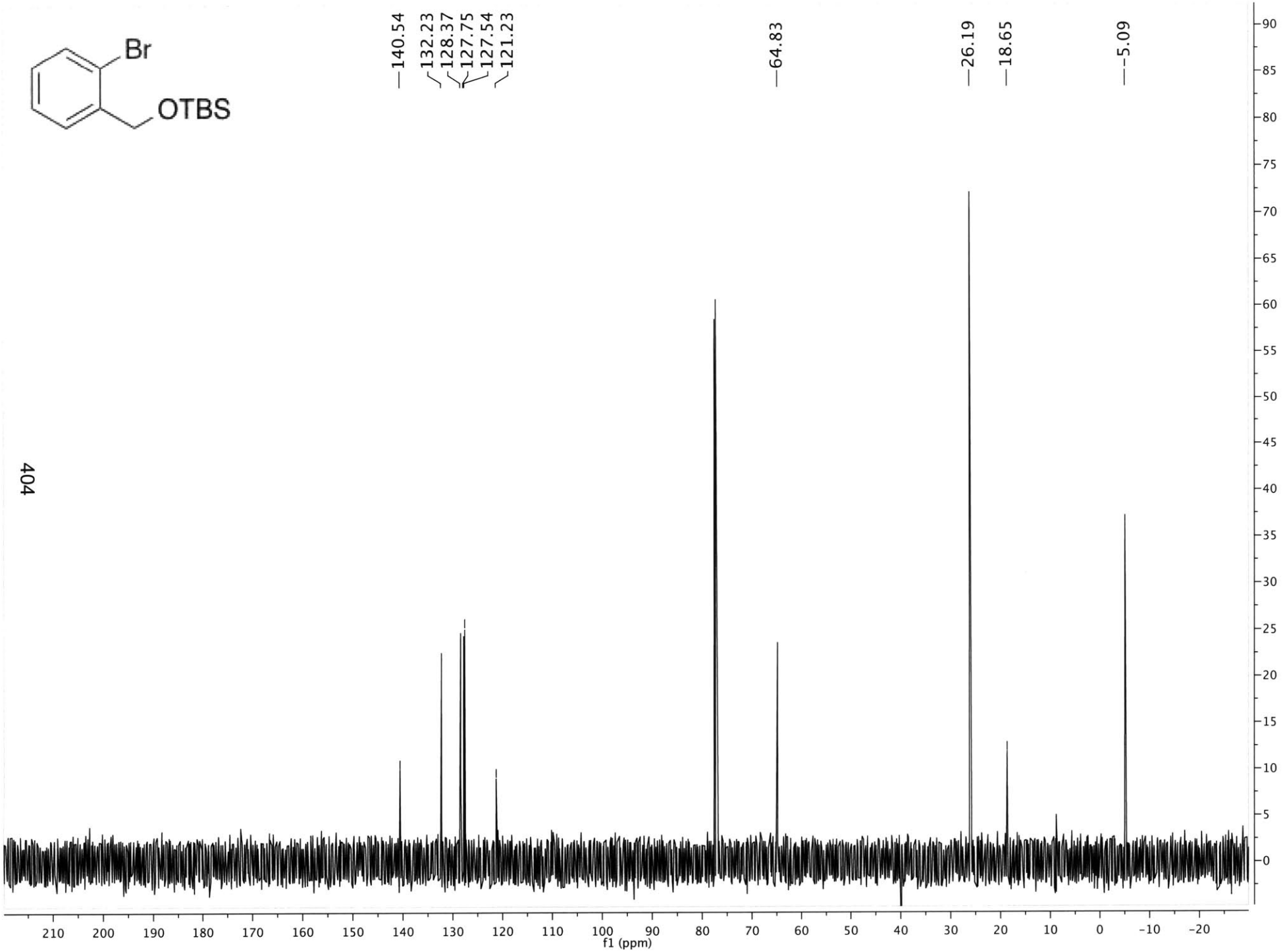

Br
OTBS
138.56
132.89
131.97
128.15
127.40
124.83
62.74
39.86
26.17
18.57
-5.19
401
f1 (ppm)

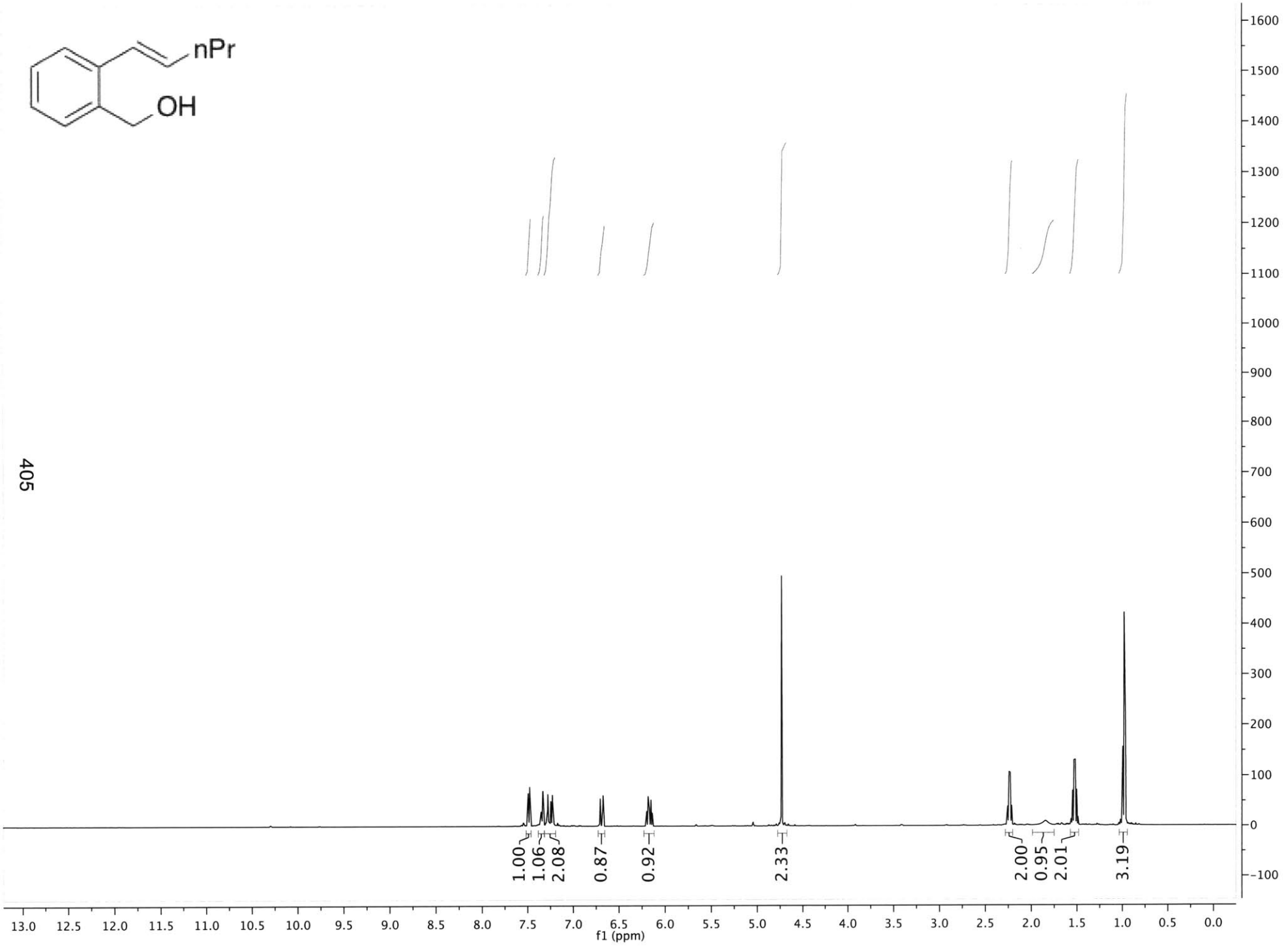

Br
OTBS
402
0.83
0.76
0.91
0.86
2.00
9.05
5.57
f1 (ppm)

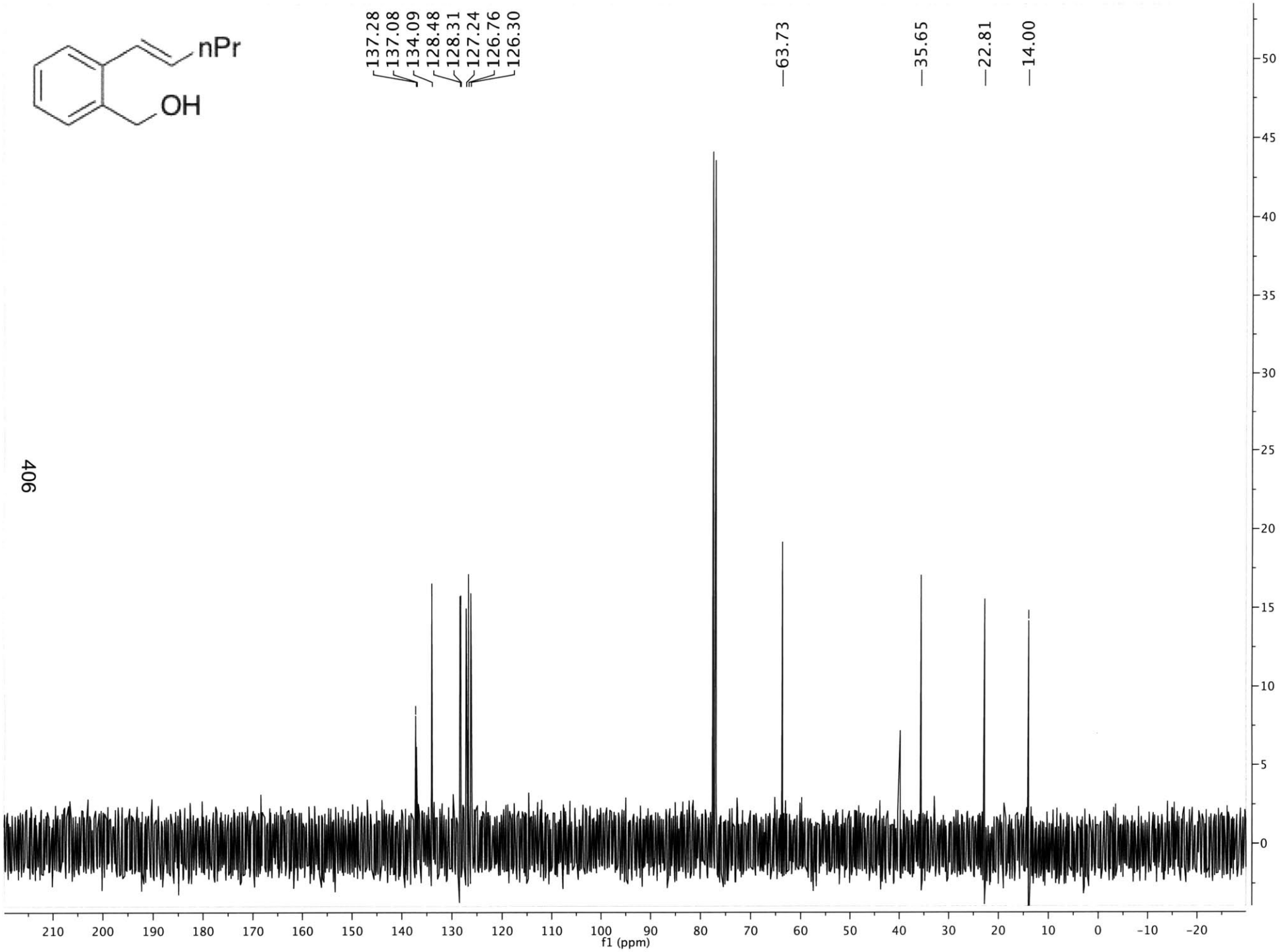

Br
OTBS

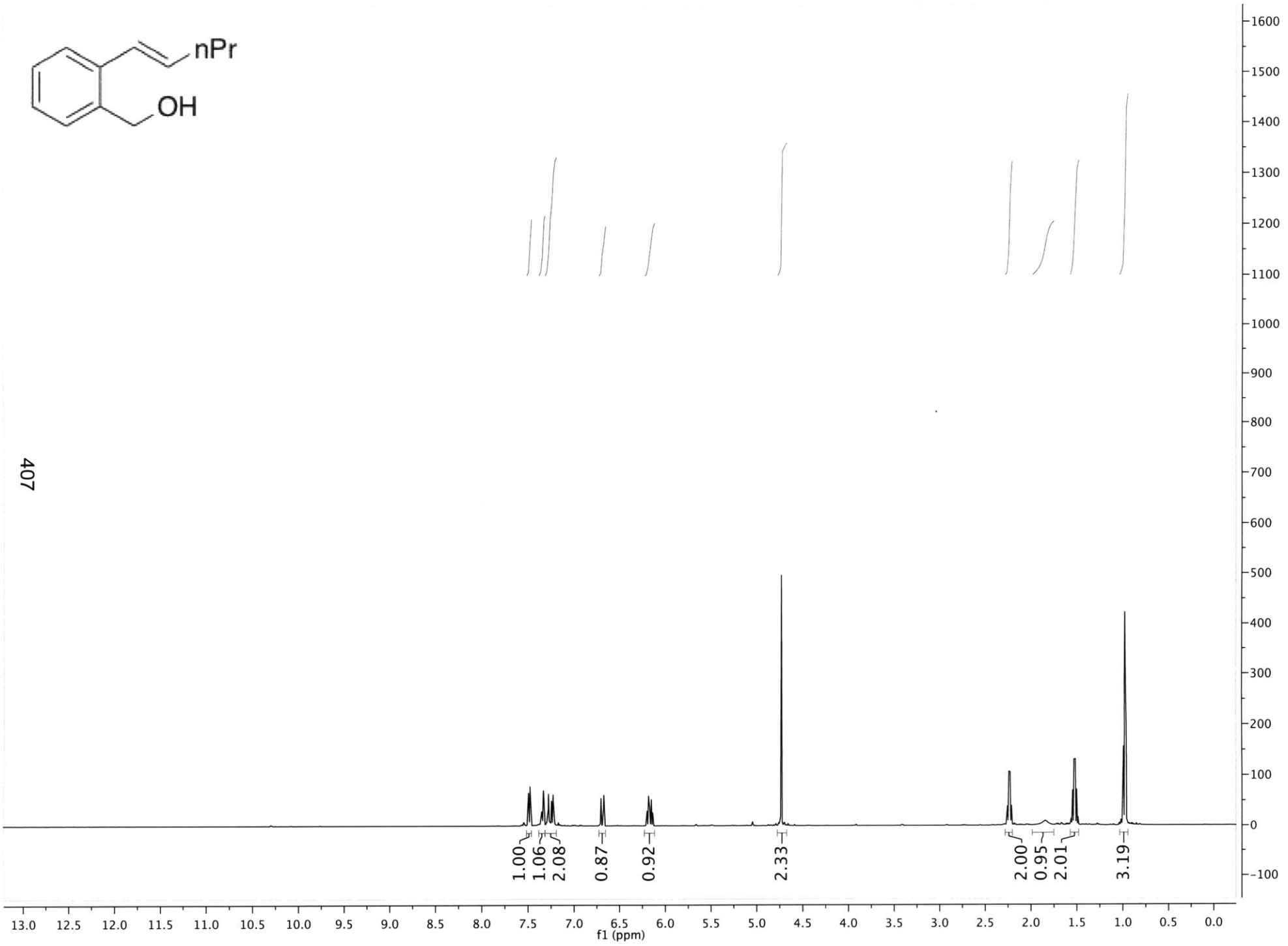
403

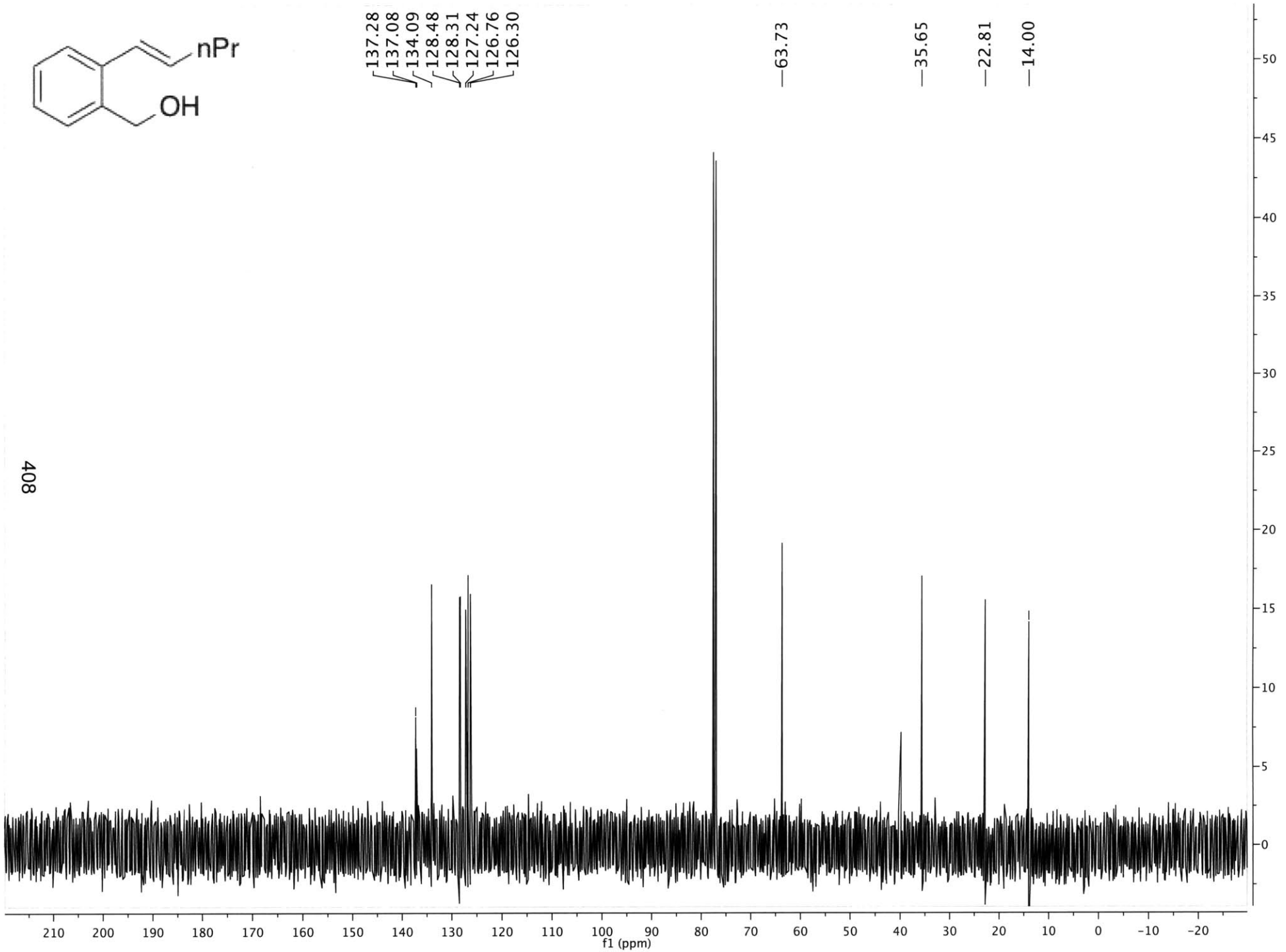
0.83
0.76
0.91
0.86
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
f1 (ppm)
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50

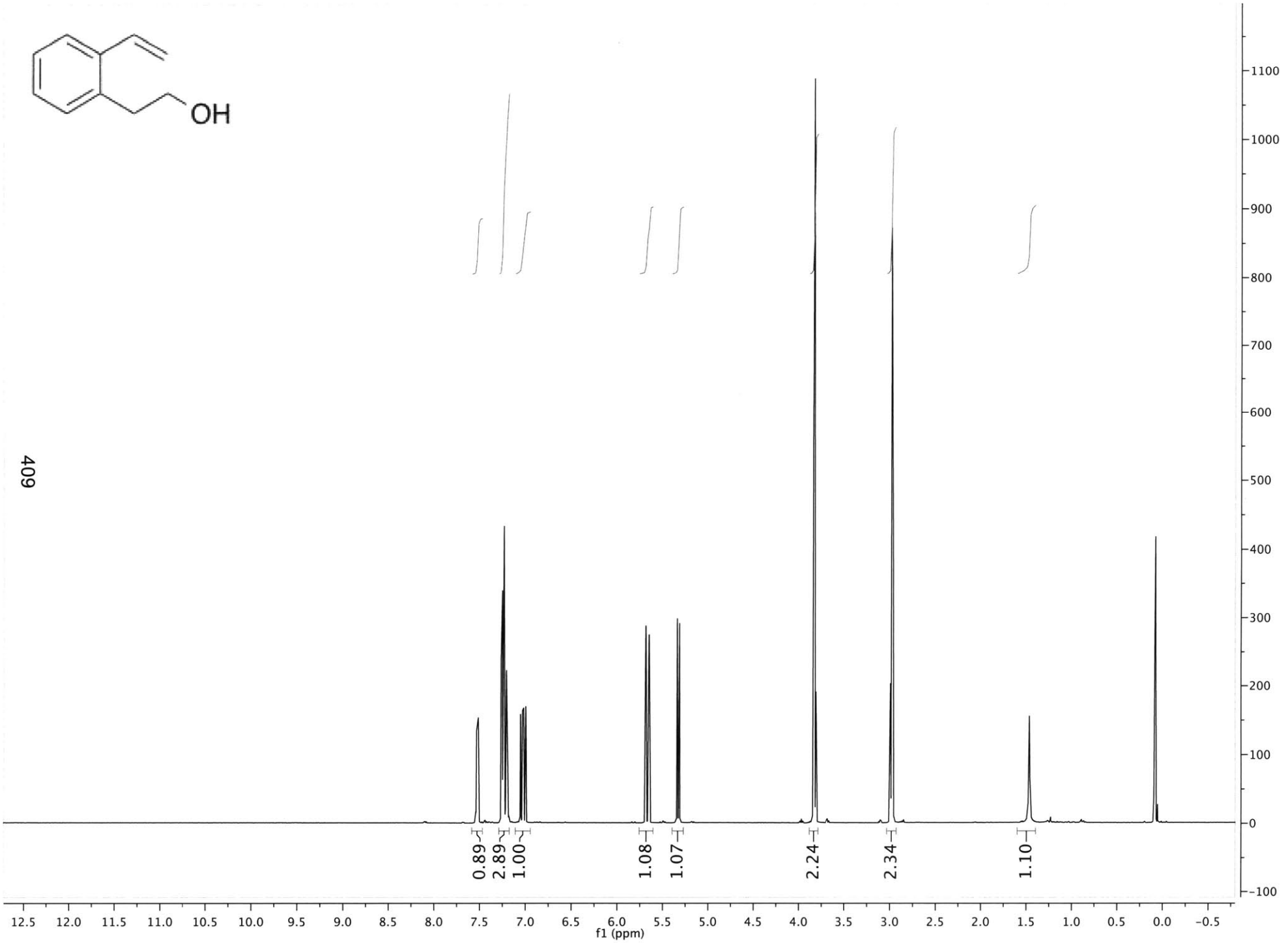

Br
OTBS
140.54
132.23
128.37
127.75
127.54
121.23
64.83
26.19
18.65
-5.09
404
f1 (ppm)

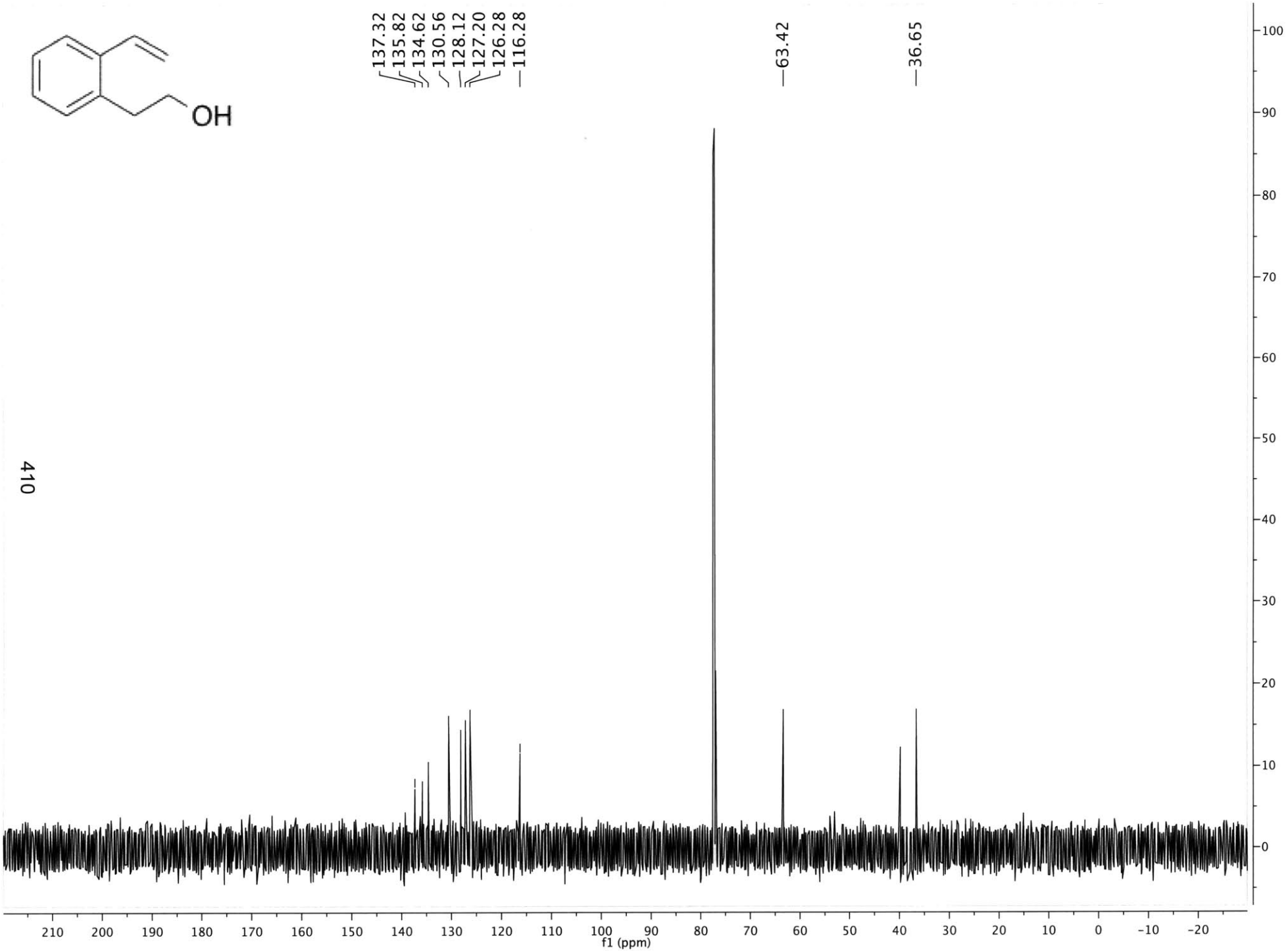

nPr
OH
405
1.00
1.06
2.08
0.87
0.92
2.33
2.00
0.95
2.01
3.19
f1 (ppm)

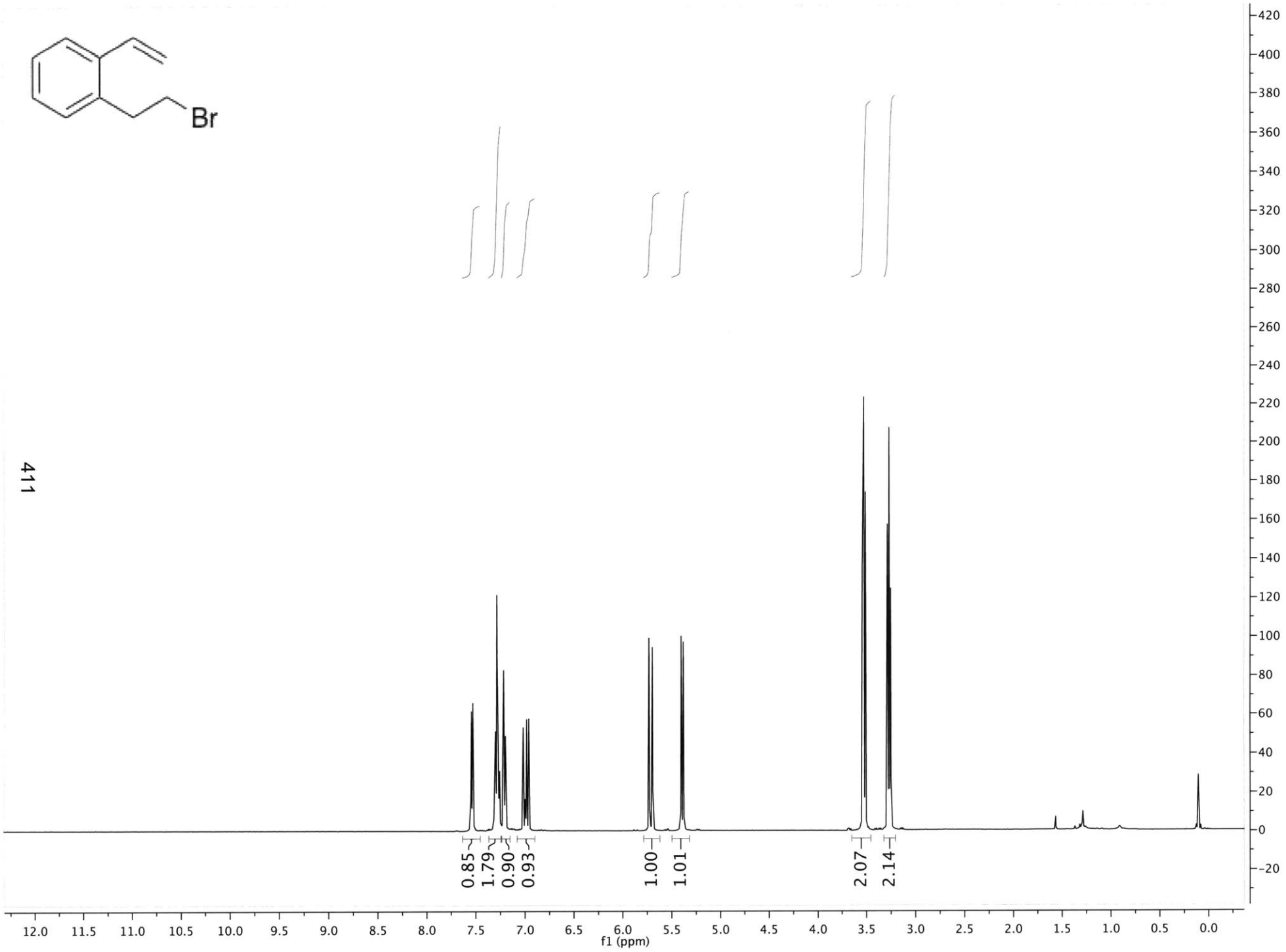

nPr
OH
137.28
137.08
134.09
128.48
128.31
127.24
126.76
126.30
63.73
35.65
22.81
14.00
406
f1 (ppm)

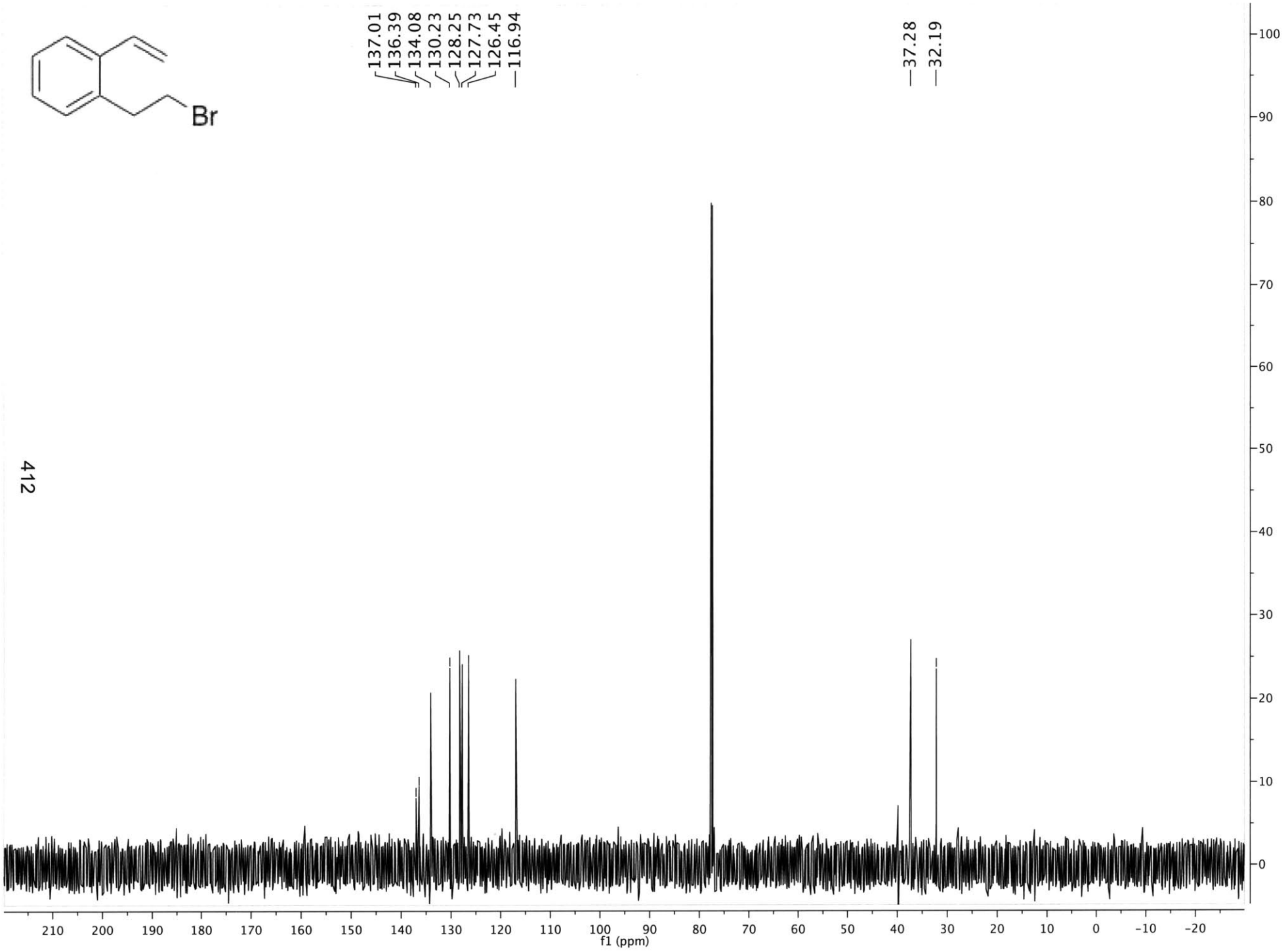

nPr
OH
407
1.00
1.06
2.08
0.87
0.92
2.33
2.00
0.95
2.01
3.19
f1 (ppm)

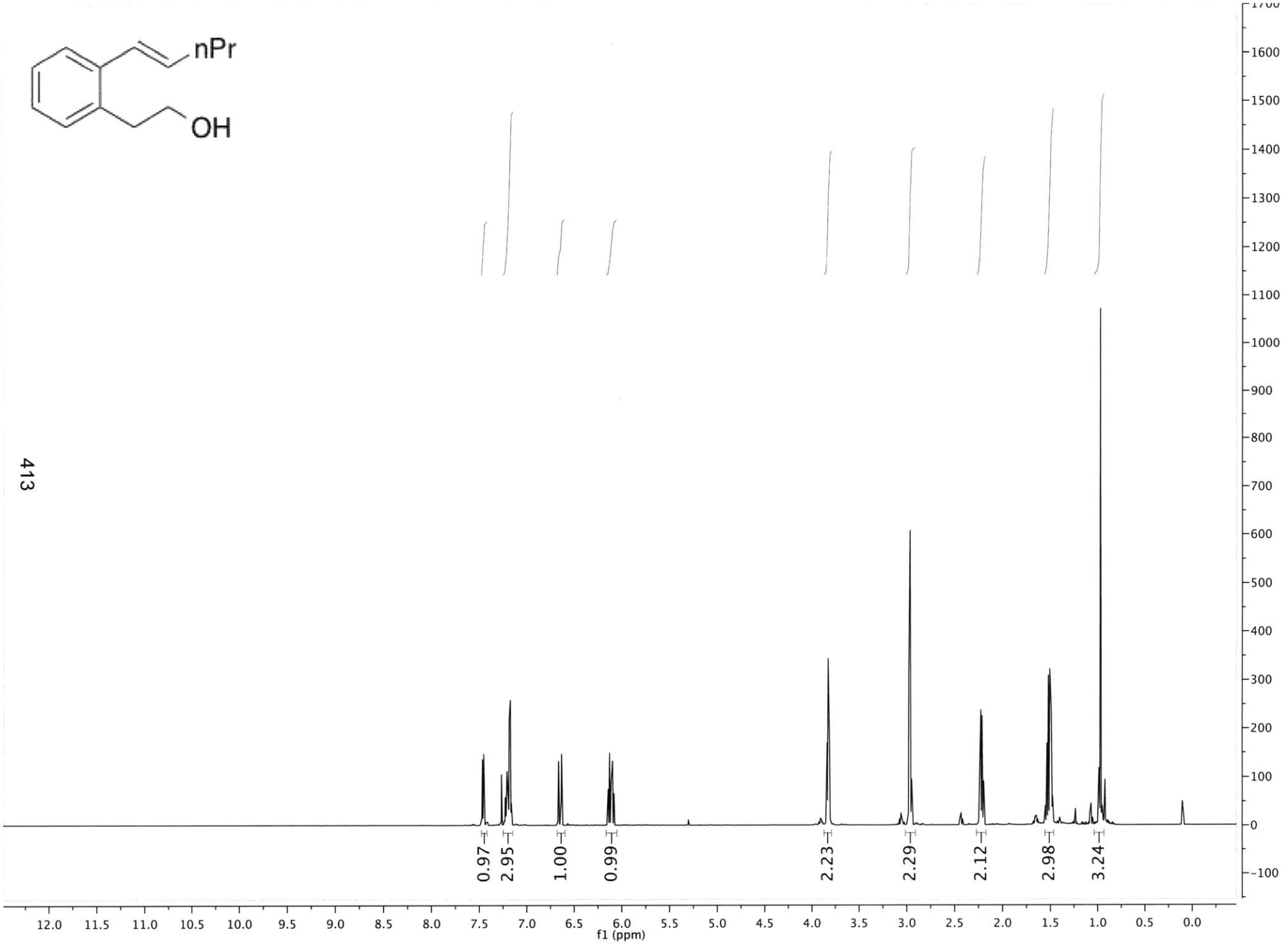

nPr
OH
137.28
137.08
134.09
128.48
128.31
127.24
126.76
126.30
63.73
35.65
22.81
14.00
408
f1 (ppm)

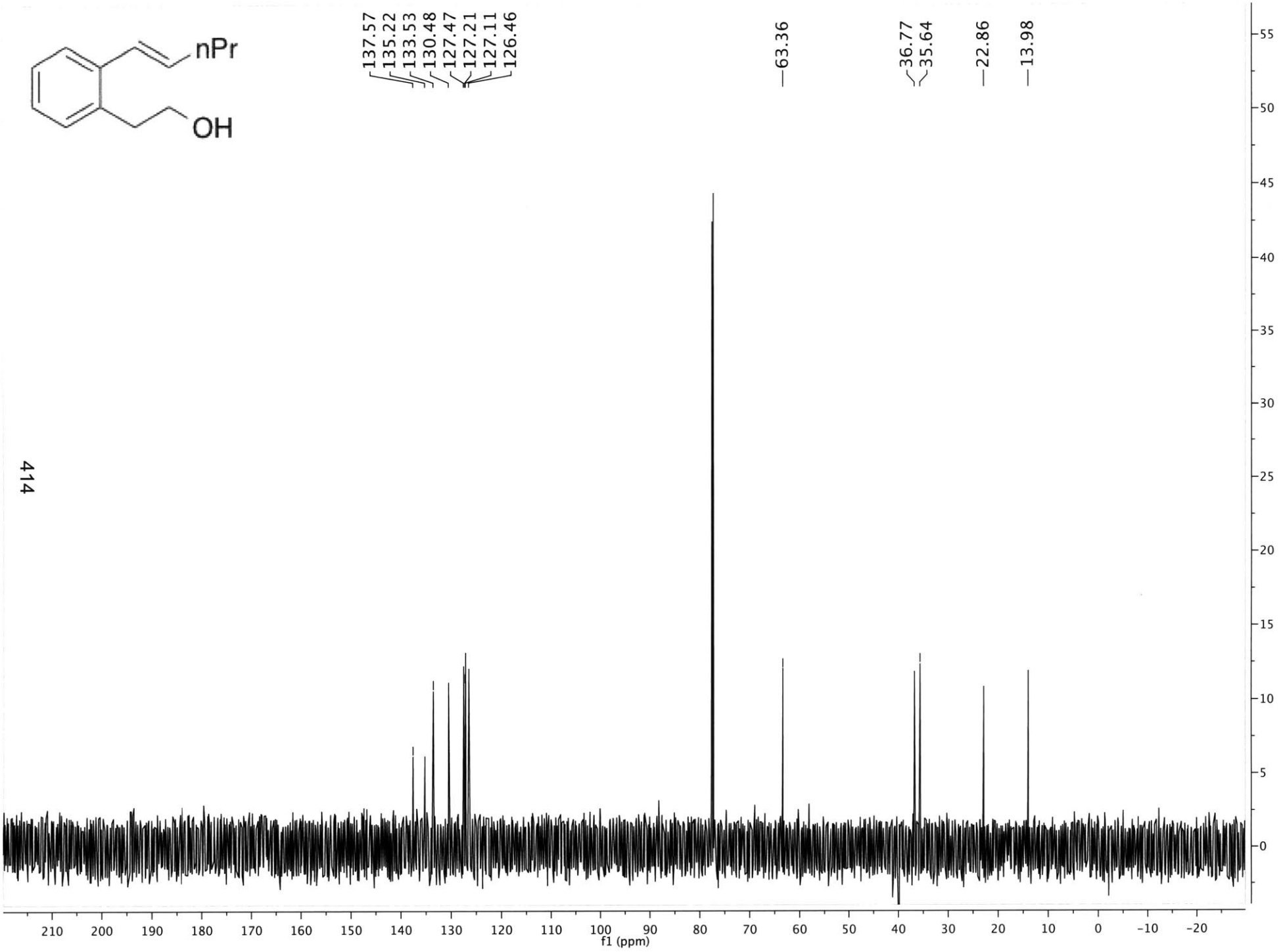

OH
409
0.89
2.89
1.00
1.08
1.07
2.24
2.34
1.10
f1 (ppm)

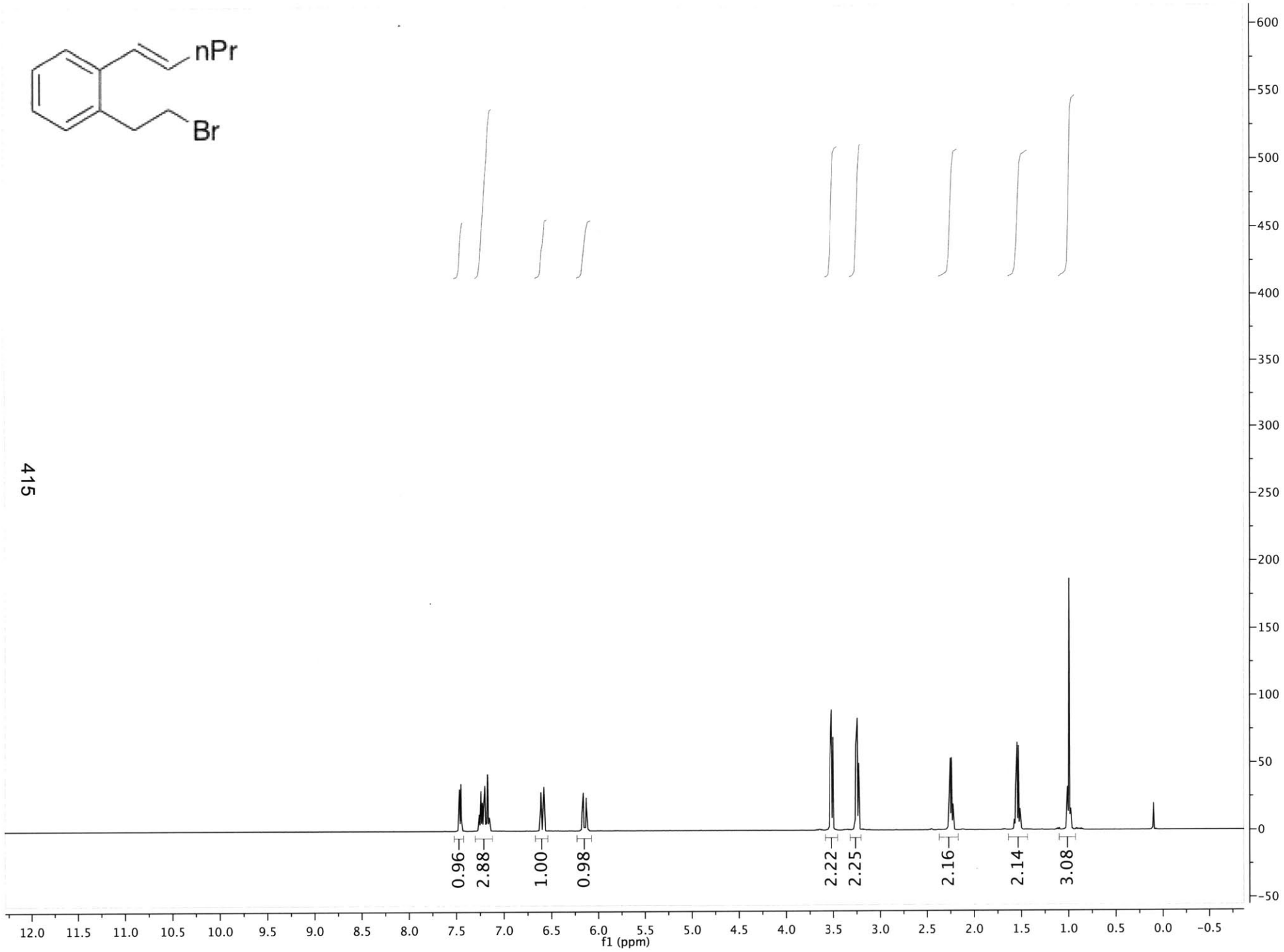

OH
137.32
135.82
134.62
130.56
128.12
127.20
126.28
116.28
63.42
36.65
410
f1 (ppm)

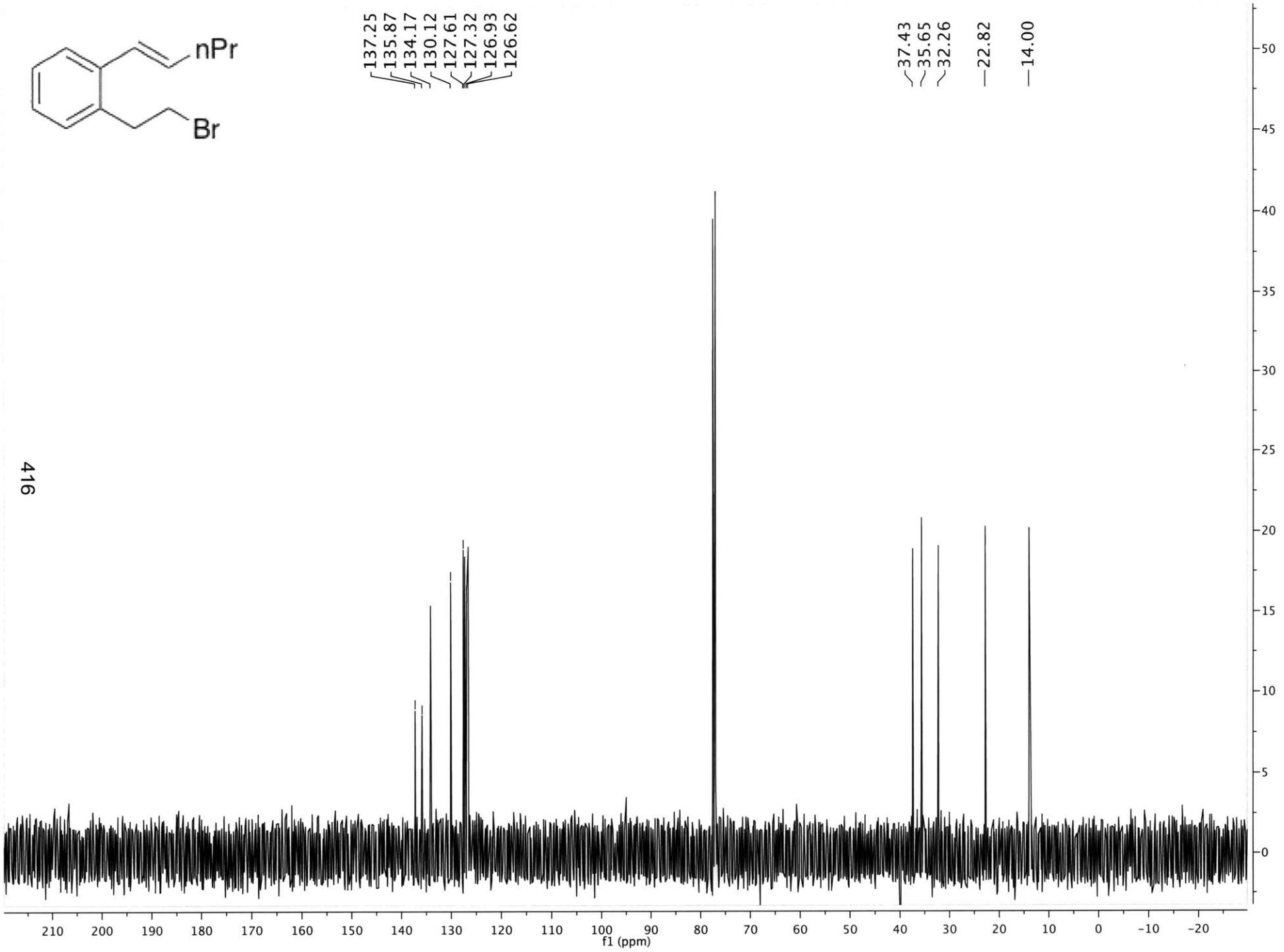

Br
411
0.85
1.79
0.90
0.93
1.00
1.01
2.07
2.14
f1 (ppm)

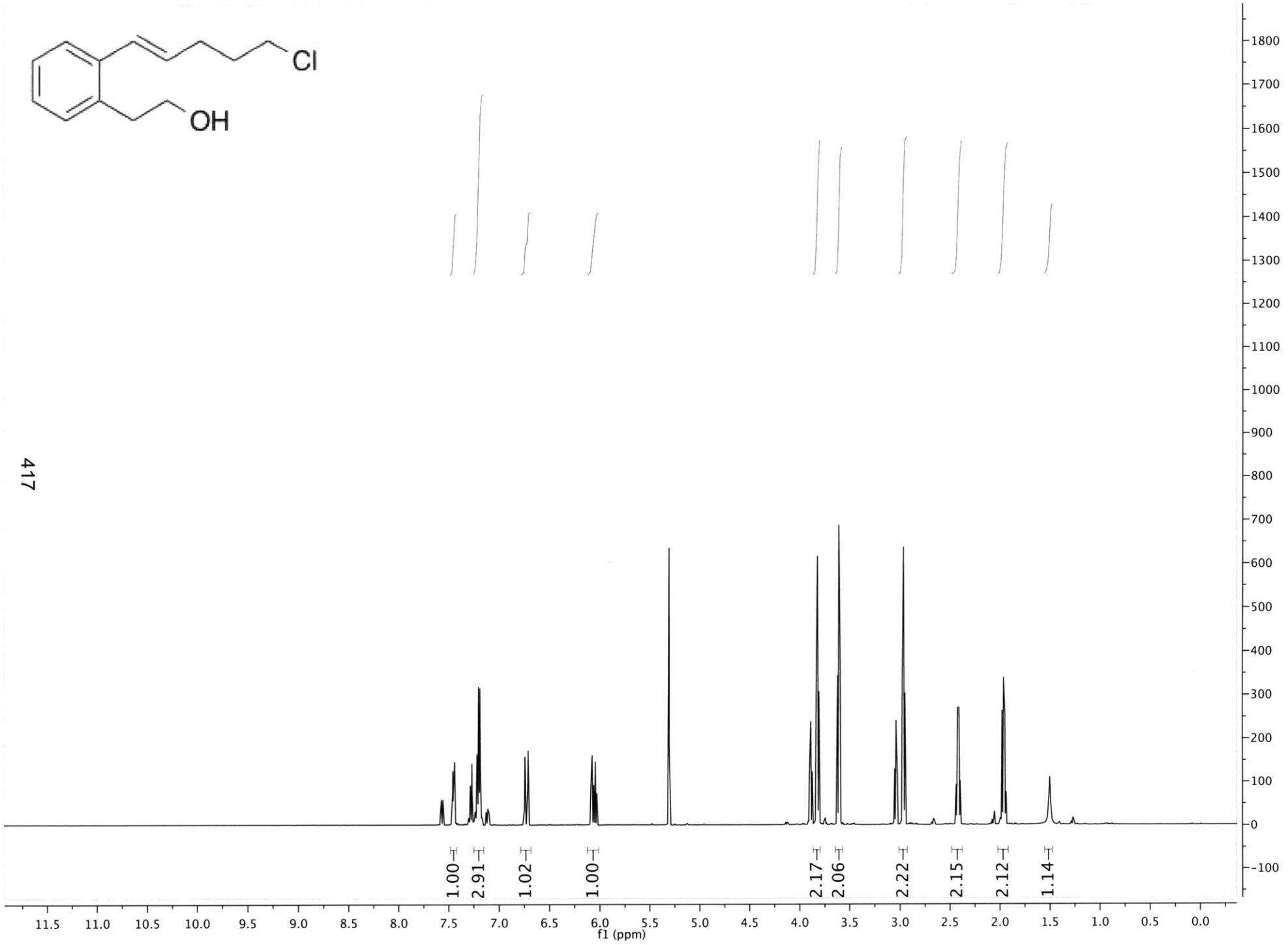

Br
137.01
136.39
134.08
130.23
128.25
127.73
126.45
116.94
37.28
32.19
412
f1 (ppm)

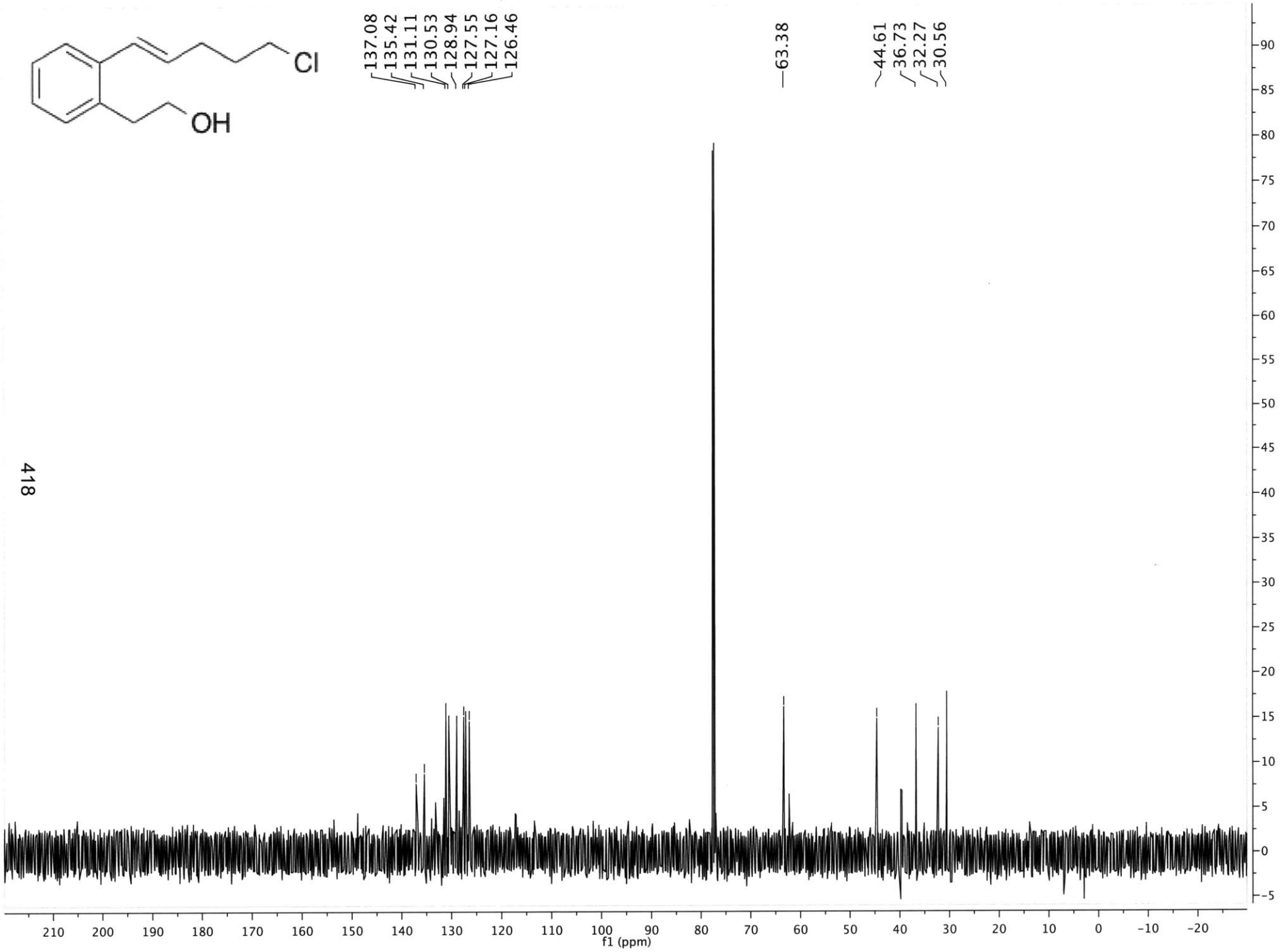

nPr
OH
413
0.97
2.95
1.00
0.99
2.23
2.29
2.12
2.98
3.24
f1 (ppm)

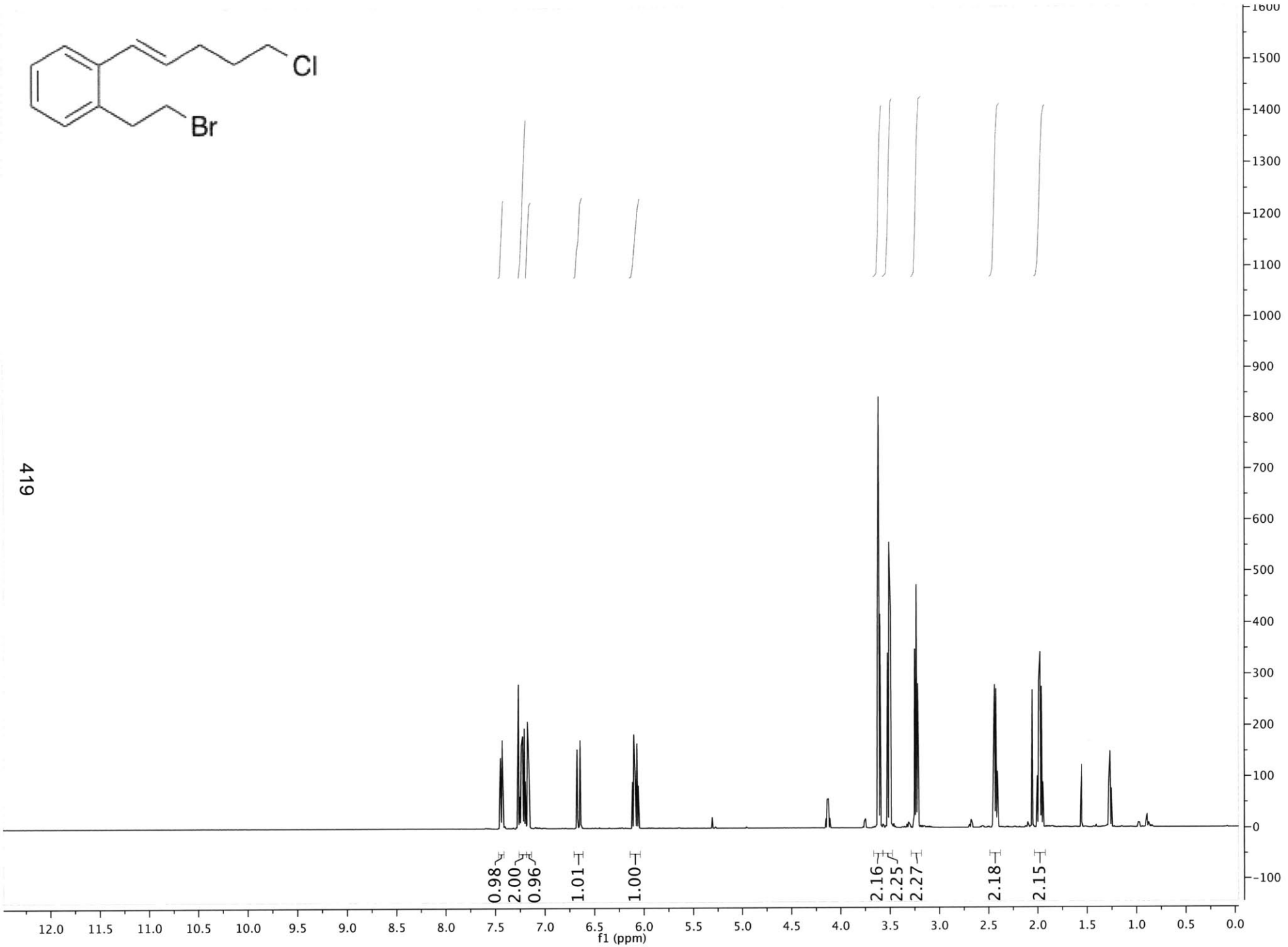

nPr
OH
137.57
135.22
133.53
130.48
127.47
127.21
127.11
126.46
63.36
36.77
35.64
22.86
13.98
414
f1 (ppm)

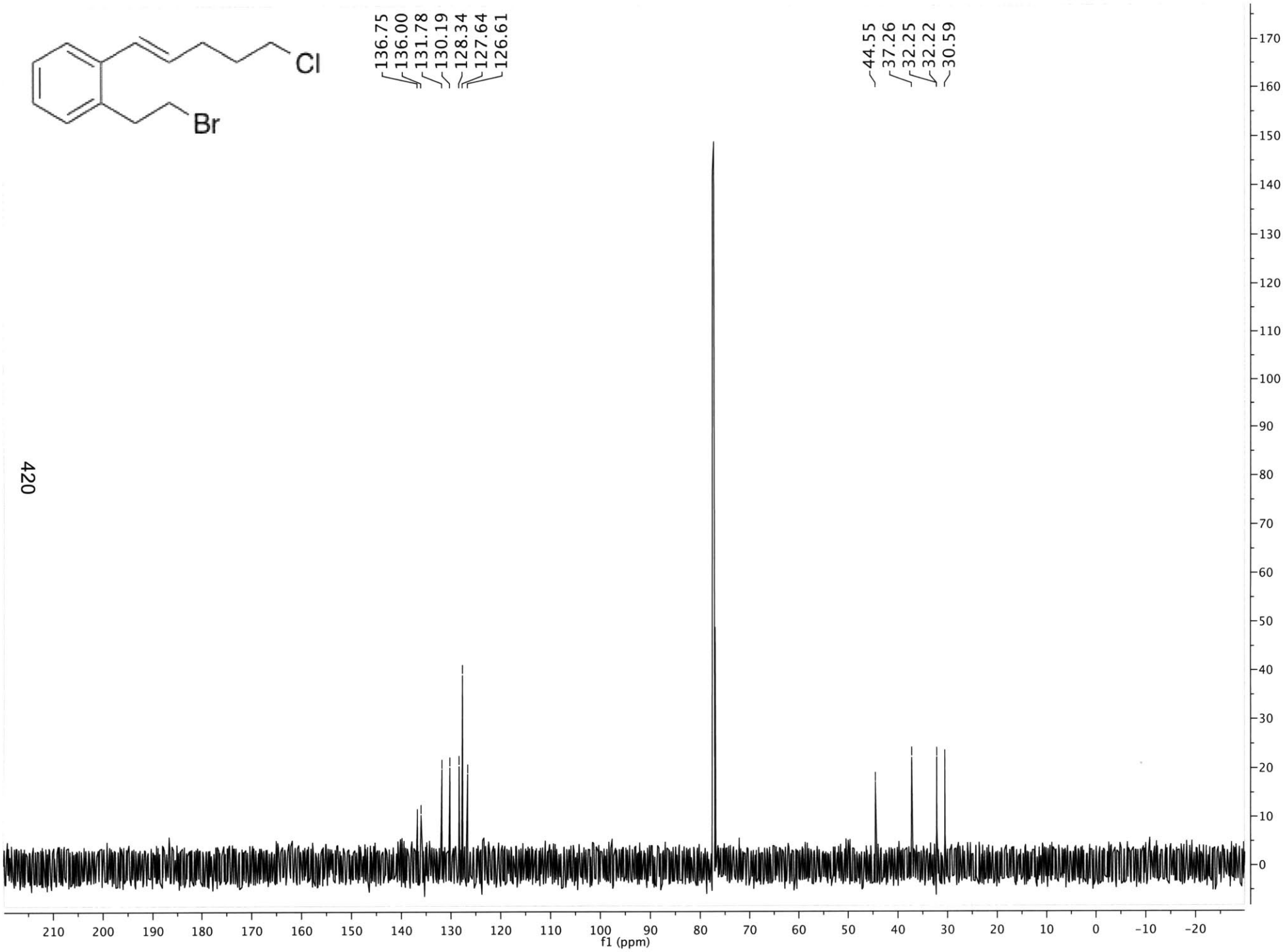

nPr
Br
415
0.96
2.88
1.00
0.98
2.22
2.25
2.16
2.14
3.08
f1 (ppm)

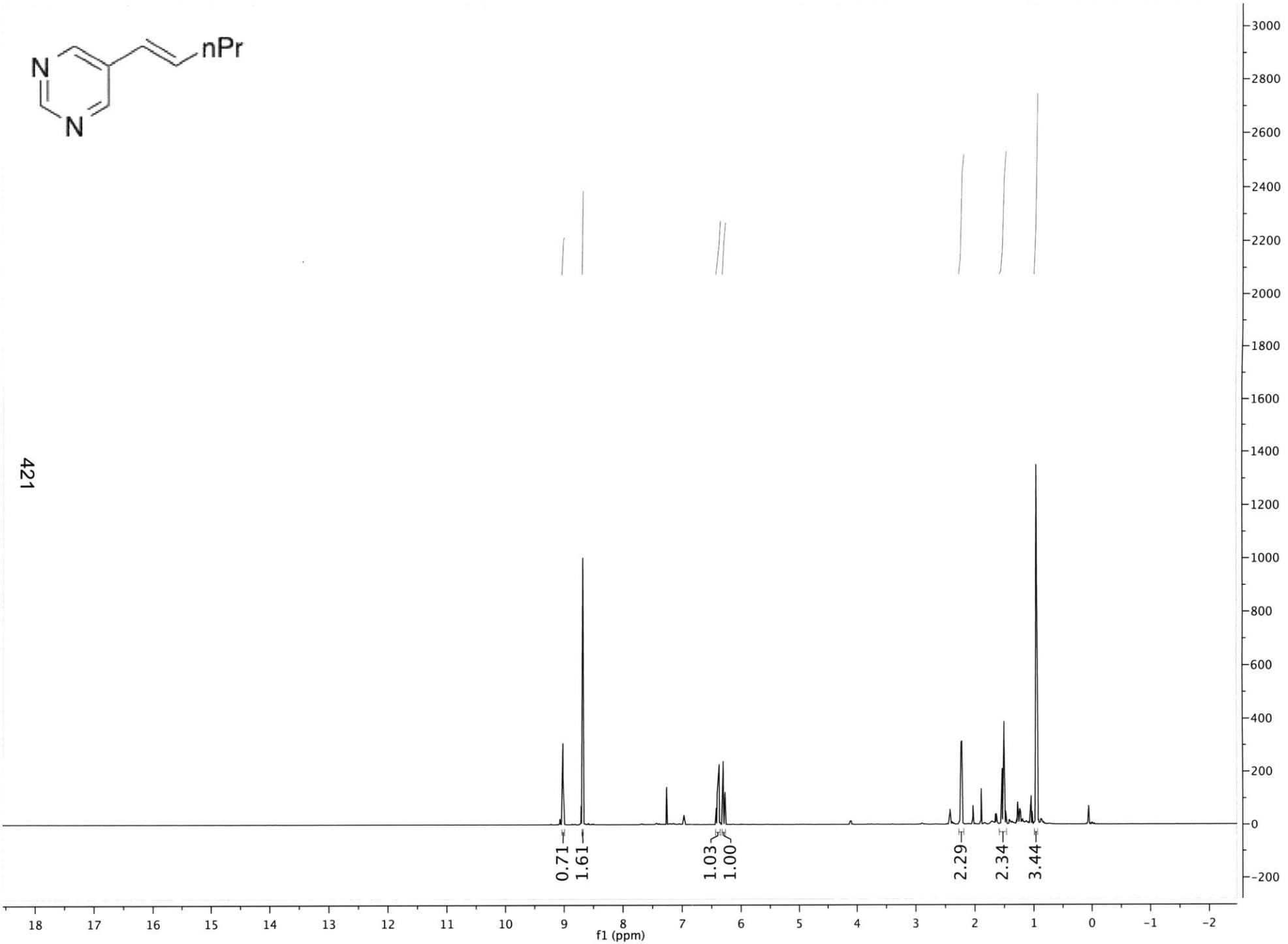

nPr
Br
137.25
135.87
134.17
130.12
127.61
127.32
126.93
126.62
37.43
35.65
32.26
22.82
14.00
416
f1 (ppm)

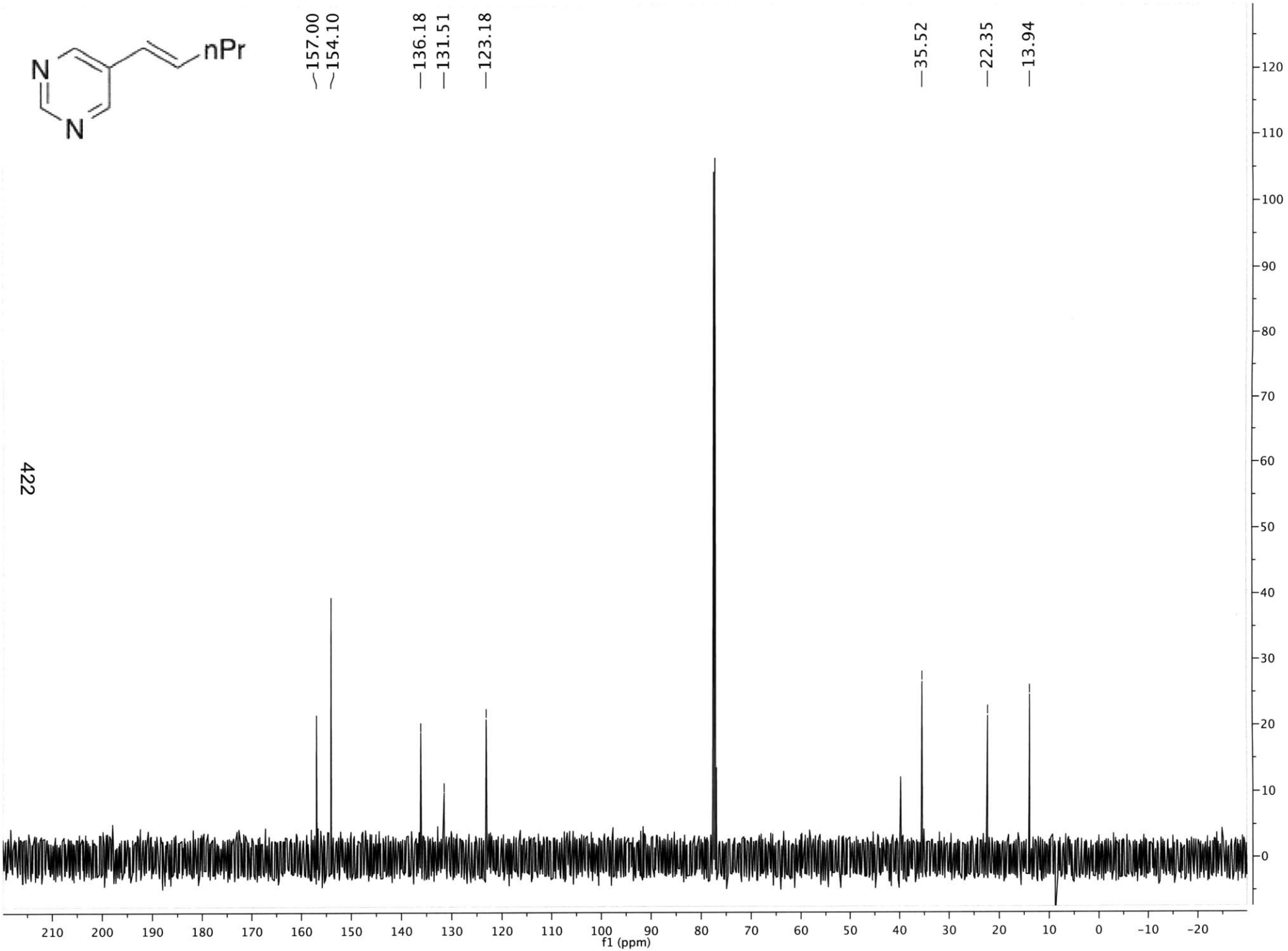

Cl
OH
417
1.00
2.91
1.02
1.00
2.17
2.06
2.22
2.15
2.12
1.14
f1 (ppm)

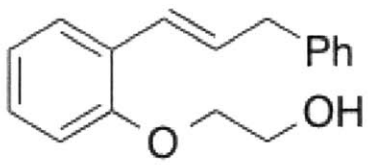

Cl
OH
137.08
135.42
131.11
130.53
128.94
127.55
127.16
126.46
63.38
44.61
36.73
32.27
30.56
418
f1 (ppm)


Cl
Br
419
0.98
2.00
0.96
1.01
1.00
2.16
2.25
2.27
2.18
2.15
f1 (ppm)


Cl
Br
136.75
136.00
131.78
130.19
128.34
127.64
126.61
44.55
37.26
32.25
32.22
30.59
420
f1 (ppm)


nPr
N
N
421
0.71
1.61
1.03
1.00
2.29
2.34
3.44
f1 (ppm)

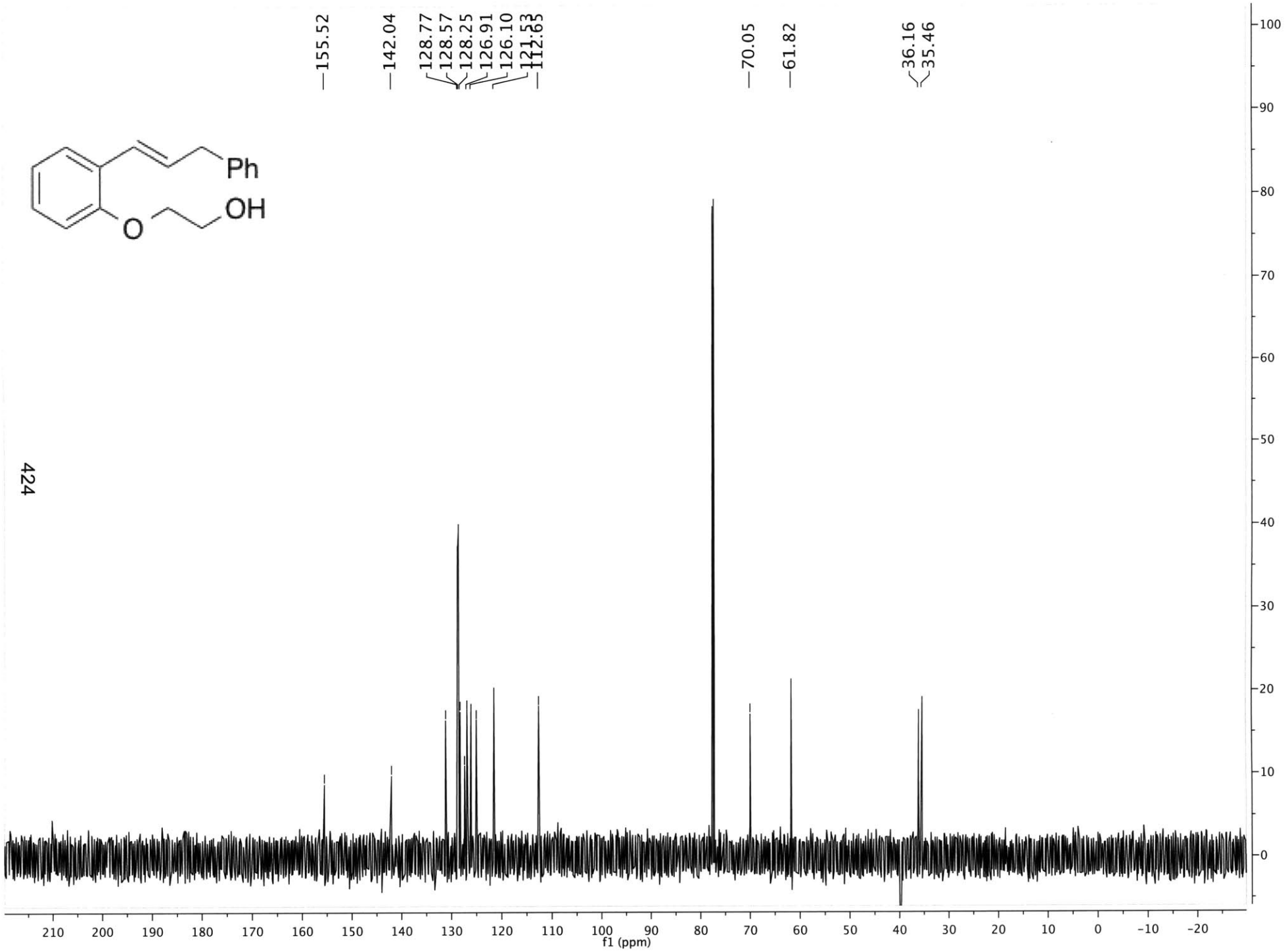

nPr
N
N
157.00
154.10
136.18
131.51
123.18
35.52
22.35
13.94
422
f1 (ppm)

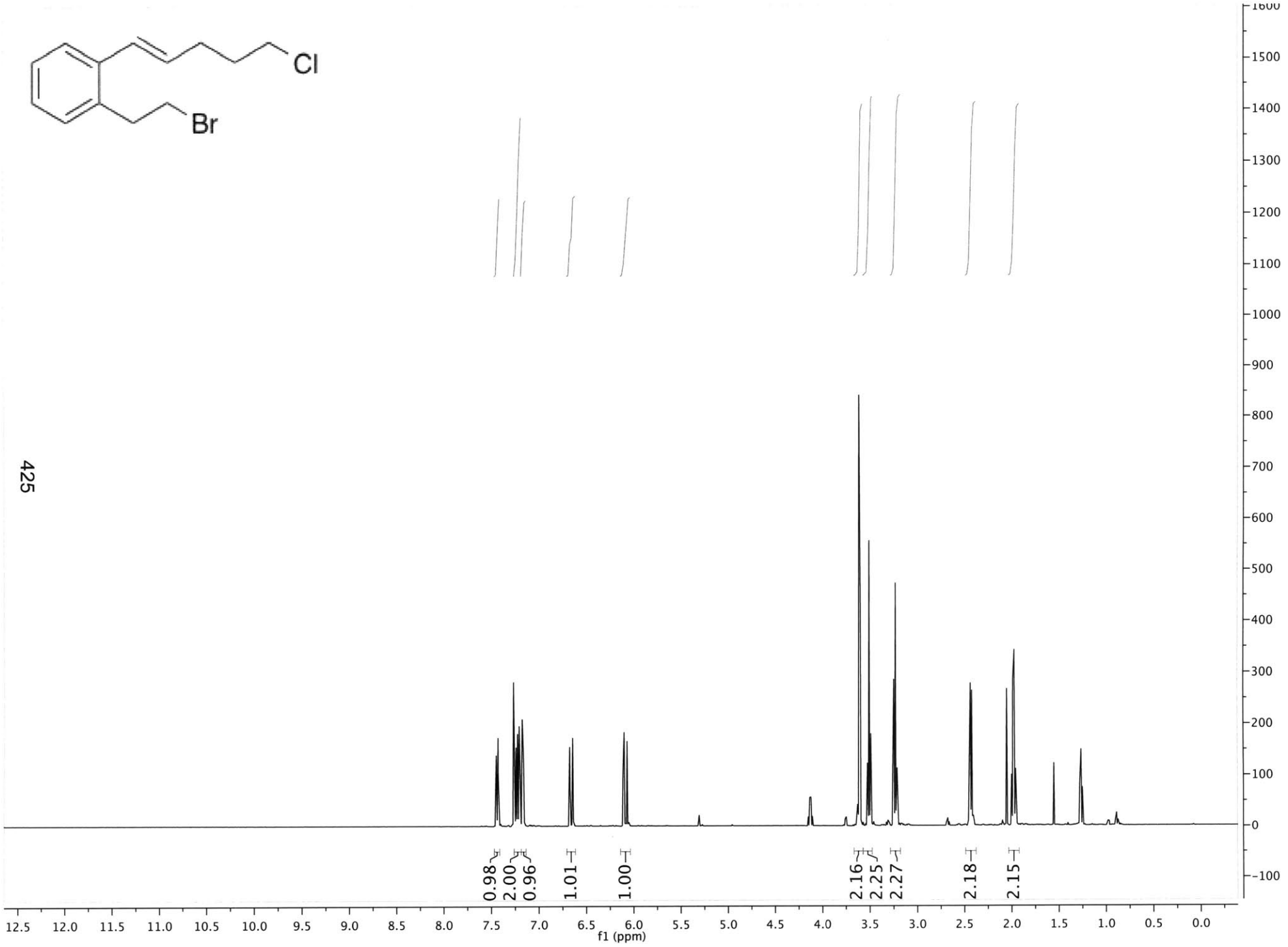


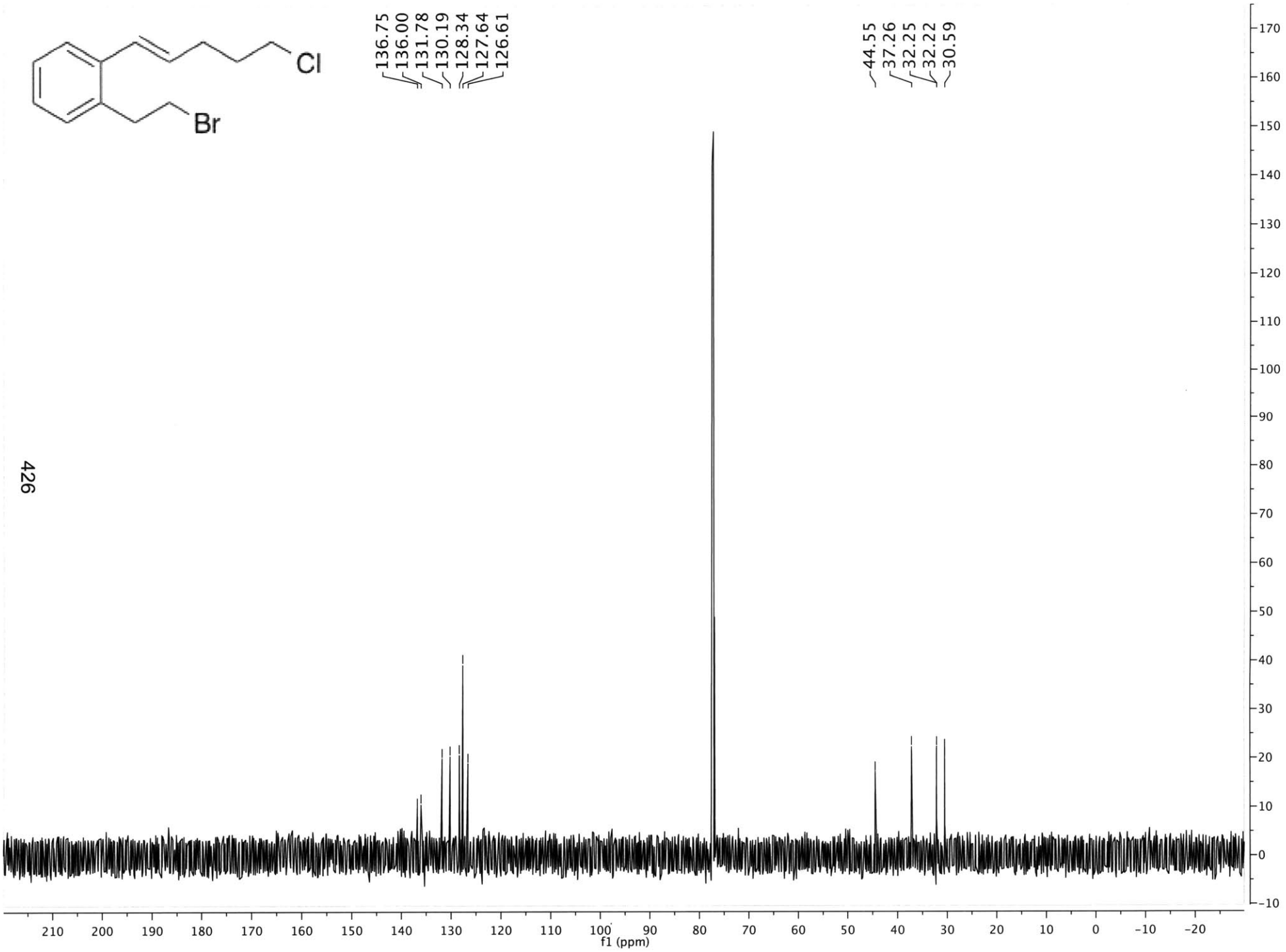
423

1.12
2.00
4.22
1.12
1.14
1.05
1.15
2.39
2.39
2.39
2.49
0.94

f1 (ppm)


155.52
142.04
128.77
128.57
128.25
126.91
126.10
121.53
112.83
70.05
61.82
36.16
35.46
Ph
OH
O
424
f1 (ppm)


Cl
Br
425
0.98
2.00
0.96
1.01
1.00
2.16
2.25
2.27
2.18
2.15
f1 (ppm)


Cl
Br
136.75
136.00
131.78
130.19
128.34
127.64
126.61
44.55
37.26
32.25
32.22
30.59
426
f1 (ppm)

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