OVERCOMING REGIOSELECTIVITY CHALLENGES IN IRIDIUM CATALYZED C–H BORYLATION VIA NONCOVALENT INTERACTIONS AND ADVANCES ON CROSS COUPLING REACTIONS OF ARYL IMIDAZOLYLSULFONATES

By

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ABSTRACT

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Direct functionalization of C–H bonds reduces the number of synthetic steps for a target molecule enhancing efficiency and avoiding undesired waste material. Iridium catalyzed C–H activation-borylation (CHB) is an established method to access aryl boronic esters. Regioselectivity challenges can arise when multiple hydrogens are present in the molecule. This thesis describes the design of novel strategies to selective direct the CHB to one specific position.

Ortho selective CHB has the challenge to go against the traditional CHB selectivity dictated by steric effects. Previously, our group reported a strategy for highly *ortho*-selective CHB of anilines by using a small B_2eg_2 (eg = ethanediol) as the borylating reagent. However, the products were unstable and transesterification with pinacol was needed. Chapter 2 builds upon this issue and presents a solution based on the modulation of the size of the boron partner. Small diboron partners retain the high *ortho* regioselectivity for CHB of aniline but larger borylating reagents generate more stable products. In our estimation, B_2bg_2 (bg = 1,2-butanediol) represents the best balance of reactivity, regioselectivity and stability.

Remote functionalization including *para* selective reactions are difficult because a potential directing group would be far from the desired reactive site. Chapter 3 details how *para* CHB of tetraalkylammonium sulfates and sulfamates have been achieved using bipyridine-ligated Ir boryl catalysts. Selectivities can be modulated by both the length of the alkyl groups in the tetraalkylammonium cations and the substituents on the bipyridine ligands. Ion pairing, where the

alkyl groups of the cation shield the *meta* C−H bonds in the counteranions, is proposed to account for *para* selectivity. The 4,4'-dimethoxy-2,2'-bipyridine ligand gave superior selectivities.

The next chapter describes how intramolecular hydrogen bonding (IMHB) can lead to steric shielding effects that can direct CHB regiochemistry. Bpin/arene IMHB can promote remote borylations of N-borylated anilines, 2-amino-N-alkylpyridine, tetrahydroquinolines, indoles and 1-borylated naphthalenes. Our studies support molecular geometries with the Bpin orientation controlled by a C–H•••O IMHB. Calculated rotation barriers to displace the Bpin group are above 4 kcal/mol, suggesting that the planar ground conformation of the borylated arenes is retained during CHB. This study informs researchers to evaluate not only inter- but also intramolecular noncovalent interactions as potential drivers of remote CHB regioselectivity.

The borylated products from CHB can be further manipulated in Suzuki-Miyaura cross-coupling (SMC) with aryl halides as the typical electrophilic partner. Aryl imidazolylsulfonates are nongenotoxic electrophiles that can be used in palladium catalyzed SMC to avoid halogenated materials. Chapter 5 shows the efforts towards a nickel-catalyzed SMC of aryl imidazolyl-sulfonates. Results show considerable amounts of the corresponding diarylsulfate formed during the reaction. Interestingly, the diaryl sulfa byproducts were found to be competent electrophilic partners for both palladium and nickel-catalyzed SMC.

In summary, this thesis presents novel methodologies to access challenging transformations as the *para* borylations of phenols, anilines and benzyl alcohols. This was possible by the analysis of the different components of the catalytic system: design of ligands, diboron partners and substrate directing groups and how they interact during the reaction. Finally, the potential of aryl imidazolylsulfonates as nongenotoxic pseudohalides in nickel-catalyzed SMC was evaluated.

To my family.
Thanks for your patience and continued support.

ACKNOWLEDGMENTS

I decided to write this section at the end, because I knew it will be the most difficult part to write. How do you summarize and describe in some words the impact that family, friends, and mentors have in your life? I believe the PhD journey is not only about gaining knowledge, but also about personal and professional growth. I will try my best in the next paragraphs to say thank you and express my gratitude.

I need to recognize that I began the PhD with more questions than certainties. I knew that my passion was in Organic Chemistry, but I was not sure where did I want to go or who I want to be. I can't find another word other than luck to describe the fortune to meet and work with you Professor Robert Edward Maleczka, Jr. I learned what it means to be a mentor when I met you. With your guidance and your example, I found again my motivation and realized how fun research can be. The freedom you gave me to pursuit the projects I wanted and your support that allowed me to be involved in programs outside chemistry helped find the pathway I want to follow in my future. The impact you had in my life is impossible to describe in words; the least I can say is that I will be forever thankful with you.

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courses you taught me and towards these years. Your comments truly helped me become a better chemist.

During a Chemistry PhD, the lab becomes your second home and your labmates your second family. In this family, my older brother would be the now Professor Jonathan E. Dannatt, your guidance and our everyday discussions about chemistry truly taught me how to conduct research. Thank you for your friendship and mentorship towards me which are unvaluable. To my friends and exlabmates Dr. Ruwi Jayasundara and Dr. Suzi Miller, thank you for making everyday more enjoyable and for being such wonderful partners in the projects we collaborate later on. To my labmates, collaborators and friends: Thomas Oleskey, Arzoo Chhabra, Feng Yilong (Deuca) and Lauren Kotsull, I really enjoyed working with you guys and I learned a lot from everyone, sorry if I was a little bossy sometimes. I am sure you will become great chemists and I am excited to listen about your new discoveries in the future. Also, I would like to thank Thomas for the late "coffee" drinks he prepared when we needed to spend long days at the lab. To Emmanuel Maloba, you become a close friend to me, and I hope you know I will be there for you if you need me as you were there for me during these years. To Dr. Badru-Deen Barry, Dr. Fangyi Shen, Austin King, our adopted labmembers: Anshu Yadav and Aditya Patil, and the boron group: Alex O'Connell, Chris Peruzzi, Pauline Mansour and Cash Jowers, it has been an honor to work with you guys and I wish you all the best in your future endeavors.

Life has ups and downs and friends that help you navigate in the difficult moments and celebrate the good ones are unreplaceable. Each of you guys: Dr. Katarina Lynn Keel, Dr. Peng Chao, Dr. Shafaat Shishir, Dr. Dhwani Kansal and future doctors Seokjoo Lee and Kiyoto Aramis Tanemura, have been wonderful friends during grad school and the time I shared with you will be always in my heart. A special thanks to Kat for her support during the most difficult PhD moments.

To my siblings from another parents: Ana Belen Gutierrez, Antonio Prada, Ruben Villareal and Andrea Broncano, even if we are far away in different countries, our friendship has perdure and I owe you part of this PhD to you guys. A special thanks to my brother Dr. Emiliano Deustua, there are not enough words to express my gratitude to you, you become family to me during these years and I hope someday I can give you back at least 1% of what you have done for me, thank you. I have been blessed to find a great group of close friends here in Michigan and this journey would not be the same without you guys: Carolina Vargas, Carol Morales, Kimberly Morales, Cristina Castillo, Jorge Anaya, Dr. Marco Lopez, Marcela Tabares, Dr. Fernando Aguate, Maria Pia Garcia, Paulo Izquierdo, Viviana Ortiz, Andres Galindo, Dr. James Cabrera and my homie Emilie Cole.

The main reason I was able to finish this journey is because of the support of my family which deserved my biggest thanks. I would like to write this paragraph in Spanish to thank them. Mama, Maria Rosario Bastidas Quispe, nosotros sabemos lo difícil que han sido estos años desde Olaya, no tengo palabras para agradecerle todo el amor y el apoyo que me ha dado. Este doctorado se lo dedico a usted, espero que este título me ayude a regresarle una parte de lo que usted ha hecho por mí. Papa y hermanita: Claudio Montero Mullo y Liz Paola Montero Bastidas (Oshin) gracias también a ustedes por el amor, el apoyo y la paciencia pues sé que este camino del doctorado ha tomado tiempo, pero finalmente llegamos a esta meta.

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KEY TO ABREVIATIONS

°C	Celsius degrees
δ	chemical shift
λ	wavelength
Aq	aqueous
B_2pin_2	Bis(pinacolato)diboron
BCP	Bond Critical Point
Boc	tert-butyloxycarbonyl
bs	broad single peak in NMR spectrum
CHB	C–H activation/borylation
CHS	C–H activation/silylation
cod	1,5-cyclooctadiene
d	double peak in NMR spectrum
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DFT	Density Functional Theory
DG	directing group
DMAP	4-Dimethylaminopyridine
DMF	dimethylformamide
DoM	directed ortho metalation
dtbpy	4,4’diterbutyl-2,2’-bipyridine
EAS	electrophilic aromatic substitution
EI	Electron ionization

eg	ethylene glycol
equiv	equivalents
ESI	Electrospray ionization
GC-MS	Gas Chromatography-Mass Spectrometry
h	hours
HBpin	4,4,5,5-Tetramethyl-1,3,2-dioxaborolane
HRMS	High resolution Mass Spectrometry
IMHB	Intramolecular Hydrogen Bonding
J	coupling constant
kcal	kilocalories
M	molar
MHz	Megahertz
min	minutes
mL	milliliters
mol	moles
mol %	mole percentage
mp	melting point
n-Pr	*n*-propyl
n-Bu	*n*-butyl
NBS	N-bromosuccinimide
nm	nanometers
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect

ppm	parts per million
q	quartet peak in NMR spectrum
Q-TOF	quadrupole time-of-flight
QTAIM	Quantum Theory of Atoms in Molecules
rt	room temperature
s	seconds
s	single peak in NMR spectrum
SMC	Suzuki-Miyaura cross-coupling
t	triplet peak in NMR spectrum
TBAF	Tetra-n-butylammonium fluoride
TBHP	tert-Butyl hydroperoxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	Triisopropyl silane
tmphen	tetramethylphenanthroline
μL	microliters
W	watts
wt.	by weight

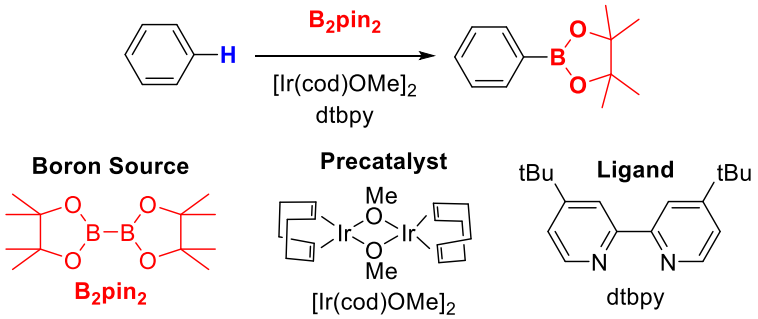
CHAPTER 1.

INTRODUCTION

1.1. Iridium-Catalyzed C–H Borylations

As organic chemists, we look to create tools that can mold one molecule into another that is completely new. Nowadays, the chemistry world seeks economical syntheses and tools that convert widely available compounds to others not as abundant. The key piece of this puzzle would be an easily installed group with the versatility to be replaced by a diverse array of other functionalities. C–H activation/borylation reactions (CHB) are a robust method to break ubiquitous C–H bonds and place a boronic ester in place of the hydrogen (**Scheme 1.1**). Due to the p empty orbital of boron and the possibility of the C–B bond to be involved in transmetalation steps, aryl boronic esters are precursors to C–C and different C–Heteroatom bonds.

Scheme 1.1: Iridium catalyzed CHB

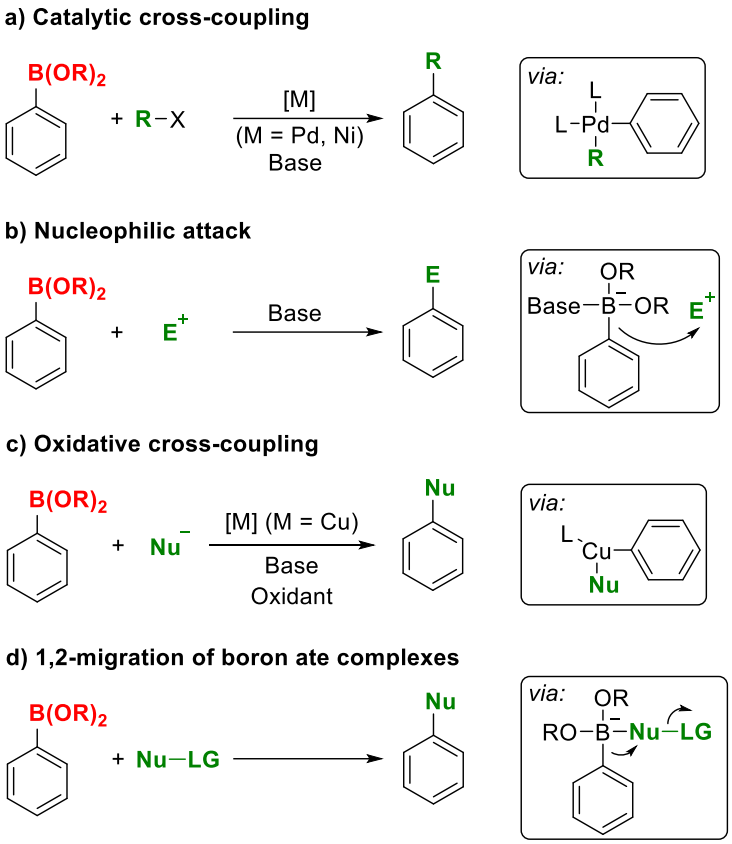


1.2. Diversification of Aryl Boronic Esters

Catalytic cross-coupling, nucleophilic attack to an electrophile, oxidative cross-coupling, and 1,2-migration of boron ate complexes are among the more common processes aryl boronic esters undergo (**Scheme 1.2**).[1,2] Akira Suzuki shared the 2010 Novel Prize for the development of a cross-coupling reaction of aryl boronic esters with aryl halides;[3] which based on a 2011 survey is the most common method used in pharma to create C–C bonds.[4] Other common reactions of

aryl boronic esters include Liebeskind-Srogl coupling with thioesters,[5] Petasis reaction with imines,[6–8] and Chan-Lam coupling with alcohols and amines.[9] Functionalization of aryl boronic acids and esters can be approached through more than one mechanism in some cases. For example, bromination can occur via nucleophilic attack to N-bromosuccinimide (NBS) or via copper catalyzed oxidative coupling with bromide salts like KBr.[2,10]

Scheme 1.2: Types of reactions of aryl boronic acids and esters

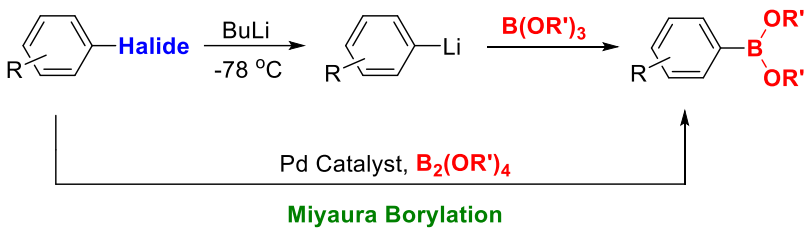


1.3. Traditional Synthesis of Aryl Boronic Esters

Owing to the attractive characteristics of aryl boronic esters, their synthesis has been a subject of research well before appearance of CHB. Traditional methods to access boronic esters includes transmetallation of the corresponding halide (**Scheme 1.3**) followed by addition of a trialkyl borate to afford the final product.[1] Miyaura developed a more directed route that involves

Pd-catalyzed coupling of an aryl halide with a base activated diboron or borane reagent. Although this method improves the step economy, the need for aryl halides can be limiting owing to substrate availability and/or other issues associated with aryl halides.

Scheme 1.3: Traditional methods for the synthesis of aryl boronic acids and esters



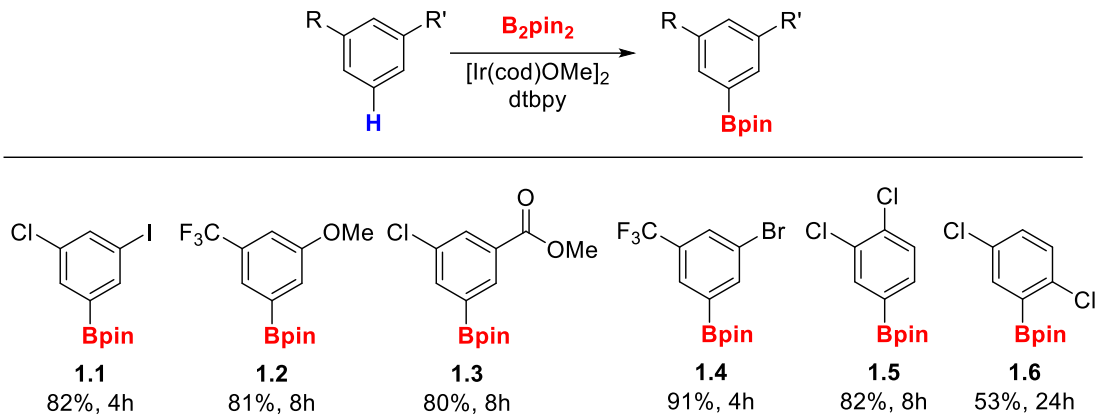
CHB is a way to generate aryl boronic esters without the need for a preinstalled halogen. Indeed, since the first thermal iridium catalyzed C-H borylation (CHB) of arenes was reported by the Smith group,[11] CHB has increasingly become the method of choice for the generation of aryl boronic esters. Its high functional group tolerance and the ability to tune the catalyst system for specific regioselectivities are among the attractive features of CHB. Nowadays, the standard procedure for CHB (**Scheme 1.1**) involves B_2pin_2 (pin = pinacolate) or HBpin as the boron partner, $[Ir(cod)OMe]_2$ (cod = 1,5-cyclooctadiene) as the precatalyst and 4,4′-di-tert-butyl-2,2′-dipyridyl (dtbpy) as the ligand.

1.4. CHB: Regioselectivity, Mechanism and Applications

CHB-regiochemistry is controlled by steric factors.[12,13] Substituents around the aromatic ring can block the access of the iridium catalyst to C–H bonds (**Scheme 1.4**). 1,3-Disubstiuted arenes will lead to the 5-selective borylated product selectively regardless of the electronics of the substituents as shown by the formation of **1.1**-**1.4** (**Scheme 1.4**).[14] The chlorine atoms in 1,2-dichlorobenzene block the 3 and 6 positions leaving the product **1.5** as the only isomer generated. The steric presence of a neighboring substituent can be overcome if no other C–H bond is available as shown by the successful (but sluggish) formation of **1.6**. **Scheme 1.4** highlights the functional

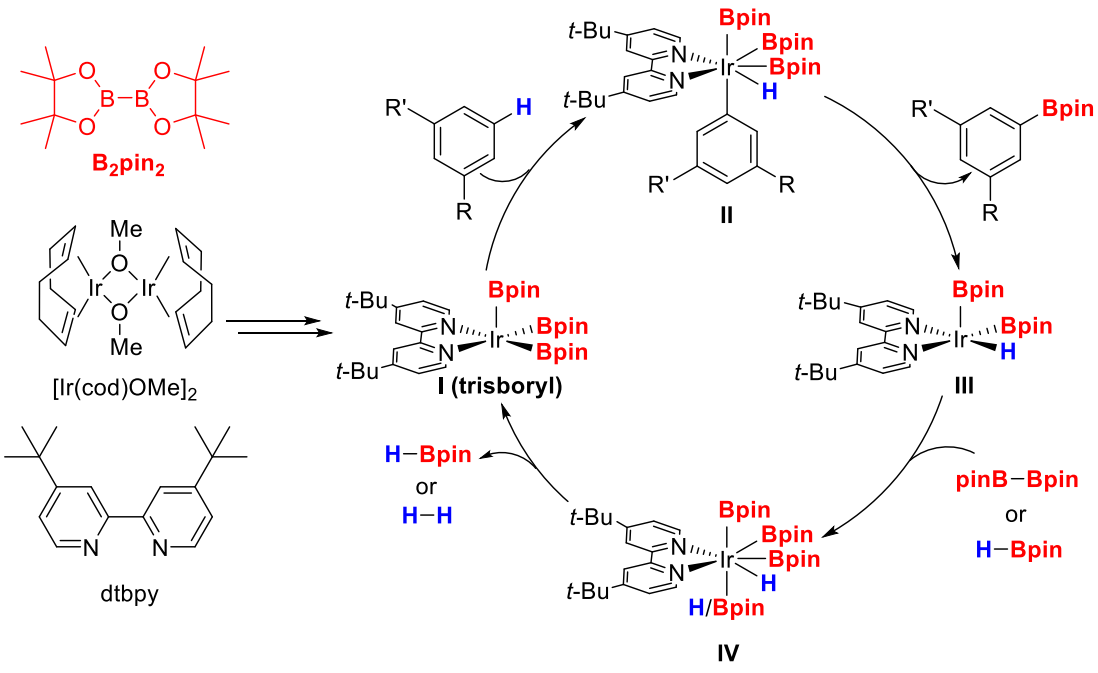
group tolerance of CHB; most strikingly, the tolerance of halogens contrasts with traditional cross coupling reactions catalyzed by metals like palladium.

Scheme 1.4: Sterically driven CHB regisoelectivity



As stated above, $[Ir(cod)OMe]_2$ or other viable Ir(I) reagents are precatalysts. Mechanistic studies support trisboryl Ir(III) **I** as the active form of the catalyst (**Scheme 1.5**).[15,16]

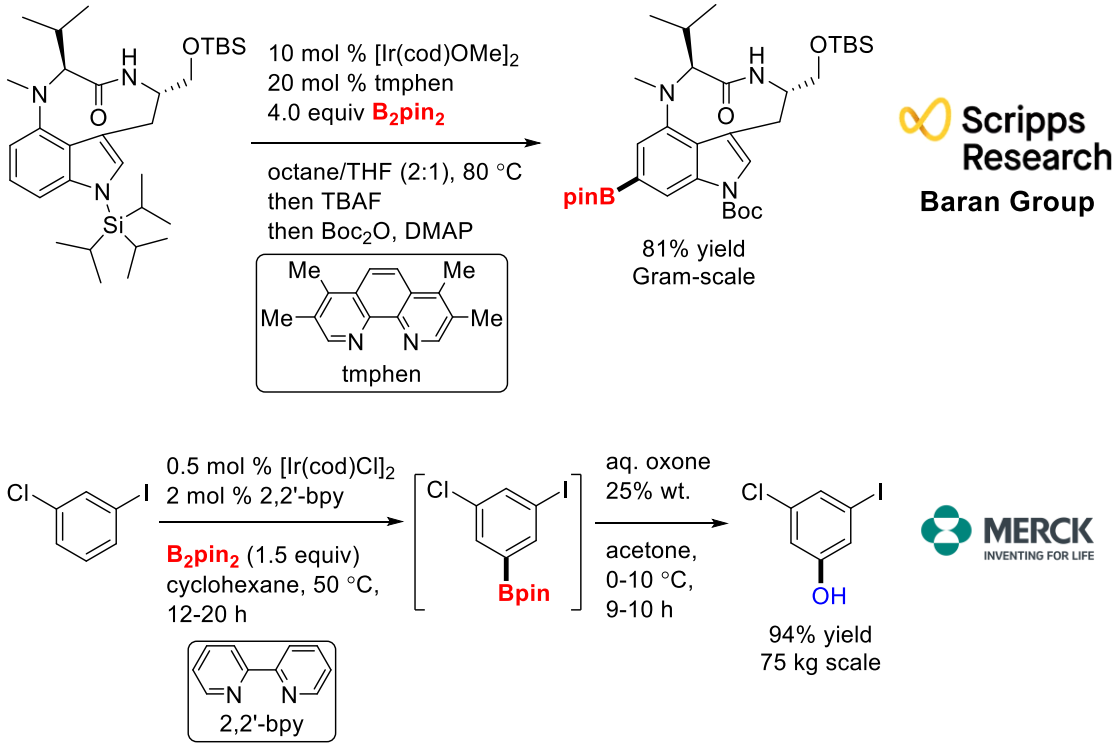
Scheme 1.5: Mechanism of CHB



After formation of trisboryl **I**, a rate determining C-H activation occurs at the iridium center to yield an Ir(V) complex **II**. The arene approaches the metal so as to minimize steric interactions, i.e. from the 5-position for a 1,3-disubstitued arene. After reductive elimination, the borylated product and intermediate **III** is formed. To recover **I**, B_2pin_2 or HBpin adds to the metal center to form **IV** followed by reductive elimination of HBPin or H_2 respectively to complete the catalytic cycle.

CHB has found utility in both academia and industry (**Scheme 1.6**). Baran's research group employed CHB as part of the total synthesis of teleocidins B-1−B-4.[17] An N-TPS protected indole intermediate with substituents at C3 and C4 yield the 6-borylated product selectively. Merck's research laboratories made use of CHB to access the *meta* phenol from 1-chloro-3-iodobenzene via a one pot CHB/oxidation strategy.[18]

Scheme 1.6: Examples of the application of CHB in academia and industry.



This method, initially developed during the Maleczka's group collaboration with the Smith group,[19,20] uses oxone as the oxidant to be added to the crude borylation mixture and yield the corresponding phenol. Researchers at Merck scaled up this reaction to 75 kilograms, which shows how robust CHB reactions are.

1.5. *Ortho* regioselective CHB

CHB-regioselectivity can be switched to the sterically less available *ortho* position by manipulating the ligand and/or using different directing groups (DG). Three strategies for *ortho*-regioselective CHB are: chelate direction, relay direction and direction via an outer-sphere mechanism.[21] In the chelate directed mechanism, a DG interacts with the iridium center of the trisboryl complex **I**; different types of ligands can leave an open site in **I** for this interaction. Monodentate ligands like triaryl phosphines and arsines can be used to direct *ortho*-CHB of ketones and esters respectively.[22–26] The substrate scope can be expanded if the phosphine ligand is supported by a silica surface (Silica-SMAP-Ir) (**Figure 1.1a**).[27,28]

Unfortunately, monodentate ligands do not stabilize the trisboryl **I** resulting in a loss of activity for CHB. Hemilabile ligands can allow for *ortho*-directed CHB without losing reactivity. Pyridine hydrazones, 2-picolylamine and 8-amino quinoline are used for *ortho*-borylations of phenyl hydrazones, benzylamines and benzaldehydes respectively (**Figure 1.1b**).[29–35] Highly active *ortho*-CHB of phenol derivatives, benzoic acid derivatives and aryl imines among others can be performed with bidentate ligands (**Figure 1.1c**).[36] One site of the ligand coordinates to the metal via a dative bond while another atom forms a sigma bond with the iridium center replacing one boron of the trisboryl **I**. Some substrates with specially strong directing groups can also serve as ligands with this last approach e.g. benzyl phosphines and dithioacetal arenes.[37,38]

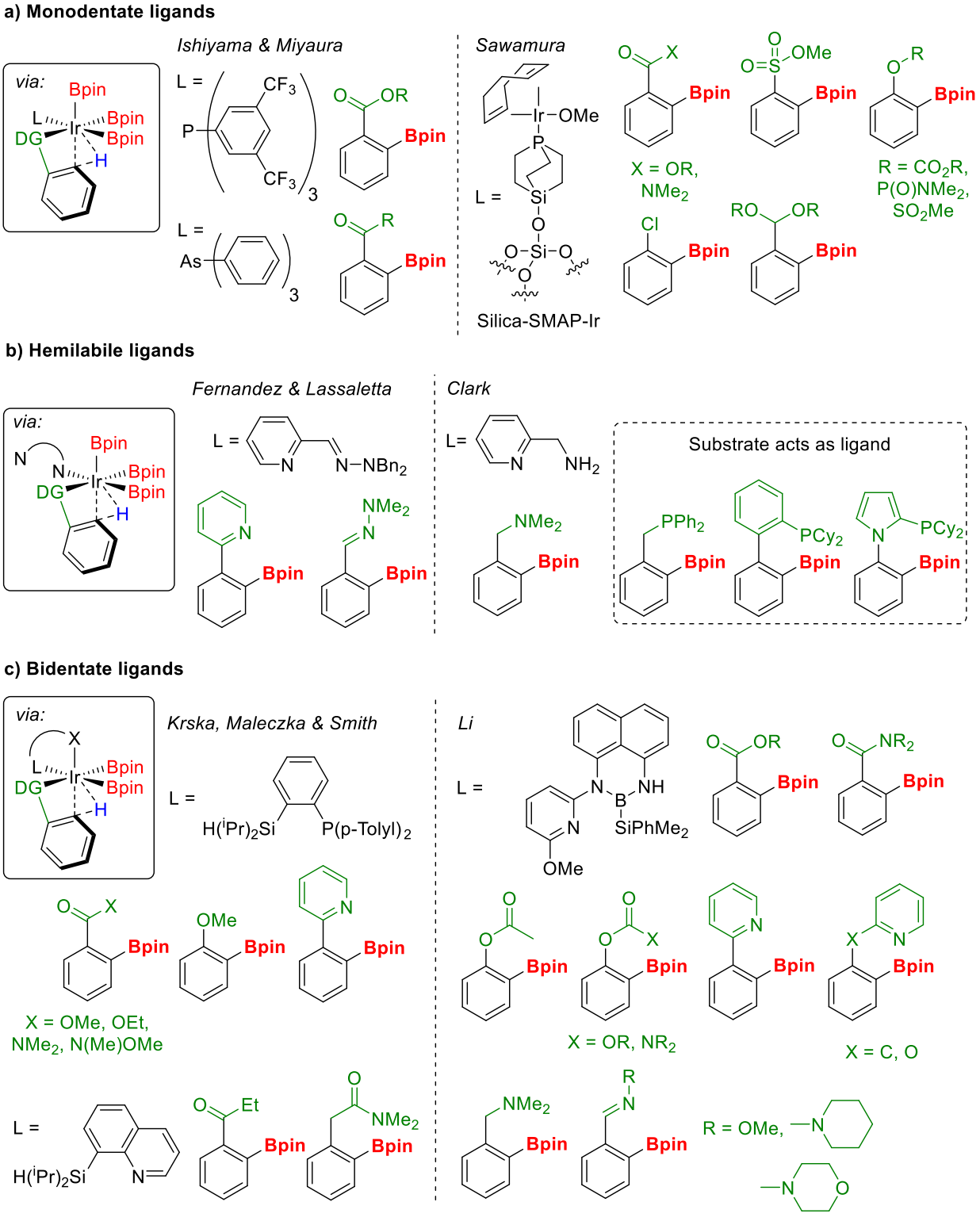
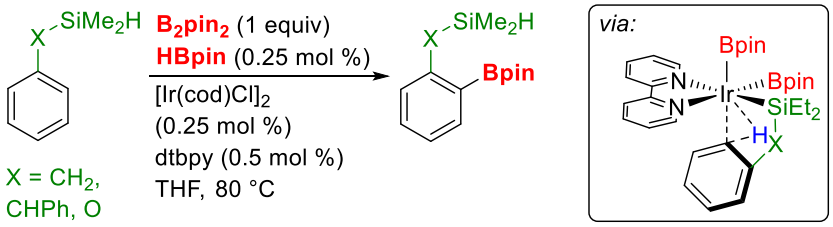


Figure 1.1: Ligands used for *ortho*-CHB via chelate directed mechanism

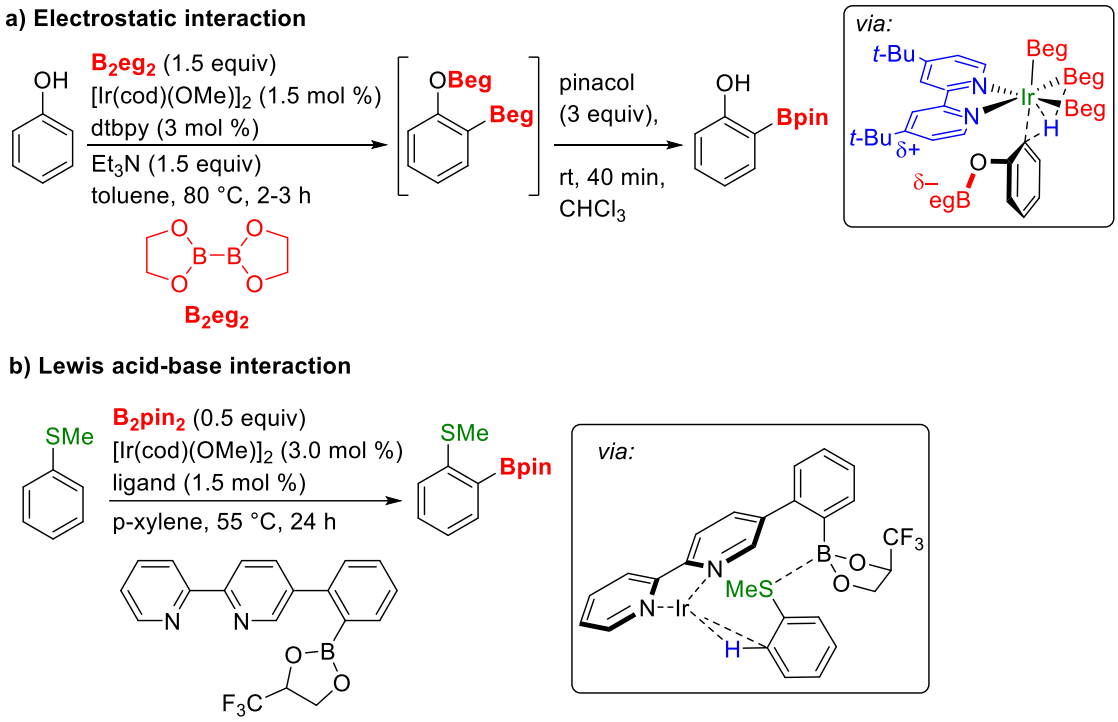
Ortho-CHB can also be directed via the formation of a sigma bond between the metal center and the directing group; this is called a relay directed mechanism (**Scheme 1.7**). Hartwig and cowrokers developed this strategy with pendant silane as directing group.[39] Si-H inserts on the trisboryl **I** and elimination of HBpin leaves an open space for the C-H activation, enabling *ortho*-CHB of benzylic silanes and phenols. Phenols form first a hydrosilyl ether that is removed after the CHB in a one pot process.[39,40]

Scheme 1.7: *Ortho*-CHB via relay directed mechanism



Chelate and relay directed mechanisms direct *ortho*-CHB via strong interactions between the metal and a DG. These strong interactions can reduce significantly the reactivity of the substrates. Weak interactions between the catalyst and the substrate ($\Delta\Delta G^{\ddagger}$ = 2.7 kcal.mol^{-1}) can be enough to get high regioselectivity (99:1 at 25 °C). Based on this principle, *ortho*-CHB can be directed by non-covalent interactions between the DG and the ligand via an outer-sphere mechanism. Electrostatic interactions can direct the *ortho*-CHB of phenols (**Scheme 1.8a**).[41] Borylation of the hydroxyl group yields an electron rich (δ-) O-glycolate that is attracted to the electron deficient (δ+) dtbpy ligand of the catalyst. B_2pin_2 does not give high regioselectivity due to steric repulsions. A less crowded B_2eg_2 (eg = ethylene glycol) works better. Transesterification of the product yields the more stable aryl boronic acid pinacol ester for isolation. Another example of an outer-sphere mechanism is the *ortho*-CHB of thioanisoles, directed by a Lewis acid-base interaction (**Scheme 1.8b**).[42] The empty orbital of the boron ligand interacts with the lone pair on the sulfur of the substrate.

Scheme 1.8: *Ortho*-CHB via outer-sphere mechanism



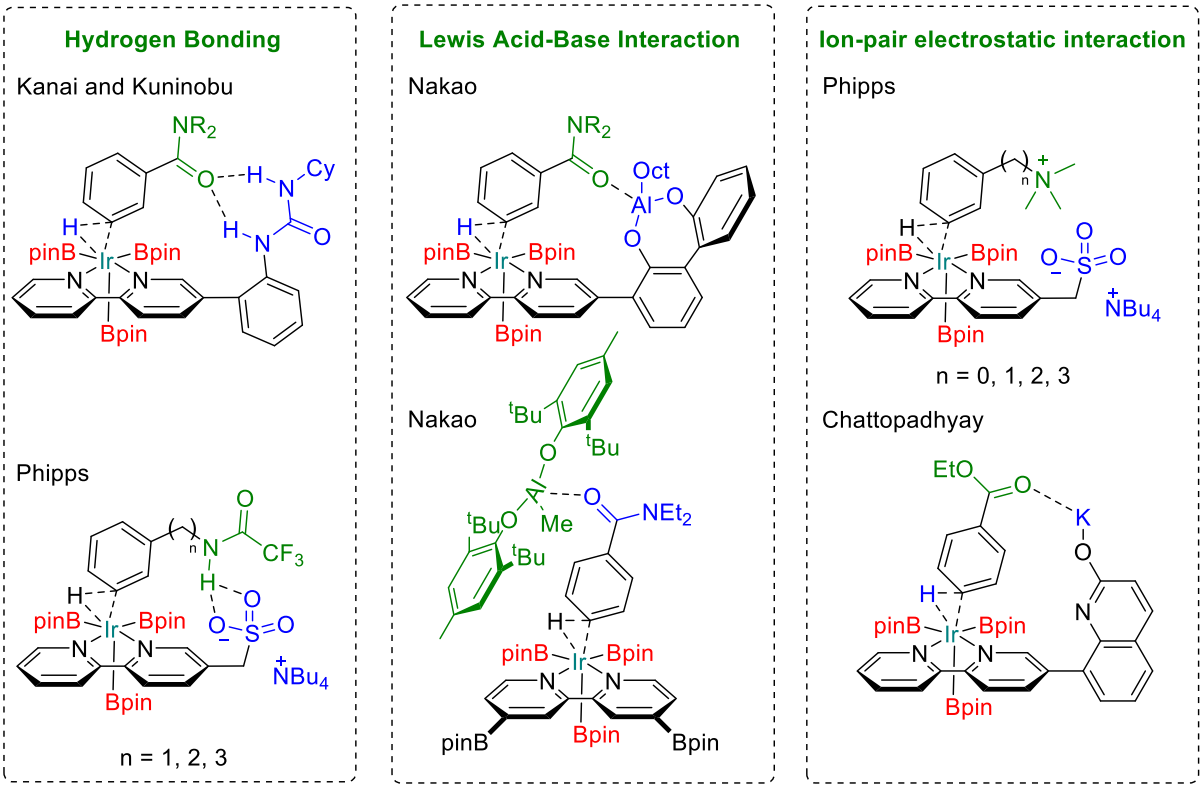
1.6. *Meta* and *Para* Regioselective CHB

Although asymmetrical 1,3-disubsitued arenes can yield exclusively the *meta* borylated product in most of the cases; any other arrangement of substituents will lead to a mixture of products. Remote functionalization like *meta* and *para* CHB is difficult to achieve because any potential directing group is distal from the reactive position. Fortunately, strategies based on noncovalent interactions have been found to direct CHB to remote positions (**Scheme 1.9**). Kanai and Kuninobus's group made the first report in this area. Urea-type ligands as hydrogen bond donors and benzamide reagents as acceptors led to *meta* borylated products.[43,44] Later, the Phipps group showed that bipyridine ligands with sulfated pendant groups can also direct *meta* CHB of benzylamine, phenethylamine and phenylpropylamine derived amides by intermolecular hydrogen bonding.[45] These directing groups vary by the length between the phenyl group and the amide; interestingly the selectivity remains even as the degrees of freedom increase with every methylene

group added. Additionally, the sulfated bipyridine ligand can direct *meta* CHB of phenyl, benzyl, phenylethyl and phenylpropyl ammonium compounds by ion-pair electrostatic interactions.[46–49]

Para CHB have also succumbed to noncovalent interactions as directors for selectivity; although there are fewer reported examples than for *meta* CHB. One example comes from the Chattopadhyay group which invokes a potassium ion as a linker between the phenyl ester substrate and an anionic ligand by virtue of ion-pair electrostatic and Lewis acid-base interactions.[50] Lewis acid-base interactions have also been applied to *meta* and *para* CHB of benzamides by Nakao's group. *Meta* CHB of benzamides is directed by a bipyridine ligand with an aluminum Lewis acid pendant group.[51] Meanwhile, a bulky aluminum Lewis acid additive is used to direct the *para* CHB of benzamides.[52] The Lewis acid coordinates to the amide creating a steric shield that blocks the *meta* position leaving the *para* C–H as the only viable reactive site

Scheme 1.9: *Meta*- and *para*-CHB directed by noncovalent interactions.



1.7. Conclusions

CHB is an established method to access aryl boronic esters with unique selectivities. Noncovalent interactions are sufficient to direct CHB to any position desired by careful design of the ligand with the right choice of directing group and with key additives in some cases. One component less explored when optimizing CHB reactions is the diboron partners. Our group has shown that modifications of the diboron reagent, a component less commonly screened during CHB optimization, can lead to significant improvement of selectivities. In the next chapter we will discuss how modulation of the diboron partner affects CHB selectivity and the stability of the borylated products. *Para* CHB remains scarce and novel methods are required. In the following chapters, we described how steric shielding effects directed by both inter- and intramolecular noncovalent interactions can be used to direct *para* CHB in an array of directing groups.

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CHAPTER 2.

BALANCING ACTIVITY AND REGIOSELECTIVITY IN *ORTHO* C–H BORYLATIONS OF ANILINES BY MODULATING THE DIBORON PARTNER

2.1. Introduction

Anilines can be found in dyes, agrochemicals, pharmaceuticals, and polymers (**Figure 2.1**).[1] Historically, anilines were important compounds for the synthesis of diazo dyes; aniline yellow is the first example in this class. Aniline can also be found in other types of colorants; one famous example being indigo which gives the blue color to jeans.[1] The use of anilines as agrochemicals is also known, with one of the most prominent examples being alachlor, which is the second most used herbicide in US. The aniline skeleton also appears in therapeutically important molecules like diazepam and the vitamins riboflavin (vitamin B_2) and folic acid. Furthermore, anilines also have a presence in polymer chemistry, where common examples include the polymer Kevlar and 2-mercaptobenzothiazole (MBT), an additive in polymerization.

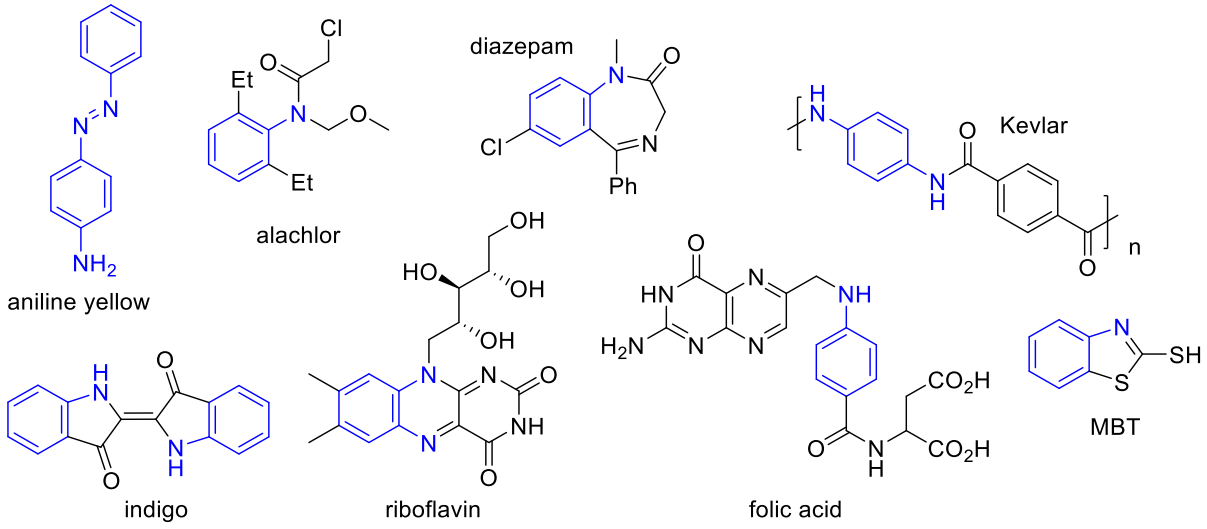
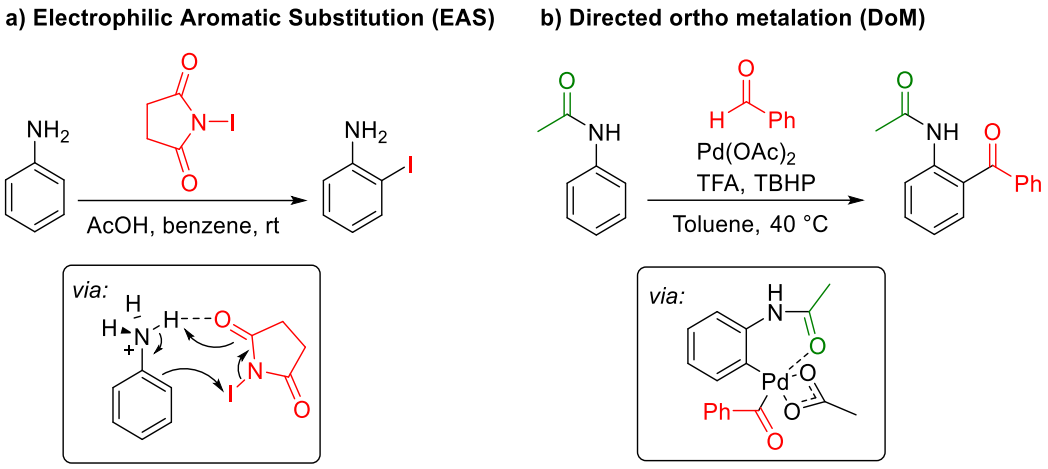


Figure 2.1: Examples of dyes, agrochemicals, pharmaceuticals, biomolecules, and polymers with an aniline ring

Traditional functionalization of anilines is done by electrophilic aromatic substitution (EAS), which affords mainly the *para* isomer. Regioselectivity can be switched under special

conditions; one example is the *ortho*-iodination of anilines with N-iodosuccinimide (NIS) under acidic conditions using non-polar solvents (**Scheme 2.1a**).[2] The hydrogen bond between the protonated aniline and the carbonyl group of the NIS directs iodine to the *ortho* position. Aside from this case, *ortho*-functionalization of anilines is commonly accomplished through directed *ortho*-metalation (DoM). For instance, acylation of amides can afford the *ortho*-acylated product via palladium C-H activation (**Scheme 2.1b**).[3,4] The mechanism of this reaction involves chelation of the carbonyl to the metal center directing the regioselectivity of the C-H oxidative addition. This methodology, while seemingly useful, requires the introduction of a directing group in the aniline which limits functional group tolerance and reduces the step economy efficiency.

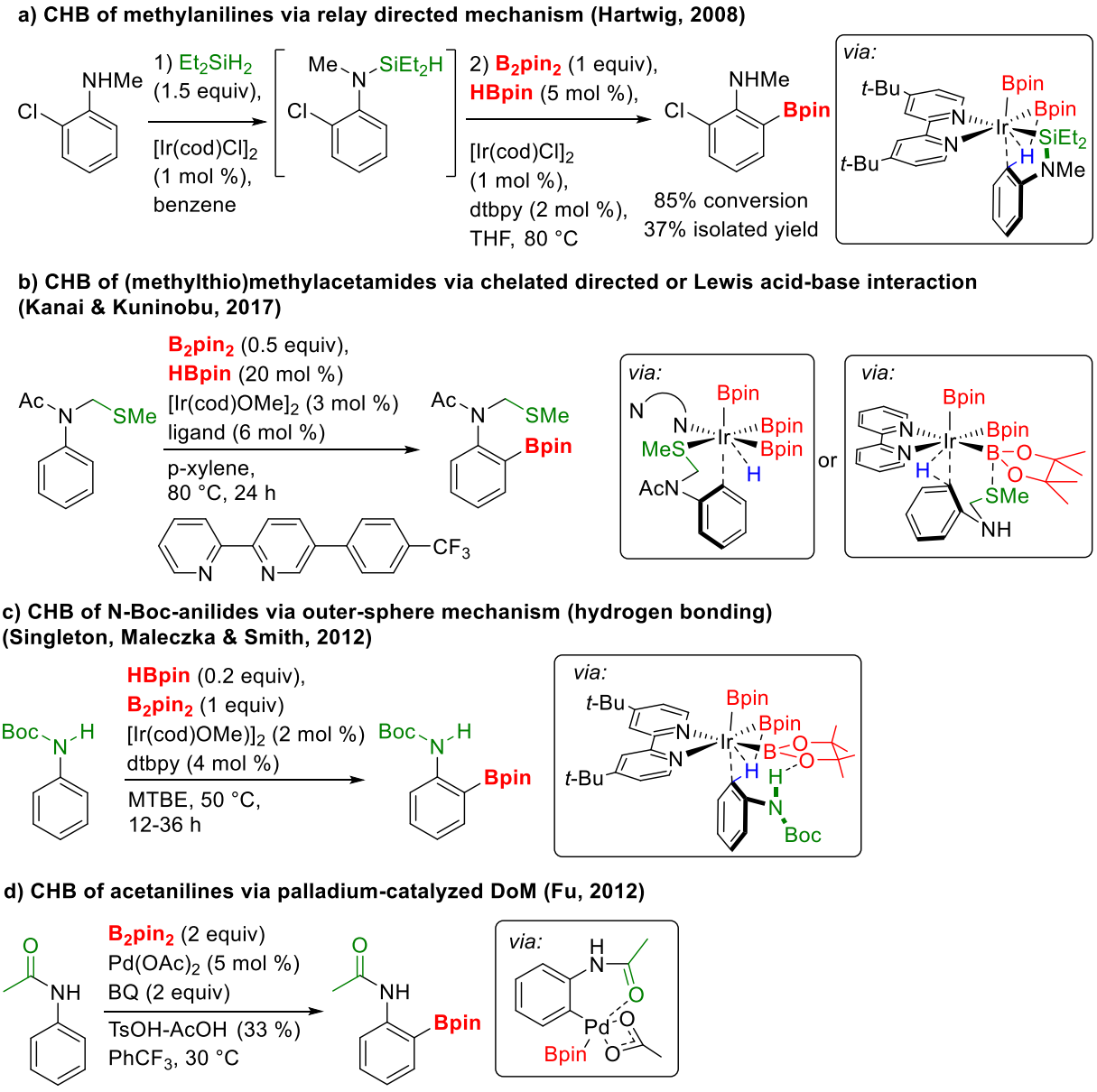
Scheme 2.1: Selected examples of *ortho* functionalization of anilines



To overcome the limitations of DoM, a traceless method to selectively functionalize anilines is needed. Furthermore, it would be synthetically attractive if the methodology could give access to a wide variety of functional groups. *Ortho*-borylation of anilines can be a good strategy because aryl boronic acids and esters are versatile precursors.[5] Biaryls, benzyl amines, benzyl alcohols, aryl halides, aryl cyanides, trifluoro toluenes, benzoic acids, anilines, phenols, etc. can be synthesized via boron exchange reactions.[5,6] The first reports of this methodology installed a directing group in the aniline prior to CHB. Hartwig used a relay directing mechanism for the

ortho-CHB of 2-chloro-N-methyl aniline. However, this method was only used on one substrate and was low yielding (37%, **Scheme 2.2a**).[7]

Scheme 2.2: *Ortho*-CHB of anilines with pre-installation of a directing group

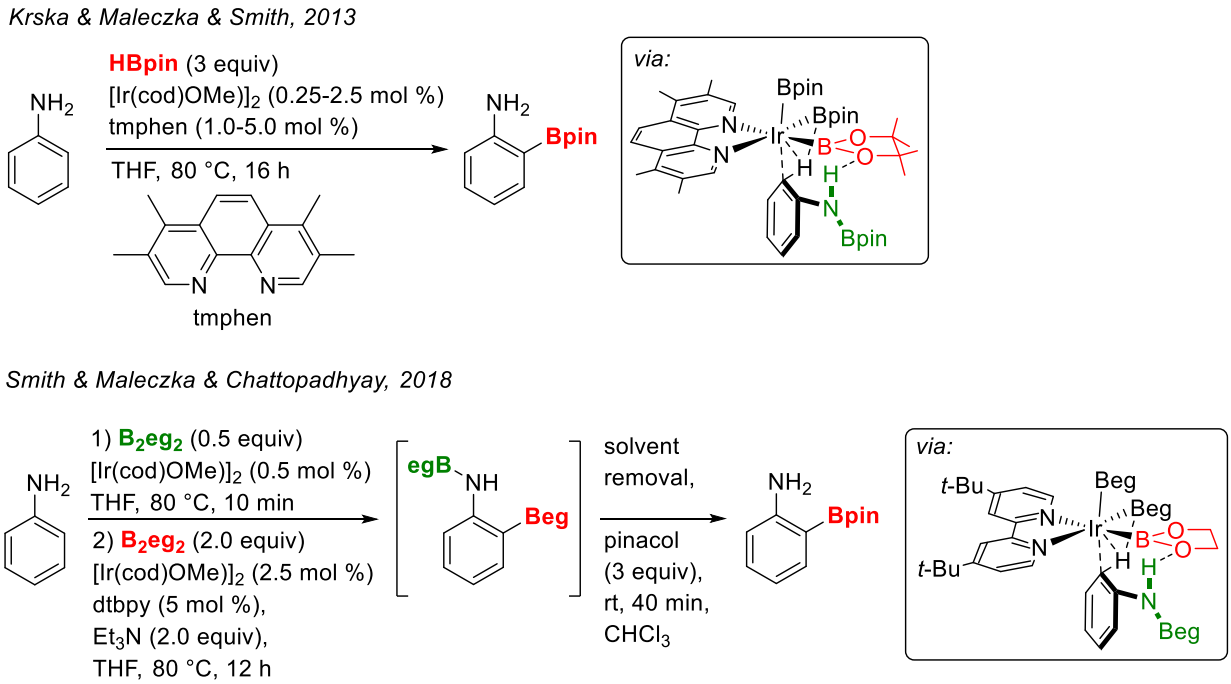


Introduction of a (methylthio)methyl group in acetanilides can also direct *ortho*-CHB. It is believed that this goes through a chelate directed mechanism with an hemilabile ligand or an outer-sphere mechanism with an Lewis acid-base interaction (**Scheme 2.2b**).[8] Singleton, Maleczka and Smith showed that *ortho*-CHB of *N*-(Boc)-anilines are also possible due to a hydrogen bond N–

H•••O between the hydrogen of the aniline and the oxygen in one of the Bpins on the iridium (**Scheme 2.2c**).[9] Aside from Ir-catalyzed CHB, Pd-catalyzed DoM is another option for the *ortho*-CHB of acetanilides (**Scheme 2.2d**).[10]

Traceless *ortho*-CHB of anilines can improve step and atom economy efficiency (**Scheme 2.3**). In 2013, Krska, Maleczka and Smith reported the first traceless *ortho*-borylation of anilines using HBpin as the boron partner.[11] It is proposed that ArNH–Bpin is formed first followed by *ortho*-CHB that is directed by a similar hydrogen bond interaction N–H•••O as that proposed for *N*-(Boc)-anilines (**Scheme 2.2c**). This protocol works well only when there is a C4 substituent on the substrate.

Scheme 2.3: Traceless *ortho*-CHB of anilines



In 2018, it was reported that using B_2eg_2 as the boronic partner yields high *ortho* regioselectivity without the necessity of a C4 substituent (**Scheme 2.3**).[12] This improvement in selectivity is due to the decreased steric demand of the Beg group that stabilizes the transition state.

However, high catalyst loadings were used and the borylated (2-Beg)$ArNH_2$ product needed to be treated with pinacol to convert it to the more stable (2-Bpin)$ArNH_2$, allowing practical purification.

If one could remove the last esterification step and retain the regioselectivity of CHB, the result would be a very valuable asset. Boronic partners bulkier than B_2eg_2 may yield more stable borylated products, allowing for the possibility of direct isolation, but at the risk of reducing the *ortho* CHB regioselectivity. Herein, we sought to find a balance between regioselectivity and stability of the borylated product for the *ortho* CHB of anilines by optimization of the diboron partner.

2.2. Results and Discussion

2.2.1. Regioselectivity of a novel diboron partner: B_2pg_2

A variety of diboron partners can be envisioned with sizes lying between B_2pin_2 and B_2eg_2. Our journey began with the simplest version, B_2pg_2 (pg = propylene glycol), which present a pendant methyl group in each glycolate chain of B_2eg_2. Preliminary studies by Behnaz Ghaffari showed that B_2pg_2 yields a highly *ortho* regioselective CHB of aniline like B_2eg_2 (unpublished results). The B_2pg_2 was made starting with a racemic mixture of propylene glycol that should lead to a racemic mixture of B_2pg_2. Addition of NMR shift reagents helped to measure the ratio of the stereoisomers in the B_2pg_2 mixture (**Figure 2.2**). As expected, the two B_2pg_2 diastereomers are present in a 50:50 mixture corresponding to the *meso* isomer (*S,R*)-B_2pg_2 and an equimolar mixture of the enantiomers (*S,S*)-B_2pg_2 and (*R,R*)-B_2pg_2.

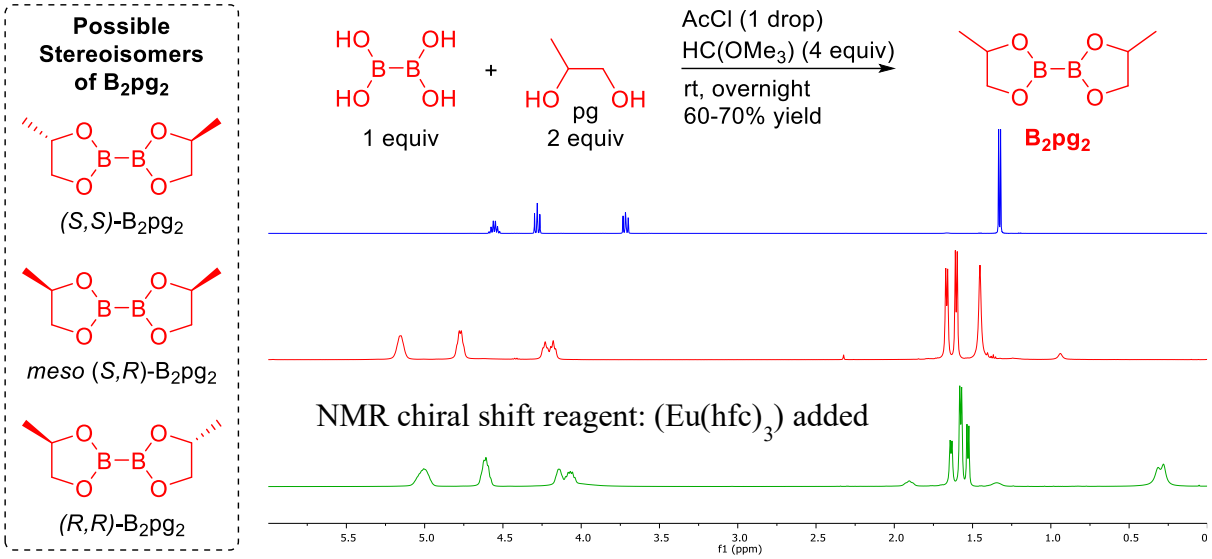
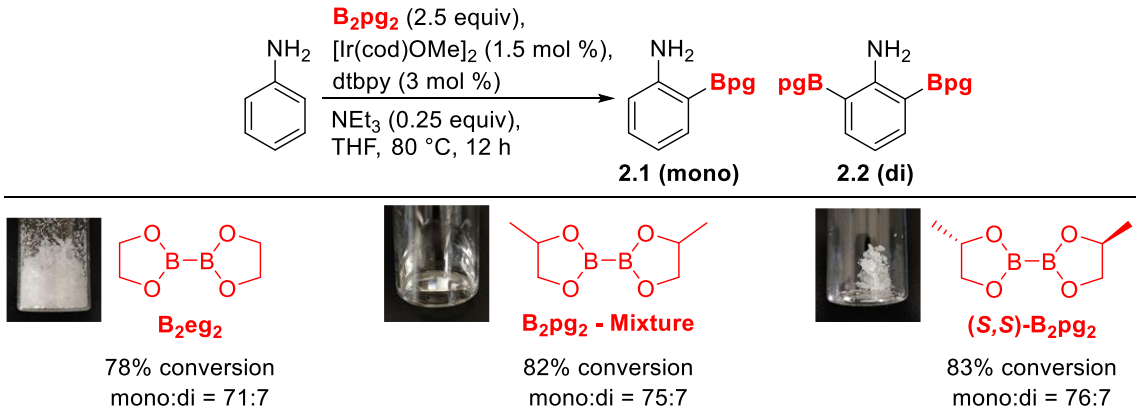


Figure 2.2: ^{1}H NMR of a racemic mixture of B_2pg_2 with NMR shift reagents

We wondered if the individual stereoisomers of B_2pg_2 would induce as high selectivity as the mixture of stereoisomers. We made the pure (*S*,*S*)-B_2pg_2 enantiomer from (*S*)-propylene glycol and tested it under CHB conditions (**Scheme 2.4**). Comparable reactivity and regioselectivity were found with (*S*,*S*)-B_2pg_2 and the mixture of stereoisomers. This result suggests that all the diasteromers in the B_2pg_2 mixture are equally efficient for the *ortho* CHB of anilines. We continued our studies with the mixture of B_2pg_2 stereoisomers as its synthesis is less expensive than making the pure enantiomers.

Scheme 2.4: CHB regioselectivity of aniline with B_2eg_2, racemic B_2pg_2 and (*S*)-B_2pg_2

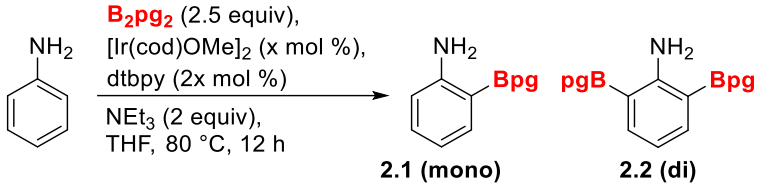


2.2.2. Optimization of reaction conditions: catalyst loading

The previously reported *ortho* CHB of anilines with B_2eg_2 did not need extended screening of conditions since high regioselectivity and very good yields were obtained early during the optimization.[12] We wondered if milder conditions, e.g. lower catalyst loading, boron partner equivalents and temperature, could achieve comparable conversions with B_2pg_2 as the boron partner.

Catalyst loading is another important parameter to explore for the CHB of anilines. By increasing the catalyst loading one can improve conversions of CHB, but it is not synthetically desirable to invest in more catalyst than necessary. Catalyst loadings from 1.0 to 2.5 mol % of $[Ir(cod)OMe]_2$ were screened for the *ortho*-CHB of aniline (**Table 2.1**). A slight improvement in conversion was seen with 1.5 mol % of $[Ir(cod)OMe]_2$ respect to the use of 1.0 mol % catalyst loading, but conversion remained unchanged even with 2.0-2.5 mol % of catalyst.

Table 2.1: Optimization of reaction conditions: catalyst loading [a]



% $[Ir(cod)OMe]_2$	% conversion	% ortho	% diborylated
1.0	62	60	2
1.5	80	74	6
2.0	81	73	8
2.5	81	74	7

[a] Reaction conditions: aniline (1 mmol), B_2pg_2 (2.5 mmol), $[Ir(cod)OMe]_2$ (0.01 mmol), dtbpy (0.02 mmol), Et_3N (2 mmol), THF (3 mL), 80 °C, 12 h

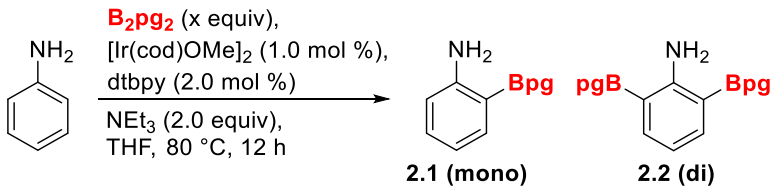
This project was a group effort with Seokjoo Lee, who also performed screening of conditions to evaluate the effect of base loading, boron partner and temperature on CHB. These studies were done at the same time as the experiments shown above, and thus initial loading

conditions of 1 mol % of $[Ir(cod)OMe]_2$ were used instead of the optimized 1.5 mol %. Seokjoo's results are presented in the following paragraphs of **Section 2.2.3**.

2.2.3. Optimization of reaction conditions: boron partner equivalents and temperature

The amount of B_2pg_2 were varied to find how many equivalents of boron partner is necessary for successful CHB (**Table 2.2**). There is a clear improvement in conversion as the equivalents of B_2pg_2 increase and using 2.5 equivalents of B_2pg_2 was found to be the best choice. More than one equivalent is necessary for good conversions because the first step is the formation of PhN(H)Bpg, which uses one equivalent of boron partner per equivalent of aniline.

Table 2.2: Optimization of reaction conditions: boron partner equivalents [a]



B_2pg_2 (equiv)	% conversion	1 (%)	2 (%)
1	4	4	0
1.5	44	43	0
2	68	65	2
2.5	83	76	7

[a] Reaction conditions: aniline (1 mmol), B_2pg_2 (x mmol), $[Ir(cod)OMe]_2$ (0.01 mmol), dtbpy (0.02 mmol), Et_3N (2 mmol), THF (3 mL), 80 °C, 12 h

CHB of aniline at different temperatures was also evaluated. Reactions were followed by ^1H NMR over a period of time (**Figure 2.3**). When the reaction was performed at 40 °C, it appeared slightly slower than at 60 °C and at 80 °C. However, all the reactions achieve the same conversions to both monoborylated and diborylated product in the end. This study was performed before the catalyst loading screen. Therefore, it will be important to perform the same temperature experiment with 1.5 mol % of $[Ir(cod)OMe]_2$. If a same pattern is displayed, a lower temperature than 80 °C is a viable reaction condition.

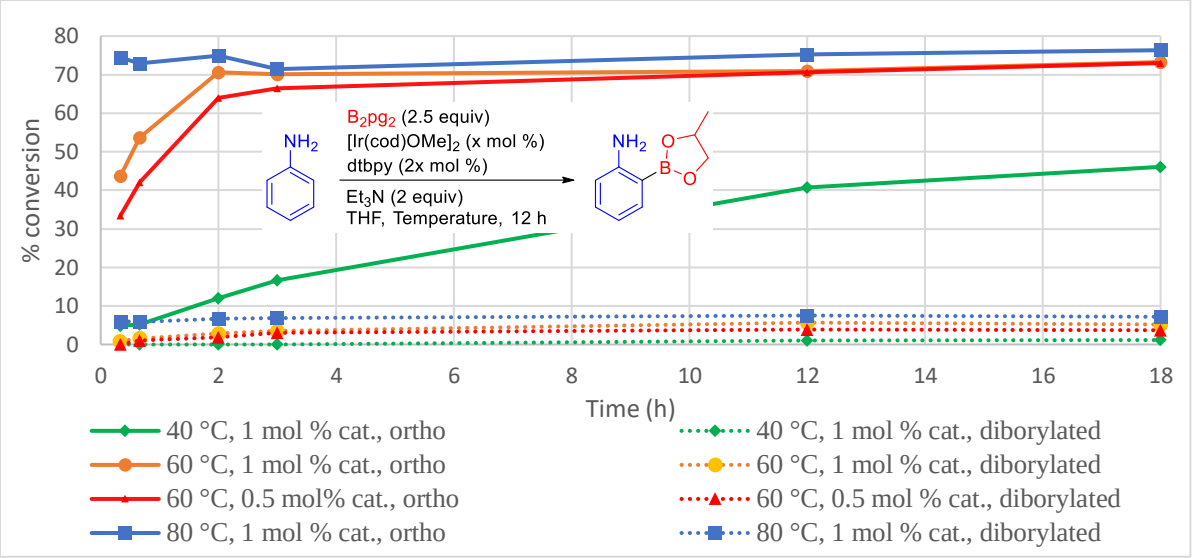
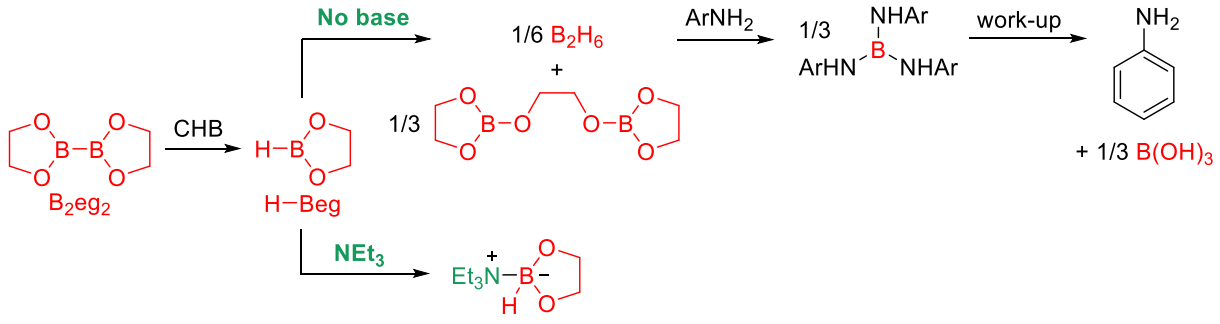


Figure 2.3: Optimization of reaction conditions: effect of the temperature.

2.2.4. Effect of the base for ortho-CHB of aniline

Ortho-CHB of phenols and anilines with B_2eg_2 is improved by addition of triethyl amine. It was proposed that the purpose of the base is to stabilize the H–Beg side product in order to avoid undesirable reactions. Trimethylamine has been reported to stabilize this type of compounds by complexation: HBeg•NMe_3.[13,14] The idea is that triethylamine might have the same effect on *ortho*-CHB of anilines with B_2eg_2 (**Scheme 2.5**).[12,15] When the base is absent, the borane might react with the aniline to generate a trianiline borane, which will be unactive towards CHB with B_2eg_2.

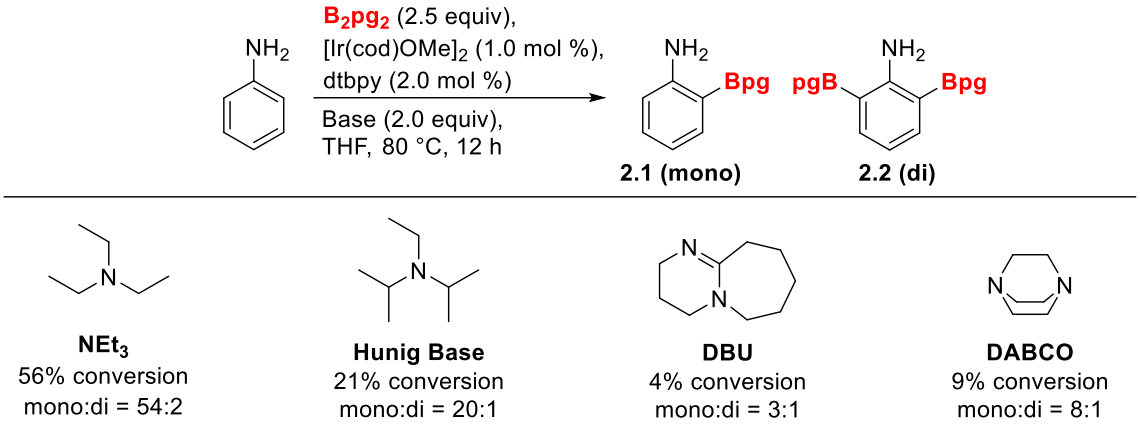
Scheme 2.5: Role of triethylamine in the CHB of phenols and anilines.



Other amines like diisopropylethyl amine (DIPEA, Hünig base), DBU and DABCO were also tested for *ortho*-CHB of aniline to observe if they have a similar or greater effect than

triethylamine (**Scheme 2.6**). However, triethyl amine was the best, affording the highest conversion as well as the selective formation of the *ortho*-monoborylated product.

Scheme 2.6: Base effect on the *ortho* CHB of aniline [a]



[a] Reaction conditions: aniline (1 mmol), B_2pg_2 (2.5 mmol), $[Ir(cod)OMe]_2$ (0.01 mmol), dtbpy (0.02 mmol), base (2 mmol), THF (3 mL), 80 °C, 12 h

Effect of the equivalents of triethylamine on the *ortho*-borylation of anilines was evaluated; results are shown in **Figure 2.4**. Conversions to the ortho monoborylated aniline are represented by the bars in blue and the diborylated product by the bars in orange. Surprisingly, there is formation of the *ortho*-borylated product even without base. Increasing the amount of base to 0.5 equivalents improves the conversion considerably. Excess of base harms the reaction. Perhaps excess base can break the N–B bond of the intermediate PhN(H)Bpg thereby losing reactivity. Lower reactivity with Hunig base, DBU and DABCO might be due to the large sizes of these bases in comparison to triethylamine. The HBeg•Base complex may be destabilized by sterics when a larger base is attached to the borane. Therefore, we tested diethylmethyl amine and ethyldimethyl amine which should be smaller than triethylamine. Conversions comparable to those with triethylamine were found.

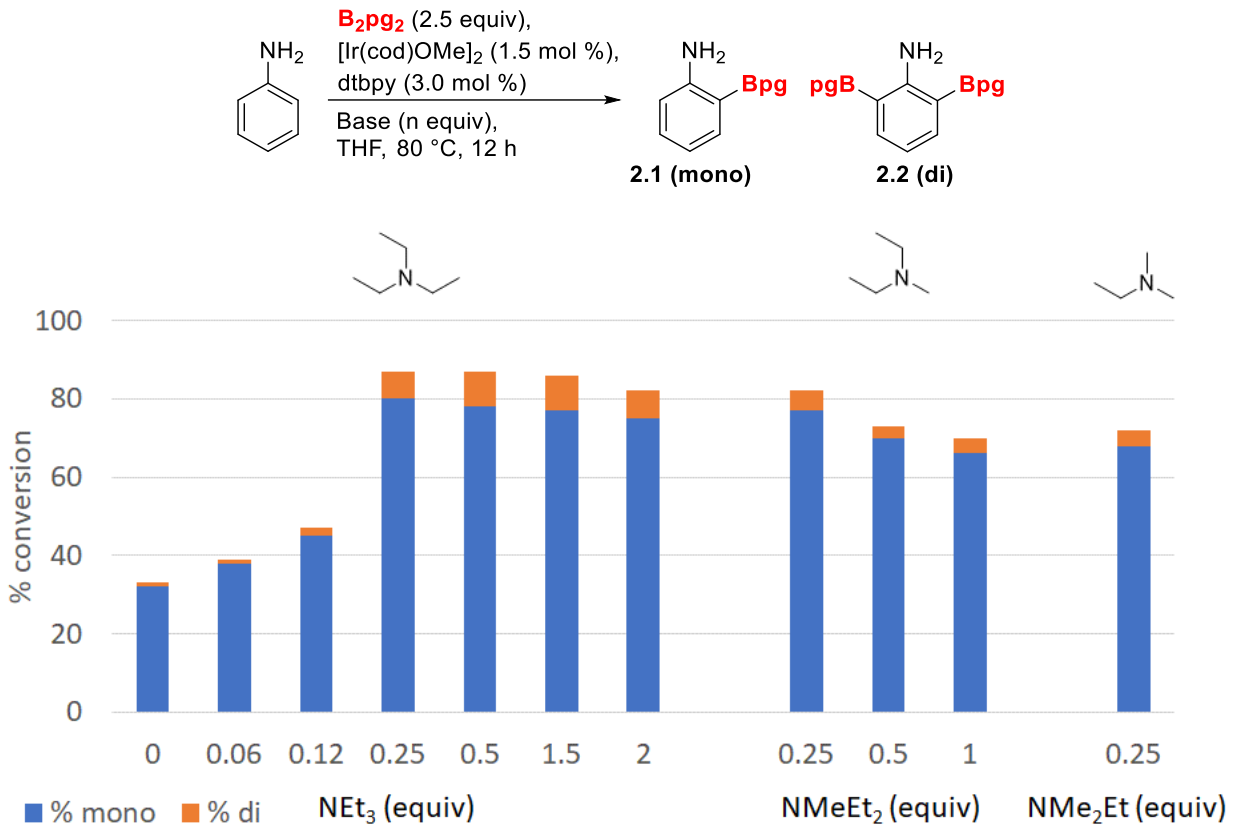


Figure 2.4: Screening of trialkylamine bases and effect of equivalents on *ortho* CHB of aniline

2.2.5. Modulating the diboron partner

With the optimized conditions in hand, we continue to evaluate different diboron partners and find which leads to the best balance of *ortho* regioselectivity and stability of the borylated product for the CHB of anilines. Diboranes were synthesized from the corresponding glycol and $B_2(OH)_4$ via a procedure developed in the Smith lab by Ryan Fornwald (unpublished results). Diboron partners with an ethyl pendant group (B_2bg_2) and with two pendant methyl groups in the glycolate chain (B_2mpg_2 and $B_2((2R,3R)bg)_2$) were prepared (**Figure 2.5**). CHB of unsubstituted aniline was evaluated with the diboron partners at different equivalents of triethylamine. In terms of reactivity, 0.25 equiv of base was optimal for all the cases. Diboron partners with one pendant alkyl group in the glycolate backbone (B_2pg_2 and B_2bg_2) retain the high regioselectivity for *ortho*

CHB of aniline. Introduction of additional alkyl chains in the boron partner (B_2mpg_2 and $B_2((2R,3R)bg)_2$)) has a detrimental effect on the selectivity yielding the *meta* and *para* products (gray and yellow bars respectively).

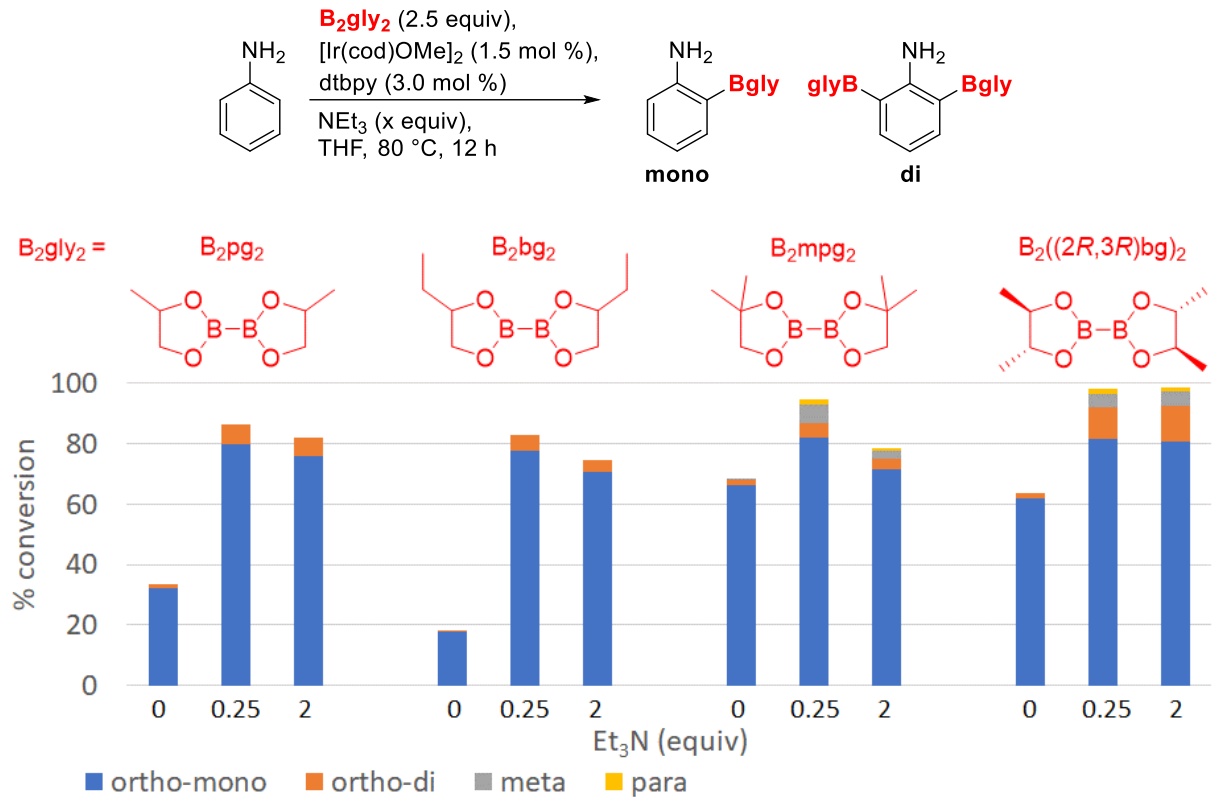
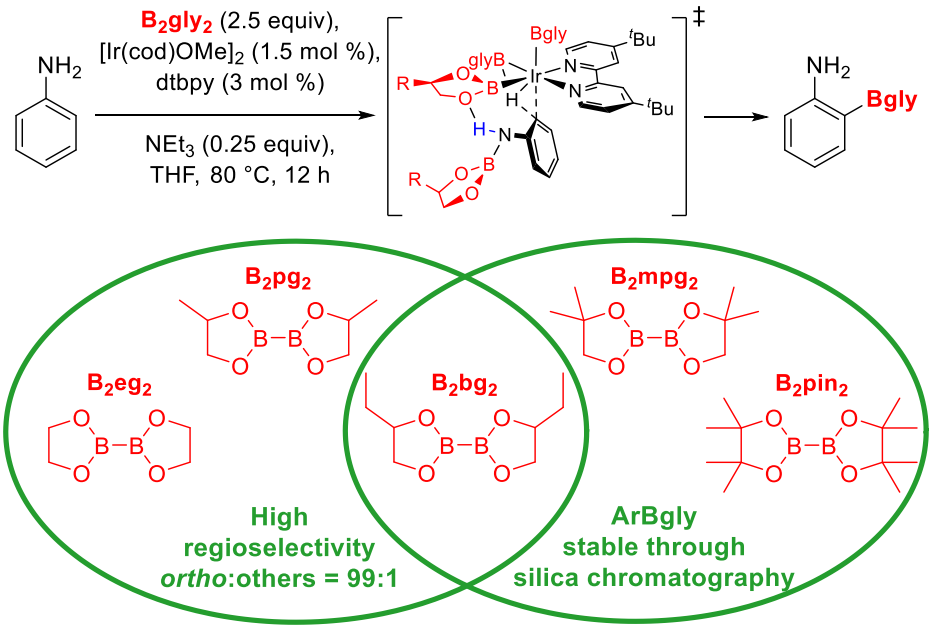


Figure 2.5: Effect of diboron partner on the *ortho* CHB of aniline

Attempts at product purification by silica chromatography showed us that ArBeg and ArBpg decompose, but ArBbg and ArBmpg survive. As stated above, B_2bg_2 was more selective towards the ortho borylated product than B_2mpg_2. Therefore, B_2bg_2 represents the best balance of reactivity, regioselectivity and stability (**Scheme 2.7**).

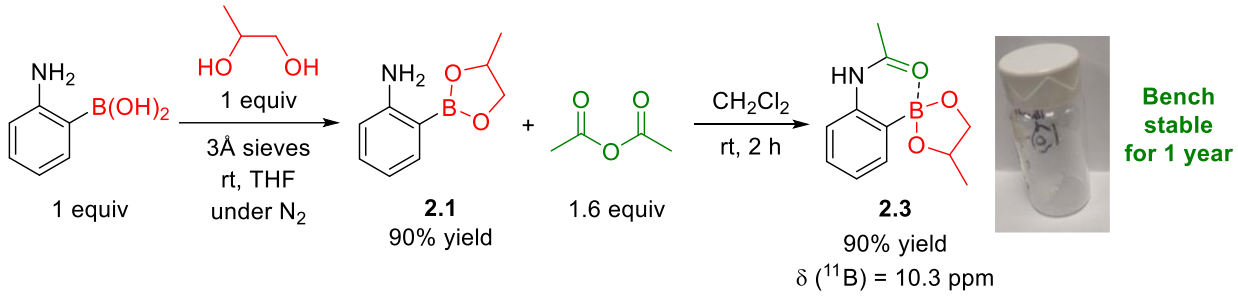
Scheme 2.7: Balance between regioselectivity and stability for the *ortho* CHB of aniline



2.2.6. Factors controlling stability of the borylated product

Ortho borylated anilines with small boron groups tend to be unstable. A smaller glycolate chain around the boron group can leave the boron atom more exposed to attack by nucleophiles. We speculate that hydrolysis or reactions with silica during chromatography are responsible for the troubles during isolation of ArBpg. A previous report has shown that an *ortho* borylated acetamide with a Beg group hydrolyzes slower than the corresponding *meta* or *para* borylated acetamides.[16] To further evaluate our hypothesis, we synthesized **2.3**, which has an acetamide group in the aniline that can coordinate to the boron blocking any potential side reaction (**Scheme 2.8**). Amide **2.3** is a crystalline solid that is bench stable even after 1 year as shown by ^{1}H NMR. The ^{11}B NMR chemical shift of 10.3 ppm for a C–Bgly group is shielded with respect to the common range 25-30 ppm for this type of boron. This is indicative of the boron atom coordinating with a Lewis base like the acetamide group.

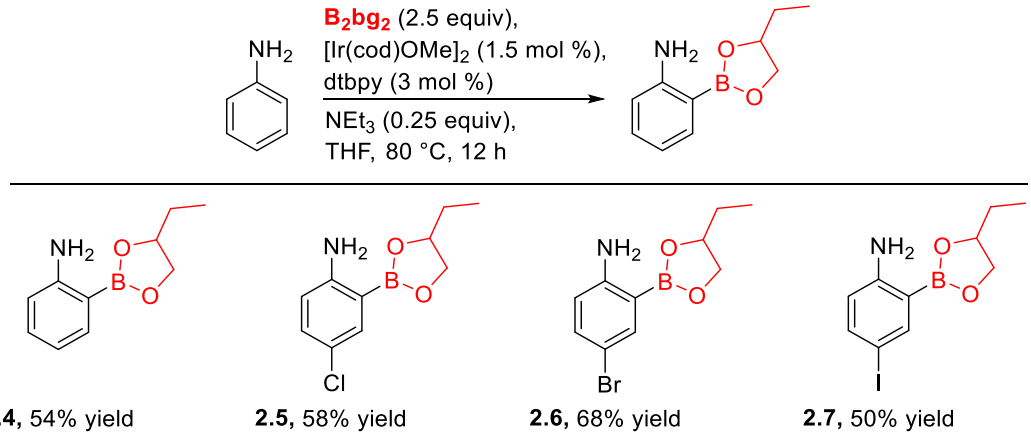
Scheme 2.8: Synthesis of a stable *ortho* borylated aniline via intramolecular interaction



2.2.7. Substrate Scope

We wondered if the stability conferred by the Bbg group in *ortho* borylated anilines as well as the high selectivity induced by B_2bg_2 could be extrapolated to other substituted anilines. In fact, this was the case for **2.5-2.7** which were isolated under the same optimized conditions of **2.4** (**Scheme 2.9**). Although moderate yields were obtained, this protocol obviates the previously needed transesterification step with pinacol.

Scheme 2.9: Synthesis of a stable *ortho* borylated aniline via CHB



2.3. Conclusions

In summary, *ortho* CHB of anilines can achieve high selectivities with B_2bg_2 as the diboron partner and yield products that can be isolated directly without the need of a transesterification step. Diboron partners with one pendant alkyl group in the glycolate backbone (B_2pg_2 and B_2bg_2)

retain the high regioselectivity for *ortho* CHB of aniline but additional alkyl chains in the boron partner (B_2mpg_2 and $B_2(2R,3R)bg_2$) has a detrimental effect on the selectivity. The best conversions for each diboron partner were obtained using 0.25 equivalents of triethyl amine; excess or lower amounts of base were detrimental for the formation of the *ortho*-borylated aniline Attempts at product purification by silica chromatography showed that ArBeg and ArBpg decompose, but ArBbg and ArBmpg survive. Unwanted reactions during purification might occur from nucleophilic attack to the boron. In fact, *ortho* borylated acetamide with Bpg is stabilized by an intramolecular Lewis acid-base interaction. This report shows some of the benefits and unique selectivities that can be achieved by modulating the diboron partner; a reagent not commonly screened during development of CHB reactions.

2.4. Experimental

2.4.1. General Information

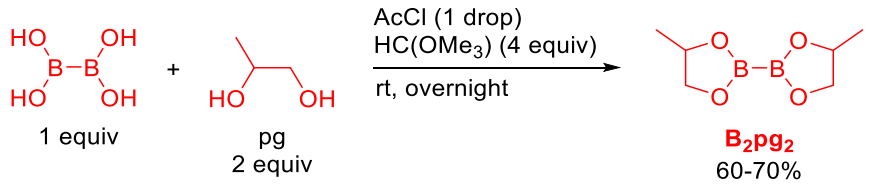
All commercially available chemicals were used as received unless otherwise indicated. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) $[Ir(OMe)COD]_2$ was prepared from a well reported procedure in the literature.[17] Tetrahydrofuran (THF) were refluxed over sodium/benzophenone ketyl, distilled and degassed twice before borylation. Column chromatography was performed on flash silica gel (ACME). Thin layer chromatography was performed on 0.25 mm thick aluminum-backed silica gel plates purchased from Merck and visualized with ultraviolet light (λ = 254 nm).

^1H, ^{13}C, and ^{11}B NMR spectra were recorded on Agilent DirectDrive2 (500 MHz for ^1H, 126 MHz for ^{13}C and 160 MHz for ^{11}B). All coupling constants are apparent *J* values measured at the indicated field strengths in Hertz (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, bs = broad singlet, dt = doublet of triplet, td = triplet of doublet, ttt = triplet of triplet

of triplet). Spectra taken in $CDCl_3$ were referenced to 7.26 ppm in ^1H NMR and 77.2 ppm in ^{13}C NMR. ^{11}B NMR spectra were referenced to neat BF_3•Et_2O as the external standard. ^{13}C NMR resonances for the boron-bearing carbon atom were not observed due to quadrupolar relaxation. High-resolution mass spectra were acquired at the MSU Mass Spectrometry facility using a Waters QTOF Ultima mass spectrometer (ESI).

2.4.2. Synthesis of diboron partners

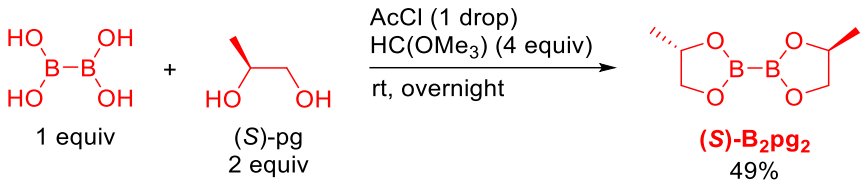
Synthesis of racemic B_2pg_2



$B_2(OH)_4$ (3.59 g, 40 mmol, 1 equiv) and $CH(OMe)_3$ (16.98 g, 160 mmol, 4 equiv) were stirred in a Schlenk flask and the suspension was degassed with N_2 for 15 minutes. One drop of acetyl chloride, AcCl, was added and the mixture became a homogenous solution. Propylene glycol (pg, 6.09 g, 80 mmol, 2 equiv) was added and the reaction was stirred at room temperature overnight. The mixture was concentrated and then distilled under reduce pressure to yield 4.20 g of B_2pg_2 as a colorless oil (62% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 4.62 – 4.51 (m, 1H), 4.28 (dd, *J* = 9.0, 7.9 Hz, 1H), 3.71 (ddd, *J* = 9.0, 7.4, 1.0 Hz, 1H), 1.33 (dd, *J* = 6.2, 0.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 73.4, 73.3, 71.9, 21.6. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.7. GC-MS (EI) *m/*z calcd for $C_6H_{12}B_2O_4$ [M] 170.1, found: 170.1

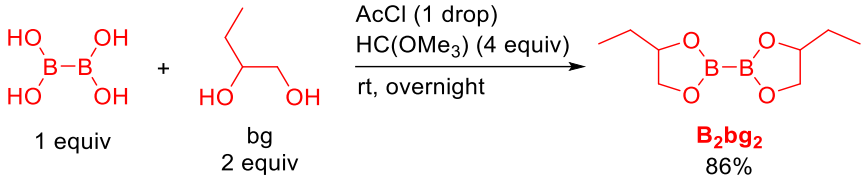
Synthesis of (*S*)-B_2pg_2



$B_2(OH)_4$ (896 mg, 10 mmol, 1 equiv) and $CH(OMe)_3$ (4.24 g, 40 mmol, 4 equiv) were stirred in a Schlenk flask and the suspension was degassed with N_2 for 15 minutes. One drop of acetyl chloride, AcCl, was added and the mixture became a homogenous solution. (*S*)-Propylene glycol ((*S*)-pg, 1.52 g, 20 mmol, 2 equiv) was added and the reaction was stirred at room temperature overnight. The mixture was concentrated and then distilled under reduce pressure. A solid crashed out on the distilled arm and receiving flask that after recollection yielded 840 mg of (*S*)-B_2pg_2 as a white solid (49% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 – 4.46 (m, 1H), 4.25 (dd, *J* = 9.0, 7.9 Hz, 1H), 3.69 (dd, *J* = 9.0, 7.4 Hz, 1H), 1.30 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 73.5, 72.1, 21.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.7. GC-MS (EI) *m/*z calcd for $C_6H_{12}B_2O_4$ [M] 170.1, found: 170.1

Synthesis of B_2bg_2

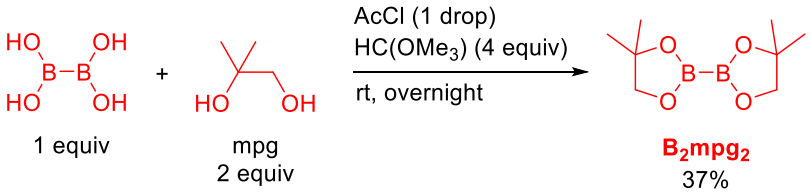


$B_2(OH)_4$ (3.59 g, 40 mmol, 1 equiv) and $CH(OMe)_3$ (16.98 g, 160 mmol, 4 equiv) were stirred in a Schlenk flask and the suspension was degassed with N_2 for 15 minutes. One drop of acetyl chloride, AcCl, was added and the mixture becomes a homogenous solution. Butylene glycol (bg, 7.21 g, 80 mmol, 2 equiv) was added and the reaction was stirred at room temperature

overnight. The mixture was concentrated and then distilled under reduce pressure to yield 6.78 g of B_2bg_2 as a colorless oil (86% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 – 4.30 (m, 1H), 4.23 (dd, *J* = 9.0, 8.1 Hz, 1H), 3.77 (ddd, *J* = 9.0, 7.3, 1.7 Hz, 1H), 1.73 – 1.50 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.44, 70.19, 28.79, 28.78, 9.13. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.62. GC-MS (EI) *m/*z calcd for $C_8H_{16}B_2O_4$ [M] 198.1, found: 198.1

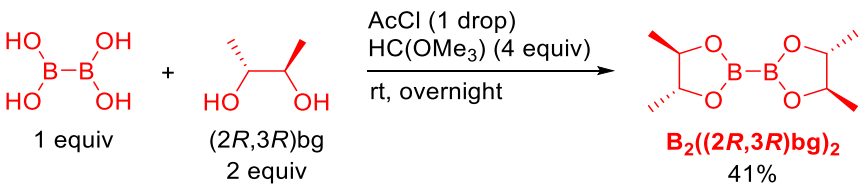
Synthesis of B_2mpg_2



$B_2(OH)_4$ (896 mg, 10 mmol, 1 equiv) and $CH(OMe)_3$ (4.24 g, 40 mmol, 4 equiv) were stirred in a Schlenk flask and the suspension was degassed with N_2 for 15 minutes. One drop of acetyl chloride, AcCl, was added and the mixture becomes a homogenous solution. 2-methyl-1,2-propandiol (mpg, 1.80 g, 20 mmol, 2 equiv) was added and the reaction was stirred at room temperature overnight. The mixture was concentrated and then distilled under reduce pressure to yield 730 mg of B_2mpg_2 as a colorless oil (37% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 1H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.27, 77.10, 28.40. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.81. GC-MS (EI) *m/*z calcd for $C_8H_{16}B_2O_4$ [M] 198.1, found: 198.1

Synthesis of $B_2((2R,3R)bg)_2$

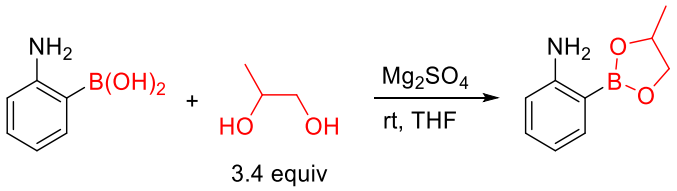


$B_2(OH)_4$ (896 mg, 10 mmol, 1 equiv) and $CH(OMe)_3$ (4.24 g, 40 mmol, 4 equiv) were stirred in a Schlenk flask and the suspension was degassed with N_2 for 15 minutes. One drop of acetyl chloride, AcCl, was added and the mixture becomes a homogenous solution. (2*R*,3*R*)-butanediol ((2*R*,3*R*)bg, 1.80 g, 20 mmol, 2 equiv) was added and the reaction was stirred at room temperature overnight. The mixture was concentrated and then distilled under reduce pressure to yield 820 mg of $B_2(2R,3R)bg_2$ as a colorless oil (41% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (qd, *J* = 4.0, 2.1 Hz, 4H), 1.33 – 1.22 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.3, 20.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.5. GC-MS (EI) *m/*z calcd for $C_8H_{16}B_2O_4$ [M] 198.1, found: 198.1

2.4.3. Synthesis of *ortho, meta* and *Para* Bpg-borylated aniline by transesterification

Synthesis of *ortho* borylated aniline with a Bpg group by transesterification (2.1)

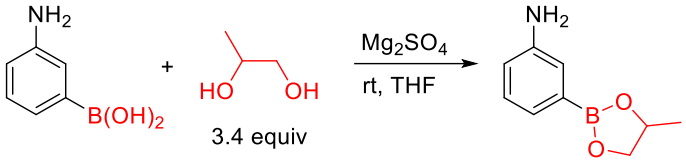


2-Aminophenyl boronic acid (274 mg, 2 mmol, 1 equiv), 1,2-propandiol (517 mg, 6.8 mmol, 3.4 equiv), Mg_2SO_4 anhydrous (100 mg) and THF (1.6 mL) were placed in a round bottom flask and stirred overnight at room temperature. After 12 h, the mixture was concentrated and purified by column chromatography with silica gel (hexane: ethyl acetate = 4: 1 as eluent) to remove the excess of diol. The fractions containing product were collected and concentrated to give 56 mg of **2.1** as a colorless oil (16% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.2, 1.7 Hz, 1H), 6.69 (td, *J* = 7.3, 1.0 Hz, 1H), 6.61 (dd, *J* = 8.2 Hz, 0.9 Hz, 1H), 4.84-4.53 (m, 3H), 4.44 (dd, *J* =

8.8, 7.6 Hz, 1H), 3.88 (dd, *J* = 8.8, 7.2 Hz, 1H), 1.41 (d, *J* = 6.2 Hz, 3H). ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.4. HRMS (ESI) *m/z* calcd for $C_9H_{13}BNO_2$ $[M+H]^+$ 178.1039, found: 178.1043.

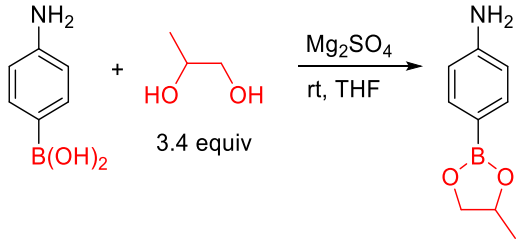
Synthesis of *meta* borylated aniline with a Bpg group by transesterification



3-Aminophenyl boronic acid (274 mg, 2 mmol, 1 equiv), 1,2-propandiol (517 mg, 6.8 mmol, 3.4 equiv) and THF (1.6 mL) were placed in a round bottom flask and stirred overnight at room temperature. After 12 h, the mixture was concentrated and purified by column chromatography with silica gel (hexane: ethyl acetate = 3: 2 as eluent) to remove the excess of diol. The fractions containing product were collected and concentrated to give 300 mg of the product as a colorless oil (85% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.17 (m, 2H), 7.15 (dd, *J* = 2.6, 0.9 Hz, 1H), 6.81 (ddd, *J* = 7.6, 2.6, 1.5 Hz, 1H), 4.71 (ddt, *J* = 13.7, 7.5, 6.2 Hz, 1H), 4.44 (dd, *J* = 8.8, 7.7 Hz, 1H), 3.88 (dd, *J* = 8.8, 7.2 Hz, 1H), 3.66 (s, 2H), 1.41 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.82, 128.84, 124.99, 121.16, 118.18, 73.71, 72.50, 21.80. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.44.

Synthesis of *para* borylated aniline with a Bpg group by transesterification

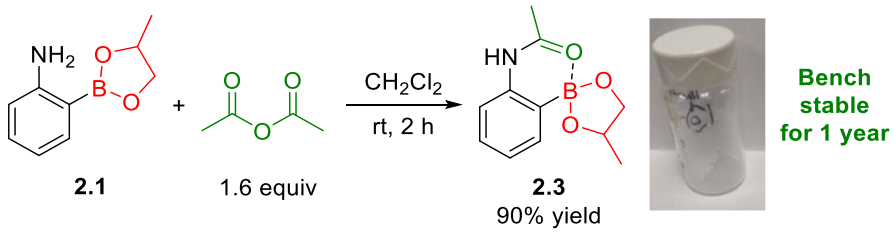


4-Aminophenyl boronic acid hydrochloride (347 mg, 2 mmol, 1 equiv) was fractionated between ethyl acetate and NaOH 0.01 M. The organic phase was evaporated and 1,2-propandiol (517 mg, 6.8 mmol, 3.4 equiv), THF (1.6 mL) were added. The reaction mixture was stirred

overnight at room temperature. After 12 h, the mixture was concentrated and purified by column chromatography with silica gel (hexane: ethyl acetate = 3: 2 as eluent) to remove the excess of diol. The fractions containing product were collected and concentrated to give 160 mg of the product as a light brown solid (45% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 2H), 6.73 – 6.64 (m, 2H), 4.68 (ddt, *J* = 13.7, 7.4, 6.3 Hz, 1H), 4.41 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.85 (dd, *J* = 8.8, 7.2 Hz, 3H), 1.40 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.38, 136.43, 114.15, 73.45, 72.35, 21.77. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.38. HRMS (ESI) *m/z* calcd for $C_9H_{13}BNO_2$ $[M+H]^+$ 178.1039, found: 178.1039.

2.4.4. Synthesis of *ortho* borylated acetamide with a Bpg group by transesterification (2.3)



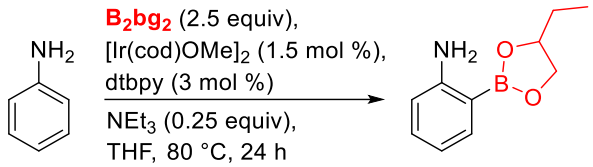
2.1 1.6 equiv **2.3** 90% yield

In a 20 mL vial, **2.1** (177 mg, 1 mmol, 1 equiv) was stirred with acetic anhydride (0.15 mL, 1.6 mmol, 1.6 equiv) in DCM (2.7 mL) at room temperature. After 2 h, the mixture was concentrated under reduce pressure and diethyl ether was added to crashed out a solid. The white solid was filtrate to yield 197 mg of **2.3** (90% yield, mp 192.5-194.5 °C)

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.39 (bs, 1H), 7.59 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.17 (m, 2H), 6.96 (d, *J* = 7.5 Hz, 1H), 4.52 (dq, *J* = 12.2, 6.1 Hz, 1H), 4.27 (dd, *J* = 8.3, 6.1 Hz, 1H), 3.70 (t, *J* = 7.9 Hz, 1H), 1.64 (s, 3H), 1.34 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 137.9, 133.2, 128.6, 126.6, 116.1, 71.7, 71.5, 21.1, 20.6. ^{11}B NMR (160 MHz, $CDCl_3$) δ 10.4.

2.4.5. CHB of anilines with B_2bg_2 as diboron partner

Borylation of aniline with B_2bg_2 (2.4)

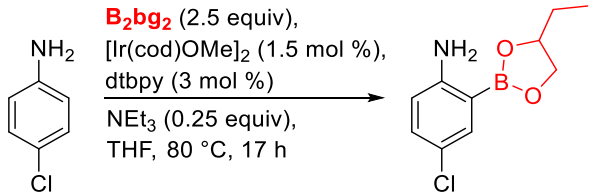


2.4, 54% yield

In a nitrogen filled glove box, a 5.0 mL conical vial was charged with $[Ir(cod)(OMe)]_2$ (10 mg, 1.5 mol %), dtbpy (8 mg, 3.0 mol %), B_2bg_2 (495 mg, 2.5 mmol, 2.5 equiv), aniline (93 mg, 1.0 mmol, 1 equiv) and Et_3N (0.04 mL, 0.25 mmol, 0.25 equiv) in dry THF (3.0 mL). The vial was capped with a teflon pressure cap, taken out of the glove box and stirred into a pre-heated aluminum block at 80 °C. After 24 h, the mixture was concentrated under reduced pressure and purified by gradient column chromatography with silica gel (hexane/ethyl acetate 10:90 → hexane/ ethyl acetate 30:70). The fractions containing product were collected to yield 103 mg of **2.4** as a thick oil (54% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.2, 1.7 Hz, 1H), 6.69 (ddd, *J* = 7.2, 7.5, 1.0 Hz, 1H), 6.61 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.71 (bs, 2H), 4.52 (dtd, *J* = 7.8, 6.9, 5.8 Hz, 1H), 4.40 (dd, *J* = 8.8, 7.8 Hz, 1H), 3.95 (dd, *J* = 8.8, 6.9 Hz, 1H), 1.80 – 1.61 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 137.0, 133.0, 117.1, 115.0, 78.5, 70.5, 29.1, 9.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.5.

Borylation of 4-chloroaniline with B_2bg_2 (2.5)

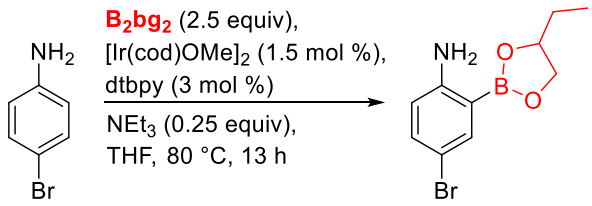


2.5, 58% yield

In a nitrogen filled glove box, a 5.0 mL conical vial was charged with $[Ir(cod)(OMe)]_2$ (10 mg, 1.5 mol %), dtbpy (8 mg, 3.0 mol %), B_2bg_2 (495 mg, 2.5 mmol, 2.5 equiv), 4-chloroaniline (127 mg, 1.0 mmol, 1 equiv) and Et_3N (0.04 mL, 0.25 mmol, 0.25 equiv) in dry THF (3.0 mL). The vial was capped with a teflon pressure cap, taken out of the glove box and stirred into a pre-heated aluminum block at 80 °C. After 17 h, the mixture was concentrated under reduced pressure and purified by gradient column chromatography with silica gel (hexane/ethyl acetate 10:90 → hexane/ ethyl acetate 20:80). The fractions containing product were collected to yield 131 mg of **2.5** as a thick oil (58% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.6 Hz, 1H), 7.15 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.54 (d, *J* = 8.6 Hz, 1H), 4.71 (bs, 2H), 4.52 (dtd, *J* = 7.8, 7.0, 5.7 Hz, 1H), 4.41 (dd, *J* = 8.9, 7.8 Hz, 1H), 3.95 (dd, *J* = 8.9, 7.0 Hz, 1H), 1.78 – 1.61 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1, 136.0, 132.8, 121.8, 116.4, 78.7, 70.7, 29.0, 9.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.1.

Borylation of 4-bromoaniline with B_2bg_2 (2.6)



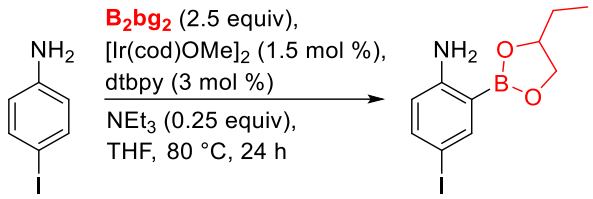
2.6, 68% yield

In a nitrogen filled glove box, a 5.0 mL conical vial was charged with $[Ir(cod)(OMe)]_2$ (10 mg, 1.5 mol %), dtbpy (8 mg, 3.0 mol %), B_2bg_2 (495 mg, 2.5 mmol, 2.5 equiv), 4-bromoaniline (172 mg, 1.0 mmol, 1 equiv) and Et_3N (0.04 mL, 0.25 mmol, 0.25 equiv) in dry THF (3.0 mL). The vial was capped with a teflon pressure cap, taken out of the glove box and stirred into a pre-heated aluminum block at 80 °C. After 13 h, the mixture was concentrated under reduced pressure

and purified by gradient column chromatography with silica gel (hexane/ethyl acetate 10:90 → hexane/ ethyl acetate 20:80). The fractions containing product were collected to yield 183 mg of **2.6** as a thick oil (68% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 2.5 Hz, 1H), 7.28 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 4.72 (bs, 2H), 4.52 (dtd, *J* = 7.8, 7.0, 5.7 Hz, 1H), 4.41 (dd, *J* = 8.9, 7.8 Hz, 1H), 3.95 (dd, *J* = 8.9, 7.0 Hz, 1H), 1.80 – 1.61 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 139.0, 135.6, 116.9, 108.9, 78.7, 70.7, 29.0, 9.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.0.

Borylation of 4-iodoaniline with B_2bg_2 (2.7)



2.7, 50% yield

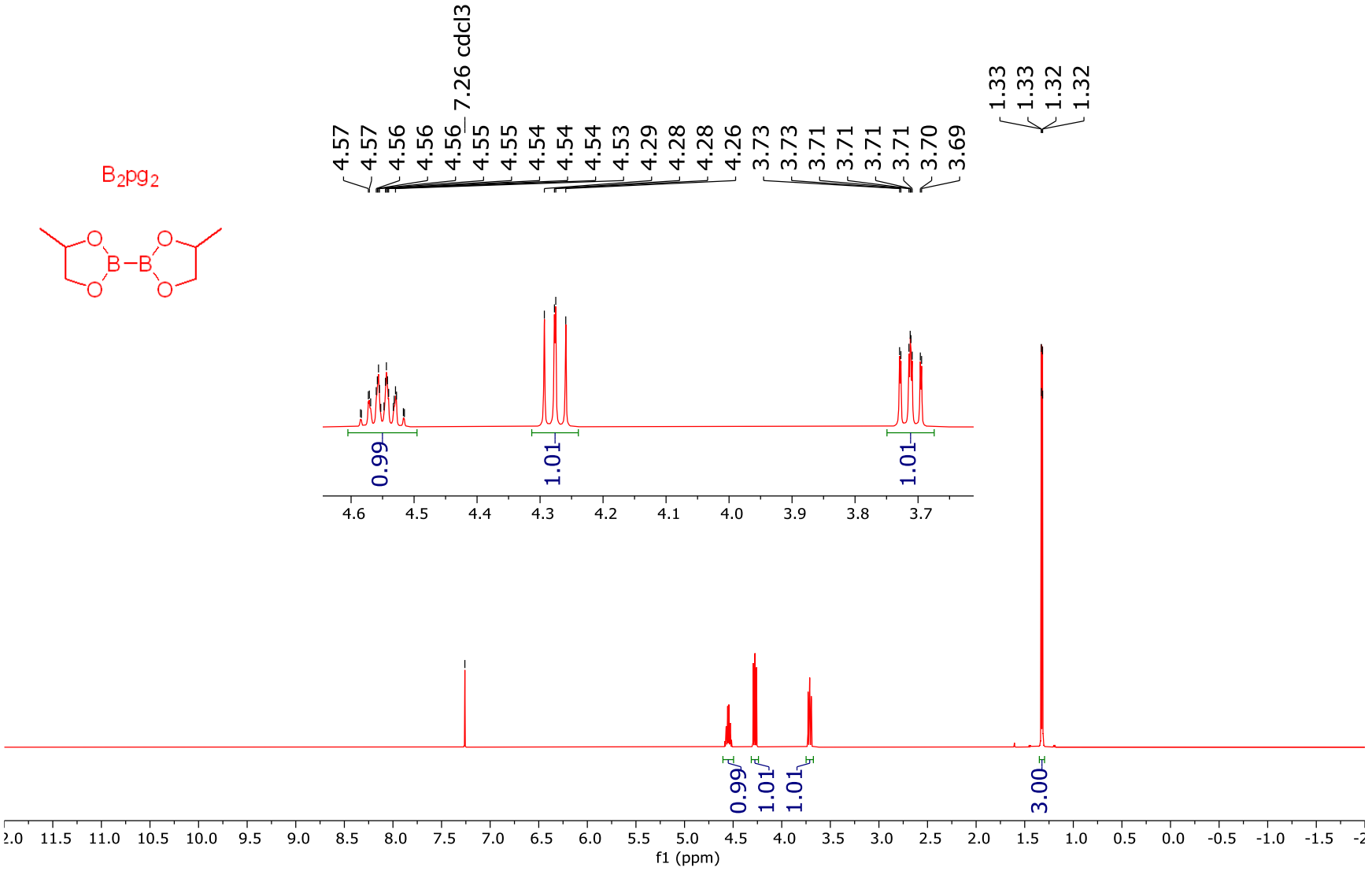
In a nitrogen filled glove box, a 5.0 mL conical vial was charged with $[Ir(cod)(OMe)]_2$ (10 mg, 1.5 mol %), dtbpy (8 mg, 3.0 mol %), B_2bg_2 (495 mg, 2.5 mmol, 2.5 equiv), 4-iodoaniline (219 mg, 1.0 mmol, 1 equiv) and Et_3N (0.04 mL, 0.25 mmol, 0.25 equiv) in dry THF (3.0 mL). The vial was capped with a teflon pressure cap, taken out of the glove box and stirred into a pre-heated aluminum block at 80 °C. After 24 h, the mixture was concentrated under reduced pressure and purified by gradient column chromatography with silica gel (hexane/ethyl acetate 10:90 → hexane/ ethyl acetate 30:70). The fractions containing product were collected to yield 158 mg of **2.7** as a thick oil (50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.3 Hz, 1H), 7.44 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.41 (d, *J* = 8.5 Hz, 1H), 4.51 (ddd, *J* = 7.8, 7.0, 5.7 Hz, 1H), 4.40 (dd, *J* = 8.9, 7.8 Hz, 1H), 4.18 (bs, 1H), 3.94 (dd, *J* = 8.9, 7.0 Hz, 1H), 1.80 – 1.60 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 153.0, 145.1, 141.2, 138.0, 117.4, 78.7, 70.7, 29.0, 9.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.7.

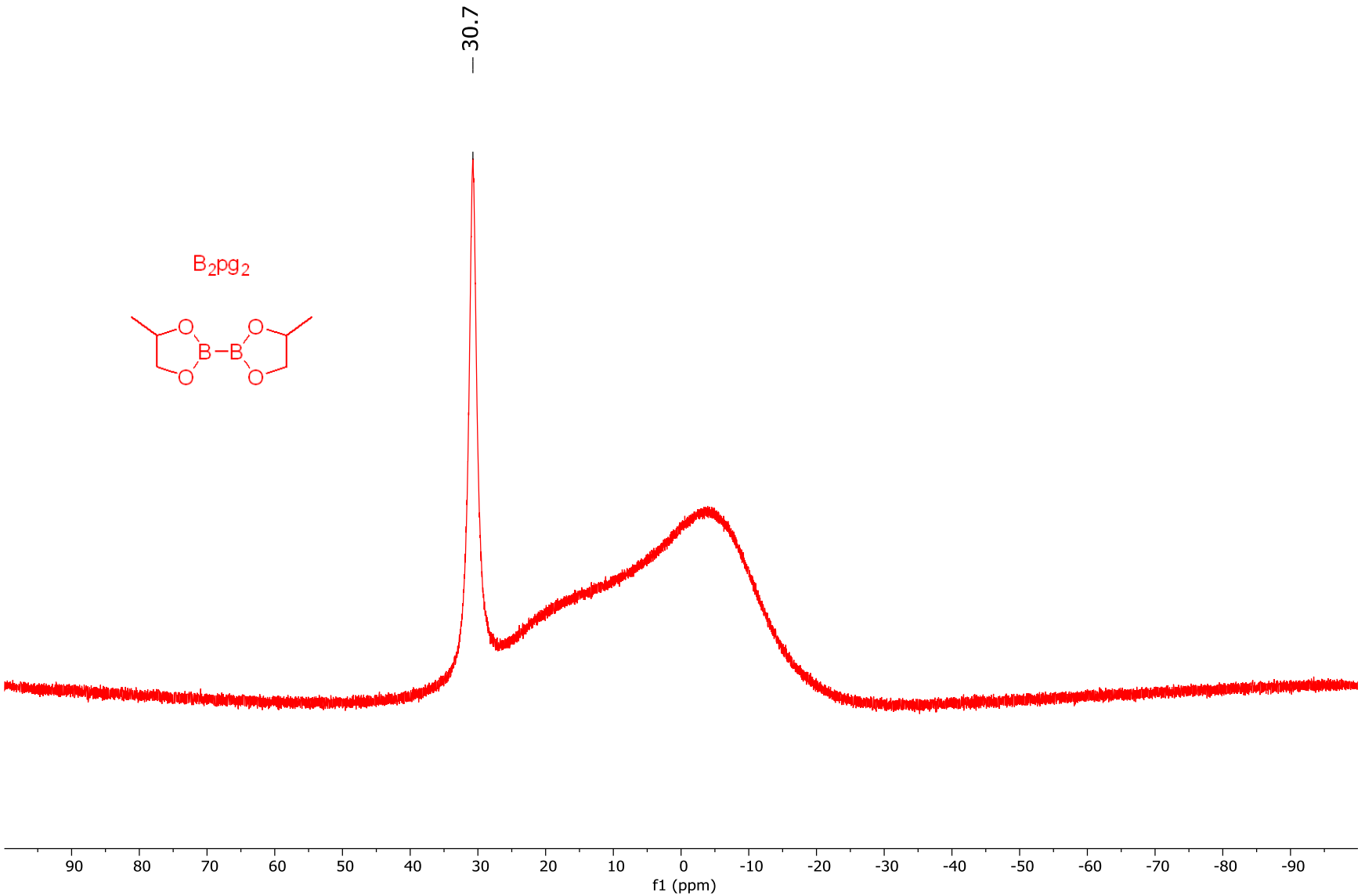
APPENDIX

^{1}H NMR of racemic B_2pg_2 ($CDCl_3$, 500 MHz)

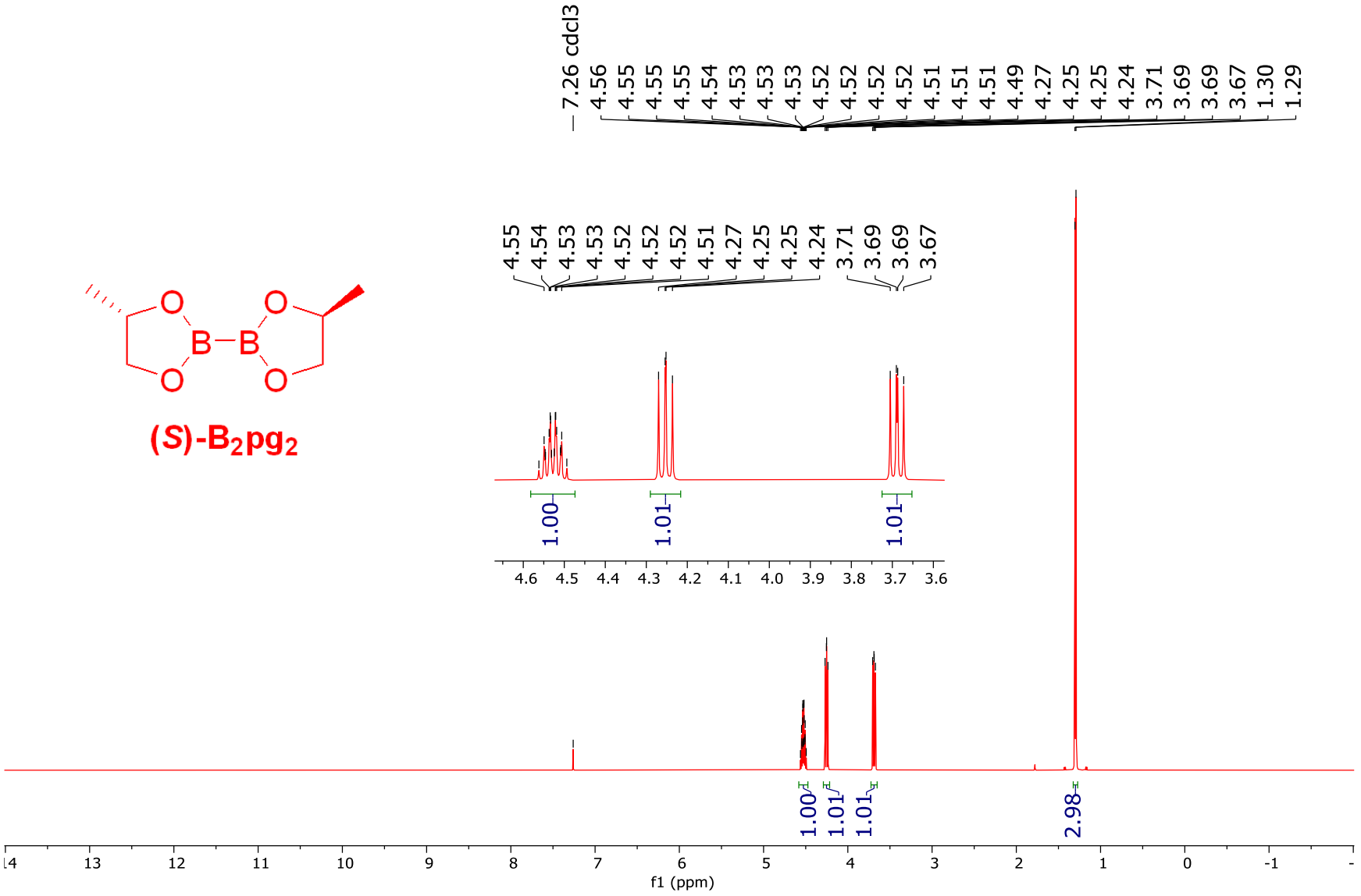


^{13}C NMR of racemic B_2pg_2 ($CDCl_3$, 126 MHz)

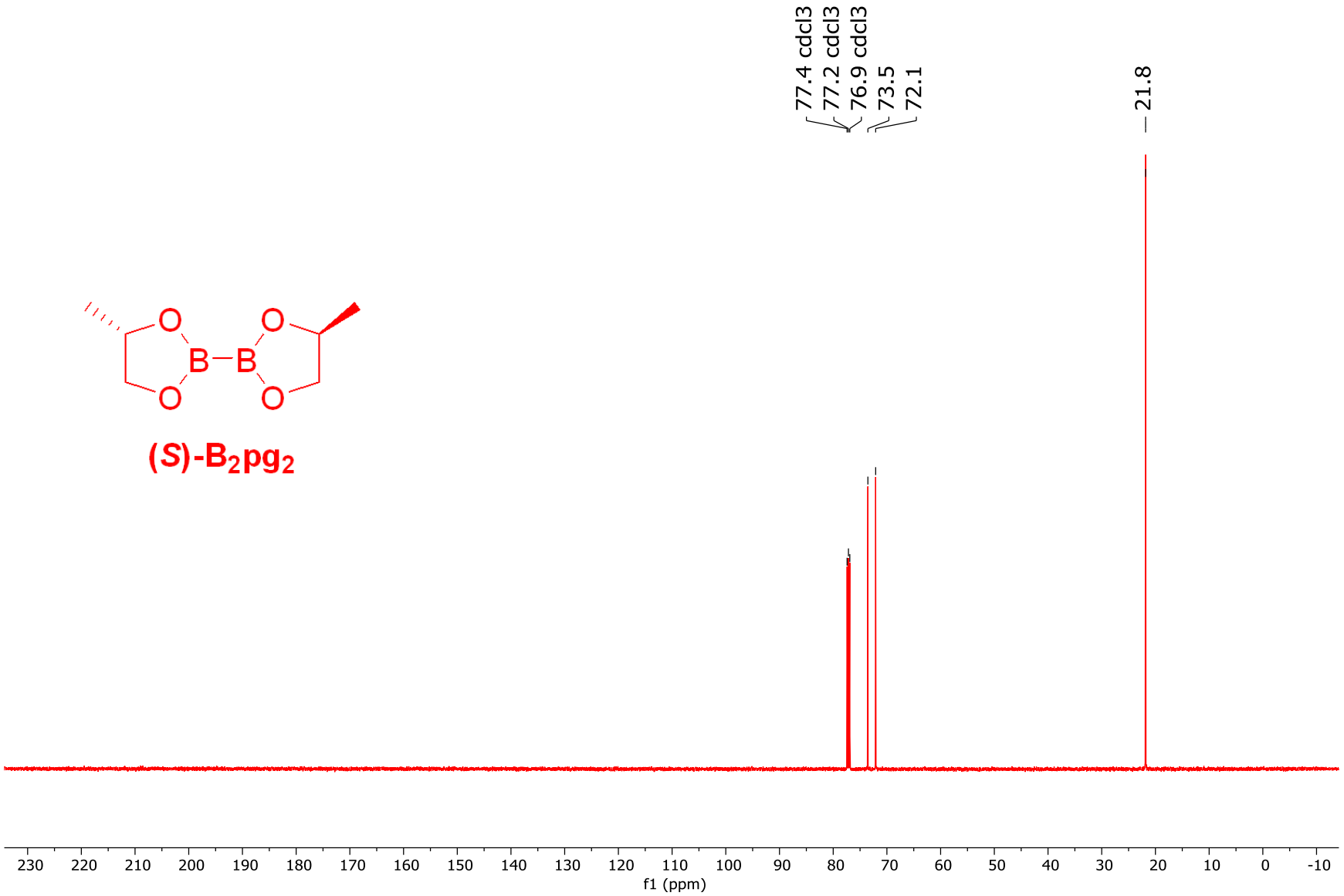
^{11}B NMR of racemic B_2pg_2 ($CDCl_3$, 160 MHz)



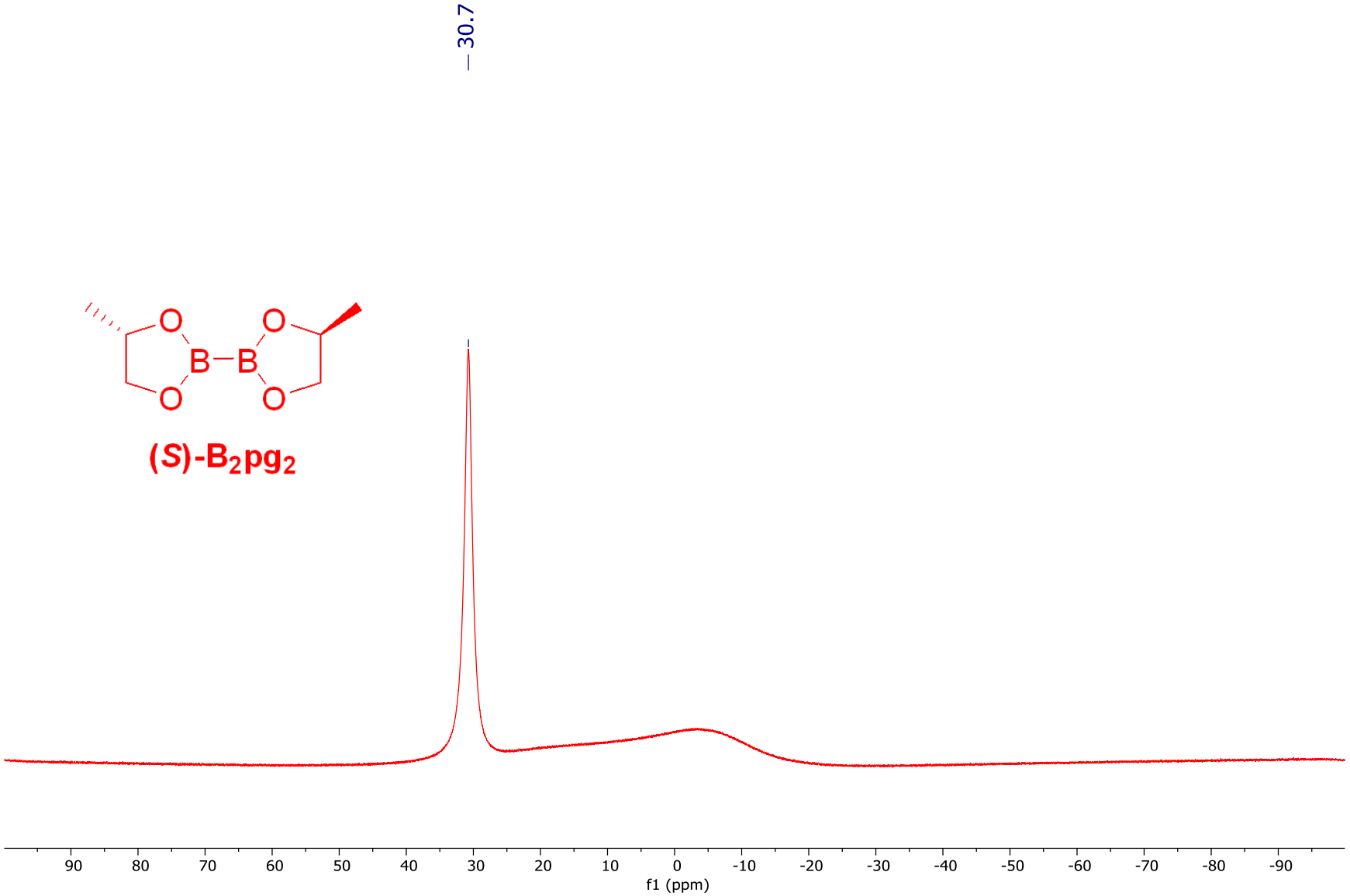
^{1}H NMR of (*S*)-B_2pg_2 ($CDCl_3$, 500 MHz)



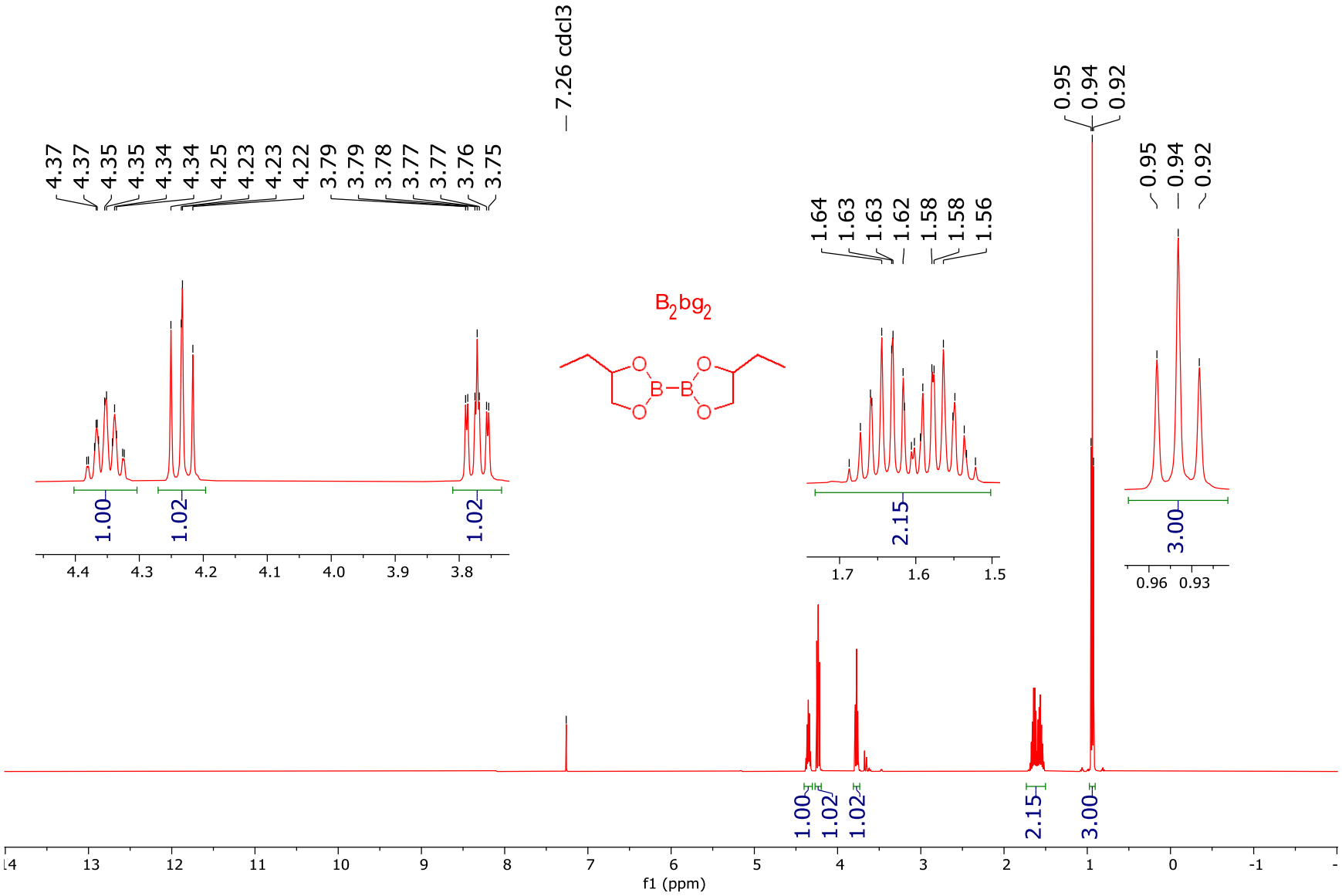
^{13}C NMR of (*S*)-B_2pg_2 ($CDCl_3$, 126 MHz)



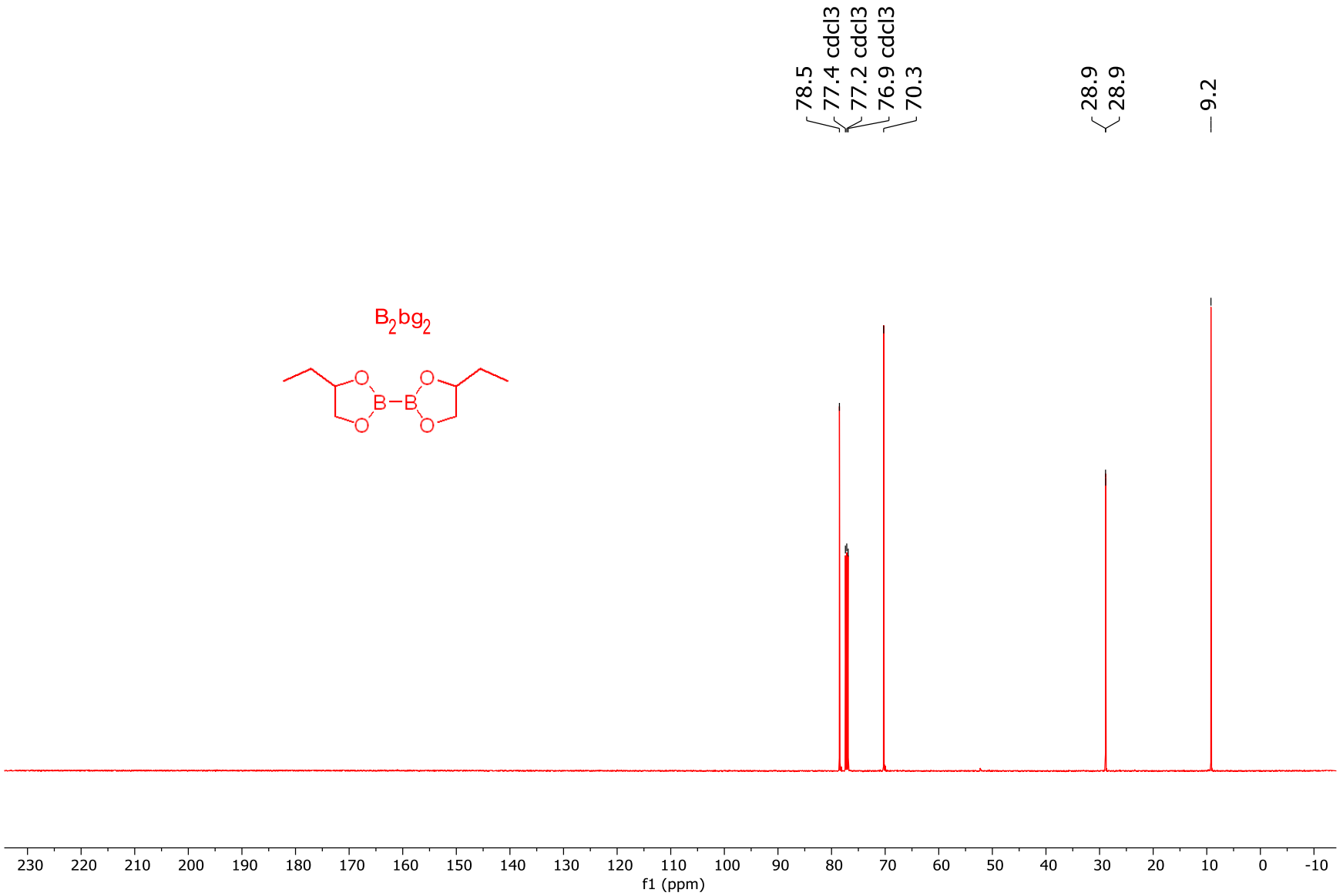
^{11}B NMR of (*S*)-B_2pg_2 ($CDCl_3$, 160 MHz)



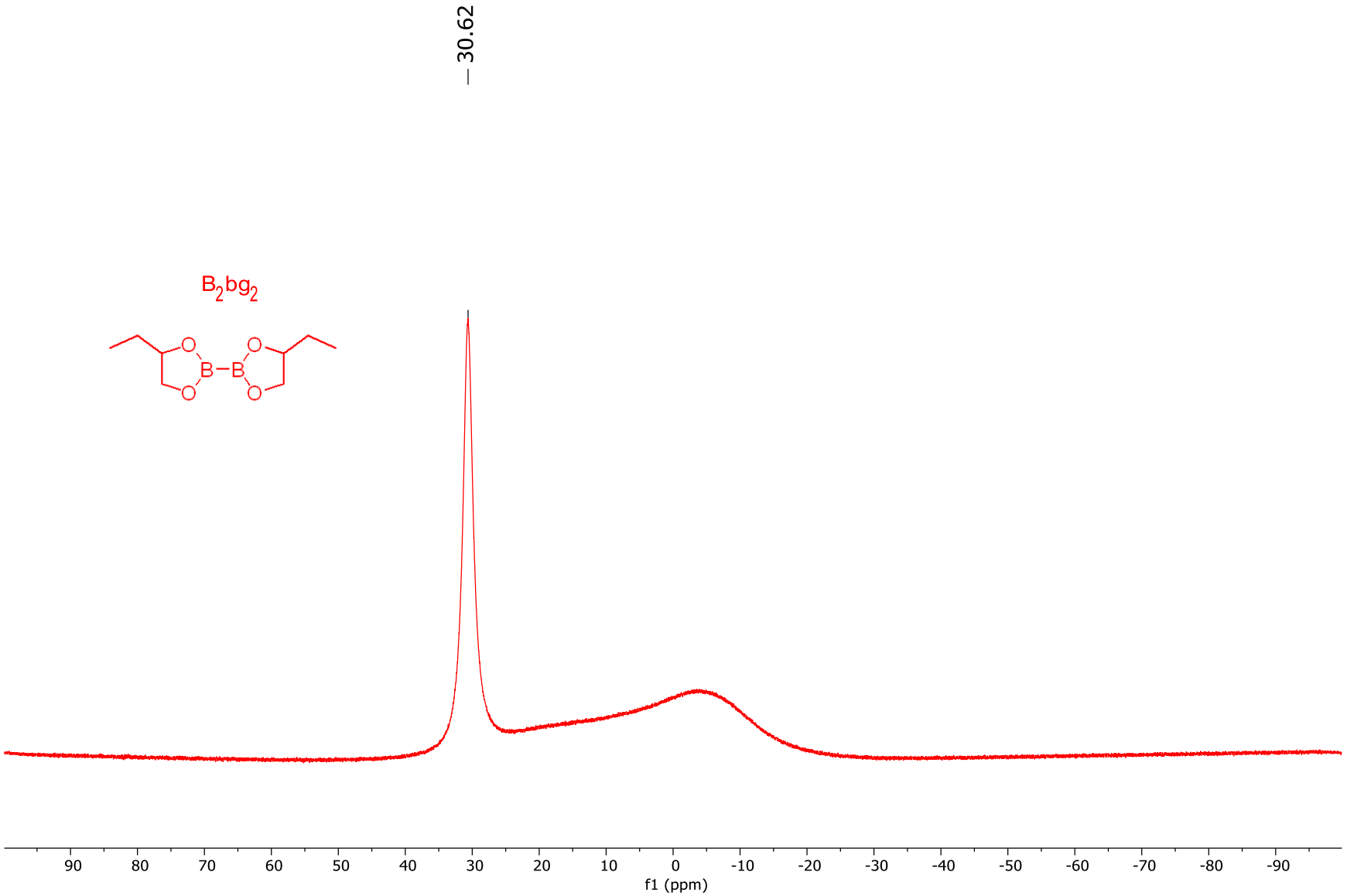
^{1}H NMR of B_2bg_2 ($CDCl_3$, 500 MHz)



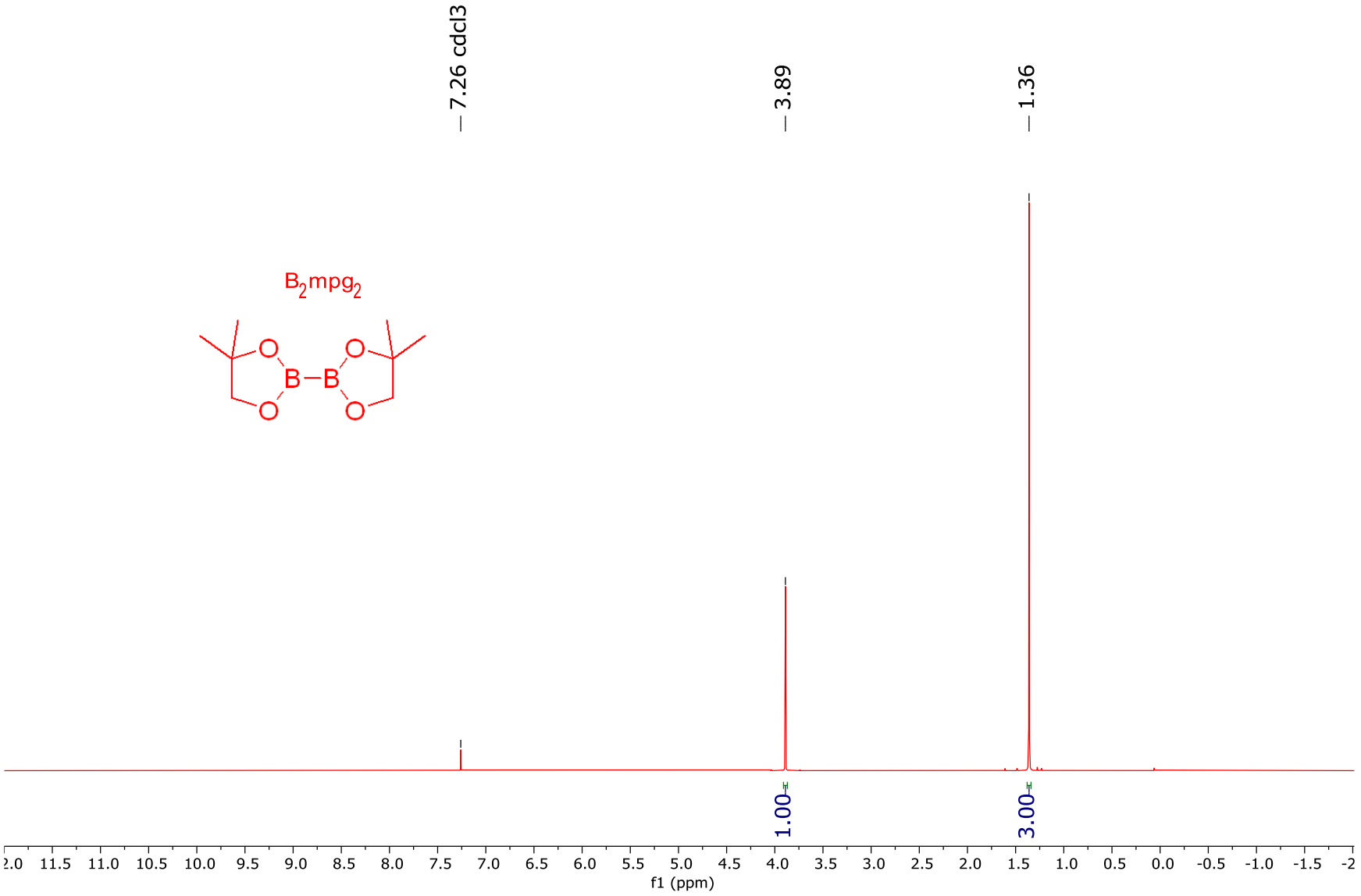
^{13}C NMR of B_2bg_2 ($CDCl_3$, 126 MHz)



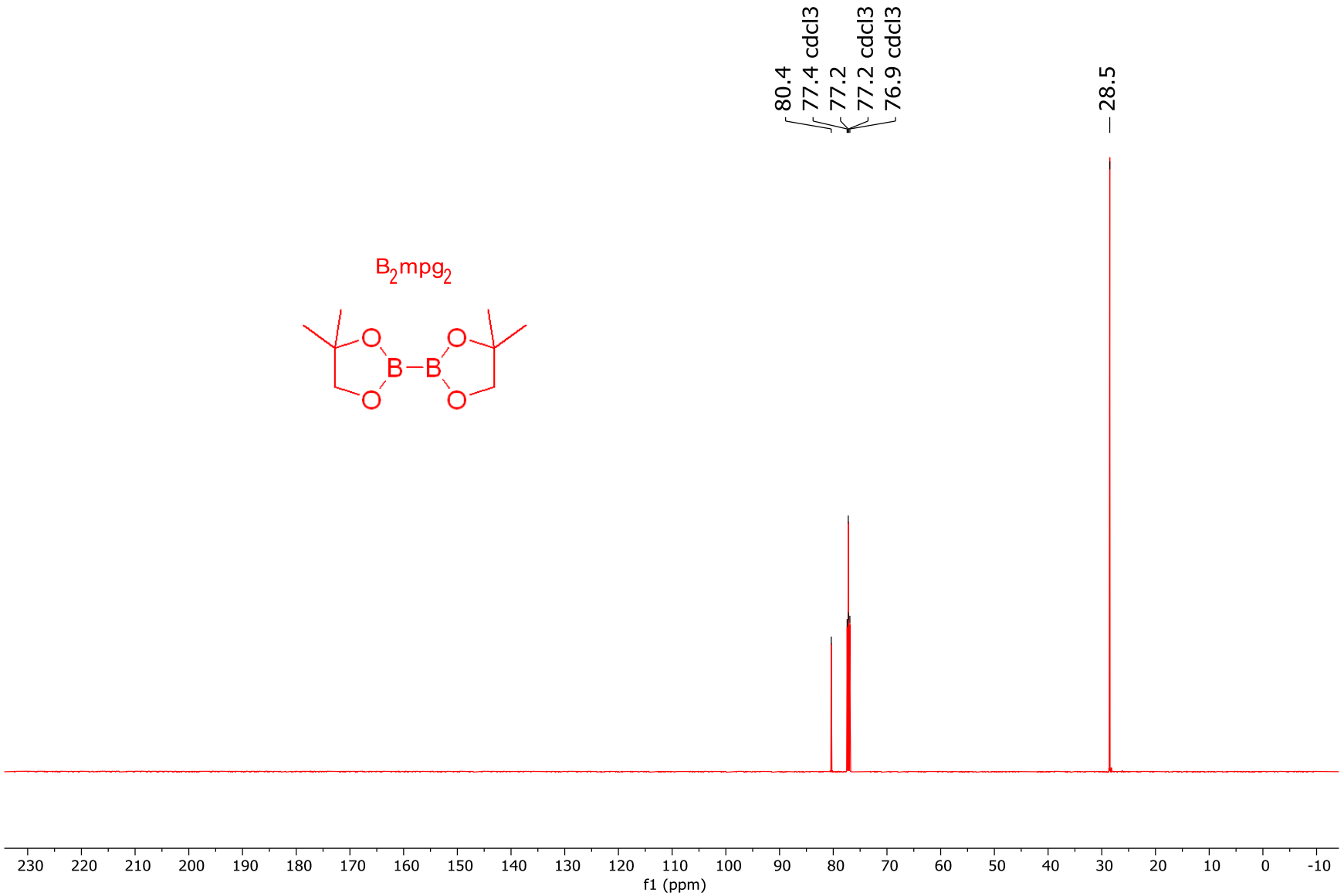
^{11}B NMR of B_2bg_2 ($CDCl_3$, 160 MHz)



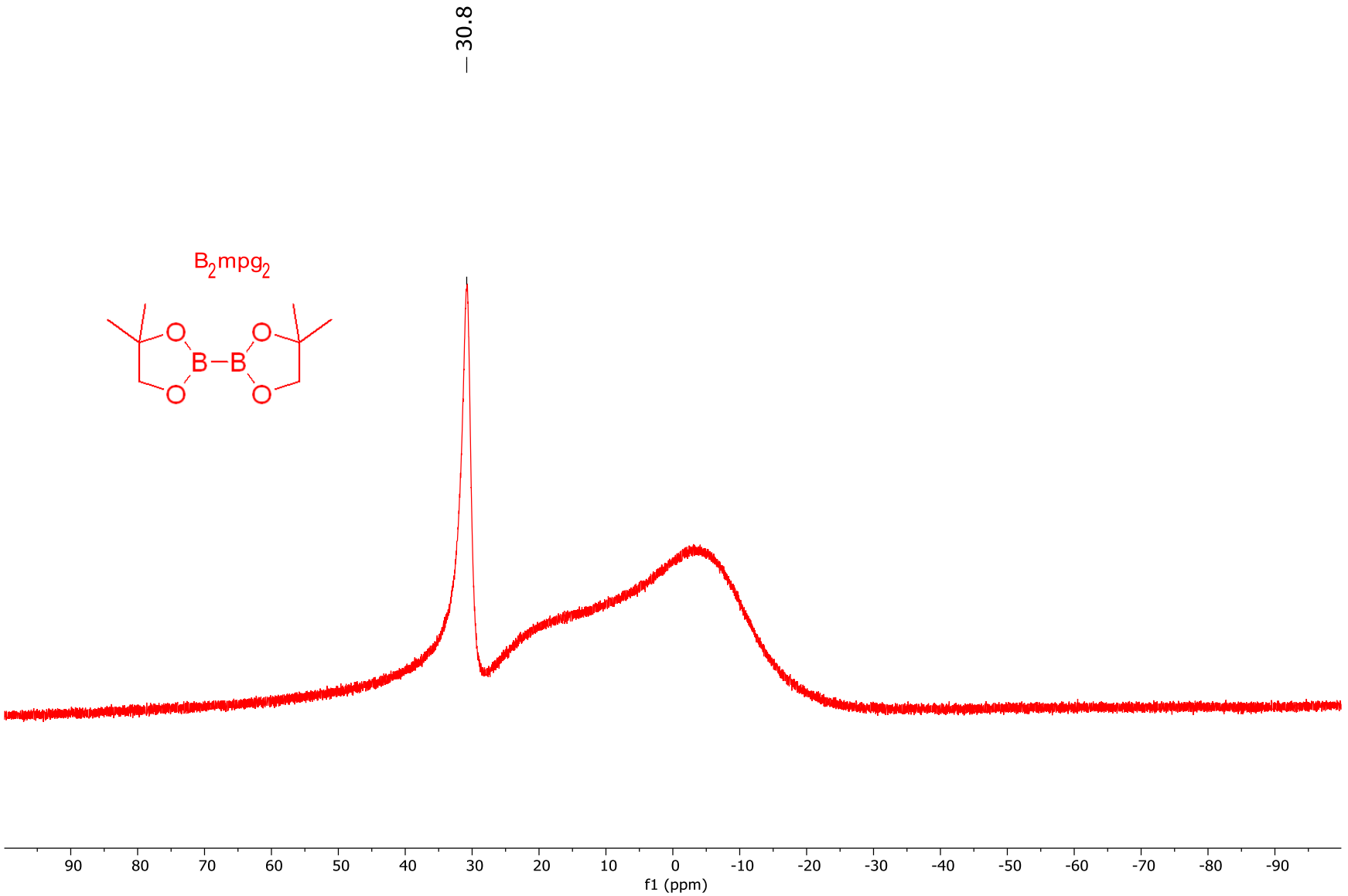
^{1}H NMR of B_2mpg_2 ($CDCl_3$, 500 MHz)



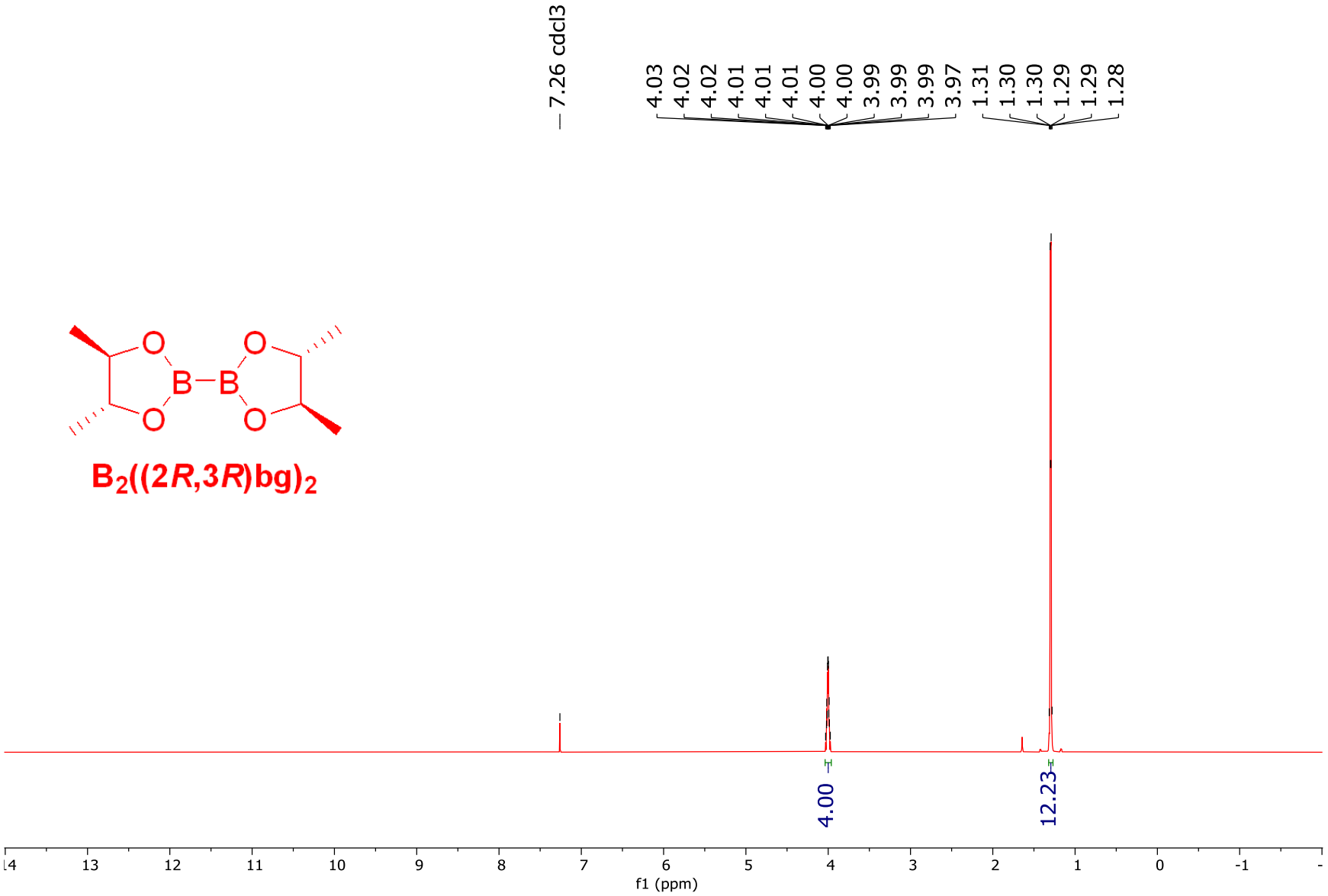
^{13}C NMR of B_2mpg_2 ($CDCl_3$, 126 MHz)



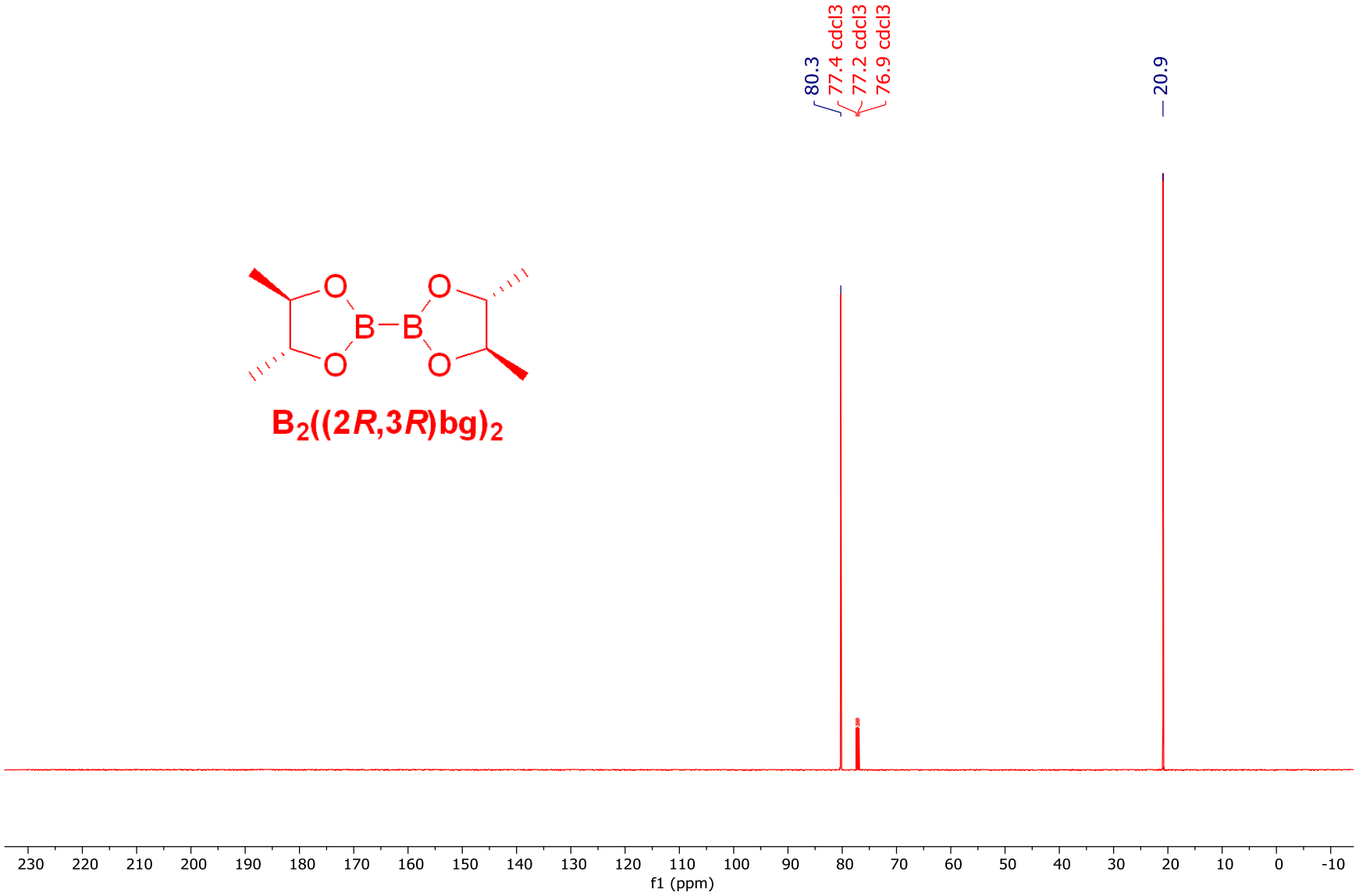
^{11}B NMR of B_2mpg_2 ($CDCl_3$, 160 MHz)



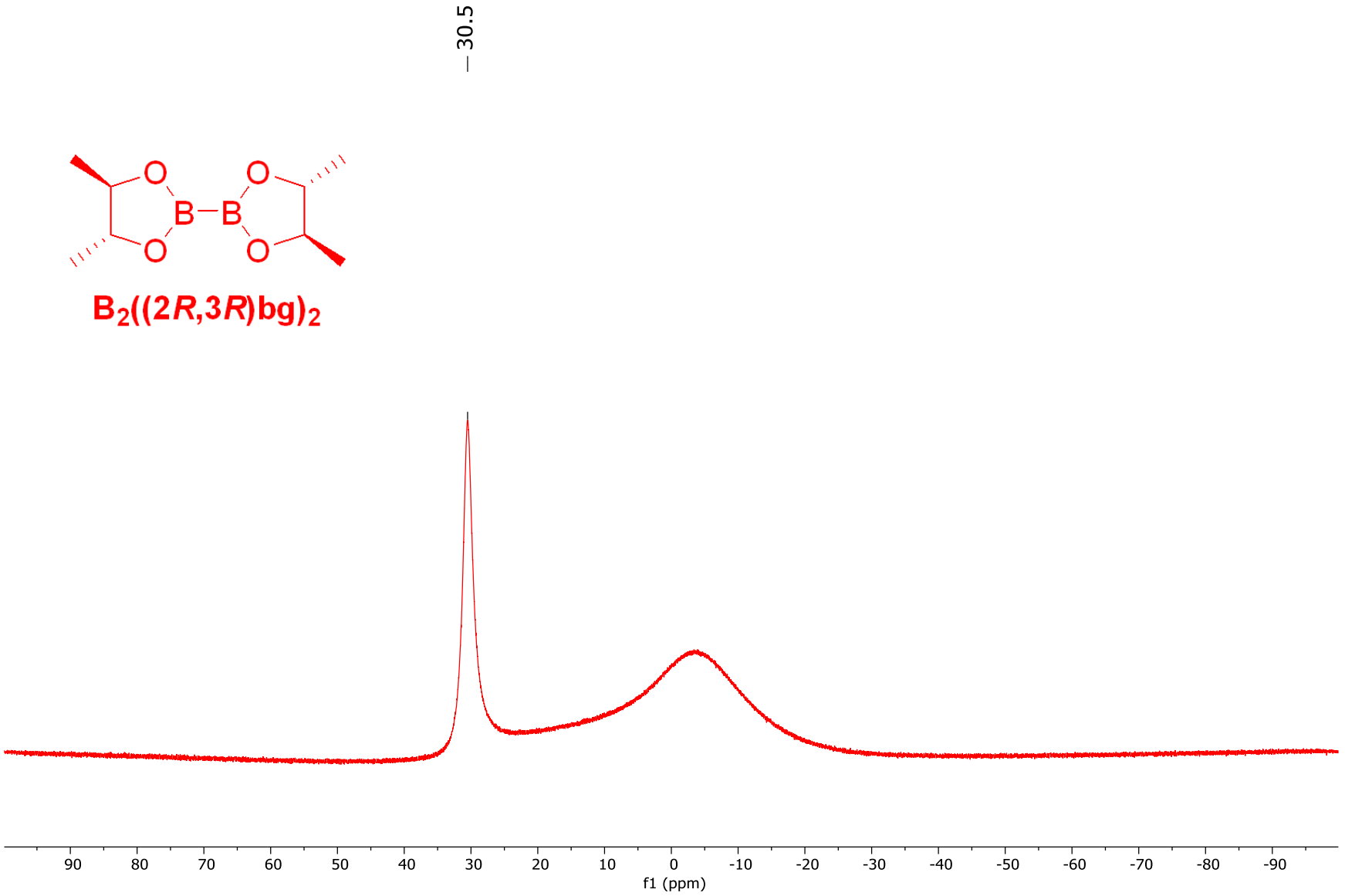
^{1}H NMR of $B_2((2R,3R)bg)_2$ ($CDCl_3$, 500 MHz)



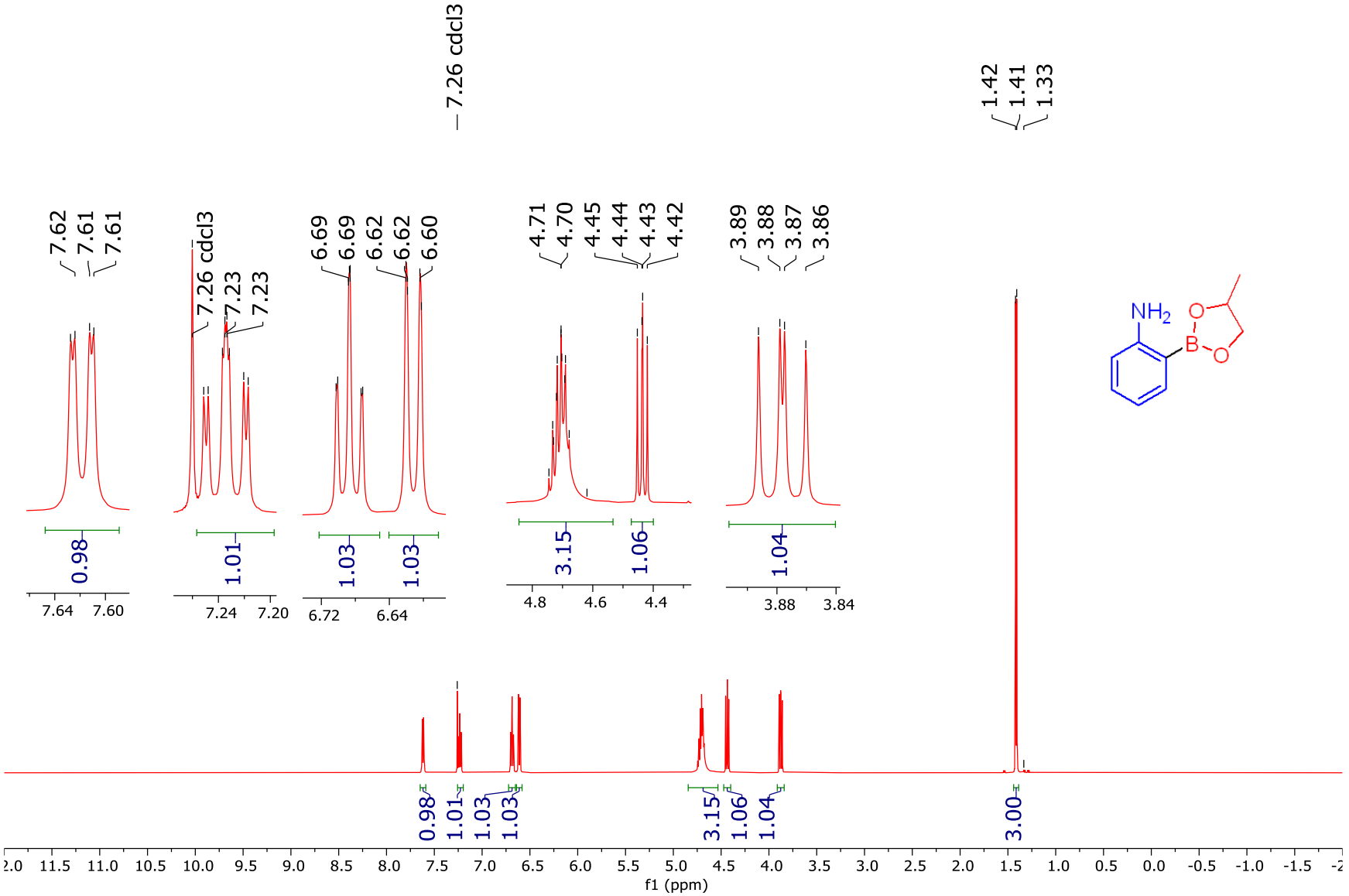
^{13}C NMR of $B_2((2R,3R)bg)_2$ ($CDCl_3$, 126 MHz)



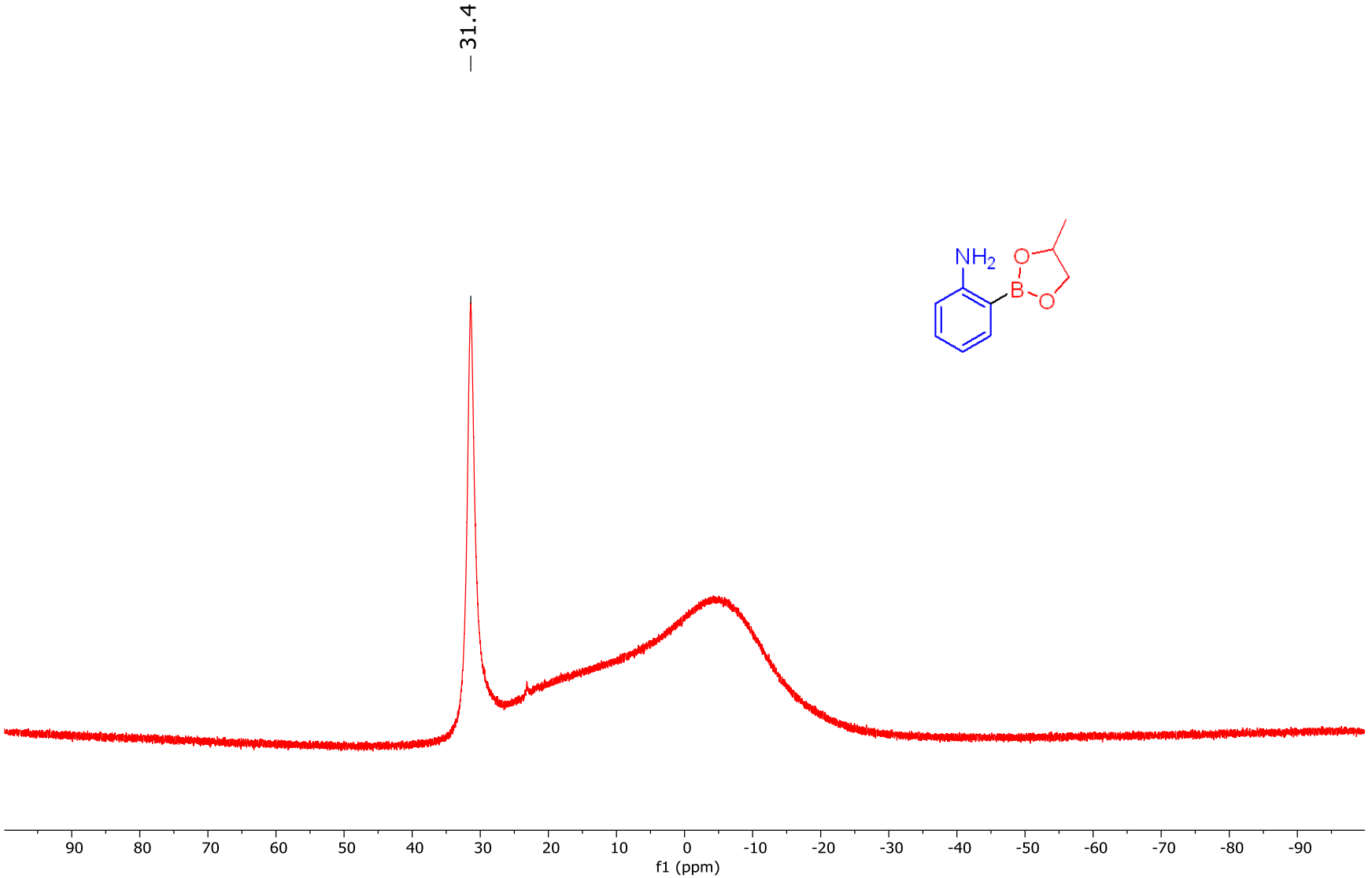
^{11}B NMR of $B_2((2R,3R)bg)_2$ ($CDCl_3$, 160 MHz)



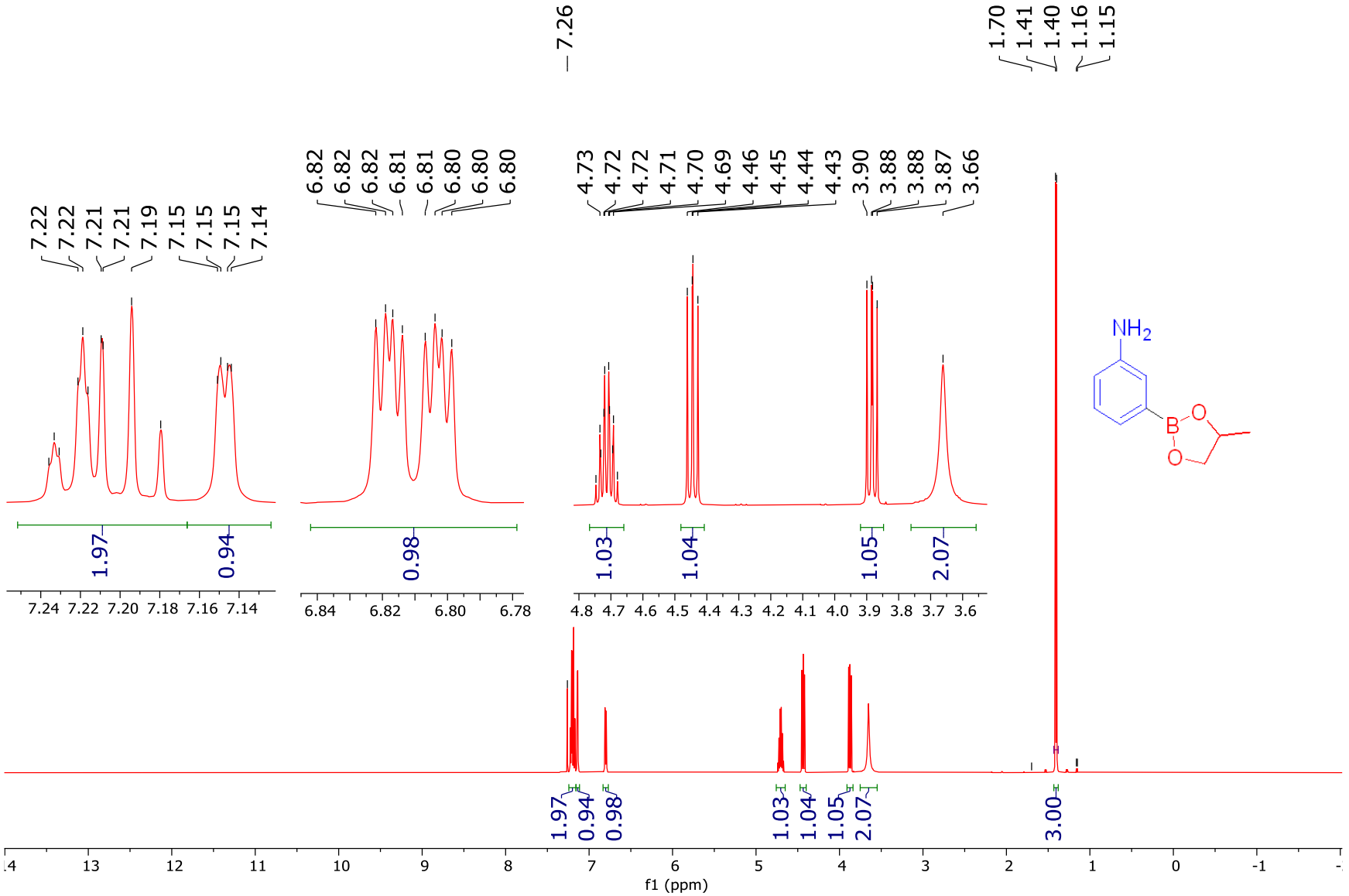
^{1}H NMR of *ortho* Bpg-borylated aniline (2.1) ($CDCl_3$, 500 MHz)



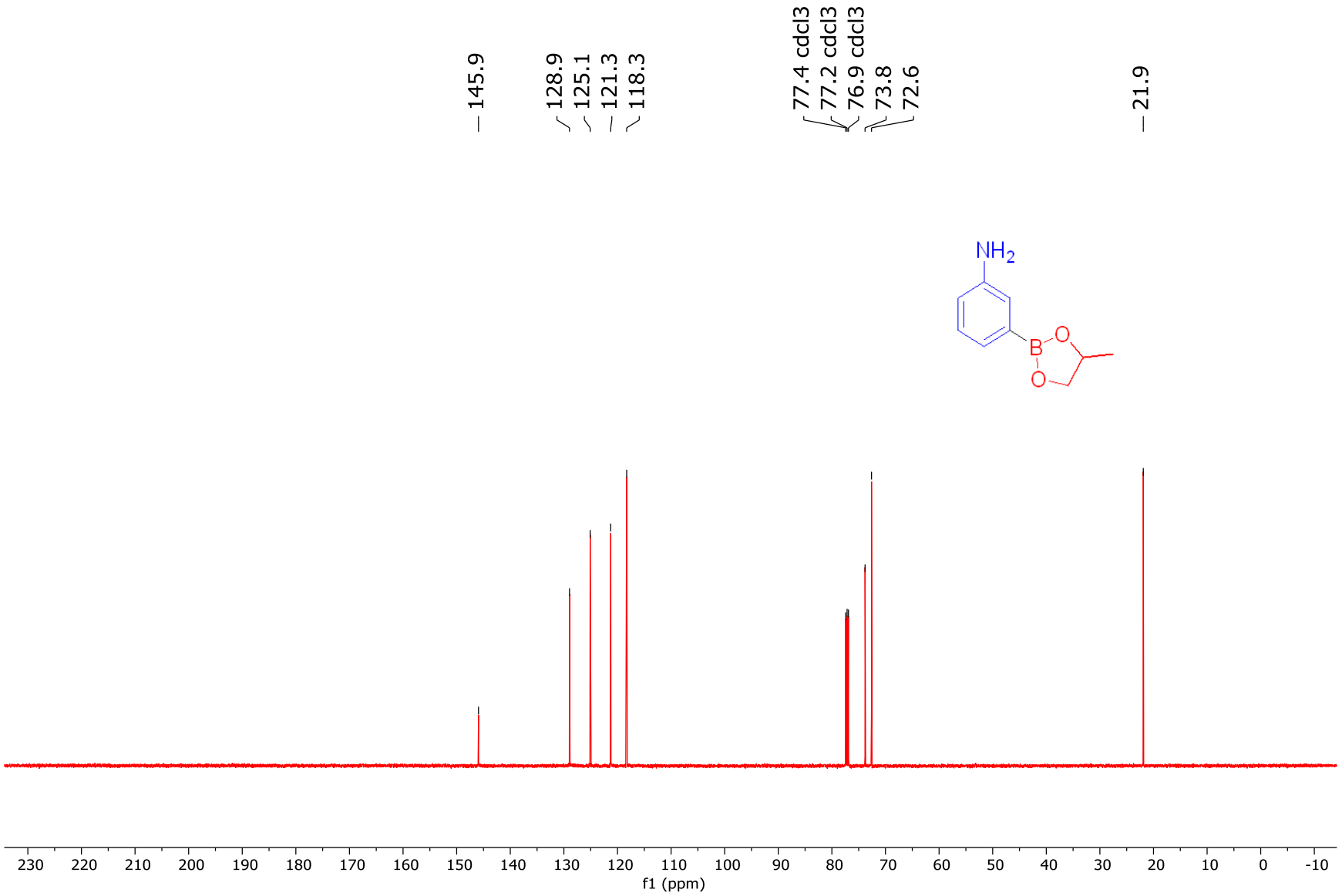
^{11}B NMR of *ortho* Bpg-borylated aniline (2.1) ($CDCl_3$, 160 MHz)



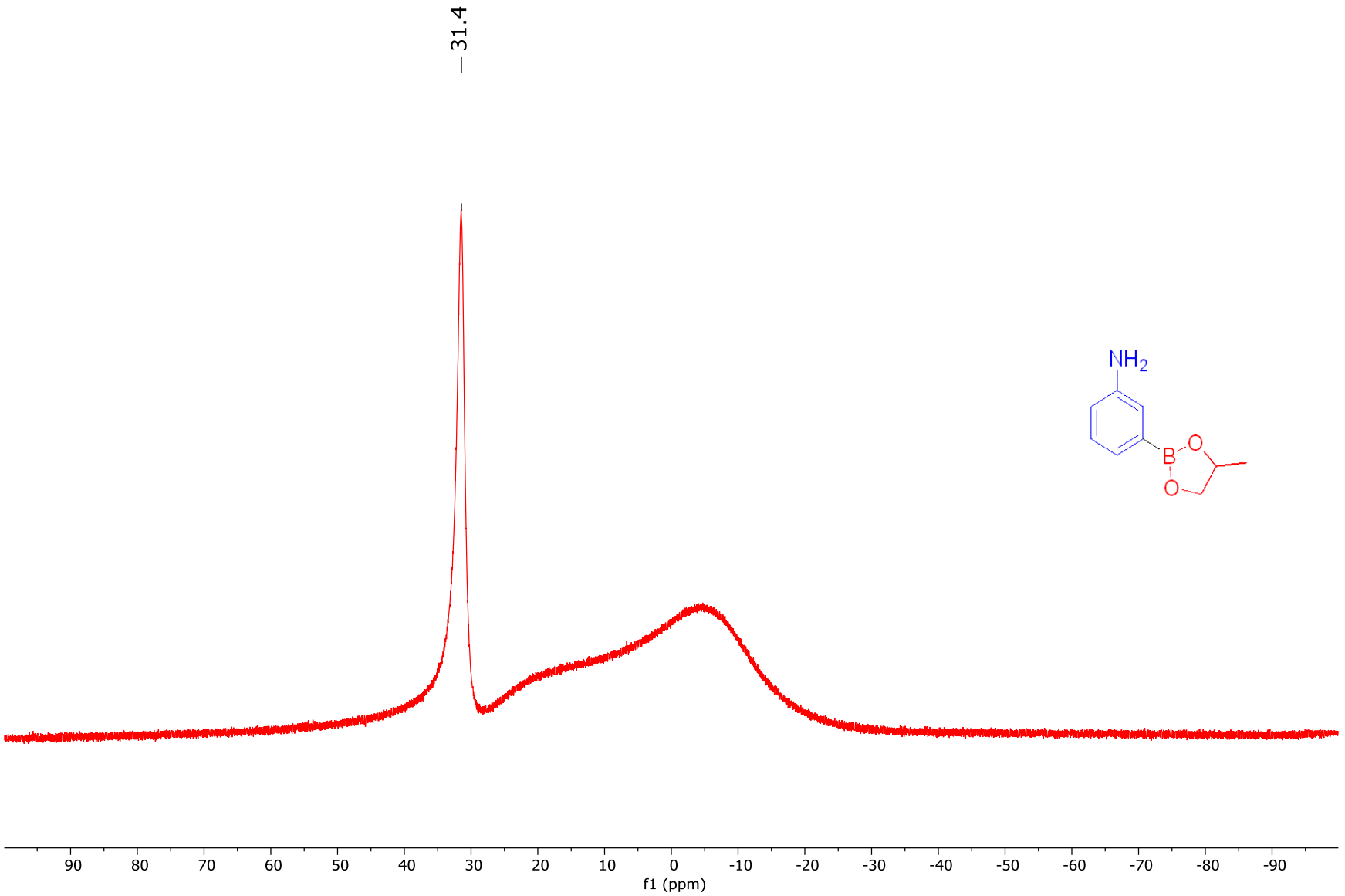
^{1}H NMR of *meta* Bpg-borylated aniline ($CDCl_3$, 500 MHz)



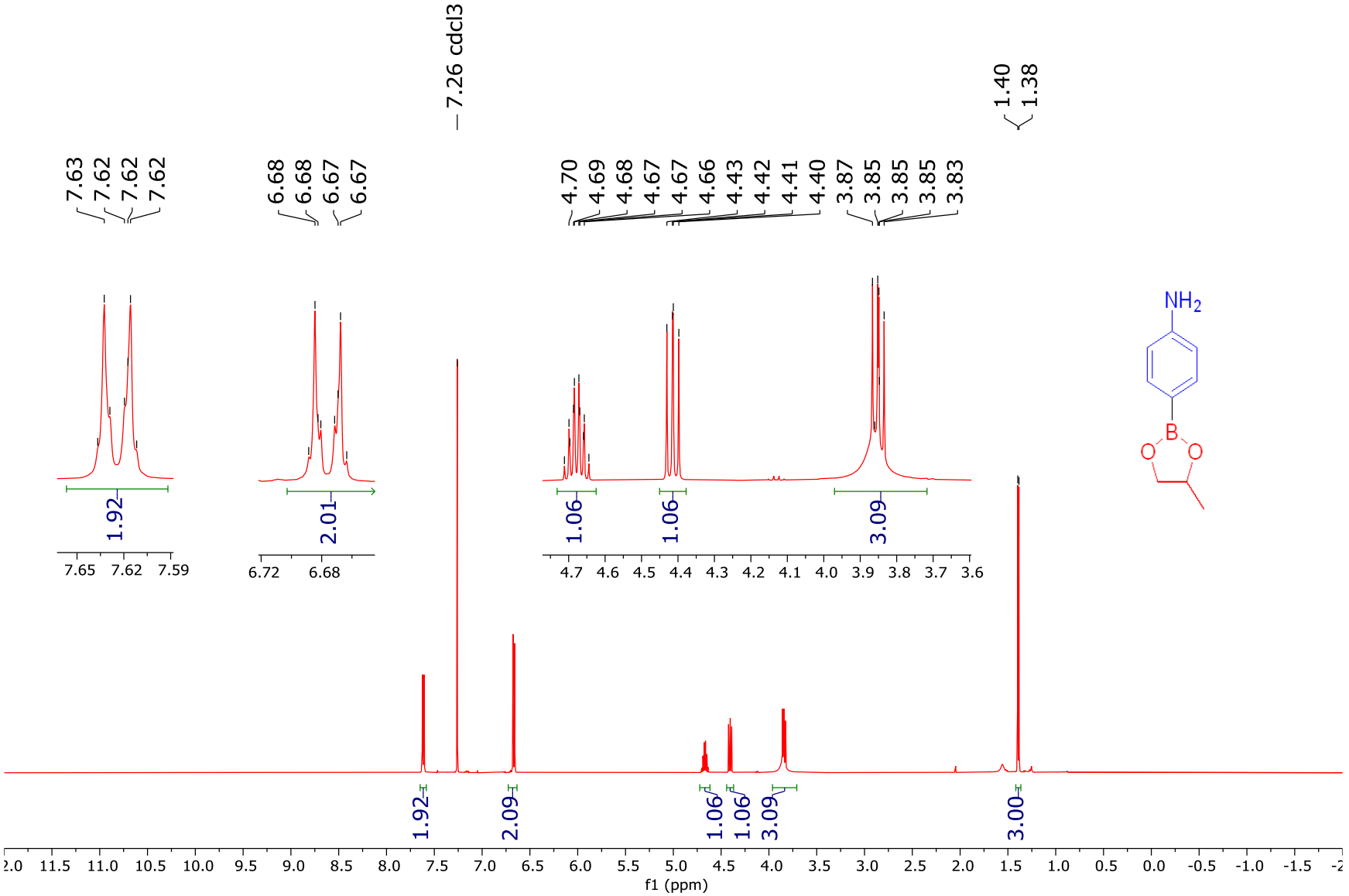
^{13}C NMR of *meta* Bpg-borylated aniline ($CDCl_3$, 126 MHz)



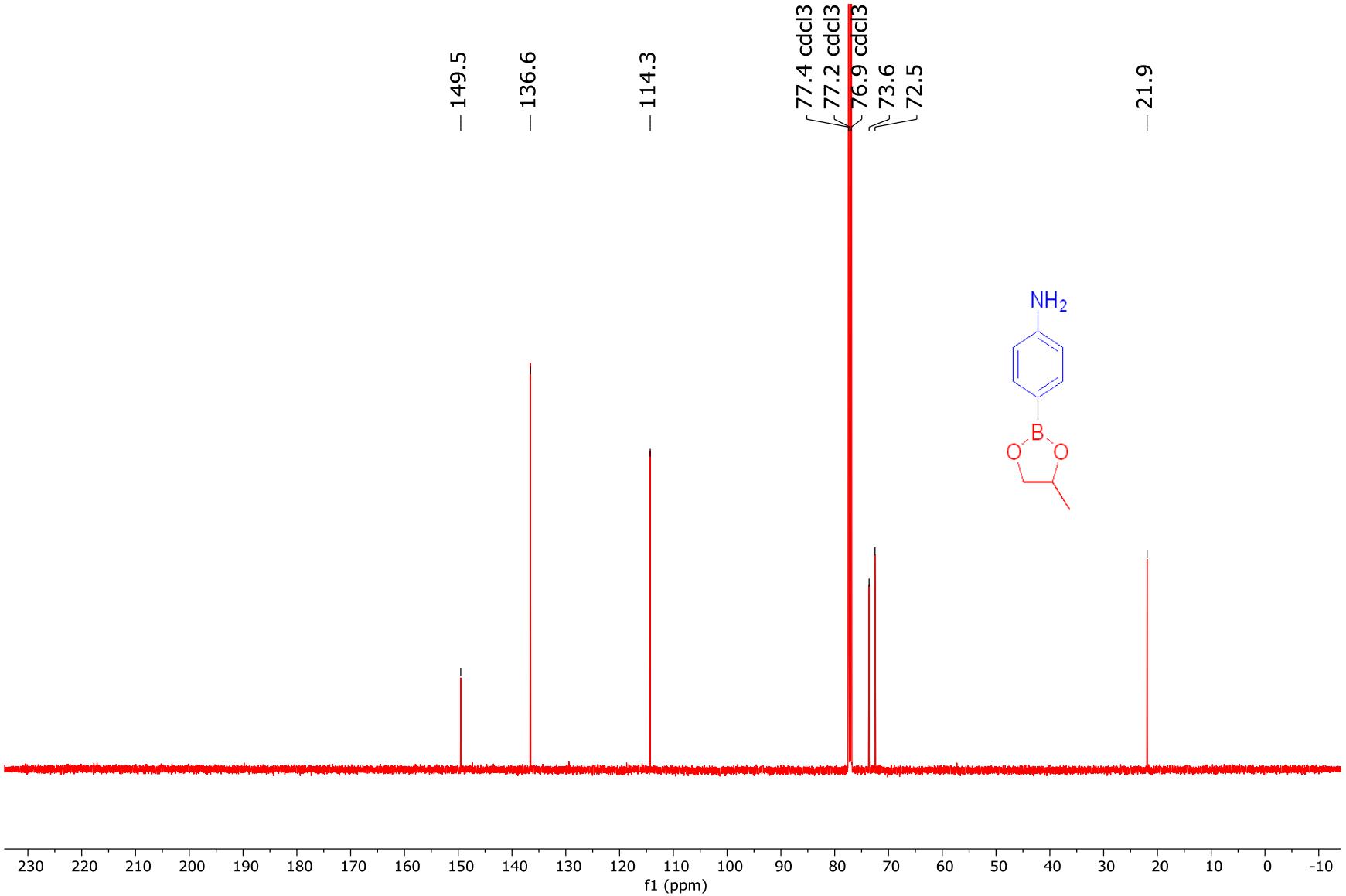
^{11}B NMR of *meta* Bpg-borylated aniline ($CDCl_3$, 160 MHz)



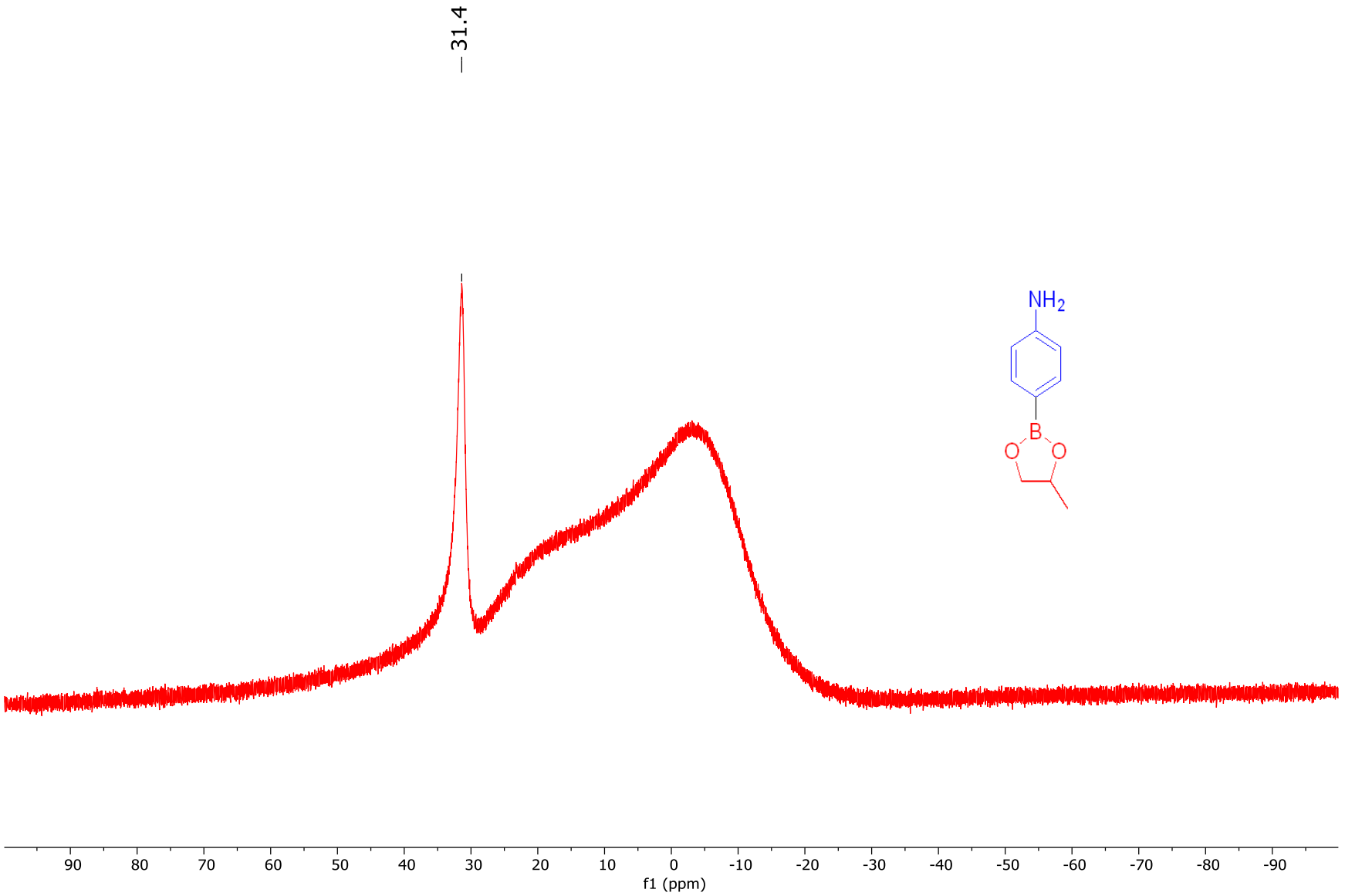
^{1}H NMR of *Para* Bpg-borylated aniline ($CDCl_3$, 500 MHz)



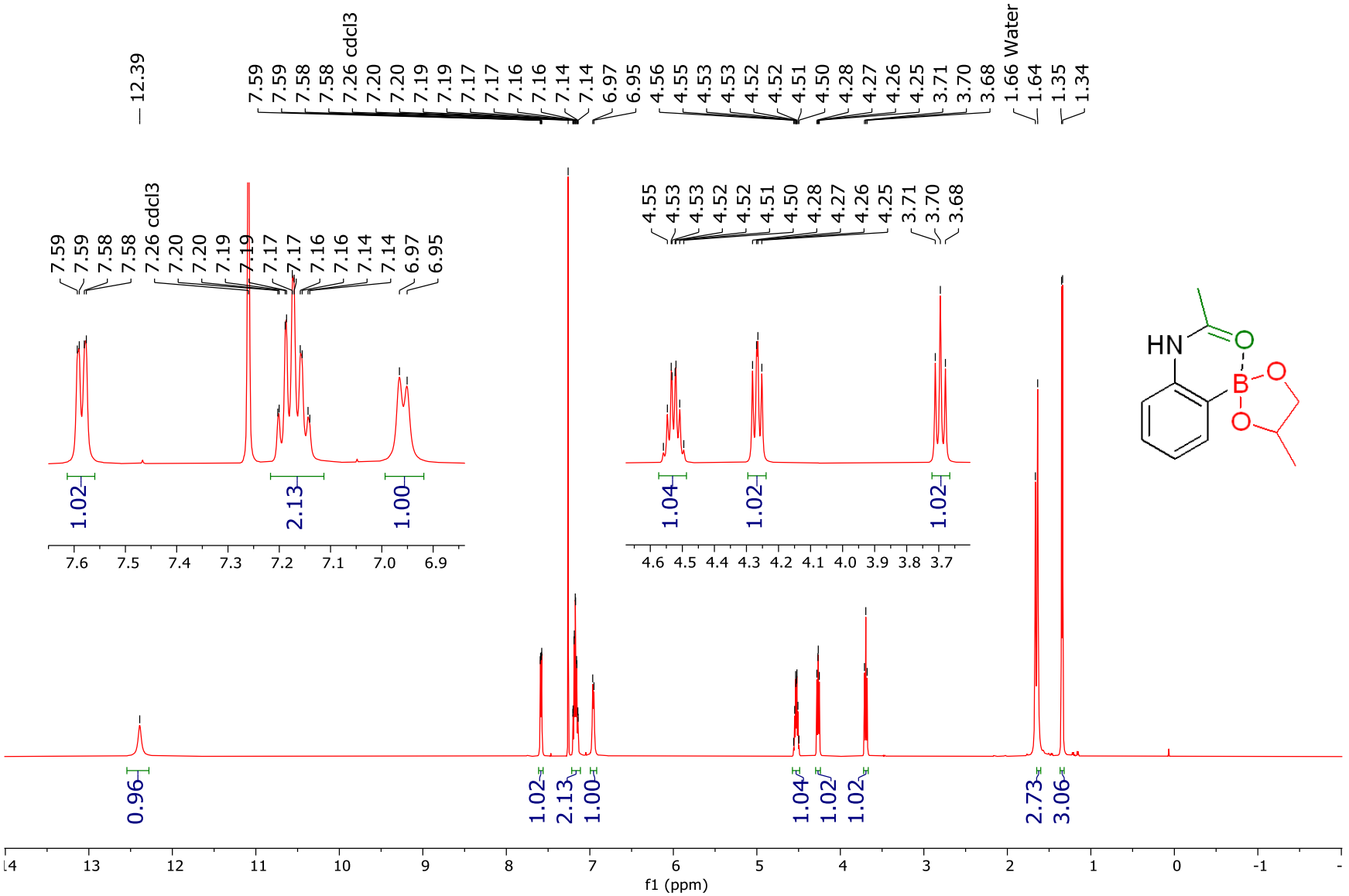
^{13}C NMR of *Para* Bpg-borylated aniline ($CDCl_3$, 126 MHz)



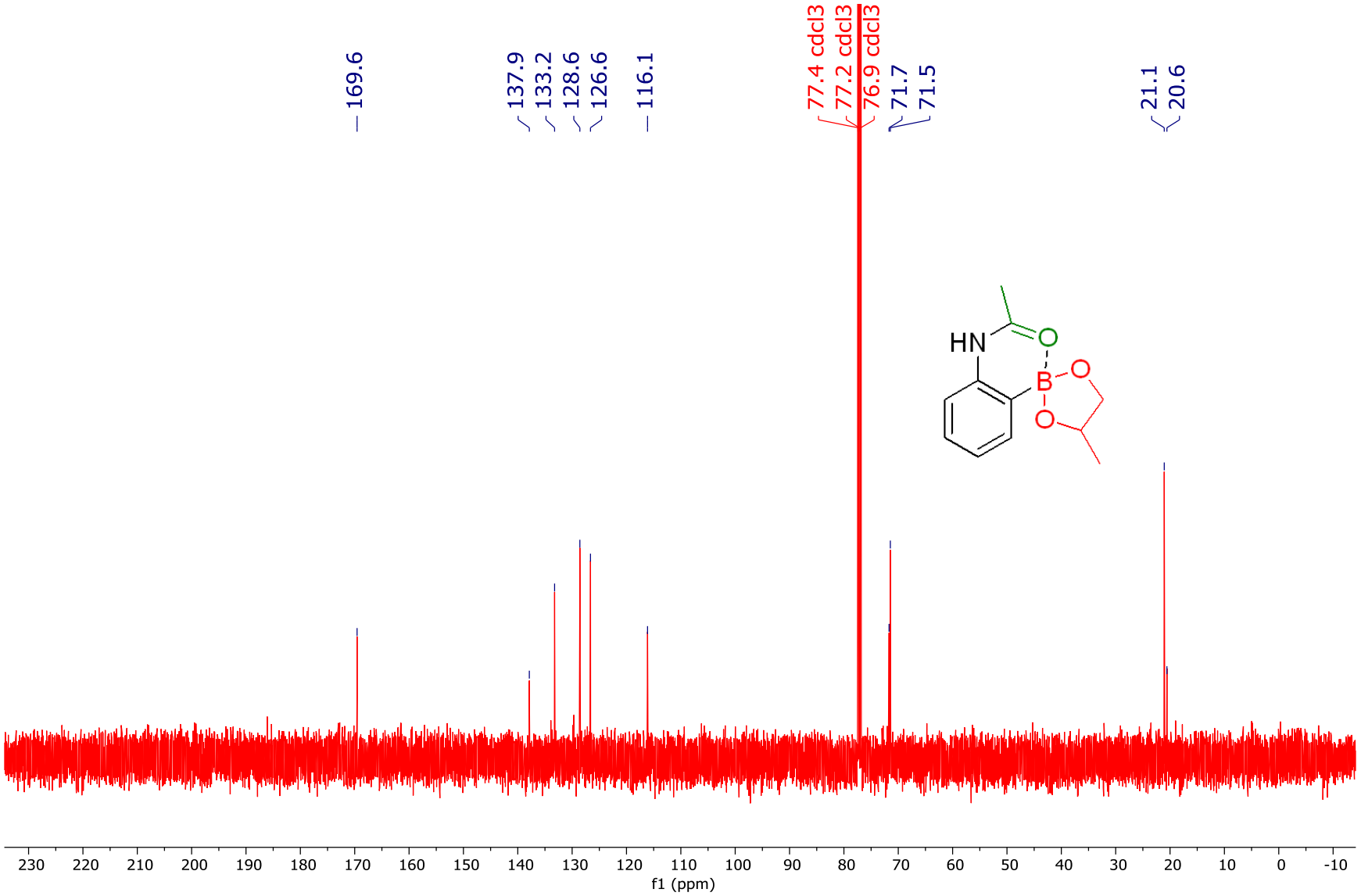
^{11}B NMR of *Para* Bpg-borylated aniline ($CDCl_3$, 160 MHz)



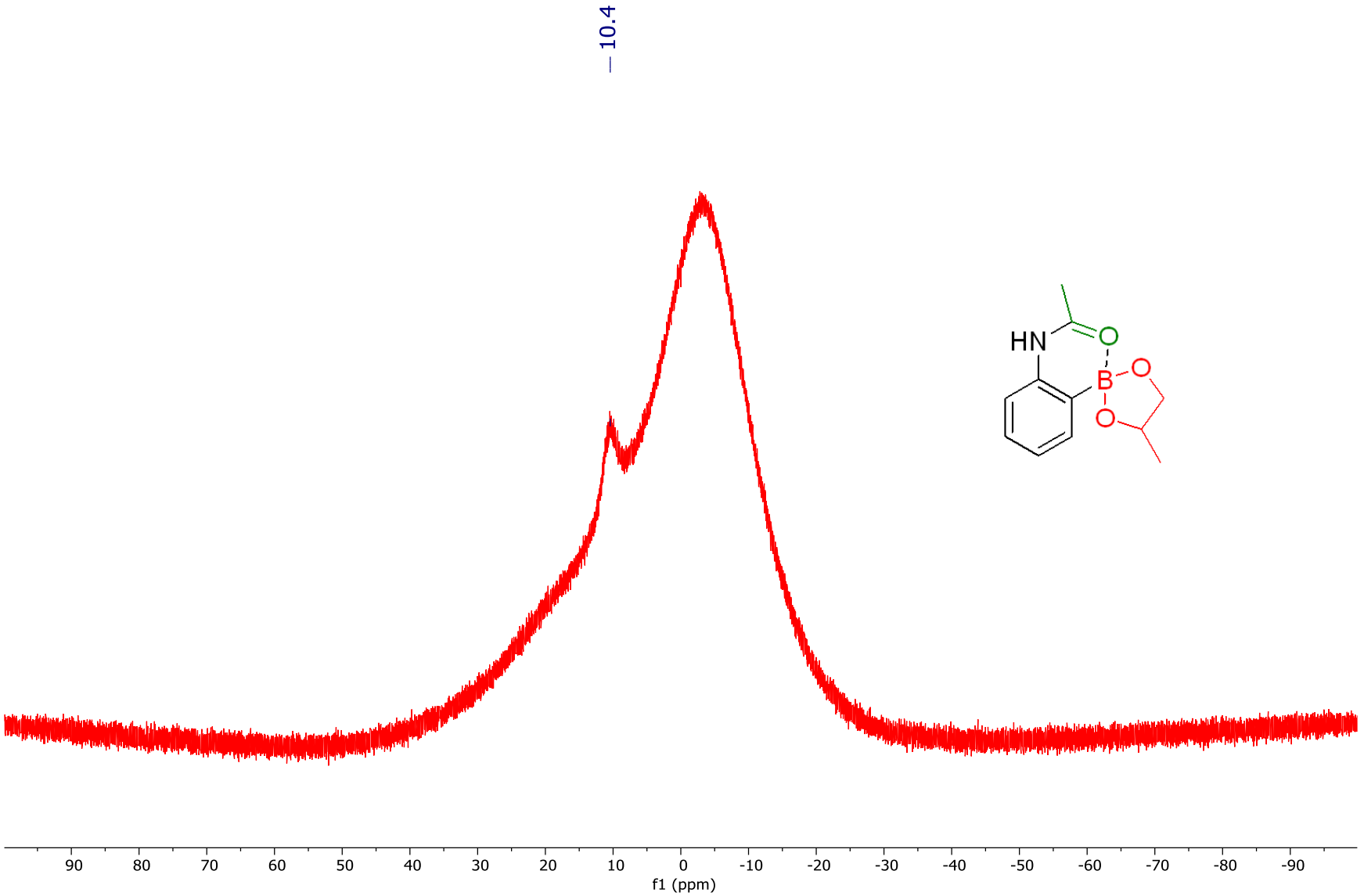
^{1}H NMR of *ortho* Bpg-borylated phenylacetamide (2.3) ($CDCl_3$, 500 MHz)



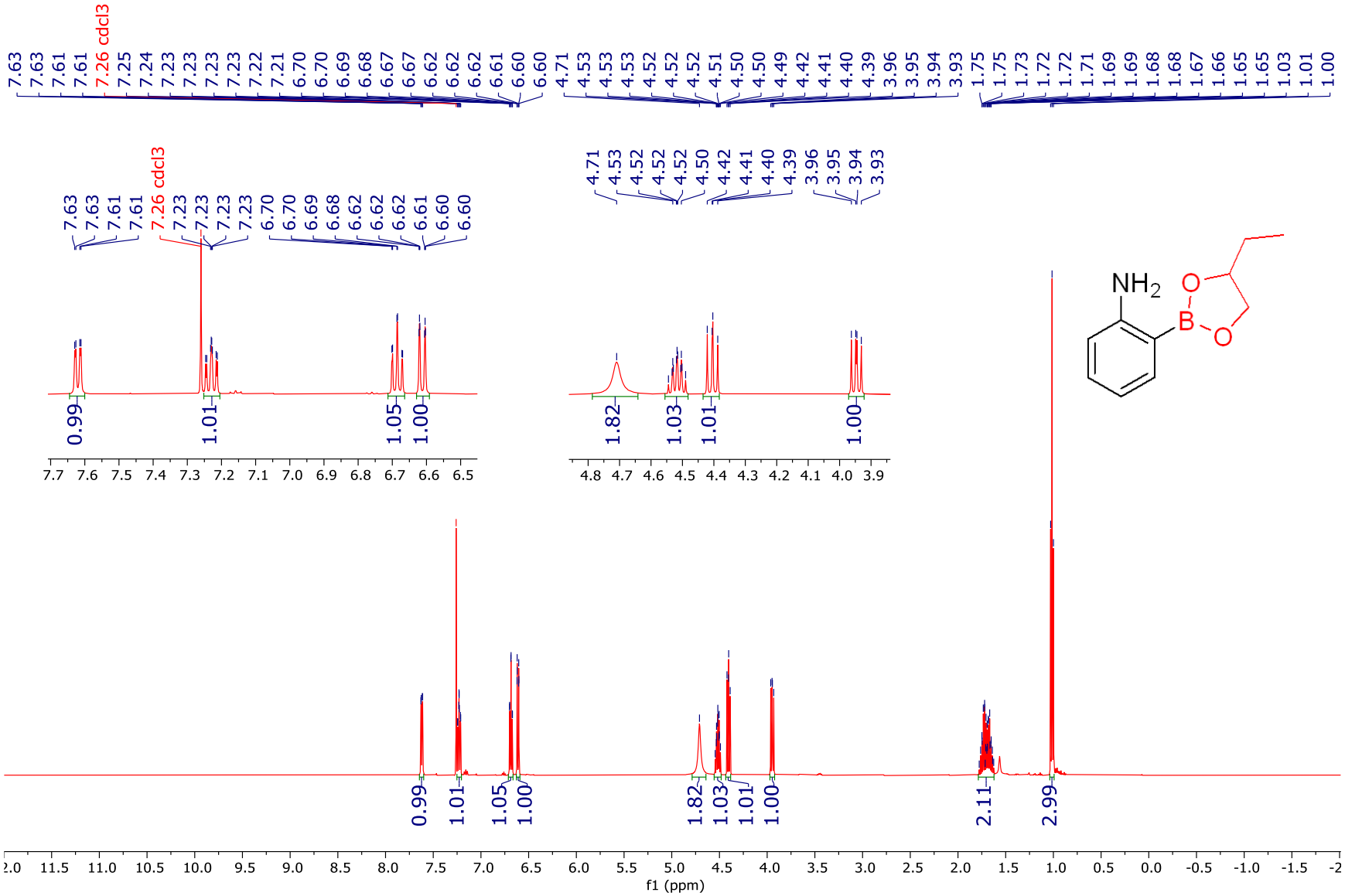
^{13}C NMR of *ortho* Bpg-borylated phenylacetamide (2.3) ($CDCl_3$, 160 MHz)



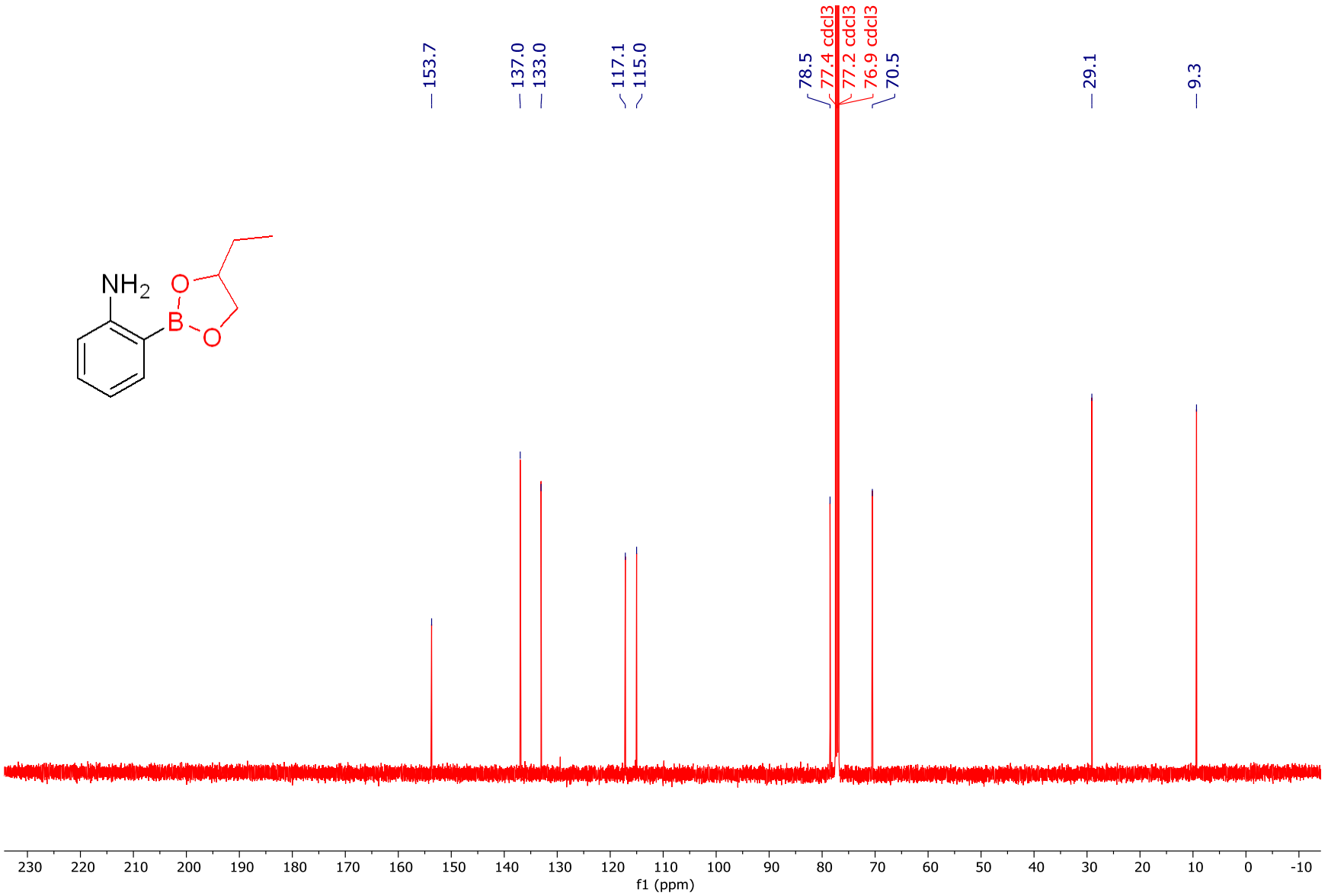
^{11}B NMR of *ortho* Bpg-borylated phenylacetamide (2.3) ($CDCl_3$, 126 MHz)



^{1}H NMR of *ortho* Bbg-borylated aniline (2.4) ($CDCl_3$, 500 MHz)



^{13}C NMR of *ortho* Bbg-borylated aniline (2.4) ($CDCl_3$, 160 MHz)



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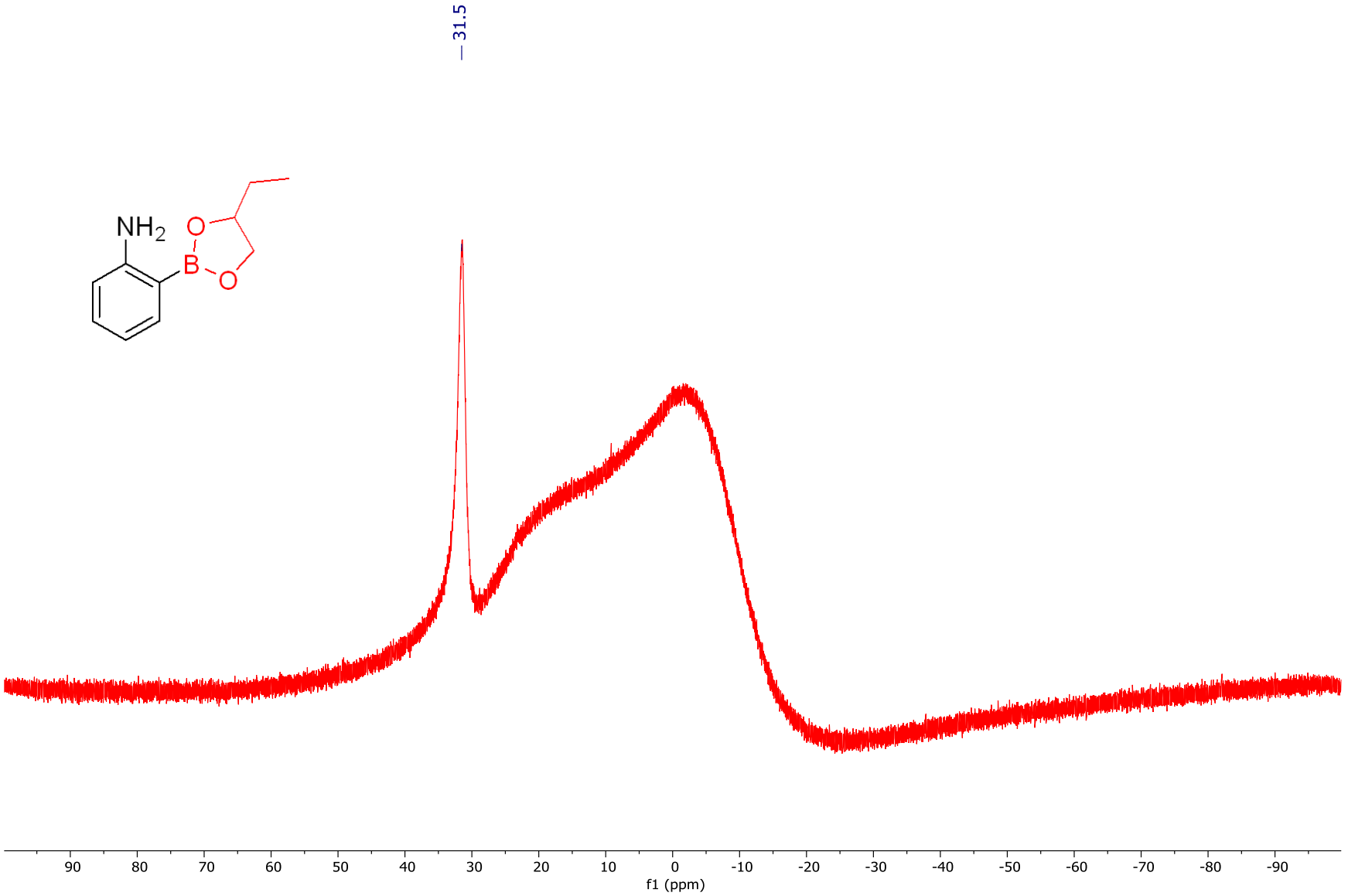

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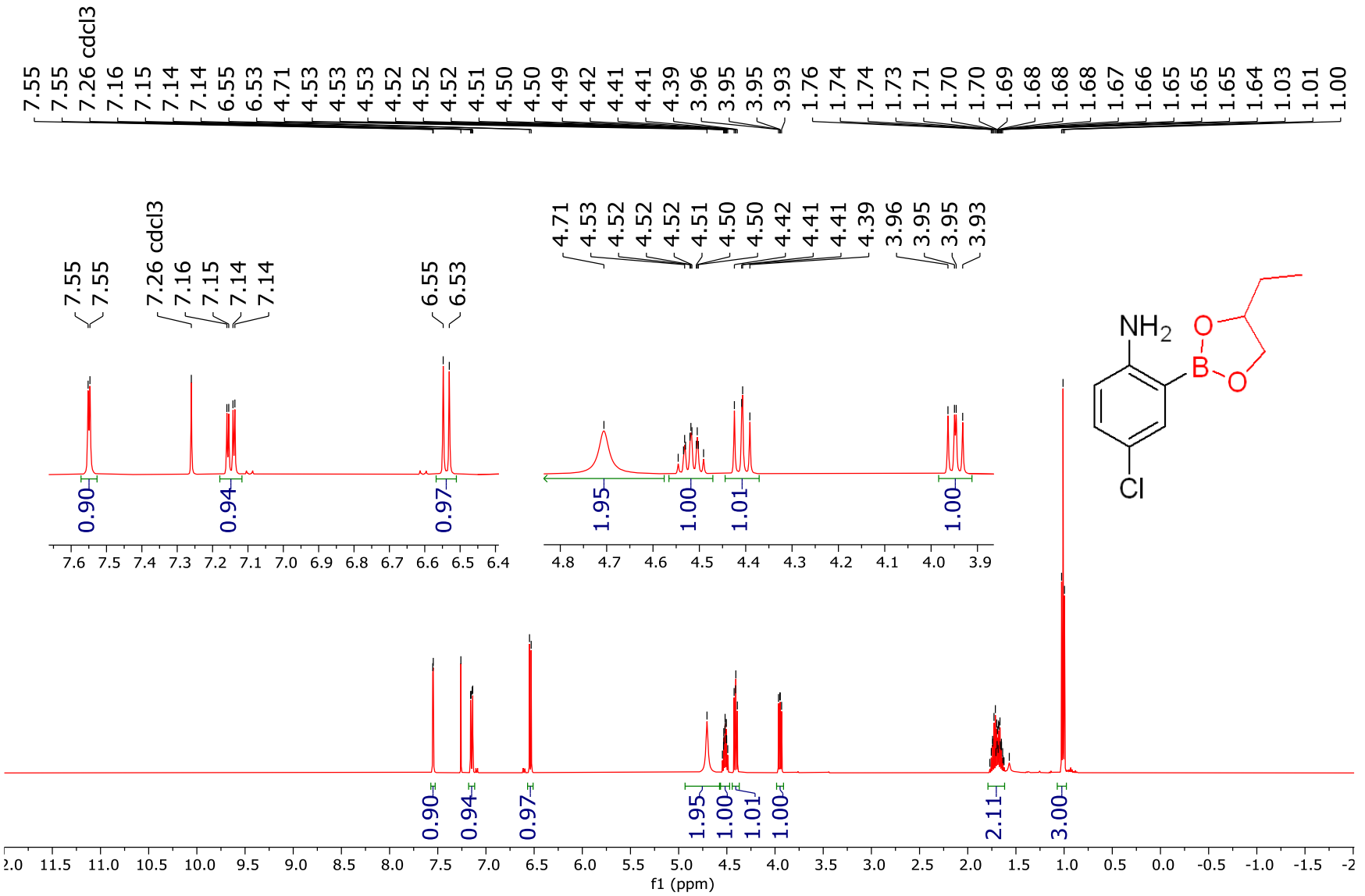

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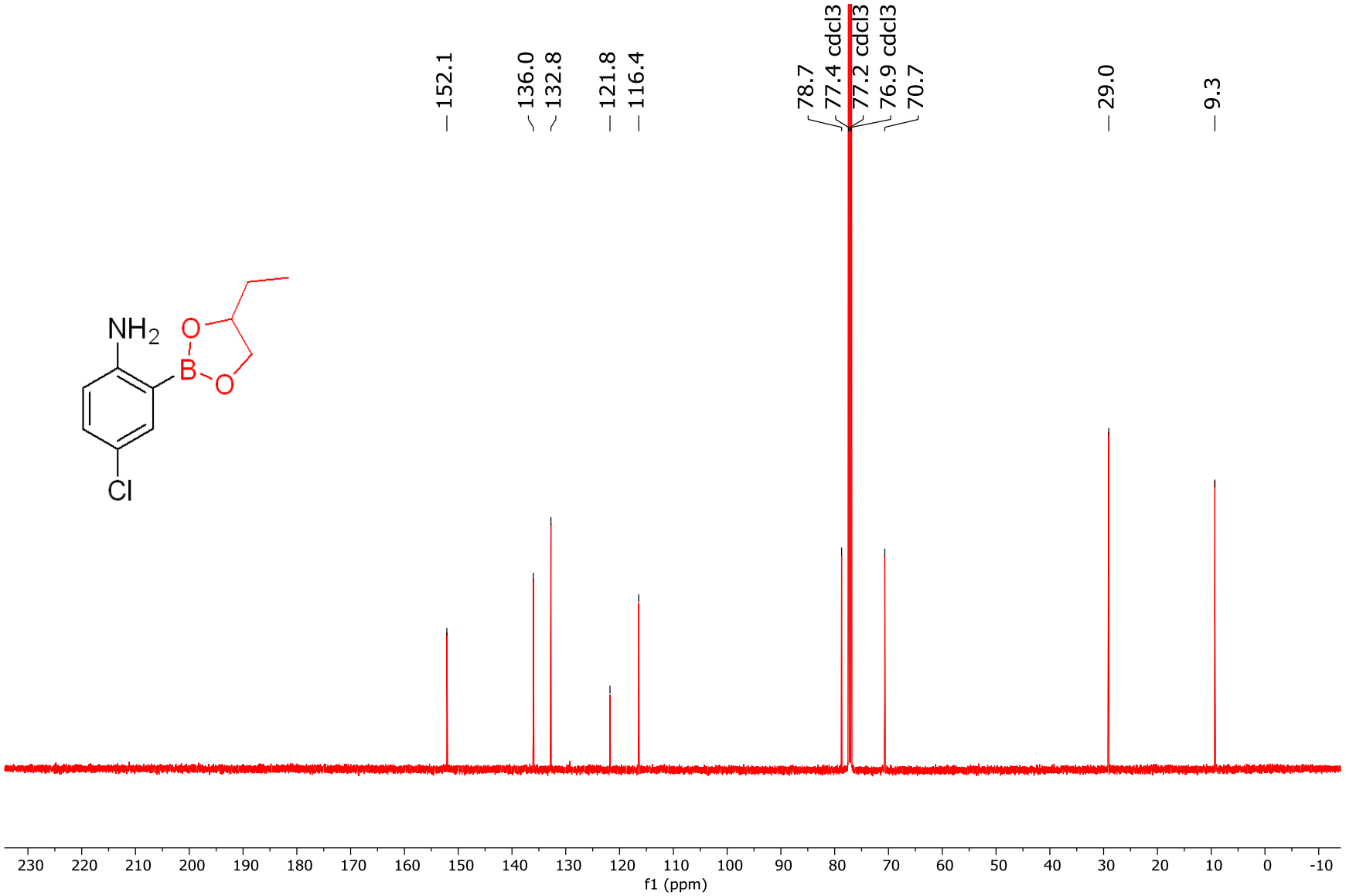
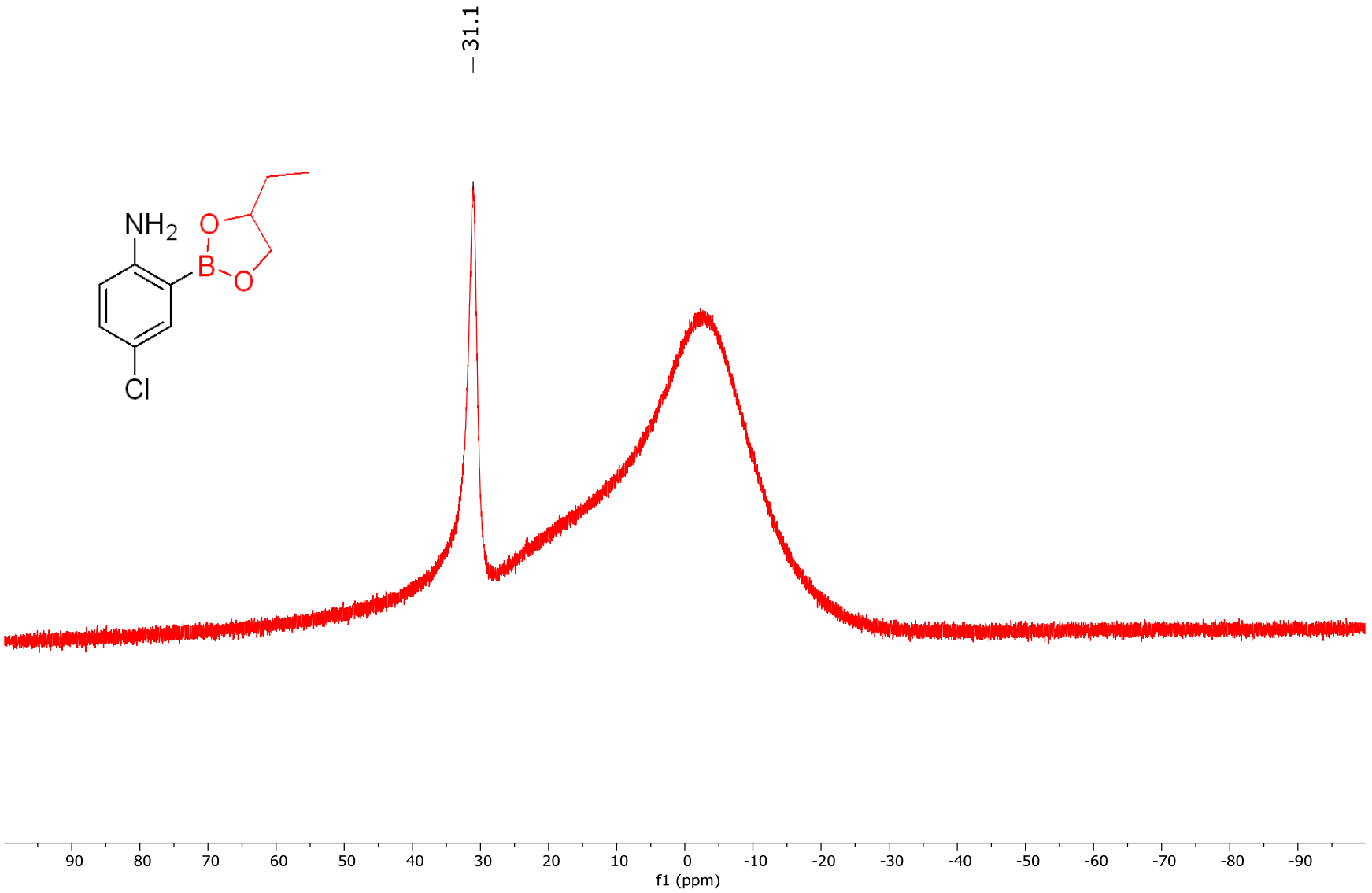
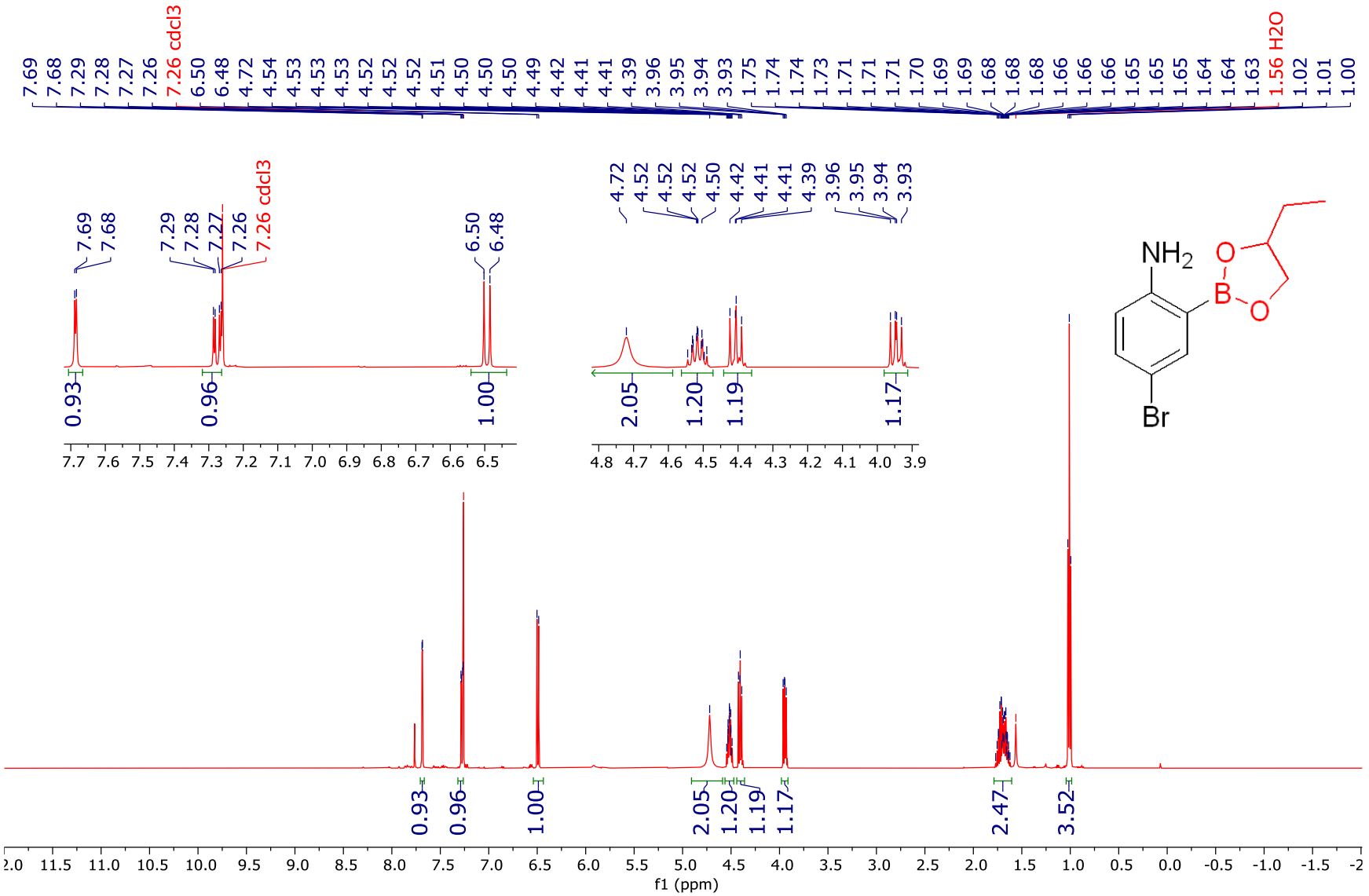


^{11}B NMR of *ortho* Bbg-borylated 4-chloroaniline (2.5) ($CDCl_3$, 126 MHz)



^{1}H NMR of *ortho* Bbg-borylated 4-bromoaniline (2.6) ($CDCl_3$, 500 MHz)



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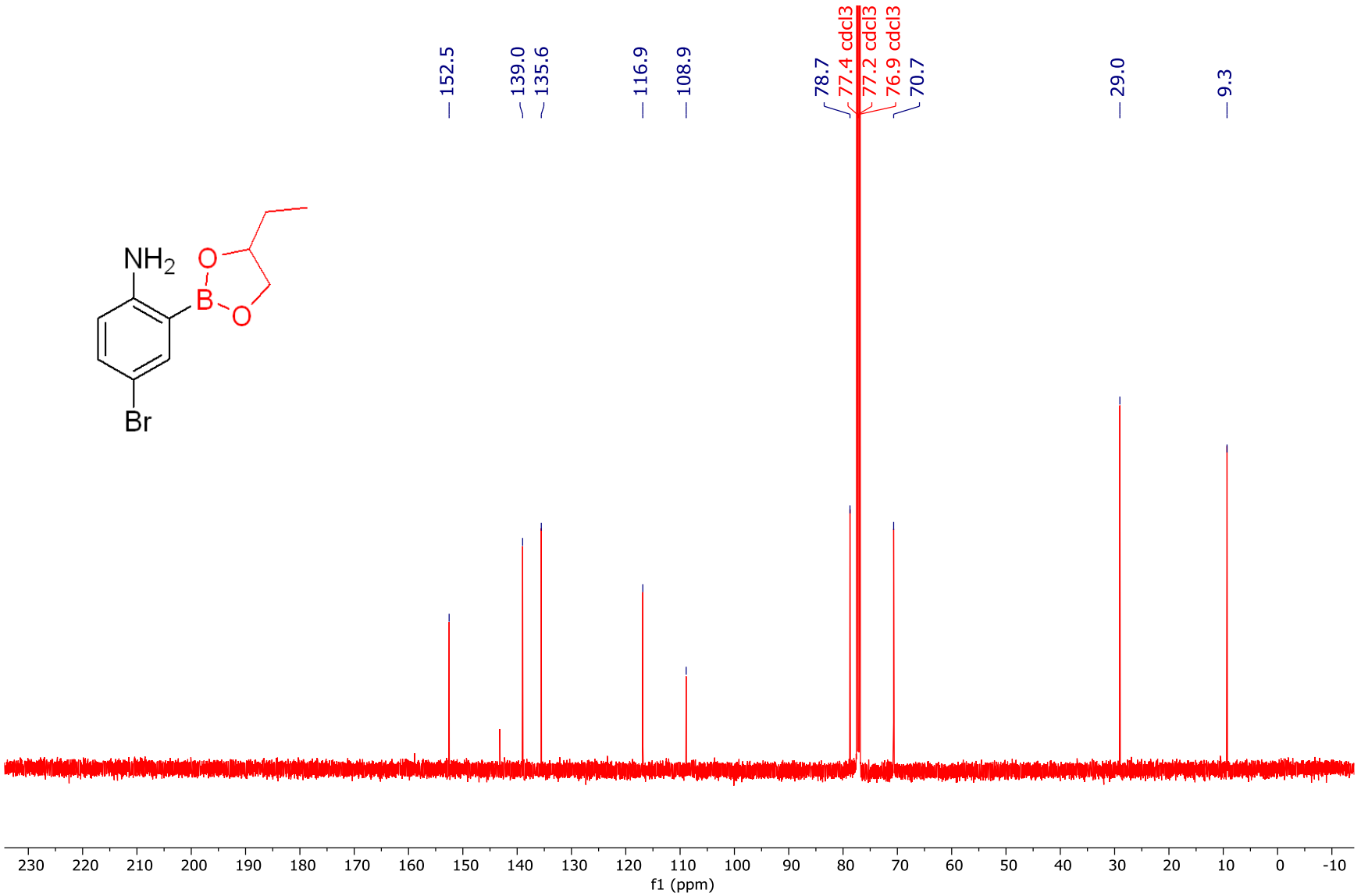
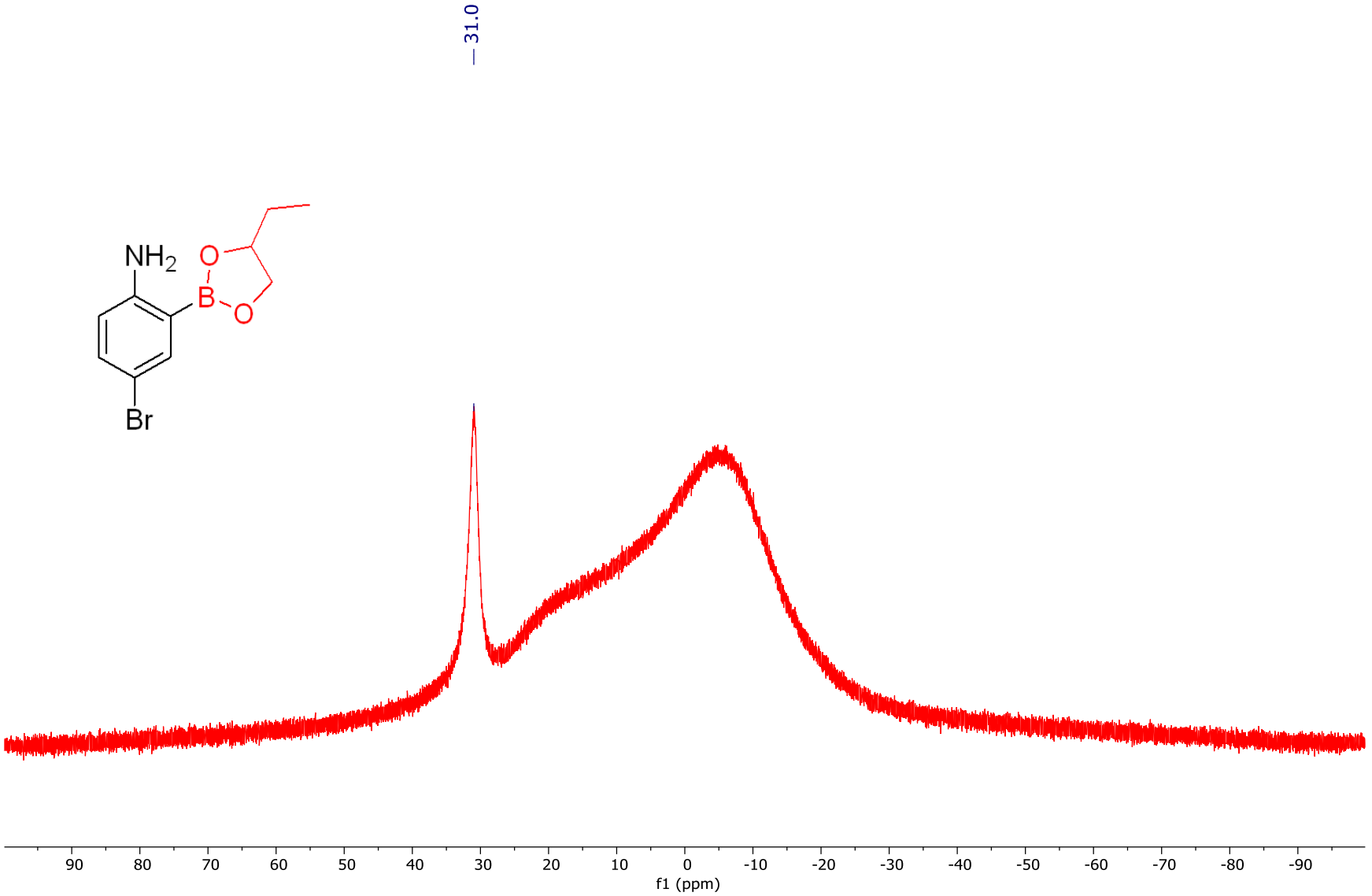


^{11}B NMR of *ortho* Bbg-borylated 4-bromoaniline (2.6) ($CDCl_3$, 126 MHz)



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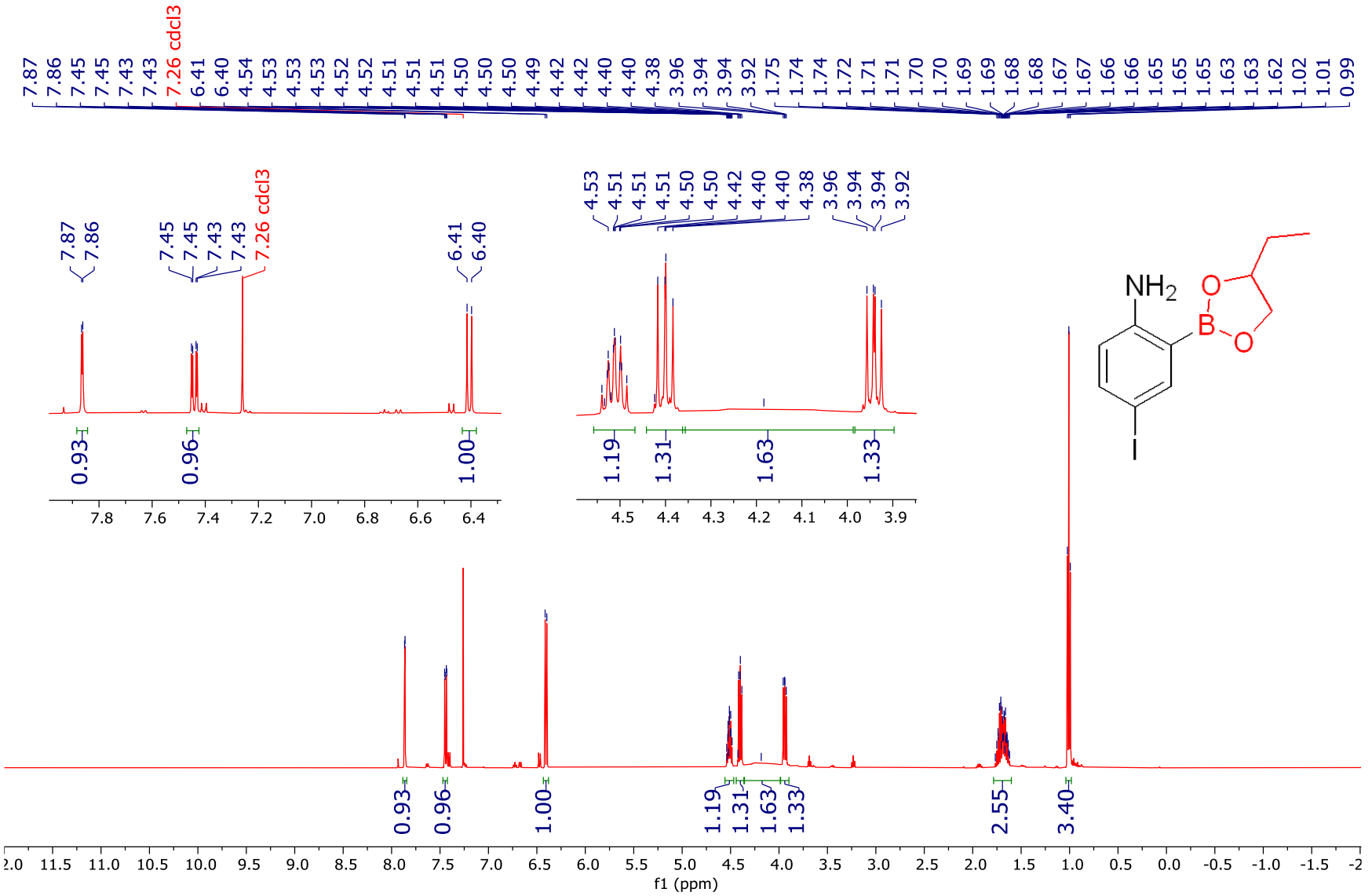
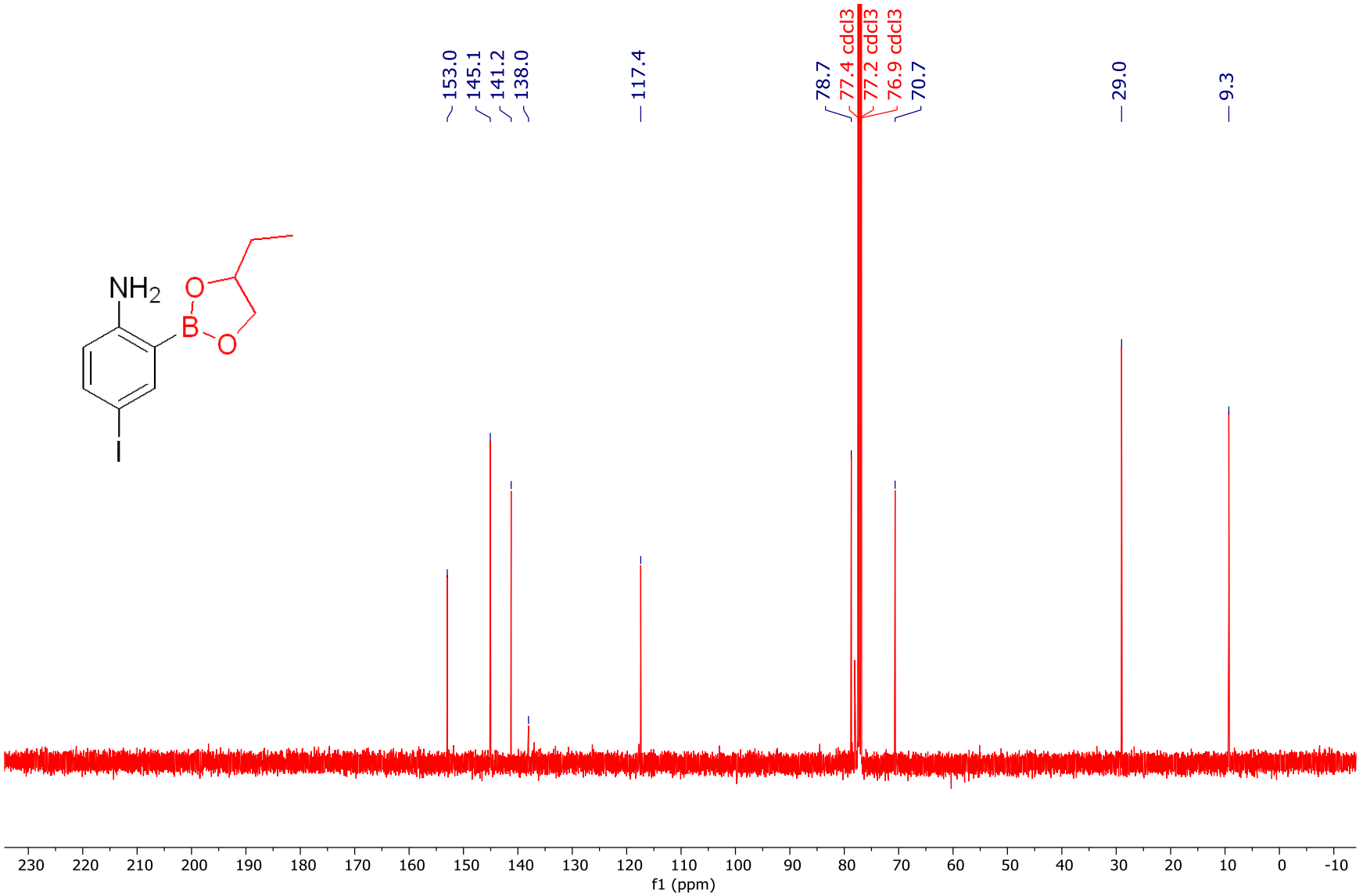
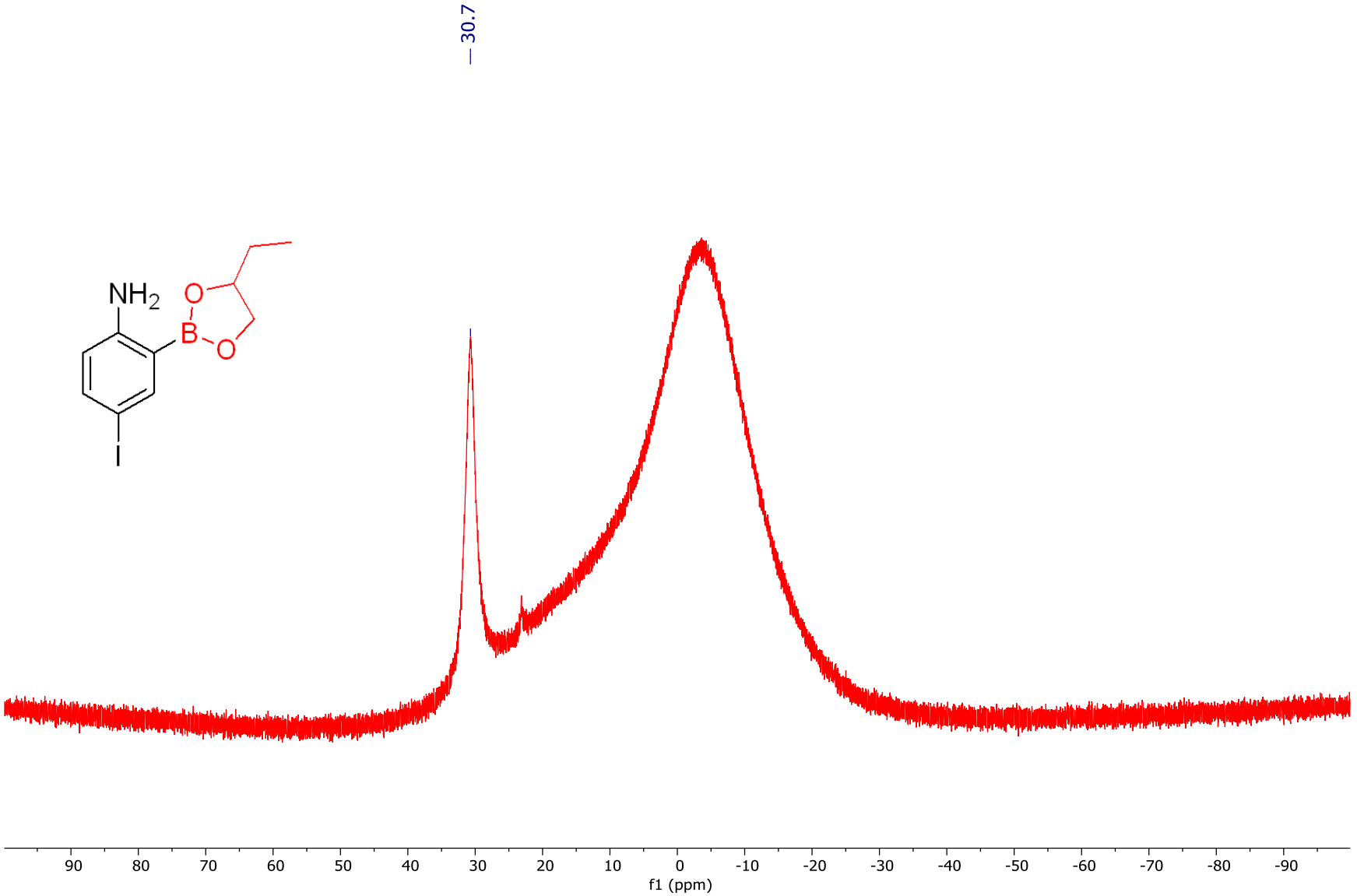


^{13}C NMR of *ortho* Bbg-borylated 4-iodoaniline (2.7) ($CDCl_3$, 160 MHz)



^{11}B NMR of *ortho* Bbg-borylated 4-iodoaniline (2.7) ($CDCl_3$, 126 MHz)



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CHAPTER 3.

PARA-SELECTIVE, IRIDIUM-CATALYZED C−H BORYLATIONS OF SULFATED PHENOLS, BENZYL ALCOHOLS, AND ANILINES DIRECTED BY ION-PAIR ELECTROSTATIC INTERACTIONS

3.1. Introduction

For two competing pathways, a difference in barrier heights of 2.5 kcal·mol^{-1} is sufficient for 99% of the reactants to follow the favored pathway in a chemical reaction. This is lower than the barrier for converting the anticonformer of butane to the gauche form.[1] In transition-metal mediated reactions, a classic mode for selectively functionalizing bonds in a substrate relies on the coordination of an atom in a reactant functional group to the metal center of a compound or catalytic intermediate. The magnitudes of the ligand−metal interactions are at least an order of magnitude greater than the difference in barrier heights necessary for 99:1 selectivity. Consequently, design of catalysts where selectivity is conferred by weakly coordinating groups,[2] as well as catalysts that leverage even weaker interactions (e.g., hydrogen-bonding, ion-pairing, dipole−dipole, etc.) for selective transformations,[3,4] is attracting significant attention.

C−H functionalizations offer both atom and step economical means of converting ubiquitous C−H bonds to a range of functional groups.[5,6] CHB convert C−H bonds to C−B bonds and are mediated by both metal and metal-free catalysts.[7–9] CHB reactions are valuable due to (i) facile substitution of the boron moiety by numerous functional groups and (ii) functional group tolerance of CHB catalysts, particularly those containing Ir.

The first Ir CHB catalysts enabled C(sp^2)−H functionalizations with high selectivity for the most sterically accessible C−H bonds.[10–12] In substrates where multiple C−H bonds are sterically accessible, early generation catalysts often give isomer mixtures, as well as multiply borylated

products. To overcome these limitations, more selective Ir catalysts have been designed. The first examples were *ortho*-selective,[13] relying on strongly coordinating functional groups in the substrate,[14,15] while later reports exploited weaker interactions for ortho selectivity.[16,17]

By comparison, *meta* and *para* CHBs pose different challenges because their C−H bonds are farther from the functional group. One *meta*-selective CHB has been ascribed to a classical chelate-directed mechanism,[18] while others rely on Ir ligands bearing groups that engage in noncovalent interactions with substrate functional groups to effect *meta* CHB.[19–24]

Figure 3.1 depicts approaches for *para*-selective CHB. The first CHBs with high *para* selectivity involved electrophilic additions of borenium cations to arenes bearing ortho, *para*-directors.[25] Sterically directed CHBs rely on hindered phosphine ligands and substrates with large substituents.[26,27] More recently, *para* borylations of esters and amides have been achieved through noncovalent interactions with K ions or coordination of the amide oxygen to hindered Lewis acids.[28,29]

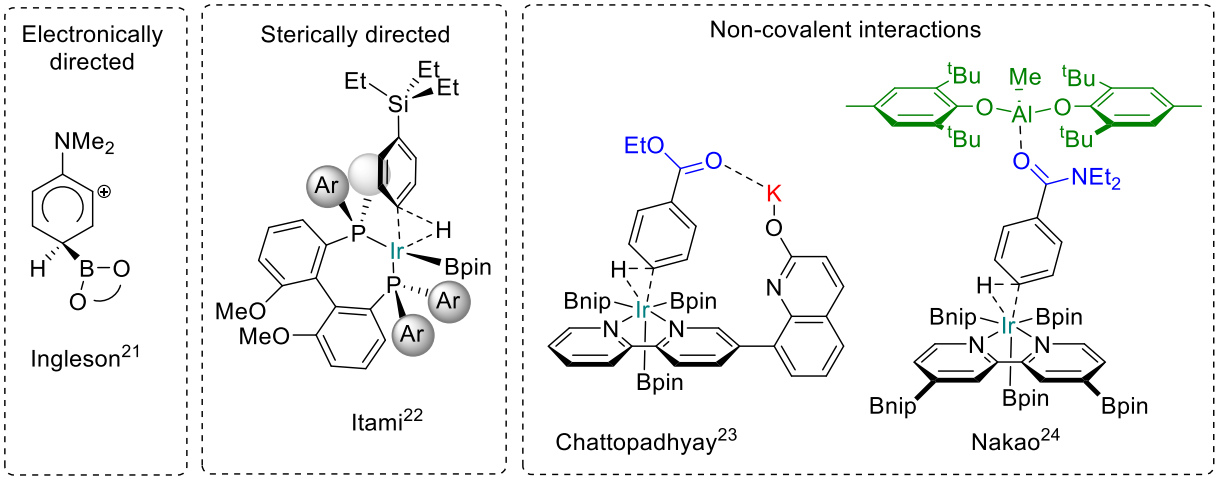


Figure 3.1: *Para* C−H borylations

3.2. Results and Discussion

3.2.1. Unexpected Discovery

Our inspiration was based on the Phipps' group ion-pair directed CHBs with one key difference.[20,22] Instead of using oppositely charged groups on the ligand and substrate, combinations where groups on the ligand and substrate had the same charge were surveyed with the expectation that *para* borylation would be favored because electrostatic repulsions between the ligand and substrate would be minimized. However, a control experiment where tetrabutylammonium 2-chlorophenyl sulfate (**3.1a'**) was subjected to standard borylation conditions with a neutral bipyridine ligand (sealed tube with B_2pin_2 as the boron source, 1.5 mol % $[Ir(cod)OMe]_2$ as the precatalyst and 3 mol % dtbpy as the ligand, in THF at 80 °C) showed promising results with 6:1 *para* to *meta* regioselectivity (**Figure 3.2**). We hypothesized that substrate ion-pairing interactions, where the n-butyl groups of the cation shield the *meta* C–H bonds of the counter-anions, accounted for the *para* selectivity.

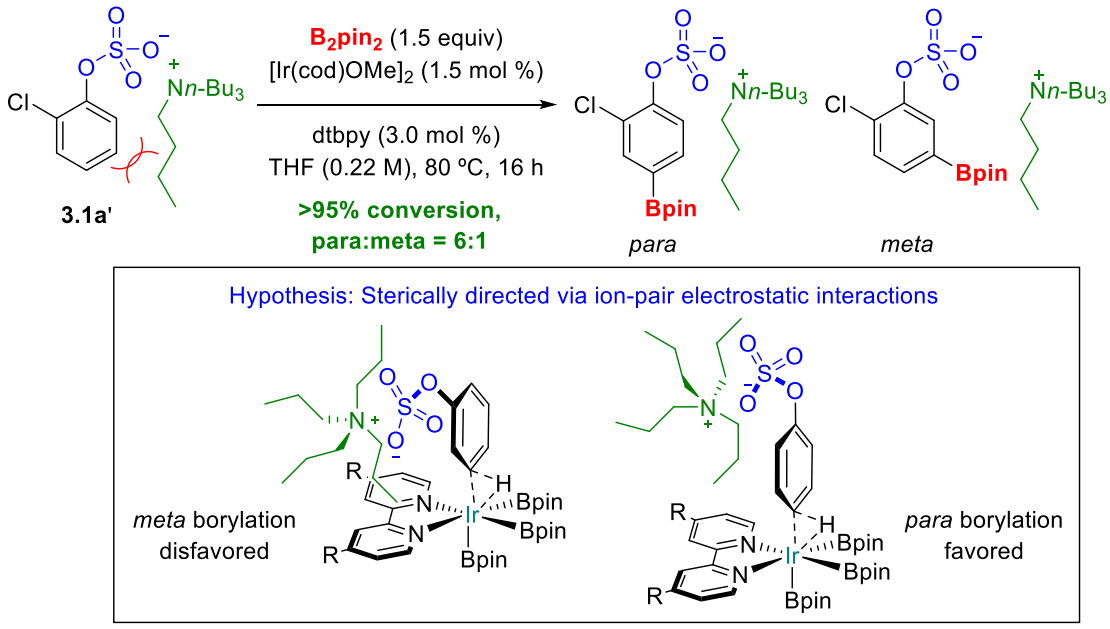
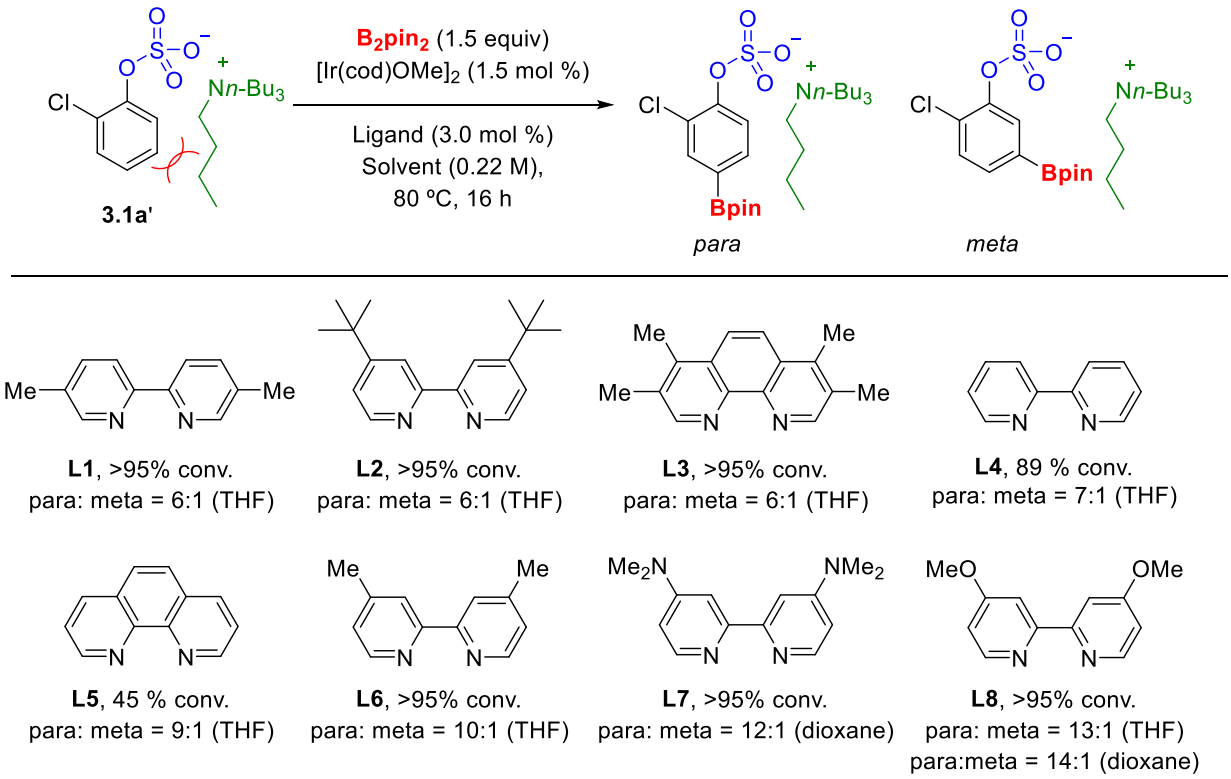


Figure 3.2: *Para* C–H borylation sterically driven by ion-pair electrostatic interactions

3.2.2. Optimization of Conditions

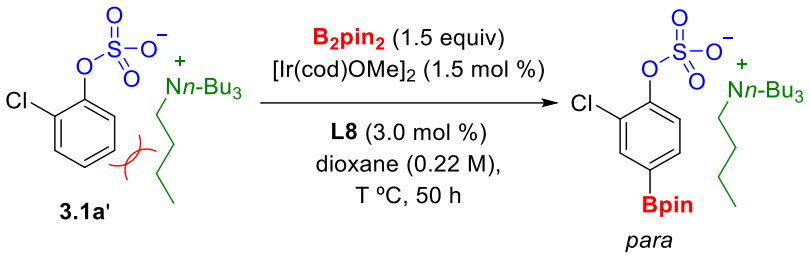
In Nakao's study, ligand geometry played a key role in enhancement of the *para* selectivity.[29] Similarly, we have observed that ligand choice can impact CHB regiochemistry where there is little steric differentiation between different arene C–H bonds.[30] Therefore, we tested commercially available substituted bipyridine and phenanthroline ligands (**Scheme 3.1**) in CHB reactions run at 80 °C. The reactivity of the ligands is in accordance with previously noted electronic effects,[31] with electron-rich ligands affording a more active system relative to electron-poor ligands. The borylation in THF with 4,4'-dimethoxy-2,2'-bipyridine (**L8**) as the ligand went to >95% conversion and afforded the best *para* selectivity (13:1). This observation is notable in that **L8** is a nontraditional CHB ligand. Switching the solvent to dioxane slightly increased the *para* selectivity, whereas other apolar solvents worsened regioselectivity.

Scheme 3.1: Ligand effect on *para* CHB of **3.1a'**



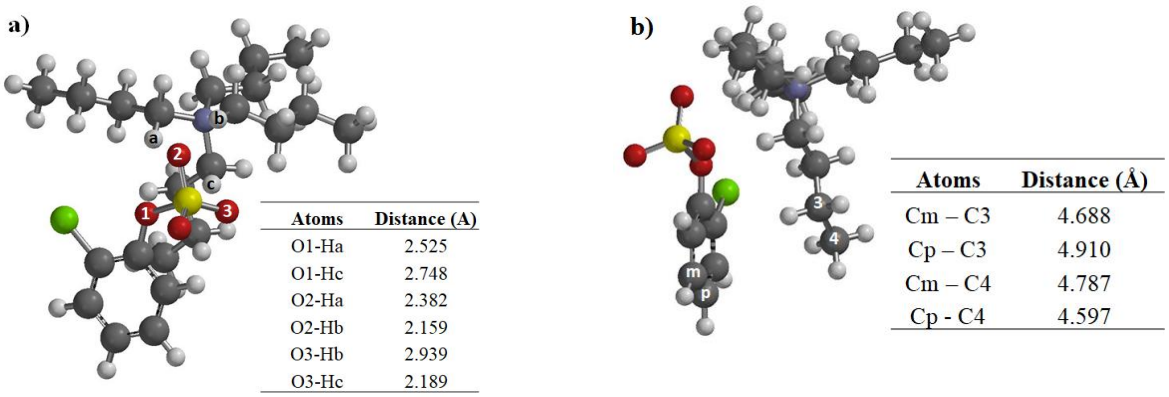
Running the reactions at lower temperature (60 °C and 40 °C) further improved the *para* selectivity while still allowing for full conversion (**Table 3.1**). The reaction at room temperature afforded 21:1 *para* selectivity, but starting material remained even after 50 h.

Table 3.1: Temperature effect on *para* CHB of 3.1'



T (°C)	% conv	*p:m*
rt	83	21:1
40	100	17:1
60	100	16:1
80	100	14:1

With the experiments in **Scheme 3.1** and **Table 3.1** establishing 4,4'-dimethoxy-2,2'-bipyridine **L8** and dioxane as our ligand and solvent of choice, we next investigated the effect of the tetraalkylammonium salt on *para* selectivity. DFT geometry optimization of **1a'**, using the B3LYP functional and 6-31G* basis set for all the atoms in a vacuum media, places one alkyl chain of the cation parallel to the aromatic ring in support of the presence of a steric shield (**Figure 3.3**). Looking more in detail, we observed relative short distances between the alpha hydrogens in the alkylammonium cation with the oxygens in the sulfate (**Figure 3.3a**) which suggests to us an intermolecular hydrogen bond interaction. Tetraalkylammonium cations have been described as hydrogen bond donors by previous studies.[32] The intermolecular hydrogen bond can help maintain the tetralkyl ammonium in the conformation needed for a steric shield during the CHB reaction. We also observed an intriguing difference between the distances of the *meta* Cm and *para* Cp carbons in the arene to carbons C3 and C4 in the cation (**Figure 3.3b**). C3 is closest to Cm than Cp as expect, but surprisingly C4 is closest to Cp than Cm. This led us to propose that a slightly shorter alkyl chain would still block the *meta* position but leave the *para* position more exposed, thus potentially leading to improved *para* selectivity.



Atoms	Distance (A)
O1-Ha	2.525
O1-Hc	2.748
O2-Ha	2.382
O2-Hb	2.159
O3-Hb	2.939
O3-Hc	2.189

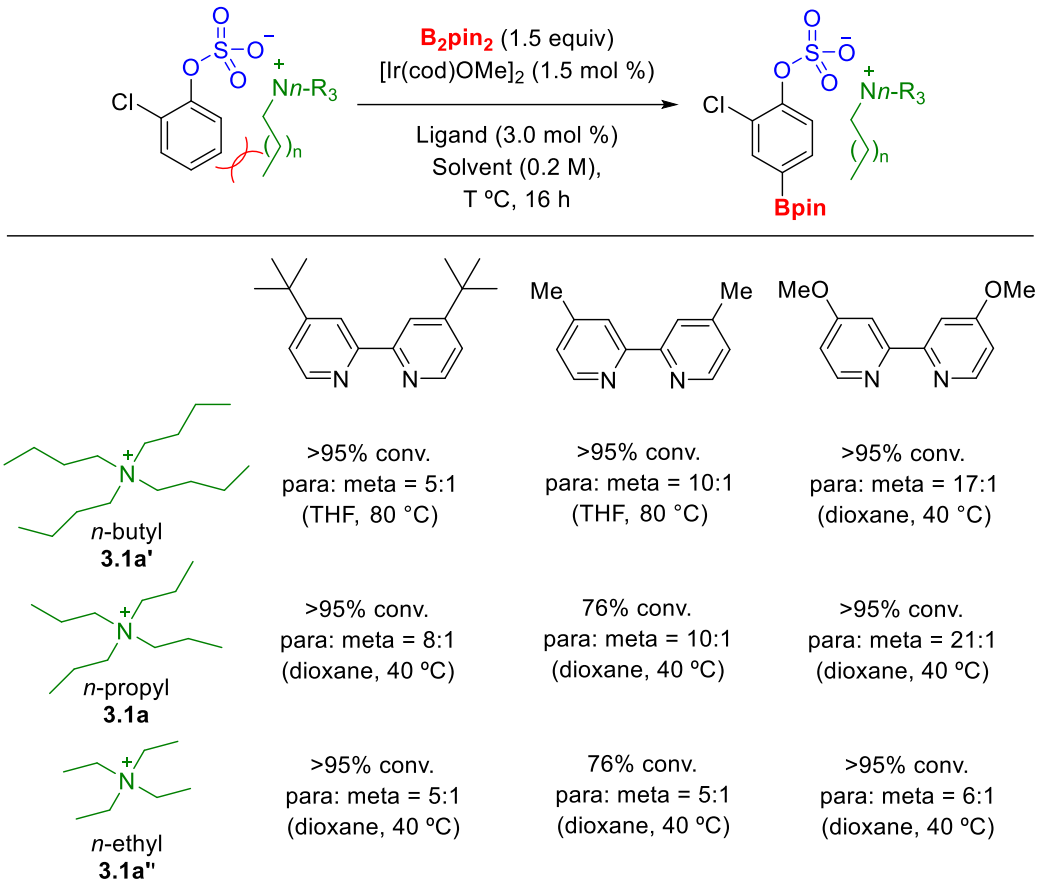
Atoms	Distance (Å)
Cm – C3	4.688
Cp – C3	4.910
Cm – C4	4.787
Cp - C4	4.597

Figure 3.3: Lowest energy conformation geometry of **1a'** (front and lateral view)

As shown in **Scheme 3.2**, the CHB of tetrapropylammonium 2-chlorophenyl sulfate (**3.1a**) validated this hypothesis, as running the reaction with ligand **L8** in dioxane at 40 °C pushed the *para* selectivity to 22:1. We also examined tetraethylammonium 2-chlorophenyl sulfate (**3.1a''**) as a substrate. In terms of chain shortening, clearly diminishing returns had set in as the *para* selectivity decreased to 6:1.

Based on our results, we chose to test a series of phenol derived sulfates with *n*-Pr_4N^+ as the counterion to determine substrate scope (**Scheme 3.3**). During the course of this project, we become aware that the Phipps group has developed a similar approach to *para*-selective borylation. Fortunately, our works complement each other, and we are grateful to them for agreeing to publish their results in a back-to-back fashion with our own.[33,34] We focused more on a deep optimization of reaction conditions as shown above, from which we discovered the key role of the ligand and the importance of the careful design of the cation. On the other hand, Phipps group expanded the steric shielding effect driven by ion-pair electrostatic interactions to a diverse array of scaffolds although with lower selectivity than our protocol in the substrates we shared. For comparison, the selectivities obtained by the Phipps group are shown in brackets in **Scheme 3.3**. This lower selectivity comes mainly from the use of the standard ligand dtbpy (**L2**) and higher temperatures.

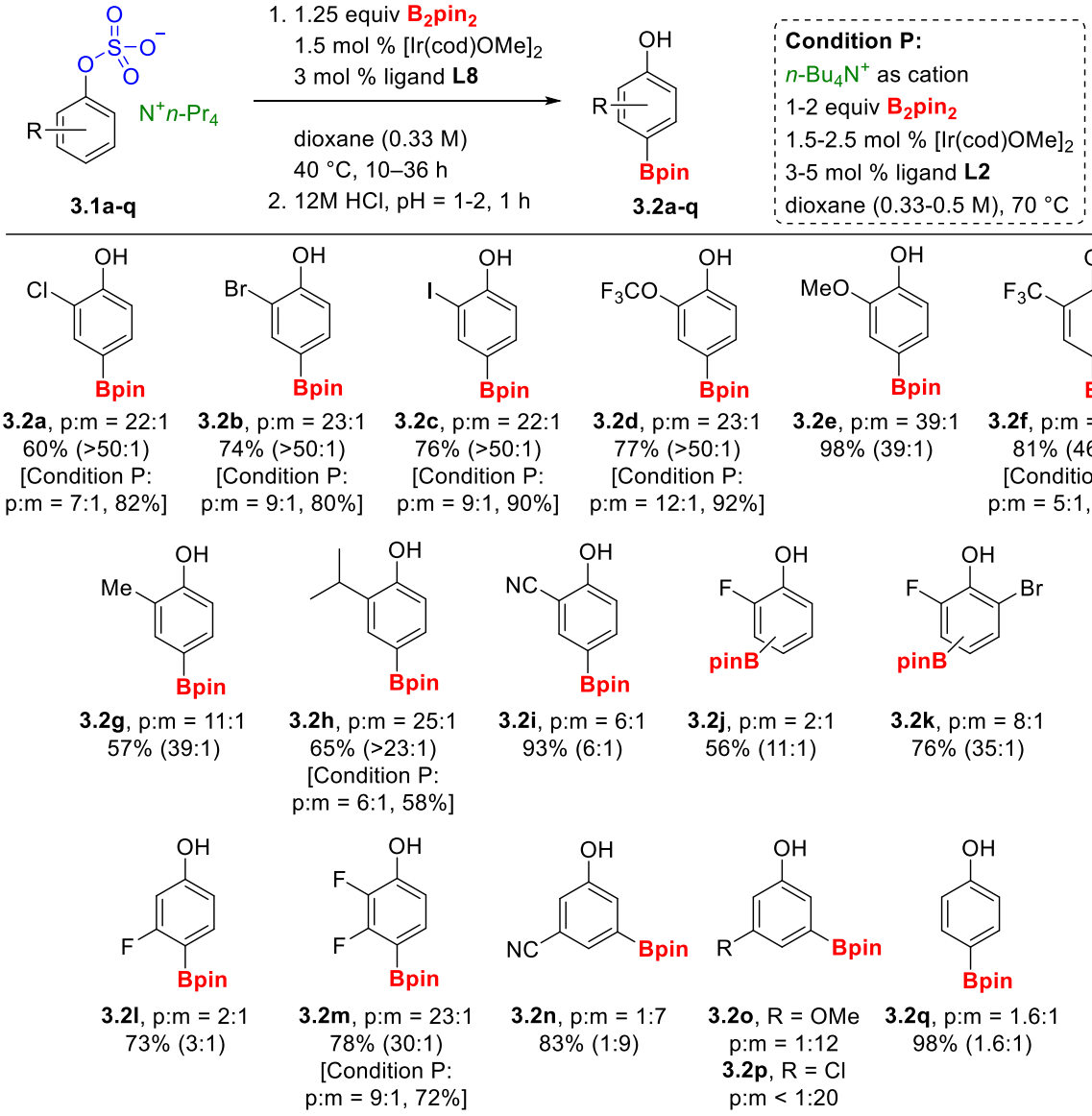
Scheme 3.2: Effect of alkyl chain length and ligand on *para* CHB of 2-chlorophenyl sulfates



3.2.3. *Para* CHB of sulfated phenols

As illustrated in **Scheme 3.3**, borylations of a series of 2-substituted phenol derived sulfates produced the *para* regioisomer as the major isomer, often with >20:1 selectivity. Most isolated yields were in the 70−80% range. Notably upon isolation the *para* to *meta* isomer was enhanced, in some cases to >50:1. *Ortho* substituents with lone pairs favor the *para* selectivity (**3.2a-e**) which bears some relationship to previous reports of these groups favoring *meta* CHB;[35] in our case that position is *para* respect to the sulfated group. The selectivity drops by half without lone pairs in the *ortho* substituent as exhibit by **3.2f** and **3.2g**. A larger *ortho* substituent like isopropyl in **3.1h** seems to improve the selectivity by twice if its compare with **3.1g** which have a smaller methyl group.

Scheme 3.3: Borylation of phenol derived sulfates



[a] *Para*/*meta* ratios were measured by ^{1}H NMR on crude reaction mixtures of the borylated sulfates. Yields refer to isolated material with the *para/meta* ratio of the isolated material given in parentheses (**3.2o** and **3.2p** were not isolated). Conditions P refers to the reaction conditions employed by the Phipps group.

Given that CHB ortho to small substituents is common,[36] borylation at the C-3 and C-5 *meta* CH bonds of 2-cyano-(**3.2i**) and 2-fluorophenol sulfate (**3.2j**) are possible. Indeed, analysis of the crude reaction mixture indicated that **3.2i** gave a mixture of the *para* to 5-Bpin to 3,5-diBpin products in a ratio of approximately 7.5:1:0.4. For substrates **3.1j** and **3.1k**, the observed minor

isomer was that with the Bpin *ortho* to the fluoro group and no diborylation was observed. Given this preference, it was perhaps somewhat surprising that 3-fluorophenol sulfate (**3.1l**) produced a relatively large amount of the *meta* regioisomer. In comparison, 2,3-difluorophenol sulfate (**3.1m**) yielded the *para* borylated product in relatively high selectivity (23:1). The ten-fold improvement from **3.2l** to **3.2m** is in accordance with the previously observed improvement of selectivity conferred by *ortho* substituents with lone pairs.

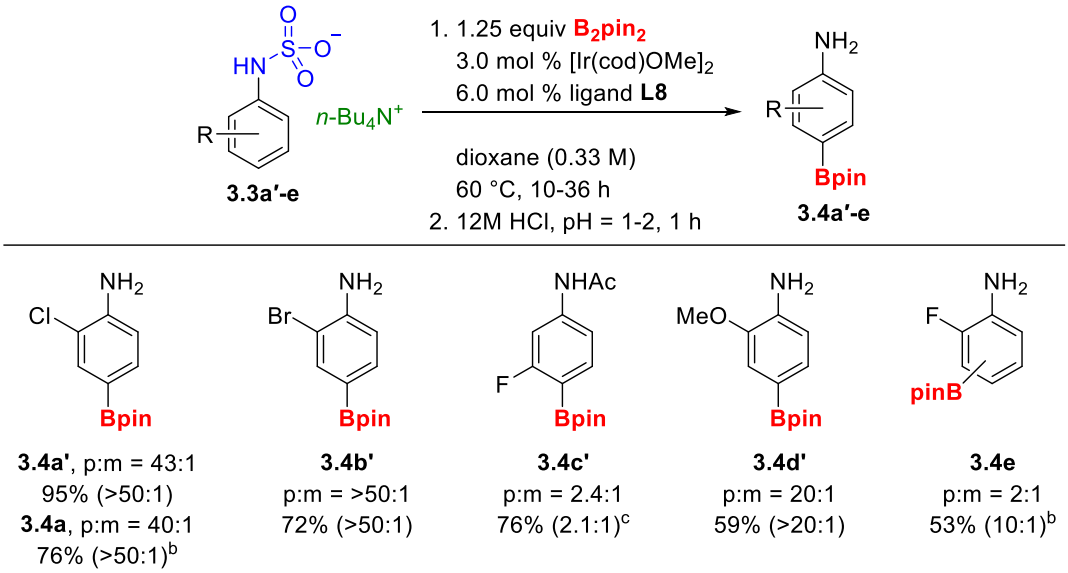
Not surprising was that the CHB of 3-substituted phenol sulfates (**3.1n−p**) gave the *meta* isomer as the major product, showing that such ion-pair interactions are limited in their ability to overcome steric crowding of the *para* CH position. Last, we borylated the sulfate of phenol (**3.1q**) and observed the *para*, *meta*, and 3,5-*dimeta* Borylated products in a ratio of 4.4:1:1.8, or a *para*/*meta* ratio of 1.6:1. This result is consistent with the assumption that the ion pairing can only block one *meta* site and thus the reactions need a 2-substituent to sterically block the second *meta* CH bond.

3.2.4. *Para* CHB of sulfated anilines

Turning to anilines (**Scheme 3.4**), we subjected tetrapropylammonium 2-chlorophenylsulfamate (**3.3a**) to our now standard conditions. The *para* selectivity (40:1) was even better than that observed for **3.1a**. Questioning if the chain length of the tetraalkylammonium salt would also impact the *para* selectivity for aniline derivatives, we prepared and reacted the tetrabutylammonium salt (**3.3a'**). In contrast to the phenol sulfates, employing this counterion met with 43:1 *para* selectivity and a higher isolated yield. Owing to this result and that the tetrabutylammonium salts are somewhat easier to prepare and isolate, we chose *n*-Bu_4N^+ as the counterion for CHBs of a series of aniline sulfamates. The *para* selectivities for **3.3b'** and **3.3d'** were excellent, while again selectivity for a 3-fluoro substrate (**3.3c'**) suffered, giving only a 2.4:1

para/*meta* ratio. Isolation of the hydrolyzed aniline following borylation of **3.3c'** proved difficult. Therefore, the reaction was quenched with acetyl chloride, facilitating the isolation of **3.4c'**. The Phipps group applied their protocol to **3.3a'** and **3.3b'** as well and got very good selectivity as ours even with their nonoptimal conditions. This highlights the intrinsic tendency to yield the *para* borylated product of phenyl sulfamates respect to phenyl sulfates.

Scheme 3.4: Borylation of aniline derived sulfamates

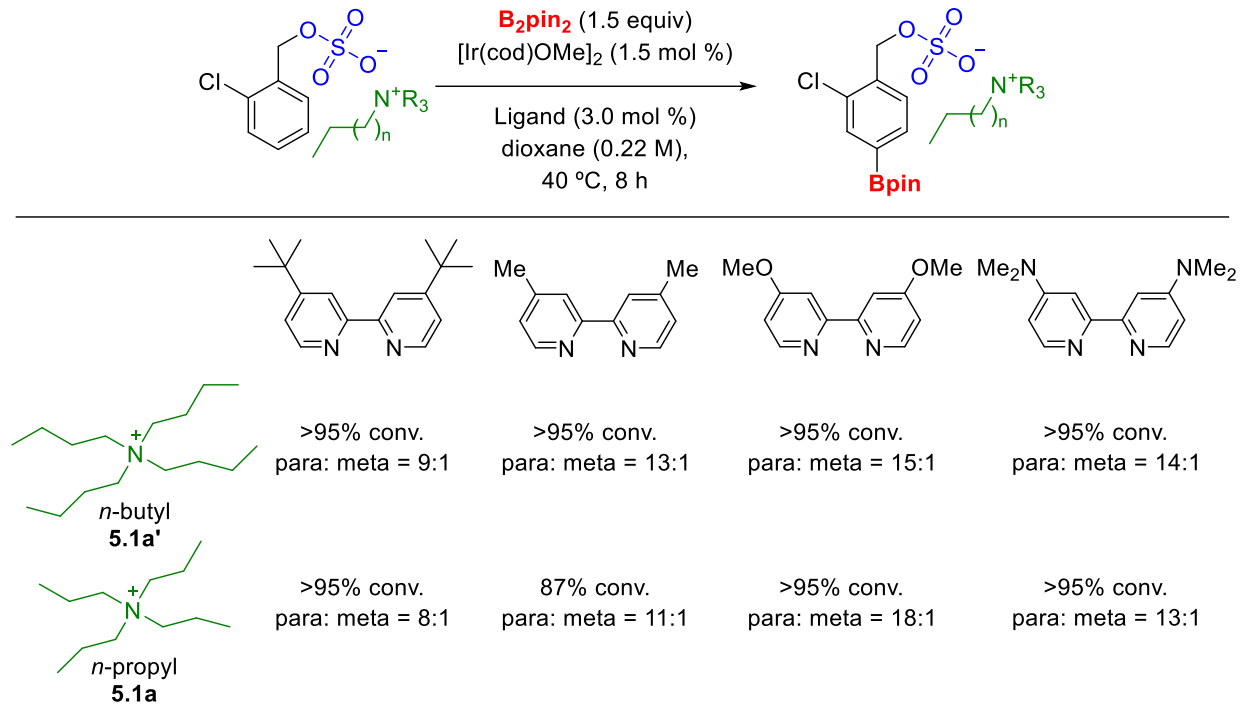


[a] *Para*/*meta* ratios were measured by ^{1}H NMR (or ^{19}F NMR for **3.4c'**) on crude reaction mixtures of the borylated sulfamates. Yields refer to isolated material with the *para*/*meta* ratio of the isolated material given in parentheses. [b] Run with the *n*-Pr_4N^+ counterion. [c] Product isolated as the acetamide.

3.2.5. *Para* CHB of sulfated benzyl alcohols

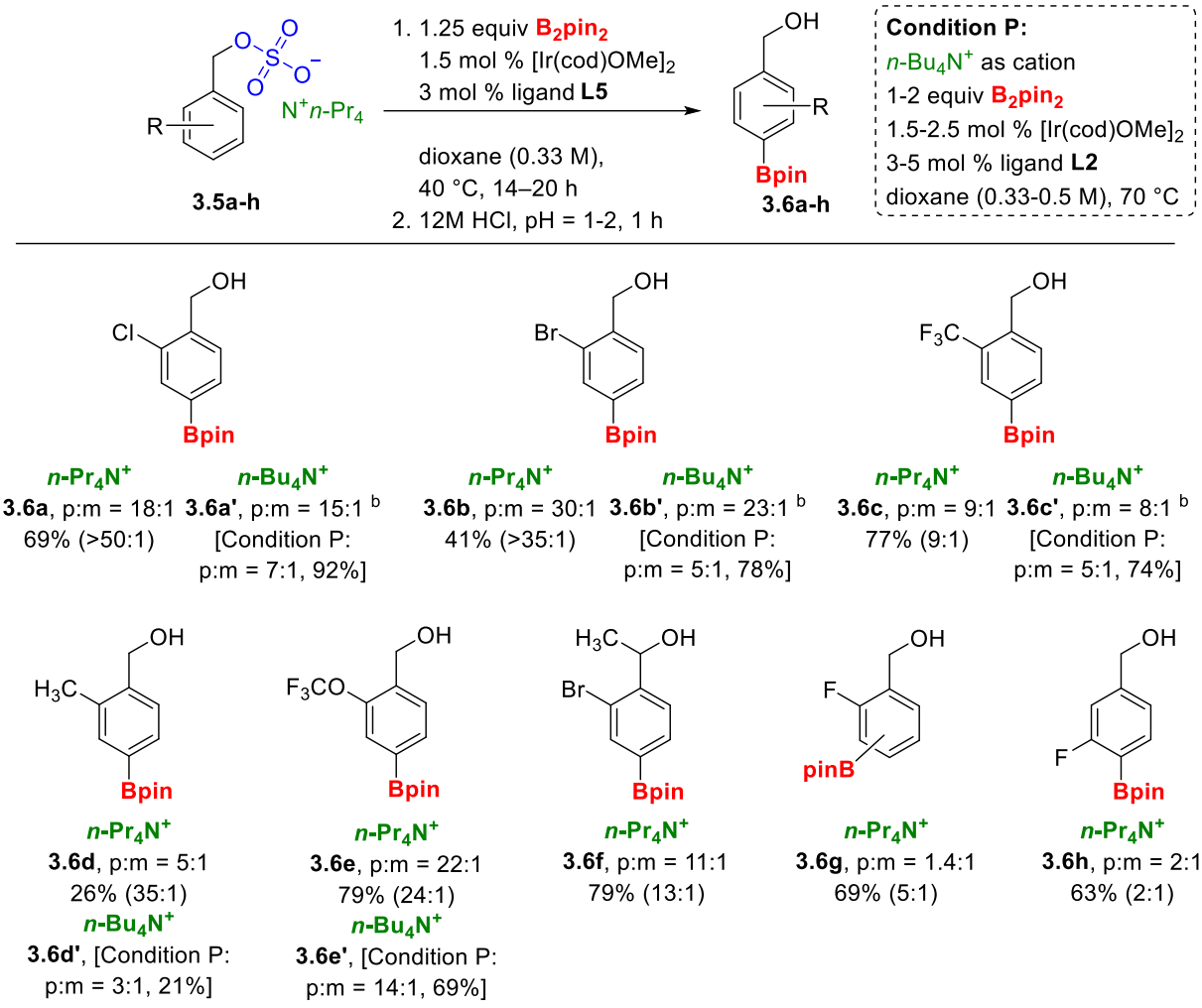
Finally, we surveyed benzyl alcohol derived sulfates and fortunately the *para* borylated product was observed in significant selectivities. We began by optimizing the counterion and ligand of 2-chlorobenzyl sulfate (**Scheme 3.5**) which again were key factors on the *para* CHB regioselectivity. Although having an additional methylene group in benzyl sulfates respect to phenyl sulfates, tetrapropyl ammonium cations were found to be optimal for this case as well. L3 was again the best ligand choice to reach a 18:1 selectivity.

Scheme 3.5: Effect of alkyl chain length and ligand on *para* CHB of 2-chlorobenzyl sulfate



Generally, benzyl alcohol derived sulfates reacted with somewhat diminished *para* selectivity relative to their phenol and aniline counterparts (**Scheme 3.6**). Products **3.6b** and **3.6d** were generated in lower yields owing in part to lower conversions and, for **3.6d**, loss of the *meta* isomer upon isolation. Again, borylation of a substrate with fluorine in the 2-position (**3.5g**) afforded a significant amount of product with the Bpin ortho to the fluorine. By applying the CHB conditions to the *n*-Bu_4N^+ counterion, **3.5a**–**3.5c** revealed that the counterion has a similar influence on the regioselectivity as observed for the phenols. For comparison, the selectivities obtained by the Phipps group are shown in brackets, the lower values are due to the nonoptimized conditions used in that protocol.

Scheme 3.6: Borylation of benzyl alcohol derived sulfates



[a] *Para*/*meta* ratios were measured by ^{1}H NMR on crude reaction mixtures of the borylated sulfates. Yields refer to isolated material with the *para*/*meta* ratio of the isolated material given in parentheses. [b] Run with the *n*-Bu_4N^+ counterion.

3.3. Conclusions

In summary, ion-pair electrostatic interactions can be used to direct Ir-catalyzed borylation to the *para* position of sulfates and sulfamates derived from phenols, anilines, and benzyl alcohols. We hypothesize that the source of the *para* selectivity is a steric block created by the carbon chain of the tetrabutylammonium counterion. For sulfates derived from phenols and benzyl alcohols, n-Pr_4N^+ salts gave better selectivity than their *n*-Bu_4N^+ counterparts. The chain length of

tetralkylammonium salt was not as influential on the borylation of the sulfamates derived from anilines. Notably, optimal results were observed with the nontraditional CHB ligand 4,4'-dimethoxy-2,2'-bipyridine. This serves to remind the community to look beyond dtbpy or tmphen when optimizing CHB reactions.

3.4. Experimental Procedures

3.4.1. General Information

All commercially available chemicals were used as received unless otherwise indicated. Bis(pinacolato)diboron (B_2pin_2) was generously supplied by BoroPharm, Inc. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) $[Ir(cod)(OMe)]_2$ was made by a literature procedure [37] or purchased from Sigma-Aldrich. Dioxane was refluxed over sodium/benzophenone ketyl, distilled and degassed.

Column chromatography was performed on 240 - 400 mesh Silica P-Flash silica gel. Thin layer chromatography was performed on 0.25 mm thick aluminum–backed silica gel plates and visualized with ultraviolet light (λ = 254 nm) and alizarin stain to visualize boronic esters according to a literature procedure.[38]

^1H, ^{13}C, ^{11}B and ^{19}F NMR spectra were recorded on a Varian 500 MHz DD2 Spectrometer equipped with a 1H-19F/15N-31P 5 mm Pulsed Field Gradient (PFG) Probe, or an Innova 300 MHz spectrometer equipped with a QUAD ($^1H/^{19}F$ and ^{11}B) PFG probe. Spectra taken in $CDCl_3$ referenced to 7.26 ppm in ^1H NMR and 77.0 ppm in ^{13}C NMR. Spectra taken in C_6D_6 referenced to 7.16 ppm in ^1H NMR and 128.06 ppm in ^{13}C NMR. ^{11}B NMR spectra were referenced to neat $BF_3 \cdot Et_2O$ as the external standard. ^{19}F NMR spectra taken in $CDCl_3$ were referenced with C_6F_6 as internal standard to -161.64 ppm.

Resonances for the boron-bearing carbon atom were not observed due to quadrupolar relaxation. All coupling constants are apparent *J* values measured at the indicated field strengths in Hertz (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, bs = broad singlet). NMR spectra were processed for display using the MNova software program with only phasing and baseline corrections applied.

High-resolution mass spectra (HRMS) were obtained at the Michigan State University Mass Spectrometry Service Center using electrospray ionization (ESI+ or ESI-) on quadrupole time-of-flight (Q-TOF) instruments. Melting points were measured in a capillary melting point apparatus and are uncorrected.

3.4.2. Determining Product Ratios by NMR Integration

Product ratios were determined by integration of ^{1}H or ^{19}F NMR spectra. To verify the accuracy of the ^{1}H NMR integration, stock solutions of commercial samples of 3-chloro-4-hydroxyphenylBpin (*meta* borylated **3.2a**) and 4-chloro-3-hydroxyphenylBpin (*para* borylated **3.2a**) were accurately mixed in known amounts with Hamilton gas-tight micro syringes. The ratio determined by integration was compared to the known ratio. All ^{1}H NMR spectra were taken at 500 MHz with 32 scans and a delay of 10 seconds. All spectra were processed in MNova software with application of an auto-phase correction and a Bernstein polynomial fit baseline correction, followed by manual peak integration.

Two 0.196 M stock solutions of 3-chloro-4-hydroxyphenylBpin (*meta* borylated **3.2a**) and 4-chloro-3-hydroxyphenylBpin (*para* borylated **3.2a**) were prepared as follows: A mass of 50.0 mg of commercial 3-chloro-4-hydroxyphenylBpin (*meta*-**3.2a**) was dissolved in $CDCl_3$ in a 1.0 mL volumetric flask and $CDCl_3$ was added up to the mark. A mass of 100.0 mg of commercial 4-

chloro-3-hydroxyphenylBpin (*para*-**3.2a**) was dissolved in $CDCl_3$ in a 2.0 mL volumetric flask and $CDCl_3$ was added up to the mark.

A volume of 6 µL of *meta*-**3.2a** stock solution was diluted with $CDCl_3$ to 1.0 mL in a 1.0 mL volumetric flask, resulting in a 1.18 x 10^{-3} M solution. A volume of 600 µL of this solution was transferred into an NMR tube, making 7.0 x 10^{-7} mols of the *meta*-**3.2a** compound present in the sample. A ^{1}H NMR spectrum was taken. *Meta*-**3.2a** was clearly observed and all peaks integrated properly, with the data as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 1.2 Hz, 1H), 7.34 – 7.27 (m, 2H), 5.47 (s, 1H), 1.33 (s, 12H). The ^{1}H data for the commercial sample of *para*-**3.2a** was as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 1.5 Hz, 1H), 7.62 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 5.75 (s, 1H), 1.33 (s, 12H).

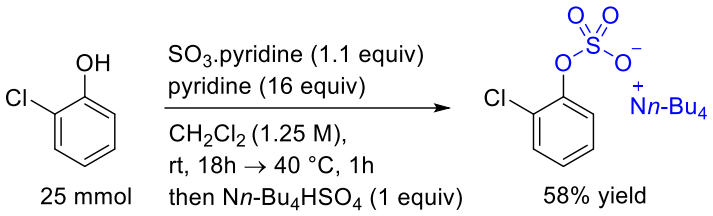
A sequence of additions of 50 microliters of *para*-**3.2a** stock solution was added directly into the NMR tube and NMR spectra were taken after each addition. For each 50 microliters of stock solution added, 9.8 x 10^{-6} mols of *para* compound was introduced into the NMR tube. This was repeated 4 times for a total of 3.92 x 10^{-5} mols *para*-**3.2a** compound to 7.0 x 10^{-7} mols of *meta*-**3.2a** compound, a 56-fold excess of *para*-**3.2a** compound. The integration of the peak at 7.43 ppm of the *meta*-**3.2a** compound was compared to the integration of the peak at 7.77 ppm of the *para*-**3.2a** compound for all determinations of *para*:*meta* ratio. The results are shown in **Table 3.2**. All NMR spectra are shown in the Appendix section.

Table 3.2: Integration of known ratios of *para*-2a to *meta*-2a

entry	**mols *para*-2a**	**mols *meta*-2a**	**calculated *para*:*meta* ratio**	**integrated *para*:*meta* ratio**
1	0	7.0 x 10^{-7}	--	--
2	9.8 x 10^{-6}	7.0 x 10^{-7}	14:1	14.10:1.00
3	1.96 x 10^{-5}	7.0 x 10^{-7}	28:1	27.26:1.00
4	2.94 x 10^{-5}	7.0 x 10^{-7}	42:1	44.19:1.00
5	3.92 x 10^{-5}	7.0 x 10^{-7}	56:1	54.68:1.00

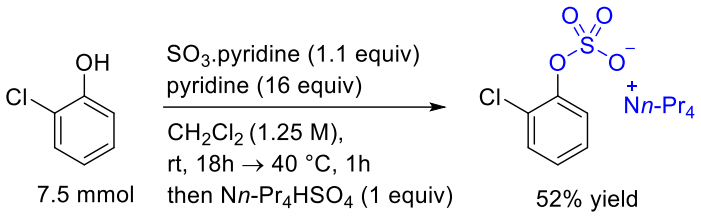
3.4.3. Preparation of Sulfated Phenols

Synthesis of tetrabutylammonium 2-chlorophenyl sulfate (3.1a′)



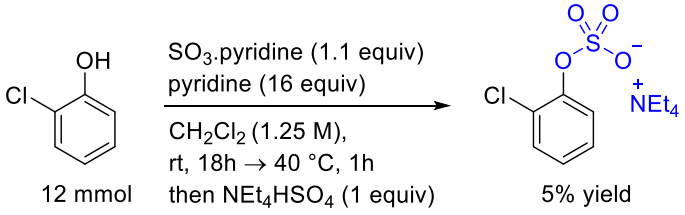
2-Chlorophenol (3.21 g, 25 mmol) and SO_3•pyridine complex (4.39 g, 27.5 mmol) were placed in a 100 mL round bottom flask. Pyridine (33 mL) and dry dichloromethane (20 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (300 mL) was added and the mixture was washed once with dichloromethane (1 x 300 mL). The aqueous phase was treated with tetrabutylammonium hydrogensulfate (8.45 g, 25 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 300 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum **3.1a′** (6.56 g, 58% yield) was isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.29 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.15 (td, *J* = 7.9, 1.6 Hz, 1H), 6.95 (td, *J* = 7.9, 1.5 Hz, 1H), 3.23–3.01 (m, 8H), 1.64–1.45 (m, 8H), 1.35 (m, 8H), 0.93 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8, 129.7, 127.3, 125.3, 123.8, 122.1, 58.4, 23.8, 19.6, 13.7. HRMS (ESI) *m/z* calc for $C_6H_4ClO_4S$ $[M–Nn\text{-}Bu_4]^-$ 206.9519, found 206.9722.

Synthesis of tetrapropylammonium 2-chlorophenyl sulfate (3.1a)



2-Chlorophenol (0.964 g, 7.5 mmol) and SO_3•pyridine complex (1.31 g, 8.2 mmol) were placed in a 100 mL round bottom flask. Pyridine (10 mL) and dry dichloromethane (6 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (90 mL) was added and the mixture was washed once with dichloromethane (1 x 90 mL). The aqueous phase was treated with tetrapropyl ammonium hydrogensulfate (2.12 g, 7.5 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 90 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1a**) was obtained as a white solid (1.53 g, 52% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.29 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.15 (td, *J* = 8.0, 1.7 Hz, 1H), 6.95 (td, *J* = 7.8, 1.5 Hz, 1H), 3.15–3.01 (m, 8H), 1.59 (m, *J* = 17.0, 7.3 Hz, 8H), 0.91 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8, 129.8, 127.4, 125.5, 124.0, 122.3, 60.3, 15.6, 10.8. HRMS (ESI) *m/z* calc for $C_6H_4ClO_4S$ $[M–Nn\text{-}Bu_4]^-$ 206.9519, found 206.9505.

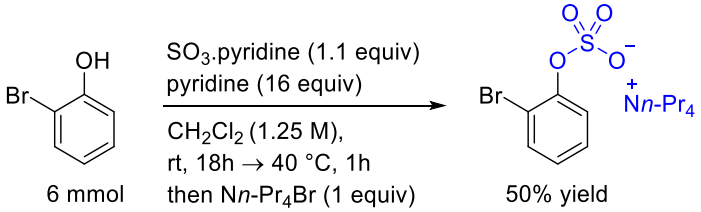
Synthesis of tetraethylammonium 2-chlorophenyl sulfate (3.1a′′)



2-Chlorophenol (1.54 g, 12 mmol) and SO_3•pyridine complex (2.1 g, 12.2 mmol) were placed in a 100 mL round bottom flask. Pyridine (16 mL) and dry dichloromethane (10 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (140 mL) was added and the mixture was washed once with dichloromethane (1 x 140 mL). The aqueous phase was treated with tetraethyl ammonium hydrogensulfate (2.73 g, 12 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The concentrated oil was dissolved in dichloromethane (50 mL) and washed once with 0.1 M NaOH aq. (1 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was concentrated by rotary evaporation. This hexane/ether process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1a"**) was obtained as a white solid (216 mg, 5% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.18 (td, *J* = 8.0, 1.6 Hz, 1H), 7.00 (td, *J* = 8.0, 1.5 Hz, 1H), 3.21 (q, *J* = 7.3 Hz, 8H), 1.21 (t, *J* = 7.3, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 129.9, 127.5, 125.7, 124.4, 122.4, 52.4, 7.5. HRMS (ESI) *m/z* calcd for $C_6H_4ClO_4S$ $[M–NEt_4]^-$ 206.9519, found 206.8556.

Synthesis of tetrapropylammonium 2-bromophenyl sulfate (3.1b)

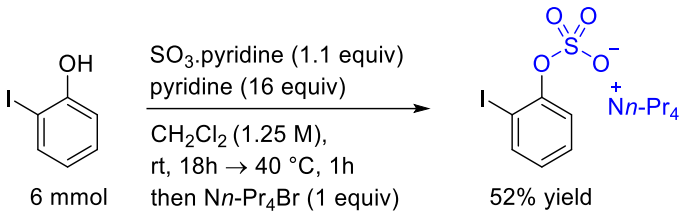


2-Bromophenol (1.038 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were

added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes were added and the suspension was concentrated by rotary evaporation. This process was repeated the product was obtained as a white solid. After overnight drying under high vacuum (**3.1b**) was obtained as a white solid (1.31 g, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.41 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.14 (ddd, *J* = 8.3, 8.0, 1.6 Hz, 1H), 6.84 (td, *J* = 8.0, 1.5 Hz, 1H), 3.11–2.82 (m, 8H), 1.52 (m, 8H), 0.84 (t, *J* = 7.4 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 132.7, 128.0, 124.3, 121.8, 114.6, 60.0, 15.4, 10.6. HRMS (ESI) *m/z* calcd for $C_6H_4BrO_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 250.9014, found 250.9032.

Synthesis of tetrapropylammonium 2-iodophenyl sulfate (3.1c)

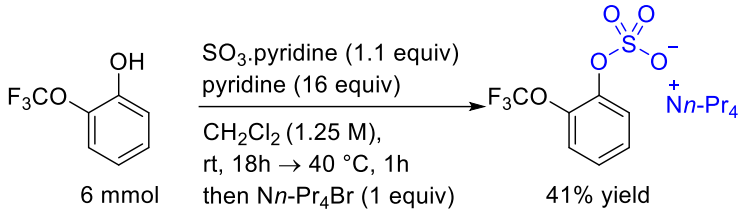


2-Iodophenol (1.32 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes

and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1c**) was obtained as a white solid (1.51 g, 52% yield).

^{1}H NMR (500 MHz, $CDCl_3$) 7.63 (m, 2H), 7.15 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 6.68 (td, *J* = 7.6, 1.5 Hz, 1H), 3.10–2.90 (m, 8H), 1.60–1.40 (m, 8H), 0.83 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 138.9, 129.1, 124.8, 120.8, 89.5, 60.2, 15.5, 10.8. HRMS (ESI) *m/z* calcd. for $C_6H_4IO_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 298.8875, found 298.8890.

Synthesis of tetrapropylammonium 2-(trifluoromethoxy)phenyl sulfate (3.1d)

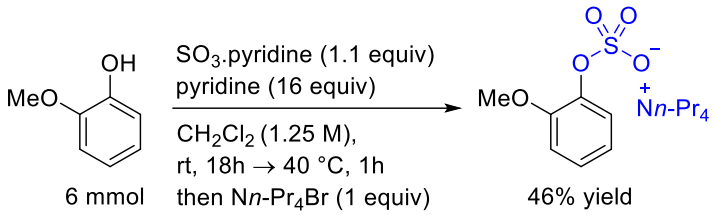


2-(Trifluoromethoxy)phenol (1.07 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1d**) was obtained as a white solid (1.09 g, 41% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.23 – 7.10 (m, 2H), 7.00 (t, *J* = 7.1 Hz, 1H), 3.27 – 2.89 (m, 8H), 1.85 – 1.40 (m, 8H), 0.90 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 146.0, 139.7, 127.4, 123.4, 122.5, 122.0, 120.7 (q, *J* = 257 Hz), 60.3, 15.5, 10.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.3. HRMS (ESI) *m/z* calcd. for $C_7H_4F_3O_5S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 256.9732, found 256.9768.

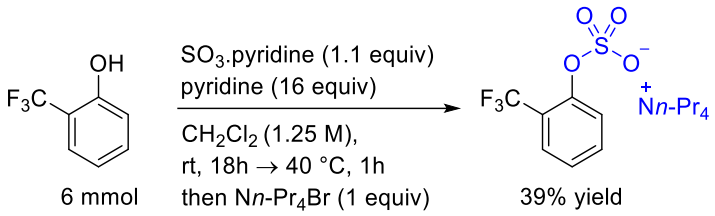
Synthesis of tetrapropylammonium 2-methoxyphenyl sulfate (3.1e)



2-Methoxyphenol (0.74 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1e**) was obtained as a white solid (1.08 g, 46% yield).

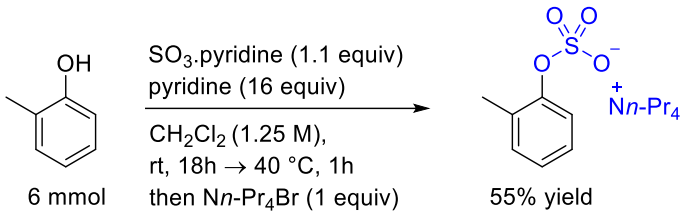
^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.97 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H), 6.87 – 6.80 (m, 2H), 3.79 (s, 3H), 3.26 – 3.04 (m, 8H), 1.68 – 1.46 (m, 8H), 0.92 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 143.1, 123.9, 122.0, 120.7, 113.1, 60.3, 56.4, 15.6, 10.8. HRMS (ESI) *m/z* calcd. for $C_7H_7O_5S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 203.0014, found 203.0053.

Synthesis of tetrapropylammonium 2-(trifluoromethyl)phenyl sulfate (3.1f)



2-(Trifluoromethyl)phenol (0.973 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1f**) was obtained as a white solid (0.991 g, 39% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.39 (td, *J* = 8.0, 1.6 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 3.13–2.93 (m, 8H), 1.67–1.45 (m, 8H), 0.85 (t, *J* = 7.4 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.9 (q, *J* = 1.8 Hz), 132.8 (s), 126.2 (q, *J* = 5.0 Hz), 123.5 (q, *J* = 272.4 Hz), 122.2 (s), 120.7 (s), 120.4 (q, *J* = 30.6 Hz), 60.1, 15.4, 10.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ –60.9. HRMS (ESI) *m/z* calcd. for $C_7H_4F_3O_4S$ $[M–Nn\text{-}Pr_4]^-$ 240.9782, found 240.9784.

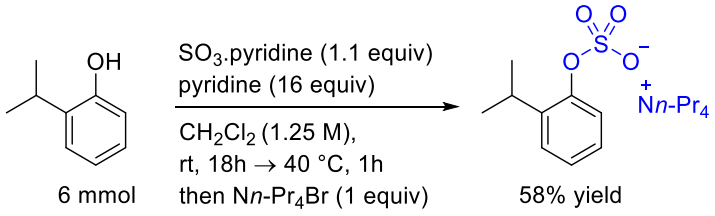
Synthesis of tetrapropylammonium 2-methylphenyl sulfate (3.1g)



2-Methylphenol (0.645 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes were added and the suspension was concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1g**) was obtained as a yellowish white solid (1.24 g, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.09 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.05 (td, *J* = 7.7, 1.7 Hz, 1H), 6.94 (td, *J* = 7.7, 1.2 Hz, 1H), 3.17 – 2.88 (m, 8H), 2.31 (s, 3H), 1.69 – 1.43 (m, 8H), 0.91 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.8, 131.2 130.5, 126.2, 123.8, 122.0, 60.2, 16.9, 15.5, 10.8. HRMS (ESI) *m/z* calcd for $C_7H_7O_4S$ $[M–Nn\text{-}Pr_4]^-$ 187.0065, found 187.0069.

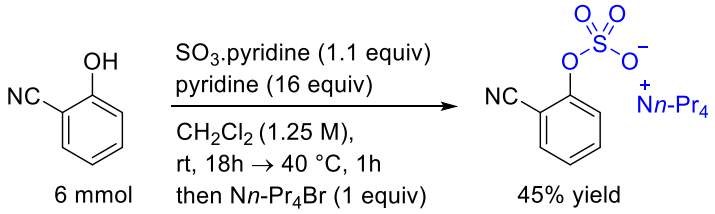
Synthesis of tetrapropylammonium 2-isopropylphenyl sulfate (3.1h)



2-Isopropylphenol (0.645 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1h**) was obtained as a white solid (1.39 g, 58% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.16 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.01 (td, *J* = 7.3, 2.1 Hz, 1H), 6.98 (td, *J* = 7.3, 1.6 Hz, 1H), 3.53 (p, *J* = 6.9 Hz, 1H), 3.13 – 2.94 (m, 8H), 1.59 – 1.44 (m, 8H), 1.14 (d, *J* = 7.0 Hz, 6H), 0.88 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 140.9, 125.9, 125.7, 123.9, 121.5, 60.2, 26.4, 23.3, 15.5, 10.7. HRMS (ESI) *m/z* calcd. for $C_9H_{11}O_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 215.0378, found 215.0397.

Synthesis of tetrapropylammonium 2-cyanophenyl sulfate (1i)

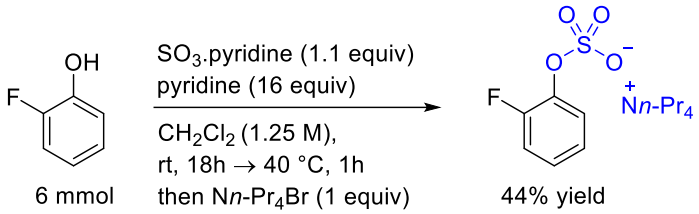


2-Cyanophenol (0.714 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70

mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1i**) was obtained as a white solid (1.03 g, 45% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.45 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.44 (td, *J* = 7.6, 1.8 Hz, 1H), 7.04 (td, *J* = 7.6, 1.1 Hz, 1H), 3.26 – 2.73 (m, 8H), 1.62 (m, 8H), 0.89 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 133.9, 132.8, 123.1, 120.9, 116.8, 104.5, 60.2, 15.4, 10.6. HRMS (ESI) *m/z* calcd. for $C_7H_4NO_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 197.9861, found 197.8931.

Synthesis of tetrapropylammonium 2-fluorophenyl sulfate (3.1j)

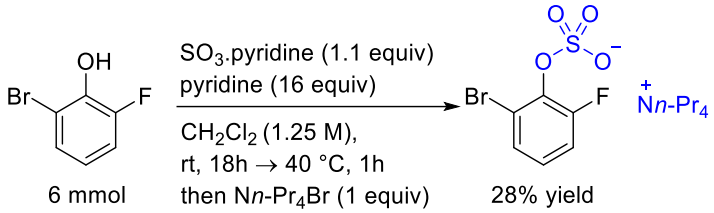


2-Fluorophenol (0.673 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation.

This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1j**) was obtained as a white solid (1.00 g, 44% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.60 (m, 1H), 7.07–6.94 (m, 3H), 3.23–3.03 (m, 8H), 1.76 – 1.46 (m, 8H), 0.93 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3 (d, *J* = 247.1 Hz), 141.2 (d, *J* = 11.3 Hz), 124.2 (d, *J* = 7.1 Hz), 124.0 (d, *J* = 3.8 Hz), 123.8, 116.1 (d, *J* = 18.8 Hz), 60.3, 15.6, 10.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.6. HRMS (ESI) *m/z* calcd. for $C_6H_4FO_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 190.9814, found 190.9830.

Synthesis of tetrapropylammonium 2-bromo-6-fluorophenyl sulfate (3.1k)

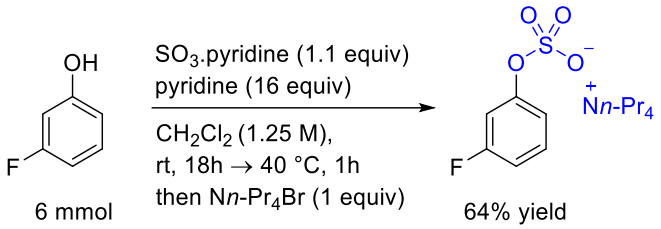


2-Bromo-6-fluorophenol (1.15 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1k**) was obtained as a white solid (0.78 g, 28% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.2 Hz, 1H), 6.97 (t, *J* = 8.2 Hz, 1H), 6.89 (td, J = 8.2, 5.1 Hz, 1H), 3.16 – 2.96 (m, 8H), 1.63 – 1.42 (m, 8H), 0.89 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126

MHz, $CDCl_3$) δ 156.7 (d, *J* = 253.7 Hz), 139.7 (d, *J* = 14.6 Hz), 128.3 (d, *J* = 3.5 Hz), 125.5 (d, *J* = 8.1 Hz), 119.8 (d, *J* = 1.9 Hz), 115.7 (d, *J* = 19.9 Hz), 60.2, 15.5, 10.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ –121.2 (dd, *J* = 8.2, 5.1 Hz). HRMS (ESI) *m/z* calcd. for $C_6H_3BrFO_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 268.8919, found 268.8919.

Synthesis of tetrapropylammonium 3-fluorophenyl sulfate (3.1l)

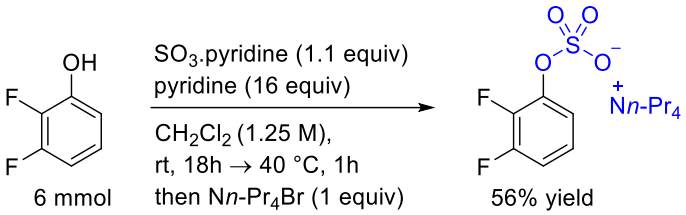


3-Fluorophenol (0.673 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes were added and the suspension was concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1l**) was obtained as a white solid (1.46 g, 64% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (td, *J* = 8.2, 6.8 Hz, 1H), 7.13 (dt, *J* = 10.6, 2.4 Hz, 1H), 7.06 (ddd, *J* = 8.2, 2.4, 0.9 Hz, 1H), 6.73 (tdd, *J* = 8.2, 2.4, 0.9 Hz, 1H), 3.15–2.90 (m, 8H), 1.68–1.51 (m, 8H), 0.92 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8 (d, *J* = 244.6 Hz), 154.8 (d, *J* = 11.2 Hz), 129.6 (d, *J* = 9.6 Hz), 116.5 (d, *J* = 2.9 Hz), 110.1 (d, *J* = 21.1 Hz), 108.4 (d, *J* =

24.3 Hz), 60.3, 15.5, 10.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ –112.5 (m) HRMS (ESI) *m/z* calcd. for $C_6H_4FO_4S$ [M–N*n*-Pr_4]$^-$ 190.9814, found 190.9821.

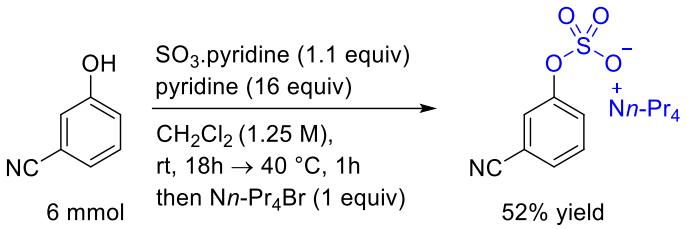
Synthesis of tetrapropylammonium 2,3-difluorophenyl sulfate (3.1m)



2,3-Difluorophenol (0.78 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1m**) was obtained as a white solid (1.33 g, 56% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (ddt, *J* = 8.4, 6.9, 1.6 Hz, 1H), 6.91 (tdd, *J* = 8.4, 6.2, 2.2 Hz, 1H), 6.82 (dddd, *J* = 9.7, 8.4, 6.8, 1.6 Hz, 1H), 3.23 – 2.95 (m, 8H), 1.60 (m, 8H), 0.91 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0 (dd, *J* = 246.4, 11.0 Hz), 143.2 (dd, *J* = 248.2, 14.0 Hz), 142.8 (dd, *J* = 8.7, 2.6 Hz), 122.7 (dd, *J* = 8.3, 5.1 Hz), 118.7 (d, *J* = 3.3 Hz), 111.7 (d, *J* = 17.1 Hz), 60.3, 15.4, 10.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ –137.9 (ddd, *J* = 20.3, 9.7, 6.2 Hz), –155.0 (dt, *J* = 20.3, 6.8 Hz). HRMS (ESI) *m/z* calcd. for $C_6H_3F_2O_4S$ [M–N*n*-Pr_4]$^-$ 208.9720, found 208.8767.

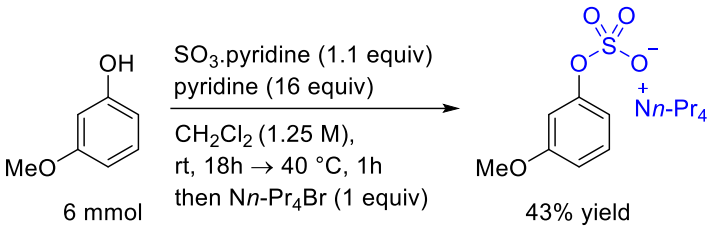
Synthesis of tetrapropylammonium 3-cyanophenyl sulfate (3.1n)



3-Cyanophenol (0.72 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1n**) was obtained as a white solid (1.19 g, 52% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 2.4, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.2, 2.4, 1.3 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.31 (dt, *J* = 7.6, 1.4 Hz, 1H), 3.24 – 2.94 (m, 8H), 1.60–1.72 (m, 8H), 0.95 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 130.1, 127.0, 125.8, 124.1, 118.8, 112.5, 60.5, 15.6, 10.8. HRMS (ESI) *m/z* calcd. for $C_7H_4NO_4S$ [M–N*n*-Pr_4]$^-$ 197.9861, found 197.9884.

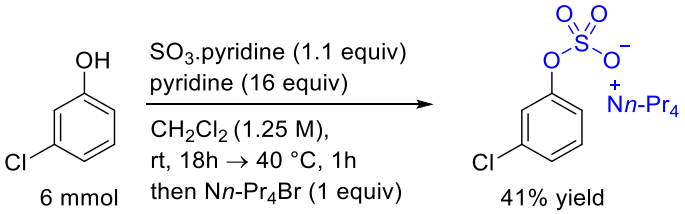
Synthesis of tetrapropylammonium 3-methoxyphenyl sulfate (3.1o)



3-Methoxyphenol (0.74 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1o**) was obtained as a white solid (1.01 g, 43 yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (t, *J* = 8.2 Hz, 1H), 6.96-6.85 (m, 2H), 6.57 (dt, *J* = 8.2, 1.8 Hz, 1H), 3.71 (s, 3H), 3.11 – 3.03 (m, 8H), 1.63 – 1.46 (m, 8H), 0.90 (t, *J* = 7.3 Hz, 12H).^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 154.7, 129.2, 113.4, 109.2, 107.1, 60.2, 55.3, 15.5, 10.8. HRMS (ESI) *m/z* calcd. for $C_7H_7O_5S$ $[M–Nn\text{-}Pr_4]^-$ 203.0014, found 203.0050.

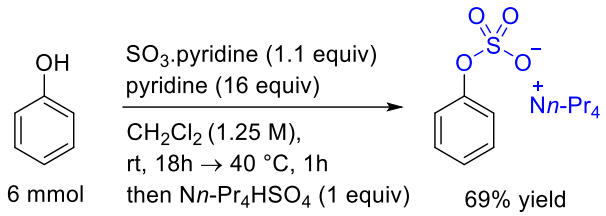
Synthesis of tetrapropylammonium 3-chlorophenyl sulfate (3.1p)



3-Chlorophenol (0.77 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evapoation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1p**) was obtained as a white solid (0.96 g, 41% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 2.1 Hz, 1H), 7.18 – 7.12 (m, 2H), 6.99 (dt, *J* = 6.5, 2.1 Hz, 1H), 3.20 – 2.91 (m, 8H), 1.64 – 1.46 (m, 8H), 0.91 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 133.5, 129.5, 123.2, 120.8, 119.0, 59.8, 15.1, 10.4. HRMS (ESI) *m/z* calcd. for $C_6H_4ClO_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 206.9519, found 206.9544.

Synthesis of tetrapropylammonium 1-phenyl sulfate (3.1q)



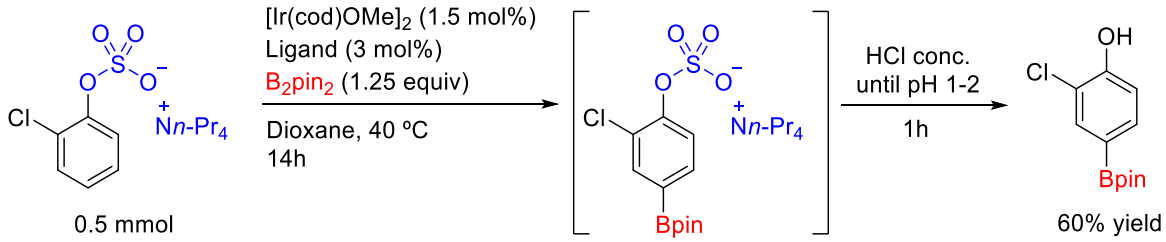
Phenol (0.56 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at 40 ºC for 7 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3

x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in a clear oil. To the concentrated oil, hexanes and ether were added and the suspension was again concentrated by rotary evaporation. This process was repeated until the product was obtained as a white solid. After overnight drying under high vacuum (**3.1q**) was obtained as a white solid (1.50 g, 69% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.17 (m, 2H), 7.01 (td, *J* = 7.0, 5.4 Hz, 1H), 3.14 – 2.89 (m, 8H), 1.70 – 1.35 (m, 8H), 0.89 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 128.8, 123.4, 121.0, 60.1, 15.4, 10.7. HRMS (ESI) *m/z* calcd. for $C_6H_5O_4S$ [M–N*n*-Pr_4]$^-$ 172.9909, found 173.0117.

3.4.4. CHB of Sulfated Phenols

***Para* borylation of tetrapropyl ammonium 2-chlorophenyl sulfate (3.2a)**



96% conversion, *para : meta* = 22:1
60% isolated yield, *para : meta* = >20 : 1

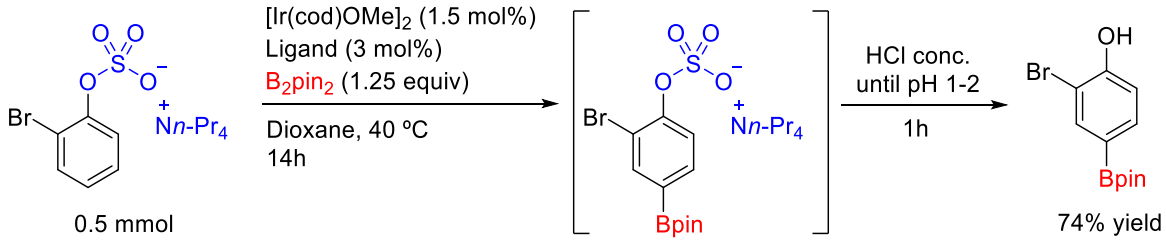
In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-chlorophenyl sulfate (197 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 14 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and washed with hexanes (0.5 mL). The

hexane layer was decanted, and the remaining solution subjected to chromatographic separation with silica gel ($CHCl_3$ as eluent) to give 76 mg of *para* borylated 2-chlorophenol with traces of the *meta* isomer (< 2%) as a white solid (60% yield, mp 118.6–120.1 °C). The NMR data were consistent with previously reported NMR values.[33]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.4 Hz, 1H), 7.61 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.04 (bs, 1H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 135.8, 135.2, 120.0, 116.0, 84.1, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.2. HRMS (ESI) *m/z* calcd. for $C_{12}H_{15}BClO_3$ $[M–H]^-$ 253.0803, found 253.1007.

Performing the same borylation with tetraethylammonium 2-chlorophenyl sulfate gave a *para:meta* ratio of 6:1, while borylation of tetrabutylammonium 2-chloro sulfate gave a *para:meta* ratio of 17:1.

***Para* borylation of tetrapropyl ammonium 2-bromophenyl sulfate (3.2b)**



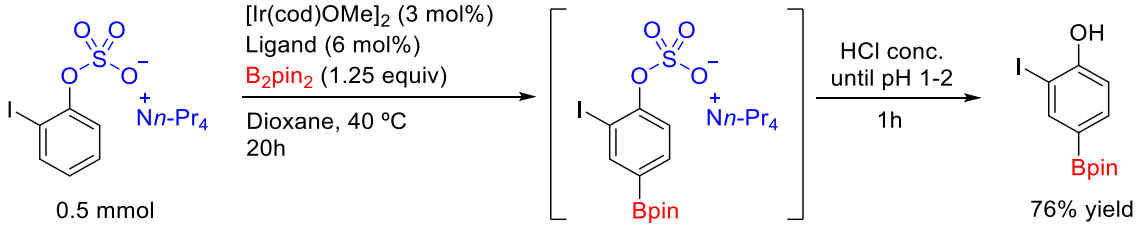
98% conversion, *para : meta* = 23:1
74% isolated yield, *para : meta* = >20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-bromophenyl sulfate (219 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 14 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the

resultant mixture was stirred for 1 h. The solution was concentrated and washed with hexanes (0.5 mL). The hexane layer was decanted, and the remaining solution subjected to chromatographic separation with silica gel ($CHCl_3$ as eluent) to give 110 mg of *para* borylated 2-bromophenol with traces of the *meta* isomer (< 2%) as a white solid (74% yield, mp 118.4–119.6 °C). The NMR data were consistent with previously reported values.[39]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.5 Hz, 1H), 7.64 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 5.92 (bs, 1H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 138.8, 136.0, 115.8, 110.4, 84.1, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.1. HRMS (ESI) *m/z* calcd. for $C_{12}H_{15}BBrO_3$ $[M–H]^-$ 297.0298, found 297.0304.

***Para* borylation of tetrapropyl ammonium 2-iodophenyl sulfate (3.2c)**



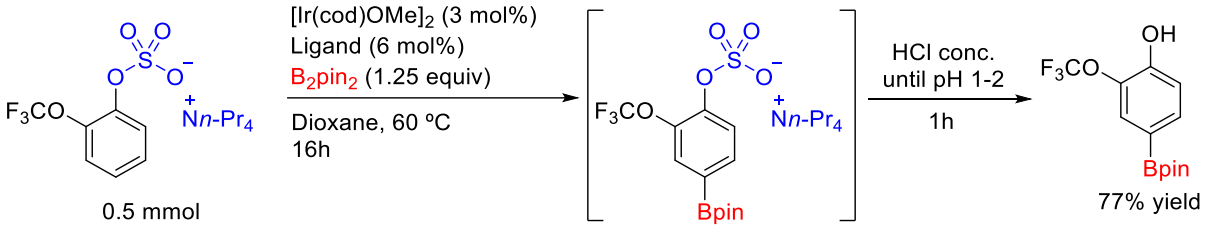
>99.9% conversion, *para : meta* = 22:1
76% isolated yield, *para : meta* = >20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-iodophenyl sulfate (243 mg, 0.5 mmol), [[Ir(cod)(OMe)]$_2$ (10 mg, 3 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 20 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and subjected directly to chromatographic separation with silica gel ($CHCl_3$ as eluent) to give 132 mg of *para* borylated 2-

iodophenol with traces of the *meta* isomer (< 2%) as a white solid (76% yield, mp 119.7–121.2 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.89 (bs, 1H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 145.3, 137.0, 114.8, 86.0, 84.1, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.8. HRMS (ESI) m/z calcd for $C_{12}H_{15}BIO_3$ $[M–H]^-$ 345.0159, found 345.0211.

***Para* borylation of tetrapropyl ammonium 2-trifluoromethoxyphenyl sulfate (3.2d)**

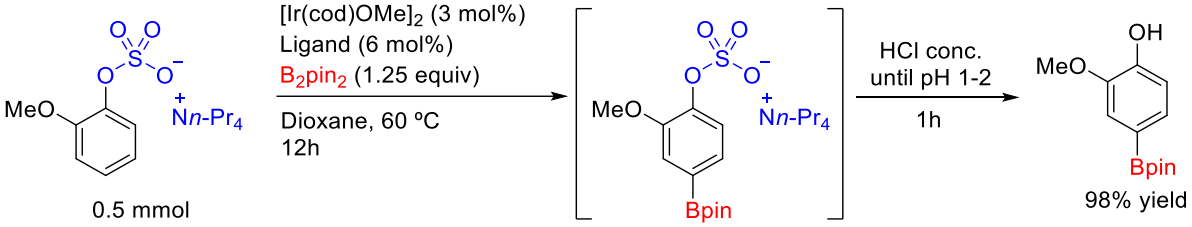


96% conversion, *para : meta* = 23:1
77% isolated yield, *para : meta* = >20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-trifluoromethoxyphenyl sulfate (198 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 16 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel (4% EtOAc in $CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with hexanes (0.5 mL). The hexane layer was decanted and the residue was evaporated to give 117 mg of a mixture of *para* borylated 2-trifluoromethoxyphenol with traces of the *meta* isomer (<2%) as a white solid (77% yield, mp 129.6–131.9 °C)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.63 (d, *J* = 8.08 Hz, 1H), 7.01 (d, *J* = 8.08 Hz, 1H), 5.97 (bs, 1H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 136.4 (q, *J* = 1.91 Hz), 135.1, 127.8, 120.8 (q, *J* = 259.0 Hz), 117.0, 84.2, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.7. HRMS (ESI) m/z calcd for $C_{13}H_{15}BF_3O_4$ $[M–H]^-$ 303.1015, found 303.1244.

***Para* borylation of tetrapropylammonium 2-methoxyphenyl sulfate (3.2e)**



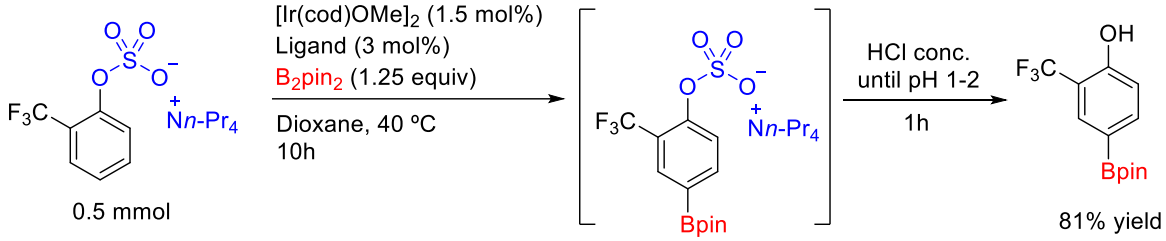
>99.9% conversion, *para : meta* = 39:1
98% isolated yield, *para : meta* = 39 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-methoxyphenyl sulfate (195 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 12 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent) to give 122 mg of a mixture of *para* borylated 2-methoxyphenol with the *meta* isomer (*para*:*meta* = 39:1) as a white solid (98% yield, mp 96.7–100.0 °C)

^{1}H NMR (500 MHz, C_6D_6) δ 7.76 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.50 (d, *J* = 1.3 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.00 (bs, 1H), 3.16 (s, 3H), 1.15 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 149.6, 146.6,

129.9, 117.1, 114.8, 83.6, 55.1, 25.0. ^{11}B NMR (160 MHz, C_6D_6) δ 31.2. HRMS (ESI) m/z calcd for $C_{13}H_{18}BO_4$ $[M–H]^-$ 249.1298, found 249.0159.

***Para* borylation of tetrapropyl ammonium 2-trifluoromethylphenyl sulfate (3.2f)**



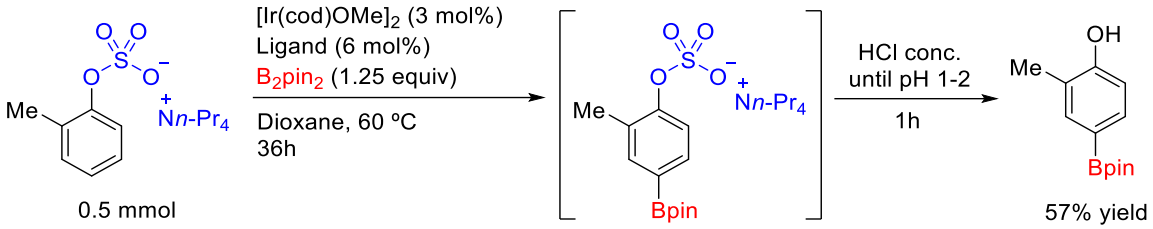
>99.9% conversion, *para : meta* = 11:1
81% isolated yield, *para : meta* = 46 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-trifluoromethylphenyl sulfate (214 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 10 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and washed with hexanes (0.5 mL). The hexane layer was decanted, and the remaining solution subjected to chromatographic separation with silica gel (12% EtOAc in $CHCl_3$ as eluent) to give 116 mg of *para* borylated 2-trifluoromethylphenol with traces of the *meta* isomer (*para*:*meta* = 46:1) as a white solid (81% yield, mp 128.1–129.9 °C). The NMR data were consistent with previously reported NMR values.[33]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.6 Hz, 1H), 7.80 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.98 (bs, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 1.35 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7 (q, *J* = 1.9 Hz), 140.1, 134.1 (q, *J* = 4.7 Hz), 124.1 (q, *J* = 272.3 Hz), 116.9, 116.7 (q, *J* = 30.5 Hz), 84.5, 24.8.

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ –60.6. HRMS (ESI) m/z calcd for $C_{13}H_{15}BF_3O_3$ $[M–H]^-$ 287.1066, found 286.9732.

***Para* borylation of tetrapropyl ammonium 2-methylphenyl sulfate (3.2g)**

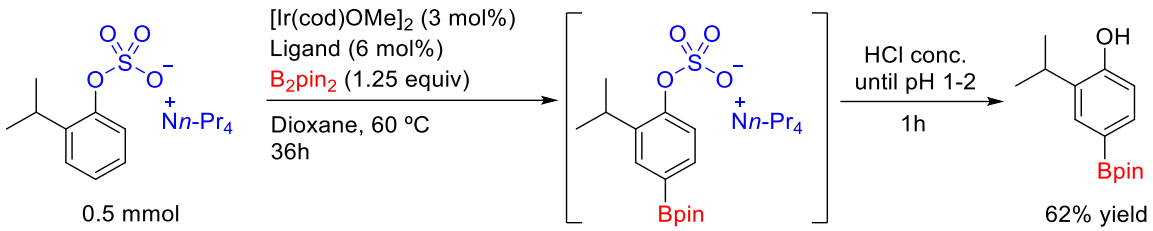


73% conversion, *para : meta* = 11:1
57% isolated yield, *para : meta* = 39 : 1

2-Methylphenyl sulfate (187 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 °C. After 36 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and washed with hexanes (0.5 mL). The hexane layer was decanted, and the remaining solution subjected to chromatographic separation with silica gel ($CHCl_3$ as eluent) to give 67 mg of *para* borylated 2-methylphenol with traces of the *meta* isomer (*para*:*meta* = 39:1) as a white solid (57% yield, mp 100.0–102.4 °C). The NMR values were consistent with previously reported NMR values.[40]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 1.7 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 5.81 (bs, 1H), 2.24 (s, 3H), 1.35 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 138.0, 134.3, 123.5, 114.6, 83.8, 24.9, 15.6. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.6. HRMS (ESI) m/z calcd for $C_{13}H_{18}BO_3$ $[M–H]^-$ 233.1349, found 233.1367.

***Para* borylation of tetrapropyl ammonium 2-isopropylphenyl sulfate (3.2h)**

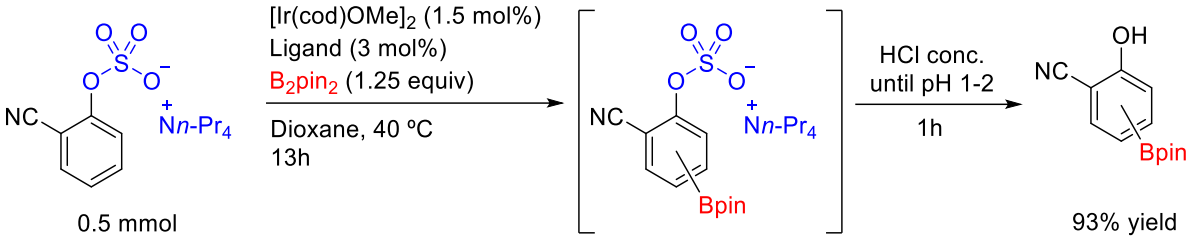


62% conversion, *para : meta* = 25:1
62% isolated yield, *para : meta* = 23 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-isopropylphenyl sulfate (201 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 36 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and subjected directly to chromatographic separation with silica gel (2% EtOAc in $CHCl_3$ as eluent) to give 81 mg of *para* borylated 2-isopropylphenol with traces of the meta isomer (*para*:*meta* = 23:1) as a white solid (62% yield, mp 138.3–145.9 °C). The NMR values were consistent with previously reported NMR values.[41]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.6 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.82 (s, 1H), 3.23 (hept, *J* = 6.9 Hz, 1H), 1.36 (s, 12H), 1.26 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 134.1, 134.0, 133.5, 114.9, 83.8, 27.2, 24.9, 22.6. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.7. HRMS (ESI) m/z calcd for $C_{15}H_{22}BO_3$ $[M–H]^-$ 261.1662, found 261.1696.

***Para* borylation of tetrapropylammonium 2-cyanophenyl sulfate (3.2i)**



>99.9% conversion, *para : meta : dimeta* = 7.5 : 1 : 0.4
93% isolated yield, *para : meta : dimeta* = 7.5 : 1 :0.4

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-cyanophenyl sulfate (193 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 13 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel (4% EtOAc in $CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 117 mg of a mixture of *para* borylated 2-cyanophenol with the *meta* and *dimeta* isomers (*para*:*meta*:*dimeta* = 7.5:1:0.4) as a white solid (93% yield, mp 156.6–162.8 °C). The NMR data were consistent with previously reported NMR values.[42]

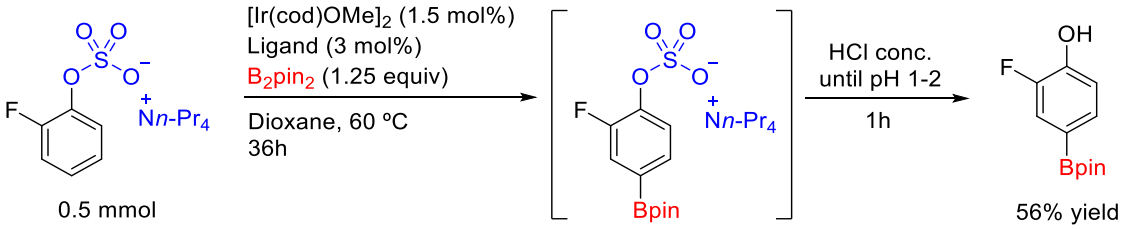
Para:

^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.7 Hz, 1H), 8.15-7.55 (bs, 1H), 7.83 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 141.0, 140.5, 116.6, 116.0, 99.5, 84.4, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.7. HRMS (ESI) m/z calcd for $C_{13}H_{15}BNO_3$ $[M–H]^-$ 244.1145, found 244.0003.

Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15-7.55 (bs, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 0.9 Hz, 1H), 7.34 (dd, *J* = 7.6, 0.9 Hz, 1H), 1.32 (s, 12H). Carbon peaks were indistinguishable due to the small amount of the *meta* isomer in the mixture. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.4. HRMS (ESI) m/z calcd for $C_{13}H_{15}BNO_3$ $[M–H]^-$ 244.1145, found 244.0003.

***Para* borylation of tetrapropyl ammonium 2-fluorophenyl sulfate (3.2j)**



>99.9% conversion, *para : meta : dimeta* = 2.3 : 1 : 0.2
56% isolated yield, *para : meta* = 11 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-fluorophenyl sulfate (189 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 36 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and washed with hexanes (0.5 mL). The hexane layer was decanted, and the remaining solution subjected to chromatographic separation with silica gel (10% EtOAc in $CHCl_3$ as eluent) to give 67 mg of a mixture of *para* and *meta* borylated 2-fluorophenol (*para*:*meta* = 11:1) as a white solid (56% yield, mp 85.0-91.0 °C). The NMR data were consistent with previously reported NMR values, designated as compound **22a** in the cited paper.[43]

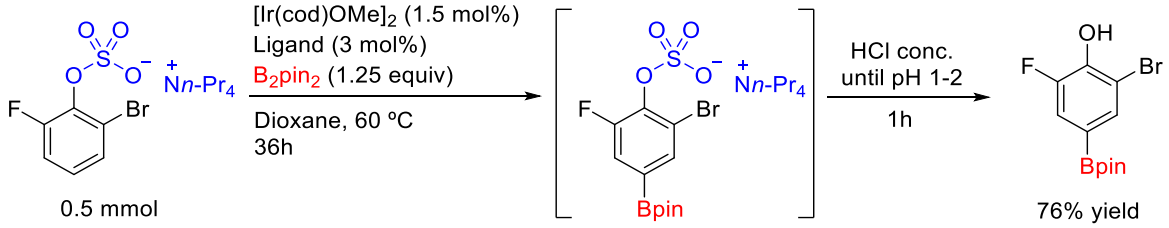
Para:

^{1}H NMR (500 MHz, C_6D_6) δ 7.81 (dd, *J* = 11.1, 1.4 Hz, 1H), 7.71 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.84 (t, *J* = 8.1 Hz, 1H), 1.08 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 151.1 (d, *J* = 239.2 Hz), 146.9 (d, *J* = 13.9 Hz), 132.1 (d, *J* = 3.4 Hz), 121.7 (d, *J* = 15.8 Hz), 117.2 (d, *J* = 1.7 Hz), 83.6, 24.4. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ –139.7 (dd, J = 11.1, 8.1 Hz). HRMS (ESI) m/z calcd for $C_{12}H_{15}BFO_3$ $[M–H]^-$ 237.1098, found 237.1097.

Meta:

^{1}H NMR (500 MHz, C_6D_6) δ 7.49 (ddd, *J* = 7.4, 5.0, 1.7 Hz, 1H), 6.93 (ddd, *J* = 8.7, 8.0, 1.7 Hz, 1H), 6.74 (ddd, *J* = 8.0, 7.4, 0.7 Hz, 1H).^{13}C NMR (126 MHz, C_6D_6) δ 155.6 (d, *J* = 243.3 Hz), 143.8 (d, *J* = 16.1 Hz), 124.4 (d, *J* = 3.9 Hz), 120.6 (d, *J* = 2.8 Hz), 83.7, 24.4 (owing to the small amount of the isomer in the mixture some peaks were not observed). ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ –129.1 (dd, J = 8.7, 5.0 Hz). HRMS (ESI) m/z calcd for $C_{12}H_{15}BFO_3$ $[M–H]^-$ 237.1098, found 237.1097.

***Para* borylation of tetrapropylammonium 2-bromo-6-fluorophenyl sulfate (3.2k)**



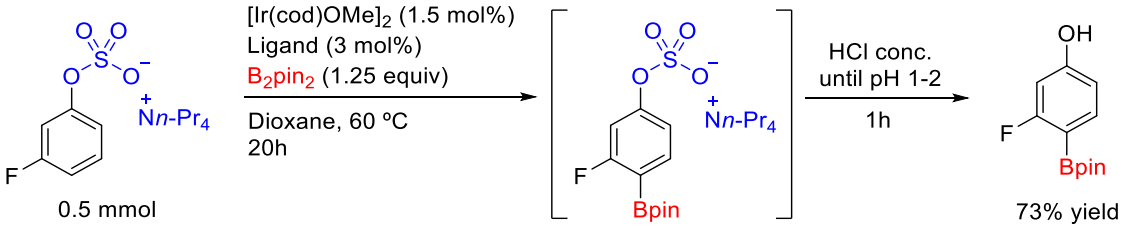
>99.9% conversion, *para : meta* = 8 : 1
76% isolated yield, *para : meta* = 35 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-bromo-6-fluorophenyl sulfate (228 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (128 mg, 0.5 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-

heated to 40 °C. After 12 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 120 mg of a mixture of *para* borylated 2-bromo-6-fluorophenol with traces of the *meta* isomer (*para*:*meta* = 35:1) as a white solid (76% yield, mp 127.6–129.0 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.3 Hz, 1H), 7.44 (dd, *J* = 10.3, 1.3 Hz, 1H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8 (d, *J* = 246.0 Hz), 144.1 (d, *J* = 14.7 Hz), 134.3 (d, *J* = 3.0 Hz), 121.2 (d, *J* = 16.6 Hz), 110.8 (d, *J* = 1.6 Hz), 84.4, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ –134.7 (d, *J* = 10.2 Hz). HRMS (ESI) m/z calcd for $C_{12}H_{14}BBrFO_3$ $[M–H]^-$ 315.0203, found 314.8771.

***Para* borylation of tetrapropyl ammonium 3-fluorophenyl sulfate (3.2l)**



>99.9% conversion, *para : meta* = 2.3 : 1
73% isolated yield, *para : meta* = 3 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 3-fluorophenyl sulfate (189 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 20 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant

mixture was stirred for 1 h. The solution was concentrated and washed with hexanes (0.5 mL). The hexane layer was decanted, and the remaining solution subjected to chromatographic separation with silica gel (12% EtOAc in $CHCl_3$ as eluent) to give 87 mg of a mixture *para* borylated 3-fluorophenol with the *meta* isomer (*para*:*meta* = 3:1) as a white solid (73% yield, mp 89.4-91.2 °C) The NMR values were consistent with previously reported values.[44]

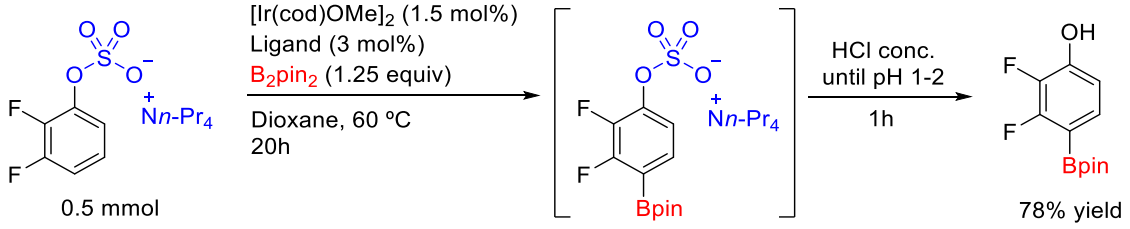
Para:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.2, 7.1 Hz, 1H), 6.76 (bs, 1H), 6.61 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.51 (dd, *J* = 10.9, 2.2 Hz, 1H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6 (d, *J* = 250.4 Hz), 160.8 (d, *J* = 12.3 Hz), 138.0 (d, *J* = 10.2 Hz), 111.6 (d, *J* = 2.6 Hz), 103.1 (d, *J* = 27.3 Hz), 84.1, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.4. ^{19}F NMR (470 MHz, $CDCl_3$) δ –100.6 (dd, *J* = 10.9, 7.1 Hz). HRMS (ESI) m/z calcd for $C_{12}H_{15}BFO_3$ $[M–H]^-$ 237.1098, found 237.1320.

Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (m, 2H), 6.67 (dt, *J* = 9.4, 2.4 Hz, 1H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4 (d, *J* = 246.6 Hz), 156.8 (d, *J* = 10.5 Hz), 117.2 (d, *J* = 2.5 Hz), 113.1 (d, *J* = 19.8 Hz), 106.3 (d, *J* = 24.4 Hz), 84.5, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.4. ^{19}F NMR (470 MHz, $CDCl_3$) δ –112.4 (t, *J* = 9.4 Hz). HRMS (ESI) m/z calcd for $C_{12}H_{15}BFO_3$ $[M–H]^-$ 237.1098, found 237.1320.

Para borylation of tetrapropyl ammonium 2,3-difluorophenyl sulfate (3.2m)

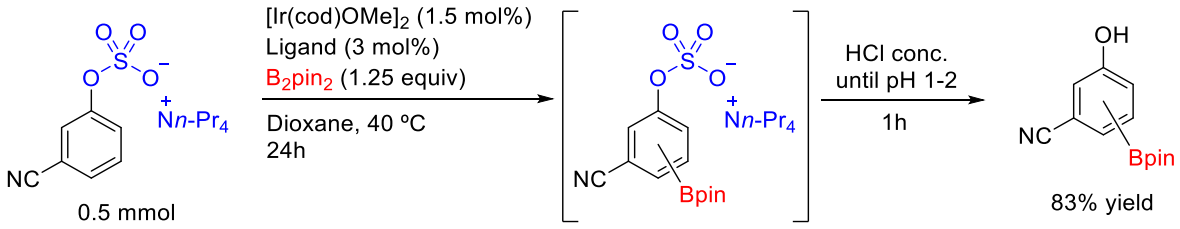


>99.9% conversion, *para : meta* = 23 : 1
78% isolated yield, *para : meta* = 30 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2,3-difluorophenyl sulfate (198 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 20 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and subjected directly to chromatographic separation with silica gel (10% EtOAc in $CHCl_3$ as eluent) to give 100 mg of a mixture of *para* borylated 2,3-difluorophenol with the *meta* isomer (*para:meta* = 30:1) as a white solid (78% yield, mp 125.2–125.9 °C)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (ddd, *J* = 8.3, 6.0, 2.2 Hz, 1H), 6.75 (ddd, *J* = 8.3, 7.1, 1.6 Hz, 1H), 5.95 (bs, 1H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4 (dd, *J* = 251.9, 9.6 Hz), 148.4 (dd, *J* = 11.0, 2.9 Hz), 140.0 (dd, *J* = 240.9, 16.6 Hz), 130.9 (dd, *J* = 9.0, 4.8 Hz), 112.8 (d, *J* = 2.9 Hz), 84.3, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ –127.7 (dd, *J* = 21.3, 6.0 Hz), –164.6 (ddd, *J* = 21.3, 7.1, 2.2 Hz). HRMS (ESI) m/z calcd for $C_{12}H_{14}BF_2O_3$ $[M–H]^-$ 255.1004, found 254.9811.

***Para* borylation of tetrapropylammonium 3-cyanophenyl sulfate (3.2n)**

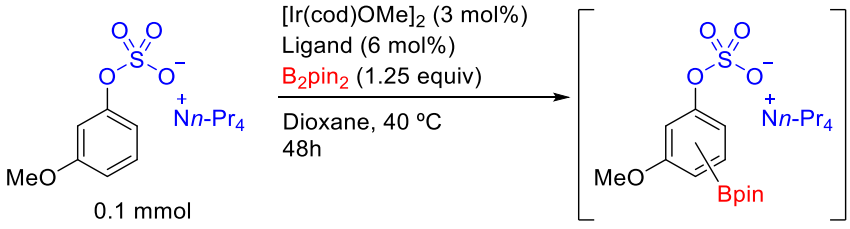


>99.9% conversion, *para : meta* = 1 : 7
83% isolated yield, *para : meta* = 1 : 9.3

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 3-cyanophenyl sulfate (192 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 24 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel (2% EtOAc in $CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with water (0.5 mL). The water layer was decanted and the residue was dried to give 102 mg of a mixture of *para* borylated 3-cyanophenol with the *meta* isomer (*para*:*meta* = 1:9.3) as a white solid (83% yield, mp 131.8–146.0 °C)

^1H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 1H), 7.47 (dd, *J* = 2.7, 1.0 Hz, 1H), 7.20 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.44 (bs, 1H), 1.33 (s, 13H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 130.2, 126.4, 121.1, 118.7, 112.4, 84.6, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.5. HRMS (ESI) m/z calcd for $C_{13}H_{15}BNO_3$ $[M–H]^-$ 244.1145, found 244.1147.

***Para* borylation of tetrapropylammonium 3-methoxyphenyl sulfate (3.2o)**

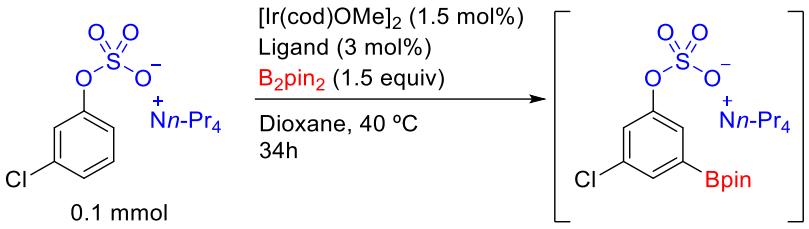


80% conversion, *para : meta* = 1 : 12

In a glove box, a 3.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 3-methoxyphenyl sulfate (39 mg, 0.1 mmol), $[Ir(cod)(OMe)]_2$ (0.3 mL of 0.01 M solution, 3 mol %), 4,4′-dimethoxy-2,2′-bipyridine (0.2 mL of 0.03 M solution, 6.0 mol %) and B_2pin_2 (32 mg,

0.125 mmol). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio.

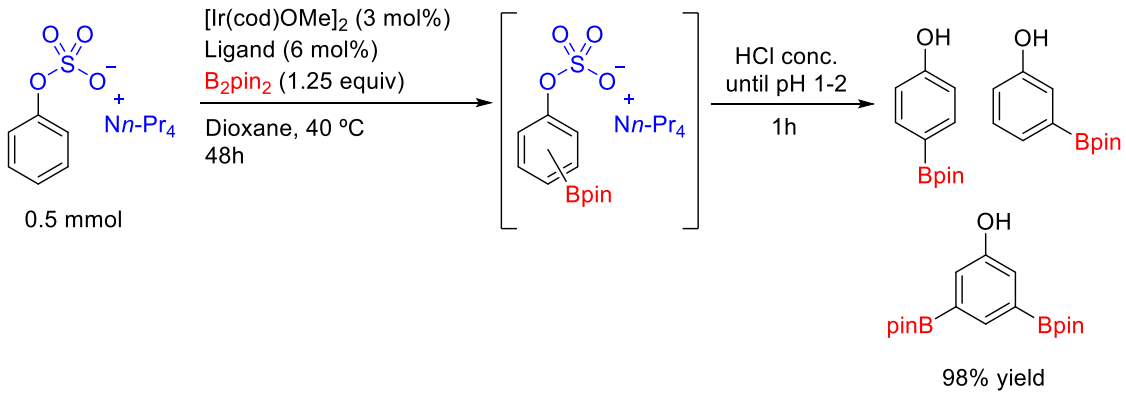
Para borylation of tetrapropyl ammonium 3-chlorophenyl sulfate (3.2p)



87% conversion, *para : meta* < 1 : 20

In a glove box, a 3.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 3-chlorophenyl sulfate (39 mg, 0.1 mmol), [Ir(cod)(OMe)]$_2$ (0.1 mL of 0.015 M solution, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (0.1 mL of 0.03 M solution 3.0 mol %), B_2pin_2 (38 mg, 0.15 mmol) and dioxane (0.2 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 34 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio.

Para borylation of tetrapropylammonium phenyl sulfate (3.2q)



>99.9% conversion, *para : meta : dimeta* = 4.4 : 1 : 1.8
98% isolated yield, *para : meta : dimeta* = 4.5 : 1 : 2.0

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropylammonium phenyl sulfate (180 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol, 1.0 equiv) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ^oC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel (2% EtOAc in $CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with water (0.5 mL). The water layer was decanted and the residue was dried to give 123 mg of a mixture of *para* borylated phenol with the *meta* and *dimeta* isomer (*para*:*meta:dimeta* = 1:0.22:0.44) as a colorless oil (98% yield). The NMR data of the borylated compounds in the mixture were in accordance with the literature reported data.[45]

Para:

^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 5.73 (s, 1H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 136.9, 115.0, 83.8, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.9.

Meta:

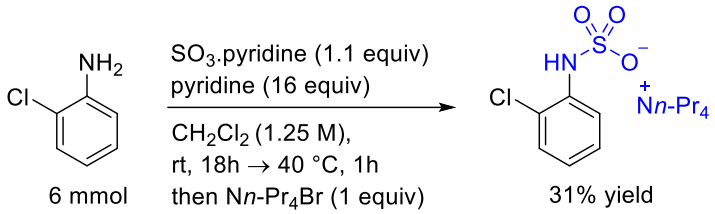
^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (1H), 7.26 (2H), 6.95 (ddd, *J* = 8.1, 2.7, 1.1 Hz, 1H), 5.29 (s, 1H), 1.34 (s, 12H). The peaks at 7.26 and 6.95 are overlap with the *para* isomer and the solvent peak. ^3C NMR (126 MHz, $CDCl_3$) δ 155.2, 129.4, 127.2, 121.2, 118.5, 84.0, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.9.

Dimeta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (t, *J* = 1.0 Hz, 1H), 7.36 (d, *J* = 1.0 Hz, 2H), 5.16 (s, 1H), 1.33 (s, 24H). ^{3}C NMR (126 MHz, $CDCl_3$) δ 154.6, 133.5, 124.1, 83.9, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) 30.9.

3.4.5. Preparation of Sulfated Anilines

Synthesis of tetrapropylammonium 2-chlorophenyl sulfamate (3.3a)

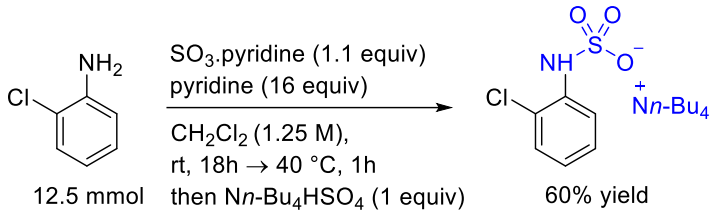


2-Chloroaniline (0.77 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (150 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropylammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the concentrated oil, hexanes, and ether were added and the suspension was again evaporated. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.3a**) was obtained as a light orange solid (0.72 g, 31% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.08 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.99 (ddd, *J* = 8.3, 7.7, 1.5 Hz, 1H), 6.61 (td, *J* = 7.7, 1.6 Hz, 1H), 6.50 (bs, 1H), 3.03 – 2.79 (m, 8H), 1.44 (m, 8H), 0.80 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) 138.8, 128.4, 127.2, 119.9,

119.4, 117.2, 59.8, 15.2, 10.5. HRMS (ESI) m/z calcd for $C_6H_5ClNO_3S$ [M–N*n*-Pr_4]$^-$ 205.9679, found 205.8718

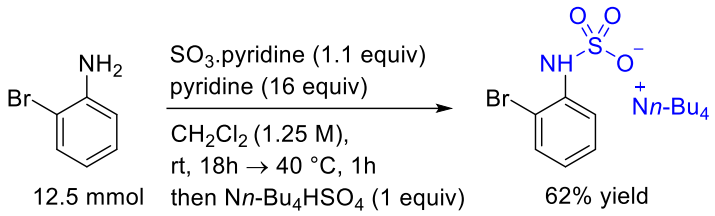
Synthesis of tetrabutylammonium 2-chlorophenyl sulfamate (3.3a´)



2-Chloroaniline (1.63 g, 12.74 mmol) and SO_3•pyridine complex (2.19 g, 13.75 mmol) were placed in a 100 mL round bottom flask. Pyridine (17 mL) and dry dichloromethane (10 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (150 mL) was added and the mixture was washed once with dichloromethane (1 x 150 mL). The aqueous phase was treated with tetrabutylammonium hydrogen sulfate (4.24 g, 12.5 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the concentrated oil, hexanes, and ether were added and the suspension was again evaporated. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.3a′**) was obtained as a tannish white solid (3.821 g, 60% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.8, 1H), 7.11 (t, J – 7.8 Hz, 1H), 6.71 (t, J = 7.8 Hz, 1H), 6.65 (bs, 1H), 3.30 – 2.98 (m, 8H), 1.60 – 1.45 (m, 8H), 1.42 – 1.13 (m, 8H), 0.94 (t, *J* = 7.4 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 128.6, 127.6, 120.1, 119.8, 117.6, 58.6, 24.0, 19.8, 13.8. HRMS (ESI) m/z calcd for $C_6H_5ClNO_3S$ [M–N*n*-Bu_4]$^-$ 205.9679, found 205.9897.

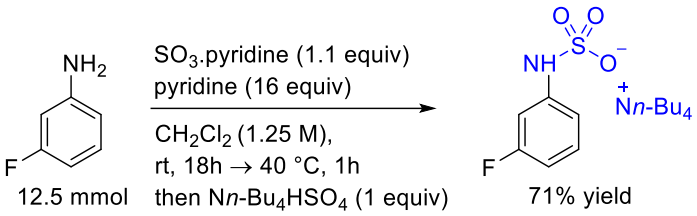
Synthesis of tetrabutylammonium 2-bromophenyl sulfamate (3.3b´)



2-Bromoaniline (2.14 g, 12.5 mmol) and SO_3•pyridine complex (2.19 g, 13.75 mmol) were placed in a 100 mL round bottom flask. Pyridine (17 mL) and dry dichloromethane (10 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (150 mL) was added and the mixture was washed once with dichloromethane (1 x 150 mL). The aqueous phase was treated with tetrabutylammonium hydrogen sulfate (4.24 g, 12.5 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in an oil. To the concentrated oil, hexanes, and ether were added and the suspension was again evaporated. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.3b′**) was obtained as a white solid (3.84 g, 62% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.15 (ddd, *J* = 8.3, 7.3, 1.5 Hz, 1H), 6.67 (bs, 1H), 6.65 (ddd, J = 8.0, 7.3, 1.5 Hz, 1H), 3.22 – 3.15 (m, 8H), 1.62 – 1.52 (m, 8H), 1.37 (m, 8H), 0.95 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.3, 131.9, 128.3, 120.5, 117.7, 110.5, 58.6, 24.0, 19.8, 13.8. HRMS (ESI) m/z calcd for $C_6H_5BrNO_3S$ $[M–N\textit{n}\text{-}Bu_4]^-$ 249.9173, found 249.8044.

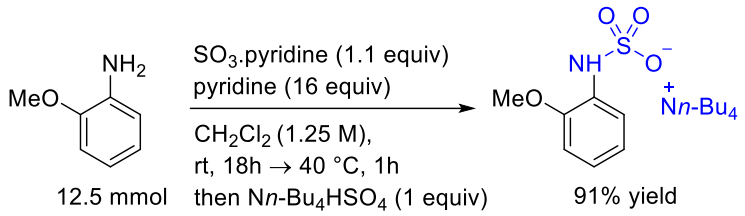
Synthesis of tetrabutylammonium 3-fluorophenyl sulfamate (3.3c´)



3-Fluoroaniline (1.3872 g, 12.5 mmol) and SO_3•pyridine complex (2.19 g, 13.75 mmol) were placed in a 100 mL round bottom flask. Pyridine (17 mL) and dry dichloromethane (10 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (150 mL) was added and the mixture was washed once with dichloromethane (1 x 150 mL). The aqueous phase was treated with tetrabutylammonium hydrogen sulfate (4.25 g, 12.5 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in an oil. To the concentrated oil, hexanes, and ether were added and the suspension was again evaporated. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.3c′**) was obtained as a light orange solid (4.12 g, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 6.88 (m, 3H), 6.78 (dd, *J* = 7.6, 1.9 Hz, 1H), 6.44 (td, *J* = 8.5, 2.5 Hz, 1H), 3.19 – 3.08 (m, 8H), 1.51 (m, 8H), 1.33 (m, 8H), 0.91 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2 (d, *J* = 241.3 Hz), 144.6 (d, *J* = 11.2 Hz), 129.3 (d, *J* = 9.8 Hz), 112.1 (d, *J* = 2.3 Hz), 105.5 (dd, *J* = 21.5, 2.0 Hz), 103.4 (d, *J* = 25.5 Hz), 58.0, 23.5, 19.4, 13.4. ^{19}F NMR (470 MHz, $CDCl_3$) δ –113.4 (ddd, *J* = 11.7, 8.4, 6.7 Hz). HRMS (ESI) m/z calcd for $C_6H_5FNO_3S$ [M–N*n*-Bu_4]$^-$ 189.9974, found 189.9108.

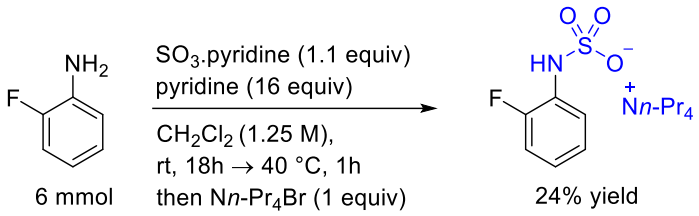
Synthesis of tetrabutylammonium 2-methoxyphenyl sulfamate (3.3d´)



o-Anisidine (1.34 g, 11 mmol) and SO_3•pyridine complex (2.19 g, 13.75 mmol) were placed in a 100 mL round bottom flask. Pyridine (17 mL) and dry dichloromethane (10 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (150 mL) was added and the mixture was washed once with dichloromethane (1 x 150 mL). The aqueous phase was treated with tetrabutylammonium hydrogen sulfate (4.24 g, 12.5 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in an oil. To the concentrated oil, hexanes, and ether were added and the suspension was again evaporated. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.3d′**) was obtained as a pinkish white solid (4.88 g, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.81 (ddd, *J* = 7.8, 6.4, 2.4 Hz, 1H), 6.74 (ddd, *J* = 7.1, 6.4, 1.4 Hz, 1H), 6.72 (dd, *J* = 7.1, 2.4 Hz, 1H), 6.63 (bs, 1H), 3.74 (s, 3H), 3.23 – 3.04 (m, 8H), 1.52 (m, 8H), 1.35 (m, 8H), 0.93 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.0, 132.5, 121.2, 119.4, 116.6, 109.8, 58.5, 55.6, 24.0, 19.7, 13.8. HRMS (ESI) m/z calcd for $C_7H_8NO_4S$ [M–N*n*-Bu_4]$^-$ 202.0174, found 202.0198.

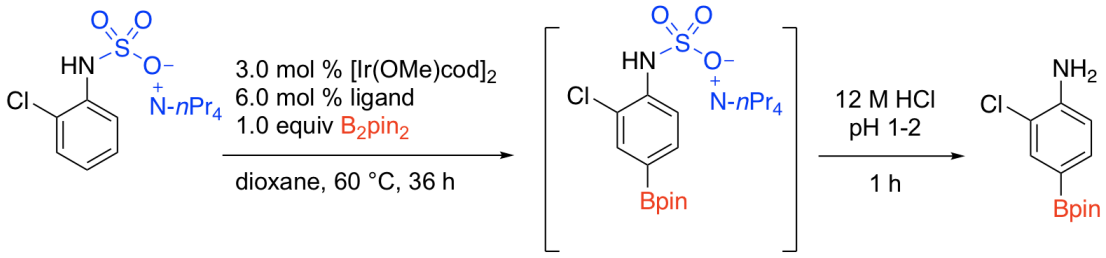
Synthesis of tetrapropylammonium 2-fluorophenyl sulfamate (3.3e)



2-Fluoroaniline (0.67 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in an oil. To the concentrated oil, hexanes and ether were added and the suspension was again evaporated. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.3e**) was obtained as a white solid (0.55 g, 24% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (td, *J* = 8.4, 1.7 Hz, 1H), 6.91 (ddd, *J* = 8.4, 7.7, 1.5 Hz, 1H), 6.86 (ddd, *J* = 11.2, 8.1, 1.5 Hz, 1H), 6.68 (dddd, *J* = 8.1, 7.7, 5.0, 1.7 Hz, 1H), 6.24 (s, 1H), 3.09 – 3.01 (m, 8H), 1.61 – 1.49 (m, 8H), 0.89 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3 (d, *J* = 238.6 Hz), 130.8 (d, *J* = 11.7 Hz), 124.3 (d, *J* = 3.6 Hz), 119.8 (d, *J* = 7.1 Hz), 118.5 (d, *J* = 2.2 Hz), 114.2 (d, *J* = 19.2 Hz), 60.2, 15.5, 10.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ –134.5 (ddd, *J* = 10.9, 8.4, 5.0 Hz). HRMS (ESI) m/z calcd for $C_6H_5FNO_3S$ [M–N*n*-Pr_4]$^-$ 189.9974, found 190.0019.

3.4.6. CHB of Sulfated Anilines

***Para* borylation of tetrapropylammonium 2-chlorophenyl sulfamate (3.4a)**



86% conversion, *para : meta* = 40 : 1
76% isolated yield, *para : meta* > 50 : 1

In a glove box, a 5.0 mL Wheaton microreactor equipped with a stir bar was charged with tetrapropylammonium 2-chlorophenyl sulfamate (196 mg, 0.5 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 3.0 mol %), B_2pin_2 (128 mg, 0.5 mmol, 1 equiv) and dioxane (1.5 mL). The microreactor was capped with a Supelco teflon pressure cap and placed into an aluminum block pre-heated to 60 °C. After 36 h, an aliquot of the reaction was removed and concentrated under vacuum. The residue was dissolved in $CDCl_3$ and a ^1H NMR spectrum showed 86% conversion with a ratio of 40:1 *para* to *meta* borylation. Crude *para* borylated 2-chlorosulfamate:

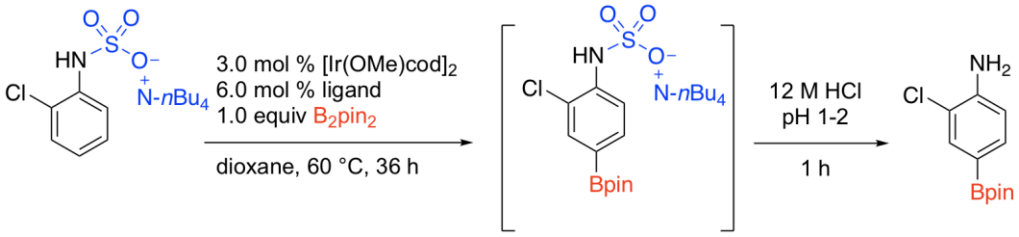
^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 1.4 Hz, 1H), 7.52 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.82 (s, 1H), 3.10 – 3.03 (m, 8H), 1.62 – 1.52 (m, 8H), 1.28 (s, 12H), 0.93 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1, 134.2, 116.4, 83.6, 82.9, 67.0, 60.1, 24.8, 24.5, 15.5, 10.7.

Concentrated HCl was added (2 drops, pH = 1–2) and the resultant mixture was stirred for 1 h. TLC eluting in CH_2Cl_2 showed the appearance of a new spot at r_f = 0.5, whereas the crude borylated sulfamate did not move off the baseline. The solution was concentrated and pumped down under vacuum. The crude material was dissolved in CH_2Cl_2 and applied to a 5 g silica plug

packed in 1:99 hexane/CH_2Cl_2 to yield 96 mg of *para* borylated 2-chloroaniline as a white solid. (76% yield, mp 100–102 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.3 Hz, 1H), 7.49 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 4.24 (s, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) 145.5, 136.0, 134.3, 118.7, 114.9, 83.6, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.5. HRMS (ESI) m/z calcd for $C_{12}H_{18}BClNO_2$ $[M+H]^+$ 254.1119, found 254.1151.

***Para* borylation of tetrabutylammonium 2-chlorophenyl sulfamate (3.4a′)**



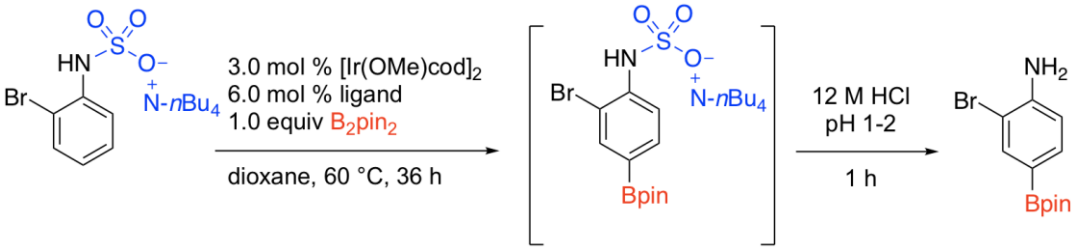
98% conversion, *para : meta* = 43 : 1
95% isolated yield, *para : meta* > 50 : 1

In a glove box, a 5.0 mL Wheaton microreactor equipped with a stir bar was charged with tetrabutylammonium 2-chlorophenyl sulfamate (225 mg, 0.5 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6.0 mol %), B_2pin_2 (128 mg, 0.5 mmol, 1.0 equiv) and dioxane (1.5 mL). The microreactor was capped with a Supelco teflon pressure cap and placed into an aluminum block pre-heated to 60 °C. After 36 h, an aliquot of the reaction was removed and concentrated under vacuum. The residue was dissolved in $CDCl_3$ and a ^{1}H NMR spectrum showed 98% conversion with a ratio of 43:1 *para* to *meta* borylation. Concentrated HCl was added (2 drops, pH = 1–2) and the resultant mixture was stirred for 1 h. TLC eluting in CH_2Cl_2 showed the appearance of a new spot at r_f = 0.5, whereas the crude borylated sulfamate did not move off the baseline. The solution was concentrated and pumped down under vacuum. The crude material was dissolved in CH_2Cl_2 and applied to a 5 g silica plug packed in 1:99 hexane/CH_2Cl_2

to yield 120 mg of *para* borylated 2-chloroaniline as a white solid. (95% yield, mp 100–102 °C). The NMR data were consistent with previously reported values.[33]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.3 Hz, 1H), 7.49 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 4.24 (s, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) 145.5, 136.0, 134.3, 118.8, 114.9, 83.6, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.6. HRMS (ESI) m/z calcd for $C_{12}H_{18}BClNO_2$ $[M+H]^+$ 254.1119, found 254.1310.

***Para* borylation of tetrabutylammonium 2-bromophenyl sulfamate (3.4b′)**



89% conversion, *para : meta* = 66 : 1
72% isolated yield, *para : meta* > 50 : 1

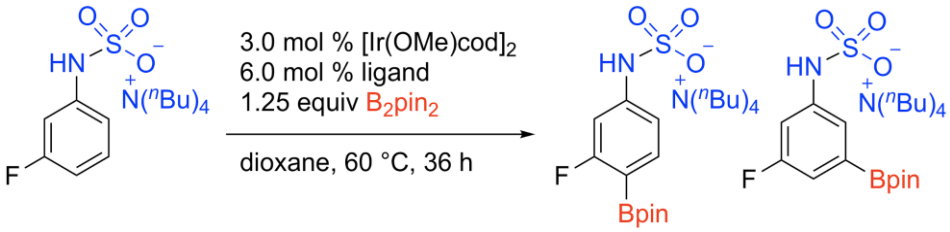
In a glove box, a 5.0 mL Wheaton microreactor equipped with a stir bar was charged with tetrabutylammonium 2-bromophenyl sulfamate (247 mg, 0.5 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol%), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6.0 mol %), B_2pin_2 (128 mg, 0.5 mmol, 1.0 equiv) and dioxane (1.5 mL). The microreactor was capped with a Supelco teflon pressure cap and placed into an aluminum block pre-heated to 60 °C. After 36 h, an aliquot of the reaction was removed and concentrated under vacuum. The residue was dissolved in $CDCl_3$ and a ^{1}H NMR spectrum showed 89% conversion with a ratio of 66:1 *para* to *meta* borylation. *Para* borylated 2-bromosulfamate determined from the crude reaction mixture:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.79 (m, 1H), 7.75 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.57 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.86 (s, 1H), 3.25 – 3.09 (m, 8H), 1.56 (m, 8H), 1.37 (m, 8H), 1.29 (s, 12H), 0.97 – 0.93 (m, 12H).

Concentrated HCl was added (2 drops, pH = 1–2) and the resultant mixture was stirred for 1 h. TLC eluting in CH_2Cl_2 showed the appearance of a new spot at r_f = 0.5, whereas the crude borylated sulfamate did not move off the baseline. The solution was concentrated and pumped down under vacuum. The crude material was dissolved in CH_2Cl_2 and applied to a 5 g silica plug packed in 1:99 hexane/CH_2Cl_2 to yield 128 mg material. ^{1}H NMR showed B_2pin_2 contamination in the isolated product. The mass of B_2pin_2 was calculated from mol fraction based on NMR integrations and subtracted from the mass of the isolated material. The mass of *para* borylated 2-bromoaniline present in the material was 88 mg. (72% yield). The material was washed in cold hexane and dried under vacuum to yield 55 mg of the pure *para* borylated 2-bromoaniline. (37% yield, mp 101–102 °C). NMR data was consistent with previously reported NMR values.[46]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 4.29 (s, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 139.3, 135.0, 114.8, 108.9, 83.6, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.1. HRMS (ESI) m/z calcd for $C_{12}H_{18}BBrNO_2$ $[M+H]^+$ 298.0614, found 298.0787.

***Para* borylation of tetrabutylammonium 3-fluorophenyl sulfamate (3.4c′)**



96% conversion, *para : meta* = 2.8 : 1

In a glove box, a 5.0 mL Wheaton microreactor equipped with a stir bar was charged with tetrabutylammonium 3-fluorophenyl sulfamate (216 mg, 0.5 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6 mol %), B_2pin_2 (159 mg, 0.625 mmol, 1.25 equiv) and dioxane (1.5 mL). The microreactor was capped with a Supelco teflon pressure

cap and placed into an aluminum block pre-heated to 60 ºC. After 36 h, an aliquot of the reaction was removed and diluted with $CDCl_3$ and a ^{19}F NMR spectrum showed 96% conversion with a ratio of 2.8:1 *para* to *meta* borylation. Characterization data was determined from the crude mixture of borylated material and borate byproducts.

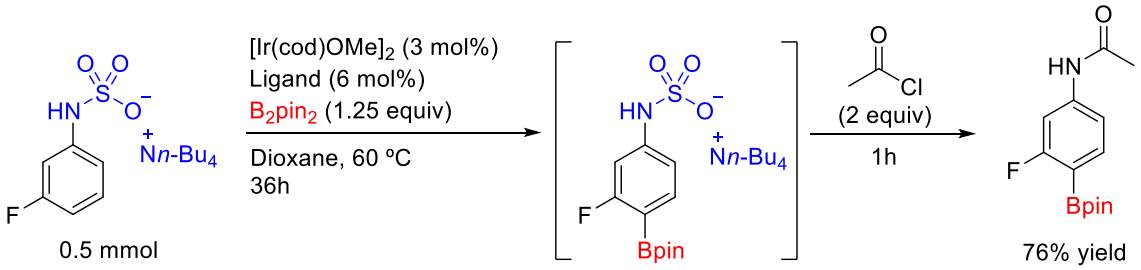
Para borylated 3-fluorophenyl sulfamate:

^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 8.1, 7.1 Hz, 1H), 6.93 (dd, *J* = 12.1, 1.9 Hz, 1H), 6.73 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.91 (s, 1H), 3.16 – 3.07 (m, 8H), 1.48 (m, 8H), 1.33 – 1.28 (m, 8H), 1.27 (s, 12H), 0.88 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5 (d, *J* = 247.9 Hz), 147.7 (d, *J* = 12.1 Hz), 137.1 (d, *J* = 10.2 Hz), 111.9 (d, *J* = 2.1 Hz), 102.9 (d, *J* = 28.8 Hz), 83.8, 58.6, 50.7, 24.8, 24.0, 19.6, 13.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ –105.54.

Meta borylated 3-fluorophenyl sulfamate:

^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (dt, *J* = 11.6, 2.4 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H), 6.85 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.75 (s, 1H), 3.17 – 3.06 (m, 8H), 1.48 (m, 8H), 1.30 (m, 8H), 1.25 (s, 12H), 0.88 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2 (d, *J* = 242.9 Hz), 144.0 (d, *J* = 10.2 Hz), 129.6 (d, *J* = 9.9 Hz), 112.2 (d, *J* = 20.0 Hz), 107.2 (d, *J* = 26.0 Hz), 83.7, 58.6, 24.8, 23.9, 19.6, 13.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ –117.5. HRMS (ESI) m/z calcd for $C_{12}H_{16}BFNO_5S$ $[M–N\textit{n}\text{-}Bu_4]^-$ 316.0826, found 316.1525.

Borylation of tetrabutylammonium 3-fluorophenyl sulfamate - Acylation work-up (3.4c′)



96% conversion, *para : meta* = 2.4 : 1
76% isolated yield, *para : meta* = 2.1 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrabutyl ammonium 3-fluorophenyl sulfamate (216 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ^oC. After 36 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *para*:*meta* ratio. Acetyl chloride (0.08 mL, 1 mmol) was added and the resultant mixture was stirred for 4 h. The solution was concentrated and passed through a plug of silica gel (2% EtOAc in $CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with water (2 mL). The water layer was decanted and the residue was dried to give 106 mg of a mixture of *para* borylated N-(3-fluorophenyl)acetamide with the *meta* isomer (*para*:*meta* = 2.1:1) as a white solid (76% yield, mp 147.1–146.7 °C) NMR data was consistent with previously reported NMR values.[47]

Para:

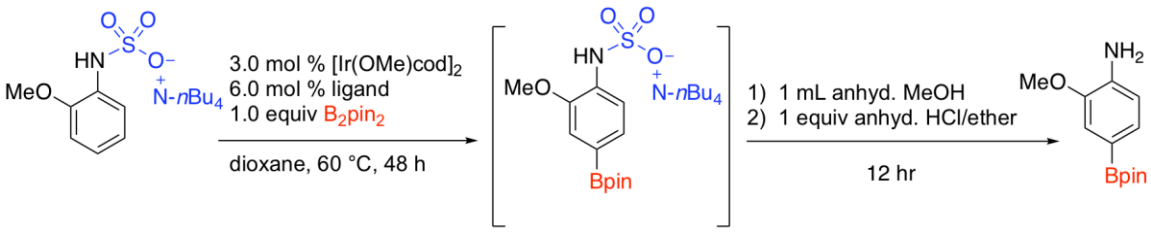
^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (bs, 1H), 7.65 (dd, *J* = 8.1, 6.8 Hz, 1H), 7.47 (dd, *J* = 11.4, 1.9 Hz, 1H), 7.14 (dd, *J* = 8.1, 1.9 Hz, 1H), 2.17 (s, 3H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 167.8 (d, *J* = 250.0 Hz), 142.6 (d, *J* = 11.7 Hz), 137.4 (d, *J* = 9.7 Hz), 114.3, 106.5 (d, *J* = 29.6 Hz), 83.9, 24.8, 24.7. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.0. ^{19}F NMR (470 MHz, $CDCl_3$) δ –100.6 (dd, *J* = 11.4, 6.8 Hz).

Meta:

^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 11.1, 2.3 Hz, 1H), 7.62 (bs, 1H), 7.35 (dd, *J* = 2.3, 0.8 Hz, 1H), 7.20 (dd, *J* = 8.3, 2.3 Hz, 1H), 2.16 (s, 3H), 1.31 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 162.8 (d, *J* = 246.0 Hz), 139.1 (d, *J* = 10.2 Hz), 121.1 (d, *J* = 2.8 Hz), 116.6 (d, *J* = 19.7 Hz), 110.4 (d, *J* = 26.9 Hz), 84.3, 24.8, 24.7. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.0. ^{19}F NMR (470

MHz, $CDCl_3$) δ –112.1 (dd, *J* = 11.1, 8.3 Hz). HRMS (ESI) m/z calcd for $C_{14}H_{18}BFNO_3$ $[M–H]^-$ 278.1364, found 278.1364.

***Para* borylation of tetrabutylammonium 2-methoxyphenyl sulfamate (3.4d′)**



75% conversion, *para : meta* = 20: 1
59% isolated yield, *para : meta* > 20 : 1

In a glove box, a 5.0 mL Wheaton microreactor equipped with a stir bar was charged with tetrabutylammonium 2-methoxyphenyl sulfamate (222 mg, 0.5 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6 mol %), B_2pin_2 (128 mg, 0.5 mmol, 1.0 equiv) and dioxane (1.5 mL). The microreactor was capped with a Supelco teflon pressure cap and placed into an aluminum block pre-heated to 60 °C. After 48 h, an aliquot of the reaction was removed and concentrated under vacuum. The residue was dissolved in $CDCl_3$ and a ^1H NMR spectrum showed 75% conversion with a ratio of 20:1 *para* to *meta* borylation.

Para borylated 2-methoxyphenyl sulfamate determined from the crude material:

^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.08 (s, 1H), 6.76 (s, 1H), 3.75 (s, 3H), 3.07 – 3.00 (m, 8H), 1.42 (p, *J* = 7.8 Hz, 8H), 1.31 – 1.23 (m, 8H), 1.26 (s, 12H), 0.87 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 135.3, 128.8, 115.3, 115.2, 83.3, 24.8, 24.5, 23.8, 19.5, 13.7. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.9.

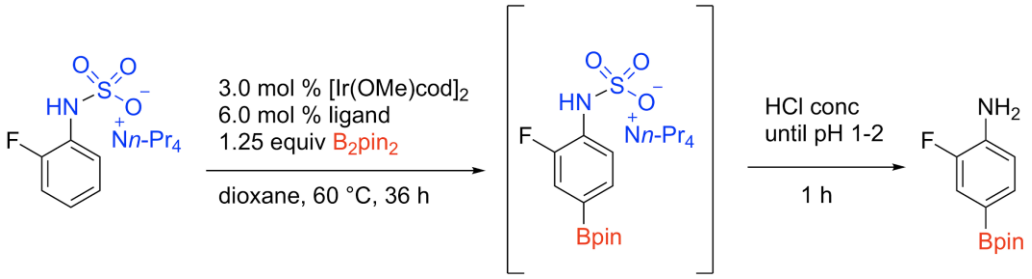
Anhydrous methanol (1 mL) was added to the reaction with stirring. 1M HCl in ether (0.5 mmol, 0.5 mL, 1 equiv) was added dropwise by syringe, until the pH was 7. The mixture was stirred 12 hours, then concentrated to a brown oil. The crude material was dissolved in CH_2Cl_2 and

applied to a 7 g silica plug eluting in CH_2Cl_2. After 100 mL CH_2Cl_2 was eluted, the eluent was changed to 1:1:98 ethyl acetate:triethylamine:CH_2Cl_2. Fractions were combined and concentrated to 68 mg of a pale pink solid, 59% yield, m.p 116–117 °C.

Para borylated 2-methoxyaniline:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.20 (d, *J* = 1.3 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 4.00 (s, 2H), 3.89 (s, 3H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4, 139.5, 128.8, 115.8, 114.0, 83.3, 55.5, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.9. HRMS (ESI) m/z calcd for $C_{13}H_{21}BNO3$ $[M+H]^+$ 250.1614, found 250.1677.

Para borylation of tetrapropylammonium 2-fluorophenyl sulfamate (3.4e)



94% conversion, *para : meta* = 2 : 1
53% isolated yield, *para : meta* = 10 : 1

In a glove box, a 5.0 mL Wheaton microreactor equipped with a stir bar was charged with tetrapropylammonium 2-fluorophenyl sulfamate (188 mg, 0.5 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6 mol %), B_2pin_2 (159 mg, 0.625 mmol, 1.25 equiv) and dioxane (1.5 mL). The microreactor was capped with a Supelco teflon pressure cap and placed into an aluminum block pre-heated to 60 °C. After 36 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent) to give 62 mg

of a mixture of *para* borylated 2-fluoroaniline with the *meta* isomer (*para*:*meta* = 10:1) as a white solid (53% yield, mp 90.6–96.2 °C).

Para:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 2H), 6.77 – 6.69 (m, 1H), 3.94 (br s, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1 (d, *J* = 239.2 Hz), 137.6 (d, *J* = 12.5 Hz), 131.5 (d, *J* = 3.2 Hz), 121.0 (d, *J* = 16.2 Hz), 115.9 (d, *J* = 3.0 Hz), 83.6, 24.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ –137.2 (dd, *J* = 11.7, 8.7 Hz). ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.3

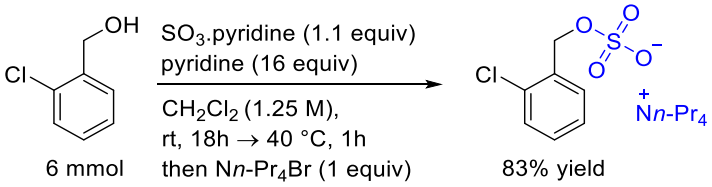
Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (ddd, *J* = 7.6, 5.1, 1.8 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.87 (ddd, *J* = 9.4, 7.6, 1.8 Hz, 1H), 3.78 (br s, 2H), 1.36 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7 (d, *J* = 243.6 Hz), 134.3 (d, *J* = 14.8 Hz), 125.2 (d, *J* = 7.1 Hz), 124.0 (d, *J* = 3.6 Hz), 120.0 (d, *J* = 4.3 Hz), 83.8, 24.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ –125.5 (dt, *J* = 9.4, 5.1 Hz). ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.3.

HRMS (ESI) m/z calcd for $C_{12}H_{18}BFNO_2$ $[M+H]^+$ 238.1415, found 238.1488.

3.4.7. Preparation of Sulfated Benzyl Alcohols

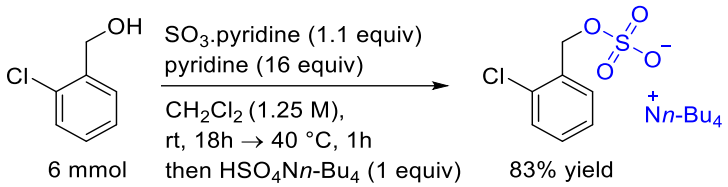
Synthesis of tetrapropylammonium 2-chlorobenzyl sulfate (3.5a)



2-Chlorobenzyl alcohol (0.86 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1

x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Diethyl ether and hexanes were added to evaporate the solvent to dryness and the product was obtained as a white solid (2.02 g, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.5, 1.8Hz, 1H), 7.26 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.19 (td, *J* = 7.5, 1.5 Hz, 1H), 7.15 (td, *J* = 7.5, 1.8 Hz, 1H), 5.14 (s, 2H), 3.26 – 2.93 (m, 8H), 1.74 – 1.46 (m, 8H), 0.96 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.4, 132.0, 128.9, 128.6, 128.3, 126.4, 65.4, 60.0, 15.3, 10.5. HRMS (ESI) m/z calcd for $C_7H_6ClO_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 220.9675, found 220.9680.

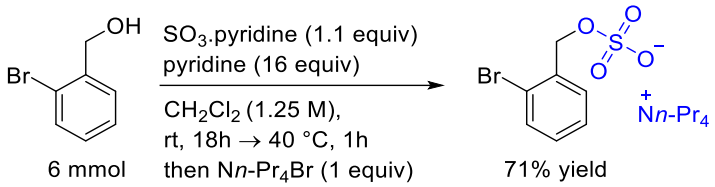
Synthesis of tetrabutylammonium 2-chlorobenzyl sulfate (3.5a´)



2-Chlorobenzyl alcohol (0.86 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrabutyl ammonium hydrogen sulfate (2.13 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Diethyl ether and hexanes were added to evaporate the solvent to dryness and the product was obtained as a white solid (2.28 g, 83% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.5, 1.8Hz, 1H), 7.26 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.19 (td, *J* = 7.5, 1.5 Hz, 1H), 7.15 (td, *J* = 7.5, 1.8 Hz, 1H), 5.13 (s, 2H), 3.34 – 3.04 (m, 8H), 1.56 (dq, *J* = 11.9, 8.0, 7.5 Hz, 8H), 1.35 (h, *J* = 7.4 Hz, 8H), 0.92 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 131.9, 128.8, 128.6, 128.2, 126.4, 65.4, 58.1, 23.6, 19.4, 13.4. HRMS (ESI) m/z calcd for $C_7H_6ClO_4S$ $[M–N\textit{n}\text{-}Bu_4]^-$ 220.9675, found 220.9689.

Synthesis of tetrapropylammonium 2-bromobenzyl sulfate (3.5b)

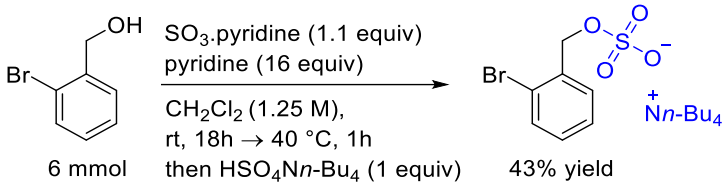


2-Bromobenzyl alcohol (1.12 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated, resulting in an oil. To the concentrated oil, hexanes and ether were added and the suspension was again evaporated. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.5b**) was obtained as a white solid (1.93 g, 71% yield)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.42 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.21 (td, *J* = 7.7, 1.2 Hz, 1H), 7.05 (td, *J* = 7.7, 1.7 Hz, 1H), 5.04 (s, 2H), 3.14 – 3.07 (m, 8H), 1.68 – 1.50 (m, 8H), 0.90 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.2, 132.0, 129.2, 128.7,

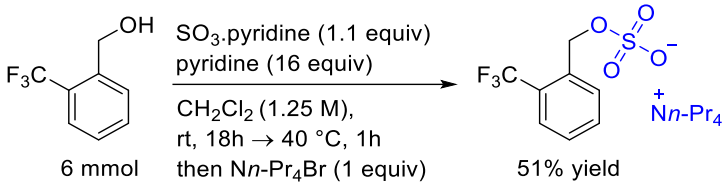
127.2, 121.9, 67.9, 60.2, 15.5, 10.8. HRMS (ESI) m/z calcd for $C_7H_6BrO_4S$ [M–N*n*-Pr_4]$^-$ 264.91702, found 264.7968.

Synthesis of tetrabutylammonium 2-bromobenzyl sulfate (3.5b′)



2-Bromobenzyl alcohol (1.12 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrabutyl ammonium hydrogen sulfate (2.13 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the concentrated oil, hexanes and ether were added and the suspension was again evaporated. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.5b'**) was obtained as a white solid (1.321 g, 43% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.14 (ddd, *J* = 7.8, 7.4, 1.2 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.4, 1.8 Hz, 1H), 4.97 (s, 2H), 3.24 – 2.98 (m, 8H), 1.60 – 1.37 (m, 8H), 0.83 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.0, 131.8, 128.9, 128.5, 127.0, 121.6, 67.6, 59.9, 15.2, 10.5. HRMS (ESI) m/z calcd for $C_7H_6BrO_4S$ [M–N*n*-Bu_4]$^-$ 264.9170, found 264.9280.

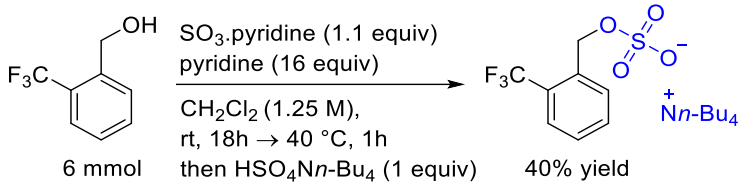
Synthesis of tetrapropylammonium 2-trifluoromethylbenzyl sulfate (3.5c)



2-Trifluoromethylbenzyl alcohol (1.06 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the concentrated oil, hexanes and ether were added and the suspension was again evaporate. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.5c**) was obtained as a white solid (1.34 g, 51% yield).

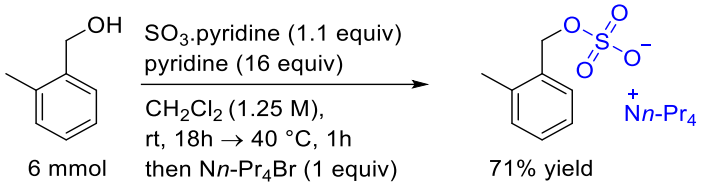
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 5.18 (s, 2H), 3.28–2.91 (m, 8H), 1.69–1.42 (m, 8H), 0.90 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5, 131.8, 129.1, 127.1, 126.8 (q, *J* = 31 Hz), 125.2 (q, *J* = 5.67 Hz), 124.3 (q, *J* = 275 Hz), 64.5 (q, *J* = 3.3 Hz), 60.2, 15.46, 10.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ -59.91. HRMS (ESI) m/z calcd for $C_8H_6F_3O_4S$ [M–N*n*-Pr_4]$^-$ 254.9939, found 254.8768.

Synthesis of tetrabutylammonium 2-trifluoromethylbenzyl sulfate (3.5c')



2-Trifluoromethylbenzyl alcohol (1.06 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrabutylammonium hydrogensulfate (2.04 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the concentrated oil, hexanes and ether were added and the suspension was again evaporate. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.5c'**) was obtained as a white solid (1.20 g, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.47 (td, *J* = 7.7, 1.2 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 5.22 (s, 2H), 3.36 – 3.09 (m, 8H), 1.61–1.50 (m, 8H), 1.39–1.29 (m, 8H), 0.91 (t, *J* = 7.4 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7 (q, *J* = 1.9 Hz), 131.7, 129.1, 126.9, 126.7 (q, *J* = 30.6 Hz), 125.1 (q, *J* = 5.8 Hz), 124.3 (q, *J* = 273.7 Hz), 64.5 (q, *J* = 3.1 Hz), 58.5, 23.8, 19.6, 13.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ -59.94. HRMS (ESI) m/z calcd for $C_8H_6F_3O_4S$ $[M–N\textit{n}\text{-}Bu_4]^-$ 254.9939, found 255.0028.

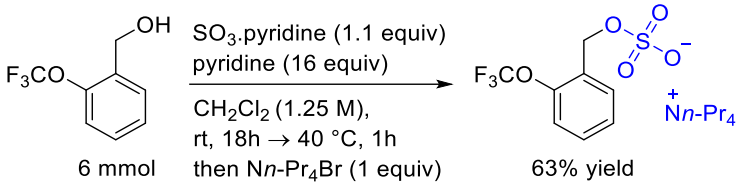
Synthesis of tetrapropylammonium 2-methylbenzyl sulfate (3.5d)



o-Tolylmethanol (0.73 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the concentrated oil, hexanes and ether were added and the suspension was again evaporate. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.5d**) was obtained as a white solid (1.41 g, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.13 – 7.01 (m, 3H), 4.96 (s, 2H), 3.11 – 2.84 (m, 8H), 2.29 (s, 3H), 1.60–1.44 (m, 8H), 0.88 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.9, 135.5, 129.9, 128.8, 127.7, 125.5, 67.0, 60.1, 18.8, 15.4, 10.7. HRMS (ESI) m/z calcd for $C_8H_9O_4S$ $[M–Nn\text{-}Pr_4]^-$ 201.0222, found 201.0271.

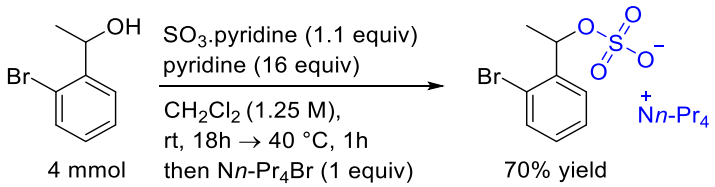
Synthesis of tetrapropylammonium 2-(trifluoromethoxy)benzyl sulfate (3.5e)



(2-(Trifluoromethoxy)phenyl)methanol (1.15 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was heated to 40 ºC for 1 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the concentrated oil, hexanes and ether were added and the suspension was again evaporate. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.5e**) was obtained as a white solid (1.72 g, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.13 (dp, *J* = 7.5, 1.7 Hz, 1H), 5.09 (s, 2H), 3.20 – 2.95 (m, 8H), 1.70 – 1.43 (m, 8H), 0.91 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2 (q, *J* = 1.9 Hz), 130.8, 129.7, 128.4, 126.7, 120.5 (q, *J* = 257.3 Hz), 120.0, 62.7, 60.3, 15.5, 10.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.02. HRMS (ESI) m/z calcd for $C_8H_6F_3O_5S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 270.9888, found 270.9895.

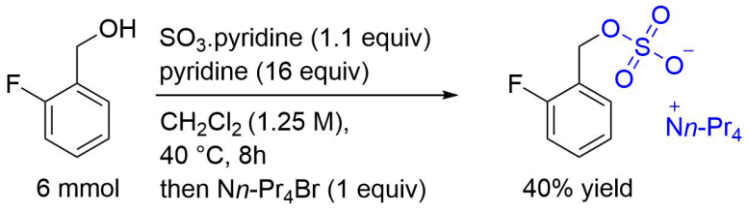
Synthesis of tetrapropylammonium 1-(2-bromophenyl)ethyl sulfate (3.5f)



1-(2-Bromophenyl)ethan-1-ol (0.80 g, 4 mmol) and SO_3•pyridine complex (0.70 g, 4.4 mmol) were placed in a 100 mL round bottom flask. Pyridine (5.3 mL) and dry dichloromethane (3.3 mL) were added and the mixture was stirred at rt for 18 h. After this time, the reaction was

heated to 40 ºC for 1 h. Water (50 mL) was added and the mixture was washed once with dichloromethane (1 x 50 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.06 g, 4 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the concentrated oil, hexanes and ether were added and the suspension was again evaporate. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.5f**) was obtained as a white solid (1.30 g, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.41 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.24 (td, *J* = 7.7, 1.2 Hz, 1H), 7.03 (td, *J* = 7.7, 1.7 Hz, 1H), 5.71 (q, *J* = 6.4 Hz, 1H), 3.17 – 2.88 (m, 8H), 1.66 – 1.54 (m, 8H), 1.51 (d, *J* = 6.4 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 13H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 132.1, 128.1, 127.9, 127.4, 120.8, 74.2, 60.2, 23.2, 15.5, 10.8. HRMS (ESI) m/z calcd for $C_8H_8BrO_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 278.9327, found 278.9380.

Synthesis of tetrapropylammonium 2-fluorobenzyl sulfate (3.5g)

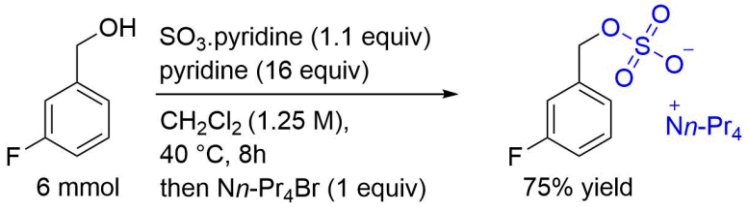


(2-Fluorophenyl)methanol (0.76, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at 40 ºC for 8 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the concentrated oil, hexanes and ether were added and the suspension was again

evaporate. This hexane/ether process was repeated until following the evaporation of solvent the product was obtained as a white solid. After overnight drying under high vacuum (**3.5g**) was obtained as a white solid (0.94 g, 40% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (td, *J* = 7.5, 1.8 Hz, 0H), 7.18 (tdd, *J* = 7.6, 5.2, 1.8 Hz, 0H), 7.02 (td, *J* = 7.5, 1.2 Hz, 0H), 6.92 (ddd, *J* = 9.7, 8.2, 1.2 Hz, 0H), 5.03 (d, *J* = 1.4 Hz, 0H), 3.58 – 2.62 (m, 1H), 1.89 – 1.24 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 160.41 (d, *J* = 246.9 Hz), 130.52 (d, *J* = 4.0 Hz), 129.21 (d, *J* = 7.9 Hz), 124.83 (d, *J* = 14.4 Hz), 123.88 (d, *J* = 3.7 Hz), 114.81 (d, *J* = 21.4 Hz), 62.26 (d, *J* = 4.4 Hz), 60.18 (d, *J* = 2.3 Hz), 15.45, 10.67.^{19}F NMR (470 MHz, $CDCl_3$) δ –122.02 (d, *J* = 8.4 Hz), –164.90. HRMS (ESI) m/z calcd for $C_7H_6FO_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 204.9971, found 205.0033.

Synthesis of tetrapropylammonium 3-fluorobenzyl sulfate (3.5h)



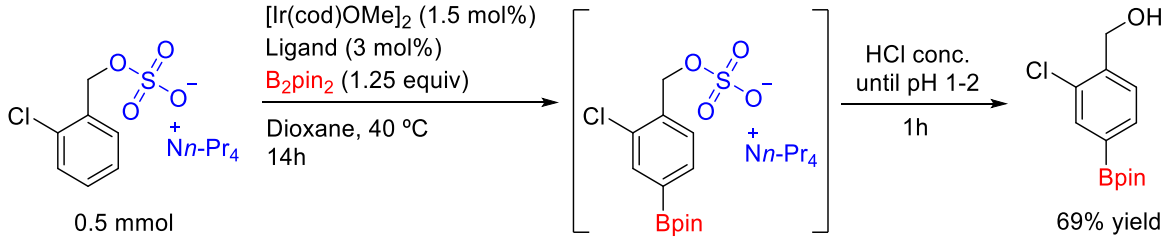
(3-Fluorophenyl)methanol (0.76 g, 6 mmol) and SO_3•pyridine complex (1.05 g, 6.6 mmol) were placed in a 100 mL round bottom flask. Pyridine (8 mL) and dry dichloromethane (5 mL) were added and the mixture was stirred at 40 ºC for 8 h. Water (70 mL) was added and the mixture was washed once with dichloromethane (1 x 70 mL). The aqueous phase was treated with tetrapropyl ammonium bromide (1.60 g, 6 mmol) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 70 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the concentrated oil, hexanes and ether were added and the suspension was again evaporate. This hexane/ether process was repeated until following the evaporation of solvent the

product was obtained as a white solid. After overnight drying under high vacuum (**3.5h**) was obtained as a white solid (1.75 g, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (td, *J* = 8.1, 6.0 Hz, 1H), 7.14 – 6.94 (m, 2H), 6.94 – 6.76 (m, 1H), 4.92 (s, 1H), 3.58 – 2.54 (m, 7H), 1.93 – 1.25 (m, 8H), 0.87 (t, *J* = 7.3 Hz, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.62 (d, *J* = 244.9 Hz), 140.46 (d, *J* = 7.5 Hz), 129.62 (d, *J* = 8.1 Hz), 123.18 (d, *J* = 2.8 Hz), 114.53 (dd, *J* = 21.8, 1.5 Hz), 114.15 (d, *J* = 21.2 Hz), 67.84 (d, *J* = 1.9 Hz), 60.20, 15.43, 10.66. ^{19}F NMR (470 MHz, $CDCl_3$) δ –116.13 – –118.06 (m), –164.90. HRMS (ESI) m/z calcd for $C_7H_6FO_4S$ $[M–N\textit{n}\text{-}Pr_4]^-$ 204.9971, found 205.0026.

3.4.8. CHB of Sulfated Benzyl Alcohols

***Para* borylation of tetrapropyl ammonium 2-chlorobenzyl sulfate (3.6a)**



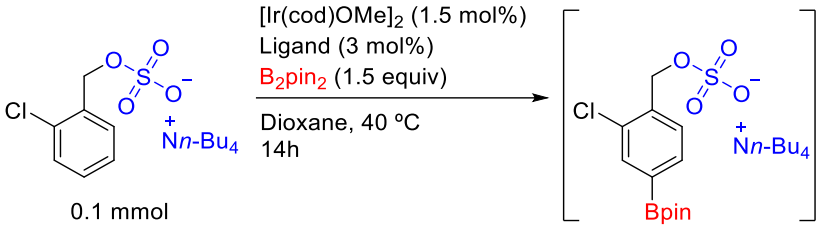
>99.9% conversion, *para : meta* = 18 : 1
69% yield, *para : meta* > 20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-chlorobenzyl sulfate (204 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 12 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and washed with hexanes (0.5 mL). The hexane layer was decanted, and the remaining solution subjected to chromatographic separation

with silica gel (6% EtOAc in $CHCl_3$ as eluent) to give 93 mg of *para*-borylated 2-chlorobenzyl alcohol as an oil (69% yield)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 4.76 (s, 2H), 2.36 (s, 1H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 135.3, 133.2, 132.2, 127.8, 84.2, 62.7, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) 30.6. HRMS (APCI+) m/z calcd for $C_{13}H_{17}BClO_2$ [M–OH^-] 251.1010, found 251.1057.

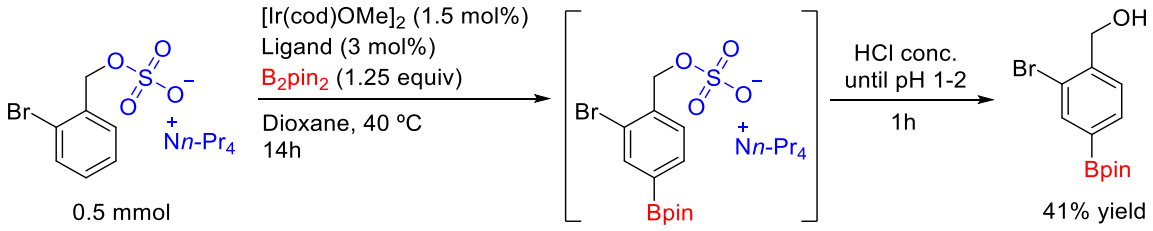
***Para* borylation of tetrabutyl ammonium 2-chlorobenzyl sulfate (3.6a′)**



>99.9% conversion, *para : meta* = 15 : 1

In a glove box, a 3.0 mL Wheaton microreactor was charged with tetrabutyl ammonium 2-chlorobenzyl sulfate (46 mg, 0.1 mmol), $[Ir(cod)(OMe)]_2$ (0.1 mL of 0.015 M solution, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (0.1 mL of 0.03 M solution 3.0 mol %), B_2pin_2 (38 mg, 0.15 mmol) and dioxane (0.2 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 14 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio.

***Para* borylation of tetrapropyl ammonium 2-bromobenzyl sulfate (3.6b)**

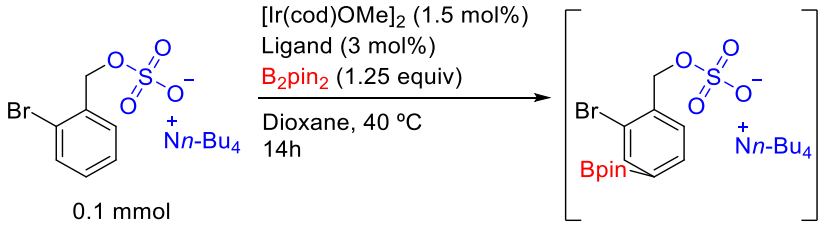


82% conversion, *para : meta* = 30 : 1
41% yield, *para : meta* = 35 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-bromo benzyl sulfate (226 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 12 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and subjected directly to chromatographic separation with silica gel (10% EtOAc in $CHCl_3$ as eluent) to give 64 mg of *para* borylated 2-bromobenzyl alcohol with traces of the *meta* (*para:meta* = 35:1) isomer as an oil (41% yield)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.1 Hz, 1H), 7.73 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 4.74 (s, 2H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 138.5, 133.9, 127.9, 122.2, 84.2, 65.0, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) 30.3. HRMS (APCI+) m/z calcd for $C_{13}H_{17}BBrO_2$ [M–OH–] 295.0505, found 295.0595.

***Para* borylation of tetrabutyl ammonium 2-bromobenzyl sulfate (3.6b′)**

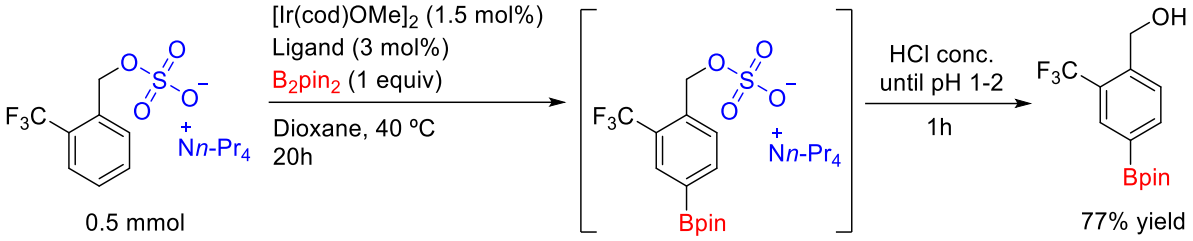


>99.9% conversion, *para : meta* = 23 : 1

In a glove box, a 3.0 mL Wheaton microreactor was charged with tetrabutyl ammonium 2-bromobenzyl sulfate (51 mg, 0.1 mmol), $[Ir(cod)(OMe)]_2$ (0.1 mL of 0.015 M solution, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (0.1 mL of 0.03 M solution 3.0 mol %), B_2pin_2 (32 mg, 0.125 mmol) and dioxane (0.2 mL). The microreactor was capped with a teflon pressure cap and placed

into an aluminum block pre-heated to 40 °C. After 14 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio.

***Para* borylation of tetrapropyl ammonium 2-trifluoromethylbenzyl sulfate (3.6c)**

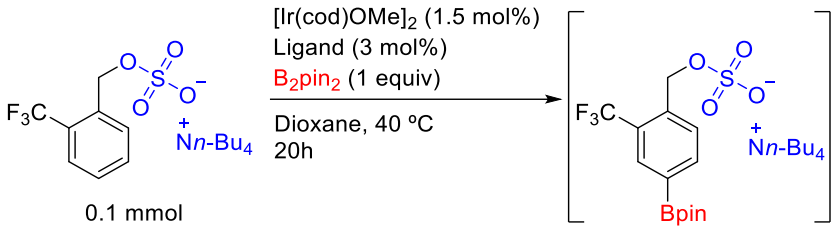


>99.9% conversion, *para : meta* = 9 : 1
77% yield, *para : meta* = 9 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-trifluoromethyl benzyl sulfate (221 mg, 0.5 mmol), [Ir(cod)(OMe)]$_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (128 mg, 0.5 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 20 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel (4% EtOAc in $CHCl_3$ as eluent) to give 117 mg of a mixture of *para* borylated 2-trifluorobenzyl alcohol with the *meta* isomer (*para*:*meta* = 9:1) as an oil (77% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 4.84 (s, 2H), 2.80 (bs, 1H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3 (q, *J* = 1.6 Hz), 138.4 (q, *J* = 1.4 Hz), 131.8 (q, *J* = 5.6 Hz), 127.5, 126.3 (q, *J* = 30.7 Hz), 124.5 (q, J = 275.0 Hz), 84.3, 61.1 (q, *J* = 5.5 Hz), 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) 30.8. ^{19}F NMR (470 MHz, $CDCl_3$) -63.2. HRMS (APCI+) m/z calcd for $C_{14}H_{17}BF_3O_2$ [M–OH–] 285.1274, found 285.1302.

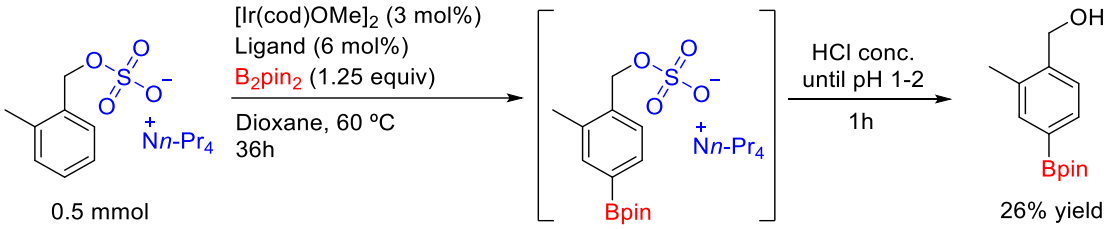
***Para* borylation of tetrabutyl ammonium 2-trifluoromethylbenzyl sulfate (3.6c′)**



>99.9% conversion, *para : meta* = 8 : 1

In a glove box, a 3.0 mL Wheaton microreactor was charged with tetrabutylammonium 2-trifluoromethylbenzyl sulfate (50 mg, 0.1 mmol), $[Ir(cod)(OMe)]_2$ (0.1 mL of 0.015 M solution, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (0.1 mL of 0.03 M solution 3.0 mol %), B_2pin_2 (25 mg, 0.10 mmol) and dioxane (0.2 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 20 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio.

***Para* borylation of tetrapropyl ammonium 2-methylbenzyl sulfate (3.6d)**



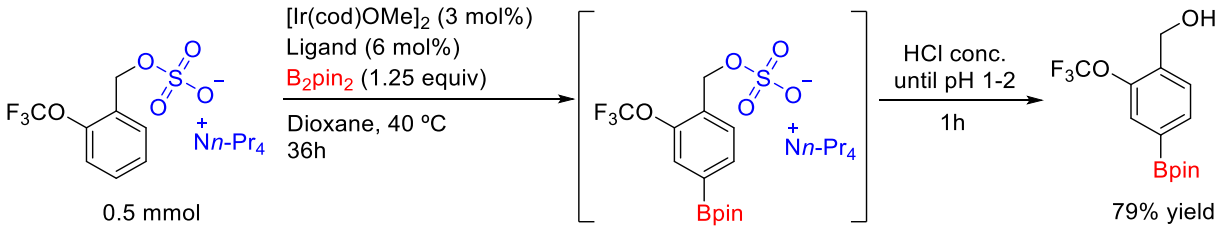
78% conversion, *para : meta* = 5 : 1
26% yield, *para : meta* = 35 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropylammonium 2-methyl benzyl sulfate (194 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 °C. After 36 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant

mixture was stirred for 1 h. The solution was concentrated and subjected directly to chromatographic separation with silica gel (1.5% EtOAc in $CHCl_3$ as eluent) to give 33 mg of *para* borylated 2-methylbenzyl alcohol with traces of the *meta* (*para:meta* = 35:1) isomer as a colorless oil (26% yield)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 4.73 (d, *J* = 4.6 Hz, 2H), 2.36 (s, 3H), 1.58 (bs, 1H) 1.36 (s, 13H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.84, 136.57, 135.10, 132.64, 126.50, 83.77, 63.48, 24.85, 18.41. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.01. HRMS (APCI+) m/z calcd for $C_{14}H_{20}BO_2$ [M–OH–] 231.1556, found 231.1573.

***Para* borylation of tetrapropyl ammonium 2-trifluoromethoxybenzyl sulfate (3.6e)**

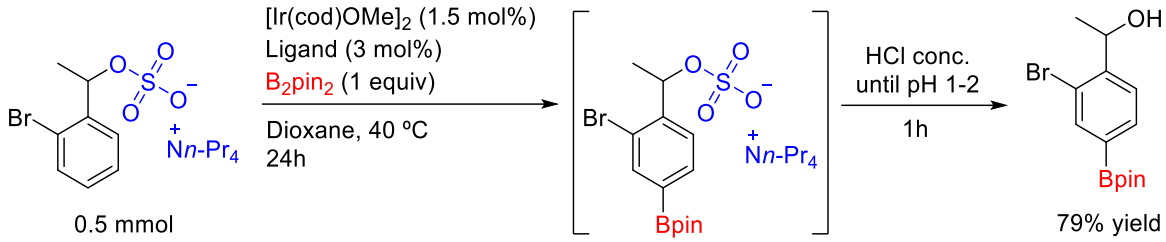


>99.9% conversion, *para : meta* = 22 : 1
79% yield, *para : meta* = 24 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-trifluoromethoxy benzyl sulfate (229 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), 4,4′-dimethoxy-2,2′-bipyridine (6.6 mg, 6.0 mol %), B_2pin_2 (159 mg, 0.625 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 °C. After 36 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel (2% EtOAc in $CHCl_3$ as eluent) to give 126 mg of a mixture of *para* borylated 2-trifluoromethoxyphenol with the *meta* isomer (*para*:*meta* = 24:1) as an oil (79% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.61 (d, *J* = 1.0 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 4.75 (s, 2H), 2.69 (bs, 1H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.1, 136.4, 133.3, 128.0, 126.1, 120.4 (q, *J* = 257.5 Hz), 84.1, 59.4, 24.7. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.20. ^{19}F NMR (470 MHz, $CDCl_3$) δ -60.26. HRMS (APCI+) m/z calcd for $C_{14}H_{17}BF_3O_3$ [M–OH–] 301.1223, found 301.1248.

***Para* borylation of tetrapropyl ammonium 1-(2-bromophenyl)ethyl sulfate (3.6f)**



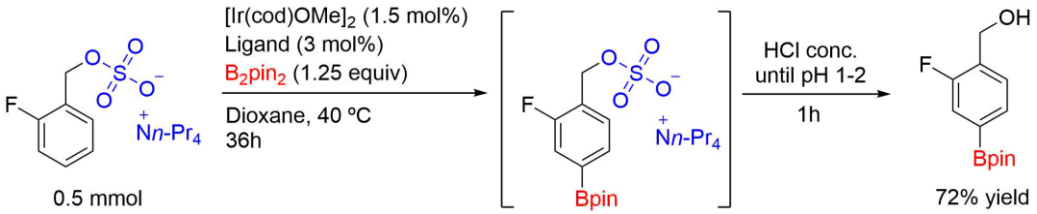
>99.9% conversion, *para : meta* = 11 : 1
79% yield, *para : meta* = 13 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 1-(2-bromophenyl)ethyl sulfate (233 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (128 mg, 0.5 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 24 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent) to give 129 mg of a mixture of *para* borylated 1-(2-bromophenyl)ethan-1-ol with the *meta* isomer (*para*:*meta* = 13:1) as an oil (79% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.1 Hz, 1H), 7.75 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 5.23 (q, *J* = 6.4 Hz, 1H), 2.24 (bs, 1H), 1.47 (d, *J* = 6.4 Hz, 3H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 138.8, 134.1, 126.1, 121.6, 84.1, 69.3, 24.8, 23.5. ^{11}B NMR

(160 MHz, $CDCl_3$) δ 30.4. HRMS (APCI+) m/z calcd for $C_{14}H_{19}BBrO_2$ [M–OH–] 309.0661, found 309.0687.

***Para* borylation of tetrapropyl ammonium 2-fluorobenzyl sulfate (3.6g)**

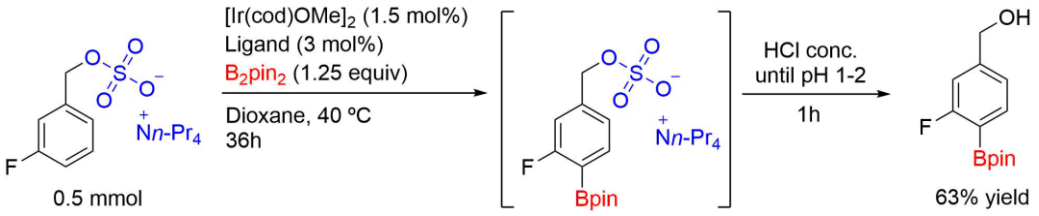


97% conversion, *para : meta : dimeta* = 7 : 1 : 4
72% yield, *para : meta : dimeta* = 10.6 : 1 : 1.2

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 2-fluorobenzyl sulfate (196 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.626 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 °C. After 36 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel (5% EtOAc in $CHCl_3$ as eluent) to give 91.2 mg of a mixture of *para* borylated (2-fluorophenyl)methanol with the *meta* isomer and diborylated product (*para*:*meta:di* = 10.6:1:1.2) as an oil (69% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 1H), 7.48 – 7.37 (m, 2H), 4.75 (d, *J* = 12.7 Hz, 3H), 2.17 (bs, 1H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1 (d, *J* = 246.6 Hz), 130.9 (d, *J* = 14.7 Hz), 130.6 (d, *J* = 3.4 Hz), 128.5 (d, *J* = 3.9 Hz), 120.8 (d, *J* = 19.5 Hz), 84.1, 59.2 (d, *J* = 4.6 Hz), 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.47.^{19}F NMR (470 MHz, $CDCl_3$) δ –108.48, –112.94 (d, *J* = 6.6 Hz), –124.36, –164.90 (t, *J* = 0.9 Hz). HRMS (APCI+) m/z calcd for $C_{13}H_{17}BFO_2$ [M–OH–] 235.1306, found 235.1337.

***Para* borylation of tetrapropyl ammonium 3-fluorobenzyl sulfate (3.6h)**



>99.9% conversion, *para : meta* = 2 : 1
63% yield, *para : meta* = 1.9 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with tetrapropyl ammonium 3-fluorobenzyl sulfate (196 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (5 mg, 1.5 mol %), 4,4′-dimethoxy-2,2′-bipyridine (3.3 mg, 3.0 mol %), B_2pin_2 (159 mg, 0.626 mmol) and dioxane (1.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 °C. After 36 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* ratio. HCl 12 M was added until pH = 1–2 and the resultant mixture was stirred for 1 h. The solution was concentrated and passed through a plug of silica gel (4% EtOAc in $CHCl_3$ as eluent) to give 79.1 mg of a mixture of *para* borylated (3-fluorophenyl)methanol with the *meta* isomer (*para*:*meta* = 1.9:1) as an oil (63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.6, 6.2 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.01 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.65 (s, 2H), 2.71 (bs, 1H), 2.62 (bs, 1H), 1.35 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4 (d, *J* = 250.9 Hz), 162.7 (d, *J* = 246.8 Hz), 147.3 (d, *J* = 8.0 Hz), 143.1 (d, *J* = 6.3 Hz), 136.9 (d, *J* = 8.2 Hz), 128.4 (d, *J* = 2.8 Hz), 121.5 (d, *J* = 3.0 Hz), 119.9 (d, *J* = 19.5 Hz), 116.5 (d, *J* = 21.9 Hz), 113.2 (d, *J* = 24.6 Hz), 84.2, 83.9, 75.1, 64.3 (d, *J* = 1.7 Hz), 64.2 (d, *J* = 1.8 Hz), 24.8, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ –103.79, –107.40 (m), –117.31, –164.90. HRMS (APCI+) m/z calcd for $C_{13}H_{17}BFO_2$ [M–OH–] 235.1306, found 235.1387.

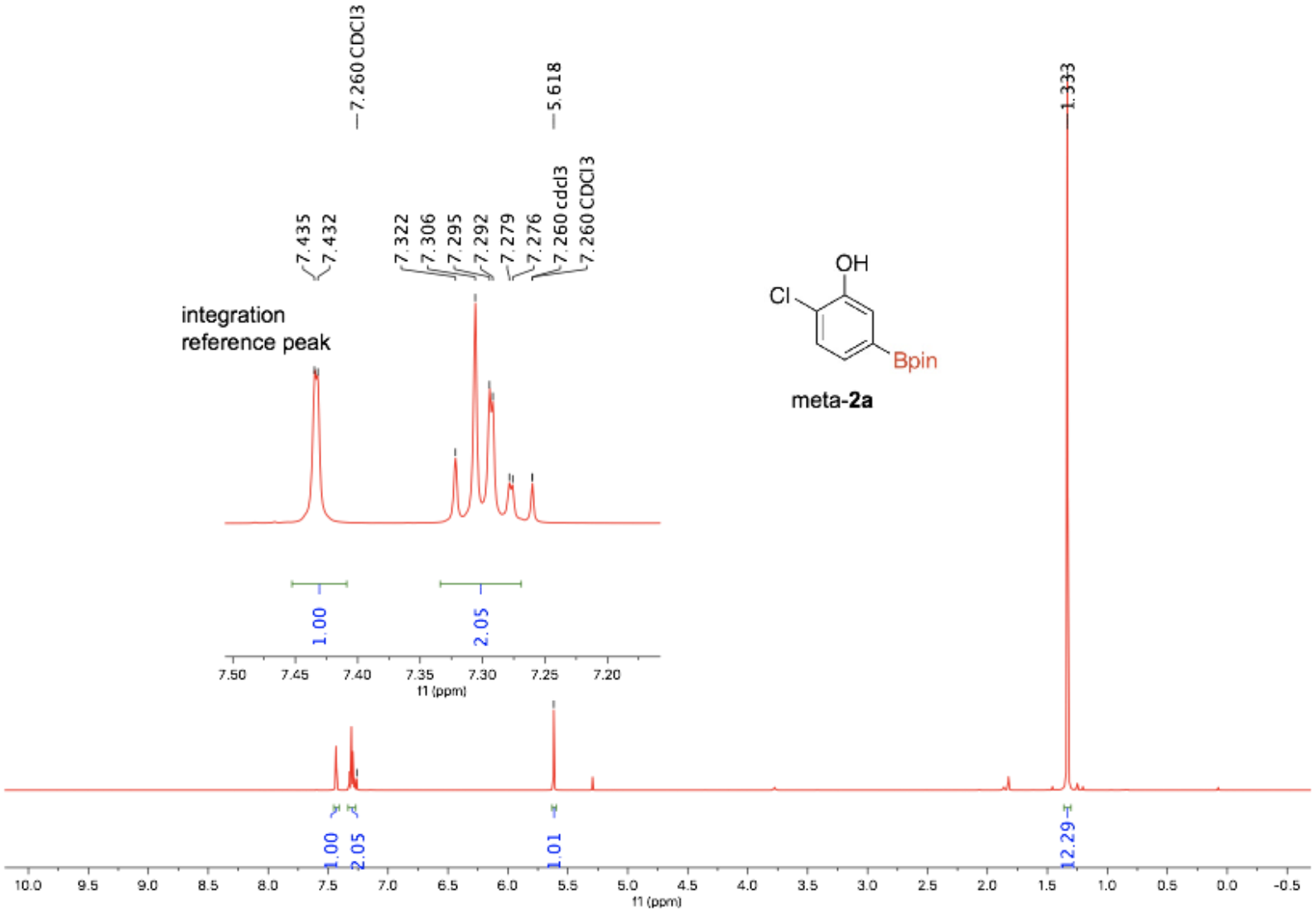
3.5. Notes

Parts of this chapter were reprinted with permission from Montero Bastidas, J. R.; Oleskey, T. J.; Miller, S. L.; Smith, M. R., III; Maleczka, R. E., Jr. *Para*-Selective, Iridium-Catalyzed C−H Borylations of Sulfated Phenols, Benzyl Alcohols, and Anilines Directed by Ion-Pair Electrostatic Interactions. *J. Am. Chem. Soc.* **2019**, *141*, 15483-15487. Copyright 2021 American Chemical Society

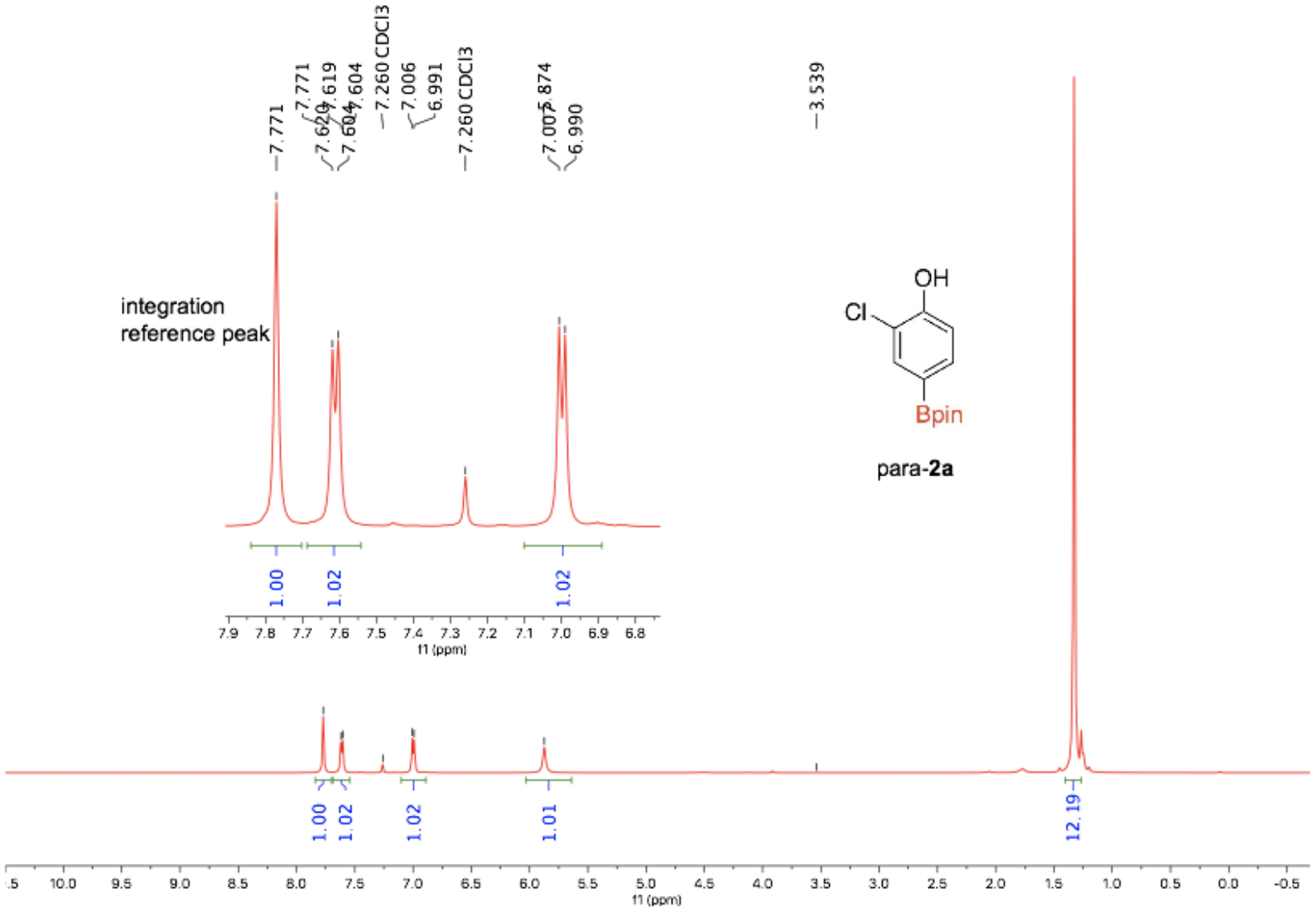
The work presented in this chapter was not all conducted by Montero Bastidas, J. R. Substrate exploration was a team effort with Oleskey, T. J. (sulfated phenols and benzyl alcohols) and Miller, S. L. (sulfated anilines).

APPENDIX

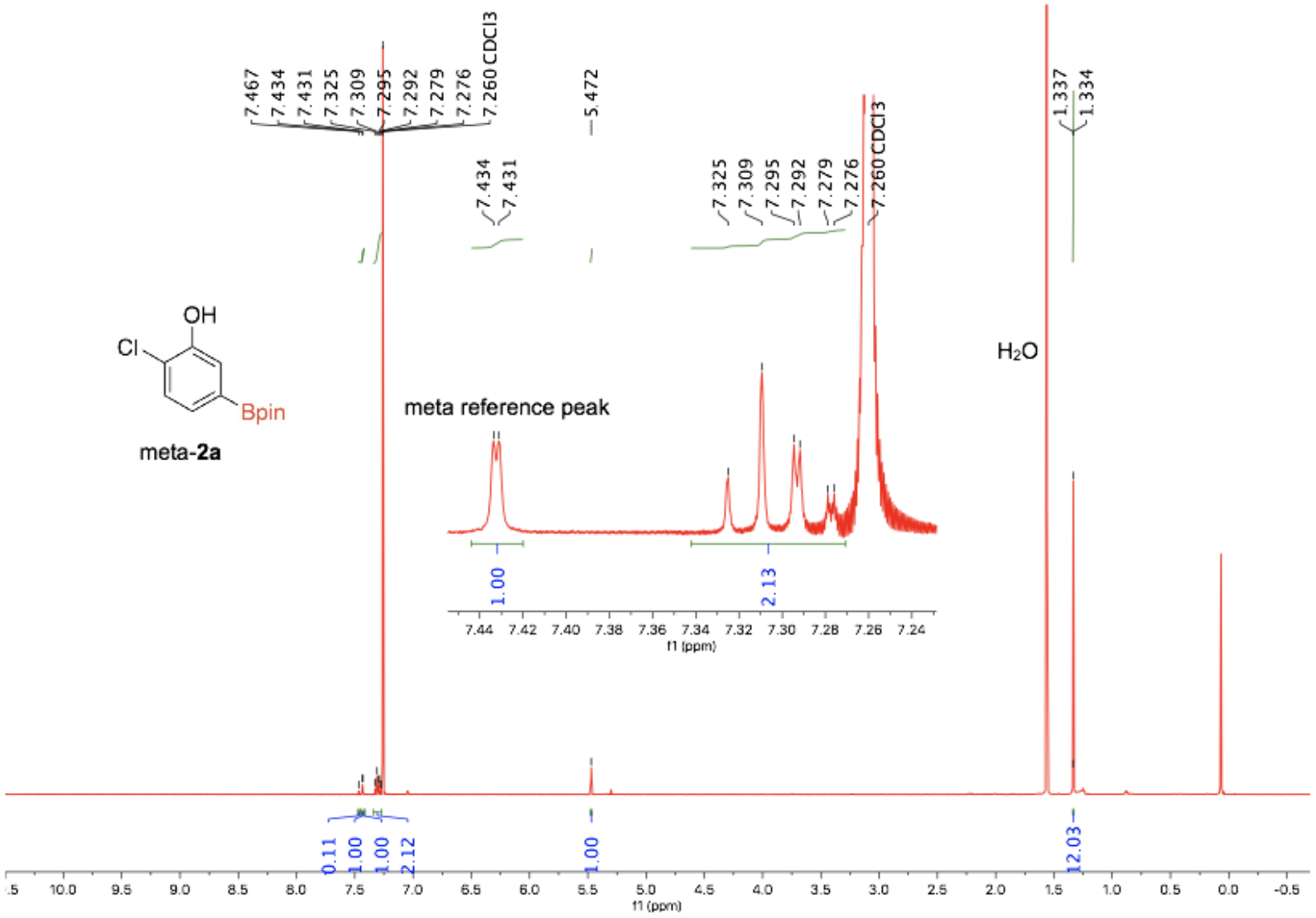
^{1}H NMR of commercial 4-chloro-3-hydroxyphenylBpin (*meta* borylated 2-chlorophenol, 3.2a) (500 MHz, $CDCl_3$)



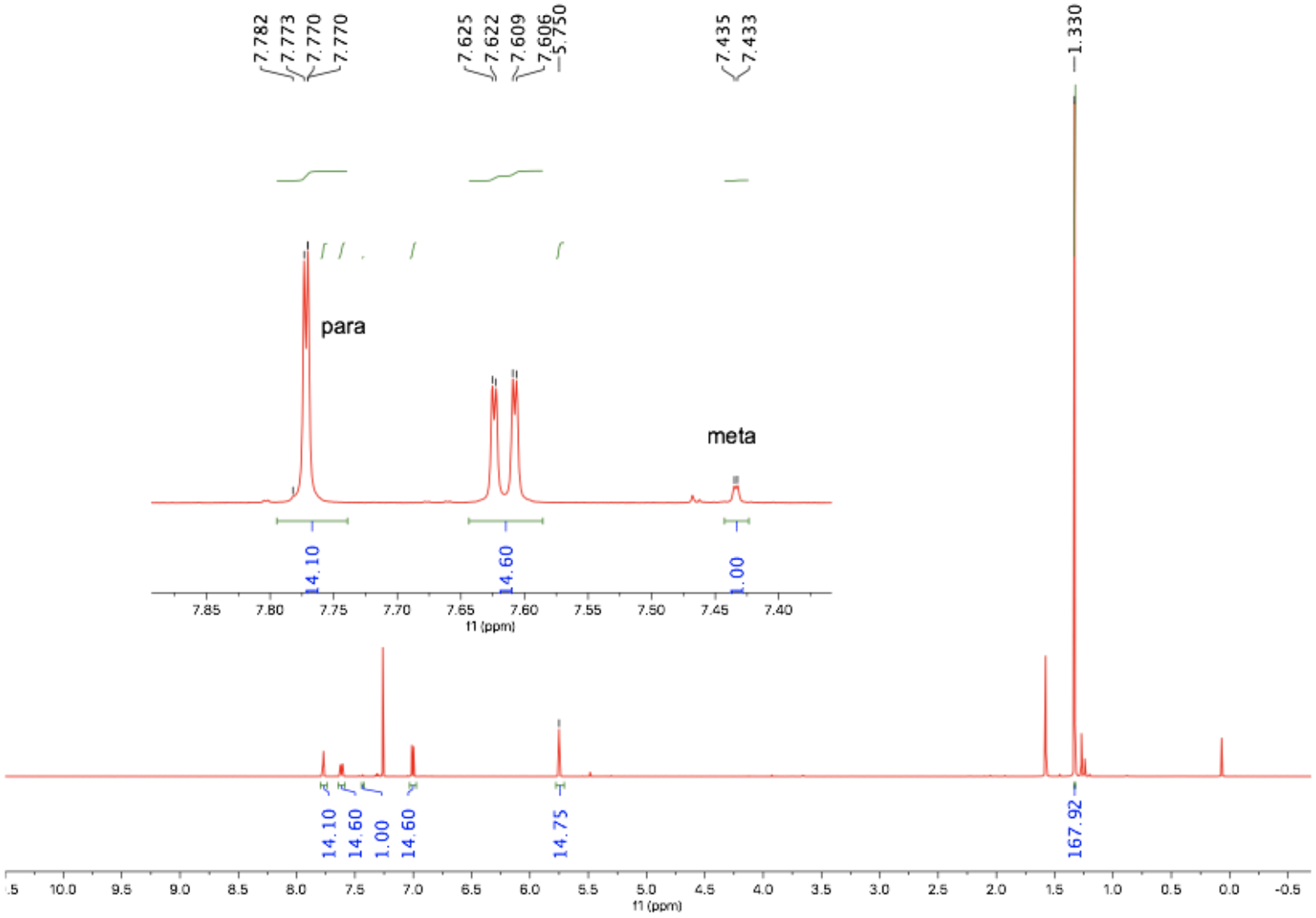
^{1}H NMR of commercial 3-chloro-4-hydroxyphenylBpin (*Para* borylated 2-chlorophenol) (500 MHz, $CDCl_3$)



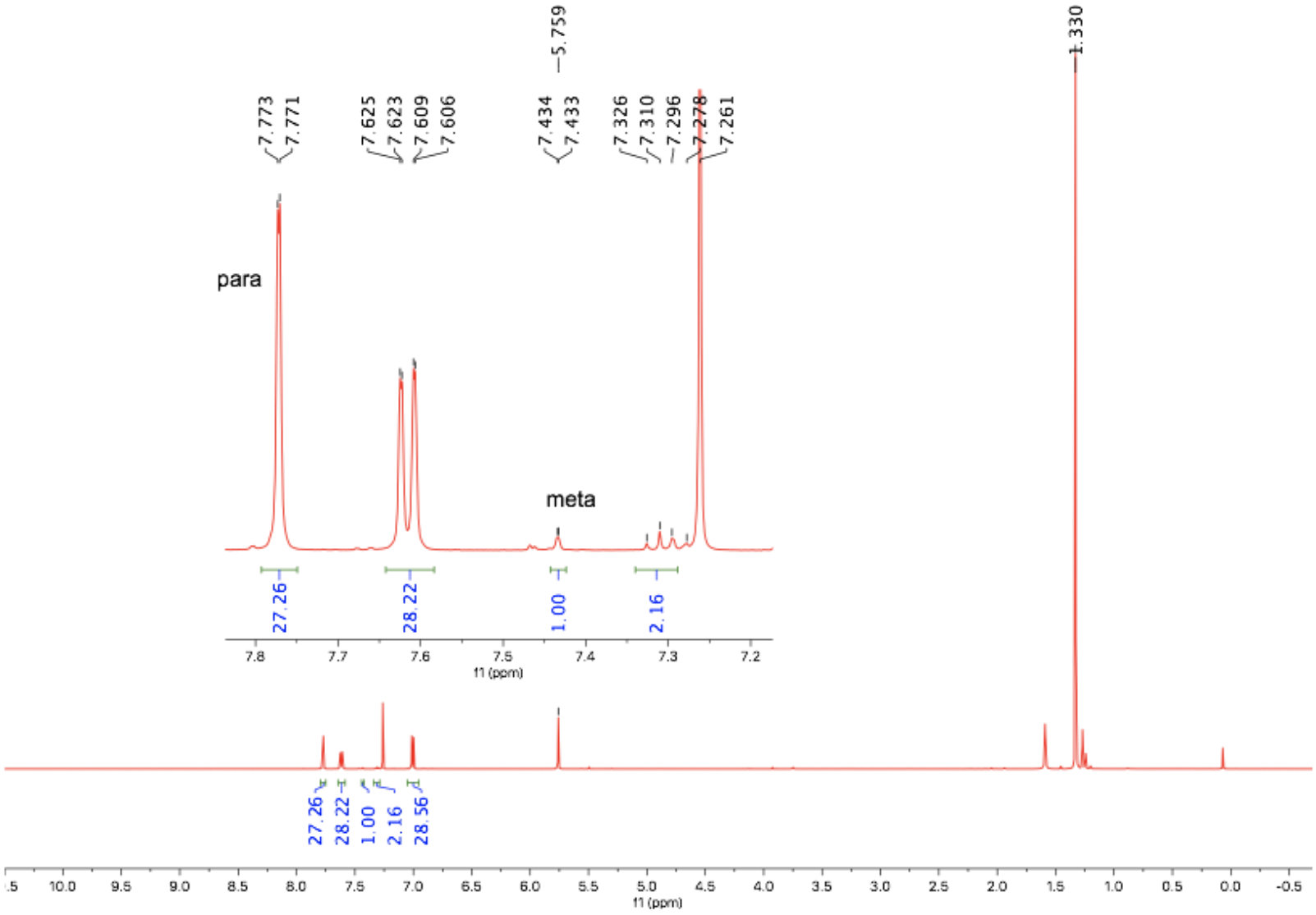
^{1}H NMR control spectrum of 7.0 x10^{-7} mols *meta*-2a (500 MHz, $CDCl_3$)



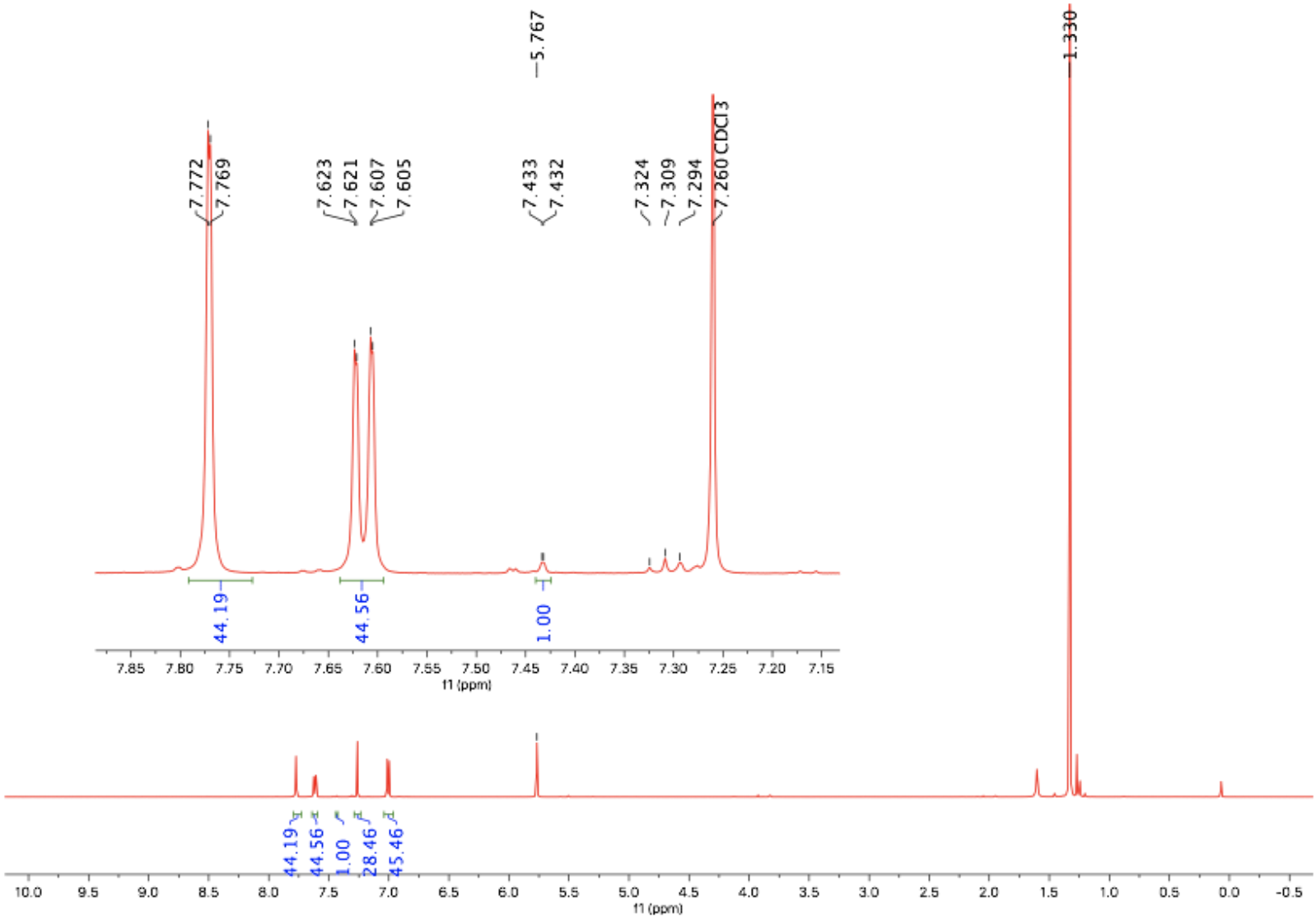
^{1}H NMR spectrum of 14:1 mixture of *para*-3.2a to *meta*-3.2a (500 MHz, $CDCl_3$)



^{1}H NMR spectrum of 28:1 mixture of *para*-3.2a to *meta*-3.2a (500 MHz, $CDCl_3$)

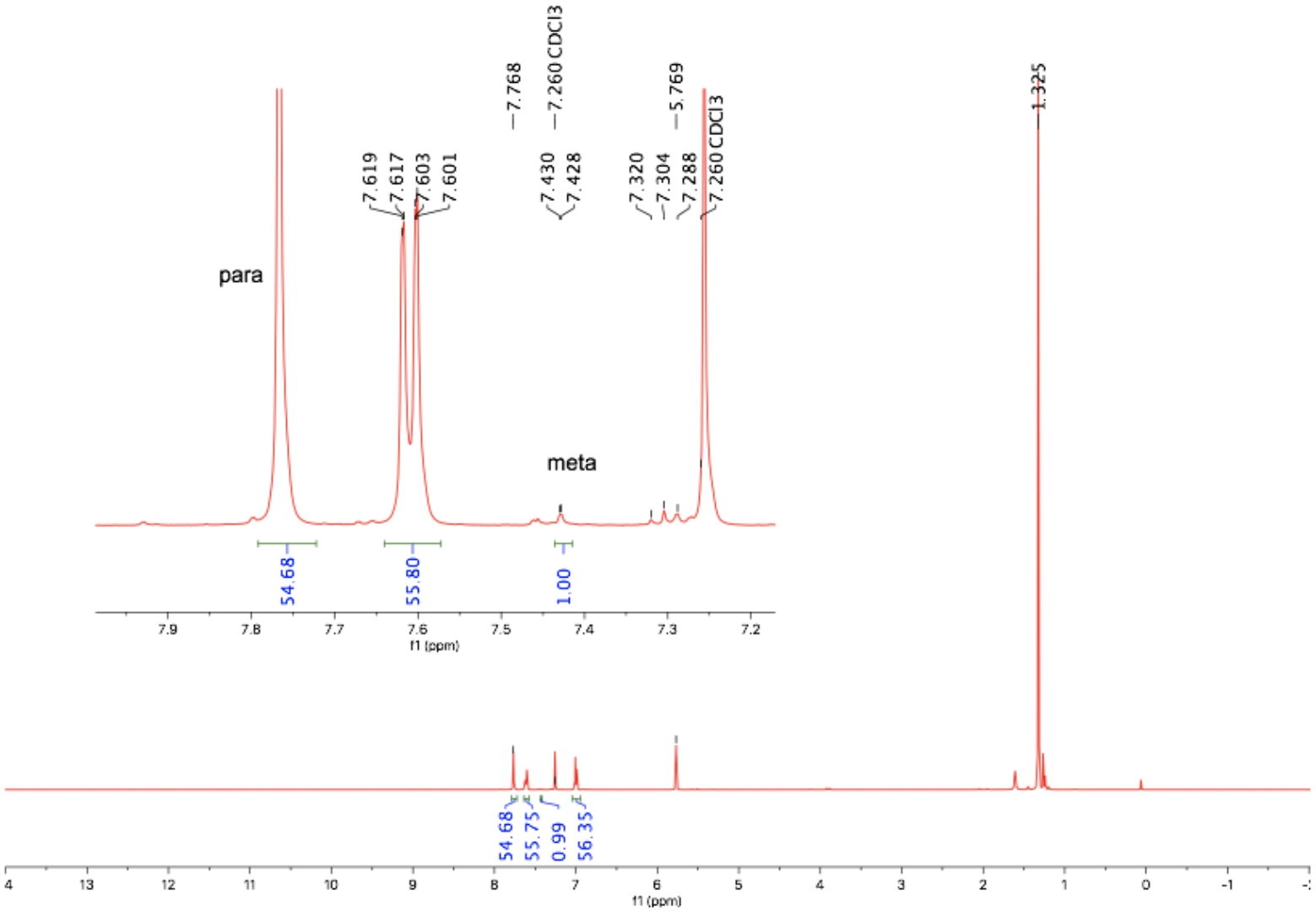


^{1}H NMR spectrum of 42:1 mixture of *para*-3.2a to *meta*-3.2a

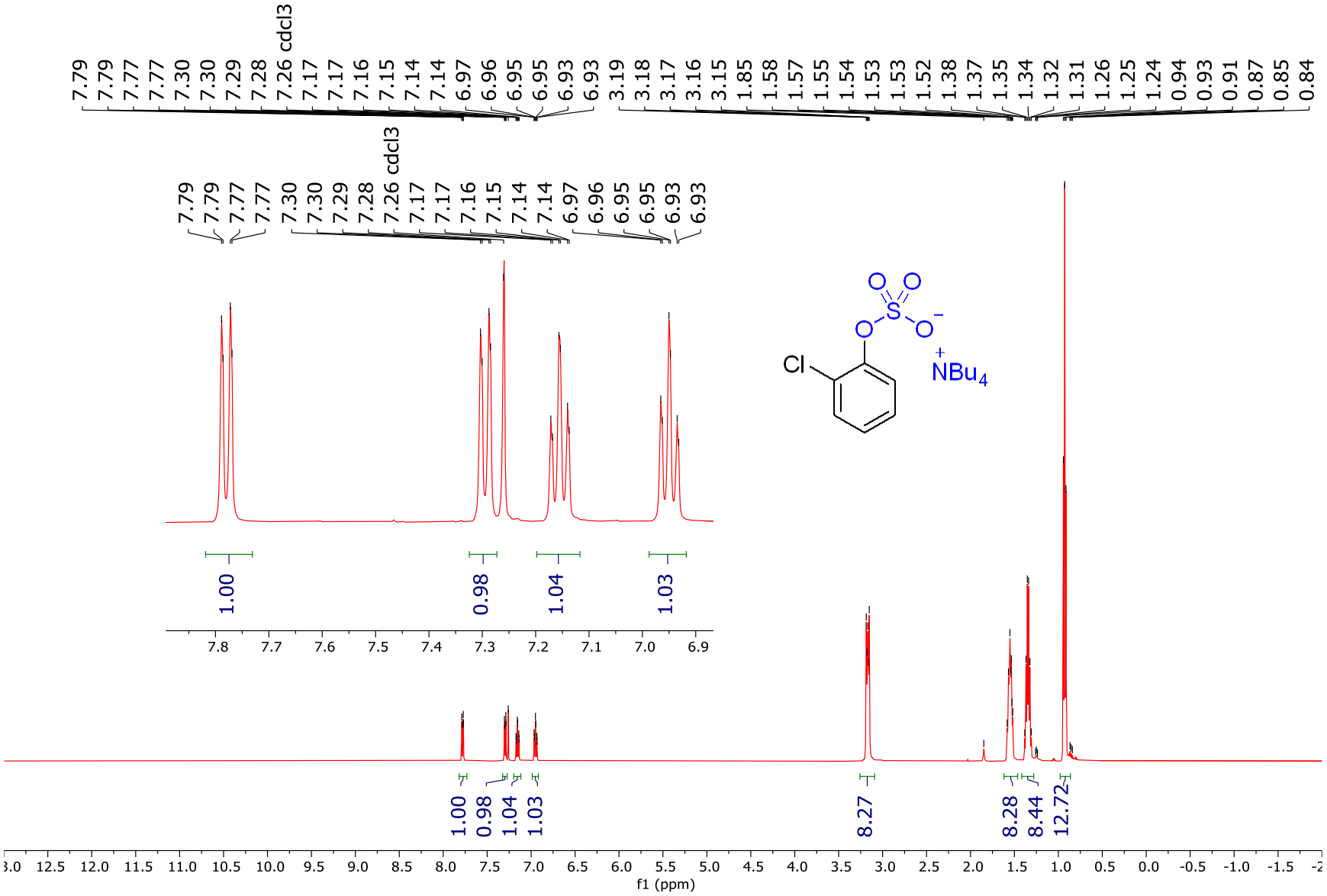


Conditions: 25 °C, 500 MHz, $CDCl_3$

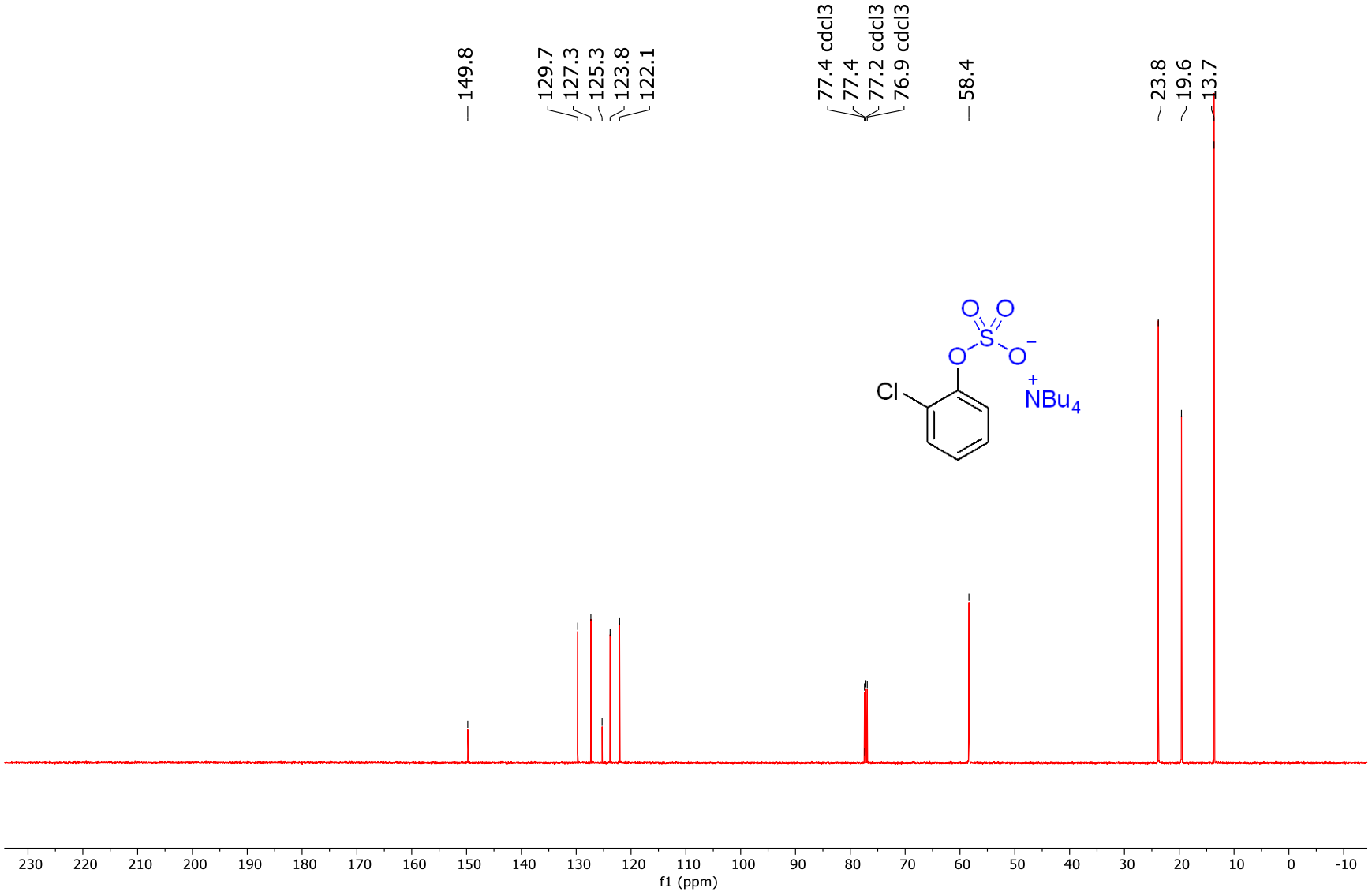
^{1}H NMR spectrum of 56:1 mixture of *para*-3.2a to *meta*-3.2a (500 MHz, $CDCl_3$)



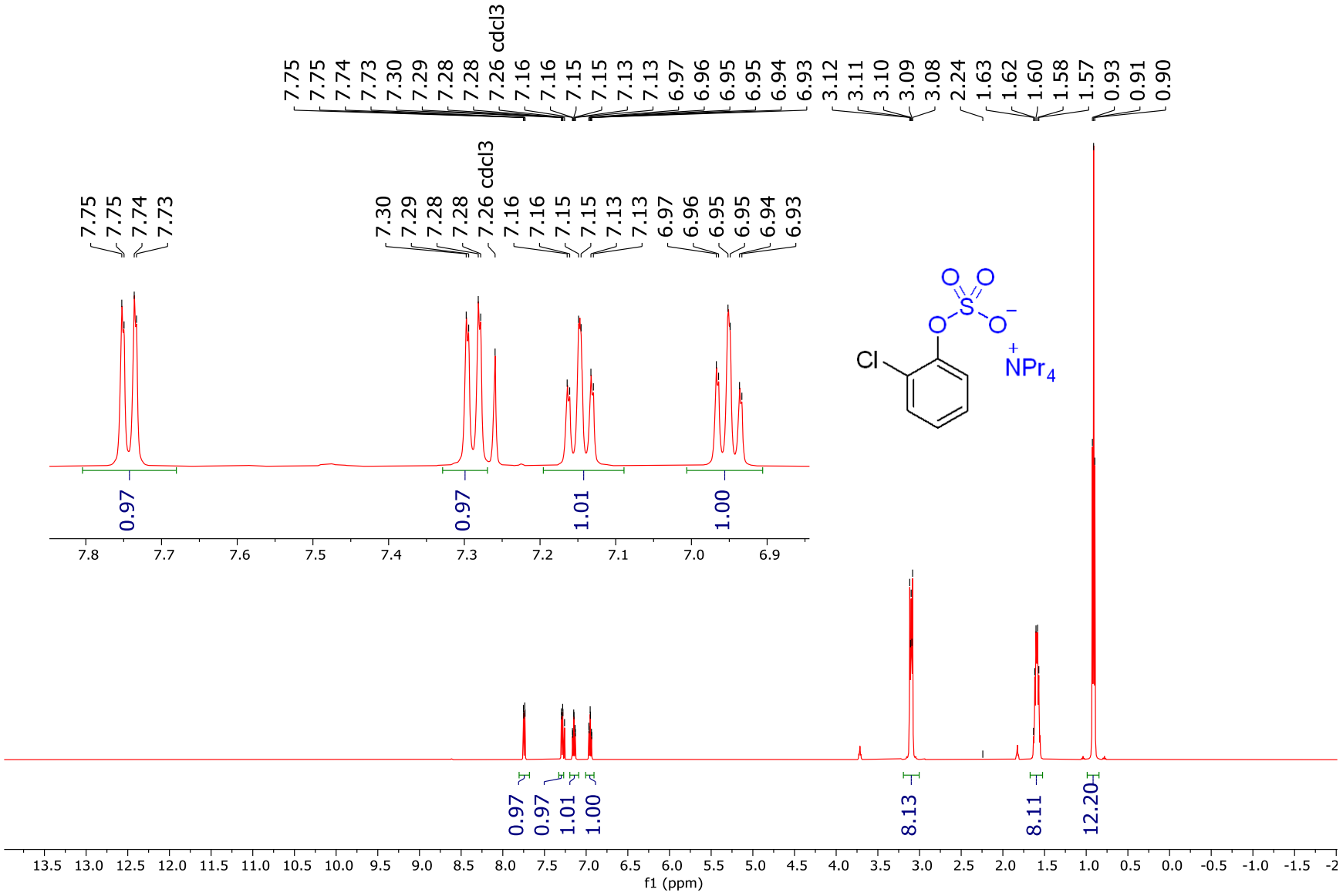
^{1}H NMR spectrum of tetrabutylammonium 2-chlorosulfate (3.1a′) (500 MHz, $CDCl_3$)



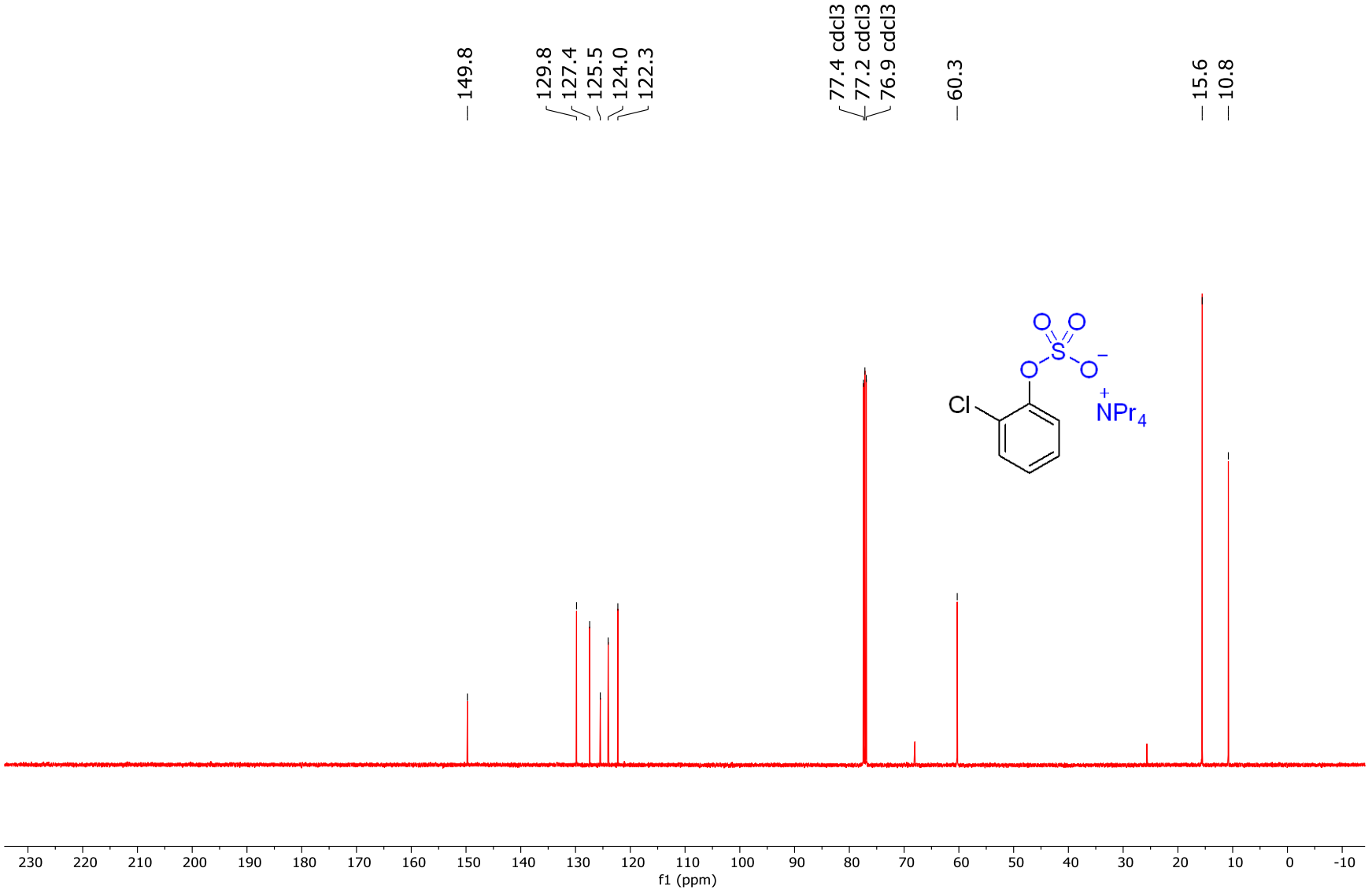
^{13}C NMR spectrum of tetrabutylammonium 2-chlorosulfate (3.1a′) (126 MHz, $CDCl_3$)



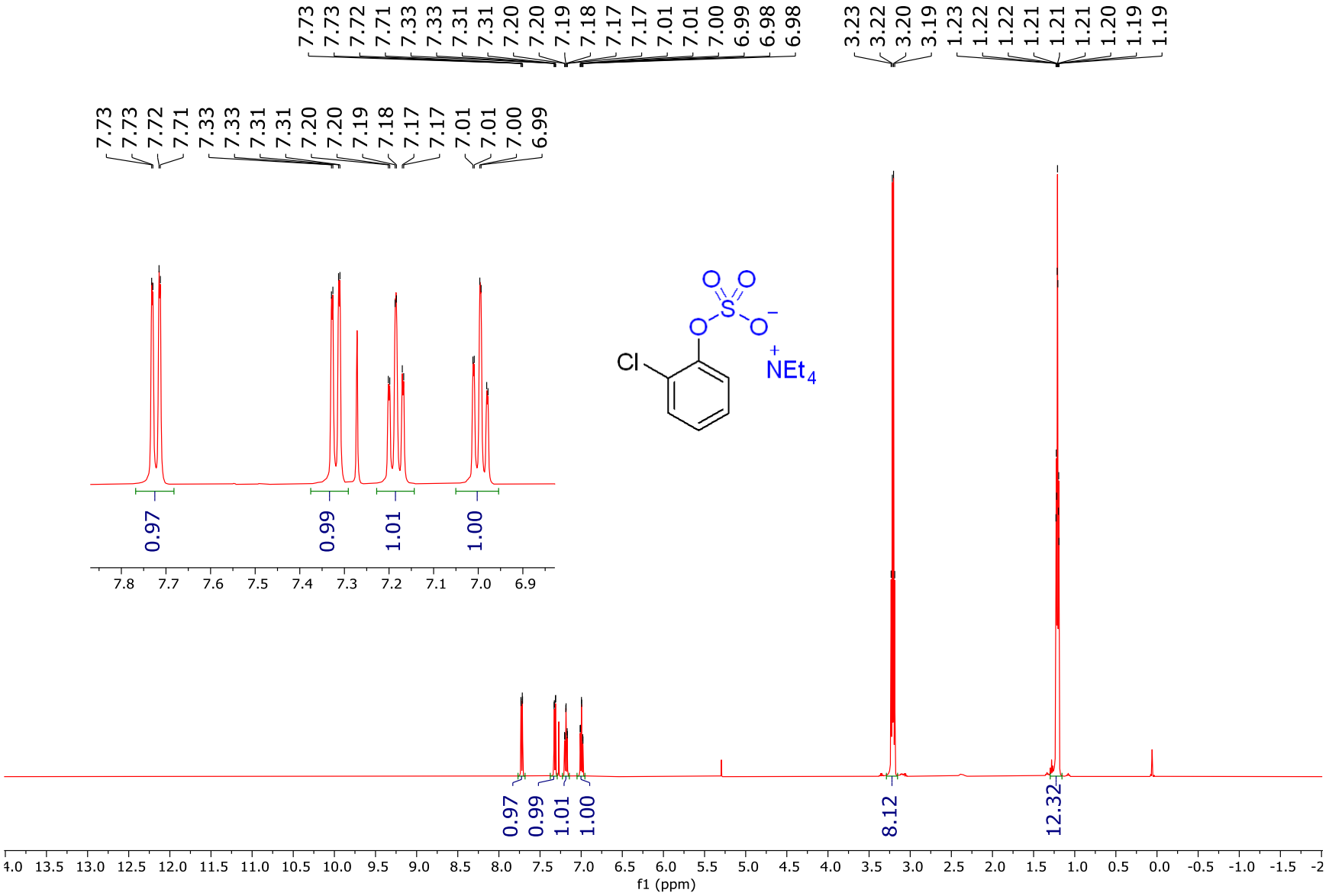
^{1}H NMR spectrum of tetrapropylammonium 2-chlorosulfate (3.1a) (500 MHz, $CDCl_3$)



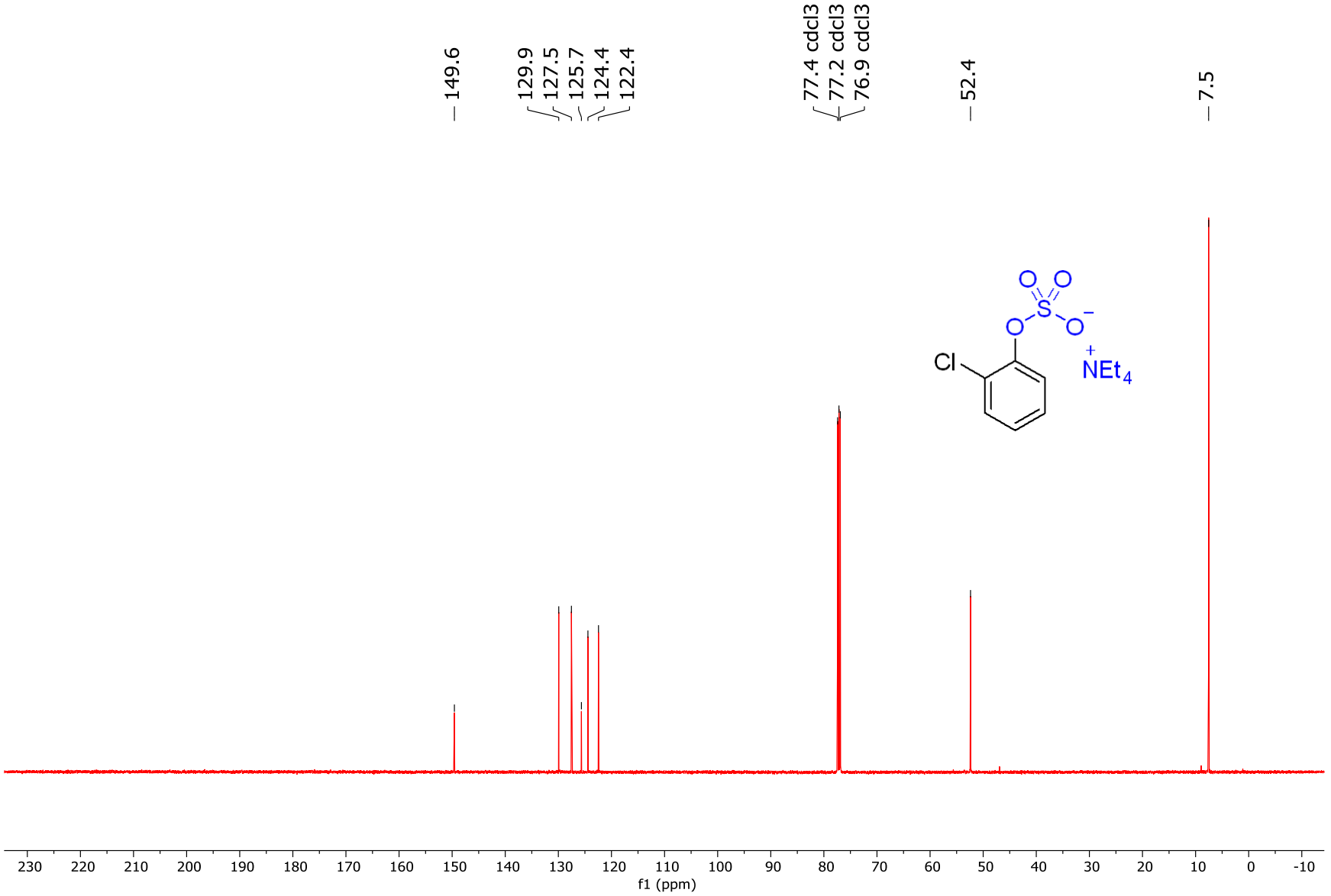
^{13}C NMR spectrum of tetrapropylammonium 2-chlorophenylsulfate (3.1a) (126 MHz, $CDCl_3$)



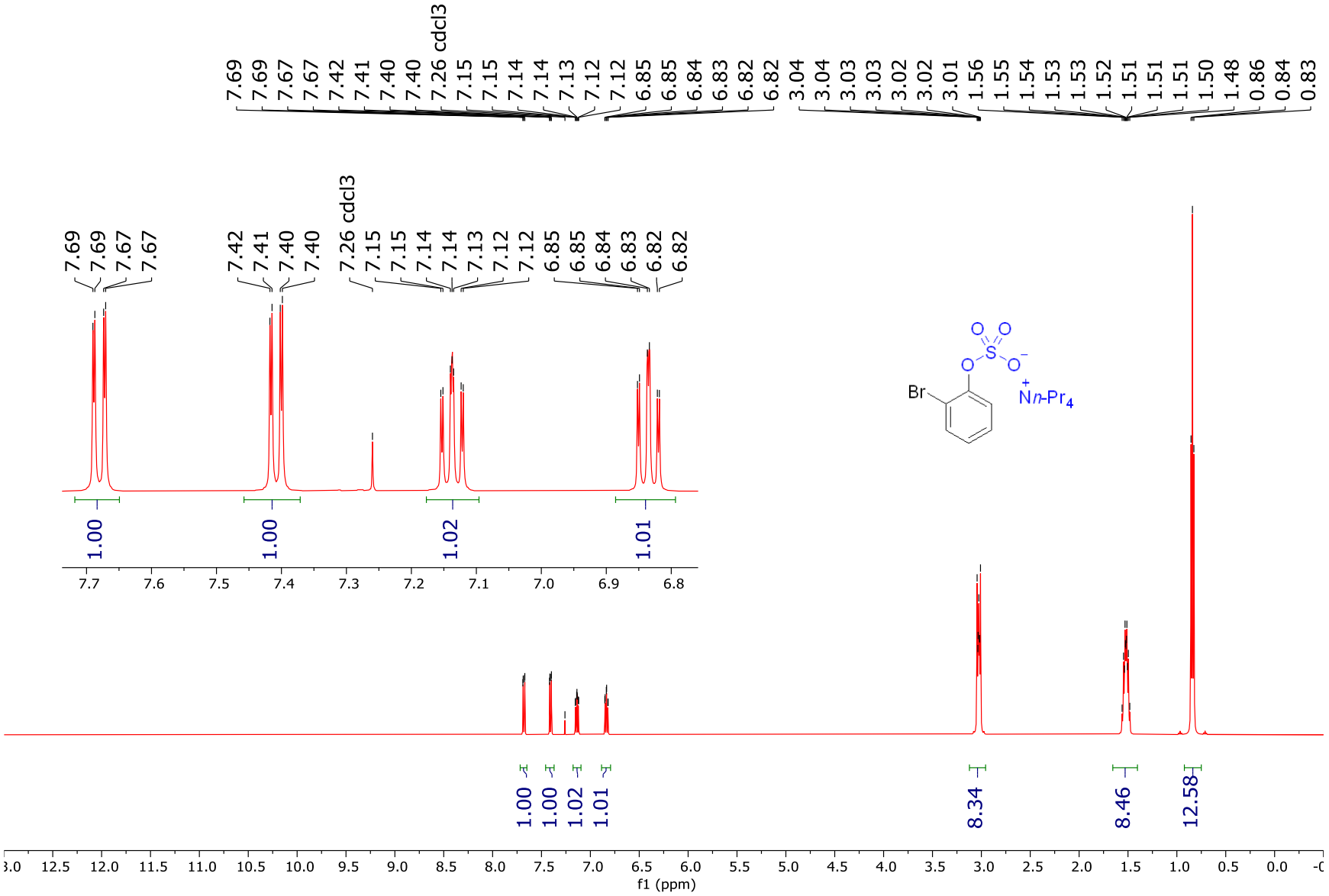
^{1}H NMR spectrum of tetraethylammonium 2-chlorophenylsulfate (3.1a′′) (500 MHz, $CDCl_3$)



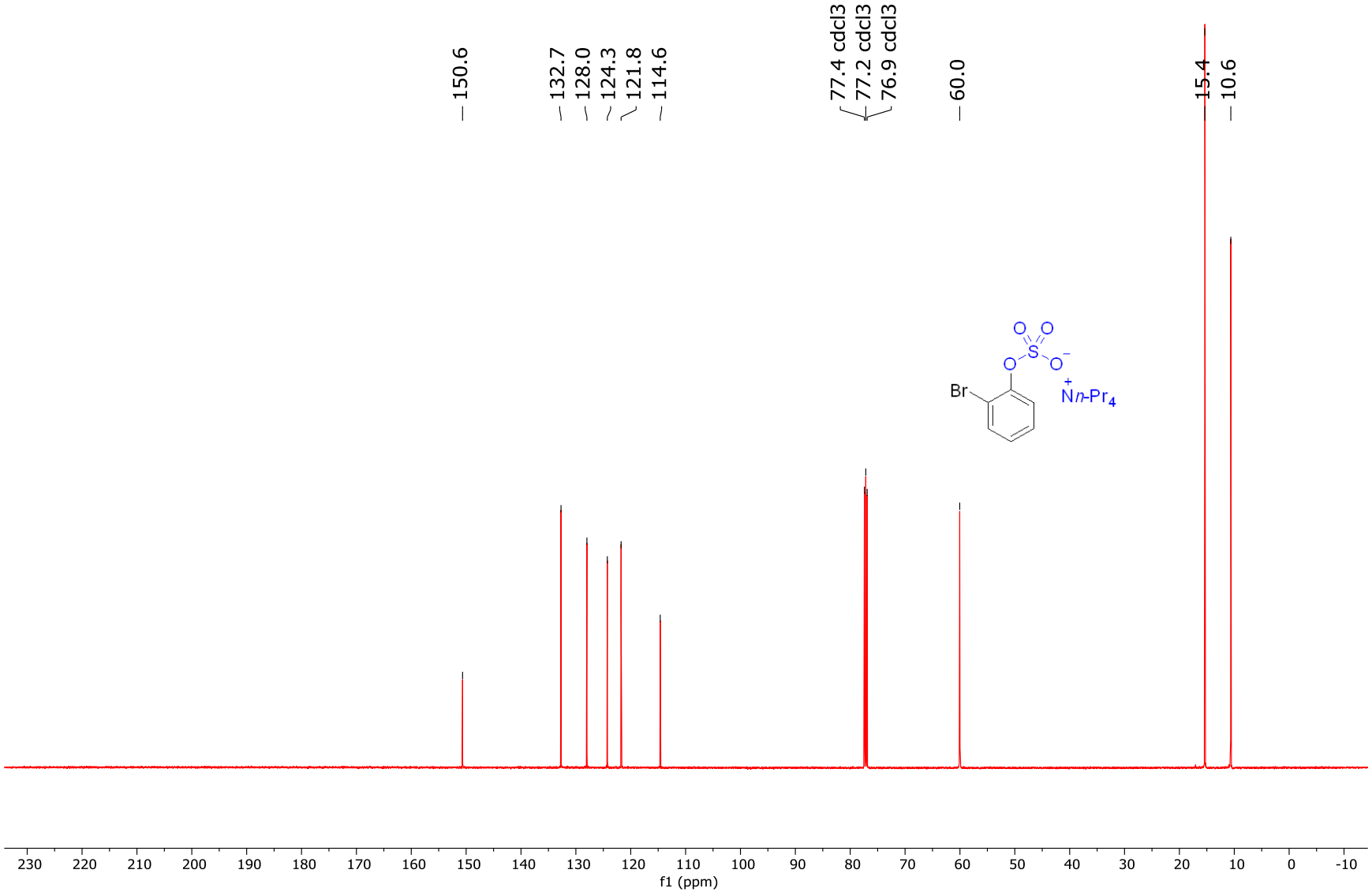
^{13}C NMR spectrum of tetraethylammonium 2-chlorophenylsulfate (3.1a′′) (126 MHz, $CDCl_3$)



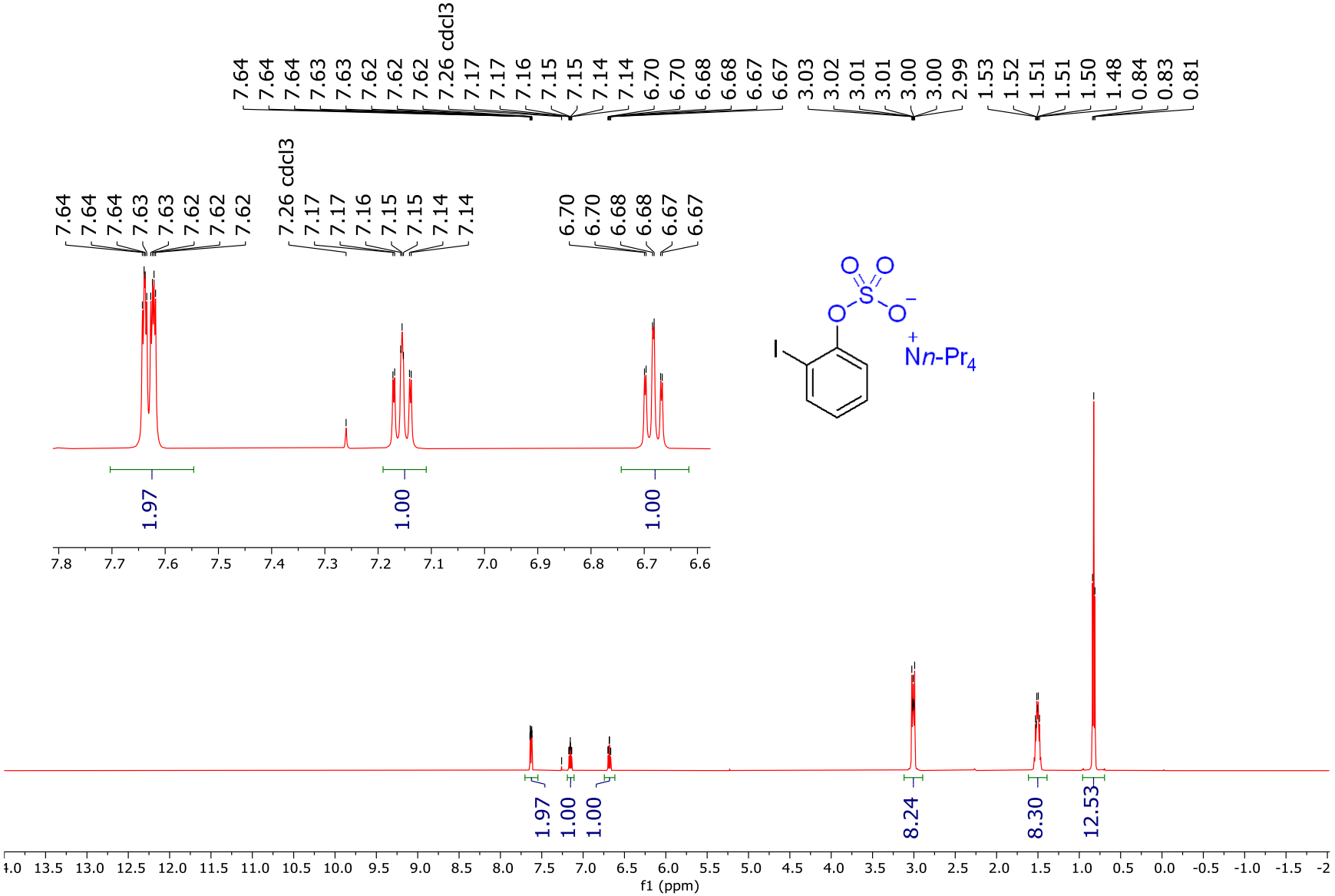
^{1}H NMR spectrum of tetrapropylammonium 2-bromophenylsulfate (3.1b) (500 MHz, $CDCl_3$)



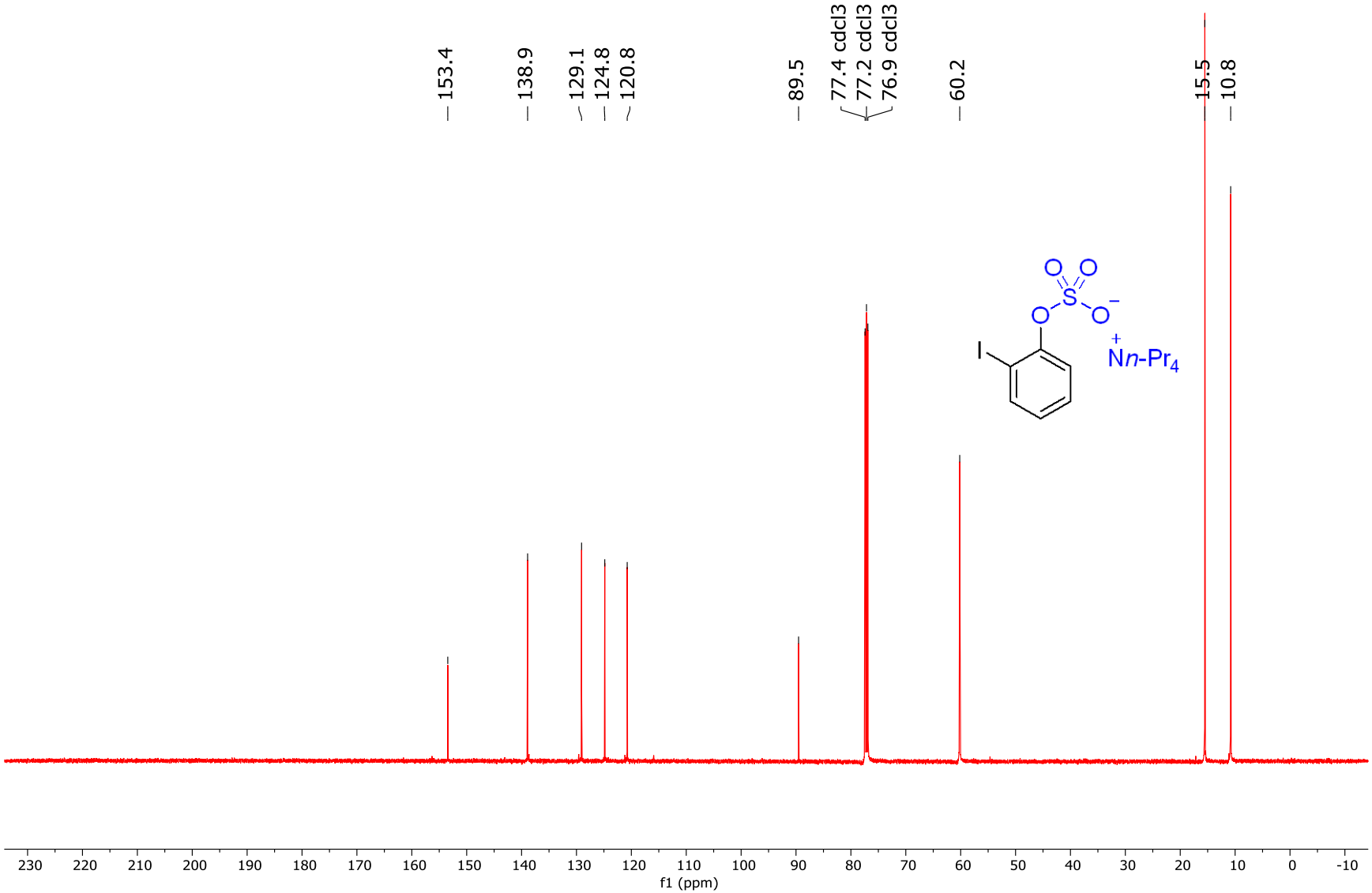
^{13}C NMR spectrum of tetrapropylammonium 2-bromophenylsulfate (3.1b) (126 MHz, $CDCl_3$)



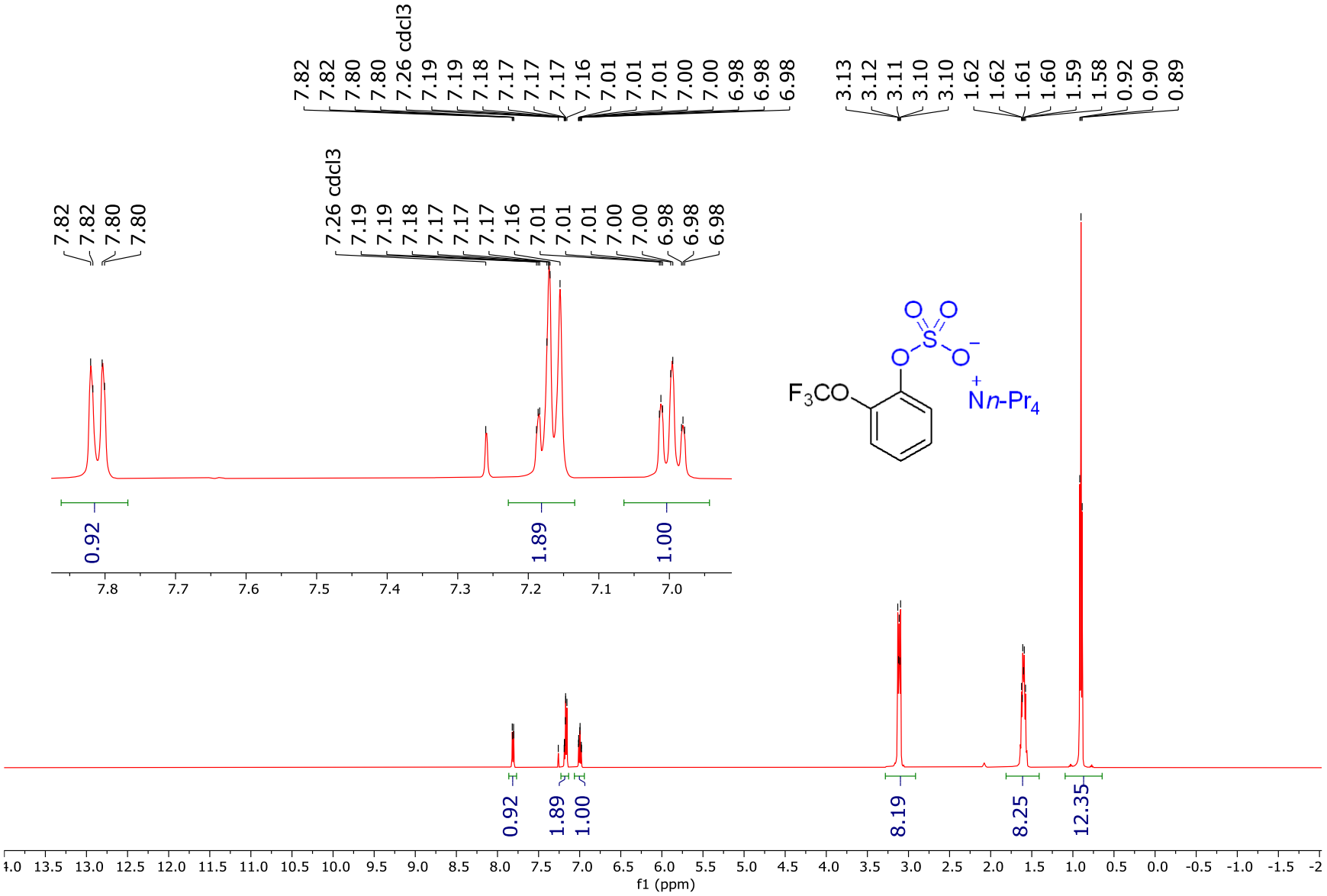
^{1}H NMR spectrum of tetrapropylammonium 2-iodophenylsulfate (3.1c) (500 MHz, $CDCl_3$)



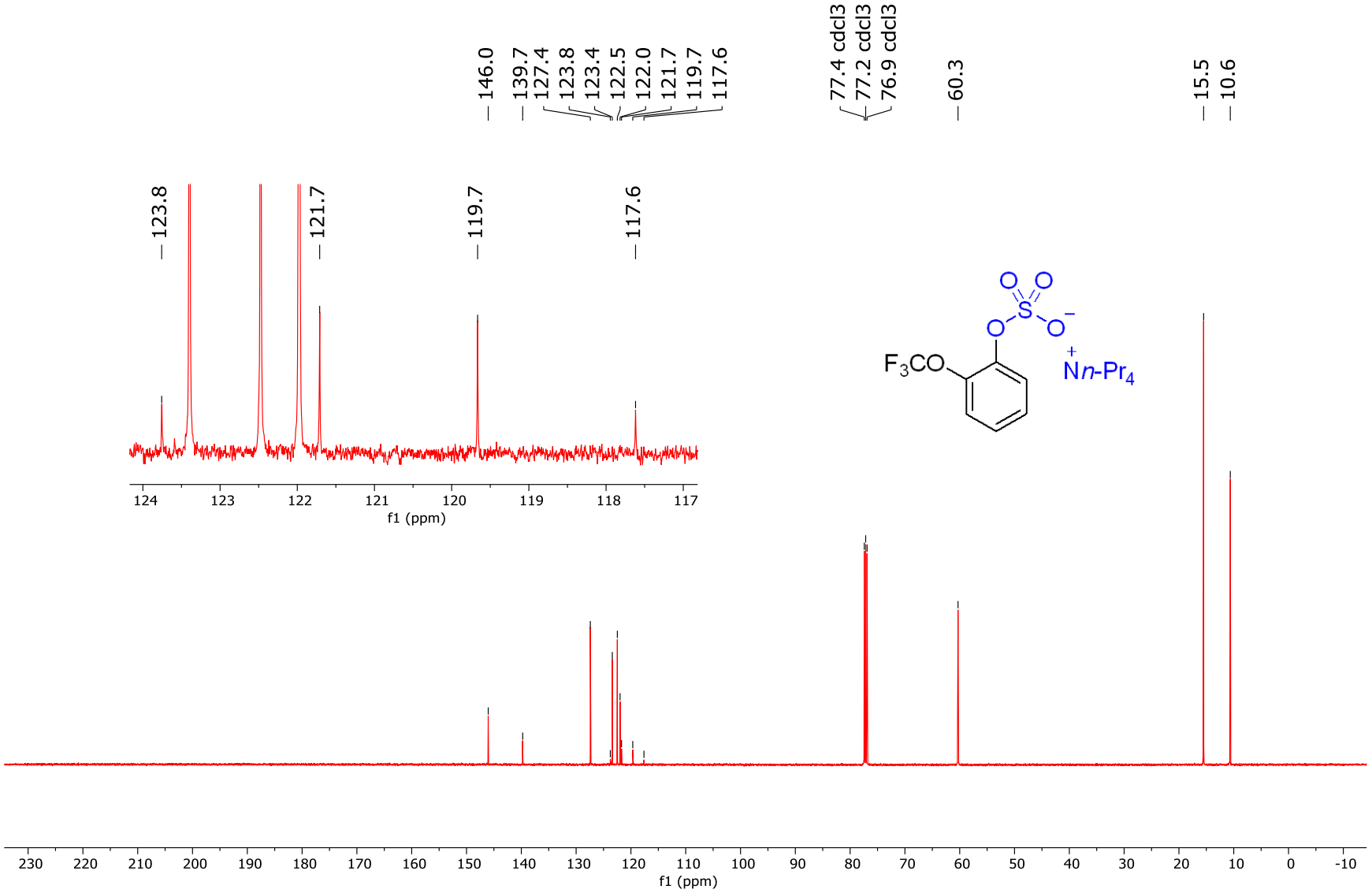
^{13}C NMR spectrum of tetrapropylammonium 2-iodophenylsulfate (3.1c) (126 MHz, $CDCl_3$)



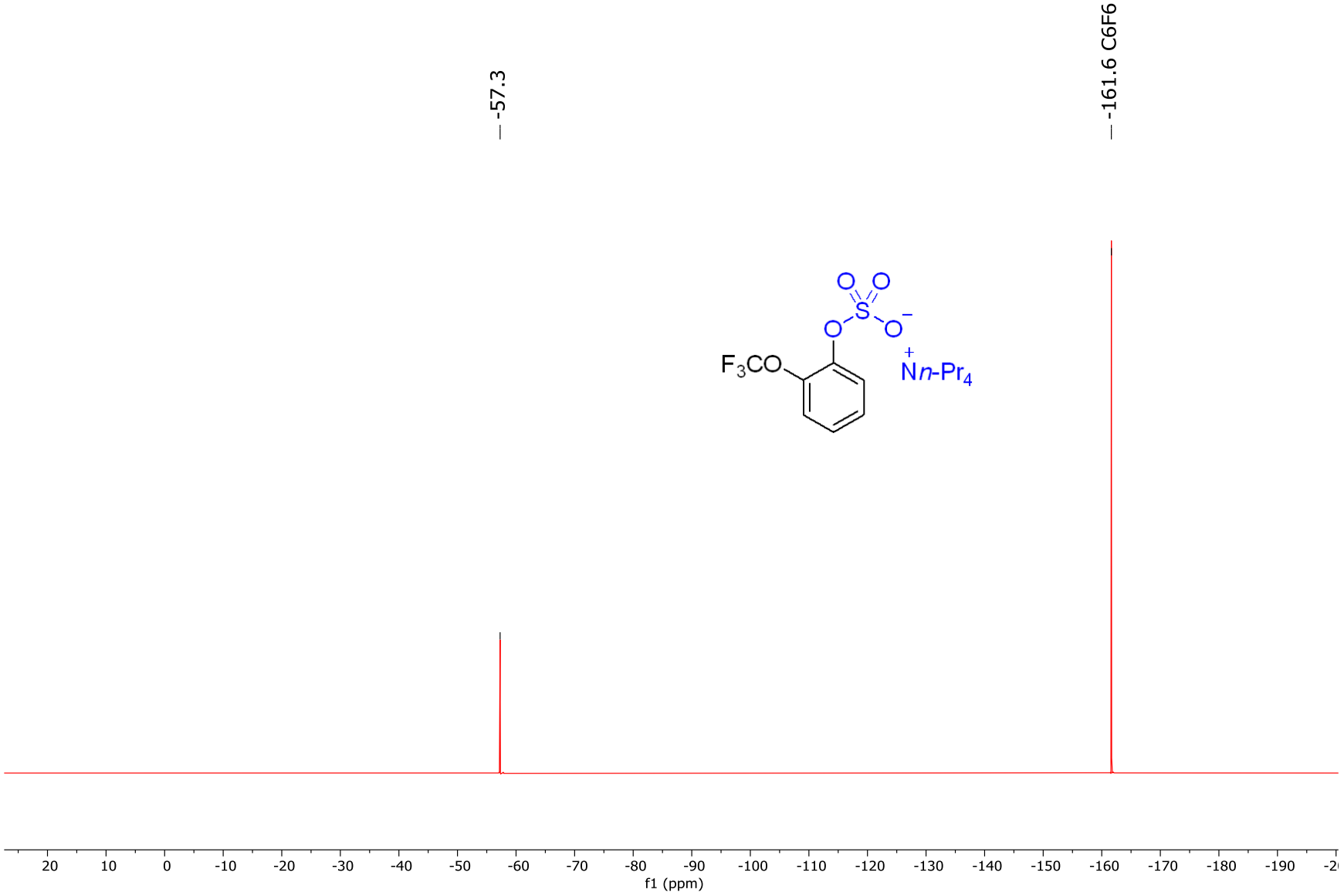
^{1}H NMR spectrum of 2-(trifluoromethoxy)phenylsulfate (3.1d) (500 MHz, $CDCl_3$)



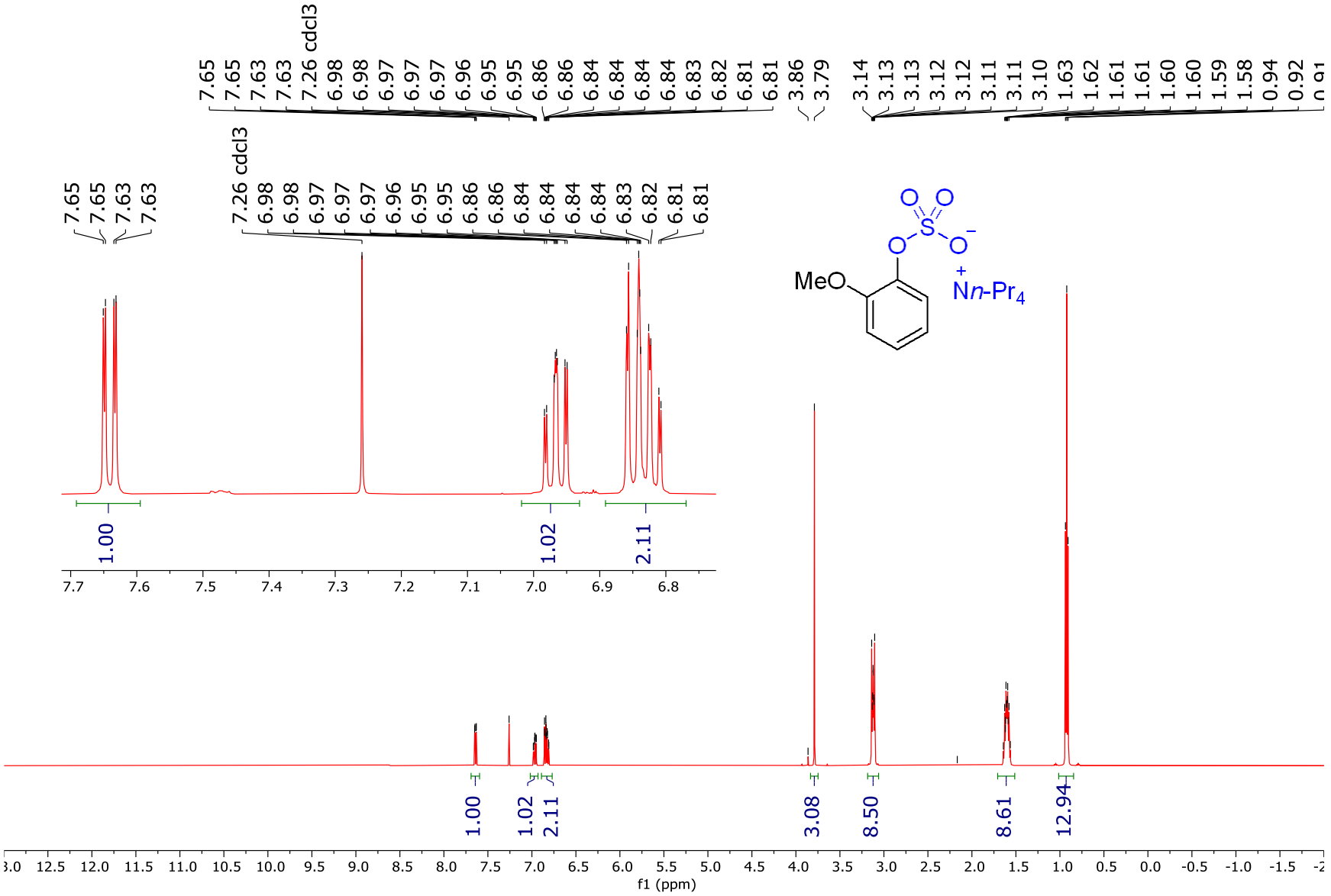
^{13}C NMR spectrum of 2-(trifluoromethoxy)phenylsulfate (3.1d) (126 MHz, $CDCl_3$)



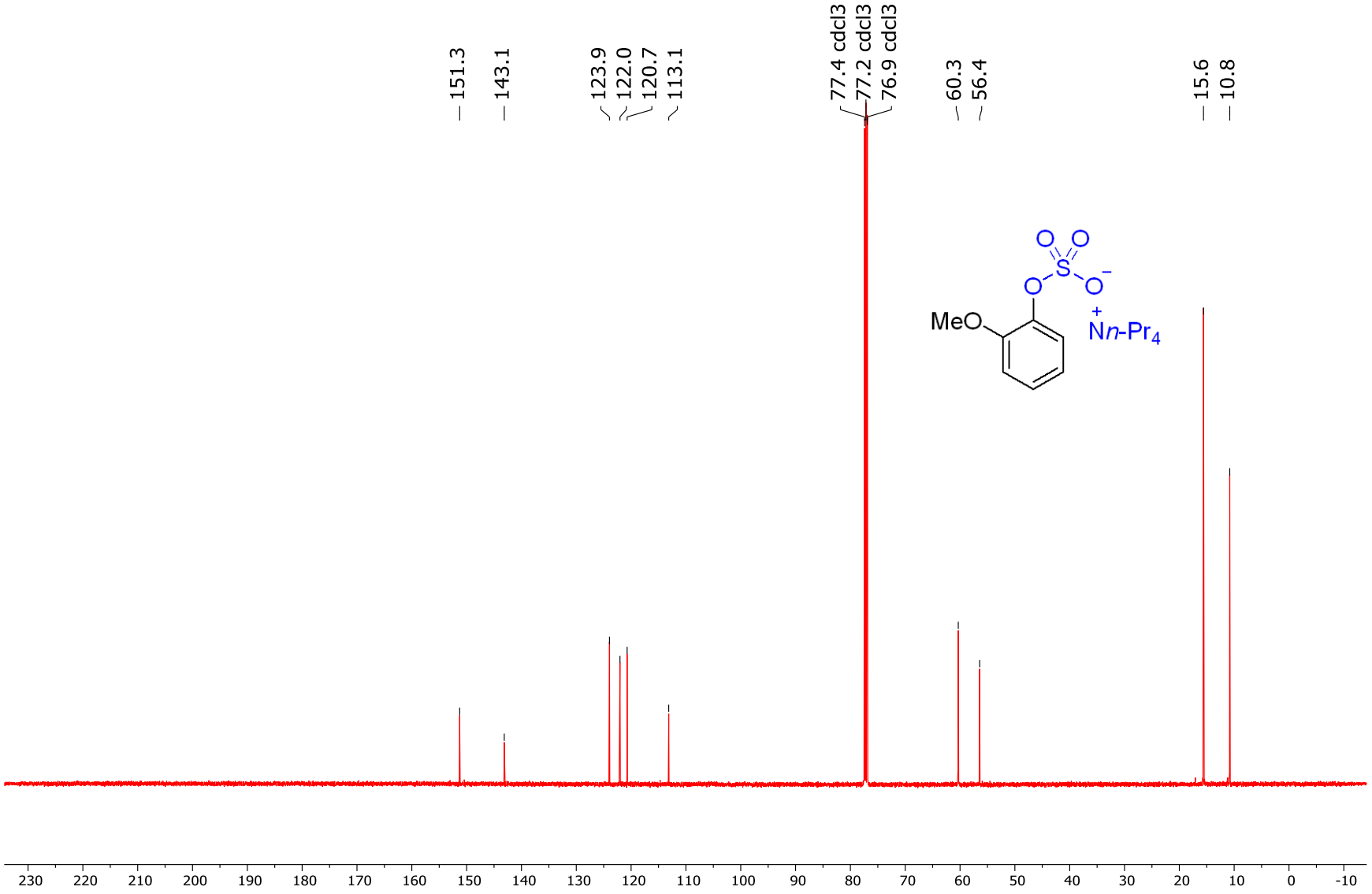
^{19}F NMR spectrum of 2-(trifluoromethoxy)phenylsulfate (3.1d) (470 MHz, $CDCl_3$)



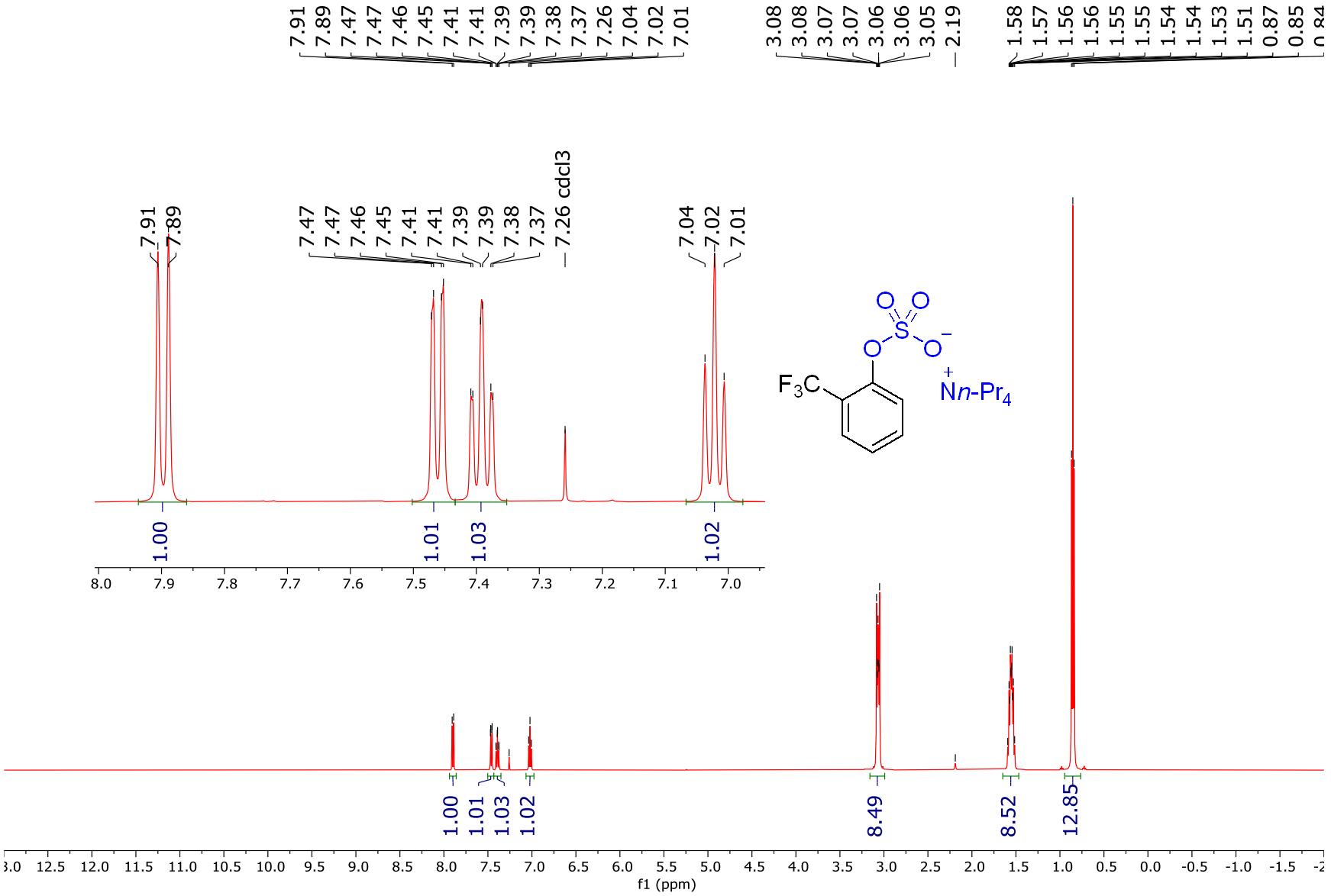
^{1}H NMR spectrum of tetrapropylammonium 2-methoxyphenylsulfate (3.1e) (500 MHz, $CDCl_3$)



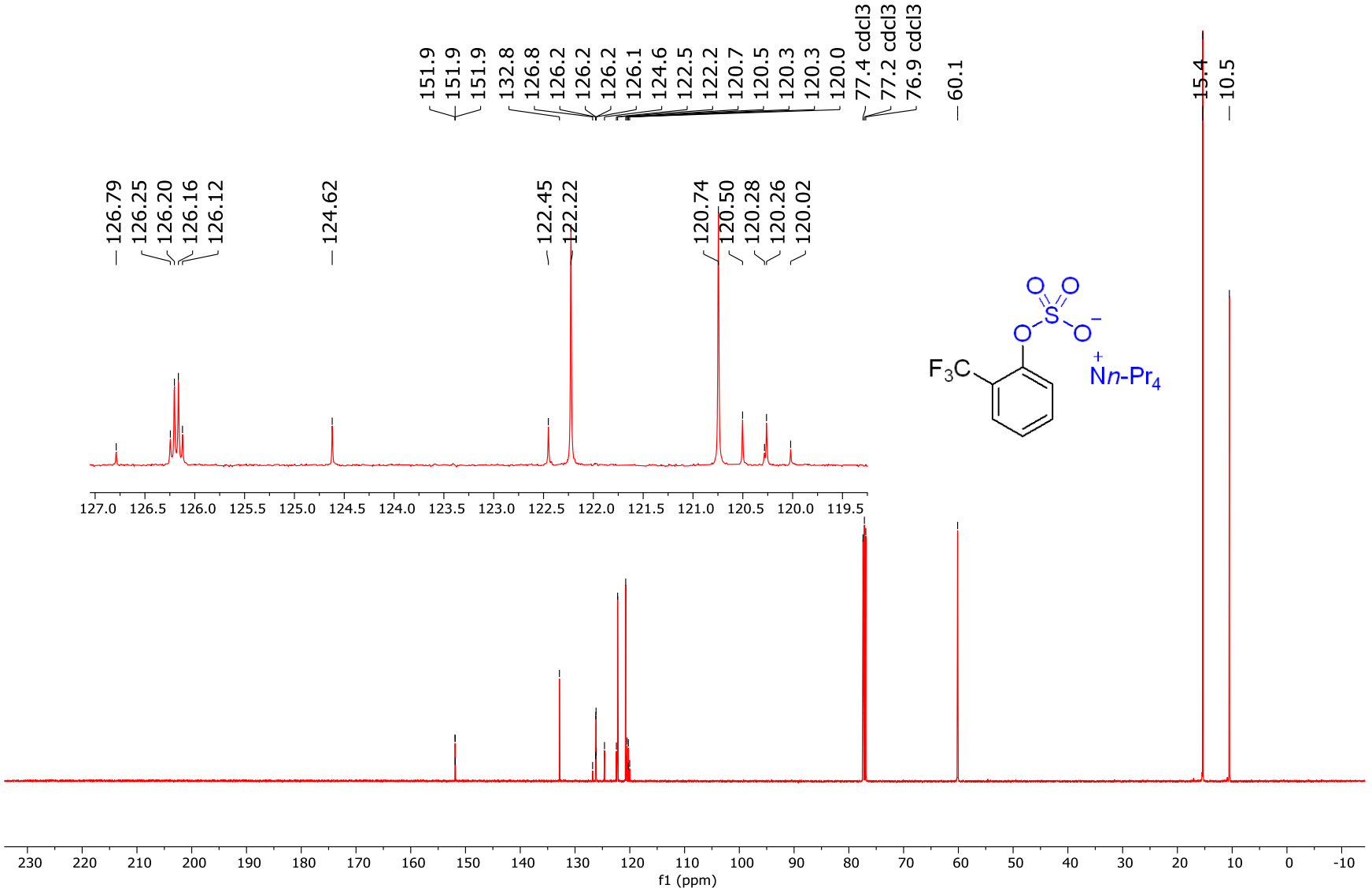
^{13}C NMR spectrum of tetrapropylammonium 2-methoxyphenylsulfate (3.1e) (126 MHz, $CDCl_3$)



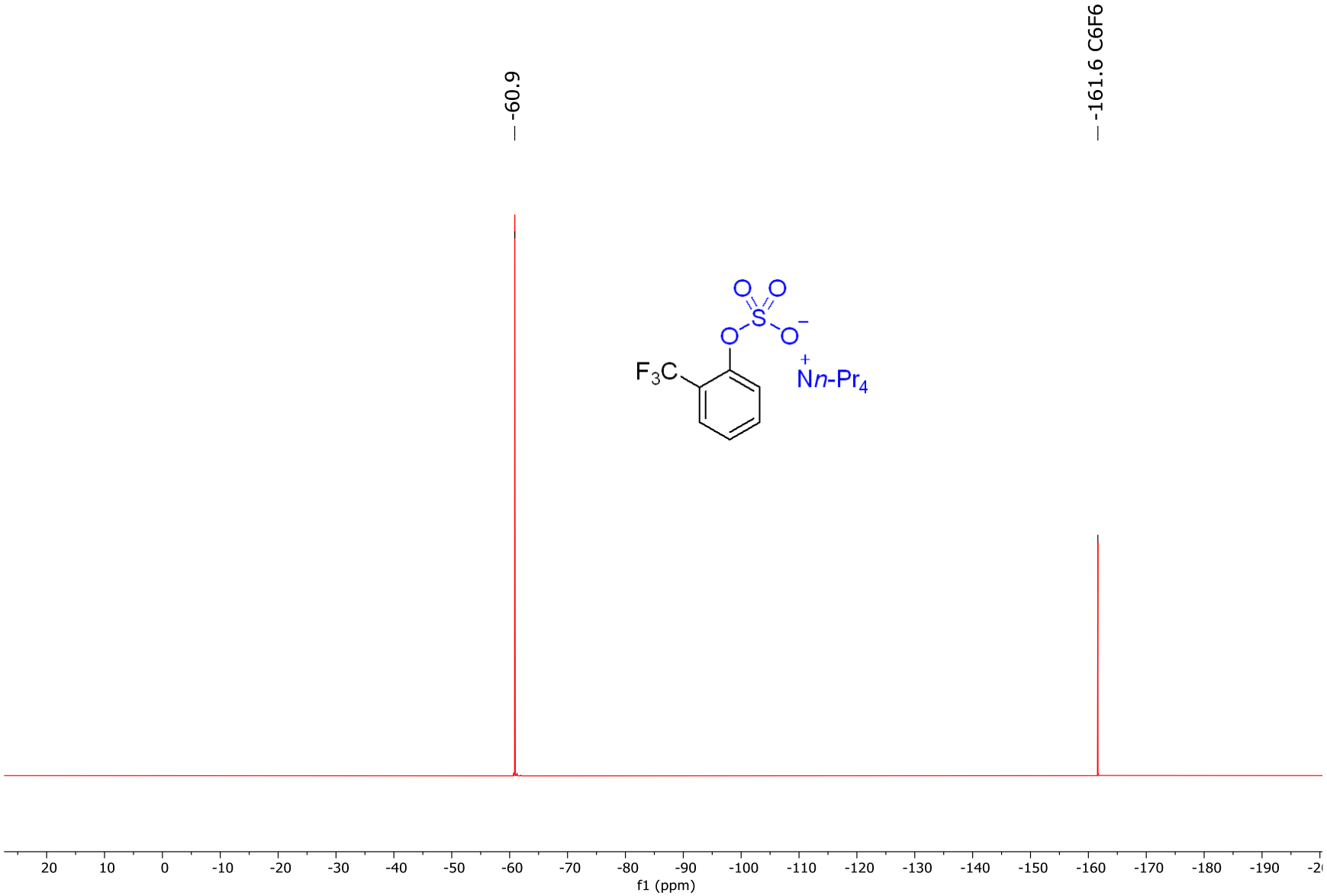
^{1}H NMR spectrum of tetrapropylammonium 2-(trifluoromethyl)phenylsulfate (3.1f) (500 MHz, $CDCl_3$)



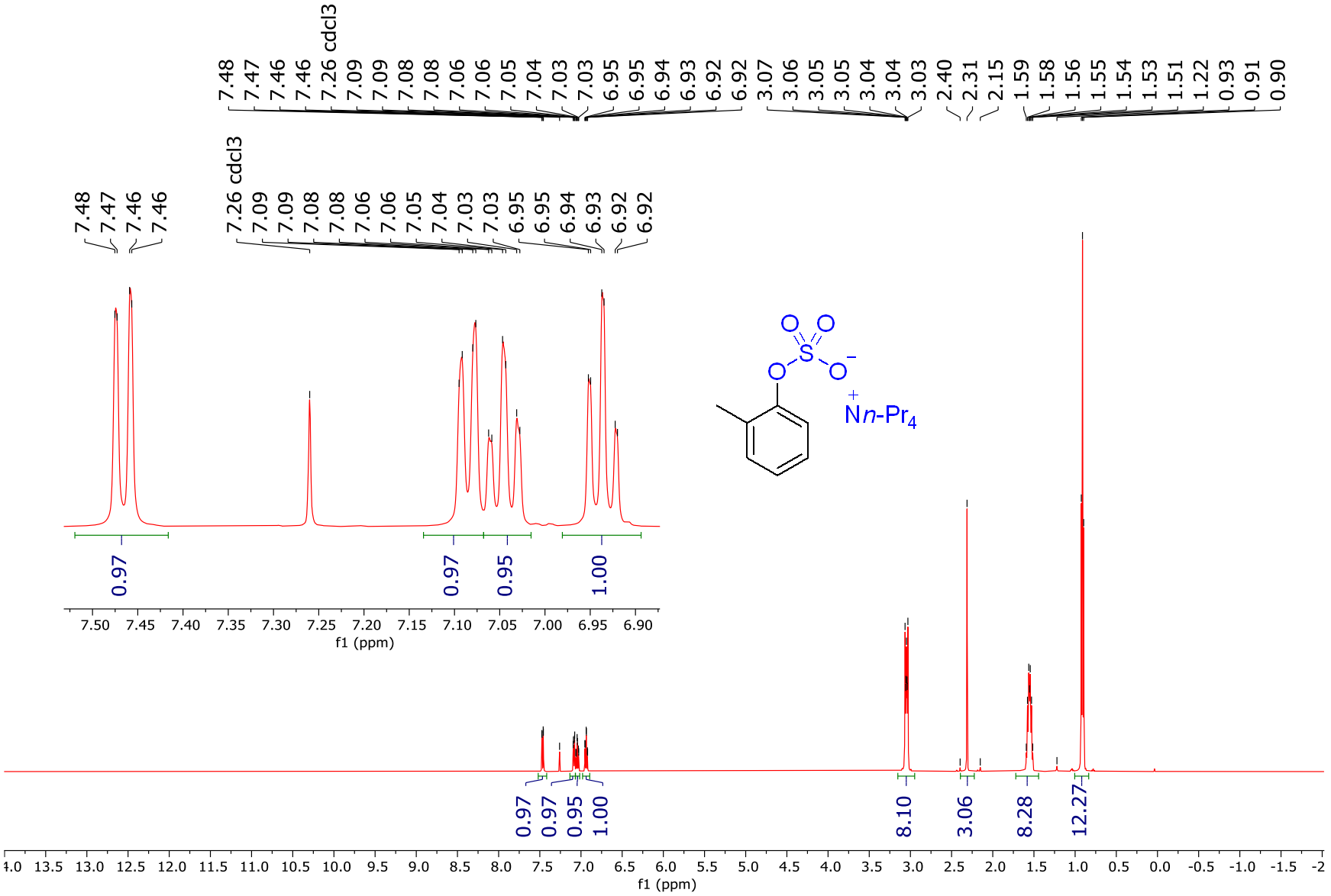
^{13}C NMR spectrum of tetrapropylammonium 2-(trifluoromethyl)phenylsulfate (3.1f) (126 MHz, $CDCl_3$)



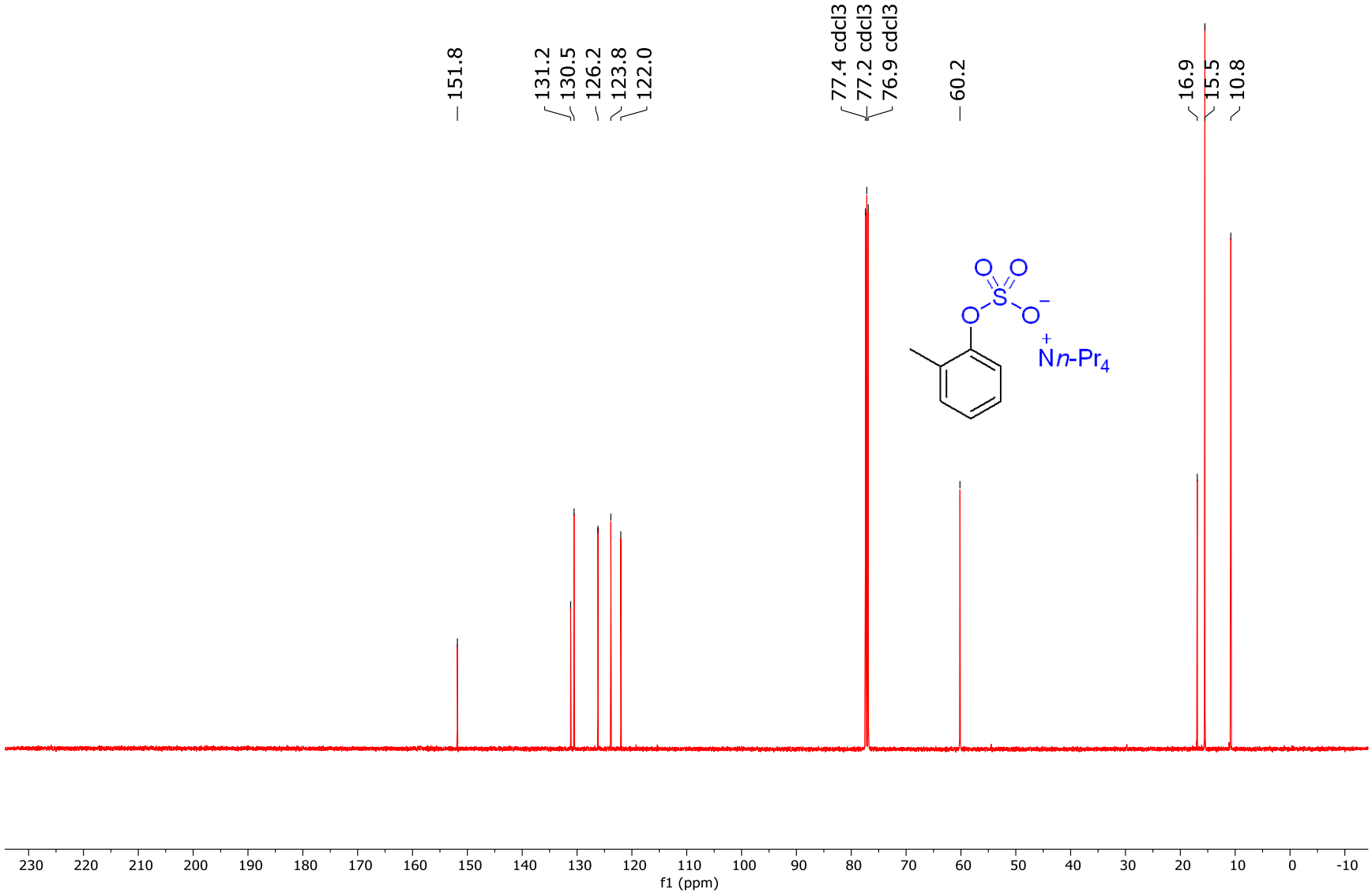
^{19}F NMR spectrum of tetrapropylammonium 2-(trifluoromethyl)phenylsulfate (3.1f) (470 MHz, $CDCl_3$)



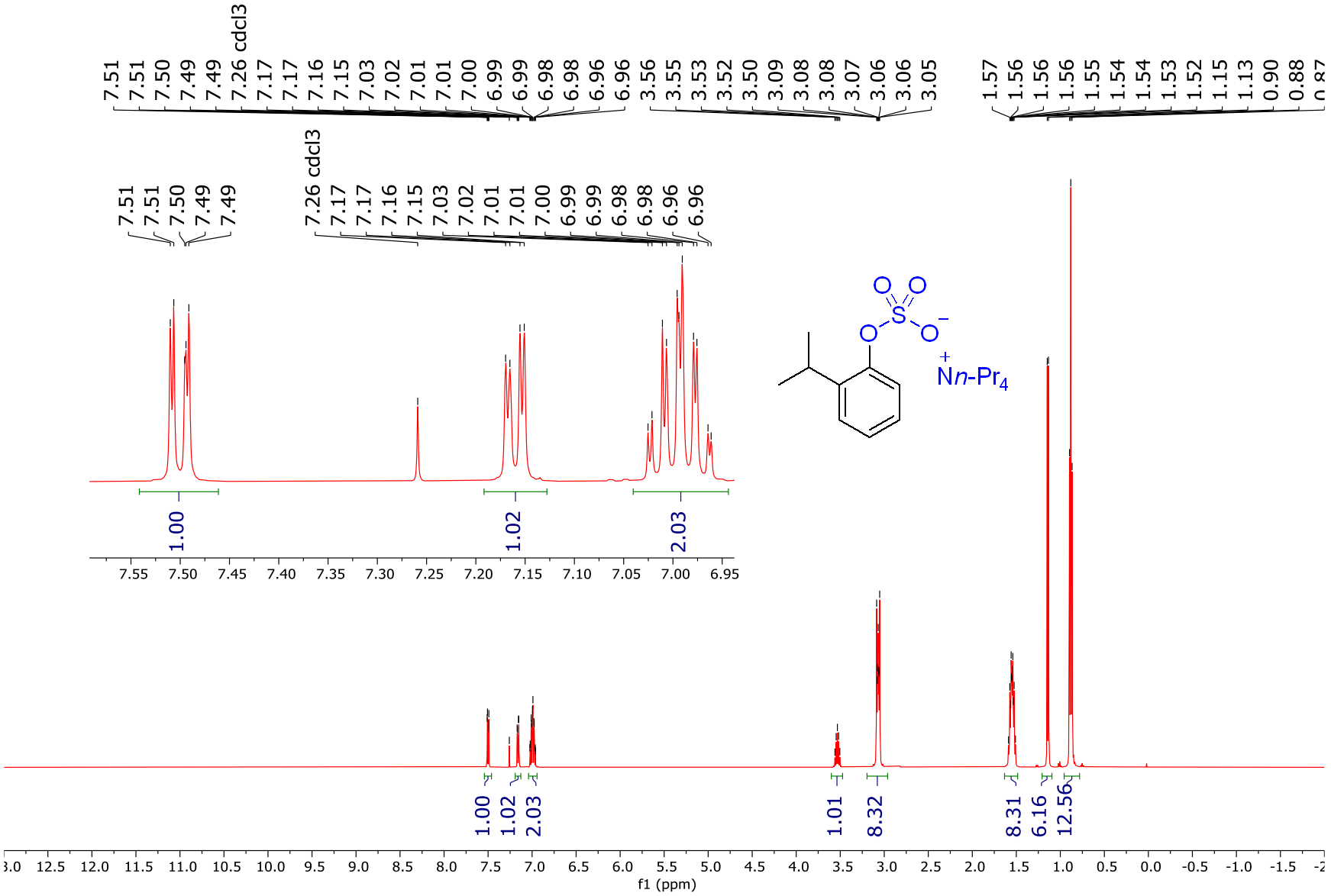
^{1}H NMR spectrum of tetrapropylammonium 2-methylphenylsulfate (3.1g) (500 MHz, $CDCl_3$)



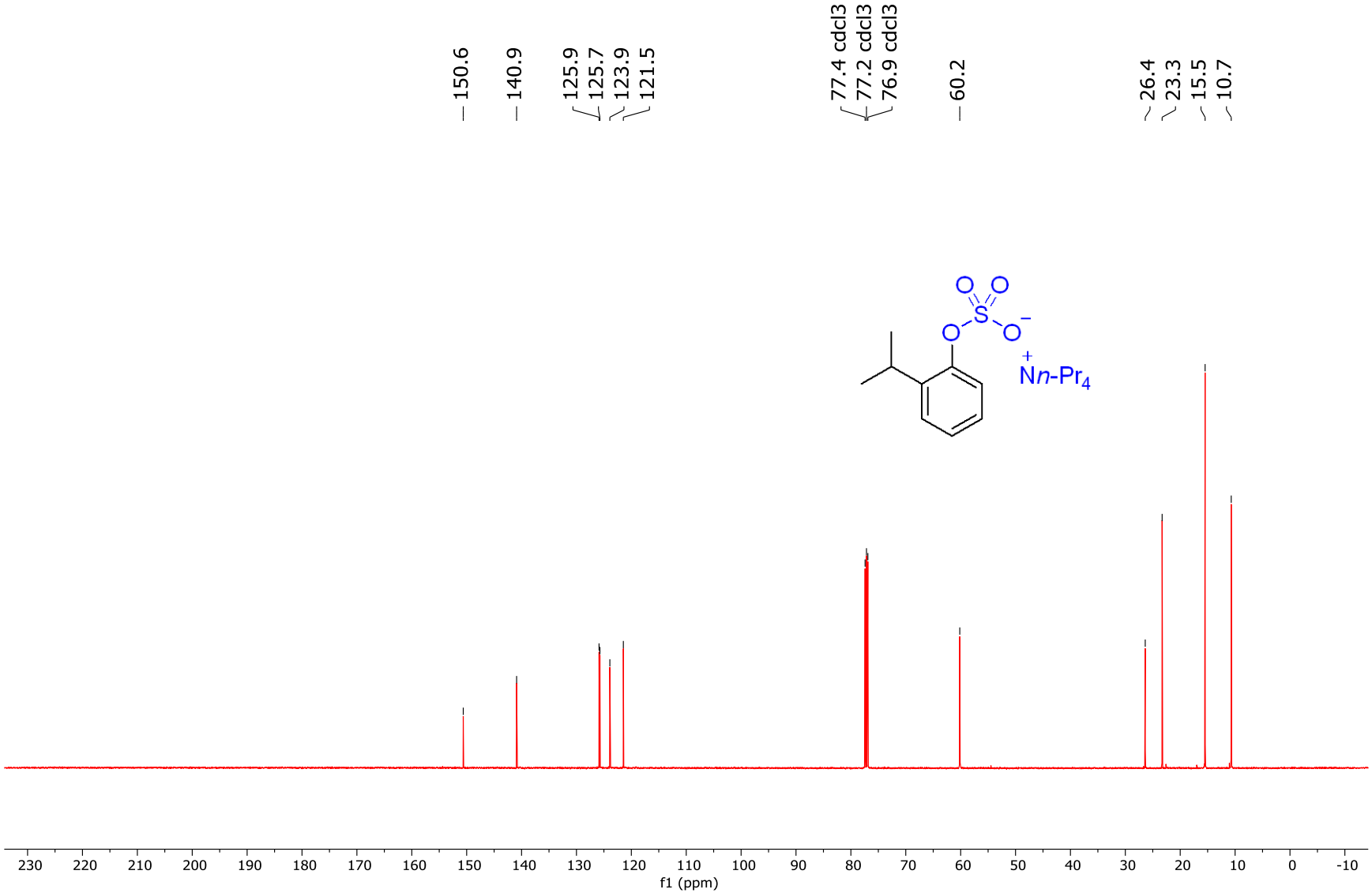
^{13}C NMR spectrum of tetrapropylammonium 2-methylphenylsulfate (3.1g) (126 MHz, $CDCl_3$)



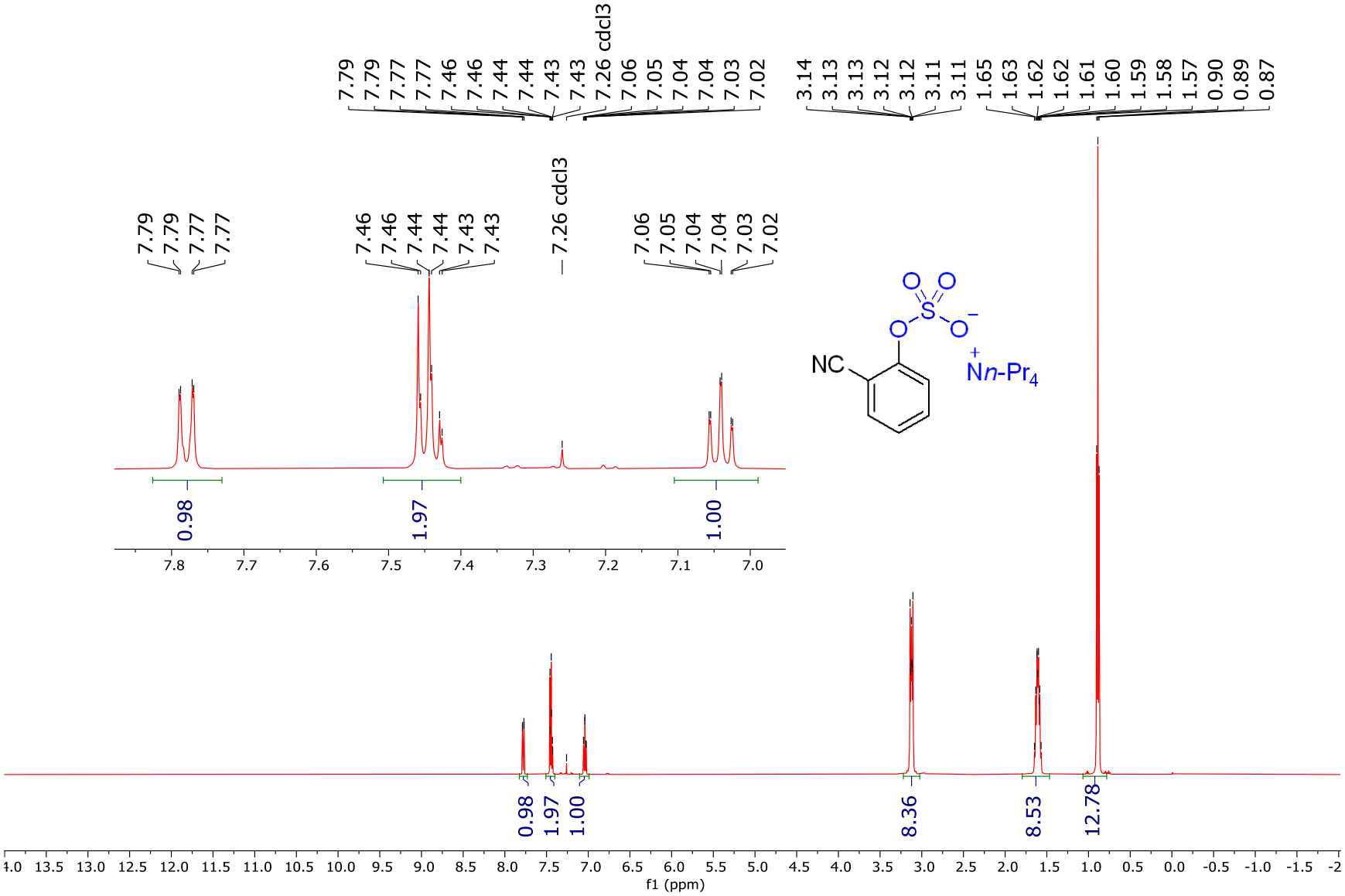
^{1}H NMR spectrum of tetrapropylammonium 2-isopropylphenylsulfate (3.1h) (500 MHz, $CDCl_3$)



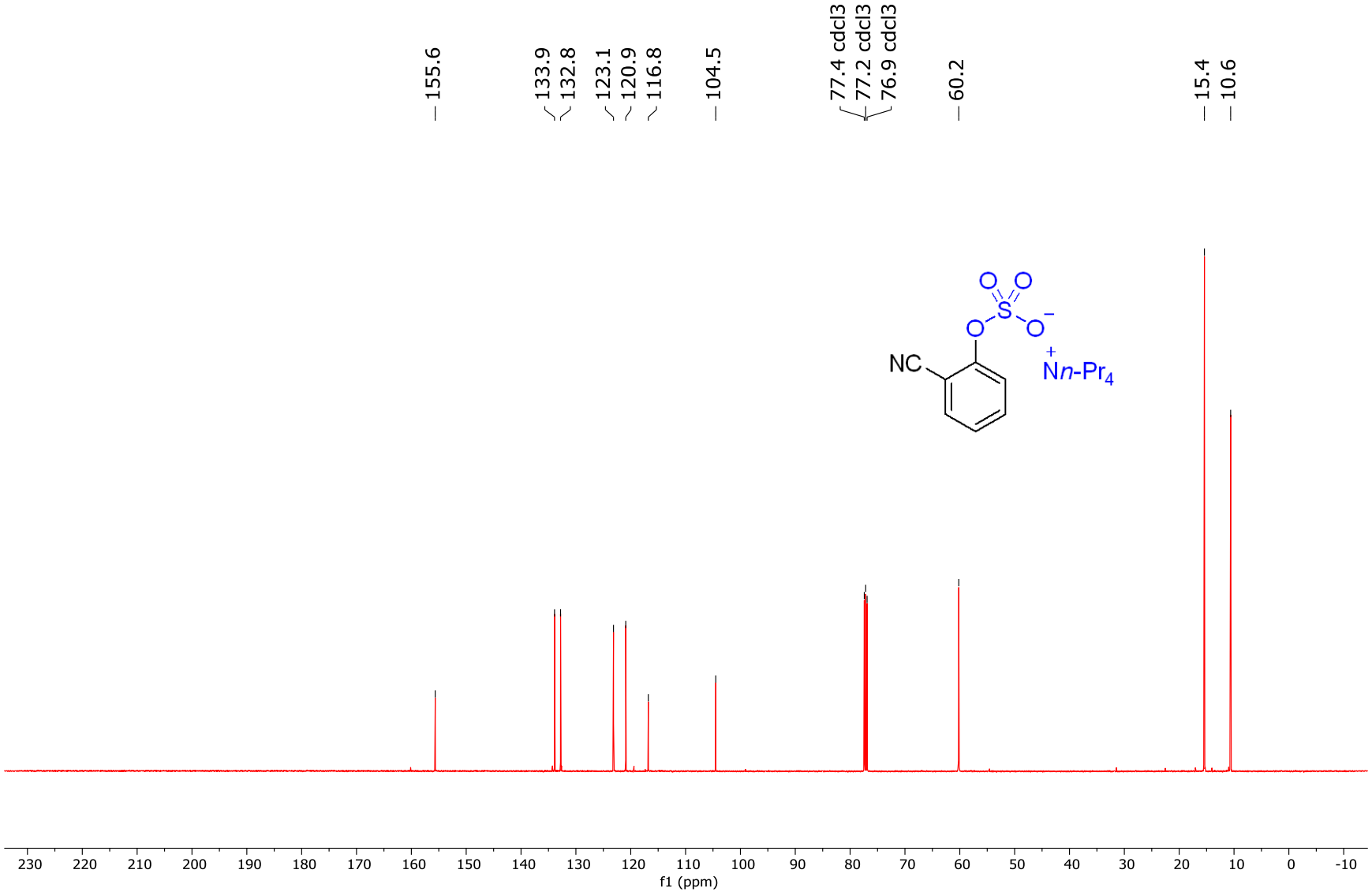
^{13}C NMR spectrum of tetrapropylammonium 2-isopropylphenylsulfate (3.1h) (126 MHz, $CDCl_3$)



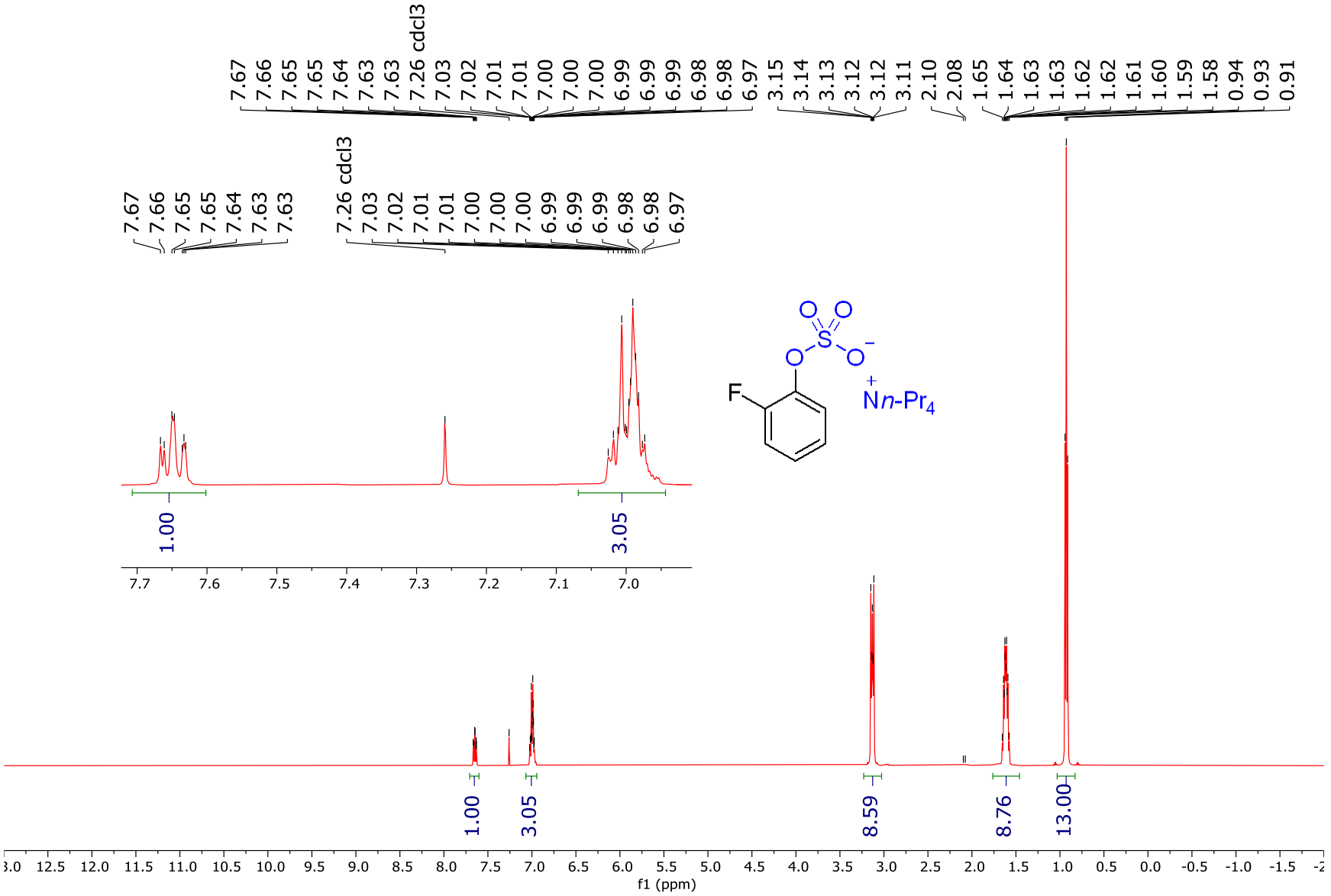
^{1}H NMR spectrum of tetrapropylammonium 2-cyanophenylsulfate (3.1i) (500 MHz, $CDCl_3$)



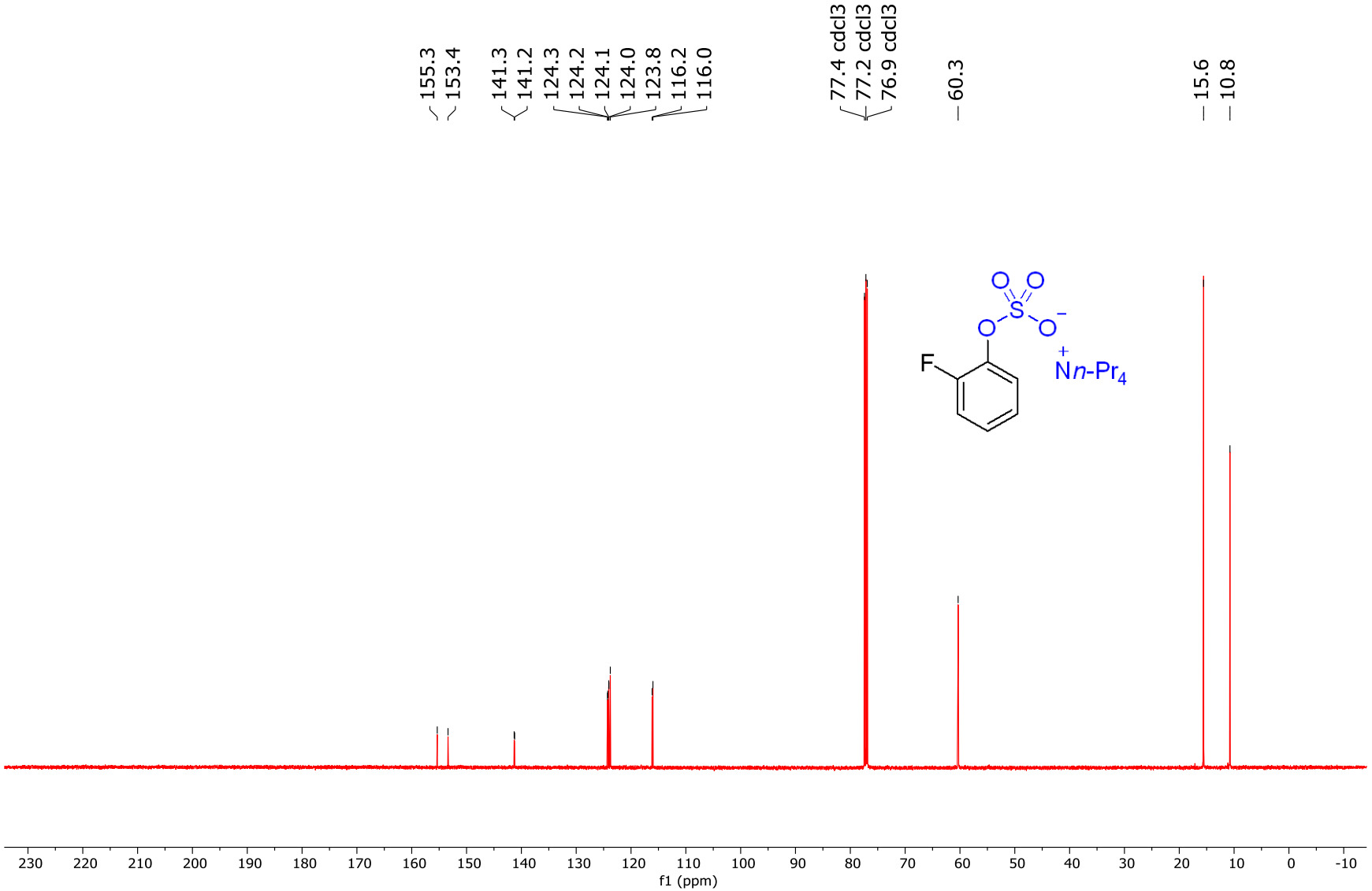
^{13}C NMR spectrum of tetrapropylammonium 2-cyanophenylsulfate (3.1i) (126 MHz, $CDCl_3$)



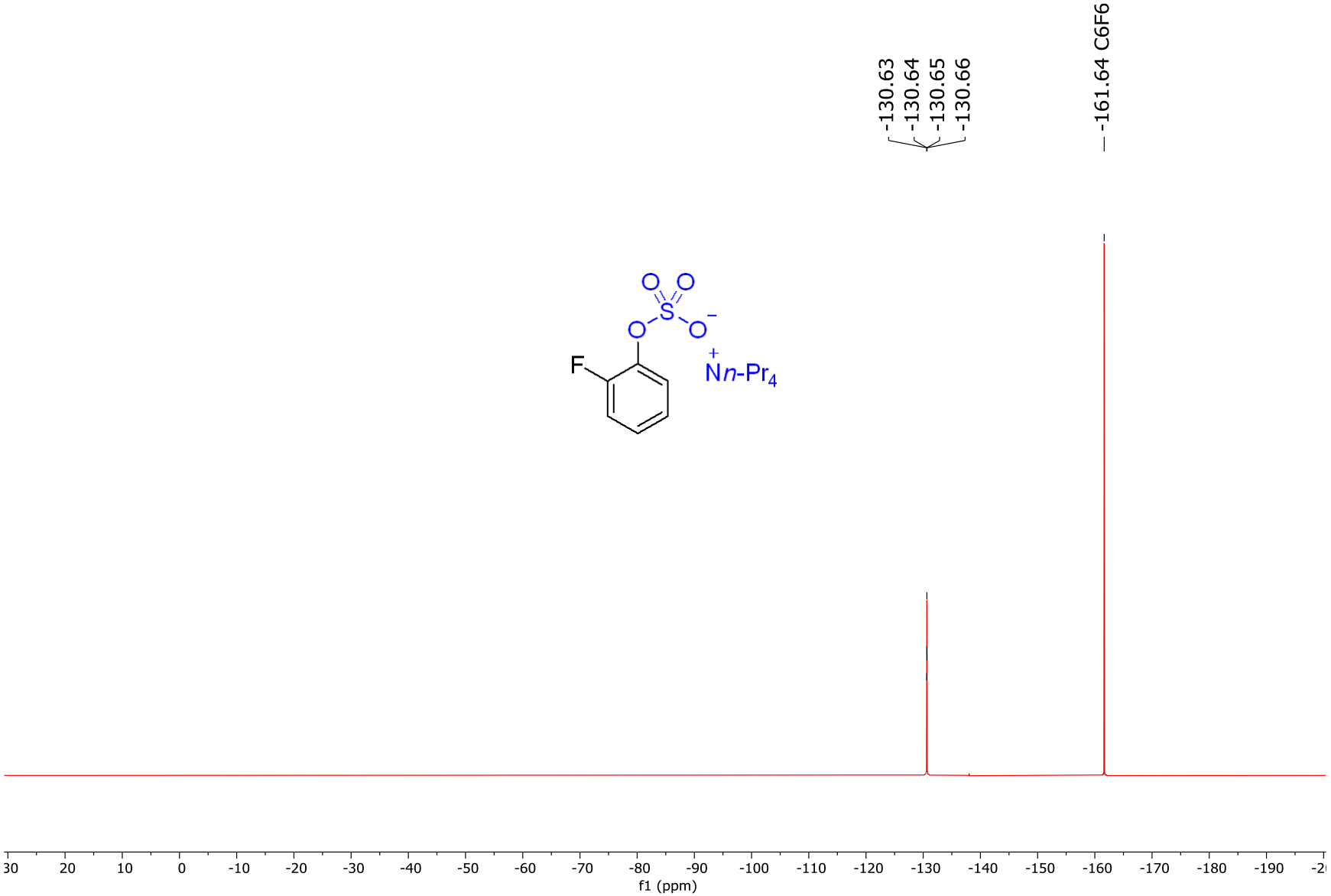
^{1}H NMR spectrum of tetrapropylammonium 2-fluorophenylsulfate (3.1j) (500 MHz, $CDCl_3$)



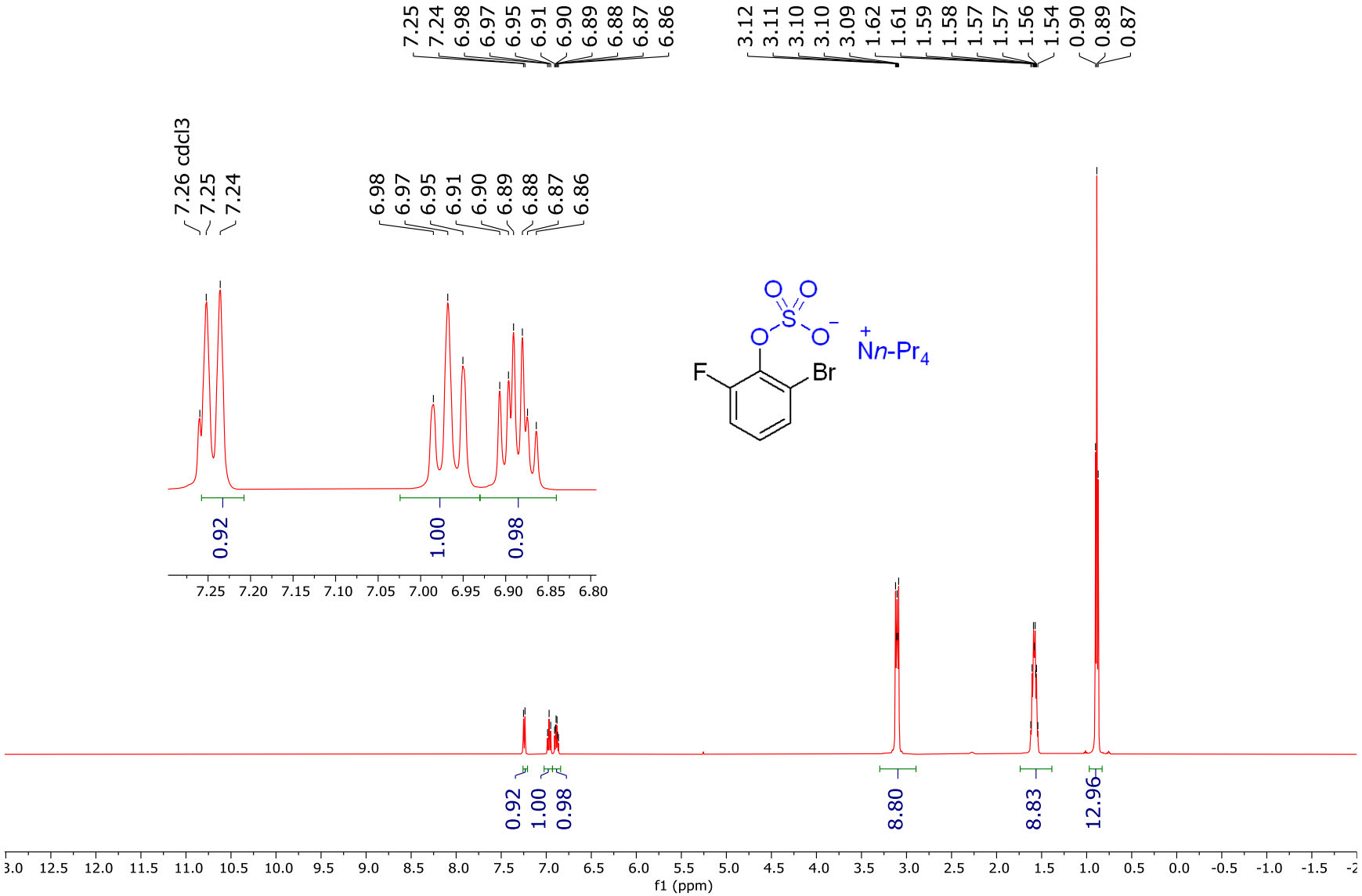
^{13}C NMR spectrum of tetrapropylammonium 2-fluorophenylsulfate (3.1j) (126 MHz, $CDCl_3$)



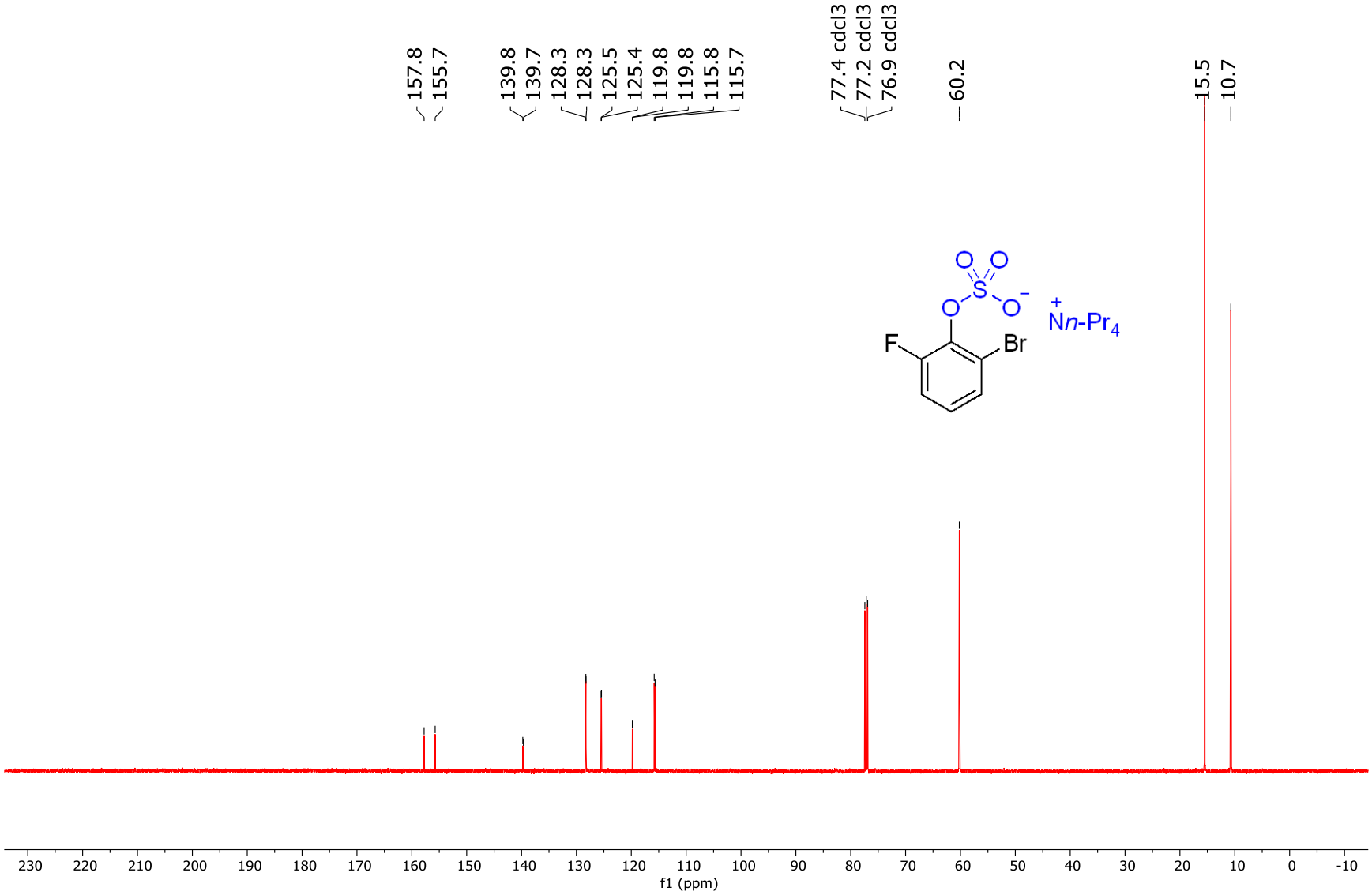
^{19}F NMR spectrum of tetrapropylammonium 2-fluorophenylsulfate (3.1j) (470 MHz, $CDCl_3$)



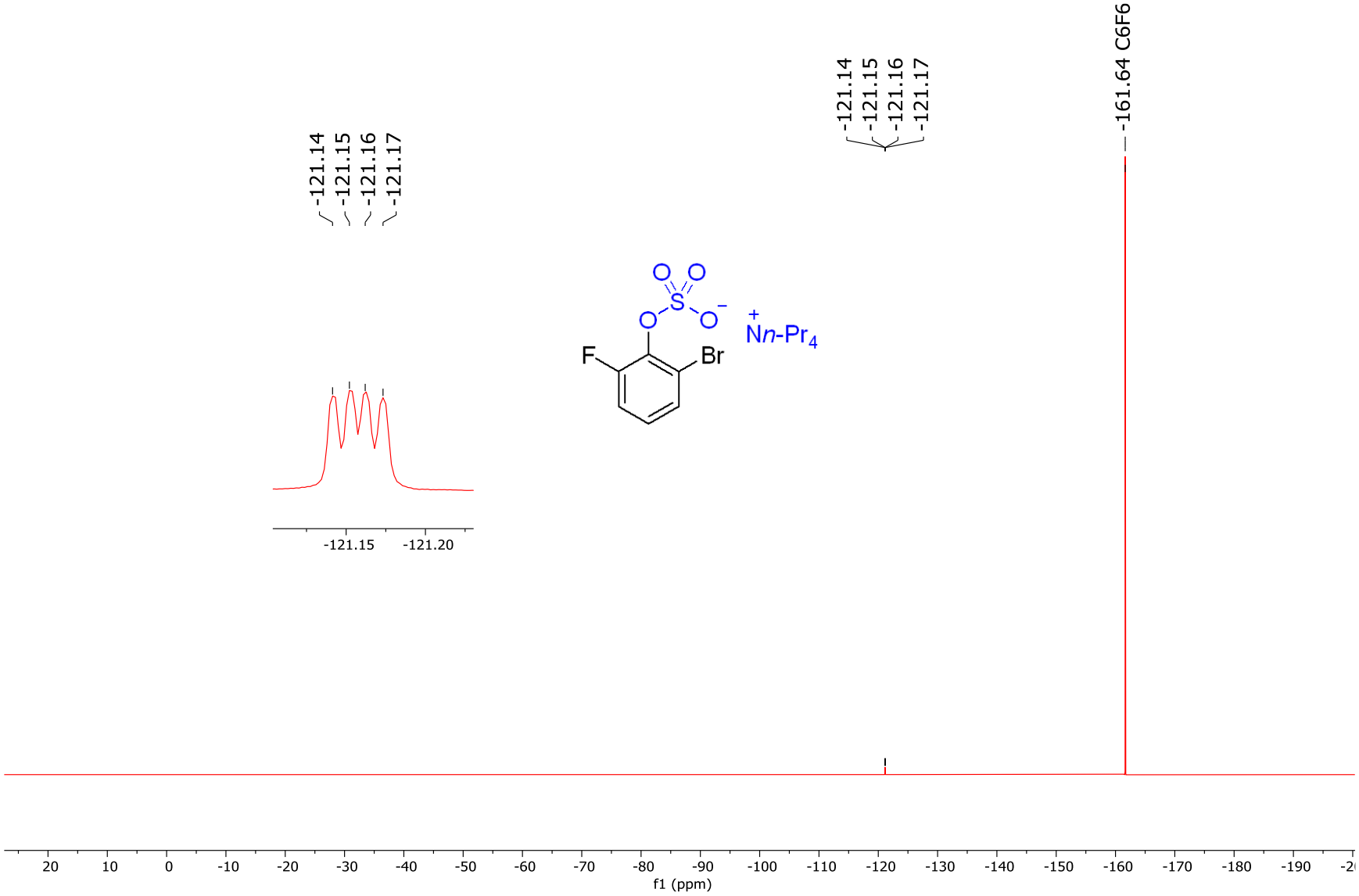
^{1}H NMR spectrum of tetrapropylammonium 2-bromo-6-fluorophenylsulfate (3.1k) (500 MHz, $CDCl_3$)



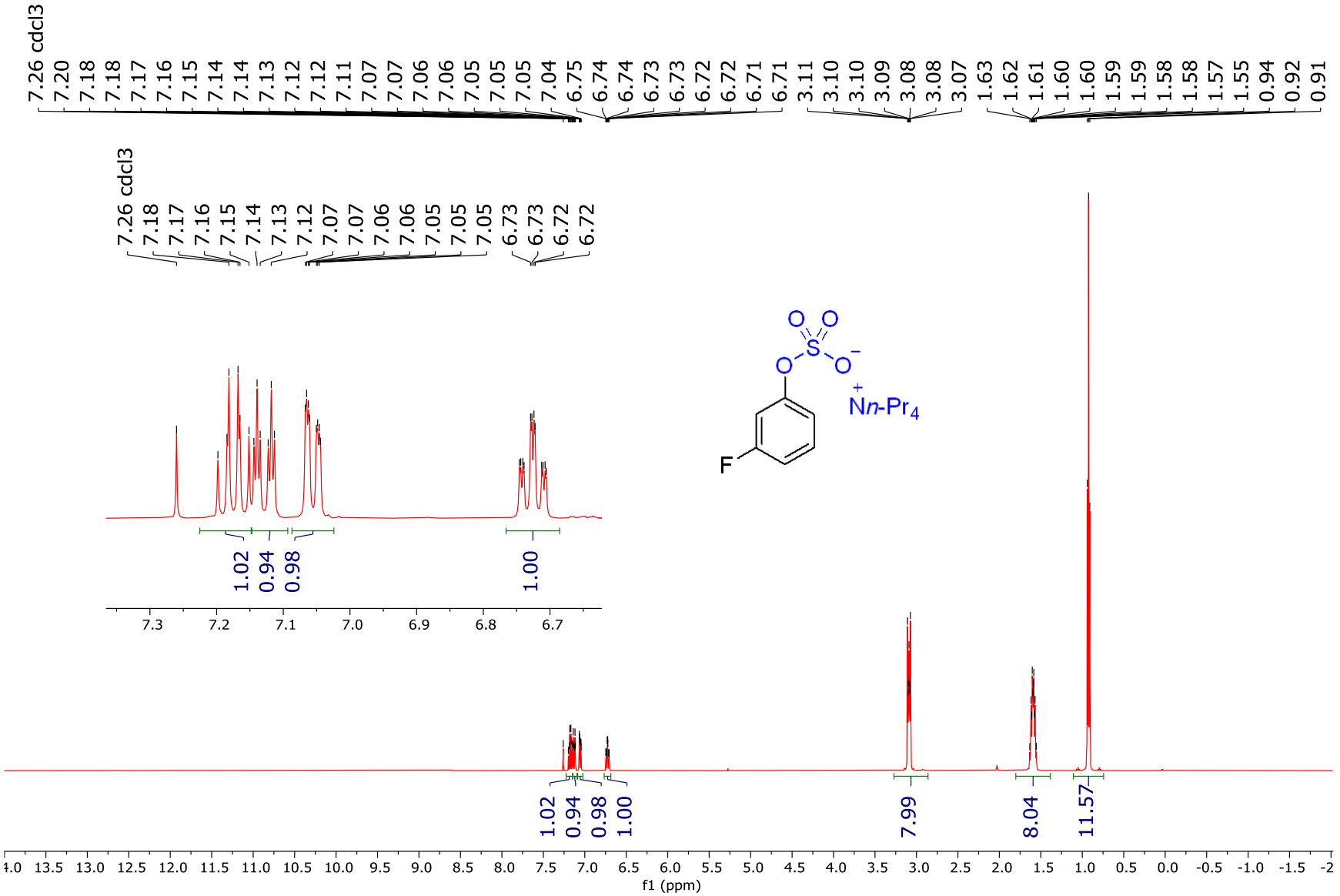
^{13}C NMR spectrum of tetrapropylammonium 2-bromo-6-fluorophenylsulfate (3.1k) (126 MHz, $CDCl_3$)



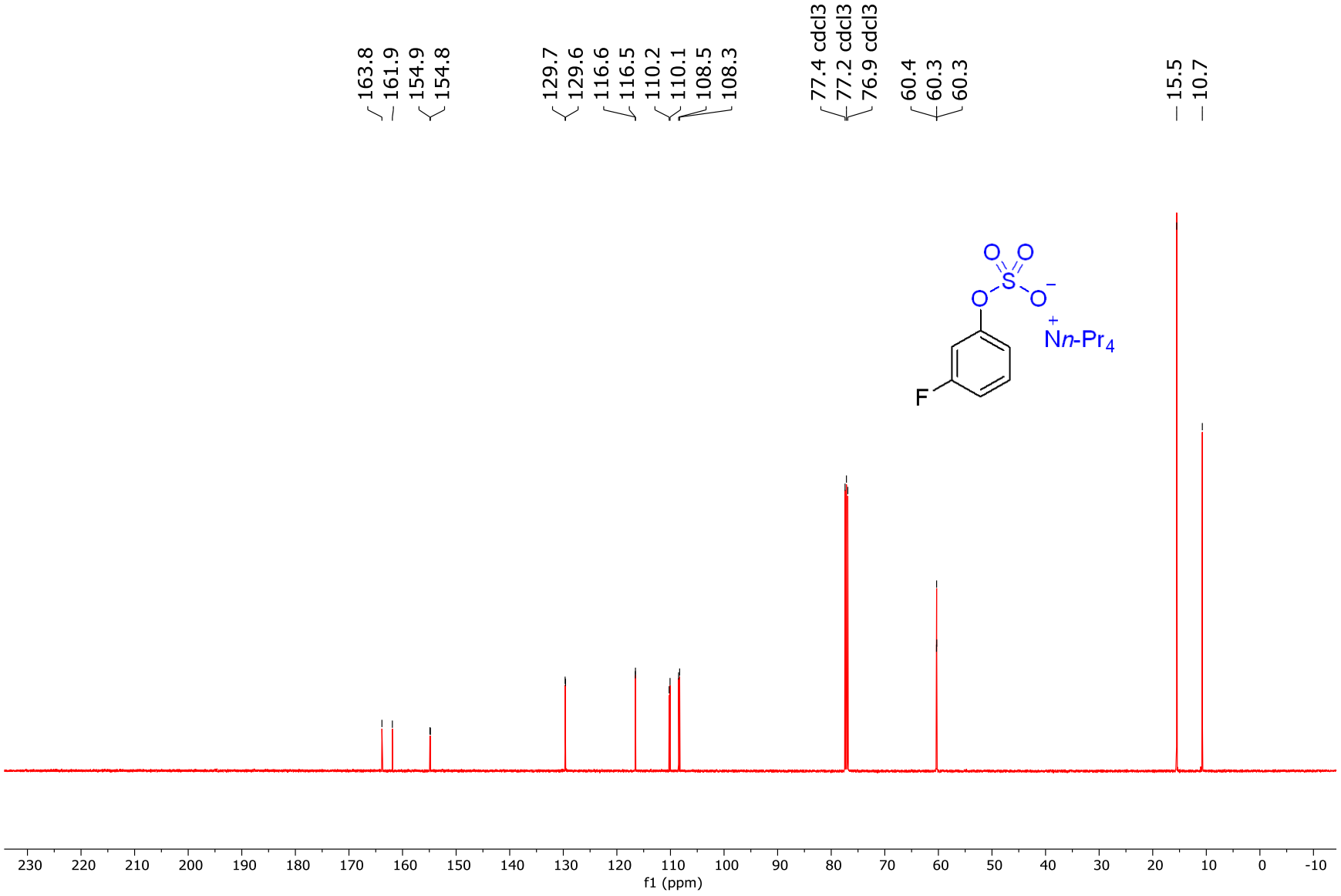
^{19}F NMR spectrum of 2-bromo-6-fluorophenylsulfate (3.1k) (470 MHz, $CDCl_3$)



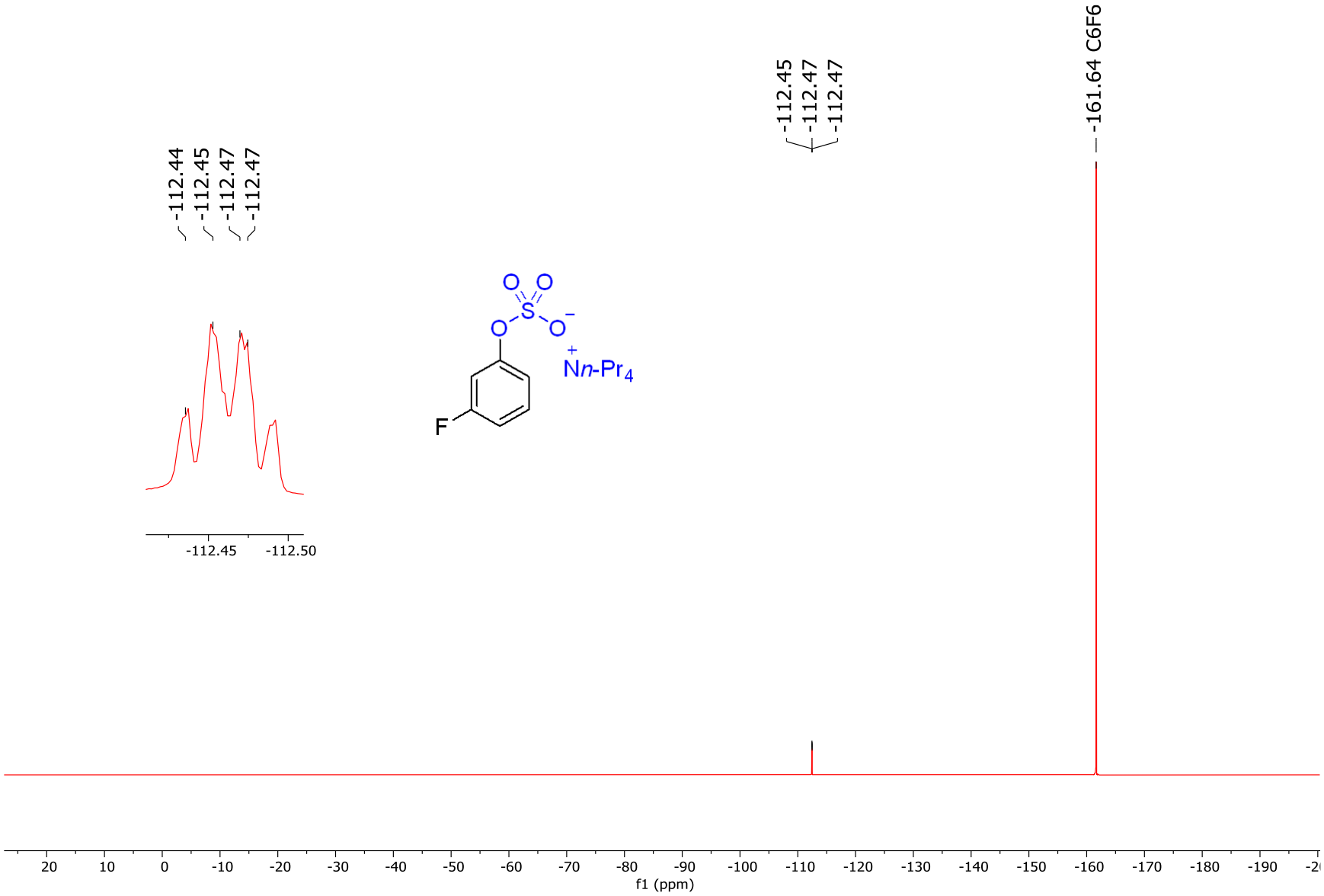
^{1}H NMR spectrum of tetrapropylammonium 3-fluorophenylsulfate (3.1l) (500 MHz, $CDCl_3$)



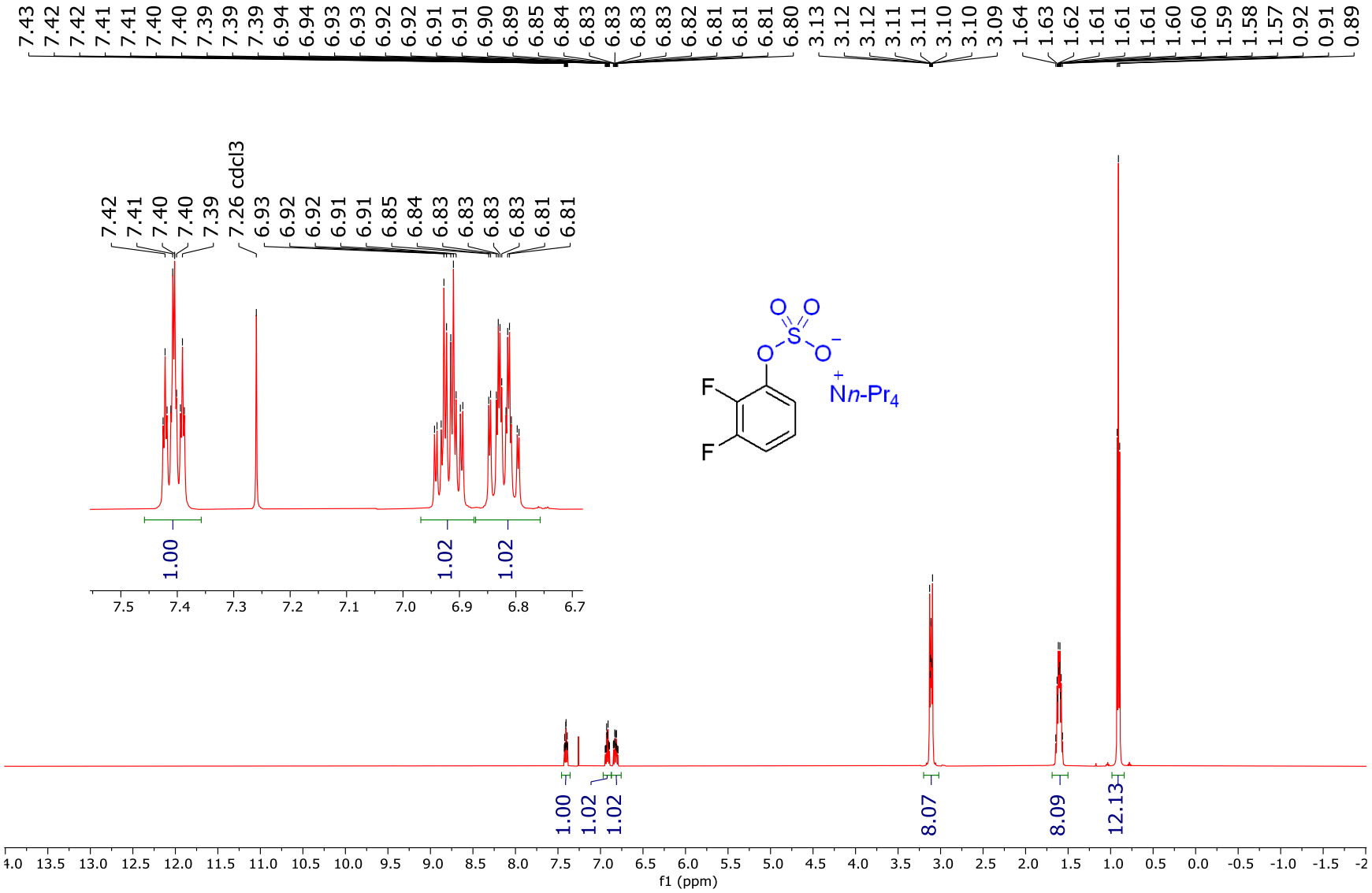
^{13}C NMR spectrum of tetrapropylammonium 3-fluorophenylsulfate (3.1l) (126 MHz, $CDCl_3$)



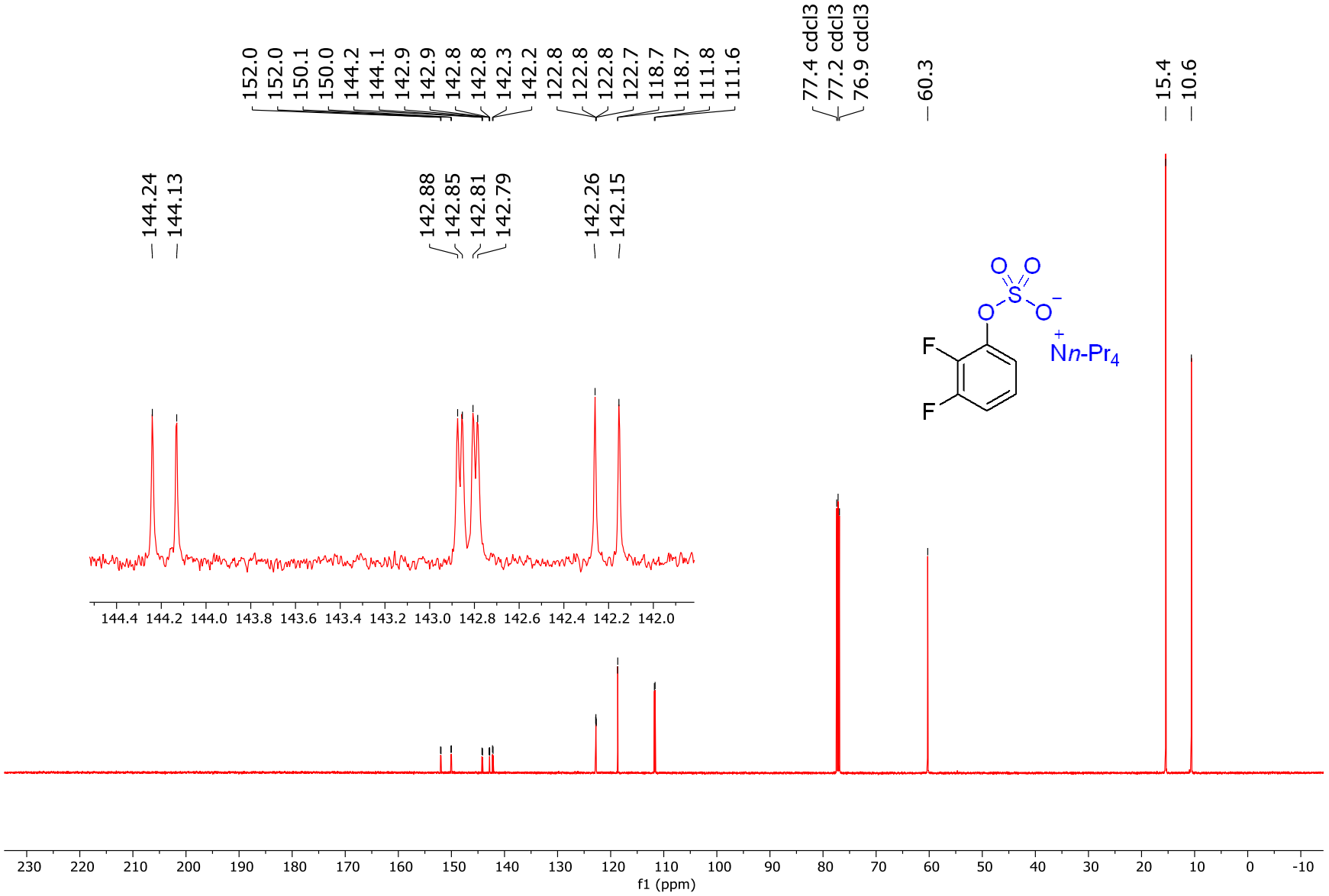
^{19}F NMR spectrum of tetrapropylammonium 3-fluorophenylsulfate (3.1l) (470 MHz, $CDCl_3$)



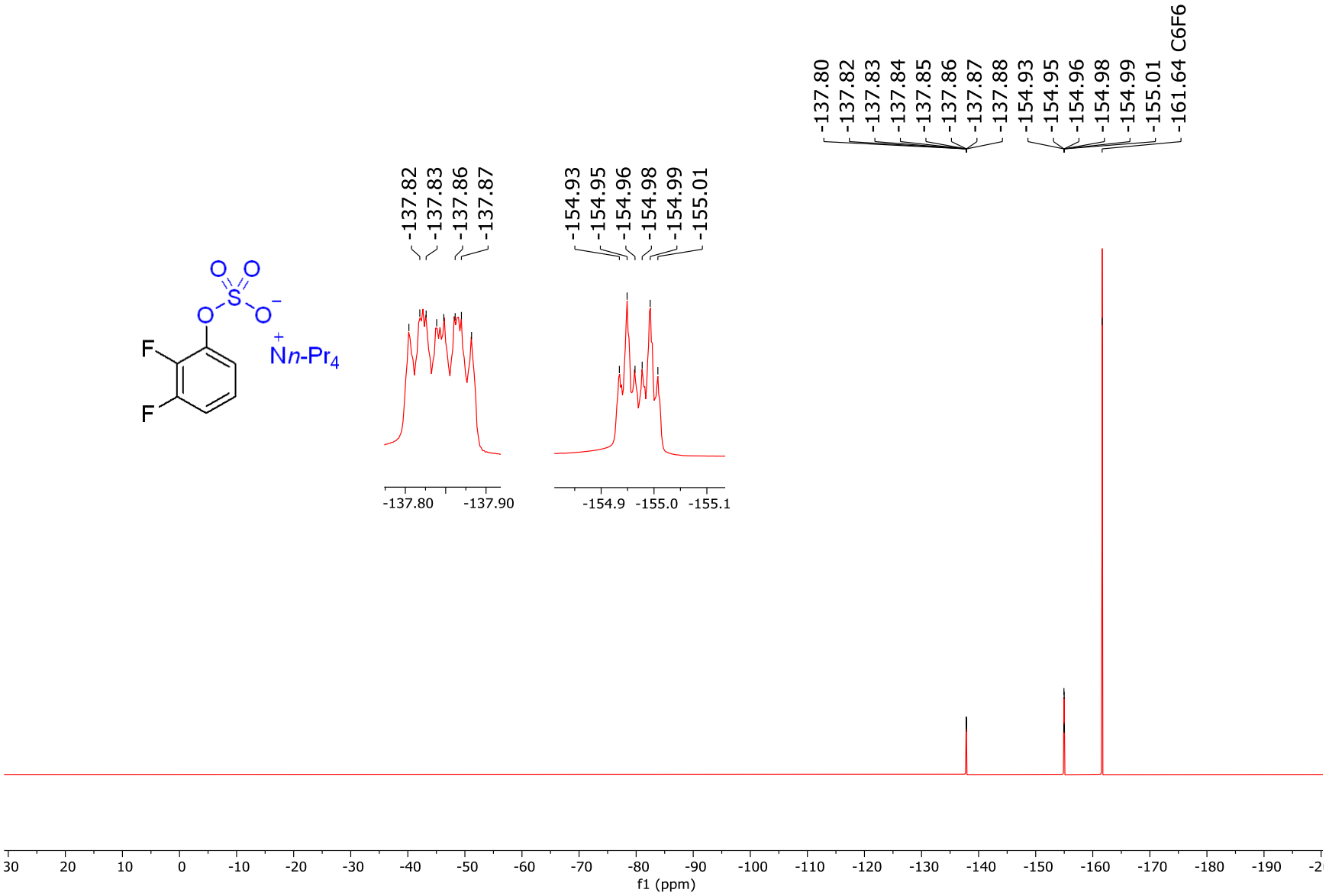
^{1}H NMR spectrum of tetrapropylammonium 2,3-difluorophenylsulfate (3.1m) (500 MHz, $CDCl_3$)



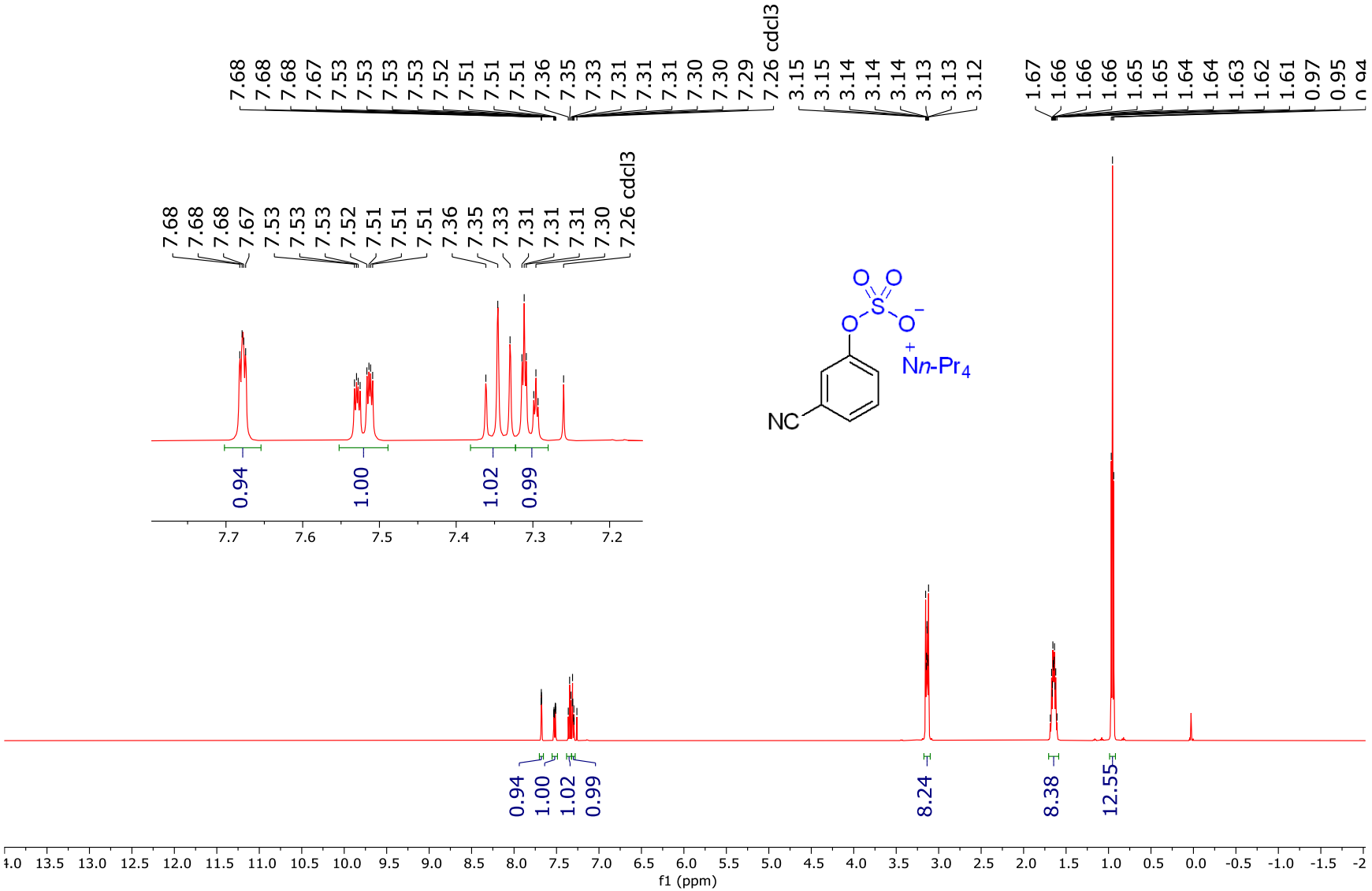
^{13}C NMR spectrum of tetrapropylammonium 2,3-difluorophenylsulfate (3.1m) (126 MHz, $CDCl_3$)



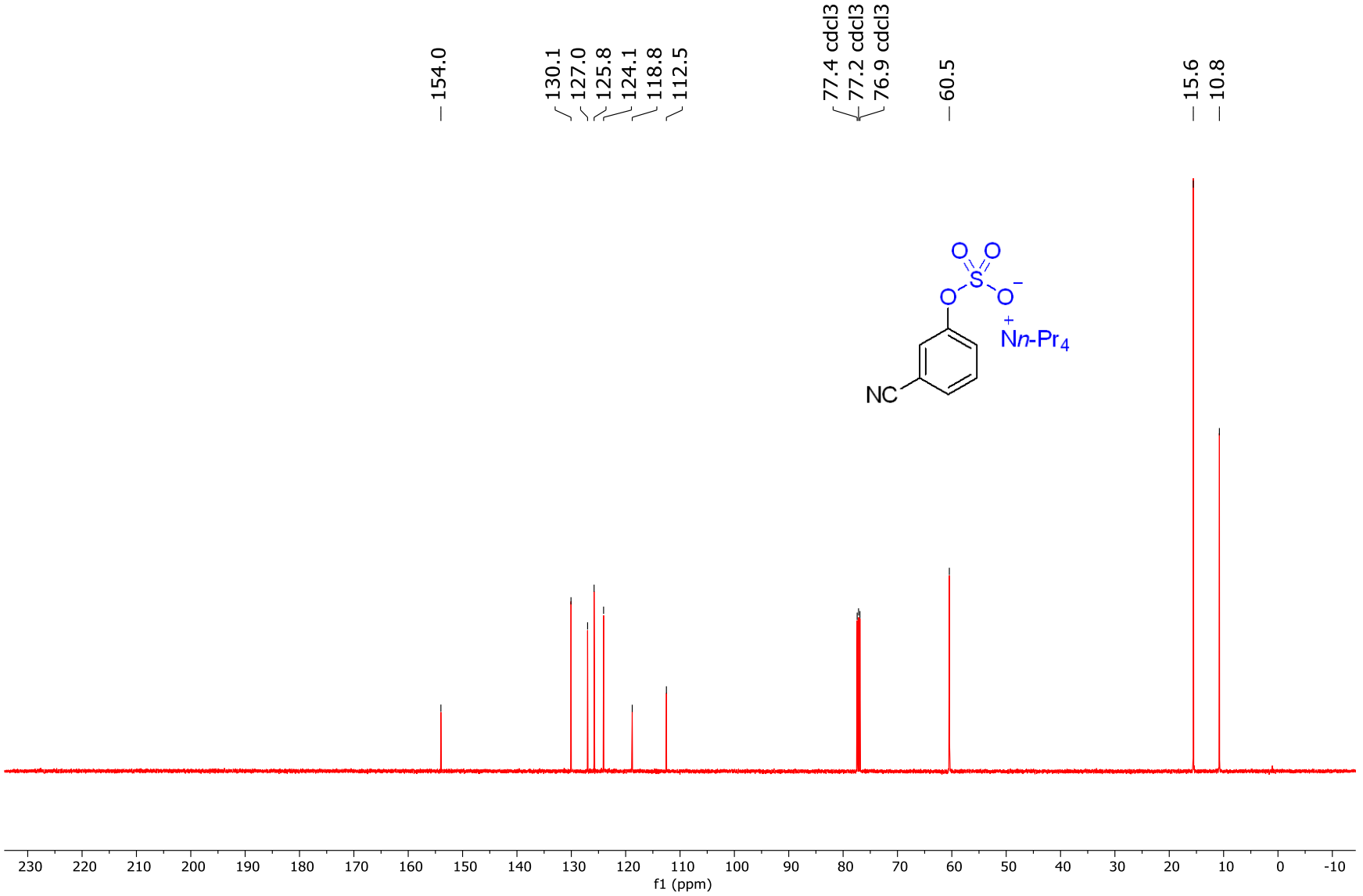
^{19}F NMR spectrum of tetrapropylammonium 2,3-difluorophenylsulfate (3.1m) (470 MHz, $CDCl_3$)



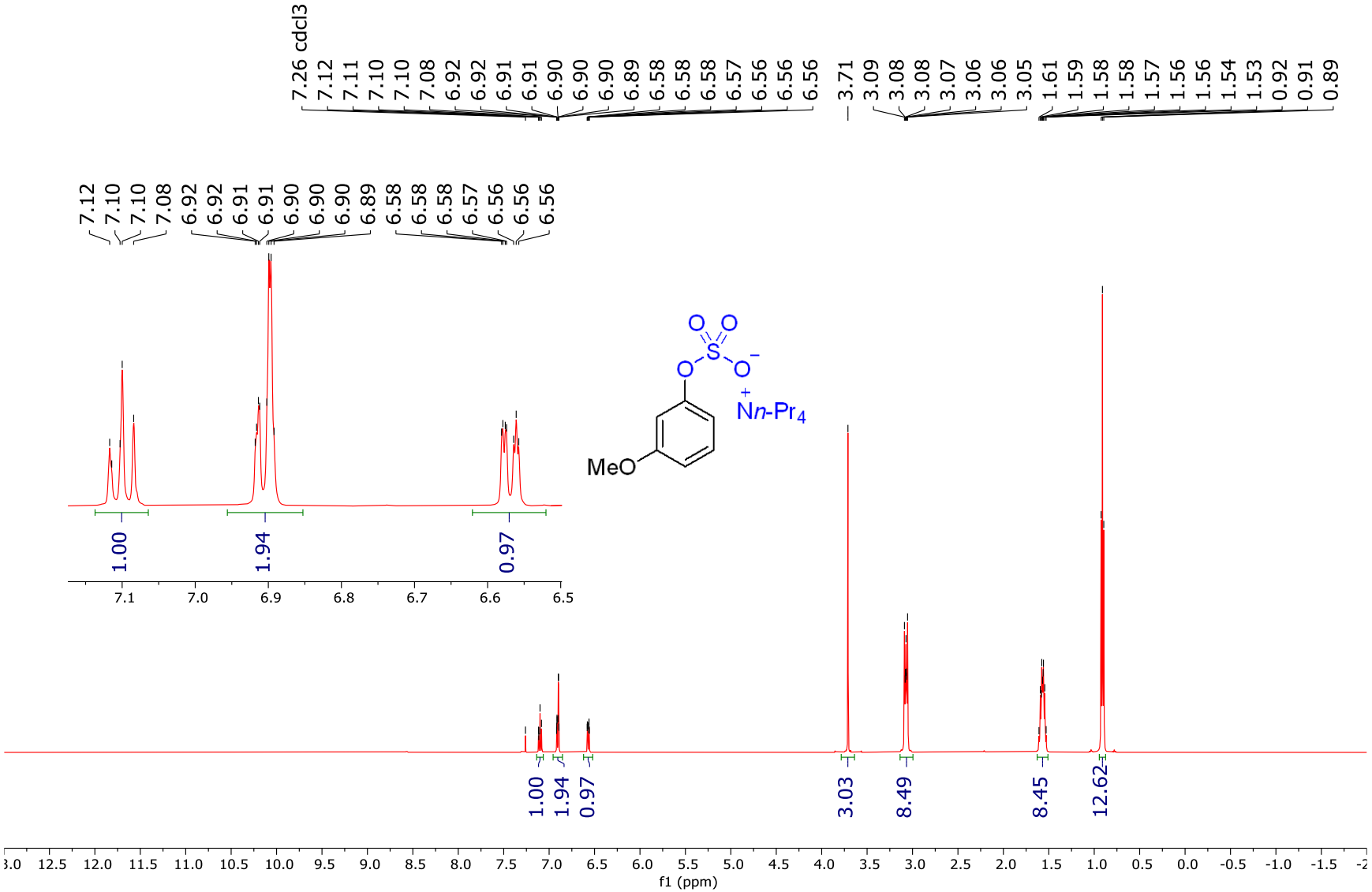
^{1}H NMR spectrum of tetrapropylammonium 3-cyanophenylsulfate (3.1n) (500 MHz, $CDCl_3$)



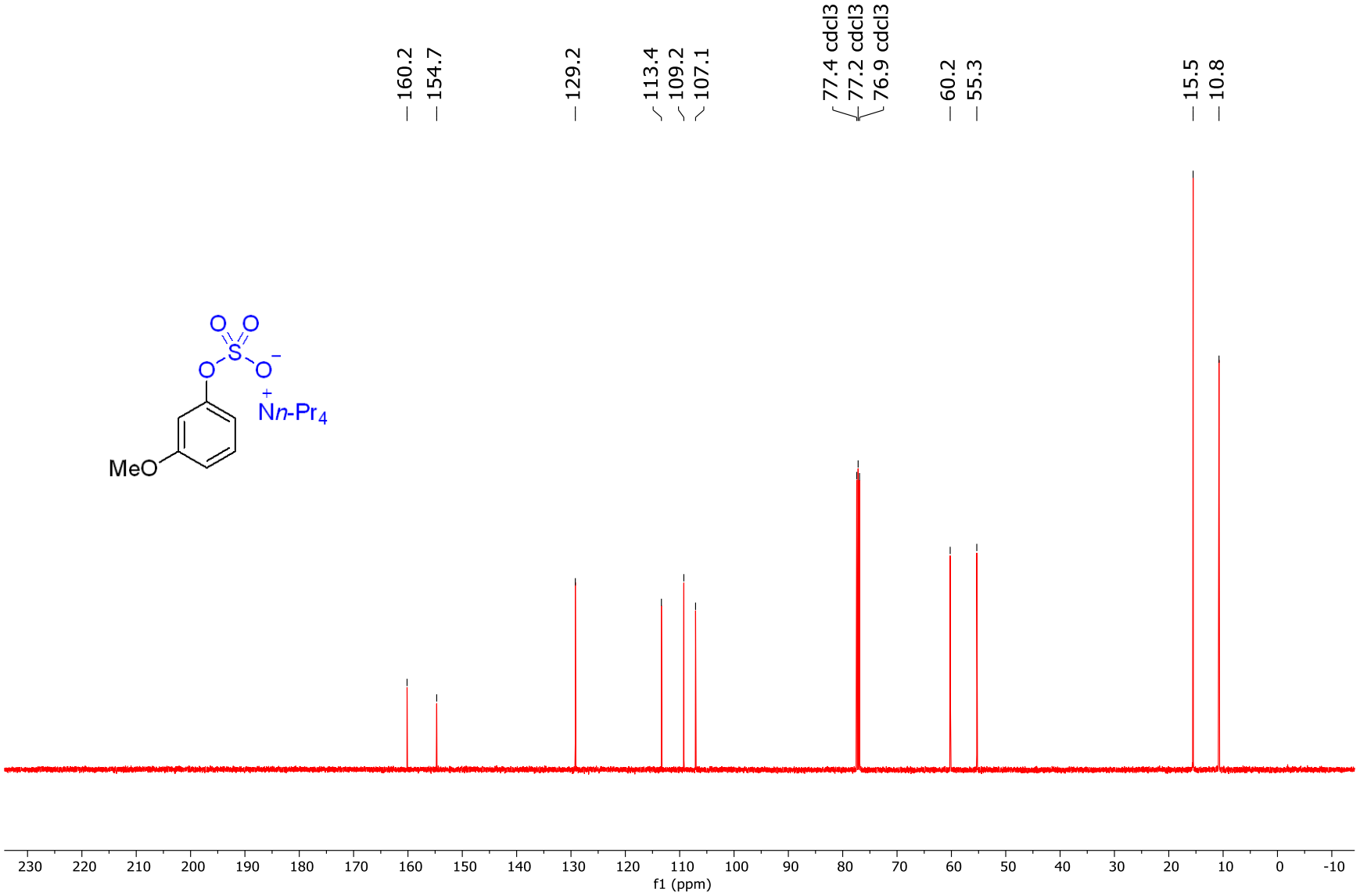
^{13}C NMR spectrum of tetrapropylammonium 3-cyanophenylsulfate (3.1n) (126 MHz, $CDCl_3$)



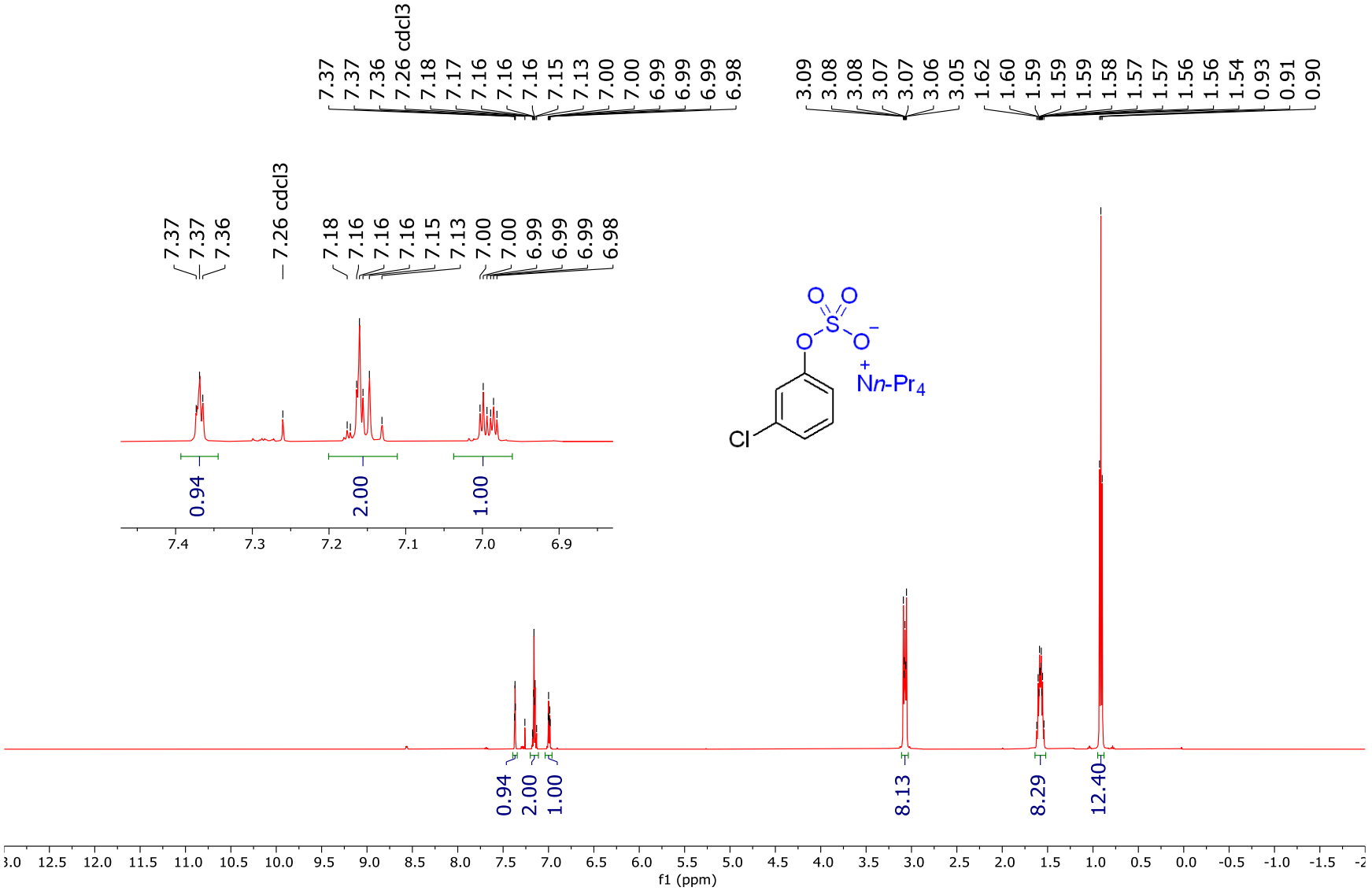
^{1}H NMR spectrum of tetrapropylammonium 3-methoxyphenylsulfate (3.1o) (500 MHz, $CDCl_3$)



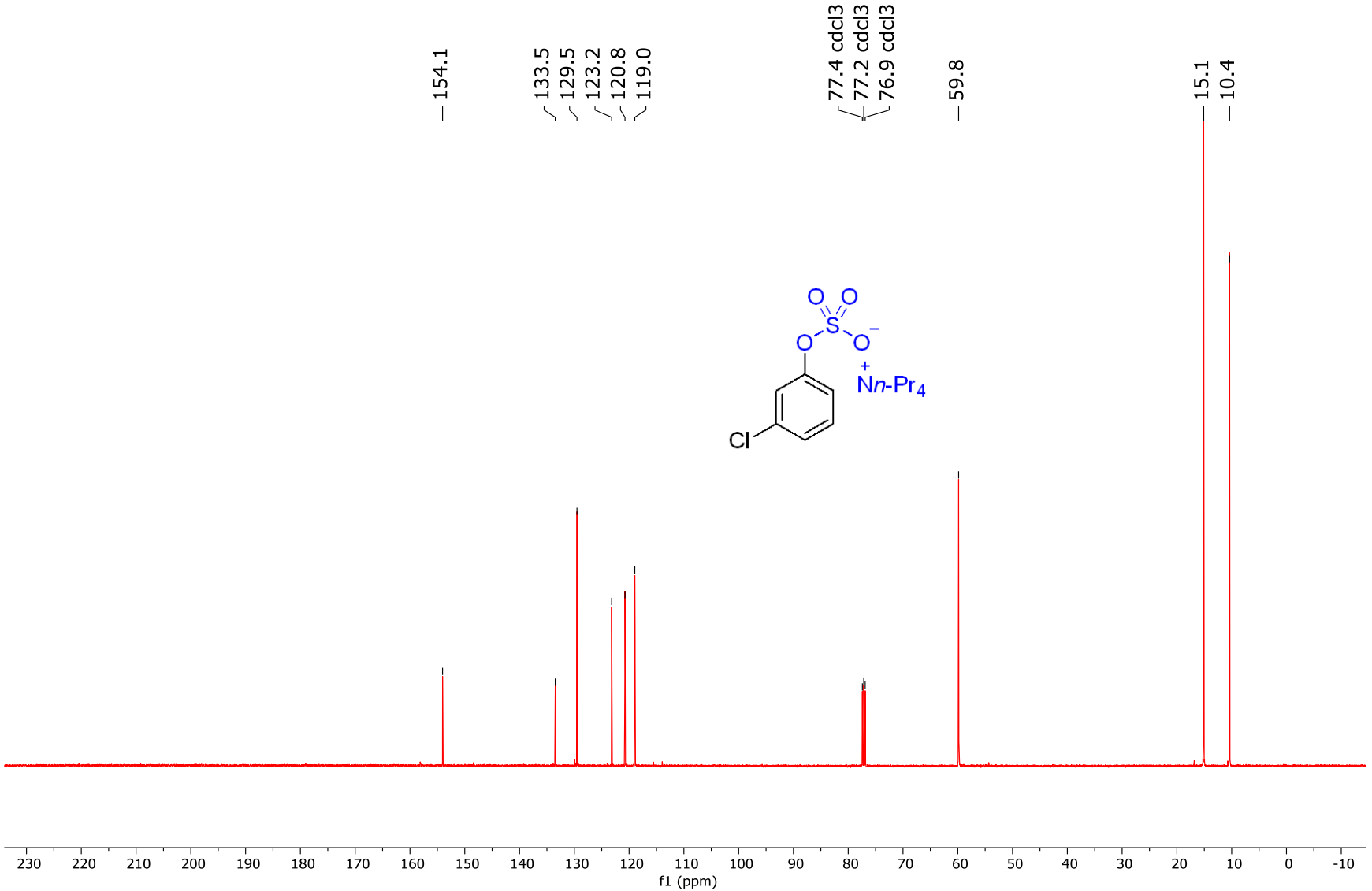
^{13}C NMR spectrum of tetrapropylammonium 3-methoxyphenylsulfate (3.1o) (126 MHz, $CDCl_3$)



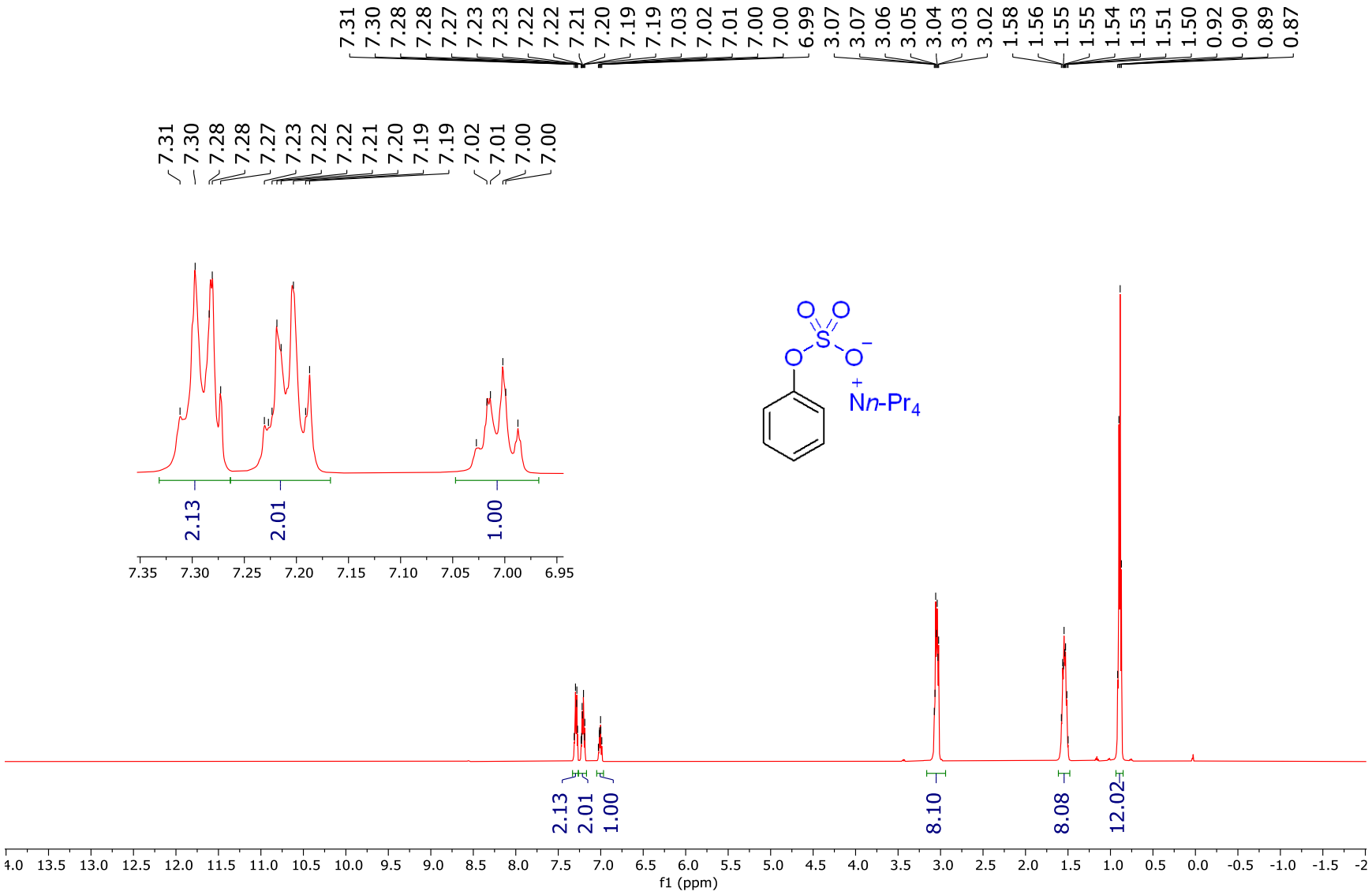
^{1}H NMR spectrum of tetrapropylammonium 3-chlorophenylsulfate (3.1p) (500 MHz, $CDCl_3$)



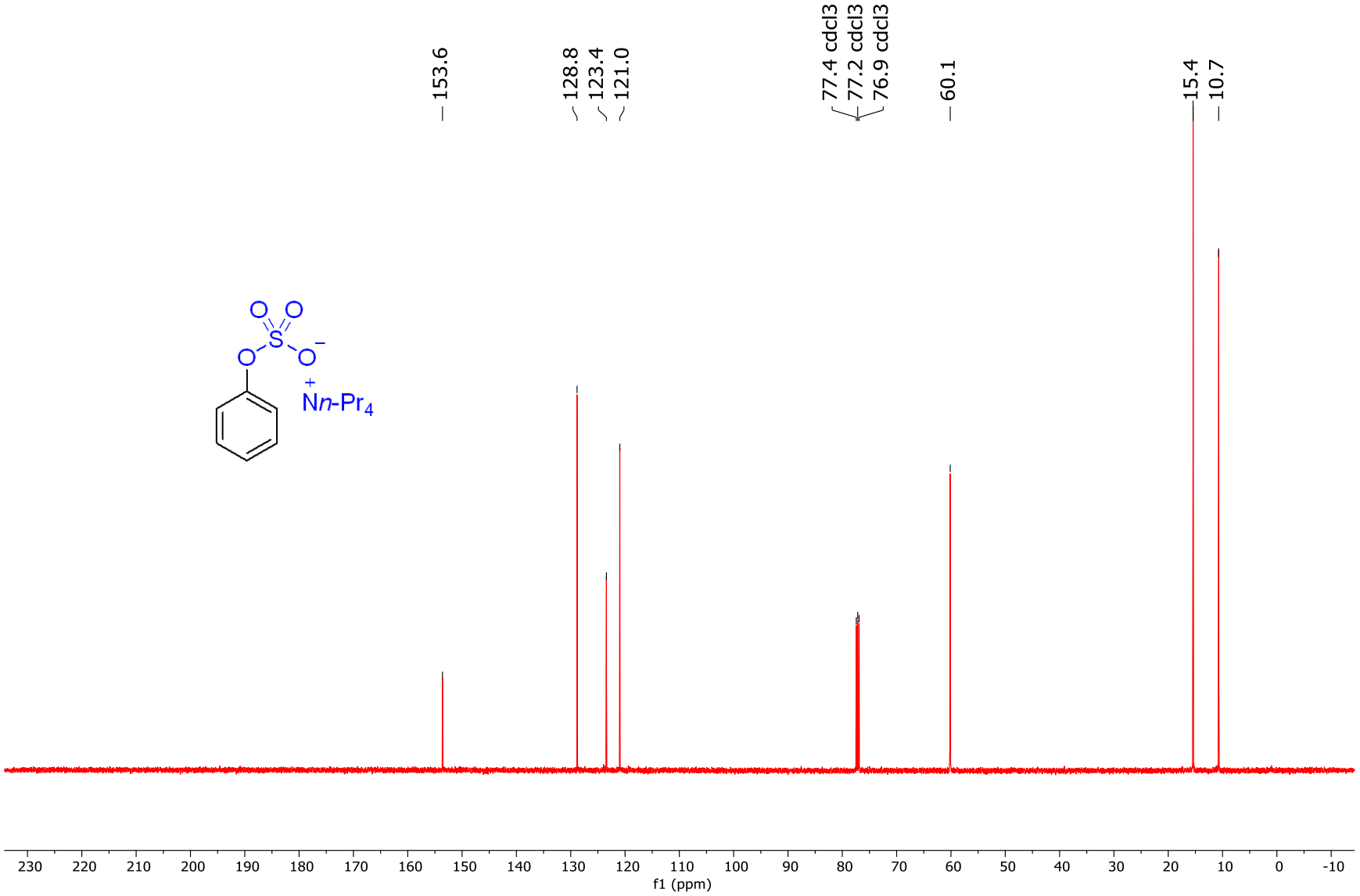
^{13}C NMR spectrum of tetrapropylammonium 3-chlorophenylsulfate (3.1p) (126 MHz, $CDCl_3$)



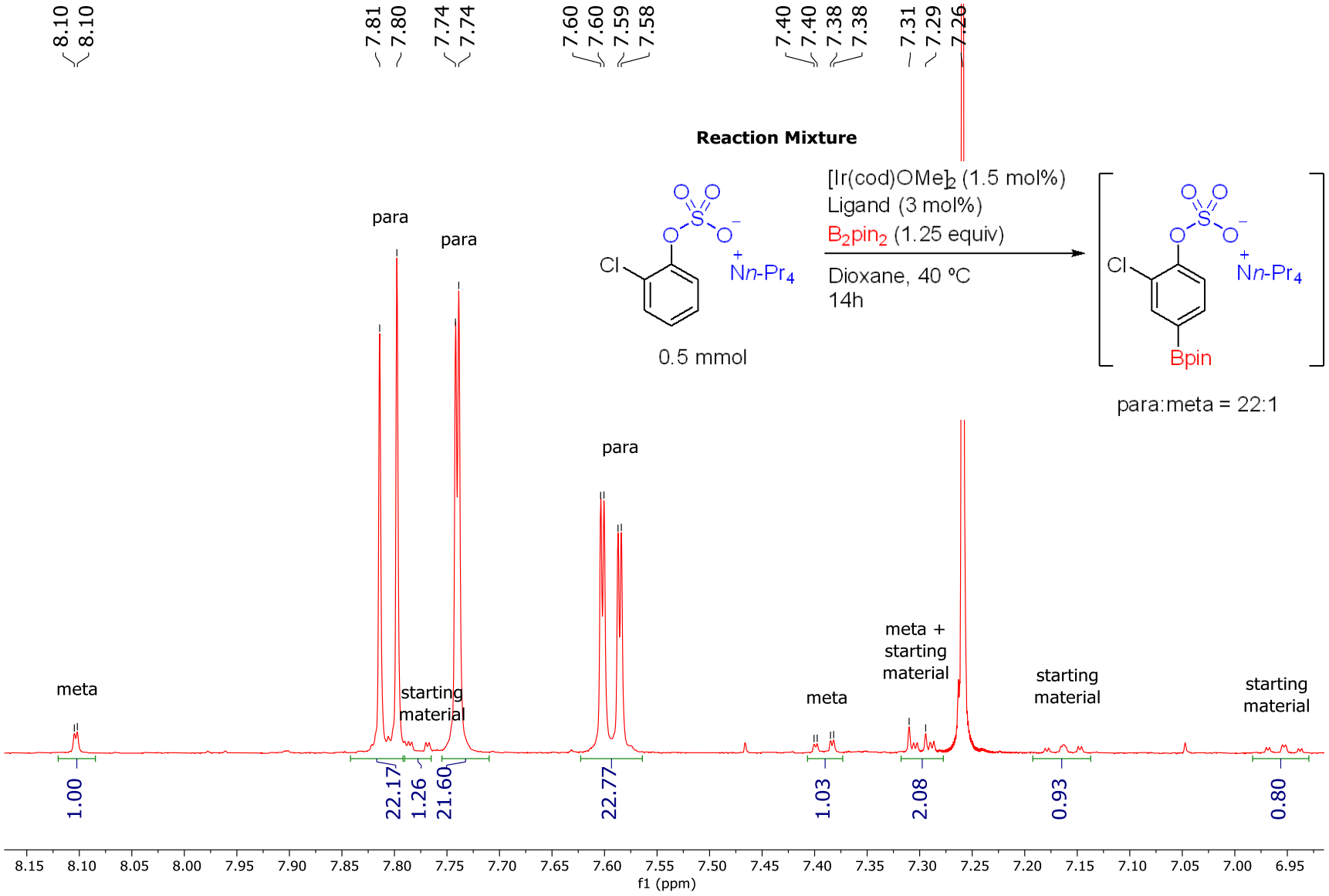
^{1}H NMR spectrum of tetrapropylammonium 2-phenylsulfate (3.1q) (500 MHz, $CDCl_3$)



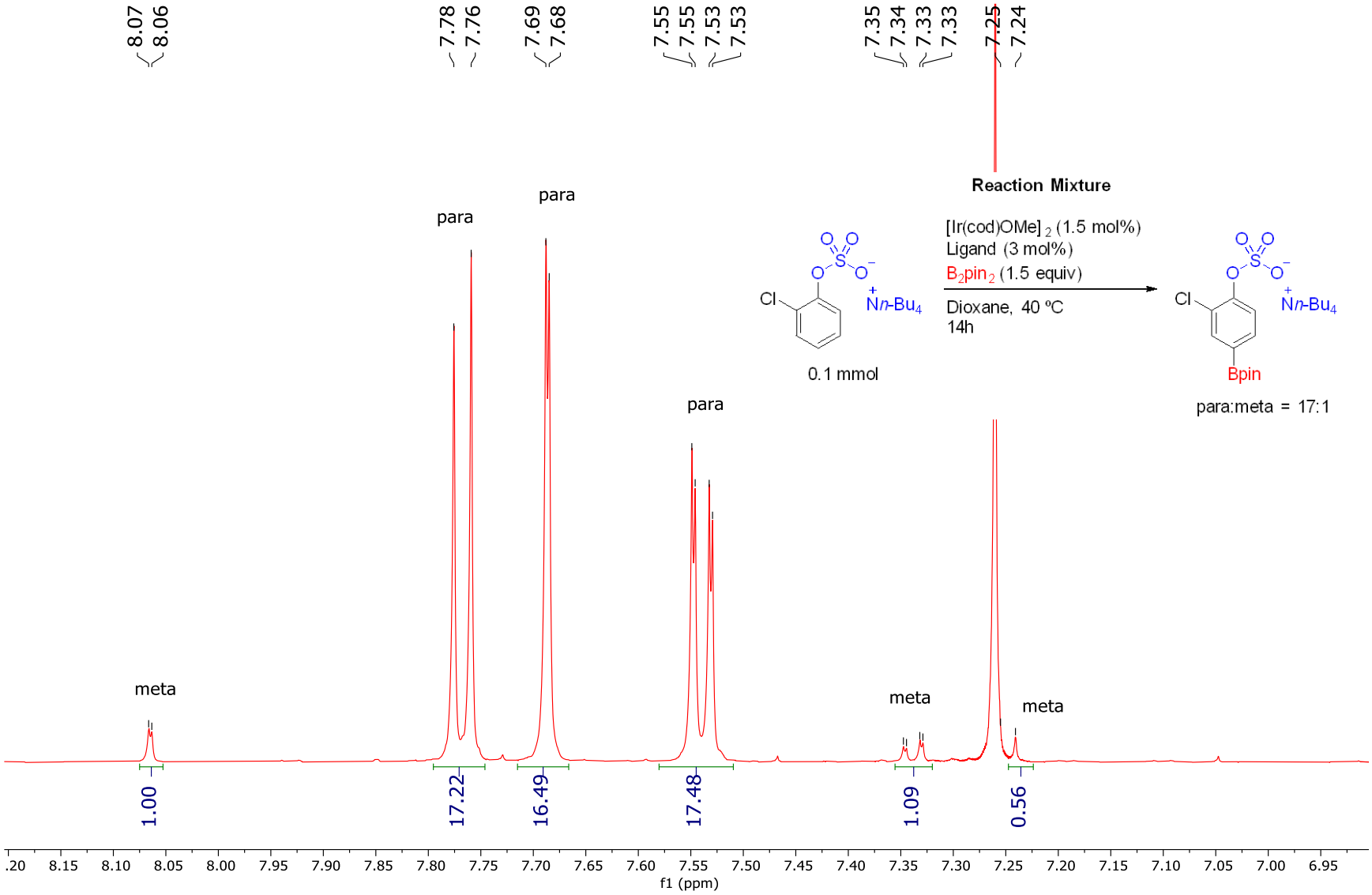
^{13}C NMR spectrum of tetrapropylammonium 2-phenylsulfate (3.1q) (126 MHz, $CDCl_3$)



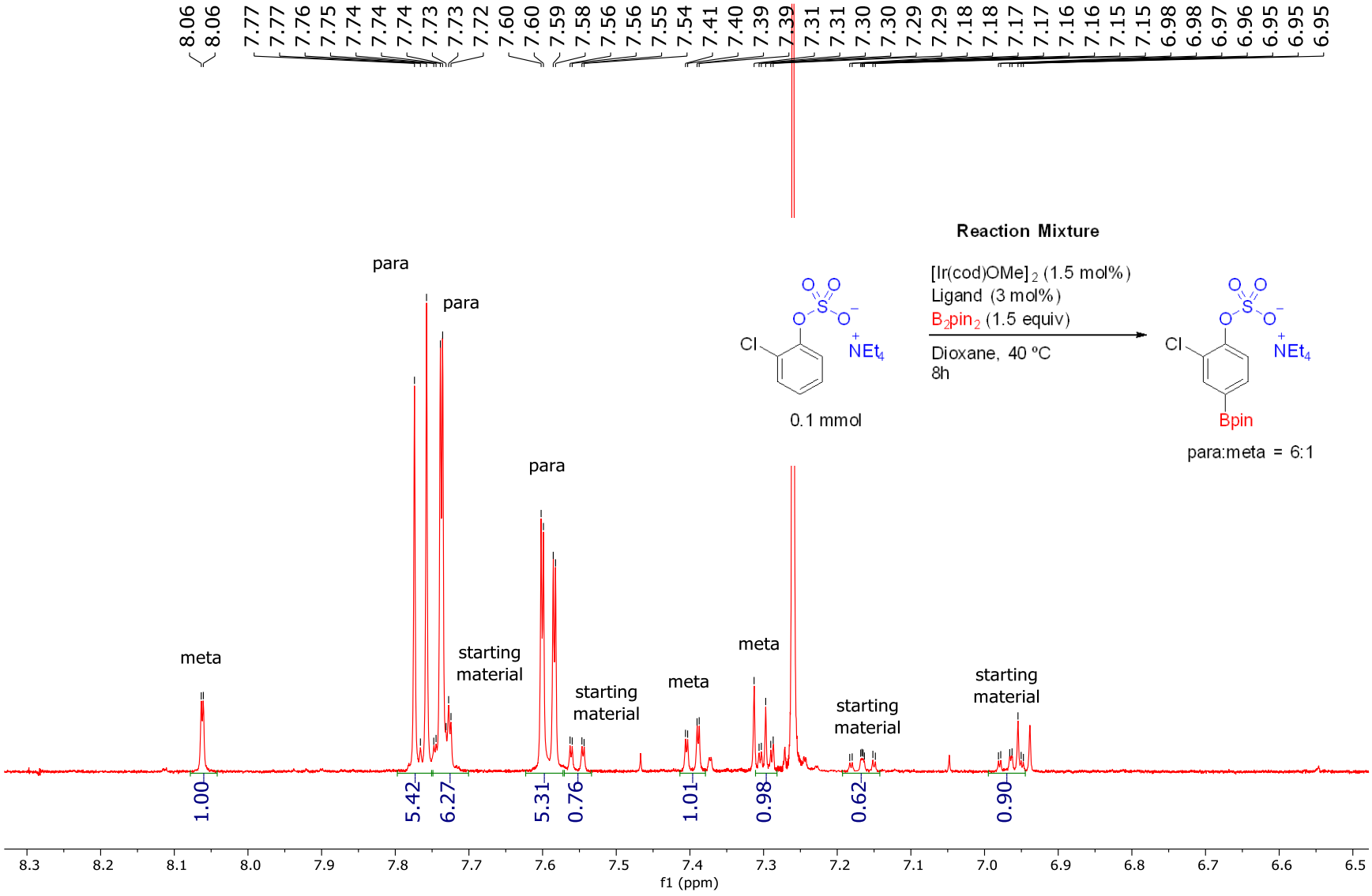
^{1}H NMR reaction mixture for the *Para* borylation of tetrapropylammonium 2-chlorophenylsulfate (3.2a) (500 MHz, $CDCl_3$)



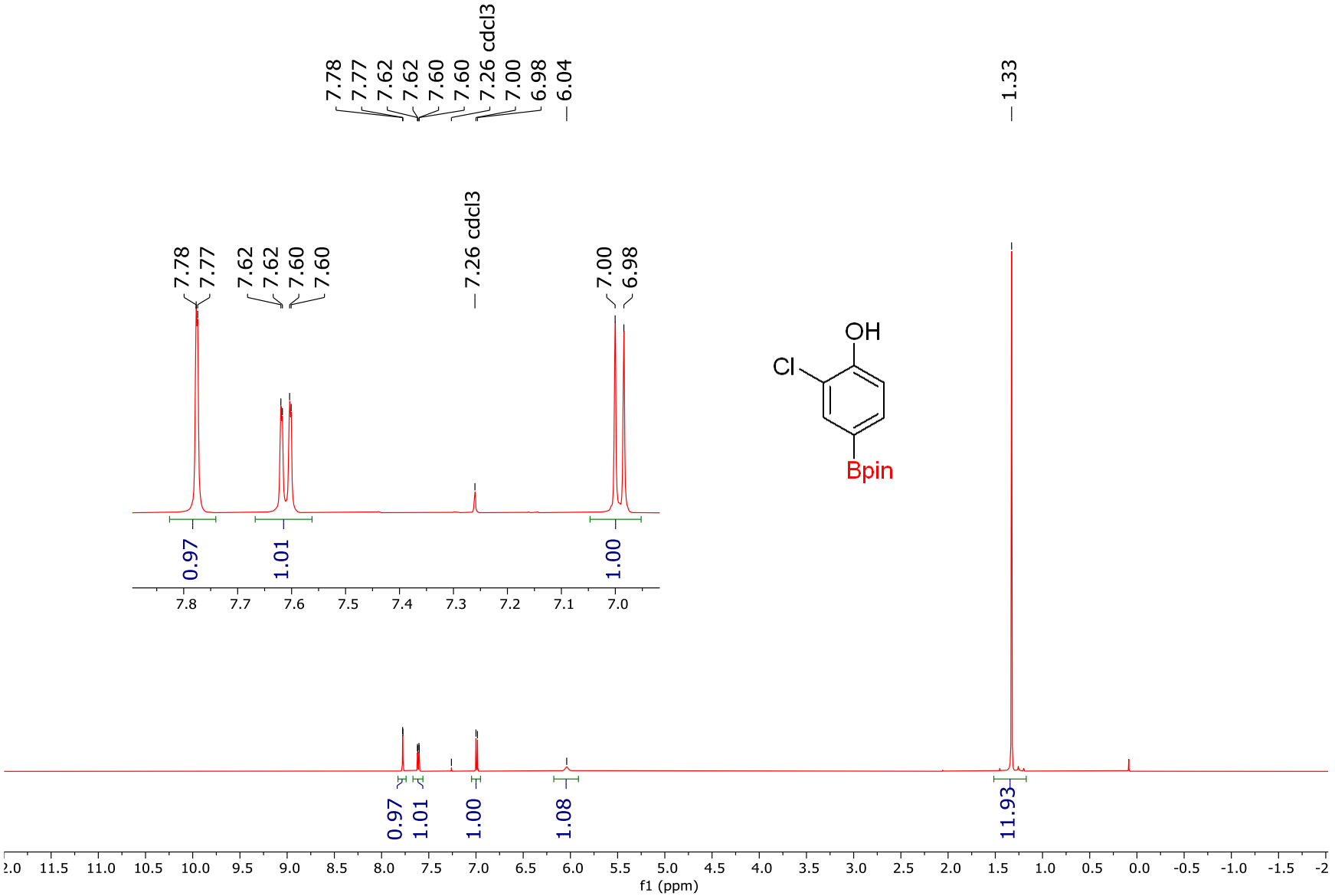
^{1}H NMR reaction mixture for the *Para* borylation of tetrabutylammonium 2-chlorophenylsulfate (3.2a') (500 MHz, $CDCl_3$)



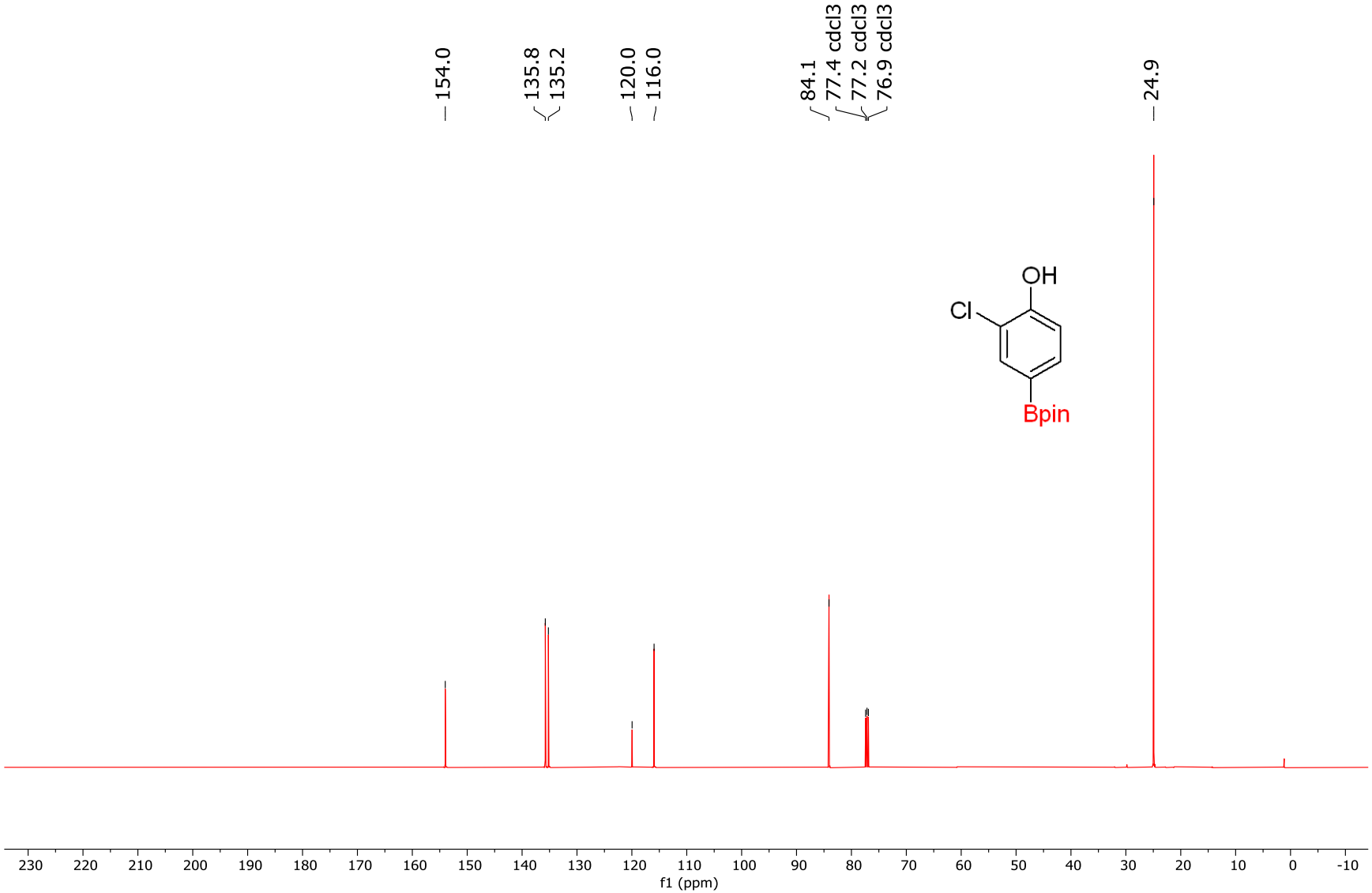
^{1}H NMR reaction mixture for the *Para* borylation of tetraethylammonium 2-chlorophenylsulfate (3.2a'') (500 MHz, $CDCl_3$)



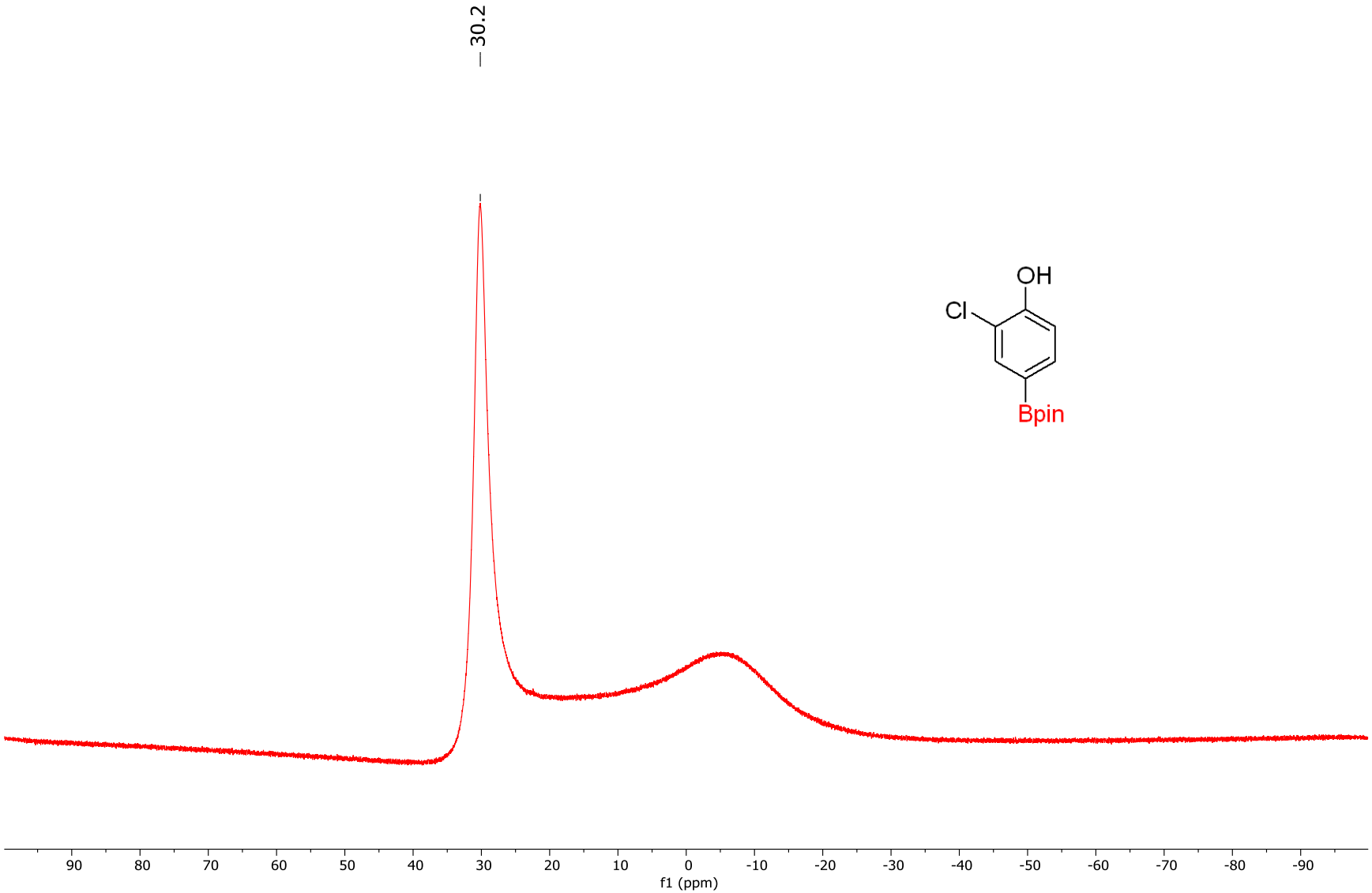
^{1}H NMR spectrum of *Para* borylated 2-chlorophenol (3.2a) (500 MHz, $CDCl_3$)



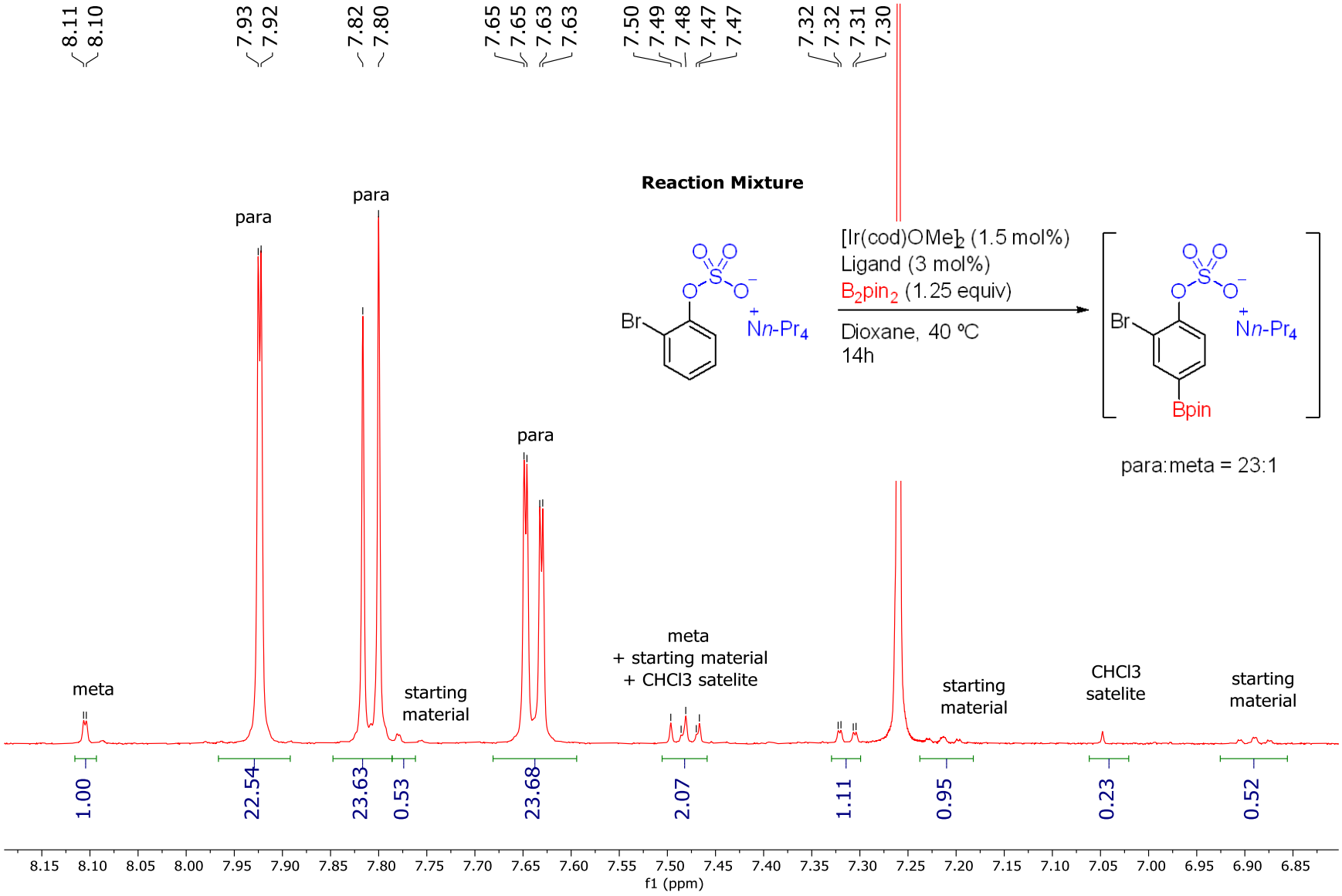
^{13}C NMR spectrum of *Para* borylated 2-chlorophenol (3.2a) (126 MHz, $CDCl_3$)



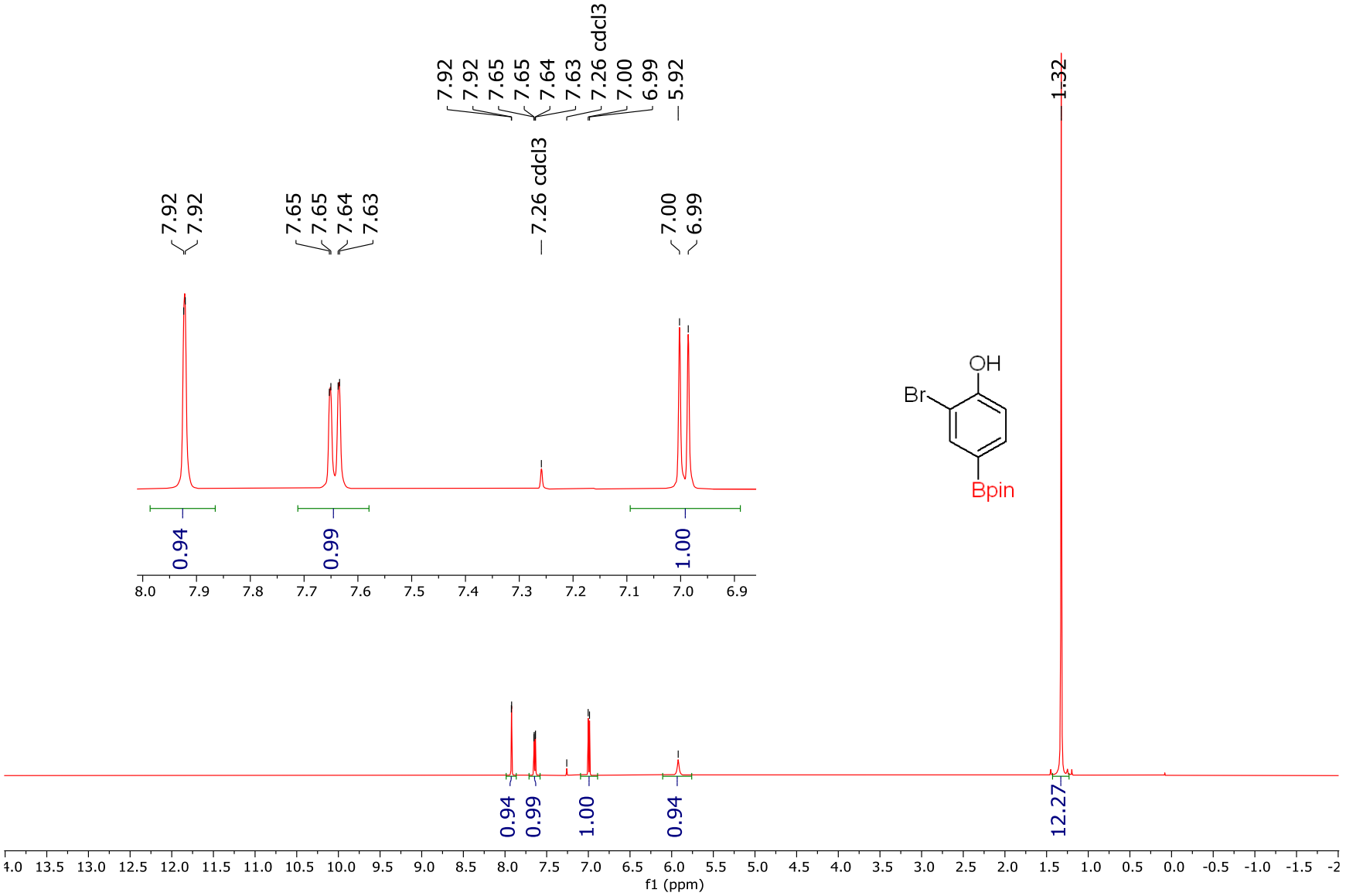
^{11}B NMR spectrum of *Para* borylated 2-chlorophenol (3.2a) (160 MHz, $CDCl_3$)



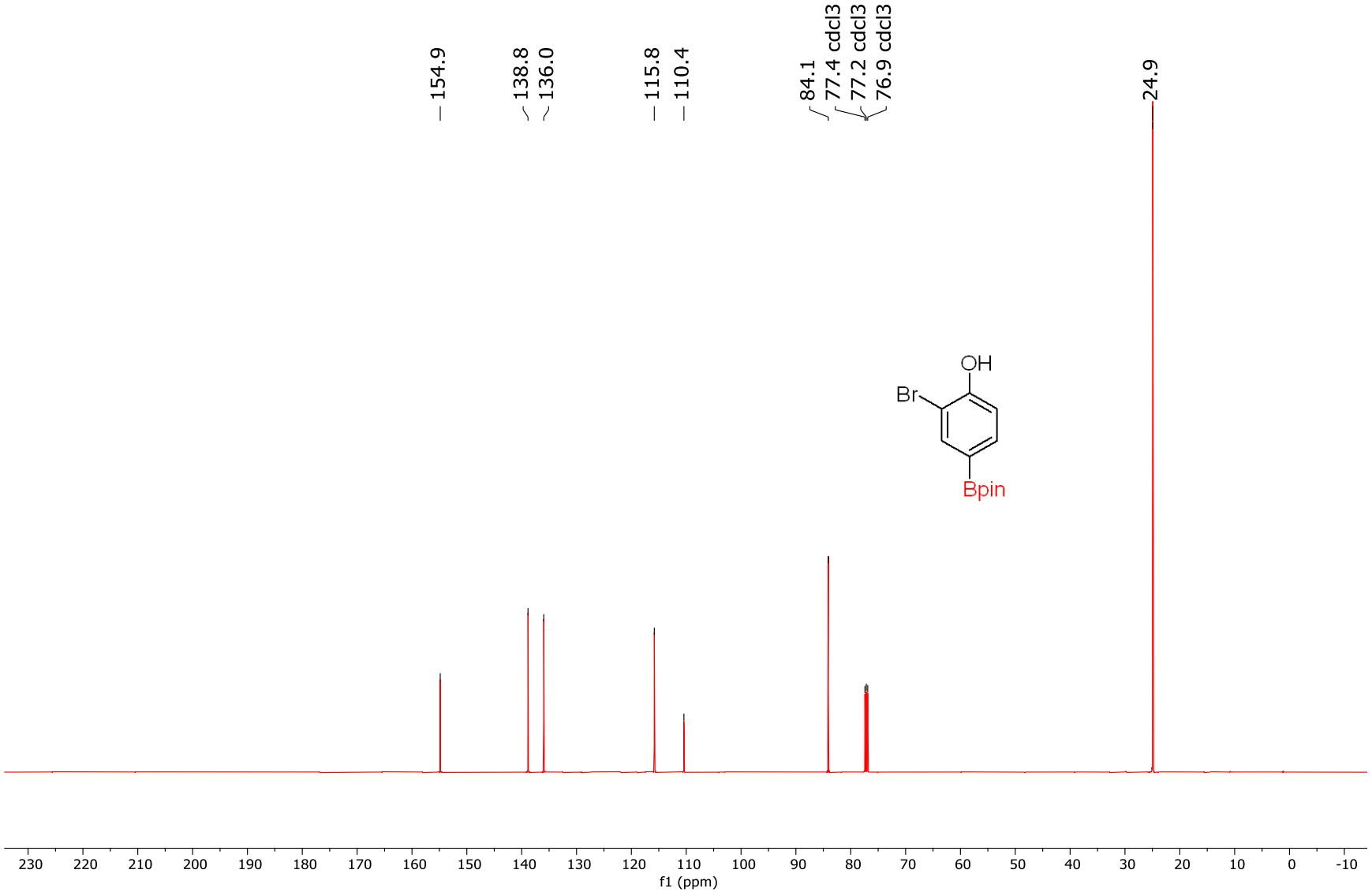
^{1}H NMR reaction mixture for the *Para* borylation of tetrapropyl ammonium 2-bromophenylsulfate (3.2b) (500 MHz, $CDCl_3$)



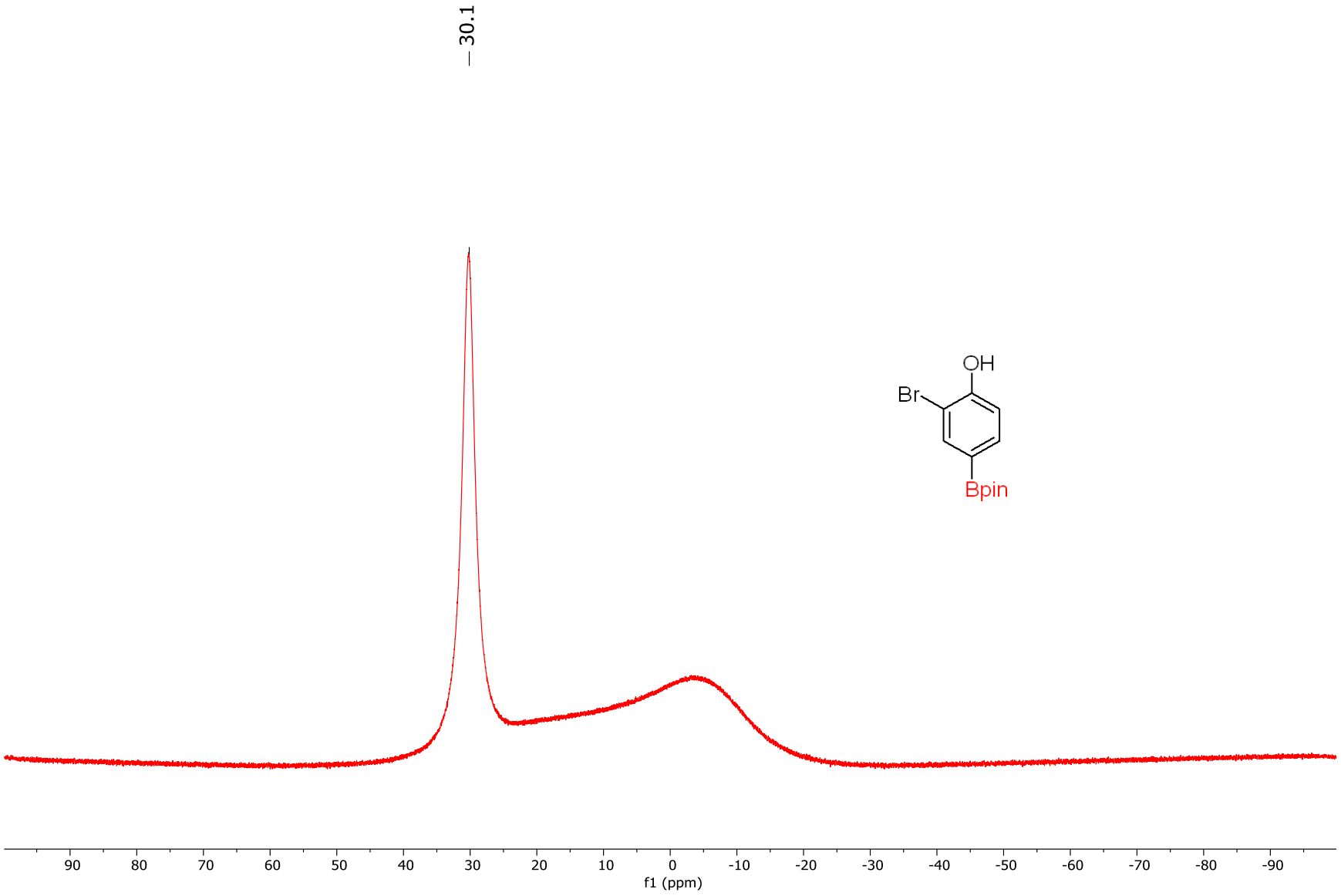
^{1}H NMR spectrum of *Para* borylated 2-bromophenol (3.2b) (500 MHz, $CDCl_3$)



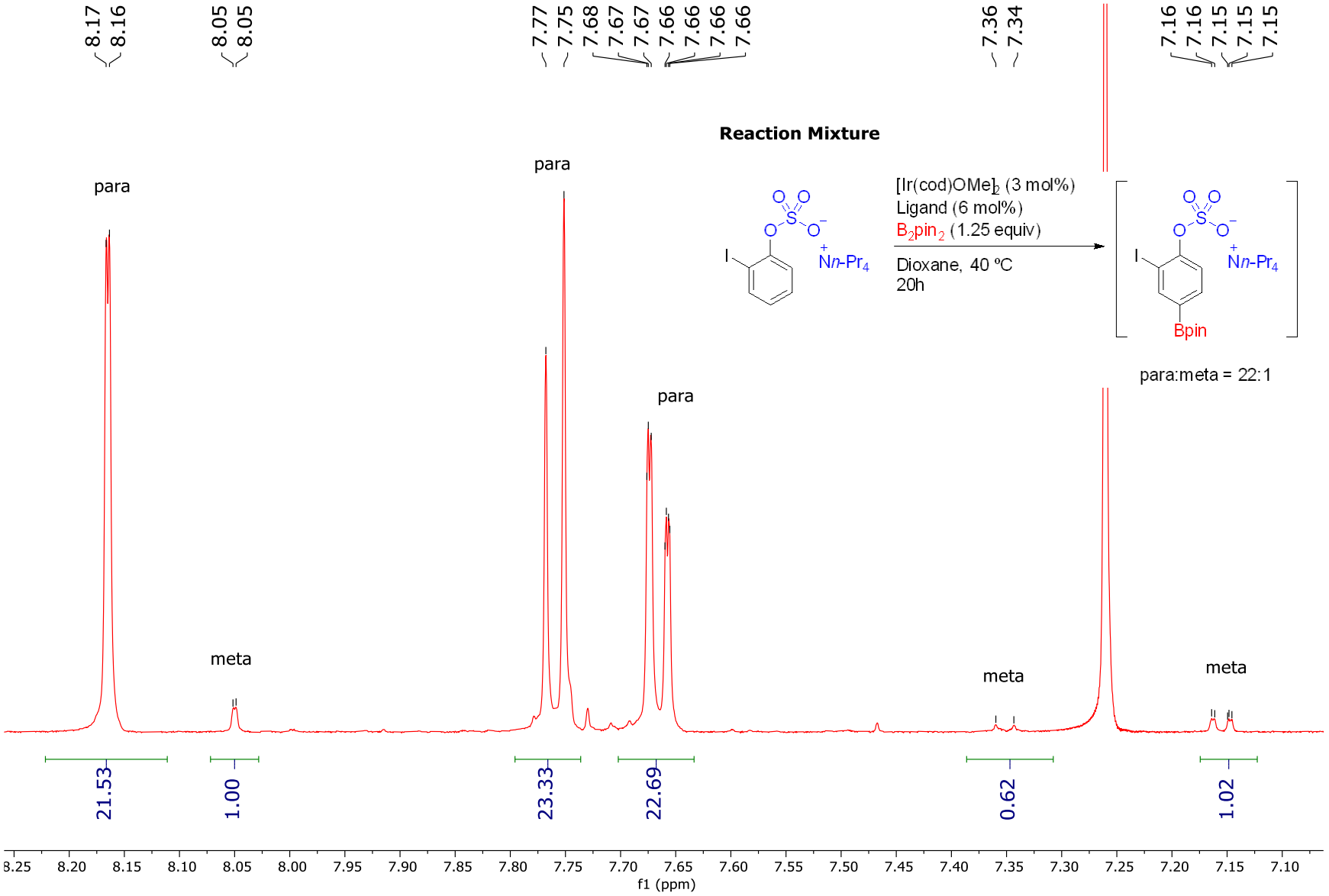
^{13}C NMR spectrum of *Para* borylated 2-bromophenol (3.2b) (126 MHz, $CDCl_3$)



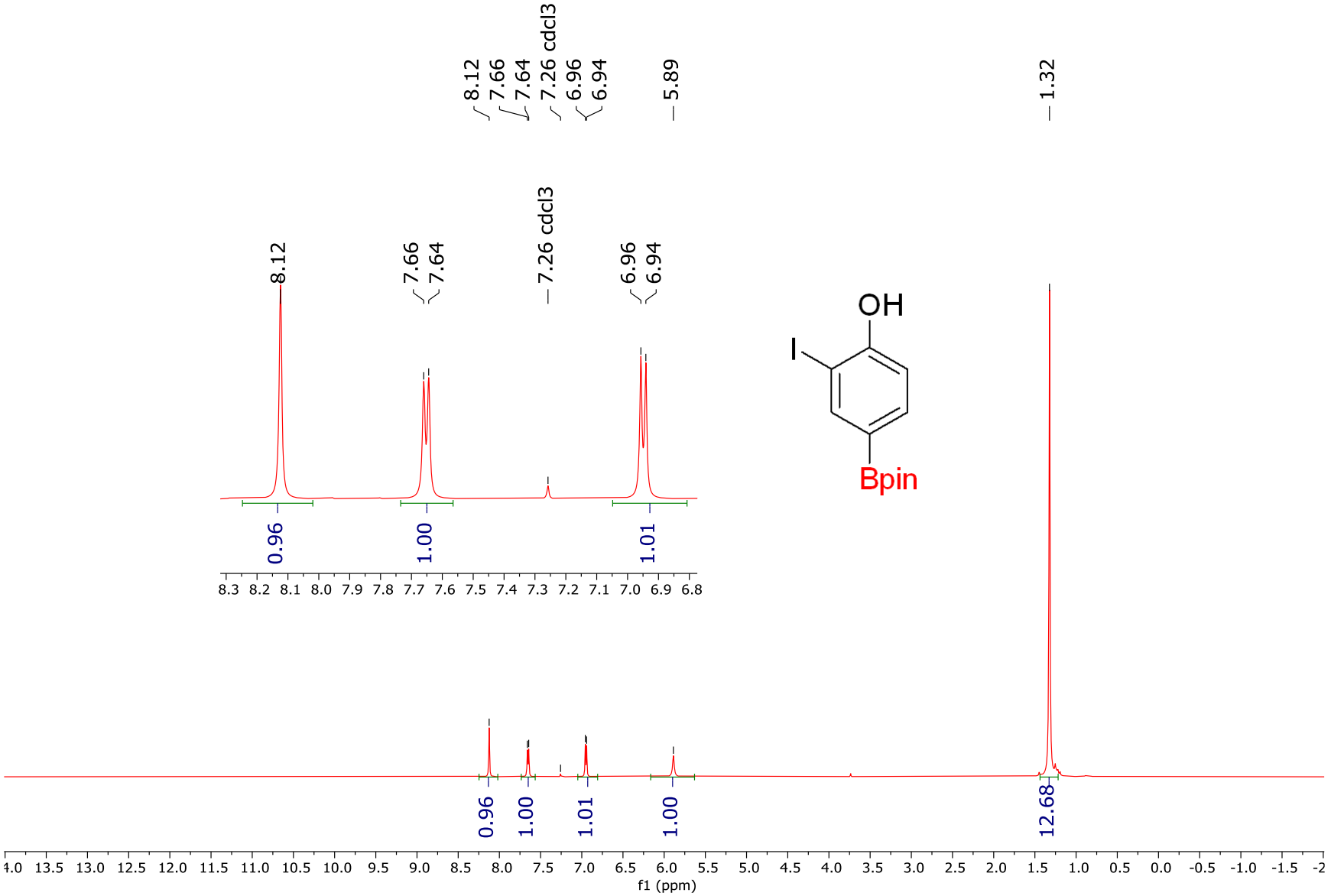
^{11}B NMR spectrum of *Para* borylated 2-bromophenol (3.2b) (160 MHz, $CDCl_3$)



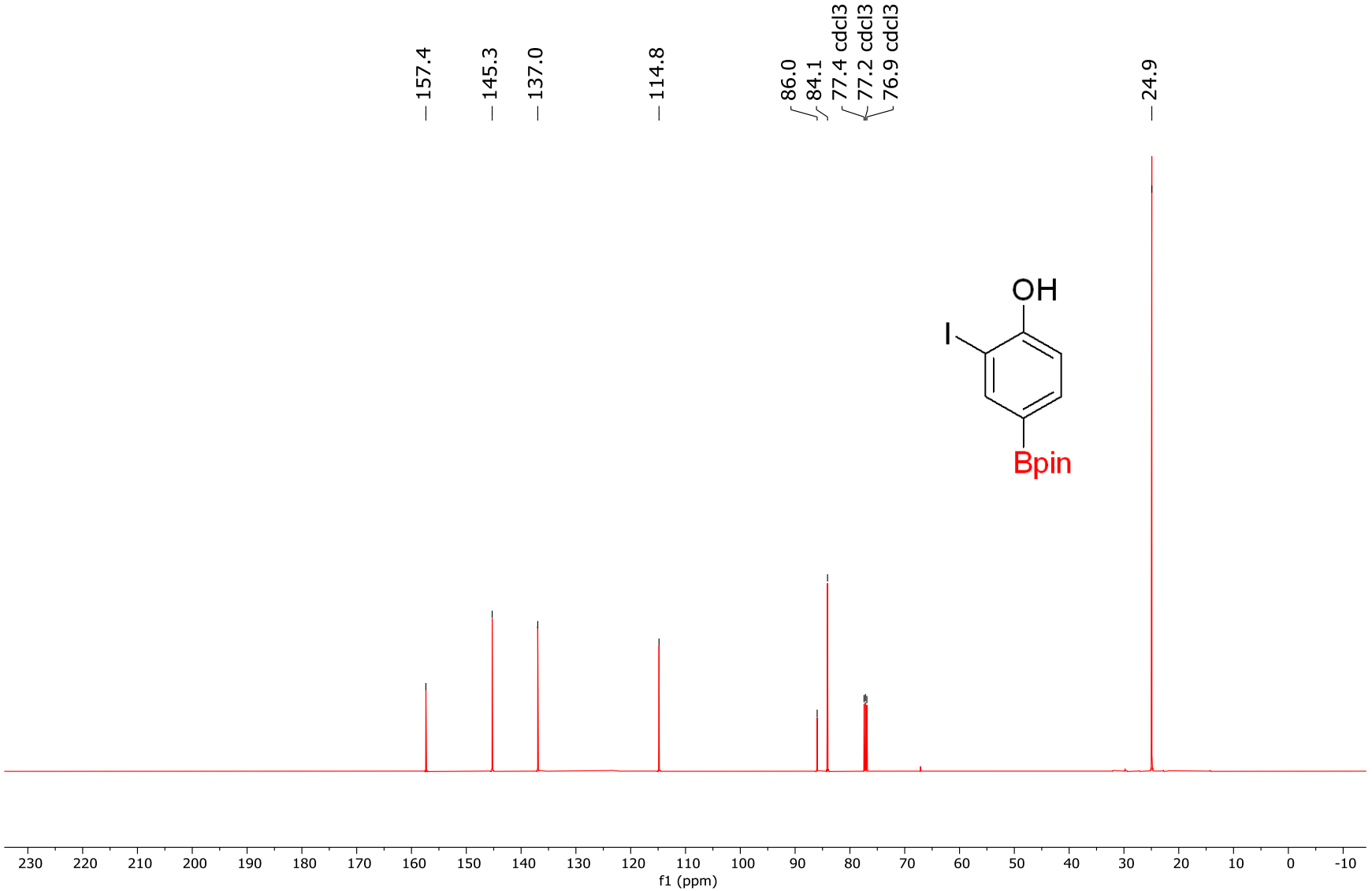
^{1}H NMR reaction mixture for *Para* borylation of tetrapropyl ammonium 2-iodophenylsulfate (crude 3.2c) (500 MHz, $CDCl_3$)



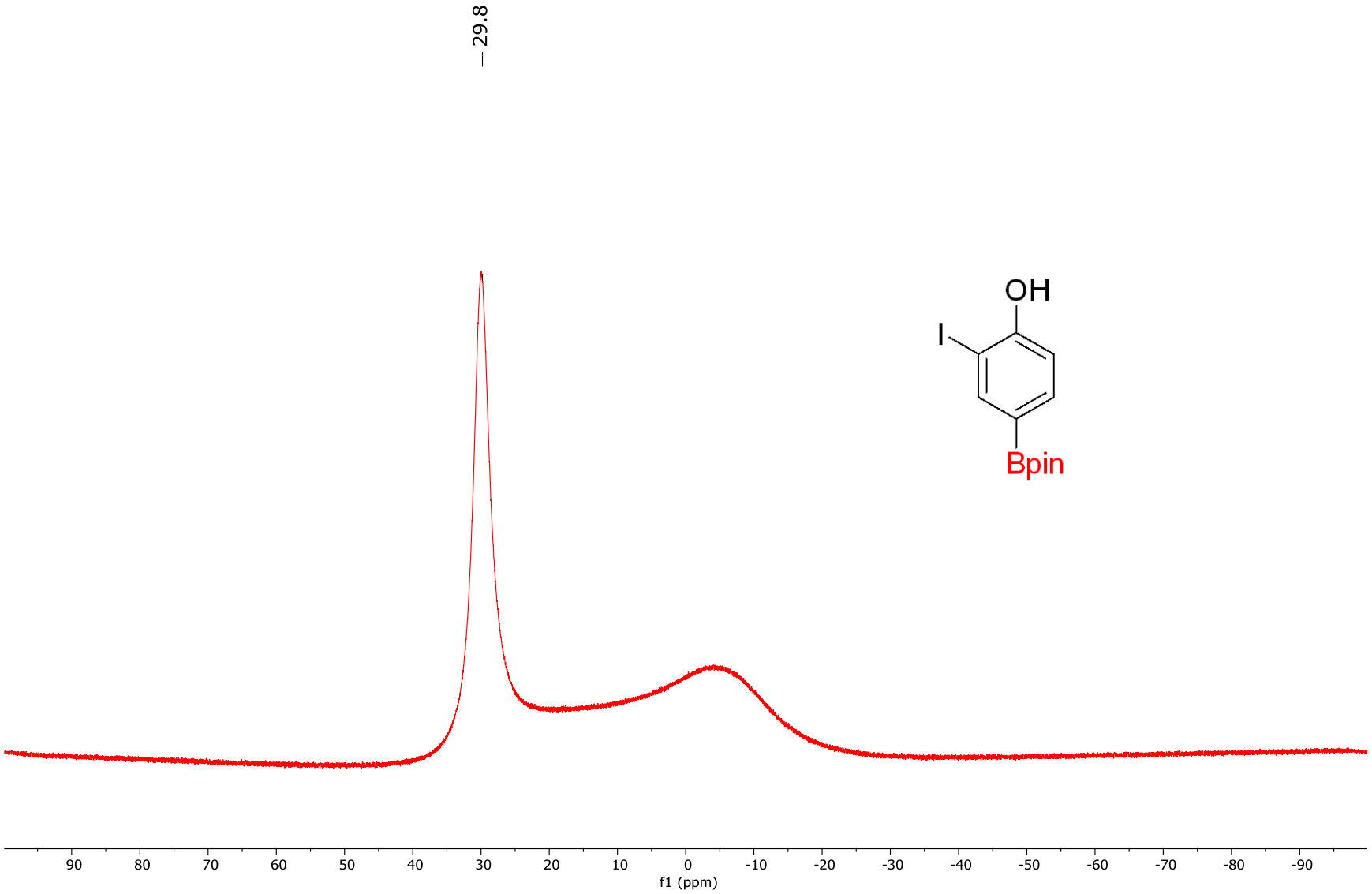
^{1}H NMR spectrum of *Para* borylated 2-iodophenol (3.2c) (500 MHz, $CDCl_3$)



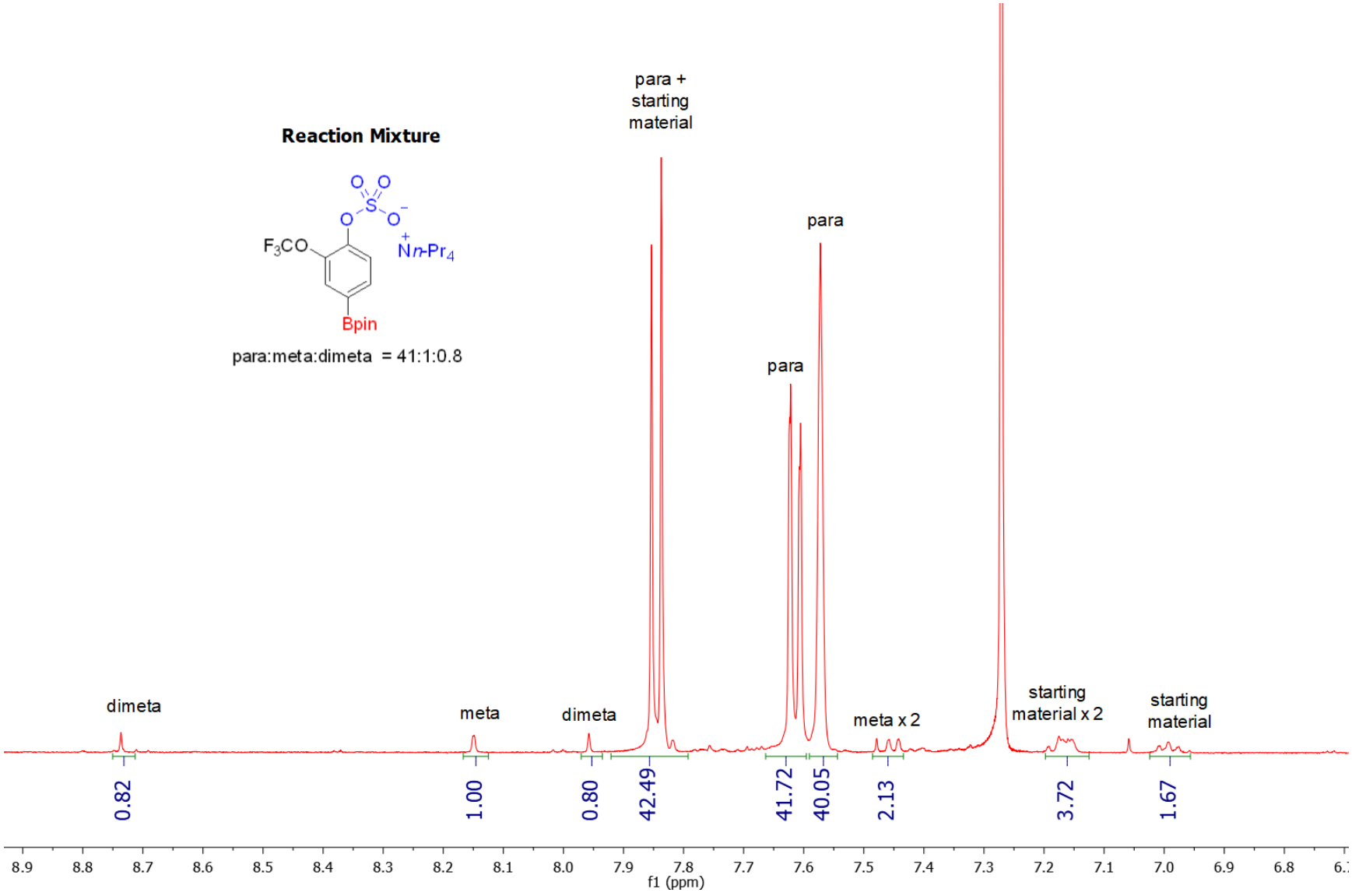
^{13}C NMR spectrum of *Para* borylated 2-iodophenol (3.2c) (126 MHz, $CDCl_3$)



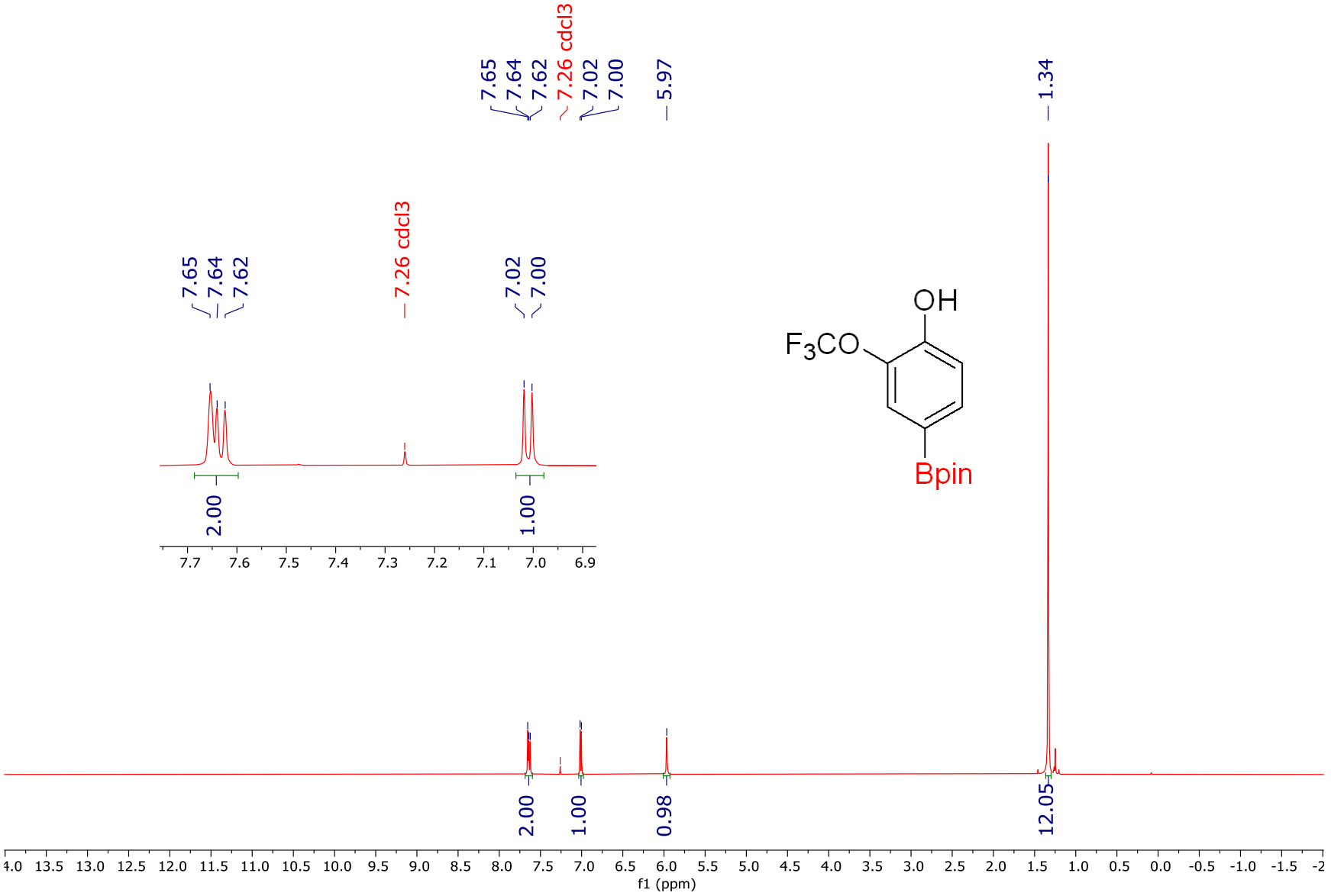
^{11}B NMR spectrum of *Para* borylated 2-iodophenol (3.2c) (160 MHz, $CDCl_3$)



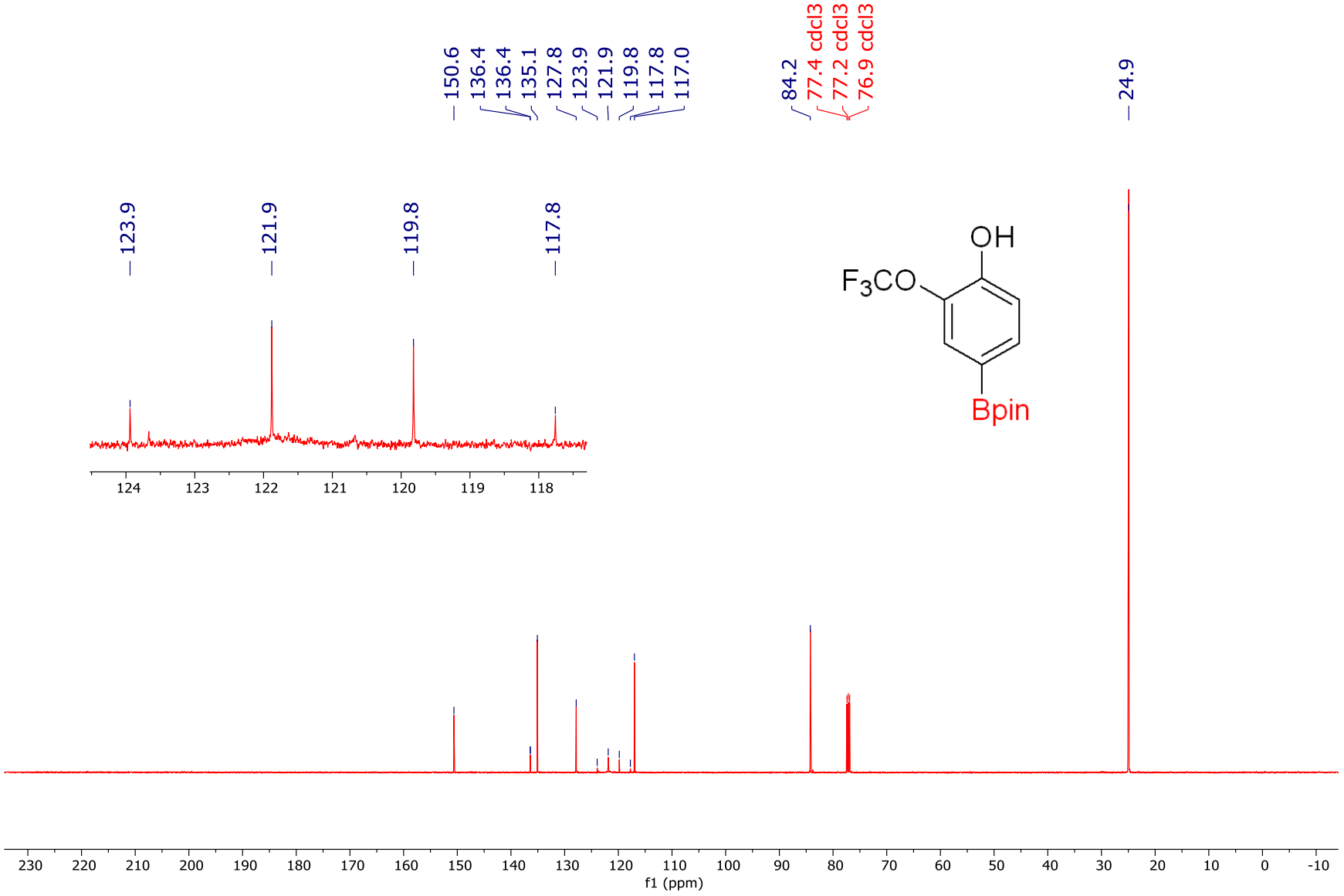
^{1}H NMR reaction mixture of para-borylated tetrapropylammonium 2-(trifluoromethoxy)phenylsulfate (3.2d) (500 MHz, $CDCl_3$)



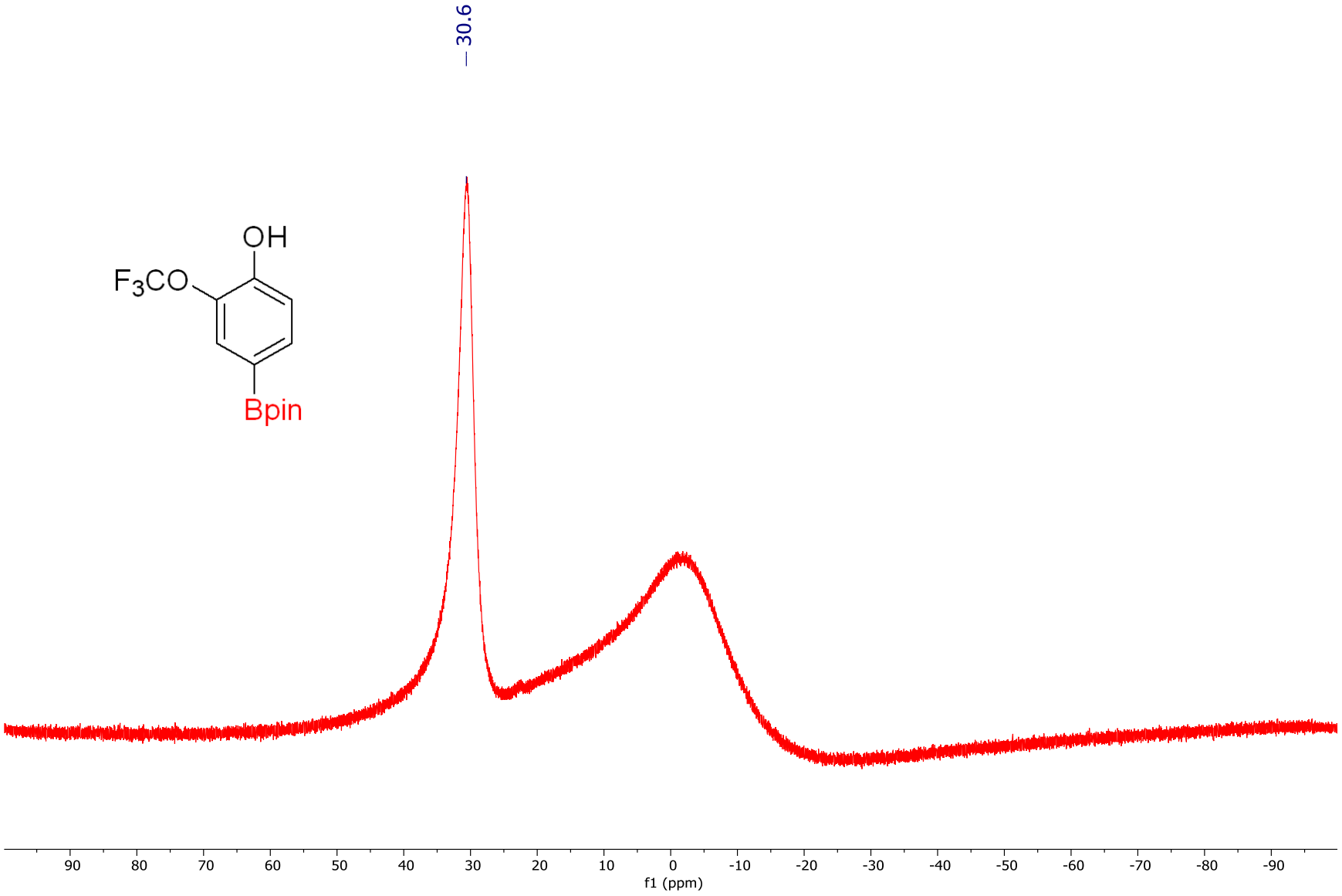
^{1}H NMR spectrum of *Para* borylated 2(trifluoromethoxy)phenol (3.2d) (500 MHz, $CDCl_3$)



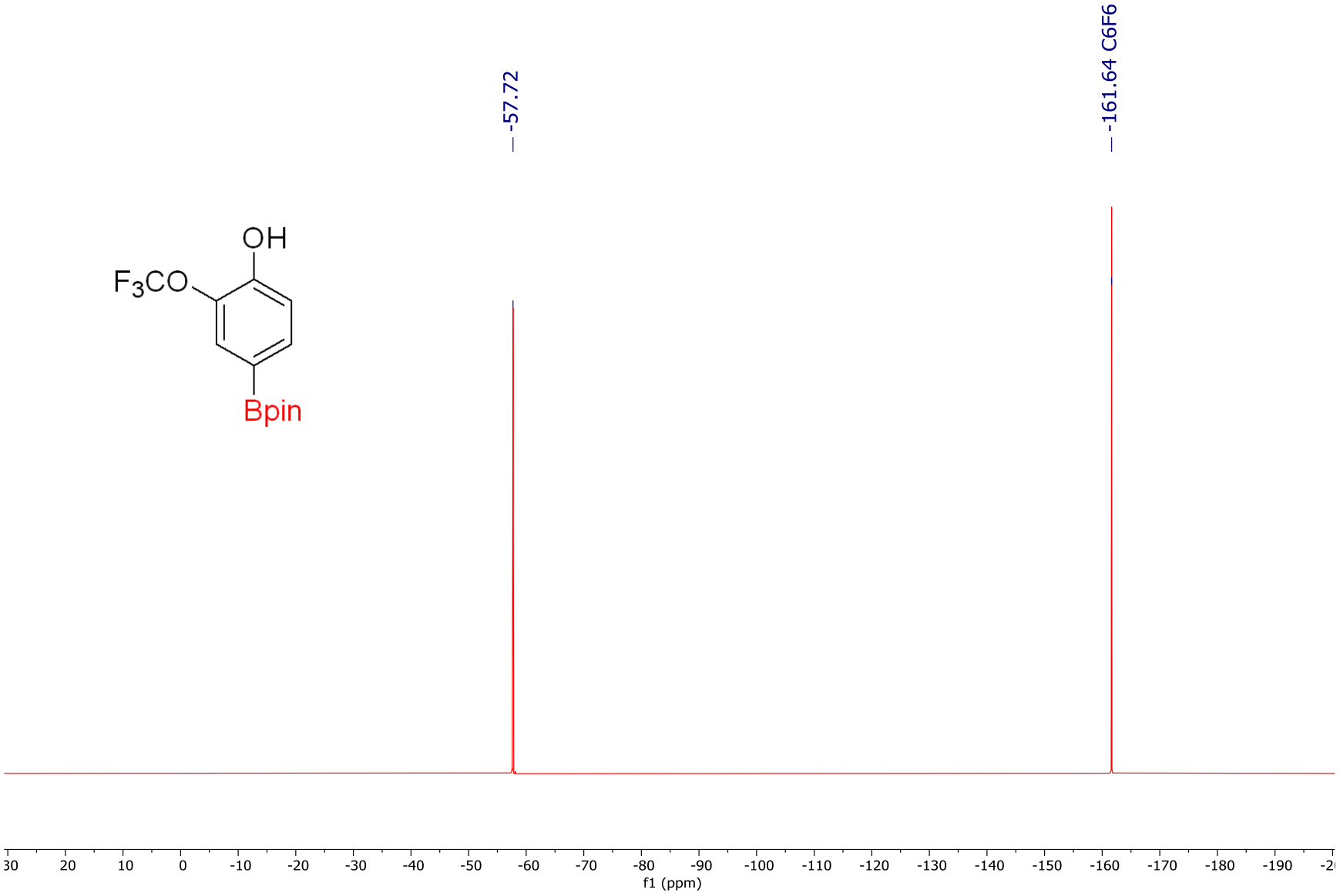
^{13}C NMR spectrum of *Para* borylated 2-(trifluoromethoxy)phenol (3.2d) (126 MHz, $CDCl_3$)



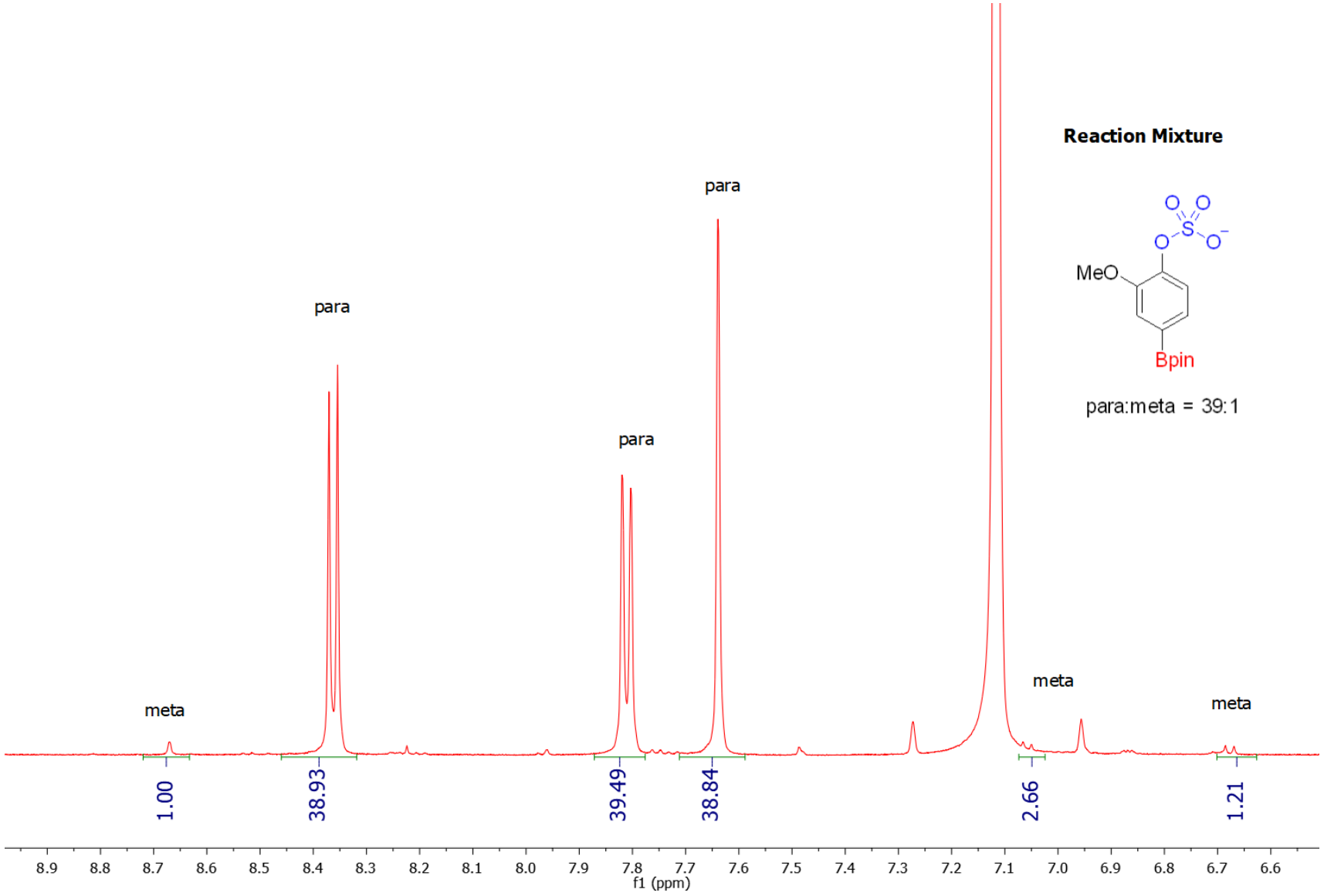
^{11}B NMR spectrum of *Para* borylated 2-(trifluoromethoxy)phenol (3.2d) (160 MHz, $CDCl_3$)



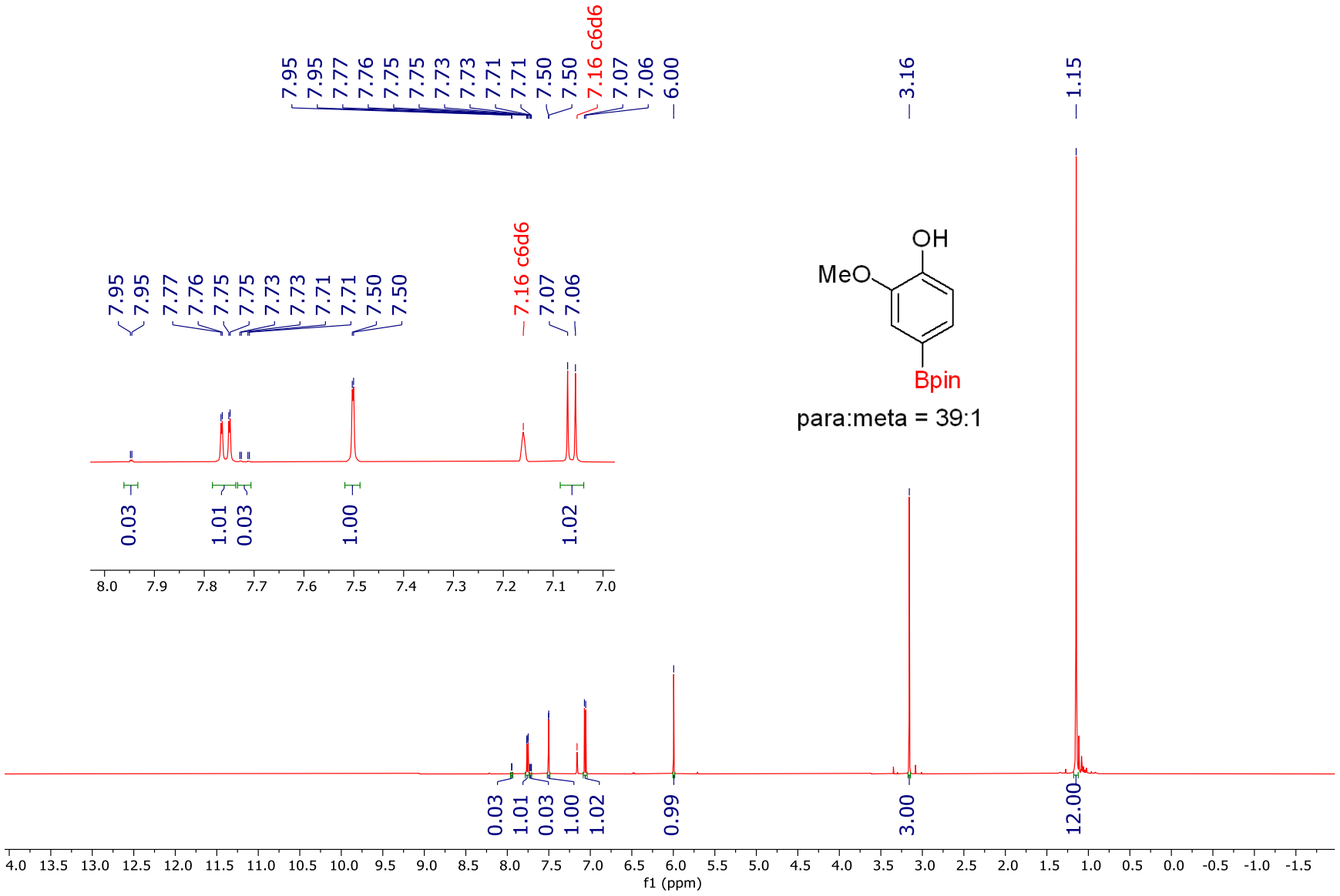
^{19}F NMR spectrum of *Para* borylated 2-(trifluoromethoxy)phenol (3.2d) (470 MHz, $CDCl_3$)



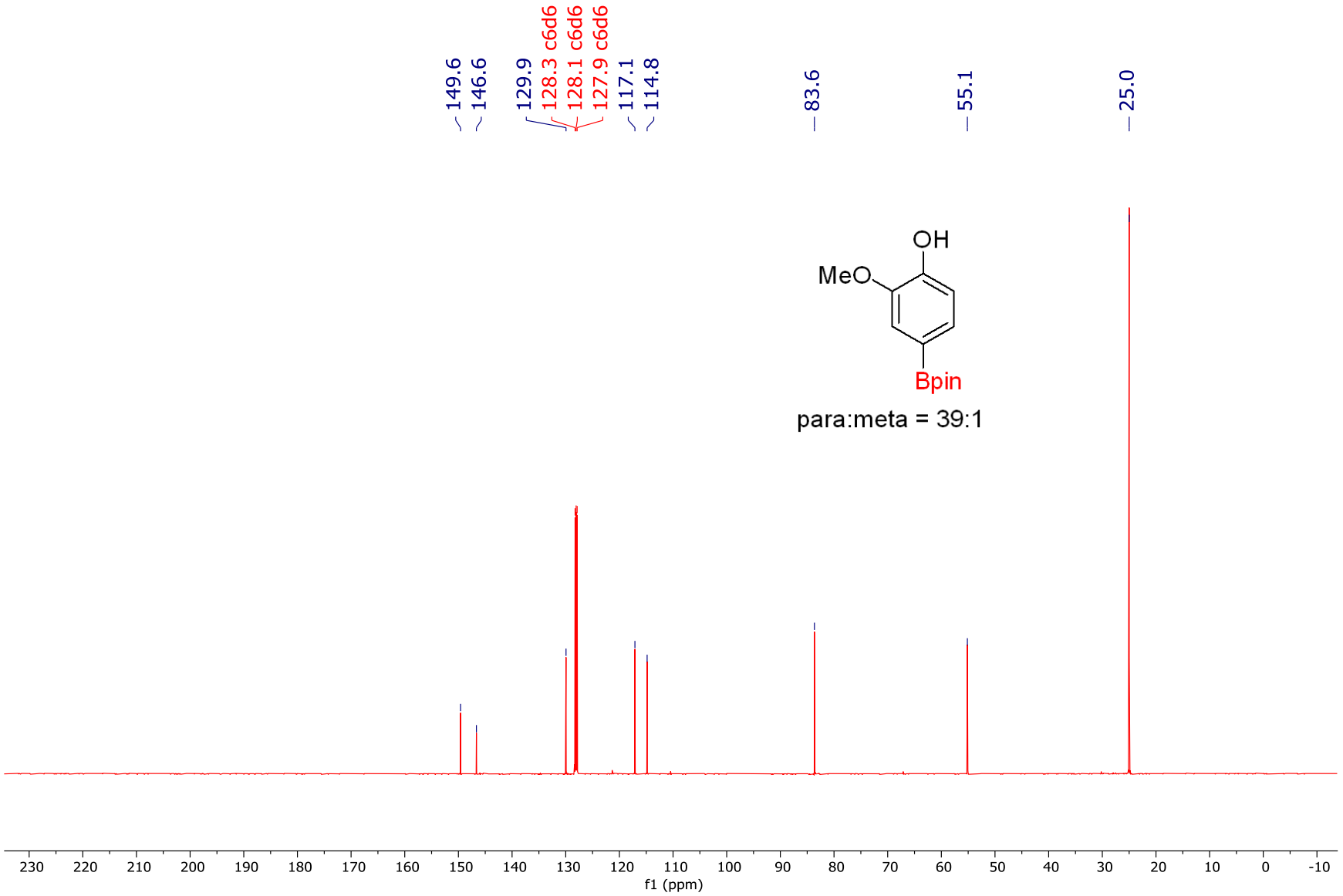
^{1}H NMR reaction mixture of *para*-borylated tetrapropylammonium 2-methoxyphenylsulfate (crude 3.2e) (500 MHz, $CDCl_3$)



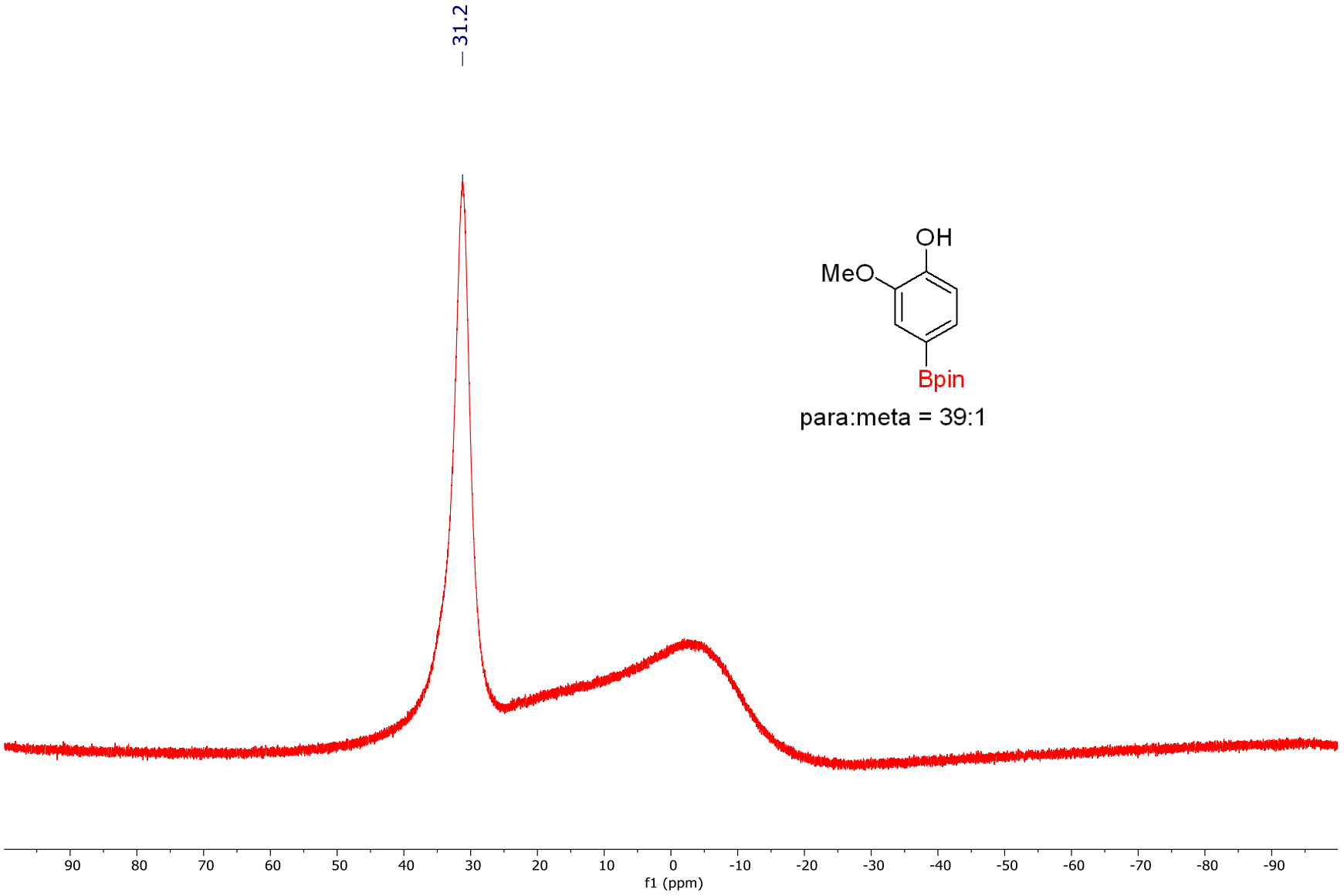
^{1}H NMR spectrum of *Para* borylated 2-methoxyphenol (3.2e) (500 MHz, C_6D_6)



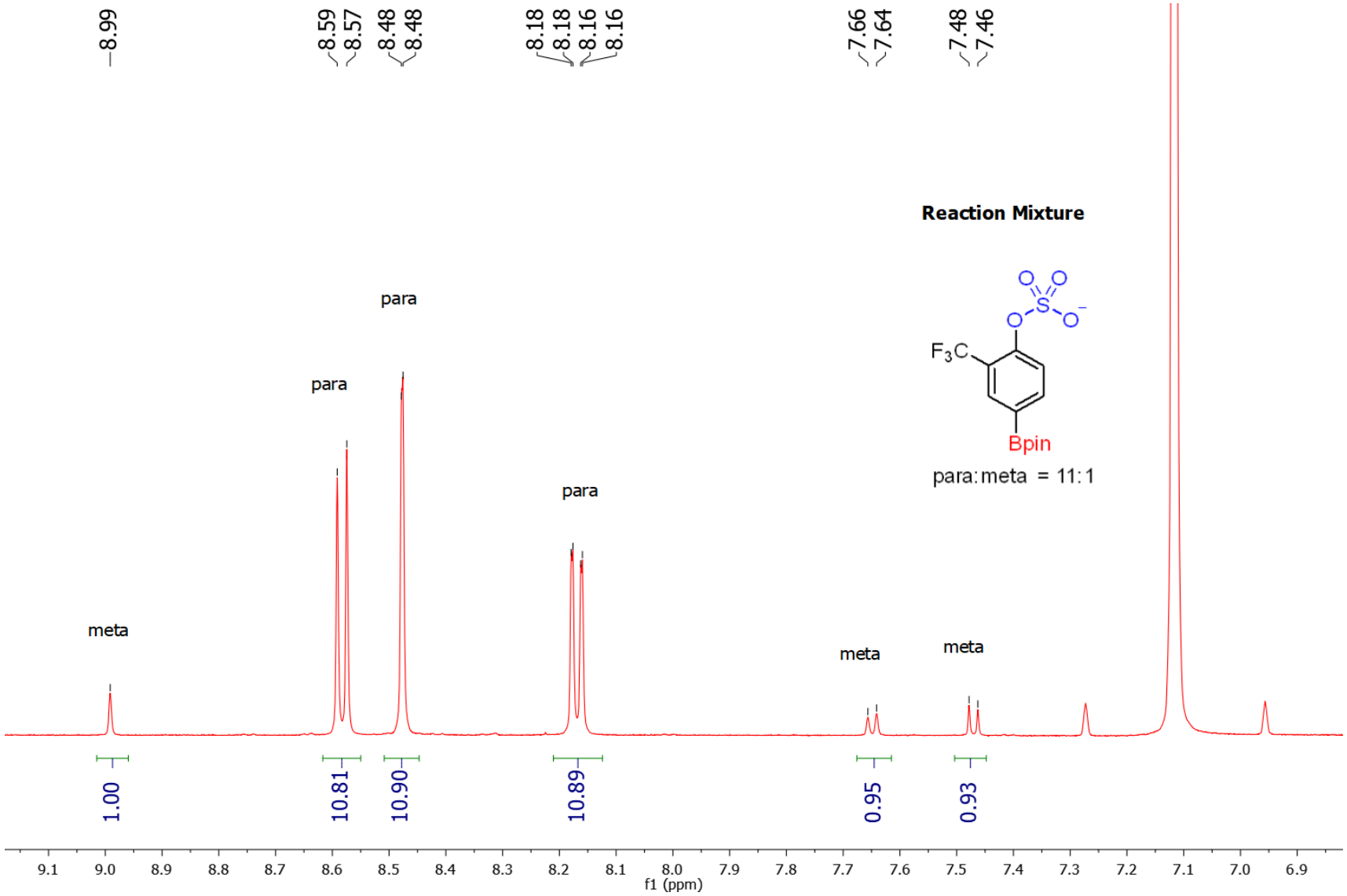
^{13}C NMR spectrum of *Para* borylated 2-methoxyphenol (3.2e) (126 MHz, C_6D_6)



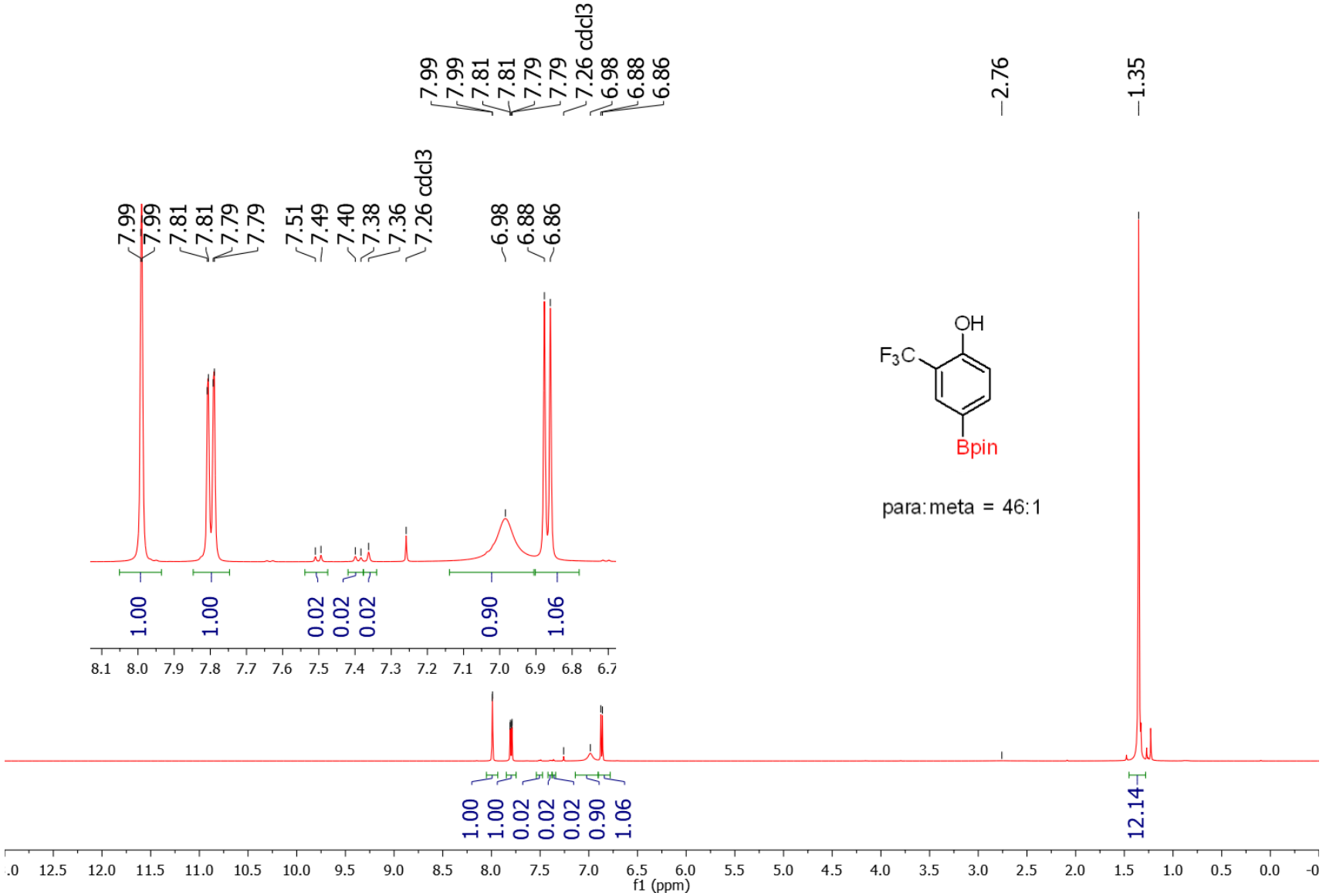
^{11}B NMR spectrum of *Para* borylated 2-methoxyphenol (3.2e) (160 MHz, C_6D_6)



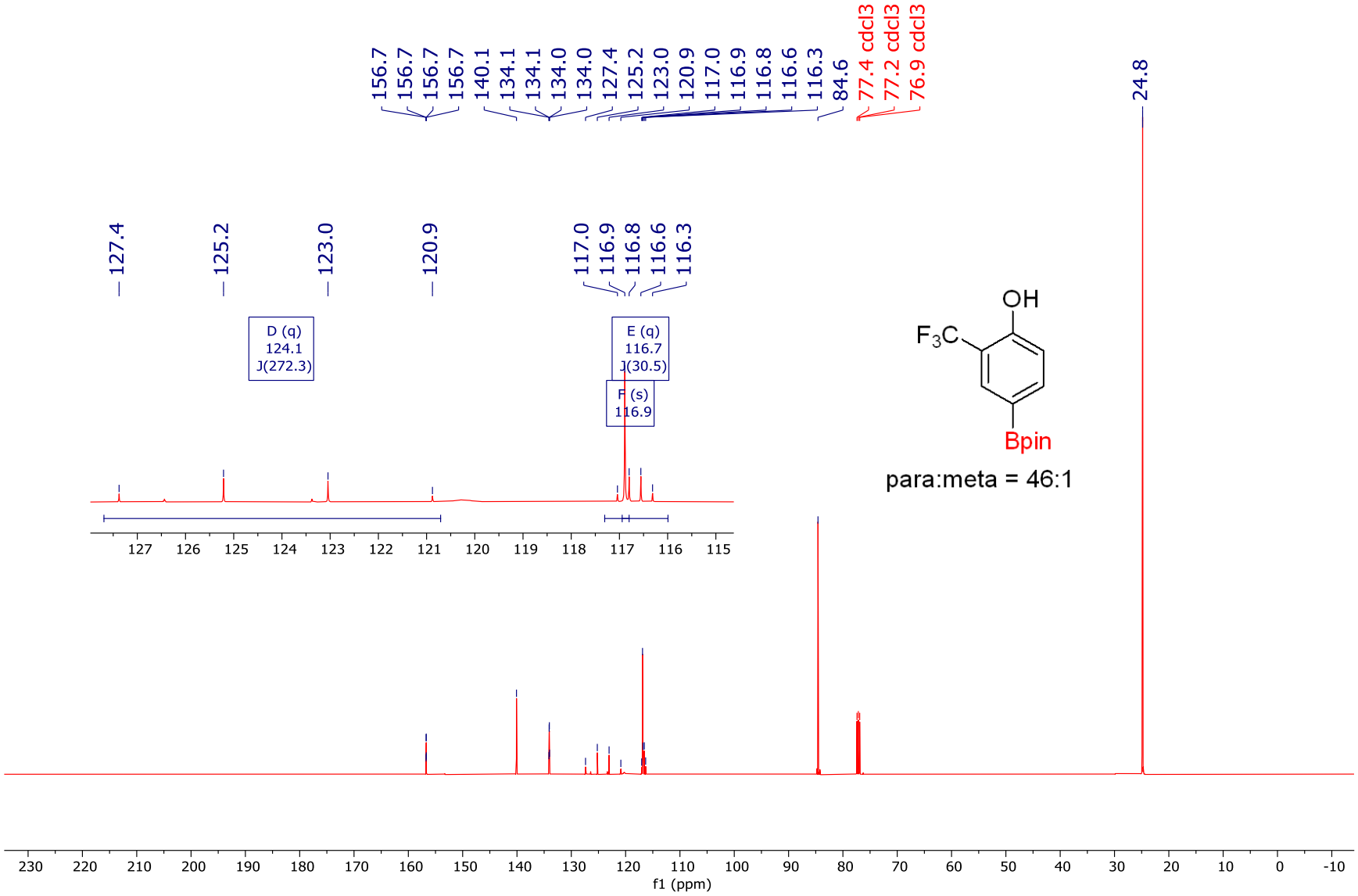
^{1}H NMR reaction mixture of *para*-borylated tetrapropylammonium 2-trifluoromethylphenylsulfate (3.2f) (500 MHz, C_6D_6)



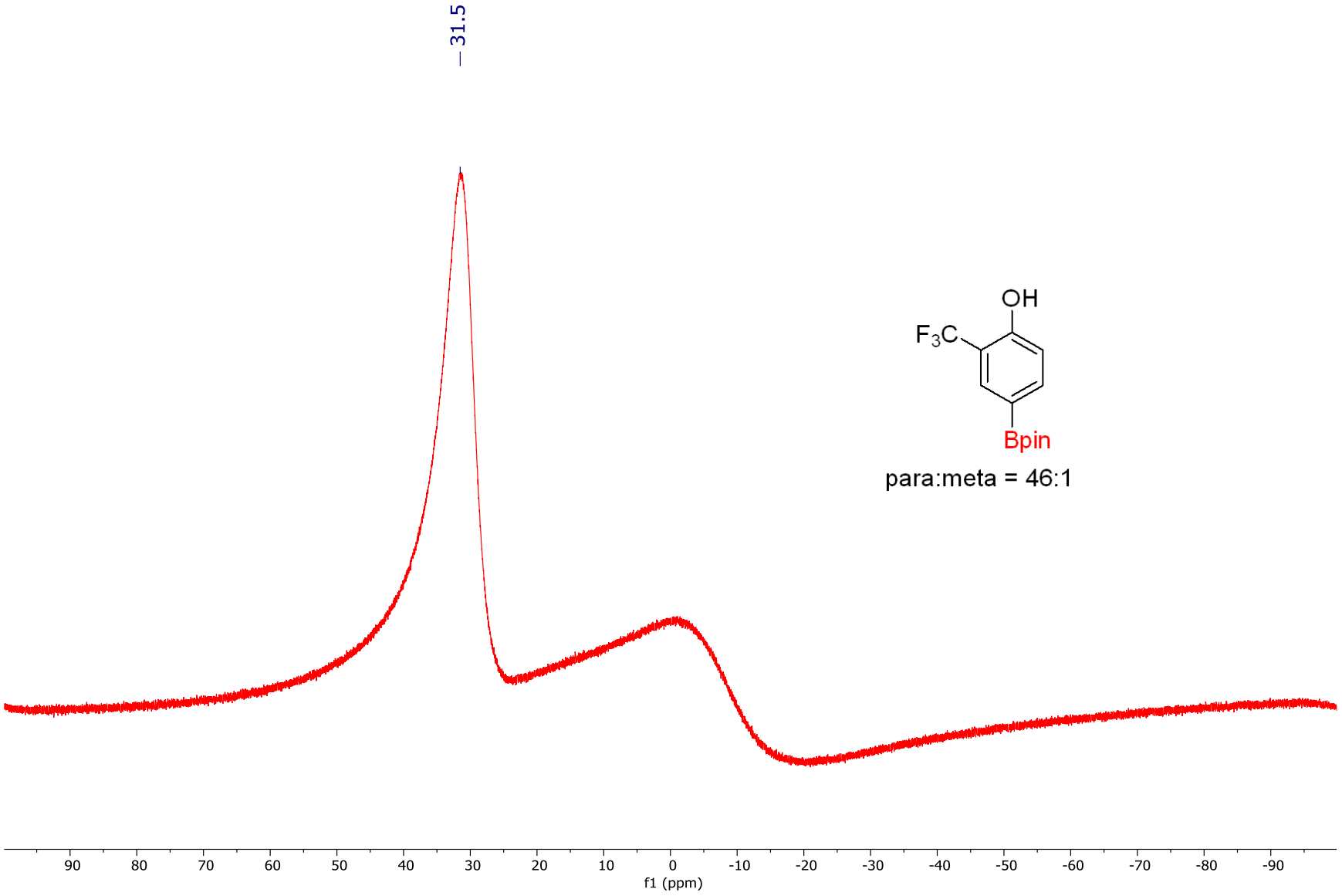
^{1}H NMR spectrum of *Para* borylated 2-trifluoromethylphenol (3.2f) (500 MHz, $CDCl_3$)



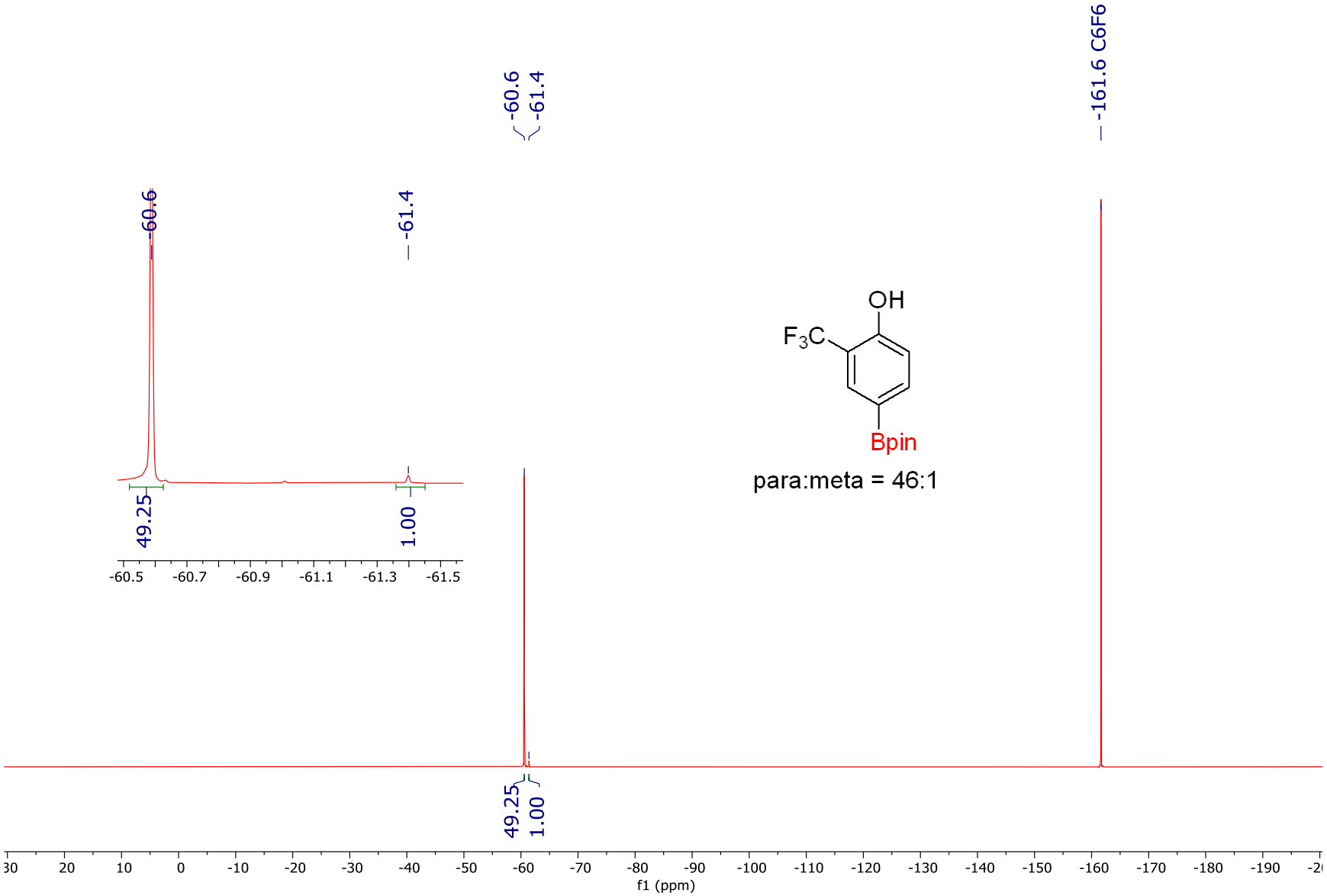
^{13}C NMR spectrum of *Para* borylated 2-trifluoromethylphenol (3.2f) (126 MHz, $CDCl_3$)



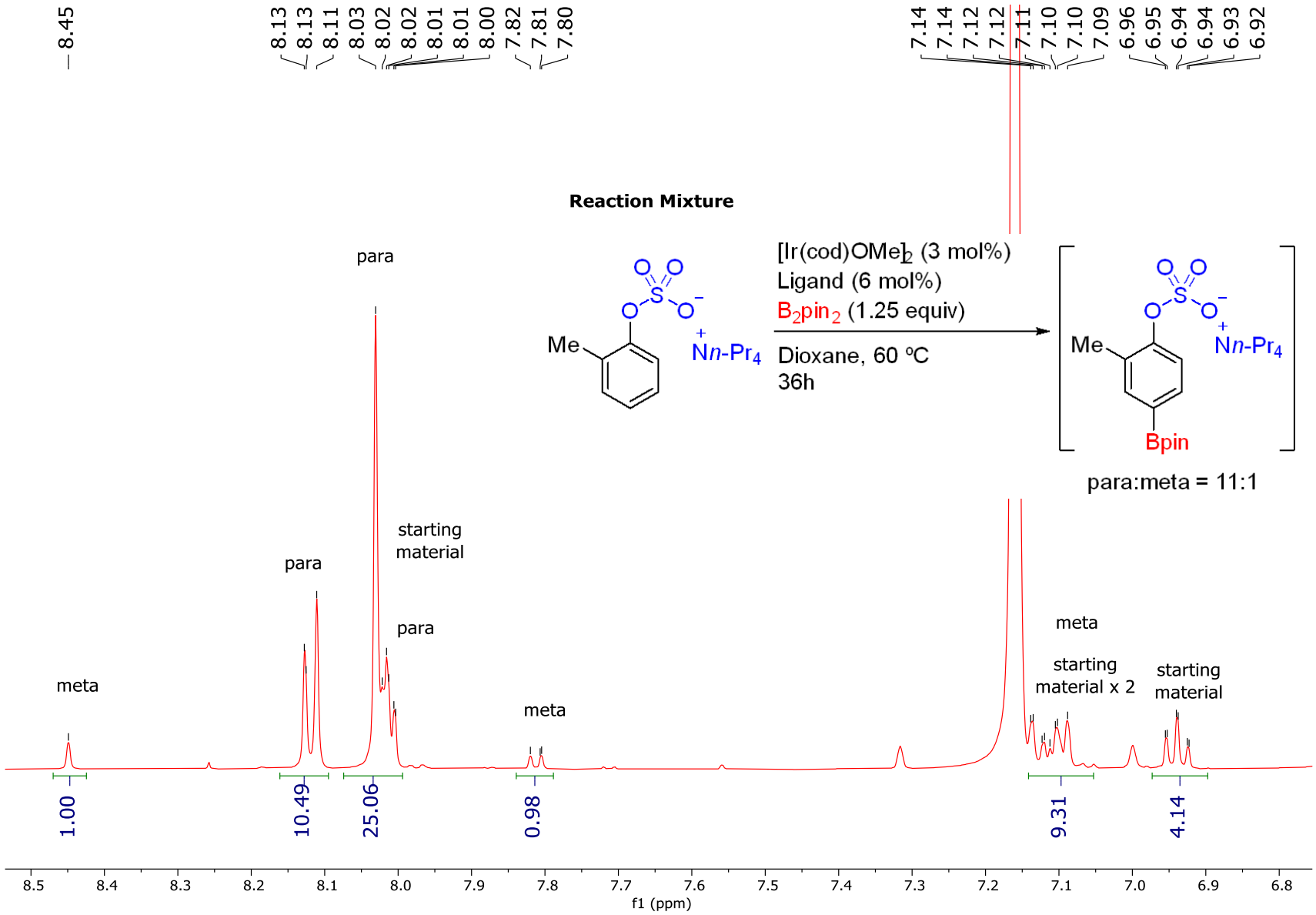
^{11}B NMR of *Para* borylated 2-trifluoromethylphenol (3.2f) (160 MHz, $CDCl_3$)



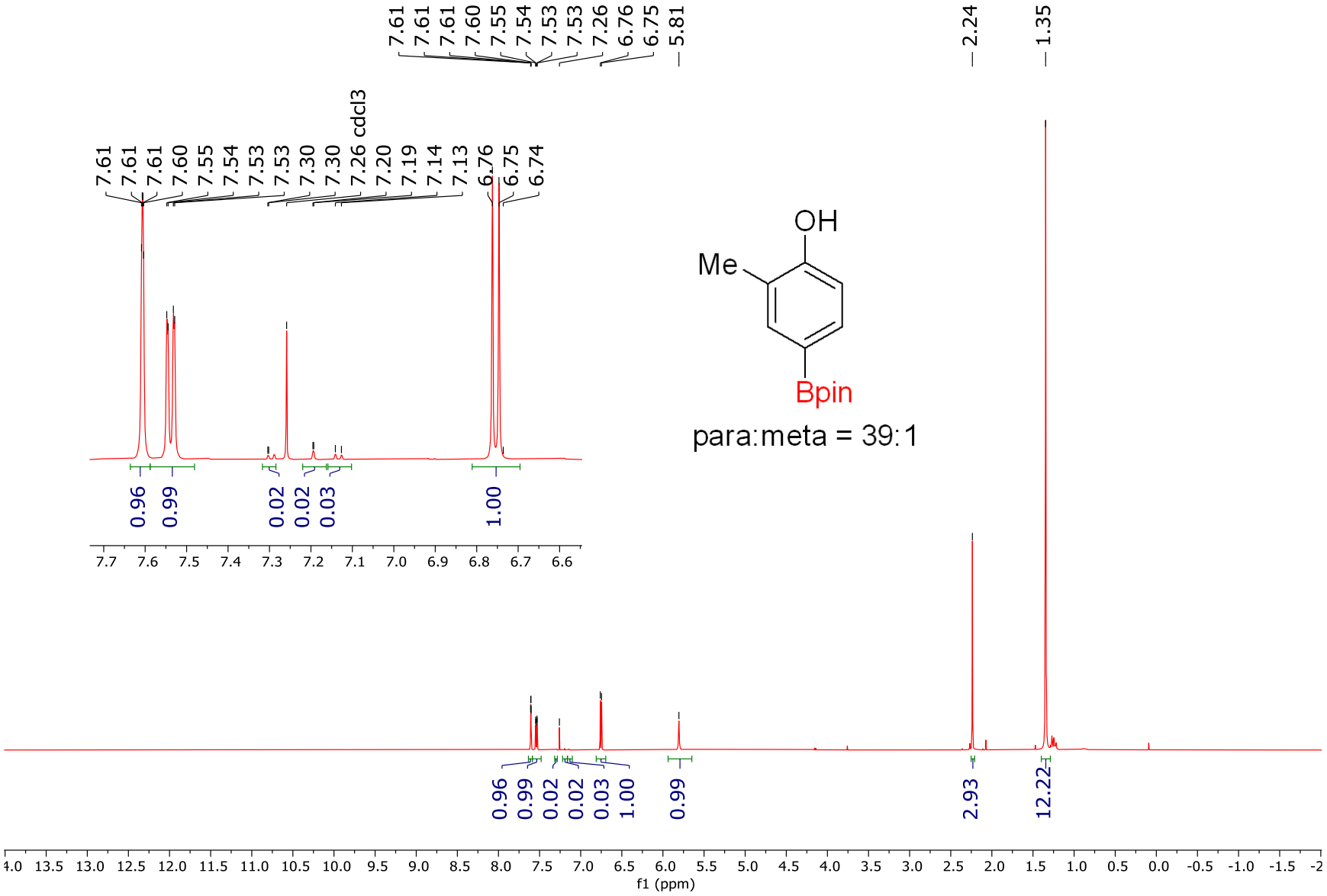
^{19}F NMR spectrum of 2-trifluoromethylphenol (3.2f) (470 MHz, $CDCl_3$)



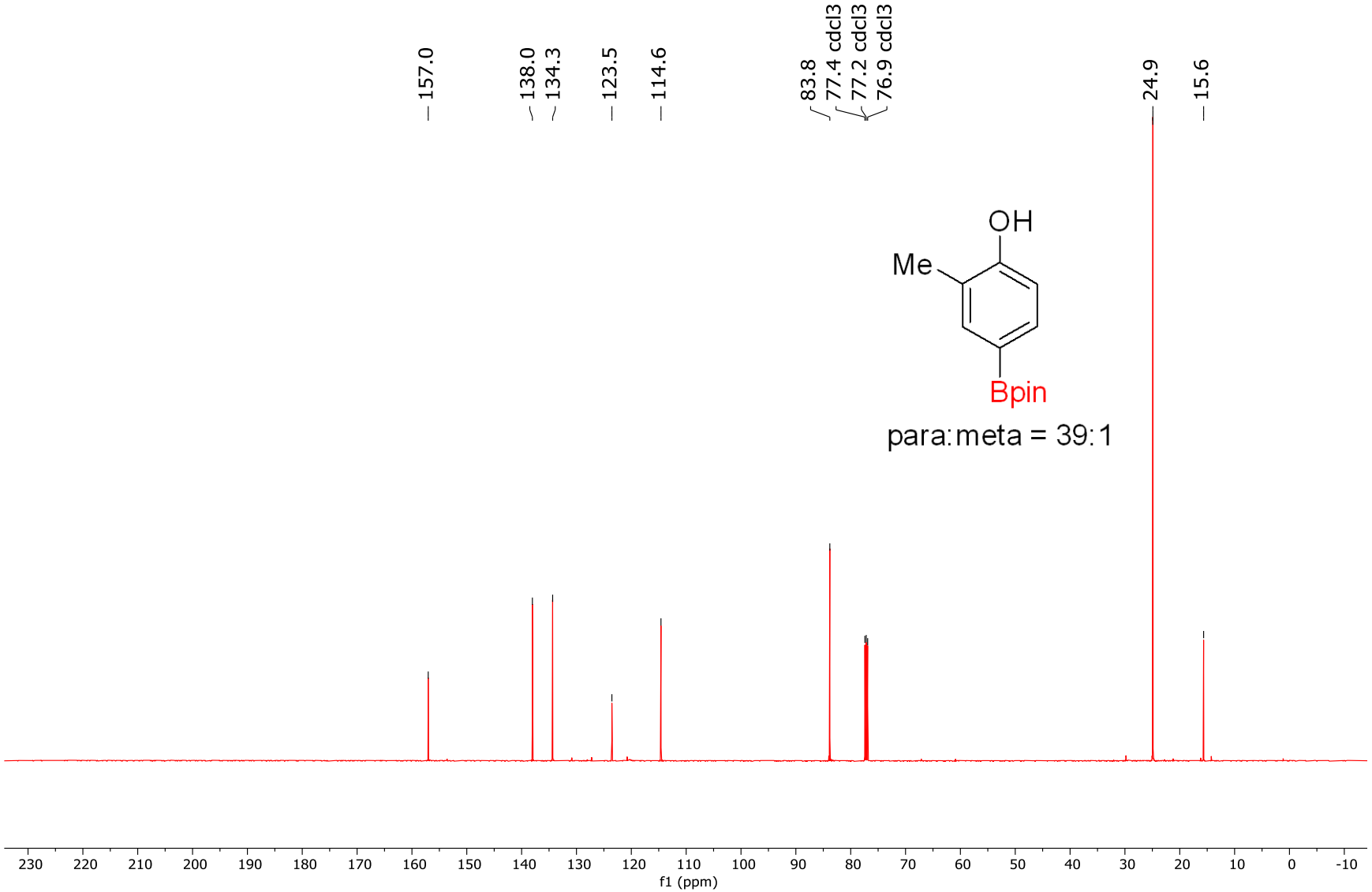
^{1}H NMR reaction mixture for the *Para* borylation of tetrapropyl ammonium 2-methylphenylsulfate (3.2g) (500 MHz, C_6D_6)



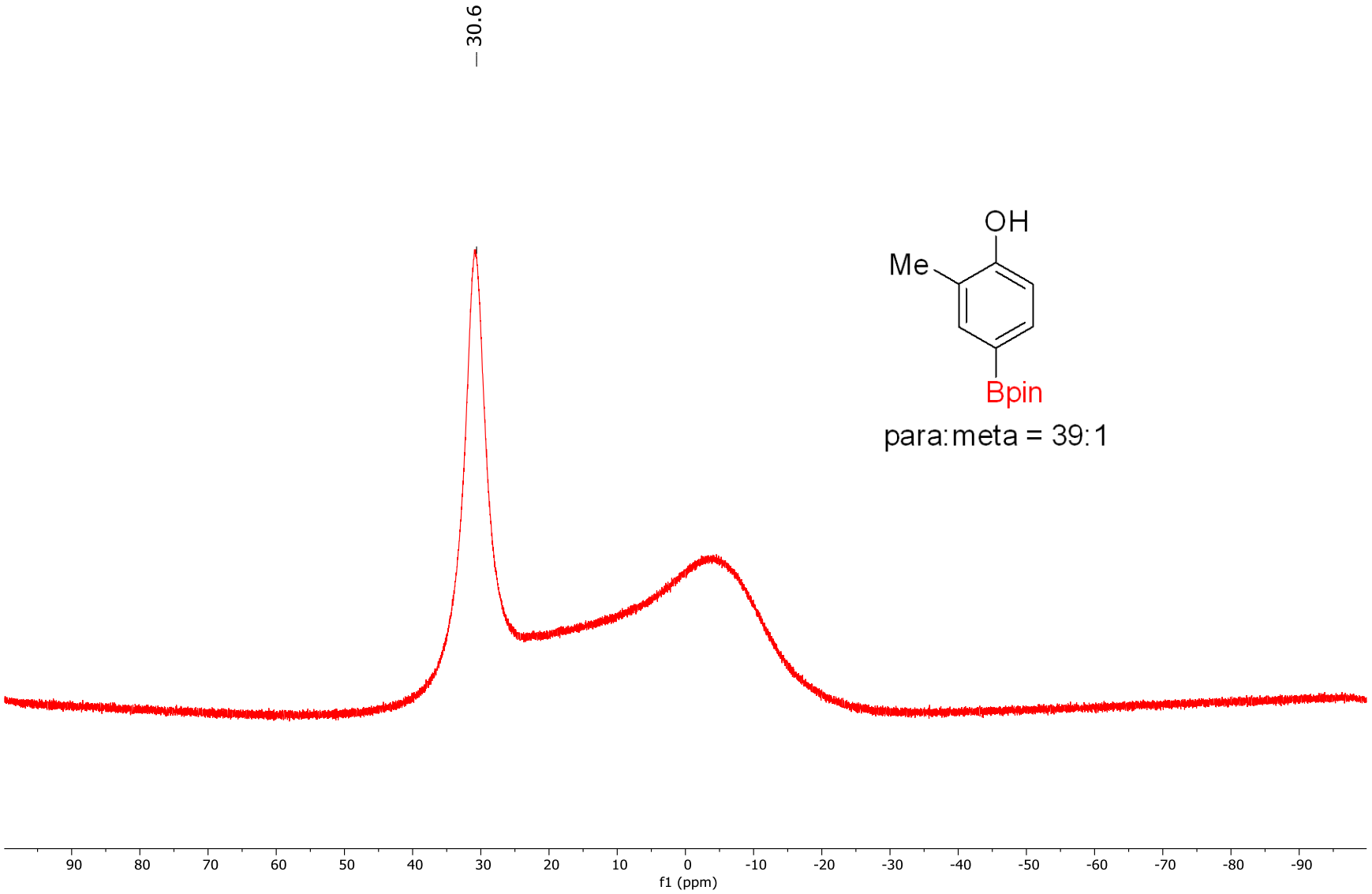
^{1}H NMR spectrum of *Para* borylated 2-methylphenol (3.2g) (500 MHz, $CDCl_3$)



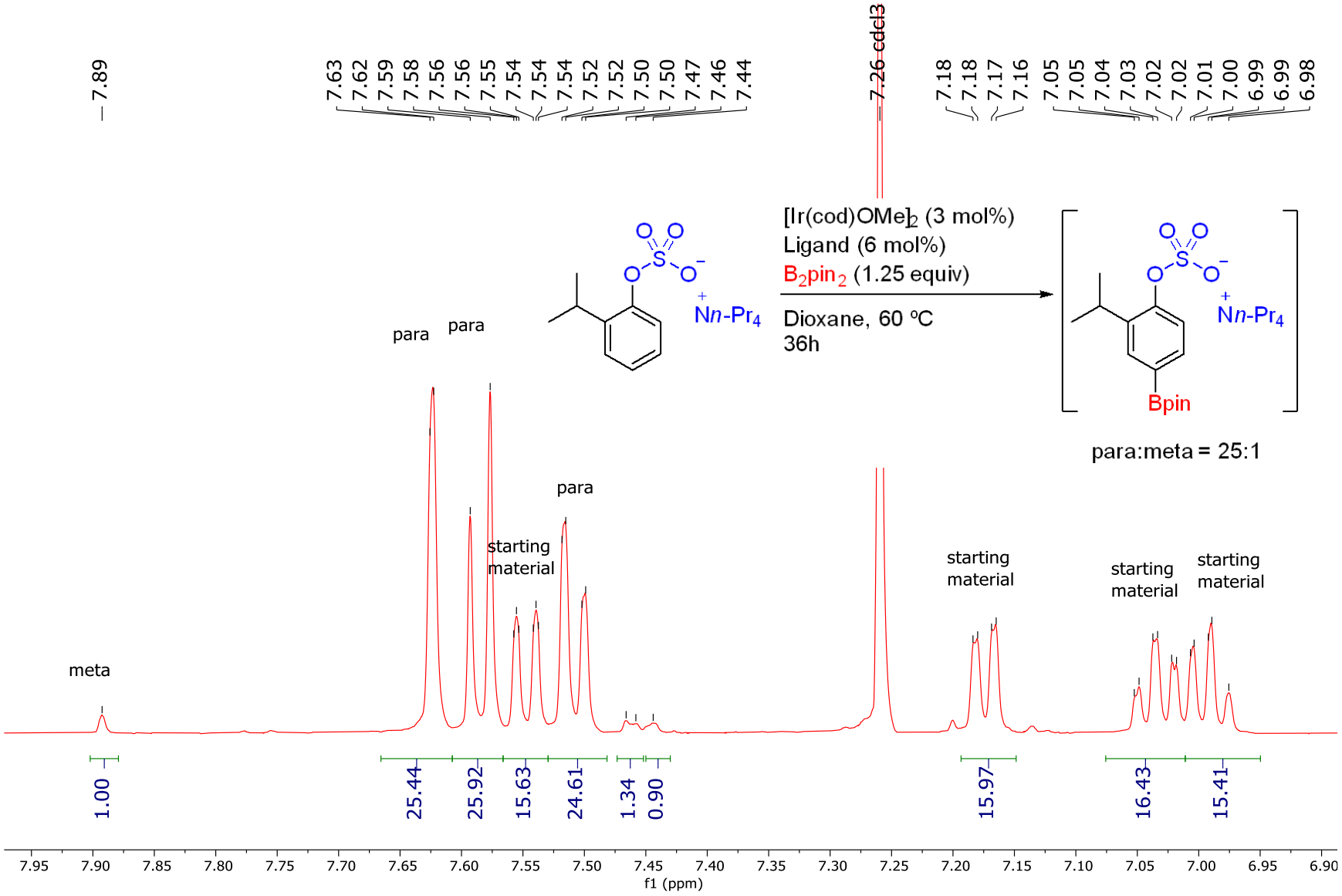
^{13}C NMR spectrum of *Para* borylated 2-methylphenol (3.2g) (126 MHz, $CDCl_3$)



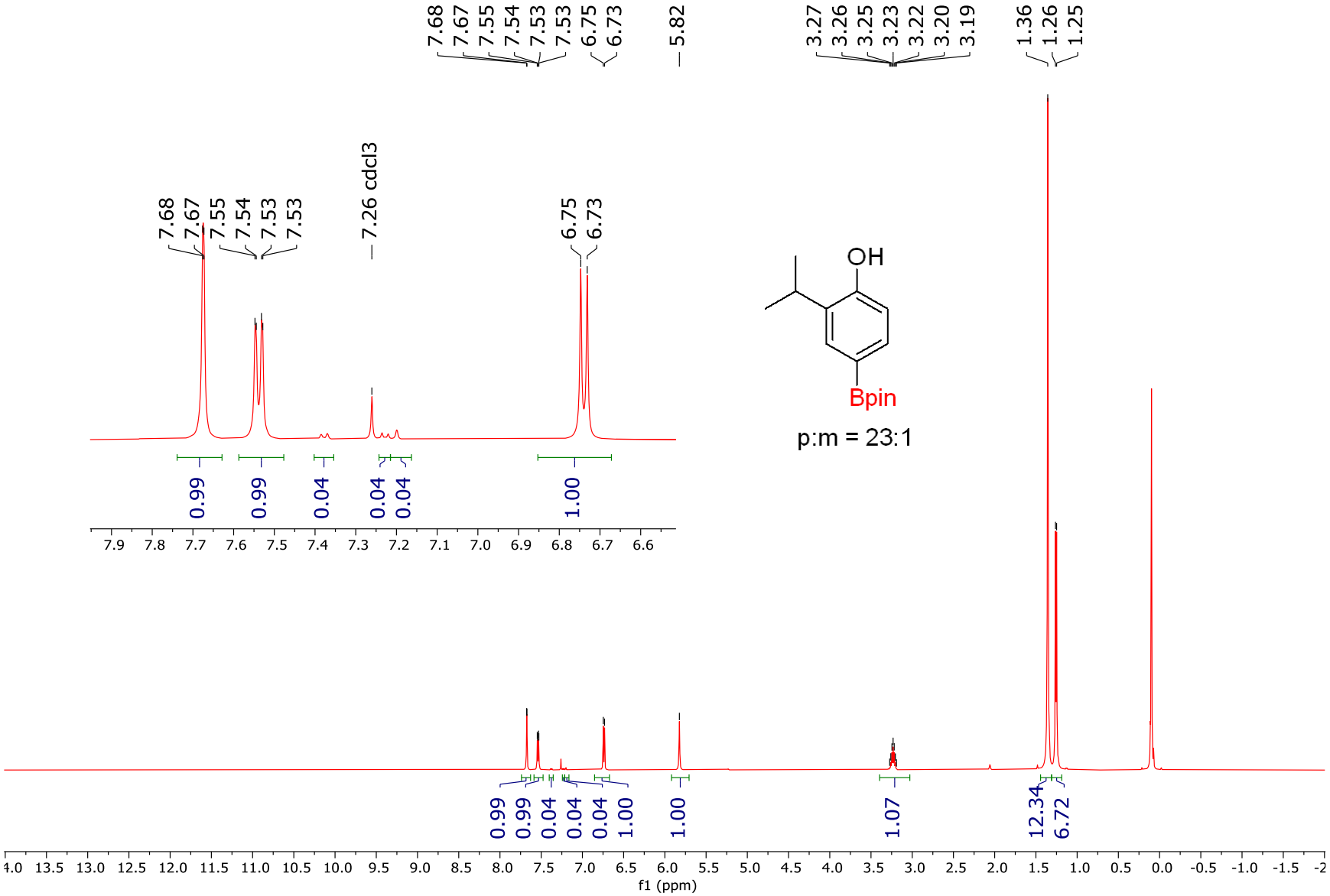
^{11}B NMR spectrum of *Para* borylated 2-methylphenol (3.2g) (160 MHz, $CDCl_3$)



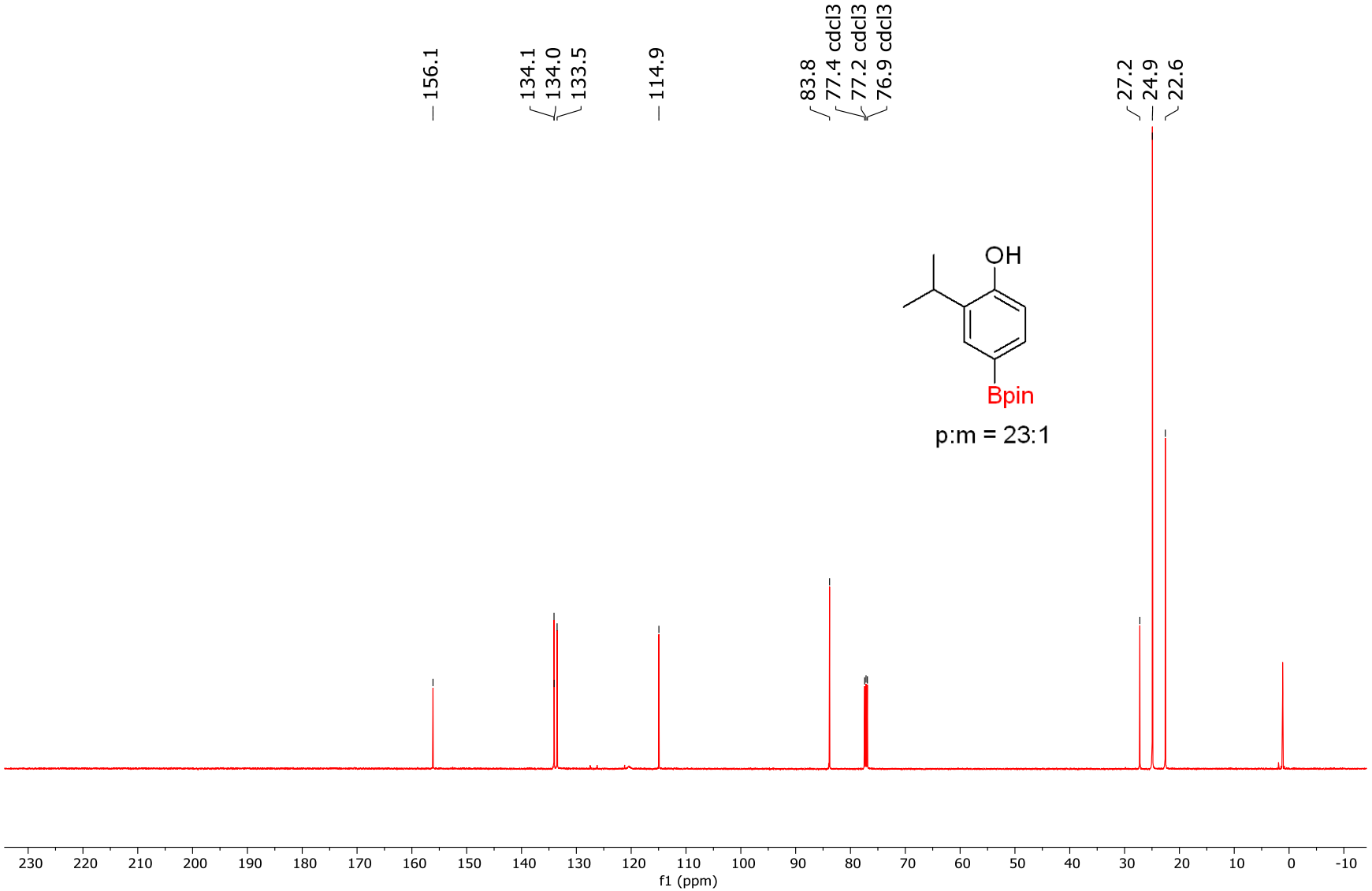
^{1}H NMR reaction mixture of *Para* borylation of tetrapropylammonium 2-isopropylphenylsulfate (3.2h) (500 MHz, $CDCl_3$)



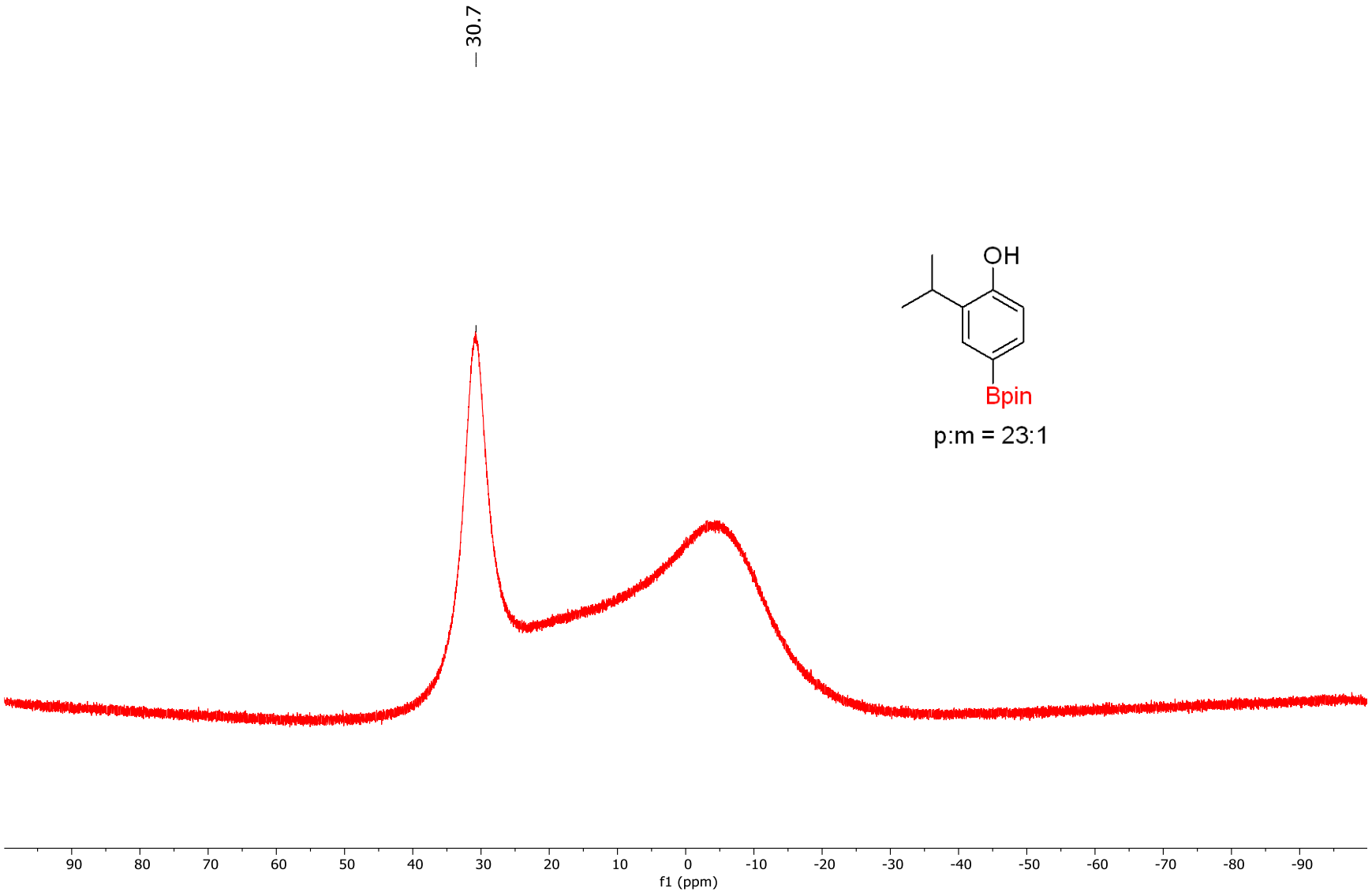
^{1}H NMR spectrum of *Para* borylated 2-isopropylphenol (3.2h) (500 MHz, $CDCl_3$)



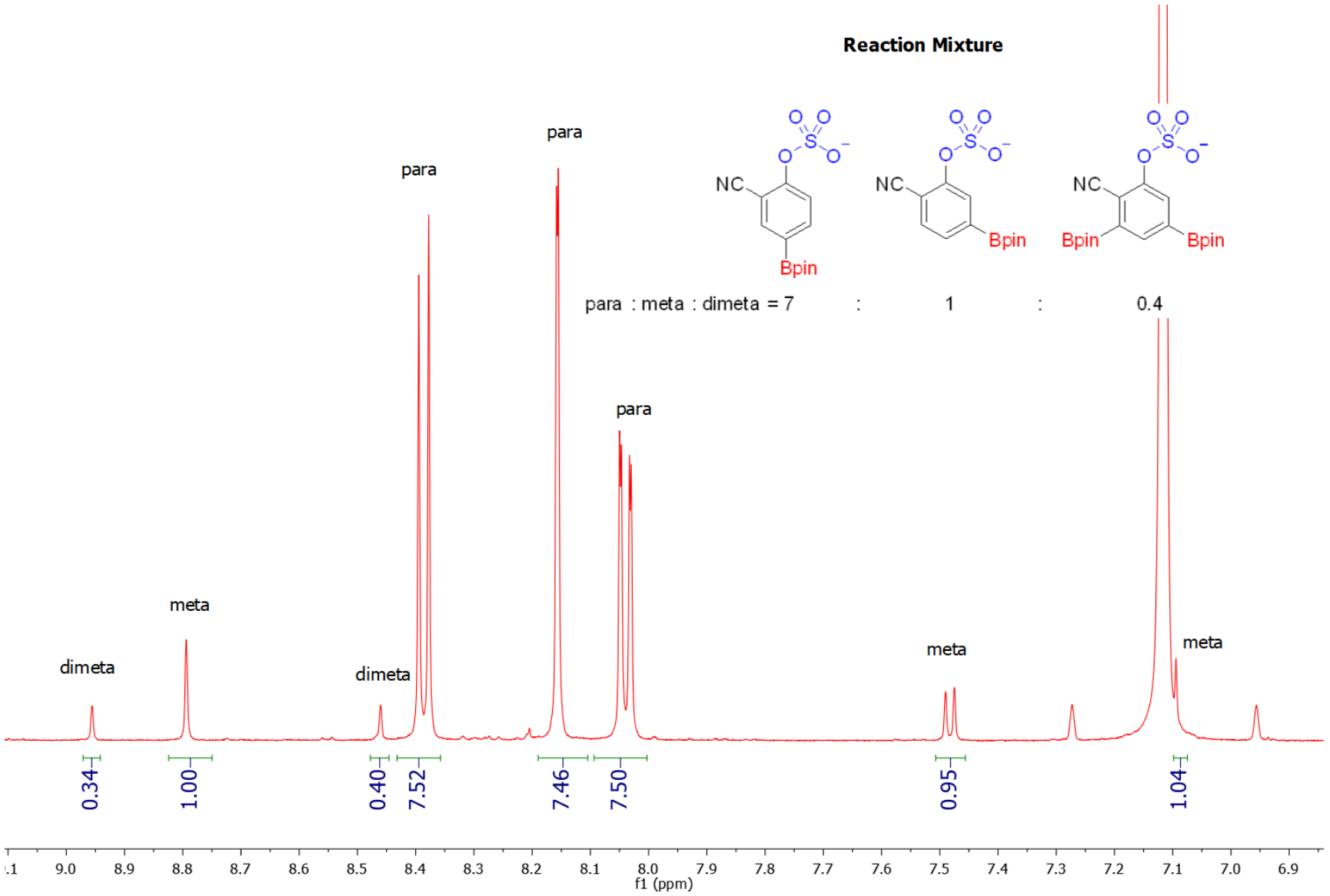
^{13}C NMR spectrum of *Para* borylated 2-isopropylphenol (3.2h) (126 MHz, $CDCl_3$)



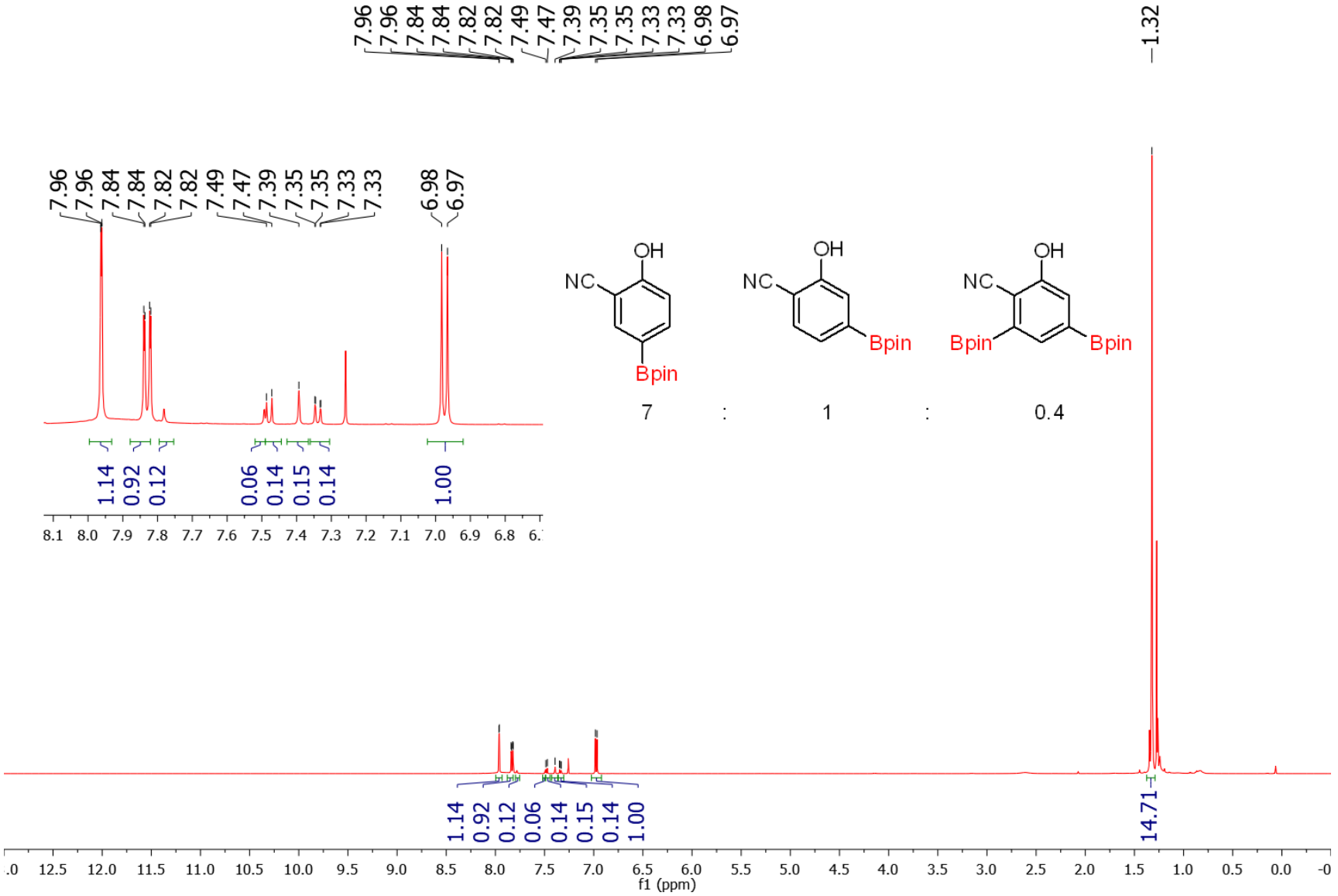
^{11}B NMR spectrum of *Para* borylated 2-isopropylphenol (3.2h) (160 MHz, $CDCl_3$)



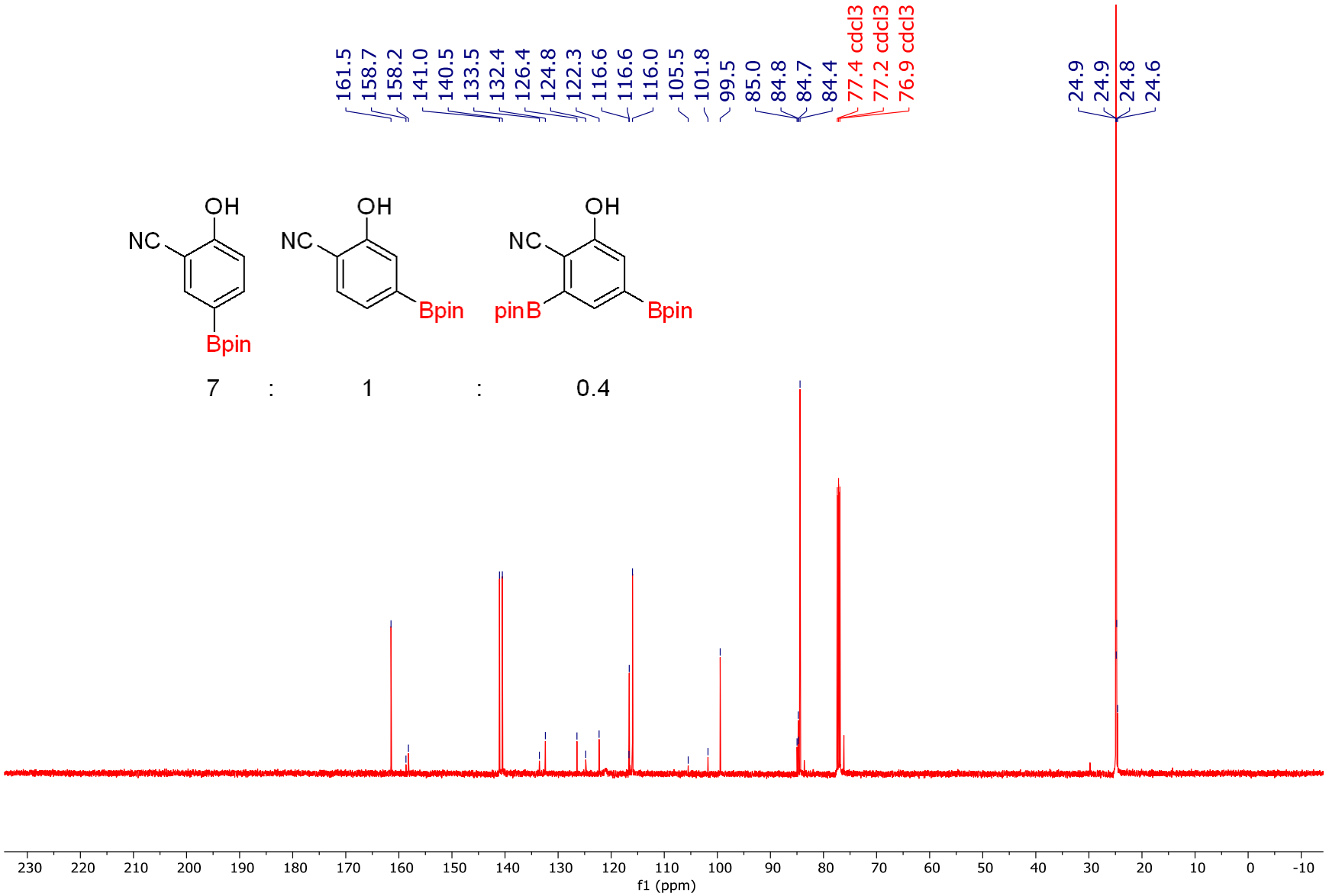
^{1}H NMR reaction mixture of *Para* borylation of tetrapropylammonium 2-cyanophenylsulfate (crude 3.2i) (500 MHz, C_6D_6)



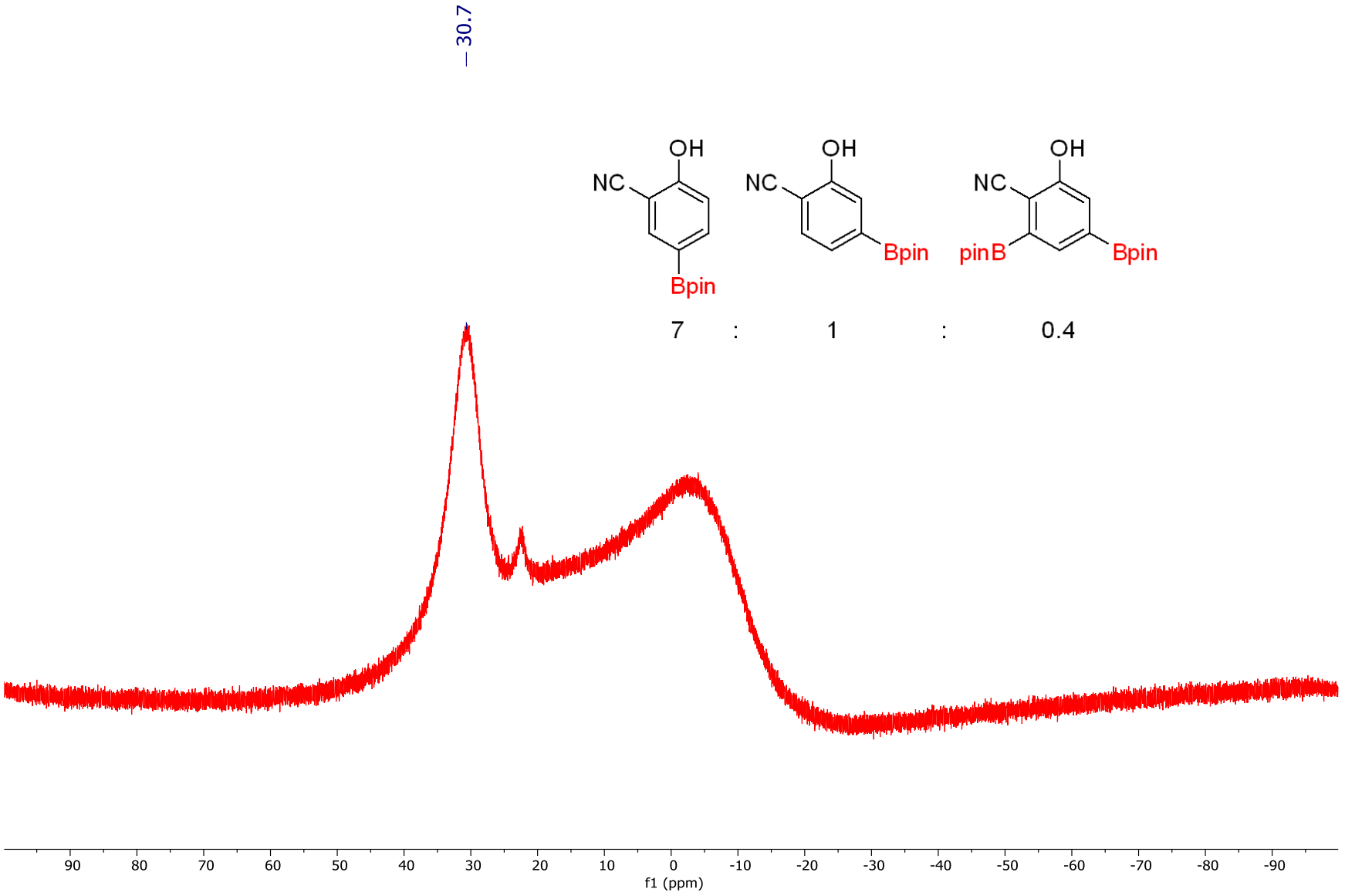
^{1}H NMR spectrum of mixture of borylated 2-cyanolphenol regioisomers (3.2i) (500 MHz, $CDCl_3$)



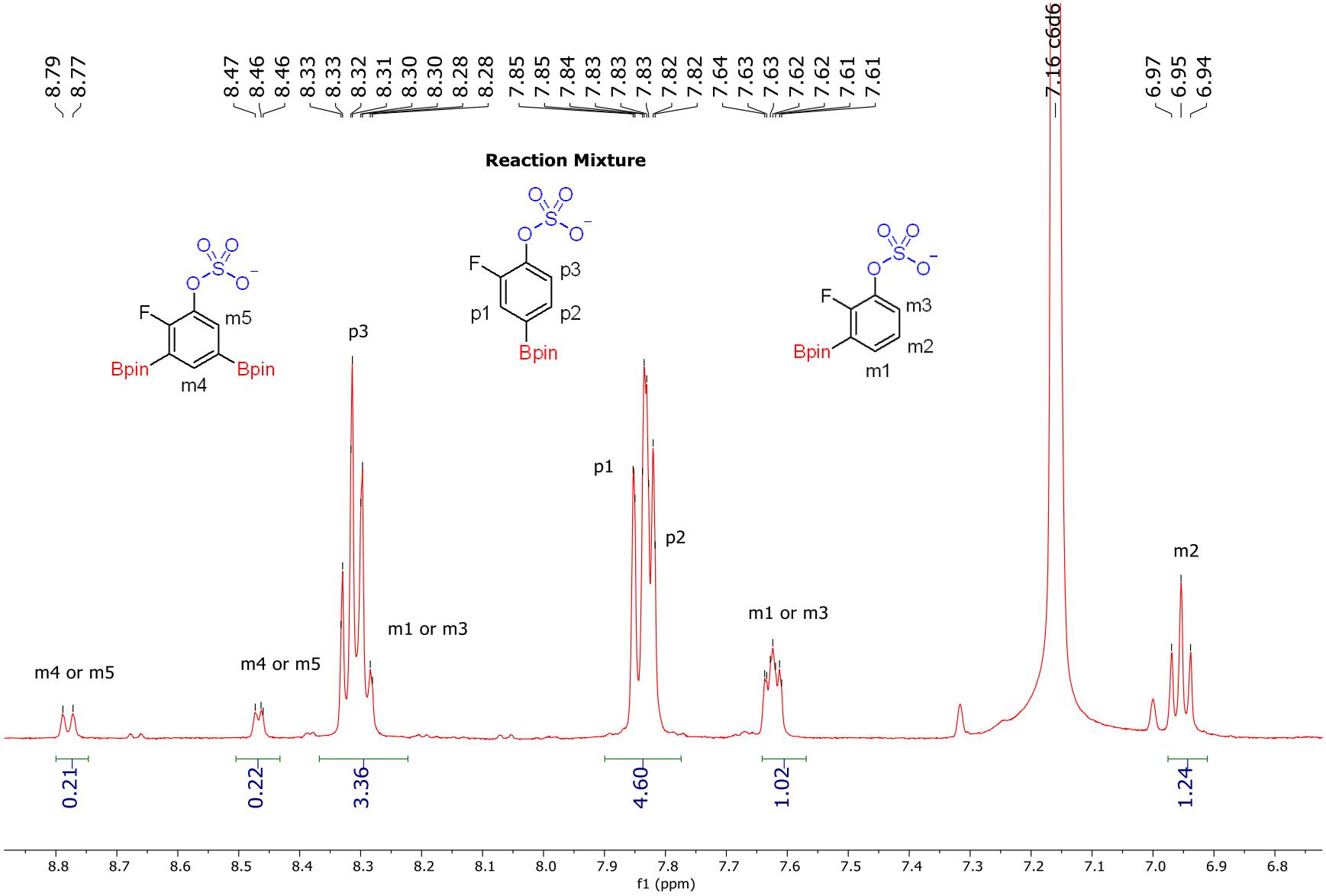
^{13}C NMR spectrum of mixture of borylated 2-cyanolphenol regioisomers (3.2i) (126 MHz, $CDCl_3$)



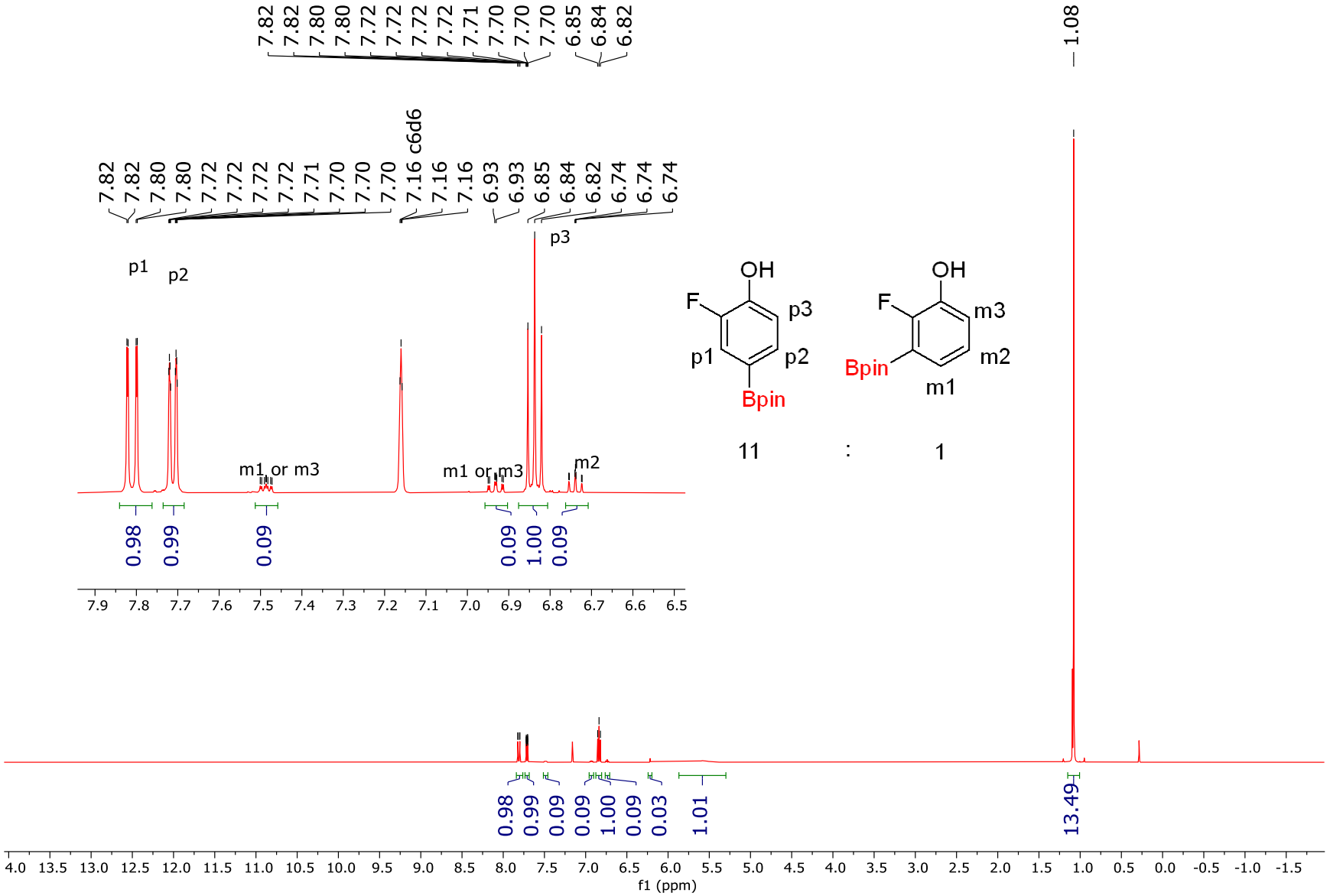
^{11}B NMR spectrum of borylated mixture 2-cyanophenol regioisomers (3.2i) (160 MHz, $CDCl_3$)



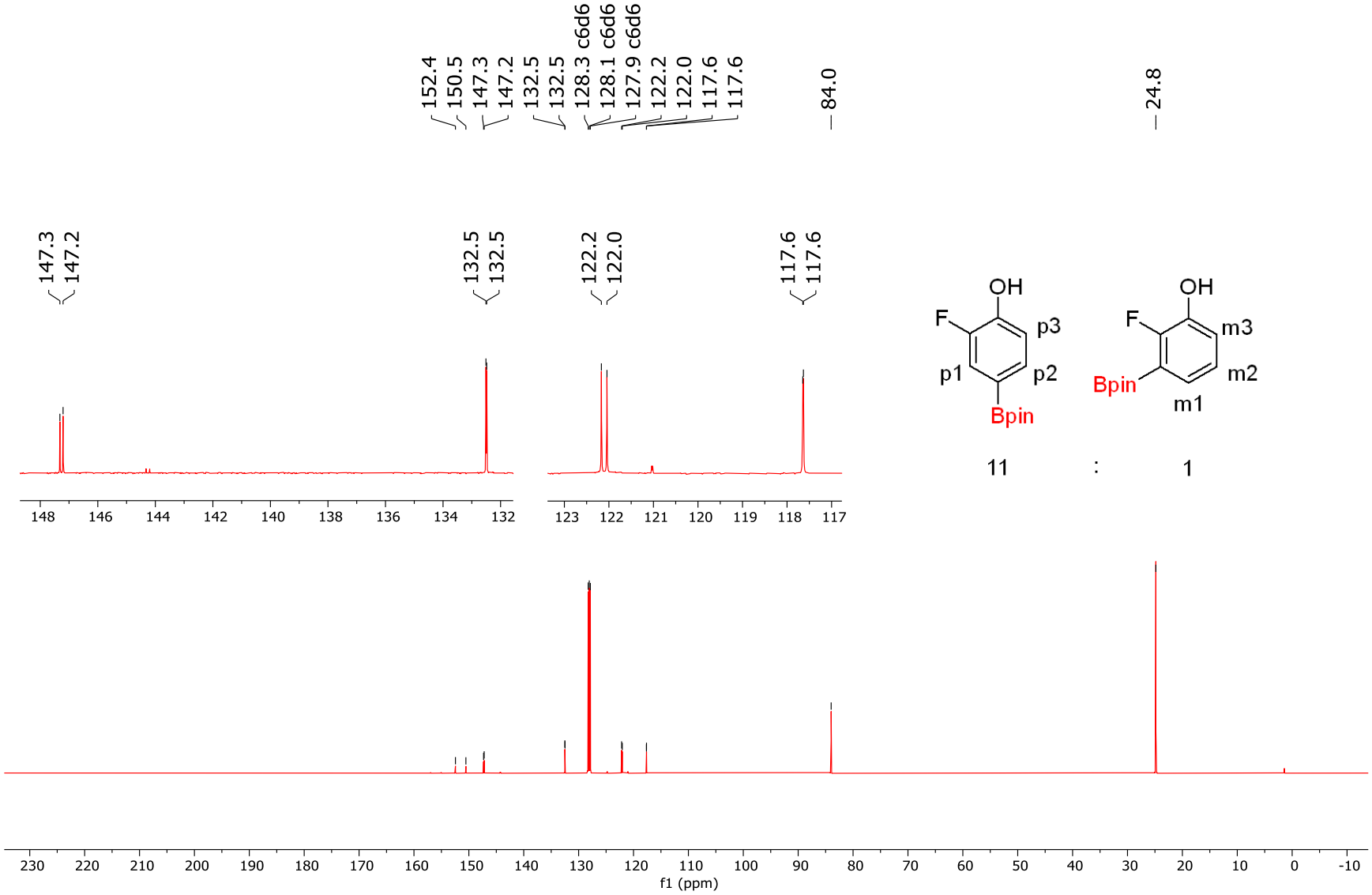
^{1}H NMR reaction mixture for the *Para* borylation of tetrapropylammonium 2-fluorophenylsulfate (3.2j) (500 MHz, C_6D_6)



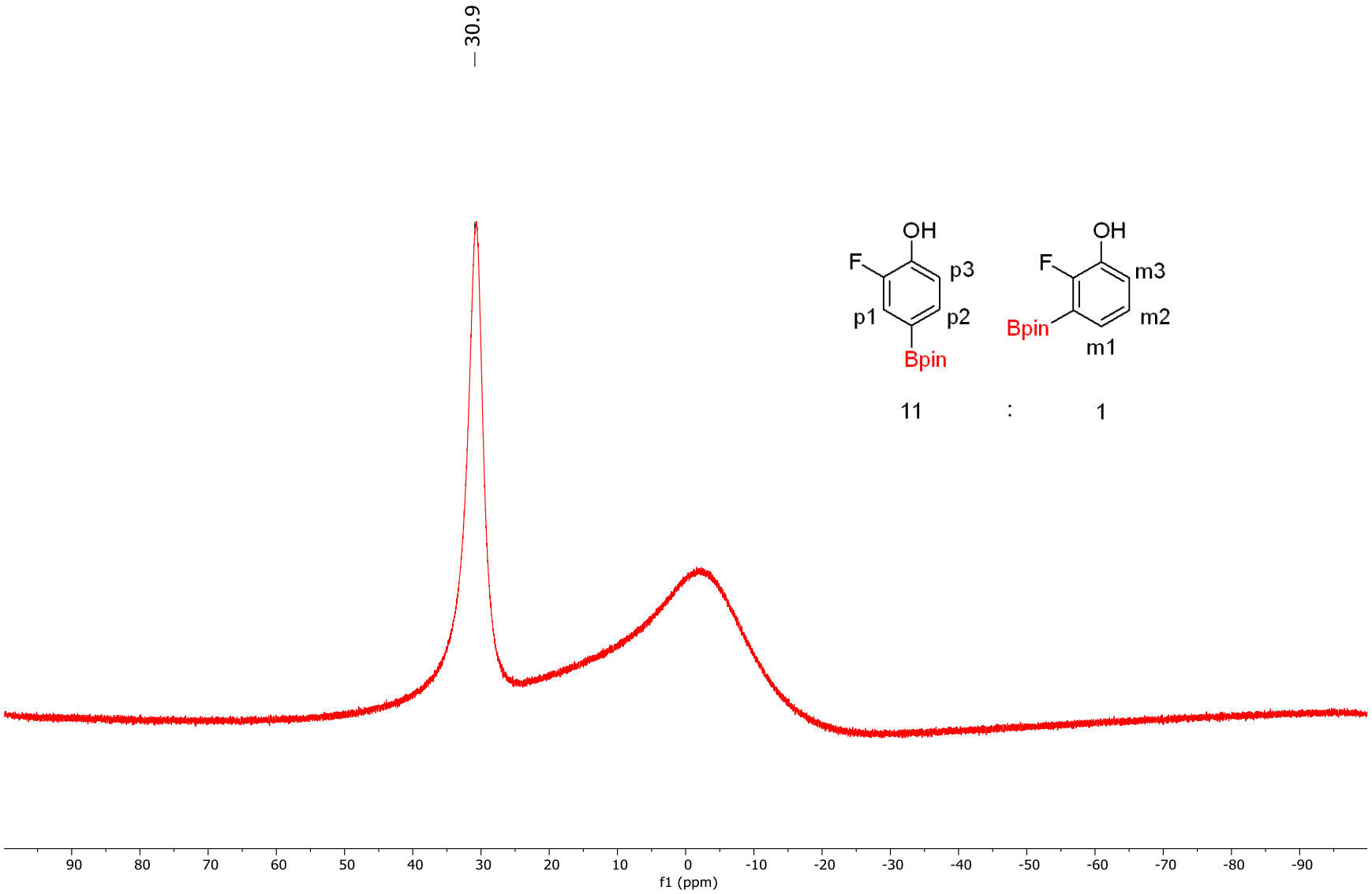
^{1}H NMR spectrum of borylated 2-fluorophenol regioisomers (3.2j) (500 MHz, C_6D_6)



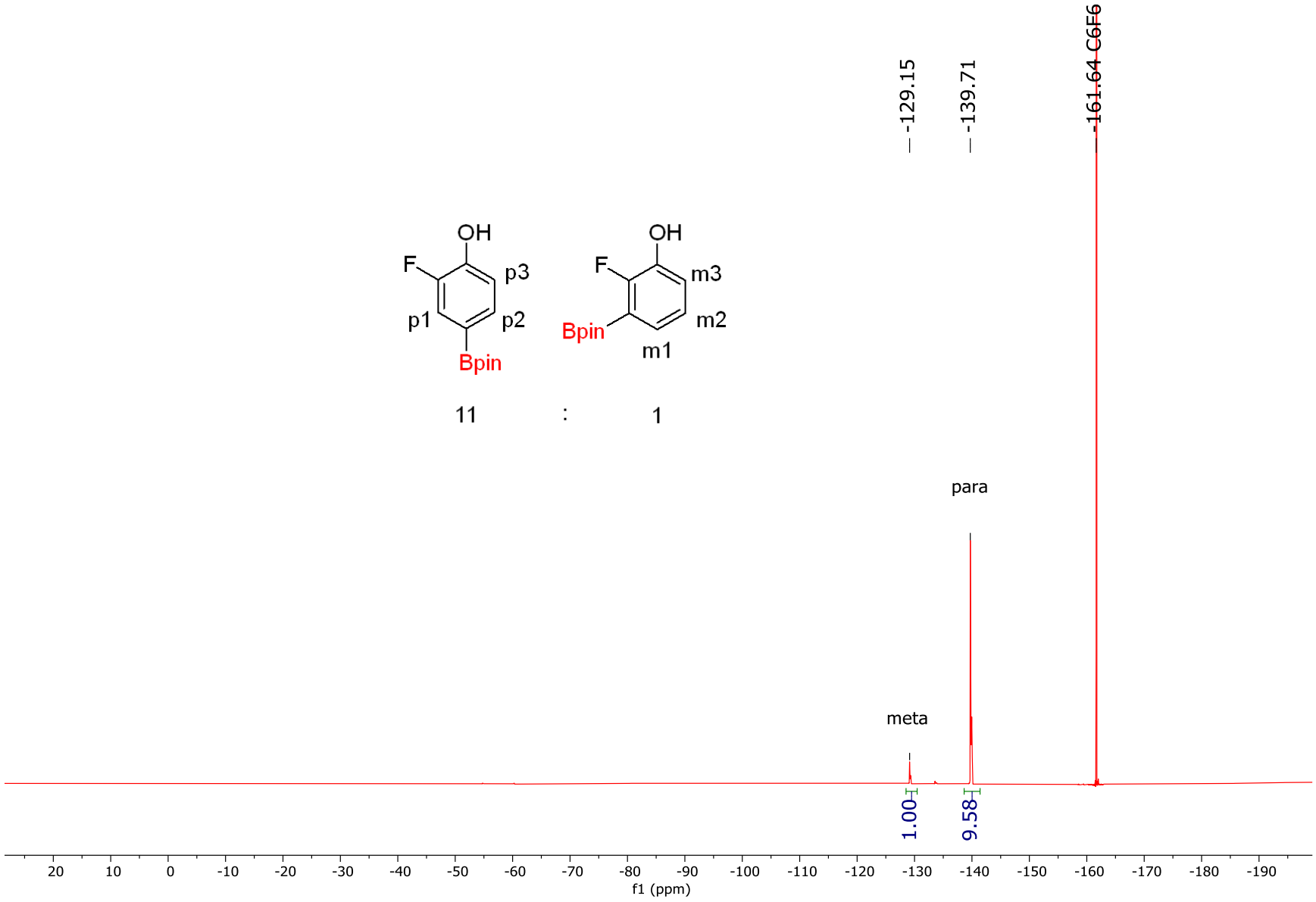
^{13}C NMR spectrum of borylated 2-fluorophenol regioisomers (3.2j) (126 MHz, C_6D_6)



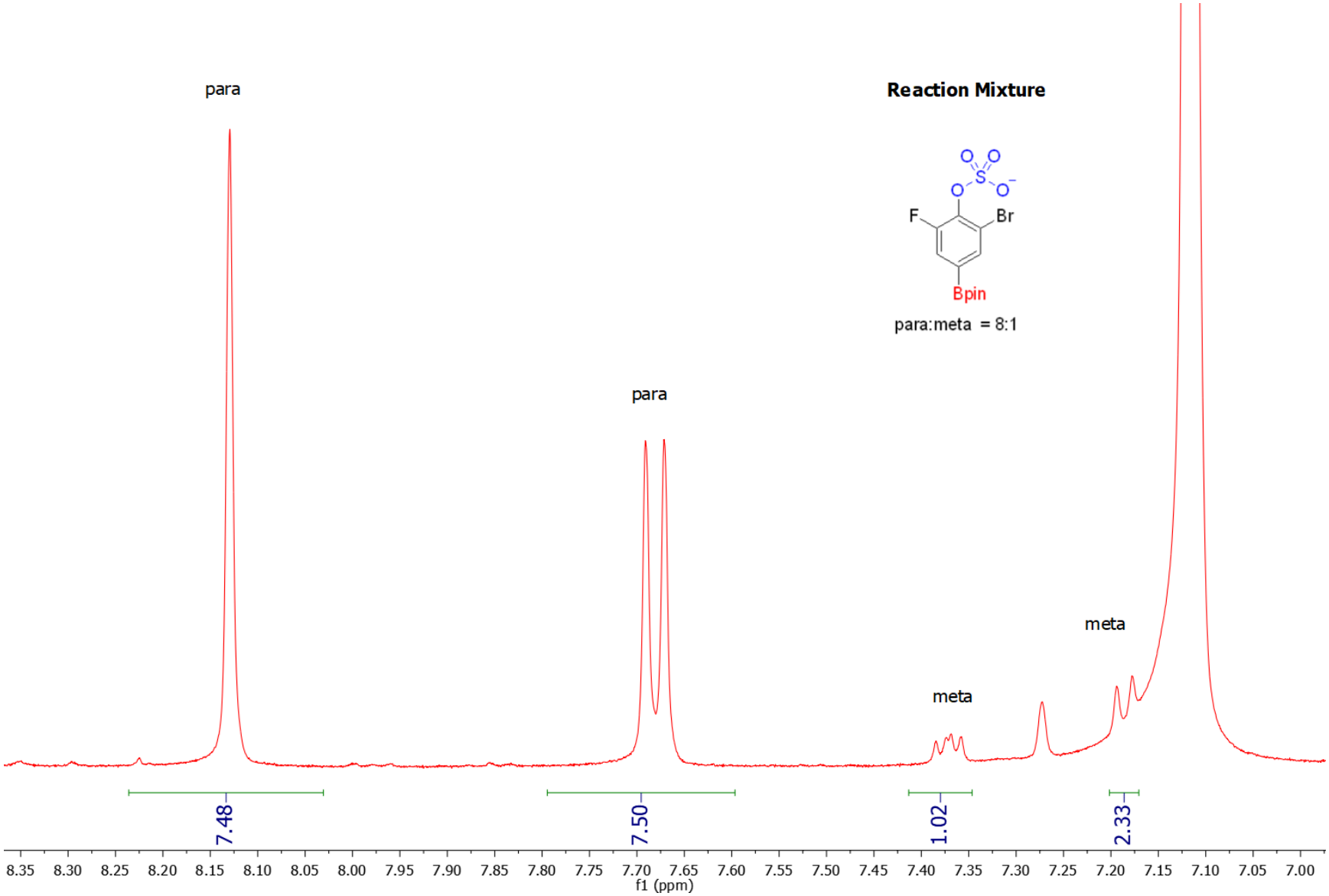
^{11}B NMR spectrum of borylated 2-fluorophenol regioisomers (3.2j) (160 MHz, C_6D_6)



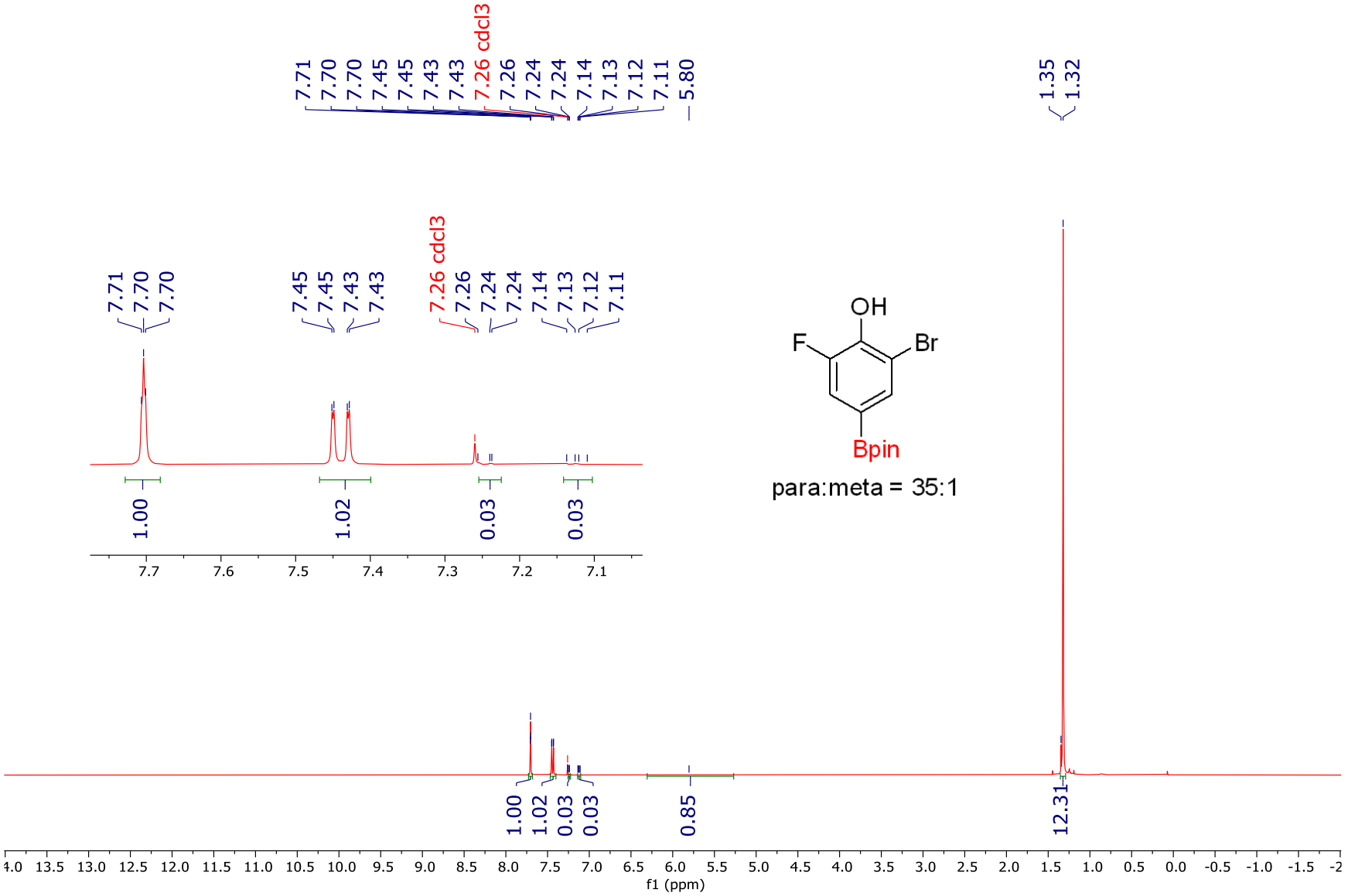
^{19}F NMR spectrum of borylated 2-fluorophenol regioisomers (3.2j) (470 MHz, C_6D_6)



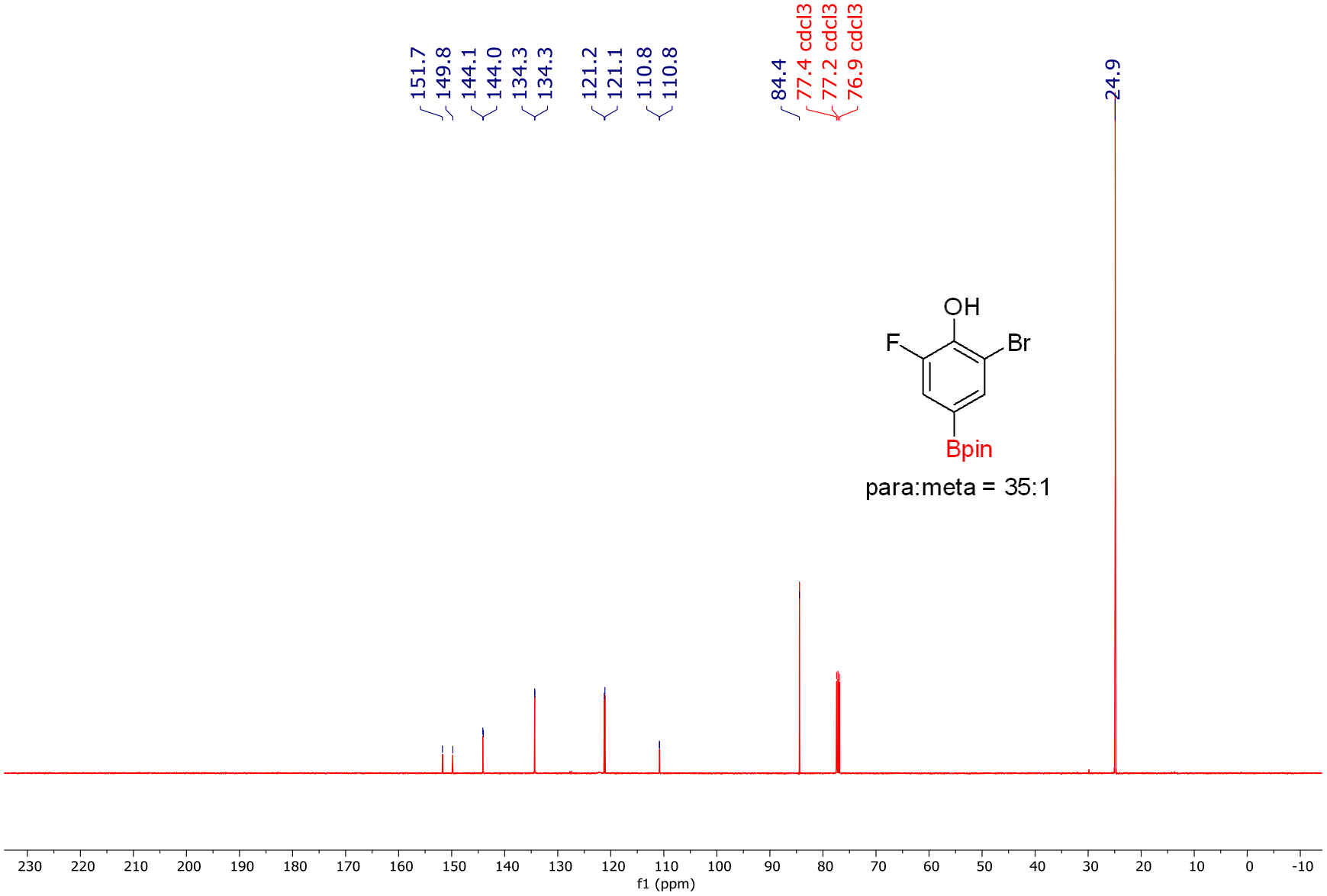
^{1}H NMR reaction mixture of *Para* borylated tetrapropylammonium 2-bromo-6-fluorophenylsulfate (3.2k) (500 MHz, C_6D_6)



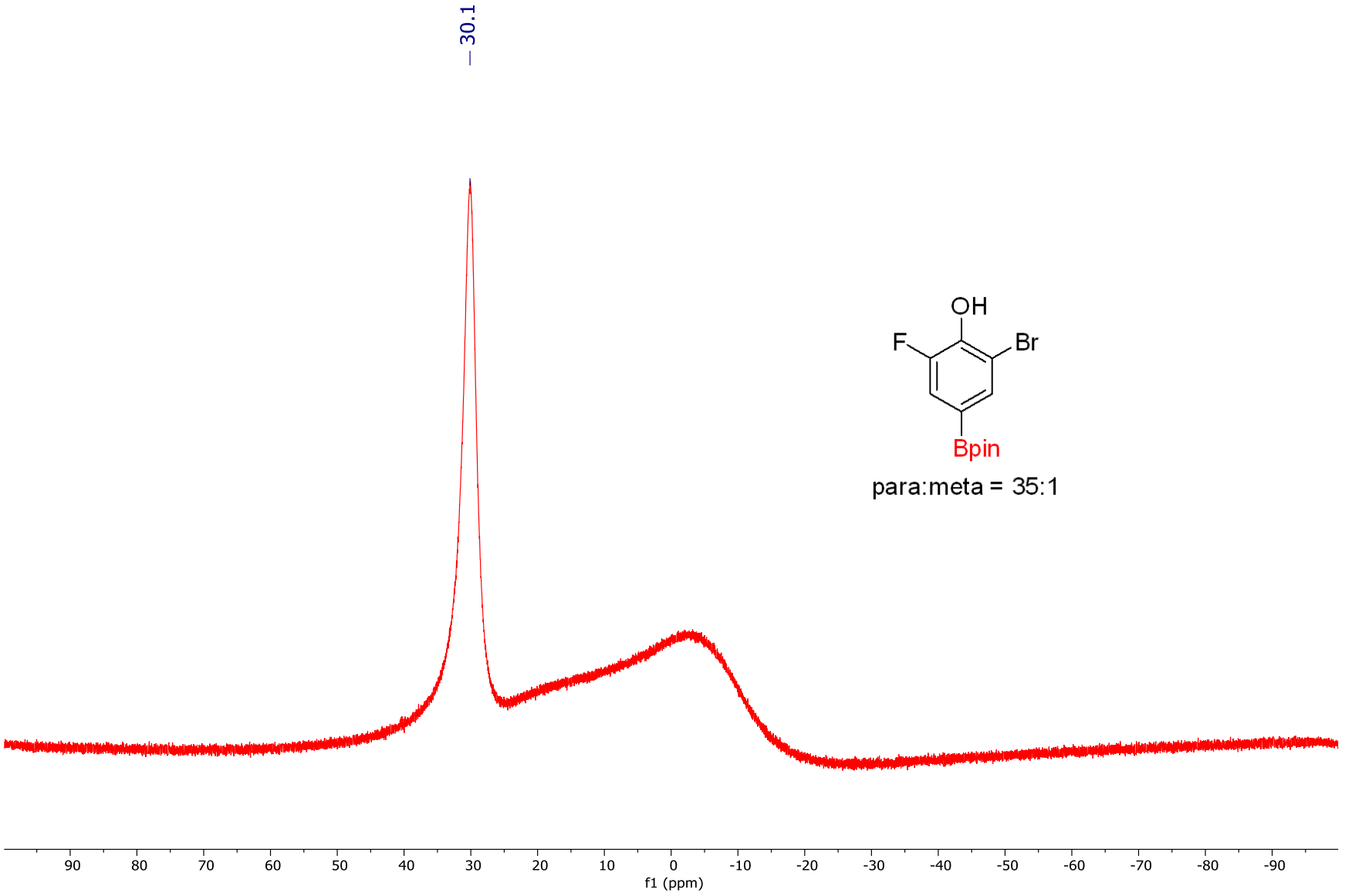
^{1}H NMR spectrum of *Para* borylated 2-bromo-6-fluorophenol (3.2k) (500 MHz, $CDCl_3$)



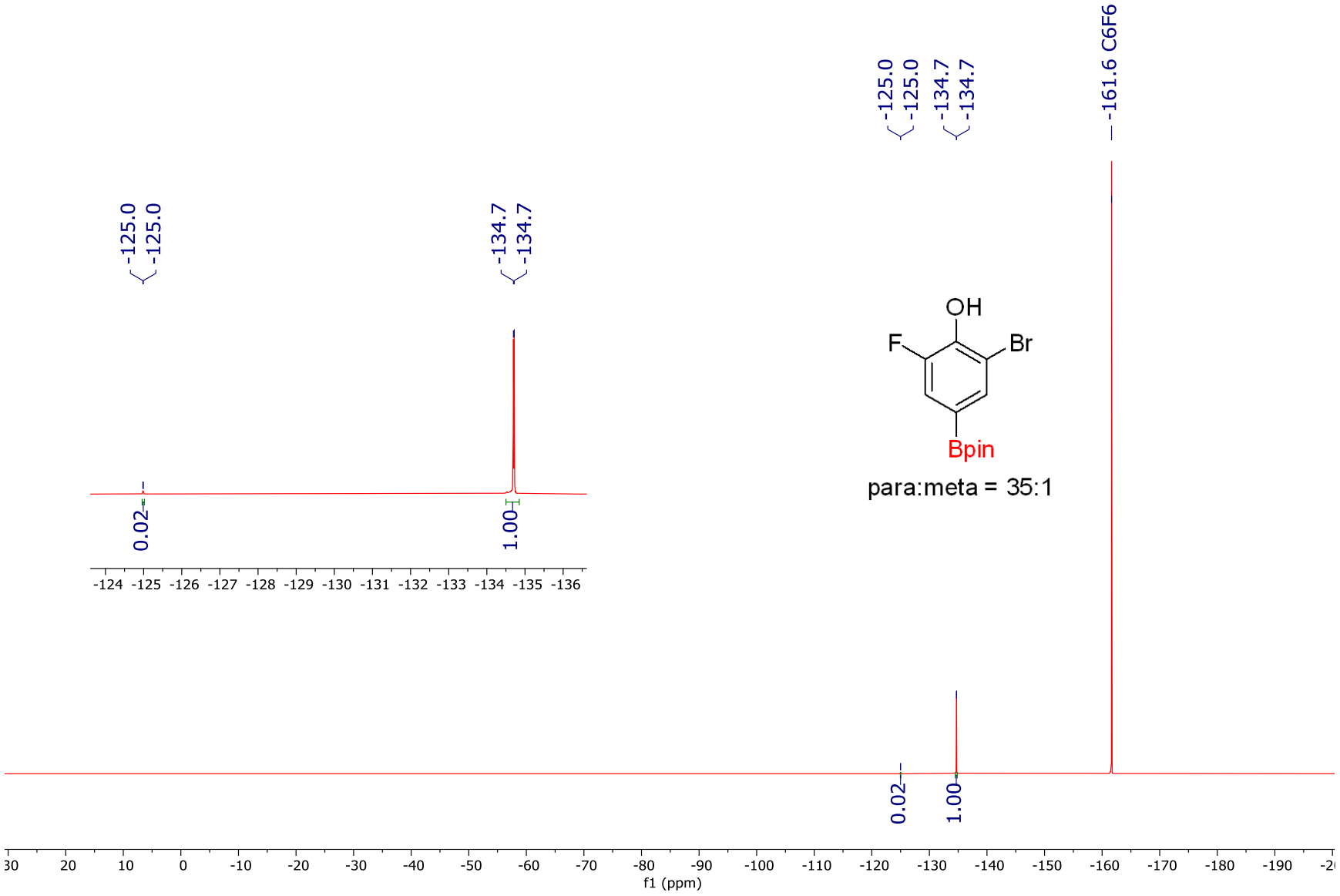
^{13}C NMR spectrum of *Para* borylated 2-bromo-6-fluorophenol (3.2k) (126 MHz, $CDCl_3$)



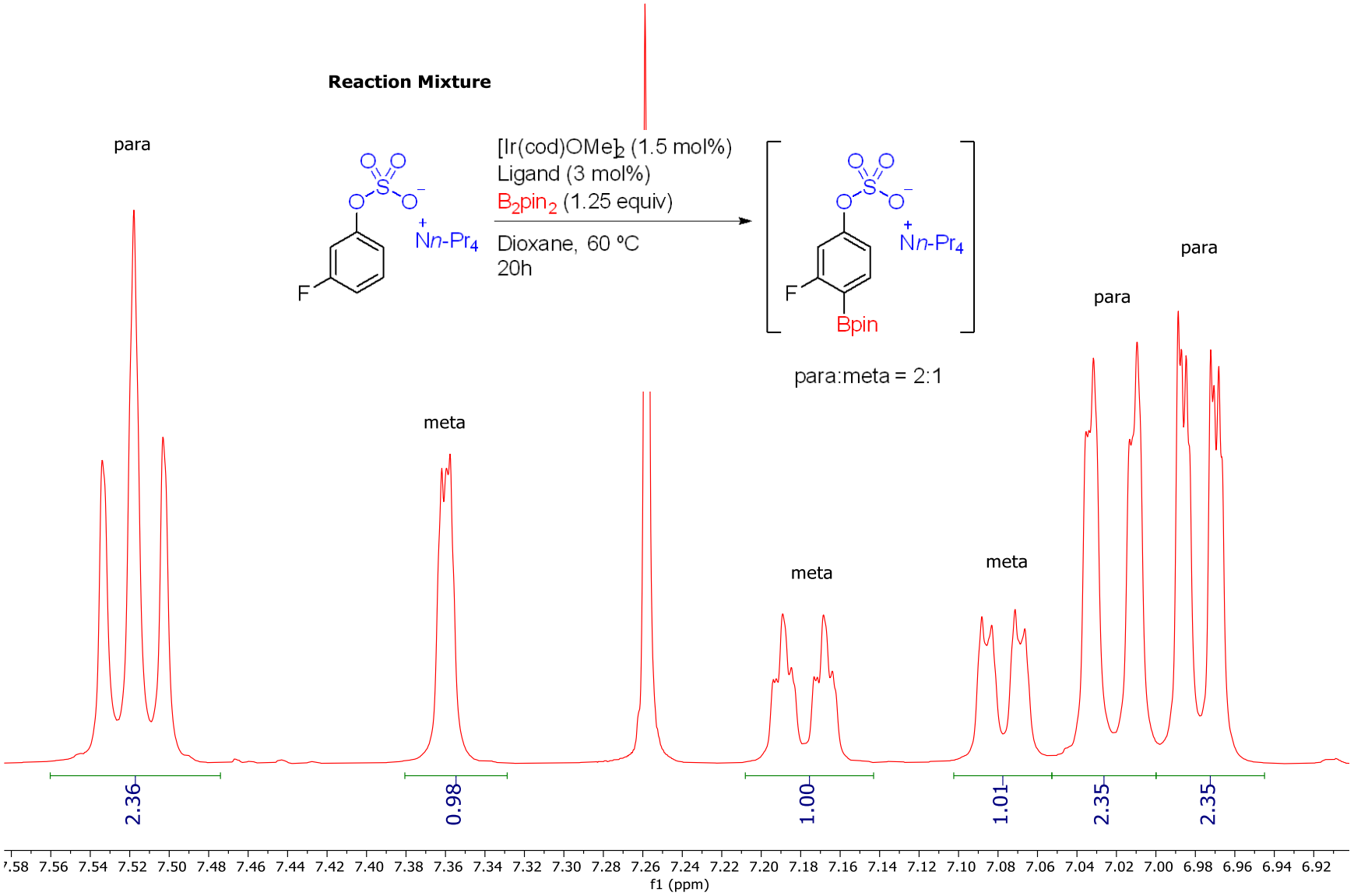
^{11}B NMR spectrum of *Para* borylated 2-bromo-6-fluorophenol (3.2k) (160 MHz, $CDCl_3$)



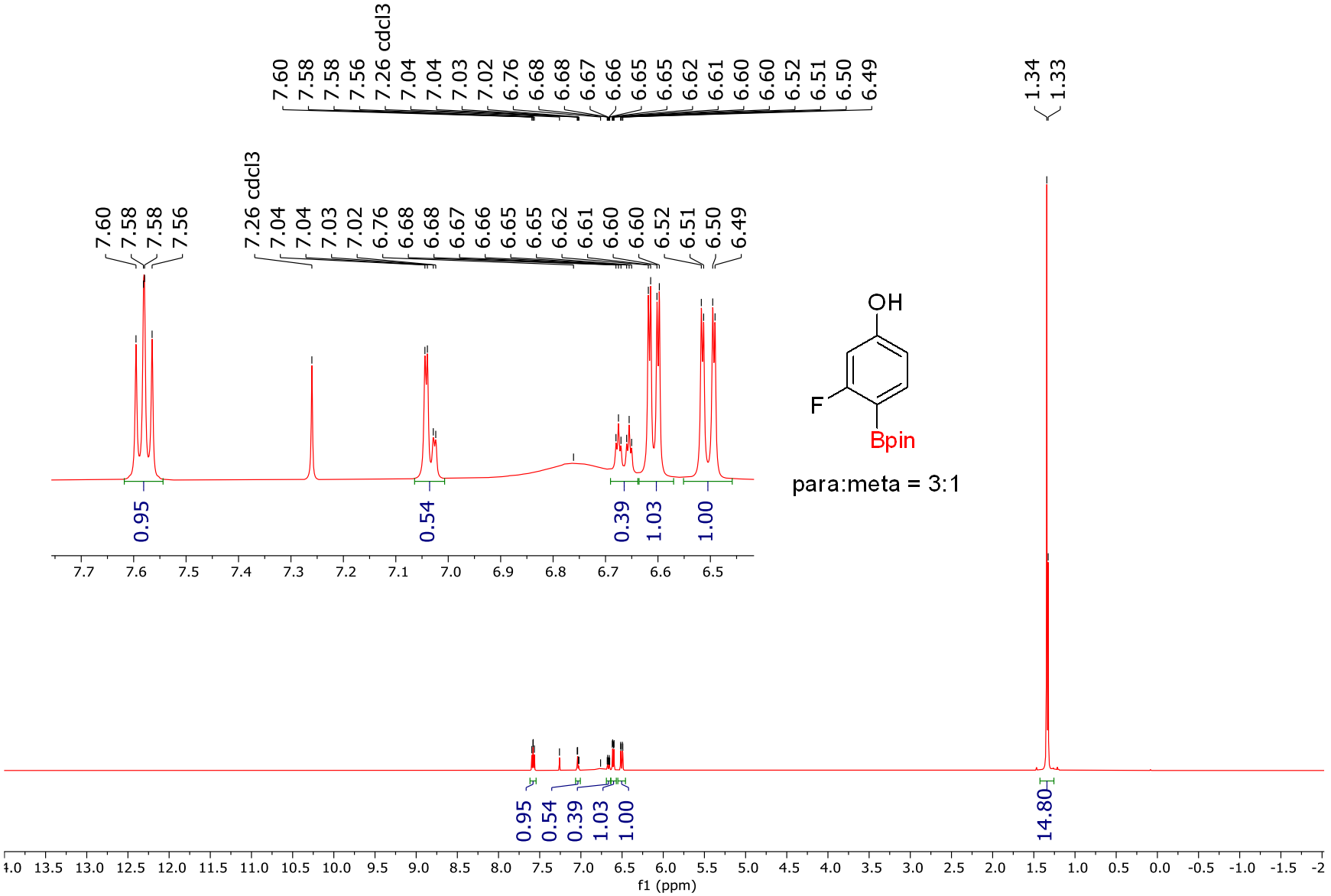
^{19}F NMR spectrum of *Para* borylated 2-bromo-6-fluorophenol (3.2k) (470 MHz, $CDCl_3$)



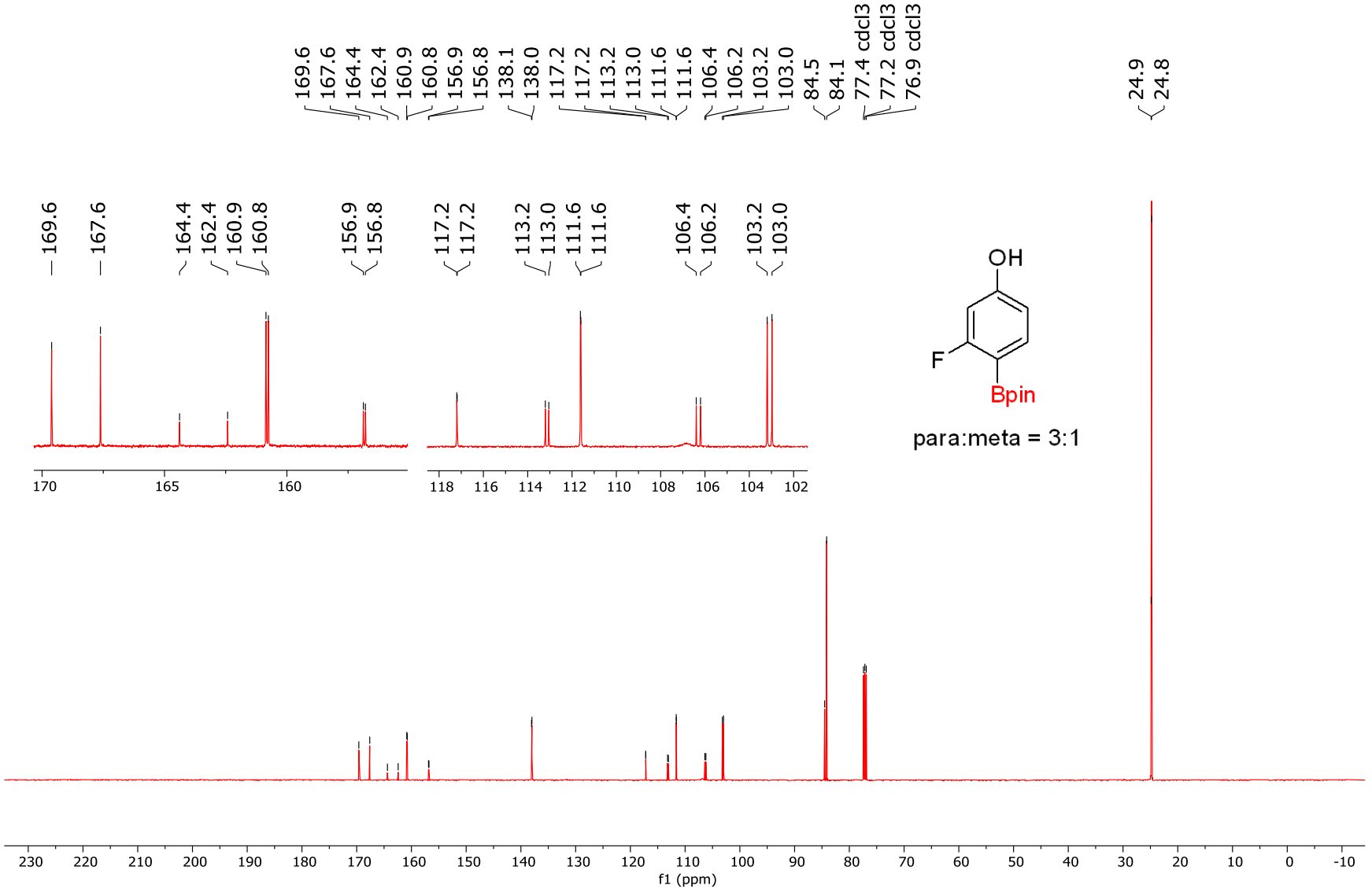
^{1}H NMR reaction mixture for the *Para* borylation of tetrapropylammonium 3-fluorophenylsulfate (3.2l) (500 MHz, $CDCl_3$)



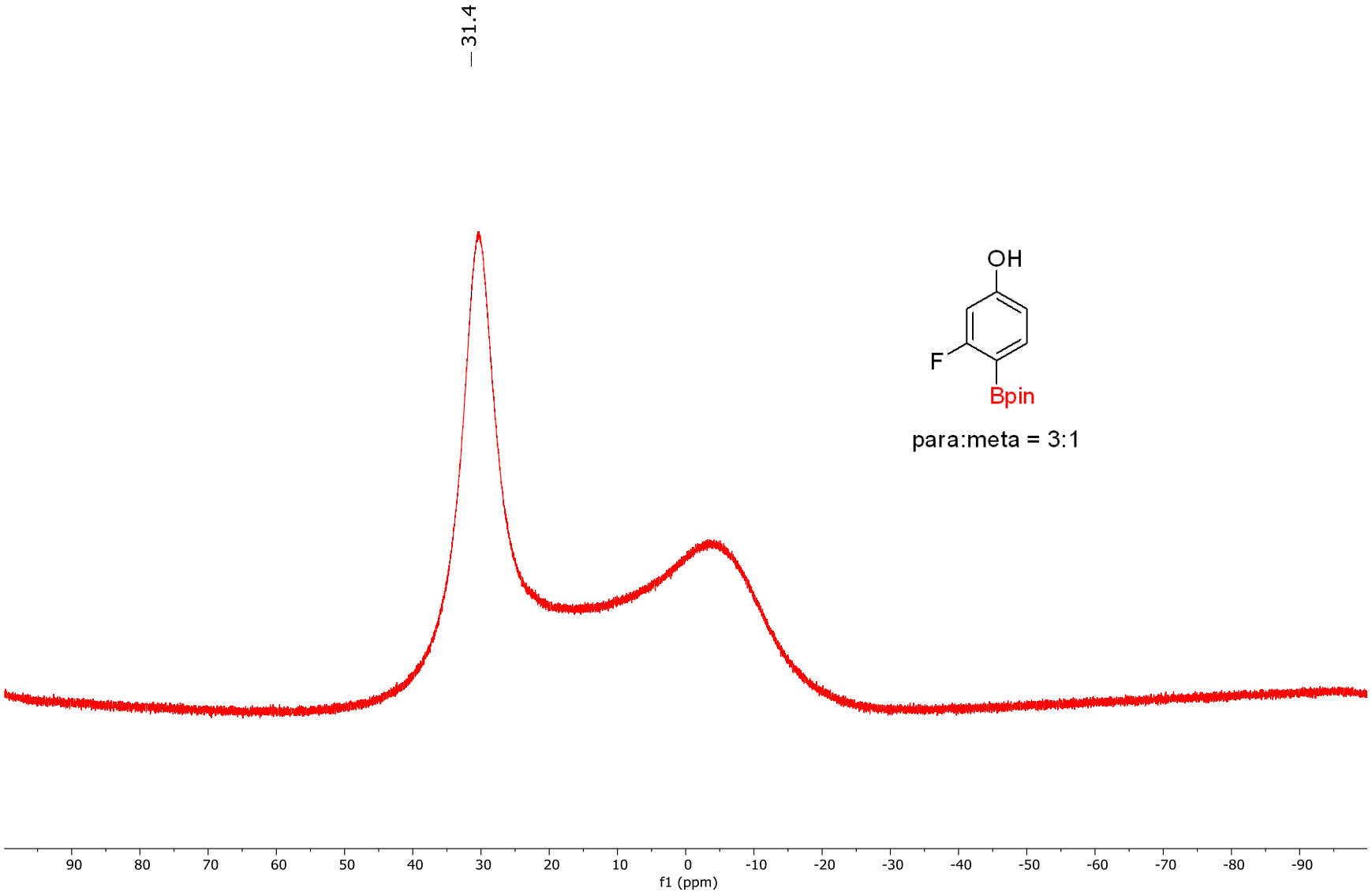
^{1}H NMR spectrum of *Para* borylated 3-fluorophenol (3.2l) (500 MHz, $CDCl_3$)



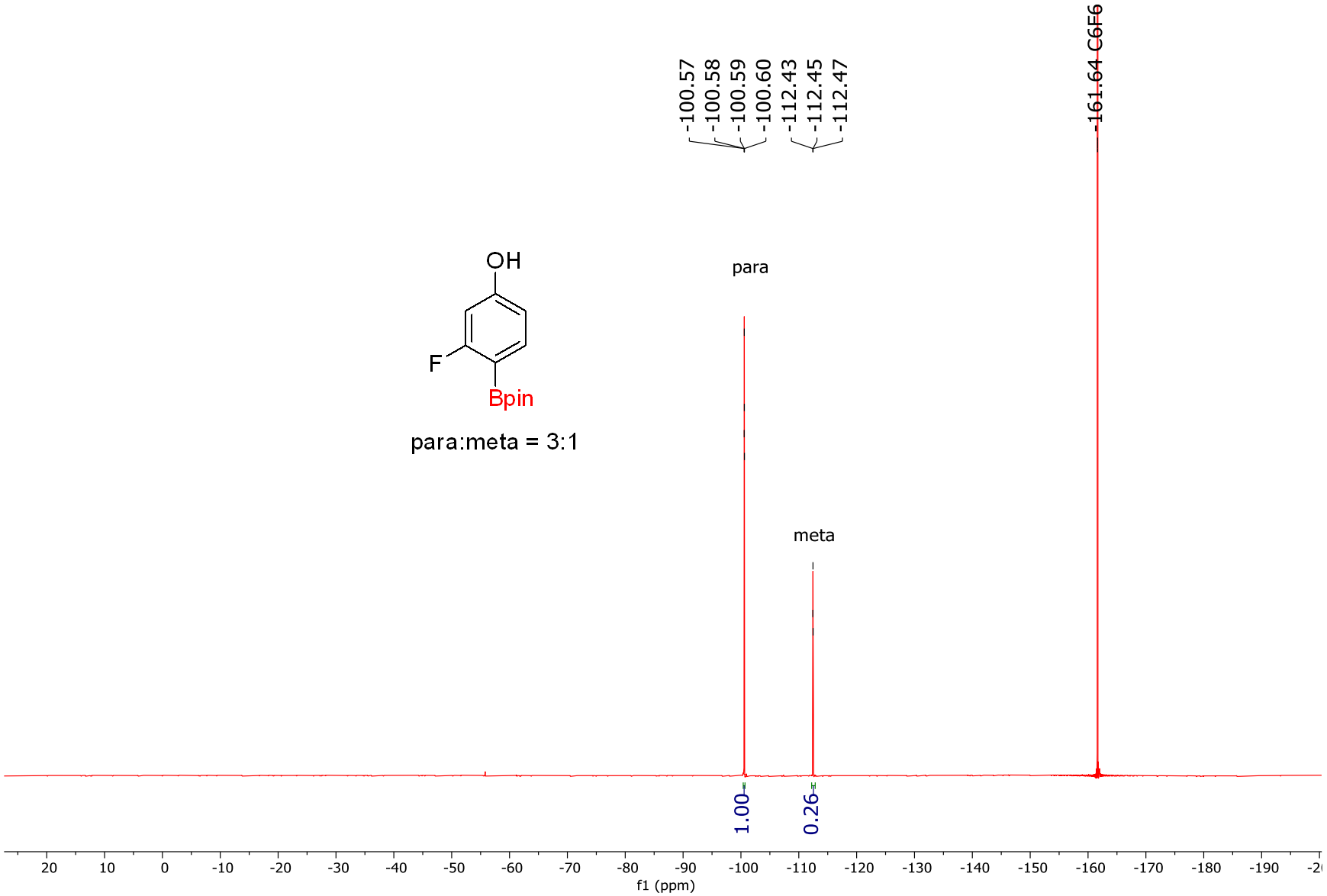
^{13}C NMR spectrum of *Para* borylated 3-fluorophenol (3.2l) (126 MHz, $CDCl_3$)



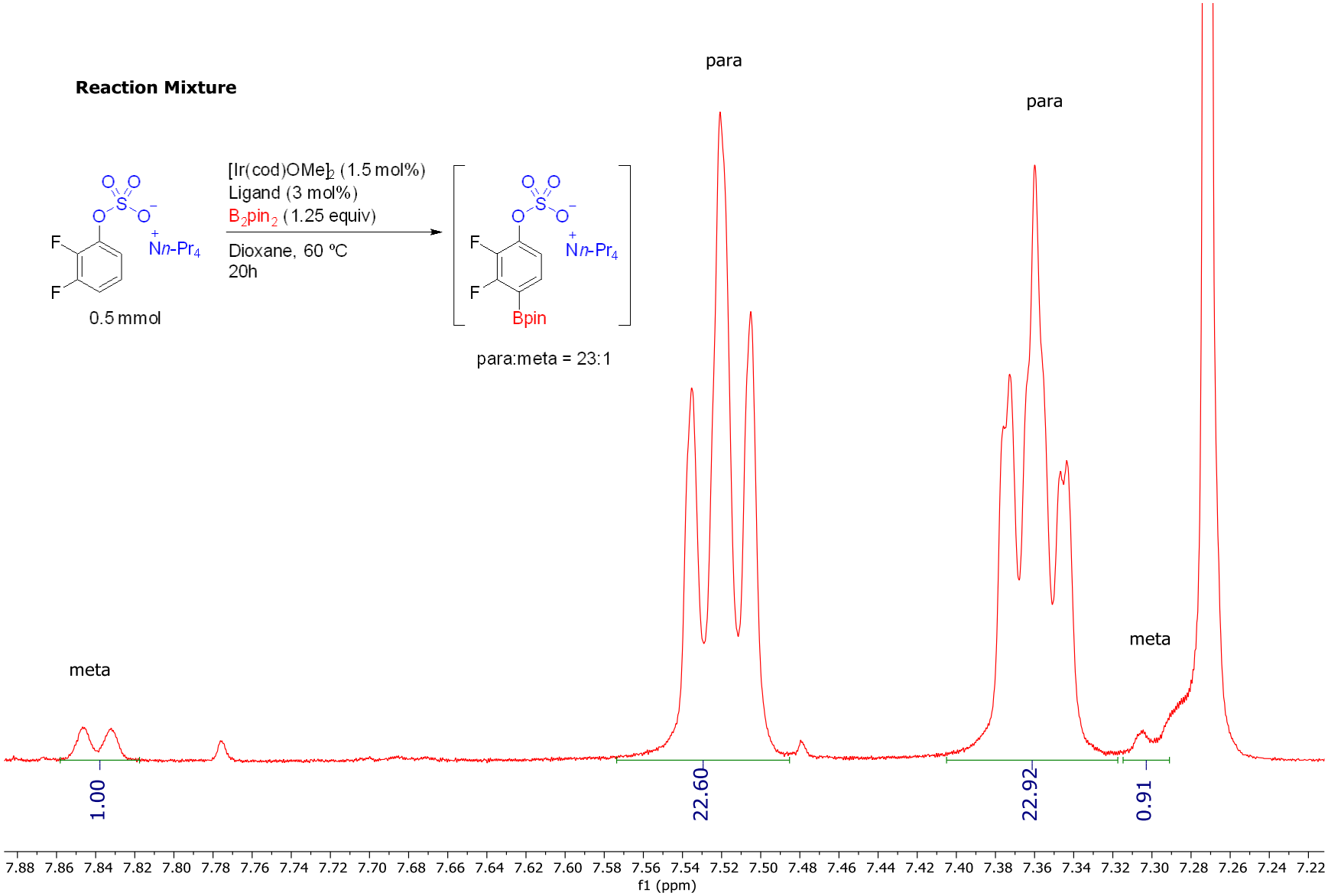
^{11}B NMR spectrum of *Para* borylated 3-fluorophenol (3.2l) (160 MHz, $CDCl_3$)



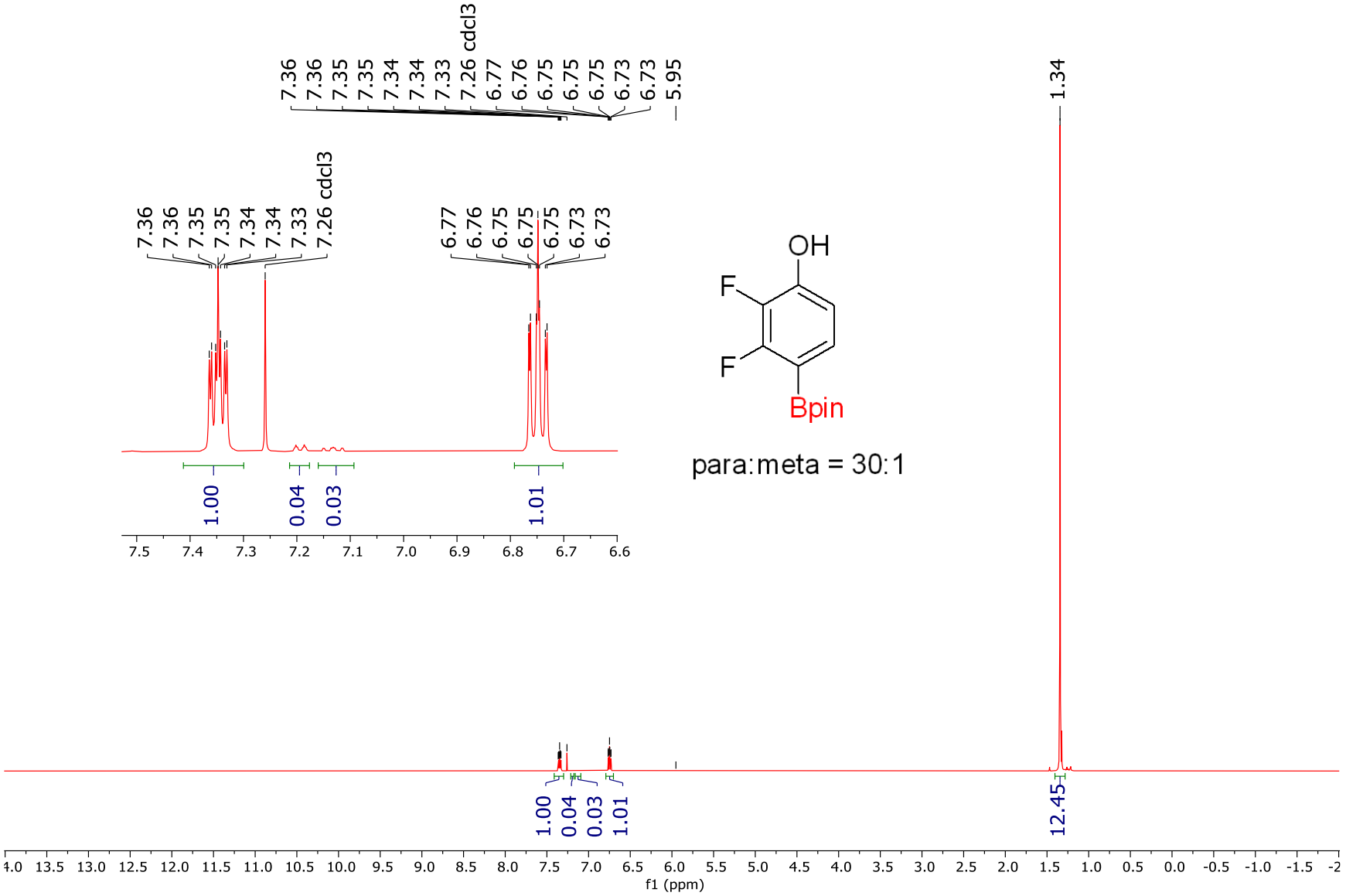
^{19}F NMR spectrum of *Para* borylated 3-fluorophenol (3.2l) (470 MHz, $CDCl_3$)



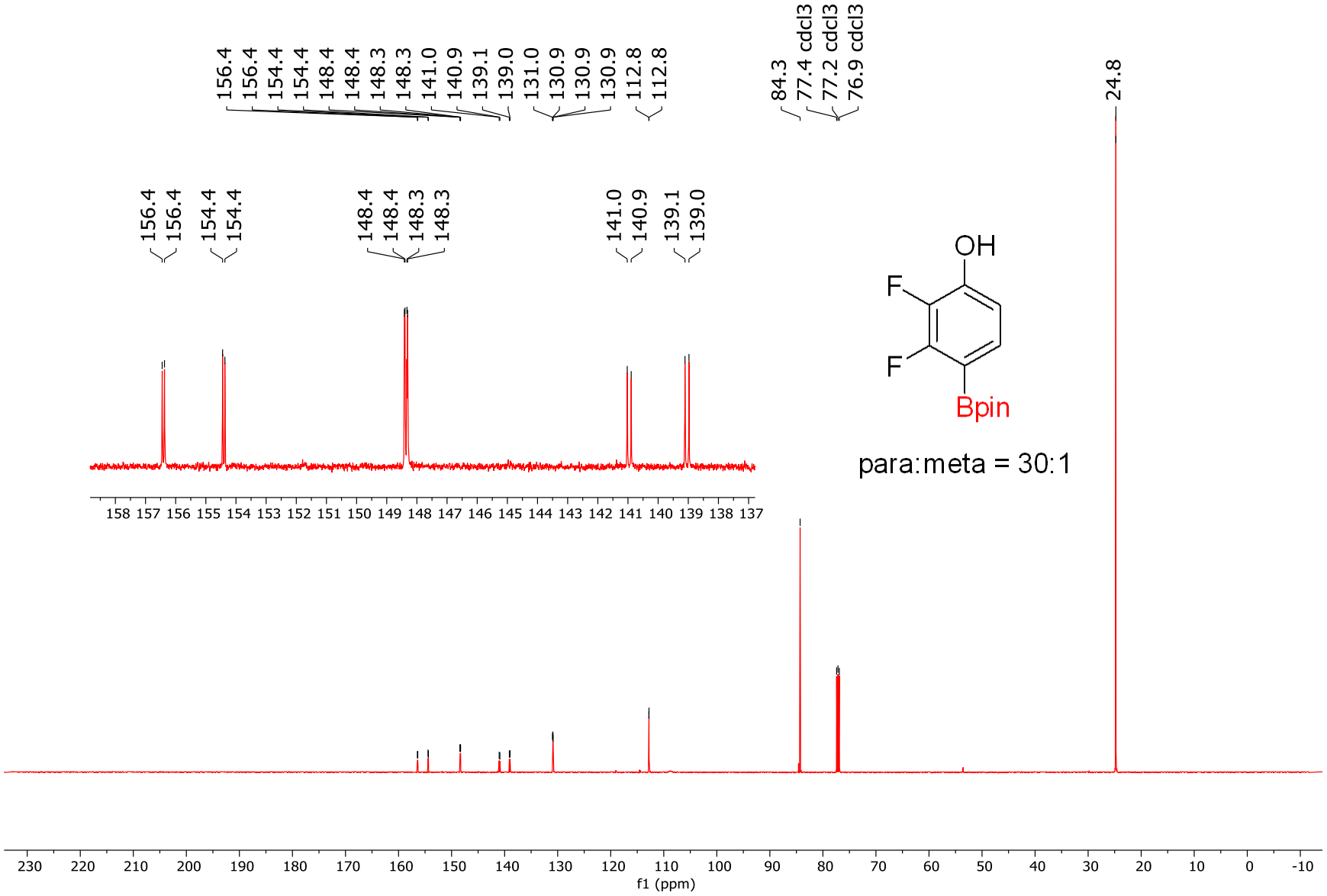
^{1}H NMR reaction mixture for the *Para* borylation of tetrapropylammonium 2,3-difluorophenylsulfate (3.2m) (500 MHz, $CDCl_3$)



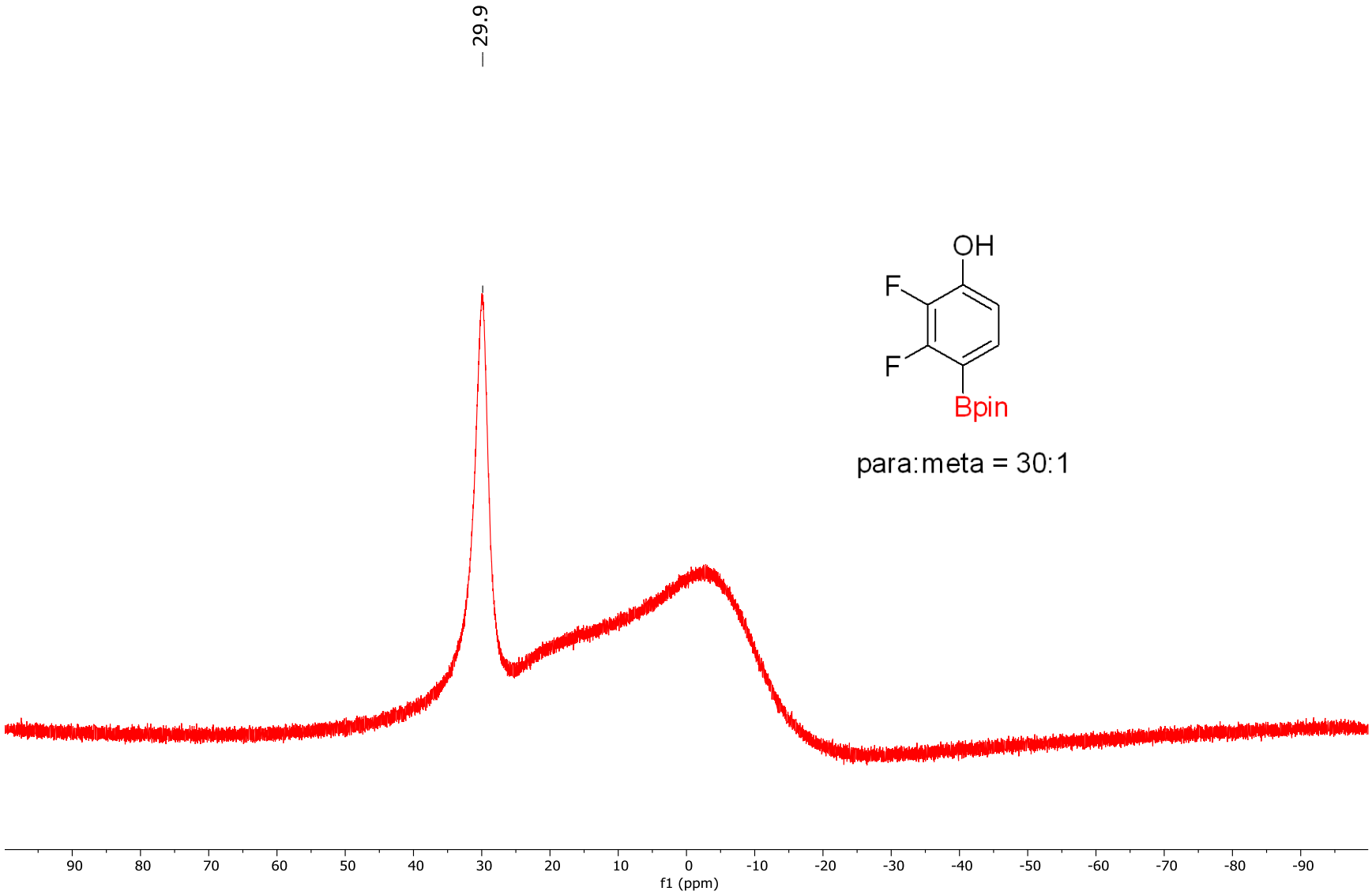
^{1}H NMR spectrum of *Para* borylated 2,3-difluorophenol (3.2m) (500 MHz, $CDCl_3$)



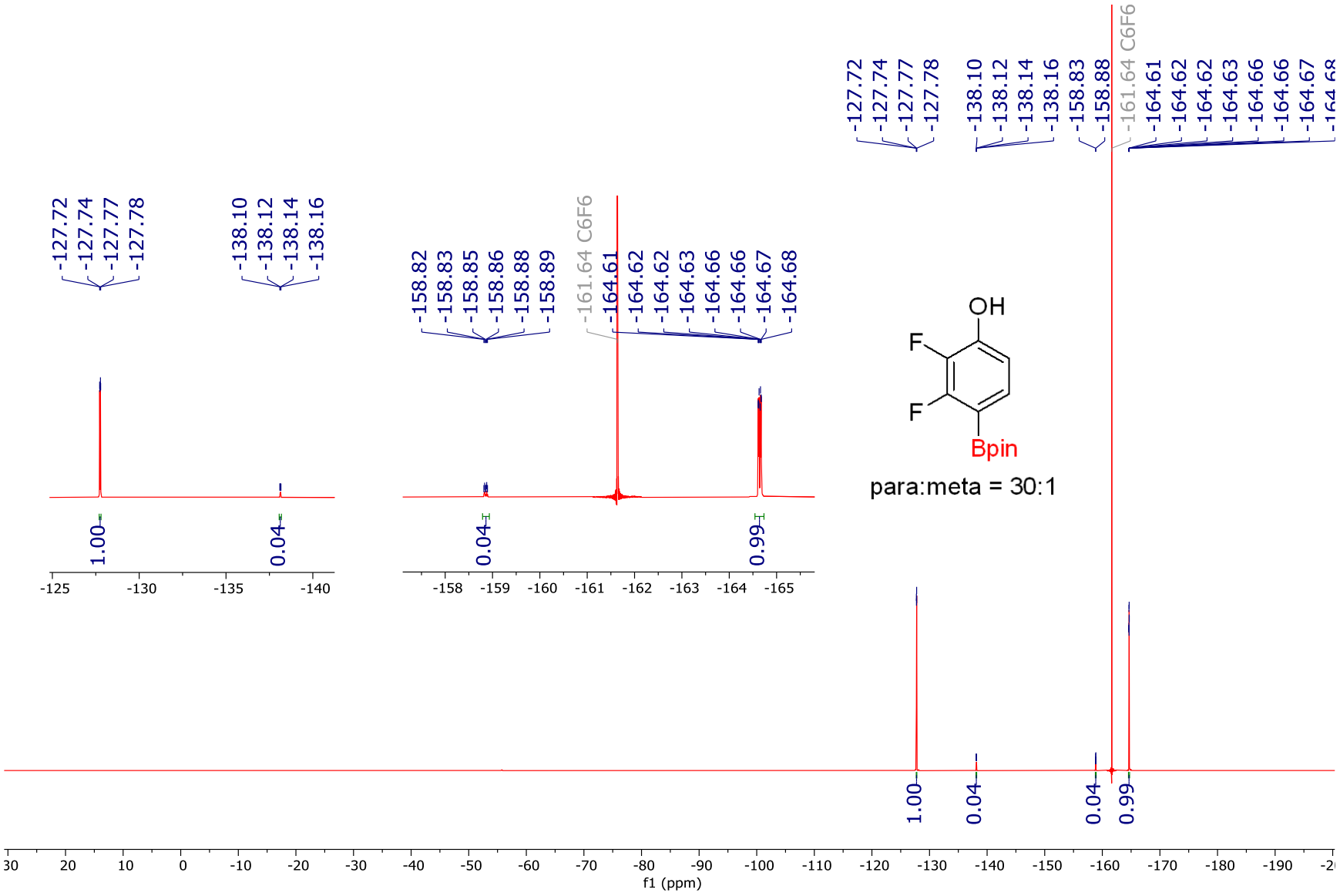
^{13}C NMR spectrum of *Para* borylated 2,3-difluorophenol (3.2m) (126 MHz, $CDCl_3$)



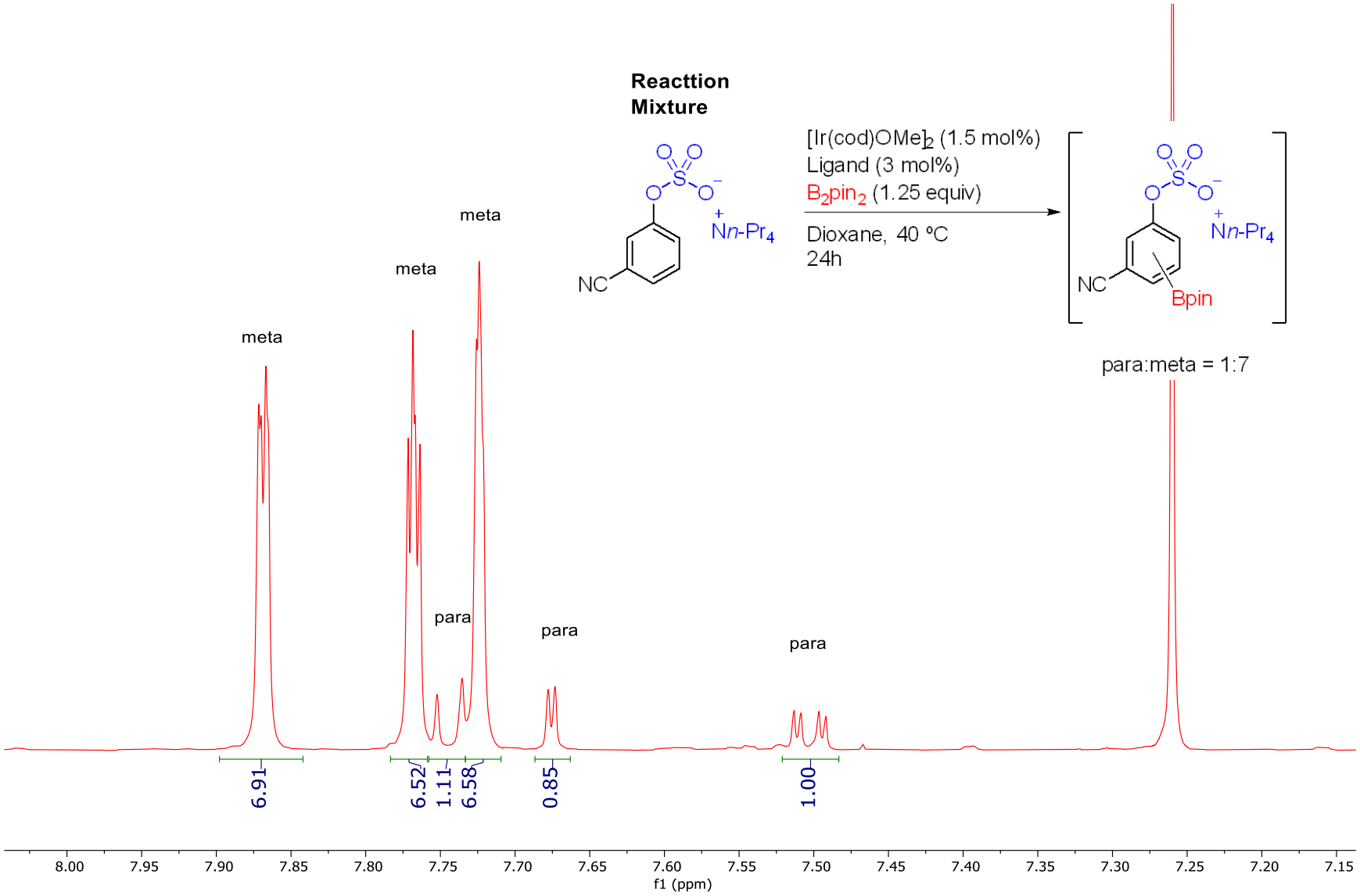
^{11}B NMR spectrum of *Para* borylated 2,3-difluorophenol (3.2m) (160 MHz, $CDCl_3$)



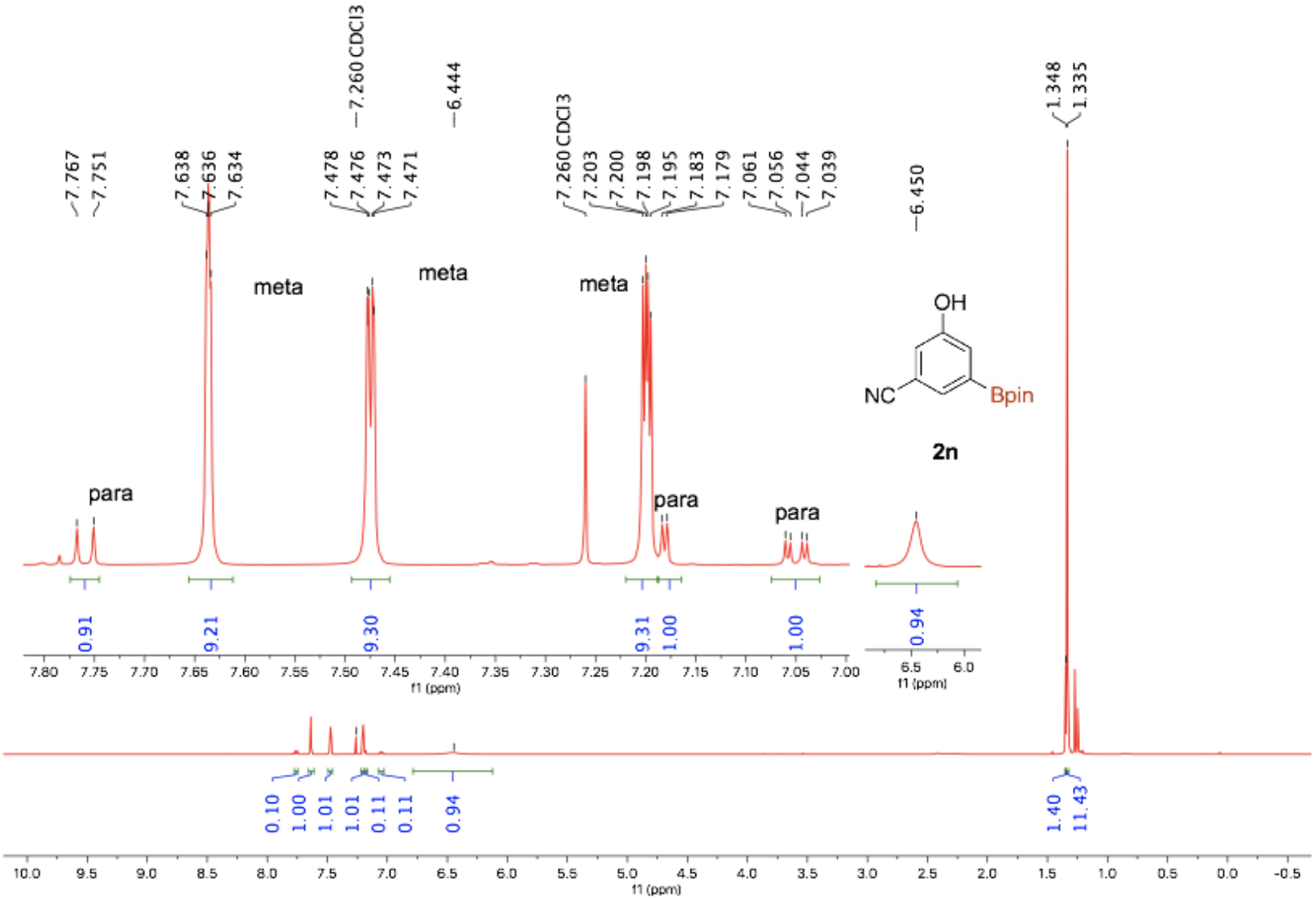
^{19}F NMR spectrum of *Para* borylated 2,3-difluorophenol (3.2m) (470 MHz, $CDCl_3$)



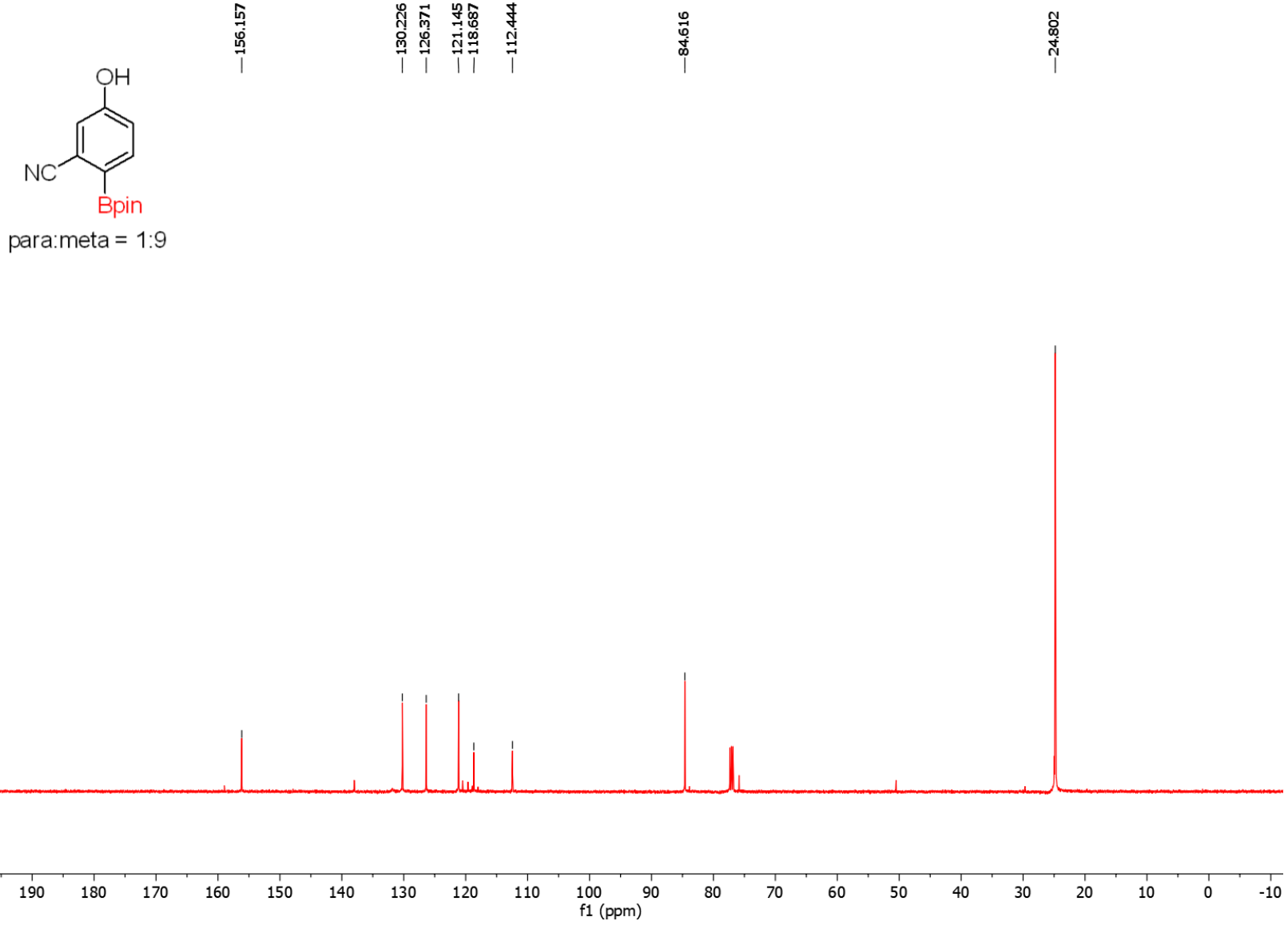
^{1}H NMR reaction mixture of *para*-borylated tetrapropylammonium 3-cyanophenylsulfate (crude 3.2n) (500 MHz, $CDCl_3$)



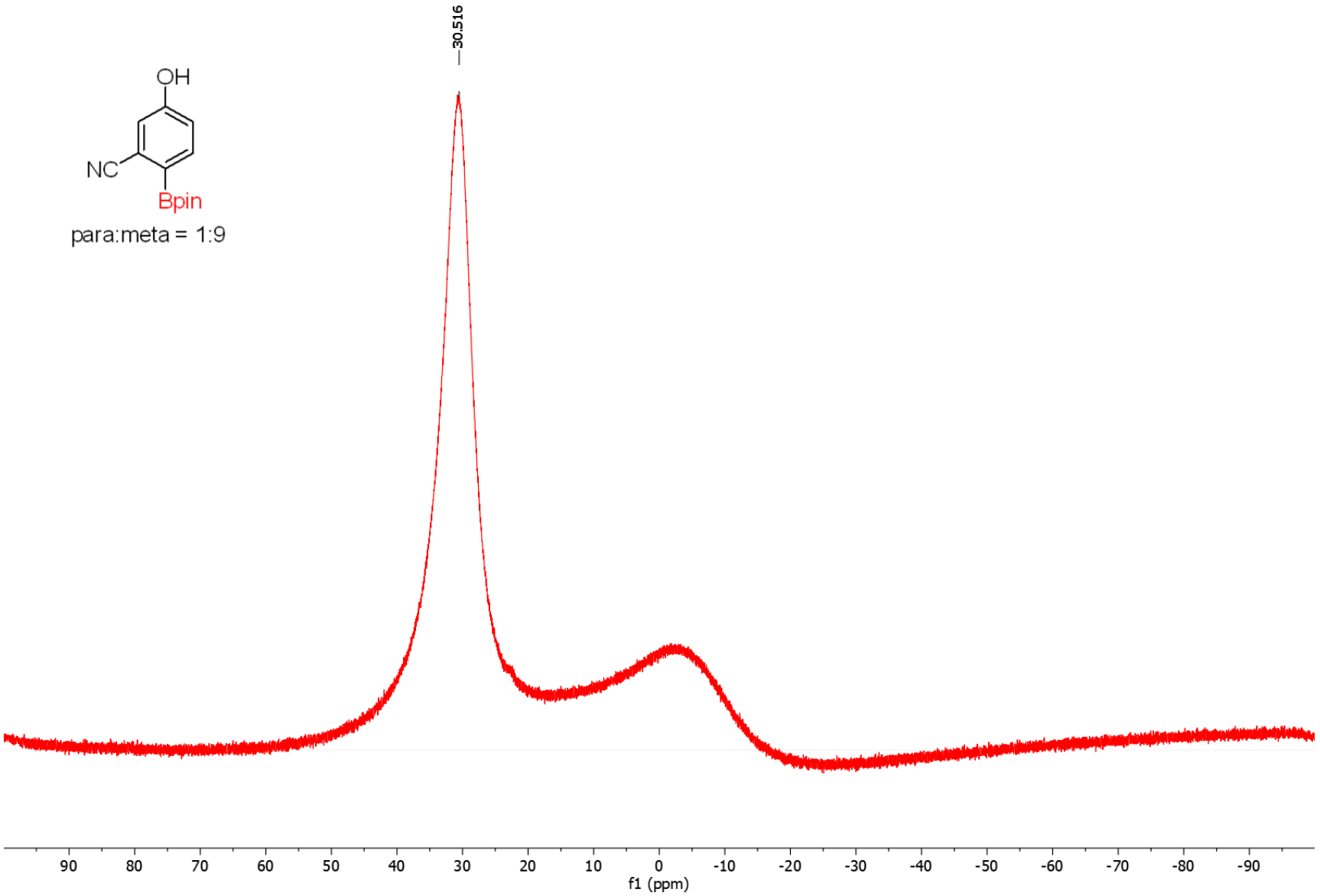
^{1}H NMR spectrum of *para*-borylated 3-cyanophenylsulfate (3.2n) (500 MHz, $CDCl_3$)



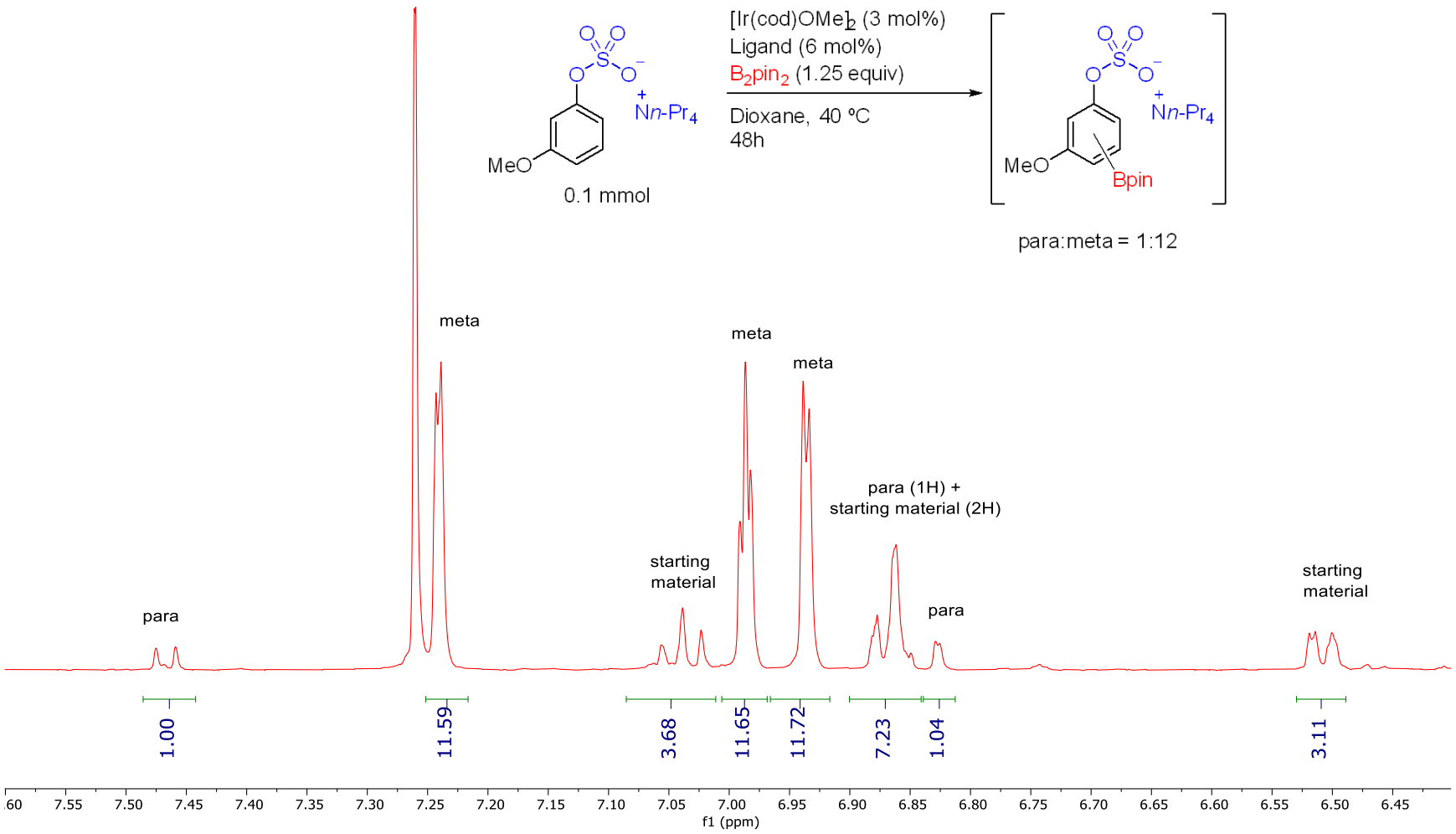
^{13}C NMR spectrum of *para* borylated 3-hydroxybenzonitrile (3.2n) (126 MHz, $CDCl_3$)



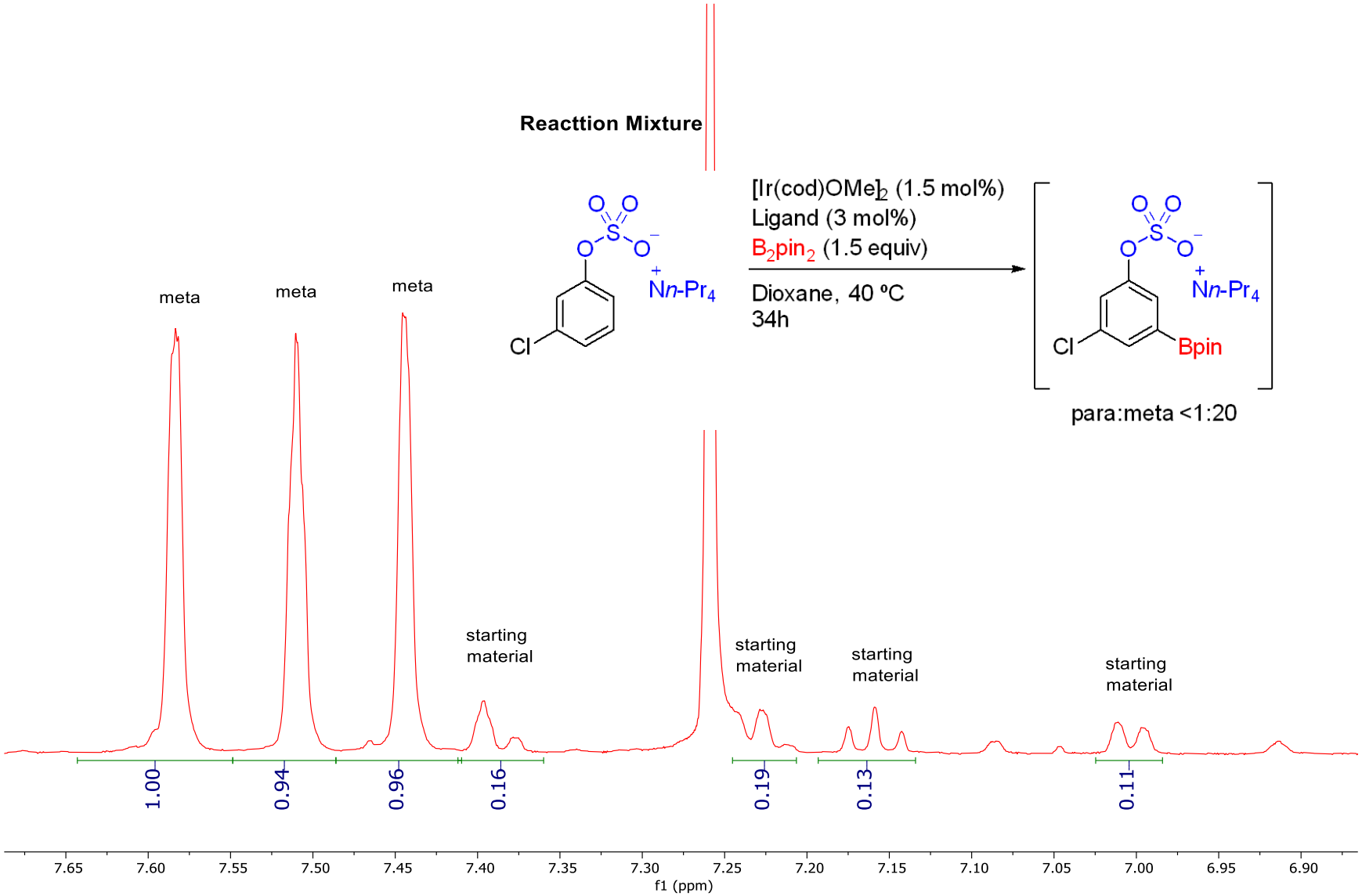
^{11}B NMR spectrum of *para* borylated 3-hydroxybenzonitrile (3.2n) (160 MHz, $CDCl_3$)



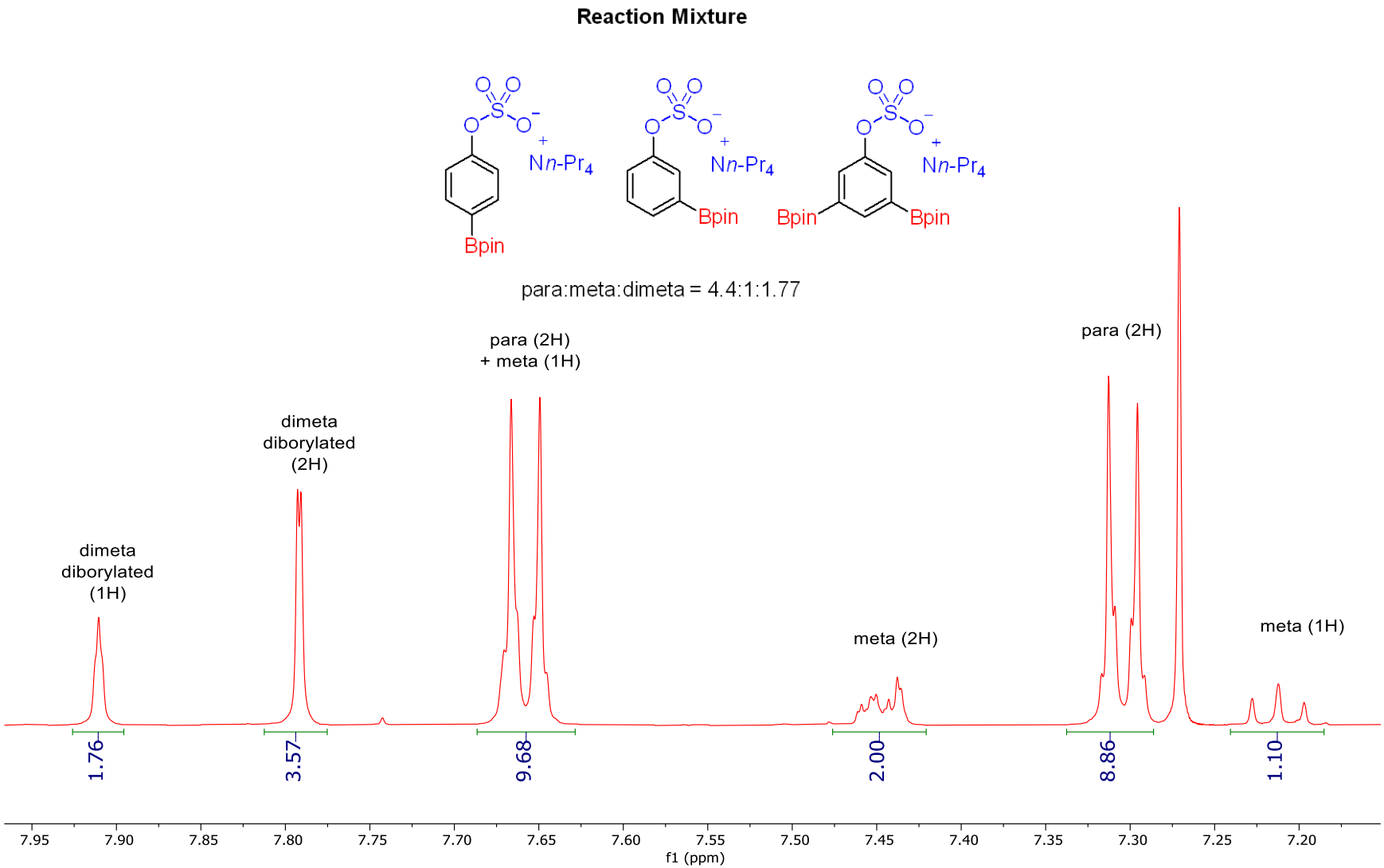
^{1}H NMR reaction mixture of *para* borylated tetrapropylammonium 3-methoxyphenylsulfate (crude 3.2o) (500 MHz, $CDCl_3$)



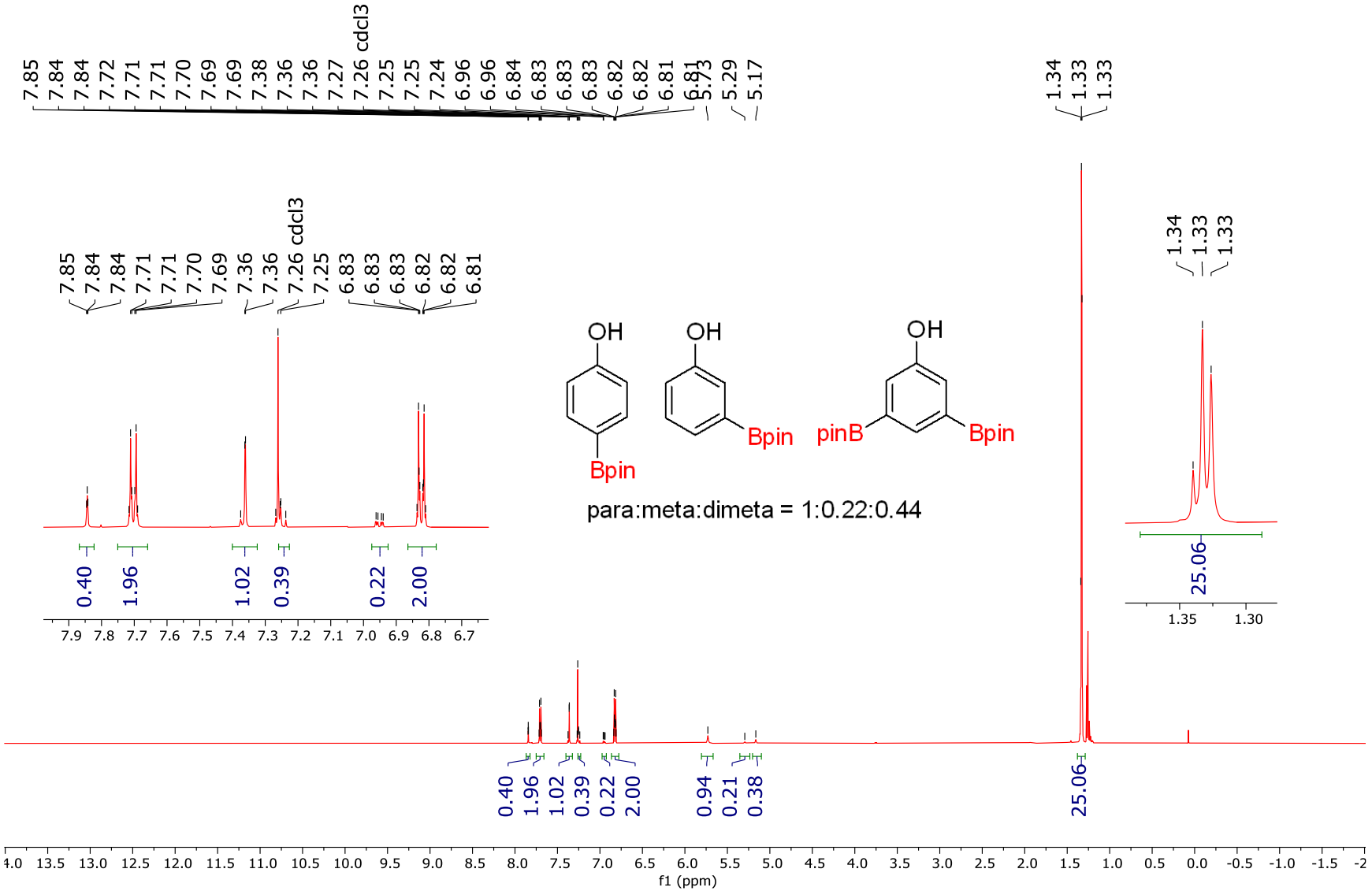
^{1}H NMR reaction mixture of *para* borylated tetrapropylammonium 3-chlorophenylsulfate (crude 3.2p) (500 MHz, C_6D_6)



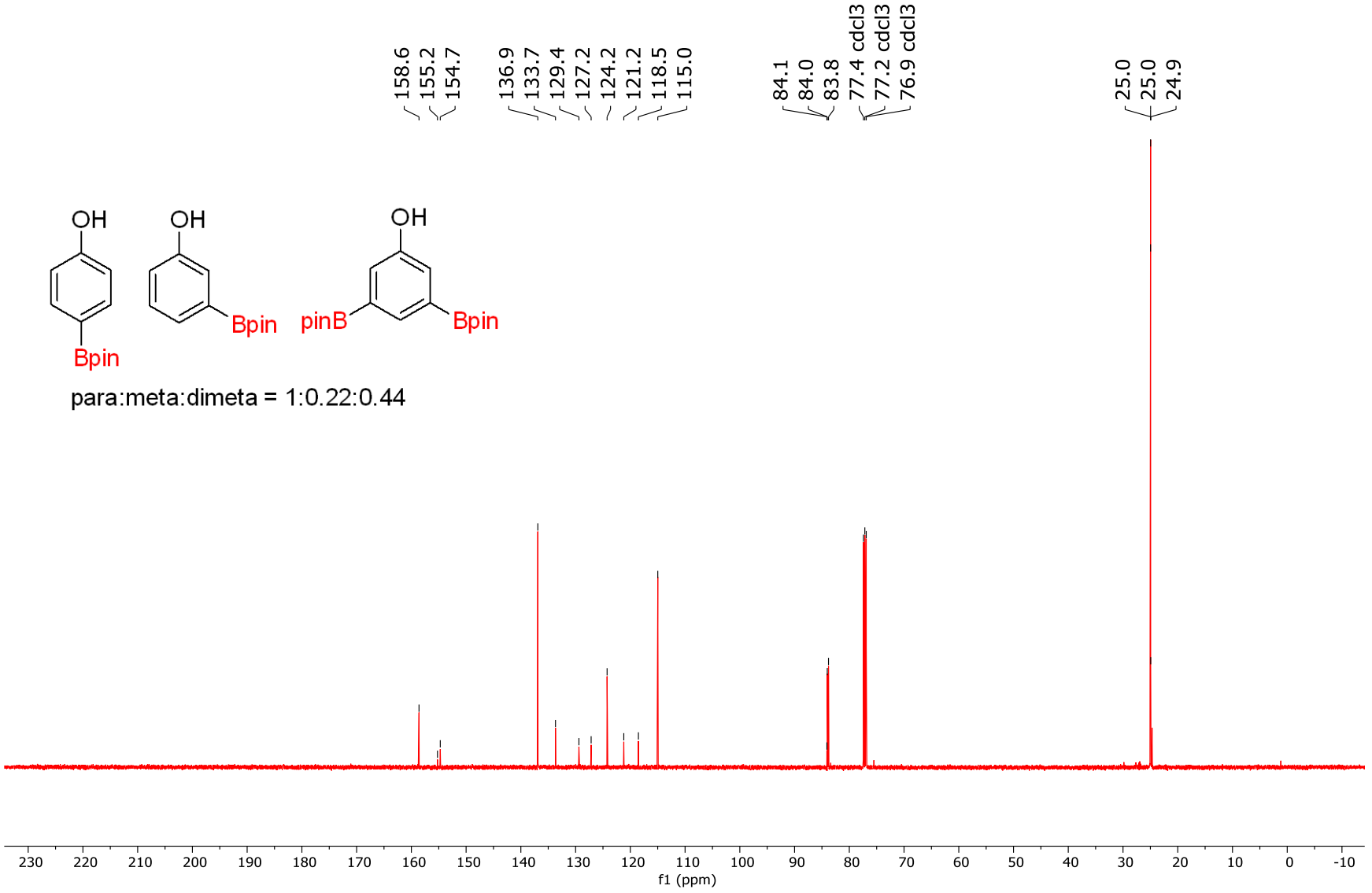
^{1}H NMR reaction mixture of borylation of tetrapropylammonium phenylsulfate (crude 3.2q) (500 MHz, $CDCl_3$)



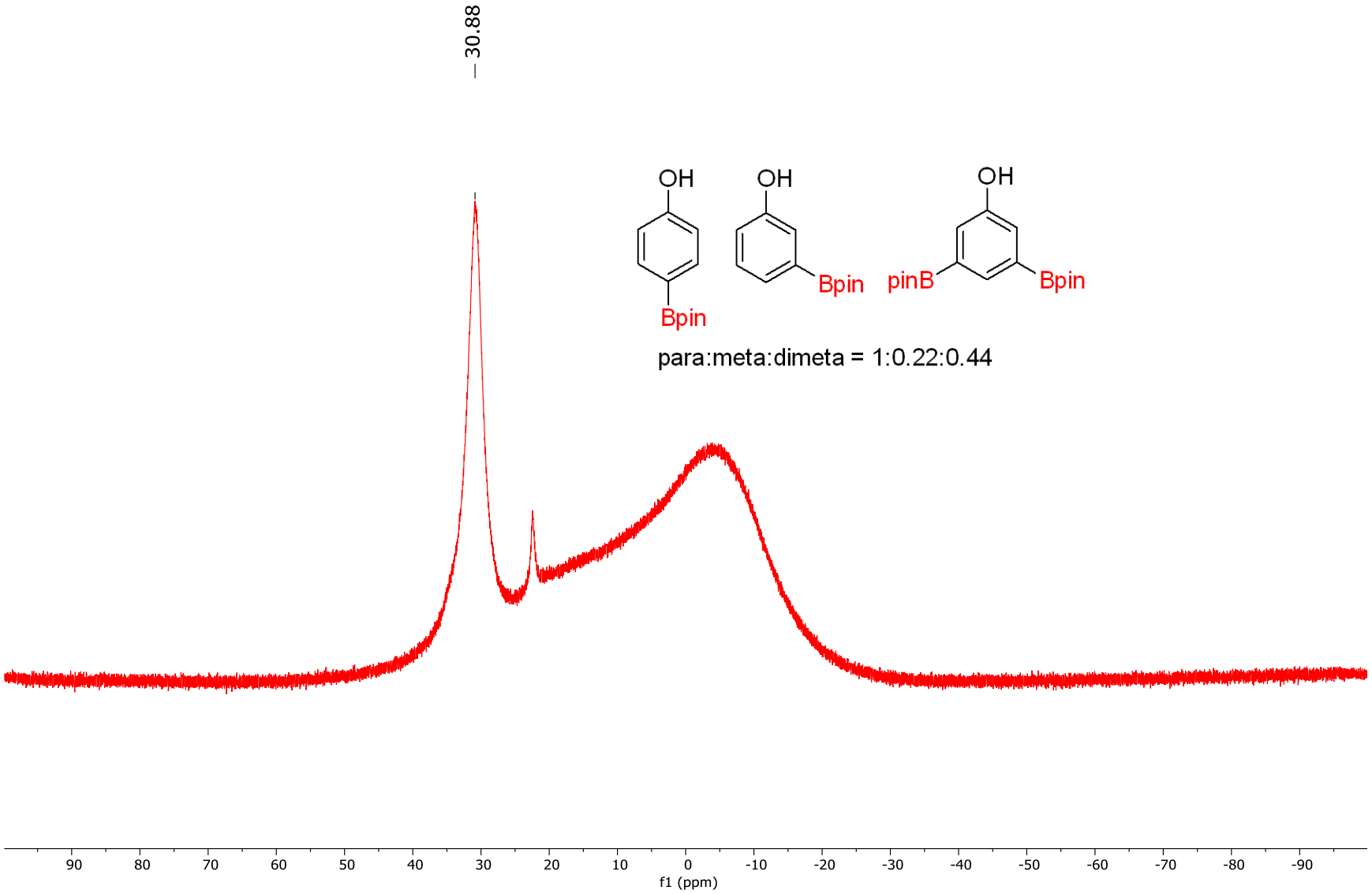
^{1}H NMR spectrum of *para* borylated phenol (3.2q) (500 MHz, $CDCl_3$)



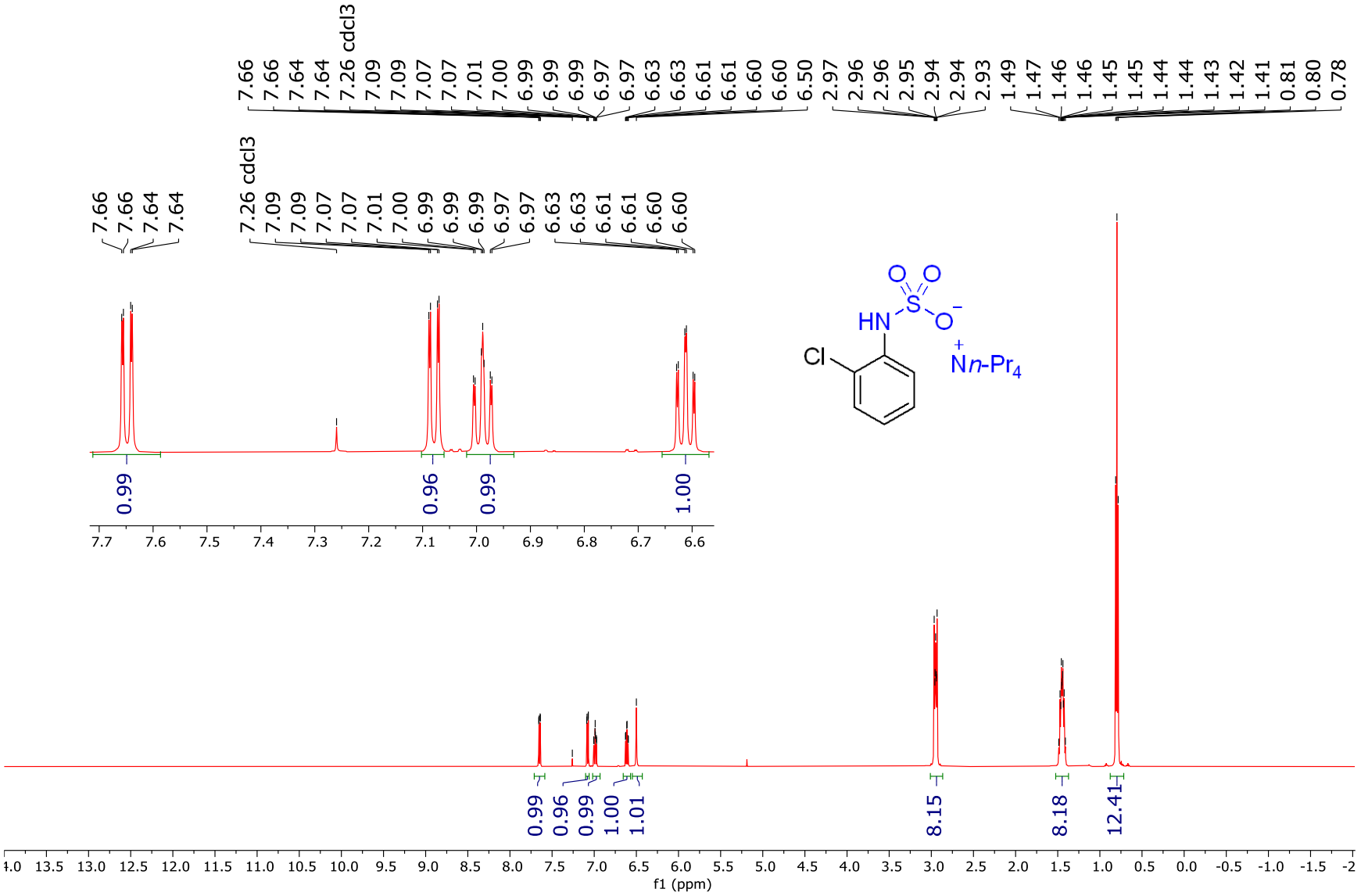
^{13}C NMR spectrum of *para* borylated phenol (3.2q) (126 MHz, $CDCl_3$)



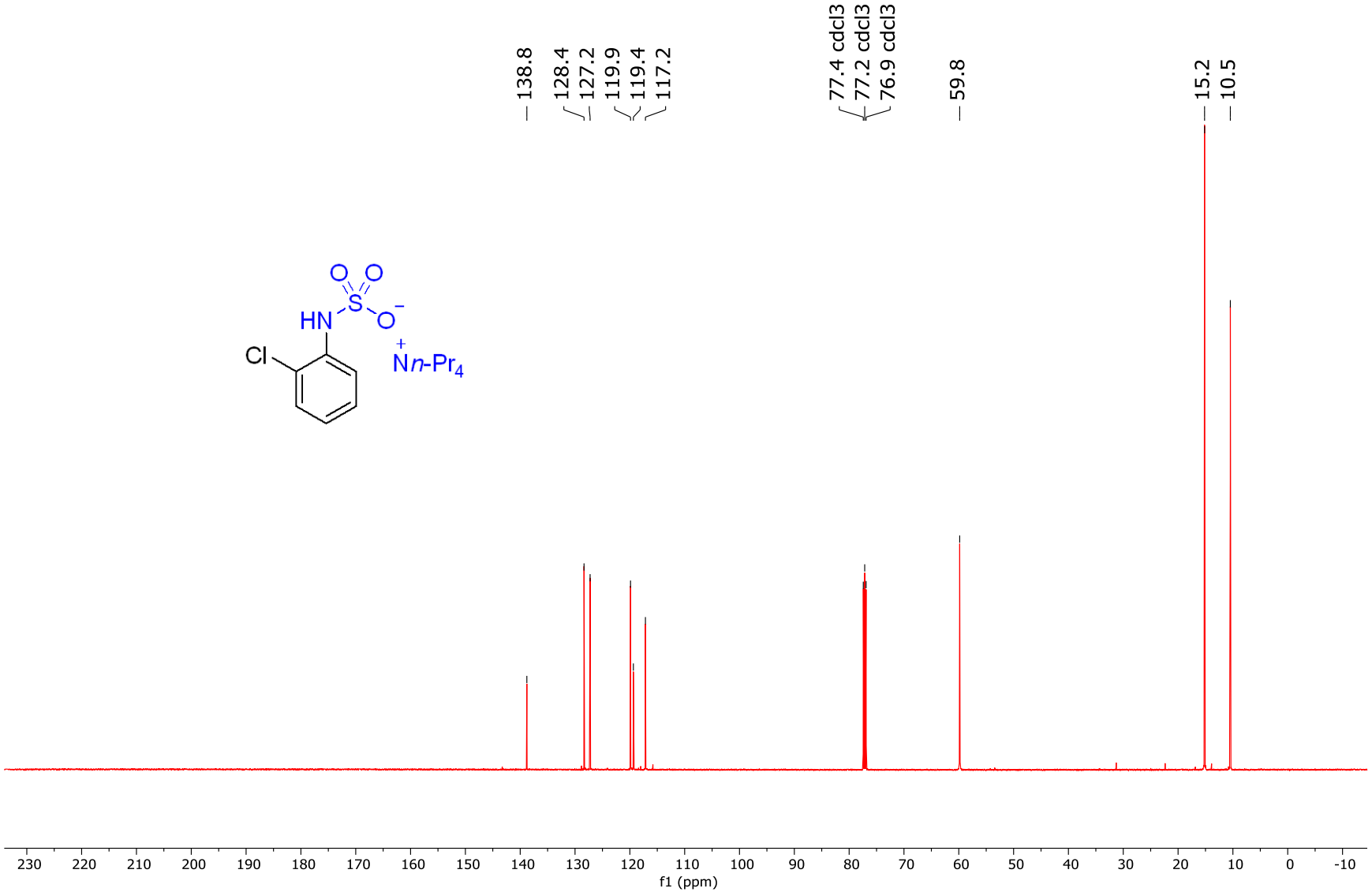
^{11}B NMR spectrum of *para* borylated phenol (3.2q) (160 MHz, $CDCl_3$)



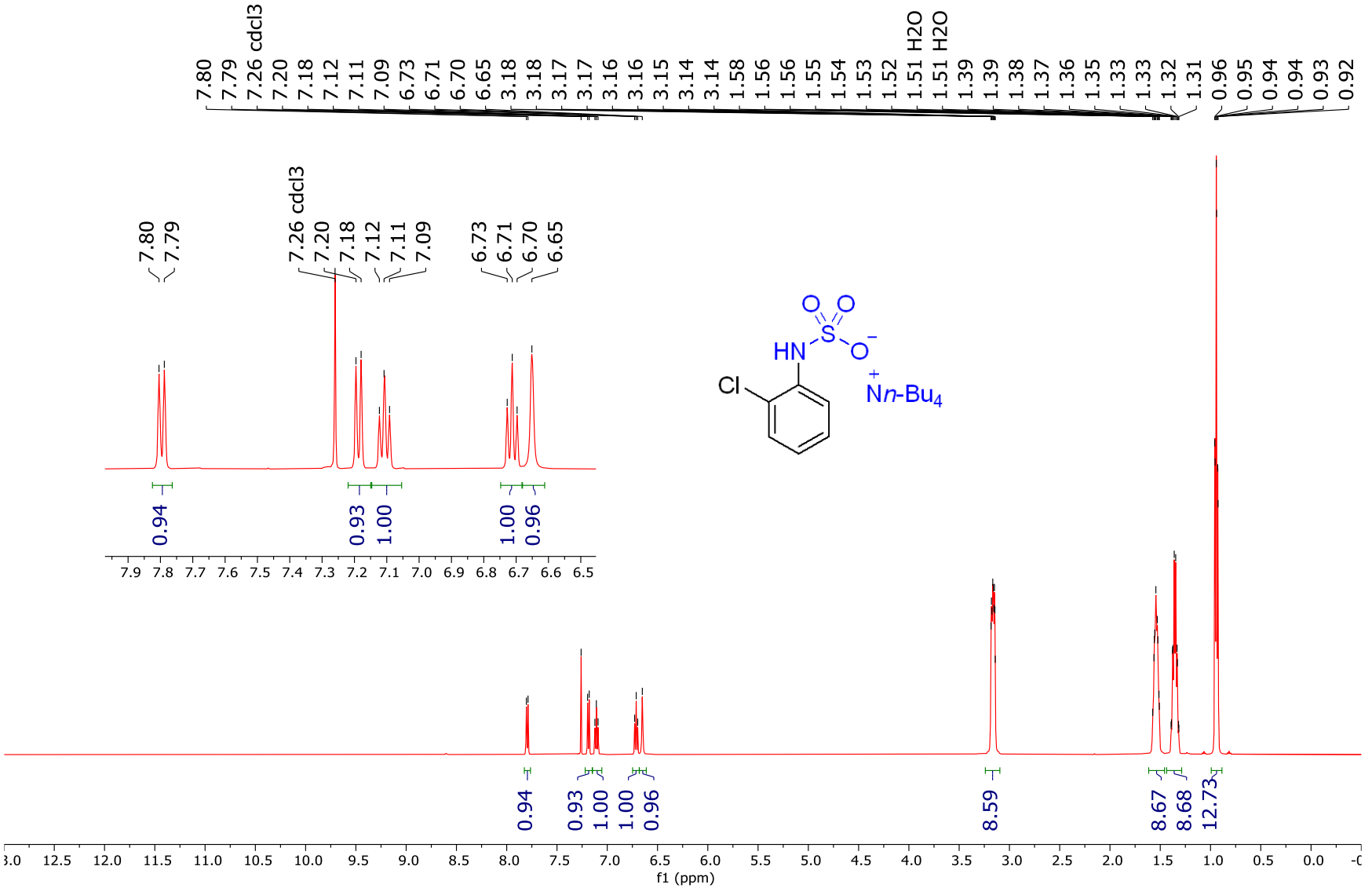
^{1}H NMR spectrum of tetrapropylammonium 2-chlorophenylsulfamate (3.3a) (500 MHz, $CDCl_3$)



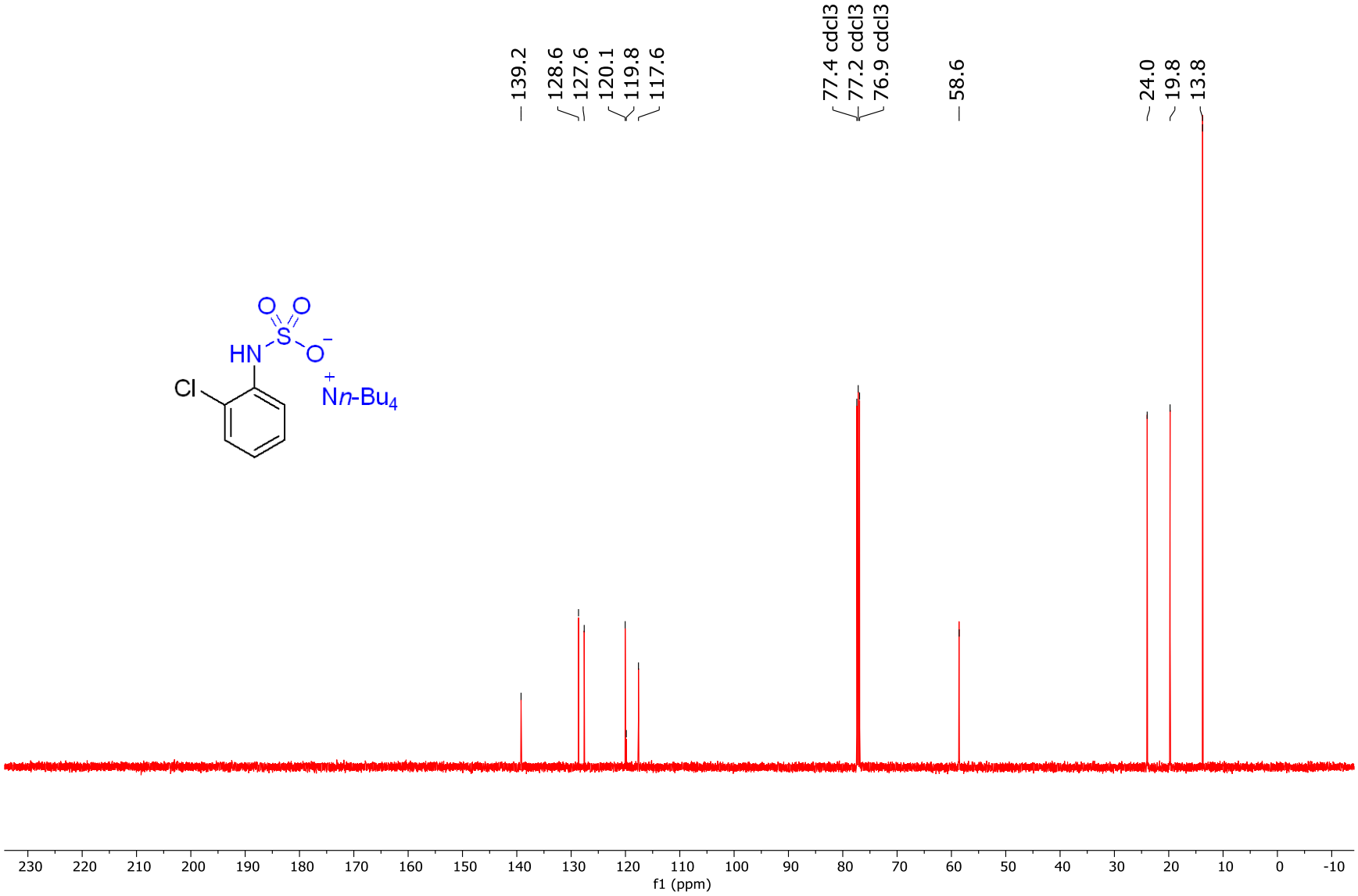
^{13}C NMR spectrum of tetrapropylammonium 2-chlorophenylsulfamate (3.3a) (126 MHz, $CDCl_3$)



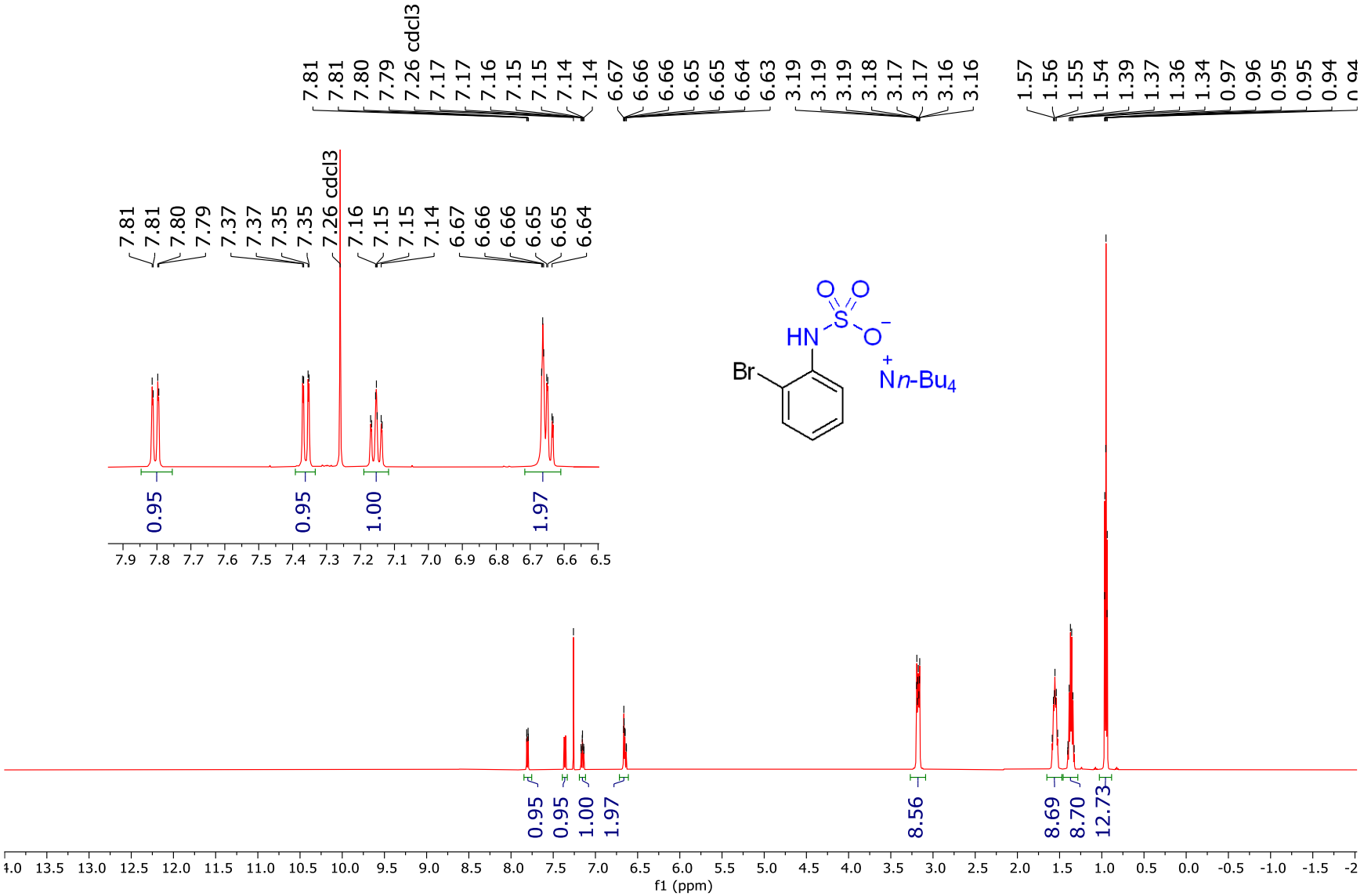
^{1}H NMR spectrum of tetrabutylammonium 2-chlorophenyl sulfamate (3.3a′) (500 MHz, $CDCl_3$)



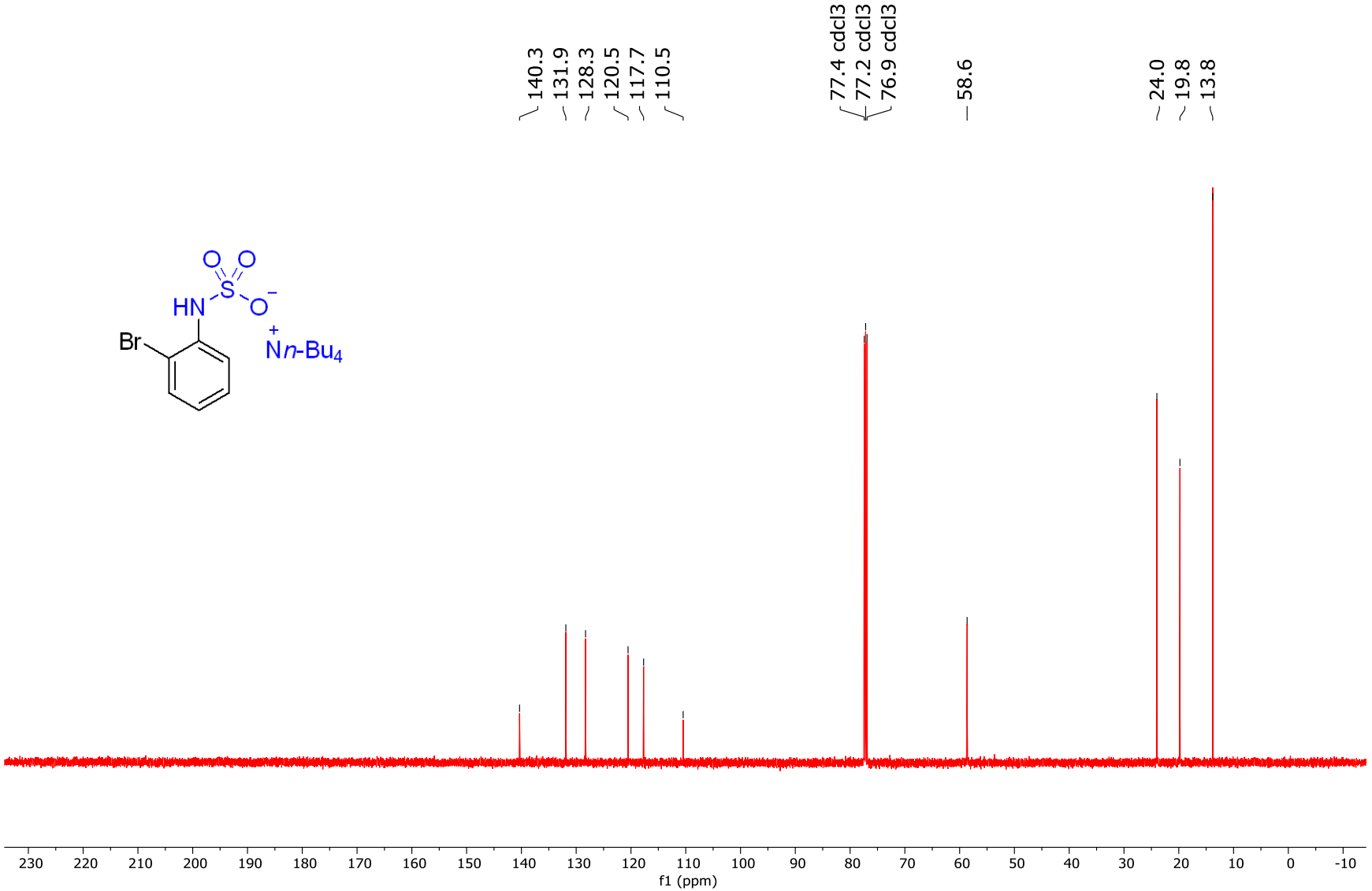
^{13}C NMR spectrum of tetrabutylammonium 2-chlorophenylsulfamate (3.3a′) (126 MHz, $CDCl_3$)



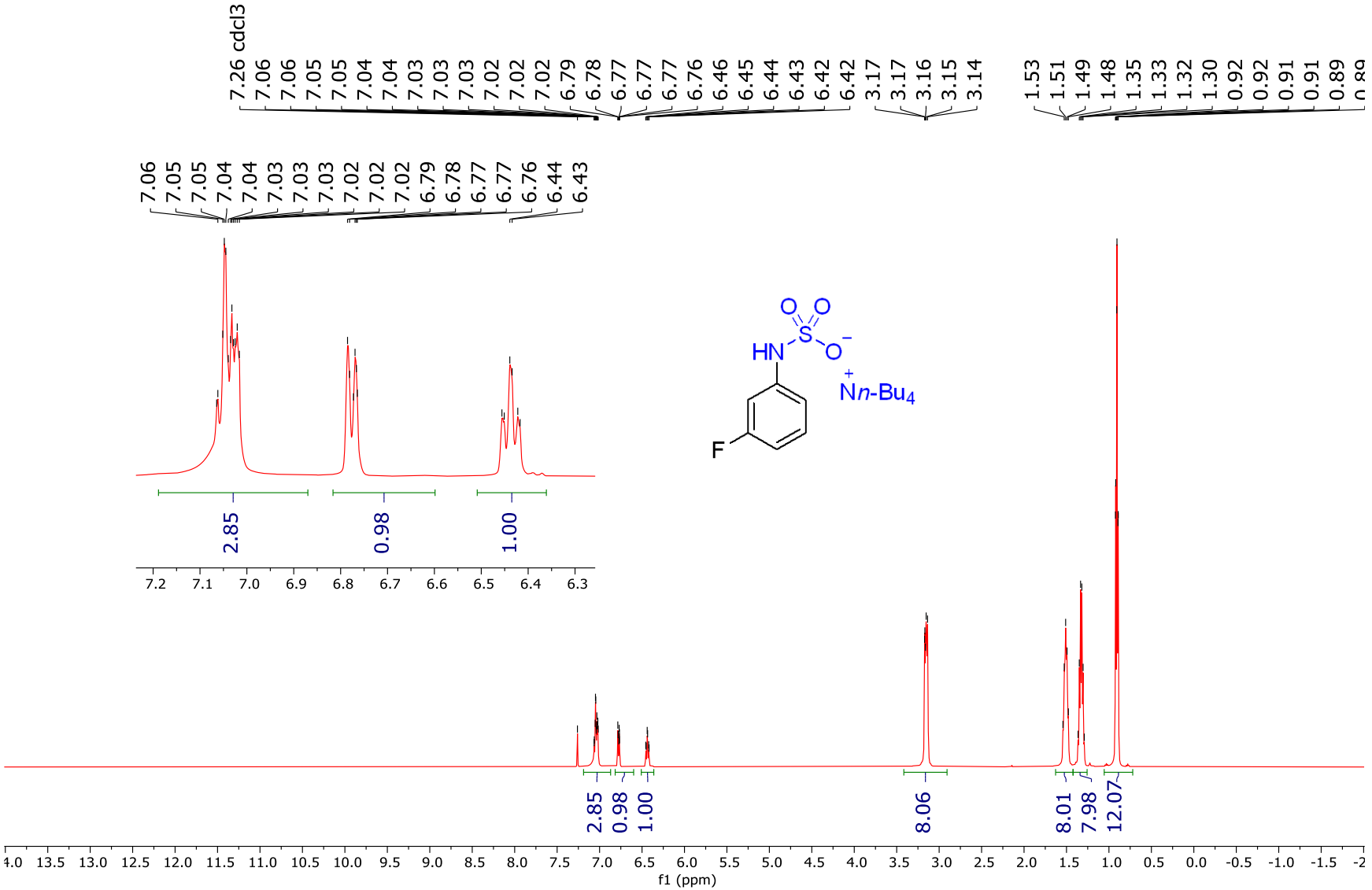
^{1}H NMR spectrum of tetrabutylammonium 2-bromophenylsulfamate (3.3b′) (500 MHz, $CDCl_3$)



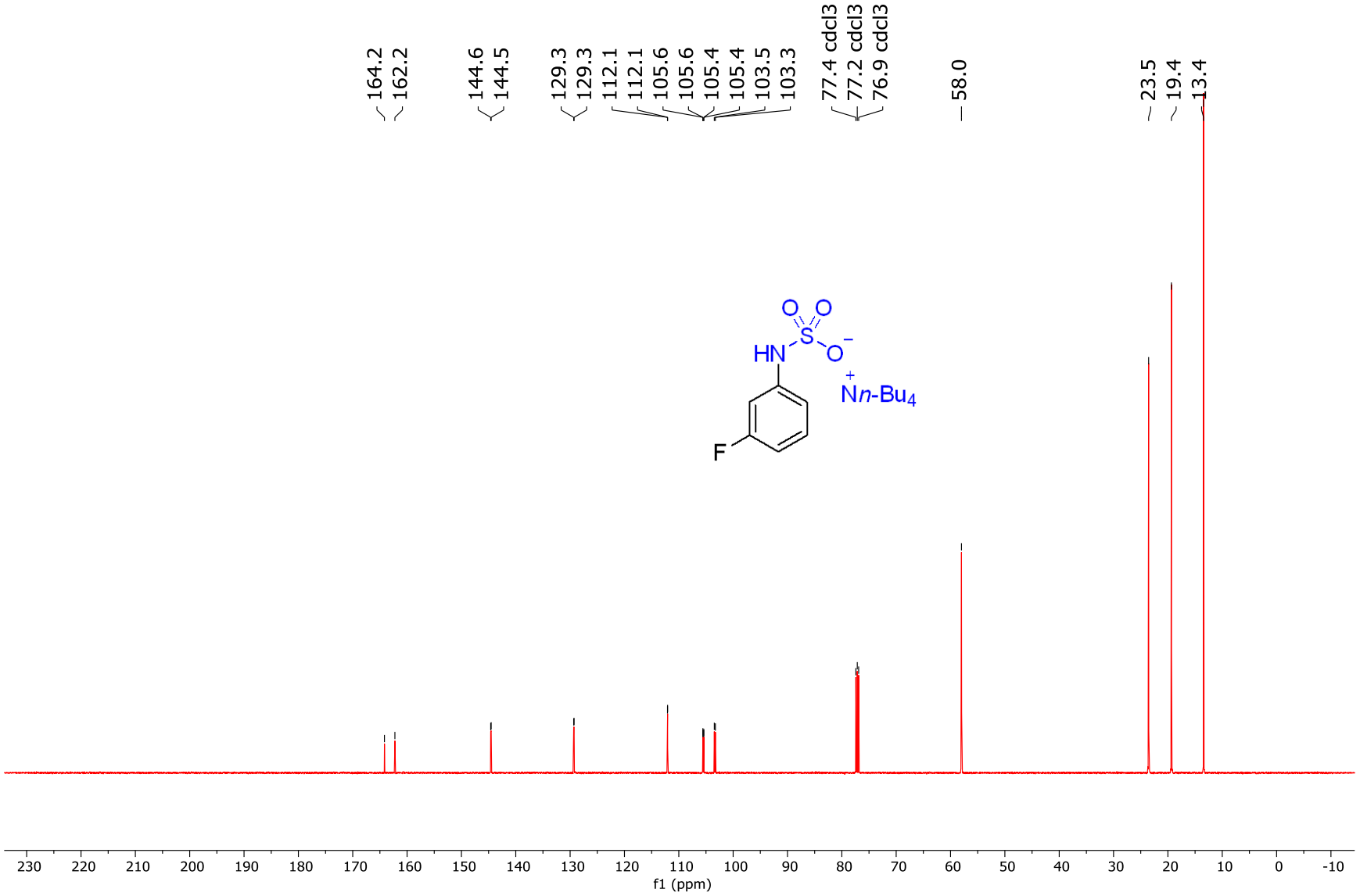
^{13}C NMR spectrum of tetrabutylammonium 2-bromophenylsulfamate (3.3b′) (126 MHz, $CDCl_3$)



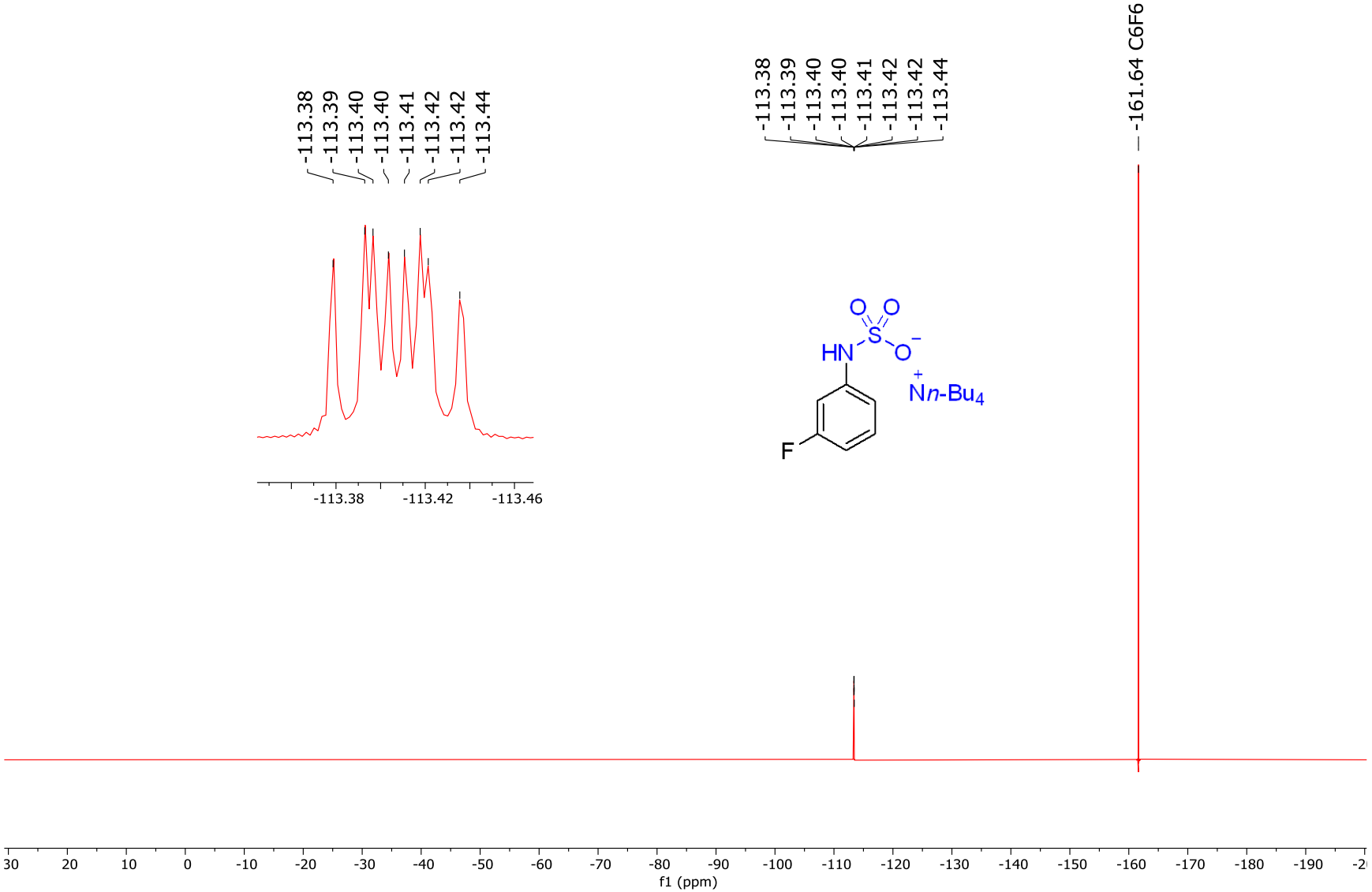
^{1}H NMR spectrum of tetrabutylammonium 3-fluorophenylsulfamate (3.3c′) (500 MHz, $CDCl_3$)



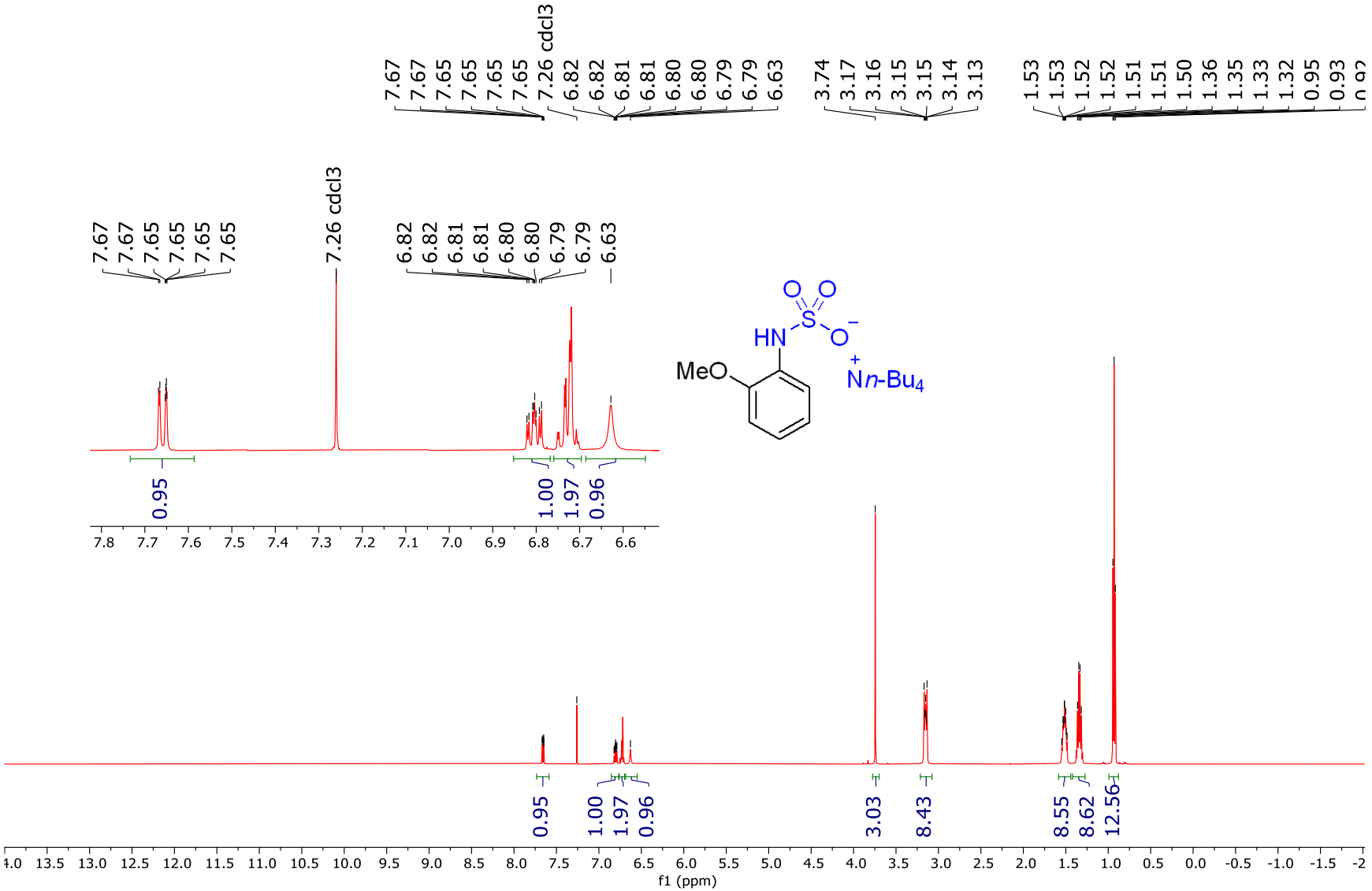
^{13}C NMR spectrum of tetrabutylammonium 3-fluorophenylsulfamate (3.3c′) (126 MHz, $CDCl_3$)



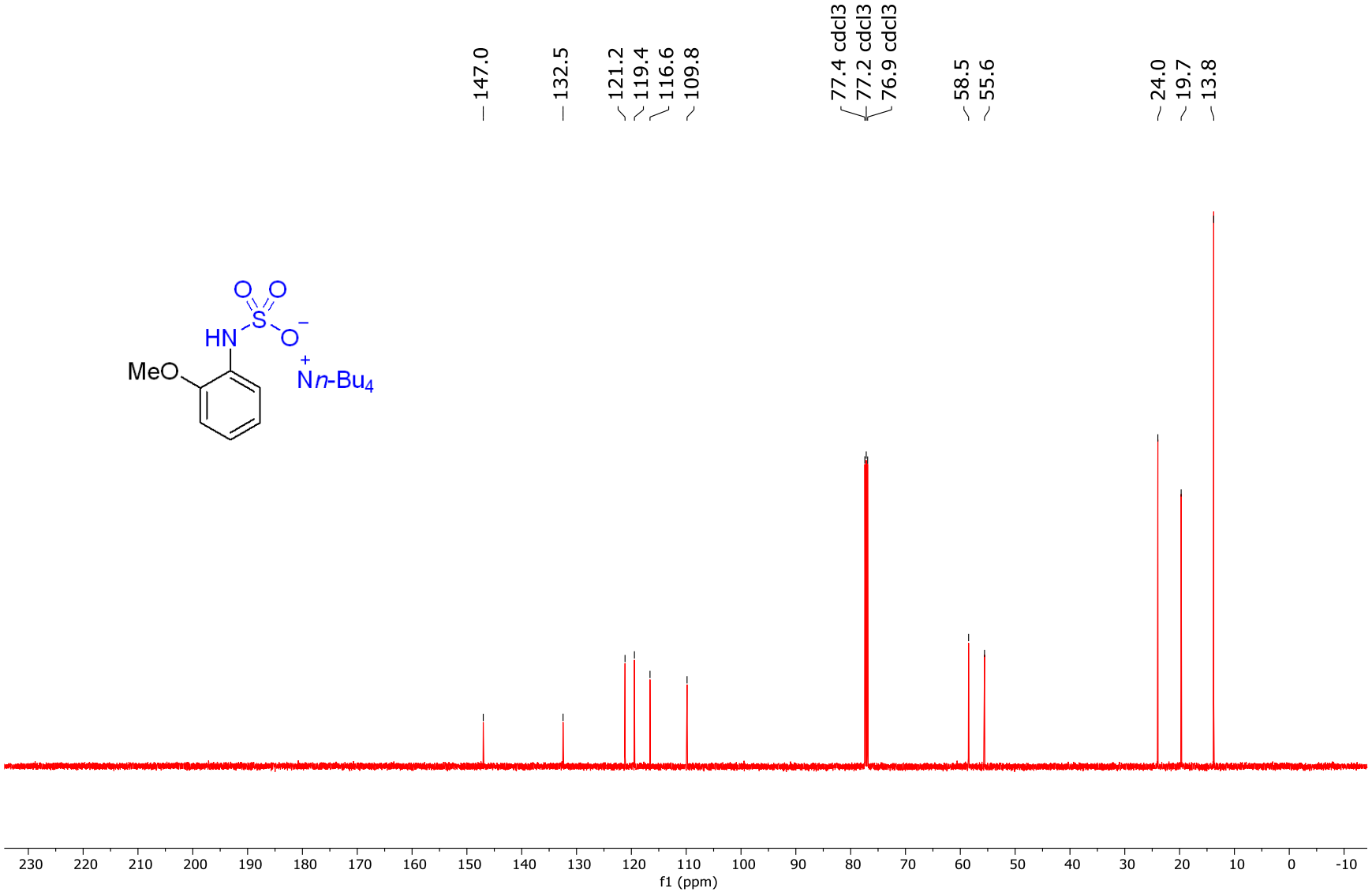
^{19}F NMR spectrum of terabutylammonium 3-fluorophenylsulfamate (3.3c′) (470 MHz, $CDCl_3$)



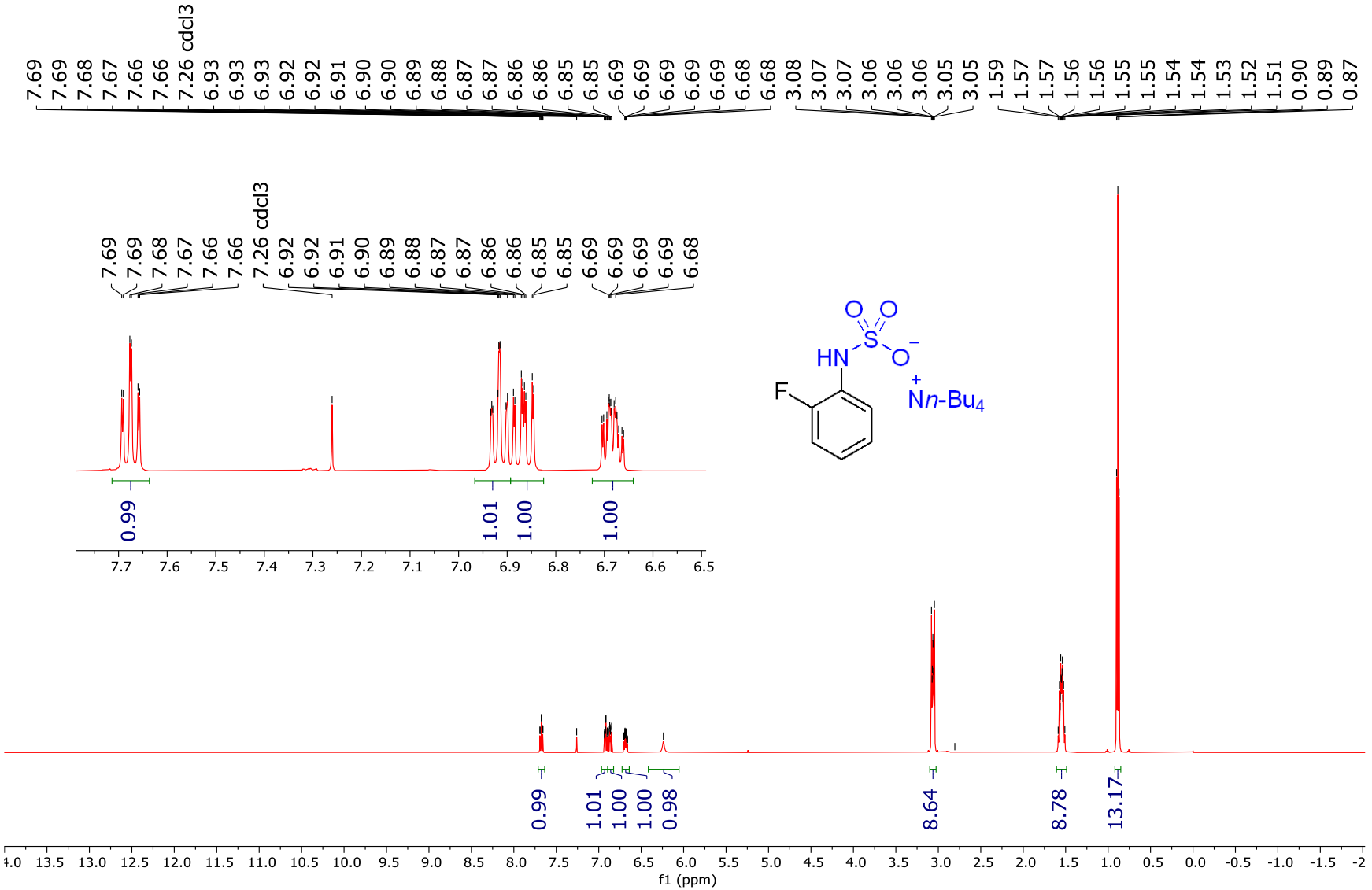
^{1}H NMR spectrum of tetrabutylammonium 2-(methoxy)phenylsulfamate (3.3d′) (500 MHz, $CDCl_3$)



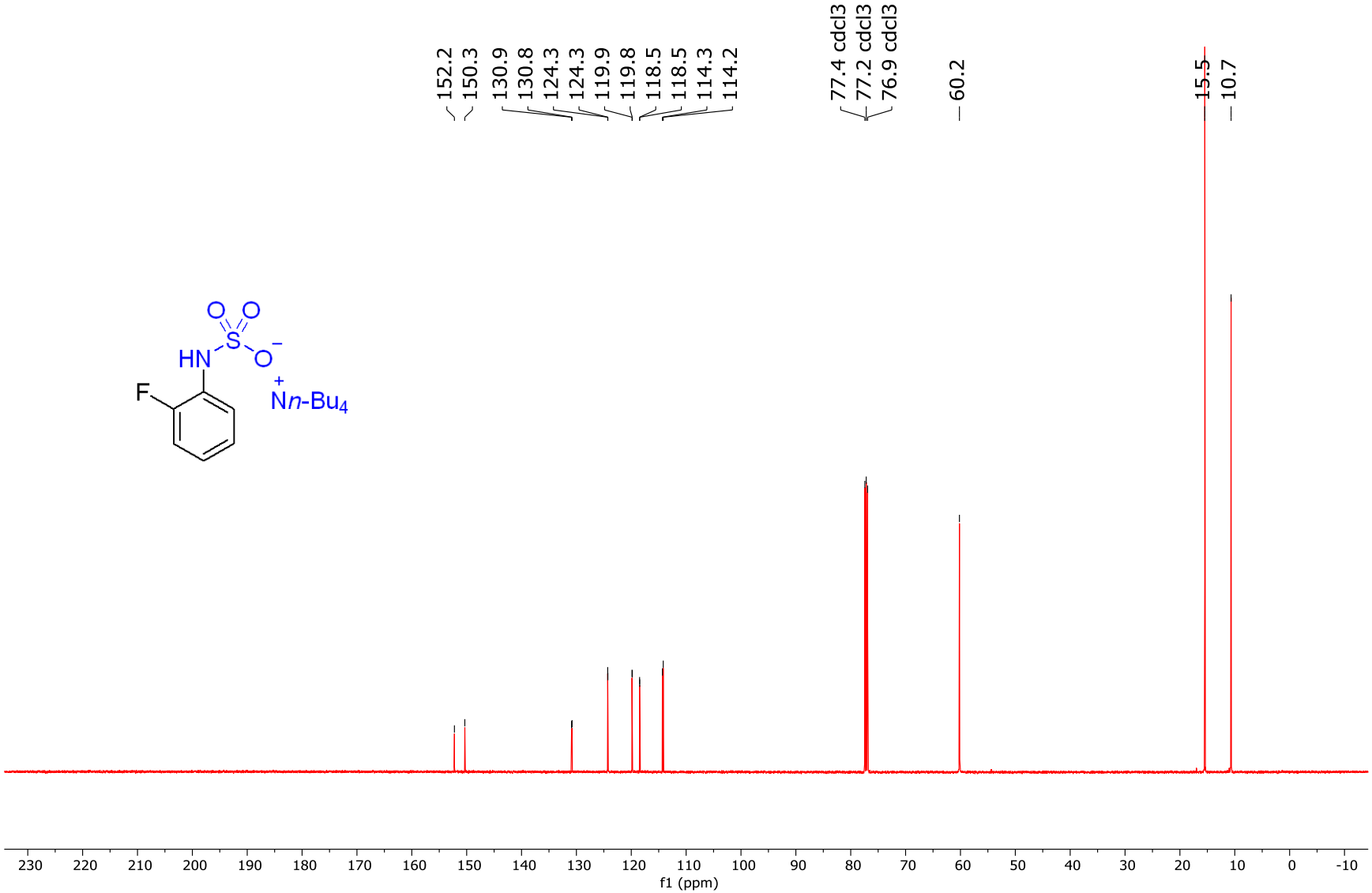
^{13}C NMR spectrum of tetrabutylammonium 2-(methoxy)phenylsulfamate (3.3d′) (126 MHz, $CDCl_3$)



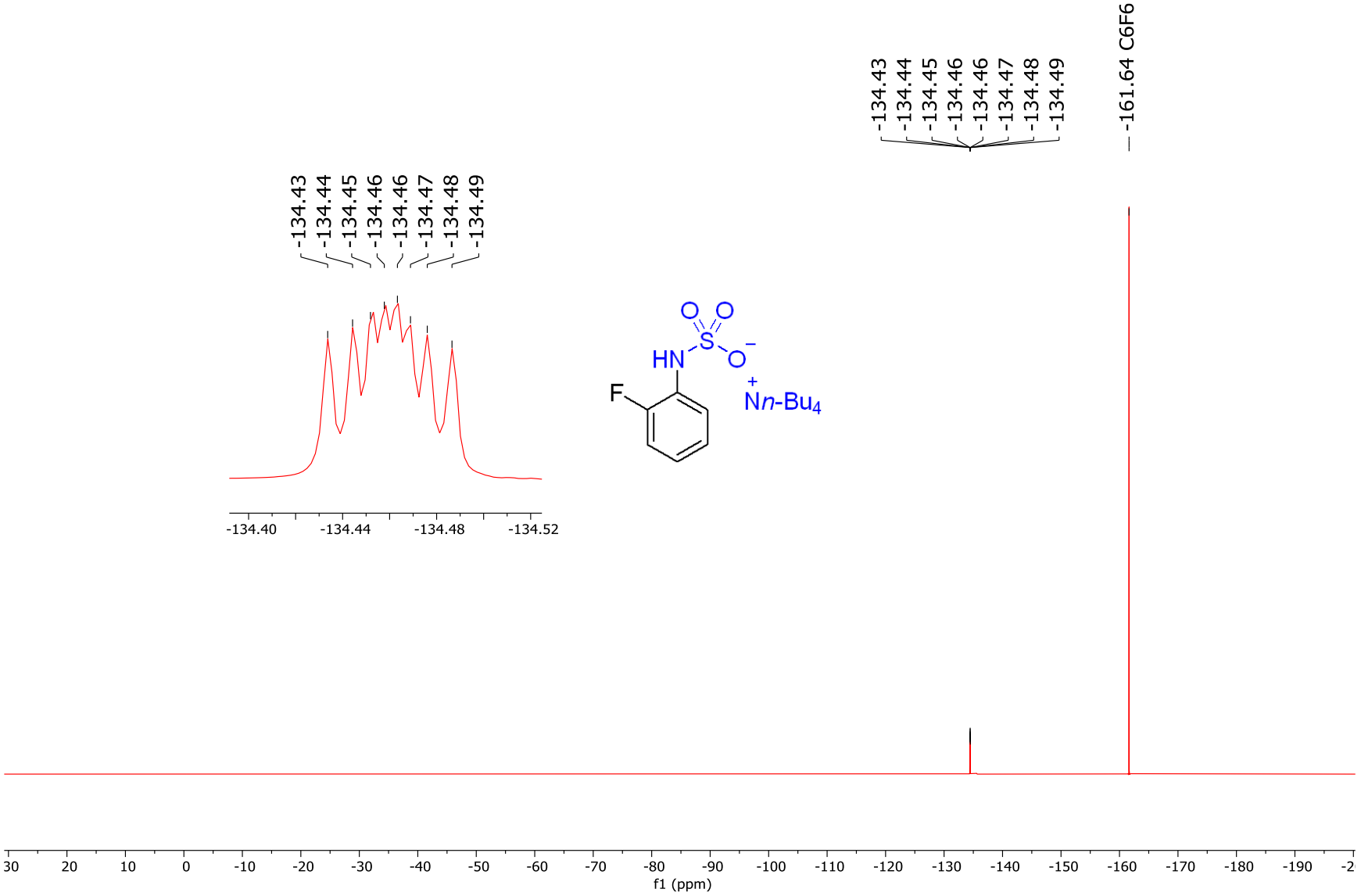
^{1}H NMR spectrum of tetrapropylammonium 2-fluorophenylsulfamate (3.3e) (500 MHz, $CDCl_3$)



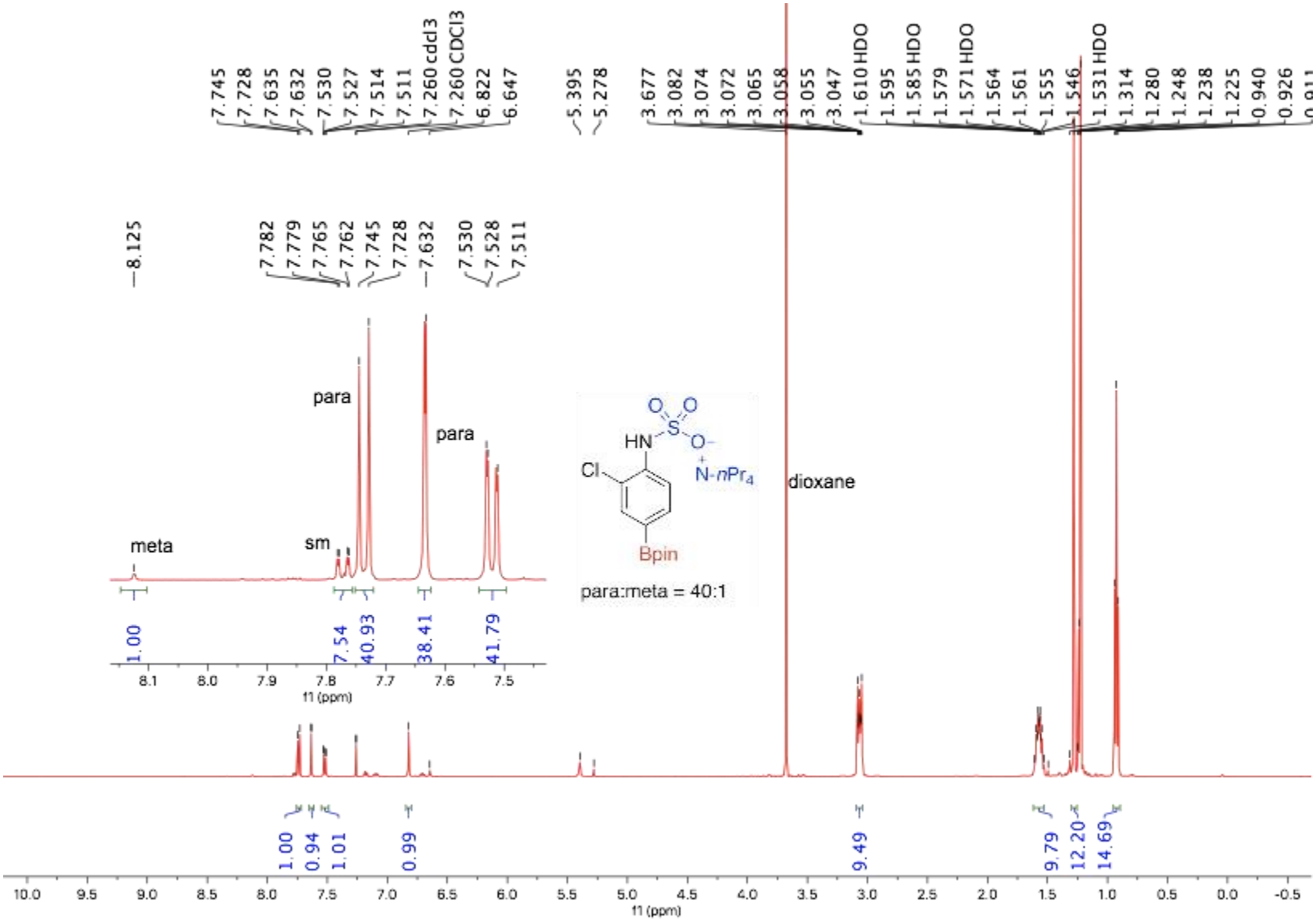
^{13}C NMR spectrum of tetrapropylammonium 2-fluorophenylsulfamate (3.3e) (126 MHz, $CDCl_3$)



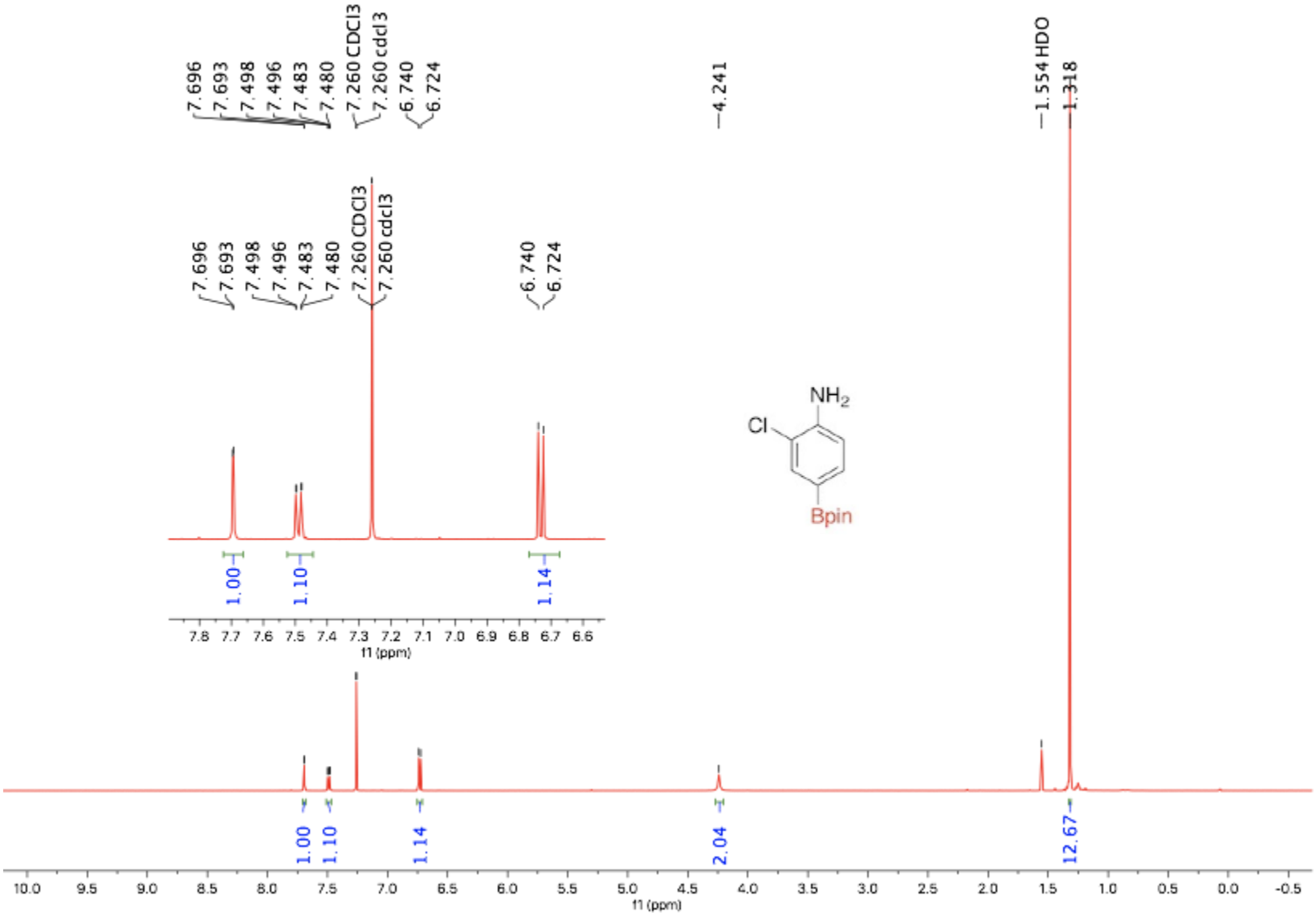
^{19}F NMR spectrum of tetrapropylammonium 2-fluorophenylsulfamate (3.3e) (470 MHz, $CDCl_3$)



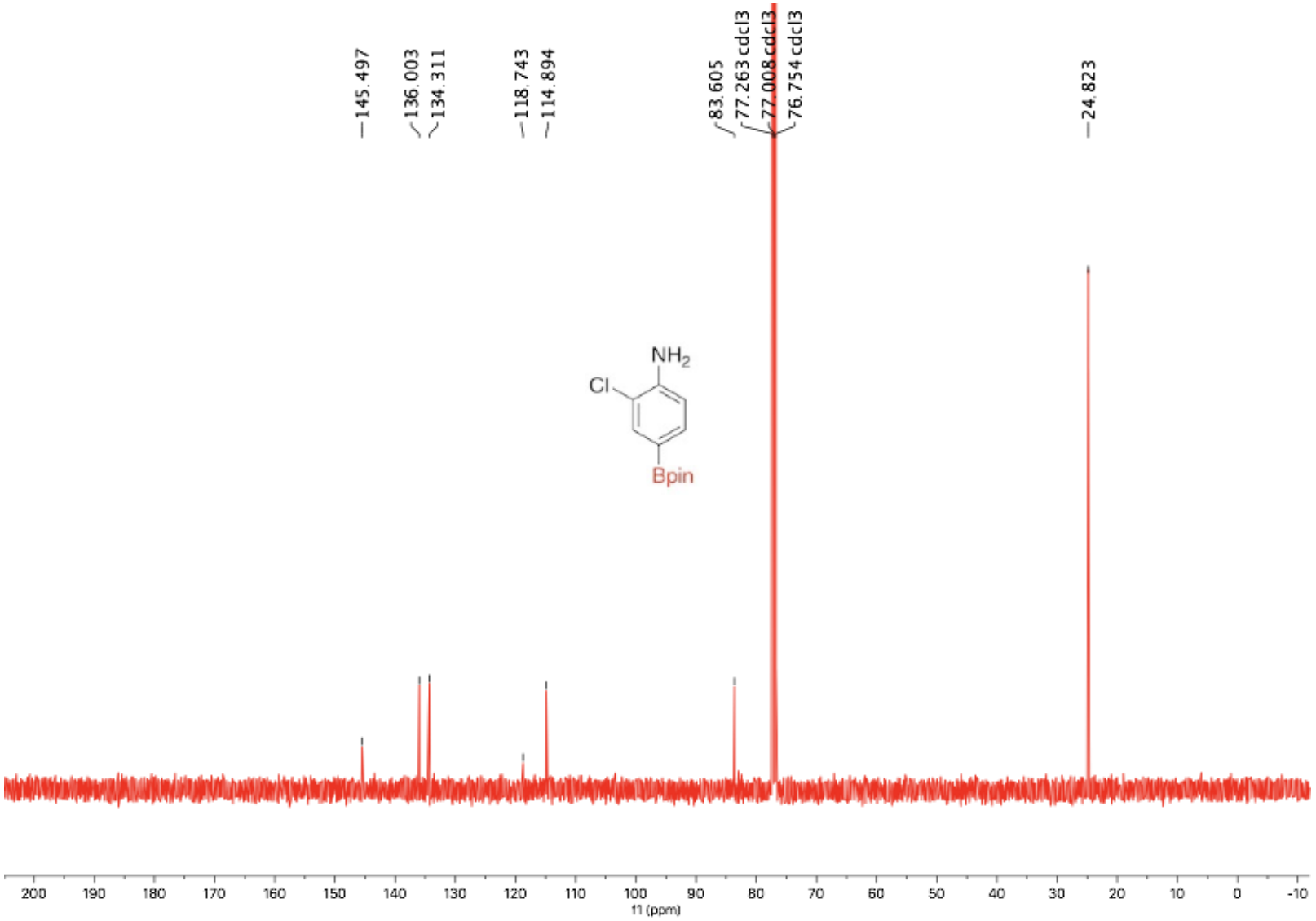
^{1}H NMR reaction mixture of *para* borylation of tetrapropylammonium 2-chlorophenylsulfamate (crude 3.4a) (500 MHz, $CDCl_3$)



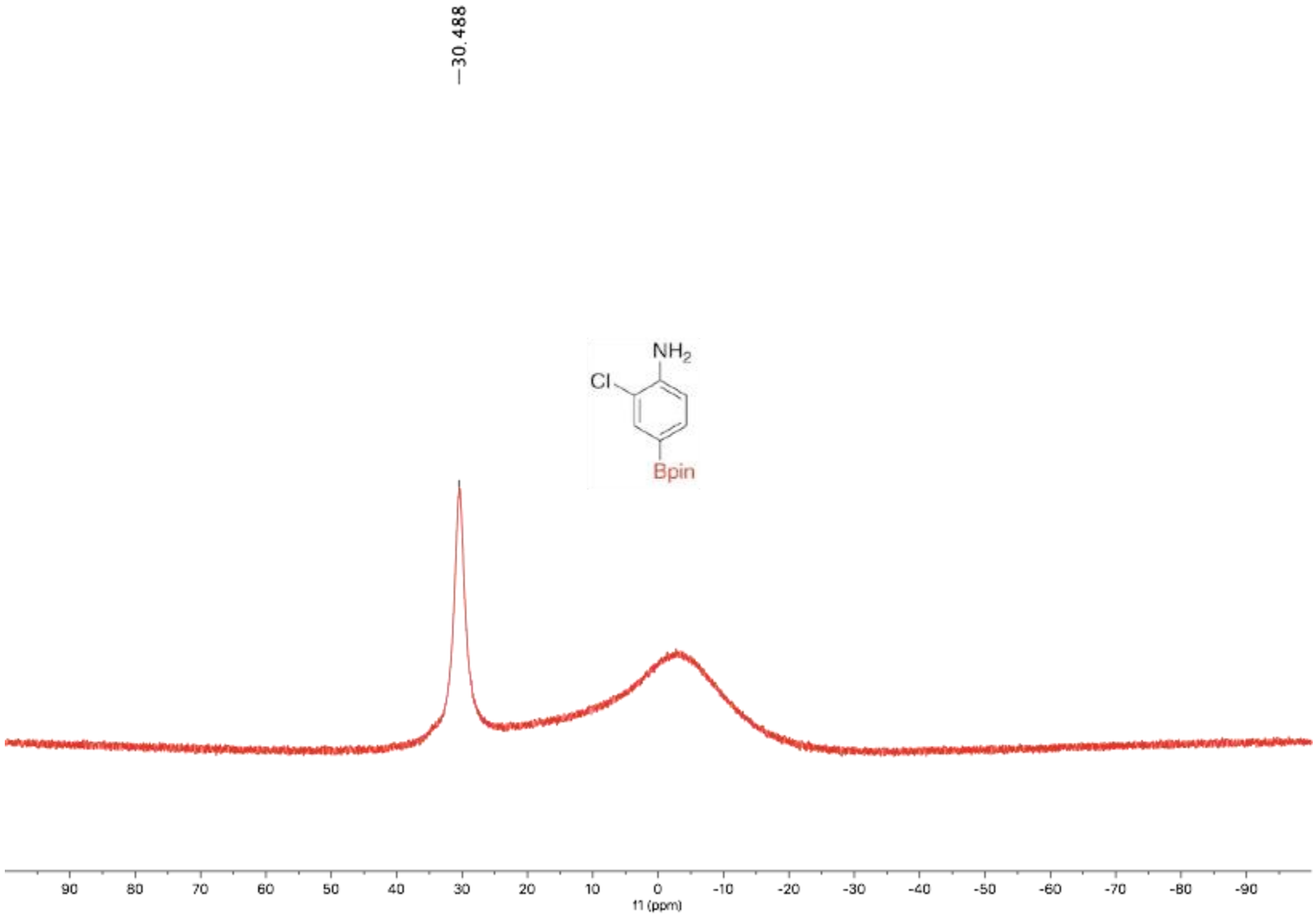
^{1}H NMR spectrum of *para* borylated 2-chloroaniline (3.4a) (500 MHz, $CDCl_3$)



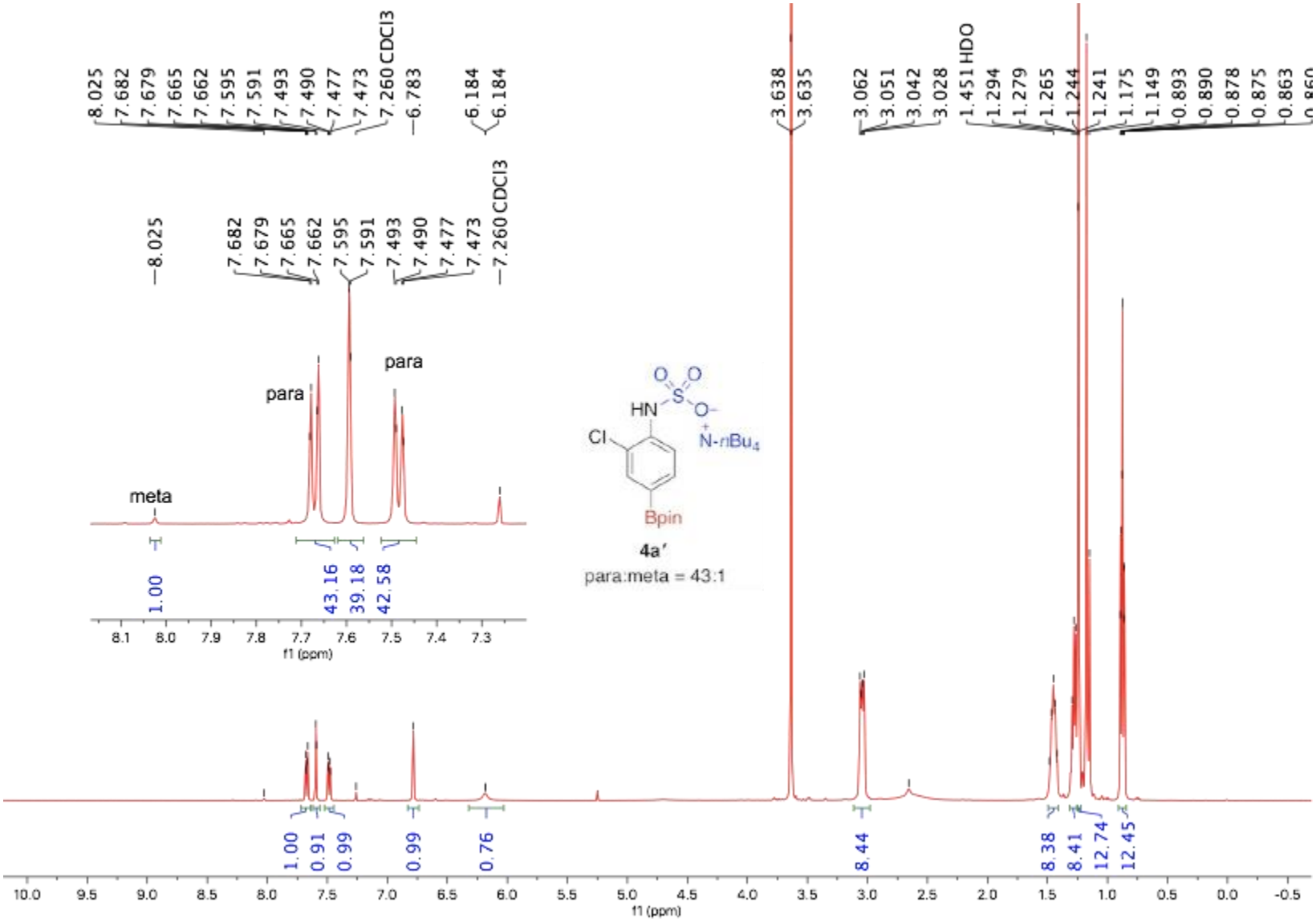
^{13}C NMR spectrum of *para* borylated 2-chloroaniline (3.4a) (126 MHz, $CDCl_3$)



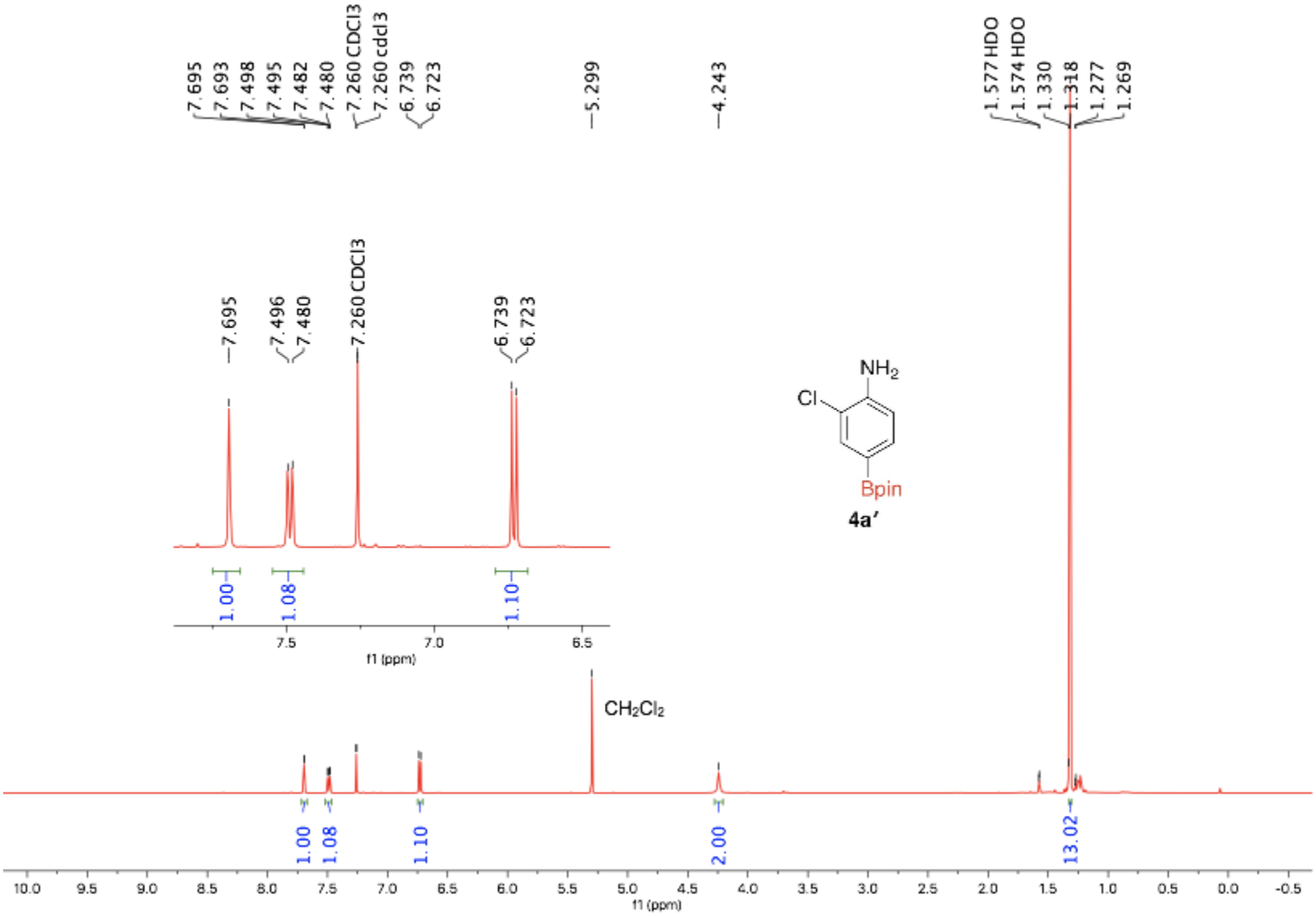
^{11}B NMR spectrum of *para* borylated 2-chloroaniline (3.4a) (160 MHz, $CDCl_3$)



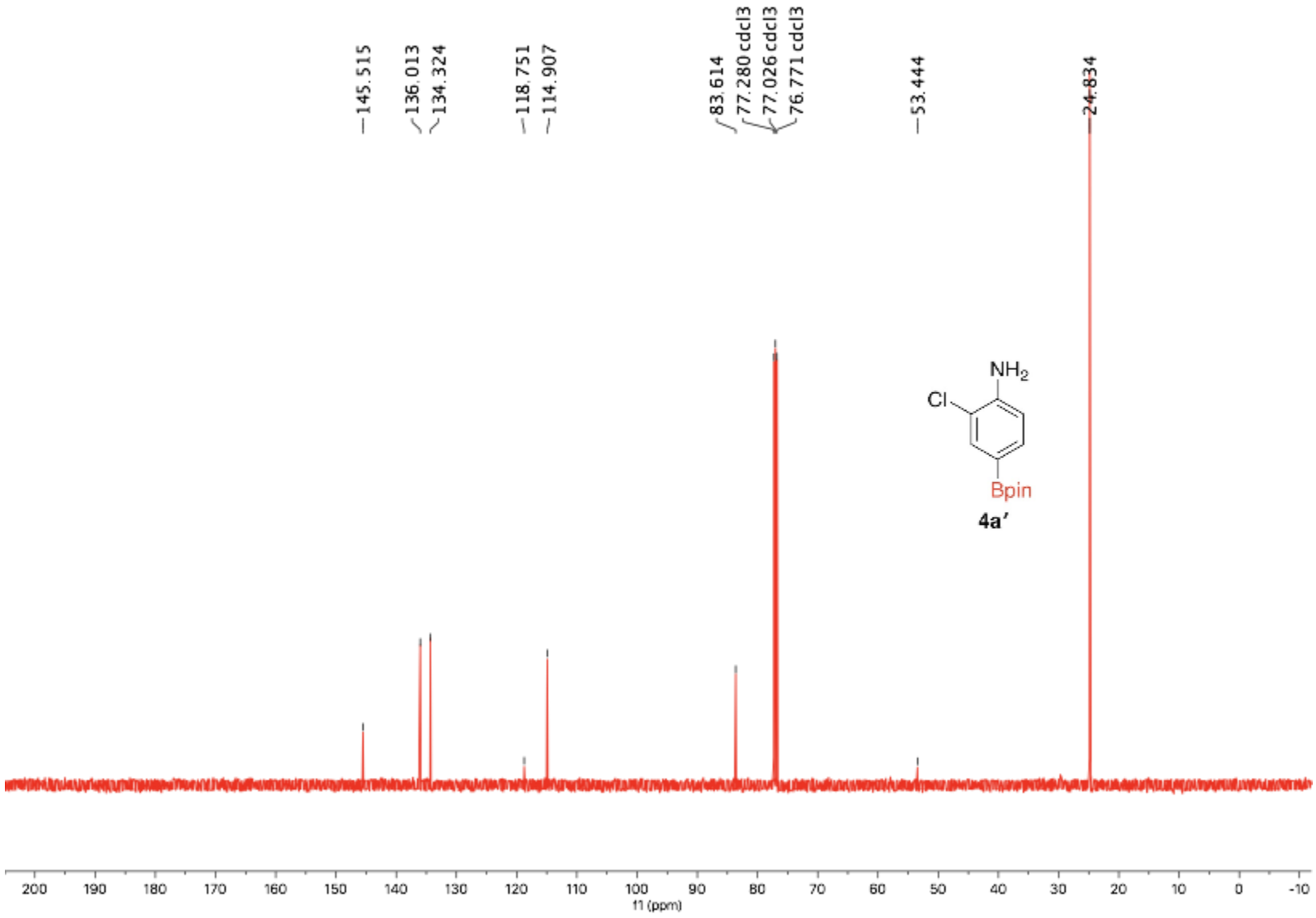
^{1}H NMR reaction mixture of *para* borylation of tetrabutylammonium 2-chlorophenylsulfamate (crude 3.4a′) 500 MHz, $CDCl_3$



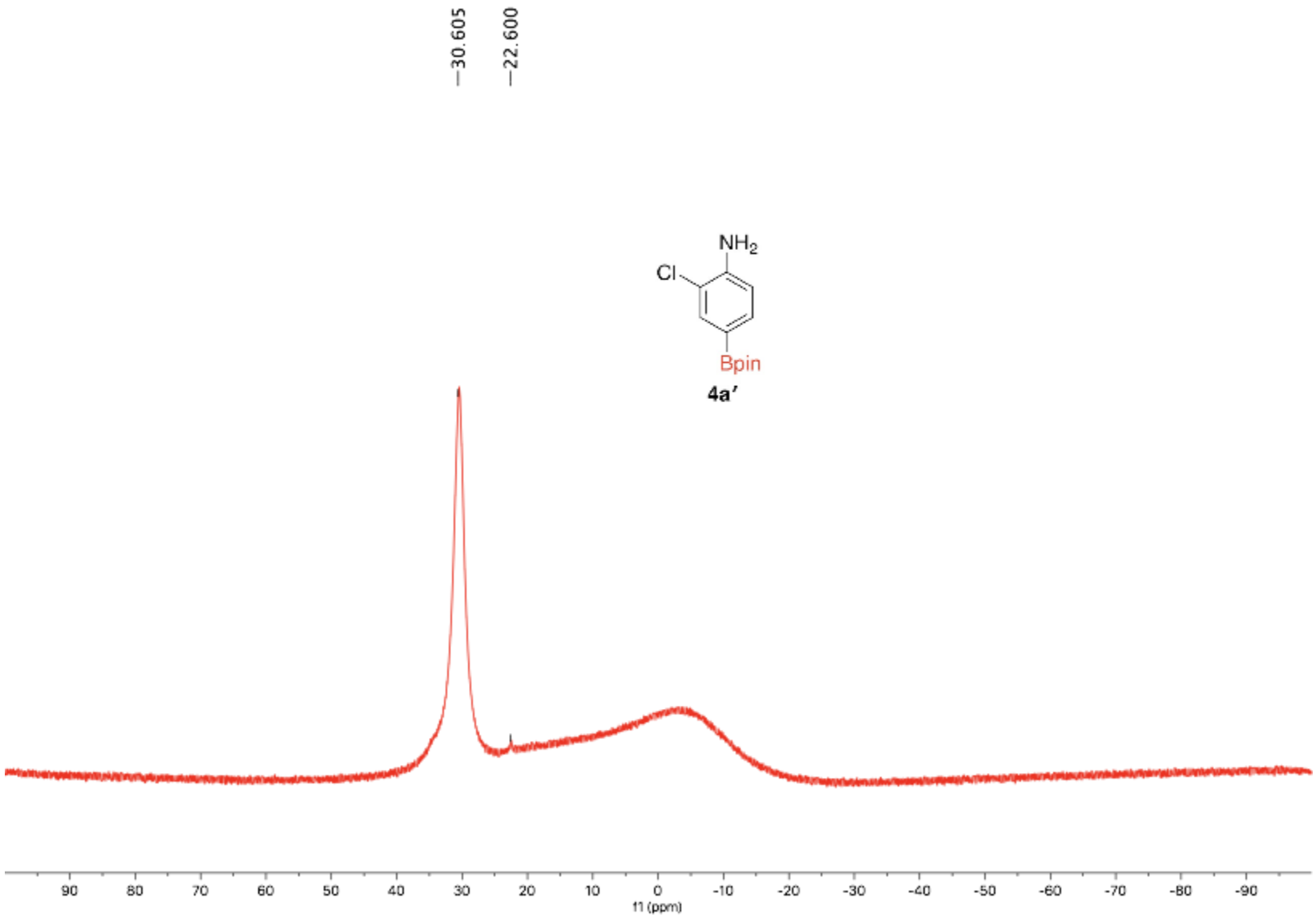
^{1}H NMR spectrum of *para* borylated 2-chloroaniline (3.4a′) (500 MHz, $CDCl_3$)



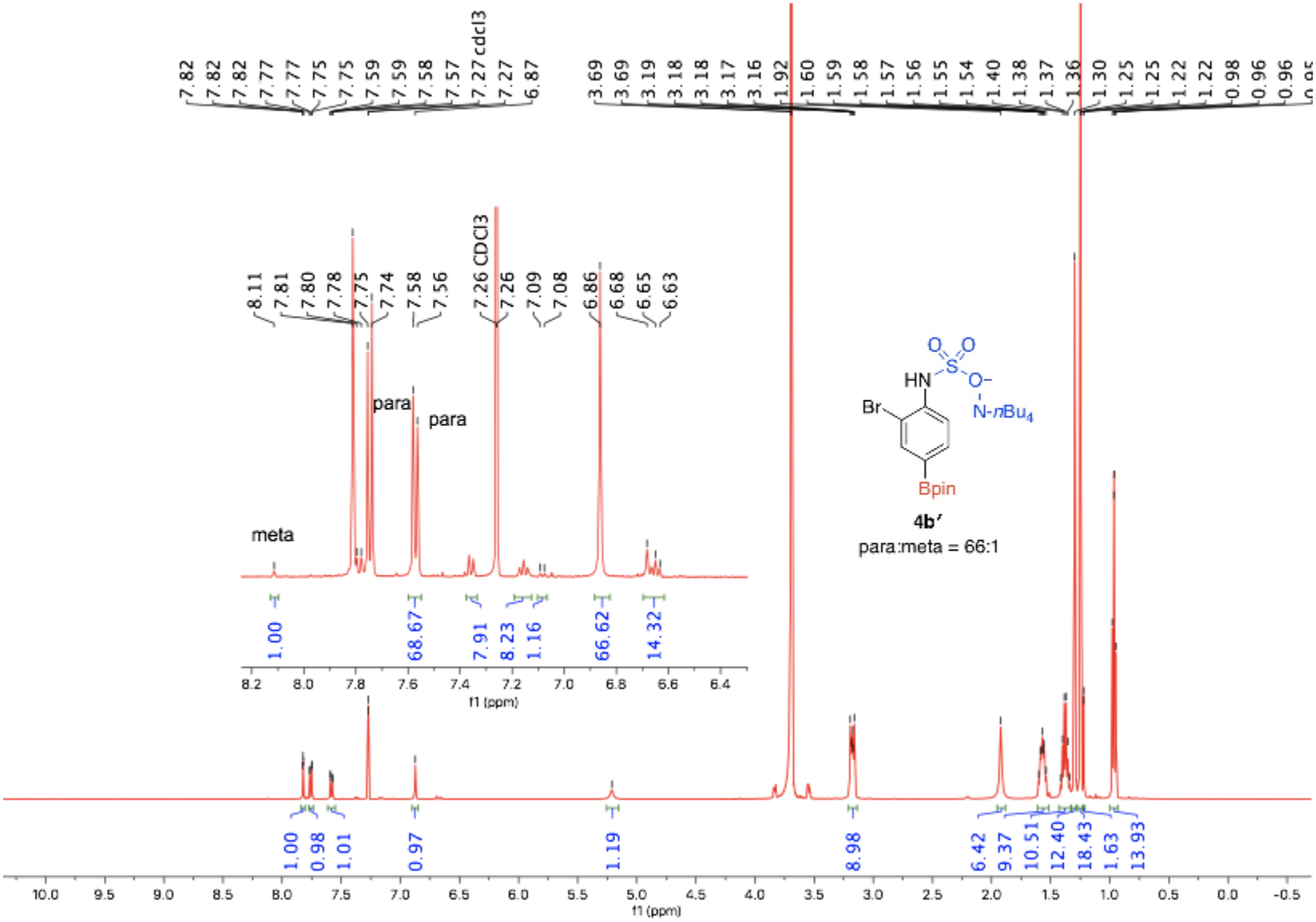
^{13}C NMR spectrum of *para* borylated 2-chloroaniline (3.4a′) (126 MHz, $CDCl_3$)



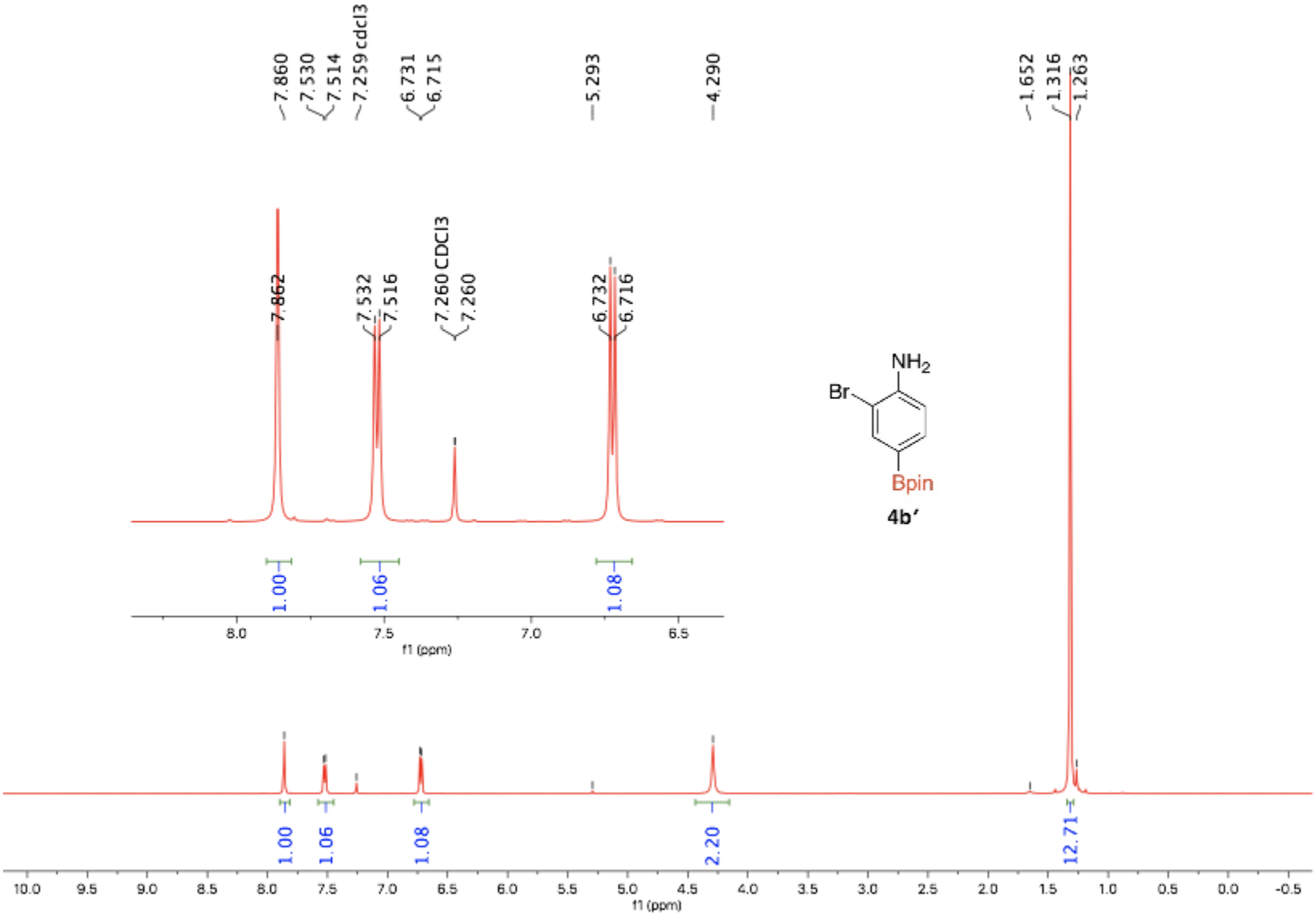
^{11}B NMR spectrum of *para* borylated 2-chloroaniline (3.4a′) (160 MHz, $CDCl_3$)



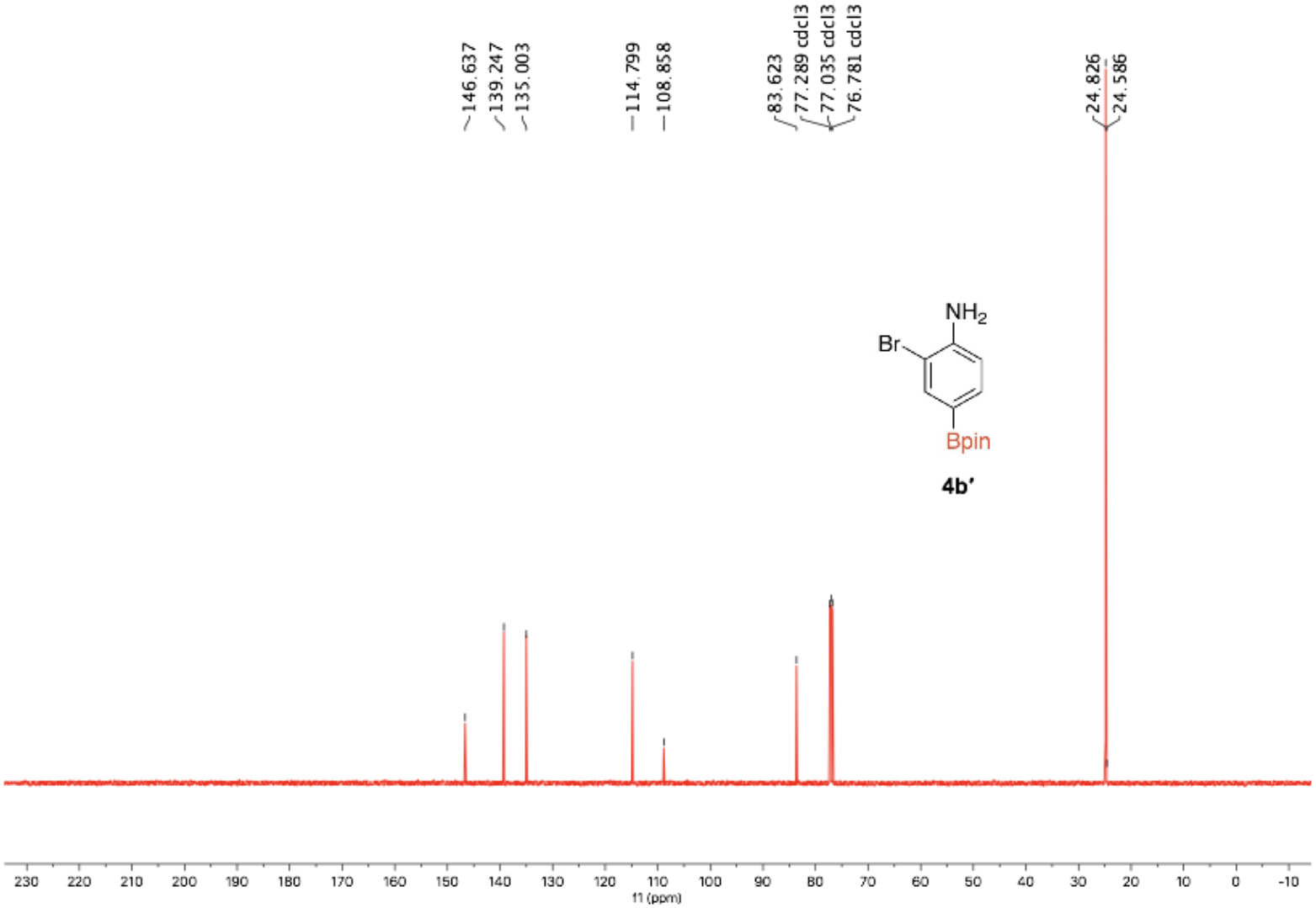
^{1}H NMR reaction mixture of *para* borylation of tetrabutylammonium 2-bromophenylsulfamate (crude 3.4b′) (500 MHz, $CDCl_3$)



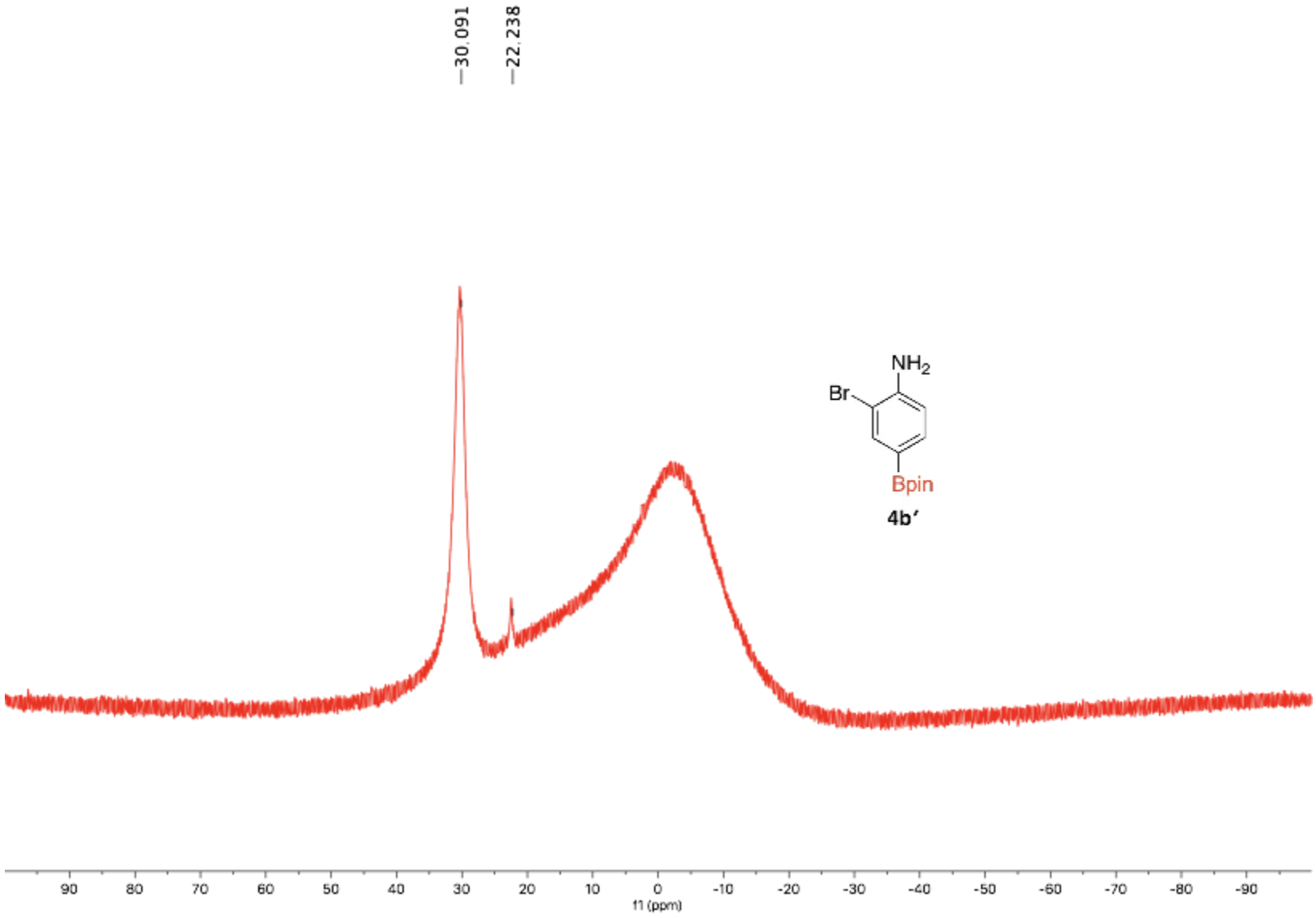
^{1}H NMR spectrum of *para*-borylated 2-bromoaniline (3.4b′) (500 MHz, $CDCl_3$)



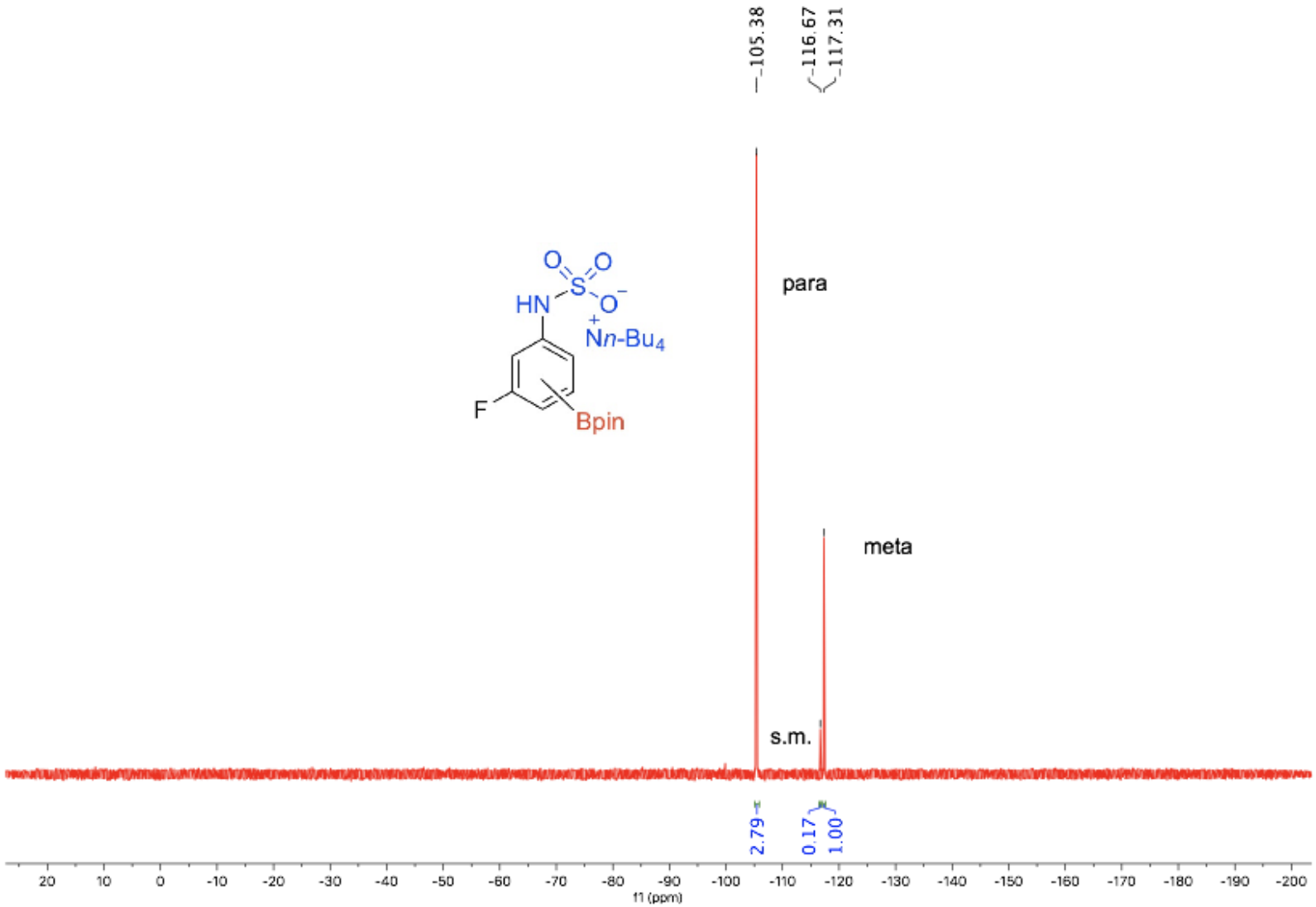
^{13}C NMR spectrum of *para*-borylated 2-bromoaniline (3.4b′) (126 MHz, $CDCl_3$)



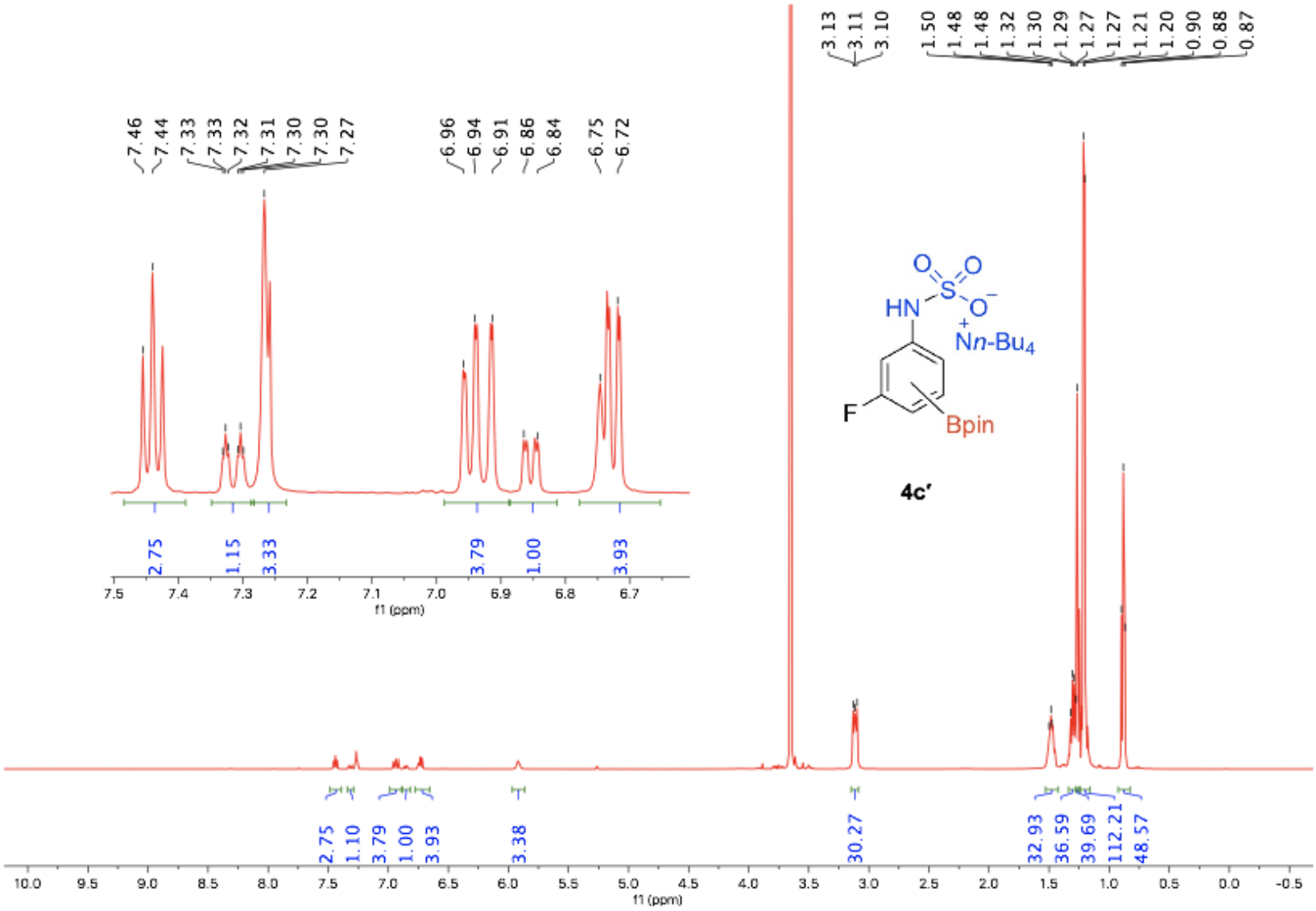
^{11}B NMR spectrum of *para* borylated 2-bromoaniline (3.4b′) (160 MHz, $CDCl_3$)



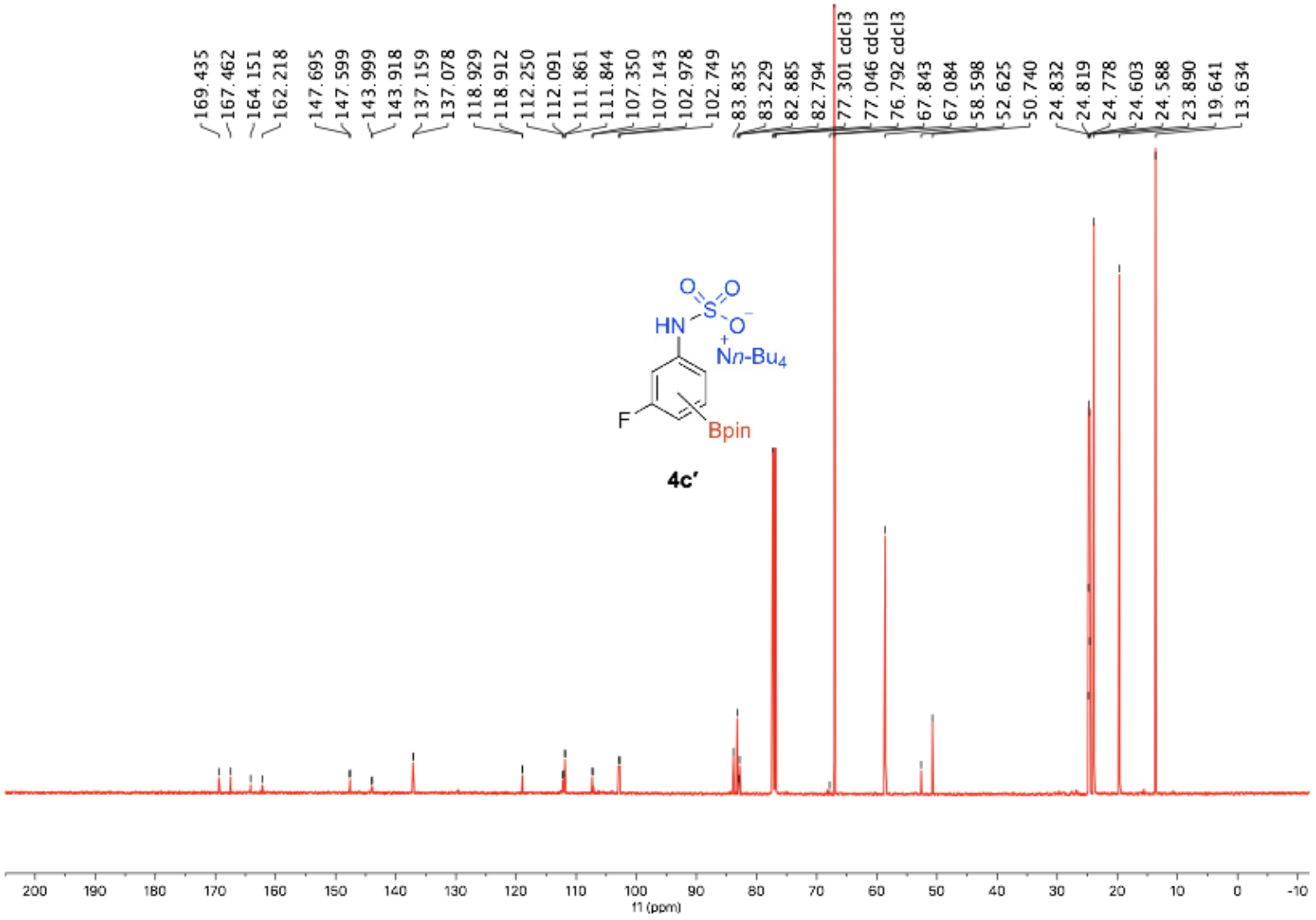
^{19}F NMR reaction mixture of *para* borylation of tetrabutylammonium 3-fluorophenylsulfamate (3.4c′) (470 MHz, $CDCl_3$)



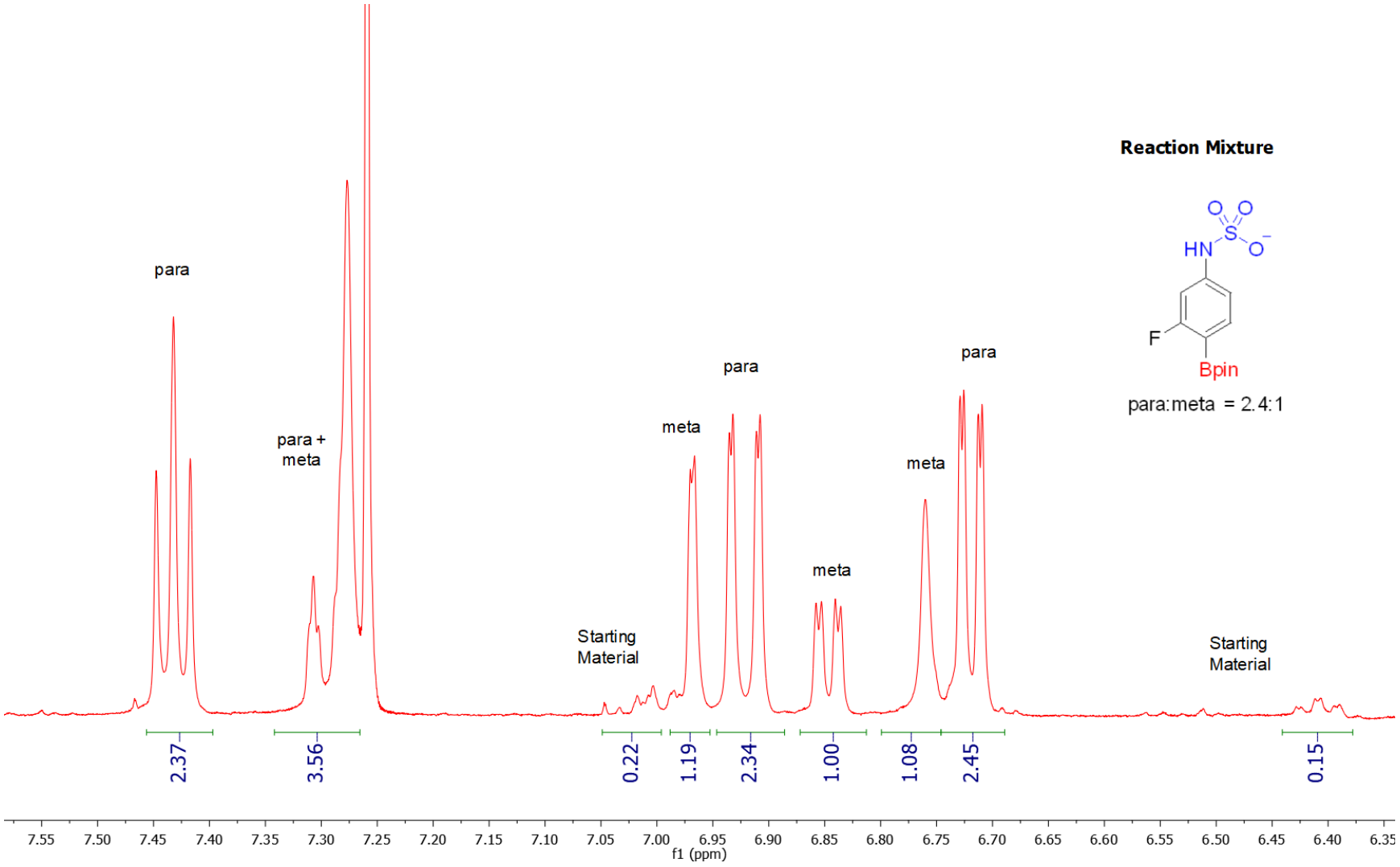
^{1}H NMR reaction mixture of *para* borylation of tetrabutylammonium 3-fluorophenylsulfamate (crude 3.4c′) (500 MHz, $CDCl_3$)



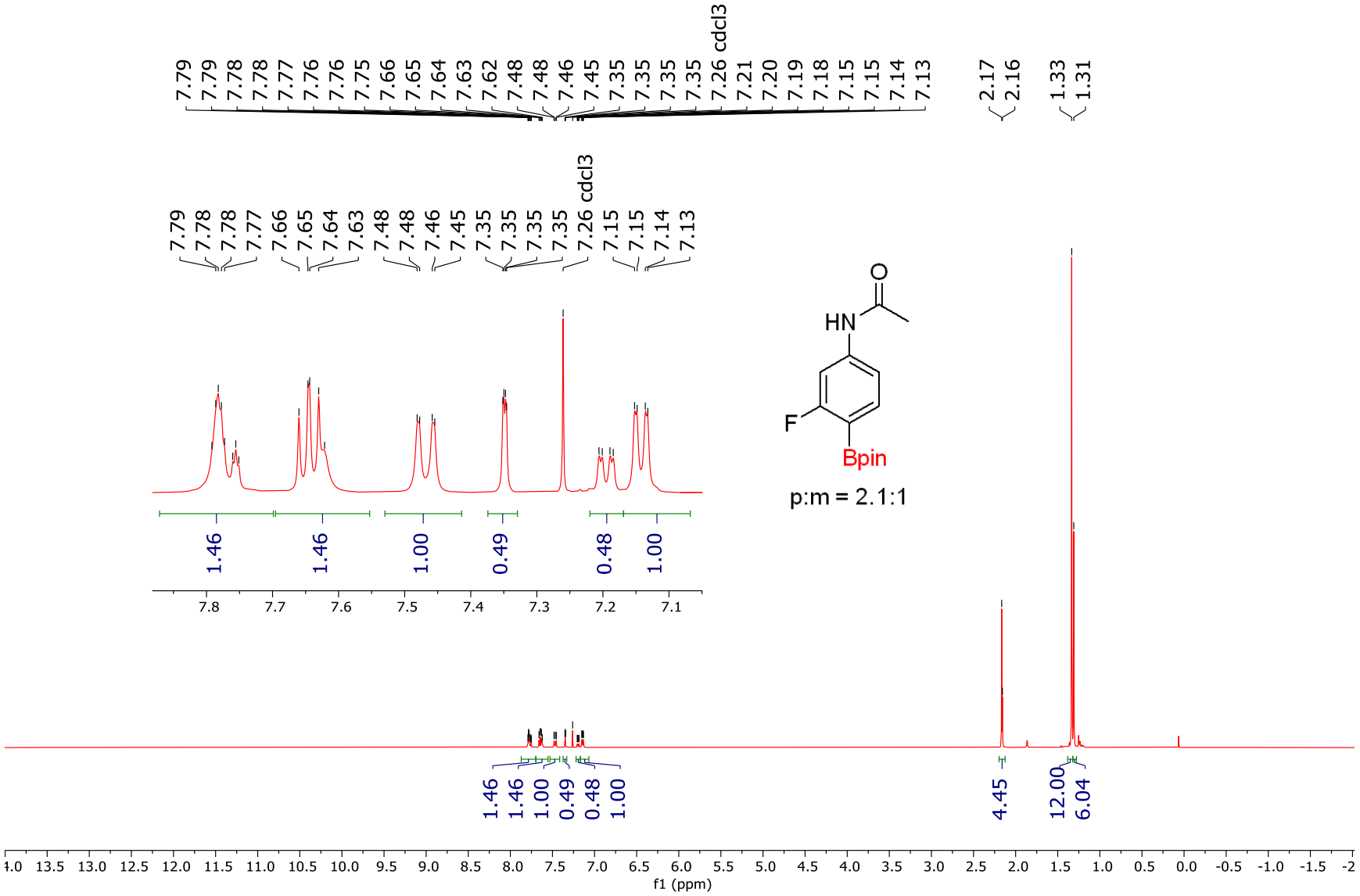
^{13}C NMR reaction mixture of *para* borylation of tetrabutylammonium 3-fluorophenylsulfamate (crude 3.4c′) (500 MHz, $CDCl_3$)



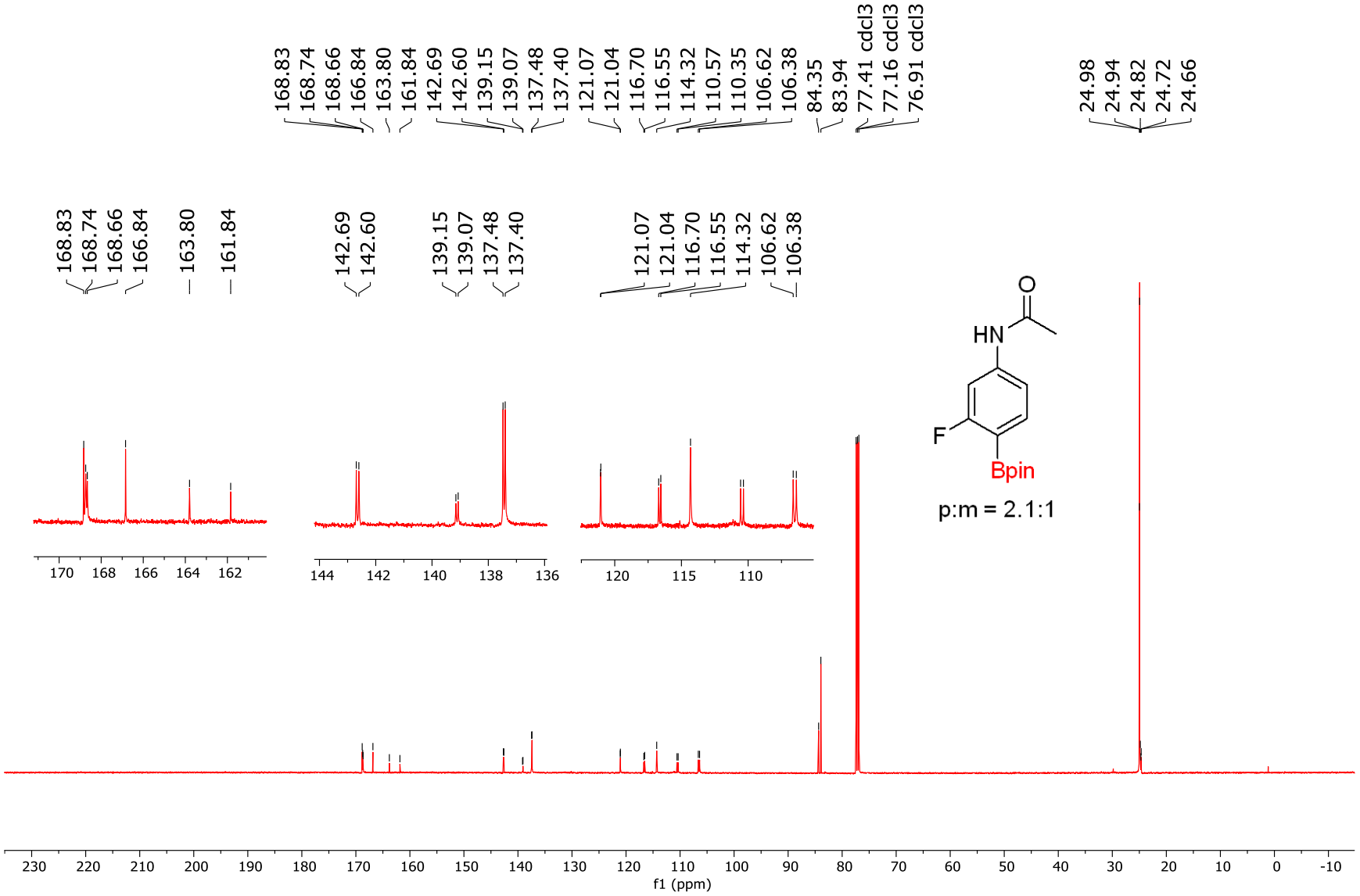
^{1}H NMR spectrum of reaction mixture of *para* borylation of tetrabutylammonium 3-fluorophenylsulfamate previous acetylation (crude 3.4c′) (500 MHz, $CDCl_3$)



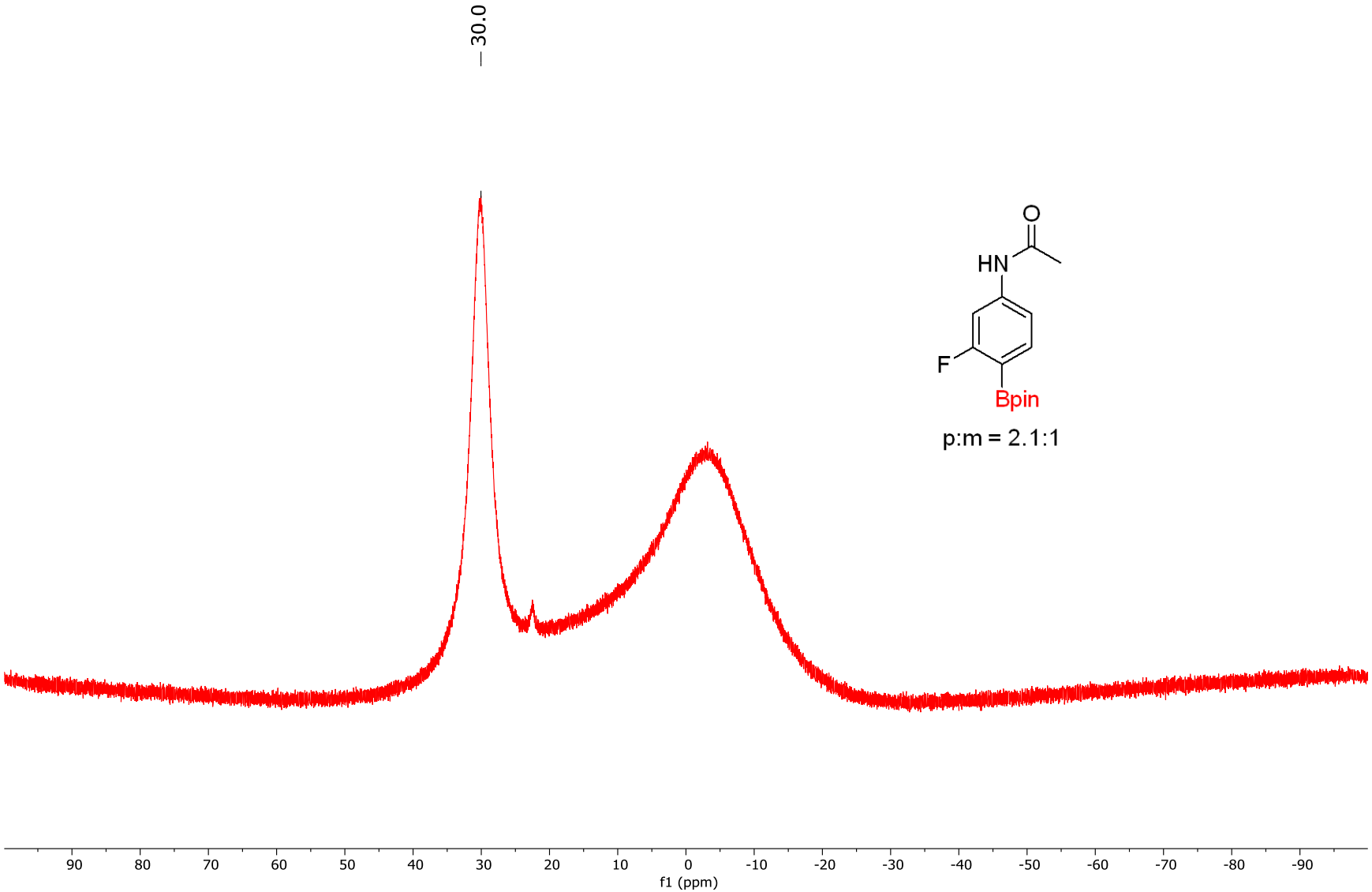
^{1}H NMR spectrum of *para* borylated N-(3-fluorophenyl)acetamide (3.4c′) (500 MHz, $CDCl_3$)



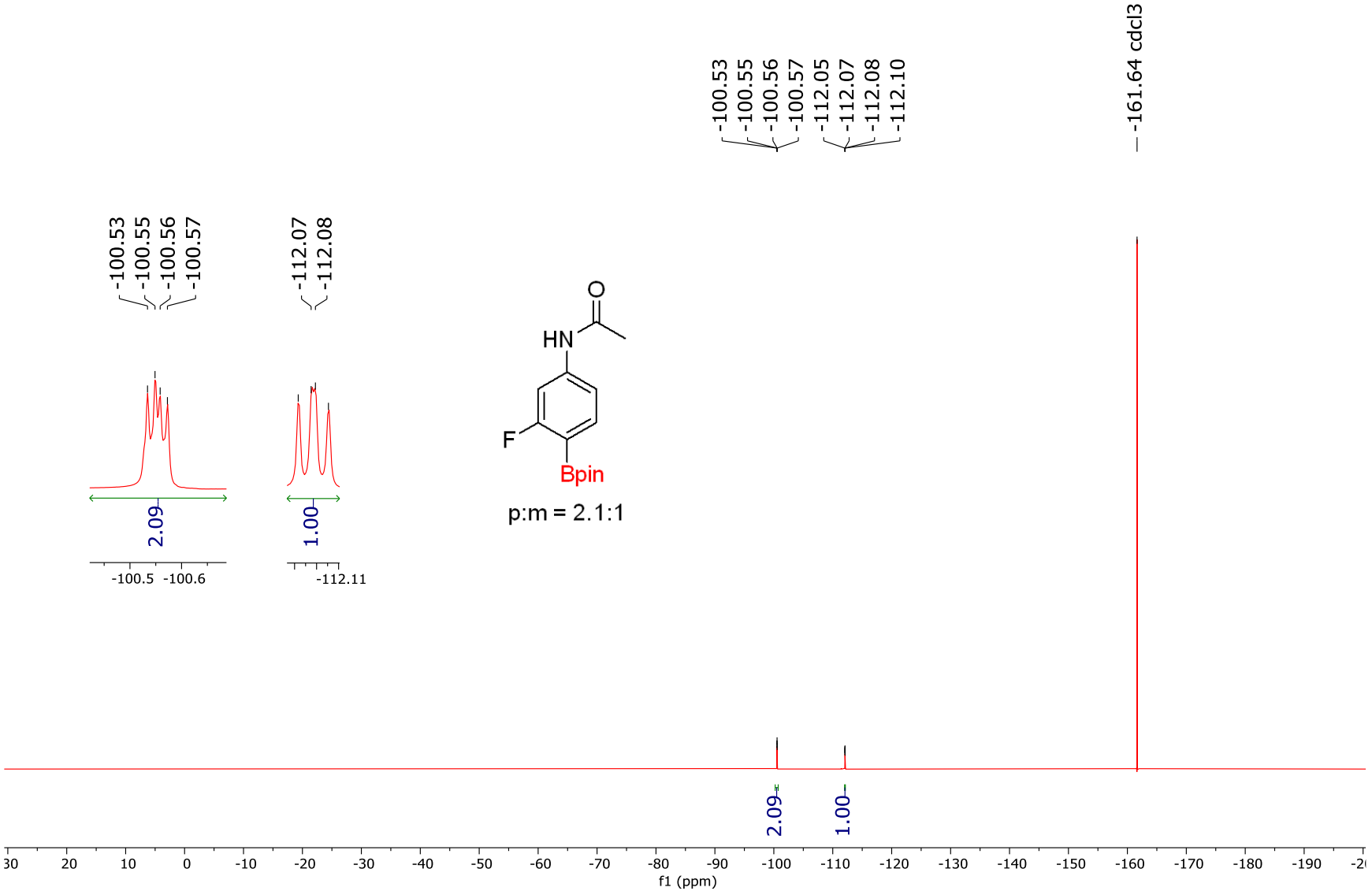
^{13}C NMR spectrum of *para* borylated N-(3-fluorophenyl)acetamide (3.4c′) (126 MHz, $CDCl_3$)



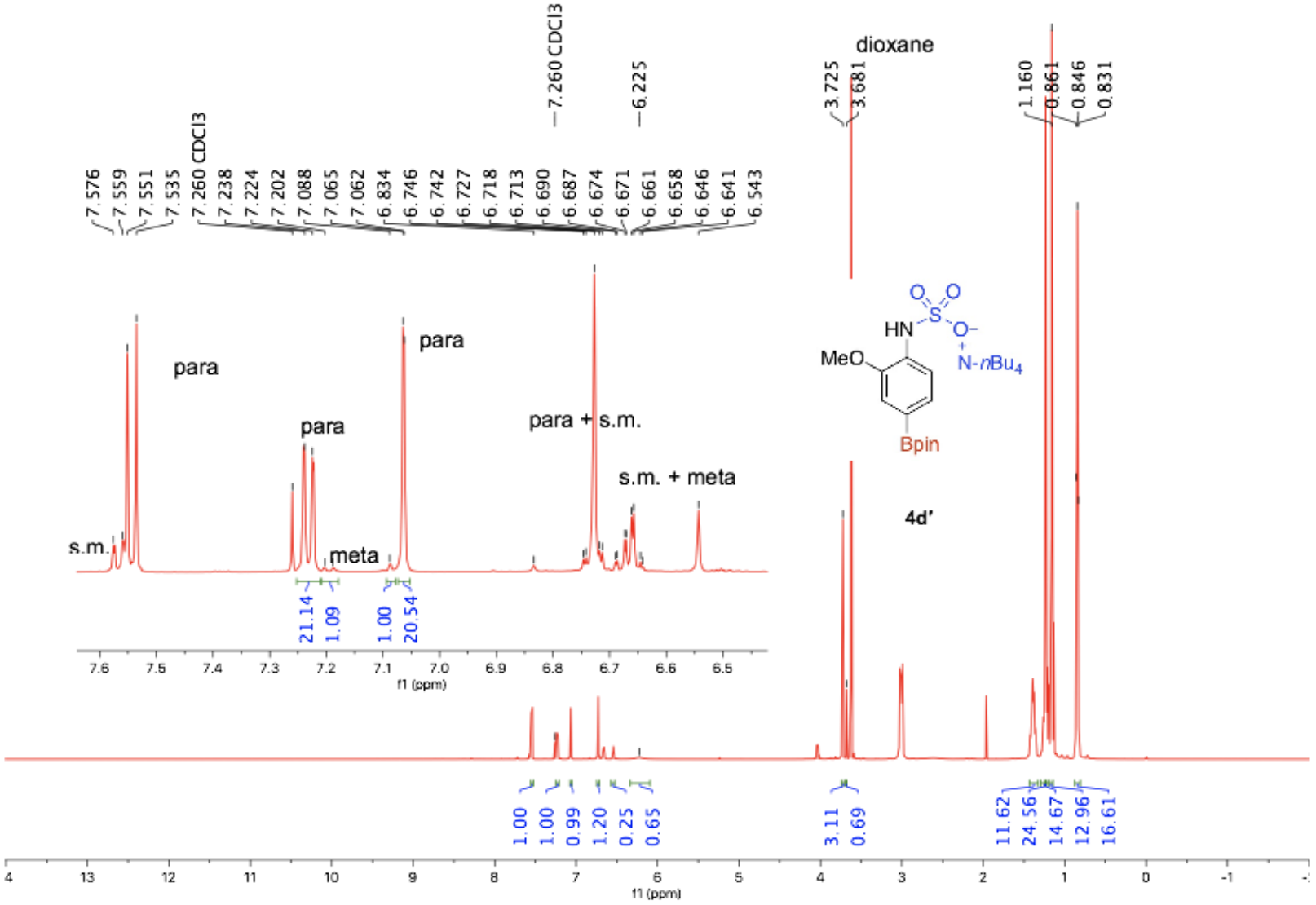
^{11}B NMR spectrum of *para* borylated N-(3-fluorophenyl)acetamide (3.4c′) (160 MHz, $CDCl_3$)



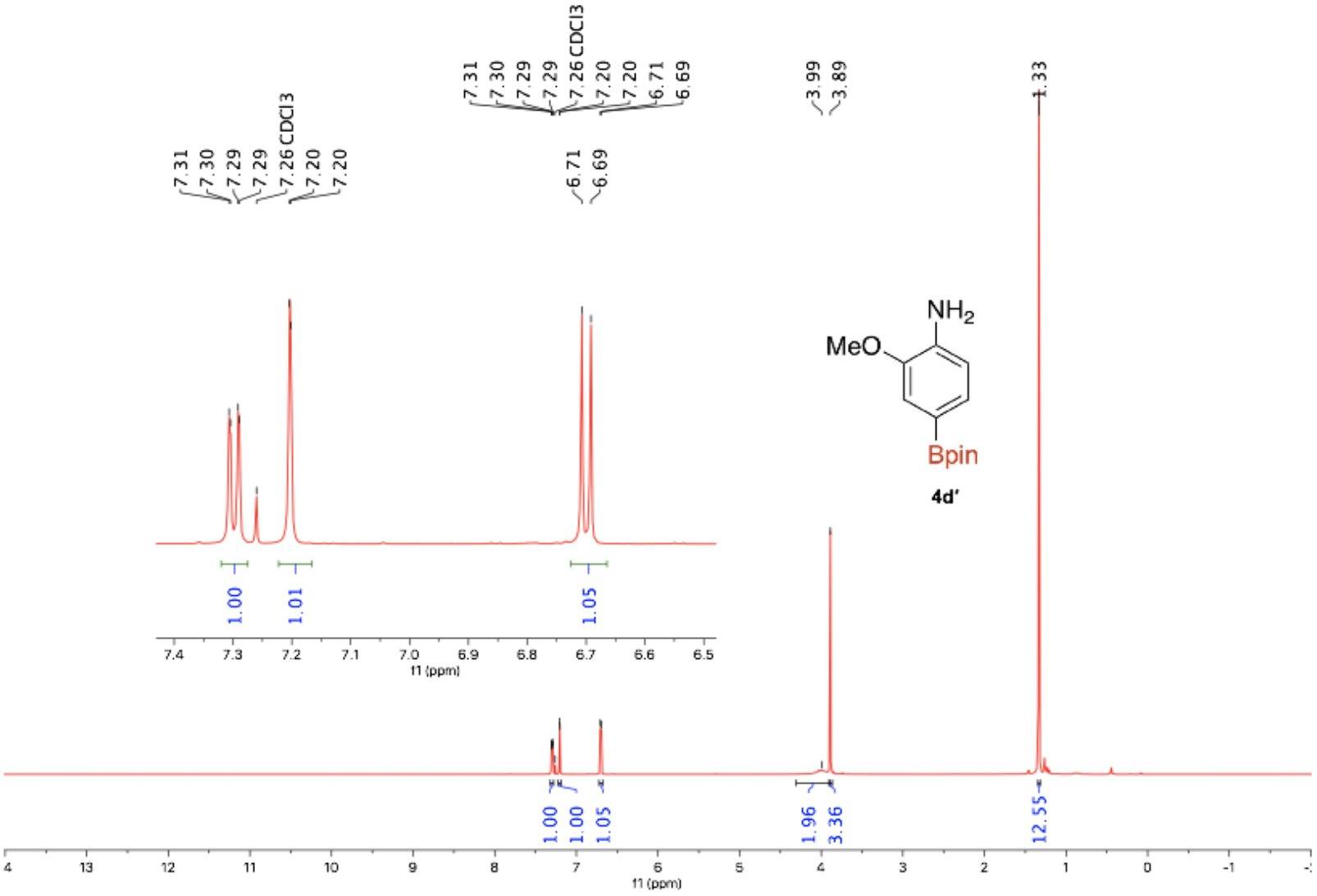
^{19}F NMR spectrum of *para* borylated N-(3-fluorophenyl)acetamide (3.4c′) (470 MHz, $CDCl_3$)



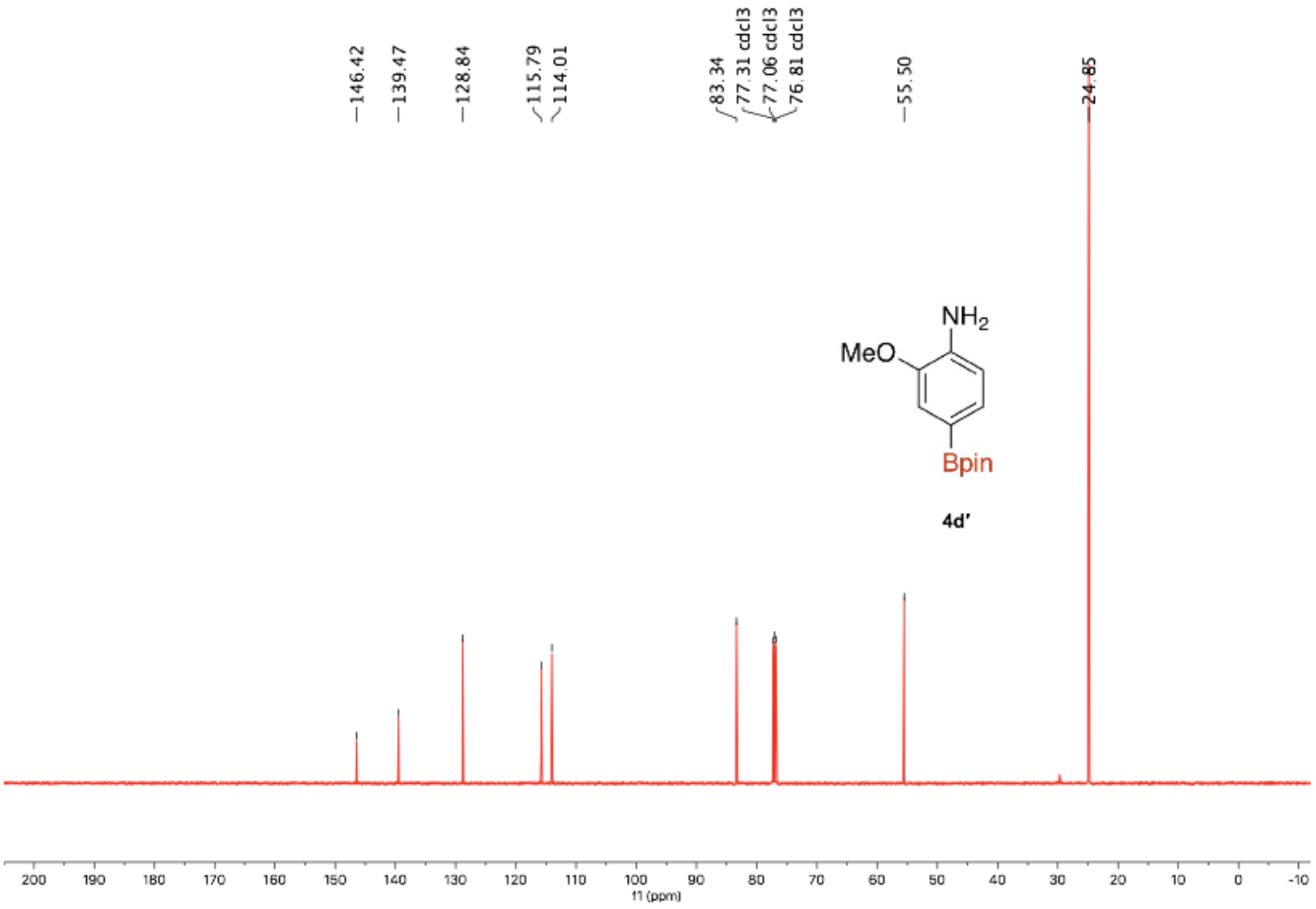
^{1}H NMR reaction mixture of *para* borylation of tetrabutylammonium 2-methoxyphenylsulfamate (3.4d′) (500 MHz, $CDCl_3$)



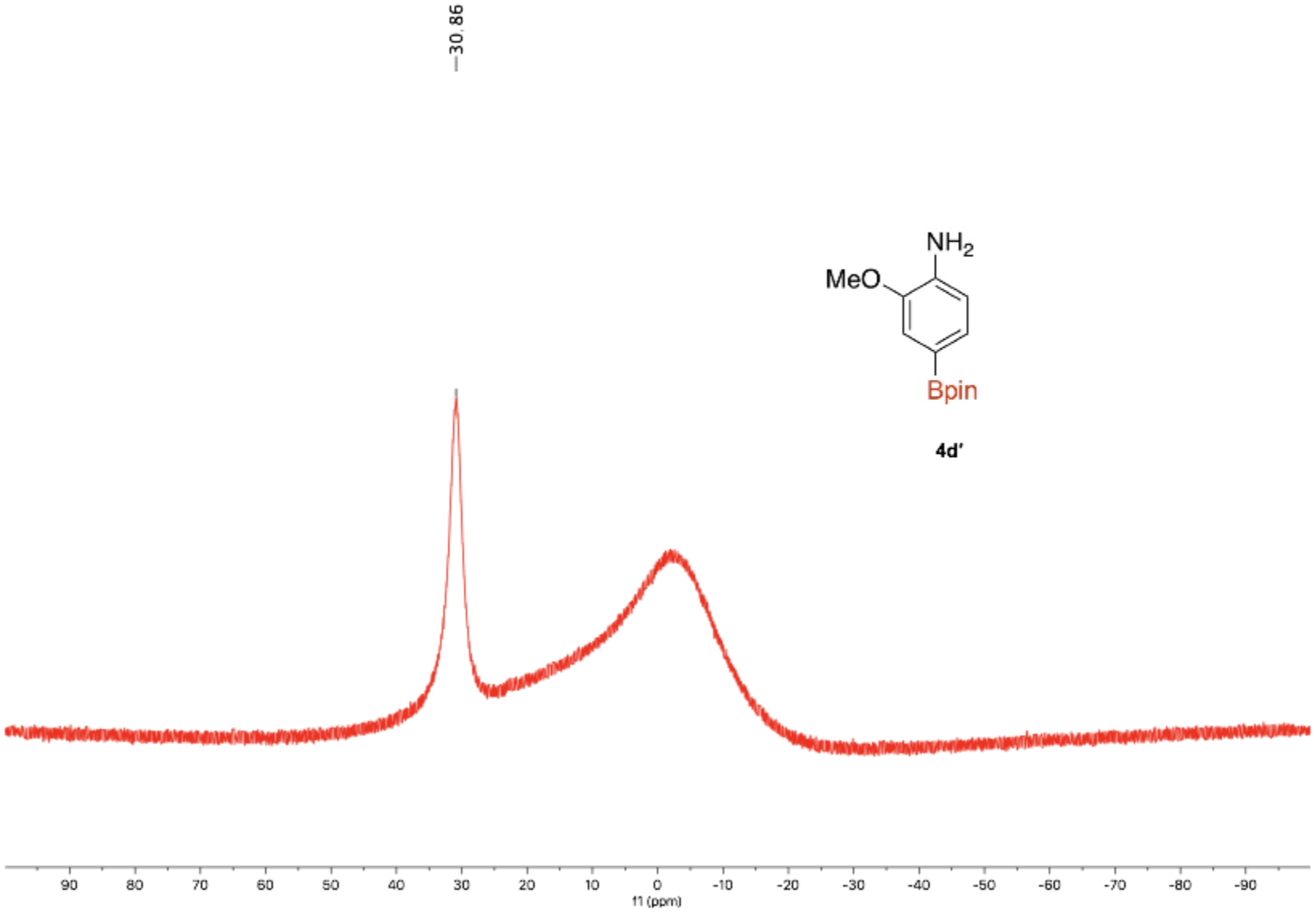
^{1}H NMR spectrum *para* borylated 2-methoxyaniline (3.4d′) (500 MHz, $CDCl_3$)



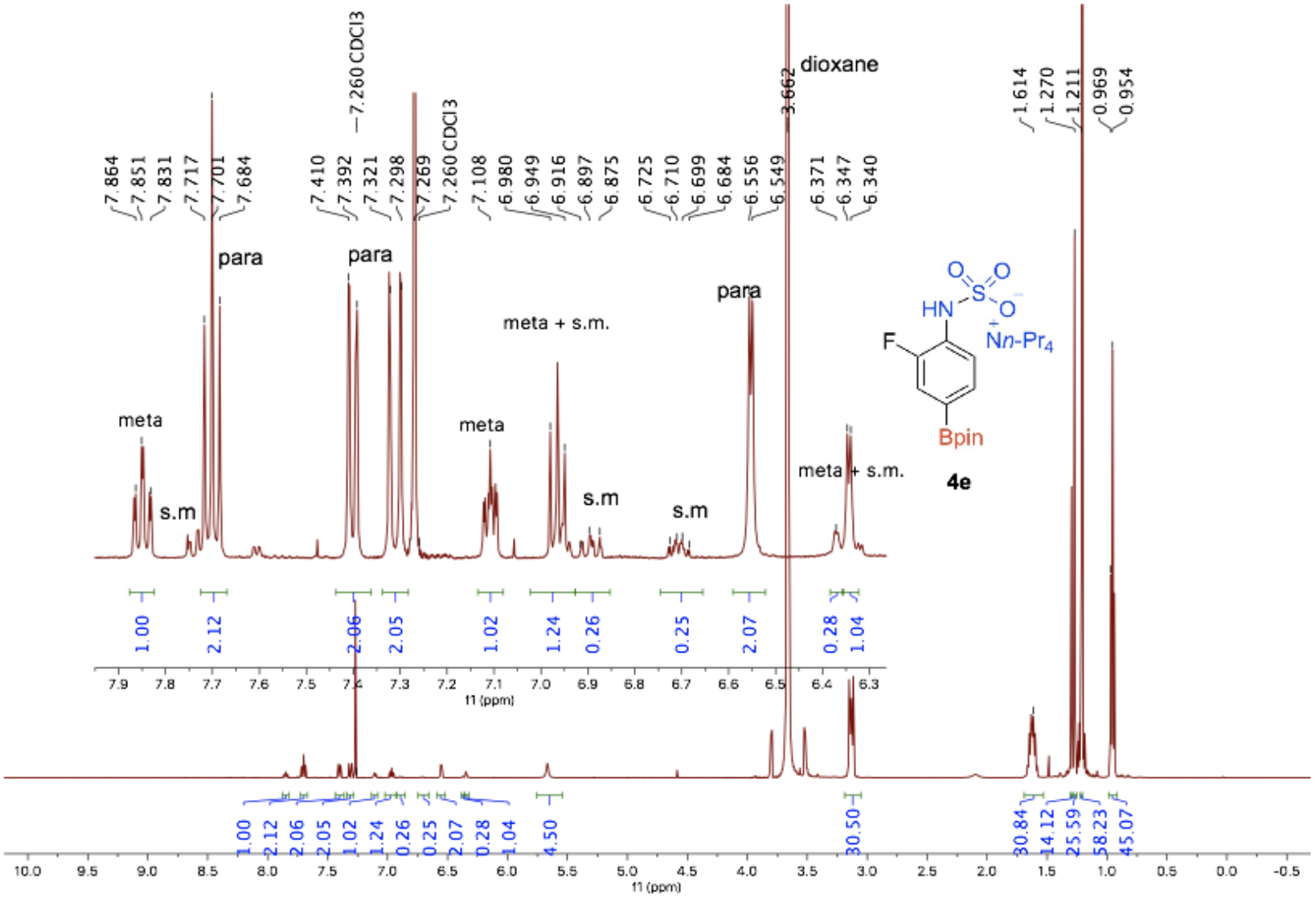
^{13}C NMR spectrum *para* borylated 2-methoxyaniline (3.4d′) (126 MHz, $CDCl_3$)



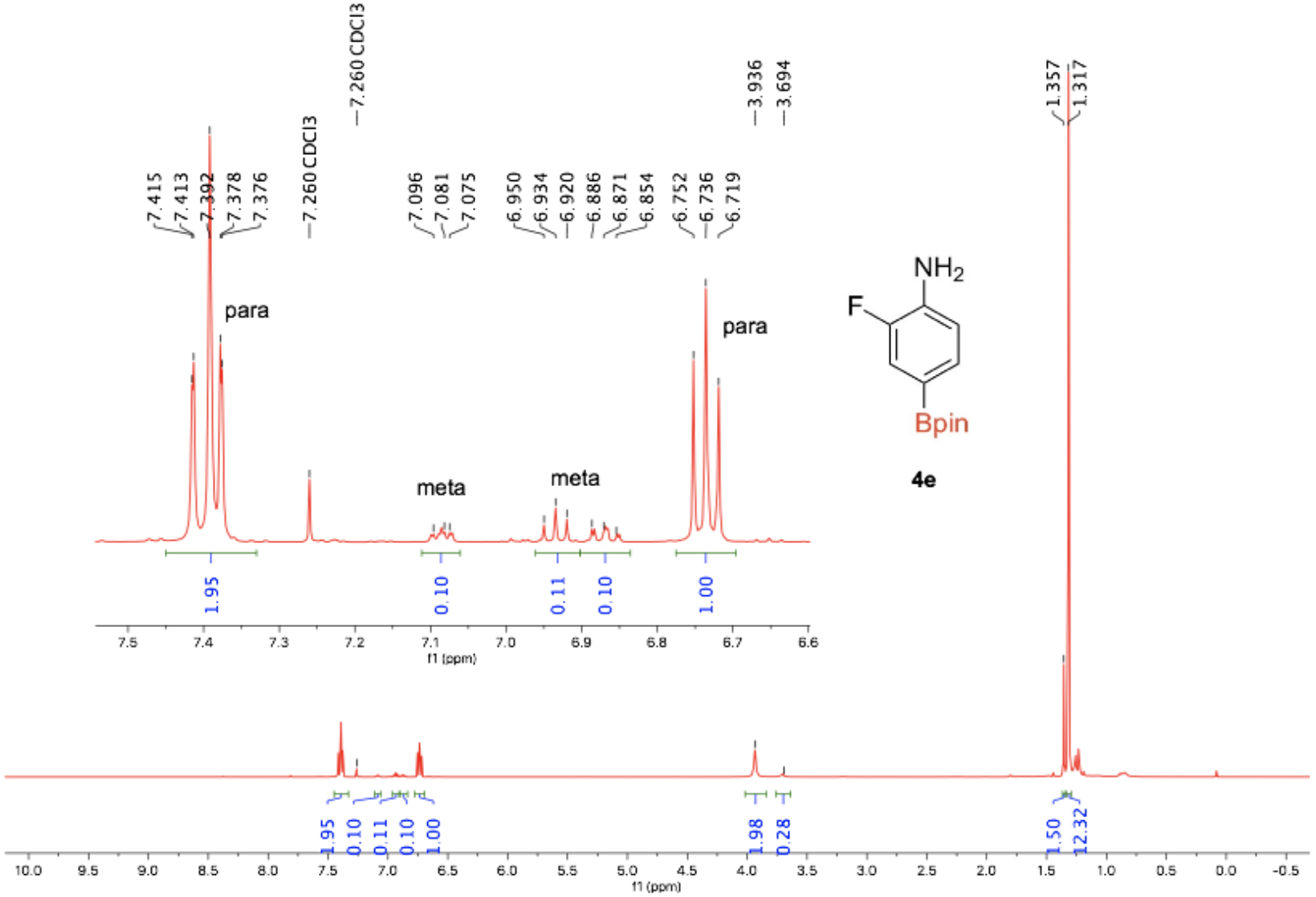
^{11}B NMR spectrum *para* borylated 2-methoxyaniline (3.4d′) (160 MHz, $CDCl_3$)



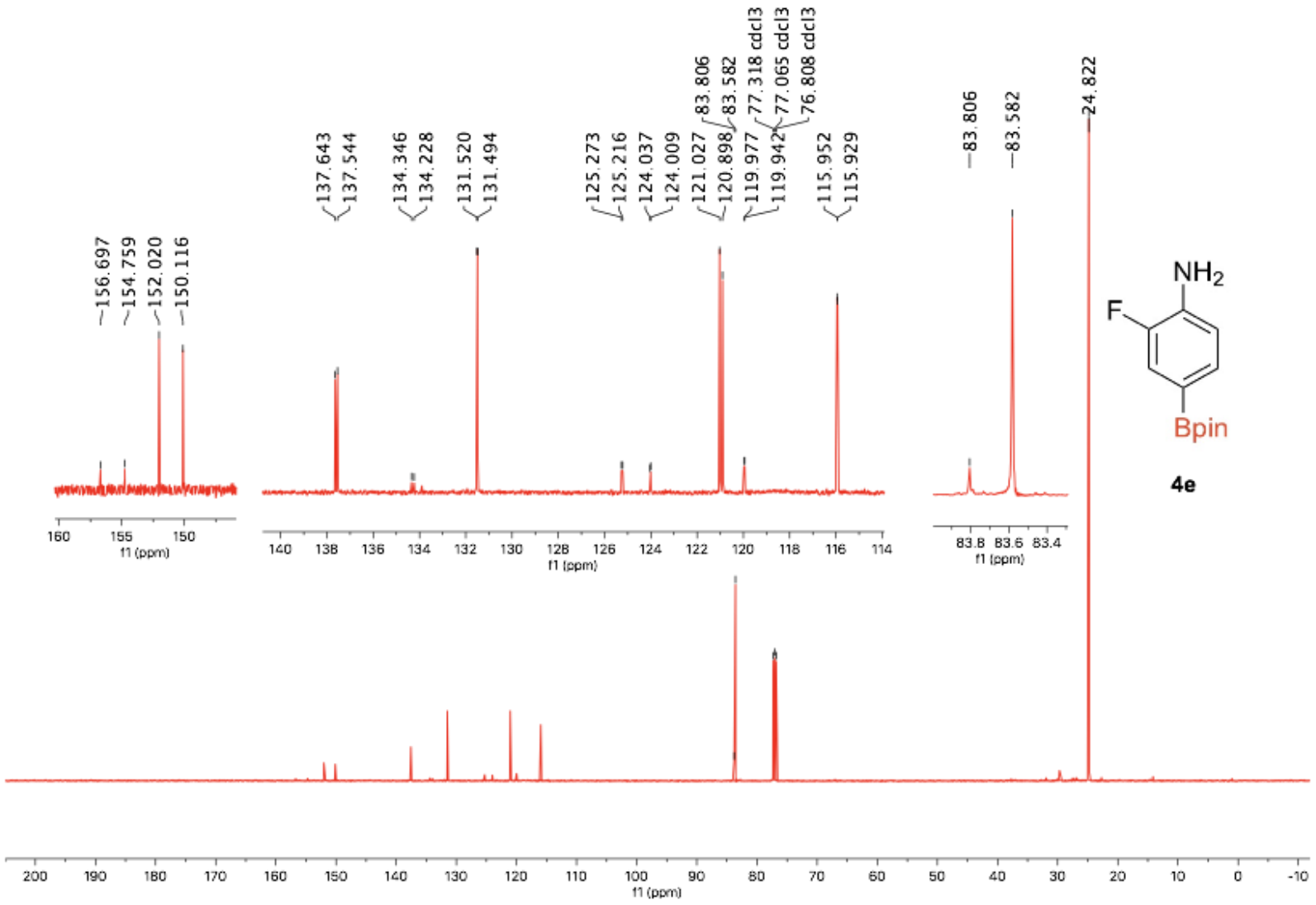
^{1}H NMR reaction mixture of *para* borylation of tetrapropylammonium 2-fluorophenylsulfamate (crude 3.4e) (500 MHz, $CDCl_3$)



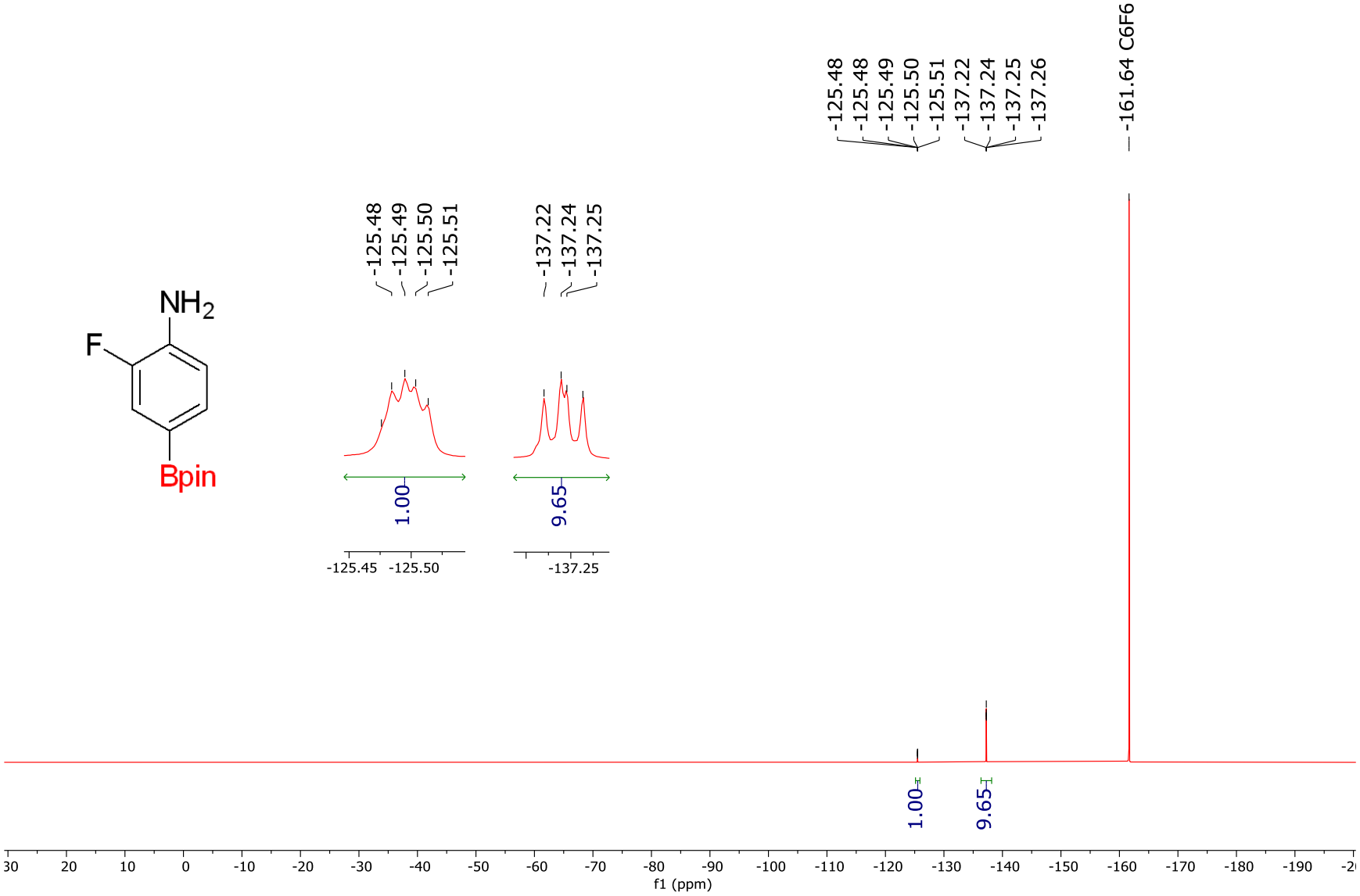
^{1}H NMR spectrum *para* borylated 2-fluoroaniline (3.4e) (500 MHz, $CDCl_3$)



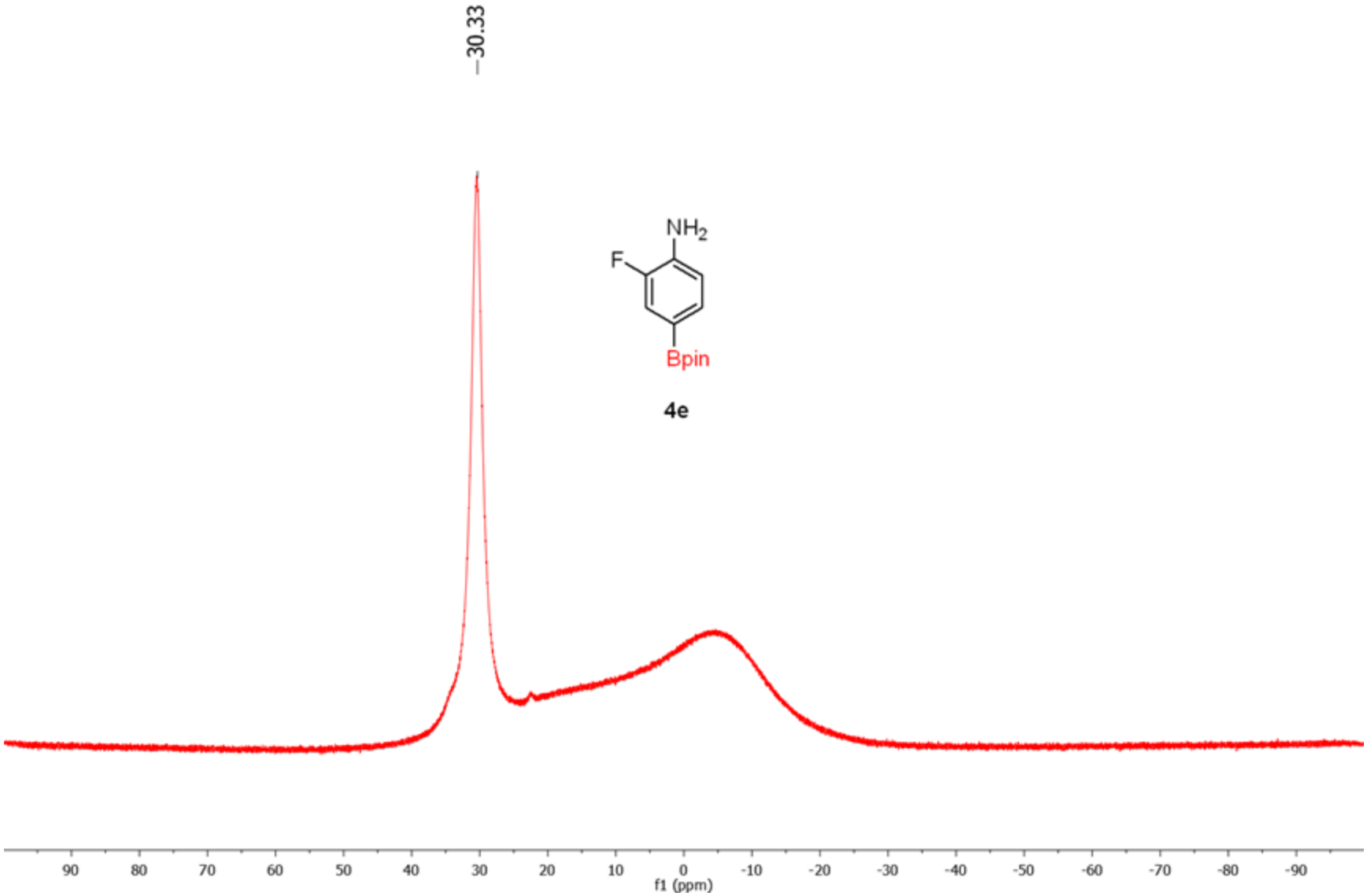
^{13}C NMR spectrum *para* borylated 2-fluoroaniline (3.4e) (126 MHz, $CDCl_3$)



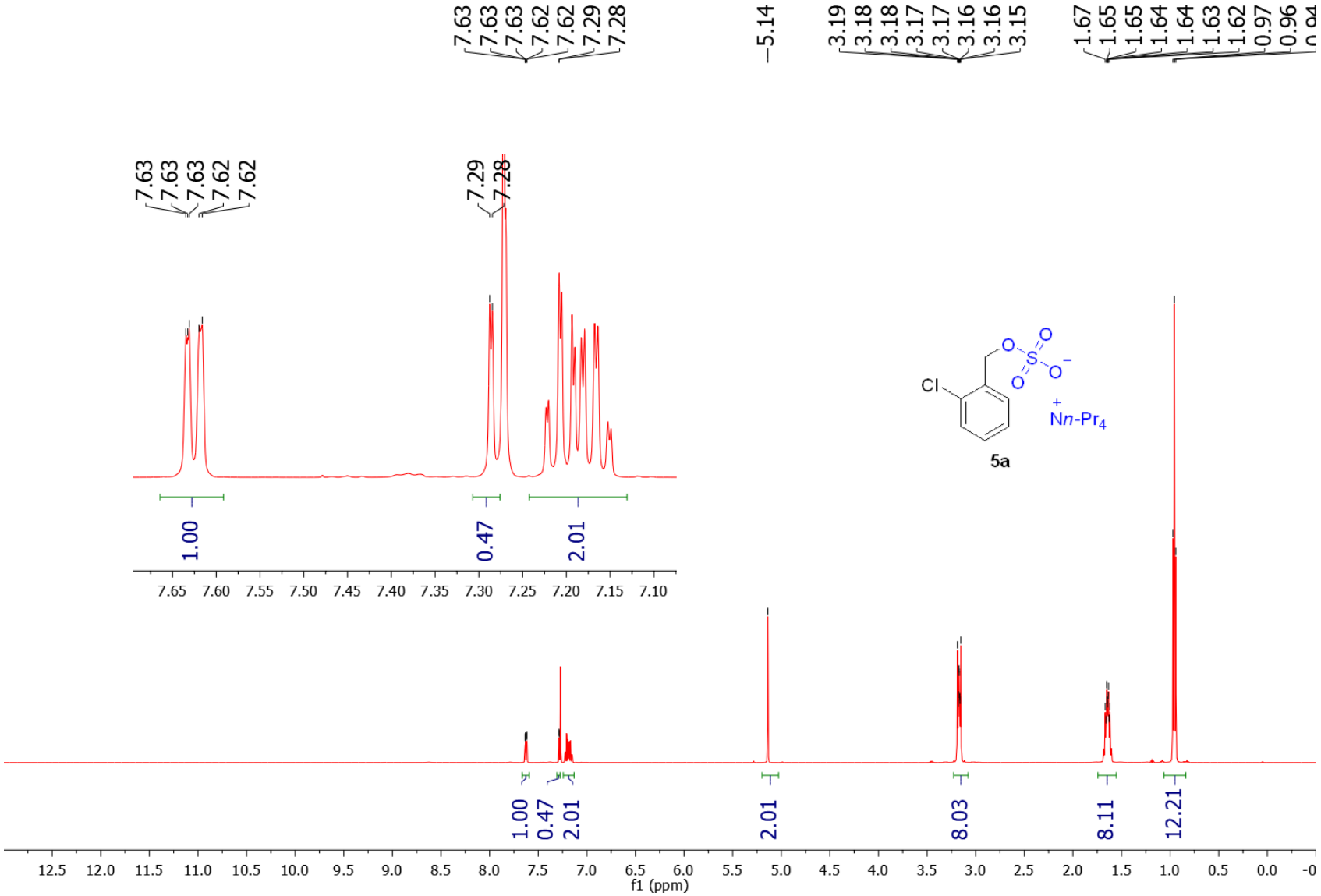
^{19}F NMR spectrum *para* borylated 2-fluoroaniline (3.4e) (470 MHz, $CDCl_3$)



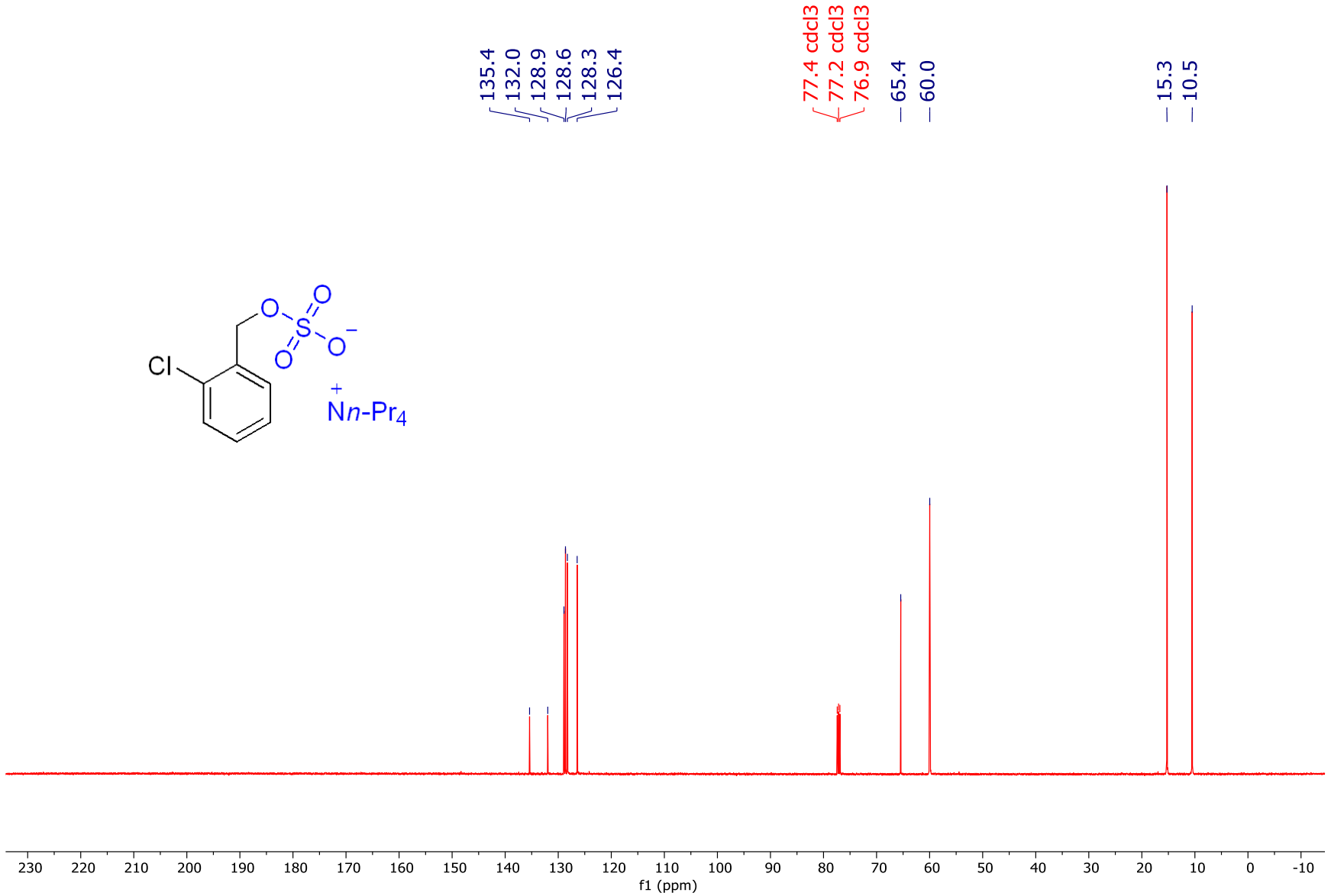
^{11}B NMR spectrum *para* borylated 2-fluoroaniline (3.4e) (160 MHz, $CDCl_3$)



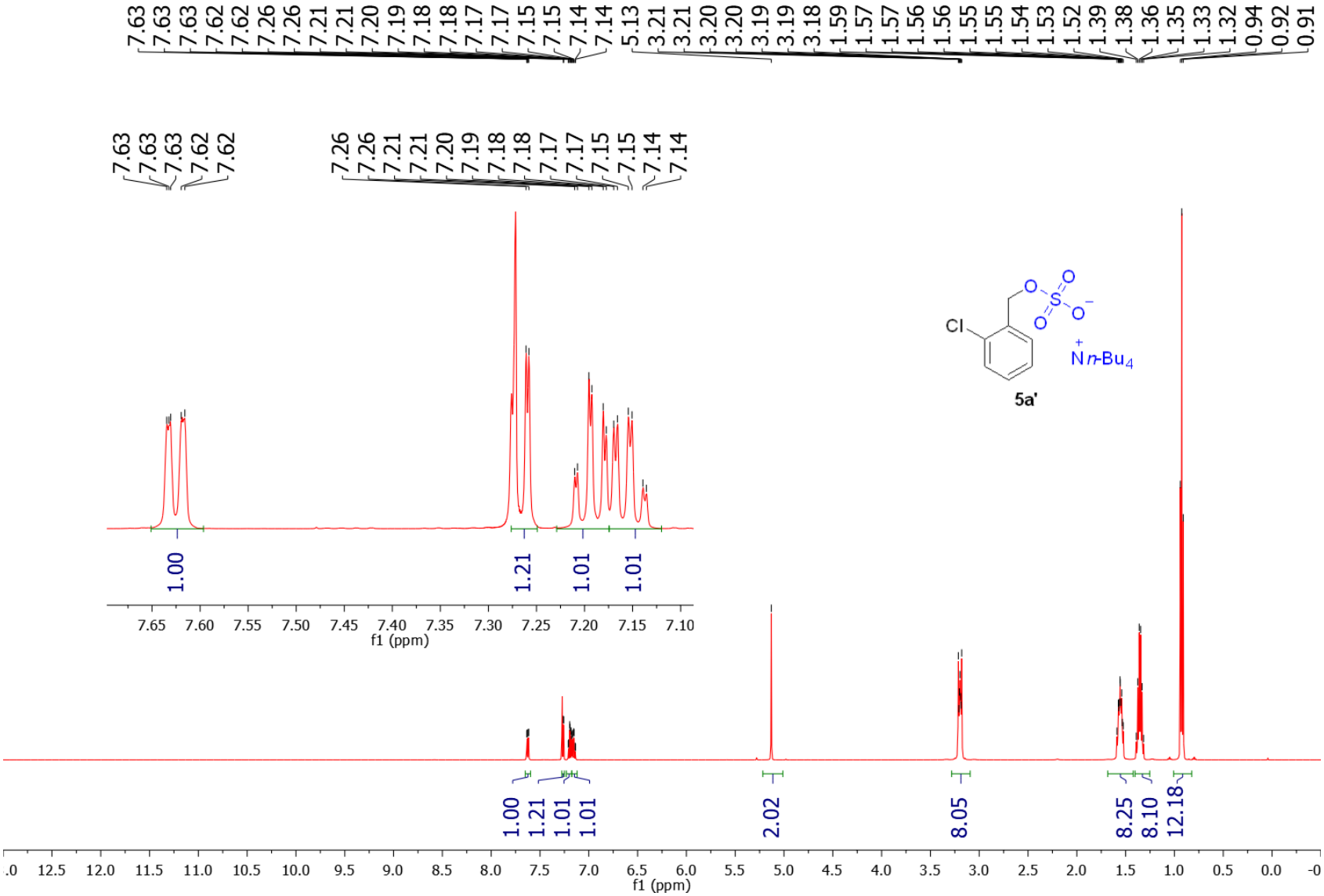
^{1}H NMR spectrum of tetrapropylammonium 2-chlorobenzylsulfate (3.5a) (500 MHz, $CDCl_3$)



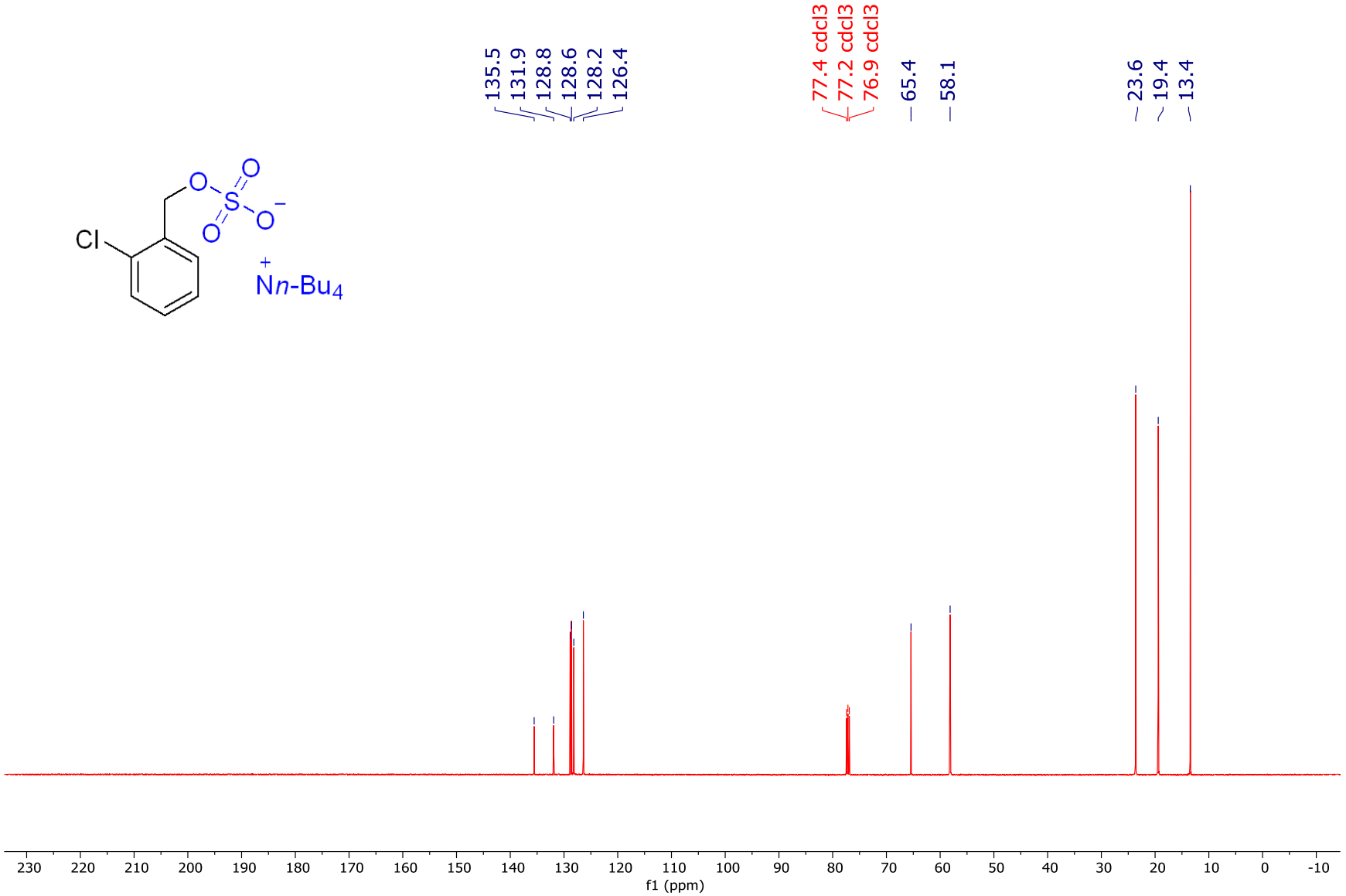
^{13}C NMR spectrum of tetrapropylammonium 2-chlorobenzylsulfate (3.5a) (126 MHz, $CDCl_3$)



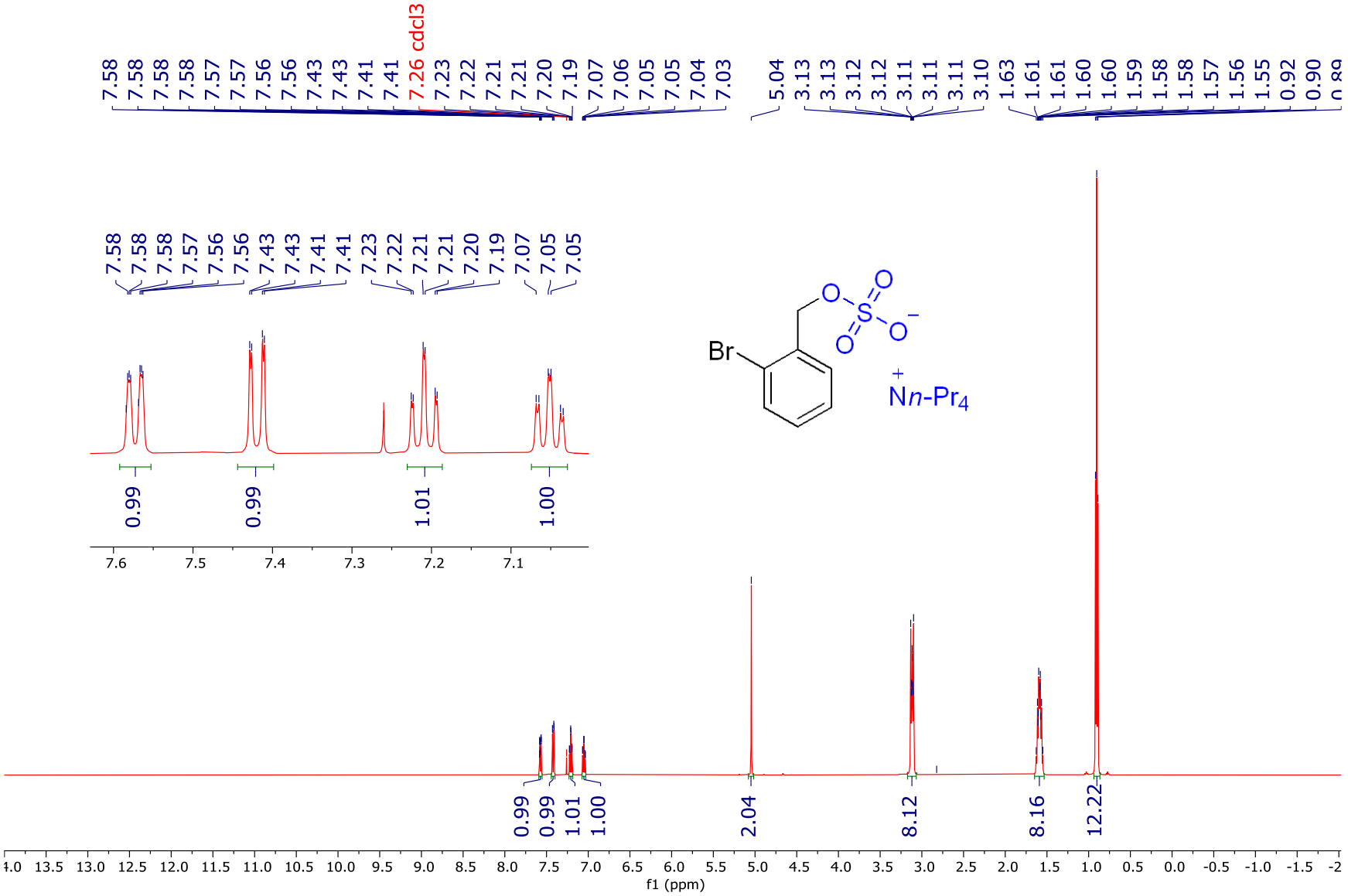
^{1}H NMR spectrum of tetrabutylammonium 2-chlorobenzylsulfate (3.5a′) (500 MHz, $CDCl_3$)



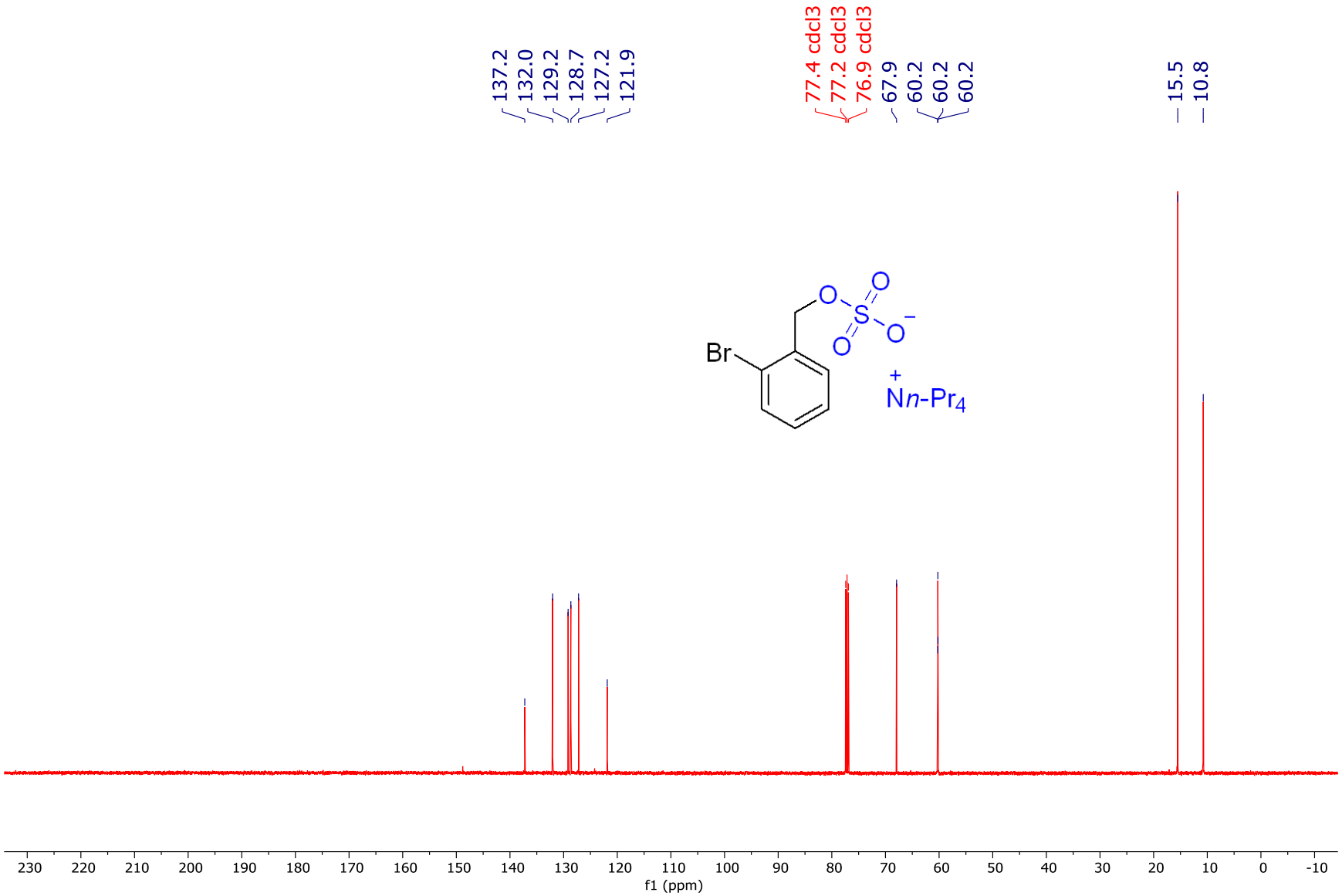
^{13}C NMR spectrum of tetrabutylammonium 2-chlorobenzylsulfate (3.5a') (126 MHz, $CDCl_3$)



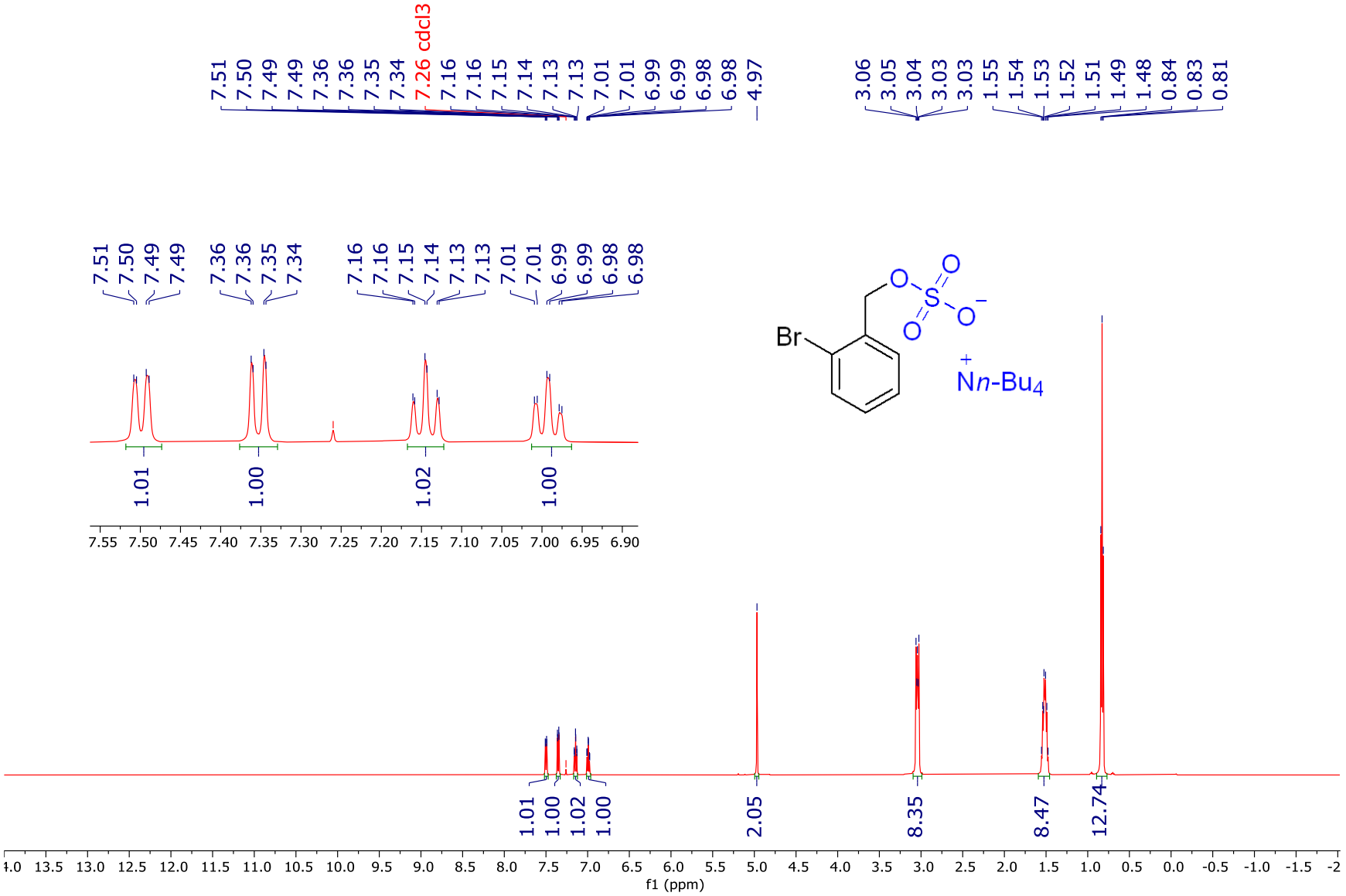
^{1}H NMR spectrum of tetrapropylammonium 2-bromobenzylsulfate (3.5b) (500 MHz, $CDCl_3$)



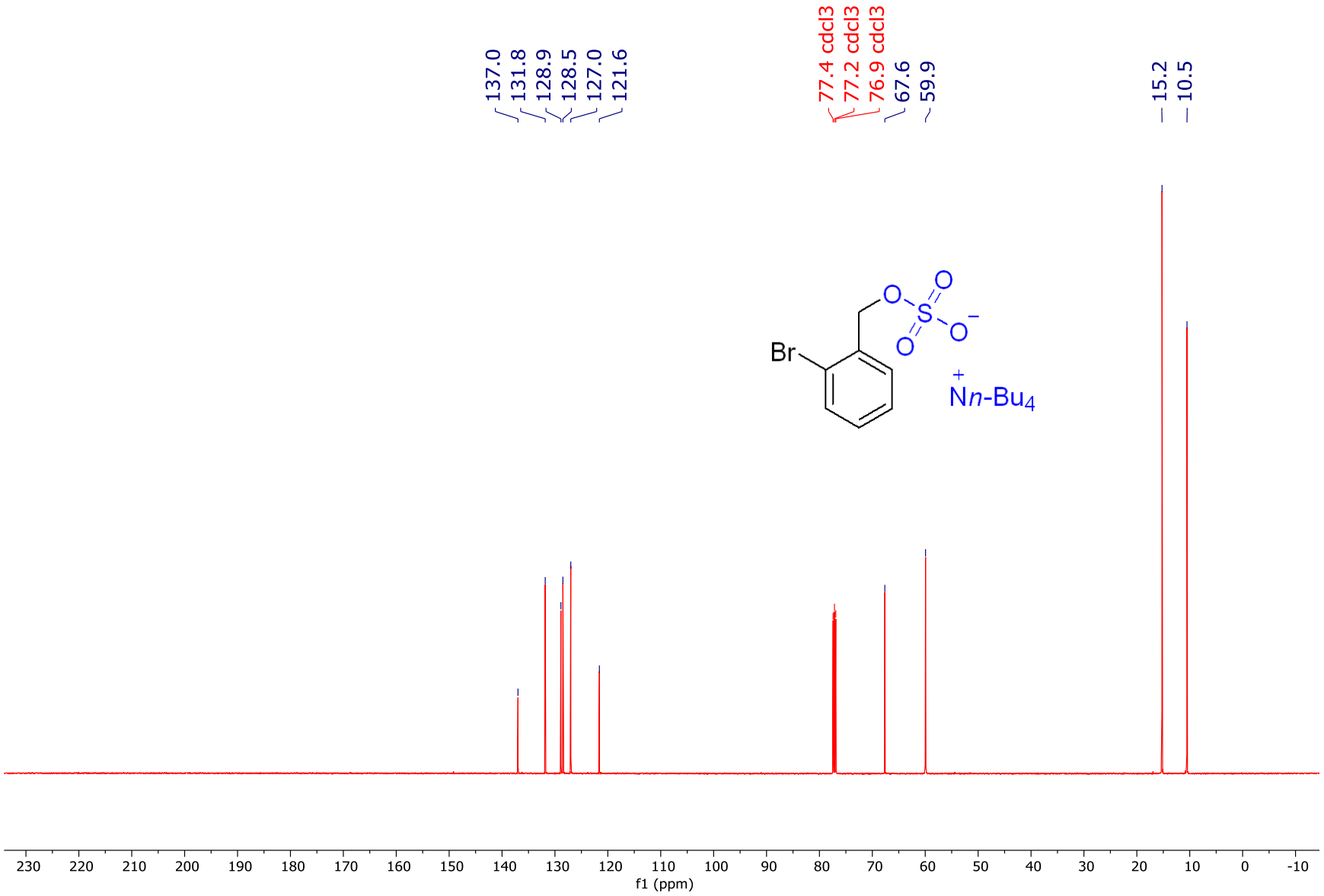
^{13}C NMR spectrum of tetrapropylammonium 2-bromobenzylsulfate (3.5b) (126 MHz, $CDCl_3$)



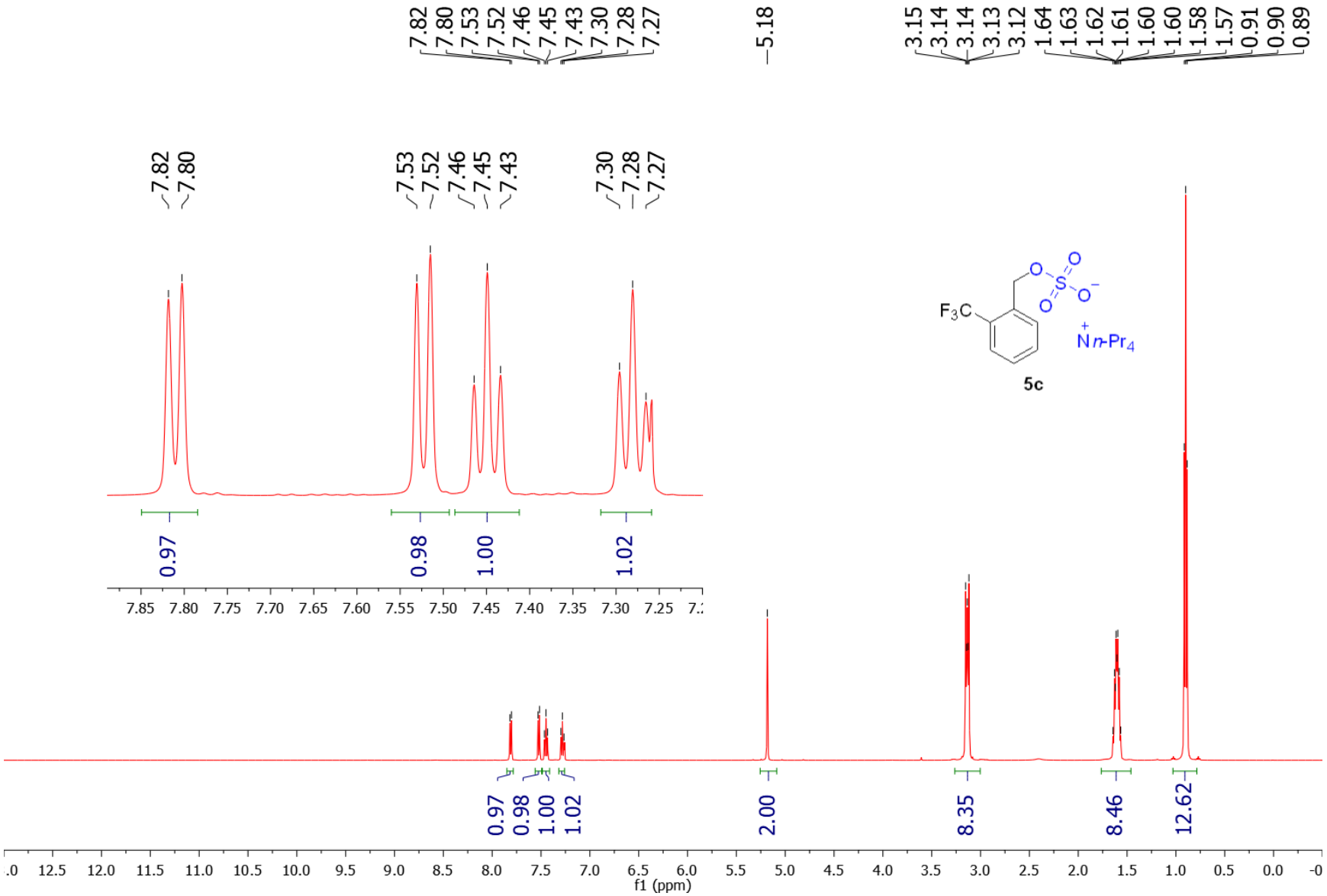
^{1}H NMR spectrum of tetrabutylammonium 2-bromobenzylsulfate (3.5b') (500 MHz, $CDCl_3$)



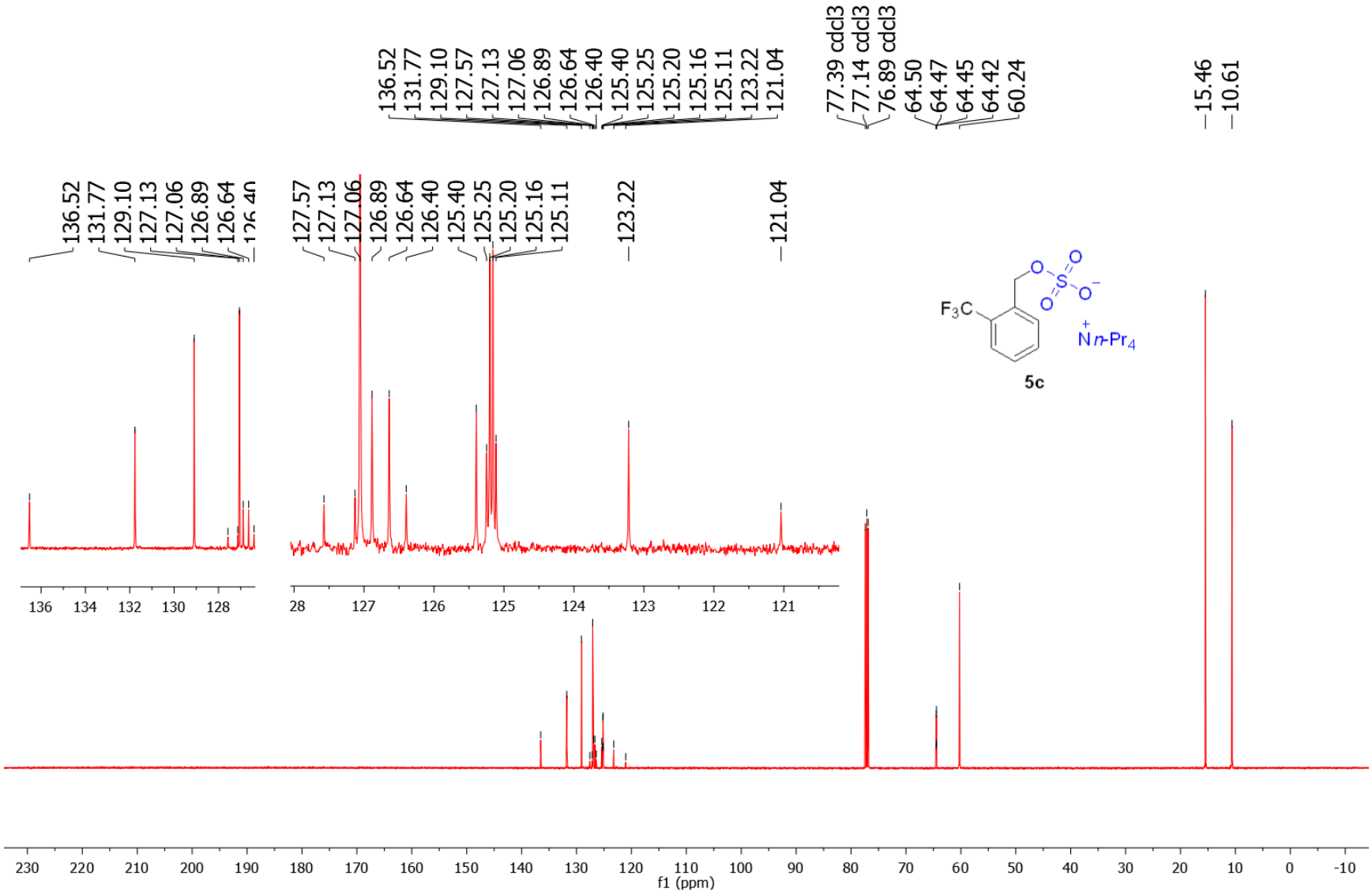
^{13}C NMR spectrum of tetrabutylammonium 2-bromobenzylsulfate (3.5b') (126 MHz, $CDCl_3$)



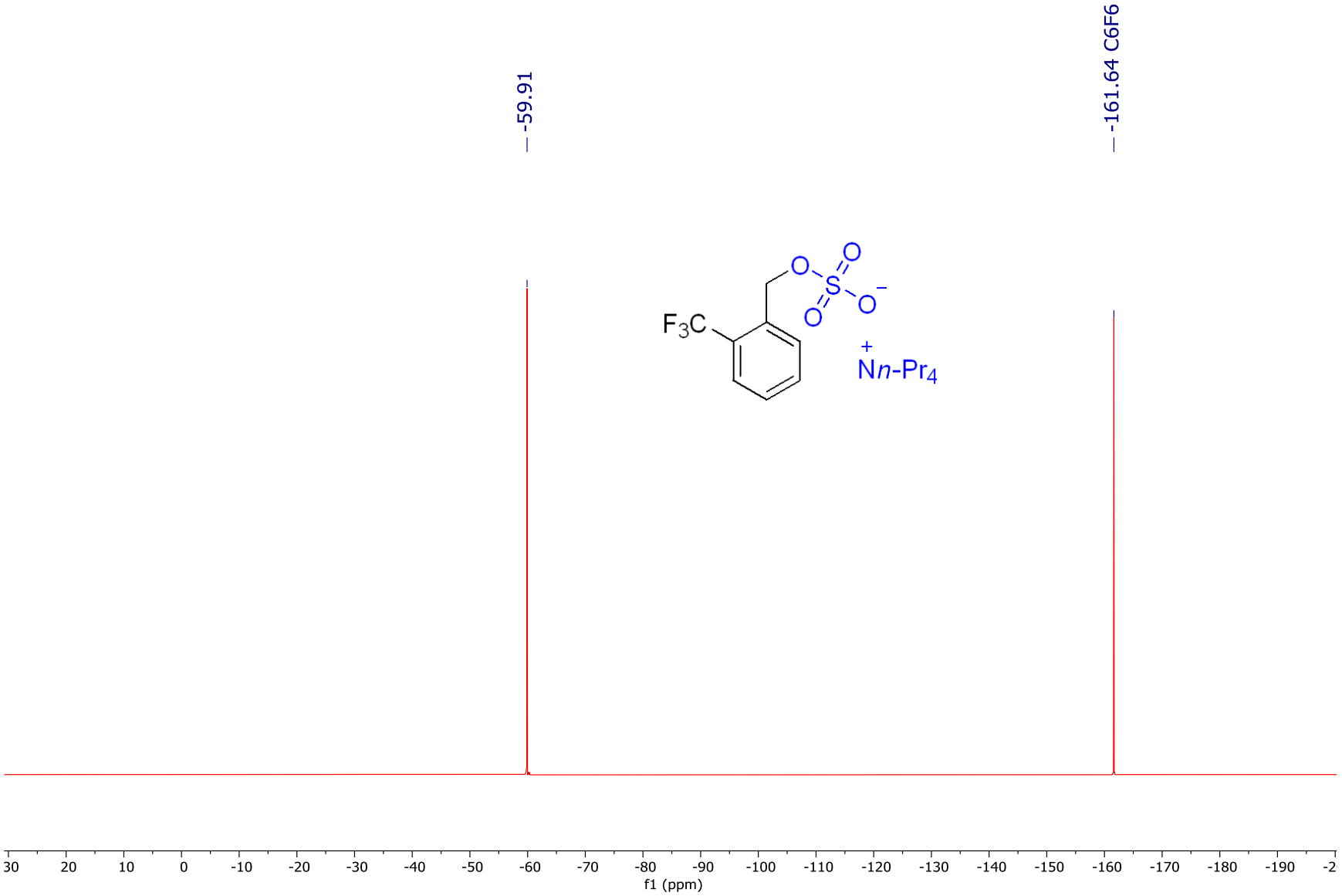
^{1}H NMR spectrum of tetrapropylammonium 2-trifluoromethylbenzylsulfate (3.5c) (500 MHz, $CDCl_3$)



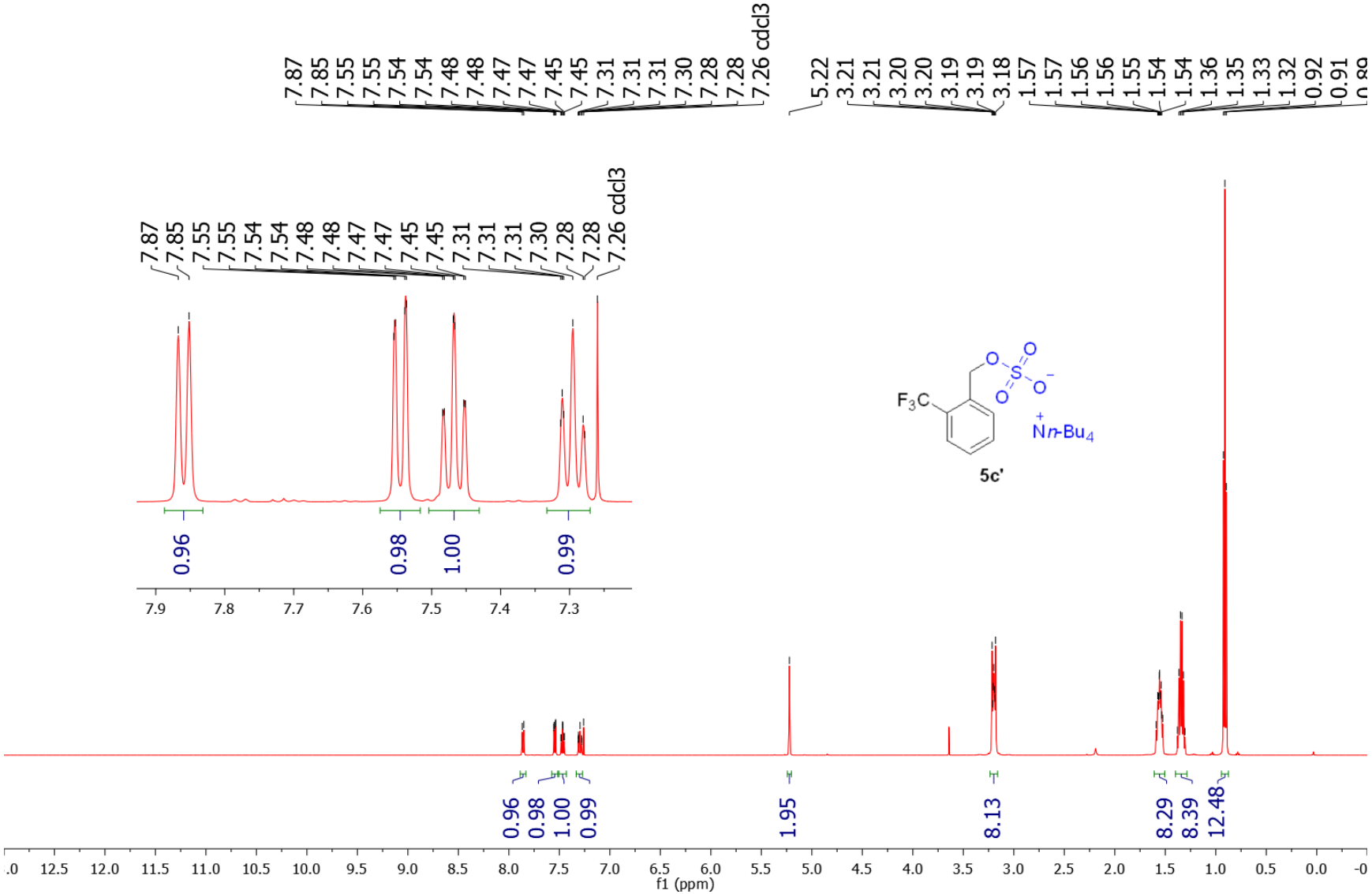
^{13}C NMR spectrum of tetrapropylammonium 2-trifluoromethylbenzylsulfate (3.5c) (126 MHz, $CDCl_3$)



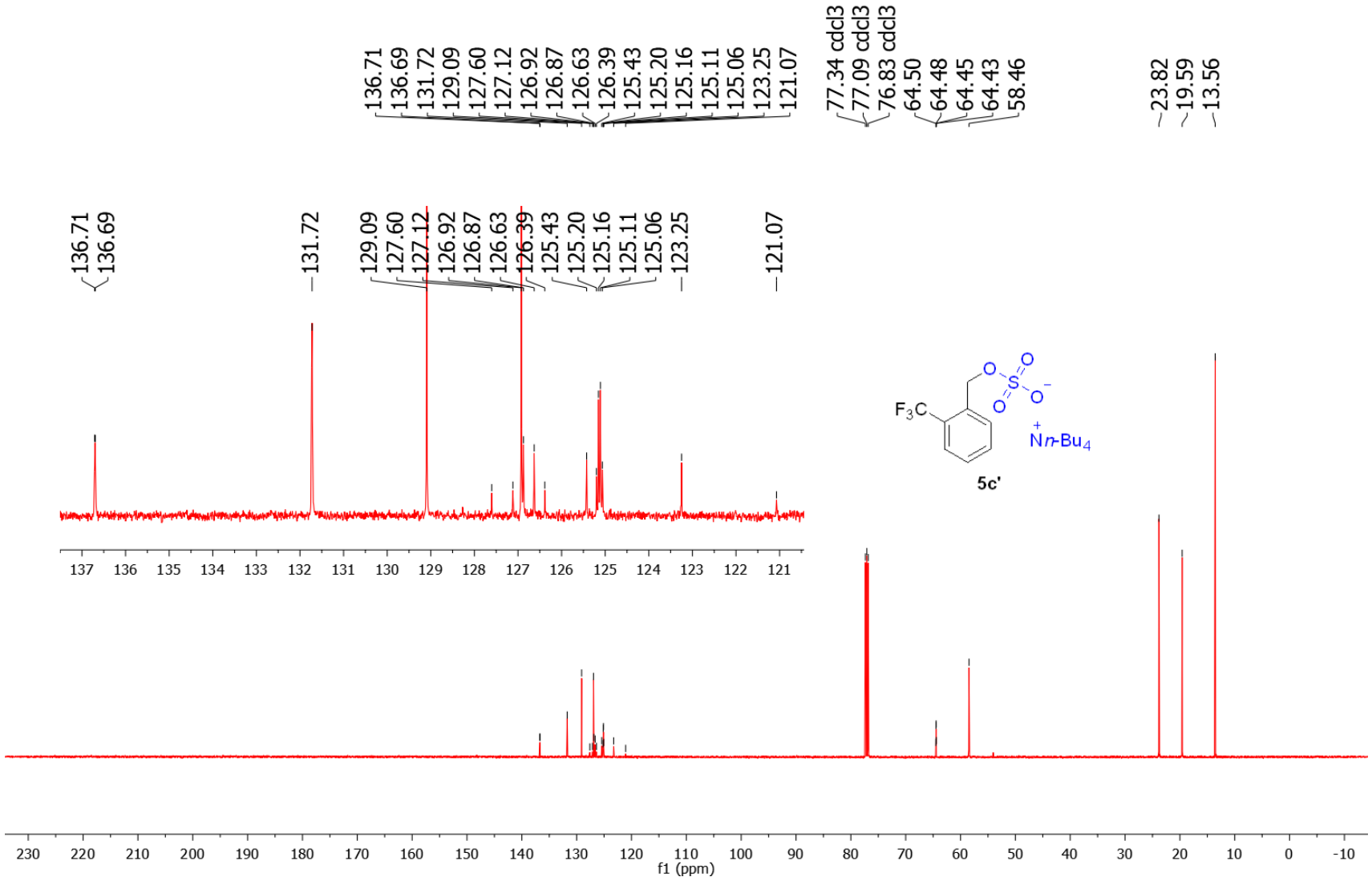
^{19}F NMR spectrum of tetrapropylammonium 2-trifluoromethylbenzylsulfate (3.5c) (470 MHz, $CDCl_3$)



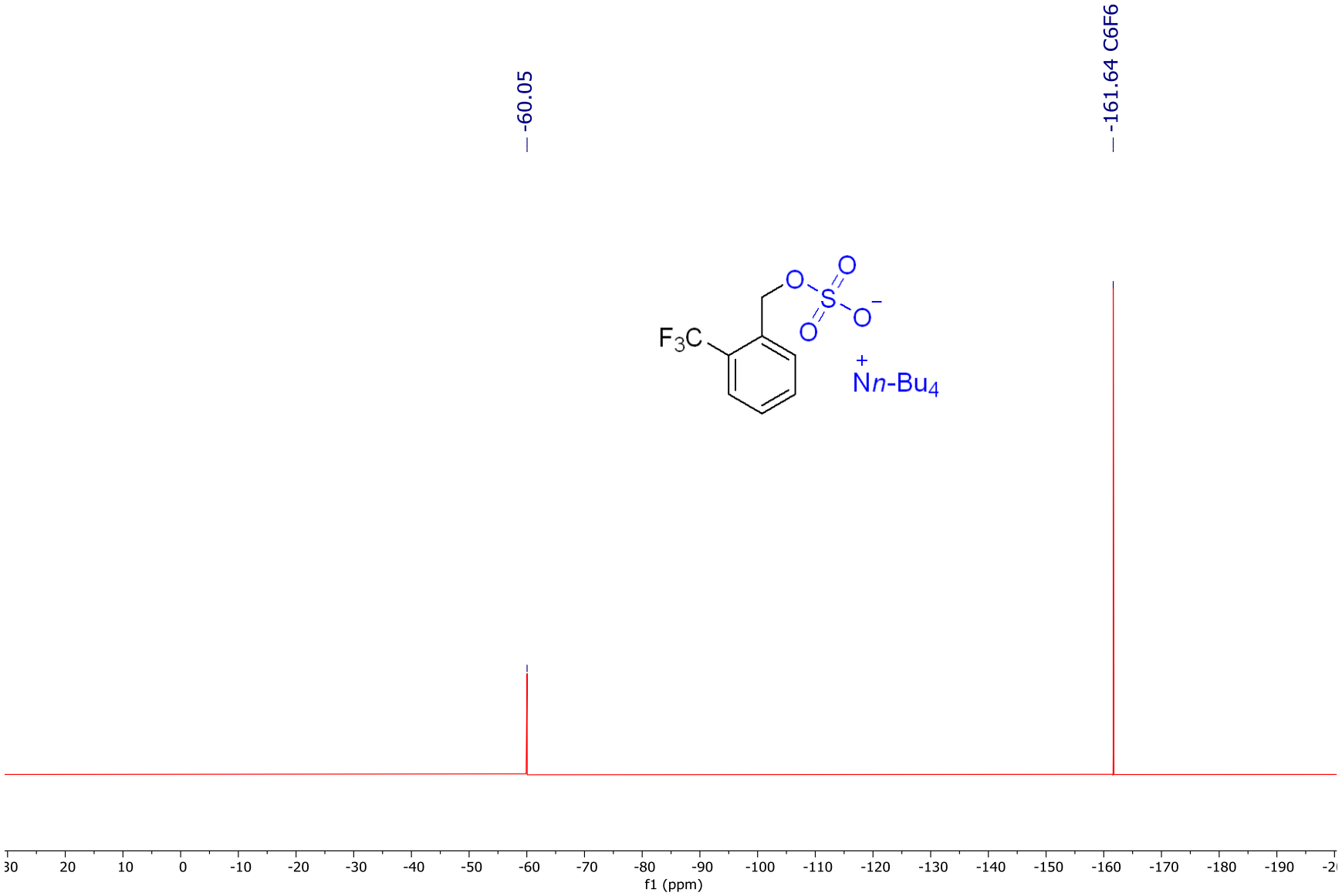
^{1}H NMR spectrum of tetrabutylammonium 2-trifluoromethylbenzylsulfate (3.5c′) (500 MHz, $CDCl_3$)



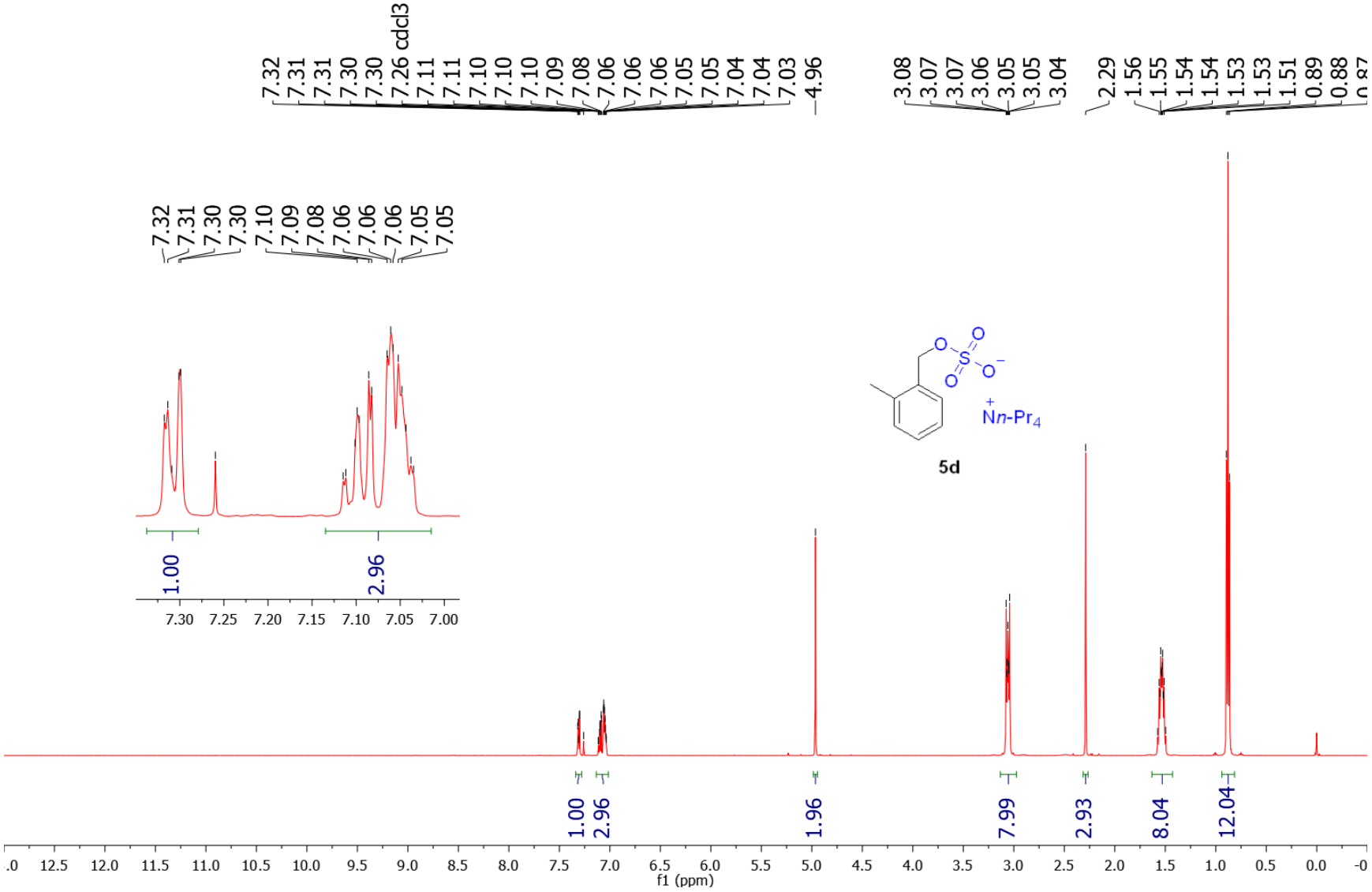
^{13}C NMR spectrum of tetrabutylammonium 2-trifluoromethylbenzylsulfate (3.5c′) (126 MHz, $CDCl_3$)



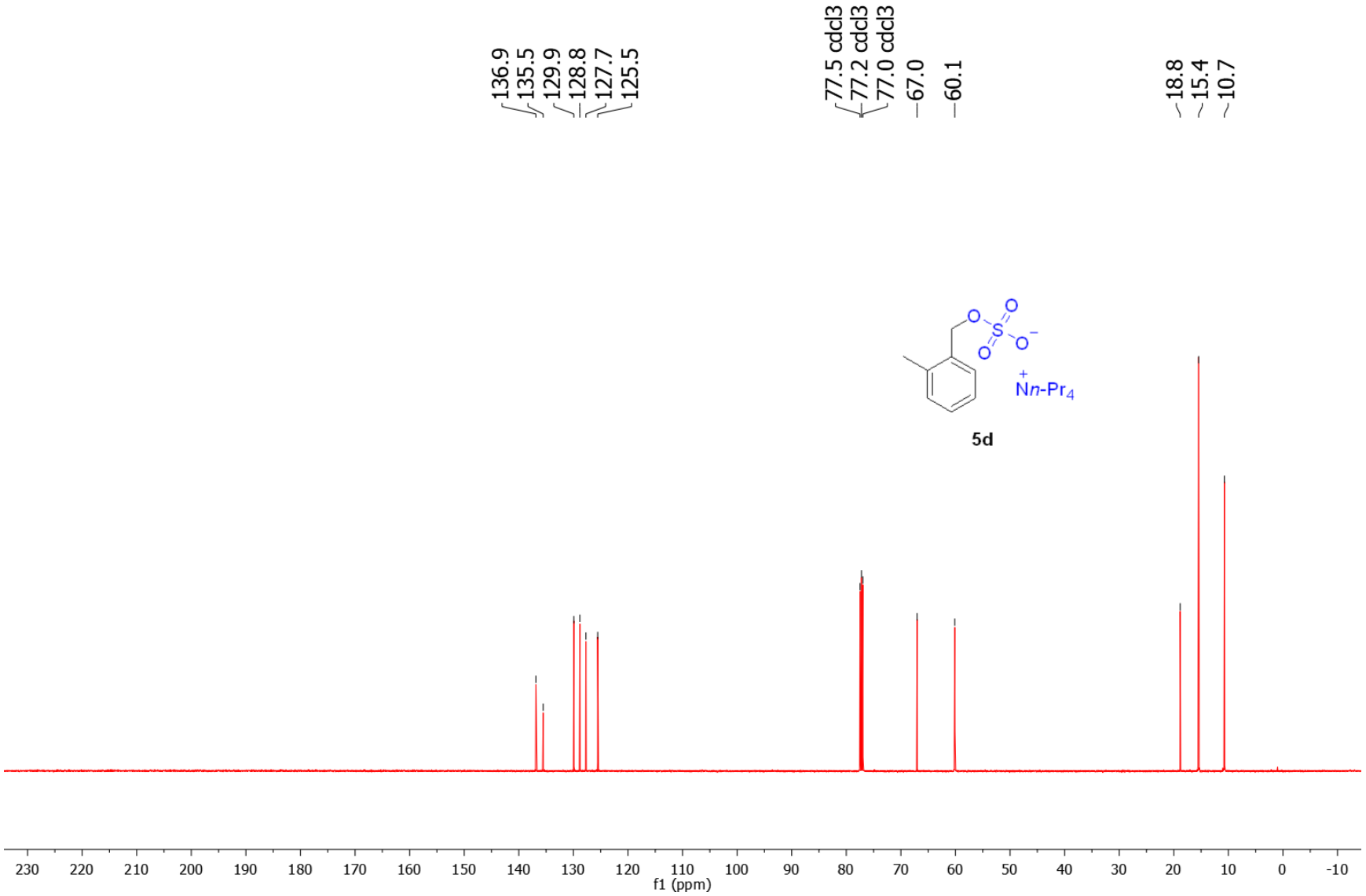
^{19}F NMR spectrum of tetrabutylammonium 2-trifluoromethylbenzylsulfate (3.5c′) (470 MHz, $CDCl_3$)



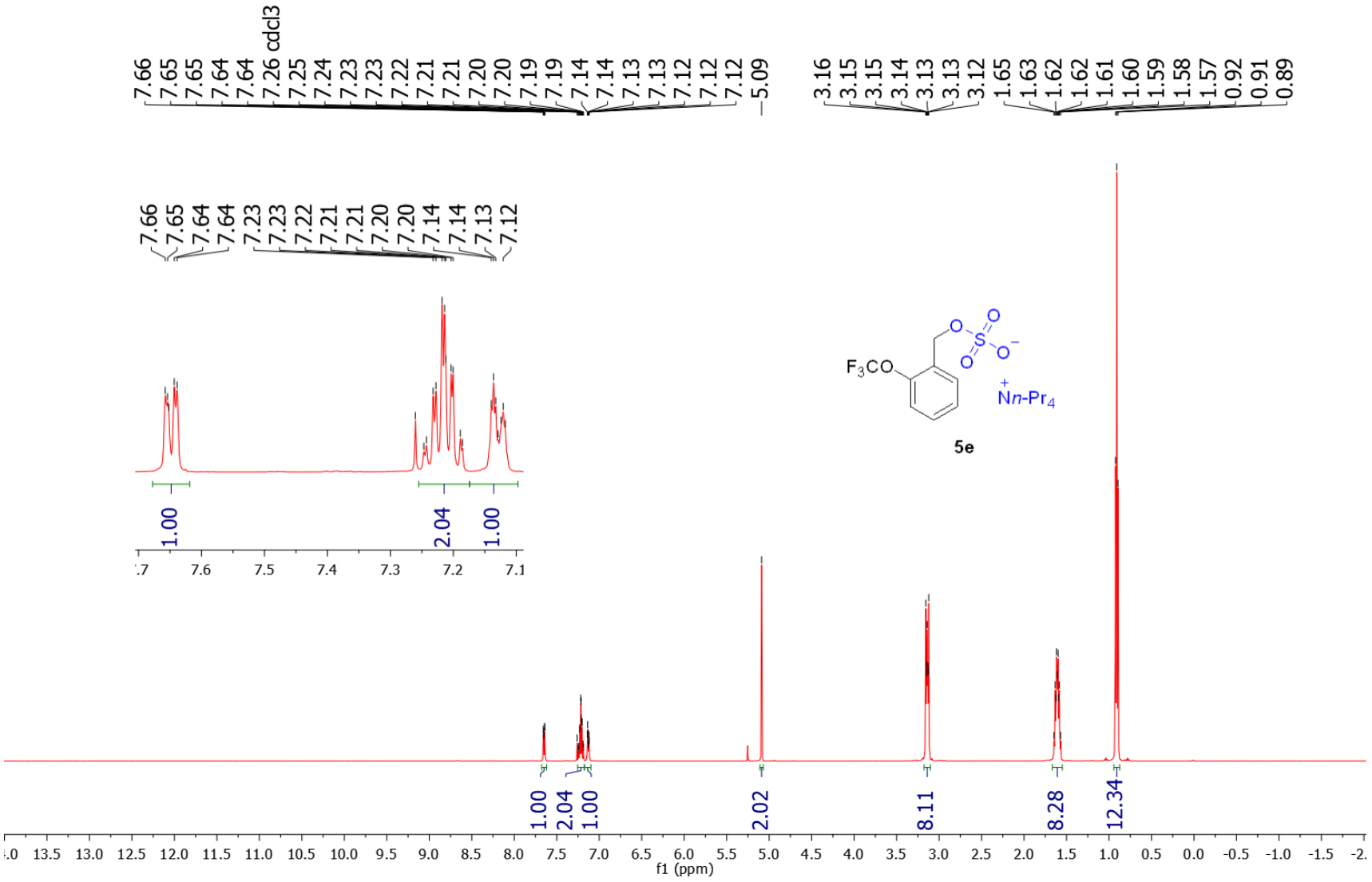
^{1}H NMR spectrum of tetrapropylammonium 2-methylbenzylsulfate (3.5d) (500 MHz, $CDCl_3$)



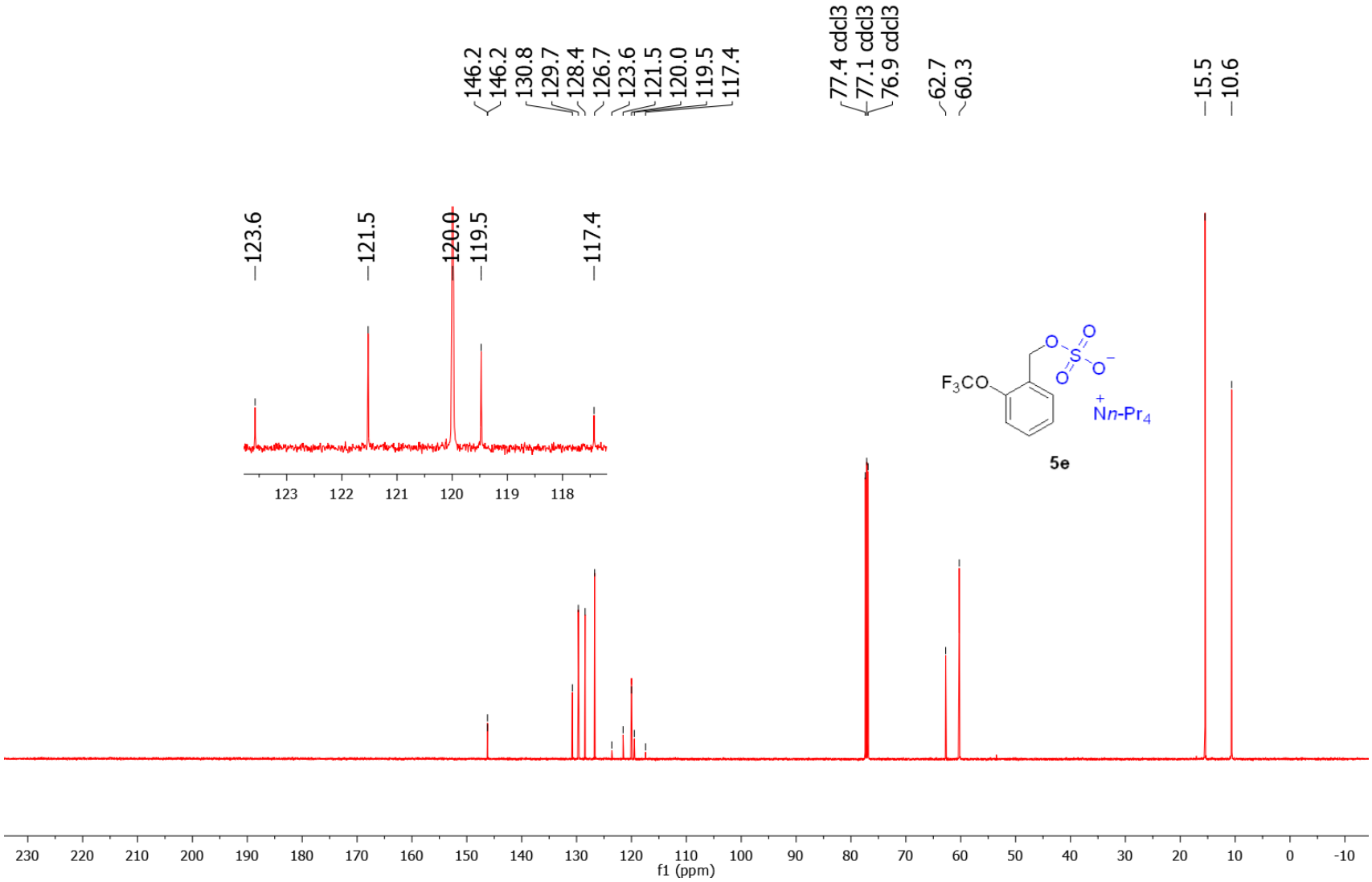
^{13}C NMR spectrum of tetrapropylammonium 2-methylbenzylsulfate (3.5d) (126 MHz, $CDCl_3$)



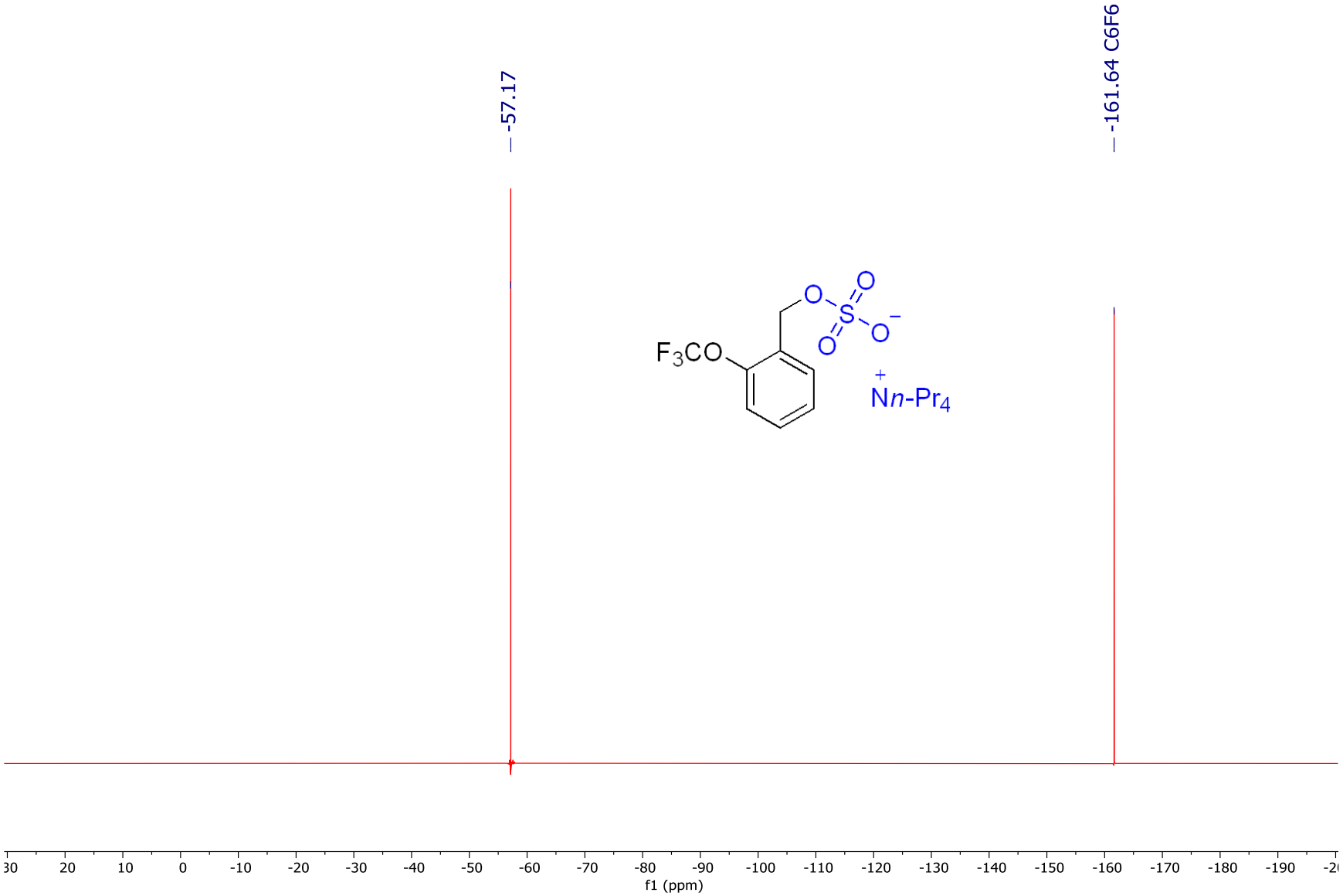
^{1}H NMR spectrum of tetrapropylammonium 2-(trifluoromethoxy)benzylsulfate (3.5e) (500 MHz, $CDCl_3$)



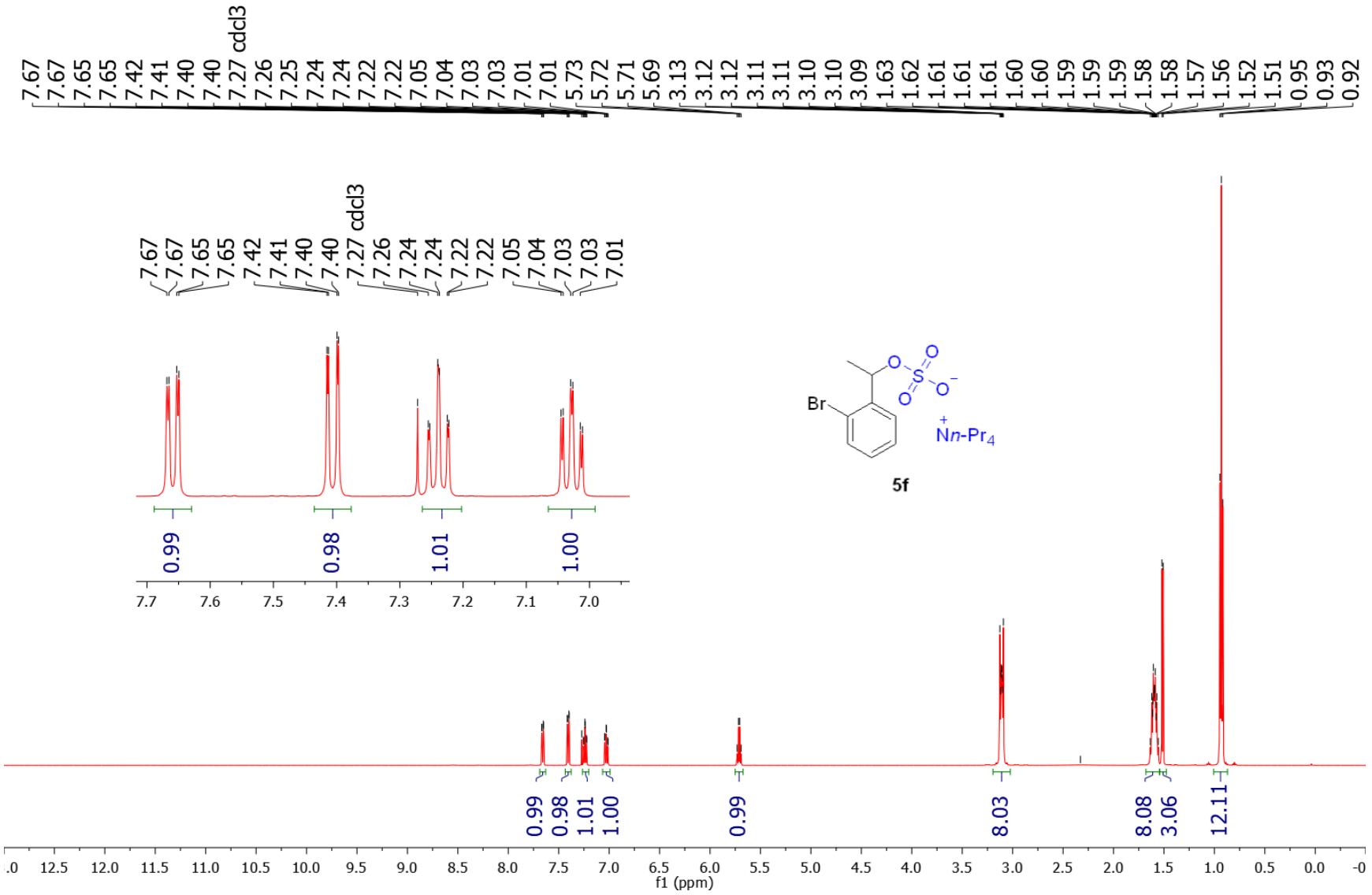
^{13}C NMR spectrum of tetrapropylammonium 2-(trifluoromethoxy)benzylsulfate (3.5e) (126 MHz, $CDCl_3$)



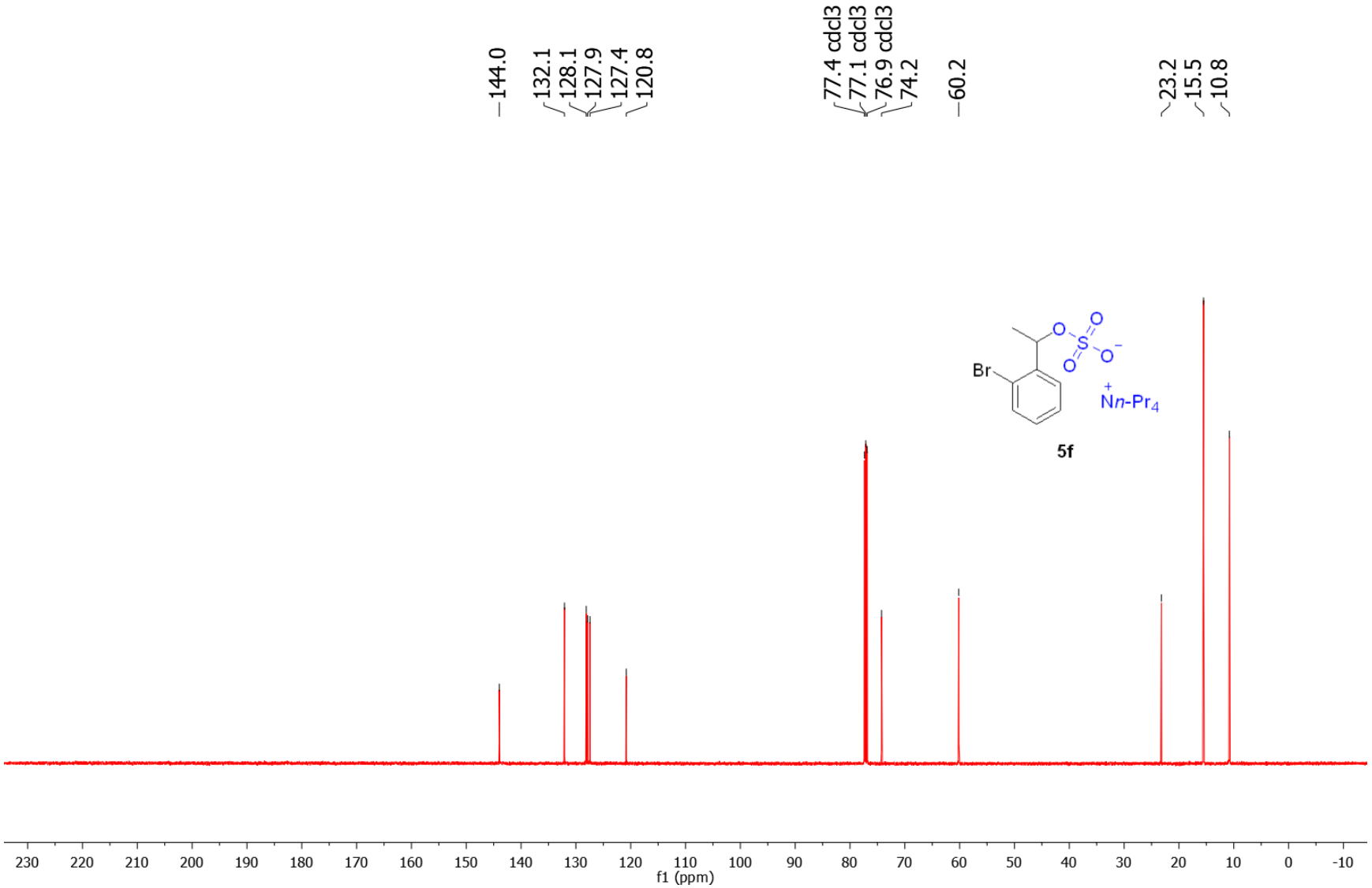
^{19}F NMR spectrum of tetrapropylammonium 2-(trifluoromethoxy)benzylsulfate (3.5e) (470 MHz, $CDCl_3$)



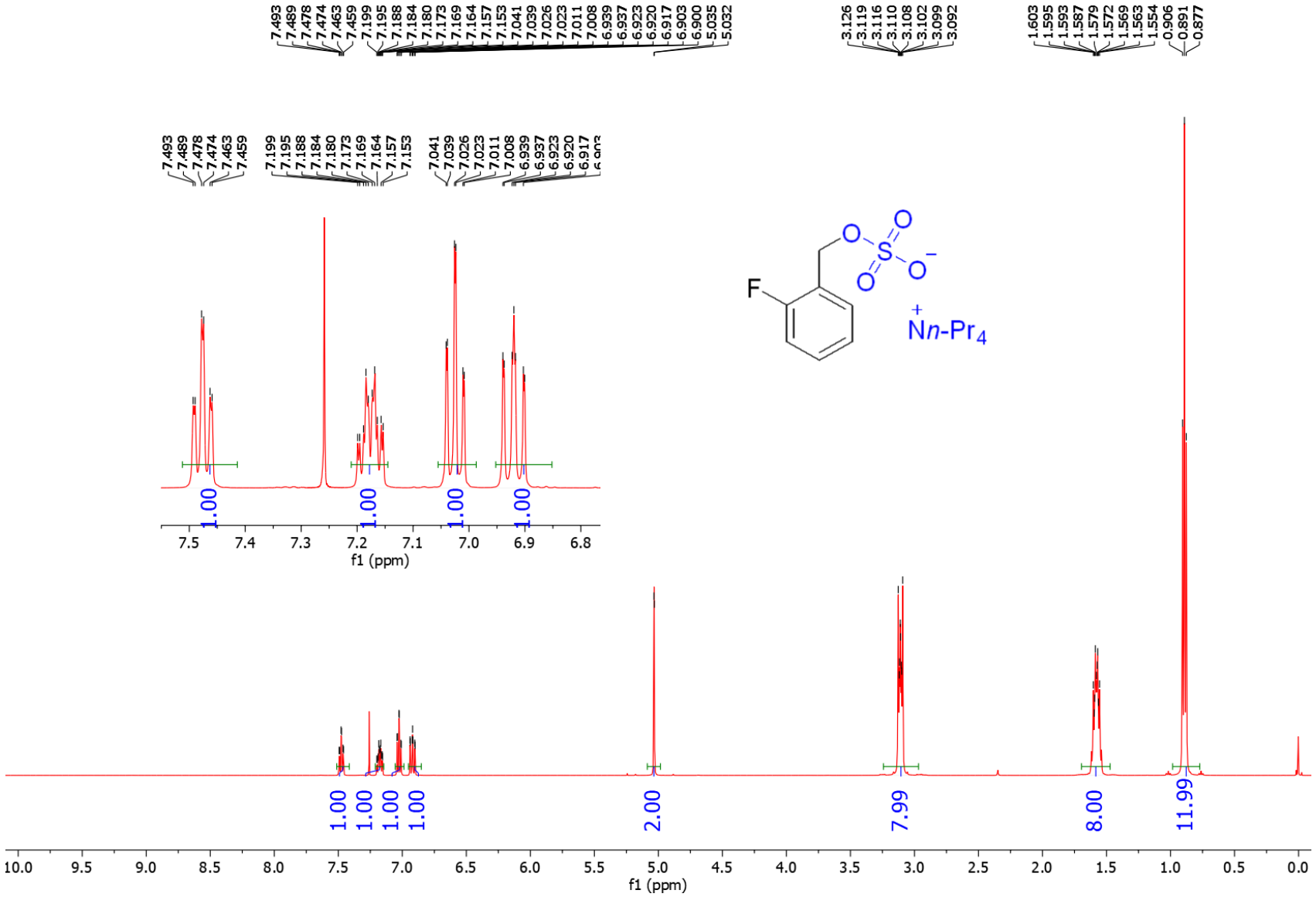
^{1}H NMR spectrum of tetrapropylammonium 1-(2-bromophenyl)ethyl sulfate (3.5f) (500 MHz, $CDCl_3$)



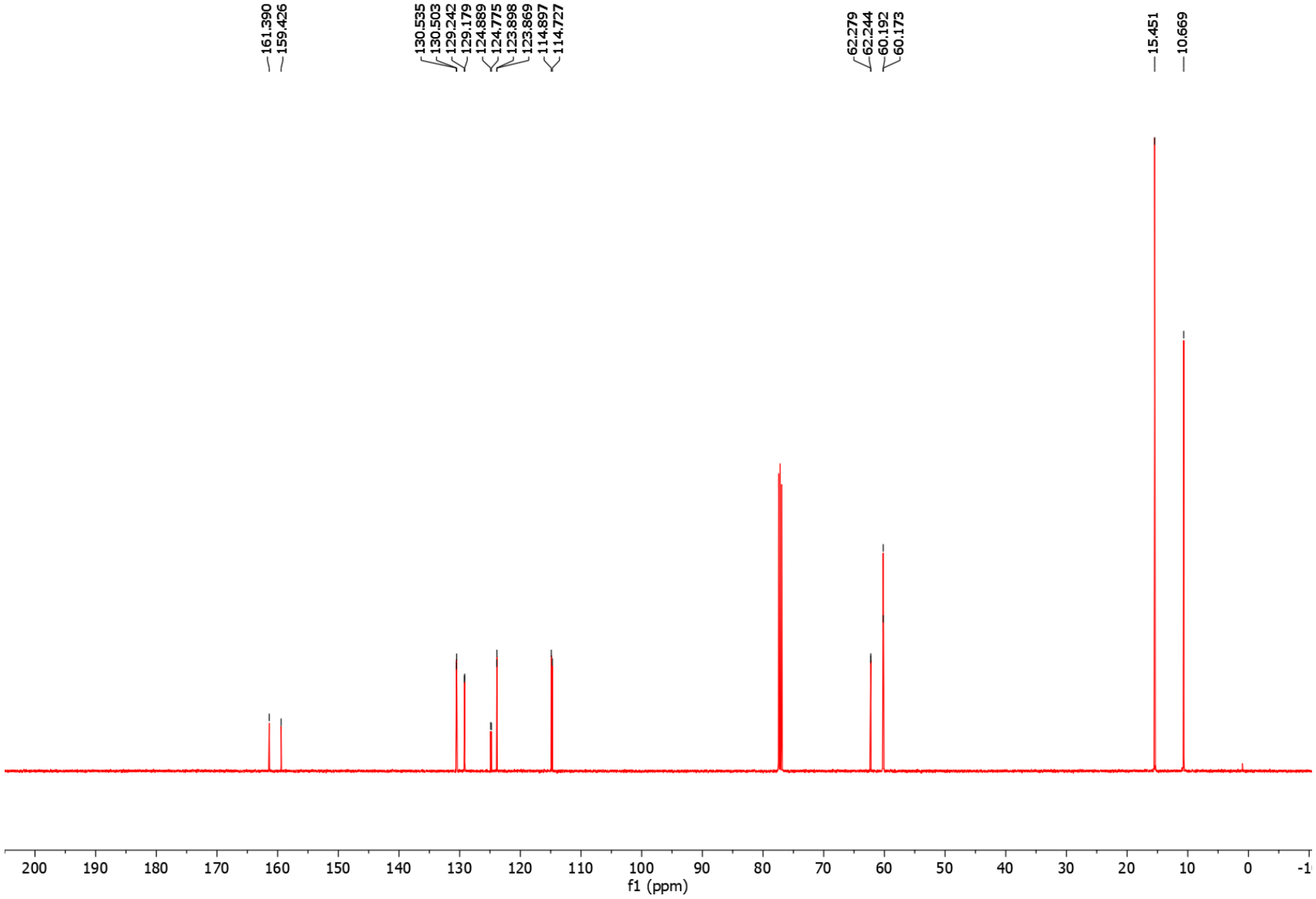
^{13}C NMR spectrum of tetrapropylammonium 1-(2-bromophenyl)ethyl sulfate (3.5f) (126 MHz, $CDCl_3$)



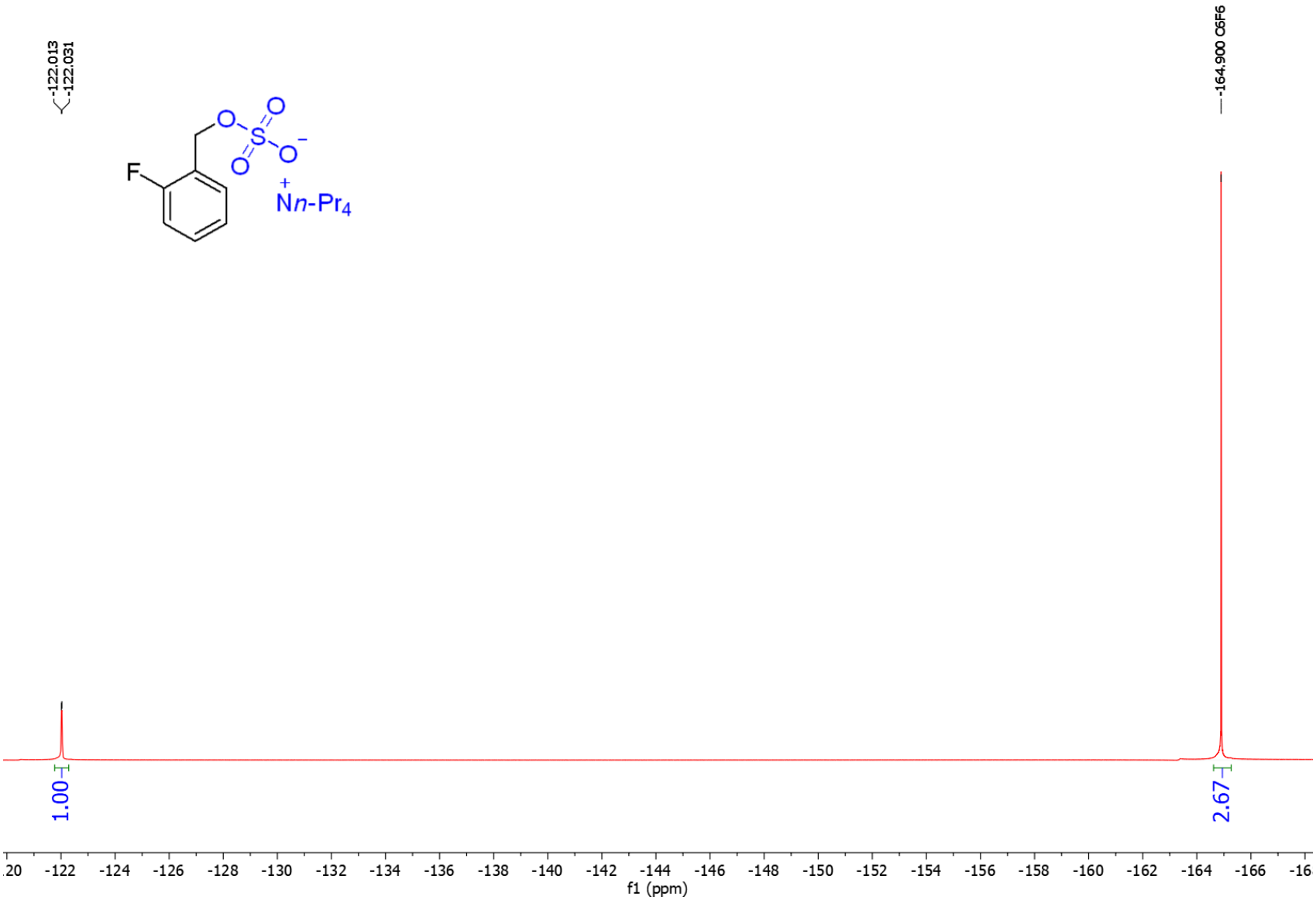
^{1}H NMR spectrum of tetrapropylammonium 2-fluorobenzyl sulfate (3.5g) (500 MHz, $CDCl_3$)



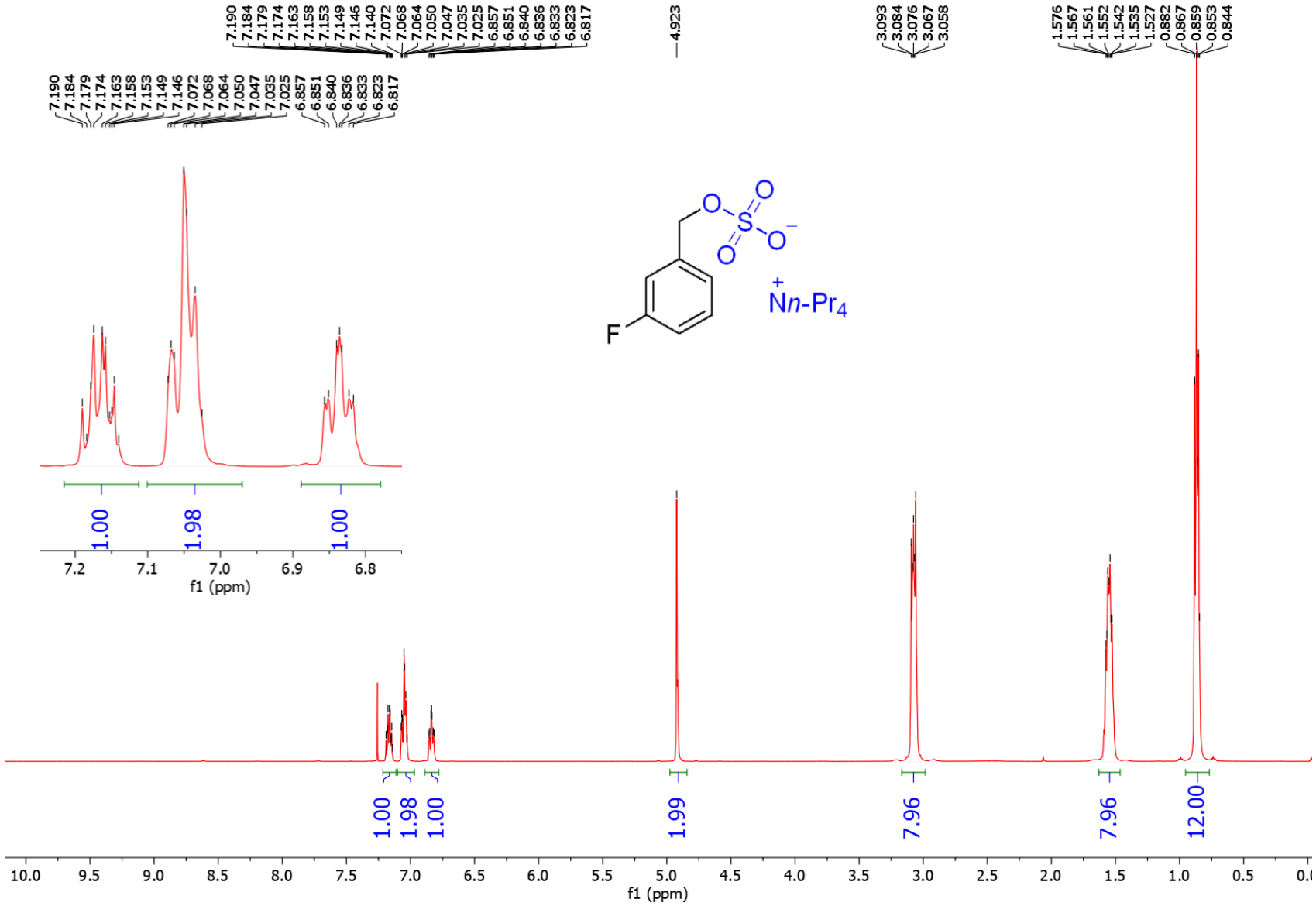
^{13}C NMR spectrum of tetrapropylammonium 2-fluorobenzyl sulfate (3.5g) (126 MHz, $CDCl_3$)



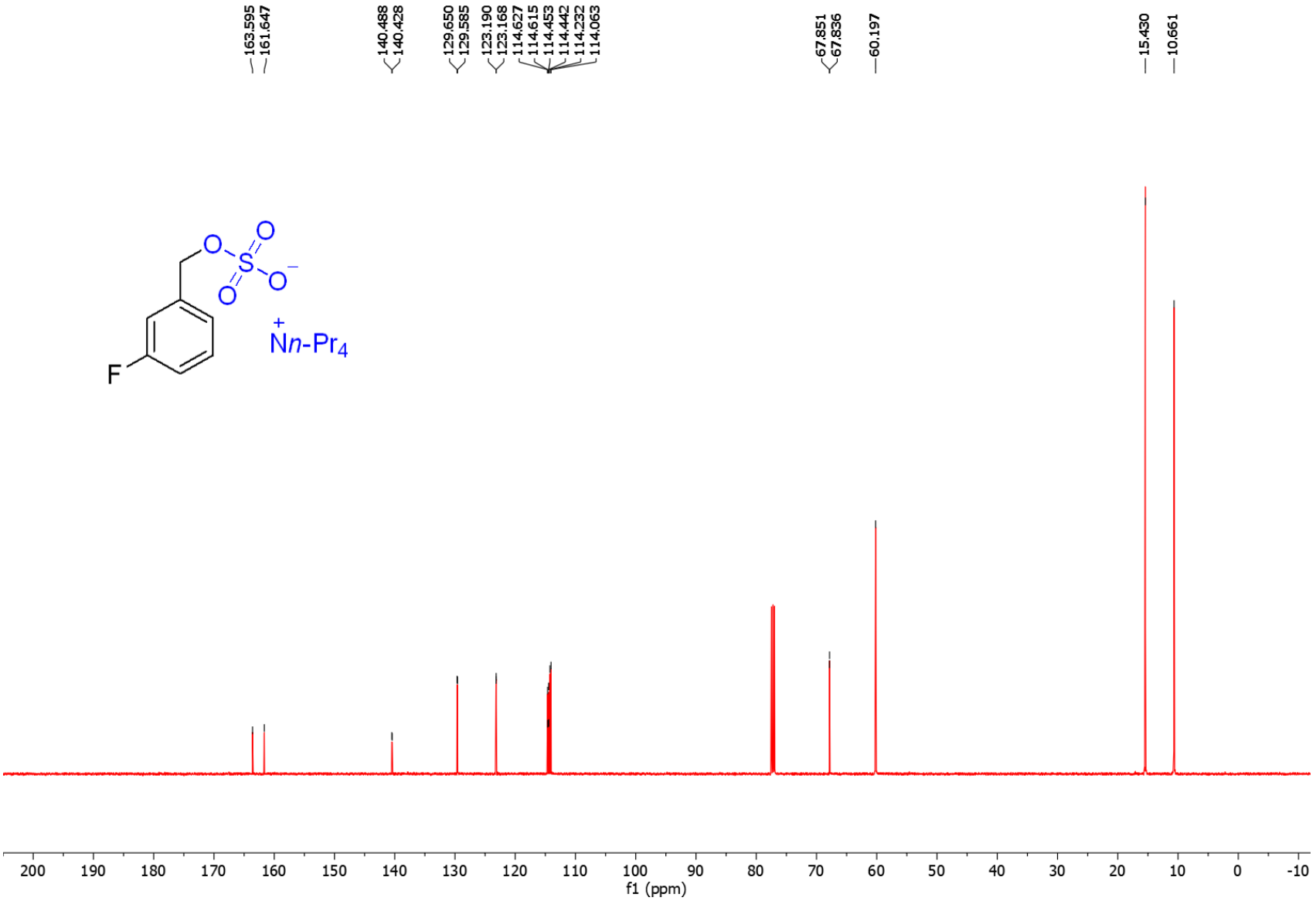
^{19}F NMR spectrum of tetrapropylammonium 2-fluorobenzyl sulfate (3.5g) (470 MHz, $CDCl_3$)



^{1}H NMR spectrum of tetrapropylammonium 3-fluorobenzyl sulfate (3.5h) (500 MHz, $CDCl_3$)

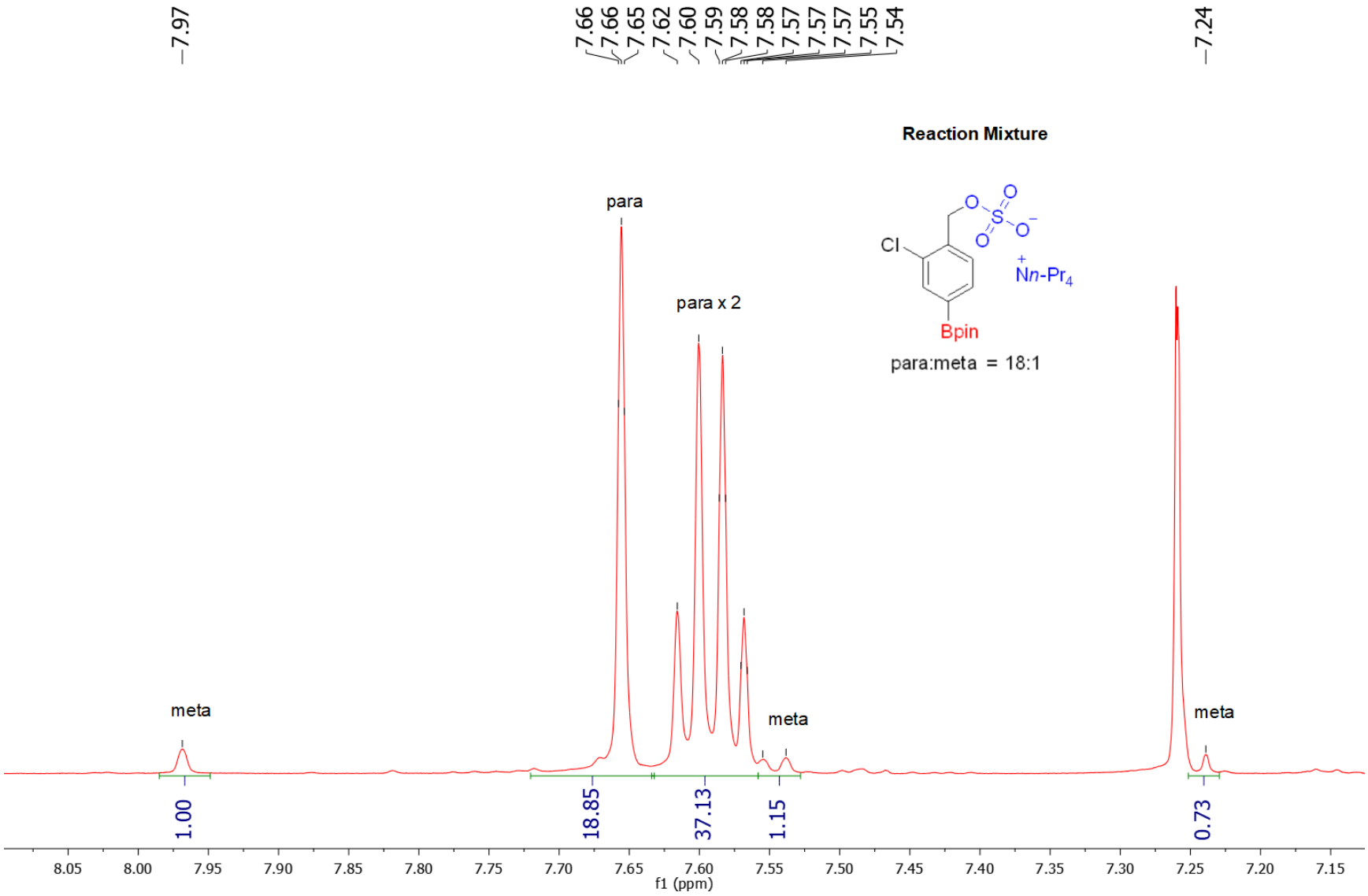


^{13}C NMR spectrum of tetrapropylammonium 3-fluorobenzyl sulfate (3.5h) (126 MHz, $CDCl_3$)

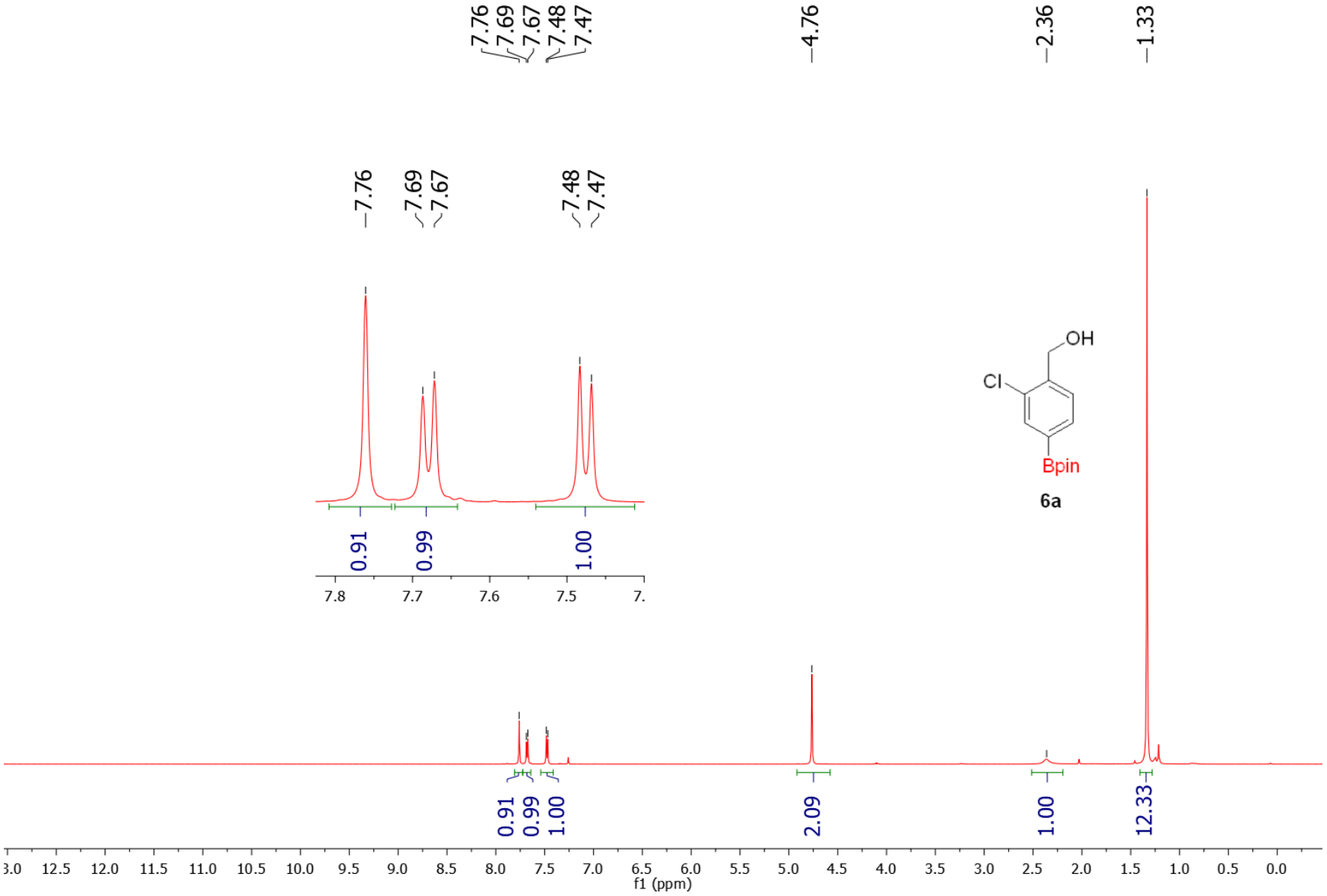


^{13}C NMR spectrum of tetrapropylammonium 3-fluorobenzyl sulfate (3.5h) (470 MHz, $CDCl_3$)

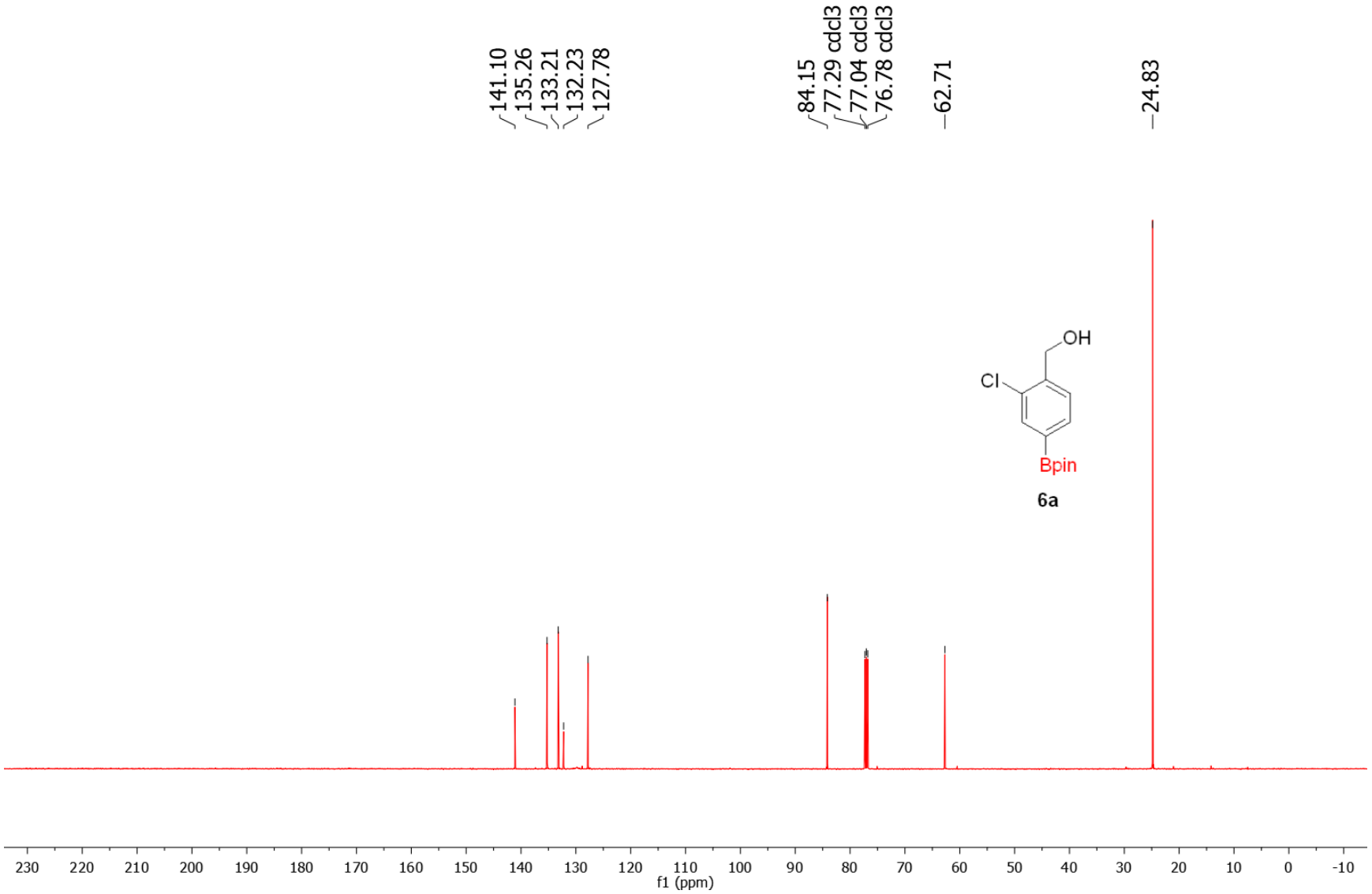
^{1}H NMR reaction mixture of *para* borylation of tetrapropylammonium 2-chlorobenzylsulfate (crude 3.6a) (500 MHz, $CDCl_3$)



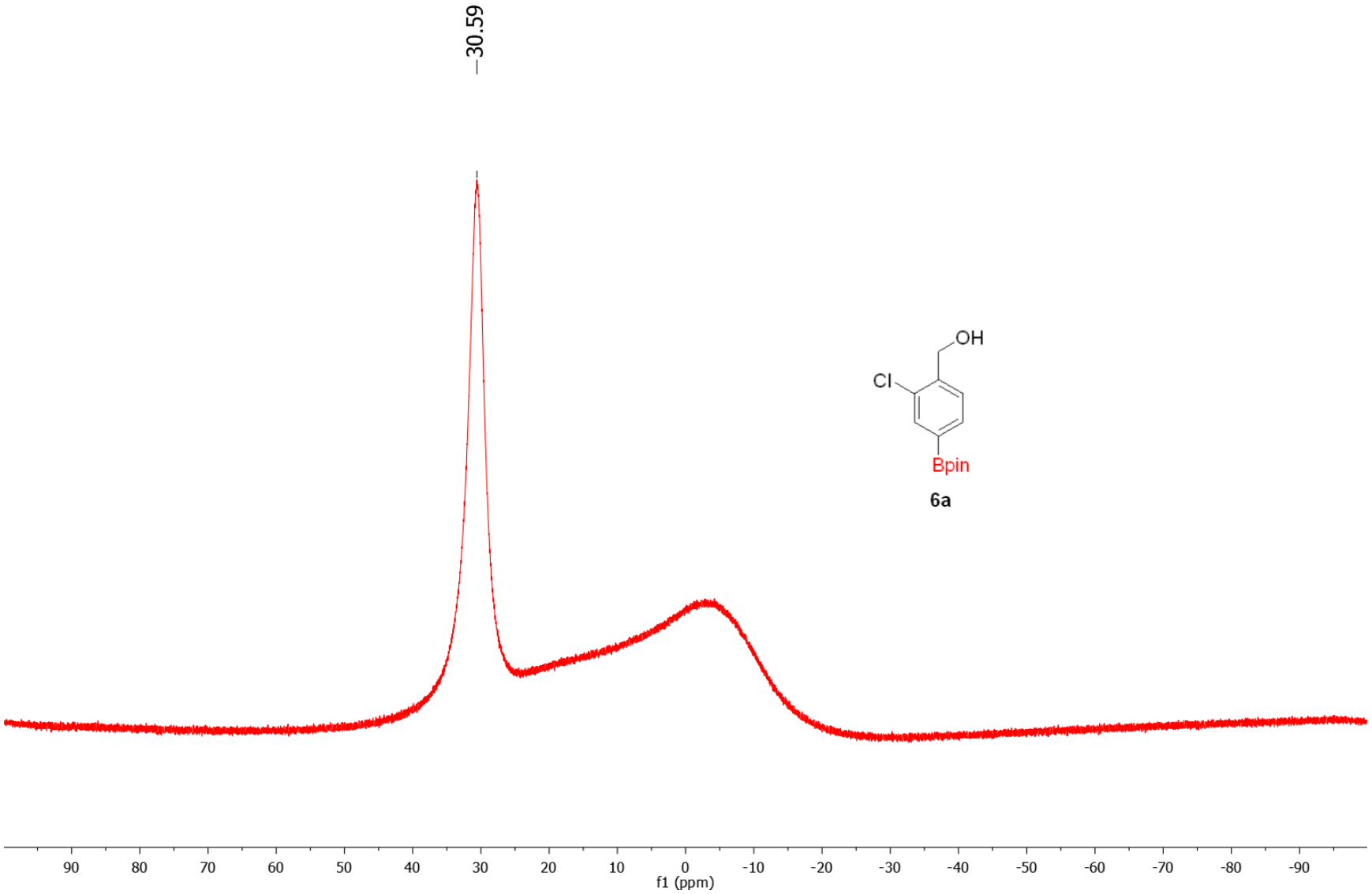
^{1}H NMR spectrum of *para* borylated 2-chlorobenzylalcohol (3.6a) (500 MHz, $CDCl_3$)



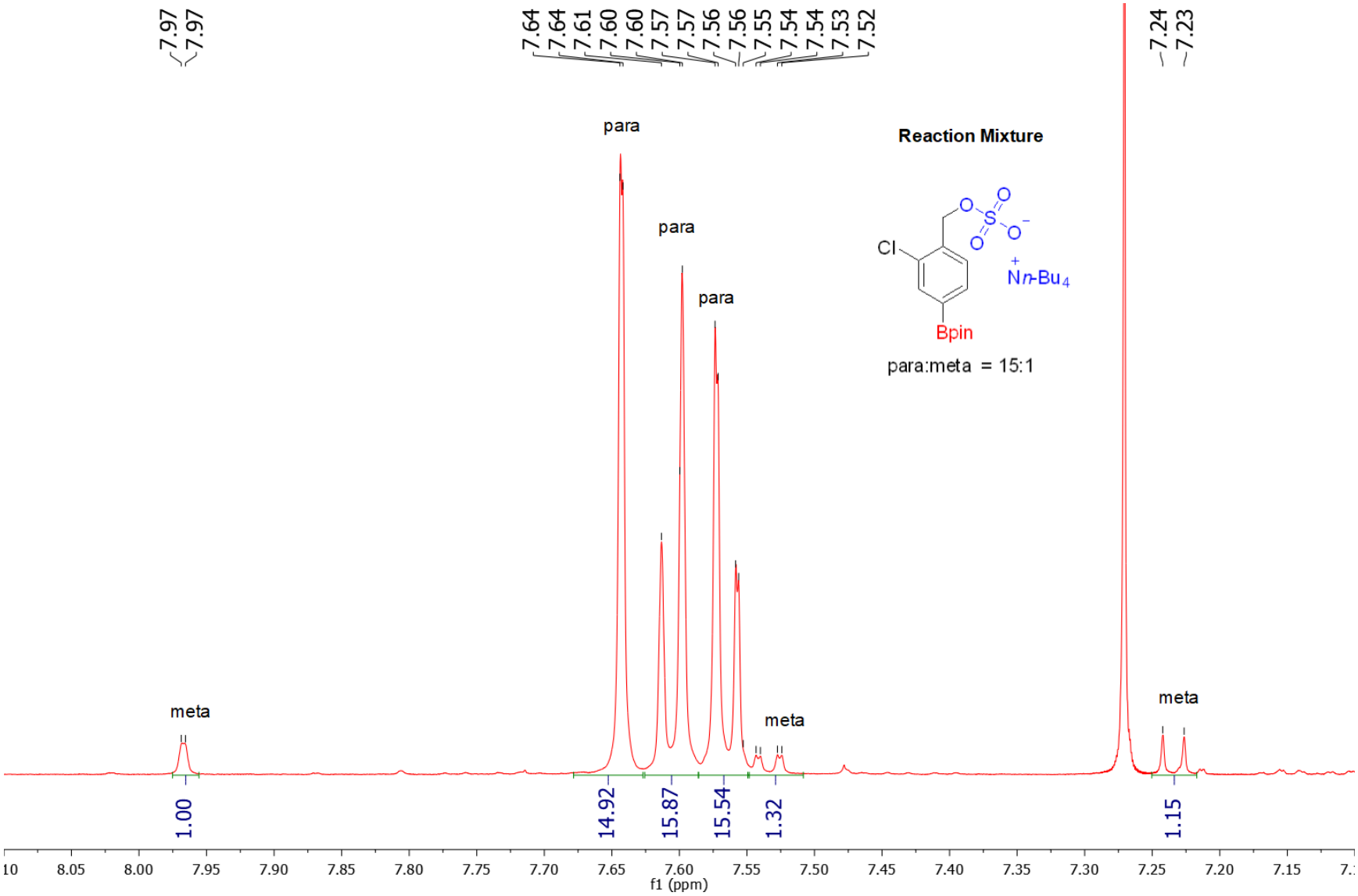
^{13}C NMR spectrum of *para* borylated 2-chlorobenzylalcohol (3.6a) (126 MHz, $CDCl_3$)



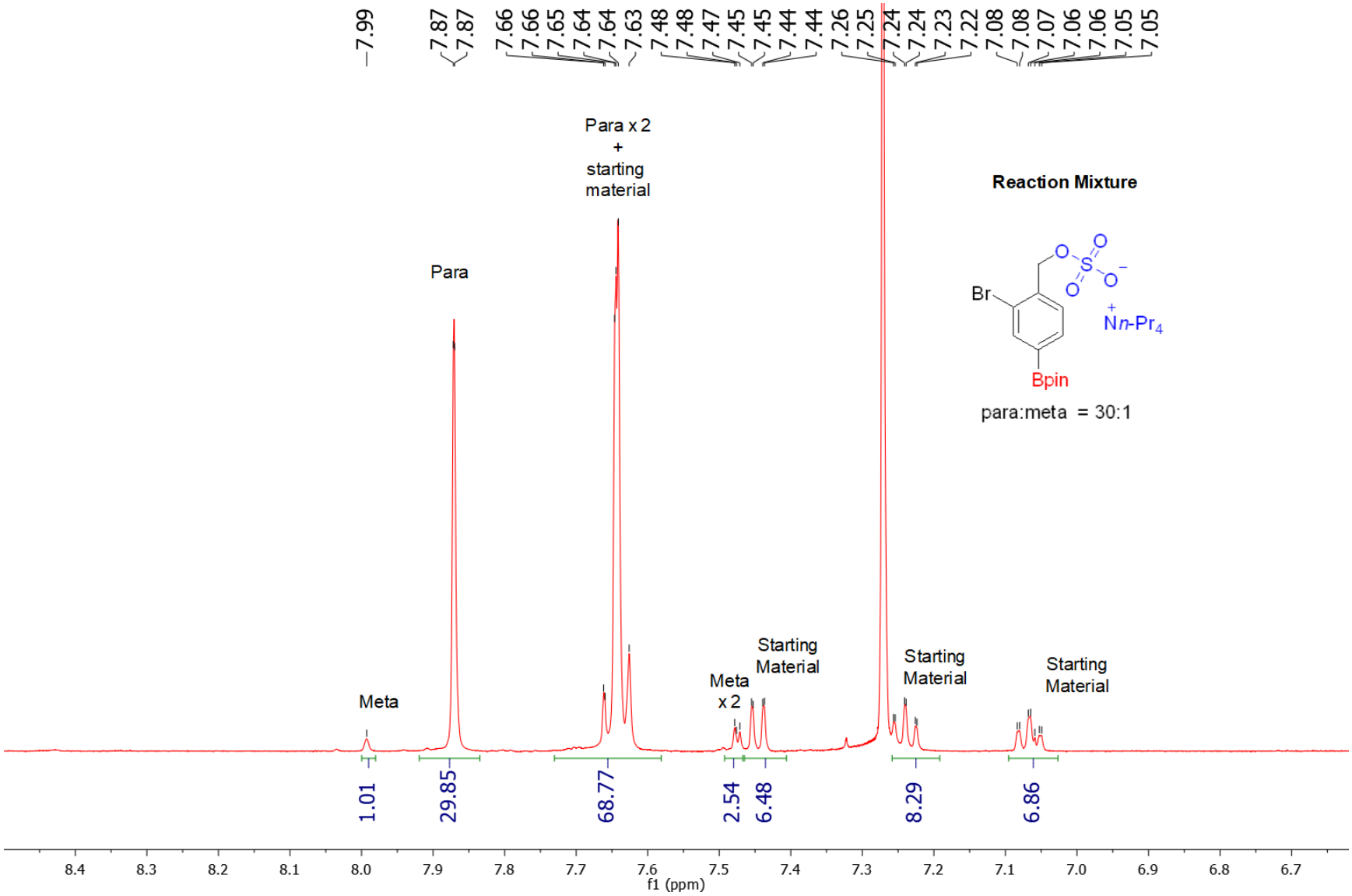
^{11}B NMR spectrum of *para* borylated 2-chlorobenzylalcohol (3.6a) (160 MHz, $CDCl_3$)



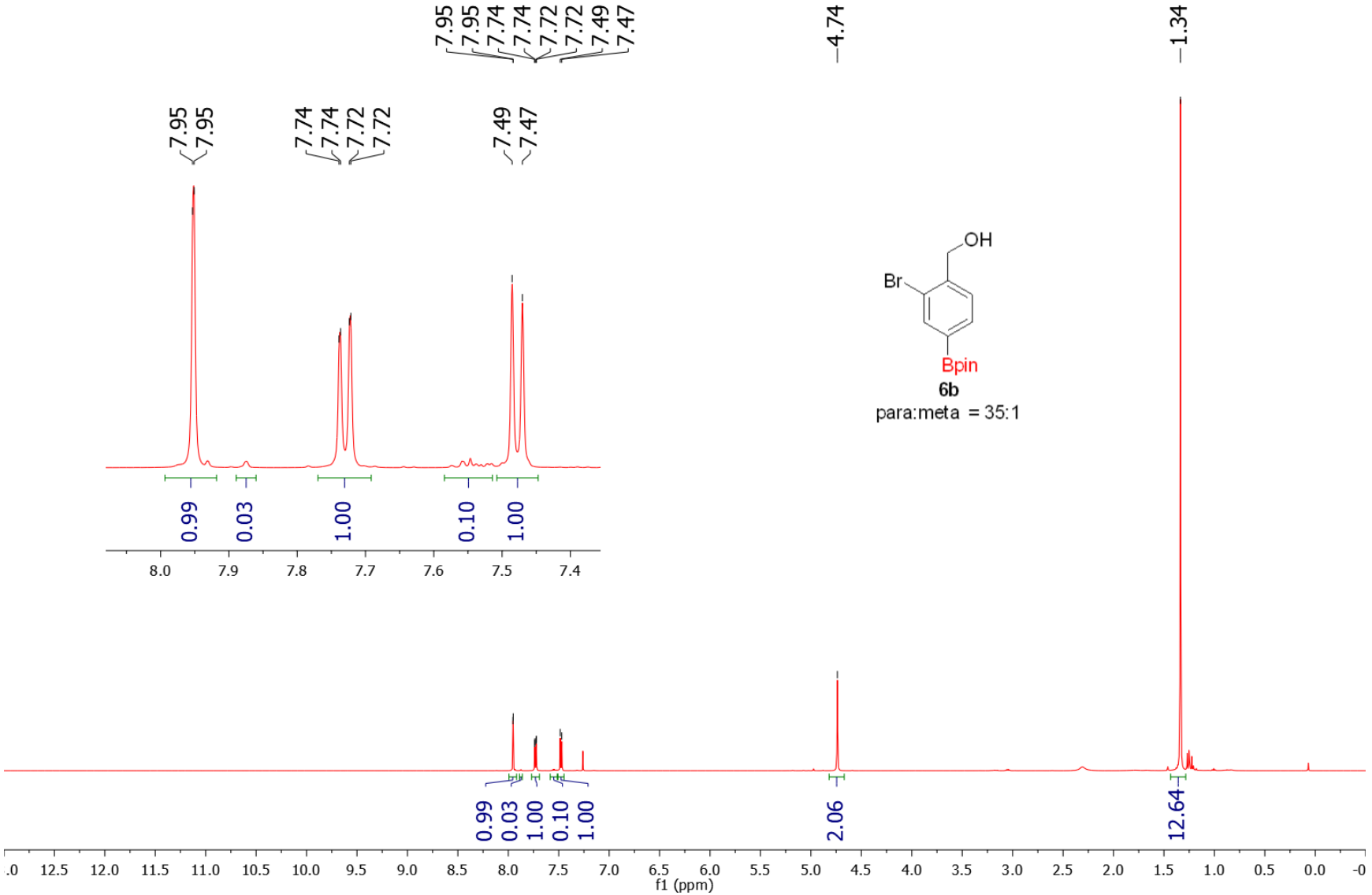
^{1}H NMR reaction mixture of *para* borylation of tetrabutylammonium 2-chlorobenzylsulfate (crude 3.6a') (500 MHz, $CDCl_3$)



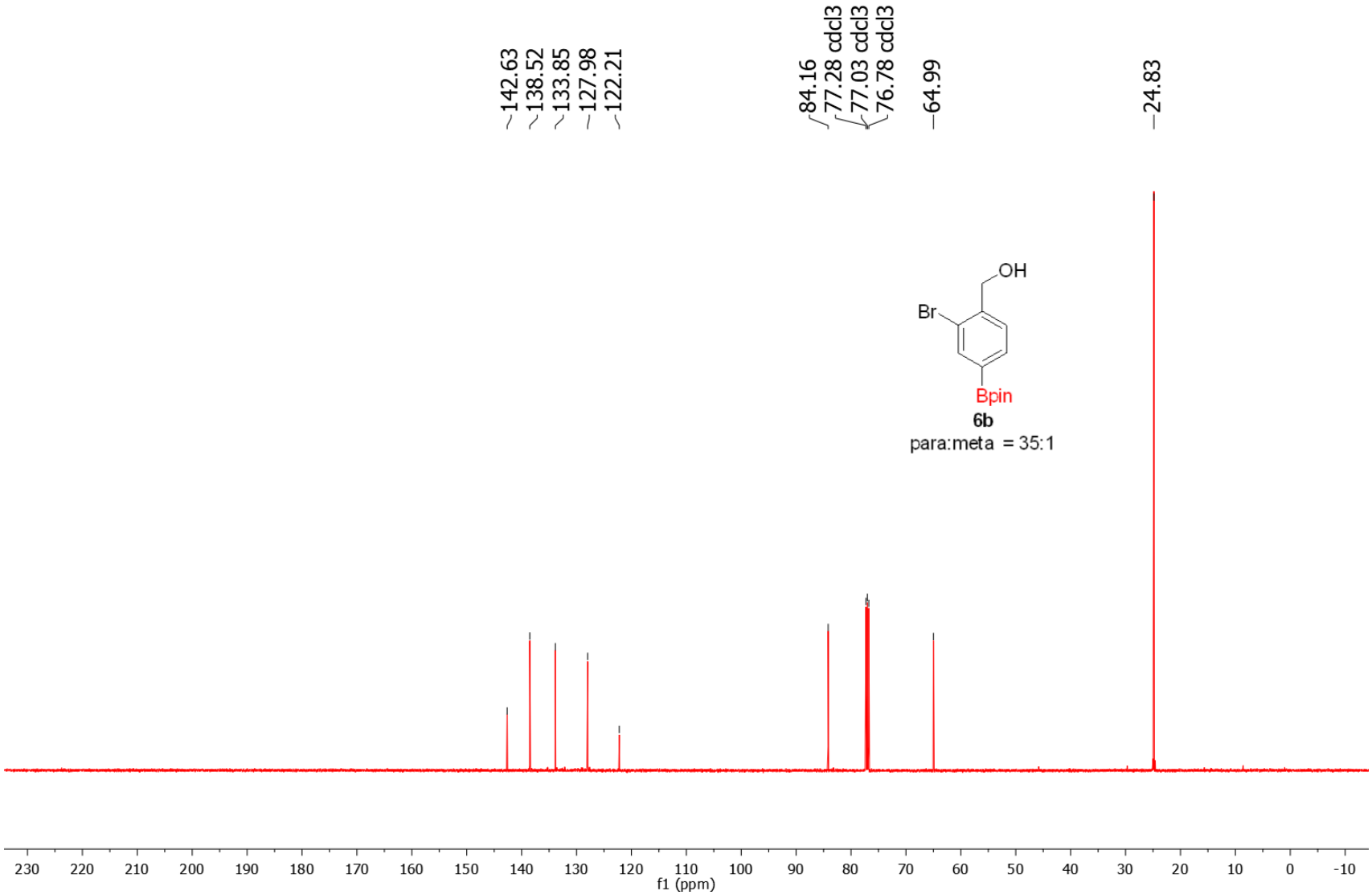
^{1}H NMR reaction mixture of *para* borylation of terapropylammonium 2-bromobenzylsulfate (crude 3.6b) 500 MHz, $CDCl_3$



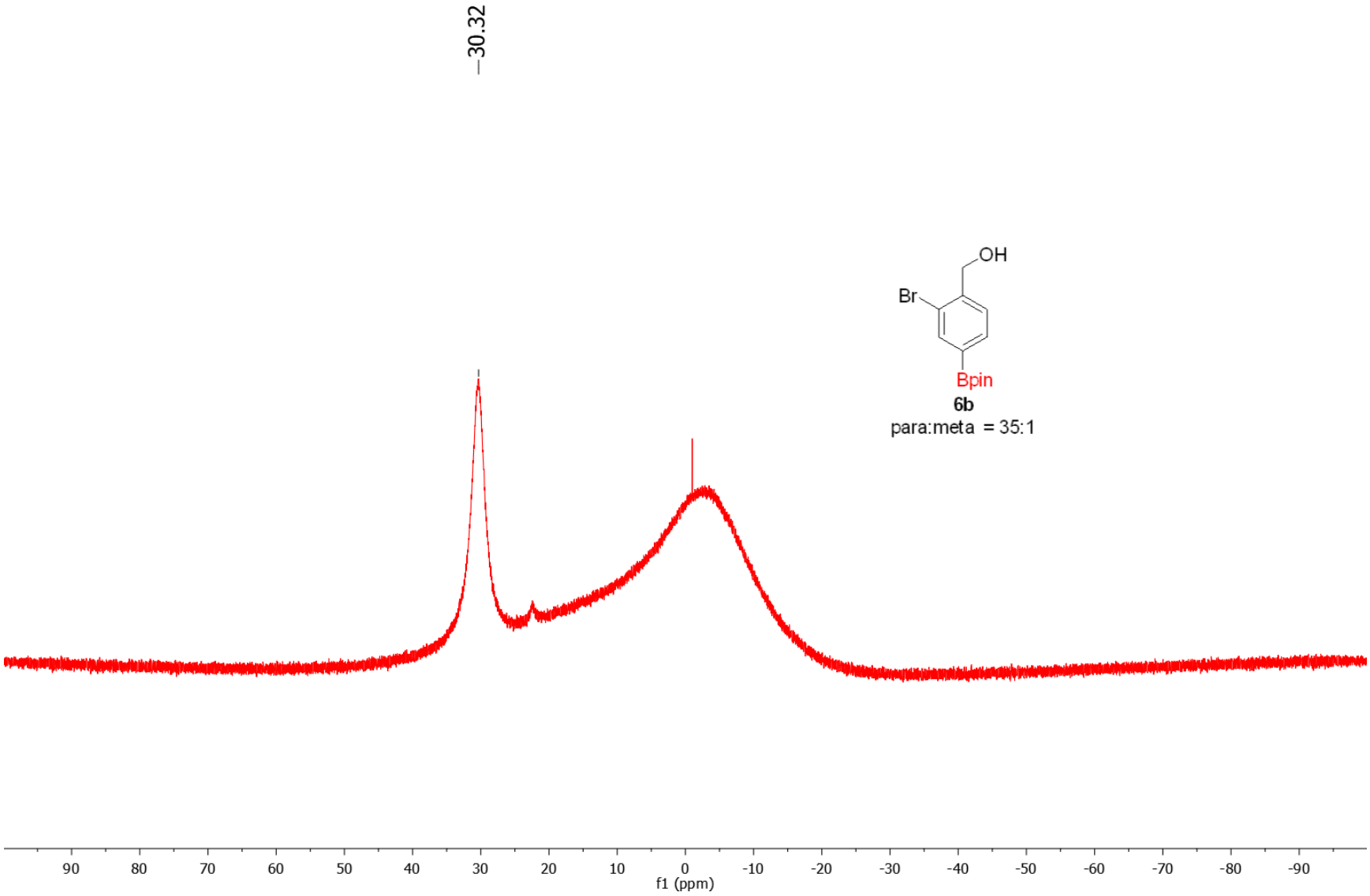
^{1}H NMR spectrum of reaction mixture of *para* borylation of 2-bromobenzylsulfate (3.6b) (500 MHz, $CDCl_3$)



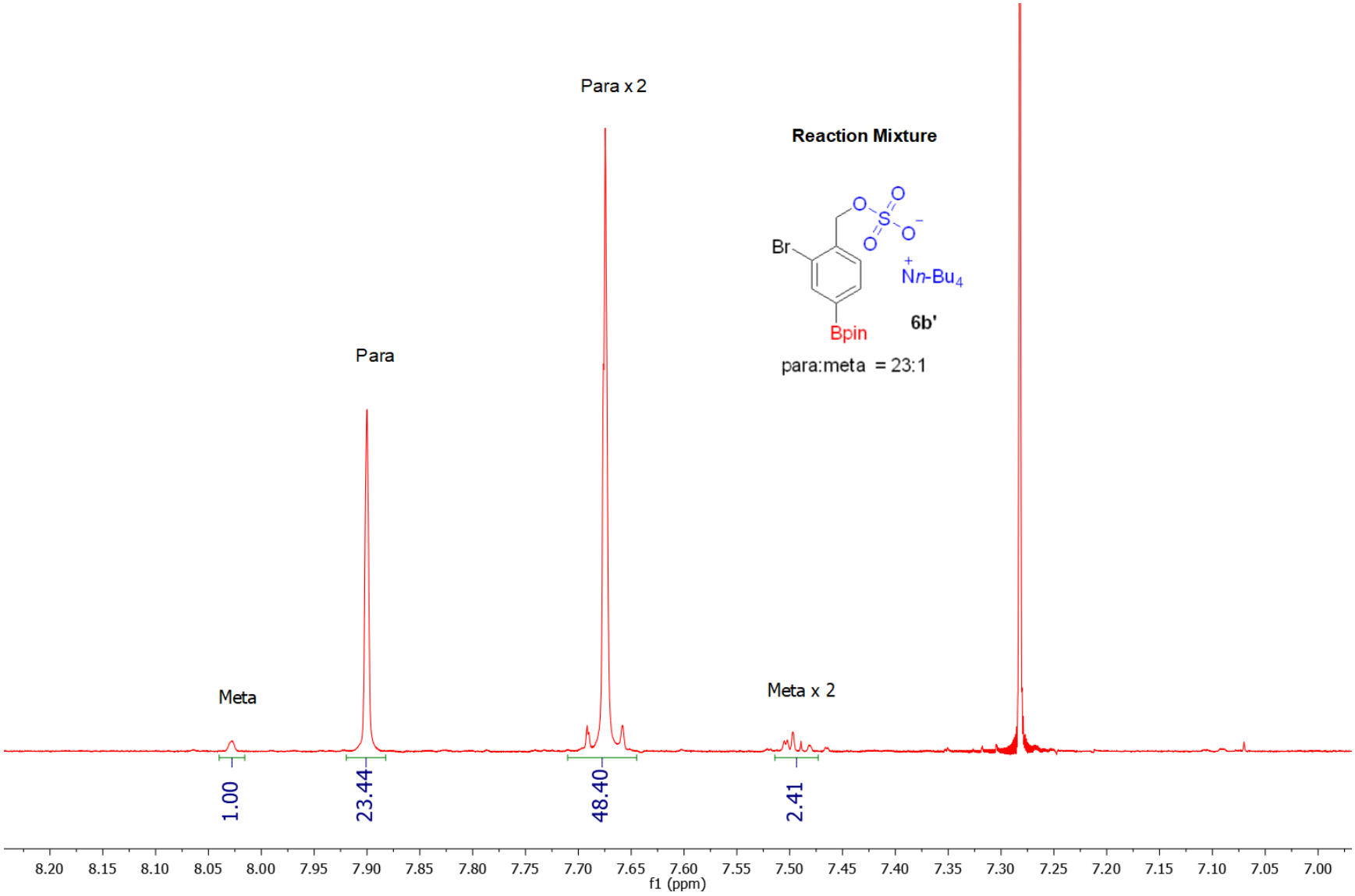
^{13}C NMR spectrum of *para* borylated 2-bromobenzylalcohol (3.6b) (126 MHz, $CDCl_3$)



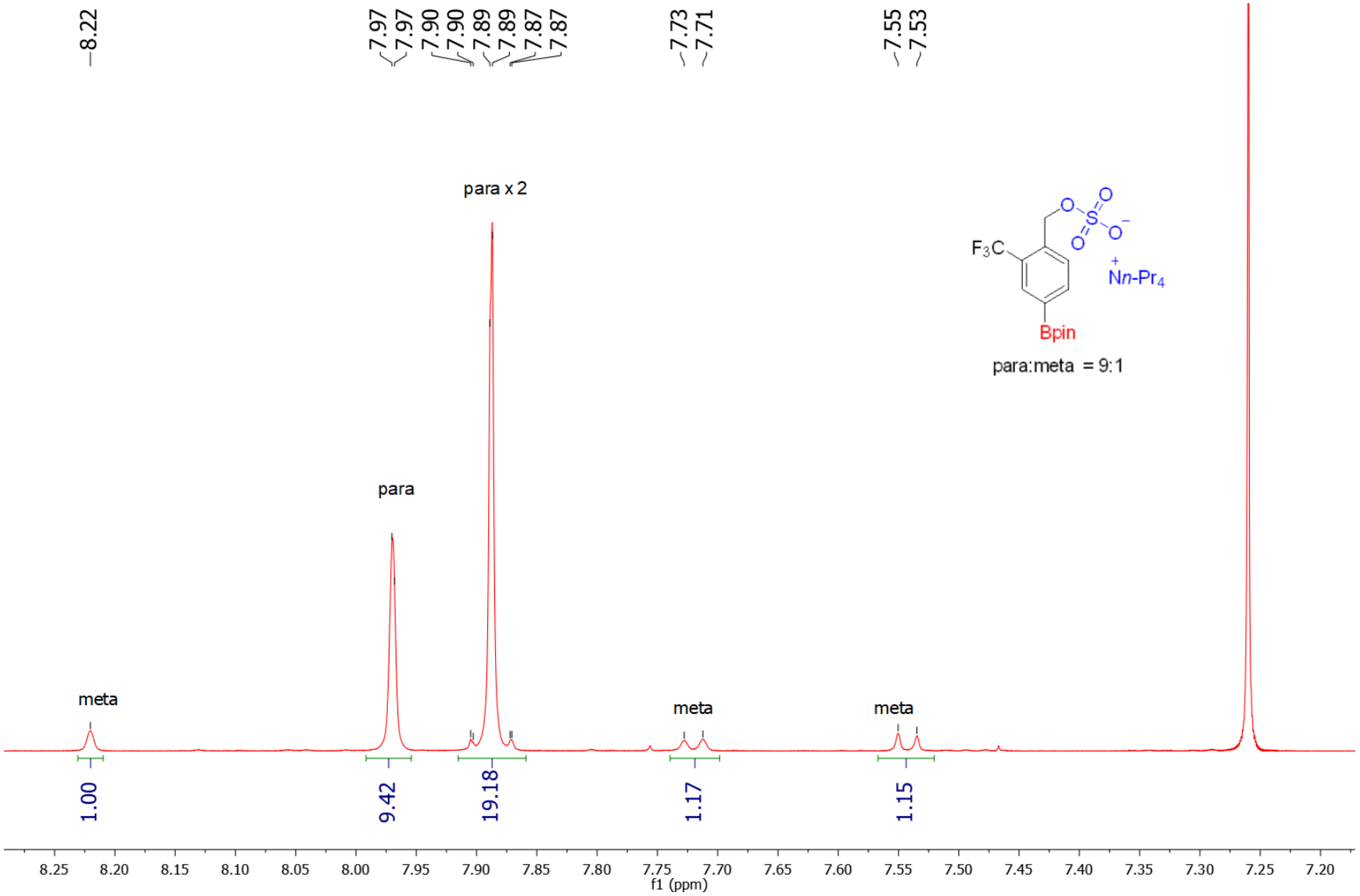
^{11}B NMR of *para* borylated 2-bromobenzylalcohol (3.6b) (160 MHz, $CDCl_3$)



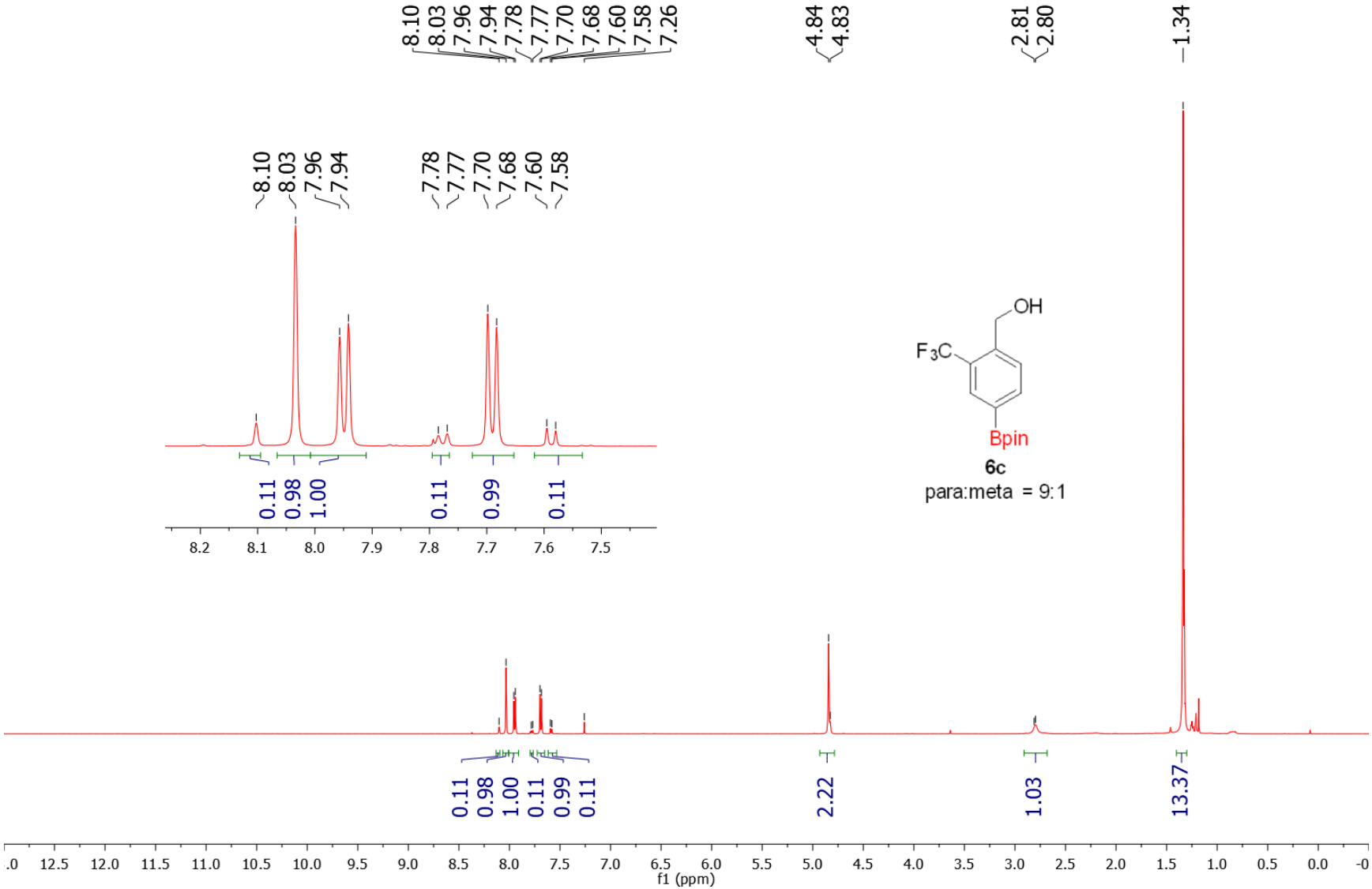
^{1}H NMR reaction mixture of *para* borylation of tetrabutylammonium 2-bromobenzylsulfate (crude 3.6b′) (500 MHz, $CDCl_3$)



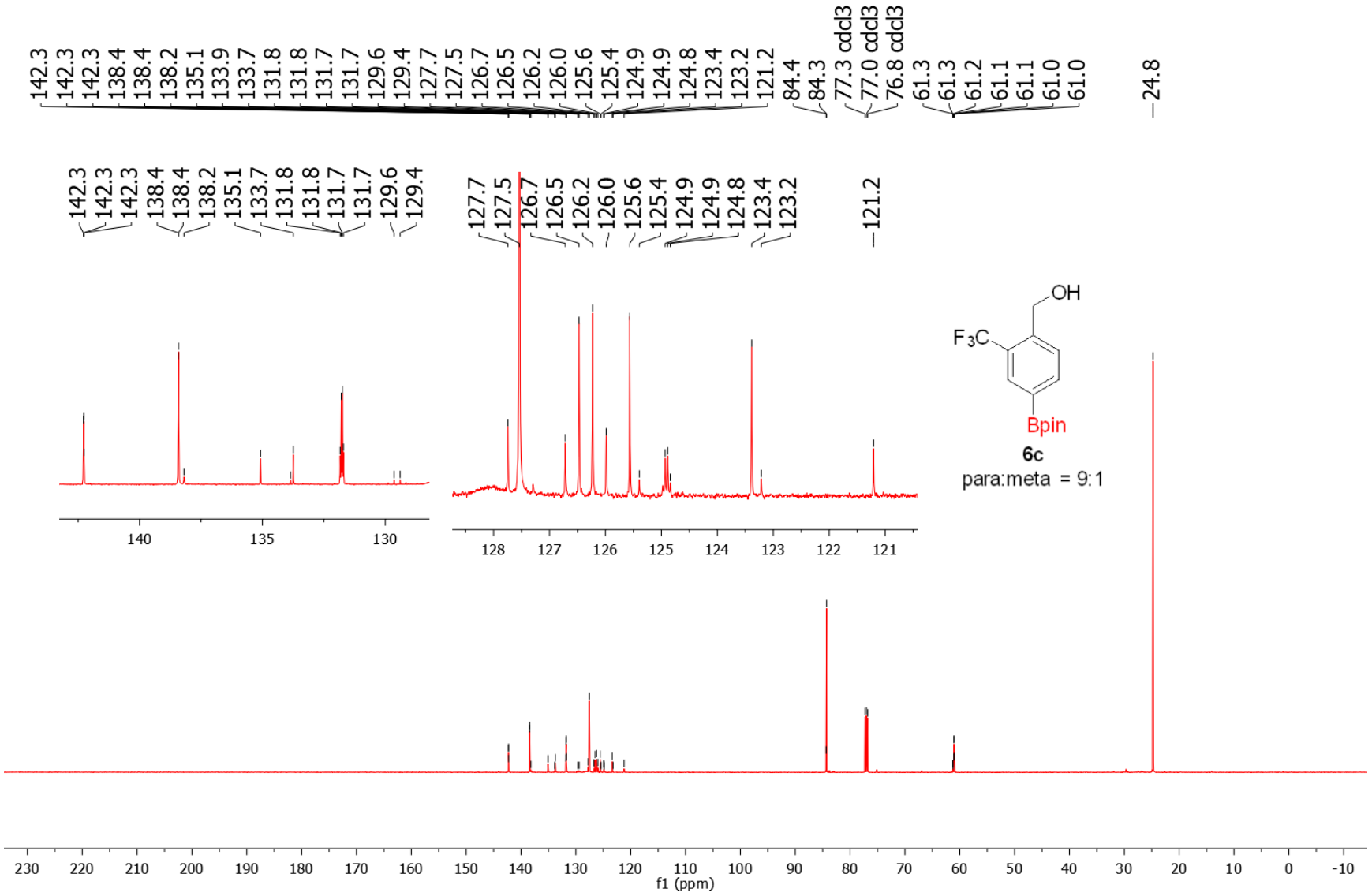
^{1}H NMR reaction mixture of *para* borylation of 2-(trifluoromethyl)benzylsulfate (crude 3.6c) (500 MHz, $CDCl_3$)



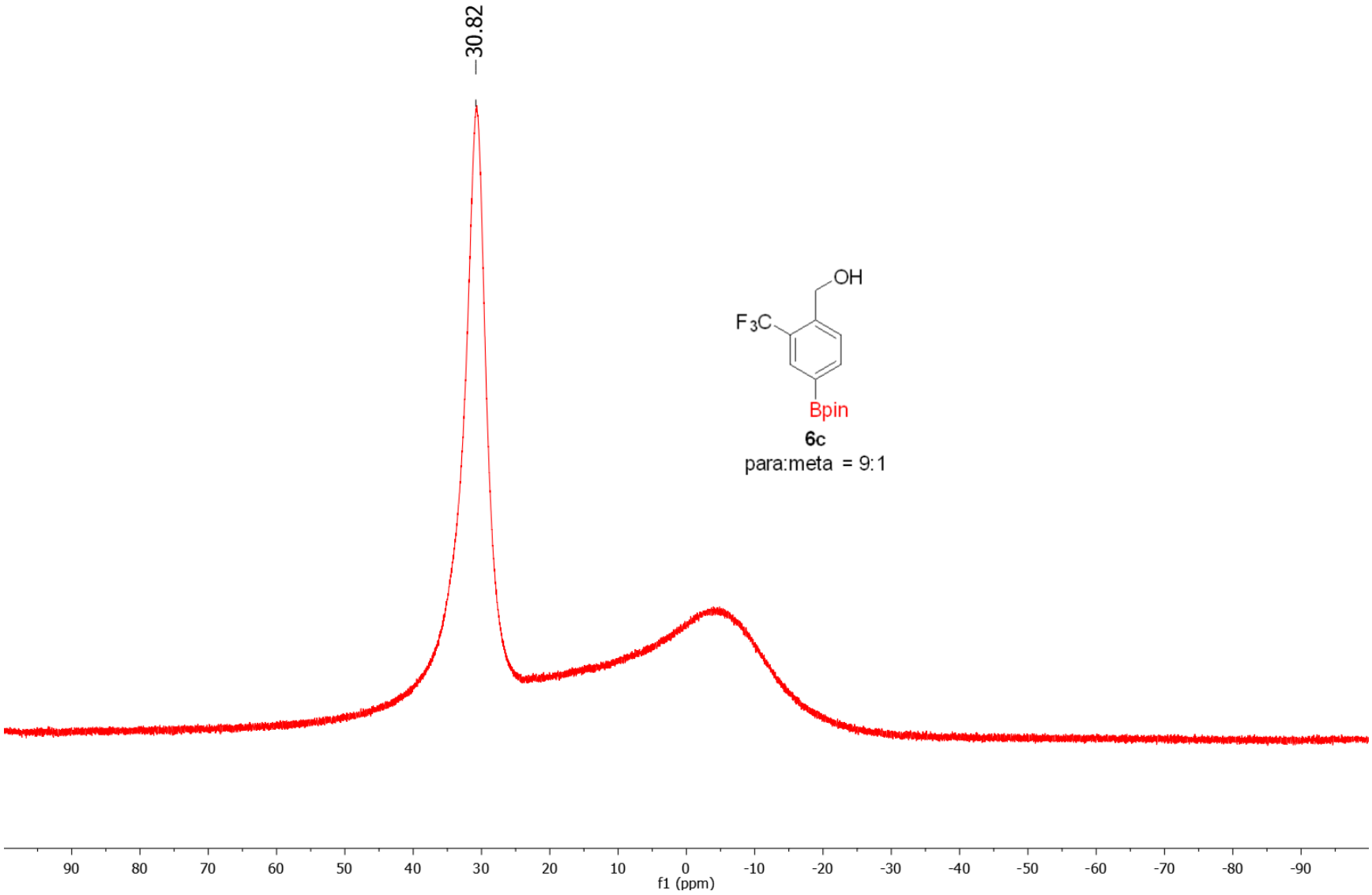
^{1}H NMR spectrum of *para* borylated 2-(trifluoromethyl)benzylalcohol (3.6c) (500 MHz, $CDCl_3$)



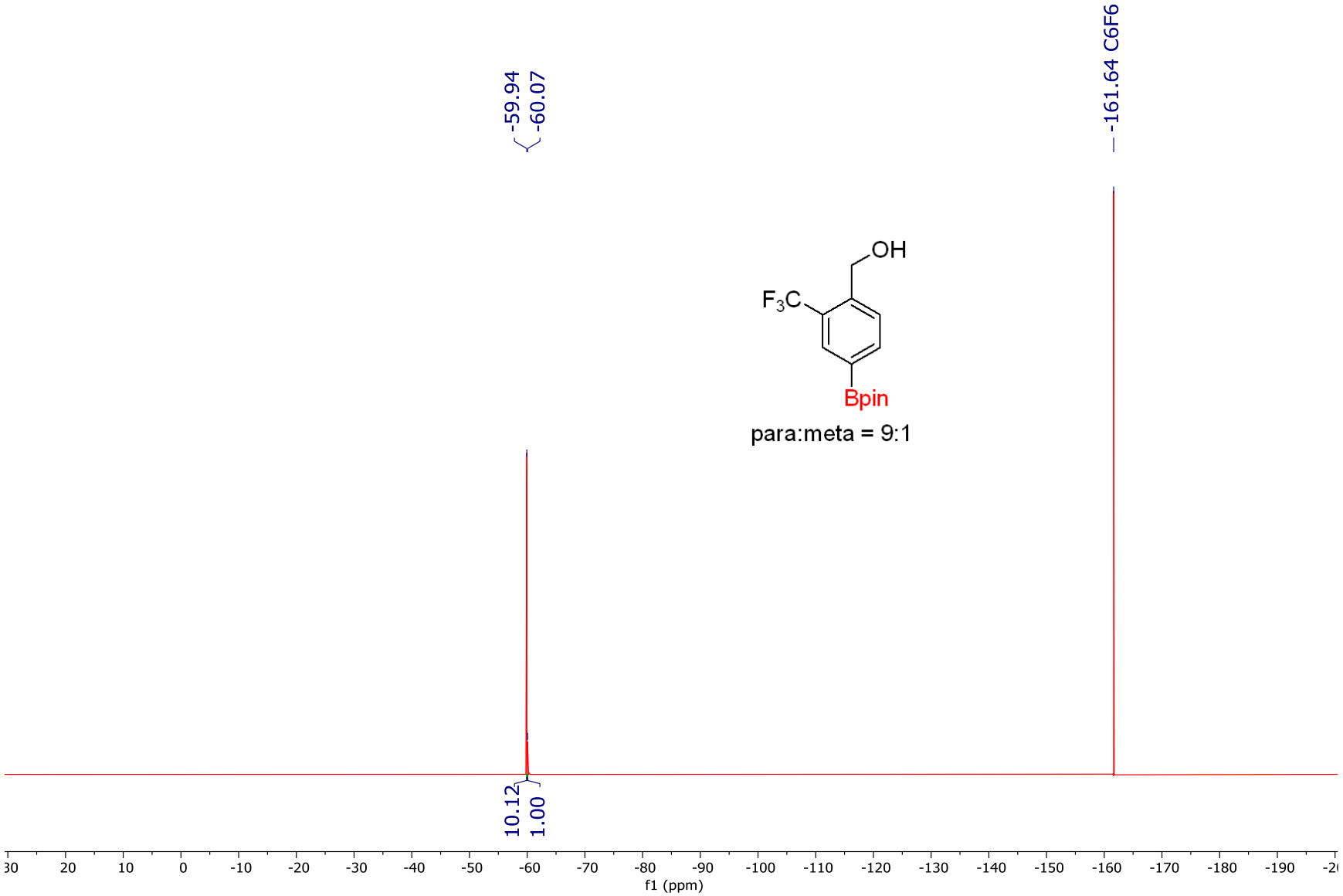
^{13}C NMR spectrum of *para* borylated 2-(trifluoromethyl)benzylalcohol (3.6c) (126 MHz, $CDCl_3$)



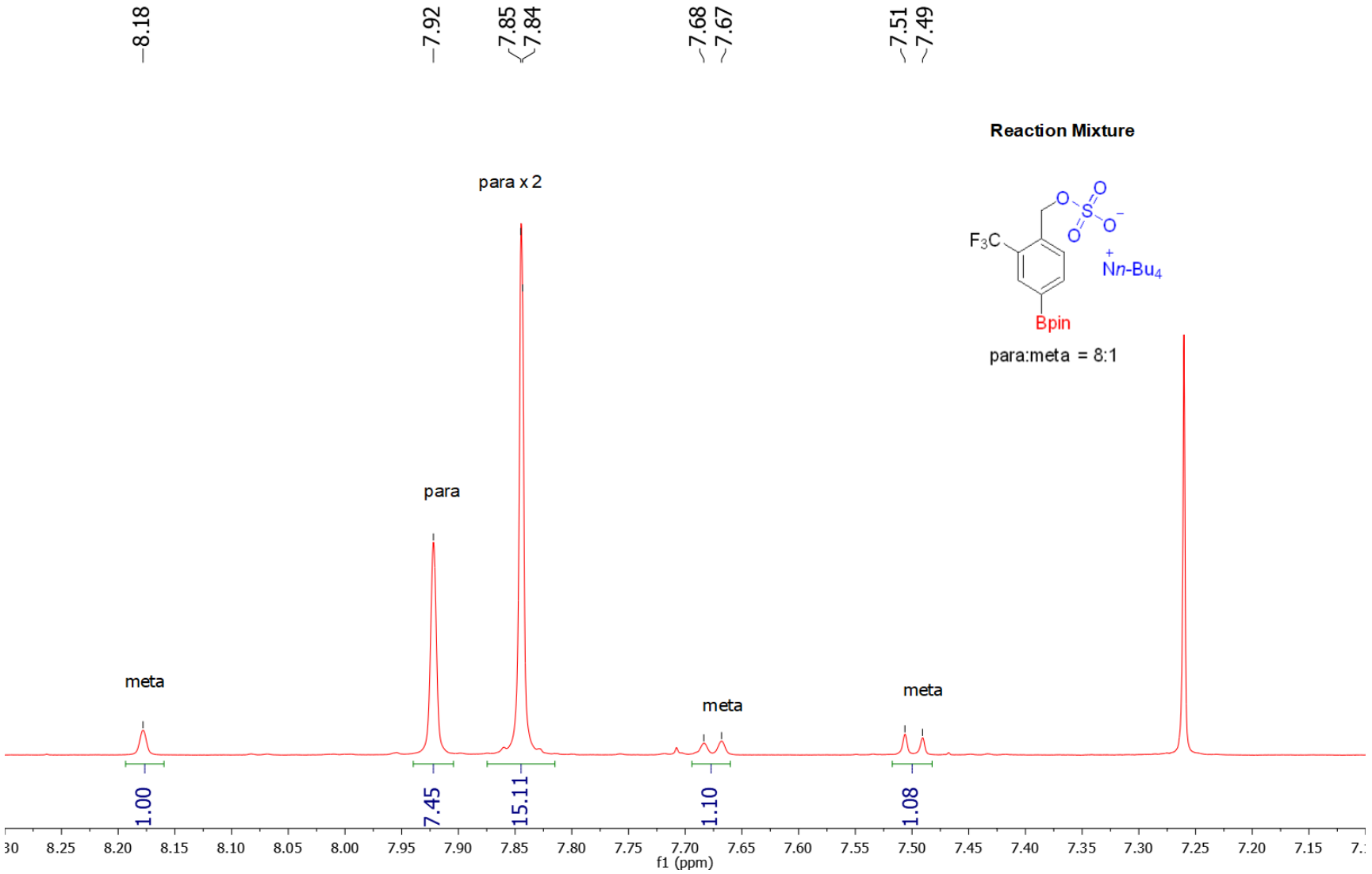
^{11}B NMR spectrum of *para* borylated 2-(trifluoromethyl)benzylalcohol (3.6c) (160 MHz, $CDCl_3$)



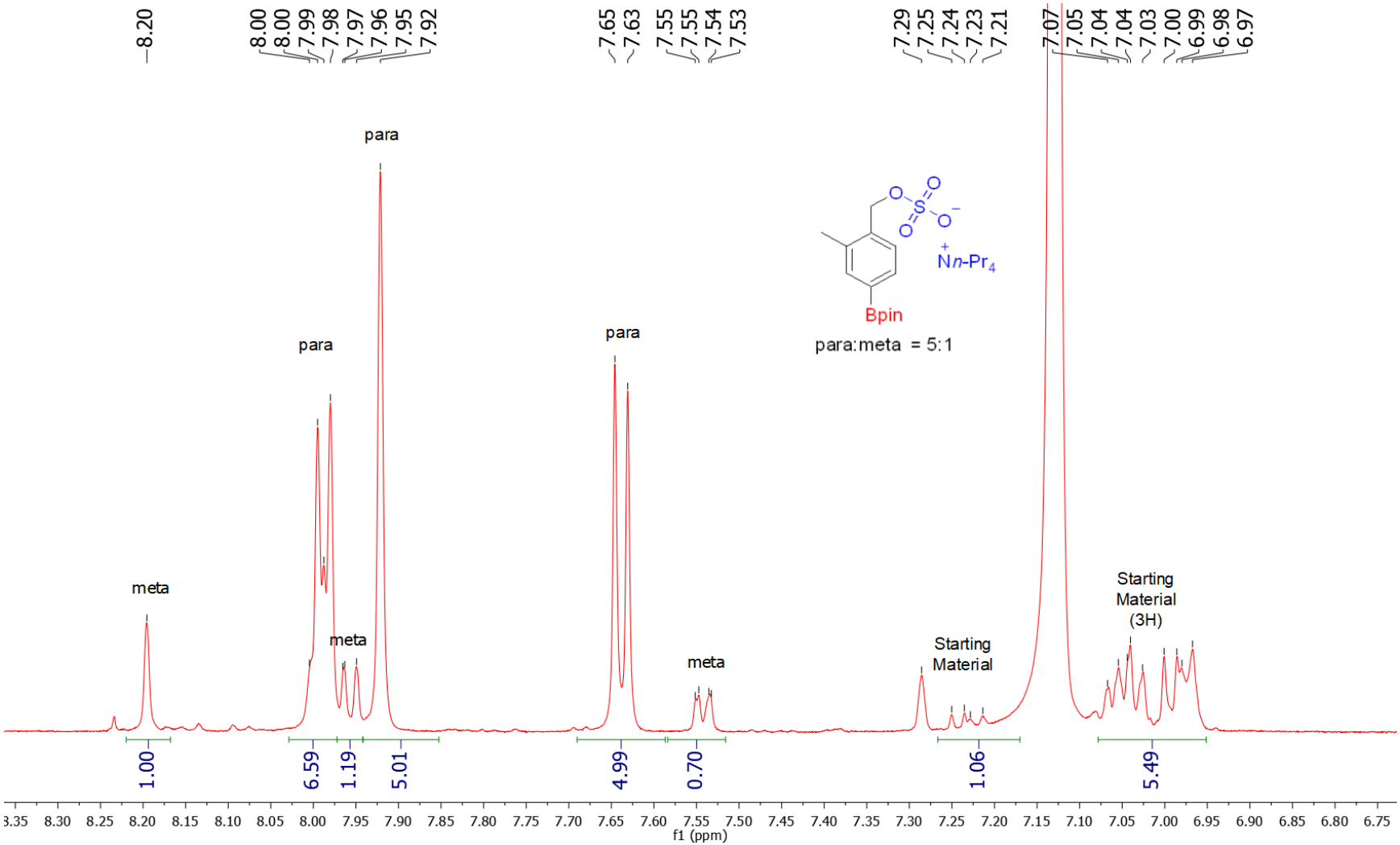
^{19}F NMR spectrum of *para* borylated 2-(trifluoromethyl)benzylalcohol (3.6c) (470 MHz, $CDCl_3$)



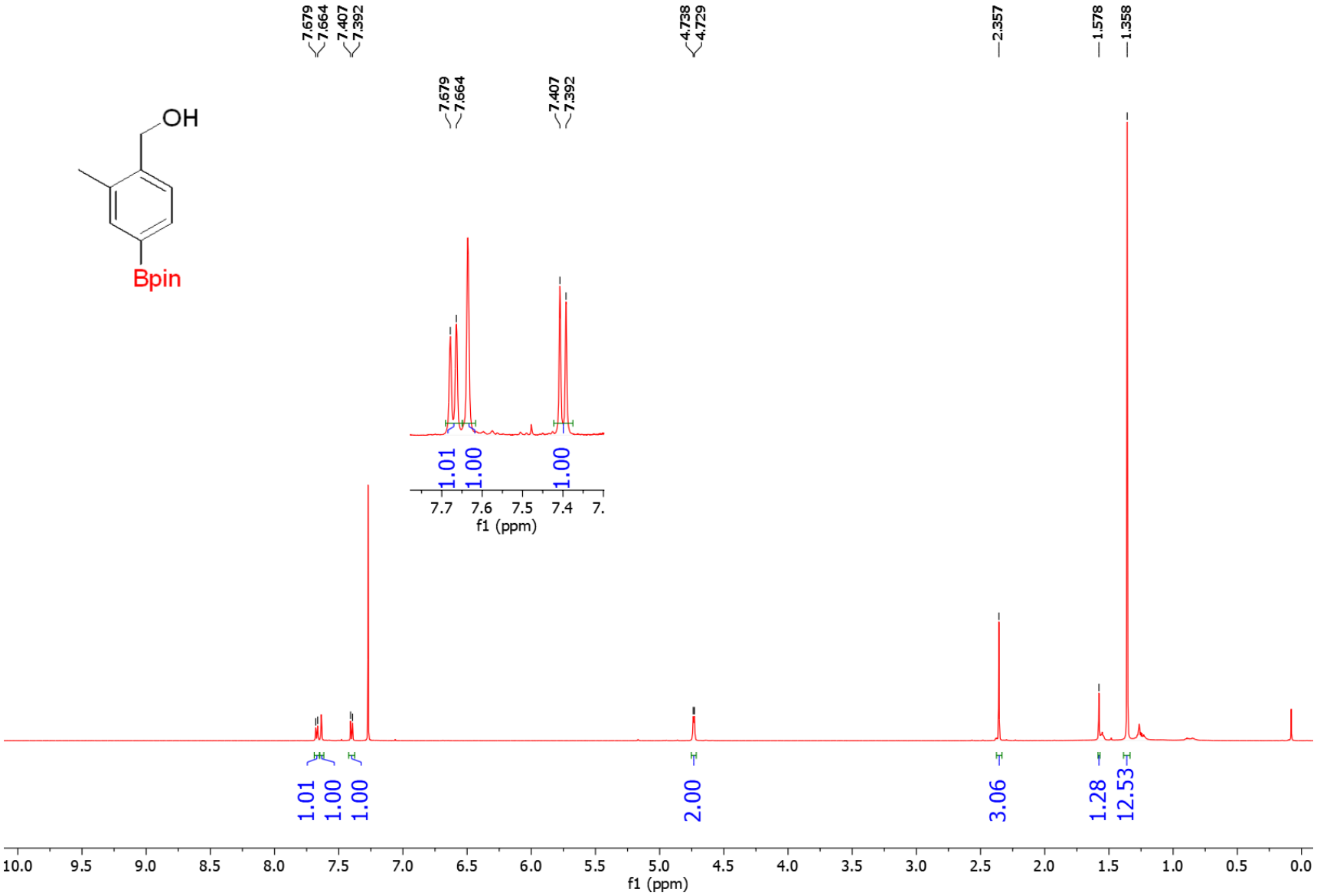
^{1}H NMR reaction mixture of *para* borylation of 2-(trifluoromethyl)benzylsulfate (crude 3.6c') (500 MHz, $CDCl_3$)



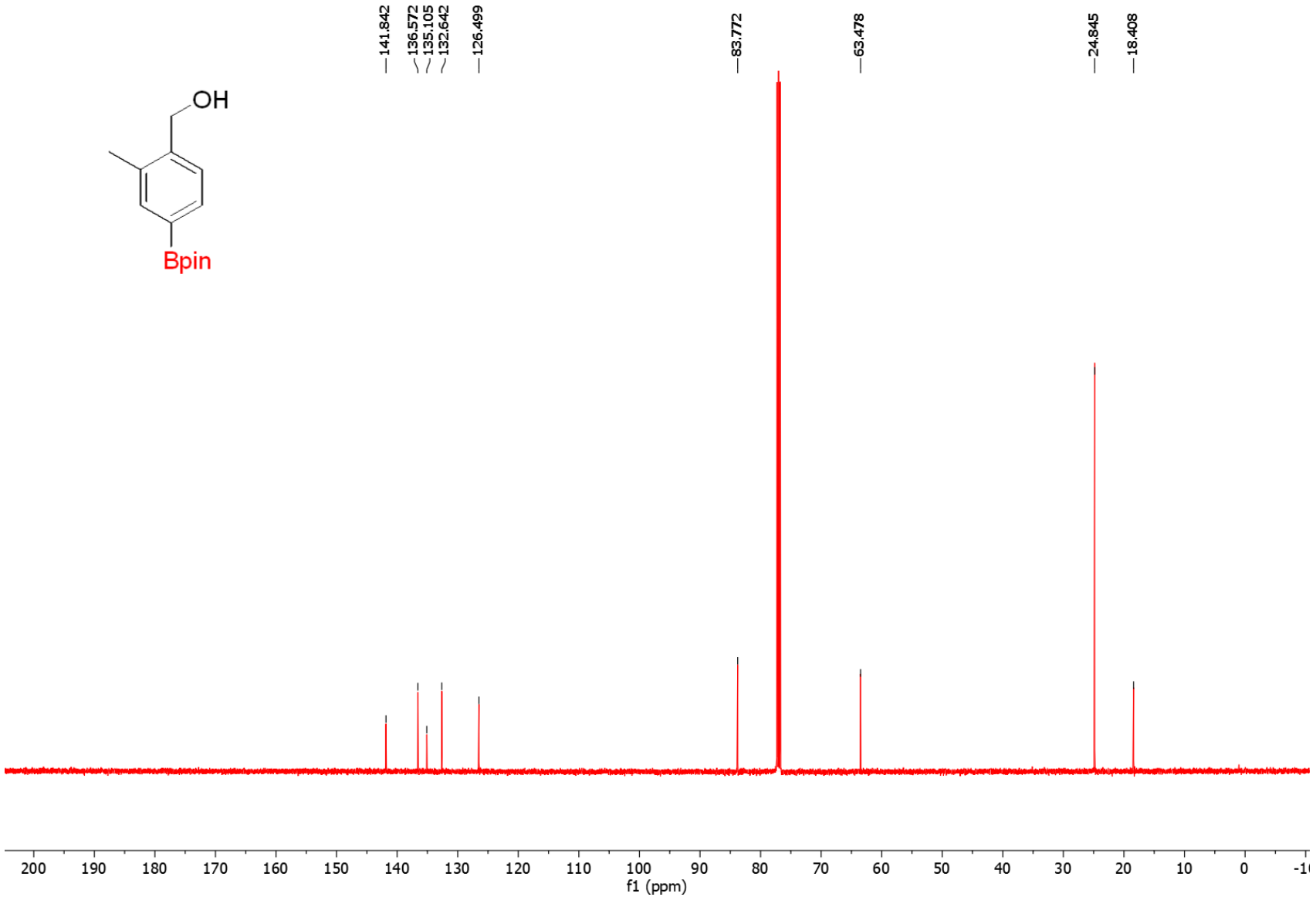
^{1}H NMR reaction mixture of *para* borylation of 2-methylbenzylsulfate (crude 3.6d) (500 MHz, $CDCl_3$)



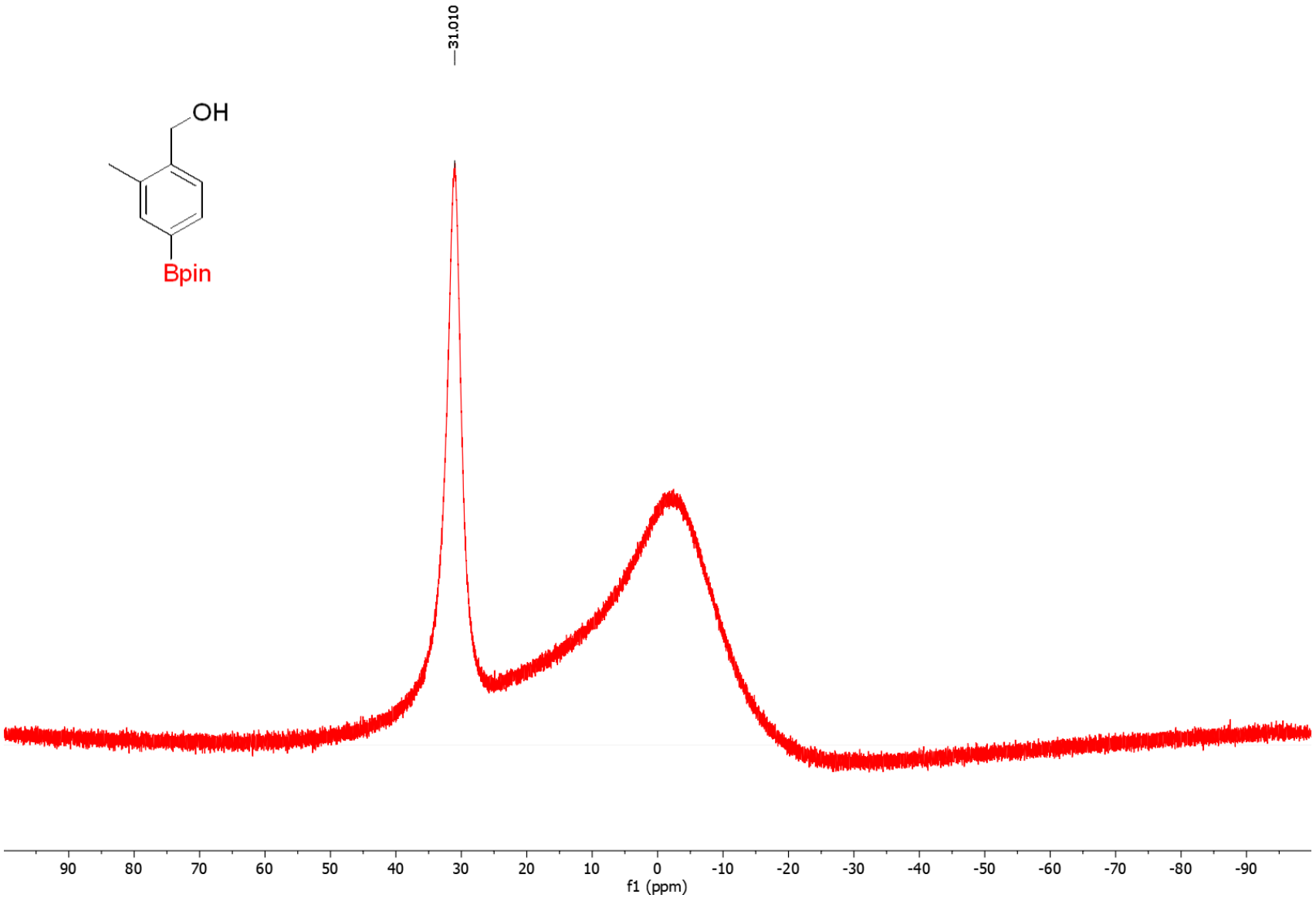
^{1}H NMR spectrum of *para* borylated 2-(methyl)benzylalcohol (3.6d) (500 MHz, $CDCl_3$)



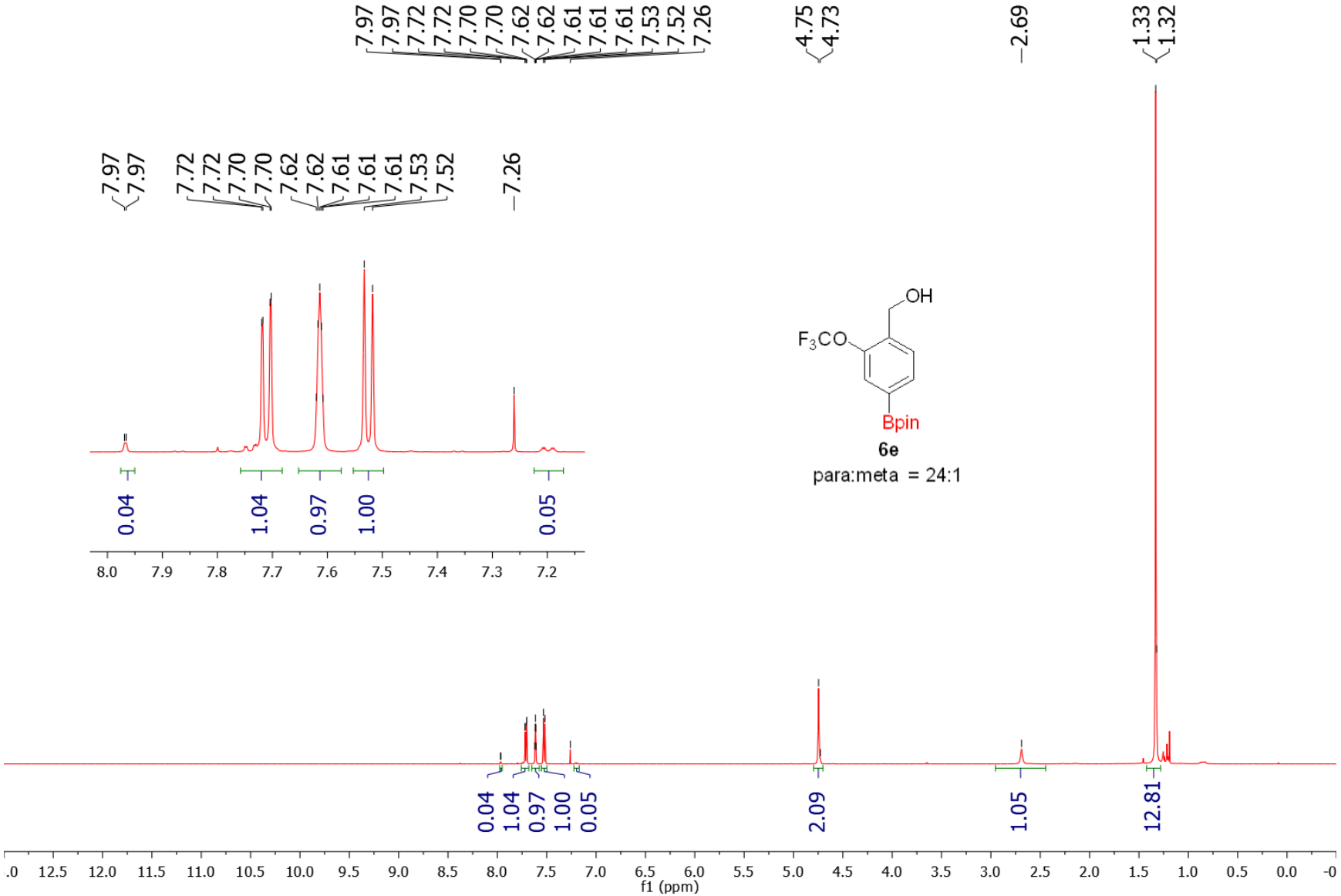
^{13}C NMR spectrum of *para* borylated 2-(methyl)benzylalcohol (3.6d) (126 MHz, $CDCl_3$)



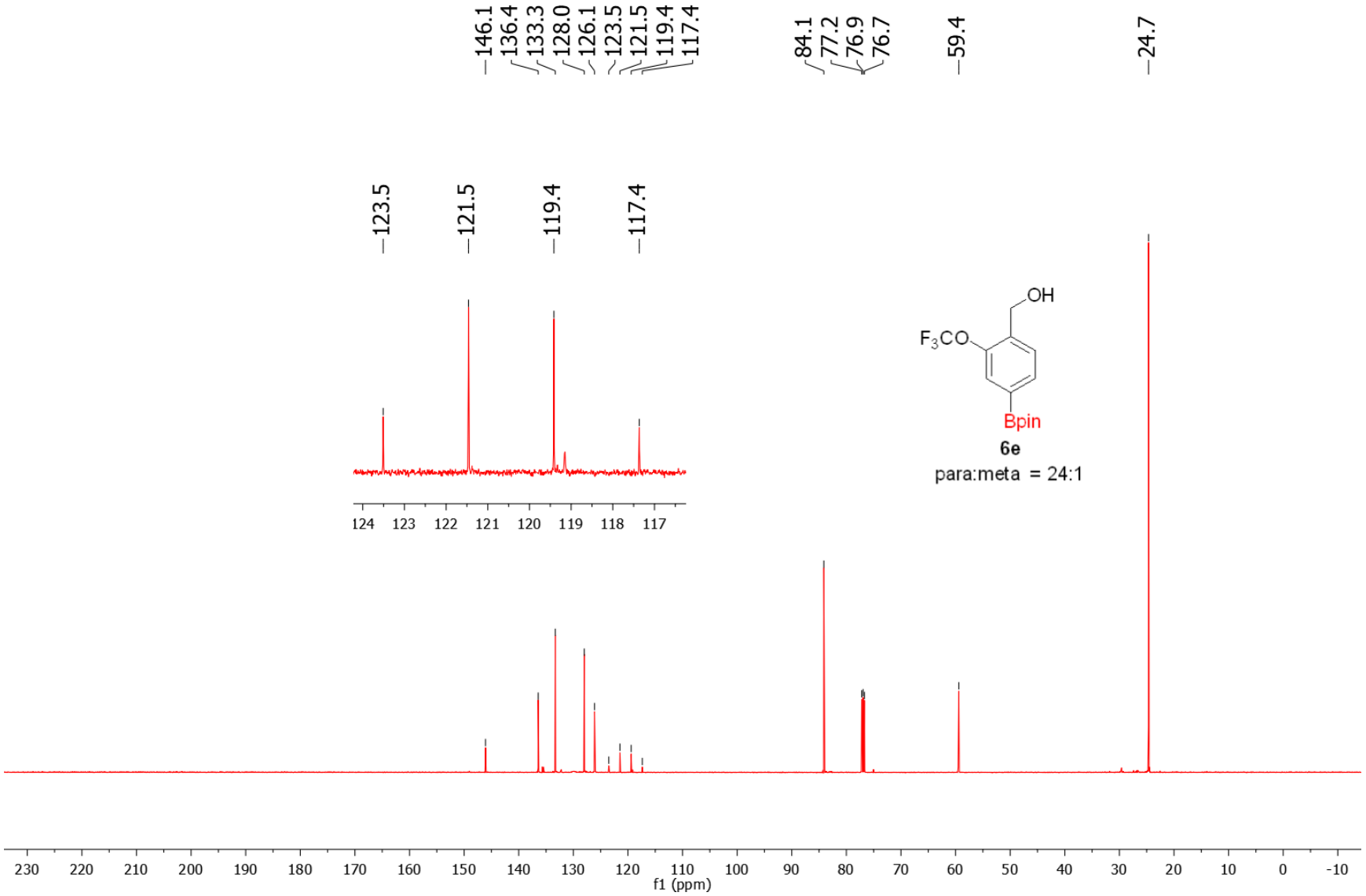
^{11}B NMR spectrum of *para* borylated 2-(methyl)benzylalcohol (3.6d) (160 MHz, $CDCl_3$)



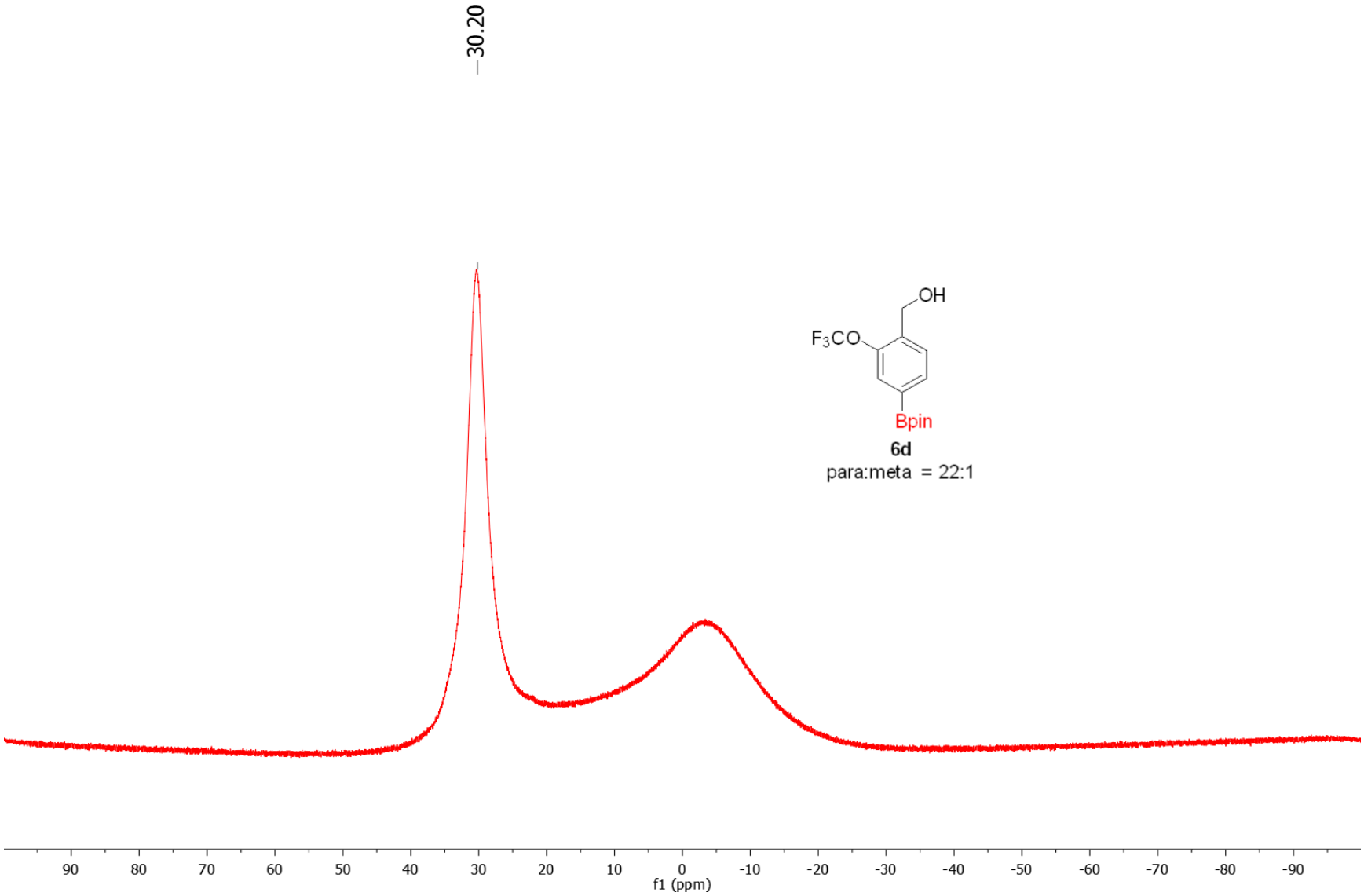
^{1}H NMR spectrum of *para* borylated 2-(trifluoromethoxy)benzyl alcohol (3.6e) (500 MHz, $CDCl_3$)



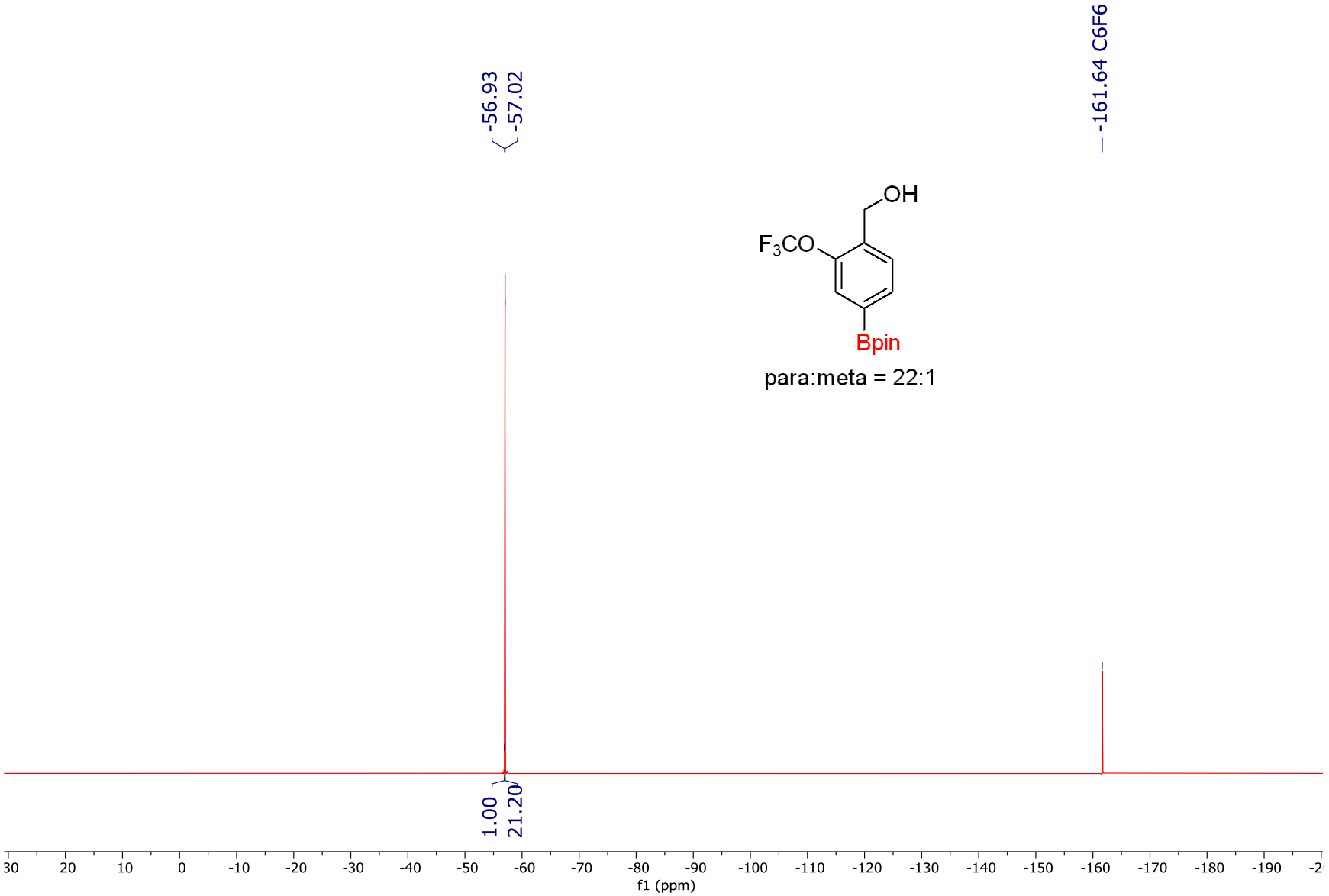
^{13}C NMR spectrum of *para* borylated 2-(trifluoromethoxy)benzyl alcohol (3.6e) (126 MHz, $CDCl_3$)



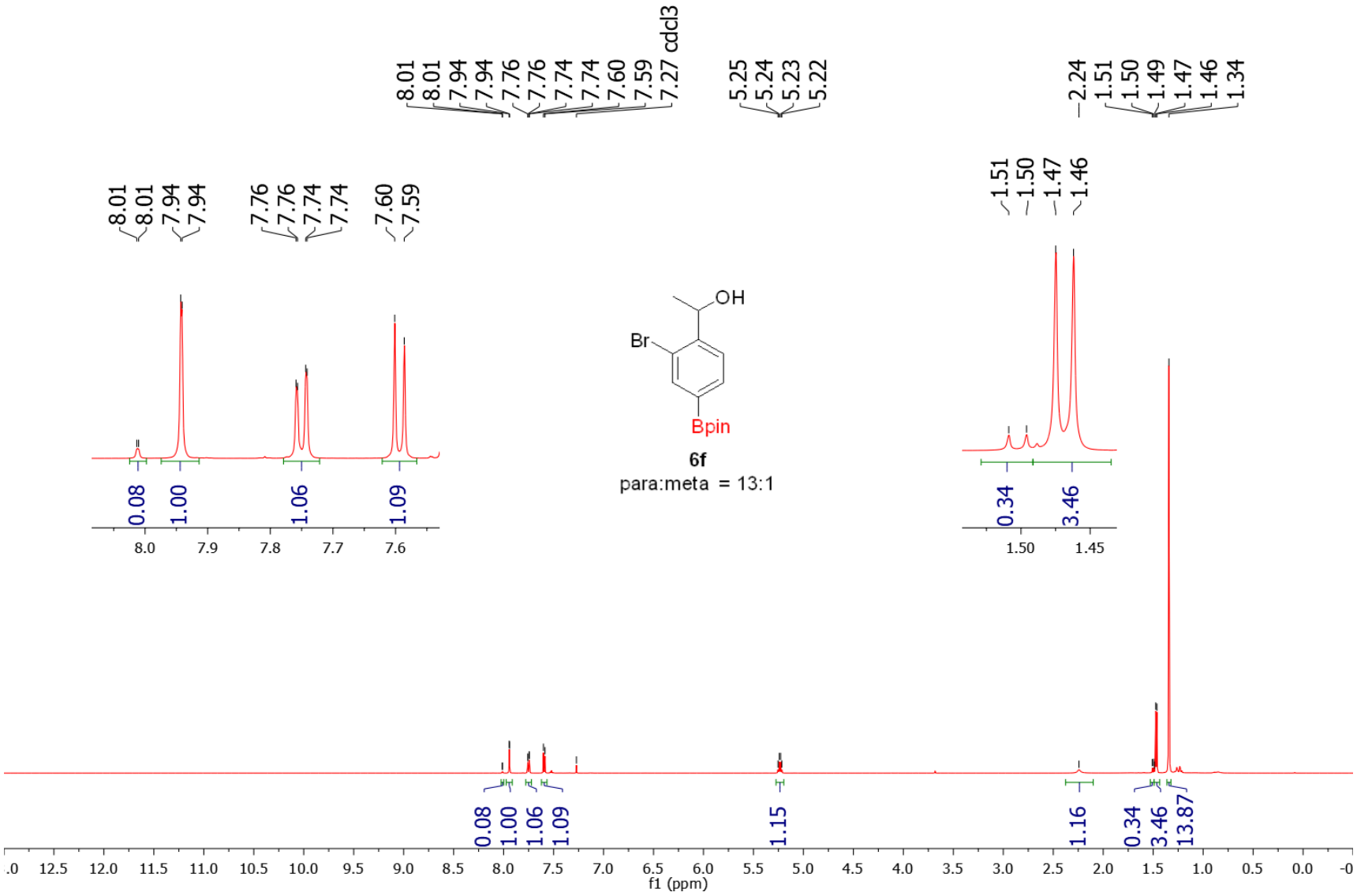
^{11}B NMR spectrum of *para* borylated 2-(trifluoromethoxy)benzyl alcohol (3.6e) (160 MHz, $CDCl_3$)



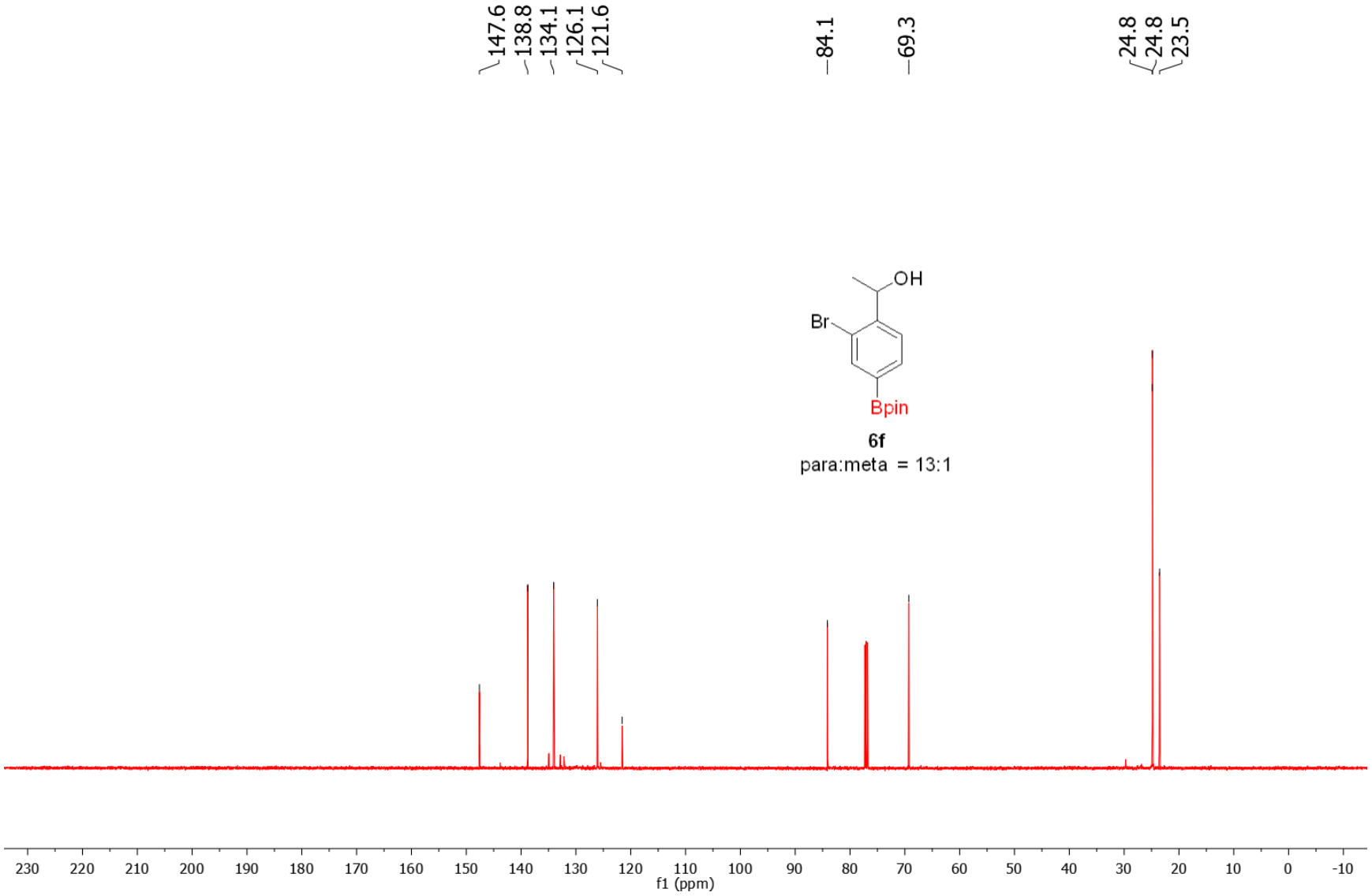
^{19}F NMR spectrum of *para* borylated 2-(trifluoromethoxy)benzyl alcohol (3.6e) (470 MHz, $CDCl_3$)



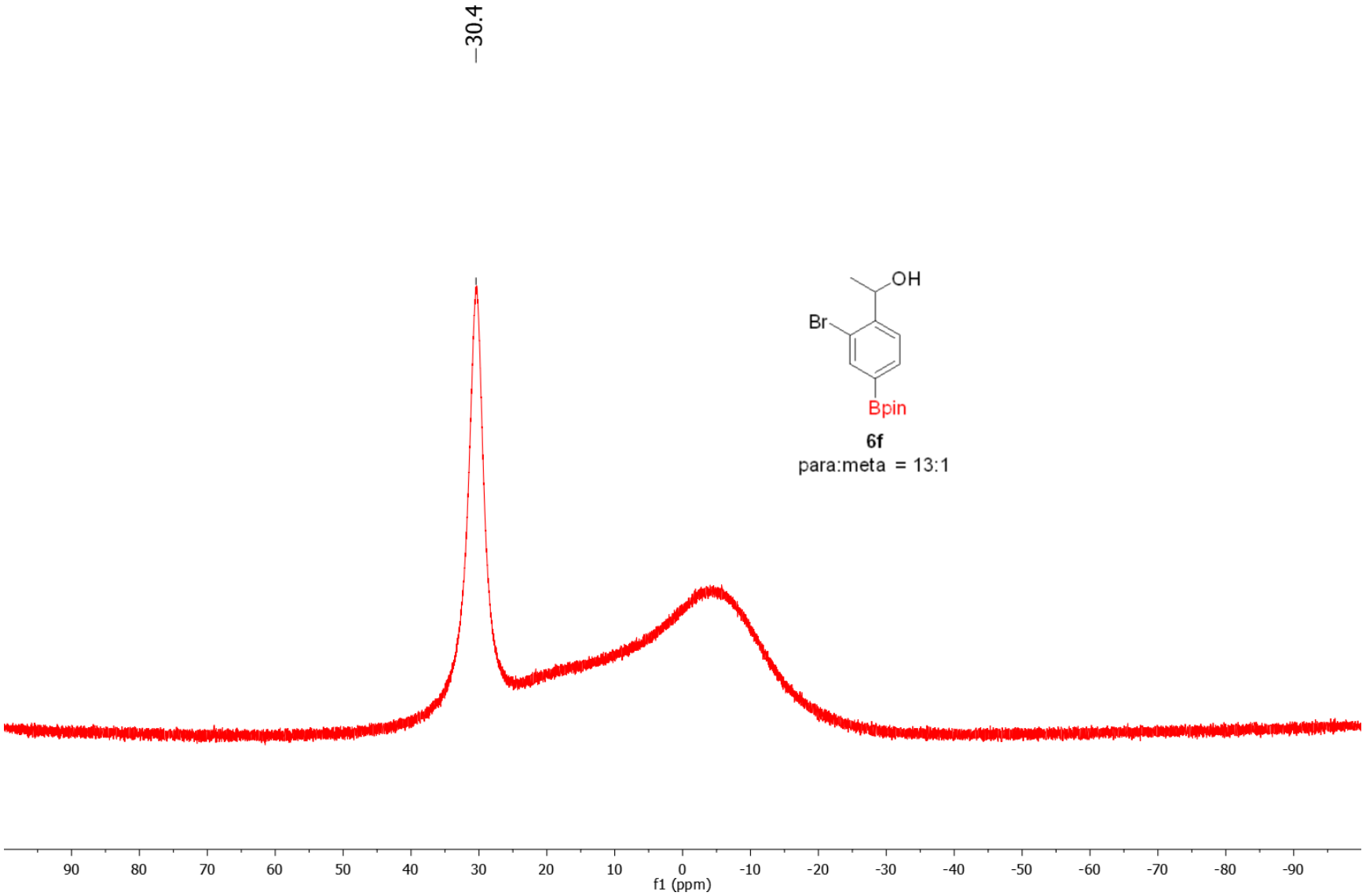
^{1}H NMR spectrum of *para* borylated 1-(2-bromophenyl)ethanol (3.6f) (500 MHz, $CDCl_3$)



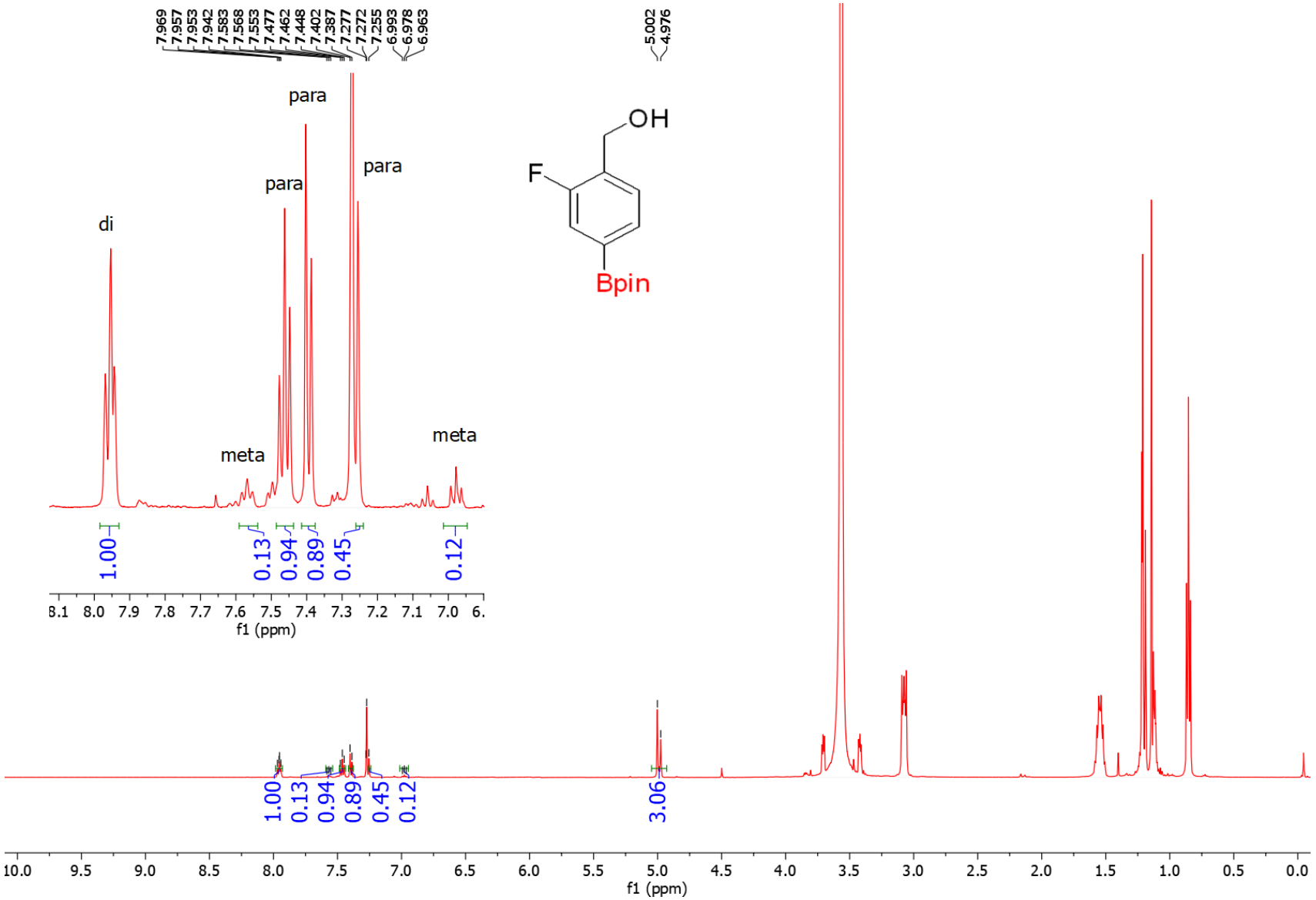
^{13}C NMR spectrum of *para* borylated1-(2-bromophenyl)ethanol (3.6f) (126 MHz, $CDCl_3$)



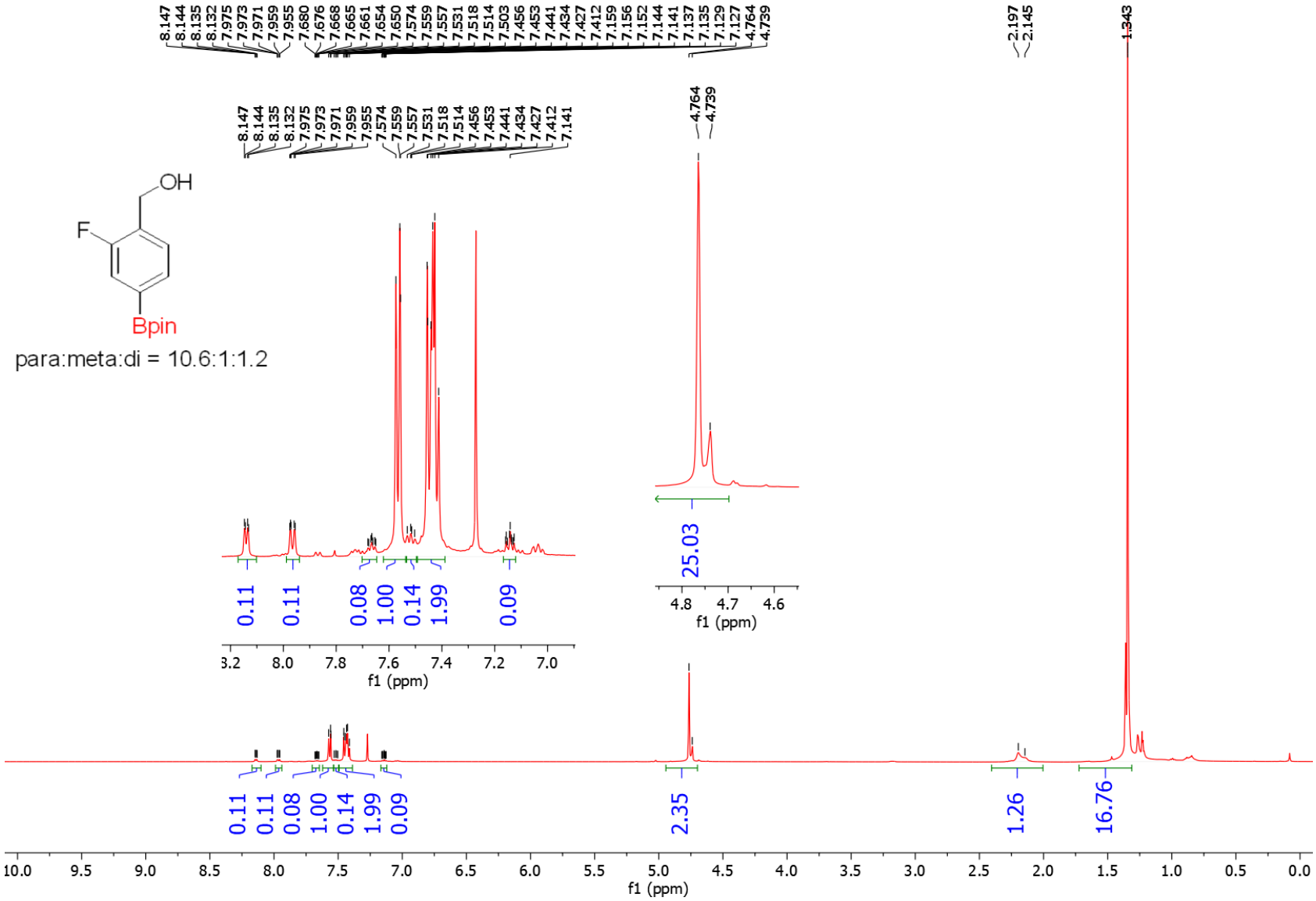
^{11}B NMR spectrum of *para* borylated 1-(2-bromophenyl)ethanol (3.6f) (160 MHz, $CDCl_3$)



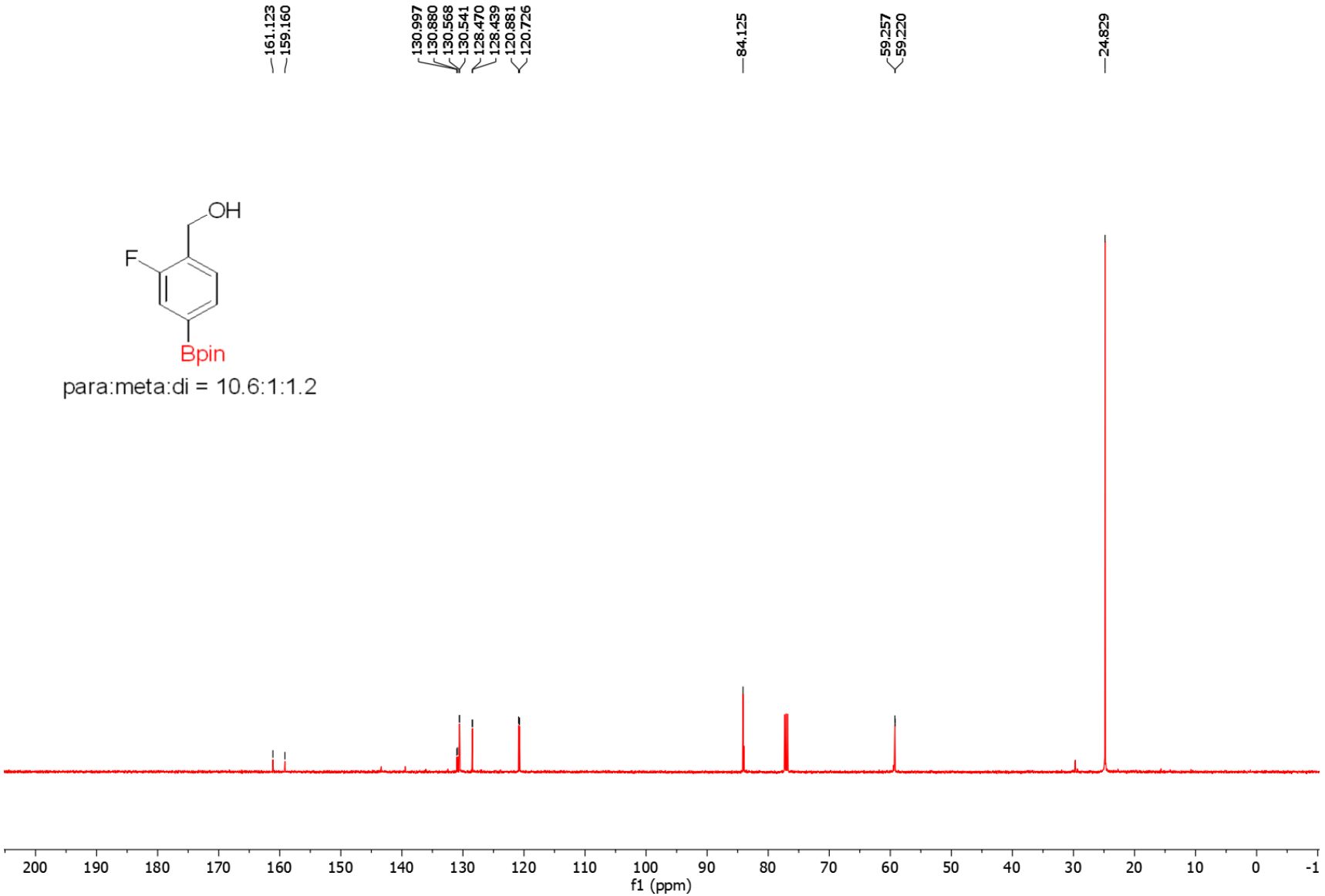
^{1}H NMR spectrum of *para* borylated (2-fluorophenyl)methanol crude reaction mixture (3.6g) (500 MHz, $CDCl_3$)



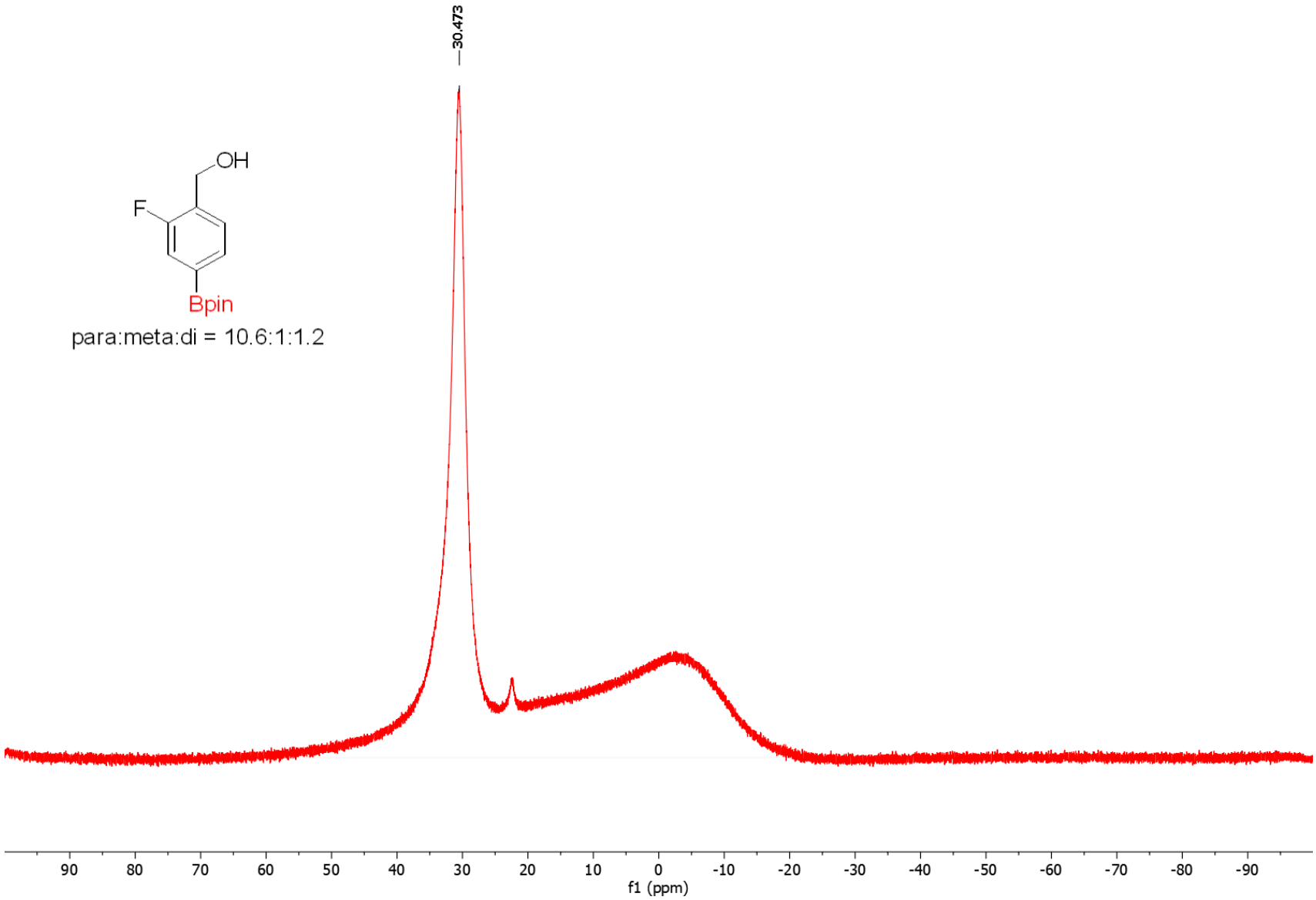
^{1}H NMR spectrum of *para* borylated (2-fluorophenyl)methanol (3.6g) (500 MHz, $CDCl_3$)



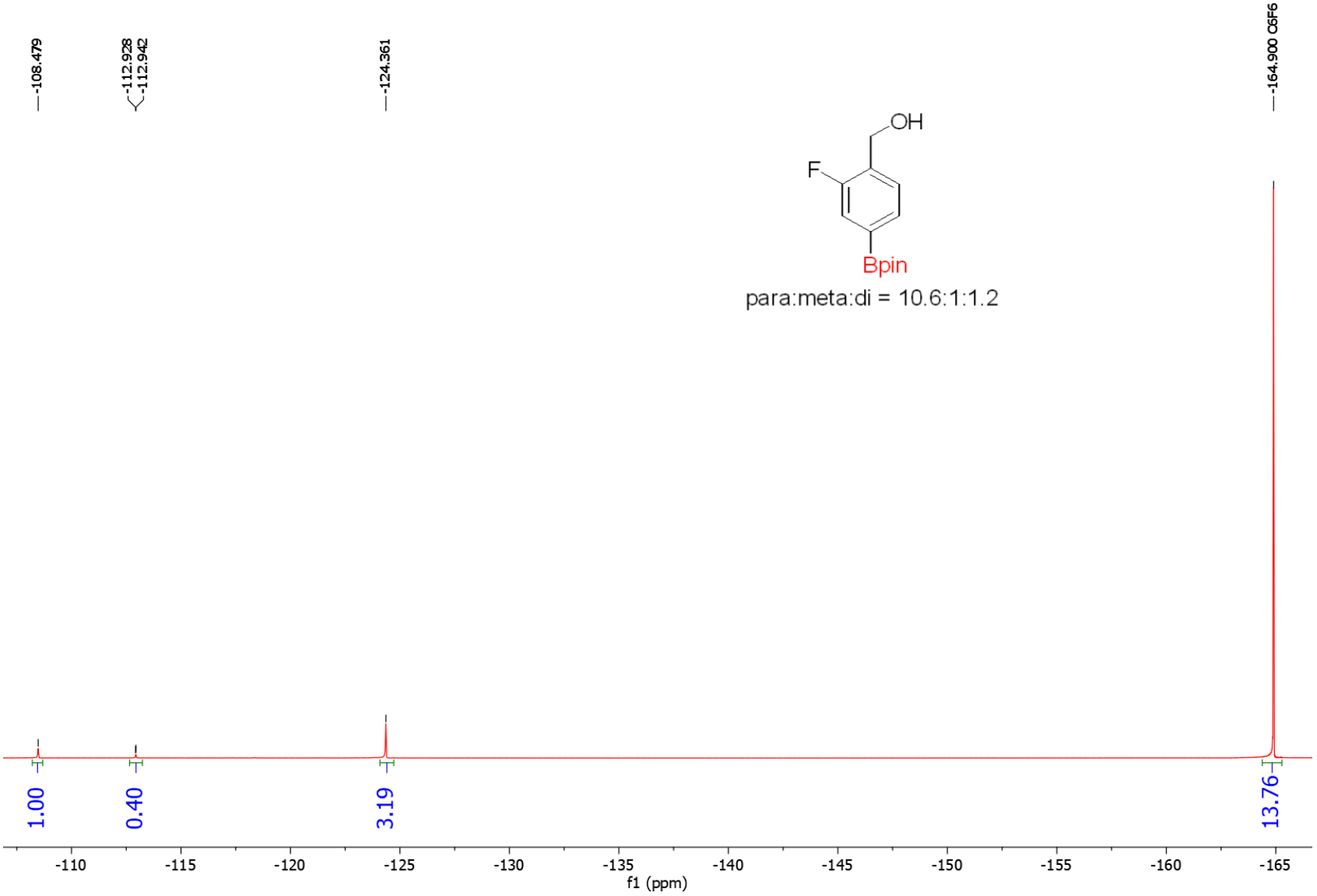
^{13}C NMR spectrum of *para* borylated (2-fluorophenyl)methanol (3.6g) (126 MHz, $CDCl_3$)



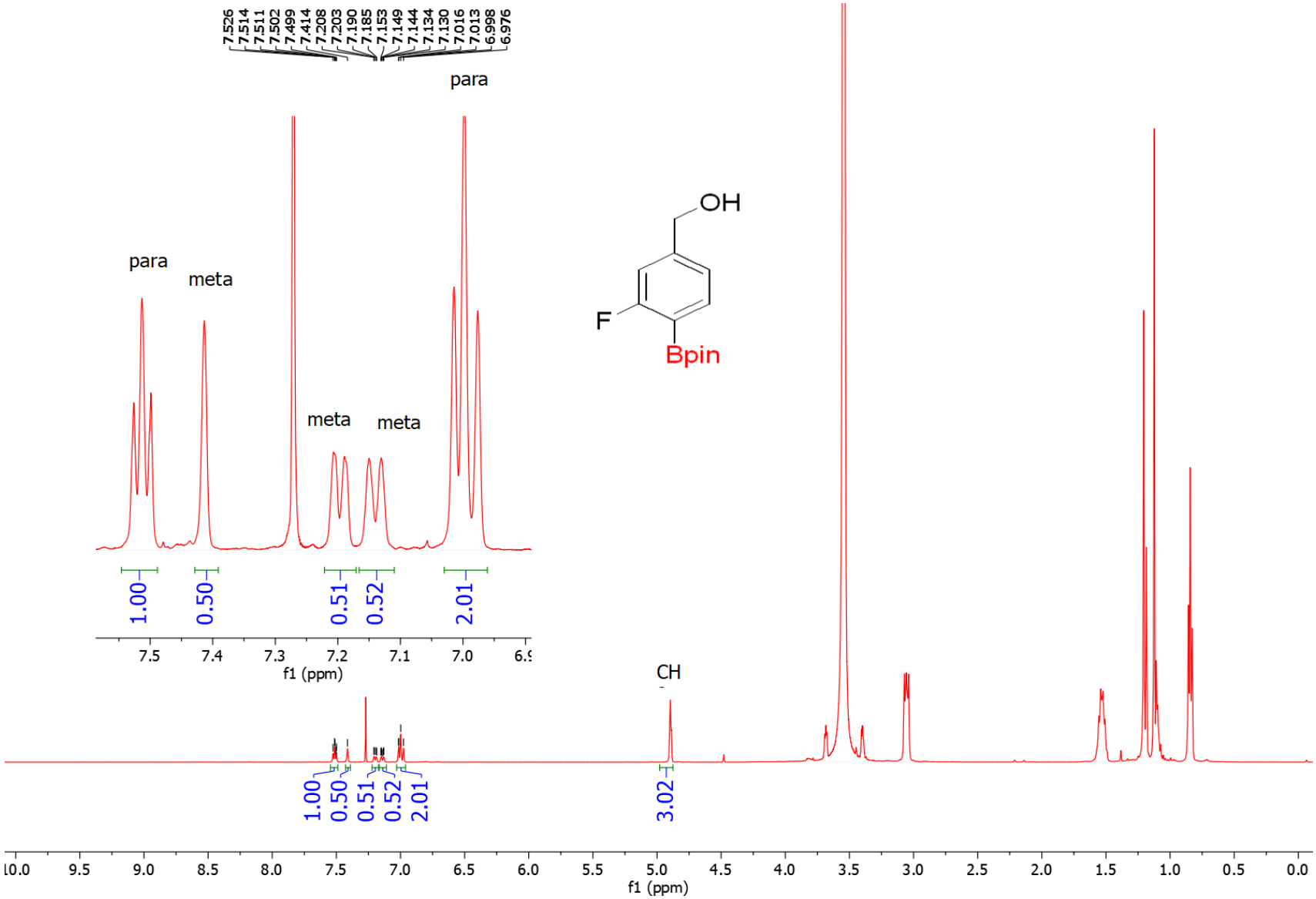
^{11}B NMR spectrum of *para* borylated (2-fluorophenyl)methanol (3.6g) (160 MHz, $CDCl_3$)



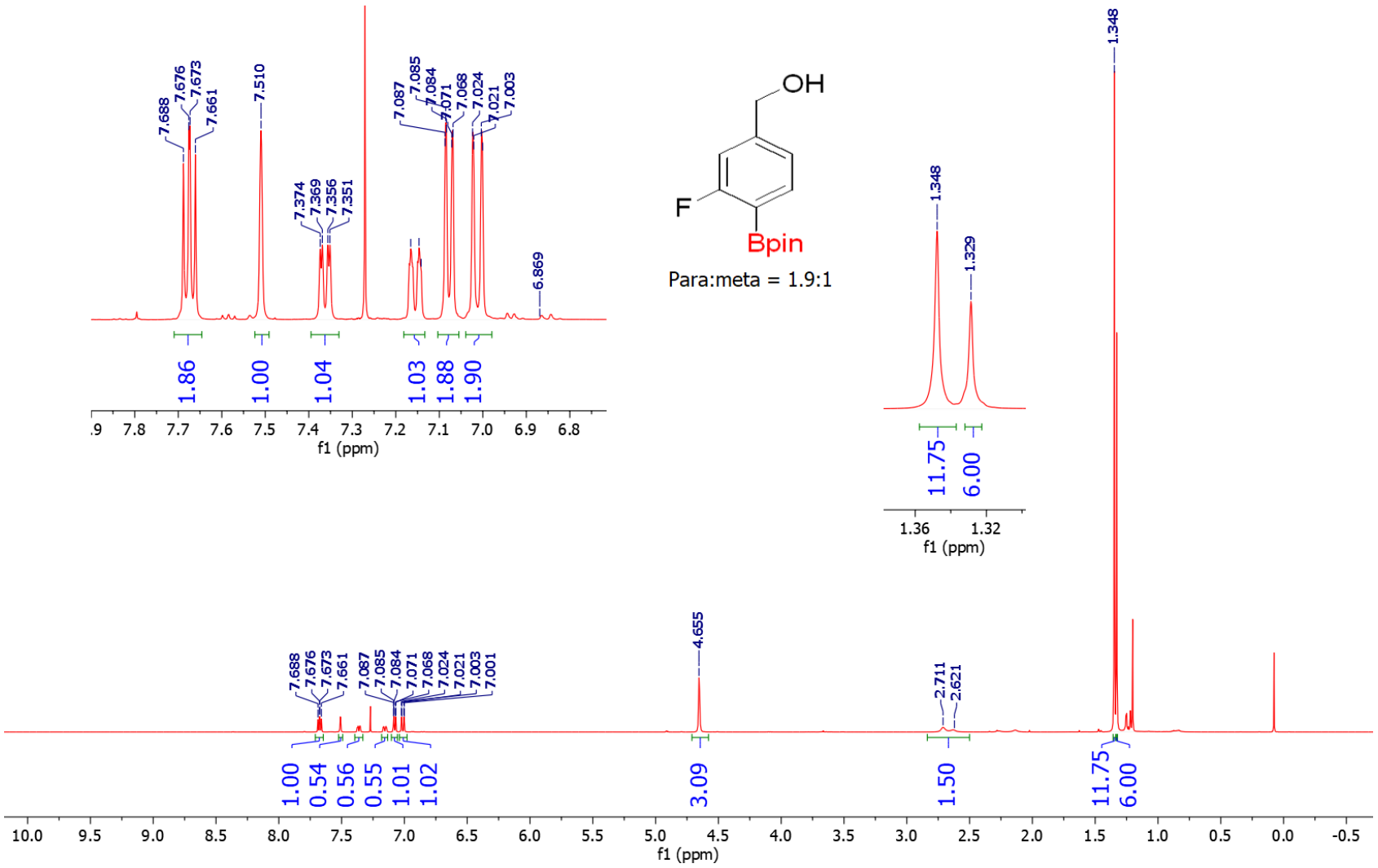
^{19}F NMR spectrum of borylated (2-fluorophenyl)methanol (3.6g) (470 MHz, $CDCl_3$)



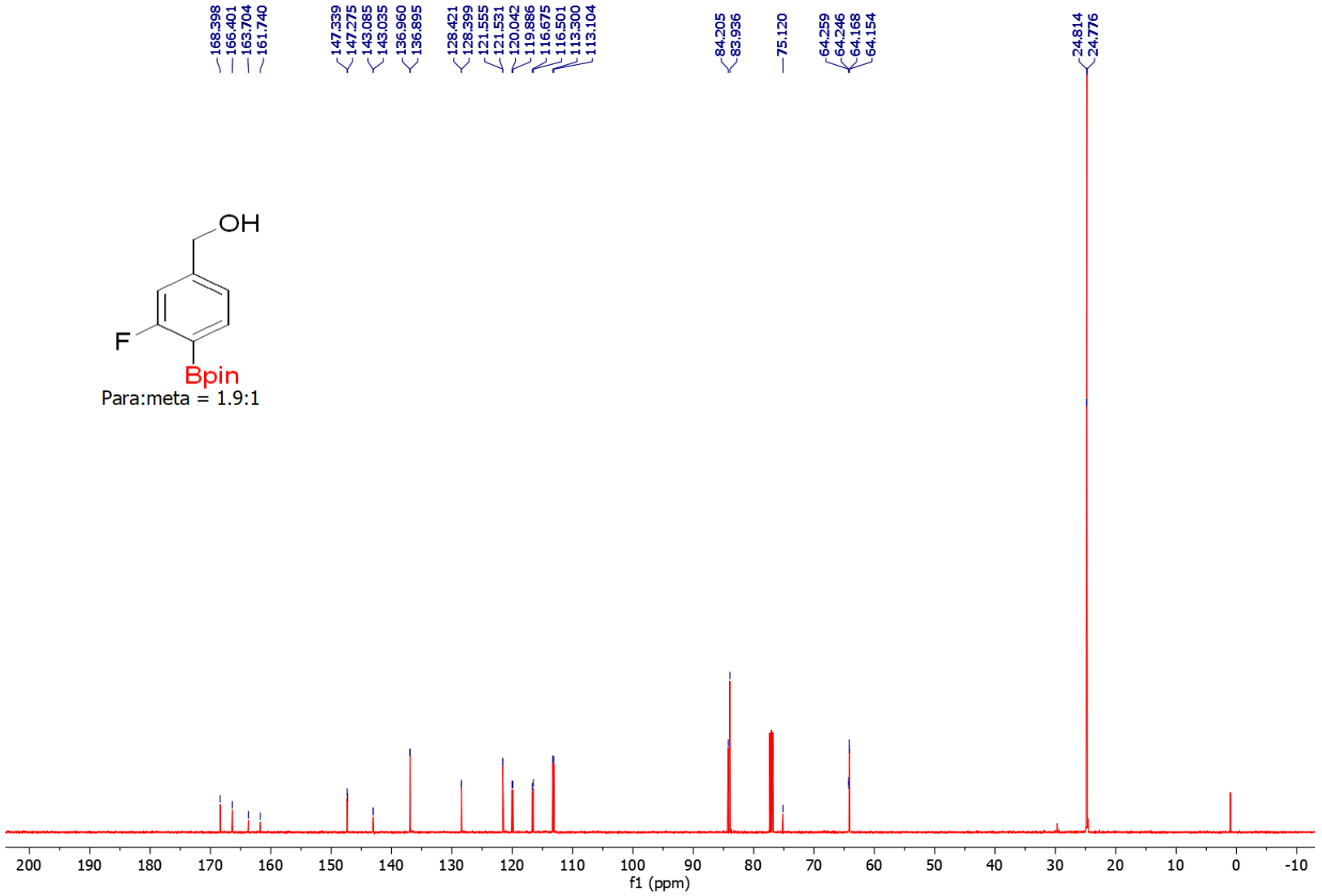
^{1}H NMR spectrum of *para* borylated (3-fluorophenyl)methanol crude reaction mixture (3.6h) (500 MHz, $CDCl_3$)



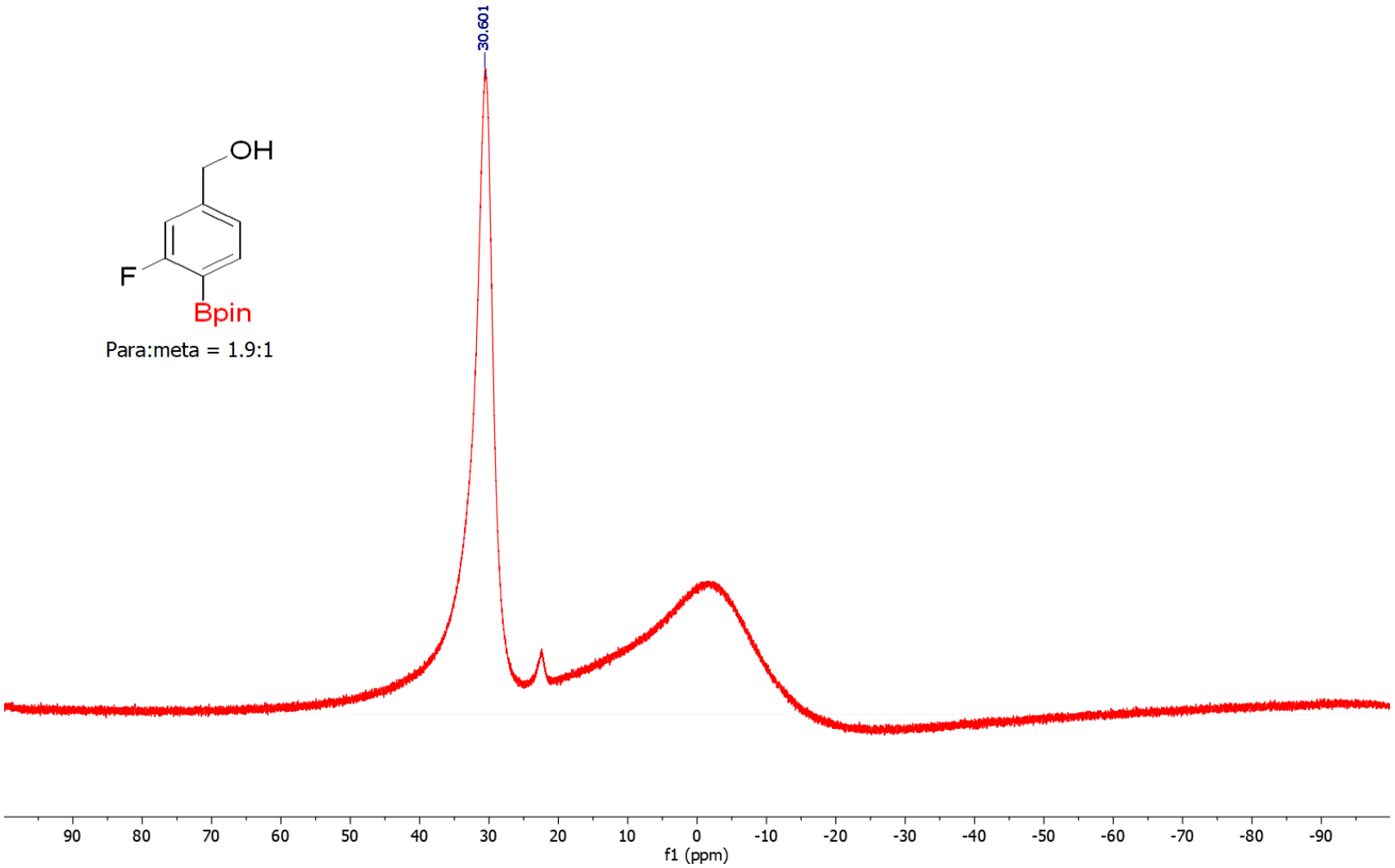
^{1}H NMR spectrum of *para* borylated (3-fluorophenyl)methanol (3.6h) (500 MHz, $CDCl_3$)



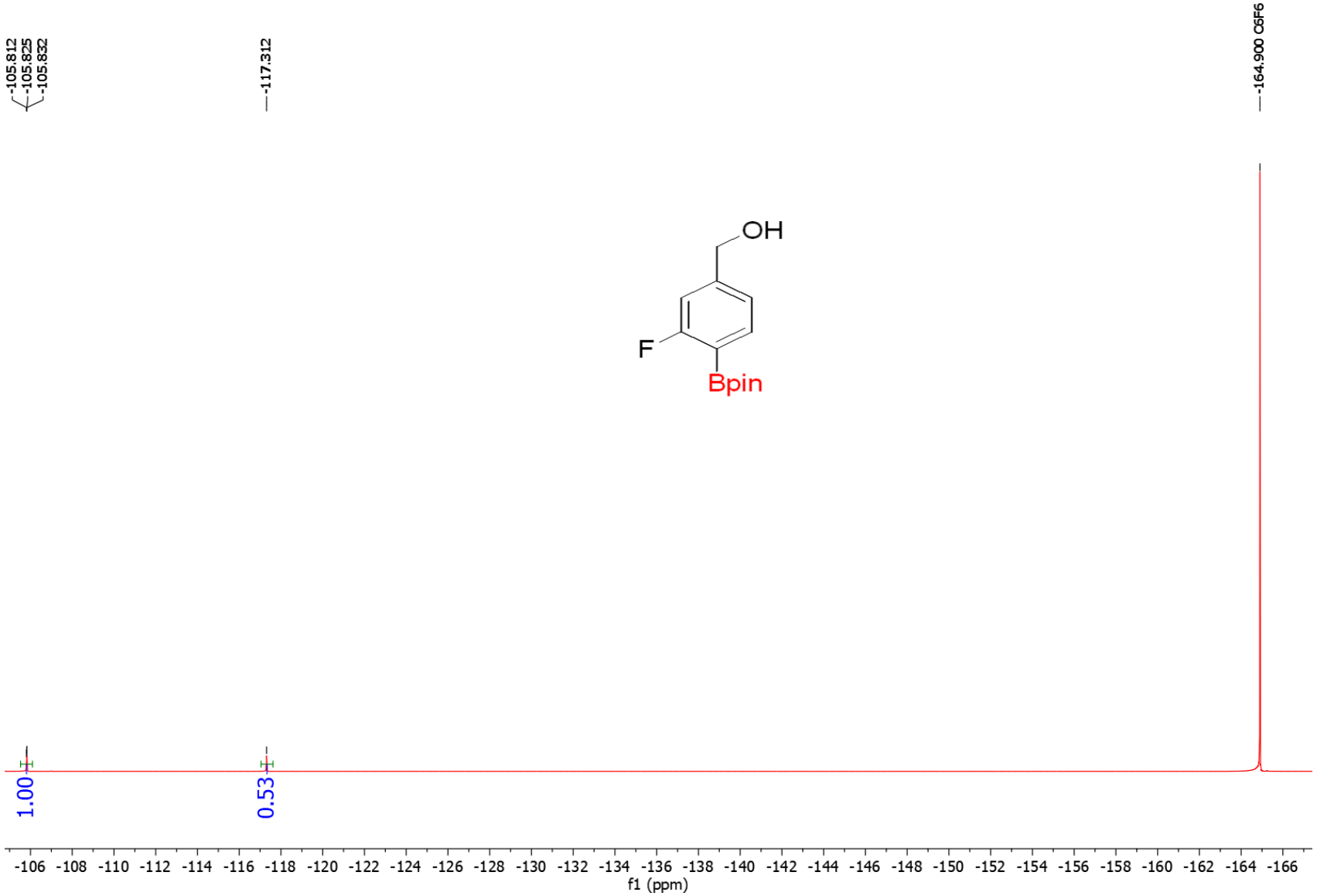
^{13}C NMR spectrum of *para* borylated (3-fluorophenyl)methanol (3.6h) (126 MHz, $CDCl_3$)



^{11}B NMR spectrum of *para* borylated (3-fluorophenyl)methanol (3.6h) (160 MHz, $CDCl_3$)



^{19}F NMR spectrum of borylated (3-fluorophenyl)methanol (3.6h) (470 MHz, $CDCl_3$)



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CHAPTER 4.

STERIC SHIELDING EFFECTS INDUCED BY INTRAMOLECULAR C–H•••O HYDROGEN BONDING: REMOTE BORYLATION DIRECTED BY BPIN GROUPS

4.1. Introduction

Nowadays, C–H bonds can be diversified via different C–H functionalization methods. Yet, targeting one C–H reactive site in the presence of like C–H bonds remains challenging.[1,2] Although considered weak, noncovalent interactions can differentiate the energetics of otherwise similar reactive sites. In the area of sp^2 C–H activation, pre-installed directing groups can interact with the catalyst via hydrogen bonding, Lewis acid-base or electrostatic interactions to selective functionalize the *ortho*, *meta* or *para* position.[3–9] Nonetheless, selective reactions at distal C–H sites often require construction of long and complex directing groups/ligands.[7–11] A different strategy uses steric shields to block nearby C–H bonds thus leaving the distal position as the only viable reactive site. For instance, Nakao's group used Lewis acidic additives that interact with aryl amides to shield the *meta* position and thereby afford selective *para* functionalization.[12–15] The complementary approach where intramolecular noncovalent interactions create steric shields leading to remote functionalization is far less common.

Iridium catalyzed C–H borylation (CHB) is currently a standard protocol to make aryl boronic esters.[16–18] In the last decade, *ortho* regioselective sp^2 CHB has been achieved by means of chelating and relay directing groups as well as outer sphere interactions.[4,7,19] In 2013, our group reported that *meta* and *para* substituted anilines yield the corresponding *ortho* borylated product courtesy of an N–H hydrogen bonding with the catalyst.[20] Unexpectedly, 2-methoxyaniline gave selectively the *para* borylated aniline. A similar result was reported by the Phipps group during their CHB of 2-chloroaniline (**Figure 4.1a**).[21] It was proposed that electronic effects might play a

role in the change of selectivity for 2-chloro and 2-methoxyaniline, but no experiments were done to corroborate this hypothesis.

More recently, we and the Phipps group independently developed a protocol for *para* CHB of anilines directed by ion-pair electrostatic interactions of sulfamates with bulky tetraalkylammonium counterions (**Figure 4.1b**).[21,22] Here the selectivity is presumably the result of a steric shield created when one of the alkyl chains in the cation orientates toward the aromatic ring blocking the *meta* position and leaving the *para* exposed to CHB. We wondered if a different sort of steric shielding might be playing a role as well in the *para* CHB of 2-methoxy and 2-chloroaniline mentioned above.

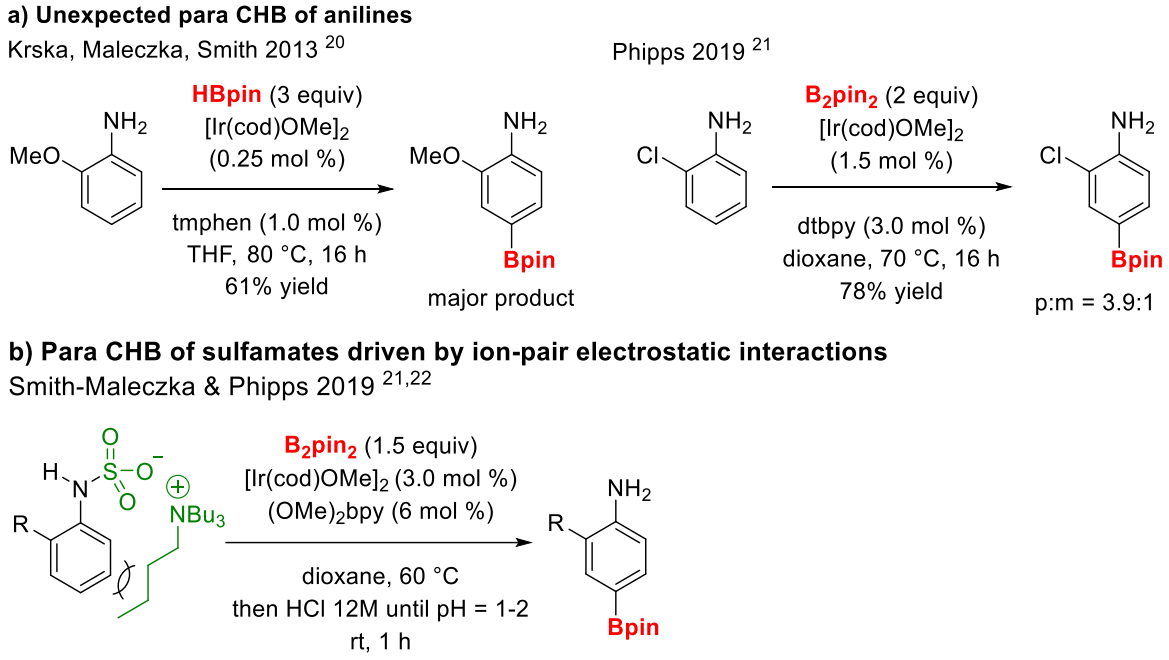


Figure 4.1: a) Unexpected *para* CHB of anilines (only reported compounds), b) Previously reported *para* CHB of anilines driven by ion-pair electrostatic interactions

It is well documented that N-borylation of N-unsubstituted anilines occurs rapidly under CHB conditions.[20] We hypothesized that in the presence of an *ortho* substituent like methoxy or chloro, the N–Bpin group could orientate towards the *meta* C–H where it would act as a steric shield and lead to a *para* selective CHB (**Figure 4.2**). Bpin is an attractive steric shield for N-

unsubstituted anilines since it is installed *in situ* and its removal occurs upon work-up with methanol. This contrasts with our previous approach to access *para* borylated anilines, which required a step to install the sulfamate group and where highly acidic conditions were needed for its removal.

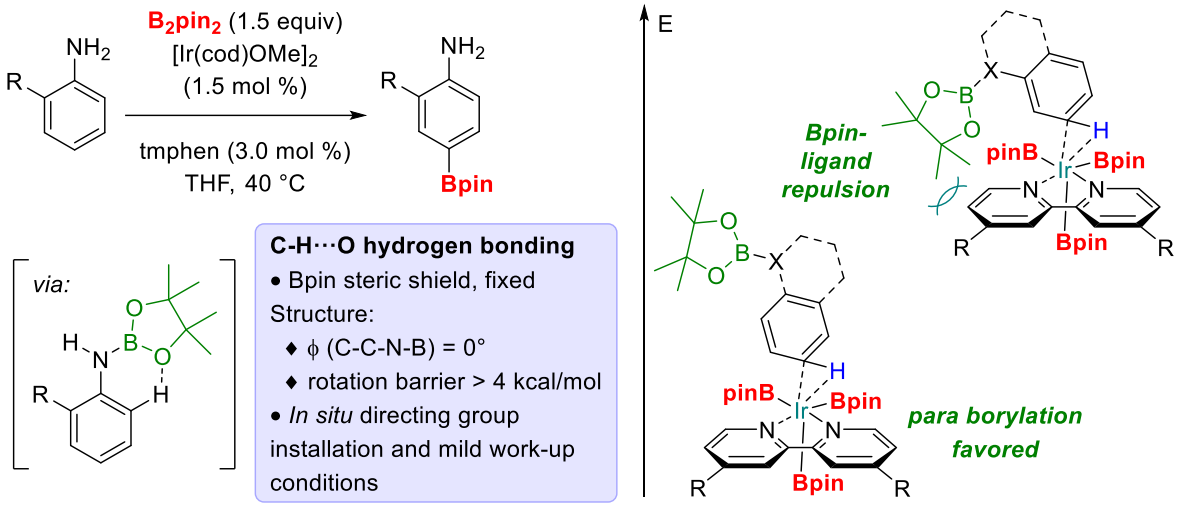


Figure 4.2: This approach: remote CHB driven by intramolecular hydrogen bonding

4.2. RESULTS AND DISCUSSION

4.2.1. *Para* C–H borylation of anilines, N-alkylated anilines and indoles.

4.2.1.1. Optimization of Conditions

We set out examine a *para* selectivity by virtue of a Bpin steric shield was a general phenomenon. To do so, we first looked to optimize the reaction on 2-chloroaniline. Starting with our previously reported conditions, we compared the regioselectivity when B_2pin_2 was used in place of HBpin and found that the former yielded an improved *para* to *meta* ratio. With B_2pin_2 as the new boron partner we compared the effects of temperature and solvent (**Figure 4.3**). Cyclohexane gave higher selectivity especially at lower temperatures, but conversion dropped relative to THF. The best balance between reactivity and selectivity was found with THF at 40 ºC. After 4 h, the conversion was 61% and >90% after 24 h.

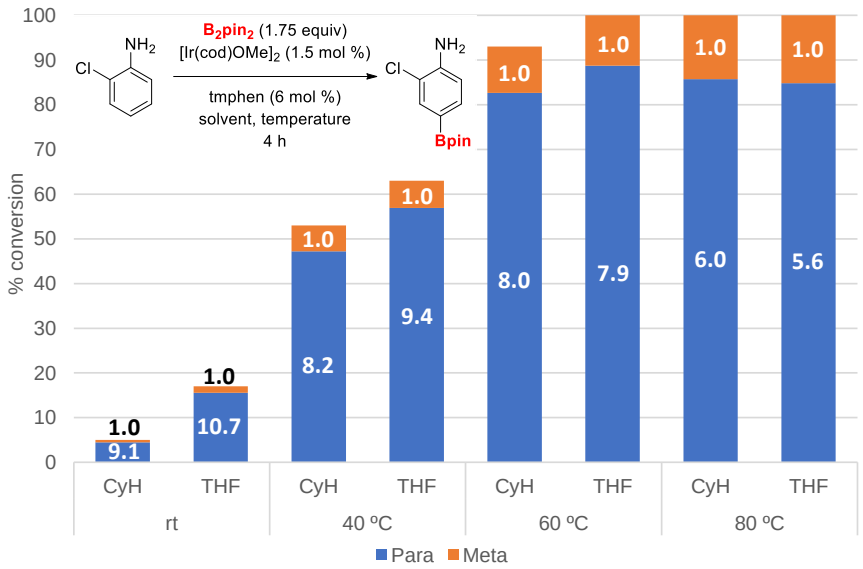
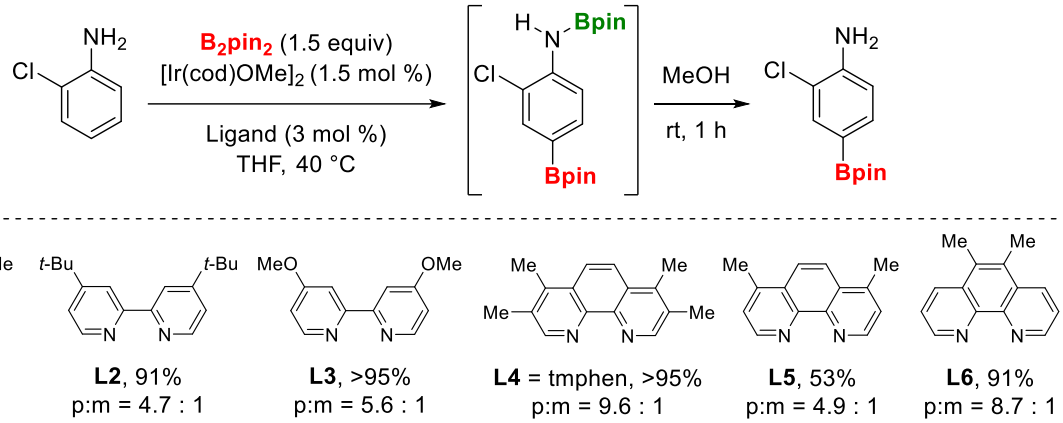


Figure 4.3: Temperature and solvent effect on *para* CHB of 2-chloroaniline. Blue and orange bars represent conversion to the *para* and *meta* isomer, respectively. CyH: cyclohexane, THF: tetrahydrofuran

With these conditions in hand, we evaluated the effect of the ligand and the diboron partner (**Scheme 4.1**). Bipyridine ligands (**L1**–**L3**) gave modest *para*/*meta* ratios (~5:1). Notably, 4,4'-dimethoxy-2,2'-bipyridine (**L3**), which was optimal in our previous *para* directed CHB of sulfamate salts, did not prove superior in this scenario. Selectivity with ligand **L5** was similar, but yield suffered.

Scheme 4.1: Ligand effect on the selectivity of the *para* CHB of 2-chloroaniline [a]



L1, >95%
p:m = 5.4 : 1

L2, 91%
p:m = 4.7 : 1

L3, >95%
p:m = 5.6 : 1

L4 = tmphen, >95%
p:m = 9.6 : 1

L5, 53%
p:m = 4.9 : 1

L6, 91%
p:m = 8.7 : 1

[a] The *para* to *meta* ratio (p:m) and conversions were calculated by ^{1}H NMR from the crude reaction mixture.

In contrast, the *para*/*meta* ratio doubled with phenanthrolines **L4** and **L6**, while yield remained high. We choose tmphen (**L4**) to continue our studies due to it being slightly better than **L6** in terms of regioselectivity and yield.

4.2.1.2. *Para* CHB of anilines

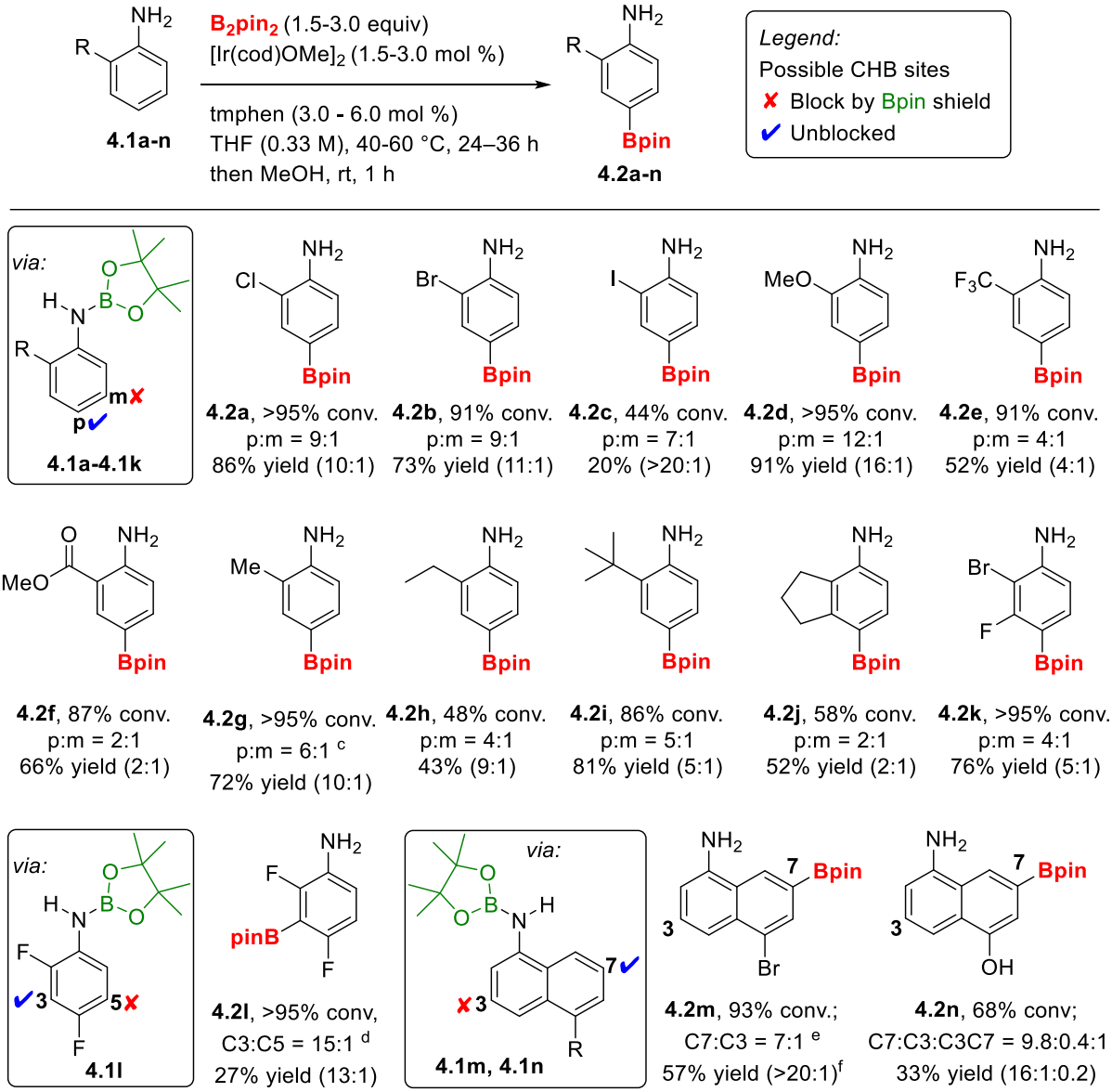
With these conditions in hand, we evaluated the *para* borylation of different anilines (**Scheme 4.2**). *Ortho* substituents with free electron pairs (**4.2a**–**4.2d**) favored *para* borylated with > 7:1 selectivity. Similar electronic effects in CHB have been observed when there is a small steric difference between two reactive sites.[12,21–25] In contrast, **4.2e** with a trifluoromethyl ortho substituent saw selectivity drop to 4:1. Benzoate **4.2f** with an electron withdrawing group by resonance gave an even lower ratio of 2 to 1 *para* to *meta*. This is result bears some relationship to previous reports of ester groups favoring *para* CHB; in our case that position is *meta* respect to the aniline nitrogen.[24,26]

The size of alkyl *ortho* substituents (**4.2g**–**4.2i**) showed little effect, as *para* to *meta* ratios only ranged from 4:1 to 6:1. It should be noted that the 6:1 observed for 2-methylaniline (**2g**) was achieved by forming the N-Bpin bond prior to the CHB. This suggests that N-Bpin formation is slow in this case. The Bpin steric shield even overcame the steric presence of a fused cyclopentyl and fluoro substituents as substrates **4.2j** and **4.2k** favored *para* borylation albeit slightly. This was not great surprise as borylation next to these groups have been previously observed as minor products; the major regioisomers being those from CHB of the more accessible position.[17,23,25,27–30]

As stated above, fluorine atoms are relatively small and CHB next to them is observed. CHB of 2,4-difluoroaniline (**4.1l**) presented a more interesting scenario. In this case, were the N–Bpin orientated away from the *ortho* fluorine, the resultant steric shield would block the 5-position

leaving the 3-borylation as the only option. This was the result as C3 borylation occurred with a 15:1 preference over C5 borylation.

Scheme 4.2: *Para* CHB of anilines driven by a N–Bpin steric shield [a,b]



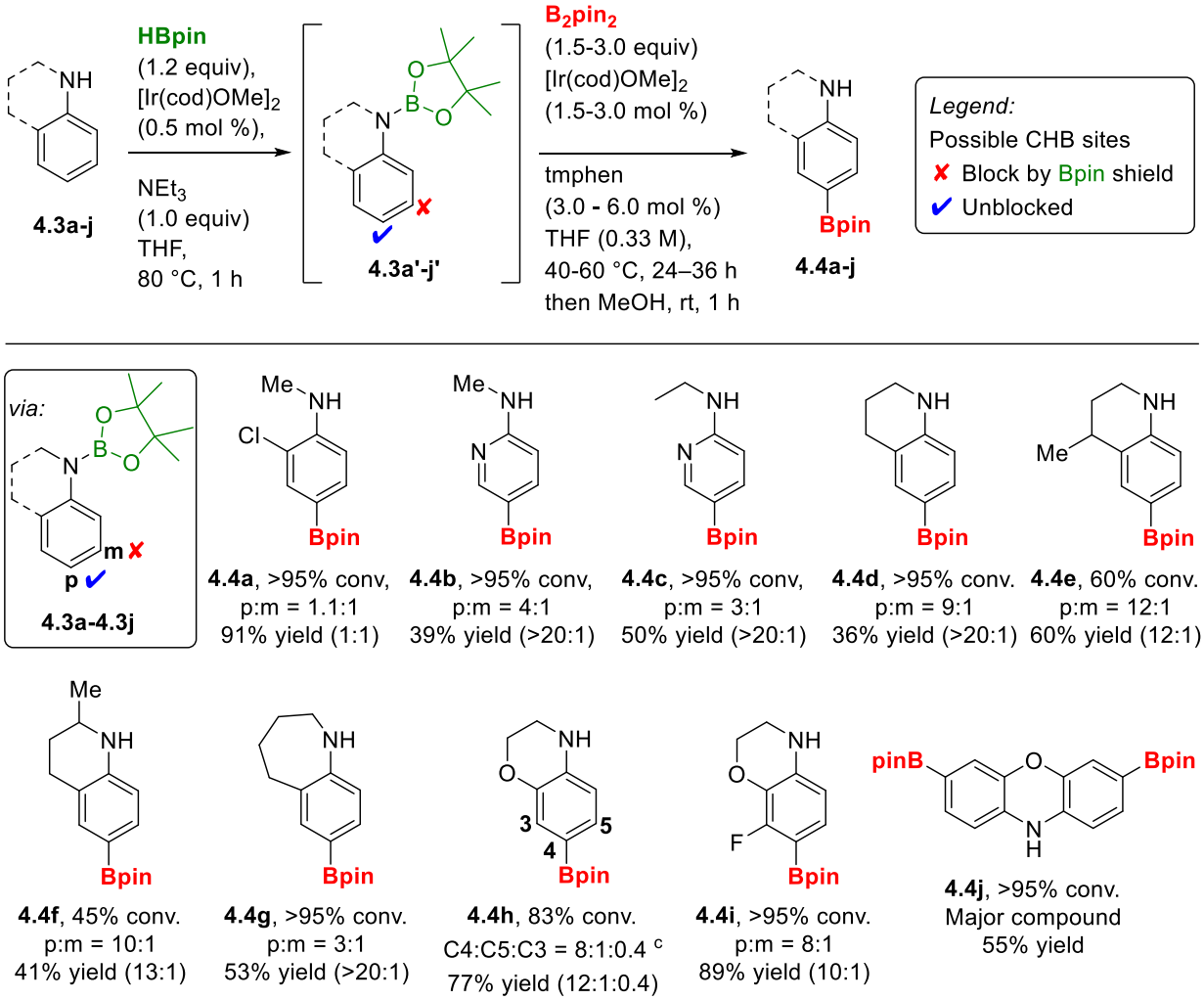
[a] Conversions and regioselectivities were measured by 1H NMR on crude reaction mixtures. Yields refer to isolated material with the ratio of major to minor products in the isolated material given in parentheses. [b] **p** and **m** refer to *para* and *meta* product, respectively. [c] N–Bpin bond formed prior to CHB with HBpin (1.2 equiv), [Ir(cod)OMe]2 (0.5 mol %), THF, 80 °C, 2h; under standard condition (A) the results are 61% conv.; **p**:**m** = 4:1 with 47% yield (>20:1) [d] **C3** and **C5** refer to 3- and 5- borylated product, respectively. [e] **C3** and **C7** refer to 3- and 7- borylated product respectively and **C3C7** refers to the 3,7-diborylated product. [f] regioselectivity confirm by x-ray crystallography.

To probe other substrates with substituents at the *ortho* and *para* C–H positions, we examined the CHB of N-borylated 5-substitued 1-naphthyl amines **4.1m** and **4.1n**. In these substrates, C4, C6, and C8 would be blocked from CHB by substituents, leaving only C3 and C7 sterically unencumbered. However, were our hypothesis correct, the N-Bpin would sterically shield C3, thus favoring C7 in a CHB. Indeed, borylation of **4.1m** and **4.1n** yield their 7-borylated product selectively (C7/C3 7:1 and 10:1 respectively). In the case of **4.1n**, a small amount of diborylation was observed.

4.2.1.3. *Para* CHB of N-alkylated anilines

We next turned our attention to other *in situ* borylated scaffolds, namely N-alkylated anilines. Unfortunately, CHB of 2-chloro-N-methylaniline **4.3a** was not *para* selective under the optimized conditions (**Scheme 4.3**). A slow rate of N–Bpin formation could explain the lack of selectivity. However, even after preformation of the N–Bpin bond no selectivity was observed. Thus, we considered other explanations. This led us to propose that a reluctance of N-borylated **4.3a** to orientate in the same plane as the aromatic ring, which per our hypothesis creates the N–Bpin steric shield, is responsible for the observed regiochemical result. Such a hypothesized planar conformation is supported by modeling the lowest energy conformation of N-borylated intermediates of N-unsubstituted anilines (see **Section 2.3** and **Figure 4.6** for further discussion). In contrast, N-borylated 2-chloro-N-methyl aniline does not adopt a planar conformation (see **Section 2.3** and **Figure 4.9** for details) owing to a $A_{(1,3)}$ interaction between the N-methyl with the *ortho* chlorine. As N-borylated N-alkyl-2-aminopyridines should lack this steric clash, **4.3b** and **4.3c** should be *para* selective. This proved to be the case with **4.4b** and **4.4c** both being the major (4:1) CHB products.

Scheme 4.3: *Para* CHB of alkylated anilines driven by a N–Bpin steric shield [a,b]



[a] Conversions and regioselectivities were measured by ^{1}H NMR on crude reaction mixtures. Yields refer to isolated material with the ratio of major to minor products in the isolated material given in parentheses. [b] **p** and **m** refer to *para* and *meta* product, respectively. [c] **C3, C4** and **C5** refer to 3-, 4- and 5- borylated product, respectively.

1,2,3,4-Tetrahydroquinolines also drew our attention as in these N-alkylated anilines the covalent chain that links the aromatic ring with the nitrogen should allow the N-borylated intermediate to achieve a pseudo planar conformation (**Scheme 4.3**). *Para* products **4.4d**–**4.4j** were obtained as the major regioisomer from their corresponding 1,2,3,4-tetrahydroquinolines. The size of the saturated ring does influence the level of selectivity, as illustrated in **4.4g** where the selectivity was only 2:1. Adding a methyl group about the saturated ring did not significantly

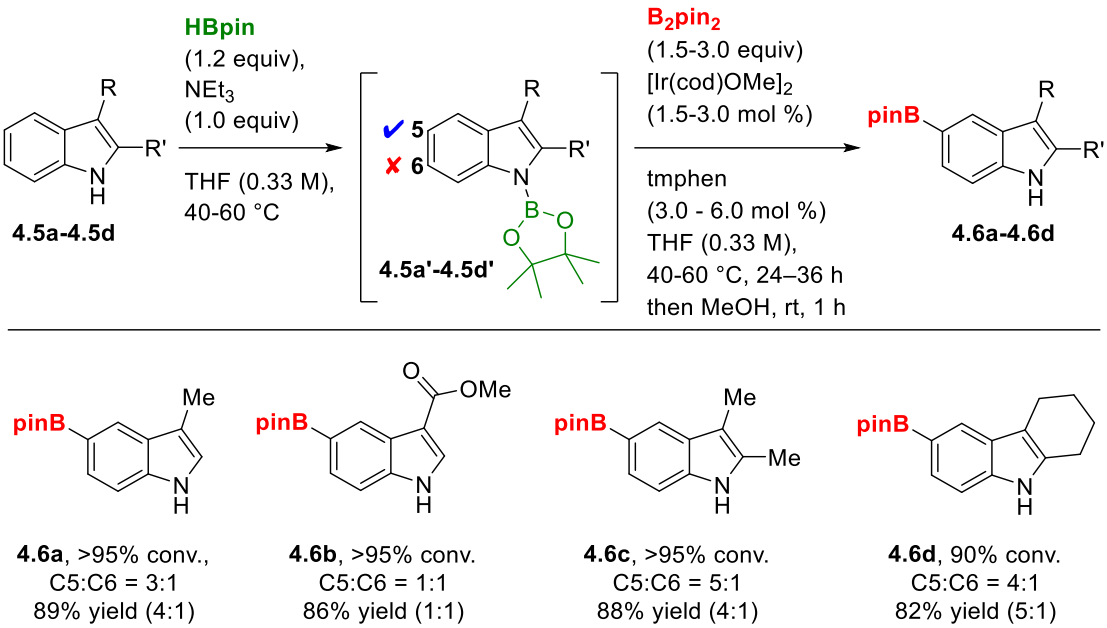
change the selectivity as show by products **4.4d**–**4.4f**. With **4.3h**, borylation next to the oxygen was also observed, but the *para* product still predominated (8:1). The fluorinate version of **4.3h**, namely **4.3i**, was equally selective. Diborylation of phenoxazine **4.3j** mainly yielded the bis *para* compound along with multiple minor products.

4.2.1.4. C5 CHB of Indoles

N-Borylation of indoles is known to block the C2 CHB normally seen in the parent compounds, instead yielding the corresponding 3-borylated product.[20] We asked if in an N-borylated 3-subsitued indole, the N–Bpin would shield the closer C6 position leading to the corresponding 5-borylated indoles. C5 borylation of indoles has been elusive besides some specific examples employing electrophilic borylation with borenium cations. The examples are limited to N-methyl carbazole or are trigger by the use of an amine pivaloate directing group at the 4 position.[31,32] A protocol to access 3,5-diborylated indoles has been reported but suffers from low conversions (< 30%).[33]

Under our optimized conditions and after formation of the N–Bpin intermediate, 3-methylindole **4.5a** yielded the 5-borylated with a modest 3:1 selectivity over the minor 5-borylated isomer (**Scheme 4.4**). Replacement of the methyl group by a methyl ester as in **4.5b** resulted in the loss of selectivity. However, the presence of substituents at both C2 and C3 impacted selectivity little as shown in **4.6c** and **4.6d**. It should be stated that for **4.5c** and **4.5d**, formation of the N–Bpin intermediate is slow and additional HBpin and $[Ir(cod)OMe]_2$ as well as a 3-hour reaction time was needed to afford full N-borylation.

Scheme 4.4: C5-CHB of 3-substitued indoles driven by a N–Bpin steric shield [a,b]



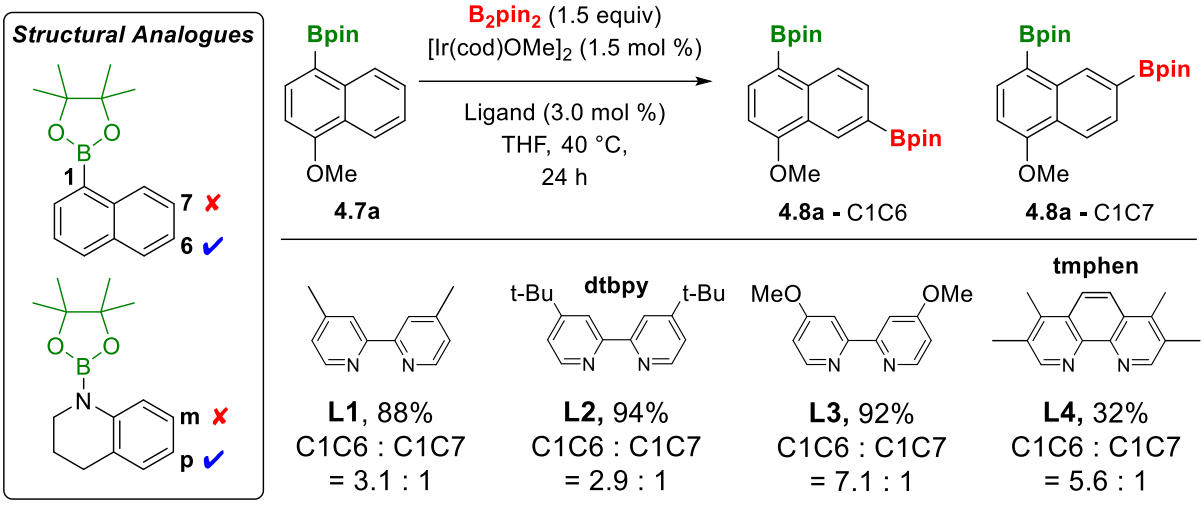
[a] Conversions and regioselectivities were measured by ^{1}H NMR on crude reaction mixtures. Yields refer to isolated material with the ratio of major to minor products in the isolated material given in parentheses. [b] **C5** and **C6** refer to 5- and 6- borylated product, respectively.

4.2.2. C6 borylation of 1-borylated naphthalenes.

4.2.2.1. Borylations

We speculated that Bpin groups can create a steric shield even when not part of a N–Bpin moiety. We thus focused on 1-borylated naphthalenes, which could bear geometries similar to those of N-borylated 2-substitued anilines and N-borylated tetrahydroquinolines (**Scheme 4.5**). If so, the Bpin derived steric shield would block the C7-position leaving the C6-position available for CHB. Borylation of 1-borylated naphthalene **4.7a** supported our proposition and yielded the 1,6-diborylated product selectively. A ligand screening showed that 4,4'-dimethoxy-2,2'-bypiridine (**L3**) was the best choice for the C6-borylation of 1-borylated naphthalenes. This result is potentially valuable as C6 functionalization of naphthalenes remains rare.[34] A notable exception, comes from Nakao's group where a 1-naphtyl amide was made to undergo C6-alkylation by using an aluminum Lewis acid as a steric shield.[13,14]

Scheme 4.5: Ligand effect on the selectivity of the C6 CHB of 1-borylated naphthalenes[a]

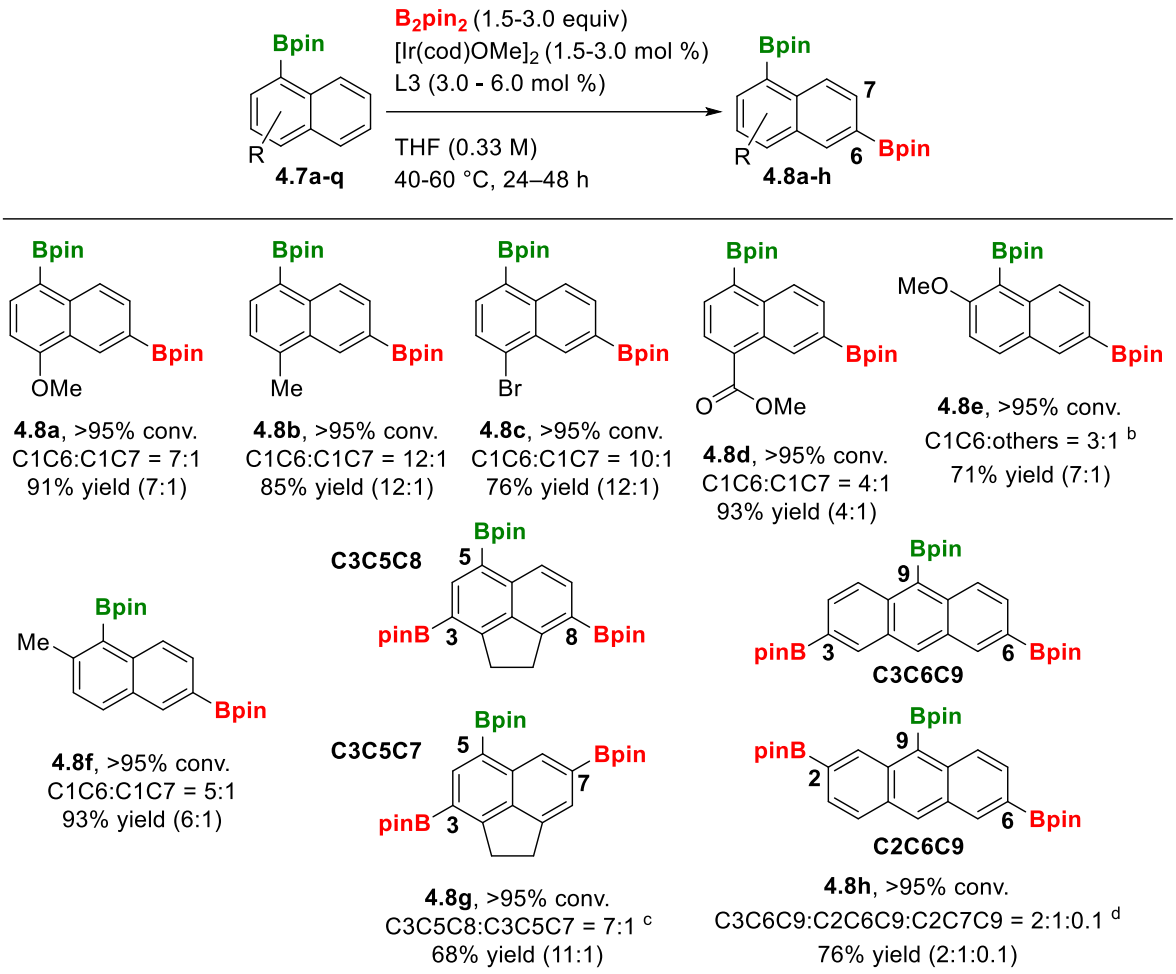


As shown in **Scheme 4.6**, a substituent on the C2- or C4-position is needed to avoid borylation at C3 (**4.7b**–**4.7f**). 5-Bpin acenaphthene **4.7g** borylated at both the expected C8 position and at C3. Under conditions that promote diborylation, 3,5,8-triborylated product **4.8g** was obtained as the major product along with the 3,5,7-triborylated product as a minor isomer. The Bpin shield in 9-borylated anthracene **4.7h** enabled remote borylation of both sides of the molecule leading to a 2:1 mixture of 3,6,9-triborylated and 2,6,9-triborylated products (**4.8h**).

4.2.2.2. Silylations

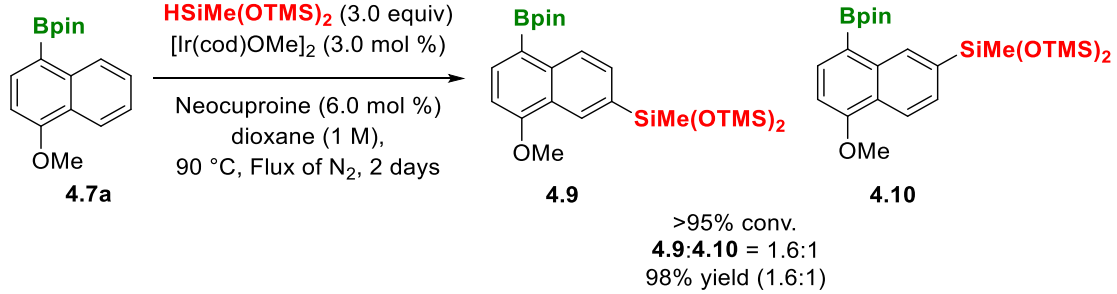
Iridium catalyzed C–H silylations (CHS) share similar features with CHB reactions, including regiochemical outcomes being traditionally driven by sterics. We tested if CHS of 1-borylated naphthalene would lead to a C6-silylated product. Subjecting **4.7a** to Hartwig's CHS conditions revealed a slight (1.6:1) preference for the C6- vs C7-silylated products **4.9** and **4.10** (**Scheme 4.7**).[35] Ligand optimization was problematic since neocuproine is a unique ligand that is key to gaining synthetically useful CHS yields. As the field of undirected CHS evolves, new ligands may improve the C6 selectivity of 1-borylated naphthalenes.

Scheme 4.6: C6 borylation of 1-borylated naphthalenes [a]



[a] **C1C6** and **C1C7** refer to 1,6- and 1,7-diborylated naphthalene products, respectively. Conversions and **C1C6**/**C1C7** ratios were measured by ^{1}H NMR on crude reaction mixtures. Yields refer to isolated material with the **C1C6**/**C1C7** ratio of the isolated material given in parentheses. [b] For **8e** there was an unknown minor isomer in the mixture besides the 7-borylated. [c] **C3C5C8** and **C3C5C7** refers to 3,5,8- and 3,5,7-triborylated acenaphthene, respectively. [d] **C3C6C9**, **C2C6C9** and **C2C7C9** refers to 3,6,9-, 2,6,9- and 2,7,9-triborylated anthracene, respectively.

Scheme 4.7: C–H silylation of 1-borylated naphthalenes



4.2.3. Mechanistic Studies.

We began this study by suggesting the unusual *para* selective CHB of 2-methoxy and 2-chloroaniline came about by virtue of a N–Bpin steric shielding in contrast to the previously evoked electronic drivers. This steric shielding hypothesis could be understandably challenged as free rotation around the C–N and N–B bonds can avoid any steric perturbation caused by the N–Bpin group. Moreover, even in the orientation that maximizes the putative steric shield, one could question if the N–Bpin group is close enough to the *meta* C–H so as to block its borylation. To address these questions and better understand the observed selectivities we performed the experiments describe bellow.

Steel and Marder have shown that ^{1}H NMR chemical shifts can be qualitative predictors of CHB selectivity when there is not a steric difference between two reactive sites.[24] More deshielded hydrogens are expected to be more acidic and more reactive towards CHB. Based on 1D-NOE and 2D NMR experiments, we assigned the ^{1}H NMR chemical shifts of N-borylated 2-chloro (**4.1a'**) and 2-tertbutylaniline (**4.1i'**) (**Figure 4.4**). We acquired the spectra in THF-d_8 so as to best simulate solution structures present during the CHB. Spectra for both compounds had the *meta* proton appearing more downfield than the *para* proton. Per Steel and Marder, this would suggest the *meta* position should be electronically favored in a CHB. However, a preference for *para* borylation is the experimentally observed result. This points to factors besides electronic effects being responsible for the *para* preference. A closer comparison of the ^{1}H NMR of the N-borylated intermediate versus the non-borylated version of 2-chloro and 2-tertbutyl aniline revealed a surprising deshielding effect on the chemical shift of the *ortho* proton after N-borylation (**Figure 4.4**). This displacement was also observed in other NMR solvents (C_6D_6, acetone-d_6, $CDCl_3$, pyridine-d_5). We attribute the downfield chemical shift movement to an intramolecular C–H•••O

hydrogen bonding (IMHB) between the oxygen of the N–Bpin group and the *ortho* hydrogen in the aniline. Deshielding effects on chemical shifts caused by hydrogen bonds are well documented,[36–38] and one of the closest examples to our system is the IMHB present in N1,N'-diBoc protected pyridine-2-yl guanidine **4.11a–c**.[39] In this scenario, a C–H ••• N IMHB is said to change the conformation, vs. analogous compound lacking a Boc group, to one where the pertinent protons are deshielded.

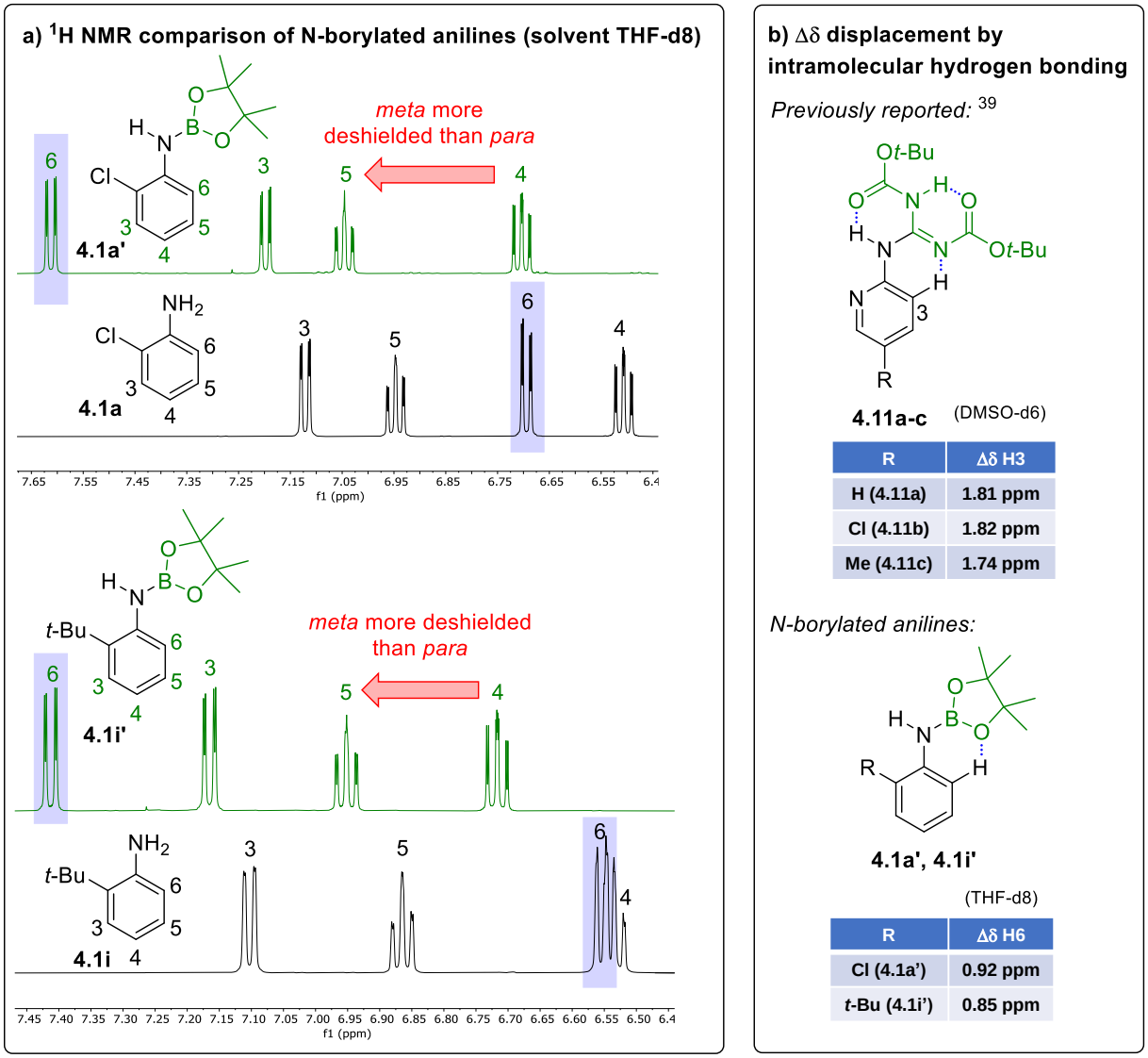


Figure 4.4: [1]H NMR comparison of N-borylated and unborylated 2-chloro and 2-methylaniline, and Δδ displacement due to C–H•••N and C–H•••O IMHB in **4.11a-c** and **4.1a'**, **4.1i'** respectively

While the NMR studies argued against electronic effects being responsible for the *para* borylation of anilines, those studies did not shed light on the question of whether the N–Bpin group is actually close enough to the *meta* position to act as a steric shield. To begin addressing this question, we ran CHB reactions with larger diboron partners as B_2hg_2 and B_2pp_2 (**Figure 4.5a**). B_2hg_2 proved less reactive than B_2pin_2 in accordance with a previous report,[40] but the selectivity for the *para* position improved. We tested a novel diboron partner for CHB, B_2pp_2, and interestingly the conversion to the borylated product was greater than with B_2hg_2. The largest *para* to *meta* ratio was also found with B_2pp_2, which is consistent with our steric shield hypothesis. While this improved selectivity could be due to the size of the installed N–Bpp group, a B_2pp_2 derived trisboryl active catalyst could also influence regiochemistry. Thus, we generated N–Bpin and N–Bpp compounds from 2-chloro and 2-methylaniline. These intermediates were then independently reacted under the same CHB conditions with B_2pin_2 as the diboron partner (**Figure 4.5b**). For 2-chloroaniline, the N–Bpp borylated derivative yielded a higher *para/meta* ratio as compared to the N–Bpin substrate. For 2-methylaniline, there was no observable change in selectivity; this may be a reflection of 2-methylaniline being inherently less *para* selective than 2-chloroaniline.

To probe the significance of the IMHB acceptor ability of N-Bpin toward selectivity, we decided to generate N–BBN, a boron group without oxygen, on the aniline. With an N–BBN in place, the *para* selectivity dramatically drops for both 2-chloro and 2-methylaniline. This further supports IMHB playing a direct role in selectivity. With N–BBN generated from 3-methylindole the CHB regiochemical preference flips and the C6-borylated isomer is major (2:1) as opposed to the C5 selectivity (3:1) seen with N–Bpin.

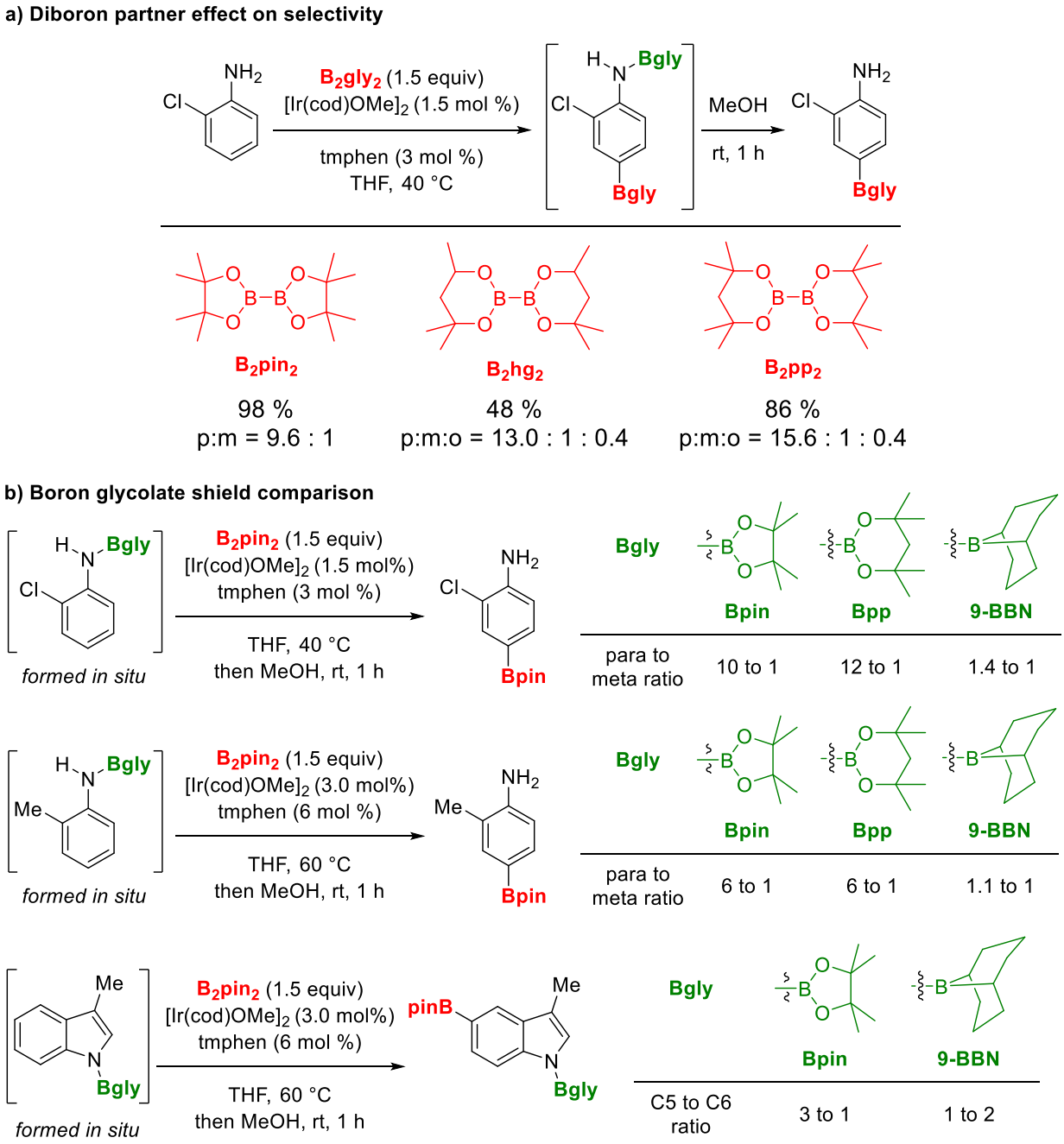


Figure 4.5: a) Diboron partner effect on CHB of 2-chloroaniline, b) Boron glycolate shield effect on the CHB of 2-chloroaniline, 2-methylaniline and 2-methylindole.

Seeking further evidence of IMHB involvement, we examined the N-borylated anilines with the Quantum Theory of Atoms in Molecules (QTAIM) developed by Bader.[41] QTAIM is used to identify IMHB based on a topological analysis of the electronic distribution. Bond critical points (BCP) are defined as the position between two atoms were the electron density reaches a minimum.

QTAIM identifies BCP when two atoms are connected by any type of bond including interactions as IMHB. We used a B3LYP functional and 6-311++G(d,p) basis set to optimize the geometry of N-borylated 2-chloro and 2-methylaniline (**Figure 4.6a**). This basis set has been previously reported to work well when IMHB is present.[42] The QTAIM analysis of both N-borylated anilines shows a BCP between the oxygen of the N–Bpin group and the *ortho* hydrogen of the aromatic ring supporting the existence of a C–H•••O IMHB. An additional BCP is found in N-borylated 2-chloroaniline between the chloride and the N–H. This additional N–H•••Cl IMHB can be one contributor to the greater *para* CHB selectivity of 2-chloroaniline vs. 2-methylaniline.

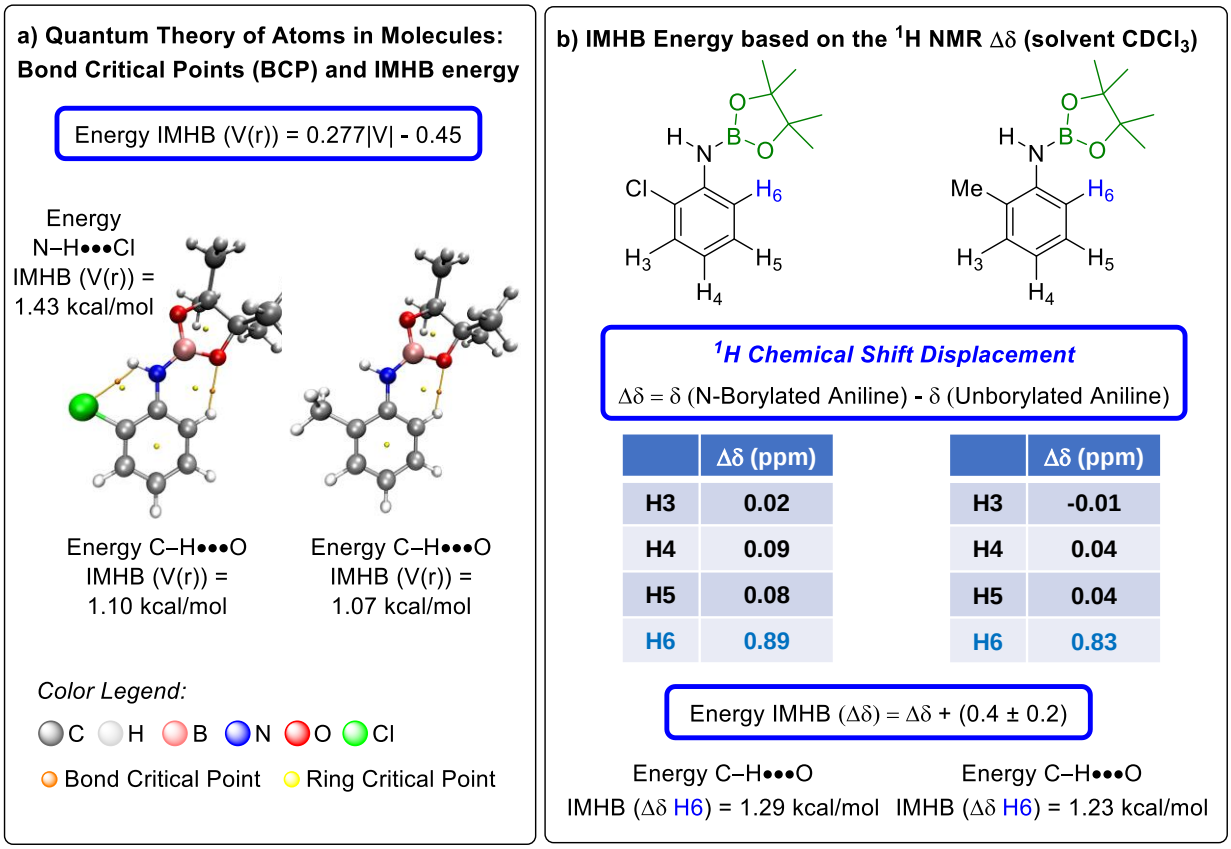


Figure 4.6: a) QTAIM analysis of N-borylated 2-chloro and 2-methylaniline (left and right respectively), b) ^{1}H NMR chemical shift deviation of N-borylated 2-chloro and 2-methylaniline respect to the unborylated anilines.

The energy of hydrogen bonds can be estimated with the potential energy density (V(r)) at the BCP found with QTAIM. The linear relationship initially found by Espinosa *et. al.* has been

adapted by Afonin *et. al.* for the case of IMHB including cases with C–H•••O interactions.[42,43] Using Afonin's corrected equation to calculate the C–H•••O IMHB energy of N-borylated 2-chloro and 2-methylaniline gave comparable energies corresponding to 1.10 kcal/mol and 1.07 kcal/mol respectively (**Figure 4.6a**). Experimentally, IMHB energies can be estimated by a linear relationship with the ^{1}H chemical shift difference of the hydrogen involved in the IMHB in the target molecule versus a reference in which no IMHB occurs (**Figure 4.6b**).[42,44] This equation was found with ^{1}H NMR taken in $CDCl_3$ and therefore we used $CDCl_3$ for this experiment. We choose the non-borylated aniline as the reference and found an energy of 1.29 and 1.23 kcal/mol for the IMHB of 2-chloro and 2-methylaniline respectively, which is close to the energy given by QTAIM.

One potential pitfall in attributing *para* selectivity to IMHB Bpin shielding is the assumption that there is only one energy minimum on the conformational energy surface. For example, the presence of a second local minimum where the plane of the N–Bpin is orthogonal to the plane containing the aryl ring could erode selectivity if (i) the second local minimum has a comparable or lower Gibbs' energy than the IMHB local minimum, and (ii) the barrier connecting the local minima is small. Indeed, theory predicts that there are local minima similar to the aforementioned scenario for N-borylated 2-chloroaniline and 2-methylaniline at 5.4 and 3.1 kcal/mol relative to their respective IMHB local minima (**Figure 4.7**), and the corresponding transition states that connect these local minima are 6.6 and 4.6 kcal/mol above the IMHB local minima. Based on the energies of the higher energy local minima, theory predicts that more than 99% on the N-borylated anilines adopt the IMHB structures. These findings support the hypothesis that IMHB between the Bpin O and the C6 proton creates a steric shield that accounts for the *para* selectivity.

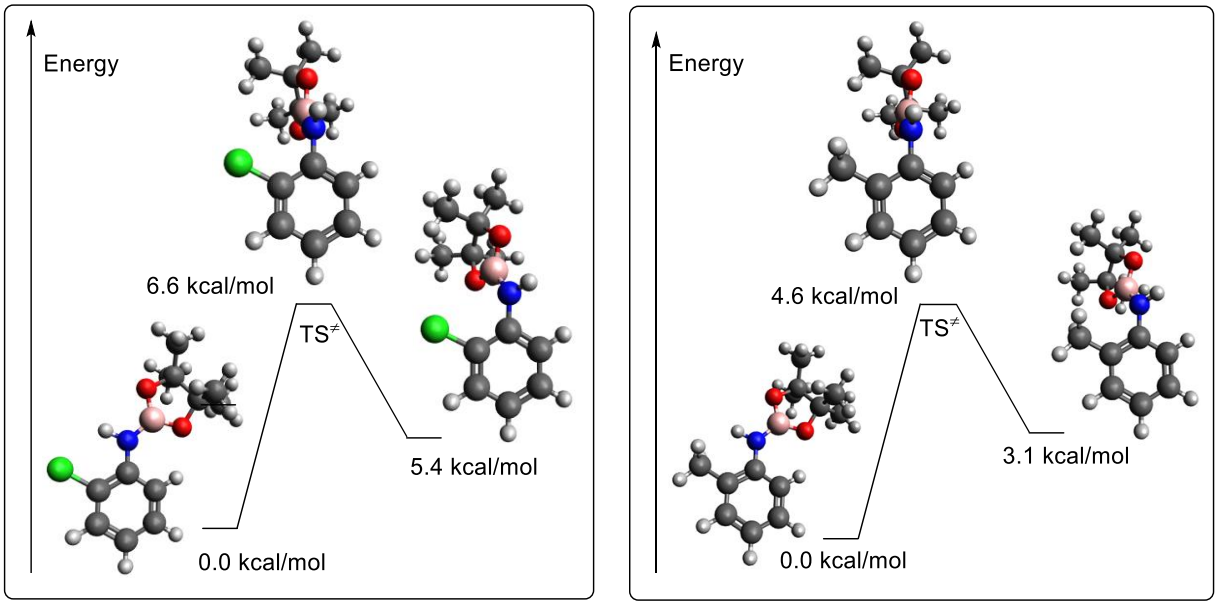


Figure 4.7: C–N rotation barrier for N-borylated 2-chloroaniline (left) and 2-methylaniline (right).

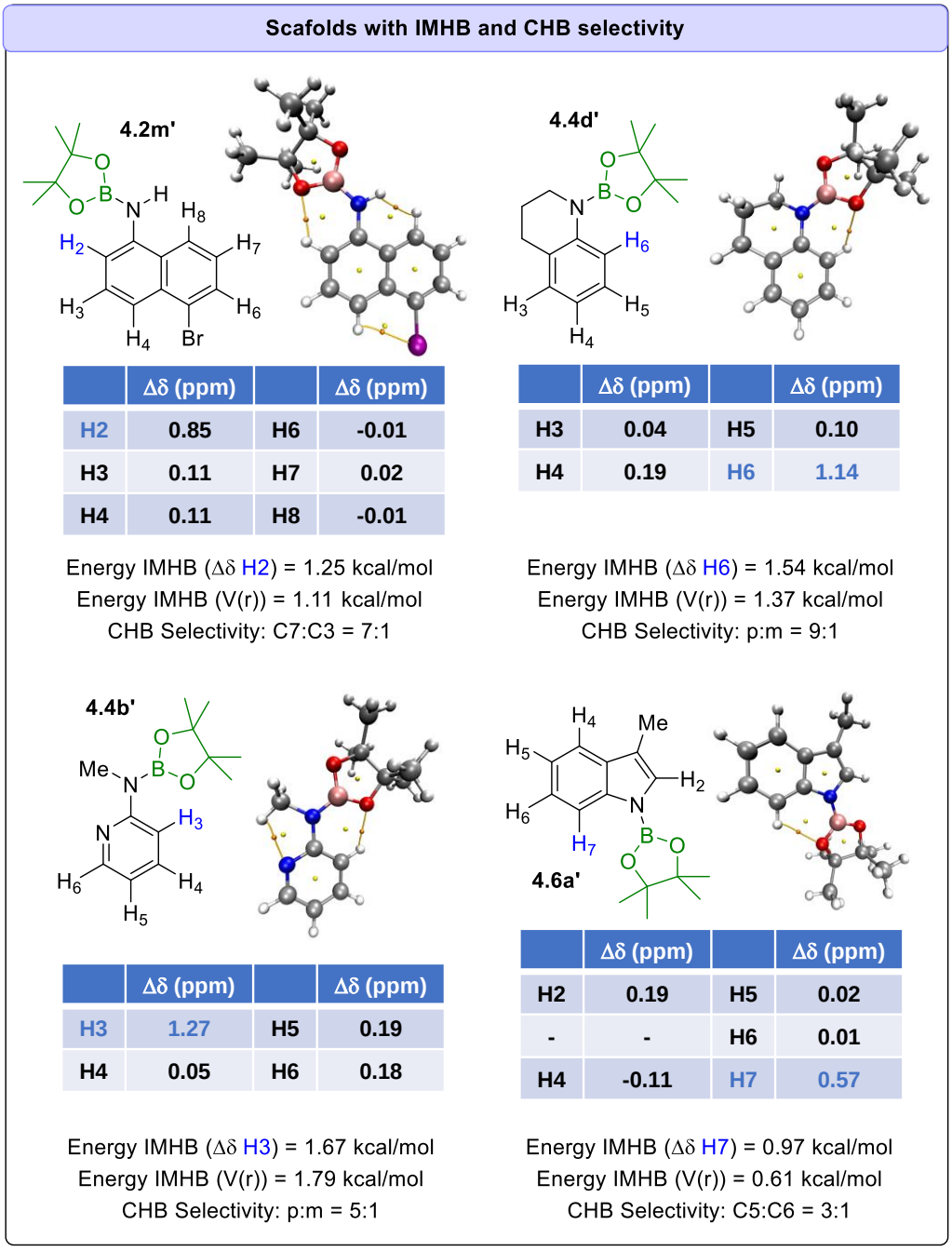
We next asked if similar relationships could be found in other scaffolds with and without IMHB (Figure 4.8 and 4.9). Accordingly, good CHB selectivities are seen for substrates when protons proximal to Bpin substituents have the largest ^{1}H NMR chemical shift displacement, as well as a BCP between that proton and the Bpin O from QTAIM analysis. Specific examples are described below.

The H2 of N-borylated 5-bromo-1-aminonaphthalene **4.1m'** shows a 0.85 ppm difference from the reference 5-bromo-1-aminonaphthalene. By comparison, all the other protons deviate by <0.2 ppm. QTAIM shows a BCP that supports an IMHB with an energy of 1.25 kcal/mol, which is close to 1.11 kcal/mol calculated based on the spectroscopically observed ^{1}H NMR chemical shift displacement. As expected, 5-bromo-1-aminonaphthalene undergoes a C7-selective borylation by blocking the C3 position (**Scheme 4.2**). In contrast, N-borylated 2-methylnaphthalene **4.1o'** show no evidence of C–H•••O IMHB with the naphthalene as the hydrogen bond donor. H8 might be available for IMHB but Δδ is only 0.30 ppm, which is close to the Δδ of H4 (0.28 ppm), suggesting that chemical shift displacement results from electronic

effects after N-borylation. No BCP is detected with the arene as the hydrogen bond donor, but a BCP corresponding to a C–H•••O IMHB between the N–Bpin and the methyl group is found. The lack of IMHB with the naphthalene ring might be due to steric effects that disrupts any 7-member ring IMHB from happening. Accordingly, no selectivity was found under CHB reaction conditions.

As shown in **Scheme 4.3**, the CHB regioselectivity of N-alkylated aniline depends on the scaffold. CHB of N-borylated 2-chloro-N-methyl aniline **4.3a'** did not show any selectivity. The steric clash between the N–Me and Cl groups prevents IMHB formation with the Bpin O. While chemical shift for H6 is 0.57 ppm, the significant displacement of 0.45 ppm for H4 again suggests that electronic effects are the actors. CHB of N-borylated 2-amino-N-methylpyridine **4.3b'** gave the *para* borylated aniline selectively. This selectivity is astounding since *meta* selectivity would be expected by the strong electronic effects show by pyridines in CHB reactions.[45,46] Both QTAIM analysis (1.67 kcal/mol) and chemical shift displacement (1.79 kcal/mol) support Bpin shielding from C–H•••O IMHB as the directing element.

Tetrahydroquinolines are also exhibit *para* selectivity in CHB reactions, but that could be explained by the fact that rotation about the C–N bond is impossible and N→B p-bonding lock the N–Bpin group in place. Nonetheless, QTAIM and Δδ show evidence for IMHB in **4.3d'** with an energy comparable to N-borylated 2-amino-N-methylpyridine. Indoles have similar conformational constraints to appropriately place the N–Bpin group. However, this group of compounds gave low to moderate selectivities. A BCP is found by QTAIM of **4.5a'** but only a 0.57 ppm of difference in chemical shifts is calculated. We speculate that the lower selectivity for indoles is due to (i) the angles of the 5-member bicyclic ring increasing the distance between the Bpin O and the H at C7 and (ii) a decrease in the negative charge on the Bpin O since the N lone pairs of indoles are weak p-donors.



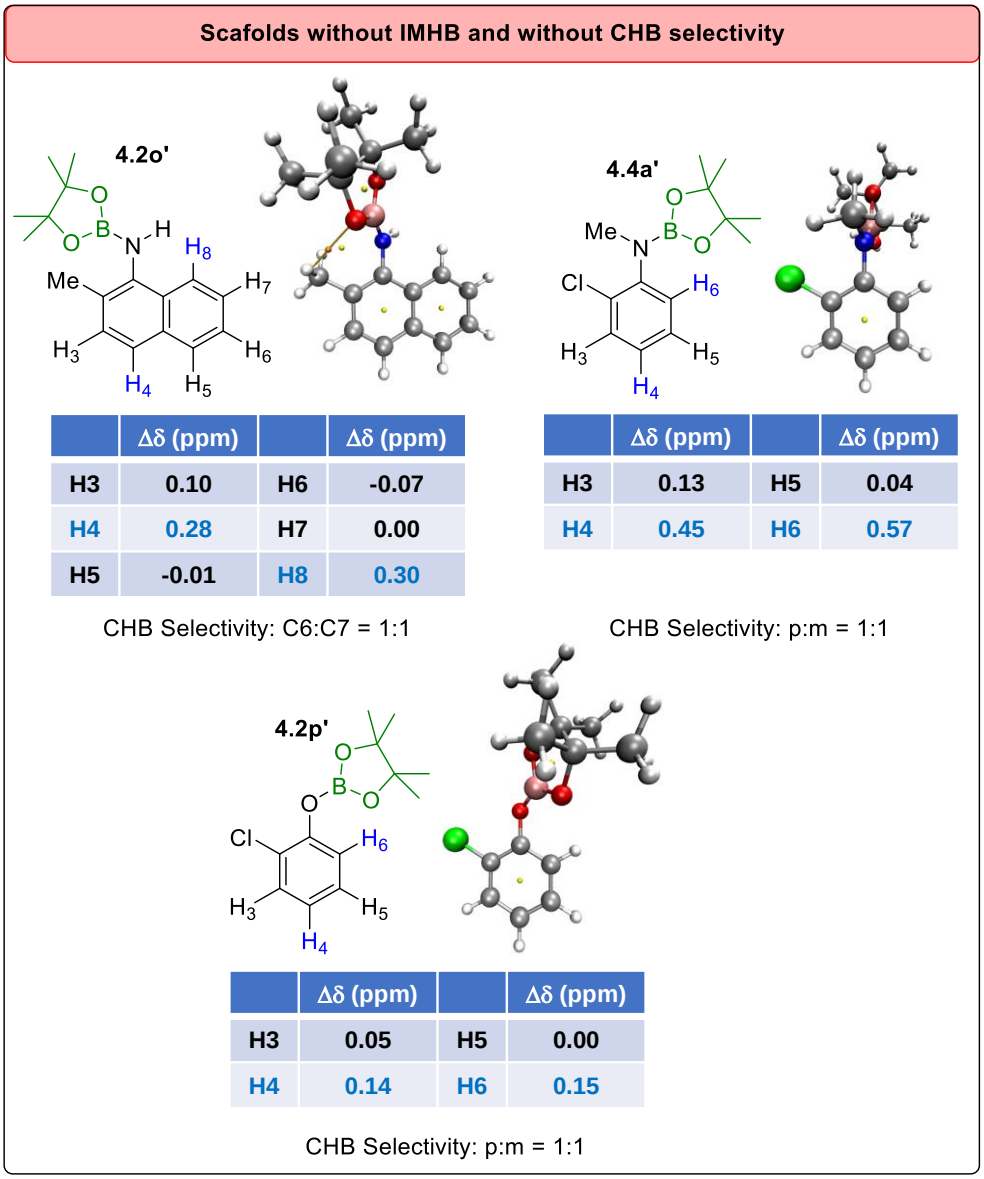
	Δδ (ppm)		Δδ (ppm)
H2	0.85	H6	-0.01
H3	0.11	H7	0.02
H4	0.11	H8	-0.01

	Δδ (ppm)		Δδ (ppm)
H3	0.04	H5	0.10
H4	0.19	H6	1.14

	Δδ (ppm)		Δδ (ppm)
H3	1.27	H5	0.19
H4	0.05	H6	0.18

	Δδ (ppm)		Δδ (ppm)
H2	0.19	H5	0.02
-	-	H6	0.01
H4	-0.11	H7	0.57

Figure 4.8: Correlation between presence of IMHB and remote CHB selectivity. The ^{1}H NMR chemical shift displacements are shown by the numbers in blue respect to the corresponding non-borylated compound as reference. The lowest energy conformations are shown which were calculated by B3LYP functional and 6-311++G(d,p) basis set. QTAIM was performed in each optimized structure and the critical points are shown by the dots in orange (BCP) and yellow (RCP). The energy of the C–H•••O IMHB was calculate from V(r) at the corresponding BCP by using Afonin's equation and by the displacement of the ^{1}H NMR chemical shift of the proton involved in the IMHB.



	Δδ (ppm)		Δδ (ppm)
H3	0.10	H6	-0.07
H4	0.28	H7	0.00
H5	-0.01	H8	0.30

	Δδ (ppm)		Δδ (ppm)
H3	0.13	H5	0.04
H4	0.45	H6	0.57

	Δδ (ppm)		Δδ (ppm)
H3	0.05	H5	0.00
H4	0.14	H6	0.15

Figure 4.9: Correlation between absence of IMHB and CHB selectivity. The ^{1}H NMR chemical shift displacements are shown by the numbers in blue respect to the corresponding non-borylated compound as reference. The lowest energy conformations are shown which were calculated by B3LYP functional and 6-311++G(d,p) basis set. QTAIM was performed in each optimized structure and the critical points are shown by the dots in orange (BCP) and yellow (RCP).

In our efforts to expand the Bpin steric effect to other directing groups without nitrogen, we found that CHB of 2-chlorophenol **4.1p** did not show selectivity. Neither QTAIM nor Δδ show any evidence of IMHB, which explains the experimental result.

4.2.4. Application of IMHB to remote borylation

4.2.4.1. 7-member ring IMHB

Inspired by the literature precedents,[37,38,42] we sought to see if a 7-member ring can be created with IMHB to N–Bpin groups. As explained in the previous section, steric effects can disrupt IMHB and therefore a 7-member ring IMHB with arenes as hydrogen bond donors are not common. However, exceptions appear when hydrogen bond donor contain a bicyclic moiety with a 5- and 6-member fused rings.[46–48] We proposed that 3-aminoindazoles would form a 7-member IMHB after N-Borylation. We were pleased to find that N-methyl-3-aminoindazol **4.11** undergoes a C6-selective CHB (**Figure 4.10**).

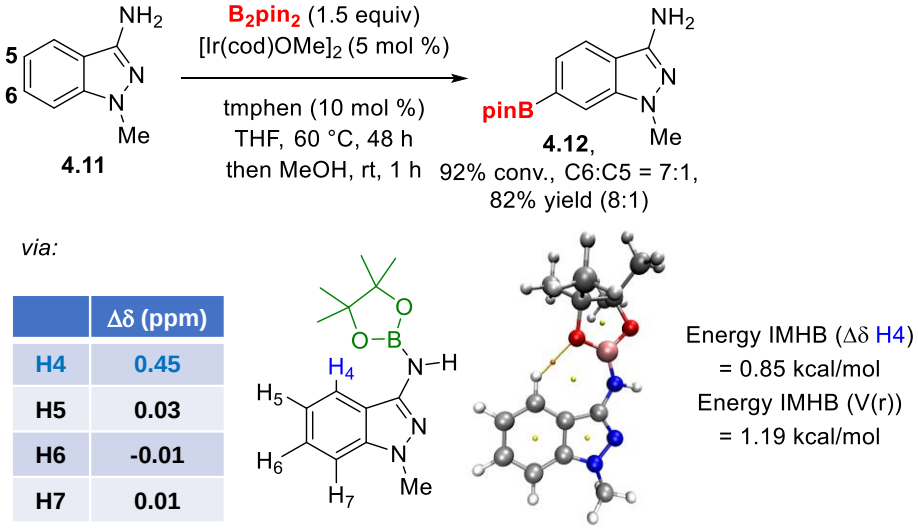


Figure 4.10: 7-member ring IMHB: C6 borylation of 3-aminoindazol.

^{1}H NMR comparison of the N-borylated indazol versus the unborylated version shows a significant movement of the chemical shift of the C4 proton, as expected with an IMHB. QTAIM provides more support to this conclusion by recognizing a C–H•••O BCP between the C4 proton and the oxygen in the Bpin group. The calculate energy by QTAIM and Δδ are a comparable 1.19 and 0.85 kcal/mol respectively.

4.2.4.2. Pyrimidines as directing groups.

Certainly, Bpin is not the first IMHB acceptor found in molecules. Nitrogen heterocycles have appeared as part of IMHB networks including C–H•••N interactions within heteroarenes.[47–49] Pyridines, pyrimidines and triazines are key motifs of biologically active pharmaceuticals and therefore their potential use as steric shields via IMHB drew our attention.[50–56]. In particular, we became interested in osimertinib, an epidermal growth factor receptor tyrosine kinase inhibitor, which presents a pyrimidine group attached to an indole skeleton.[57] We subjected osimertinib analogue **4.13** to CHB conditions (**Figure 4.11**). The C6-borylated indole **4.14** was produced, although with moderate selectivity. We were fortunate to crystallize **4.13** and the crystal structure showed the C–H•••N that we had proposed with the pyrimidine groups as the hydrogen bond acceptor and the C4 hydrogen of the indole being the hydrogen bond donor. We used the x-ray coordinates to evaluate the QTAIM topology of **4.13** and found a BCP that supports the IMHB C–H•••N. Next, changes in ^{1}H NMR of **4.13** taking N-methylindole as the reference were calculated. Surprisingly, we found that both C2 and C4 hydrogens showed a significant chemical shift displacement. We propose that in solution the pyrimidine ring may equilibrate between two conformations involving IMHB with H2 and H4. The IMHB energy for H4 calculate from $\Delta\delta$ is 1.13 kcal/mol, which is higher than that calculated by QTAIM. This difference might be due to the different conformations found in solution in contrast to the solid state.

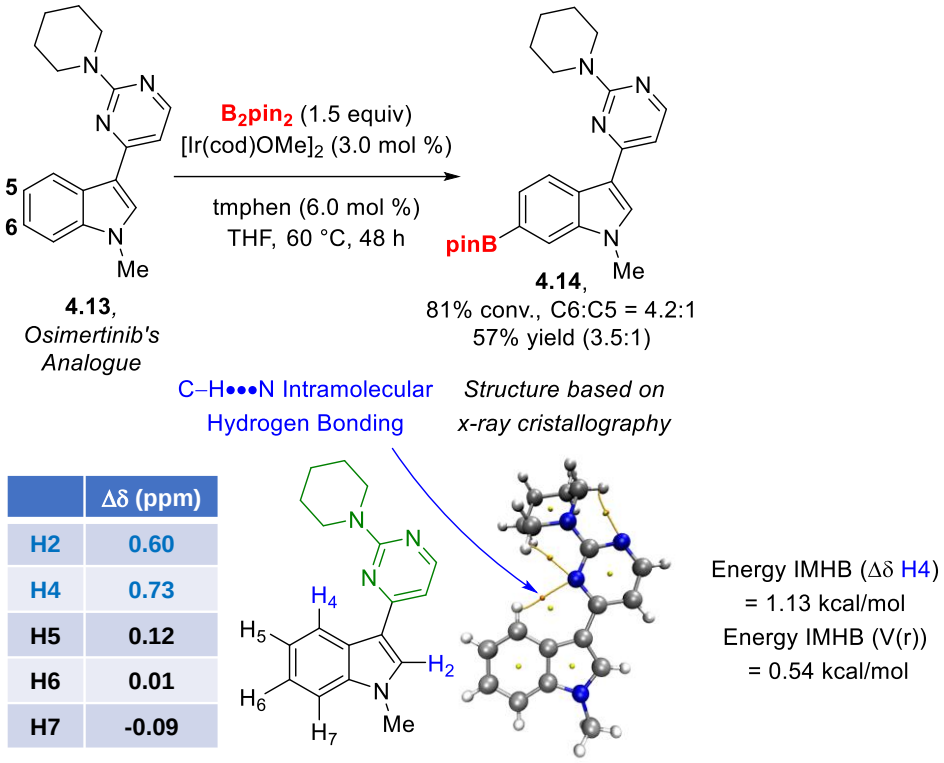


Figure 4.11: Expanding IMHB to other scaffolds: C6 borylation of an Osimertinib analogue with a pyrimidine directing group directed by a C–H•••N IMHB.

4.3. Conclusions

A diverse array of regioselective remote CHBs can be driven by intramolecular steric shields created via IMHB. The previously inexplicable *para* CHB found with 2-chloro and 2-methoxy aniline now is explained by a Bpin steric shield generated after *in situ* N-borylation. Furthermore, N–Bpin steric shields can lead to *para* CHB of other *ortho* substituted anilines, 7-borylation of 1-naphtylamines, *para* CHB of certain N-alkylated anilines, and to the elusive 5-borylation of indoles. Bpin steric shielding can be extended to motifs without nitrogen, such as 1-borylated naphthalenes, which undergo C6-selective CHB. The wide variety of scaffolds that can be selectively borylated at remote positions due to a Bpin group highlights the versatility of intramolecular steric shields.

We traced back the remote CHB selectivity to the presence of a C–H•••O IMHB in N-borylated intermediates with the Bpin as the hydrogen bond acceptor. A BCP found by QTAIM

and a characteristic ^{1}H NMR chemical shift displacement of the hydrogen bond donor, the *ortho* aniline hydrogen after N-borylation here, is support for an IMHB. The energetic cost to disrupt the planarity of the N-borylated anilines and the necessity of an oxygen in the boryl group to achieve a *para* CHB also support the observed selectivity to involve IMHB. A 7-member ring IMHB can also produce the steric as shown in the C6-selective borylation of N-methyl-3-aminoindazole. Finally, a C5-borylation of the indole ring in an osimertinib analogue where a pyrimidine forms the steric shield via a C–H•••N IMHB further expands this means of remote regiocontrol. We anticipate that our efforts presented here will be used to design other methods for remote functionalization driven by intramolecular interactions.

4.4. Experimental Procedures

4.4.1. General Information

All commercially available chemicals were used as received unless otherwise indicated. Bis(pinacolato)diboron (B_2pin_2) was generously supplied by BoroPharm, Inc. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) $[Ir(cod)(OMe)]_2$ was purchased from Sigma-Aldrich. THF was refluxed over sodium/benzophenone ketyl, distilled and degassed. Anhydrous dioxane was purchased from Sigma-Aldrich and used as received. Hexane and cyclohexane were refluxed over calcium hydride, distilled and degassed. 3,4,7,8-Tetramethyl-1,10-phenanthroline (tmphen) and neocuproine were purchased from Combi-blocks and recrystallized from ethanol. 2-chloroaniline, 2-methoxyaniline, 2-methylaniline, 2-ethylaniline, 2-tertbutylaniline and tetrahydroquinoline were distilled over dried molecular sieves prior to use.

Column chromatography was performed on 240 - 400 mesh Silica P-Flash silica gel. Thin layer chromatography was performed on 0.25 mm thick aluminum-backed silica gel plates and

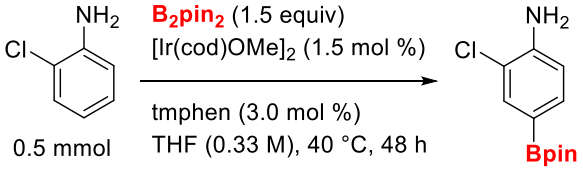
visualized with ultraviolet light (λ = 254 nm) and alizarin stain to visualize boronic esters according to a literature procedure.[58]

^{1}H, ^{13}C, ^{11}B and ^{19}F NMR spectra were recorded on a Varian 500 MHz DD2 Spectrometer equipped with a 1H-19F/15N-31P 5 mm Pulsed Field Gradient (PFG) Probe. Spectra taken in $CDCl_3$ were referenced to 7.26 ppm in ^{1}H NMR and 77.2 ppm in ^{13}C NMR. Spectra taken in C_6D_6 were referenced to 7.16 ppm in ^{1}H NMR and 128.1 ppm in ^{13}C NMR. Spectra taken in DMSO-d_6 were referenced to 2.50 ppm in ^{1}H NMR and 39.5 ppm in ^{13}C NMR. Spectra taken in acetone-d_6 were referenced to 2.05 ppm in ^{1}H NMR and 29.8 ppm in ^{13}C NMR. Spectra taken in THF-d_8 were referenced to 3.58 ppm in ^{1}H NMR and 67.2 ppm in ^{13}C NMR. ^{11}B NMR spectra were referenced to neat $BF_3 \cdot Et_2O$ as the external standard. ^{13}C NMR resonances for the boron-bearing carbon atom were not observed due to quadrupolar relaxation; nonetheless an assignment was possible by correlations shown in gHMBCAD. All coupling constants are apparent *J* values measured at the indicated field strengths in Hertz (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, bs = broad singlet). NMR spectra were processed for display using the MNova software program with only phasing and baseline corrections applied.

High-resolution mass spectra (HRMS) were obtained at the Molecular Metabolism and Disease Mass Spectrometry Core facility and at the Mass Spectrometry Service Center at Michigan State University using electrospray ionization (ESI+ or ESI-) on quadrupole time-of-flight (Q-TOF) instruments.

4.4.2. *Para* CHB of anilines

Para borylation of 2-chloroaniline (2a)

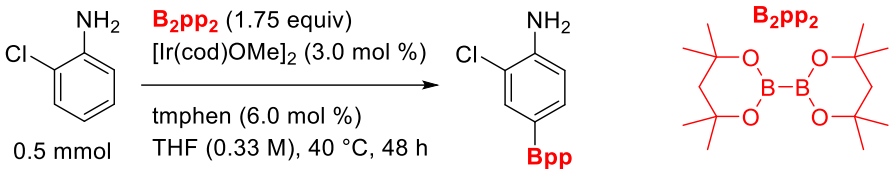


>95% conversion, *para : meta* = 9 : 1
86% isolated yield, *para : meta* = 10 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-chloroaniline (64 mg, 0.5 mmol, 1 equiv) and tmphen (3.6 mg, 3.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 109 mg of *para* borylated **2a** with a minor byproduct corresponding to the *meta* borylated isomer (*para*:*meta* = 10:1) as a white solid (86% yield). The NMR data were consistent with previously reported values, designated as compound **4a'** in the cited paper.[22]

^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.2 Hz, 1H), 7.49 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.73 (dd, *J* = 7.9 Hz, 1H), 4.22 (bs, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.6, 136.1, 134.4, 118.8, 115.0, 83.7, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.4. HRMS (ESI) m/z calcd for $C_{12}H_{18}BClNO_2$ $[M+H]^+$ 254.1119, found 254.1116

***Para* borylation of 2-chloroaniline (2a')**

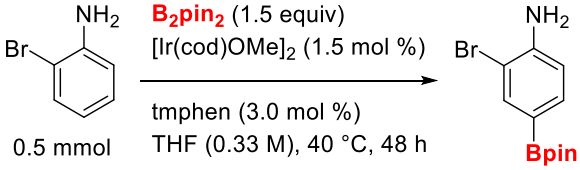


76% conversion, *para : meta* = 16 : 1
42% isolated yield, *para : meta* > 20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-chloroaniline (64 mg, 0.5 mmol, 1 equiv) and tmphen (7.1 mg, 6.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (10.0 mg, 3.0 mol %) and B_2pp_2 (247 mg, 0.88 mmol, 1.75 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 56 mg of **2a'** as a white solid (42% yield, mp 84-86 °C).

^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.4 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 4.15 (bs, 2H), 1.89 (s, 2H), 1.41 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 135.1, 133.5, 118.8, 115.0, 70.8, 49.1, 31.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 26.1. HRMS (ESI) m/z calcd for $C_{13}H_{20}BClNO_2$ $[M+H]^+$ 268.1276, found 268.1264

***Para* borylation of 2-bromoaniline (2b)**

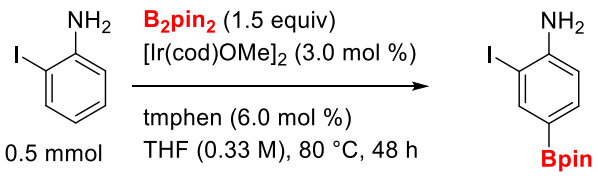


91% conversion, *para : meta* = 9 : 1
73% isolated yield, *para : meta* = 11 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-bromoaniline (86 mg, 0.5 mmol, 1 equiv) and tmphen (3.6 mg, 3.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with water (1 mL). The water layer was decanted and the residue was dried to give 109 mg of *para* borylated **2b** with a minor byproduct corresponding to the *meta* borylated isomer (*para*:*meta* = 11:1) as a light brown solid (73% yield). The NMR data were consistent with previously reported values, designated as compound **4b'** in the cited paper.[21]

^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.4 Hz, 1H), 7.52 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 4.22 (bs, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8, 139.3, 135.1, 114.9, 109.0, 83.7, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.3. HRMS (EI) m/z calcd for $C_{12}H_{18}BBrNO_2$ $[M+H]^+$ 298.0614, found 298.0613

***Para* borylation of 2-iodoaniline (2c)**

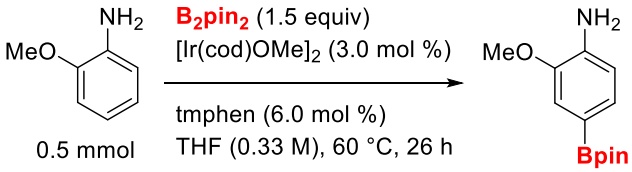


44% conversion, *para : meta* = 7 : 1
20% isolated yield, *para : meta* = >20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-iodoaniline (109 mg, 0.5 mmol, 1 equiv) and tmphen (7.1 mg, 3.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (10.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and subjected to chromatographic se*para*tion with silica gel ($CHCl_3$ as eluent) to give 34 mg of **2c** as a white solid (20% yield, mp 113-115 °C). The ^{1}H NMR data were consistent with previously reported values, designated as compound **3d** in the cited paper. The ^{13}C NMR data were consistent except one peak corresponding to the C–I not reported in the cited paper.[22]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 1.4 Hz, 1H), 7.55 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 4.31 (s, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.3, 145.9, 136.1, 113.9, 84.0, 83.7, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.2. GC-MS (EI) m/z calcd for $C_{12}H_{17}BINO_2$ [M] 345.0, found 344.9

***Para* borylation of 2-methoxyaniline (2d)**



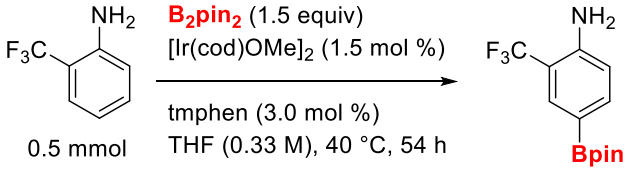
97% conversion, *para : meta* = 12 : 1
91% isolated yield, *para : meta* = 16 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-methoxyaniline (62 mg, 0.5 mmol, 1 equiv) and tmphen (7.1 mg, 3.0 mol %) in THF (0.5 mL). In a se*para*te tube,

$[Ir(cod)(OMe)]_2$ (10.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 26 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with water (3 mL). The water layer was decanted and the residue was dried to give 114 mg of *para* borylated **2d** with traces of a minor byproduct corresponding to the *meta* borylated isomer (*para*:*meta* = 16:1) as a light red solid (91% yield). The NMR data were consistent with previously reported values, designated as compound **4d'** in the cited paper.[21]

^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.20 (d, *J* = 1.3 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 3.97 (bs, 2H), 3.89 (s, 3H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.5, 139.6, 128.9, 115.9, 114.1, 83.4, 55.6, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.8. HRMS (ESI) m/z calcd for $C_{13}H_{21}BNO_3$ $[M+H]^+$ 250.1614, found 250.1605

***Para* borylation of 2-trifluoromethylaniline (2e)**



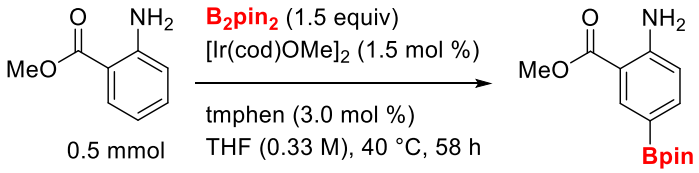
91% conversion, *para : meta* = 4 : 1
52% isolated yield, *para : meta* = 4 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-trifluoromethylaniline (81 mg, 0.5 mmol, 1 equiv) and tmphen (3.5 mg, 3.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL)

were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 54 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with water (2 mL). The water layer was decanted and the residue was dried to give 74 mg of *para* borylated **2e** with a minor byproduct corresponding to the *meta* borylated isomer (*para*:*meta* = 4:1) as a brown oil (52% yield). The NMR data were consistent with previously reported values, designated as compound **3b** in the cited paper.[58]

^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.71 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 4.28 (bs, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1 (q, J = 1.9 Hz), 139.4 (q, J = 0.9 Hz), 133.7 (q, J = 4.9 Hz), 125.2 (q, J = 272.3 Hz), 116.2, 113.1 (q, J = 29.8 Hz), 83.8, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.5. HRMS (ESI) m/z calcd for $C_{13}H_{18}BF_3NO_2$ $[M+H]^+$ 288.1383, found 288.1372

***Para* borylation of methyl 2-aminobenzoate (2f)**



87% conversion, *para : meta* = 2 : 1
66% isolated yield, *para : meta* = 2 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with methyl 2-aminobenzoate (76 mg, 0.5 mmol, 1 equiv) and tmphen (3.5 mg, 3.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL)

were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 58 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with water (2 mL). The water layer was decanted and the residue was dried to give 92 mg of a mixture of *para* borylated methyl 2-aminobenzoate **2f** with the *meta* isomer (*para*:*meta* = 2:1) as a white brownish solid (66% yield). The NMR data of the *para* isomer were consistent with previously reported values, designated as compound **a** in the cited paper.[59]

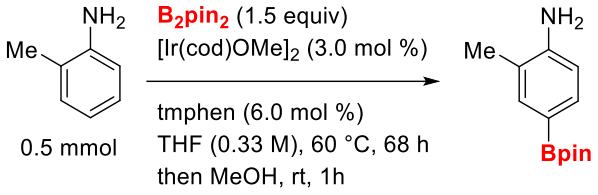
Para:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 1.6 Hz, 1H), 7.66 (dd, J = 8.2, 1.6 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 5.89 (bs, 2H), 3.85 (s, 3H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 152.8, 140.2, 139.0, 116.0, 110.3, 83.6, 51.5, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.9. HRMS (ESI) m/z calcd for $C_{14}H_{21}BNO_4$ $[M+H]^+$ 278.1564, found 278.1552

Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 1.1 Hz, 1H), 7.04 (dd, *J* = 7.9, 1.1 Hz, 1H), 5.89 (bs, 2H), 3.86 (s, 3H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 149.5, 130.3, 123.5, 122.0, 112.8, 84.2, 51.7, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.9. HRMS (ESI) m/z calcd for $C_{14}H_{21}BNO_4$ $[M+H]^+$ 278.1564, found 278.1552

***Para* borylation of 2-methylaniline (2g)**

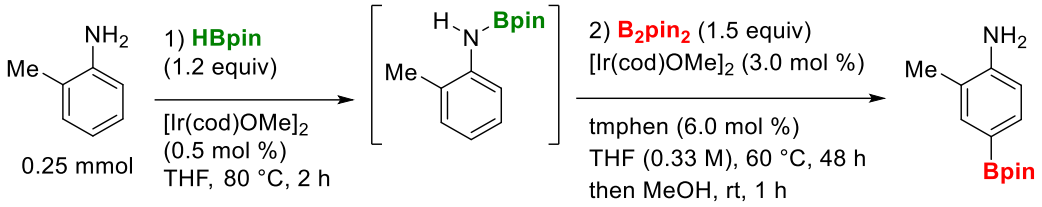


61% conversion, *para : meta* = 4 : 1
47% isolated yield, *para : meta* > 20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-methylaniline (54 mg, 0.5 mmol, 1 equiv) and tmphen (7.1 mg, 6.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (9.9 mg, 3.0 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 68 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent) to remove the iridium residue. The fractions containing product were collected, concentrated and passed through silica gel column chromatography (chloroform/ethyl acetate 98:2) to give 55 mg of **2g** as a light-yellow solid (47% yield). The NMR data were consistent with previously reported values.[60]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.50 (m, 2H), 6.66 (d, *J* = 7.8 Hz, 1H), 3.81 (s, 2H), 2.16 (s, 3H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7, 137.3, 134.2, 121.2, 114.1, 83.4, 24.9, 17.1. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.7. HRMS (ESI) m/z calcd for $C_{13}H_{21}BNO_2$ $[M+H]^+$ 234.1665, found 234.1654

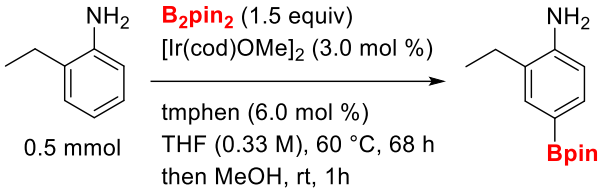
With N-Bpin bond preformation:



>95% conversion, *para : meta* = 6 : 1
72% isolated yield, *para : meta* = 10 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-methylaniline (0.1 mL of a 2.5 M solution in THF, 0.25 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (0.1 mL of a 12.5 mM solution in THF, 0.5 mol %), HBpin (38 mg, 0.3 mmol, 1.2 equiv) and THF (0.05 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. In a se*para*te tube, a solution of $[Ir(cod)(OMe)]_2$ (22 mg, 16.6 mM, 0.033 mmol) and B_2pin_2 (423 mg, 0.83 M, 1.66 mmol) in THF (2.0 mL) was prepared. The microreactor was charged with tmphen (3.6 mg, 6.0 mol %), THF (0.05 mL) and with 0.45 mL of the solution containing $[Ir(cod)(OMe)]_2$ (3 mol %) and B_2pin_2 (0.37 mmol, 1.5 equiv). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para:meta* borylation ratio. MeOH (1.25 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel (chloroform/ethyl acetate 98:2). The fractions containing product were collected, concentrated and washed with water (4 mL). The water layer was decanted and the residue was dried to give 42 mg of a *para* borylated 2-methylaniline **2g** with the *meta* isomer as a minor byproduct (*para*:*meta* = 10:1) as a yellow solid (72% yield).

***Para* borylation of 2-ethylaniline (2h)**



48% conversion, *para : meta* = 4 : 1
43% isolated yield, *para : meta* = 9 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-methylaniline (54 mg, 0.5 mmol, 1 equiv) and tmphen (7.1 mg, 6.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (9.9 mg, 3.0 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 68 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through silica gel column chromatography (chloroform/ethyl acetate 98:2). The fractions containing product were collected, concentrated to give 53 mg of *para* borylated **2h** with traces of the *meta* isomer (*para*:*meta* = 9:1) as a white brownish solid (43% yield).

Para:

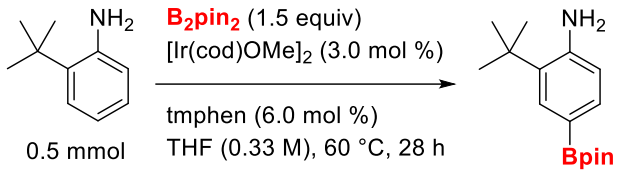
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 1.6 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 3.84 (s, 2H), 2.53 (q, *J* = 7.5 Hz, 2H), 1.34 (s, 12H), 1.26 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 135.5, 134.2, 127.0, 114.6, 83.3, 24.9, 24.1, 13.2. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.7. HRMS (ESI) m/z calcd for $C_{14}H_{23}BNO_2$ $[M+H]^+$ 248.1822, found 248.1812

7 mg of a minor fraction containing mainly the *meta* isomer (*meta*:*para* = 2:1) was isolated as well (6% yield)

Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.13 (d, *J* = 1.2 Hz, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 3.77 (bs, 2H), 2.54 (q, *J* = 7.0 Hz, 2H), 1.33 (s, 12H), 1.25 (t, *J* = 7.0 Hz, 3H). HRMS (ESI) m/z calcd for $C_{14}H_{23}BNO_2$ $[M+H]^+$ 248.1822, found 248.1812

***Para* borylation of 2-tertbutylaniline (2i)**



86% conversion, *para : meta* = 5 : 1
81% isolated yield, *para : meta* = 5 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with methyl 2-tertbutylaniline (75 mg, 0.5 mmol, 1 equiv) and tmphen (7.1 mg, 6.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (10.0 mg, 3.0 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 28 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 111 mg of the *para* borylated 2-tertbutylaniline **2i** with a minor byproduct corresponding to the *meta* isomer (*para*:*meta* = 5:1) as a white brownish solid (81% yield).

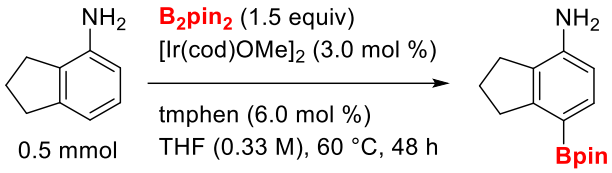
Para:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.5 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 4.00 (bs, 2H), 1.45 (s, 9H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7, 134.3, 133.5, 132.4, 117.0, 83.3, 34.3, 29.8, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.1. HRMS (ESI) m/z calcd for $C_{16}H_{27}BNO_2$ $[M+H]^+$ 276.2135, found 276.2131

Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.8 Hz, 1H), 7.21 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.12 (d, *J* = 1.3 Hz, 1H), 4.00 (bs, 2H), 1.43 (s, 9H), 1.34 (s, 12H).

***Para* borylation of 4-aminoindan (2j)**



58% conversion, *para : meta* = 2 : 1
52% isolated yield, *para : meta* = 2 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with methyl 4-aminoindan (67 mg, 0.5 mmol, 1 equiv) and tmphen (7.1 mg, 6.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (10.0 mg, 3.0 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through silica gel column chromatography (chloroform/ethyl acetate 100:0 → chloroform/ethyl acetate 96:4). The fractions containing product were collected and concentrated to give 67 mg of a mixture of

the *para* borylated 4-aminoindan **2j** with the *meta* isomer (*para*:*meta* = 2:1) as a yellowish solid (52% yield).

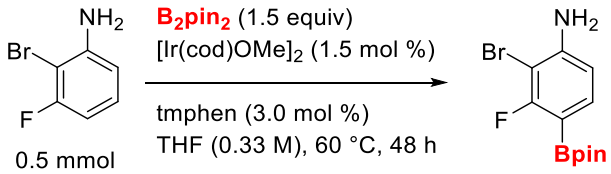
Para:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 3.71 (bs, 2H), 3.14 (t, *J* = 7.5 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.09 (p, *J* = 7.5 Hz, 3H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 153.3, 145.4, 135.5, 127.6, 114.2 (C–B observed by HMBC), 111.7, 82.9, 34.5, 29.1, 25.0, 24.5. (assignments based on HSQC and HMBC correlations). ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.2. HRMS (ESI) m/z calcd for $C_{15}H_{23}BNO_2$ $[M+H]^+$ 260.1822, found 260.1818

Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.97 (s, 1H), 3.71 (bs, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.09 (p, *J* = 7.4 Hz, 7H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2, 142.2, 132.5, 127.6 (C–B observed by HMBC), 121.3, 118.8, 83.6, 33.0, 29.7, 24.9, 24.8. (assignments based on HSQC and HMBC correlations). ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.2. HRMS (ESI) m/z calcd for $C_{15}H_{23}BNO_2$ $[M+H]^+$ 260.1822, found 260.1818

***Para* borylation of 2-bromo-3-fluoroaniline (2k)**



>95% conversion, *para : meta* = 4 : 1
76% isolated yield, *para : meta* = 5 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with methyl 2-bromo-3-fluoroaniline (95 mg, 0.5 mmol, 1 equiv) and tmphen (3.5 mg, 3.0 mol %) in THF (0.5 mL). In a se*para*te tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the

microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 120 mg of the *para* borylated 2-bromo-3-fluoroaniline **2k** with a minor byproduct corresponding to the *meta* isomer (*para*:*meta* = 5:1) as a white solid (76% yield).

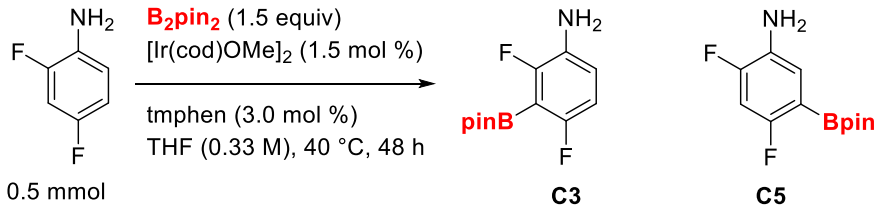
Para:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 8.2, 6.4 Hz, 1H), 6.50 (dd, *J* = 8.2, 0.9 Hz, 1H), 4.42 (bs, 2H), 1.32 (s, 12H). ^{19}F NMR (470 MHz, $CDCl_3$) δ -94.86 (dd, *J* = 6.4, 2.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4 (d, *J* = 250.3 Hz), 149.0 (d, *J* = 3.9 Hz), 135.8 (d, *J* = 10.2 Hz), 110.3 (d, *J* = 2.4 Hz), 96.0 (d, *J* = 26.0 Hz), 83.7, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.8. HRMS (ESI) m/z calcd for $C_{12}H_{17}BBrFNO_2$ $[M+H]^+$ 316.0520, found 316.0501

Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (t, *J* = 1.1 Hz, 1H), 6.89 (dd, *J* = 8.5, 1.1 Hz, 1H), 4.42 (bs, 2H), 1.32 (s, 12H). ^{19}F NMR (470 MHz, $CDCl_3$) δ -107.45 (d, *J* = 8.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6 (d, *J* = 245.7 Hz), 145.8 (d, *J* = 2.5 Hz), 116.8 (d, *J* = 2.4 Hz), 110.5 (d, *J* = 21.0 Hz), 99.7 (d, *J* = 23.4 Hz), 84.3, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.8. HRMS (ESI) m/z calcd for $C_{12}H_{17}BBrFNO_2$ $[M+H]^+$ 316.0520, found 316.0501

***Para* borylation of 2,4-difluoroaniline (2l)**



>95% conversion, **C3** : **C5** = 15 : 1
27% isolated yield, **C3** : **C5** = 13 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with methyl 2-fluoro-4-fluoroaniline (65 mg, 0.5 mmol, 1 equiv) and tmphen (3.5 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a silica gel column chromatography (chloroform/ethyl acetate 24:1 as eluent). The fractions containing product were collected and concentrated to give 34 mg of the **C3**-borylated 2-fluoro-4-fluoroaniline **2l** with a minor byproduct corresponding to the **C5** isomer (**C3**:**C5** = 13:1) as a pale brownish solid (27% yield).

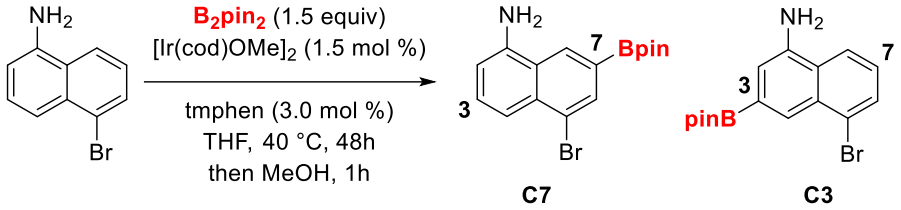
3-borylated product, major isomer:

^{1}H NMR (500 MHz, C_6D_6) δ 6.48 (td, *J* = 8.5, 1.4 Hz, 1H), 6.10 (ddd, *J* = 9.9, 8.5, 5.6 Hz, 1H), 2.77 (bs, 2H), 1.13 (s, 12H). ^{19}F NMR (470 MHz, C_6D_6) δ -114.8 (dt, *J* = 8.5, 4.3 Hz), -121.8 (dd, *J* = 9.9, 4.0 Hz). ^{13}C NMR (126 MHz, C_6D_6) δ 158.8 (dd, *J* = 241.2, 11.6 Hz), 154.2 (dd, *J* = 244.1, 12.4 Hz), 130.8 (dd, *J* = 14.8, 3.3 Hz), 118.9 (dd, *J* = 9.4, 5.6 Hz), 110.6 (dd, *J* = 24.8, 3.9 Hz), 83.6, 24.4. ^{11}B NMR (160 MHz, C_6D_6) δ 30.2. HRMS (ESI) m/z calcd for $C_{12}H_{17}BF_2NO_2$ $[M+H]^+$ 256.1320, found 256.1310

5-borylated product, major isomer:

^{1}H NMR (500 MHz, C_6D_6) δ 7.13 (dd, *J* = 10.5, 5.6 Hz, 0H), 6.54 (dd, *J* = 11.2, 8.5 Hz, 0H), 2.77 (bs, 2H), 1.13 (s, 12H). ^{19}F NMR (470 MHz, C_6D_6) δ -111.9 (dt, *J* = 10.2, 5.2 Hz), -126.1 (td, *J* = 10.8, 5.0 Hz).

C7 borylation of 5-bromo-1-naphthylamine (2m)

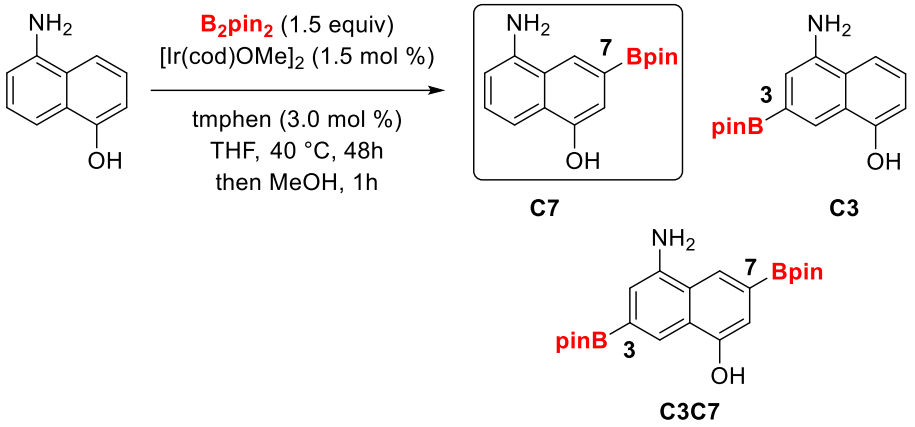


93% conversion, **C7** : **C3** = 7 : 1
57% isolated yield, **C7** : **C3** > 20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 5-bromo-1-naphthylamine (111 mg, 0.5 mmol, 1 equiv) and tmphen (3.6 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and **7:3** borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 99 mg of *para* borylated **2m** with only traces of the 3-borylated isomer (**C7**:**C3** > 20:1) as a light brown solid (57% yield, mp 190-192 °C). The solid was recrystallized over toluene to confirm the structure by x-ray crystallography. The CIF file is available for download from the CCDC and may be referenced by CCDC deposition 2062023.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.3 (t, *J* = 1.0 Hz, 1H), 8.1 (d, *J* = 1.0 Hz, 1H), 7.7 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.4 (dd, *J* = 8.5, 7.5 Hz, 1H), 6.8 (dd, *J* = 7.5, 1.0 Hz, 1H), 4.3 (bs, 2H), 1.4 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 134.6, 134.5, 129.2, 128.8, 124.1, 123.4, 118.0, 110.7, 84.3, 25.0. C–B not observed due to quadrupolar relaxation. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.4. HRMS (ESI) m/z calcd for $C_{16}H_{20}BBrNO_2$ [M+H] 348.0770, found 348.0759

C7 borylation of 5-hydroxy-1-naphthylamine (2n)



68% conversion, **C7** : **C3 : C3C7** = 9.8 : 0.4 : 1
33% isolated yield, **C7** : **C3 : C3C7** = 16 : 1 : 0.2

In a glove box, a 5.0 mL Wheaton microreactor was charged with 5-hydroxy-1-naphthylamine (80 mg, 0.5 mmol, 1 equiv) and tmphen (3.6 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, the microreactor was brought out of the glove box, open to air and MeOH (2.5 mL) was added. The mixture was stirred for 1 h. An aliquot of the reaction mixture was taken, evaporated and analyzed directly by ^{1}H NMR to find the conversion and **C7:C3:C3C7** borylation ratio. The mixture was passed through silica gel column chromatography (chloroform/ethyl acetate 9:1 → chloroform/ethyl acetate 4:1 as eluent). The

fractions containing product were collected to give 47 mg of C7-borylated **2n** with minor byproducts corresponding to the C3-borylated and C3,C7-diborylated isomers (**C7**:**C3:C3C7** = 16:1:0.2) as a purple solid (33% yield).

C7 borylated product:

^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 7.87 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 7.06 (s, 1H), 6.66 (dd, *J* = 7.5, 1.1 Hz, 1H), 5.66 (bs, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, DMSO-d6) δ 152.4, 145.3, 127.4, 126.7, 123.6, 121.2, 111.7, 109.5, 108.3, 83.4, 24.8. ^{11}B NMR (160 MHz, DMSO-d6) δ 31.8. HRMS (ESI) m/z calcd for $C_{16}H_{21}BNO_3$ $[M+H]^+$ 286.1614, found 286.1604

C3 borylated product:

^{1}H NMR (500 MHz, DMSO-d6) δ 9.94 (s, 1H), 7.84 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.21 (m, 1H), 6.96 (s, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 5.66 (bs, 2H), 1.32 (s, 12H). HRMS (ESI) m/z calcd for $C_{16}H_{21}BNO_3$ $[M+H]^+$ 286.1614, found 286.1604

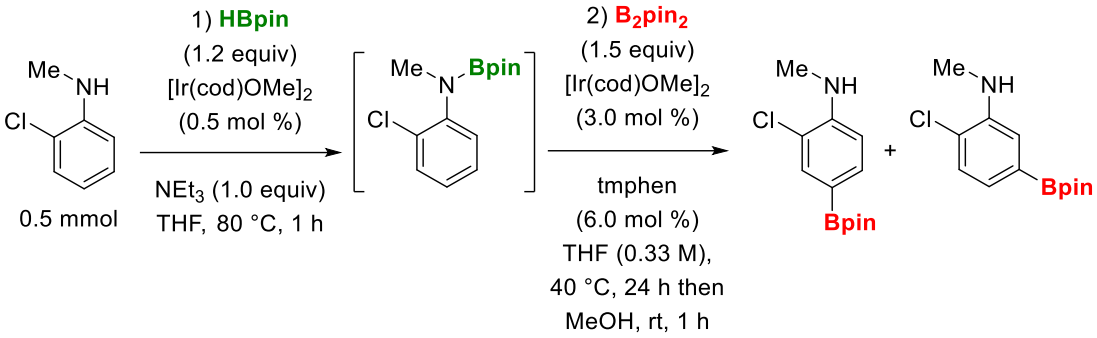
A second fraction was collected corresponding to 39 mg of C7-borylated **2n** with a minor byproduct corresponding to the C3,C7-diborylated product (**C7:C3C7** = 4:1) (25% yield). This fraction was taken as reference to make the assignment of the C3,C7-diborylated isomer.

C3-C7 diborylated product:

^{1}H NMR (500 MHz, DMSO-d6) δ 9.84 (s, 1H), 7.85 (s, 1H), 7.81 (s, 1H), 7.06 (s, 1H), 6.97 (s, 1H), 5.68 (bs, 2H), 1.32 (s, 12H), 1.30 (s, 12H). HRMS (ESI) m/z calcd for $C_{22}H_{32}B_2NO_5$ [M] 412.2467, found 412.3779.

4.4.3. *Para* CHB of N-alkylated anilines

Unselective Borylation of 2-chloro-N-methylaniline (4a)

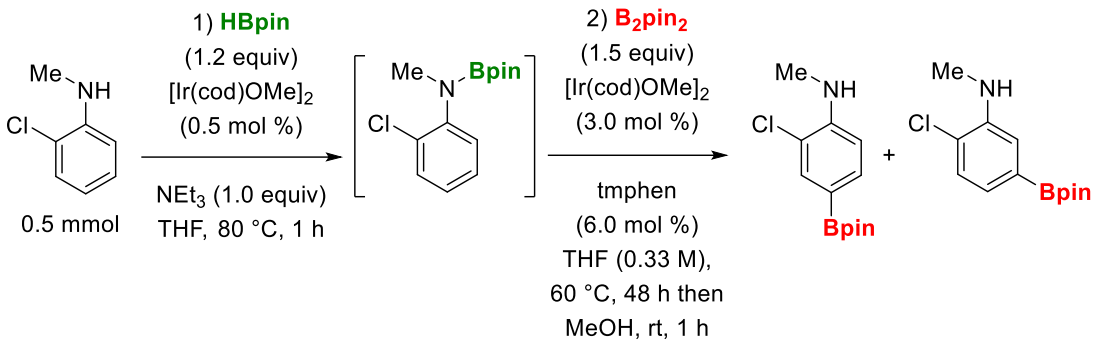


>95% conversion, *para : meta* = 1 : 1
91% isolated yield, *para : meta* = 1 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-chloro-N-methyl aniline (71 mg, 0.5 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (1.7mg, 0.5 mol %), HBpin (77 mg, 0.6 mmol, 1.2 equiv), NEt_3 (0.08 mL, 0.5 mmol), and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. The microreactor was charged $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), B_2pin_2 (190 mg, 0.75 mmol), and THF (0.5 mL). The reaction was then stirred for 5 minutes over which the reaction turned a dark golden color. tmphen (3.6 mg, 6.0 mol %) and THF (0.5 mL) was then added causing the reaction to turn a dark green color. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 24 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR showing complete conversion and a 1:1 *para : meta* borylation ratio. MeOH (2.25 mL) was added resulting in vigorous bubbling, and the mixture was stirred for 1 h at room temperature. The mixture was concentrated and passed through a plug of silica gel (2 cm x 5 cm) (hexane/ethyl acetate 4:1 as eluent). The fractions containing product were collected and concentrated to give 122 mg of a *para*

and *meta* borylated 2-chloro-N-methylaniline **4a** as a mixture of isomers (*para*:*meta* = 1:1) as a white solid (91% yield).

The reaction was repeated but this time the *para* and *meta* isomer were separate for characterization.



>95% conversion, *para : meta* = 1 : 1
1.1% isolated yield, *para : meta* = > 20 : 1
13% isolated yield, *para : meta* = < 1 : 20

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-chloro-N-methyl aniline (71 mg, 0.5 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (1.7mg, 0.5 mol %), HBpin (77 mg, 0.6 mmol, 1.2 equiv), NEt_3 (0.08 mL, 0.5 mmol), and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. The microreactor was charged $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), B_2pin_2 (190 mg, 0.75 mmol), and THF (0.5 mL). The reaction was then stirred for 5 minutes over which the reaction turned a dark golden color. tmphen (3.6 mg, 6.0 mol %) and THF (0.5 mL) was then added causing the reaction to turn a dark green color. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR showing complete conversion and a 1:1 *para : meta* borylation ratio. MeOH (2.25 mL) was added resulting in vigorous bubbling, and the mixture was stirred for 1 h at room temperature. The mixture was concentrated and passed through a plug of silica gel (2 cm x 5 cm) (chloroform as eluent). The

fractions containing product were collected and concentrated to give a first fraction containing 1.4 mg of *para* borylated 2-chloro-N-methylaniline **4a** (1% yield). The fraction was too small to take an accurate ^{13}C NMR but the peaks could be obtained by subtracting the *meta* carbon peaks from the *para*/*meta* mixture isolated previously. The NMR data of the *para* isomer were consistent with previously reported NMR values.[61]

Para:

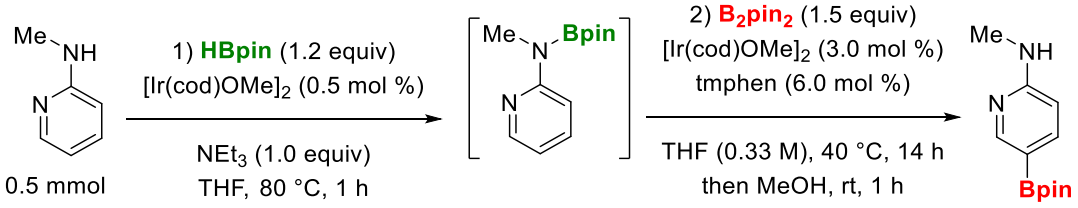
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.4 Hz, 1H), 7.60 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 4.60 (bs, 1H), 2.92 (d, *J* = 5.2 Hz, 3H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4, 135.4, 134.9, 118.7, 109.8, 83.6, 30.3, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.9. HRMS (ESI) m/z calcd for $C_{13}H_{20}BClNO_2$ $[M+H]^+$ 268.1276, found 268.1273

A second fraction was collected corresponding to 17.3 mg of *meta* borylated 2-chloro-N-methylaniline **4a** (13% yield).

Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.7 Hz, 1H), 7.08 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.07 (d, *J* = 1.4 Hz, 1H), 4.32 (bs, 1H), 2.95 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 128.6, 123.8, 122.5, 116.5, 84.0, 30.7, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.8. HRMS (ESI) m/z calcd for $C_{13}H_{20}BClNO_2$ $[M+H]^+$ 268.1276, found 268.1271

***Para* Borylation of N-methyl-2-aminopyridine (4b)**

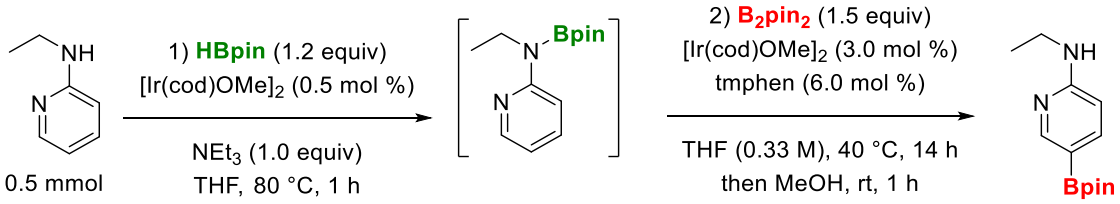


>95% conversion, *para : meta* = 4 : 1
39% isolated yield, *para : meta* > 20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with N-methyl-2-aminopyridine (54 mg, 0.5 mmol, 1 equiv), HBpin (77 mg, 0.6 mmol, 1.2 equiv), $[Ir(cod)(OMe)]_2$ (1.7 mg, 0.5 mol %), triethylamine (0.08 mL, 0.5 mmol, 1.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution and with tmphen (7.1 mg, 6.0 mol %). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 14 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel (ethyl acetate as eluent). The fractions containing product were collected and concentrated to give 46 mg of *para* borylated **4b** with traces of the *meta* isomer (*para*:*meta* > 20:1) as a white solid (39% yield, mp 101-103 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.78 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.32 (dd, *J* = 8.4, 0.9 Hz, 1H), 5.10 (d, *J* = 5.1 1H), 2.90 (d, *J* = 5.1 Hz, 3H), 1.30 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2, 155.4, 143.6, 104.8, 83.4, 28.9, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.8. HRMS (ESI) m/z calcd for $C_{12}H_{20}BN_2O_2$ $[M+H]^+$ 235.1618, found 235.1602

***Para* Borylation of N-ethyl-2-aminopyridine (4c)**

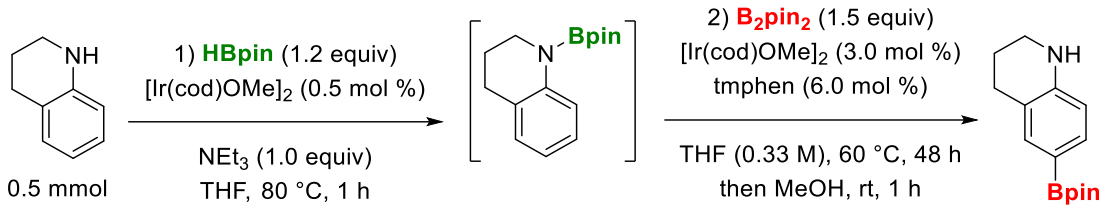


>95% conversion, *para : meta* = 3 : 1
50% isolated yield, *para : meta* > 20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with N-ethyl-2-aminopyridine (61 mg, 0.5 mmol, 1 equiv), HBpin (77 mg, 0.6 mmol, 1.2 equiv), $[Ir(cod)(OMe)]_2$ (1.7 mg, 0.5 mol %), triethylamine (0.08 mL, 0.5 mmol, 1.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution and with tmphen (7.1 mg, 6.0 mol %). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 14 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel (ethyl acetate as eluent). The fractions containing product were collected, concentrated and 3 mL of water were added. The water layer was decanted and extracted with ethyl acetate (3 mL). The organic layer was separated and concentrated to give 62 mg of *para* borylated **4c** with traces of the *meta* isomer (*para*:*meta* > 20:1) as a white solid (50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.77 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.31 (dd, *J* = 8.4, 0.9 Hz, 1H), 5.29 (d, *J* = 5.8 Hz, 1H), 3.24 (qd, *J* = 7.2, 5.8 Hz, 2H), 1.28 (s, 12H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 154.7, 144.2, 105.0, 83.5, 36.9, 24.9, 14.7. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.1. HRMS (ESI) m/z calcd for $C_{13}H_{22}BN_2O_2$ $[M+H]^+$ 249.1774, found 249.1759

***Para* Borylation of 1,2,3,4-tetrahydroquinoline (4d)**



>95% conversion, *para : meta* = 11 : 1
36% isolated yield, *para : meta* > 20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 1,2,3,4-tetrahydroquinoline (60 mg, 0.5 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (1.7mg, 0.5 mol %), HBpin (77 mg, 0.6 mmol, 1.2 equiv), NEt_3 (0.08 mL, 0.5 mmol), and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. The microreactor was charged $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), B_2pin_2 (190 mg, 0.75 mmol), and THF (0.5 mL). The reaction was then stirred for 5 minutes over which the reaction turned a dark golden color. tmphen (3.6 mg, 6.0 mol %) and THF (0.5 mL) was then added causing the reaction to turn a dark green color. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR showing complete conversion and a 9:1 *para : meta* borylation ratio. MeOH (2.25 mL) was added resulting in vigorous bubbling, and the mixture was stirred for 1 h at room temperature. The mixture was concentrated and passed through a plug of silica gel (chloroform/hexane/ethyl acetate 7:2:1 as eluent). The fractions containing product were collected as two groups and concentrated to give 46.7 mg of a *para* borylated 1,2,3,4-tetrahydroquinoline **4d** as a colorless oil (36% yield) with the *meta* isomer as a minor byproduct being collected as a white solid at 4.3 mg (3% yield). The NMR data of the *para* isomer were consistent with previously reported values, designated as compound **33a** in the cited paper.[62]

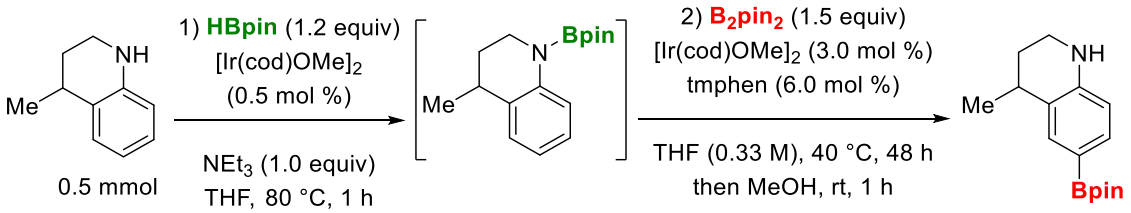
Para:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.39 (m, 2H), 6.45-6.40 (m, 1H), 4.09 (bs, 1H), 3.31 (t, *J*=5.5, 2H), 2.76 (t, J = 6.3, 2H), 1.95-1.87 (m, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 136.4, 133.9, 120.3, 113.2, 83.2, 41.9, 26.9, 24.9, 22.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.6. HRMS (ESI) m/z calcd for $C_{15}H_{23}BNO_2$ $[M+H]^+$ 260.1822, found 260.1814

Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.91 (s, 1H), 3.81 (bs, 1H), 3.34 – 3.21 (m, 2H), 2.77 (t, *J* = 6.3 Hz, 2H), 1.93 (p, *J* = 6.5 Hz, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 129.2, 125.1, 123.5, 120.5, 83.6, 42.2, 27.3, 25.0, 22.2. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.6. HRMS (ESI) m/z calcd for $C_{15}H_{23}BNO_2$ $[M+H]^+$ 260.1822, found 260.1814

***Para* Borylation of 4-methyl-1,2,3,4-tetrahydroquinoline (4e)**



60% conversion, *para : meta* = 12 : 1
60% isolated yield**,** *para : meta* = 12 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with the 4-methyl-1,2,3,4-tetrahydroquinoline (74 mgs, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (1.7 mg, 0.5 mol %), HBpin (77 mg, 0.6 mmol, 1.2 equiv), triethylamine (0.08 mL, 0.5 mmol, 1.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL)

were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution and with tmphen (7.1 mg, 6.0 mol %). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a column of silica gel (chloroform as eluent). The fractions containing product were collected to give 72 mg of *para* borylated **4e** with a minor byproduct corresponding to the *meta* borylated isomer (*para*:*meta* = 16:1) as a yellow sticky solid (53% yield). The *para* product was characterized by ^{1}H-NOE.

Major Para Borylated Product:

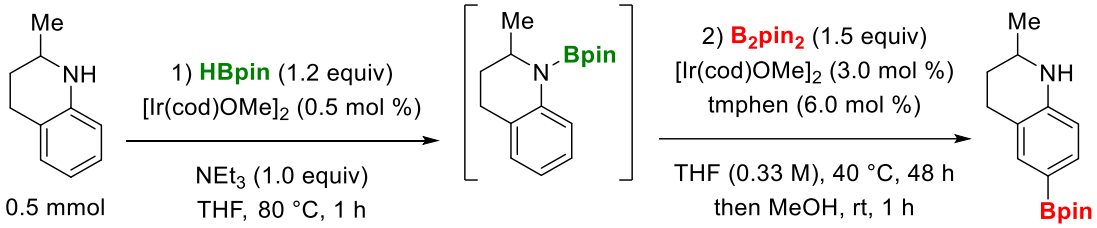
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 4.12 (bs, 1H), 3.40 – 3.26 (m, 2H), 2.98 – 2.87 (m, 1H), 2.01 – 1.90 (m, 1H), 1.74 – 1.62 (m, 1H), 1.33 (s, 12 H), 1.31 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.0, 135.4, 134.0, 125.4, 113.2, 83.2, 38.6, 30.2, 29.4, 25.0, 24.9 (two inequivalent types of methyl groups in the Bpin group), 22.6. ^{11}B NMR (160 MHz, $CDCl_3$) 30.9. HRMS (ESI) m/z calcd for $C_{16}H_{25}BNO_2$ $[M+H]^+$ 274.1978, found 274.1982

A second fraction was collected corresponding to 9.6 mg of *para* borylated **4e** with a minor byproduct corresponding to the *meta* borylated isomer (*para*:*meta* = 4:1) (7% yield). This fraction was taken as reference to make the assignment of the *meta* borylated isomer. The total yield adds up to 60% (*para : meta* = 12 : 1).

Minor Meta Borylated Product:

^{1}H NMR (500 MHz, $CDCl_3$) 7.08 (s, 2H), 6.93 (s, 1H), 3.40 – 3.26 (m, 2H), 2.98 – 2.87 (m, 1H), 2.01 – 1.90 (m, 1H), 1.74 – 1.62 (m, 1H), 1.33 (s, 12 H), 1.31 (d, J = 7.0 Hz, 3H). HRMS (ESI) m/z calcd for $C_{16}H_{25}BNO_2$ $[M+H]^+$ 274.1978, found 274.1982

***Para* Borylation of 2-methyl-1,2,3,4-tetrahydroquinoline (4f)**



45% conversion, *para : meta*= 10 : 1
41% isolated yield**,** *para : meta*= 13 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with the 2-methyl-1,2,3,4-tetrahydroquinoline (74 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (1.7 mg, 0.5 mol %), HBpin (77 mg, 0.6 mmol, 1.2 equiv), triethylamine (0.08 mL, 0.5 mmol, 1.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution and with tmphen (7.1 mg, 6.0 mol %). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a column of silica gel (chloroform as an eluent). The fractions containing product were collected and concentrated to give 48 mg of *para* borylated **4f** with only traces of the *meta*

isomer (*para*:*meta* > 20:1) as a white solid (35% yield). The NMR data were consistent with previously reported values, designated as compound **3u** in the cited paper.[63]

Para isomer (C6)

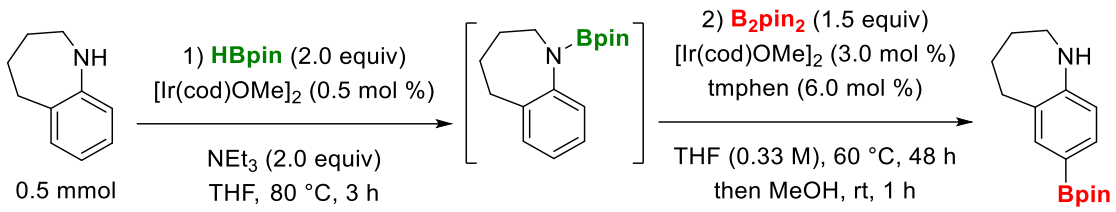
^{1}H NMR (500 MHz, C_6D_6) δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.90 (s, 1H), 6.28 (d, *J* = 8.0, 1H), 3.36 – 3.19 (bs, 1H), 3.00 – 2.83 (m, 1H), 2.61 – 2.45 (m, 2H), 1.49 – 1.40 (m, 1H), 1.34 – 1.23 (m, 1H), 1.18 (s, 12H), 0.74 (d, *J* = 5.7 Hz, 3H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 2H), 6.43 (d, *J* = 7.9 Hz, 1H), 3.93 (bs, 1H), 3.43 (ddd, *J* = 9.5, 6.3, 3.1 Hz, 1H), 2.91 – 2.66 (m, 2H), 1.99 – 1.87 (m, 1H), 1.57 (dddd, *J* = 12.8, 11.1, 9.7, 5.4 Hz, 1H), 1.32 (s, 12H), 1.21 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 147.9, 137.2, 134.6, 119.8, 113.5, 83.1, 47.0, 30.1, 26.7, 25.1, 22.4. ^{11}B NMR (160 MHz, C_6D_6) δ 31.6. HRMS (ESI) m/z calcd for $C_{16}H_{25}BNO_2$ $[M+H]^+$ 274.1978, found 274.1982

A second fraction was collected corresponding to 8.2 mg of a mixture of the *meta* and *para* borylated isomer (*para*:*met*a = 1:1) (6% yield). This fraction was taken as reference to make the assignment of the *meta* borylated isomer. The total yield adds up to 41% (*para : meta*= 13 : 1).

Meta isomer (C7)

^{1}H NMR (500 MHz, C_6D_6) 7.63 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.26 (d, *J* = 1.1 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 3.26 – 3.12 (bs, 1H), 2.97 – 2.86 (m, 1H), 2.62 – 2.44 (m, 2H), 1.59 – 1.40 (m, 1H), 1.38 – 1.22 (m, 1H), 1.16 (s, 12H), 0.78 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 144.8, 129.2, 124.4, 124.2, 121.4, 83.4, 47.2, 30.3, 27.1, 25.0, 22.5. ^{11}B NMR (160 MHz, C_6D_6) δ 31.0. HRMS (ESI) m/z calcd for $C_{16}H_{25}BNO_2$ $[M+H]^+$ 274.1978, found 274.1982

***Para* Borylation of 2,3,4,5-tetrahydro-1H-benzo[b]azepine (4g)**



92% conversion, *para : meta* = 3 : 1
53% isolated yield, *para : meta* > 20 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2,3,4,9-tetrahydro-1*H*-carbazole (86 mg, 0.5 mmol, 1 equiv), HBpin (154 mg, 1 mmol, 2 equiv), triethylamine (0.16 mL, 1 mmol, 2.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 3 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution and with tmphen (7.1 mg, 6.0 mol %). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para*:*meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and purified with a silica column (ethyl acetate:chloroform 1:25 as eluent). The fractions containing product were collected, concentrated to give 72 mg of *para* borylated **4g** with only traces of the *meta* borylated isomer (*para*:*meta* > 20:1) as yellowish solid (53% yield). *Para* isomer is assigned equivocally by gCOSY and NOE.

Major isomer, Para, (C7)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 3.95 (bs, 1H), 3.12 – 3.00 (m, 2H), 2.91 – 2.75 (m, 2H), 1.84 – 1.74 (m, 2H), 1.70 – 1.61 (m, 2H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 137.8, 133.6, 132.0, 118.7, 83.4, 48.6, 35.8, 31.6,

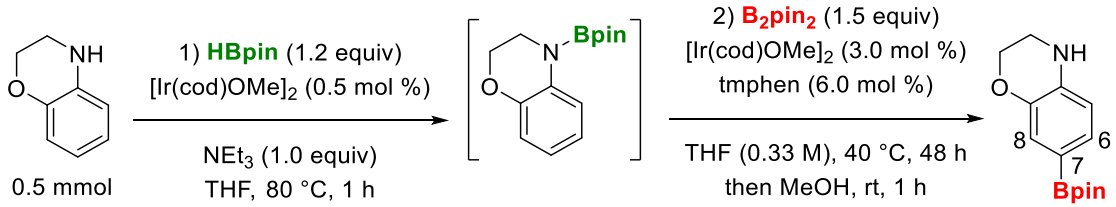
26.8, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.5. HRMS (ESI) m/z calcd for $C_{16}H_{25}BNO_2$ $[M+H]^+$ 274.1978, found 274.2035.

A second fraction was collected corresponding to 29 mg of a mixture of *para* borylated **4g** with the *meta* isomer (*para*:*meta* = 1:1) (21% yield). This fraction was taken as reference to make the assignment of the *meta* borylated isomer.

Minor isomer, Meta, (C8)

^{1}H NMR (500 MHz, $CDCl_3$) 7.29 (d, *J* = 7.4 Hz, 1H), 7.19 (s, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 3.89 (bs, 1H), 3.15 – 2.97 (m, 2H), 2.82 – 2.72 (m, 2H), 1.87 – 1.71 (m, 2H), 1.69 – 1.55 (m, 2H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.9, 137.5, 130.4, 127.7, 125.8, 83.5, 48.6, 35.8, 31.6, 26.8, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.2. HRMS (ESI) m/z calcd for $C_{16}H_{25}BNO_2$ $[M+H]^+$ 274.1978, found 274.2035

***Para* Borylation of 3,4-dihydro-2H-benzo[b][1,4]oxazine (4h)**



83% conversion **C7 : C6 : C8** = 29 : 1 : 3
77% isolated yield, **C7 : C6 : C8** = 17 : 1 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with the 3,4-dihydro-2*H*-benzo[1,4]oxazine (68 mgs, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (1.7 mg, 0.5 mol %), HBpin (77 mg, 0.6 mmol, 1.2 equiv), triethylamine (0.08 mL, 0.5 mmol, 1.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution

and with tmphen (7.1 mg, 6.0 mol %). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and **C7:C6:C8** borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel (chloroform/ethylacetate as eluent, 50:1). The fractions containing product were collected to give 83 mg of 7-borylated **4h** with minor byproducts corresponding to the 6-borylated and 8-borylated isomers (**C7:C6:C8 =** 17:1:1) as pale yellow solid (77% yield). The NMR data of the 7-borylated isomer were consistent with previously reported NMR values, designated as compound **13e** in the cited paper.[64]

7-borylated isomer, major isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 2H), 6.56 (d, *J* = 8.1 Hz, 1H), 4.24 – 4.19 (m, 2H), 3.95 (bs, 1H), 3.44 (t, *J* = 4.5 Hz, 3H), 1.31 (s, 11H). ^{1}H NMR (500 MHz, C_6D_6) δ 7.94 (s, 1H), 7.78 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.32 (d, *J* = 7.8 Hz, 1H), 3.70 – 3.65 (m, 2H), 2.80 (bs, 1H), 2.56 – 2.51 (m, 2H), 1.13 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 144.0, 137.5, 129.4, 124.0, 115.0, 83.5, 64.7, 41.0, 25.2. ^{11}B NMR (160 MHz, C_6D_6) δ 31.4. HRMS (ESI) m/z calcd for $C_{14}H_{21}BNO_3$ $[M+H]^+$ 262.1614, found 262.1614

6-borylated isomer, minor isomer:

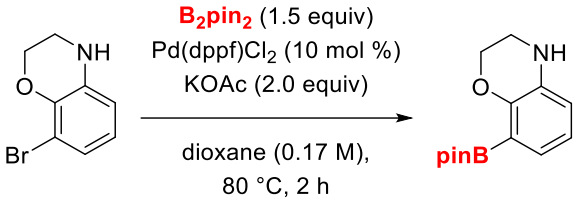
^{1}H NMR (500 MHz, C_6D_6) 7.65 (dd, *J* = 7.5, 1.1 Hz 1H), 7.3 (d, *J* = 8.0 Hz, 1H), 7.0 (s, 1H), 3.73 – 3.70 (m, 2H), 2.56 – 2.51 (m, 2H), 1.17 (s, 12H). HRMS (ESI) m/z calcd for $C_{14}H_{21}BNO_3$ $[M+H]^+$ 262.1614, found 262.1614]

8-borylated isomer, minor isomer:

^{1}H NMR (500 MHz, C_6D_6) 7.67 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 6.34 (d, *J* =1.6 Hz, 1H), 3.88 – 3.85 (m, 2H), 2.59 – 2.56 (m, 2H), 1.15 (s, 12H). HRMS (ESI) m/z calcd for $C_{14}H_{21}BNO_3$ $[M+H]^+$ 262.1614, found 262.1614

8-borylated isomer was assigned by preparing the title compound by Miyaura Borylation.

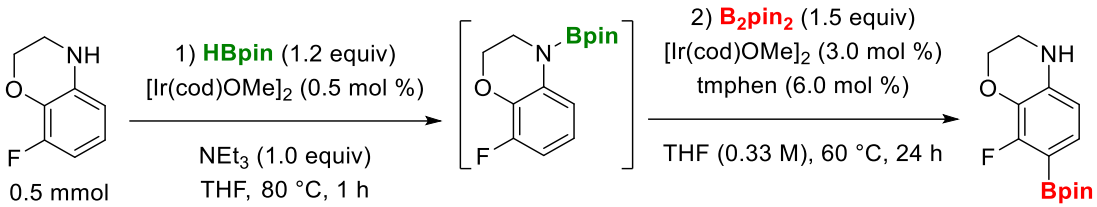
Miyaura Borylation of 8-bromo-3,4-dihydro-2H-benzo[b][1,4]oxazine



In a glove box, a 5.0 mL Wheaton microreactor was charged with the 8-bromo-3,4-dihydro-2H-1,4-benzoxazine (68 mg, 0.5 mmol) and dioxane (3 mL). KOAc (98 mg, 1.0 mmol, 2.0 equiv), bis(pinacolato)diboron (190 mg, 0.75 mmol, 1.5 equiv) and [1,1'-bis(diphenylphosphino) ferrocene]dicholoropalladium(II) (37 mg, 0.05 mol, 10 mol %) were added to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 2 h, the mixture was concentrated and passed through a plug of silica gel (dichloromethane as eluent). The product was collected and concentrated to give 50 mg of the borylated product as an orange solid (38% yield, mp 121-123 °C).

^{1}H NMR (500 MHz, C_6D_6) 7.66 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.43 (dd, *J* =7.7, 1.7, 1H), 3.88 (m, 2H), 2.60 (m, 2H), 1.16 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6 δ 149.8, 133.7, 126.8, 120.6,118.8 ,83.0, 65.0, 40.5, 24.8. ^{11}B NMR (160 MHz, C_6D_6) δ 31.5. GC-MS (EI) m/z calcd for $C_{14}H_{20}BNO_3$ [M] 261.2, found 261.1

***Para* Borylation of 8-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (4i)**



>95% conversion, *para : meta* = 8 : 1
89% isolated yield, *para : meta* = 10 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 8-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (77 mg, 0.5 mmol), $[Ir(cod)(OMe)]_2$ (1.7mg, 0.5 mol %), HBpin (77 mg, 0.6 mmol, 1.2 equiv), NEt_3 (0.08 mL, 0.5 mmol), and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. The microreactor was charged $[Ir(cod)(OMe)]_2$ (10 mg, 3 mol %), B_2pin_2 (190 mg, 0.75 mmol), and THF (0.5 mL). The reaction was then stirred for 5 minutes over which the reaction turned a dark golden color. tmphen (3.6 mg, 6.0 mol %) and THF (0.5 mL) was then added causing the reaction to turn a dark green color. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 24 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR showing complete conversion and a 8:1 *para : meta* borylation ratio. The mixture was concentrated and passed through a plug of silica gel (2 cm x 5 cm) (hexane/ethyl acetate 7:3 as eluent). The fractions containing product were collected, concentrated and washed with water (2 mL). The water layer was decanted and the residue was dried to yield 68 mg of a *para* borylated **4i** with the *meta* isomer as a minor byproduct (*para*:*meta* = 10:1) as a tan solid that darkened over time (89% yield).

Para:

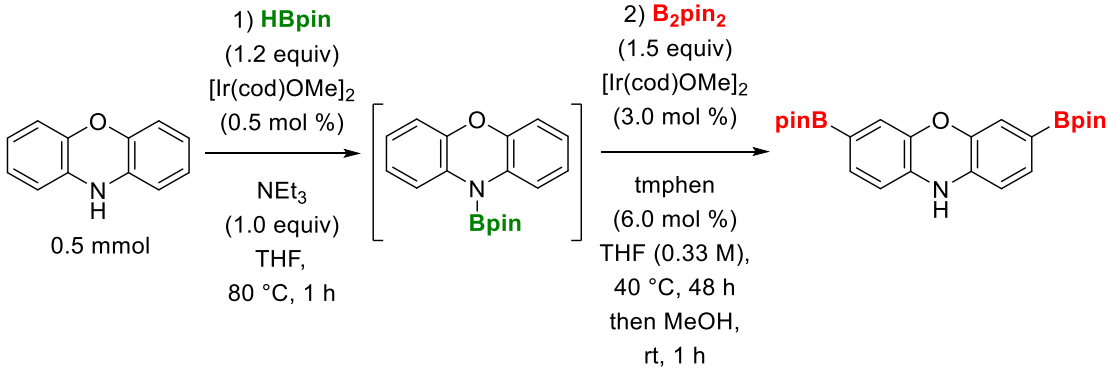
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 8.1, 5.9 Hz, 1H), 6.33 (dd, *J* = 8.1, 0.9), 4.28-4.22(m, 2H), 4.14-4.05 (m, 1H), 3.54-3.39 (m, 2H), 1.32 (s, 12H). ^{19}F NMR (470 MHz, $CDCl_3$) δ -127.4

(d, *J* = 6.7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5 (d, *J* = 248.1 Hz), 138.8 (dd, *J* = 5.3, 3.3 Hz), 131.4 (d, *J* = 15.3 Hz), 128.0 (d, *J* = 9.6 Hz), 110.0 (d, *J* = 2.4 Hz), 83.4, 64.9, 40.7, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.3. HRMS (ESI) m/z calcd for $C_{14}H_{20}BFNO_3$ $[M+H]^+$ 280.1520, found 280.1508

Meta:

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, J = 10.78, 1.16 Hz, 1H), 6.82 (s, 1H), 4.33-4.30 (m, 1H), 4.14-4.05 (m, 1H), 3.54-3.39 (m, 2H), 1.31 (s, 12H). ^{19}F NMR (470 MHz, $CDCl_3$) δ -138.73 (d, J = 10.8 Hz). HRMS (ESI) m/z calcd for $C_{14}H_{20}BFNO_3$ $[M+H]^+$ 280.1520, found 280.1508

***Para* Borylation of 10*H*-phenoxazine (4j)**



>95% conversión to major diborylated product
55% isolated yield of major diborylated product

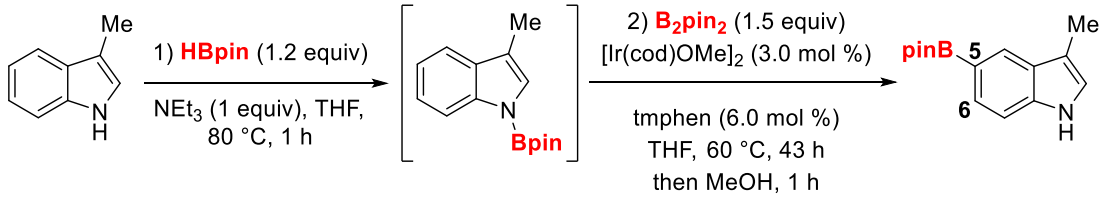
In a glove box, a 5.0 mL Wheaton microreactor was charged with HBpin (67 mg, 1 mmol, 1 equiv, 10*H*-phenoxazine (86 mg, 0.5 mmol, 1 equiv), triethylamine (0.08 mL, 1 mmol, 1.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution and with tmphen (7.1 mg, 6.0 mol %). The microreactor was

capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken, dissolve in DMSO-d6 and analyzed directly by ^{1}H NMR. Diborylated **4j** appeared as the major isomer (**4j**:others ≅ 2:1), the NMR data were consistent with previously reported NMR values designated as compound **PR1** in the cited paper.[65] MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through silica gel gradient column chromatography (ethyl acetate/chloroform 1:50 → ethyl acetate/chloroform 1:25 as eluent). The mixture was passed one more time through silica gel gradient column chromatography with the same solvent system (ethyl acetate/chloroform 1:50 → ethyl acetate/chloroform 1:25 as eluent). The fractions containing product were collected, concentrated to give 15 mg of mostly **4j** (**4j**:others ≅ 4:1) as a bright yellow solid (7% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.6 Hz, 2H), 7.04 (s, 2H), 6.33 (d, *J* = 7.7 Hz, 2H), 5.50 (bs, 1H), 1.31 (s, 24H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.4, 133.9, 131.0, 121.6, 112.9, 83.7, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6. GC-MS (EI) m/z calcd for $C_{24}H_{31}B_2NO_5$ [M] 435.2, found 435.1

4.4.4. C5 CHB of Indoles

C5 Borylation of 3-methyl indole (6a)



>95% conversion, **C5** :**C6** = 3 : 1
89% isolated yield, **C5** : **C6** = 4 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 3-methyl indole (66 mg, 0.5 mmol, 1 equiv), HBpin (77 mg, 0.6 mmol, 1.2 equiv), triethylamine (0.08 mL, 0.5 mmol, 1.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into

an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution and with tmphen (7.1 mg, 6.0 mol %). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 43 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and **5**:**6** borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 114 mg of 5-borylated **6a** with a minor byproduct corresponding to the 6-borylated isomer (**C5**:**C6** = 4:1) as a white solid (89% yield). The ^{1}H NMR data of the 5-borylated isomer were consistent with previously reported values.[66]

C5-borylated product:

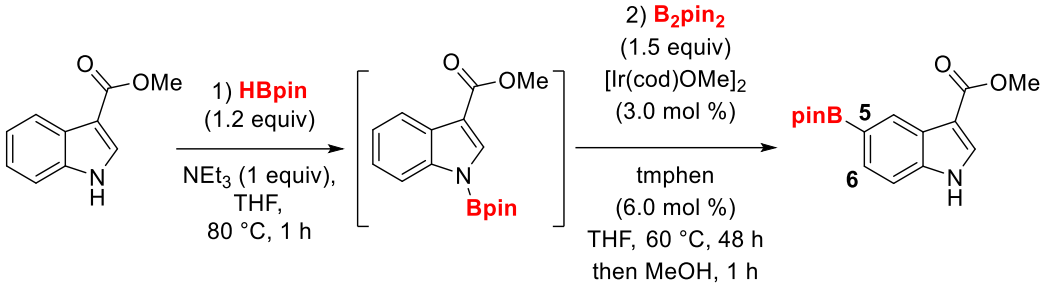
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (q, *J* = 0.9 Hz, 1H), 8.00 (bs, 1H), 7.67 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.32 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.93 (dq, *J* = 2.3, 1.1 Hz, 1H), 2.36 (d, *J* = 1.1 Hz, 3H), 1.40 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 128.1, 128.1, 126.8, 121.7, 112.5, 110.5, 83.6, 25.0, 9.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6. HRMS (ESI) m/z calcd for $C_{15}H_{21}BNO_2$ $[M+H]^+$ 258.1665, found 258.1649

C6-borylated product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (bs, 1H), 7.87 (d, *J* = 0.9 Hz, 1H), 7.67 (dd, *J* = 8.1, 1.1 Hz, 3H), 7.63 – 7.55 (m, 2H), 7.01 (dq, *J* = 2.2, 1.1 Hz, 1H), 2.35 (d, *J* = 1.1 Hz, 3H), 1.39 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1, 130.8, 125.0, 123.3, 118.3, 118.1, 111.8, 83.7, 25.0, 9.8.

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6. HRMS (ESI) m/z calcd for $C_{15}H_{21}BNO_2$ $[M+H]^+$ 258.1665, found 258.1649

C5 Borylation of methyl indole-3-carboxylate (6b)



>95% conversion, **C5** : **C6** = 1 : 1
86% isolated yield, **C5** : **C6** = 1 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with methyl indole-3-carboxyltae (88 mg, 0.5 mmol, 1 equiv), HBpin (77 mg, 0.6 mmol, 1.2 equiv), triethylamine (0.08 mL, 0.5 mmol, 1.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution and with tmphen (7.1 mg, 6.0 mol %). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and **5**:**6** borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel (chloroform/ethyl acetate 9:1). The fractions containing product were collected, concentrated and washed with water (3 mL). The water layer was decanted and the residue was dried to give 130 mg of 5-borylated and

6-borylated isomers **6b** (**C5**:**C6** = 1:1) as a beige solid (86% yield). The ^{1}H NMR data of the 5-borylated isomer in DMSO-d6 were consistent with previously reported values.[67]

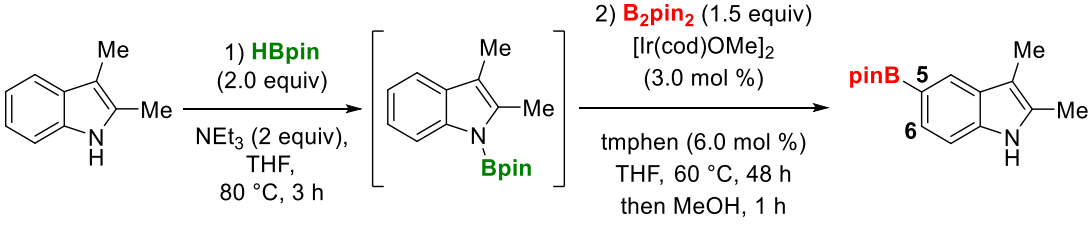
C5-borylated product:

^{1}H NMR (500 MHz, DMSO-d6) δ 12.04 (bs, 1H), 8.41 (s, 1H), 8.11 (d, *J* = 2.9 Hz, 1H), 7.51 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.46 (dd, *J* = 8.2, 0.9 Hz, 1H), 3.81 (d, *J* = 2.9 Hz, 3H), 1.31 (s, 12H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (bs, 1H), 8.67 (d, *J* = 1.1 Hz, 1H), 7.91 (d, *J* = 3.0 Hz, 1H), 7.70 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 3.93 (s, 3H), 1.37 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 138.3, 131.5, 129.3, 129.1, 125.4, 111.2, 109.2, 83.8, 51.4, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6. HRMS (ESI) m/z calcd for $C_{16}H_{21}BNO_4$ $[M+H]^+$ 302.1564, found 302.1563

C6-borylated product:

^{1}H NMR (500 MHz, DMSO-d6) δ 12.04 (bs, 1H), 8.19 (d, *J* = 3.1 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 1.0 Hz, 1H), 7.47 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.81 (d, *J* = 3.1 Hz, 3H), 1.31 (s, 12H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (bs, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 3.0 Hz, 1H), 7.91 (d, *J* = 0.9 Hz, 1H), 7.70 (dd, *J* = 8.0, 0.9 Hz, 1H), 3.93 (s, 3H), 1.37 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 136.0, 132.4, 128.3, 128.0, 120.9, 118.6, 108.9, 83.9, 51.3, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6. HRMS (ESI) m/z calcd for $C_{16}H_{21}BNO_4$ $[M+H]^+$ 302.1564, found 302.1563

C5 Borylation of 2,3-dimethyl indole (6c)



>95% conversion, **C5** : **C6** = 5 : 1
88% isolated yield, **C5** : **C6** = 4 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2,3-dimethyl-1*H*-indole (73 mg, 0.5 mmol, 1 equiv), HBpin (154 mg, 1 mmol, 2 equiv), triethylamine (0.16 mL, 1 mmol, 2.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution and with tmphen (7.1 mg, 6.0 mol %). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and C6:C5 borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel (chloroform as an eluent). The fractions containing product were collected and concentrated to yield 43 mg of the 5-borylated **6c** with a minor byproduct corresponding to the 6-borylated isomer (**C5**:**C6** = 8:1) as a yellowish solid (32% yield). The NMR data of the 5-borylated major isomer were consistent with previously reported values.[68]

5-borylated product, major isomer

^{1}H NMR (500 MHz, C_6D_6) 8.59 (d, *J* = 1.0 Hz, 1H), 8.18 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.13 (d, *J* = 8.1, 1H), 6.61 (bs, 1H), 2.08 (s, 3H), 1.80 (s, 3H), 1.17 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 138.2, 130.4, 130.0, 128.4,127.0, 110.2, 107.8, 83.5, 25.3, 11.3, 8.7. ^{11}B NMR (160 MHz, C_6D_6) δ 32.4. HRMS (ESI) m/z calcd for $C_{16}H_{23}BNO_2$ $[M+H]^+$ 272.1822, found 272.1826

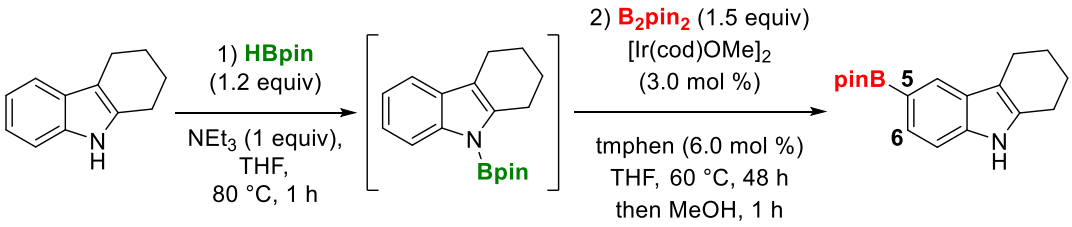
A second fraction was collected corresponding to 76 mg of the 5-borylated **6c** with a minor byproduct corresponding to the 6-borylated isomer (**C5:C6** = 3:1) (56% yield). This fraction was

taken as reference to make the assignment of the 6-borylated isomer. The total yield adds up to 88% (**C5** : **C6** = 4 : 1).

6-borylated isomer, minor product

^{1}H NMR (500 MHz, C_6D_6) 8.13 (dd, *J* = 7.9, 0.9 Hz, 1H), 8.05 (d, *J* = 0.9 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H) 6.61 (bs, 1H), 2.07 (s, 3H), 1.78 (s, 3H), 1.21 (s, 12H). HRMS (ESI) m/z calcd for $C_{16}H_{23}BNO_2$ $[M+H]^+$ 272.1822, found 272.1826

C5 Borylation of 2,3,4,9-tetrahydro-1H-carbazole (6d)



>95% conversion, **C5**:**C6** = 4:1
82% isolated yield, **C5**:**C6** = 5:1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2,3,4,9-tetrahydro-1*H*-carbazole (86 mg, 0.5 mmol, 1 equiv), HBpin (154 mg, 1 mmol, 2 equiv), triethylamine (0.16 mL, 1 mmol, 2.0 equiv) and THF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 3 h, the microreactor was brought back to the glove box. In a separate tube, $[Ir(cod)(OMe)]_2$ (10 mg, 3.0 mol %) and B_2pin_2 (190 mg, 1.5 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The microreactor was charged with the $[Ir(cod)(OMe)]_2/B_2pin_2$ solution and with tmphen (7.1 mg, 6.0 mol %). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and **5**:**6** borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and purified with a silica column (chloroform as an eluent).

The fractions containing product were collected and concentrated to yield 71 mg of the 5-borylated **6d** with a minor byproduct corresponding to the 6-borylated isomer (**C5:C6** = 5:1) as yellowish solid (82% yield).

5-borylated isomer, minor product

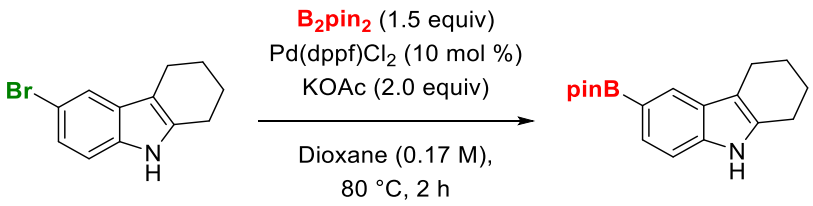
^{1}H NMR (500 MHz, C_6D_6) δ 8.58 (s, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 7.17 – 7.12 (m, 1H), 6.57 (bs, 1H), 2.61-2.54 (m, 2H), 2.23-2.17 (m, 2H), 1.61-1.55 (m, 4H), 1.21 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 138.5, 135.4, 133.6, 131.1, 126.5, 110.7, 110.3, 83.3, 25.2, 23.6, 23.4, 23.2, 21.1. ^{11}B NMR (160 MHz, C_6D_6) δ 31.6. HRMS (ESI) m/z calcd for $C_{18}H_{25}BNO_2$ $[M+H]^+$ 298.1978, found 298.1982

6-borylated isomer, minor product

^{1}H NMR (500 MHz, C_6D_6) 8.15 (d, *J* = 7.8 Hz, 1H), 8.10 (s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 6.64 (bs, 1H), 2.61-2.54 (m, 2H), 2.23-2.17 (m, 2H), 1.61-1.55 (m, 4H), 1.22 (s, 12H). HRMS (ESI) m/z calcd for $C_{18}H_{25}BNO_2$ $[M+H]^+$ 298.1978, found 298.1982

The major 6-borylated isomer was confirmed by synthesizing the compound independently via Miyaura borylation.

Miyaura Borylation of 6-bromo-2,3,4,9-tetrahydro-1H-carbazole



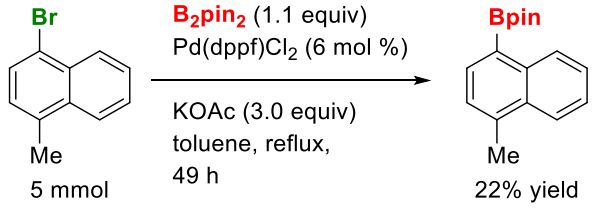
In a glove box, a 5.0 mL Wheaton microreactor was charged with 6-bromo-2,3,4,9-tetrahydro-1H-carbazole (125 mg, 0.5 mmol) and dioxane (3 mL). KOAc (98 mg, 1.0 mmol, 2.0 equiv), bis(pinacolato)diboron (190 mg, 0.75 mmol, 1.5 equiv) and [1,1'-bis(diphenylphosphino) ferrocene]dicholoropalladium(II) (37 mg, 0.05 mol, 10 mol %) were added to the microreactor.

The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 2 h, the mixture was concentrated and passed through a plug of silica gel (dichloromethane as eluent). The product was collected and concentrated to give 72 mg of the borylated product as an orange solid (48% yield, mp 135-137 °C).

^{1}H NMR (500 MHz, C_6D_6) δ 8.62 (s, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 7.16 – 7.14 (m, 1H), 6.32 (bs, 1H), 2.61 (m, 2H), 2.18 (m, 2H), 1.58 (m, 4H), 1.21 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 138.5, 135.4, 133.8, 131.6, 126.4, 110.6, 110.3, 83.4, 25.1, 23.6, 23.4, 23.2, 21.1. ^{11}B NMR (160 MHz, C_6D_6) δ 31.8. HRMS (ESI) m/z calcd for $C_{18}H_{25}BNO_2$ $[M+H]^+$ 298.1978, found 298.1958

4.4.5. Synthesis 1-borylated naphthalenes

Miyaura Borylation of 1-bromo-4-methylnaphthalene (7b)

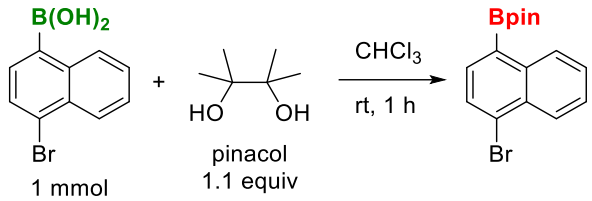


In a glove box, a 100 mL Schlenk flask was charged with 1-bromo-4-methylnaphthalene (1.10 g, 5 mmol, 1 equiv), B_2pin_2 (1.40 g, 5.5 mmol, 1.1 equiv), $Pd(dppf)Cl_2$ (220 mg, 6 mol %) and KOAc (1.47 g, 15 mmol, 3.0 equiv) in toluene (65 mL). The flask was covered with a septum, brought out of the glove box and connected to a condenser under nitrogen. The reaction was heated to 110 ºC for 2 days. The solution was concentrated under vacuum and redissolved in dichloromethane (150 mL). The mixture was washed with water (50 mL) and the aqueous layer was extracted with dichloromethane (2 x 150 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The residue was passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give an oil which solidifies upon addition of MeOH. The solid was filtered and dried overnight

under vacuum to obtained **6a** as a white solid (300 mg, 22% yield, mp 82-84 °C, lit 77-79 °C).[69] The NMR data were consistent with previously reported values, designated as compound **2r** in the cited paper.[69,70]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 8.0, 2.4 Hz, 1H), 8.02 (dd, *J* = 7.7, 2.2 Hz, 1H), 7.99 (d, *J* = 7.0 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.33 (d, *J* = 6.9 Hz, 1H), 2.72 (s, 3H), 1.43 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 137.1, 135.8, 132.5, 129.1, 126.1, 126.1, 125.5, 124.3, 83.7, 25.1, 20.1. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6. HRMS (ESI) m/z calcd for $C_{17}H_{22}BO_2$ $[M+H]^+$ 269.1713, found 269.1698

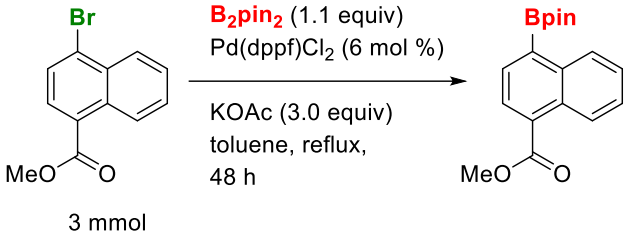
Pinacol esterification of 4-bromonaphthalene-1-boronic acid (7c)



A 20 mL vial was charged with 4-bromonaphthalene-1-boronic acid (251 mg, 1 mmol, 1 equiv), pinacol (130 mg, 1.1 mmol, 1.1 equiv) in chloroform (8 mL). The flask was capped and stirred for 1 h at room temperature. The solution was concentrated under vacuum and redissolved in ethyl acetate (5 mL). The mixture was washed two times with water (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduce pressure to give 229 mg of **5c** as a white solid (69% yield, mp 97-99 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 – 8.78 (m, 1H), 8.35 – 8.26 (m, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.64 – 7.57 (m, 2H), 1.43 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 135.8, 131.8, 129.4, 129.0, 127.5, 127.4, 127.3, 127.1, 84.1, 25.1. (no C-B bond observed due to quadrupolar relaxation). ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.3. HRMS (ESI) m/z calcd for $C_{16}H_{18}BBrO_2Na$ $[M+Na]^+$ 355.0481, found 355.0730

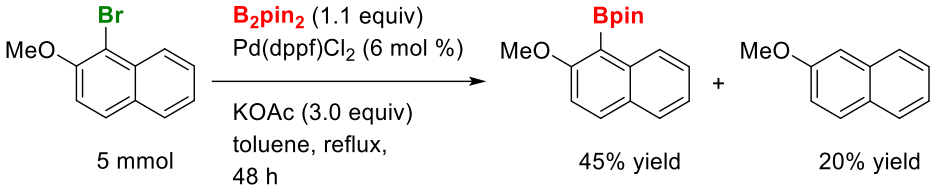
Miyaura Borylation of methyl 4-bromo-1-naphthoate (7d)



In a glove box, a 100 mL Schlenk flask was charged with methyl 4-bromo-1-naphthoate (795 mg, 3 mmol, 1 equiv), B_2pin_2 (838 mg, 3.3 mmol, 1.1 equiv), $Pd(dppf)Cl_2$ (132 mg, 6 mol %) and KOAc (882 mg, 9 mmol, 3.0 equiv) in toluene (65 mL). The flask was covered with a septum, brought out of the glove box and connected to a condenser under nitrogen. The reaction was heated to 110 ºC for 2 days. The solution was concentrated under vacuum and redissolved in dichloromethane (150 mL). The mixture was washed with water (50 mL) and the aqueous layer was extracted with dichloromethane (2 x 150 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The mixture was passed through silica gel column chromatography (petroleum ether/ethyl acetate 40:1 as eluent). The fractions containing product were collected and concentrated to give 753 mg of **7d** as a white greenish solid (80% yield, mp 69-71 °C). The NMR data were consistent with previously reported values.[71]

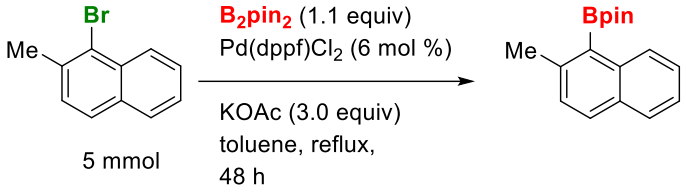
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 – 8.74 (m, 2H), 8.10 – 8.04 (m, 2H), 7.64 – 7.55 (m, 2H), 4.01 (s, 3H), 1.44 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 137.4, 134.0, 130.8, 130.2, 128.9, 128.5, 127.3, 126.6, 125.9, 84.3, 52.4, 25.1. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.5. HRMS (ESI) m/z calcd for $C_{18}H_{22}BO_4$ $[M+H]^+$ 313.1611, found 313.1598

Miyaura Borylation of 1-bromo-2-methoxynaphthalene (7e)



In a glove box, a 100 mL Schlenk flask was charged with 1-bromo-2-methoxynaphthalene (1.18 g, 5 mmol, 1 equiv), B_2pin_2 (1.40 g, 5.5 mmol, 1.1 equiv), $Pd(dppf)Cl_2$ (220 mg, 6 mol %) and KOAc (1.47 g, 15 mmol, 3.0 equiv) in toluene (65 mL). The flask was covered with a septum, brought out of the glove box and connected to a condenser under nitrogen. The reaction was heated to 110 ºC for 2 days. The solution was concentrated under vacuum and redissolved in dichloromethane (150 mL). The mixture was washed with water (50 mL) and the aqueous layer was extracted with dichloromethane (2 x 150 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The residue was passed through a plug of silica gel ($CHCl_3$ as eluent) to get a mixture of the product with the 2-methoxynaphthalene as the byproduct. The mixture was passed through silica gel column chromatography ($CHCl_3$ as eluent) to remove the byproduct. The fractions containing product were collected and concentrated to yield 644 mg of **7e** as a white solid (45% yield, mp 97-99 °C, lit 93-94 °C).[72] The NMR data were consistent with previously reported values, designated as compound **9** in the cited paper.[72] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dq, *J* = 8.5, 0.9 Hz, 1H), 7.86 (d, *J* = 9.0 Hz,1H), 7.76 (dt, *J* = 8.2, 0.8 Hz,1H), 7.44 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.31 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.22 (d, *J* = 9.0 Hz, 1H), 3.92 (s, 3H), 1.49 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.6, 137.2, 131.8, 129.0, 128.3, 126.9, 126.7, 123.4, 113.0, 84.1, 56.7, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.2. HRMS (ESI) m/z calcd for $C_{17}H_{22}BO_3$ $[M+H]^+$ 285.1662, found 285.1654

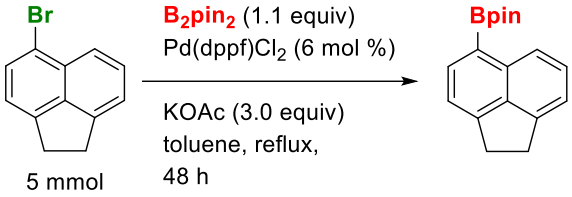
Miyaura Borylation of 1-bromo-2-methylnaphthalene (7f)



In a glove box, a 100 mL Schlenk flask was charged with 1-bromo-2-methylnaphthalene (1.10 g, 5 mmol, 1 equiv), B_2pin_2 (1.40 g, 5.5 mmol, 1.1 equiv), $Pd(dppf)Cl_2$ (220 mg, 6 mol %) and KOAc (1.47 g, 15 mmol, 3.0 equiv) in toluene (65 mL). The flask was covered with a septum, brought out of the glove box and connected to a condenser under nitrogen. The reaction was heated to 110 ºC for 2 days. The solution was concentrated under vacuum and redissolved in dichloromethane (150 mL). The mixture was washed with water (50 mL) and the aqueous layer was extracted with dichloromethane (2 x 150 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The residue was passed through silica gel column chromatography (petroleum ether/dichloromethane 3:1 as eluent) to remove the byproduct. The fractions containing product were collected and concentrated to give 737 mg of **7f** as a white solid (55% yield, mp 90-92 °C, lit 92-94 °C).[73] The NMR data were consistent with previously reported values, designated as compound **3d** in the cited paper.[73,74]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.46 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.39 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 2.64 (s, 3H), 1.49 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 136.7, 131.5, 129.7, 128.6, 128.3, 127.6, 126.1, 124.7, 84.1, 25.2, 22.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.5. HRMS (ESI) m/z calcd for $C_{17}H_{22}BO_2$ $[M+H]^+$ 269.1713, found 269.1697

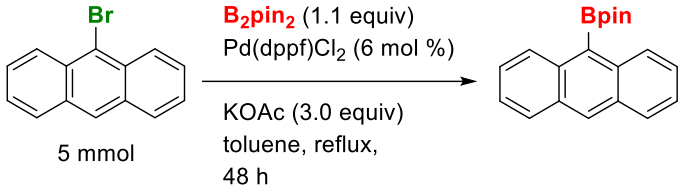
Miyaura Borylation of 5-bromoacenaphthene (7g)



In a glove box, a 100 mL Schlenk flask was charged with 5-bromoacenaphthene (1.16 g, 5 mmol, 1 equiv), B_2pin_2 (1.40 g, 5.5 mmol, 1.1 equiv), $Pd(dppf)Cl_2$ (220 mg, 6 mol %) and KOAc (1.47 g, 15 mmol, 3.0 equiv) in toluene (65 mL). The flask was covered with a septum, brought out of the glove box and connected to a condenser under nitrogen. The reaction was heated to 110 ºC for 2 days. The solution was concentrated under vacuum and redissolved in dichloromethane (50 mL). The mixture was washed with water (50 mL) and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The residue was passed through silica gel column chromatography (petroleum ether/dichloromethane 3:1 as eluent) to remove the byproduct. The fractions containing product were collected and concentrated to give 810 mg of **7g** as a white solid (58% yield, mp 101-103 °C, lit 105-107 °C).[75] The NMR data were consistent with previously reported values, designated as compound **43** in the cited paper.[75]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 6.9 Hz, 1H), 7.53 (dd, *J* = 8.4, 6.9 Hz, 1H), 7.32 (d, *J* = 6.9 Hz, 1H), 7.31 (d, *J* = 6.9 Hz, 1H), 3.41 (s, 4H), 1.44 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 146.1, 139.0, 137.7, 135.5, 128.3, 123.8, 119.2, 118.9, 83.5, 30.6, 30.3, 25.1. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.5. HRMS (ESI) m/z calcd for $C_{18}H_{22}BO_2$ $[M+H]^+$ 281.1713, found 281.1696

Miyaura Borylation of 9-Bromoanthracene (7h)

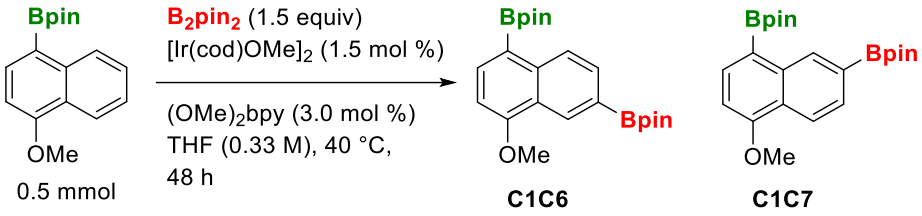


In a glove box, a 100 mL Schlenk flask was charged with 9-bromoanthracene (1.28 g, 5 mmol, 1 equiv), B_2pin_2 (1.40 g, 5.5 mmol, 1.1 equiv), $Pd(dppf)Cl_2$ (220 mg, 6 mol %) and KOAc (1.47 g, 15 mmol, 3.0 equiv) in toluene (65 mL). The flask was covered with a septum, brought out of the glove box and connected to a condenser under nitrogen. The reaction was heated to 110 ºC for 2 days. The solution was concentrated under vacuum and redissolved in dichloromethane (50 mL). The mixture was washed with water (50 mL) and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The residue was passed through silica gel column chromatography (hexane/dichloromethane 60:40 as eluent) to remove the byproduct. The fractions containing product were collected and concentrated to give 1.27 g of **7h** as a white solid (83% yield, mp 137-139 °C, lit 138 °C).[74] The NMR data were consistent with previously reported values, designated as compound **20a** in the cited paper.[74,76]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.48 (d, *J* = 8.7 Hz, 2H), 8.01 (d, *J* = 7.9 Hz, 2H), 7.51 (dd, *J* = 8.7, 6.5 Hz, 2H), 7.46 (dd, *J* = 7.9, 6.5 Hz, 2H), 1.60 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0, 131.3, 129.6, 128.9, 128.4, 125.9, 125.0, 84.5, 25.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ 33.0. HRMS (ESI) m/z calcd for $C_{20}H_{22}BO_2$ $[M+H]^+$ 305.1713, found 305.1700

4.4.6. C6 CHB of 1-borylated naphthalenes

C6 Borylation of 4-methoxy-1-naphthalene boronic acid, pinacol ester (8a)



>95% conversion, **C1C6** : **C1C7** = 7 : 1
91% isolated yield, **C1C6** : **C1C7** = 7 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with **7a** (143 mg, 0.5 mmol, 1 equiv) and 4,4'-dimethoxy-2,2'-bypiridine (3.3 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *C6:C7* borylation ratio. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with water (6 mL). The water layer was decanted and the residue was dried to give 187 mg of 6-borylated **8a** with a minor byproduct corresponding to the 7-borylated isomer (**C1C6**:**C1C7** = 7:1) as a white solid (91% yield).

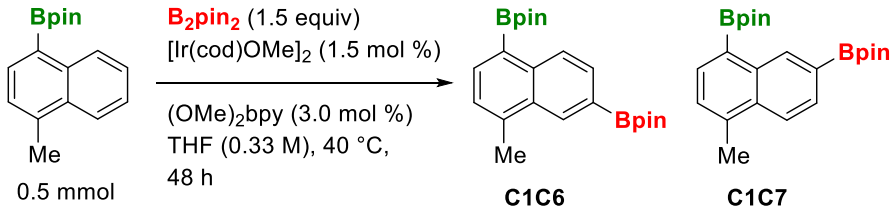
C6 Borylated Product:

^1H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.92 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.02 (s, 3H), 1.41 (s, 12H), 1.39 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 140.0, 138.2, 131.8, 130.2, 127.3, 124.8, 103.3, 83.8, 83.5, 55.5, 25.1, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.2. HRMS (ESI) m/z calcd for $C_{23}H_{33}B_2O_5$ $[M+H]^+$ 411.2514, found 411.2501

C7 Borylated Product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.83 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 4.01 (s, 3H), 1.44 (s, 12H), 1.40 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 137.4, 136.4, 136.3, 129.6, 127.1, 121.1, 104.2, 83.8, 83.6, 55.6, 25.1, 25.1. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.2. HRMS (ESI) m/z calcd for $C_{23}H_{33}B_2O_5$ $[M+H]^+$ 411.2514, found 411.2501

C6 Borylation of 4-methylnaphthalene-1-boronic acid, pinacol ester (8b)



>95% conversion, **C1C6** : **C1C7** = 12 : 1
85% isolated yield, **C1C6** : **C1C7** = 12 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with **7b** (134 mg, 0.5 mmol, 1 equiv) and 4,4'-dimethoxy-2,2'-bypiridine (3.3 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *C6:C7* borylation ratio. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 167 mg of C6 borylated product **8b** with a minor C7 borylated byproduct (**C1C6**:**C1C7** = 12:1) as a white solid (85% yield).

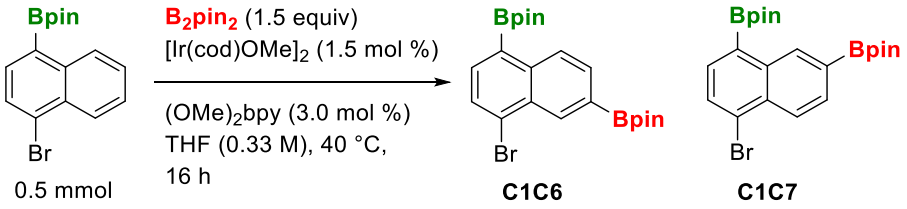
C6 Borylated Product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.4 Hz, 1H), 8.54 (s, 1H), 8.02 (d, *J* = 6.9 Hz, 1H), 7.92 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.33 (dd, *J* = 6.9, 1.1 Hz, 1H), 2.79 (s, 3H), 1.42 (s, 12H), 1.40 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 138.8, 136.8, 132.4, 131.8, 130.9, 128.1, 126.1, 83.9, 83.7, 25.1, 25.0, 20.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.9. HRMS (ESI) m/z calcd for $C_{23}H_{33}B_2O_4$ $[M+H]^+$ 395.2565, found 325.2167

C7 Borylated Product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.87 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.36 (dd, *J* = 7.2, 1.2 Hz, 1H), 2.72 (s, 3H), 1.46 (s, 12H), 1.40 (s, 12H). ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.9. HRMS (ESI) m/z calcd for $C_{23}H_{33}B_2O_4$ $[M+H]^+$ 395.2565, found 325.2167

C6 Borylation of 4-bromonaphthalene-1-boronic acid, pinacol ester (8c)



>95% conversion, **C1C6** : **C1C7** = 10 : 1
76% isolated yield, **C1C6** : **C1C7** = 12 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with **7c** (166 mg, 0.5 mmol, 1 equiv) and 4,4'-dimethoxy-2,2'-bypiridine (3.3. mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 16 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *C6:C7* borylation ratio. The mixture was

concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 175 mg of C6 borylated product **6b** with a minor C7 borylated byproduct (**C1C6** : **C1C7** = 12:1) as a white solid (76% yield).

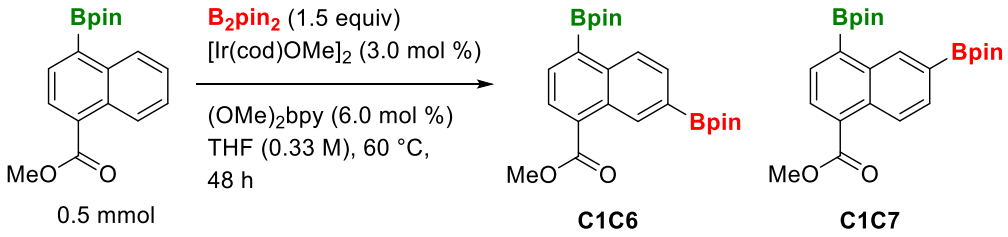
C6 Borylated Product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 – 8.71 (m, 2H), 7.95 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 1.42 (s, 12H), 1.40 (s, 12H). ^{1}H NMR (500 MHz, C_6D_6) δ 9.41 (dd, *J* = 1.2, 0.7 Hz, 1H), 9.30 (dd, *J* = 8.5, 0.7 Hz, 1H), 8.39 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.06 (d, *J* = 7.4 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 1.11 (s, 12H), 1.08 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.9, 136.8, 135.3, 132.0, 131.1, 129.4, 128.2, 128.0, 84.1, 84.1, 25.1, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.8. HRMS (ESI) m/z calcd for $C_{22}H_{30}B_2BrO_4$ $[M+H]^+$ 459.1514, found 459.1498

C7 Borylated Product:

^{1}H NMR (500 MHz, C_6D_6) δ 9.90 (dd, *J* = 1.2, 0.7 Hz, 1H), 8.49 (dd, *J* = 8.5, 0.7 Hz, 1H), 8.31 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 1.15 (s, 12H), 1.14 (s, 12H). HRMS (ESI) m/z calcd for $C_{22}H_{30}B_2BrO_4$ $[M+H]^+$ 459.1514, found 459.1498

C6 Borylation of 4-methylnaphthalene-1-boronic acid, pinacol ester (8d)



>95% conversion, **C1C6** : **C1C7** = 4 : 1
93% isolated yield, **C1C6** : **C1C7** = 4 : 1

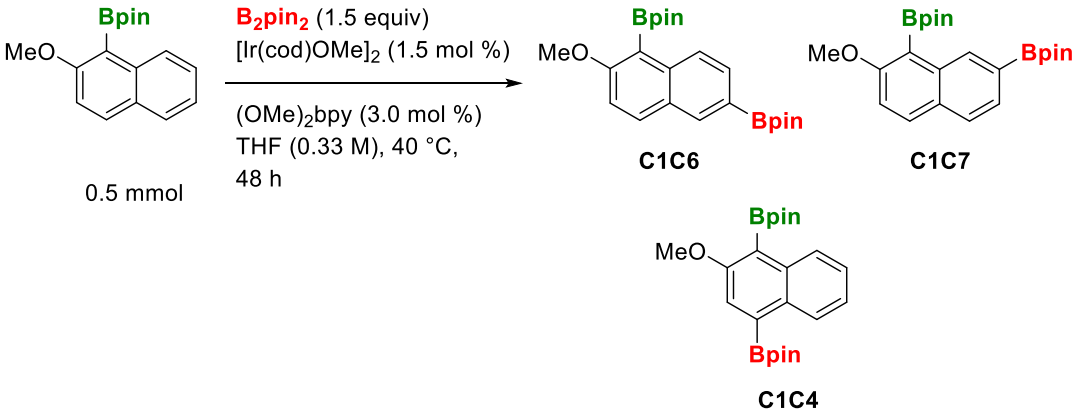
In a glove box, a 5.0 mL Wheaton microreactor was charged with **7d** (156 mg, 0.5 mmol, 1 equiv) and 4,4'-dimethoxy-2,2'-bypiridine (6.5 mg, 6.0 mol %) in THF (0.5 mL). In a separate

tube, $[Ir(cod)(OMe)]_2$ (10.0 mg, 3.0 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and *C6:C7* borylation ratio. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 204 mg of C6 borylated product **8d** with a minor C7 borylated byproduct (**C1C6**:**C1C7** = 4:1) as a white solid (93% yield).

C6 Borylated Product:

^1H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.78 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 7.2 Hz, 1H), 7.95 (dd, *J* = 8.5, 1.3 Hz, 1H), 4.01 (s, 3H), 1.40 (s, 12H), 1.36 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 138.8, 134.9, 133.6, 131.3, 130.9, 130.0, 128.1, 127.8, 84.1, 83.9, 52.3, 25.0, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.8. HRMS (ESI) m/z calcd for $C_{24}H_{33}B_2O_6$ $[M+H]^+$ 439.2463, found 439.2447

C6 Borylation of 2-methoxyphthalene-1-boronic acid, pinacol ester (8e)



>95% conversion, **C1C6** : **C1C7 : C1C4** = 4 : 1 : 0.4
71% isolated yield, **C1C6** : **C1C7 : C1C4** = 9 : 0.3 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with **7e** (142 mg, 0.5 mmol, 1 equiv) and 4,4'-dimethoxy-2,2'-bypiridine (3.3 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *C6:C7* borylation ratio. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected and concentrated to give 145 mg of 6-borylated product **6b** with a couple of minor isomers corresponding to the 7-borylated byproduct and an unknown isomer tentatively assigned as the 4-borylated isomer (**C1C6** : **C1C7 : C1C4** = 9 : 0.3 : 1) as a colorless oil (71% yield).

1,6-diborylated product, major isomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 1.2 Hz, 1H), 7.89 (d, *J* = 9.1 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.20 (d, *J* = 9.1 Hz, 1H), 3.91 (s, 3H), 1.47 (s, 12H), 1.37 (s, 12H). ^{1}H NMR (500 MHz, C_6D_6) δ 8.70 (d, *J* = 1.3 Hz, 1H), 8.40 (d, *J* = 8.4 Hz, 1H), 8.26 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 1H), 3.41 (s, 3H), 1.23 (s, 12H), 1.16 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 139.0, 136.7, 132.7, 131.2, 128.3, 126.0, 112.7, 84.1, 83.8, 56.5, 25.0, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.2. HRMS (ESI) m/z calcd for $C_{23}H_{33}B_2O_5$ $[M+H]^+$ 411.2514, found 411.2499

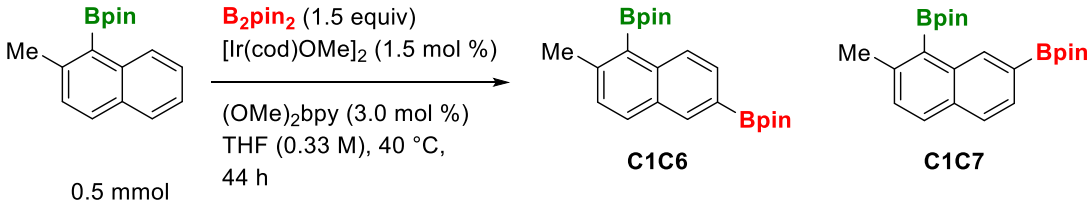
1,7-diborylated product, minor isomer

^{1}H NMR (500 MHz, C_6D_6) δ 9.08 (d, *J* = 1.1 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.06 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 3.45 (s, 3H), 1.37 (s, 12H), 1.15 (s, 12H).

1,4-diborylated product, minor isomer (tentative assignment)

^{1}H NMR (500 MHz, C_6D_6) δ 9.28 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.32 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.13 (s, 1H), 7.44 (ddd, *J* = 8.4, 6.7, 1.7 Hz, 1H), 7.40 (ddd, *J* = 8.0, 6.7, 1.4 Hz, 1H), 3.53 (s, 3H), 1.26 (s, 12H), 1.15 (s, 12H).

C6 Borylation of 2-methylphthalene-1-boronic acid, pinacol ester (8f)



>95% conversion, **C1C6** : **C1C7** = 5 : 1
93% isolated yield, **C1C6** : **C1C7** = 6 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with **7f** (134 mg, 0.5 mmol, 1 equiv) and 4,4'-dimethoxy-2,2'-bypiridine (3.3 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 44 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *C6:C7* borylation ratio. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing

product were collected and concentrated to give 184 mg of C6 borylated product **8f** with a minor C7 borylated byproduct (**C1C6** : **C1C7** = 6:1) as a white solid (93% yield).

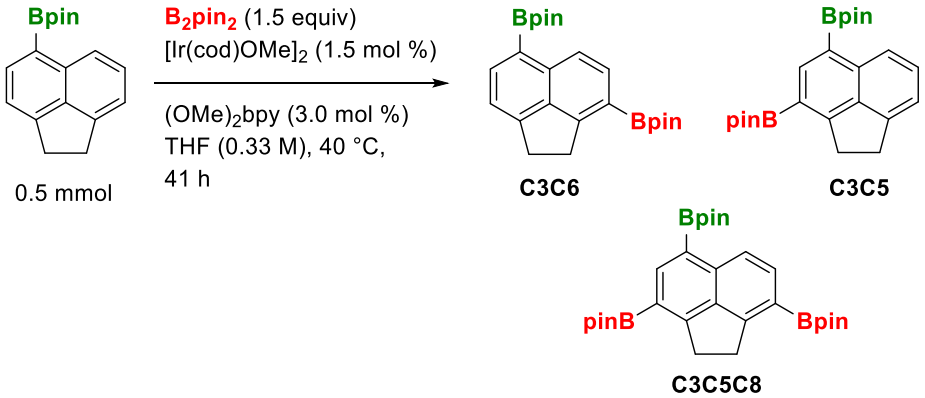
C6 Borylated Product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.83 (dd, J = 8.4, 1.3 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 2.64 (s, 3H), 1.53 (s, 12H), 1.37 (s, 12H). ^{1}H NMR (500 MHz, C_6D_6) δ 8.75 (s, 1H), 8.69 (d, *J* = 8.4 Hz, 1H), 8.33 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 2.63 (s, 3H), 1.16 (s, 12H), 1.15 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 143.5, 139.5, 137.6, 131.6, 131.4, 130.9, 129.1, 127.7, 83.7, 83.7, 25.1, 25.0, 23.2. ^{11}B NMR (160 MHz, C_6D_6) δ 32.5. HRMS (ESI) m/z calcd for $C_{23}H_{33}B_2O_4$ $[M+H]^+$ 395.2565, found 395.2555

C7 Borylated Product:

^{1}H NMR (500 MHz, C_6D_6) δ 9.31 (d, *J* = 1.0 Hz, 1H), 8.16 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.69 (d, *J* = 8.1, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 8.3, 1H), 2.62 (s, 3H), 1.32 (s, 12H), 1.02 (s, 12H). HRMS (ESI) m/z calcd for $C_{23}H_{33}B_2O_4$ $[M+H]^+$ 395.2565, found 395.2555

C3-C8 Diborylation of acenaphtene-5-boronic acid, pinacol ester (8g)



68% conversion, **C3C6** : **C3C5** : **C3C5C8** = 1 : 1.6 : 0.8
5% isolated yield, **C3C6** : **C3C5** = 1 : 0.8

In a glove box, a 5.0 mL Wheaton microreactor was charged with **7g** (140 mg, 0.5 mmol, 1 equiv) and 4,4'-dimethoxy-2,2'-bypiridine (3.3 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 41 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and **C3C6** : **C3C5** : **C3C5C8** borylation ratio. The mixture was concentrated and passed through silica gel column chromatography (chloroform as eluent). The fractions containing product were collected and concentrated. One fraction containing 10 mg of monoborylated products (based on GC-MS) **C3C6** and **C3C5** in 1 to 0.8 ratio and without reactant was isolated (5% yield).

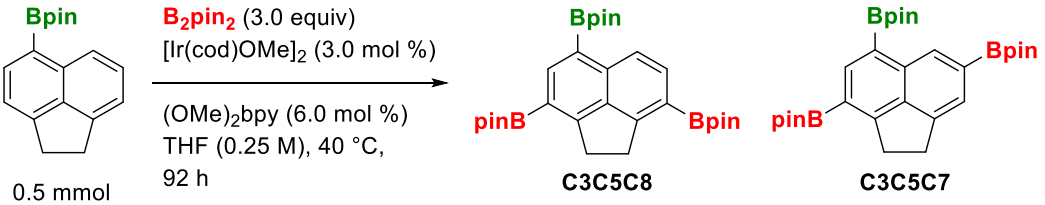
3,6-diborylated product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.4, 1.0 Hz, 1H), 8.06 (d, *J* = 6.9 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.29 (dt, *J* = 6.9, 1.4 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.40 – 3.32 (m, 2H), 1.41 (s, 12H), 1.37 (s, 12H). GC-MS (EI) m/z calcd for $C_{24}H_{32}B_2O_4$ [M] 406.2, found 406.1

3,5-diborylated product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.38 – 8.34 (dd, *J* = 8.3, 0.7, 1H), 7.52 (dd, *J* = 8.3, 6.8 Hz, 1H), 7.29 (dt, *J* = 6.9, 1.4 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.40 – 3.32 (m, 2H), 1.41 (s, 12H), 1.37 (s, 12H). GC-MS (EI) m/z calcd for $C_{24}H_{32}B_2O_4$ [M] 406.2, found 406.1

The reaction was repeated with more equivalents of B_2pin_2 and higher loadings of catalyst-ligand:



>95% conversion, **C3C5C8** : **C3C5C7** = 7 : 1
68% isolated yield, **C3C5C8** : **C3C5C7** = 11 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with **7g** (140 mg, 0.5 mmol, 1 equiv) and 4,4'-dimethoxy-2,2'-bypiridine (6.6 mg, 6.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (10.0 mg, 3.0 mol %) and B_2pin_2 (381 mg, 1.5 mmol, 3.0 equiv) in THF (1.5 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 92 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and **C3C5C8** : **C3C5C7** borylation ratio. The mixture was concentrated and passed through a plug of silica gel (chloroform as eluent). The fractions containing product were collected and concentrated to give 181 mg of the 3,5,8-triborylated acenaphthene **8g** with a minor byproduct corresponding to the 3,5,7-triborylated isomer as a white solid (68% yield).

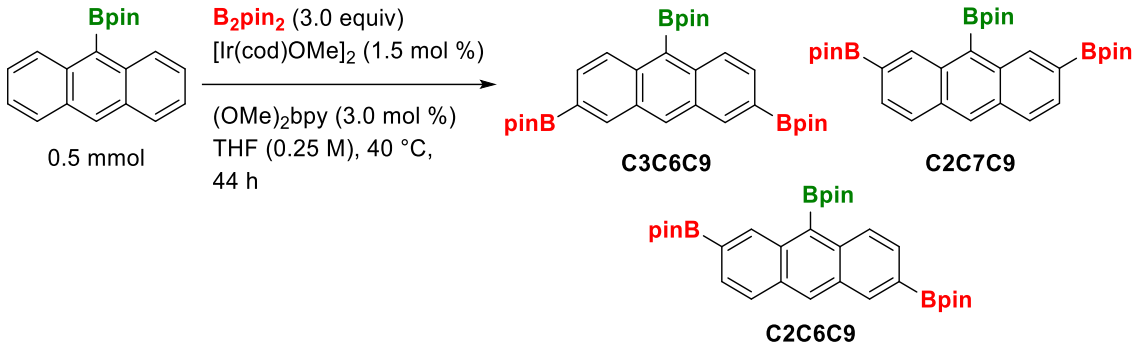
3,5,8 Triborylated Product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 3.55 (s, 4H), 1.42 (s, 12H), 1.39 (s, 12H), 1.38 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 157.6, 144.0, 138.8, 137.6, 134.8, 122.9, 83.5, 83.4, 83.4, 32.5, 32.1, 25.1, 25.1, 25.1. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6. HRMS (ESI) m/z calcd for $C_{30}H_{44}B_3O_6$ $[M+H]^+$ 533.3417, found 533.34

3,5,7 Triborylated Product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.39 (s, 1H), 7.70 (s, 1H), 3.55 (s, 4H), 1.45 (s, 12H), 1.40 (s, 12H), 1.38 (s, 12H). HRMS (ESI) m/z calcd for $C_{30}H_{44}B_3O_6$ $[M+H]^+$ 533.3417, found 533.3412

C3-C9 Diborylation of anthracene-9-boronic acid, pinacol ester (8h)



>95% conversion, **C3C6C9** : **C2C6C9** : **C2C7C9** = 2 : 1 : 0.1
76% yield, **C3C6C9** : **C2C6C9** : **C2C7C9** = 2 : 1 : 0.1

In a glove box, a 5.0 mL Wheaton microreactor was charged with **7h** (152 mg, 0.5 mmol, 1 equiv) and 4,4'-dimethoxy-2,2'-bypiridine (3.3 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (381 mg, 1.5 mmol, 3.0 equiv) in THF (1.5 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 44 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and **369** : **269** : **279** borylation ratio. The mixture was concentrated and passed through a plug of silica gel (chloroform as eluent). The fractions containing product were collected and concentrated to give 249 mg of the 3,6,9- and 2,6,9-triborylated anthracene **8h** with minor byproducts corresponding to the 2,7,9-triborylated isomer and excess B_2pin_2 (**C3C6C9** : **C2C6C9** : **C2C7C9 : B_2pin_2** = 2 : 1 : 0.1 :1.2 as a yellow solid (76% yield of the borylated products).

3,6,9 Triborylated Product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.55 (s, 2H), 8.40 (d, *J* = 8.7, 2H), 7.83 (dd, J = 8.7, 1.3, 2H), 1.56 (s, 12H), 1.40 (s, 24H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 137.9, 132.0, 130.6,

130.2, 127.4, 84.0, 83.6, 25.2, 25.1. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.5. HRMS (ESI) m/z calcd for $C_{32}H_{44}B_3O_6$ [M] 557.3417, found 557.3410

2,6,9 Triborylated Product:

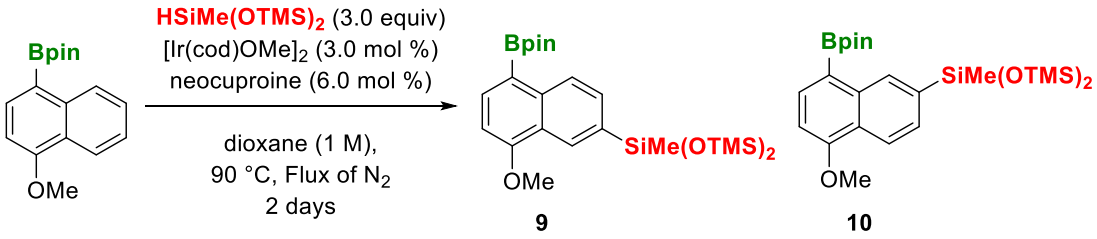
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (d, *J* = 1.1 Hz, 1H), 8.55 (d, *J* = 1.1 Hz, 1H), 8.49 (s, 1H), 8.33 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 8.6 Hz, 1H), 7.81 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.75 (dd, *J* = 8.6, 1.1 Hz, 1H), 1.60 (s, 12H), 1.40 (s, 12H), 1.38 (s, 12H). HRMS (ESI) m/z calcd for $C_{32}H_{44}B_3O_6$ [M] 557.3417, found 557.3410

2,7,9 Triborylated Product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (d, *J* = 1.0 Hz, 2H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 1.65 (s, 12H) (some peaks were not observable due to the overlap with other signals). HRMS (ESI) m/z calcd for $C_{32}H_{44}B_3O_6$ [M] 557.3417, found 557.3410

4.4.7. Silylation of 1-borylated naphthalenes

C6 Silylation of 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



>95% conversion, **9**:**10** = 1.6:1
98% isolated yield, **9**:**10** = 1.6:1

In a glove box, a 5.0 mL Wheaton microreactor was charged with **7a** (142 mg, 0.5 mmol, 1 equiv), $[Ir(cod)(OMe)]_2$ (10.0 mg, 3.0 mol %), neocuproine (6.2 mg, 6.0 mol %) and $HSiMe(OTMS)_2$ (334 mg, 1.5 mmol, 3.0 equiv) in dioxane (0.4 mL). The microreactor was connected to a condenser, capped with a septum and brought out of the glove box. The microreactor was connected to a continuous flux of nitrogen with a Schlenk line and heated to 90

ºC. After 48 h, an aliquot of the reaction mixture was taken and dried to analyze the conversion and **9**:**10** silylation ratio by ^{1}H NMR. MeOH (1.0 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with water (2 mL). The water layer was decanted and the residue was dried to give 248 mg of a mixture of **9** and **10** (**9**:**10** = 1.6:1) as a tan solid (98% yield).

6-silylated product:

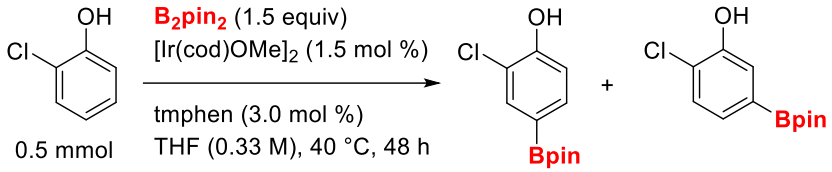
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 8.4, 0.8 Hz, 1H), 8.57 (dd, *J* = 1.3, 0.8 Hz, 1H), 8.07 (d, *J* = 7.8, 1H), 7.73 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 4.04 (s, 3H), 1.47 – 1.40 (s, 12H), 0.36 (s, 3H), 0.16 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 138.8, 137.6, 134.6, 130.9, 128.2, 127.1, 124.7, 118.5 (C–B, observed by gHMBCAD), 103.3, 83.5, 55.6, 25.1, 2.1, 0.3. ^{29}Si NMR (99 MHz, $CDCl_3$) δ 8.39, -33.62. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.4. HRMS (ESI) m/z calcd for $C_{24}H_{42}BO_5Si_3$ $[M+H]^+$ 505.2433 , found 505.2418

5-silylated product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (dd, *J* = 1.1, 0.8 Hz, 1H), 8.28 (dd, *J* = 8.3, 0.8 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.65 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 4.02 (s, 3H), 1.47 – 1.40 (s, 12H), 0.41 (s, 3H), 0.16 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 137.4, 137.0, 136.8, 134.4, 128.8, 126.1, 120.9, 119.1 (C–B, observed by gHMBCAD), 103.7, 83.5, 55.6, 25.1, 2.1, 0.1. ^{29}Si NMR (99 MHz, $CDCl_3$) δ 8.48, -33.15. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.4. HRMS (ESI) m/z calcd for $C_{24}H_{42}BO_5Si_3$ $[M+H]^+$ 505.2433 , found 505.2418

4.4.8. CHB of substrates without selectivity

***Para* borylation of 2-chlorophenol (2p)**



>95% conversion, *para*:*meta* = 1 : 1
73% isolated yield, *para*:*meta* = 1.4 : 1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-chlorophenol (64 mg, 0.5 mmol, 1 equiv) and tmphen (3.6 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 14 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and *para:meta* borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected, concentrated and washed with water (4 mL). The water layer was decanted and the residue was dried to give 93 mg of a mixture of *para* and *meta* borylated **2p** (*para*:*meta* = 1.4:1) as a light orange solid (73% yield). The NMR data of the *para* and *meta* borylated isomers were consistent with previously reported values.[76–78]

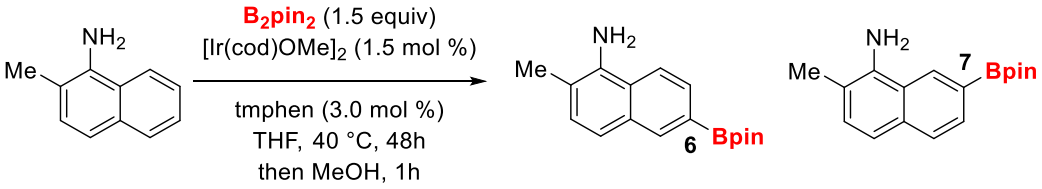
Para borylated product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.5 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 5.88 (bs, 1H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 135.8, 135.2, 120.0, 115.9, 84.1, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.4.

Meta borylated product:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 1.3 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.29 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.88 (bs, 1H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0, 128.8, 127.6, 123.3, 122.4, 84.2, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$) δ 30.4.

CHB borylation of 2-methyl-1-naphthylamine (2o)



89% conversion, **6**:**7** = 1.3:1
61% isolated yield, **6**:**7** = 1.6:1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 2-methyl-1-naphthylamine (79 mg, 0.5 mmol, 1 equiv) and tmphen (3.6 mg, 3.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 1.5 mol %) and B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 40 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and **6:7** borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$ as eluent). The fractions containing product were collected to give 87 mg of a mixture of 6- and 7- borylated **2o** (**6**:**7** = 1.6:1) as a brown oil (61% yield)

C6 borylated product

^{1}H NMR (500 MHz, C_6D_6) δ 8.8 (s, 1H), 8.2 (d, *J* = 8.4 Hz, 1H), 7.6 (d, *J* = 8.4 Hz, 2H), 7.3 (d, *J* = 8.2 Hz, 2H), 7.0 (d, *J* = 8.2 Hz, 2H), 3.6 (bs, 2H), 1.9 (s, 3H), 1.2 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 139.7, 137.9, 133.2, 129.7, 129.6, 125.2, 120.1, 119.0, 117.2, 83.8, 25.1, 17.7. ^{11}B NMR

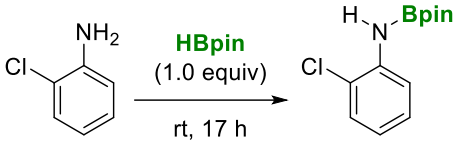
(160 MHz, C_6D_6) δ 31.7. HRMS (ESI) m/z calcd for $C_{17}H_{23}BNO_2$ $[M+H]^+$ 284.1822, found 284.1812

C7 borylated product

^{1}H NMR (500 MHz, C_6D_6) δ 8.8 (s, 1H), 8.2 (d, *J* = 8.2 Hz, 1H), 7.7 (d, *J* = 8.2 Hz, 1H), 7.2 (d, *J* = 8.1 Hz, 1H), 7.1 (d, *J* = 8.1 Hz, 1H), 3.6 (bs, 2H), 1.9 (s, 3H), 1.2 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) 140.7, 135.6, 131.1, 129.7, 128.2, 125.0, 123.1, 117.9, 115.7, 83.9, 25.1, 17.5. ^{11}B NMR (160 MHz, C_6D_6) δ 31.7. HRMS (ESI) m/z calcd for $C_{17}H_{23}BNO_2$ $[M+H]^+$ 284.1822, found 284.1812

4.4.9. Synthesis N-borylated scaffolds

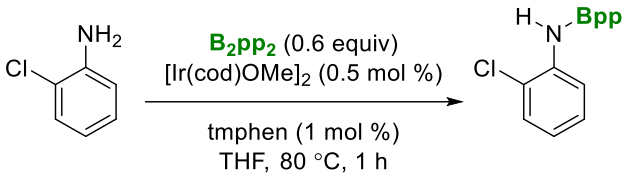
Synthesis of N-Bpin borylated 2-chloroaniline (1a')



In a glovebox, under a N_2 atmosphere, a 5.0 mL Wheaton microreactor was charged with 2-chloroaniline (383 mg, 3 mmol, 1 equiv) and HBpin (384 mg, 3 mmol, 1 equiv). The reaction was stirred at room temperature for 17 h. From the final mixture, 51 mg was measured, dissolved in 0.6 mL of $CDCl_3$ (0.33 M solution) and transfer to J-Young NMR tube. TMS internal standard was added as reference. It is important to note that the reaction can be completed in one hour if $[Ir(cod)OMe]_2$ (0.5 mol %) is added and the reaction heated at 80 °C.

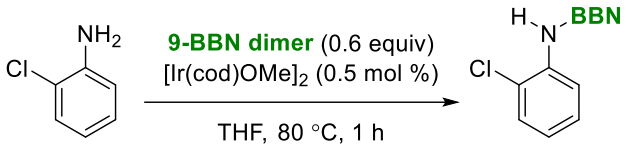
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.25 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.13 (ddd, *J* = 8.4, 7.3, 1.5 Hz, 1H), 6.77 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 1H), 5.33 (bs, 1H), 1.31 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1, 128.9, 127.6, 121.5, 120.5, 118.5, 83.1, 24.6. ^{11}B NMR (160 MHz, $CDCl_3$) δ 24.1.

Synthesis of N-Bpp borylated 2-chloroaniline



In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with 2-chloroaniline (32 mg, 0.25 mmol, 1 equiv), B_2pp_2 (42 mg, 0.15 mmol, 0.6 equiv), $[Ir(cod)OMe]_2$ (1 mg, 0.5 mol %) and tmphen (0.6 mg, 1 mol %) in THF (0.25 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1h, the mixture was concentrated under reduce pressure without heating inside of the glove box. The mixture was redissolved in C_6D_6 (0.6 mL, 0.4 M solution) and transfer to a J-Young NMR tube. ^{1}H NMR (500 MHz, C_6D_6) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.06 (dd, *J* = 8.3, 7.3 Hz, 1H), 6.53 (dd, *J* = 8.0, 7.3, 1.3 Hz, 1H), 5.45 (bs, 1H), 1.37 (s, 2H), 1.14 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 141.7, 129.3, 127.8, 121.9, 120.2, 119.2, 71.5, 48.7, 31.7. ^{11}B NMR (160 MHz, C_6D_6) δ 25.3.

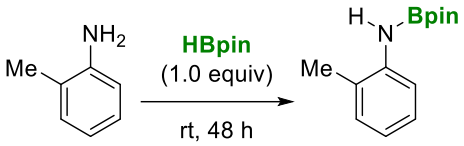
Synthesis of N-BBN borylated 2-chloroaniline



In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with 2-chloroaniline (0.05 mL of a 2 M solution in THF, 0.10 mmol, 1 equiv), 9-BBN dimer (15 mg, 0.06 mmol, 0.6 equiv) and $[Ir(cod)OMe]_2$ (0.15 mL of 3.3 mM solution in THF, 0.5 mol %) in THF. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1h, the mixture was concentrated under reduce pressure without heating inside of the glove box. The mixture was redissolved in C_6D_6 and transfer to a J-Young NMR tube.

^{1}H NMR (500 MHz, C_6D_6) δ 7.20 – 7.14 (dd, J = 8.1, 1.5 Hz 1H), 7.12 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.85 (td, *J* = 7.7, 1.5 Hz, 1H), 6.63 (td, *J* = 7.7, 1.6 Hz, 1H), 6.10 (bs, 1H). The peaks in the aliphatic region were difficult to identify as they overlap with those of the 9BBN dimer residue. ^{11}B NMR (160 MHz, C_6D_6) δ 52.2. Other peaks were observed in the ^{11}B NMR spectrum corresponding to 9-BBN borates (58.7 and 56.3 ppm) and 9-BBN dimer (27.8 ppm).[77–79]

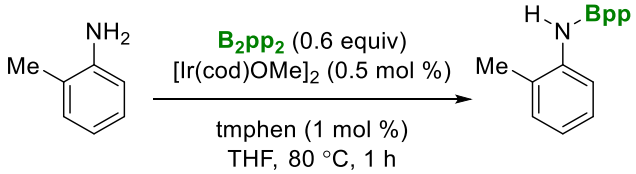
Synthesis of N-Bpin borylated 2-methylaniline (1g')



In a glovebox, under a N_2 atmosphere, 2-methylaniline (3 mmol, 321 mg, 1 equiv) and HBpin (3 mmol, 384 mg, 1 equiv) were charged in a 5 mL vial and stirred at room temperature for 48 h. From the final mixture, 47 mg was measured, dissolved in 0.6 mL of $CDCl_3$ (0.33 M solution) and transfer to J-Young NMR tube. It is important to note that the reaction can be completed in one hour if $[Ir(cod)OMe]_2$ (0.5 mol %) is added and the reaction heated at 80 °C. It is important to note that the reaction can be completed in one hour if $[Ir(cod)OMe]_2$ (0.5 mol %) is added and the reaction heated at 80 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 1H), 7.14 (dd, *J* = 8.1, 7.2 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.5, 7.2 Hz, 1H), 2.21 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 142.1, 130.5, 127.4, 124.4, 120.6, 118.4, 82.7, 24.7, 17.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ 24.1.

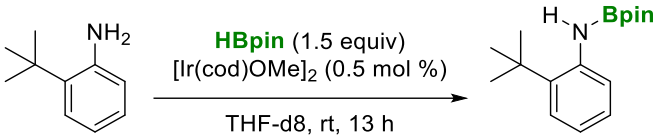
Synthesis of N-Bpp borylated 2-methylaniline



In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with 2-methylaniline (27 mg, 0.25 mmol, 1 equiv), B_2pp_2 (42 mg, 0.15 mmol, 0.6 equiv), $[Ir(cod)OMe]_2$ (1 mg, 0.5 mol %) and tmphen (0.6 mg, 1 mol %) in THF (0.25 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 1h, the mixture was concentrated under reduce pressure without heating inside of the glove box. The mixture was redissolved in C_6D_6 (0.6 mL, 0.4 M solution) and transfer to a J-Young NMR tube.

^{1}H NMR (500 MHz, C_6D_6) δ 8.10 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.26 (dd, *J* = 8.2, 7.3 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.82 (td, *J* = 7.3, 1.3 Hz, 1H), 4.47 (bs, 1H), 1.83 (s, 3H), 1.43 (s, 2H), 1.21 (s, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 143.2, 130.5, 127.3, 124.4, 119.9, 118.6, 71.2, 48.9, 31.8, 17.7. ^{11}B NMR (160 MHz, C_6D_6) δ 25.3.

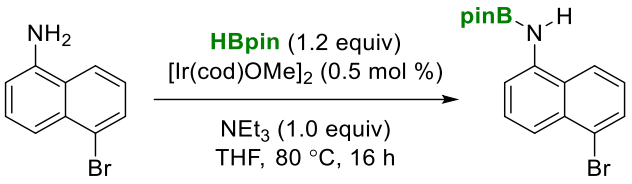
Synthesis of N-borylated 2-tertbutylaniline (1i')



In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with 2-tertbutylaniline (37 mg, 0.25 mmol, 1 equiv), HBpin (48 mg, 0.375 mmol, 1.5 equiv) and $[Ir(cod)OMe]_2$ (0.8 mg, 0.5 mol %) in THF-*d8* dried over alumina (0.75 mL). The microreactor was capped with a teflon pressure cap and stirred at room temperature. After 13 h, the mixture was transfer to a J-Young NMR tube.

^{1}H NMR (500 MHz, THF-*d8*) δ 7.41 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.17 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.95 (ddd, *J* = 8.1, 7.2, 1.6 Hz, 1H), 6.72 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1H), 4.89 (bs, 1H), 1.36 (s, 9H), 1.23 (s, 12H). ^{13}C NMR (126 MHz, THF-*d8*) δ 142.2, 137.0, 127.1, 126.4, 122.2, 121.2, 83.0, 34.6, 30.4, 24.8. ^{11}B NMR (160 MHz, THF-*d8*) δ 24.0.

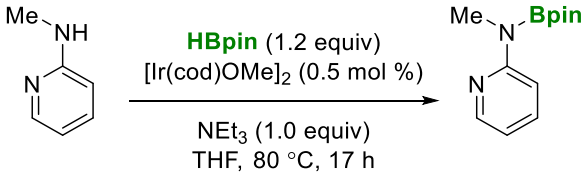
Synthesis of N-Bpin borylated 5-bromo-1-aminonaphthalene (1m')



In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with 5-bromo-1-aminonaphthalene (44 mg, 0.20 mmol, 1 equiv), HBpin (31 mg, 0.24 mmol, 1.2 equiv), $[Ir(cod)OMe]_2$ (0.2 mL of 5 mM solution in THF, 0.5 mol %), NEt_3 (0.04 mL, 0.20 mmol, 1 equiv) in THF (0.2 mL). The microreactor was capped with a teflon pressure cap and stirred at 80 °C. After 16 h, the mixture was concentrated under reduce pressure without heating inside of the glove box. The mixture was redissolved in $CDCl_3$ (0.6 mL, 0.33 M solution) and transfer to a J-Young NMR tube.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 2H), 7.74 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.65 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.48 (t, *J* = 8.1 Hz, 1H), 7.25 (dd, *J* = 8.5, 7.4 Hz, 1H), 5.26 (bs, 1H), 1.33 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 132.8, 129.9, 127.9, 126.5, 125.3, 123.9, 120.3, 120.0, 115.2, 83.2, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 24.4.

Synthesis of N-Bpin borylated N-methyl-2-aminopyridine (3b')

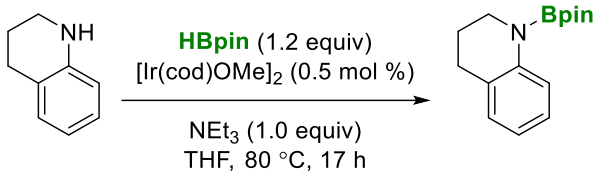


In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with 2-amino-N-methylpyridine (22 mg, 0.20 mmol, 1 equiv), HBpin (31 mg, 0.24 mmol, 1.2 equiv), $[Ir(cod)OMe]_2$ (0.8 mg, 0.5 mol %), NEt_3 (0.04 mL, 0.20 mmol, 1 equiv) in THF (0.2 mL). The microreactor was capped with a teflon pressure cap and stirred at 80 °C. After 17 h, the mixture

was concentrated under reduce pressure without heating inside of the glove box. The mixture was redissolved in $CDCl_3$ (0.6 mL, 0.33 M solution) and transfer to a J-Young NMR tube.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (ddd, *J* = 5.0, 2.1, 0.9 Hz, 1H), 7.63 (dt, *J* = 8.6, 1.0 Hz, 1H), 7.46 (ddd, *J* = 8.6, 7.1, 2.1 Hz, 1H), 6.74 (ddd, *J* = 7.1, 5.0, 1.0 Hz, 1H), 3.15 (s, 3H), 1.29 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 147.3, 136.7, 115.6, 114.5, 83.2, 32.4, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 24.9.

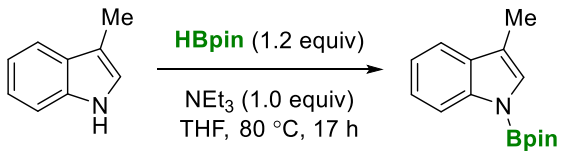
Synthesis of N-Bpin borylated tetrahydroquinoline (3d')



In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with tetrahydroquinoline (27 mg, 0.20 mmol, 1 equiv), HBpin (31 mg, 0.24 mmol, 1.2 equiv), $[Ir(cod)OMe]_2$ (0.8 mg, 0.5 mol %), NEt_3 (0.04 mL, 0.20 mmol, 1 equiv) in THF (0.2 mL). The microreactor was capped with a teflon pressure cap and stirred at 80 °C. After 17 h, the mixture was concentrated under reduce pressure without heating inside of the glove box. The mixture was redissolved in $CDCl_3$ (0.6 mL, 0.33 M solution) and transfer to a J-Young NMR tube.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.08 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H), 7.02 (dt, *J* = 7.5, 1.4 Hz, 1H), 6.82 (td, *J* = 7.3, 1.2 Hz, 1H), 3.52 – 3.46 (m, 2H), 2.82 (t, *J* = 6.7 Hz, 2H), 1.94 – 1.81 (m, 2H), 1.31 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0, 129.6, 126.2, 125.9, 120.4, 120.2, 82.7, 44.2, 27.9, 24.8, 23.4. ^{11}B NMR (160 MHz, $CDCl_3$) δ 24.2.

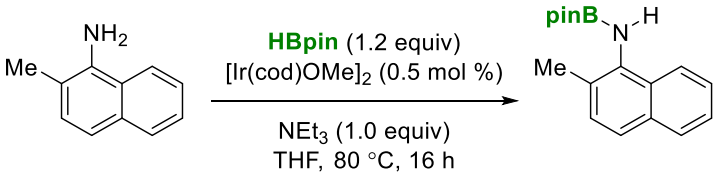
Synthesis of N-Bpin borylated 3-methylindole (5a')



In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with 3-methylindole (26 mg, 0.20 mmol, 1 equiv), HBpin (31 mg, 0.24 mmol, 1.2 equiv), NEt_3 (0.04 mL, 0.20 mmol, 1 equiv) in THF (0.2 mL). The microreactor was capped with a teflon pressure cap and stirred at 80 °C. After 17 h, the mixture was concentrated under reduce pressure without heating inside of the glove box. The mixture was redissolved in $CDCl_3$ (0.6 mL, 0.33 M solution) and transfer to a J-Young NMR tube. TMS was added as an internal standard.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.50 (ddd, *J* = 7.8, 1.3, 0.8 Hz, 1H), 7.23 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 7.17 (ddd, *J* = 7.8, 7.1, 0.9 Hz, 1H), 7.14 (q, *J* = 1.3 Hz, 1H), 2.28 (d, *J* = 1.3 Hz, 3H), 1.37 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7, 132.0, 126.1, 122.7, 120.9, 118.6, 116.0, 114.7, 84.2, 24.8, 9.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ 24.4.

Synthesis of N-Bpin borylated 2-methyl-1-aminonaphthalene (1o')

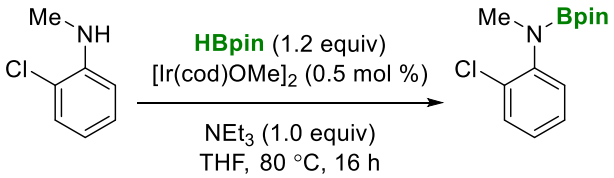


In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with 2-methyl-1-aminonaphthalene (31 mg, 0.20 mmol, 1 equiv), HBpin (31 mg, 0.24 mmol, 1.2 equiv), $[Ir(cod)OMe]_2$ (0.2 mL of 5 mM solution in THF, 0.5 mol %), NEt_3 (0.04 mL, 0.20 mmol, 1 equiv) in THF (0.2 mL). The microreactor was capped with a teflon pressure cap and stirred at 80 °C. After 16 h, the mixture was concentrated under reduce pressure without heating inside of the glove box. The mixture was redissolved in $CDCl_3$ (0.6 mL, 0.33 M solution) and transfer to a J-Young NMR tube.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.78 – 7.73 (ddd, J = 8.1, 1.4, 0.9 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.45 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.38 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 4.32 (bs, 1H), 2.45 (s, 3H), 1.26 (s, 12H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 134.8, 133.0, 130.8, 129.7, 129.3, 128.0, 125.6, 124.8, 124.4, 123.0, 82.9, 24.7, 19.2. ^{11}B NMR (160 MHz, $CDCl_3$) δ 24.0.

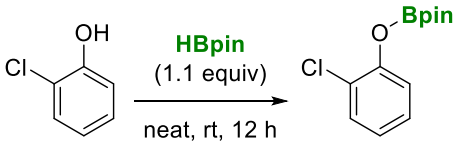
Synthesis of N-Bpin borylated 2-chloro-N-methylaniline (5a')



In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with 2-chloro-N-methylaniline (28 mg, 0.20 mmol, 1 equiv), HBpin (31 mg, 0.24 mmol, 1.2 equiv), $[Ir(cod)OMe]_2$ (0.2 mL of 5 mM solution in THF, 0.5 mol %), NEt_3 (0.04 mL, 0.20 mmol, 1 equiv) in THF (0.2 mL). The microreactor was capped with a teflon pressure cap and stirred at 80 °C. After 16 h, the mixture was concentrated under reduce pressure without heating inside of the glove box. The mixture was redissolved in $CDCl_3$ (0.6 mL, 0.33 M solution) and transfer to a J-Young NMR tube.

^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 1H), 7.25 – 7.17 (m, 2H), 7.09 (ddd, *J* = 7.9, 6.8, 2.3 Hz, 1H), 2.97 (s, 3H), 1.24 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 132.6, 130.2, 129.6, 127.6, 126.5, 82.9, 37.4, 24.7. ^{11}B NMR (160 MHz, $CDCl_3$) δ 23.8.

Synthesis of O-Bpin borylated 2-chlorophenol (1p')



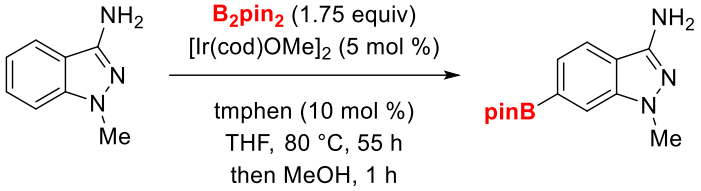
In a glovebox, under a N_2 atmosphere, a 3.0 mL Wheaton microreactor was charged with 2-chlorophenol (26 mg, 0.2 mmol, 1 equiv) and HBpin (28 mg, 0.22 mmol, 1.1 equiv). The microreactor was capped with a teflon pressure cap and stirred at room temperature. After 12 h,

the mixture was dissolved in $CDCl_3$ (0.6 mL, 0.33 M solution) and transfer to a J-Young NMR tube. TMS was added as an internal standard.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.21 – 7.13 (m, 2H), 7.01 (ddd, *J* = 7.8, 6.6, 2.2 Hz, 1H), 1.31 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7, 130.2, 127.8, 125.3, 124.4, 121.5, 84.1, 24.7. ^{11}B NMR (160 MHz, $CDCl_3$) δ 21.7.

4.4.10. Applications of IMHB to remote borylation

C6 Borylation of 3-amino-N-methyl indazole (12)

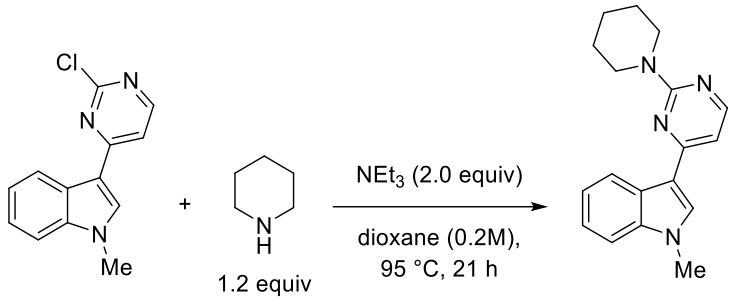


92% conversion, **6**:**5** = 6:1
82% isolated yield, **6**:**5** = 8:1

In a glove box, a 5.0 mL Wheaton microreactor was charged with 3-amino-N-methyl indazole (74 mg, 0.5 mmol, 1 equiv) and tmphen (12 mg, 10.0 mol %) in THF (0.5 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (16.6 mg, 5.0 mol %) and B_2pin_2 (222 mg, 0.875 mmol, 1.75 equiv) in THF (1.0 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 80 ºC. After 55 h, an aliquot of the reaction mixture was taken and analyzed directly by ^{1}H NMR to find the conversion and **6**:**5** borylation ratio. MeOH (2.5 mL) was added and the mixture was stirred for 1 h. The mixture was concentrated and passed through a plug of silica gel ($CHCl_3$/MeOH 24:1 as eluent). The fractions containing product were collected, concentrated and washed with water (4 mL). The water layer was decanted and the residue was dried to give 112 mg of the 6-borylated 3-amino-N-methyl indazole **12** with a minor byproduct corresponding to the 5-borylated isomer (**6**:**5** = 8:1) as a tan solid (82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.53 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.42 (dd, *J* = 8.1, 0.7 Hz, 1H), 4.08 (bs, 2H), 3.87 (s, 3H), 1.37 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.9, 141.3, 123.8, 118.8, 116.2, 115.9, 84.1, 35.0, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.2. HRMS (ESI) m/z calcd for $C_{14}H_{21}BN_3O_2$ $[M+H]^+$ 274.1727, found 274.1722

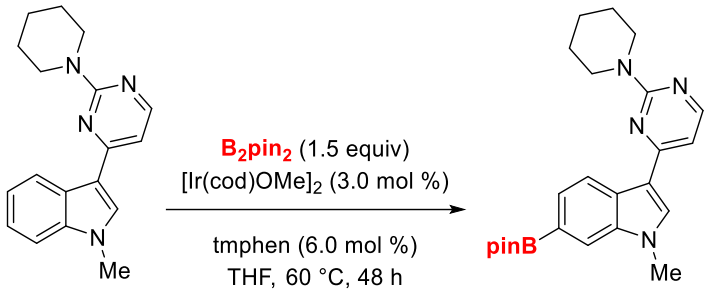
Synthesis Osimertinib's Analogue (13)



A 100 mL round bottom flask was charged with 3-(2-Chloropyrimidin-4-yl)-1-methylindole (487 mg, 2 mmol, 1 equiv), piperidine (204 mg, 2.4 mmol, 1.2 equiv) and triethylamine (405 mg,4 mmol, 2.0 equiv) in dioxane (10 mL). The flask was connected to a condenser and heated to 95 ºC. After 21 h, the reaction was cool down to room temperature and concentrated under reduce pressure. 10 mL of water was added and extracted with ethyl acetate (3 x 10 mL). The organic layers were collected, concentrated and recrystallized over ethyl acetate. The precipitate was filtrated and dried under vacuum to yield 180 mg of osimertinib's analogue **13** (31% yield, mp 127-129 °C). The structure was confirmed by x-ray crystallography.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 8.25 (d, *J* = 5.3 Hz, 1H), 7.74 (s, 1H), 7.36 (ddd, *J* = 7.7, 1.5, 0.9 Hz, 1H), 7.34-7.24 (m, 2H), 6.79 (d, *J* = 5.3 Hz, 1H), 3.91 (dd, *J* = 6.2, 4.1 Hz, 4H), 3.85 (s, 3H), 1.75 – 1.64 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1, 162.1, 157.1, 138.0, 130.9, 126.2, 122.5, 122.1, 121.2, 114.7, 109.8, 105.0, 45.1, 33.4, 26.0, 25.2. HMRS (ESI) m/z calcd for $C_{18}H_{21}N_4$ $[M+H]^+$ 293.1766, found 293.1740

C6 Borylation of Osimertinib's Analogue (14)



81% conversion, **6**:**5** = 4.2:1
57% isolated yield, **6**:**5** = 3.5:1

In a glove box, a 5.0 mL Wheaton microreactor was charged with Osimertinib's analogue **13** (73 mg, 0.25 mmol, 1 equiv) and tmphen (3.5 mg, 6.0 mol %) in THF (0.3 mL). In a separate tube, $[Ir(cod)(OMe)]_2$ (5.0 mg, 3.0 mol %) and B_2pin_2 (95 mg, 0.375 mmol, 1.5 equiv) in THF (0.5 mL) were stirred for 5 min. The $[Ir(cod)(OMe)]_2/B_2pin_2$ solution was transferred to the microreactor. The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. After 48 h, an aliquot of the reaction mixture was taken and analyzed directly by ^1H NMR to find the conversion and **6**:**5** borylation ratio. The mixture was concentrated and passed through a plug of silica gel (chloroform/ethyl acetate 4:1 as eluent). The fractions containing product were collected and concentrated to give 60 mg of 6-borylated product **14** with a minor 5-borylated byproduct (**6**:**5** = 3.5:1) as a yellow solid (57% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 8.1, 0.8 Hz, 1H), 8.25 (d, *J* = 5.2 Hz, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.71 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.79 (d, *J* = 5.2 Hz, 1H), 3.95 – 3.88 (m, 4H), 3.87 (s, 3H), 1.73 – 1.64 (m, 6H), 1.39 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9, 157.1, 137.7, 132.2, 128.7, 127.1, 122.1, 121.2, 116.6, 114.8, 105.0, 83.8, 45.1, 33.5, 26.0, 26.0, 25.0. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.5. HRMS (ESI) m/z calcd for $C_{24}H_{32}BN_4O_2$ $[M+H]^+$ 419.2618, found 419.2594

4.5. Notes

The work presented in this chapter was not all conducted by Jose R. Montero Bastidas. Substrate exploration was a team effort with Arzoo Chhabra (N-alkylated anilines and indoles), Yilong Feng (N-unsubstituted anilines and 1-borylated naphthalenes) and Thomas J. Oleskey (N-alkylated anilines).

APPENDIX

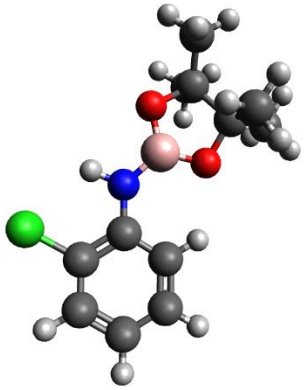
Computational Procedures and Results

Calculations of structures, energies, and frequencies employed default procedures in Gaussian16 unless otherwise noted.[80] Complete structures and energetics are provided in sections below. B3LYP/6-311++G** was used as basis set for all the calculations. All absolute energies are in Hartrees. All relative energies are presented in kcal/mol.

1a'-I, 2-ClPhNHBpin

E(RB3LYP) = -1158.14241950
Zero-point correction = 0.278990
(Hartree/Particle)
Thermal correction to Energy = 0.295671
Thermal correction to Enthalpy = 0.296616
Thermal correction to Gibbs Free Energy = 0.234713
Sum of electronic and zero-point Energies = -1157.863429
Sum of electronic and thermal Energies = -1157.846748
Sum of electronic and thermal Enthalpies = -1157.845804
Sum of electronic and thermal Free Energies = -1157.907706

E (Thermal)	CV	S
Kcal/mol	cal/mol-kelvin	cal/mol-Kelvin
185.537	65.666	130.285



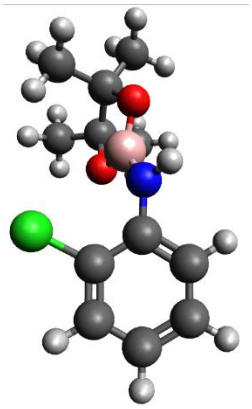
C 4.15958 1.73993 -0.10510
C 2.89530 2.32500 -0.15572
C 1.74639 1.54480 -0.11873
C 1.82273 0.14394 -0.02728
C 3.11064 -0.42109 0.02122
C 4.26182 0.35518 -0.01668
H 5.05573 2.34765 -0.13468
H 2.79828 3.40250 -0.22643
H 0.76959 2.00627 -0.16154
H 5.22847 -0.13078 0.02369
N 0.68870 -0.66604 0.01135
H 0.89448 -1.65502 0.05877
C -2.66432 0.80804 0.17580
C -2.93990 -0.71069 -0.16167
B -0.69497 -0.33629 0.01190
O -1.64944 -1.32519 0.11865
O -1.23223 0.92641 -0.09118
C -3.40109 1.81230 -0.70360
H -4.48337 1.70799 -0.58623
H -3.12641 2.82749 -0.40853
H -3.14980 1.68670 -1.75641
C -2.86884 1.14734 1.65613
H -2.47312 2.14697 1.84738
H -3.92750 1.13990 1.92593
H -2.34044 0.44460 2.30376
C -3.24041 -0.95712 -1.64468
H -3.22160 -2.03255 -1.83288
H -4.22572 -0.57657 -1.92419
H -2.49203 -0.48876 -2.28762
C -3.99493 -1.38508 0.70896
H -4.96922 -0.90493 0.58105
H -4.09334 -2.43250 0.41546
H -3.72528 -1.35505 1.76429
Cl 3.28628 -2.17736 0.13339

1a'-II, 2-ClPhNHBpin-90

E(RB3LYP) = -1158.13265068
Zero-point correction = 0.278175
(Hartree/Particle)
Thermal correction to Energy = 0.295041
Thermal correction to Enthalpy = 0.295985
Thermal correction to Gibbs Free Energy = 0.233547

Sum of electronic and zero-point Energies = -1157.854475
Sum of electronic and thermal Energies = -1157.837610
Sum of electronic and thermal Enthalpies = -1157.836666
Sum of electronic and thermal Free Energies = -1157.899103

E (Thermal)	CV	S
Kcal/mol	cal/mol-kelvin	cal/mol-Kelvin
185.141	66.107	131.411

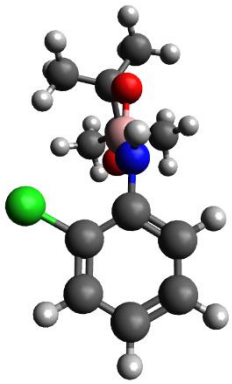


C 4.51567 -0.36205 0.67915
C 4.05521 -1.60707 0.25466
C 2.79360 -1.71951 -0.31682
C 1.96491 -0.60302 -0.50087
C 2.46479 0.64520 -0.09715
C 3.71763 0.76292 0.50123
H 5.49214 -0.26142 1.13805
H 4.66905 -2.49116 0.38238
H 2.41678 -2.69019 -0.62090
H 4.06591 1.74209 0.80447
N 0.69966 -0.75935 -1.10657
H 0.70252 -1.32245 -1.94512
C -2.22986 -0.01297 0.94448
C -2.83918 -0.17900 -0.50510
B -0.57815 -0.46944 -0.55718
O -1.73749 -0.79666 -1.23135
O -0.80426 0.10700 0.66822
C -2.68081 1.23432 1.69769
H -3.76139 1.21696 1.86650
H -2.18655 1.27002 2.67107
H -2.42418 2.14476 1.15711
C -2.41010 -1.25574 1.82380
H -1.79731 -1.14315 2.72057
H -3.45069 -1.38377 2.13175
H -2.08739 -2.16137 1.30555
C -3.13432 1.15863 -1.19344
H -3.36000 0.97057 -2.24527
H -3.99249 1.66269 -0.74236
H -2.27314 1.82843 -1.14699
C -4.05328 -1.09762 -0.59600
H -4.88481 -0.70224 -0.00569
H -4.38042 -1.16708 -1.63591
H -3.82383 -2.10407 -0.24667
Cl 1.55396 2.11687 -0.39421

1a'-TS, 2-ClPhNHBpin-TS

E(RB3LYP) = -1158.13204019
Zero-point correction = 0.277867 (Hartree/Particle)
Thermal correction to Energy = 0.293961
Thermal correction to Enthalpy = 0.294905
Thermal correction to Gibbs Free Energy = 0.234849
Sum of electronic and zero-point Energies = -1157.854174
Sum of electronic and thermal Energies = -1157.838079
Sum of electronic and thermal Enthalpies = -1157.837135
Sum of electronic and thermal Free Energies = -1157.897191

E (Thermal)	CV	S
Kcal/mol	cal/mol-kelvin	cal/mol-Kelvin
184.463	64.275	126.399

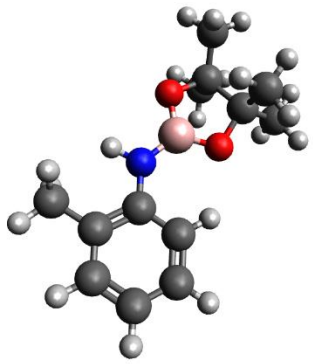


C 4.38222 -0.81032 0.60621
C 3.76642 -1.84213 -0.09878
C 2.54421 -1.61712 -0.72435
C 1.91373 -0.36943 -0.67130
C 2.55799 0.65507 0.03812
C 3.77777 0.44115 0.67551
H 5.33205 -0.97352 1.10220
H 4.23123 -2.81949 -0.15602
H 2.04586 -2.41260 -1.26623
H 4.24549 1.25404 1.21618
N 0.66838 -0.16945 -1.32549
H 0.71901 0.06448 -2.30671
C -2.24422 -0.52961 0.83366
C -2.83505 0.21078 -0.43257
B -0.60319 -0.16548 -0.70618
O -1.77207 0.03749 -1.41276
O -0.80940 -0.37706 0.63822
C -2.61559 0.08891 2.17755
H -3.69779 0.05938 2.33383
H -2.14176 -0.47770 2.98232
H -2.27834 1.12245 2.25033
C -2.53633 -2.03473 0.84545
H -1.93481 -2.50280 1.62752
H -3.58956 -2.23967 1.05242
H -2.27308 -2.49900 -0.10747
C -3.01037 1.71945 -0.22273
H -3.22921 2.18492 -1.18615
H -3.83515 1.93816 0.45992
H -2.10022 2.17452 0.17344
C -4.11624 -0.39459 -0.99686
H -4.92525 -0.34708 -0.26230
H -4.42766 0.16917 -1.87919
H -3.97364 -1.43336 -1.29382
Cl 1.84204 2.25668 0.12270

1g'-I, 2-MePhNHBpin

E(RB3LYP) = -737.845073111
Zero-point correction = 0.315939 (Hartree/Particle)
Thermal correction to Energy = 0.333040
Thermal correction to Enthalpy = 0.333984
Thermal correction to Gibbs Free Energy = 0.271726
Sum of electronic and zero-point Energies = -737.529134
Sum of electronic and thermal Energies = -737.512034
Sum of electronic and thermal Enthalpies = -737.511089
Sum of electronic and thermal Free Energies = -737.573347

E (Thermal)	CV	S
Kcal/mol	cal/mol-kelvin	cal/mol-Kelvin
208.985	67.867	131.033



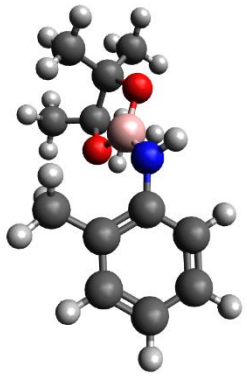
C 4.47681 1.26201 -0.10037
C 3.26594 1.94481 -0.17941
C 2.06055 1.25165 -0.13956
C 2.04598 -0.14503 -0.01684
C 3.26863 -0.84901 0.06346
C 4.46182 -0.12557 0.01926
H 5.41815 1.79808 -0.13198
H 3.25312 3.02515 -0.27456
H 1.12250 1.78559 -0.20406
H 5.40002 -0.66815 0.08133
N 0.83763 -0.86285 0.02481
H 0.94986 -1.86395 0.08117

C -2.40193 0.84698 0.16916
C -2.78354 -0.65138 -0.15524
B -0.51569 -0.43288 0.01873
O -1.54140 -1.35212 0.13440
O -0.96705 0.86270 -0.09854
C -3.06773 1.89317 -0.71834
H -4.15471 1.86607 -0.60046
H -2.72210 2.88888 -0.43156
H -2.82587 1.74201 -1.77003
C -2.58288 1.21192 1.64673
H -2.11688 2.18228 1.83003
H -3.63949 1.28158 1.91605
H -2.10523 0.47880 2.30013
C -3.09822 -0.88827 -1.63711
H -3.15548 -1.96395 -1.81656
H -4.05344 -0.44116 -1.92263
H -2.31699 -0.47924 -2.28145
C -3.88656 -1.24111 0.71772
H -4.82402 -0.69431 0.58221
H -4.05848 -2.28171 0.43357
H -3.61838 -1.22015 1.77368
C 3.29338 -2.35268 0.19544
H 4.32034 -2.71703 0.24941
H 2.81770 -2.84932 -0.65913
H 2.77848 -2.69465 1.10129

1g'-II, 2-MePhNHBpin-90

E(RB3LYP) = -737.839939421
Zero-point correction = 0.315566 (Hartree/Particle)
Thermal correction to Energy = 0.332718
Thermal correction to Enthalpy = 0.333662
Thermal correction to Gibbs Free Energy = 0.271494
Sum of electronic and zero-point Energies = -737.524373
Sum of electronic and thermal Energies = -737.507221
Sum of electronic and thermal Enthalpies = -737.506277
Sum of electronic and thermal Free Energies = -737.568446

E (Thermal)	CV	S
Kcal/mol	cal/mol-kelvin	cal/mol-Kelvin
208.784	68.018	130.845



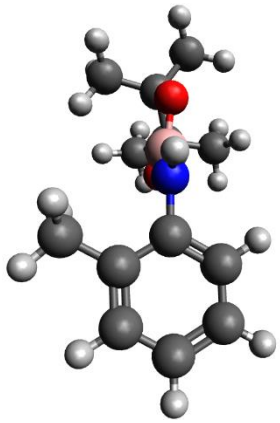
C 4.65224 0.08784 0.59421
C 4.22079 -1.23574 0.55196
C 2.94842 -1.52624 0.07268
C 2.09444 -0.51321 -0.38182
C 2.53317 0.82530 -0.37488
C 3.81004 1.09504 0.13226
H 5.63835 0.33355 0.97160
H 4.86363 -2.03677 0.89938
H 2.59466 -2.55229 0.05786
H 4.15549 2.12399 0.14192
N 0.81621 -0.87792 -0.88786
H 0.82622 -1.71507 -1.45438
C -2.14995 0.40174 0.82425
C -2.75195 -0.35603 -0.42508
B -0.47021 -0.48581 -0.44129
O -1.60997 -1.12490 -0.89463
O -0.74198 0.51635 0.46453
C -2.70402 1.80283 1.06169
H -3.77697 1.76520 1.27049
H -2.20755 2.24986 1.92594
H -2.53820 2.45316 0.20311
C -2.21391 -0.41772 2.11832
H -1.60539 0.07688 2.87822
H -3.23681 -0.49723 2.49422
H -1.81820 -1.42506 1.97227
C -3.16093 0.58514 -1.56443
H -3.37425 -0.01186 -2.45363
H -4.05638 1.15843 -1.31243
H -2.35918 1.28431 -1.81166
C -3.88924 -1.32227 -0.10874

H -4.74578 -0.79011 0.31488
H -4.21721 -1.81223 -1.02833
H -3.57646 -2.09602 0.59197
C 1.69026 1.94567 -0.92885
H 1.25331 1.66465 -1.89162
H 2.29617 2.84201 -1.07556
H 0.86161 2.19329 -0.26149

1g'-TS, 2-MePhNHBpin-TS

E(RB3LYP) = -737.837858104
Zero-point correction = 0.314905 (Hartree/Particle)
Thermal correction to Energy = 0.331451
Thermal correction to Enthalpy = 0.332395
Thermal correction to Gibbs Free Energy = 0.271852
Sum of electronic and zero-point Energies = -737.522953
Sum of electronic and thermal Energies = -737.506407
Sum of electronic and thermal Enthalpies = -737.505463
Sum of electronic and thermal Free Energies = -737.566006

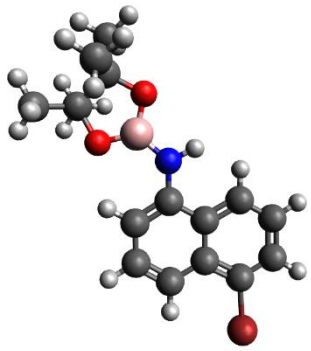
E (Thermal)	CV	S
Kcal/mol	cal/mol-kelvin	cal/mol-Kelvin
207.988	66.369	127.424



C 4.50911 -0.69761 0.49300
C 3.80803 -1.62299 -0.27523
C 2.58025 -1.26490 -0.82652
C 2.04483 0.00778 -0.61990
C 2.74452 0.94906 0.15652
C 3.97647 0.57247 0.70216
H 5.46622 -0.96132 0.92922
H 4.21024 -2.61562 -0.44370
H 2.01735 -1.97183 -1.42563
H 4.52547 1.29004 1.30353
N 0.78520 0.34741 -1.21192
H 0.82873 0.74194 -2.14096
C -2.13706 -0.60294 0.74495
C -2.75374 0.31613 -0.38401
B -0.49125 0.14437 -0.64781
O -1.66178 0.40004 -1.34080
O -0.71523 -0.31428 0.63401
C -2.58705 -0.27586 2.16537
H -3.66648 -0.41568 2.27366
H -2.08679 -0.94529 2.86878
H -2.33761 0.74865 2.44068
C -2.31383 -2.10077 0.46802
H -1.69598 -2.66287 1.17143
H -3.35282 -2.41479 0.59467
H -1.99404 -2.35883 -0.54390
C -3.04755 1.74377 0.09283
H -3.27697 2.36422 -0.77617
H -3.90255 1.77452 0.77265
H -2.18469 2.17963 0.60108
C -3.97515 -0.26080 -1.09316
H -4.80068 -0.40714 -0.39065
H -4.30924 0.43406 -1.86709
H -3.74921 -1.21364 -1.57125
C 2.18265 2.32635 0.40464
H 1.99008 2.85805 -0.53166
H 2.87513 2.92523 0.99935
H 1.23087 2.27275 0.94067

2m', 5-Br-1-NHBpinNaphthalene

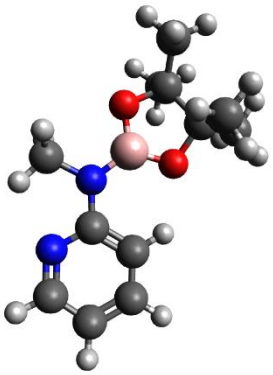
E(RB3LYP) = -3425.73395581



C 2.40473 -1.59944 0.14472
C 1.16628 -2.18738 0.22361
C -0.01262 -1.42172 0.22684
C 0.04002 -0.04182 0.13739
C 1.31768 0.61316 0.02727
C 2.51272 -0.19083 0.04661
H 3.30210 -2.20133 0.15566
H 1.08810 -3.26654 0.29592
H -0.97317 -1.91116 0.30491
C 3.75982 0.49359 -0.04383
N -1.12906 0.73015 0.15778
H -0.98490 1.72278 0.25435
C -4.42328 -0.81030 -0.31014
C -4.76085 0.64206 0.21217
B -2.49920 0.35685 0.07304
O -3.48267 1.32498 0.06255
O -2.99824 -0.92220 -0.00475
C -5.15658 -1.94236 0.40071
H -6.23699 -1.85420 0.25600
H -4.83813 -2.90133 -0.01404
H -4.94652 -1.95007 1.46991
C -4.56334 -0.95730 -1.82900
H -4.12545 -1.91025 -2.13296
H -5.61131 -0.94674 -2.13766
H -4.03729 -0.15970 -2.35780
C -5.11861 0.68211 1.70232
H -5.14305 1.72342 2.03020
H -6.09908 0.23919 1.89269
H -4.37659 0.15505 2.30600
C -5.80858 1.39394 -0.60194
H -6.76976 0.87296 -0.57383
H -5.95235 2.39051 -0.17862
H -5.50354 1.51011 -1.64156
C 1.44197 2.02032 -0.10657
C 2.67111 2.62707 -0.19537
C 3.85112 1.85763 -0.15778
H 0.56282 2.65049 -0.15997
H 2.74252 3.70330 -0.30055
Br 5.41147 -0.49697 -0.01251
H 4.81856 2.33755 -0.22484

4b', 2-NMeBpinPyridine

E(RB3LYP) = -753.876320116

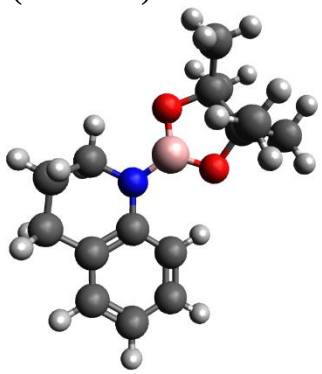


C 4.59628 -0.98599 0.07518
C 3.41953 -1.72565 0.21564
C 2.19193 -1.08787 0.18394
C 2.16066 0.31339 0.00374
N 3.28862 1.01998 -0.12687
C 4.46399 0.38418 -0.09082
H 5.57286 -1.45313 0.09667
H 3.45854 -2.80101 0.35341
H 1.27550 -1.64593 0.29423
H 5.34183 1.01550 -0.20231
N 0.94891 1.02919 -0.04071
C 1.00487 2.50378 -0.14108
C -2.13105 -0.98463 -0.17275
C -2.64863 0.46704 0.16404
B -0.36496 0.46689 -0.01712
O -1.47658 1.28100 -0.11625
O -0.70157 -0.86735 0.09603
C -2.69570 -2.09651 0.70513
H -3.78063 -2.16870 0.58783
H -2.26064 -3.05366 0.40879
H -2.46805 -1.93326 1.75818
C -2.27621 -1.35302 -1.65357
H -1.72124 -2.27391 -1.84430
H -3.32141 -1.51972 -1.92470

H -1.86966 -0.57307 -2.30080
C -2.98515 0.66157 1.64737
H -3.14137 1.72579 1.83555
H -3.89547 0.12600 1.92724
H -2.17031 0.32077 2.28980
C -3.80043 0.96144 -0.70537
H -4.68397 0.32993 -0.57602
H -4.06693 1.97929 -0.41221
H -3.53101 0.97473 -1.76114
H 2.04233 2.81455 -0.20074
H 0.53503 2.95930 0.73327
H 0.47130 2.84234 -1.03100

4d', N-Bpin-Tetrahydroquinoline

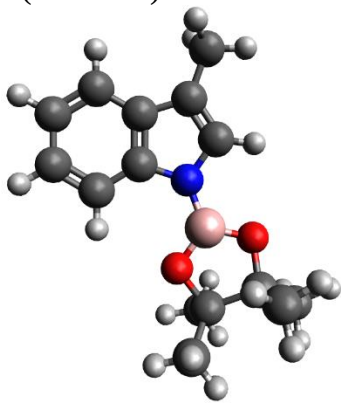
E(RB3LYP) = -815.273863261



C 4.08084 1.92046 -0.01367
C 2.82492 2.43070 -0.33950
C 1.72862 1.58498 -0.44391
C 1.85481 0.20369 -0.21431
C 3.12434 -0.31959 0.11185
C 4.21202 0.55474 0.20495
H 4.94121 2.57473 0.06754
H 2.69575 3.49210 -0.52141
H 0.76056 1.99063 -0.69843
H 5.18402 0.14319 0.46180
N 0.73139 -0.65910 -0.32392
C 1.03506 -2.08548 -0.52749
C -2.51078 0.89967 0.39876
C -2.91428 -0.48700 -0.23570
B -0.63107 -0.27878 -0.17056
O -1.65509 -1.21304 -0.20297
O -1.10490 1.00320 0.03319
C -3.24614 2.11106 -0.16555
H -4.32031 2.03713 0.02670
H -2.87870 3.01904 0.31790
H -3.08945 2.21317 -1.23916
C -2.57686 0.90780 1.93053
H -2.09446 1.81561 2.29854
H -3.60914 0.89689 2.28866
H -2.05208 0.05026 2.35702
C -3.33441 -0.38035 -1.70664
H -3.40338 -1.38604 -2.12674
H -4.30817 0.10376 -1.81339
H -2.60179 0.18066 -2.29083
C -3.95214 -1.28169 0.55077
H -4.89691 -0.73398 0.61133
H -4.14437 -2.23114 0.04587
H -3.60944 -1.50076 1.56175
C 3.34791 -1.80170 0.35166
C 2.03792 -2.57326 0.51411
H 3.98807 -1.93736 1.22908
H 3.90562 -2.21640 -0.49805
H 1.61695 -2.41207 1.51221
H 2.20746 -3.64832 0.40117
H 1.45104 -2.22685 -1.53455
H 0.10208 -2.64217 -0.47376

6a', N-Bpin-3-MeIndole

E(RB3LYP) = -814.071515122

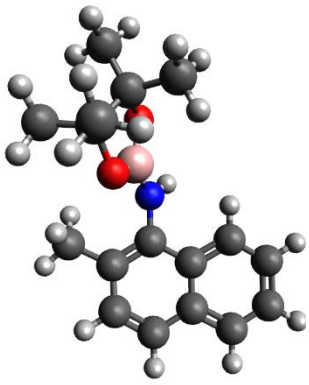


H 5.14678 0.08149 0.00419
C 4.19951 -0.44625 -0.02309
C 1.72884 -1.84782 -0.09737
C 2.98866 0.25850 0.00861
C 4.16742 -1.83369 -0.09040
C 2.94452 -2.52456 -0.12717
C 1.76628 -0.45498 -0.02816
H 5.09589 -2.39319 -0.11564
H 2.94634 -3.60755 -0.18094
H 0.78683 -2.37873 -0.12854
C 2.66574 1.66779 0.07483
C 1.30724 1.75048 0.07562

H 0.67192 2.62150 0.11694
N 0.71974 0.47661 0.01448
C 3.64284 2.80045 0.13049
H 4.29474 2.81009 -0.74972
H 4.29118 2.72670 1.01028
H 3.12840 3.76297 0.17507
B -0.69525 0.24141 0.01074
O -1.27093 -0.99887 -0.09788
O -1.60459 1.26525 0.11670
C -2.92129 0.69816 -0.16054
C -2.69920 -0.83232 0.16607
C -2.91865 -1.17681 1.64291
C -3.46799 -1.80286 -0.72364
C -3.21741 0.96692 -1.63996
C -3.94490 1.40601 0.72042
H -2.36652 -0.49993 2.29827
H -2.55924 -2.19151 1.82563
H -3.97695 -1.13380 1.91075
H -3.20914 -1.67797 -1.77465
H -4.54632 -1.66192 -0.60823
H -3.22929 -2.82907 -0.43593
H -2.48853 0.47770 -2.28959
H -3.16250 2.04243 -1.82036
H -4.21642 0.62267 -1.91762
H -3.67175 1.35806 1.77416
H -4.93691 0.96332 0.59412
H -4.00597 2.45832 0.43442

2o', 2-Me-1-NHBpinNaphthalene

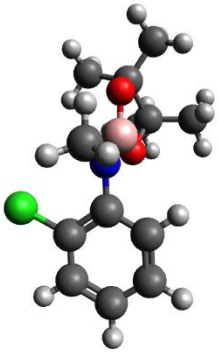
E(RB3LYP) = -891.515826157



C -3.67719 1.66320 0.45152
C -2.58242 2.42796 0.14468
C -1.38810 1.86424 -0.37617
C -1.31580 0.48843 -0.54283
C -2.43787 -0.34449 -0.21624
C -3.64078 0.25834 0.26984
H -4.58389 2.12449 0.82834
H -2.62652 3.50428 0.27602
C -0.25340 2.78103 -0.75497
C -4.75797 -0.56422 0.56751
N -0.14901 -0.12527 -1.07099
H -0.32261 -0.78924 -1.81308
C 3.02380 0.35435 0.68900
C 3.28938 -0.91348 -0.21770
B 1.16423 -0.14361 -0.54106
O 2.17715 -0.85895 -1.15382
O 1.57521 0.49436 0.60815
C 3.40885 0.19390 2.15627
H 4.48321 0.01637 2.25908
H 3.16399 1.10930 2.69963
H 2.87097 -0.62933 2.62560
C 3.63562 1.64048 0.12150
H 3.25757 2.49299 0.68969
H 4.72540 1.63450 0.20008
H 3.36456 1.78386 -0.92654
C 3.17005 -2.23797 0.54611
H 3.16946 -3.05963 -0.17334
H 4.00689 -2.38402 1.23333
H 2.24022 -2.28713 1.11697
C 4.59169 -0.88142 -1.01137
H 5.45558 -0.85082 -0.34127
H 4.66880 -1.78475 -1.62070
H 4.63517 -0.02089 -1.67850
C -2.40502 -1.75882 -0.34905
C -3.50546 -2.52931 -0.04984
C -4.69901 -1.92777 0.40676
H -3.45349 -3.60727 -0.15573
H -5.56048 -2.54399 0.63833
H -5.66607 -0.09305 0.92963
H -1.49173 -2.24286 -0.67163
H -0.61700 3.80028 -0.90141
H 0.22845 2.45008 -1.67825
H 0.51640 2.80187 0.02119

4a', 2-Cl-PhN-Me-N-Bpin

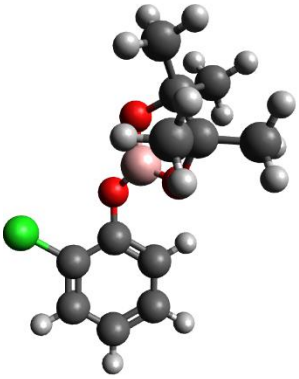
E(RB3LYP) = -1197.44604322



C 4.09641 1.48225 -0.40930
C 3.79028 0.19767 -0.84902
C 2.64477 -0.43727 -0.37703
C 1.78790 0.18362 0.54373
C 2.11995 1.47479 0.96741
C 3.25700 2.12478 0.49796
H 4.98677 1.97656 -0.78038
H 4.42674 -0.31201 -1.56118
Cl 2.27127 -2.04541 -0.98335
H 3.48721 3.12682 0.84088
N 0.62532 -0.46178 1.05158
C 0.83547 -1.43642 2.12671
C -2.33126 0.88961 -0.59690
C -2.89234 -0.40558 0.11427
B -0.66107 -0.17368 0.54084
O -1.82226 -0.73053 1.04604
O -0.89341 0.68850 -0.51222
C -2.71211 1.03778 -2.06664
H -3.79677 1.11999 -2.18159
H -2.25907 1.94608 -2.47032
H -2.35938 0.19424 -2.65937
C -2.65071 2.18243 0.16367
H -2.06834 2.99791 -0.27045
H -3.71009 2.44101 0.09323
H -2.38365 2.09966 1.21954
C -3.03937 -1.60004 -0.83591
H -3.23745 -2.49701 -0.24519
H -3.86742 -1.45926 -1.53489
H -2.12500 -1.76763 -1.40888
C -4.17921 -0.20354 0.90799
H -4.99536 0.11197 0.25172
H -4.46941 -1.14587 1.37826
H -4.05461 0.54089 1.69410
H 1.45909 1.96132 1.67545
H 1.27547 -0.95607 3.00770
H 1.49845 -2.24503 1.80502
H -0.12606 -1.86498 2.40592

2p', 2-Cl-PhOBpin

E(RB3LYP) = -1178.01233752

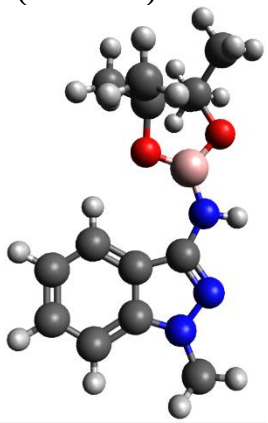


C 4.11914 1.57969 0.13942
C 2.99116 2.25020 -0.32899
C 1.82407 1.54697 -0.61038
C 1.76869 0.16568 -0.42007
C 2.90638 -0.50089 0.05036
C 4.07529 0.20127 0.32847
H 5.03126 2.12240 0.35713
H 3.01707 3.32301 -0.48018
H 0.94169 2.05939 -0.97125
H 4.94080 -0.33850 0.69129
O 0.66317 -0.57168 -0.74087
C -2.42968 0.60394 0.67540
C -2.89325 -0.43968 -0.41995
B -0.62552 -0.28083 -0.39293
O -1.64583 -1.12128 -0.74501
O -1.02888 0.82262 0.31494
C -3.15084 1.94640 0.64033
H -4.21794 1.81706 0.84137
H -2.73918 2.60204 1.41078
H -3.03536 2.44224 -0.32317
C -2.43364 0.03493 2.09770
H -1.91934 0.73507 2.75917
H -3.45125 -0.10555 2.46944
H -1.91119 -0.92276 2.14703
C -3.39014 0.21644 -1.71268
H -3.49972 -0.55448 -2.47796
H -4.35883 0.70131 -1.57051
H -2.68109 0.96014 -2.08306

C -3.89811 -1.47974 0.06343
H -4.82874 -1.00179 0.38214
H -4.13226 -2.16562 -0.75352
H -3.50330 -2.06644 0.89234
Cl 2.86076 -2.23482 0.29547

11', 3-NHBpin-N-Me-Indazole

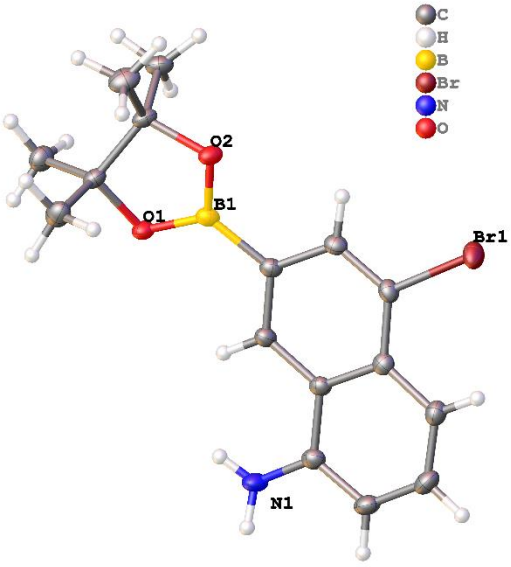
E(RB3LYP) = -885.473191201

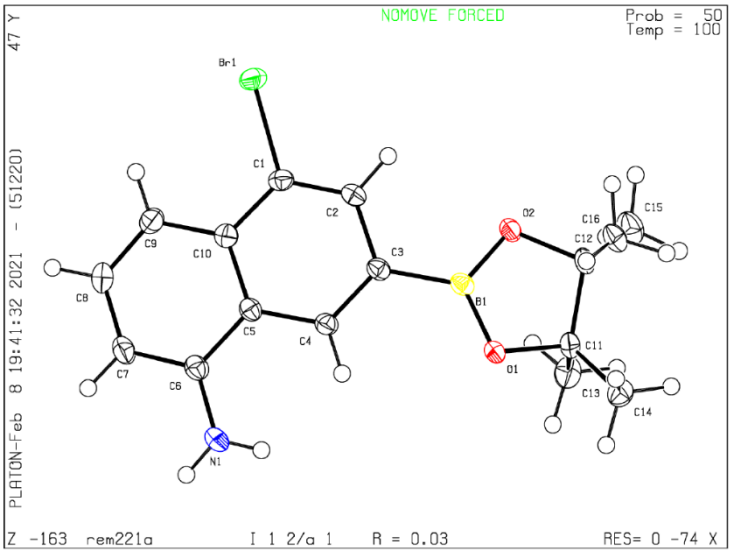


H 0.43893 1.81533 0.21240
C 1.49838 1.60878 0.15919
C 4.29664 1.06784 0.01667
C 1.95463 0.28316 0.05019
C 2.43185 2.63061 0.19608
C 3.81622 2.36056 0.12620
C 3.35027 0.03059 -0.02462
H 2.09822 3.65826 0.28269
H 4.51903 3.18574 0.16191
H 5.36030 0.86751 -0.02996
C 1.36679 -1.02845 -0.00250
N 2.29901 -1.96016 -0.09726
N 3.50565 -1.31815 -0.13403
N 0.03776 -1.44339 0.03732
C 4.72650 -2.08999 -0.08482
H 5.51462 -1.56608 -0.62865
H 4.54223 -3.04959 -0.56585
H 5.05664 -2.26457 0.94559
B -1.21026 -0.77330 0.00905
H -0.02499 -2.45386 0.03828
O -1.42780 0.58676 0.03287
O -2.38319 -1.50289 -0.04241
C -2.84527 0.80237 -0.24466
C -3.47992 -0.57645 0.19111
C -2.96768 1.07830 -1.74728
C -3.31360 2.01344 0.55509
C -3.81522 -0.64251 1.68590
C -4.67852 -1.02670 -0.63778
H -2.63176 0.22376 -2.33837
H -2.33830 1.93358 -2.00188
H -3.99678 1.31330 -2.02932
H -3.09269 1.90507 1.61665
H -4.39017 2.16350 0.43438
H -2.80657 2.91072 0.19287
H -4.42166 -1.13341 -1.69137
H -5.50388 -0.31477 -0.54720
H -5.02764 -1.99627 -0.27568
H -2.96787 -0.32897 2.29952
H -4.05663 -1.67522 1.94610
H -4.67508 -0.01563 1.93418

Xray structure of 7-borylated 5-bromo-1-naphthylamine (2m)

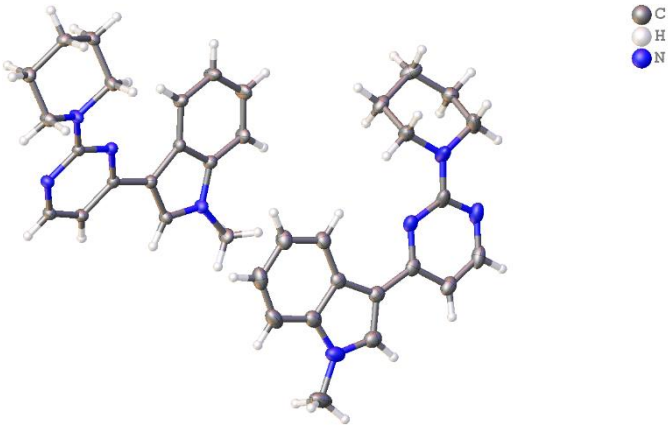
Formula	$C_{16}H_{19}BBrNO_2$
CCDC	2062023
$D_{calc.}$/ g cm^{-3}	1.475
μ/mm^{-1}	3.591
Formula Weight	348.04
Colour	colourless
Shape	needle
Size/mm^3	0.23×0.09×0.04
T/K	99.9(5)
Crystal System	monoclinic
Space Group	$I2/a$
a/Å	17.0799(2)
b/Å	6.25799(8)
c/Å	29.8888(4)
α/°	90
β/°	101.0603(12)
γ/°	90
V/Å^3	3135.35(7)
Z	8
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K□
Θ_{min}/°	3.013
Θ_{max}/°	76.503
Measured Refl's.	17475
Indep't Refl's	3172
Refl's I≥2 □(I)	3032
R_{int}	0.0312
*Para*meters	202
Restraints	0
Largest Peak	0.854
Deepest Hole	-0.510
GooF	1.071
wR_2 (all data)	0.0685
wR_2	0.0678
R_1 (all data)	0.0272
R_1	0.0262

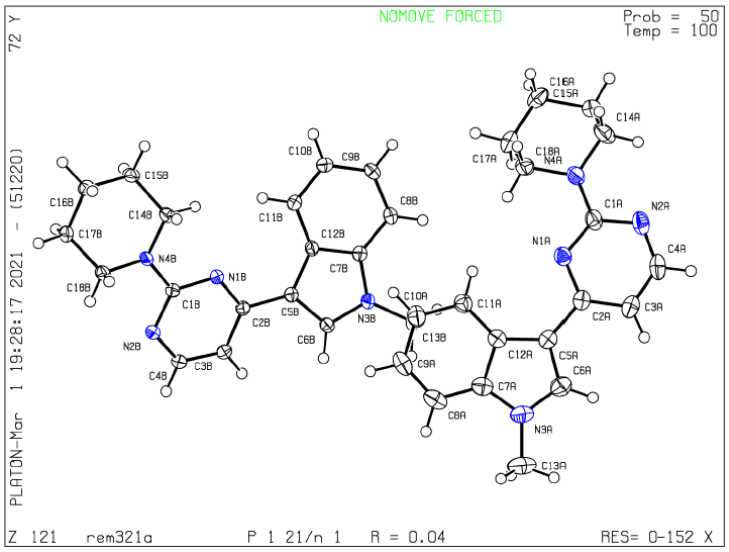




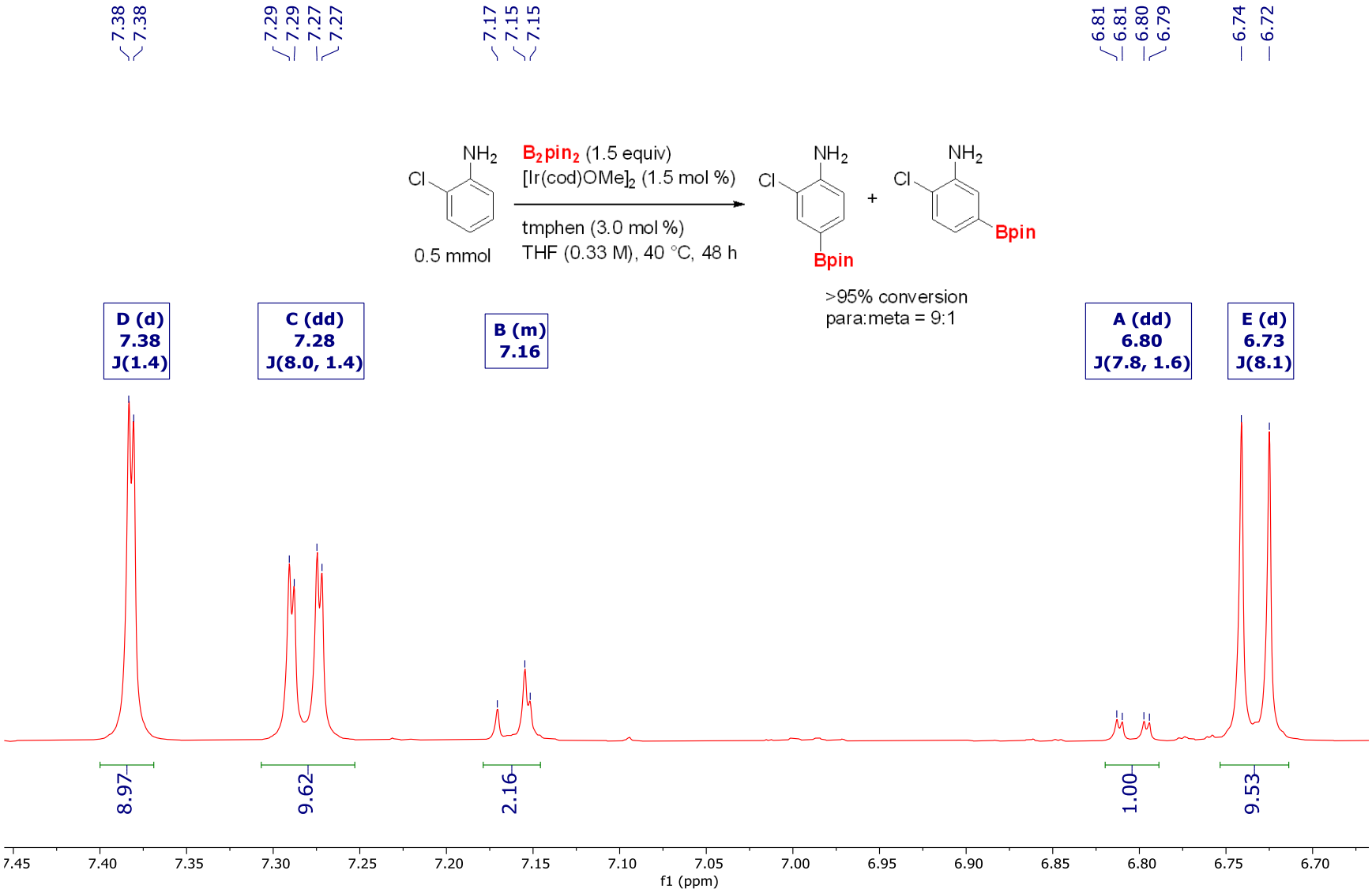
X-ray structure of osimertinib's analogue (13)

Formula	$C_{36}H_{40}N_8$
CCDC	2067392
$D_{calc.}$/ g cm^{-3}	1.288
μ/mm^{-1}	0.616
Formula Weight	584.76
Colour	colourless
Shape	plate
Size/mm^3	0.25×0.23×0.06
T/K	100.01(10)
Crystal System	monoclinic
Space Group	$P2_1/n$
a/Å	17.7018(2)
b/Å	9.27126(10)
c/Å	19.4100(2)
α/°	90
β/°	108.7478(14)
γ/°	90
V/Å^3	3016.52(7)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K$_a$
Θ_{min}/°	2.942
Θ_{max}/°	77.052
Measured Refl's.	23287
Indep't Refl's	5935
Refl's I≥2 s(I)	5229
R_{int}	0.0330
*Para*meters	399
Restraints	0
Largest Peak	0.572
Deepest Hole	-0.444
GooF	1.050
wR_2 (all data)	0.1124
wR_2	0.1083
R_1 (all data)	0.0473
R_1	0.0421

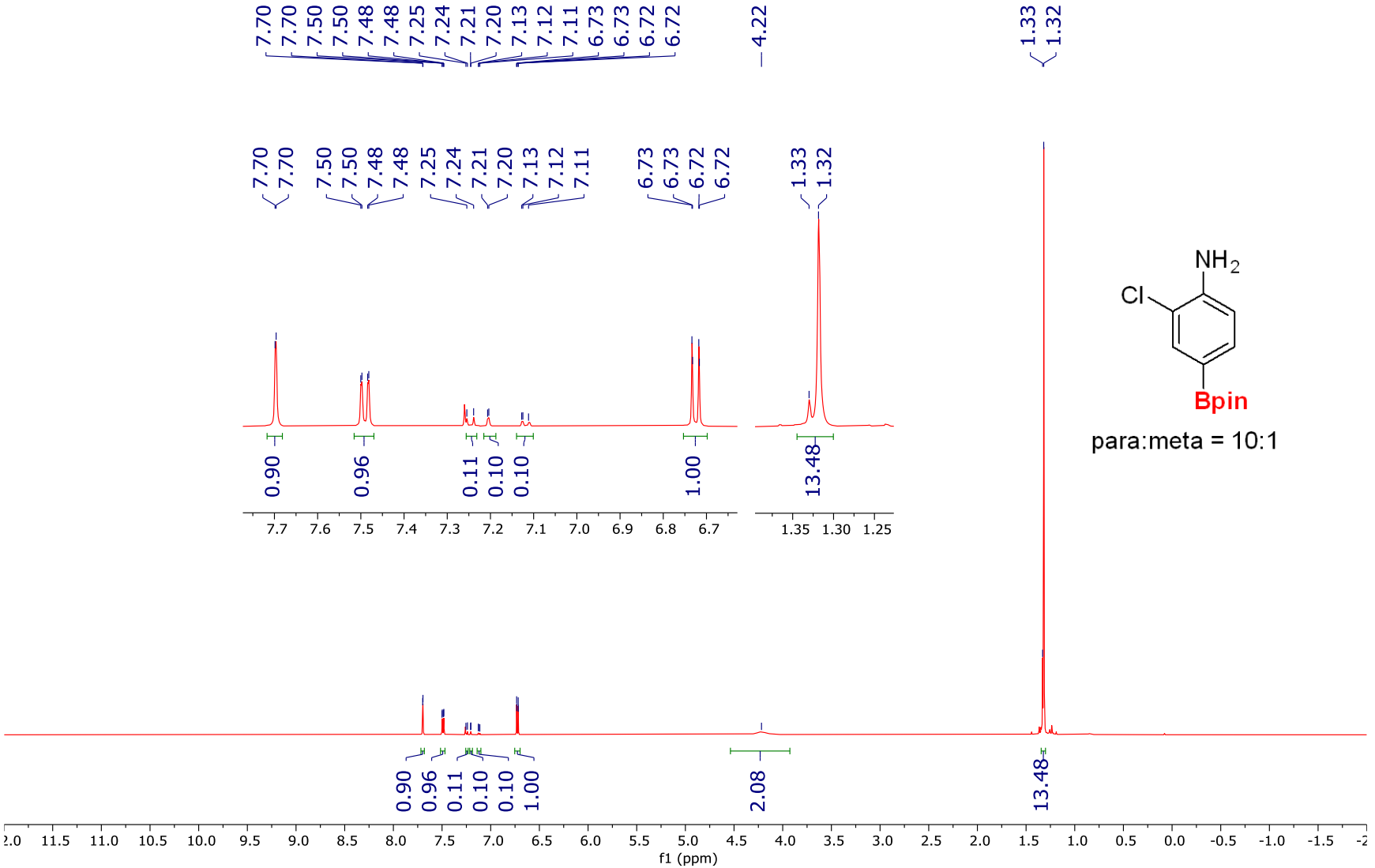




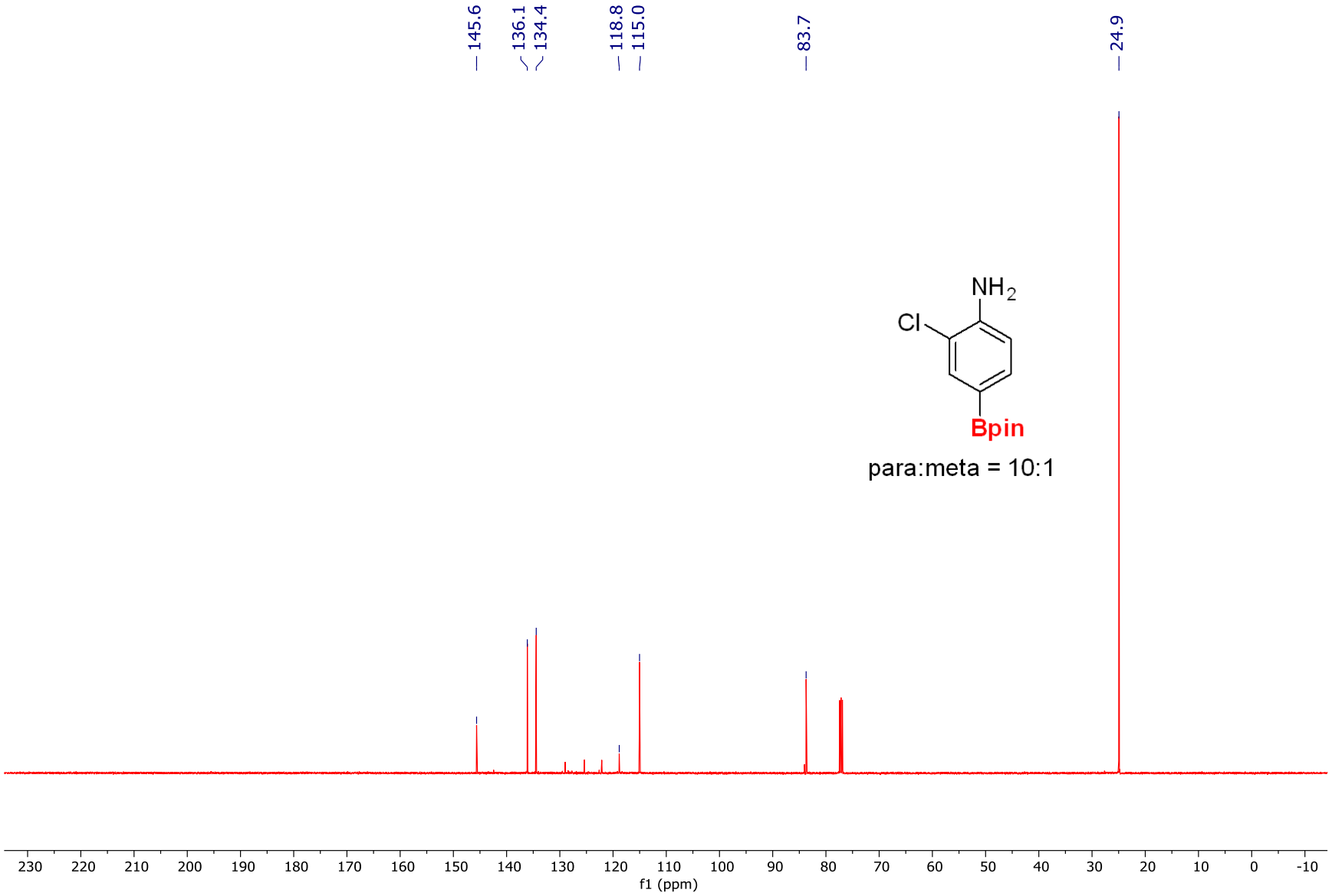
***Para* CHB of 2-chloroaniline (4.2a) (DMSO-d6, 500 MHz)**



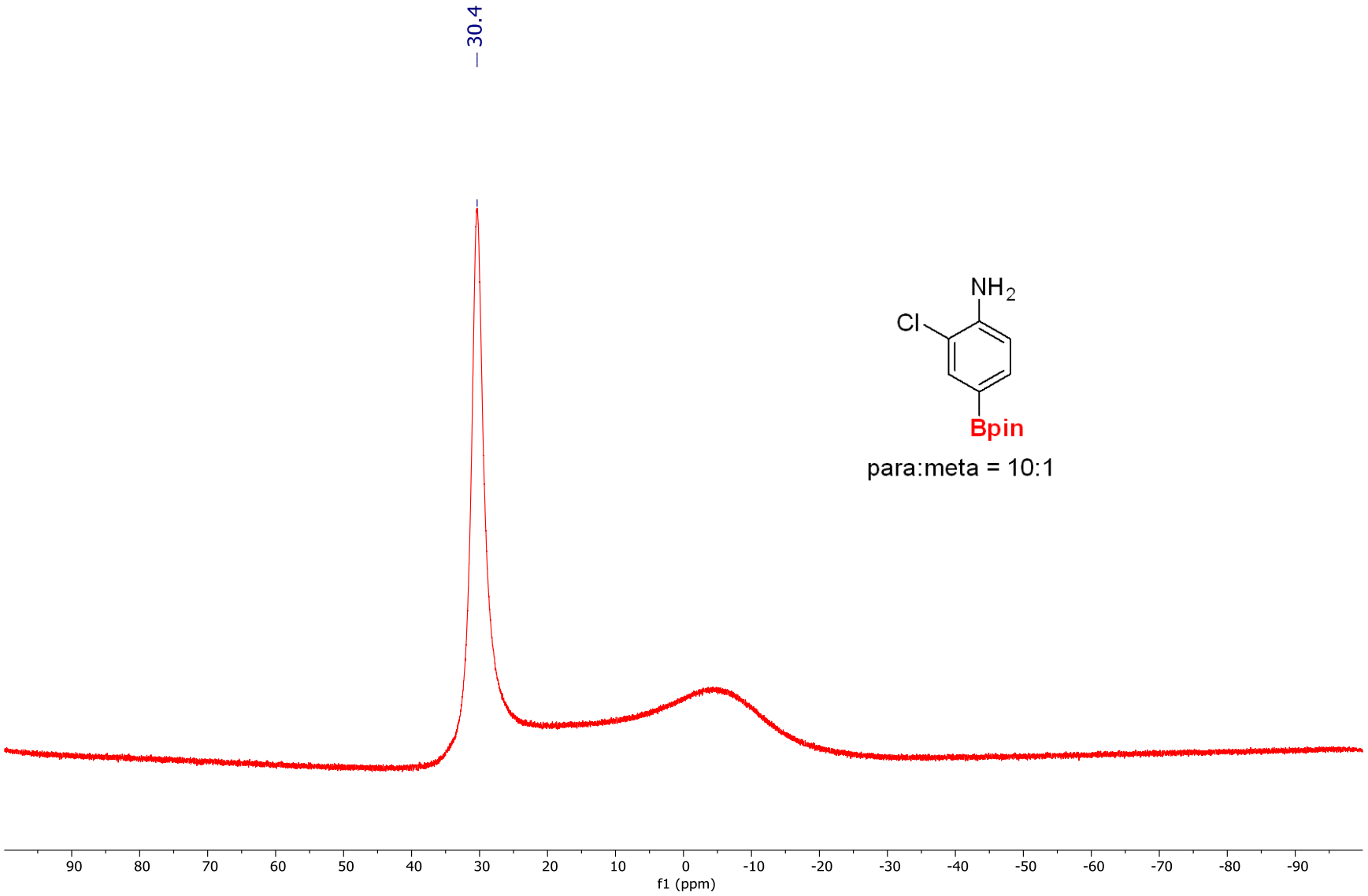
^{1}H NMR of *para* borylated 2-chloroaniline (4.2a) ($CDCl_3$, 500 MHz)



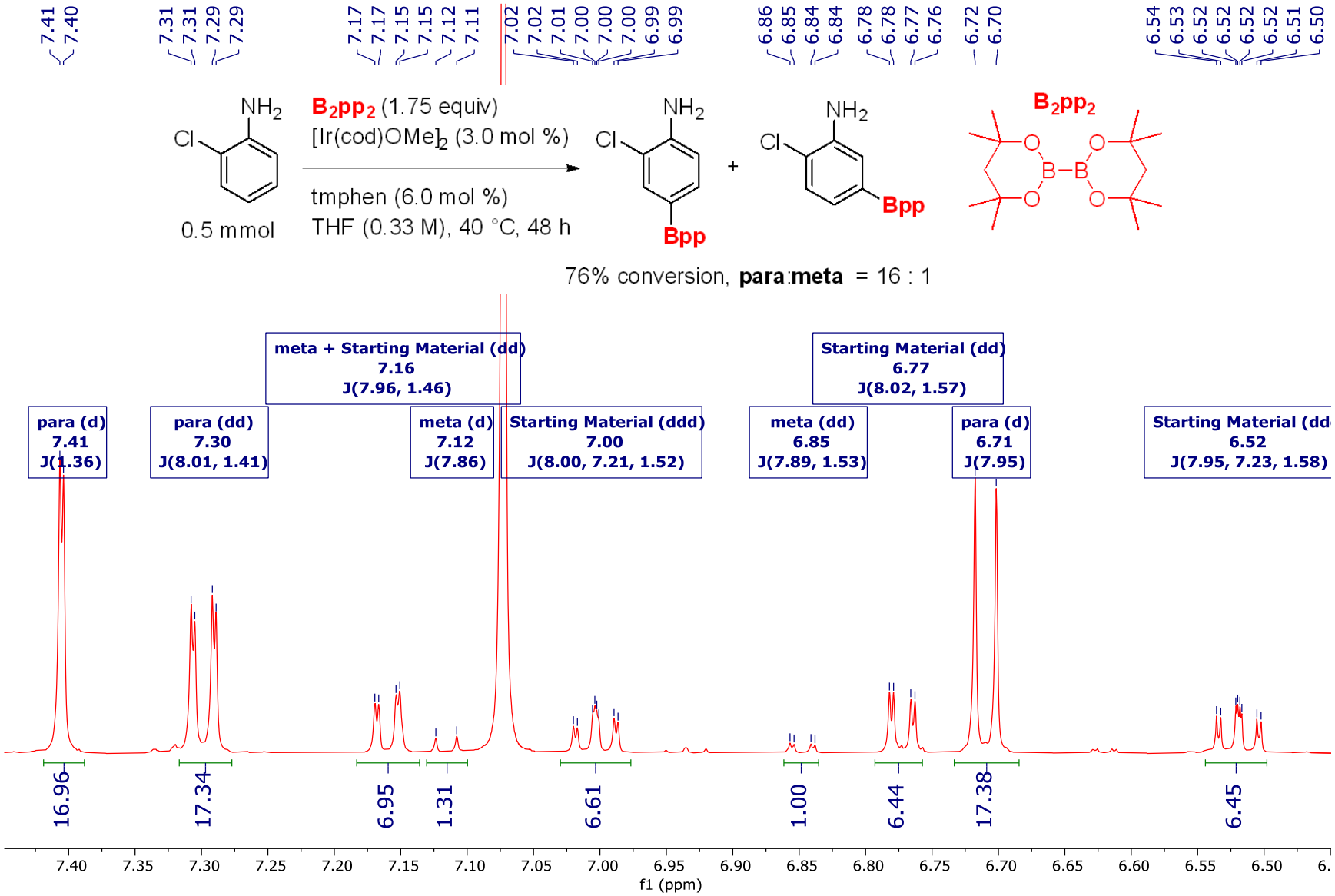
^{13}C NMR of *para* borylated 2-chloroaniline (4.2a) ($CDCl_3$, 126 MHz)



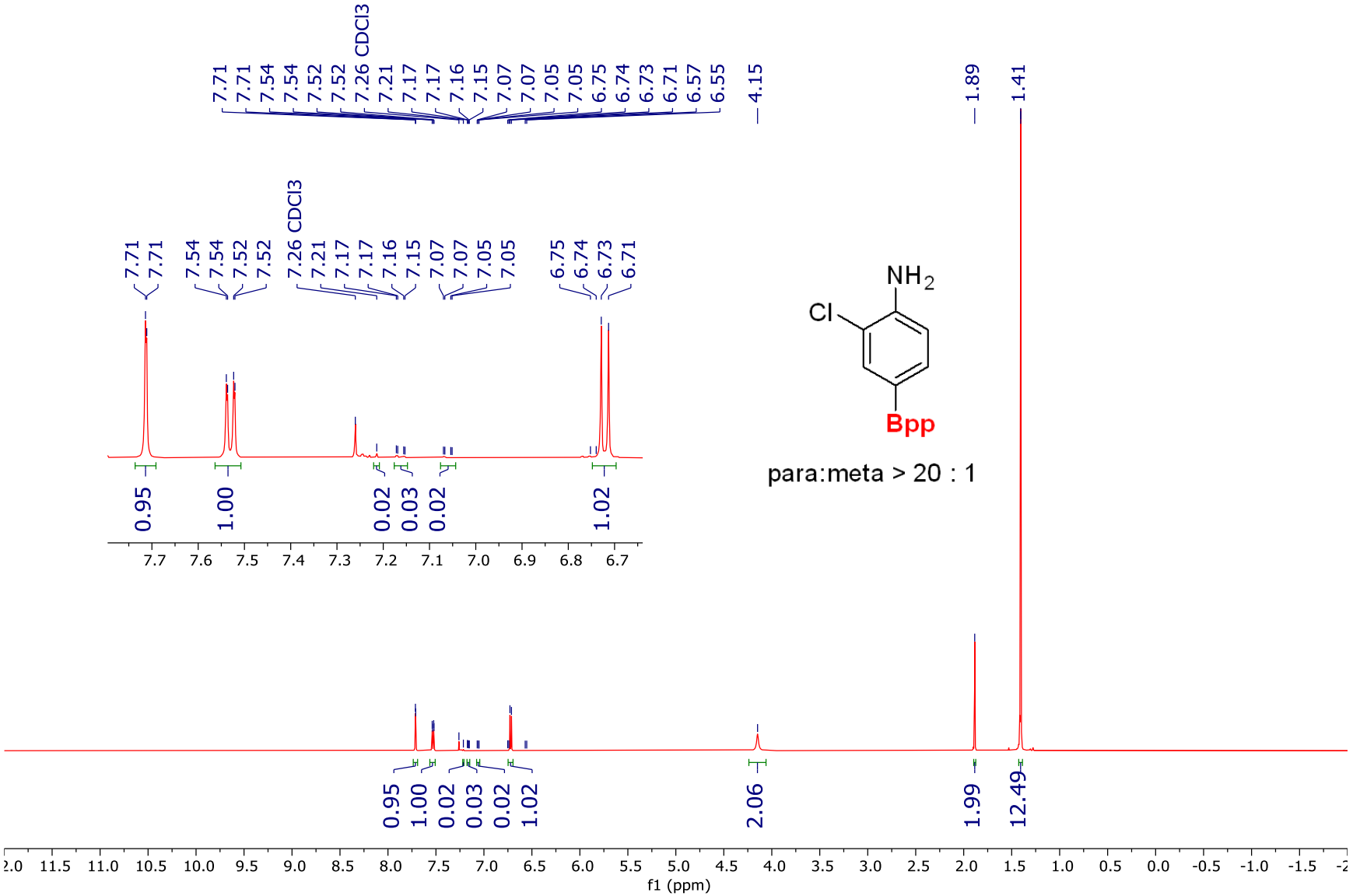
^{11}B NMR of *para* borylated 2-chloroaniline (4.2a) ($CDCl_3$, 160 MHz)



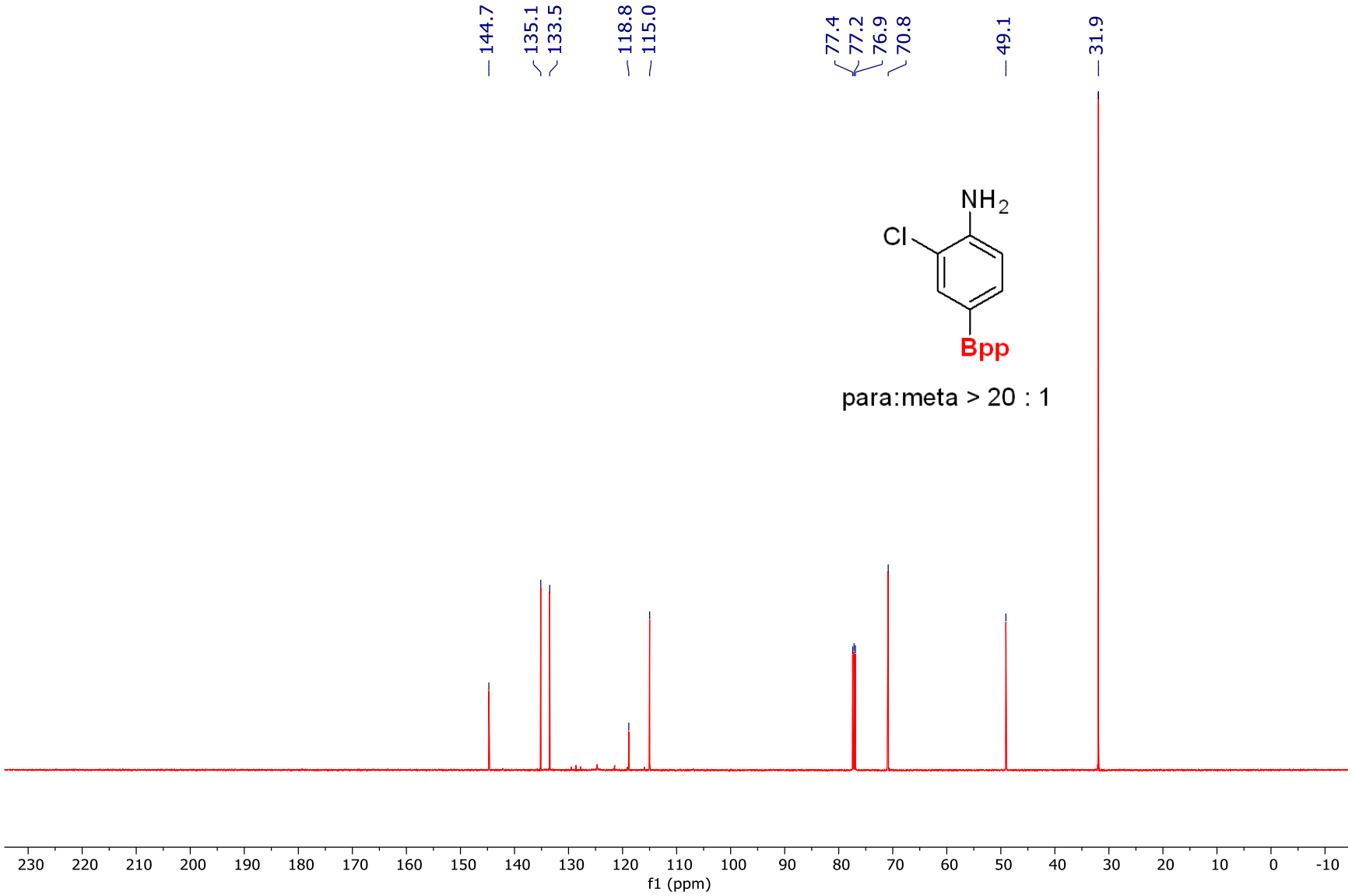
***Para* CHB of 2-chloroaniline with B_2pp_2 (4.2a') (DMSO-d6, 500 MHz)**



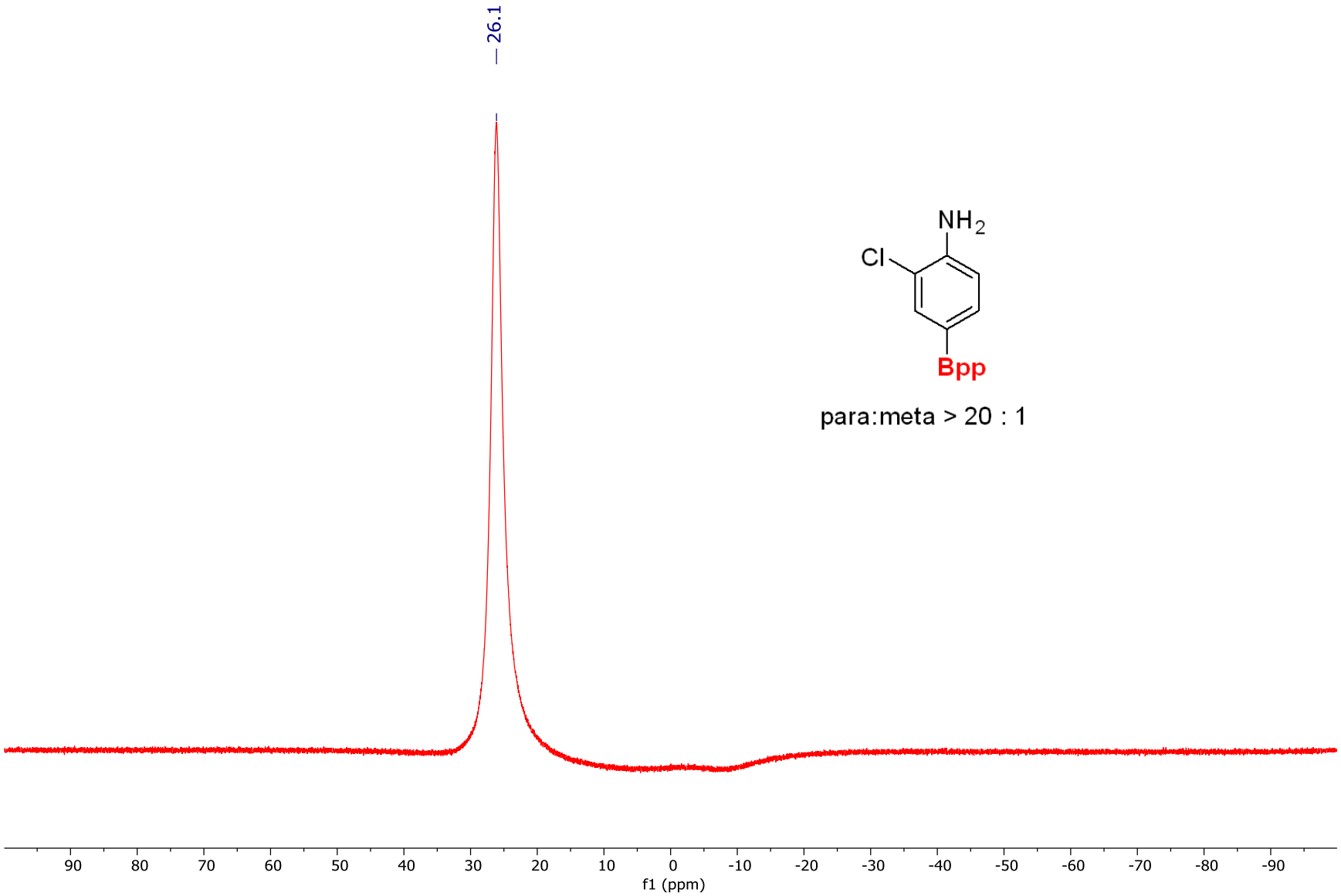
^{1}H NMR of *para* borylated 2-chloroaniline with B_2pp_2 (4.2a') ($CDCl_3$, 500 MHz)



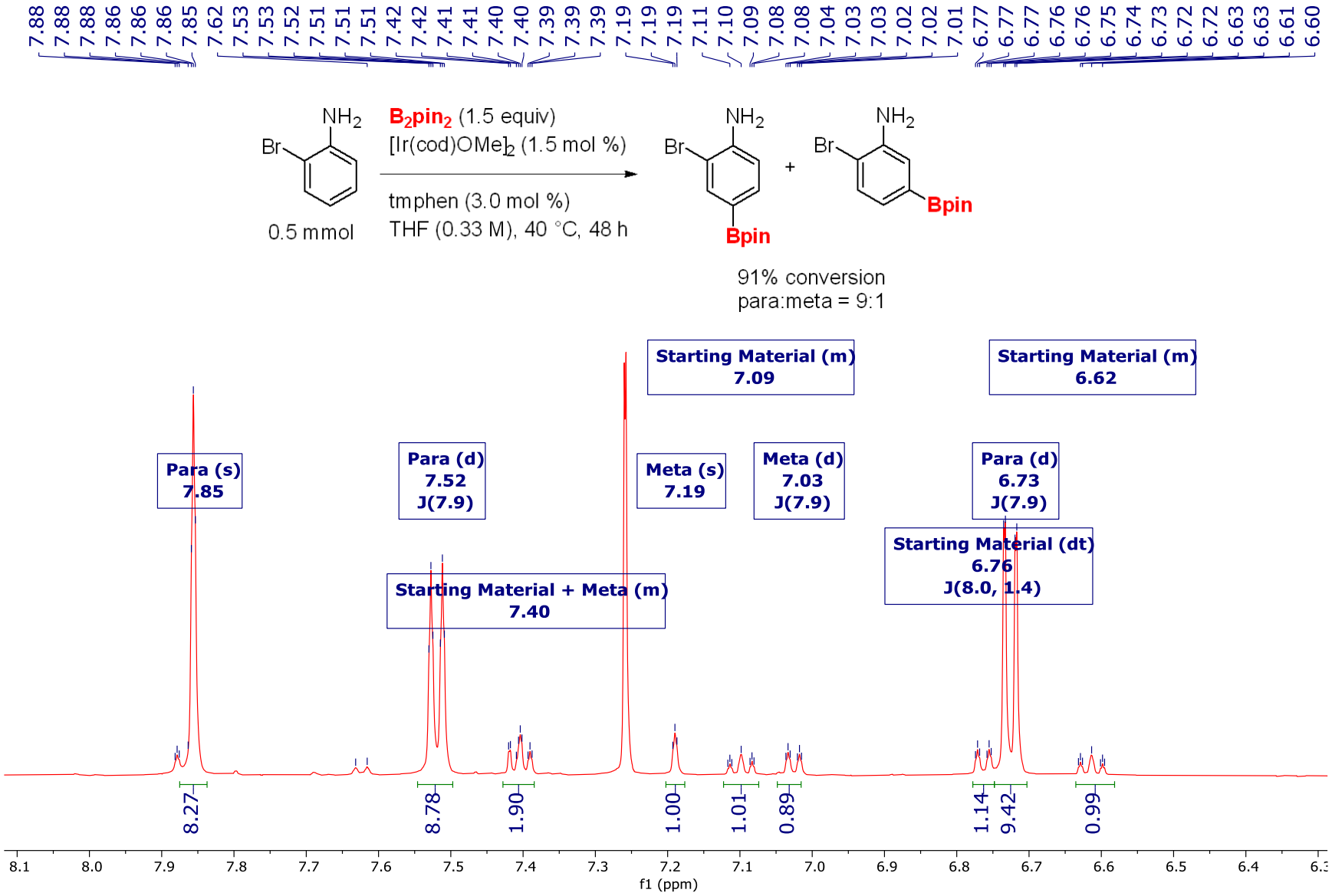
^{13}C NMR of *para* borylated 2-chloroaniline with B_2pp_2 (4.2a') ($CDCl_3$, 126 MHz)



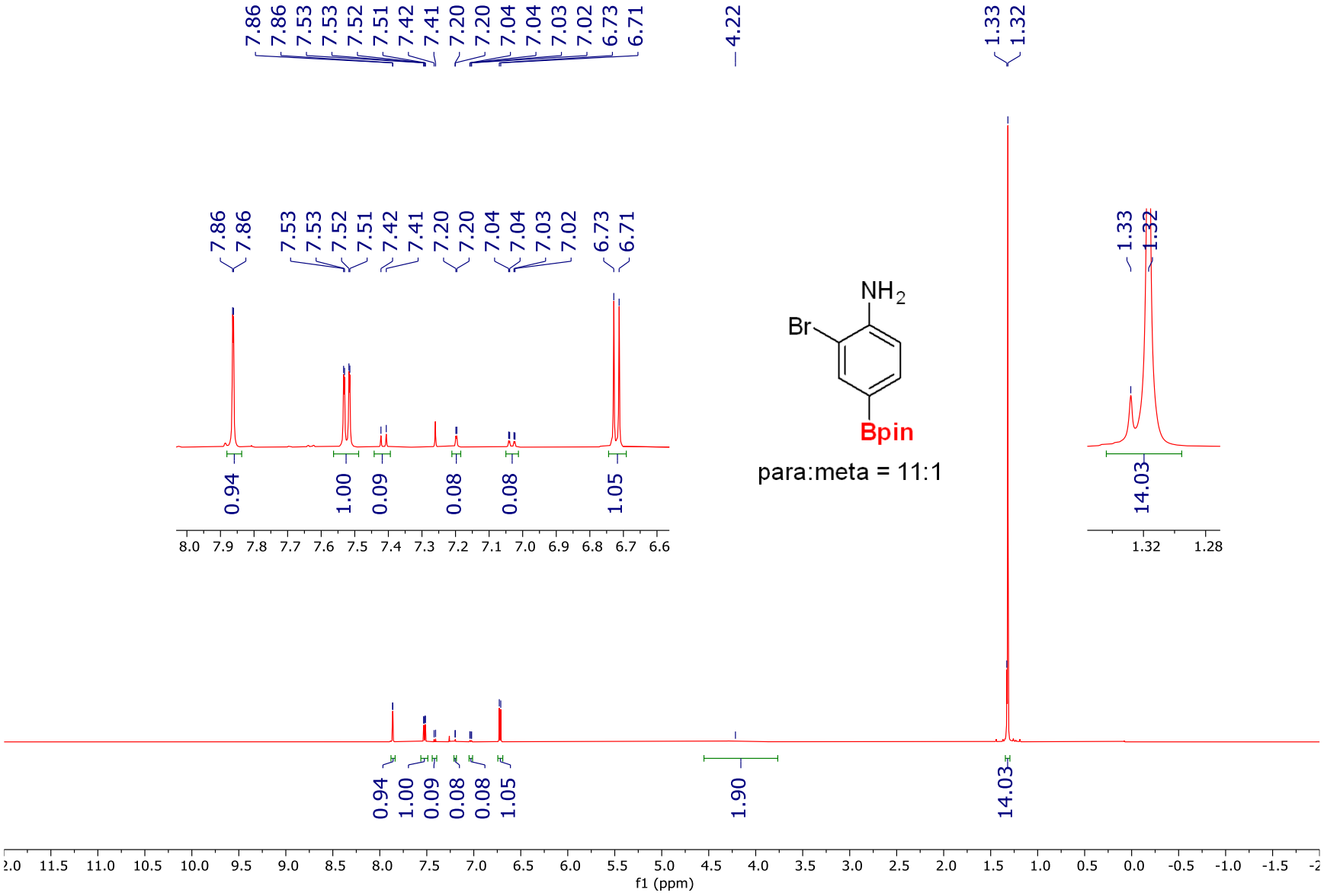
^{11}B NMR of *para* borylated 2-chloroaniline with B_2pp_2 (4.2a') ($CDCl_3$, 160 MHz)



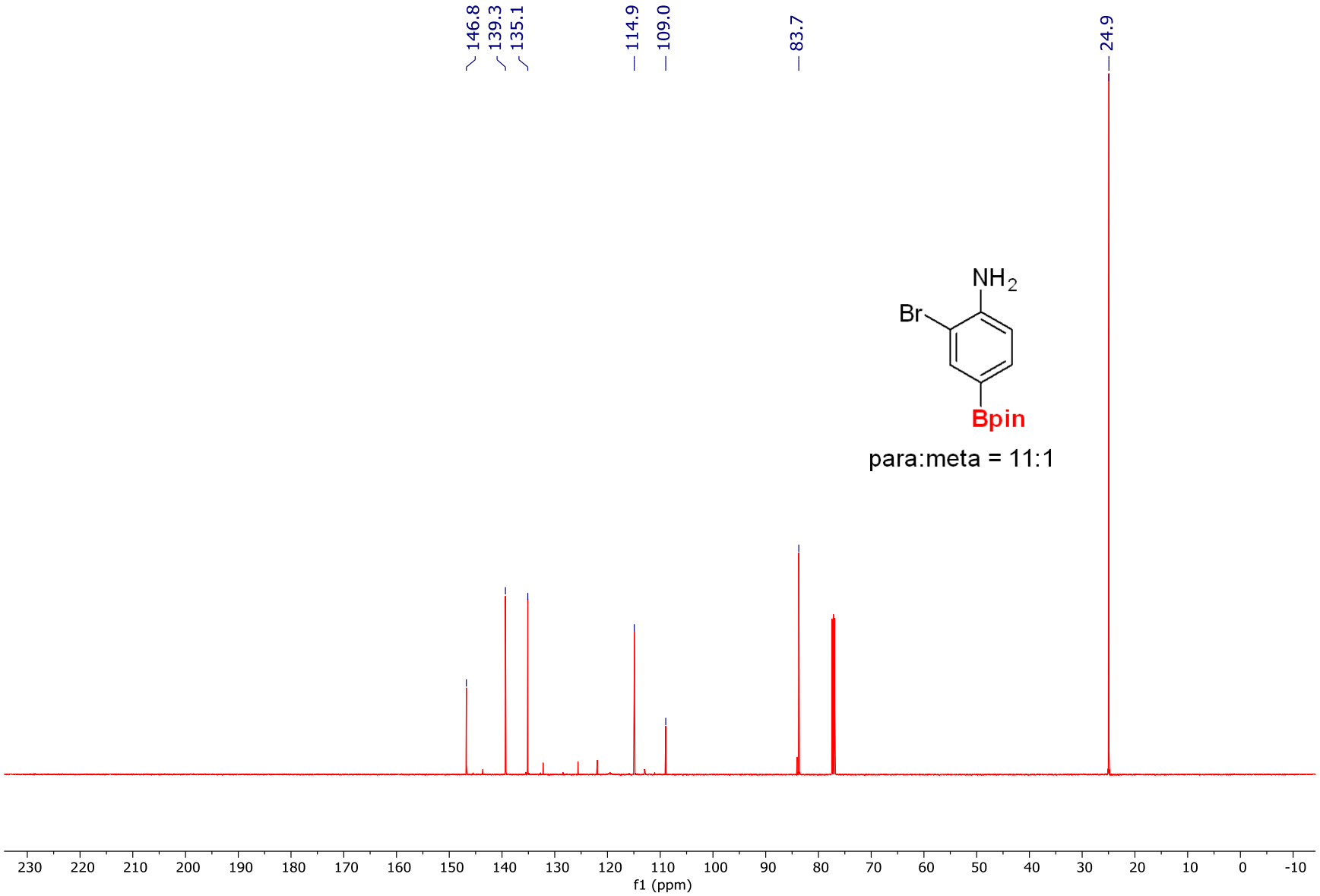
***Para* CHB of 2-bromoaniline (4.2b) ($CDCl_3$, 500 MHz)**



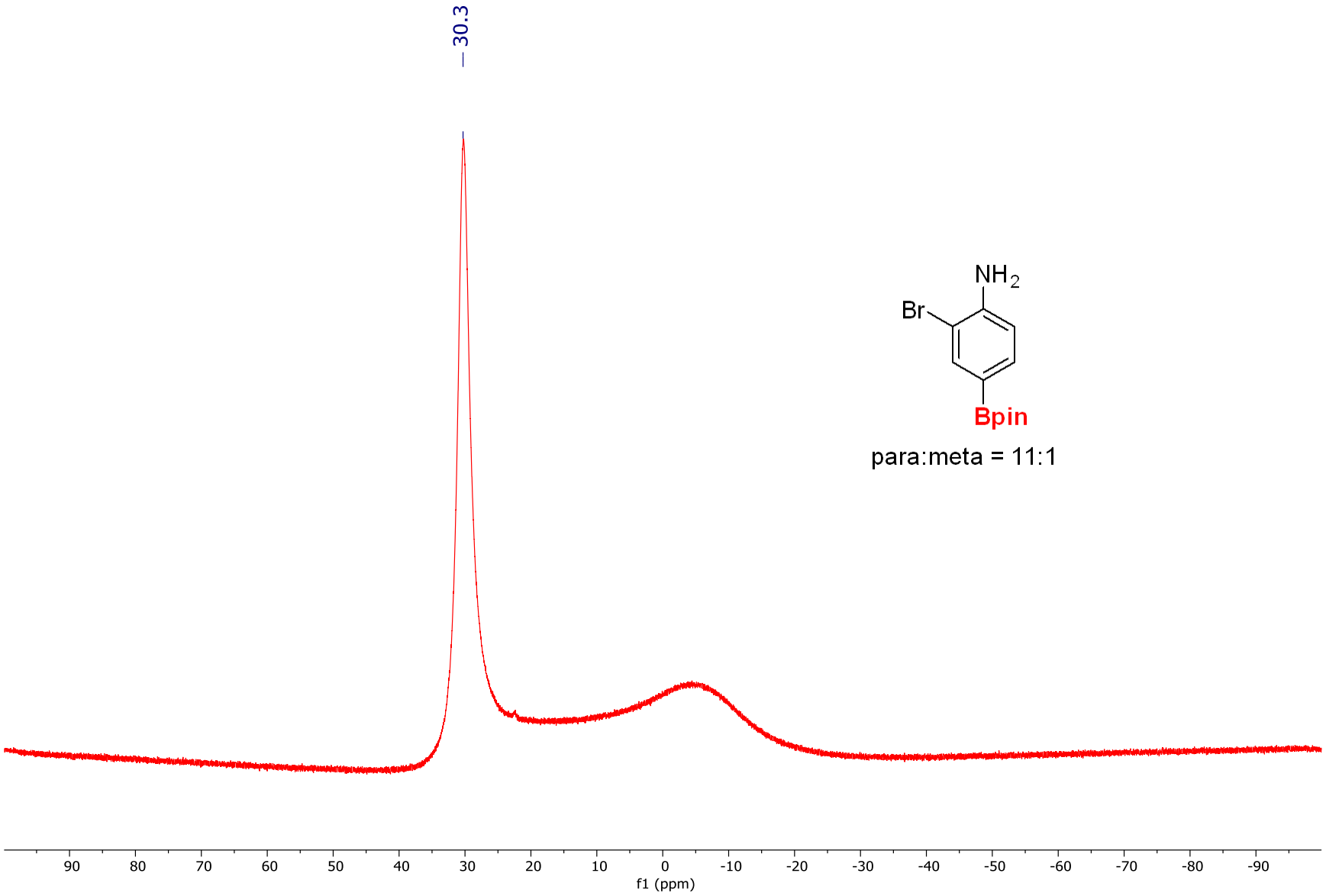
^{1}H NMR of *para* borylated 2-bromoaniline (4.2b) ($CDCl_3$, 500 MHz)



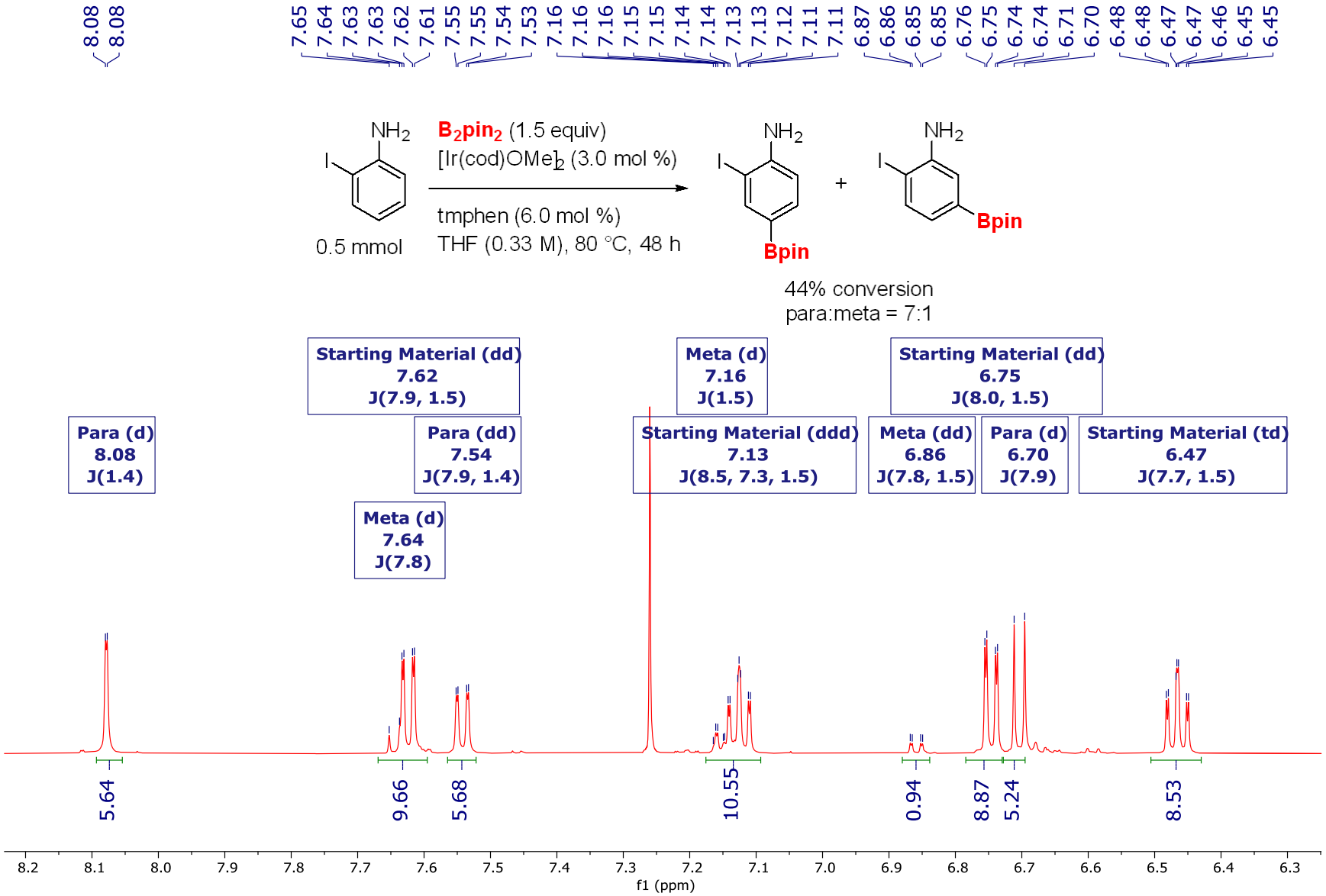
^{13}C NMR of *para* borylated 2-bromoaniline (4.2b) ($CDCl_3$, 126 MHz)



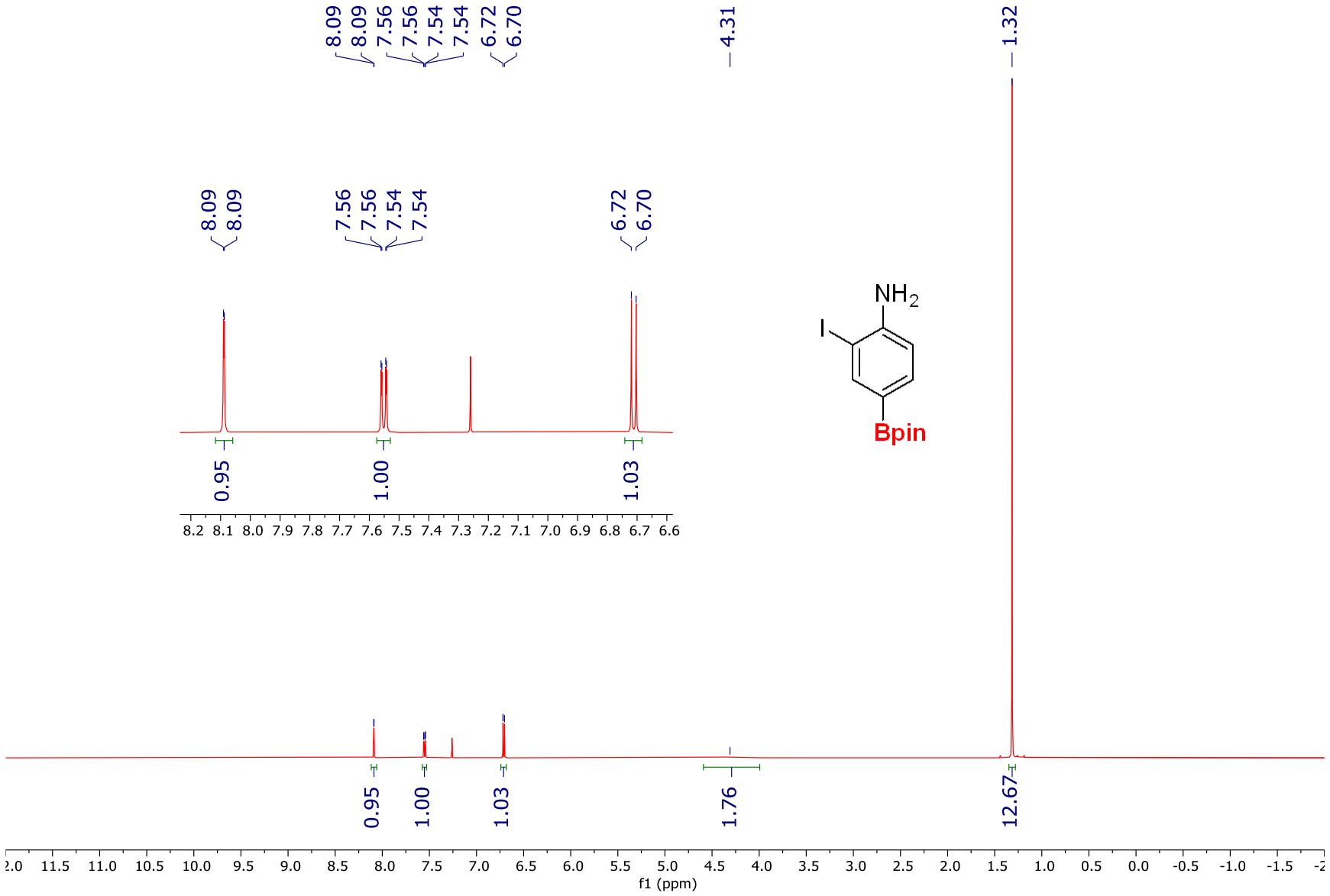
^{11}B NMR of *para* borylated 2-bromoaniline (4.2b) ($CDCl_3$, 160 MHz)



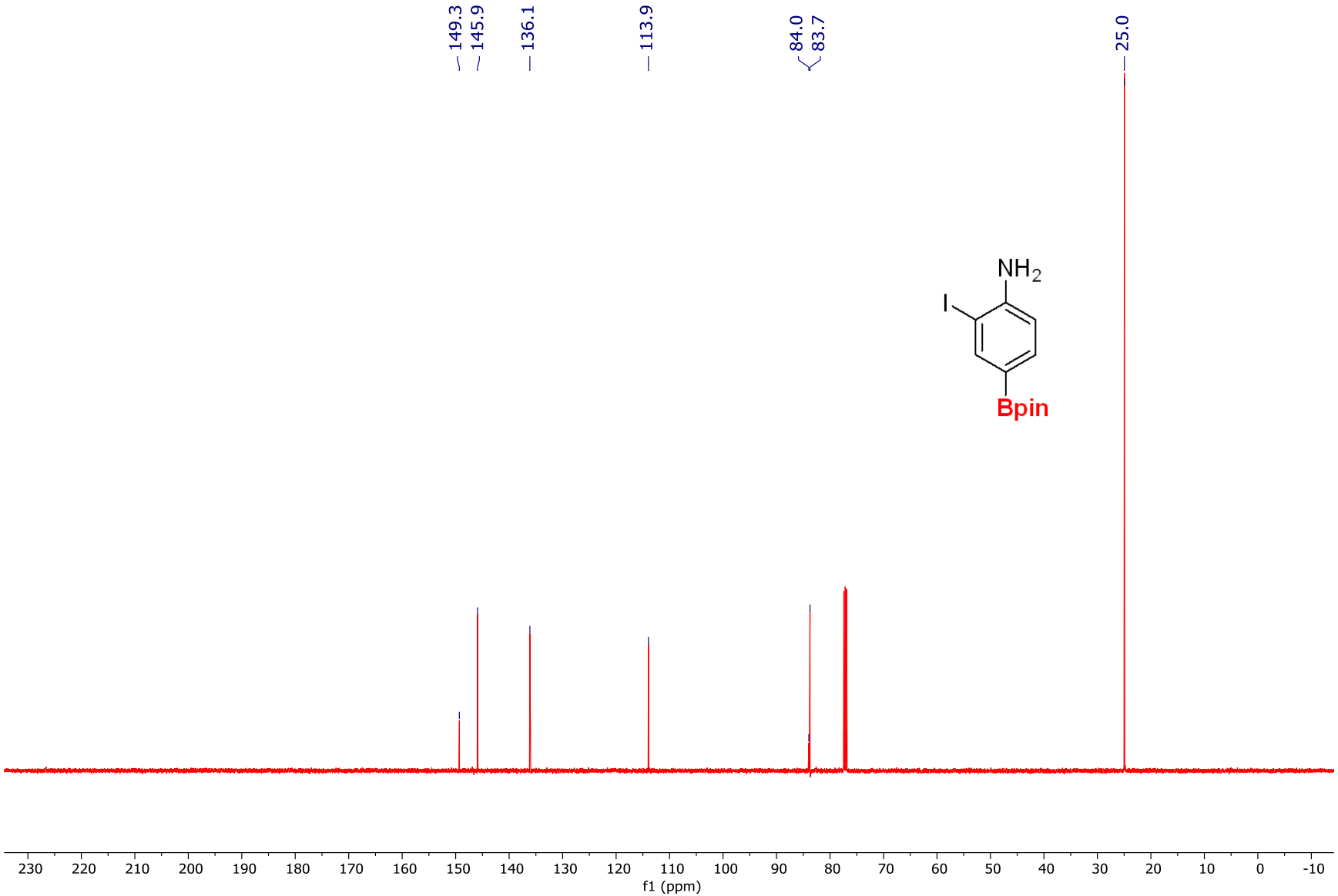
***Para* CHB of 2-iodoaniline (4.2c) ($CDCl_3$, 500 MHz)**



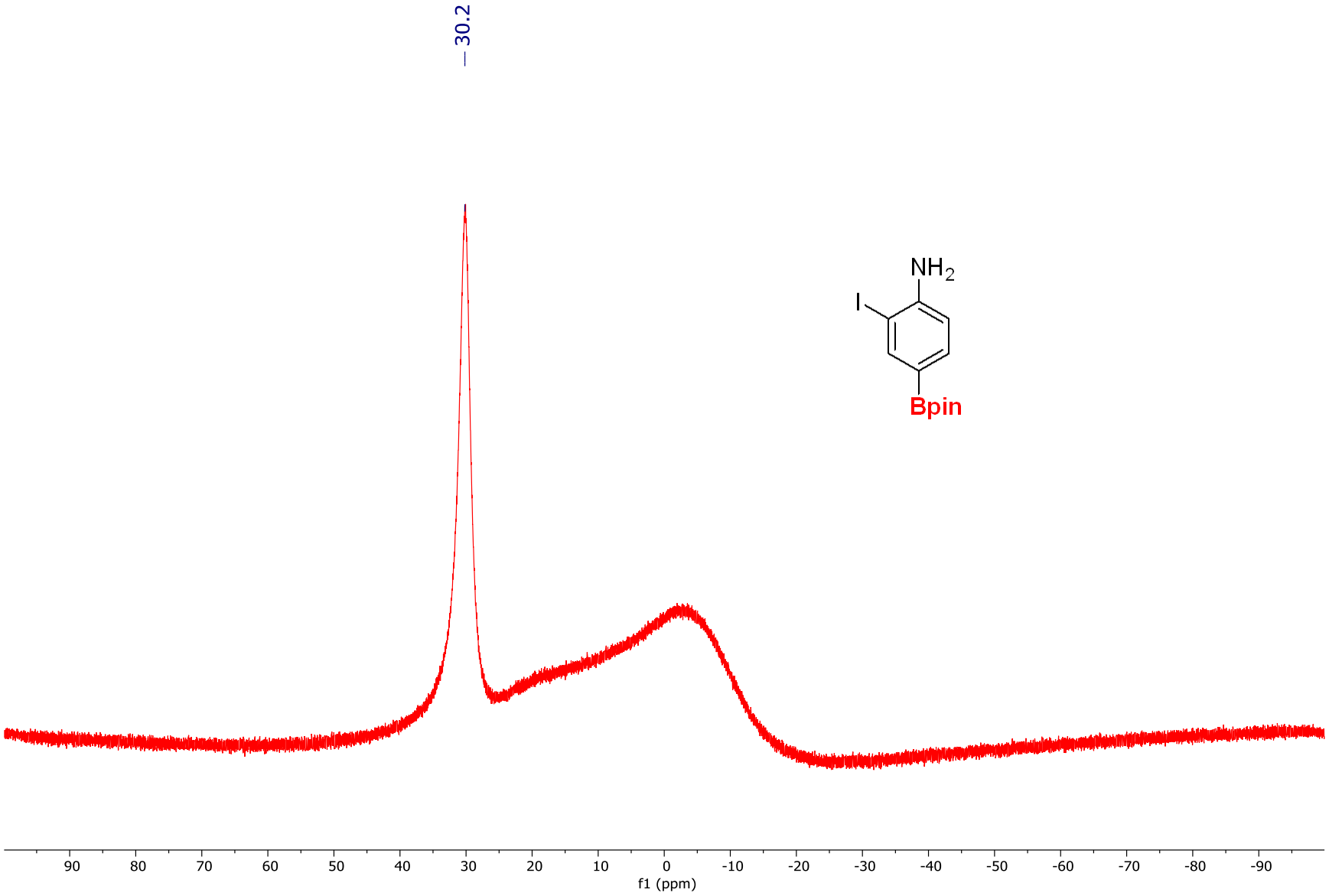
^{1}H NMR of *para* borylated 2-iodoaniline (4.2c) ($CDCl_3$, 500 MHz)



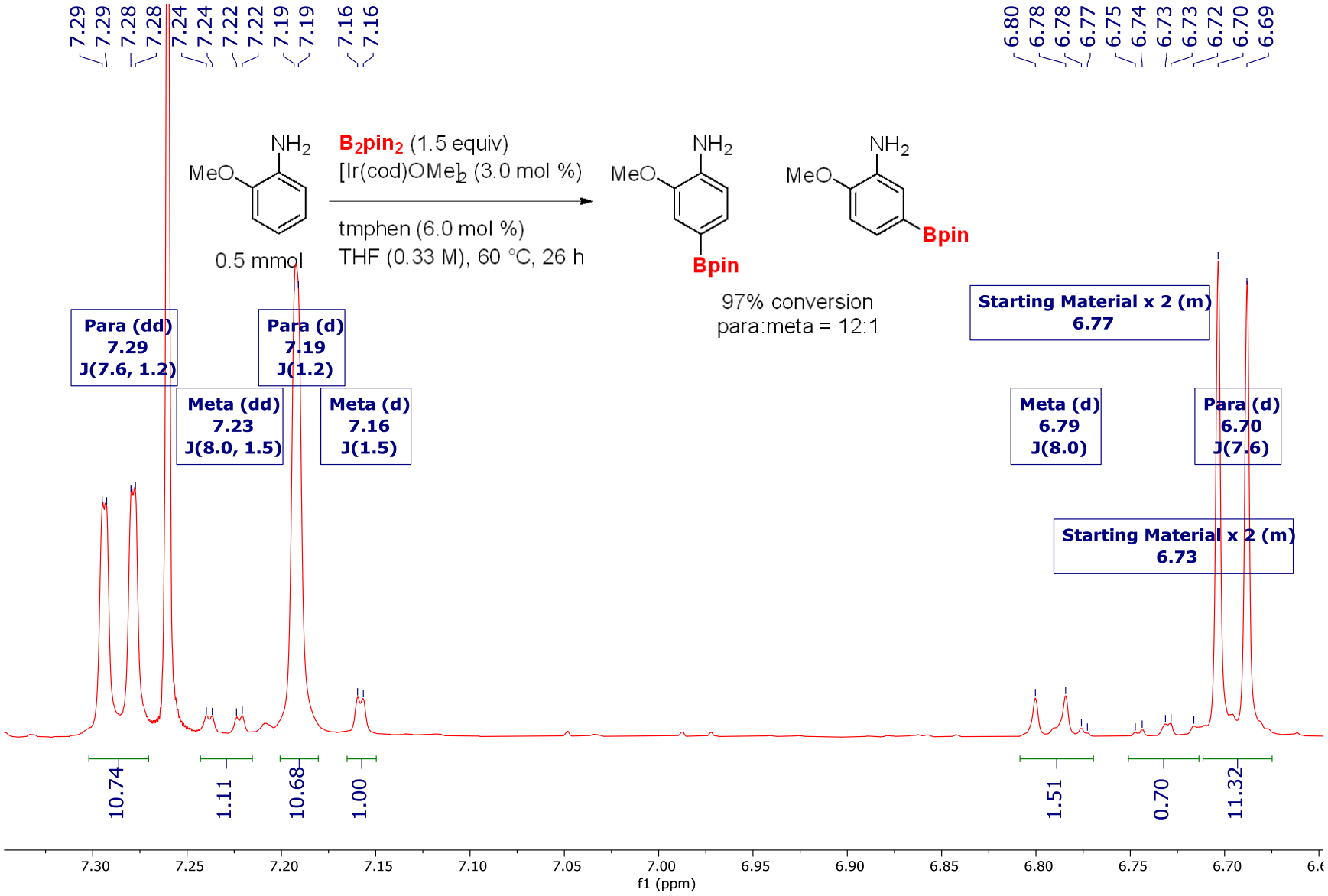
^{13}C NMR of *para* borylated 2-iodoaniline (4.2c) ($CDCl_3$, 126 MHz)



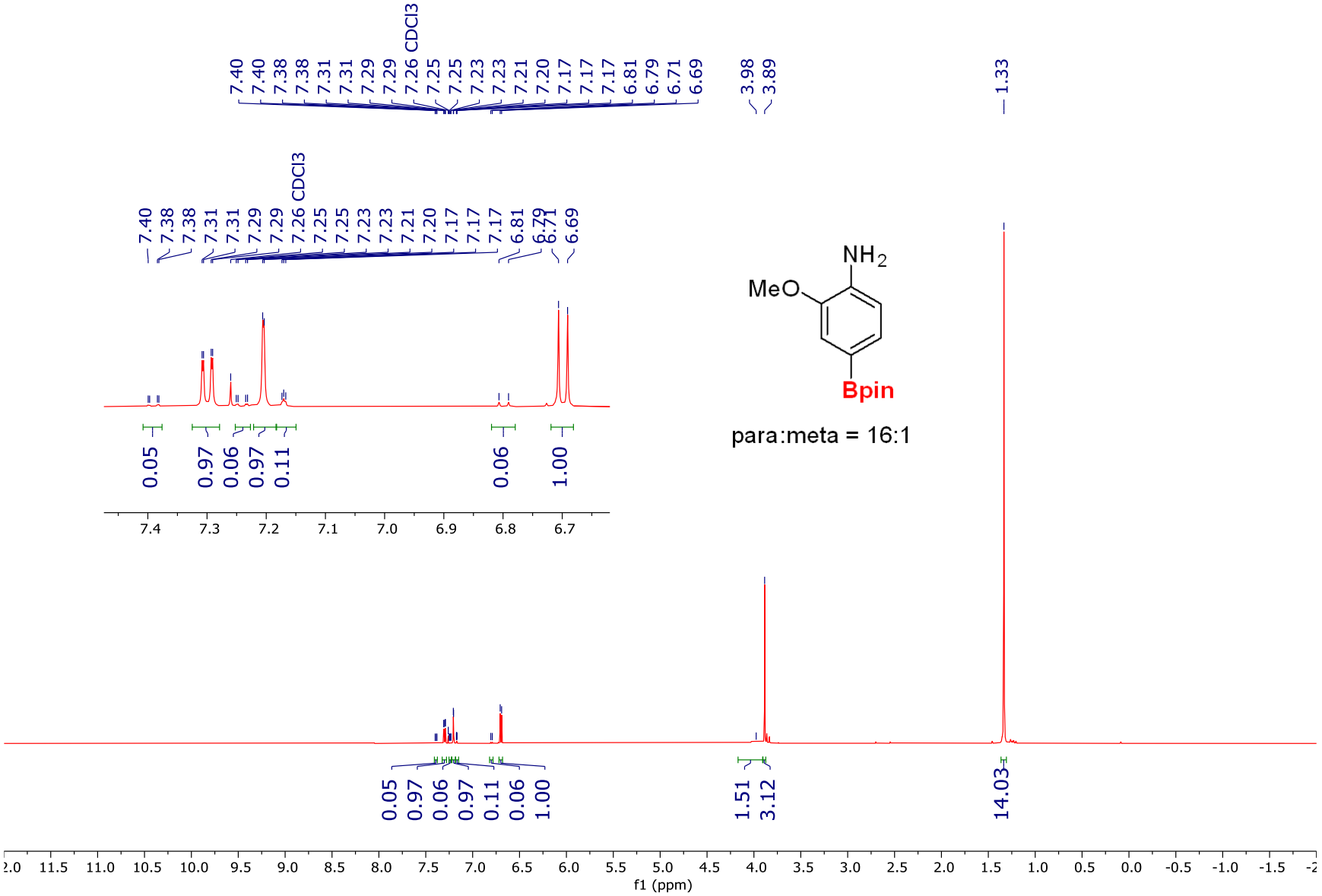
^{11}B NMR of *para* borylated 2-iodoaniline (4.2c) ($CDCl_3$, 160 MHz)



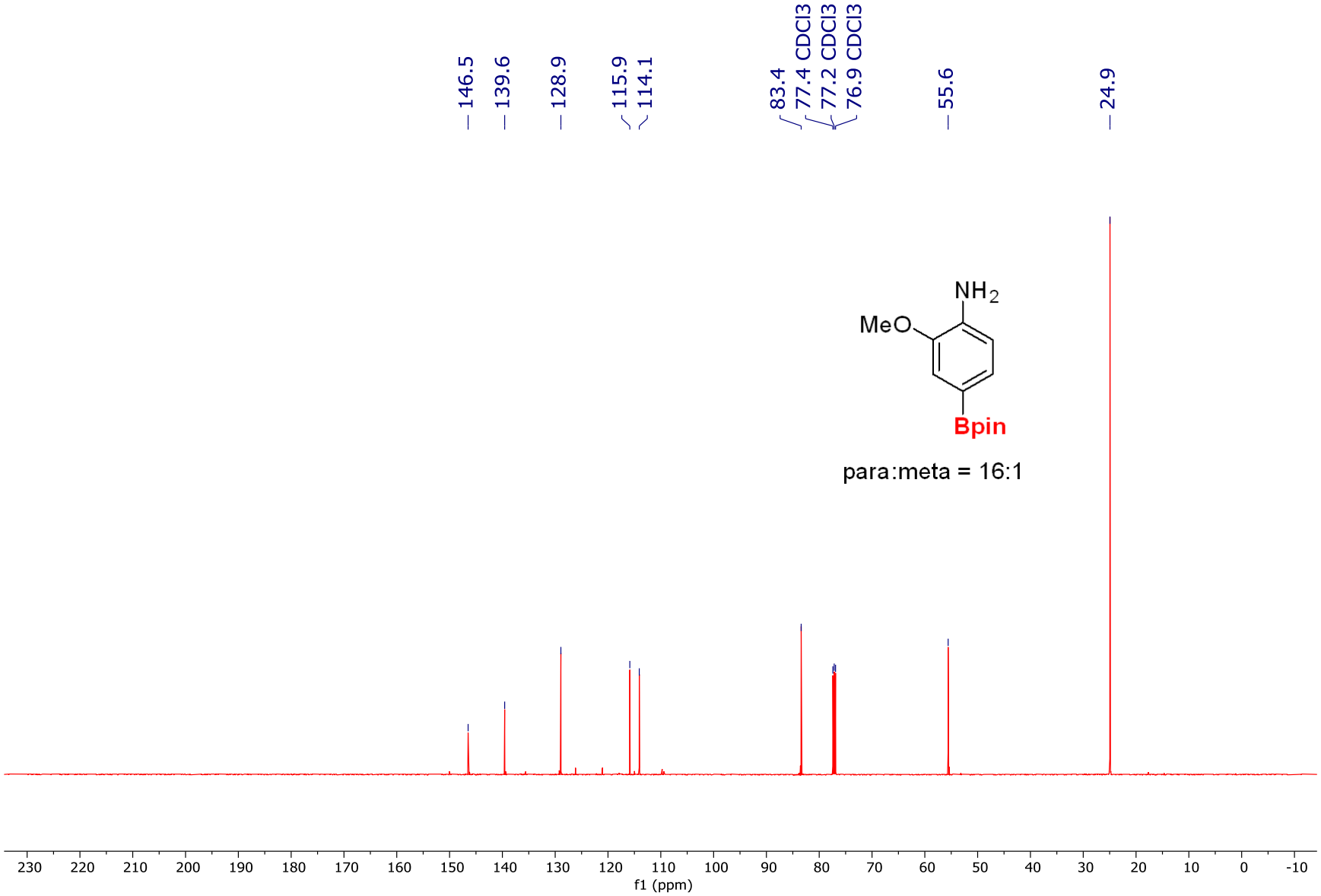
***Para* CHB of 2-methoxyaniline (4.2d) ($CDCl_3$, 500 MHz)**



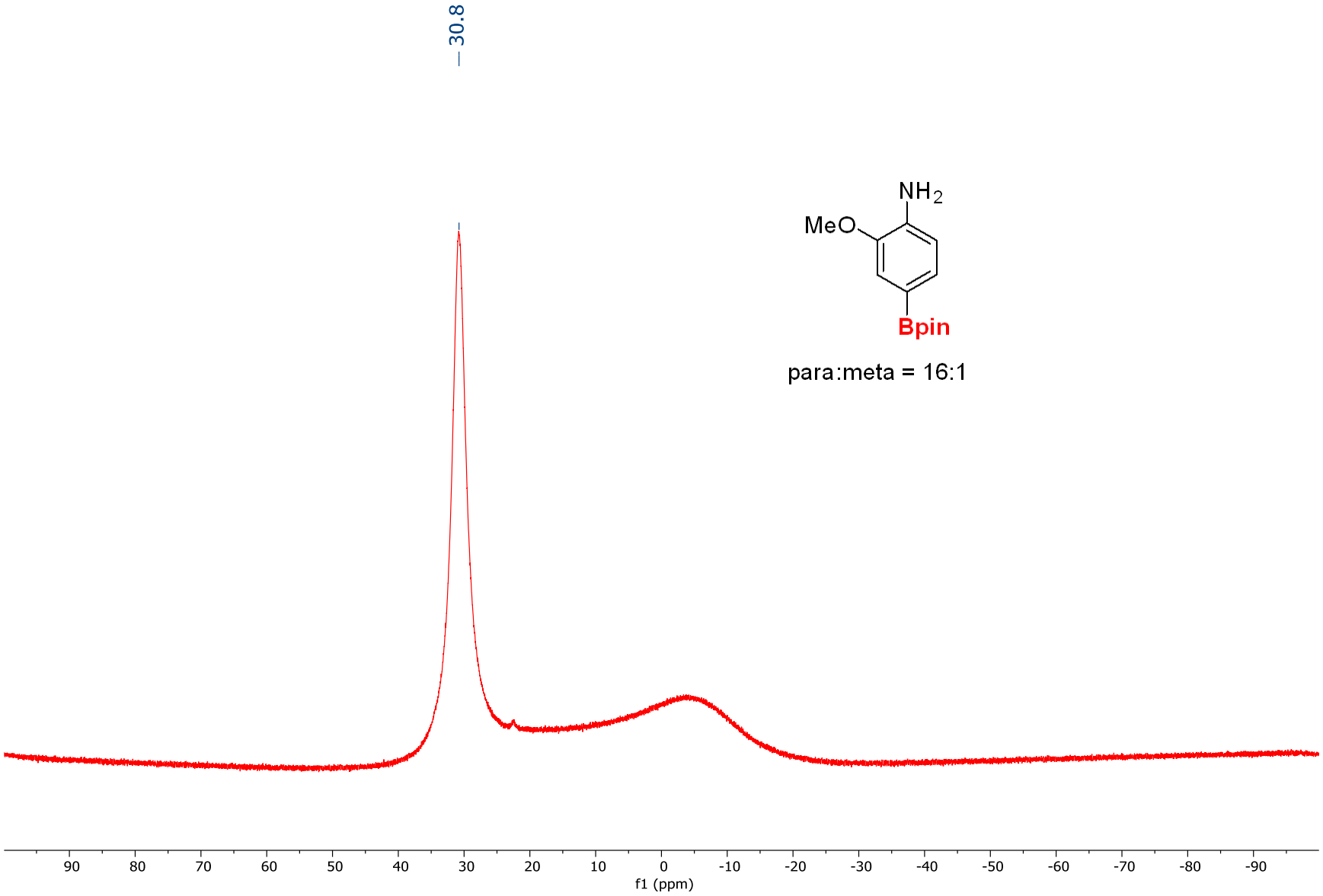
^{1}H NMR of *para* borylated 2-methoxyaniline (4.2d) ($CDCl_3$, 500 MHz)



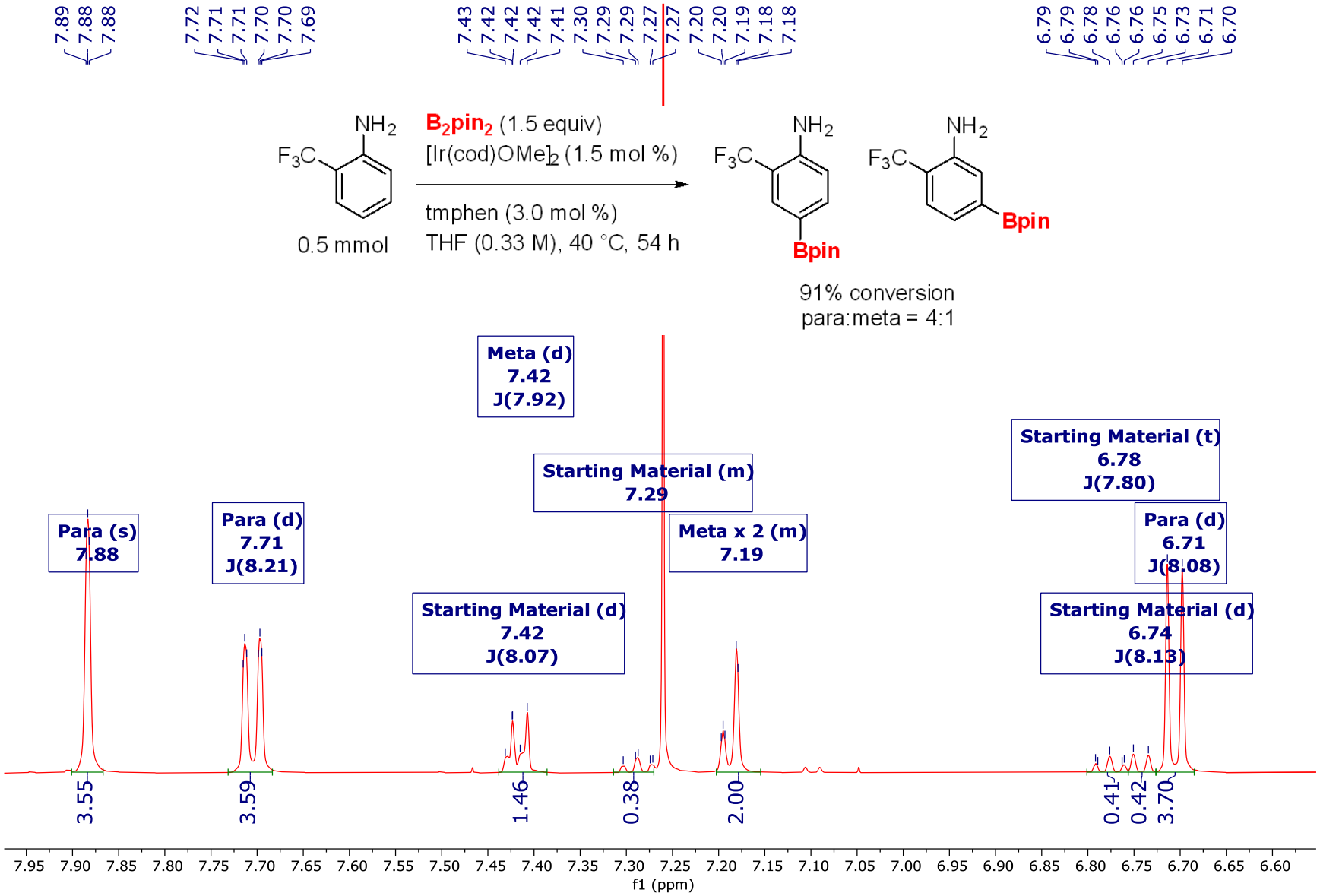
^{13}C NMR of *para* borylated 2-methoxyaniline (4.2d) ($CDCl_3$, 126 MHz)



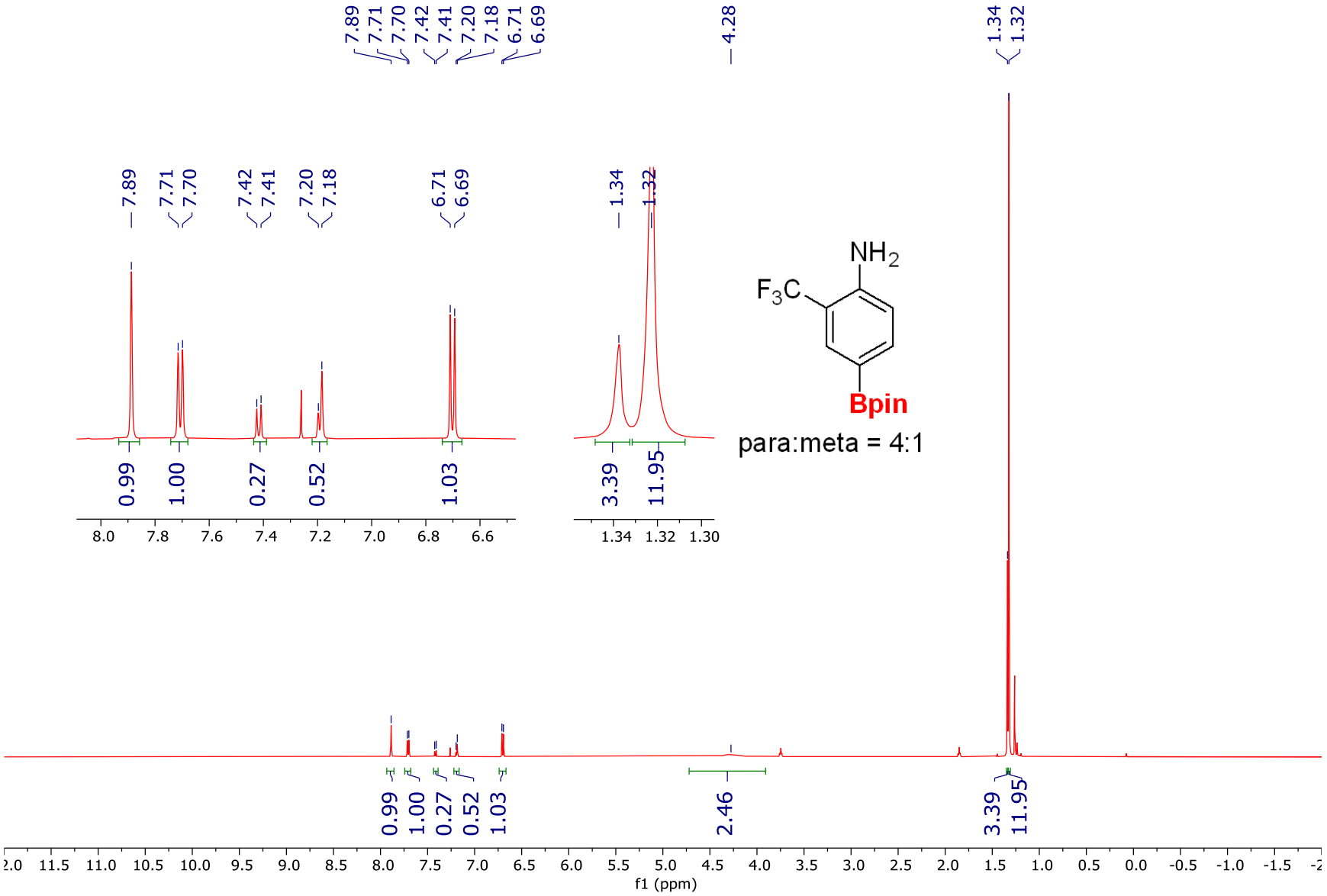
^{11}B NMR of *para* borylated 2-methoxyaniline (4.2d) ($CDCl_3$, 160 MHz)



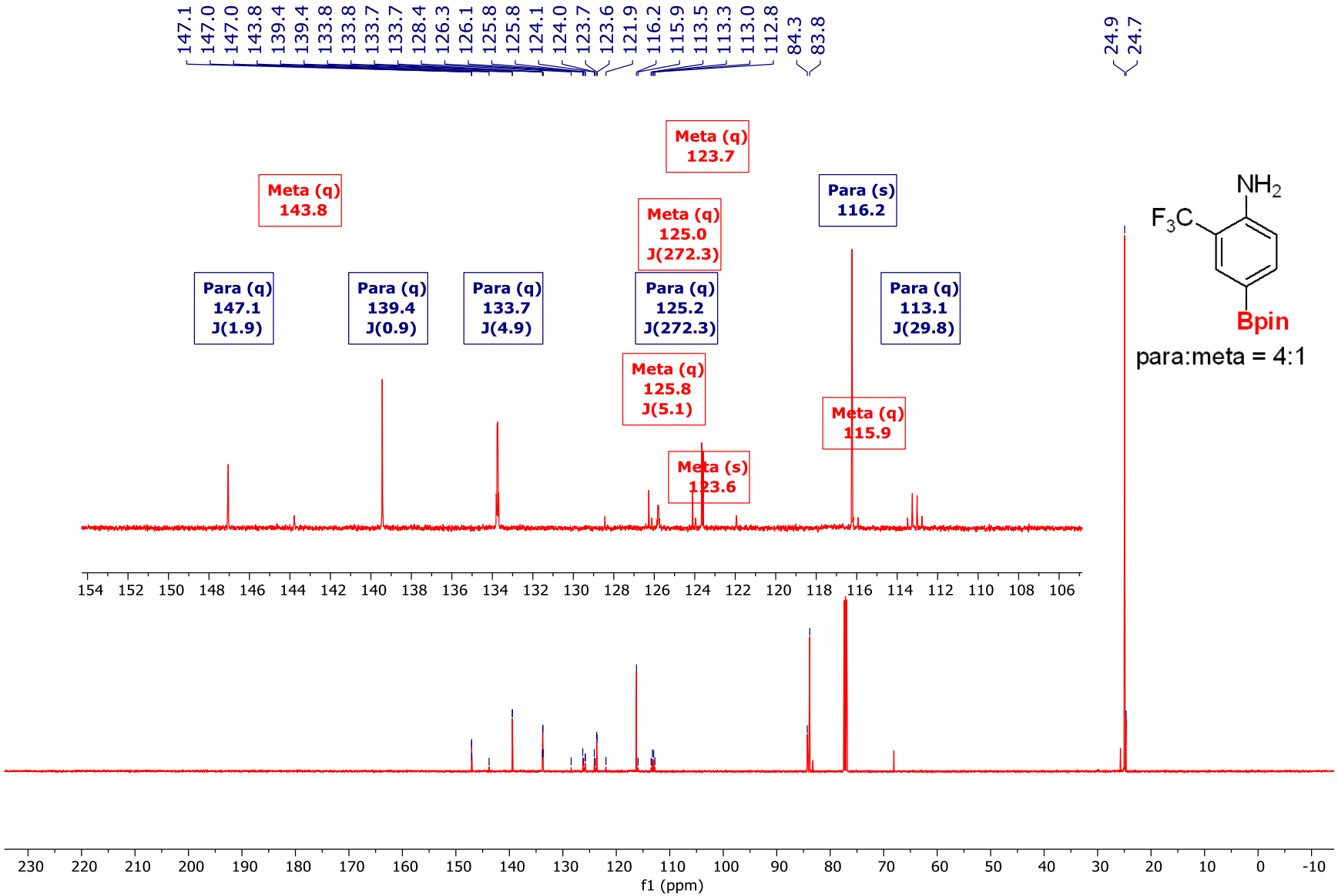
***Para* CHB of 2-trifluoromethylaniline (4.2e) ($CDCl_3$, 500 MHz)**



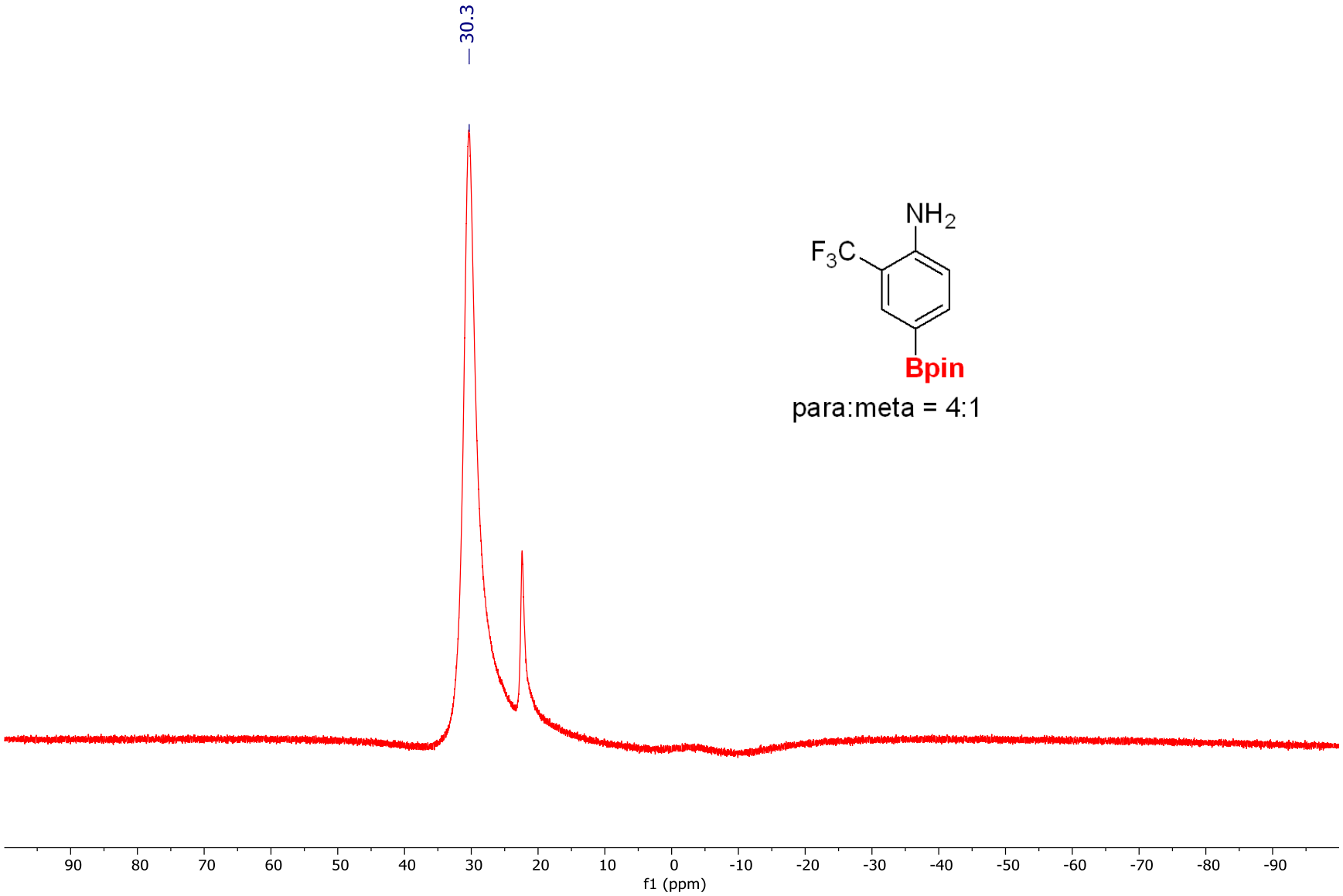
^{1}H NMR of *para* borylated 2-trifluoromethylaniline (4.2e) ($CDCl_3$, 500 MHz)



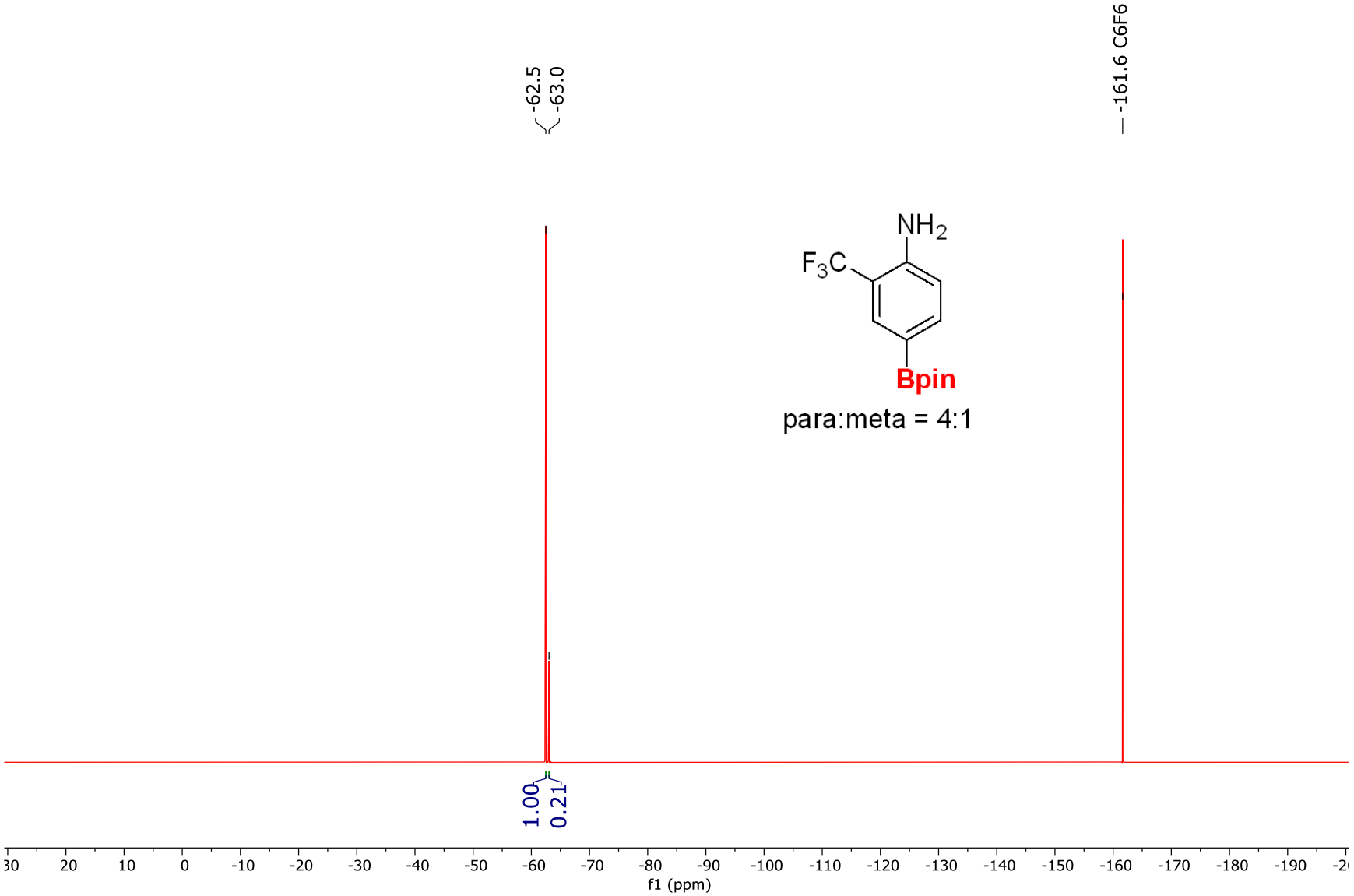
^{13}C NMR of *para* borylated 2-trifluoromethylaniline (4.2e) ($CDCl_3$, 126 MHz)



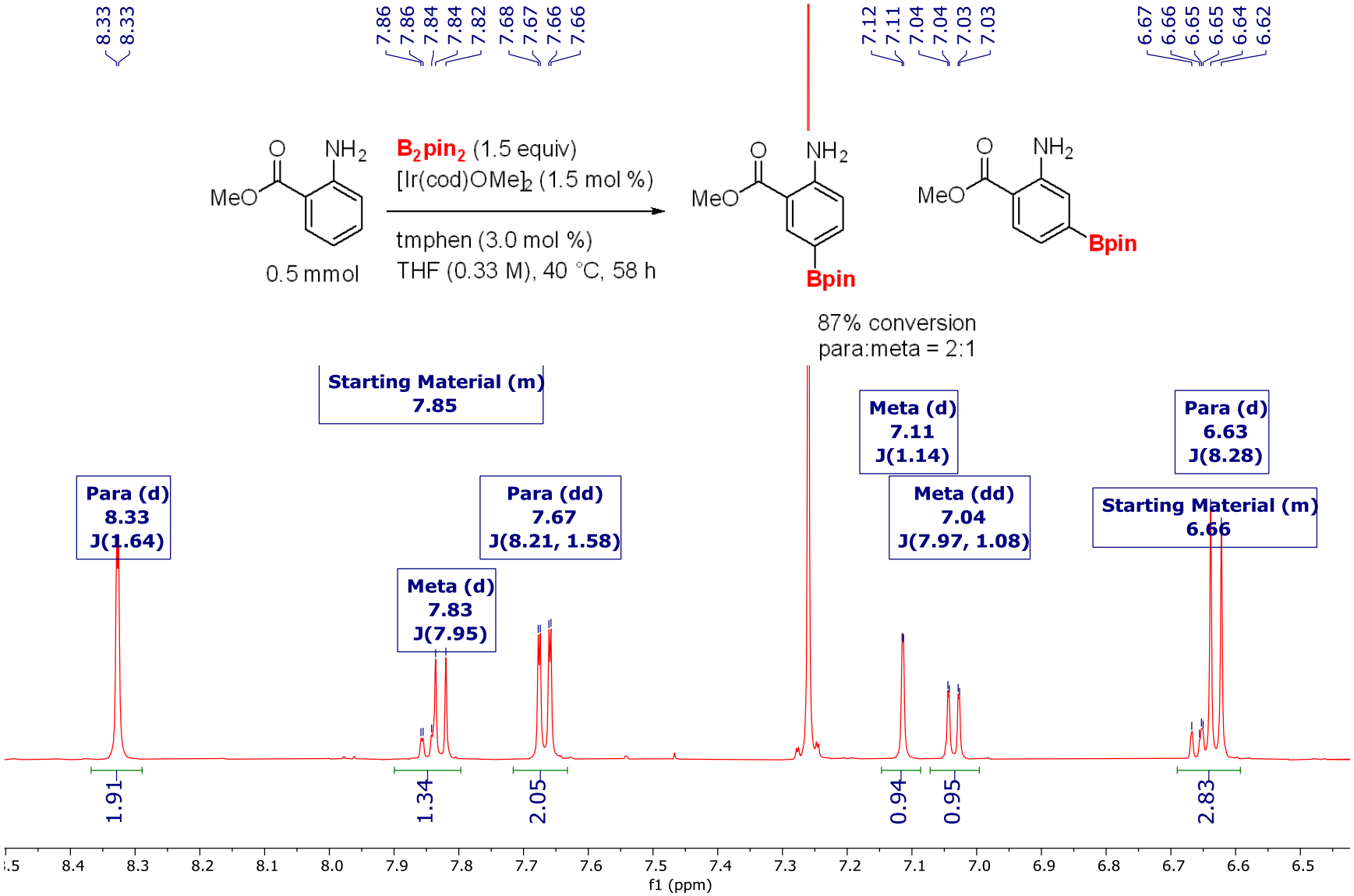
^{11}B NMR of *para* borylated 2-trifluoromethylaniline (4.2e) ($CDCl_3$, 160 MHz)



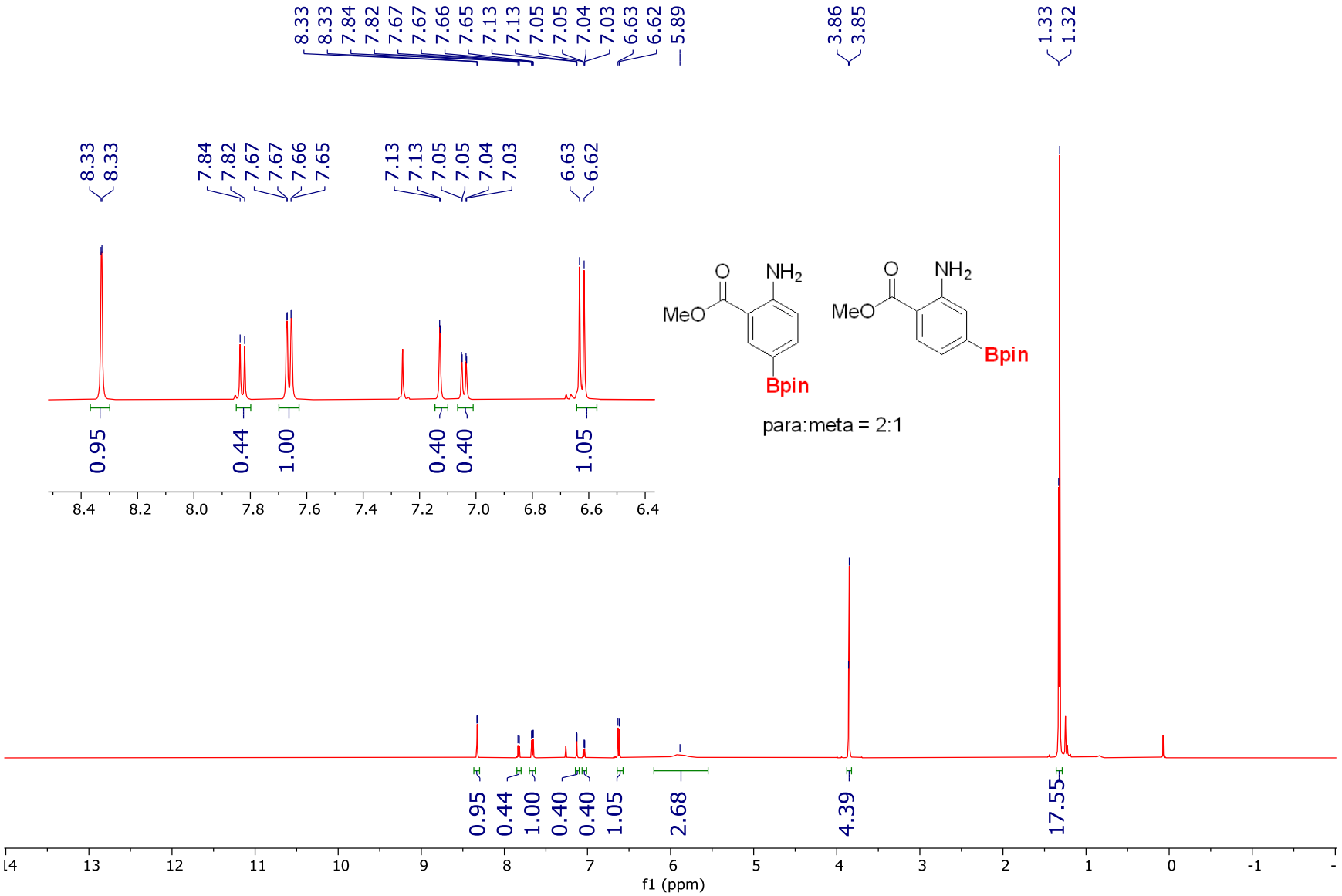
^{19}F NMR of *para* borylated 2-trifluoromethylaniline (4.2e) ($CDCl_3$, 470 MHz)



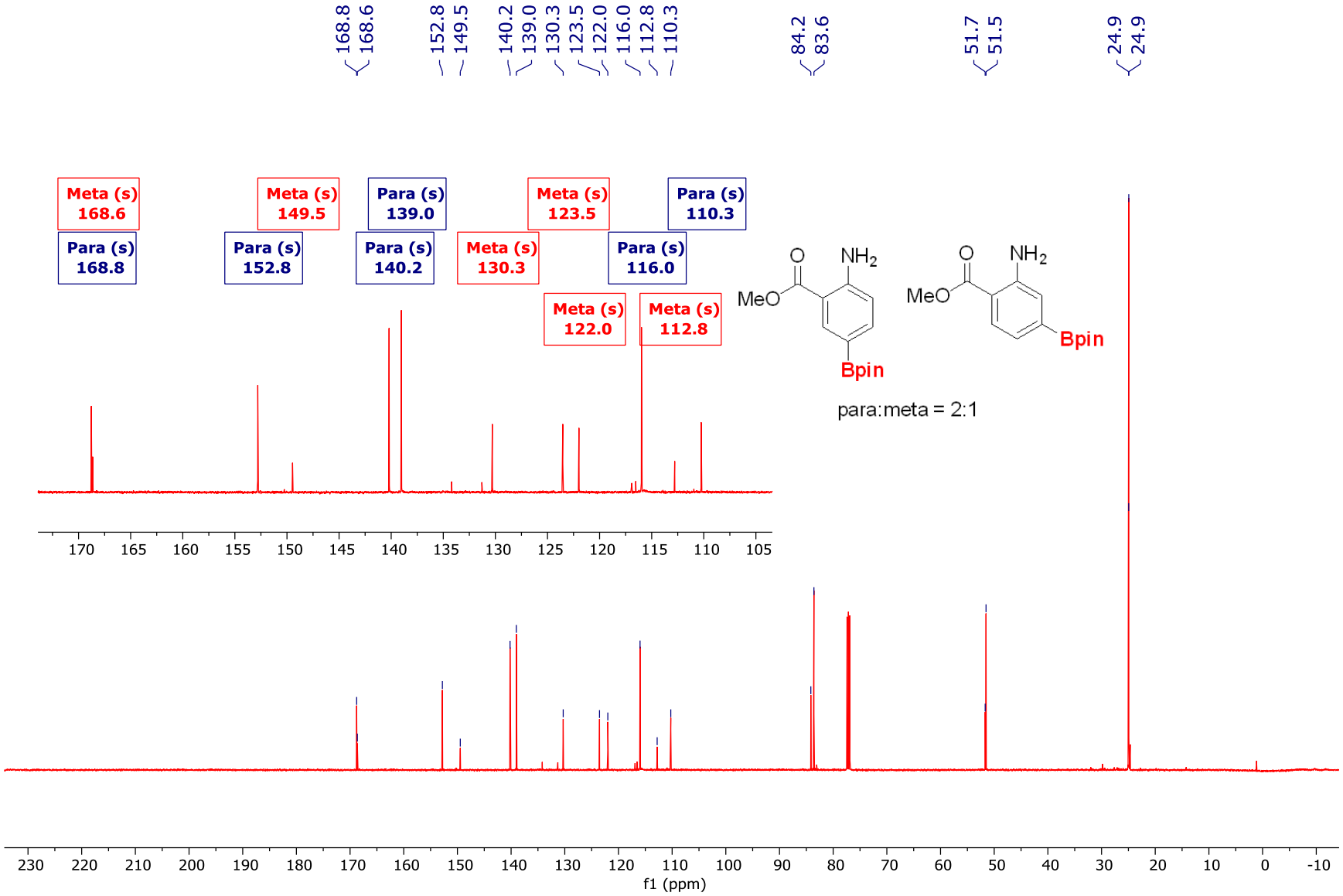
***Para* CHB of methyl 2-aminobenzoate (4.2f) ($CDCl_3$, 500 MHz)**



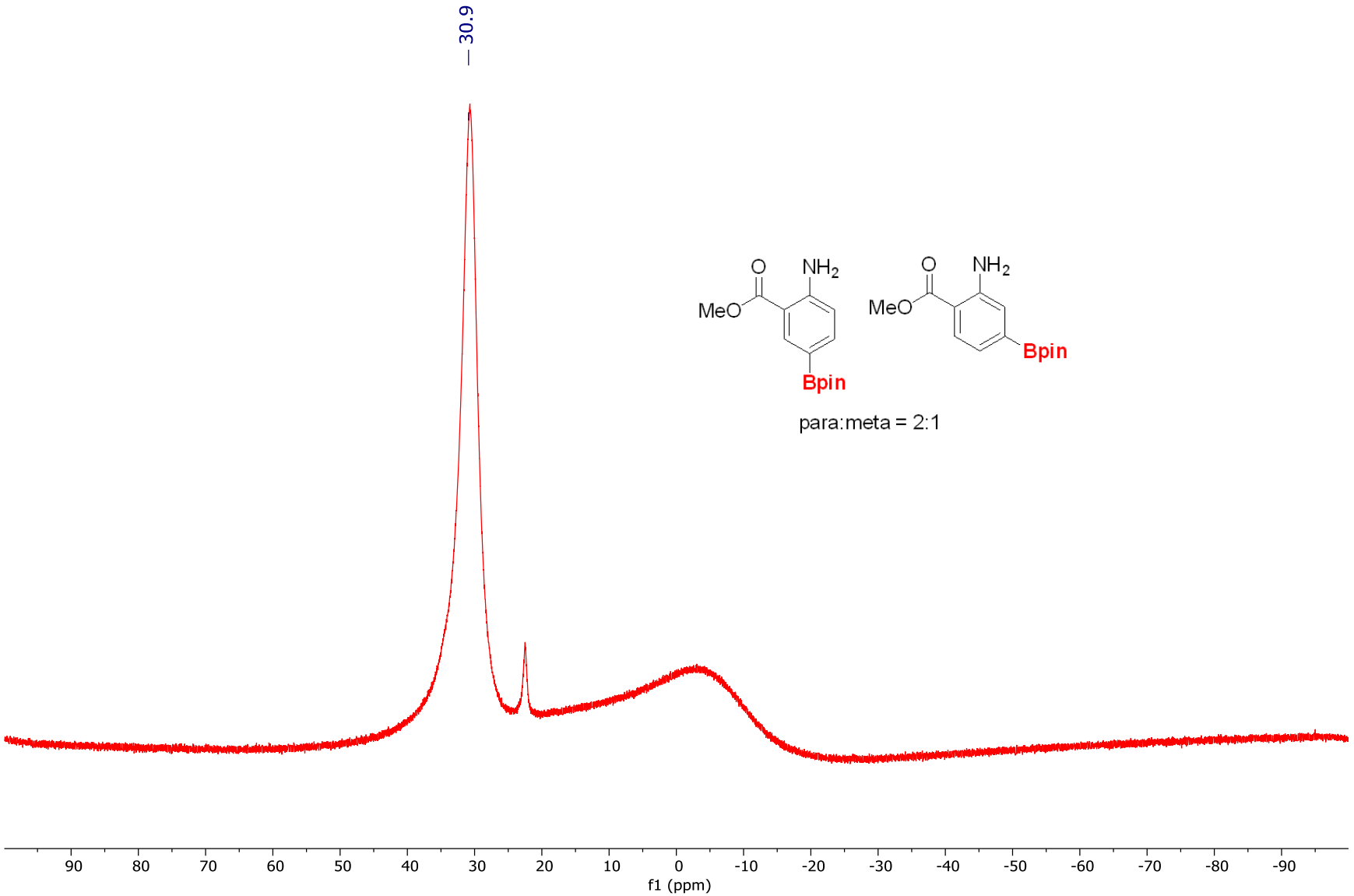
^{1}H NMR of *para* borylated methyl 2-aminobenzoate (4.2f) ($CDCl_3$, 500 MHz)



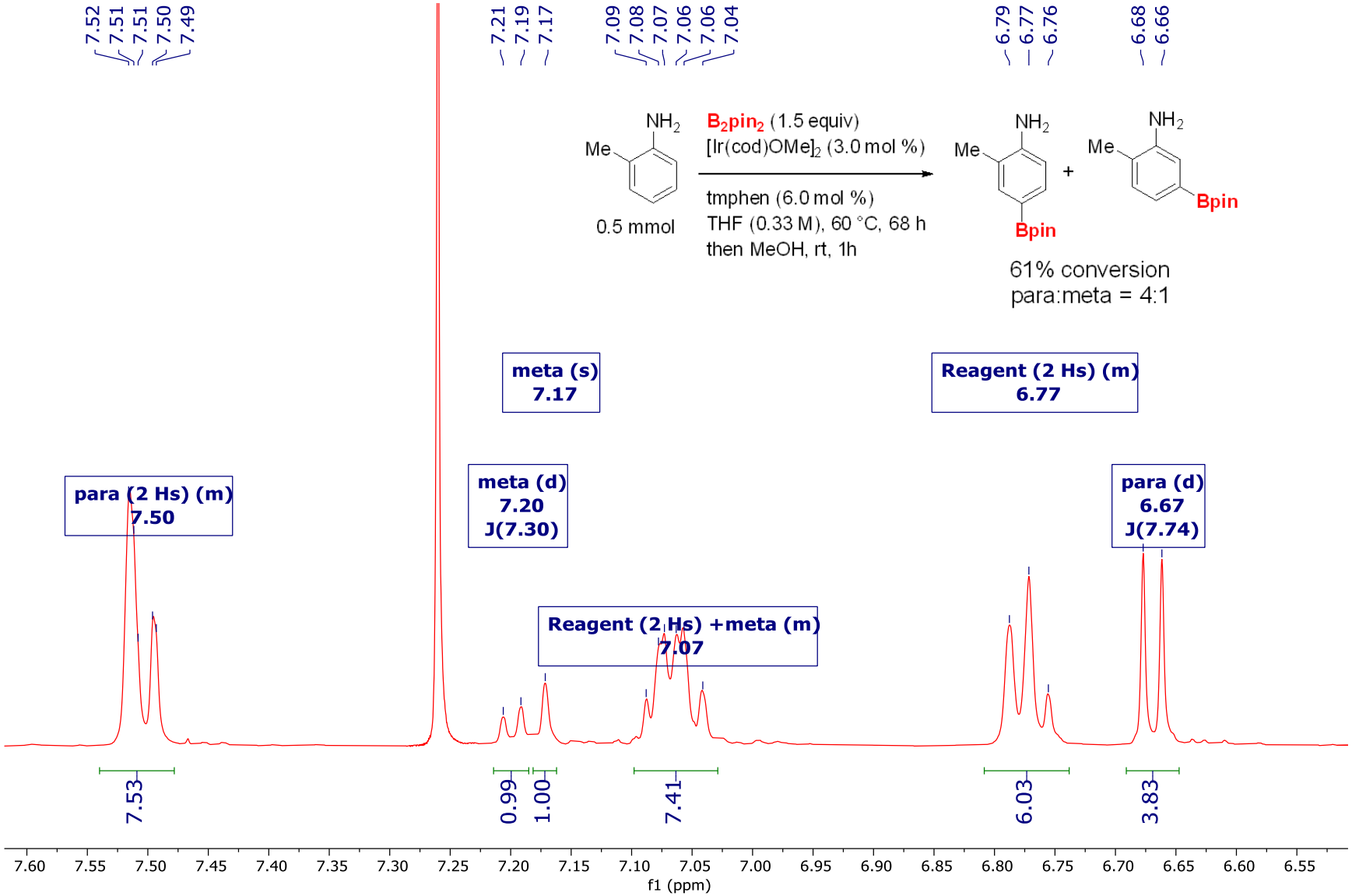
^{13}C NMR of *para* borylated methyl 2-aminobenzoate (4.2f) ($CDCl_3$, 126 MHz)



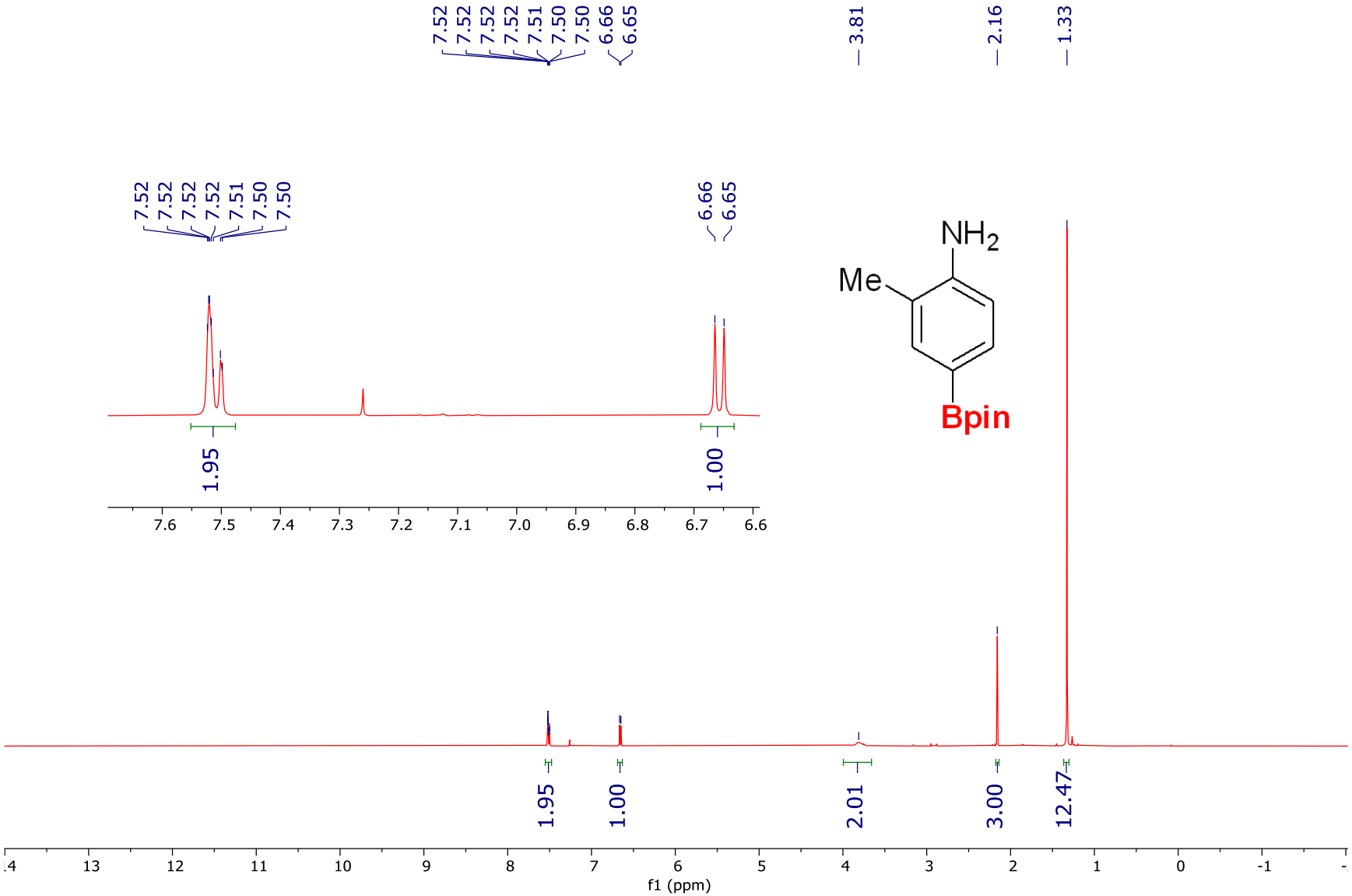
^{11}B NMR of *para* borylated methyl 2-aminobenzoate (4.2f) ($CDCl_3$, 160 MHz)



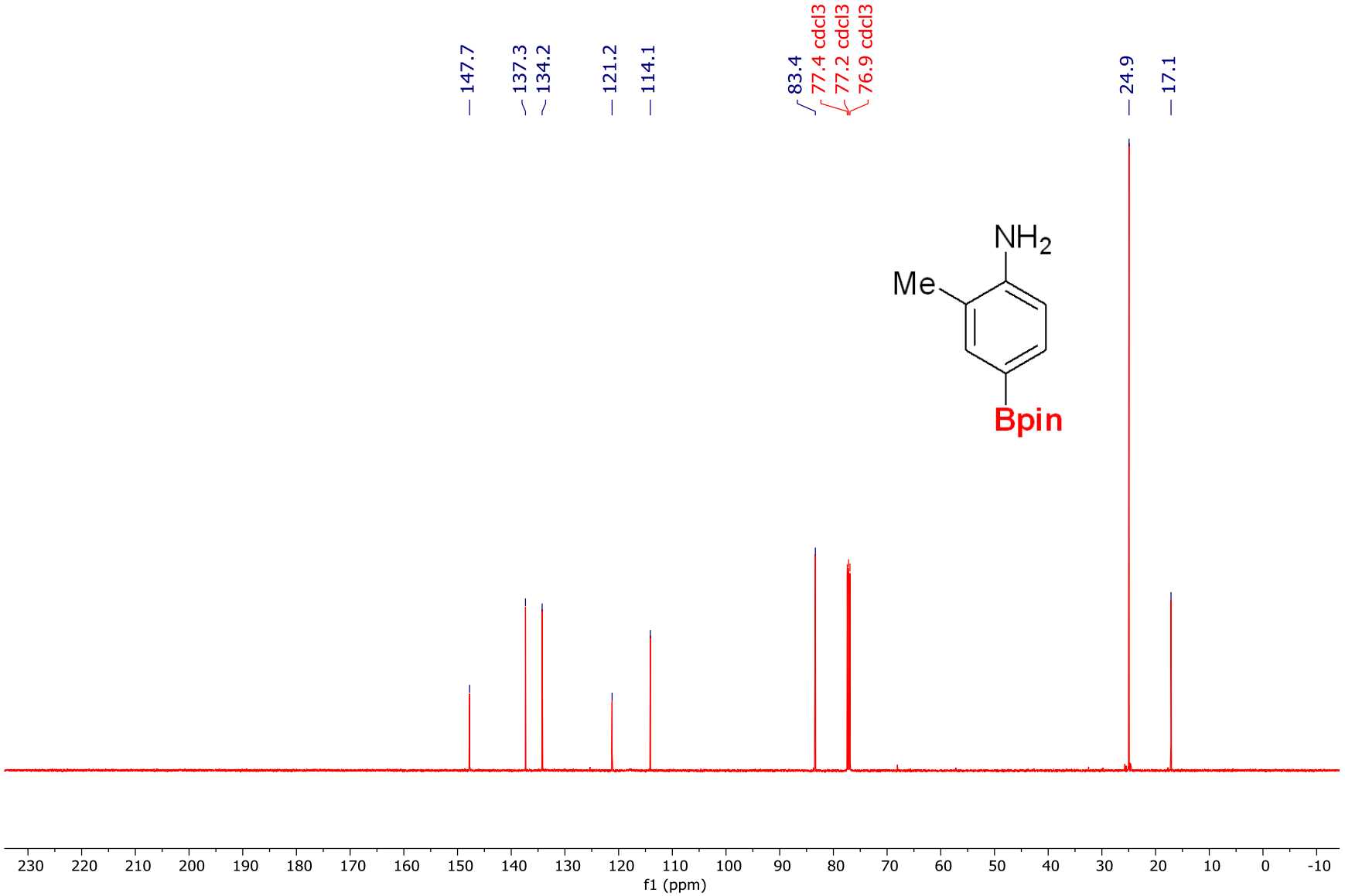
***Para* CHB of 2-methylaniline (4.2g) ($CDCl_3$, 500 MHz)**



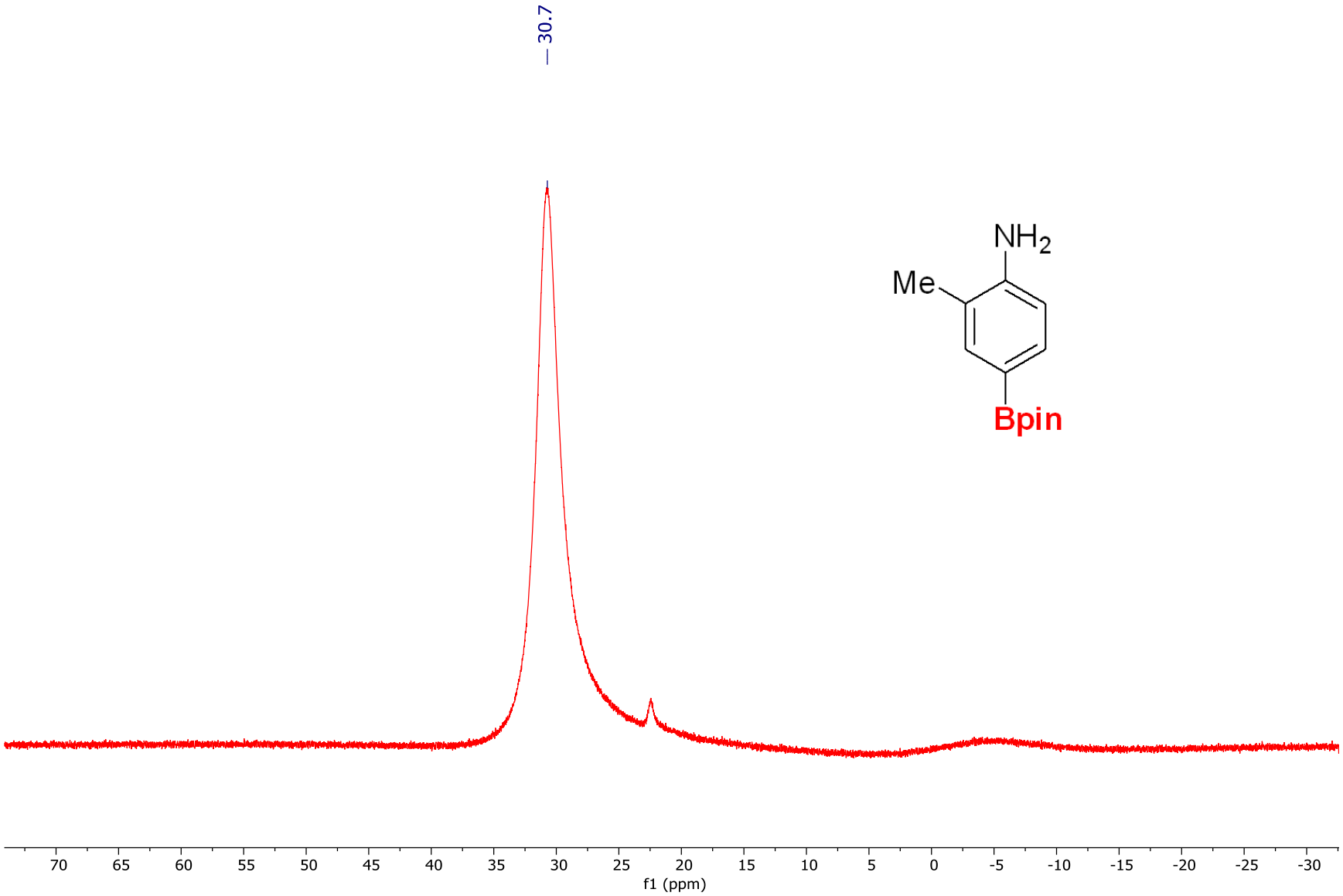
^{1}H NMR of *para* borylated 2-methylaniline (4.2g) ($CDCl_3$, 500 MHz)



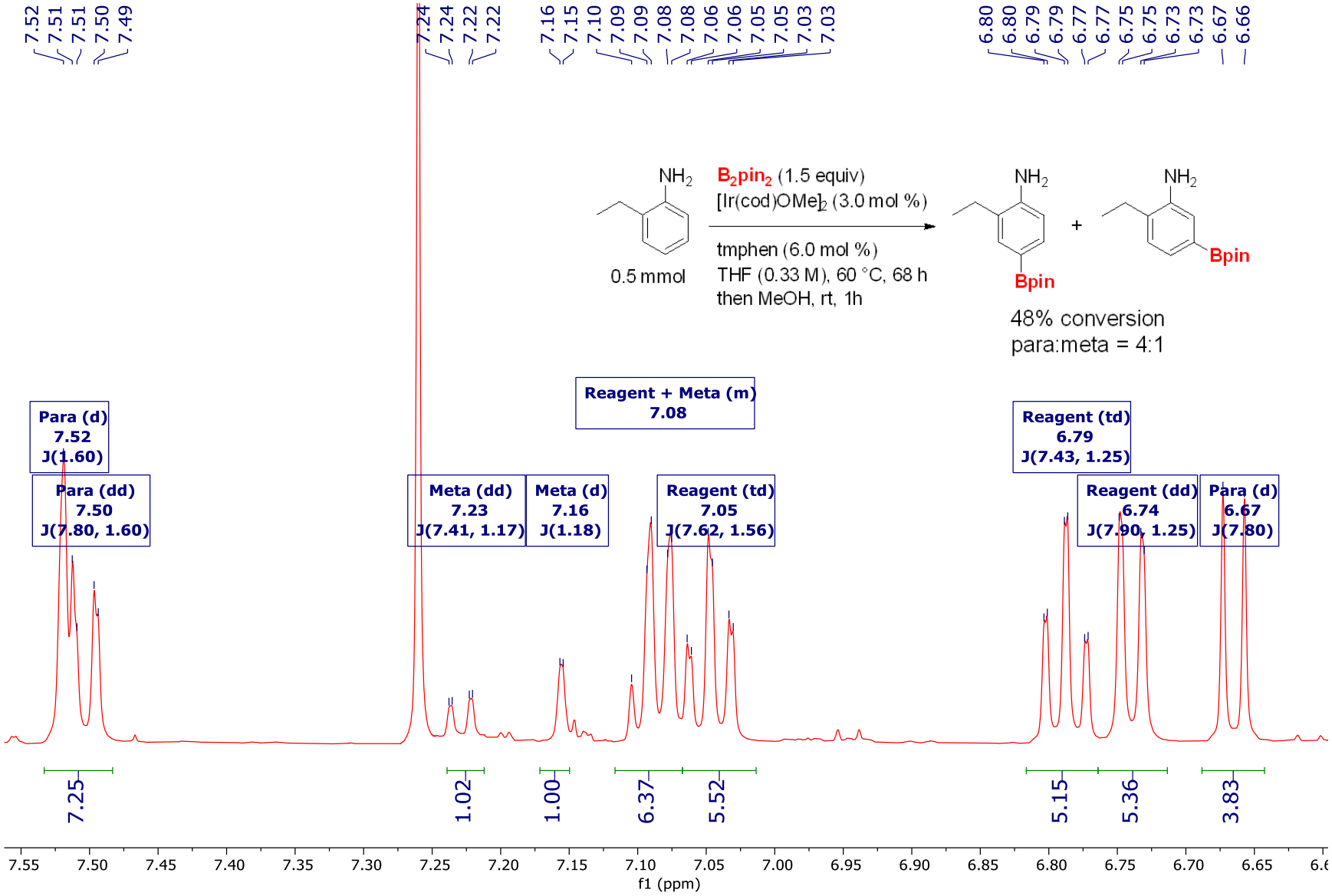
^{13}C NMR of *para* borylated 2-methylaniline (4.2g) (126 MHz, $CDCl_3$)



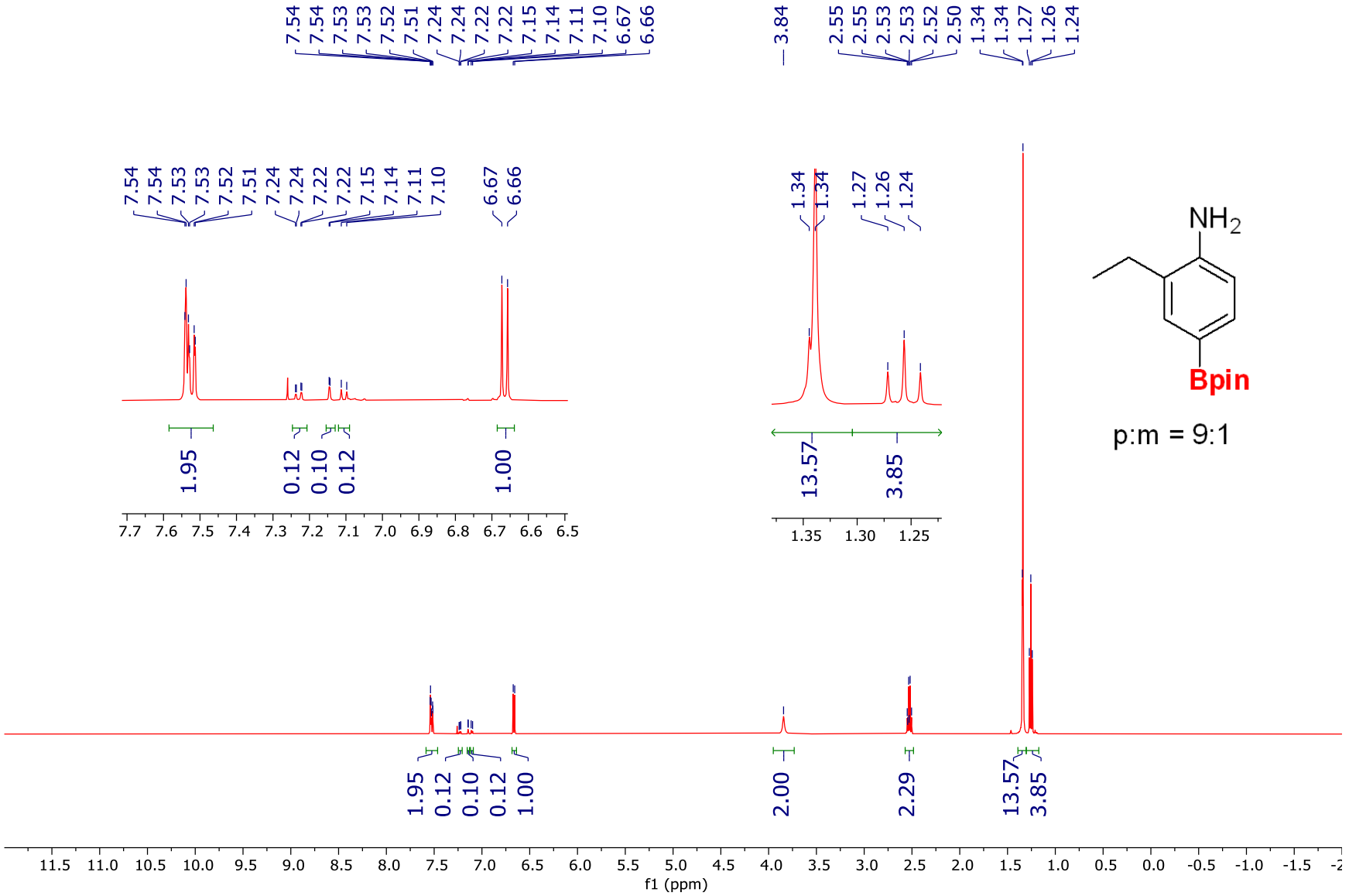
^{11}B NMR of *para* borylated 2-methylaniline (4.2g) (160 MHz, $CDCl_3$)



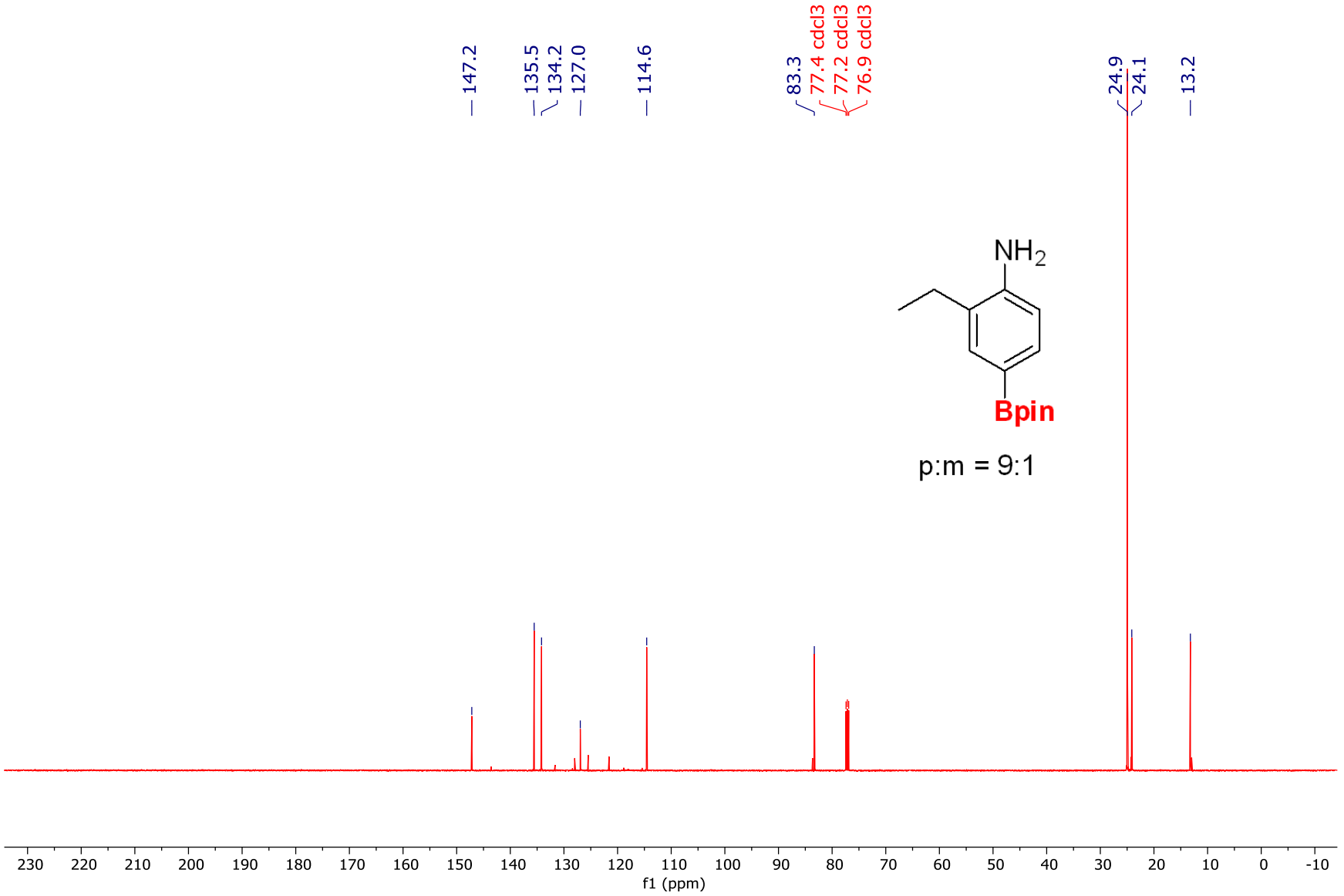
***Para* CHB of 2-ethylaniline (4.2h) ($CDCl_3$, 500 MHz)**



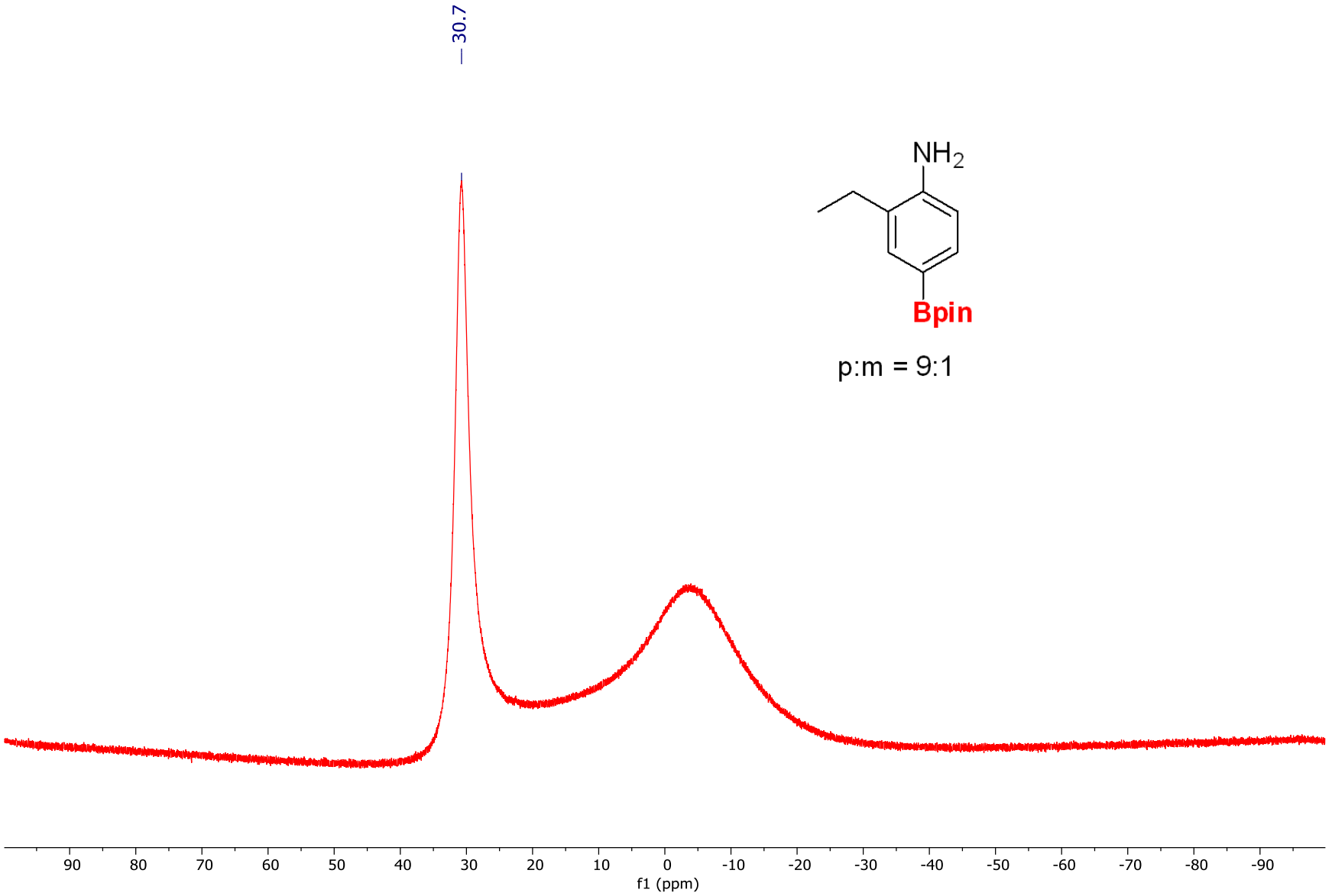
^{1}H NMR of *para* borylated 2-ethylaniline (4.2h) ($CDCl_3$, 500 MHz)



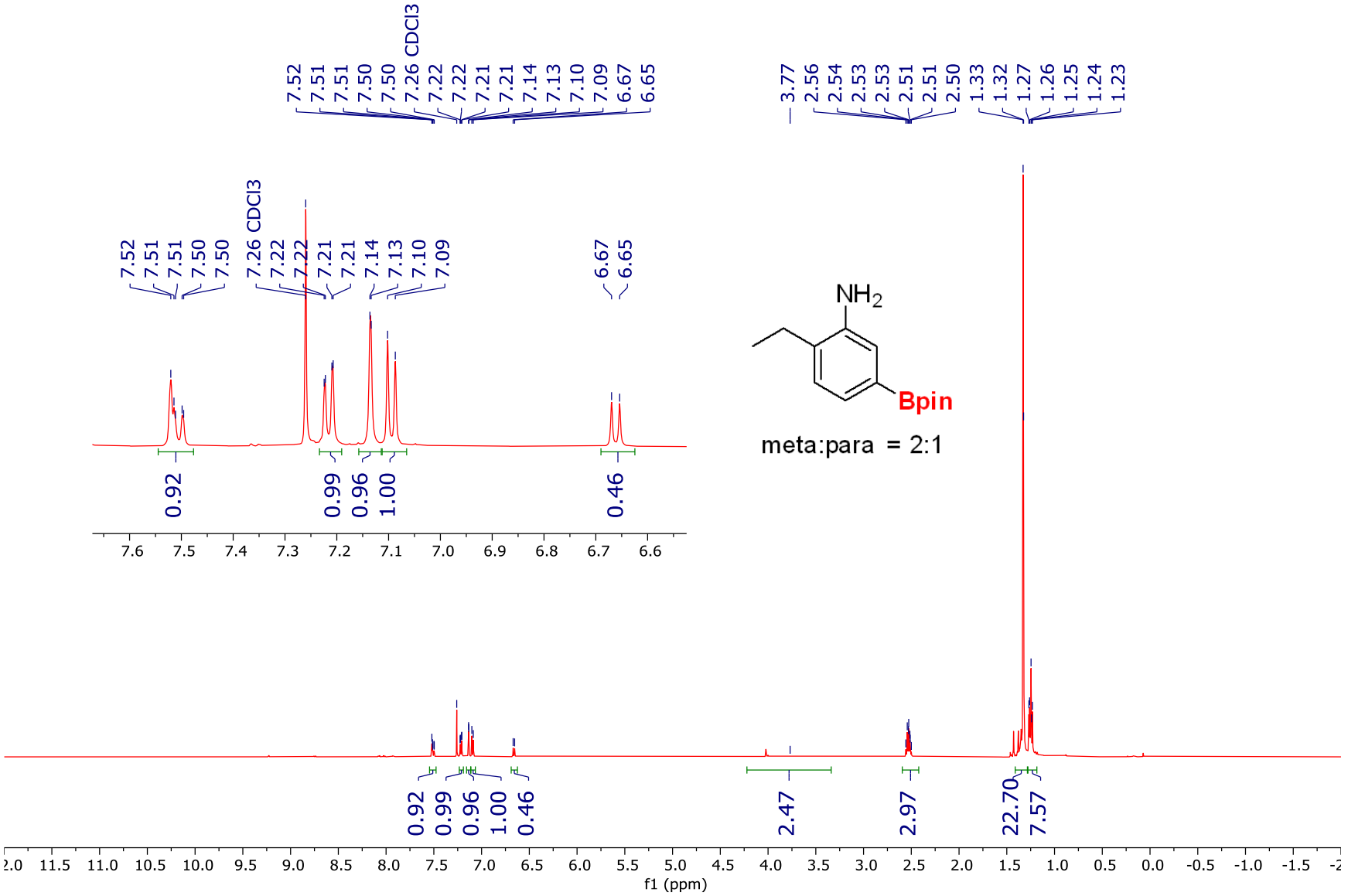
^{13}C NMR of *para* borylated 2-ethylaniline (4.2h) (126 MHz, $CDCl_3$)



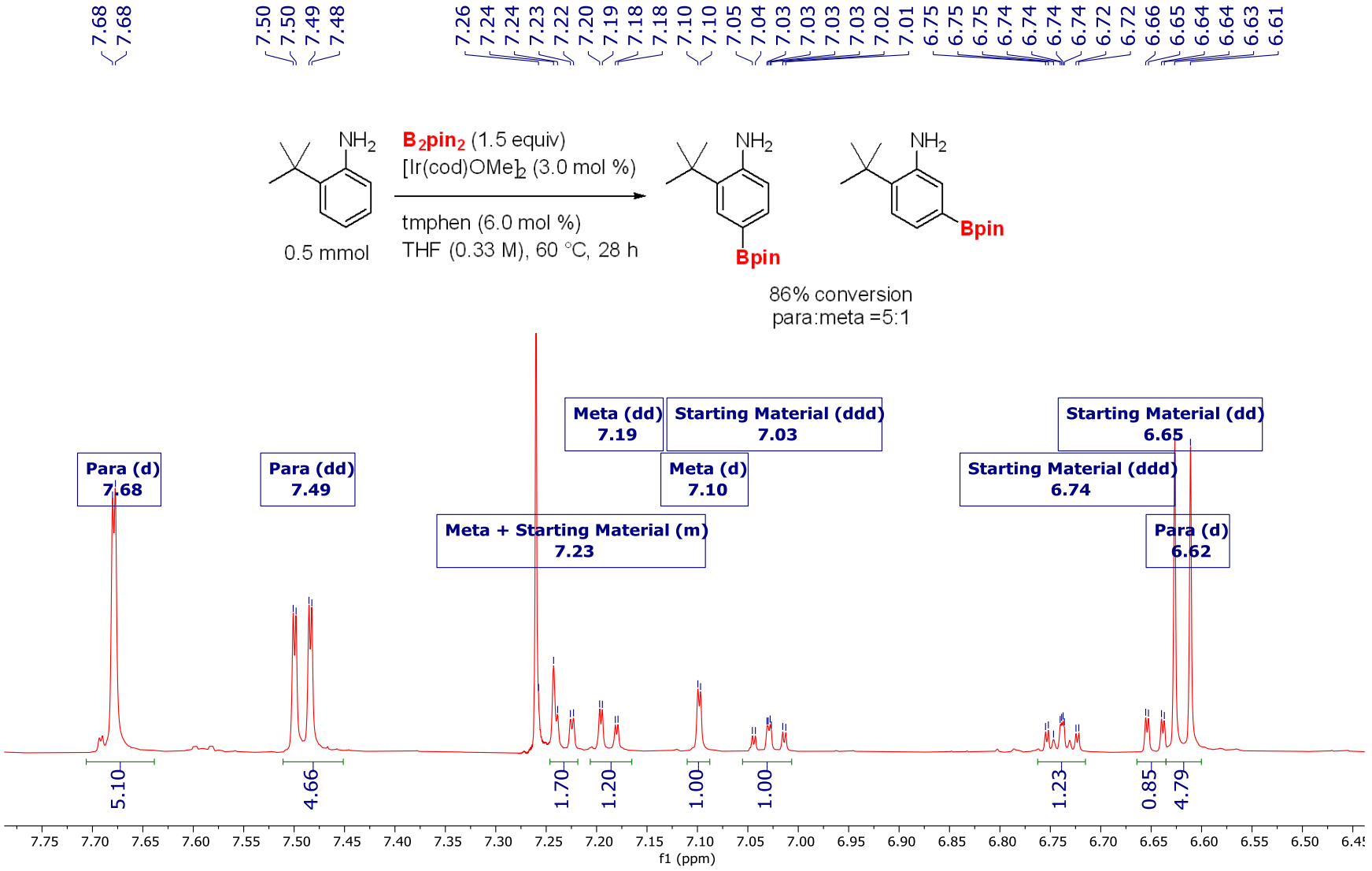
^{11}B NMR of *para* borylated 2-ethylaniline (4.2h) ($CDCl_3$, 160 MHz)



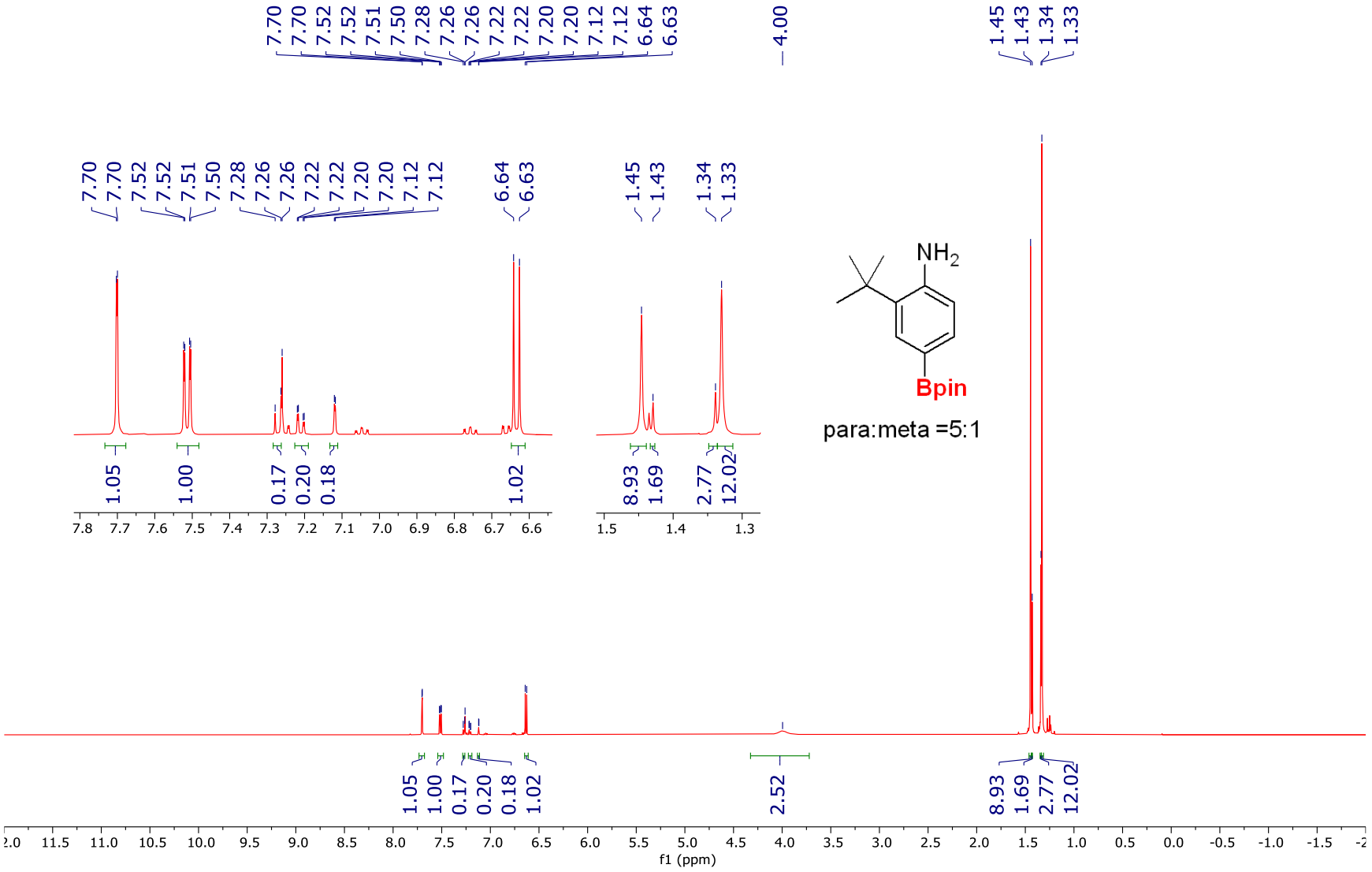
^{1}H NMR of meta borylated 2-ethylaniline (4.2h) ($CDCl_3$, 500 MHz)



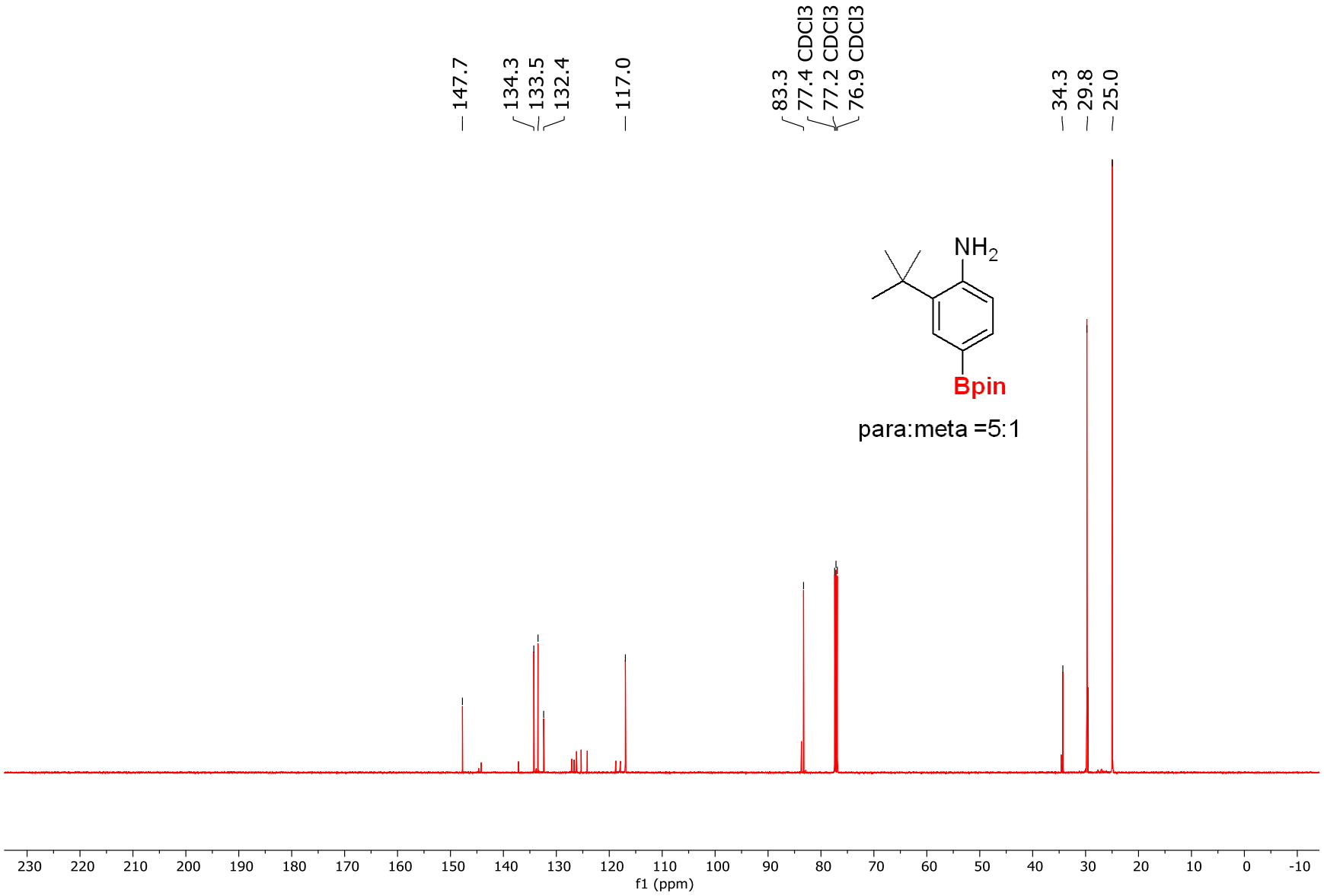
***Para* CHB of 2-tertbutylaniline (4.2i) ($CDCl_3$, 500 MHz)**



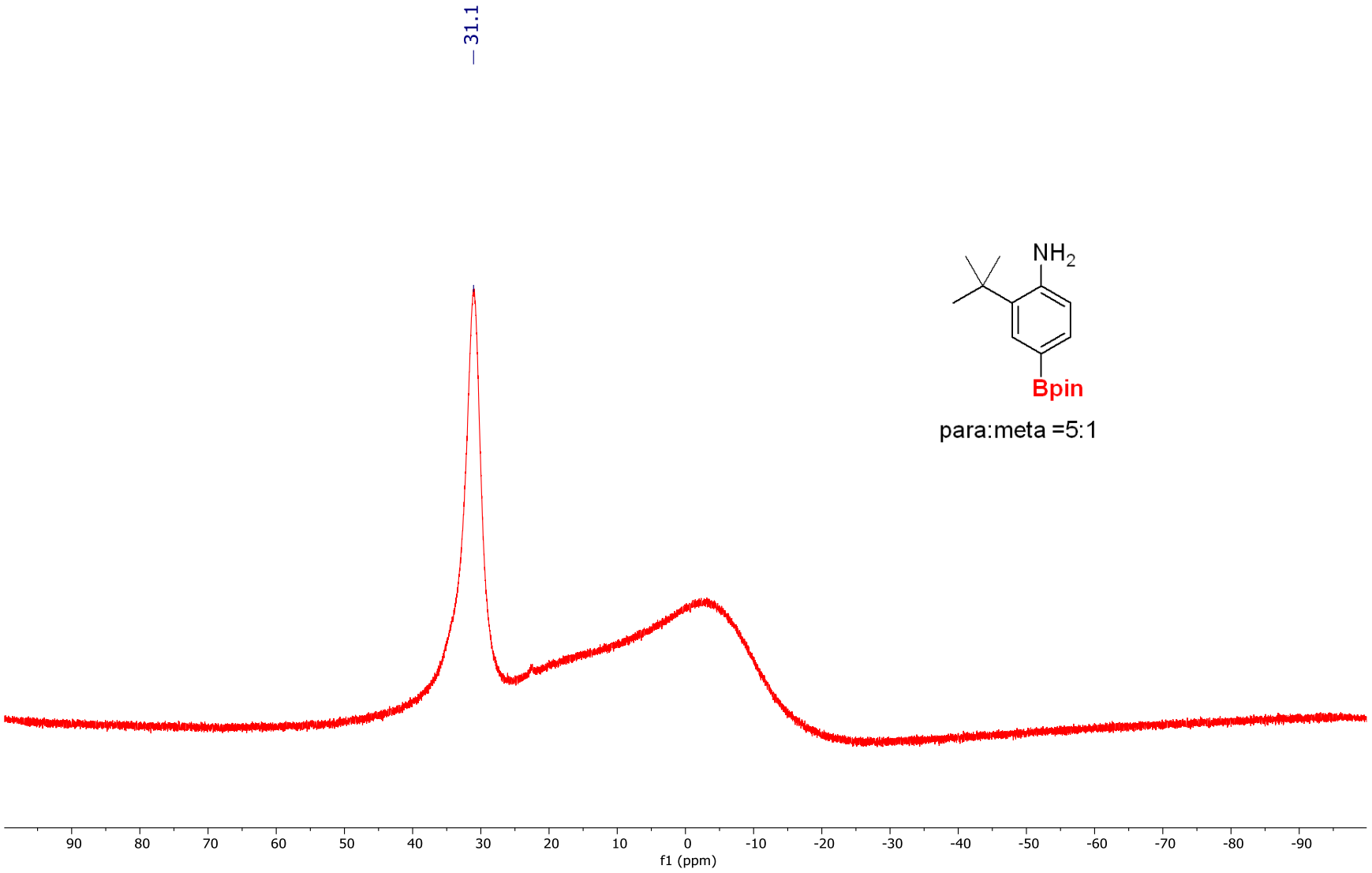
^{1}H NMR of *para* borylated 2-tertbutylaniline (4.2i) ($CDCl_3$, 500 MHz)



^{13}C NMR of *para* borylated 2-tertbutylaniline (4.2i) ($CDCl_3$, 500 MHz)

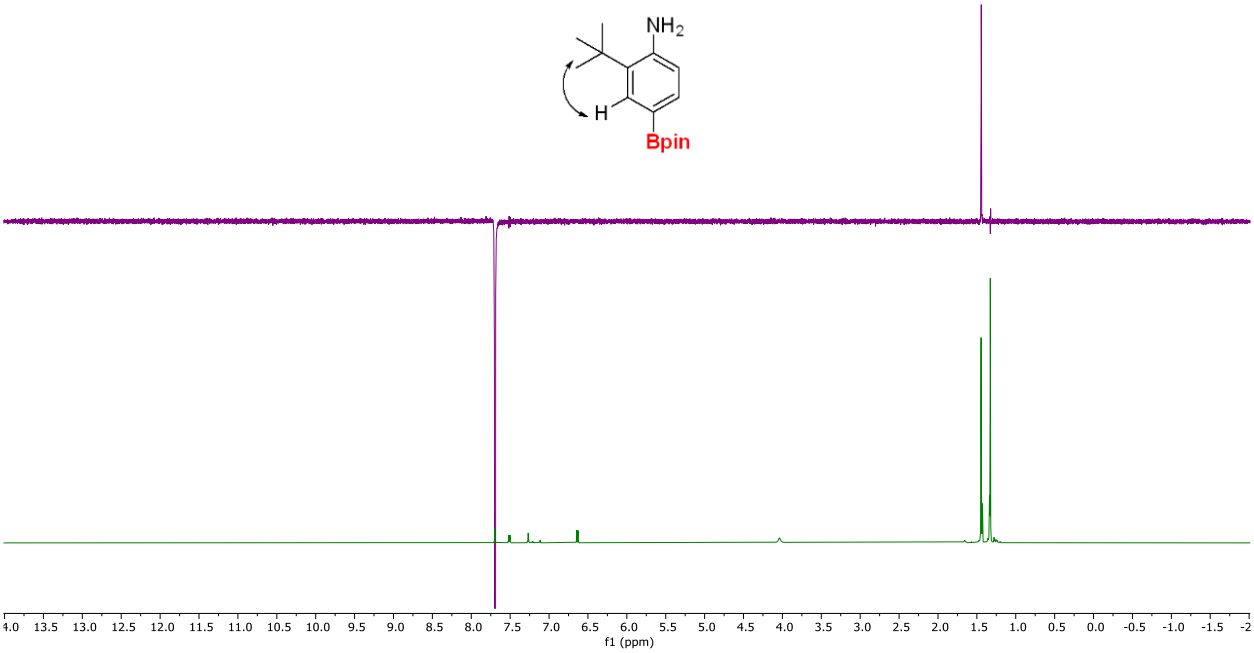


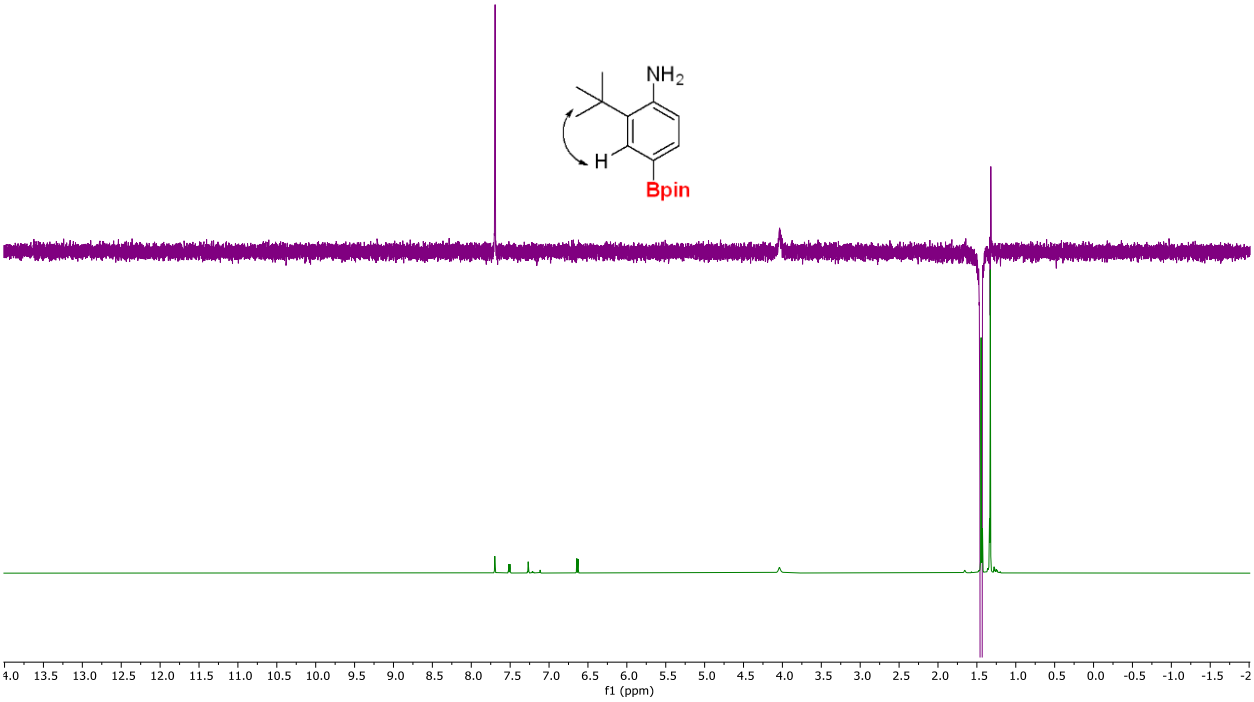
^{11}B NMR of *para* borylated 2-tertbutylaniline (4.2i) ($CDCl_3$, 160 MHz)



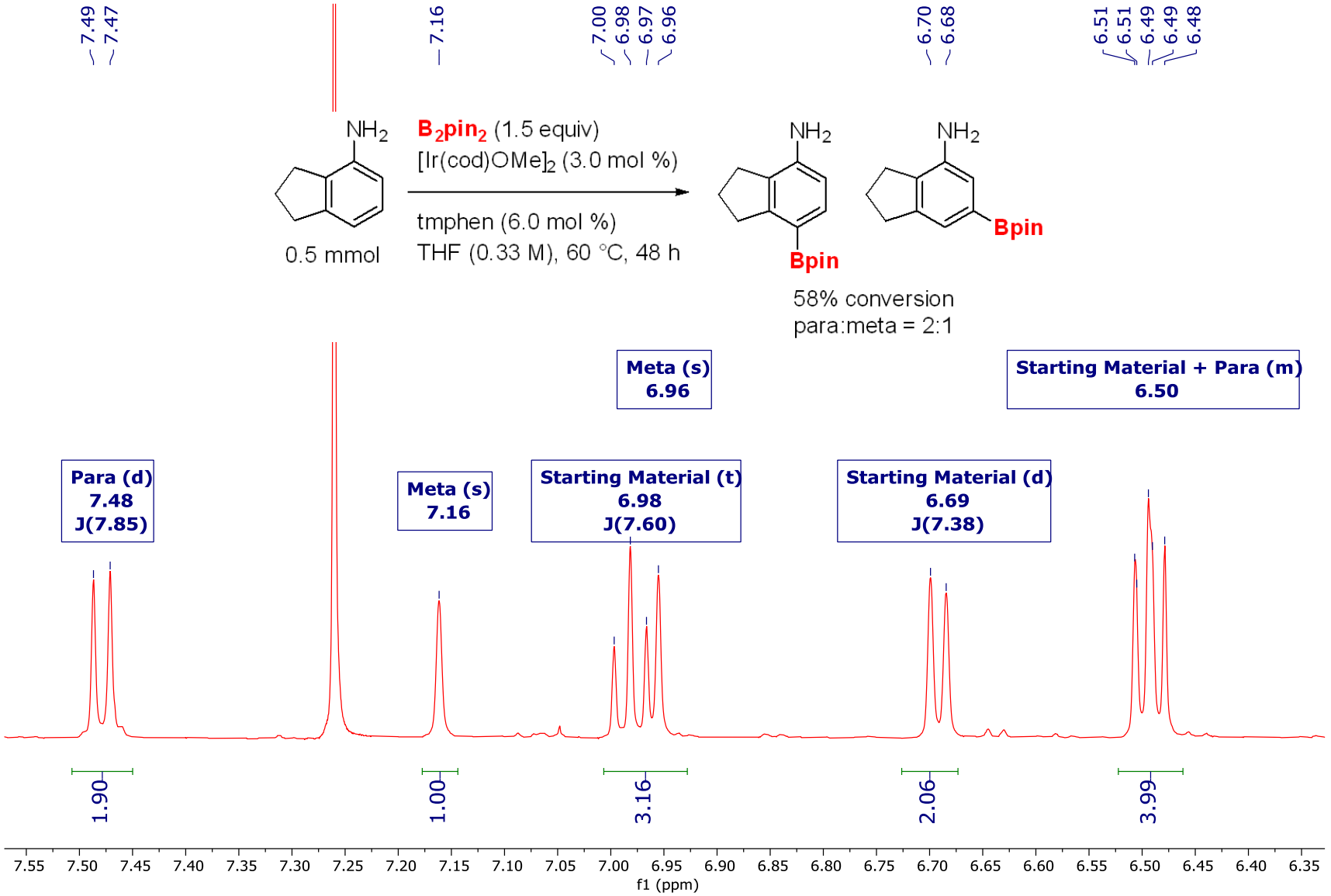
1D-NOE of *para* borylated 2-tertbutylaniline (4.2i) ($CDCl_3$, 500 MHz)

Identification of the *para* isomer

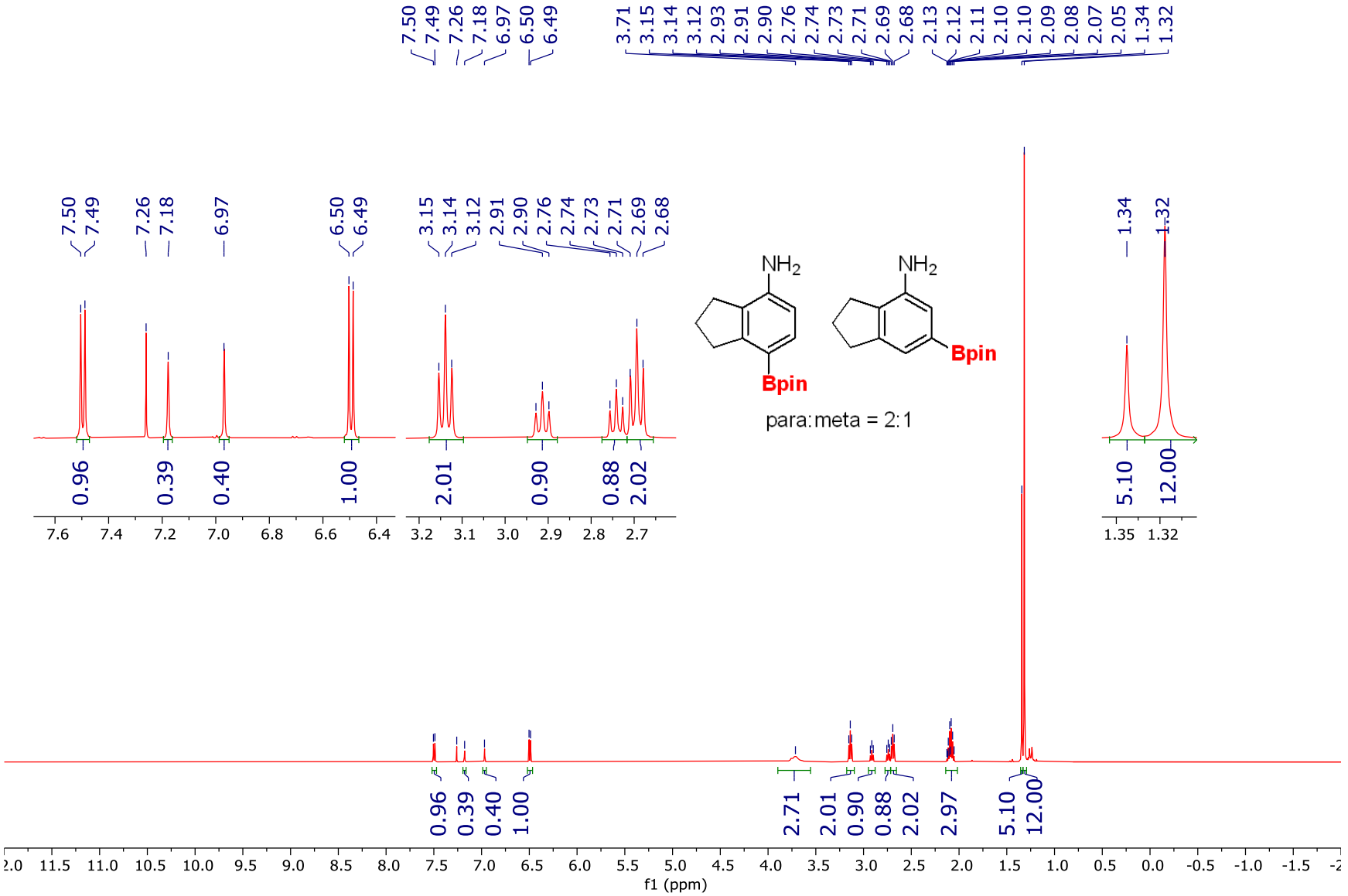




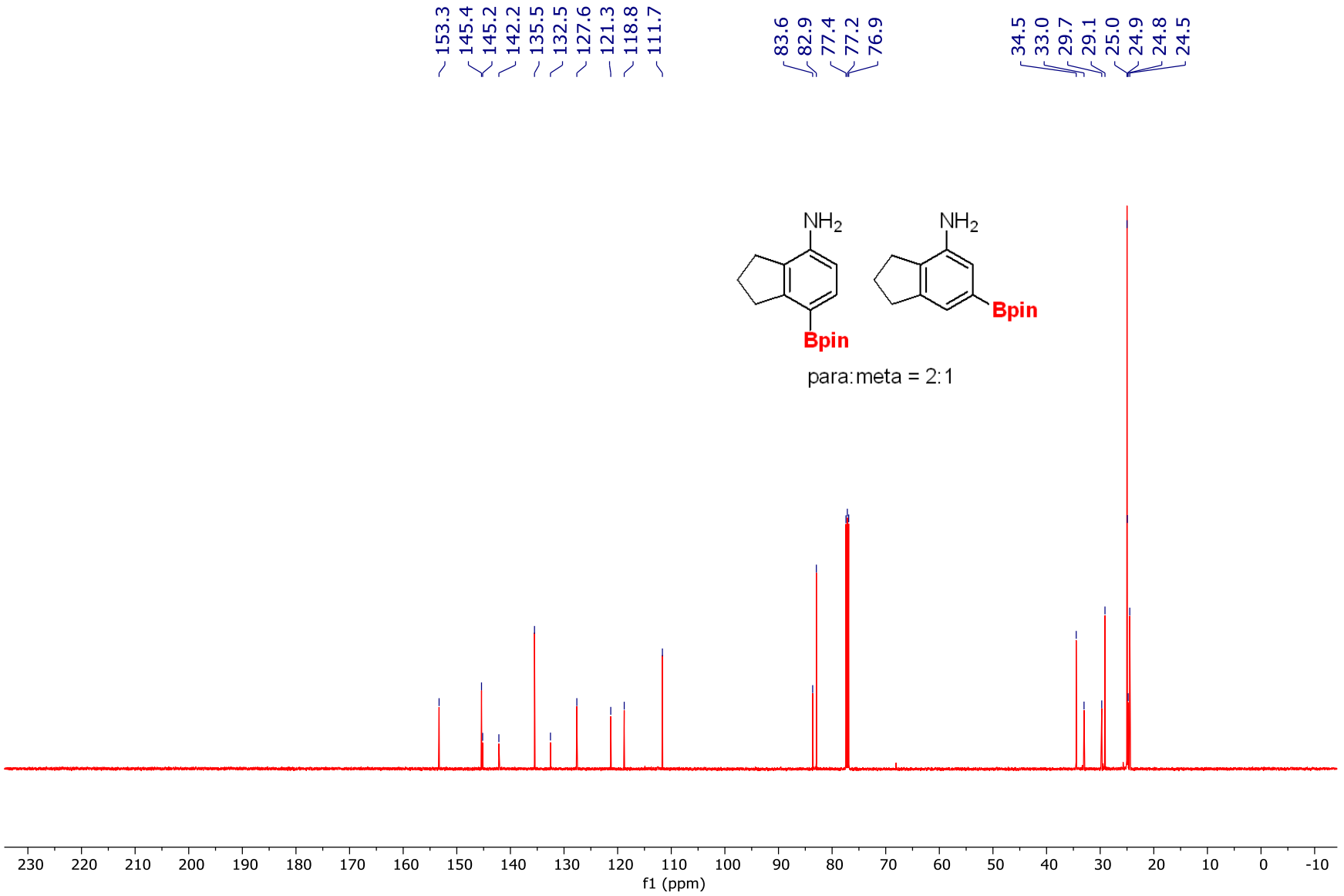
***Para* CHB of 4-aminoindan (4.2j) ($CDCl_3$, 500 MHz)**



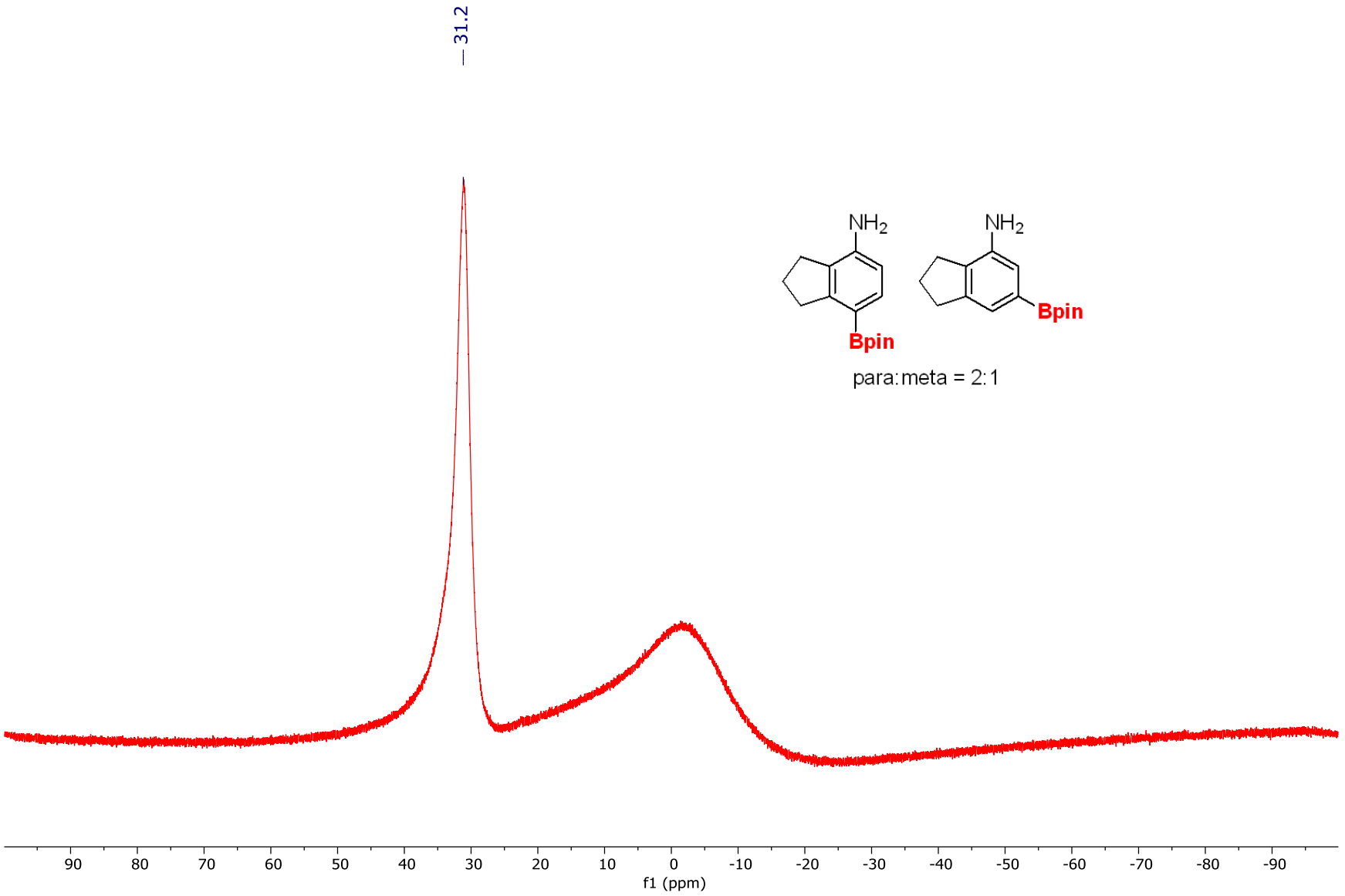
^{1}H NMR of *para* borylated 4-aminoindan (4.2j) ($CDCl_3$, 500 MHz)



^{13}C NMR of *para* borylated 4-aminoindan (4.2j) (126 MHz, $CDCl_3$)

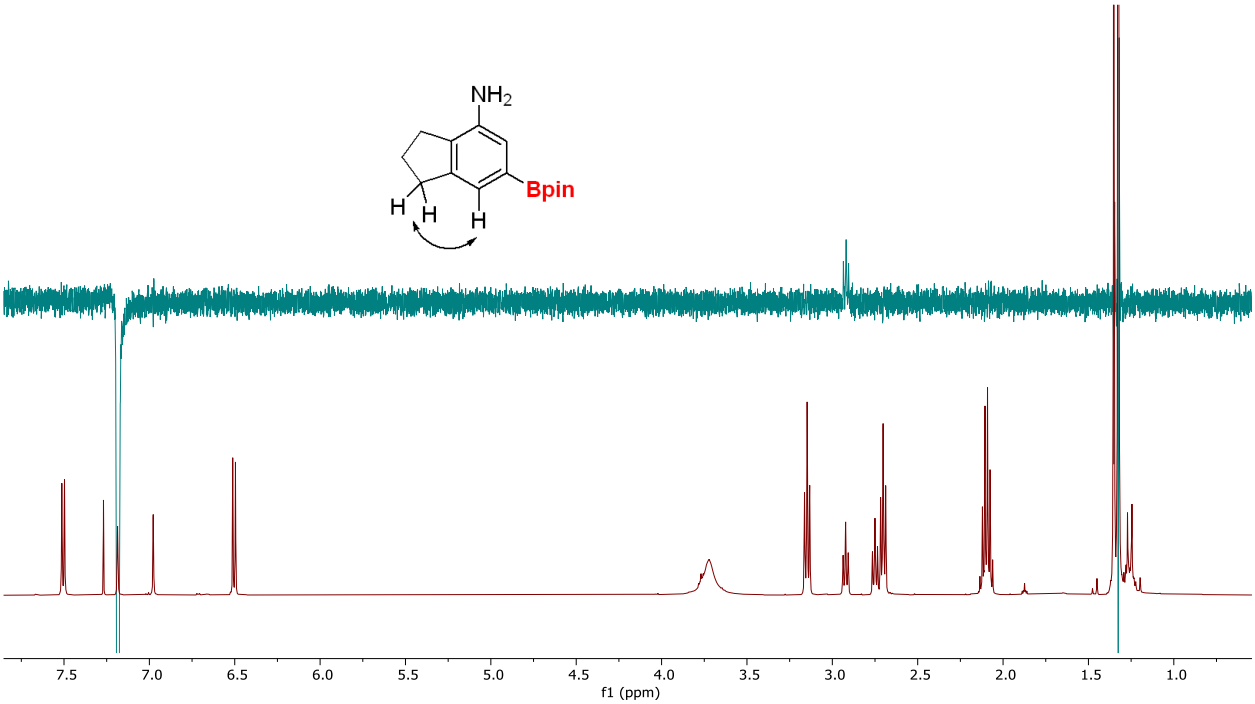


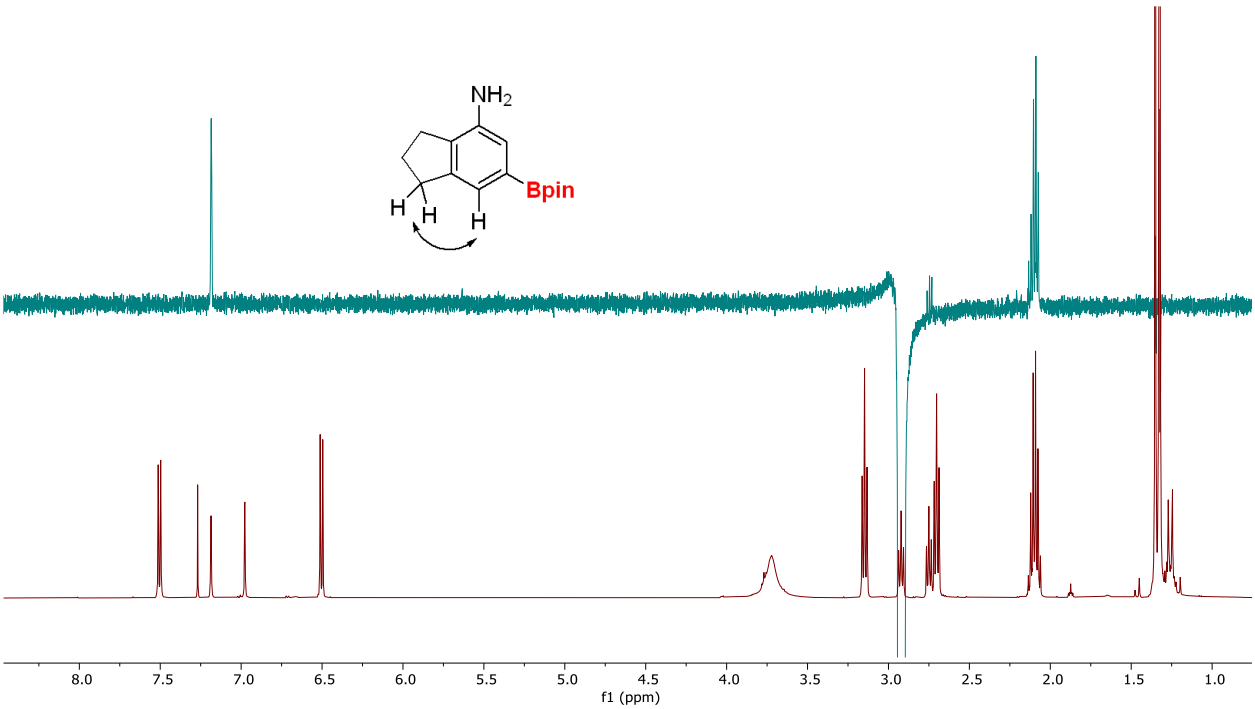
^{11}B NMR of *para* borylated 4-aminoindan (4.2j) ($CDCl_3$, 160 MHz)



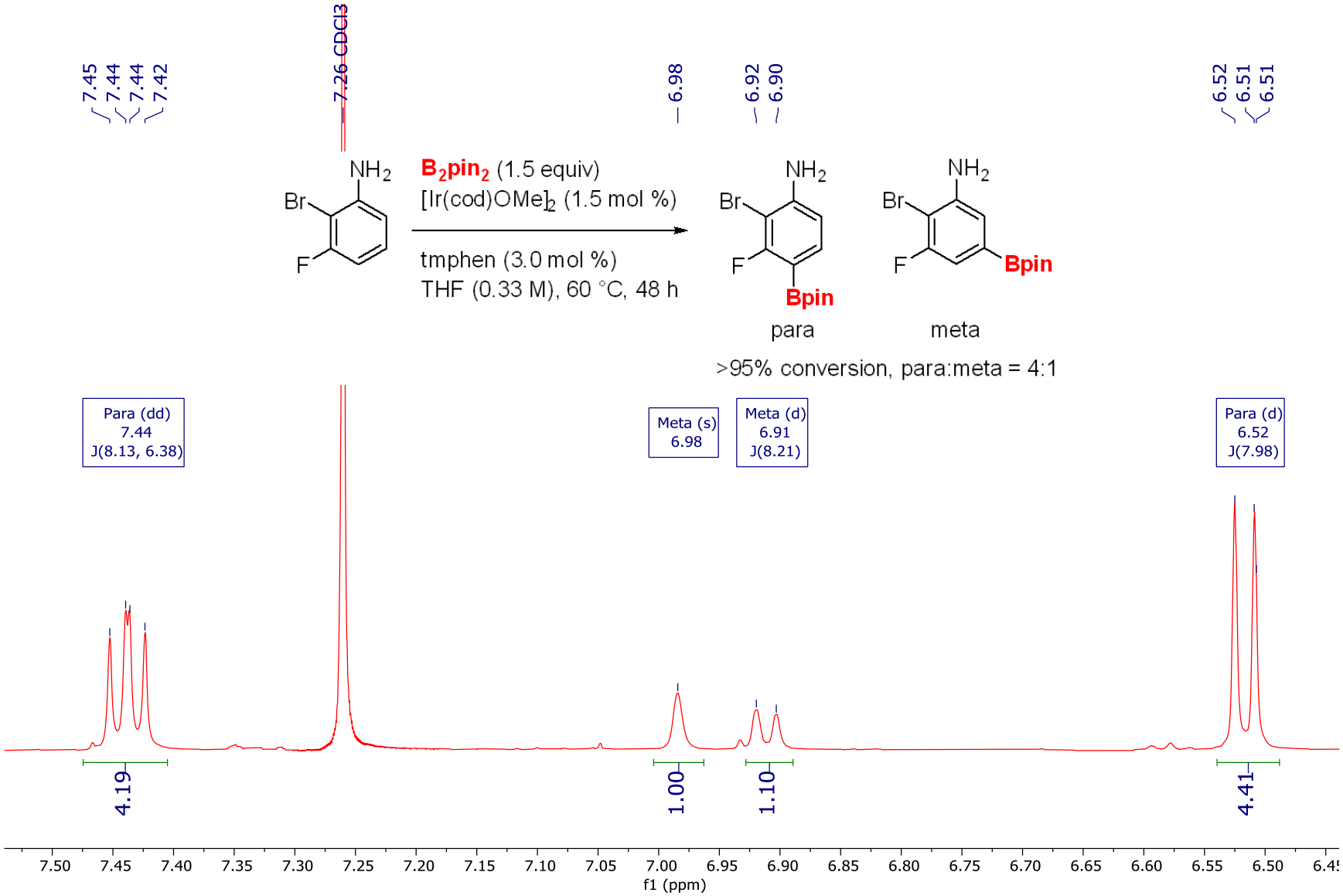
1D-NOE of *para* borylated 4-aminoindan (4.2j) ($CDCl_3$, 500 MHz)

Identification of the *meta* isomer

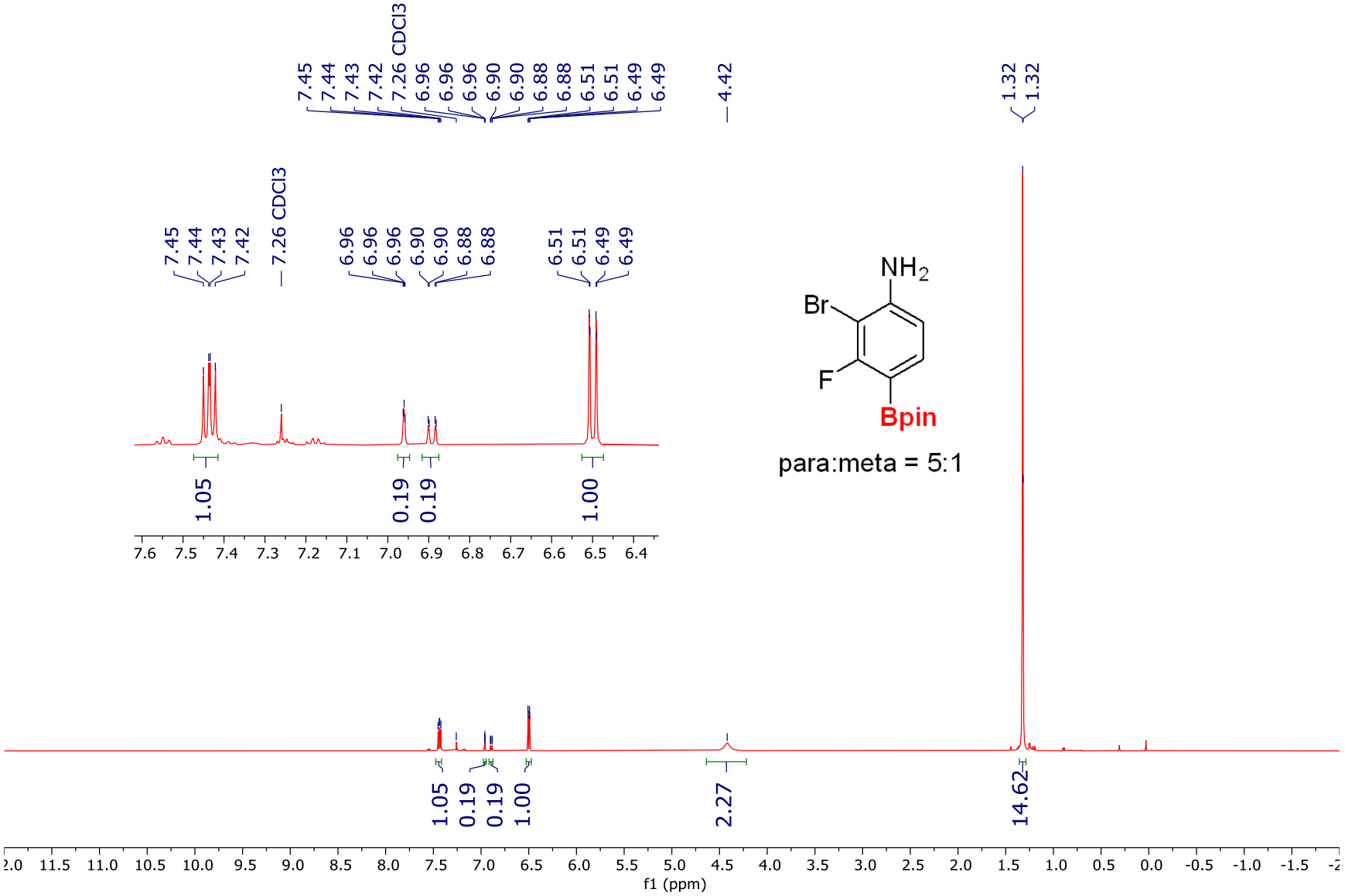




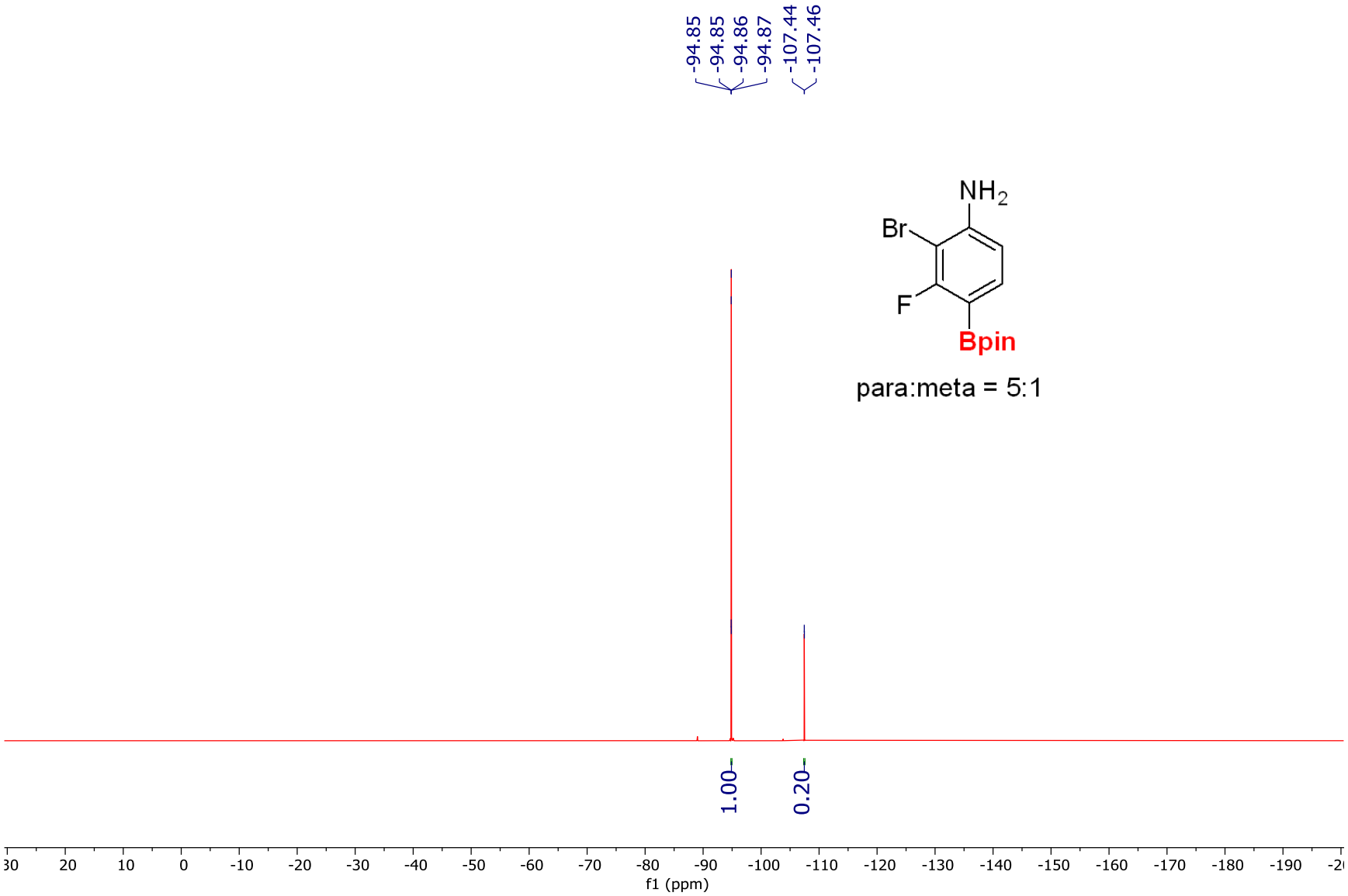
***Para* borylation of 2-bromo-3-fluoroaniline (4.2k) ($CDCl_3$, 500 MHz)**



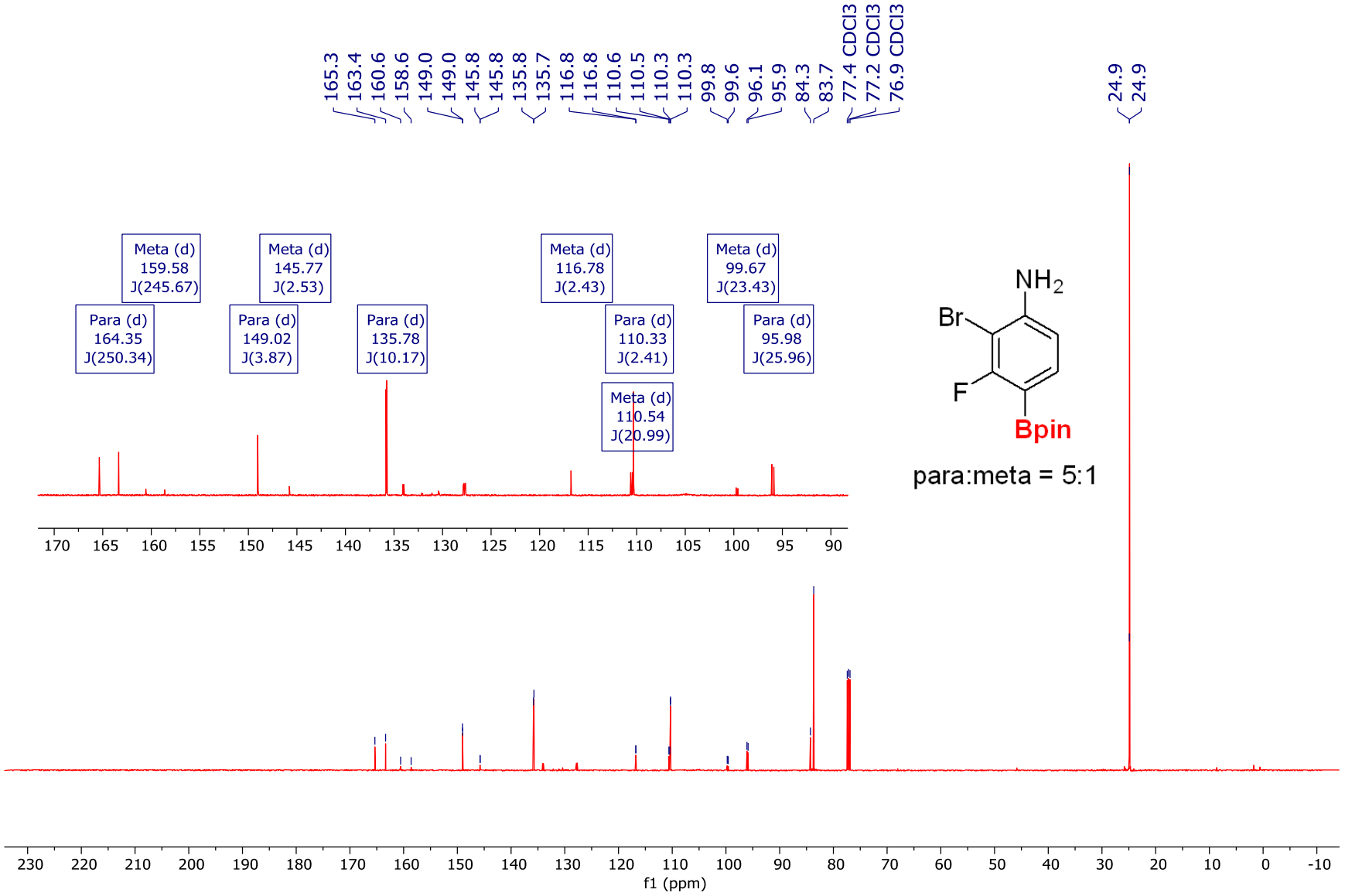
^{1}H NMR of *para* borylated 2-bromo-3-fluoroaniline (4.2k) ($CDCl_3$, 500 MHz)



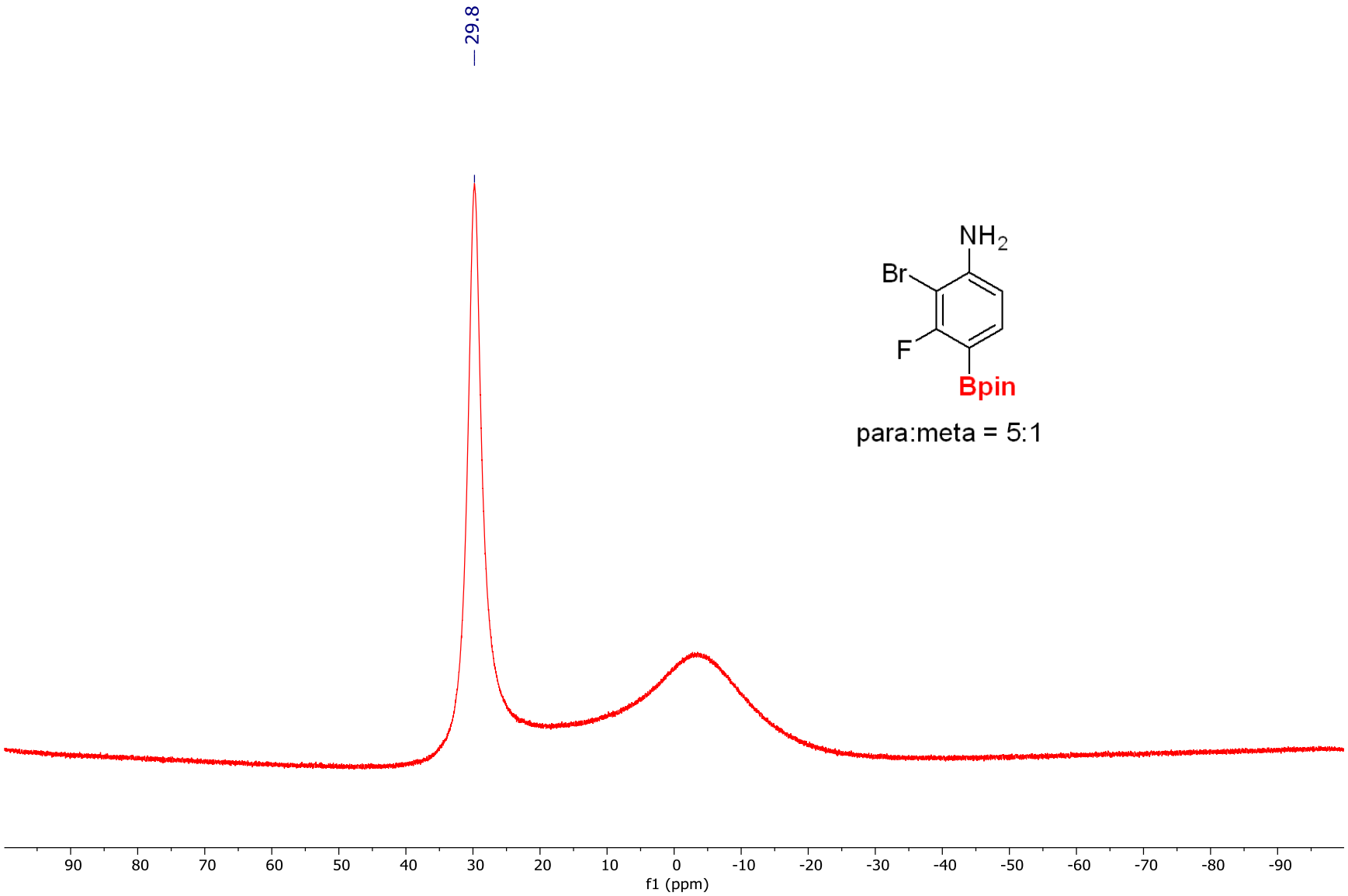
^{19}F NMR of *para* borylated 2-bromo-3-fluoroaniline (4.2k) ($CDCl_3$, 470 MHz)



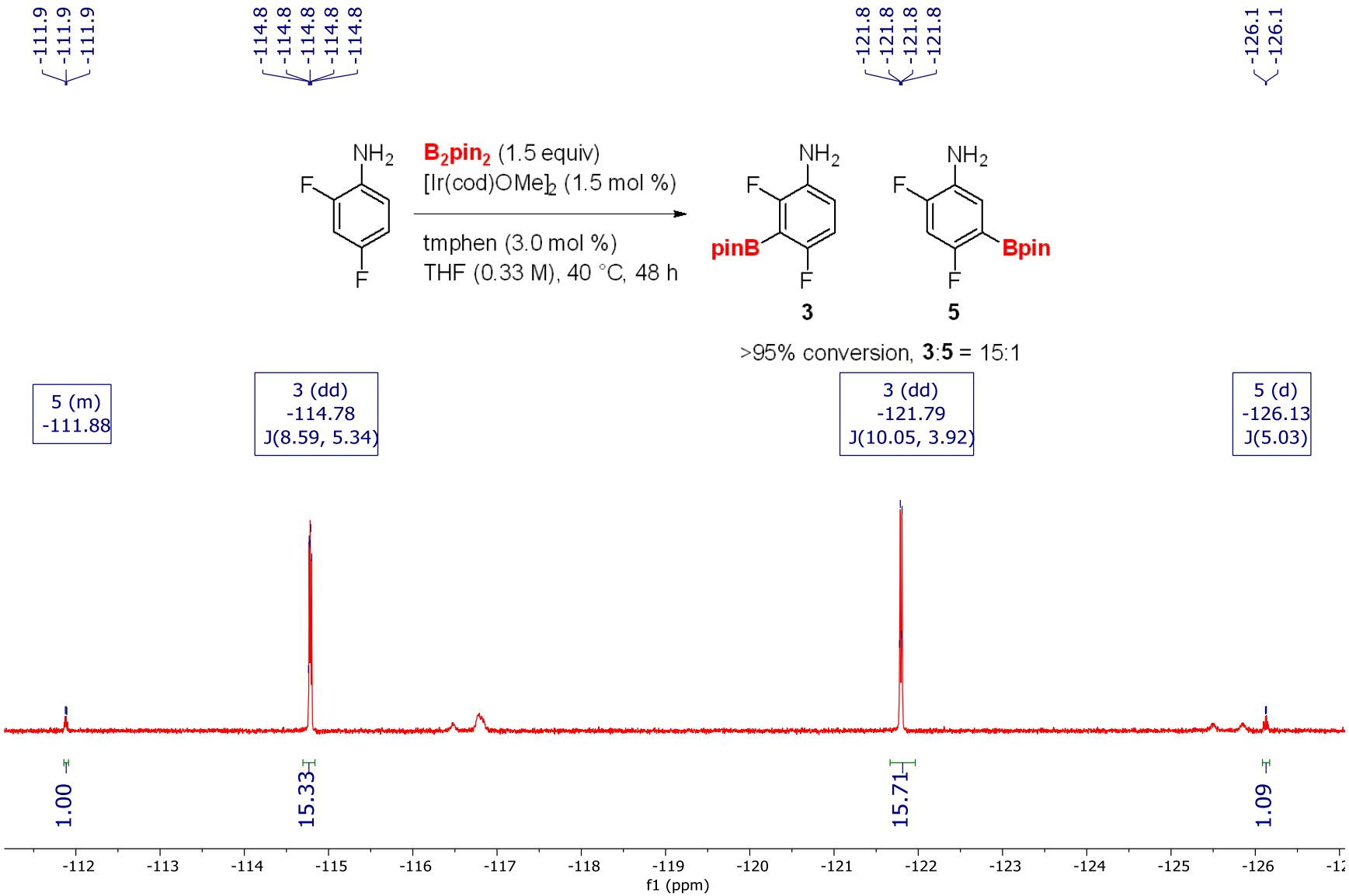
^{13}C NMR of *para* borylated 2-bromo-3-fluoroaniline (4.2k) ($CDCl_3$, 126 MHz)



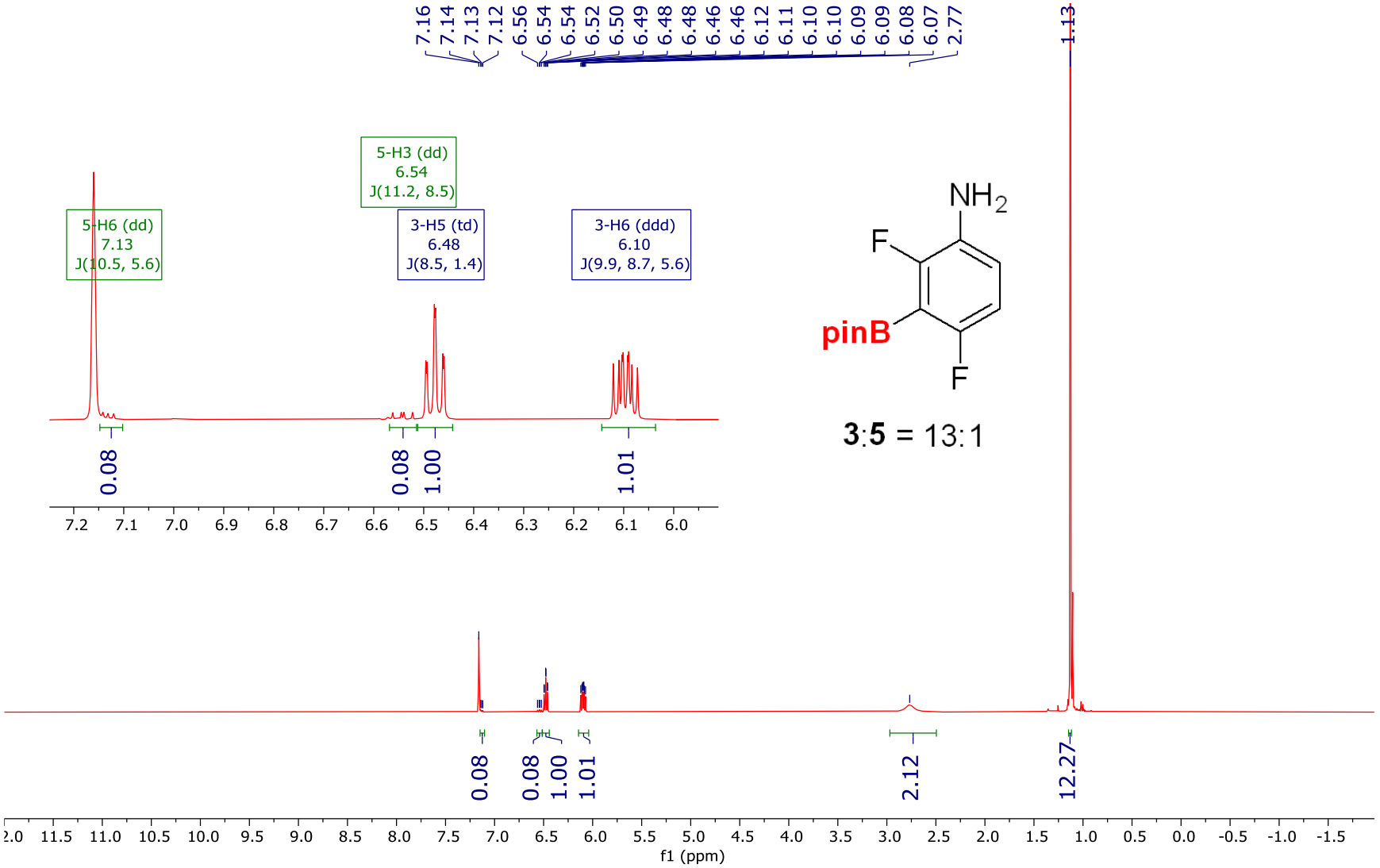
^{11}B NMR of *para* borylated 2-bromo-3-fluoroaniline (4.2k) ($CDCl_3$, 126 MHz)



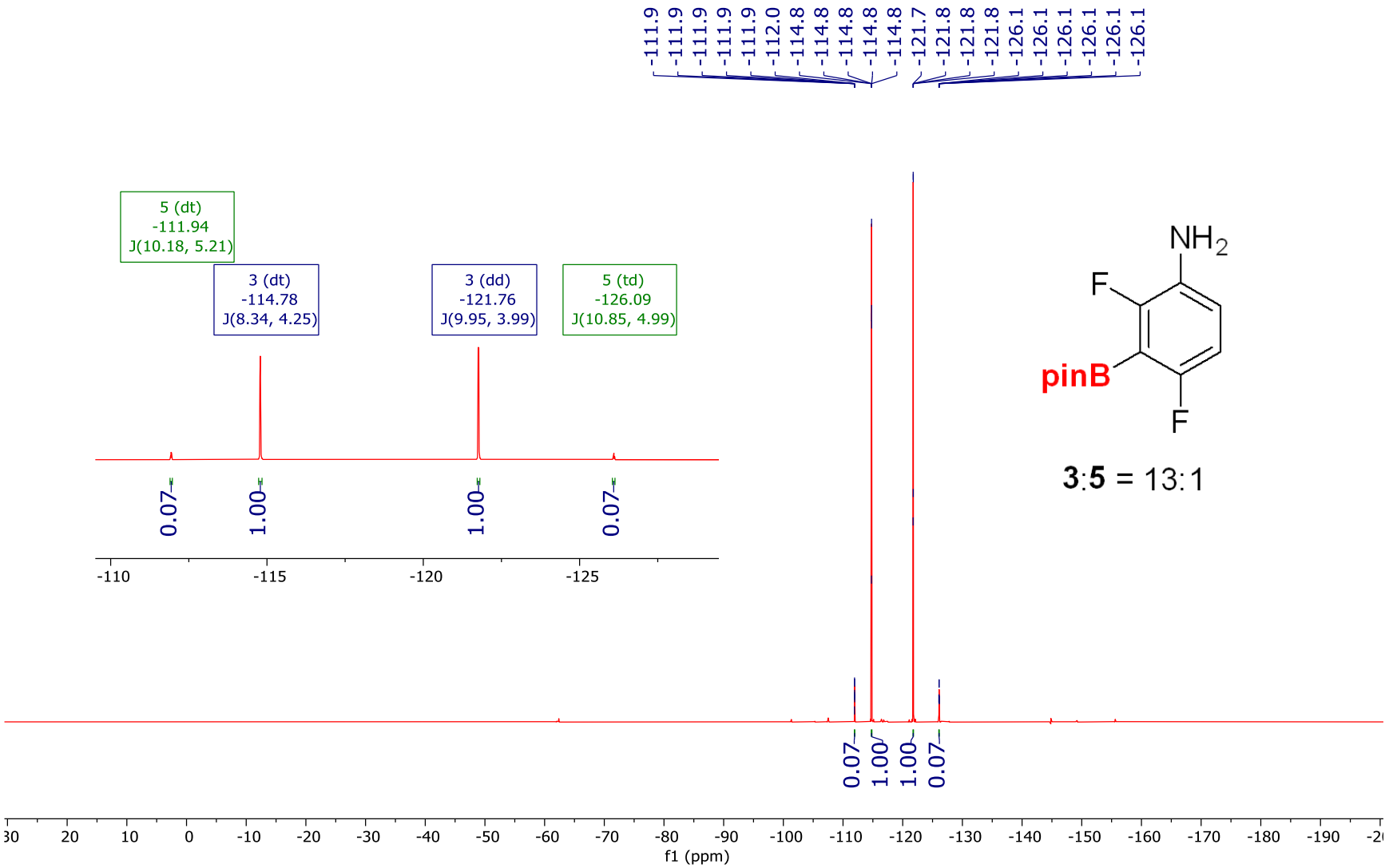
^{19}F NMR of *para* borylation of 2,4-difluoroaniline (4.2l) (C_6D_6, 470 MHz)



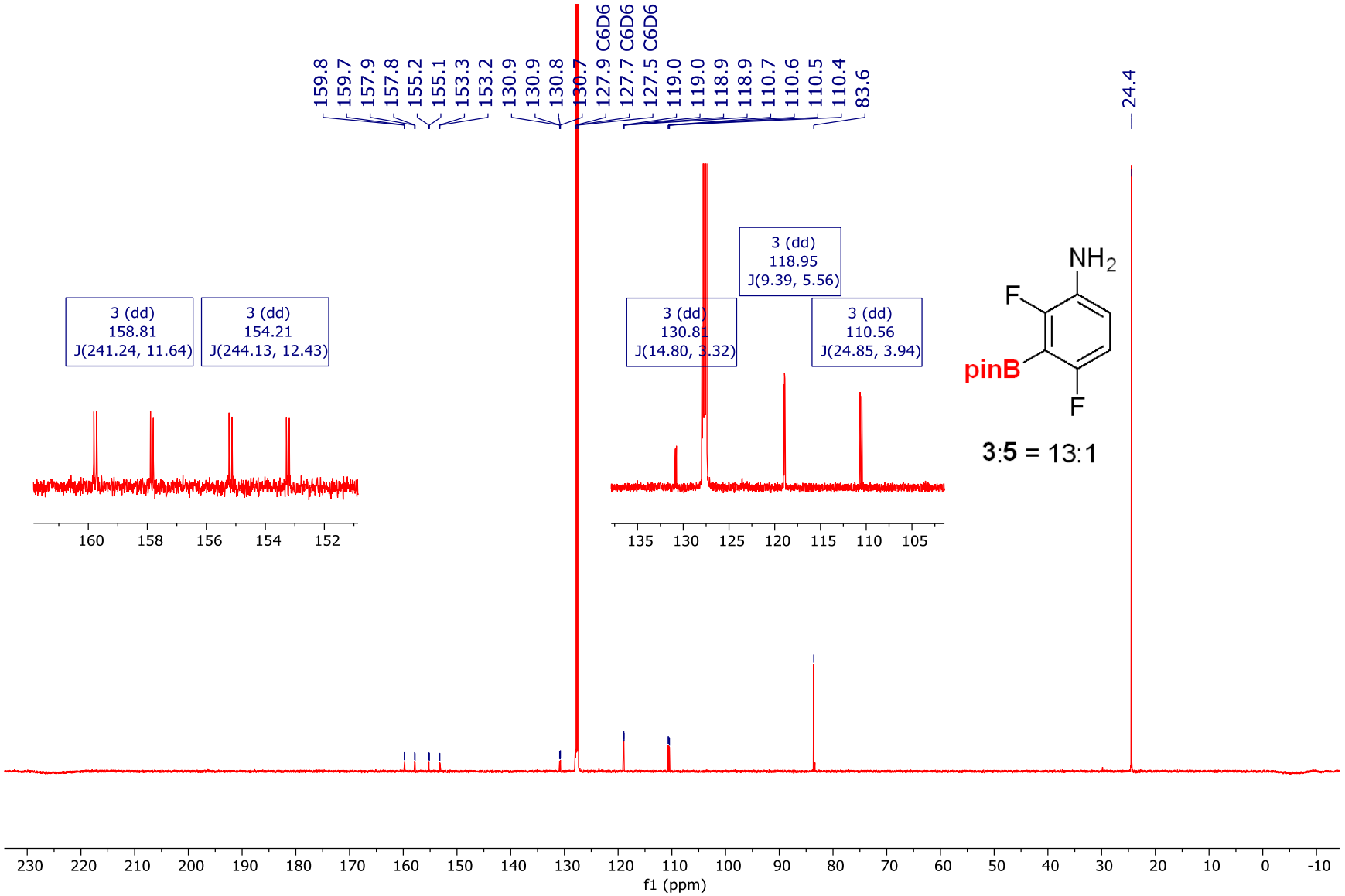
^{1}H NMR of *para* borylated 2,4-difluoroaniline (4.2l) (C_6D_6, 500 MHz)



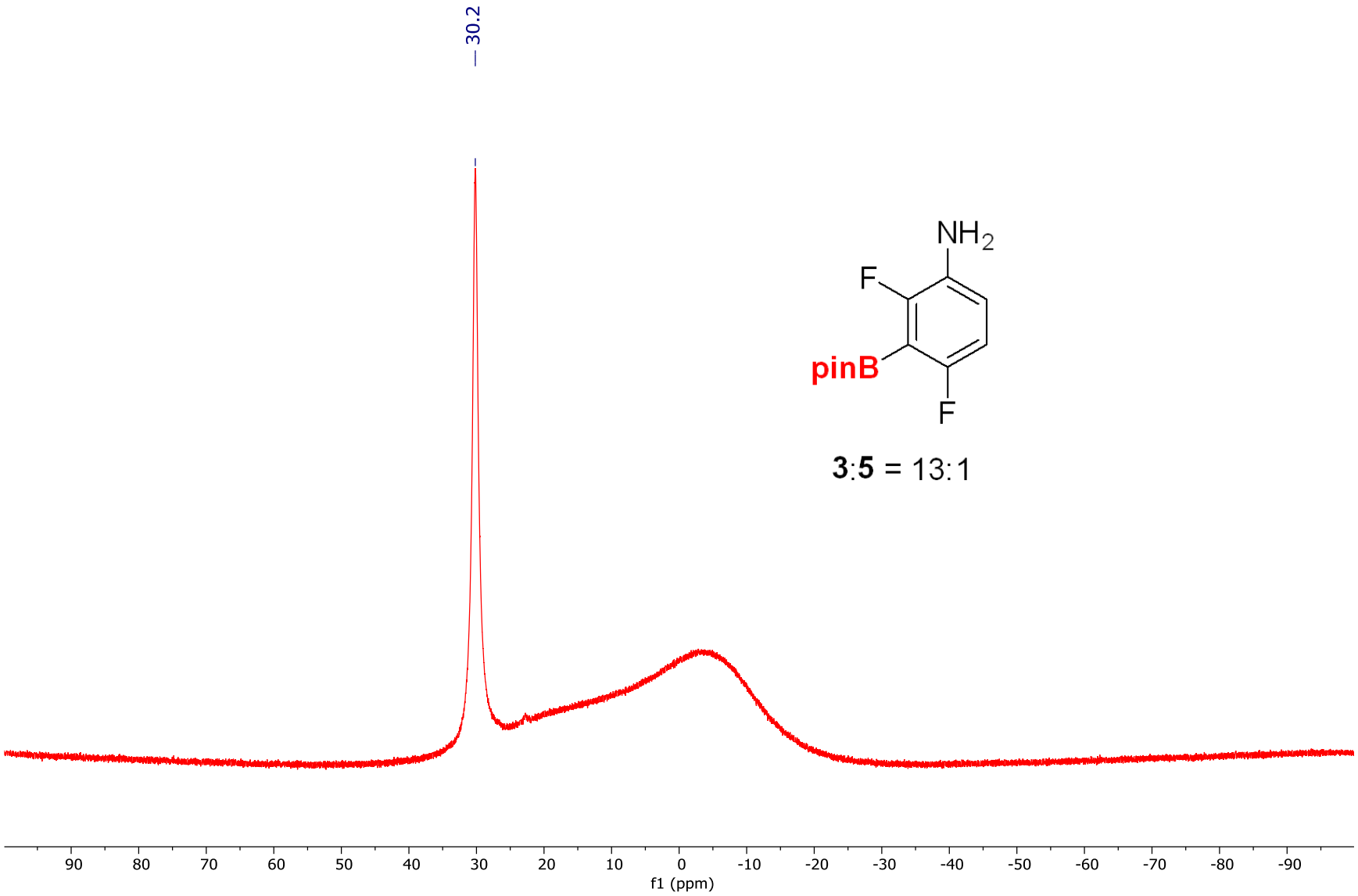
^{19}F NMR of *para* borylated 2,4-difluoroaniline (4.2l) (C_6D_6, 470 MHz)



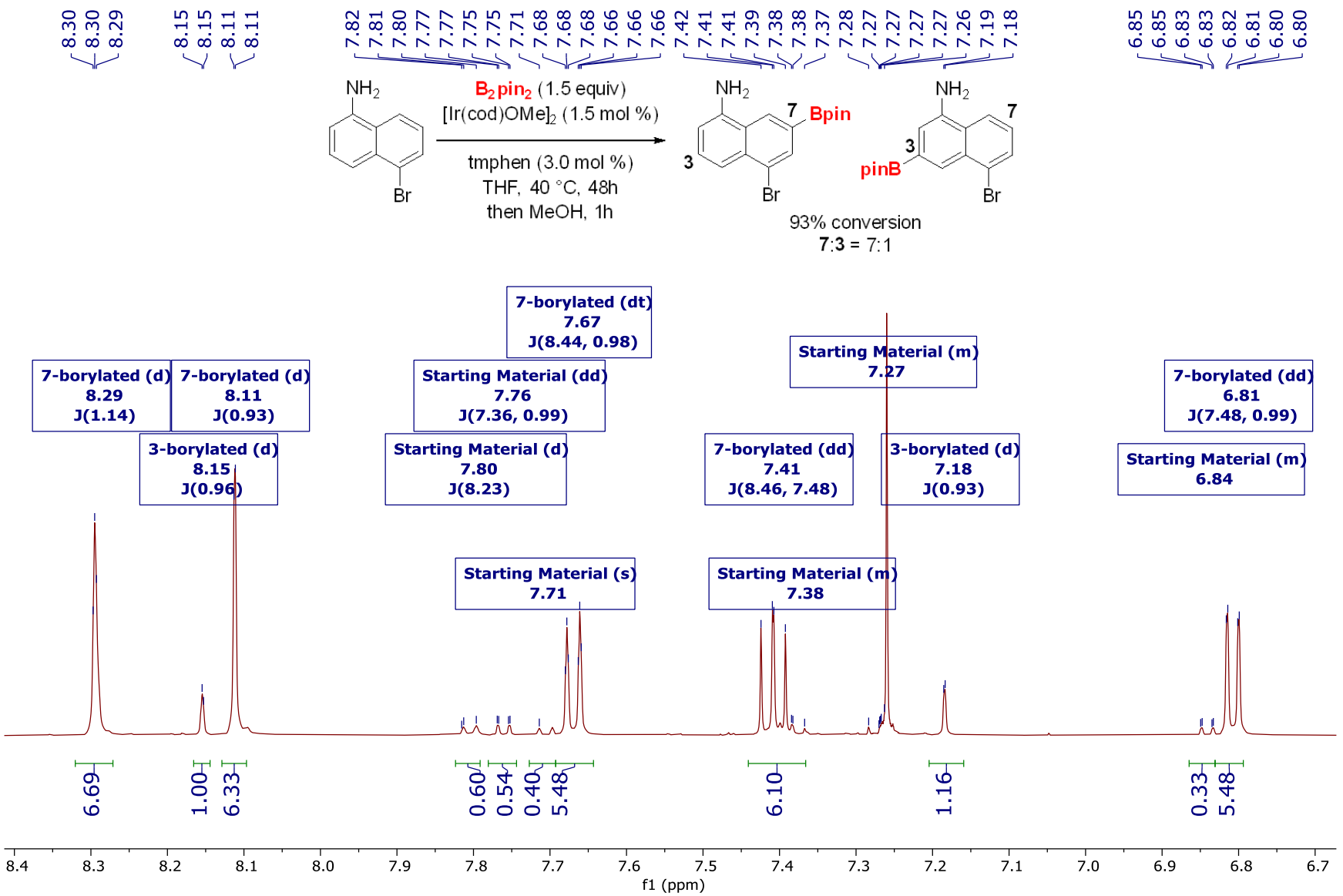
^{13}C NMR of *para* borylated 2,4-difluoroaniline (4.2l) (C_6D_6, 126 MHz)



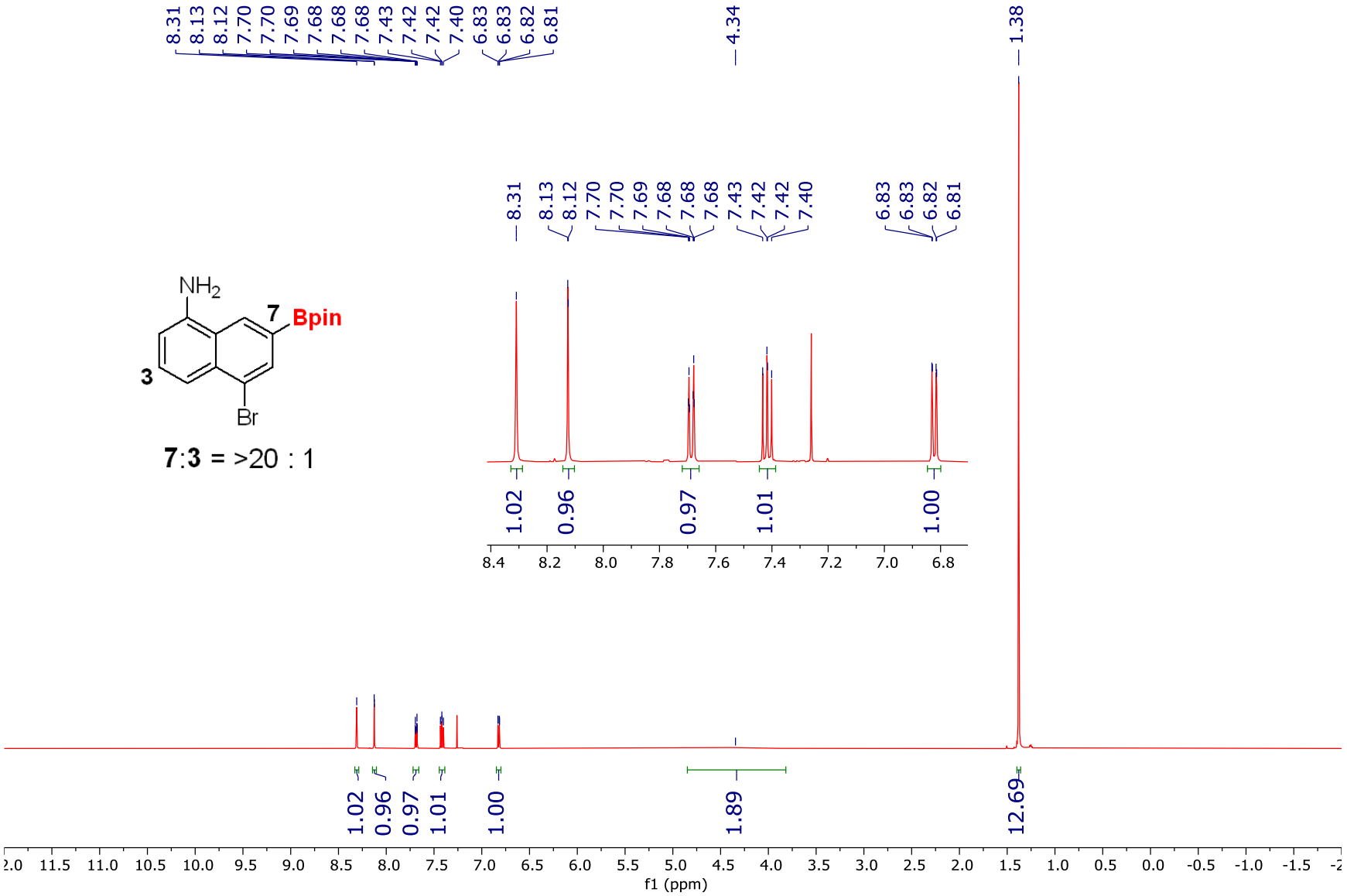
^{11}B NMR of *para* borylated 2,4-difluoroaniline (4.2l) (C_6D_6, 126 MHz)



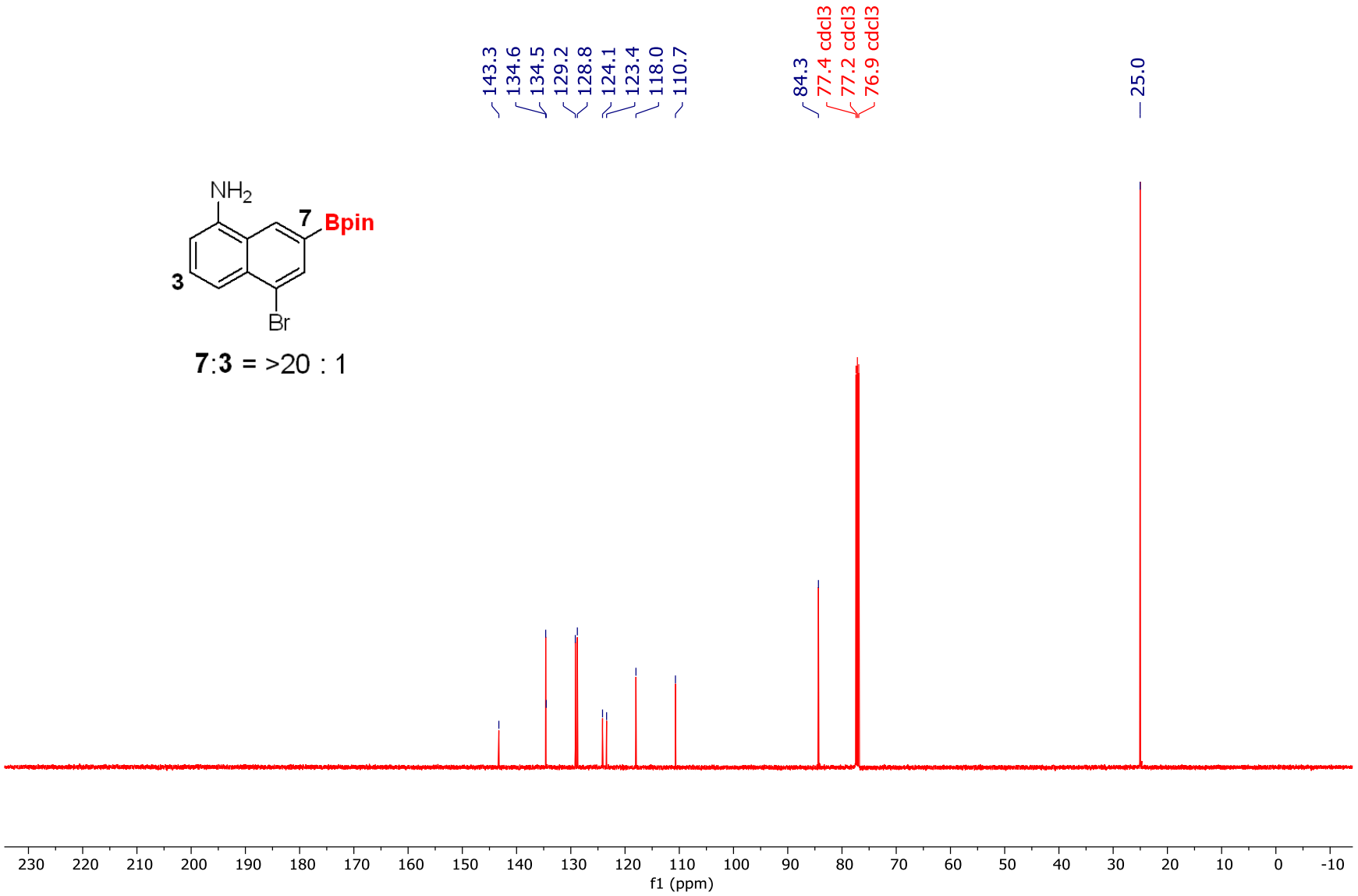
***Para* CHB of 7-borylated 5-bromo-1-naphthylamine (4.2m) ($CDCl_3$, 500 MHz)**



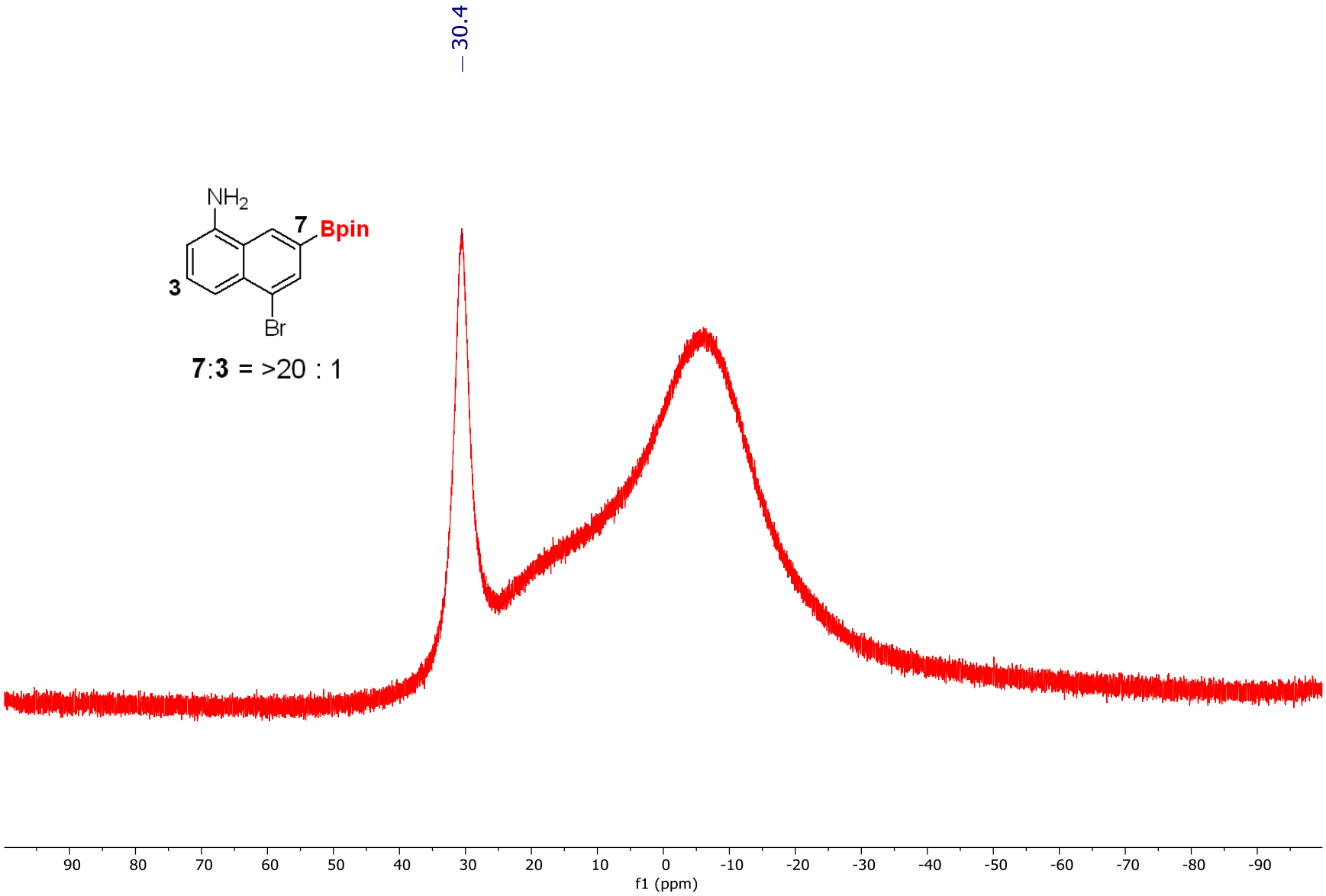
^{1}H NMR of 7-borylated 5-bromo-1-naphtylamine (4.2m) ($CDCl_3$, 500 MHz)



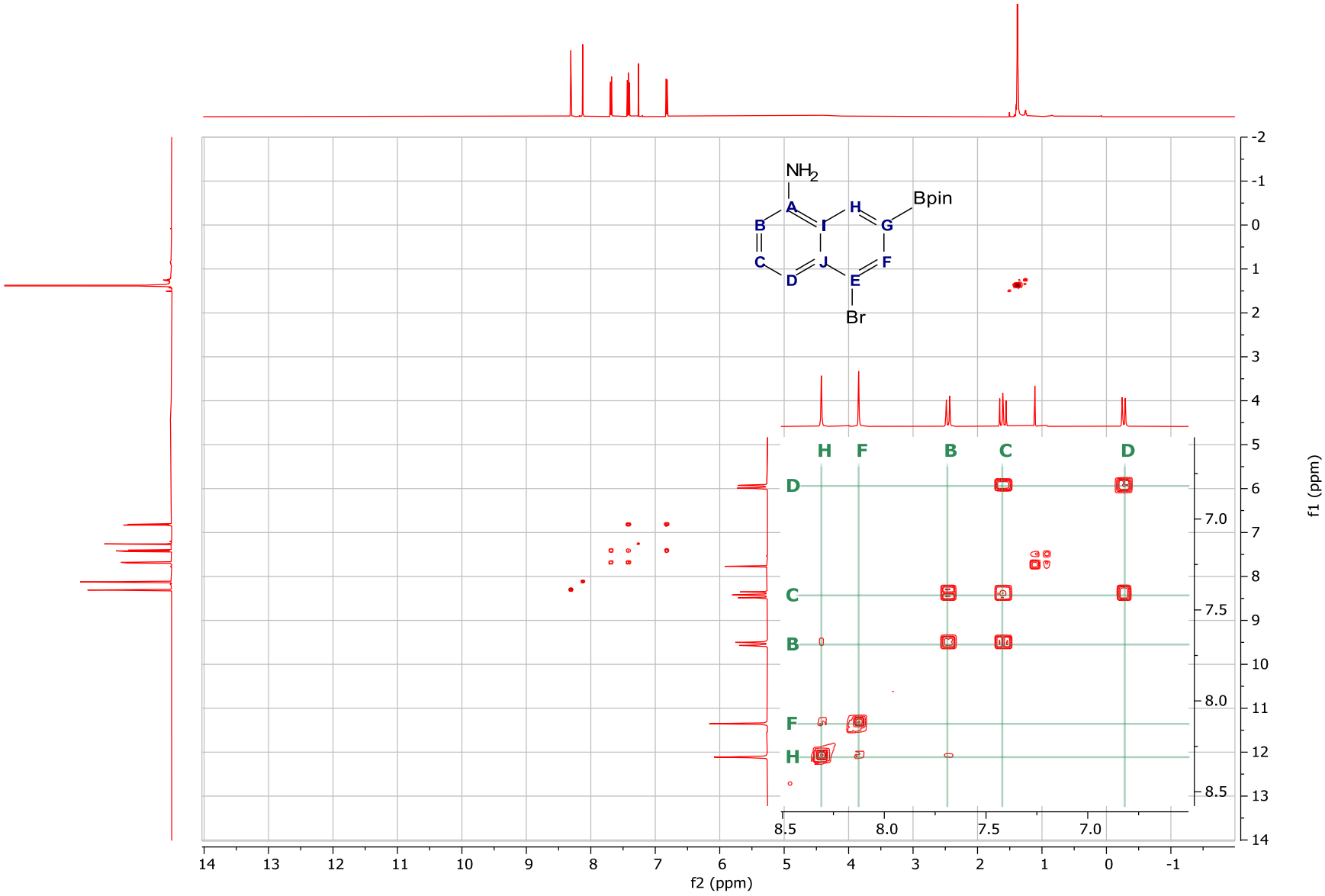
^{13}C NMR of 7-borylated 5-bromo-1-naphtylamine (4.2m) ($CDCl_3$, 126 MHz)



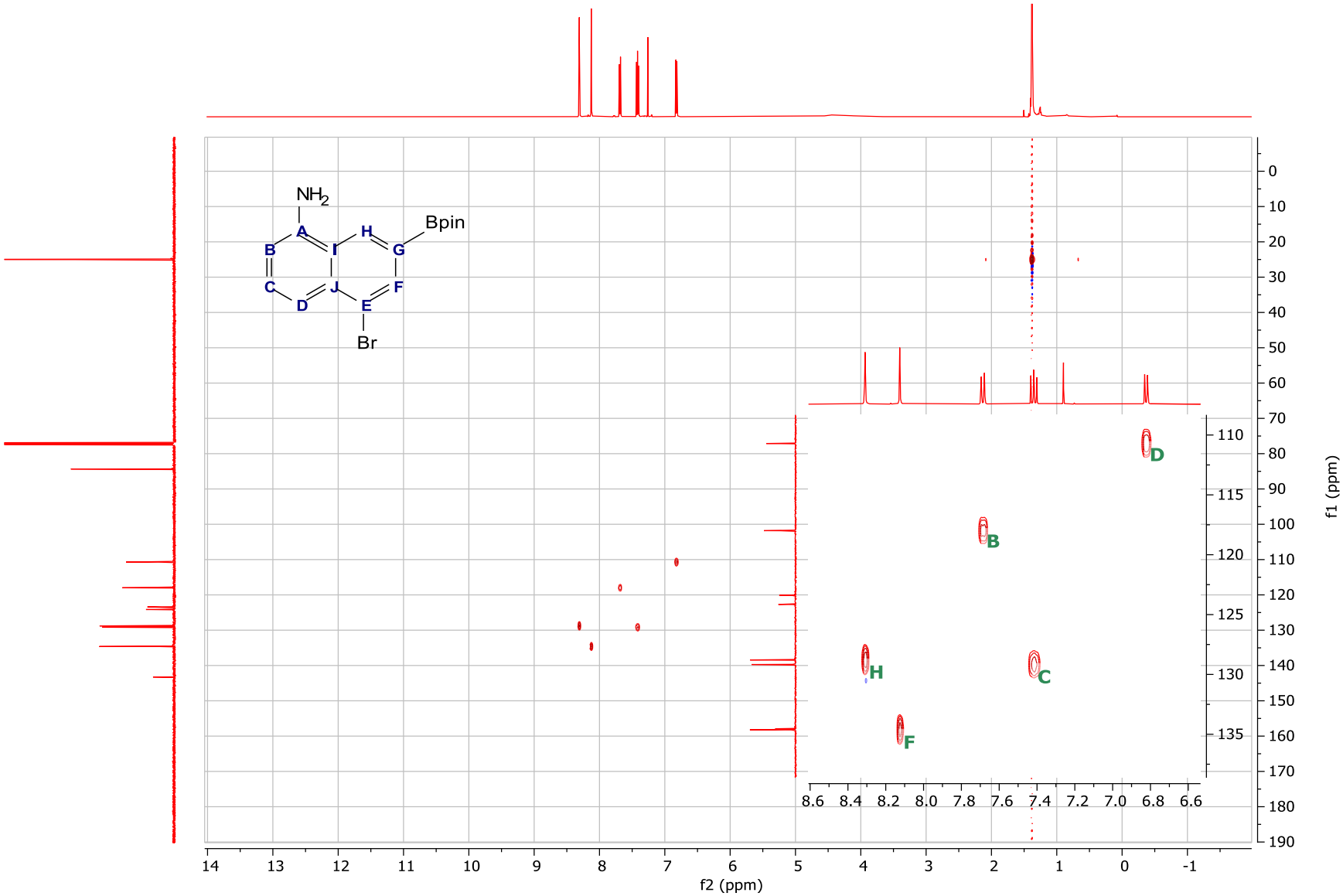
^{11}B NMR of 7-borylated 5-bromo-1-naphtylamine (4.2m) ($CDCl_3$, 160 MHz)



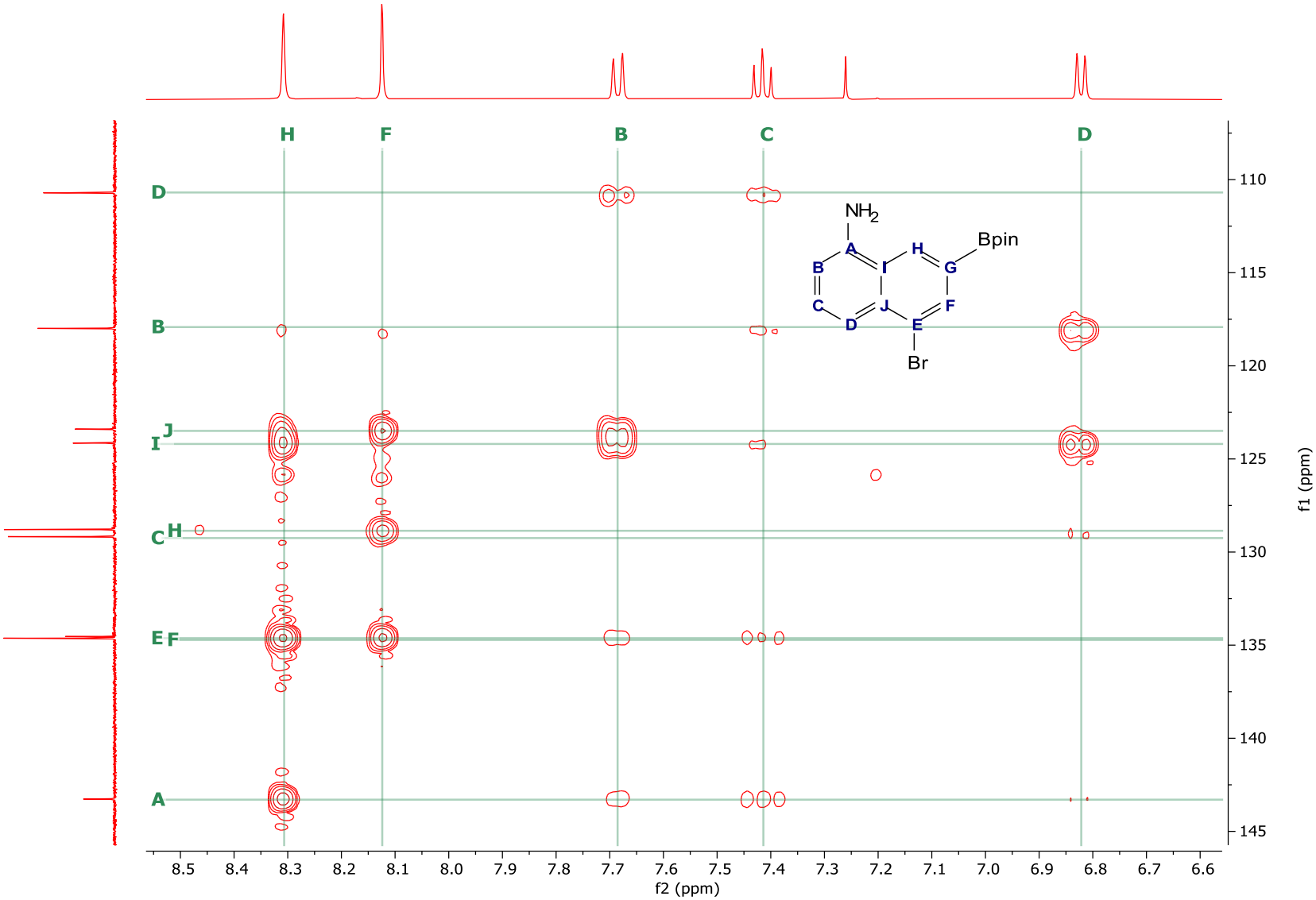
gCOSY of 7-borylated 5-bromo-1-naphtylamine (4.2m) ($CDCl_3$, 500 MHz)



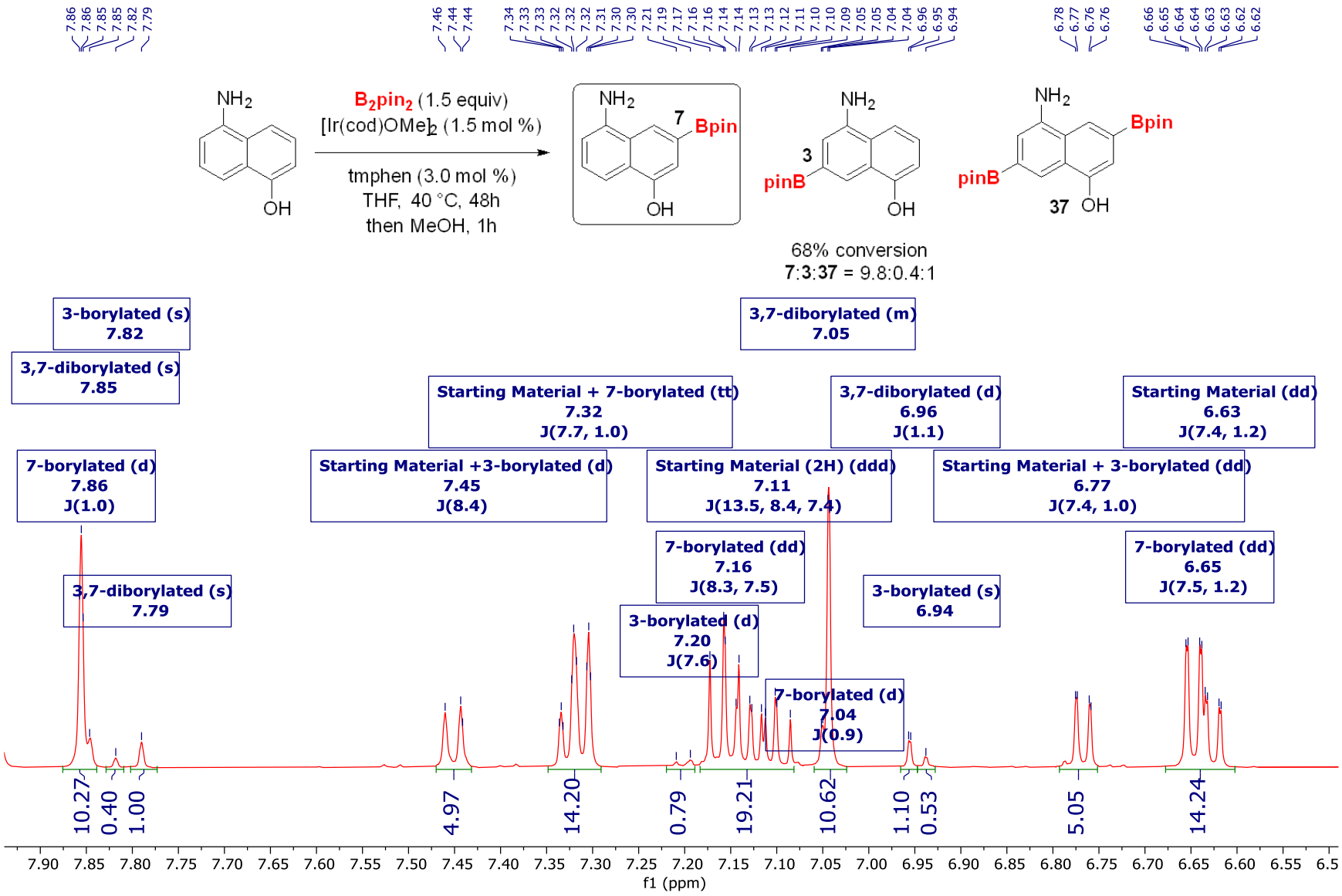
gHSQCAD of 7-borylated 5-bromo-1-naphtylamine (4.2m) ($CDCl_3$, 500 MHz)



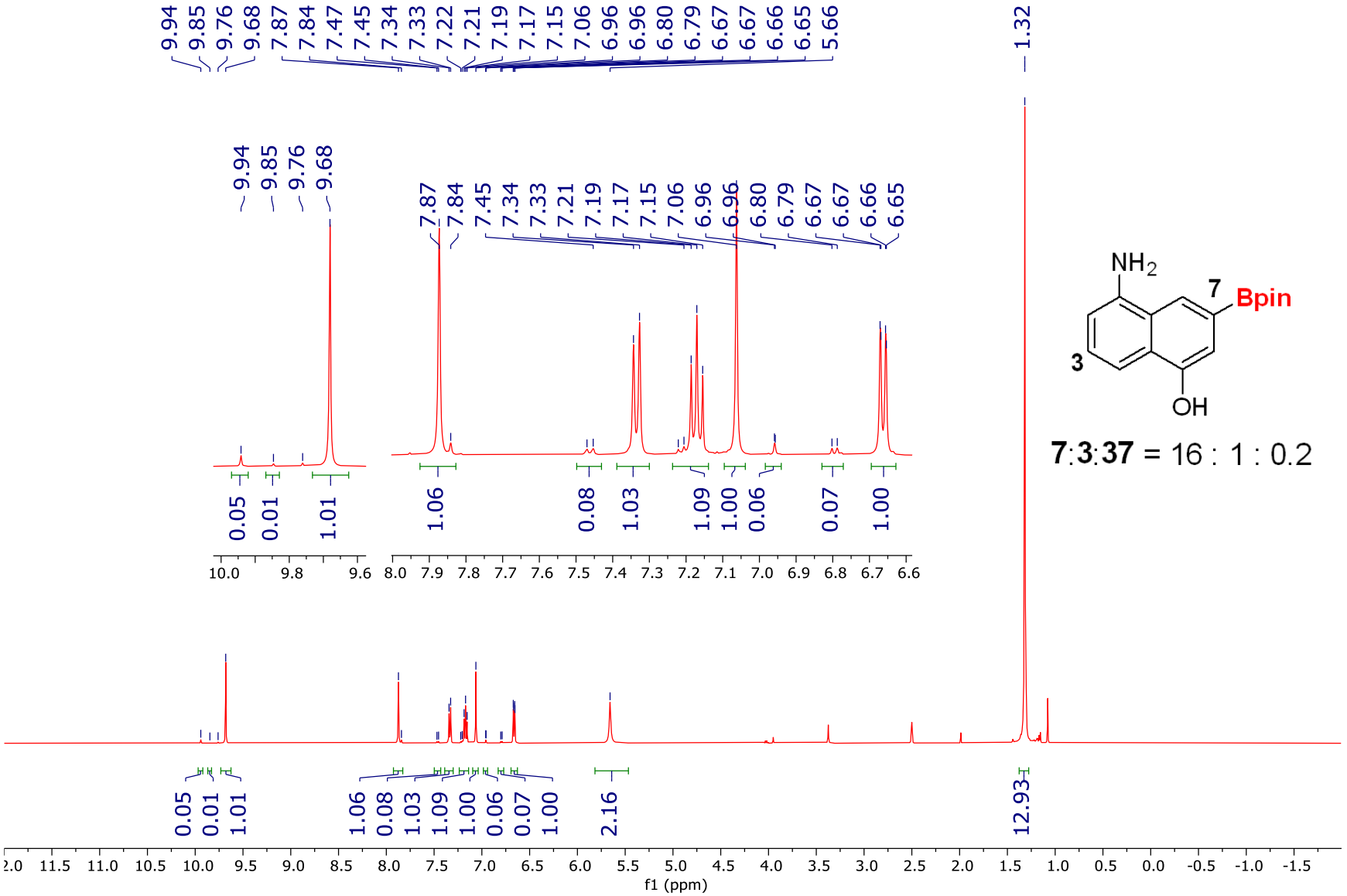
gHMBCAD of 7-borylated 5-bromo-1-naphtylamine (4.2m) ($CDCl_3$, 500 MHz, Jnxh = 5 Hz)



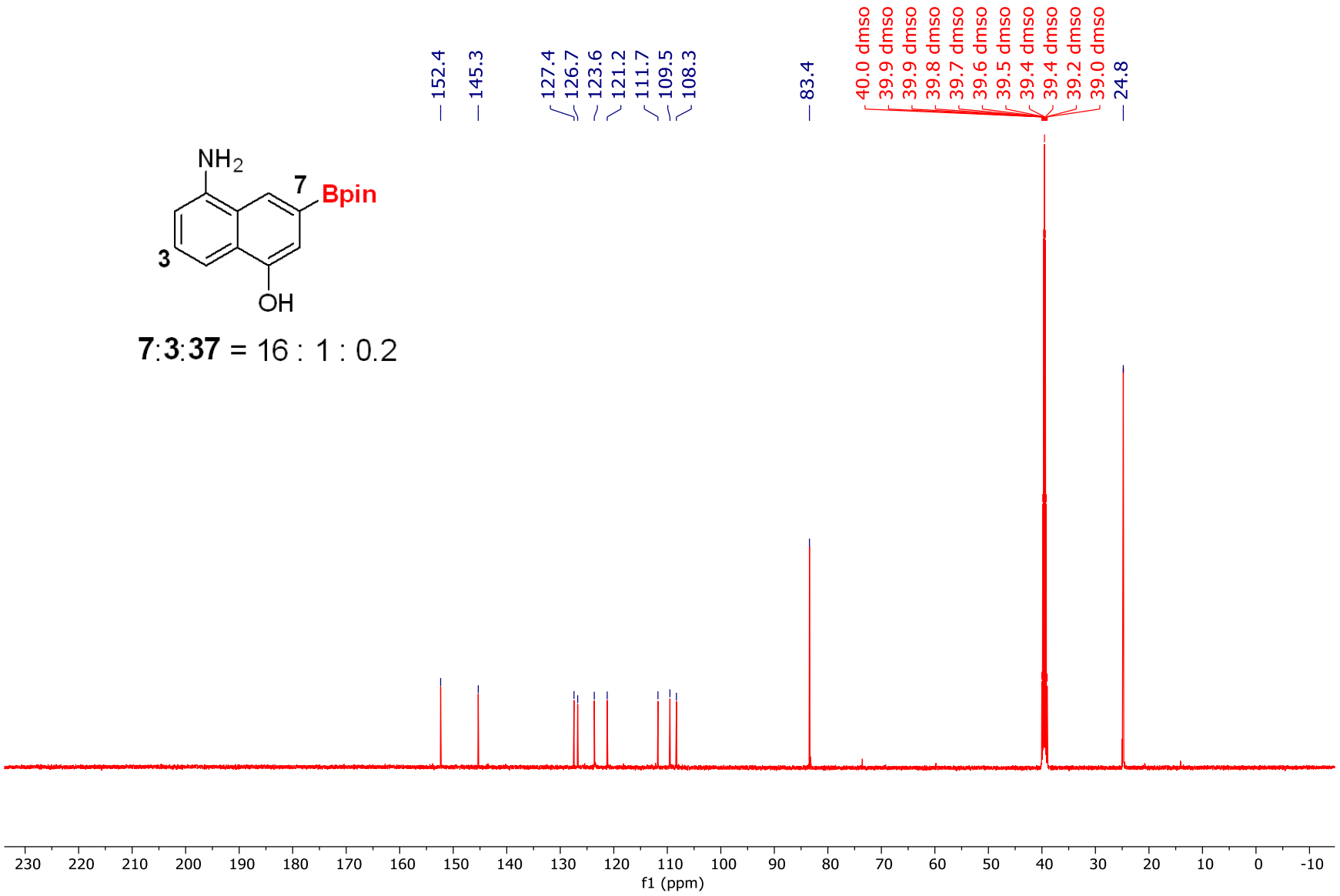
C7 CHB of 5-hydroxy-1-naphthylamine (4.2n) (DMSO-d6, 500 MHz)



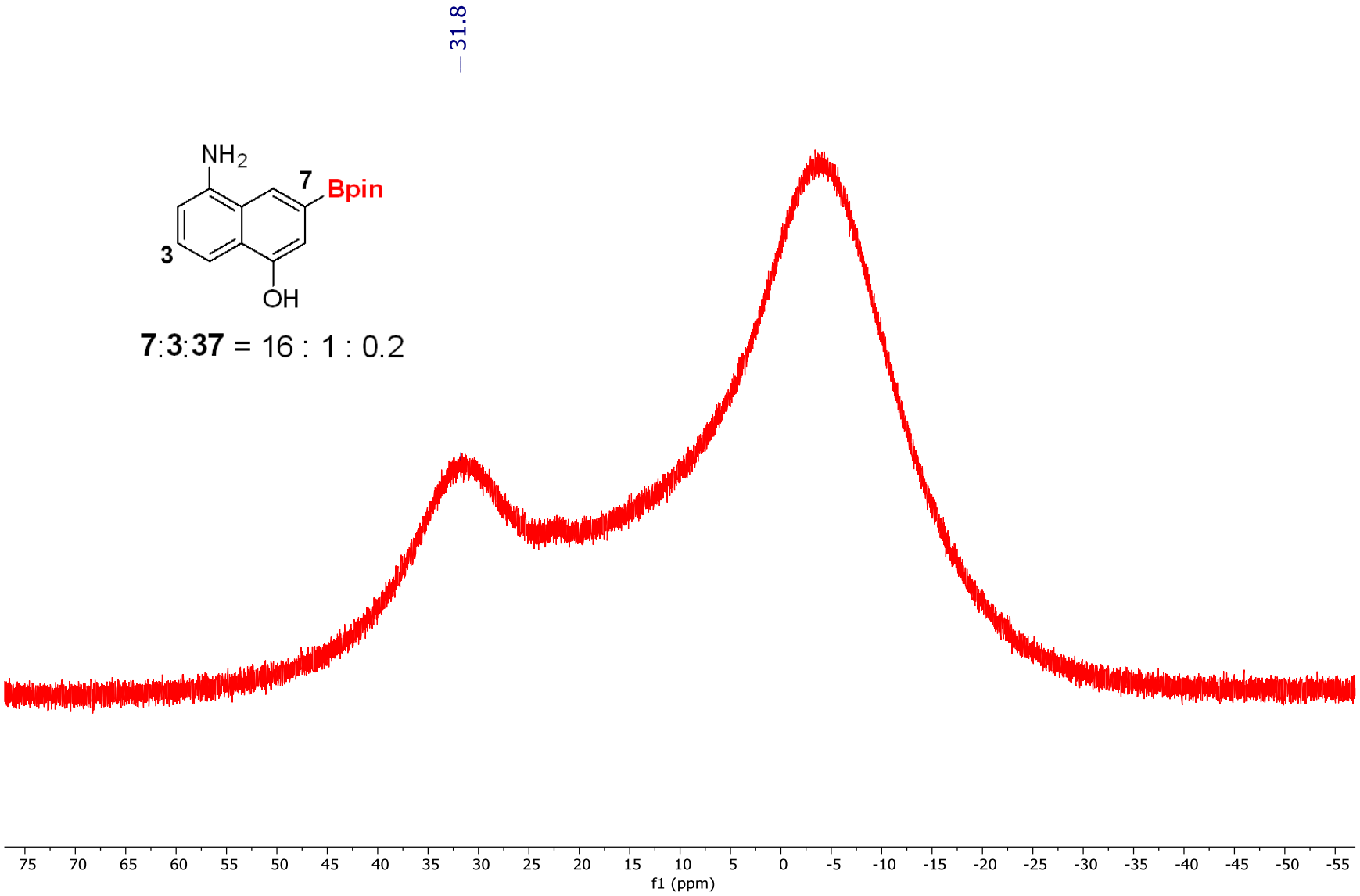
[1]H NMR of 7-borylated 5-hydroxy-1-naphthylamine (4.2n) (DMSO-d6, 500 MHz)



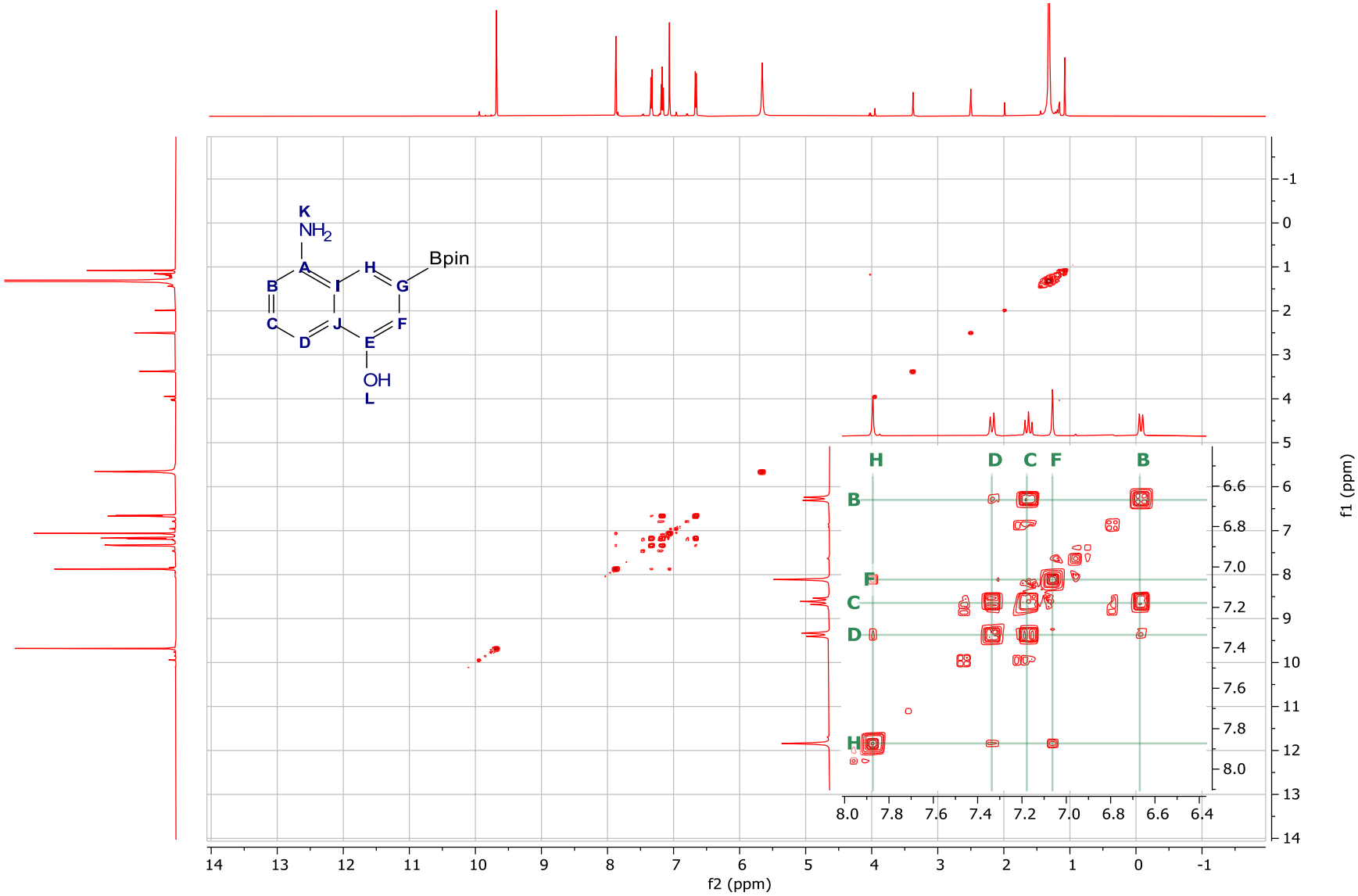
^{13}C NMR of 7-borylated 5-hydroxy-1-naphthylamine (4.2n) (DMSO-d6, 126 MHz)



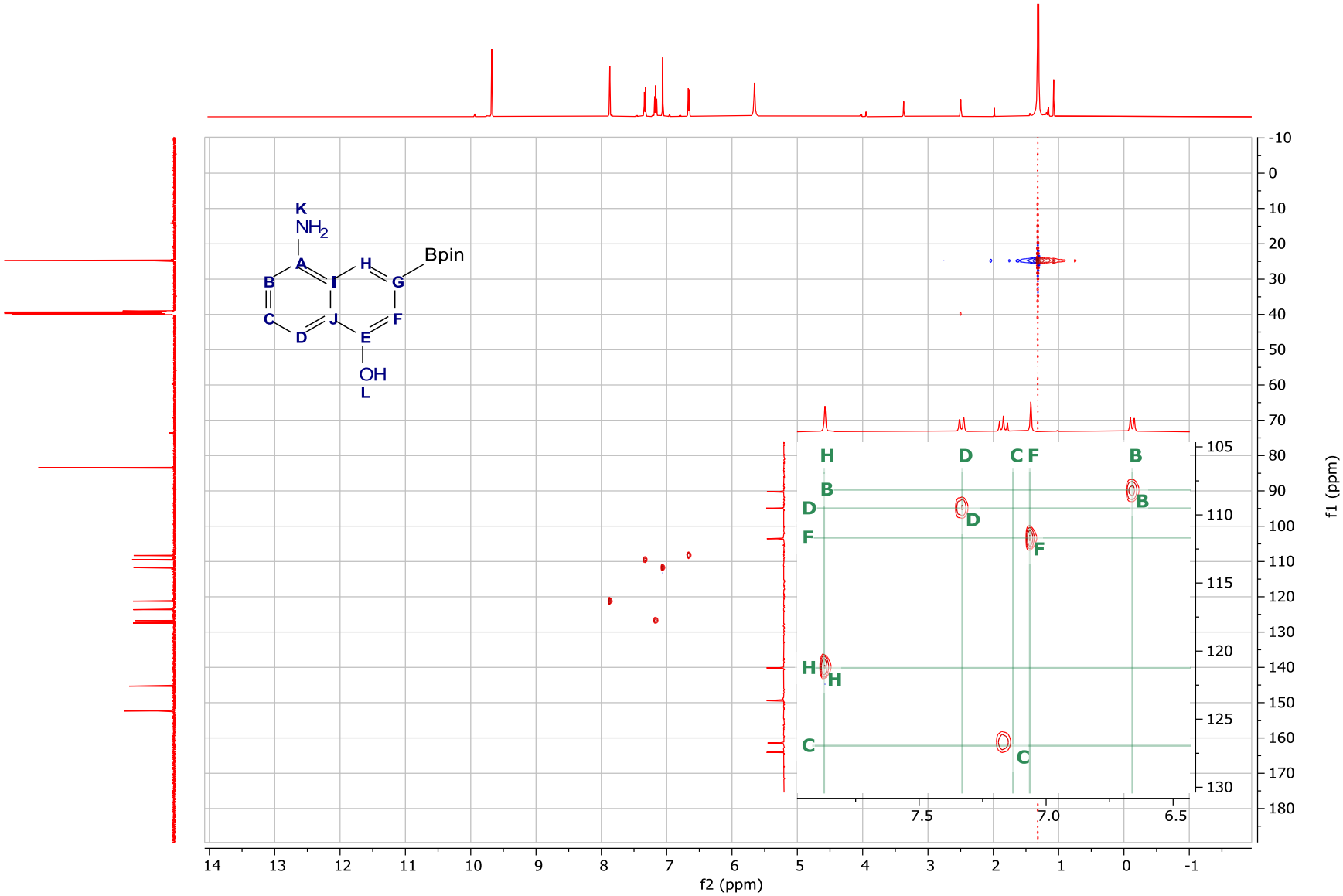
^{11}B NMR of 7-borylated 5-hydroxy-1-naphthylamine (4.2n) (DMSO-d6, 160 MHz)



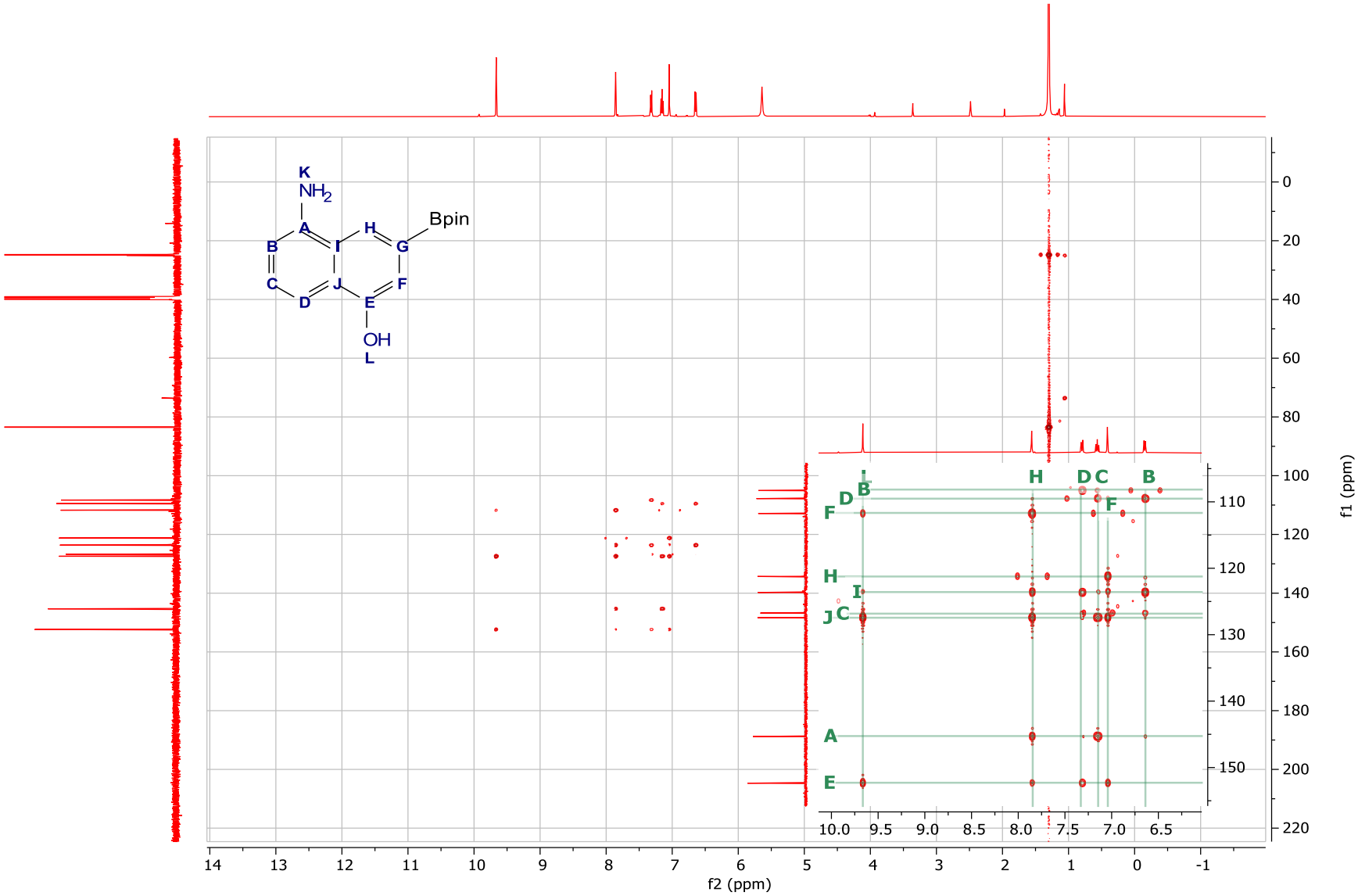
gCOSY of 7-borylated 5-hydroxy-1-naphthylamine (4.2n) (DMSO-d6, 500 MHz)



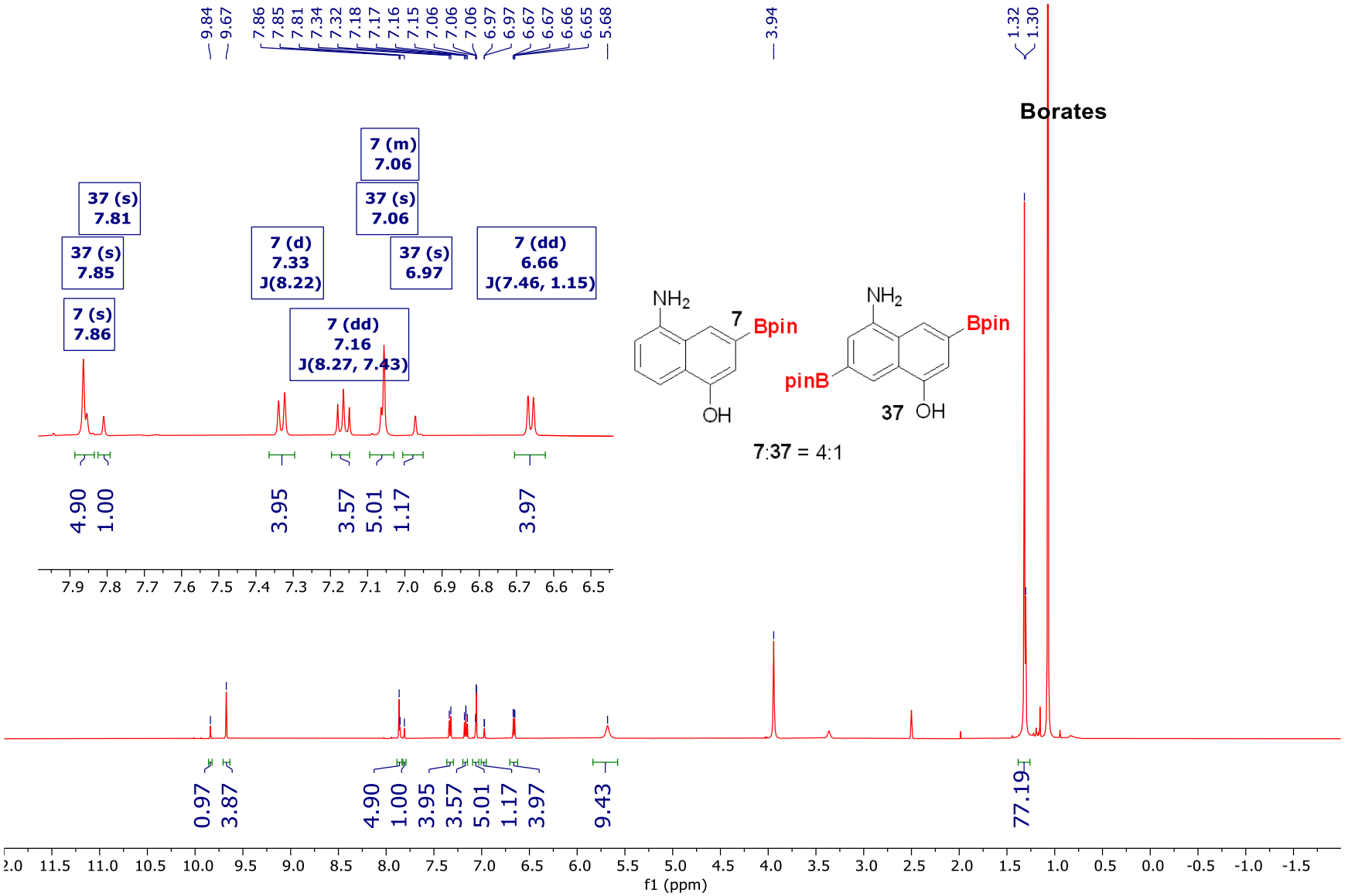
HSQCAD NMR of 7-borylated 5-hydroxy-1-naphthylamine (4.2n) (DMSO-d6, 500 MHz)



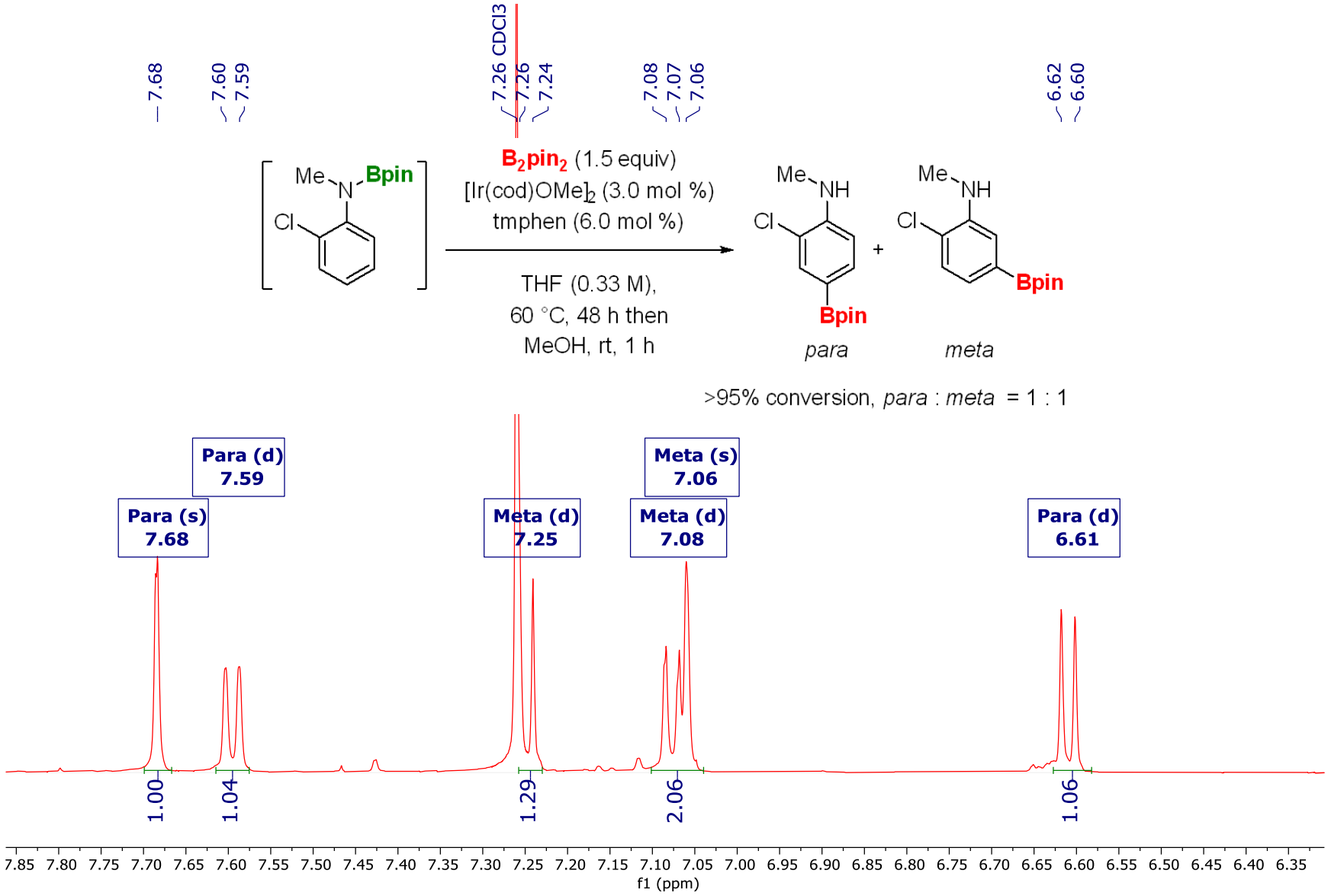
gHMBCAD NMR of 7-borylated 5-hydroxy-1-naphthylamine (4.2n) (DMSO-d6, 500 MHz)



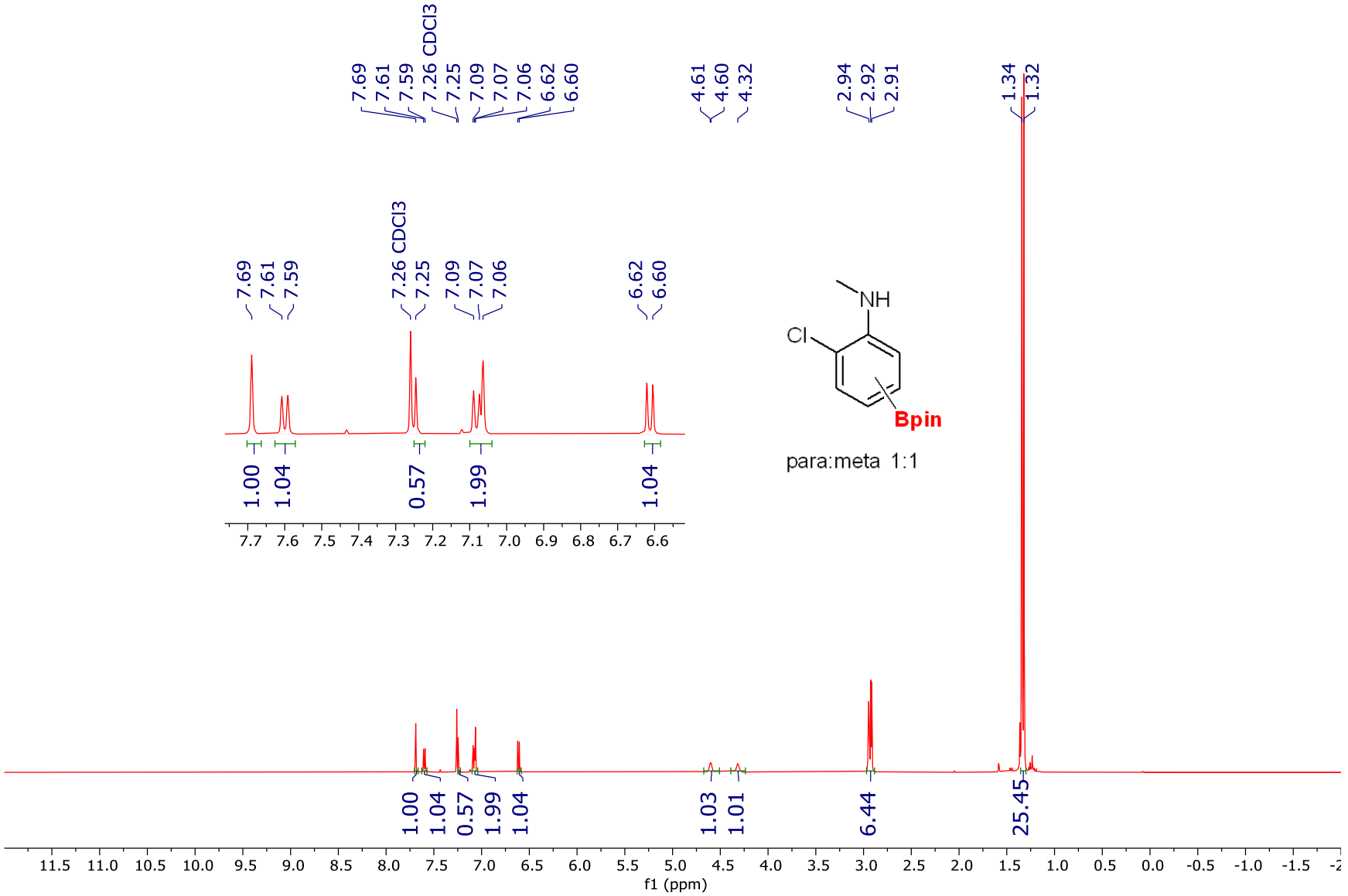
^{1}H NMR of 7-borylated and 3,7-diborylated 5-hydroxy-1-naphthylamine (4.2n) (DMSO-d6, 500 MHz)



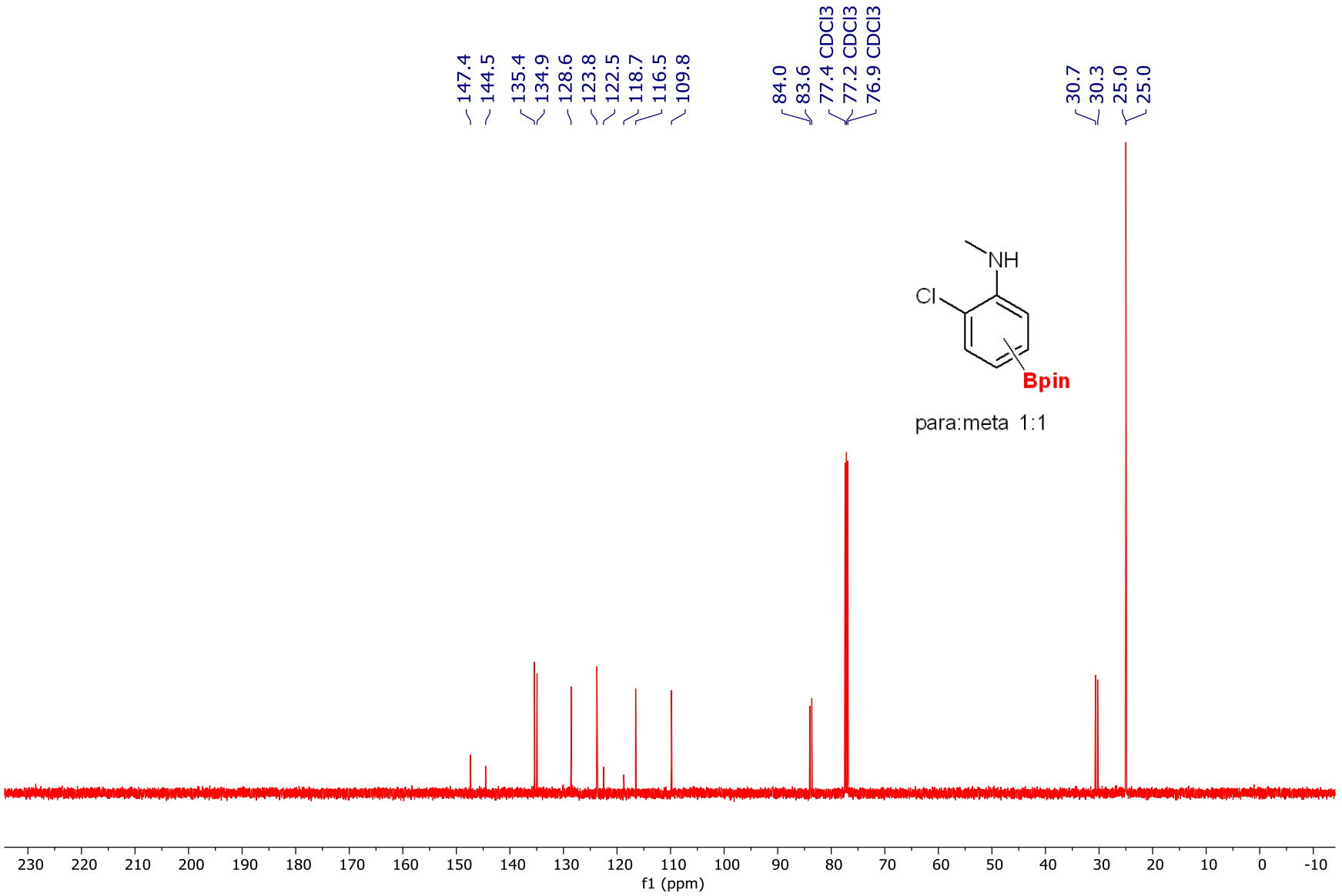
Unselective Borylation of 2-chloro-N-methylaniline (4.4a) ($CDCl_3$, 500 MHz)



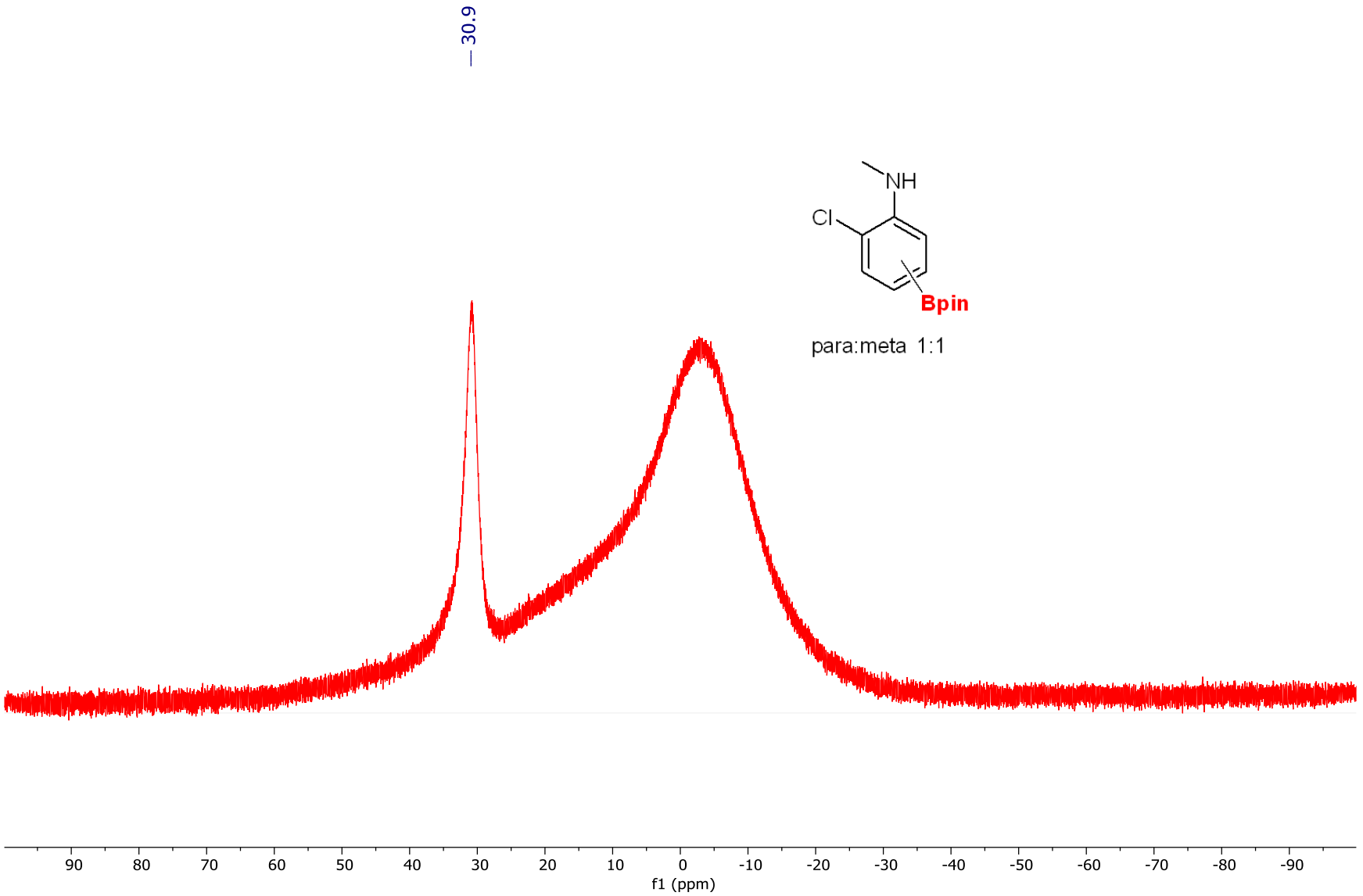
^{1}H NMR of *para* and *meta* borylated 2-chloro-N-methylaniline (4.4a) ($CDCl_3$, 500 MHz)



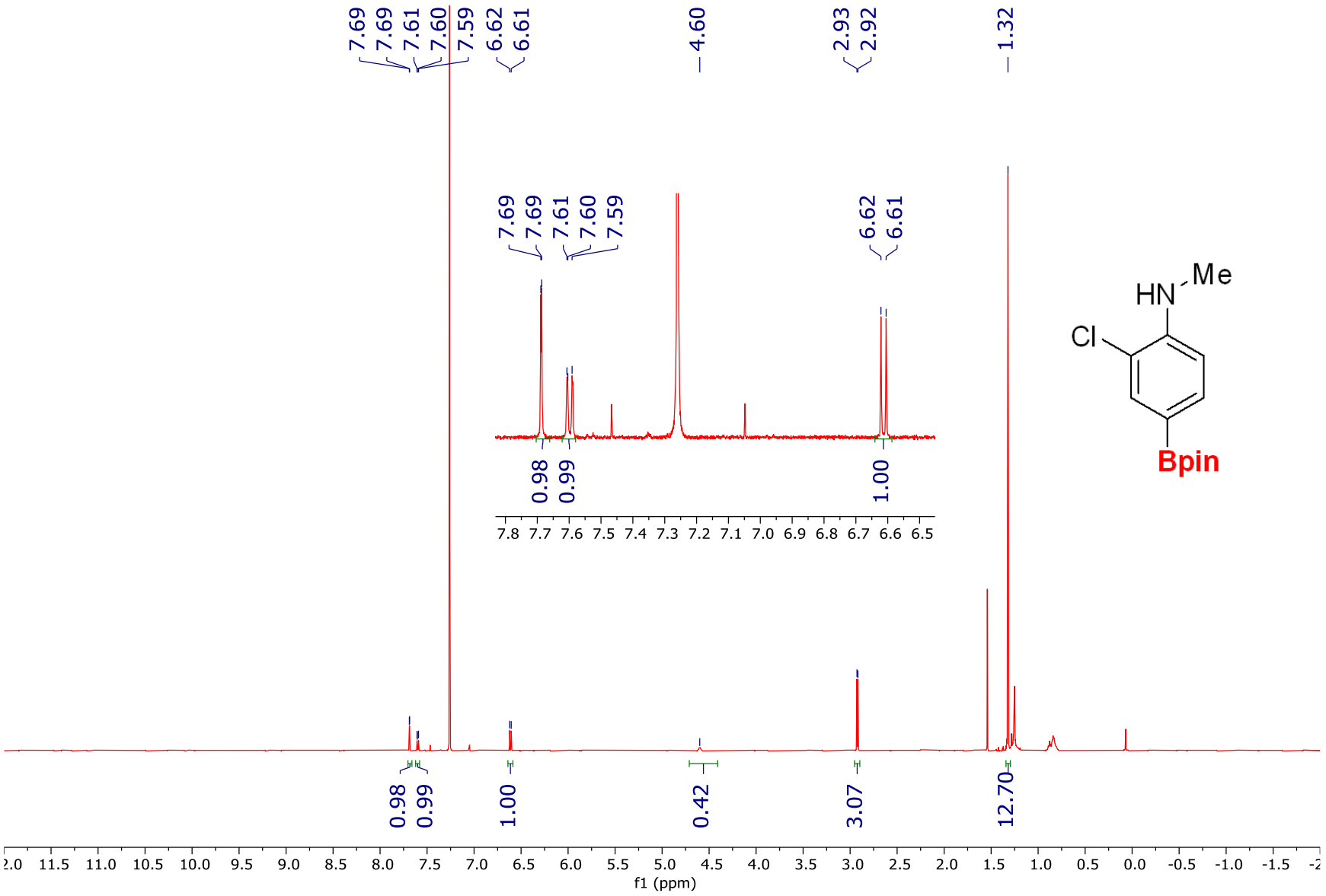
^{13}C NMR of *para* and *meta* borylated 2-chloro-N-methylaniline (4.4a) ($CDCl_3$, 126 MHz)



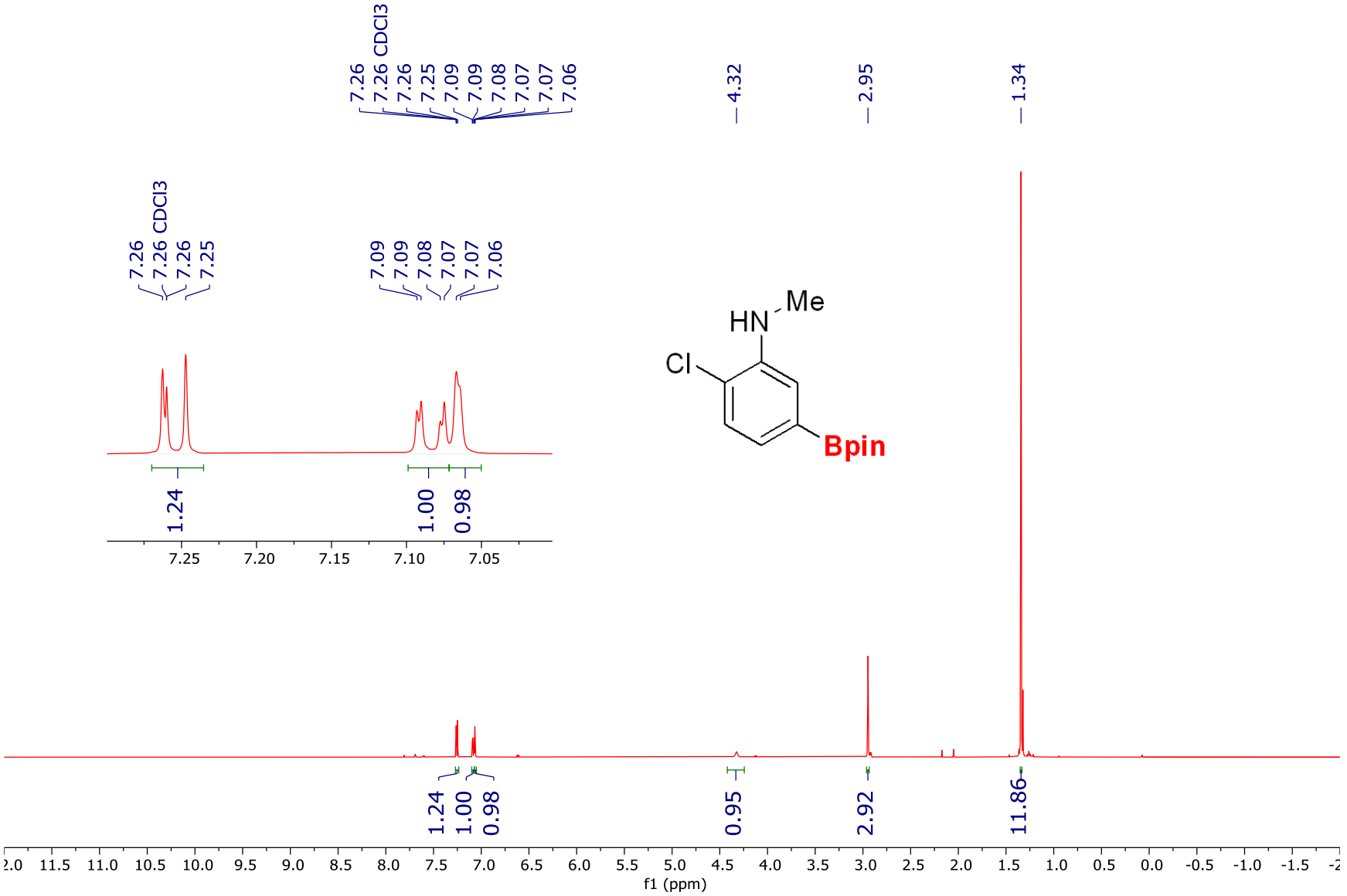
^{11}B NMR of *para* and *meta* borylated 2-chloro-N-methylaniline (4.4a) ($CDCl_3$, 126 MHz)



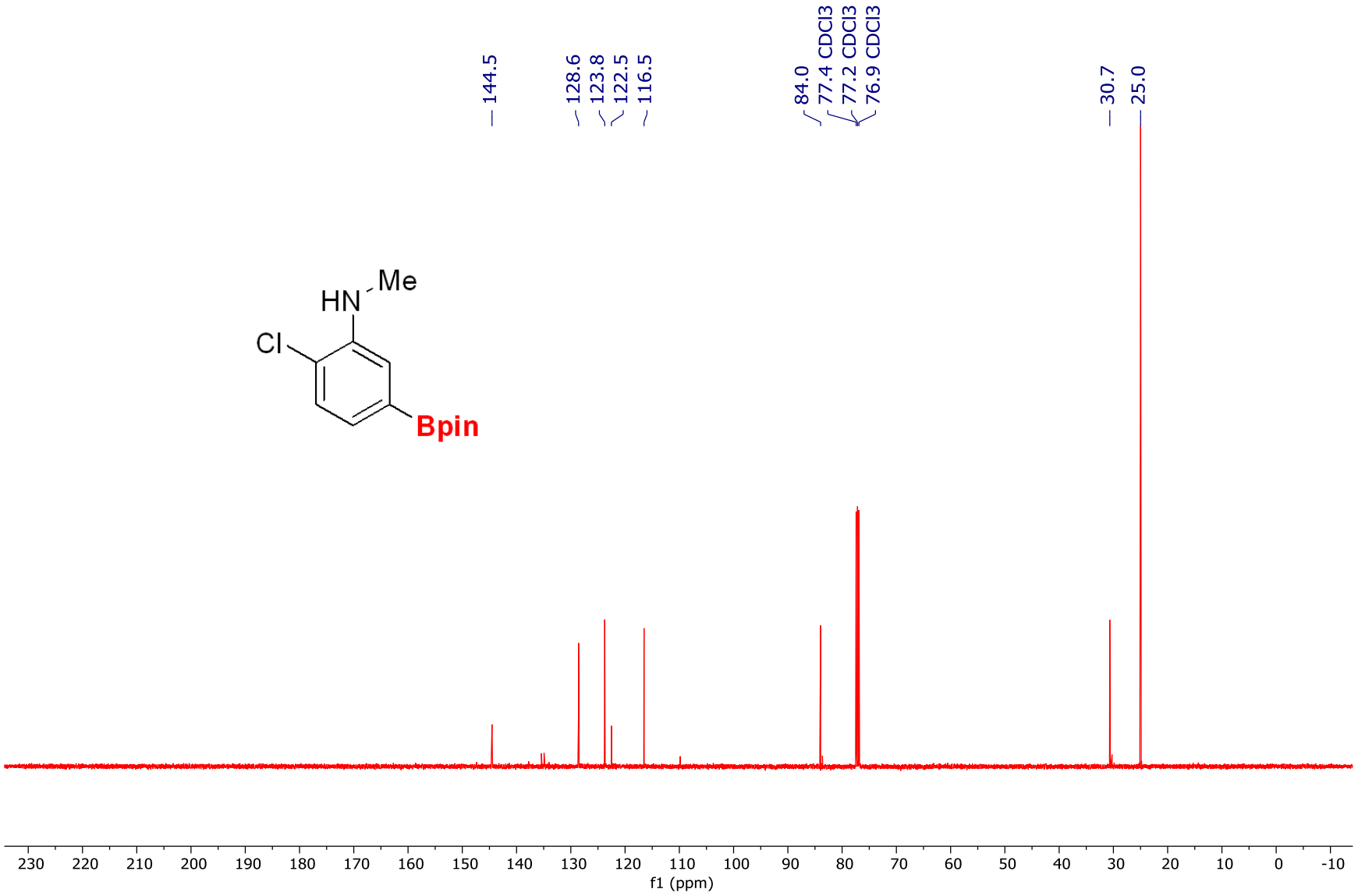
^{1}H NMR of *para* borylated 2-chloro-N-methylaniline (4.4a) ($CDCl_3$, 500 MHz)



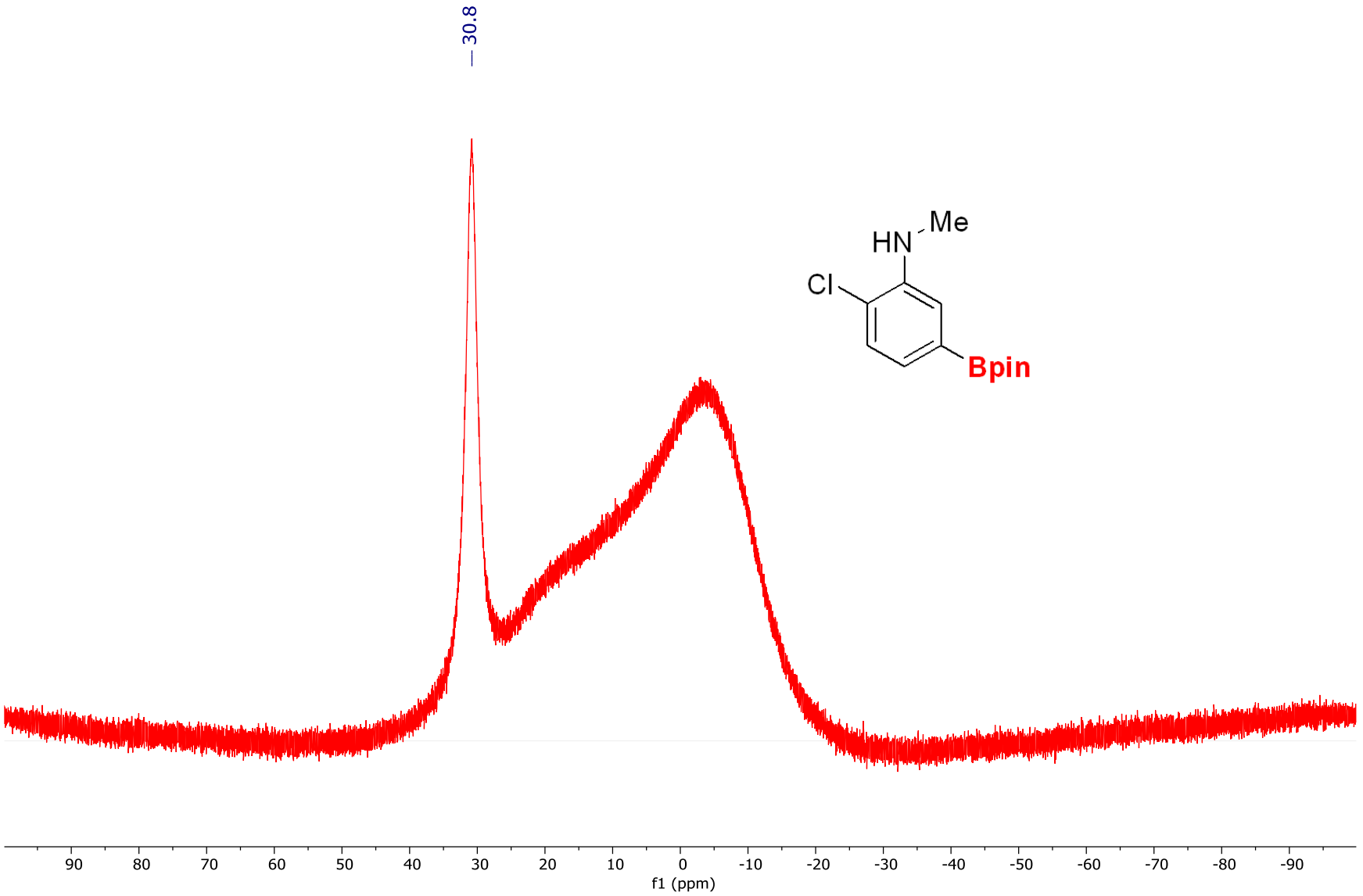
^{1}H NMR of *meta* borylated 2-chloro-N-methylaniline (4.4a) ($CDCl_3$, 500 MHz)



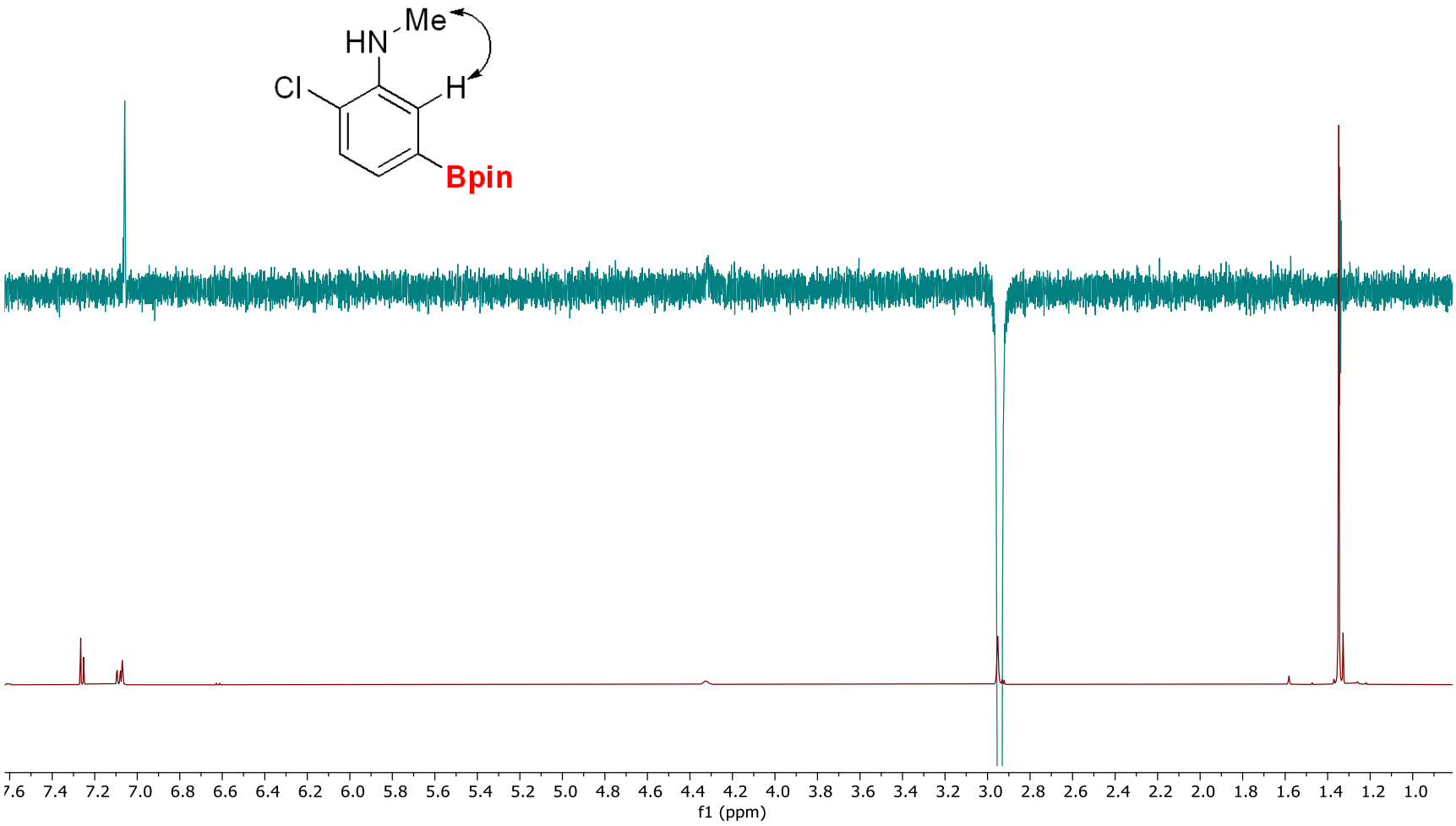
^{13}C NMR of *meta* borylated 2-chloro-N-methylaniline (4.4a) ($CDCl_3$, 126 MHz)



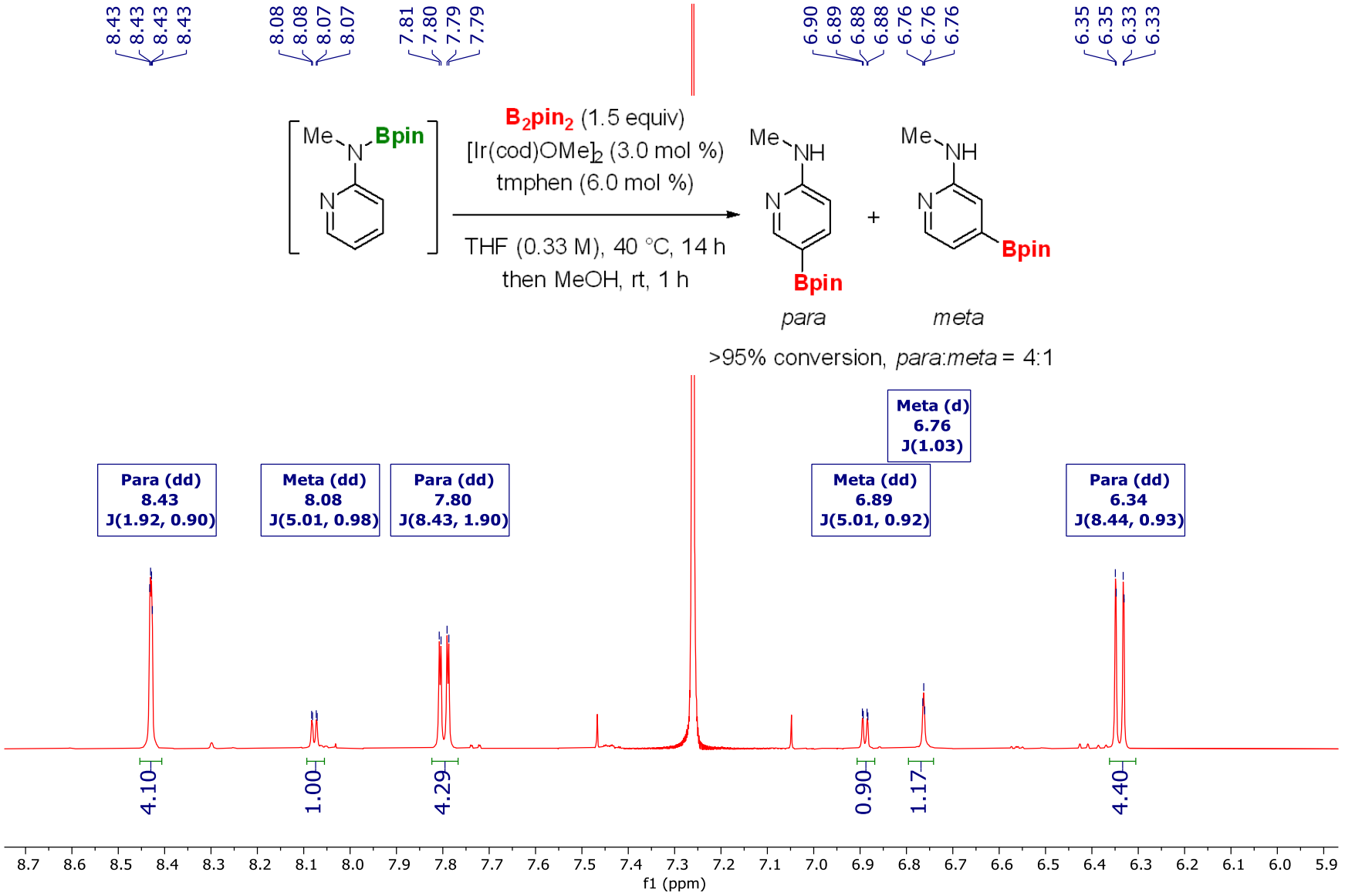
^{11}B NMR of *meta* borylated 2-chloro-N-methylaniline (4.4a) ($CDCl_3$, 126 MHz)



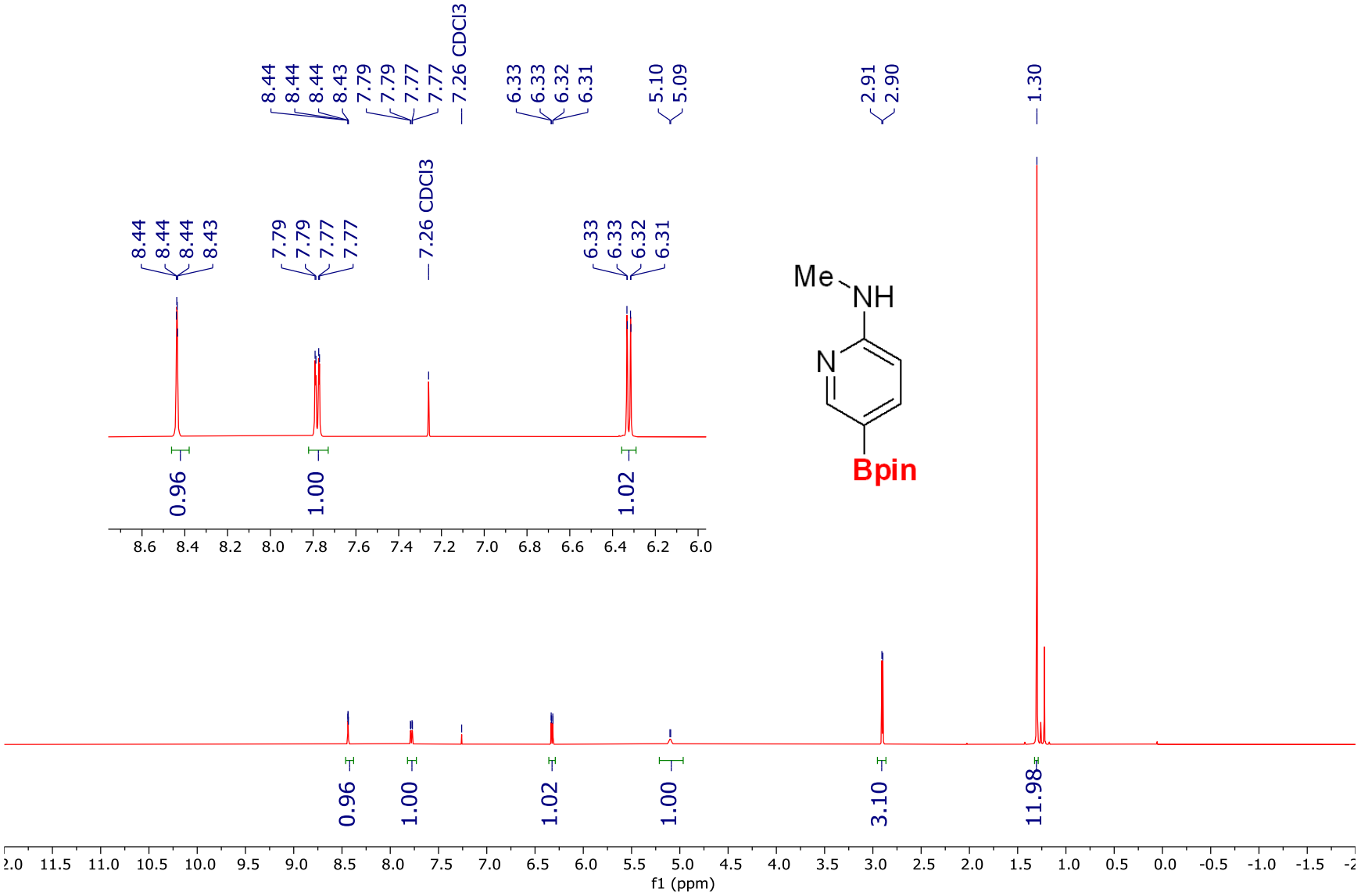
1D-NOE of *meta* borylated 2-chloro-N-methylaniline (4.4a) ($CDCl_3$, 500 MHz)



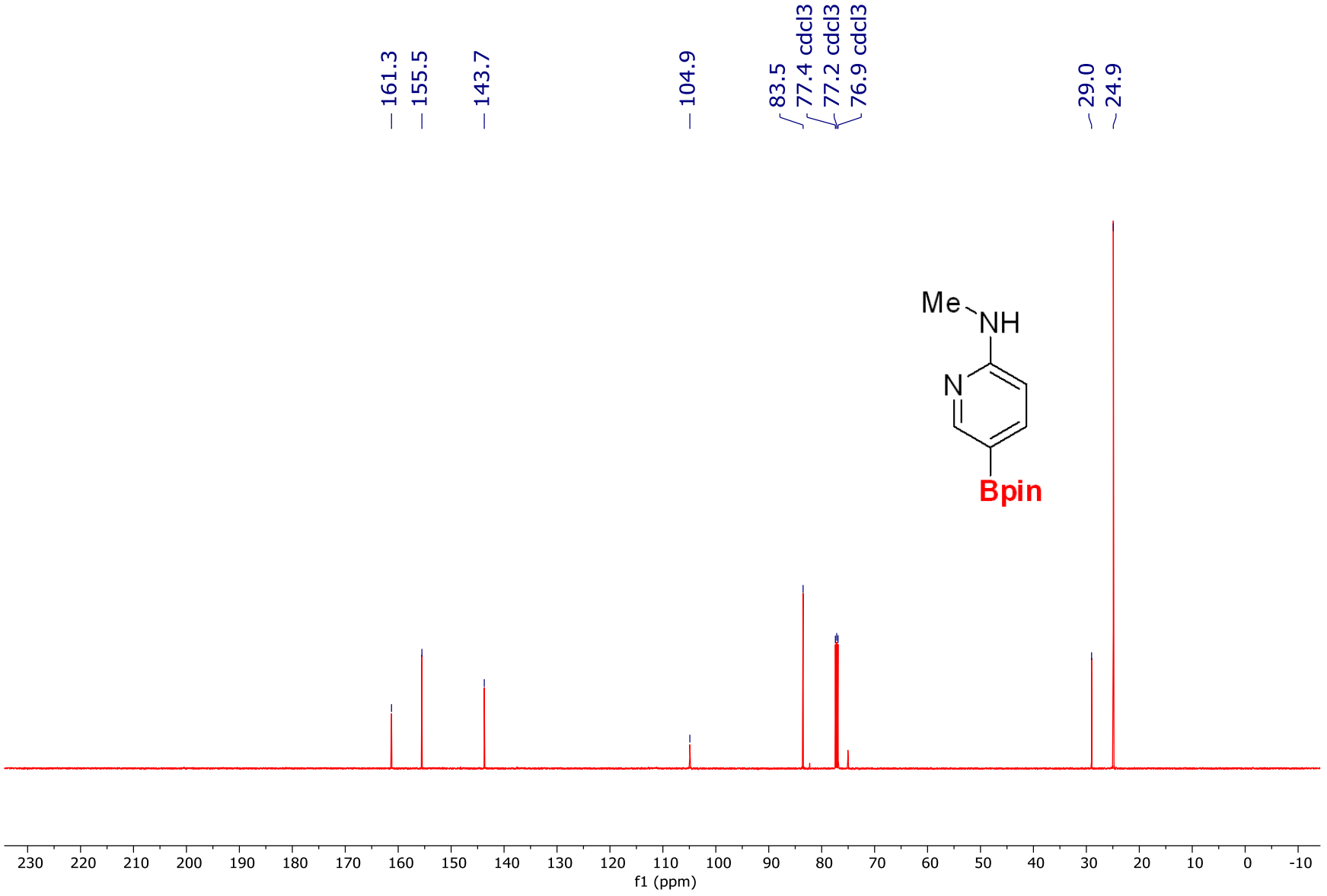
***Para* CHB of 2-amino-N-methylpyridine (4.4b) ($CDCl_3$, 500 MHz)**



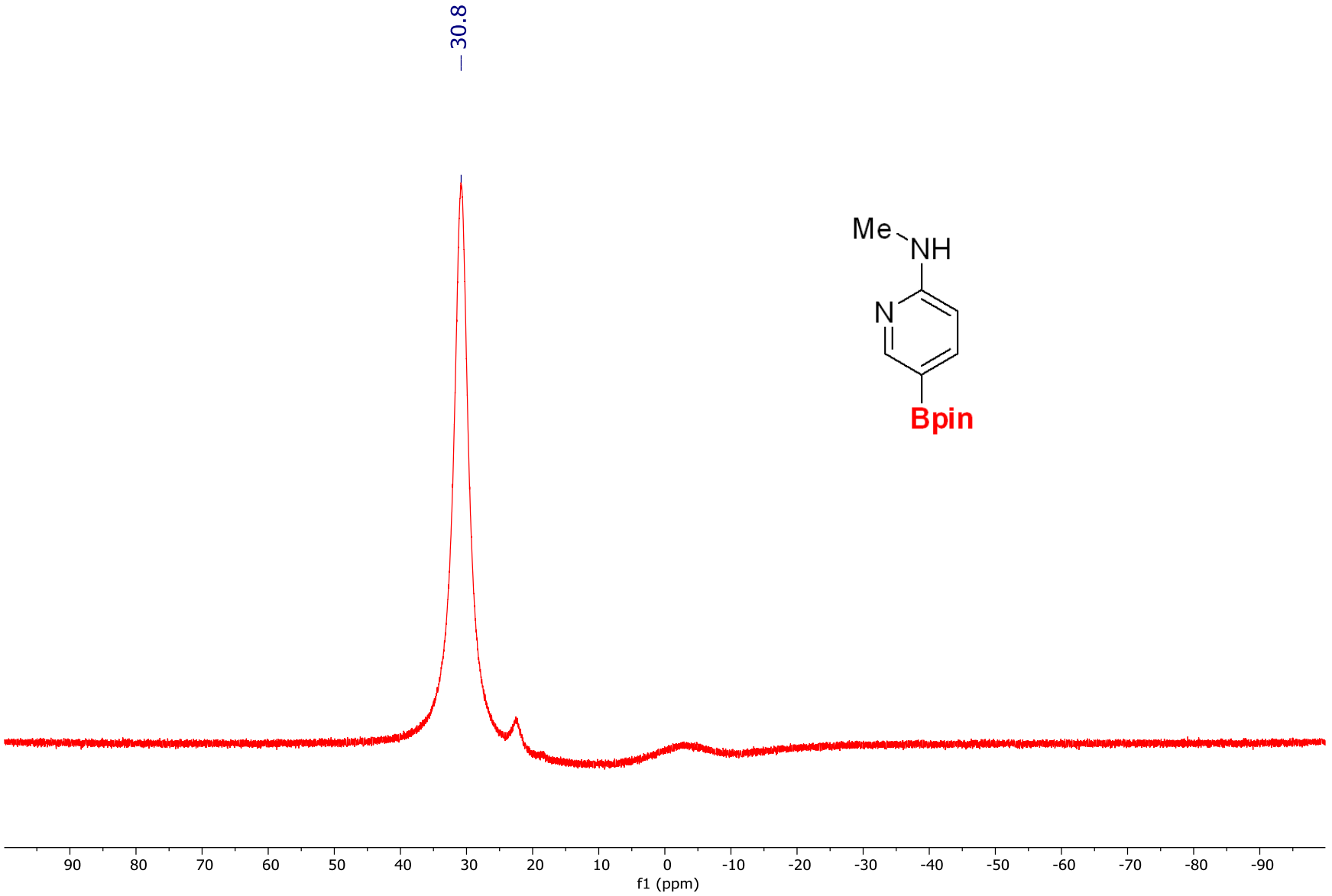
^{1}H NMR of *para* borylated 2-amino-N-methylpyridine (4.4b) ($CDCl_3$, 500 MHz)



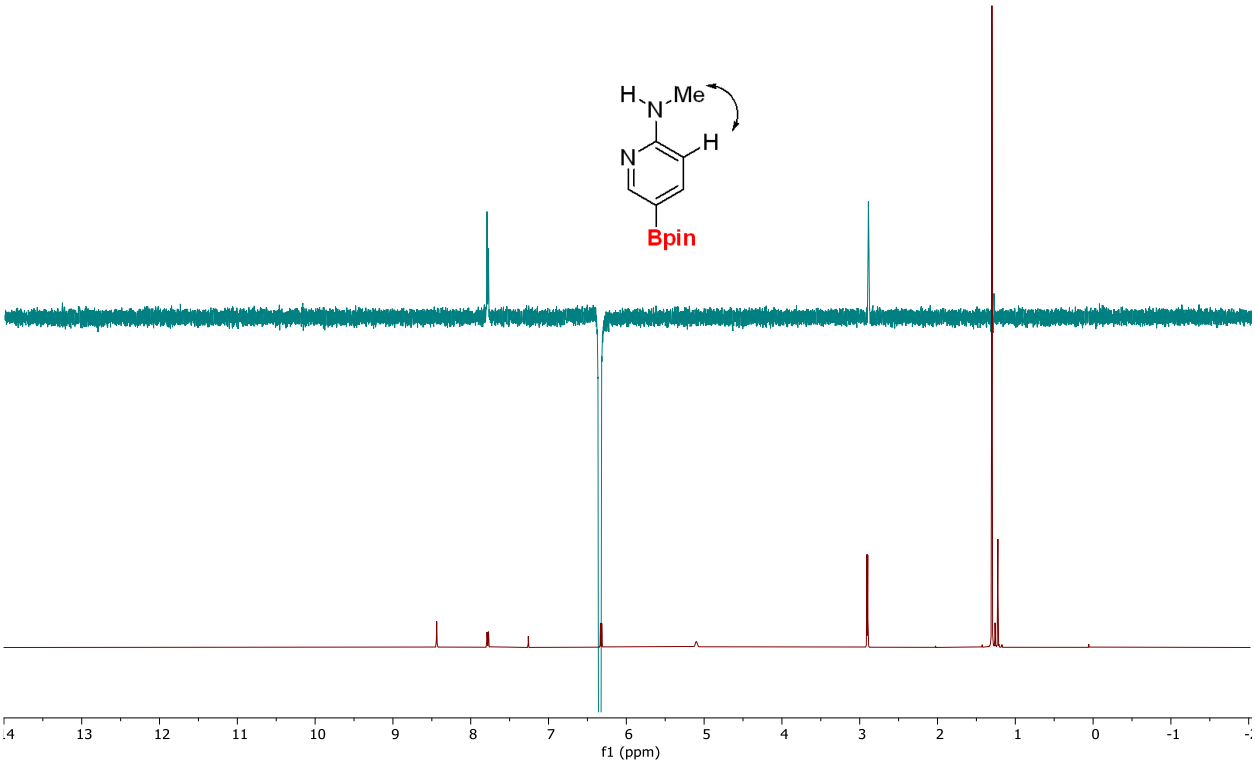
^{13}C NMR of *para* borylated 2-amino-N-methylpyridine (4.4b) ($CDCl_3$, 126 MHz)

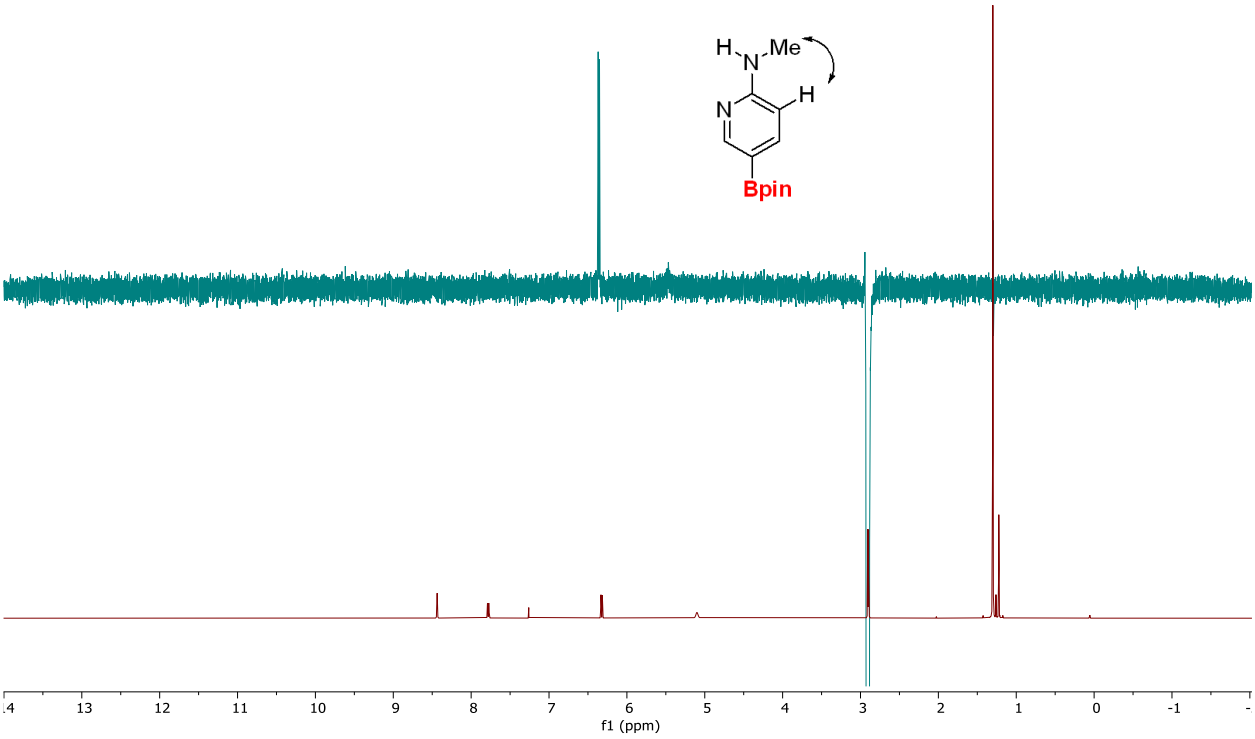


^{11}B NMR of *para* borylated 2-amino-N-methylpyridine (4.4b) ($CDCl_3$, 160 MHz)

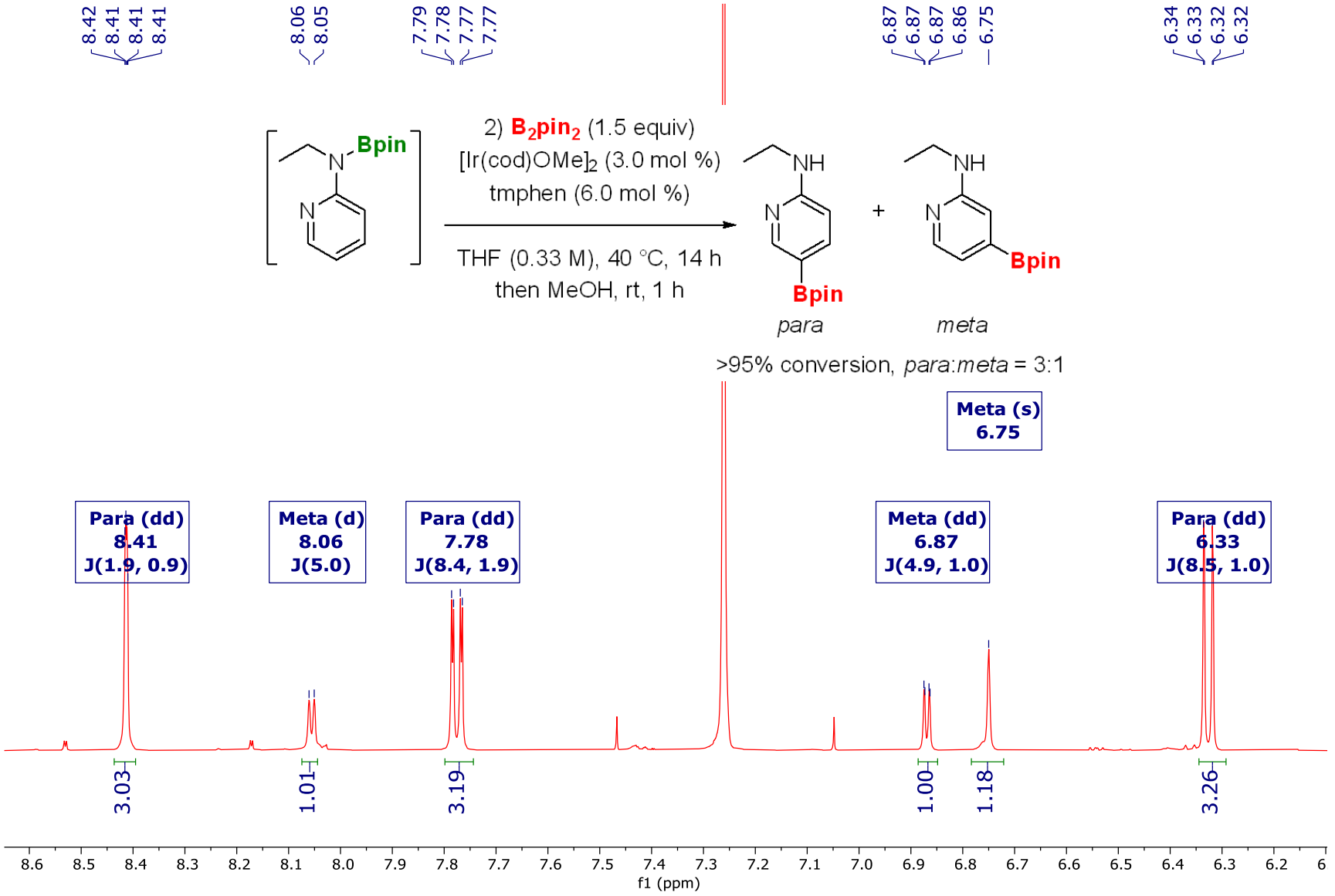


1D-NOE of *para* borylated 2-amino-N-methylpyridine (4.4b) ($CDCl_3$, 500 MHz)

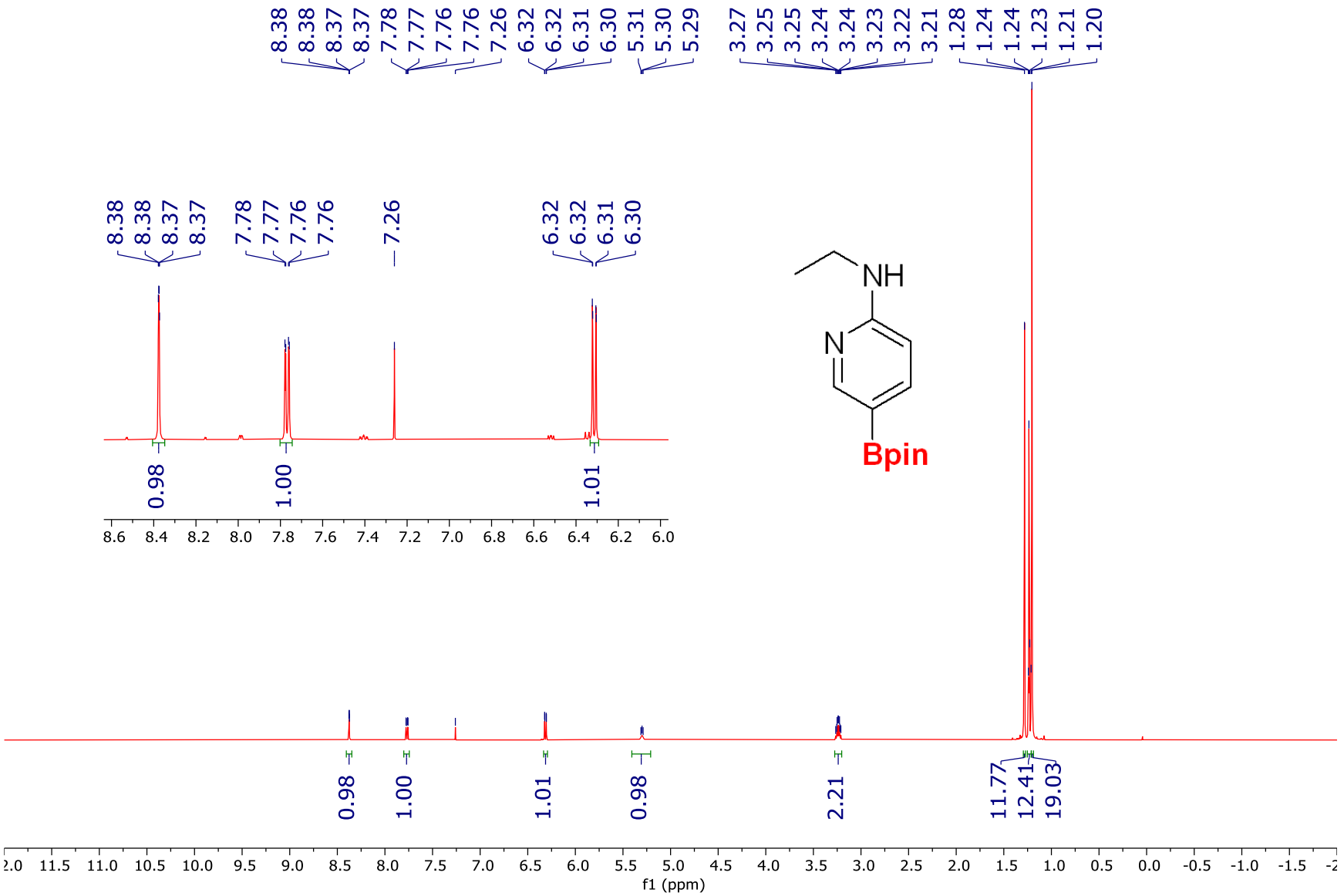




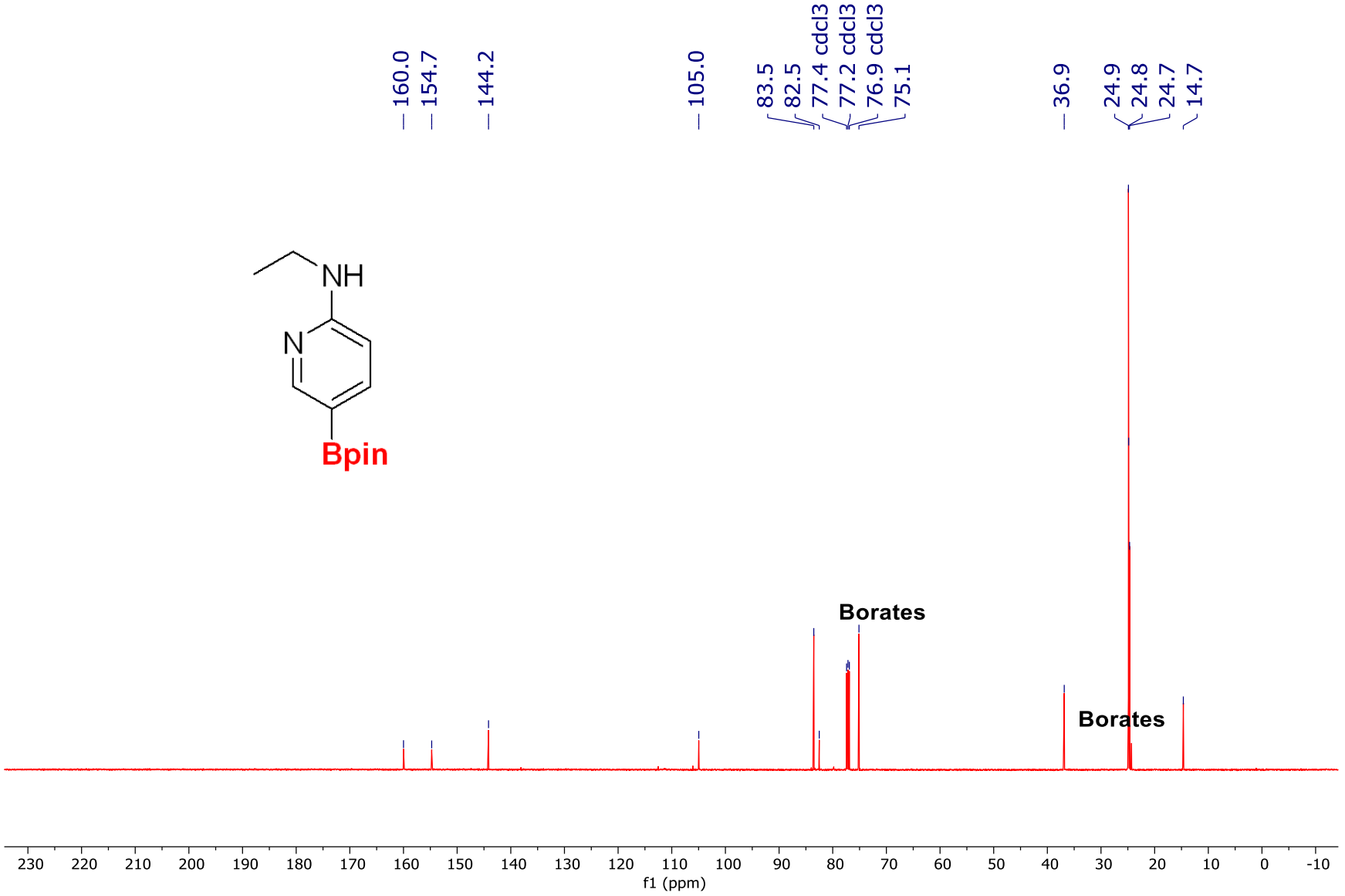
***Para* CHB of 2-amino-N-ethylpyridine (4.4c) ($CDCl_3$, 500 MHz)**



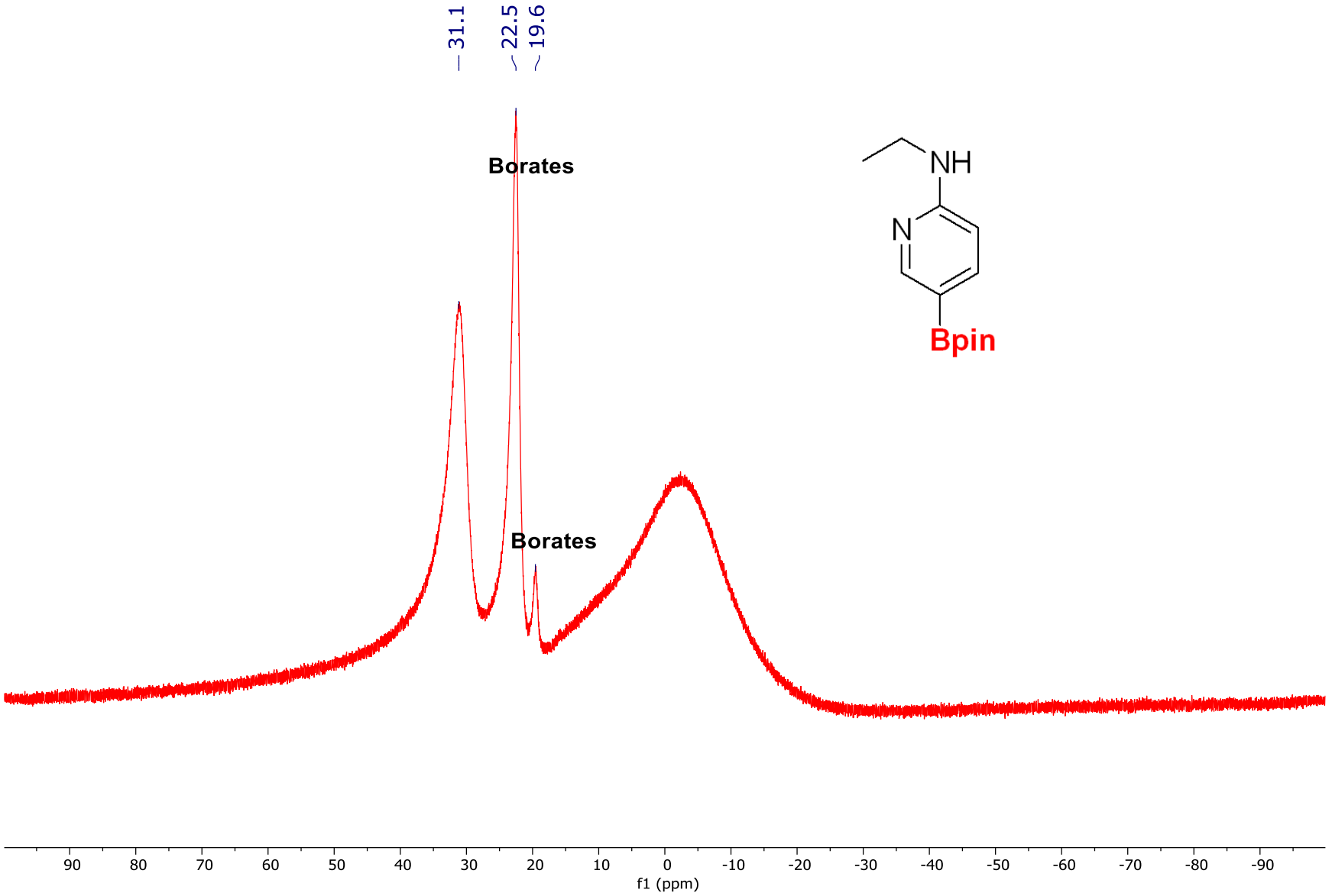
^{1}H NMR of *para* borylated 2-amino-N-ethylpyridine (4.4c) ($CDCl_3$, 500 MHz)



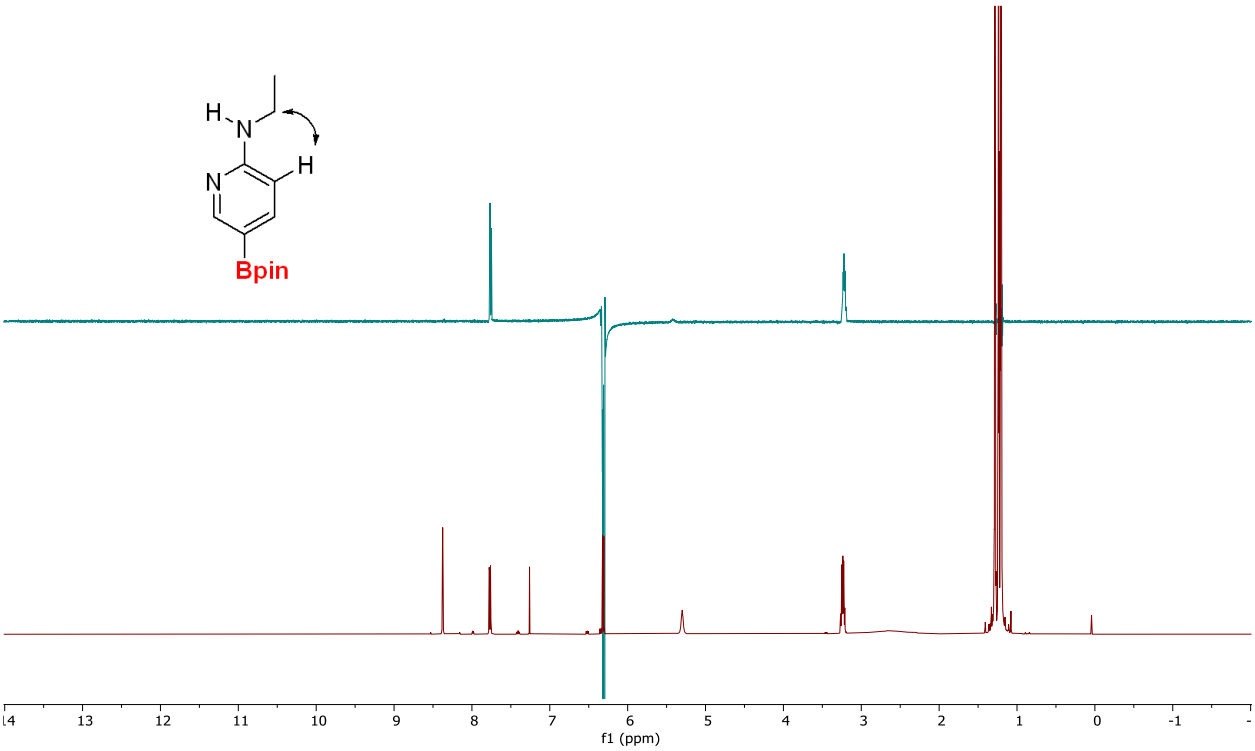
^{13}C NMR of *para* borylated 2-amino-N-ethylpyridine (4.4c) ($CDCl_3$, 126 MHz)

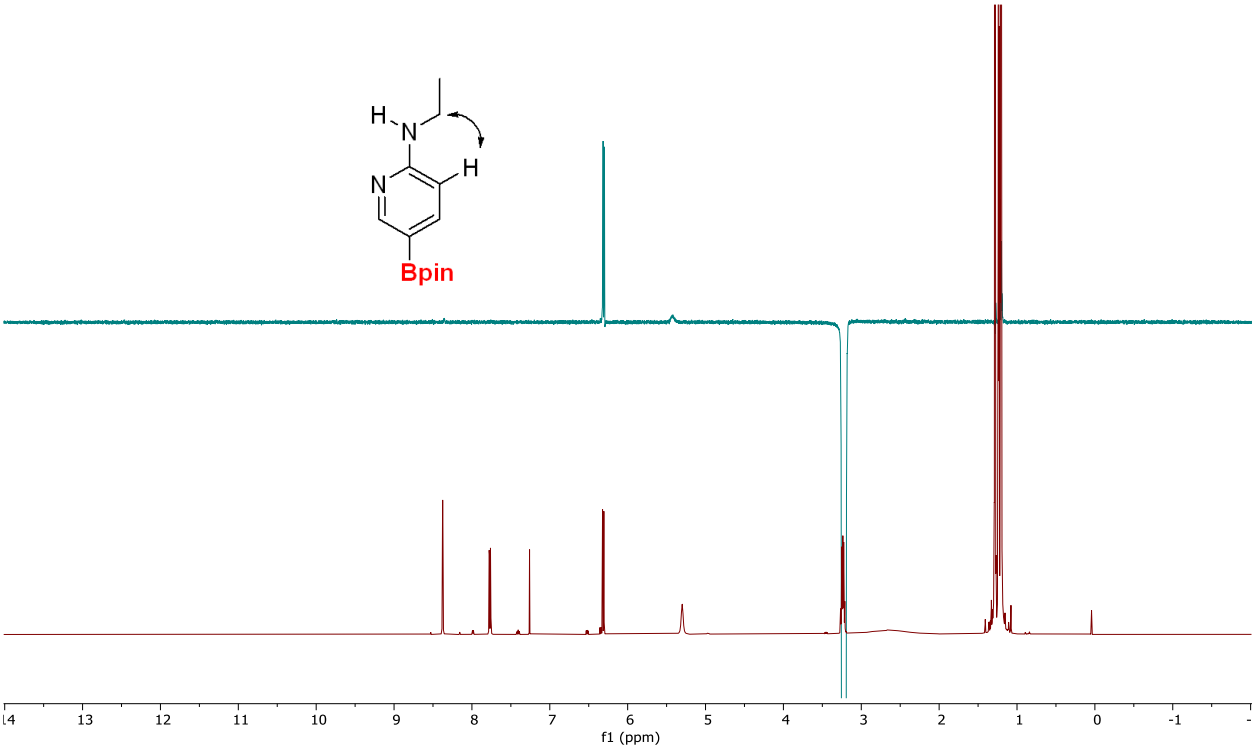


^{11}B NMR of *para* borylated 2-amino-N-ethylpyridine (4.4c) ($CDCl_3$, 160 MHz)

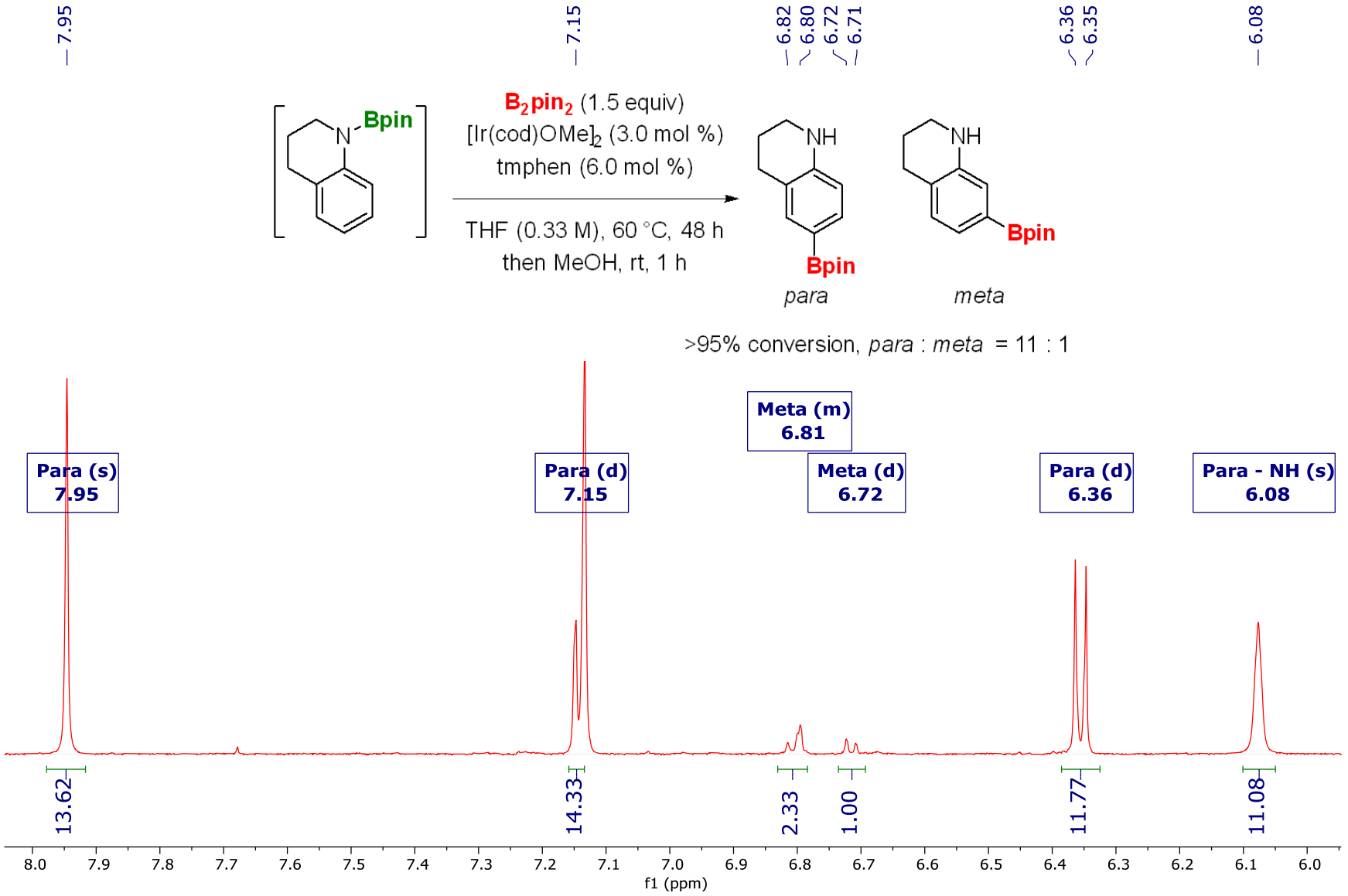


1D-NOE of *para* borylated 2-amino-N-ethylpyridine (4.4c) ($CDCl_3$, 500 MHz)

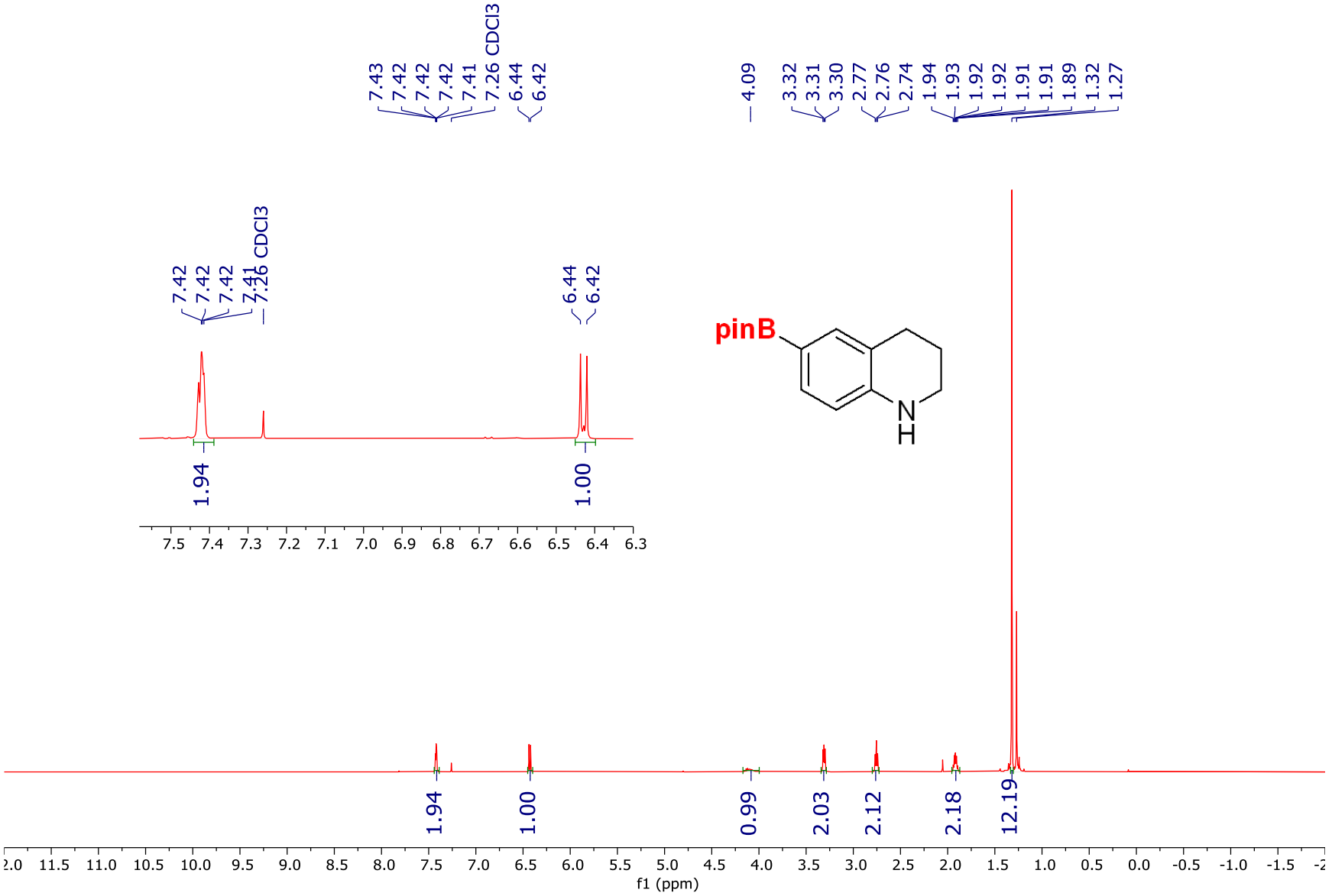




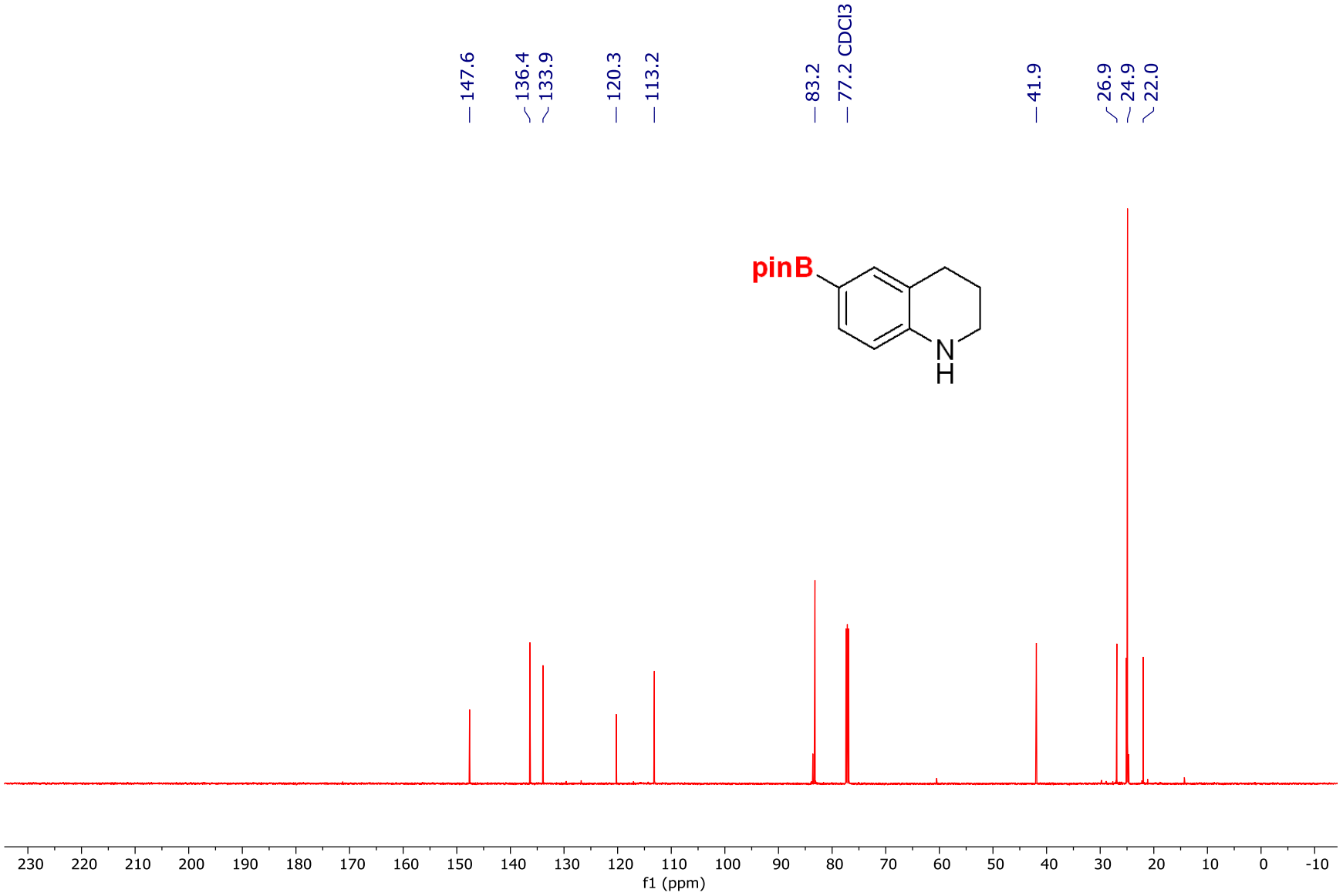
***Para* CHB of 1,2,3,4-tetrahydroquinoline (4.4d) (DMSO-d6, 500 MHz)**



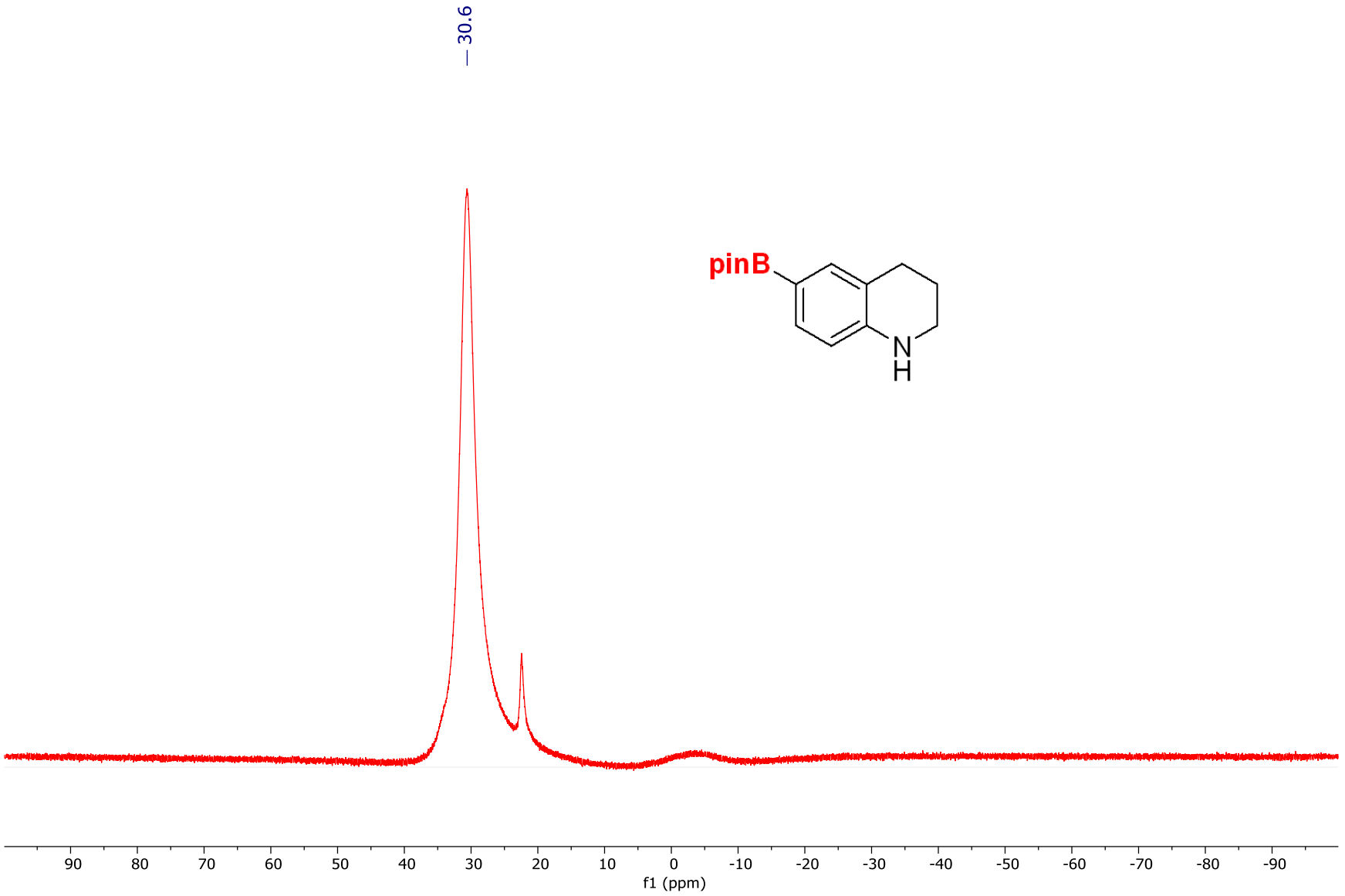
^{1}H NMR of *para* borylated 1,2,3,4-tetrahydroquinoline (4.4d) ($CDCl_3$, 500 MHz)



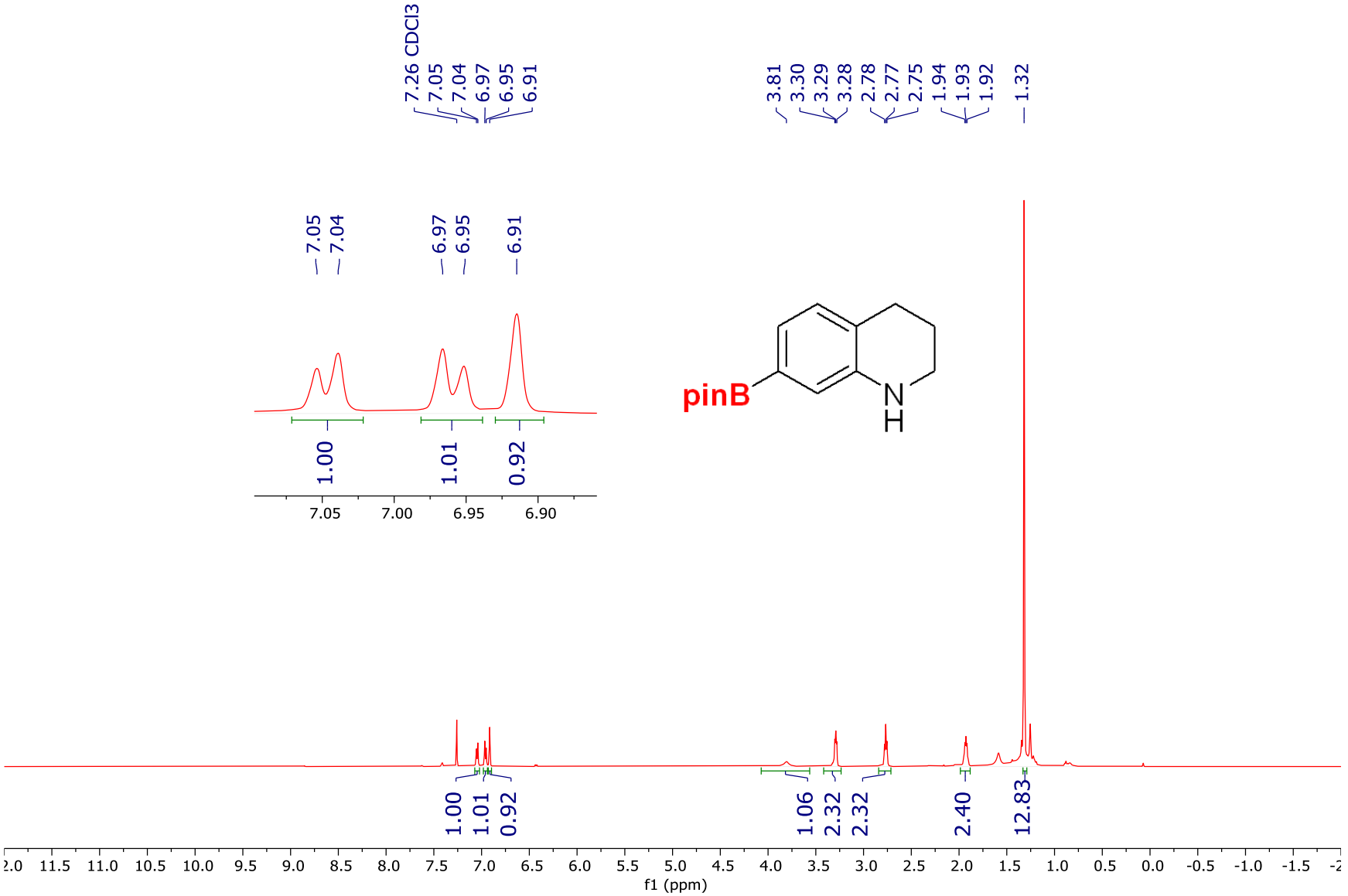
^{13}C NMR of *para* borylated 1,2,3,4-tetrahydroquinoline (4.4d) ($CDCl_3$, 126 MHz)



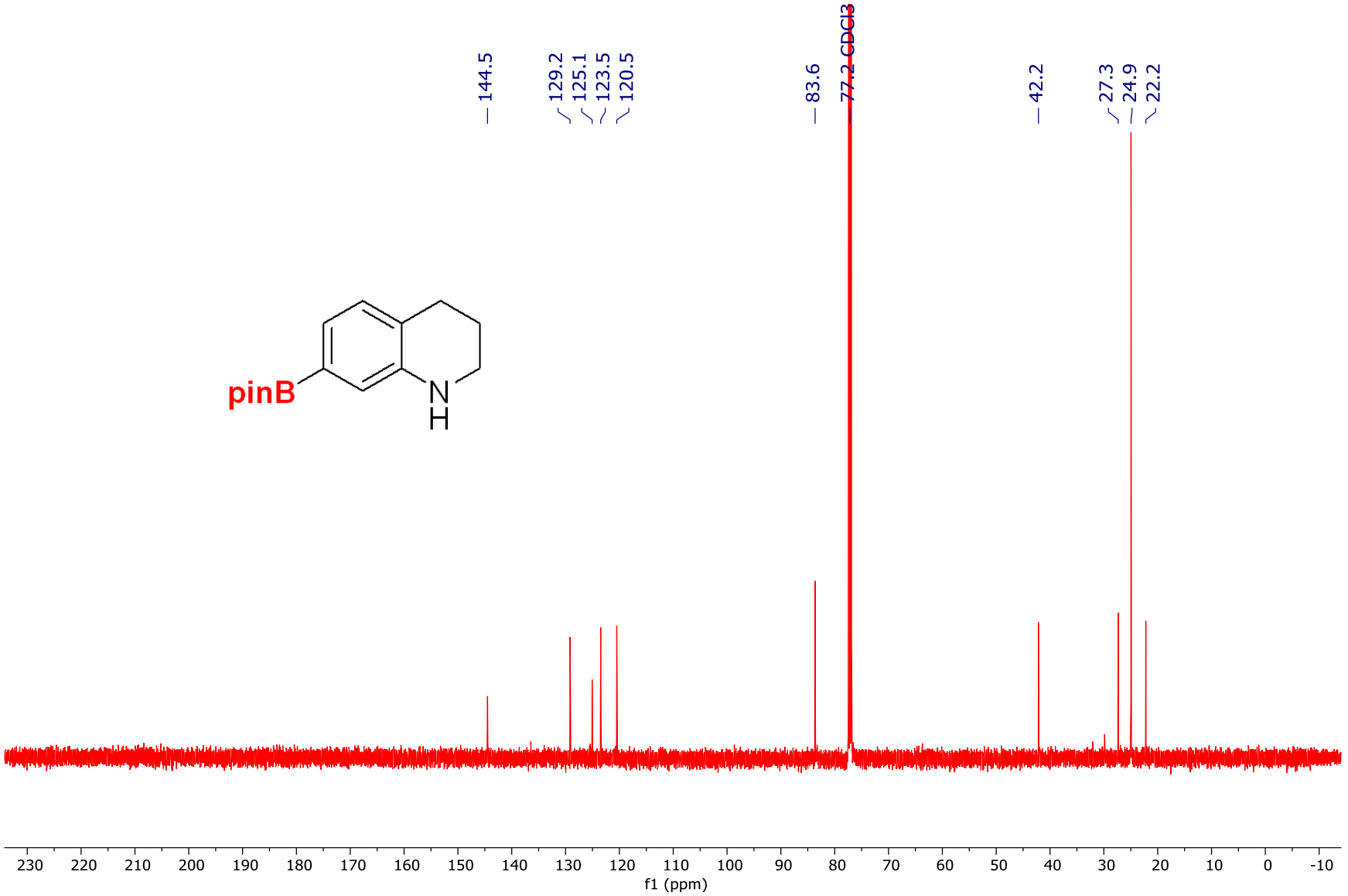
^{11}B NMR of *para* borylated 1,2,3,4-tetrahydroquinoline (4.4d) ($CDCl_3$, 126 MHz)



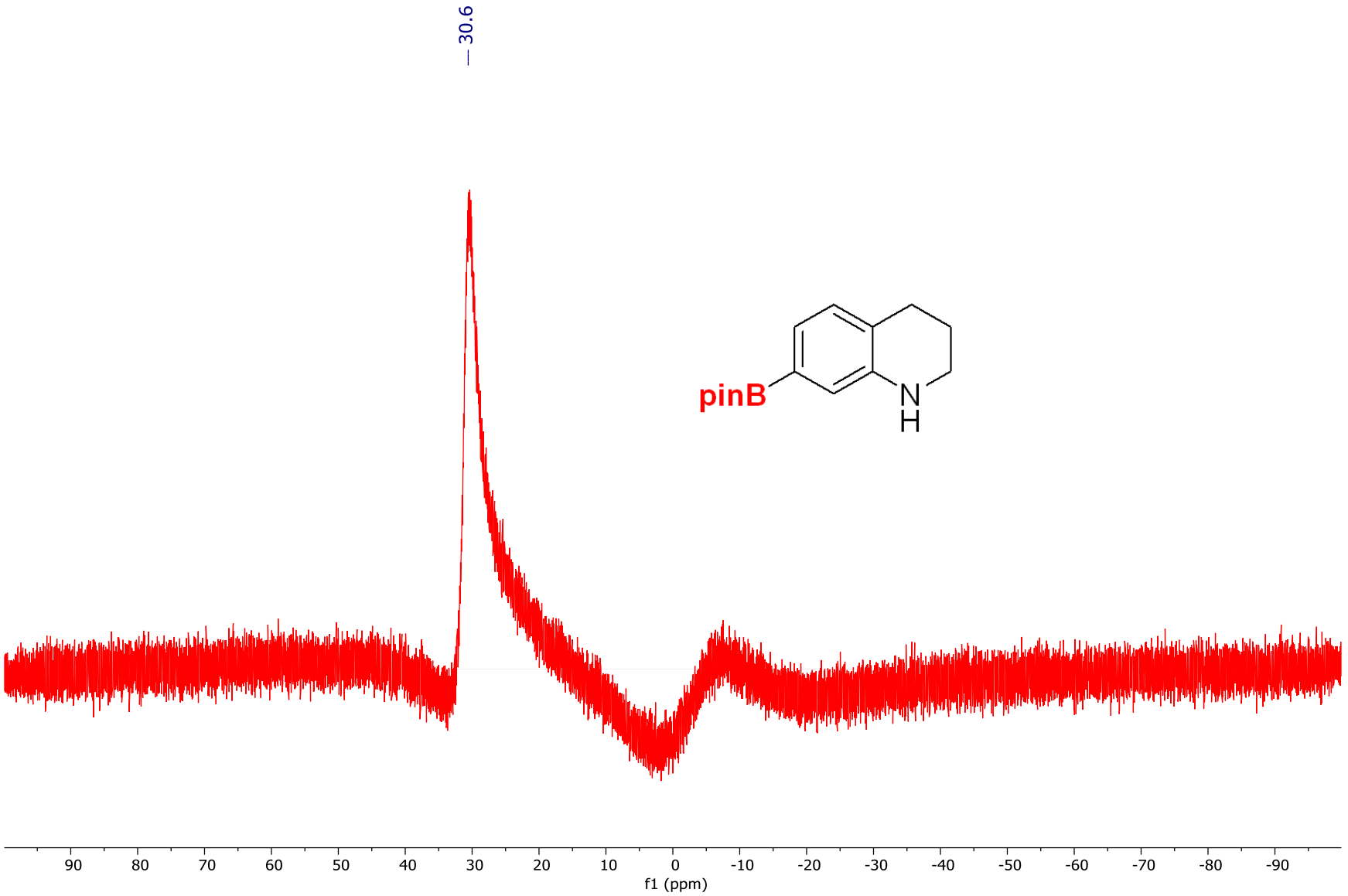
^{1}H NMR of *meta* borylated 1,2,3,4-tetrahydroquinoline (4.4d) ($CDCl_3$, 500 MHz)



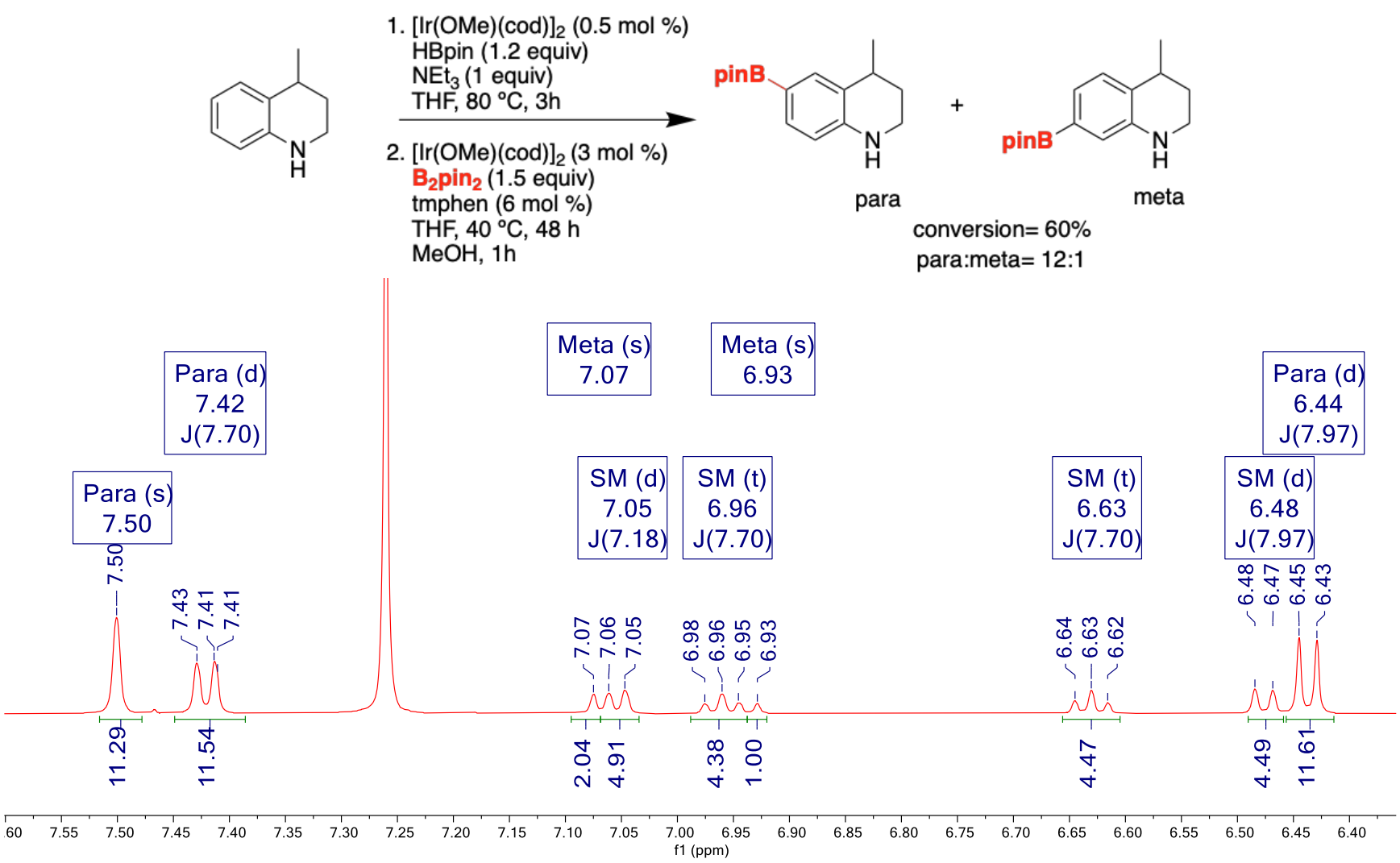
^{13}C NMR of *meta* borylated 1,2,3,4-tetrahydroquinoline (4.4d) ($CDCl_3$, 126 MHz)



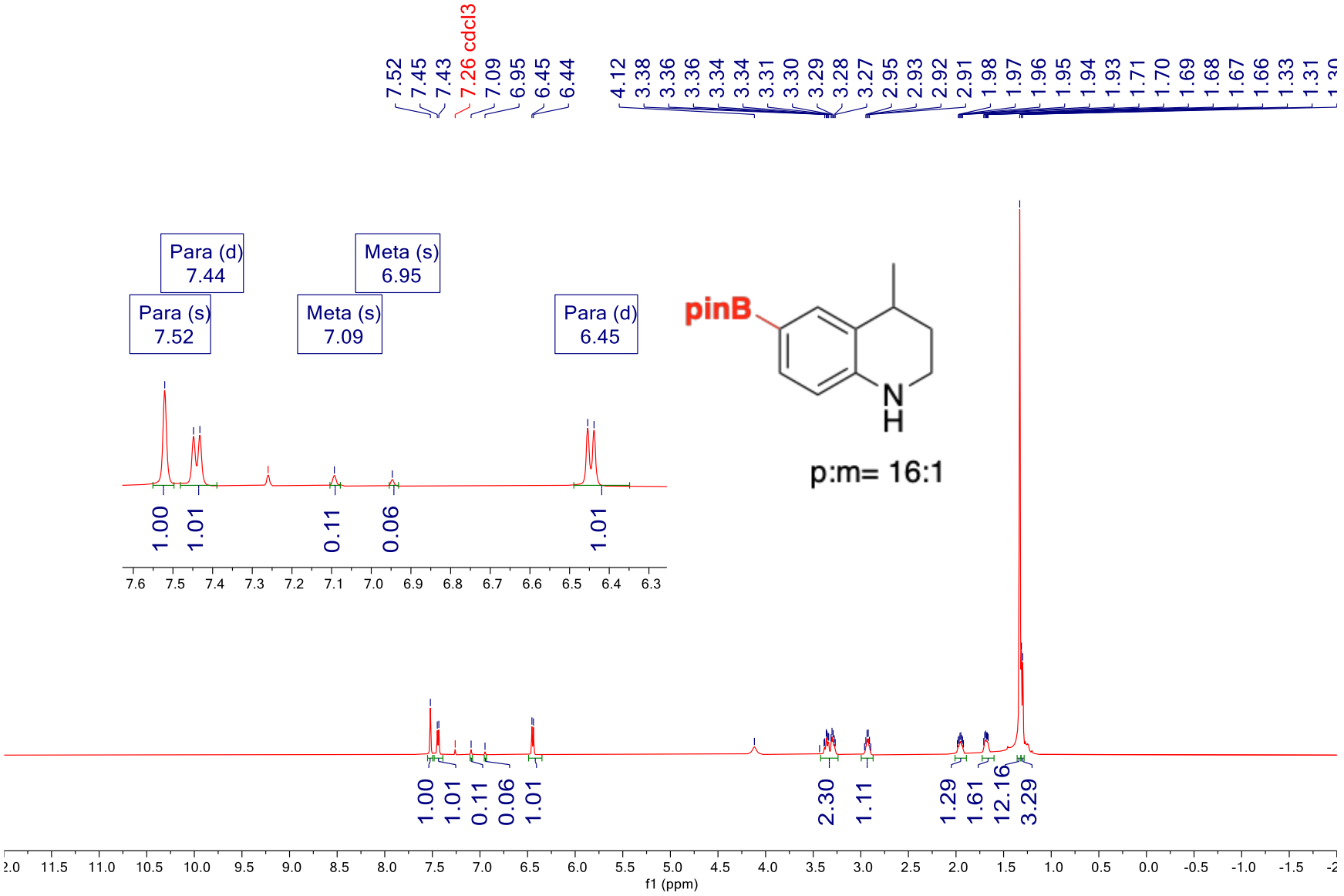
^{11}B NMR of *meta* borylated 1,2,3,4-tetrahydroquinoline (4.4d) ($CDCl_3$, 126 MHz)



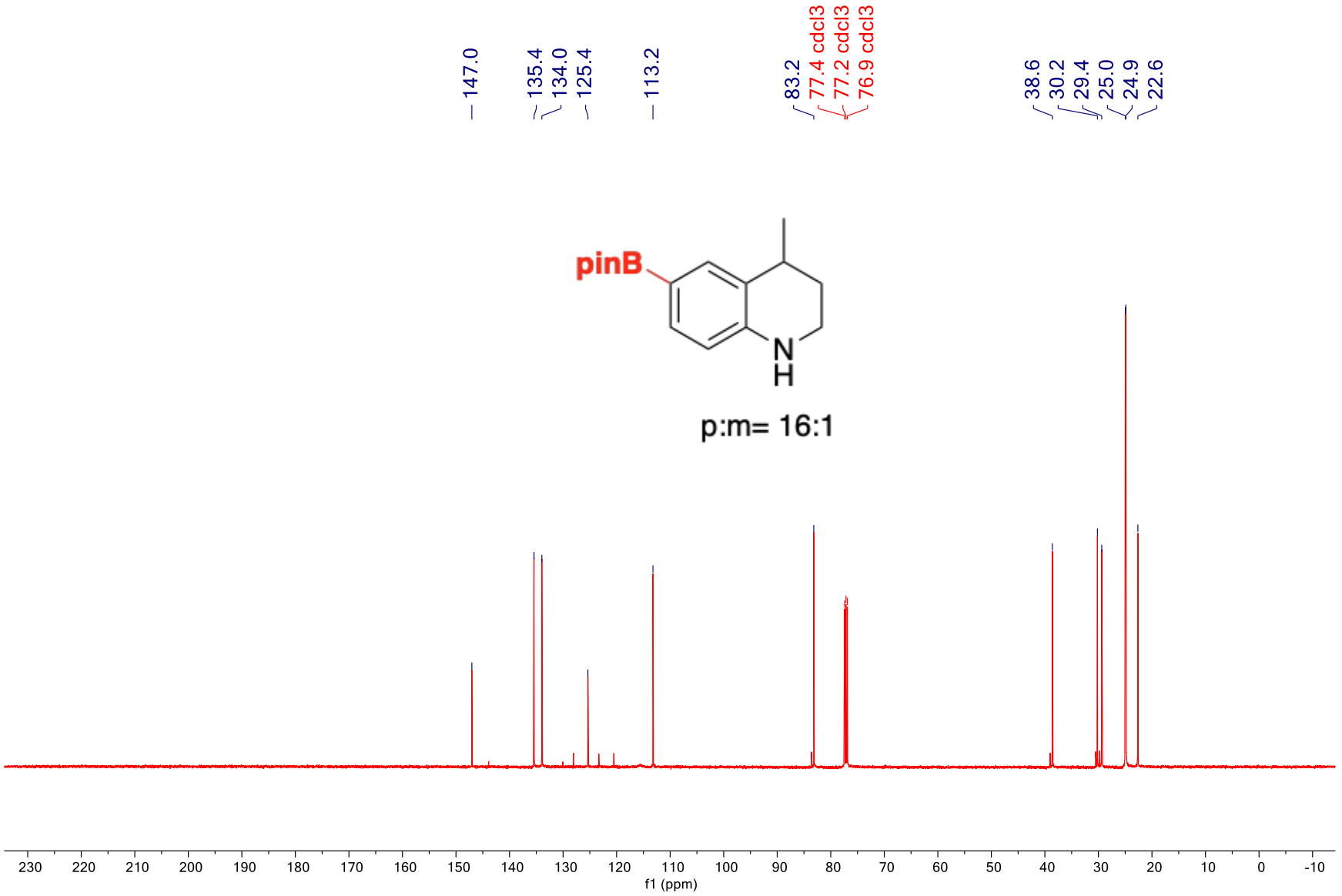
***Para* CHB of 4-methyl-1,2,3,4-tetrahydroquinoline (4.4e) ($CDCl_3$, 500 MHz)**



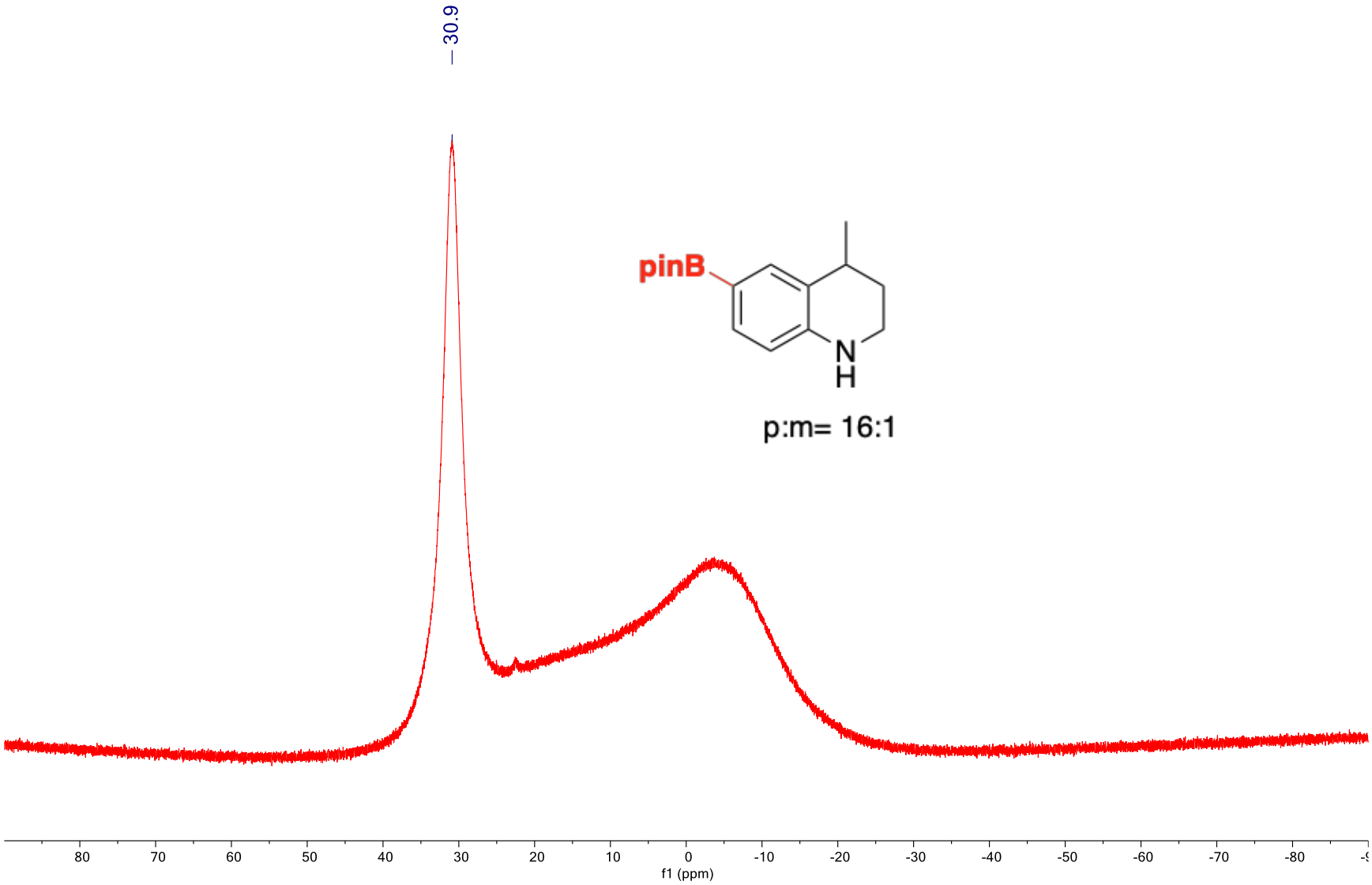
^{1}H NMR of *para* borylated 4-methyl-1,2,3,4-tetrahydroquinoline (4.4e) ($CDCl_3$, 500 MHz)



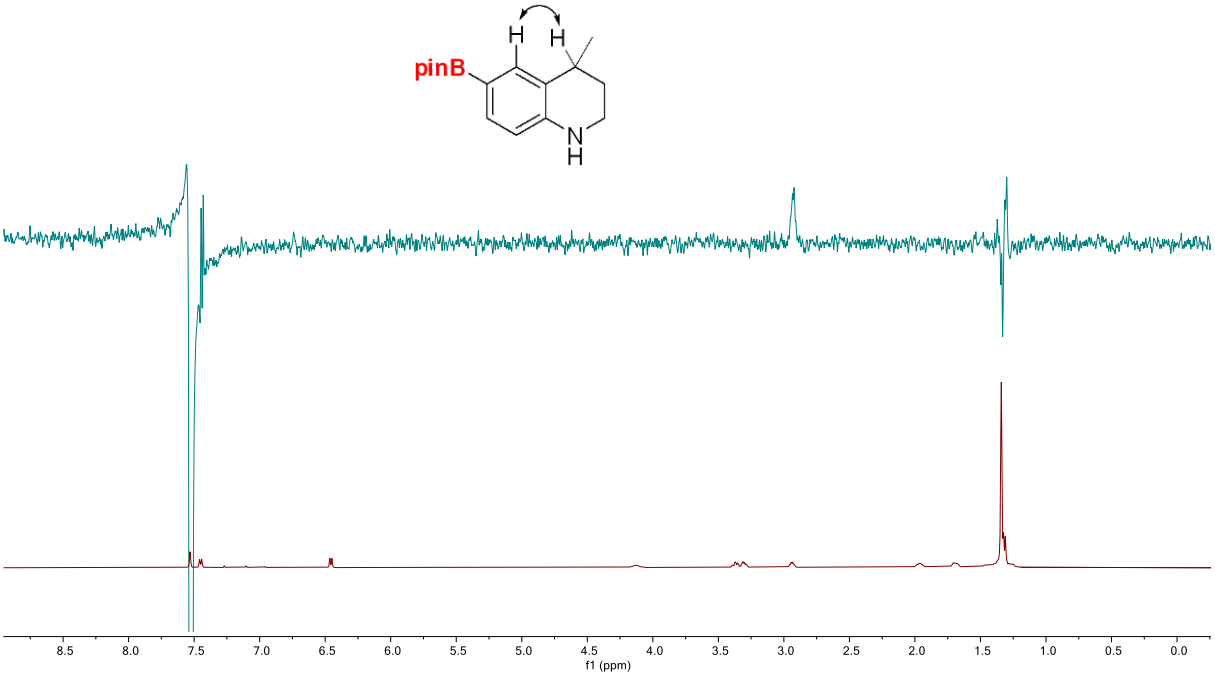
^{13}C NMR of *para* borylated 4-methyl-1,2,3,4-tetrahydroquinoline (4.4e) ($CDCl_3$, 126 MHz)

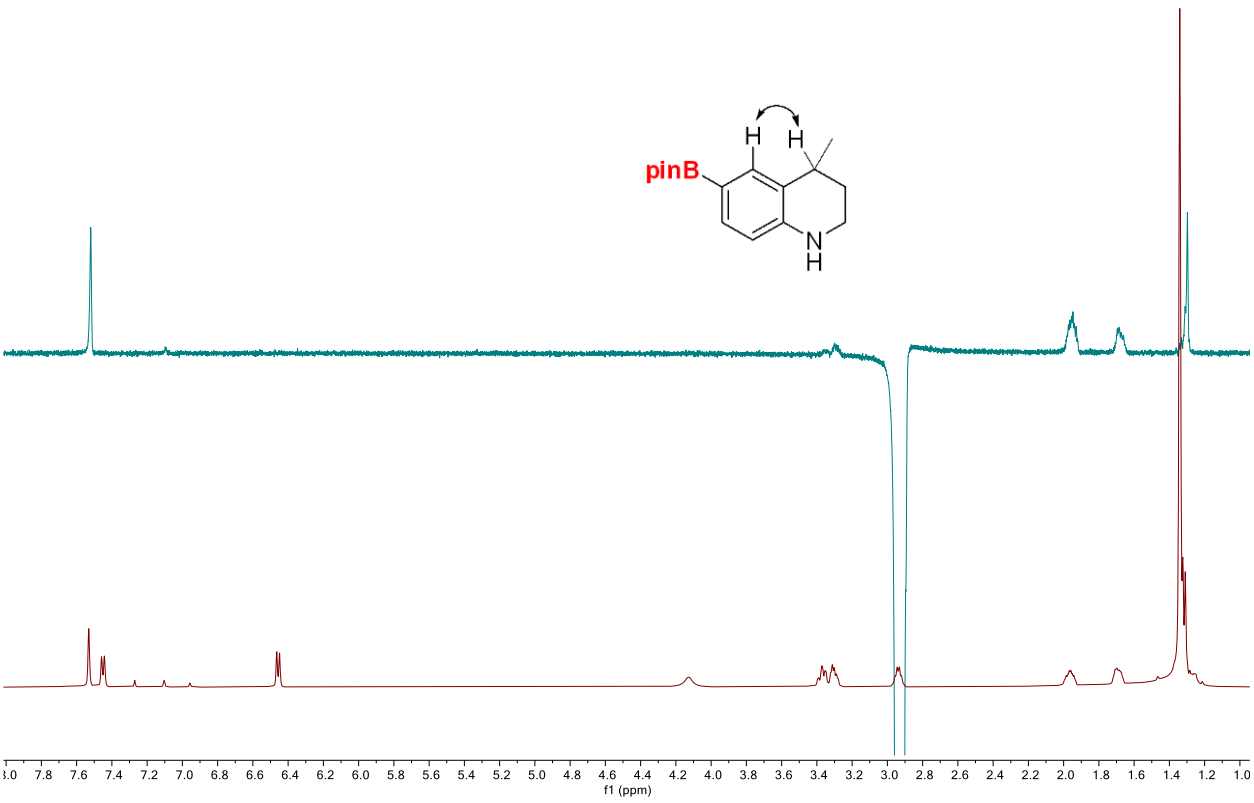


^{11}B NMR of *para* borylated 4-methyl-1,2,3,4-tetrahydroquinoline (4.4e) ($CDCl_3$, 160 MHz)

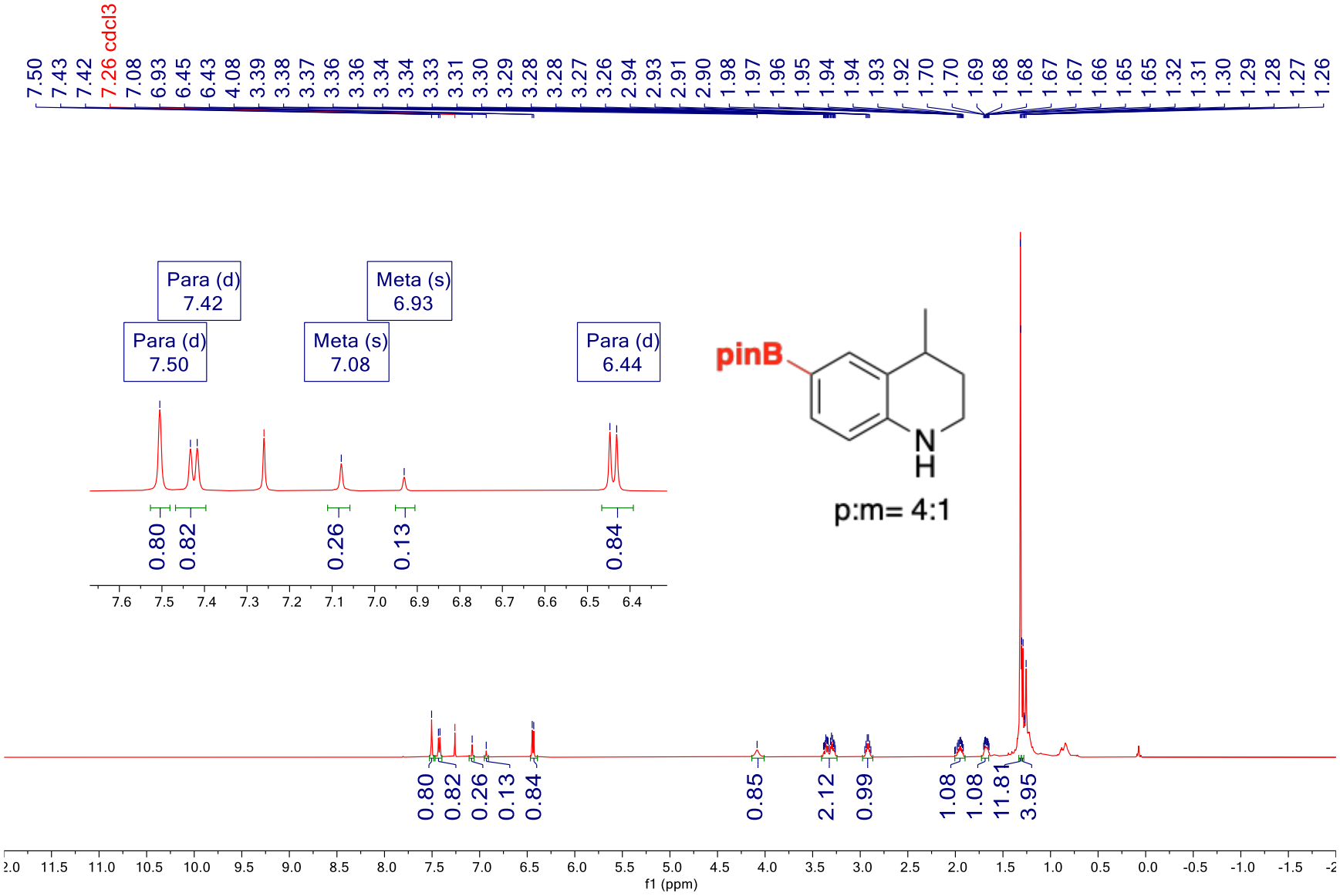


1D-NOE of ^{1}H NMR of *para* borylated 4-methyl-1,2,3,4-tetrahydroquinoline (4.4e) ($CDCl_3$, 500 MHz)

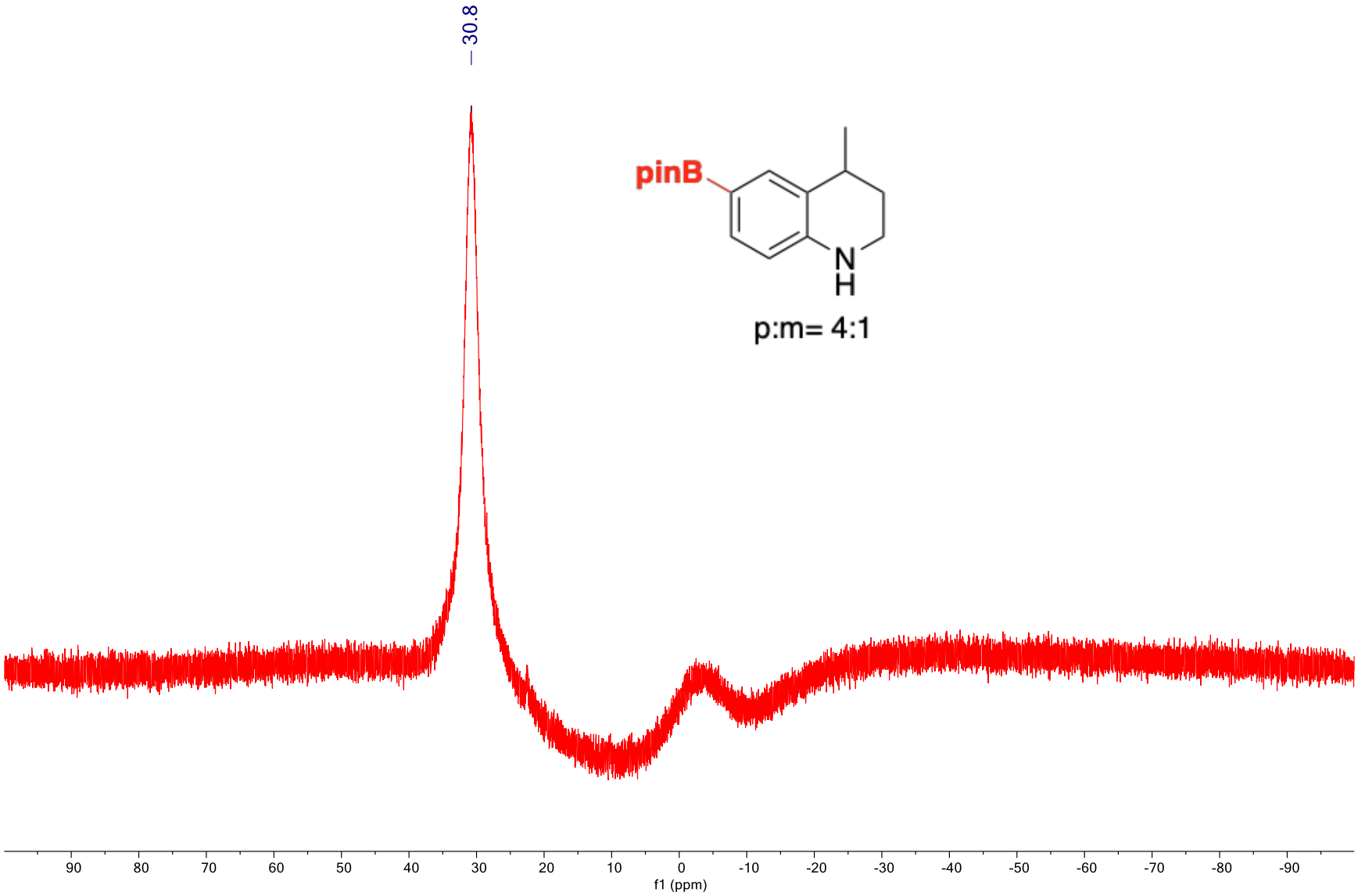




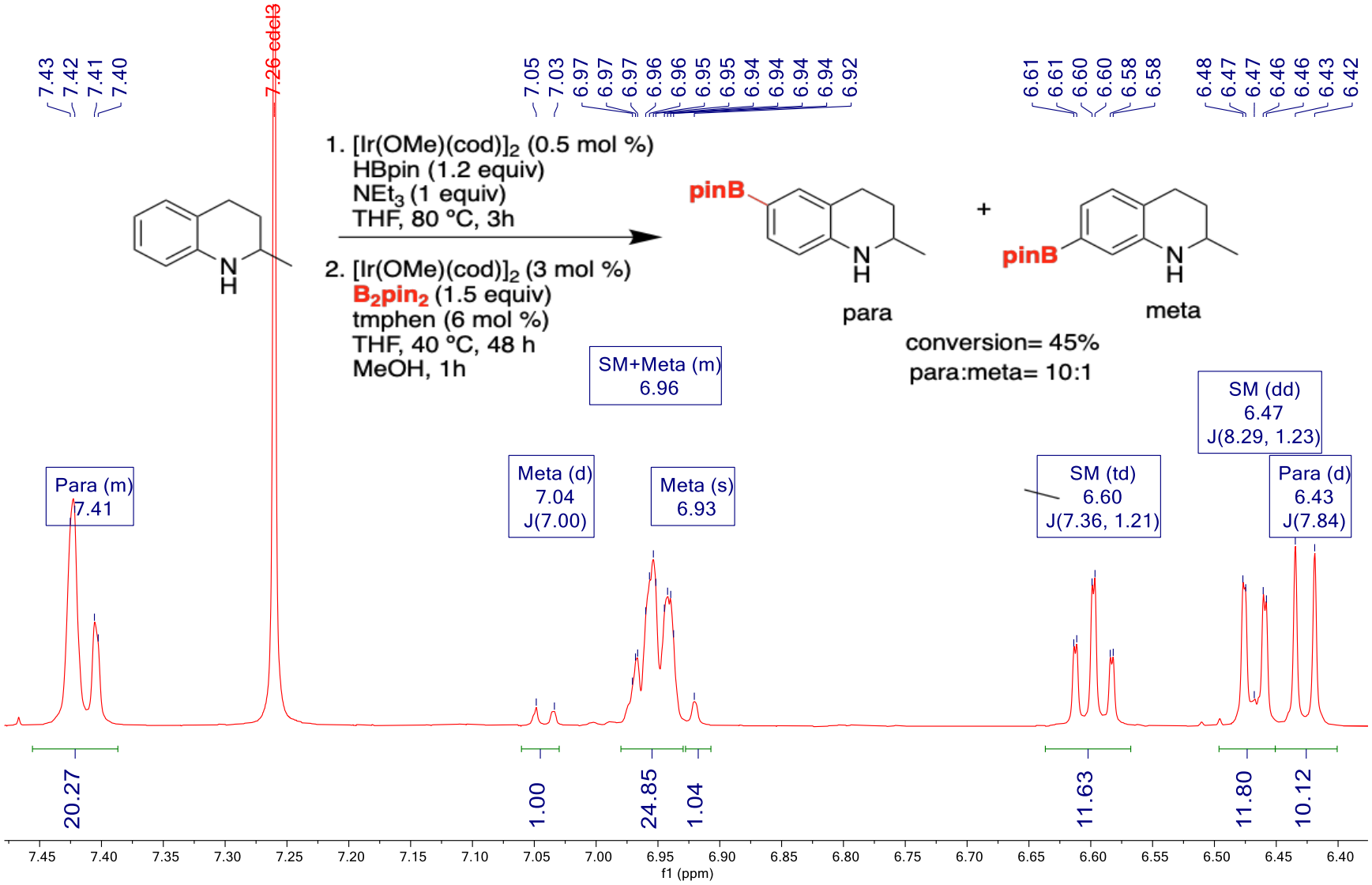
^{1}H NMR of *para* borylated 4-methyl-1,2,3,4-tetrahydroquinoline, second fraction (4.4e) ($CDCl_3$, 500 MHz)



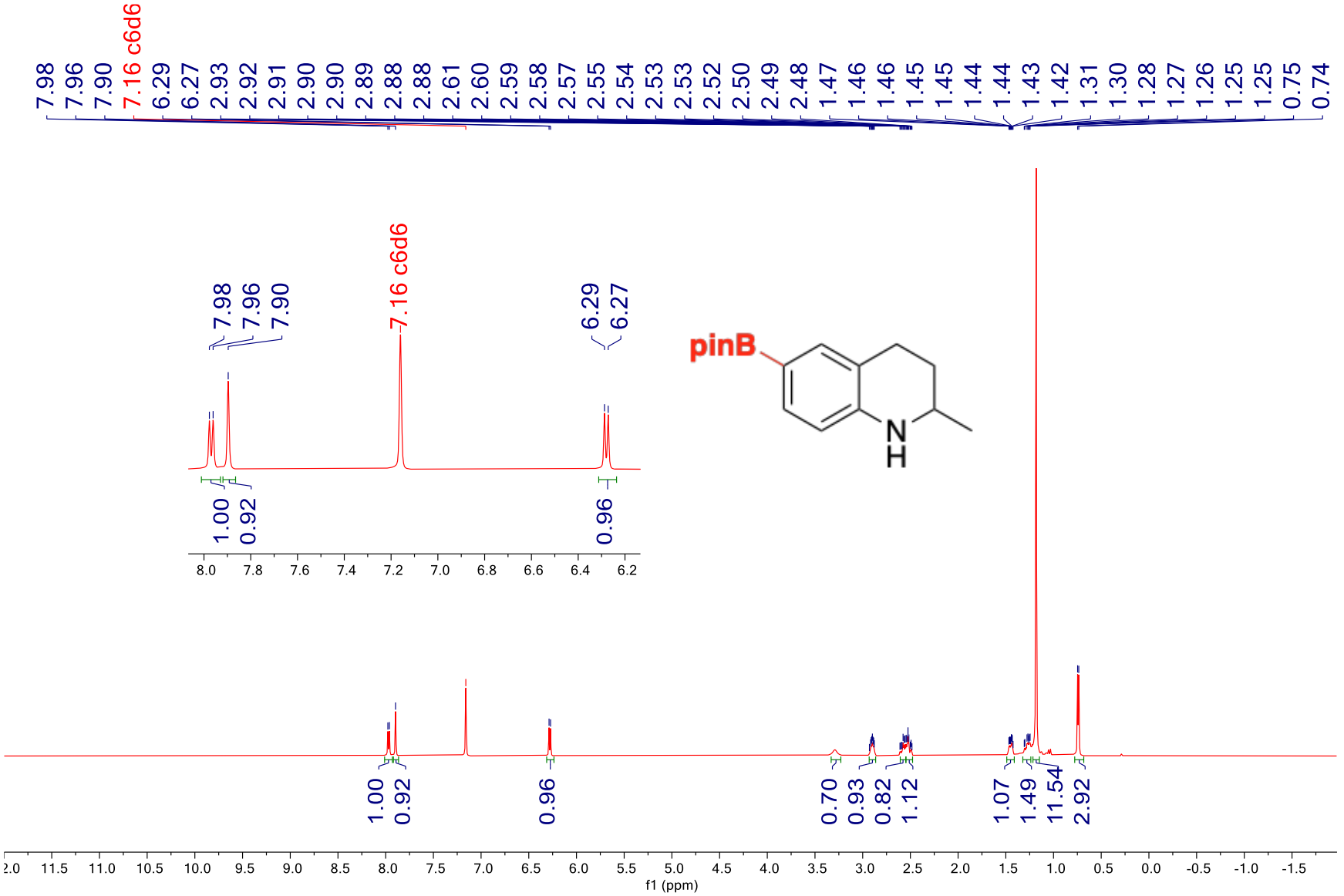
^{11}B NMR of *para* borylated 4-methyl-1,2,3,4-tetrahydroquinoline, second fraction (4.4e) ($CDCl_3$, 160 MHz)



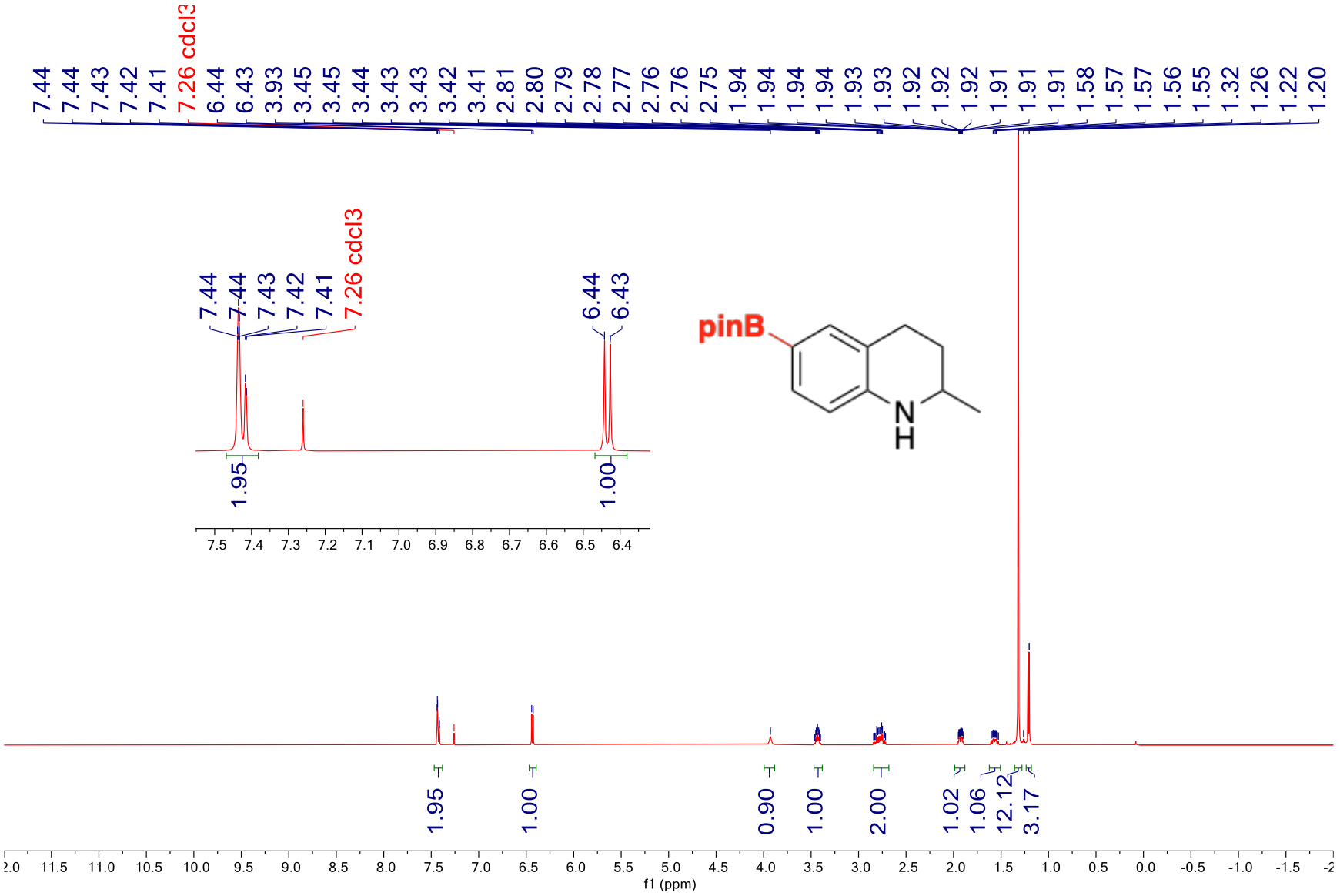
***Para* CHB of 2-methyl-1,2,3,4-tetrahydroquinoline (4.4f) ($CDCl_3$, 500 MHz)**



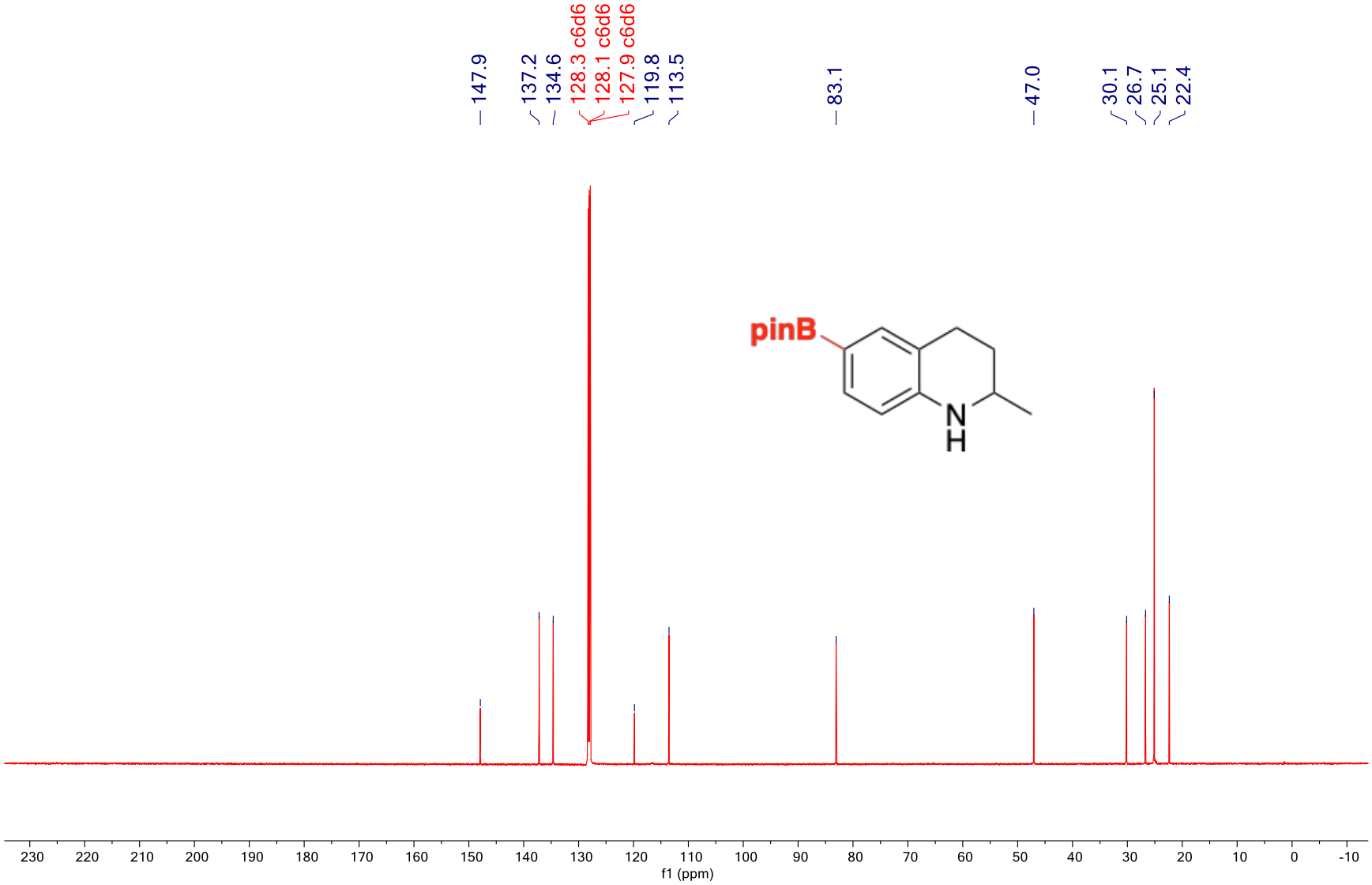
^{1}H NMR of *para* borylated 2-methyl-1,2,3,4-tetrahydroquinoline (4.4f) (C_6D_6, 500 MHz)



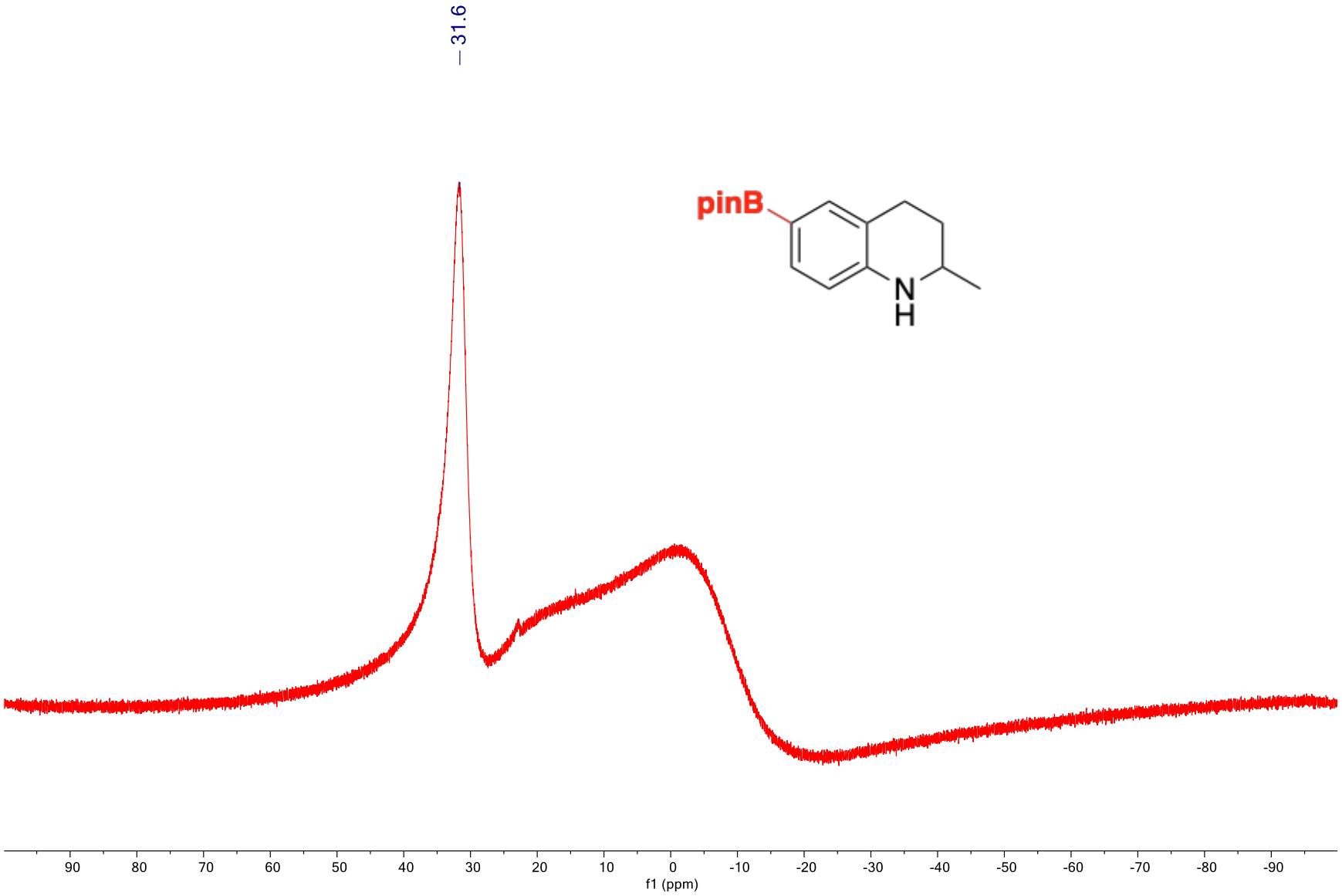
^{1}H NMR of *para* borylated 2-methyl-1,2,3,4-tetrahydroquinoline (4.4f) ($CDCl_3$, 500 MHz)



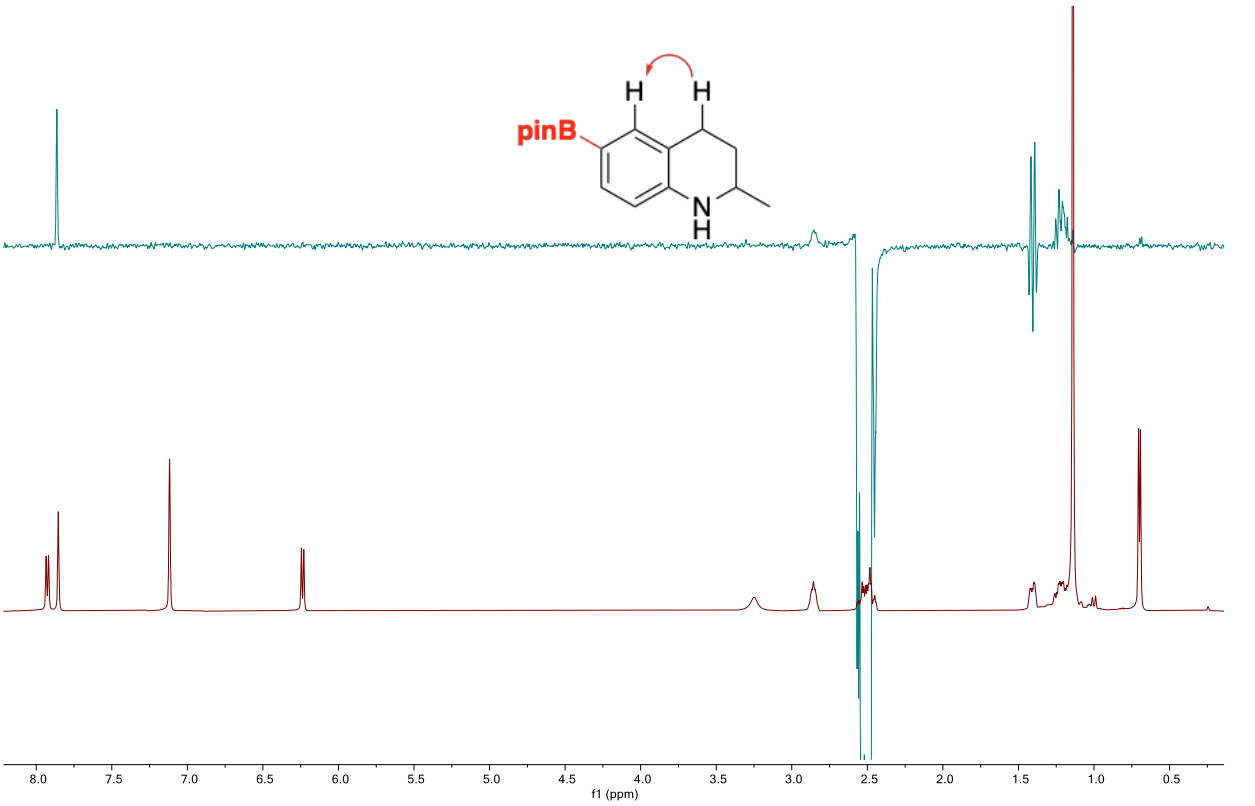
^{13}C NMR of *para* borylated 2-methyl-1,2,3,4-tetrahydroquinoline (4.4f) (C_6D_6, 126 MHz)

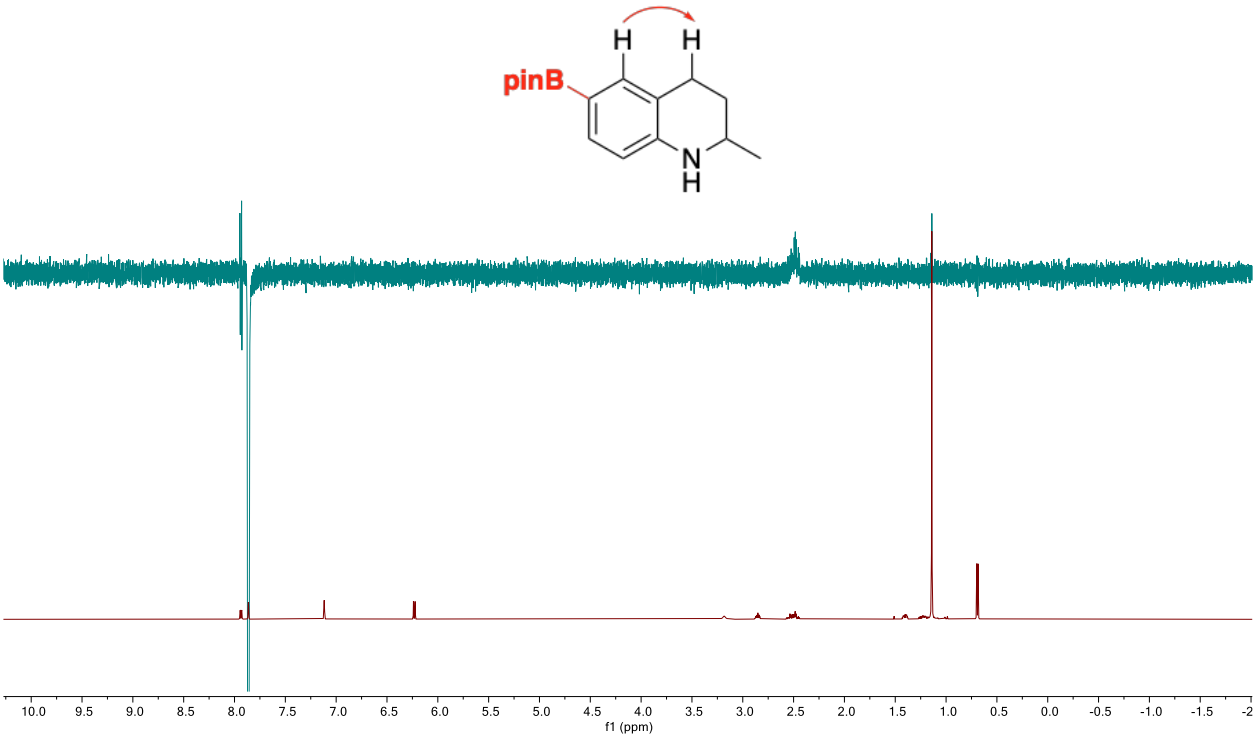


^{11}B NMR of *para* borylated 2-methyl-1,2,3,4-tetrahydroquinoline (4.4f) (C_6D_6, 160 MHz)

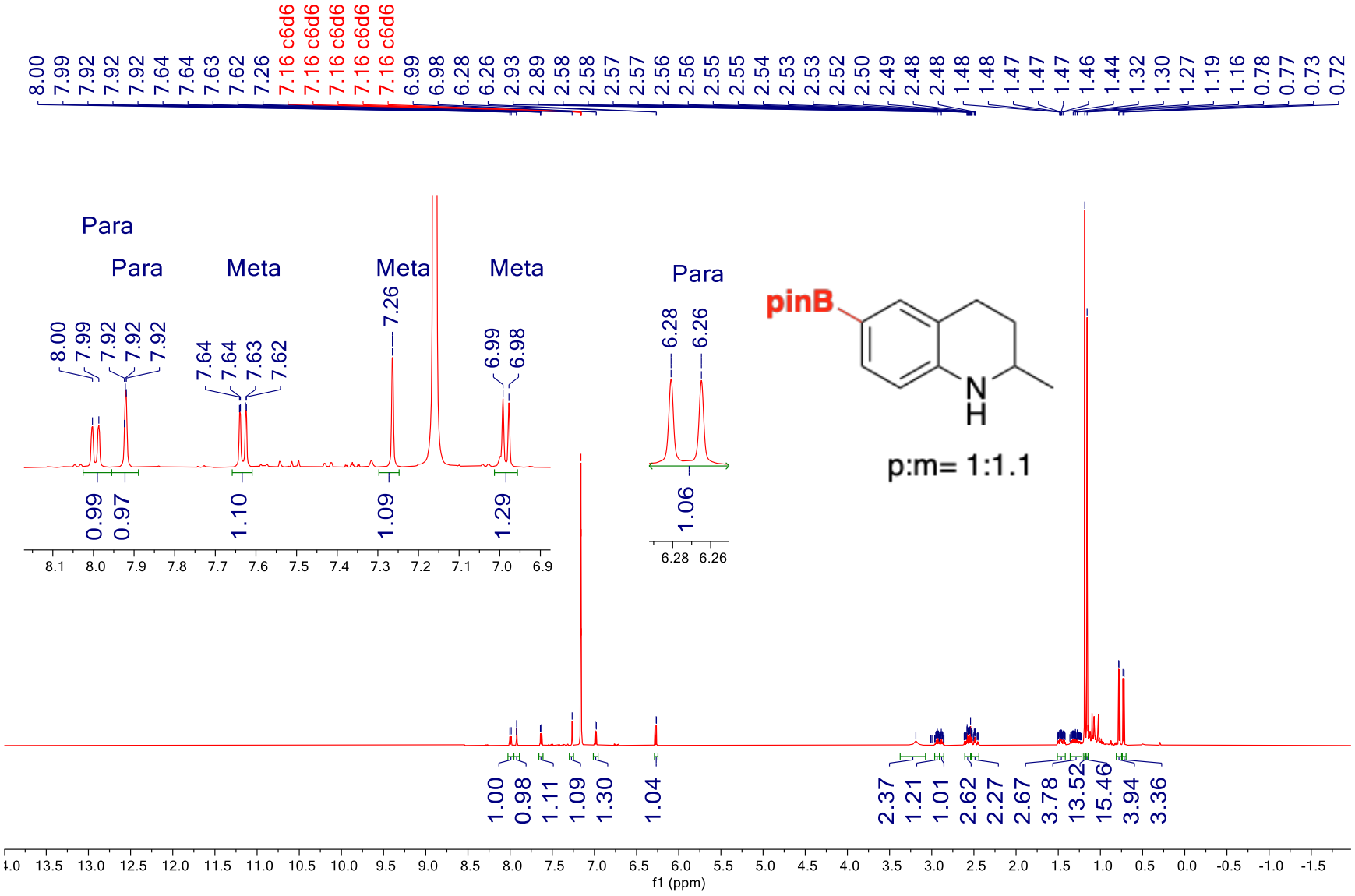


1D-NOE of *para* borylated 2-methyl-1,2,3,4-tetrahydroquinoline (4.4f) (C_6D_6, 500 MHz)

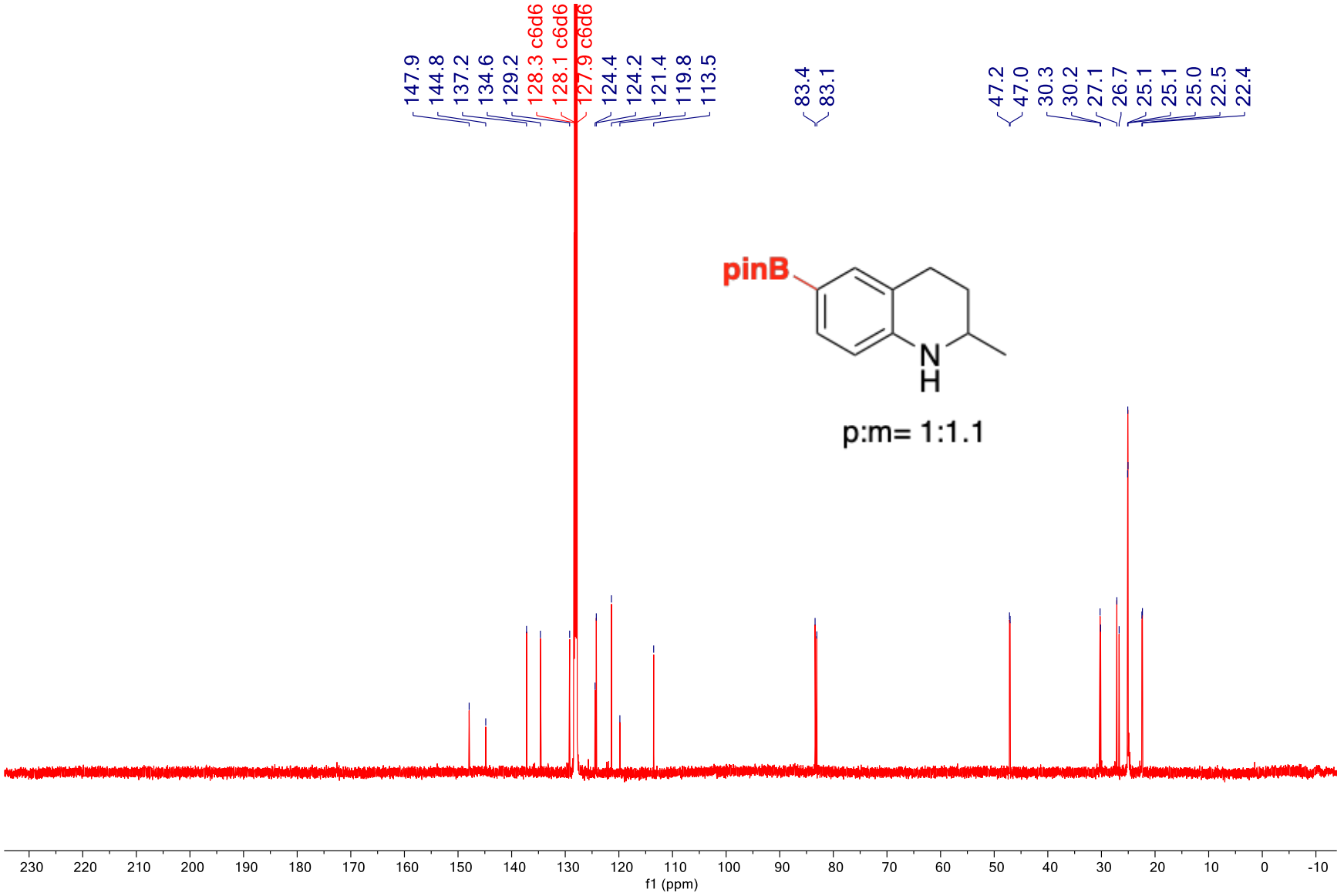




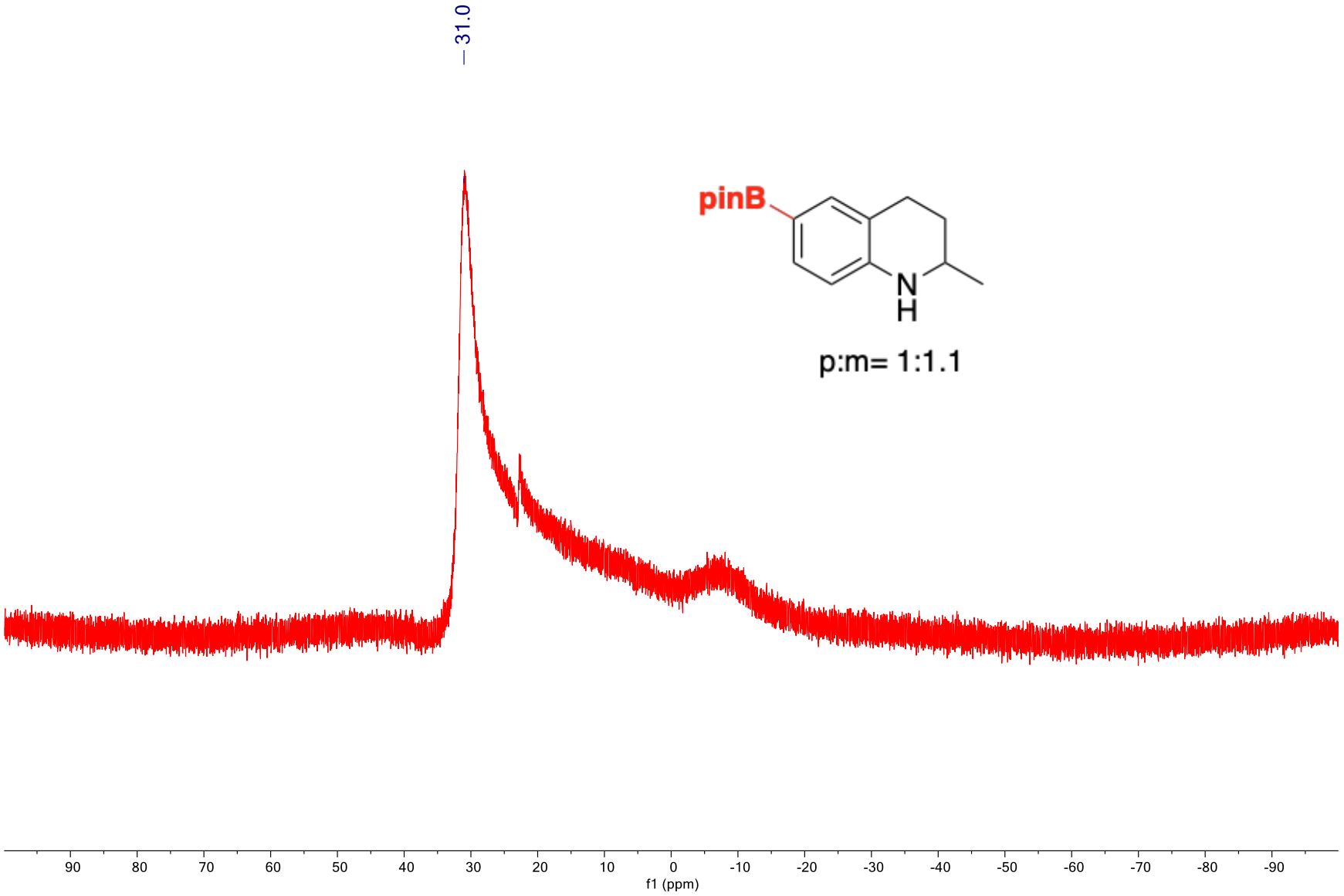
^{1}H NMR of *para* and *meta* borylated 2-methyl-1,2,3,4-tetrahydroquinoline, second fraction (4.4f) (C_6D_6, 500 MHz)



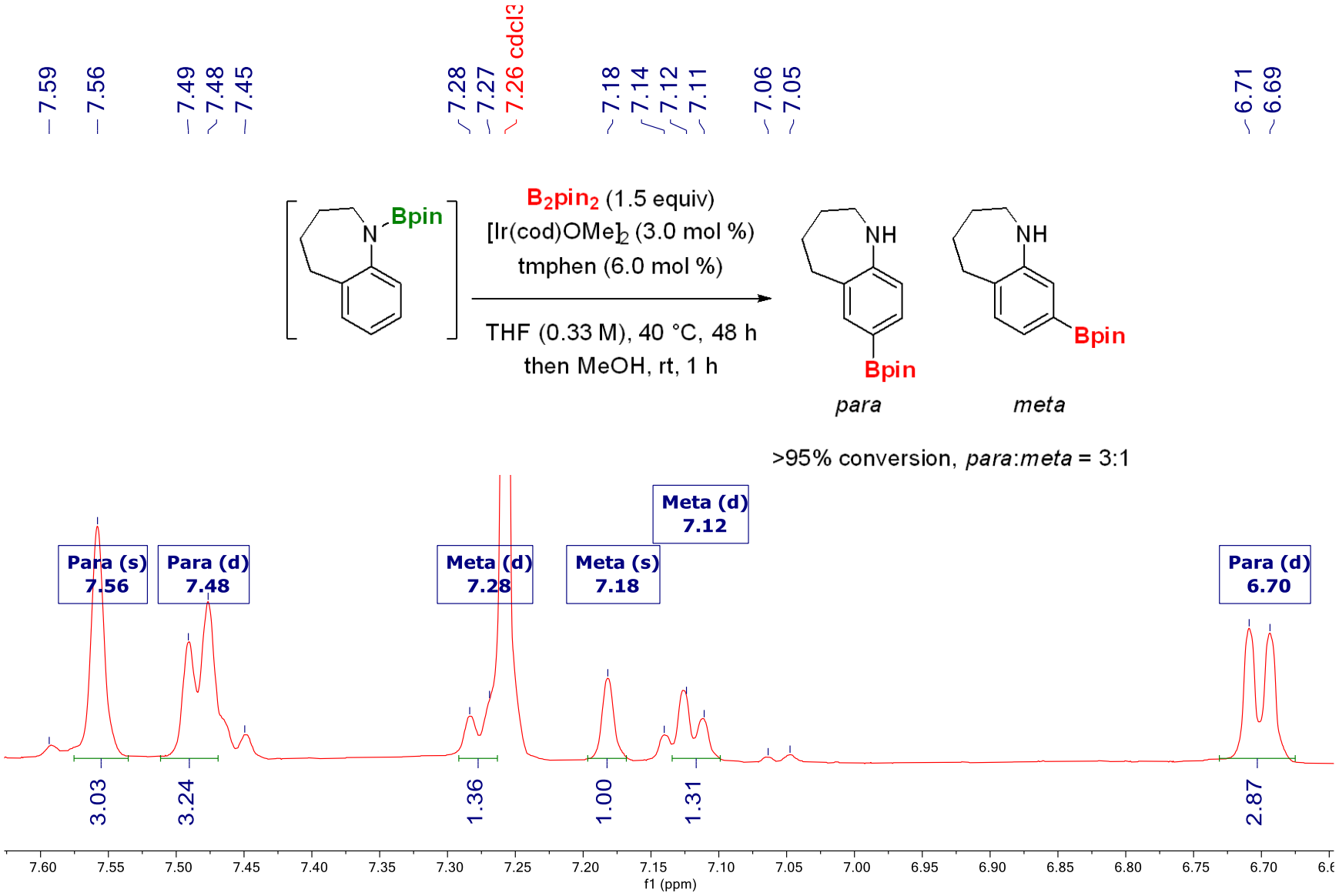
^{13}C NMR of *para* and *meta* borylated 2-methyl-1,2,3,4-tetrahydroquinoline, second fraction (4.4f) (C_6D_6, 126 MHz)



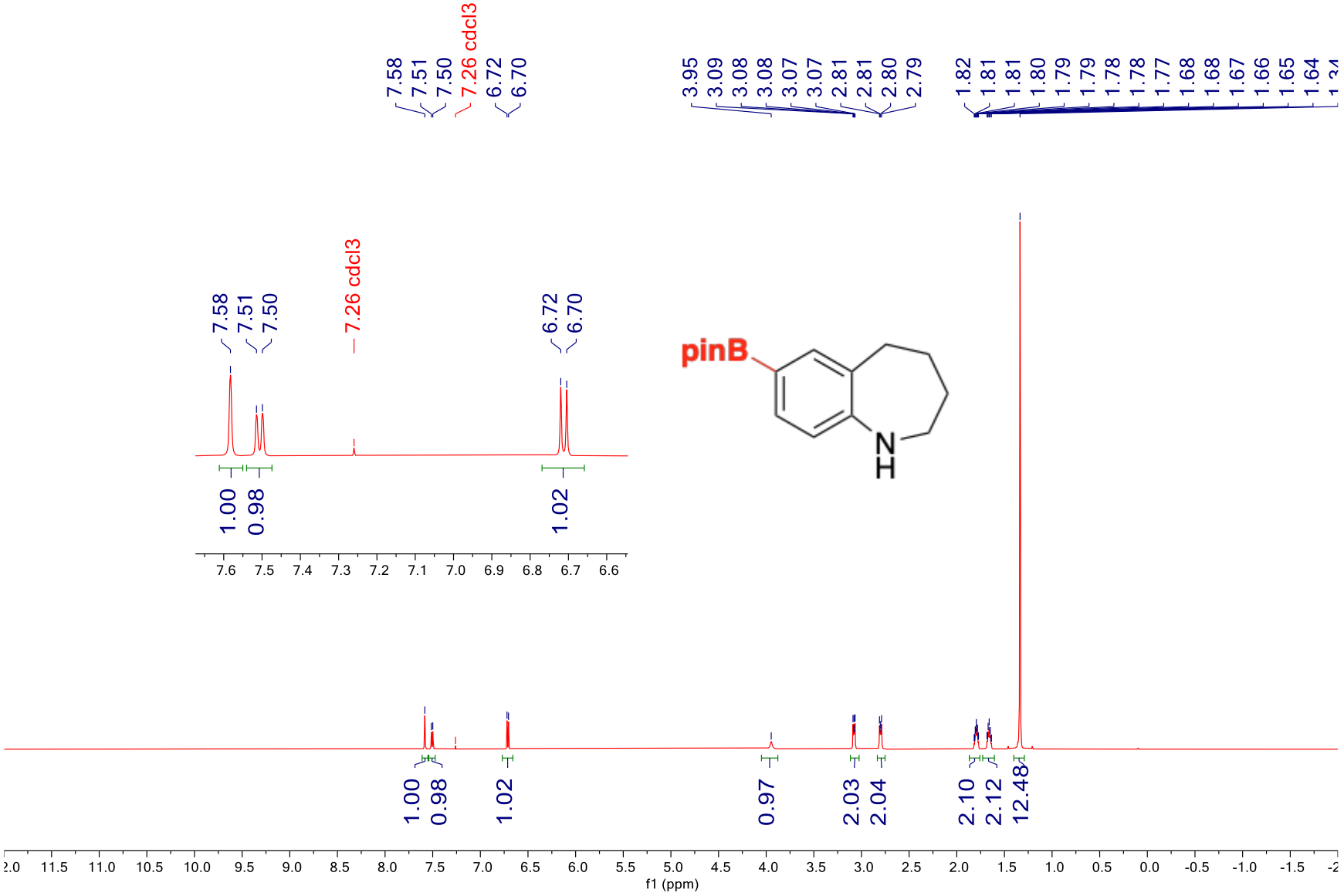
^{11}B NMR of *para* and *meta* borylated 2-methyl-1,2,3,4-tetrahydroquinoline, second fraction (4.4f) (C_6D_6, 160 MHz)



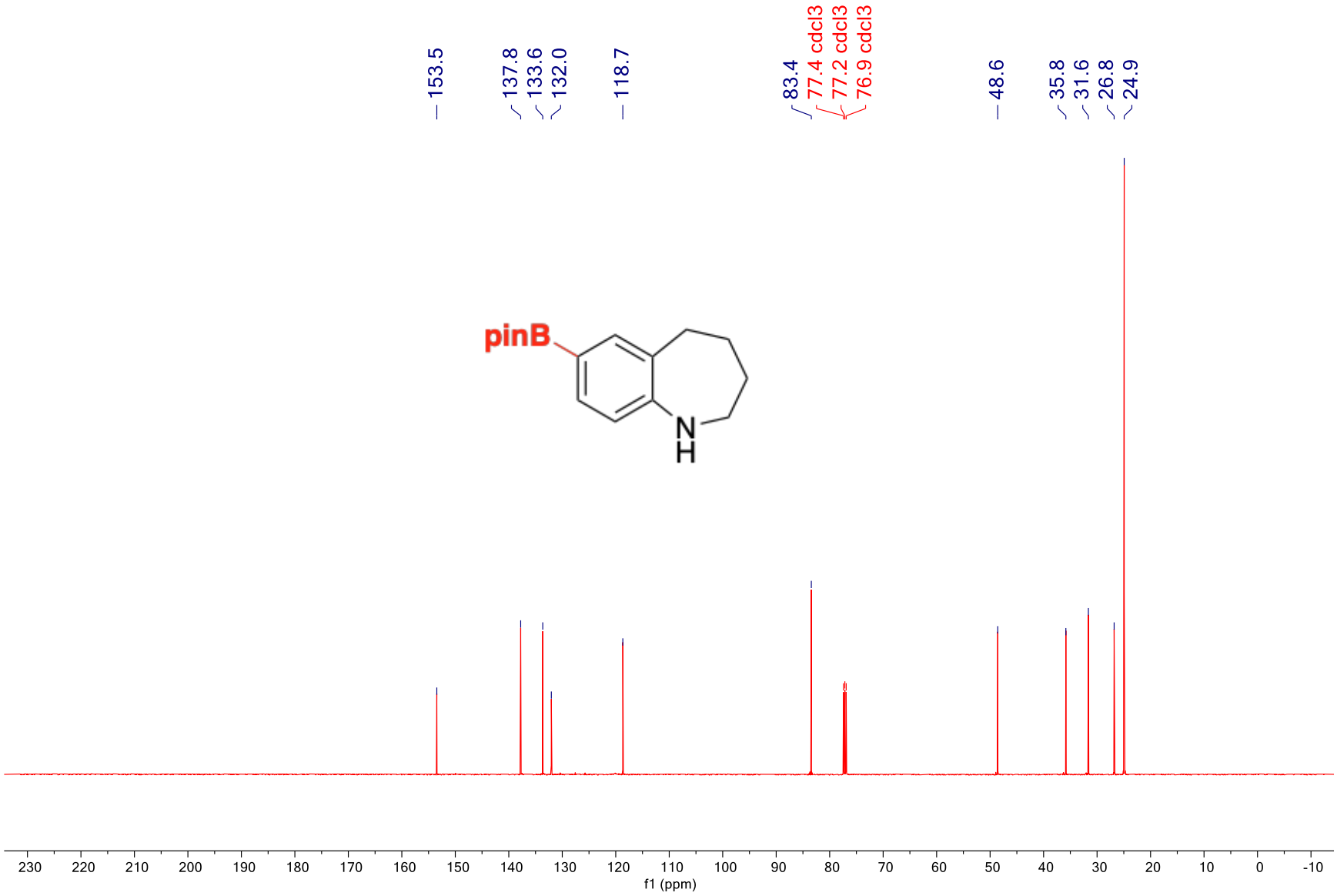
***Para* Borylation of 2,3,4,5-tetrahydro-1H-benzo[b]azepine (4.4g) ($CDCl_3$, 500 MHz)**



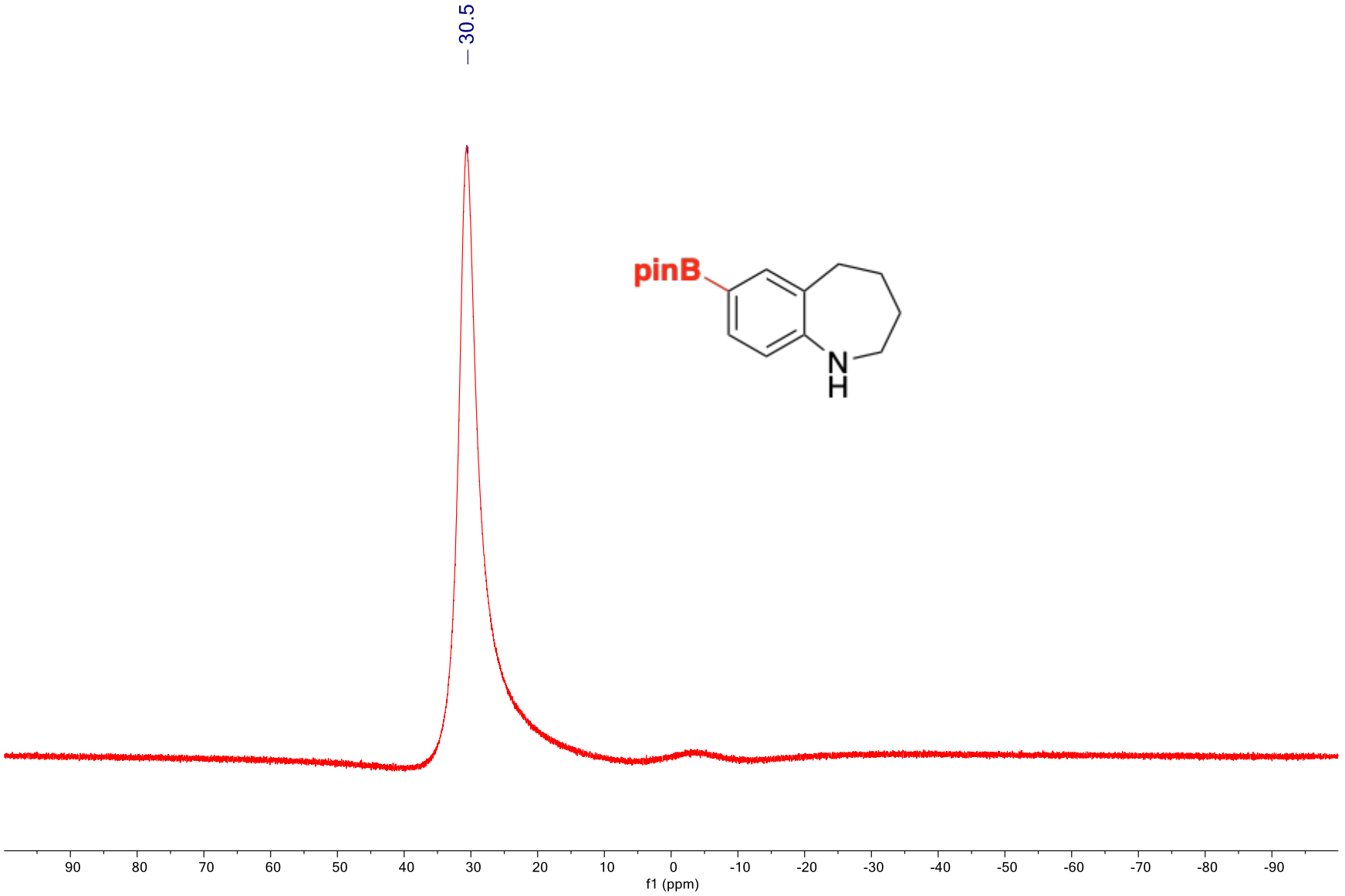
^{1}H NMR of *para* borylated 2,3,4,5-tetrahydro-1H-benzo[b]azepine (4.4g) ($CDCl_3$, 500 MHz)



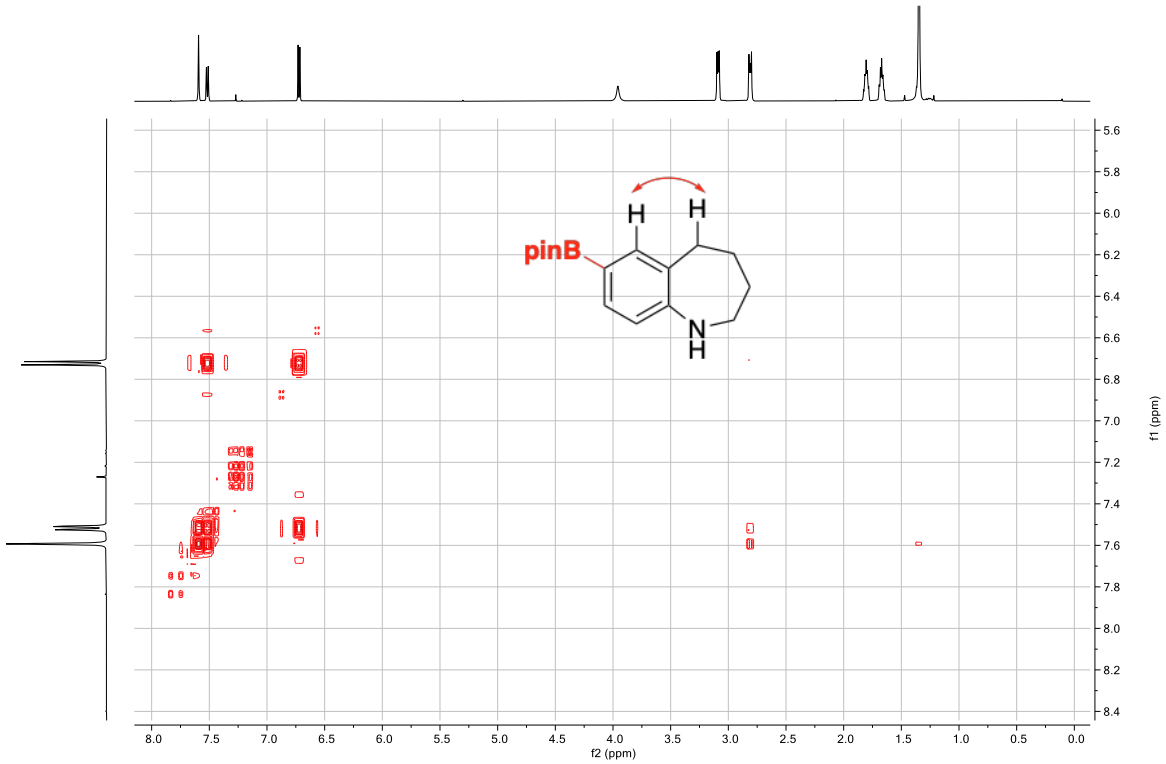
^{13}C NMR of *para* borylated 2,3,4,5-tetrahydro-1H-benzo[b]azepine (4.4g) ($CDCl_3$, 126 MHz)



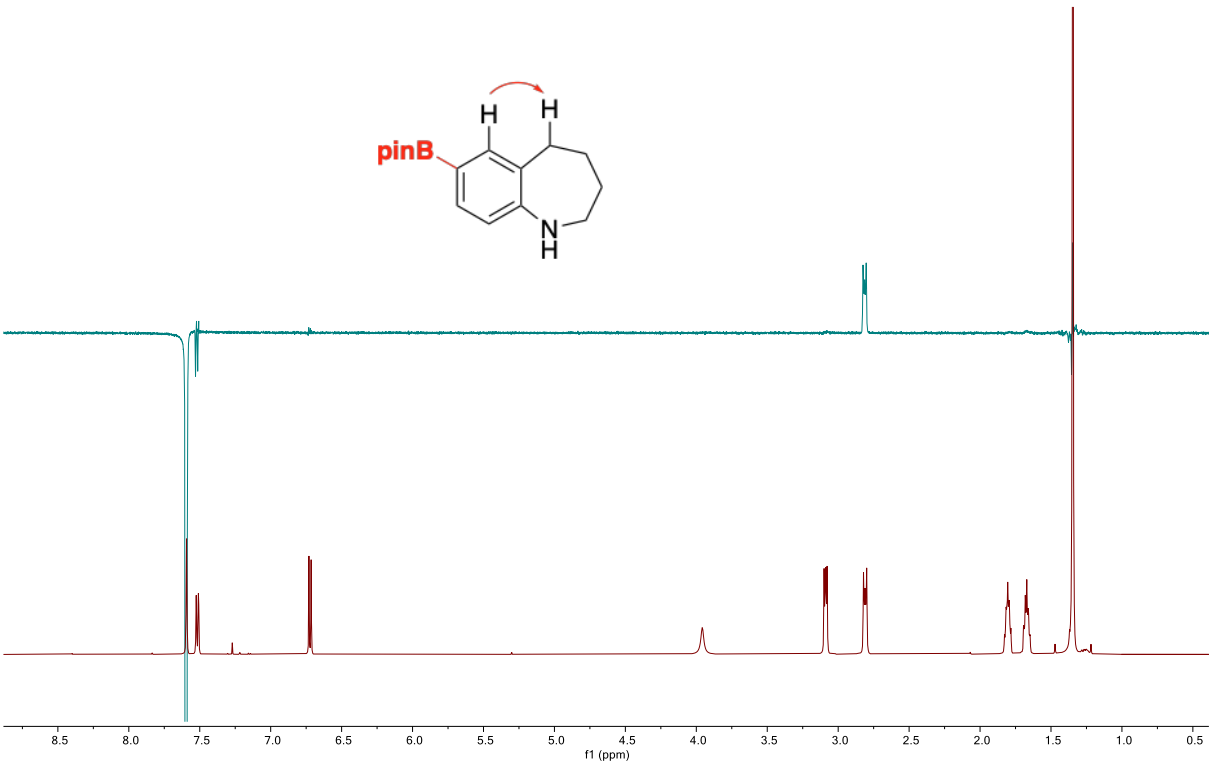
^{11}B NMR of *para* borylated 2,3,4,5-tetrahydro-1H-benzo[b]azepine (4.4g) ($CDCl_3$, 160 MHz)



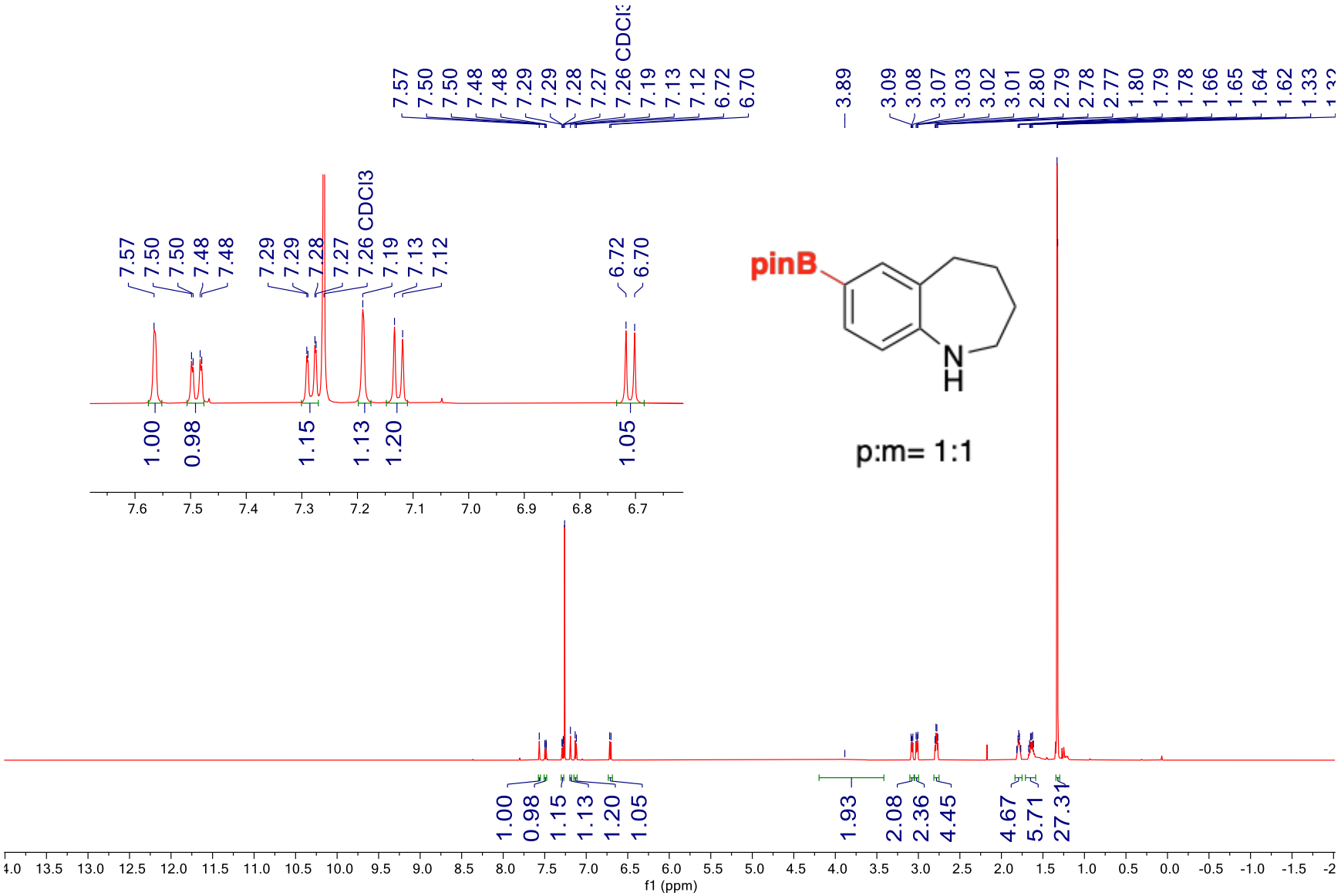
gCOSY of *para* borylated 2,3,4,5-tetrahydro-1H-benzo[b]azepine (4.4g) ($CDCl_3$, 500 MHz)



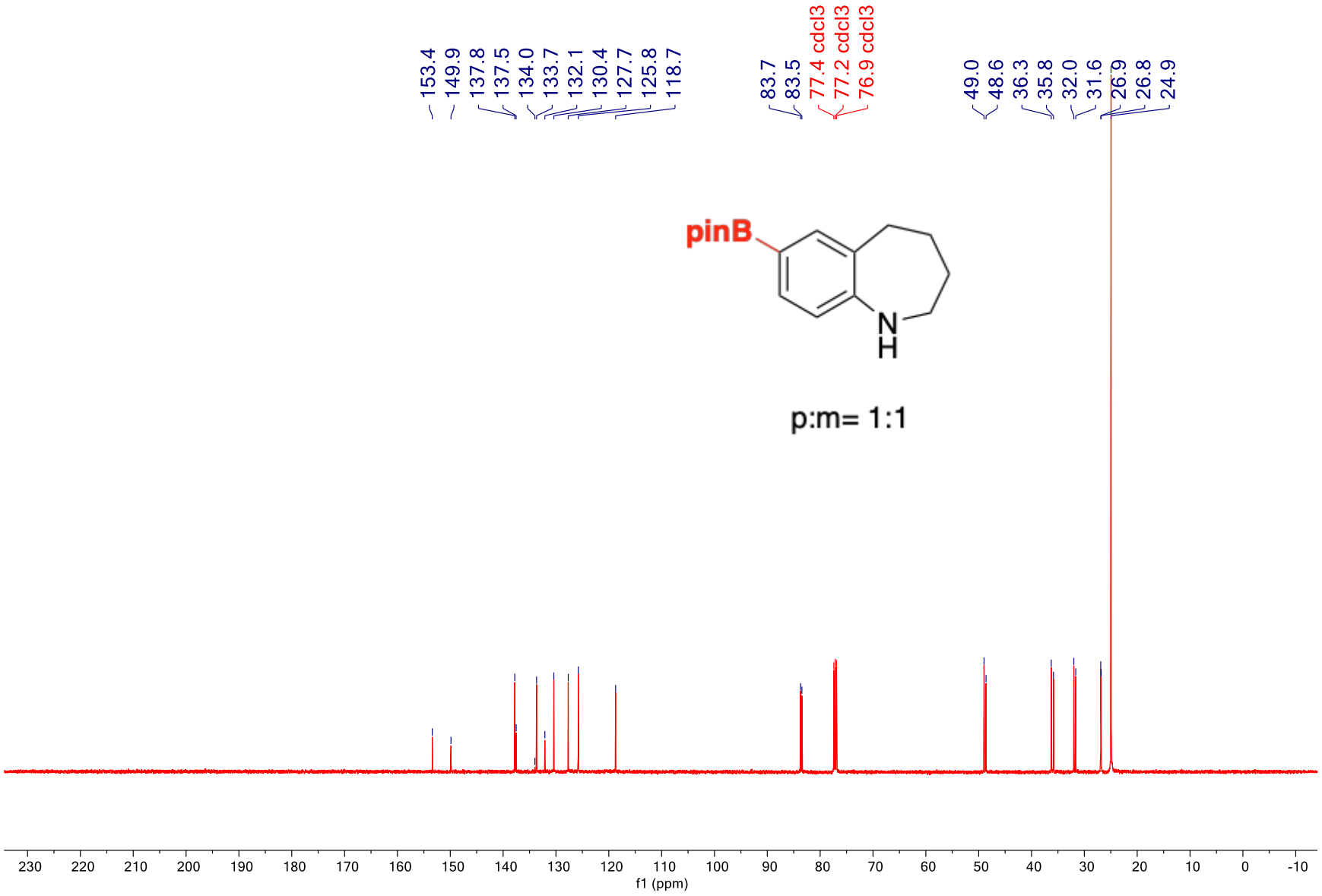
1D-NOE of *para* borylated 2,3,4,5-tetrahydro-1H-benzo[b]azepine ($CDCl_3$, 500 MHz)



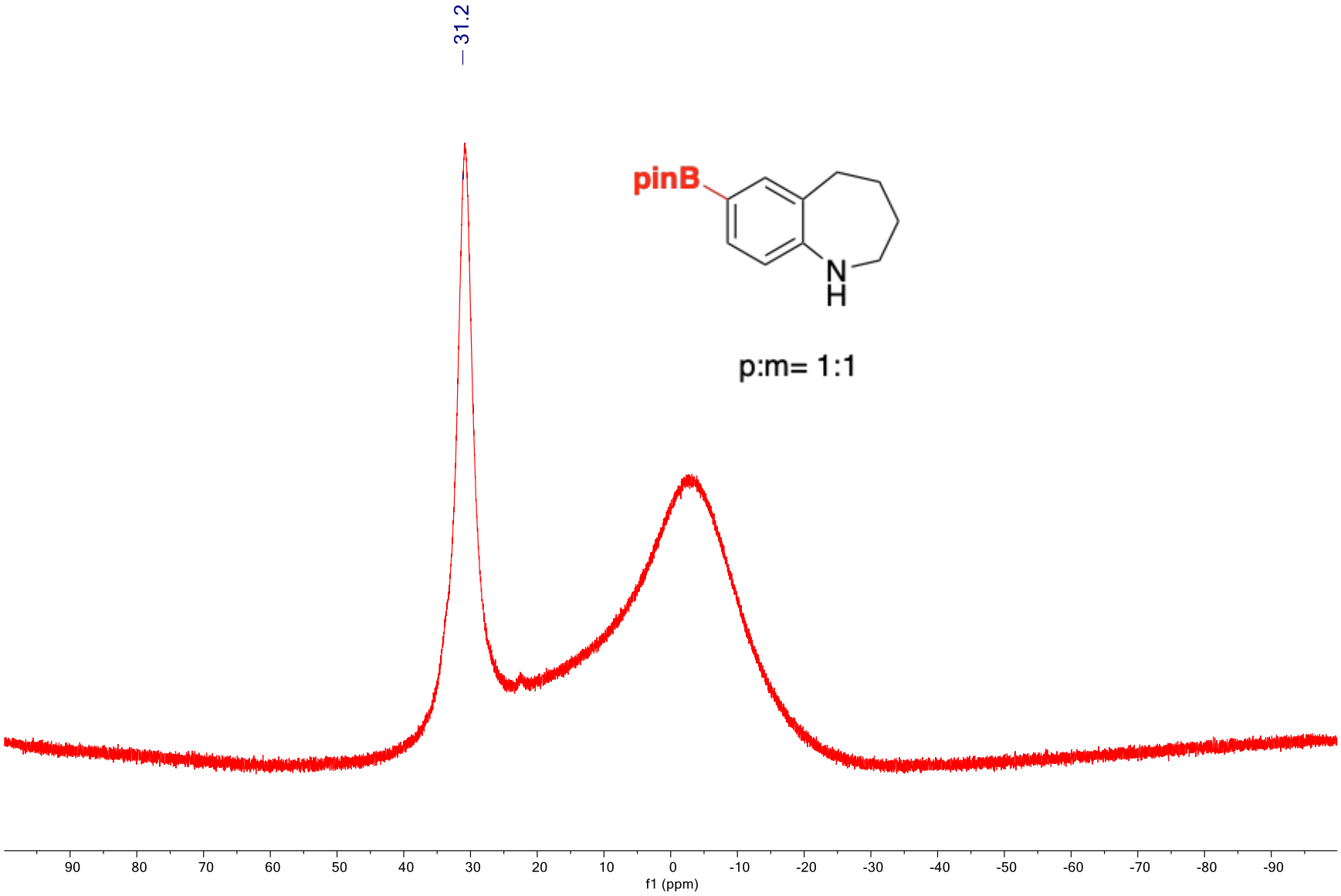
^{1}H NMR of *para* and *meta* borylated 2,3,4,5-tetrahydro-1H-benzo[b]azepine, second fraction (4.4g) ($CDCl_3$, 500 MHz)



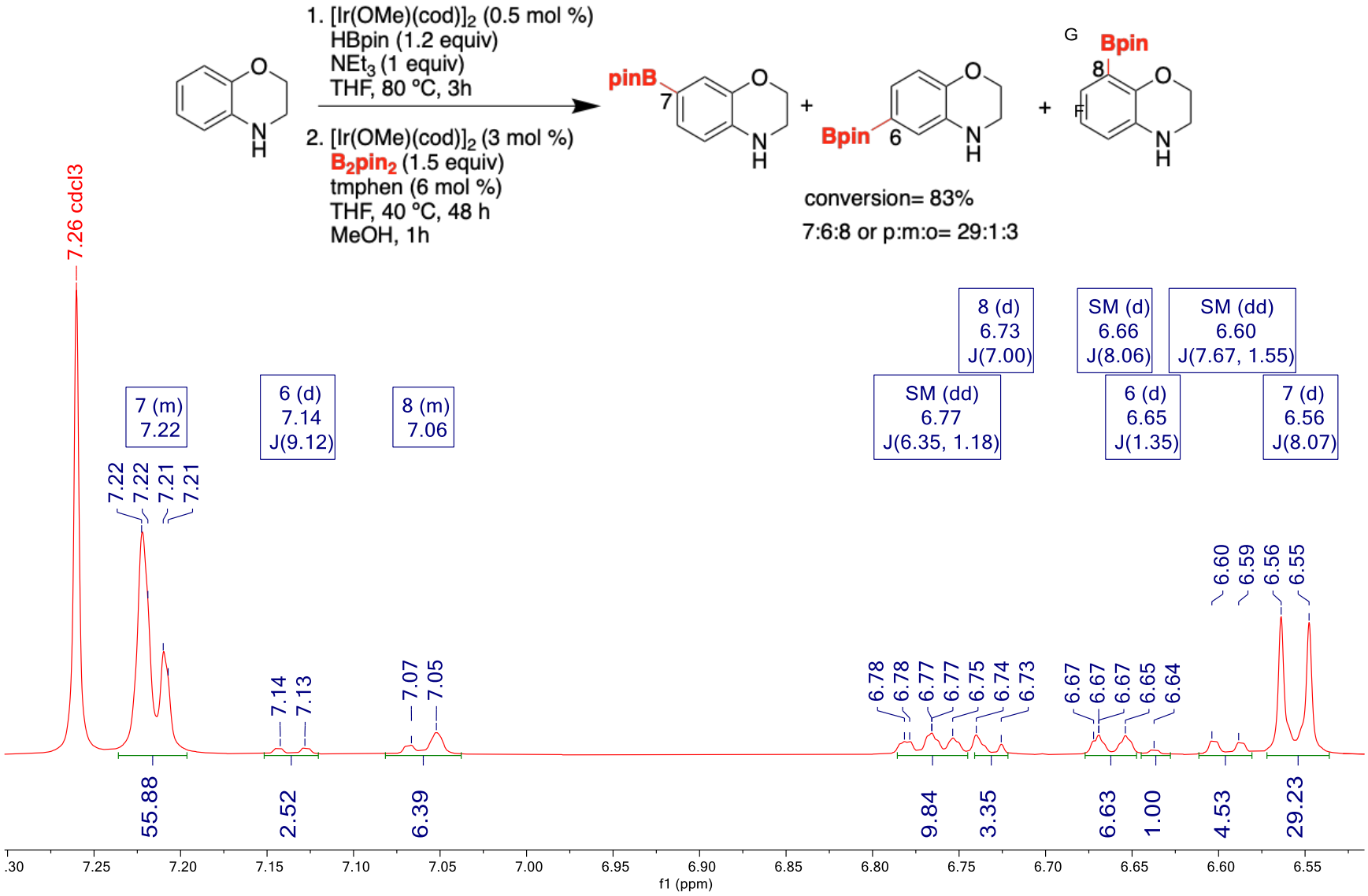
^{13}C NMR of *para* and *meta* borylated 2,3,4,5-tetrahydro-1H-benzo[b]azepine, second fraction (4.4g) ($CDCl_3$, 126 MHz)



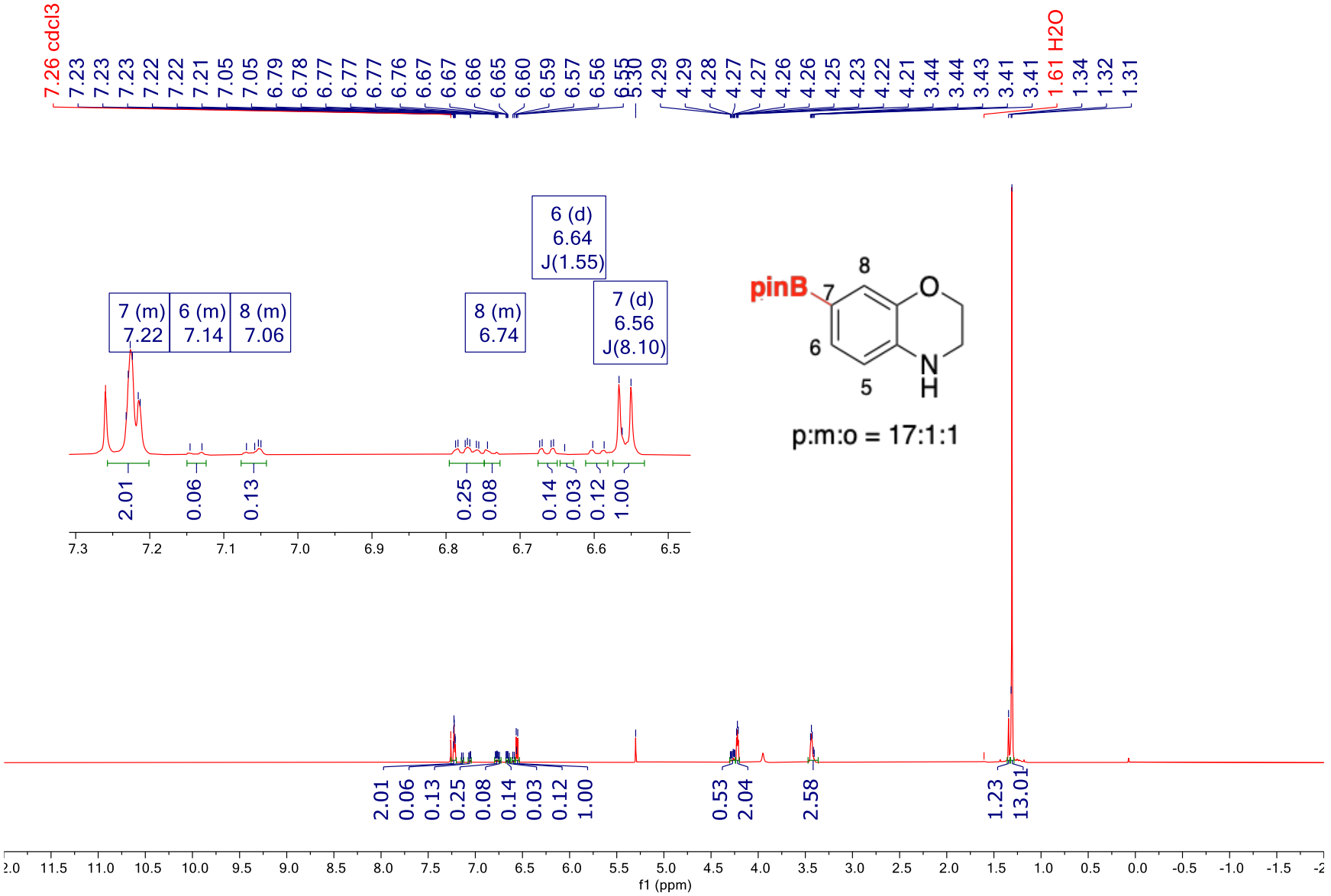
^{11}B NMR of *para* and *meta* borylated 2,3,4,5-tetrahydro-1H-benzo[b]azepine, second fraction (4.4g) ($CDCl_3$, 160 MHz)



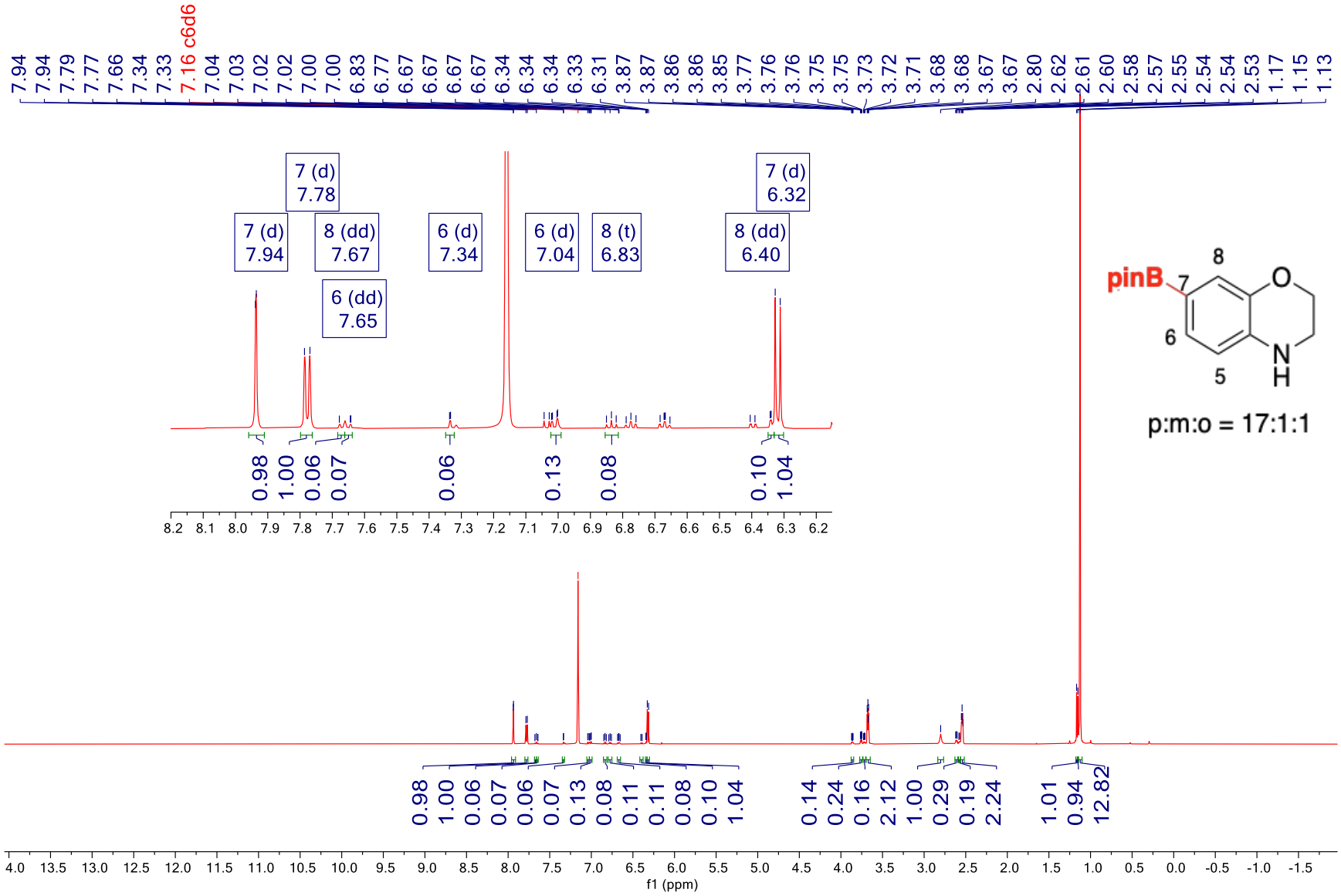
***Para* CHB of 3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4h) ($CDCl_3$, 500 MHz)**



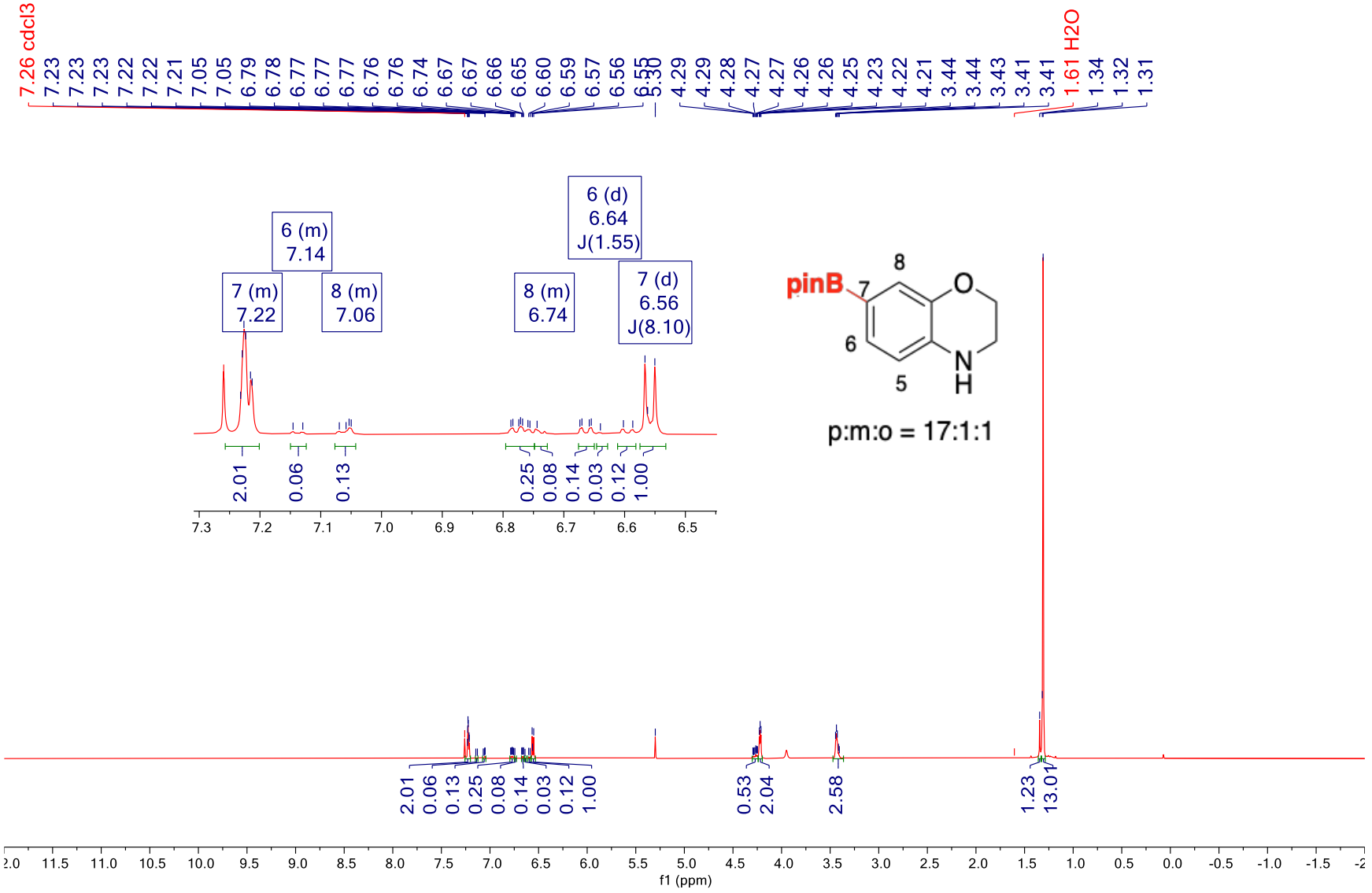
^{1}H NMR of *para* borylated 3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4h) ($CDCl_3$, 500 MHz)



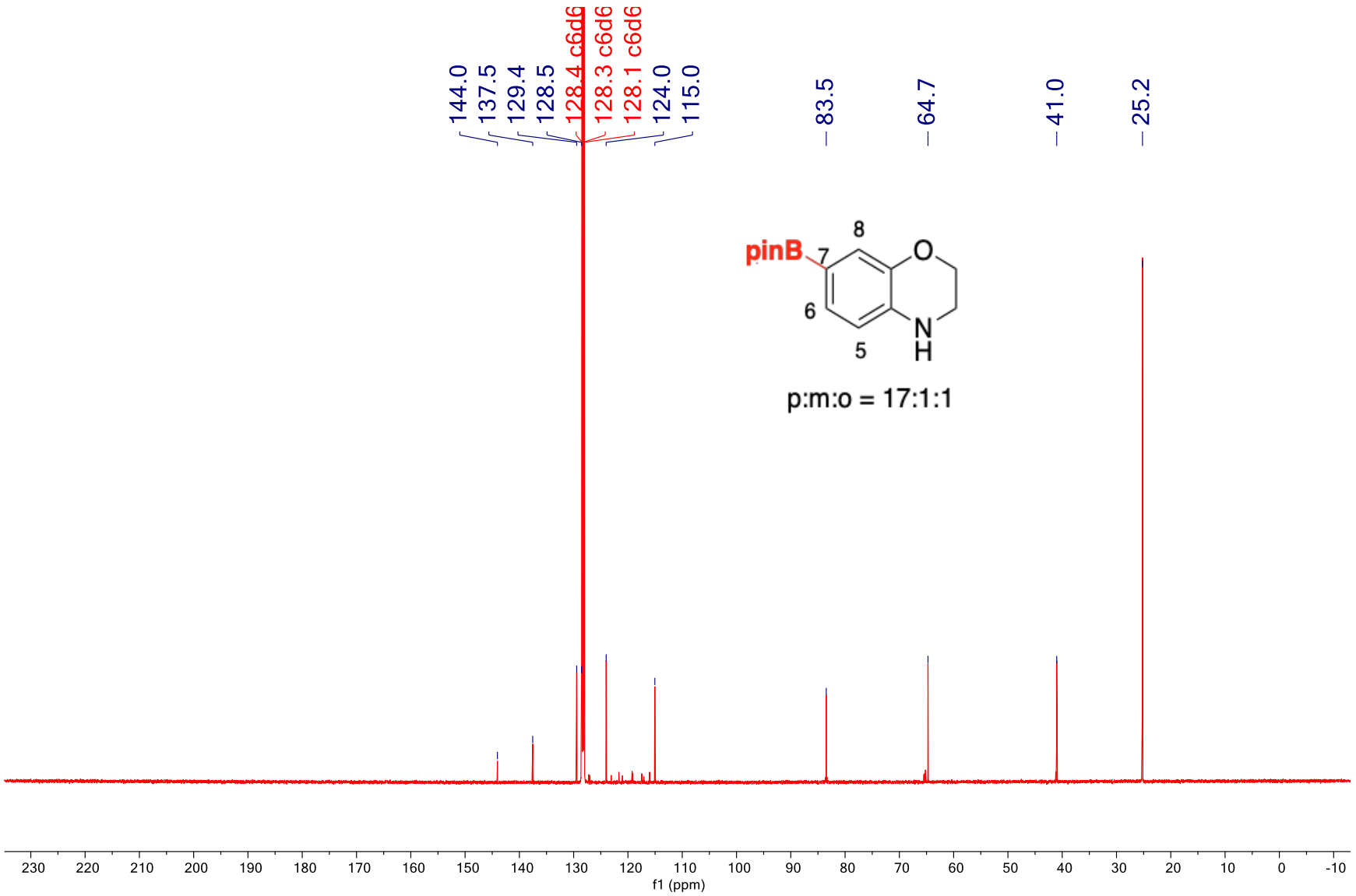
^{1}H NMR of *para* borylated 3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4h) (C_6D_6, 500 MHz)



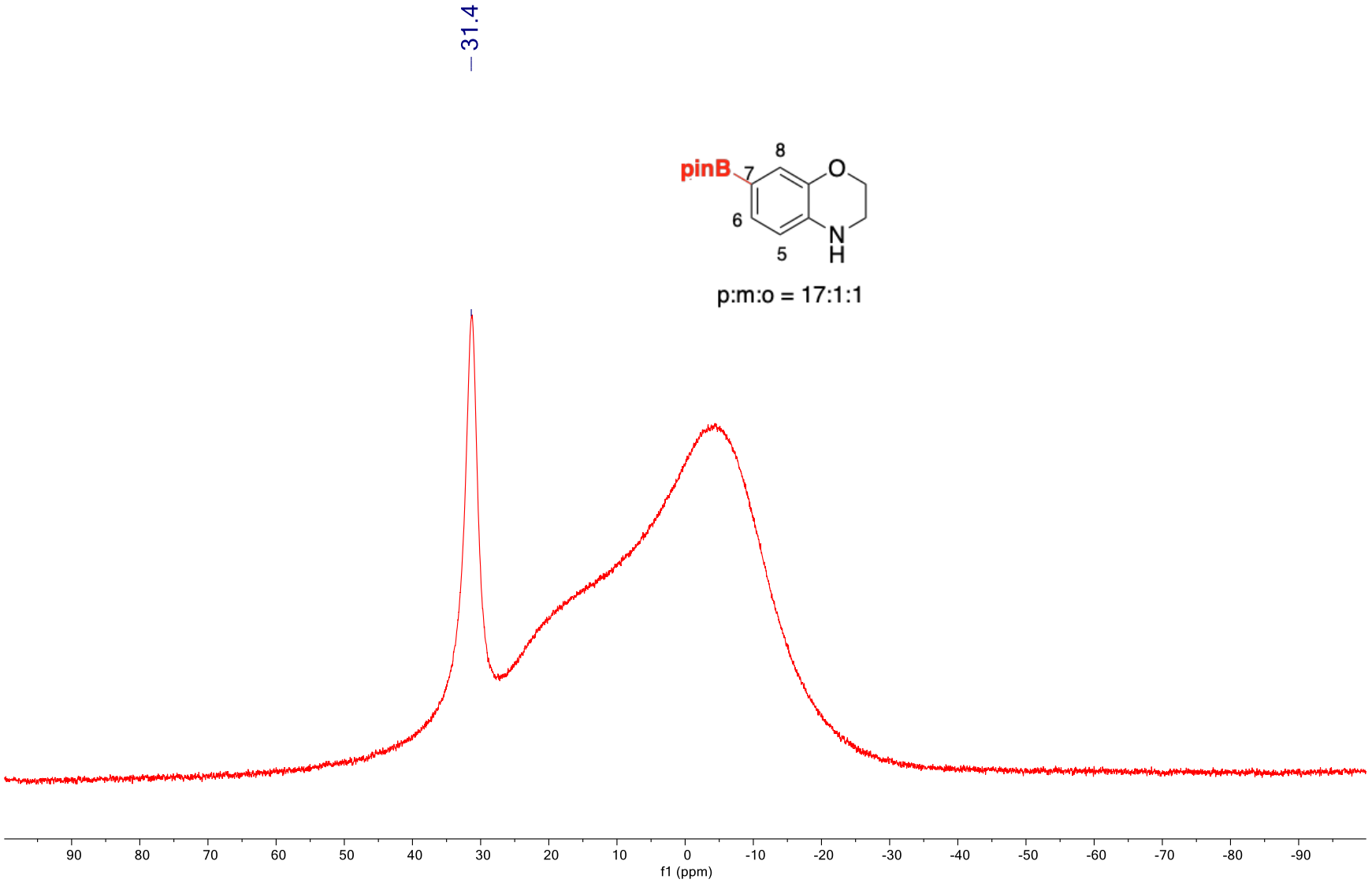
^{1}H NMR of *para* borylated 3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4h) ($CDCl_3$, 500 MHz)



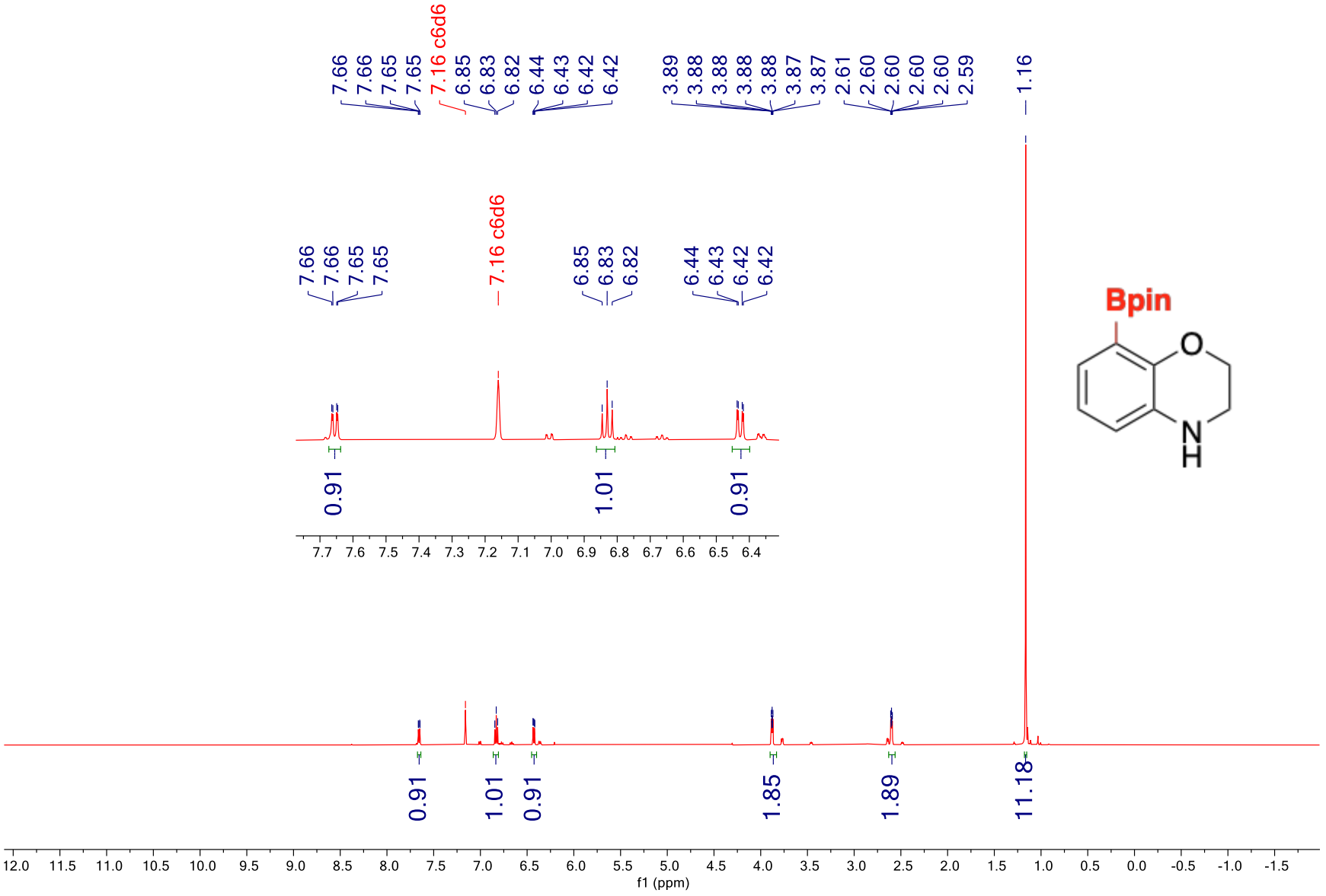
^{13}C NMR of *para* borylated 3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4h) (C_6D_6, 126 MHz)



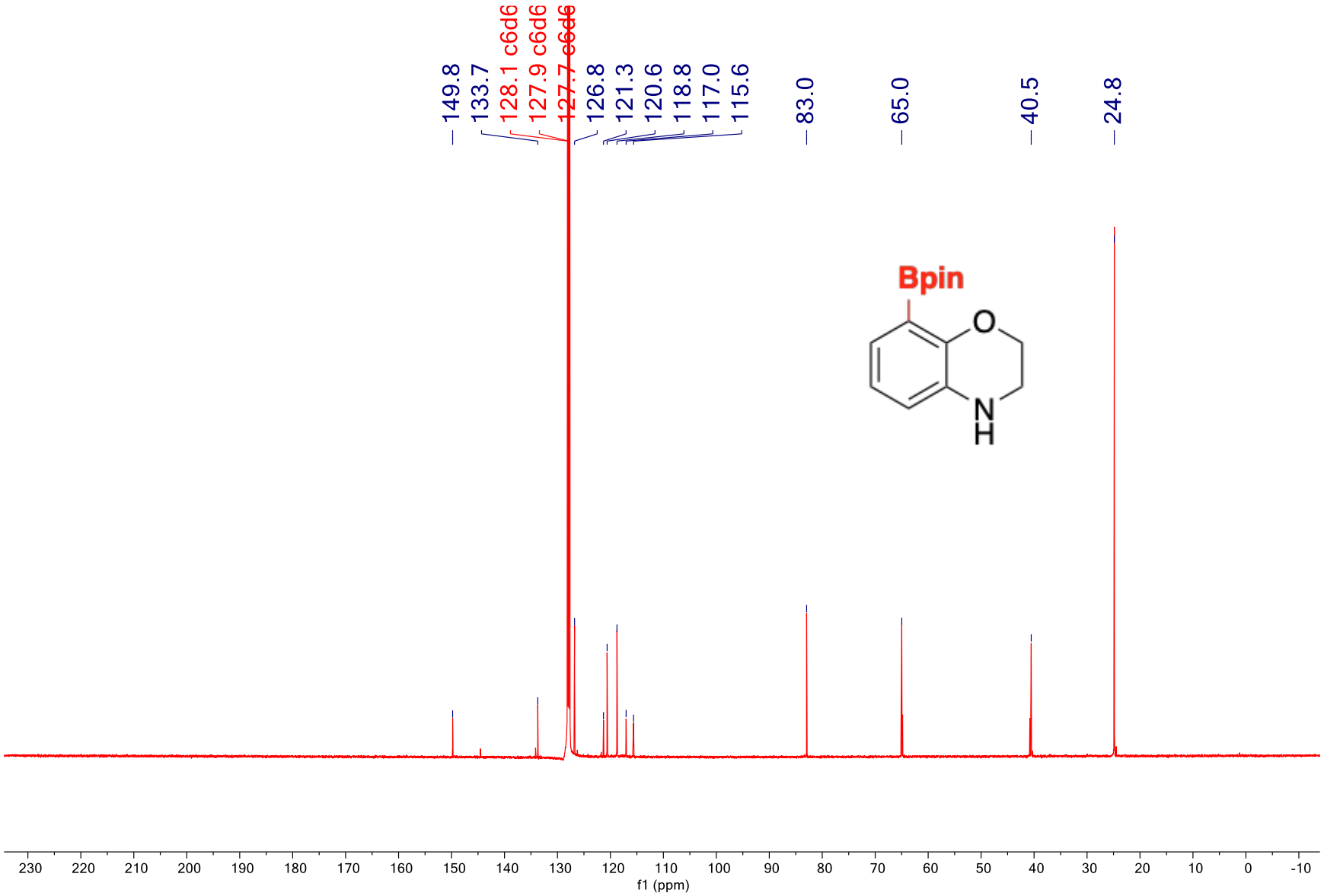
^{11}B NMR of *para* borylated 3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4h) (C_6D_6, 126 MHz)



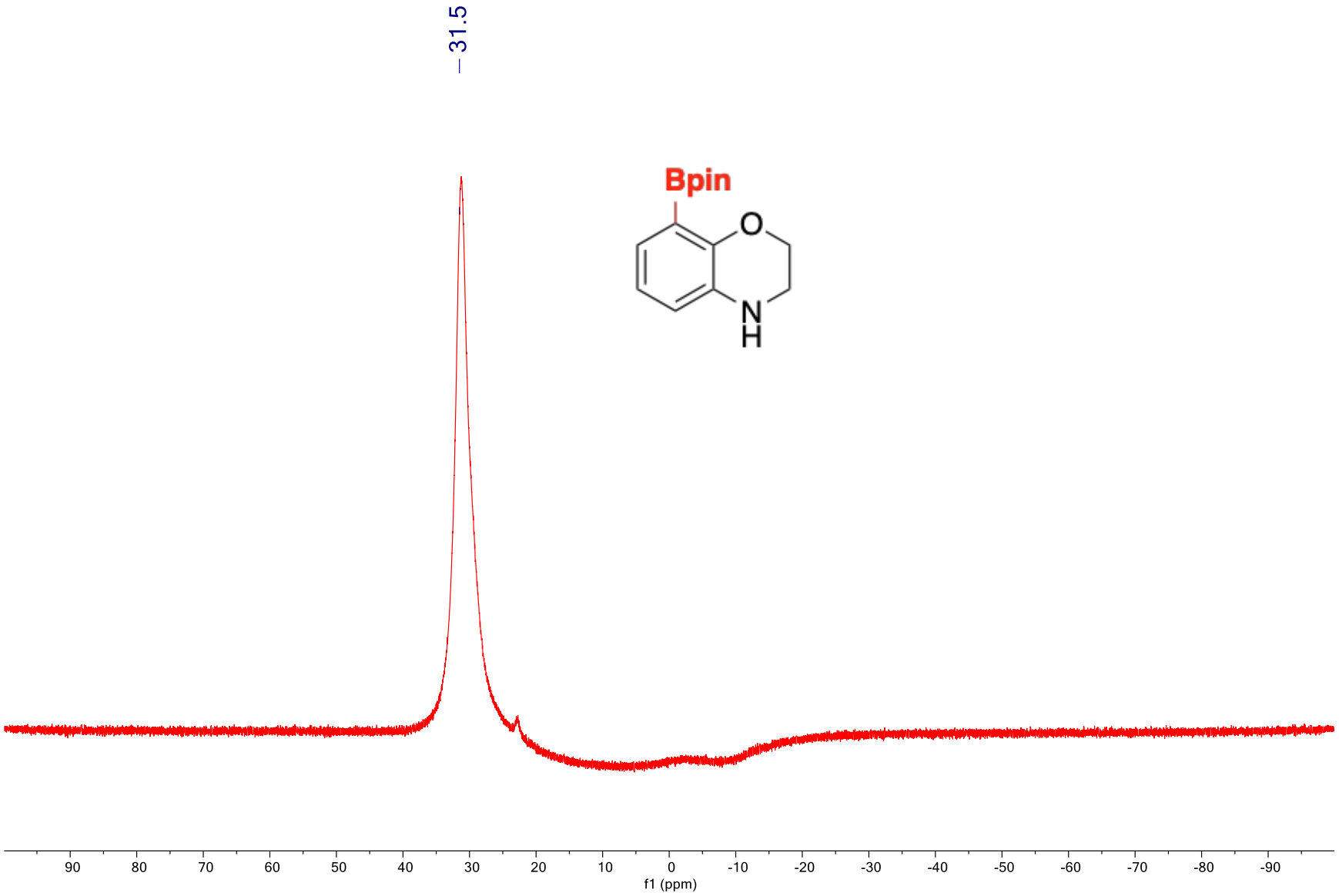
^{1}H NMR of 8-borylated 2-amino-N-methylpyridine (4.4h) (C_6D_6, 500 MHz)



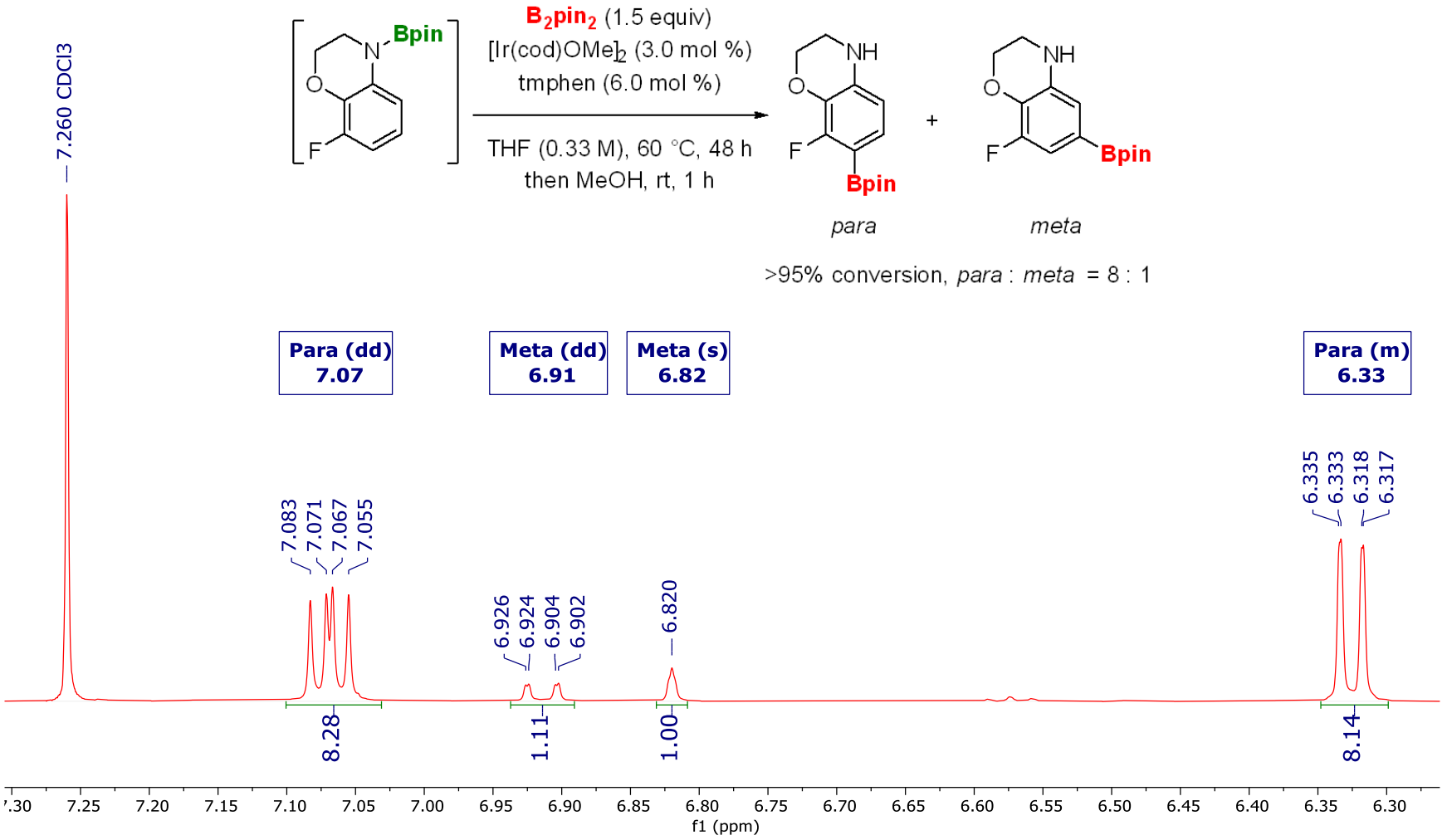
^{13}C NMR of 8-borylated 2-amino-N-methylpyridine (4.4h) (C_6D_6, 126 MHz)



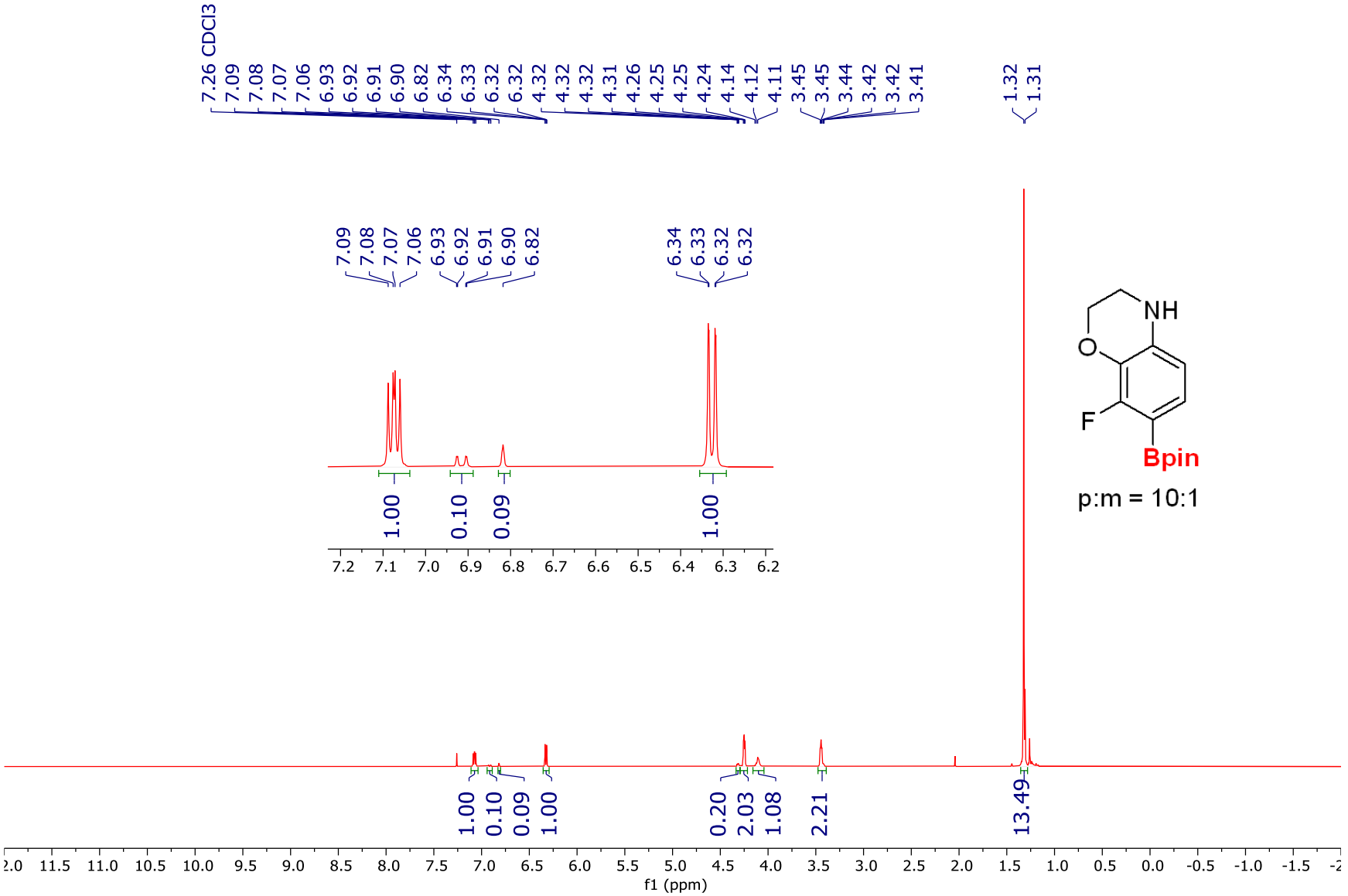
^{11}B NMR of 8-borylated 2-amino-N-methylpyridine (4.4h) (C_6D_6, 126 MHz)



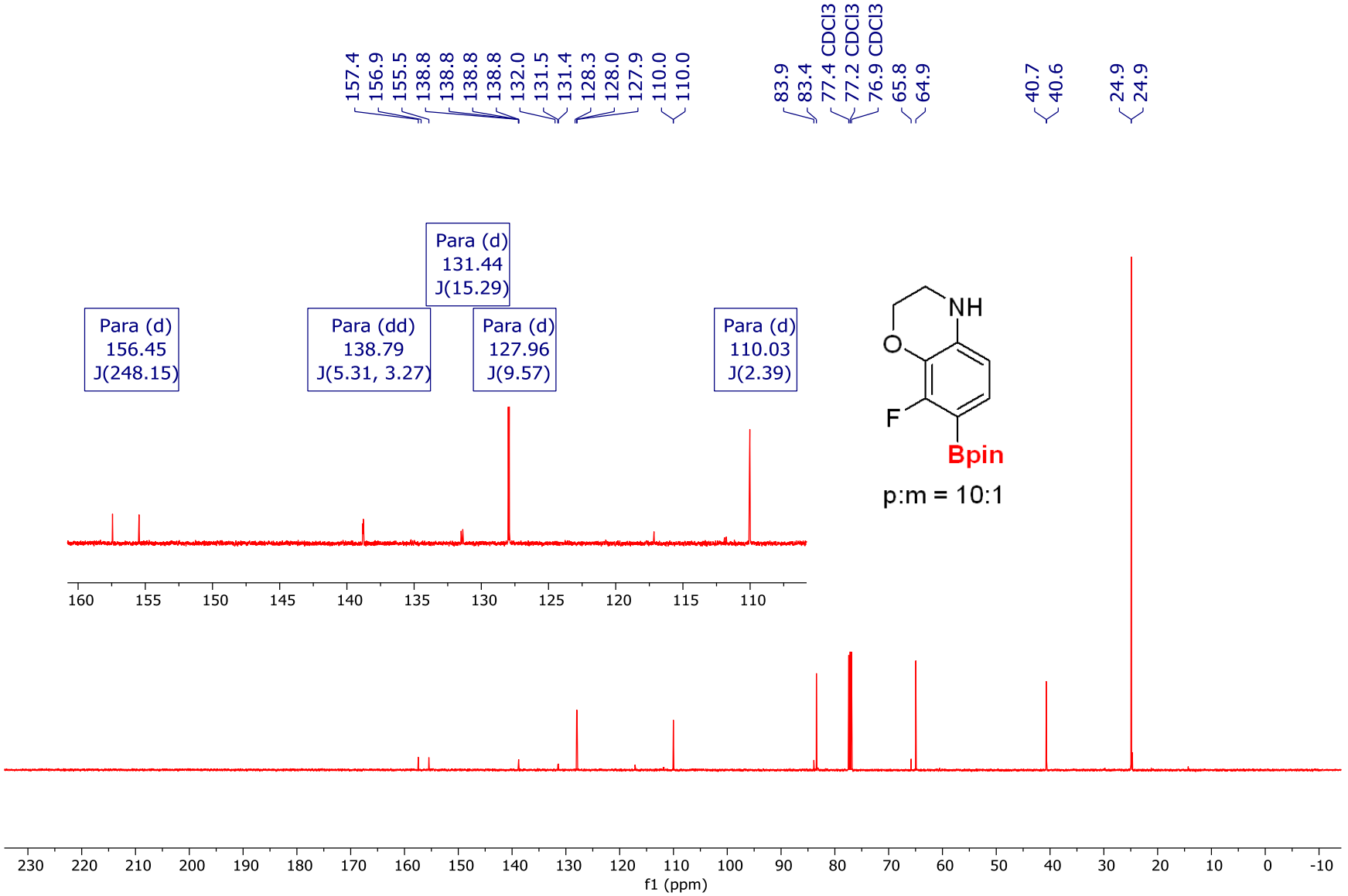
***Para* CHB of 8-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4i) ($CDCl_3$, 500 MHz)**



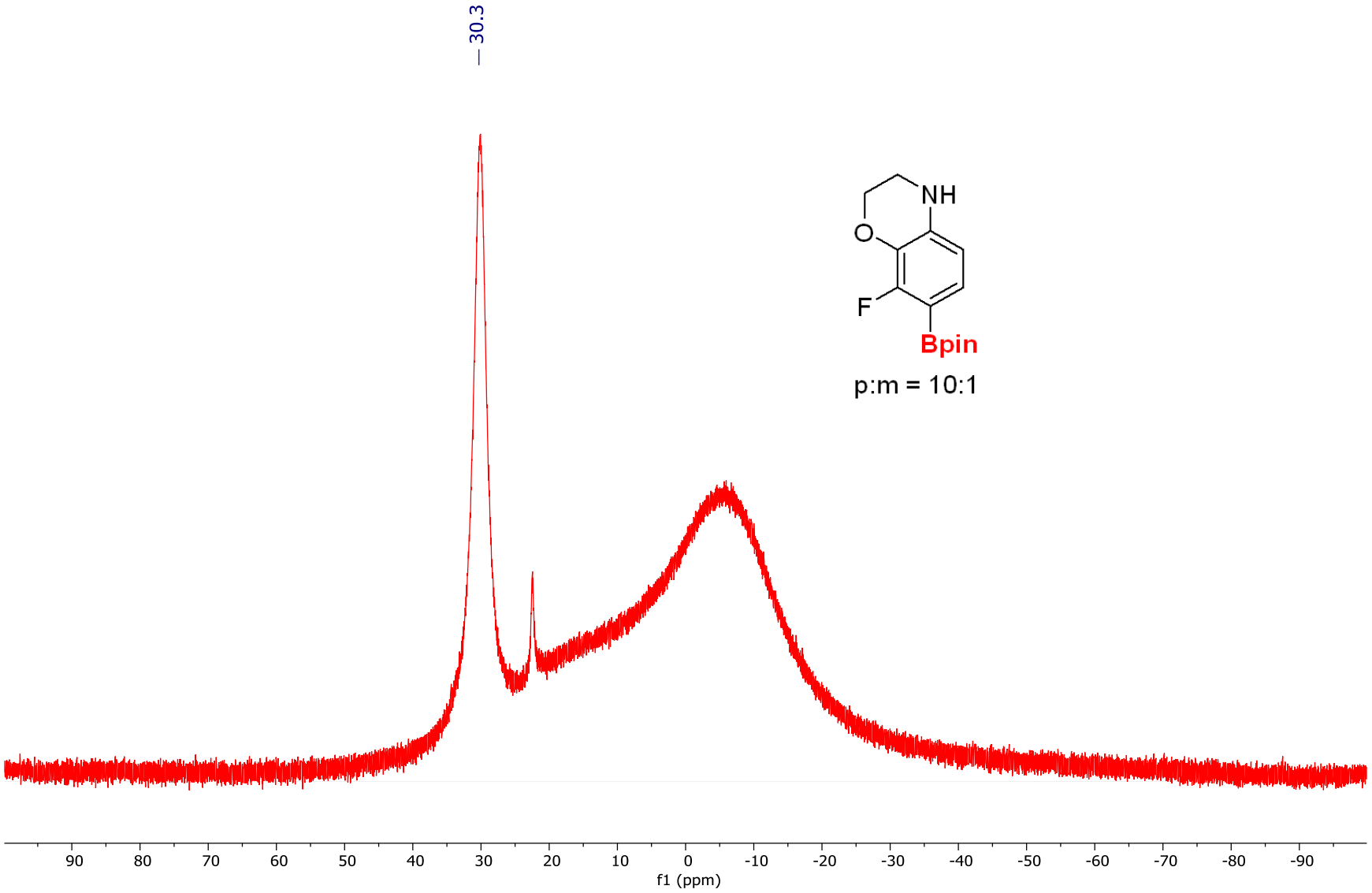
^{1}H NMR of *para* borylated 8-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4i) ($CDCl_3$, 500 MHz)



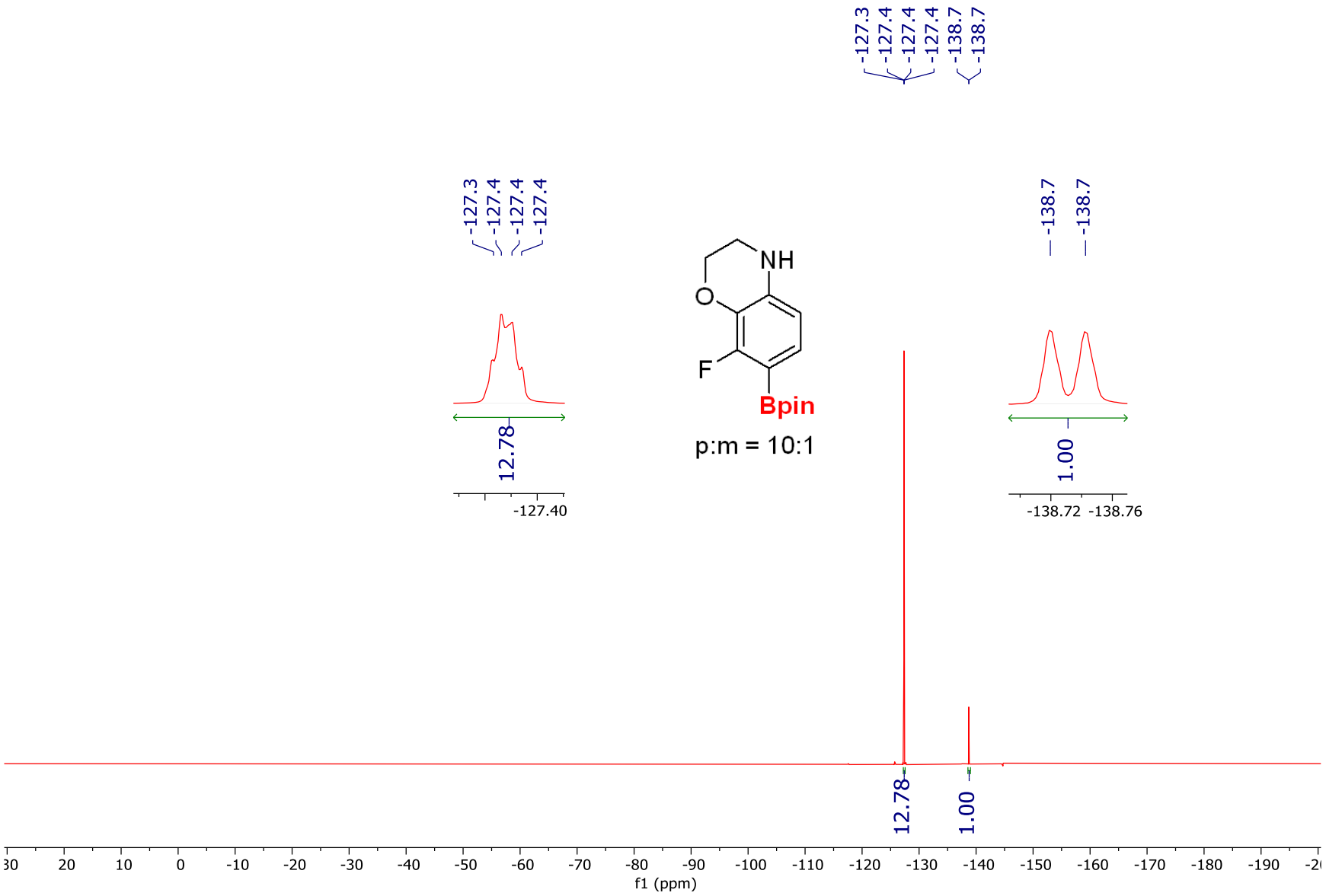
^{13}C NMR of *para* borylated 8-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4i) ($CDCl_3$, 126 MHz)



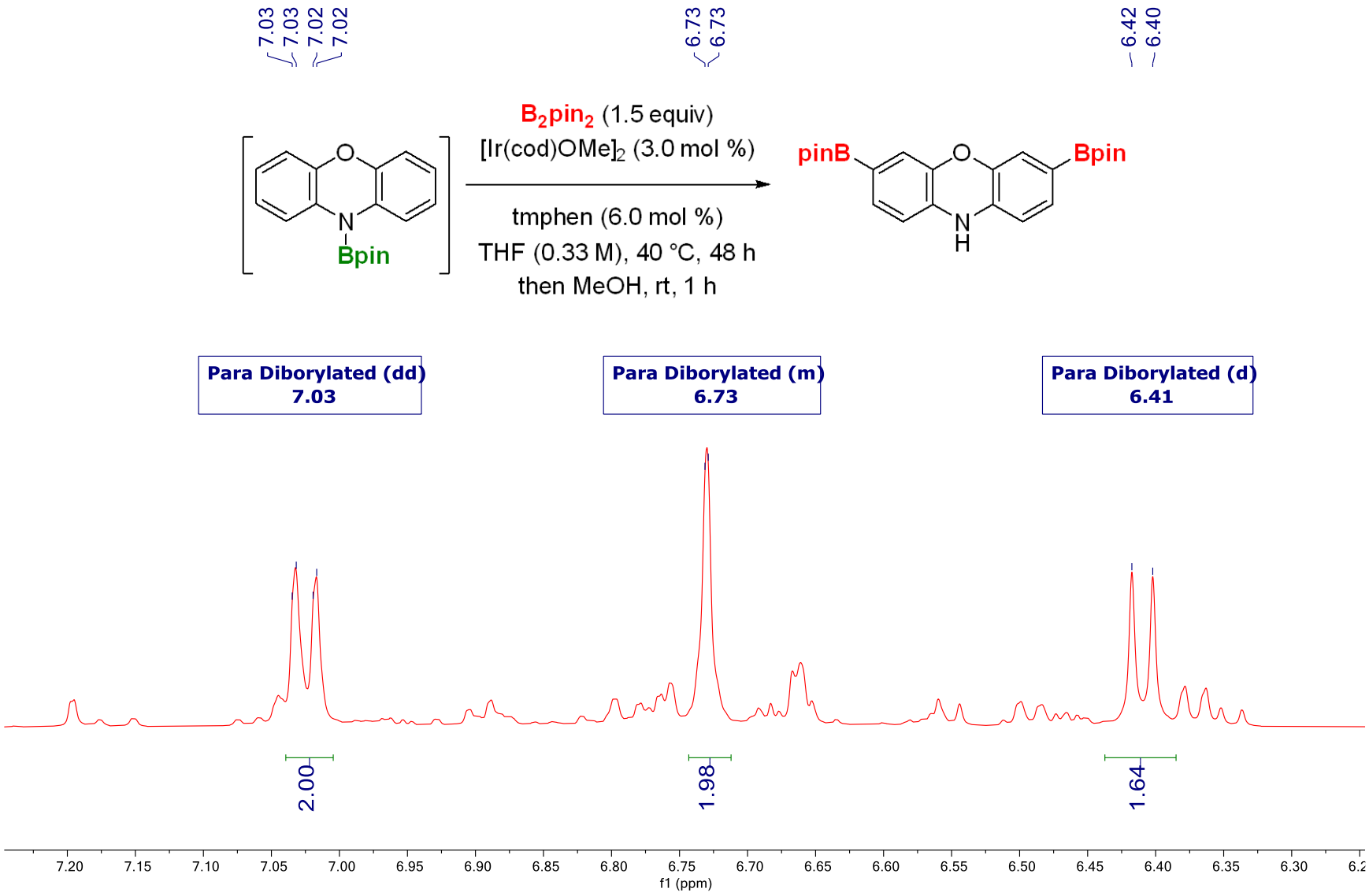
^{11}B NMR of *para* borylated 8-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4i) ($CDCl_3$, 126 MHz)



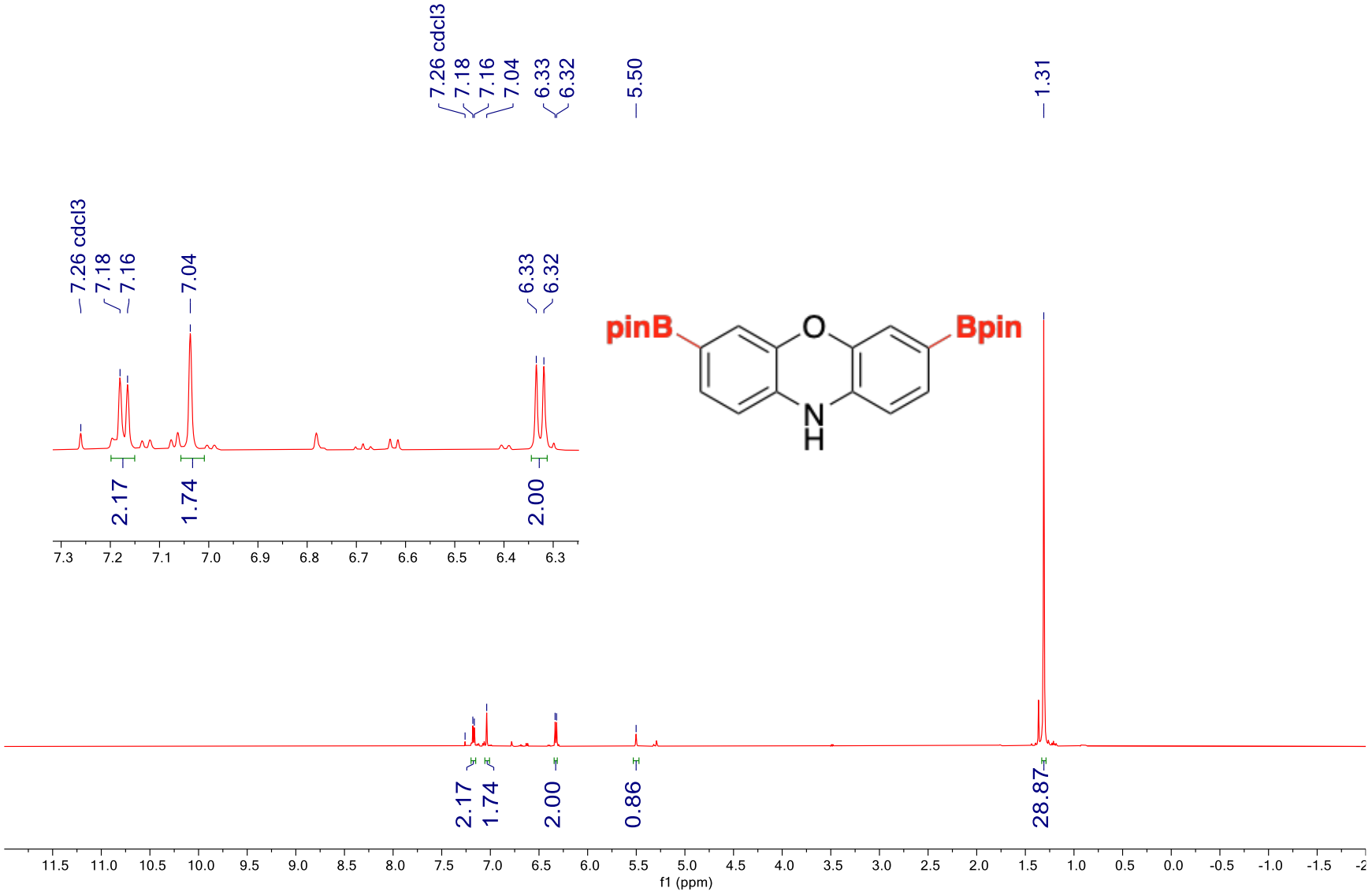
^{19}F NMR of *para* borylated 8-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (4.4i) ($CDCl_3$, 126 MHz)



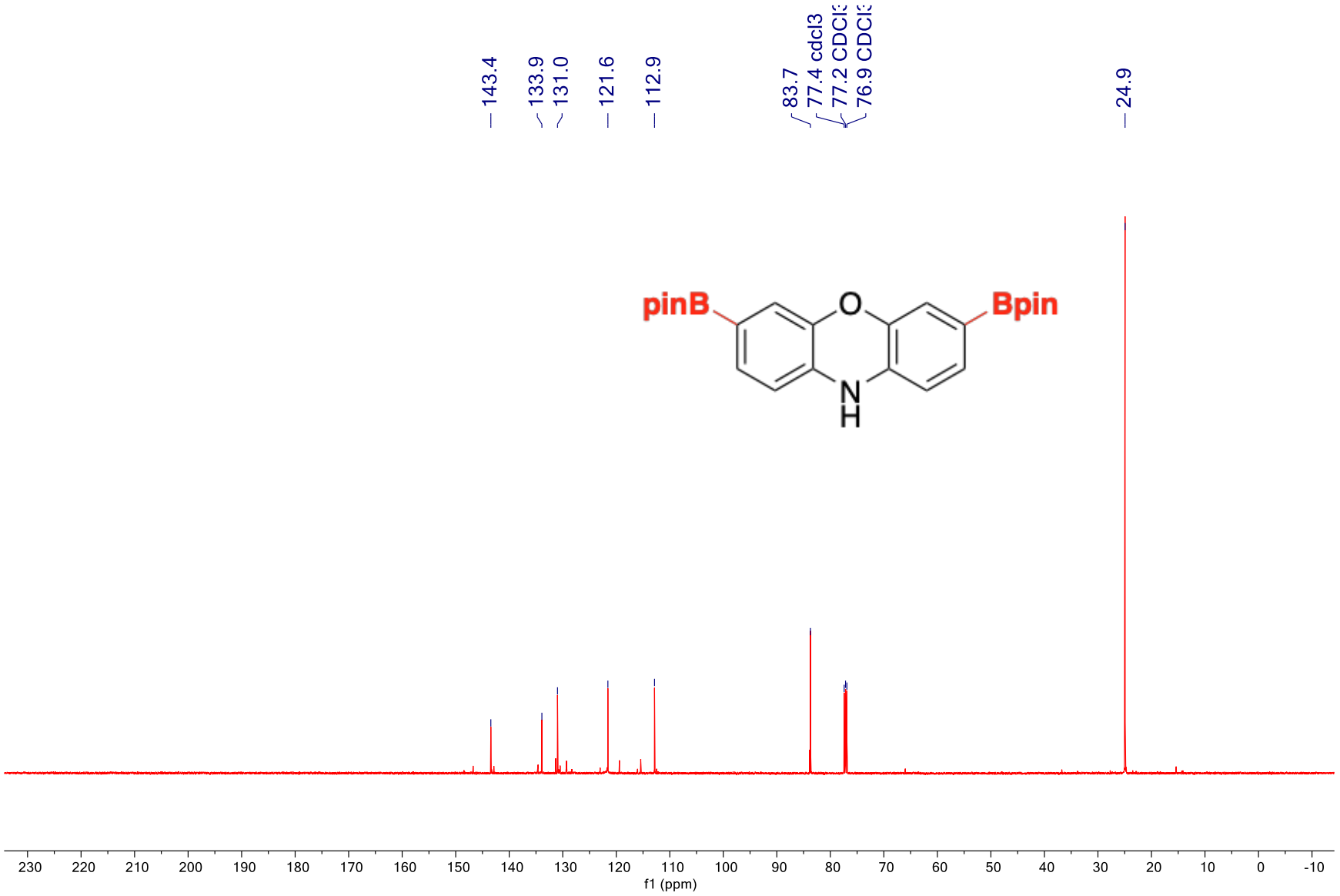
***Para* Borylation of 1,2,3,4-tetrahydroquinoline (4.4j) (DMSO-d6, 500 MHz)**



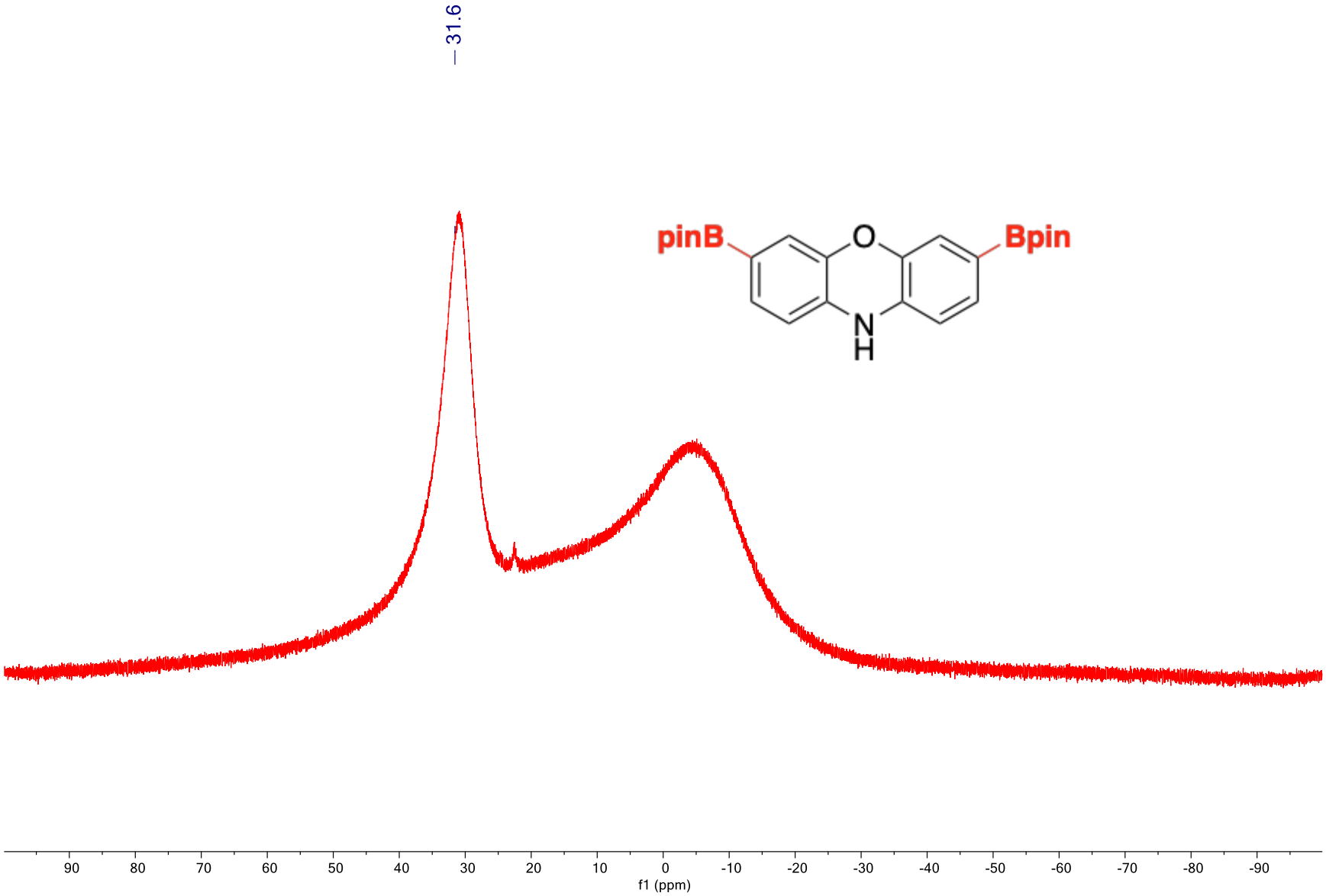
^{1}H NMR of *para* diborylated 10*H*-phenoxazine (4.4j) ($CDCl_3$, 500 MHz)



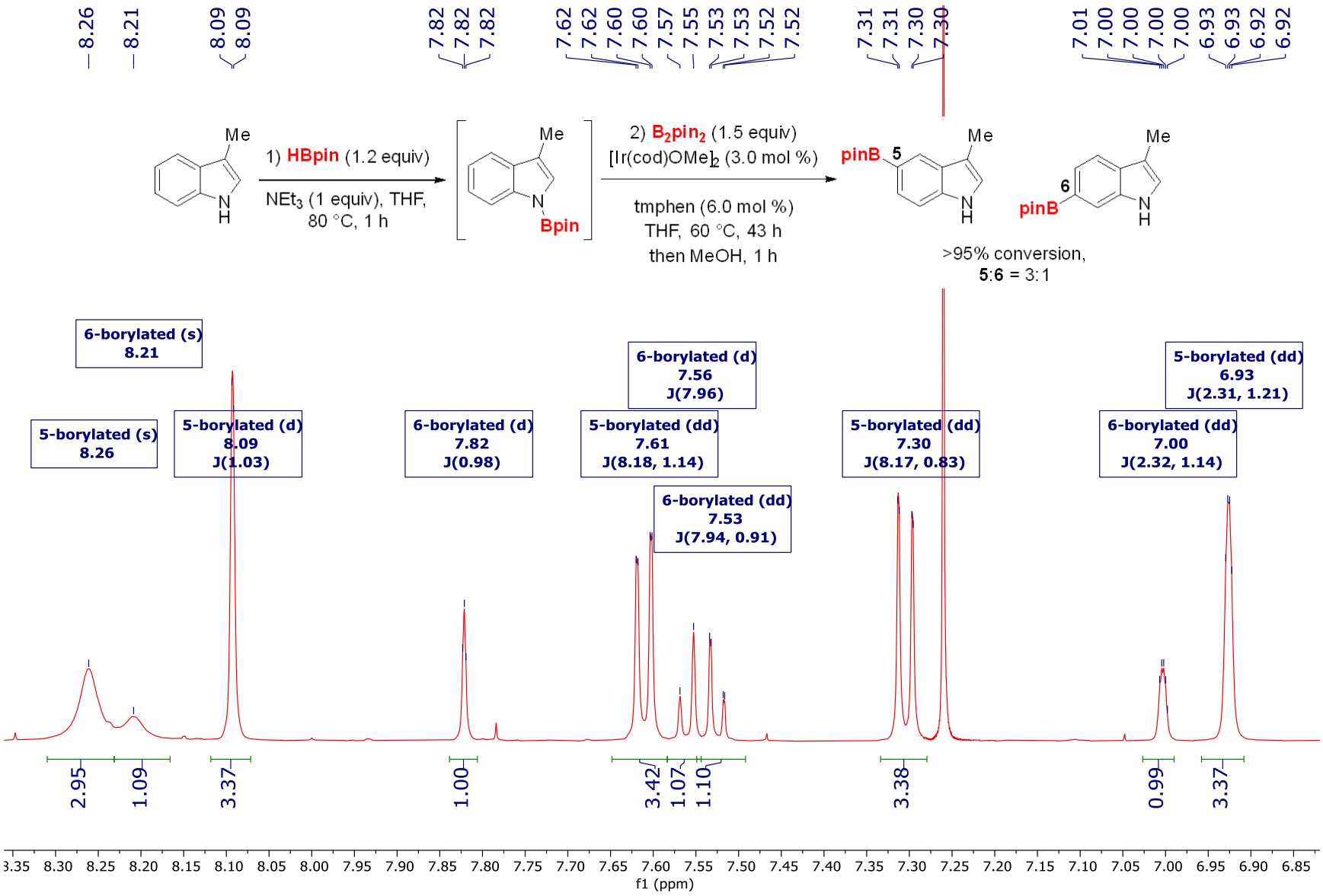
^{13}C NMR of *para* diborylated 10*H*-phenoxazine (4.4j) ($CDCl_3$, 126 MHz)



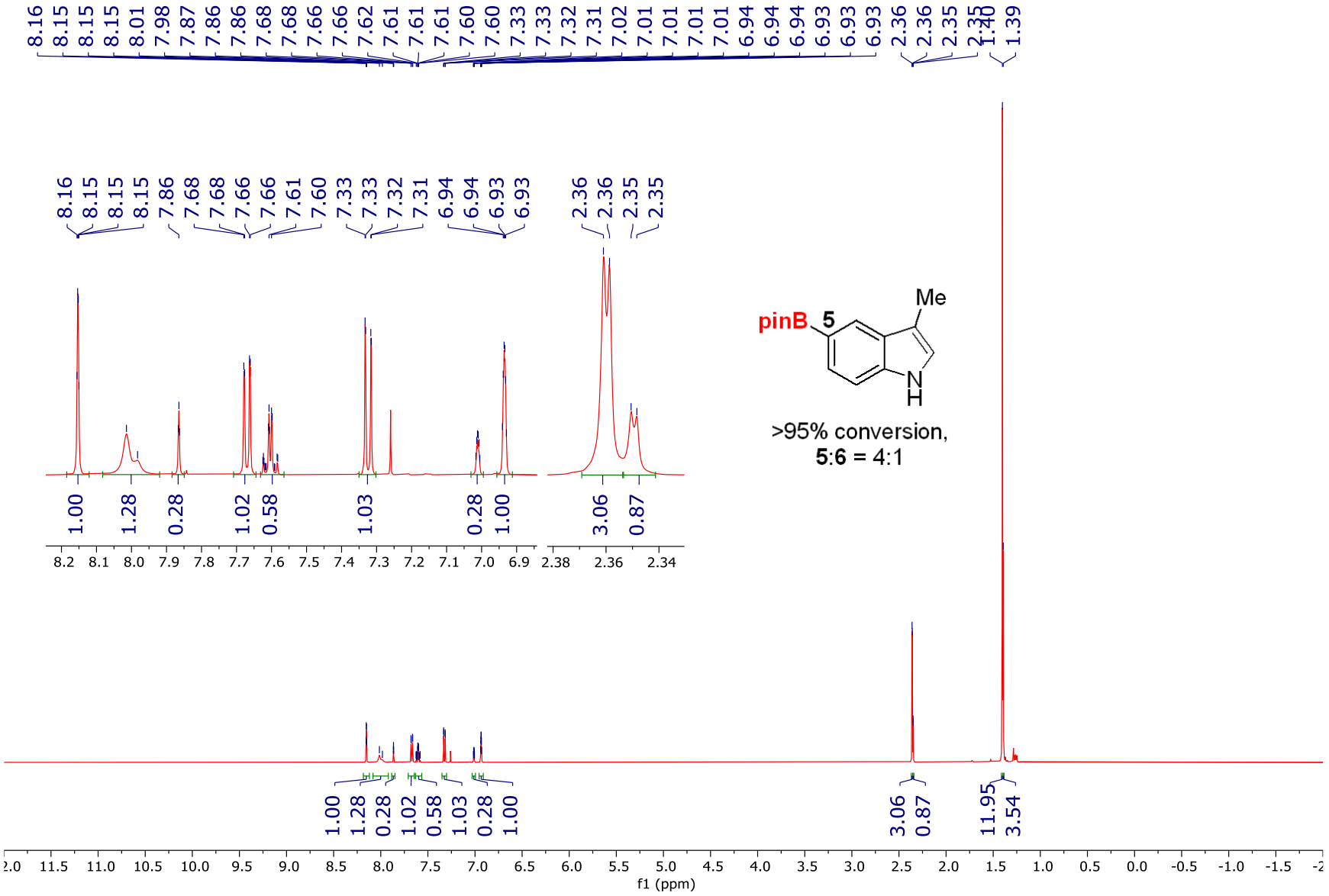
^{11}B NMR of *para* diborylated 10*H*-phenoxazine (4.4j) ($CDCl_3$, 126 MHz)



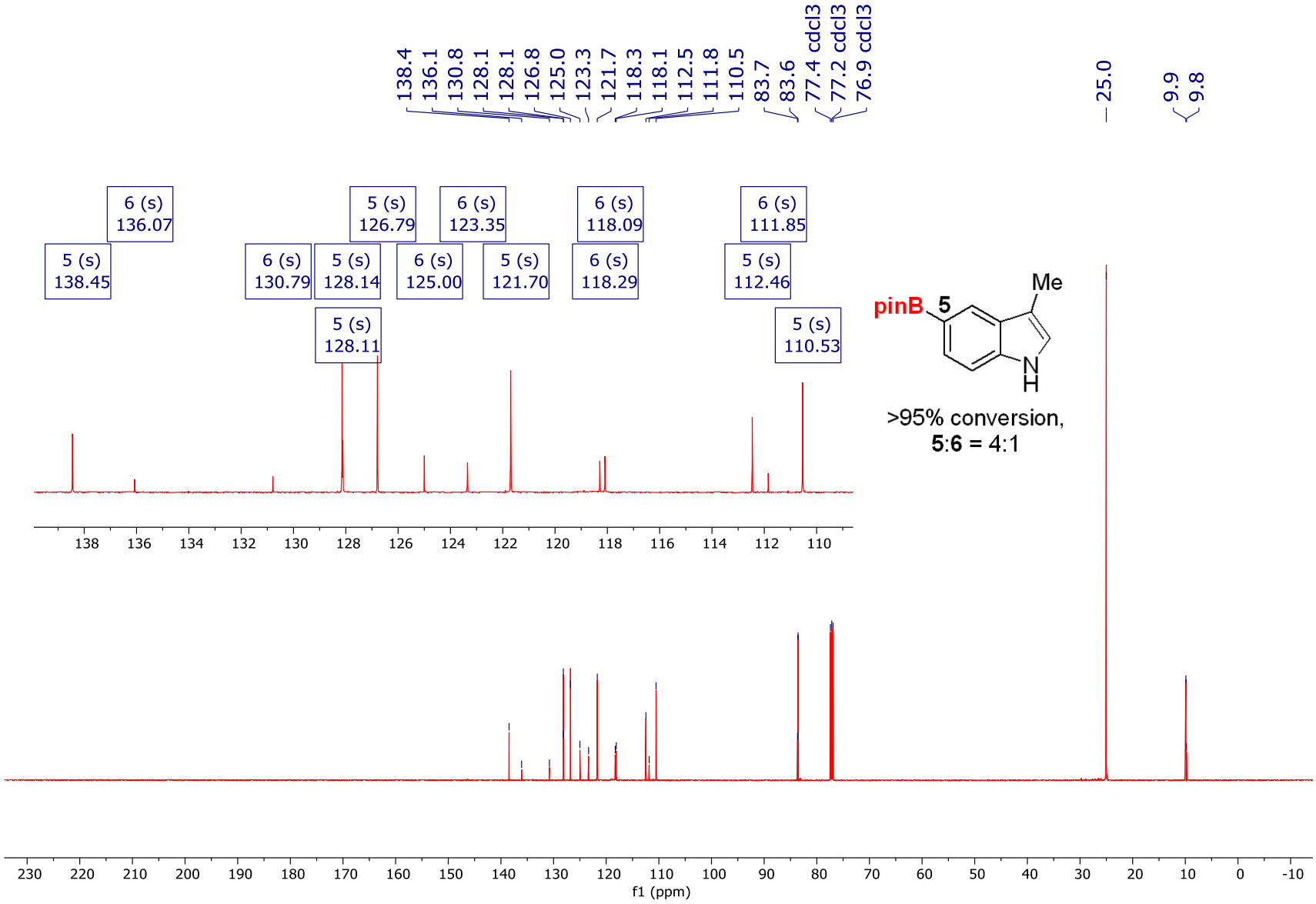
C5 CHB of 5-borylated 3-methyl indole (4.6a) ($CDCl_3$, 500 MHz)



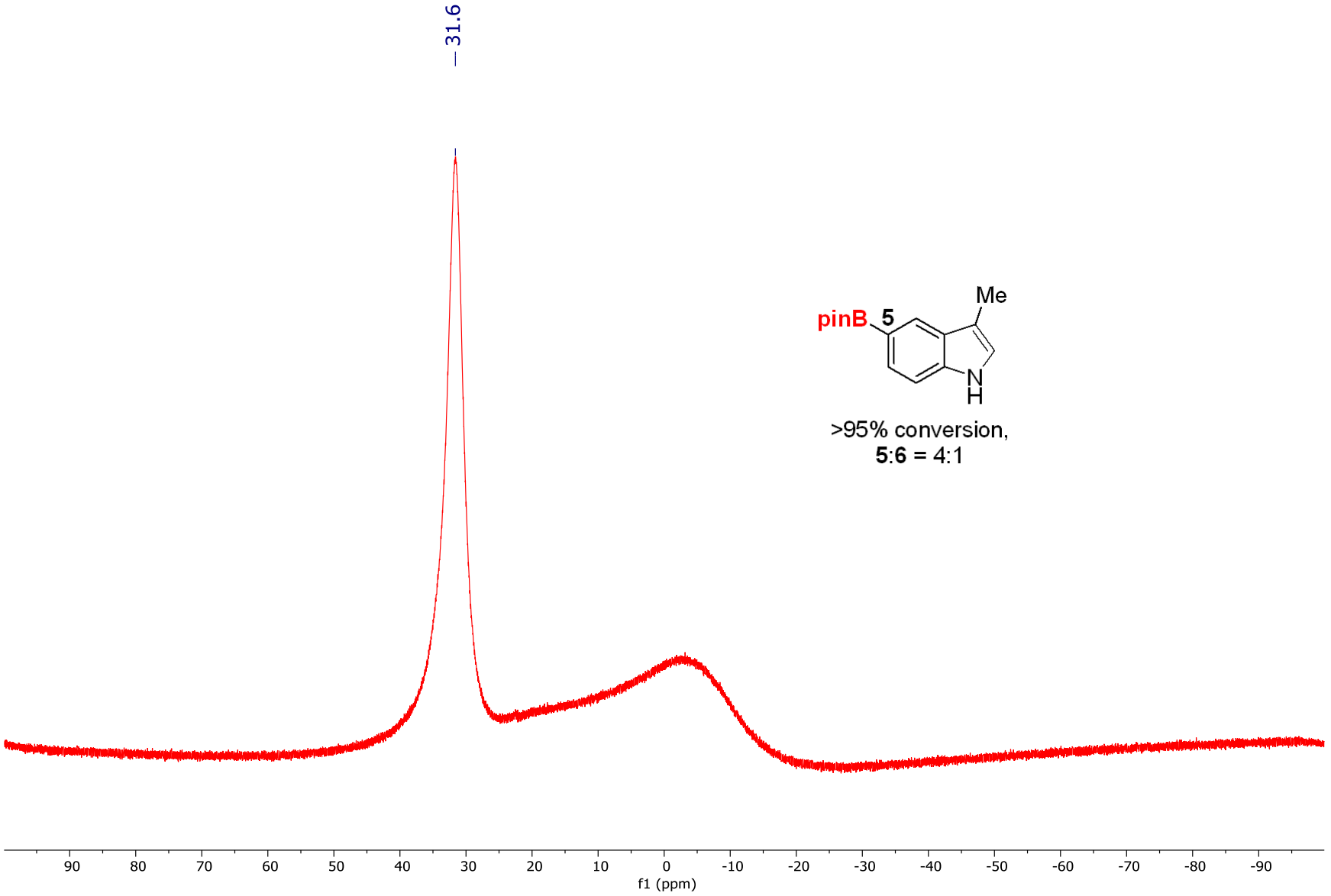
^{1}H NMR of 5-borylated 3-methyl indole (4.6a) ($CDCl_3$, 500 MHz)



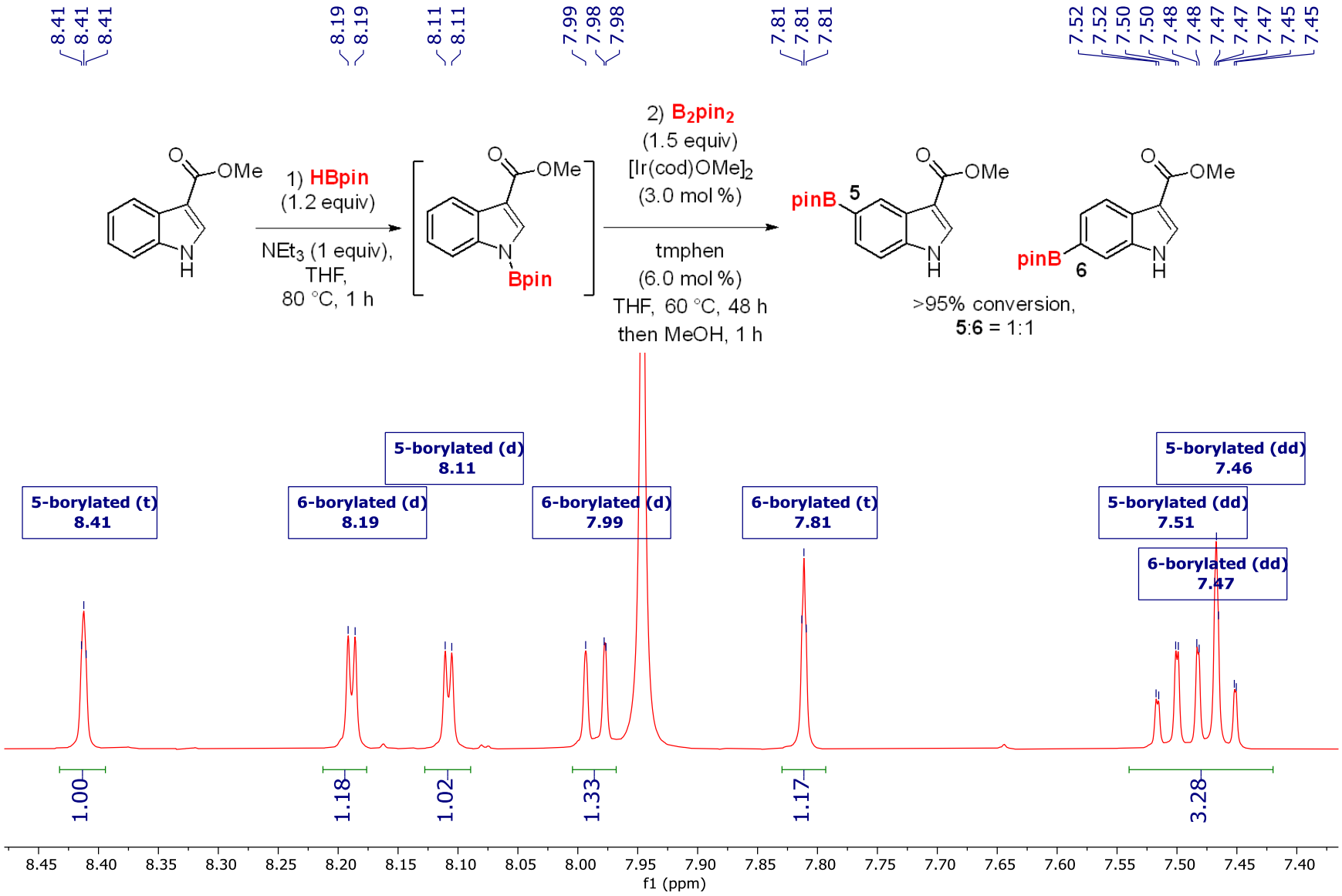
^{13}C NMR of 5-borylated 3-methyl indole (4.6a) ($CDCl_3$, 126 MHz)



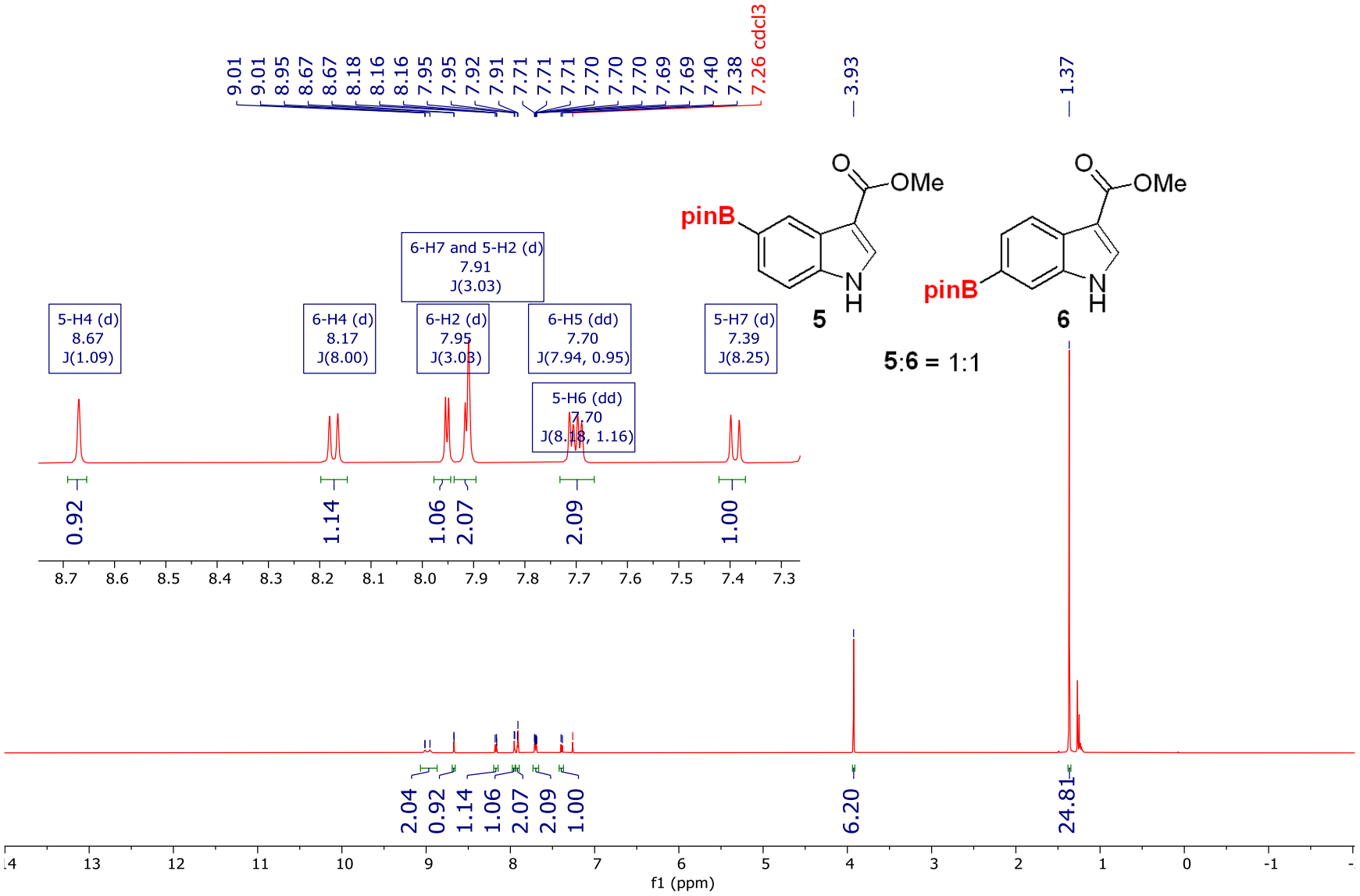
^{11}B NMR of 5-borylated 3-methyl indole (4.6a) ($CDCl_3$, 160 MHz)



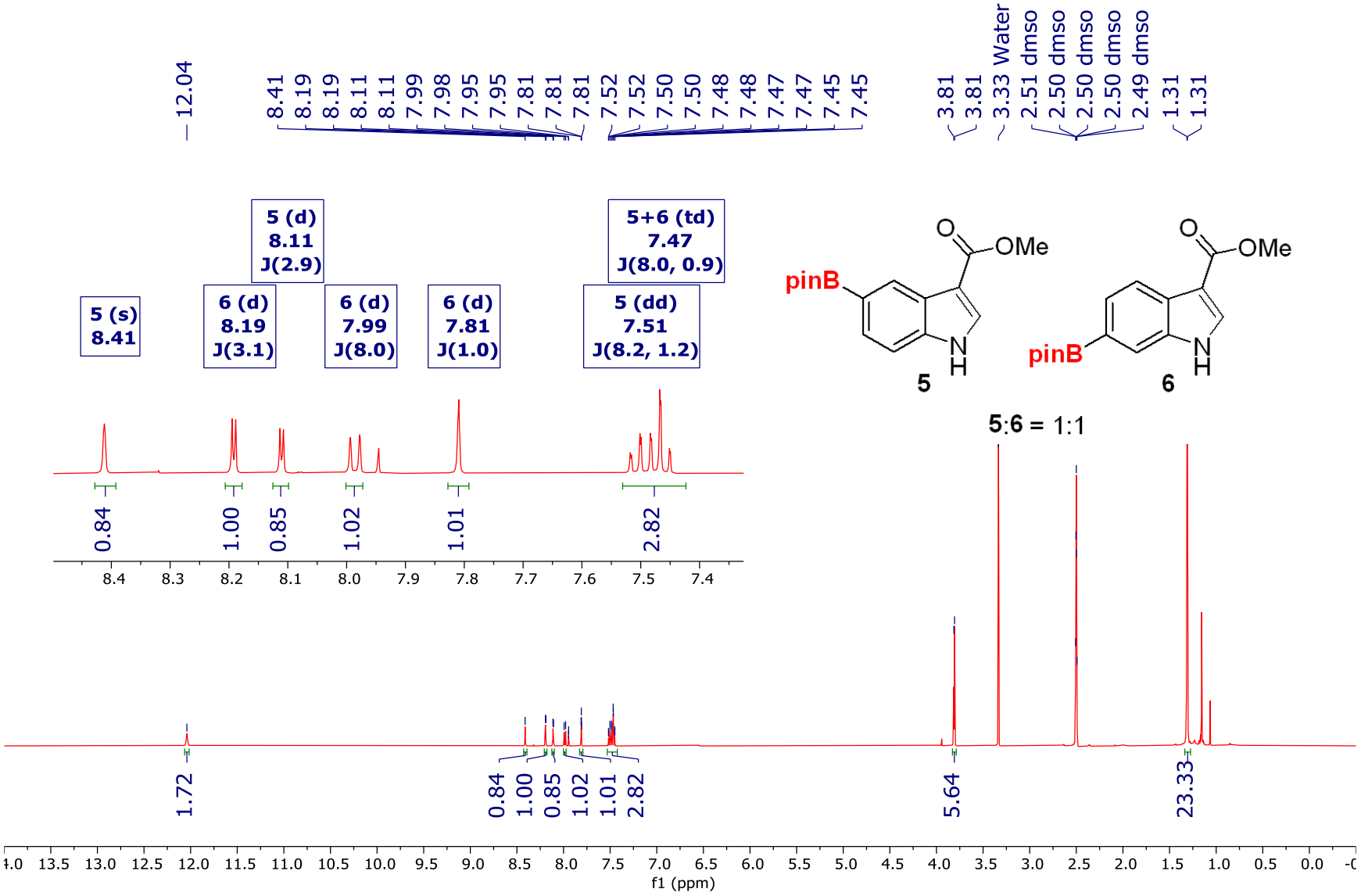
C5 CHB of 5-borylated methyl indole-3-carboxylate (4.6b) (DMSO-d6, 500 MHz)



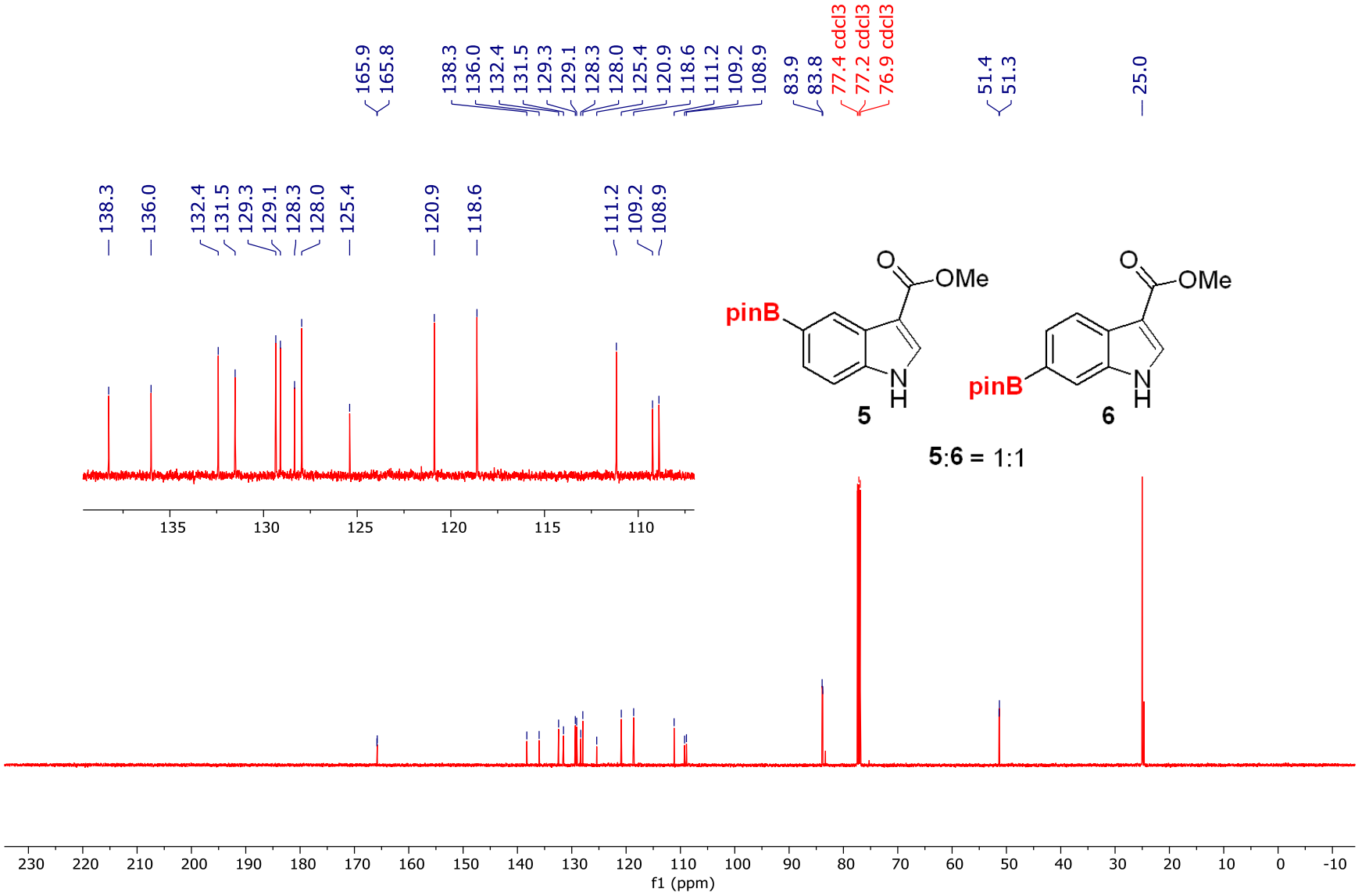
^{1}H NMR of 5- and 6-borylated methyl indole-3-carboxylate (4.6b) ($CDCl_3$, 500 MHz)



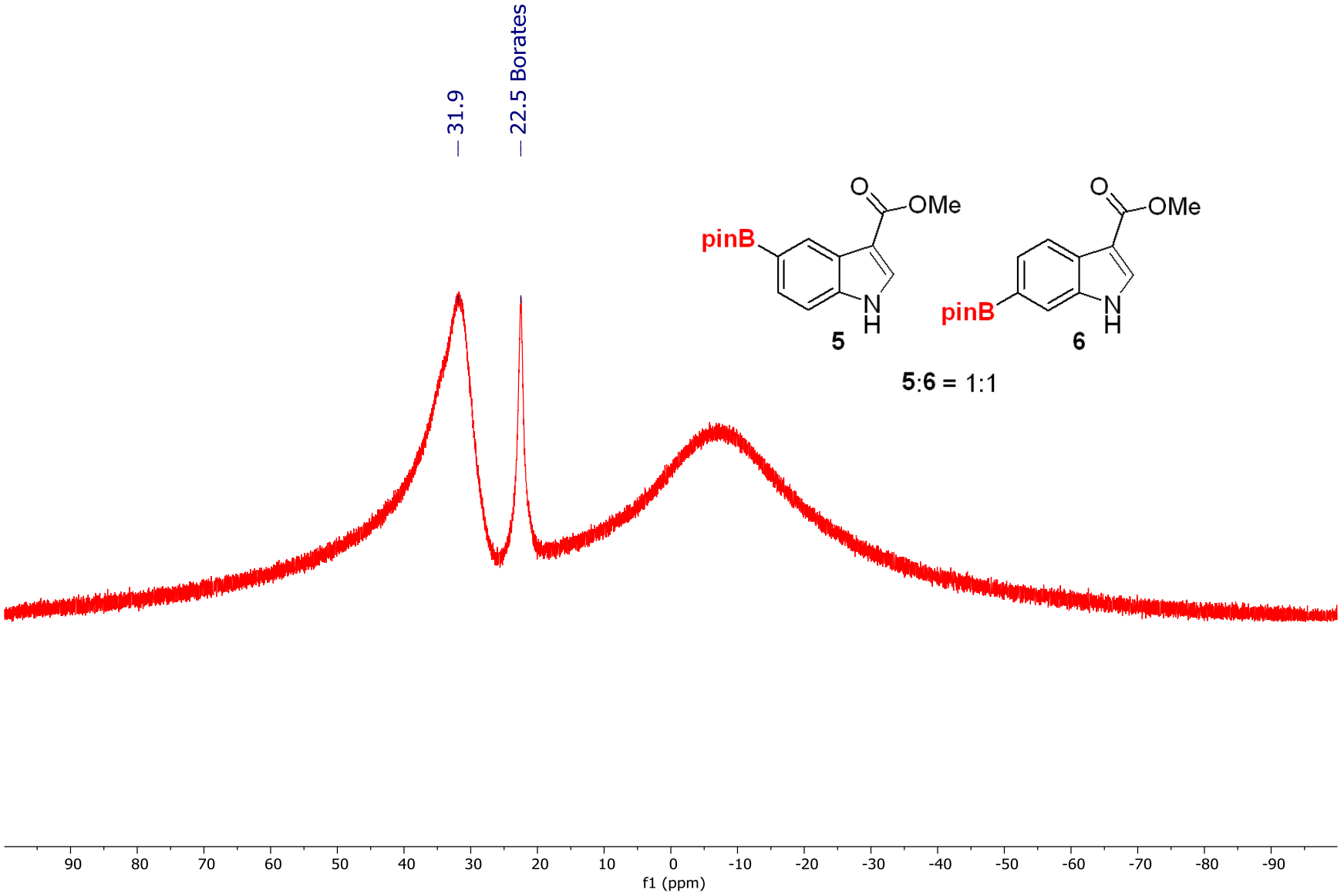
^{1}H NMR of 5- and 6-borylated methyl indole-3-carboxylate (4.6b) (DMSO-d6, 500 MHz)



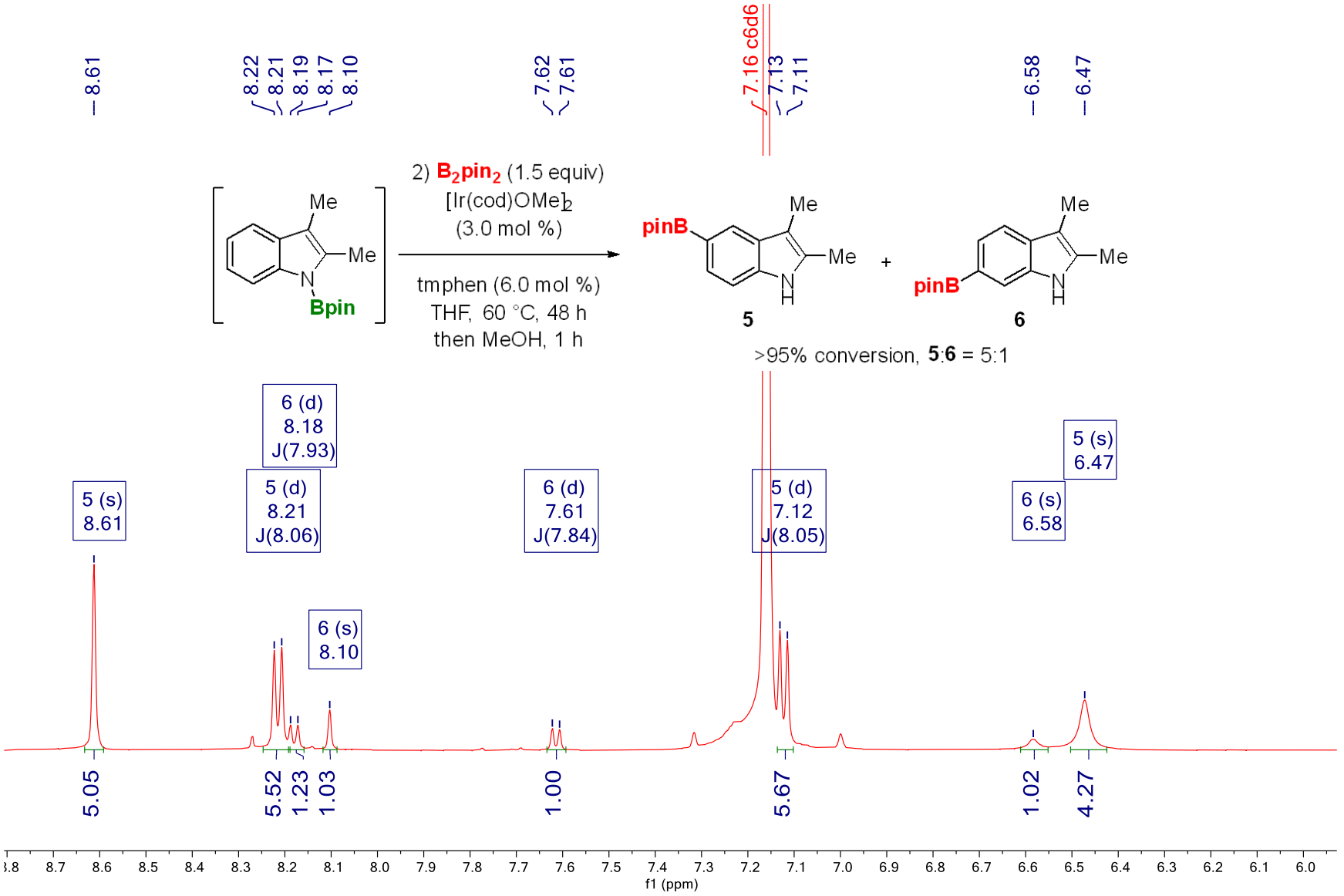
^{13}C NMR of 5- and 6-borylated methyl indole-3-carboxylate (4.6b) ($CDCl_3$, 126 MHz)



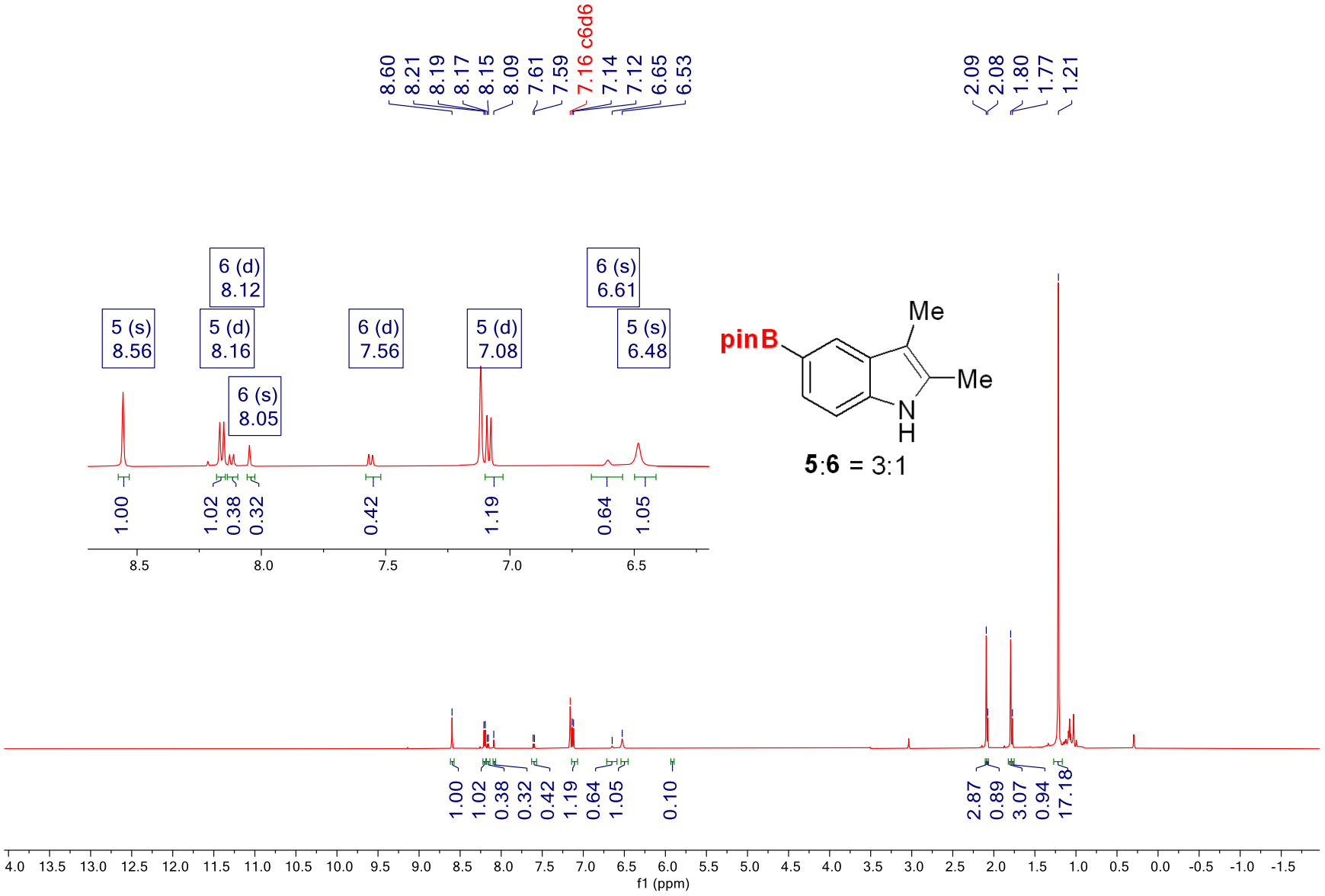
^{11}B NMR of 5- and 6-borylated methyl indole-3-carboxylate (4.6b) ($CDCl_3$, 160 MHz)



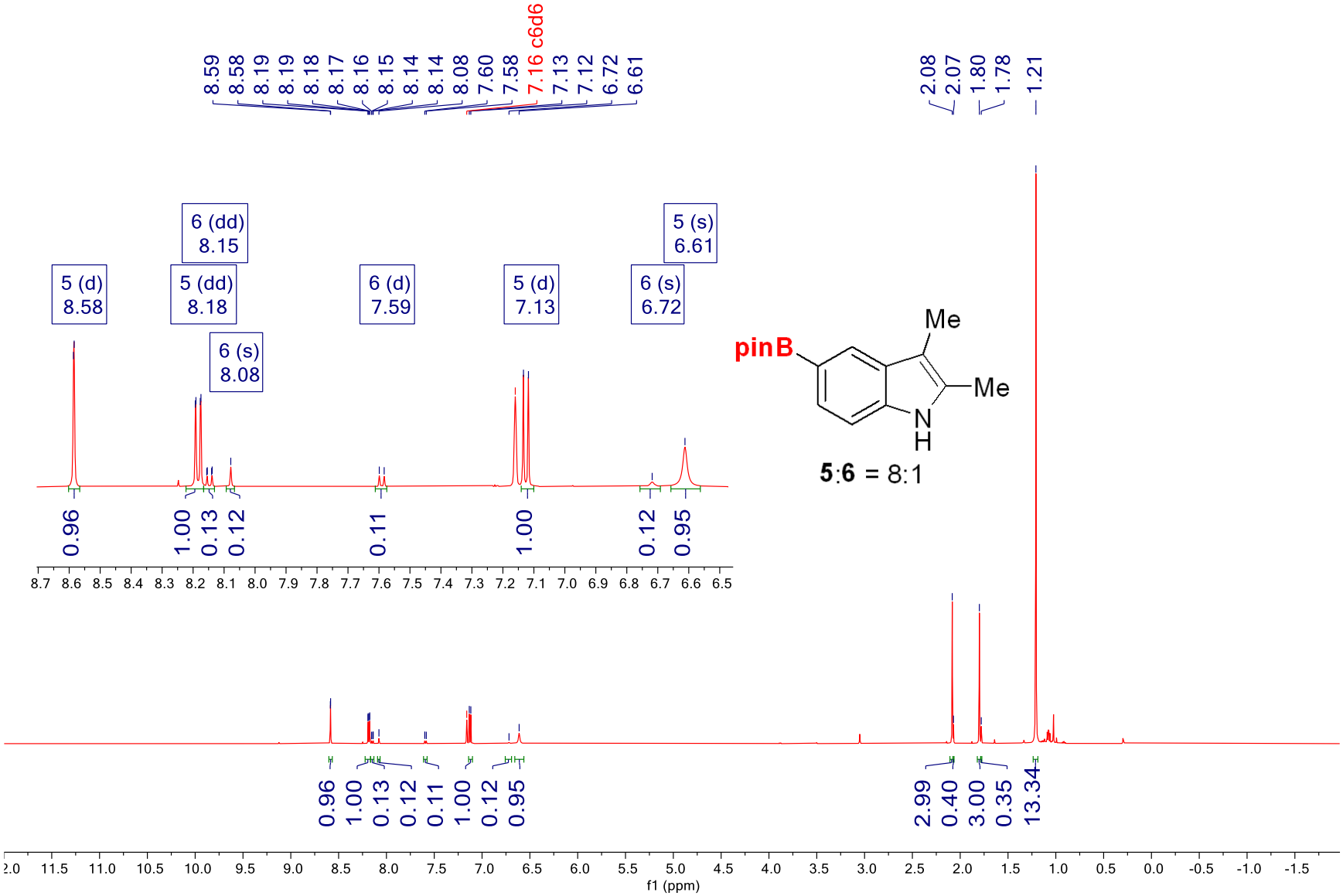
C5 CHB of 2,3-dimethyl indole (4.6c) (C_6D_6, 500 MHz)



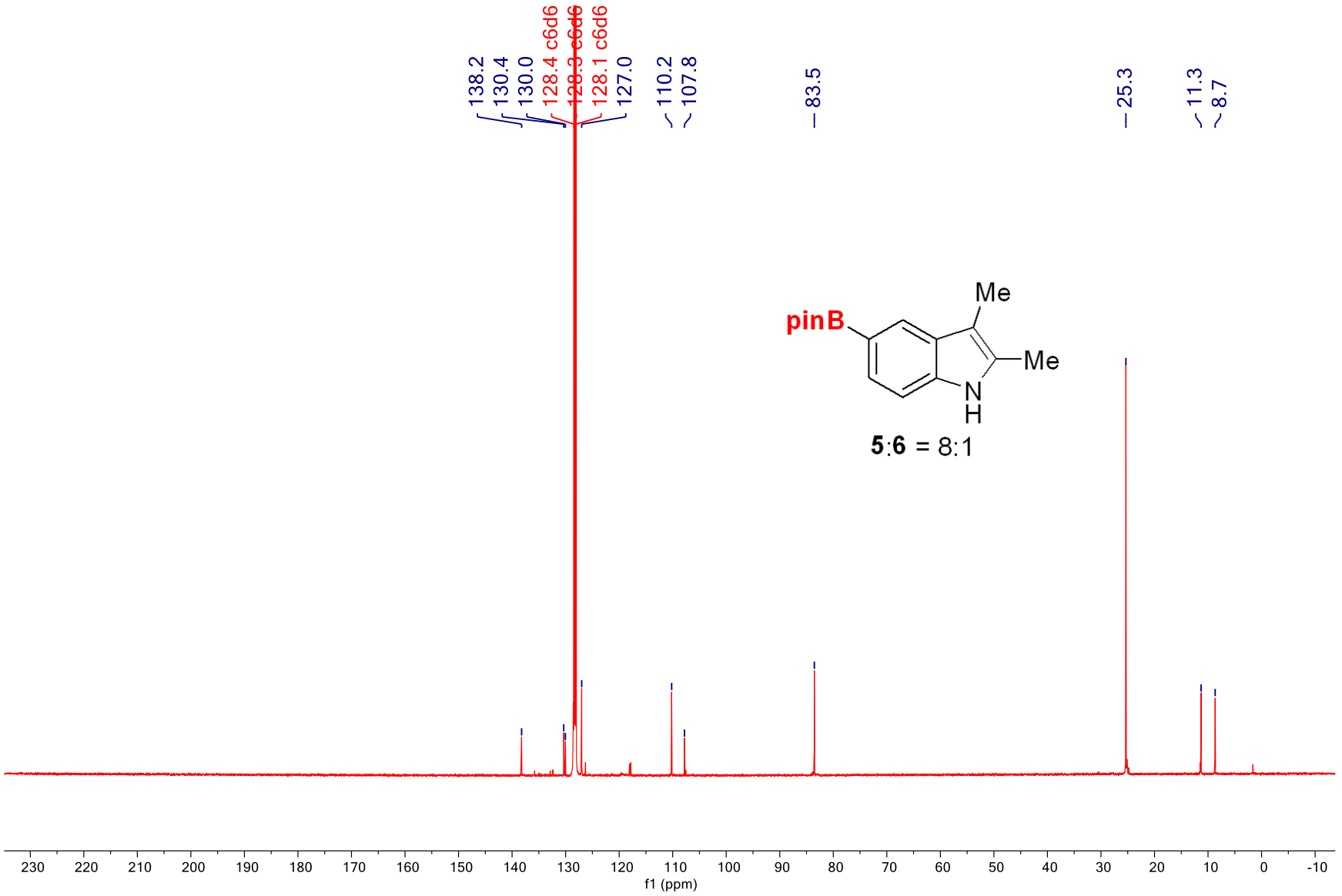
^{1}H NMR of C5 and C6 borylated 2,3-dimethyl indole, first fraction (4.6c) (C_6D_6, 500 MHz)



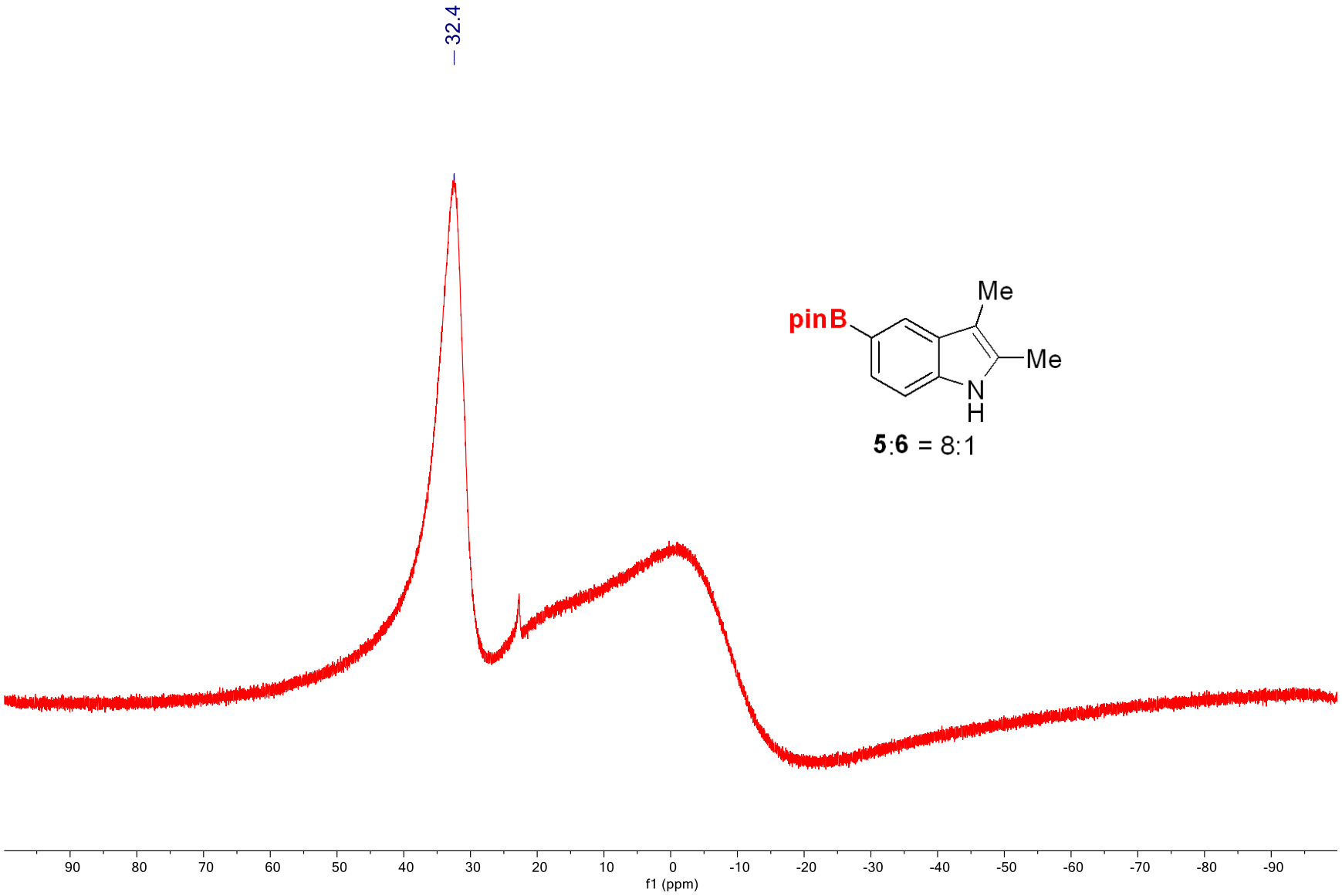
^{1}H NMR of C5 borylated 2,3-dimethyl indole (4.6c) (C_6D_6, 500 MHz)



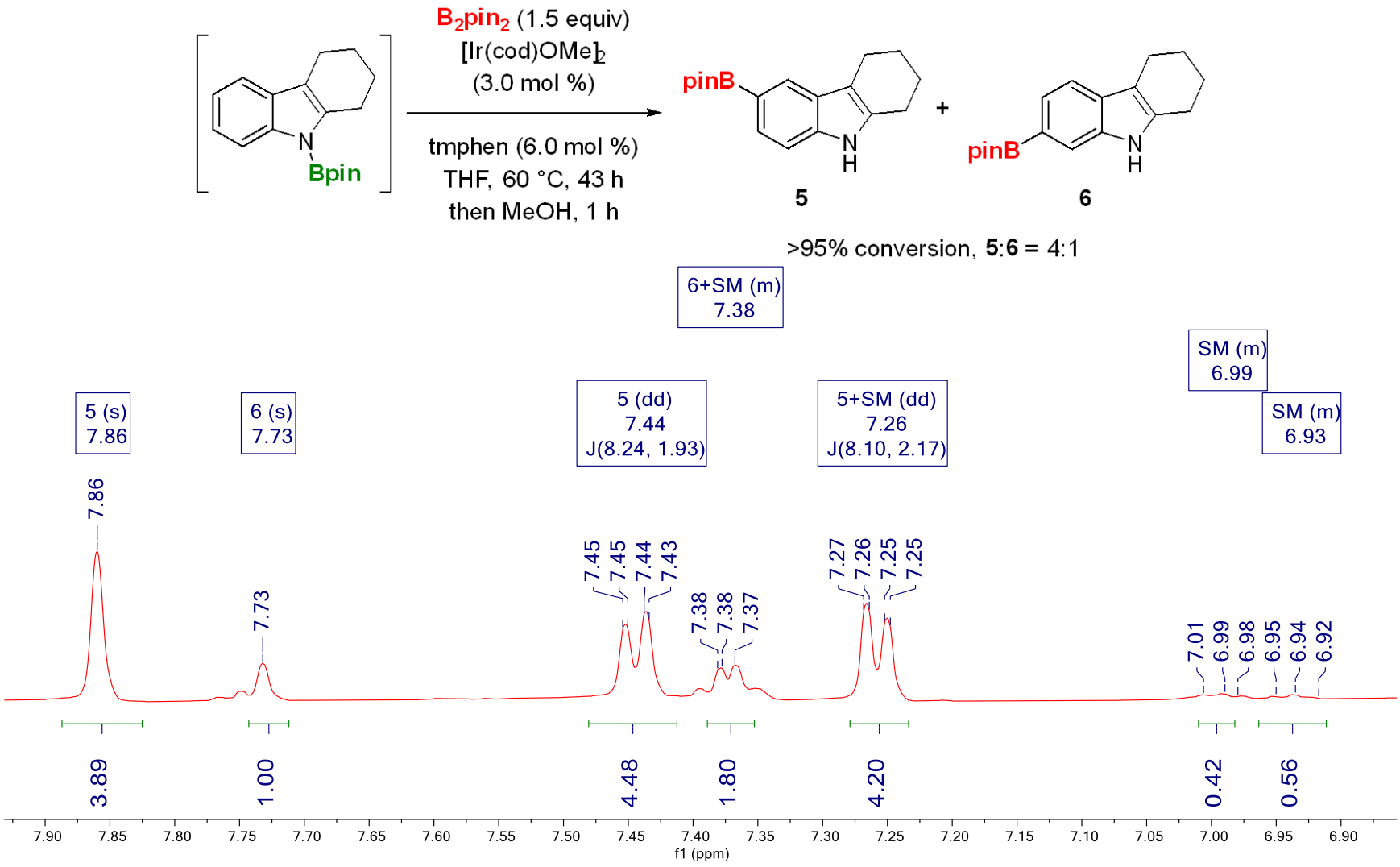
^{13}C NMR of C5 borylated 2,3-dimethyl indole (4.6c) (C_6D_6, 126 MHz)



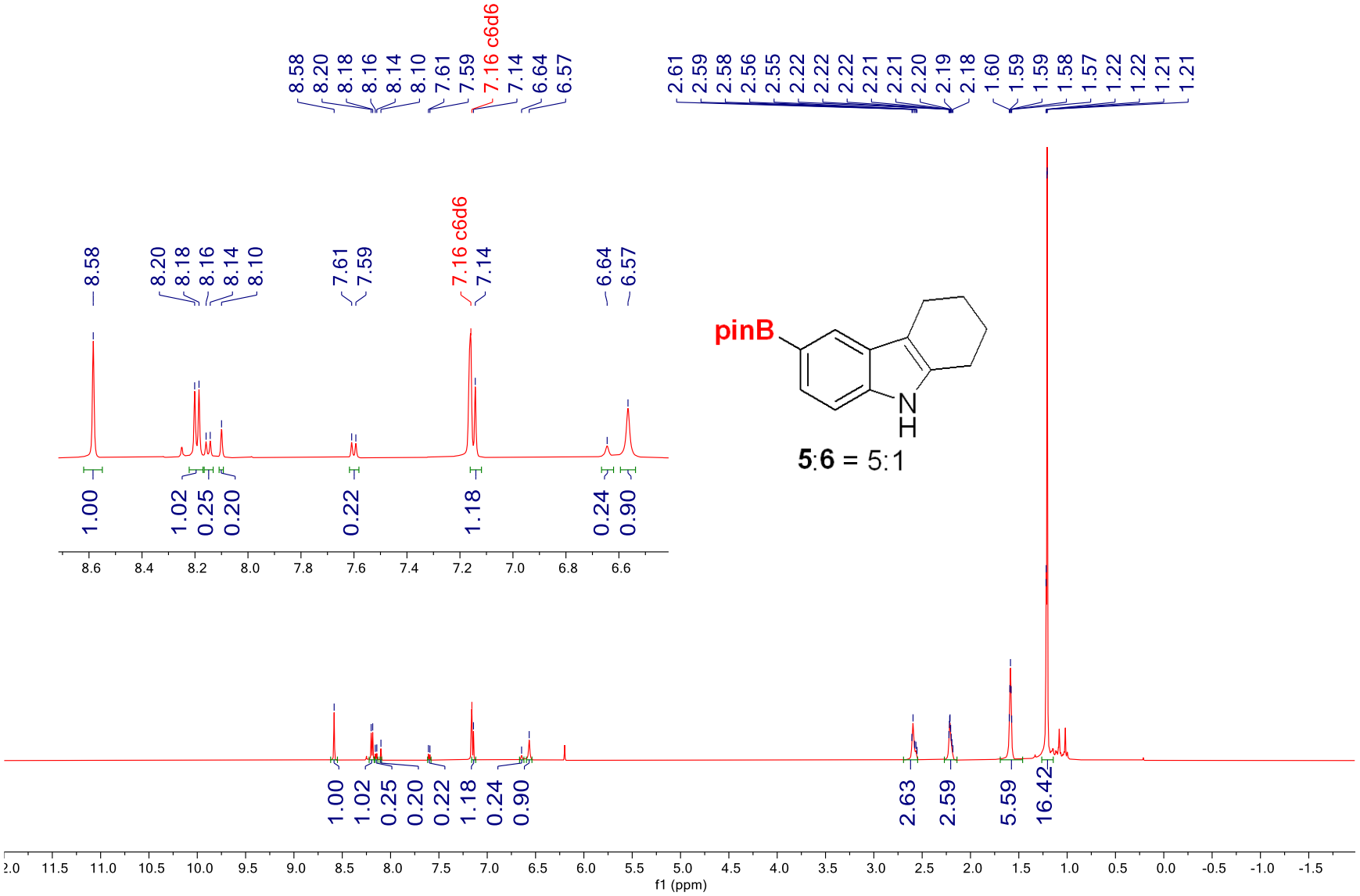
^{11}B NMR of C5 borylated 2,3-dimethyl indole (4.6c) (C_6D_6, 126 MHz)



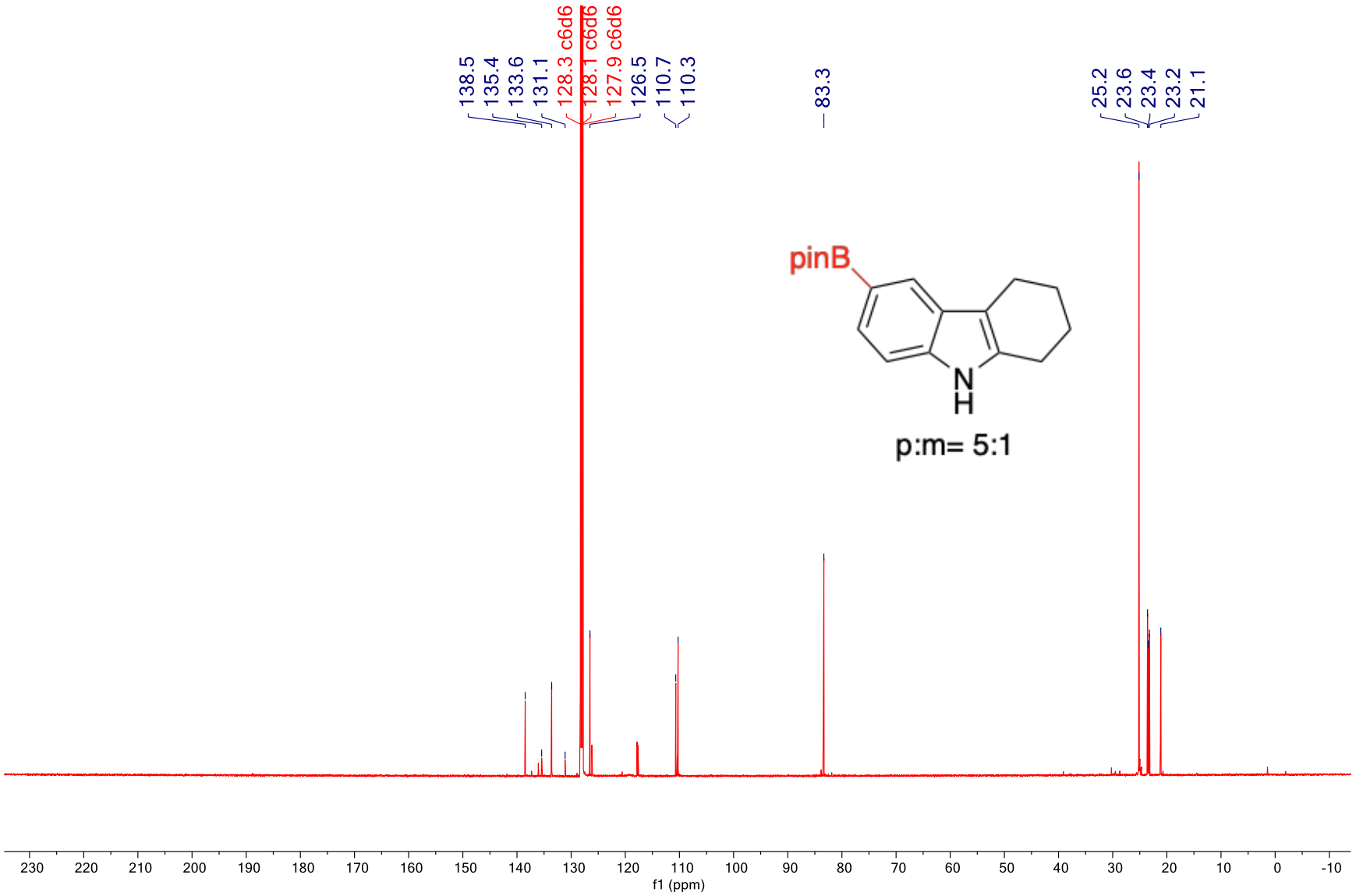
5 CHB of 2,3,4,9-tetrahydro-1H-carbazole (4.6d) (acetone-d6, 500 MHz)



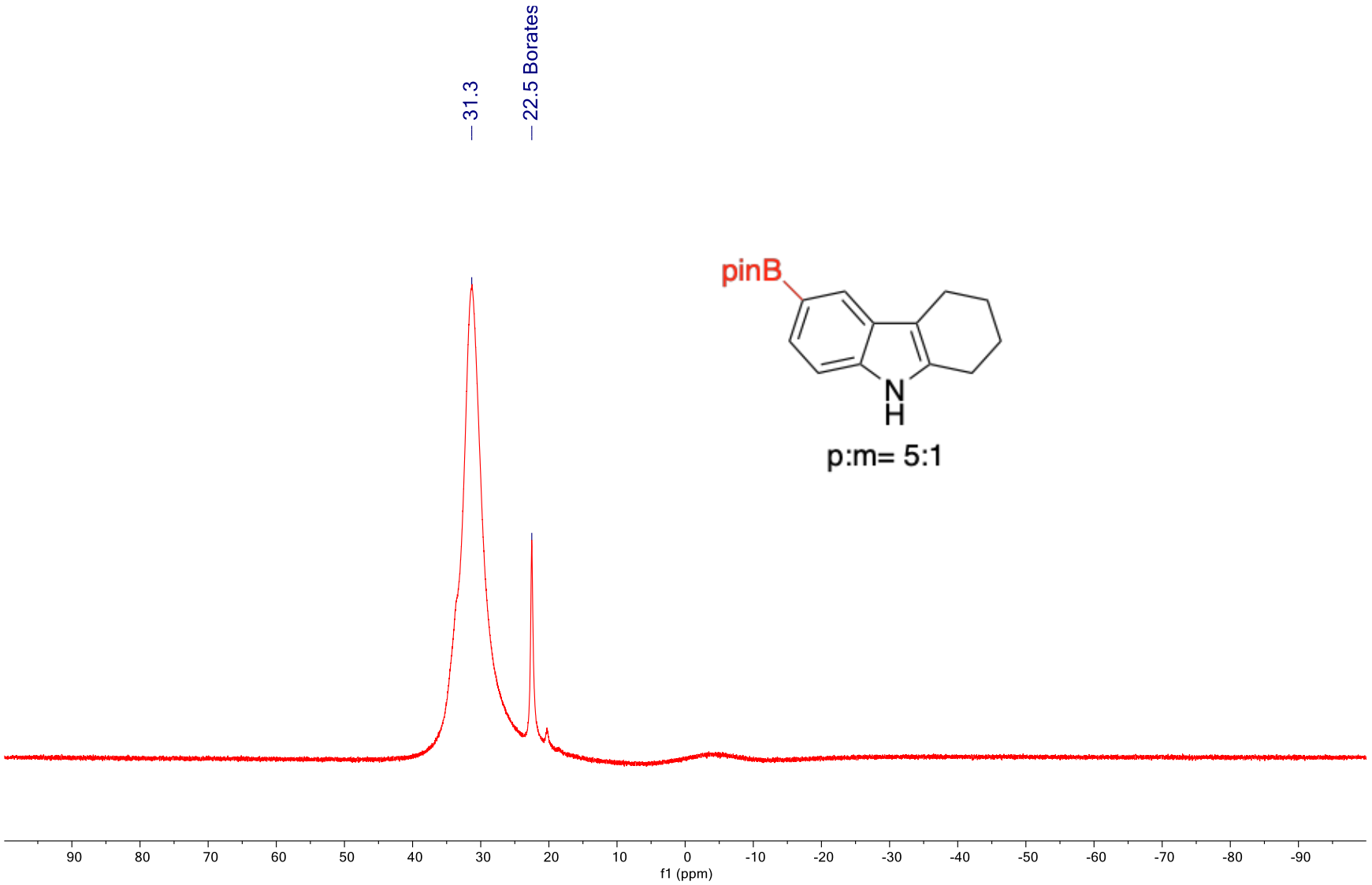
^{1}H NMR of 5-borylated 2,3,4,9-tetrahydro-1H-carbazole (4.6d) (C_6D_6, 500 MHz)



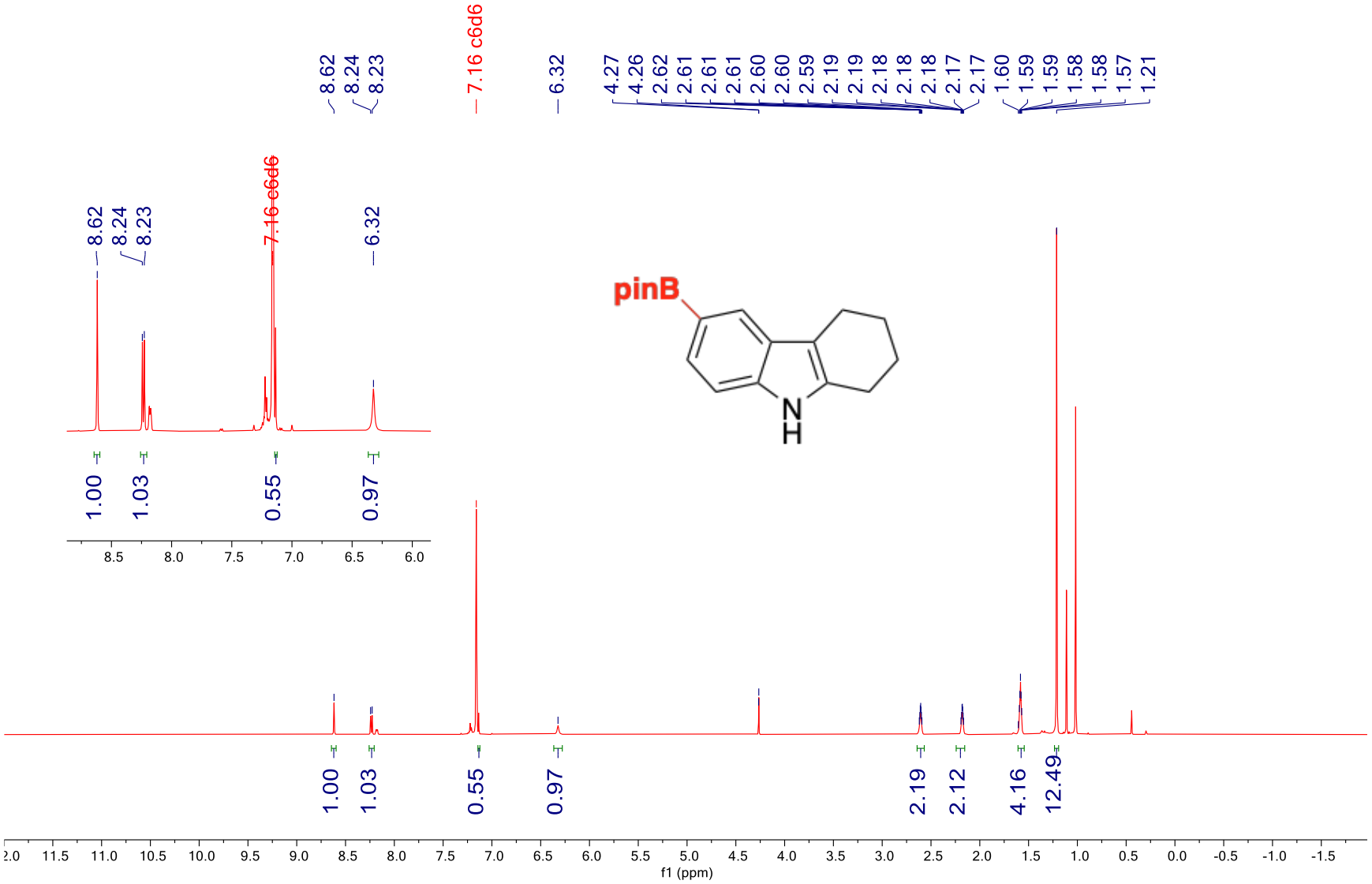
^{13}C NMR of 5-borylated 2,3,4,9-tetrahydro-1H-carbazole (4.6d) (C_6D_6, 126 MHz)



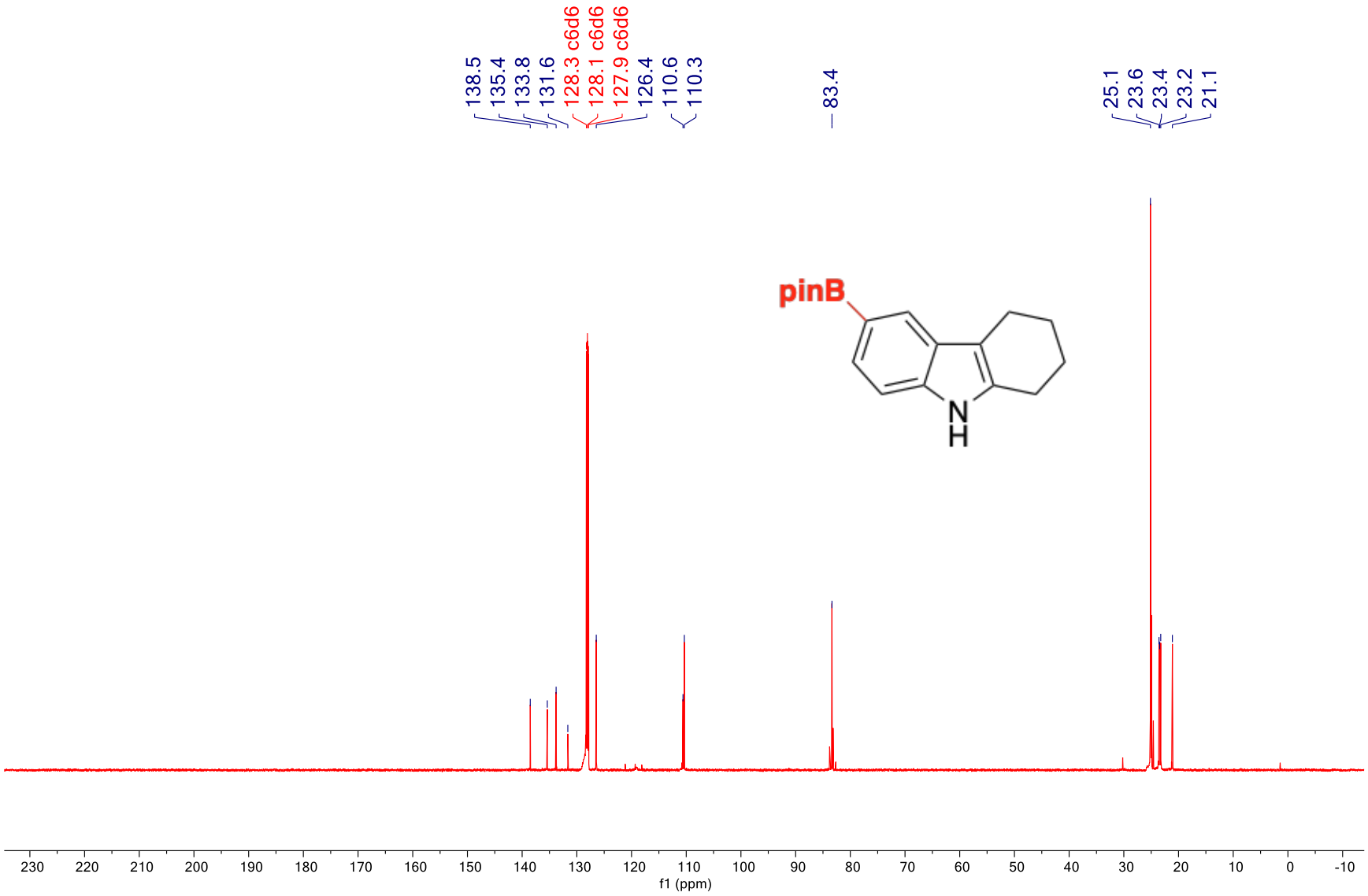
^{11}B NMR of 5-borylated 2,3,4,9-tetrahydro-1H-carbazole (4.6d) (C_6D_6, 126 MHz)



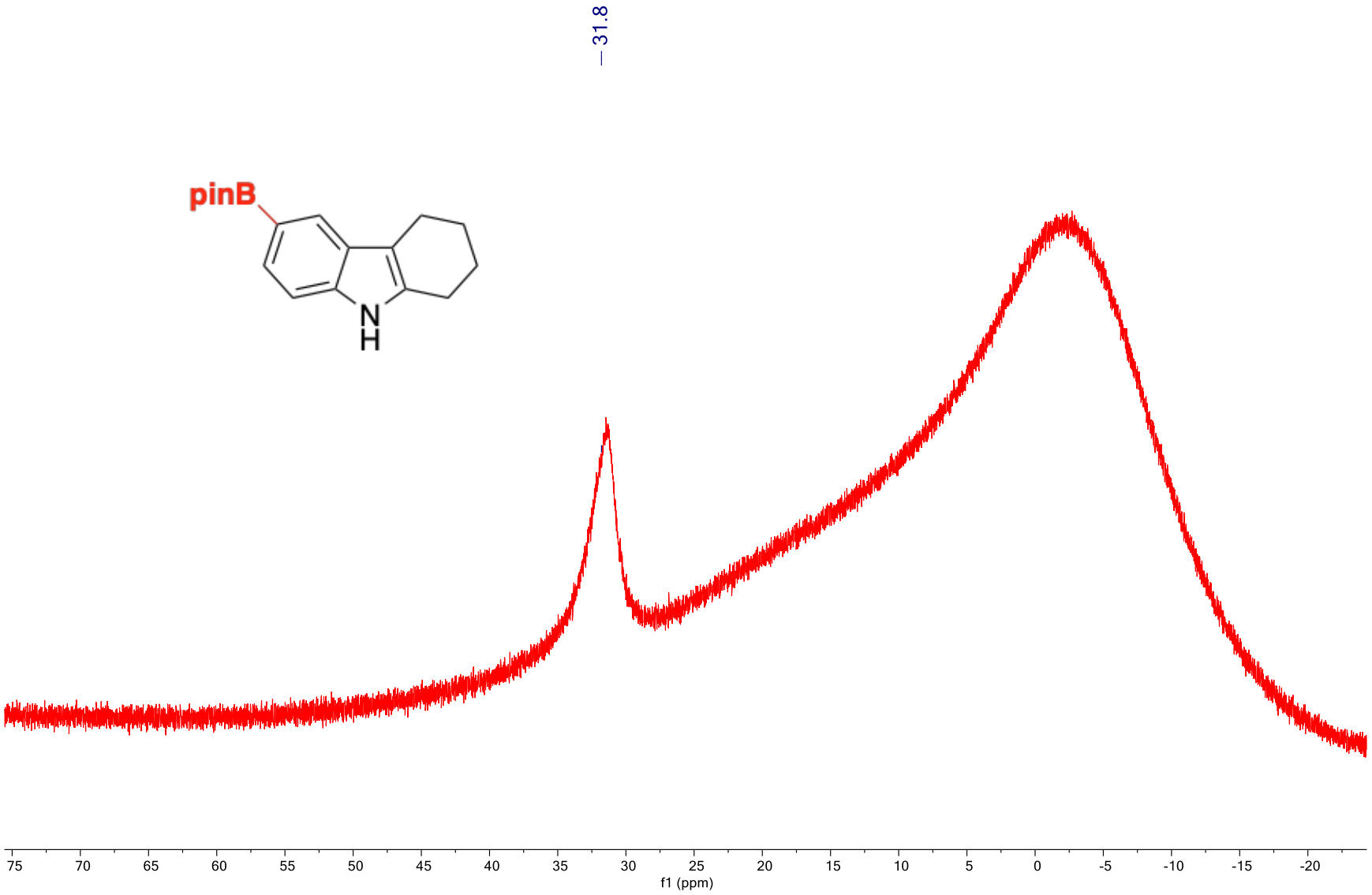
^{1}H NMR of 5-borylated 2,3,4,9-tetrahydro-1H-carbazole by Miyaura Borylation (4.6d) (C_6D_6, 500 MHz)



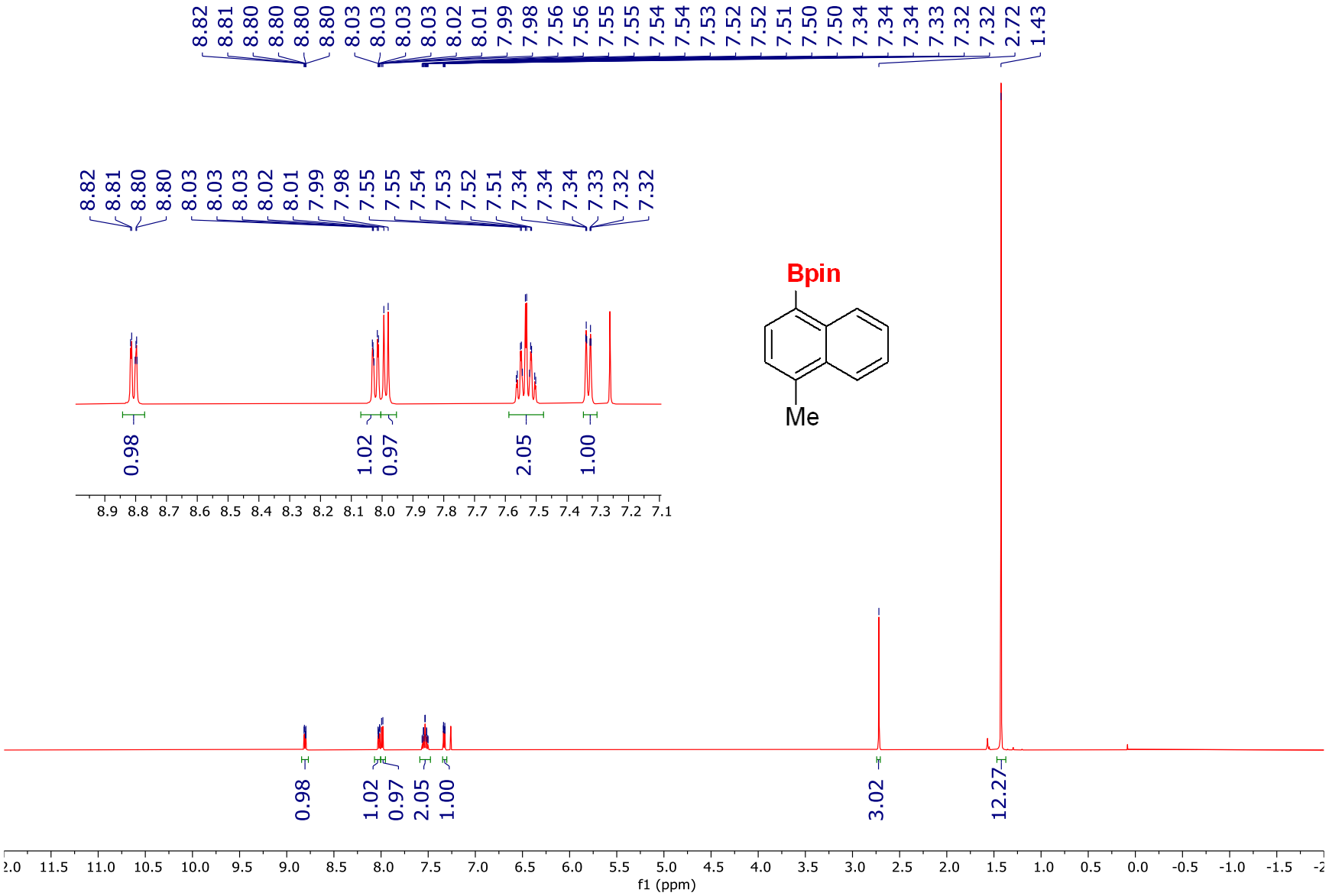
^{13}C NMR of 5-borylated 2,3,4,9-tetrahydro-1H-carbazole by Miyaura Borylation (4.6d) (C_6D_6, 126 MHz)



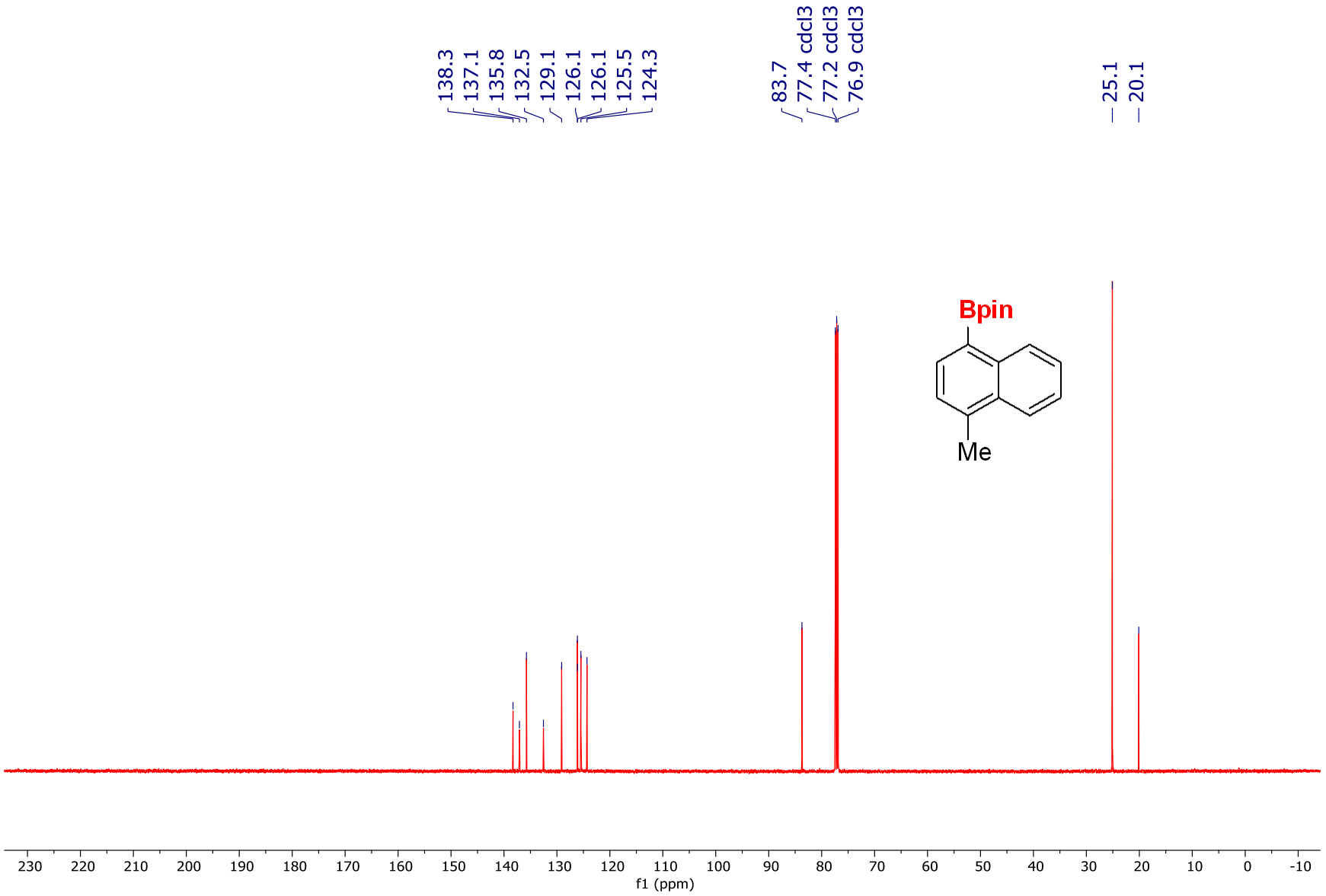
^{11}B NMR of 5-borylated 2,3,4,9-tetrahydro-1H-carbazole by Miyaura Borylation (4.6d) (C_6D_6, 126 MHz)



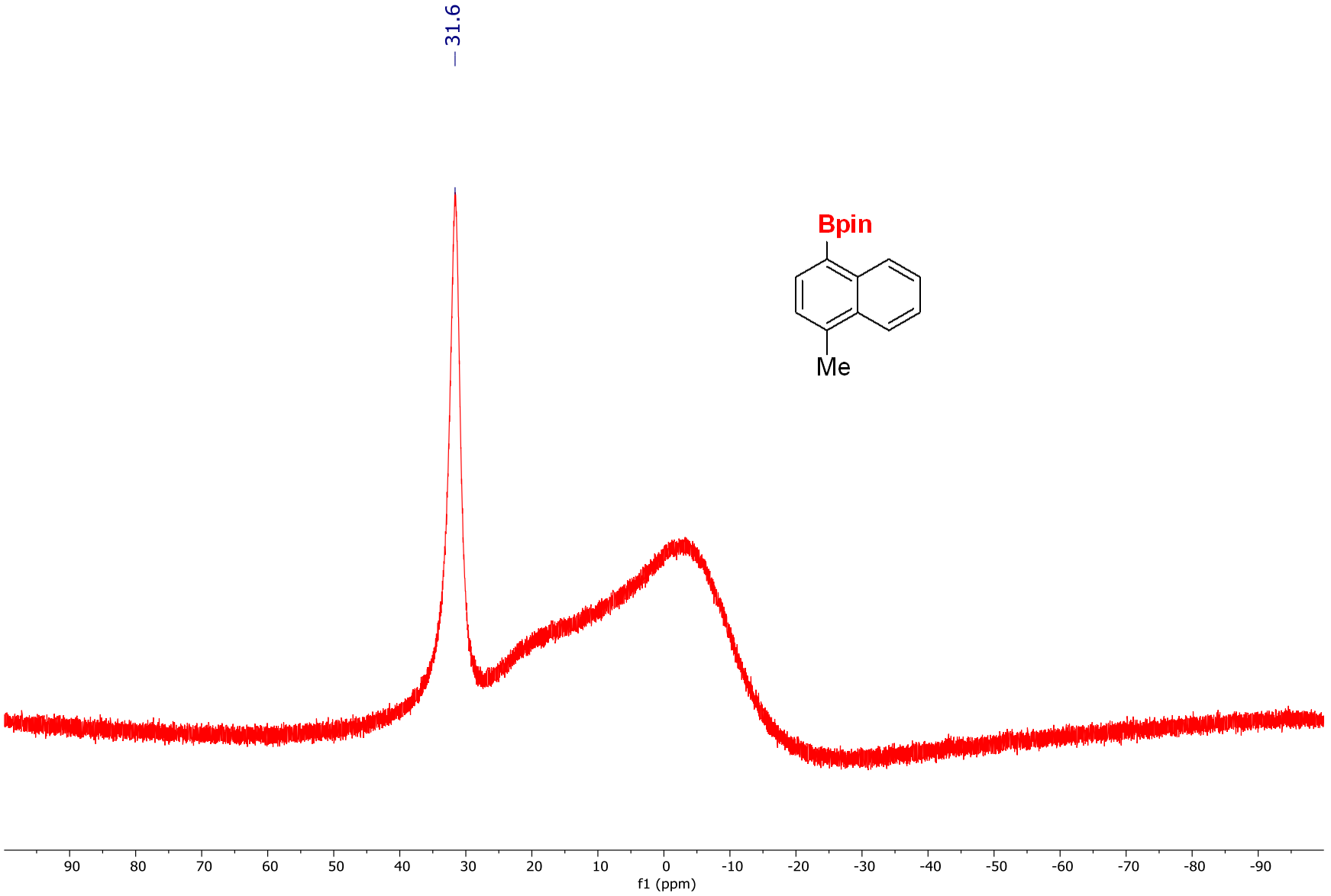
^{1}H NMR of 4-Methylnaphthalene-1-boronic acid, pinacol ester (4.7b) ($CDCl_3$, 500 MHz)



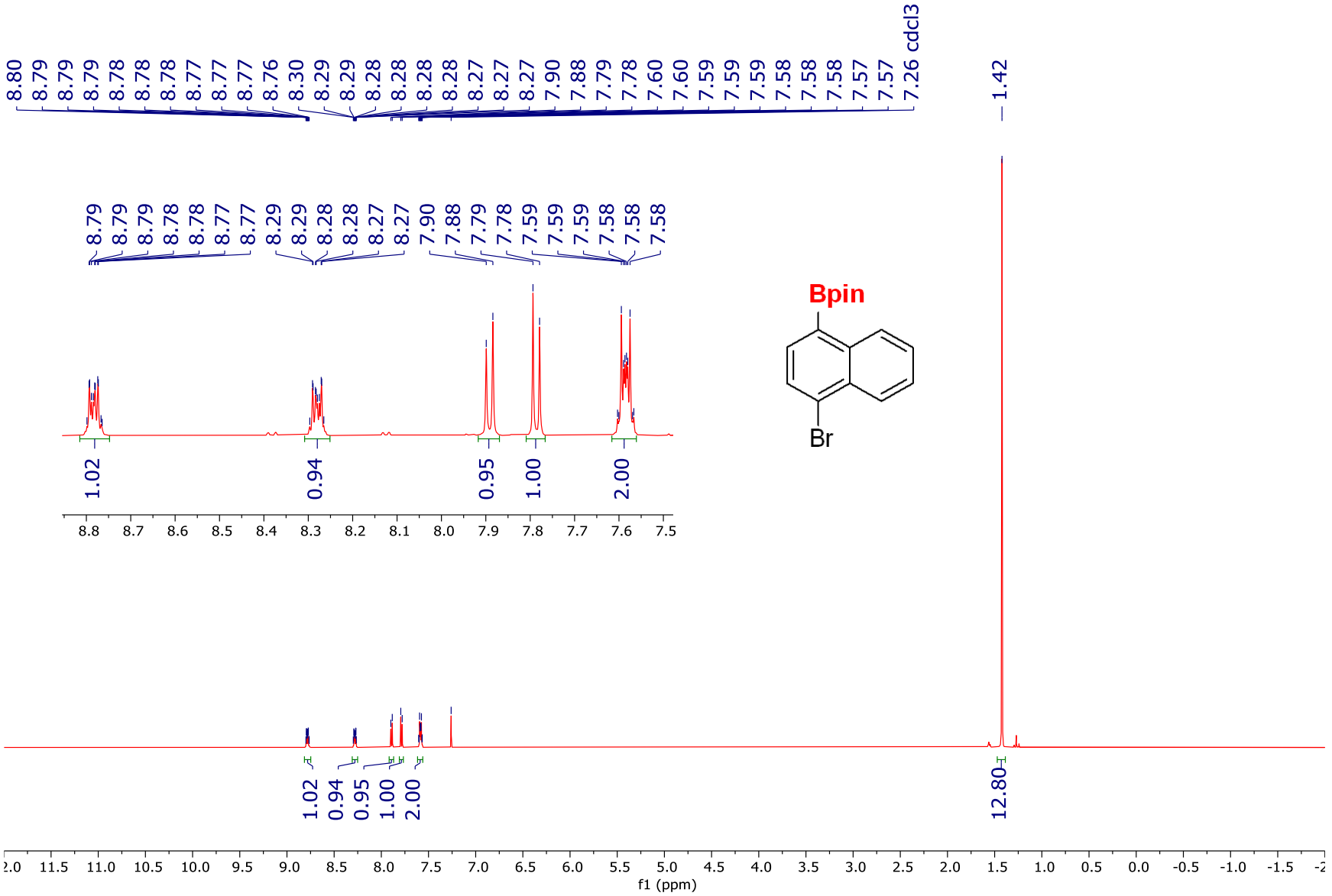
^{13}C NMR of 4-Methylnaphthalene-1-boronic acid, pinacol ester (4.7b) ($CDCl_3$, 126 MHz)



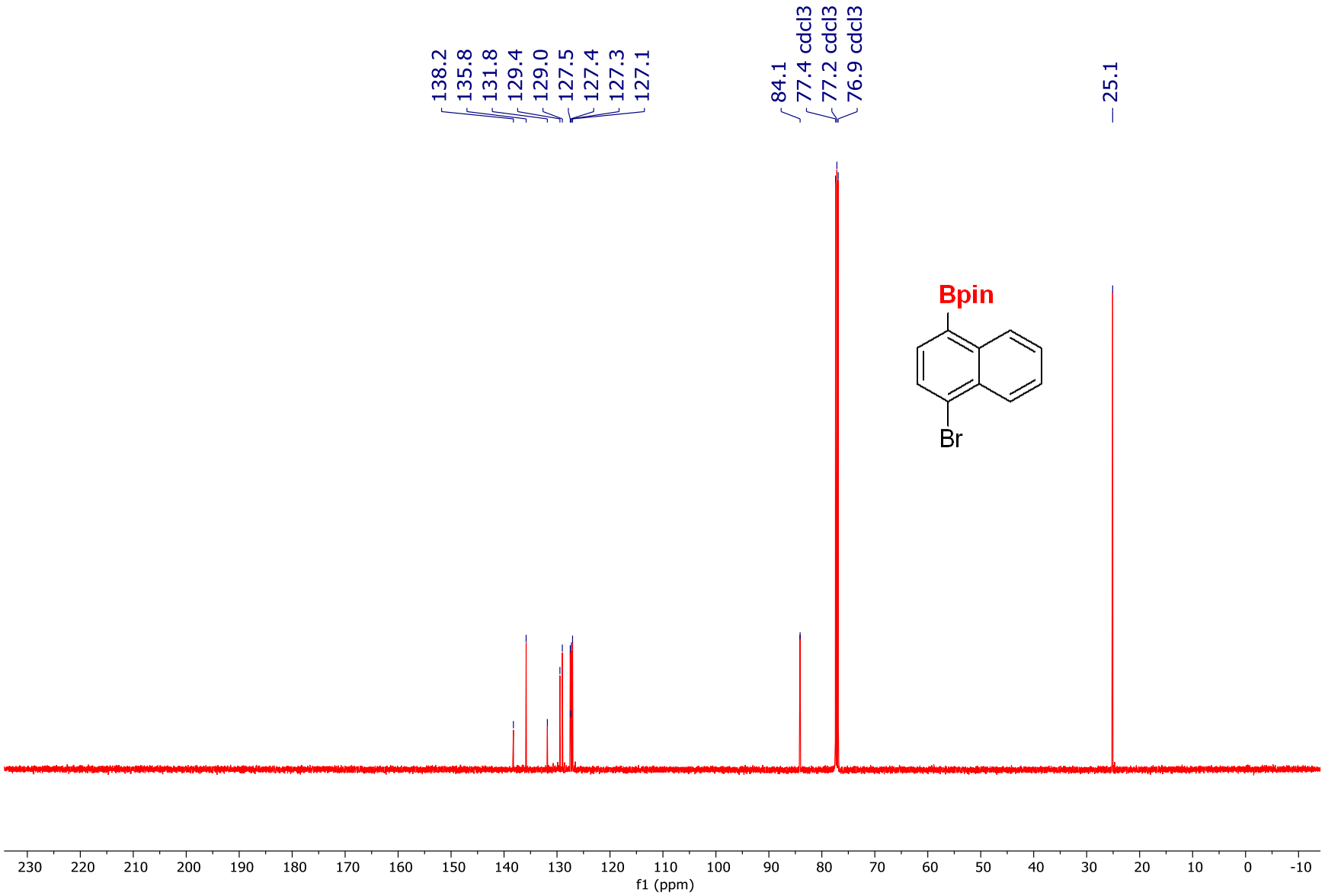
^{11}B NMR of 4-Methylnaphthalene-1-boronic acid, pinacol ester (4.7b) ($CDCl_3$, 160 MHz)



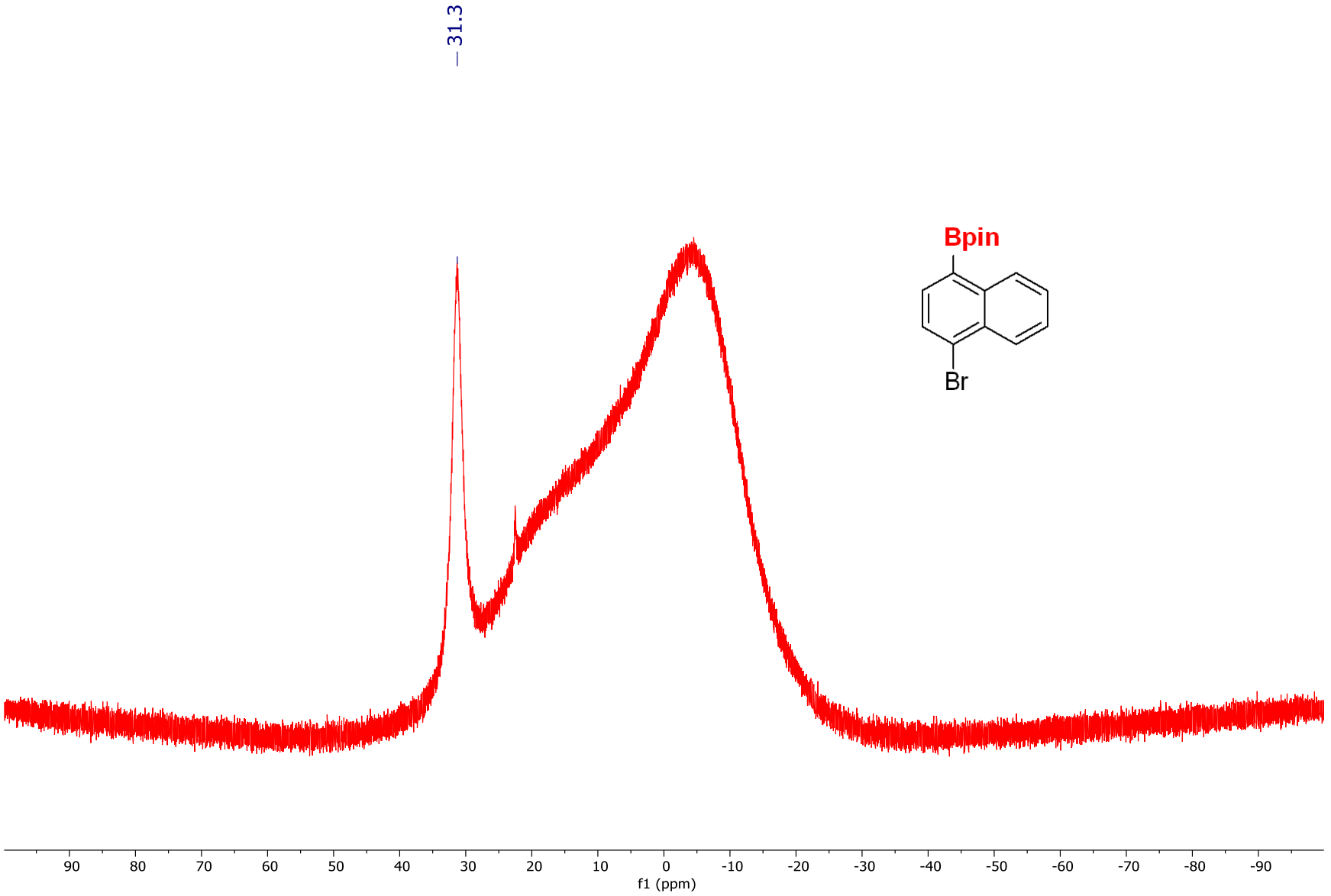
^{1}H NMR of 4-bromonaphthalene-1-boronic acid, pinacol ester (4.7c) ($CDCl_3$, 500 MHz)



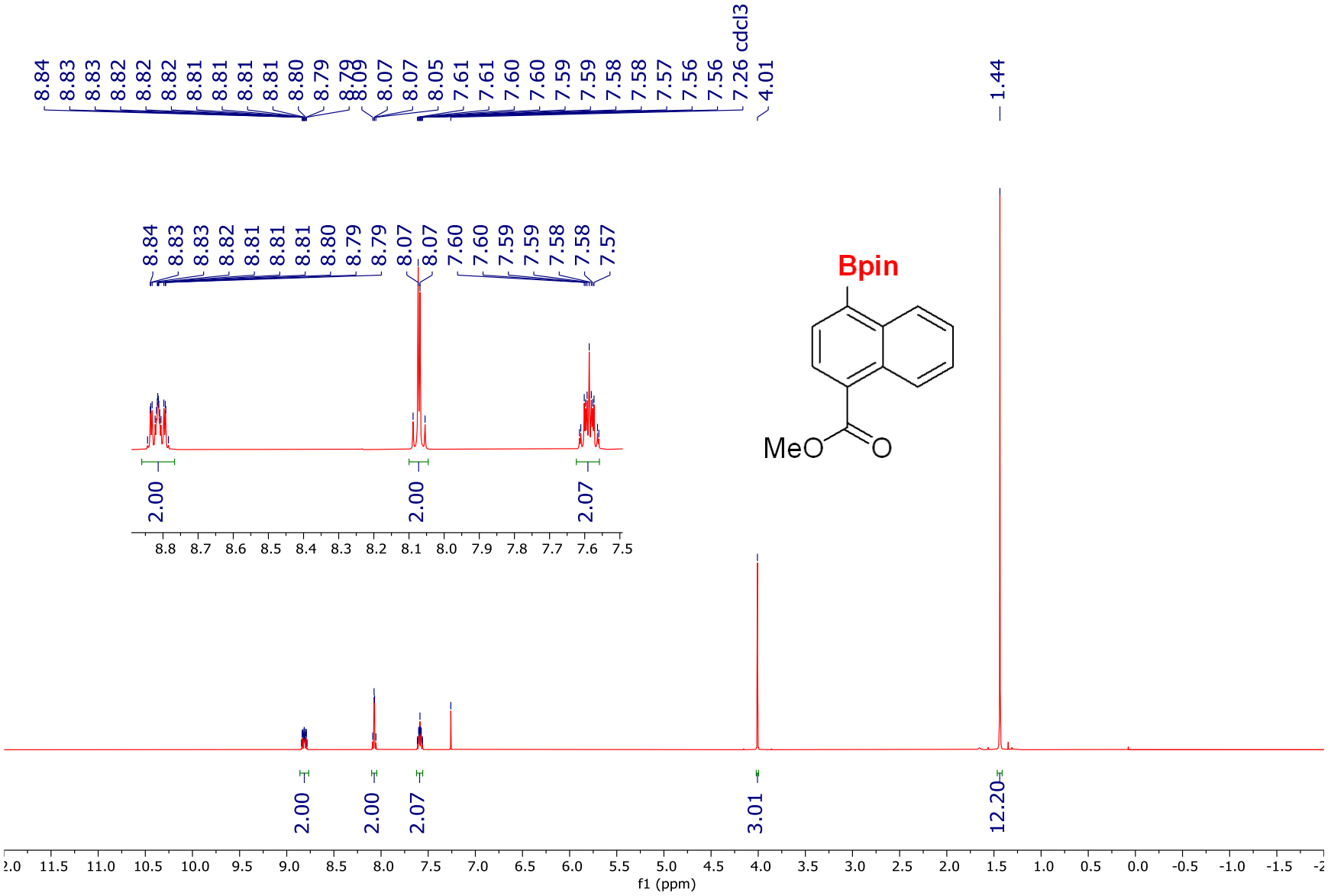
^{13}C NMR of 4-bromonaphthalene-1-boronic acid, pinacol ester (4.7c) ($CDCl_3$, 126 MHz)



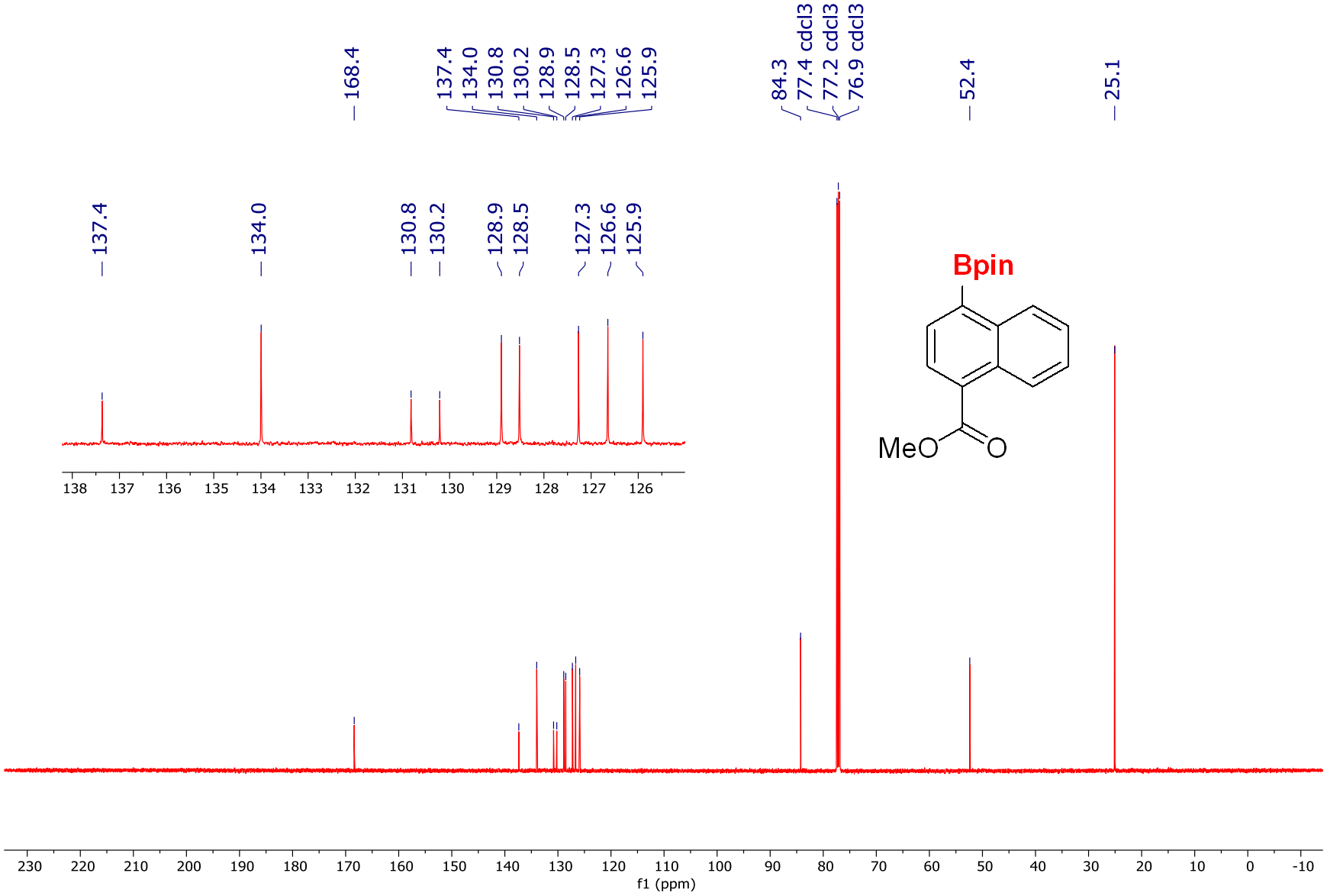
^{11}B NMR of 4-bromonaphthalene-1-boronic acid, pinacol ester (4.7c) ($CDCl_3$, 160 MHz)



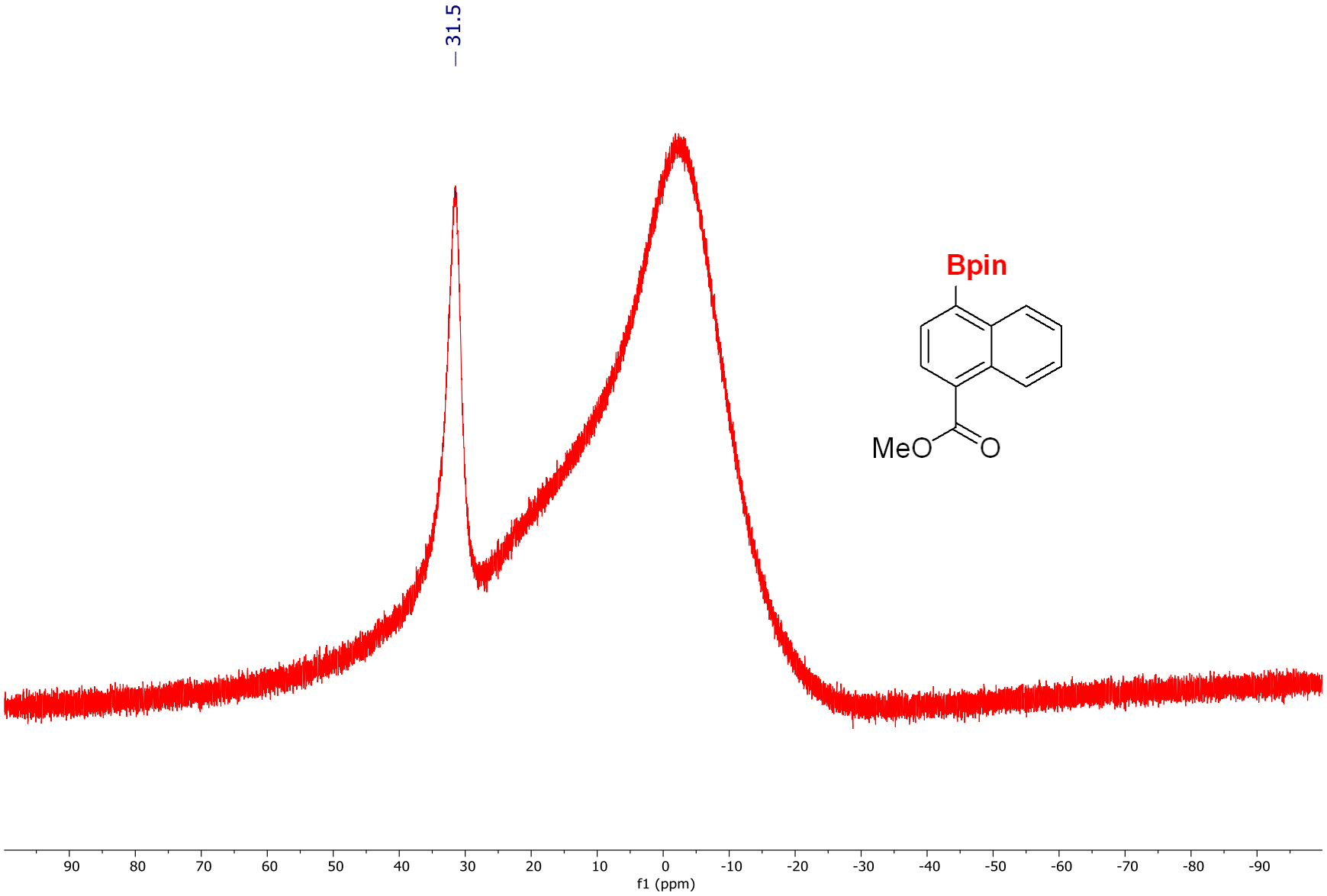
^{1}H NMR of methyl 4-(4,4',5,5'-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthoate (4.7d) ($CDCl_3$, 500 MHz)



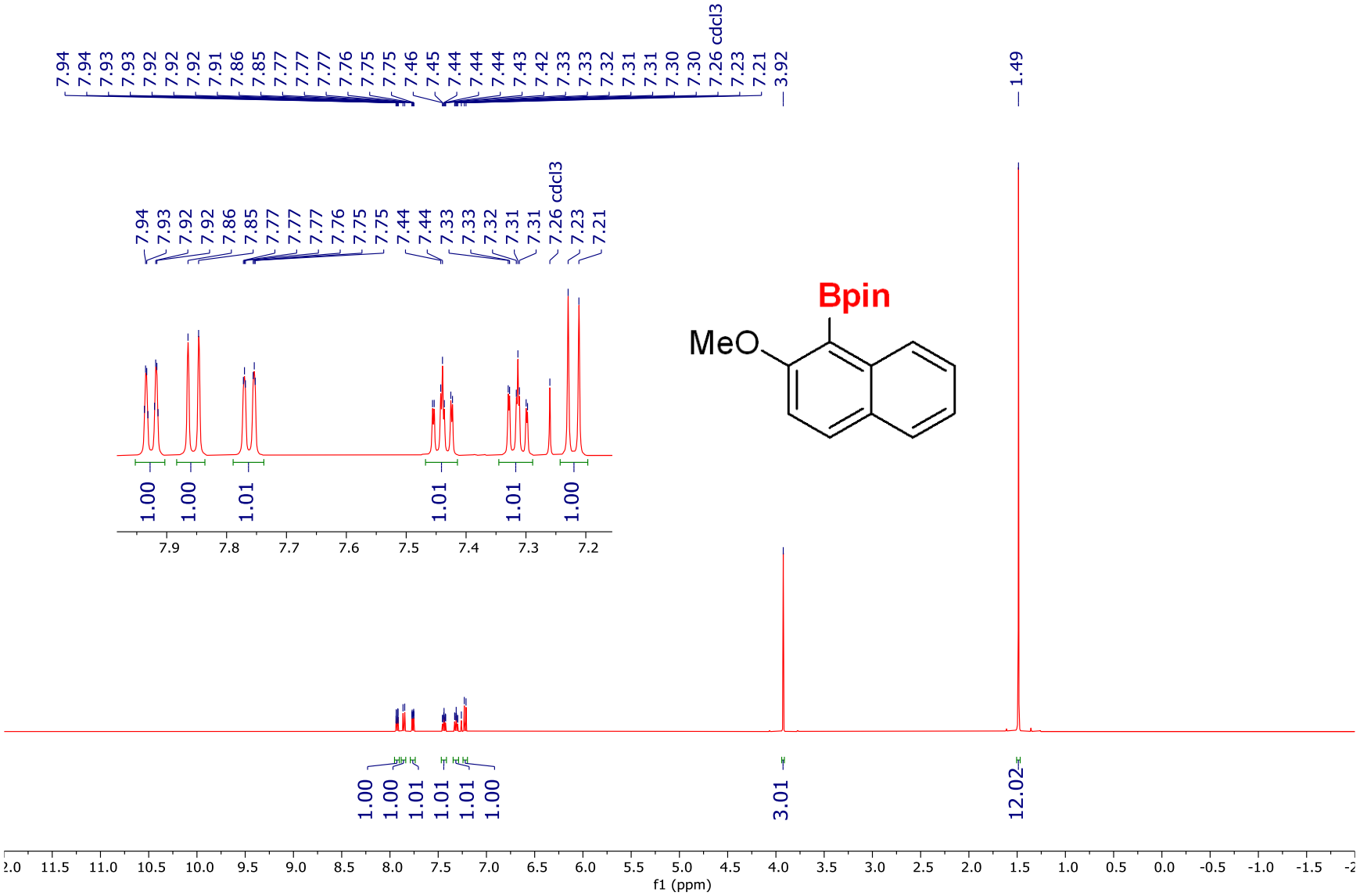
^{13}C NMR of methyl 4-(4,4',5,5'-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthoate (4.7d) ($CDCl_3$, 126 MHz)



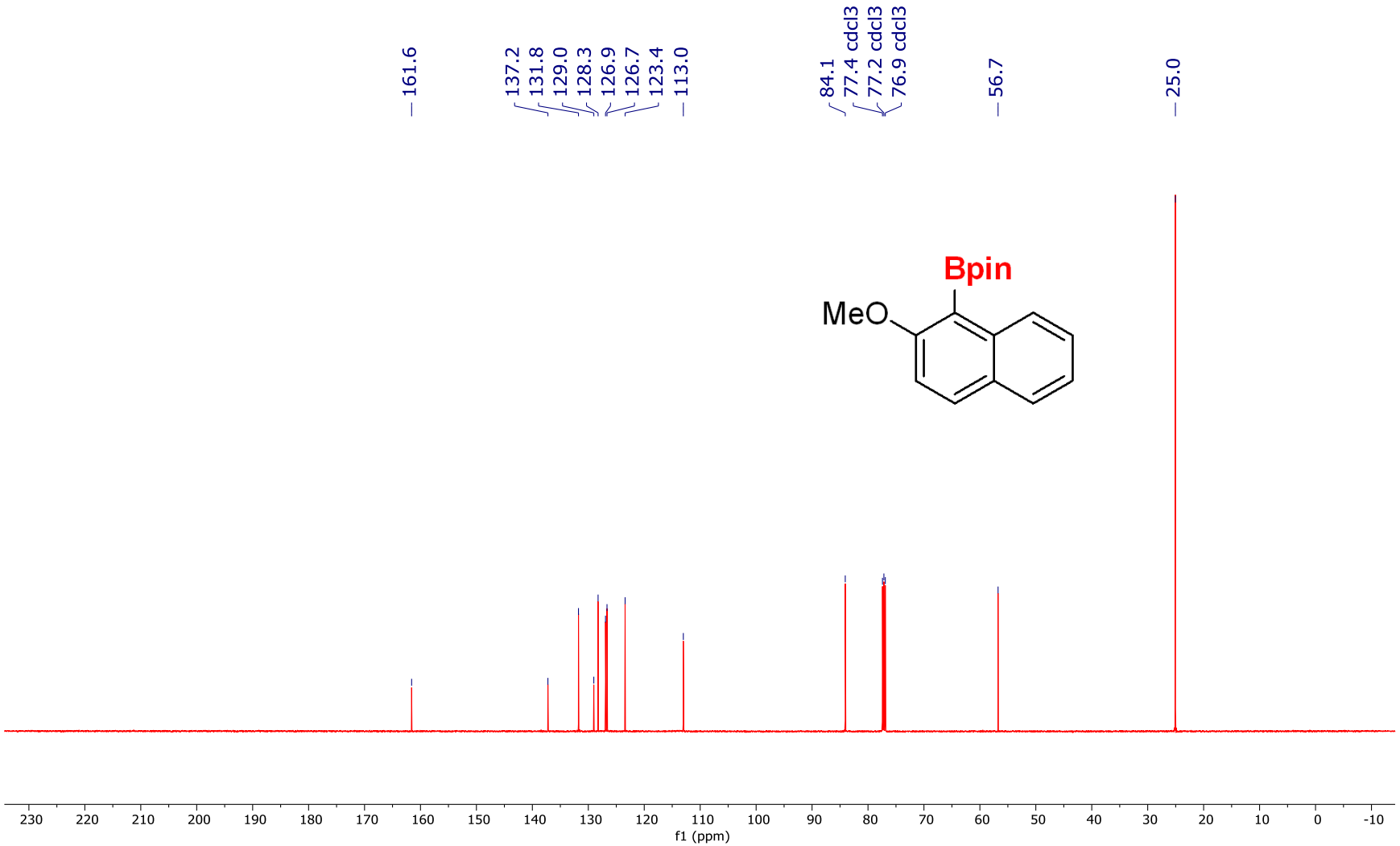
^{11}B NMR of methyl 4-(4,4',5,5'-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthoate (4.7d) ($CDCl_3$, 160 MHz)



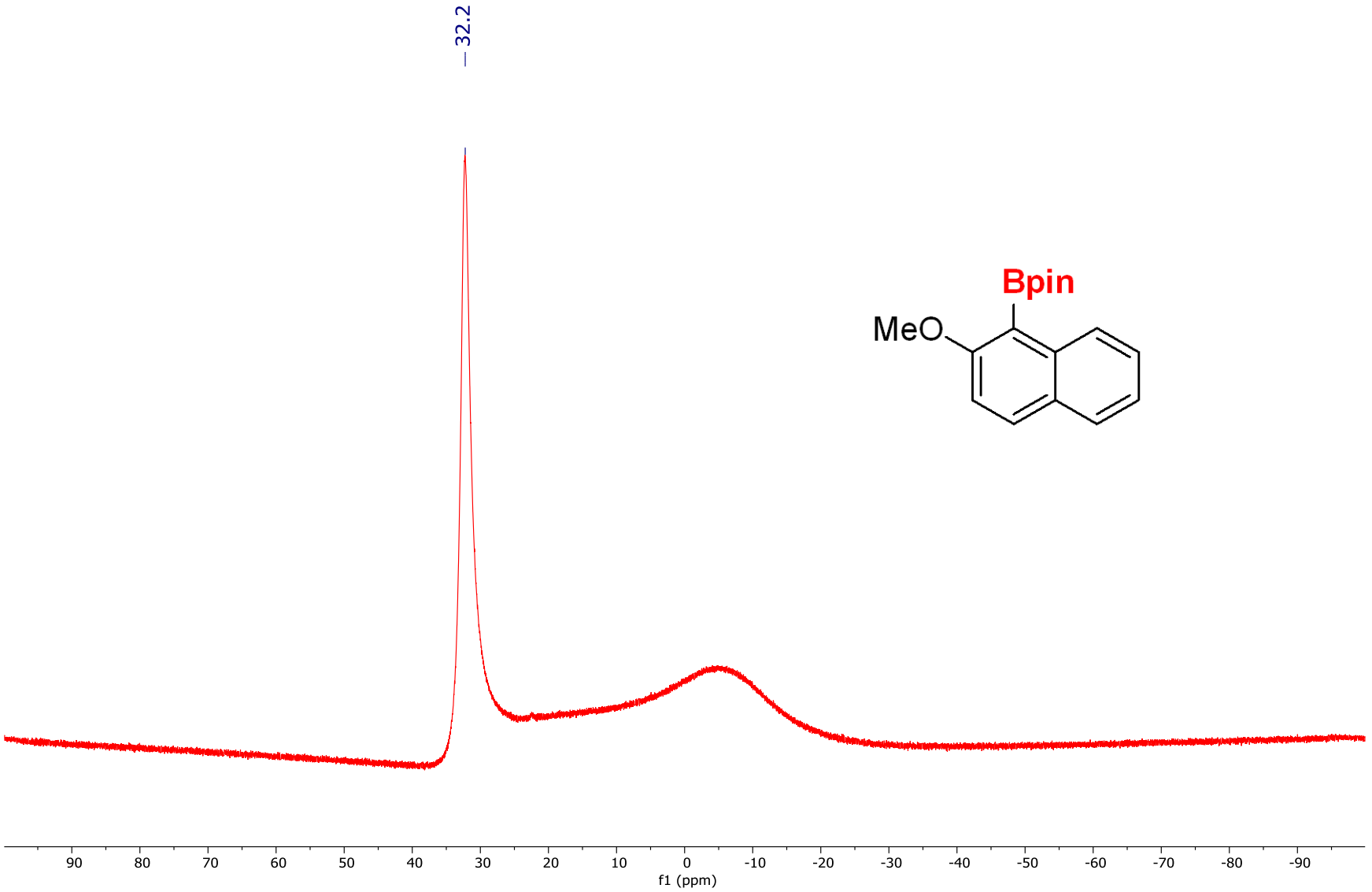
^{1}H NMR of 2-methoxynaphthalene-1-boronic acid, pinacol ester (4.7e) ($CDCl_3$, 500 MHz)



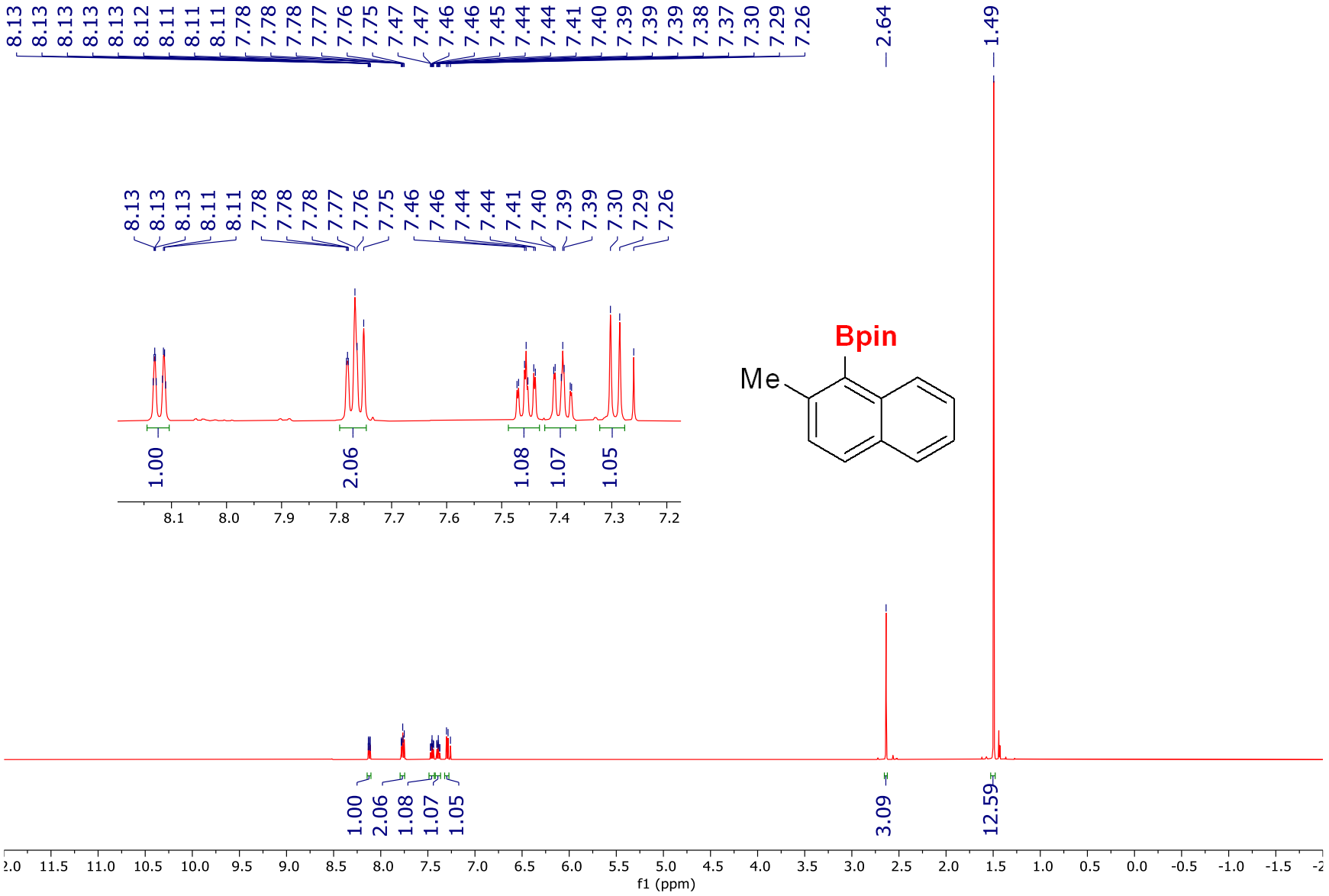
^{13}C NMR of 2-methoxynaphthalene-1-boronic acid, pinacol ester (4.7e) ($CDCl_3$, 126 MHz)



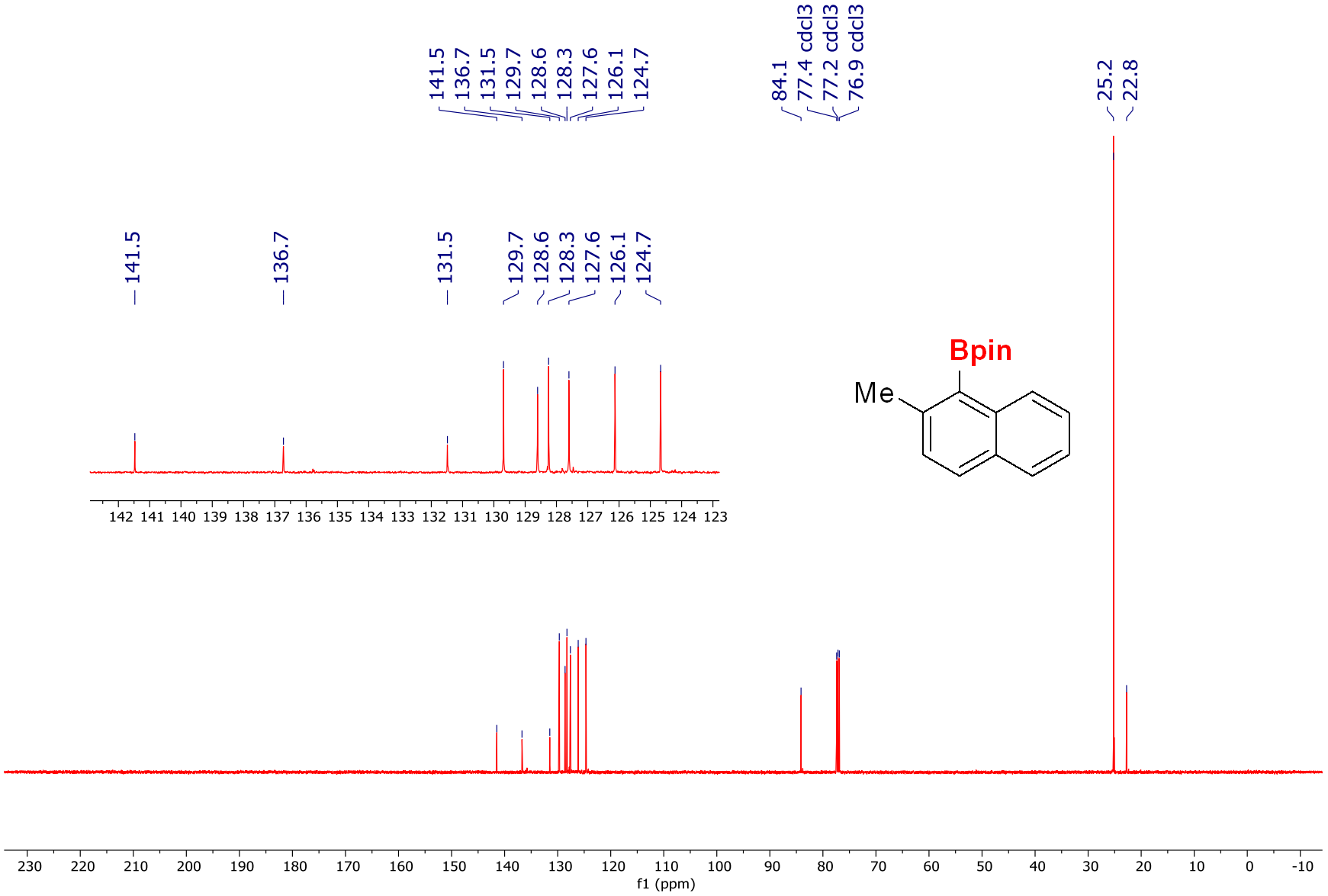
^{11}B NMR of 2-methoxynaphthalene-1-boronic acid, pinacol ester (4.7e) ($CDCl_3$, 160 MHz)



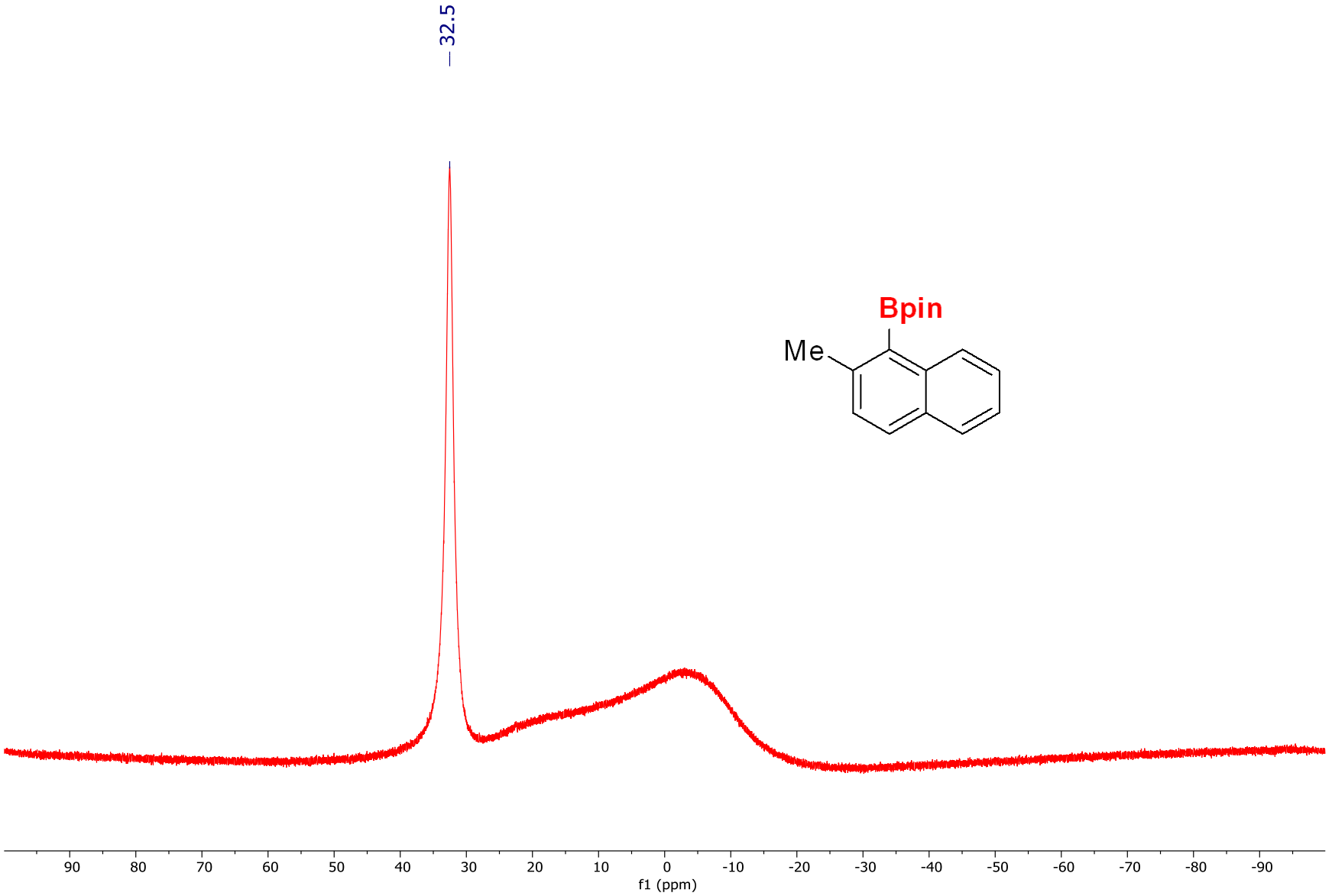
^{1}H NMR of 2-methylnaphthalene-1-boronic acid, pinacol ester (4.7f) ($CDCl_3$, 500 MHz)



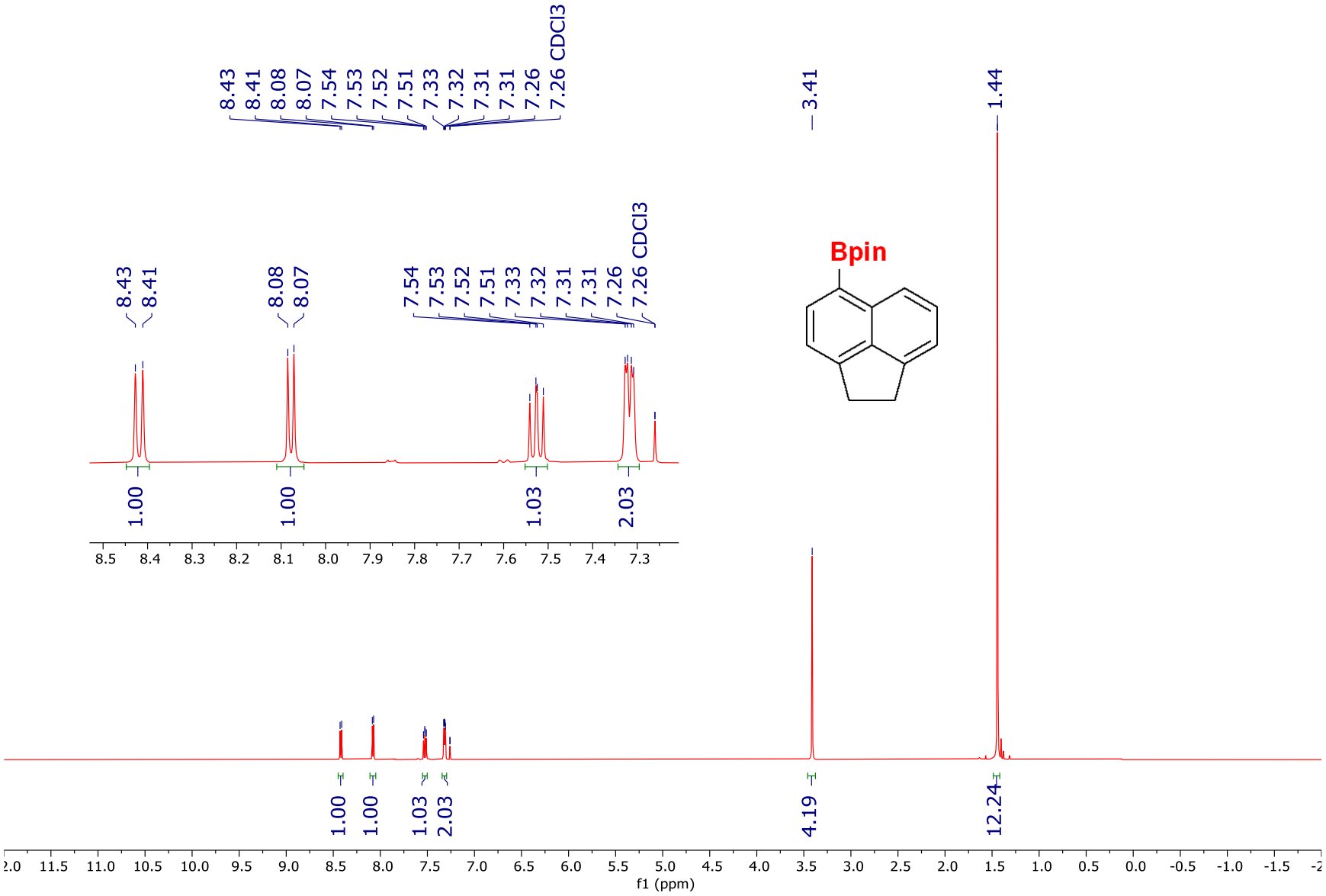
^{13}C NMR of 2-methylnaphthalene-1-boronic acid, pinacol ester (4.7f) ($CDCl_3$, 126 MHz)



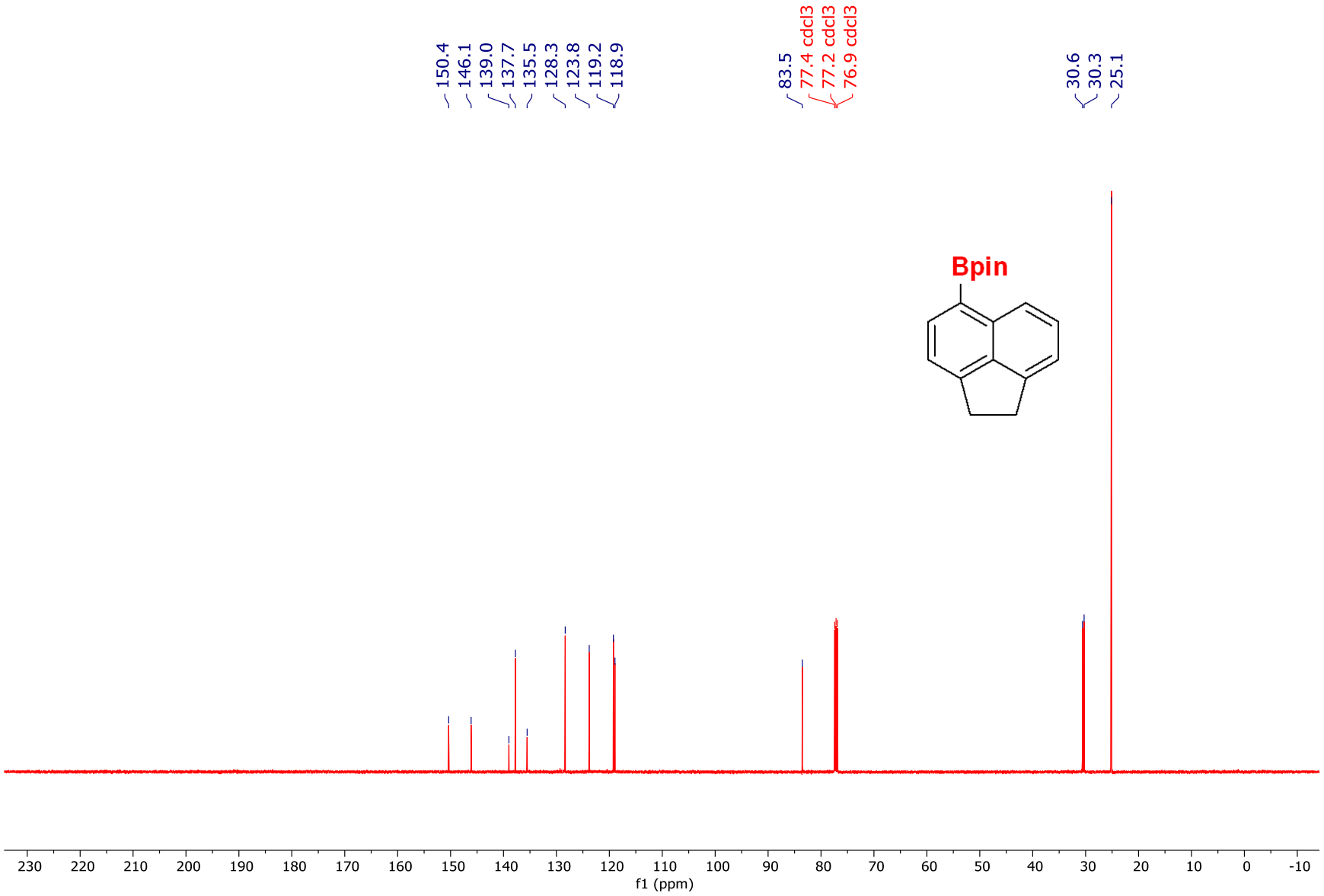
^{11}B NMR of 2-methylnaphthalene-1-boronic acid, pinacol ester (4.7f) ($CDCl_3$, 160 MHz)



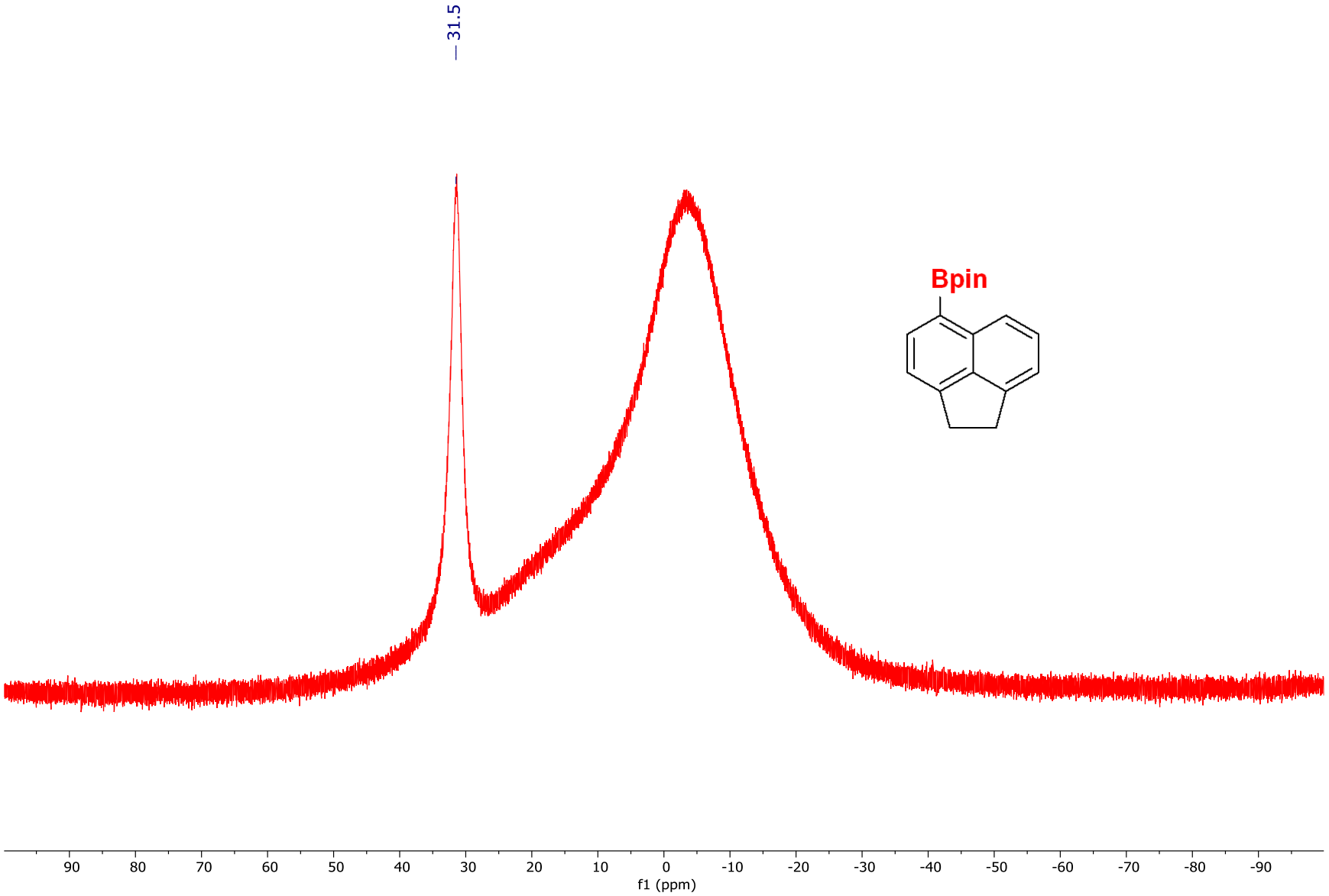
^{1}H NMR of acenaphthene-5-boronic acid, pinacol ester (4.7g) ($CDCl_3$, 500 MHz)



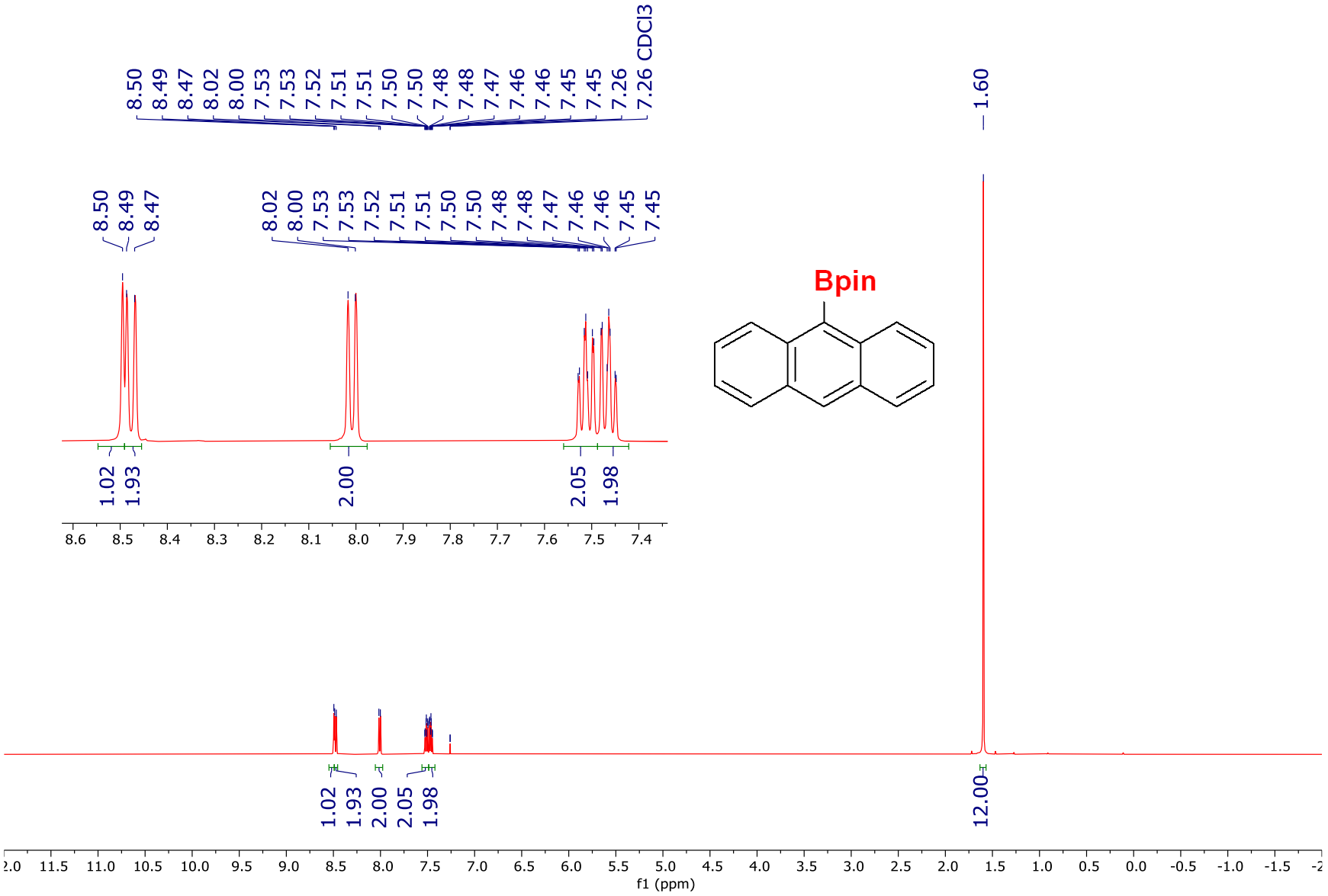
^{13}C NMR of acenaphthene-5-boronic acid, pinacol ester (4.7g) ($CDCl_3$, 126 MHz)



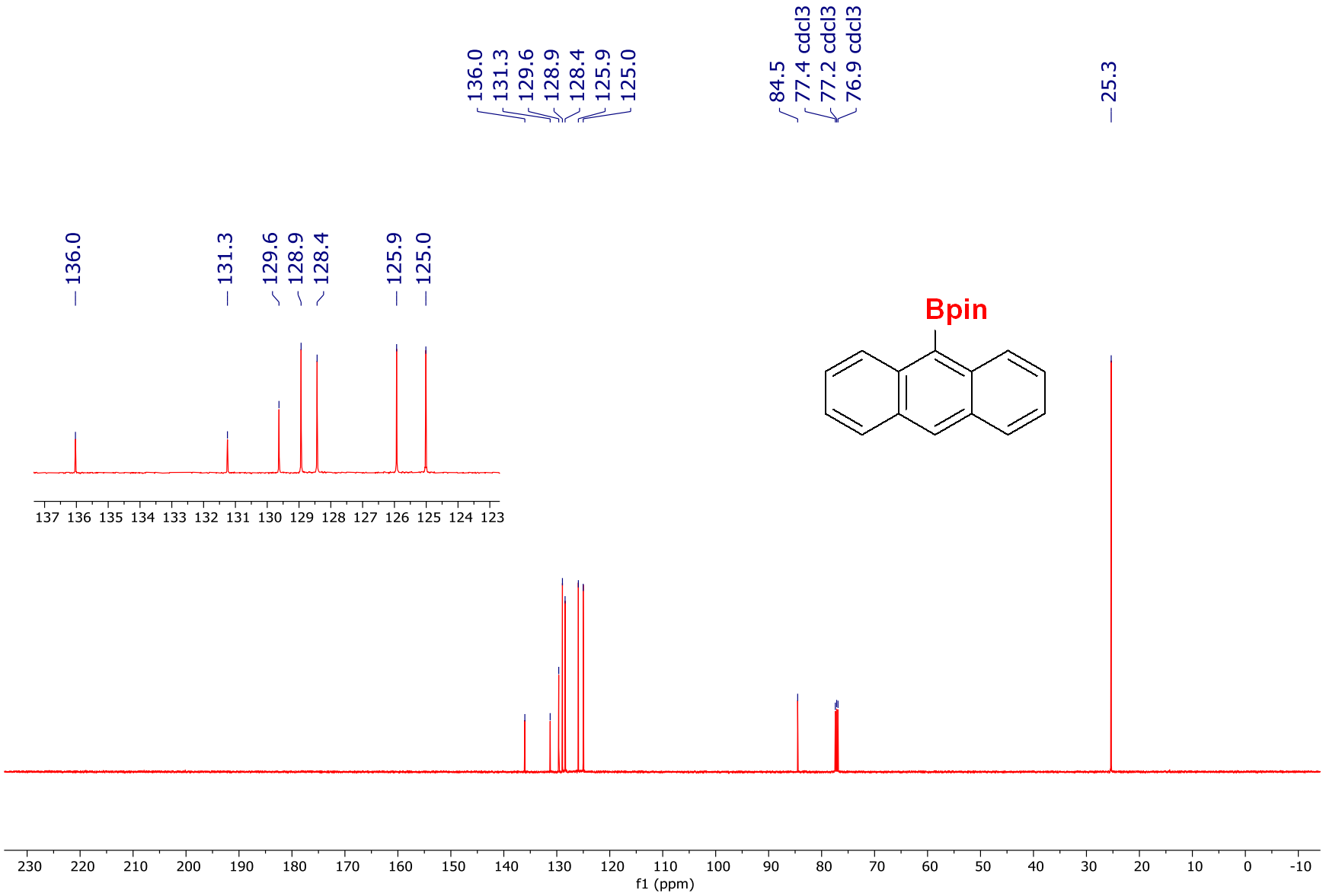
^{11}B NMR of acenaphthene-5-boronic acid, pinacol ester (4.7g) ($CDCl_3$, 160 MHz)



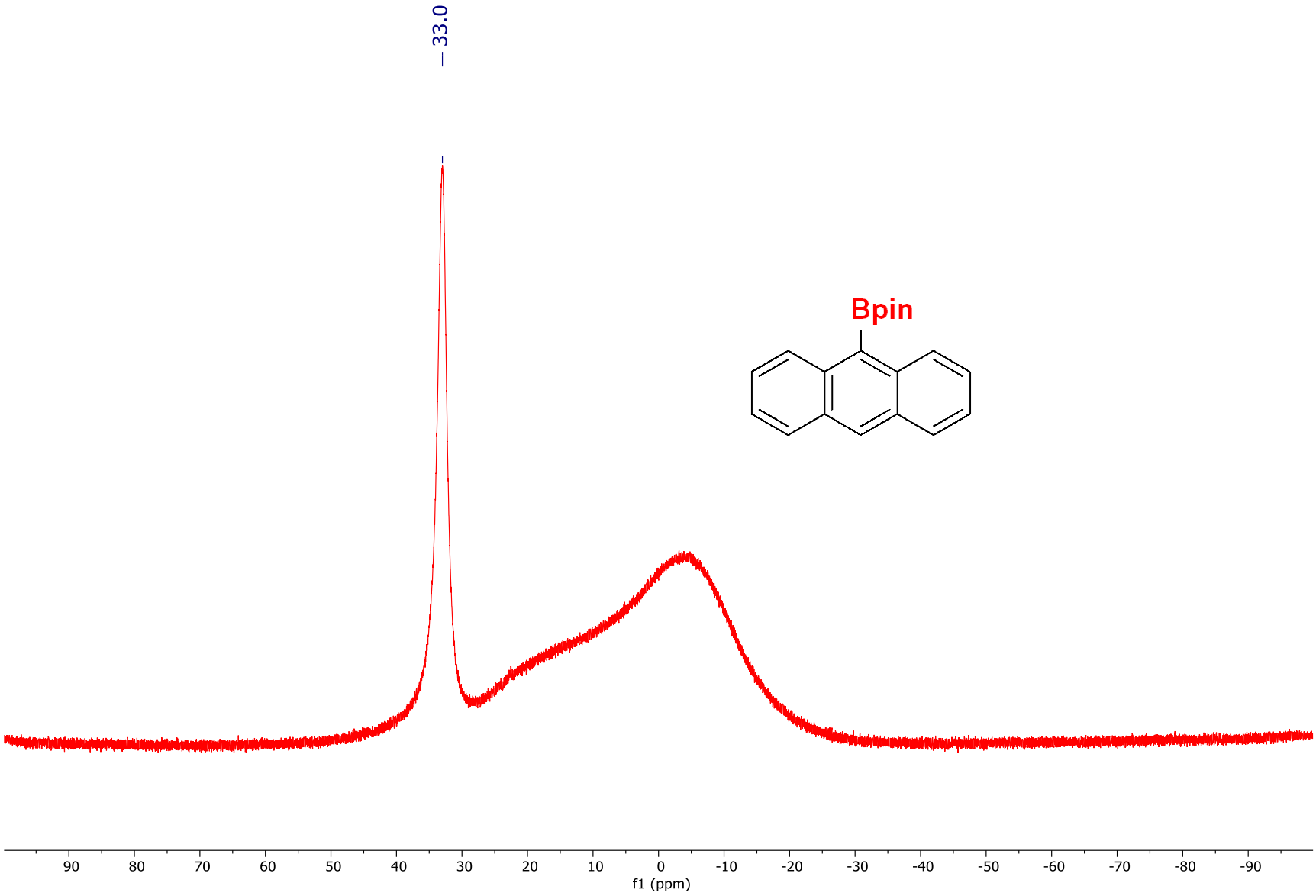
^{1}H NMR of anthracene-9-boronic acid, pinacol ester (4.7h) ($CDCl_3$, 500 MHz)



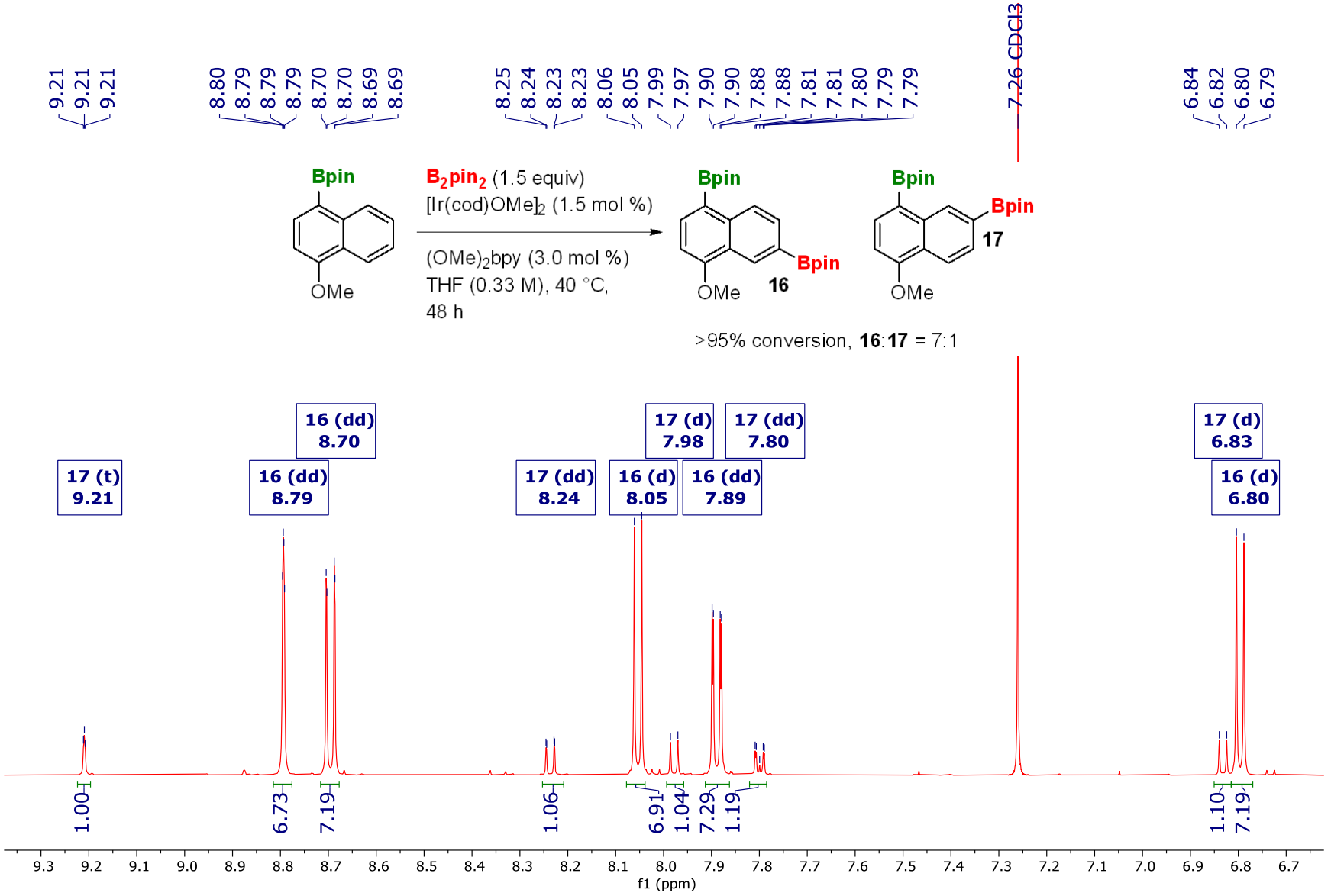
^{13}C NMR of anthracene-9-boronic acid, pinacol ester (4.7h) ($CDCl_3$, 126 MHz)



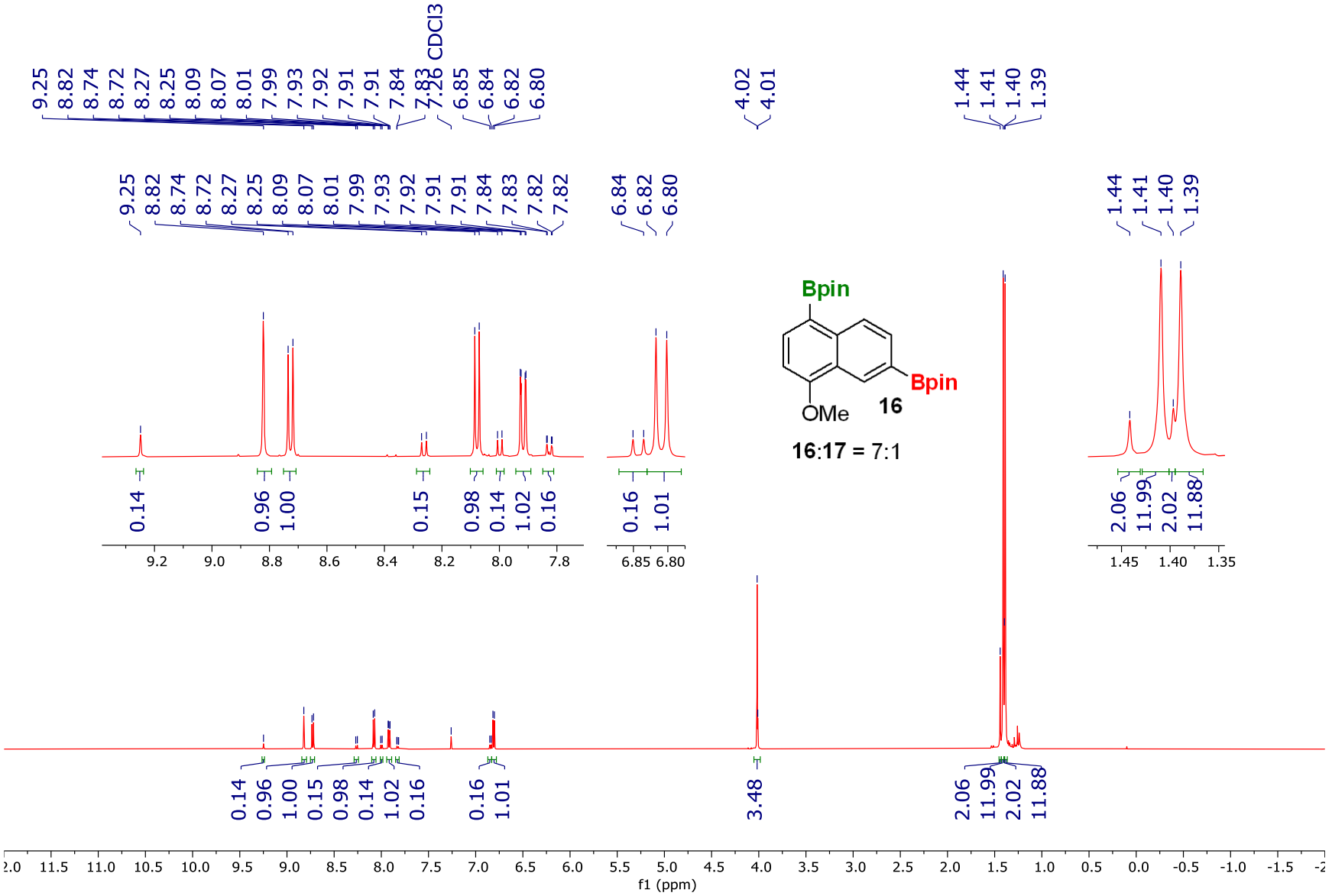
^{11}B NMR of anthracene-9-boronic acid, pinacol ester (4.7h) ($CDCl_3$, 160 MHz)



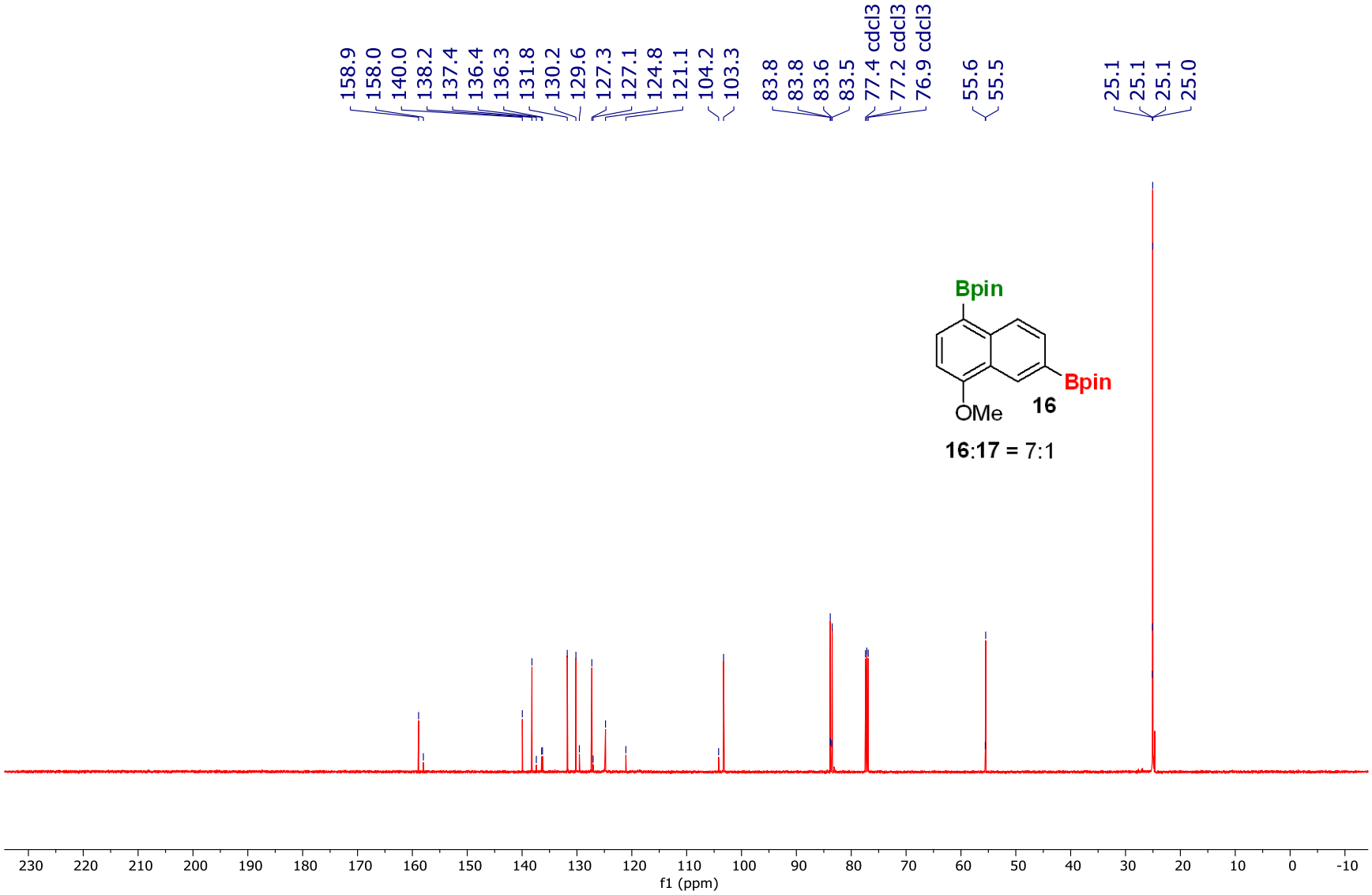
C6 Borylation of 4-methoxy-1-naphthalene boronic acid, pinacol ester (4.8a) ($CDCl_3$, 500 MHz)



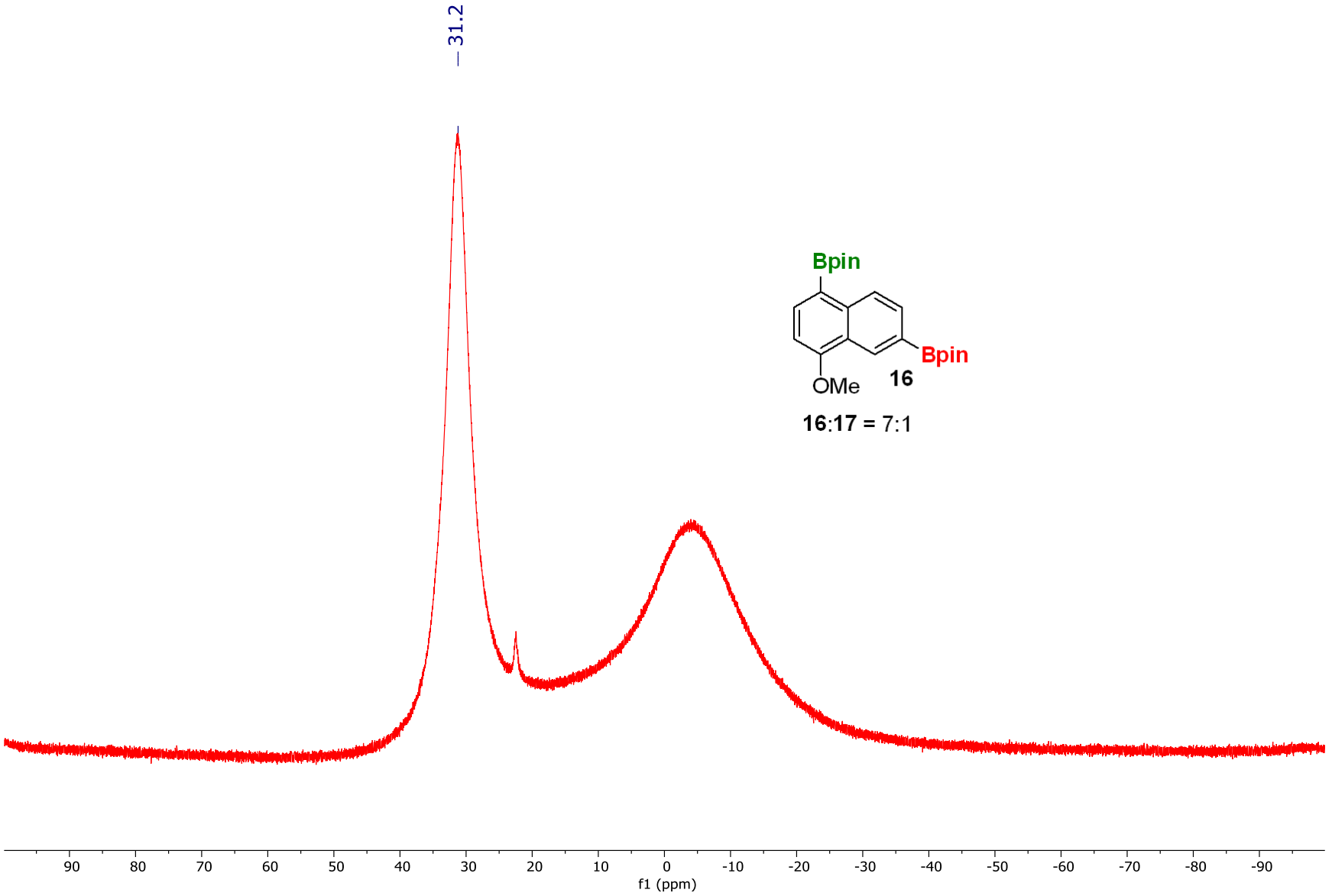
^{1}H NMR of 4-methoxy-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8a) ($CDCl_3$, 500 MHz)



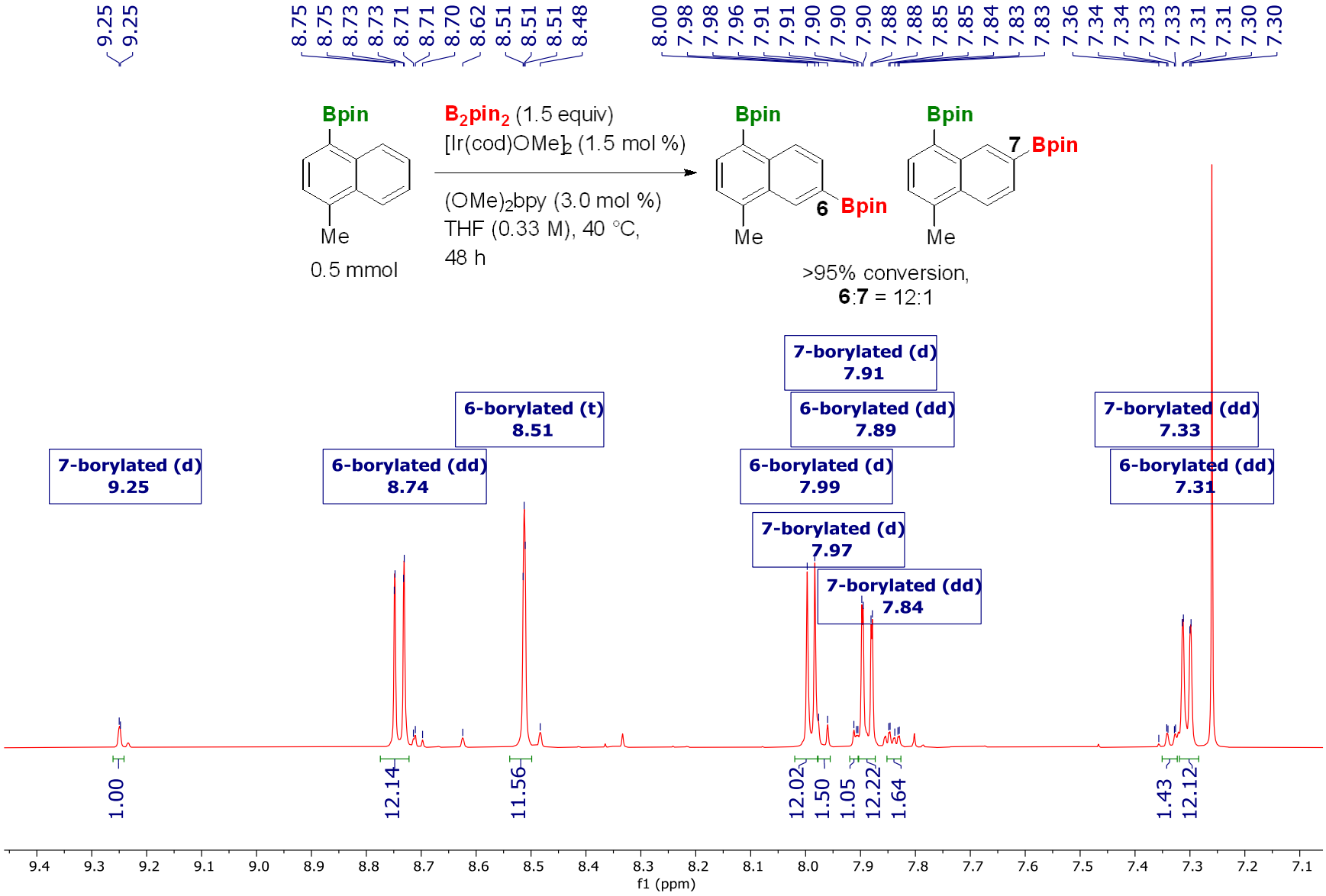
^{13}C NMR of 4-methoxy-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8a) ($CDCl_3$, 126 MHz)



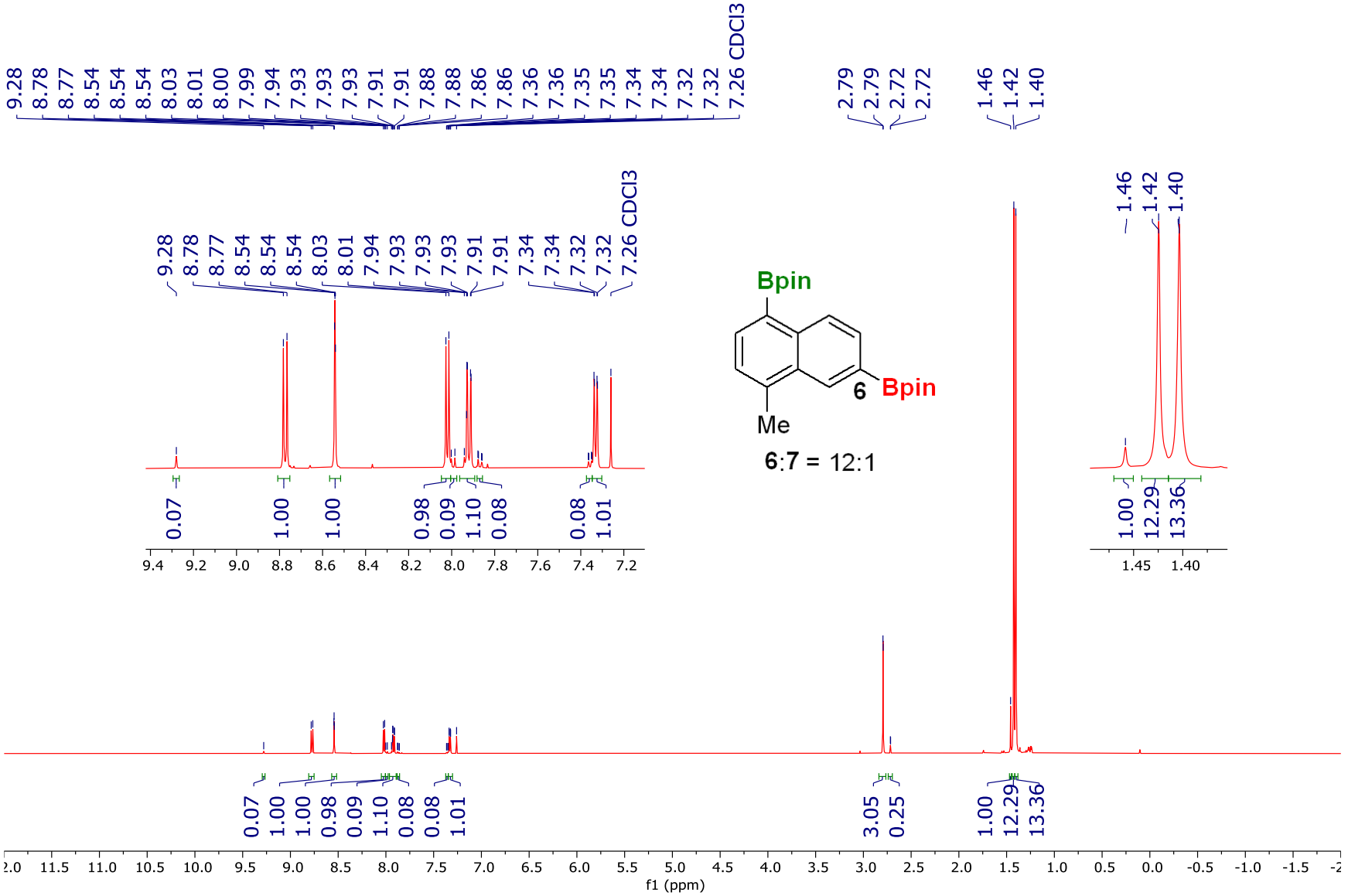
^{11}B NMR of 4-methoxy-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8a) ($CDCl_3$, 126 MHz)



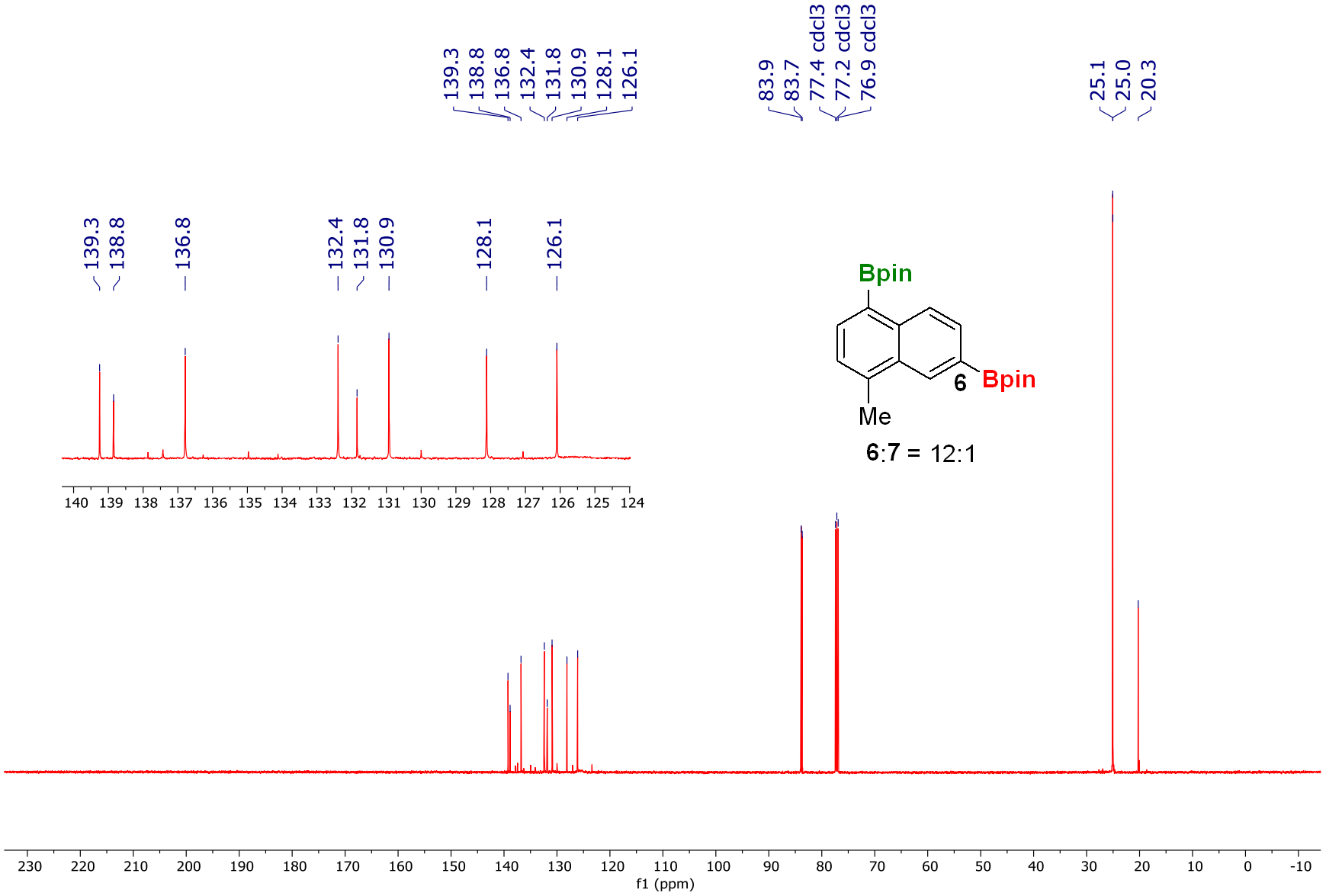
C6 Borylation of 4-methylnaphthalene-1-boronic acid, pinacol ester (4.8b) ($CDCl_3$, 126 MHz)



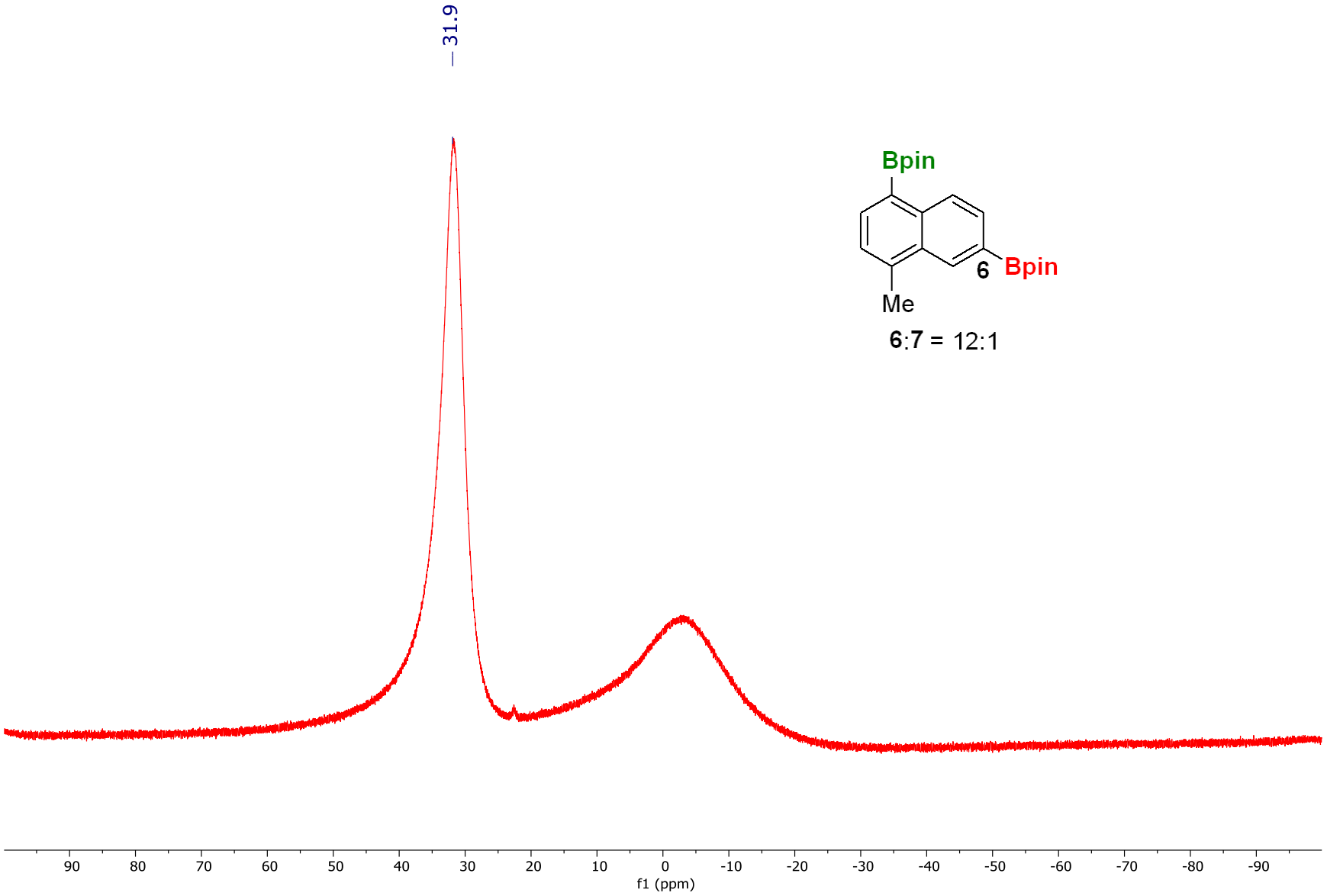
^{1}H NMR of 4-methyl-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8b) ($CDCl_3$, 500 MHz)



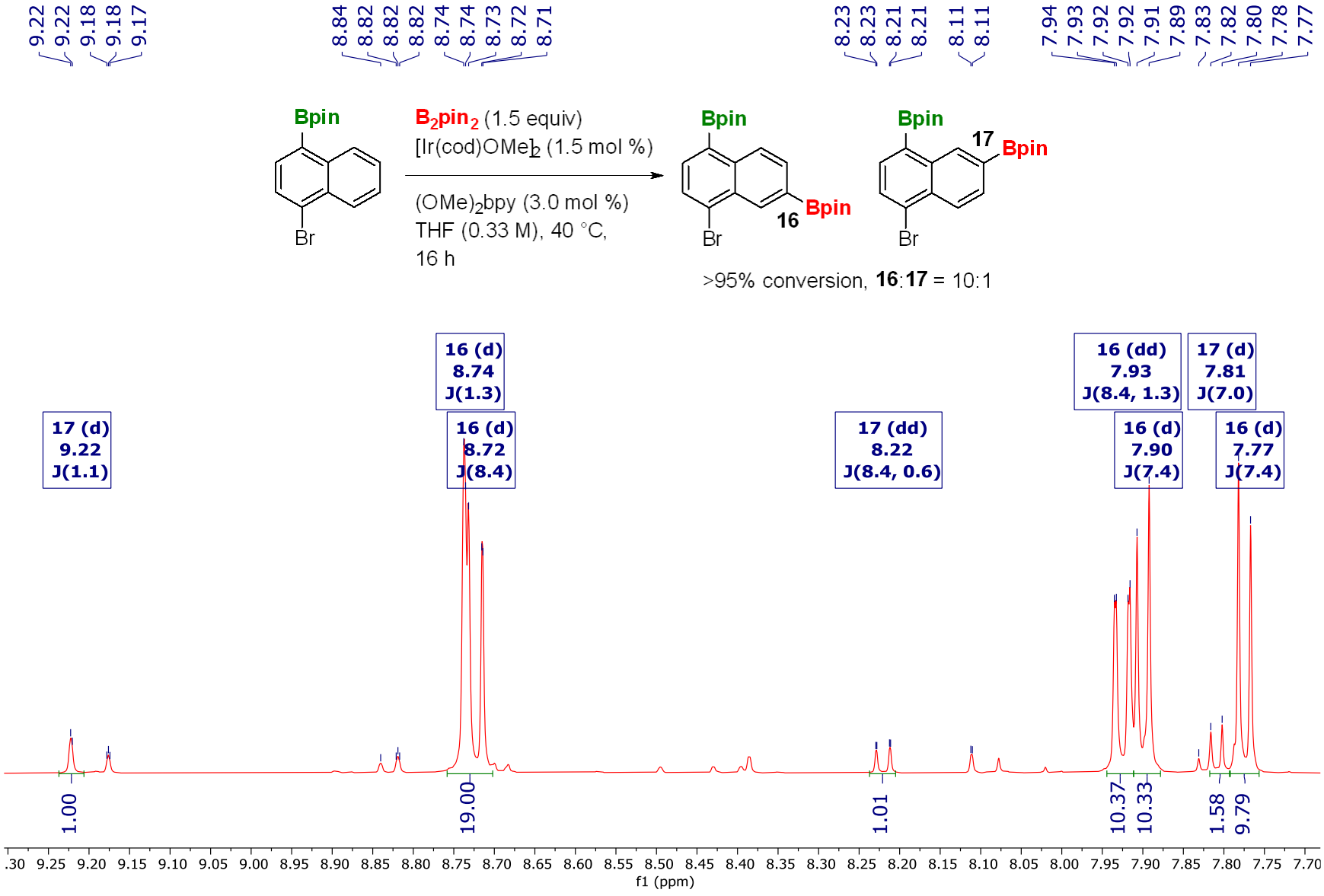
^{13}C NMR of 4-methyl-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8b) ($CDCl_3$, 126 MHz)



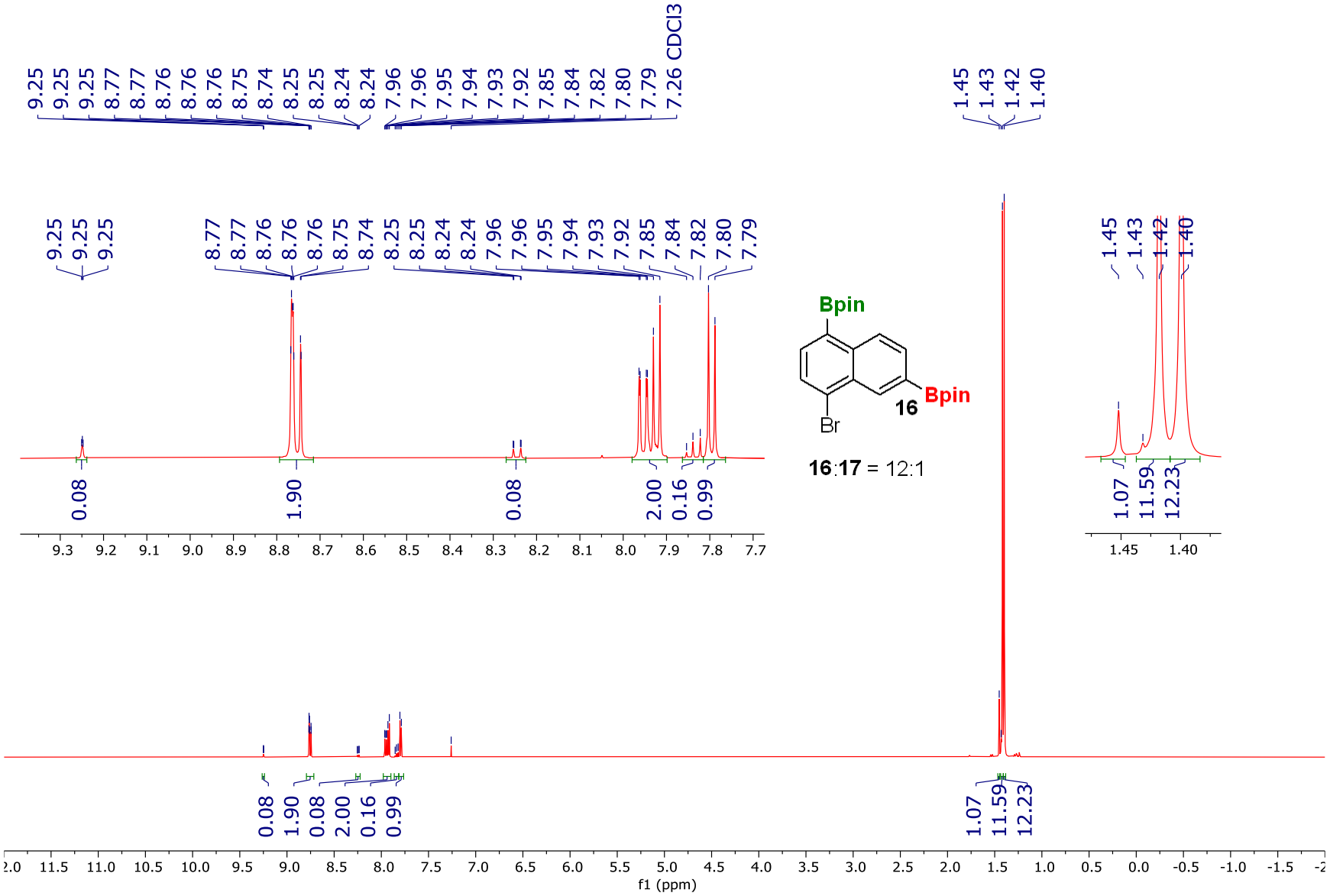
^{11}B NMR of 4-methyl-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8b) ($CDCl_3$, 160 MHz)



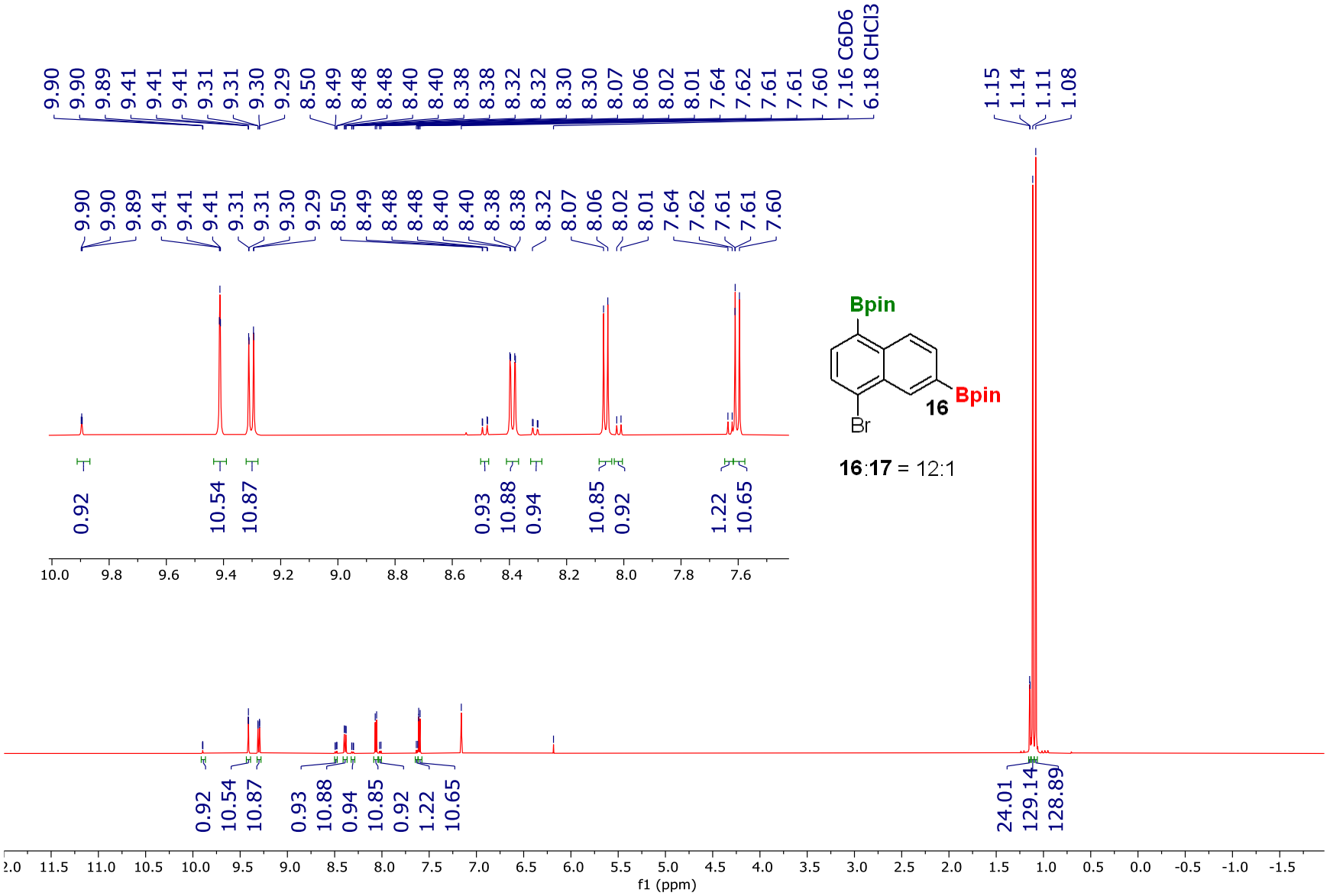
C6 Borylation of 4-bromonaphthalene-1-boronic acid, pinacol ester (4.8c) ($CDCl_3$, 126 MHz)



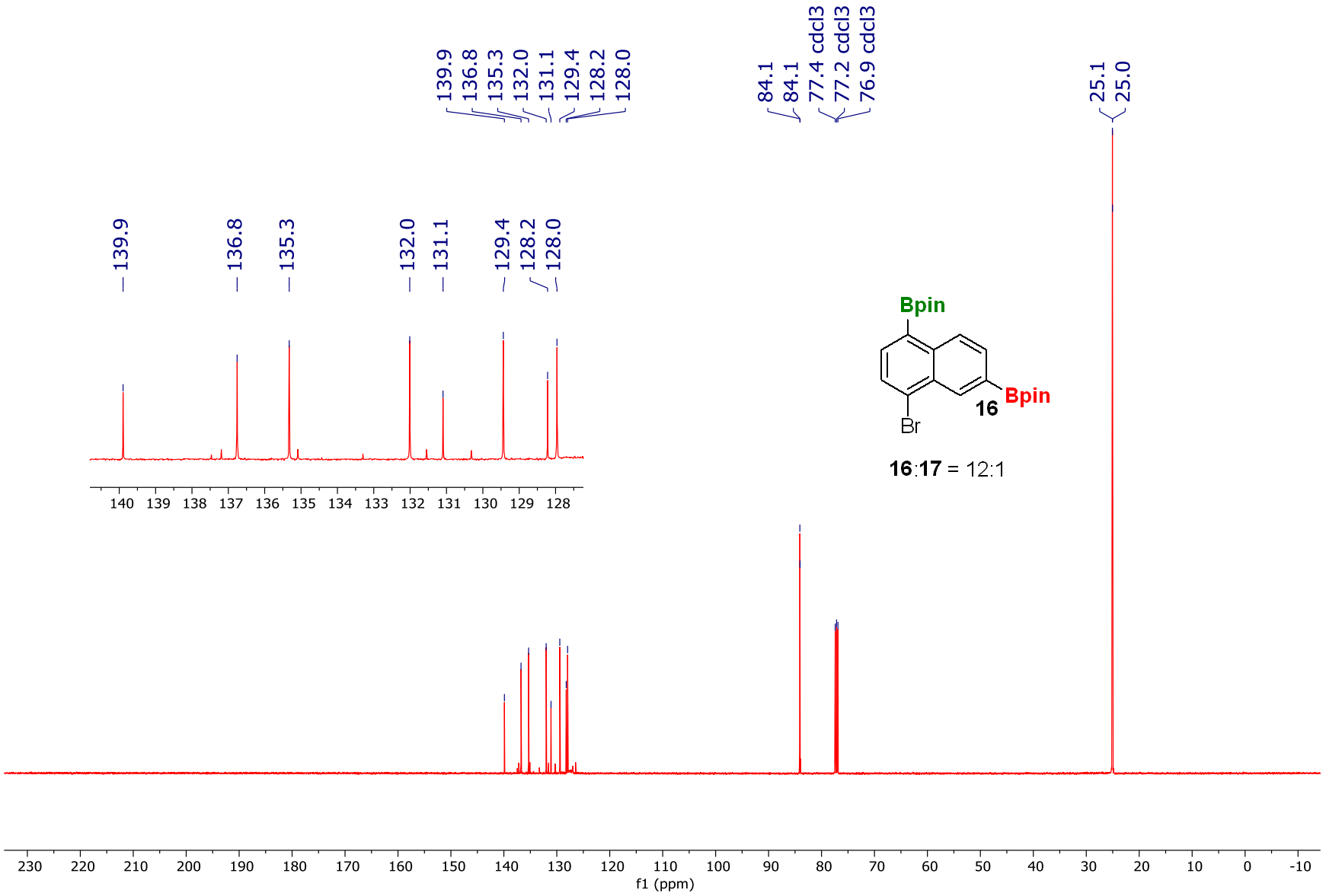
^{1}H NMR of 4-bromo-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8c) ($CDCl_3$, 500 MHz)



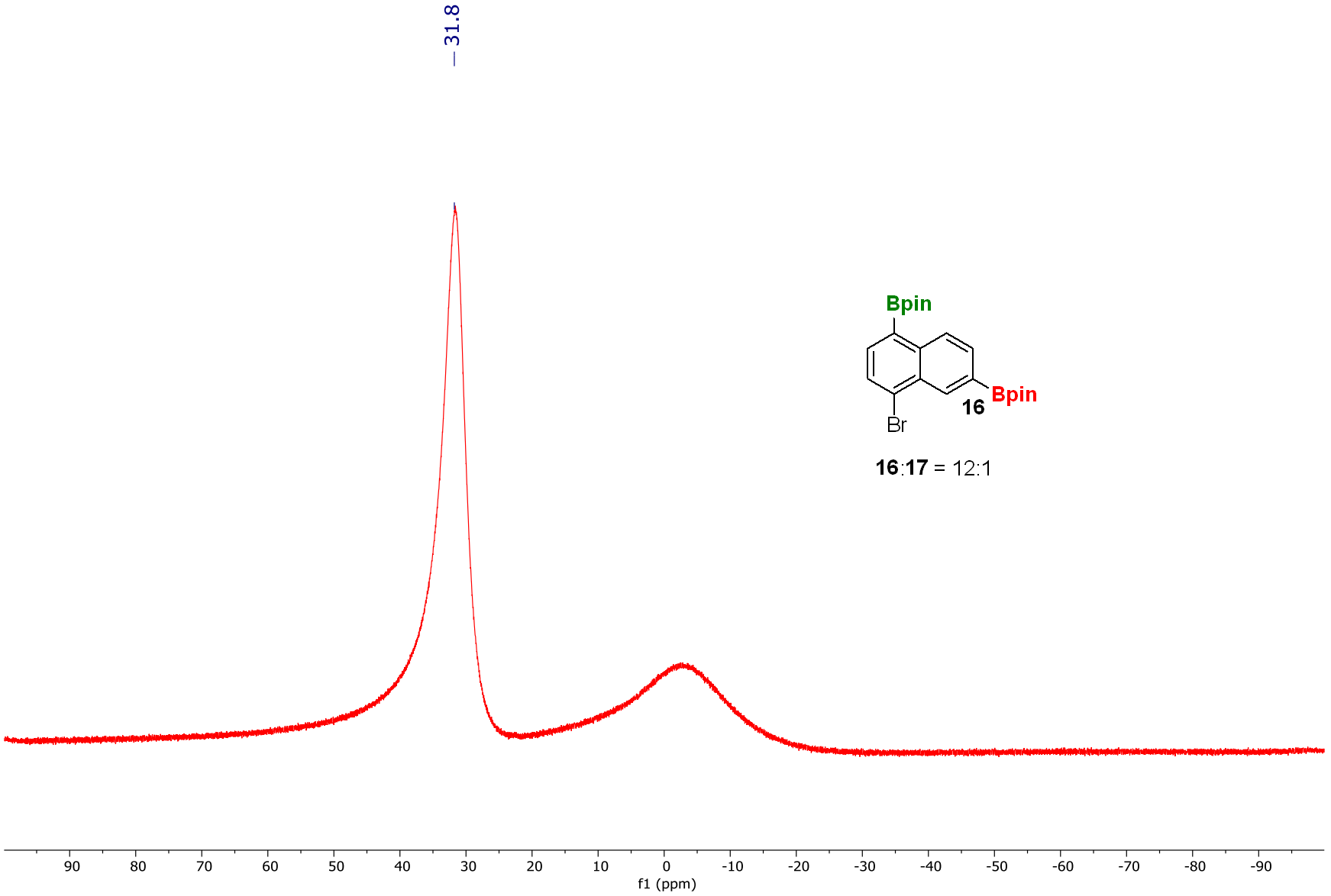
^{1}H NMR of 4-bromo-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8c) (C_6D_6, 500 MHz)



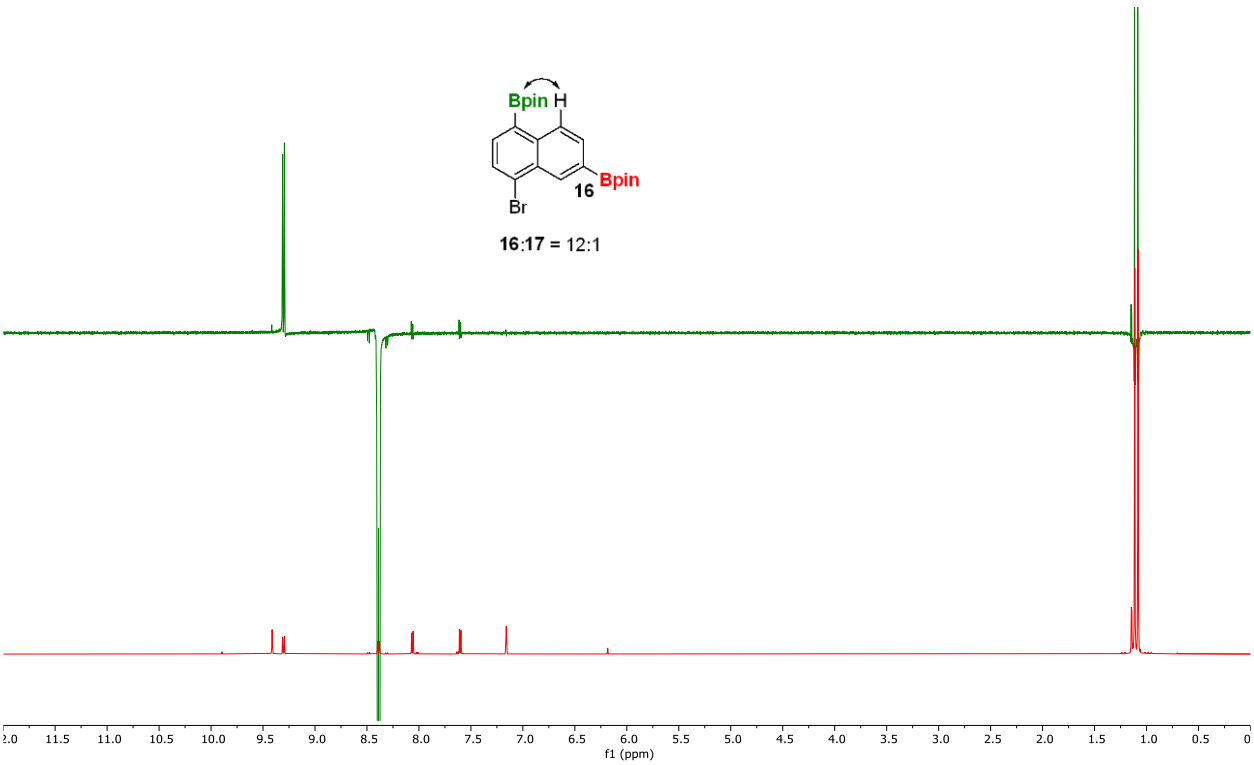
^{13}C NMR of 4-bromo-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8c) ($CDCl_3$, 126 MHz)

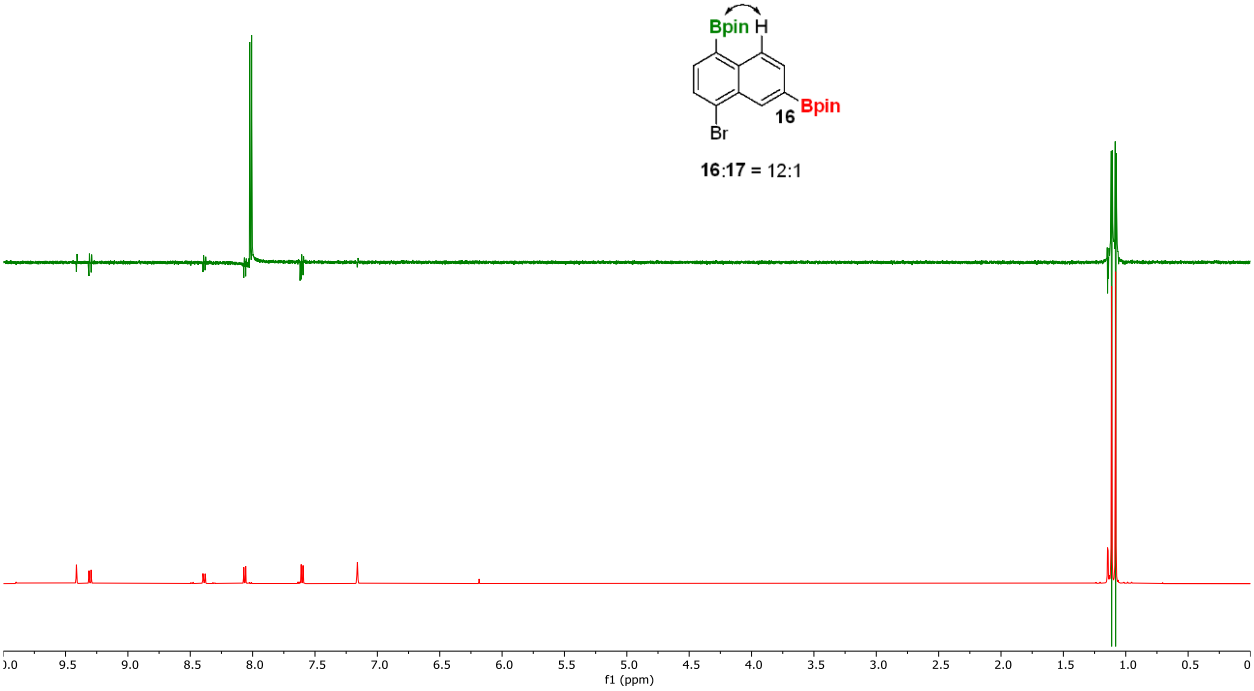


^{11}B NMR of 4-bromo-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8c) ($CDCl_3$, 160 MHz)

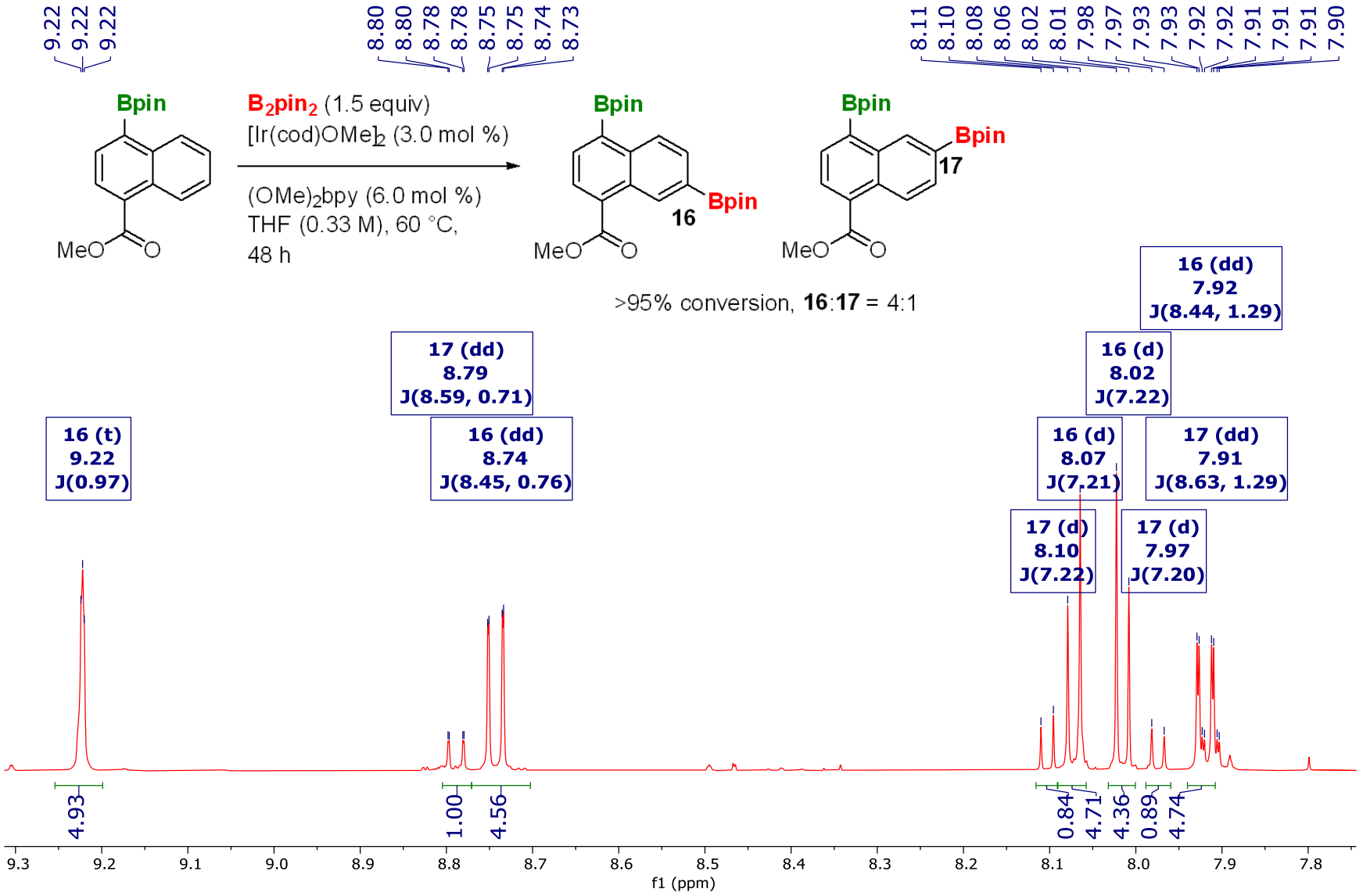


1D-NOE of 4-bromo-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8c) (C_6D_6, 500 MHz)
Identification of the C6 isomer

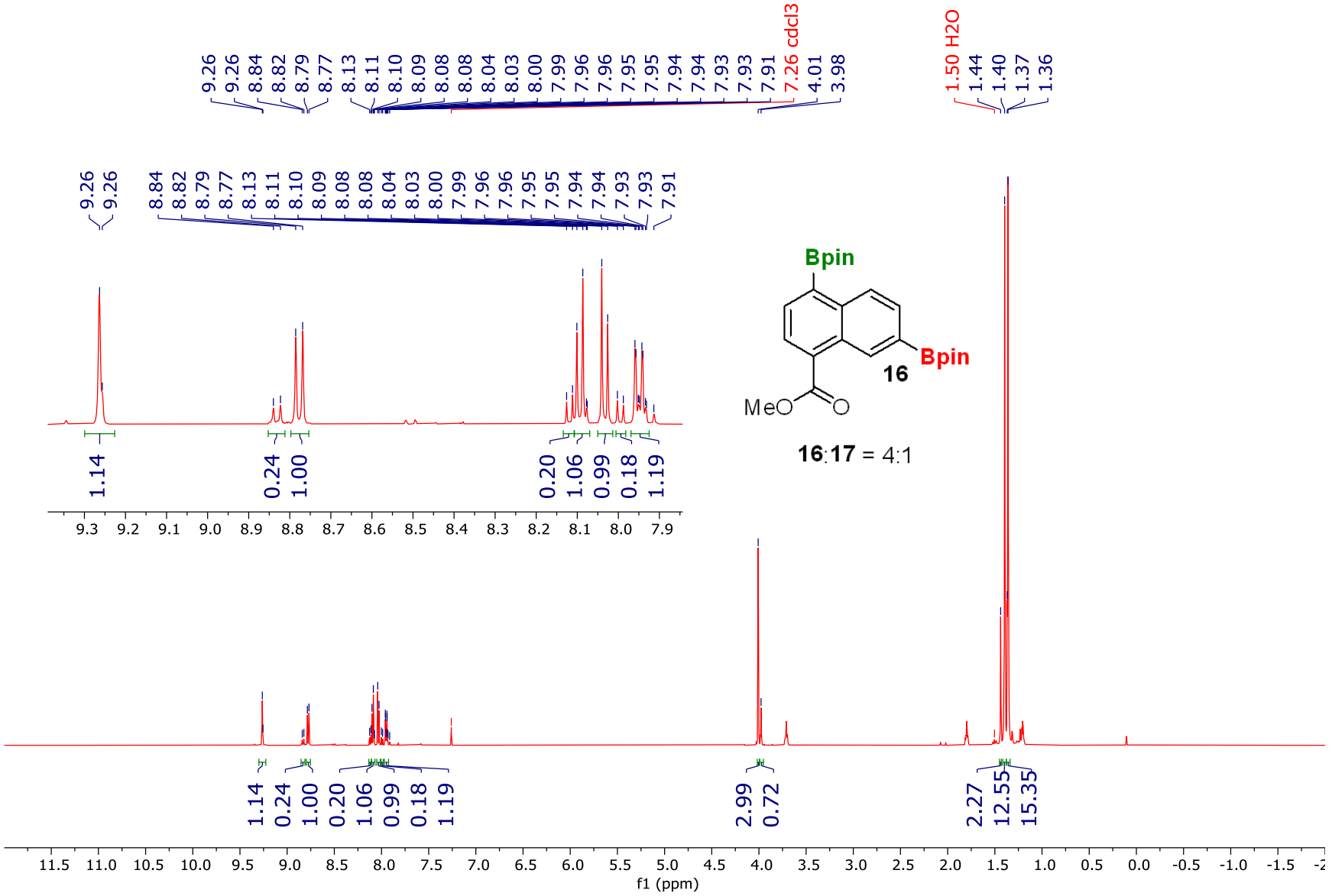




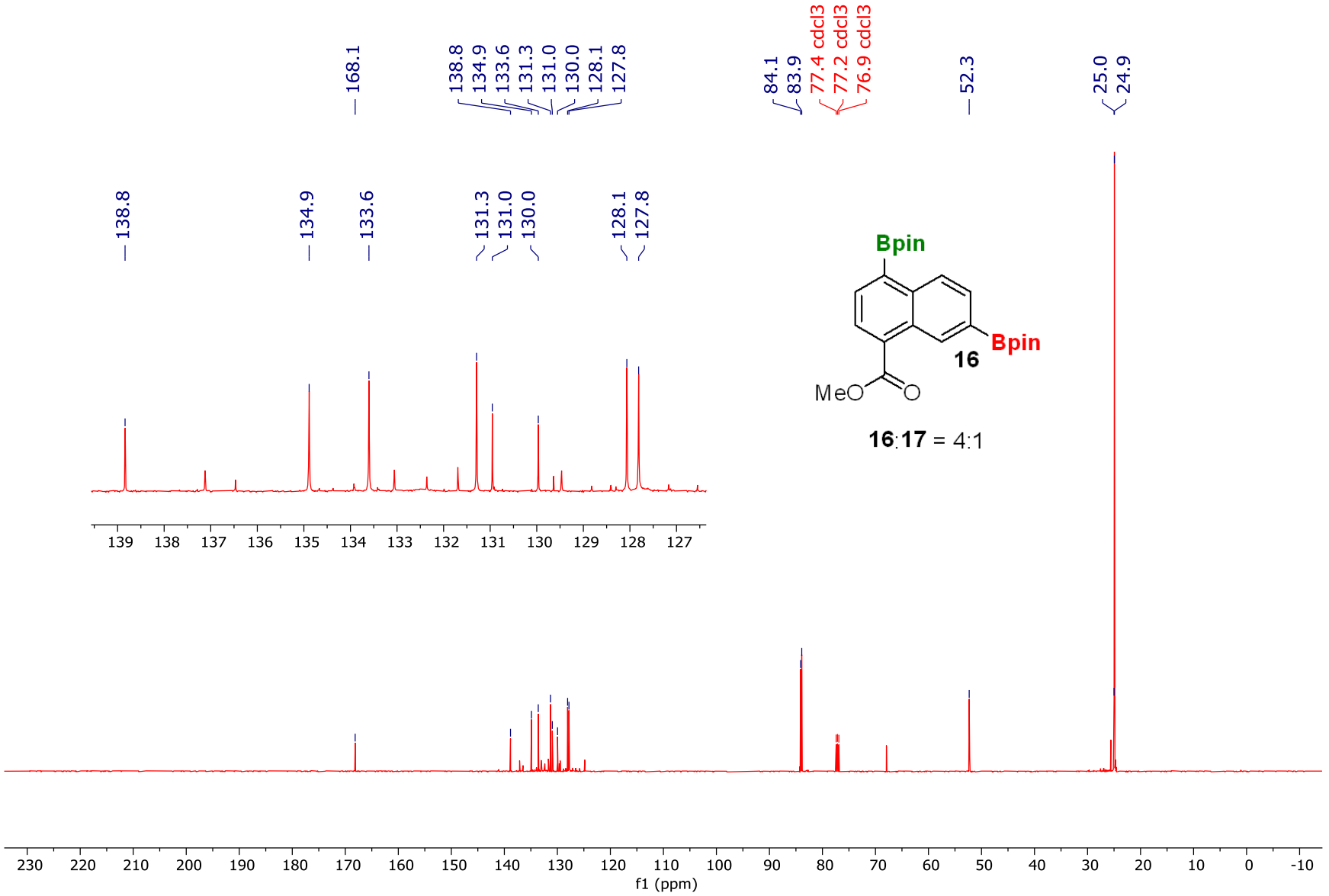
C6 Borylation of methyl 4-naphthoate-1-boronic acid, pinacol ester (4.8d) ($CDCl_3$, 500 MHz)



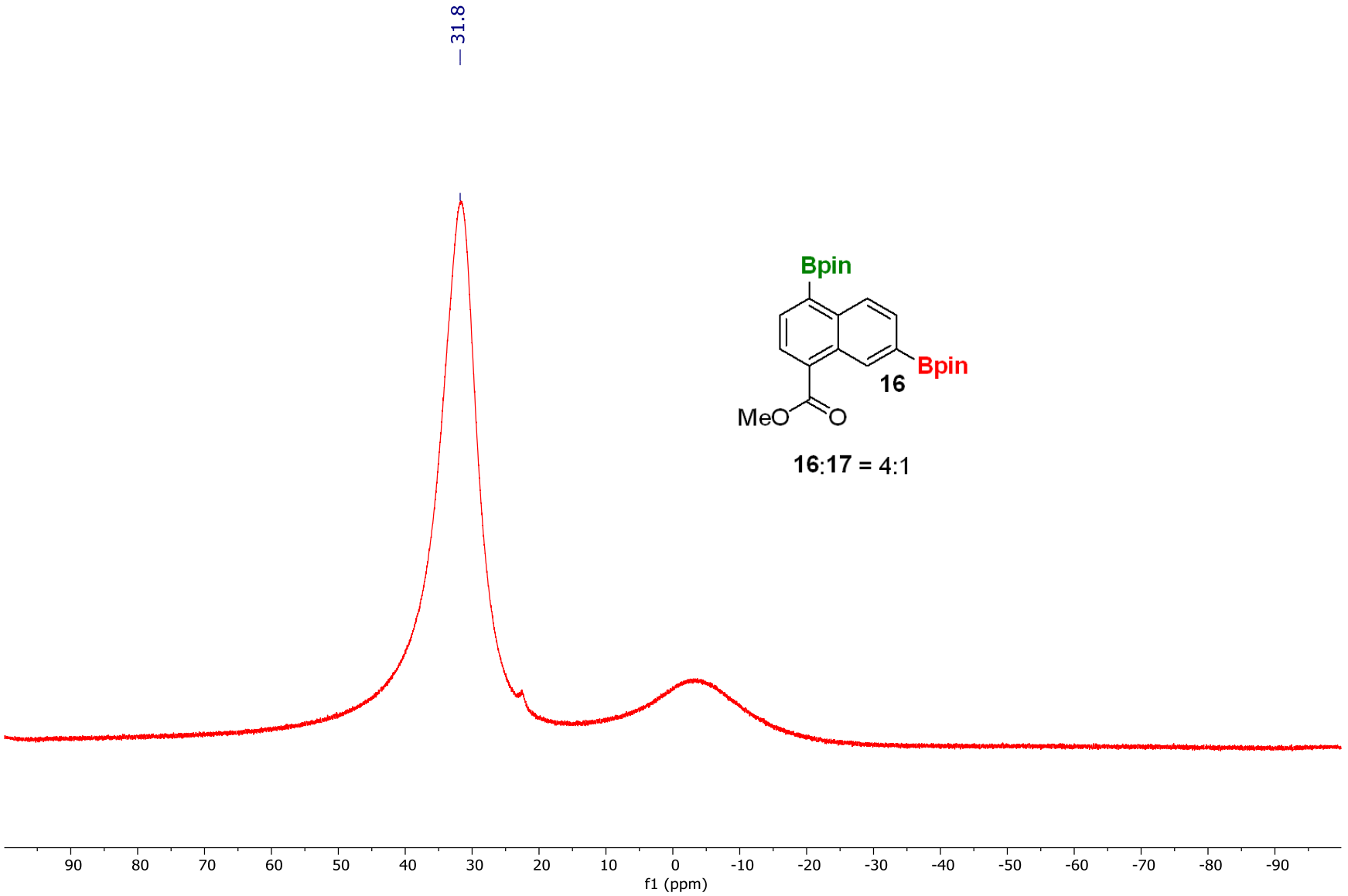
^{1}H NMR of methyl 4-naphthoate-1,6-diboronic acid bis(pinacol) ester (4.8d) ($CDCl_3$, 500 MHz)



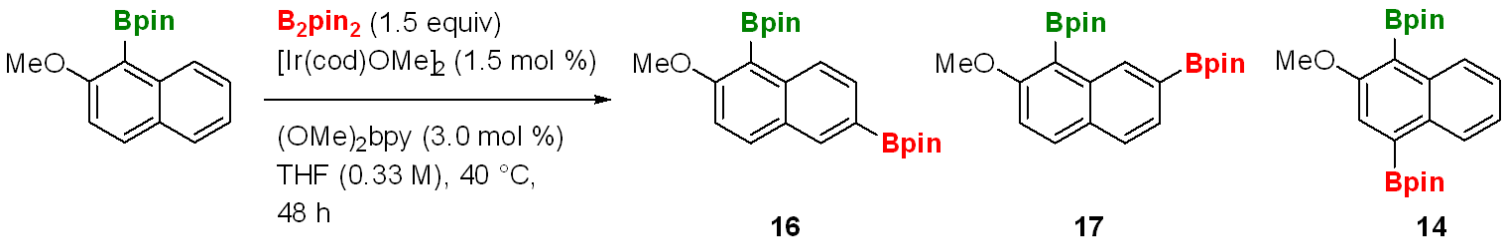
^{13}C NMR of methyl 4-naphthoate-1,6-diboronic acid bis(pinacol) ester (4.8d) ($CDCl_3$, 126 MHz)



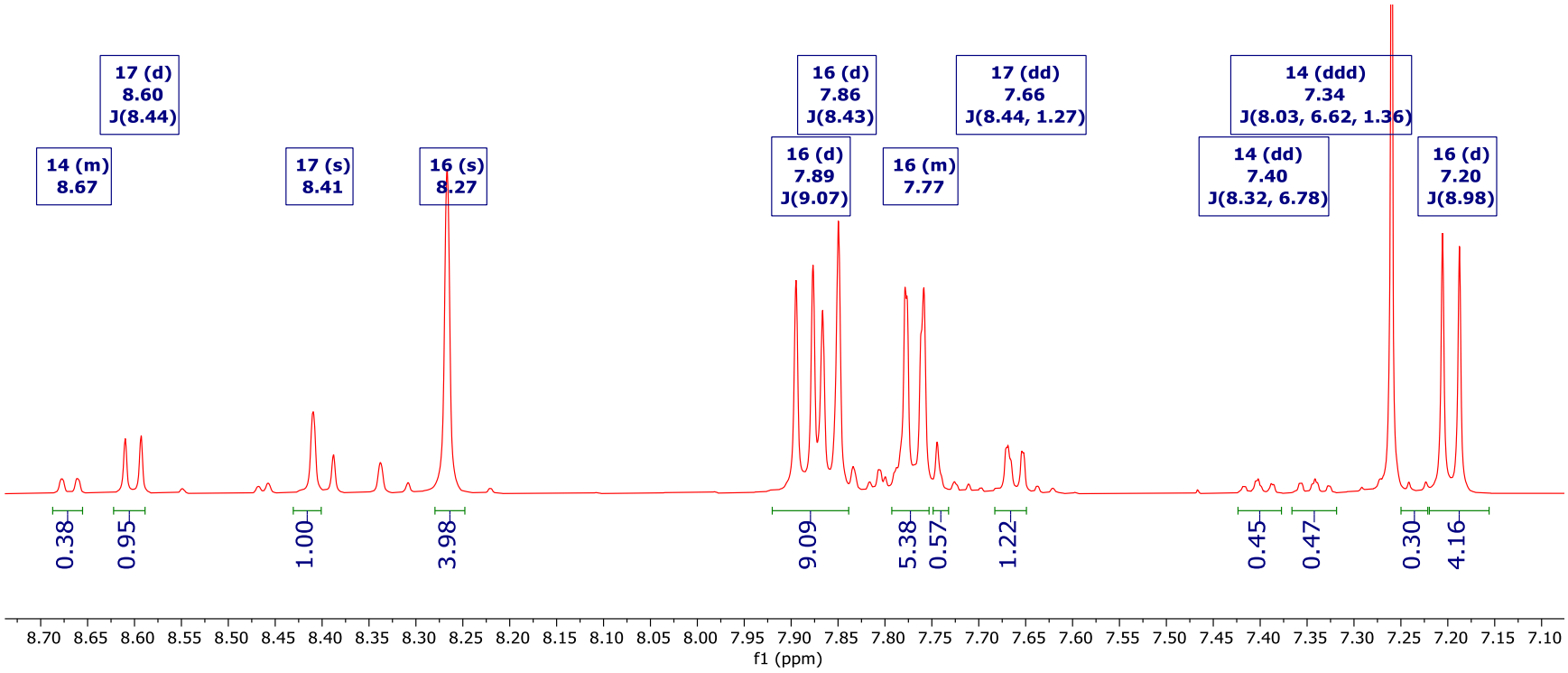
^{11}B NMR of methyl 4-naphthoate-1,6-diboronic acid bis(pinacol) ester (4.8d) ($CDCl_3$, 160 MHz)



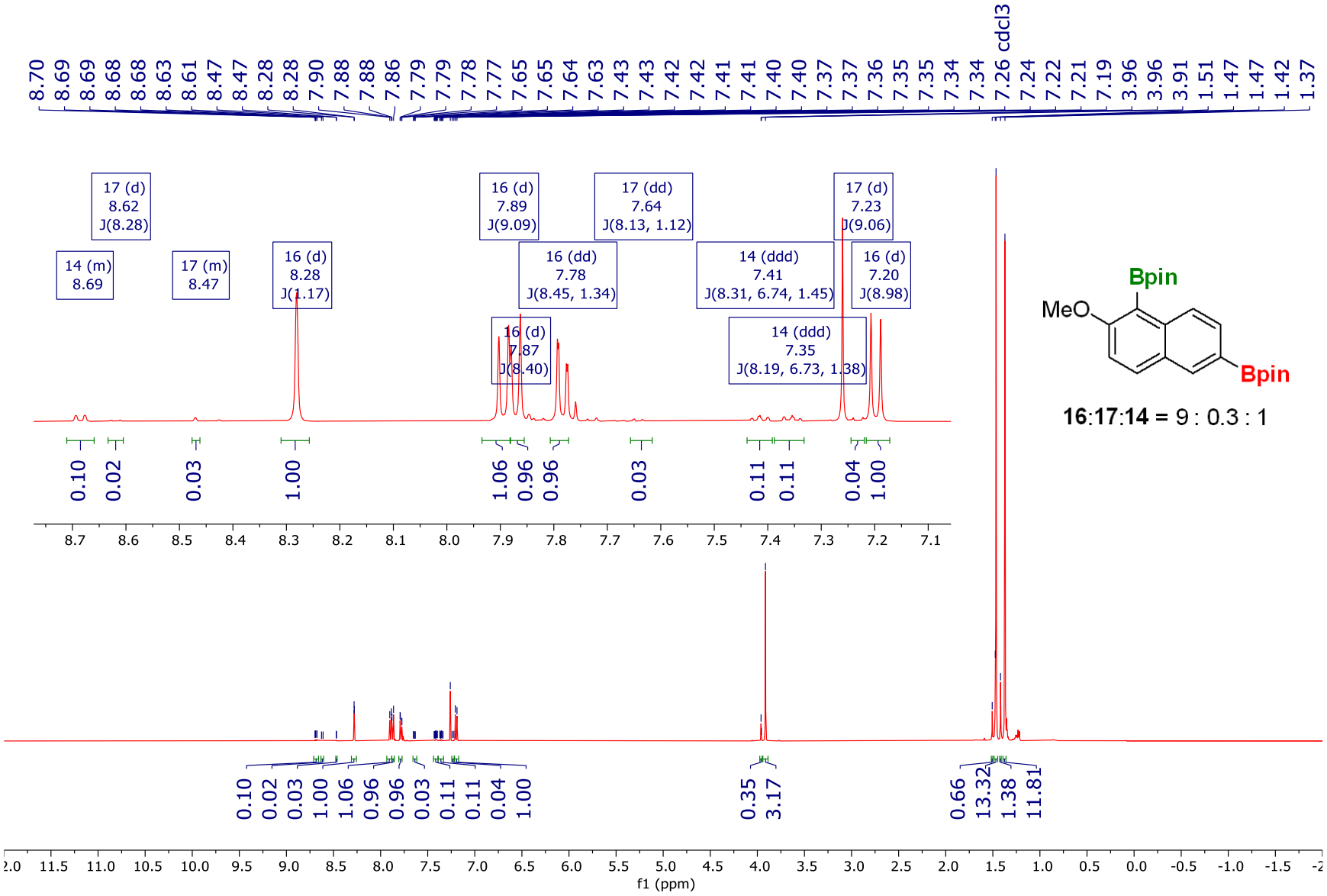
6-Borylation of 2-methoxynaphthalene-1-boronic acid, pinacol ester (4.8e) ($CDCl_3$, 126 MHz)



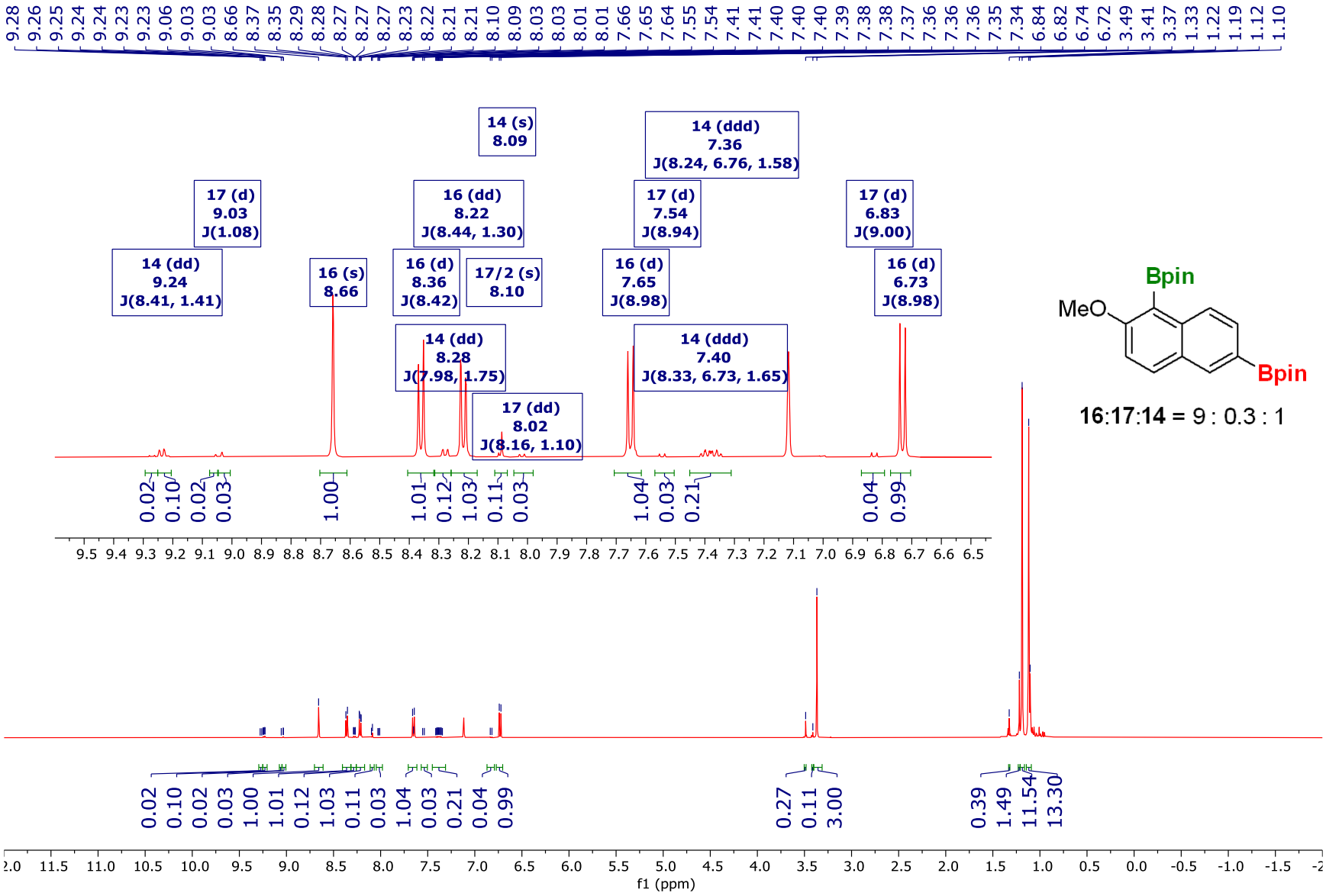
>95% conversion, **16**:**17**:**14** = 4 : 1 : 0.4



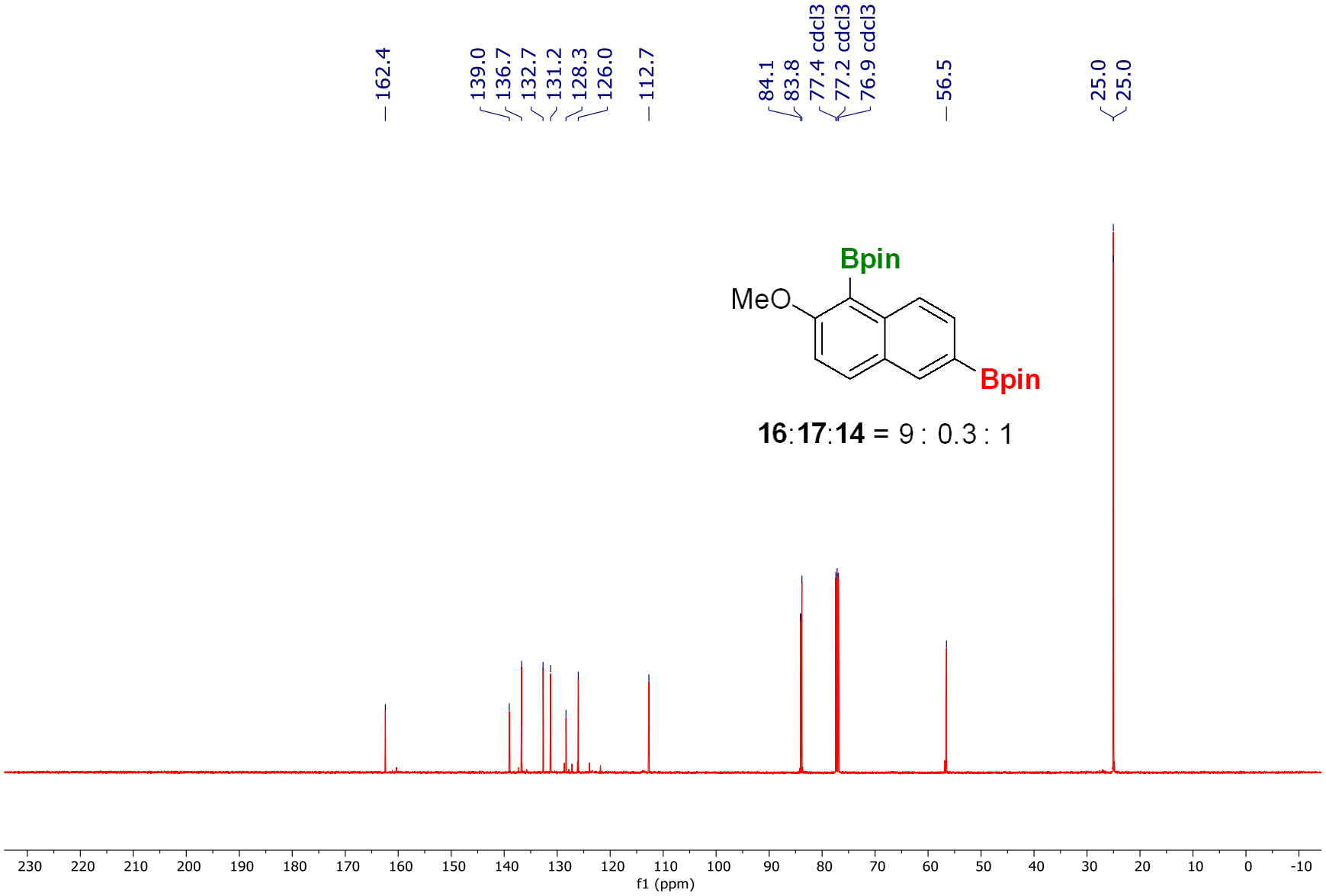
^{1}H NMR of 2-methoxy-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8e) ($CDCl_3$, 500 MHz)



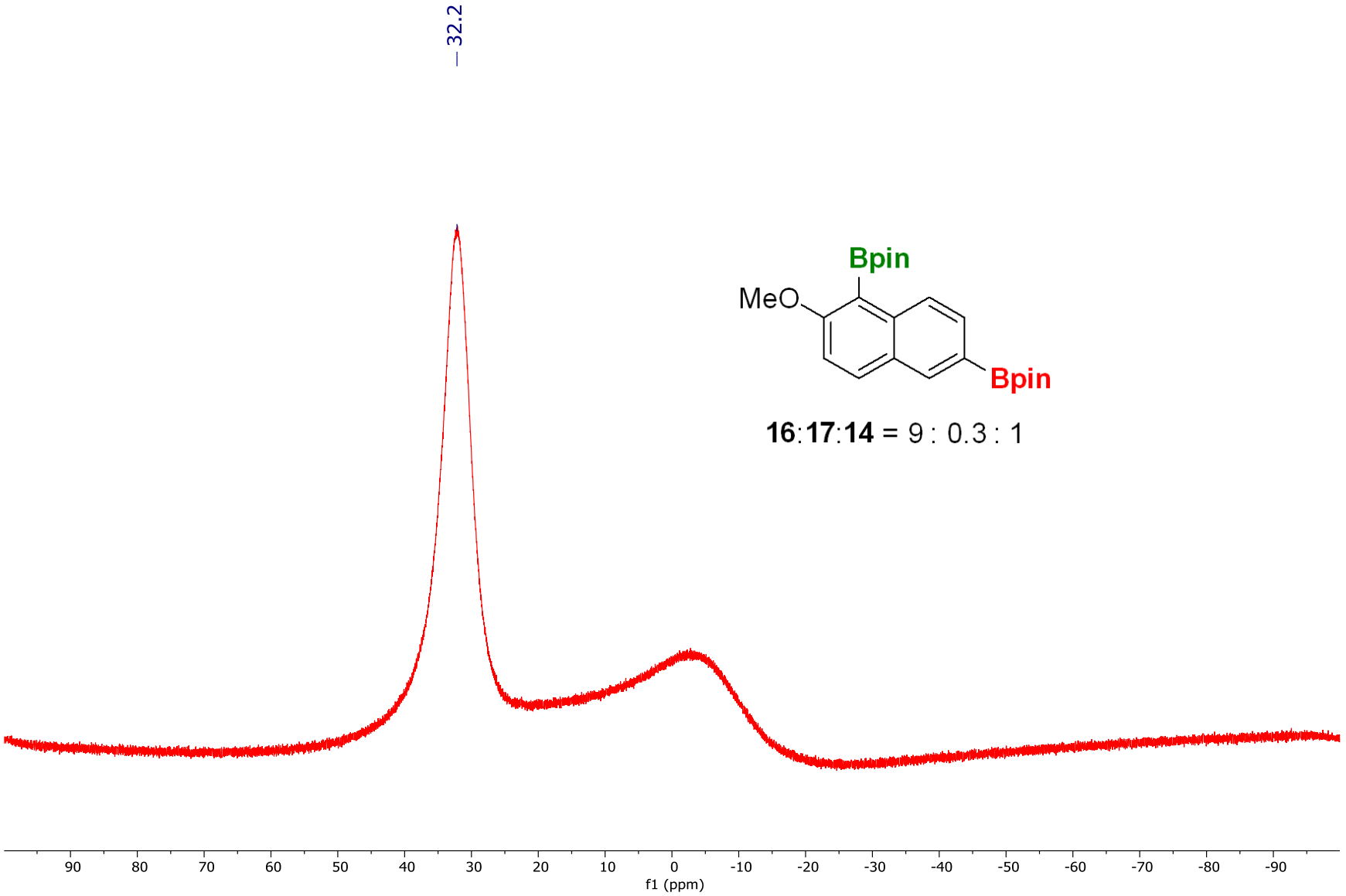
^{1}H NMR of 2-methoxy-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8e) (C_6D_6, 500 MHz)



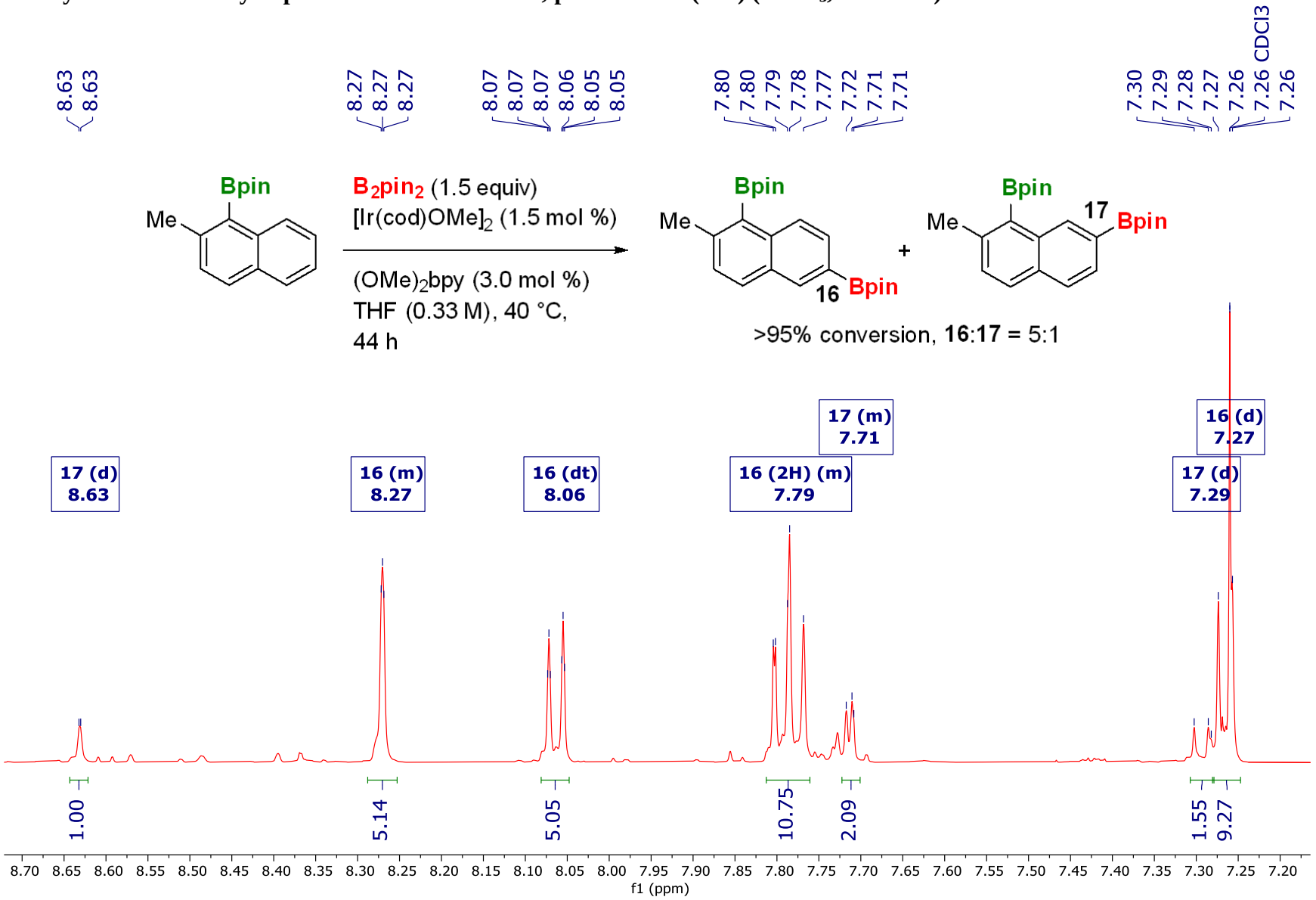
^{13}C NMR of 2-methoxy-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8e) ($CDCl_3$, 126 MHz)



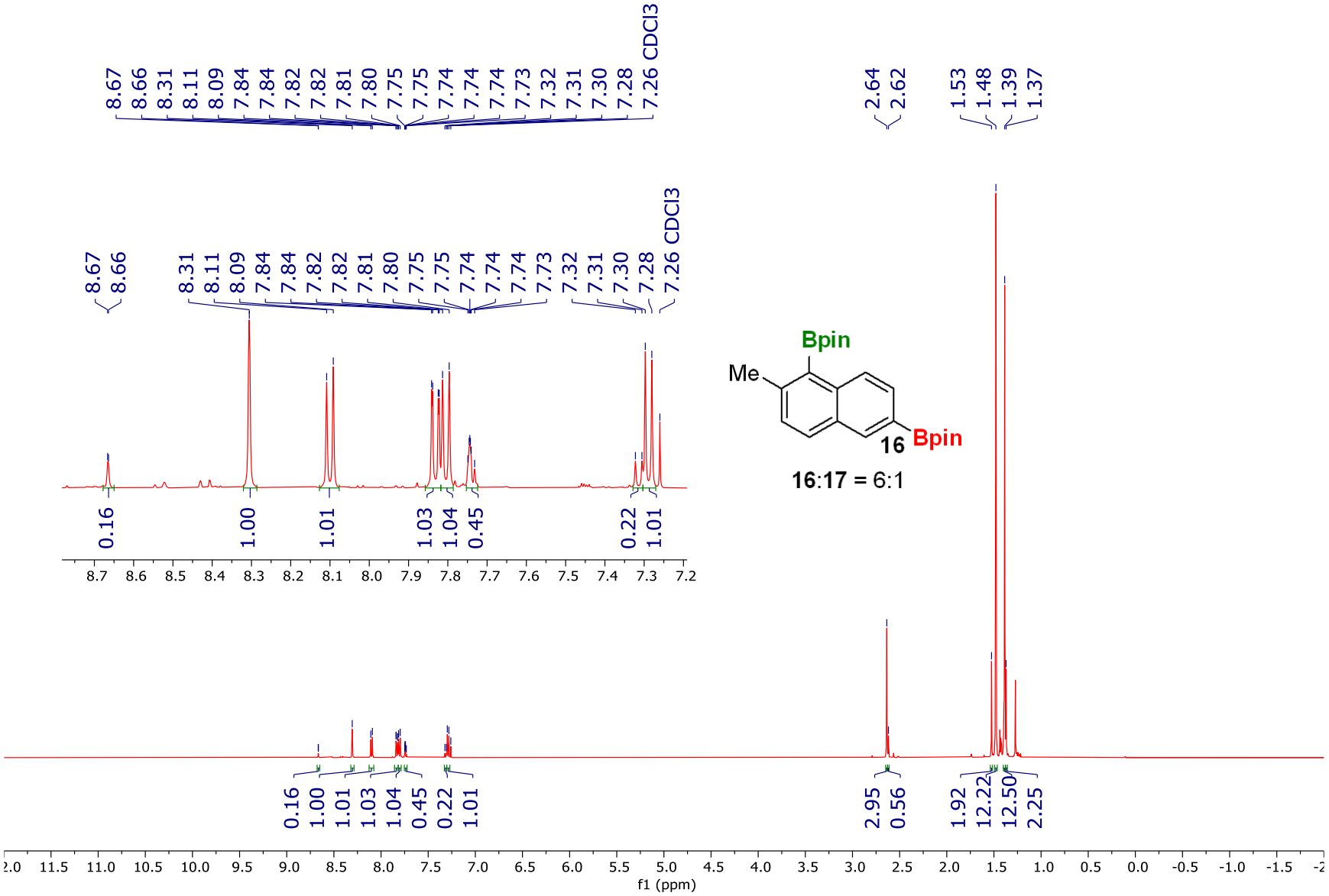
^{11}B NMR of 2-methoxy-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8e) ($CDCl_3$, 160 MHz)



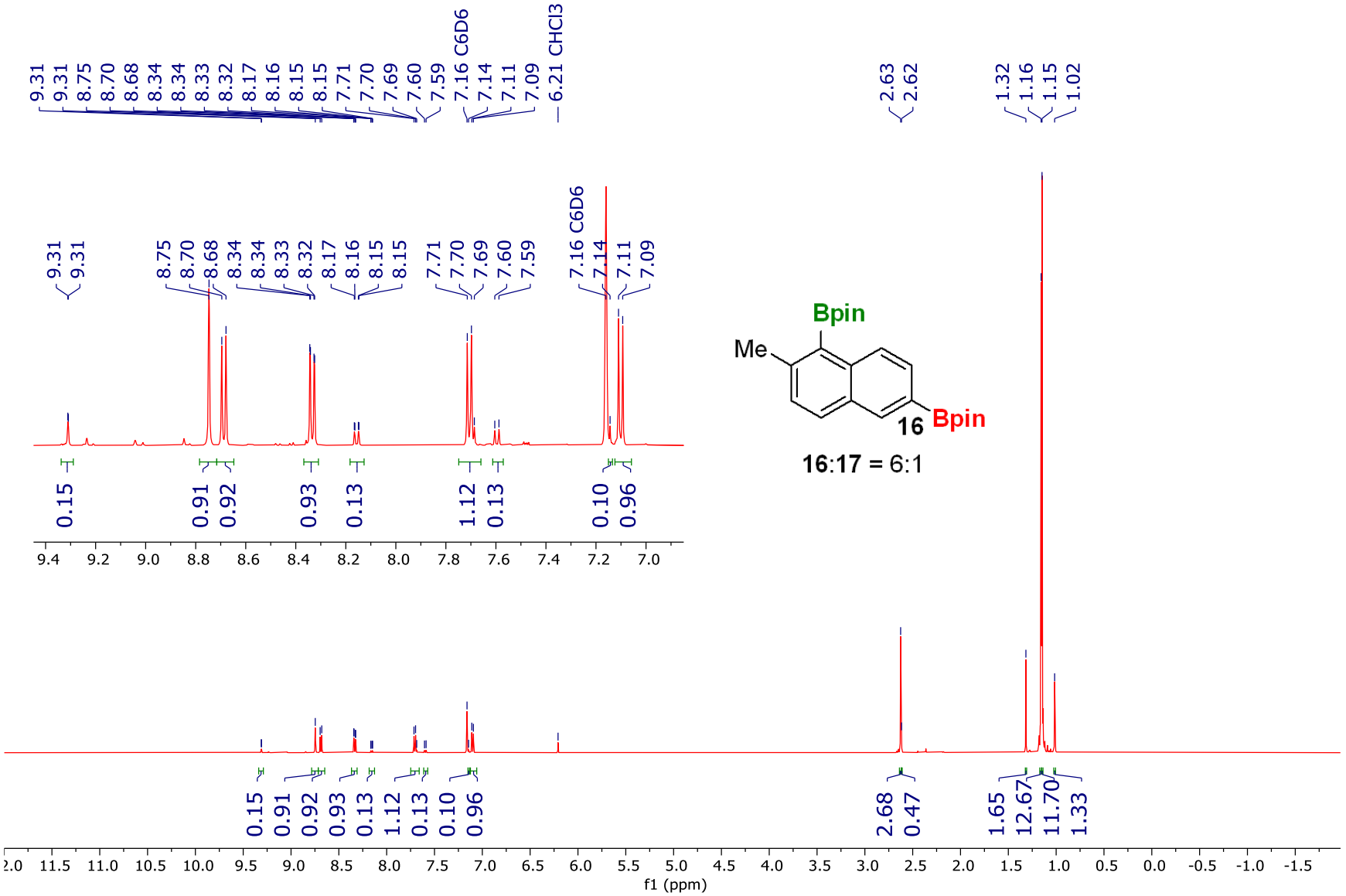
6-Borylation of 2-methylnaphthalene-1-boronic acid, pinacol ester (4.8f) ($CDCl_3$, 126 MHz)



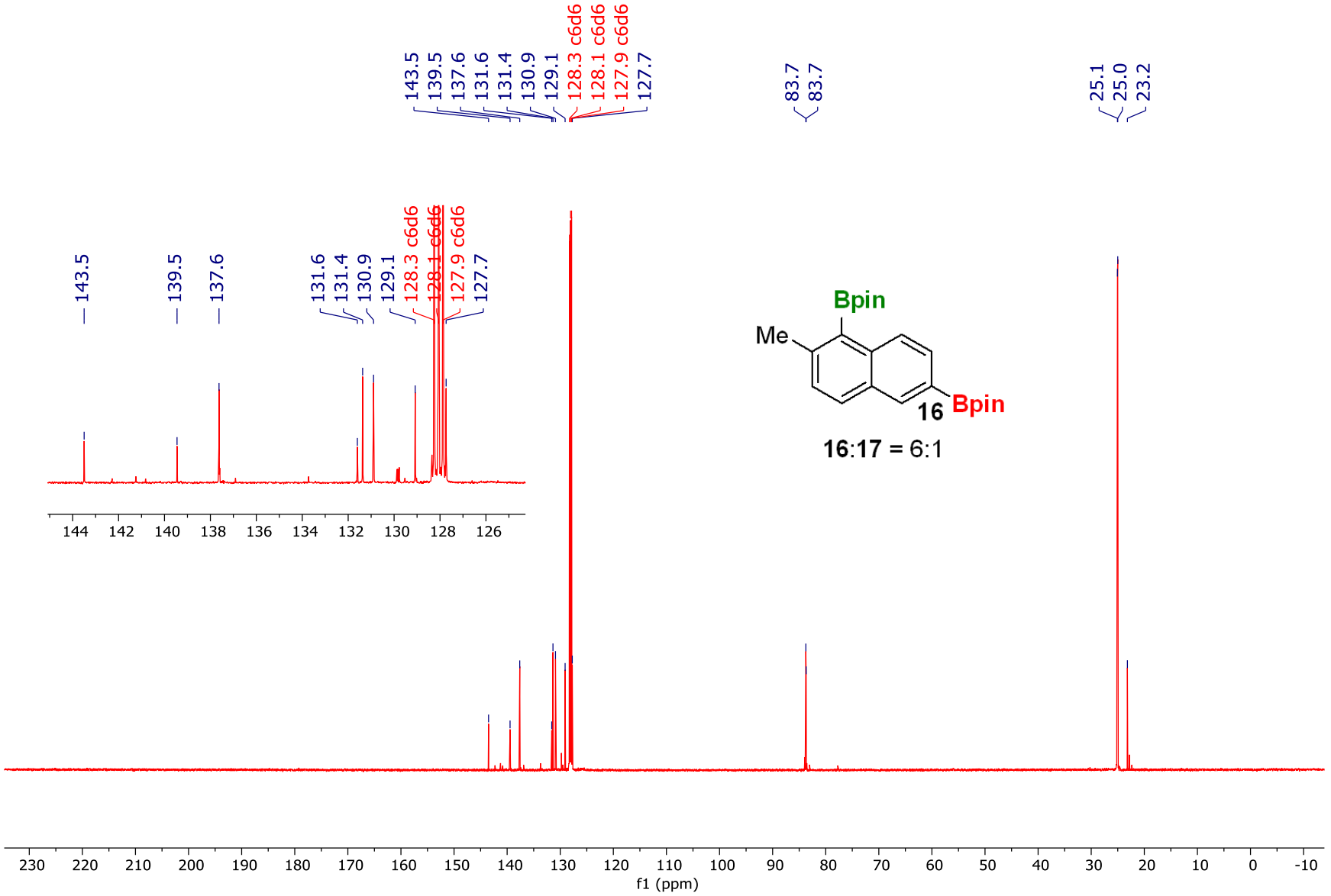
^{1}H NMR of 2-methyl-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8f) ($CDCl_3$, 500 MHz)



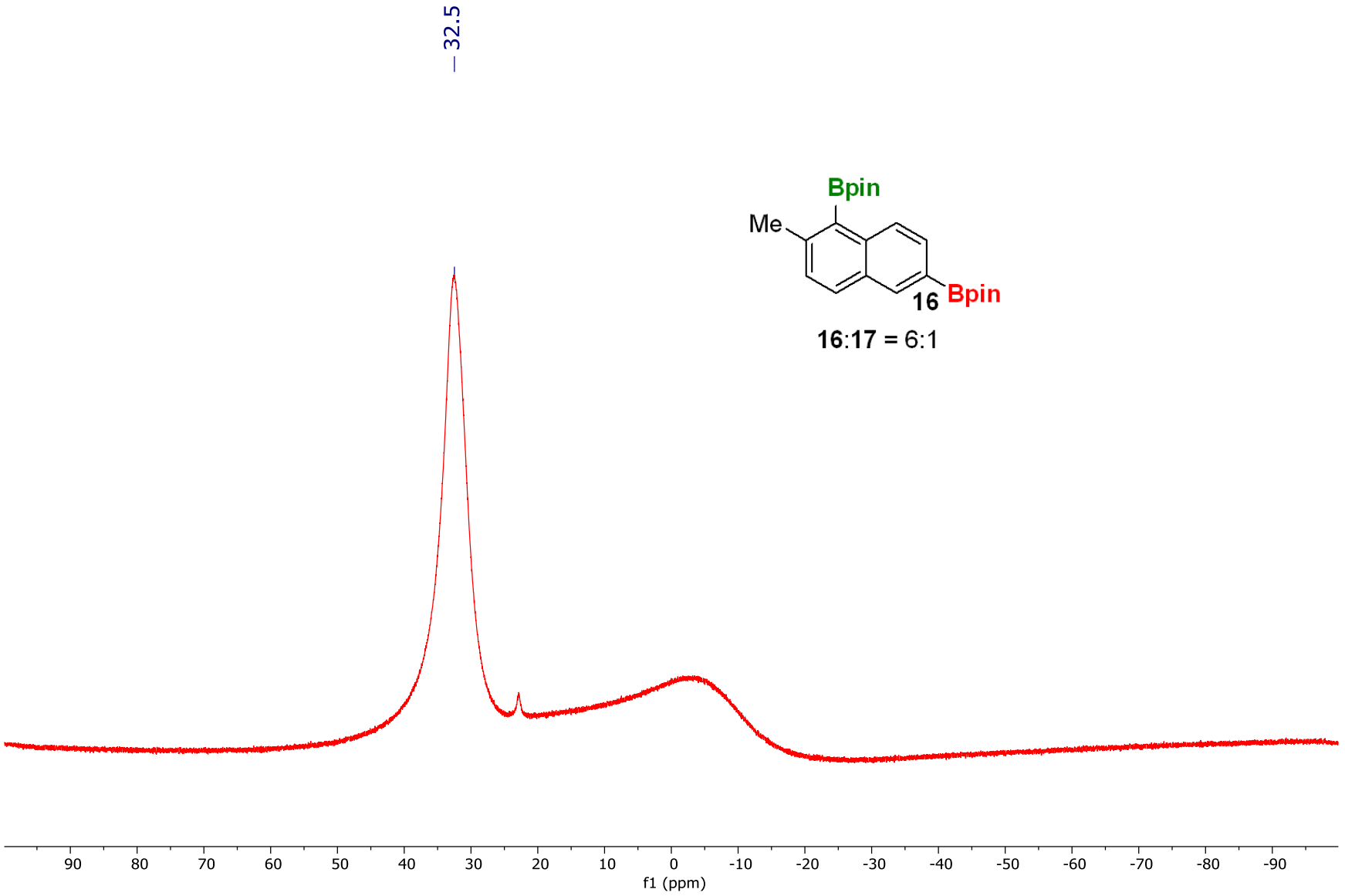
^{1}H NMR of 2-methyl-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8f) (C_6D_6, 500 MHz)



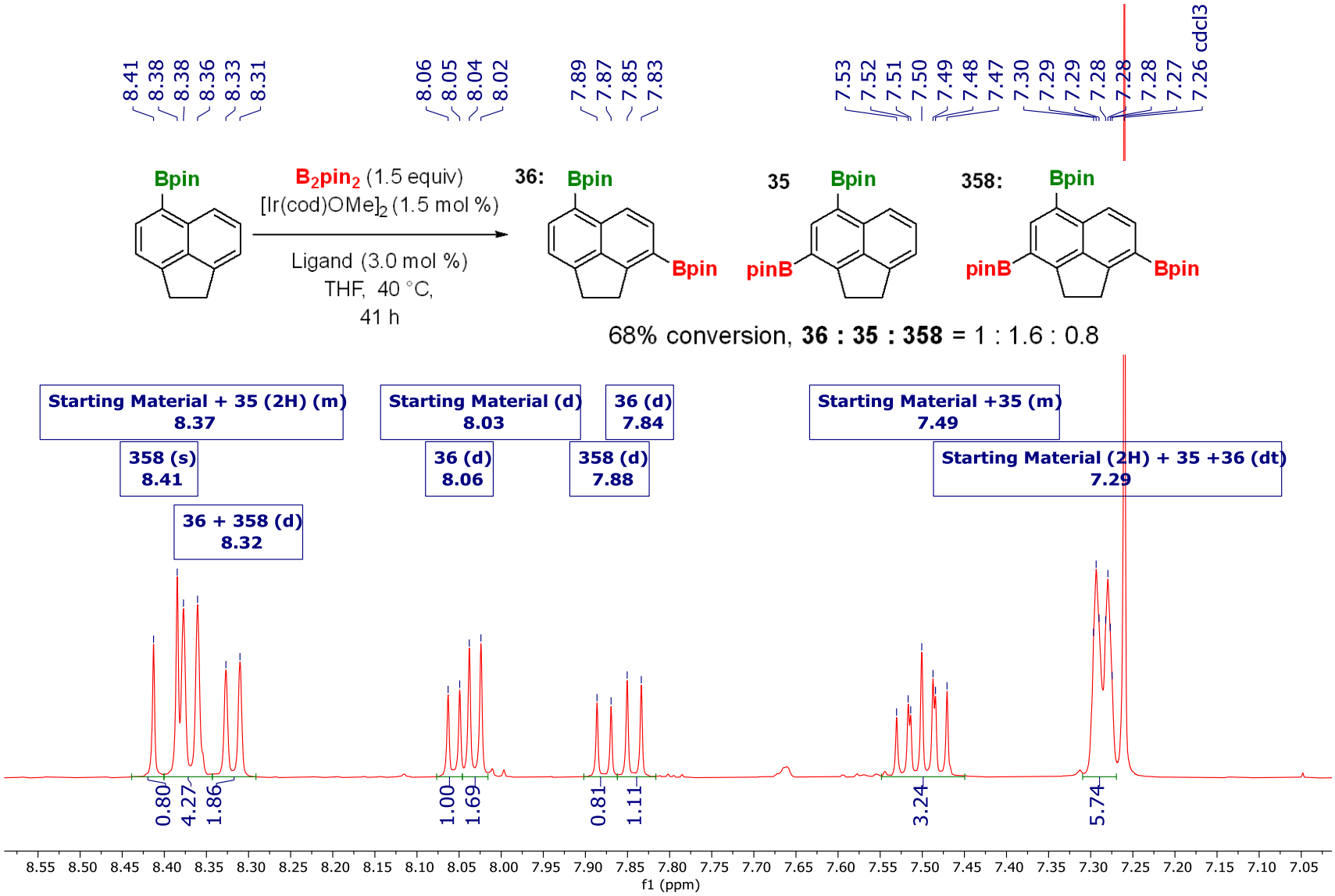
^{13}C NMR of 2-methyl-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8f) (C_6D_6, 126 MHz)



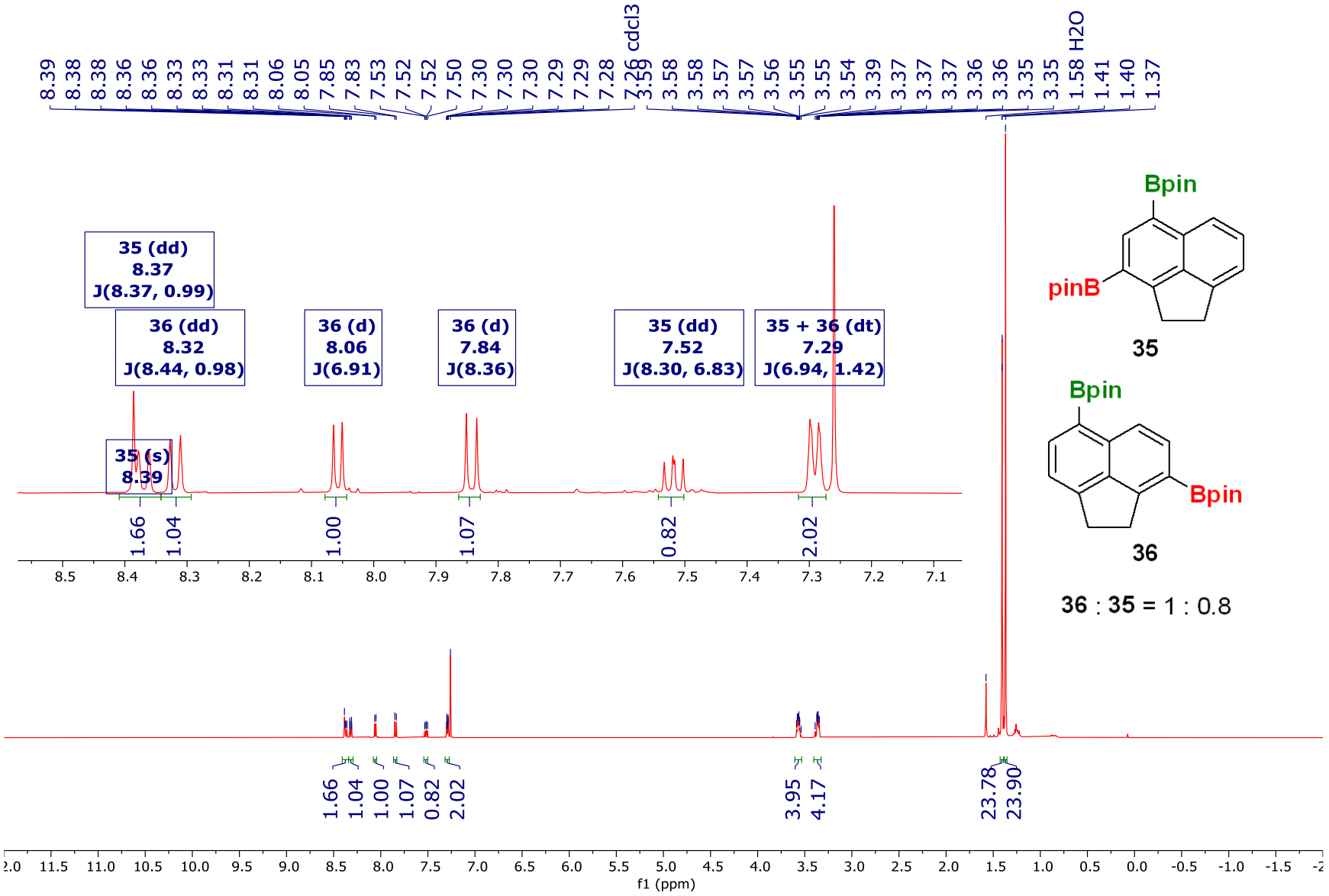
^{11}B NMR of 2-methyl-1,6-naphthalenediboronic acid bis(pinacol) ester (4.8f) (C_6D_6, 160 MHz)



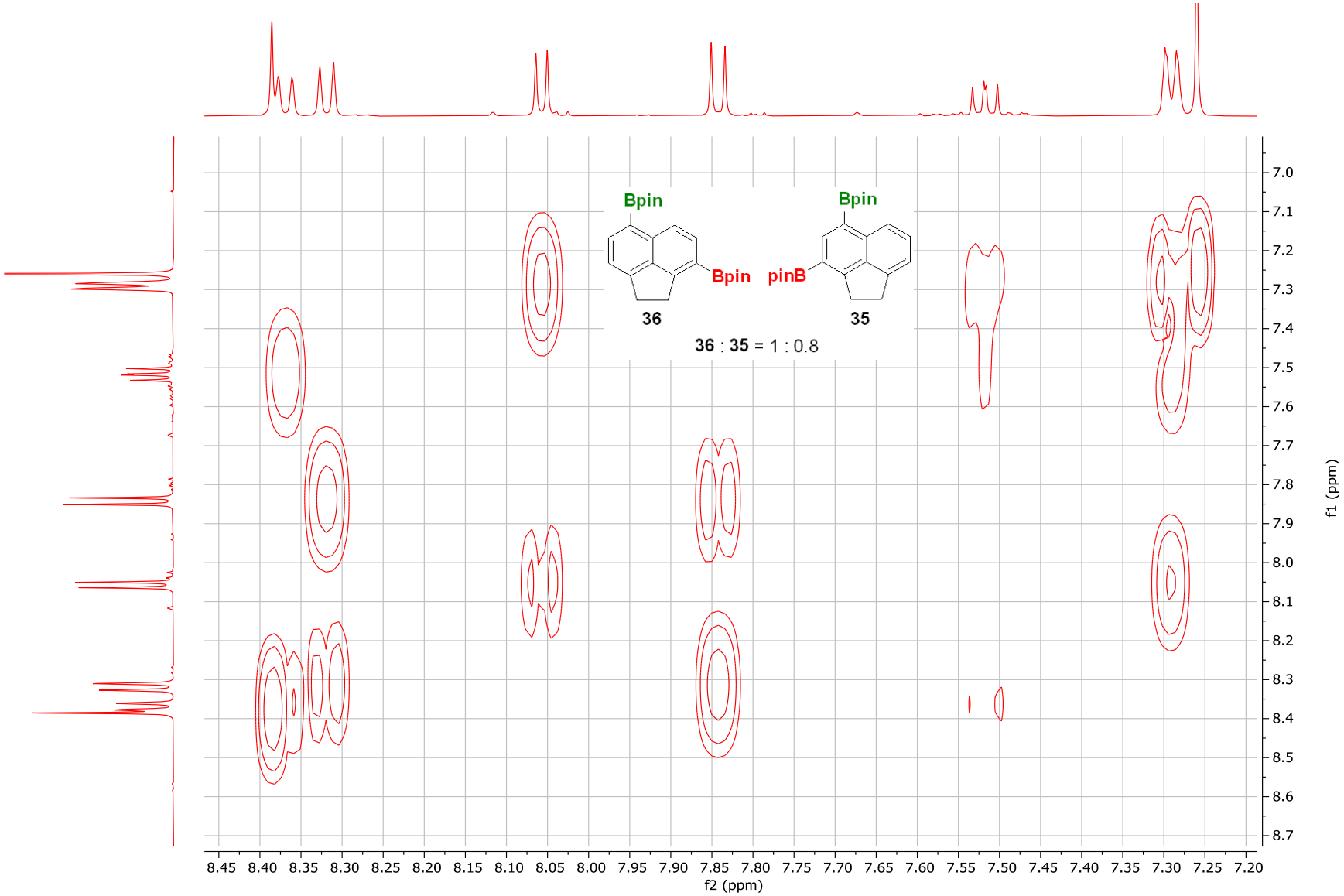
C3 & C8 Borylation of acenaphthene-5-boronic acid, pinacol ester (4.8g) ($CDCl_3$, 500 MHz)



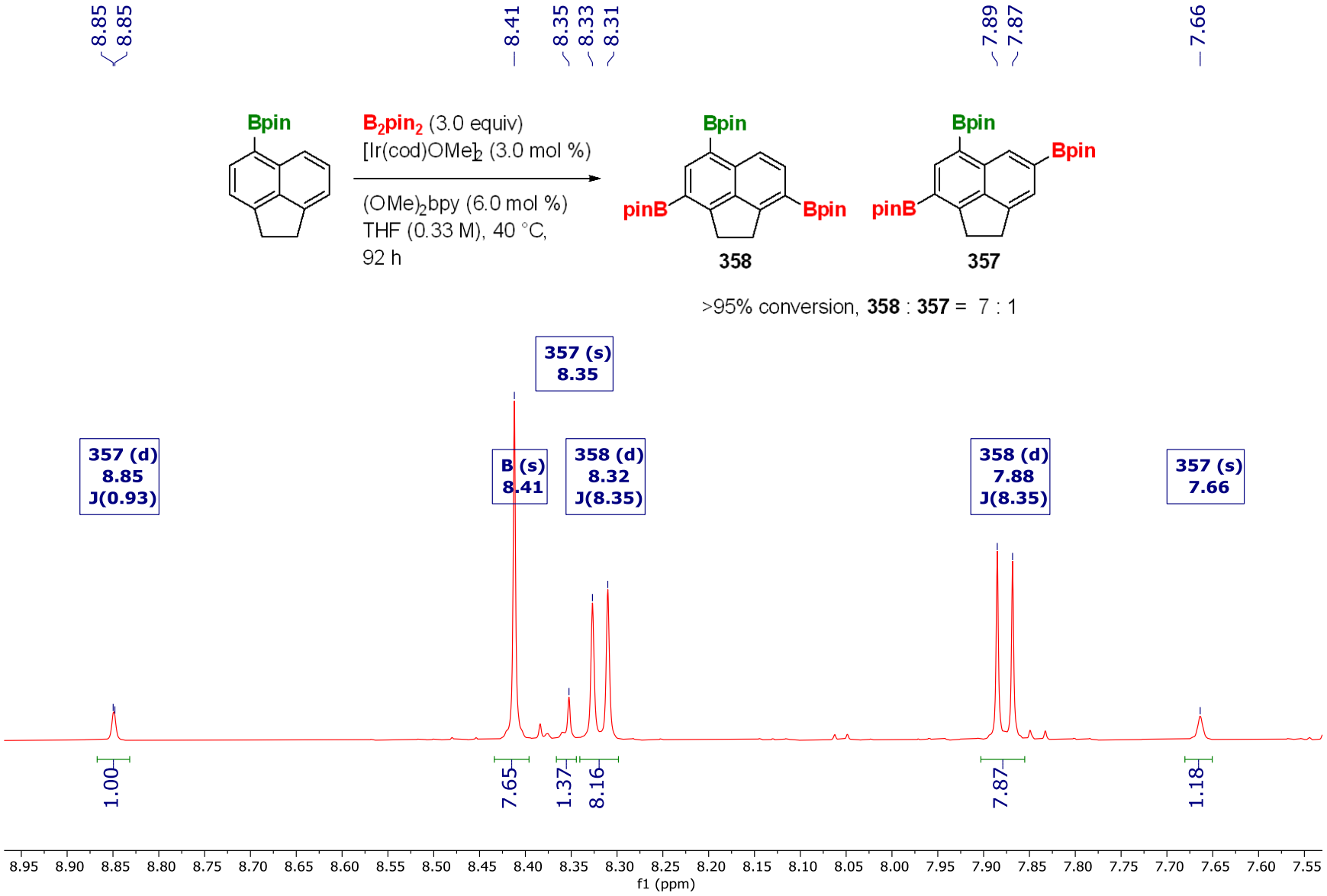
^{1}H NMR of 3,5 and 3,6-acenaphthenediboronic acid bis(pinacol) ester (4.8g) ($CDCl_3$, 500 MHz)



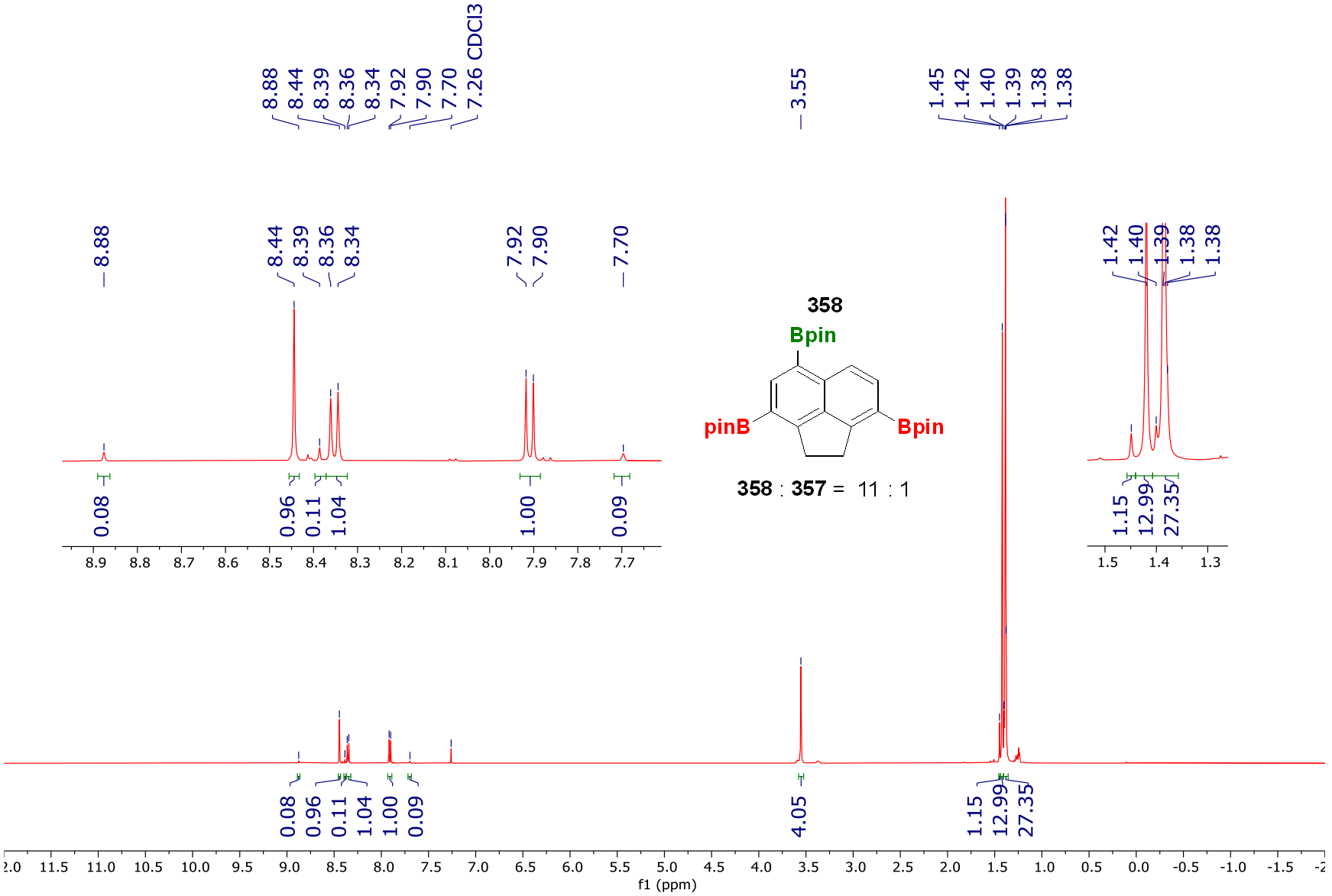
gCOSY of 3,5 and 3,6-acenaphthenediboronic acid bis(pinacol) ester (4.8g) ($CDCl_3$, 500 MHz)



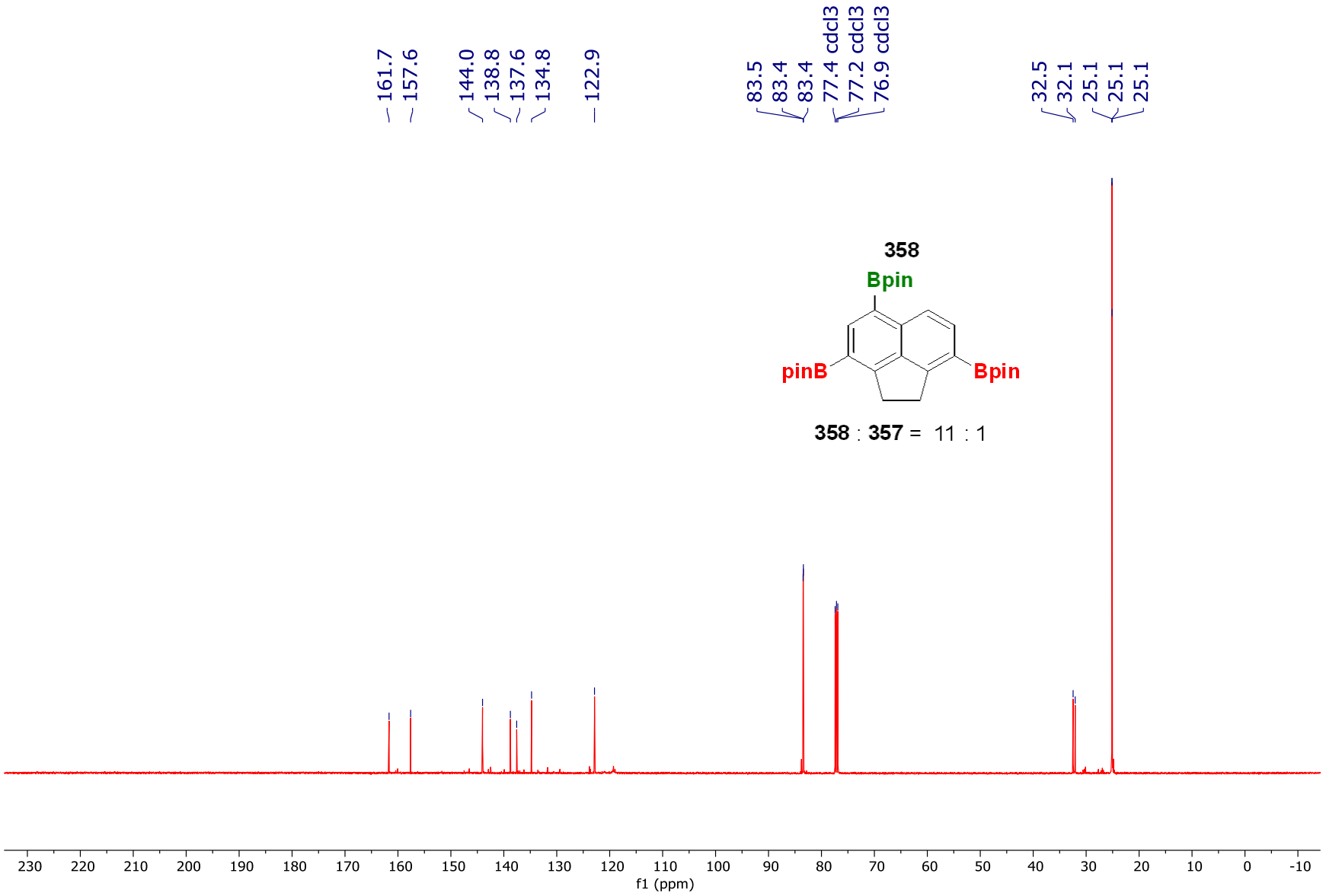
C3/C8 & C3/C7 Diborylation of acenaphthene-5-boronic acid, pinacol ester (4.8g) ($CDCl_3$, 500 MHz)



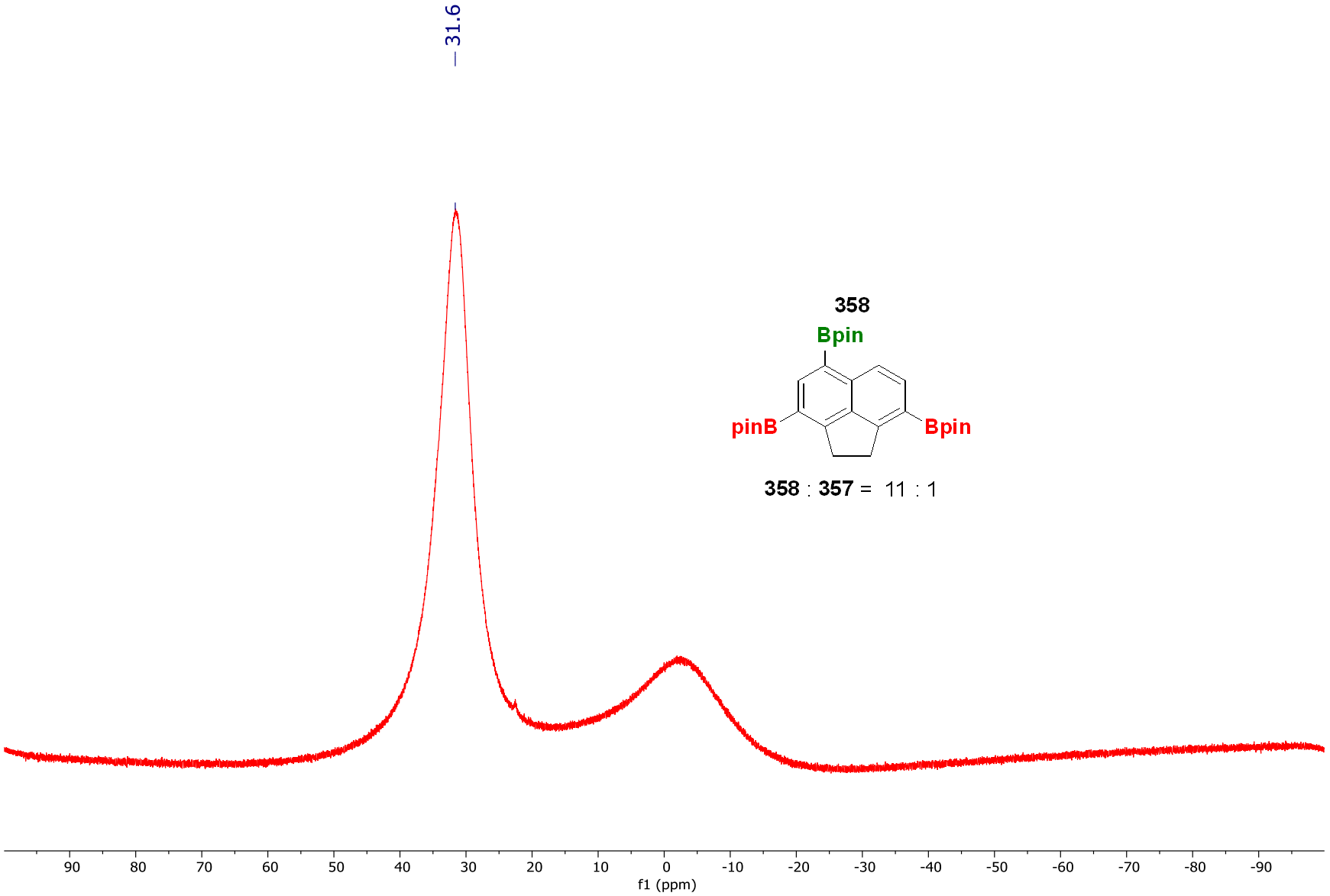
^{1}H NMR of 3,5,8-acenaphthenetriboronic acid bis(pinacol) ester (4.8g) ($CDCl_3$, 500 MHz)



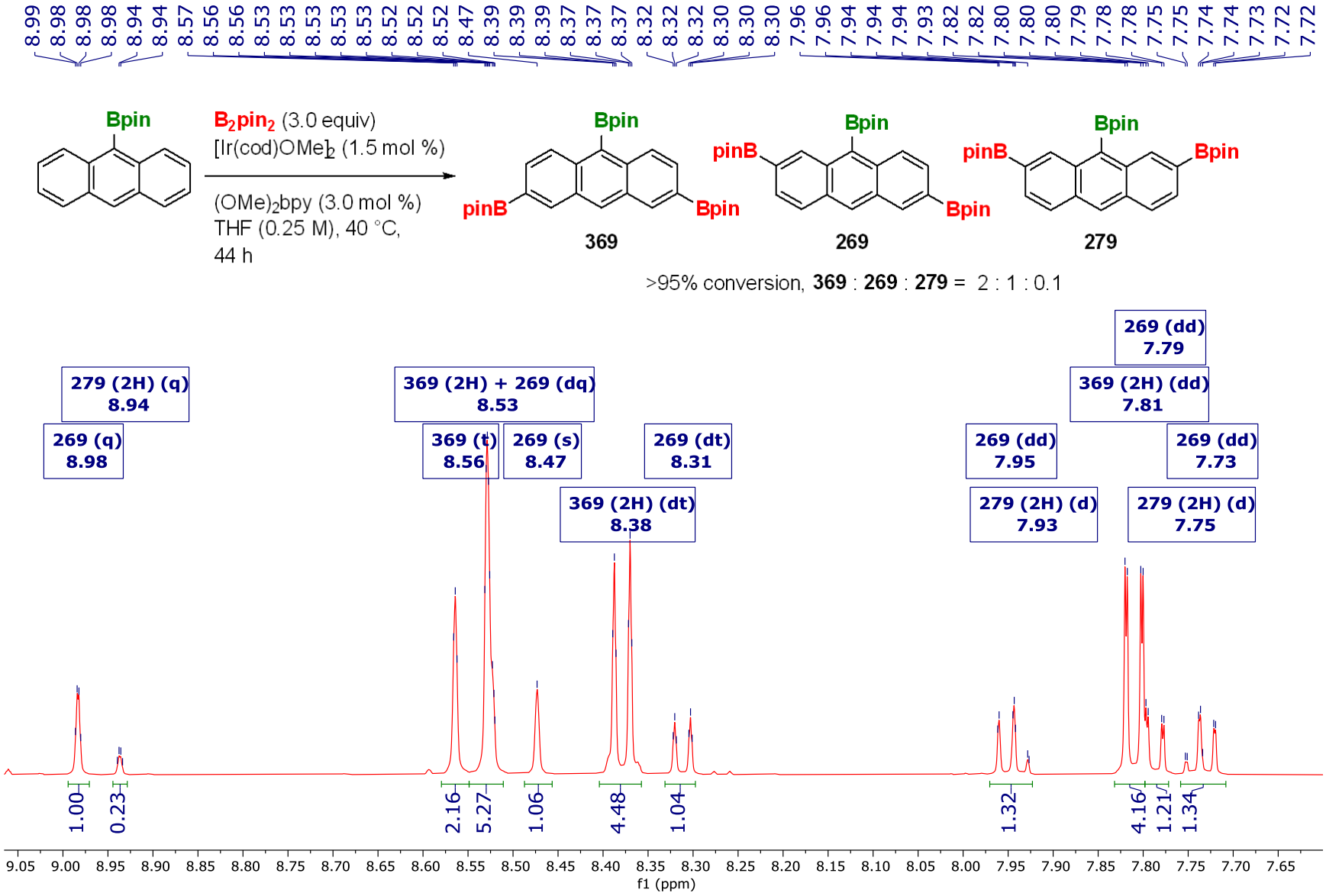
^{13}C NMR of 3,5,8-acenaphthenetriboronic acid bis(pinacol) ester (4.8g) ($CDCl_3$, 126 MHz)



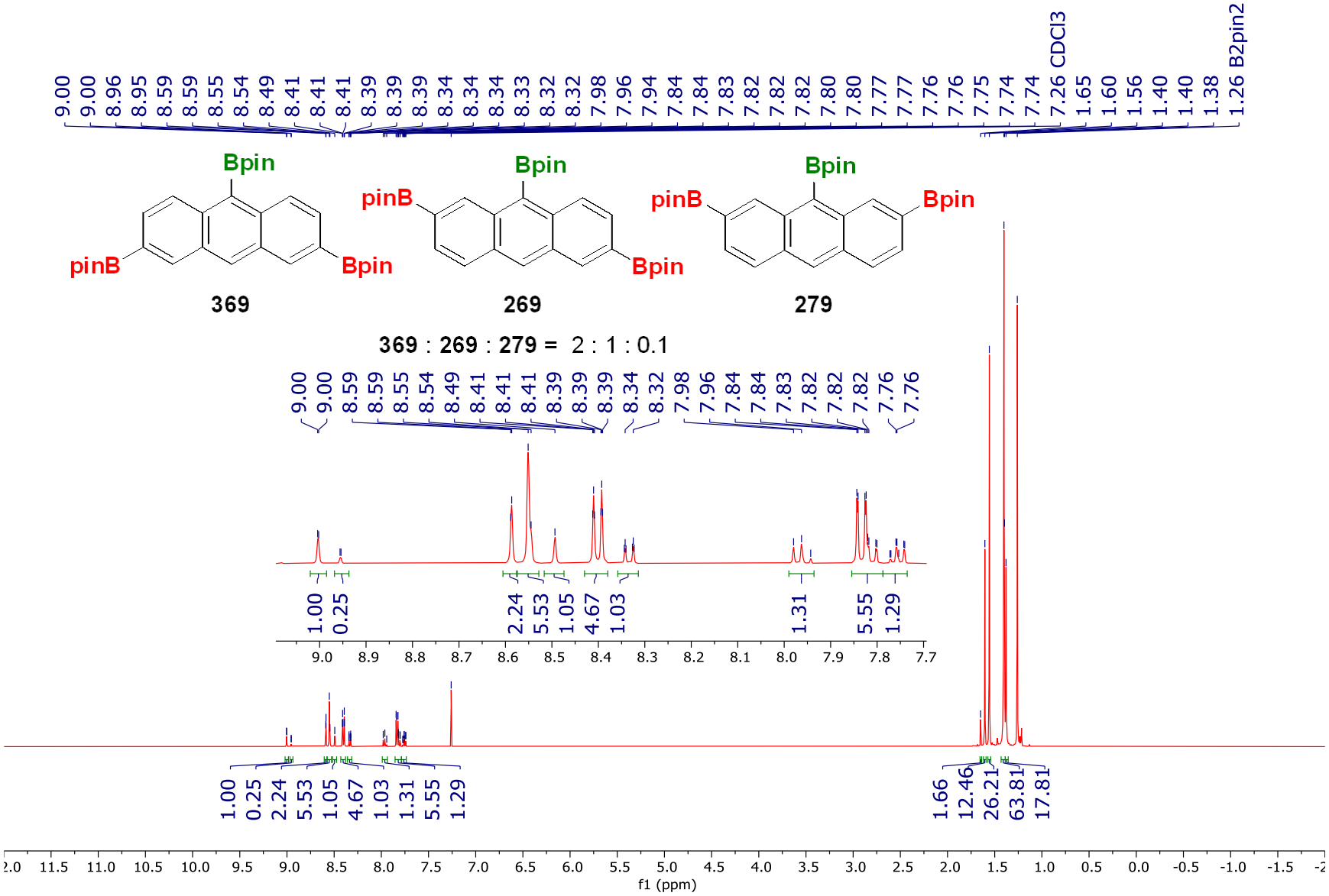
^{11}B NMR of 3,5,8-acenaphthenetriboronic acid bis(pinacol) ester (4.8g) ($CDCl_3$, 160 MHz)



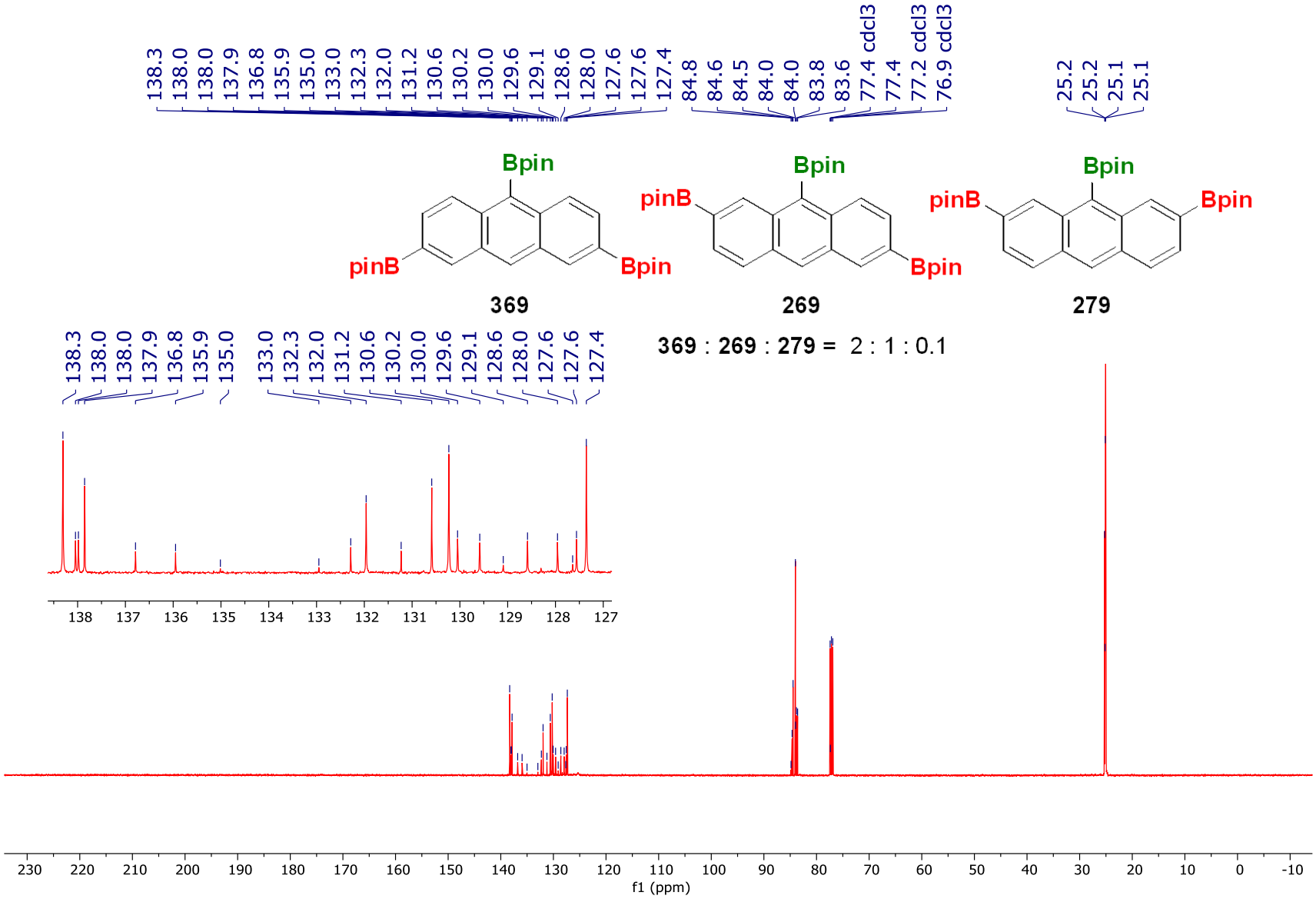
C3/C6 Diborylation of anthracene-9-boronic acid, pinacol ester (4.8h) ($CDCl_3$, 500 MHz)



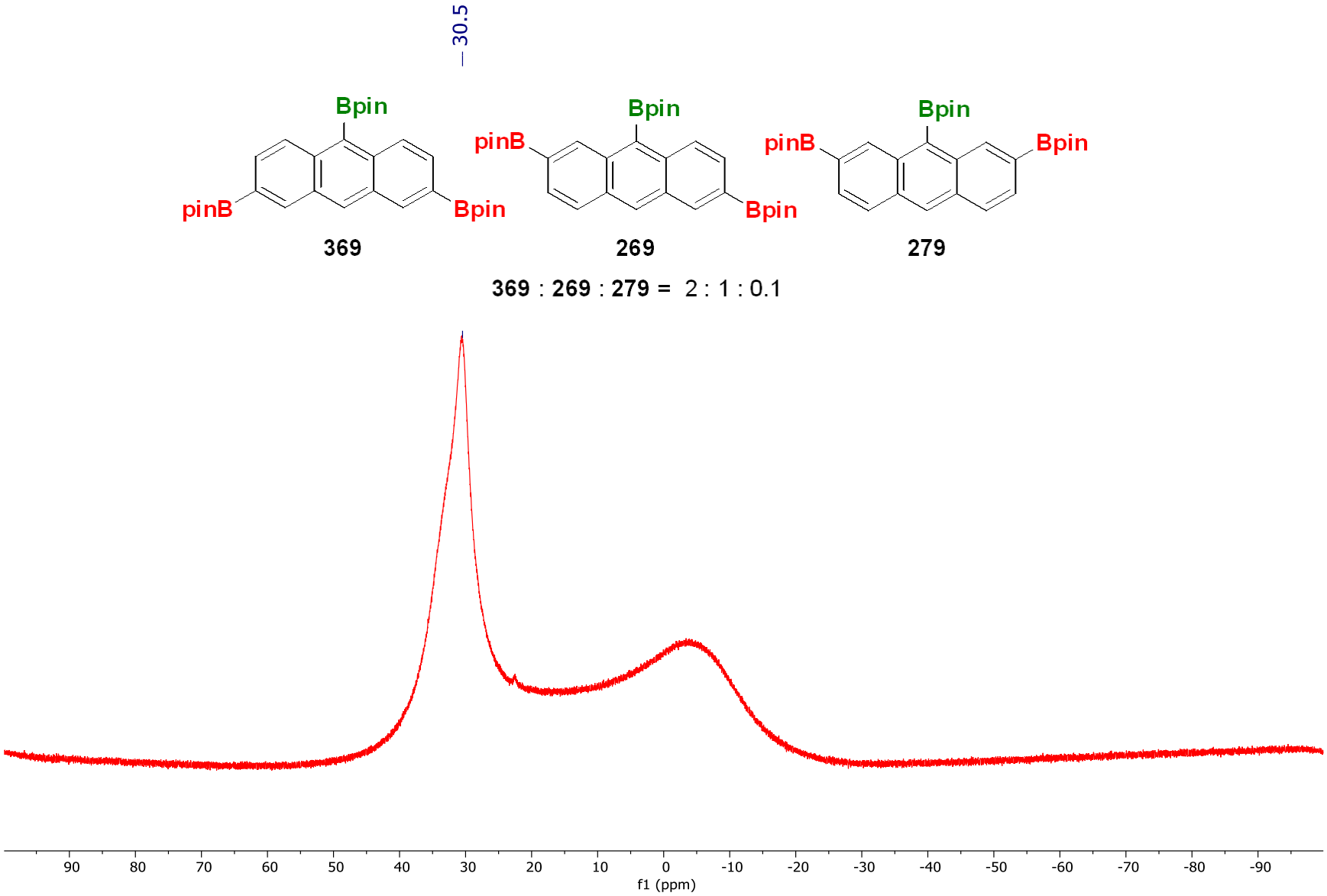
^{1}H NMR of 3,6,9-/2,6,9-/2,7,9-anthracenetriboronic acid bis(pinacol) ester (4.8h) ($CDCl_3$, 500 MHz)



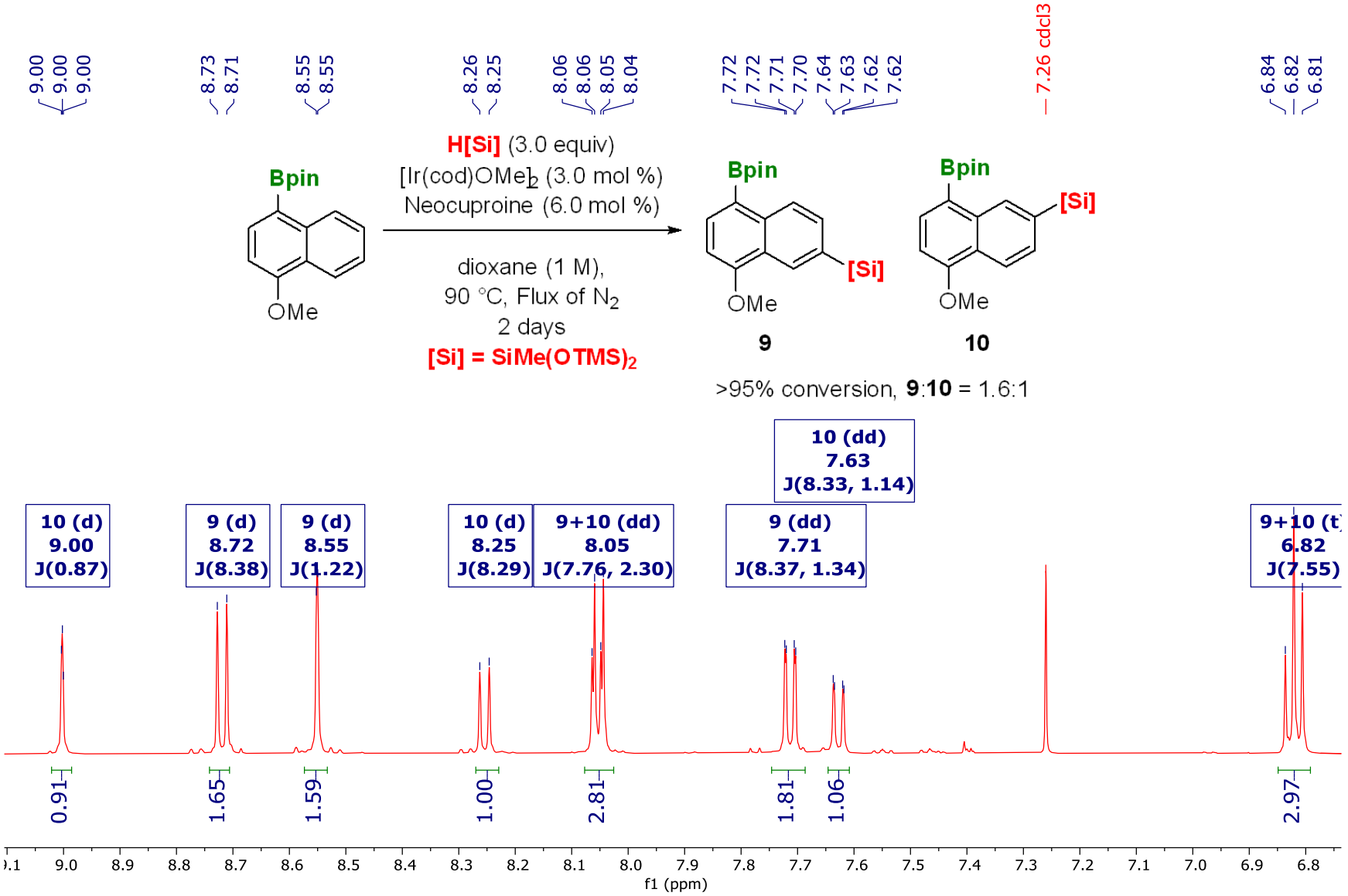
^{13}C NMR of 3,6,9-/2,6,9-/2,7,9-anthracenetriboronic acid bis(pinacol) ester (4.8h) ($CDCl_3$, 126 MHz)



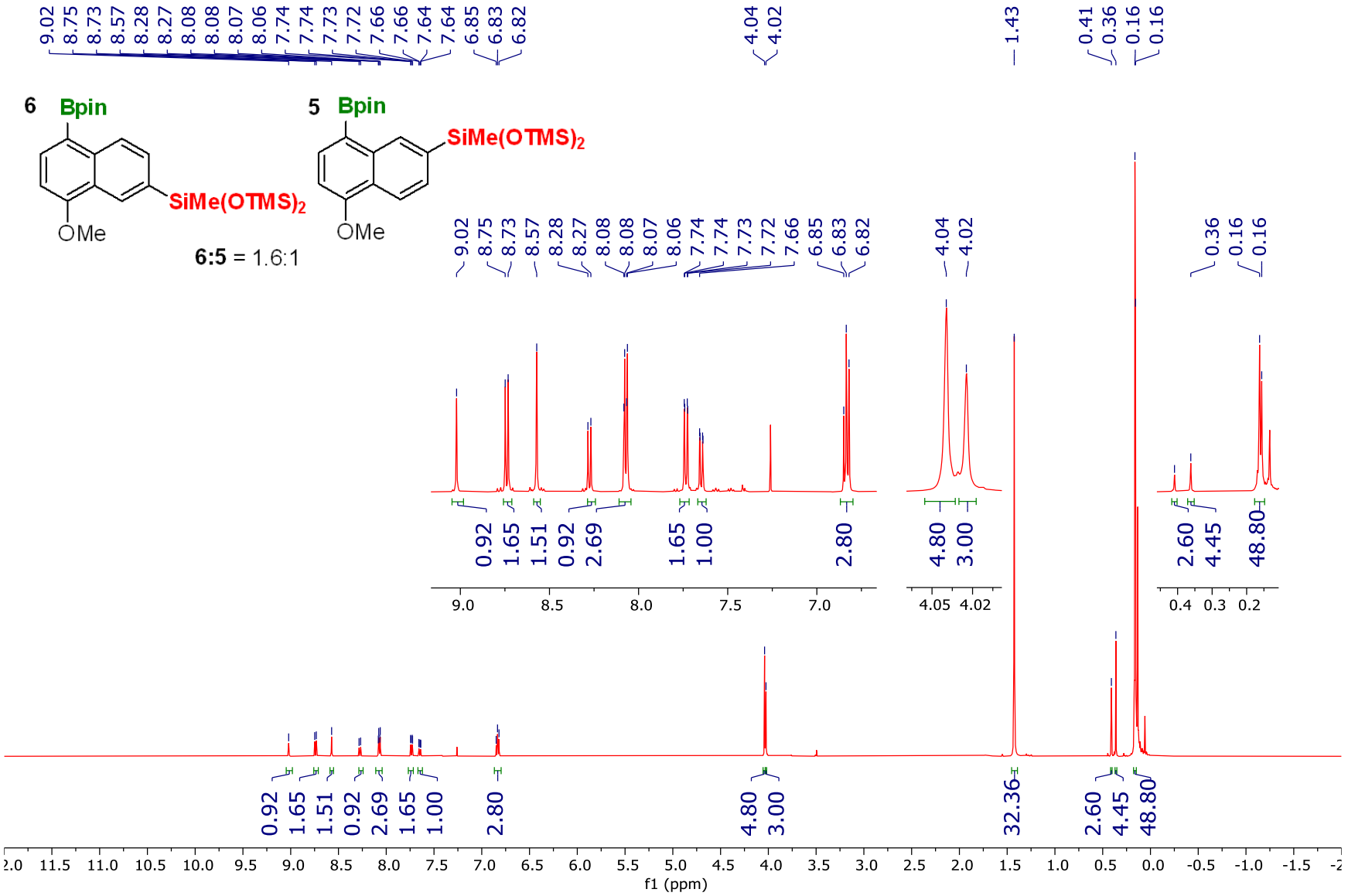
^{11}B NMR of 3,6,9-/2,6,9-/2,7,9-anthracenetriboronic acid bis(pinacol) ester (4.8h) ($CDCl_3$, 160 MHz)



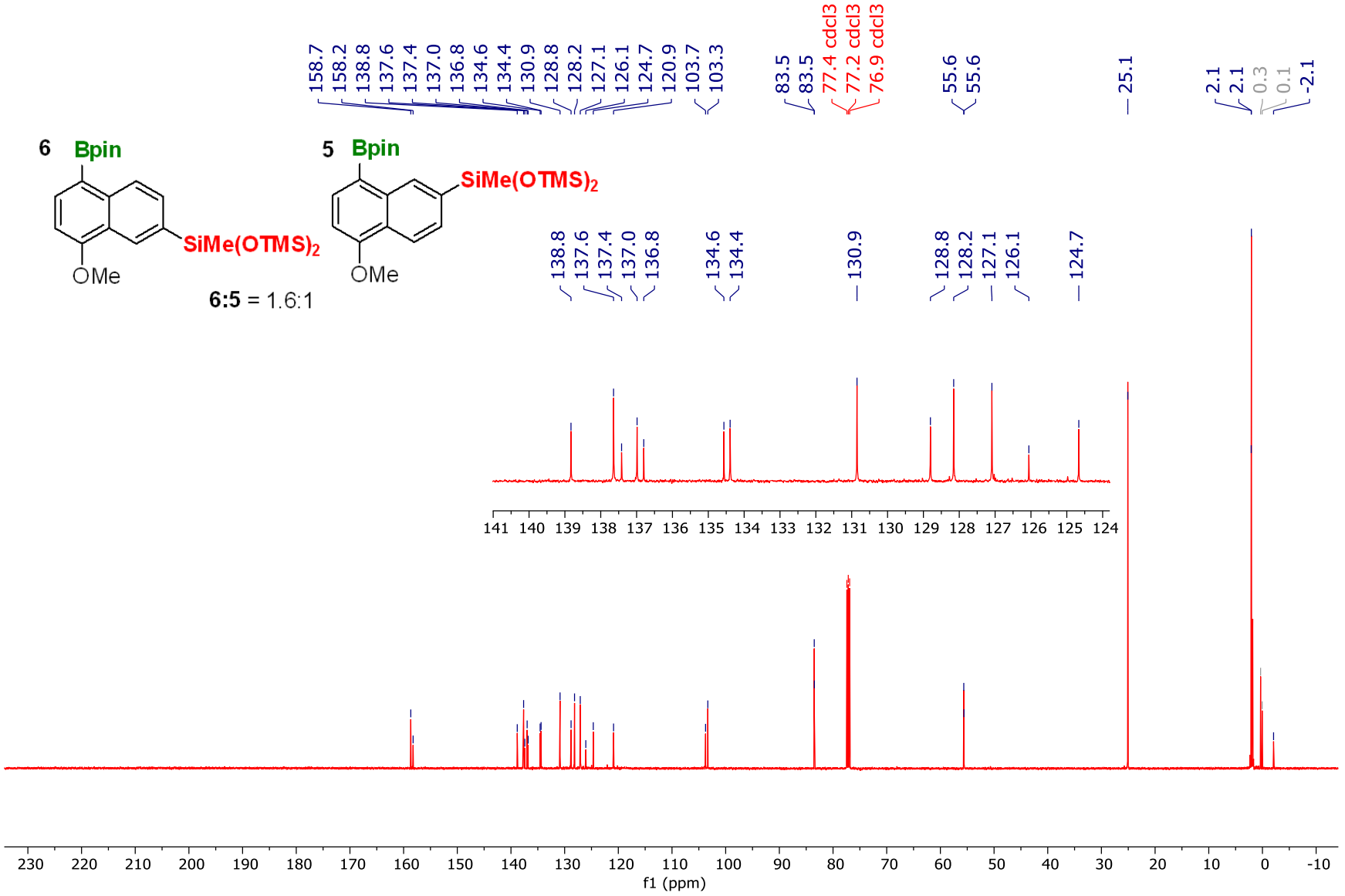
C6 Silylation of 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9 & 4.10) ($CDCl_3$, 500 MHz)



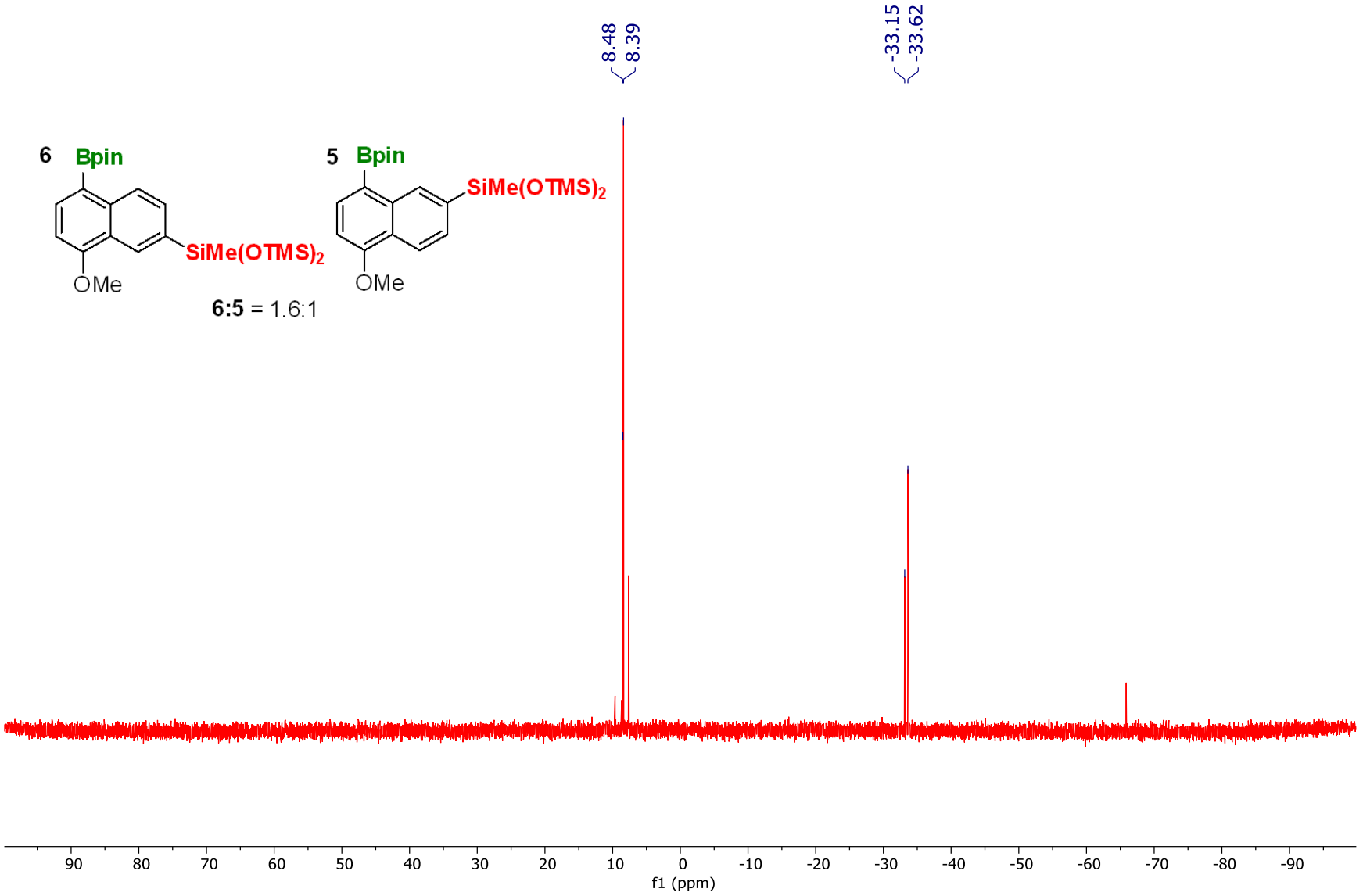
^{1}H NMR of 6-Silylated 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9 & 4.10) ($CDCl_3$, 500 MHz)



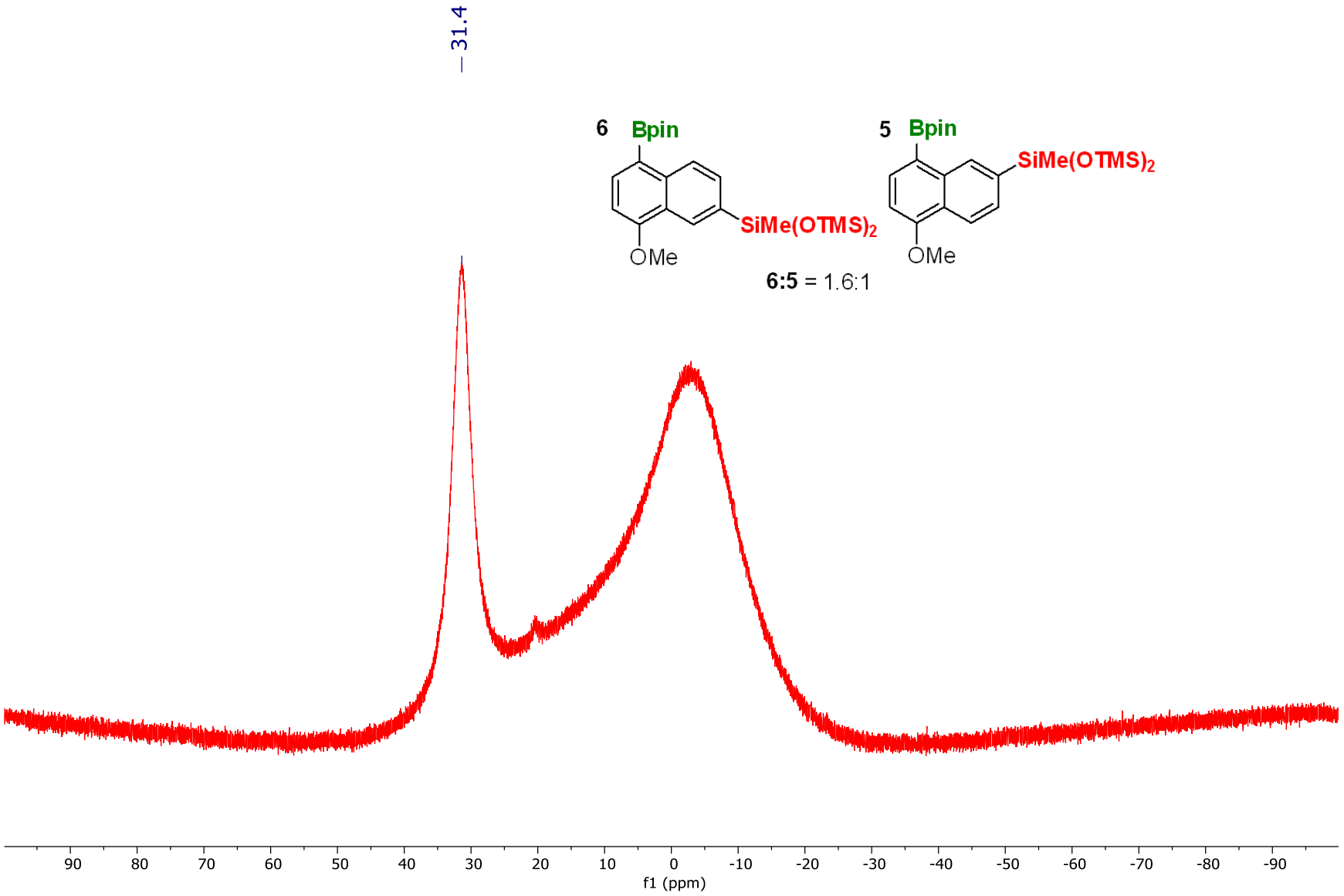
^{13}C NMR of 6-Silylated 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9 & 4.10) ($CDCl_3$, 126 MHz)



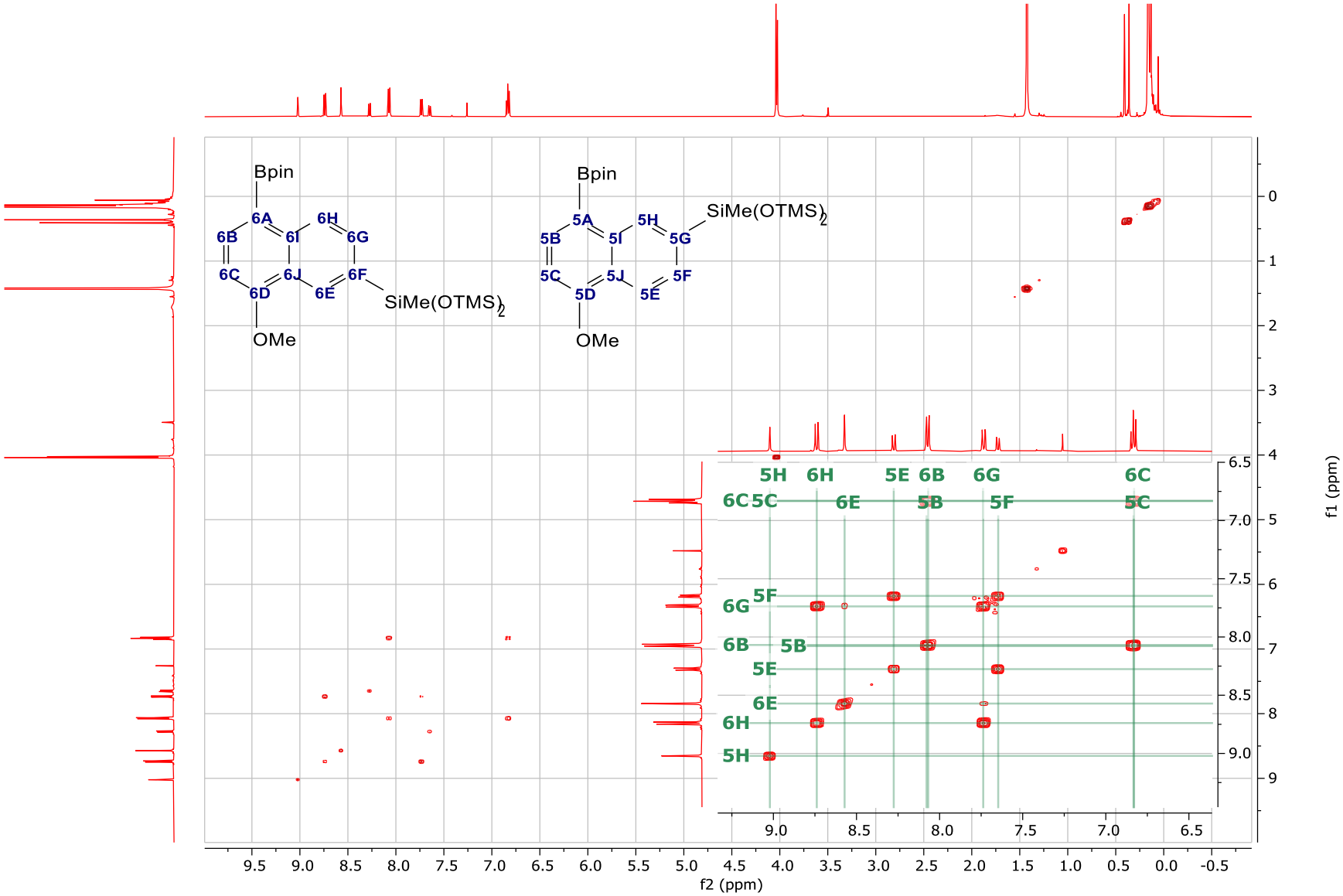
^{29}Si NMR of 6-Silylated 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9 & 4.10) ($CDCl_3$, 99 MHz)



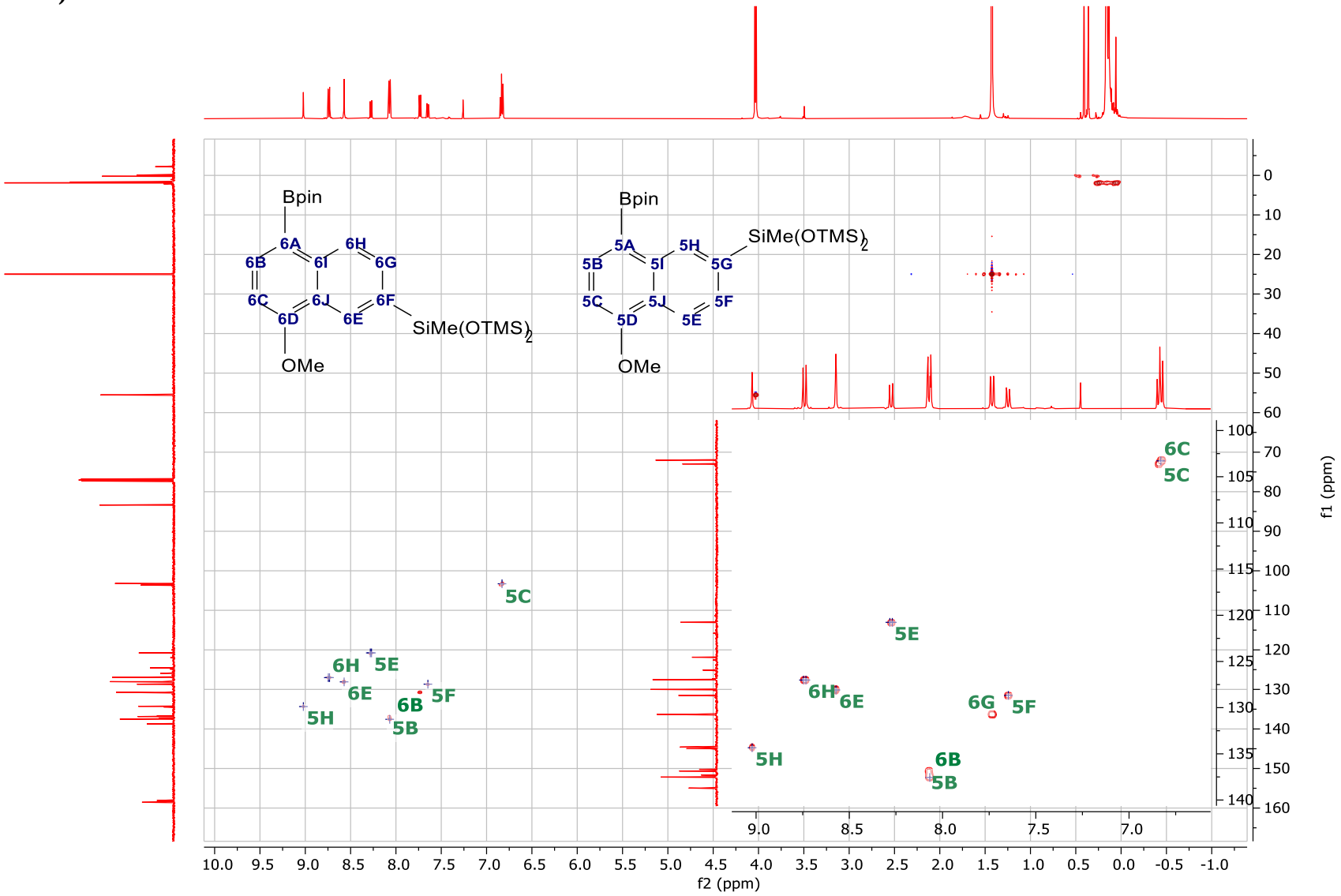
^{11}B NMR of 6-Silylated 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9 & 4.10) ($CDCl_3$, 160 MHz)



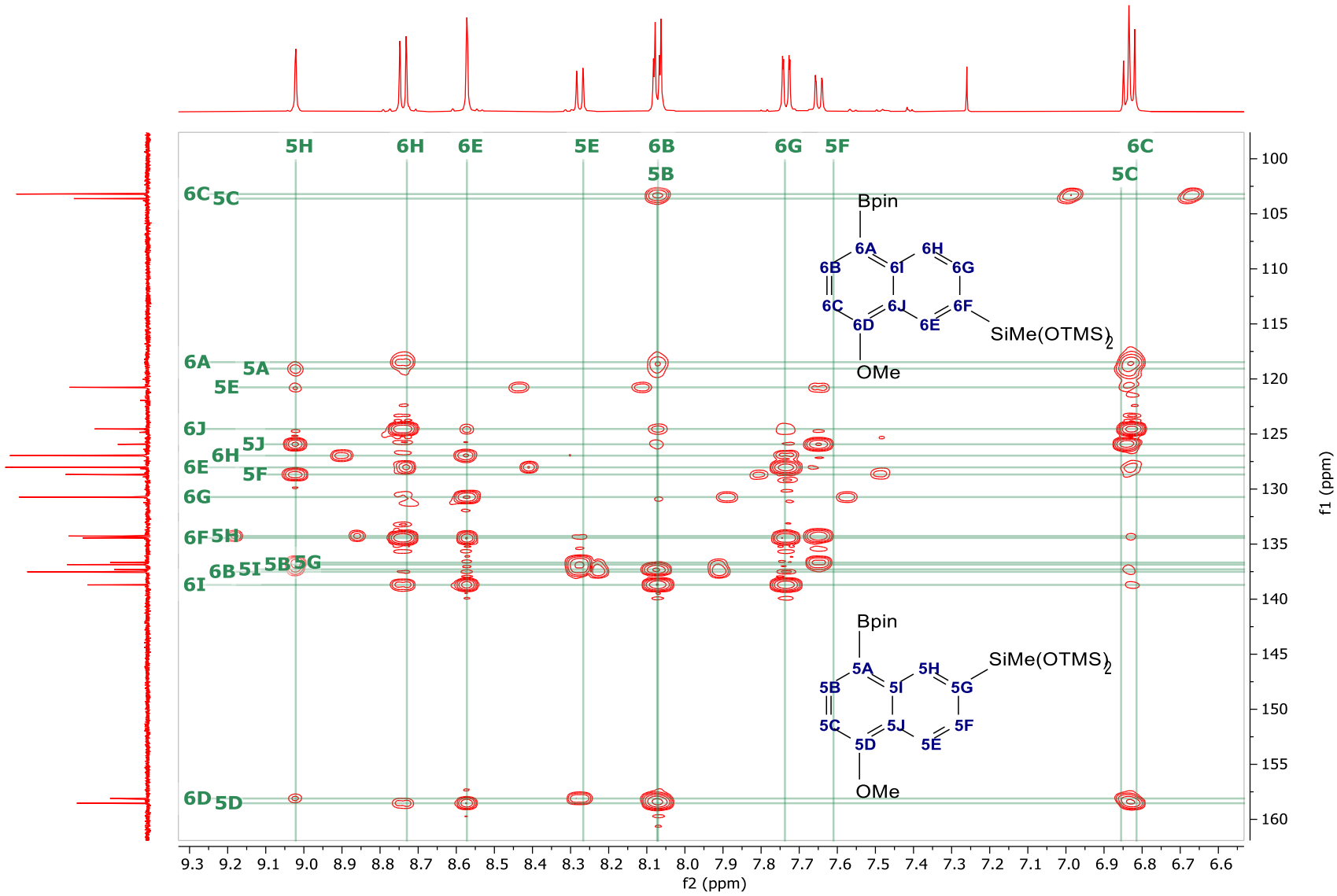
gCOSY of 6-Silylated 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9 & 4.10) ($CDCl_3$, 500 MHz)



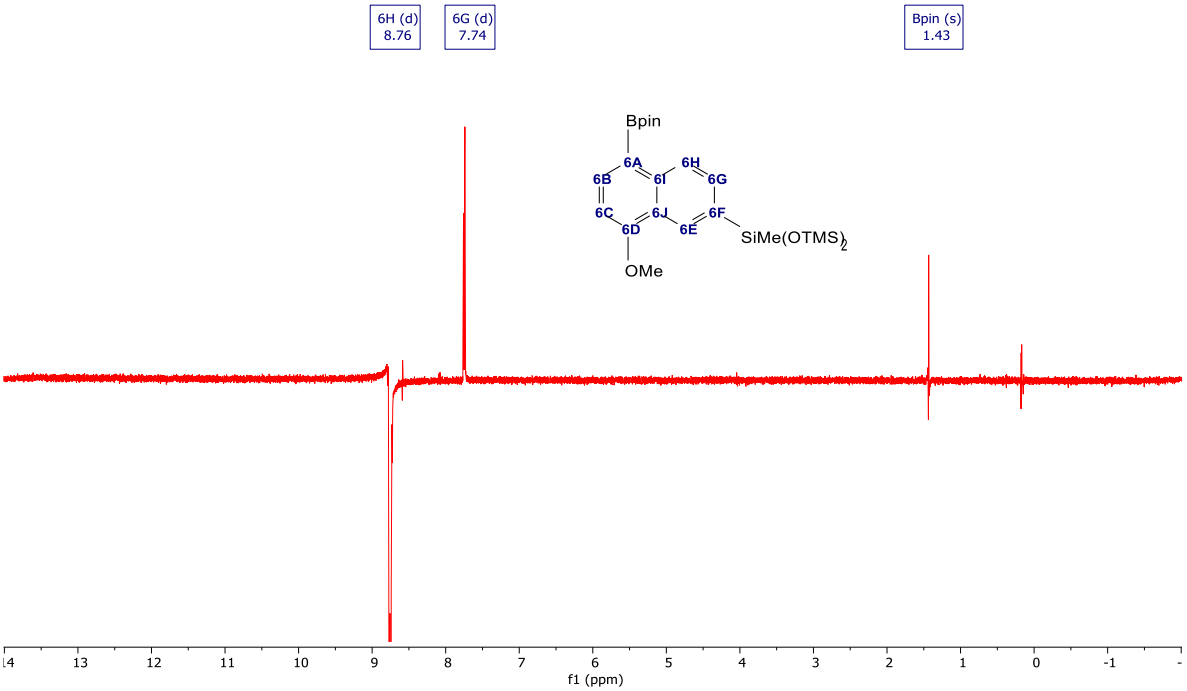
gHSQCAD of 6-Silylated 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9 & 4.10) ($CDCl_3$, 500 MHz)

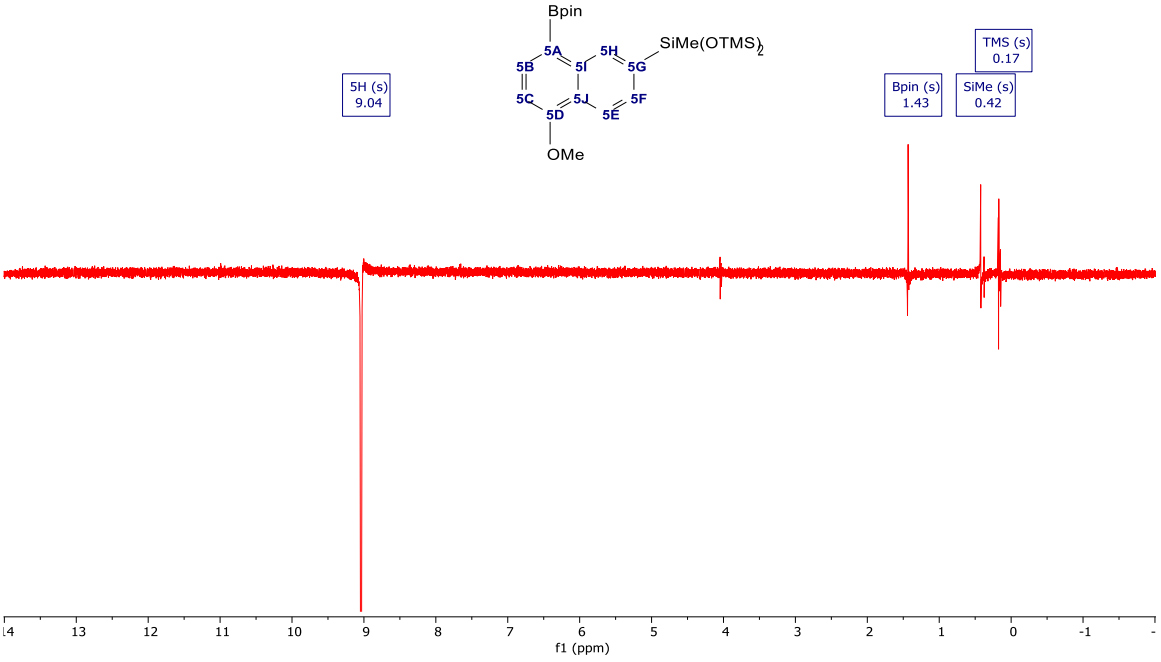


gHMBCAD of 6-Silylated 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9 & 4.10) ($CDCl_3$, 500 MHz)

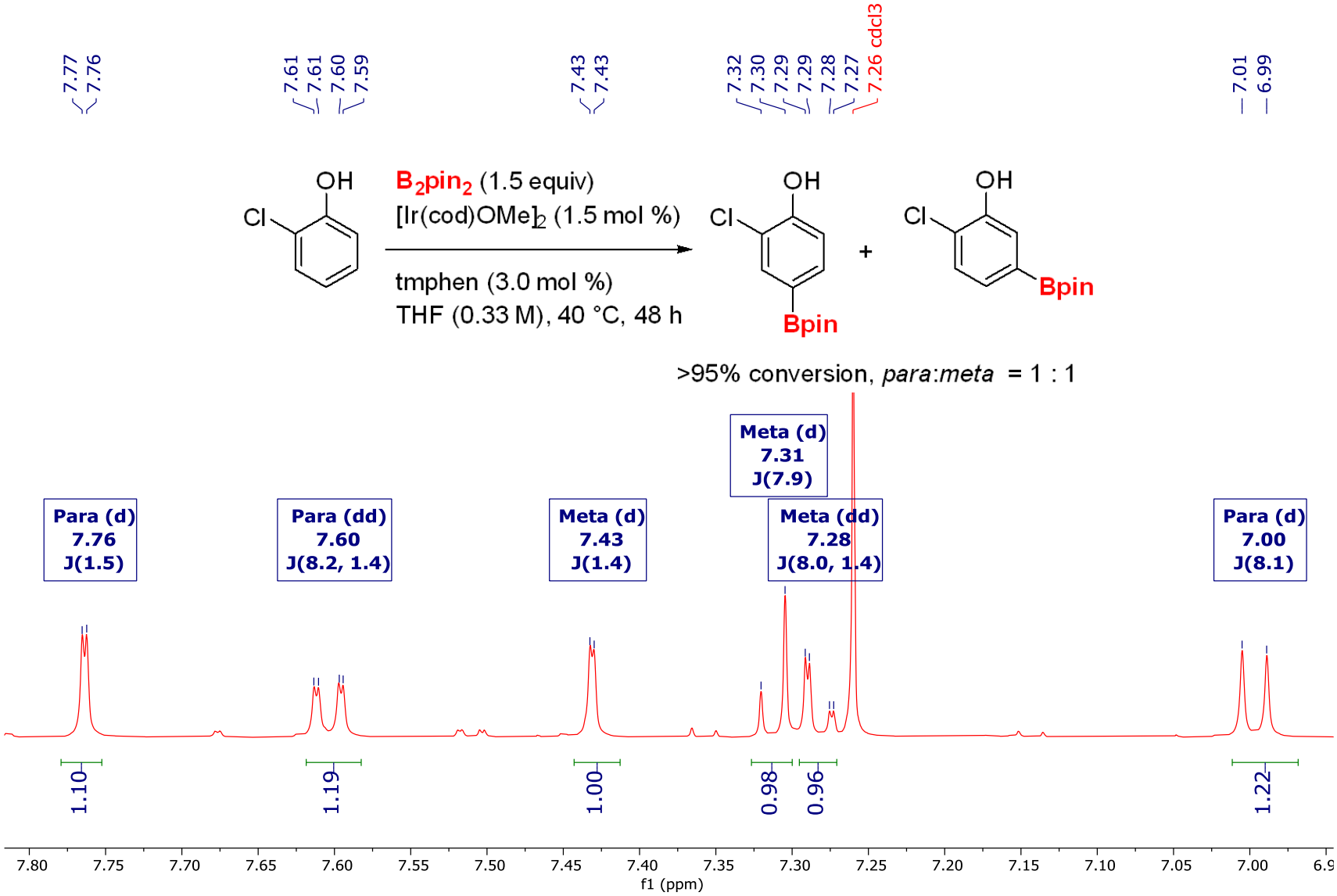


NOE of 6-Silylated 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9 & 4.10) ($CDCl_3$, 500 MHz)

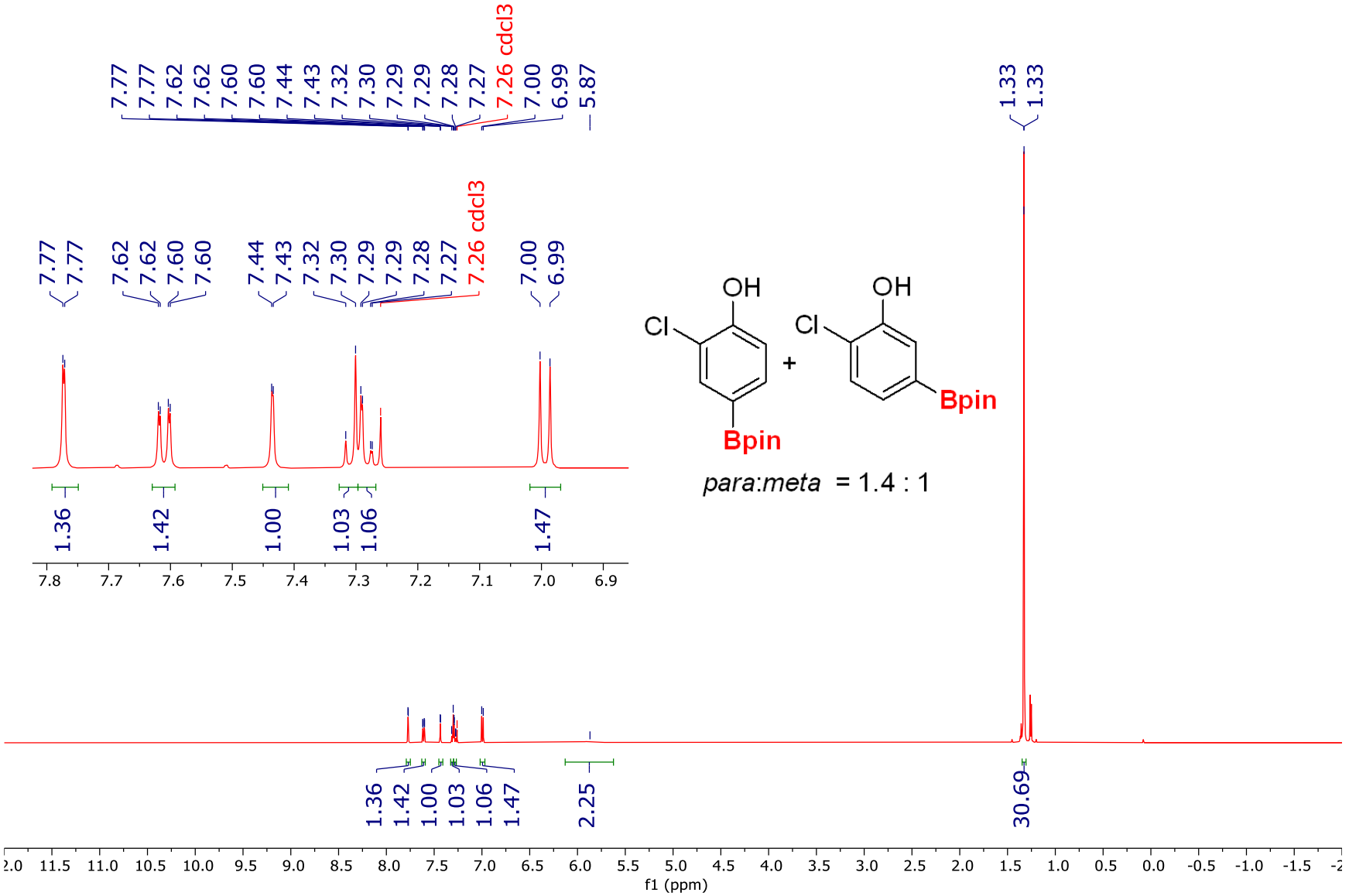




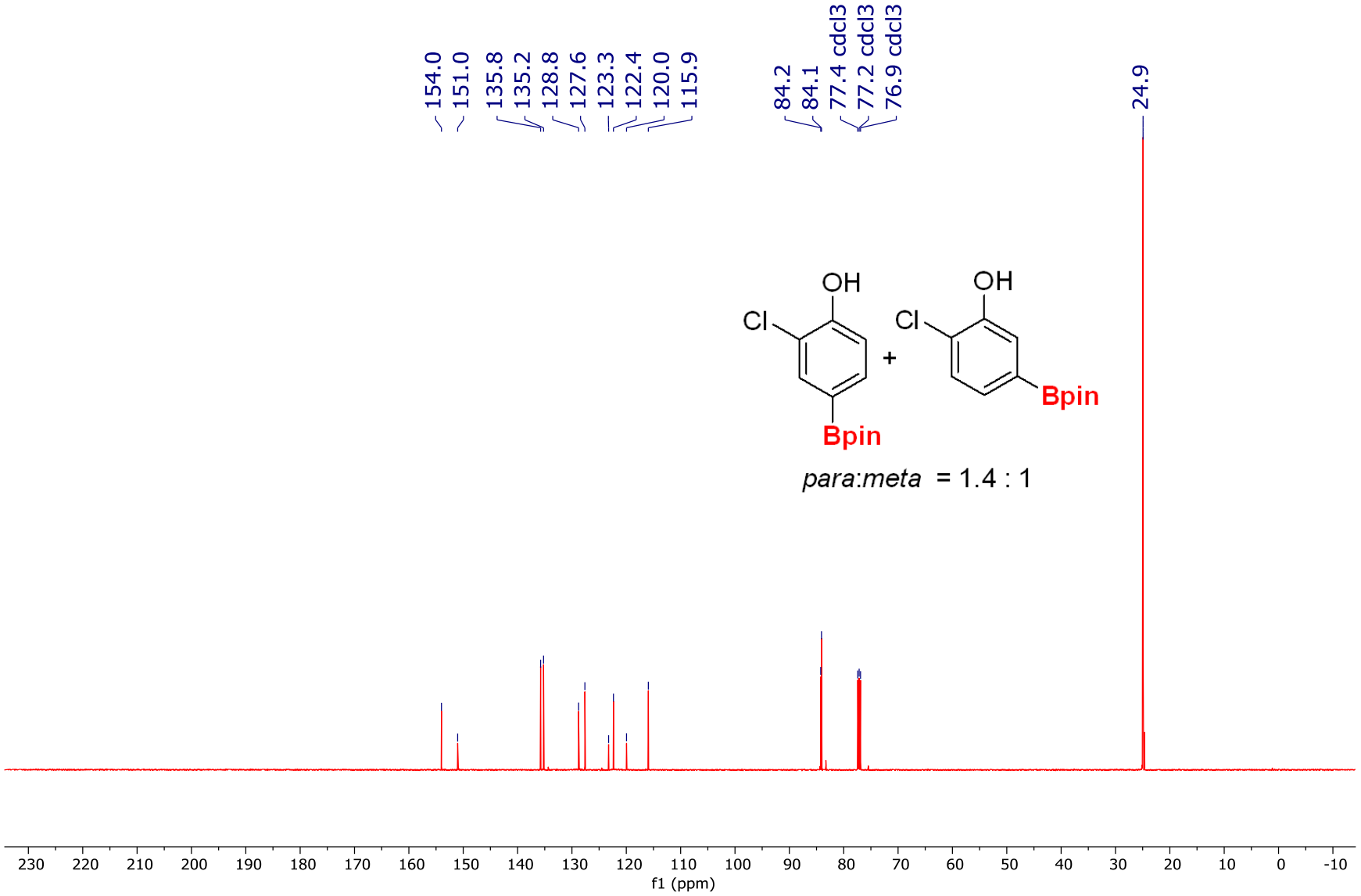
CHB of 2-chlorophenol (4.2p) ($CDCl_3$, 500 MHz)



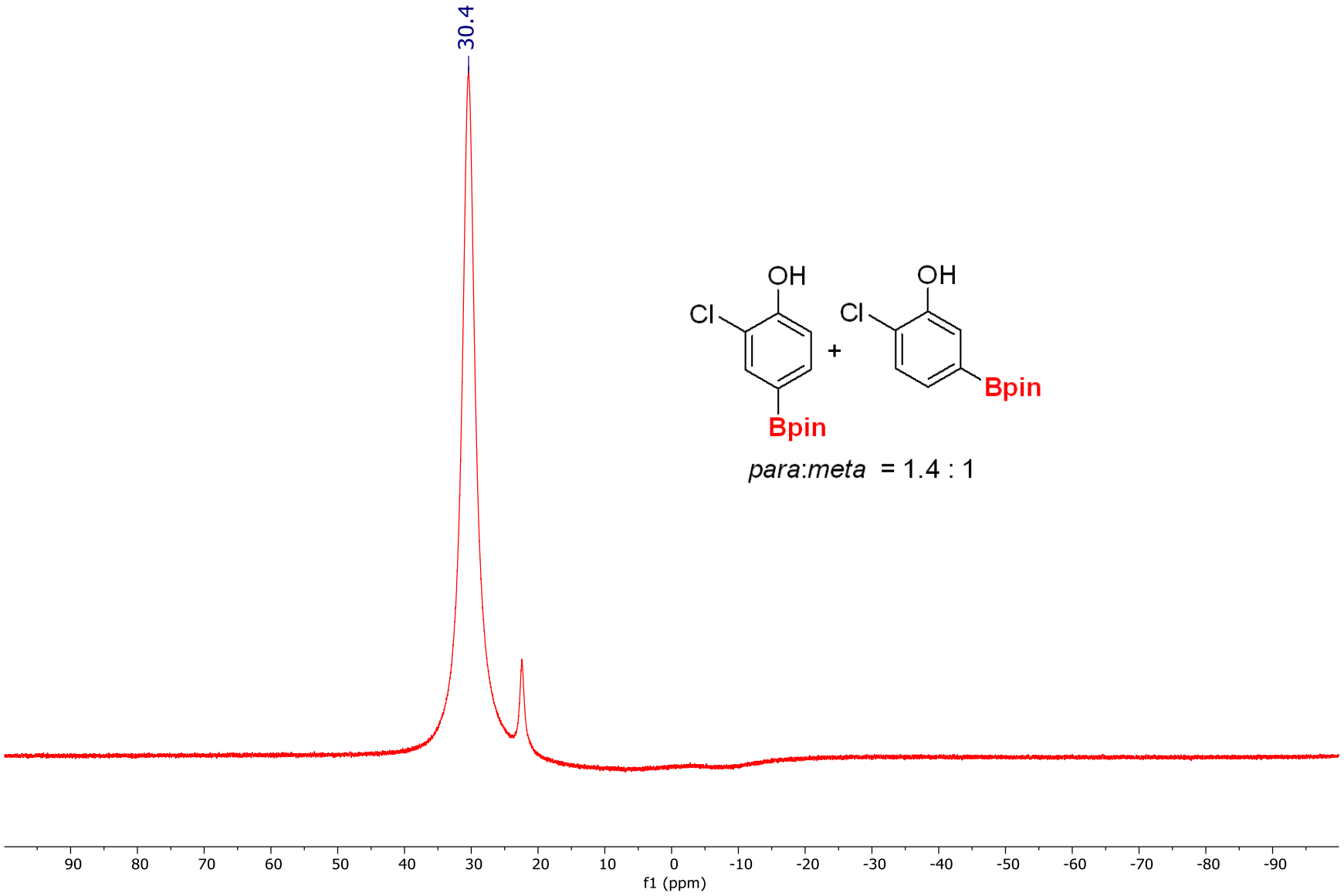
^{1}H NMR of *para* and *meta* borylated 2-chlorophenol (4.2p) ($CDCl_3$, 500 MHz)



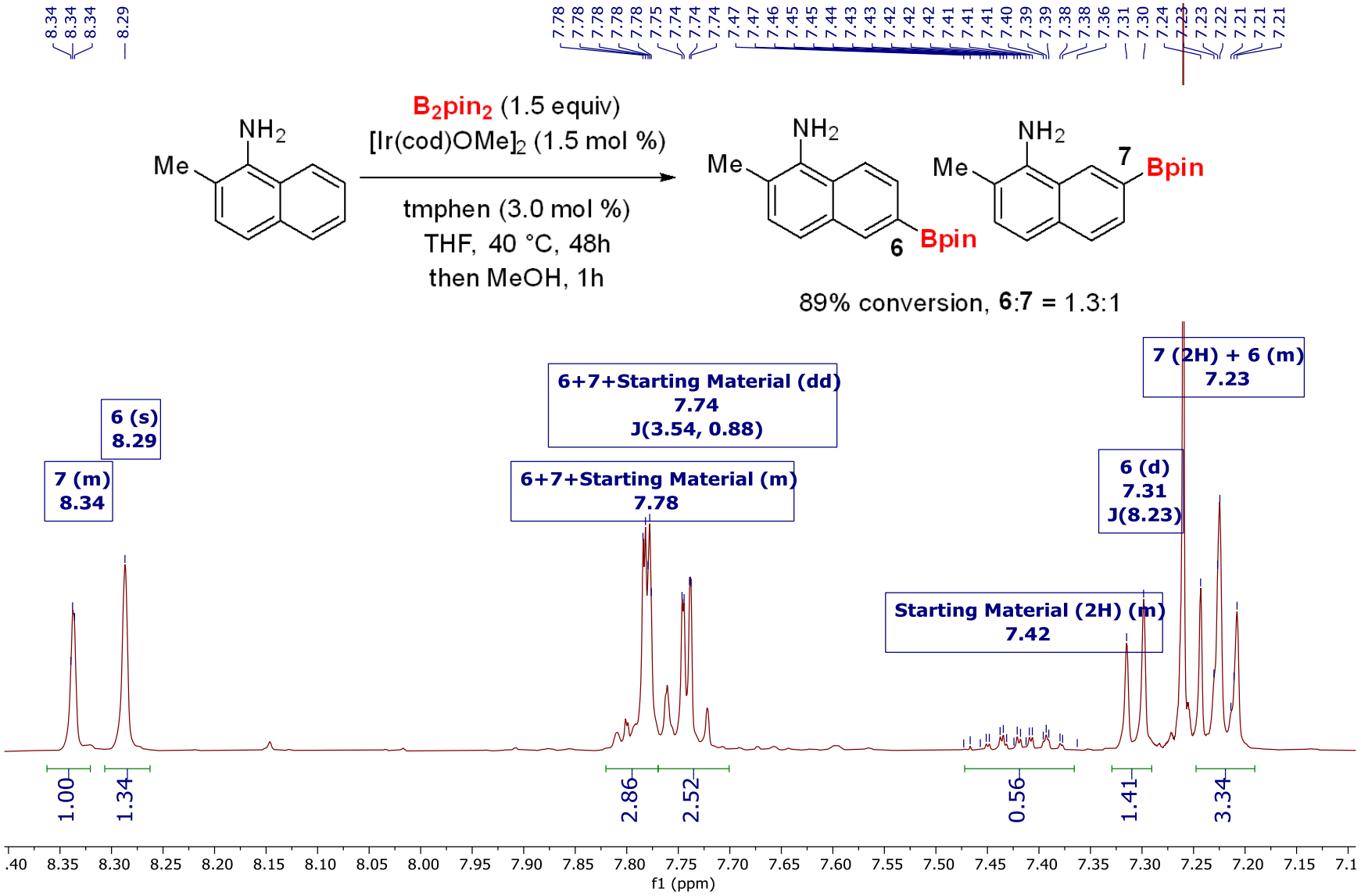
^{13}C NMR of *para* and *meta* borylated 2-chlorophenol (4.2p) ($CDCl_3$, 126 MHz)



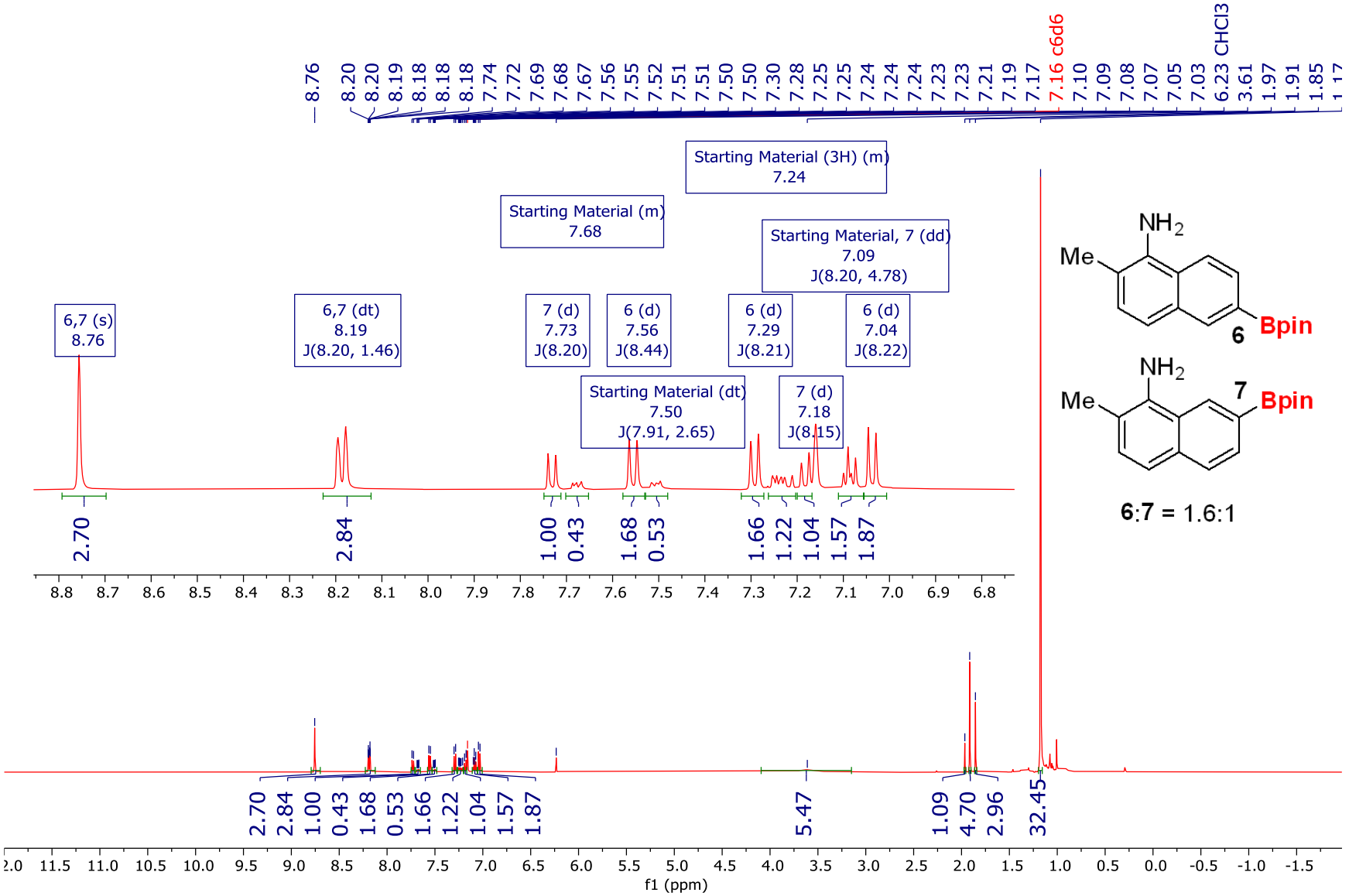
^{11}B NMR of *para* and *meta* borylated 2-chlorophenol (4.2p) ($CDCl_3$, 160 MHz)



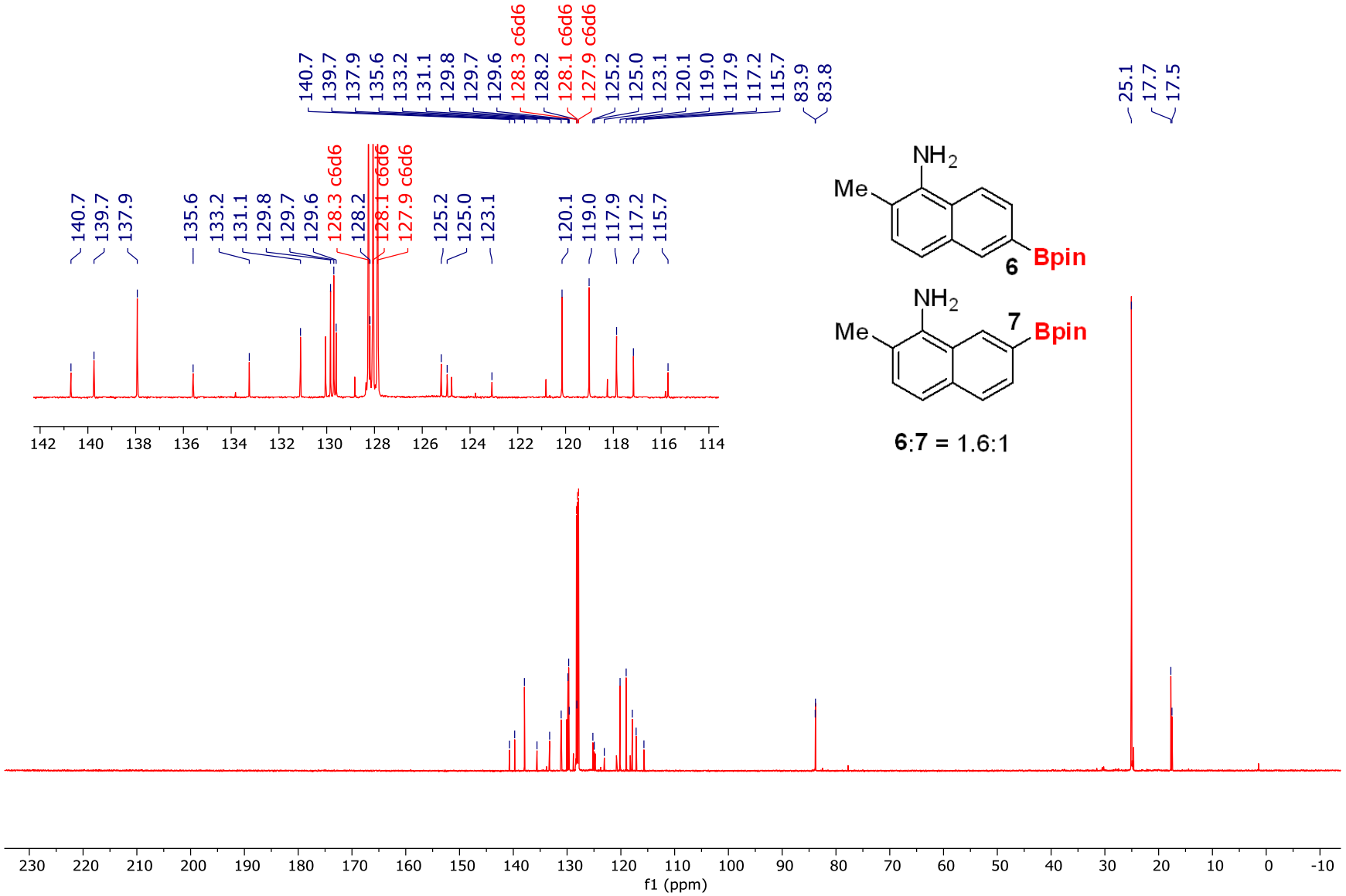
CHB borylation of 2-methyl-1-naphthylamine (4.2o) ($CDCl_3$, 500 MHz)



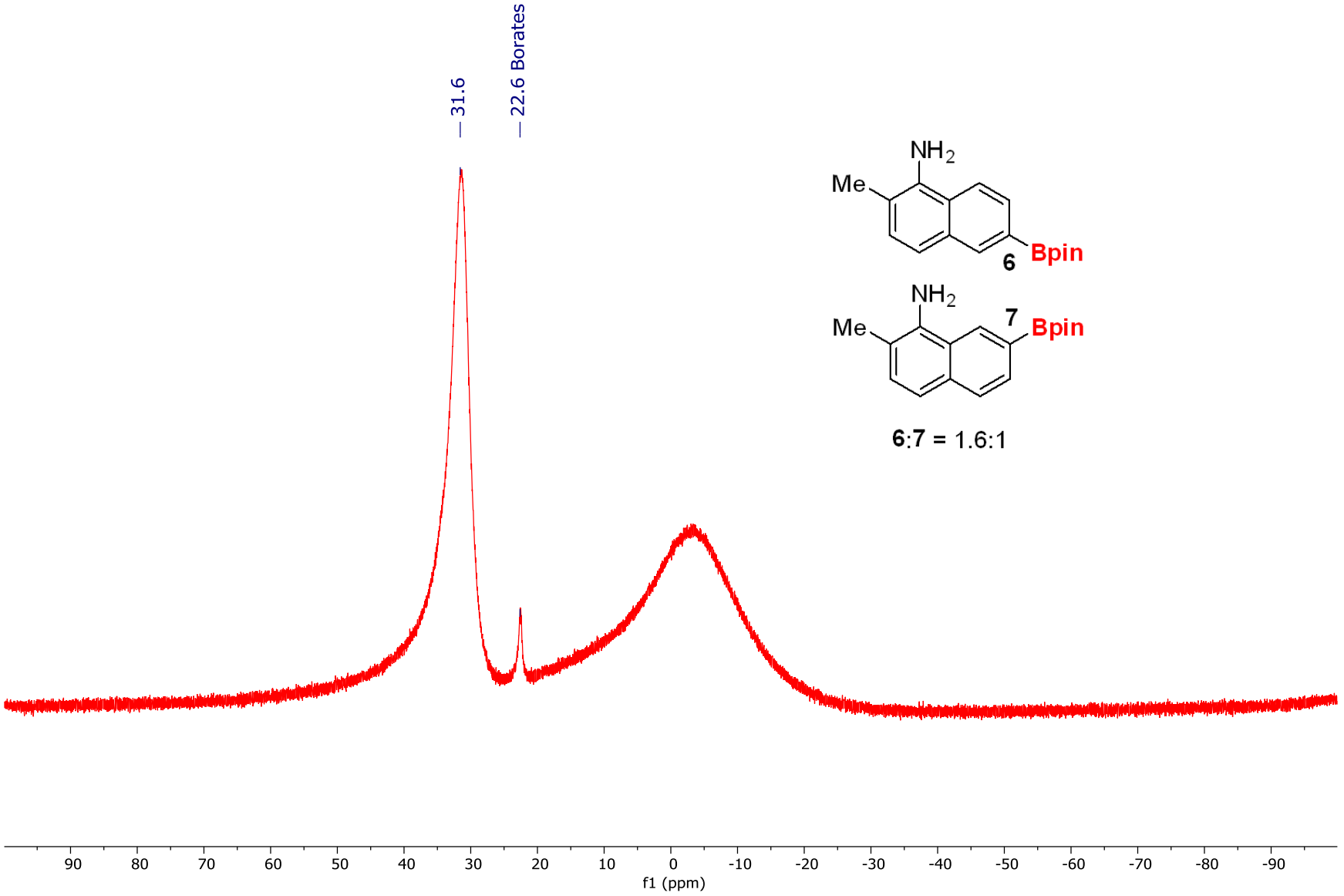
^{1}H NMR of 6- and 7-borylated 2-methyl-1-naphthylamine (4.2o) (C_6D_6, 500 MHz)



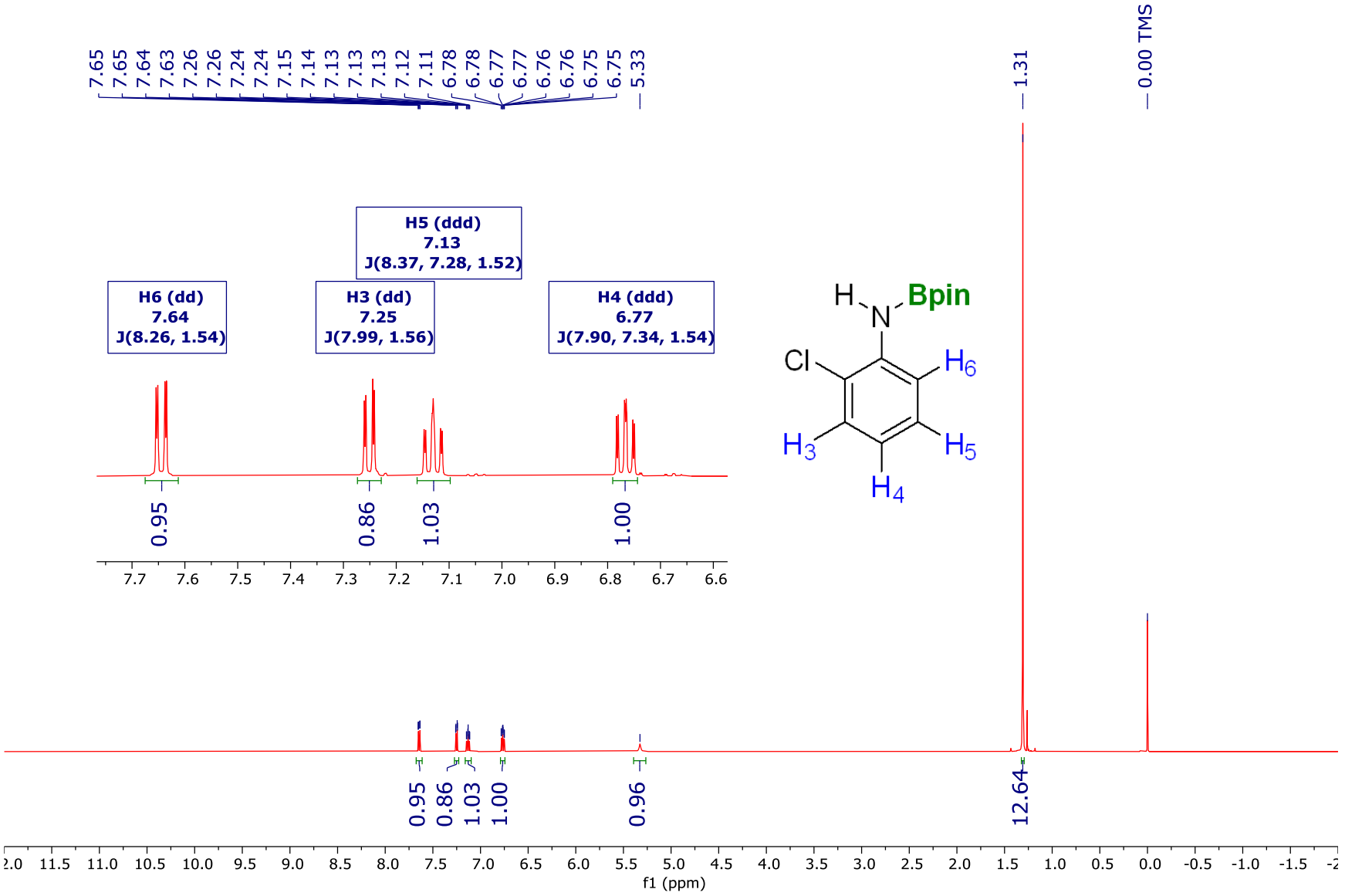
^{13}C NMR of 6- and 7-borylated 2-methyl-1-naphthylamine (4.2o) (C_6D_6, 126 MHz)



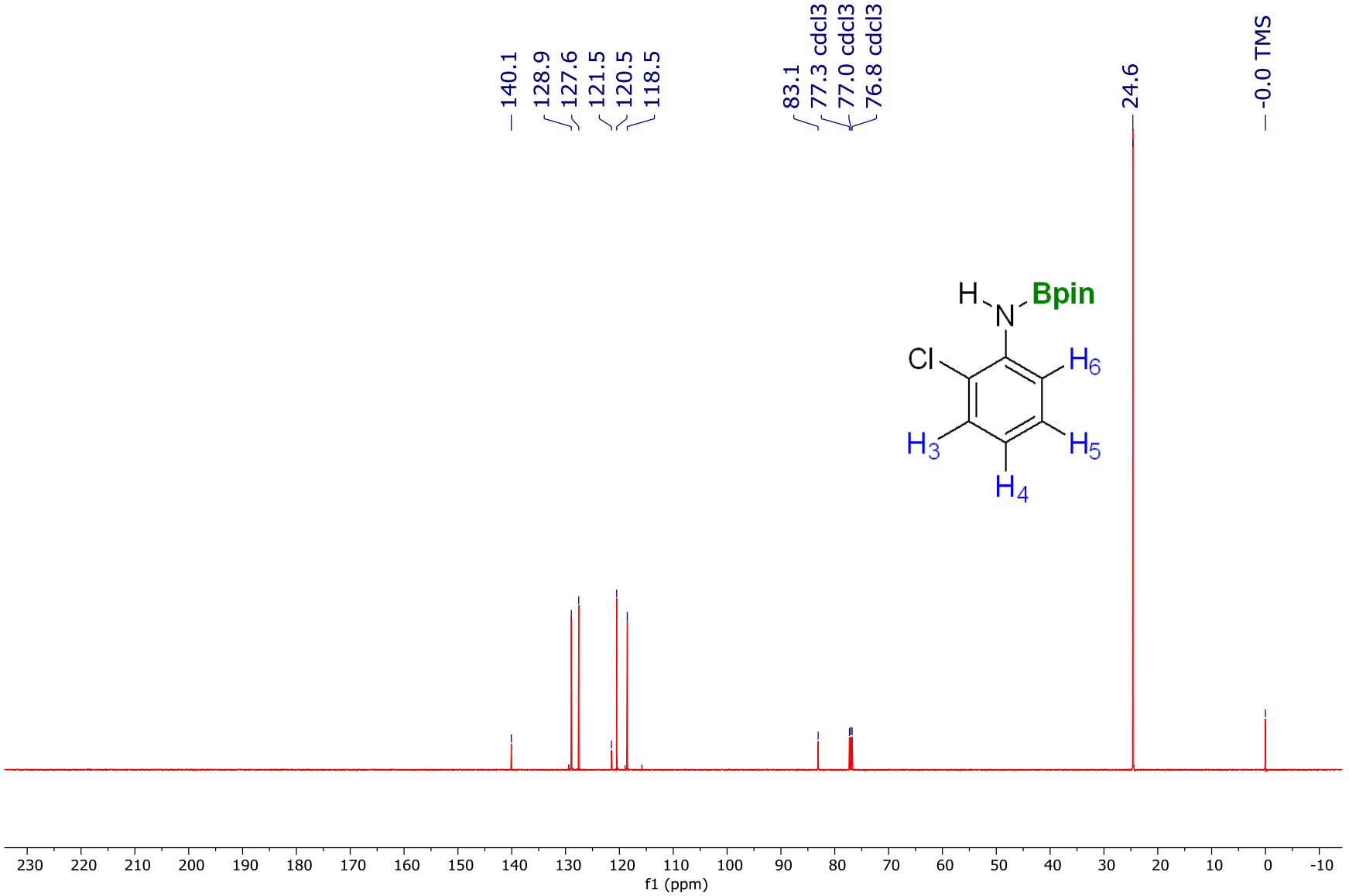
^{11}B NMR of 6- and 7-borylated 2-methyl-1-naphthylamine (4.2o) (C_6D_6, 160 MHz)



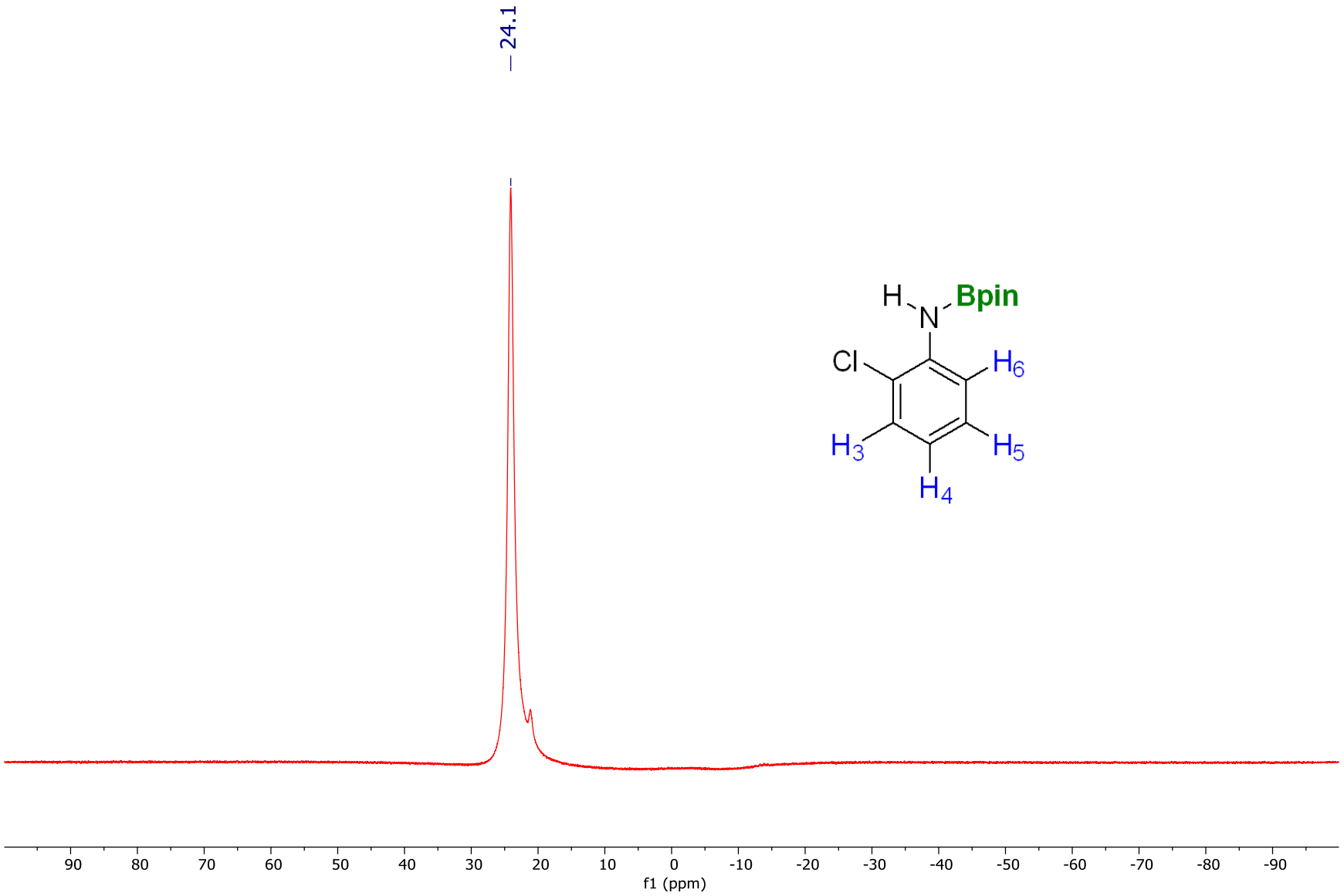
^{1}H NMR of N-Bpin borylated 2-chloroaniline (4.1a') ($CDCl_3$, 500 MHz)



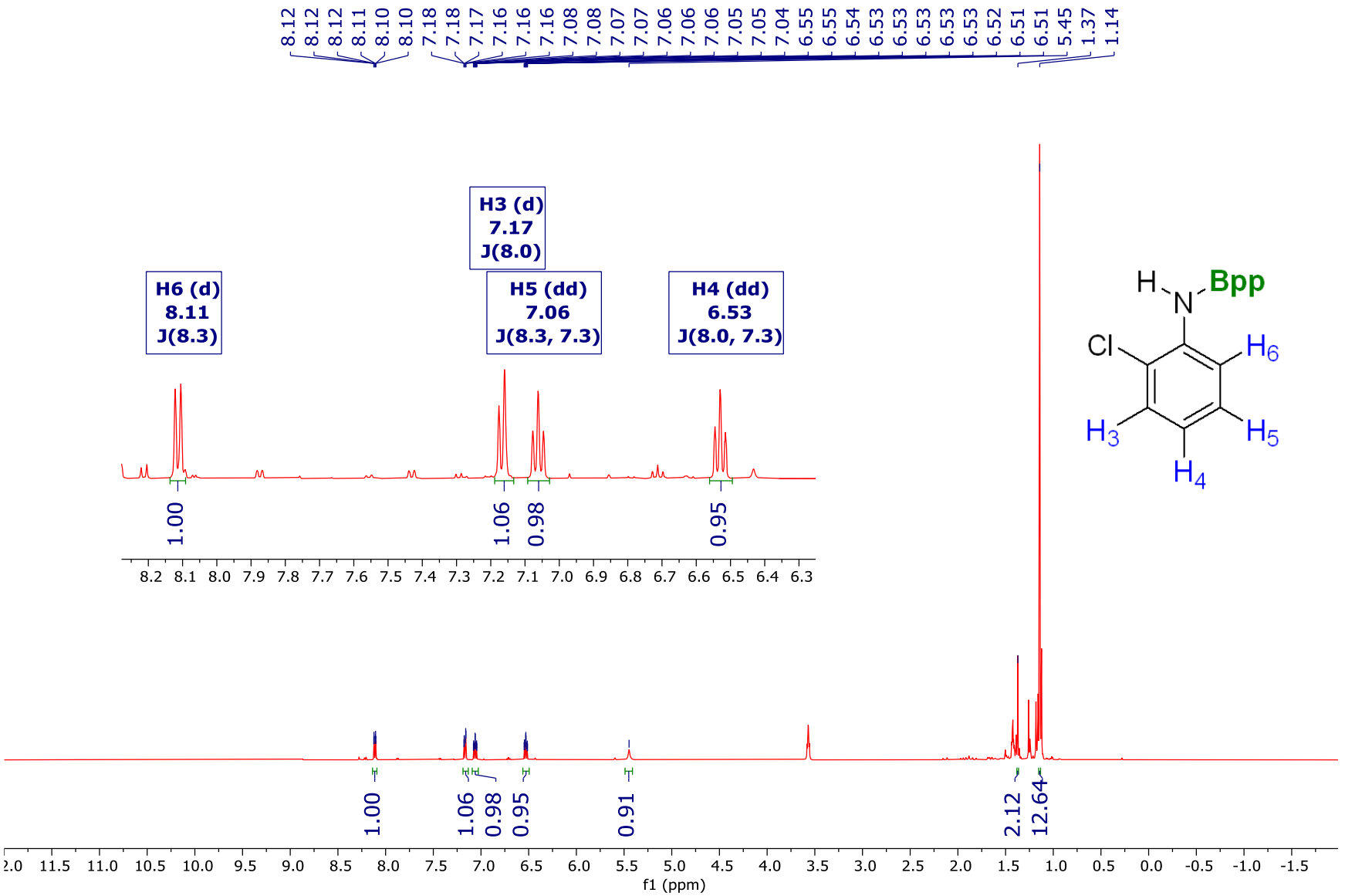
^{13}C NMR of N-Bpin borylated 2-chloroaniline (4.1a') ($CDCl_3$, 126 MHz)



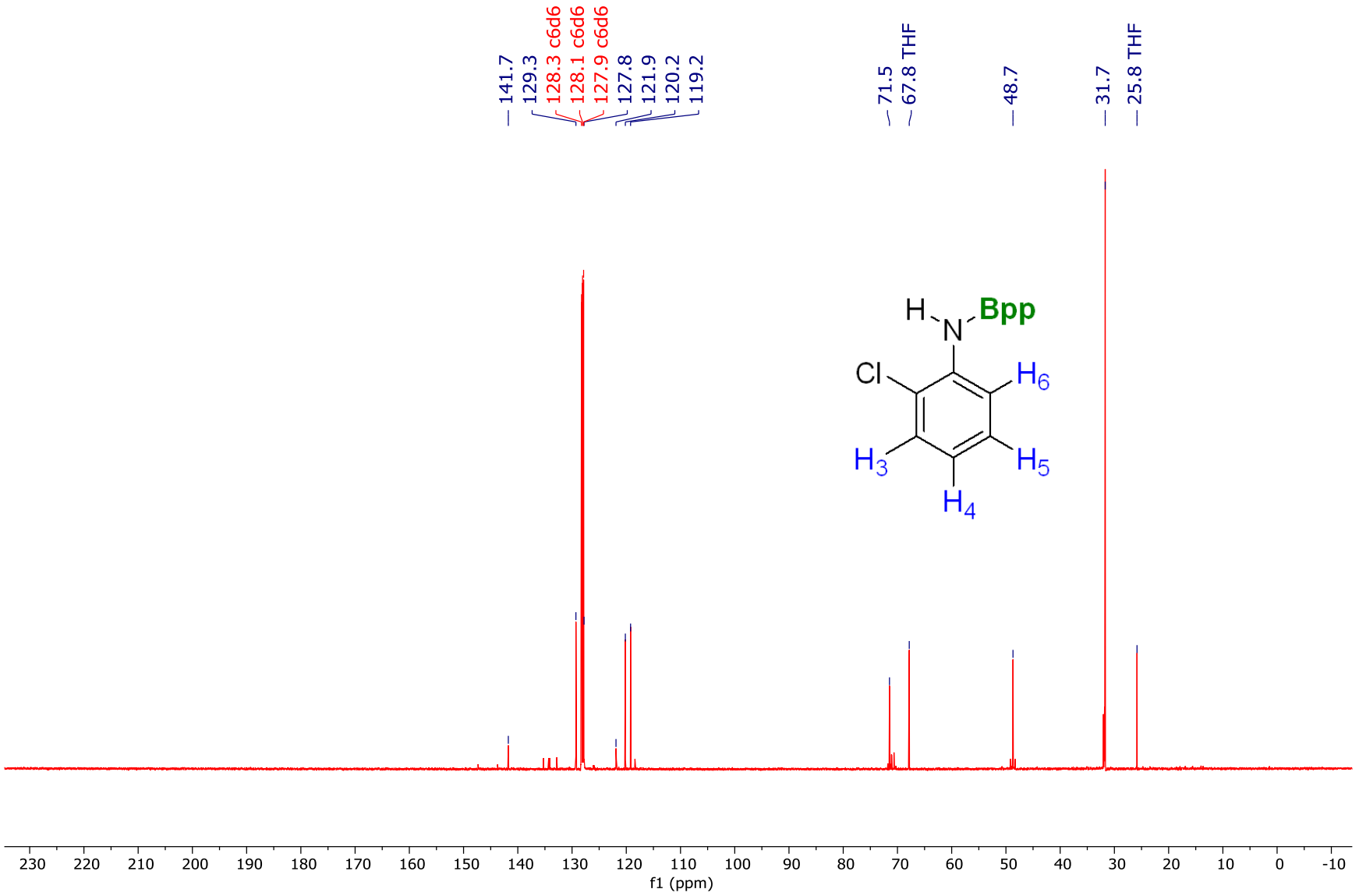
^{11}B NMR of N-Bpin borylated 2-chloroaniline (4.1a') ($CDCl_3$, 160 MHz)



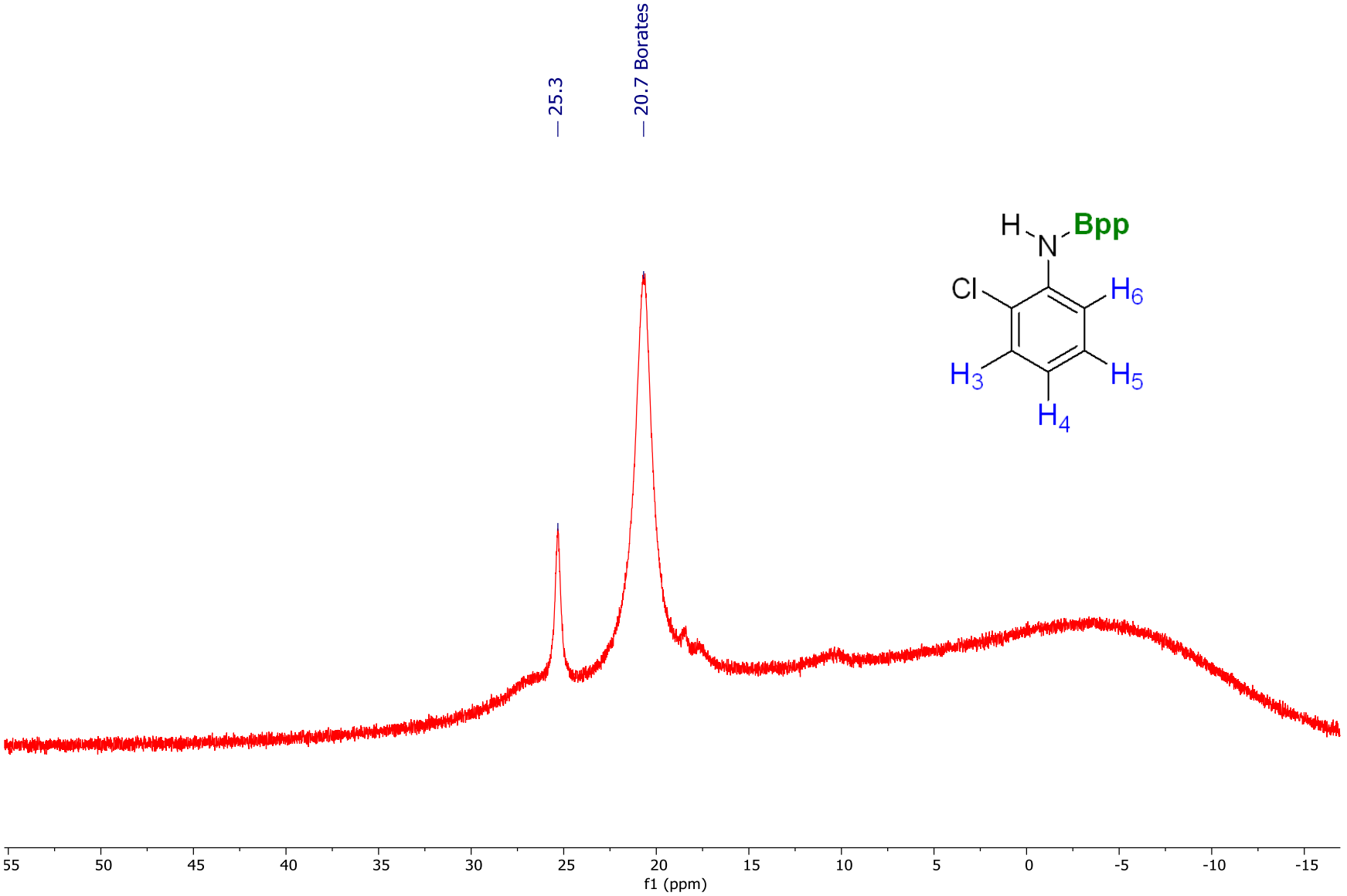
^{1}H NMR of N-Bpp borylated 2-chloroaniline (C_6D_6, 500 MHz)



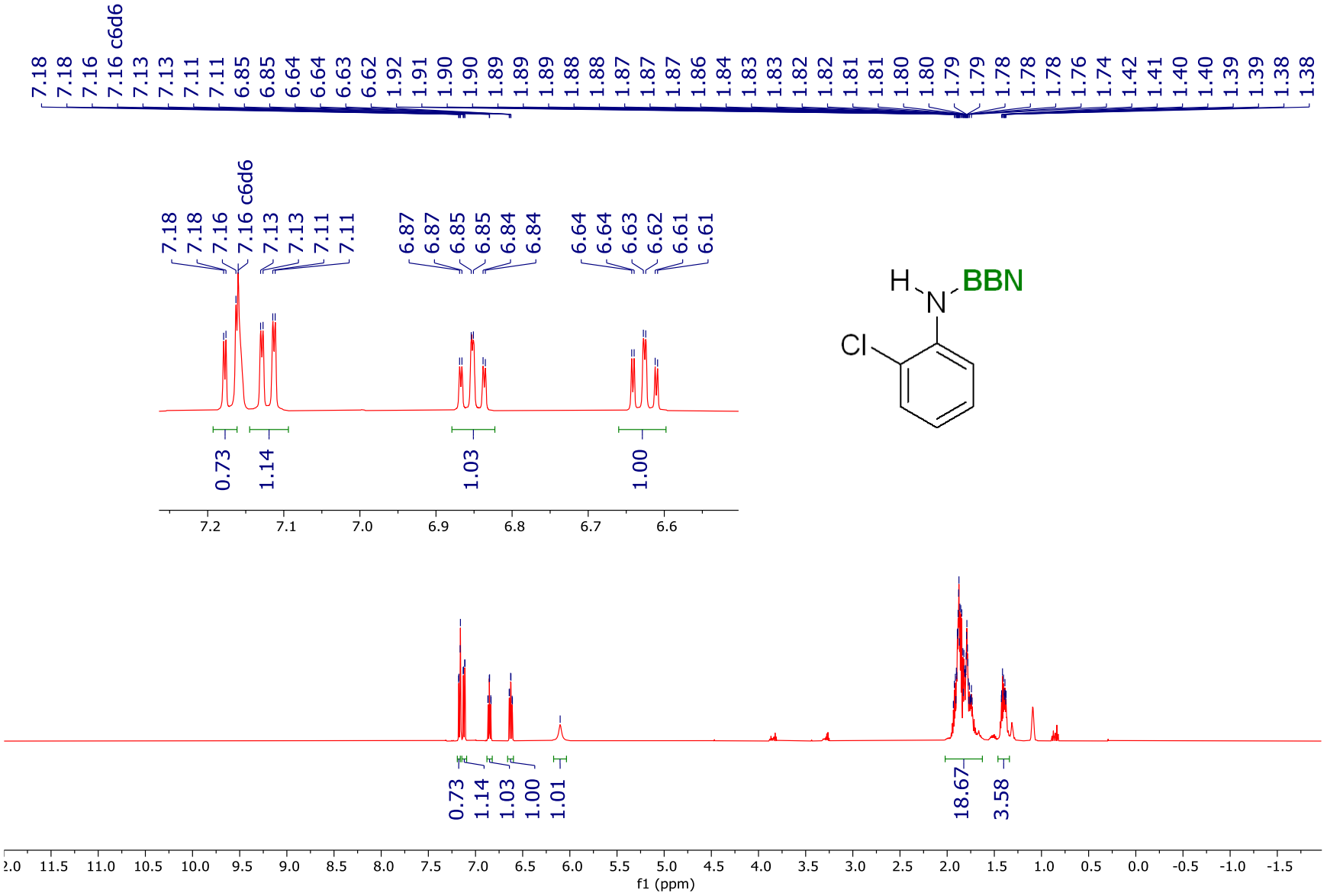
^{13}C NMR of N-Bpp borylated 2-chloroaniline (C_6D_6, 126 MHz)



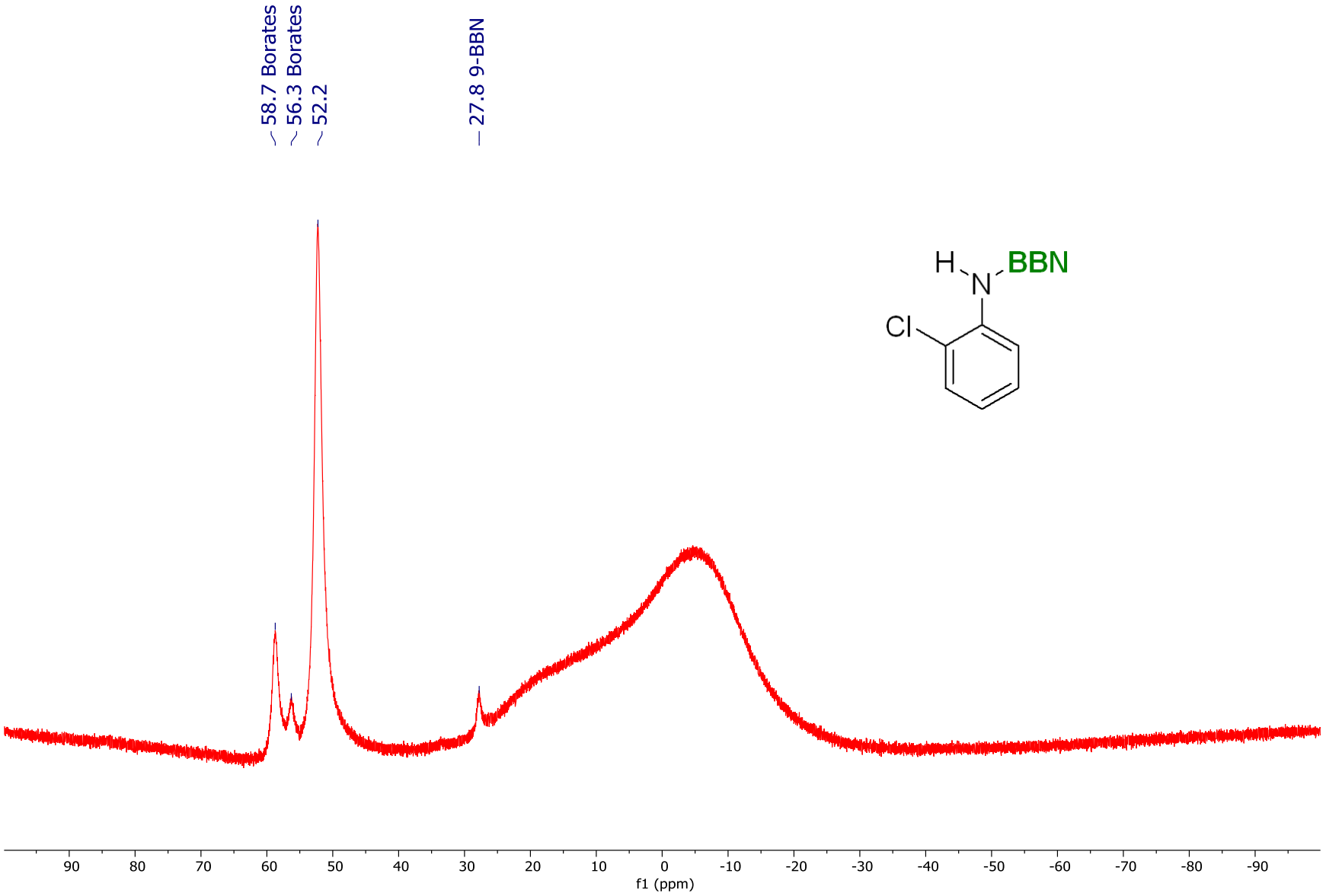
^{11}B NMR of N-Bpp borylated 2-chloroaniline (C_6D_6, 160 MHz)



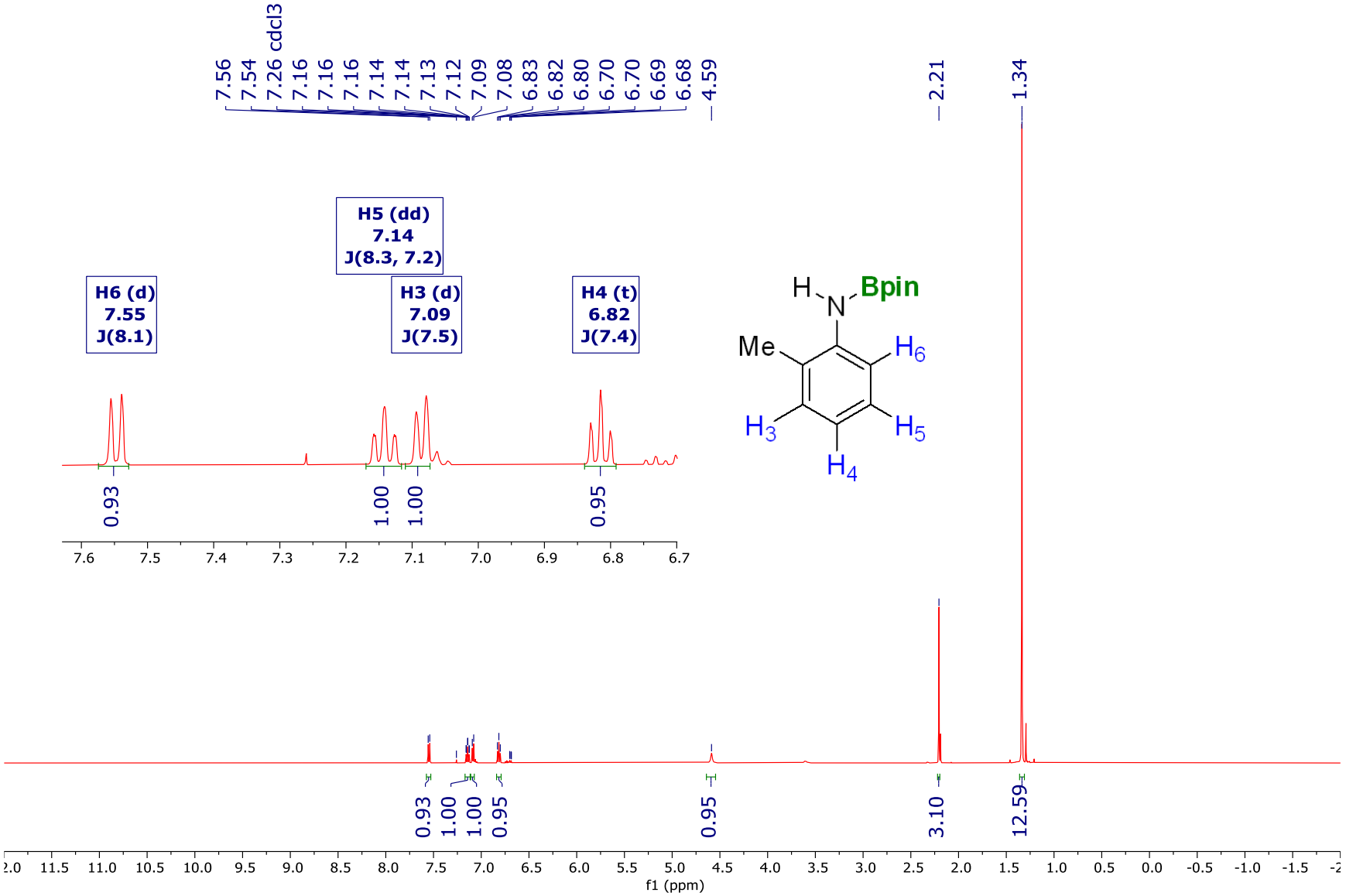
^{1}H NMR of N-BBN borylated 2-chloroaniline (C_6D_6, 500 MHz)



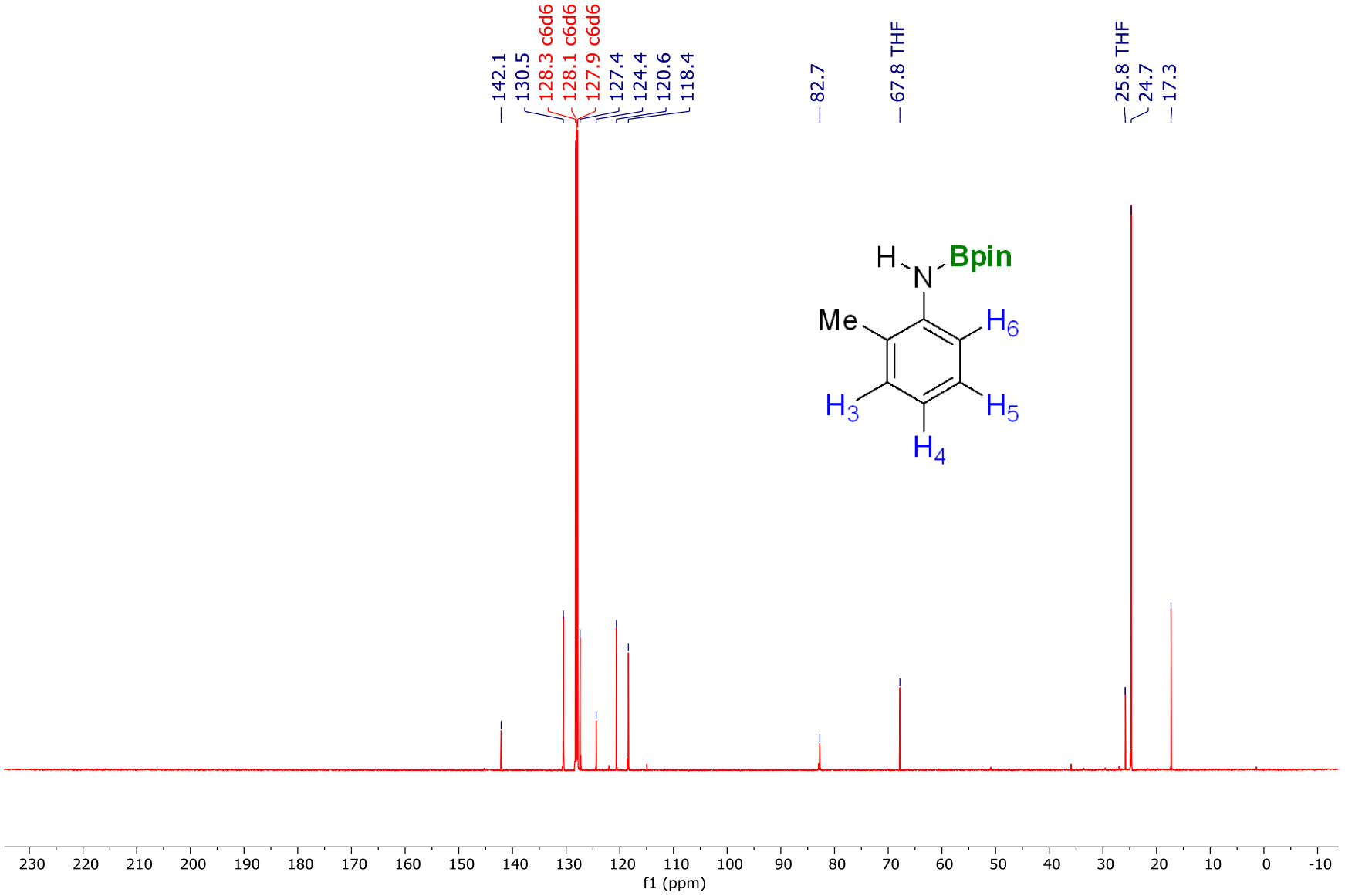
^{11}B NMR of N-BBN borylated 2-chloroaniline (C_6D_6, 160 MHz)



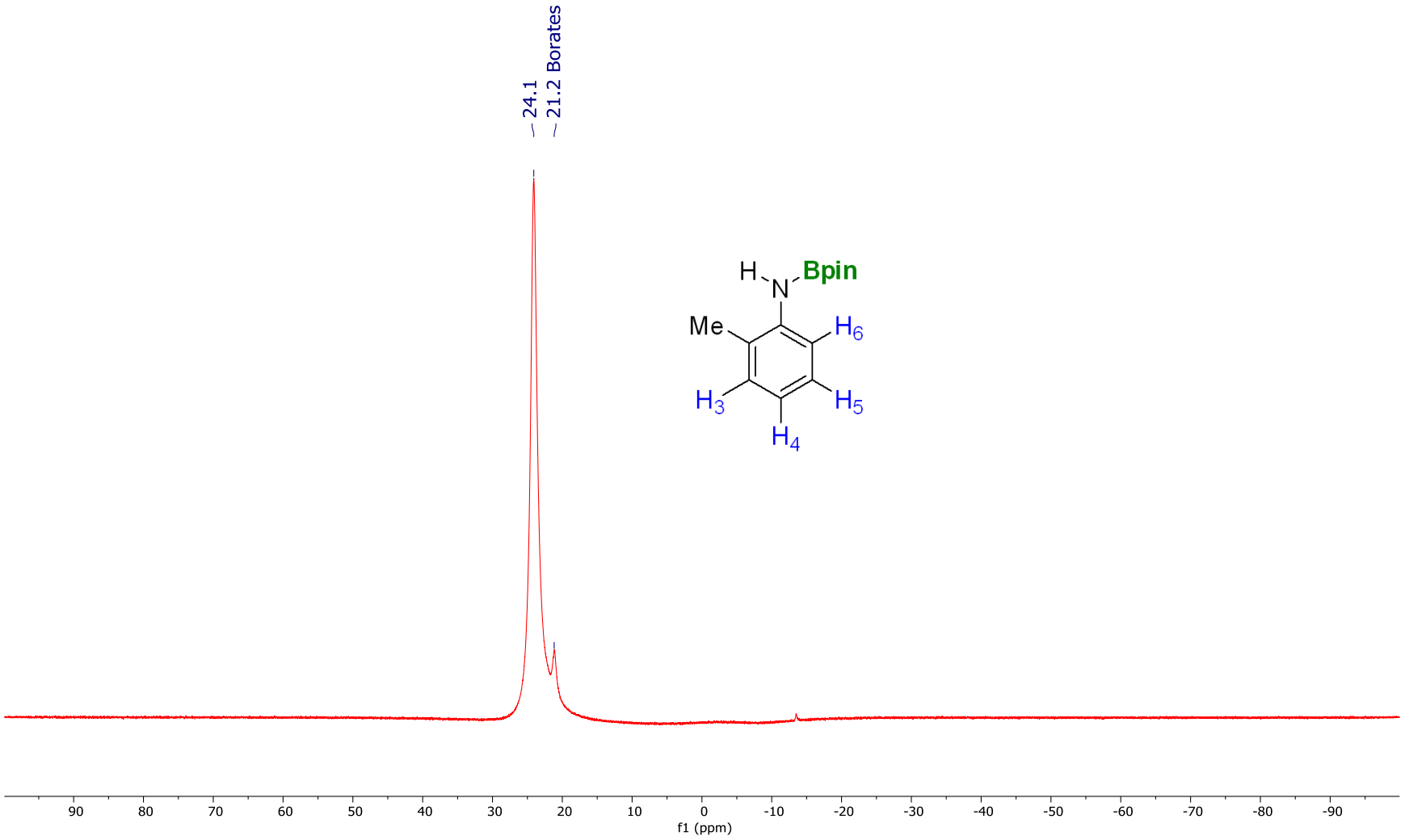
^{1}H NMR of N-Bpin borylated 2-methylaniline (4.1g') ($CDCl_3$, 500 MHz)



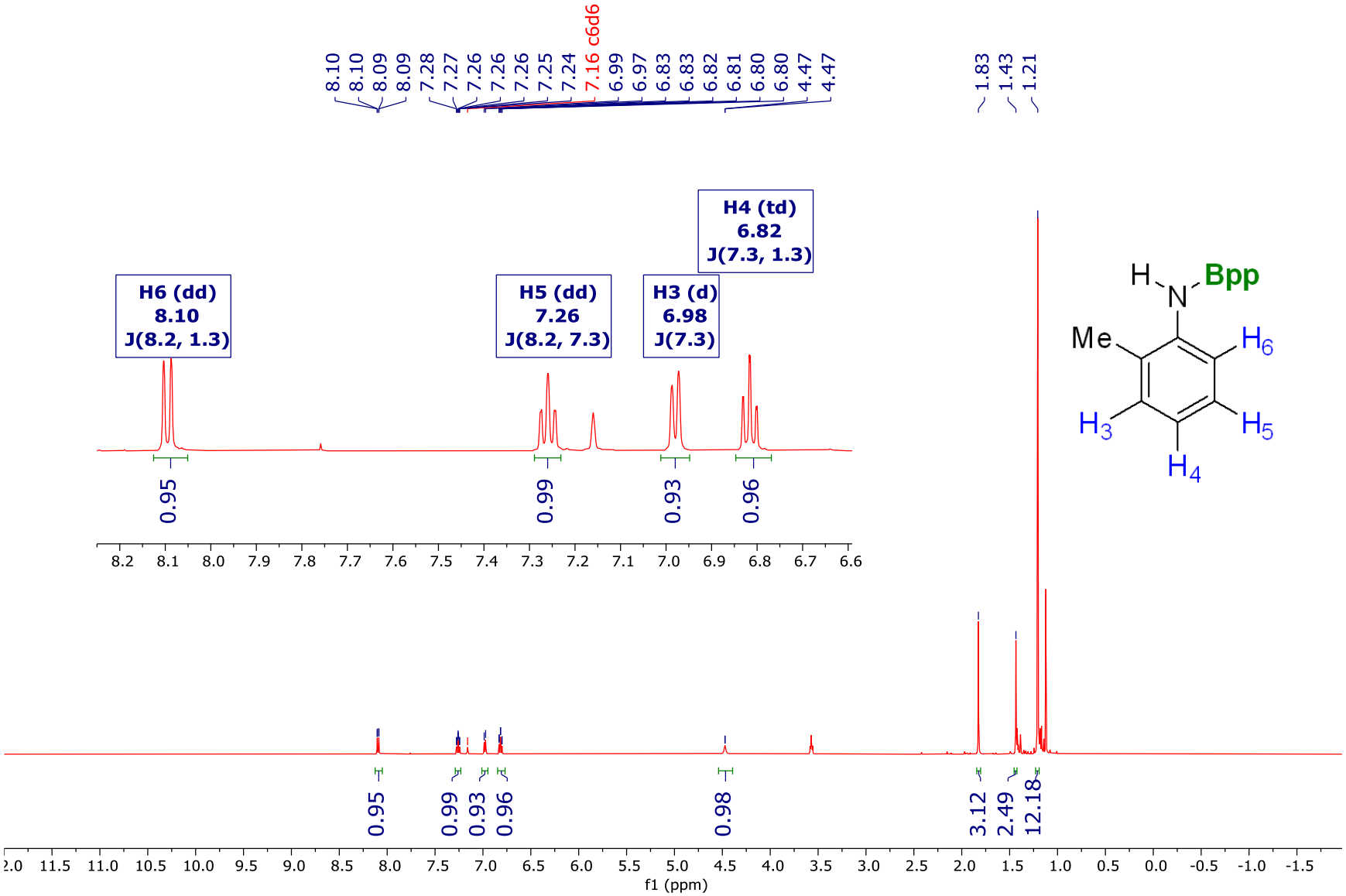
^{13}C NMR of N-Bpin borylated 2-methylaniline (4.1g') (C_6D_6, 126 MHz)



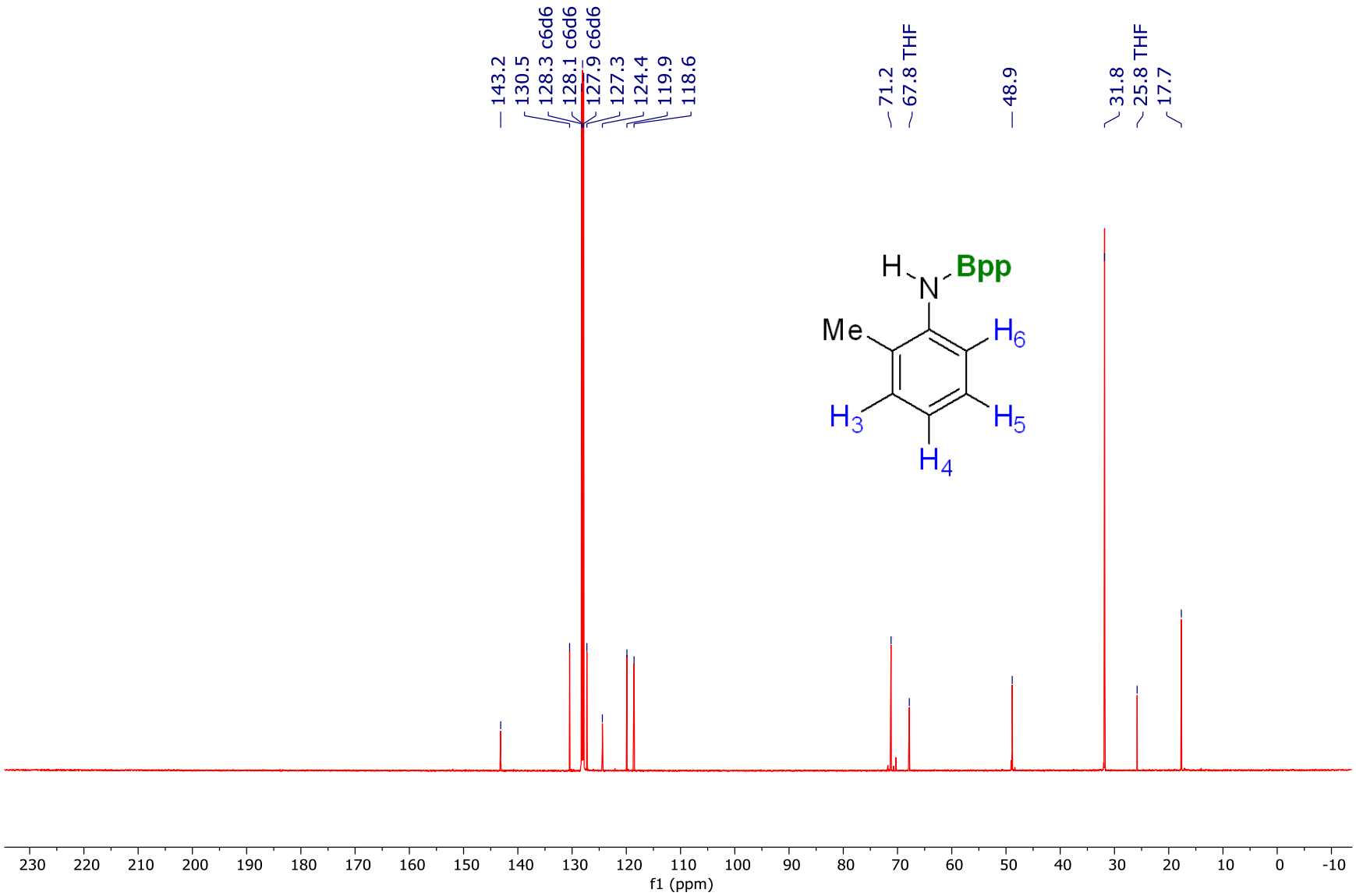
^{11}B NMR of N-Bpin borylated 2-methylniline (4.1g') ($CDCl_3$, 160 MHz)



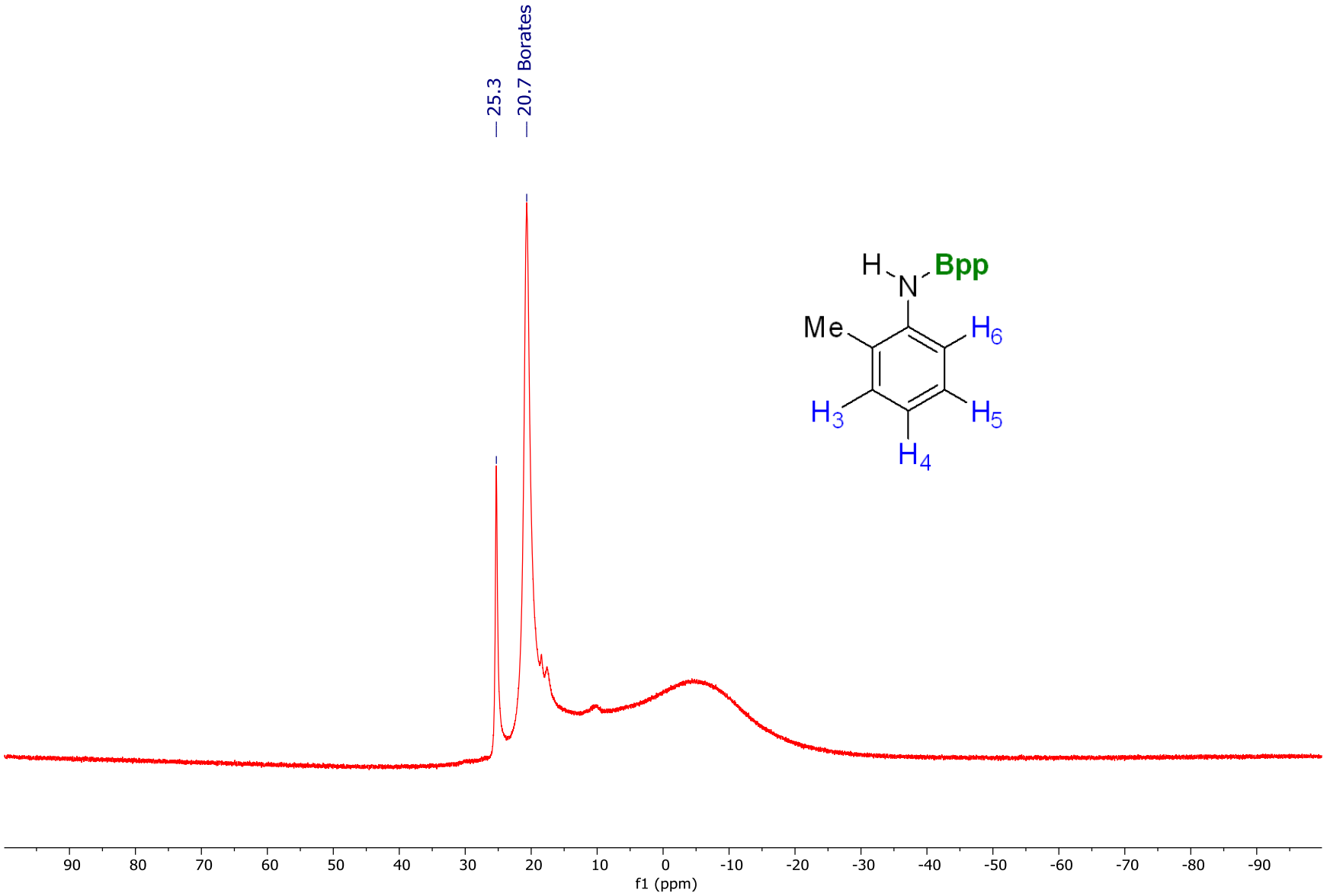
^{1}H NMR of N-Bpp borylated 2-methylaniline (C_6D_6, 500 MHz)



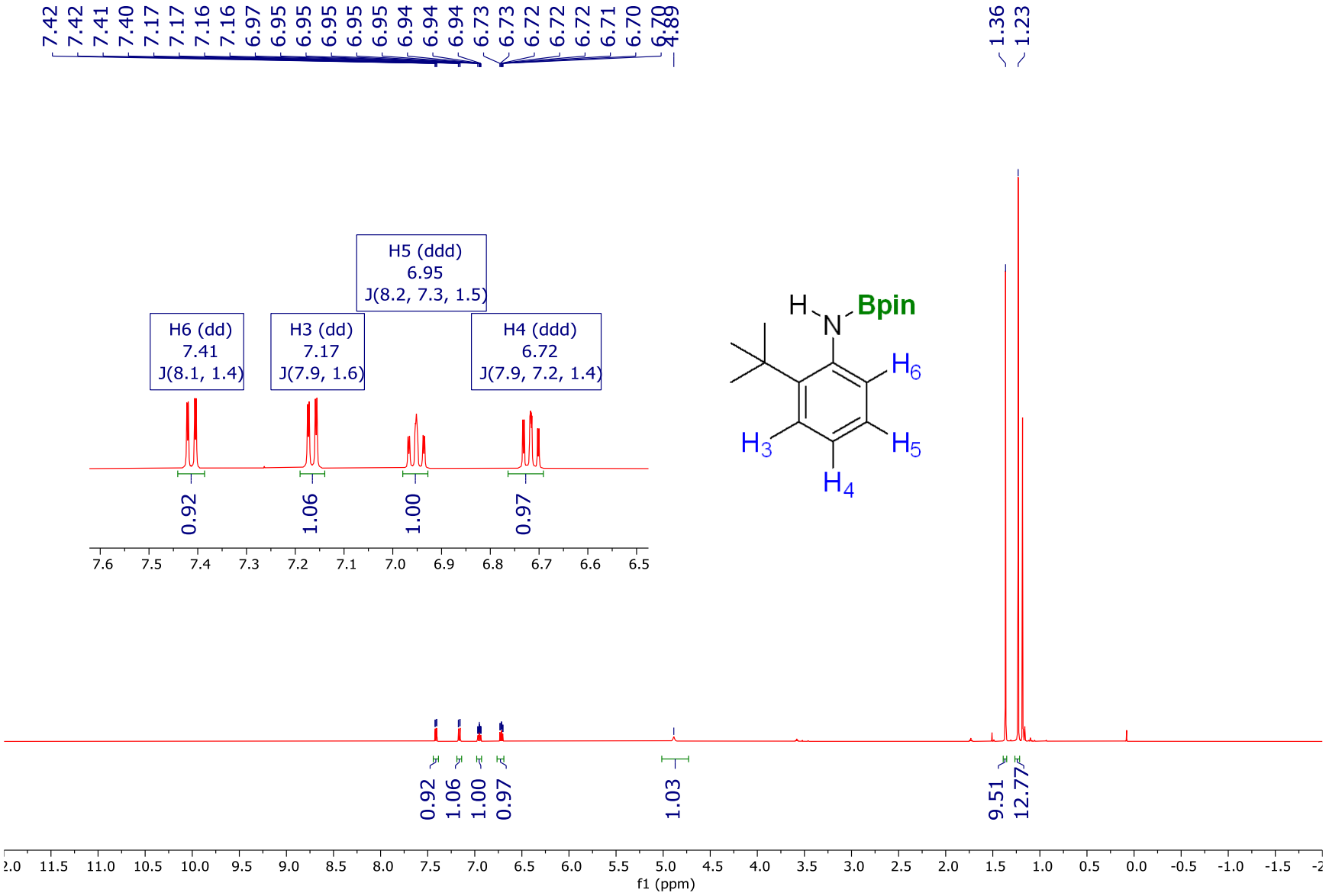
^{13}C NMR of N-Bpp borylated 2-methylaniline (C_6D_6, 126 MHz)



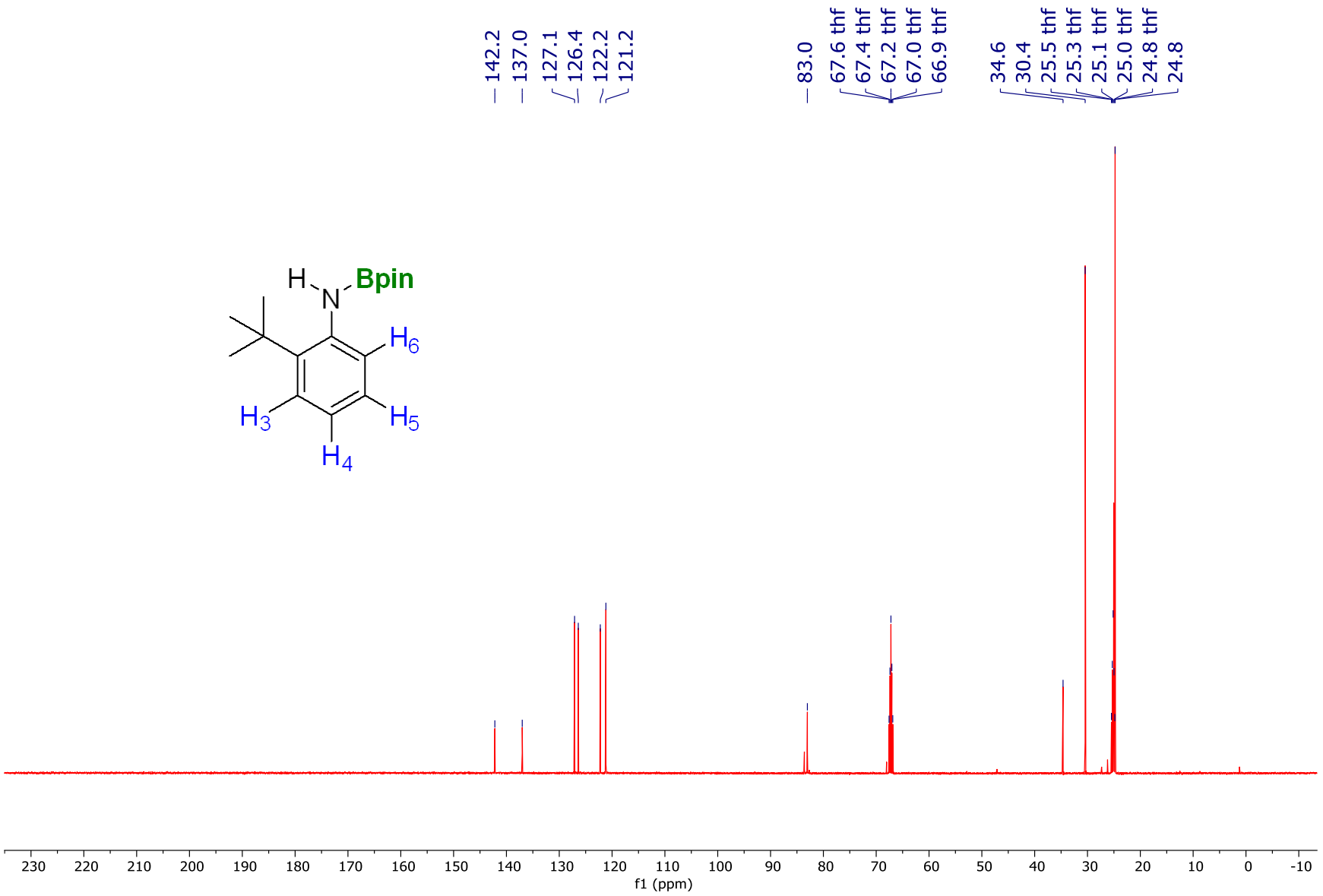
^{11}B NMR of N-Bpp borylated 2-methylaniline (C_6D_6, 160 MHz)



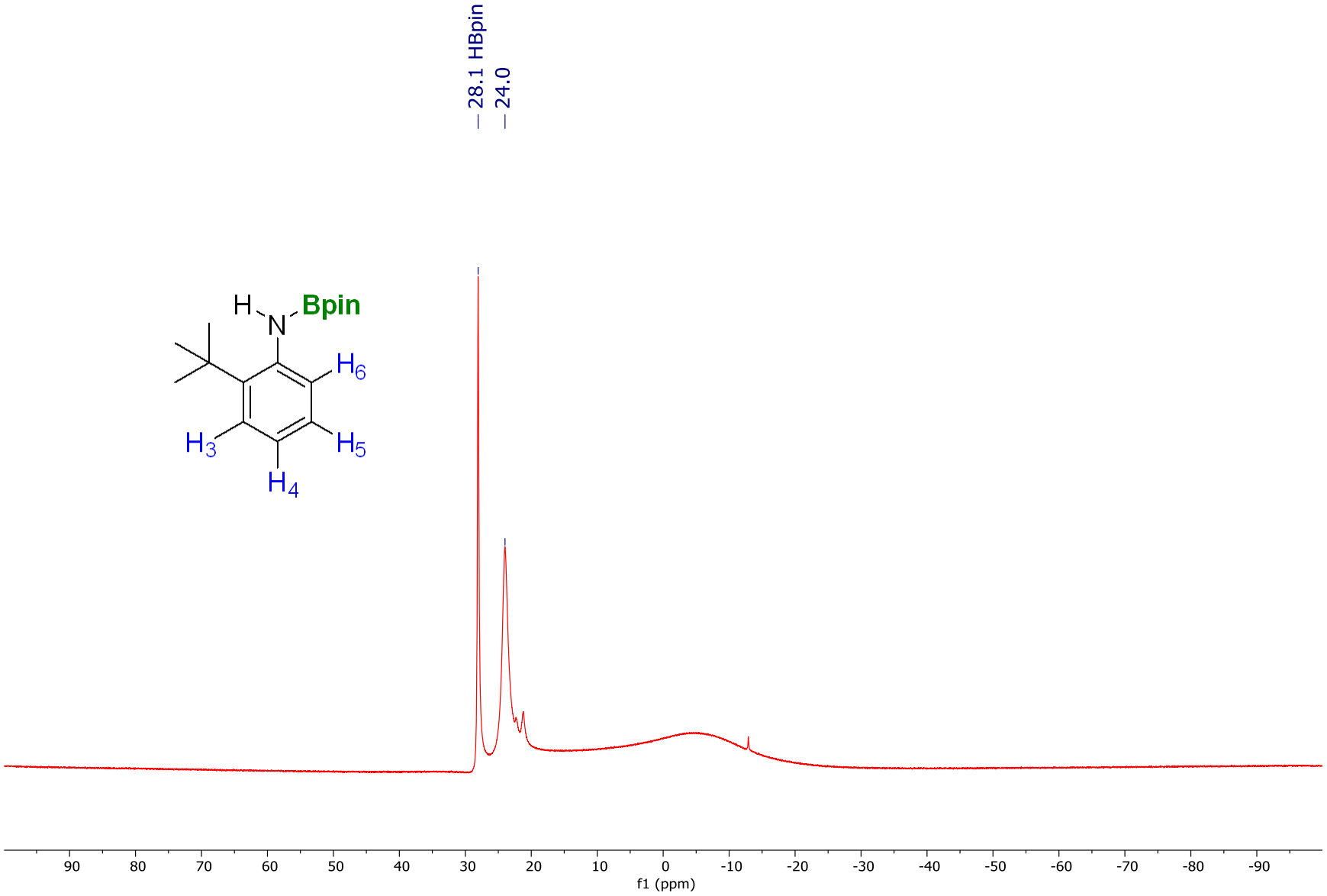
^{1}H NMR of N-Bpin borylated 2-tertbutylaniline (4.1i') (THF-*d8*, 500 MHz)



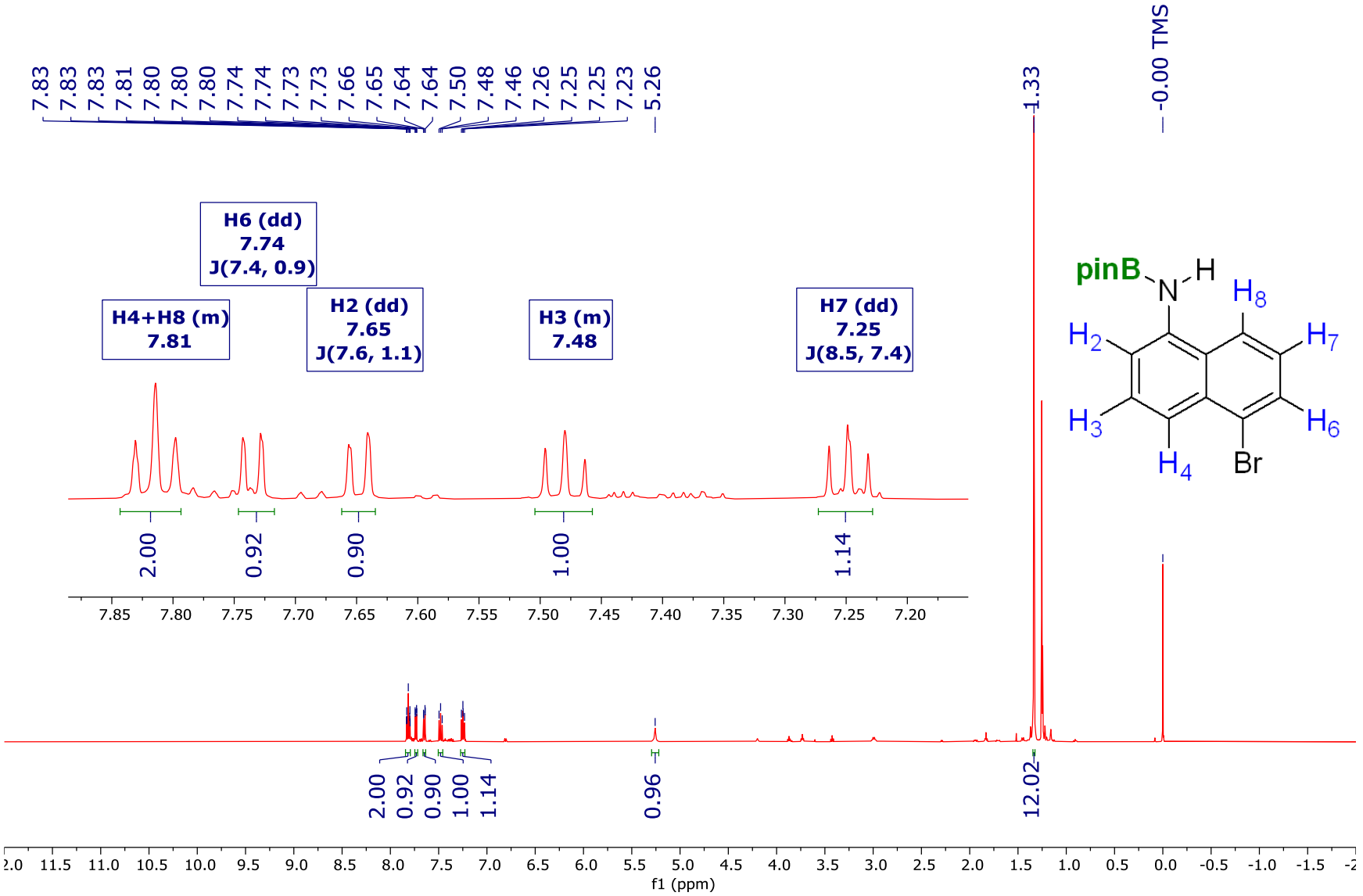
^{13}C NMR of N-Bpin borylated 2-tertbutylaniline (4.1i') (THF-*d8*, 126 MHz)



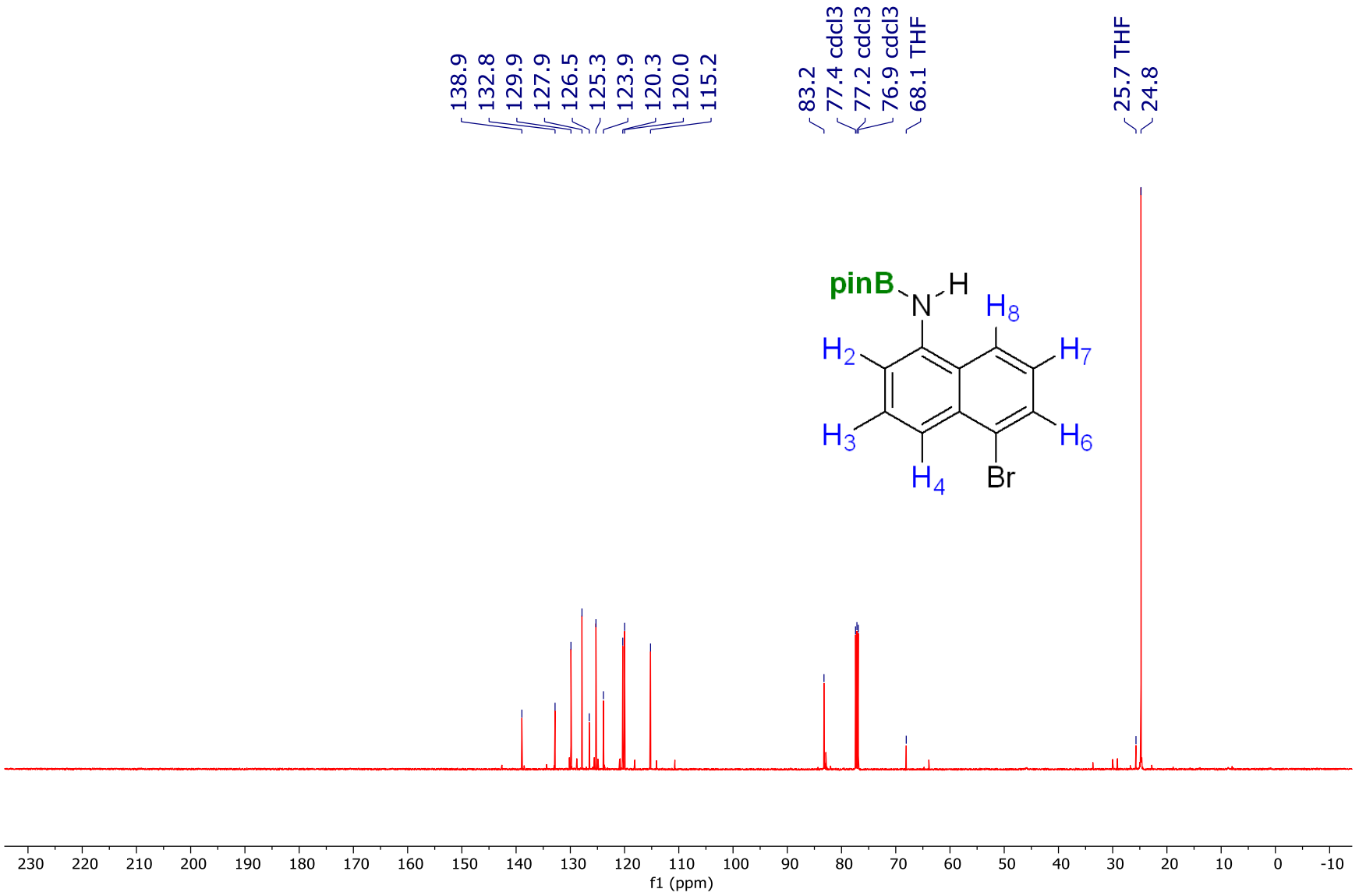
^{11}B NMR of N-Bpin borylated 2-tertbutylaniline (4.1i') (THF-*d8*, 160 MHz)



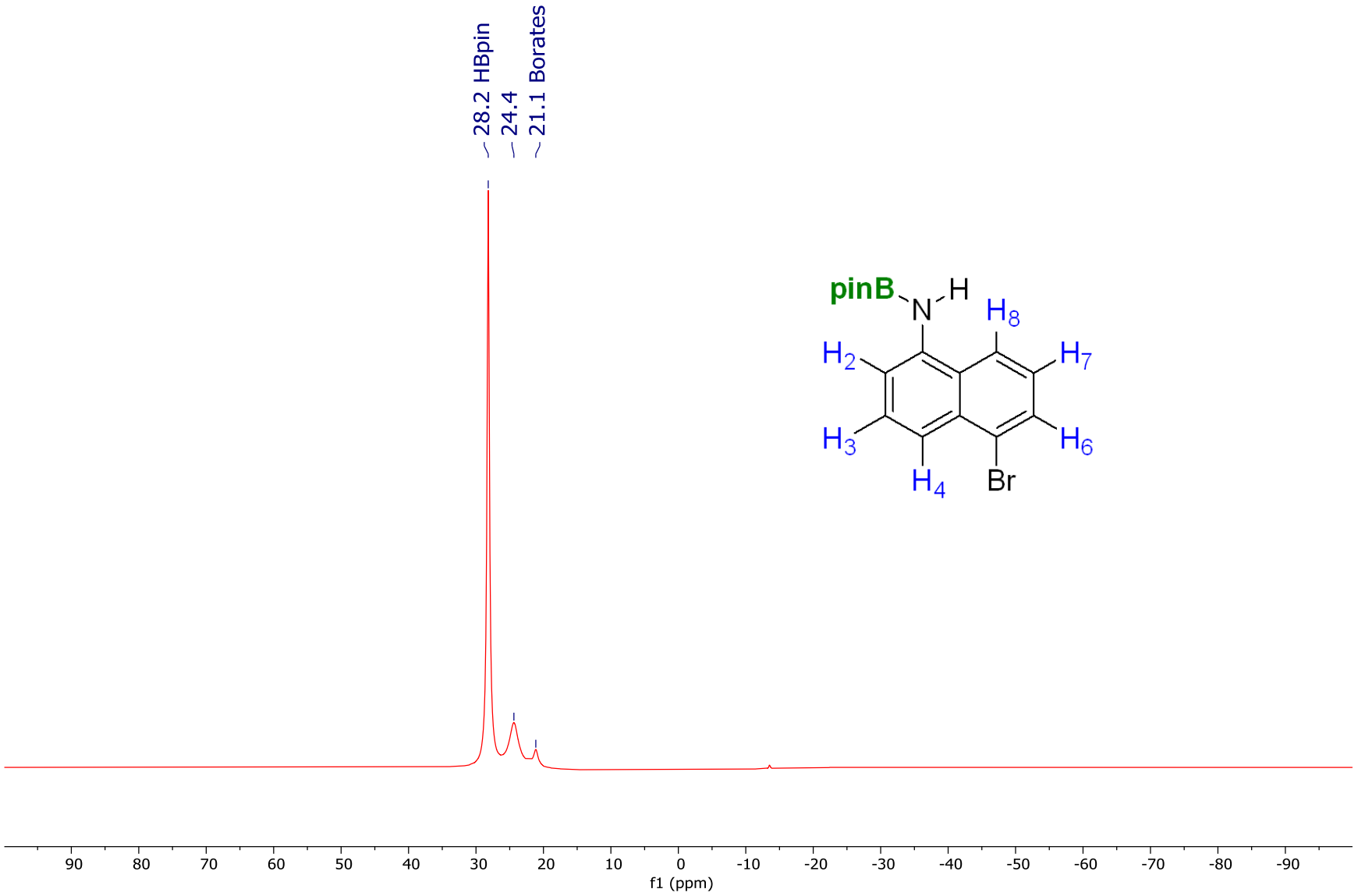
^{1}H NMR of N-Bpin borylated 5-bromo-1-aminonaphthalene (4.1m') ($CDCl_3$, 500 MHz)



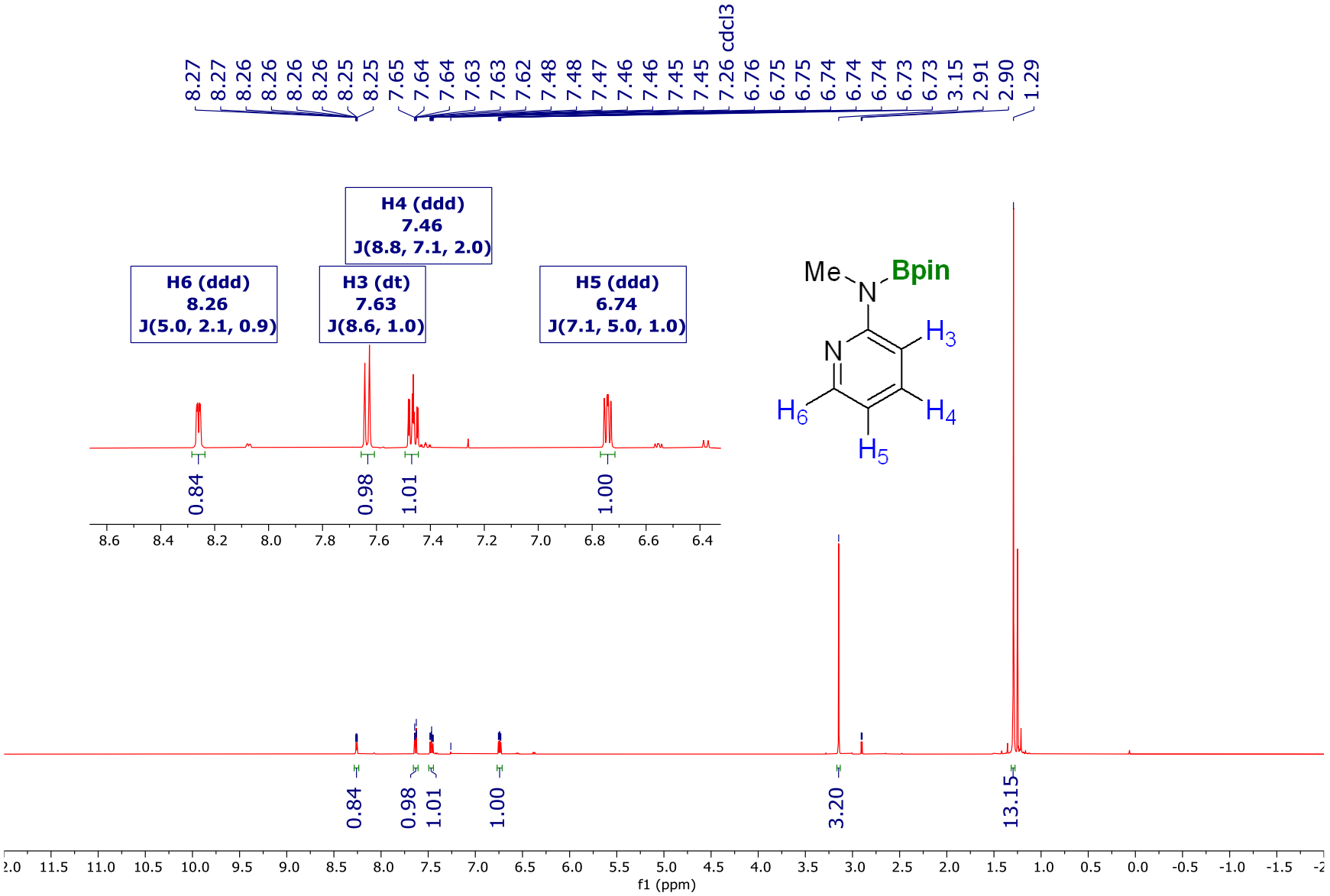
^{13}C NMR of N-Bpin borylated 5-bromo-1-aminonaphthalene (4.1m') ($CDCl_3$, 126 MHz)



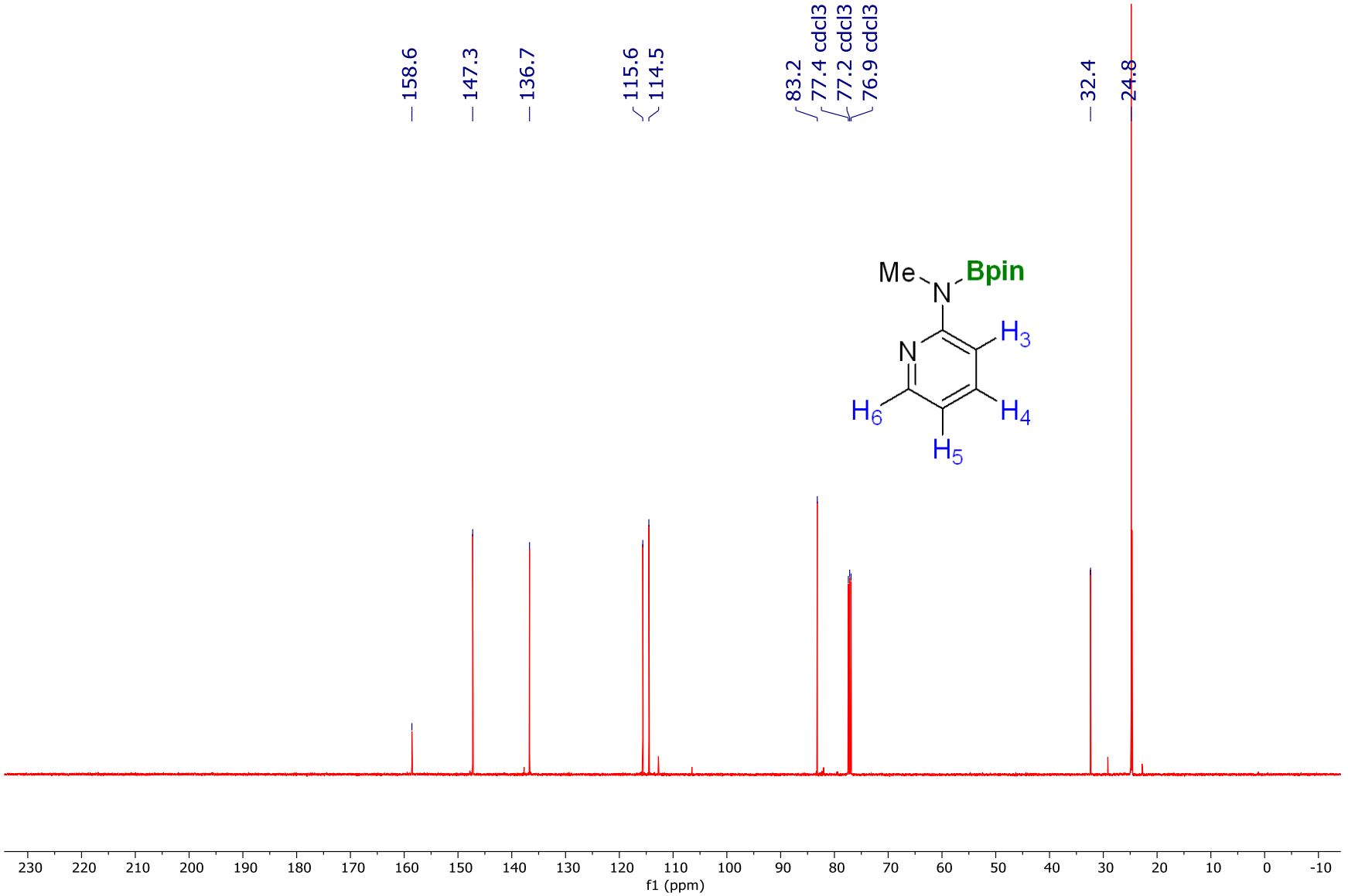
^{11}B NMR of N-Bpin borylated 5-bromo-1-aminonaphthalene (4.1m') ($CDCl_3$, 160 MHz)



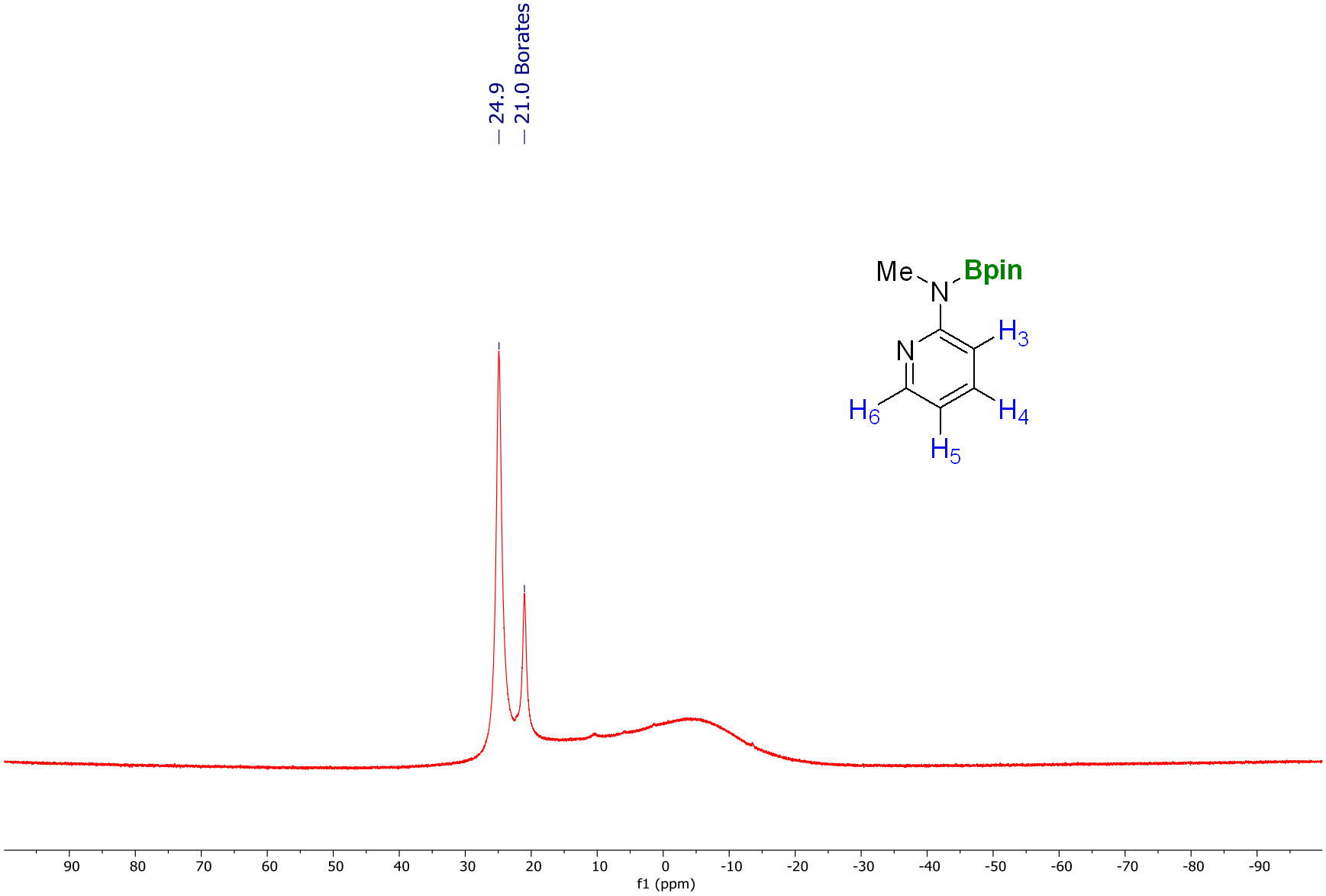
^{1}H NMR of N-Bpin borylated 2-amino-N-methylpyridine (4.3b') ($CDCl_3$, 500 MHz)



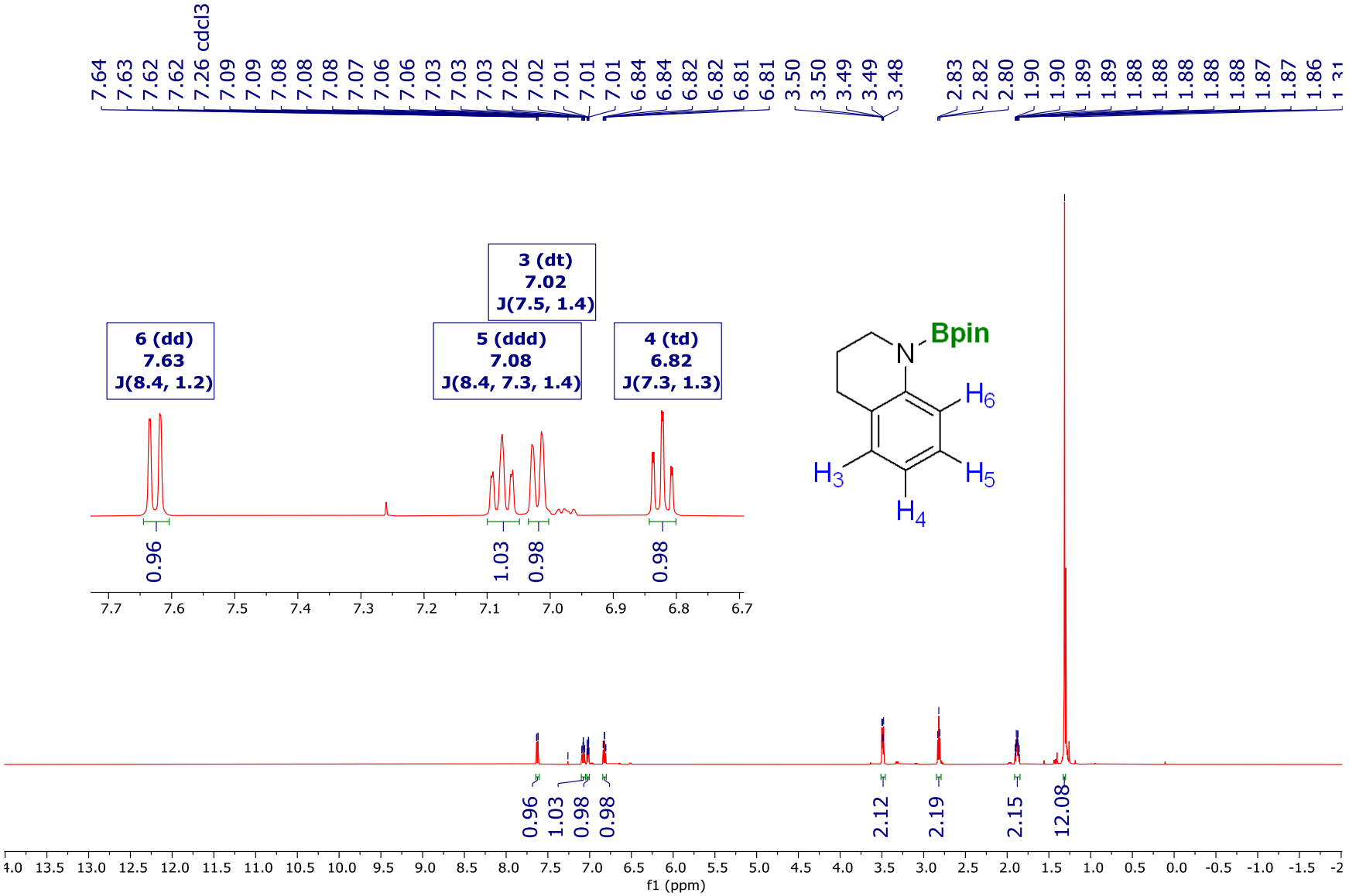
^{13}C NMR of N-Bpin borylated 2-amino-N-methylpyridine (4.3b') ($CDCl_3$, 126 MHz)



^{11}B NMR of N-Bpin borylated 2-amino-N-methylpyridine (4.3b') ($CDCl_3$, 160 MHz)



^{1}H NMR of N-Bpin borylated Tetrahydroquinoline (4.3d') ($CDCl_3$, 500 MHz)



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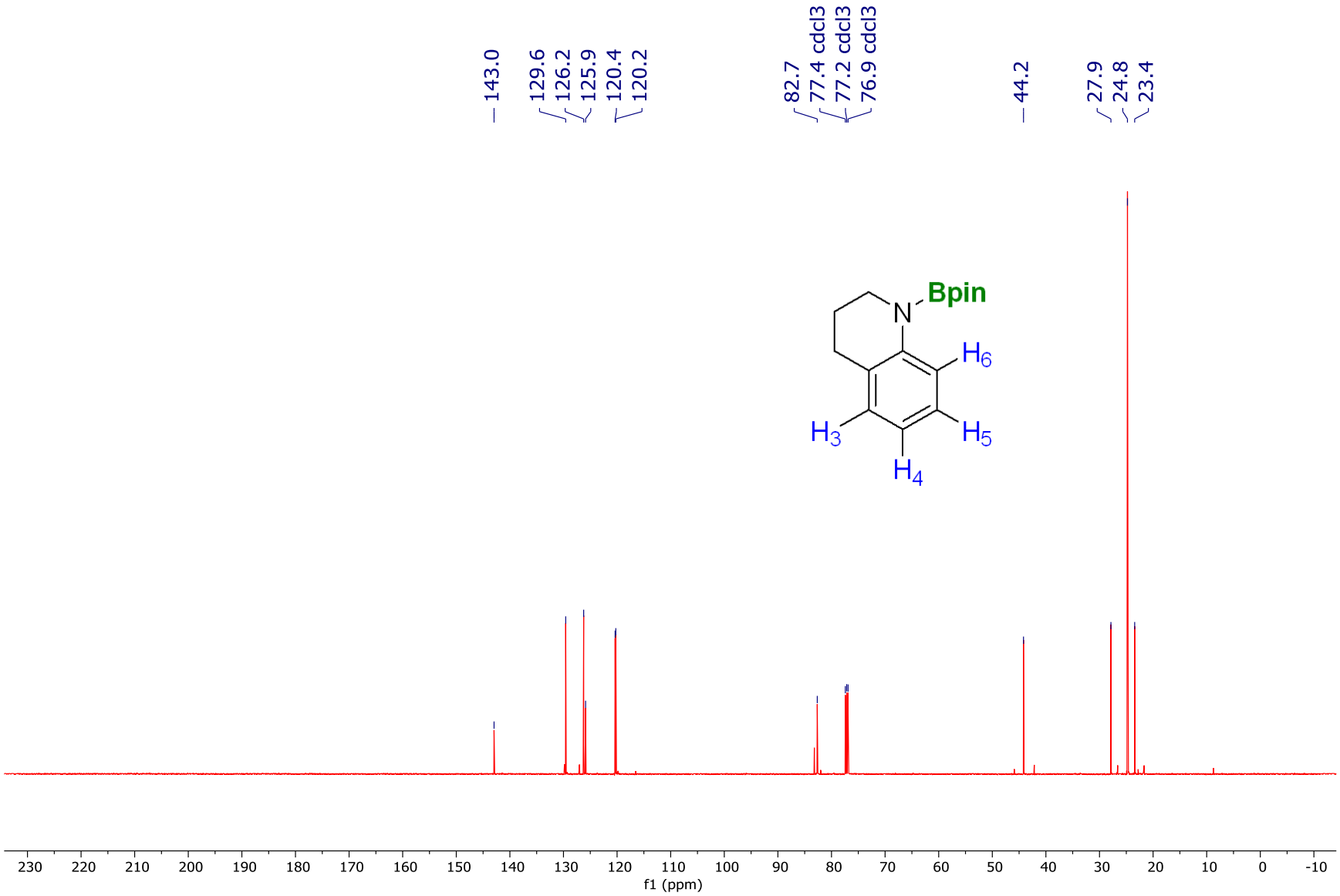

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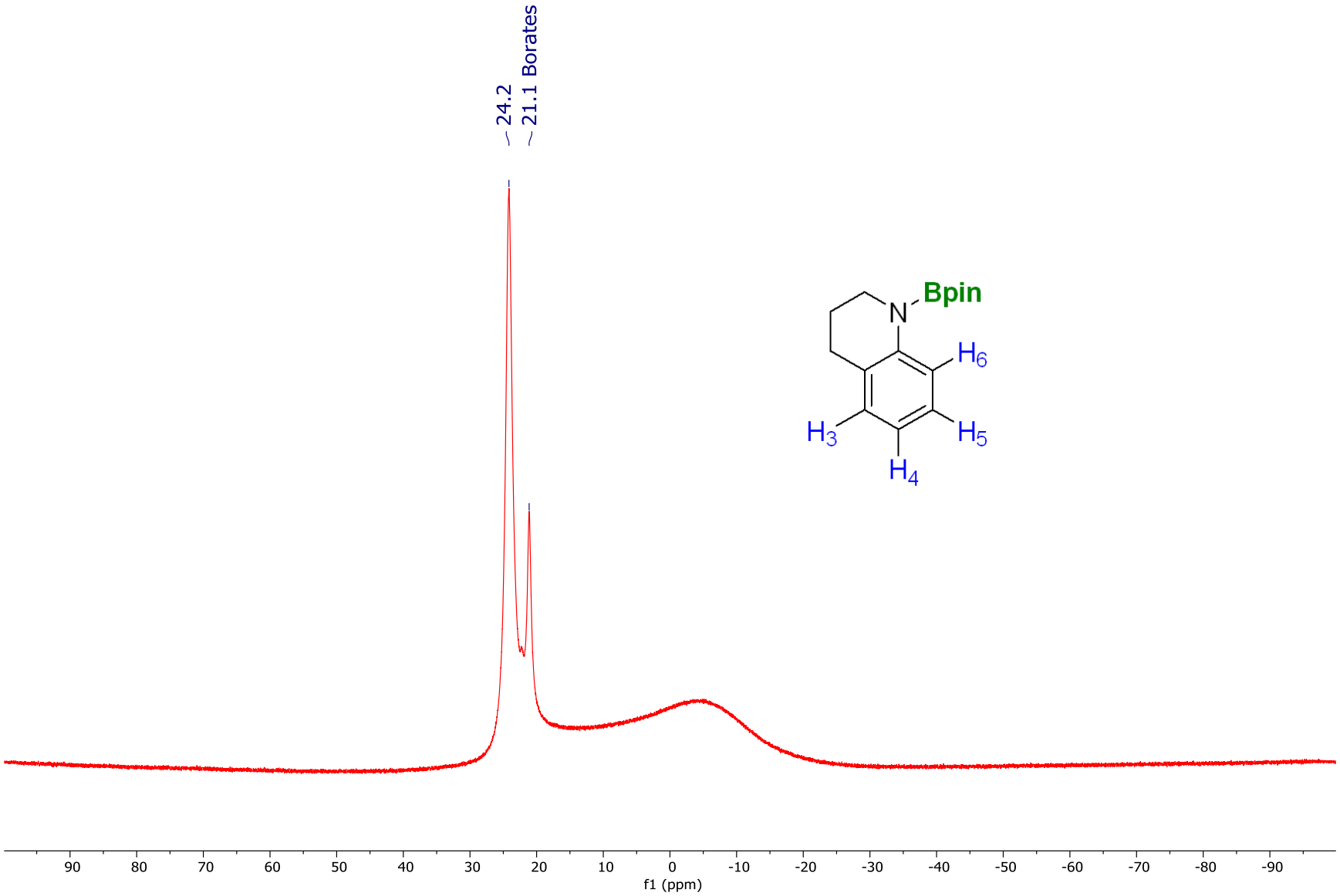

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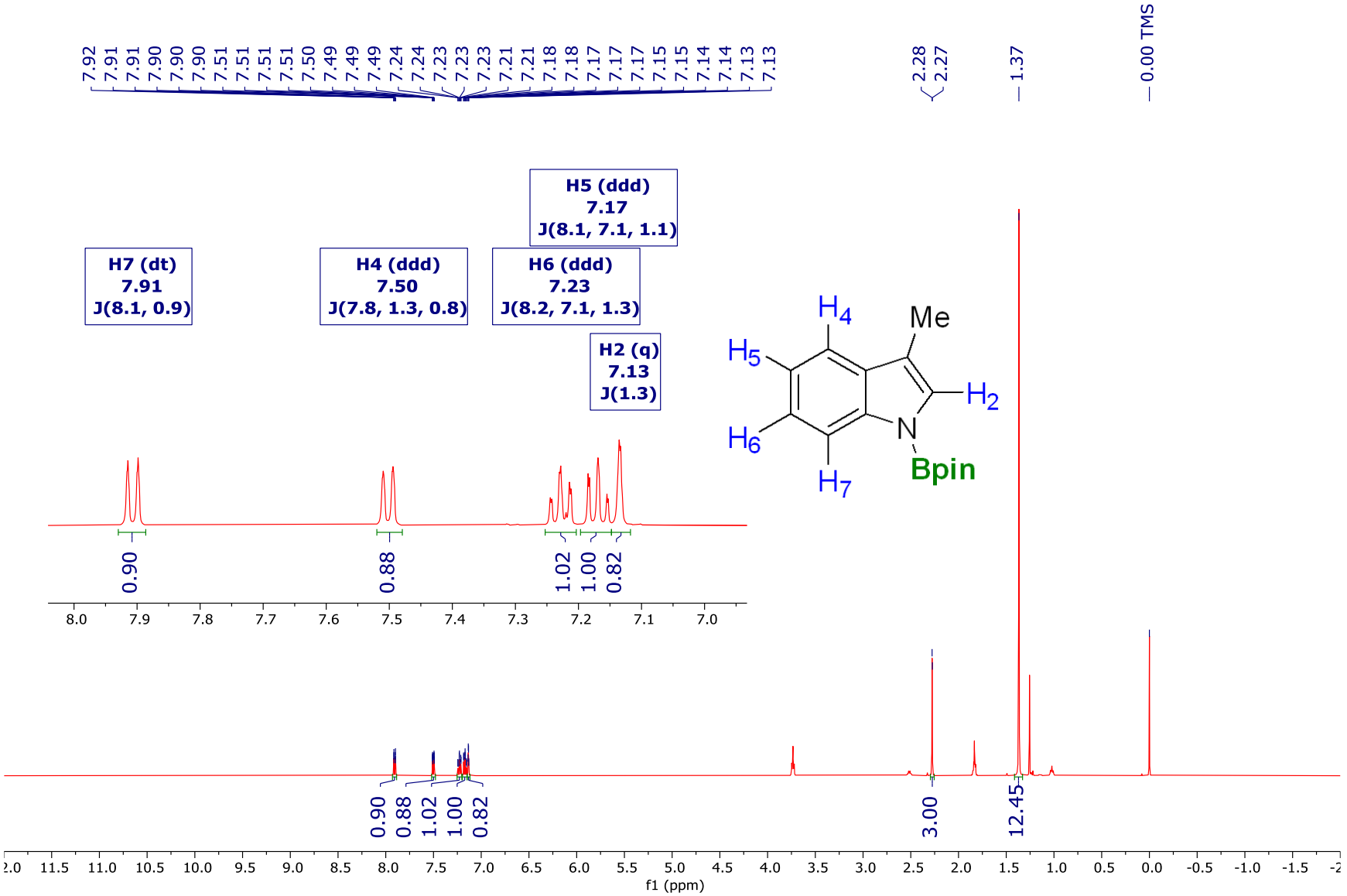
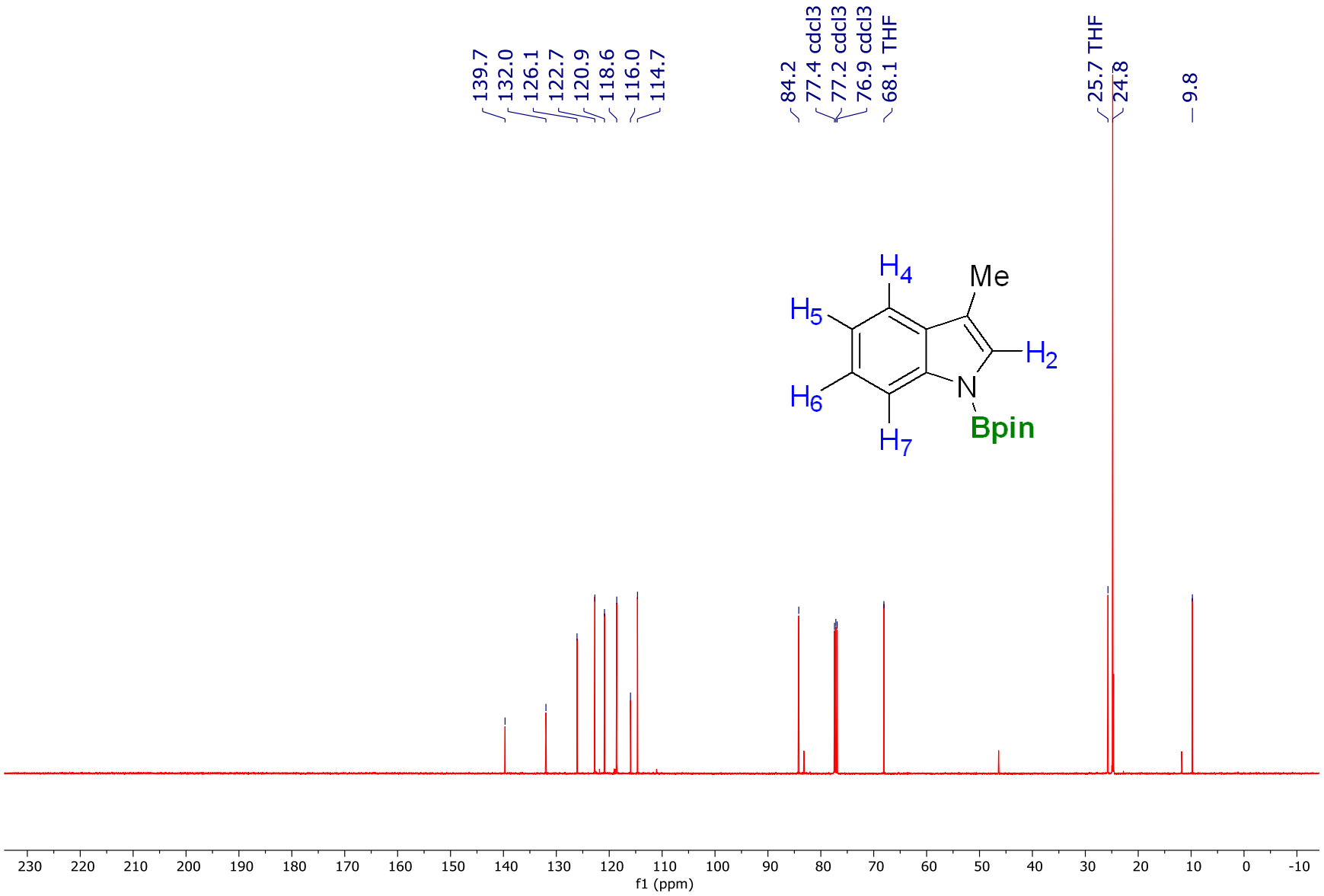
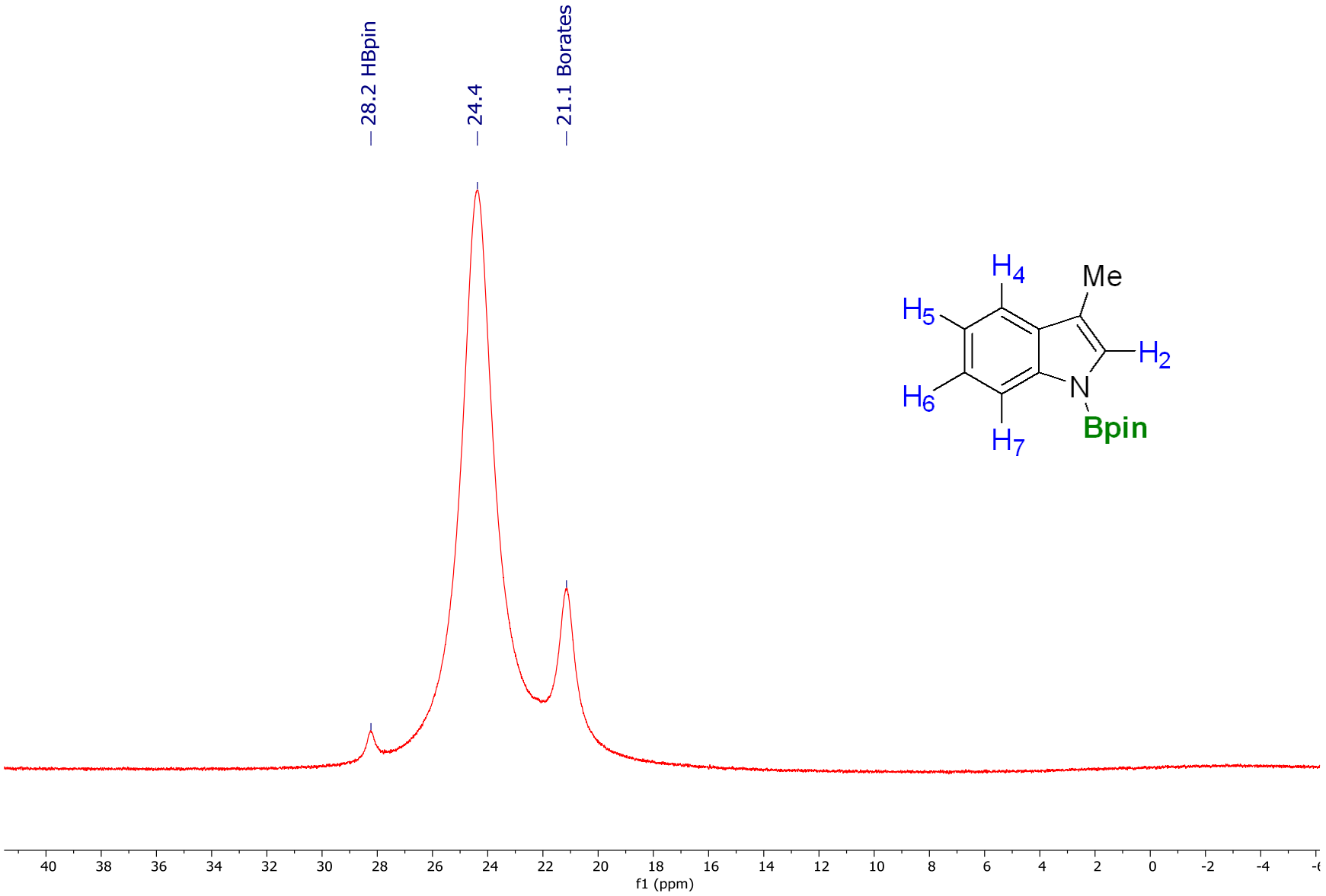


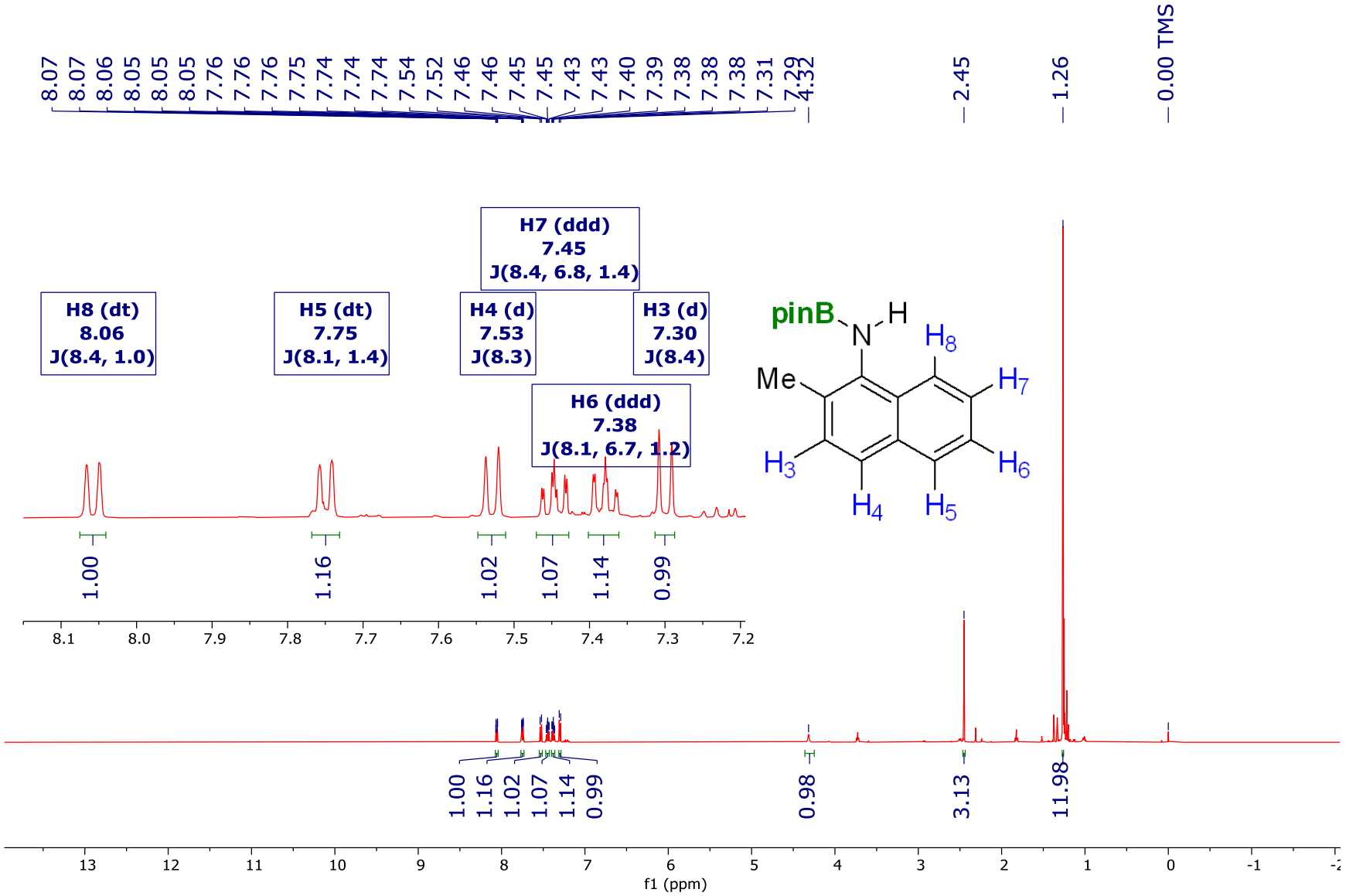
^{13}C NMR of N-Bpin borylated 3-methyl indole (4.5a') ($CDCl_3$, 126 MHz)



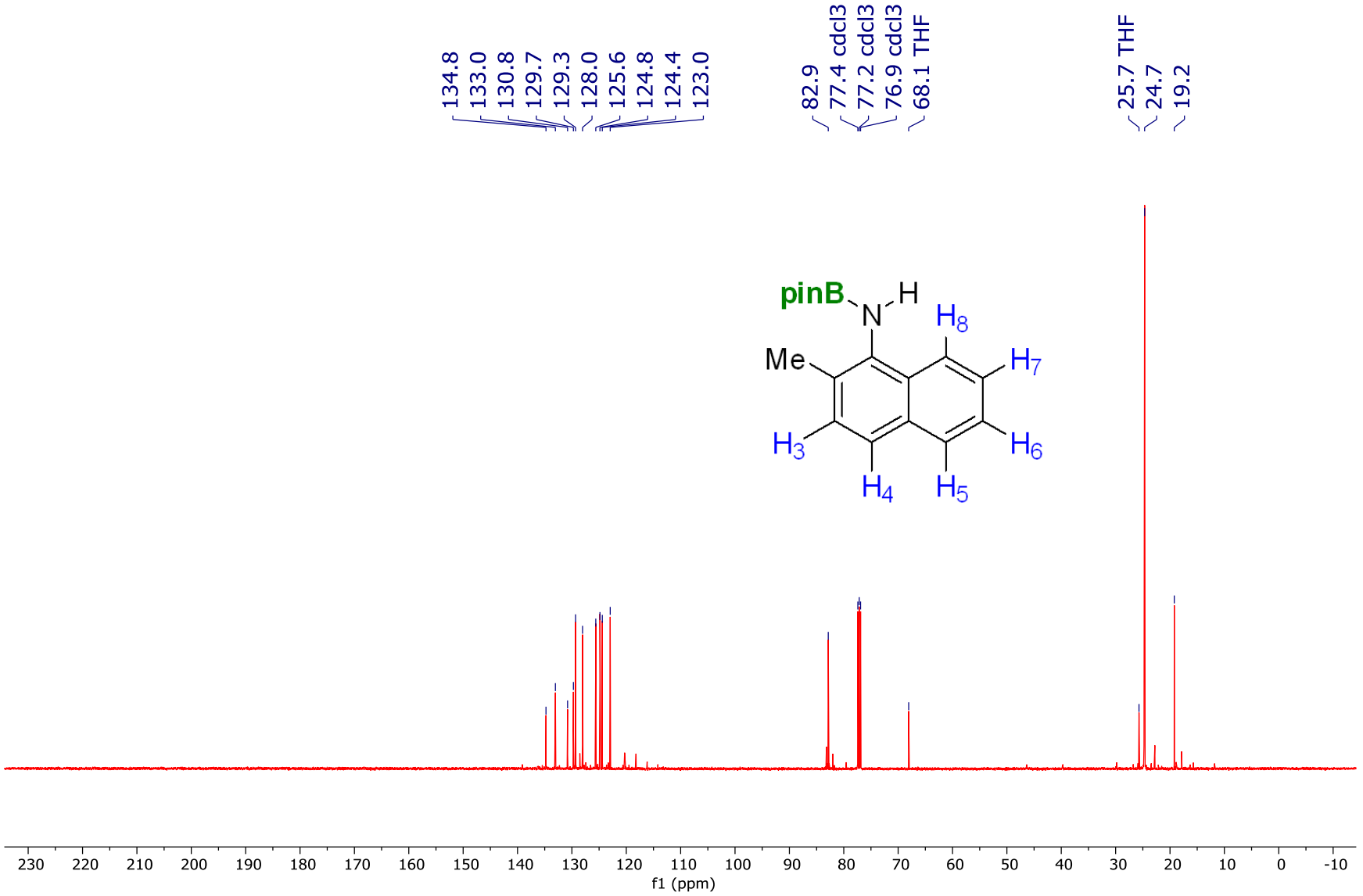
^{11}B NMR of N-Bpin borylated 3-methyl indole (4.5a') ($CDCl_3$, 160 MHz)



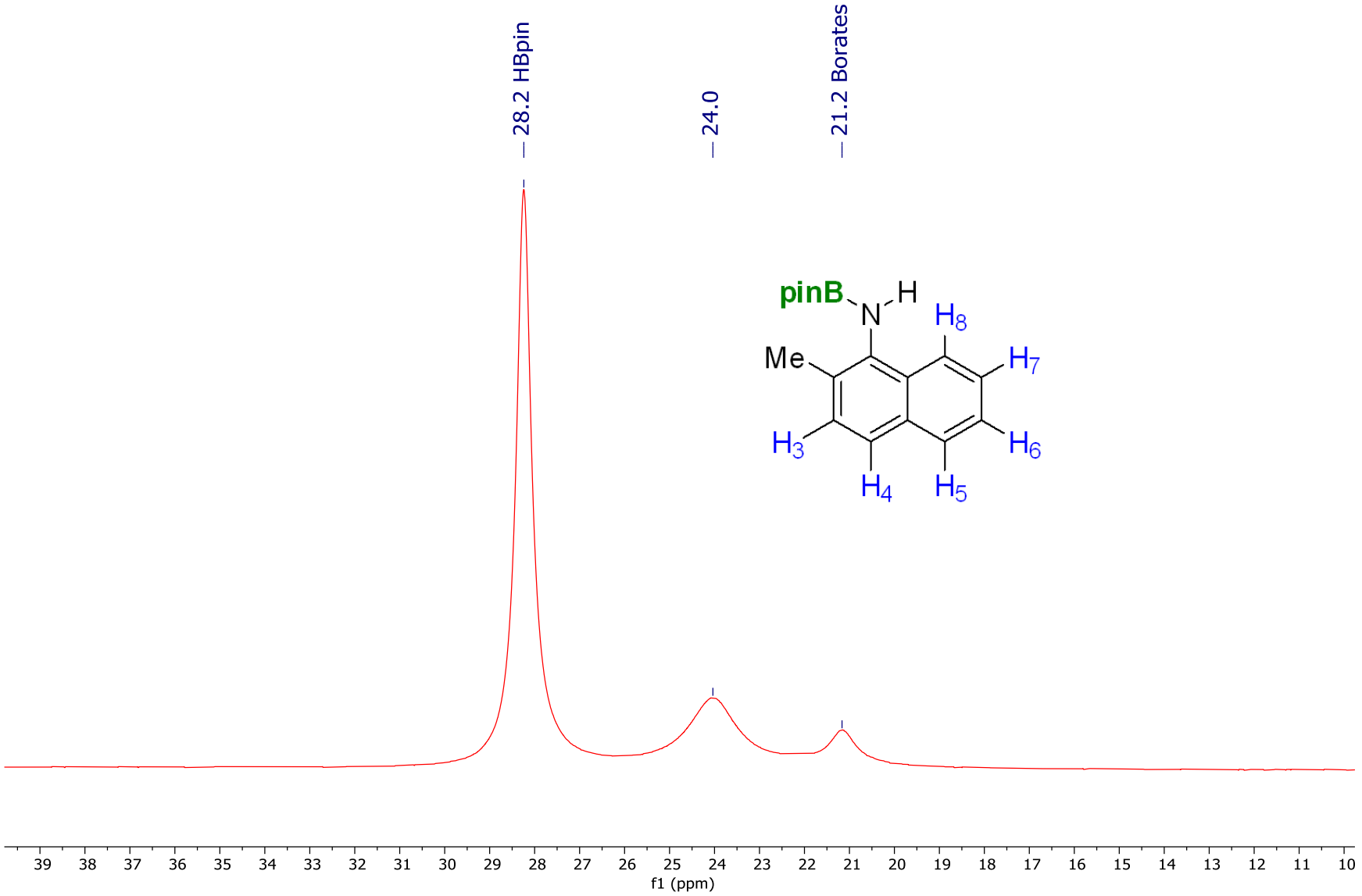
^{1}H NMR of N-Bpin borylated 1-amino-2-methylnaphthalene (4.1o') ($CDCl_3$, 500 MHz)



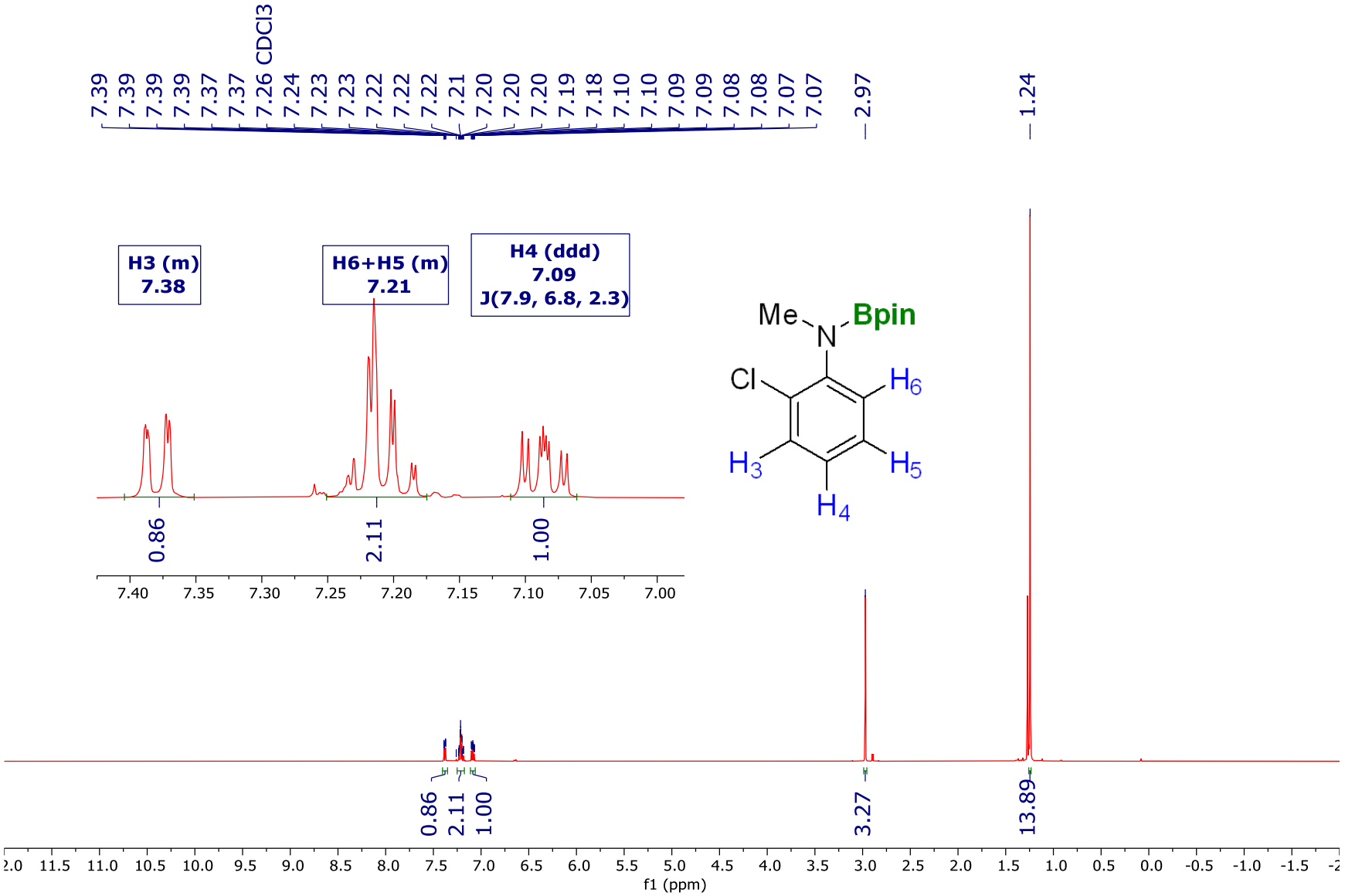
^{13}C NMR of N-Bpin borylated 1-amino-2-methylnaphthalen (4.1o') ($CDCl_3$, 126 MHz)



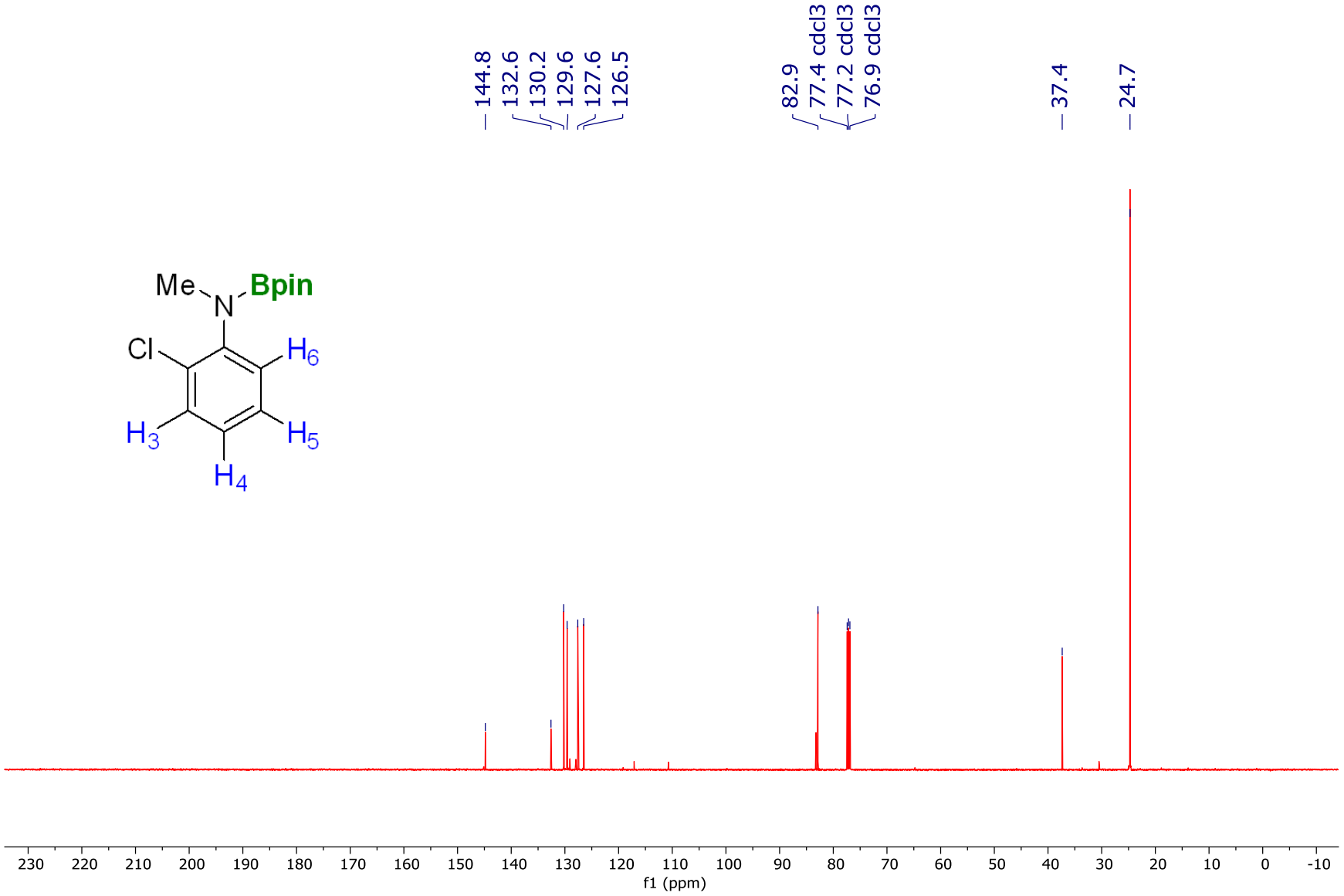
^{11}B NMR of N-Bpin borylated 1-amino-2-methylnaphthalen (4.1o') ($CDCl_3$, 160 MHz)



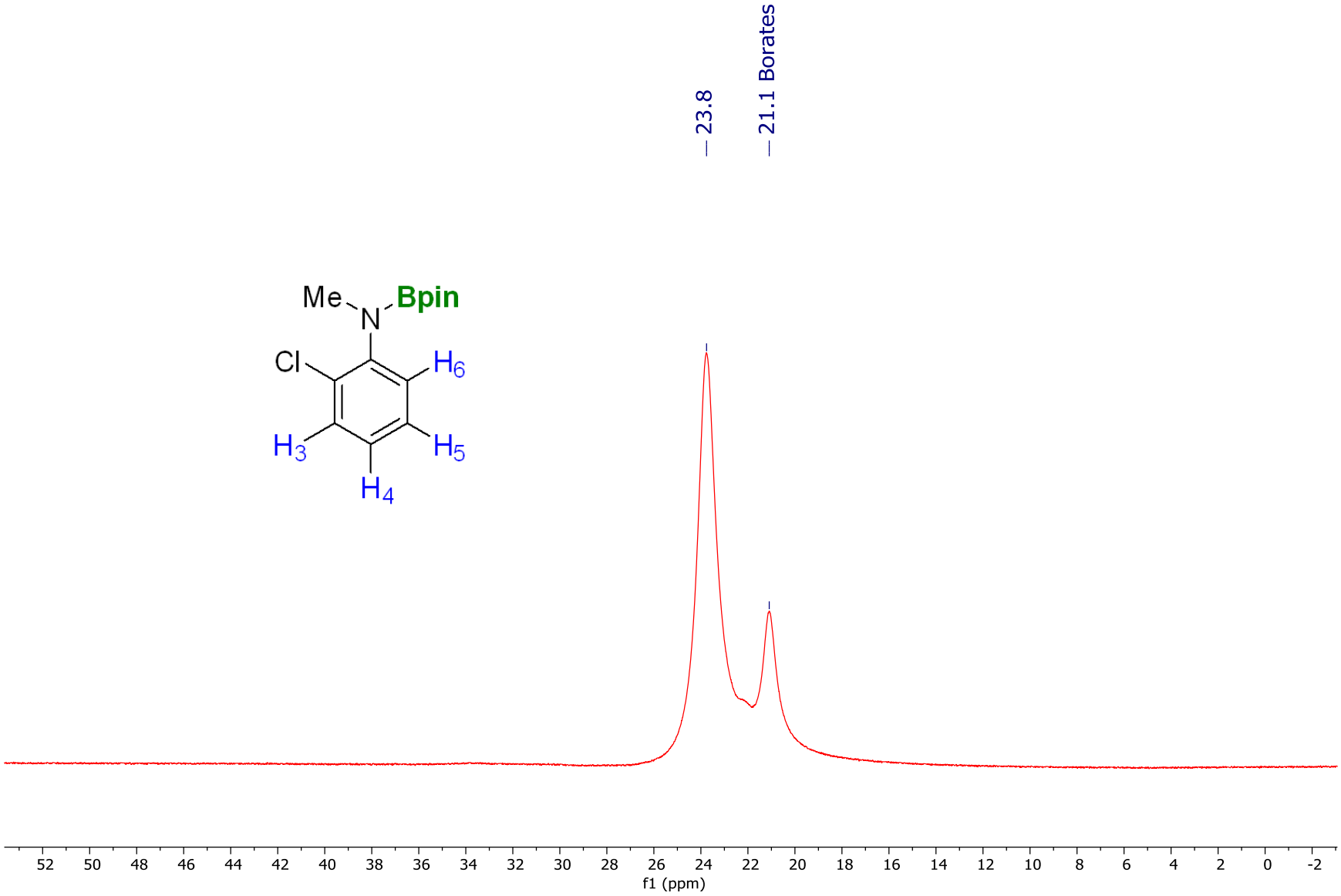
^{1}H NMR of N-Bpin borylated 2-chloro-N-methylaniline (4.3a') ($CDCl_3$, 500 MHz)



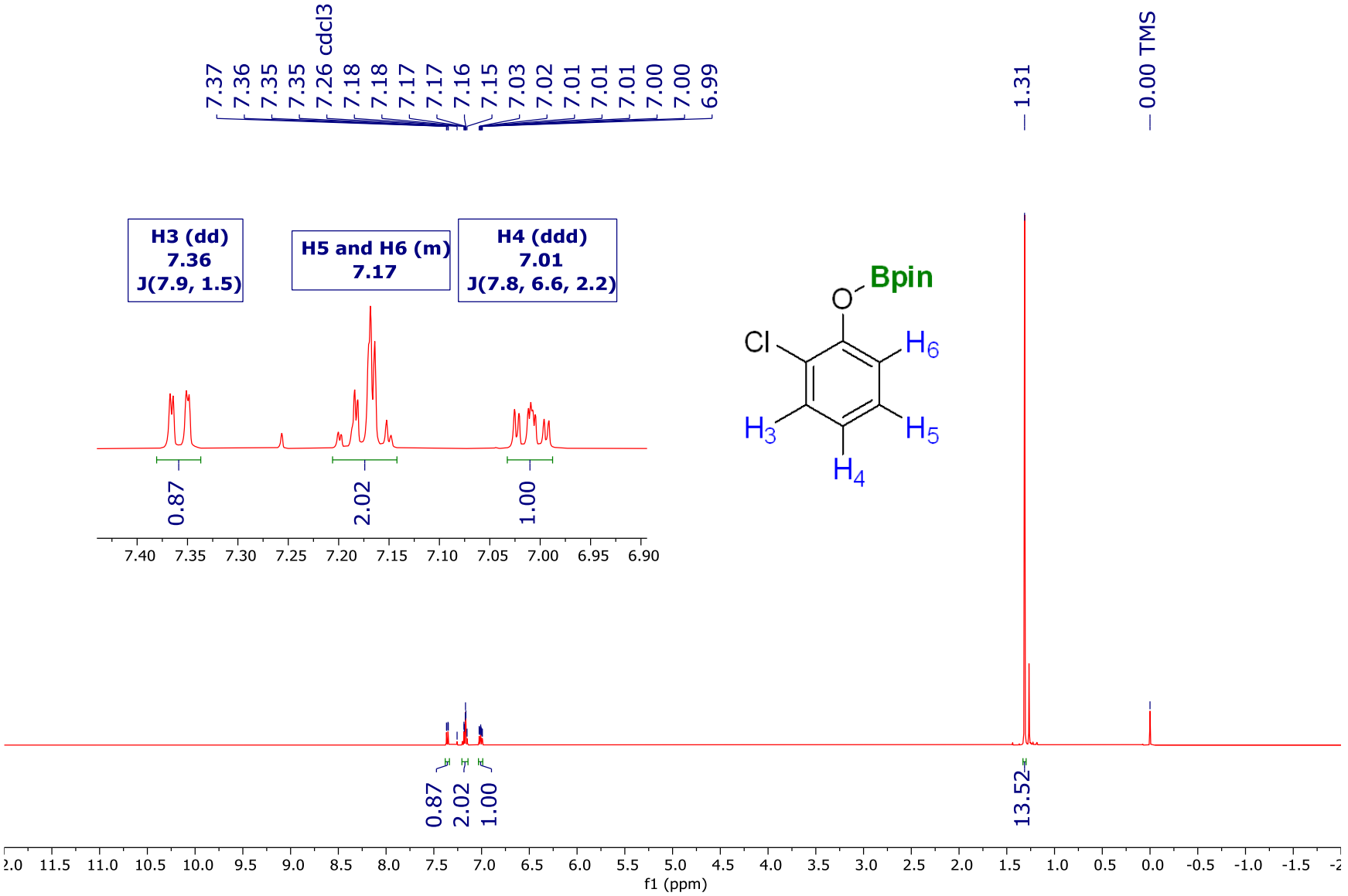
^{13}C NMR of N-Bpin borylated 2-chloro-N-methylaniline (4.3a') ($CDCl_3$, 126 MHz)



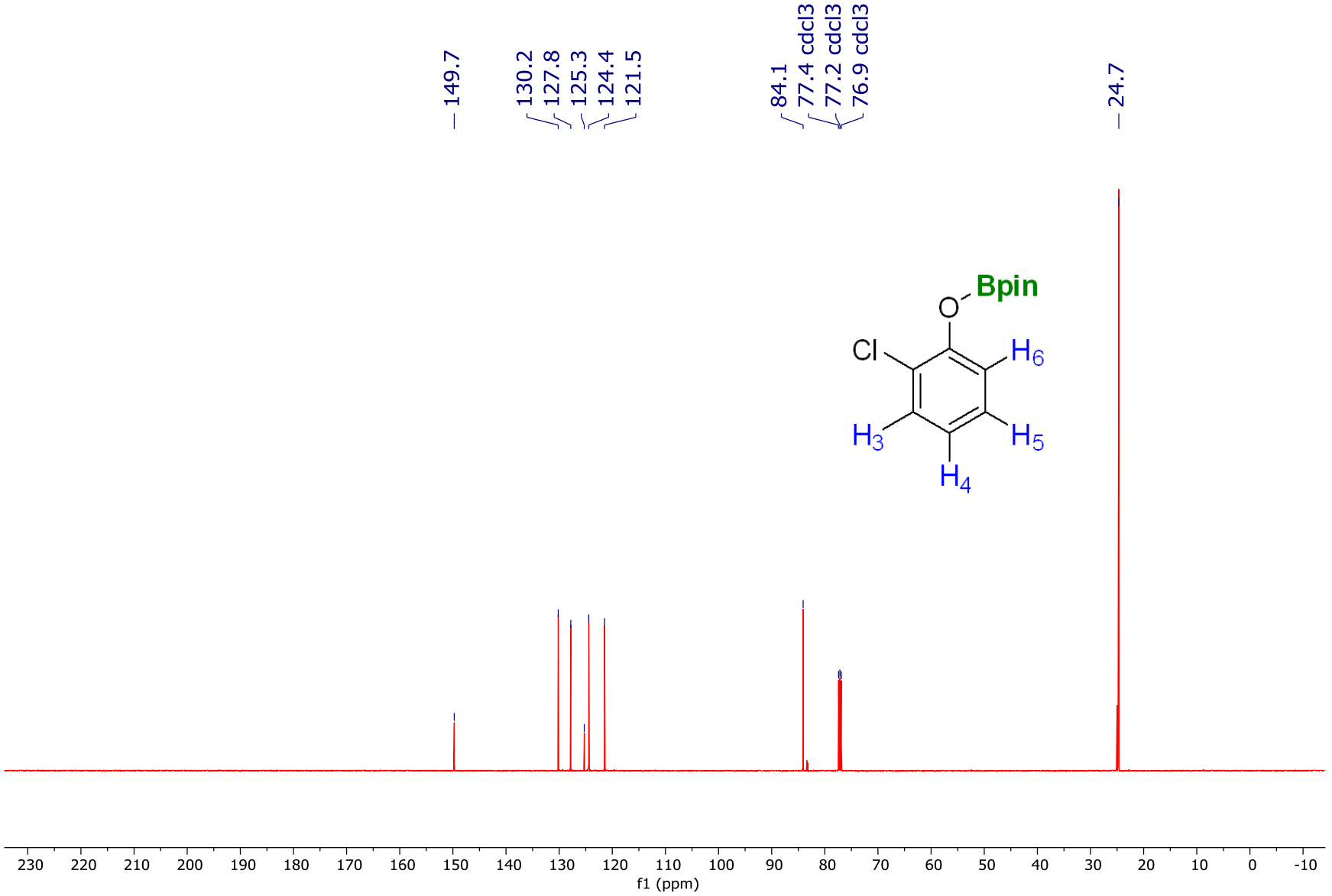
^{11}B NMR of N-Bpin borylated 2-chloro-N-methylaniline (4.3a') ($CDCl_3$, 160 MHz)



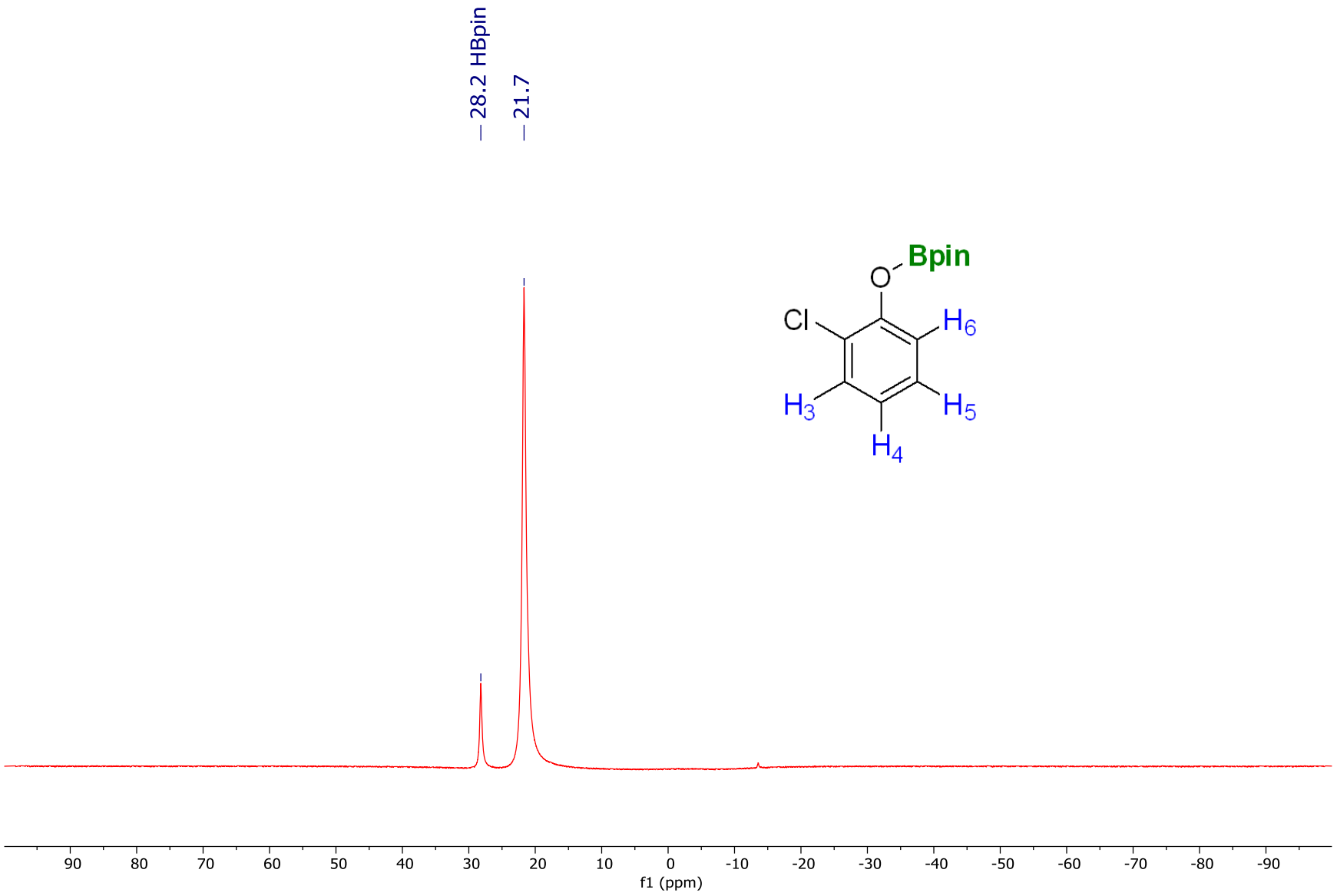
^{1}H NMR of O-Bpin borylated 2-chlorophenol (4.1p') ($CDCl_3$, 500 MHz)



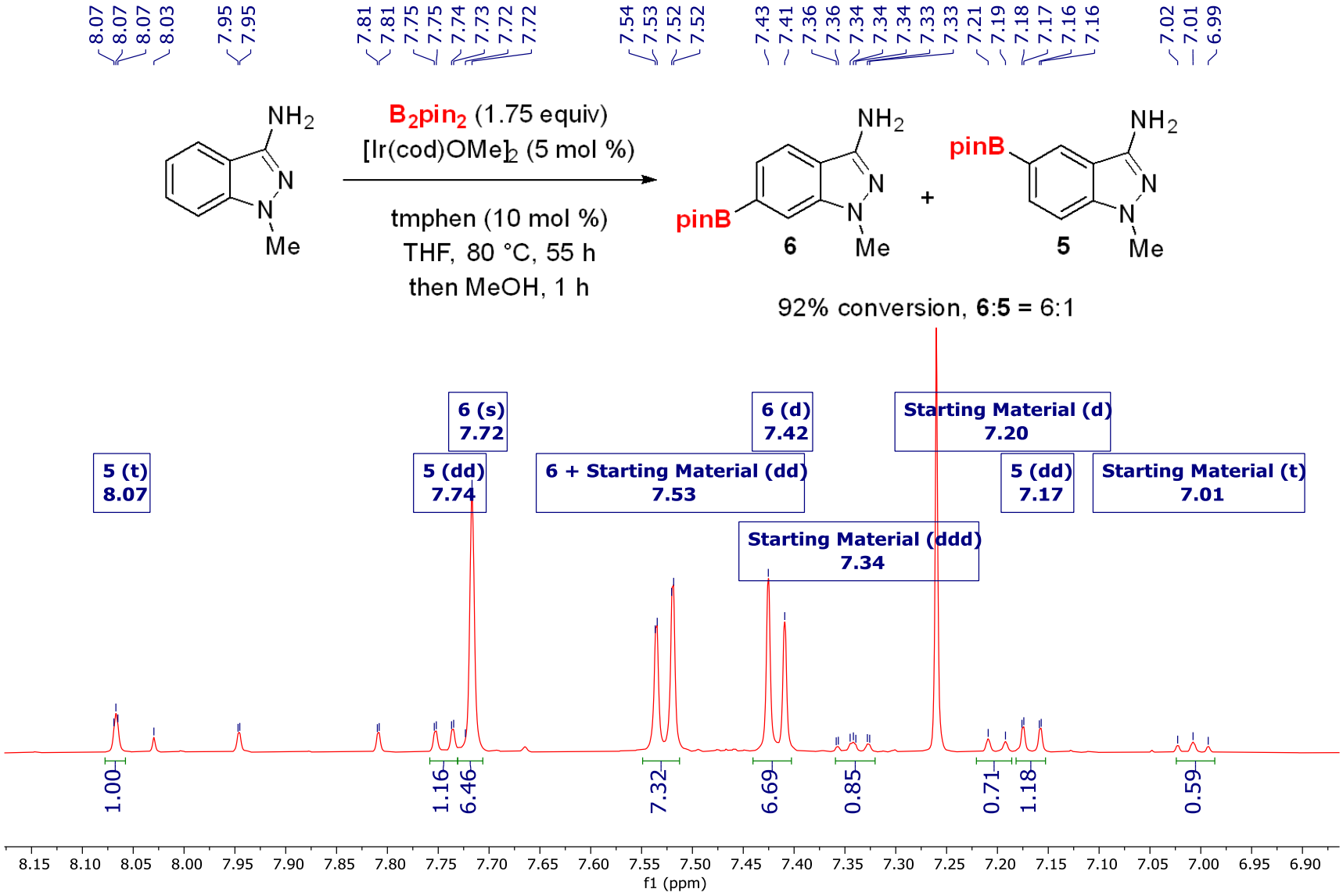
^{13}C NMR of O-Bpin borylated 2-chlorophenol (4.1p') ($CDCl_3$, 126 MHz)



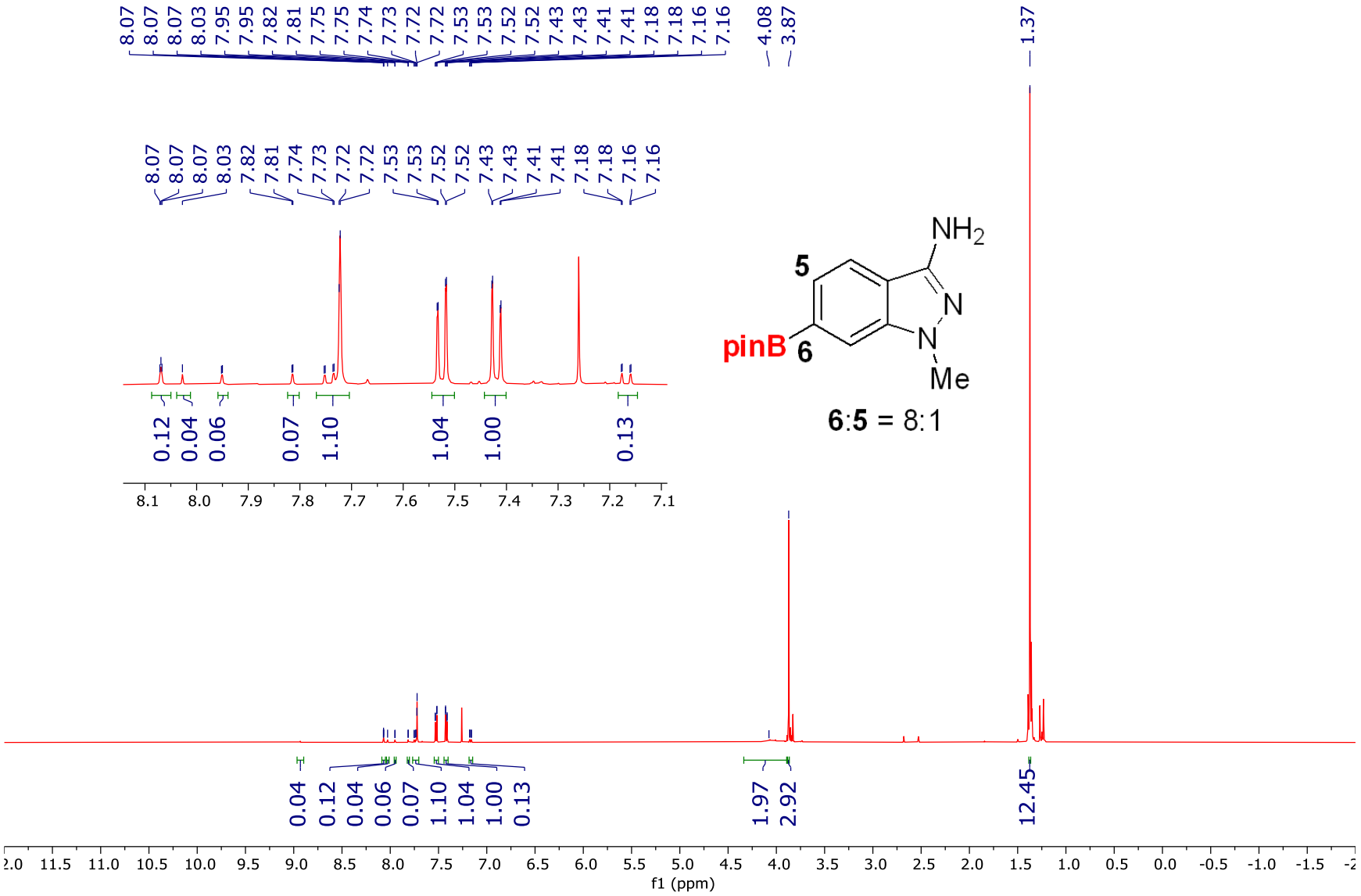
^{11}B NMR of O-Bpin borylated 2-chlorophenol (4.1p') ($CDCl_3$, 160 MHz)



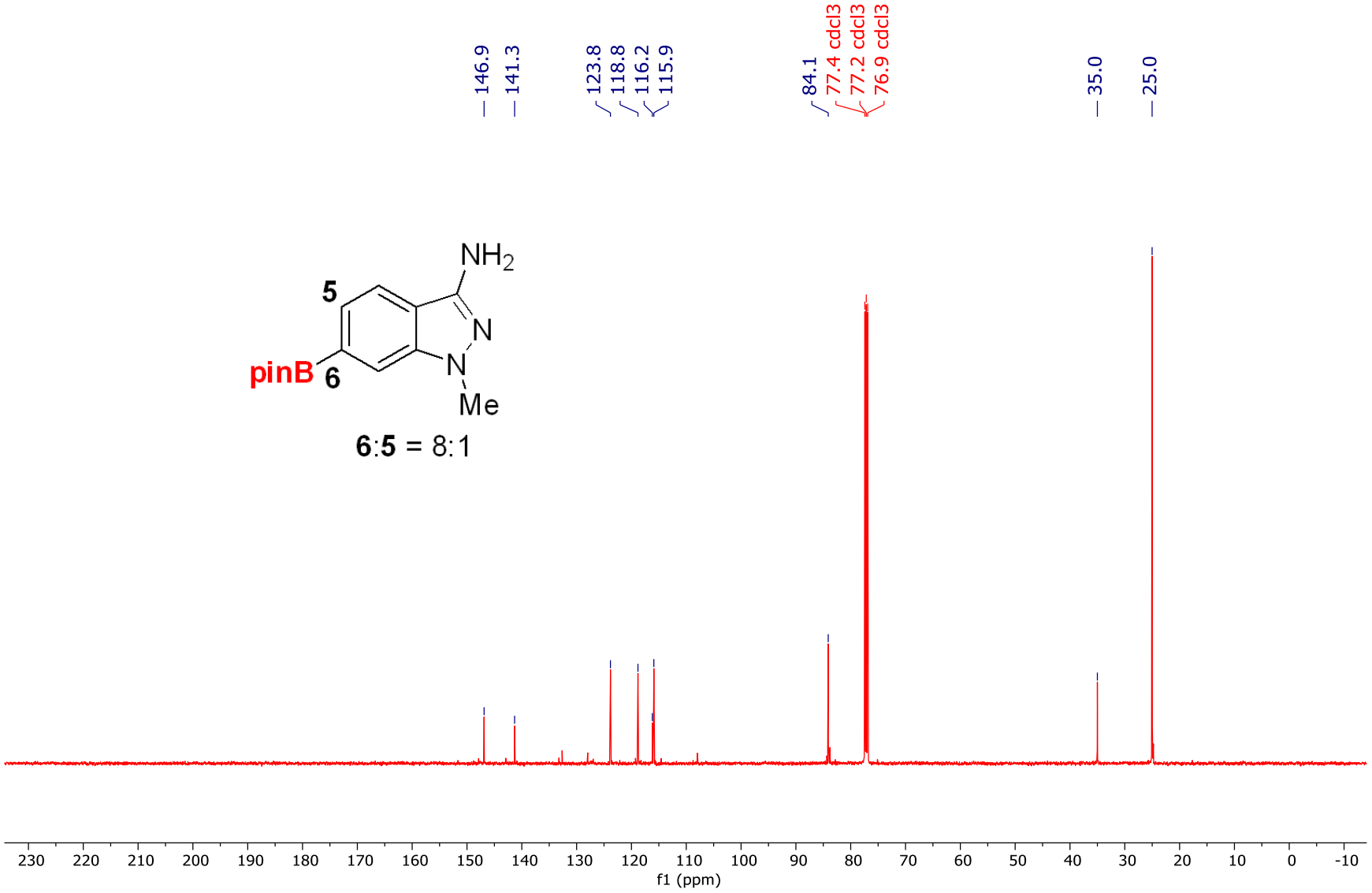
C6 CHB of 3-amino-N-methyl indazole (4.12) ($CDCl_3$, 500 MHz)



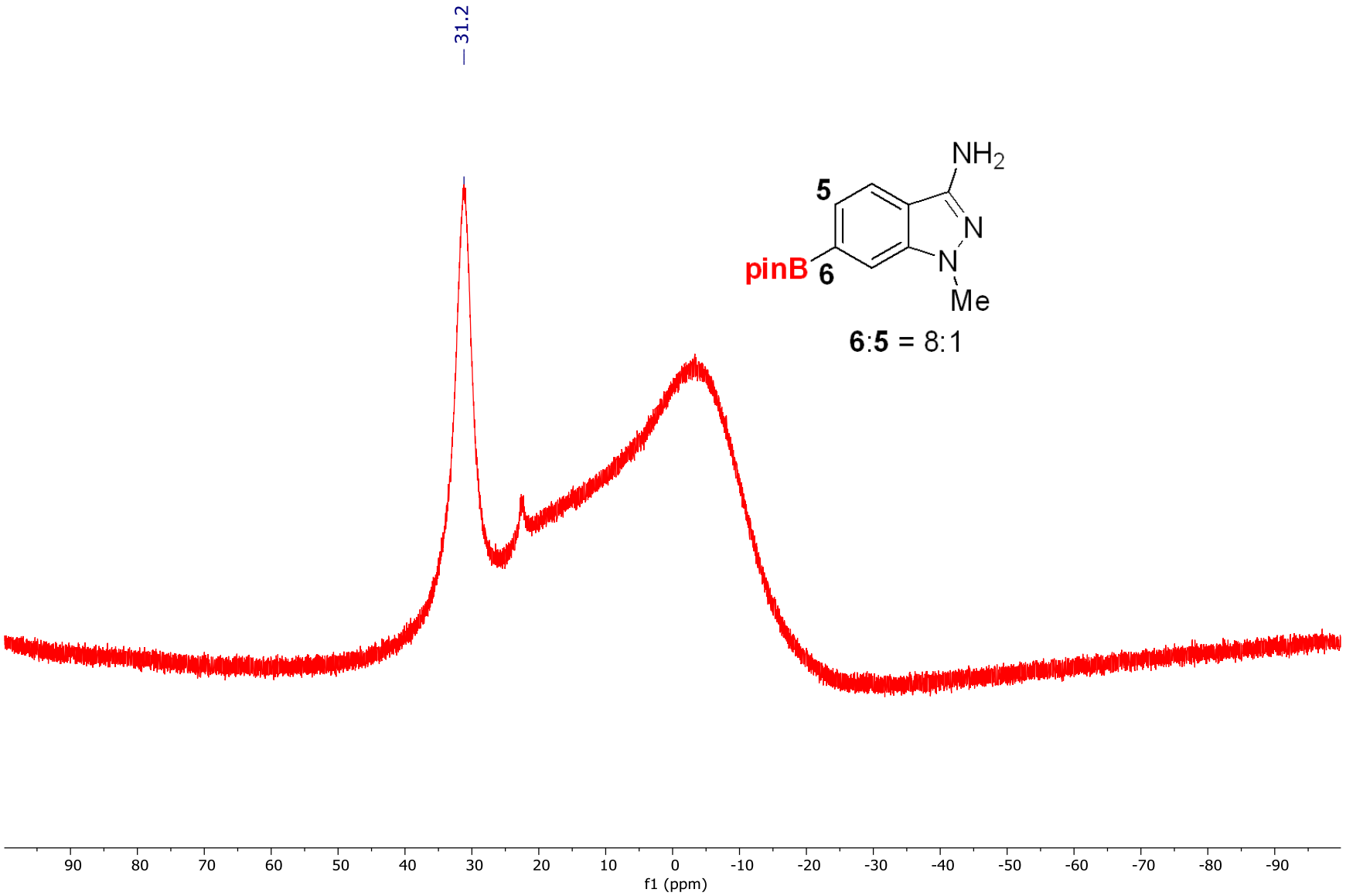
^{1}H NMR of C6-borylated 3-amino-N-methyl indazole (4.12) ($CDCl_3$, 500 MHz)



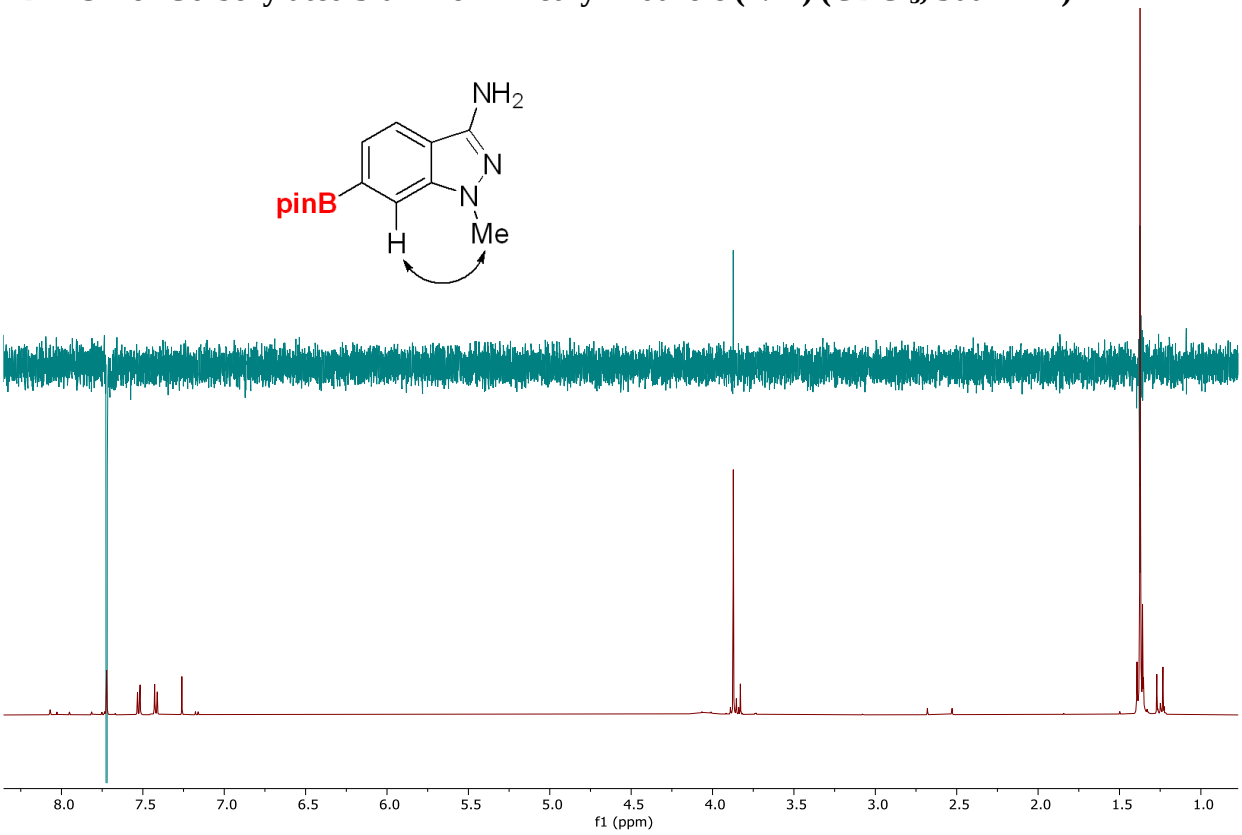
^{13}C NMR of C6-borylated 3-amino-N-methyl indazole (4.12) ($CDCl_3$, 126 MHz)

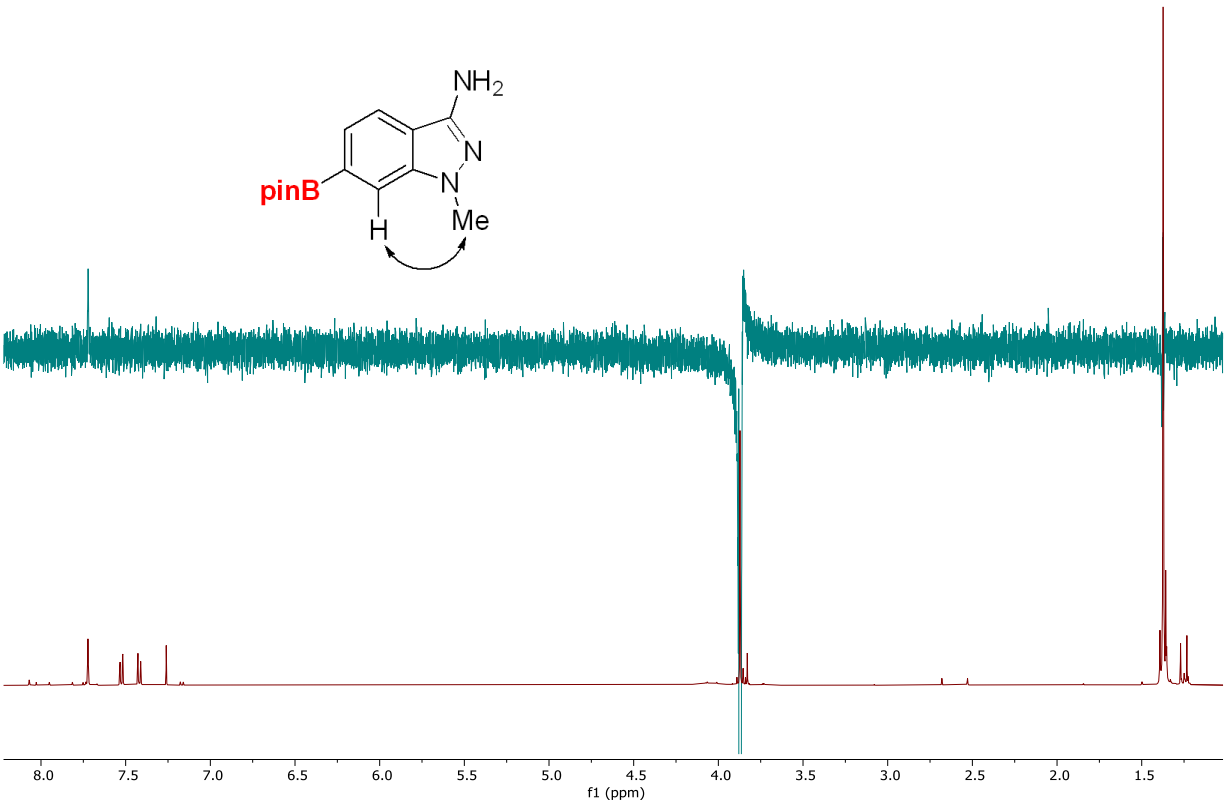


^{11}B NMR of C6-borylated 3-amino-N-methyl indazole (4.12) ($CDCl_3$, 160 MHz)

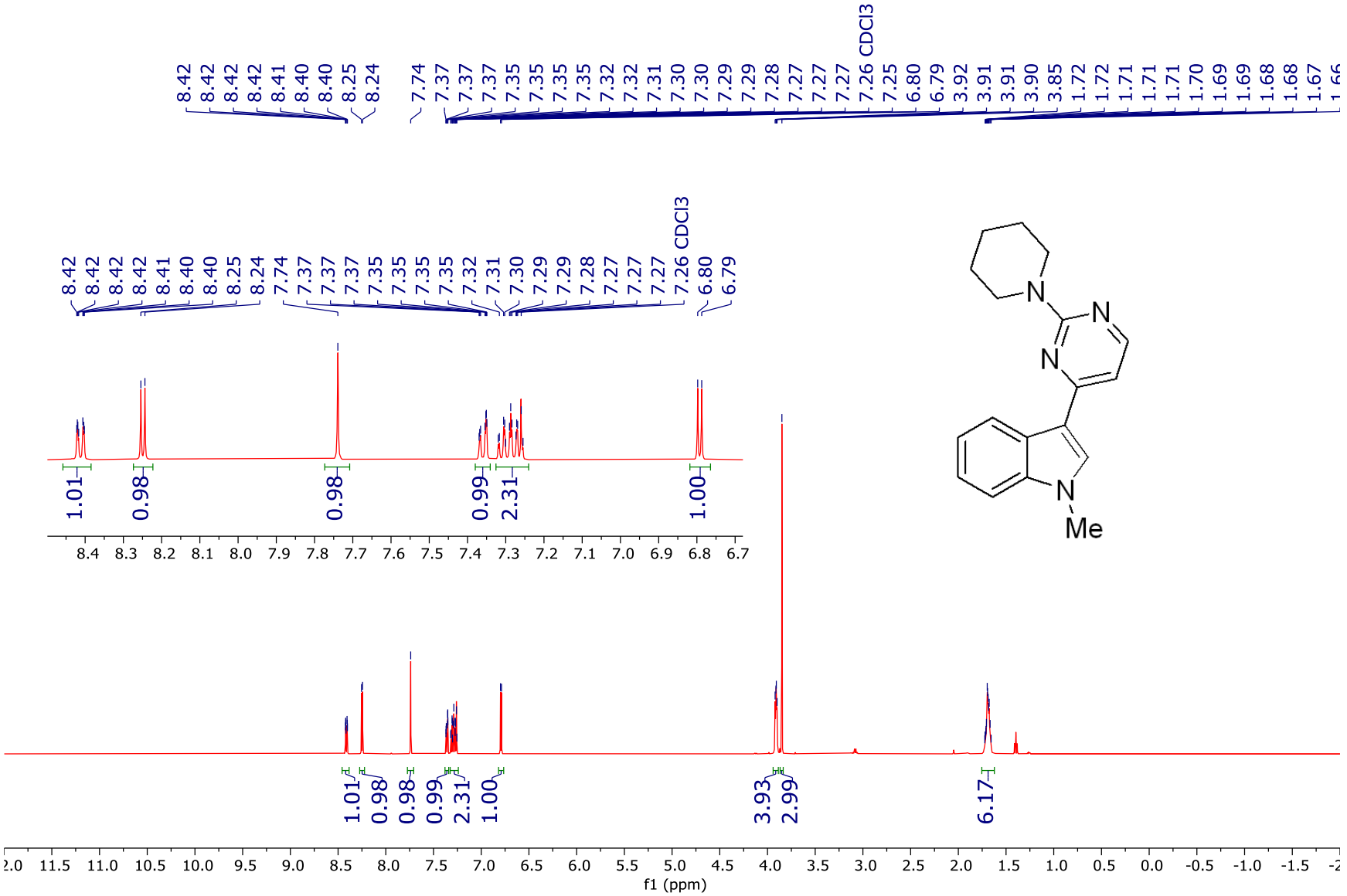


1D-NOE of C6-borylated 3-amino-N-methyl indazole (4.12) ($CDCl_3$, 500 MHz)

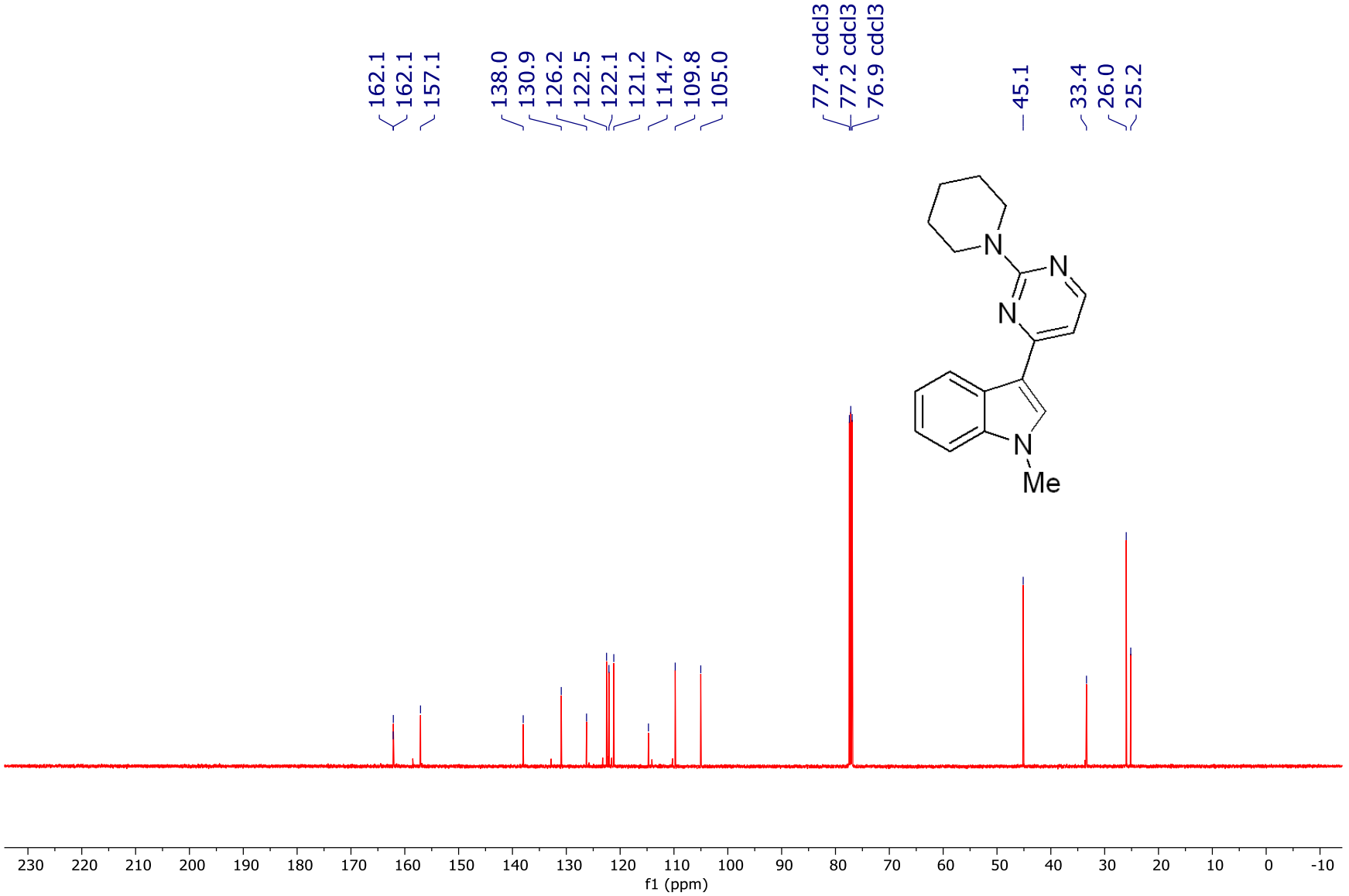




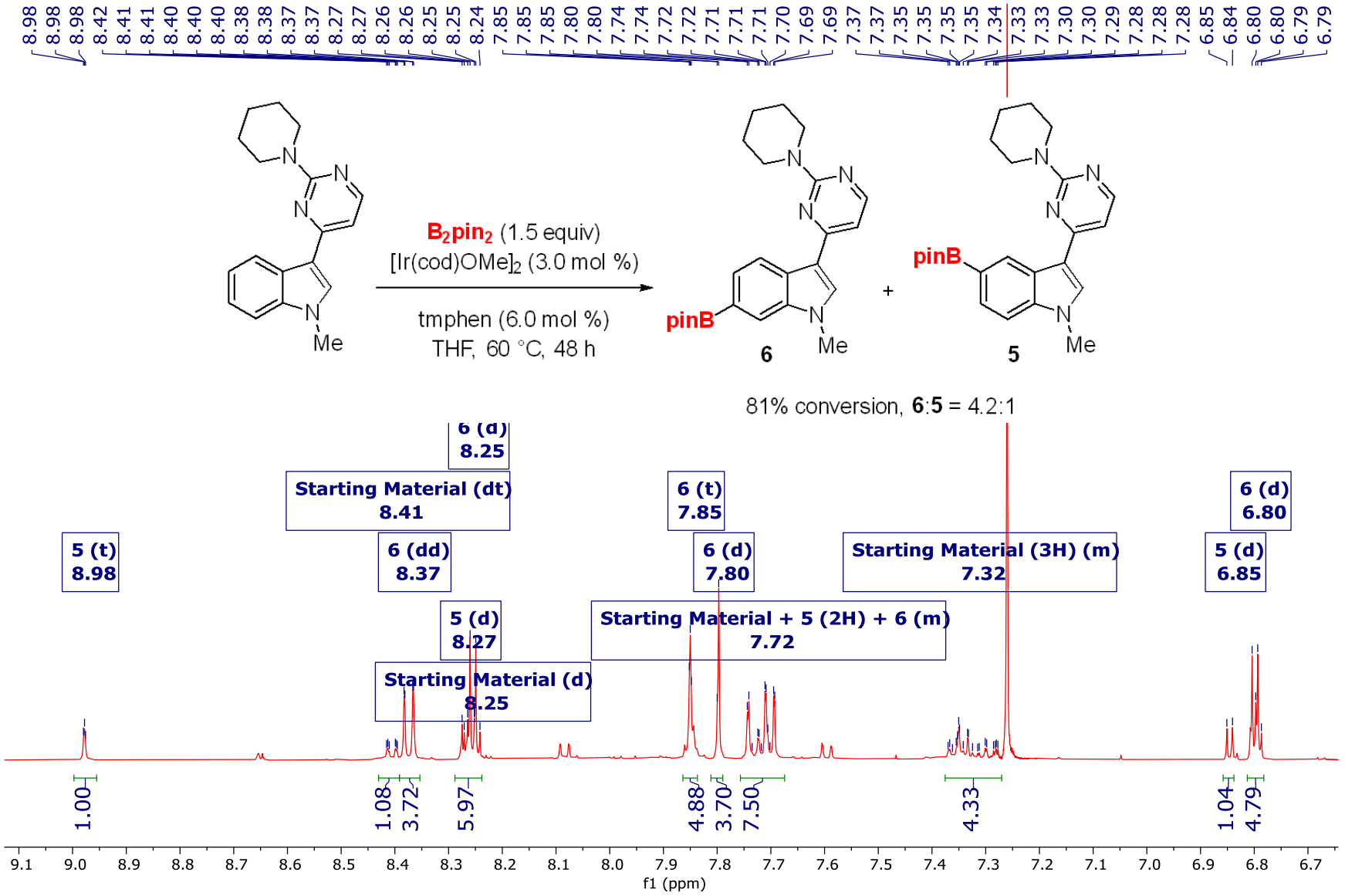
^{1}H NMR of Osimertinib's Analogue 4.13 ($CDCl_3$, 500 MHz)



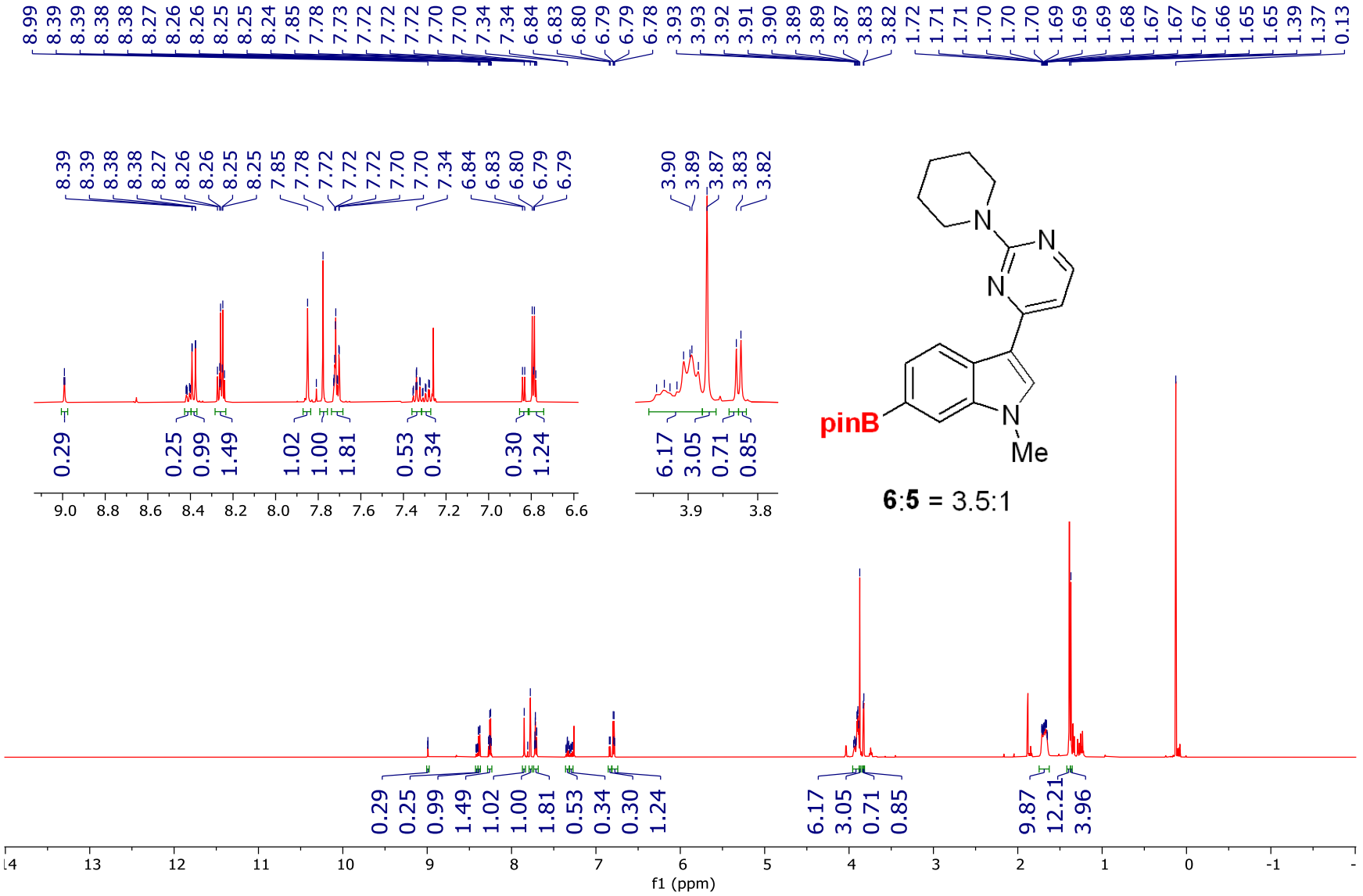
^{13}C NMR of Osimertinib's Analogue 4.13 ($CDCl_3$, 126 MHz)



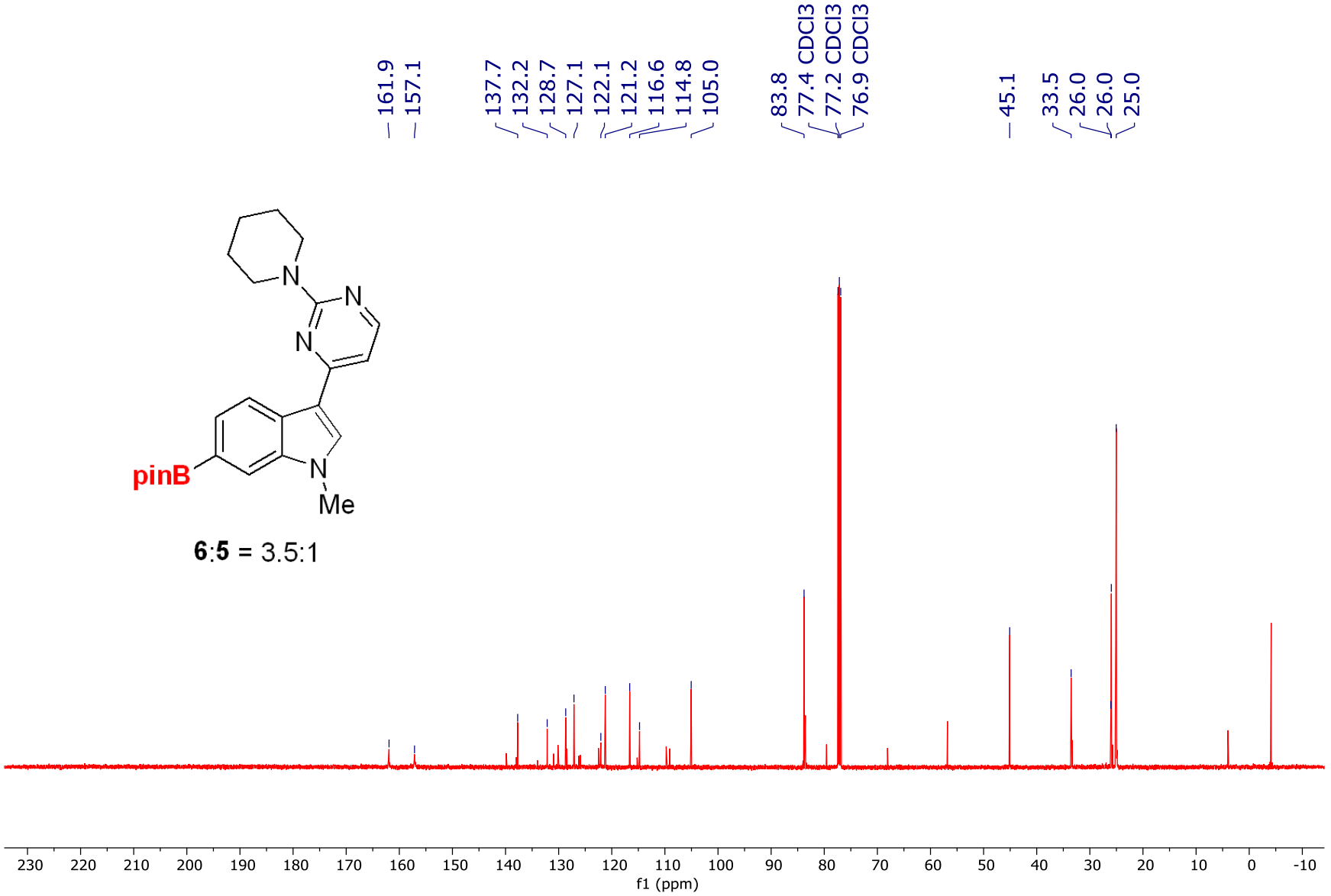
C6 CHB of Osimertinib's Analogue 4.14 ($CDCl_3$, 500 MHz)



^{1}H NMR of 6-borylated Osimertinib's Analogue 4.14 ($CDCl_3$, 500 MHz)



^{13}C NMR of 6-borylated Osimertinib's Analogue 4.14 ($CDCl_3$, 126 MHz)



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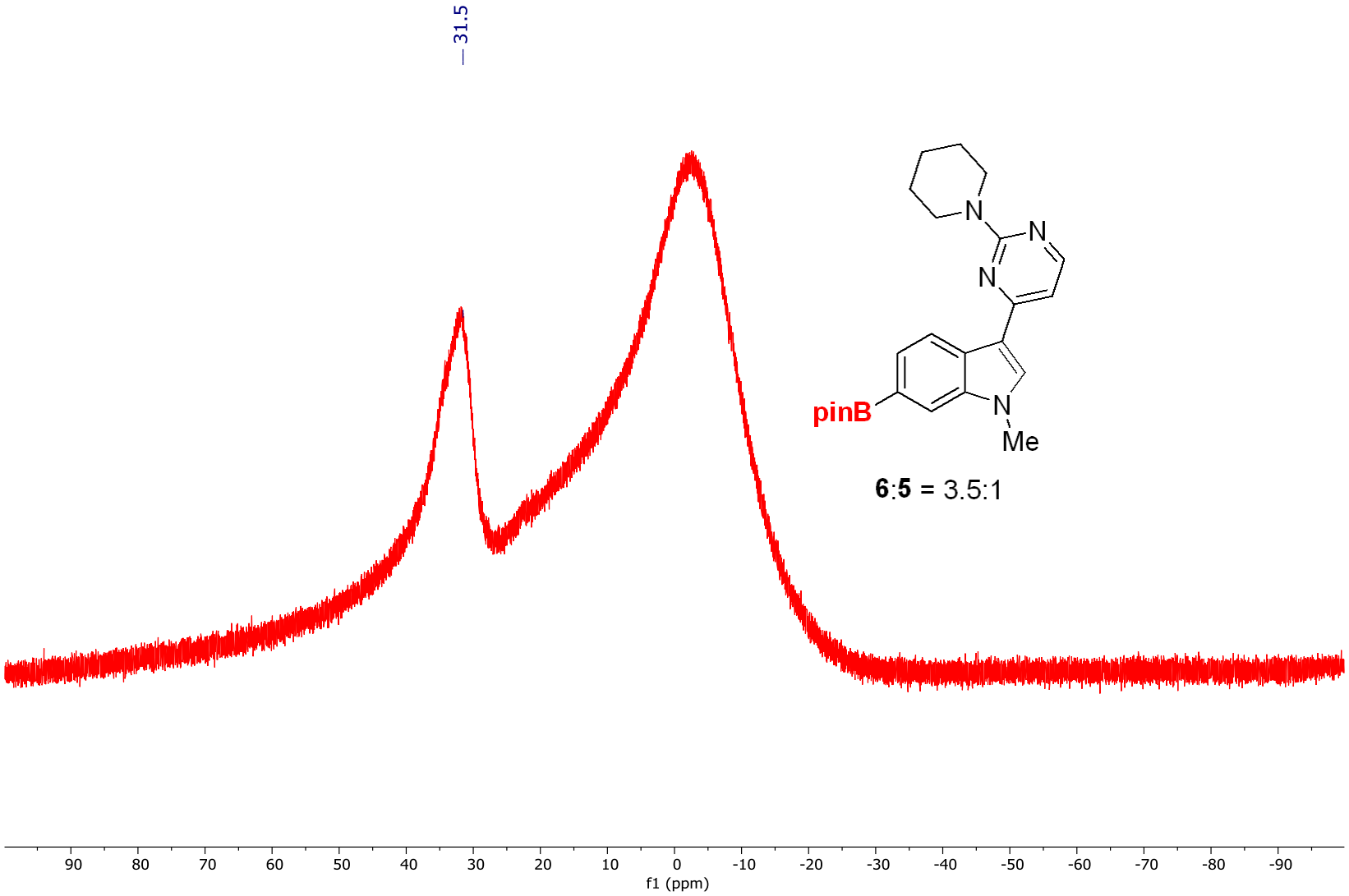

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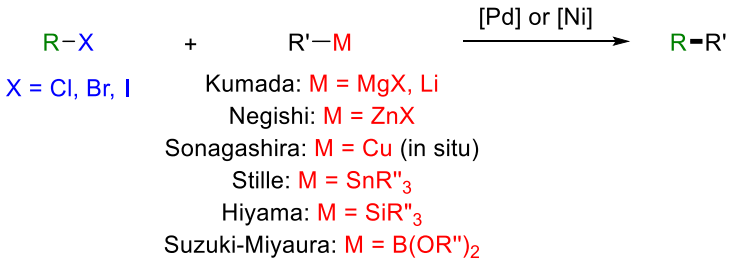
CHAPTER 5.

STUDY OF REACTIVITY OF ARYL IMIDAZOLYLSULFONATES IN SUZUKI-MIYAURA CROSS-COUPLING REACTIONS

5.1. Introduction

The 2010 Nobel Prize in Chemistry was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their contributions to cross-coupling reactions in organic synthesis.[1] Cross-coupling is a useful method for the creation of carbon-carbon bonds from an electrophile, usually a halide, and an organometallic compound that acts as nucleophile via palladium or nickel catalysis (**Scheme 5.1**). Kumada reported the first cross-coupling reaction using Grignard reagents. Several efforts have been made since then to expand the reactant scope. Negishi, Sonagashira, Stille and Hiyama demonstrated that organozinc, organocuprate, organotin and organosilicon compounds, respectively, can be used in cross-coupling reactions as well.[2]

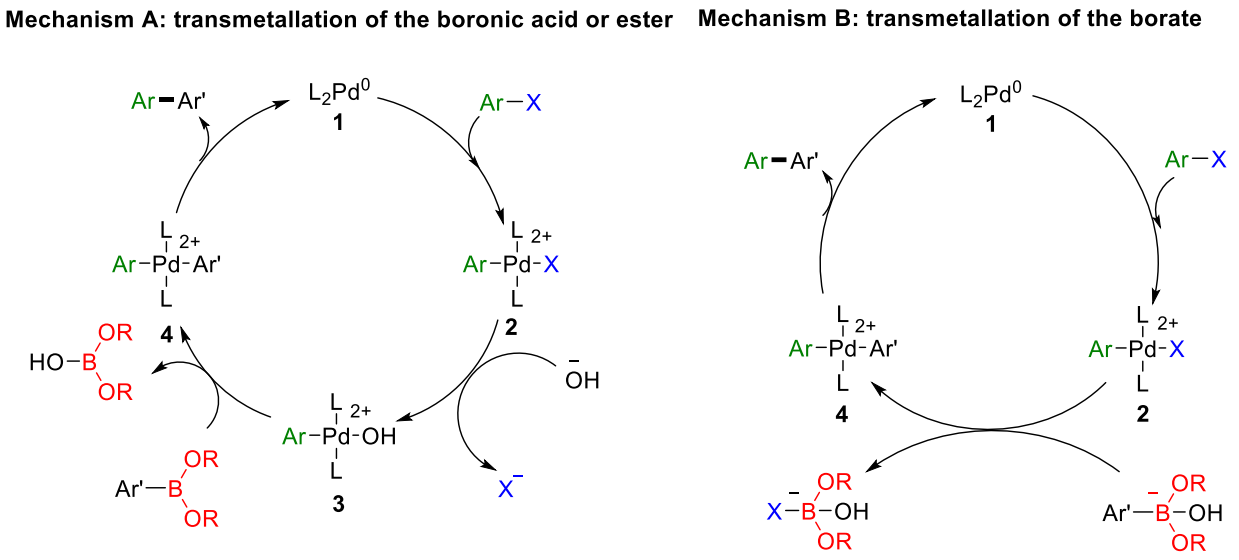
Scheme 5.1: Types of cross-coupling reactions with different nucleophiles



In 1979, Suzuki and Miyaura reported the use of boronic acids and esters as nucleophiles in cross-coupling reactions. Nowadays, Suzuki-Miyaura cross-coupling (SMC) has become by far the most useful cross-coupling method in industry due to the availability and stability of boronic partners. This is reflected on the number of scientific publications and patents that use SMC.[3] SMC requires the presence of base and two mechanisms are postulated according to the role of the base (**Scheme 5.2**).[4–14] Both mechanisms have the same main steps: oxidative addition (**1→2**),

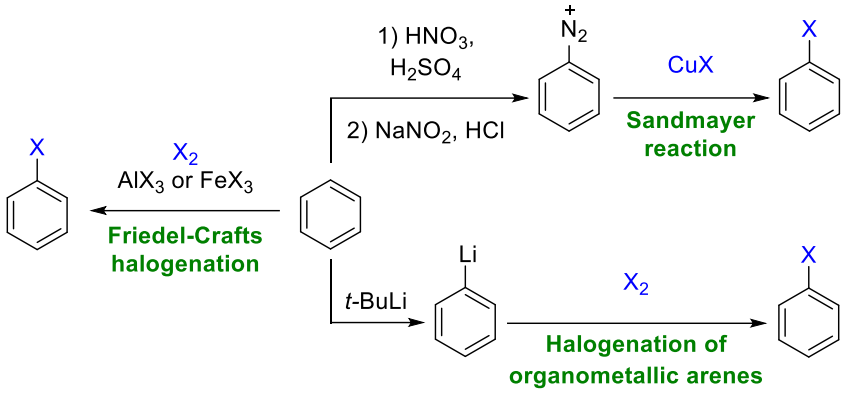
transmetallation (**2→4**), and reductive elimination (**4→1**); the difference is in how the base promote the transmetallation step. In **mechanism A**, the base reacts with **2** to make a hydroxo palladium **3**, which can transmetallate with the boronic acid or ester. In **mechanism B**, the base reacts with the boronic acid or ester to produce the borate, which transmetallates with **2**. Experimental data of Pd-catalyzed SMC of aryl boronic acids supports **mechanism A** due to the poor reactivity of the borate in the transmetallation step. Nonetheless, **mechanism B** cannot be discarded especially with boronic esters or under nickel catalysis.

Scheme 5.2: Possible mechanisms for SMC



There are some concerns over the use of halides as electrophilic partners in SMC. Aryl halides need to be synthesized previously via Friedel-Craft electrophilic halogenation, Sandmeyer type reactions or halogenation of organometallic arenes starting from available aromatic compounds (**Scheme 5.3**).[15–17] Low functional group tolerance, poor regioselectivity and overhalogenation related to these methods limit the access to aryl halides. Furthermore, production of metal halogenated salts as byproduct in the synthesis of aryl halides, as well as in the cross-coupling reactions, can cause serious health and environmental problems.[18,19]

Scheme 5.3: Traditional methods for the synthesis of aryl halides



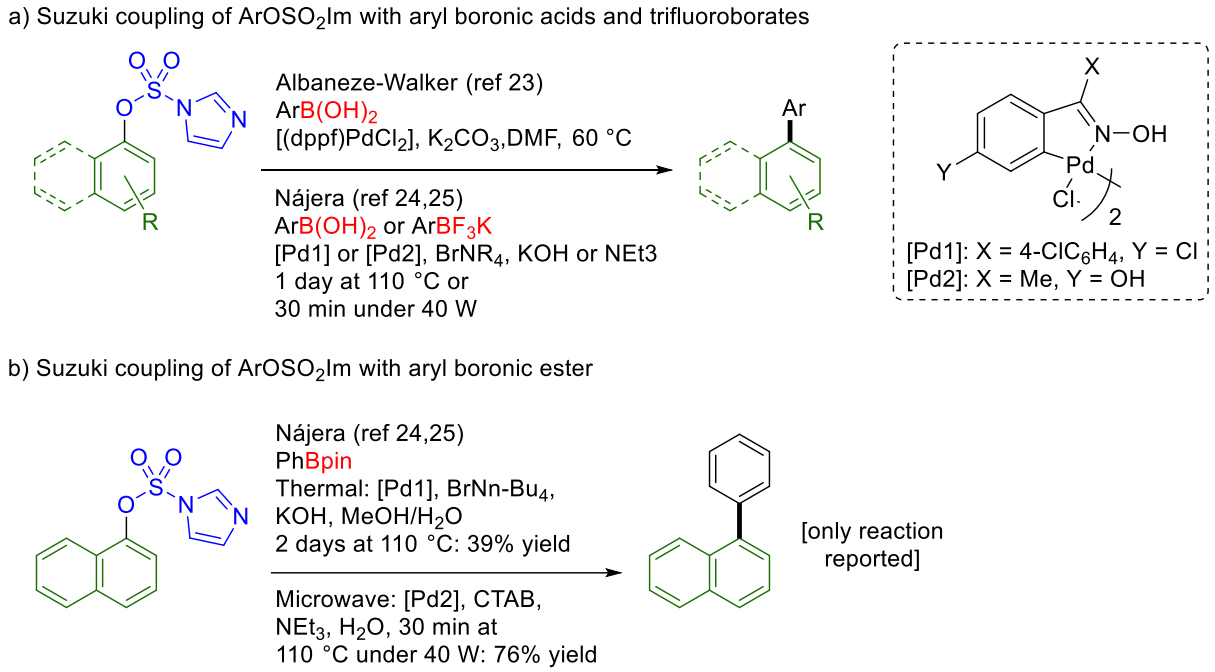
These issues have spurred the search for alternative electrophiles. Among the common alternatives, electrophiles based on phenol are good candidates because they can be produced from the coal-based industry or as derivatives of lignin, giving access to them at low cost. Triflates were the first alternative tested due to their comparable reactivity with halides, but low stability led to search for other options.[20] Tosylates and mesylates are more stable than triflates. However, tosylates and mesylates offer much less reactivity than triflates and these three types of sulfonates degrade to potentially genotoxic byproducts.[21,22]

In 2009, Albeneze-Walker reported the use of aryl imidazolylsulfonates as a new electrophile for SMC (**Scheme 5.4a**).[23] Imidazolylsulfonates are degraded in water to produce imidazole and sulfuric acid, instead of the potentially genotoxic products produced by other aryl or alkyl sulfonates. Furthermore, the study showed that the reactivity of imidazolylsulfonates is comparable to triflates and they can be stored for months without loss of reactivity. Therefore, imidazolsulfonates are a green, reactive, and stable electrophile for SMC.[23]

Alonso and Najera expanded the use of aryl imidazolylsulfonates in SMC by developing a protocol under aqueous conditions using oxime-palladacycles (**Scheme 5.4b**).[24,25] This methodology works well with both aryl and alkenyl boronic acids and trifluoroborates. Among the attractive features of this protocol are the low catalyst loading of 1 mol % Pd, the option to run the

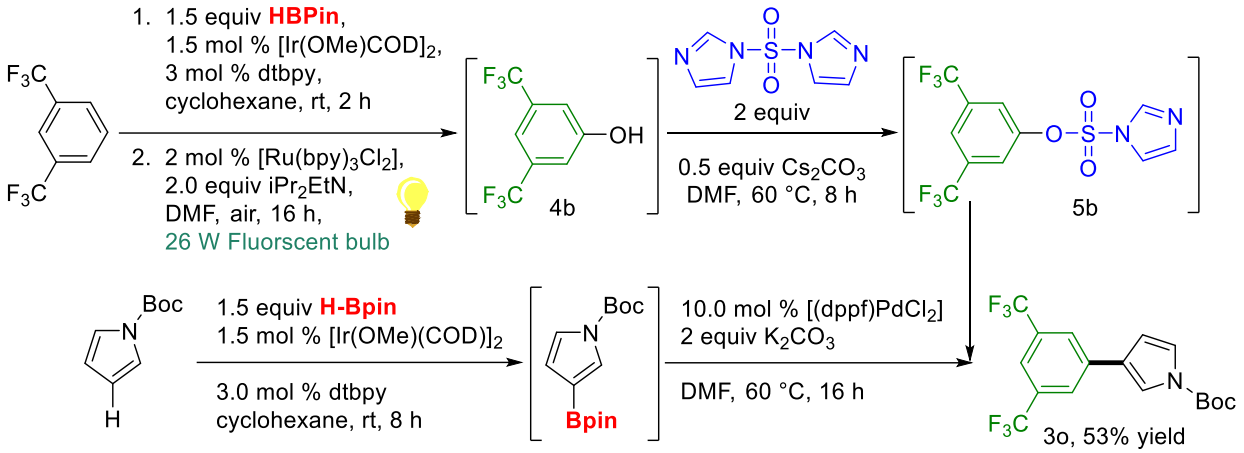
reaction under microwave conditions and the *in situ* imidazolylsulfonate formation of the phenol followed by the SMC.

Scheme 5.4: Reported SMC of aryl imidazolylsulfonates with boronic nucleophiles



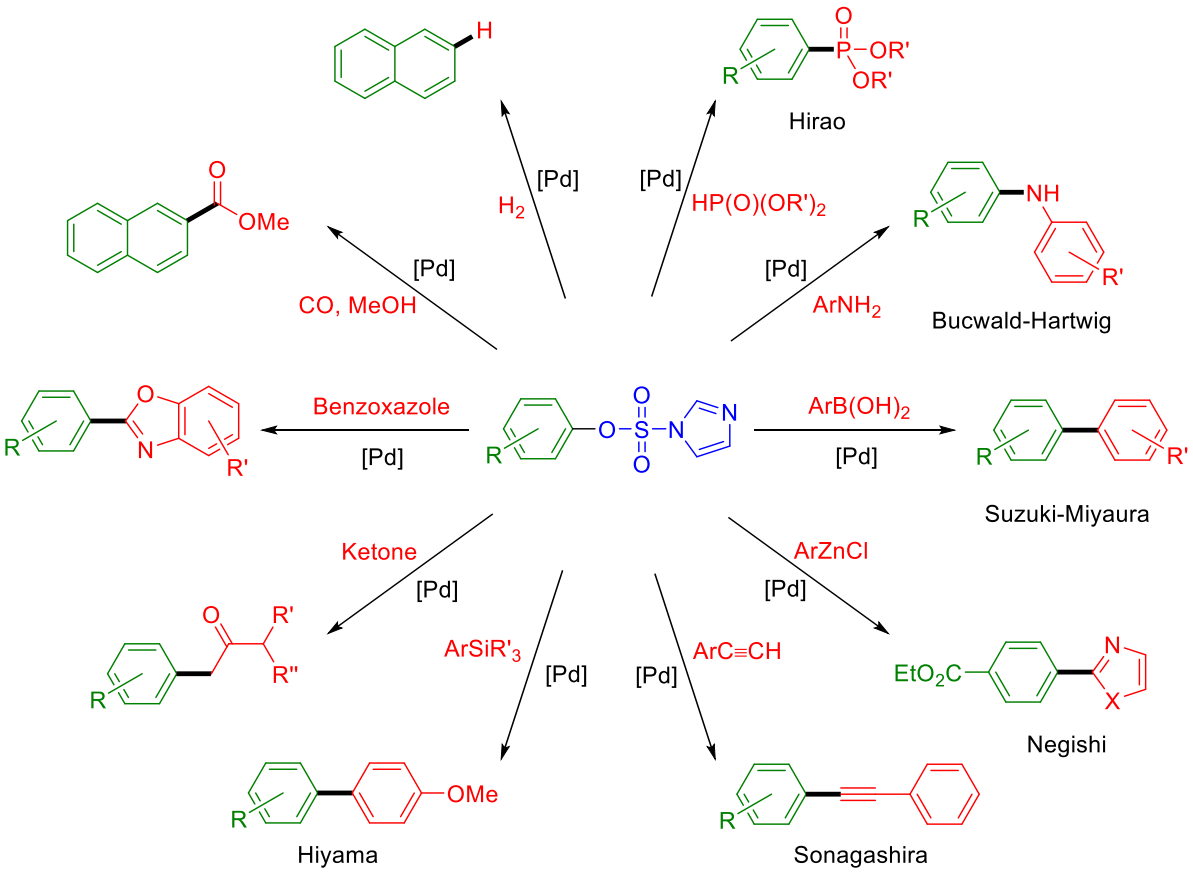
The Maleczka and Smith groups have also worked in this field developing a green one pot SMC of unfunctionalized arenes via the formation of aryl imidazolylsulfonates (**Scheme 5.5**). *in situ* C-H borylation of the corresponding arene followed by photocatalytic oxidation produce the phenol. This is then treated with sulfonyldiimidazole to yield the aryl imidazolylsulfonate. In a separate flask, the boronic partner is generated *in situ* by the C-H borylation of an heteroarene. The aryl imidazolylsulfonate is added to the flask containing the boronic ester without further purification and SMC is performed. This is a practical protocol that avoids completely the use of halides.

Scheme 5.5: One pot C-H borylation/oxidation route to aryl imidazolylsulfonate and their incorporation into C-H borylation/SMC



Before the discovery by Albaneze-Walker, imidazolylsulfonate was used as a leaving group in substitution and elimination reactions throughout carbohydrate and nucleoside chemistry. After 2009, aryl imidazolylsulfonate emerged as a new electrophilic alternative for cross-coupling reactions (**Scheme 5.6**).[26] Aryl imidazolylsulfonates can be coupled not only with aryl boronic acids but also with organozinc, alkynes and organosilicon reagents via Negishi, copper-free Sonagashira and Hiyama reactions.[23,27] Aryl imidazolylsulfonates can be used as coupling partners in the C-H activation of heteroarenes and ketones as well. Oxazoles and benzoaxazoles are arylated at carbon C2; competition studies show that aryl imidazolylsulfonates are more reactive than bromides in this case.[28] Arylation of ketones occurs regioselectively at the least steric position and diarylation of the product does not happen; this used to be a problem with other electrophiles.[29] Moreover, aryl imidazolylsulfonates can insert their aryl group into carbon monoxide via palladium catalysis; addition of methanol then release an ester as the final product.[23]

Scheme 5.6: Metal-catalyzed cross-coupling reactions of aryl imidazolylsulfonates



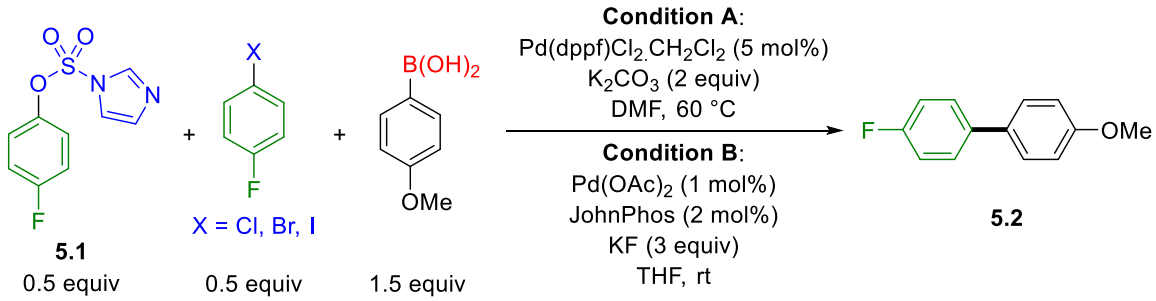
On the other hand, coupling reactions of aryl imidazolylsulfonates can form bonds between carbon and atoms different than carbon. Albaneze-Walker reported the hydrogenolysis of naphtyl imidazolylsulfonate catalyzed by palladium on carbon; this was the only substrate tested theoretically other compounds may also work.[23] Later, phosphorylation of aryl imidazolylsulfonates was developed using H-phosphonate as the coupling partner, analogous to Hirao's report with aryl halides.[30] Finally, aryl imidazolylsulfonates can be useful precursors of anilines via Bucwald-Hartwig amination.[31] Since the first emergence of imidazolylsulfonates as coupling partners, the evolution of its applicability as an electrophile demonstrates its important versatility as a novel option for coupling reactions.

Owing to the advantages of aryl imidazolyl sulfonates, we desire to expand its applicability in SMC. Aryl imidazolyl sulfonates are as reactive as triflates for palladium catalyzed SMC, we wondered how the reactivity of this electrophile will compare to the most traditional electrophiles: aryl halides. This insight will help the spread of the use of this pseudohalide in organic synthesis. On the other hand, SMC promoted by earth abundant metals like nickel has gained considerable attention due to the increasing shortage of metals like palladium. Herein, we also report our efforts on the development of a nickel-catalyzed SMC of aryl imidazolyl sulfonates.

5.2. Results and Discussion

5.2.1. Aryl imidazolyl sulfonates vs aryl halides

The reactivity comparison between aryl imidazolylsulfonates and halides was done to gain a knowledge of the general reactivity of this novel electrophile. Two sets of reaction conditions were chosen. **Condition A** uses $Pd(dppf)Cl_2$ as the catalyst and follows the parameters reported for the SMC of aryl imidazolylsulfonates by Albaneze-Walker.[23] **Condition B** uses $Pd(OAc)_2$ and JohnPhos, a Buchwald type ligand, under optimized mild conditions for the cross coupling of aryl halides.[32] **Figure 5.1** shows a comparison between aryl imidazolsulfonates's and aryl halide's SMC rate of conversion. Aryl imidazolsulfonates coupled faster than the chloride under both **Conditions A** and **B**. Respect to the bromide and iodide, the aryl imidazolylsulfonates reacted slower. This is in accordance with the established behavior of the reactivity of aryl halides in SMC: aryl iodides react faster than bromides and these faster than chlorides.



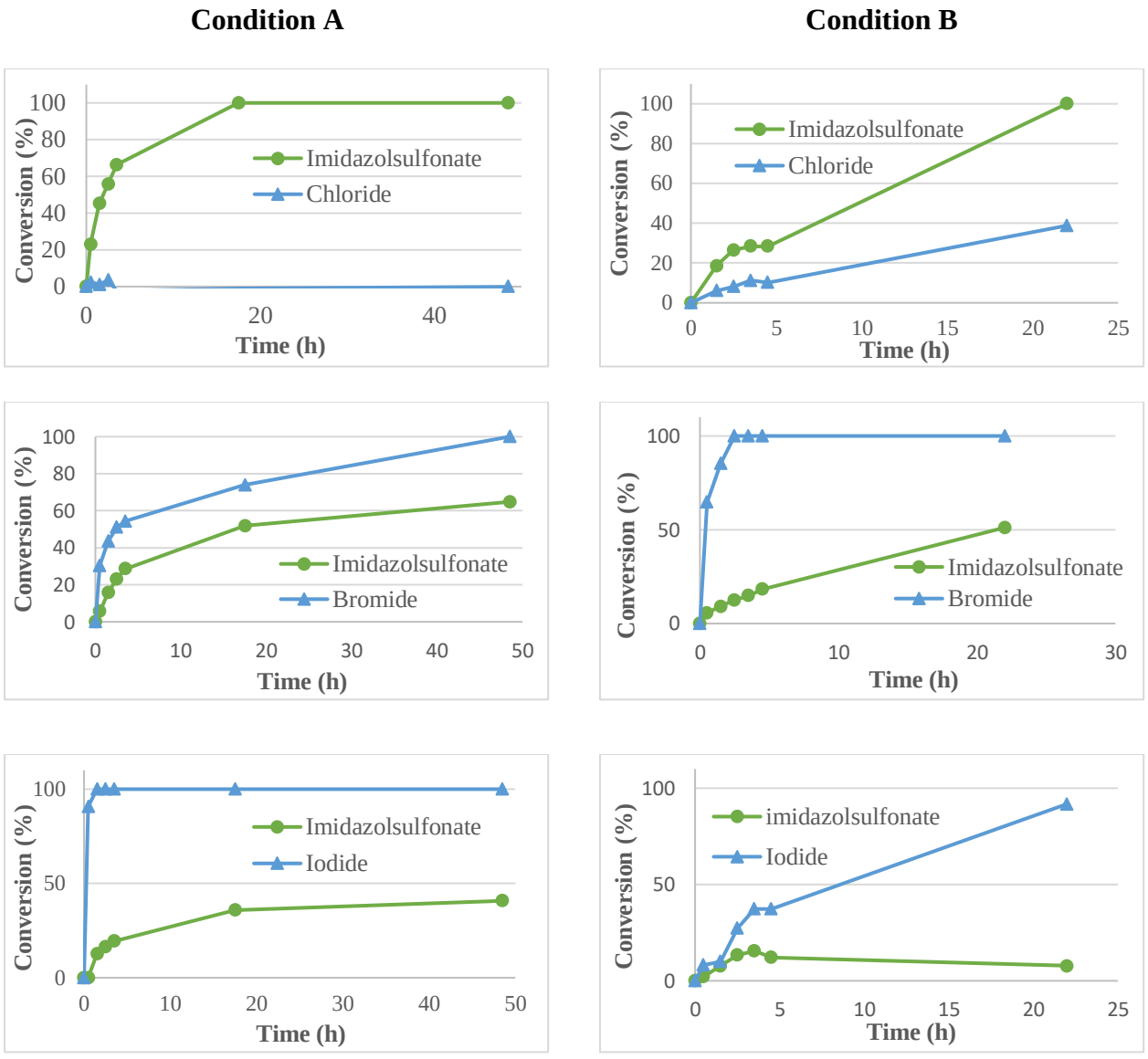
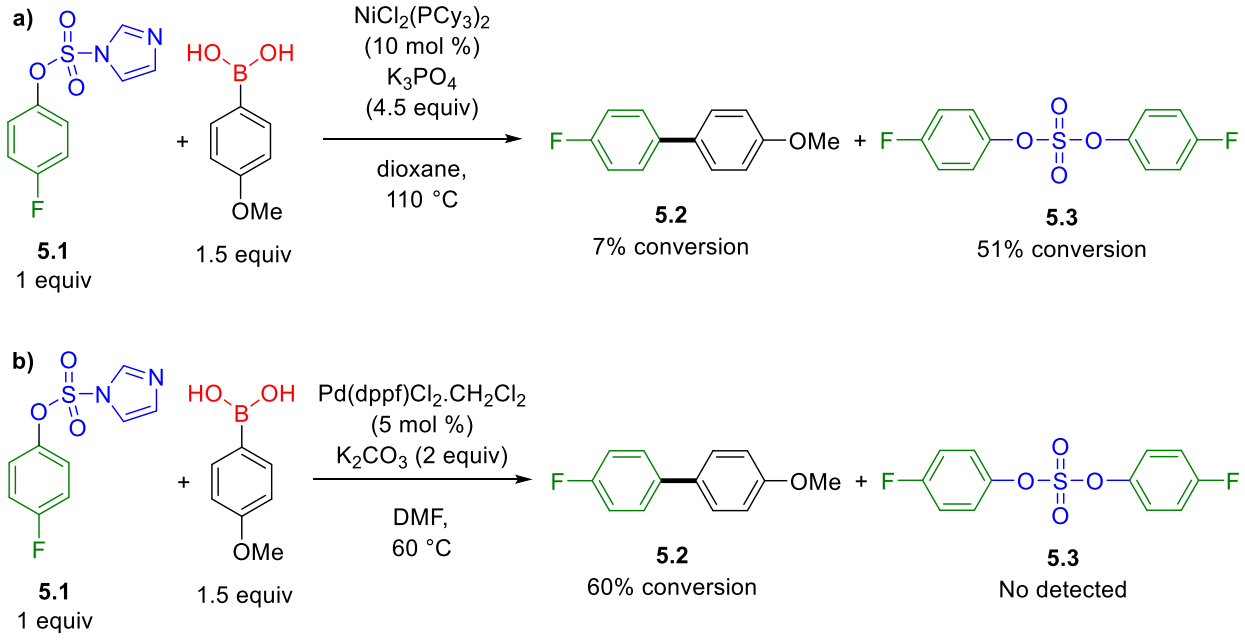


Figure 5.1: SMC reactivity comparison between 4-fluorophenyl imidazolylsulfonates vs halides.

5.2.2. Unexpected results in the nickel-catalyzed SMC of aryl imidazolylsulfonates

The nickel-catalyzed SMC of aryl imidazolylsulfonates was attempted using conditions previously reported for the SMC of phenol derived electrophiles (**Scheme 5.7a**).[33] ^{19}F NMR of the reaction mixture shows formation of cross-coupled product **5.2** with an unexpected product. Compound **5.2** was made previously from the SMC of the corresponding aryl phosphate. After work-up of the reaction mixture, it was discovered that diaryl sulfate **5.3** was the identity of the side product. After 67 hours, 51% of the aryl imidazolylsulfonate converted to compound **5.3**. Diaryl sulfate **5.3** was synthesized by a known method widely report in the literature to further support this assignment.[34] This result was surprising since no diaryl sulfate was reported during the palladium cross-coupling of aryl imidazolyl-sulfonates. No diaryl sulfate was seen either by GC-MS or ^{19}F NMR after performing the palladium-catalyzed reaction (**Scheme 5.7b**).

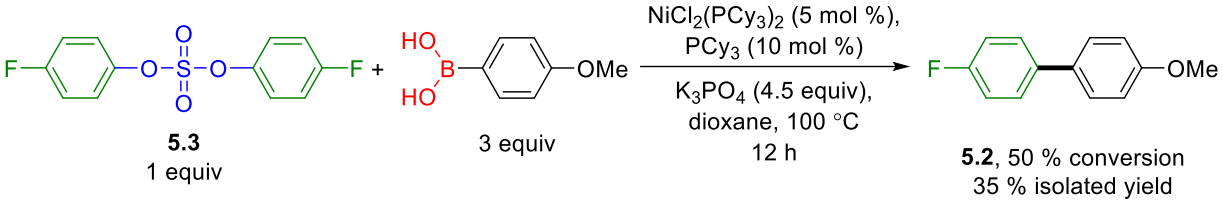
Scheme 5.7: Nickel and palladium-catalyzed SMC of 4-fluorophenyl imidazolylsulfonate



5.2.3. Nickel-catalyzed SMC of diaryl sulfates:

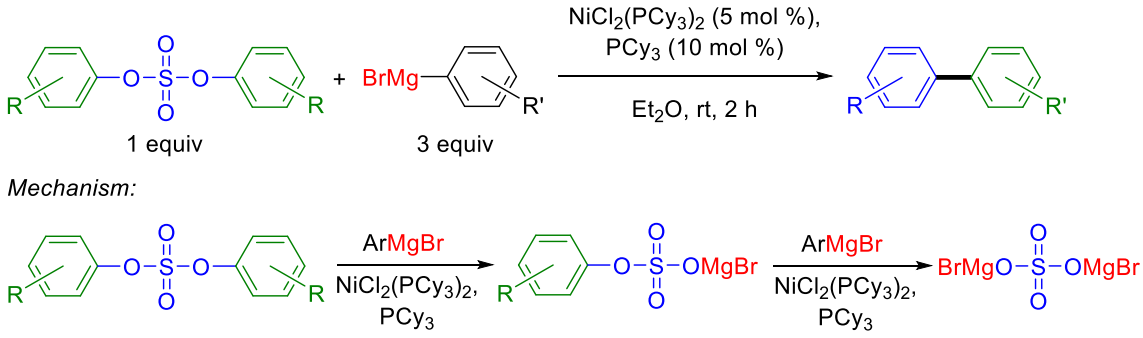
Furthermore, it was demonstrated that diaryl sulfate **5.3** can undergo SMC under the same conditions used for aryl imidazolylsulfonates (**Scheme 5.8**). Based on this discovery, it was believed that diaryl sulfates would be another environmentally friendly electrophile alternative for SMC. Therefore, some studies were performed to gain knowledge on the SMC of diaryl sulfates. First, the reaction in **Scheme 5.8** was followed by ^{19}F NMR. After 12 hours no reagent was left, but the low yield of the isolated product (35 %) suggested that another product was being formed.

Scheme 5.8: Nickel-catalyzed SMC of bis(4-fluorophenyl) sulfate



In the literature, there are reports of Kumada cross-couplings of diaryl sulfates (**Scheme 5.9**).[34] It has been proposed that the mechanism goes through the formation of a magnesium sulfate salt as an intermediate. The study identified the sulfate salt by ESI-MS and it was demonstrated that the sulfate salt can undergo Kumada cross-coupling successfully.

Scheme 5.9: Previously report nickel-catalyzed Kumada coupling of diaryl sulfates

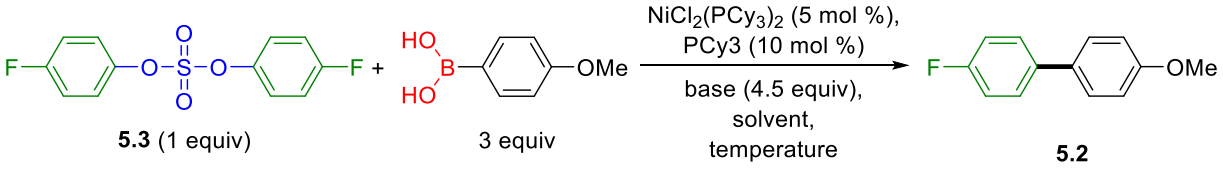


It was thought that the SMC of the diaryl sulfate (**Scheme 5.8**) might also go through the sulfate salt, which precipitate out of solution and therefore cannot be seen by ^{19}F NMR. After

repeating the reaction and adding a certain amount of internal standard C_6F_6 at the end, the real conversion (50 %) to the product **5.2** was measured.

Some attempts were made to improve the conversion of the SMC of diaryl sulfate. If the sulfate salt is an intermediate, changing solvent, temperature or the nature of the base can change the solubility of the salt and perhaps improve the cross-coupling. Using K_3PO_4 as base, the best solvent was dioxane and increasing temperature until reflux also improved the conversion (**Table 5.1**, entries 1-4). Other bases like Cs_2CO_3 and Mg_3PO_4 were not effective (entries 5-9). Mg_3PO_4 is not soluble in organic solvents and therefore all conversion to product is lost (entries 7-9).

Table 5.1: Optimization of reaction conditions for SMC of diaryl sulfates[a]



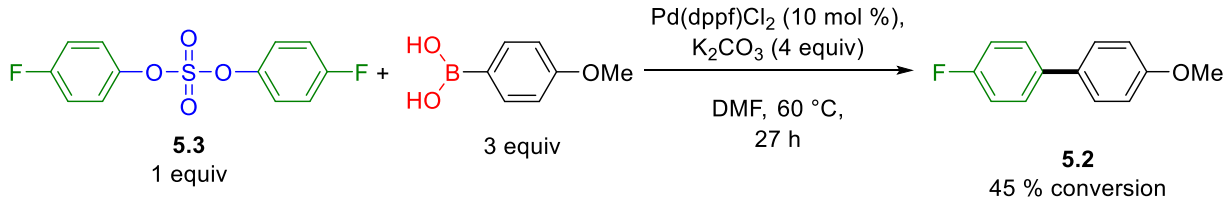
5.3 (1 equiv) 3 equiv **5.2**

Entry	Base	Solvent	Temperature	Conversion (%)
1	K_3PO_4	Dioxane	rt	33
2	K_3PO_4	Dioxane	110 °C	50
3	K_3PO_4	Et_2O	rt	36
4	K_3PO_4	THF	rt	36
5	Cs_2CO_3	THF	rt	0
6	Cs_2CO_3	THF	40 °C	5
7	Mg_3PO_4	Dioxane	110 °C	0
8	Mg_3PO_4	Et_2O	rt	0
9	Mg_3PO_4	THF	40 °C	0

[a] Reaction conditions: **5.3** (0.2 mmol), 4-MeOPhB(OH)$_2$ (0.6 mmol), $NiCl_2(PCy_3)_2$ (0.01 mmol), PCy_3 (0.02 mmol), base (0.9 mmol), solvent (2 mL), 24 h

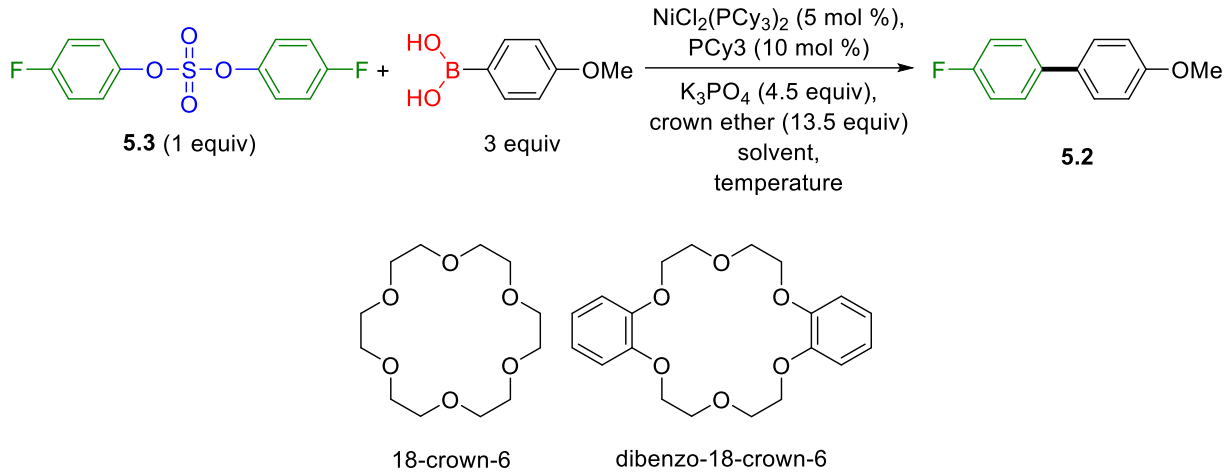
Palladium catalysis was also attempted for SMC of diaryl sulfates (**Scheme 5.10**). Similar conversion as with nickel catalysis was obtained.

Scheme 5.10: Palladium-catalyzed SMC of diaryl sulfate



The next reaction condition attempted was using crown ethers to dissolve the sulfate salt intermediate (**Table 5.2**). 18-crown-6 and dibenzo-18-crown-6 were used because they are known to trap potassium cations. In fact, upon addition of the ether, a new peak was seen by ^{19}F NMR. While it was suspected that the ether helped dissolve the sulfate salts, the crown ethers also trap the base K_3PO_4 which may explain the decrease in conversion respective to the reactions without addition of crown ether.

Table 5.2: Optimization of reaction conditions for SMC of diaryl sulfates with crown ethers [b]



Entry	Crown ether	Solvent	Temperature	Conversion (%)
1	18-crown-6	dioxane	110 °C	12
2	18-crown-6	THF	110 °C	0
3	dibenzo-18-crown-6	dioxane	110 °C	27

[b] Reaction conditions: **5.3** (0.2 mmol), 4-MeOPhB(OH)$_2$ (0.6 mmol), $NiCl_2(PCy_3)_2$ (0.01 mmol), PCy_3 (0.02 mmol), K_3PO_4 (0.9 mmol), crown ether (2.7 mmol), solvent (4 mL), 24 h

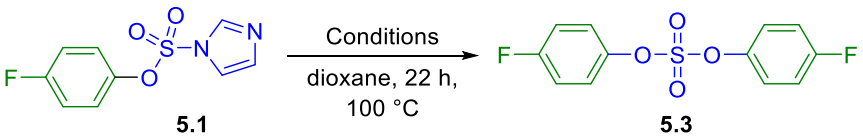
Based on these results, the best conversion for the SMC of diaryl sulfate was afforded with $Ni(PCy_3)Cl_2$, PCy_3, and K_3PO_4 in dioxane (**Scheme 5.8**) or with $Pd(dppf)Cl_2$ and K_2CO_3 in DMF

(**Scheme 5.10**). Although high yields were not obtained, due to the formation of the sulfate salt, it is noteworthy that the SMC of diaryl sulfates can be done in both nickel and palladium conditions.

5.2.4. Conditions for the formation of diaryl sulfate from aryl imidazolylsulfonate

We returned to our main goal: development of a nickel-catalyzed SMC of aryl imidazolyl sulfonates. Previously, formation of diaryl sulfate during the SMC prevent us to find optimal conditions. Uncovering the conditions which promote the formation of diaryl sulfates during the SMC is key to overcome this issue. Control reactions were performed in the presence of each component of the SMC: base, Ni catalyst, boronic acid (**Table 5.3**, entries 1-4). No diaryl sulfate product was formed with any of these components alone but combining the boronic acid with the base produced diaryl sulfate in 60% conversion (**Table 5.3**, entry 5).

Table 5.3: Test of reaction conditions for the formation of diaryl sulfates [c]



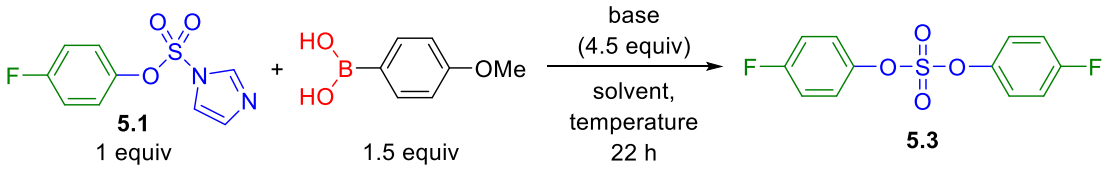
Entry	Conditions	Conversion (%)
1	None	0
2	K_3PO_4	0
3	$NiCl_2(PCy_3)_2$	0
4	4-MeOPhB$(OH)_2$	0
5	4-MeOPhB$(OH)_2$, K_3PO_4	60

[c] Reaction conditions: 4-FPhOSO$_2$Im (0.25 mmol), 4-MeOPhB$(OH)_2$ (0.375 mmol), $NiCl_2(PCy_3)_2$ (0.025 mmol), K_3PO_4 (1.125 mmol), dioxane (2 mL), 22 h

It can be concluded that the combination of the base, boronic acid and solvent is crucial for the formation of the diaryl sulfate. In the study of reactivity between aryl imidazolylsulfonates and other electrophiles different conditions will be used to avoid such diaryl sulfate formation. Therefore, it is important to have a good understanding on how certain conditions lead to the formation of the diaryl sulfate (**Table 5.4**). Solvents like dioxane, toluene and THF with K_3PO_4 as

base were chosen because these are common conditions used for the cross-coupling of phenol derivatives (entries 1-8). It can be deduced that an increase in temperature promotes the formation of diaryl sulfate. Additionally, changing the solvent also affects the conversion; in general, dioxane enhances formation of **5.3** more than THF or toluene. Interestingly, the reaction was performed with K_2CO_3 and DMF at 60 °C and only a small amount of diaryl sulfate was formed. This supports the observed effectiveness of palladium catalyzed SMC of aryl imidazolylsulfonate (**Scheme 5.7b**) under these conditions.

Table 5.4: Effect of reaction conditions in the formation of diaryl sulfates [a]



Entry	Base	Solvent	Temperature	Conversion (%)
1	K_3PO_4	Dioxane	60 °C	22
2	K_3PO_4	Dioxane	80 °C	37
3	K_3PO_4	Dioxane	100 °C	60
4	K_3PO_4	Toluene	60 °C	0
5	K_3PO_4	Toluene	80 °C	3
6	K_3PO_4	Toluene	100 °C	5
7	K_3PO_4	THF	25 °C	0
8	K_3PO_4	THF	40 °C	1
9	K_2CO_3	DMF	60 °C	3.8
10	K_2CO_3	DMF	100 °C	42

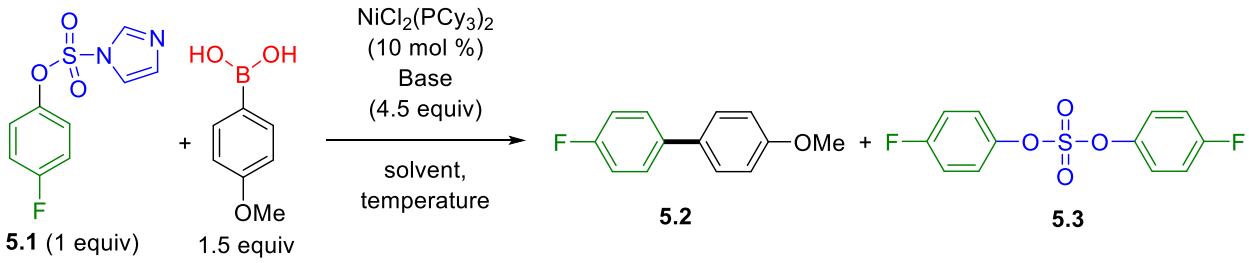
[a] Reaction conditions: **5.1** (0.25 mmol), 4-MeOPhB(OH)$_2$ (0.375 mmol), base (1.125 mmol), solvent (2 mL), 24 h

5.2.5. Nickel catalyzed SMC of aryl imidazolylsulfonates

Based on the results of **Table 5.4**, the SMC of aryl imidazolylsulfonate was performed under the conditions that gave the lowest yields of the diaryl sulfate (**Table 5.5**). K_3PO_4 with toluene or THF formed small amounts of diaryl sulfate but also little conversion to cross-coupling product **5** (entries 1-2). With DMF as the solvent, the main product was the diaryl sulfate (entry

3). Using DMF and K_2CO_3 at 60 °C does not make diaryl sulfate **6** as expected but the cross-coupling product **5** was not obtained either (entry 4). Changing the base to KF (entry 5) does not affect these results. In summary, conditions that do not promote formation of diaryl sulfate give lower conversions to the cross-coupling product.

Table 5.5: Nickel catalyzed SMC of aryl imidazolylsulfonates at different reaction conditions



Entry	Base	Solvent	Temperature	Time	Conversion 5 (%)	Conversion 6 (%)
1	K_3PO_4	Toluene[e]	100 °C	22 h	5	16
				44 h	4	19
				66 h	7	35
2	K_3PO_4	THF[e]	40 °C	22 h	6	10
				44 h	7	13
				66 h	5	19
3	K_3PO_4	DMF[f]	60 °C	22 h	15	77
				44 h	12	81
4	K_2CO_3	DMF[f]	60 °C	22 h	0	0
5	KF	DMF[f]	60 °C	22 h	2	0

[e] Reaction conditions: **5.1** (0.25 mmol), 4-MeOPhB$(OH)_2$ (0.375 mmol), $NiCl_2(PCy_3)_2$ (0.025 mmol), base (1.125 mmol), solvent (2 mL).[f] Reaction conditions: **5.1** (0.42 mmol), 4-MeOPhB$(OH)_2$ (0.64 mmol), $NiCl_2(PCy_3)_2$ (0.042 mmol), base (0.85 mmol), solvent (2.5 mL)

5.3. Conclusions

Aryl imidazolyl sulfonates have emerged as novel pseudohalides for cross-coupling reactions. Its reactivity is comparable to triflates as previously reported, and to bromides as described here. Attempts to expand its utility to nickel-catalyzed SMC have not been promising due to the formation of a diarylsulfate side product. Presence of boronic acid and base are sufficient to promote the decomposition of aryl imidazolylsulfonates to diarylsulfates.

Unfortunately, conditions that diminished the formation of the diarylsulfate also harm the production of the cross-coupled product. Nonetheless, the diaryl sulfates have shown to be alternative electrophiles for nickel-catalyzed SMC although with conversion lower than 50%. It is hypothesized that precipitation of an aryl sulfate salt after coupling of one aryl group stop the reaction to go further.

5.4. Experimental Procedures

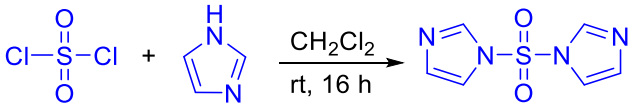
5.4.1. General Materials and Methods

All commercially available chemicals were used as received unless otherwise indicated. All solvents were reagent grade. All the electrophiles and the catalyst $Ni(PCy_3)_2Cl_2$ were prepared based on reported methods. Tetrahydrofuran (THF) was distilled from sodium/benzophenone under nitrogen atmosphere before use. Toluene was distilled from CaH_2 under nitrogen atmosphere before use. Dioxane was distilled from sodium/benzophenone under nitrogen atmosphere before use. K_3PO_4, K_2CO_3 and KF were dehydrated at 150 °C under vacuum overnight and use immediately. Column chromatography was performed on flash silica gel (ACME). Thin layer chromatography was performed on 0.25 mm thick aluminum-backed silica gel plates purchased from Merck and visualized with ultraviolet light (λ = 254 nm).

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Agilent DirectDrive2 (500 MHz for ^{1}H, 126 MHz for ^{13}C and 470 MHz for ^{19}F). All coupling constants are apparent *J* values measured at the indicated field strengths in Hertz (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, bs = broad singlet, dt = doublet of triplet, td = triplet of doublet, ttt = triplet of triplet of triplet). High-resolution mass spectra were acquired at the MSU Mass Spectrometry facility using a Waters QTOF Ultima mass spectrometer (ESI).

5.4.2. Synthesis of reagents: electrophiles and catalyst

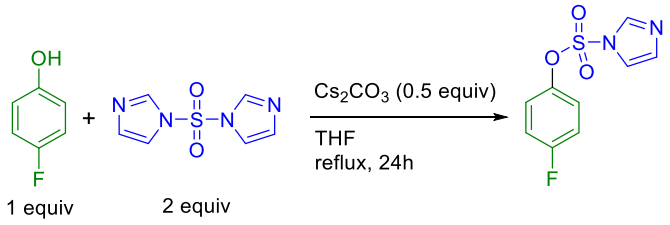
1,1'-sulfonylbis(1H-imidazole) [26]



Sulfonyl chloride (3.48 mL, 43 mmol) and dichloromethane (20 mL) were placed on a round bottom flask submerged on a dry ice bath. Other flask was charged with imidazole (14 g, 206 mmol) and dissolve with dichloromethane (147 mL). After all the imidazole was dissolved, the mixture was cooled in a dry ice bath and the sulfonyl chloride solution was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. After vacuum filtration, the filtrate was evaporated under reduce pressure until dryness. The solid obtained was recrystallized with isopropanol (70 mL). The mixture was cooled in an ice bath and then filtrated. 1,1'-Sulfonylbis(1H-imidazole) was obtained as a white solid in 69% yield (5.91 g). ^{1}H NMR data match with those reported by Sigma Aldrich.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (t, *J* = 1.0 Hz, 1H), 7.32 (t, *J* = 1.5 Hz, 1H), 7.19 – 7.15 (m, 1H)

4-fluorophenyl 1H-imidazole-1-sulfonate (5.1) [24,44]

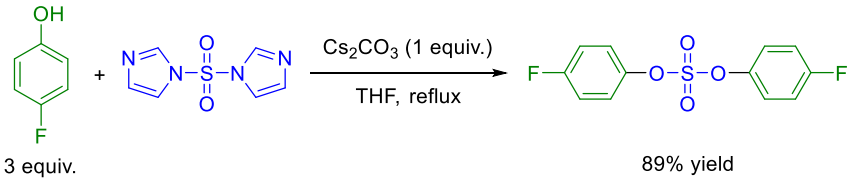


A round bottom flask was charged with 4-fluorophenol (750 mg, 6.7 mmol), 1,1'-sulfonylbis(1H-imidazole) (2.65 g, 13.4 mmol), Cs_2CO_3 (1.09 g, 3.35 mmol) and THF (22.5 mL). The solution was stirred at room temperature for 24 hours. Solvent was evaporated under reduced pressure. The mixture was partitioned between ethyl acetate (15 mL) and water (15 mL). The

organic phase was washed with a saturated solution of NH_4Cl (15 mL) and with brine (15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash column chromatography (hexane: ethyl acetate = 1: 1) afforded 4-fluorophenyl 1H-imidazole-1-sulfonate in 77 % yield (1.25 g) as a white solid. NMR data matches those reported in the literature.[44]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (t, *J* = 1.0 Hz, 1H), 7.29 (t, *J* = 1.5 Hz, 1H), 7.17 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.08 – 7.02 (m, 2H), 6.94 – 6.87 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.8 (d, *J* = 249 Hz), 144.63 (d, *J* = 3.8 Hz), 137.46 (s), 131.50 (s), 123.12 (d, *J* = 8.8 Hz), 118.28 (s), 117.18 (d, *J* = 23.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ -111.6 (m). HRMS (ESI) *m/z* calcd for $C_9H_8FN_2O_3S$ $[M+H]^+$ 243.0240, found: 243.0240.

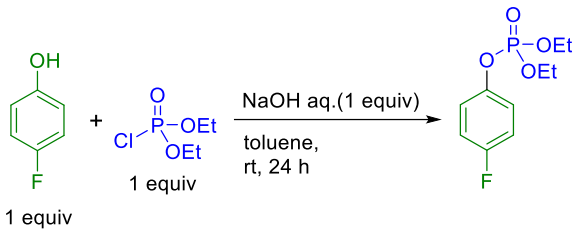
Bis(4-fluorophenyl) sulfate (5.3)



4-fluorophenol (1.68 g, 15 mmol), 1,1'-sulfonylbis(1H-imidazole) (991 mg, 5 mmol), $CsCO_3$ (1.63 g, 5 mmol) and THF (5 mL) were placed in a round bottom flask. The mixture was stirred and heated until reflux overnight. The reaction mixture was filtrated under vacuum and the filtrate was evaporated until dryness. Purification by flash column chromatography (hexane: ethyl acetate = 4:1) afforded compound **5.3** in 89% yield (1.27g).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (m, 4H), 7.12 (m, 4H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 161.3 (d, J = 990 Hz), 146.0 (d, 15 Hz), 122.8 (d, 35 Hz), 116.9 (d, 95 Hz). ^{19}F NMR (500 MHz, $CDCl_3$): δ -113.3 (m).

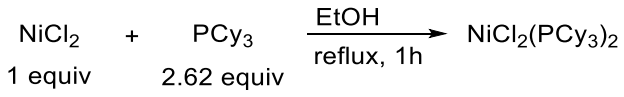
Diethyl (4-fluorophenyl) phosphate [45]



A Schlenk flask was charged with 4-fluorophenol (897 mg, 8 mmol) and toluene (9.2 mL). The Schlenk flask was degassed with nitrogen for 15 minutes. Schlenk flask was placed under an ice bath and diethyl chlorophosphate (1.2 mL, 8 mmol) was added dropwise. The reaction mixture was degassed with nitrogen for 15 minutes. NaOH aqueous (1.8 mL of NaOH 4.4 M) was added to the Schenk flask. The reaction mixture was degassed for 15 minutes and left at room temperature for 24 hours. The organic phase was separated from the aqueous phase and then it was washed with NaOH aqueous (8 mL of NaOH 10 % w/w). The organic layer was washed with water (8 mL) and the solvent was evaporated under reduced pressure. Diethyl (4-fluorophenyl) phosphate was obtained in 50% yield (1.02 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (dqd, *J* = 9.5, 3.9, 1.2 Hz, 1H), 7.05 – 6.97 (m, 1H), 4.20 (dqd, *J* = 8.2, 7.1, 3.7 Hz, 2H), 1.34 (td, *J* = 7.1, 1.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.63 (d, *J* = 244 Hz), 146.60 (dd, *J* = 6.9, 2.5 Hz), 121.4 (dd, *J* = 7.6, 5.0 Hz), 116.20 (d, *J* = 23.9 Hz), 64.65 (d, *J* = 6.3 Hz), 16.08 (d, *J* = 7.6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ -118.0 (m). HRMS (ESI) *m/*z calcd for $C_{10}H_{15}FO_4P$ $[M+H]^+$ 249.0692, found: 249.0692.

Bis(tricyclohexyl)nickel (II) dichloride [38]



Ethanol (50 mL) was degassed with nitrogen for 15 minutes. One Schlenk flask was charged with $NiCl_2$ (1.25 g, 9.7 mmol) and purged with nitrogen and vacuum three times with 5

minutes per cycle. Degassed ethanol (25 mL) was transferred via positive pressure with a cannula to the Schlenk flask charged with $NiCl_2$. The mixture was heated until a yellow dark homogenous solution was obtained (approx. 70 °C). Another Schenk flask was charged with PCy_3 (7.10 g, 25.4 mmol) and purged with nitrogen and vacuum three times with 5 minutes per cycle. The degassed ethanol (25 mL) and $NiCl_2$ solution were transferred via positive pressure with a cannula to the Schlenk flask charged with PCy_3. A condenser was connected to the flask and the reaction mixture was heated until reflux for 1 hour. The reaction mixture was left to cool down at room temperature. The reaction mixture was filtered, the solid was washed with cold ethanol (25 mL) and diethyl ether (25 mL). The solid was dried overnight under vacuum to afford a reddish-purple product in 84% yield (5.66 g). UV-Vis matched those reported in the literature.[47]

UV-Vis: 276 nm, 393 nm, 514-532 nm (500)

5.4.3. Cross coupling reactions

General Procedure for the SMC

Method A:

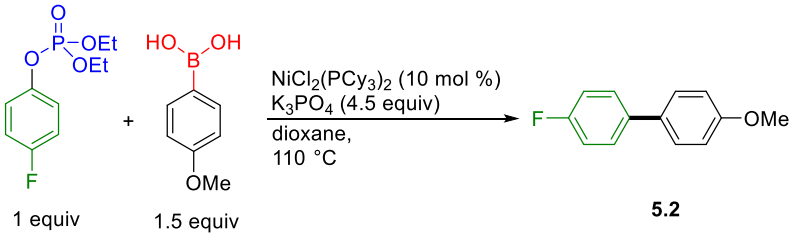
A Schlenk flask was charged with the boronic acid, the catalyst, and the base. The Schlenk flask was purged with nitrogen and vacuum three times with 5 minutes per cycle. Another flask was charged with the electrophile(s), the ligand, and the solvent. The solution was stirred and degassed with nitrogen for 15 minutes, then it was transferred via a positive pressure through a cannula to the Schlenk flask. The reaction mixture was degassed for 15 minutes and then stirred at room temperature or heated in an oil bath with a fitted condenser. Reactions in **Scheme 5.7a, 5.8, 5.10** and **Table 5.1, 5.2** were run with this method.

Method B:

In a nitrogen filled glove box, a 5.0 mL conical vial was charged with the electrophile(s), boronic acid, catalyst, ligand, base, and solvent. The vial was capped with a teflon pressure cap. If the reaction was run at room temperature, the vial was left inside of the glove box. If the reaction need to be heated, the vial was taken out of the glove box and placed into a pre-heated aluminum block at the indicated temperature. Reactions in **Figure 5.1**, **Scheme 5.8, Table 5.3**, **5.4** and **5.5** were run with this method.

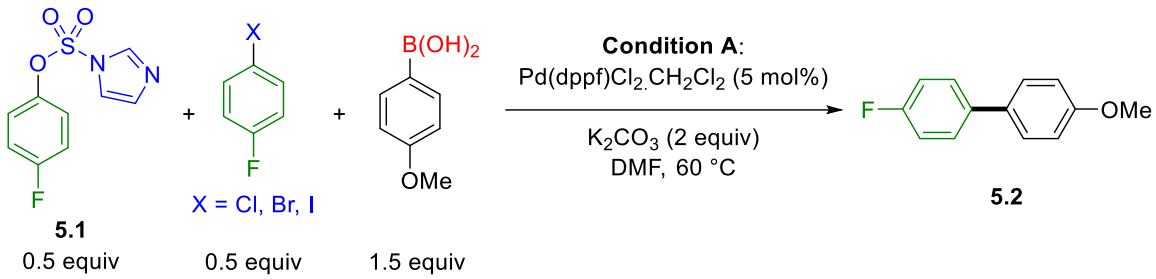
Reactions were followed by ^{19}F NMR using C_6F_6 as standard. In the case of coupling of aryl sulfates a measured amount of C_6F_6 (1/6 equivalents respect to the diaryl sulfate) was added at the end of the reaction to have a quantitative measurement of the conversion.

4-fluoro-4'-methoxy-1,1'-biphenyl (5.2)



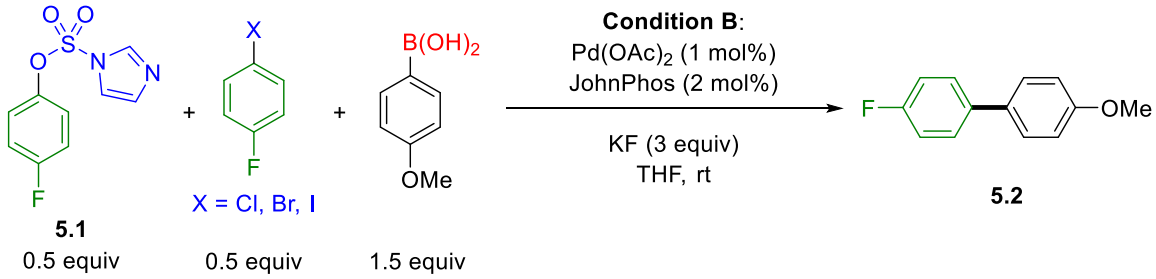
Method A was followed with this quantity of reagents: 4-Fluorophenyl diethyl phosphate (372 mg, 1.5 mmol), 4-methoxyphenyl boronic acid (342 mg, 2.25 mmol), $NiCl_2(PCy_3)_2$ (104 mg, 0.15 mmol, K_3PO_4 (1.43 g, 6.75 mmol), and dioxane (6 mL), no extra ligand was added. After 24 h the reaction was stopped, and the mixture was evaporated under reduced pressure. Purification by flash column chromatography (hexane: ethyl acetate = 9:1) afford compound **5.2** in 77% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 7.53 – 7.44 (m, 4H), 7.14 – 7.06 (m, 2H), 7.01 – 6.94 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.06 (d, *J* = 246 Hz), 159.07 (s), 136.94 (d, *J* = 2.5 Hz), 132.81 (s), 128.19 (d, *J* = 8.8 Hz), 128.01 (s), 115.51 (d, *J* = 21.4 Hz), 114.22 (s), 55.35 (s).

SMC Reactivity Comparison Imidazolylsulfonates Vs Halides (Figure 5.1): condition A



In a nitrogen filled glove box, a 5.0 mL Wheaton microreactor was charged with 4-fluorophenyl imidazolyl sulfonate (0.5 mL of a 0.42 M solution in DMF, 0.21 mmol, 0.5 equiv) and the corresponding aryl halide: 1-chloro-4-fluorobenzene (28 mg, 0.21 mmol, 0.5 equiv) or 1-bromo-4-fluorobenzene (37 mg, 0.21 mmol, 0.5 equiv) or 1-fluoro-4-iodobenzene (47 mg, 0.21 mmol, 0.5 equiv). The conical vial was charged with 4-methoxyphenyl boronic acid (1 mL of a 0.64 M solution in DMF, 0.64 mmol, 1.5 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.5 mL of a 0.042 M solution in DMF, 5 mol %), K_2CO_3 (117 mg, 0.85 mmol, 2 equiv) in DMF (0.5 mL). The microreactor was capped with a teflon pressure cap and placed into an aluminum block pre-heated to 60 ºC. The reaction mixture was monitored over time by taking aliquots and analyzing them by ^{19}F NMR.

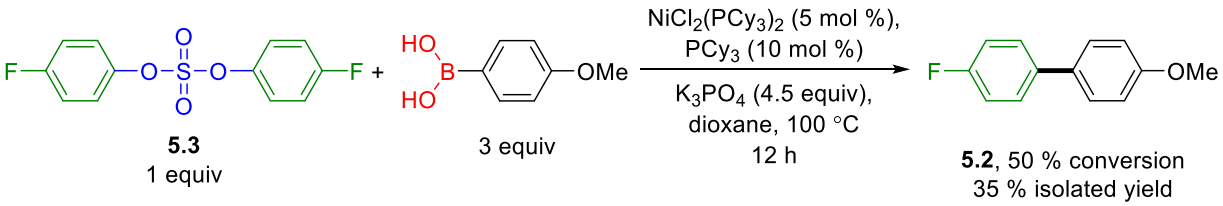
SMC Reactivity Comparison Imidazolylsulfonates Vs Halides (Figure 5.1): condition B



In a nitrogen filled glove box, a 5.0 mL Wheaton microreactor was charged with 4-fluorophenyl imidazolyl sulfonate (121 mg, 0.50 mmol, 0.5 equiv) and the corresponding aryl halide: 1-chloro-4-fluorobenzene (65 mg, 0.50 mmol, 0.5 equiv) or 1-bromo-4-fluorobenzene (87

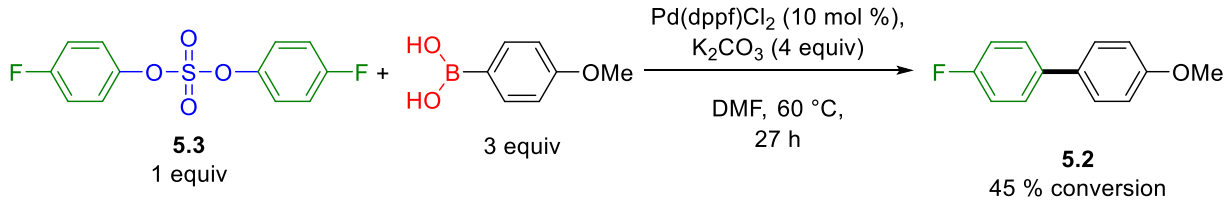
mg, 0.50 mmol, 0.5 equiv) or 1-fluoro-4-iodobenzene (111 mg, 0.50 mmol, 0.5 equiv). The conical vial was charged with 4-methoxyphenyl boronic acid (228 mg, 1.5 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 1 mol %), JohnPhos (6.0 mg, 2 mol %), KF (174 mg, 3.0 mmol, 3 equiv) in THF (3.0 mL). The microreactor was capped with a teflon pressure cap and stirred at room temperature. The reaction mixture was monitored over time by taking aliquots and analyzing them by ^{19}F NMR.

Nickel-catalyzed SMC of bis(4-fluorophenyl)sulfate



A 10 mL Schlenk flask was charged with 4-methoxyphenyl boronic acid (91 mg, 0.6 mmol, 3 equiv), $NiCl_2(PCy_3)_2$ (6.9 mg, 5 mol %), PCy_3 (5.6 mg, 10 mol %) and K_3PO_4 (191 mg, 0.9 mmol, 4.5 equiv). The Schlenk flask was purged with nitrogen and vacuum three times with 5 minutes per cycle. Bis(4-fluorophenyl)sulfate (57 mg, 0.20 mmol, 1 equiv) was dissolved in dioxane (2 mL) in a 10 mL round bottom flaks and sparged with nitrogen for 15 minutes. The bis(4-fluorophenyl)sulfate solution was transferred to the Schlenk flask via cannula under a positive pressure of nitrogen. Extra dioxane (1.5 mL) was added to the Schlenk flask. A condenser was connected to the Schlenk flask and the mixture was heated to 100 °C. After 3 h, the mixture was concentrated under reduce pressure and passed through silica column chromatography (hexane/ethyl acetate 98:2 as eluent). The fractions containing product were collected and concentrated to give 28 mg of **5.2** as a white solid (35% yield). To measure the conversion, the reaction was repeated under the same conditions and set up described above. The reaction was cool down and C_6F_6 (12 mg, 0.07 mmol) was added as an internal standard. An aliquot of the mixture was analyzed by ^{19}F NMR to measure the conversion (50% conversion).

Palladium-catalyzed SMC of bis(4-fluorophenyl)sulfate



5.3
1 equiv

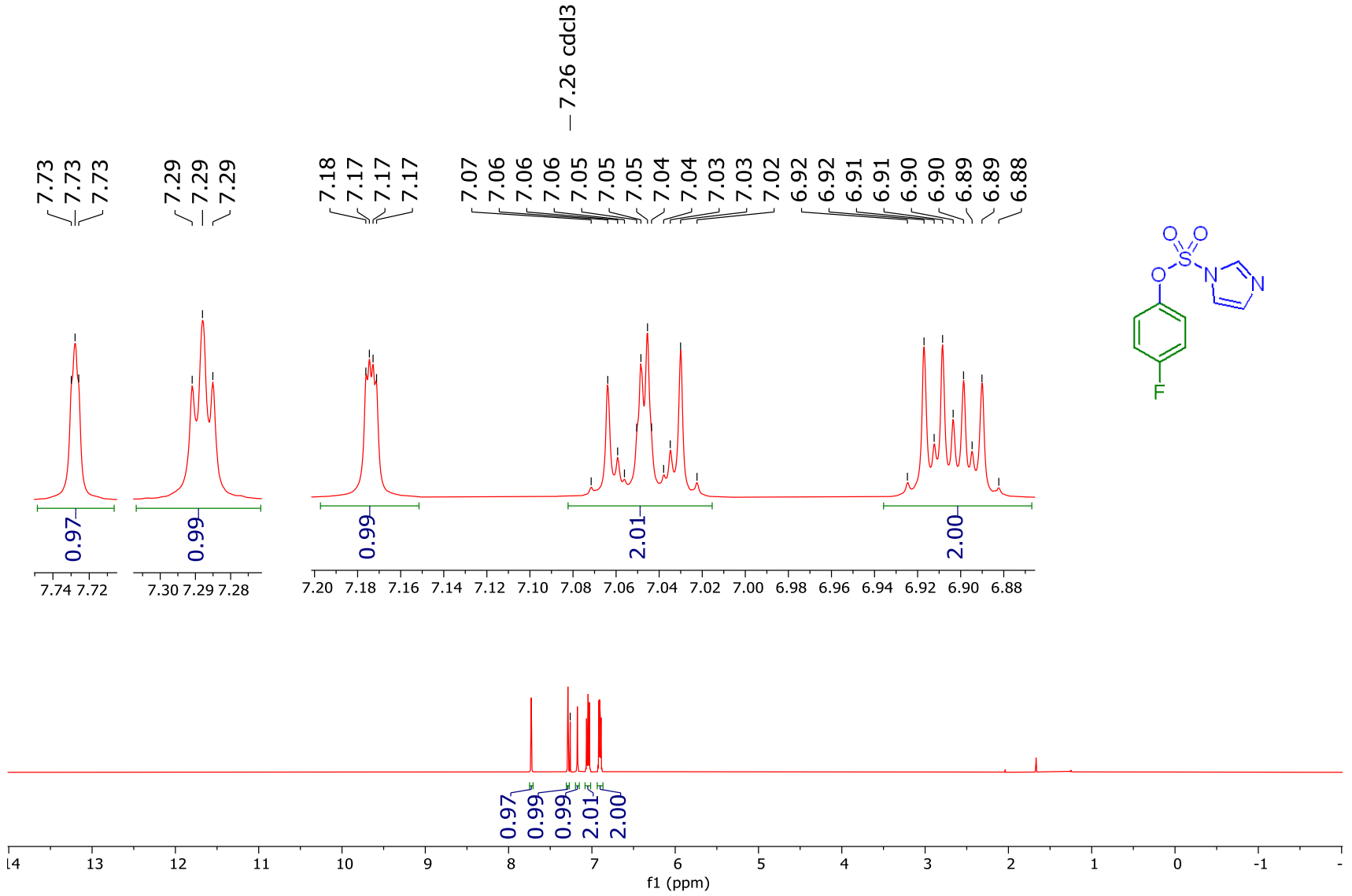
3 equiv

5.2
45 % conversion

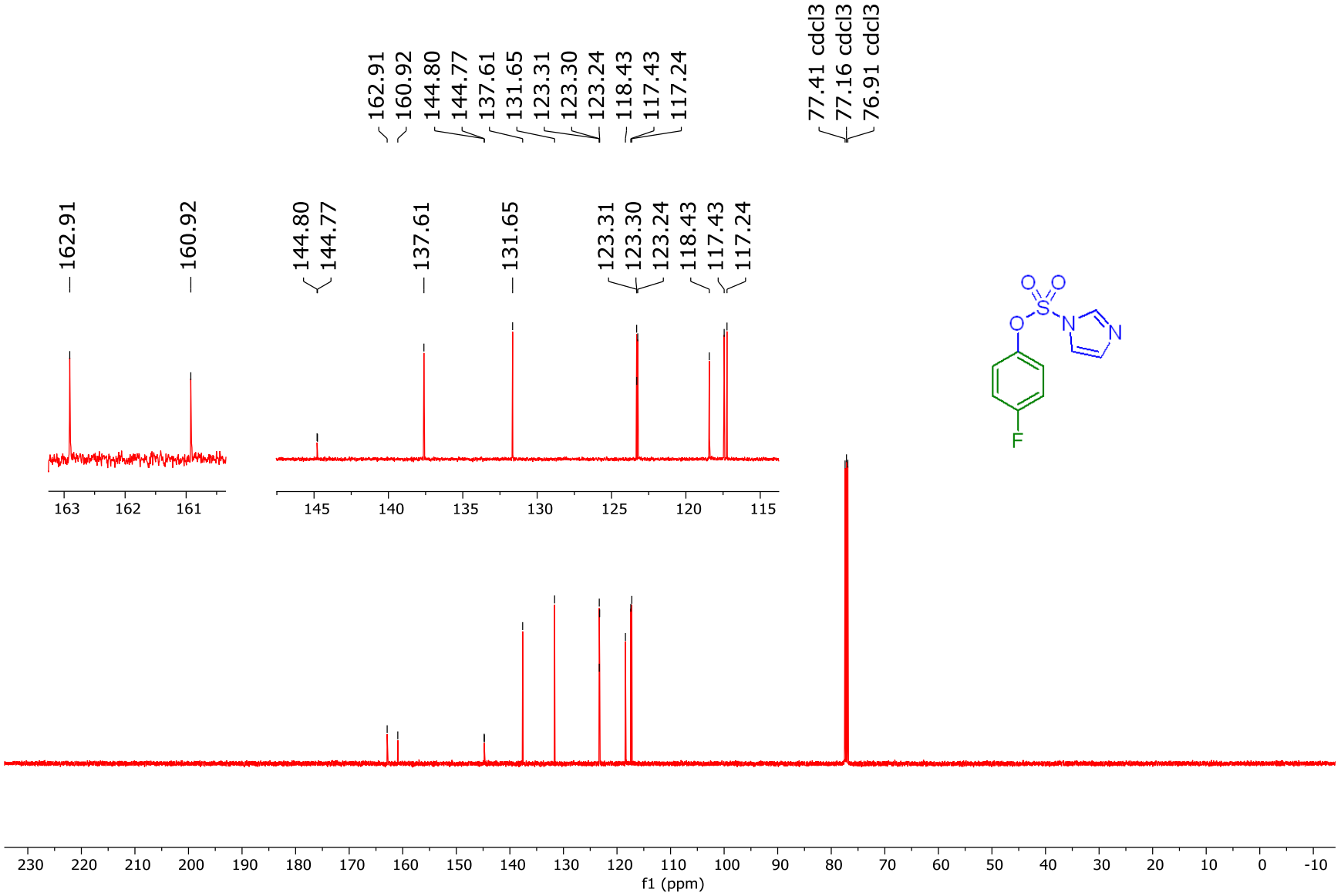
A 10 mL Schlenk flask was charged with 4-methoxyphenyl boronic acid (97 mg, 0.63 mmol, 3 equiv), $Pd(dppf)Cl_2$ (15 mg, 10 mol %) and K_2CO_3 (117 mg, 0.85 mmol, 4 equiv). The Schlenk flask was purged with nitrogen and vacuum three times with 5 minutes per cycle. Bis(4-fluorophenyl)sulfate (61 mg, 0.21 mmol, 1 equiv) was dissolved in DMF (2.5 mL) in a 10 mL round bottom flaks and sparged with nitrogen for 15 minutes. The bis(4-fluorophenyl)sulfate solution was transferred to the Schlenk flask via cannula under a positive pressure of nitrogen. A condenser was connected to the Schlenk flask and the mixture was heated to 60 °C. After 27 h, the mixture was cool down and C_6F_6 (12 mg, 0.07 mmol) was added as an internal standard. An aliquot of the mixture was analyzed by ^{19}F NMR to measure the conversion (45% conversion).

APPENDIX

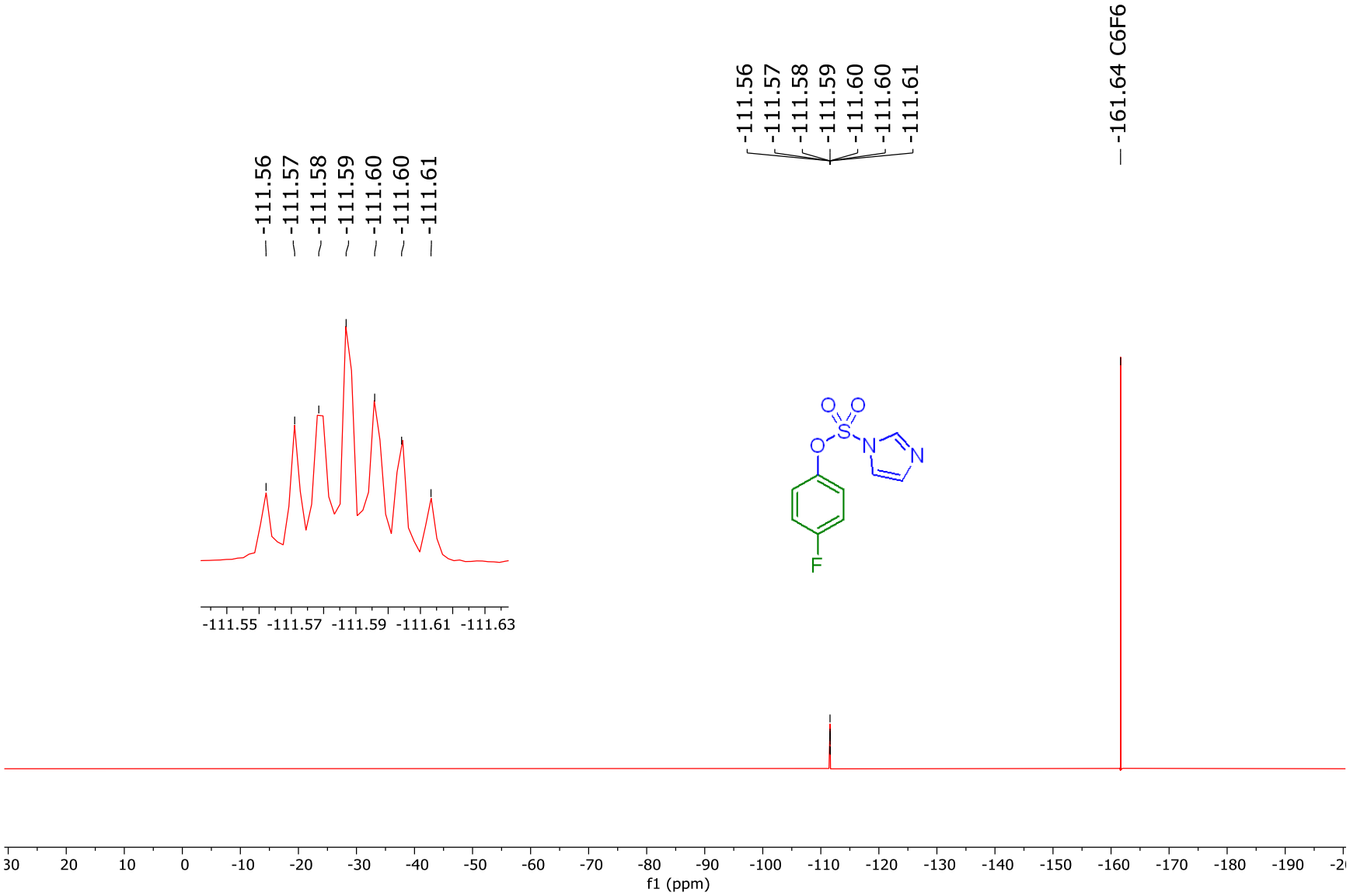
^{1}H NMR of 4-fluorophenyl imidazolylsulfonate (500 MHz, $CDCl_3$) (5.1)



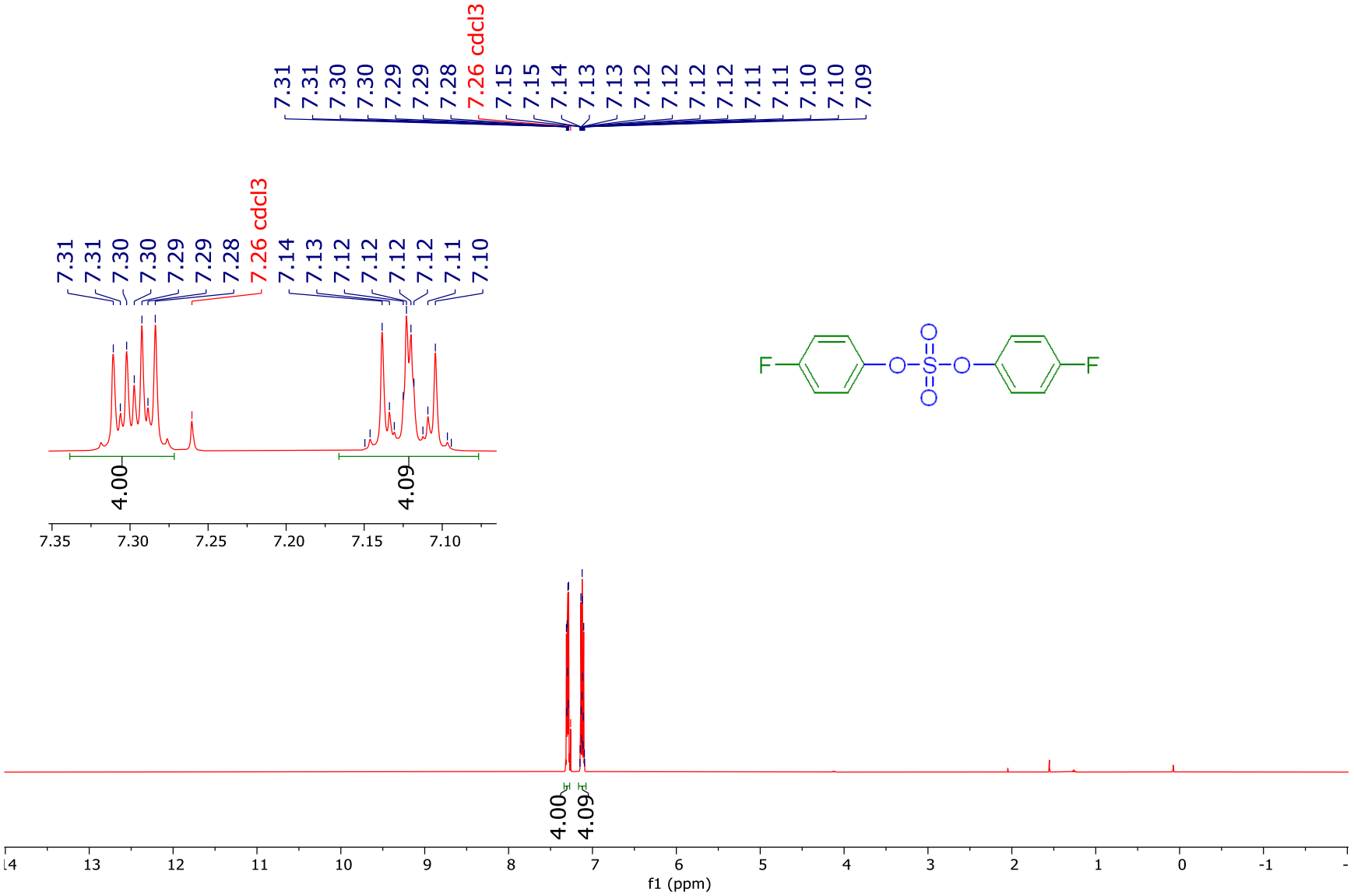
^{13}C NMR of 4-fluorophenyl imidazolylsulfonates (126 MHz, $CDCl_3$) (5.1)



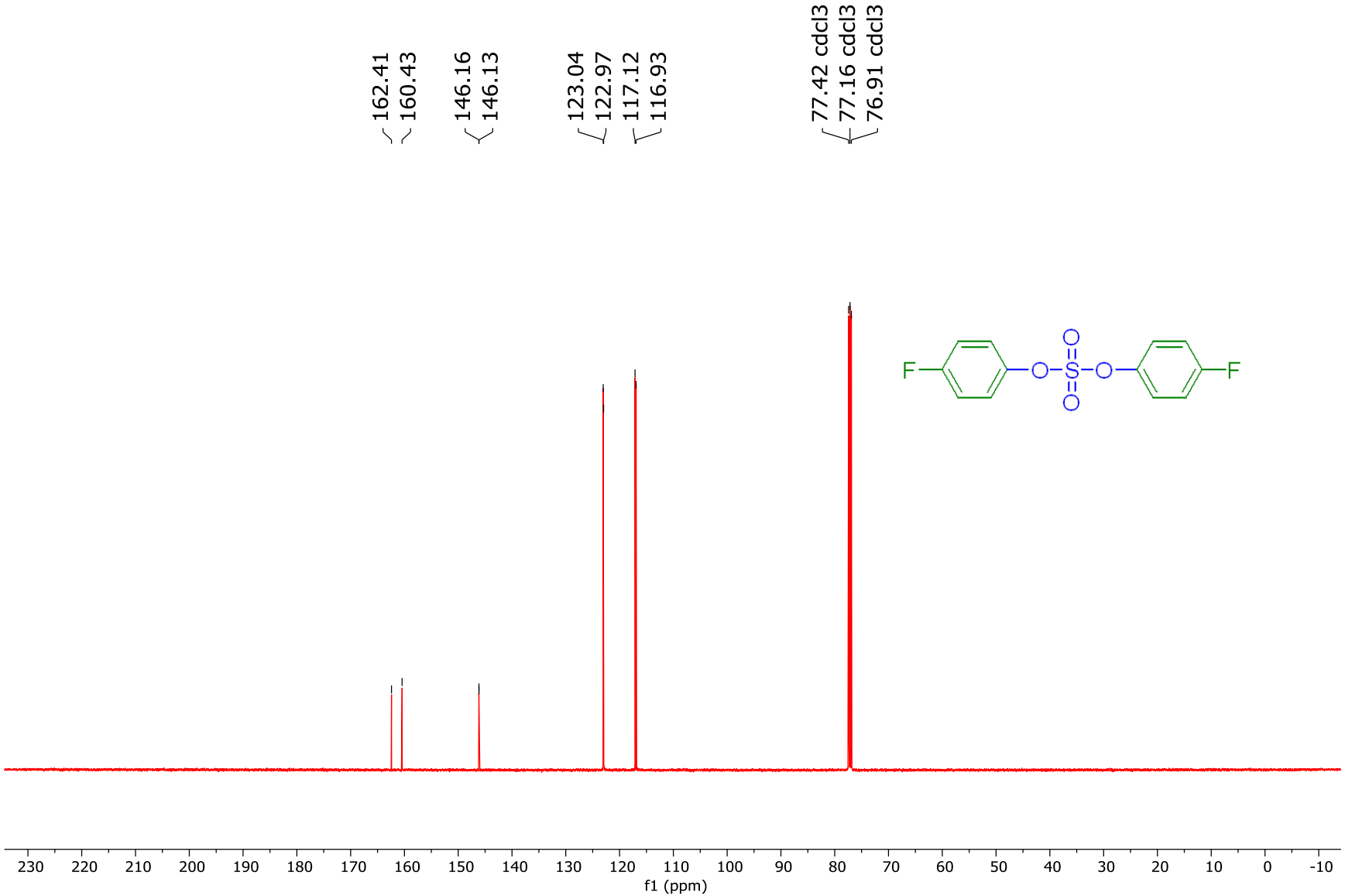
^{19}F NMR of 4-fluorophenyl imidazolylsulfonate (470 MHz, $CDCl_3$) (5.1)



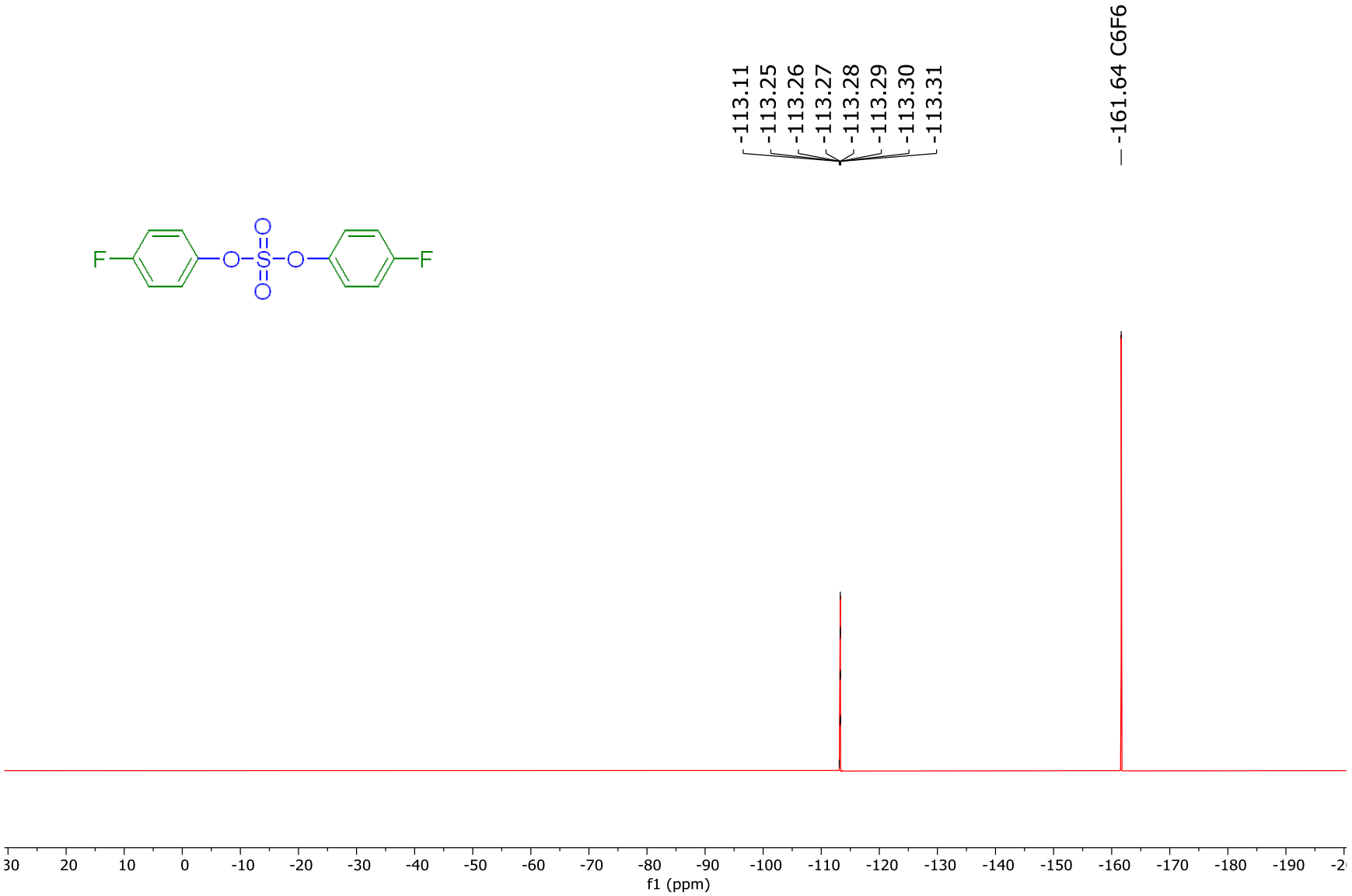
^{1}H NMR of bis(4-fluorophenyl) sulfate (500 MHz, $CDCl_3$) (5.3)



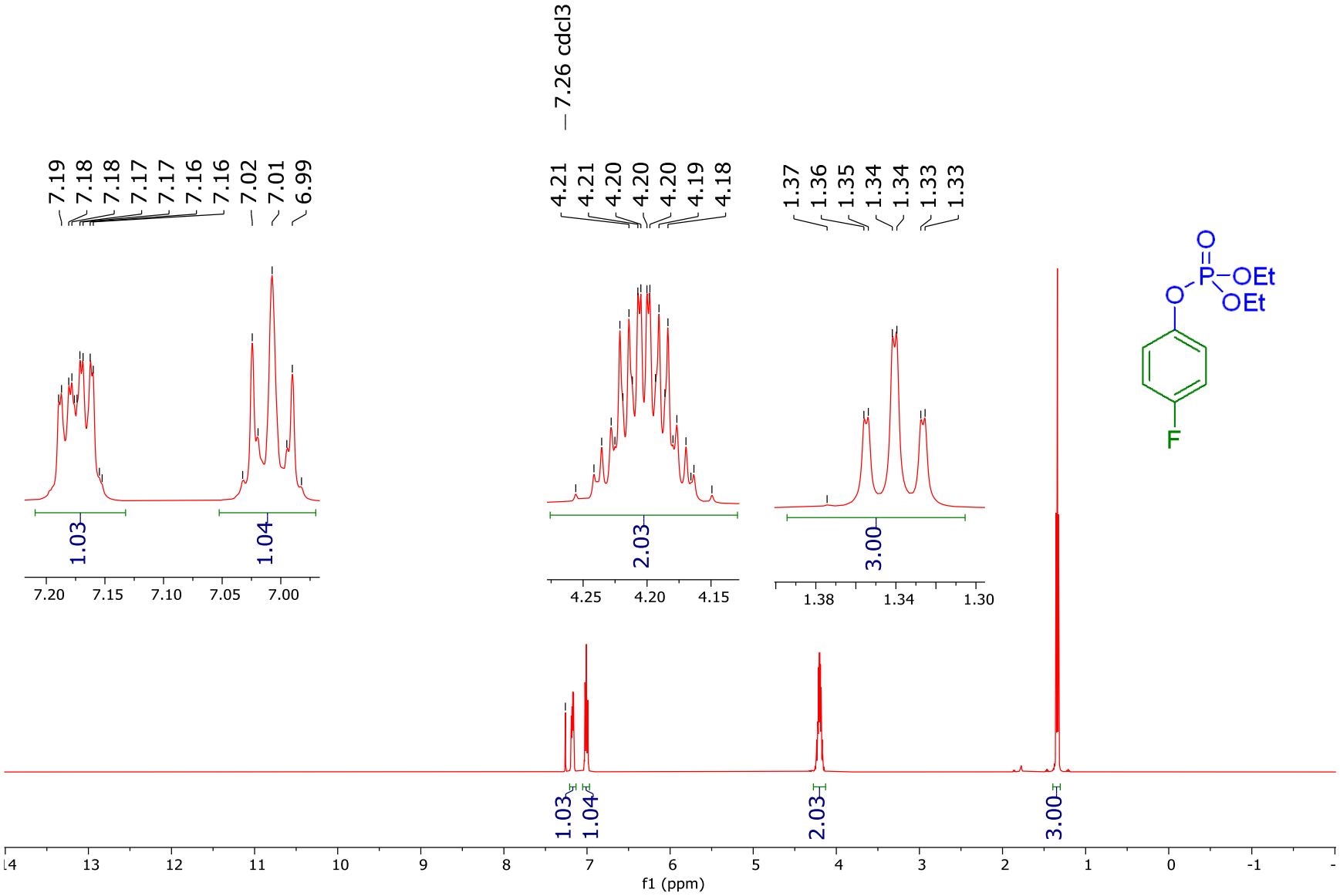
^{13}C NMR of bis(4-fluorophenyl) sulfate (126 MHz, $CDCl_3$) (5.3)



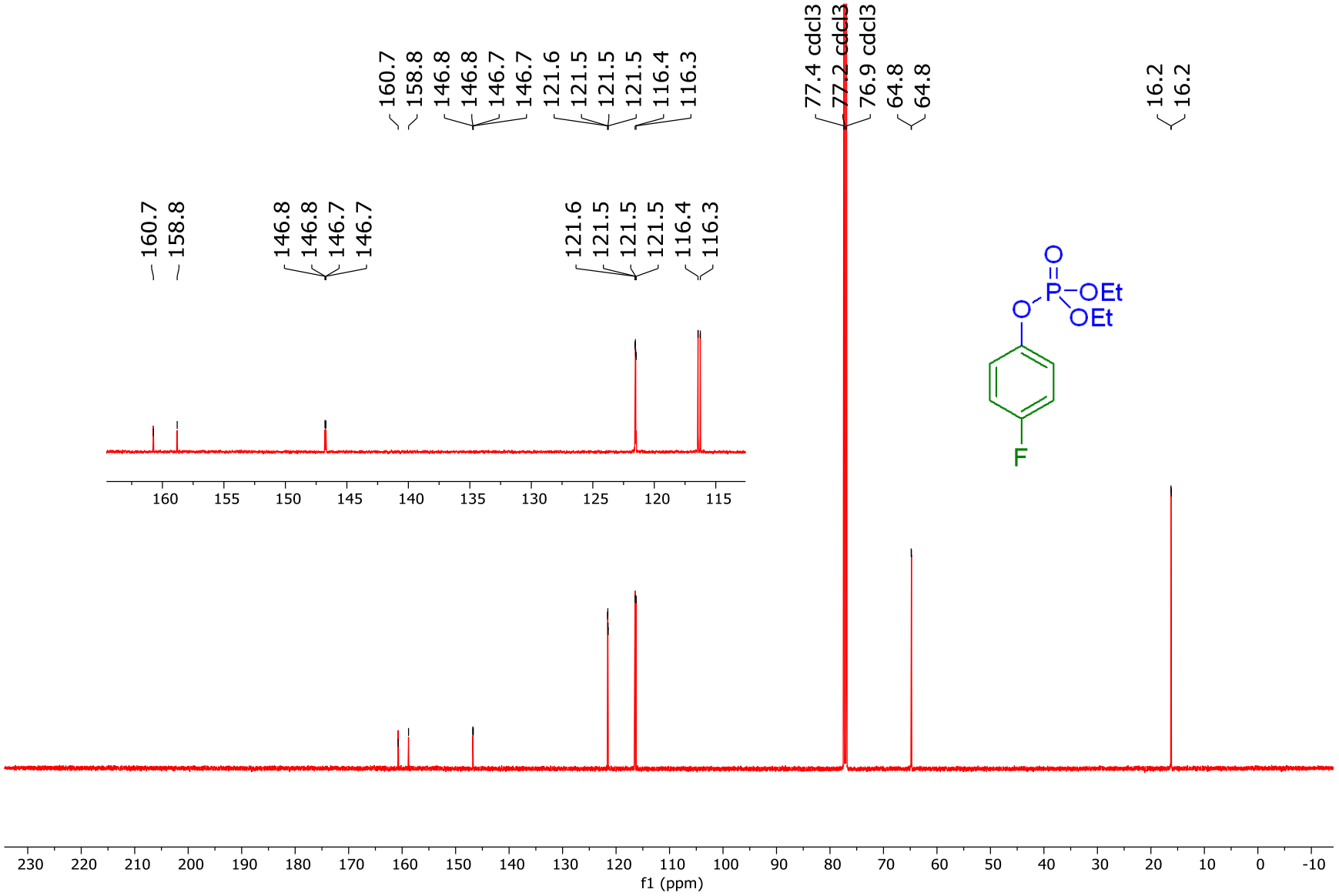
^{19}F NMR of bis(4-fluorophenyl) sulfate (470 MHz, $CDCl_3$) (5.3)



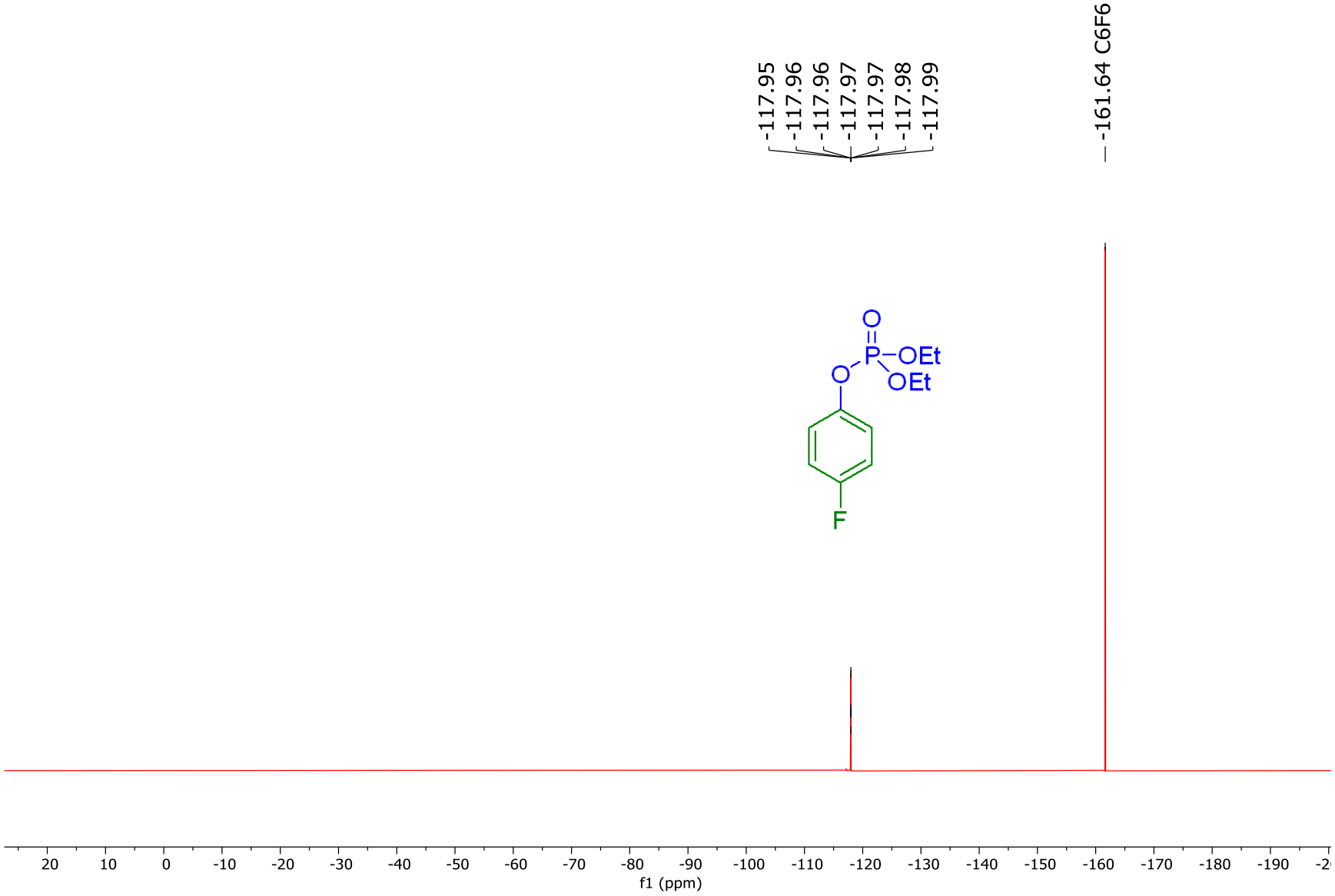
^{1}H NMR of diethyl (4-fluorophenyl) phosphate (500 MHz, $CDCl_3$)



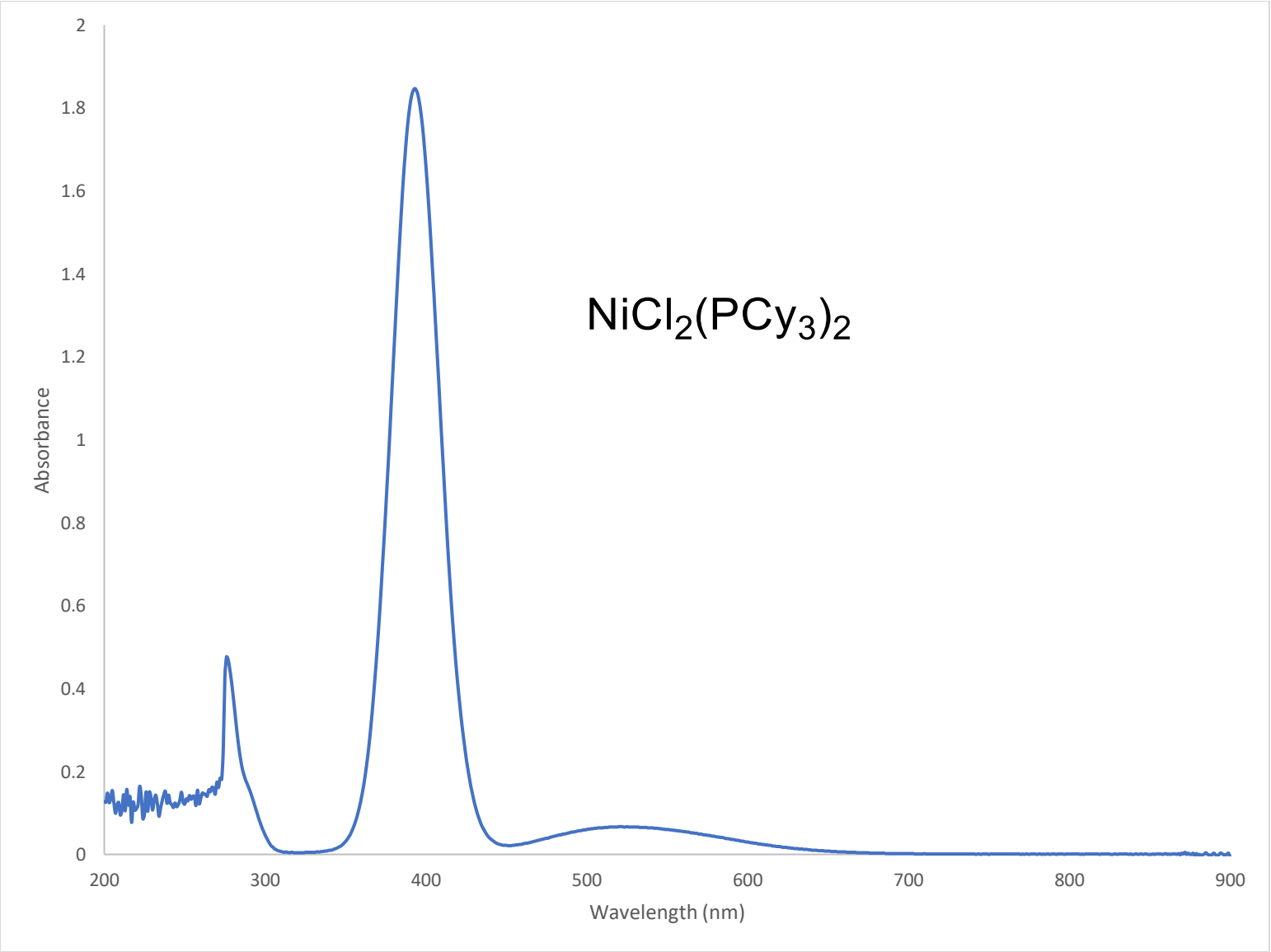
^{13}C NMR of diethyl (4-fluorophenyl) phosphate (126 MHz, $CDCl_3$)



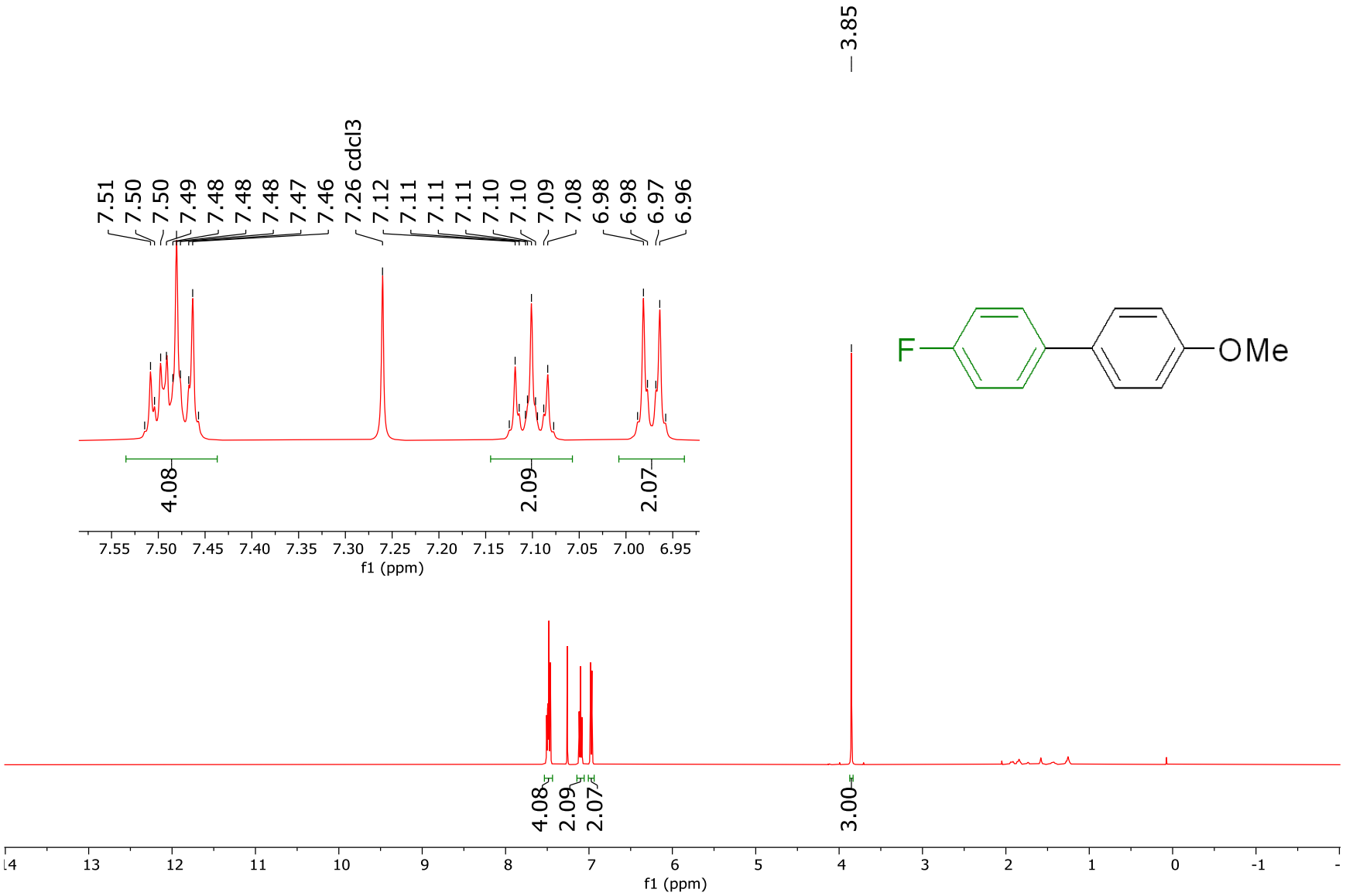
^{19}F NMR of diethyl (4-fluorophenyl) phosphate (470 MHz, $CDCl_3$)



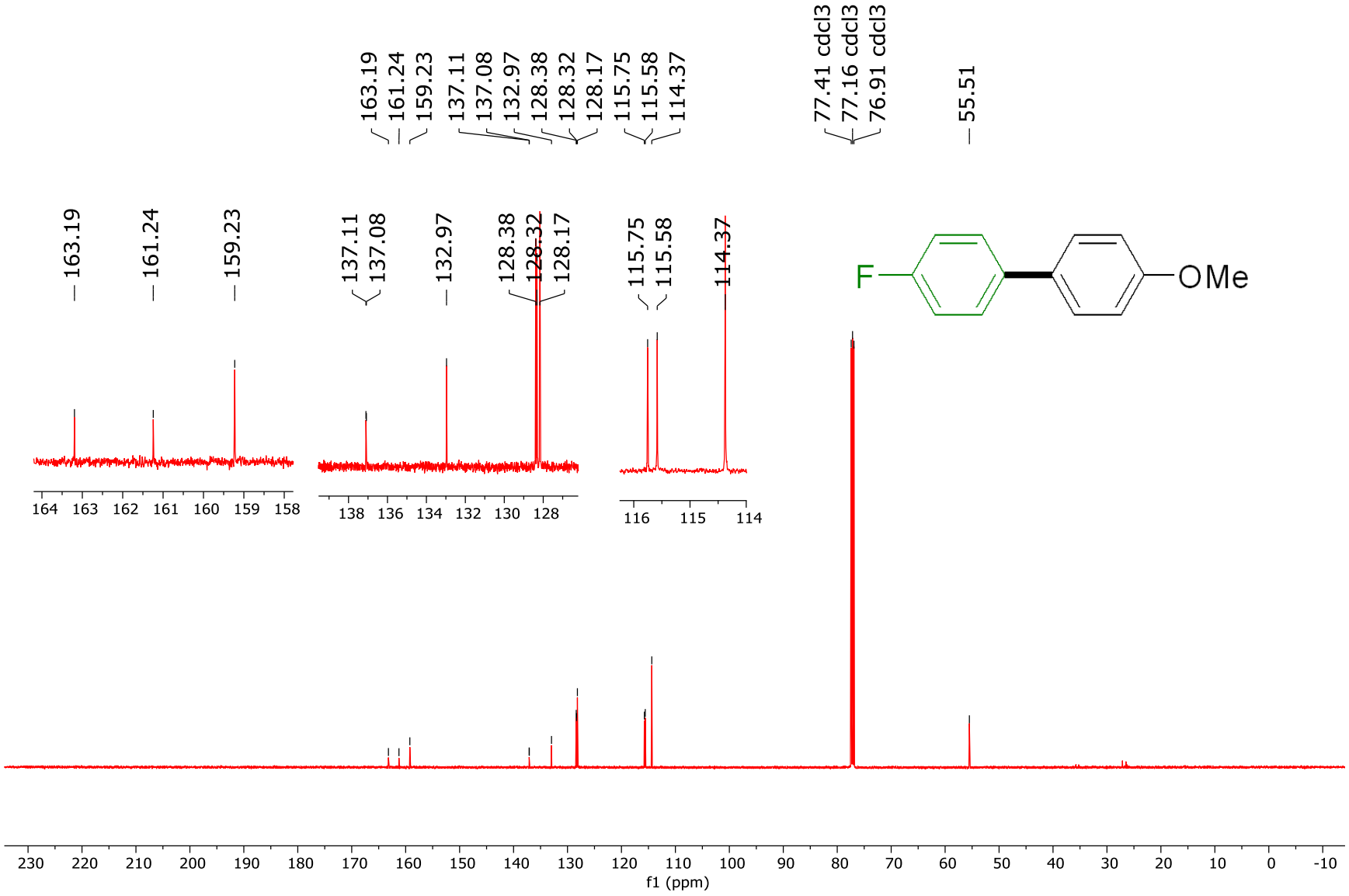
UV-Vis of bis(tricyclohexyl)nickel (II) dichloride



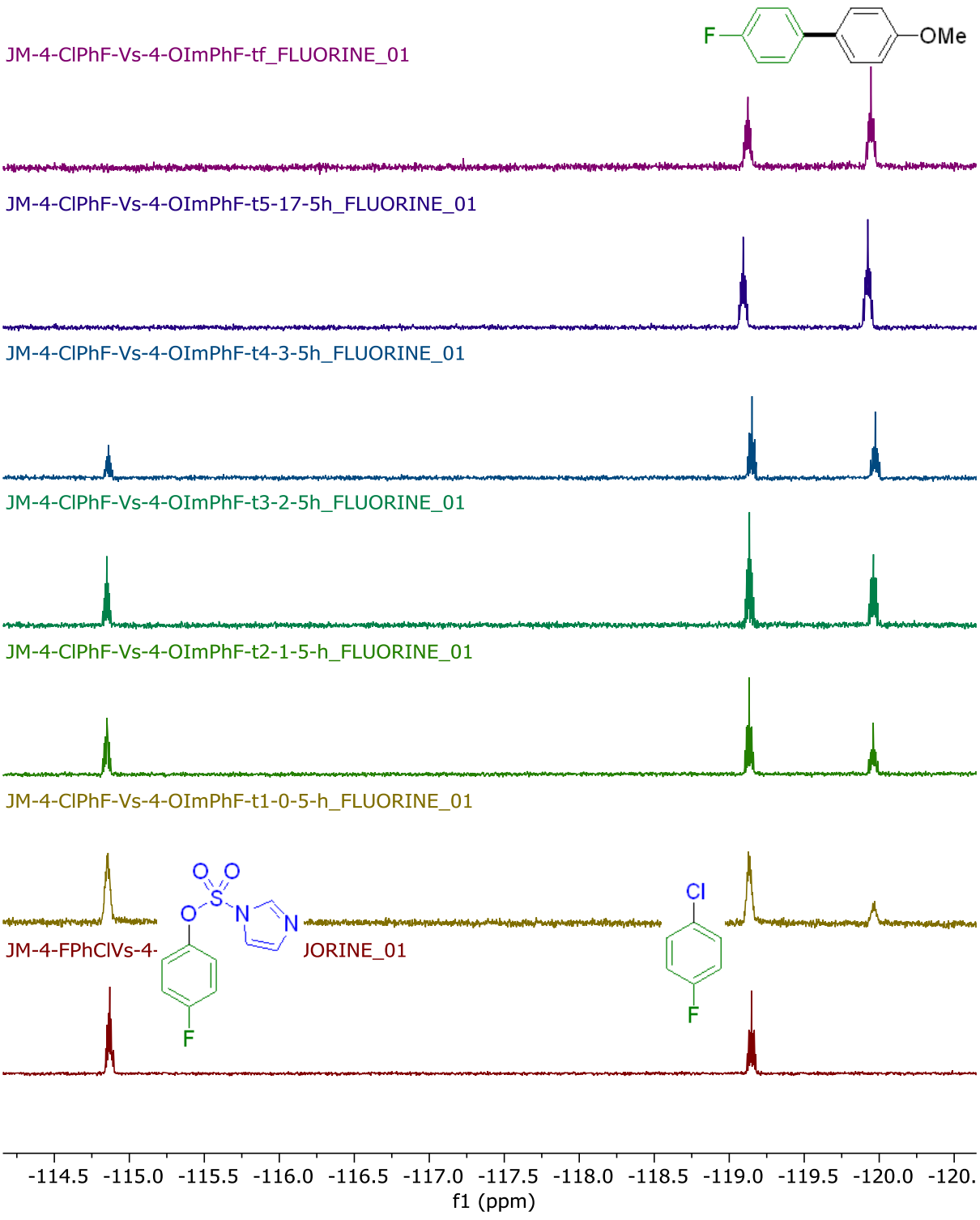
^{1}H NMR of 4-fluoro-4'-methoxy-1,1'-biphenyl (500 MHz, $CDCl_3$) (5.2)



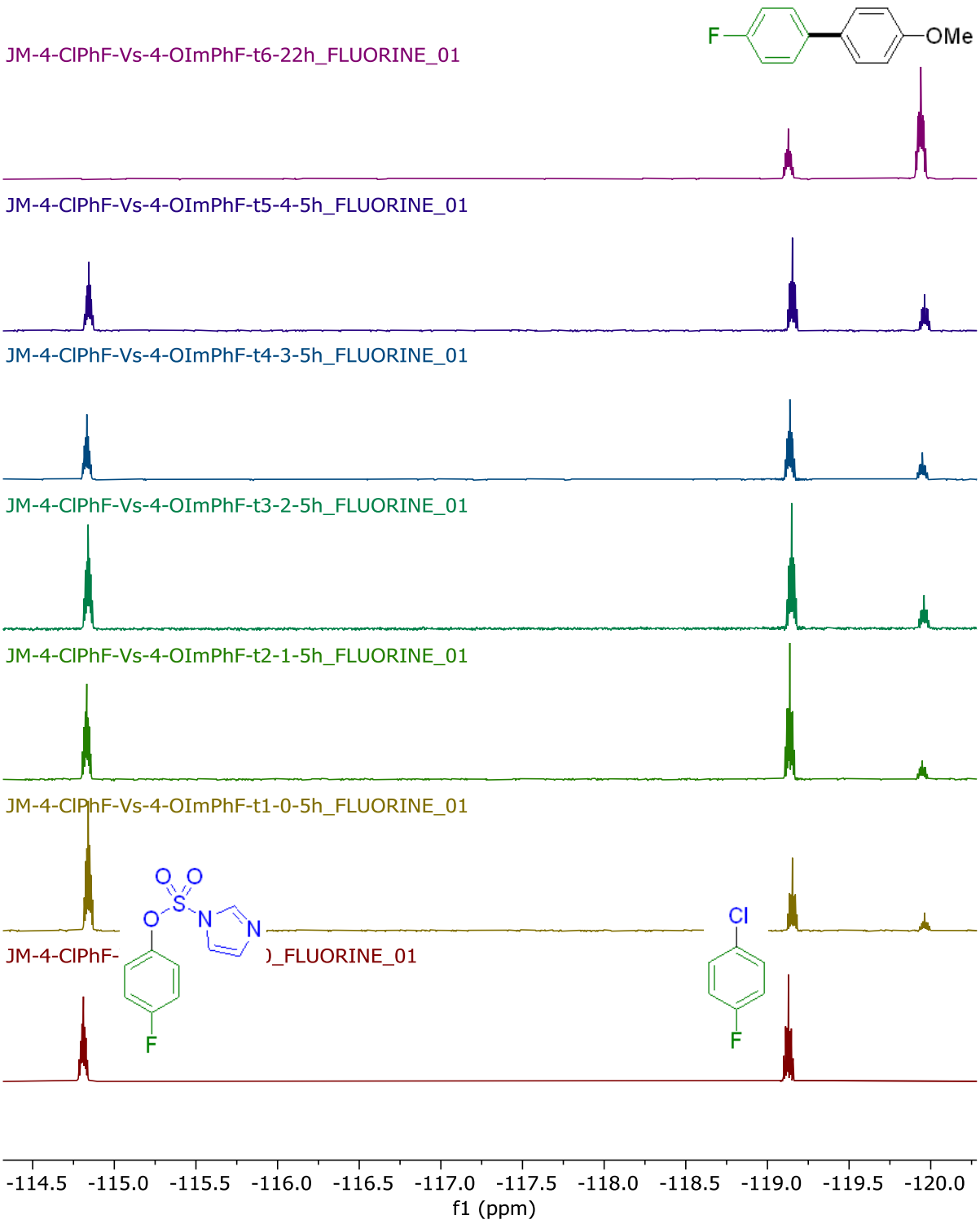
^{13}C NMR of 4-fluoro-4'-methoxy-1,1'-biphenyl (126 MHz, $CDCl_3$) (5.2)



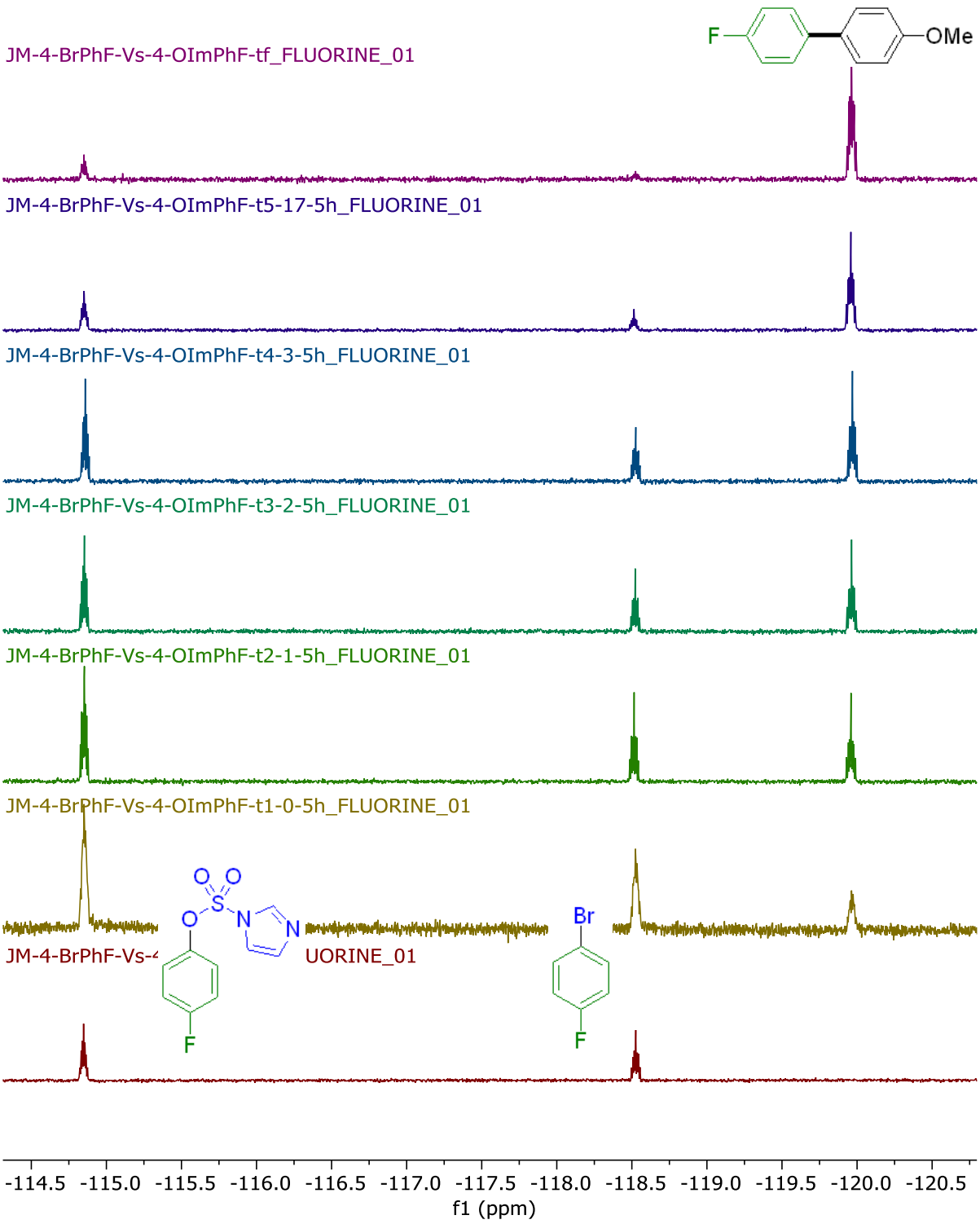
Reactivity Comparison of 4-fluorophenyl chloride vs 4-fluorophenyl imidazolyl sulfonate (condition A): ^{19}F NMR of SMC over time (470 MHz, $CDCl_3$)



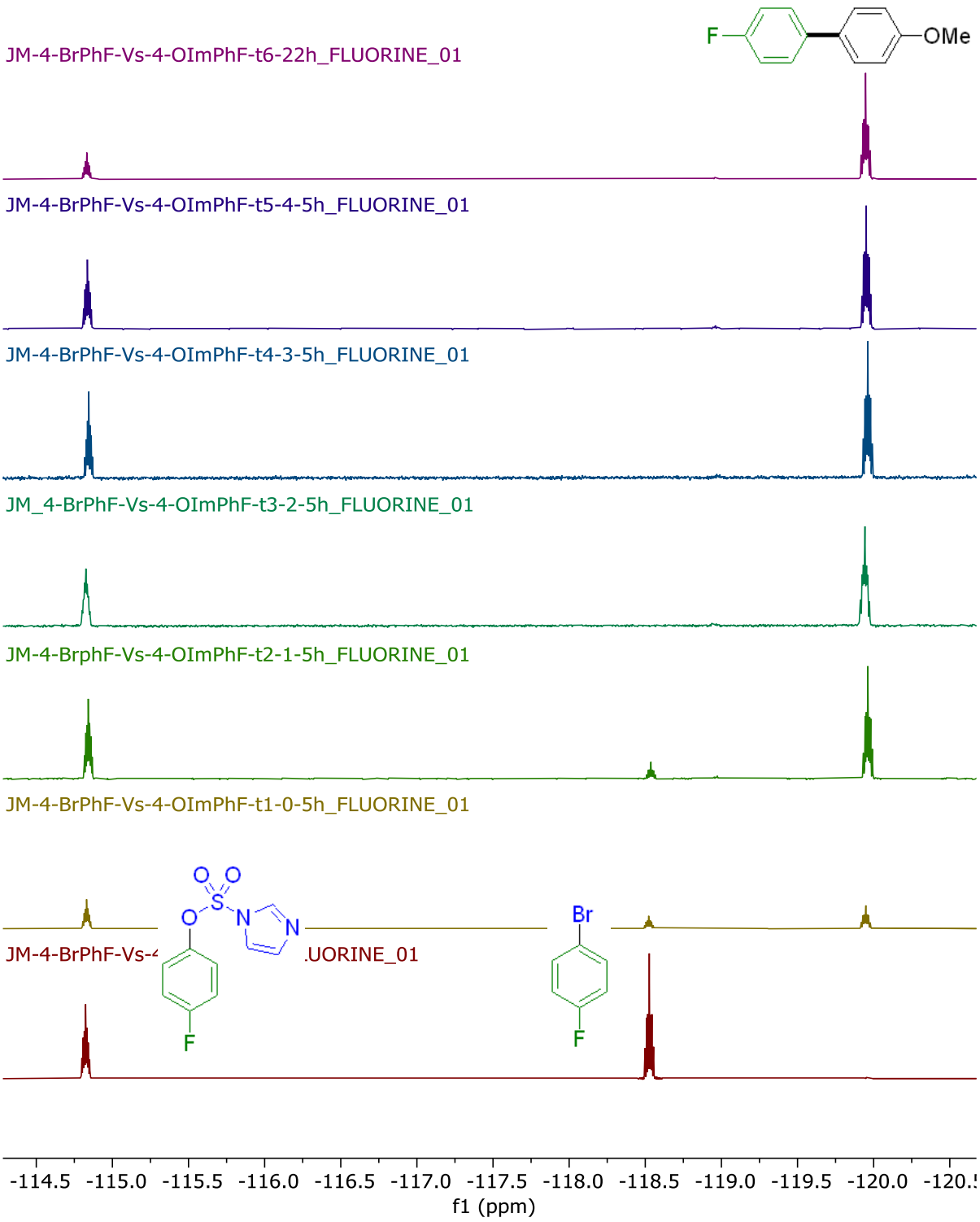
Reactivity Comparison of 4-fluorophenyl chloride vs 4-fluorophenyl imidazolyl sulfonate (condition B): ^{19}F NMR of SMC over time (470 MHz, $CDCl_3$)



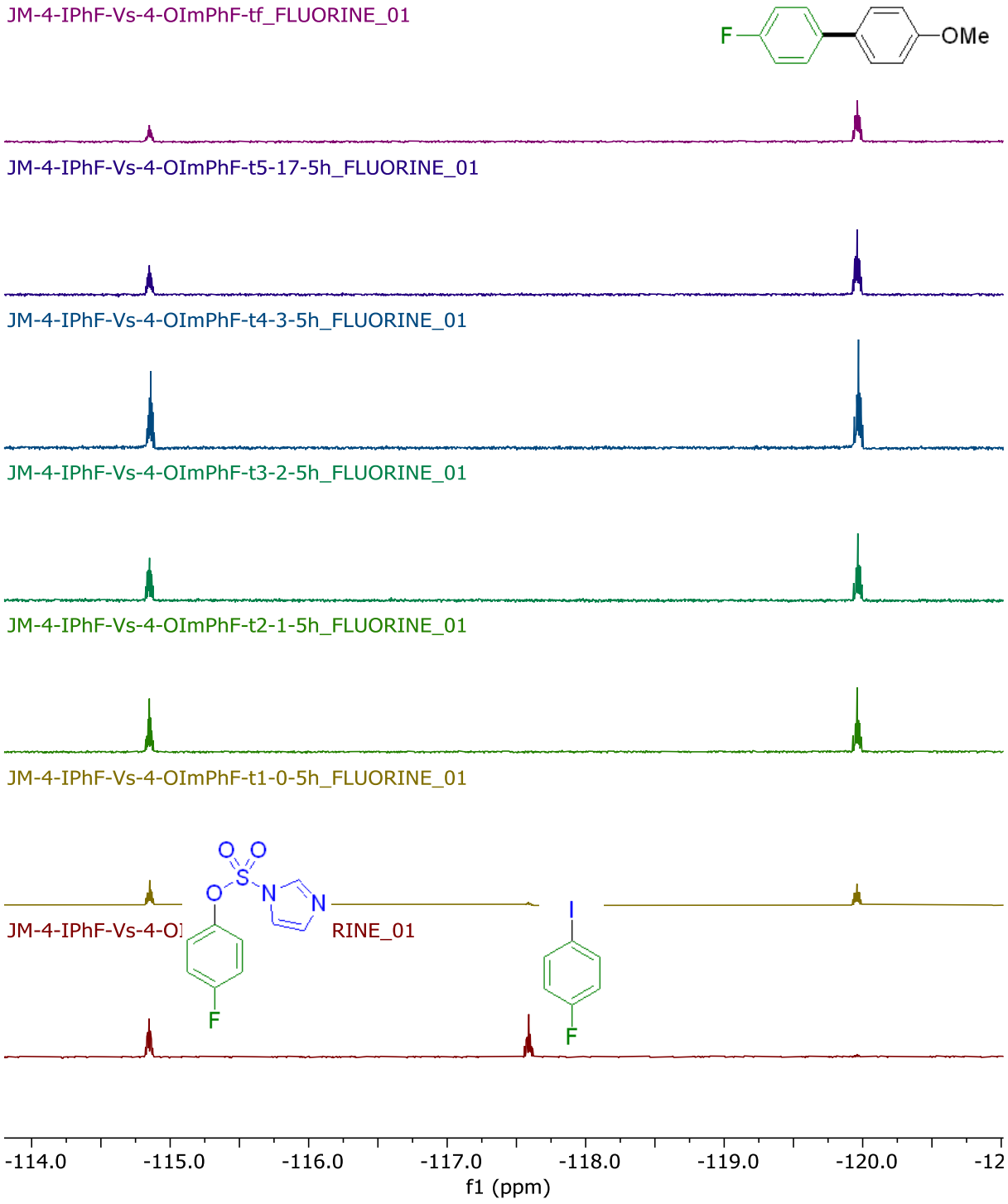
Reactivity Comparison of 4-fluorophenyl bromide vs 4-fluorophenyl imidazolyl sulfonate (condition A): ^{19}F NMR of SMC over time (470 MHz, $CDCl_3$)



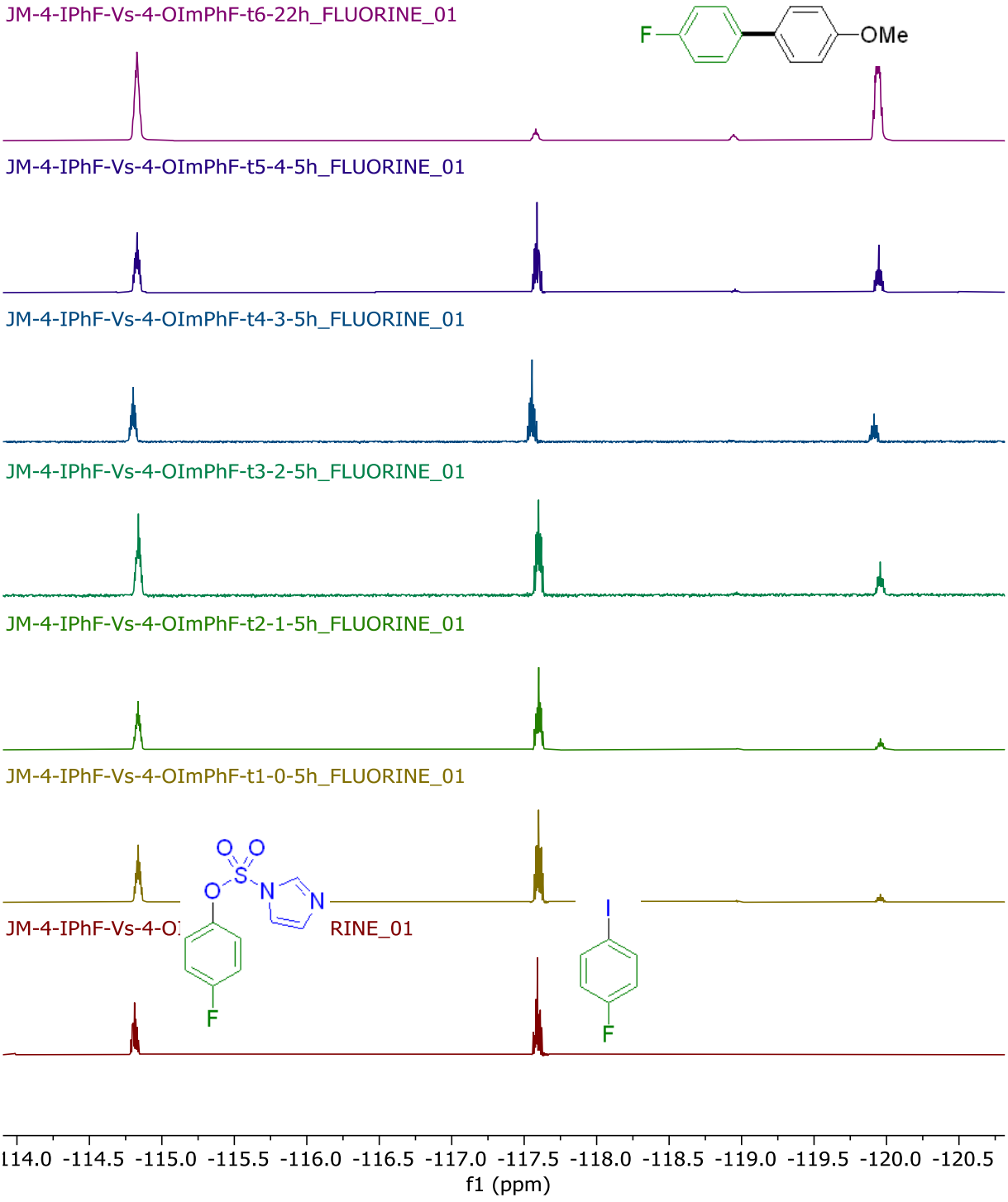
Reactivity Comparison of 4-fluorophenyl bromide vs 4-fluorophenyl imidazolyl sulfonate (condition B): ^{19}F NMR of SMC over time (470 MHz, $CDCl_3$)



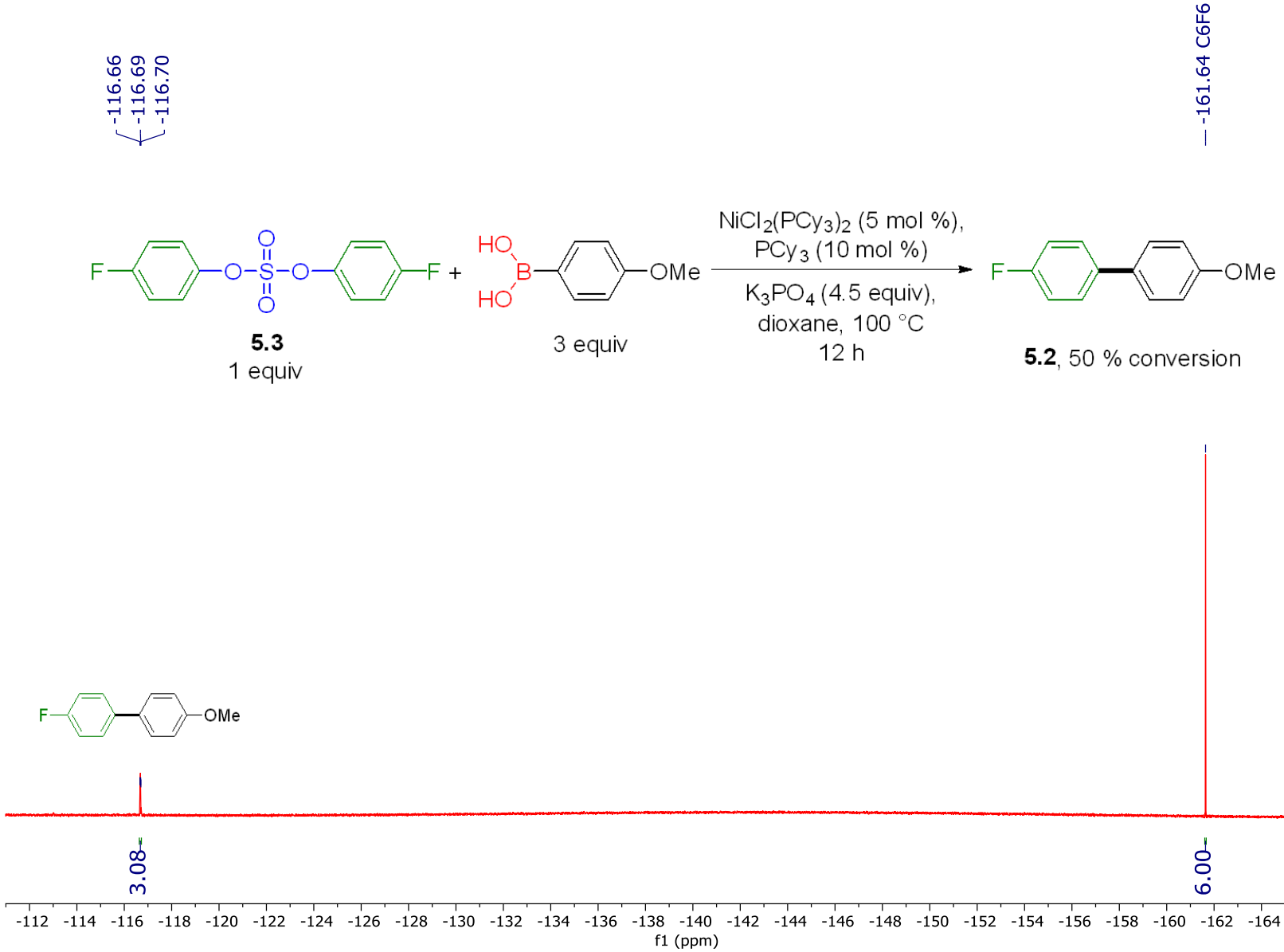
Reactivity Comparison of 4-fluorophenyl iodide vs 4-fluorophenyl imidazolyl sulfonate (condition A): ^{19}F NMR of SMC over time (470 MHz, $CDCl_3$)



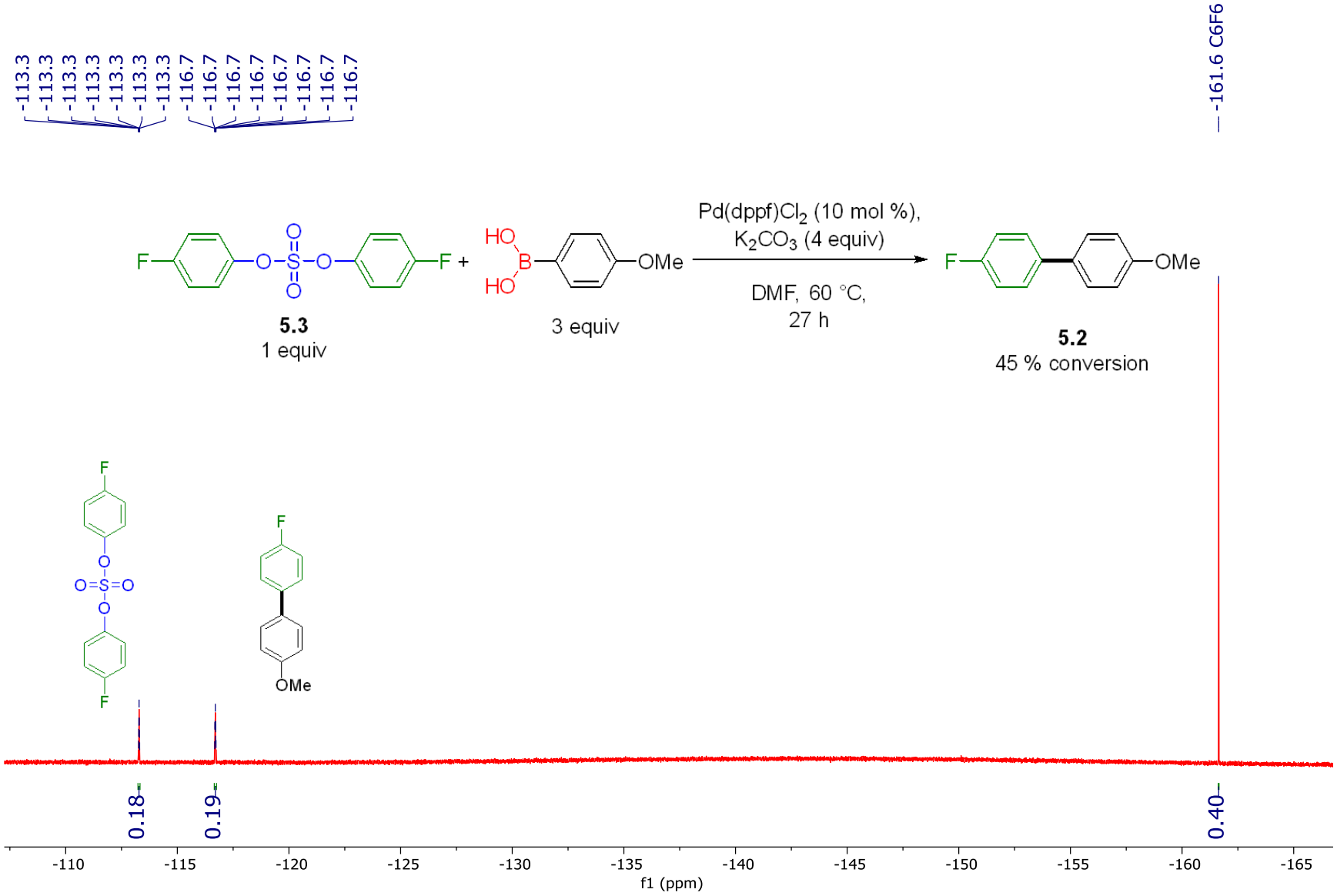
Reactivity Comparison of 4-fluorophenyl iodide vs 4-fluorophenyl imidazolyl sulfonate (condition B): ^{19}F NMR of SMC over time (470 MHz, $CDCl_3$)



^{19}F NMR of nickel-catalyzed SMC of bis(4-fluorophenyl)sulfate (470 MHz, $CDCl_3$)



^{19}F NMR of palladium-catalyzed SMC of bis(4-fluorophenyl)sulfate (470 MHz, $CDCl_3$)



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