Exploring New Reaction Pathways Mediated by Palladium(IV) Complexes

BY

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Submitted to the graduate degree program in Chemistry and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Date approved: July 23, 2013

Abstract

Carbon-carbon bond-forming processes featuring palladium catalysts play an important role in the synthesis of biologically active organic compounds. In the early 2000s, Canty, Sanford, Ritter and others have focused on studying palladium complexes in the oxidation state Palladium(IV). The Pd^{II}-Pd^{IV} transformations possess distinct advantages over the traditional catalytic process mediated by palladium in the oxidation states Palladium(0) and Palladium(II). In these transformations, reductive elimination to form new C-C bonds from the Pd^{IV} intermediate is expected to occur at a faster rate than β-hydride elimination. Overall, the $C(sp^3)$-$C(sp^3)$ bond coupling is expected to be favorable.

In the past decade, the Malinakova group has been studying the synthesis of unique pallada(II)cycles and exploring their reactivity with different electrophilic organic oxidants. These studies established that allyl halides as well as vinyl and alkynyl iodonium salts are capable of producing Pd^{IV} complexes possessing three Pd-C bonds. A stable Pd^{IV} complex was isolated, characterized and shown to mediate the formation of a heterocycle. In this Dissertation, the synthesis of various Pd^{IV} complexes and studies aimed at explaining the range of fundamental transformations at the Pd^{IV}-center beyond reductive elimination are presented.

Chapter One discusses a general introduction into Palladium(IV) chemistry which includes a comparison between Pd^{0}-Pd^{II} and Pd^{II}-Pd^{IV} catalytic cycles. This introduction also documents the observed and the proposed advantages of Palladium(IV) complexes in the applications to organic synthesis.

Chapter Two constitutes a review of Palladium(IV) complexes in organometallic chemistry with particular emphases on the following themes in Palladium(IV) chemistry: (1) the use of strong oxidants to create various Pd-carbon or Pd-heteroatom bonds; (2) the presence of stabilizing ligands to aid in isolating the Pd^{IV} complexes; (3) the overview of known organometallic transformations being mediated by the Pd^{IV}-center

Chapter Three provides the preliminary studies into the use of diazonium salt oxidants to generate Pd^{IV} complexes at low temperatures. The Pd^{IV} complexes feature the tripodal tris(pyrazol-1-yl)borate (Tp) ligand as well as two Pd-C(sp^3) bonds and the oxidant generates a new Pd-C(sp^2) bond. Detailed ^1H NMR spectroscopic studies at low temperature provided the evidence of the formation for the (Tp)Pd^{II} intermediate via ligand exchange and the formation of the desired Pd^{IV} complexes in solution.

Chapter Four describes the study of Pd^{IV}-mediated C-H activation in an organic oxidant yielding Pd^{IV} complexes with multiple Pd-C(sp^2/sp^3) bonds. Reductive elimination generates a complex heterocycle featuring two new C(sp^2)-C(sp^3) bonds. Detailed low temperature ^1H NMR spectroscopic studies monitor the formation of the Pd^{IV} intermediates, give insight into the oxidative addition and C-H activation pathway during the reaction sequence and confirm carbon-carbon bond-formation by establishing the structure of the final organic product.

Chapter Five details the synthesis of stable Pd^{IV} complexes featuring different auxiliary ligands. These Pd^{IV} complexes, which also possess the stabilizing tripodal Tp ligand, are generated in the presence of iodonium salts. The chapter reports our studies on the effect of the electronic

properties of auxiliary ligands on the reactivity of the Pd^{IV} complex. The studies detailed in the chapter were aimed at exploring the C-H activation in organic substrates induced by the Pd^{IV} complexes. However, initial work indicated a limited scope of ligand substitution reactions, which prevented us from realizing the desired C-H activation on the organic substrate. Detailed ligand exchange studies with nucleophiles/additives are described in this chapter.

Acknowledgements

I would like to dedicate this work to my husband Kolbe Scheetz, my daughter Elizabeth Scheetz, and all my family members, the Ruffies, the Russells and the Scheetzes, who have given me their love and support during my doctoral work. I would not have been able to complete this work without you and I am grateful for everything you have given me.

I would also like to thank my boss, Dr. Helena Malinakova, and my group members, Dr. Lucas McCormick and Sandeep Raikar, as well. Without their guidance, support and wisdom, I would not have been able to complete my dissertation work. I would also like to thank the University of Kansas NMR Personnel, Dr. Justin Douglas and Sarah Neuenswander, for all the help they gave me with all my NMR studies.

Thank you to all my friends I have made throughout my time at KU. I will cherish the memories we have made during my tenure at KU. I hope to keep in contact with all of you as my family and I move forward in our lives.

A special thank you is owed to Dr. Jackson, Dr. Tunge, Dr. Barybin and Dr. Gegenheimer as well. I appreciate the time you have taken to serve on my committee.

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Abbreviations

Å	angstrom
Acetone-d_6	acetone (deuterated)
Ac	acetyl
Ar	aryl
B	base
Bpy	bipyrdine
t-Bu	*tert*-butyl
$CDCl_3$	chloroform (deuterated)
COSY	correlation spectroscopy
dba	dibenzylideneacetone
DCM	dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
dppe	1,2-bis(diphenylphosphino)ethane
E	electrophile
equiv.	equivalent(s)
Et	ethyl
et al.	and others
F-TEDA-BF_4	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
g	gram(s)
GC-MS	Gas Chromatography-Mass Spectrometry
h	hour(s)

HMBC	Heteronuclear multiple-bond correlation spectroscopy
HSQC	Heteronuclear single-bond correlation spectroscopy
L	ligand
Me	methyl
M	moles per liter
MHz	megahertz
min	minutes
mg	milligram(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
NFTPT	*N*-fluoro-2,4,6-trimethylpyridinum triflate
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
phen	1,10-phenanthroline
ppm	parts per million
pz	pyrazolyl
R_f	retention factor
S_N2	bimolecular nucleophilic substitution
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin layer chromatography
tmeda	tetramethylethylenediamine
Tp	tris(pyrazoly-1-yl)borate
X, Z	auxiliary ligands

Chapter One

Introduction to Palladium(IV) Chemistry

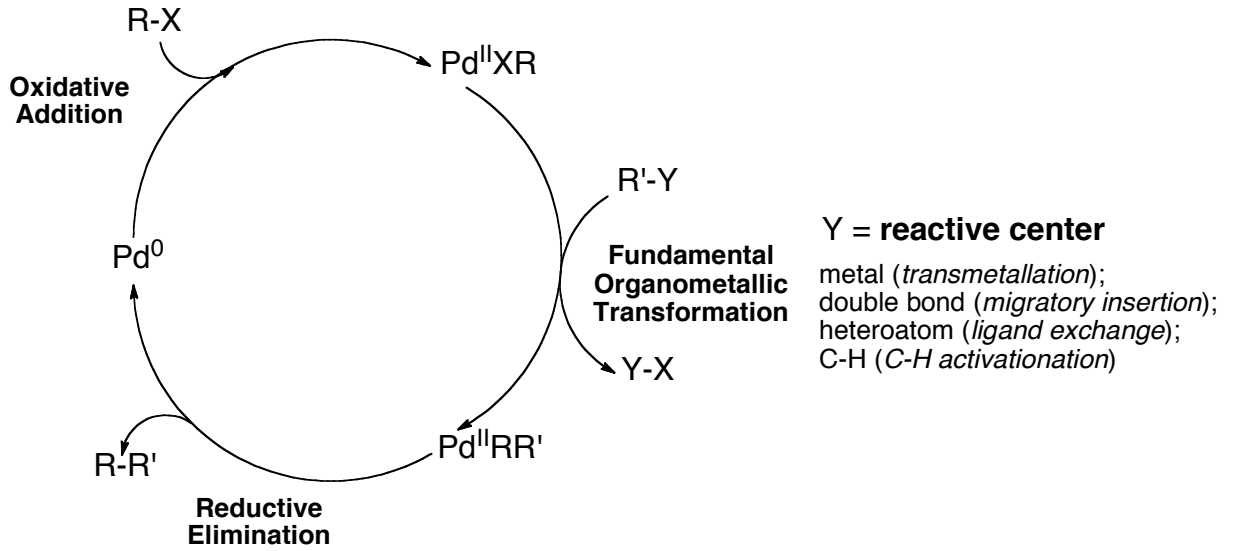
1.1: Introduction

Bond-forming reactions performed by palladium catalysts have played a significant role in synthetic organic chemistry. During the reactions, the palladium catalyst serves as the reactive center that activates carbons allowing for the formation of new carbon-atom bonds. This process is used to install heteroatoms[1-3], synthesize heterocycles[4], medicinal products[5] and other complex organic products[6].

In the Pd-catalyzed bond-forming reactions, there are two possible catalytic pathways that differ in the oxidation state of the starting Palladium catalyst. The most common pathway involves the lower oxidation states of palladium, or Pd^{0}-Pd^{II} complexes, as the intermediates and the active centers in the catalytic bond-forming reaction. This pathway is proposed in catalytic systems that feature weak oxidants or in the presence of electron-rich substrates.

1.2: Palladium(0)-Palladium(II) versus Palladium(II)-Palladium(IV)

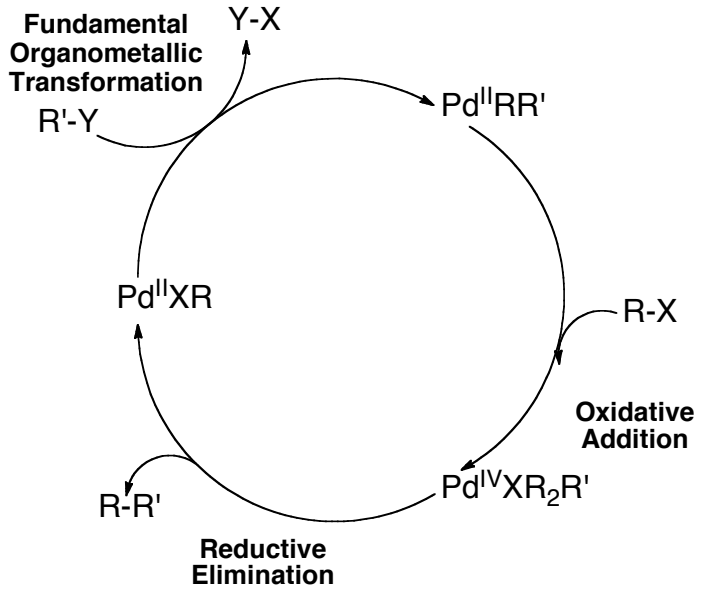
The reaction starts with oxidative addition to the Pd^{0} catalyst to form a new Pd^{II} intermediate that contains the organic fragment for the bond-forming reaction. The next step involves a fundamental organometallic transformation such as migratory insertion, transmetallation, C-H activation or ligand exchange (Scheme 1.1) that has two important requirements: first; the transformation does not change the oxidation state of the Pd^{II} intermediate and second; the transformation inserts the second organic fragment necessary for the bond-forming reaction. Reductive elimination from the new Pd^{II} intermediate returns the starting Pd^{0} catalyst and yields the desired organic product with the newly coupled bond (Scheme 1.1).



Scheme 1.1: Traditional Pd^0/Pd^{II} catalytic cycle

The other possible catalytic pathway involves the higher oxidation states of palladium, or Pd^{II}-Pd^{IV} complexes, as the intermediates and the active centers in the catalytic bond-forming processes. These were initially proposed as the active centers in reactions that featured strong oxidants or electron-deficient substrates.

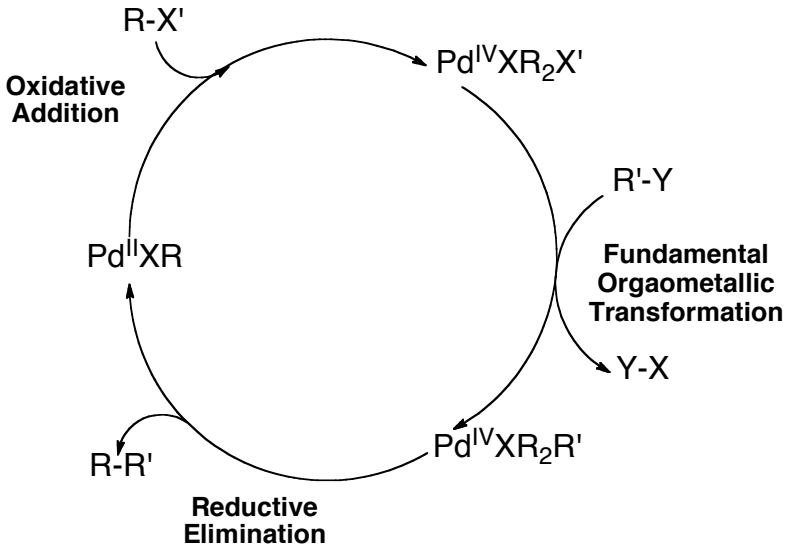
The Pd^{II}-Pd^{IV} catalytic reactions start with the fundamental organometallic transformation at the initial Pd^{II} catalyst to form a new Pd^{II} intermediate. This transformation does not change the oxidation state of the Pd catalyst and inserts the new organic fragment needed for the bond-forming process. Next oxidative addition into the Pd^{II} intermediate occurs and forms the new Pd^{IV} intermediate, which contains another organic fragment. This new fragment can either be involved in the coupling process or can remain on the catalyst for the next cycle. Reductive elimination from the Pd^{IV} intermediate returns the starting Pd^{II} catalyst and yields the desired organic product with the newly coupled bond (Scheme 1.2).



Scheme 1.2: Traditional Pd^{II}/Pd^{IV} catalytic cycle

Within the last 10 years, Pd^{IV} research has shifted towards investigating the stability of the Pd^{IV} intermediates and studying what possible fundamental organometallic transformations, such as C-H bond activation, can be done at the Pd^{IV} center in order to expand the synthetic applications of the Pd^{II}-Pd^{IV} catalytic cycles. These transformations would functionalize organic compounds in ways that cannot be done by the other Pd-catalyzed bond-forming pathways, allowing for synthesis of new and unique organic compounds.

When investigating the reactivity of the Pd^{IV} intermediates, authors typically use "model complexes" to build the desired Pd^{IV} complexes. In these model complexes, it is important that the oxidation of the initial Pd^{II} complex creates a stable Pd^{IV} intermediate that can be detected through traditional organic techniques such as isolation, NMR or X-Ray analysis. Reductive elimination from the Pd^{IV} intermediate then gives the desired organic product featuring the newly coupled bond and returns the starting Pd^{II} catalyst (Scheme 1.3).



Scheme 1.3: Recent Pd^{II}/Pd^{IV} Catalytic Studies

1.3: Unique Features of Palladium(IV) Complexes for Applications in Catalysis

Kinetic studies were performed to gain a better understanding of the differences between the Pd^{II}-Pd^{IV} catalytic cycle and the traditional Pd^{0}-Pd^{II} catalytic cycle. The first kinetic investigation into the oxidative addition of MeI to [$PdMe_2$(bpy)] revealed that the initial Pd^{II} catalyst is inserted into the C(sp^3)-I bond via an S_N2 mechanism. The subsequent reductive elimination step released ethane featuring a new C(sp^3)-C(sp^3) bond and the Pd^{II} catalyst. Little to no formation of any C(sp^3)-I bonds occurred in the reductive elimination step.[7-8]

Further kinetic studies determined that the oxidative addition step in Pd^{II}-Pd^{IV} catalytic cycles occurs via a similar S_N2 mechanism regardless of the starting C(sp^3)-X starting material. The subsequent reductive elimination step in the Pd^{II}-Pd^{IV} catalytic cycle, however, showed an ability to form new bonds featuring C(sp^3) centers rather than C(sp^2) centers. This bond formation is

different than Pd^{0}-Pd^{II} catalytic cycles, which show a preference towards the formation of new bonds featuring $C(sp^2)$ centers.

The overall preference for bond formation via reductive elimination in a Pd^{II}-Pd^{IV} catalytic cycle is: $C(sp^3)$-$C(sp^3)$ > $C(sp^2)$-$C(sp^3)$ > $C(sp^3)$-X > $C(sp^2)$-X.[9] Using this preference, Pd^{II}-Pd^{IV} catalytic cycles are advantageous in synthetic bond-forming reactions that functionalize $C(sp^3)$ centers. However, later studies conducted by Catellani, Malinakova and Sanford show preference for the functionalization of a $C(sp^2)$ center if an Pd-aryl bond is present, [10-15] suggesting that the bond formation preference may vary depending on the reaction conditions. The discussion of these results can be seen in Chapter 2, Section 2.4.1.2 on page 27.

1.4: Chapter One Bibliography

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Chapter Two

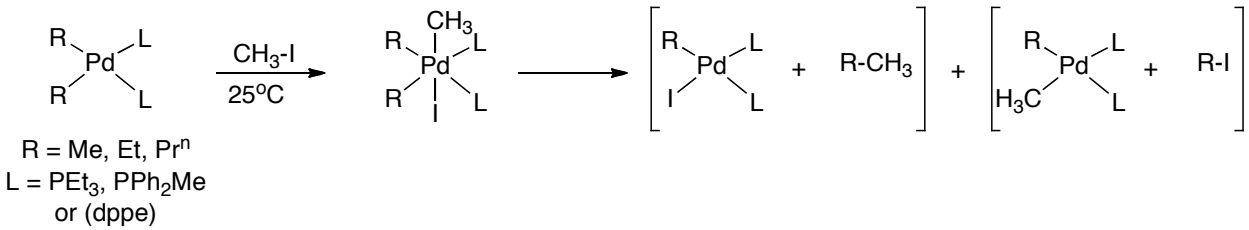
Historical Background of Palladium(IV) Chemistry

2.1: Palladium(IV) in Inorganic Chemistry

It is useful to review the history of Pd^{IV} chemistry in order to understand how Pd^{IV} chemistry may be used to develop synthetic processes.[1-2] Originally, Pd^{IV} complexes were synthesized via oxidation of Pd^{II} catalysts with halogens to yield $[L_2PdX_4]^{2-}$ complexes where X was either chloro or bromo ligands and neutral stabilizing ligands, such as nitrogen- or phosphine-based ligands.[3-6] While these highly halogenated Pd^{IV} complexes could be detected by ^1H NMR analysis, they would readily decompose during isolation making them impractical for synthetic purposes. Other studies into the synthesis of stable Pd^{IV} complexes included electrochemical oxidation of a Pd^{II} catalyst also proved to be successful.[7-8] However, electrochemical oxidation is not synthetically useful due to the limited oxidation selectivity and is mainly reserved for synthesizing Pd^{I} or Pd^{III} complexes.

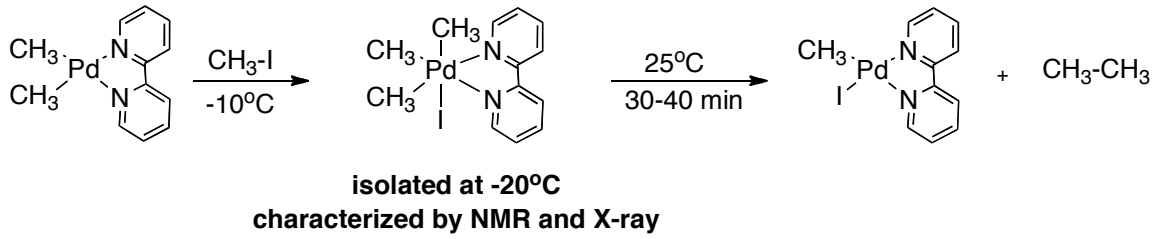
2.2: Palladium(IV) in Organometallic Chemistry

Organopalladium compounds are defined as complexes featuring at least one Pd-carbon bond. The first proposed synthesis of a Pd^{IV} complex featuring a Pd-C bond was reported in 1975 by Uson and co-workers.[9] However, these complexes were reduced easily and could not be characterized. In 1977, Yamamoto and co-workers proposed the presence of Pd^{IV} complexes resulting from the oxidation of phosphino-Pd^{II} complexes with MeI.[10] The subsequent reductive elimination from the suggested Pd^{IV} intermediate would then give various carbon-carbon bonds (Scheme 2.1). However, reductive elimination would occur readily, making isolation of the suggested Pd^{IV} intermediate difficult.



Scheme 2.1: Reported Palladium(IV) complex by Yamamoto[10]

In 1986, Canty and co-workers described the first synthesis and isolation of a Pd^{IV} complex at -20°C[11] (Scheme 2.2). The Pd^{IV} complex was synthesized via oxidation of a Pd^{II} catalyst with MeI and featured three Pd-C(sp^3) bonds as well as a bidentate nitrogen ligand. Upon reductive elimination, the Pd^{IV} complex yielded ethane at 25°C. A kinetic investigation performed on this reaction sequence determined that there was a preference in formation new C-C bond rather than new C-I bonds.

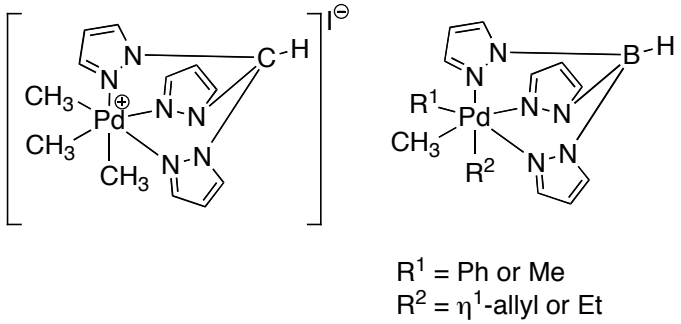


Scheme 2.2: Reported Palladium(IV) complex by Canty[11]

Further studies by Canty showed that other Pd^{IV} complexes, featuring bidentate ligands and various Pd-C(sp^3) bonds, could be isolated and characterized by ^{1}H NMR at -20°C but decomposed readily in solution to give ethane.[12-13]

In 1990 and 1995, Canty described the syntheses of the first isolable Pd^{IV} complexes at 25°C.[14-15] These isolable Pd^{IV} complexes featured three Pd-C(sp^3) bonds and utilized either the neutral

tris(pyrazolyl-1-yl)methane ligand[14] or the anionic tris(pyrazolyl-1-yl)borate ligand[15] (Scheme 2.3).



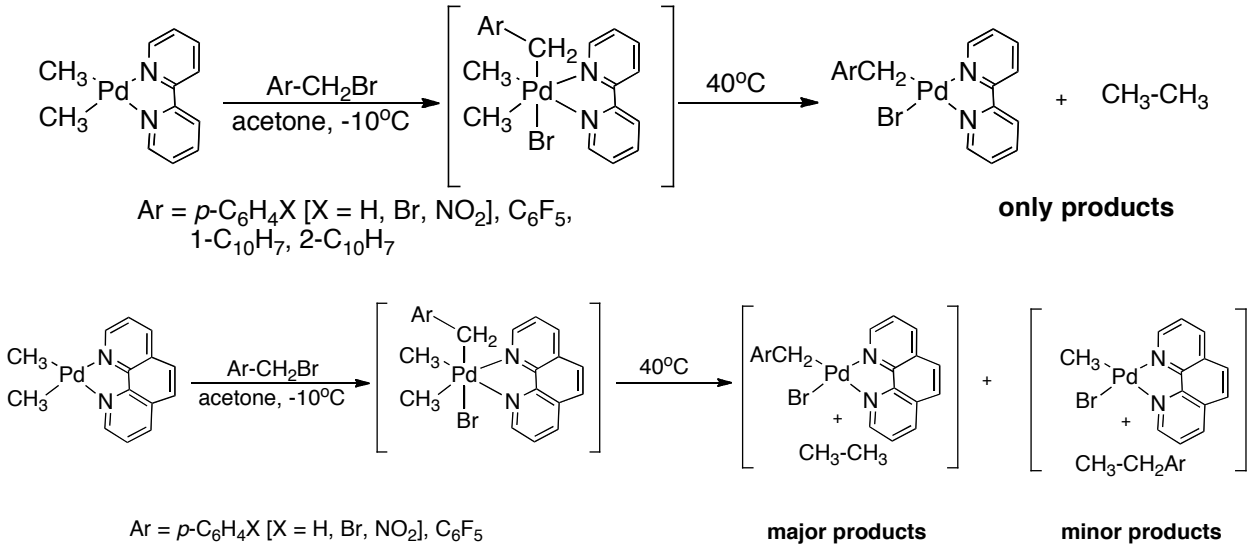
Scheme 2.3: Reported Palladium(IV) complexes featuring scorpionate ligands reported Canty[14-15]

Canty noted that the enhanced stability was due the structurally rigid N,N,N-based ligands. These tridentate ligands helped to prevent reductive elimination and allowed for the Pd^{IV} complexes to be isolated and characterized with greater ease.

As a part of this study, Canty and co-workers were also able to synthesize other Pd^{IV} complexes featuring unique Pd-C(sp^3/sp^2) bonds, such as Pd-phenyl and Pd-allyl bonds, by changing the either the oxidant or the initial Pd^{II} starting complexes. At the time, this was the first reported synthesis of Pd^{IV} complexes featuring a Pd-allyl bond.

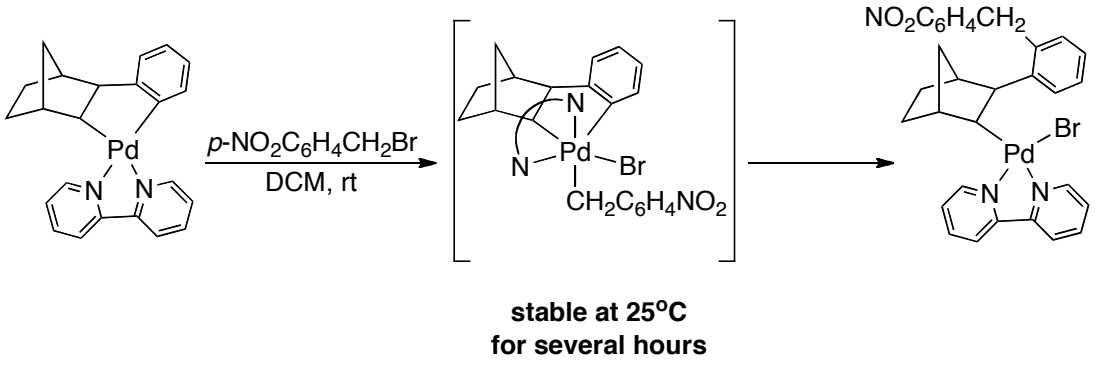
In the late 1970s, Stille and co-workers first proposed the synthesis of Pd^{IV} intermediates featuring a Pd-benzyl bond from the oxidation of a Pd^{II} complex in the presence of a benzyl chloride, but they were unable to characterize the Pd^{IV} intermediate as it underwent reductive elimination.[16] However, later studies performed by Canty and Catellani reported the successful synthesis and detection of Pd^{IV} complexes featuring a Pd-benzyl bond.[17-18]

In the study performed by Canty and co-workers, they successfully synthesized and characterized various Pd^{IV} complexes featuring either a Pd-benzyl or Pd-naphthyl bond.[17] These species were synthesized via oxidation of a Pd^{II} complex with benzyl and naphthyl bromides and featured three Pd-C(sp^3) bonds, a bidentate nitrogen ligand and a Pd-Br bond. Subsequent reductive elimination favored C(sp^3)-C(sp^3) bond formation, which agrees with the previous kinetic studies (Scheme 2.4).



Scheme 2.4: Generation of Palladium(IV) complexes featuring a Pd-Benzyl bond by Canty[17]

In 1993, an independent study done by Catellani and co-workers also described the synthesis of Pd^{IV} complex featuring a Pd-benzyl bond[18] (Scheme 2.5). In this study, Catellani synthesized the Pd^{IV} complex via oxidation of a Pd^{II}-cycle with a substituted benzyl bromide and the complex featured three Pd-C bonds, a bidentate nitrogen ligand and a Pd-Br bond. Catellani also demonstrated that the Pd^{IV} complex was stable at 25°C and reductive elimination coupled the C(sp^2)-C(sp^3) bond via migration of the aromatic ring. No C(sp^3)-C(sp^3) bonds or C-Br bonds were formed.



Scheme 2.5: Synthesis of Palladium(IV) complex featuring Pd-benzyl bond by Catellani[18]

In these studies completed by Yamamoto, Canty and Catellani, two common reaction features can be noted: (i) the use of strong oxidants to create a new Pd-C bond in the Pd^{IV} complex and (ii) the use of multidentate ligands prior to oxidation to aid in the stabilization of the newly generated Pd^{IV}-center. Current Pd^{IV} research conducted by Canty, Malinakova, Sanford and Ritter utilizes both the presence of strong oxidants and multidentate ligands to either functionalize carbon bonds through Pd^{IV} intermediates or to generate stable Pd^{IV} complexes that are isolated and taken for other fundamental organometallic transformations such as C-H activation or ligand exchange mediated by the Pd^{IV}-center.

2.3: Strong oxidants in Palladium(IV) Chemistry

In the early Pd^{IV} studies, the authors noted that a strong oxidant is needed to oxidize the stable Pd^{II} center to the desired Pd^{IV} center. To date, Pd^{IV} research has expanded to other types of strong oxidants that reportedly work well in Pd^{0}-Pd^{II} catalytic cycles as well. These various organic and inorganic strong oxidants typically create the following bonds at the Pd^{IV} center: (i) organic halides to create Pd-C(sp^3) bonds[11-14, 15, 17-18]; (ii) organic halides[18] and iodonium salt oxidants[20,25] to create Pd-C(sp^2) bonds; (iii) iodonium salt oxidants to create Pd-C(sp) bonds[20,28];

and (iv) inorganic oxidants (such as iodonium salts, oxygenating and halogenating reagents) to create Pd-heteroatom bonds[27, 30-38]. Reductive elimination from the Pd^{IV} complex generated by these oxidants yield a functionalized carbon in the final organic product.

2.3.1: Installation of Pd^{IV}-$C(sp^3)$ bonds

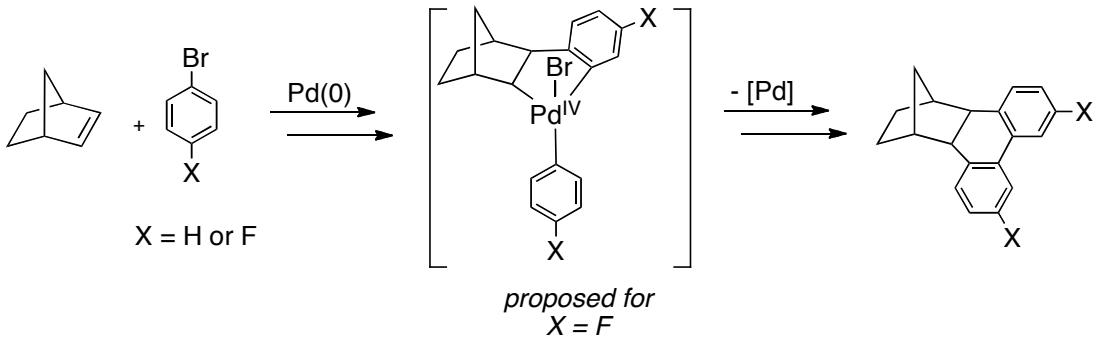
As seen in the early organic Pd^{IV} studies by Canty and Catellani described in Section 2.2 on page 9, a new Pd^{IV}-$C(sp^3)$ bond can be generated from a Pd^{II} complex in the presence of an alkyl[11-14], allyl[15] or benzyl halides.[17-18] (Scheme 2.2, 2,4, 2.5) For the halide oxidants, the scope is limited to the bromo- and iodo-based oxidants as they reportedly work well in Pd^0-Pd^{II} catalytic cycles. Reductive elimination from the Pd^{IV} complex will yield a new $C(sp^2/sp^3)$-$C(sp^3)$ bond in the final product.

Using the alkyl, allyl and benzyl oxidants, authors typically have been able to provide direct evidence of Pd^{IV} involvement in the reaction process which indicates that a Pd^{II}-Pd^{IV} catalytic cycle is responsible for the C-C coupling in the final product. Recent Pd^{IV} research conducted by Malinakova uses alkyl, allyl and benzyl oxidants to generate stable Pd^{IV} complexes, which can either then be taken for other fundamental organometallic transformations such as C-H bond activation at the Pd^{IV} center or reduced and taken for other Pd^0-Pd^{II} catalytic reactions.[19-20]

2.3.2: Installation of Pd^{IV}-$C(sp^2)$ bonds

A new Pd^{IV}-$C(sp^2)$ bond can theoretically be generated from either organic halide oxidants or from iodonium salt oxidants. However, organic halides such as aryl and vinyl halides report limited success in providing direct evidence of Pd^{IV} involvement in the reaction sequence.

In 1985, Catellani and co-workers proposed the first Pd^{IV} intermediate generated from the reaction of bromobenzene and norborene.[21] When *p*-fluorobromobenzene was used as the oxidant, the authors suggested the presence of a novel aryl-Pd^{IV}-cyclic intermediate (Scheme 2.6).

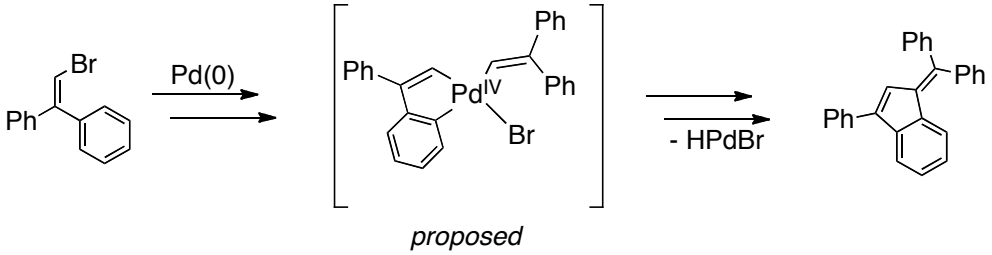


Scheme 2.6: Proposed Palladium(IV) Intermediate by Catellani[21]

Unfortunately, Catellani was unable to provide any conclusive evidence that the proposed aryl-Pd^{IV}-cycle intermediate was generated in the reaction. However, in 1993, Catellani demonstrated evidence of an aryl-Pd^{IV}-cycle intermediate in a similar reaction, suggesting that Pd^{IV} complexes can be generated when bromobenzene is the oxidant[18] (Scheme 2.5, page 13).

In 1989, de Meijere and co-workers performed a similar reaction sequence featuring iodobenzene. However, the authors did not propose the presence of the aryl-Pd^{IV} intermediate in the reaction sequence.[22] They suggested an alternative domino Heck reaction pathway involving the Pd^{0}-Pd^{II} catalytic cycle, which is typical when iodobenzene is used as the oxidant. To date, very little reliable evidence exists that a Pd^{IV} catalyst is generated in the reaction pathway in the presence of iodobenzene. This would suggest that a Pd^{II}-Pd^{IV} reaction pathway might not be present in the reaction sequence when iodobenzene is the oxidant.

For vinyl halides, it is also unlikely that a Pd^{IV}-C(sp^2) bond is generated during the reaction sequence. In 1996, Dyker and co-workers proposed that a Pd^{IV}-cyclic intermediate was generated from the oxidation of Pd^{II}-cycle and a phenyl-substituted bromoethene oxidant and reductive elimination yielded various indenes[23] (Scheme 2.7).



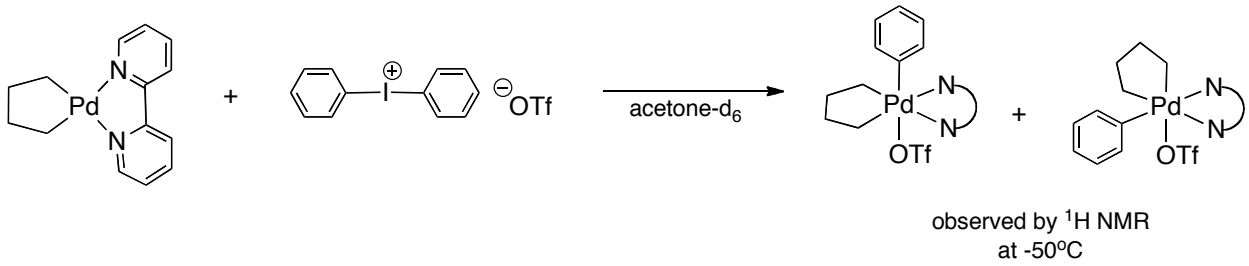
Scheme 2.7: Proposed Palladium(IV) intermediate by Dyker[23]

However, density functional theory (DFT) calculations reported by Echavarren and Martin-Matute in 2006 for a similar Pd-containing model complex determined that the presence of the proposed Pd^{IV} intermediate is unlikely and the reaction is favored to occur via a transmetallation-type reaction between two Pd^{II} complexes.[24] To date, no direct evidence of a Pd^{IV} intermediate generated by a vinyl halide oxidant has been reported.

While aryl and vinyl halides are not likely to produce Pd^{IV} intermediates in the presence of Pd^{II} catalysts, Pd^{IV} research has also explored the use of aryl and vinyl iodonium salt oxidants to generate a new Pd^{IV}-C(sp^2) bond upon oxidation. In the presence of iodonium salt oxidants, direct evidence of Pd^{IV} involvement can be provided.

In 2004, Canty and co-workers published one of the first examples where a Pd^{IV}-C(sp^2) bond was generated by an aryl iodonium oxidant.[25] In this study, the authors were able to oxidize a

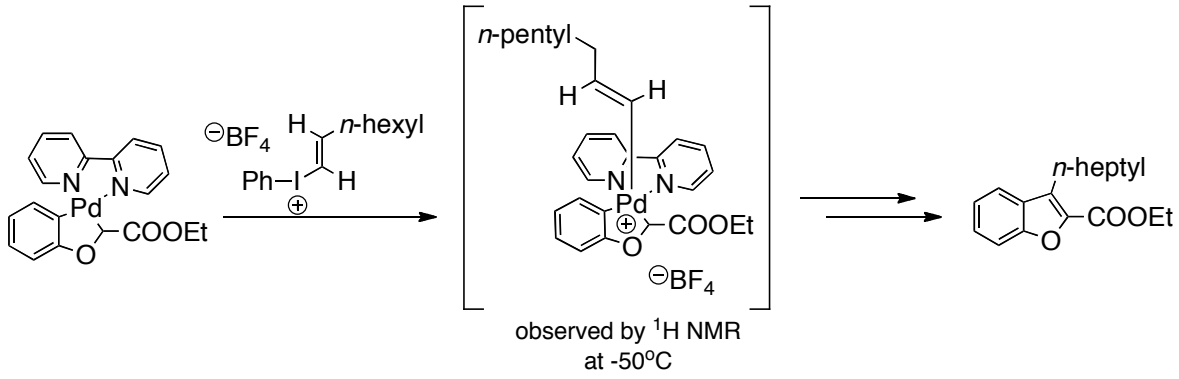
starting Pd^{II}-cycle with diphenyl iododonium triflate to yield two Pd^{IV} intermediates at -50°C, which were observed by ^1H NMR spectroscopy (Scheme 2.8).



Scheme 2.8: Observed Palladium(IV) Complexes featuring a Pd^{IV}-C(sp^2) bond by Canty[25]

Subsequent reductive elimination led to a mixture of various C-C bond forming organic products. While other aryl iodonium salts have been used in other synthetic reactions to functionalize C(sp^2)-H bonds[26-27], no direct evidence of a Pd^{IV} intermediate has been reported.

In 2008, Malinakova and co-workers demonstrated the first examples where a Pd^{IV}-C(sp^2) bond was generated by a vinyl iodonium oxidant in the presence of a Pd^{II}-cycle.[20] In this report, the authors were able to observe the formation of a Pd^{IV} intermediate by ^1H NMR detection at -50°C (Scheme 2.9). Reductive elimination produced an isolable Pd^{II} intermediate, which was taken for a Pd-catalyzed Heck reaction to yield various benzofurans.



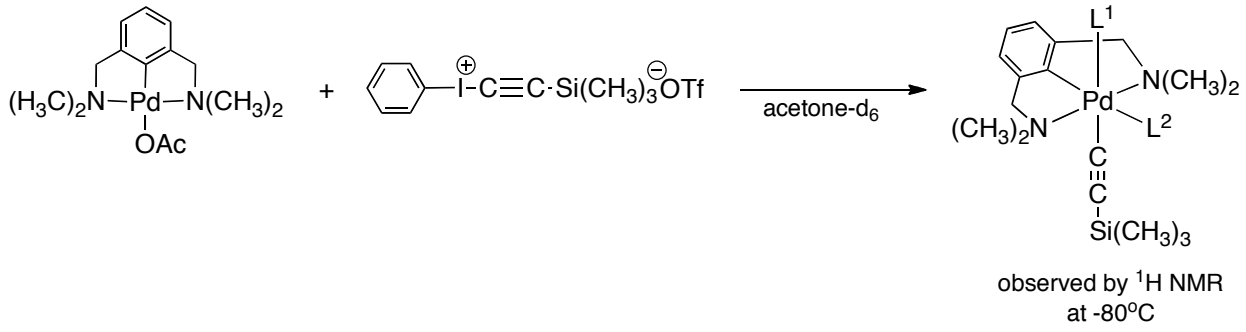
Scheme 2.9: Observed Palladium(IV) intermediate from Pallada(II)cycle by Malinakova[20]

To date, this is one of the few examples where vinyl iodonium salts have been used to functionalize $C(sp^2)$-H bonds.

2.3.3: Installation of Pd^{IV}-C(sp) bonds

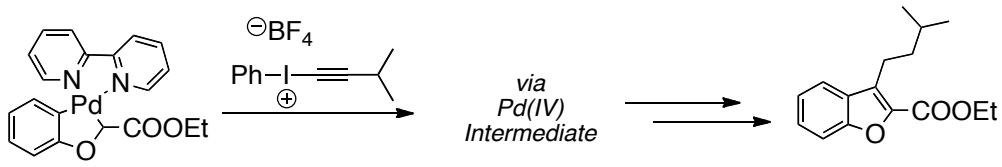
Pd^{IV} research has also focused on generating a Pd^{IV}-C(sp) bond upon oxidation. To date, there is no known organic halide that will generate a Pd^{IV}-C(sp) bond from a Pd^{II} complex. The use of terminal alkynes has been attempted but no conclusive evidence of Pd^{IV}-C(sp) bond formation exists.[28-31] Therefore, research is limited to the use of alkynyl iodonium salt oxidants to generate a Pd^{IV}-C(sp) bond, where initial studies have proven successful.

In 2006, a study by Canty and co-workers provided one of the first examples of a Pd^{IV}-C(sp) bond generated from an alkynyl iodonium salt in the presence of a Pd^{II} complex featuring a tridentate Pincer ligand[32] (Scheme 2.10). Canty was able to observe the formation a Pd^{IV} complex by low temperature ^1H NMR detection at -80°C. However, the Pd^{IV} intermediate had very poor stability and was reduced easily at -50°C in the presence of sodium halide reagents.



Scheme 2.10: Observed Palladium(IV) complex featuring Pd^{IV}-C(sp) bond by Canty[32]

In 2008, Malinakova and co-workers described another example where a proposed Pd^{IV}-C(sp) bond is generated from a Pd^{II}-cycle in the presence of an alkynyl iodonium salt[20] (Scheme 2.11).



Scheme 2.11: Proposed Palladium(IV) intermediate from Pallada(II)cycle by Malinakova[20]

Reductive elimination yielded an isolable Pd^{II} intermediate, which was taken for a Pd^{II}-catalyzed Heck reaction to yield various benzofurans. While no Pd^{IV} intermediate was observed, the reaction sequence follows a model system where a Pd^{IV} intermediate was observed at low temperature by ^{1}H NMR spectroscopy (Scheme 2.9, page 17).

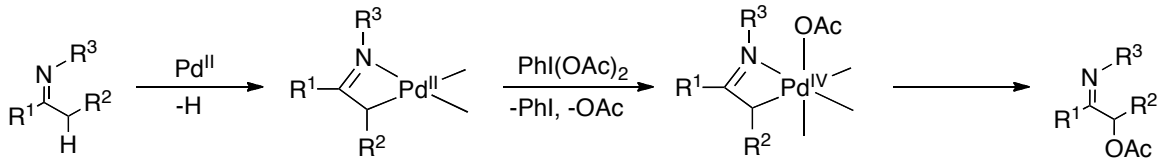
To date, there is a limited number of reports involving generation of a Pd^{IV}-C(sp) bond during a reaction sequence.

2.3.4: Installation of Pd^{IV}-heteroatom bonds

At the same time, Pd^{IV} research performed by Sanford and Ritter in the early 2000s expanded towards using inorganic oxidants to generate new Pd^{IV}-heteroatom bonds and upon reductive elimination, thereby creating new functionalized carbon bonds. The most common oxidant, phenyl iodonium diacetate, was initially explored in Pd^{II}-Pd^{IV} catalytic cycles by Crabtree and co-workers to functionalize various C(sp^2)-H bonds in various substituted arenes.[33] However, Crabtree did not provide evidence of a Pd^{IV} complex being generated during the reaction sequence.

Starting in 2004, Sanford and co-workers began exploring the use of phenyl iodonium diacetate in Pd^{II}-Pd^{IV} catalytic cycles with the goal of functionalizing various C(sp^2)-H and C(sp^3)-H

bonds through C-H activation and providing direct mechanistic evidence that a Pd^{IV} intermediate is generated during the reaction sequence[34-36] (Scheme 2.12).

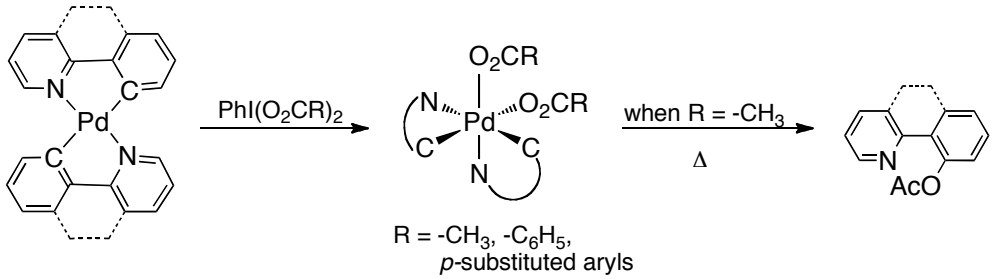


R^1, R^2 = various $C(sp^2/sp^3)$ groups
R^3 = OCH_3, NR_3, Ph

Scheme 2.12: General functionalization of $C(sp^2)$ and $C(sp^3)$ reaction pathway studied by Sanford[34-36]

In these reports, Sanford established that the acetoxylation reactions were successful for a diverse range of organic molecules and that these reactions proceeded with high selectivity[35-36].

In 2009, Sanford and co-workers published a method where they could isolate multiple stable Pd^{IV} complexes from various phenyl iodonium oxidants in the presence of a Pd^{II} complex featuring two 2-phenylpyridine-based ligands[27] (Scheme 2.13). Sanford also studied the reductive elimination pathway to determine the mechanism of the $C(sp^2)$-H functionalization.



Scheme 2.13: Synthesis of various Palladium(IV) complexes by Sanford[27]

Using the results from the 2009 report, Sanford also explored using iodonium salts to functionalize various $C(sp^3)$-H and $C(sp^2)$-H bonds. While no direct evidence of Pd^{IV} intermediate was reported, Sanford utilized the same model system (an electron deficient Pd^{II}

catalyst and an iodonium salt oxidant) that produced stable Pd^{IV} complexes (Scheme 2.13, page 20), which suggests that a Pd^{II}-Pd^{IV} catalytic cycle is responsible for the C-H bond functionalization.

Within the last five years, Pd^{IV} research has also expanded towards using oxygenating and halogenating reagents[37-42], such as I_2, Cl_2, NFTPT (which generates a Pd-F and a Pd-OTf bond) and F-TEDA-BF_4 (which generates a Pd-F bond). Typically, a Pd^{IV}-heteroatom bond is installed upon oxidation and the Pd^{IV} complex is observed at low temperatures. Reductive elimination functionalized either an C(sp^2)-H or C(sp^3)-H bond on the organic substrate.

2.4: Ligand Preference in Palladium(IV) Chemistry

When the Pd^{IV} complex was either observed at low temperatures or isolated as a stable solid, the Pd^{IV} complex typically contained a stabilizing ligand sphere to help prevent reductive elimination. The strength of the ligand sphere controlled the ability of the generated Pd^{IV} complex to undergo reductive elimination at lower temperatures. Typically, a stronger ligand sphere is needed if the Pd^{IV} complex can be reduced readily at low temperatures and cannot be isolated.

For generating a Pd^{IV}-C(sp^3) bond with allyl, alkyl and benzyl halide oxidants, Canty and Catellani used other carbon ligands (such as methyl groups) or bidentate ligands such as tmeda and bipyridine bound to the Pd^{II} center prior to oxidation. A labile ligand sphere, which contains a flexible ligand that can easily dissociate from the Pd-center, can be used because Pd^{IV}-C(sp^3)

bonds are strongly coordinating and unlikely to undergo reductive elimination at low temperatures, which allows for the detection of the corresponding Pd^{IV} complex.

For accessing Pd^{IV}-$C(sp^2)$, Pd^{IV}-C(sp) and Pd^{IV}-heteroatom bonds, complexes featuring a rigid ligand sphere, such as those involving tridentate ligands or a Pd^{II}-cyclic structure, prior to oxidation is preferred. This is due to the fact that Pd^{IV}-$C(sp^2/sp)$ and Pd^{IV}-heteroatom bonds are considered to be weakly coordinating bond and therefore, are likely to undergo reductive elimination even at low temperatures. This preference towards reductive elimination makes the detection or isolation of the desired Pd^{IV} complex more challenging at lower temperatures. However, the use of the rigid ligand sphere does not guarantee that the Pd^{IV} complex can be observed in the reaction sequence.

Two types of multidentate ligands can be used in Pd^{IV} chemistry: (i) bidentate ligands or (ii) tridentate ligands. These ligands are typically bound via strong σ donor atoms such as Nitrogen or Carbon atoms that add electron density to the Pd^{IV} -center, which aids in the stability of the proposed Pd^{IV}-center to prevent reduction and allows for the detection or isolation of the desired Pd^{IV} complex.

The multidentate ligands can be further classified into smaller subgroups depending on their role in the reaction sequence: (i) “innocent” or stabilizing ligands or (ii) “reactive” ligands. The “innocent” ligands stabilize the Pd^{IV}-center and remain bound to the Pd-center upon reductive elimination. These ligands commonly feature two or more Nitrogen atoms bound to the Pd-center. The “reactive” ligands are functionalized and released as organic products upon reduction

from the Pd^{IV}-center. These ligands commonly feature one or more Carbon atoms bound to the Pd^{IV}-center.

2.4.1: Bidentate Ligands

Bidentate ligands can coordinate to the Pd^{IV}-center via *cis*-coordination of the binding atoms with two possible isomers. In one isomer, the binding atoms occupy two equatorial sites. In the other isomer, one binding atom occupies an equatorial site and the other occupies an axial site (Figure 2.1).

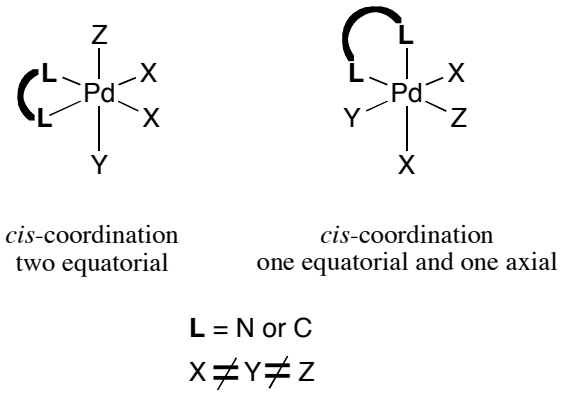


Figure 2.1: Two isomers of *Cis*-coordination in bidentate ligands

Typically, bipyridyl-based ligands (bound by either nitrogen or carbon atom) or cyclic carbon rings to produce a palladacycle are utilized in Pd^{IV} chemistry to prevent decomposition of the Pd^{IV}-center.

In the Pd^{IV} complex, the Pd-atom bond lengths are controlled by the trans effect, which is defined as the labilization or dissociation of ligands that are trans to other ligands.[60] The ligand bound to the Pd^{IV} center with the larger trans effect will increase the bond length of the ligand located directly across from it.

2.4.1.1: Nitrogen-Containing Bidentate Ligands

In the early Pd^{IV} studies performed by Canty, tmeda ligands were used to help stabilize the Pd^{IV}-center, where the nitrogen atoms were bound to the Pd^{IV}-center.[43-44] Unfortunately, the tmeda ligands were not strong enough to stabilize the Pd^{IV}-center generated upon oxidation. Therefore, the use of stronger bidentate ligands featuring either Nitrogen or Carbon binding atoms that would not dissociate from the Pd^{IV}-center at low temperatures was explored.

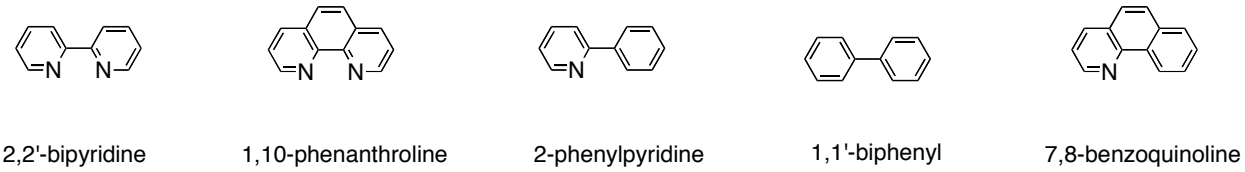


Figure 2.2: Typical bidentate ligands used in Palladium(IV) chemistry

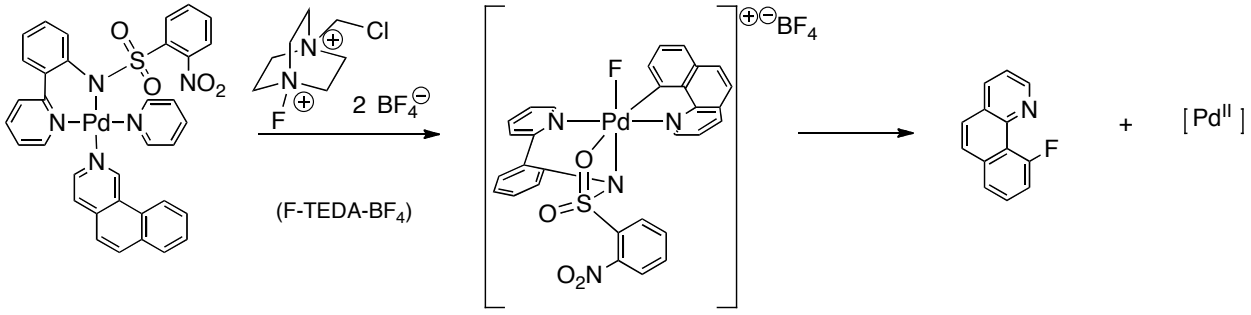
The first exploration into stronger bidentate ligands was preformed by Canty and co-workers where they reported the use of a single 2,2'-bipyridine (bpy) ligand to stabilize the Pd^{IV}-center[11] (Scheme 2.2, page 10). The bpy ligand coordinates to the Pd-center through two nitrogen donor atoms and has an overall neutral net charge (Figure 2.2). The desired Pd^{IV}-center is generated from the oxidation of the (bpy)Pd^{II} complex featuring two Pd-C(sp^3) bonds with various halide oxidants. Reduction from the Pd^{IV}-center functionalizes the carbon ligands and the bpy ligand, which acts as an innocent ligand, remains coordinated to the Pd-center.

In 1990, Canty and co-workers expanded towards the use of a single 1,10-phenanthroline (phen) ligand in the Pd^{IV} complex[17] (Scheme 2.4, page 12). The phen ligand contains an additional alkene bond between the two bipyridine rings but has similar coordination properties as the bpy ligand (Figure 2.2). Reductive elimination releases ethane as the major product while the phen

ligand remains coordinated to the Pd-center, indicating that the phen ligand acts as a stabilizing ligand.

In 2009, Sanford and co-workers demonstrated the use of two 2-phenylpryridine ligands in the Pd^{IV} complex[27] (Scheme 2.13, page 20). This ligand, which has similar coordination properties as the bpy ligand, contains a $C(sp^2)$-atom bound to the Pd-center (Figure 2.2). Reductive elimination from the Pd^{IV}-center functionalizes the $C(sp^2)$-atom on the 2-phenylpyridine ligand. This indicates that the 2-phenylpyridine ligand can be used as both an innocent ligand and a reactive ligand in Pd^{IV} complexes.

In 2010, Ritter and co-workers utilize the bpy ligand as well as the 7,8-benzoquinoline ligand in various Pd^{IV} complexes containing Pd-F bonds to explore the mechanism of C-F bond formation.



Scheme 2.14: Reported $C(sp^2)$-F bond formation from a Palladium(IV) complex by Ritter[42]

In the presence of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4), the starting (bpy)(7,8-benzoquinoline)Pd^{II} complex was oxidized to a Pd^{IV} complex featuring a new Pd-F bond (Scheme 2.14). The 7,8-benzoquinoline ligand coordinates to the Pd-center through a Nitrogen atom and through a $C(sp^2)$-atom.[42]

(Figure 2.2) Upon reductive elimination, a new organic product featuring a C(sp^2)-F bond was formed.

Ritter also utilized this synthetic method to yield two additional Pd^{IV} complexes featuring the bulky ligand sphere as well as the Pd-F bond (Figure 2.3). These Pd^{IV} complexes were then taken for further reactivity studies to explore the mechanism of C-F reductive elimination.

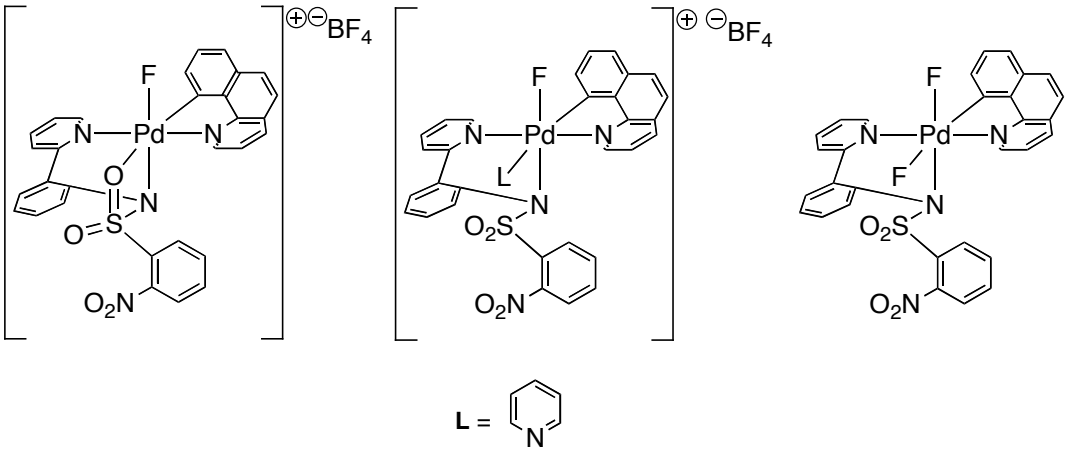
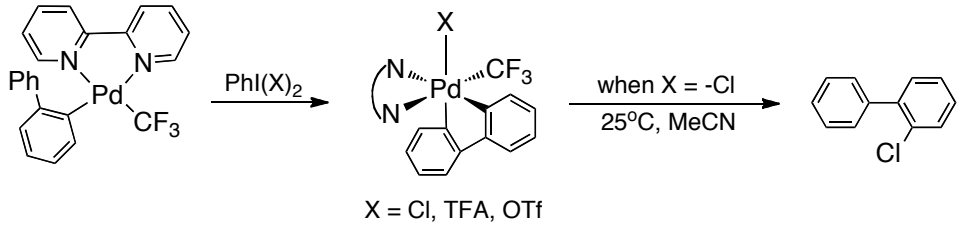


Figure 2.3: Palladium(IV) complexes featuring Pd-F bond synthesized by Ritter[42]

It is also important to note the use of the N,N,O tripodal ligands in the Pd^{IV} complexes (Figure 2.3). In this work, Ritter states that the N,N,O tripodal ligand is necessary to stabilize the Pd^{IV}-center. Other examples of tripodal ligands used in Pd^{IV} chemistry will be explained later in the Chapter.

In 2011, Sanford and co-workers reported the first use of a single 1,1'-biphenyl ligand in the Pd^{IV} complex[45] (Scheme 2.15). This ligand coordinates to the Pd-center through two C(sp^2)-atoms where a single C(sp^2)-H cente undergoes Pd^{IV}-mediated C-H activation upon oxidation.

Reductive elimination from the Pd^{IV}-center functionalizes the $C(sp^2)$-atom on the 2-phenylpyridine ligand.



Scheme 2.15: Palladium(IV) complex featuring 1,1'-biphenyl reported by Sanford[45]

To date, the use of bpy or phen ligands in Pd^{IV} chemistry is quite common and the number of ligands used is dependent on the Pd^{IV} research being conducted. Typically, when a researcher wants to explore the reactivity at the Pd^{IV}-center, the starting Pd^{II} complex features a single bpy ligand as well as other cyclic carbon-based ligands. As previously demonstrated by Canty and Sanford, the single bpy ligand stabilizes the desired Pd^{IV}-center but allows for the Pd^{IV}-center to undergo an additional transformation such as reductive elimination.

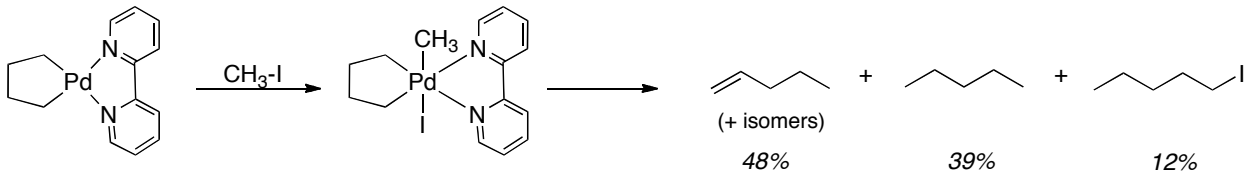
However, when a researchers wants to explore the oxidant scope or generate a new Pd^{IV} complex, two bpy or two phen ligands are used in the starting Pd^{II} complex. The two ligands stabilize the desired Pd^{IV} complex and prevent an additional chemical transformation from occurring at the Pd^{IV}-center.

2.4.1.2: Carbon-Containing Bidentate Ligands

Another bidentate ligand used in Pd^{IV} chemistry is the carbocycle ligand, which features two unique carbon centers in a sterically bulky ring bound to the Pd-center to create a Pallada(II)cycle or Pd^{II}-cycle. As mentioned above, the use of Pd^{II}-cycles also requires the

presence of another bidentate ligand that will stabilize the Pd^{IV}-center and will not be functionalized upon reduction from the Pd^{IV}-center.

In 1998, Canty and co-workers reported one of the first Pd^{II}-cycles which featured a cyclic butane ring to give two Pd^{II}-C(sp^3) bonds as well as a bpy ligand[46] (Scheme 2.16). Oxidation with methyl iodide generated the desired Pd^{IV} complex with three Pd^{IV}-C(sp^3) bonds and a Pd-I bond. Reduction from the Pd^{IV} complex gave a mixture of organic products with an alkene resulting from the β-hydride elimination as the major product.



Scheme 2.16: Pallada(IV)cycle reported by Canty[46]

The Pd^{II}-cycle has also been used by Canty to generate other Pd^{IV} complexes in the presence of iodonium oxidants[25] (Scheme 2.8, page 17). However, the products generated upon reduction were not reported.

In 1993, Catellani and co-workers described the use of a Pd^{II}-cycle containing unique Pd-C(sp^3) and Pd-C(sp^2) bonds from a norborene ring and substituted-phenyl ring[18] (Scheme 2.5, page 13) . Oxidation in the presence of a substituted-phenyl halide generates the desired Pd^{IV} complex. Reductive elimination generates a newly coupled C(sp^3)-C(sp^2) bond via migration of the aryl ring, suggesting that the functionalization C(sp^2) center on the Pd^{II}-cycle is favored.

Recently, Malinakova and co-workers have studied Pd^{II}-cycles that feature activated Pd-C(sp^3)-bond on a substituted aryl ring as well as a Pd-C(sp^2) bond (Figure 2.4).

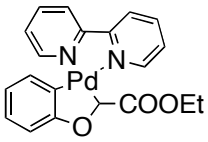
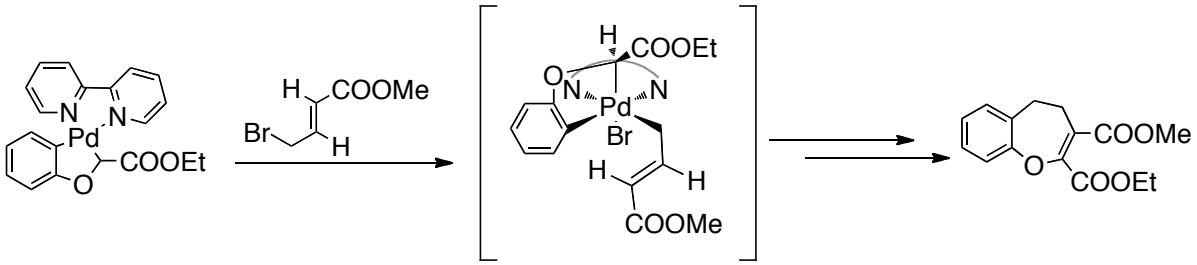


Figure 2.4: Pallada(II)cycle featuring activated C(sp^3)-center by Malinakova[19-20]

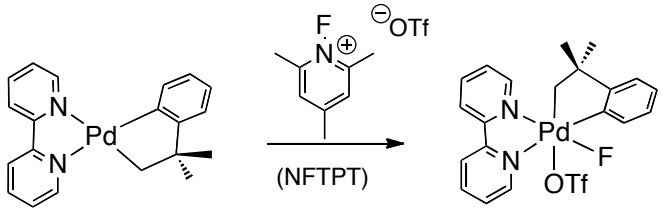
These Pd^{II}-cycles can be oxidized in the presences of alkyl bromide oxidants (Scheme 2.17) as well as iodonium salts (Scheme 2.9, page 17 and Scheme 2.11, page 19) to generate various Pd^{IV} complexes.[19-20] Subsequent reductive elimination and Heck reactions yield new heterocycles featuring a functionalized C(sp^2) bond.



Pd(IV) Intermediate
observed by ^{1}H NMR at -10°C
X-ray crystal structure

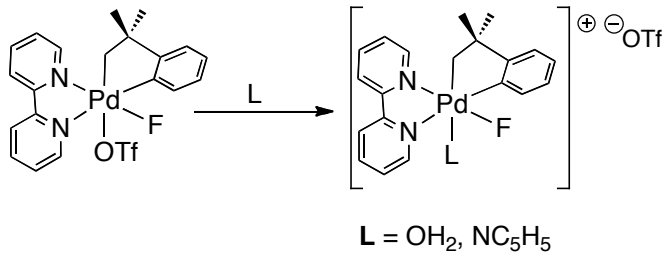
Scheme 2.17: Palladium(IV) intermediate from Pallada(II)cycle and allyl bromide oxidant observed by Malinakova[19]

In 2012, Sanford and co-workers demonstrated the use of a Pd^{II}-cycle featuring an unactivated Pd-C(sp^3) bond in the synthesis of various Pd^{IV} complexes containing a Pd-F bond[40] (Scheme 2.18). In the presence of *N*-fluoro-2,4,6-trimethylpyridinum triflate (NFTPT), the Pd^{II}-cycle was oxidized to a Pd^{IV} complex featuring a Pd-F and Pd-OTf bond.



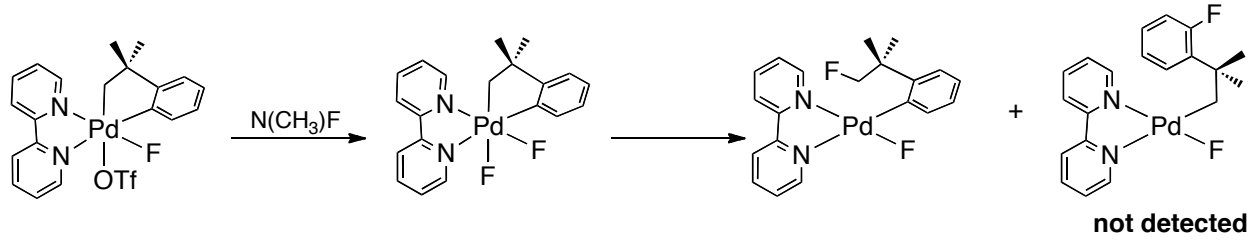
Scheme 2.18: Palladium(IV) complex from Pallada(II)cycle and NFTPT oxidant synthesized by Sanford[40]

Sanford also explored the reactivity of the Pd^{IV}-center towards nucleophilic substitution. In the presence of various weak nucleophiles, the –OTf ligand was displaced and a new Pd^{IV} complex was synthesized (Scheme 2.19).



Scheme 2.19: Nucleophilic substitution studies at Palladium(IV) center reported by Sanford[40]

Reductive elimination from the Pd^{IV} complex featuring two Pd-F bonds resulted in the selective functionalization of the unactivated $C(sp^3)$ center to yield a new C-F bond (Scheme 2.20).



Scheme 2.20: Palladium(IV)-mediated functionalization of $C(sp^3)$-bond reported by Sanford[40]

To date, Pd^{II}-cycles featuring two unique Pd-$C(sp^3)$ and Pd-$C(sp^2)$ bonds have been shown to generate a Pd^{IV} intermediate that can then functionalize the $C(sp^2)$ bond in the Pd^{II}-cycle has been demonstrated by Catellani and Malinakova.[18-20] However, when fluoride oxidants are used in the presence of a Pd^{II}-cycle featuring two unique Pd-$C(sp^3)$ and Pd-$C(sp^2)$ bonds, reduction from the Pd^{IV} intermediate functionalizes the $C(sp^3)$ bond.[40] Unfortunately, when a Pd^{II}-cycle featuring only Pd-$C(sp^3)$ bonds is used, a mixture of products is collected and little to no functionalization of $C(sp^3)$ bond is observed.[46] This suggests that while the selective bond-

forming reductive elimination needs further experimental exploration, using a Pd^{II}-cycle featuring both Pd-C(sp^3) and Pd-C(sp^2) bonds would be successful in synthetic studies to functionalize either the C(sp^2) or C(sp^3) bond.

2.4.2: Tridentate Ligands

Tridentate ligands can coordinate to the Pd^{IV} center via meridional-type (*mer*) coordination or through facial-type (*fac*) coordination. In the *mer*-coordination, the binding atoms occupy three equatorial sites. In the *fac*-coordination, the binding atoms occupy three sites belonging to the same face of the octahedron (Figure 2.5). These ligands stabilize octahedral geometry at the Pd^{IV} center, which allows for the detection, isolation and characterization of the desired Pd^{IV} complex prior to reduction.

mer-coordination *fac*-coordination

L = C, N, P, S, O, etc.

Figure 2.5: *Meridional*-coordination versus *Facial*-coordination of tridentate ligands

Two types of ligands are typically used when tridentate coordination is needed: Pincer-type (which *mer*-coordinate) and scorpionate-type (which *fac*-coordinate).

2.4.2.1: Pincer Ligands

One traditional class of tridentate ligands used in the synthesis of Pd^{IV} complex are the pincer-type ligands. Initially, the use of these ligands in palladium chemistry was reported by Shaw and

Moulton in 1976[47] but interest in using Pincer ligands has continued to expand as Pd^{IV} research has grown. To date, these ligands have been utilized in various Pd^{0}-Pd^{II} catalytic coupling reactions and in various Pd^{II}-Pd^{IV} coupling reactions, focusing mainly on the activation of various C-H bonds. Typically, these ligands can be purchased or synthesized from the starting *ortho*-substituted aryl core.

The Pincer ligands coordinate in a co-planar fashion where the atoms bind through sigma donors in the equatorial sites where one atom contains a (-1) charge while the remaining two atoms contain a neutral charge, which gives the Pincer ligand an overall (-1) charge (Figure 2.6).

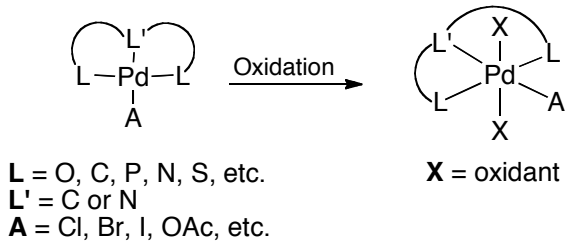
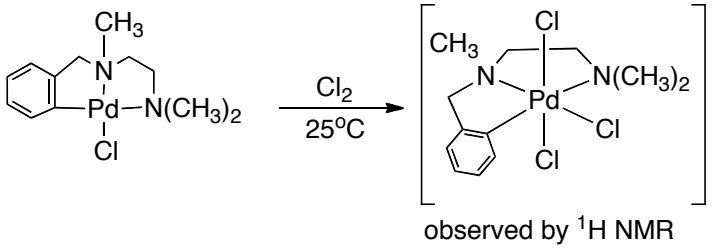


Figure 2.6: Model Pincer ligand bound to Palladium(II) and Palladium(IV) metal center

These binding atoms (L, L') include but are not limited to: carbon, oxygen, sulfur, nitrogen, and phosphorous. These binding atoms were selected due to their success in Pd^{0}-Pd^{II} studies and can be adjusted to modify the electronic and steric effects in the Pincer ligands. Pincer ligands also include the use of a counter anion or an ancillary ligand (X), which stabilizes the metal center by either adding or removing electron density from the metal center.

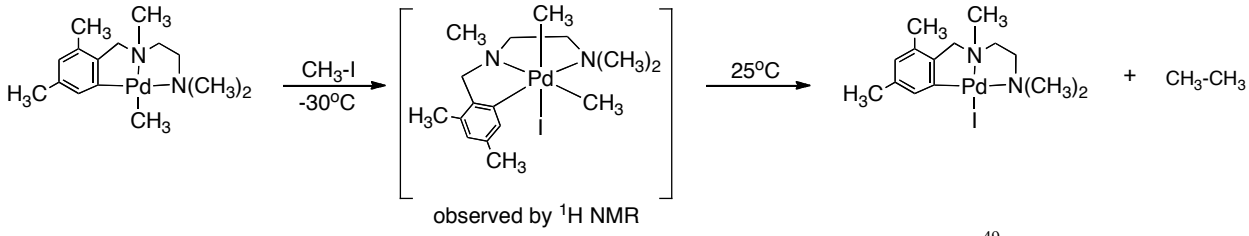
In Pd^{IV} chemistry, the most common binding atom arrangement is the C,N,N-type ligands with various counter anion ligands. However, other binding atom arrangements in Pd^{IV} chemistry include C,P,P-type, N,S,S-type and OCN-type ligands.[48]

In an early Pd^{IV} study preformed in 1993, van Koten and co-workers reported the generation of a Pd^{IV} pincer complex via the oxidation of a Pd^{II} C,N,N pincer complex with chlorine[49] (Scheme 2.21). The Pd^{IV} pincer complex was detected by in situ ^1H NMR monitoring at 25°C and decomposed after a few hours in solution.



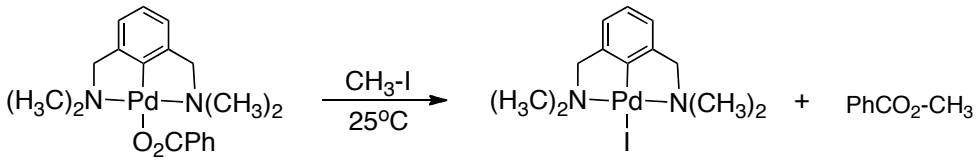
Scheme 2.21: Initial Palladium(IV) pincer complex by van Koten[49]

Utilizing a similar Pd^{II} C,N,N pincer complex, van Koten also explored the use of methyl iodide as the oxidant to generate a new Pd^{IV} pincer complex[49] (Scheme 2.22). In this reaction, the desired Pd^{IV} pincer intermediate was monitored by ^1H NMR at -30°C and upon reduction, ethane and a Pd^{II} pincer complex featuring a new Pd-I bond were produced at 25°C.



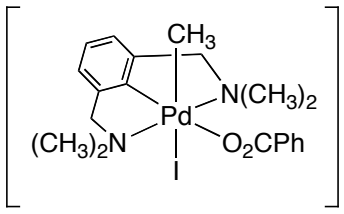
Scheme 2.22: Palladium(IV) pincer complex generated by van Koten[49]

In 2004, Canty and co-workers performed a similar reaction featuring a different Pd^{II} N,C,N pincer complex and in the presence of methyl iodide, Canty hoped to generate the corresponding Pd^{IV} pincer complex[50] (Scheme 2.23). In this reaction, phenyl acetate and a new Pd^{II} pincer complex featuring a Pd-I bond were generated at 25°C.



Scheme 2.23: Palladium(II) pincer reaction by Canty[50]

The formation of the Pd-I bond suggests a Pd^{IV} intermediate was produced during the oxidation; however, the Pd^{IV} pincer intermediate proposed by Canty (Figure 2.7) could not be detected by ^1H NMR analysis. This suggests that the formation of the desired Pd^{IV} pincer intermediate is dependent on either the binding atom order or the type of oxidant used during the reaction sequence.

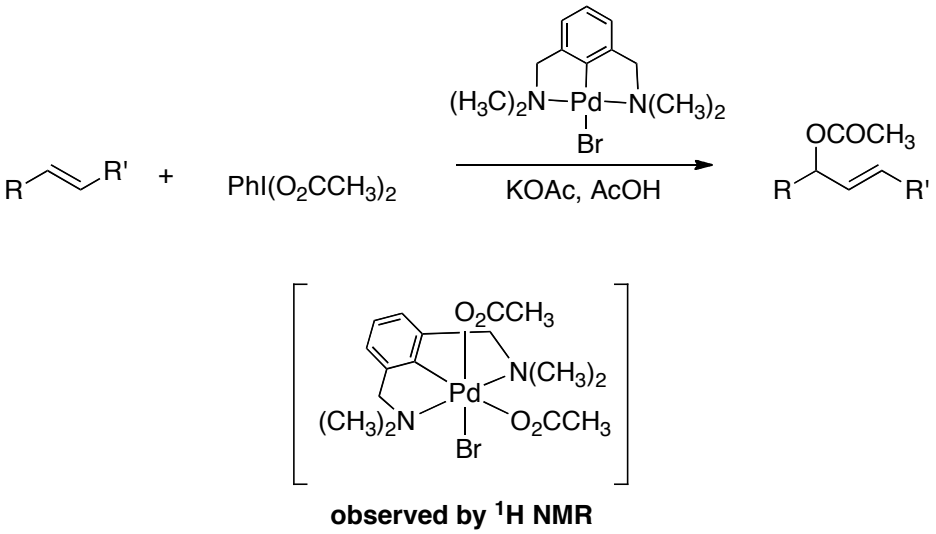


proposed Pd^{IV} intermediate
not observed by ^1H NMR

Figure 2.7: Palladium(IV) pincer intermediate proposed by Canty

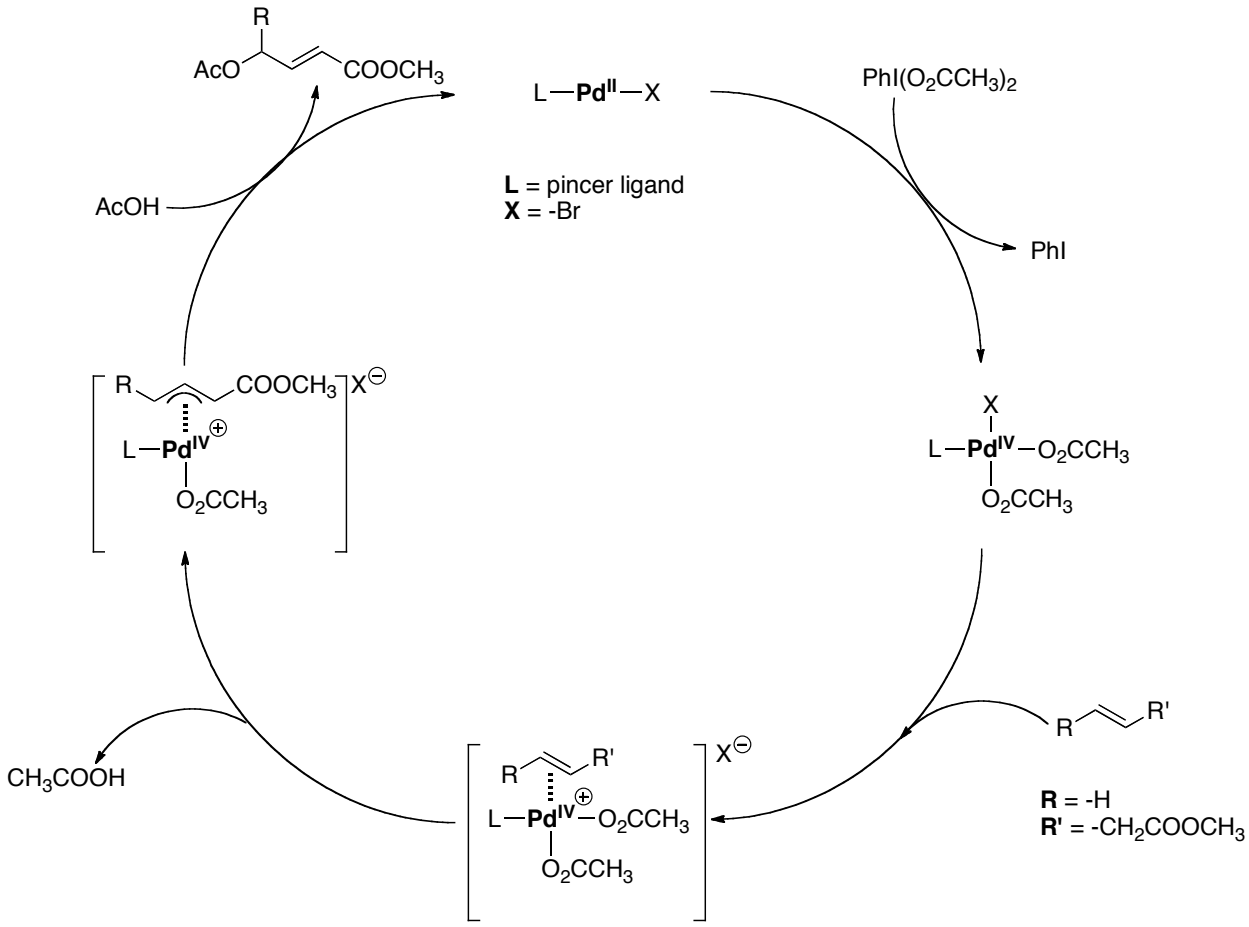
Using the same Pd^{II} N,C,N pincer complex, Canty demonstrated that in the presence of an iodonium salt oxidant, the corresponding Pd^{IV} pincer complex can be generated and observed by ^1H NMR at -80°C[32] (Scheme 2.10, page 18). However, the complex decomposed at -50°C with the addition of sodium iodide, suggesting that Pd^{IV} pincer complexes featuring N,C,N ligands are reactive at low temperatures and will undergo rapid reduction or decompose.

The use of Pd^{IV} pincer complexes in bond-coupling reactions has also been published. In 2009, Szabó and co-workers reported the generation of Pd^{IV} pincer complexes in the C-H acetoxylation of various alkenes.[26] (Scheme 2.24) In the presence of iodonium salts, the Pd^{II} N,C,N pincer complex was oxidized to the Pd^{IV} pincer intermediate and observed by ^1H NMR.



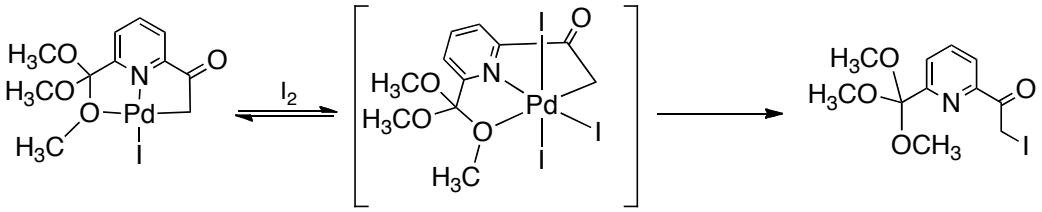
Scheme 2.24: Palladium(IV) pincer complex generated by Szabó[26]

In this report, Szabó also proposed a mechanism where the Pd^{IV} pincer complex is directly involved in the functionalization of the alkene (Scheme 2.25). This is one of the first examples where a Pd^{IV} pincer complex is a key intermediate in the C-H acetoxylation of various alkenes.



Scheme 2.25: Proposed acetoyxlation mechanism reported by Szabó

To date, Pd^{IV} pincer complexes have also been generated via oxidation with other dihalogen oxidants at low temperatures[39] (Scheme 2.26). Reductive elimination from the Pd^{IV} pincer complex functionalizes the C(sp^3)-bond on the pincer ligand.



characterized by ^{1}H NMR at -40°C

Scheme 2.26: Palladium(IV) pincer complex generated by Bautista[39]

2.4.2.2: Tris(pyrazolyl)borate ligands

Another traditional class of tridentate ligands used in Pd^{IV} chemistry are the scorpionate-type ligands. Within this class of ligands, tris(pyrazolyl)borate ligands are the most commonly used ligands in Pd^{IV} chemistry. The ligands were first introduced in 1967 and by the 1980s they were commonly used in various applications of coordination chemistry. Currently, tris(pyrazolyl)borate ligands can either be purchased or easily synthesized starting from KBH_4 salt and pyrazole at higher temperatures.[51]

The tris(pyrazolyl)borate ligands coordinate to the metal center through the lone pairs on the nitrogen atoms in the pyrazole ring, which act as strong σ donors. In Pd^{IV} complexes, two nitrogen centers bond to the Pd-center, while the third nitrogen center "curls" toward the Pd-center to bond via facial coordination. The nitrogen atoms carry a neutral charge while the boron atom carries the (-1) charge, which gives the ligand an overall charge of (-1) (Figure 2.8). The three remaining ligands, typically carbon or oxygen centers bound to the Pd-center in the remaining sites, contain the additional (-3) charge to produce the desired Pd^{IV}-center.

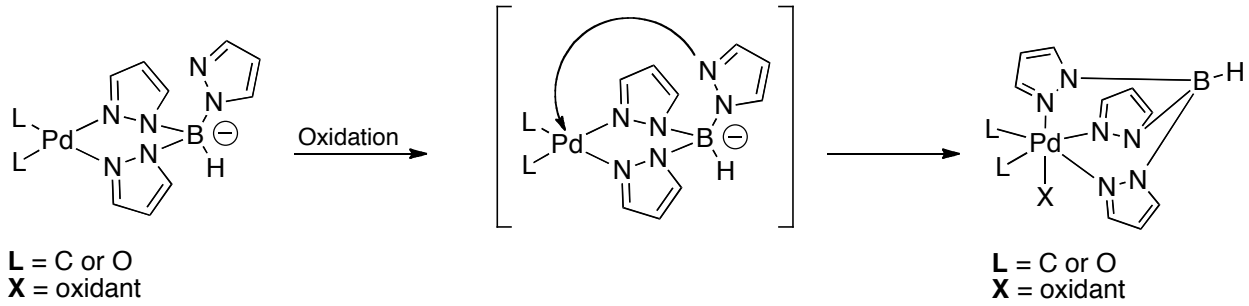


Figure 2.8: Model Tris(pyrazolyl)borate ligand bound to Palladium(II) and Palladium(IV) metal center

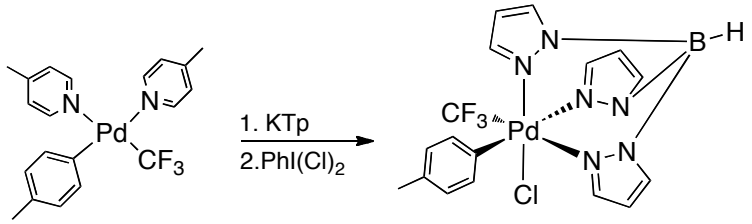
The simplest ligand, the tris(pyrazoly-1-yl)borate ligand, (Tp) contains three pyrazole moieties connected through a boron atom and is commonly used in Pd^{IV} chemistry. Other tris(pyrazolyl)

borate ligands exist where the pyrazole rings contain other substituents (such as an alkyl or aryl group) located at the remaining carbon atoms of the ring. These substituted Tp ligands coordinate in the same manner and are used in other coordination chemistry reactions.[52]

When used in Pd^{IV} chemistry, the Tp ligands are known to enhance the stability of the Pd^{IV} complex by adopting a favorable octahedral geometry at the Pd^{IV}-center, which allows for the detection, isolation and characterization of the desired Pd^{IV} complexes prior to reduction. To date there is a limited number of literature reports of stable Pd^{IV} complexes featuring Tp ligands.

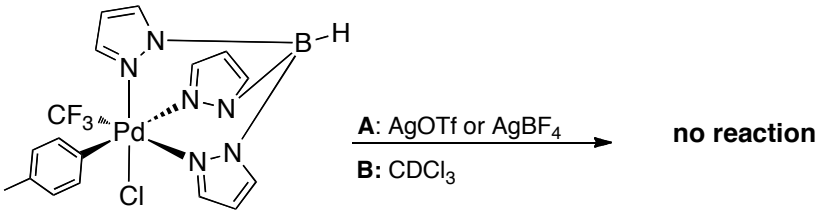
In 1995, Canty and co-workers demonstrated the first use of Tp ligands to synthesize various Pd^{IV} complexes at 25°C[15] (Scheme 2.3, page 11). The Tp ligand was installed via ligand exchange with (tmeda)Pd^{II} complexes and the subsequent oxidation with various halide oxidants produced the desired Pd^{IV} complexes. The complexes were isolated under aqueous conditions as stable solids and characterized by ^{1}H and ^{13}C NMR analyses at 25°C. Canty also noted that the complexes were stable at higher temperatures (35°C and above) suggesting that the Tp ligand was essential in the stabilization of the Pd^{IV} complexes.

In 2011, Sanford and co-workers also used the Tp ligand to explore the reactivity at the Pd^{IV}-center.[53] (Scheme 2.27) After synthesizing the desired Pd^{IV} complex from the $(4\text{-MePy})_2Pd^{II}$ complex via ligand exchange (to install the Tp ligand) and oxidation with iodobenzene dichloride, Sanford explored the reactivity of the Pd^{IV}-center towards nucleophilic substitution and decomposition.



Scheme 2.27: Synthesis of Palladium(IV) complex reported by Sanford[53]

In a 2011 study, Sanford determined that the Tp ligand is essential in stabilizing the Pd^{IV} complex for isolation but prevents nucleophilic substitution at the Pd^{IV}-center or decomposition of the Pd^{IV} complex (Scheme 2.28).



Scheme 2.28: Reactivity studies on the Palladium(IV) complex reported by Sanford[53]

The studies by Canty and Sanford demonstrate that the Tp ligand can be used to construct new Pd^{IV} complexes that can be isolated as stable solids. However, use of the ligand may limit chemical reactivity studies or organometallic transformations, such as nucleophilic substitution, performed at the Pd^{IV}-center.

2.4.3: Miscellaneous Ligands

While not a common ligand choice, phosphine-based ligands can also be used in Pd^{IV} chemistry under a few unique conditions. Monodentate phosphine ligands have been used in the synthesis of Pd^{IV} complexes when other strongly coordinating ligands (such as bulky carbon-based ligands, hydrides or multidentate nitrogen-based ligands) are present[10, 54-55] or when the

phosphine ligand is used to replace a weakly coordinating ligand (such as a triflate or a iodide) at the Pd^{IV}-center.[56] Bidentate phosphine ligands have also been used in the synthesis of Pd^{IV} complexes, but their use is limited to replacing a weakly coordinating ligand and can lead to Pd^{IV} dimers.[56]

Despite the few reported studies, phosphine ligands are typically labile at Pd centers, making them poor stabilizing ligands. Phosphine ligands can also be oxidized easily in the presence of strong oxidants. Therefore, the use of phosphine-based ligands in Pd^{IV} chemistry is limited and considered a poor choice in Pd^{IV} chemistry.[48]

2.5: Organometallic Transformations Performed at Palladium(IV) Centers

As mentioned in Chapter One, one area of focus in Pd^{IV} research involves the investigation into what possible organometallic transformations can be done at the Pd^{IV}-center. To date, three transformations have received the greatest attention: (i) reductive elimination (ii) C-H activation and (iii) nucleophilic substitution.

2.5.1: Reductive Elimination

In Pd^{IV} chemistry, reductive elimination is the most common transformation investigated by organometallic researchers as it is typically performed after the construction of a new Pd^{IV} complex. Reductive elimination is important to investigate as this transformation can indicate the stability of the new Pd^{IV}-center and give insight into the bond functionalization process upon reduction.

In 1989, Canty and co-workers reported the first investigation into Pd^{IV}-mediated reductive elimination.[13] (Scheme 2.2, page 10) In this study, Canty constructed the desired Pd^{IV} complexes and subjected the complexes to reductive elimination conditions (typically high temperatures) and monitored the organic products generated during the reaction. From these studies, Canty and co-workers established that $C(sp^3)$-$C(sp^3)$ bond formation is favored from the Pd^{IV}-center containing multiple Pd-$C(sp^3)$ bonds.

However, other Pd^{IV}-mediated reductive elimination studies performed by Cantellani[18], Malinakova[19-20] and Sanford[27, 45, 53] indicate that $C(sp^2)$-H bond functionalization is favored from a Pd^{IV}-center when an Pd-aryl bond is present in the Pd^{IV} complex. This suggests that reductive elimination from a Pd^{IV}-center prefers to functionalize the $C(sp^2)$ center when both Pd^{IV}-$C(sp^2)$ and Pd^{IV}-$C(sp^3)$ bonds are present.

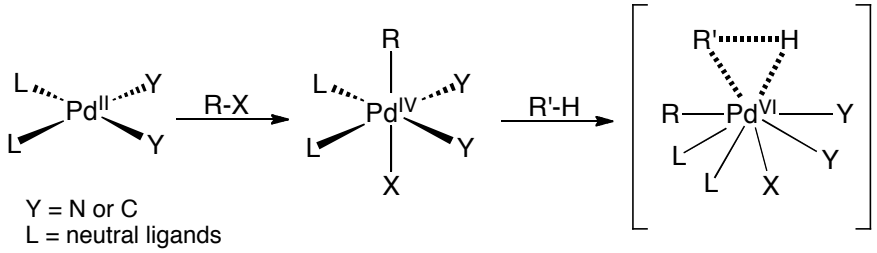
From these reductive elimination results, synthetic chemists can theoretically use Pd^{II}-Pd^{IV} catalytic cycles to functionalize $C(sp^2/sp^3)$-H bonds in organic starting materials.[57] In some cases, the reduced Pd^{II} catalyst was also taken for further chemical transformations, such as the Heck reaction, to generate complex organic products.[19-20]

2.5.2: C-H Activation

Within the last five years, there has been an increase in Pd^{IV} research focusing on C-H activation mediated at the Pd^{IV}-center. Typically, organometallic chemists, such as Sanford, have to construct new Pd^{IV} complexes that induce C-H activation on an additional substrate that is added during the course of the reaction or on a substrate tethered to the Pd^{IV} center.

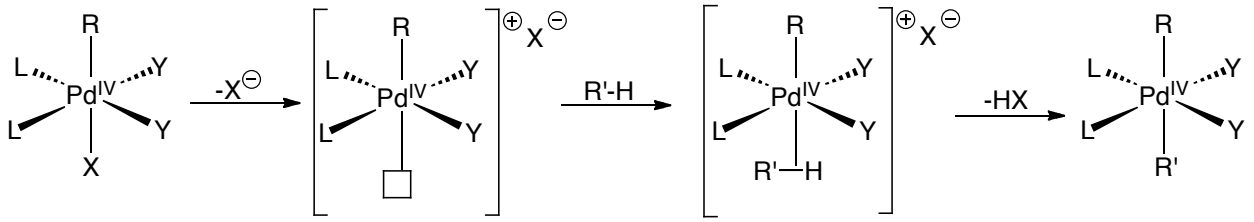
To achieve Pd^{IV}-mediated C-H activation, two following reaction pathways can be envisioned: (i) substrate addition to the Pd^{IV} complex to generate a Pd^{VI}-center or (ii) ligand removal to generate an open-coordination site at the Pd^{IV} center.

The first possible pathway requires the direct concerted addition of the substrate to the Pd^{IV} complex during the reaction course (Scheme 2.29). This substrate would coordinate to the Pd^{IV}-center to generate a new complex featuring a Pd^{VI}-center. However, this pathway is impossible as the proposed Pd^{VI}-center is electronic unfavorable and not likely to be generated during the reaction.



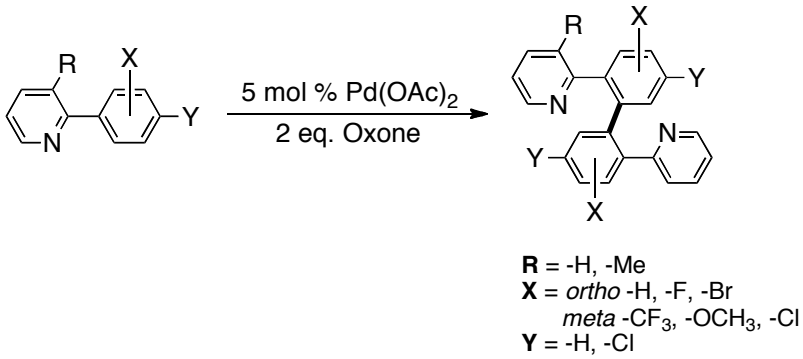
Scheme 2.29: Proposed Palladium(IV)-mediated C-H activation Pathway One

The second possible pathway requires removal of a weakly coordinating ligand from the Pd^{IV}-center to create a new cationic Pd^{IV}-center featuring an open-coordination site (Scheme 2.30). This open-coordination site would then be available for Pd^{IV}-meditated C-H activation (with or without base-assistance) on the substrate to form of a new Pd^{IV}-C(sp^2/sp^3) bond. This preferred pathway is most likely to be operating in Pd^{IV}-mediated C-H activation.



Scheme 2.30: Proposed Palldaium(IV)-mediated C-H activation Pathway Two

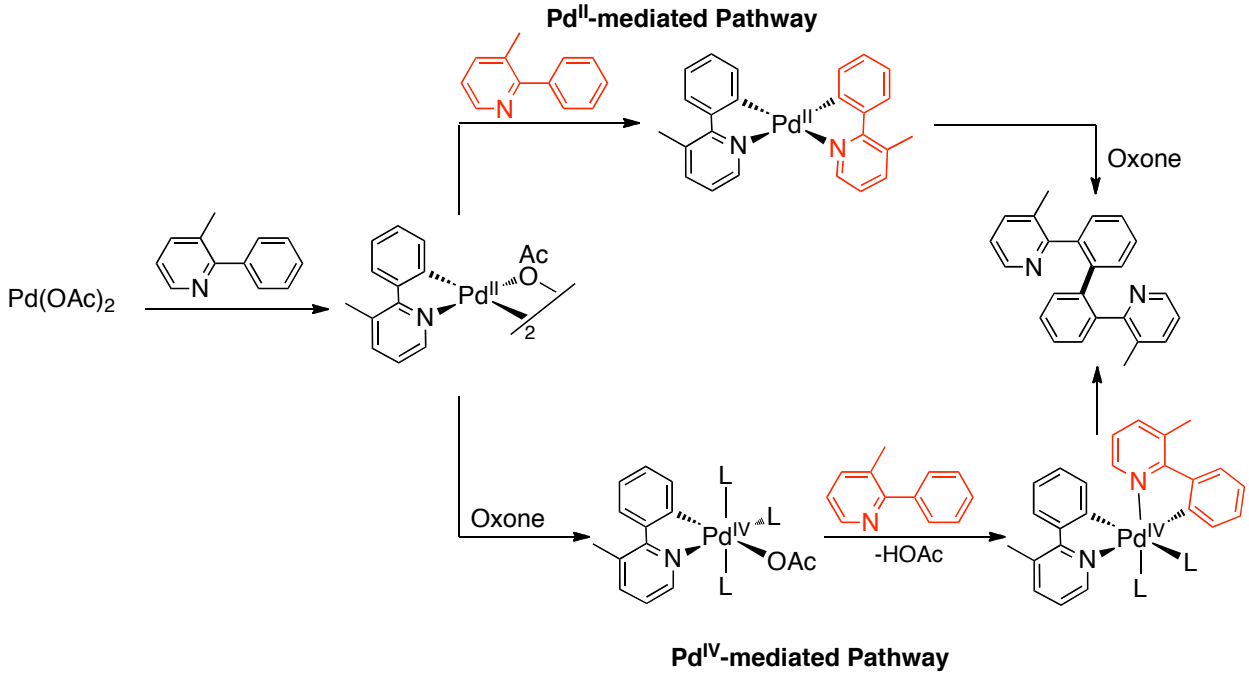
In 2006, Sanford and co-workers performed an initial investigation into the Pd^{IV}-mediated C-H activation pathway. In this report, Sanford studied the dimerization of phenanthrenes in the presence of an electron-deficient Pd^{II} catalyst and a strong oxidant[58] (Scheme 2.31).



Scheme 2.31: Dimerization of Phenanthrenes reported by Sanford[58]

After Sanford established that no transmetallation between two Pd^{II}-centers occurred during the reaction sequence, she also determined that two separate C-H activation steps were present in the reaction. The first C-H activation step on the phenanthrene substrate occurs at the Pd^{II}-center to generate a Pd^{II} dimer. Starting from the Pd^{II} dimer, Sanford then proposed two separate reaction pathways to account for the second C-H activation step: (i) the first pathway involves C-H activation at a Pd^{II}-center with reductive elimination in the presence of oxone yields the dimerized product and (ii) the second pathway involves C-H activation at a Pd^{IV}-center, which

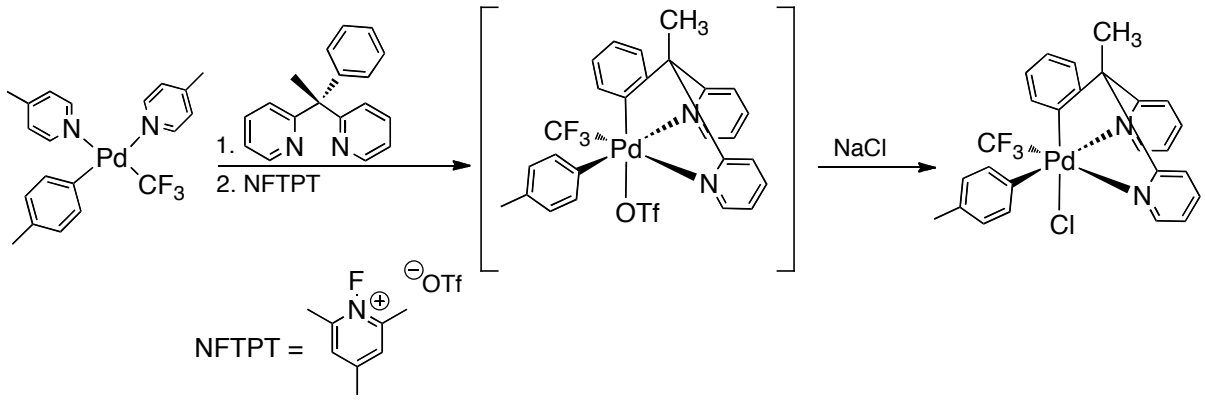
was generated in the presence of oxone, with subsequent reductive elimination yielding the dimerized product (Scheme 2.32).



Scheme 2.32: Reaction Pathway featuring Palladium(IV)-mediated C-H activation proposed by Sanford[58]

When Sanford performed equilibrium studies between the Pd^{II} dimer and the proposed Pd^{II} complex featuring the two phenanthrene substrates, the results demonstrated that the Pd^{II} dimer is the favored product in the reaction sequence. This strongly suggests that the Pd^{II}-mediated pathway is not present in the reaction sequence and that the proposed Pd^{IV}-mediated pathway is responsible for the dimerized product featuring a newly coupled $C(sp^2)$-$C(sp^2)$ bond. While Sanford was unable to obtain any direct evidence that either Pd^{IV} complex is generated during the reaction sequence, this report serves as the primary example that C-H activation can be achieved at a Pd^{IV}-center.

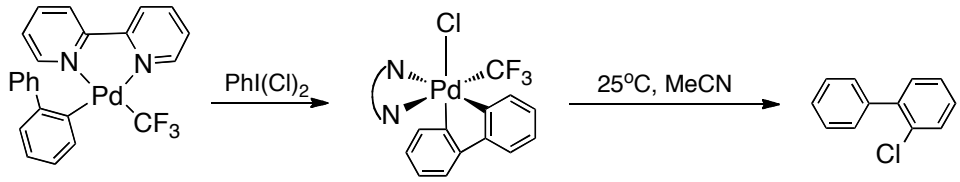
In a study conducted by Sanford in 2011, she demonstrated that Pd^{IV}-mediated C-H activation could be achieved at an activated $C(sp^2)$-center on a tridentate ligand featuring two Nitrogen atoms[53] (Scheme 2.33).



Scheme 2.33: Palladium(IV)-mediated C-H activation at an activated $C(sp^2)$-center reported by Sanford[53]

The new Pd-$C(sp^2)$ bond is formed upon ligand exchange at the Pd^{II}-center followed by subsequent oxidation in the presence of NFTPT to yield the Pd^{IV} complex featuring the activated Pd-$C(sp^2)$ bond. Addition of NaCl generated an isolable Pd^{IV} complex at 25°C. While Sanford then explored the reactivity of the Pd^{IV}-center towards nucleophilic substitution (which is described in Section 2.5.3), this Pd^{IV} complex features one of the first known examples of C-H bond activation occurring at the Pd^{IV}-center.

Using these results, in 2011 Sanford and co-workers published another example of the Pd^{IV}-mediated C-H activation but these results featured an unactivated $C(sp^2)$-center within a bidentate ligands[45] (Scheme 2.34).



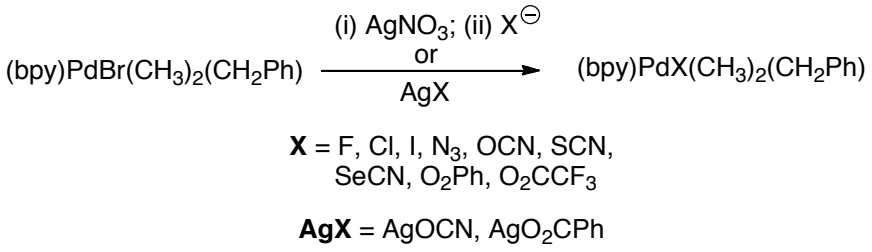
Scheme 2.34: Palladium(IV)-mediated C-H activation at an unactivated C(sp^2)-center reported by Sanford[45]

The new Pd^{IV}-C(sp^2) bond is generated upon oxidation of the initial Pd^{II} complex, featuring the unactivated C(sp^2)-H located on the phenyl ring, in the presence of iodobenzene dichloride. Reductive elimination yields an organic product featuring a new C(sp^2)-Cl bond. While more mechanistic studies need to be performed to understand the Pd^{IV}-mediated C-H activation reaction pathway, this report by Sanford suggests that a Pd^{IV}-center can be used to functionalize unactivated C(sp^2)-H bonds under appropriate reaction conditions.

2.5.3: Nucleophilic Substitution

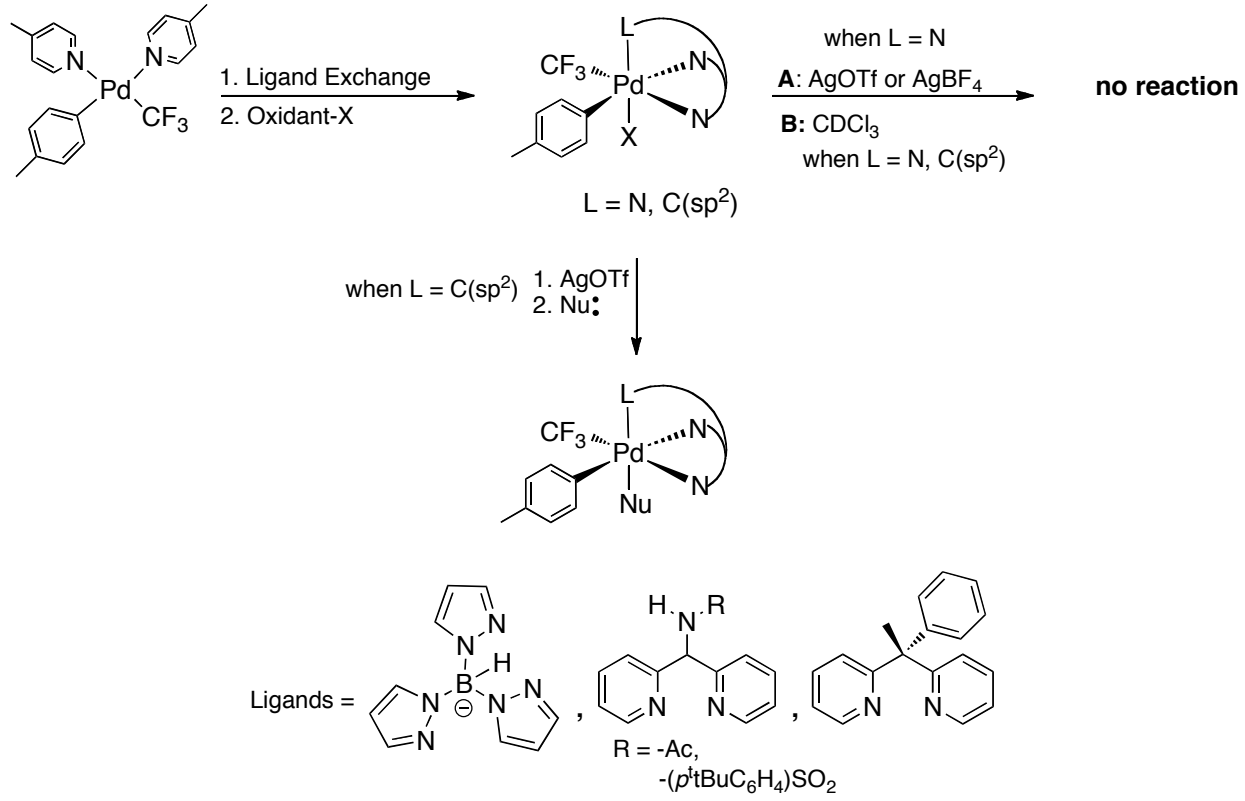
Another area of Pd^{IV} research focuses on the reactivity of the Pd^{IV}-center towards nucleophilic substitution. In this reaction pathway, organometallic chemists hope to construct new Pd^{IV}-complexes featuring labile ligands, which can be replaced with nucleophiles containing strong binding atoms that are not commonly present in Pd^{IV} complexes.

In 1992, Canty and co-workers successfully demonstrated the first example of nucleophilic substitution occurring at the Pd^{IV}-center. Starting from the synthesized Pd^{IV} complexes, Canty replaced the bromide ligand with multiple strongly coordinating ligands after addition of silver nitrate and the nucleophilic counter anions or with the addition of the silver salt containing the nucleophile[59] (Scheme 2.35). The Pd^{IV} complexes were isolated at stable solids at 25°C and characterized by ^{1}H NMR analysis.



Scheme 2.35: Nucleophilic substitution at the Palladium(IV) center reported by Canty[59]

Utilizing the results published by Canty, Sanford and co-workers also explored the reactivity of multiple Pd^{IV} complexes towards nucleophilic substitution at the Pd^{IV}-center. In 2011, Sanford constructed three Pd^{IV} complexes featuring various tripodal ligands with either Nitrogen or Carbon donor atoms[53] (Scheme 2.36).



Scheme 2.36: Reactivity studies performed at Palladium(IV) complexes reported by Sanford[53]

The Pd^{IV} complexes were generated from the starting Pd^{II} complex via ligand exchange followed by oxidation in the presence of either iodobenzene dichloride or NFTPT. The complexes were then subjected to various decomposition or nucleophilic substitution conditions.

Sanford discovered that when three Nitrogen atoms are bound to the Pd^{IV}-center, the resulting Pd^{IV} complex is unreactive and does not decompose or undergo nucleophilic substitution. However, when two Nitrogen atoms and one Carbon(sp^2) atom is bound to the Pd^{IV}-center, the resulting Pd^{IV} complex undergoes nucleophilic substitution in the presence of strong nucleophiles.

Sanford proposes that the strong binding Nitrogen atoms prevent ligand dissociation from occurring at the Pd^{IV}-center, which would then prevent decomposition and nucleophilic substitution. When weaker binding atom is present, such as an C(sp^2) atom, nucleophilic substitution can occur. This report demonstrates that the nature of the ligand bound to the Pd^{IV}-center has an important effect on the reactivity.

2.6: Future Outlook for Palladium(IV) Chemistry

By reviewing the history of Pd^{IV} chemistry, a model experimental system can be constructed and applied to future Pd^{IV} chemical exploration. This future exploration can involve but is not limited to: construction of new Pd^{IV} complexes that include the use of multidentate ligands to stabilize the Pd^{IV}-center or strong oxidants to install the desired Pd-C or Pd-heteroatom bonds; expansion towards new oxidants previously not utilized in Pd^{IV} chemistry; or studying the reactivity at the Pd^{IV}-centers which include stabilizing ligands that do not interfere with the

chemical transformation. By continuing to study Pd^{IV} chemistry, organometallic chemists can apply the desired results to palladium-catalyzed bond-forming reactions to functionalize carbon centers.

2.7: Chapter Two Bibliography

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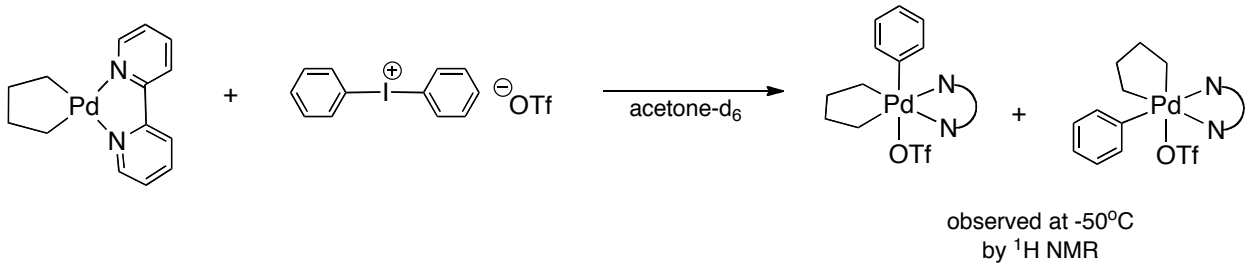
Chapter Three

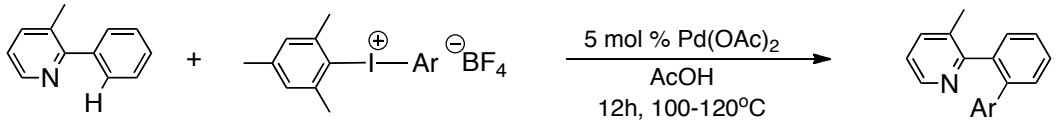
Diazonium Salts as Novel Organic Oxidants for Palladium(II) Complexes

3.1: Introduction

The goal of this project was to assess the feasibility of using aryl diazonium salts as organic oxidants to construct various Pd^{IV} complexes featuring multiple Pd-carbon bonds. To date, the only alternative oxidants available to form Pd-C(sp^2) and Pd-C(sp) bonds by oxidation of Pd^{II} complexes are iodonium salts.[1] In published reports where a diaryl iodonium salt is used as the oxidant in the presence of a Pd^{II} catalyst, the resulting Pd^{IV} complex is either observed at low temperatures, as reported by Canty,[2] (Scheme 3.1) or is not detected, as reported by Sanford[3] (Scheme 3.2).

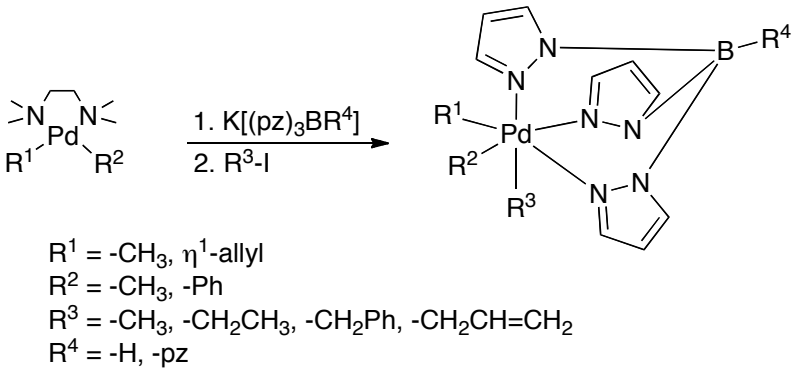


Scheme 3.1: Palladium(IV) complex generated in the presence of a diaryl iodonium salt reported by Canty[2]



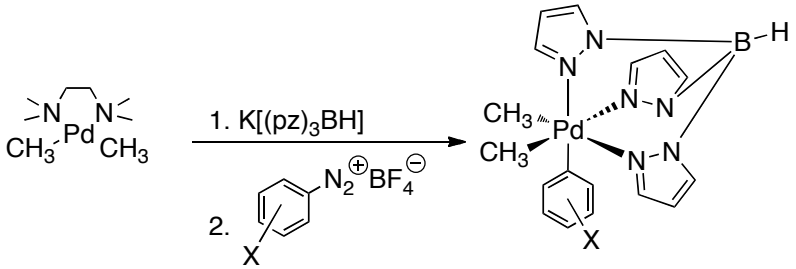
Scheme 3.2: Oxidative C-H activation with diaryl iodonium salts reported by Sanford[3]

We were inspired by Canty's work on the synthesis of Pd^{IV} complexes featuring multiple Pd-C(sp^2) and Pd-C(sp^3) bonds.[4] In this synthesis, one Pd-C(sp^3) bond is installed via oxidation of a Pd^{II} complex by an alkyl halide and the remaining Pd-C(sp^2) and Pd-C(sp^3) bonds are present in the starting Pd^{II} complex (Scheme 3.3). The tripodal tris(pyrazol-1-yl)borate (Tp) ligand aided in the stabilization of the Pd^{IV} centers and allowed for the resulting Pd^{IV} complexes to be isolated as stable solids and characterized by ^1H and ^{13}C NMR at 25°C, however copies of the spectral graphics were not provided in the publication.



Scheme 3.3: Previously reported results by Canty[4]

Aryl diazonium salts are available from various aniline compounds by the treatment of an organic nitrite with trifluoroborate, providing a wide range of potential oxidants. Diazonium salts have also been used in Pd^0-catalyzed cross-coupling reactions, where they act as the electrophile and oxidant to convert the Pd^0 to a Pd^{II} intermediate.[5] We envisioned that we could synthesize a series of complexes analogous to those prepared by Canty (Scheme 3.3) in the presence of the new aryl diazonium salt oxidant, where the Pd-C(sp^2) bond would be generated in the last step of the reaction (Scheme 3.4).



Scheme 3.4: Proposed synthesis of Palladium(IV) complex via diazonium salt oxidant

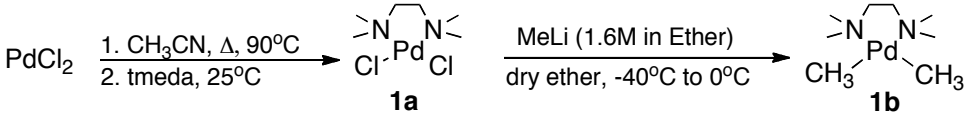
The desired Pd^{IV} complexes would be synthesized via oxidation of the starting Pd^{II} complex with various diazonium salts acting as the electrophiles and oxidant in our reactions. The staring Pd^{II} complex would feature two Pd-C(sp^3) bonds and the oxidation would install the Pd-C(sp^2) bond.

To monitor whether the diazonium salt indeed operates as the oxidant, we will use in situ ^{1}H NMR monitoring to observe the progress of the reaction. We will also use the physical description and ^{1}H NMR spectral standard reported by Canty[4] to confirm the product formation.

3.2: Synthesis of Starting Materials

3.2.1: Palladium(II) complex

The starting Pd^{II} complex was easily synthesized from $PdCl_2$ to create a new Pd^{II} complex **1a** as a yellow solid in 94% yield. This complex (**1a**) is then treated with MeLi to create the desired Pd^{II} complex **1b** as a light yellow solid in 77% yield[6] (Scheme 3.5).

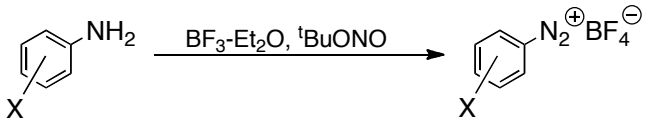


Scheme 3.5: Synthesis of starting Palladium(II) complex **1b**

The Pd^{II} complex (**1a)** can only be characterized by melting point, as ^{1}H NMR spectral analysis would only show a symmetrical tmeda ligand environment. The final Pd^{II} complex (**1b**) can be characterized by melting point and ^{1}H NMR spectral analysis. For this complex (**1b**) the signals associated with the two $-CH_3$ groups are seen at δ -0.35 ppm, which matches the reported literature values.[6]

3.2.2: Diazonium Salt Oxidants

Next, we focused on the synthesis of the starting diazonium salts, which involved the addition of trifluoroborate etherate and *t*-butyl nitrite to the corresponding aniline (Scheme 3.6).



2a: X = -H (90%)
2b: X = -*p*-CH_3O (94%)
2c: X = -*p*-F (100%)
2d: X = -*p*-CH_3 (92%)
2e: X = -*p*-CF_3 (82%)
2f: X = -*o*-CH_3 (100%)

Scheme 3.6: General synthesis of the diazonium salts

In the phenyl diazonium salt, the liquid aniline was stirred with trifluoroborate etherate in diethyl ether. After 10 minutes, a solution of the *t*-butyl nitrite was added dropwise slowly at -5°C. After stirring for 20 minutes, pentane was added to precipitate a solid.[7] The desired diazonium salt **2a** was then collected by filtration as a red solid in 82% yield and was characterized by melting point (137°C) and ^{1}H and ^{13}C NMR spectral analyses.

A series of diazonium salts (**2b-2f**) was synthesized and each was collected as a solid in good yield (Table 3.1).[8] For the diazonium salts **2b** and **2d**, the solid anilines had to be purified by vacuum sublimation prior to the treatment with the trifluoroborate etherate. To prevent hydrolysis of the diazonium salt to the corresponding hydroxy-2-phenyldiazene during the diazotization reaction, (Scheme 3.7) it is important to use the following precautions: (i) using dry THF as the reaction solvent; (ii) using fresh starting trifluoroborate and nitrite; and (iii) using the minimal amount of ether or pentane during the work-up. The final products (**2b-2f**) were also characterized by melting point[9] and ^{1}H and ^{13}C NMR spectral analyses and the data was found to be in agreement with the reported literature information available.[8]

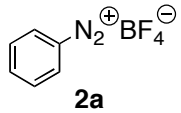
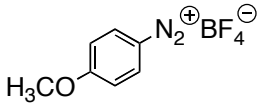
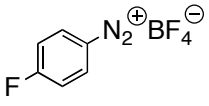
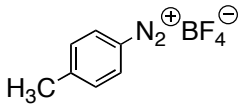
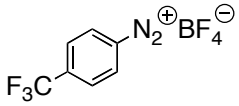
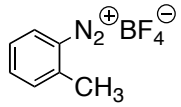
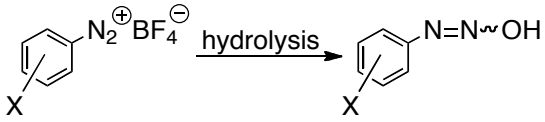
Diazonium Salt	Appearance	Yield	Characterization Data
 **2a**	Red solid	82%	mp = 137°C; ^{1}H, ^{13}C NMR
 **2b**	White solid	94%	mp = 140-142°C; ^{1}H, ^{13}C NMR
 **2c**	White solid	99%	mp = 154-155°C; ^{1}H, ^{19}F, ^{13}C NMR
 **2d**	White solid	92%	mp = 105-106°C; ^{1}H, ^{13}C NMR
 **2e**	Light yellow solid	81%	mp = 80-82°C; ^{1}H, ^{19}F, ^{13}C NMR
 **2f**	White solid	100 %	mp = 90-91°C*; decomposed prior to spectral analysis

Table 3.1: Results of Diazonium Salt Synthesis
(*) = No literature reference was found for the diazonium salt

The overall synthesis of the diazonium salts (**2a-2f**) involves complex color changes and we can use these color changes to detect any possible hydrolysis prior to ^{1}H NMR analysis. For the synthesis of the phenyl derivative (**2a**), an orange solid is produced during the work-up step, suggesting the formation of 1-hydroxy-2-phenyldiazene. For the synthesis of the *p*-methoxy derivative (**2b**), the reaction solution turns bright blue upon addition of the *t*-butyl nitrite in dry ether, suggesting the formation of 1-hydroxy-(4-methoxy)-2-phenyldiazene. Unfortunately, the hydrolyzed product cannot be separated from the desired aryl diazonium salt so it very important to minimize any hydrolysis during the synthesis.

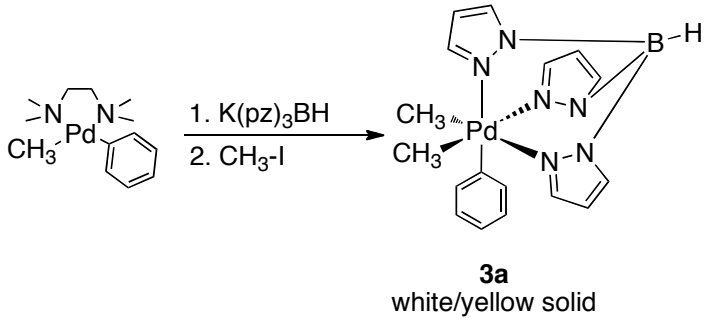


Scheme 3.7: Hydrolysis product during diazotization

Overall, the *para*-substituted diazonium salts (**2a-2e**) were found to be very stable at 25°C and did not decompose in storage at -20°C. However, the *ortho*-substituted diazonium salt (**2f**) is not stable and decomposes at 25°C after 1 week. Therefore, these diazonium salts would not be suitable for the Pd^{IV} reaction studies, as the diazonium salt could decompose prior to oxidation or lead to an unstable Pd^{IV} complex. However, this is typical for diazonium salts containing electron-donating groups at the ortho position.[9]

3.3: Initial Oxidation Studies with the Phenyl Diazonium Salt

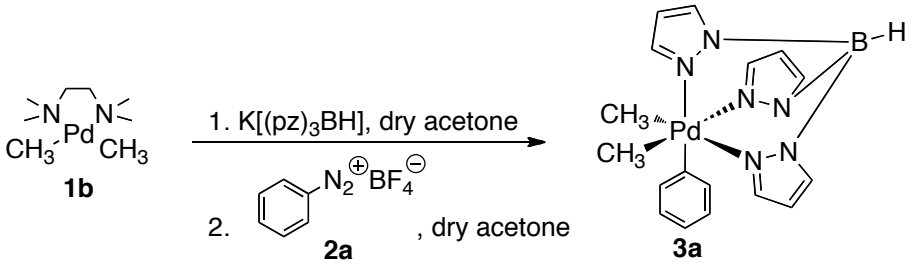
Initially, we focused on the synthesis of the Pd^{IV} complex (**3a**), which features two Pd-CH_3 bonds and a Pd-Ph bond. This complex was previously made by Canty by the oxidation of a (Tp)Pd^{II}(CH_3)(Ph) complex with methyl iodide at 35°C[4] (Scheme 3.8). Canty then isolated the complex **3a** as a yellow precipitate from a water and ethanol mixture and characterized **3a** by ^{1}H and ^{13}C NMR spectral analyses.



3a
white/yellow solid

Scheme 3.8: Previously reported synthesis by Canty[4]

Starting with the synthesized Pd^{II} complex (**1b**), we envisioned performing a ligand exchange to insert the tripodal Tp ligand followed immediately by an in situ oxidation with the phenyl diazonium salt (**2a**) in dry acetone at 25°C to produce the desired Pd^{IV} complex (**3a**). The Pd^{IV} complex would then be isolated at 25°C and characterized by ^1H NMR spectral analysis. The ligand exchange, oxidation and isolation procedures were similar to the procedures reported by Canty (Scheme 3.9).



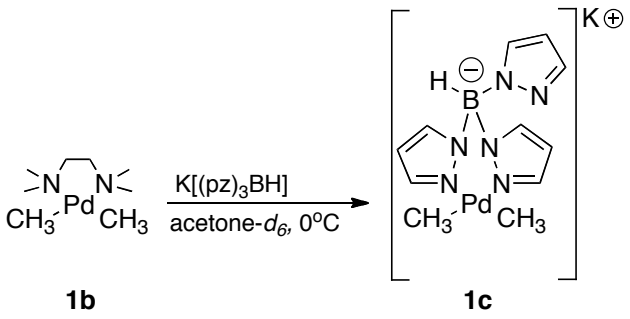
Scheme 3.9: Initial synthesis of Palladium (IV) complex **3a**

Initially, the solid **1b** and solid Tp were dissolved in dry acetone at 0°C and allowed to stir for 1 hour. At this time, the color of the reaction solution turned from yellow to clear, which lead us to believe that a ligand exchange occurred. Next, a solution of the phenyl diazonium salt (**2a**) in acetone was added to the clear reaction mixture at 25°C. The reaction solution turned orange after 2.3 hours of stirring. The solution was allowed to settle overnight at 0°C and then the liquid was removed via decantation at 25°C to collect a solid. The resulting the solid was then washed with ether and filtered to collect a solid, which became an oil upon drying under reduced pressure. ^1H NMR spectral analysis of the oil showed that it was an impure mixture with none of the signals matching those reported by Canty.

The reaction was then repeated in dry acetonitrile at both 25°C and -15°C, giving an orange solid was collected. However, the ^{1}H NMR spectral analysis of the solid did not match the reported spectrum by Canty as well. When the reaction was repeated in dry acetonitrile at -40°C, the initial reaction solution froze making the oxidation impossible. Therefore, we determined that in order to study the oxidation at -40°C, the reaction must be run in dry acetone. At this point, we decided to focus on observing the desired Pd^{IV} complex (**3a**) by in situ ^{1}H NMR monitoring and determine the proper isolation techniques at a later date. In order to properly characterize the final structure, we also wanted to confirm the formation of the intermediates arising from ligand exchange.

3.4: Ligand Exchange with Tp Ligand

To confirm that ligand exchange of tmeda and KTp was occurring, we performed an in situ ^{1}H NMR monitoring experiment at 0°C. To start, the solid **1b** and solid KTp were dissolved in acetone-d_6 at 0°C and stirred for 1 hour (Scheme 3.10).



Scheme 3.10: Successful ligand exchange

During this time, the reaction solution turned from yellow to clear. After 1 hour, an aliquot (0.4 mL) was transferred to a pre-cooled NMR tube and the resulting solution was taken for ^{1}H NMR

spectral analysis at 0°C. The NMR showed new pyrazole (*) signals, a broadening of the Tp signals (#) and unbound tmeda signals (&), so we were able to determine the presence of the new Pd^{II} intermediate (**1c)**, suggesting that a partial ligand exchange does occur at the conditions reported by Canty (Figure 3.1).

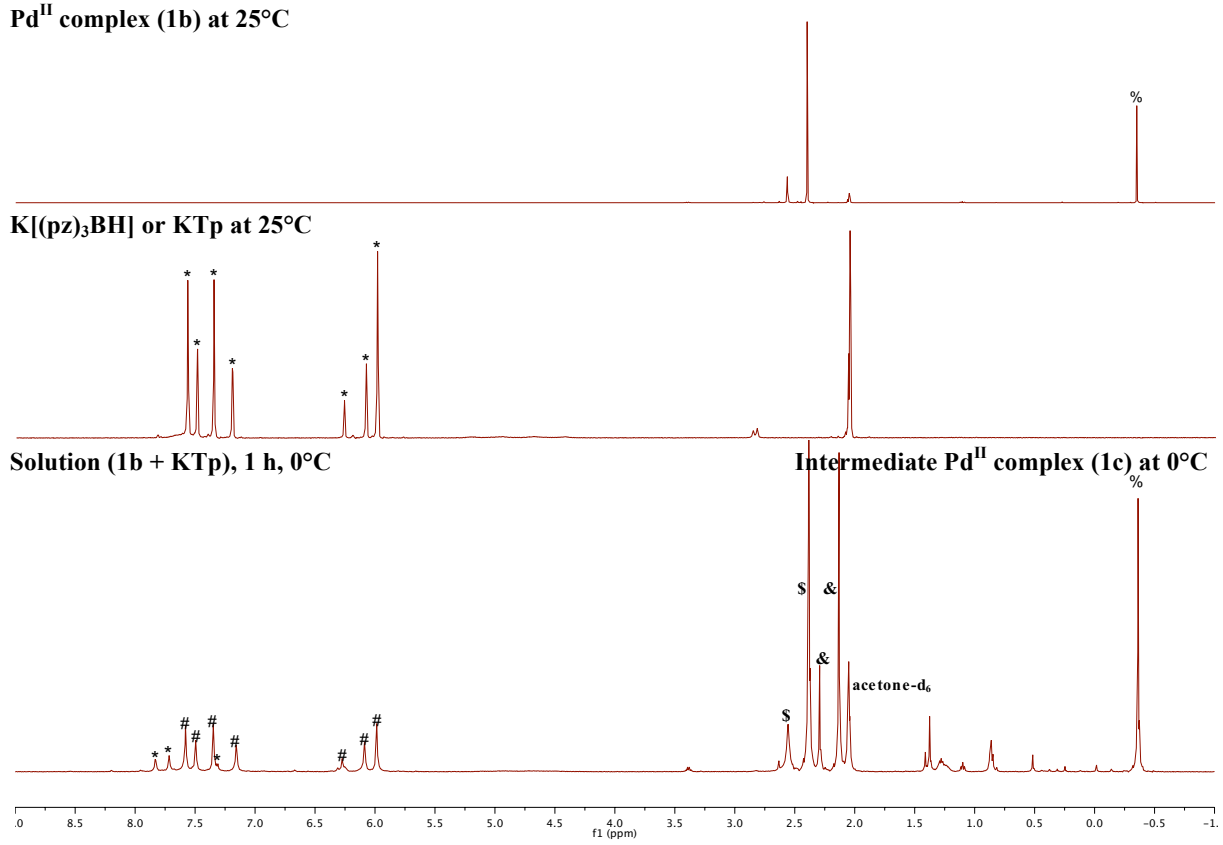
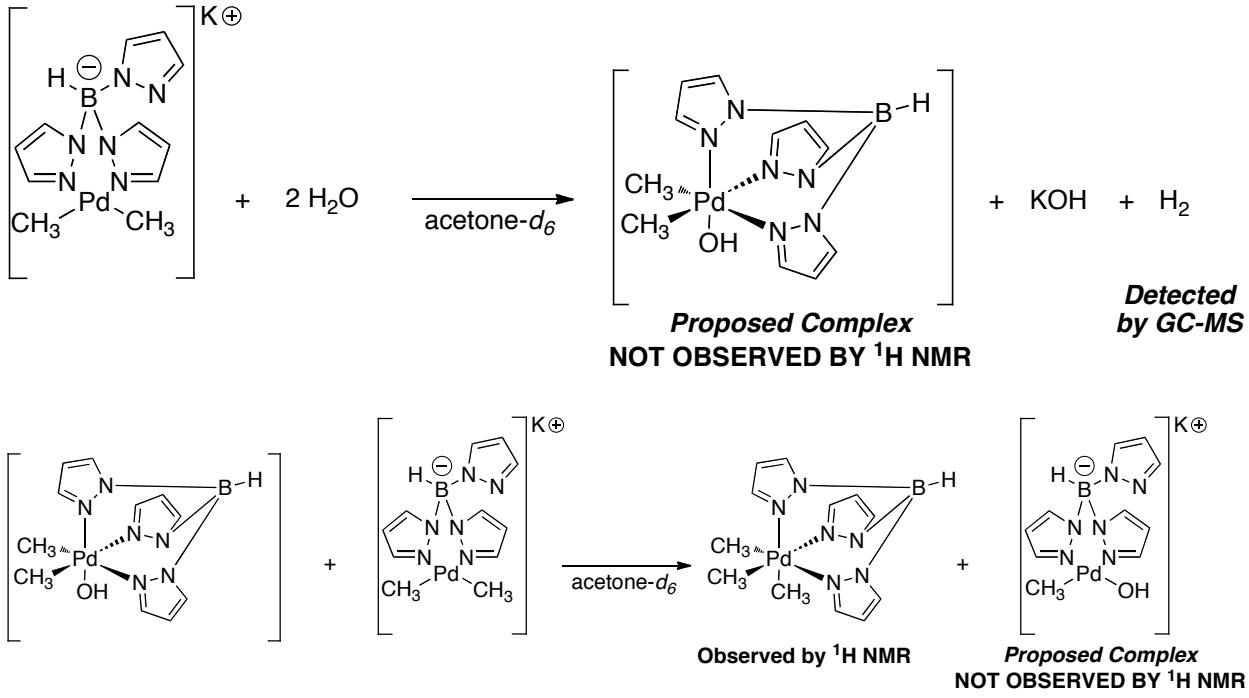


Figure 3.1: ^{1}H NMR (500 MHz, acetone-d_6) spectra of Palladium (II) complex (**1b**), KTp and Palladium(II) complex (**1c**)
(*) – new Tp signals (#) – old Tp signals (%) –Pd-CH_3 ($) – bound tmeda (&) – unbound tmeda

In the ^{1}H NMR data, we observe the formation a new Pd^{II} complex (**1c**) as well as the starting Pd^{II} complex (**1b**) and unbound KTp signals. This suggests that an equilibrium between the two Pd^{II} complexes (**1b** and **1c**) exists and upon addition of the oxidant to generate the desired Pd^{IV} complex, the ligand exchange equilibrium shifts towards the formation of **1c.**

It is important to note that the new Pd^{II} intermediate (**1c**) cannot be isolated because it's exposure to water and air would result in an unfavorable hydrolyzed Pd^{IV} product[10] (Scheme 3.11). During the oxidation by water, Canty reported the formation of hydrogen gas was detected by GC-MS analysis. While the Pd^{IV} complex featuring the hydroxyl ligand could not be detected, the complex underwent ligand exchange to yield a new Pd^{IV} complex featuring three methyl groups, which was analyzed by ^{1}H NMR.



Scheme 3.11: Oxidation of **1c** to a new Palladium(IV) complex reported by Canty[10]

3.5: Palladium(IV) complex Formation at Low Temperature

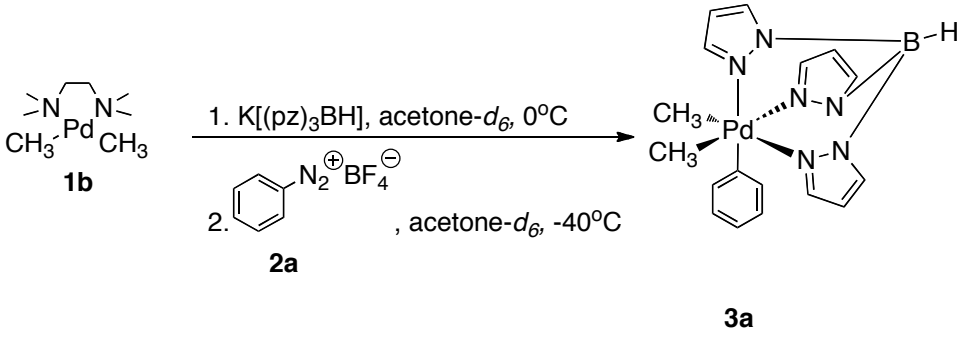
After establishing the reaction conditions for the ligand exchange, we returned to focus on the in situ oxidation with the phenyl diazonium salt (**2a**) in dry acetone at -40°C. After confirming the formation the Pd^{II} intermediate (**1c**) by the method described above, a solution of 1.1 equivalents of **2a** in acetone was added to the reaction solution at -40°C and allowed to stir for 2.3 hours. At

this time, the color of the reaction mixture changed from clear to dark orange, suggesting that a new Pd-containing species may be present.

After the fine reaction suspension was allowed to settle, the liquid was removed by low temperature filter-tipped cannulation leaving behind a yellow solid. The yellow solid was then dissolved in $CDCl_3$ and taken for ^1H NMR spectral analysis at -40°C.

The ^1H NMR spectral data for the yellow solid matched the reported values by Canty, suggesting we successfully formed the desired Pd^{IV} complex (**3a**) in solution at -40°C (Figure 3.2). A detailed discussion of the spectral data can be found in Section 3.7 on page 72.
However, when the solvent was removed under reduced pressure and the yellow solid was stored at -20°C overnight, it decomposed and became an orange oil.

In order to obtain the ^1H NMR spectra for the Pd^{IV} complex (**3a**) free of the signal for the acetone solvent, the reaction was repeated in acetone-d_6 under the same method described above to collect a yellow solid (Scheme 3.12).



Scheme 3.12: Synthesis of Palladium(IV) complex (**3a**)

The yellow solid was then dissolved in acetone-d_6 and taken for ^{1}H NMR spectral analysis at -40°C. The ^{1}H NMR spectral data for the yellow solid was in good agreement with those reported values by Canty (Figure 3.2).

For the Pd^{IV} complex (**3a**) synthesized by our method in acetone-d_6 at 500 MHz, we report the following signals: δ 7.43 (bs, 2H), 7.35 (m, 1H), 7.29 (bs, 2H), 7.05 (t, 2H), 6.87 (bs, 1H), 6.79 (t, 2H), 6.46 (d, 1H), 5.96 (bs, 2H), 1.56 (s, 6H). The reported signals by Canty for the Pd^{IV} complex in $CDCl_3$ at 300 MHz are: δ 7.70 (m, 3H), 7.62 (b, 1H), 7.24 (b, 2H), 7.03 and 6.96 (bm, 5H), 6.25 (t, 1H), 6.15 (t, 2H), 1.82 (s, 6H).[4] Unfortunately, Canty does not provide the spectral graphics for comparison, so we can only compare our signals to those reported in the experimental section. When comparing our signals with those reported by Canty, we see the same general splitting pattern of signals associated with the following signals: the pyrazole protons (*) in the Tp ligand at 7-8 ppm; the phenyl protons (#) at 7 ppm; another set of pyrazole proton (*) signals at 6-6.5 ppm; and the methyl protons (%) at 1-2 ppm. The minimal discrepancy of signals can be associated with using acetone-d_6 as the NMR solvent instead of $CDCl_3$.

This time, the yellow solid was stored in acetone-d_6 overnight at 25°C and the solution was taken for ^{1}H NMR spectral analysis the next day at 25°C. The ^{1}H NMR spectral data for the solution showed little to no decomposition overnight, suggesting that the desired Pd^{IV} complex (**3a**) is stable in solution at 25°C (Figure 3.2). Thus, the next challenge consists of isolating the complex as a solid at 25°C.

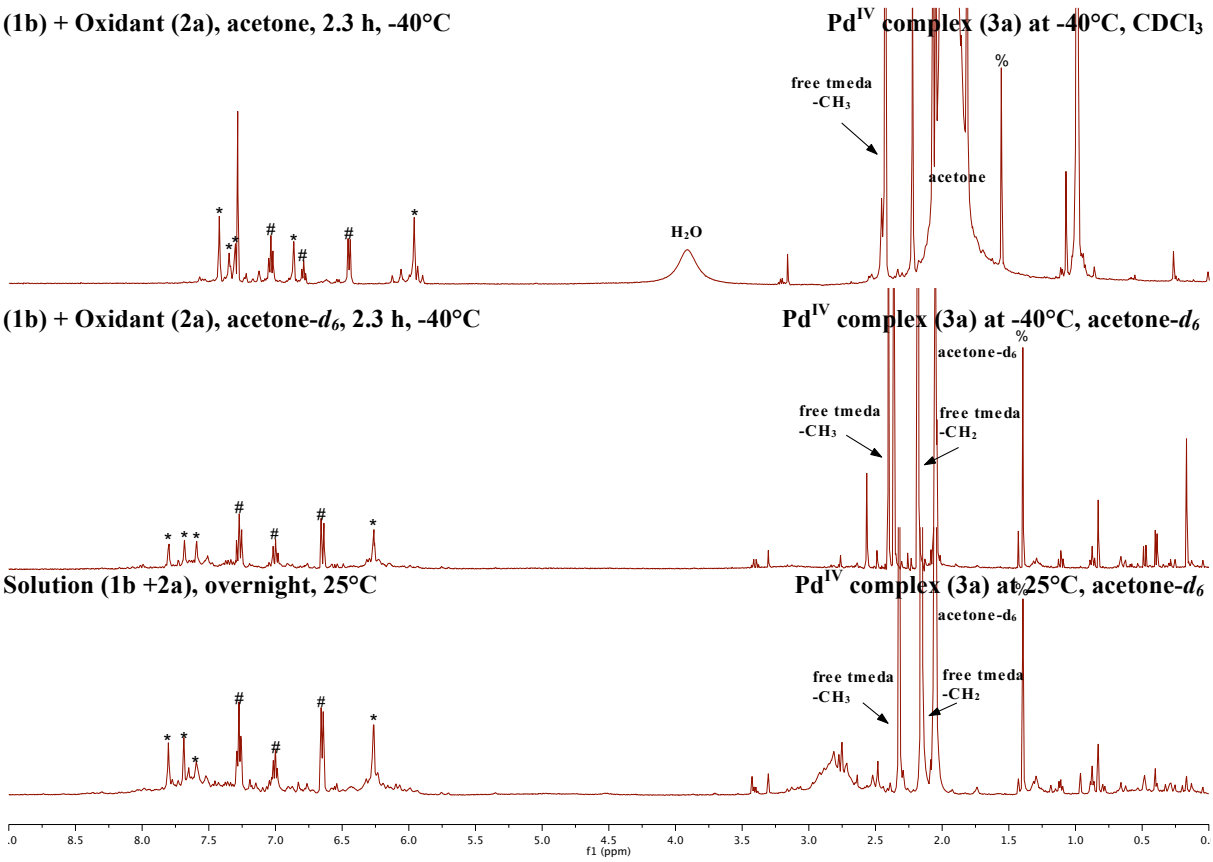
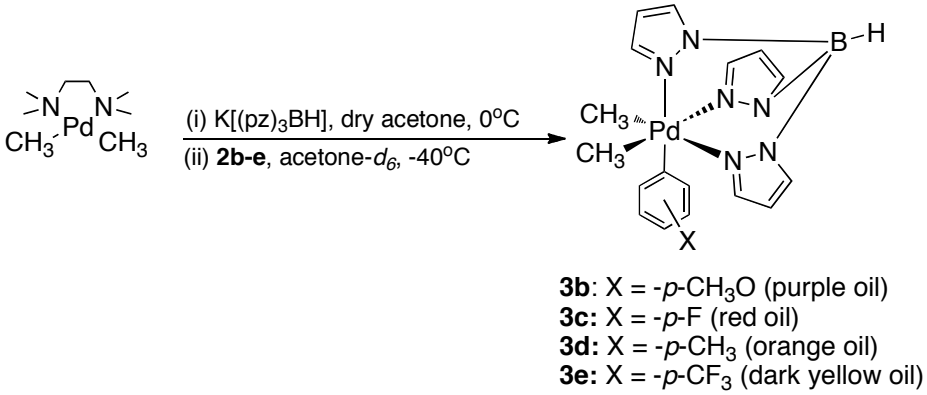


Figure 3.2: in situ ^{1}H NMR (500 MHz) spectra of Palladium(IV) complex (**3a**) at -40°C in $CDCl_3$ and acetone-d_6 and at 25°C
(*) – Tp signals (#) – Aryl signals (%) –Pd-CH_3 signals

3.6: Scope of Palladium(II) Oxidation with Diazonium Salts

After confirming the in situ generation of Pd^{IV} complex (**3a**) in solution resulting from the oxidation with the phenyl diazonium salt (**2a**), we envisioned expanding the oxidant scope to various diazonium salts (**2b-2e**) to include electron-rich substituents (**2b, 2d**) and electron-poor substituents (**2c, 2e**). During this process, we also hoped to generate new Pd^{IV} complexes featuring various phenyl rings with different *para* substituents (Scheme 3.13).



Scheme 3.13: Synthesis of Palladium(IV) complexes **3b-3e**

In this reaction series, all the Pd^{IV} complexes were prepared and isolated by the method described above (Section 3.5, page 65) for the Pd^{IV} complex **3a** and characterized by in situ ^1H NMR spectral analysis at -40°C in acetone-d_6.

When using the electron-rich *p*-methoxyphenyl diazonium salt (**2b**), the Pd^{IV} complex (**3b**) was collected as a purple oil at -40°C and the ^1H NMR spectral data for the purple oil showed new signals that were assigned to the new Pd^{IV} complex (**3b**) at -40°C (Figure 3.3). When comparing these signals for **3b** to those reported by Canty for **3a**, we notice the signals are shifted slightly downfield but the same general pattern of singlets and doublets at 7-8 ppm for the pyrazole (*) and phenyl (#) protons, triplets at 6 ppm for the pyrazole protons (*) and a singlet at 1-2 ppm for the methyl (%) protons.

When the oil was stored in acetone-d_6 overnight at 25°C and retaken for ^1H NMR spectral analysis the next day at 25°C, little to no decomposition had occurred suggesting that the synthesized Pd^{IV} complex (**3b**) is stable in solution as well (Figure 3.3).

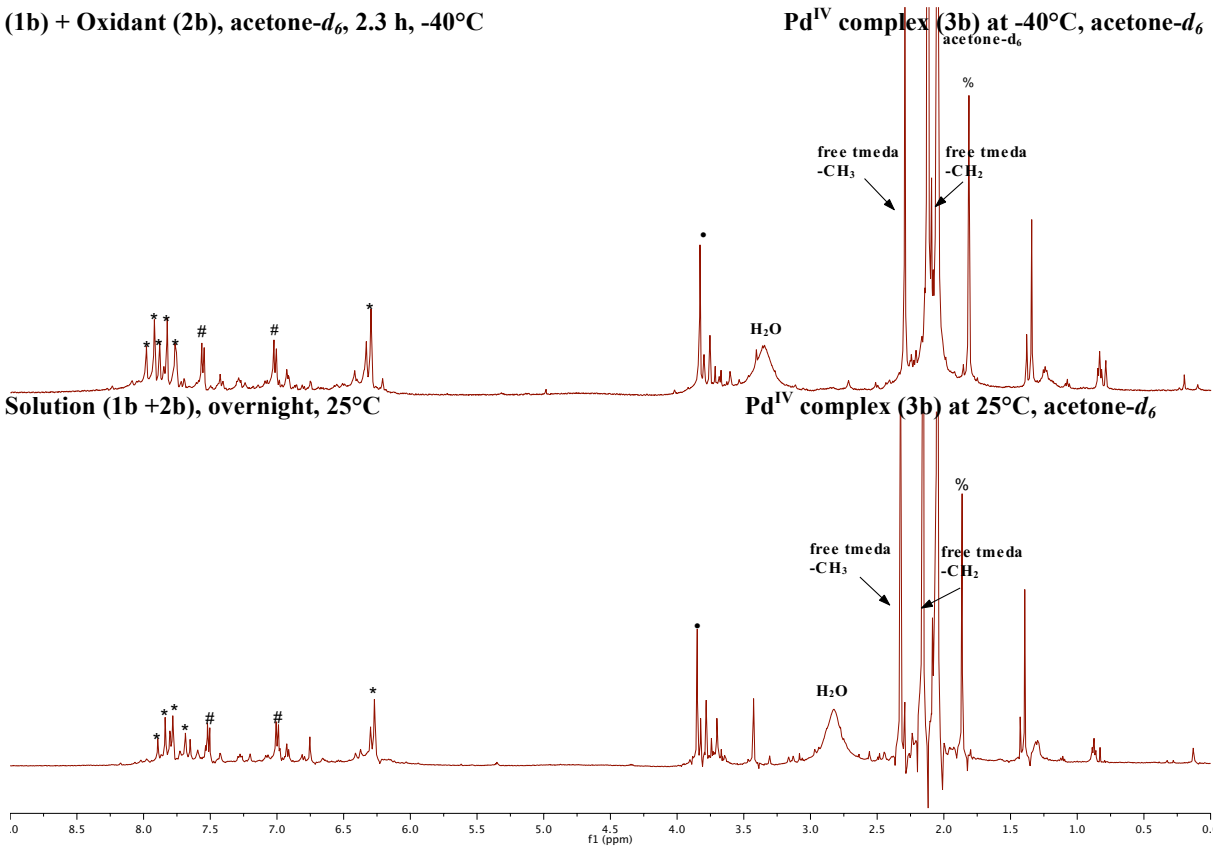


Figure 3.3: in situ ^{1}H NMR (500 MHz, acetone-d_6) spectra of Palladium(IV) complex (**3b**) at -40°C and 25°C (*) – Tp signals (#) – Aryl signals (%) –Pd-CH_3 signal (l) – Aryl-OCH_3 signal

For the electron-poor *p*-fluorophenyl diazonium salt (**2c**), the Pd^{IV} complex (**3c**) was collected as a red oil at -40°C and the ^{1}H NMR spectral data for the red oil showed new signals at -40°C (Figure 3.4). These signals are shifted even further downfield than those reported by Canty and for **3b**, but the same trend as reported above can be seen.

For the *p*-methylphenyl diazonium salt (**2d**), the Pd^{IV} complex (**3d**) was collected as an orange oil and for the *p*-trifluoromethylphenyl diazonium salt (**2e**), the Pd^{IV} complex (**3e**) was collected as dark yellow oil. The ^{1}H NMR spectral data for both complexes (**3d**, **3e**) showed new signals at -40°C that follow the same general trend as reported above (Figure 3.4).

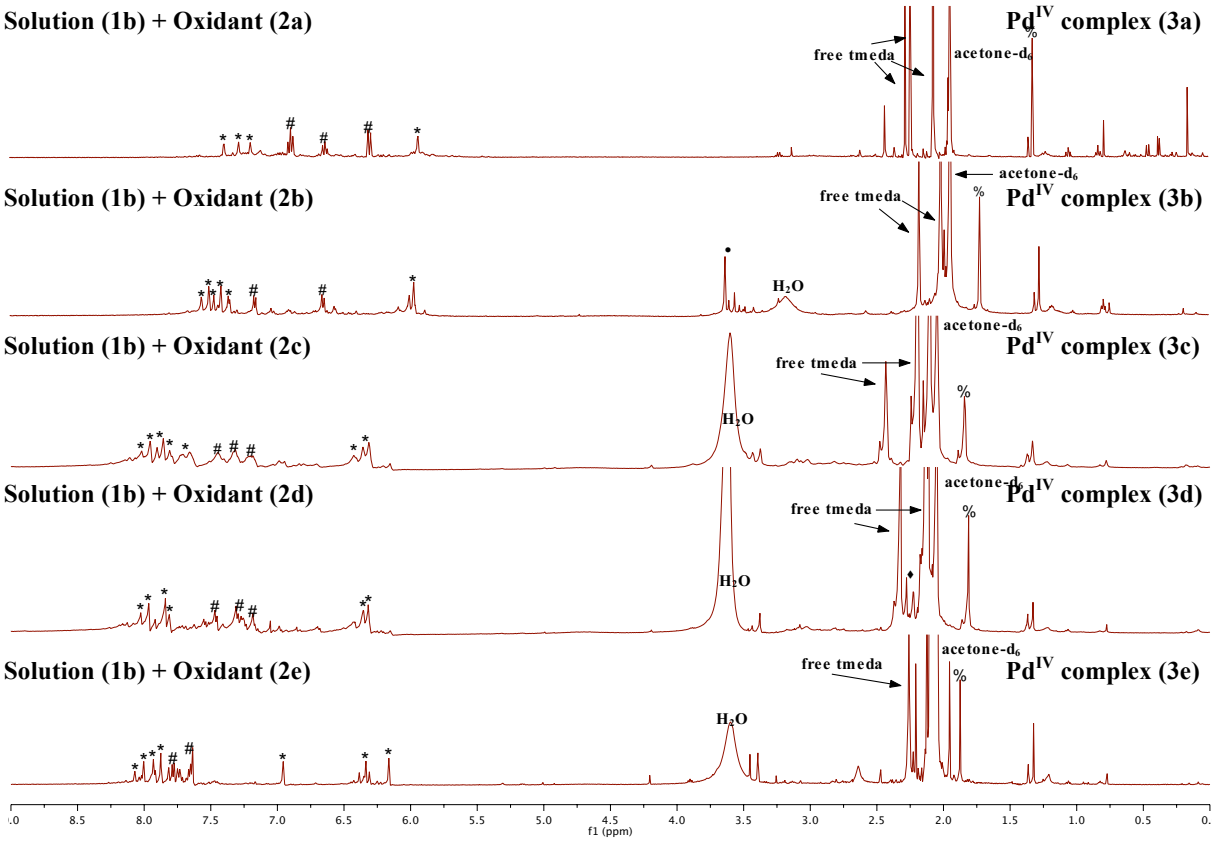


Figure 3.4: in situ ^{1}H NMR (500 MHz, acetone-d_6) spectra summary for the Palladium(IV) complexes **3a-3e** at -40°C
(*) – Tp signals (#) – Aryl signals (%) –Pd-CH_3 signals (ı) – Aryl-OCH_3 signal, (s) – Aryl-CH_3 signal

During the reaction series, we noticed that the Pd^{IV} complexes generated in solution varied in color from yellow to red to purple (Scheme 3.5). This color variation is likely due trace amounts of impurities resulting from the decomposition of the diazonium salt oxidants in our solution prior to oxidation.

Currently, no *ortho* or *meta* substituted diazonium salts have been explored. These diazonium salts have been reported to be unstable and decompose readily at various temperatures. For our experiments, we do not want a diazonium salt to decompose in solution prior to oxidation nor do we want to synthesize a Pd^{IV} complex that would decompose prior to ^{1}H NMR spectral analysis.

Therefore, the reaction scope has been limited to diazonium salts containing *para* substituents only.

3.7: Characterization of the (Tp)$Pd^{IV}(Me)_2(Ar)$ complexes

The characterization of the desired Pd^{IV} complexes (**3a-3e**) was done by ^1H NMR spectral analysis at -40°C. For the initial Pd^{IV} complex featuring the phenyl substituent (**3a**), the ^1H NMR spectral data was reported by Canty. This gave us a standard that we used when analyzing our solutions at -40°C.

For the remaining Pd^{IV} complexes (**3b-3e**), there is no reported spectral data because these complexes have not been synthesized before. Therefore, when characterizing the final Pd^{IV} complex, we focused on two main regions in the ^1H NMR spectral data.

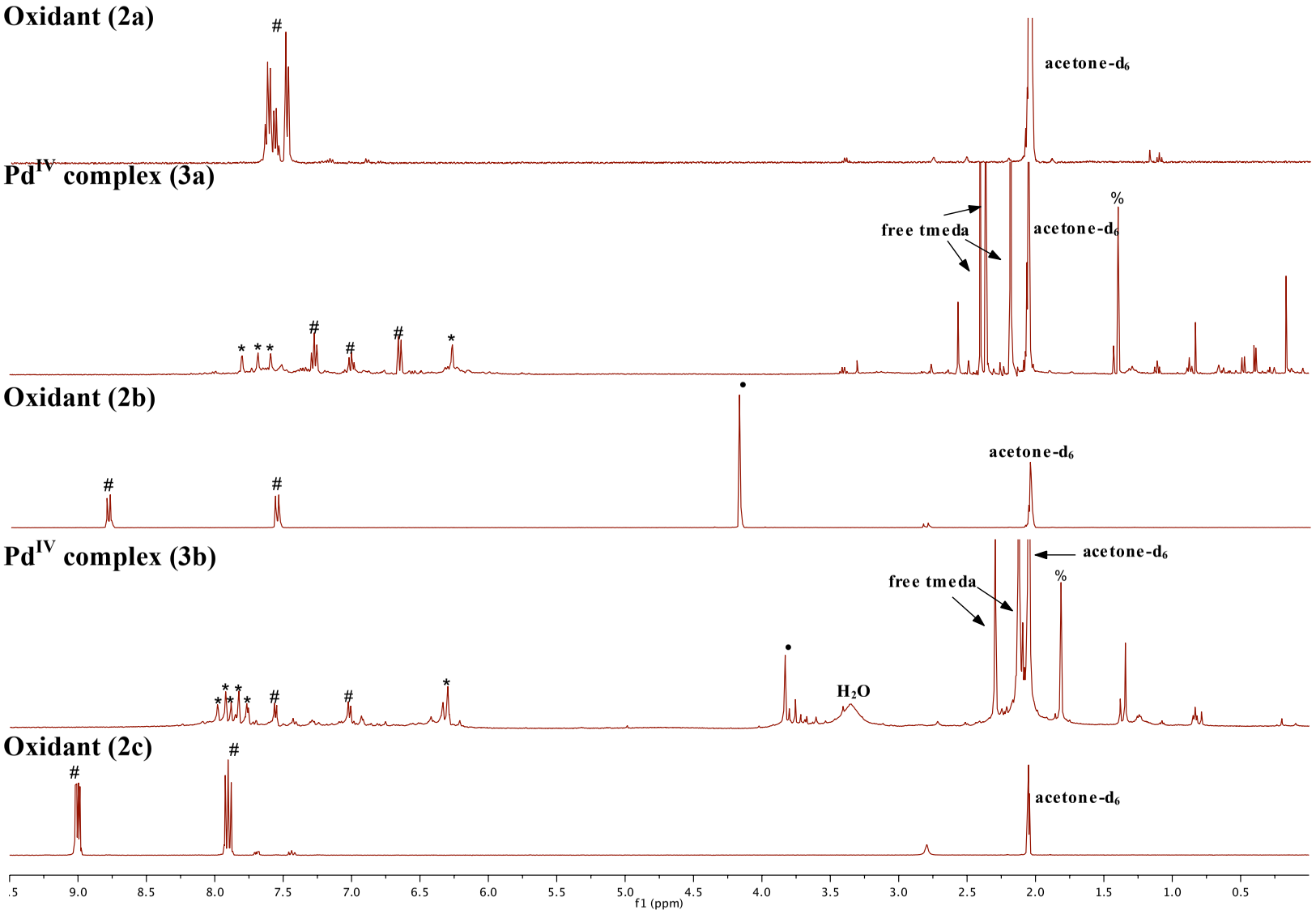
In the aromatic region (5-9 ppm), specifically looking for a shift in the pyrazole signals (*) from the Tp ligand and the proton signals (#) from the substituted phenyl ring from the diazonium salt. For our complexes, the pyrazole signals were seen in two distinct areas of the aromatic region. One set of signals is found at approximately 7.8-9.0 ppm and typically seen as either broad singlets or broad doublets. For **3b**: δ 7.98 (bs, 1H), 7.92 (bs, 2H), 7.88 (bs, 1H), 7.83 (bs, 2H), 7.76 (ds, 2H); for **3c**: δ 8.02 (bs, 2H), 7.96 (bs, 3H), 7.88 (bd, 5H), 7.81 (bs, 2H), 7.73-7.65 (m, 6H); for **3d**: δ 8.03 (bs, 2H), 7.97 (bs, 2H), 7.84 (bs, 3H), 7.81 (bs, 1H), 7.46 (bd, 2H); for **3e**: δ 8.07 (bs, 2H), 8.00 (bs, 3H), 7.93 (bt, 6H) 7.88 (s, 4H), 7.82 (s, 2H).

The other set of signals (*) is found at approximately 6.0-6.5 ppm and typically seen as a broad singlet and a triplet. For **3b**: δ 6.33 (bs, 1H), 6.30 (t, 2H); for **3c**: δ 6.43 (bs, 3H), 6.34 (bd, 5H); for **3d**: δ 6.35 (bm, 2H), 6.31 (bd, 2H); for **3e**: δ 6.96 (s, 3H), 6.34 (tt, 7H), 6.16 (bs, 3H).

The corresponding phenyl signals (#) were then found in between the pyrazole signals at 7.0-7.5 ppm, seen as either as a multiplet or as a broad doublet. For **3b**: δ 7.56 (d, 2H), 7.02 (d, 2H); for **3c**: δ 7.45 (bs, 5H), 7.32 (bs, 4H), 7.20 (t, 3H); for **3d**: δ 7.30 (bd, 3H), 7.27-7.25 (bm, 2H), 7.18 (bs, 2H); for **3e**: δ 7.78 (d, 4H), 7.74 (d, 3H), 7.65 (ts, 7H),

For the Pd^{IV} complexes (**3a-3b**), the signals reported in the aromatic region (5-9 ppm) were integrated to 13-14 proton atoms and the difference relies on whether or not the proton on the boron was found. For the remaining Pd^{IV} complexes (**3c-3e**), the signals reported in the same region are integrated to more than 14 proton atoms, suggesting that impurities are present in the reaction solution.

When we compare the pyrazole signals and the phenyl signals of the Pd^{IV} complexes (**3a-3e**) to the starting Pd^{II} intermediate (**1c**) and the corresponding diazonium salt (**2a-2e**), we notice a significant upfield shift in the signals for the phenyl protons (#) but little to no shift for the pyrazole signals (*) (Figure 3.5). This upfield shift can be caused by two possible factors: the orientation of the Pd^{IV} complex about the magnetic field or the electronegativity of Pd^{IV} complex.[11] Currently, we do not know which of the two factors is responsible for the upfield shift of the phenyl protons.


Oxidant (2a)
#
acetone-d6
Pd^IV complex (3a)
free tmeda
acetone-d6
%
*
#
Oxidant (2b)
•
acetone-d6
Pd^IV complex (3b)
acetone-d6
free tmeda
%
H2O
Oxidant (2c)
acetone-d6
f1 (ppm)

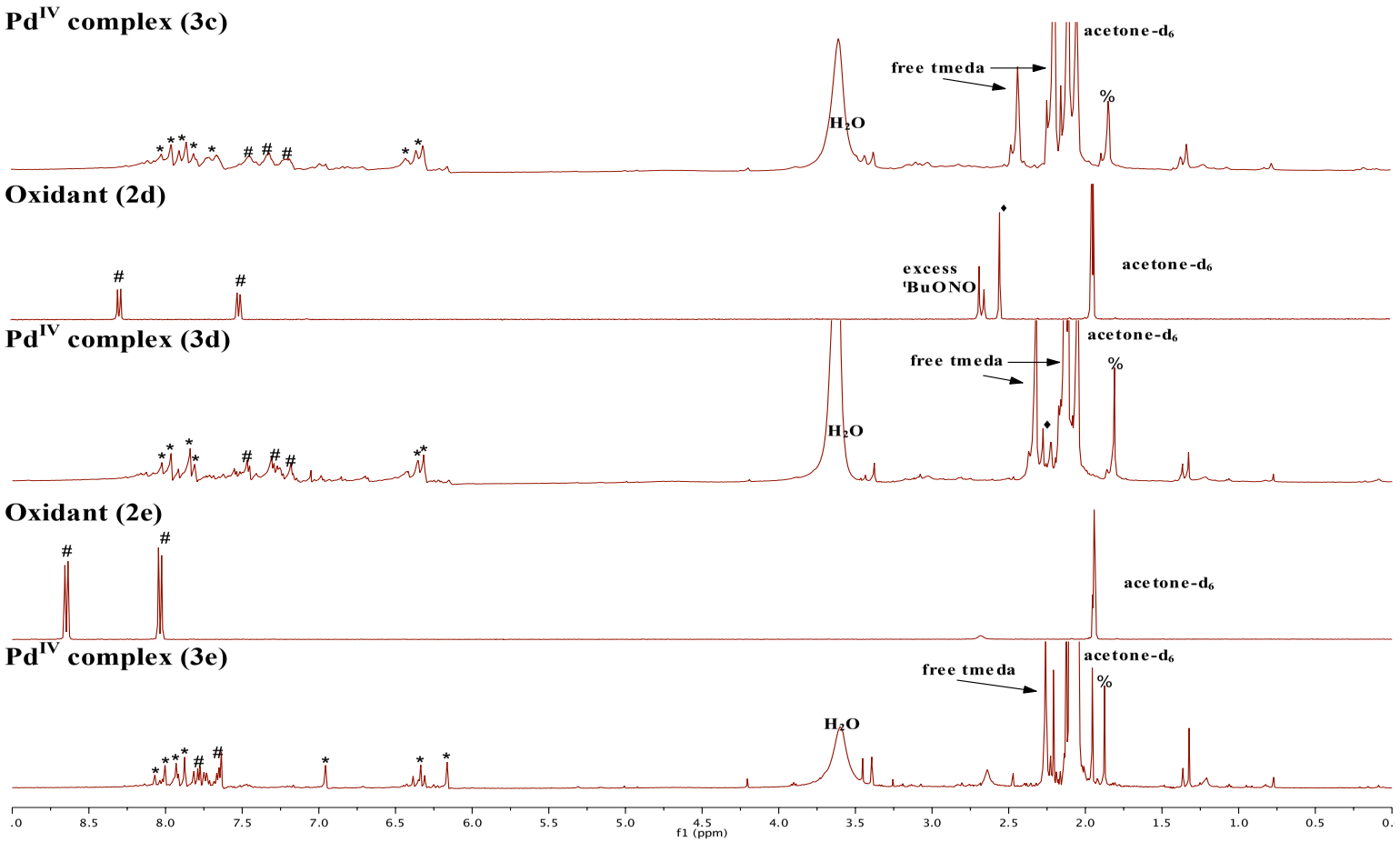


Figure 3.5: ^{1}H NMR of Diazonium Salts (**2a-2e**) and Palladium(IV) complexes (**3a-3e**)
(*) – Tp signals (#) –Aryl signals (%) –Pd-CH_3 signals (●) –Ar-OCH_3 signals (♦) –Ar-CH_3 signals
For **2a-2e**: 400 MHz, acetone-d_6, 25°C
For **3a-3e**: in situ NMR monitoring, 500 MHz, acetone-d_6, -40°C

The second region we focused on was the alkyl region (0-3 ppm), specifically looking for a shift in the methyl signals (%) on the Pd^{IV} complex. This region is difficult to elucidate due to the excess tmeda or other impurities present in the sample. However, after examining the region at approximately 1.0-2.0 ppm, one singlet is seen at approximately 1.8 ppm. For **3b**: δ 1.82 (s, 6H); for **3c**: δ 1.84 (s, 6H), 1.35 (ds, 6H); for **3d**: δ 1.81 (s, 6H), 1.35 (ds, 6H); for **3e**: δ 1.88 (s, 6H).

When comparing the methyl signals in the Pd^{II} intermediate (**1c**) and the final Pd^{IV} complexes (**3a-3e**), we notice a significant shift downfield in the methyl signals. This suggests that the methyl signals become more electron rich in the Pd^{IV} complex. However, the methyl groups may not be electron rich as the methyl signals in the Pd^{II} starting material (**1b**) and the Pd^{II} intermediate (**1c**) are seen at -0.35 ppm, which is uncharacteristic for typical methyl signals.

For the Pd^{IV} complexes with substituents that can be seen by ^1H NMR spectral analysis, we also used a shift in those signals to characterize the final Pd^{IV} complex (Figure 3.5). In Pd^{IV} complex with the *p*-methoxy phenyl ring (**3b**), the corresponding methoxy peak (●) was seen as a singlet at 3.83 ppm. In the Pd^{IV} complex with the *p*-methyl phenyl ring (**3d**), the corresponding methyl peak (s) was seen as a doublet at 2.26 ppm. Both signals are shifted upfield from the starting diazonium salts (**2b** and **2d**), (Figure 3.5) which is consistent with the upfield shift of the phenyl signals in the corresponding Pd^{IV} complex (**3b**, **3d**).

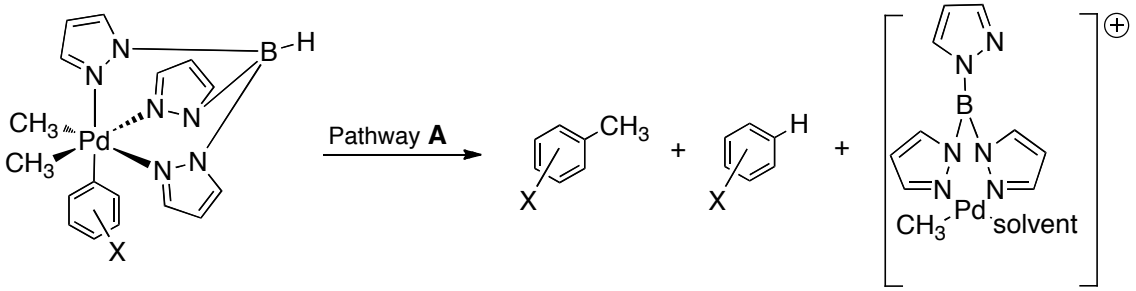
When we examine the crude spectral data for the Pd^{IV} complexes (**3c-3e**), we observe the presence of impurities signals in the aromatic and alkyl regions, which increase the integration total in the spectral data. These impurities may arrive from three possible sources: (i) reductive

elimination of the Pd^{IV} complexes in solution; (ii) oxidation of the KTp ligand in the solution; or (iii) undesired side reactions of the oxidant.

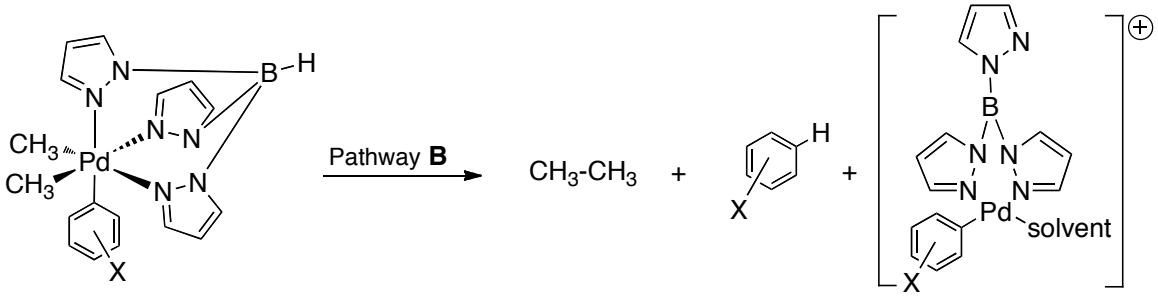
3.8: Possible Impurity Sources in ^{1}H NMR Spectral Data

3.8.1: Reductive Elimination of the Palladium(IV) complexes

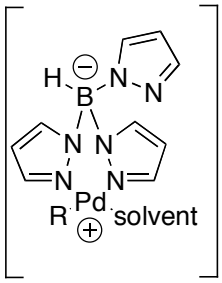
In our solution, two reductive elimination pathways are possible. In pathway **A**, (Scheme 3.14) the Pd^{IV} complex would release a toluene derivative while in pathway **B**, (Scheme 3.15) the Pd^{IV} complex would release ethane. Both pathways would also release a new Pd^{II} complex and a phenyl side product (from the excess oxidant) via a Pd^{II}-borohydride intermediate (Figure 3.6).



Scheme 3.14: Reductive elimination pathway **A** from the Palladium(IV) complex



Scheme 3.15: Reductive elimination pathway **B** from the Palladium(IV) complex



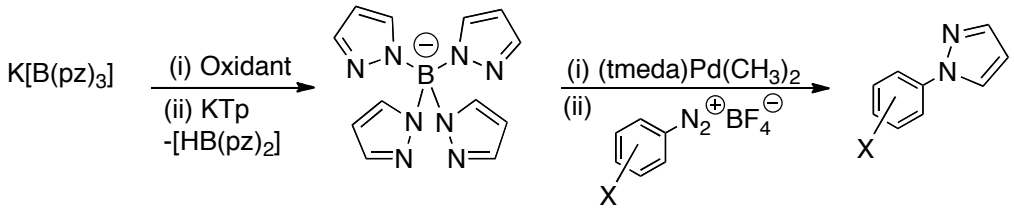
R = -CH_3 or Ar

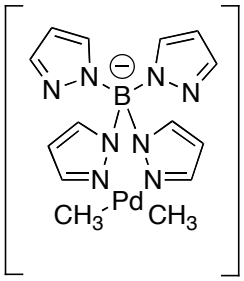
Figure 3.6: Palladium(II)-borohydride intermediate

Either pathway would yield side products that could be detected in the aromatic region of the ^{1}H NMR spectral data.

3.8.2: Oxidation of the KTp Ligand in Solution

In 2011, Sanford and co-workers report the generation of tetrapyrazolylborate anion in the presence of the free KTp ligand and a strong oxidant in their reaction solution.[12] If the tetrapyrazolylborate ligand were present in our reaction solution, it would generate a phenyl pyrazole derivative and a new Pd^{II} complex via a tetrapyrazolylborate-Pd^{II} intermediate (Scheme 3.16).





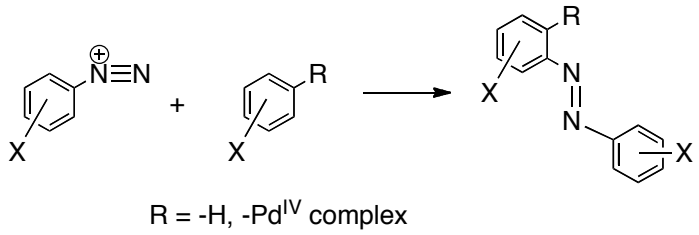
via proposed intermediate

Scheme 3.16: Ligand oxidation and subsequent reaction pathway

However, due to the lack of a strong oxidant, the unbound KTp in our solution and steric effects of the tetrapyrazolylborate-Pd^{II} intermediate, the resulting ligand will be unreactive towards the Pd^{II}-center and the ligand oxidation followed by the subsequent reaction pathway (Scheme 3.16) is unlikely to occur in our reaction solution.

3.8.3: Undesired Side Reactions of the Diazonium Salt Oxidants

In our reaction solution prior to oxidation, it is possible for the diazonium salt oxidant to react with another species present in the solution to yield an undesirable side product. A possible side reaction would be an azo coupling reaction with an electrophilic aromatic center (Scheme 3.17). As mentioned previously in this chapter (Section 3.6, page 71), this side reaction could be responsible for the highly colored Pd^{IV} complexes collected at -40°C.



Scheme 3.17: Possible Azo Coupling reaction to yield undesired side products

3.9: Isolation of Palladium(IV) complexes as Solids

After establishing the protocol for generating the Pd^{IV} complexes in solution at -40°C, we focused on isolating the Pd^{IV} complexes as stable solids at 25°C. We explored two possible experimental methods for isolating the complexes based on reported procedures for similar Pd^{IV} complexes. The first method, reported by Canty, involves the addition of water and ethanol to the reaction solution to precipitate the Pd^{IV} complex (**3a**) as a yellow/white solid.[4] The second method, reported by Sanford, involves the use of non-polar solvents (such as ether, pentane or hexane) to precipitate the Pd^{IV} complexes as solids.[13]

3.9.1: Method One

Using the isolation procedure reported by Canty[4], we focused on isolating the Pd^{IV} complex (**3a**) featuring the unsubstituted phenyl ring. After generating the complex at 25°C by the protocol established for generating the complex (**3a**) at -40°C (on page 65), water (4 mL) was added to the orange reaction solution to dissolve any salt impurities. The acetone solvent was then removed by vacuum to collect a yellow oil. Ethanol (4 mL) was then added to the oil to create an orange solution and the solution filtered through Celite (to remove any brown solid that forms during the acetone removal) to collect an orange solution. Water (4 mL) was added again to the orange solution to precipitate a yellow solid.

Removal of the water by vacuum resulted in a yellow-brown solid, which was dissolved in $CDCl_3$ and taken for ^1H NMR spectral analysis at 25°C. However, the NMR spectral data collected was mostly solvent signals and no Pd^{IV} complex (**3a**) was seen.

Despite variations in to the work-up procedure, the Pd^{IV} complex (**3a**) could not be isolated as a solid. The most challenge aspect of this method was the removal of solvent by vacuum, as the yellow solid typically decomposed under vacuum to give a black solid. Without solvent removal or drying the solid by vacuum, large solvent signals remained in the ^1H NMR spectral data, which mask any indication of the desired Pd^{IV} complex (**3a**) in the NMR sample.

When we focused on using the Pd^{IV} complex (**3b**) generated in solution at 25°C by the protocol established at -40°C, the isolation procedure proved to be unsuccessful as well. The addition of water had no effect on the purple reaction solution and, therefore, the subsequent solvent removal could not be done, preventing us from isolating the desired Pd^{IV} complex.

When examining the isolation procedure, Canty uses water and ethanol to dissolve and remove any excess oxidant (iodomethane) or side products (KI or tmeda) present in his reaction mixture. For our reaction, water and ethanol may not be the best choice of solvents to remove any excess oxidant (diazonium salt) or side products (KBF_4 or tmeda) as our impurities may not be soluble in water or ethanol. Therefore, using this work-up to precipitate the Pd^{IV} complexes would not be the best choice and we need to use a work-up that can effectively remove our excess oxidant and side products.

3.9.2: Method Two

Using this isolation procedure reported by Sanford[13], we focused on isolating the Pd^{IV} complex (**3a**), which was generated in solution at 25°C by the same method described above for generating the complex **3a** at -40°C (on page 65). After stirring, the resulting orange reaction

solution was concentrated under reduced pressure to collect an orange liquid. This liquid was then cooled to 0°C, filtered through Celite to remove any insoluble salts and concentrated to collect an orange oil. The oil was then washed with pentane (10 mL) to remove any excess oxidant. The oil was then triturated with ether at 0°C to collect an orange powder.

The powder was dissolved in $CDCl_3$ and taken for ^1H NMR spectral analysis at 25°C. Unfortunately, the spectral data contained multiple impurity signals, especially in the alkyl region (0-3 ppm), making it difficult to interpret the spectral data.

When we focused on the isolation of Pd^{IV} complex (**3b**), which was generated in solution by the method described above at 25°C, we discovered that washing the oil with hexanes removed more organic impurities and a purple/dark powder was collected after trituration with ether at 0°C. However, when the powder was dissolved in $CDCl_3$ and taken for ^1H NMR spectral analysis, the spectral data collected still contained multiple impurity signals in the alkyl region making it difficult to interpret the spectral data.

Any attempts to change the work-up did not remove any excess impurity signals in the spectral data for **3a** or for **3b**.

When examining the isolation procedure reported by Sanford, which is considered to be more of a traditional organometallic-type work-up and used in the oxidation of Pd^{II} complexes with iodonium salts, the concentration and Celite filtration are used to remove any insoluble salt impurities after ligand exchange. The non-polar solvents are used to remove any excess oxidants

(such as phenyl iodonium salts) and the trituration in ether is used to precipitate the Pd^{IV} complex and dissolve any organic impurities (such as phenyl iodide or tmeda).

For our system, using this work-up seems like the best choice to date, as the Celite filtration removes the insoluble KBF_4 salt generated after the ligand exchange and the oxidation. The non-polar solvents dissolve the excess diazonium oxidant and any organic products from the oxidation. We discovered that the choice of non-polar solvent used during this step is dependent on the oxidant used, suggesting that the choice of non-polar solvent depends on the nature of the oxidant. The trituration of ether did precipitate the desired Pd^{IV} complex, however, this step did not remove the tmeda or other organic impurities. It is possible that other organic solvents may be needed to remove the excess tmeda present in our reaction material.

Unfortunately, to date, we are still unable to isolate the Pd^{IV} complexes (**3a-3e**) generated in solution at -40°C as stable solids at 25°C or collect any ^1H NMR spectral data without large impurity signals. Because we are unable to collect the Pd^{IV} complexes (**3a-3e**) as solids, no crystal structure analysis has been collected as well.

There are two possible oxidation pathways involving diazonium salts: (i) a single electron oxidation or (ii) a two electron oxidation. The single electron oxidation has previously been reported for the Sandmeyer reaction where the diazonium salt loses a single electron to become a diazonium radical.[9] In the presence of a diazonium radical, the Cu^I catalyst is then oxidized to generate a diazonium-Cu^{II} intermediate and reduction yields a functionalized aryl product. The two electron oxidation has been previously reported by Matsuda for other Pd^0-Pd^{II} reactions

where the diazonium salt binds to the Pd^0 catalyst to generate a catonic Pd^{II} intermediate.[5] To date, we do not know which mechanistic pathway occurs in our reaction sequence.

3.10: Conclusion and Future Work

To date, we have been able to successfully generate a variety of Pd^{IV} complexes (**3a-3e**) containing an aryl-Pd^{IV} bond installed upon the oxidation of a Pd^{II} starting material with a variety of diazonium salts. We have provided spectral evidence for the generation of various Pd^{IV} complexes in solution at low temperature (Figure 3.4, page 71). In the future, we hope to establish a procedure that would allow for the isolation of the Pd^{IV} complexes as stable solids at 25°C. We also plan to explore the oxidant scope further to include *ortho*- and *meta*-substituted diazonium oxidants. If the generation of a Pd^{IV} complex containing an *ortho*-substituted aryl group proves to be successful, the new Pd^{IV} complex could then be used to mediate intramolecular C(sp^3)-H activation in the Pd^{IV} complex.

3.11: Chapter Three Experimental

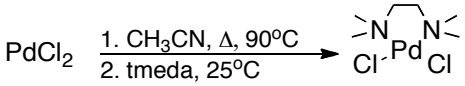
General Procedures

NMR spectra at 25°C were obtained on a Bruker DRX-400 (400 MHz ^1H and ^{19}F) and NMR spectra at -40°C were obtained on a Bruker DRX-500 (500 MHz for ^1H) in acetone-d_6. ^1H NMR chemical shifts are reported in parts per million (ppm) with the residual solvent peak (2.05 ppm) used as an internal reference. ^{19}F NMR spectra were referenced using the residual solvent peak in the ^1H NMR spectrum. ^{13}C NMR spectra were obtained on an Avance AV-III 500 and the chemical shifts are reported in parts per million (ppm) with the residual solvent peak (206.26 ppm) used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d),

triplet (t), multiplet (m), doublet of singlet (ds), doublet of multiplet (dm), triplet of singlet (ts), triplet of triplet (tt) and broad band resonance (br). Melting points are uncorrected and were taken in open capillary tubes.

Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone; acetone was purified by stirring with dry potassium carbonate (K_2CO_3) and kept over K_2CO_3; all other solvents were used as received. NMR solvents were obtained from Cambridge Isotopes and stored at 25°C. Unless otherwise specified, all reactions were carried out under an atmosphere of dry argon in oven-dried (at least 6 h at 140°C) glassware. Unless otherwise specified, all materials were used as received from commercial suppliers.

Potassium tris(pyrazol-1-yl)borate or K[$(pz)_3$BH] was purchased from TCI America and analyzed by ^{1}H and ^{13}C NMR in acetone-d_6. ^{1}H NMR (acetone-d_6): δ 7.57 (m, 2H), 7.49 (bs, 1H), 7.35 (m, 2H), 7.20 (bs, 1H), 6.27 (t, J = 4 Hz, "1H"), 6.08 (bs, 1H), 5.99 (t, J = 4 Hz, 2H). ^{13}C NMR (acetone-d_6): δ 140.37 (q, J = 15 Hz), 139.67 (s), 135.20 (q, J = 15 Hz), 134.84 (s), 105.06 (s), 104.01 (q, J = 5 Hz), 103.35 (s). *Note*: The signal observed at δ 6.27 ppm in the ^{1}H spectrum corresponds to the hydride on borate, which does not integrate to one.

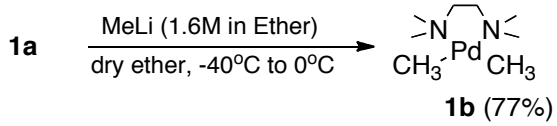


1a (97%)

Synthesis of (tmeda)Pd(Cl)$_2$ (**1a**)[6]: Under the atmosphere of Argon, palladium(II) dichloride ($PdCl_2$; 1.7733 g, 10.001 mmol, 1.0 eq) was dissolved in CH_3CN (47 mL) at 25°C and the resulting orange solution was heated to 90°C and refluxed overnight. The reaction suspension

was then cooled to 25°C while stirring and N,N,N',N'-tetramethylethylenediamine (tmeda; 2.25 mL, 15.002 mmol, 1.5 eq) was then added to the reaction suspension and the resulting yellow suspension was stirred for 20 min at 25°C. The yellow solution was then vacuum filtered over a fritted funnel and dried by vacuum to yield **1a** as a yellow solid. (2.857 g, 97%)

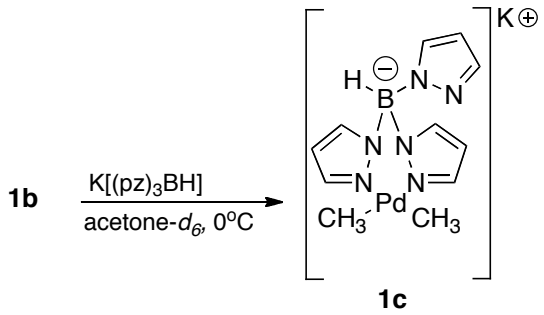
Analytical data for complex 1a: mp = 228 °C (decomposition).



1b (77%)

Synthesis of (tmeda)Pd(CH_3)$_2$ (**1b**)[6]: Under the atmosphere of Argon, (tmeda)$PdCl_2$ **1a** (1.6142 g, 5.499 mmol, 1.0 eq) was dissolved in dry Et_2O (20 mL) at 25°C and the resulting solution was cooled to -40°C. The methyllithium solution (MeLi, 1.6 M in Et_2O; 7.2 mL, 11.548 mmol, 2.1 eq) was then added dropwise to the reaction mixture at -40°C. After the addition, the reaction mixture was warmed to 0°C and stirred for 1 h. The reaction mixture was then quenched with ice water (20 mL) to remove excess MeLi. The organic layer was then extracted with Et_2O, washed with brine, dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield **1b** as yellow crystals. (1.0741 g, 77%)

Analytical data for complex 1b: mp = 122-123 °C (decomposition). ^{1}H NMR (acetone-d_6): δ 2.57 (s, 2H), 2.40 (s, 6H), -0.35 (s, 3H). ^{13}C NMR (acetone-d_6): δ60.19 (s), 50.95 (s), 48.42 (s).

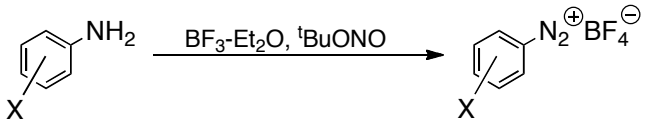


1c

Synthesis of [{(pz)$_2$(pz)$'$BH}Pd(CH$_3$)$_2^-$][K$^+$] (**1c**)[4]: Under the atmosphere of Argon, the (tmeda)Pd(CH$_3$)$_2$ **1b** (0.0127 g, 0.0503 mmol, 1.0 eq) and the potassium tris(pyrazol-1-yl)borate (K{(pz)$_3$BH} or KTp; 0.0127 g, 0.0504 mmol, 1.0 eq) were dissolved in acetone-d_6 (1.0 mL), cooled to 0°C and stirred for 1 h. After mixing, an aliquot of the reaction mixture (0.4 mL) was removed and injected into a pre-cooled NMR tube (0°C). The resulting solution was taken for low temperature ^{1}H NMR monitoring of the palladium(II) complex (**1c**).

The palladium(II) complex (**1c**) was too unstable to obtain ^{13}C NMR spectral data.

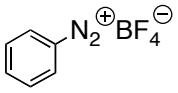
Analytical data for complex 1c: ^{1}H NMR (acetone-d_6): δ 7.83 (m, 1H), 7.74-7.73 (m, 1H) 7.58 (m, 2H), 7.50 (bs, 1H), 7.35 (bs, 1H), 7.16 (bs, 1H), 6.25 (t, J = 4 Hz, "1H"), 6.09 (bs, 1H), 5.99 (m, 2H), 2.56 (bs, 4H), 2.38 (bs, 12H), 2.29 (bs, 2H), 2.13 (bs, 6H), -0.36 (bs, 6H). *Note*: Starting palladium(II) complex (**1b**), unbound KTp and free tmeda were observed in spectral data. The signal observed at δ 6.25 ppm in the ^{1}H spectrum corresponds to the hydride on borate, which does not integrate to one. Please see the reported NMR signals for palladium(II) complex **1b**, KTp and tmeda.



2a: X = -H (90%)
2b: X = -*p*-CH_3O (94%)
2c: X = -*p*-F (100%)
2d: X = -*p*-CH_3 (92%)

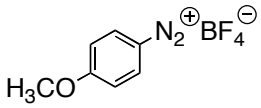
General synthesis of $(XC_6H_4)(N_2^+)(BF_4^-)$ (**2a-f**)[7-8]: Under the atmosphere of Argon, the boron trifluoride diethyl etherate solution (BF_3-Et_2O; 1.5 eq) was diluted in the necessary dry solvent (Et_2O or THF, 3-10 mL) at 25°C and then cooled (-15°C - 0°C). Aniline was then added (2.0 mmol - 5.0 mmol, 1.0 eq) at -15°C and the resulting solution was stirred for 1 h. In a separate flask, tert-butyl nitrite (^{t}BuONO; 1.2 eq) was dissolved in dry Et_2O or THF (1-5 mL) at 25°C and stirred for 10 min. The resulting ^{t}BuONO solution was then slowly added dropwise to the aniline/BF_3-Et_2O reaction mixture at (-15°C or 0°C) over 10 min. The resulting reaction mixture was stirred at (-15°C or 0°C) for 10-15 min, then warmed (-5°C or 25°C) and stirred for 15-20 min. Minimal amount of a non-polar solvent was added (pentane or Et_2O) to the solution to precipitate the product as a solid. The resulting suspension was filtered by vacuum filtration and dried under vacuum to yield the diazonium salt (**2a-2f**).

Analytical data:



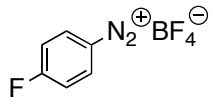
2a

$(C_6H_5)(N_2^+)(BF_4^-)$ (**2a**)[7]: Reaction was conducted in dry Et_2O at -15°C to -5°C range. Pentane was added in the work-up. Red solid (0.7860 g, 82%). mp = 137°C (decomposition). ^{1}H NMR (acetone-d_6): δ 7.65-7.56 (m, 3H), 7.48 (d, J = 8 Hz, 2H). ^{13}C NMR (acetone-d_6): δ131.34 (s), 130.93 (s), 125.49 (s).



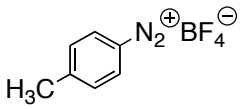
2b

(p-$CH_3OC_6H_4$)(N_2^+)(BF_4^-) (**2b**)[8]: p-Anisidine was purified by sublimation prior to reaction. Reaction was conducted in dry THF at 0°C to 25°C range. Et_2O was added in the work-up. White solid (0.2091 g, 94%). mp = 140-142°C (decomposition). ^{1}H NMR (acetone-d_6): δ 8.80-8.77 (m, 2H), 7.57-7.54 (m, 2H), 4.18 (s, 3H). ^{13}C NMR (acetone-d_6): δ 170.61 (s), 136.95 (s), 118.32 (s), 103.59 (s), 57.95 (s).



2c

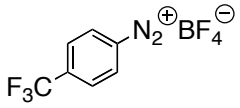
(p-FC_6H_4)(N_2^+)(BF_4^-) (**2c**)[8]: Reaction was conducted in dry THF at 0°C to 25°C range. Et_2O was added in the work-up. White solid (0.4371 g, 99%). mp = 154-155°C (decomposition). ^{1}H NMR (acetone-d_6): δ 9.00 (dd, J = 4 Hz, 8 Hz, 2H), 7.90 (t, J = 8 Hz, 2H). ^{19}F {^{1}H} NMR (acetone-d_6): δ -86.72 (s, 1F), -151.07 (s, 4F). ^{13}C NMR (acetone-d_6): δ 170.53 (d, J = 1070 Hz), 138.13 (d, J = 50 Hz), 128.73 (d, J = 100 Hz).



2d

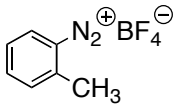
(p-$CH_3C_6H_4$)(N_2^+)(BF_4^-) (**2d**)[8]: p-Toluidine was purified by sublimation prior to reaction. Reaction was conducted in dry THF at 0°C to 25°C range. Et_2O was added in the work-up. White solid (0.3822 g, 92%). mp = 105-106°C (decomposition). ^{1}H NMR (acetone-d_6): δ 8.75 (d,

J = 8 Hz, 2H), 7.92 (d, J = 8 Hz, 2H), 2.69 (s, 3H). ^{13}C NMR (acetone-d_6): δ 156.04 (s), 133.29 (d, J = 265 Hz), 130.46 (s), 115.64 (s), 22.81 (s).



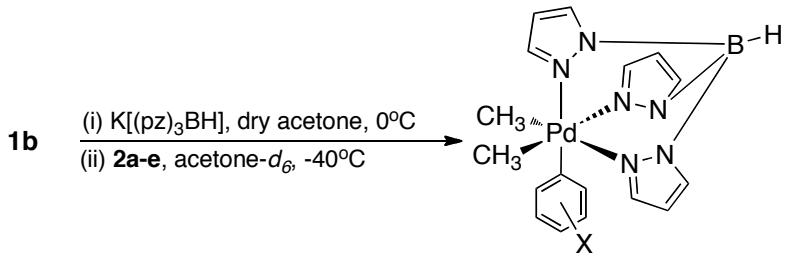
2e

(p-$CF_3C_6H_4$)(N_2^+)(BF_4^-) (**2e**)[8]: Reaction was conducted in dry THF at 0°C to 25°C range. Et_2O was added in the work-up. Light yellow solid (0.4247 g, 81%) mp = 80-82°C (evaporation). ^{1}H NMR (acetone-d_6): δ 9.13 (d, J = 8 Hz, 2H), 8.48 (d, J = 8 Hz, 2H). ^{19}F {^{1}H} NMR (acetone-d_6): δ -64.64 (s, 3F), -150.80 (s, 2F). ^{13}C NMR (acetone-d_6): δ 141.02 (s), 140.74 (s), 134.93 (s), 129.57 (q, J = 15 Hz), 124.36 (s), 122.19 (s), 121.51 (s).



2f

(o-$CH_3C_6H_4$)(N_2^+)(BF_4^-) (**2f**)[8]: Reaction was conducted in dry THF at 0°C to 25°C range. Et_2O was added in the work-up. White solid (0.5053 g, 100%). mp = 90-91°C (decomposition). Solid decomposed prior to ^{1}H and ^{13}C NMR spectral data collection.

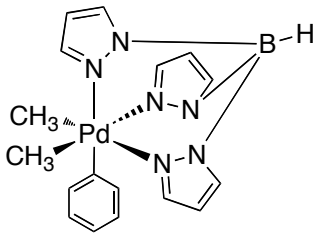


3a: X = -H
3b: X = -p-CH_3O
3c: X = -p-F
3d: X = -p-CH_3
3e: X = -p-CF_3

General procedure for the in situ formation of [{(pz)$_3$BH}Pd(CH$_3$)$_2$(XC$_6$H$_4$) (**3a-e**)[4]: Under the atmosphere of Argon, (tmeda)Pd(CH$_3$)$_2$ **1b** (0.05 mmol, 1.0 eq) and KTp (0.05 mmol, 1.0 eq) were dissolved in acetone-d_6 (0.6 mL), the solution was cooled to 0°C and stirred for 1 h. In a separate flask, diazonium salt **2a-e** (1.0-1.1 eq) was dissolved in acetone-d_6 (0.5 mL) at 25°C and stirred for 10-30 min. The solution of the palladium complex was then cooled to -40°C and the diazonium salt solution was added dropwise. The resulting solution was stirred for 1.2-2.0 h at -40°C. The liquids were removed via filter-tipped cannulation (set prior to addition of reagents) to collect the desired solid. The solid was dissolved in pre-cooled acetone-d_6 (0.3 mL) and transferred into a pre-cooled NMR tube at -40°C. The resulting solution was diluted with pre-cooled acetone-d_6 (0.1-0.2 mL), and taken for low temperature (-40°C) NMR analysis, detecting the Pd^{IV} product (**3a**-**3e**).

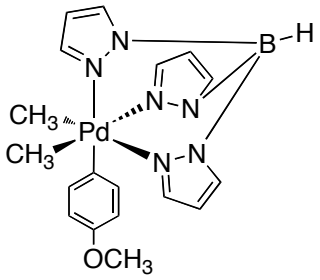
In general, excess tmeda and solvents were observed in the alkyl range (0-3 ppm) of the ^{1}H NMR spectra. For **3c**-**3e**, signals due to impurities were also detected in the aryl region as well limiting complete analysis of these complexes.

Analytical Data:



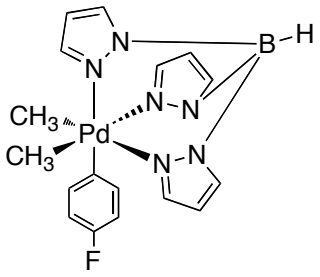
3a

[{(pz)$_3$BH}Pd(CH$_3$)$_2$(C$_6$H$_5$) (**3a**): Collected a yellow solution. ^{1}H NMR (-40°C, acetone-d_6): δ 7.43 (bs, 2H), 7.35 (m, 1H), 7.30 (m, 1H), 7.29 (bs, 2H), 7.04 (t, J = 5 Hz, 2H), 6.87 (bs, 1H), 6.79 (t, J = 10 Hz, 2H), 6.46 (d, J = 5 Hz, 1H), 5.96 (bs, 2H), 1.56 (s, 6H).



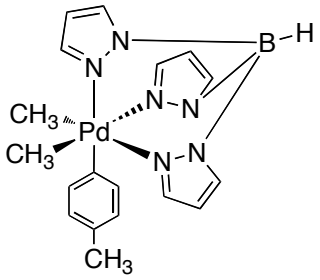
3b

[{(pz)$_3$BH}Pd(CH$_3$)$_2$(*p*-CH$_3$OC$_6$H$_4$) (**3b**): Collected a dark red/orange solution. ^{1}H NMR (-40°C, acetone-d_6): δ 7.98 (bs, 1H), 7.92 (bs, 2H), 7.88 (bs, 1H), 7.83 (bs, 2H), 7.76 (ds, J = 5 Hz, 2H), 7.56 (d, J = 10 Hz, 2H), 7.02 (d, J = 10 Hz, 2H), 6.33 (bs, 1H), 6.30 (t, J = 5 Hz, 2H), 3.83 (s, 3H), 1.82 (s, 6H).



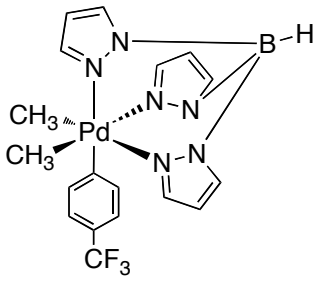
3c

[{(pz)$_3$BH}Pd(CH$_3$)$_2$(*p*-FC$_6$H$_4$) (**3c**): Collected a dark red/orange solution. ^{1}H NMR (-40°C, acetone-d_6): δ 8.02 (bs, 2H), 7.96 (bs, 3H), 7.88 (bd, *J* = 20 Hz, 5H), 7.81 (bs, 2H), 7.73-7.65 (dm, *J* = 25 Hz, 6H), 7.45 (bs, 5H), 7.32 (bs, 4H), 7.20 (t, *J* = 10 Hz, 3H), 6.43 (bs, 3H), 6.34 (bd, *J* = 25 Hz, 5H), 1.84 (s, 6H).



3d

[{(pz)$_3$BH}Pd(CH$_3$)$_2$(*p*-CH$_3$C$_6$H$_4$) (**3d**): Collected a dark orange solution. ^{1}H NMR (-40°C, acetone-d_6): δ 8.03 (bs, 2H), 7.97 (bs, 2H), 7.84 (bs, 3H), 7.81 (bs, 1H), 7.46 (bd, *J* = 10 Hz, 2H), 7.30 (bd, 3H), 7.27-7.25 (bm, 2H), 7.18 (bs, 2H), 6.35 (bm, 2H) 6.31 (bd, *J* = 5 Hz, 2H), 2.26 (d, *J* = 25 Hz, 6H), 1.81 (s, 6H).



3e

[{$(pz)_3BH$}$Pd(CH_3)_2$(p-$CF_3C_6H_4$) (**3e**): Collected a dark orange/yellow solution. ^{1}H NMR (-40°C, acetone-d_6): δ 8.07 (bs, 2H), 8.00 (bs, 3H), 7.93 (bt, J = 10 Hz, 6H), 7.88 (s, 4H), 7.82 (s, 2H), 7.78 (d, J = 10 Hz, 4H), 7.74 (d, J = 10 Hz, 3H), 7.65 (ts, J = 10 Hz, 7H), 6.96 (s, 3H), 6.34 (tt, J = 20 Hz, 5 Hz, 7H), 6.16 (bs, 3H), 1.88 (s, 6H).

3.12: Chapter Three Bibliography

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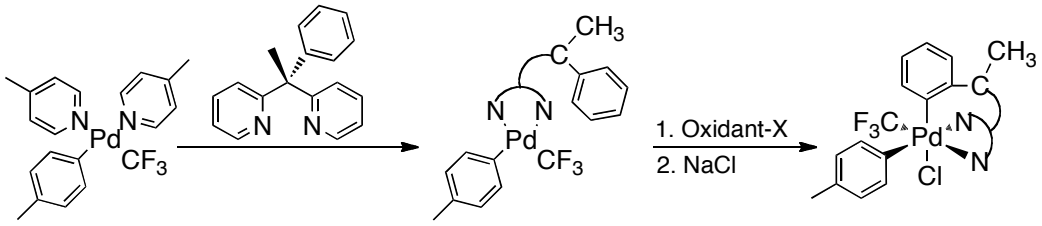
Chapter Four

Novel Annulation Reactions Utilizing Palladium(IV)-mediated C-H Activation in Organic Oxidants

4.1: Introduction

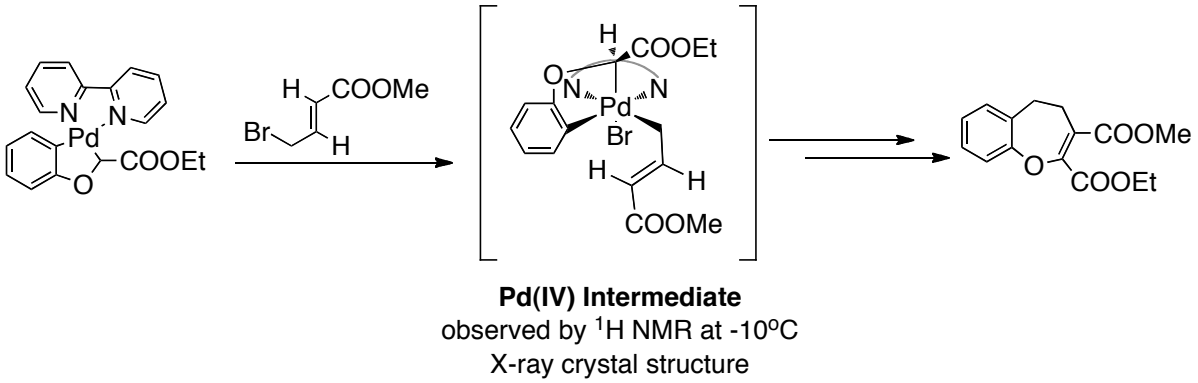
The goal of this project was to construct a novel Pd^{IV} complex, featuring multiple Pd-C(sp^2) and Pd-C(sp^3) bonds that could be used to mediate intramolecular C-H activation in an organic fragment bonded to the Pd^{IV} center. The subsequent reductive elimination pathway from this new Pd^{IV} complex would yield a complex heterocycle featuring multiple new C-C bonds. To date, only a few reports in literature provide a direct evidence for C-H activation being achieved at a Pd^{IV} center. In one report published by Sanford, they achieve intramolecular C-H activation on an unactivated C(sp^2)-H center in the Pd^{IV} complex in the presence of an inorganic oxidant[1] (Scheme 4.1).



Scheme 4.1: Previously reported Sanford results[1]

Unfortunately, no further reactions of the C-H activated ligand in these Pd^{IV} complexes were described.

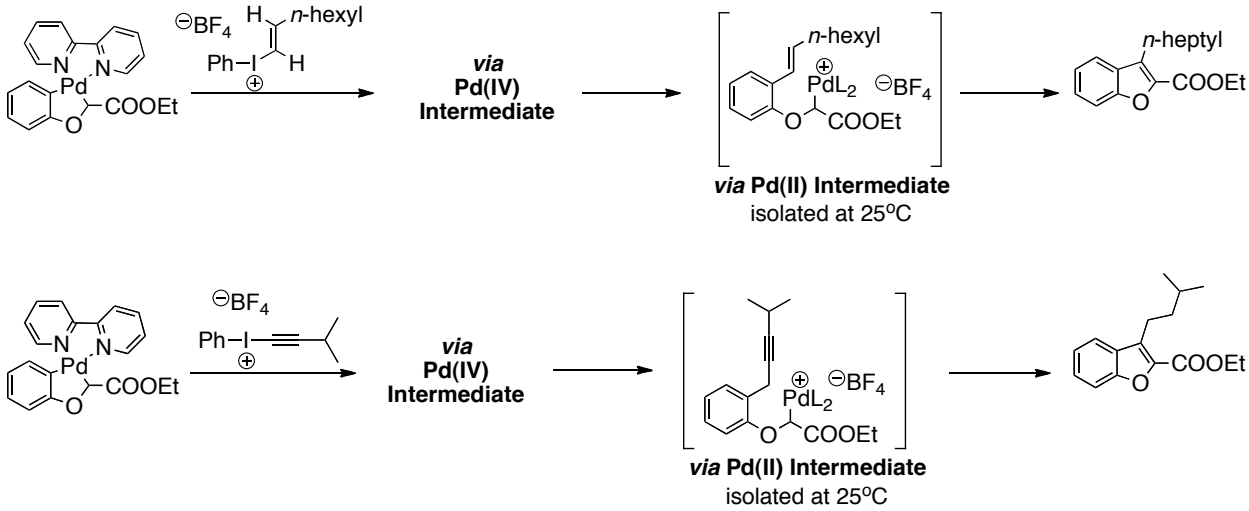
Inspiration for this project came from previous work reported by the Malinakova group on the synthesis of various Pd^{IV} complexes resulting from the oxidation of a Pd^{II}-cycle with either an allyl halide oxidant or an iodonium salt oxidant. In a report published in 2007, the Pd^{II}-cycle, which features unique Pd-C(sp^2) and Pd-C(sp^3) bonds, is oxidized in the presence of an allyl bromide to yield a new Pd^{IV} complex[2] (Scheme 4.2).



Scheme 4.2: Previously reported generation of Palladium(IV) complex by Malinakova[2]

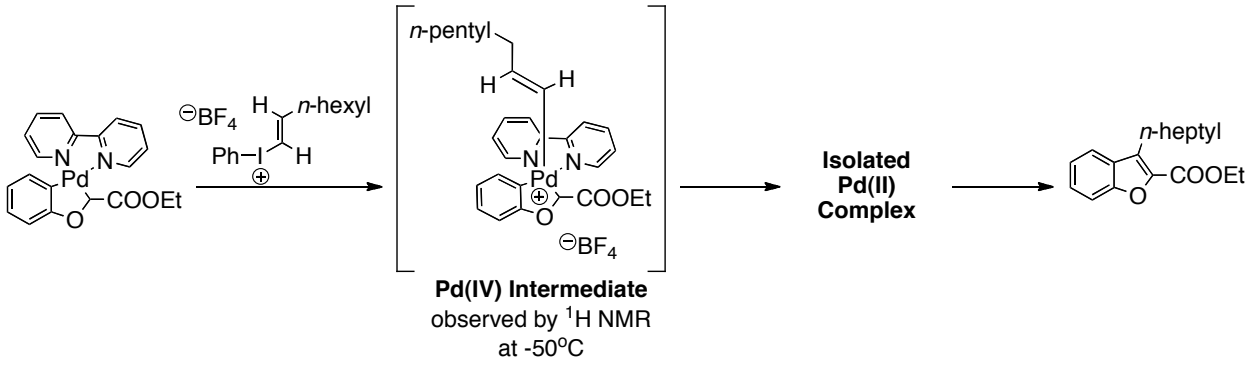
This complex was observed by ^{1}H NMR spectral analysis at -10°C and characterized by X-ray crystallography. The subsequent reductive elimination and intramolecular Heck reactions gave a substituted benzoxepine (Scheme 4.2).

In a report published in 2008, the same Pd^{II}-cycle was reacted in the presence of vinyl and alkynyl iodonium salts to synthesize new Pd^{II} complexes featuring either a new Pd-C(sp^2) or Pd-C(sp) bond installed via oxidation.[3] The subsequent intramolecular Heck reactions gave a substituted benzofuran (Scheme 4.3).



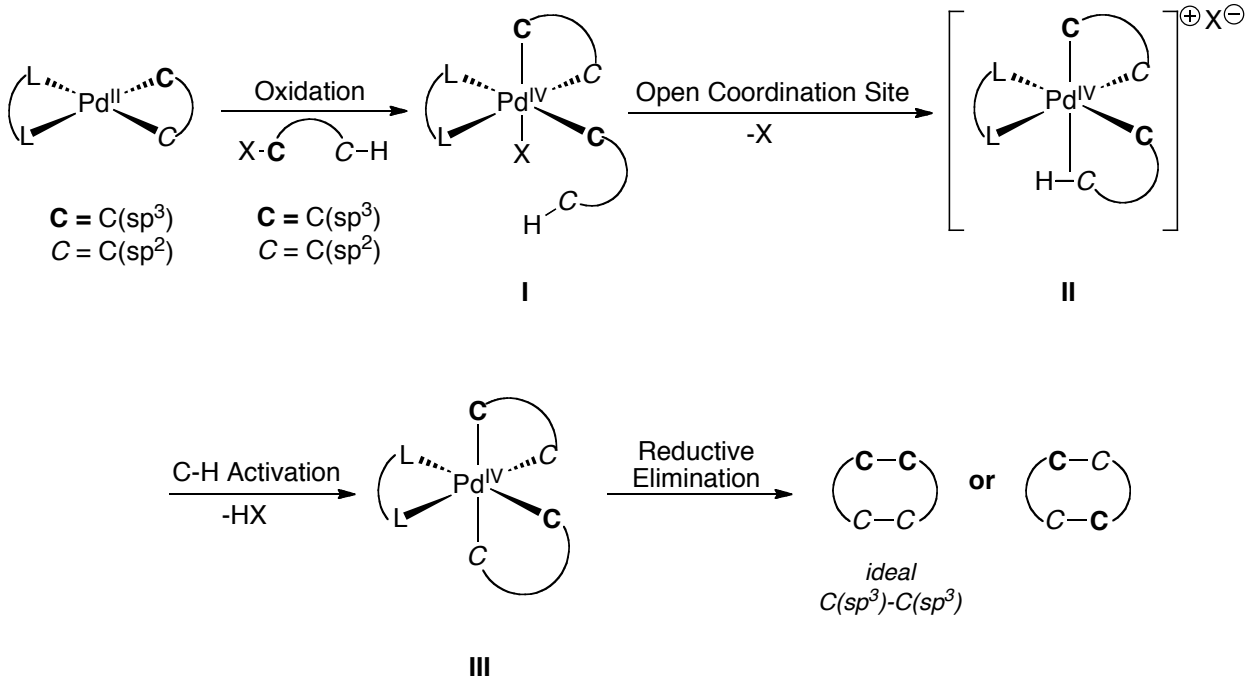
Scheme 4.3: Previously reported Pallada(II)cycle reactions by Malinakova[3]

The new insoluble Pd^{II} complexes arise from a Pd^{IV} intermediate generated by the oxidation of the stable Pd^{II}-cycle with the iodonium salts. For the case of the vinyl iodonium oxidant, the Pd^{IV} intermediate was observed by ^1H NMR spectral analysis at -50°C (Scheme 4.4).



Scheme 4.4: Previously reported generation of Palladium(IV) complex[3]

In contrast to the prior work, in which Pd^{IV} complexes underwent reductive elimination followed by a Heck reaction, our present project aimed to explore Pd^{IV}-mediated C-H activation followed by reductive elimination. We envisioned generating a new Pd^{IV} complex (**I**) from the Pd^{II}-cycle in the presence of an organic oxidant, 1-(bromomethyl)naphthalene, which features an unactivated $C(sp^2)$-H bond available for C-H activation. Then we would generate a new cationic Pd^{IV} intermediate (**II**) featuring an open a coordination site, by removal of the bromide ligand, allowing for the subsequent C-H activation at the unactivated $C(sp^2)$-H center. This would generate a new Pd^{IV} complex (**III**) that features multiple Pd-$C(sp^2)$ and Pd-$C(sp^3)$ bonds. Reductive elimination would yield a new organic heterocycle featuring two new C-C bonds, one of which might be a $C(sp^3)$-$C(sp^3)$ bond (Scheme 4.5).



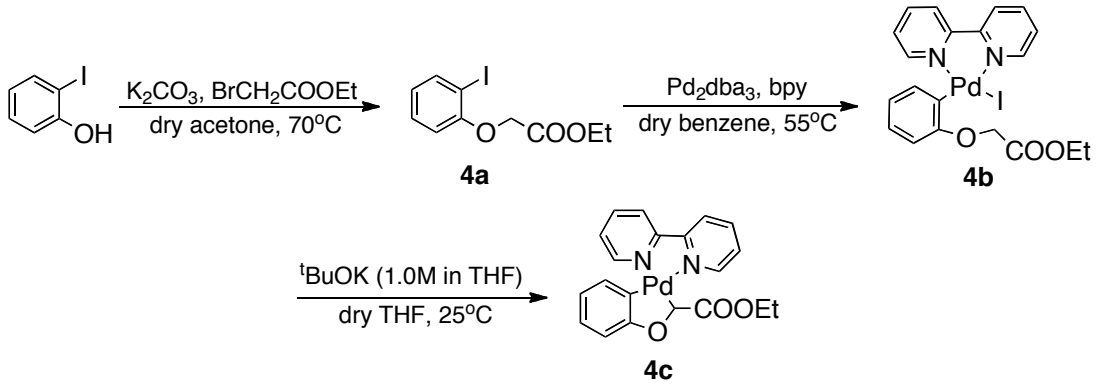
Scheme 4.5: Proposed intramolecular C-H activation pathway

To monitor the progress of the oxidation and intramolecular C-H activation, we will use low temperature in situ ^{1}H NMR monitoring experiments. To confirm the C-C coupling took place, the organic heterocycle will be collected and characterized by NMR spectral analysis.

4.2: Starting Material Synthesis

4.2.1: Pallada(II)cycle

The stable Pd^{II}-cycle was synthesized from an aryl iodide (**4a)** obtained as a clear oil from iodophenol in 96% yield. The aryl iodide (**4a**) was then reacted with Pd_2dba_3 and bpy to yield the Pd^{II} complex (**4b**) as a yellow powder in 74% yield. Complex **4b** was treated with a ^{t}BuOK solution in dry THF to synthesize the desired Pd^{II}-cycle (**4c**) as a neon yellow solid in 74% yield[2] (Scheme 4.6).

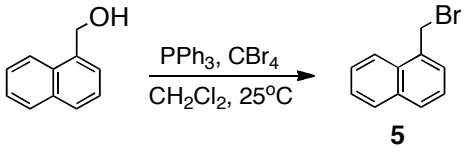


Scheme 4.6: Synthesis of Pallada(II)cycle **4c**

The aryl iodide (**4a**) and the Pd^{II} complexes (**4b, 4c**) were characterized by melting point and ^1H NMR spectral analysis. During the formation of the Pd^{II}-cycle (**4c**), it is important to carefully monitor the reaction progress by TLC as decomposition of **4c** will readily occur at 25°C in solution.

4.2.2: 1-(bromomethyl)naphthalene

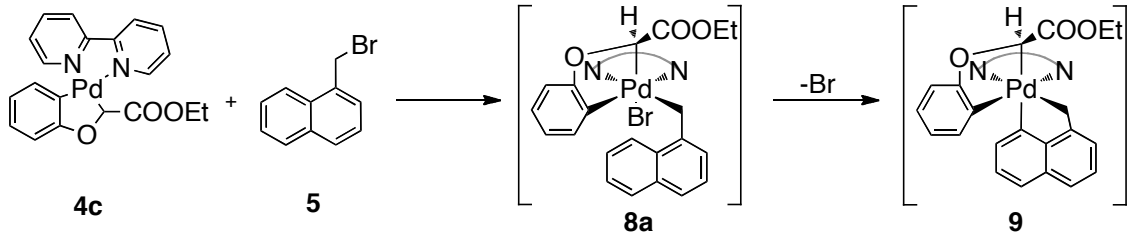
The oxidant (**5**) was synthesized from 1-naphthalene-methanol by bromination with PPh_3 and CBr_4 to collect 1-(bromomethyl)naphthalene (**5**) as a white solid in 93% yield[4] (Scheme 4.7). The oxidant (**5**) was characterized by melting point and ^1H NMR spectral analysis.



Scheme 4.7: Synthesis of 1-(bromomethyl)naphthalene **5**

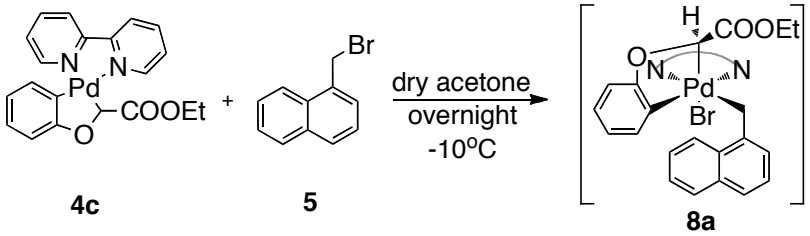
4.3: Initial Oxidative Addition and Bromide Removal Reactions

Initially, we focused on the generation of the Pd^{IV} complex (**8a**) in solution at -10°C by the oxidation of the stable Pd^{II}-cycle (**4c**) with 1-(bromomethyl)naphthalene (**5**), and we sought evidence for a subsequent in situ generation of the new Pd^{IV} complex (**9**) at -10°C by C-H Activation (Scheme 4.8). The reaction progress was monitored by ^{1}H NMR spectral analysis at -10°C.



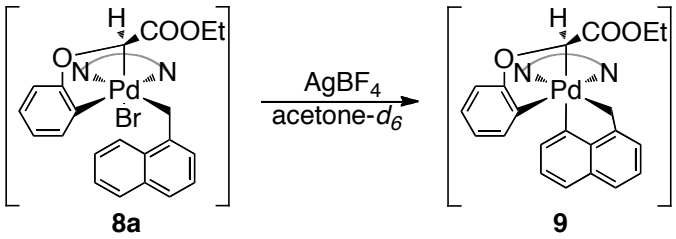
Scheme 4.8: Proposed synthesis of Palladium(IV) complexes (**8a, 9**) via Pallada(II)cycle oxidation

Following the established protocol by the Malinakova group,[2] the stable solid Pd^{II}-cycle (**4c**) and 2.0 equivalents of the solid bromide oxidant (**5**) were dissolved in dry acetone (1 mL) at 25°C, the resulting yellow solution was cooled to -10°C and stirred overnight at -10°C on a stir plate located in a freezer to control the temperature (Scheme 4.9). During this time, the reaction solution turned neon yellow from orange. After stirring, pentane was added to the reaction mixture to precipitate a solid at -10°C. The solid was then dissolved in acetone-d_6 and taken for ^{1}H NMR spectral analysis at -10°C.



Scheme 4.9: Initial attempts at generation of proposed Palladium(IV) complex **8a** in solution

After recording the spectral data, a solution of $AgBF_4$ in acetone- d_6 was added to the NMR tube containing the reaction mixture (Scheme 4.10). After 10 minutes, the ^1H NMR spectral data was collected at -10°C. During the acquisition of the ^1H NMR data, the solution in the NMR tube became dark black.



8a **9**

Scheme 4.10: Initial attempts at generation of proposed Palladium(IV) complex **9** in solution

The ^1H NMR spectral data for both reaction sequences showed new signals, indicating that a new species (either organic products or Pd-containing species) was present in the reaction mixtures (Figure 4.1). However, large water and impurity signals were present in both samples, making identification of the new species difficult. We envisioned that these signals could be removed by using fresh $AgBF_4$ reagent and by drying the solid intermediates by vacuum.

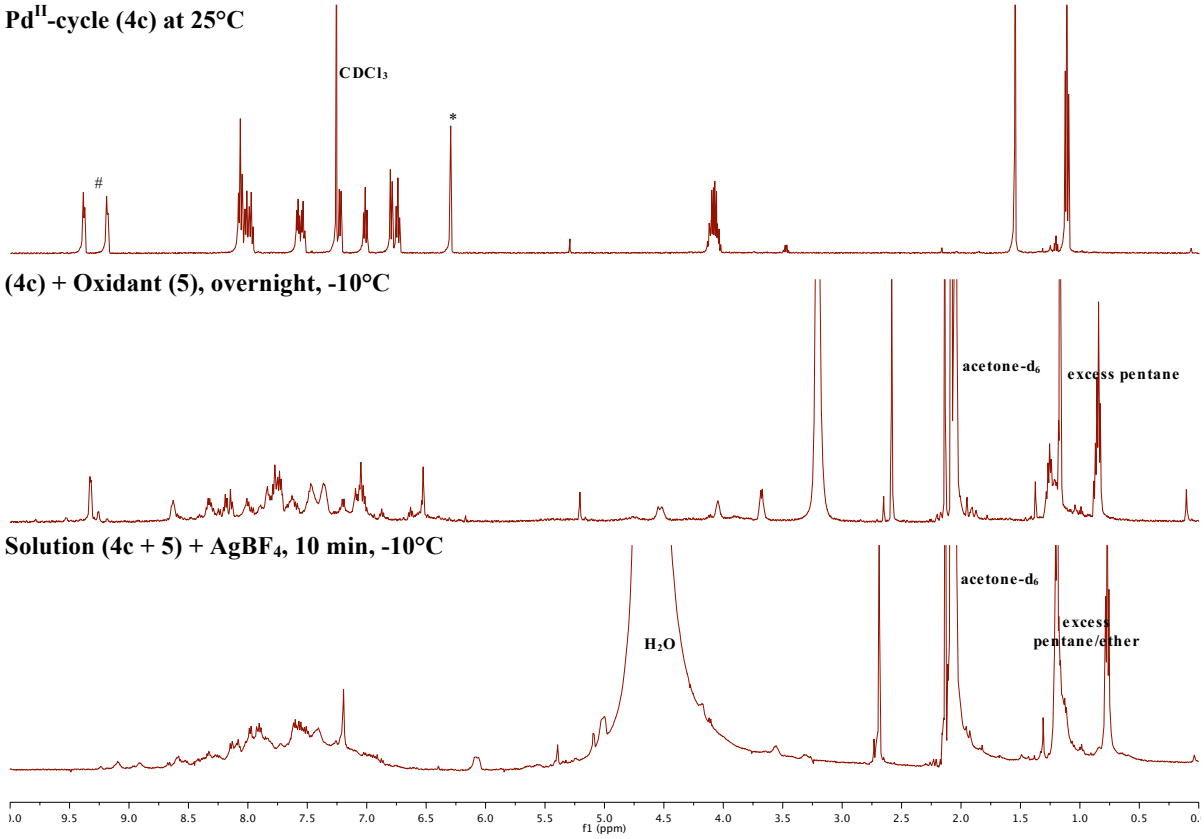


Figure 4.1: Initial in situ ^{1}H NMR (500 MHz, acetone-d_6) spectra
For Pallada(II)cycle **4c**: in $CDCl_3$; (#) - Aryl signal (*) –CH (*) signal

However, the oxidation and silver salt addition reactions were not as reproducible as we originally thought. After repeating the oxidation and silver salt addition reactions by the method described above, we had trouble purifying the solid collected for ^{1}H NMR spectral analysis. Typically, after the silver salt addition, the solid collected would readily decompose upon drying by vacuum at 25°C. In one experiment, we managed to collect a tan solid after drying under slightly reduced pressure at -10°C. However, the ^{1}H NMR spectral data revealed that the tan solid was the Pd^{II}-cycle (**4c**), indicating the initial oxidation had not occurred (Figure 4.2).

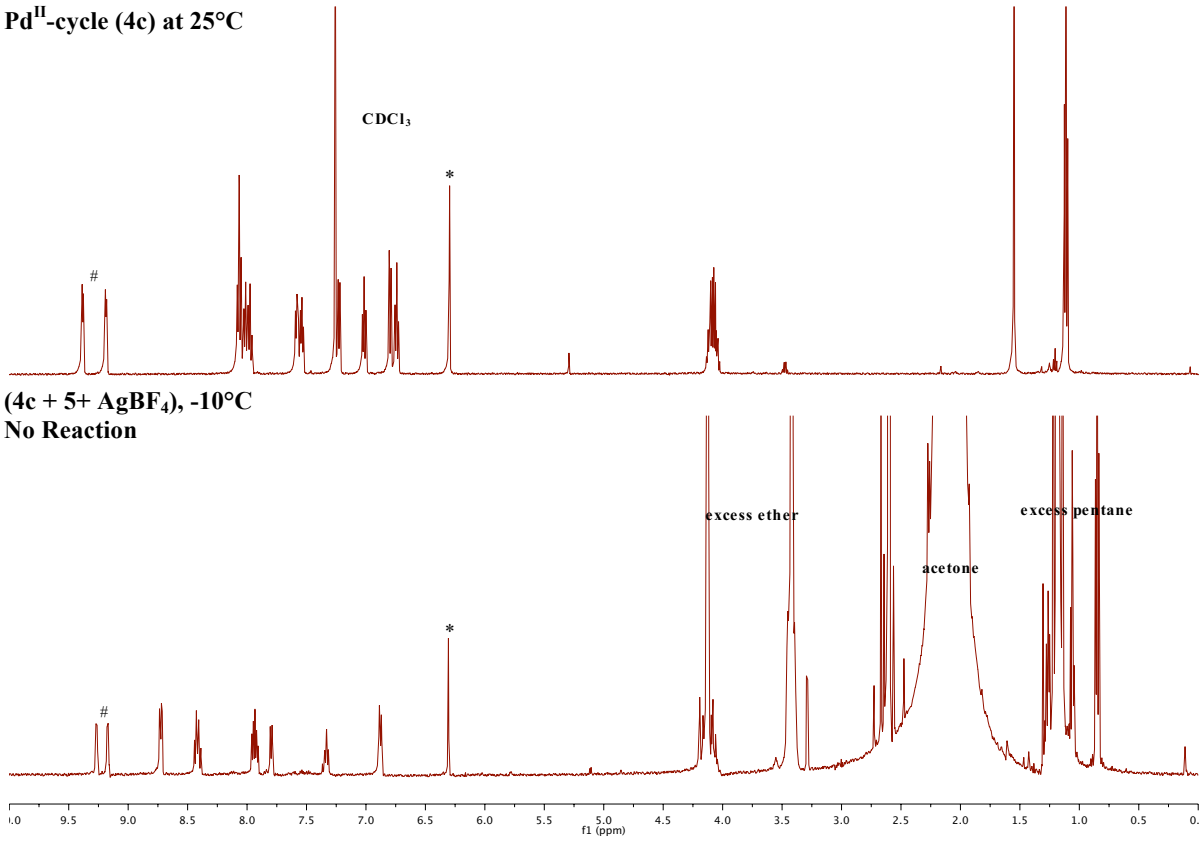


Figure 4.2: ^{1}H NMR (500 MHz, acetone-d_6) spectra of unsuccessful reaction sequence
(#) – Aryl signal (*) – CH signal

At this time, we chose to seek evidence for the oxidative addition forming the Pd^{IV} complex (**8a**) in solution before proceeding to the addition of the silver salt.

4.4: Oxidative Addition Studies to Generate Palladium(IV) complex 8a

To establish the proper reaction conditions for the oxidative addition that would lead to generating the Pd^{IV} complex (**8a**) in a good yield, we had to vary three main reaction conditions: (i) the choice of solvent; (ii) increasing the excess of the oxidant; and (iii) determining the best work-up conditions to remove any impurities.

First, we examined the solubility of the Pd^{II}-cycle (**4c**) and oxidant (**5**) in acetone at low temperatures. The Pd^{II}-cycle (**4c**) was soluble in dry acetone at -10°C but the 1-(bromomethyl)naphthalene (**5**) was not soluble. However, the bromide oxidant (**5**) was more soluble in dry DCM at -10°C. When the reaction was repeated by the method described above on page 101 at -10°C in a 1:1 mixture of dry acetone and dry DCM, a new species (either an organic product or a Pd-containing species) and unreacted oxidant (**5**) were observed by ^1H NMR spectral analysis at -10°C. When the reaction was repeated in dry DCM only to concentration the reaction mixture, no change was observed in the spectral data. Therefore, we decided to continue all future oxidative addition reactions in only dry DCM to maximize the amount of Pd-containing species generated during the oxidative addition reaction.

Next, we focused on increasing the excess of the bromide oxidant (**5**) added during the reaction sequence. By increasing the oxidant excess, we hoped to increase the yield of product formed by the oxidative addition reaction. After the solid Pd^{II}-cycle (**4c**) was dissolved in dry DCM, we ran multiple reactions in which the oxidant excess was varied from 4.0 to 125 equivalence and the reaction progress was followed by ^1H NMR spectral analysis at -10°C. The ^1H NMR data produced identical spectral data, indicating that a similar outcome was achieved.

It was determined that using 4.0 equivalents of the bromide oxidant (**5**) during the reaction sequence gave the best results, as the Pd^{II}-cycle (**4c**) was consumed and a majority of the unreacted oxidant was removed by precipitation with pentane. However, even with using 4.0 equivalents, unreacted oxidant remained in the reaction solution making the ^1H NMR spectral data difficult to interpret in the aromatic region (5-9 ppm). To remove the excess oxidant, we had

to determine the proper work-up conditions that would allow for the desired Pd^{IV} complex (**8a**) to be collected in maximum quantities.

We focused on changing the work-up procedures to remove any unreacted oxidant from our reaction mixture after treatment of the Pd^{II}-cycle (**4c**) with 4.0 equivalents of the bromide oxidant (**5**) in dry DCM at -10°C. When hexanes was added to the reaction mixture to precipitate a solid, the spectral data recorded for the solid showed that unreacted oxidant (**5**) remained in the sample indicating that the work-up was unsuccessful. When pentane was added to the reaction mixture to precipitate a solid and the solid was washed with ether, the spectral data for the isolated solid showed the presence of a new species with little to no oxidant present in the reaction sample. This indicates that using both pentane and ether for the product isolation yields the best results by ^{1}H NMR spectral analysis at -10°C (Figure 4.3).

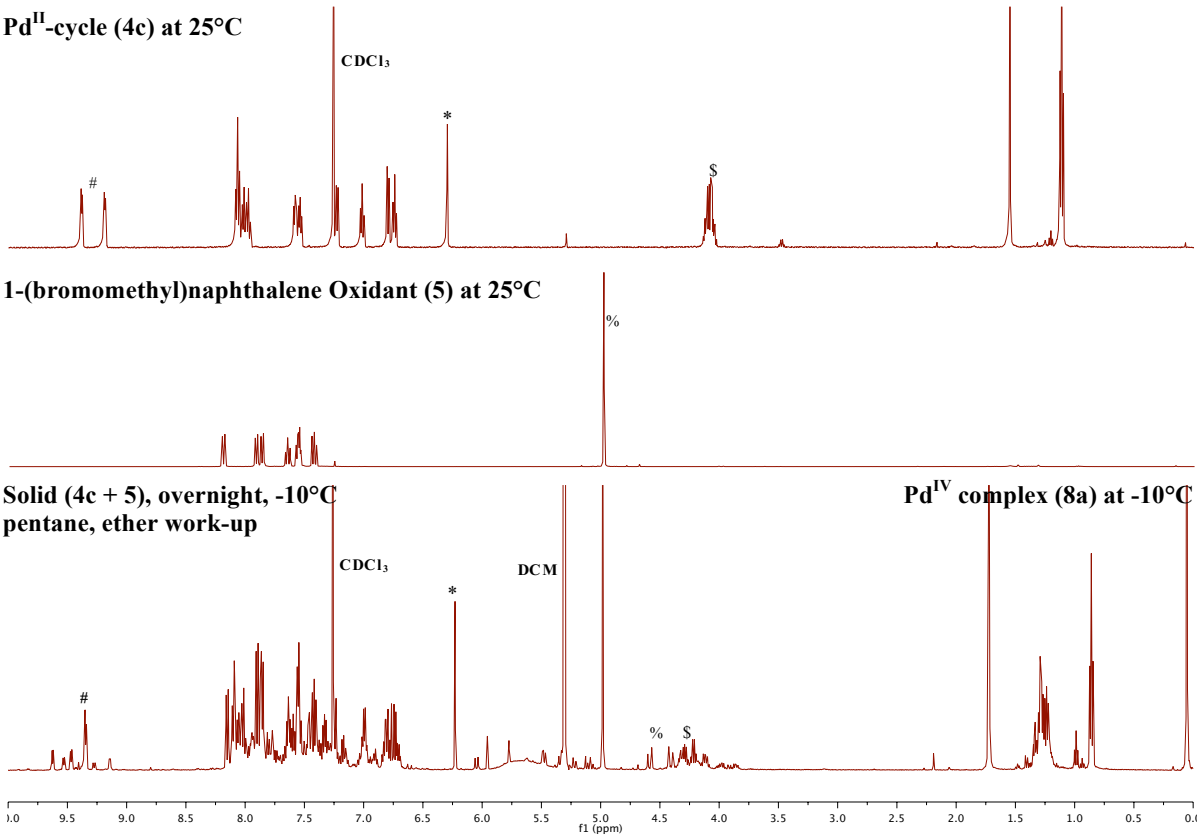
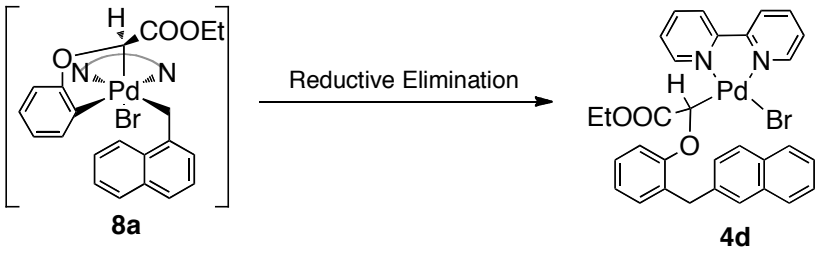


Figure 4.3: ^{1}H NMR (500 MHz, $CDCl_3$) spectra of optimized oxidative addition to generate Palladium(IV) complex (**8a**) at -10°C
(#) – Aryl signals (*) – Pd-CH signal (%) – Pd-CH_2 from oxidant (**5**)

When we compare the ^{1}H NMR data of the Pd^{II}-cycle (**4c**) and the isolated solid, we observe the aryl proton (#) signals merge to become a large doublet at δ 9.35 ppm. We also observe a slight upfield shift in both the –CH (*) signal on the Pd^{IV} center to δ 6.23 ppm and the –CH_2 (%) signal from the bromide oxidant to δ 4.39-4.60 ppm. We also observe an overall upfield shift in the aromatic region. The observed peak shifts in the spectral data for our isolated solid suggest that a new species is present in solution.

At this point, we have to ascertain what complex is present in the reaction mixtures. There are three possible products: an organic product, the desired Pd^{IV} complex (**8**) or the reduced Pd^{II}

complex (**4d**), which is generated by the reductive elimination from **8a** in the reaction mixture (Scheme 4.11).



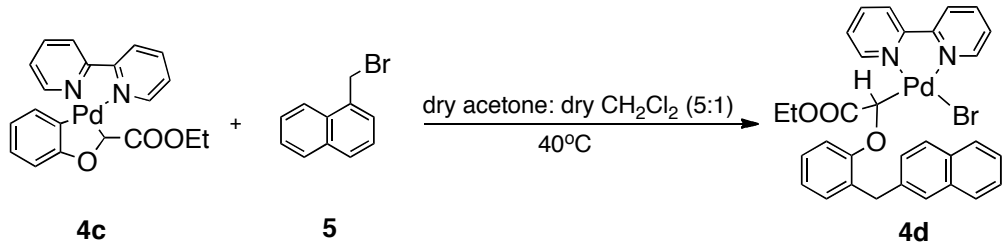
8a **4d**

Scheme 4.11: Two possible Palladium-containing products

Generation of the organic product would require higher temperatures and additional additives or reaction sequences, so it can be eliminated as a possible product. To determine whether **8a** or **4d** was generated during the reaction sequence, we had to synthesize the Pd^{II} complex (**4d)** to collect the ^{1}H spectral data and compare it to the observed spectral data at -10°C.

4.5: Synthesis of Palladium(II) complex 4d by Reductive Elimination

To synthesize the Pd^{II} complex **4d**, the solid Pd^{II}-cycle (**4c**) and 2.0 equivalents of the bromide oxidant (**5**) were dissolved in dry acetone:dry DCM (5:1, 12 mL) at 25°C to create a yellow solution[2] (Scheme 4.12). The reaction mixture was warmed to 40°C and stirred overnight. After stirring, the yellow reaction mixture was cooled to 25°C and the solvent was removed by vacuum to yield a yellow solid. The solid was washed with ether to remove any impurities and dried by vacuum filtration to produce the Pd^{II} complex (**4d**) as a fluffy yellow solid in 51% yield. The solid was dissolved in $CDCl_3$ and taken for ^{1}H NMR spectral analysis at 25°C.



4c **5** **4d**

Scheme 4.12: Synthesis of Palladium(II) complex **4d**

In the ^{1}H NMR data, (Figure 4.4) the signals observed for the Pd^{II} complex (**4d**) support the proposed structure, including the most characteristic features of the aryl protons (#), the –CH signal (*), the ester proton signals ($) and the $–CH_2$ (%) signals. These signals are distinct from those observed in our prior experiments, in which we proposed the formation of the Pd^{IV} complex (**8a**) (Scheme 4.9). This suggests that the two reactions afforded different Pd-containing species. The Pd^{IV} complex (**8a**) is generated at -10°C, and the Pd^{II} complex (**4d**) is generated at 40°C.

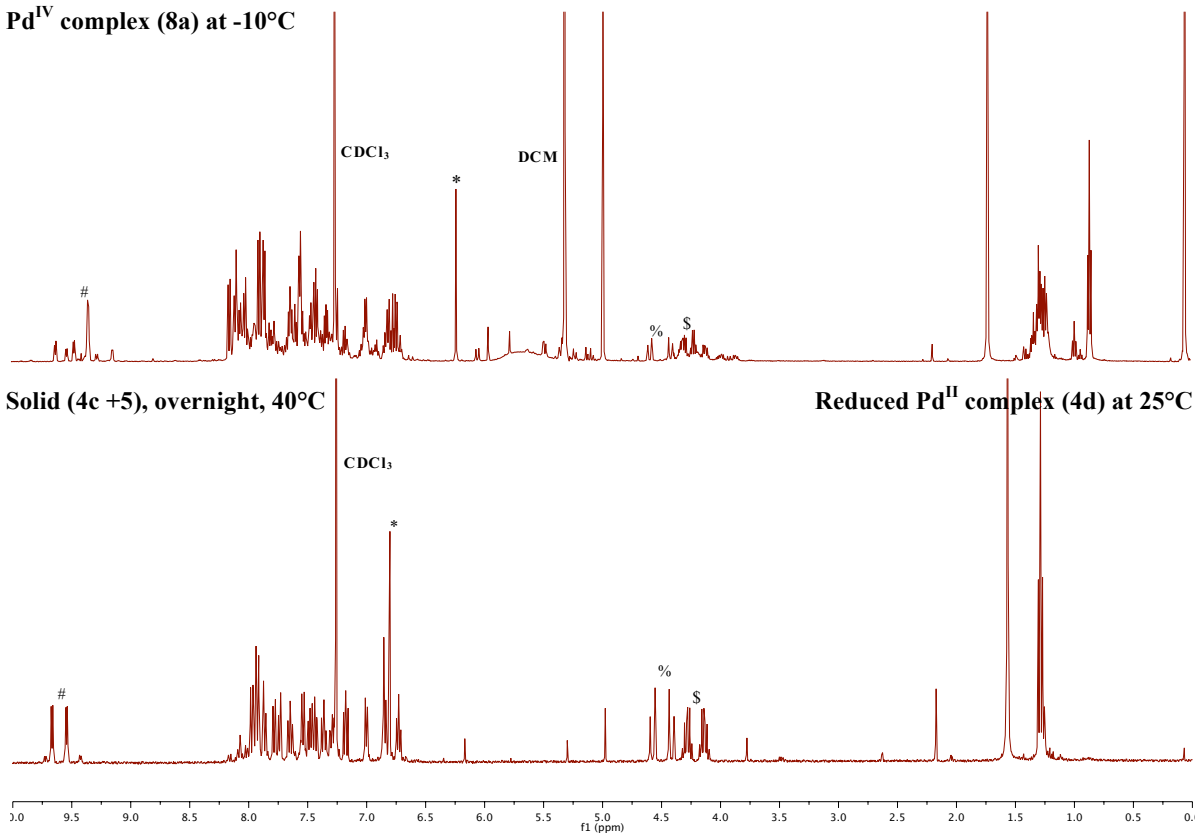
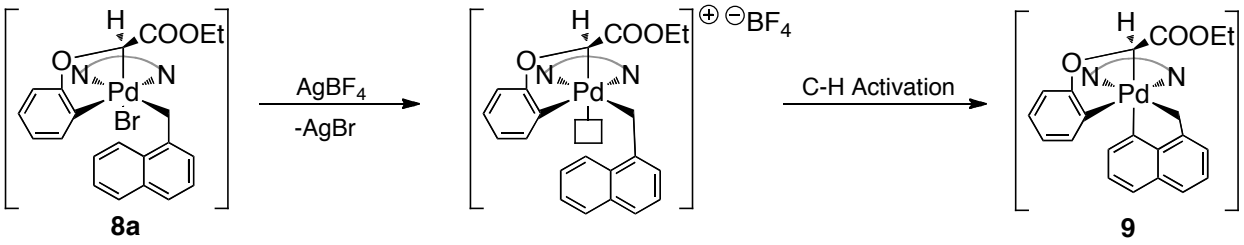


Figure 4.4: Comparison ^{1}H NMR (500 MHz, $CDCl_3$) spectra of Palladium(IV) complex (**8a**) and Palladium(II) complex (**4d**)
(#) – Aryl signals (*) – Pd-CH signal (%) – Pd-CH_2 from oxidant ($) – CH_2 from ester

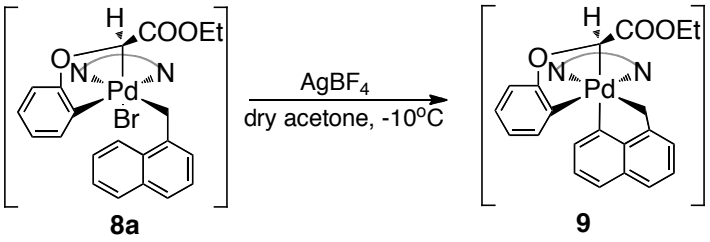
4.6: Bromide Removal by Addition of a Silver Salt

After establishing the reaction conditions to yield the Pd^{IV} complex (**8a**), we focused on removing the bromide ligand by addition of $AgBF_4$ to create an insoluble AgBr salt that would be removed by filtration. Removal of the bromide ligand would open a coordination site and generate a cationic Pd^{IV} species, which would then induce in situ C-H activation on the naphthyl substrate. This would generate a new Pd^{IV} complex (**9**) at -10°C, which we hoped to detect by ^{1}H NMR spectral analysis (Scheme 4.13).



Scheme 4.13: Proposed intramolecular C-H activation to generate Palladium(IV) complex **9**

After generating the initial Pd^{IV} complex (**8a)** by the protocol established above, we added the solid $AgBF_4$ to solid **8a** and dissolved them in acetone (1.0 mL) at -10°C to create a yellow-grey solution, which was stirred for 30 minutes at -10°C (Scheme 4.14). After stirring, the mixture was filtered through Celite to collect an orange-yellow solution. The solvent was then carefully removed by vacuum, making sure to keep the temperature below 0°C to prevent decomposition, to collect an oil. The oil was triturated with ether at -10°C to precipitate a fine golden yellow solid. The solid was dissolved in $CDCl_3$ and taken for ^1H NMR spectral analysis at -10°C.



Scheme 4.14: Initial approach to generation of Palladium(IV) complex **9**

In the ^1H NMR data, (Figure 4.5) we observed a new set of signals suggesting that a new species was generated during the reaction. We observed an upfield shift for the aryl proton (#) signals, the aromatic region and the –CH signal (*) on the Pd^{IV} center. The –CH signal, which is typically observed as a singlet, is observed as a doublet in our spectral data. A slight shift is seen for the –

CH_2 proton (%) signals adjacent to the naphthyl ring. We also observe a decrease in the ester proton ($) signal intensity.

Due to the unknown stability of the new species, we decided to let the sample warm to 25°C overnight and retake the ^1H NMR spectra anticipating that the organic product may form by reductive elimination. We would look for a signal shift in the ^1H NMR spectra, which would suggest that the desired organic product was generated at 25°C.

To collect the new product, the fine golden yellow solid was dissolved in a mixture of dry acetone and dry DCM and stirred overnight at 25°C. During this time, the reaction solution became dark brown. After stirring, the solution was filtered over Celite to collect an orange solution. The solvent was removed by vacuum to collect an orange oil, which was triturated with ether at -10°C to precipitate a tan solid. The solid was collected by filtration and dissolved in $CDCl_3$ for ^1H NMR spectral analysis at 25°C.

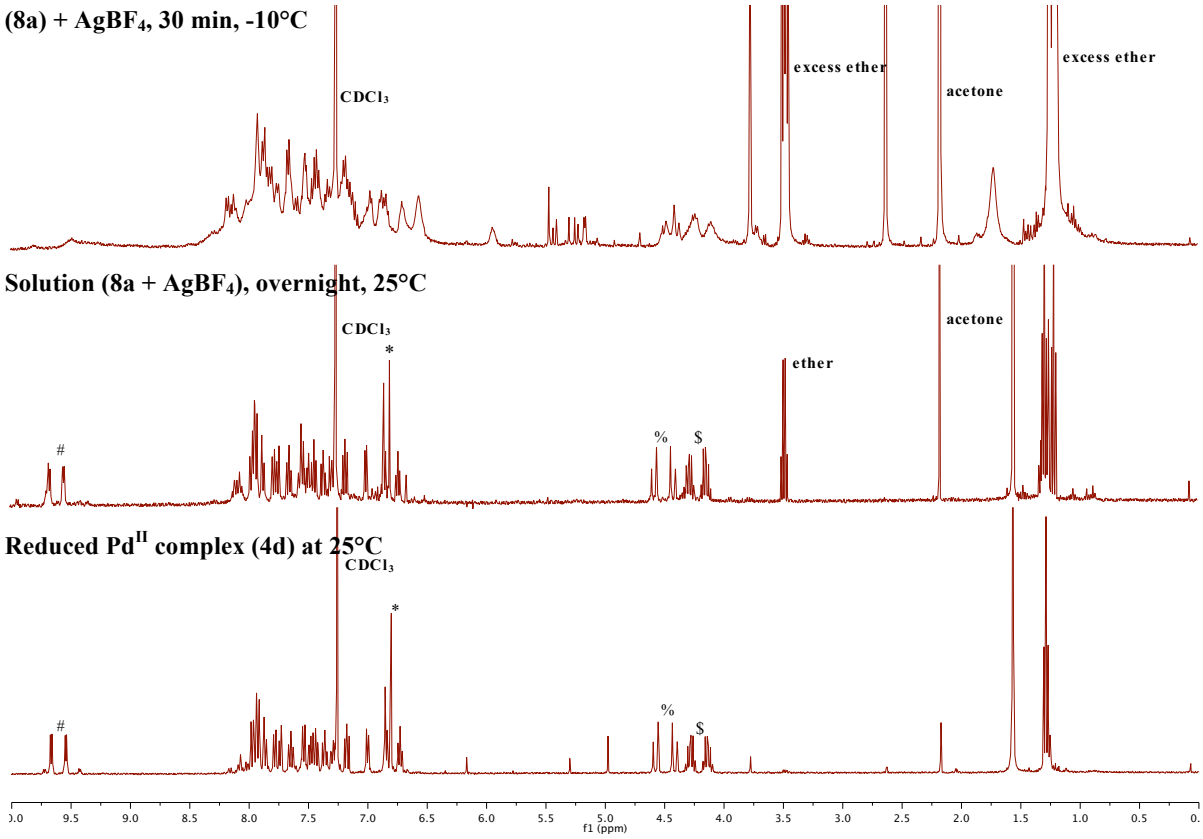


Figure 4.5: ^{1}H NMR (500 MHz, $CDCl_3$) spectra for unsuccessful silver salt addition reaction and the comparison to Palladium(II) complex (**4d**)
(#) – Aryl signals (*) – Pd-CH signal (%) – Pd-CH_2 from oxidant ($) – CH_2 from ester

In the ^{1}H NMR data, (Figure 4.5) we observed a different set of signals for the golden yellow solid than those seen at -10°C for the Pd^{IV} complex (**8a**). However, the signals for the tan solid matched the ^{1}H NMR data for the Pd^{II} complex (**4d**), (Figure 4.5) suggesting that warming the solution to 25°C did not yield the desired organic product. In order to generate **4d** in solution, the bromide ligand must still be present in the reaction solution and was not completely removed by the $AgBF_4$ (Scheme 4.14). In order to ensure for complete removal of the bromide ligand, we decided to increase the reaction time for the treatment with the $AgBF_4$ salt.

Under the reaction conditions established above on page 106, the solid $AgBF_4$ and solid Pd^{IV} complex (**8a**) were dissolved in dry acetone at -10°C and stirred for 1 hour. During this time, the reaction mixture became dark brown. After following the same isolation method on page 111 for the isolation of the fine golden yellow solid, we collected a pale yellow solid.

When we attempted to dissolve the pale yellow solid in $CDCl_3$, an insoluble black oil formed which could not be characterized by ^1H NMR spectral analysis. However, when we used acetone-d_6, the pale yellow solid dissolved and was taken for ^1H NMR spectral analysis (Figure 4.6).

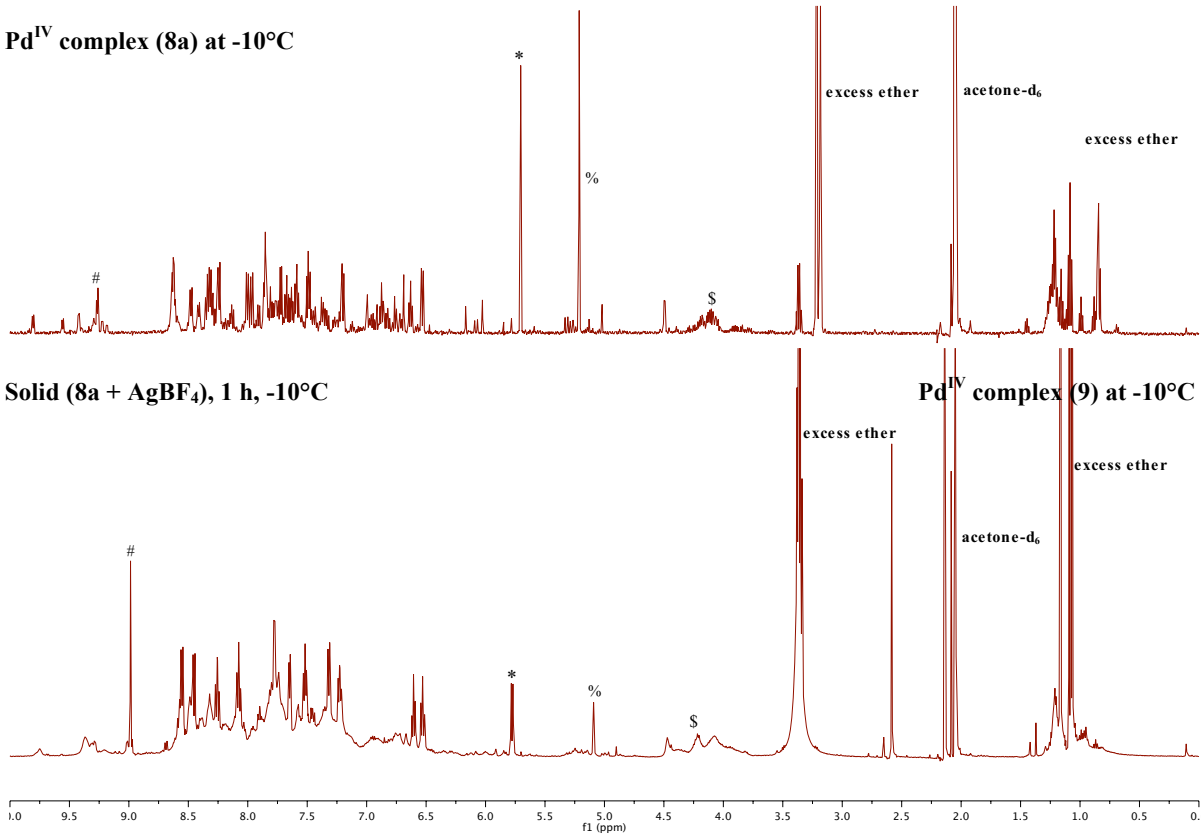


Figure 4.6: ^1H NMR (500 MHz, acetone-d_6, -10°C) spectra of Palladium(IV) complexes (**8a**) and the successful silver salt addition reaction
(#) – Aryl signals (*) – Pd-CH signal (%) – Pd-CH_2 from oxidant ($) – CH_2 from ester

The spectral data for the pale yellow solid was recorded aiming to monitor for the formation of our organic product by ^{1}H NMR spectral analysis as well. We envisioned completing the monitoring experiments by recording the spectral data every 10 minutes at various temperatures (-10°C, 0°C and 25°C).

At -10°C and 0°C, there was no observable change in the NMR spectral data. This suggests that the species generated during the $AgBF_4$ addition reaction is stable in solution up to 0°C. At 25°C, a change in the ^{1}H NMR spectral data was observed after 20 minutes with a complete change after 60 minutes (Figure 4.7).

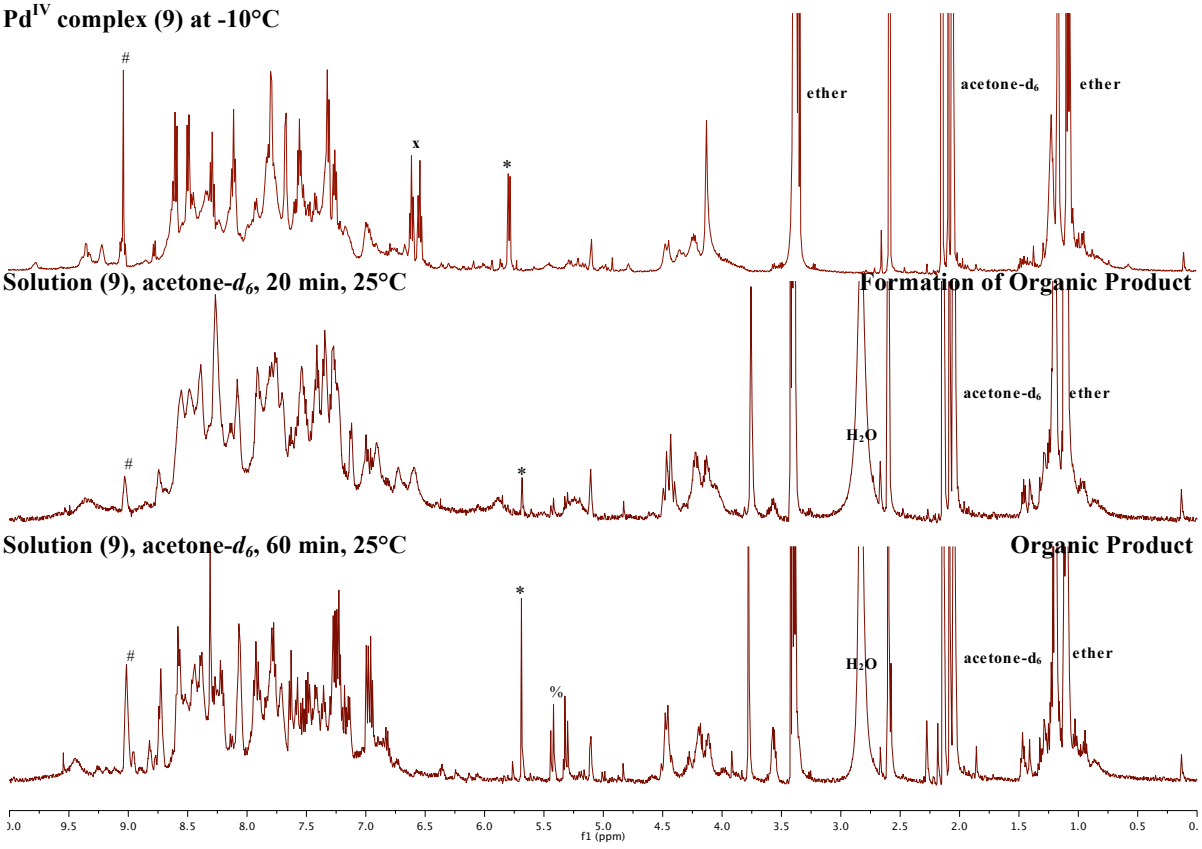


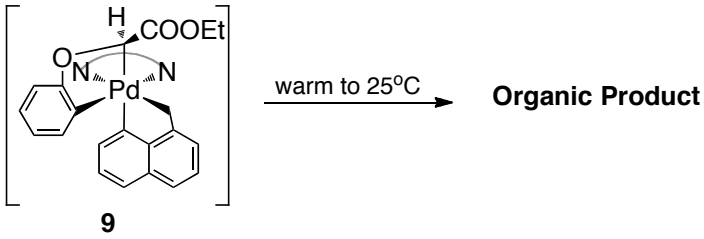
Figure 4.7: ^{1}H NMR (500 MHz, acetone-d_6) spectra for the Palladium(IV) complex (**9**) and for the in situ monitoring experiments at 25°C
(#) – Aryl signals (*) – Pd-CH signal (%) – Pd-CH_2 from oxidant (x) disappearing signal

In the ^{1}H NMR data, (Figure 4.7) we observed a disappearance in a set of doublet of triplet (x) signals from the Pd^{IV} complex (**9**). We also observed a slight upfield shift in the –CH (*) signal, which merged to a singlet. The $–CH_2$ proton (%) signals split to a doublet of doublets and we observed a downfield shift of the aromatic region. This suggests that a new species was generated when the reaction mixture is warmed to 25°C for 60 minutes.

Being confident that we were generating both Pd^{IV} complex (**8a**) and Pd^{IV} complex (**9**) and detecting the formation of a new species from the reductive elimination of Pd^{IV} complex (**9**), we focused on isolating and characterizing this final product by ^{1}H NMR spectral analysis. By characterizing the final product, we hoped to gain insight into what new C-C bonds were formed during the reductive elimination step.

4.7: Organic Product Formation and Isolation

After generating the Pd^{IV} complex (**9**) in solution by the method established above on page 114, the reaction mixture was warmed to 25°C and stirred overnight (Scheme 4.15). During this time, the reaction mixture became dark grey. After stirring, the mixture was filtered over Celite to collect an orange solution and solvent was removed by vacuum to yield a dark oil.



Scheme 4.15: Generation of organic product from Palladium(IV) complex **9**

Analysis of the oil by thin-layer chromatography (TLC) in a 1:5 Ethyl Acetate:Hexanes (EA:Hex) solvent system revealed 3 spots (Figure 4.8). After comparison with the initial Pd^{II}-cycle (**4c**), naphthyl bromide (**5**) and reductive Pd^{II} product (**4d**), we concluded that the first fraction, which is purple under UV light, was the desired organic product.

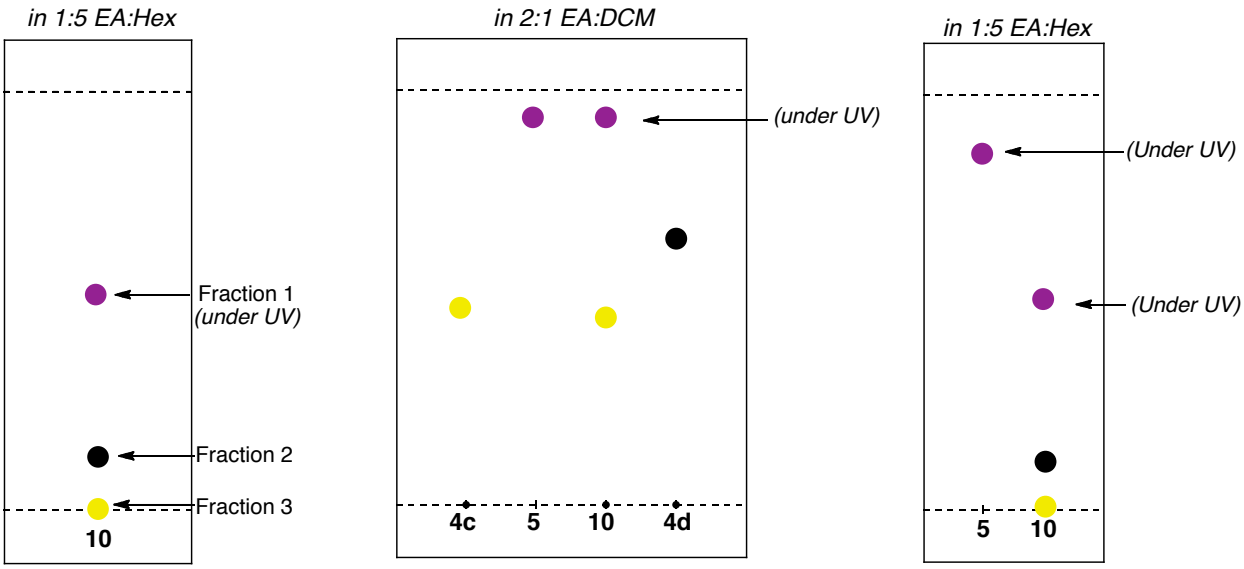


Figure 4.8: TLC analysis and comparison of organic product

4c = Pallada(II)cycle; **5** = Oxidant; **10** = Organic Product; **4d** = Reduced Palladium(II) complex

Initially, we collected the first fraction by chromographic separation on a silica column eluting with a 1:10 EA:Hex eluent system. ^{1}H NMR analysis revealed that the collected fraction contained multiple impurities. After repeating the reaction and purification by silica column, we collected the initial first fractions (which totaled 0.0280g) and they were repurified by silica column, eluting with a 1:50 EA:Hex eluent system. After solvent removal under vacuum, the fraction became a clear oil (0.0041g). This oil was dissolved in acetone-d_6 and taken for ^{1}H NMR analysis.

When the clear oil was taken for TLC analysis with a 1:5 EA:Hex eluent system, a single purple spot was observed under UV radiation with an R_f value of 0.51. The clear oil, which contained no impurities, was determined to be fraction one after comparison with the TLC plate of the initial reaction mixture (Figure 4.8).

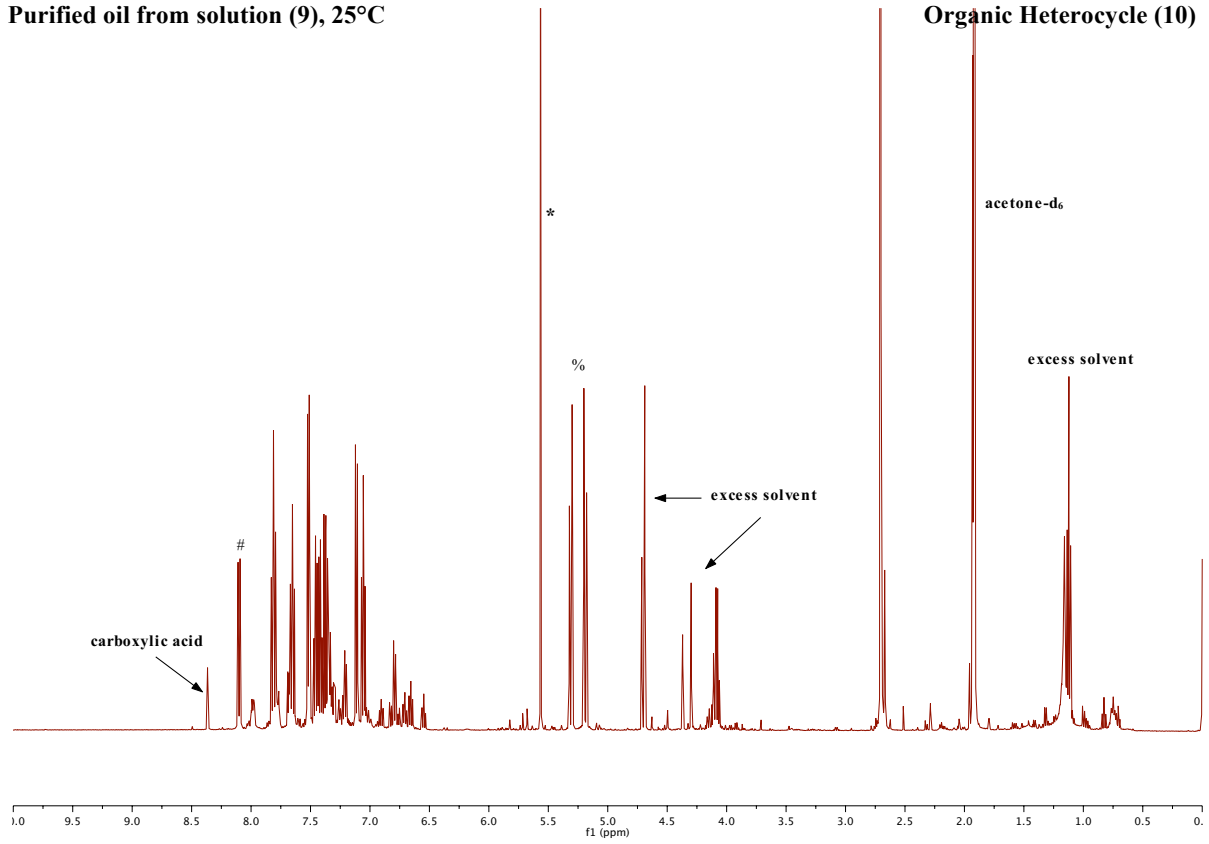
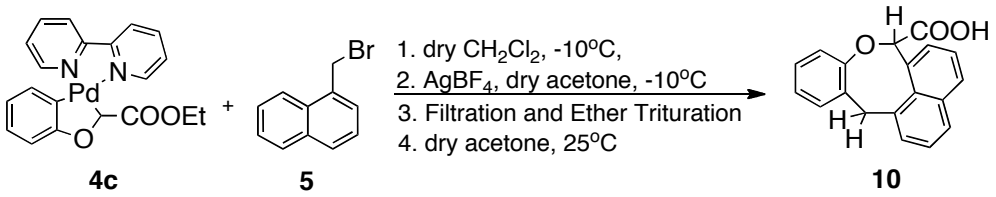


Figure 4.9: ^{1}H NMR (500 MHz, acetone-d_6) spectrum of the organic heterocycle (**10**) after purification
(#) – Aryl signal (*) – CH signal (%) – CH_2 signal

The ^{1}H NMR data revealed the desired organic product with little impurities (by TLC), which we determined to be solvent signals. In the ^{1}H NMR data, (Figure 4.9) we observed an upfield shift in both the aryl proton (#) signals to δ 8.23 ppm and in the overall aromatic region. We also observed an intense –CH singlet (*) signal at δ 5.70 ppm, an intense –CH_2 (%) signal at δ 5.30-5.46 ppm and a disappearance of the ester signals. This data is in agreement with the spectral data collected during the monitoring experiment (Figure 4.7 on page 115), suggesting that the

product collected is generated from the reduction of the Pd^{IV} complex (**9**) in solution at 25°C (Figure 4.9).

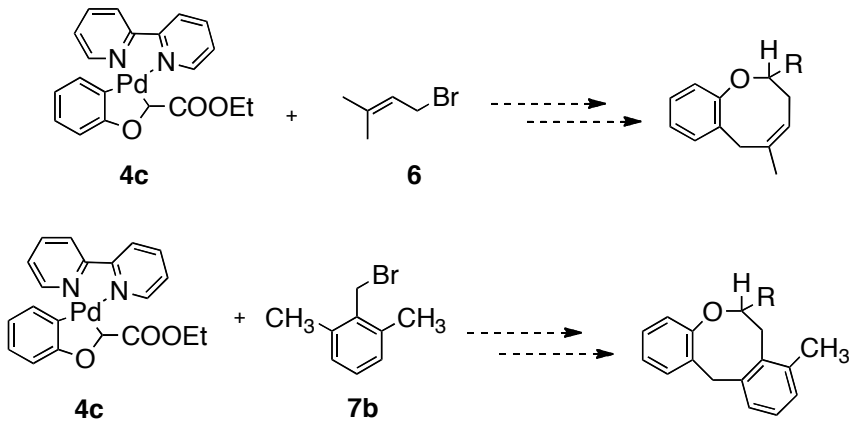
By using ^{1}H, ^{13}C and 2D NMR spectral analyses (DEPT, COSY, HSQC, HMBC), we could determine the final structure of the heterocycle (**10**) generated during the reductive elimination process (Scheme 4.16). Structural elucidation will be discussed later in this Chapter (Section 4.9.3 on page 128).



Scheme 4.16: Synthesis of Heterocycle **10** from Pallada(II)cycle **4c** and Bromide Oxidant **5**

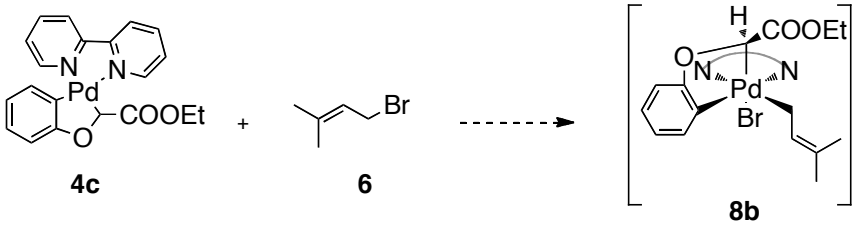
4.8: Proposed C-H Activation of an Unactivated C(sp^3)-H Center

After establishing the reaction conditions to generate two new Pd^{IV} complexes (**8a, 9**) that produced a heterocycle (**10**) through intramolecular C-H activation on the bromide oxidant (**5**), we hope to apply this model system to achieve Pd^{IV}-mediated C-H activation at an unactivated C(sp^3)-H center. We will explore organic oxidants such as 3,3-dimethylallyl bromide (**6**) and 2-(bromomethyl)-1,3-dimethylbenzene (**7b**) that feature a C(sp^3)-H bond available for C-H activation. Subsequent reductive elimination would yield a heterocycle featuring a new C(sp^2)-C(sp^3) and C(sp^3)-C(sp^3) bonds (Scheme 4.17).



Scheme 4.17: Proposed intramolecular C-H activation of a C(sp^3)-H bond

To date, we have been unable to generate the Pd^{IV} complex (**8b**) from the oxidation of the Pd^{II}-cycle (**4c**) with a commercially available allyl bromide oxidant (**6**) at -10°C (Scheme 4.18). By ^1H NMR spectral analysis, we have established two crucial reaction conditions: (i) a large excess of the oxidant (35.0 equivalents) is needed to generate a new species and (ii) reaction temperature must not exceed -10°C.

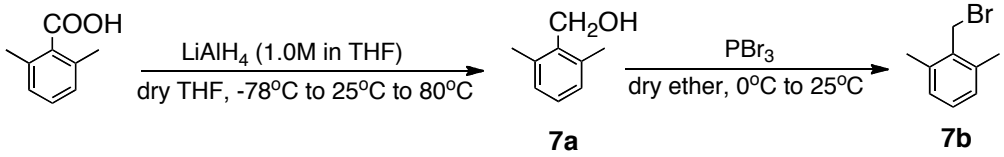


Scheme 4.18: Proposed generation of Palladium(IV) complex **8b**

If the oxidant (**6**) is not used in large excess or the reaction temperature is higher than -10°C, then an unfavorable Pd-containing side product, which is produced from two separate oxidative addition then immediate reductive elimination reaction cycles,[2] is generated. This suggests that the oxidant (**6**) is highly reactive and that oxidative addition is occurring to generate the Pd^{IV}

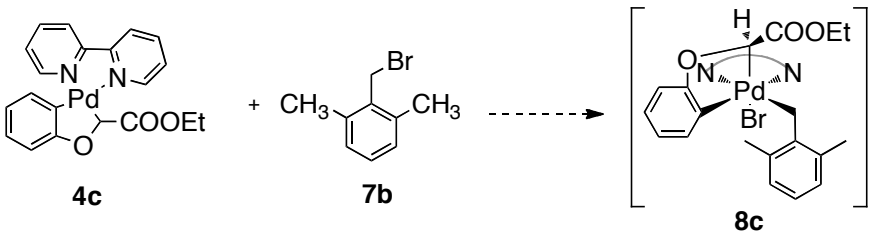
complex (**8b**) but rapid reductive elimination prevents the detection of **8b** by ^{1}H NMR spectroscopy at -10°C.

To date, the 2-(bromomethyl)-1,3-dimethylbenzene oxidant was synthesized from (2,6-dimethylphenyl)methanol (**7a**), obtained as a white solid from the reduction of 2,6-dimethylbenzoic acid in 97% yield.[5] Bromination of **7a** with PBr_3 in dry ether produced the 2-(bromomethyl)-1,3-dimethylbenzene oxidant (**7b**) as a light yellow solid in 91% yield[6] (Scheme 4.19). Both solids (**7a, 7b**) were characterized by melting point and ^{1}H NMR spectral analysis



Scheme 4.19: Synthesis of 2-(bromomethyl)-1,3-dimethylbenzene oxidant **7b**

However, we have been unable to generate the Pd^{IV} complex (**8b**) from the oxidation of the Pd^{II}-cycle (**4c**) with the benzyl oxidant (**7b**) at -10°C (Scheme 4.20).



Scheme 4.20: Proposed generation of Palladium(IV) complex **8c**

We have been able to establish that the reaction mixture must stir at 25°C for one hour then been cooled to -10°C and stirred overnight in order to yield a new species, which was detected by ^{1}H NMR spectral analysis at -10°C. This suggests that the oxidant (**7b**) is unreactive in under our

experimental conditions and that a high temperature is needed to possibly achieve oxidative addition.

This oxidant (**7b**), which features two methyl groups available for intramolecular C-H activation at an C(sp^3)-H bond, was chosen due to its similarity to the successful naphthyl bromide oxidant (**5**) and its rigidity and symmetry that is expected to position a C(sp^3) bond into the proximity of the open coordination site on Pd^{IV} generated by the silver salt addition, increasing the probability of the desired C-H activation at the C(sp^3)-H center.

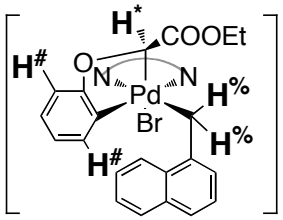
4.9: Summary of Characterization and Regiochemistry Confirmation

To monitor the progress of the oxidative addition, halide abstraction by addition of a silver salt and reductive elimination reactions to generate the Pd^{IV} complexes (**8a** and **9**) and organic heterocycles (**10**), we used low temperature ^{1}H NMR spectral analysis. A summary of the spectral analysis collected can be found on page 128. In these reactions, we focused on the changes of the chemical shifts of three key signals: the aryl proton signals (#) and the –CH signal (*) from the Pd^{II}-cycle (**4c**) and the $–CH_2$ signals (%) from the oxidant (**5**) (Figure 4.16).

In the corresponding Pd^{II}-cycle (**4c**), the aryl proton signals are observed at δ 9.38 and 9.18 ppm (doublets, 2H) and the –CH signal is observed at δ 6.30 ppm (singlet, 1H). In the oxidant the $–CH_2$ signal is observed at δ 5.00 ppm (s, 2H).

4.9.1: ^{1}H NMR Characterization of Palladium(IV) complex 8a

For our Pd^{IV} complex (**8a**), we observed the aryl proton (#) signals at δ 9.35 ppm (d, 1H) and these signals had merged from two individual doublet signals (as observed in **4c**) into an individual doublet signal. The –CH (*) signal was observed at δ 6.23 ppm (s, 1H) and the $–CH_2$ (%) signal was observed at δ 4.39-4.60 ppm (dd, 2H) and had split from a singlet (as observed in **5**) into a doublet of a doublet (Figure 4.10).

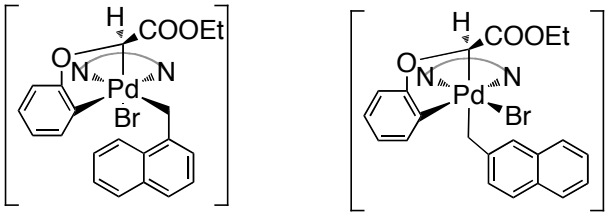


8a

Figure 4.10: Protons (Aryl protons, -CH and $–CH_2$) on Palladium(IV) Complex (**8a**) selected for monitoring by low temperature ^{1}H NMR spectroscopy

The significant upfield shift of the –CH and $–CH_2$ signals suggest that the corresponding carbons are coordinated to an electron-deficient center, most likely the oxidized Pd^{IV} center in the complex **8a**. The aryl also demonstrated a slight upfield shift, which would also suggest that the aryl ring is coordinated to the electron-deficient Pd^{IV} center.

Two possible structures can be proposed for the Pd^{IV} complex (**8a**) generated during the oxidative addition reactions: one where the $–CH_2$ bond is located in the equatorial position (**8a.1**) and one where the $–CH_2$ bond is located in the axial position (**8a.2**) (Figure 4.11). Currently, we do not know which structure is present in our reaction solution but either structure will lead to the removal of the –Br ligand or the Pd^{II} reduced products. The ^{1}H NMR spectral data suggests that a single species is present in our reaction solution.



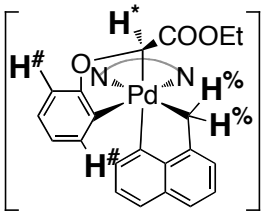
8a.1 **8a.2**

Figure 4.11: Possible structures for the Palladium(IV) complex **8a**

To date, no crystal structure data has been collected, which would be used to determine the location of the $–CH_2$ bond in our Pd^{IV} complex (**8a**). This proposed Pd^{IV} structure used in this Chapter is based on a reported crystal structure for a similar Pd^{IV} complex generated by the oxidation of the Pd^{II}-cycle (**4c**) in the presence of an allyl bromide.[2]

4.9.2: ^{1}H NMR Characterization and Structure Determination of Palladium(IV) complex 9

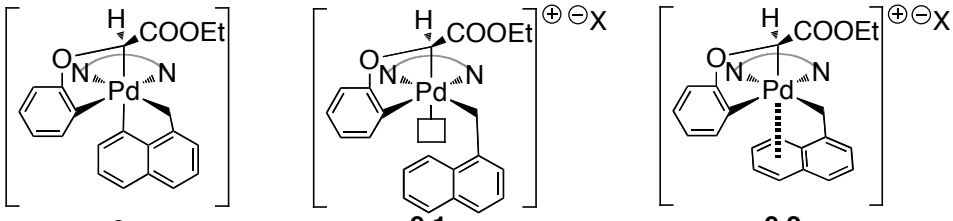
In our Pd^{IV} complex (**9**), we observed the aryl proton (#) signal as a singlet at δ 8.99 ppm; the –CH (*) signal as a doublet at δ 5.78 ppm; and the $–CH_2$ (%) signal as a singlet at δ 5.09 ppm. When compared to the Pd^{IV} complex (**8a**), we observe an upfield shift of the aryl proton and $–CH_2$ signals and the –CH signal, which is typically observed as a singlet, is observed as a doublet (Figure 4.12). The shift in these signals suggests the presence of a different electron-deficient Pd^{IV} center.



9

Figure 4.12: Protons (Aryl protons, -CH and $-CH_2$) on Palladium(IV) Complex (**9**) selected for monitoring by low temperature ^{1}H NMR spectroscopy

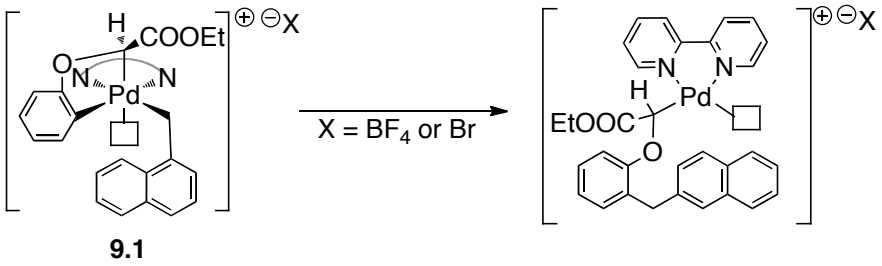
In order to form **9**, two other Pd^{IV} complexes (**9.1** and **9.2**) are formed in our reaction solution prior to Pd^{IV}-mediated C-H Activation, which would form Pd^{IV} complex (**9**) (Figure 4.13). However, we do not know which of the complexes (**9.1, 9.2** or **9**) we are observing by ^{1}H NMR spectroscopy at low temperatures.



9 **9.1** **9.2**

Figure 4.13: Possible electron-deficient Palladium(IV) centers **9, 9.1** and **9.2**

The initial cationic Pd^{IV} complex (**9.1**) arises from the removal of the bromide ligand by the silver salt to leave an open-coordination site at the cationic Pd^{IV} center. In this complex, the naphthyl ring would not interact with the Pd^{IV} center. Upon reductive elimination, we would generate a cationic Pd^{II} center and a $C(sp^2)$-$C(sp^3)$ bond (Scheme 4.21). This product, structurally similar to a Pd^{II} complex (**4d**) synthesized in this project (Section 4.5 on page 108), was not observed during the reductive elimination monitoring experiment (Section 4.6 on page 110) suggesting that the Pd^{IV} complex (**9.1**) was not present in the reaction solution.



9.1

Scheme 4.21: Reductive elimination of cationic Palladium(IV) complex **9.1**

The next cationic Pd^{IV} complex (**9.2**) arises from the pre-coordination of the naphthyl ring to the Pd^{IV} center via the open coordination site. In this complex, two pre-coordination interactions with the Pd^{IV} center are possible: (i) an agostic interaction with the C(sp^2)-H bond on the naphthyl ring or (ii) through the π-electrons on the naphthyl ring.

To identify the complex **9** or **9.2**, which differ by the presence of a Pd-C(sp^2) bond, present in our reaction solution, we have to determine if the naphthyl ring has bound to the Pd^{IV} center. If the naphthyl ring was bound to the Pd^{IV} center, we would observe an absence of the proton signal at δ 7.93 ppm, which was determined by 2D NMR spectral analyses to be the proton at the unactivated C(sp^2)-H center on the 1-(bromomethyl)naphthalene (**5**) oxidant (Figure 4.14).

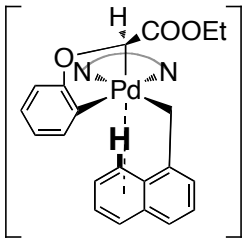


Figure 4.14: Identification of proton signal at the unactivated C(sp^2)-H center

In our ^{1}H NMR data (Figure 4.6 on page 114), we notice an absence of a signal at δ 7.93 ppm, which suggests that the Pd^{IV}-mediated C-H activation occurred in solution to yield a new Pd^{IV} complex (**9**) featuring a Pd^{IV}-C(sp^2) bond at -10°C.

From the desired C-H activated Pd^{IV} complex (**9**), we can also propose an additional two structures: one where the $–CH_2$ bond is located in the equatorial position (**9.3**) and one where the $–CH_2$ bond is located in the axial position (**9.4**) (Figure 4.15). Currently, we do not know the exact location of this bond, however, reductive elimination from either structure (**9.3** and **9.4**) would generate the observed C(sp^2)-C(sp^3) bonds in the organic heterocycle (**10**). However, the ^{1}H NMR spectral data suggests that a single species is present in our reaction solution.

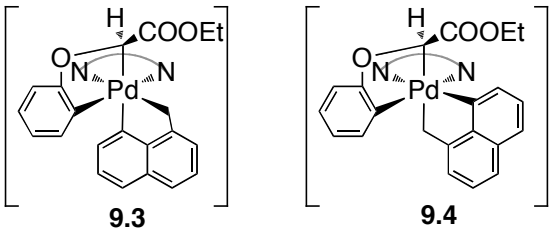


Figure 4.15: Additional possible structures for the Palladium(IV) complex (**9**) formed by C-H Activation

Decomposition afforded a yellow suspension containing a black solid upon the addition of $CDCl_3$ for spectral analysis. The suspension was filtered through Celite to collect a light yellow solution, which was taken for ^{1}H NMR spectral analysis. Unfortunately, the sample was too dilute and the ^{1}H spectral data could not be collected. The formation of the black solid suggests the newly formed Pd^{IV}-C(sp^2) bond is weak and will reduce easily to yield Pd black in solution. This is not unexpected as $CDCl_3$ is a common solvent used to promote the reduction of Pd-containing species.[1, 7-10] To prevent decomposition, the remaining ^{1}H NMR monitoring experiments and spectral analysis were completed in acetone-d_6.

However, to confirm if the desired C-H activation occurred on the C(sp^2)-H center in our oxidant (**5**) and the location of the Pd^{IV}-C(sp^2) and Pd-CH_2 bonds, we would have to obtain a crystal structure of the Pd^{IV} complex (**9**). To date, no crystal structure data has been collected.

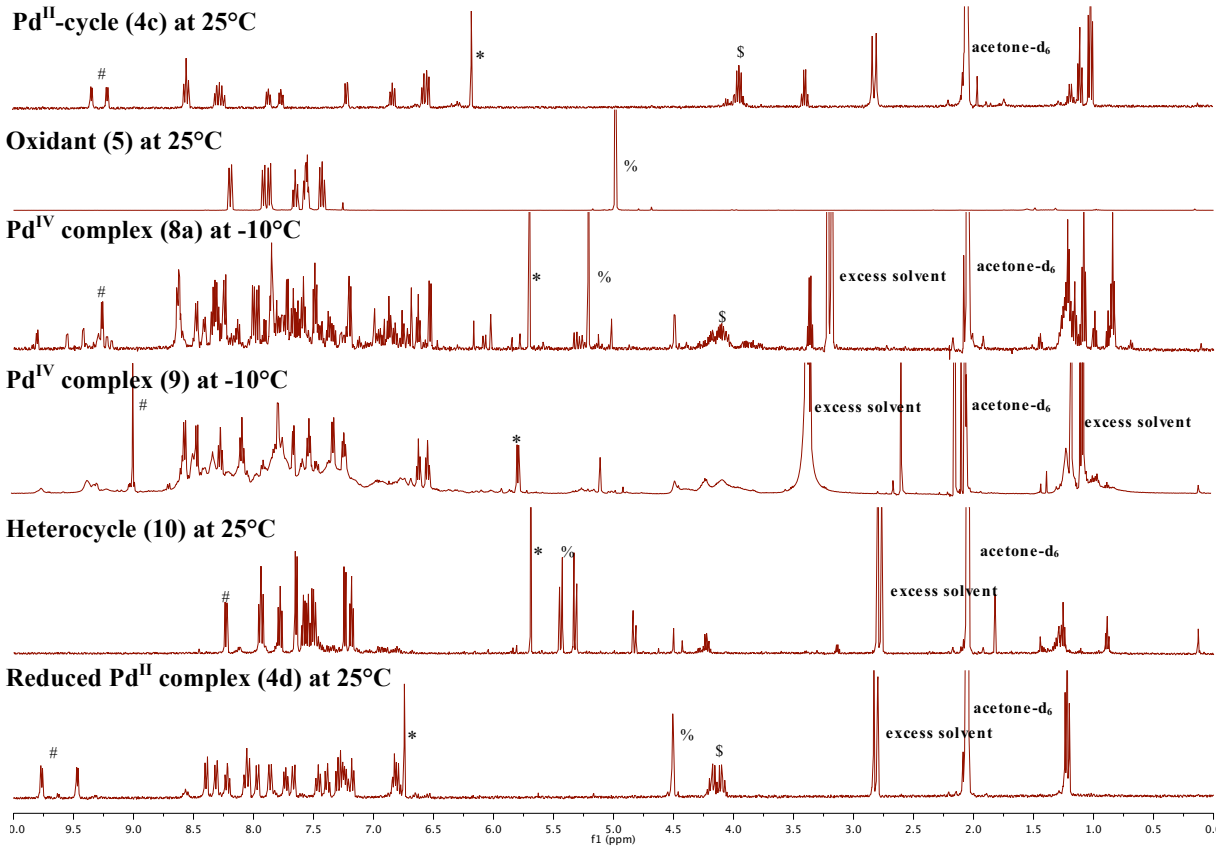


Figure 4.16: Summary of ^{1}H NMR (500 MHz, acetone-d_6) spectra reported in Chapter Four
(#) – Aryl signals (*) – Pd-CH signal (%) – Pd-CH_2 from oxidant ($) – CH_2 on ester

4.9.3: ^{1}H NMR Characterization and Structure Determination of Organic Heterocycle 10

From the Pd^{IV} complex (**9**), we generated the organic heterocycle (**10**) by the reductive elimination at 25°C. The formation of the heterocycle was monitored by ^{1}H NMR spectral analysis at various temperatures (-10°C, 0°C and 25°C) in acetone-d_6. At both -10°C and 0°C,

there was no observable shift in the spectral data after 1 hour. However, after 20 minutes at 25°C, we observed a gradual change in signals in the NMR spectra, which was complete after 60 minutes. The signal shift suggested the presence of a new species in our reaction solution.

In the ^{1}H NMR data collected during the monitoring experiment, we observed the disappearance of the signals at δ 6.57 ppm (dt, 2H) and δ 5.78 ppm (d, 1H) as well as a shift in aromatic region (δ7.0 – 9.0 ppm). We also observed the formation of the signals at δ 5.70 ppm (s, 1H) and δ 5.30-5.46 ppm (dd, 2H). After the monitoring experiments, we isolated the final organic compound by flash column chromatography and collected the ^{1}H, ^{13}C and 2D NMR spectral data.

Unfortunately, we can only run the reactions on a small scale (0.05mmol to 0.1mmol) due to the technical difficulties of keeping the reaction solution cool at -10°C. Therefore, we had to run the reaction sequence (Scheme 4.16 on page 119) multiple times and the organic phases had to combined from several runs. These organic phases were then taken for a final purification by chromographic separation on a silica column eluting with a 1:50 EA:Hex eluent system to collect the final organic product as a clear oil.

In the ^{1}H NMR data for the final organic product, the aryl proton (#) signal was observed at δ 8.23 ppm as a singlet, the –CH (*) signal was observed at δ 5.70 ppm as a singlet and the $–CH_2$ (%) was observed at δ 5.30-5.46 ppm as a doublet of doublet. The aryl proton and –CH signals shifted upfield while the $–CH_2$ signal shifted downfield.

Two possible heterocycles can be generated from the reductive elimination of Pd^{IV} complex (**9**) in solution. One heterocycle features two new $C(sp^2)$-$C(sp^3)$ bonds (**10**) and one heterocycle features a new $C(sp^3)$-$C(sp^3)$ and $C(sp^2)$-$C(sp^2)$ bond (**10.2**) (Figure 4.17).

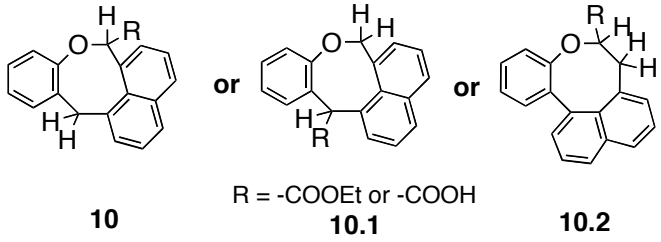


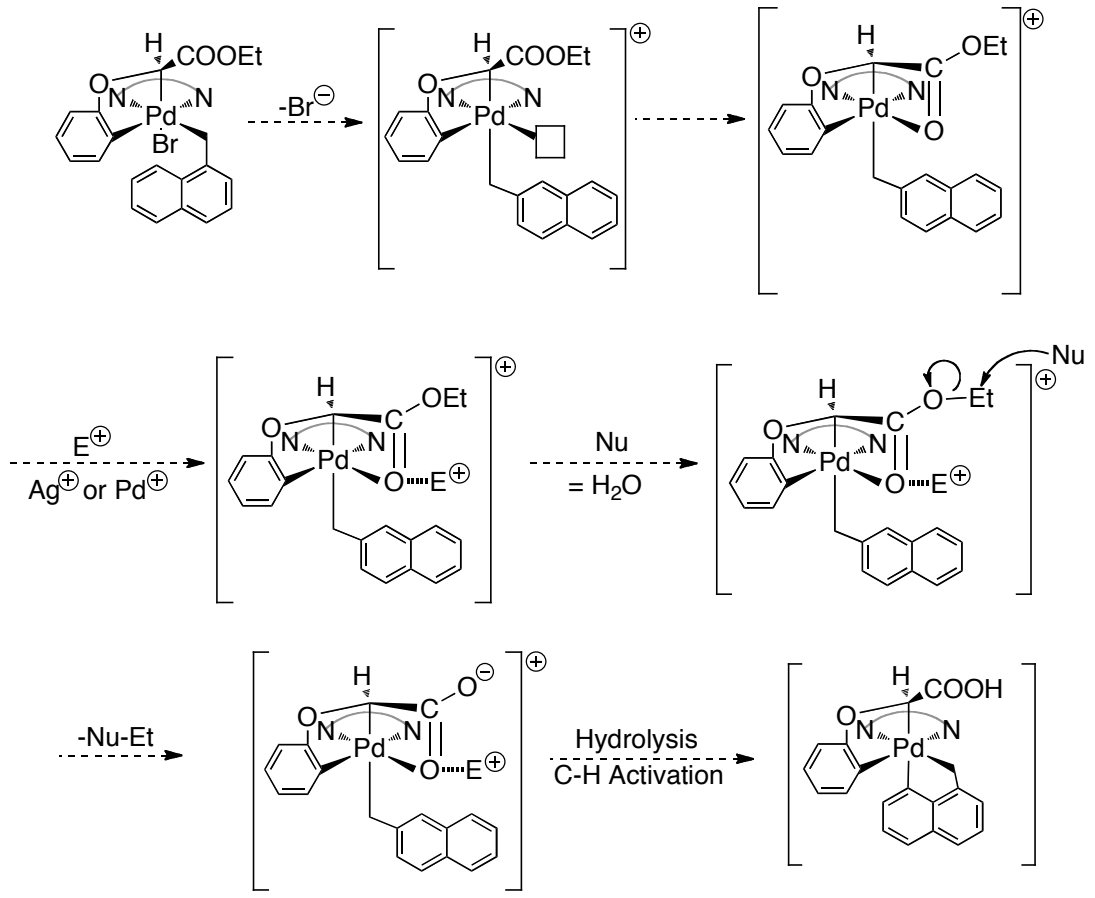
Figure 4.17: Possible heterocycles generated during the reductive elimination reaction

Using the ^1H NMR data, we can initially eliminate the structure featuring the newly coupled $C(sp^3)$-$C(sp^3)$ bond (**10.2**) as in this structure the C-H signal is predicted to be a doublet. However, in our ^1H NMR data we observe the C-H signal as a singlet at δ 5.70 ppm, suggesting that the $C(sp^3)$-$C(sp^3)$ bond (**10.2**) was not formed during the reductive elimination bond-coupling process. This is not surprising as the coupling of a $C(sp^3)$-$C(sp^3)$ bond is reported to be extremely difficult and unlikely to occur in our system. In fact, in similar systems, it has been reported that a coupled $C(sp^2)$-$C(sp^3)$ bond is observed rather than the predicted $C(sp^3)$-$C(sp^3)$ bond.

Next, we had to complete a full structure assignment of our collected heterocycle without making any assumptions about the "expected" pathways for the bond-formation. This lead us to proposed a "theoretically possible" heterocycle featuring two new $C(sp^2)$-$C(sp^3)$ bonds (**10.1**) (Figure 4.17). The two remaining structures (**10, 10.1**) then had to be analyzed by ^{13}C and 2D NMR techniques (DEPT, COSY, HSQC, HMBC) as the ^1H NMR data collected could be applied to either structure.

By using ^{13}C, DEPT, COSY and HSQC spectral analyses, we were able to determine that the R group was a carboxylic acid, not our ethyl ester group. In the ^{1}H NMR data, we observe a signal at δ 8.50 ppm (broad singlet, 1H) that is not observed in the COSY spectra, which indicates it does not correlate with any other proton in our product. In the ^{13}C NMR data, we observe a signal at δ 196.19 ppm (s). In the HSQC data, neither signal (8.50 ppm or 196.19 ppm) is observed, which suggests that neither signal correlates with any other proton or carbon atom in our product and that a carboxylic acid group is present in our product.

The carboxylic acid group was most likely generated from the ester hydrolysis after the silver salt addition (Scheme 4.22). In this reaction, after the bromide removal to open a coordination site, the ester can sit in the open coordination site. An additional electrophile (such as the free silver cation or Pd^{IV} cation) can coordinate to the ester group, which would activate the carbonyl towards nucleophilic substitution with water, which is introduced from the silver salt addition. The nucleophilic substitution reaction would then remove the ethyl group, leaving a carboxylate available for hydrolysis. Subsequent C-H activation would yield the Pd^{IV} complex containing the carboxylic acid.



Scheme 4.22: Possible ester hydrolysis to yield a carboxylic acid

In the HMBC data, we observe a correlation between the $-CH_2$ (%) signal from the oxidant at δ 5.30-5.46 ppm and the carbon signal (assigned to a carbon on the naphthyl ring) at δ 128.23 ppm. This correlation can be observed in heterocycle **10** but not in heterocycle **10.1** (Figure 4.18). This suggests that heterocycle **10** is the desired organic product generated in our reaction.

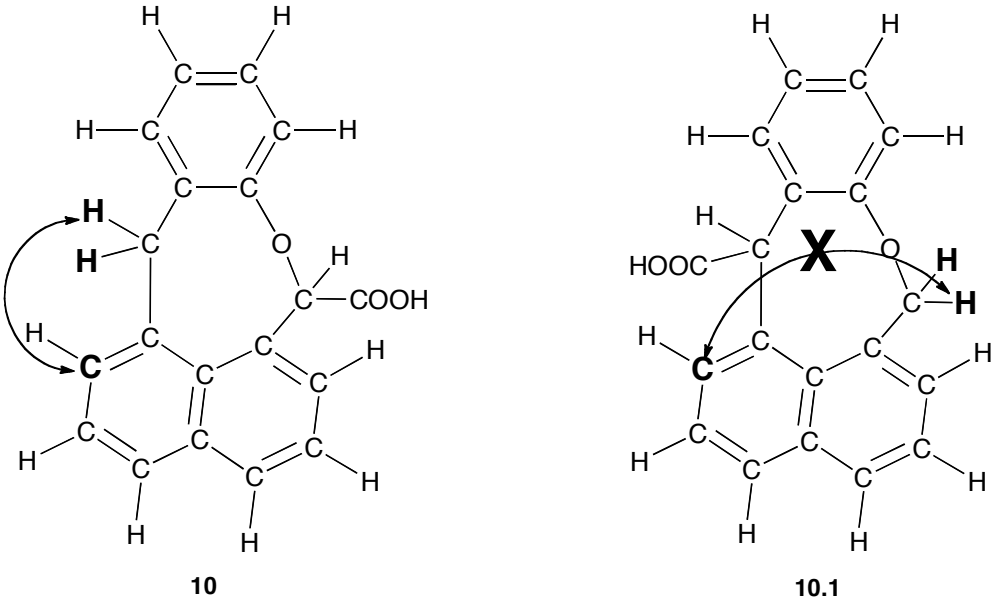


Figure 4.18: ^{1}H and ^{13}C correlation to confirm the presence of heterocycle **10**

4.10: Conclusion and Future Plans

While we have established the reaction conditions to generate two new Pd^{IV} complexes (**8a, 9**) that produced a heterocycle (**10**) through intramolecular C-H activation on the 1-(bromomethyl)naphthalene (**5**) oxidant, in the future we envision focusing on achieving Pd^{IV}-mediated C-H activation at an unactivated $C(sp^3)$-H center on an organic oxidant. Reductive elimination would yield a heterocycle featuring newly coupled $C(sp^3)$-$C(sp^3)$ bonds.

To date, we have used the model system in the presence of 3,3-dimethylallyl bromide (**6**) and 2-(bromomethyl)-1,3-dimethylbenzene (**7b**) oxidants in an attempt to generate two new Pd^{IV} complexes (**8b** and **8c**). However, neither oxidant has successfully produced a new Pd^{IV} complex in solution and further exploration into the reaction conditions is needed. We will continue to

expand towards using other organic oxidants that feature unactivated C(sp^3)-H centers available for Pd^{IV}-mediated C-H activation.

Another interesting experimental avenue we hope to explore is to expand the scope of conditions for the reductive elimination from complex **9** aiming to see whether the regiochemistry of the reductive elimination may be changed due to the change of the stereochemistry of the original Pd^{IV} complex (**9**).

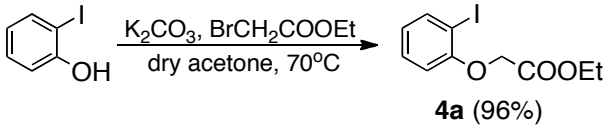
4.11: Chapter Four Experimental

General Procedures

NMR spectra at 25°C were obtained on a Bruker DRX-400 (400 MHz ^{1}H) and NMR spectra at -10°C were obtained on a Bruker DRX-500 (500 MHz for ^{1}H) in the solvent indicated. ^{1}H NMR chemical shifts are reported in parts per million (ppm) with the residual solvent peak (for acetone-d_6: 2.05 ppm; for $CDCl_3$: 7.26 ppm) used as an internal reference. ^{13}C NMR spectra were obtained on an Avance AV-III 500 and the chemical shifts are reported in parts per million (ppm) with the residual solvent peak (for acetone-d_6: 206.26 ppm; for $CDCl_3$: 77.16 ppm) used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublet (dd), doublet of triplet (dt) and doublet of multiplet (dm). Melting points are uncorrected and were taken in open capillary tubes.

Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Benzene and dichloromethane (DCM) were kept over 3Å (8-12 mesh) molecular sieves under an atmosphere of dry argon. Acetone was purified by stirring with dry potassium carbonate (K_2CO_3) and kept

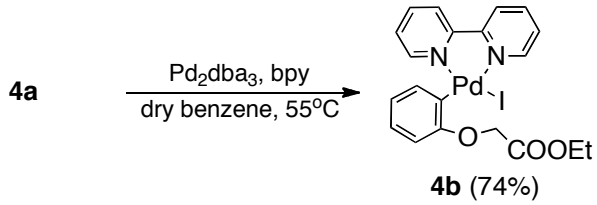
over K_2CO_3; all other solvents were used as received. NMR solvents were obtained from Cambridge Isotopes and stored at the appropriate temperatures (acetone-d_6 at 25°C; $CDCl_3$ at 0°C). Unless otherwise specified, all reactions were carried out under an atmosphere of dry argon in oven-dried (at least 6 h at 140°C) glassware. Unless otherwise specified, all materials were used as received from commercial suppliers.



4a (96%)

Synthesis of 2-[(ethoxycarbonyl)methylene]-oxy-1-iodobenzene (**4a**)[2]: Under the atmosphere of Argon, iodophenol (4.0014 g, 18.1874 mmol, 1.0 eq) and potassium carbonate (K_2CO_3; 12.56 g, 90.9370 mmol, 5.0 eq) were dissolved in dry acetone (50 mL) at 25°C. Ethylbromoacetate (5.1 mL, 45.9916 mmol, 2.5 eq) was added dropwise to the suspension at 25°C and the resulting reaction mixture was warmed to 70°C and refluxed overnight. The reaction mixture was cooled to 25°C, filtered over a plug of Celite and the solvent was removed under reduced pressure to yield a yellow-orange oil. The resulting oil was purified by silica column (1:20 Et_2O:Hex) and dried under vacuum to collect **4a** as a clear oil. (5.3600 g, 96%)

Analytical Data: R_f = 0.18 (Et_2O:Hex 1:20). ^1H NMR ($CDCl_3$): δ 7.72 (dd, J = 8 Hz, 4 Hz, 1H), 7.19 (dt, J = 8 Hz, 1 H), 6.64-6.69 (m, 2H), 4.60 (s, 2H), 4.19 (q, J = 8 Hz, 2H), 1.21 (t, J = 8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 168.32 (s), 156.70 (s), 139.81 (s), 129.45 (s), 123.59 (s), 112.43 (s), 86.52 (s), 66.40 (s), 61.49 (s), 14.21 (s).

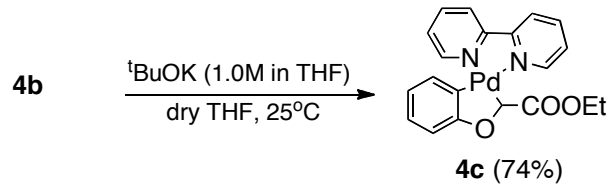


4b (74%)

Synthesis of (bpy)Pd($C_6H_4OCH_2CO_2CH_2CH_3$)(I) (**4b**)[2]: Under the atmosphere of Argon, the tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3; 0.9174 g, 1.002 mmol, 1.0 eq) and 2 2'-bipyridine (bpy; 0.0.6273 g, 4.016 mmol, 2.0 eq) were dissolved in dry C_6H_6 (30 mL) at 25°C and the reaction mixture was stirred for 10 min. In a separate flask, under the atmosphere of Argon, 2-{[(ethoxycarbonyl)methylene]-oxy}-1-iodobenzene **4a** (0.6142 g, 2.006 mmol, 1.0 eq) was dissolved in dry C_6H_6 (3 mL) at 25°C and the reaction solution then added to the Palladium reaction mixture at 25°C. The resulting reaction mixture was warmed to 60°C and refluxed for 1.6 h. After TLC analysis indicated the starting material was consumed, the dark reaction mixture was filtered over a Celite plug and the solvent was removed under reduced pressure to yield a yellow oil. The resulting oil was then deposited on Celite to afford a solid, which was placed on a bed of silica over a 150 mL-fritted funnel. The solid was then flushed with 1:5 EtOAc:Hex and 1:3 EtOAc:Hex to removed excess dibenzylideneacetone (dba). The remaining solid was then flushed with 2:1 EtOAc:Hex and EtOAc to collect a solution and the solvent was removed under reduced pressure to collect a yellow solid. The resulting solid was then triturated with Et_2O at 0°C for 1 h to afford a suspension that was filtered and dried under vacuum to collect **4b** as a yellow powder (0.8430 g, 74%)

Analytical Data: mp = 190-192 °C (decomposed) R_f = 0.48 (EtOAc:Hex 1:2). ^{1}H NMR ($CDCl_3$): δ 9.67 (d, *J* = 4 Hz, 1H), 8.07 (t, *J* = 8 Hz, 2H), 7.94-8.02 (m, 2H), 7.81 (d, *J* = 8 Hz, 2H), 7.47-7.52 (m, 1H), 7.34 (dt, *J* = 8 Hz, 4 Hz 1H), 6.96 (dt, *J* = 8 Hz, 4 Hz, 1H), 6.80 (dt, *J* = 8 Hz, 4

Hz, 1H), 6.3 (dd, J = 8 Hz, 1H), 4.91 (d, J = 16 Hz, 1H), 4.70 (d, J = 16 Hz, 1 H), 4.06 (m, 2H), 1.21 (t, J = 8Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 170.49 (s), 160.23 (s), 155.75 (s), 154.21 (s), 153.32 (s), 151.34 (s), 139.02 (s), 138.71 (s), 138.55 (s), 132.19 (s), 126.80 (s), 126.66 (s), 124.69 (s), 121.90 (s), 121.59 (s), 114.23 (s), 67.11 (s), 60.82 (s), 14.35 (s).

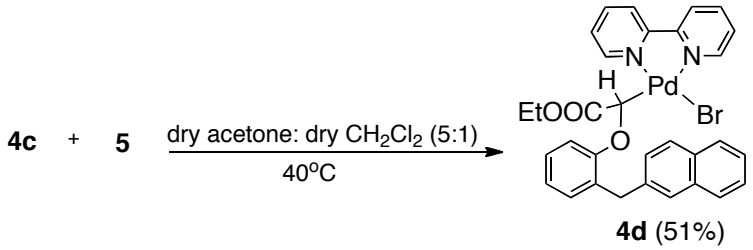


4c (74%)

Synthesis of (bpy)(Pd)($C_6H_4OCHCO_2CH_2CH_3$) **(4c)**[2]: Under the atmosphere of Argon, palladium complex **4b** (0.4010 g, 0.7051 mmol, 1.0 eq) was dissolved in dry THF (15 mL) at 25°C. The potassium tert-butoxide solution (t-BuOK; 1.0 M in THF, 0.85 mL, 0.8500 mmol, 1.2 eq) was added dropwise at 25°C and the reaction mixture was stirred for 30 min at 25°C. After TLC analysis indicated the starting material was consumed, the reaction mixture was filtered over a Celite plug and solvent was removed under reduced pressure to yield an orange oil. The resulting oil was dissolved in CH_2Cl_2 (5 mL), filtered over an alumina plug and the solvent was removed under reduced pressure to yield an orange oil. The resulting oil was then triturated with Et_2O at 0°C for 1 h to afford a suspension that was filtered and dried under vacuum to collect **4c** as a neon yellow solid (0.7051 g, 74%).

Analytical data: mp = 192-194 °C (decomposed) R_f = 0.48 (EtOAc:CH_2Cl_2 2:1). ^{1}H NMR ($CDCl_3$): δ 9.38 (d, J = 4 Hz, 1H), 9.18 (d, J = 4 Hz, 1H), 8.07 (t, J =8 Hz, 2H), 7.96-8.03 (m, 2H), 7.58 (t, J = 4 Hz, 1H), 7.54 (t, J = 4 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 7.02 (t, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.74 (t, J = 8 Hz, 1H), 6.30 (s, 1H), 4.06-4.14 (m, 2H), 1.11 (t, J = 8 Hz,

3H). ^{13}C NMR ($CDCl_3$): δ 178.31 (s), 174.64 (s), 155.59 (s), 154.63 (s), 152.65 (s), 151.12 (s), 138.74 (s), 138.47 (s), 133.82 (s), 129.84 (s), 126.17 (s), 126.05 (s), 122.14 (s), 121.49 (s), 118.38 (s), 108.70 (s), 88.07 (s), 59.80 (s), 14.41 (s).

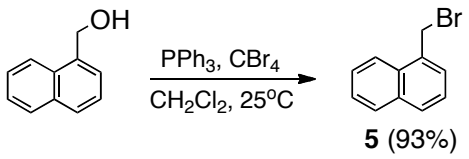


4d (51%)

Synthesis of (bpy)Pd(CH{$CO_2CH_2CH_3$}$OC_6H_4CH_2C_{10}H_7$)(Br) (**4d**)[2]: Under the atmosphere of Argon, pallada(II)cycle **4c** (0.2173 g, 0.4930mmol, 1.0 eq) and 1-(bromomethyl)naphthalene **5** (0.2183 g, 0.9873 mmol, 2.0 eq) were dissolved in 5:1 dry acetone/dry CH_2Cl_2 (12 mL) solution at 25°C and stirred for 1.3 h. The reaction mixture was then warmed to 40°C and stirred overnight. The solvent was removed from the resulting reaction mixture under reduced pressure to yield a yellow solid. The resulting solid was then washed with Et_2O and dried under vacuum to collect **4d** as a fluffy light yellow solid (0.1662 g, 51%).

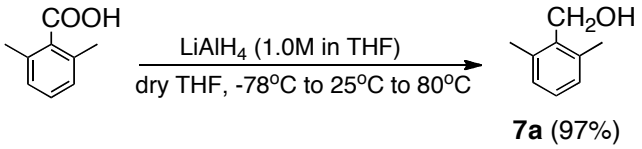
Analytical Data: mp = 195-197 °C (decomposed) R_f = 0.63 (EtOAc:CH_2Cl_2 2:1). ^{1}H NMR ($CDCl_3$): δ 9.66 (dd, *J* = 4 Hz, 1H), 9.54 (dd, *J* = 4 Hz, 1H), 7.97 (d, *J* = 8 Hz, 1H), 7.93 (d, *J* = 8 Hz, 2H), 7.86 (d, *J* = 8 Hz, 1H), 7.78 (d, *J* = 8 Hz, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.65 (dt, *J* = 8 Hz, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.42-7.50 (m, 2H), 7.36 (dt, *J* = 8 Hz, 1H), 7.18 (t, *J* = 8 Hz, 1H), 7.00 (d, *J* = 8 Hz, 1H), 6.85 (d, *J* = 4 Hz, 2H), 6.80 (s, 1H), 6.73 (dt, *J* = 8 Hz, 1H), 4.57 (d, *J* = 20 Hz, 1H), 4.42 (d, *J* = 20 Hz, 1H) 4.11-4.32 (dm, *J* = 56 Hz, 2H), 1.29 (t, *J* = 8 Hz, 3H). ^{13}C NMR (acetone-d_6): δ 174.82 (s), 156.78 (s), 156.63 (s), 155.14 (s), 153.90 (s), 152.66 (s), 151.80 (s), 141.64 (s), 140.71 (s), 140.31 (s), 137.71 (s), 134.86 (s), 133.15 (s), 130.93 (s), 129.67 (s),

129.42 (s), 128.49 (s), 128.25 (s), 127.72 (s), 127.57 (s), 127.48 (s), 126.78 (s), 126.65 (s), 126.45 (s), 125.14 (s), 124.51 (s), 123.43 (s), 121.63 (s), 115.55 (s), 60.28 (s), 58.93 (s), 33.49 (s), 14.82 (s).



Synthesis of 1-(bromomethyl)naphthalene (**5**)[4]: Under the atmosphere of Argon, 1-naphthalene-methanol (1.003 g, 6.3230 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (25 mL) at 25°C. Carbon tetrabromide (2.5167 g, 7.5884 mmol, 1.2 eq) was then added to the reaction solution at 25°C and the resulting reaction mixture was stirred for 5 min. Triphenylphosphine (1.9907 g, 7.5900 mmol, 1.2 eq) was then added slowly to the reaction mixture at 25°C and stirred for 25 min. Et_2O was then added to precipitate any triphenylphosphine derivatives and the resulting suspension was filtered by vacuum to collect a clear solution. The solvent was removed from the resulting solution under reduced pressure to yield an oil. The oil was then purified by silica column (1:5 EtOAc:Hex) and dried under vacuum to collect **5** as a white solid (1.3009 g, 93%).

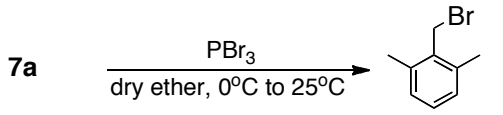
Analytical Data: mp = 48-50°C R_f = 0.85 (EtOAc:Hex 1:5). ^{1}H NMR ($CDCl_3$): δ 8.20 (d, J = 8 Hz, 1H), 7.93 (d, J = 8 Hz 1H), 7.88 (d, J = 8 Hz, 1H), 7.66 (dt, J = 8 Hz, J = 1.3 Hz, 1H), 7.55-7.59 (m, 2 H), 7.44 (t, J = 8 Hz, 1H), 5.00 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 134.03 (s), 133.26 (s), 131.05 (s), 129.82 (s), 128.86 (s), 127.77 (s), 126.62 (s), 126.25 (s), 125.39 (s), 123.73 (s), 31.74 (s).



7a (97%)

Synthesis of (2,6-dimethylphenyl)methanol (**7a**)[5]: Under the atmosphere of Argon, 2,6-dimethylbenzoic acid (0.4997 g, 3.3276 mmol, 1.0 eq) was dissolved in dry THF (24.0 mL) at 25°C and the resulting reaction solution was cooled to -78°C. The lithium aluminum hydride solution ($LiAlH_4$, 1.0 M in THF, 6.7 mL, 6.7000 mmol, 2.0 eq) was then added dropwise at -78°C and the resulting reaction mixture was stirred for 2.0 h at -78°C. The reaction mixture was then warmed to 25°C and stirred for 1.0 h then warmed to 80°C and stirred overnight. The reaction mixture was then quenched with a 10% HCl aqueous solution to remove excess $LiAlH_4$. The organic layer was then extracted with Et_2O, washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure to collect **7a** as a white solid (0.4417 g, 97%).

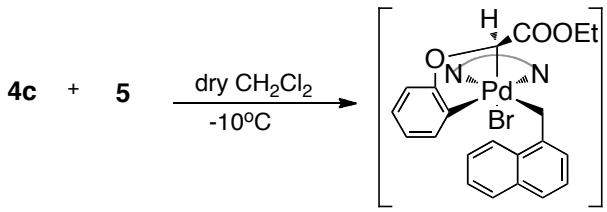
Analytical Data: mp = 74-76 °C R_f = 0.18 (EtOAc:Hex 1:9). ^{1}H NMR ($CDCl_3$): δ 7.12 (t, J = 8 Hz, 1H), 7.05 (d, J = 8 Hz, 2H), 4.75 (s, 2H), 2.44 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 137.51 (s), 136.67 (s), 128.56 (s), 128.24 (s), 59.57 (s), 29.85 (s), 19.59 (s).



7b (91%)

Synthesis of 2-(bromomethyl)-1,3-dimethylbenzene (**7b**)[6]: Under the atmosphere of Argon, (2,6-dimethylphenyl)methanol **7a** (0.8186 g, 6.0107 mmol, 1.0 eq) was dissolved in dry Et_2O (25 mL) at 25°C and the reaction solution was cooled to 0°C. Phosphine tribromide (PBr_3; 0.63 mL, 6.7026 mmol, 1.1 eq) was then added dropwise and the resulting reaction mixture was stirred at 0°C for 2 h. The reaction mixture was then warmed to 25°C and stirred overnight. The reaction mixture was then quenched with water to remove any excess phosphorous derivatives. The organic layer was extracted with Et_2O, washed with brine, dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure to collect **7b** as a light yellow solid (1.0792 g, 91%).

Analytical data: mp = 35-37 °C R_f = 0.94 (EtOAc:Hex 1:9). ^{1}H NMR ($CDCl_3$): δ 7.12 (t, J = 8 Hz, 1H), 7.04 (d, J = 8 Hz, 2 H), 4.58 (s, 2H), 2.43 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 137.62 (s), 134.17 (s), 128.75 (s), 128.61 (s), 29.48 (s), 19.39 (s).



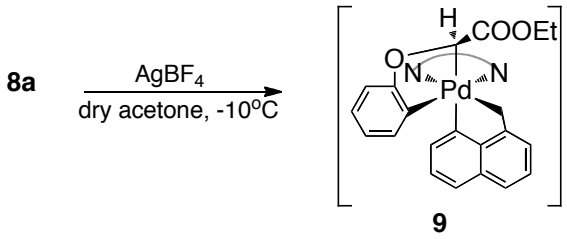
8a

Procedure for the in situ formation of (bpy)Pd(CH{$CO_2CH_2CH_3$}$OC_6H_4CH_2C_{10}H_7$)(Br) complex (**8a**): Under the atmosphere of Argon, pallada(II)cycle **4c** (0.05 mmol, 1.0 eq) and 1-(bromomethyl)naphthalene **5** (4.0 eq) were cooled to -10°C, dissolved in dry CH_2Cl_2 and the resulting reaction mixture was mixed overnight. The resulting mixture was then recooled to -

10°C and washed with pre-cooled C_5H_{12} (5 x 2.0 mL) to yield a solid and to remove any excess solvent or oxidant. The resulting solid was then washed with pre-cooled Et_2O (4 x 2.0 mL) to remove any excess oxidant and the solid **8a** was dried under vacuum at -10°C.

To collect the NMR sample, the solid Pd^{IV} complex **8a** was dissolved in deuterated NMR solvent ($CDCl_3$, 0.5 mL) and an aliquot (0.3 mL) was transferred into a pre-cooled NMR tube. The sample was then diluted with the deuterated NMR solvent ($CDCl_3$, 0.1-0.2 mL) and stored at -20°C in a freezer until the low temperature NMR was taken. The product was taken for ^1H NMR analysis at -10°C.

Analytical data: ^1H NMR ($CDCl_3$): δ 9.35 (d, *J* = 5 Hz, 1H), 8.15 (d, *J* =10 Hz, 1H), 8.10 (d, *J* =10 Hz, 2H), 8.06 (d, *J* =10 Hz, 1H), 8.02 (d, *J* =10 Hz, 1H), 7.90 (d, *J* =10 Hz, 2H), 7.86 (d, *J* =5 Hz, 2 H), 7.63 (t, *J* =10 Hz, 1 H), 7.56 (d, *J* =5 Hz, 2H), 7.42 (t, *J* =10 Hz, 1H), 7.33 (t, *J* =10 Hz, 1H), 7.24 (d, *J* =10 Hz, 1H), 7.00 (q, *J* =10 Hz, 1H), 6.80 (d, *J* =5 Hz, 1 H), 6.74 (q, *J* =5 Hz, 1H) 6.23 (s, 1H), 4.39-4.60 (dd, *J* =65 Hz, 15Hz, 2H), 4.26-4.34 (m 2H), 1.29 (t *J* =10 Hz, 3H).



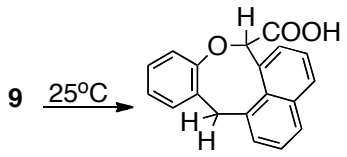
9

Synthesis for (bpy)Pd(CH{$CO_2CH_2CH_3$}$OC_6H_4CH_2C_{10}H_6$) complex (**9**): Open to air, silver tetrafluoroborate ($AgBF_4$; 0.5 mmol, 1.0 eq) was added to the palladium(IV) complex **8a** (0.5

mmol, 1.0 eq) and dissolved in dry acetone (1.0-4.0 mL) at -10°C. Under the atmosphere of Argon, the reaction suspension was mixed for 1 h. The resulting suspension was then filtered over a Celite plug, eluted with dry acetone and solvent was carefully removed under reduced pressure to collect a solid. The solid was cooled to -10°C and triturated with Et_2O (2.0-4.0 mL) for 1 h. The resulting suspension was decanted to remove excess solution and the solid was dried under vacuum at -10°C to collect **9** as a yellow powder.

To collect the NMR sample, the solid Pd^{IV} complex **9** was dissolved in the deuterated NMR solvent (acetone-d_6, 0.5 mL) and an aliquot (0.3 mL) was transferred into a pre-cooled NMR tube. The sample was then diluted with NMR solvent (acetone-d_6, 0.1-0.2 mL) and stored at -20°C in a freezer until the low temperature NMR was taken. The product was detected by ^{1}H NMR analysis at -10°C.

Analytical data: ^{1}H NMR (acetone-d_6): δ 8.99 (s, 1H), 8.55 (d, J = 5 Hz, 2H), 8.45 (d, J = 5 Hz, 2H), 8.26 (t, J = 5 Hz, 2H), 8.08 (t, J = 5 Hz, 3H), 7.78 (d, J = 5 Hz, 2H), 7.78 (d, J = 5 Hz, 2H), 7.64 (d, J = 5 Hz, 1H), 7.52 (t, J = 10 Hz, 2H), 7.32 (d, J = 10 Hz, 2H), 6.57 (dt, J = 35 Hz, 10 Hz, 2H), 5.78 (d, J = 10 Hz, 1H), 5.09 (s, 1H), 4.22-4.47 (dm, J = 125 Hz, 2H), 1.21 (m, 3H).



10

Synthesis for heterocycle $C_{19}H_{14}O_3$ (**10**): The palladium(IV) complex **9** was warmed to 25°C in solution (dry acetone or acetone-d_6) overnight. The resulting dark solution was filtered over a

plug of Celite, eluted with acetone and solvent was removed under reduced pressure to collect a dark oil. The resulting oil was purified by silica column (1:5 EtOAc:Hex) and dried by vacuum to collect **10** as a clear oil (total collected: 0.0041 g).

Analytical data: R_f = 0.51 (EtOAc:Hex 1:5). ^{1}H NMR (acetone-d_6): δ 8.50 (bs, 1H), 8.23 (d, J = 10 Hz, 1H), 7.94 (t, J = 10 Hz, 1H), 7.92 (t, J = 10 Hz, 1H), 7.78 (dt, J = 10 Hz, 5 Hz, 1H), 7.65 (d, J = 10 Hz, 2H), 7.57 (dt, J = 10 Hz, 5 Hz, 1H), 7.50 (dt, J = 10 Hz, 5 Hz, 1H), 7.25 (ds, J = 20 Hz, 1H), 7.19 (t, J = 10 Hz, 1H), 5.70 (s, 1H), 5.30-5.46 (dd, J = 65 Hz, 15 Hz, 2H). ^{13}C NMR (acetone-d_6): δ 196.19 (s), 172.38 (s), 139.92 (s), 134.78 (s), 133.16 (s), 132.70 (s), 128.23 (s), 127.27 (s), 126.13 (s), 125.35 (s), 125.22 (s), 125.03 (s), 124.05 (s), 122.03 (s), 120.75 (s), 113.36 (s), 101.74 (s), 70.56 (s).

^{1}H and COSY NMR data for Heterocycle 10:

^{1}H Signals (ppm)	**H-ID**	**COSY Data (ppm)**	**^{1}H-^{1}H Correlation ID**
8.50 (bs, 1H)	H-carboxylic acid	None	Carboxylic acid proton
8.23 (ds, 1H)	H_A	8.24: 7.64, 7.59, 7.51	H_A – $H_{D,D'}$; H_E; H_F
7.94 (t, 1H)	H_B	7.96: 7.55	H_B – H_E
7.92 (t, 1H)	$H_{B'}$	7.94: 7.48	$H_{B'}$ – H_F
7.78 (dt, 1H)	H_C	7.80: 7.26	H_C – H_G
7.65 (ds, 2H)	$H_{D, D'}$	7.66: 7.50, 7.20	$H_{D,D'}$– H_F
7.57 (dt, 1H)	H_E	7.55: 8.24, 7.95	HE – H_A; H_B or $H_{B'}$
7.50 (dt, 1H)	H_F	7.50: 7.95, 7.66	H_F – H_B or $H_{B'}$; $H_{D,D'}$
7.25 (ds, 1H)	H_G	7.26: 7.80	H_G – H_C
7.19 (t, 1H)	H_H	7:20: 7.80, 7.67, 7.65	H_H – H_C; $H_{D,D'}$
5.70 (s, 1H)	H_I	None	CH_2 proton
5.30-5.46 (dd, 2H)	$H_{J,K}$	5.46: 5.30	H_J - H_K

^{13}C, DEPT and HSQC data for Heterocycle 10:

^{13}C Signal (ppm)	DEPT Signal (Type)	C-ID	HSQC Data (ppm)
196.19	None – C	C_A	N/A
172.38	None – C	C_B	N/A
139.92	Yes – CH	C_C	7.78 - H_C
134.78	None – C	C_D	N/A
133.16	None – C	C_E	N/A
132.70	None – C	C_F	N/A
128.23	Yes – CH	C_G	7.94 - H_B
127.27	Yes – CH	C_H	7.65 - H_D
126.13	Yes – CH	C_I	7.57 - H_E
125.35	Yes – CH	C_J	7.94 - $H_{B'}$
125.22	Yes – CH	C_K	7.50 - H_F
125.03	Yes – CH	C_L	7.65 - $H_{D'}$
124.05	Yes – CH	C_M	8.23 - H_A
122.03	Yes – CH	C_N	7.19 - H_H
120.75	No – C	C_O	N/A
113.36	Yes – CH	C_P	7.25 - H_G
101.74	Yes – CH	C_Q	5.70 - H_I
70.56	Yes – CH_2	C_R	5.30-5.46 - $H_{J,K}$

HMBC data for Heterocycle 10:

^{1}H	HMBC Data (ppm)	^{13}C(^{1}H) Correlation ID
H	8.50: None	Carboxylic Acid proton
H_A	8.23: 133.16, 126.14	H_A – C_I (H_E); C_E
$H_{B/B'}$	7.95: 132.70, "125.68", 126.14	H_B – C_F; C_K (H_F); C_I (H_E)
H_C	7.79: *172.38*, 127.27, 125.03 124.05	H_C – *C_B*; C_H (H_D); C_L ($H_{D'}$); C_M (H_A)
$H_{D/D'}$	7.67: 196.19, *172.38*, 139.92, 132.70, **128.33**, 125.03, *70.78*	H_D – C_A; *C_B*; C_C (H_C); C_F; **C_G (H_B)**; C_L (H_D'); *C_R ($H_{J,K}$)*
H_E	7.59: 134.78, 132.70, **128.23**, 124.05	H_E – C_D; C_F; **C_G (H_B)**; C_M (H_A)
H_F	7.51: 133.16, 124.05	H_F – C_E; C_M (H_A)
H_G	7.25: "*171.16*", 122.03, 120.75	H_G – *C_B*; C_N (H_H); C_O
H_H	7.19: "*171.26*", "139.92", 120.75, 113.36	H_H – *C_B*; C_C (H_C); C_O; C_P (H_G)
H_I	5.70: *172.38*, *70.78*	H_I – *C_B*; *C_R ($H_{J,K}$)*
$H_{J,K}$	5.46/5.34: 132.70, **128.23**, 101.74	$H_{J,K}$ – C_F; **C_G (H_B)**; C_Q

Italicized: Initial Markers for Structure Elucidation
Bold: Confirmation of Structure **10** over Structure **10.1**

4.12: Chapter Four Bibliography

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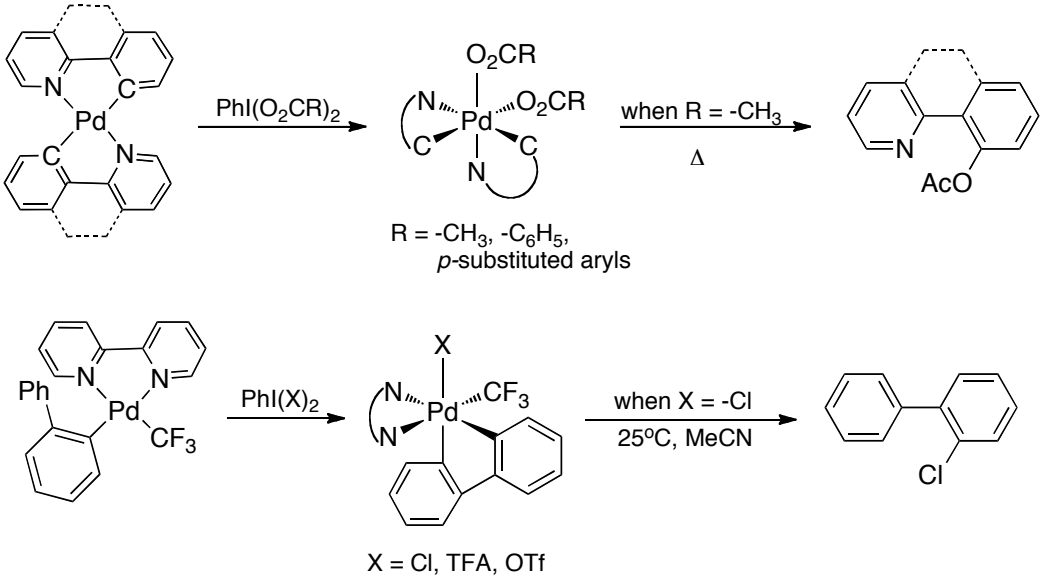
Chapter Five

Auxiliary Ligand Effects in Substitution Reactions of Novel Palladium(IV) Complexes

5.1: Introduction

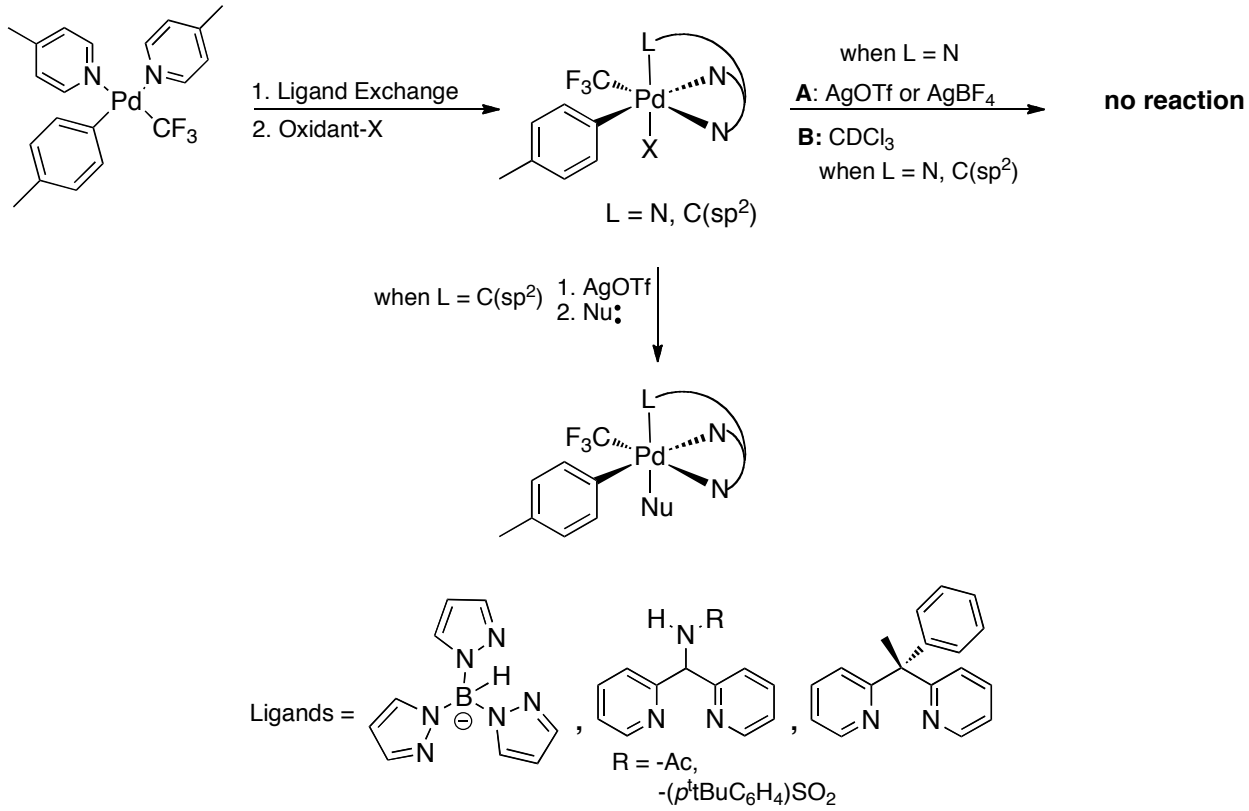
The goal of this project was to construct a Pd^{IV} complex that could be synthesized by the action of inorganic oxidants and used to induce an intermolecular C-H activation and functionalization. Such reactivity of Pd^{IV} complexes could potentially be used for selective intermolecular C-H activation of complex organic compounds.[1-3] Our approach to the construction of such complexes was inspired by reports published by Sanford and co-workers. In these reports, Sanford describes the use of bidentate or tridentate ligands (featuring both Nitrogen- or Carbon-donor atoms) to stabilize the Pd^{IV}-centers generated by the action of inorganic oxidants such as phenyl iodonium salts on Pd^{II} complexes[4-5] (Scheme 5.1).



Scheme 5.1: Previously reported Sanford results[4-5]

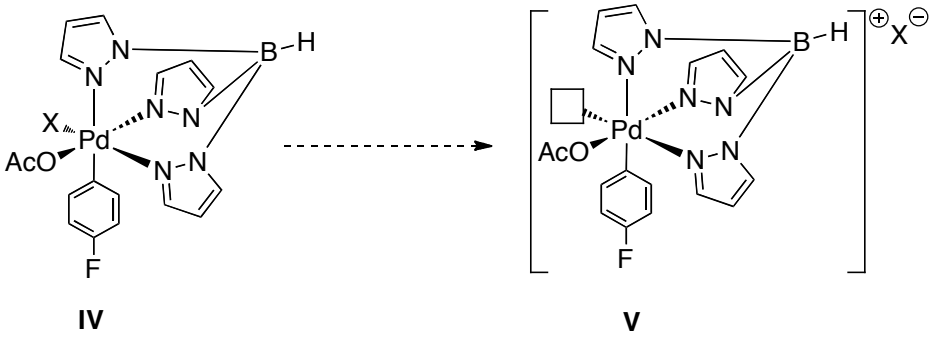
In another report, Sanford concludes that the nature of the ligand bound to the Pd^{IV}-center has an important effect on the reactivity of the Pd^{IV} complex.[6] They report that when a Nitrogen atom is bound to the Pd^{IV}-center, the resulting Pd^{IV} complex is unreactive towards reductive elimination or ligand substitution. However, when a C(sp^2) atom (installed by Pd^{IV}-mediated C-H activation)

is bound to the Pd^{IV}-center, the resulting Pd^{IV} complex underwent various ligand substitution reactions in the presence of strong nucleophiles (Scheme 5.2).



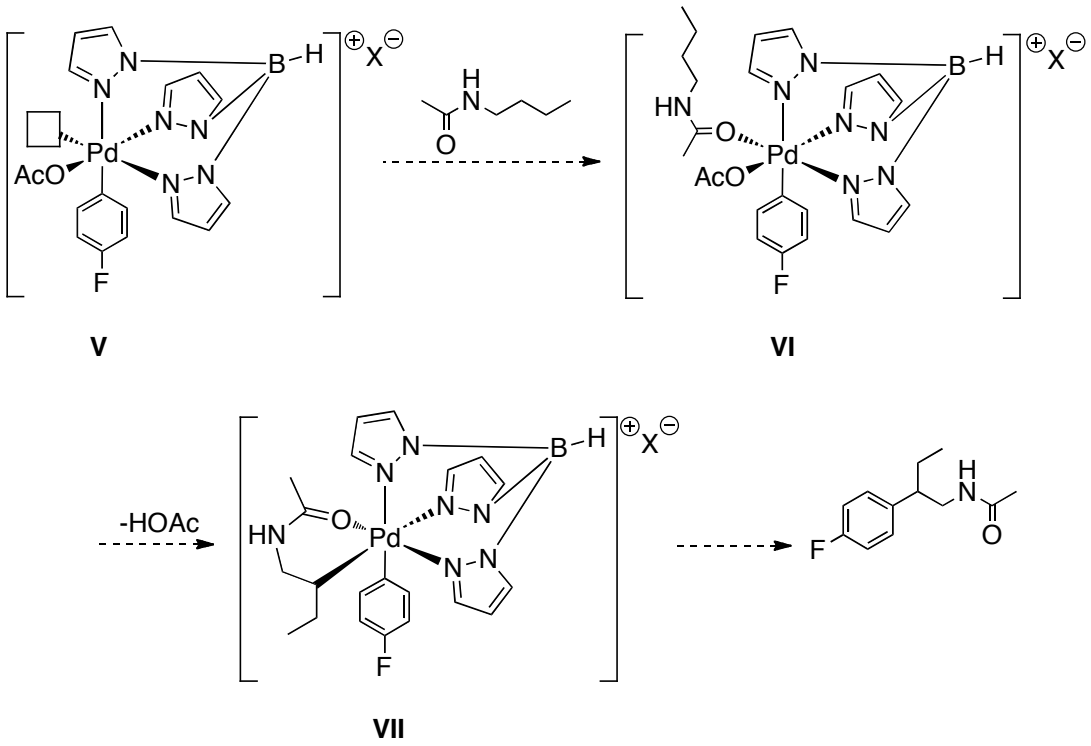
Scheme 5.2: Previously reported Sanford results on ligand effect[6]

For our project, we envisioned using a Pd^{IV} complex that contained the previously used tripodal tris(pyrazolyl)borate (Tp) ligand and a ligand (X) weakly coordinate to the Pd^{IV}-center (**IV**). Dissociation of the weakly coordinated ligand would create a cationic Pd^{IV} complex with an open coordination site (**V**) (Scheme 5.3).



Scheme 5.3: Proposed Palladium(IV) and cationic Palladium(IV) Complexes

The cationic Pd^{IV} complex (**V**) would then be poised to induce a base-assisted C-H activation in an organic substrate, such as an amide. Subsequent reductive elimination would yield a functionalized organic compound featuring a newly formed $C(sp^2)$-$C(sp^3)$ bond (Scheme 5.4).



Scheme 5.4: Proposed base-assisted C-H activation and reductive elimination pathway

To make detection of the possible Pd^{IV} intermediates easier by NMR spectroscopic analysis, we wanted to add a chemical marker on the complex. In this project, we attached an aryl ring containing a fluorine substituent on the Pd^{IV} complex that allowed for monitoring by ^{19}F NMR analysis, which is more sensitive than ^{1}H NMR analysis. We also anticipated that the fluorine-aryl substituent would be present in the final organic fragment, which would then make this Pd^{II}-Pd^{IV} pathway applicable to the synthesis of medicinally useful compounds.[7]

Recently, there has been an increase in the reports on the application of fluorine-containing ligands in Pd^{II}-Pd^{IV} chemistry due to the interest in generating C-F bonds by the reductive elimination.[8-9] In reports featuring Pd^{0}-Pd^{II} catalytic cycles, the authors observed a high stability of the Pd-F bond, which disfavored formation of a C-F bond by reductive elimination.[10-11] For Pd^{II}-Pd^{IV} catalytic cycles, so far only a few reports exist describing the formation of a C-F bond occurs by reductive elimination.[12]

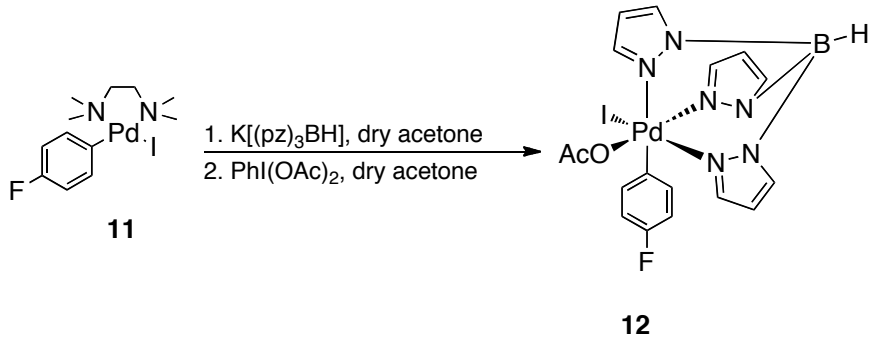
In Pd^{II}-Pd^{IV} catalytic cycles featuring a Pd-CF_3 bond, the authors report that the Pd-CF_3 bonds are also stable and the reductive elimination to generate C-CF_3 bonds remains slow.[13] For many late transition metals, the presence of a M-CF_3 bond can increase the overall stability of the metal complex when compared to complexes with a M-CH_3 bond. This increased stability can aid in the isolation and detection of the reaction intermediates prior to reductive elimination.[14]

To increase the overall stability of the Pd^{IV} complex, we envisioned using the tripodal Tp ligand, which is known to coordinate in a facially selective manner to the Pd center and stabilize octahedral geometry at the Pd^{IV}-center. This helps to prevent the Pd^{IV} complex from

decomposing prior to isolation or detection by spectroscopic analysis. Structurally similar (Tp)Pd^{IV} complexes are known to be very stable, as they can be isolated at 25°C.[6, 15]

5.2: Initial Attempts at Oxidative Addition with Phenyl Iodonium Diacetate

Starting with the previously synthesized Pd^{II} complex (**11**)[13], we attempted a simple ligand exchange to insert the tripodal Tp ligand, which would displace the tmeda from the Pd^{II} complex (**11**). Then a solution of the phenyl iodonium diacetate would be added to complete the in situ oxidation to our desired Pd^{IV} complex (**12**). This complex would then be used for the C-H activation studies. This ligand exchange and in situ oxidation procedure was similar to the procedures reported by Canty[15] and Sanford[4] (Scheme 5.5).



Scheme 5.5: Initial synthesis of proposed Palladium(IV) Complex

To our surprise, the synthesis of the proposed Pd^{IV} complex was more difficult than expected. For the ligand exchange, we followed a procedure that was established for similar Pd^{IV} complexes (**3a-3e**) and was previously discussed in this document (Chapter Three, Section 3.5, Scheme 3.12).

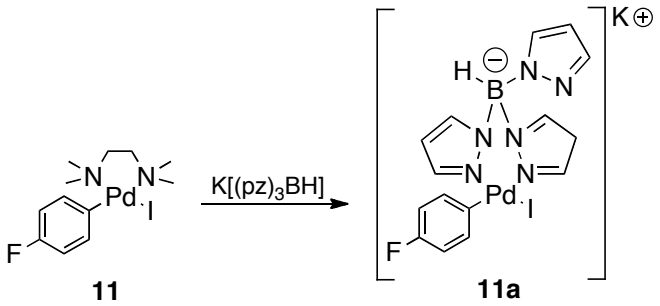
In this procedure, the solid **11** and solid KTp were dissolved in dry acetone and stirred for 1 hour at 0°C. The solution underwent a color change from orange to clear. For the oxidation, the solid phenyl iodonium diacetate was dissolved in dry acetone and the solution added dropwise to the clear solution of **11** and KTp at 25°C. During the in situ oxidation, the solution underwent a color change from clear to a dark orange, which might suggest that a new Pd species is present. A similar color change was seen during the synthesis of the Pd^{IV} complexes (**3a-3e**) previously discussed in this document (Chapter 3, Section 3.5, Scheme 3.12). After mixing for 3.5 hours, a simple work-up consisting of: (i) solvent removal under vacuum to collect an oil; (ii) addition of ether to precipitate a solid; and (iii) gravity filtration to collect the ether solution was preformed. The ether was then removed under reduced pressure to yield a solid, which became a yellow oil upon drying by vacuum. The yellow oil was dissolved in $CDCl_3$ and taken for ^{1}H and ^{19}F NMR spectral analyses. Unfortunately, the spectral data revealed no new signals and we concluded that the yellow oil was the starting Pd^{II} complex (**11**).

Due to the color change after the oxidation, we initially believed that the Pd^{IV} complex was formed in the solution but was decomposing back to starting material prior to isolation. Therefore, we focused on varying the oxidation conditions and work-up procedure. First, we lowered the reaction temperature to 0°C and repeated the reaction and work-up procedures described above. Next, we increased the amount of oxidant used in the reaction to ensure that the phenyl iodonium diacetate oxidant was not decomposing in solution. Finally, we changed to a more intensive work-up that was based on a procedure reported by Canty for the isolation of similar (Tp)Pd^{IV} complexes.

During this work-up, we filtered the orange-colored reaction mixture over Celite and removed the solvent by reduced pressure to collect an oil. The addition of ether to the oil produced a solid, which was filtered to collect the ether solution. The solvent was removed from the filtered solution by reduced pressure to collect a yellow oil. The addition of water and acetone to the oil produced a yellow solid. The solvents were then removed by decantation to collect the solid, which was washed with ether. The solid became a yellow oil upon drying by vacuum. Using these steps, it was believed that the excess tmeda and organic fragments from the oxidants would be removed to leave behind the desired Pd^{IV} complex.

Unfortunately, we were only able to collect a yellow oil after each of these reactions and this oil was determined to be the starting Pd^{II} complex (**11**) by ^{1}H and ^{19}F NMR spectral analyses. Based on these results, we determined that the initial ligand exchange was not occurring under the reaction conditions described above.

In order for ligand exchange to occur, the anionic Tp ligand must displace the neutral tmeda ligand from the Pd^{II} center in the presence of an iodide ligand (Scheme 5.6). However, when examining the proposed Pd^{II} intermediate (**11a**) from this reaction, it can be concluded that the large electron density around the iodide ligand is preventing the exchange of neutral ligand for an anionic ligand. If the anionic Tp ligand were to coordinate to the Pd^{II} center, an unfavorable large negative charge would be placed in the proximity of I^- ligand on the Pd^{II} center. The proposed Pd^{II} intermediate (**11a**) would then be too unstable and the anionic ligand would be displaced by the neutral tmeda ligand, returning the starting Pd^{II} complex (**11**). In order to have a successful ligand exchange, the iodide ligand must be removed prior to tmeda displacement.

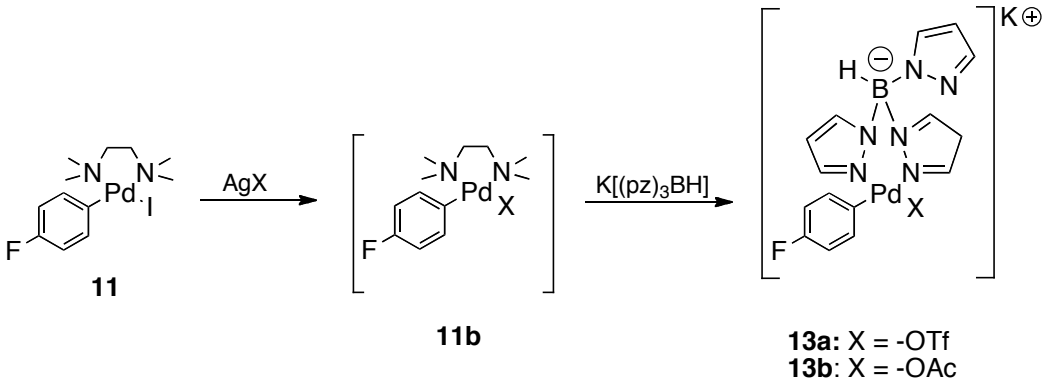


Scheme 5.6: Proposed Palladium(II) Intermediate from Ligand Exchange

5.3: Silver Salt Addition and Ligand Exchange Studies

5.3.1: Iodide Ligand Removal by Silver Triflate Salt

Reasoning that the ligand exchange was being prevented by the iodide ligand, we envisioned replacing the iodide with a weakly coordinating ligand (X) that would either remain attached to the Pd after the subsequent ligand exchange and in situ oxidation, or be replaced by an anionic ligand from the excess oxidant.



Scheme 5.7: Successful ligand exchange

To remove iodide, the solid Pd^{II} complex (**11**) and silver triflate were dissolved in acetone (or acetone-d_6 for initial monitoring experiments) and stirred for 1 hour at 25°C. After stirring, an aliquot (0.1m L) was removed, filtered over Celite (to remove the insoluble silver iodide

generated in the reaction) into an NMR tube, diluted to 0.4 mL and taken for ^{1}H and ^{19}F NMR spectral analyses (Scheme 5.7). The spectroscopic data collected showed a shift in signals in the ^{1}H spectra and new signals in the ^{19}F spectra, suggesting that a new Pd^{II} species (**11b**) may be present (Figure 5.1, 5.2).

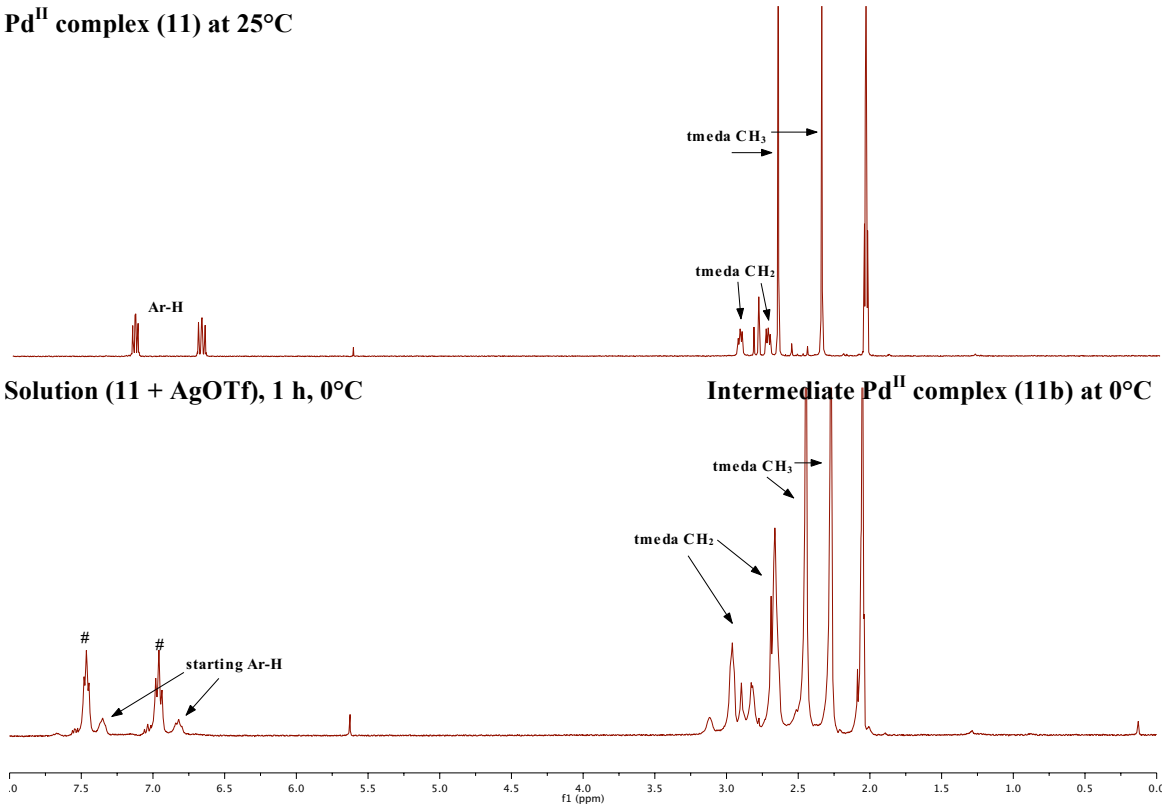


Figure 5.1: ^{1}H NMR (400 MHz, acetone-d_6) spectra for Palladium(II) complexes (**11**) and (**11b**)
(#) – Aryl protons

In the ^{1}H NMR spectral data, (Figure 5.1) we observe a new set of proton signals in the aromatic region (#) at δ 7.46 ppm (t, 2H) and 6.96 (t, 2H) and a broadening of the tmeda signals, which suggests that a new Pd^{II} species (**11b**) has been generated in the reaction solution.

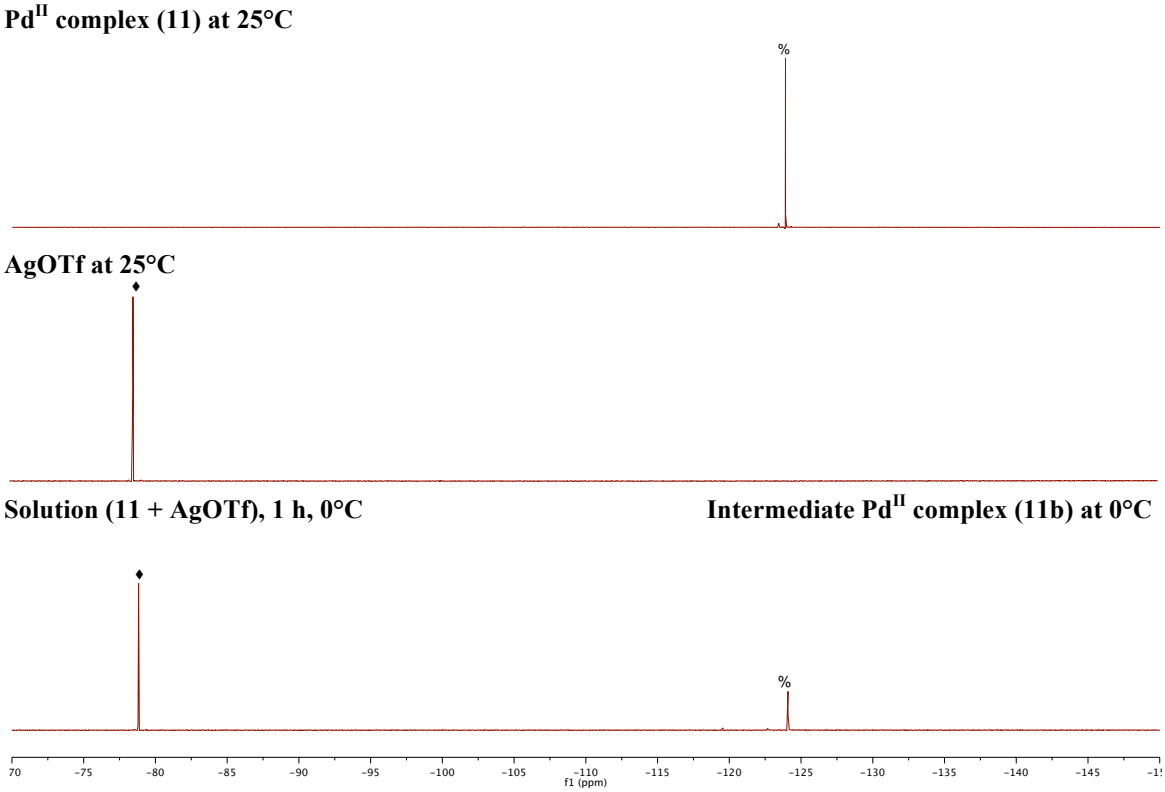


Figure 5.2: ^{19}F NMR (400 MHz, acetone-d_6) spectra for Palladium(II) complexes (**11**), (**11b**) and silver triflate (♦) – Triflate signal (%) – Aryl-F signal

In the ^{19}F NMR spectral data, (Figure 5.2) we observe the presence of the triflate signal (♦) at δ -78.60 ppm (s, 3F) and the aryl-F signal (%) which has shifted from δ -123.90 ppm to -124.08 ppm (s, 1F) in the new Pd^{II} species (**11b**). The presence of the triflate suggests that triflate is either present in the reaction solution or bound to the Pd^{II}-center, creating the new Pd^{II} species. However, due to the lack of the signal shift in the ^{19}F spectral data, we cannot conclusively establish whether our desired Pd^{II} species (**11b**) was generated.

5.3.2: Ligand Exchange with Tp Ligand

Despite this uncertainty, we proceeded with the next step. We repeated the addition of AgOTf by the method described above but after filtration through Celite, the solid KTp was added to the

reaction solution and the mixture was stirred for 1 hour at 0°C, when the reaction solution became clear. An aliquot (0.3 mL) of the clear reaction mixture was transferred to an NMR tube, diluted to 0.4 mL and taken for ^{1}H and ^{19}F NMR spectral analyses. (Scheme 5.7) The NMR data collected showed a shift in signals in both the ^{1}H and ^{19}F spectra, suggesting that ligand exchange did occur to generate a new Pd^{II} species (**13a**) (Figure 5.3, 5.4).

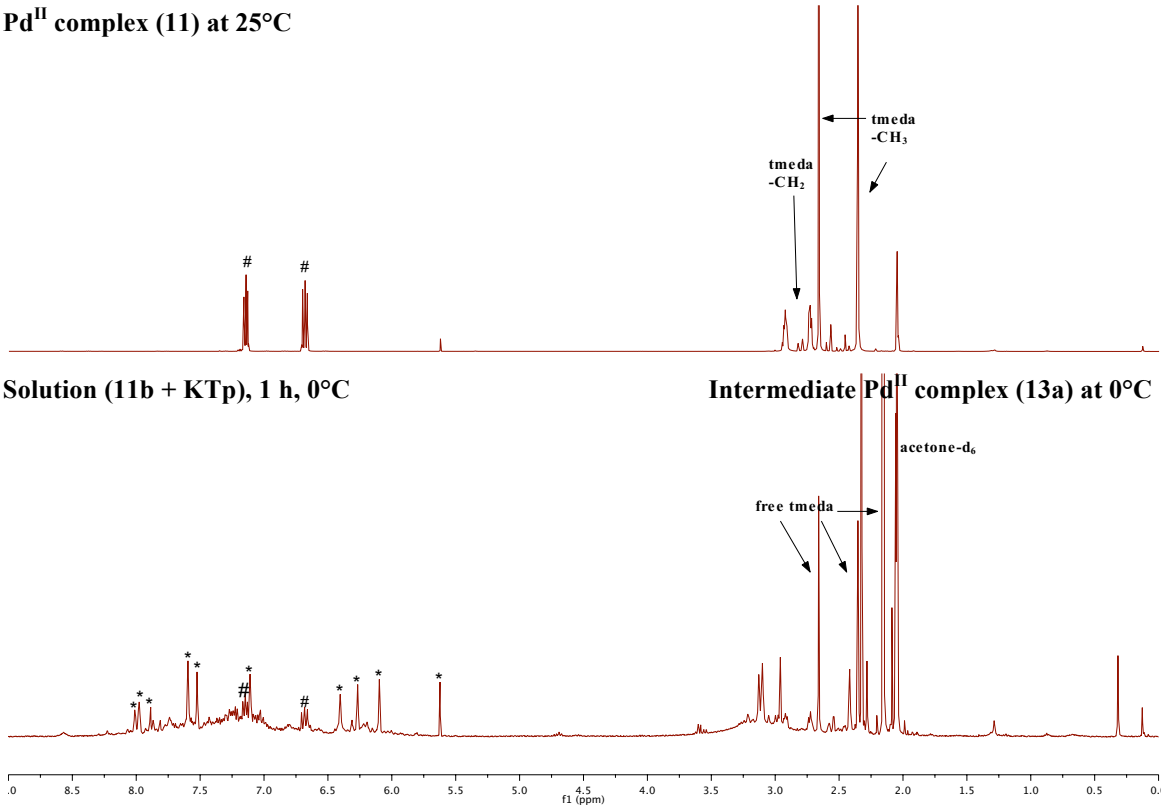


Figure 5.3: ^{1}H NMR (400 MHz, acetone-d_6) spectra for Palladium(II) complexes (**11**) and (**13a**)
(#) – Aryl signals (*) – Tp signals

In the ^{1}H spectral data for the Pd^{II} intermediate (**13a**), (Figure 5.3) we observe new aromatic proton signals (#) at δ 7.15 ppm (t, 2H) and 6.68 ppm (t, 2H), new KTp signals (*) from δ 6.0 - 8.0 ppm and free tmeda signals. The new KTp signals and free tmeda signals suggest the ligand exchange has occurred to generate the desired Pd^{II} intermediate (**13a**), which contains an aryl ring and is bound to the Tp ligand.

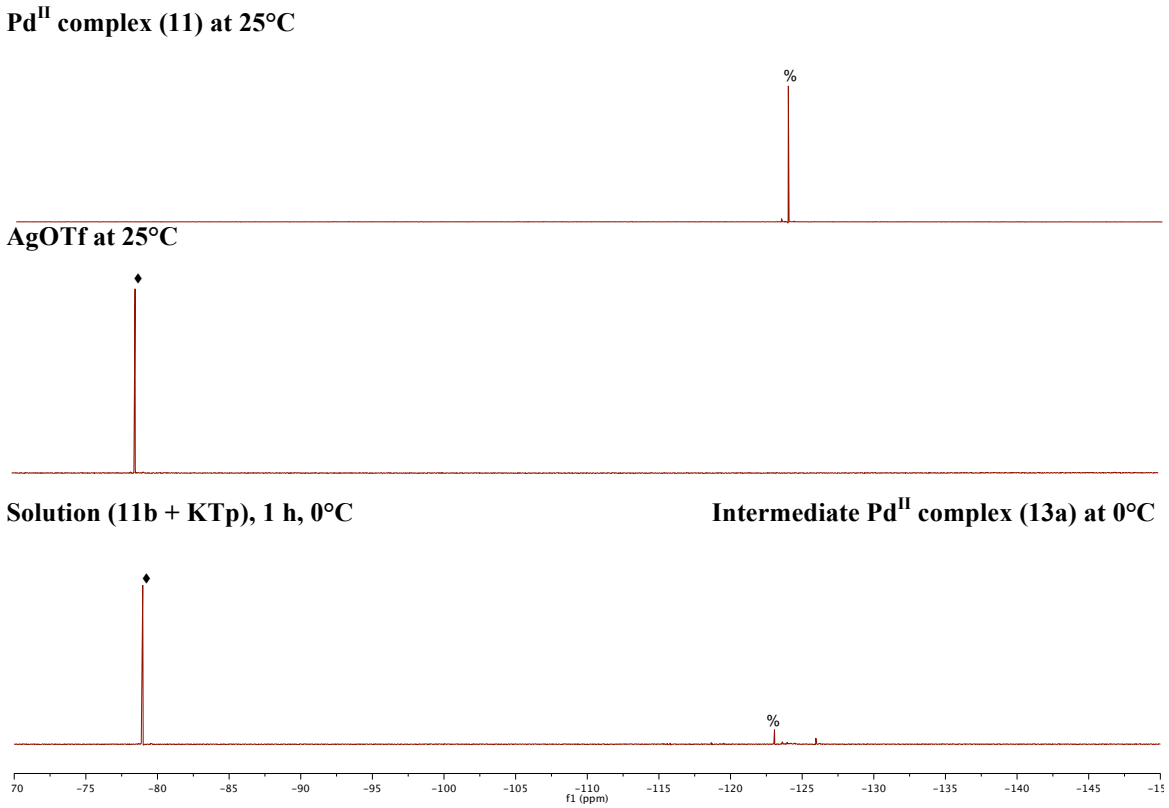


Figure 5.4: ^{19}F NMR (400 MHz, acetone-d_6) spectra for Palladium(II) complexes (**11**), (**13a**) and silver triflate (♦) – Triflate signal (%) – Aryl-F signal

In the ^{19}F spectral data, (Figure 5.4) we observe the presence of the triflate signal (♦), which has shifted from δ -78.60 ppm to -78.97 ppm (s, 3F) and a new aryl-fluoride signal (%), which has shifted to δ -123.07 ppm (s, 1F). This shift suggests that a new Pd^{II} intermediate containing the aryl-fluoride substituent has been generated in solution. However, due to the minimal shift of the triflate ligand, we cannot conclude with absolute certainty that the triflate ligand is bound to the Pd^{II}-center. The triflate signal in the ^{19}F spectral data does suggest that it is present in the reaction solution.

5.3.3: Scope of Silver Salt Addition and Ligand Exchange with Tp Ligand

The process of silver addition and ligand exchange was repeated with silver acetate by the methods described above and we observed a shift in the ^{1}H and ^{19}F NMR spectral data, suggesting the new Pd^{II} species (**13b**) is present in the reaction solution (Figure 5.5, 5.6).

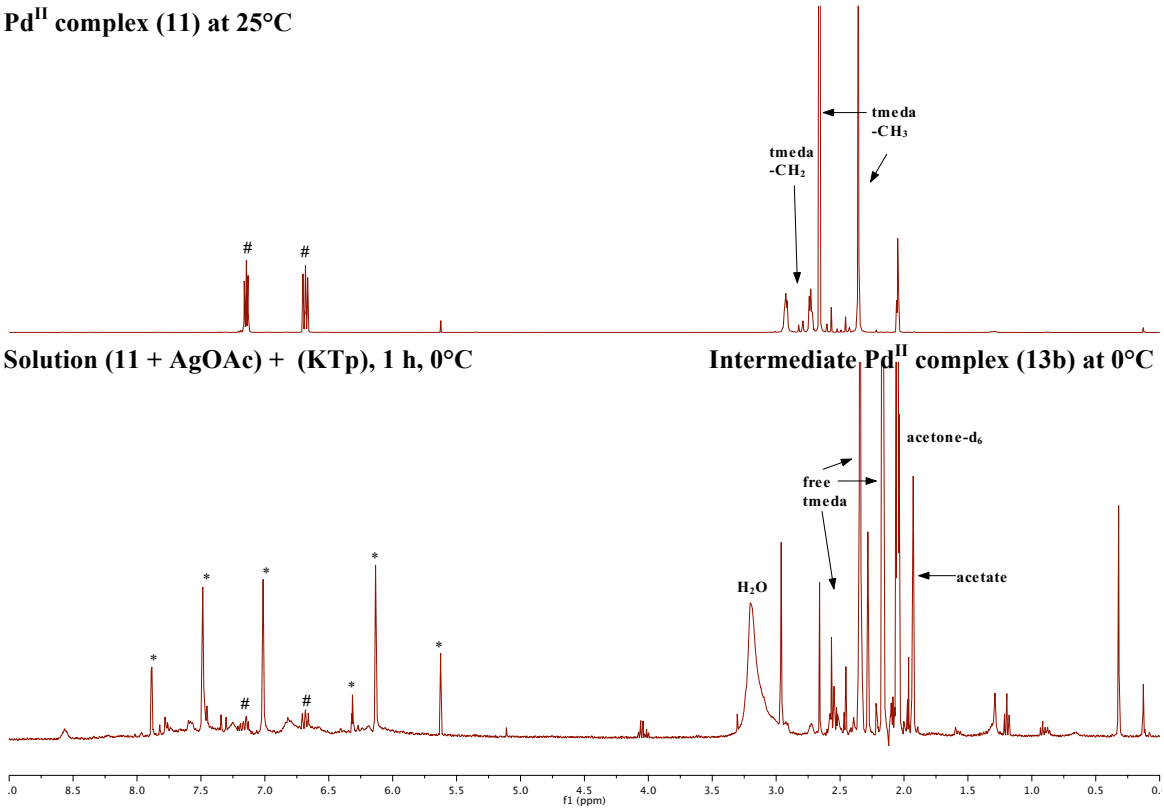


Figure 5.5: ^{1}H NMR (400 MHz, acetone-d_6) spectra for Palladium(II) complexes (**11**) and (**13b**)
(#) – Aryl signals (*) – Tp signals

In the ^{1}H spectral data for the suggested Pd^{II} intermediate (**13b**), (Figure 5.5) we observe new aryl proton signals (#), at δ 7.15 ppm (t, 2H) and 6.68 ppm (t, 2H), new KTp signals (*) from δ 6.0 - 8.0 ppm, free tmeda signals and a possible acetate signal. However, there are multiple impurities in the alkyl region (0-3 ppm), making the ^{1}H spectral data difficult to interpret.

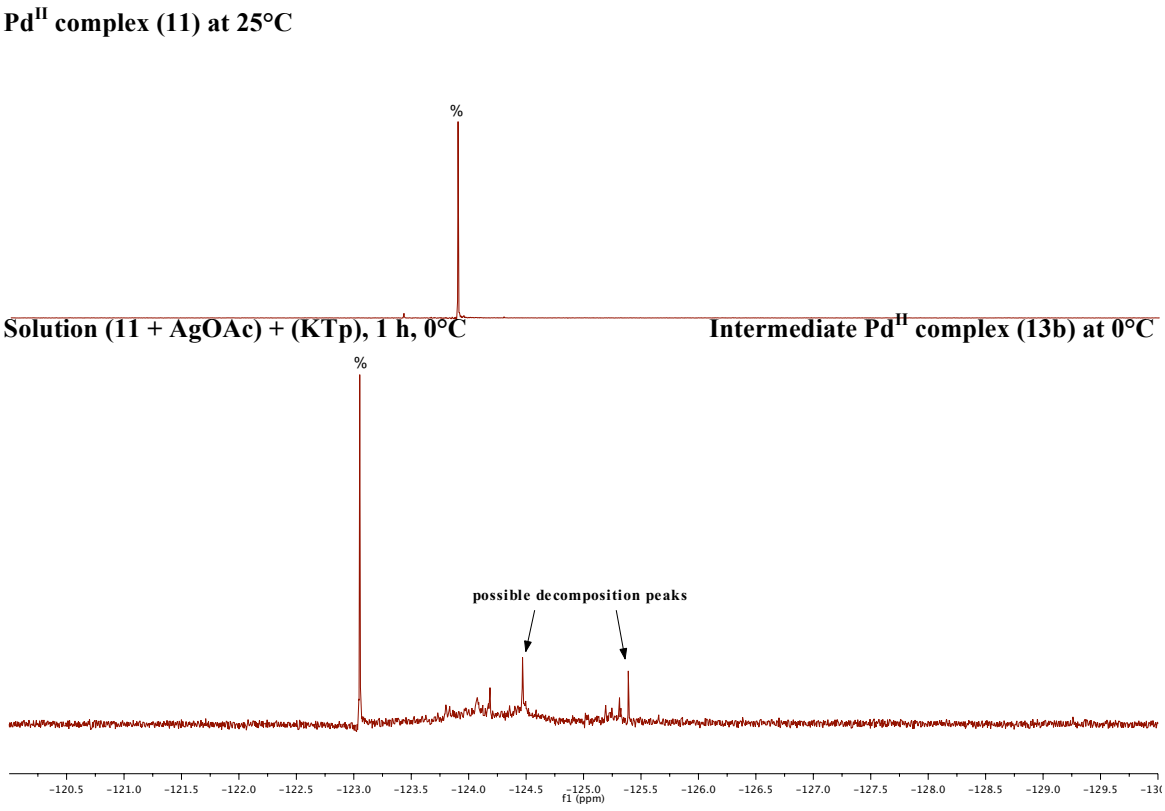
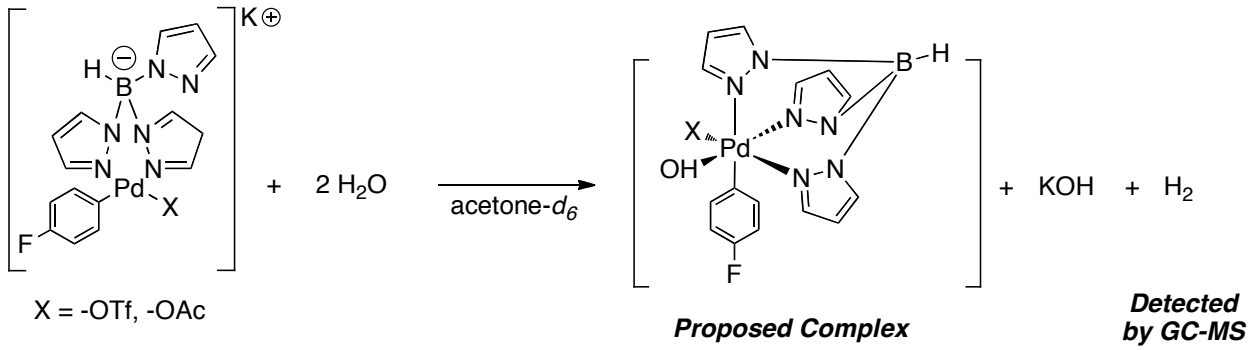


Figure 5.6: ^{19}F NMR (400 MHz, acetone-d_6) spectra for Palladium(II) complexes (**11**) and (**13b**) (%) – Aryl-F signal

In the ^{19}F spectral data, (Figure 5.6) we observe a new aryl-fluoride signal (%) at δ -123.05 ppm (s, 1F), which has shifted from δ -124.08 ppm and suggests the presence of a new Pd^{II} intermediate. We also notice two signals that have shifted upfield, which were assigned to possible aryl-fluoride decomposition products. The presence of these peaks and the diminished stability of the Pd^{II} intermediate (**13b)** and its derivatives will be discussed later in the chapter.

It is important to note that the Pd^{II} intermediates (**13a, 13b**) made in this study cannot be isolated because exposure to air and water would oxidize the intermediate to give an undesirable Pd^{IV} complex (Scheme 5.8).[16] As seen in Chapter Three on page 64 for the oxidation of a similar Pd^{II} intermediate, the formation of Hydrogen gas can be observed by GC-MS analysis.



Scheme 5.8: Oxidation of Palladium(II) intermediates (**13a, 13b**) to a new Palladium(IV) complex

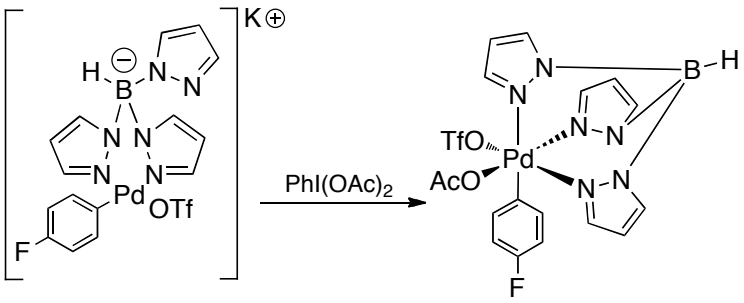
5.4: Oxidation with Phenyl Iodonium Diacetate to Synthesize Palladium(IV) complex 14a

After determining the ligand exchange reaction conditions, we focused on the synthesis of the desired Pd^{IV} complex by the oxidation of the Pd^{II} intermediate (**13a, 13b**) with phenyl iodonium diacetate. Experimentally, a solution of the diacetate oxidant in acetone was added to a solution of the Pd^{II} intermediate (**13a**) in acetone at 0°C and upon addition the clear reaction solution became orange. The reaction solution was then warmed to 25°C and allowed to stir for 15 minutes.

Next, we focused on the isolation of the new Pd^{IV} species, using the water and acetone work-up described above on page 80. However, this work-up did not remove all the organic impurities, making the NMR spectral data difficult to interpret.

We then decided to use a work-up procedure reported by Sanford for similar Pd^{IV} complexes, featuring at least one acetate ligand, generated by the oxidation of a Pd^{II} species with phenyl iodonium diacetate.[4] After following the process of sequential addition of AgOTf, KTp and $PhI(OAc)_2$ under the reaction conditions established above on page 155, we collected an orange

solution, which was filtered through Celite to remove any insoluble salt impurities and concentrated to approximately 1-2 mL by reduced pressure to collect an orange liquid. Hexanes were added to the orange liquid at 0°C to yield an orange oil, which underwent trituration with ether to produce a suspension. This suspension was filtered through Celite with ether and DCM to collect the filtrate. Solvent removal by reduced pressure produced the desired Pd^{IV} complex (**14a**) as a light orange solid in 65% yield (Scheme 5.9).



13a **14a** light orange solid 65%

Scheme 5.9: Synthesis of desired Palladium(IV) complex (**14a**)

We could also scale up the reaction from 0.1mmol to 0.5mmol but the work-up required washing the collected orange liquid repeatedly with hexane prior to the trituration with ether, which decreased the yield of our desired product from 65% to about 50%.

We could not purify the Pd^{IV} complex by flash chromatography, as analysis by thin-layer chromatography (TLC) indicated the decomposition of our product. We performed multiple analyses of the Pd^{IV} complex (**14a**) by TLC in a range of non-polar and polar solvents (1:7 Ethyl Acetate:Hexanes to 19:1 Dichloromethane:Methanol) and each analysis revealed multiple spots, which suggests that decomposition had occurred. We have also made multiple attempts at crystallization in acetone and hexanes solvent systems, however, no crystals have been collected.

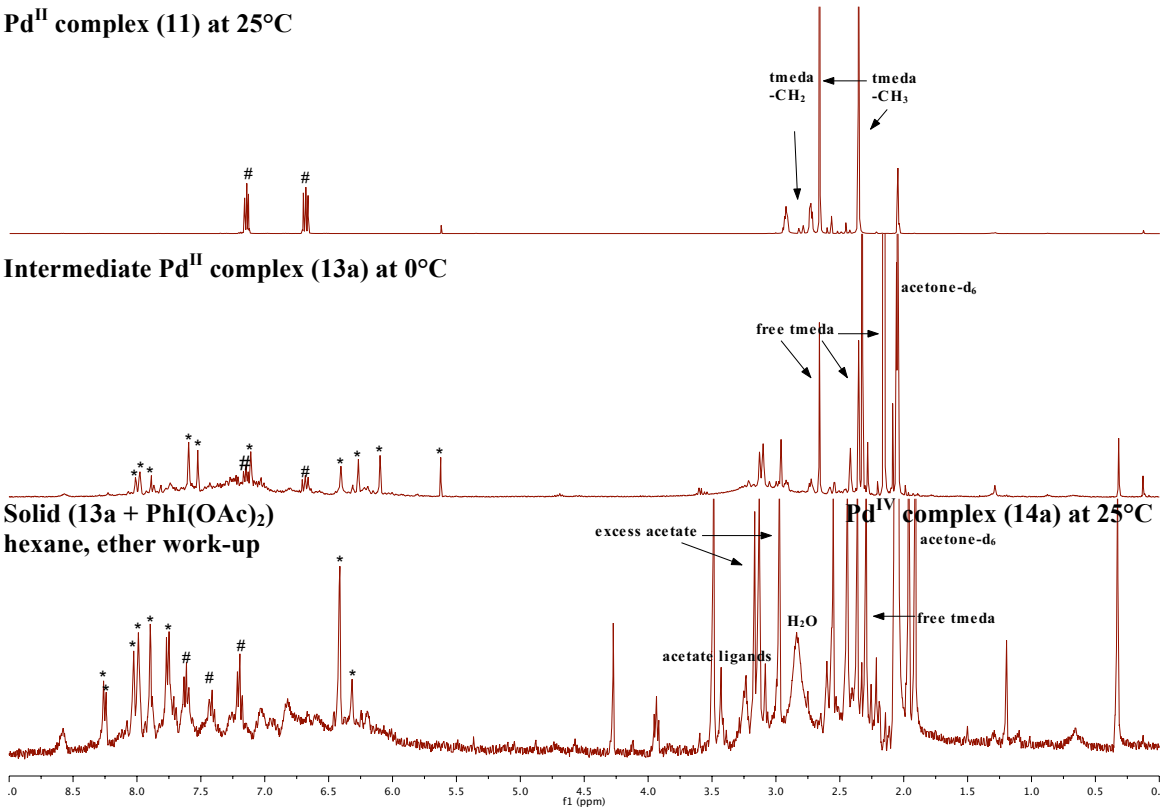


Figure 5.7: ^{1}H NMR (400 MHz, acetone-d_6) spectra for the Palladium(II) complexes (**11**) and (**13a**) and Palladium(IV) complex (**14a**)
(#) – Aryl signals (*) – Tp signals

The complex (**14a**) was characterized by ^{1}H and ^{19}F NMR spectral analyses. In the ^{1}H spectral data, (Figure 5.7) we observed a downfield shift in the aryl proton signals (#) and the Tp signals (*) in the aromatic region. In the alkyl region (0-3 ppm), we observe possible new acetate signals as well. However, large impurity signals (due to excess oxidant, free tmeda and solvents) obscure the alkyl region, making it difficult to correctly interpret the acetate signal.

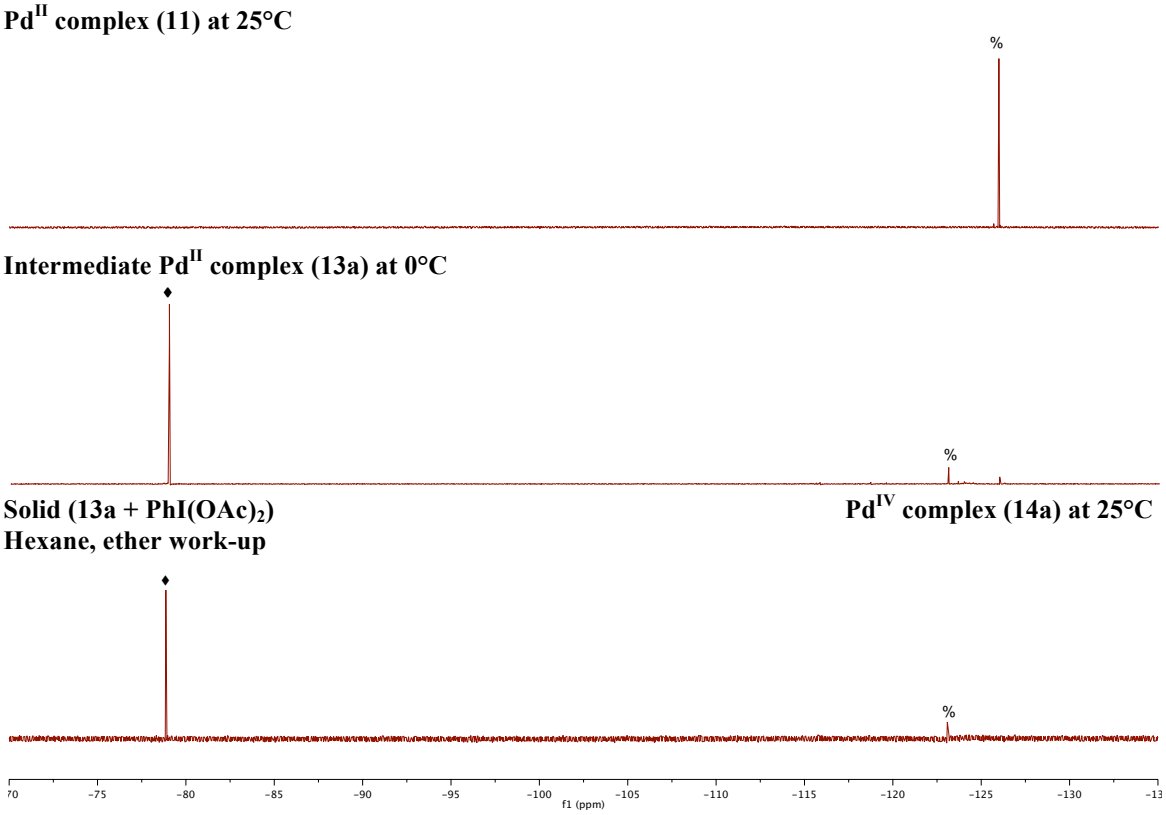


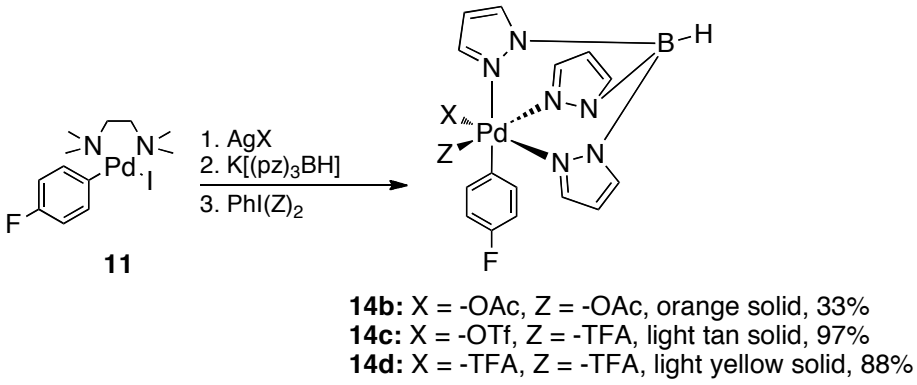
Figure 5.8: ^{19}F NMR (400 MHz, acetone-d_6) spectra for Palladium(II) complexes (**11**) and (**13a**) and Palladium(IV) complex (**14a**)
(♦) – Triflate signal (%) – Aryl-F signal

In the ^{19}F NMR spectral data, (Figure 5.8) we observe the triflate signal (♦) at δ -78.97 ppm (s, 1F) and the aryl-fluoride signal (%) at δ -123.08 ppm (s, 1F), which suggest the presence of the triflate and the aryl fluoride ligand in the Pd^{IV} complex (**14a**). Initially, it was unclear if the triflate ligand was replaced with an acetate ligand during the oxidation. After multiple purifications by the method described above on page 163 for complex (**14a**), the ^{19}F NMR spectral data consistently showed the trifluoromethyl signal associated with the triflate ligand, suggesting that the triflate ligand is bound to the Pd^{IV}-center in our complex (**14a**).

The Pd^{IV} complex (**14a**) is stable at 25°C and does not decompose over time. After 4 months of storage, ^{1}H and ^{19}F NMR analyses showed little to no decomposition of the desired Pd^{IV} complex indicating that once the complex is synthesized, it is very stable.

5.5: Auxiliary Ligand Scope for the Synthesis of Analogous Palladium(IV) complexes 14b-14d

After the successful synthesis of the initial Pd^{IV} complex (**14a**), we proceeded to explore what other silver salts and phenyl iodonium-based oxidants could be used to expand the range of the auxiliary ligands on the Pd^{IV}-center.[5] During this process, we hoped to prepare and isolate a range of new Pd^{IV} complexes by the method established above for the Pd^{IV} complex **14a**. In this reaction series, all the Pd^{IV} complexes were characterized by ^{1}H and ^{19}F NMR spectral analyses (Scheme 5.10).



Scheme 5.10: Synthesis of various Palladium(IV) complexes

First, we studied the oxidation of the Pd^{II} intermediate (**13b**) (Scheme 5.7) in the presence of phenyl iodonium diacetate, which would generate a Pd^{IV} complex with two acetate ligands coordinated to the Pd^{IV}-center (**14b**). The new Pd^{IV} complex (**14b**) was isolated as an orange

solid in 33% yield. However, this complex decomposed to a black solid while being stored at -20°C, suggesting that the Pd^{IV} complex has limited stability.

Next, we studied the oxidation of the Pd^{II} intermediate with the triflate ligand (**13a**) (Scheme 5.7) in the presence of phenyl iodonium ditrifluororacetate as the oxidant. This reaction may give us a new Pd^{IV} complex featuring two different trifluoromethyl groups, one from the triflate ligand and another from the trifluoroacetate ligand. The new Pd^{IV} complex (**14c**) was isolated as a light tan solid in 97% yield. To date, this complex has shown no decomposition at 25°C and upon storage at -20°C in the freezer for 1 year and 3 months.

Finally, we explored using silver trifluoroacetate to generate a new Pd^{II} intermediate, featuring a trifluoroacetate ligand, followed by in situ oxidation in the presence of phenyl iodonium ditrifluororacetate to create a Pd^{IV} complex (**14d**) with two trifluoroacetate ligands coordinated to the Pd^{IV}-center. We hoped to create a similar Pd^{IV} complex to the diacetate complex (**14b**) that would not decompose. The new Pd^{IV} complex (**14d**) was isolated as a light yellow solid in 88% yield. To date, this complex has shown no decomposition at 25°C and upon storage at -20°C in the freezer for 5 months.

Interestingly, when a fluorine-containing auxiliary ligand is present (either triflate (**14a, 14c**) or trifluoroacetate (**14c, 14d**)), the corresponding Pd^{IV} complex can be made in high yields and are shown to be very stable. However, when only acetate auxiliary ligands are present (**14b**), the Pd^{IV} complex is not only obtained in a lower yield but it will also decompose over time, making characterization difficult.

5.6: Summary of Characterization and Structure Elucidation

After synthesizing the unique Pd^{IV} complexes (**14a-14d**), we characterized the complexes by ^{1}H, ^{13}C and ^{19}F NMR spectral analyses. Conceivably, the complexes **14a-14d** may exist as distinct enantiomers, depending on whether the auxiliary ligands (X, Z, -aryl) are located in the axial or equatorial positions.

There were many challenging aspects to characterizing these Pd^{IV} complexes. First, very little information exists about Pd^{IV} complexes containing a Tp ligand, aryl ring and two oxygen-coordinating ligands. One complication for the lack of standards is the poor solubility of Pd^{IV} complexes in deuterated solvents. While this may seem like a unique problem, poor solubility is a common issue for similar Pd^{IV} complexes featuring two acetate-based or carboxylate ligands. A report by Sanford fails to provide any ^{13}C NMR spectral data due to the poor solubility of their Pd^{IV} complexes, which feature two acetate or carboxylate ligands and two 2-phenylpyridine-based ligands.[4]

5.6.1: ^{1}H NMR Characterization of Palladium(IV) Complexes 14a-14d

Despite multiple purification techniques by the method described above on page 163 for Pd^{IV} complex (**14a**), the poor solubility of the synthesized Pd^{IV} complexes in deuterated solvents hindered the characterization in the ^{1}H and ^{13}C NMR spectral analyses. The ^{1}H NMR spectral data is difficult to interpret due to the impurities (such as solvents, excess tmeda and excess oxidants) that exist in the alkyl range (0-3 ppm), making assignment of the acetate signals difficult. Therefore, only the aromatic region (5-9 ppm) is used to characterize the final Pd^{IV}

product. In this region, the proton signals on the phenyl fluoride ring (#) and the pyrazole signals (*) from the Tp were used to classify the Pd^{IV} complexes (**14a-14d**) (Figure 5.9).

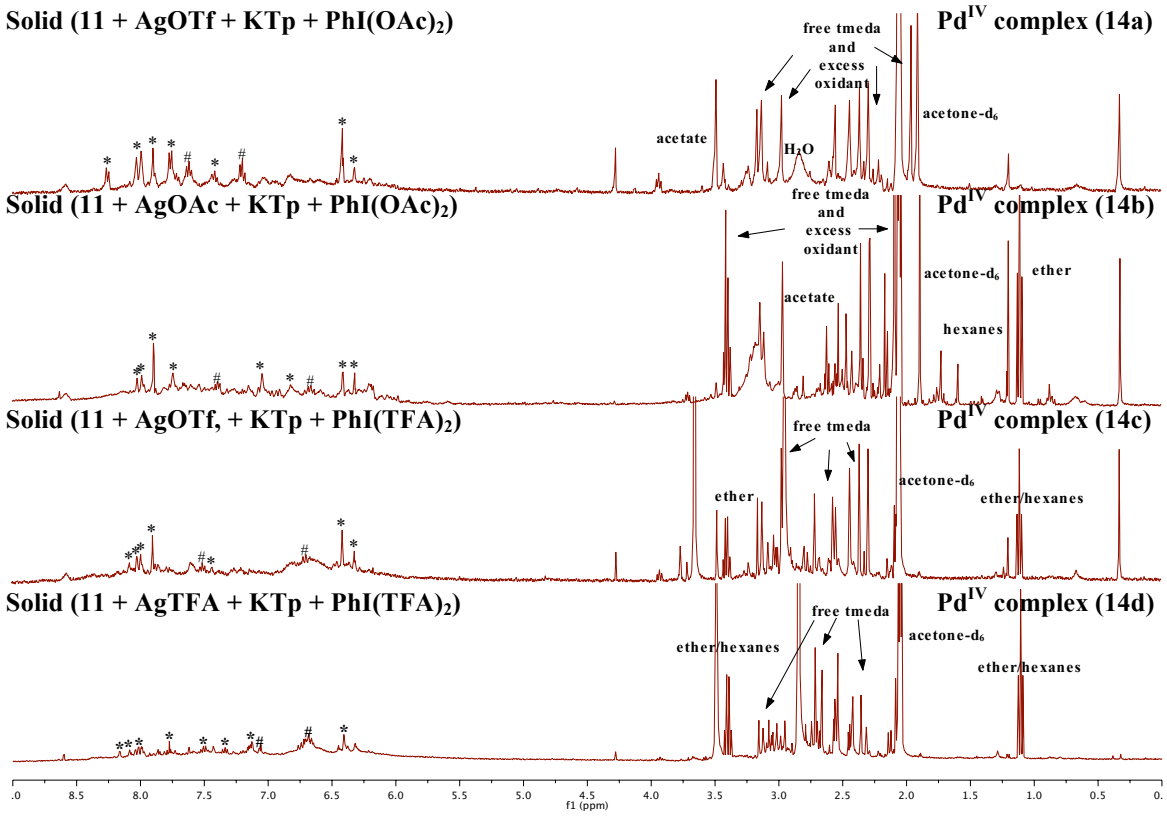


Figure 5.9: ^{1}H NMR (400 MHz, acetone-d_6) spectra for Palladium(IV) complexes (**14a** - **14d**) at 25°C
(#) – Aryl signals (*) – Tp signals

For our complexes, the pyrazole signals (*) were seen in two distinct areas of the aromatic region. The first set of signals is found at approximately 7.0-9.0 ppm as either broad singlets or broad doublets. For **14a**: δ 8.25 (d, 1H), 8.01 (d, 2H), 7.90-7.89 (m, 1H), 7.77-7.75 (m, 2H), 7.41 (t, 1H); for **14b**: δ 8.02 (m, 1H), 7.98 (m, 1H), 7.89 (ds, 1H), 7.75-7.74 (m, 2H), 7.04 (bs, 1H); for **14c**: δ 8.08 (s, 1H), 8.02 (s, 1H), 7.99 (m, 2H), 7.90 (d, 1H), 7.44-7.43 (m, 1 H); for **14d**: δ 8.13 (dd, 1H), 8.01 (dt, 2H), 7.77 (s, 1H), 7.51 (d, 1H), 7.49 (d, 1H), 7.43 (q, 1H), 7.17-7.12 (multiple peaks, 2H).

The other set of pyrazole signals (*) is found at approximately 6.0-6.5 ppm as either a singlet or broad triplet. For **14a**: δ 6.42-6.41 (m, 2H), 6.32 (t, 1H); for **14b**: δ 6.82-6.81 (m, 2H), 6.41 (s, 1H), 6.31 (t, 1H); for **14c**: δ 6.67-6.66 (m, 1H), 6.41 (t, 2H), 6.31 (t, 1H); for **14d**: δ 6.41 (t, 1H).

The phenyl proton signals (#) were typically found in between the pyrazole signals at 7.0-7.7 ppm as a multiplet or as a triplet. For **14a**: δ 7.61 (t, 2H), 7.21-7.18 (m, 2H); for **14b**: δ 7.41-7.31 (m, 2H), 6.68-6.63 (m, 1H); for **14c**: δ 7.52-7.49 (m, 2H), 6.72-6.69 (m, 2H); for **14d**: δ 7.06 (t, 1H), 6.72-6.65 (m, 4 H).

5.6.2: ^{19}F NMR Characterization of Palladium(IV) Complexes 14a-14d

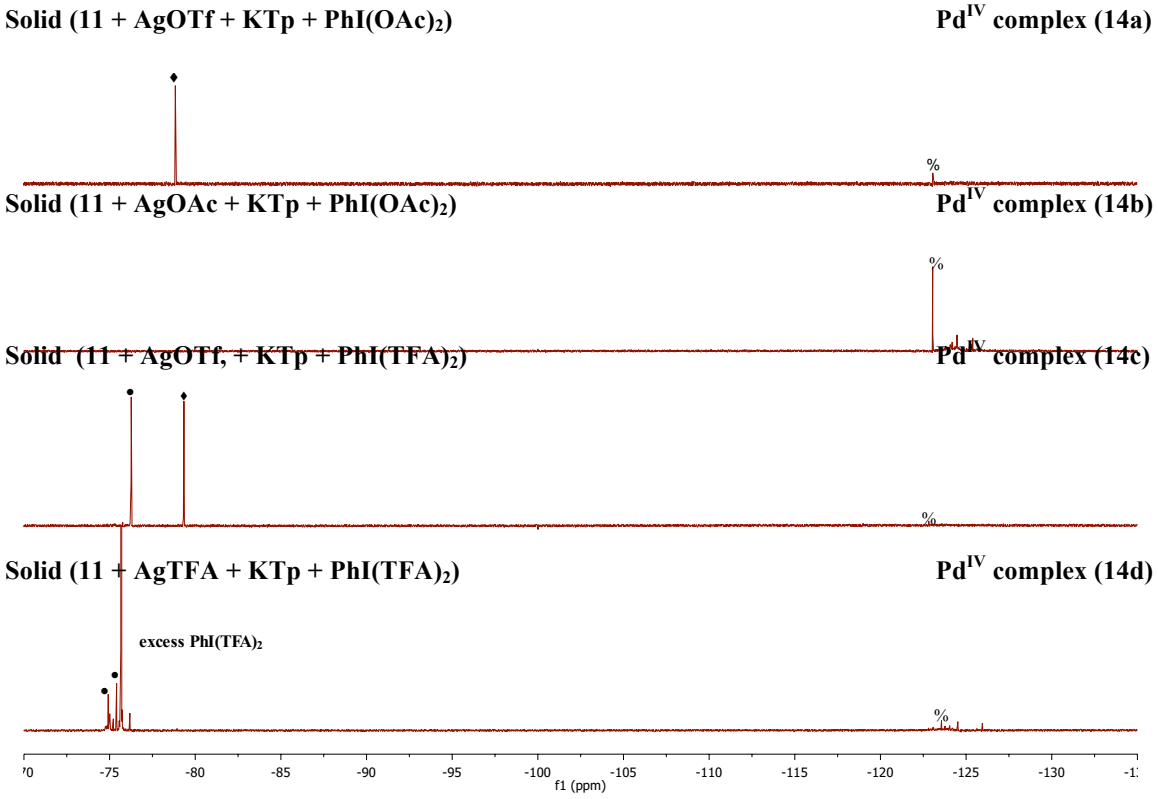


Figure 5.10: ^{19}F NMR (400 MHz, acetone-d_6) spectra for Palladium(IV) complexes (**14a** - **14d**) at 25°C (♦) – Triflate signal (●)- Trifluoroacetate signal (%) – Aryl-F signal

Despite the problems with interpreting the ^{1}H and ^{13}C spectral data, we could still use ^{19}F NMR spectral analysis to follow the formation of our Pd^{II} intermediates (**11b**, **13a, 13b**). Using ^{19}F NMR spectral data, (Figures 5.2, 5.4, 5.6) we observed a shift in either the aryl-fluoride signal (%) or the trifluoromethyl signal (♦) from the triflate during the generation of the Pd^{II} intermediates (**11b, 13a, 13b**). This downfield shift, typically observed in the aryl-fluoride signal, suggested that a new Pd-containing species was generated in the reaction solution. For **11b**: δ -78.60 ppm, (s, 3F for –OTf) -124.08 (s, 1F for Ar-F); for **13a**: δ -78.97 (s, 3F for –OTf), -123.07 (s, 1F for Ar-F); for **13b**: δ -123.05 (s, 1F for Ar-F).

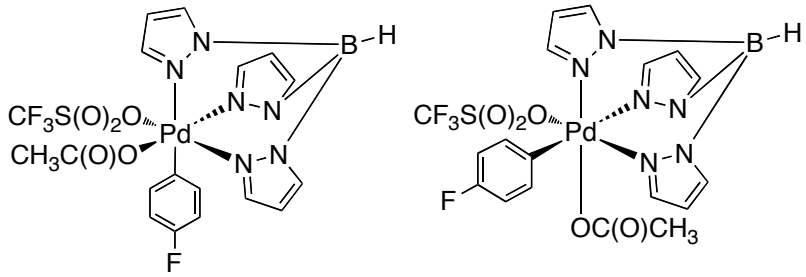
For the synthesis of our Pd^{IV} complexes (**14a-14d**), we used ^{19}F NMR spectral analysis to follow the formation of the complexes and to determine what ligands were possibly bound to the Pd^{IV}-center. In the ^{19}F spectral data, (Figure 5.10) no shift was seen in either the aryl-fluoride signal or the triflate signal. However, the desired aryl-fluoride, triflate or trifluoroacetate signals were still observed. For **14a**: δ -78.97 ppm (s, 3F for –OTf), -123.08 (s, 1F for Ar-F); for **14b**: δ -123.05 (s, 1F for Ar-F); for **14c**: δ -75.73 (s, 3F for –TFA), -78.95 (s, 3F for –OTf), -123.09 (s, 1F for Ar-F); for **14d**: δ -74.41 (s, 3F for TFA) -74.92 (s, 3F for TFA), -123.56 (s, 1F for Ar-F). This suggests that the aryl-fluoride, triflate or trifluoroacetate ligands are bound to the Pd-center in our desired Pd^{IV} complexes.

Initially, there was some doubt as to whether the triflate ligand remained bound to the Pd-center after the oxidation or if it was replaced with an acetate ligand from the phenyl iodonium acetate. However, the ^{19}F NMR spectral data for the Pd^{IV} complexes **14a, 14c** (which are generated from the Pd^{II} complex **13a**) possess a signal that corresponds to the triflate ligand. This signal strongly suggests that the triflate ligand most likely remained coordinated to the Pd^{IV}-center after the oxidation.

When the Pd^{IV} complex (**14a**) was purified multiple times by the method described above on page 163, there was no change in the triflate signal in the ^{19}F NMR spectral data. This further supports the conclusion that the triflate ligand is most likely coordinated to the Pd^{IV}-center after the oxidation.

5.6.3: Future Exploration of Auxiliary Ligand Location at Palladium(IV) Center

There are two possible structures of our Pd^{IV} complex (**14**) that we must consider. One structure contains the aryl ring located in the axial position (**14a.1**) and the other structure the aryl ring is located in the equatorial position (**14a.2**). (Figure 5.11)



14a.1 **14a.2**

Figure 5.11: Two enatiomers of the Palladium(IV) complex **14a**

However, these complexes (**14a.1** and **14a.2**) are enantiomers and were made as a racemic mixture in our synthesis, which was confirmed by ^{19}F NMR analysis. The remaining complexes **14b-14d** were also made as a racemic mixture and confirmed by ^{19}F NMR analysis.

Future work for the Pd^{IV} complexes **14a-14d** includes:

1. Further exploration of the isolation techniques to collect NMR analyses that contains little to no impurities in the alkyl region. This would allow for full characterization the Pd^{IV} complexes.

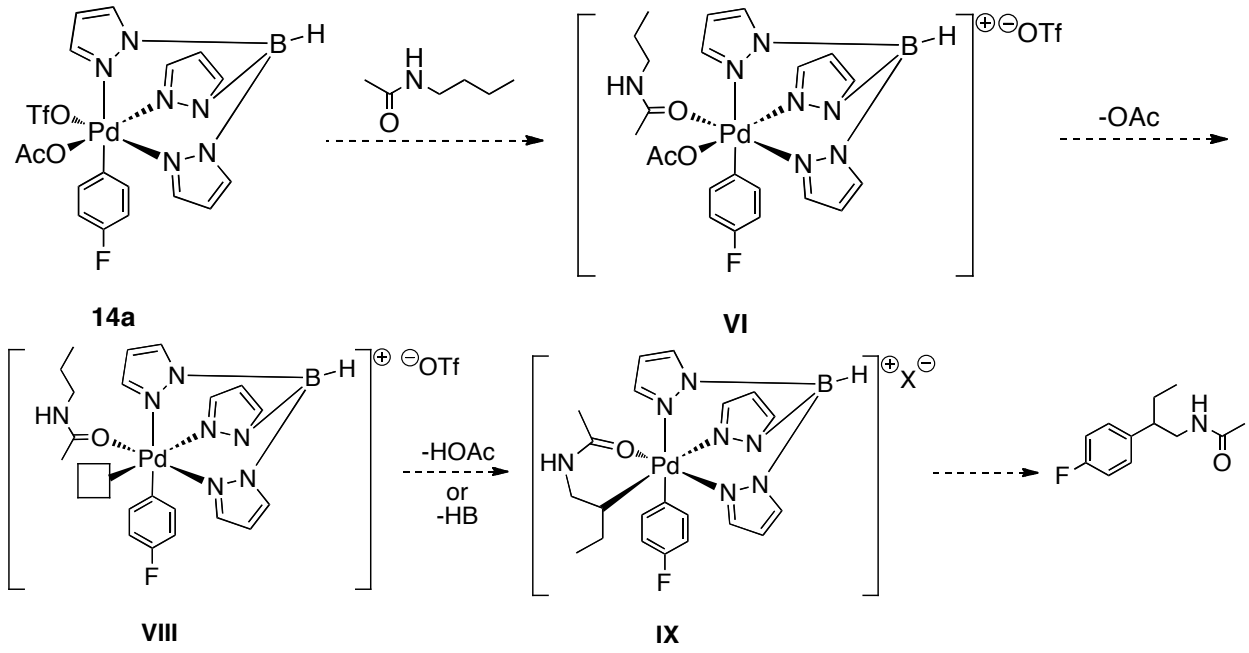
2. Collect crystal structures of the complexes **14a-14d** to determine the Pd-X and Pd-Z bond lengths in our structures. By collecting the Pd-X and Pd-Z bonds lengths, we can determine how the different ligands (–OTf, -OAc, or –TFA) can affect the reactivity at the Pd^{IV}-center. Ideally,

the longer Pd-atom bond length suggests that this auxiliary would undergo ligand dissociation to create an open coordination site at the Pd^{IV}-center.

5.7: Nucleophilic Substitution with Amide at the Palladium(IV) Center

Despite the difficulties with getting the complete characterization of the Pd^{IV} complexes, we moved forward with the exploration into what possible fundamental organometallic transformations could be done at the Pd^{IV}-center in our Pd^{IV} complex (**14a**).

We envisioned completing a base-assisted C-H Activation. A nucleophile, featuring at least one $C(sp^3)$-H bond, would be added to our Pd^{IV} complex (**14a**) in solution. Ideally, the nucleophile would displace the triflate ligand and coordinate to the Pd^{IV}-center (**VI**). Next, an additional ligand dissociation would create an open coordination site on the Pd^{IV}-center (**VIII**), which would be available for a Pd^{IV}-mediated C-H activation (with or without the assistance of base) on the carbon chain in the nucleophile to form a new Pd^{IV}-$C(sp^3)$ bond (**IX**). The subsequent reductive elimination couples the activated carbon on the nucleophile and the carbon on the aryl ring, giving a new organic product (Scheme 5.11).



Scheme 5.11: Proposed reaction pathway

In our proposed pathway, the nucleophile contains multiple C(sp^3)-H bonds available for C-H activation. Currently, we are unsure of which bond will coordinate to the Pd^{IV}-center. Two possible Pd^{IV}-C bonds may form: one will give us a 5-membered Pd^{IV}-cycle (**IXa**) and another will give us a 6-membered Pd^{IV}-cycle (**IXb**) (Figure 5.12). We reasoned the 6-membered Pd^{IV}-cycle (**IXb**) may be favored. The resulting complex would then undergo reductive elimination to yield the organic compound. The 5-membered Pd^{IV}-cycle (**IXa**), which is similar to stable Pd^{II}-cycles[17], is predicted to be more stable and could possibly be detected by NMR spectral analysis.

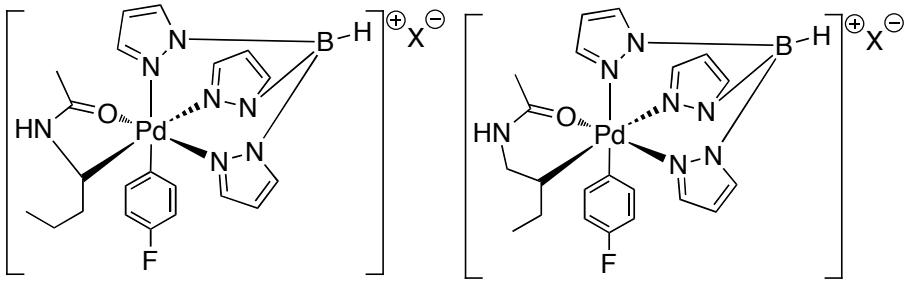
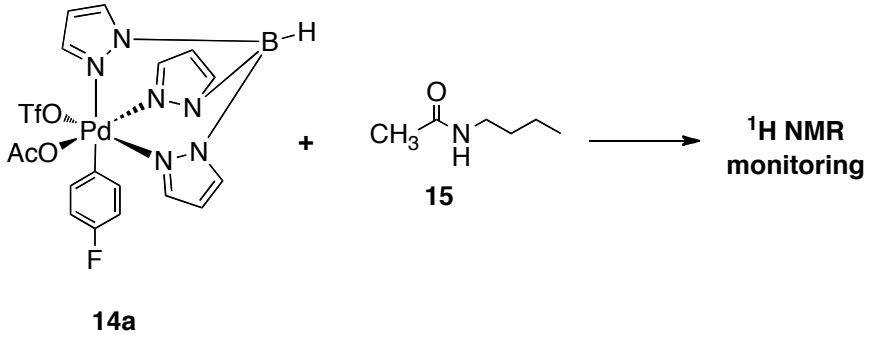


Figure 5.12: Possible Pd^{IV}-cycle formation: 5-membered (**IXa**) or 6-memberd (**IXb**)

For our first nucleophile, we choose an amide (**15**)[18] with three possible C(sp^3)-H bonds available for C-H activation. Experimentally, the solid Pd^{IV} complex (**14a**) and the amide (**15**) were dissolved in acetone-d_6 in the NMR tube and the reaction was monitored by ^{1}H NMR analysis at various temperatures (-10°C, 0°C, 25°C and 50°C) (Scheme 5.12).



Scheme 5.12: Initial C-H activation investigation

In the ^{1}H NMR spectra, we focused on monitoring the amide signals at δ1.32 ppm (●) and δ1.43 ppm (♦), which correspond to the C(sp^3)-H bonds on the butyl chain. If the proposed pre-coordination of the nucleophile or the C-H activation were to occur, a shift in peak or a different splitting pattern would be seen, indicating the amide was bound to the Pd^{IV}-center. Because the stability of the proposed Pd^{IV} species is not known, we also considered directly isolating the formed organic products by reductive elimination. By analyzing the organic product, we could

retroactively find what bonds were present in the Pd^{IV} intermediates and predict how the bonds coupled during the reductive elimination process.

However, the ^1H NMR spectral data collected matched only the starting Pd^{IV} complex (**14a**) and the amide (**15**) (Figure 5.13) at all temperatures examined, indicating no reaction had occurred. From these results, we could conclude that the amide was not strong enough to displace the triflate and coordinate to the Pd^{IV}-center as initially predicted.

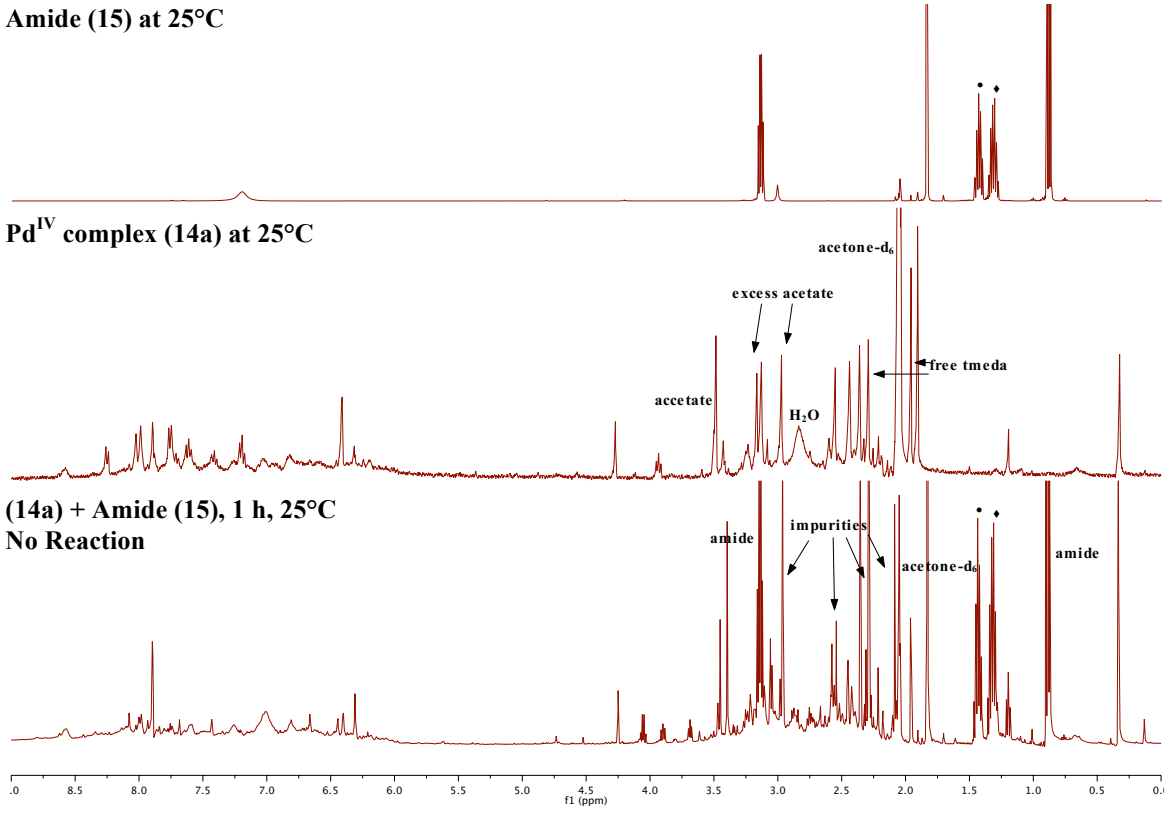
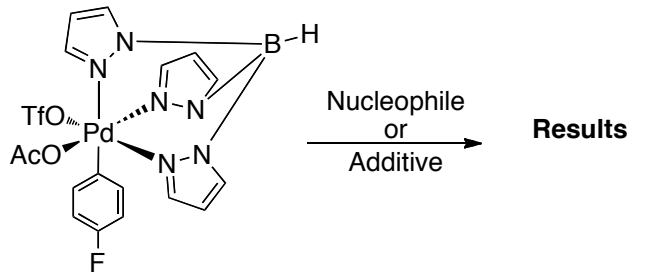


Figure 5.13: ^1H NMR (500 MHz, acetone-d_6) spectra for **15**, **14a** and **reaction mixture at 25°C** at end of monitoring
(●), (♦) – amide signals

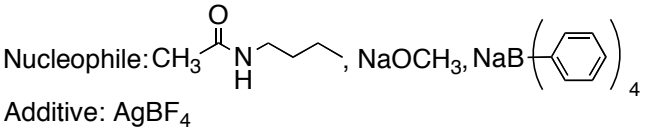
We then decided to employ additives that could assist with the displacement of the triflate ligand on the Pd^{IV} complex, as the triflate ligand has been removed in other Pd^{IV} complexes.[6] Various nucleophiles and additives were combined with Pd^{IV} complex (**14a**) in the appropriate deuterated

NMR solvents and mixed for up to 24 hours (Scheme 5.13). To monitor the reaction progress, an aliquot (0.1-0.3mL) was removed after various times (5 minutes to 24 hours) and the ^{1}H and ^{19}F NMR spectral data was taken.

5.8: Scope of Nucleophile and Additive Addition Reactions



14a



Scheme 5.13: Nucleophilic substitution reactions completed

The additive, $AgBF_4$, is reported to displace the triflate ligand through formation of an insoluble silver salt, which could be removed by filtration through Celite. To facilitate the bonding to the Pd^{IV}-center, strong nucleophiles $NaOCH_3$ and $NaB(Ph)_4$ were employed.

Unfortunately, none of the reactions were successful as the ^{1}H and ^{19}F NMR spectral analyses showed no shift in the signals and that only starting Pd^{IV} complex (**14a**) and starting nucleophile (Table 5.1).

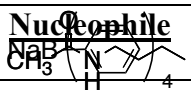
Nucleophile	Additive	Solvent	Temperature (°C)	Analysis (NMR)	Results
 **15**	N/A	acetone-d_6	-10, 0, 25, 50	^{1}H	No reaction. Only starting material seen.
N/A	$AgBF_4$	acetone-d_6	25, 50	^{1}H; ^{19}F	Decomposition signals seen after 30 minutes. Full decomposition seen after 5 hours at 25°C or after 1 hour at 50°C.
	$AgBF_4$	acetone-d_6	25, 50	^{1}H; ^{19}F	No reaction. Only starting material seen.
$NaOCH_3$	N/A	THF-d_8	25, 50	^{1}H; ^{19}F	No reaction. Only starting material seen.
	N/A	acetone-d_6	25, 50	^{1}H; ^{19}F	No reaction. Only starting material seen.

Table 5.1: Summary of results for nucleophilic substitution reactions

Initially these results were discouraging but upon closer inspection of the report by Sanford, the stability of our Pd^{IV} complex (**14a**) could be explained. In the report, Sanford notes that similar Pd^{IV} complexes featuring a tripodal ligand coordinated by three nitrogen centers are very stable and do not undergo ligand displacement, even in the presence of a silver salt, and do not decompose at 25°C in NMR solvent ($CDCl_3$) (Scheme 5.2, page 149).[6]

5.9: Conclusion and Future Direction

While we were able to synthesize four unique Pd^{IV} complexes (**14a-14d**) featuring a N,N,N-tripodal ligand, an aryl group and different auxiliary ligands, in the future we envision focusing on exploring the reactivity of the remaining Pd^{IV} complexes (**14b-14d**).

Specifically, we hope to focus on the Pd^{IV} complex featuring two acetate ligands (**14b**), as this complex readily decomposed upon storage. The decomposition suggests that the complex would be able to undergo the desired nucleophilic substitution reaction and the proposed C-H activation (Scheme 5.11) at the Pd^{IV}-center.

We also envision exploring the auxiliary ligands around the Pd^{IV}-center to see what factors can affect the ligand dissociation. It is important that we continue to use the Tp ligand in our studies, as it is not known to couple with our ligands upon reductive elimination. If we use a ligand featuring a carbon-center, the ligand could possibly undergo functionalization during the reductive elimination process.[4-5]

We will continue to expand towards using other commercially available silver salts and iodonium oxidants to explore the electronic effects of the auxiliary ligands. We also will expand to other auxiliary ligands that contain the same electronic effects but contain various carbon chain lengths.[4] By varying the size or length of the ligand, we hope to explore the effects of steric bulk on how the ligands dissociate.

5.10: Chapter Five Experimental

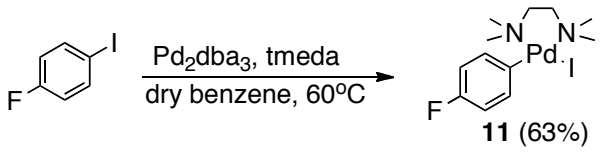
General Procedures

NMR spectra at 25°C were obtained on a Bruker DRX-400 (400 MHz ^{1}H and ^{19}F) and NMR spectra at -10°C were obtained on a Bruker DRX-500 (500 MHz for ^{1}H) in acetone-d_6. ^{1}H NMR chemical shifts are reported in parts per million (ppm) with the residual solvent peak (2.05 ppm) used as an internal reference. ^{19}F NMR spectra were referenced using the residual solvent peak in

the ^{1}H NMR spectrum. ^{13}C NMR spectra were obtained on an Avance AV-III 500 and the chemical shifts are reported in parts per million (ppm) with the residual solvent peak (206.26 ppm) used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), multiplet (m) and broad band resonance (br).

Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Benzene and dichloromethane (DCM) were kept over 3Å (8-12 mesh) molecular sieves under an atmosphere of dry argon. Acetone was purified by stirring with dry potassium carbonate (K_2CO_3) and kept over K_2CO_3; all other solvents were used as received. NMR solvents were obtained from Cambridge Isotopes and stored at 25°C. Unless otherwise specified, all reactions were carried out under an atmosphere of dry argon in oven-dried (at least 6 h at 140°C) glassware. Triethylamine was freshly distilled before use. Unless otherwise specified, all materials were used as received from commercial suppliers.

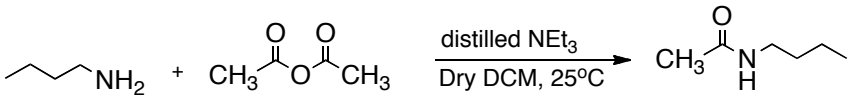
Potassium tris(pyrazol-1-yl)borate or (K[$(pz)_3$BH]) was purchased from TCI America and analyzed by ^{1}H and ^{13}C NMR in acetone-d_6. ^{1}H NMR (acetone-d_6): δ 7.57 (m, 2H), 7.49 (bs, 1H), 7.35 (m, 2H), 7.20 (bs, 1H), 6.27 (t, J = 4 Hz, "1H"), 6.08 (bs, 1H), 5.99 (t, J = 4 Hz, 2H). ^{13}C NMR (acetone-d_6): δ 140.37 (q, J = 15 Hz), 139.67 (s), 135.20 (q, J = 15 Hz), 134.84 (s), 105.06 (s), 104.01 (q, J = 5 Hz), 103.35 (s). *Note*: The signal observed at δ 6.27 ppm in the ^{1}H spectrum corresponds to the hydride on borate, which does not integrate to one.



11 (63%)

Synthesis of (tmeda)Pd(*p*-FC_6H_4)(I) (**11**)[13]: Under the atmosphere of Argon, tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3; 0.9170 g, 1.001 mmol, 1.0 eq) was dissolved in dry benzene (55 mL) at 25°C. N,N,N',N'-tetramethylethylenediamine (tmeda; 0.40 mL, 2.668 mmol, 1.3 eq) was added, and the resulting mixture was stirred at 25°C for 20 min. *p*-Fluoroiodobenzene (0.33 mL, 2.862 mmol, 1.4 eq) was added and the reaction mixture was warmed to 60°C for 3 h. In air, reaction mixture was filtered over a plug of Celite and the solvent was removed under reduced pressure. The resulting orange solid was washed with hexanes (3 x 35 mL) and then with a 50:50 mixture of Et_2O and hexanes (7 x 50 mL) until residual dibenzylideneacetone (dba) was completely removed. The resulting light orange solid was redissolved in CH_2Cl_2 (20 mL) and stirred with activated charcoal for 30 min. This dark suspension was filtered over a plug of Celite and the solvent was removed under reduced pressure to yield **11** as a light orange solid (0.5911 g, 63%).

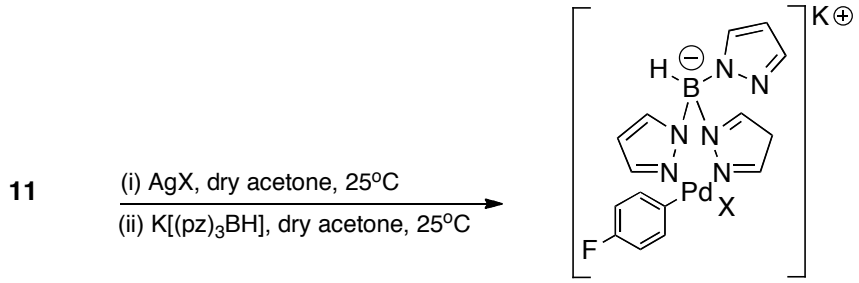
Analytical Data for complex 11: ^{1}H NMR (acetone-d_6): δ 7.17-7.13 (m, 2H), 6.71-6.66 (m, 2H), 2.94-2.91 (t, J = 4 Hz, 2H), 2.75-2.72 (t, J = 4 Hz, 2H), 2.66 (s, 6H), 2.36 (s, 6H). ^{19}F {^{1}H} NMR (acetone-d_6): δ – 125.97 (s, 1F). ^{13}C NMR (acetone-d_6): δ 162.55 (s), 160.67 (s), 139.67 (d, J = 10 Hz), 137.85 (d, J = 25 Hz), 113.36 (s), 113.21 (s), 62.84 (s), 59.02 (s), 50.08 (d, J = 81 Hz).



15 (77%)

Synthesis of N-butylacetylamide (**15**)[18]: Under the atmosphere of Argon, the N-butylamine (0.43 mL, 4.3506 mmol, 1.0 eq) was dissolved in dry CH_2Cl_2 (15 mL) at 25°C. Distilled triethylamine (NEt_3; 0.91 mL, 6.5289 mmol, 1.5 eq) was added dropwise at 25°C and the resulting solution was mixed at 25°C for 5 min. Acetic anhydride (0.62 mL, 6.5711 mmol, 1.5 eq) was added dropwise at 25°C and the reaction mixture was mixed for 25°C overnight. The reaction mixture was then washed with a 10% HCl aqueous solution (10 mL) to quench the solution. The organic layer was then extracted with CH_2Cl_2, washed with saturated $NaHCO_3$, brine, dried with Na_2SO_4, filtered and the solvent was removed under pressure to collect **15** as a clear oil (0.3837 g, 77%).

Analytical Data for amide 15: ^{1}H NMR (acetone-d_6): δ 7.20 (bs, 1H), 3.14 (q, J = 8 Hz, 2 H), 1.84 (s, 3H), 1.43 (qu, J = 8 Hz, 2H), 1.32 (qu, J = 8 Hz, 2H), 0.89 (t, J = 8 Hz, 3H). ^{13}C NMR (acetone-d_6): δ 169.85 (s), 39.49 (s), 32.58 (s), 22.93 (s), 20.72 (s), 14.08 (s).



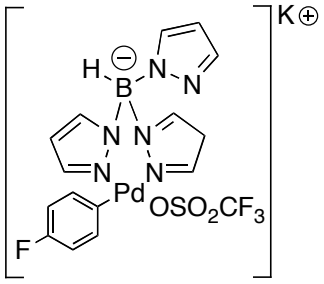
13a: X = -OTf
13b: X = -OAc

General procedure for the in situ formation of [{(pz)$_2$(pz)'BH}Pd(*p*-FC$_6$H$_4$)X$^-$][K$^+$] (**13a, 13b**)[15]: Under the atmosphere of Argon, palladium(II)complex **11** (0.1000 mmol, 1.0 eq) and silver salt (1.0 eq) were dissolved in dry acetone (2.0 mL) at 25°C and the resulting mixture was stirred at 25°C for 10 min. In air, the resulting solution was filtered over a Celite plug and washed with dry acetone (2 x 1.0 mL). The resulting solution was added into a separate flask containing the potassium tris(pyrazol-1-yl)borate (K{(pz)$_3$BH} or KTp; 0.1003 mmol, 1.0 eq) and the reaction

was stirred at 0°C for 1 h. The resulting solution was taken for NMR monitoring of product and used in the subsequent reaction.

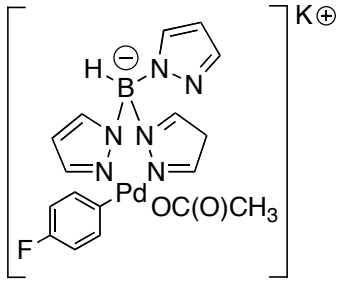
In general, the palladium(II) intermediates were not sufficiently stable to obtain ^{13}C NMR spectral data.

Analytical Data for:



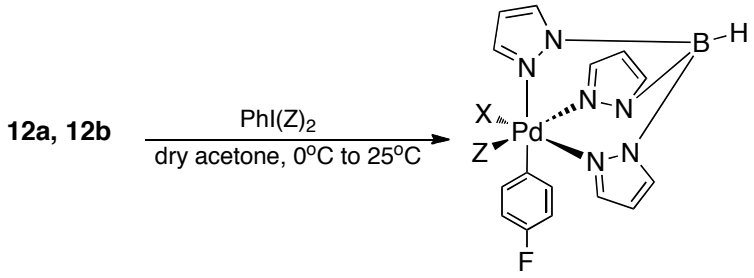
13a

[{(pz)$_2$(pz)'BH}Pd(*p*-FC$_6$H$_4$)X$^-$][K$^+$] (X = OTf) (**13a**): A dark yellow suspension was collected and filtered over a Celite plug. The resulting yellow solution was taken for ^1H, ^{19}F NMR analyses. ^1H NMR (acetone-d_6): δ 8.01 (bs, 1H), 7.98 (bs, 1H), 7.89 (s, 1H), 7.52 (bs, 2H), 7.11 (bs 2H), 6.40 (bs, 2H), 6.27 (t, J = 4 Hz, 2H), 6.10 (bs, 2H), 5.62 (bs, "1H"). ^{19}F {^1H} NMR (acetone-d_6): δ -78.97 (s, 1F), -123.07 (s, 1F). *Note:* Some starting material was seen in spectral analysis. Please consult reported NMR signals for starting Pd^{II} complex (**11**) and KTp ligand.



13b

[{(pz)$_2$(pz)'BH}Pd(*p*-FC$_6$H$_4$)X$^-$][K$^+$] (X = OAc) (**13b**): A tan suspension was collected and filtered over a Celite plug. The resulting clear solution was taken for ^{1}H, ^{19}F NMR analyses. ^{1}H NMR (acetone-d_6): δ 7.90 (d, J = 4 Hz, 1H), 7.49 (bs, 3H), 7.25 (bs, 1H), 7.01 (bs, 3H), 6.80 (bs, 2H), 6.31 (t, J = 4 Hz, 1H), 6.13 (bs, 3H), 5.62 (bs, "1H") 1.91 (s, "3H"). ^{19}F {^{1}H} NMR (acetone-d_6): δ -123.05 (s, 1F). *Note:* Some starting material was seen in spectral analysis. Please consult reported NMR signals for starting Pd^{II} complex (**11**) and KTp ligand.



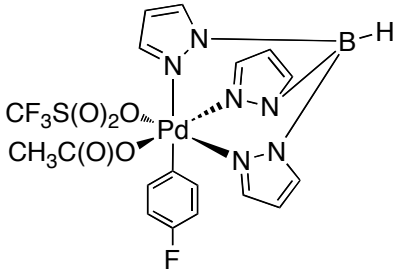
14a: X = -OTf, Z = -OAc (65%)
14b: X = -OAc, Z = -OAc (33%)
14c: X = -OTf, Z = -TFA (97%)
14b: X = -TFA, Z = -TFA (88%)

General procedure for the in situ generation of [{(pz)$_3$BH}Pd(*p*-pFC$_6$H$_4$)(X)(Z) (**14a-14d**)[4]: Under the atmosphere of Argon, PhI(Z)$_2$ oxidant (1.0-1.8 eq) was dissolved in dry acetone (1.5-3.0 mL) at 25°C and let mix for 15 min. The resulting solution was then added dropwise to the solution of the palladium(II) of complexes **13a, 13b** (1.0 eq) in dry acetone (1.0-2.0 mL) at 0°C

and stirred for 10 min then warmed to 25°C. The resulting reaction mixture was concentrated under reduced pressure to 1.0-2.0 mL and hexanes was added (5.0 mL) to create an oil. The mixture of light and heavy liquid was decanted and the heavy oil was washed with hexanes (5 x 2.0 mL) to remove any impurities. Remaining oil was cooled to -10°C and triturated with Et_2O (7.0-10.0 mL) at -10°C for 1 h to afford a suspension that was filtered over a Celite plug and washed with Et_2O. The solid atop the Celite layer was dissolved by washing with CH_2Cl_2 to collect a clear solution, which was dried under vacuum to afford the solid. If the resulting solid was tacky, the solid was purified by washing, trituration with Et_2O and filtration procedure.

In general, excess tmeda limited complete analysis of alkyl range (0-3 ppm) in the ^{1}H NMR spectra. Aryl region (5-9 ppm) contains the indicative signals used to identify products.

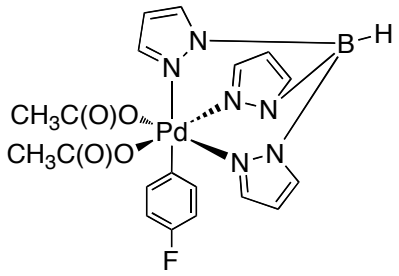
Analytical Data:



14a

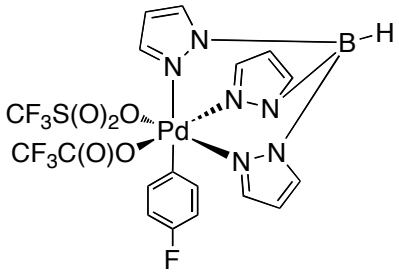
[{(pz)$_3$BH}Pd(*p*-pFC$_6$H$_4$)(X)(Z) (X = -OTf, Z = -OAc) (**14a**): Light orange solid (0.1322g, 65%). ^{1}H NMR (acetone-d_6): δ 8.25 (d, J = 4 Hz 1H), 8.01 (d, J = 16 Hz, 2H), 7.90-7.89 (m, 1H), 7.77-7.75 (m, 2H), 7.61 (t, J = 8 Hz, 2H), 7.41 (t, J = 8 Hz, 1H), 7.21-7.18 (m, 2H), 6.42-6.41 (m, 2H), 6.32 (t, J = 4 Hz, 1H), 3.49 (s, 3H). ^{19}F {^{1}H} NMR (acetone-d_6): δ -78.97 (s, 1F), -123.08 (s, 1F). ^{13}C NMR (acetone-d_6): δ 172.17-172.09 (m), 163.26 (s), 161.36 (s), 147.30 (s),

141.99 (s), 141.14 (s), 140.19 (s), 138.39 (s), 137.78-137.55 (m), 137.25-136.77 (m), 135.70-135.47 (m), 121.11 (s), 114.40-113.30 (m), 107.63 (s), 106.80 (s), 106.30 (s), 105.61-105.51 (m), 94.72 (s), 86.88 (m), 20.65-20.61 (m).



14b

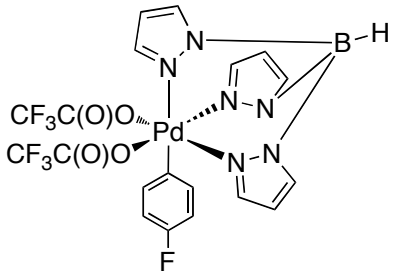
[{(pz)$_3$BH}Pd(*p*-pFC$_6$H$_4$)(X)(Z) (X = -OAc, Z = -OAc) (**14b**): Orange solid (0.0203g, 33%) Decomposes over time. ^{1}H NMR (acetone-d_6): δ 8.02 (m, 1H), 7.98 (m, 1H), 7.89 (s, 1H), 7.75-7.74 (m, 2H), 7.41-7.31 (m, 2H), 7.04 (bs, 1H), 6.82-6.81 (m, 2H), 6.68-6.63 (m, 1H), 6.41 (s, 1H), 6.31 (t, J = 4 Hz, 1H), 3.11 (s, 3H), 2.97 (s, 3H). ^{19}F {^{1}H} NMR (acetone-d_6): δ -123.05 (s, 1F). *Note*: Palladium(IV) complex not sufficiently stable to obtain ^{13}C NMR spectral data. Decomposition product was also seen in the ^{19}F NMR spectral data.



14c

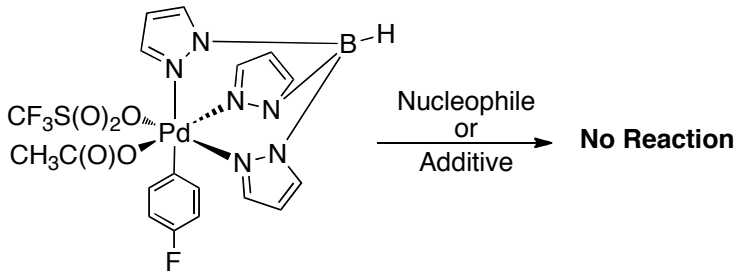
[{(pz)$_3$BH}Pd(*p*-pFC$_6$H$_4$)(X)(Z) (X = -OTf, Z = -TFA) (**14c**): Light tan powder (0.0660g, 97%) ^{1}H NMR (acetone-d_6): δ 8.08 (s, 1H), 8.02 (s, 1H), 7.99 (m, 2H), 7.90 (d, J = 4 Hz, 1H), 7.52-7.49 (m, 2H), 7.44-7.43 (m, 1 H), 6.72-6.69 (m, 2H), 6.67-6.66 (m, 1H), 6.41 (t, J = 4 Hz, 2H), 6.31 (t, J = 4 Hz, 1H). ^{19}F {^{1}H} NMR (acetone-d_6): δ -75.73 (s, 3F), -78.95 (s, 1F), -123.09 (s,

1F). ^{13}C NMR (acetone-d_6): δ 174.87 (s), 161.36-162.17 (m), 141.99 (s), 141.14 (s), 140.98 (s), 135.65 (d, J = 20 Hz), 132.24 (s), 126.12 (s), 123.54 (d, J = 20 Hz), 121.01 (s), 119.23 (s), 118.45 (s), 116.89 (s), 113.84 (d, J = 75 Hz), 107.20 (t, J = 208 Hz), 63.62 (t, J = 70 Hz), 50.96 (s), 49.25 (s), 47.95 (s), 47.45 (s), 46.08 (s).



14d

[{(pz)$_3$BH}Pd(*p*-pFC$_6$H$_4$)(X)(Z) (X = -TFA, Z = -TFA) (**14d**): Neon yellow powder (0.0337g, 88%) ^{1}H NMR (acetone-d_6): δ 8.13 (dd, J = 32 Hz, 4 Hz, 1H), 8.01 (dt, J = 12 Hz, 4 Hz, 2H), 7.77 (s, 1H), 7.51 (d, J = 4 Hz, 1H), 7.49 (d, J = 4Hz, 1H), 7.43 (q, J = 8 Hz, 1H), 7.17-7.12 (m, 2H), 7.06 (t, J = 4 Hz, 1H), 6.72-6.65 (m, 4 H), 6.41 (t, J = 4 Hz, 1H). ^{19}F {^{1}H} NMR (acetone-d_6): δ -74.41 (s, 2F), -74.92 (s, 1F), -123.56 (s, 1F). ^{13}C NMR (acetone-d_6): δ 183.29 (s), 183.05 (s), 161.38 (q, J = 130 Hz), 147.03 (s), 146.80 (s), 146.39 (s), 142.16 (d, J = 185 Hz), 140.63 (s), 137.76 (d, J =20 Hz), 136.47 (s), 135.98 (s), 135.74 (s), 135.69 (s), 135.09 (s), 134.18 (s), 132.09 (s), 129.09 (s), 118.21 (q, J = 1175 Hz), 113.03-114.05 (m), 106.98 (s), 66.15 (s), 62.76-64.29 (m), 58.94 (s), 58.50 (d, J = 190 Hz), 51.57 (d, J = 35 Hz), 47.87 (d, J = 20 Hz).

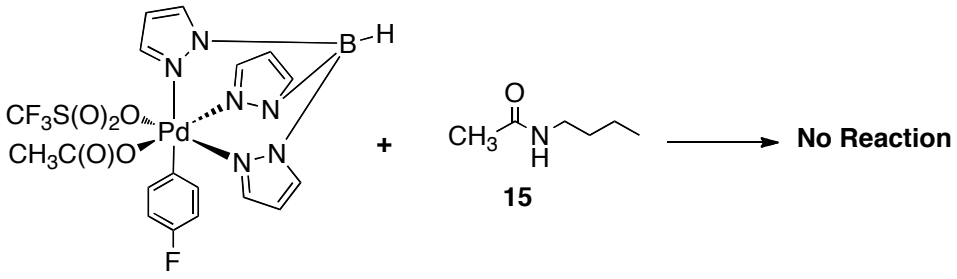


14a

General procedure for the substitution reactions with complex **14a**: Under the atmosphere of Argon, palladium(IV) complex, **14a** (0.03 g, 0.05 mmol, 1.0 eq) and the nucleophile (1.0 -1.3 eq) or additive (1.0-1.3 eq) were dissolved in the NMR solvent (0.5-1.1 mL) at 25°C in the appropriate v-vial (3.0-5.0 mL). If necessary, temperatures were adjusted at this point (-10°C – 50°C). The reaction mixture was mixed (5 min – 24.0 h). The reaction mixture was filtered through a Celite plug to collect the filtrate into an NMR tube and diluted with the NMR solvent, if necessary.

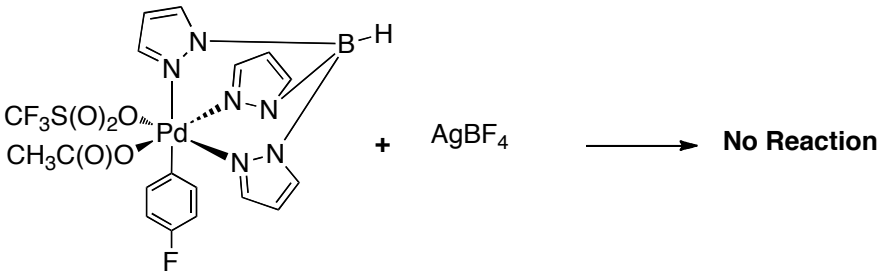
In general, the palladium(IV) complexes were not sufficiently soluble in the NMR solvent to collect ^{13}C NMR spectral data and to use ^{1}H NMR spectral data to determine product formation (except for reaction of **14a** and **15**). ^{19}F NMR spectral data was analyzed to assess the outcome due to its high sensitivity.

Analytical Data for:



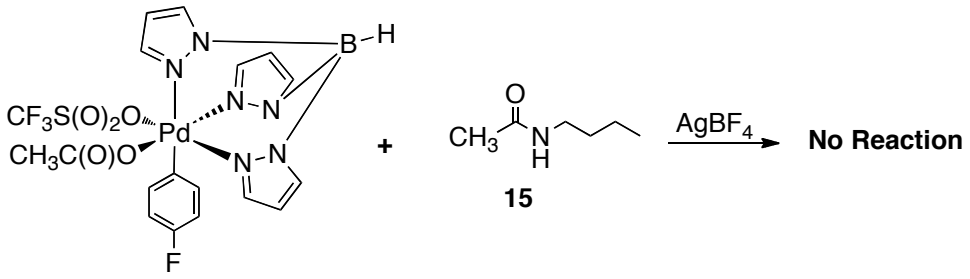
14a

(N-butylacetylamide, acetone-d_6): ^{1}H NMR analysis was performed at the following times and temperatures: 1.0 h, -10°C; 30 min, 0°C; 30 min, 25°C; 1.0 h, 50°C, 3.0 h, 50°C. No reaction occurred. ^{1}H NMR (acetone-d_6): δ 8.07 (bd, J = 4 Hz, 1 H), 7.98 (bd, J = 8 Hz, 2 H), 7.93 (bs, 2H), 7.89 (d, J = 4 Hz, 1 H), 7.68 (s, 1H), 7.43 (s, 2 H), 7.00 (bs, 4 H), 6.44 (t, J = 4 Hz, 1 H), 6.40 (bs, 1H), 6.39 (t, 2 H), 3.40 (s, 3 H), 3.13 (q, J = 8 Hz, 11H), 1.83 (s, 10 H), 1.44 (qu, J = 8 Hz, 7H), 1.32 (qu, J = 8 Hz, 8 H), 0.89 (t, J = 8 Hz, 11H). *Reported for 30 min at 25°C (after mixing 2 hr total)*.



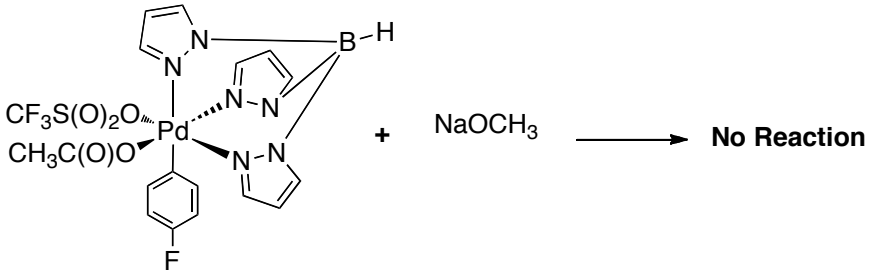
14a

(Silver tetrafluoroborate, acetone-d_6): ^{19}F NMR analysis was performed after mixing at the following times and temperatures: 30 min, 25°C; 2.5 h, 25°C; 5.5 h, 25°C; 1.0 h, 50°C. Slight decomposition within 30 min at 25°C. Major to full decomposition occurred within 2.5 h at 25°C. ^{19}F {^{1}H} NMR (acetone-d_6): δ -78.75 (s, 9H), -114.73 (s, 1H), -123.09 (s, 1H), -150.92 (s, 16H). *Reported for 30 min at 25°C*.



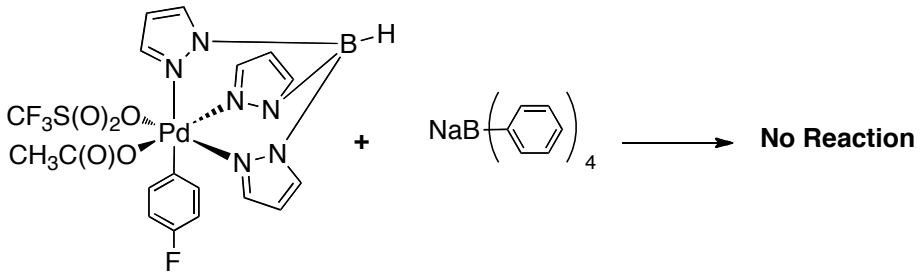
14a

(N-butylacetylamide and silver tetrafluoroborate, acetone-d_6): Palladium(IV) complex **14a** and silver salt (1.0 eq) were dissolved in acetone-d_6 and allowed to stir for 10 min at 25°C. N-butylacetylamide (1.0 eq) was dissolved in acetone-d_6 and added to the reaction mixture at 25°C. ^{19}F NMR analysis was performed after mixing at the following times and temperatures: 30 min, 25°C; 1.0 h, 25°C; 24.0 h, 25°C. No reaction occurred. ^{19}F {^{1}H} NMR (acetone-d_6): δ -78.79 (s, 3F), -114.74 (s, 0.18F), -123.09 (d, J = 136 Hz, 1 F), -151.16 (s, 5F). *Reported for 30 min at 25°C.*



14a

(Sodium methoxide, THF-d_8): ^{19}F NMR analysis was performed after mixing at the following times and temperatures: 5 min, 25°C; 1.0 h, 25°C; 24.0 h, 25°C; 1.0 h, 50°C. No reaction occurred. ^{19}F {^{1}H} NMR (THF-d_8): δ -81.17 (s, 19H), -124.64 (s, 1H). *Reported for 1 h at 25°C.*



14a

(Sodium tetraphenylborate, acetone-d_6): ^{19}F NMR analysis was performed after mixing at the following times and temperatures: 5 min, 25°C, 1.0 h, 25°C; 24.0 h 25°C; 1.0 h, 50°C. No reaction occurred. ^{19}F {^{1}H} NMR (acetone-d_6): δ -78.99 (s, 5H), -123.03 (s, 1H). *Reported for 1 h at 25°C.*

5.11: Chapter Five Bibliography

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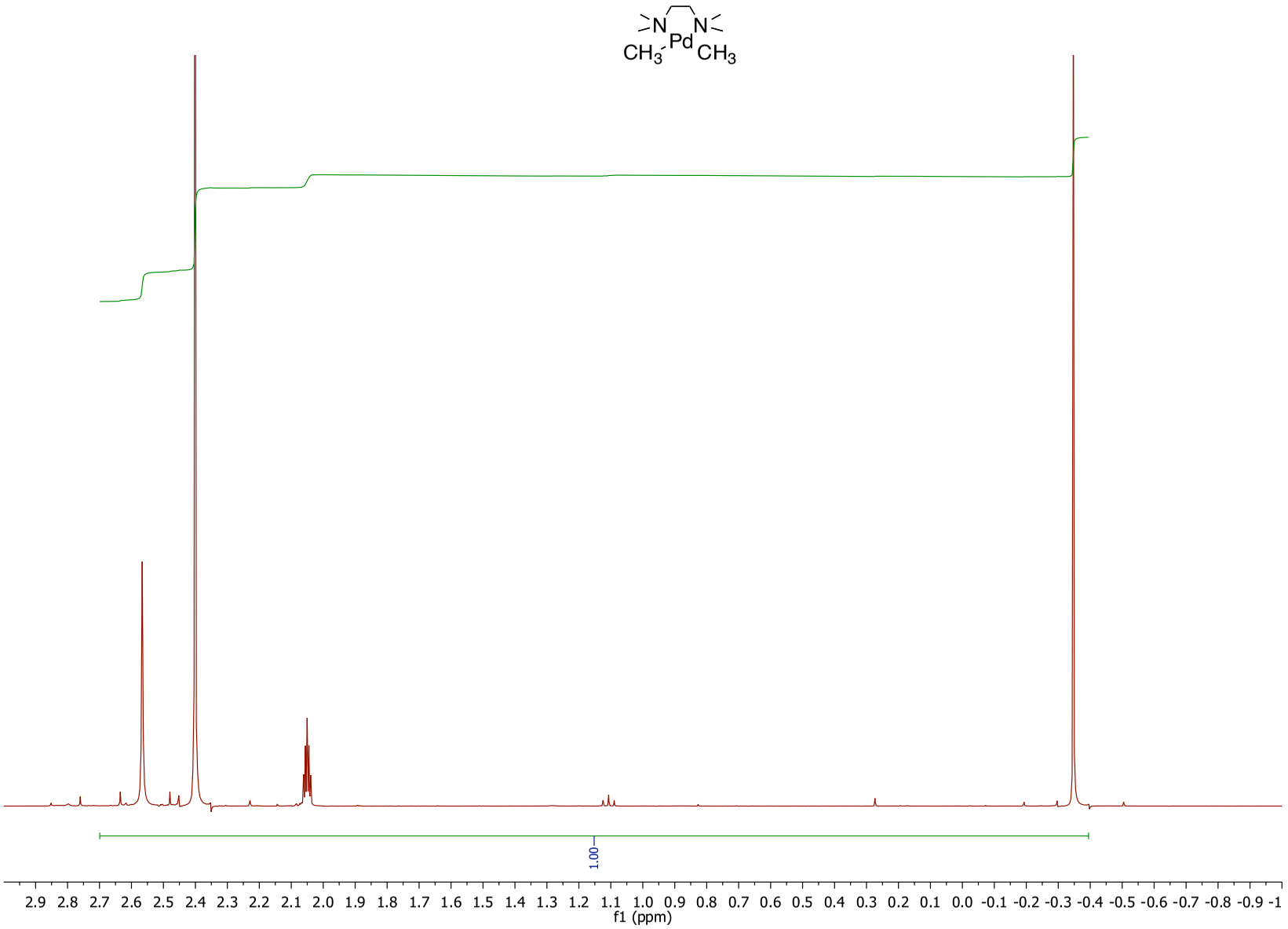
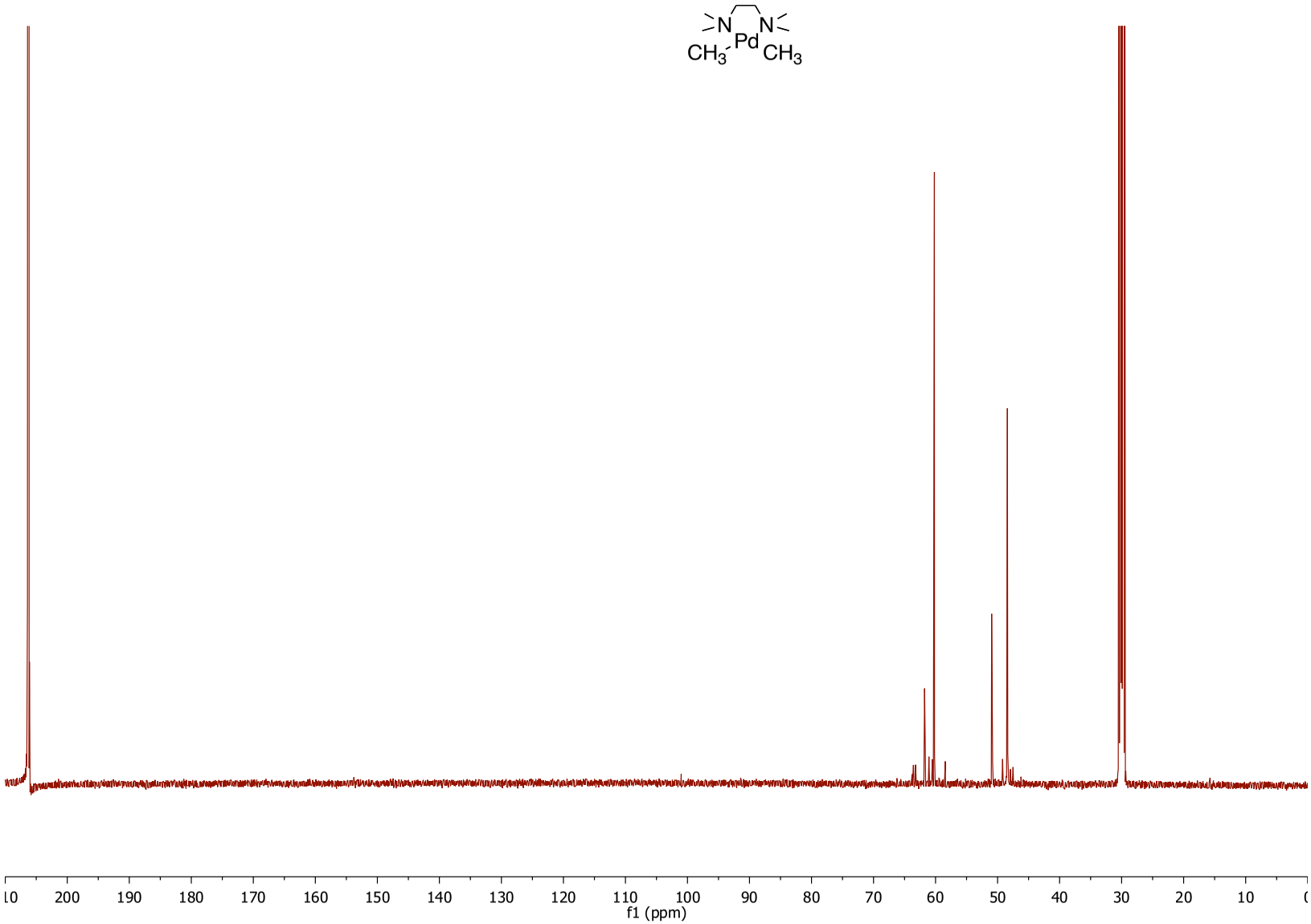
Appendix

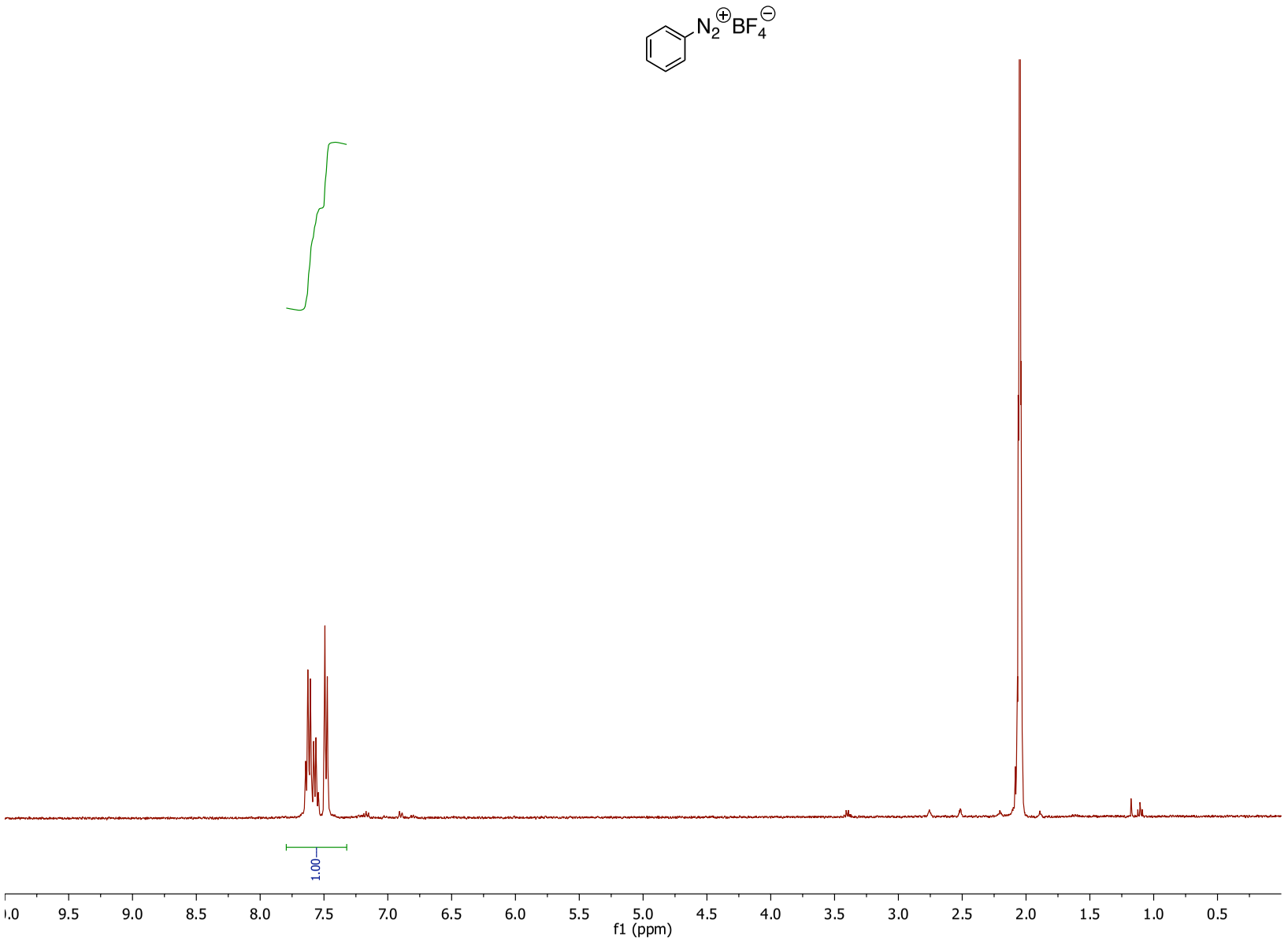
Selected NMR Spectra



^{1}H NMR (400 MHz, acetone-d_6, 25°C)



^{13}C NMR (500 MHz, acetone-d_6, 25°C)



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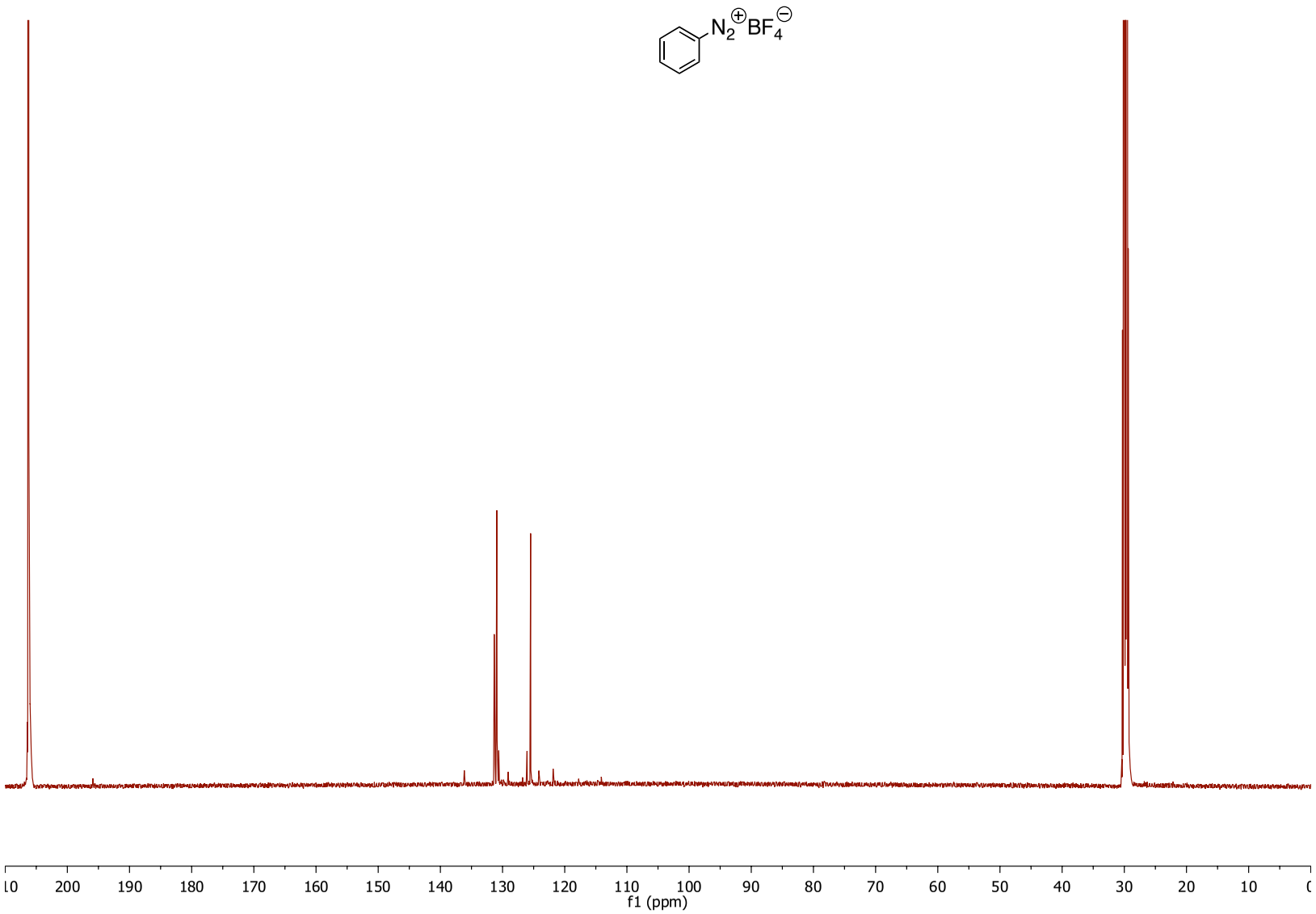

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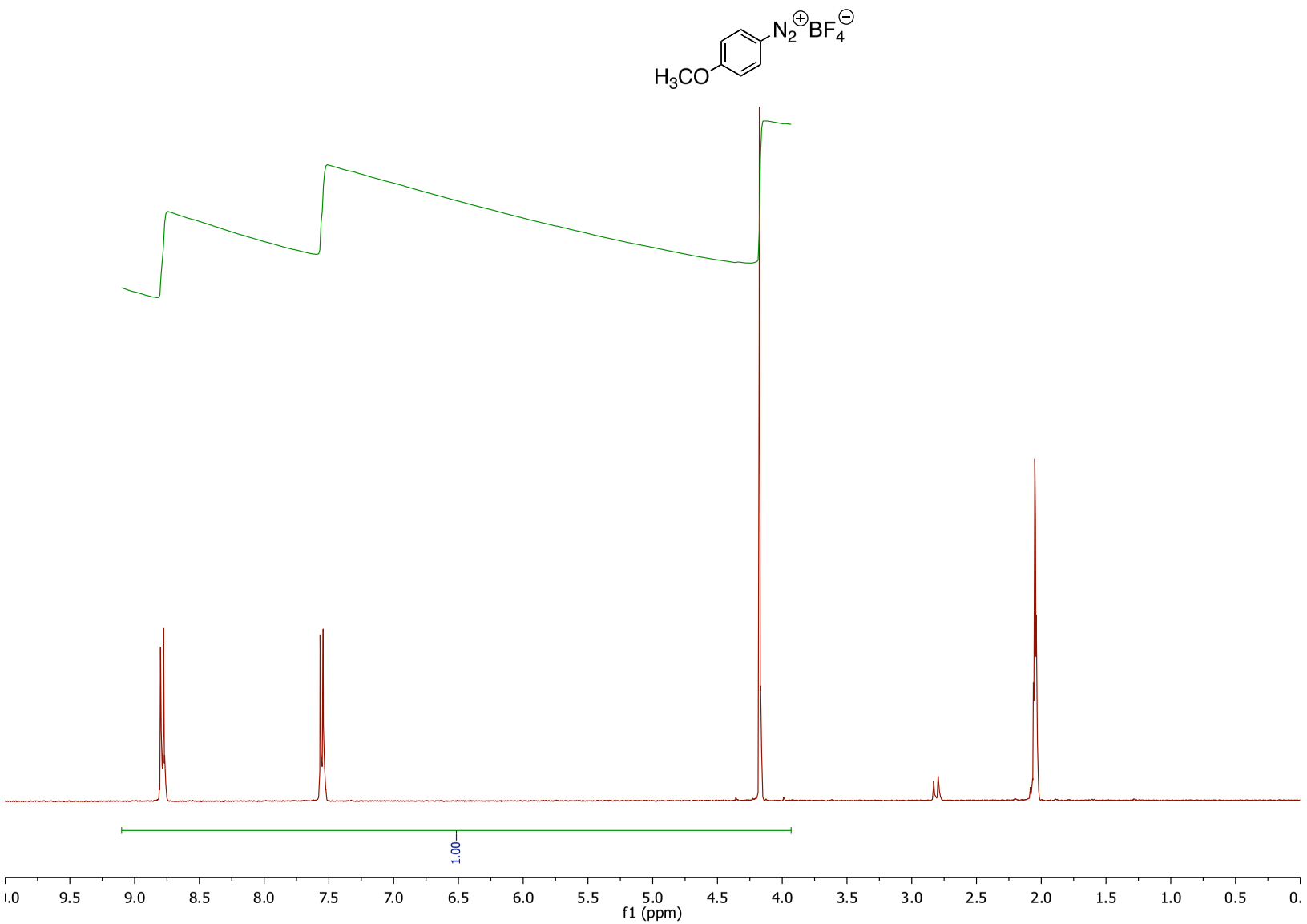

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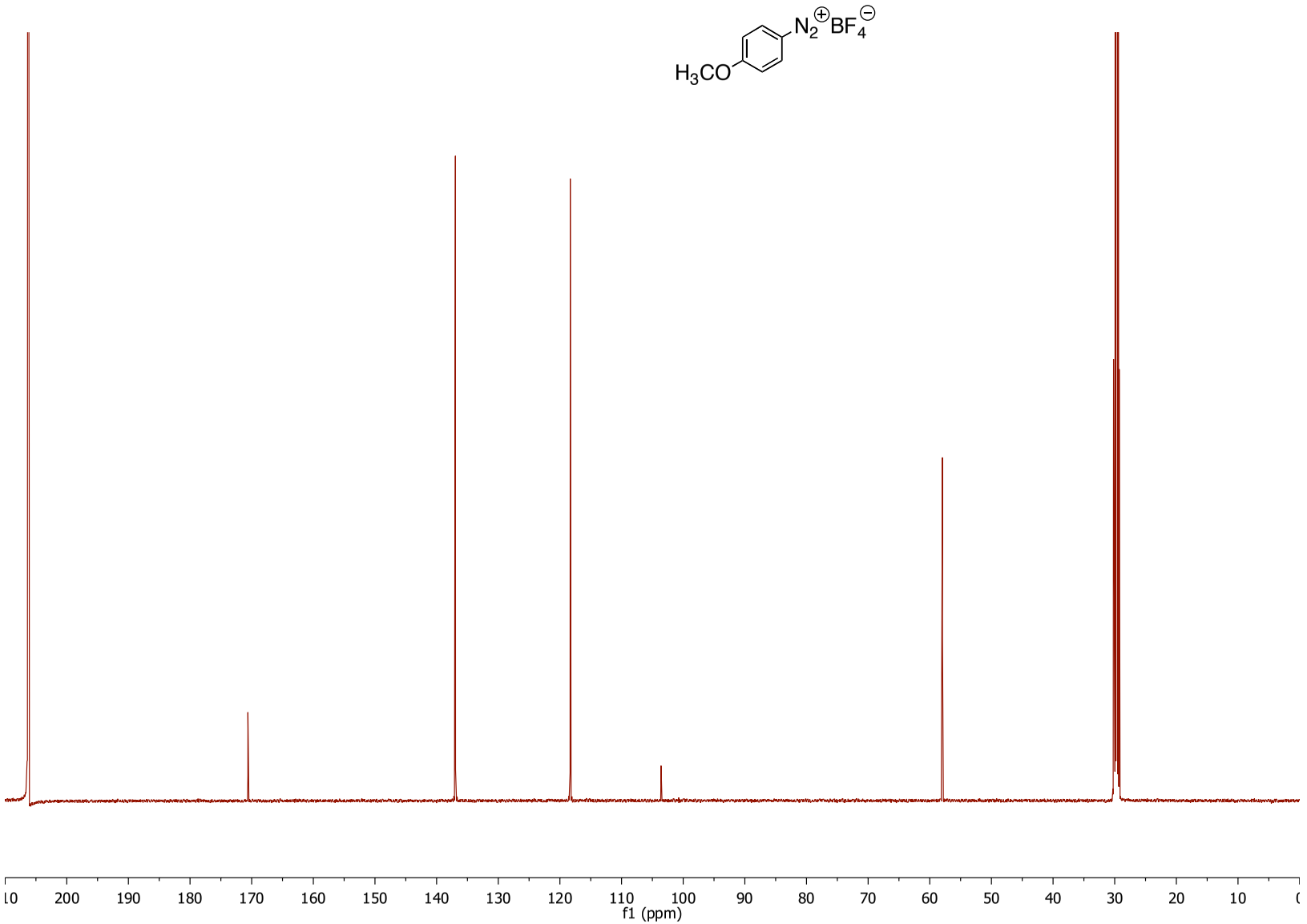

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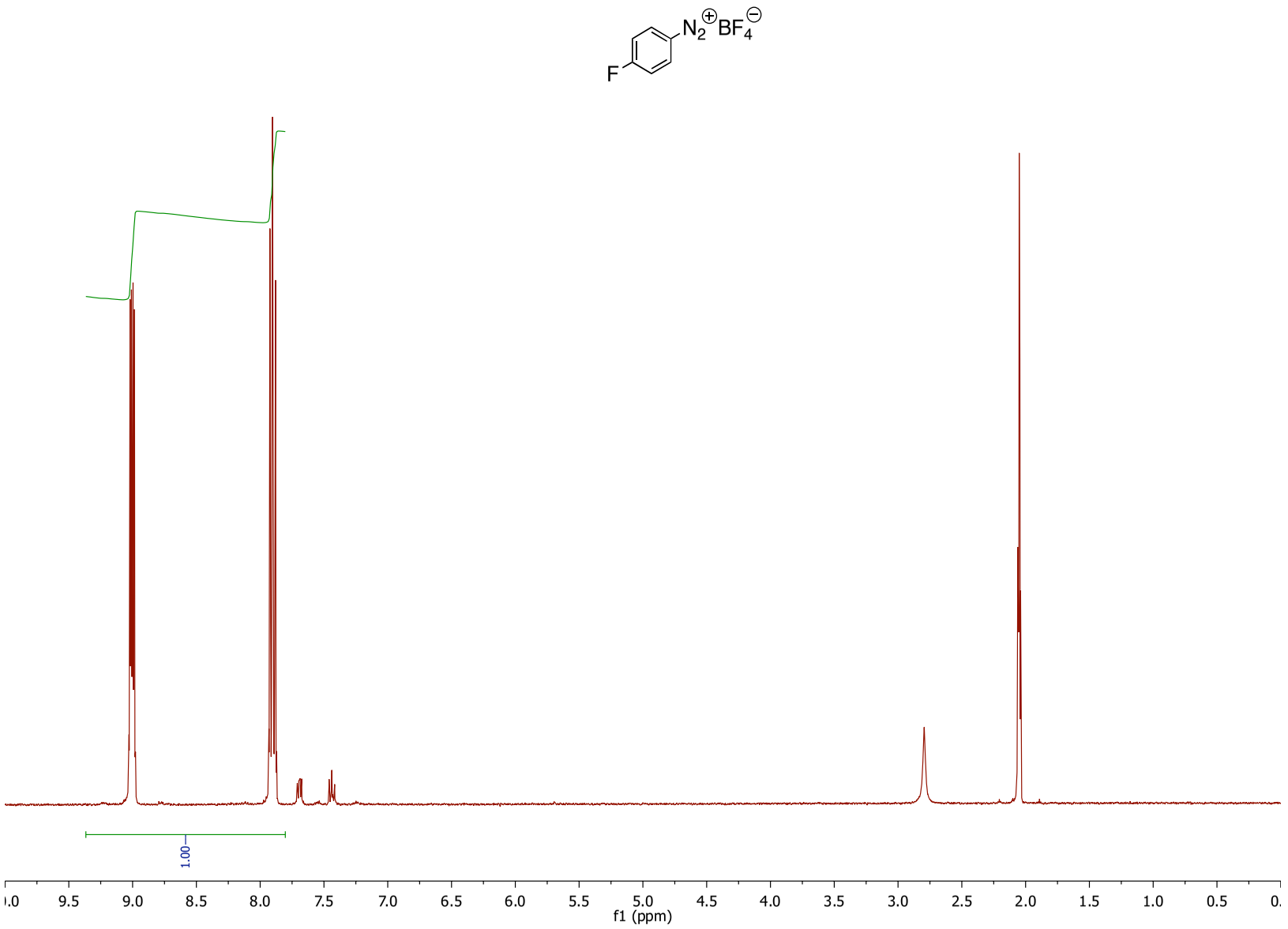
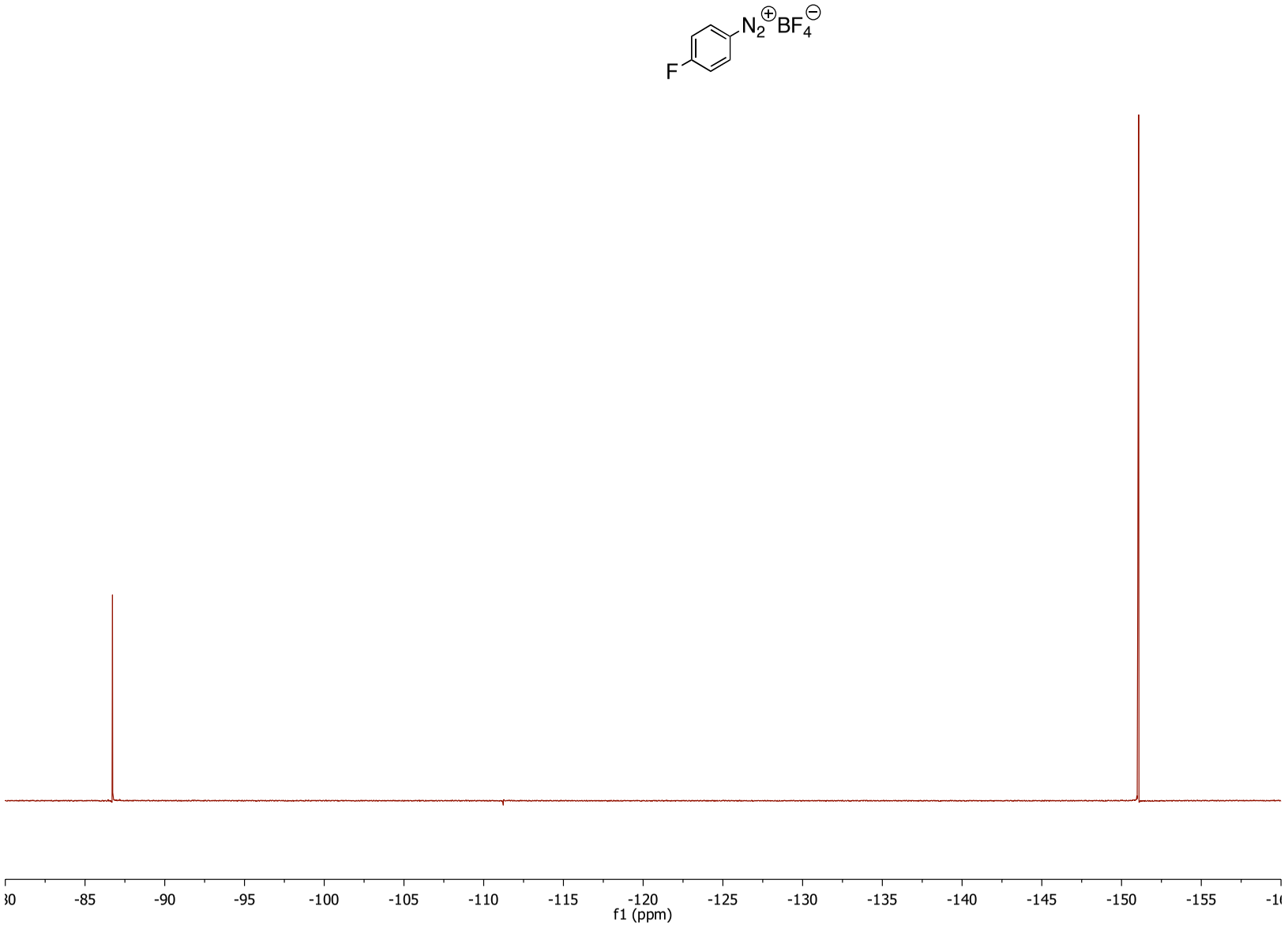
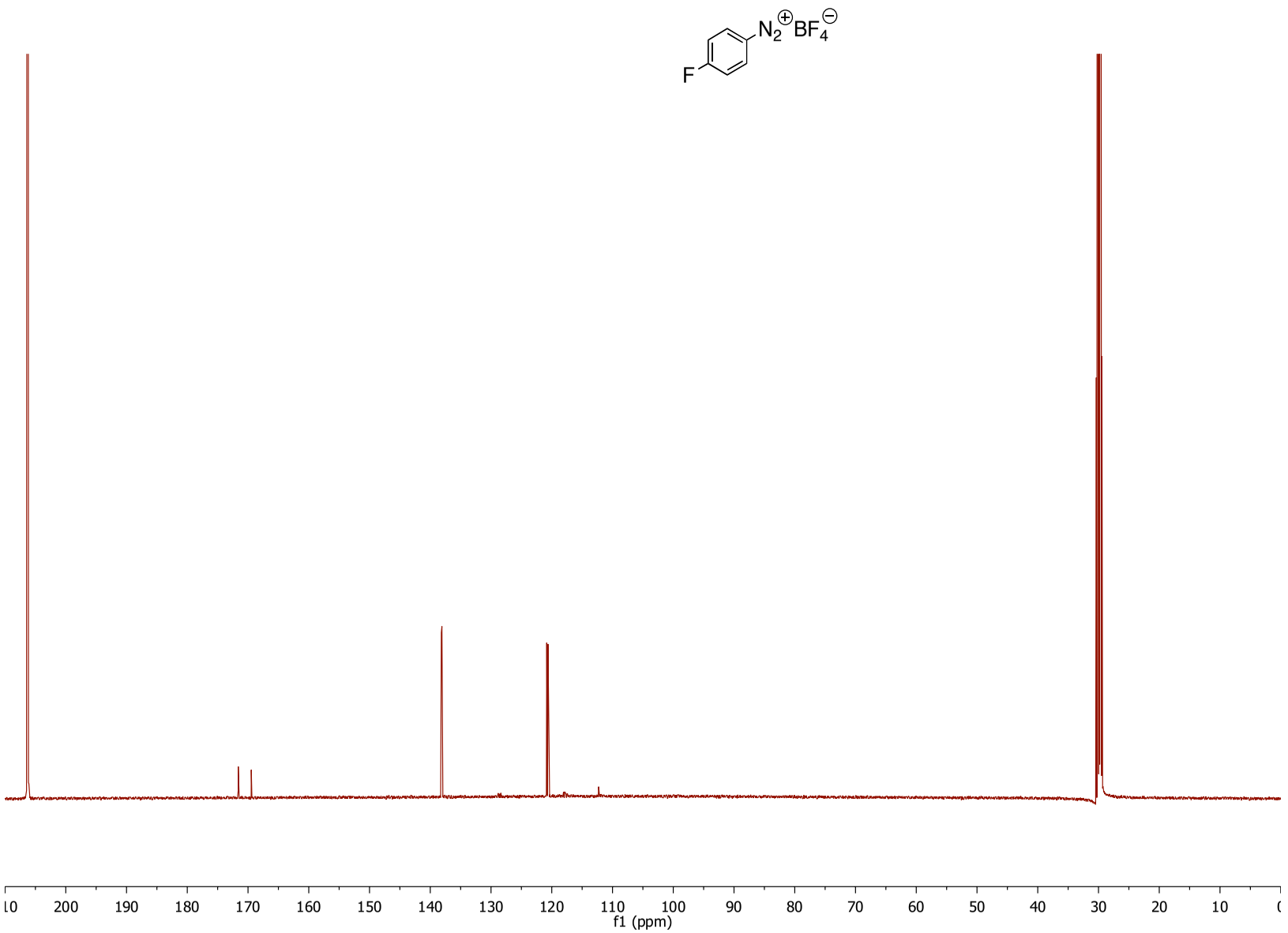


^{1}H NMR (400 MHz, acetone-d_6, 25°C)



^{19}F NMR (400 MHz, acetone-d_6, 25°C)



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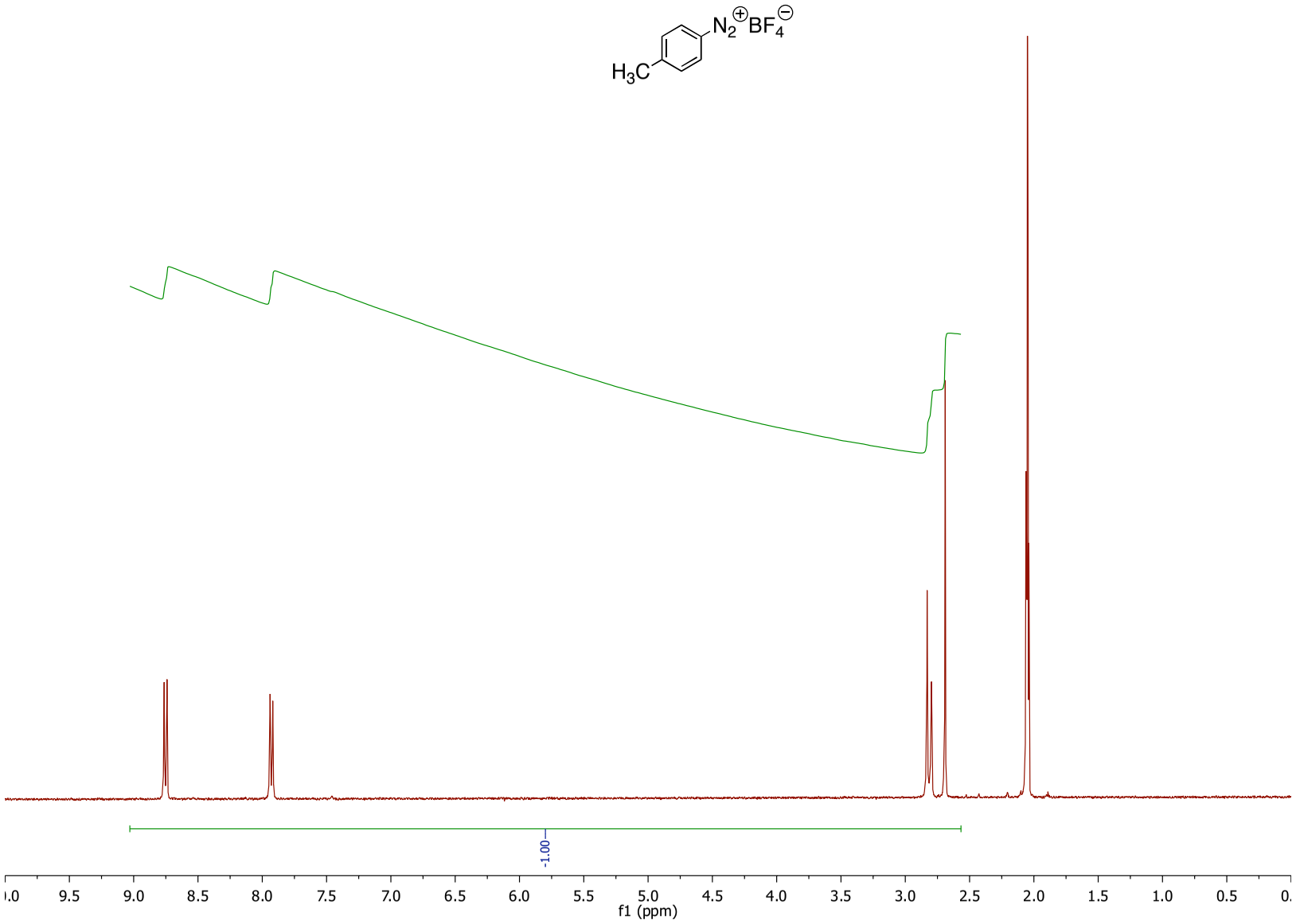

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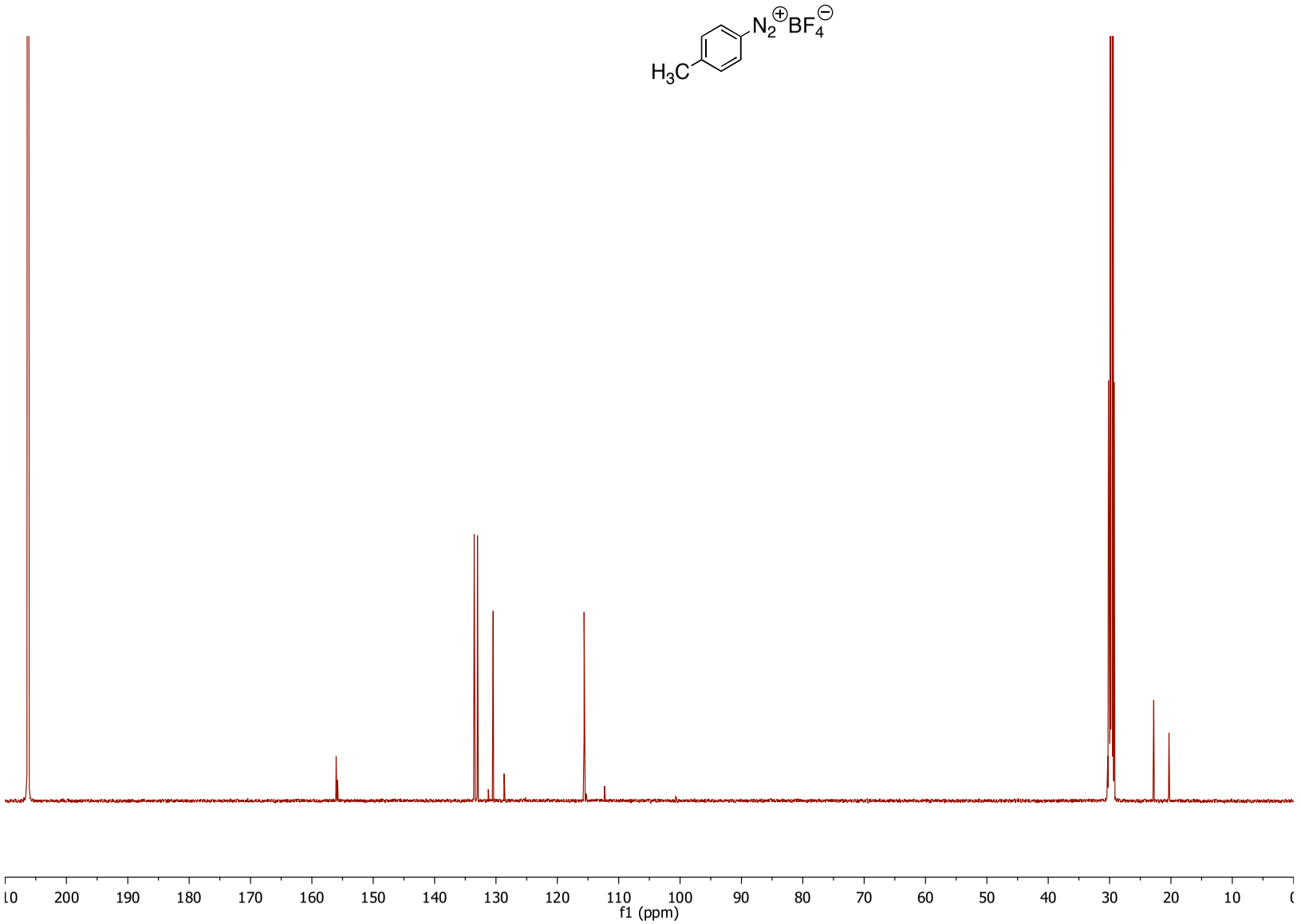

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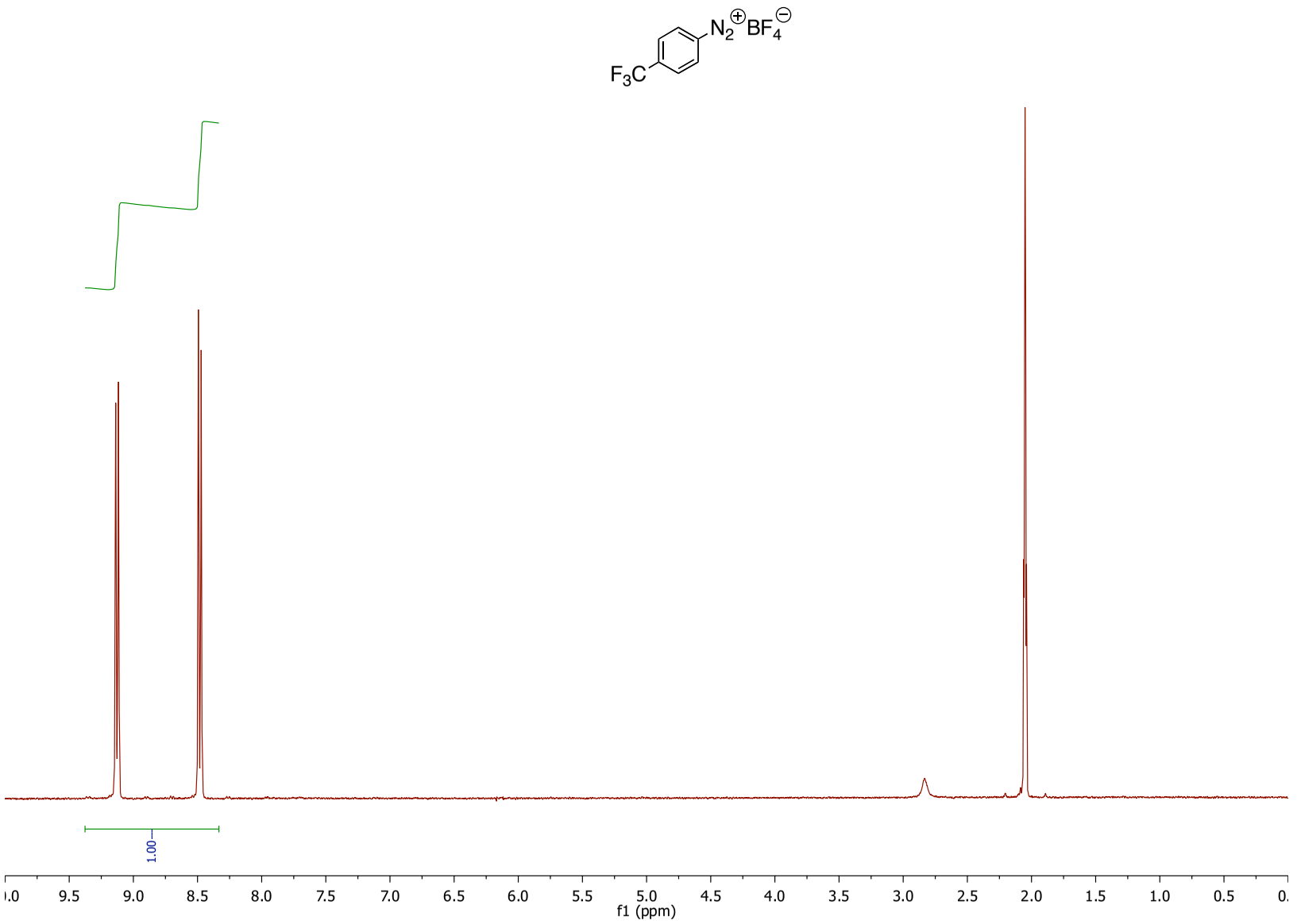

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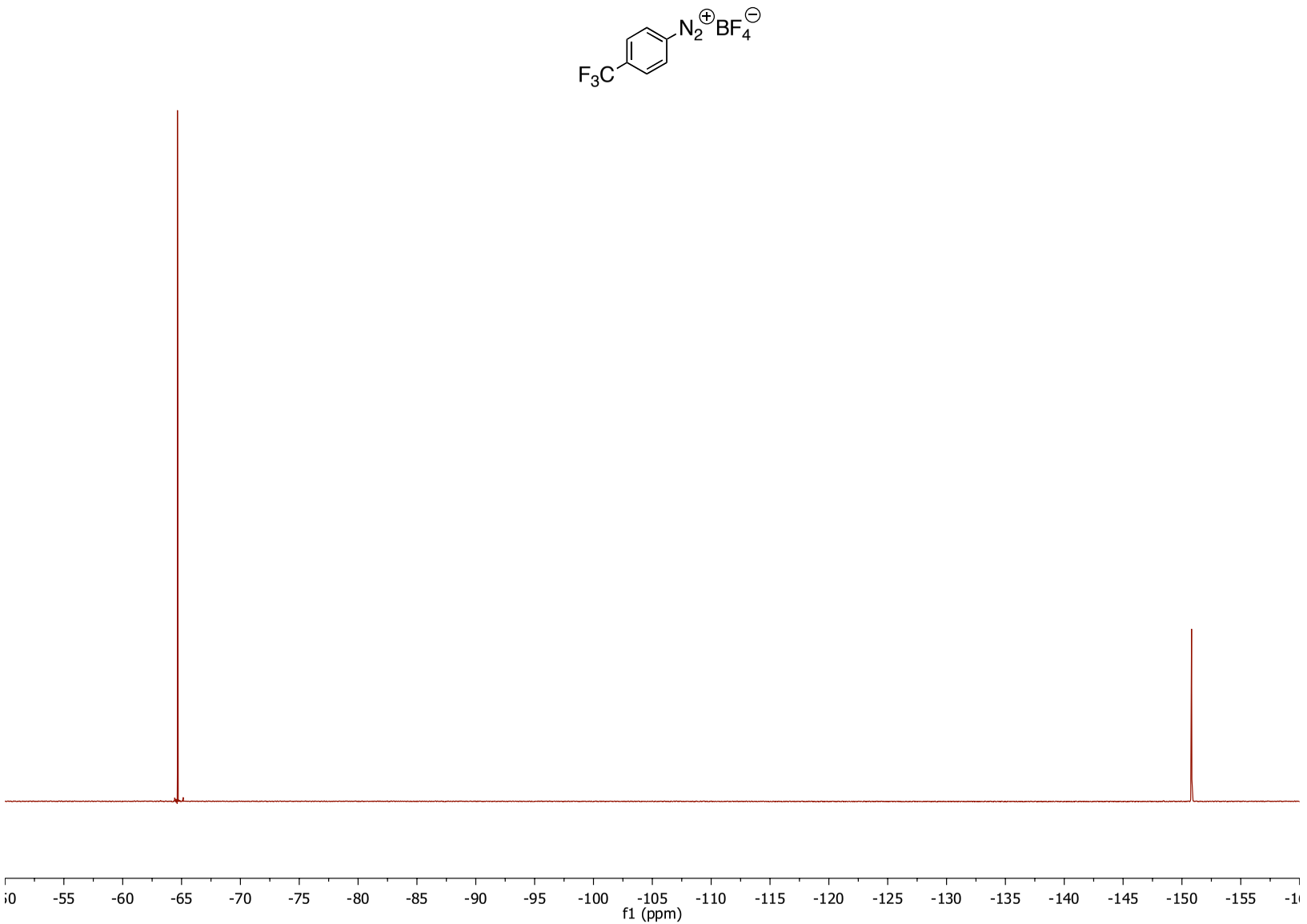

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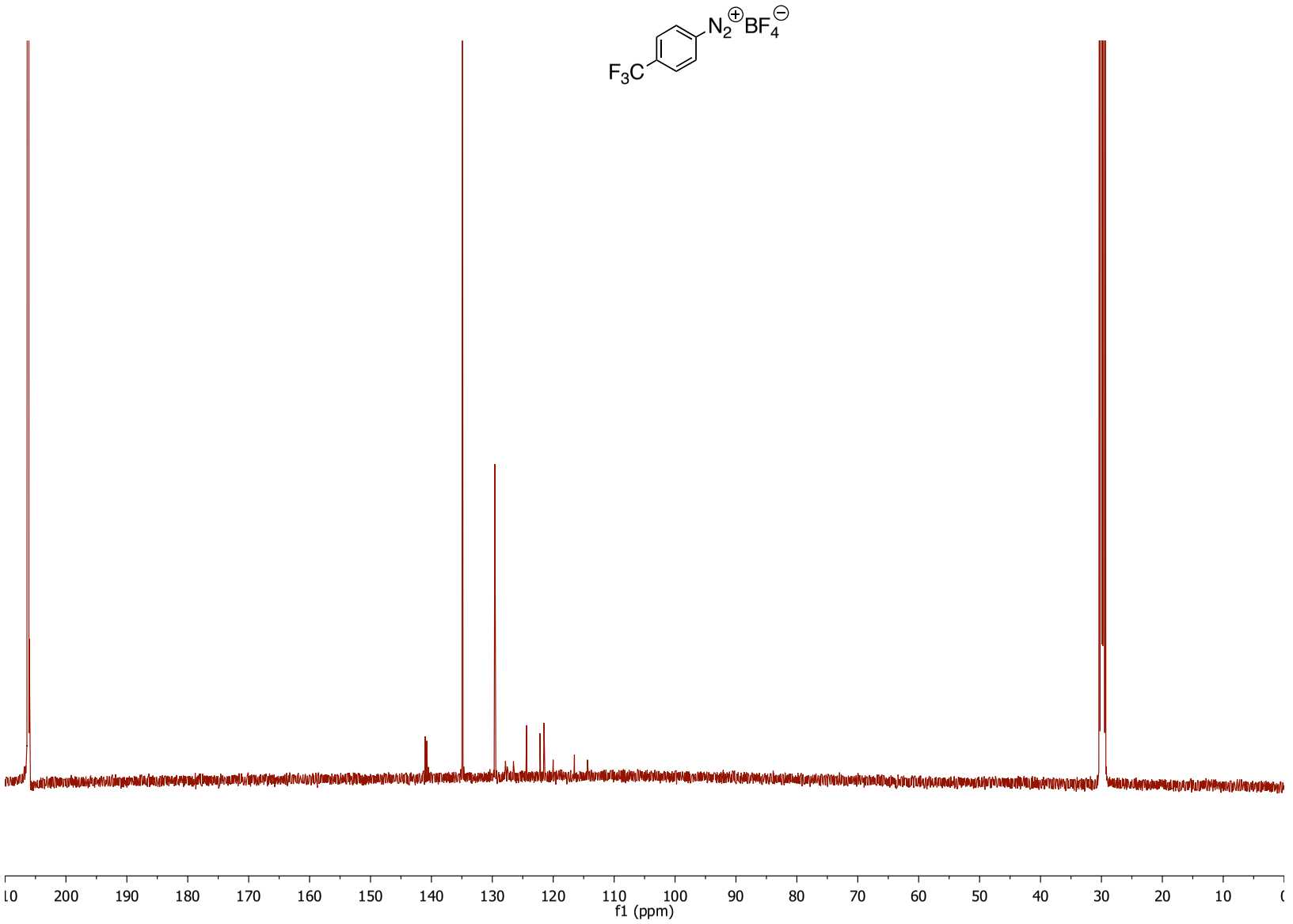

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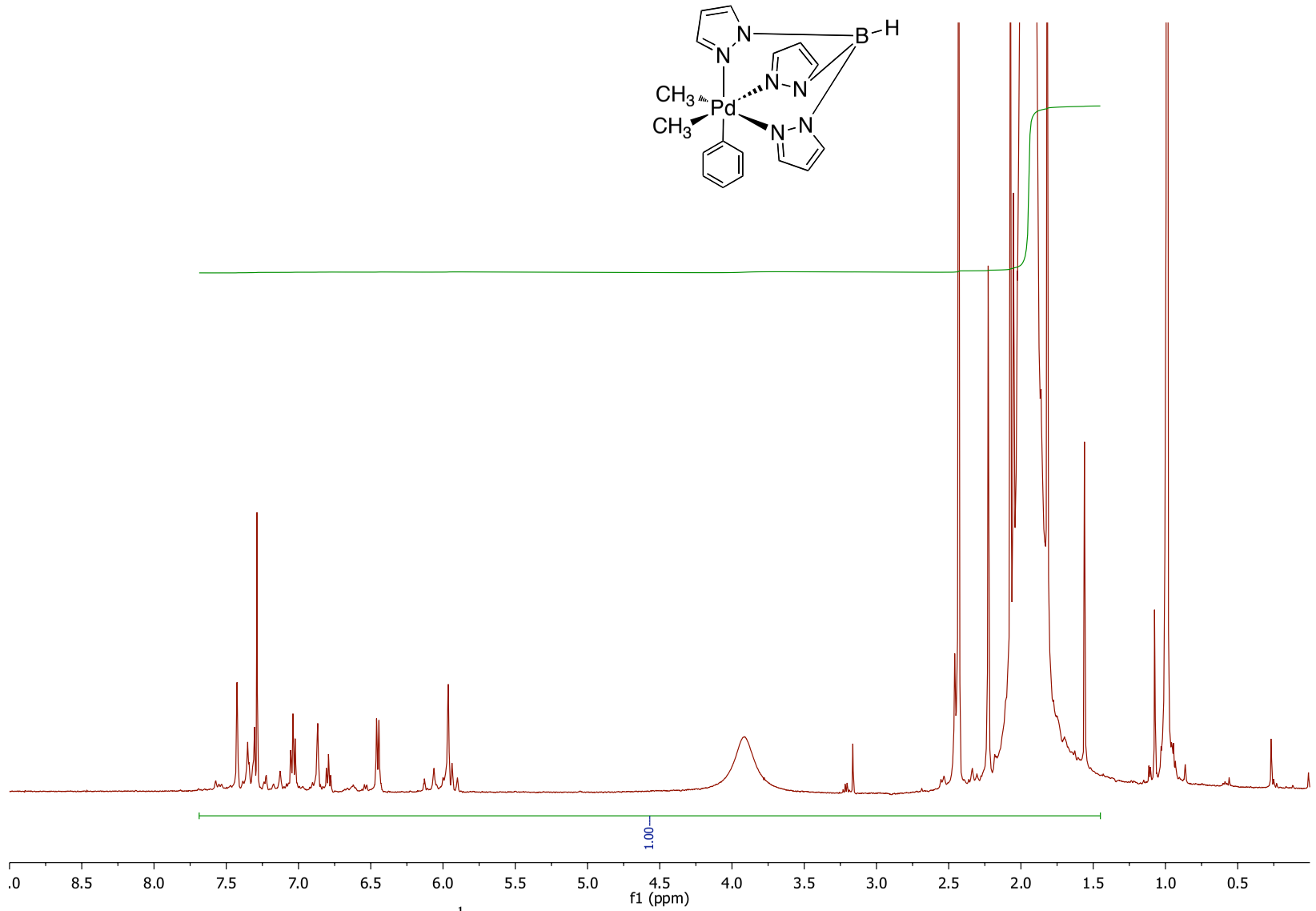
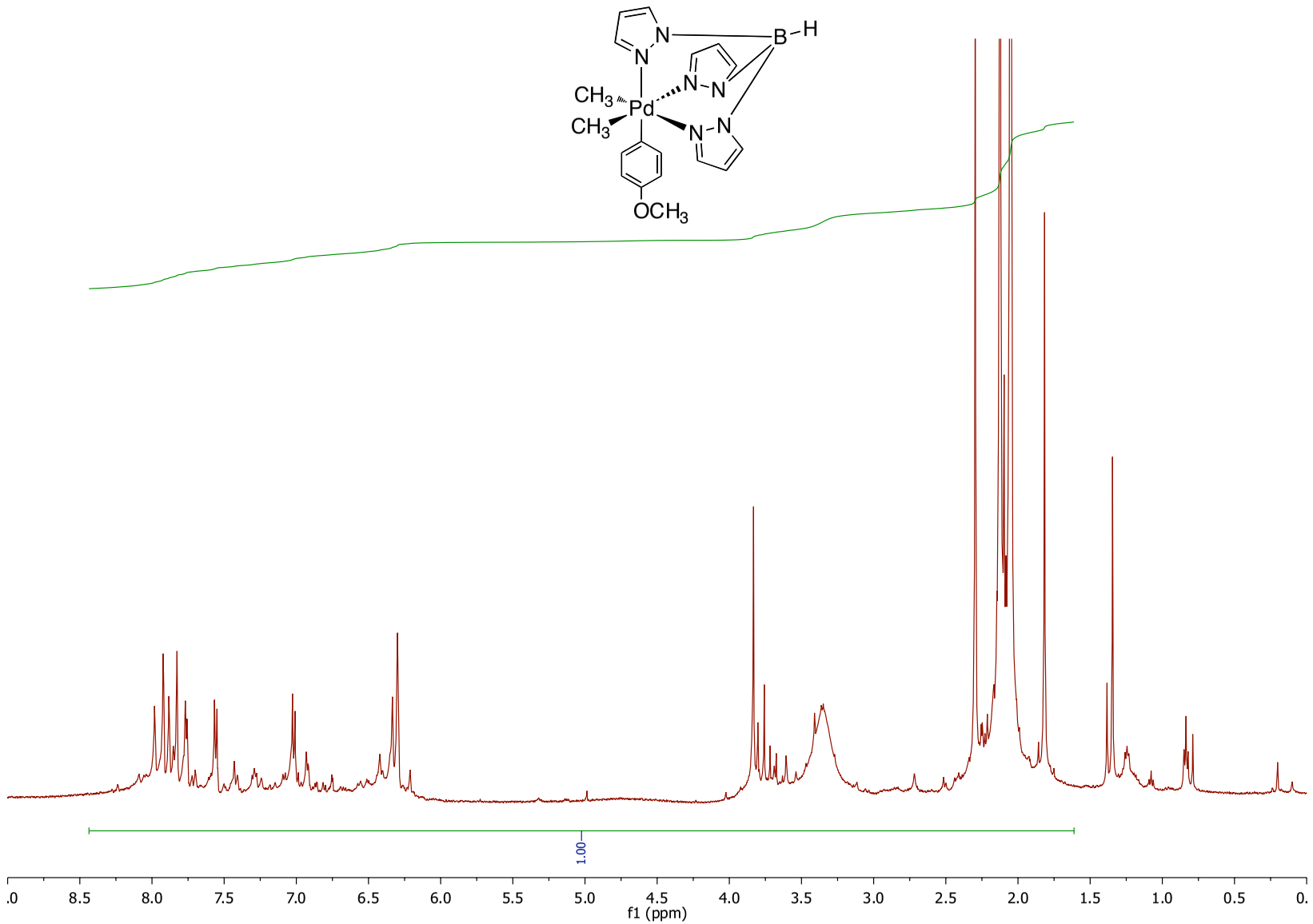
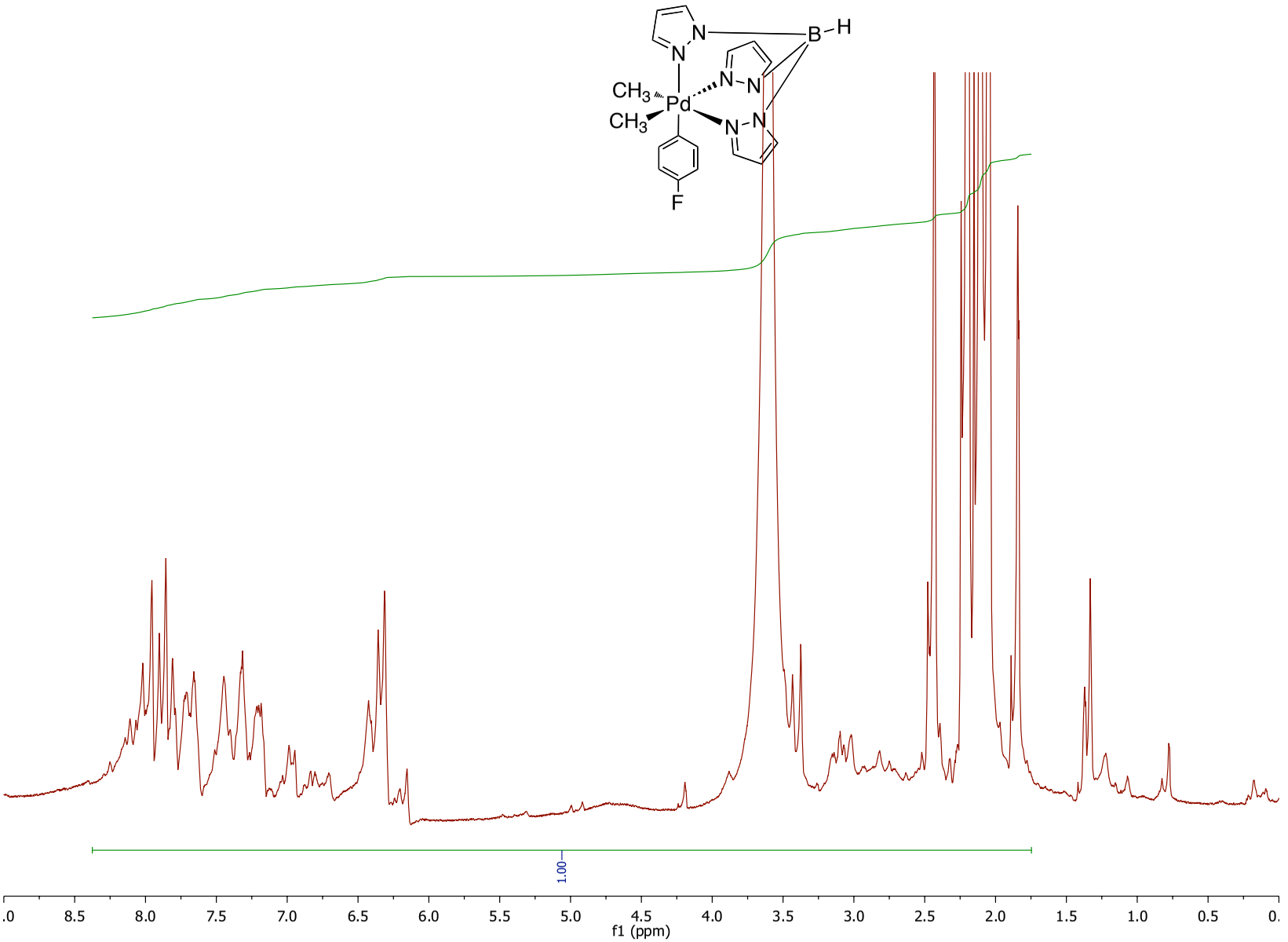


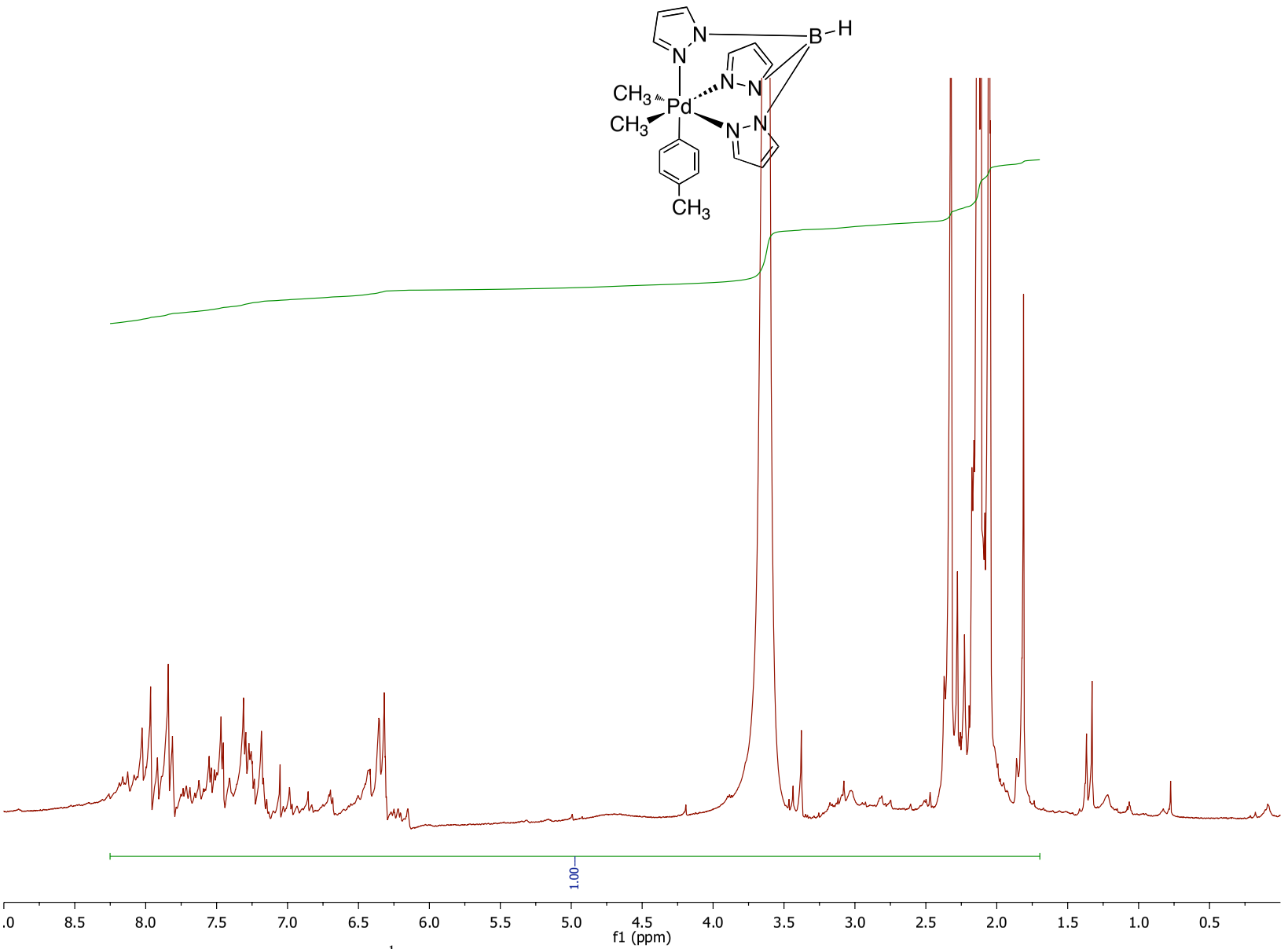
^{1}H NMR (500 MHz, acetone-d_6, -40°C)
detected in solution



^{1}H NMR (500 MHz, acetone-d_6, -40°C)
detected in solution



^{1}H NMR (500 MHz, acetone-d_6, -40°C)
detected in solution



^{1}H NMR (500 MHz, acetone-d_6, -40°C)
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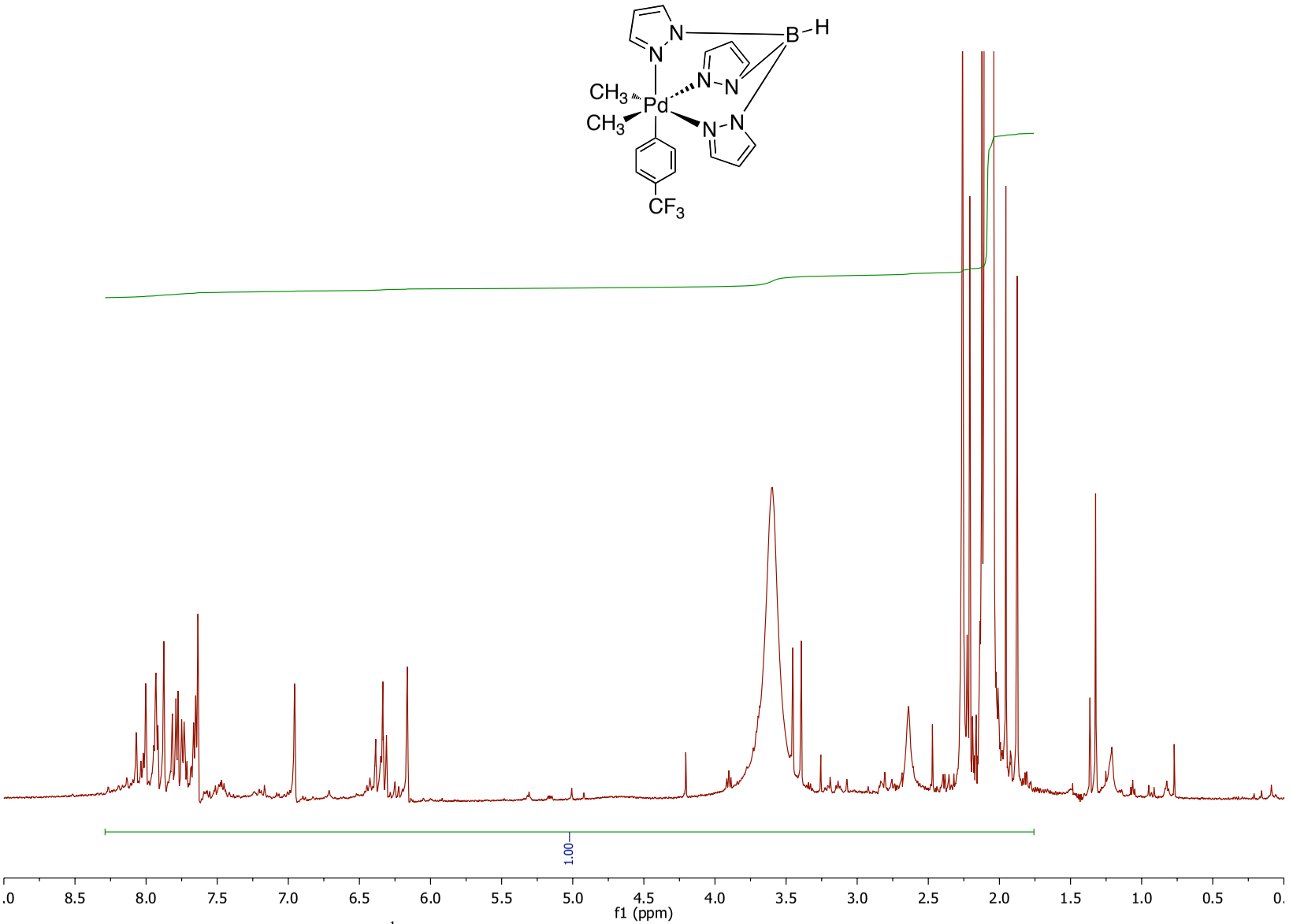
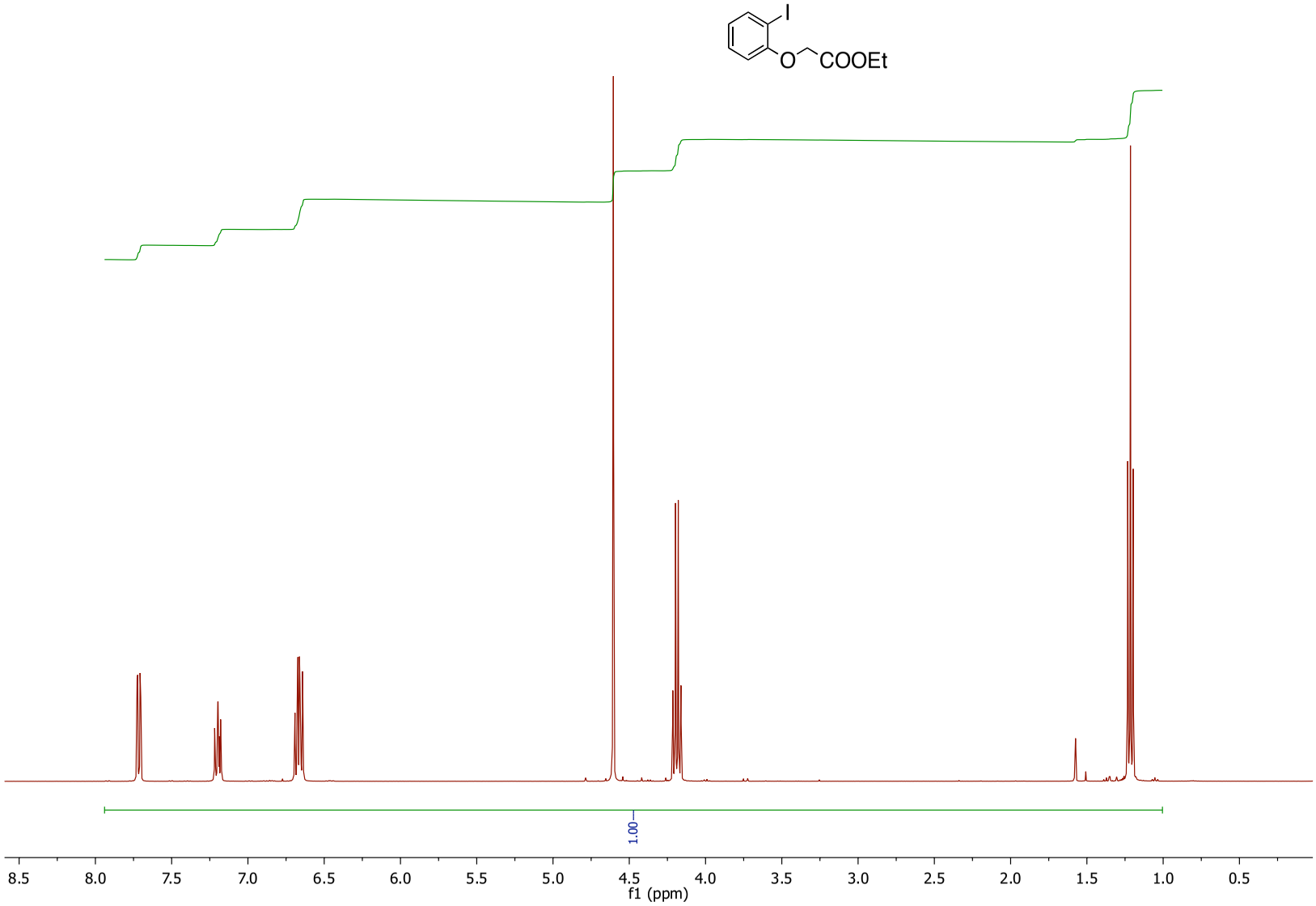
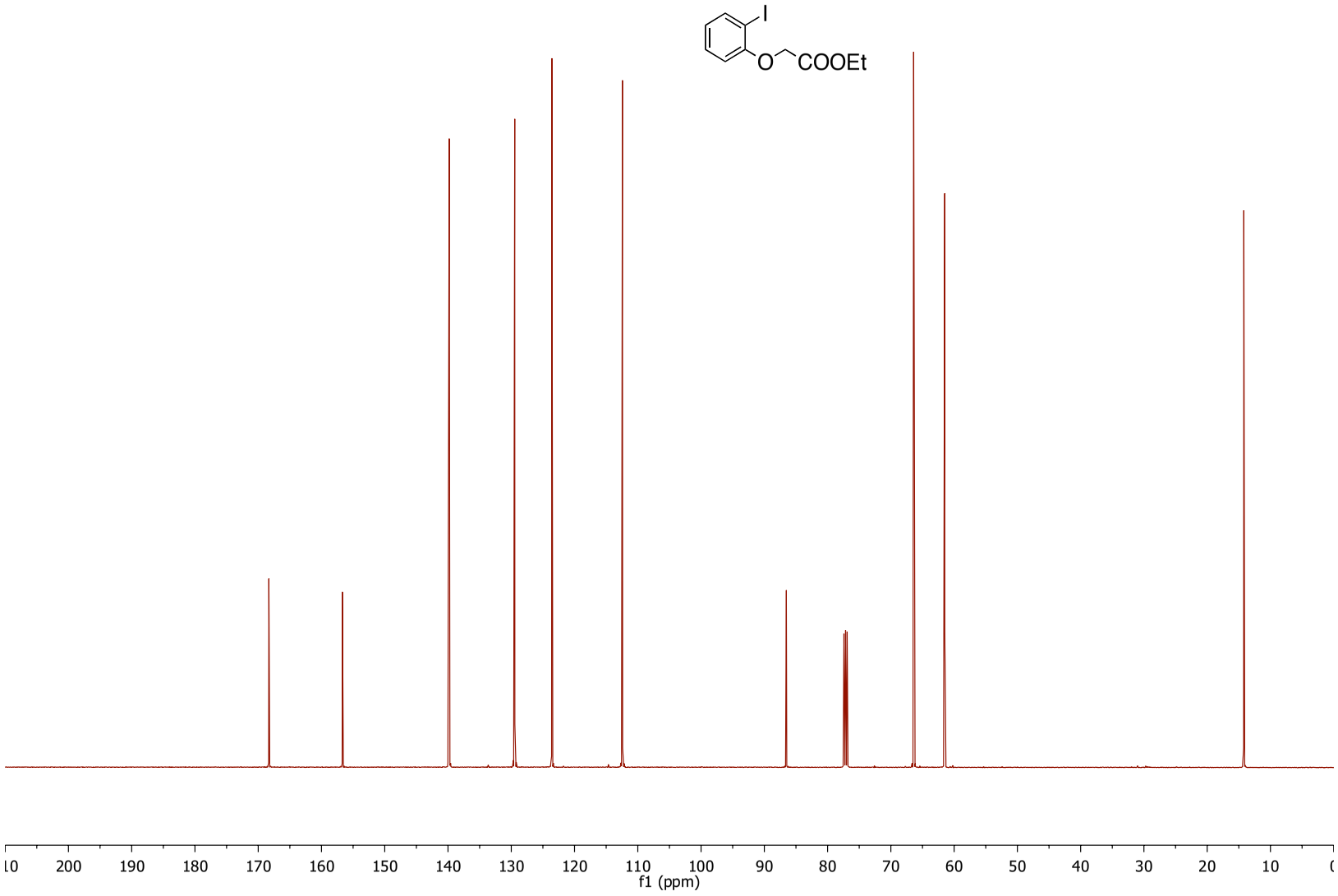


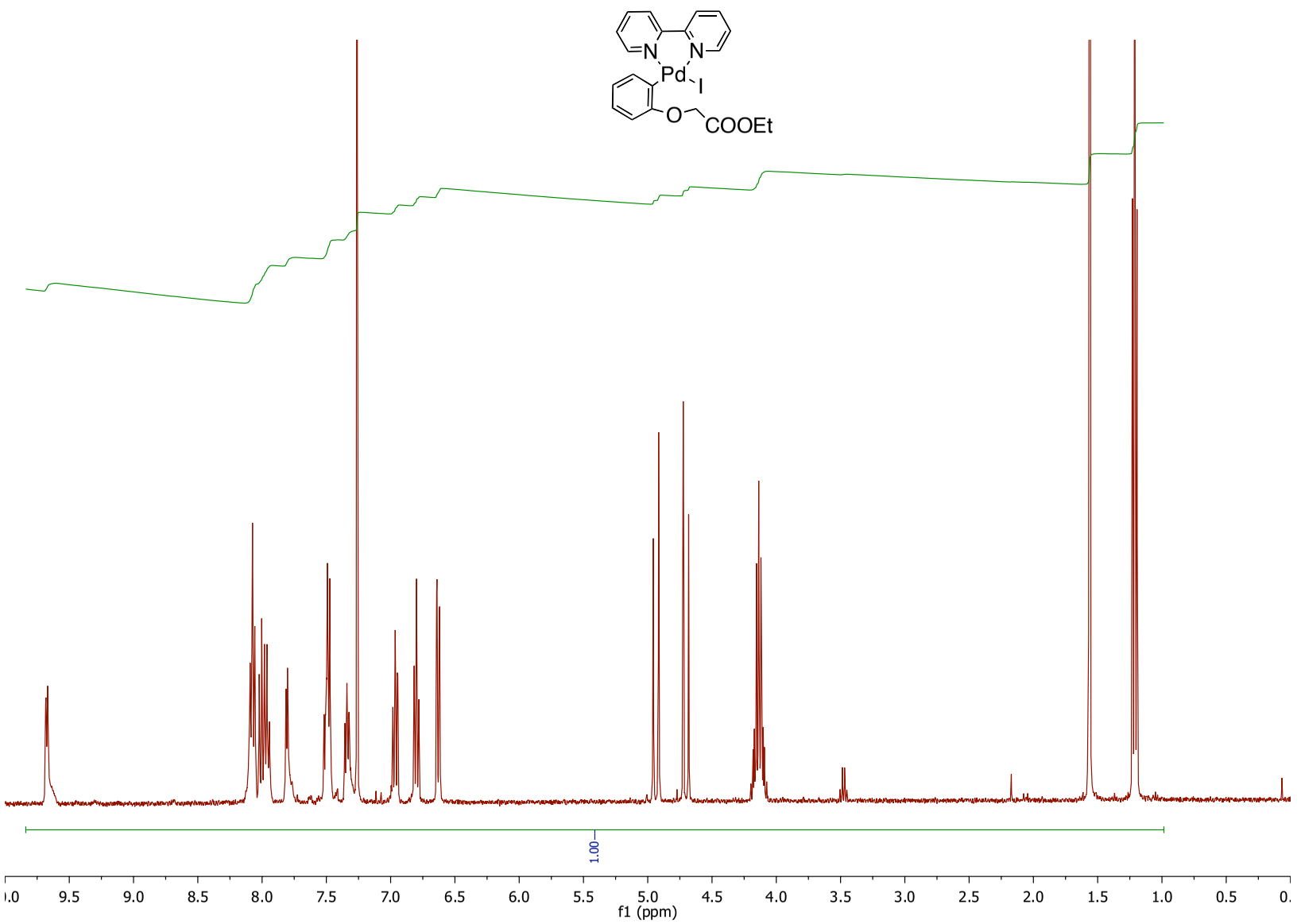
^{1}H NMR (500 MHz, acetone-d_6, -40°C)
detected in solution



^{1}H NMR (400 MHz, $CDCl_3$, 25°C)



^{13}C NMR (500 MHz, $CDCl_3$, 25°C)



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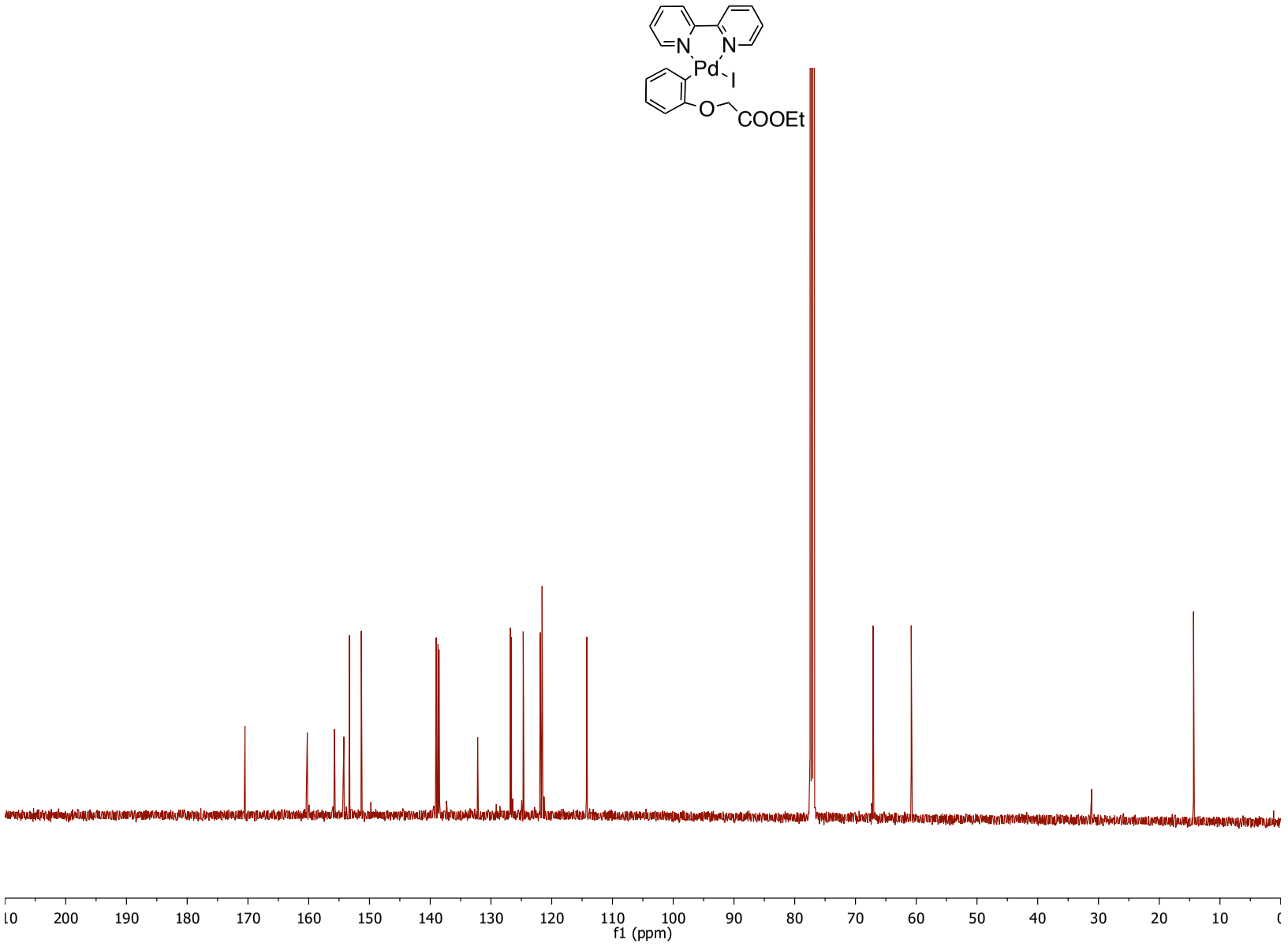

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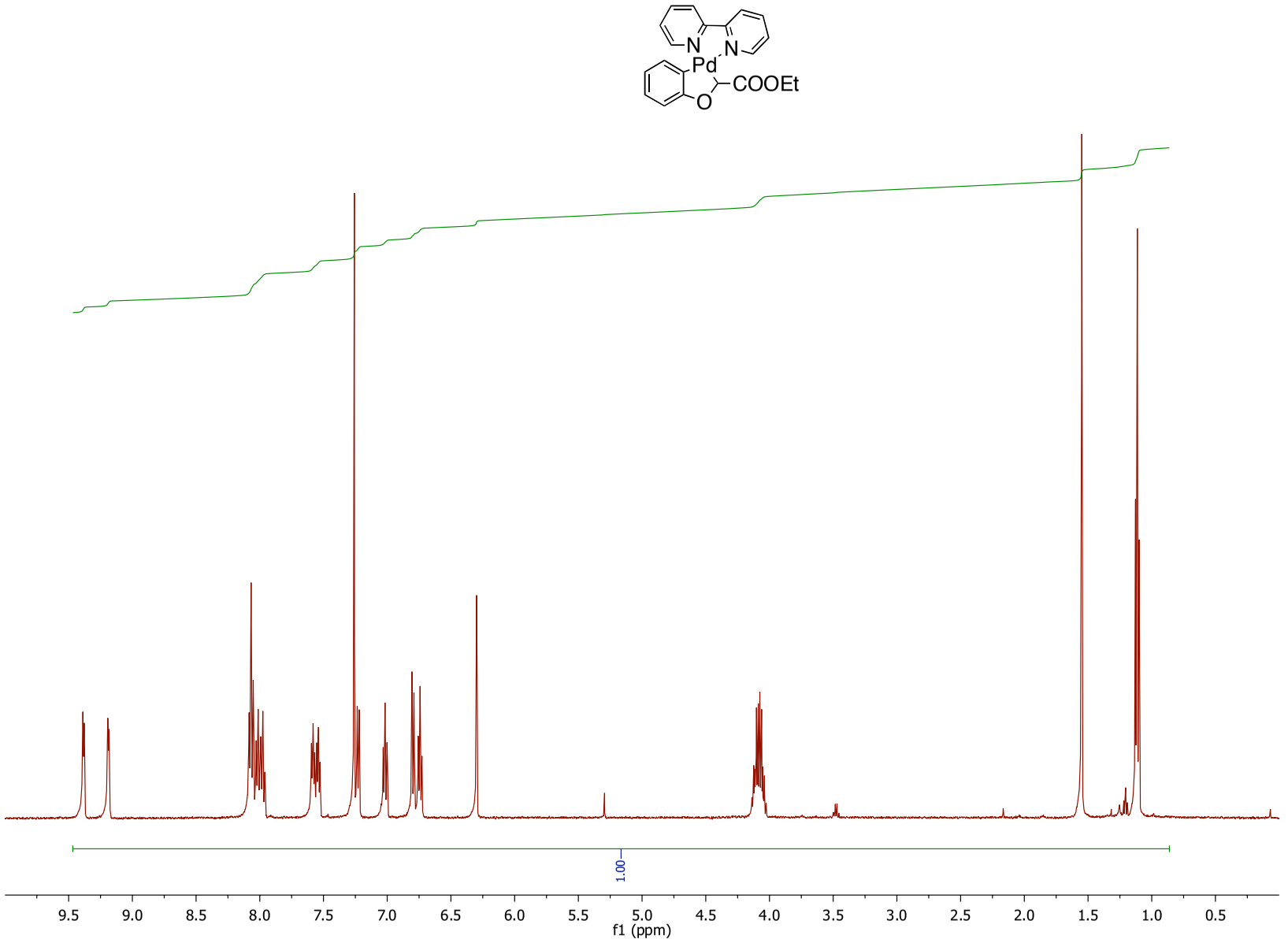

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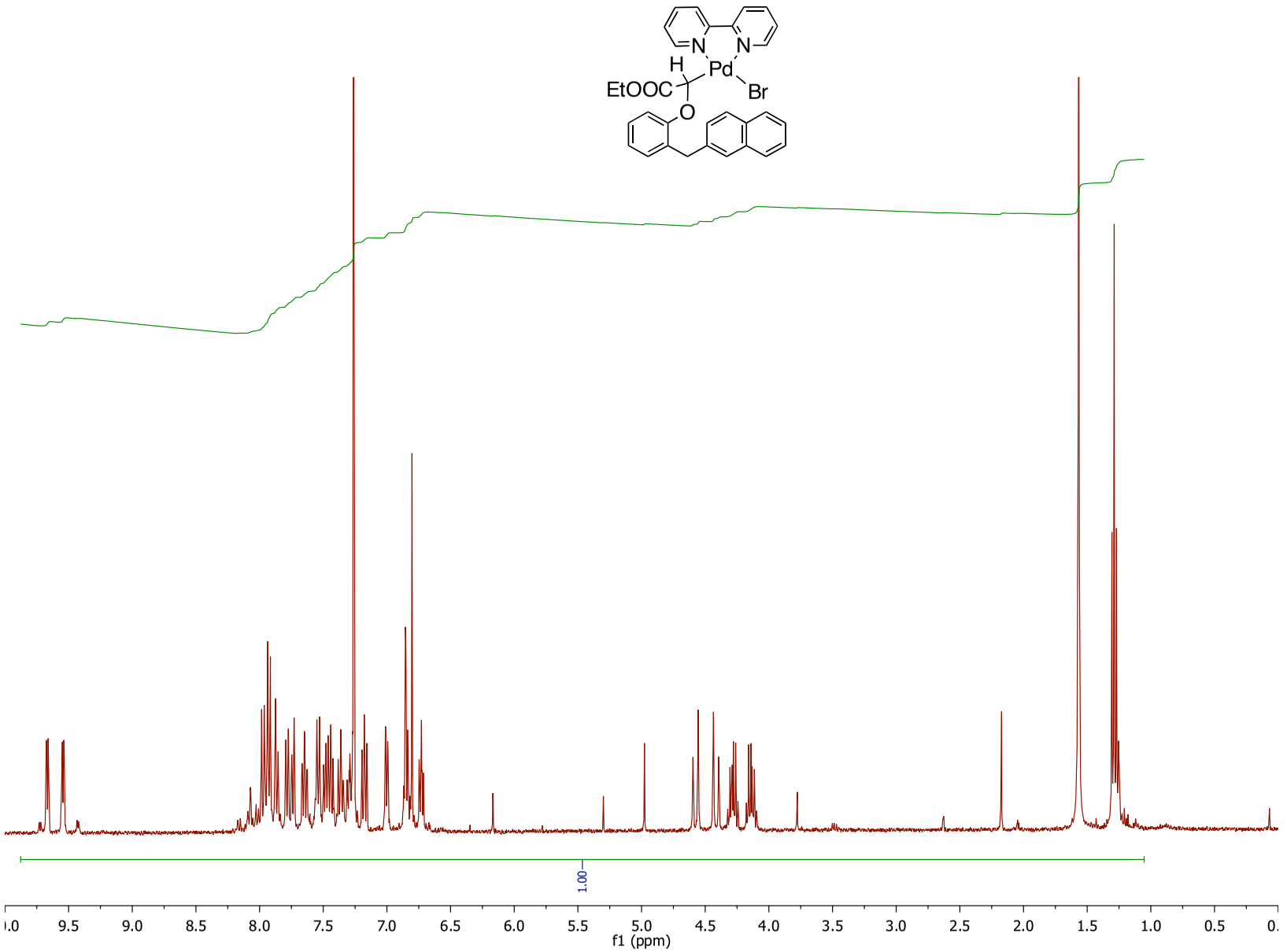

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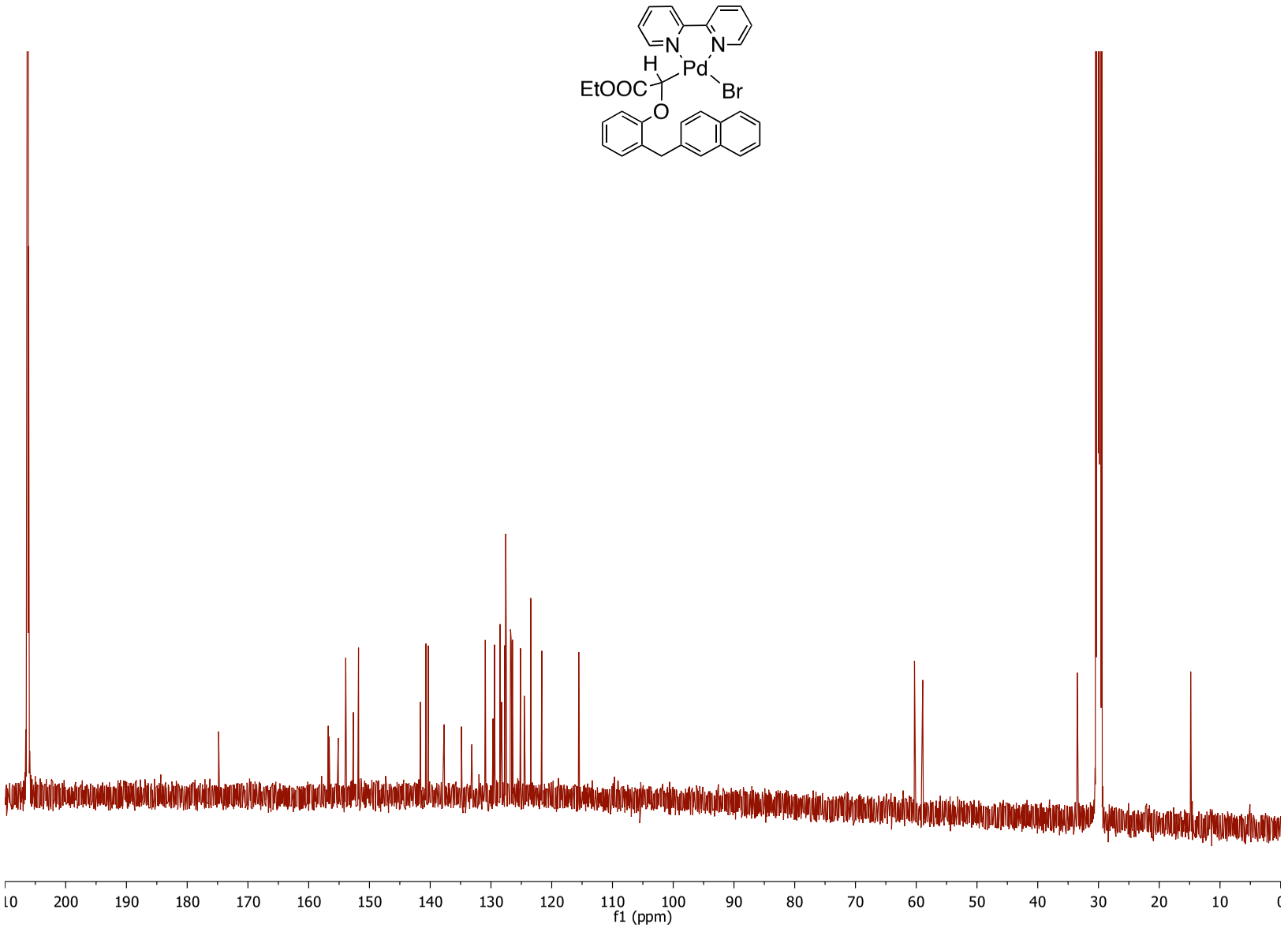

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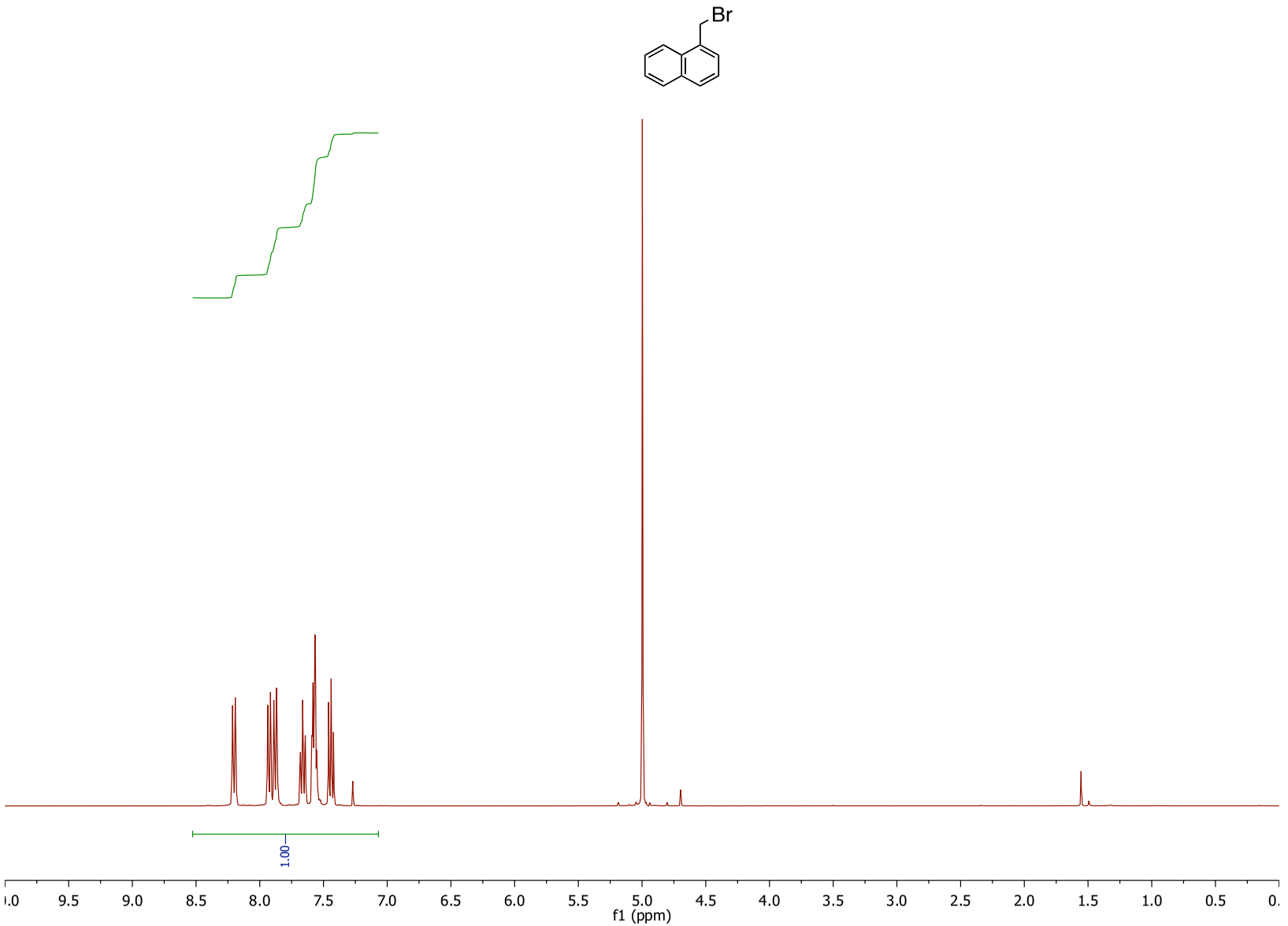

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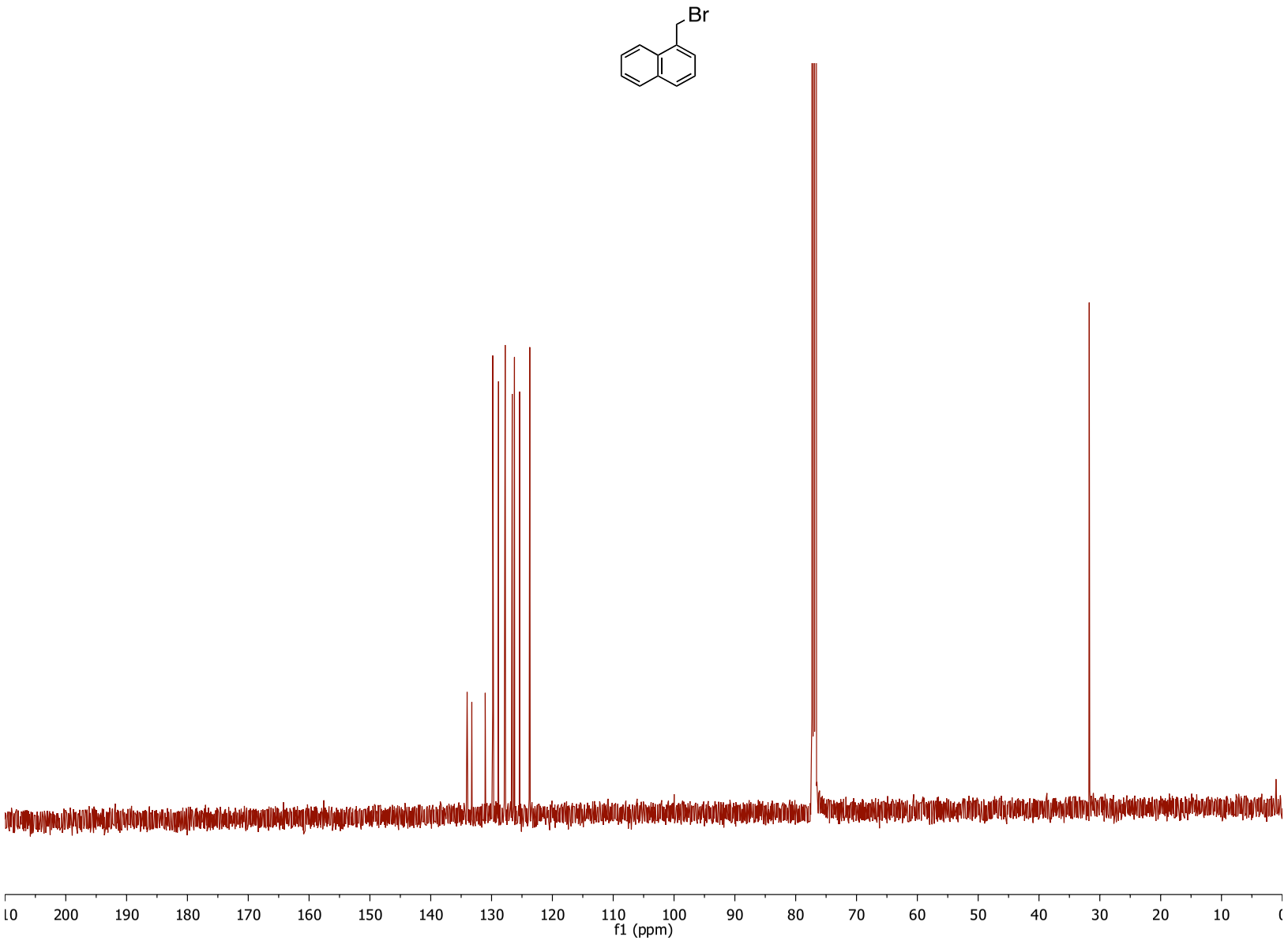

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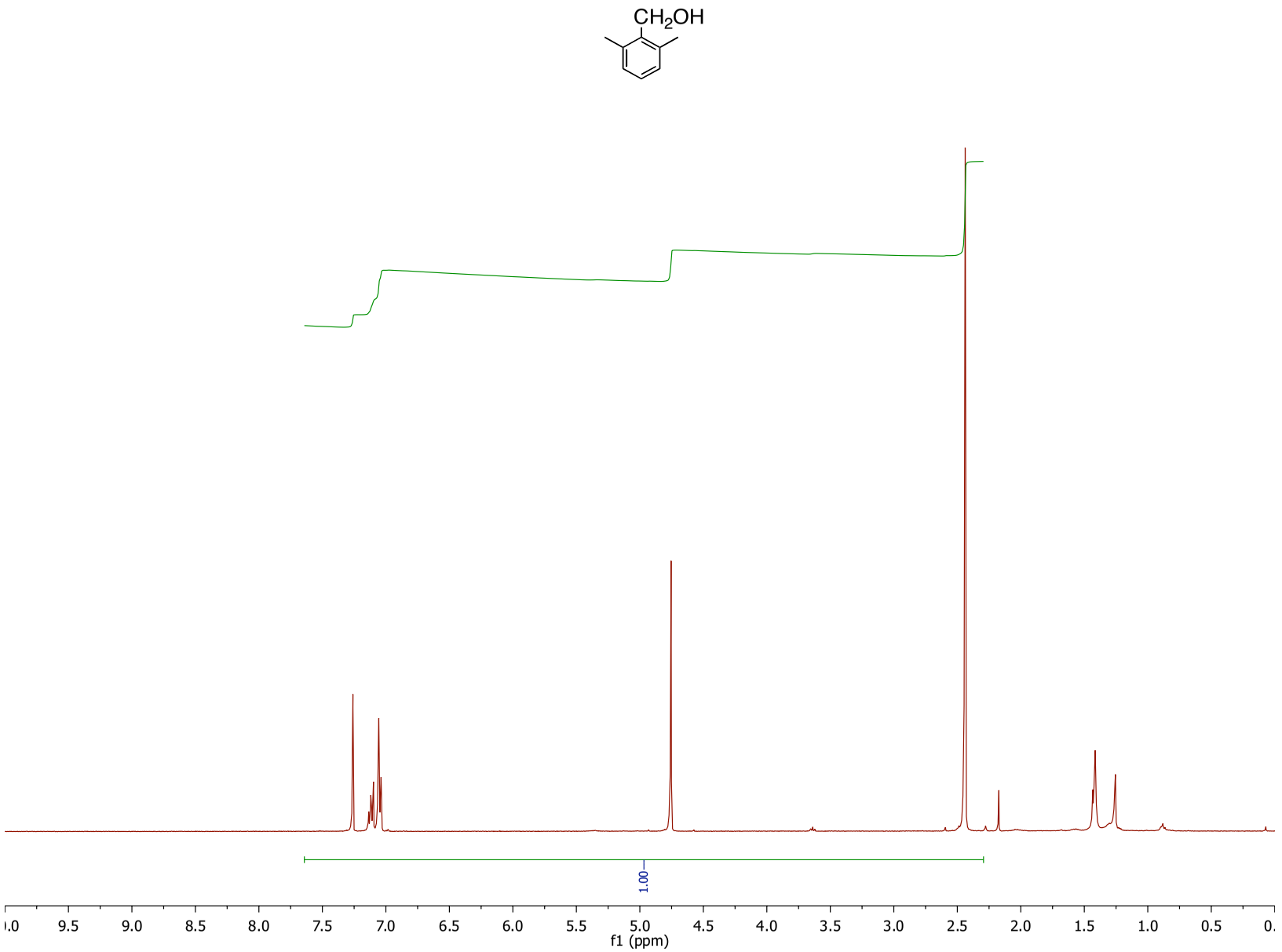

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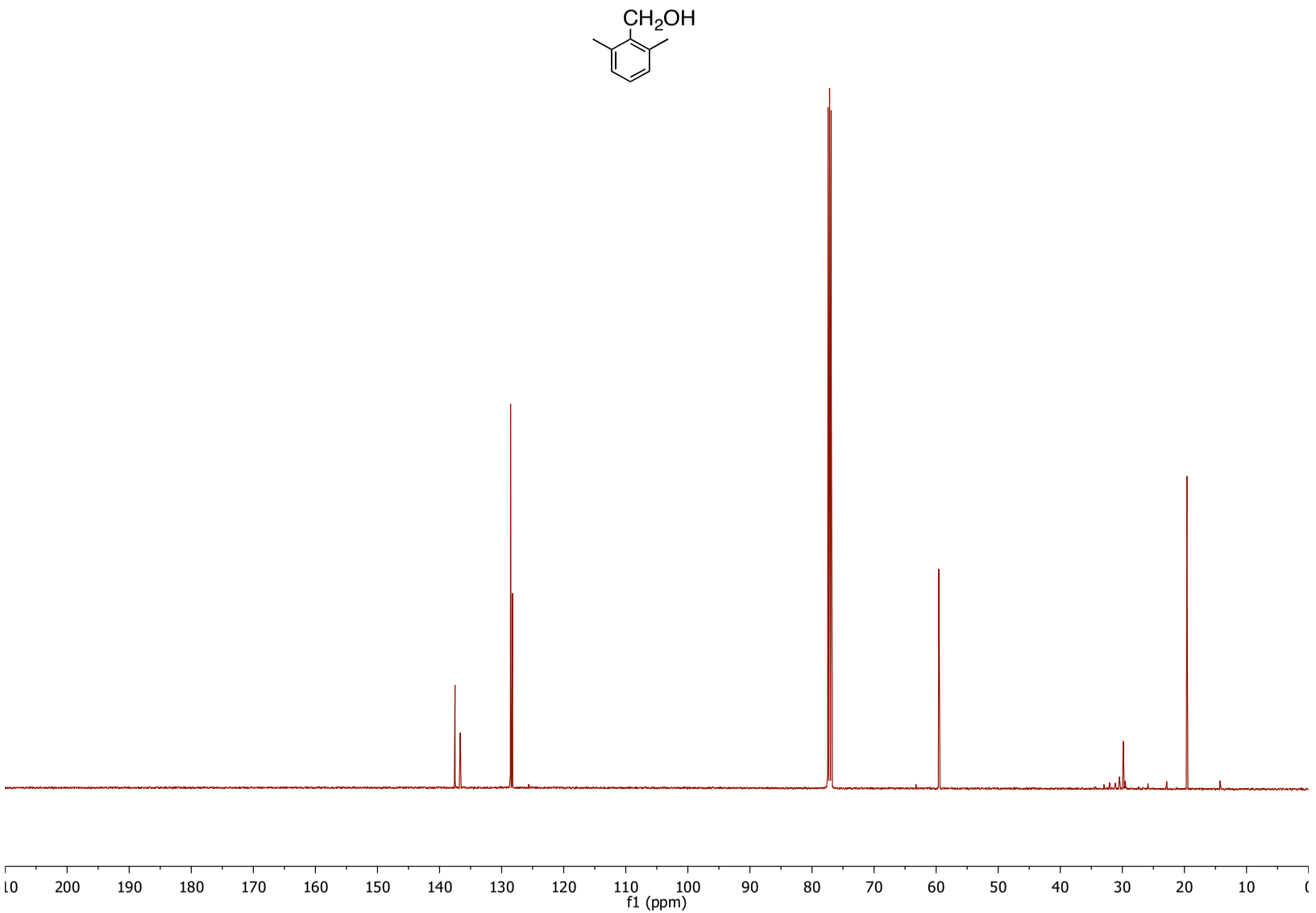

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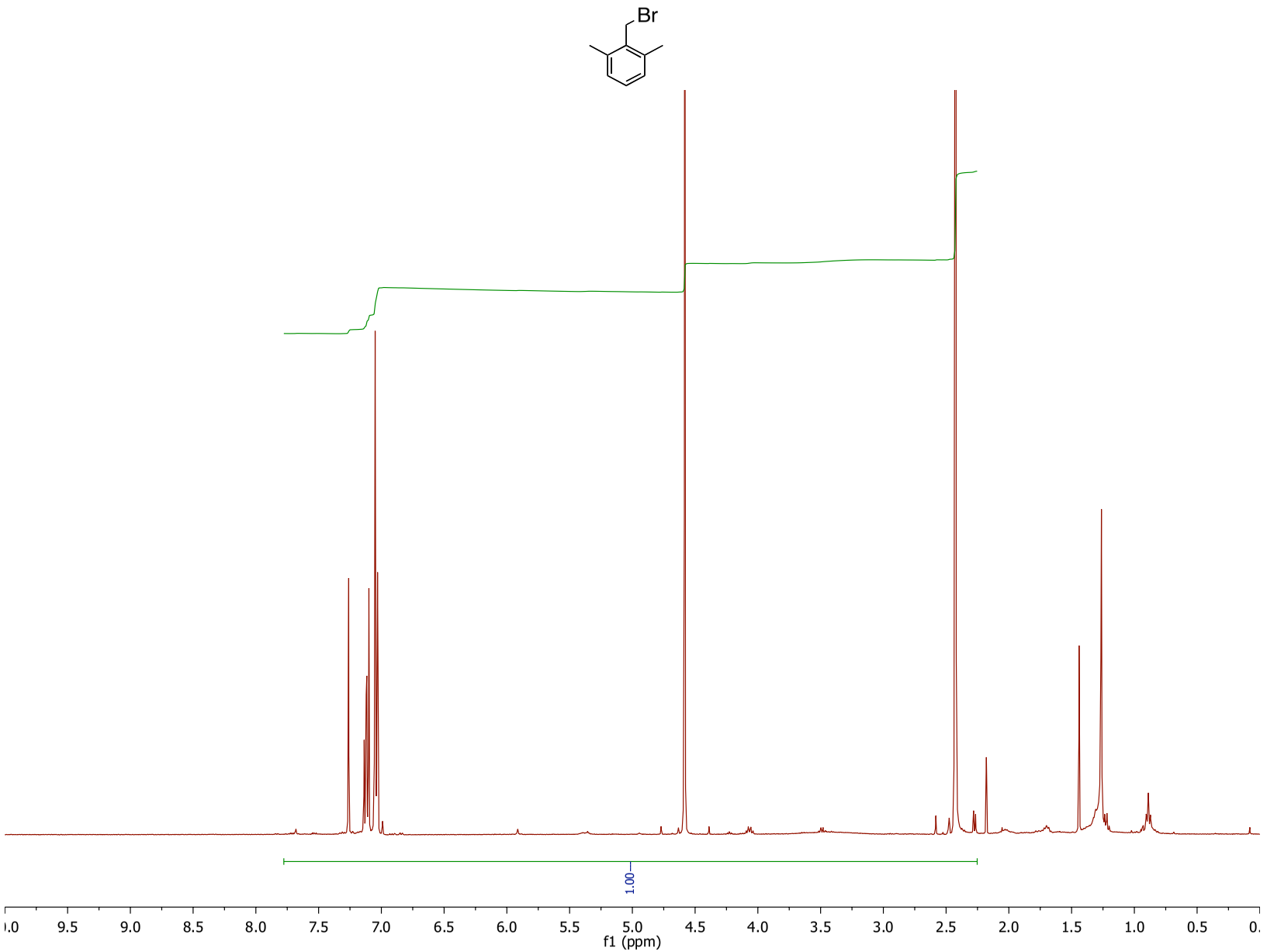
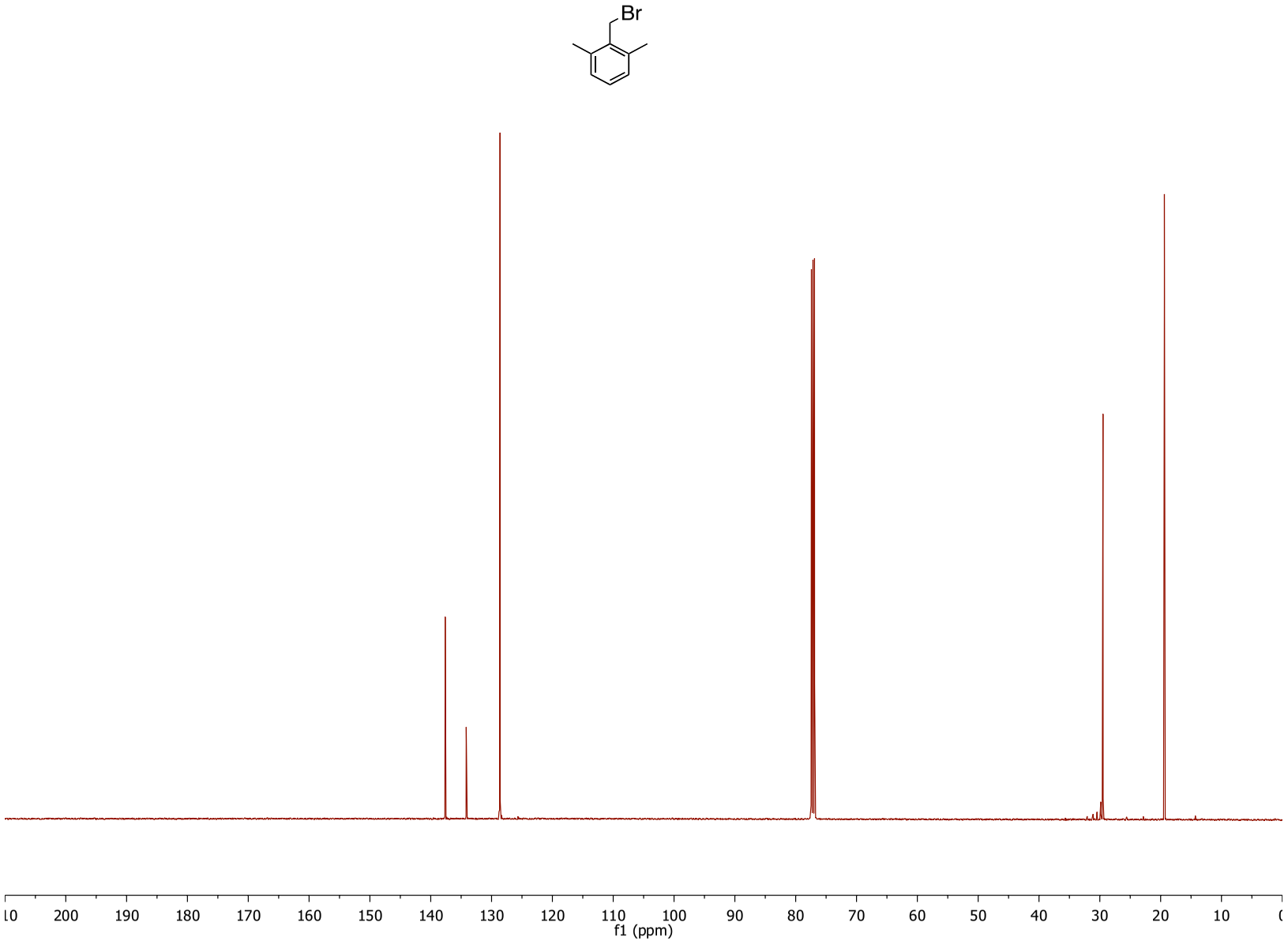
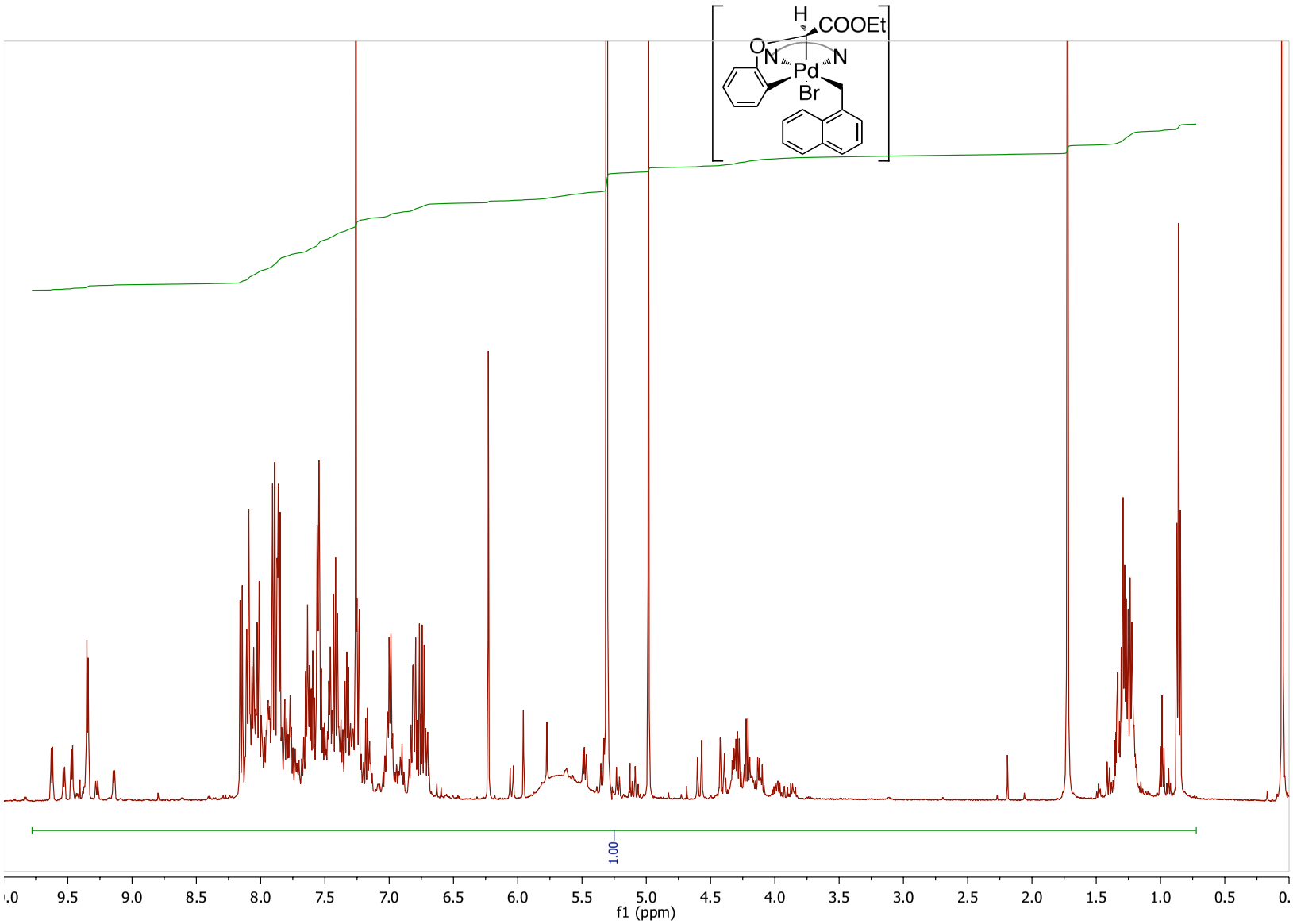


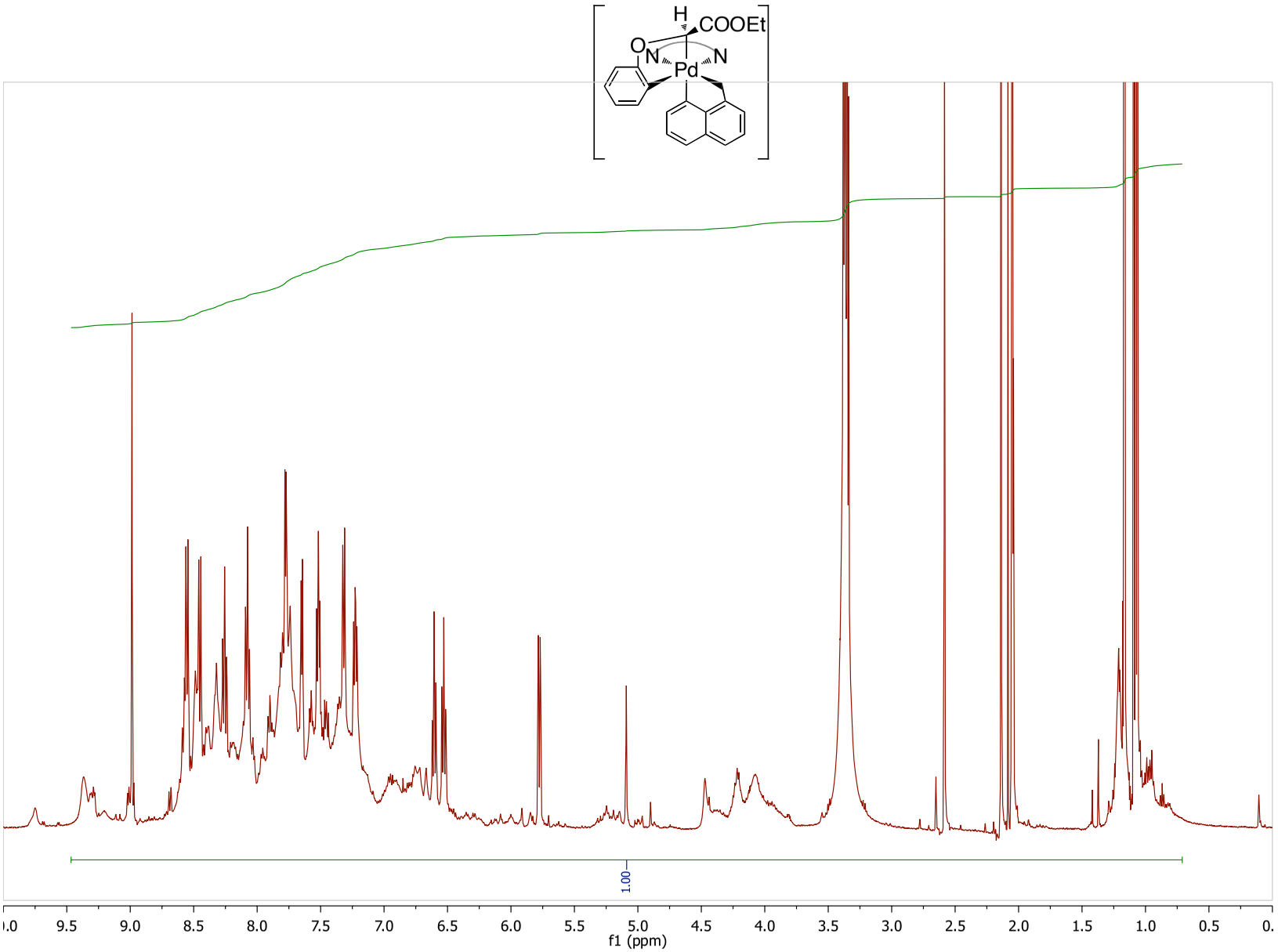
^{1}H NMR (400 MHz, $CDCl_3$, 25°C)



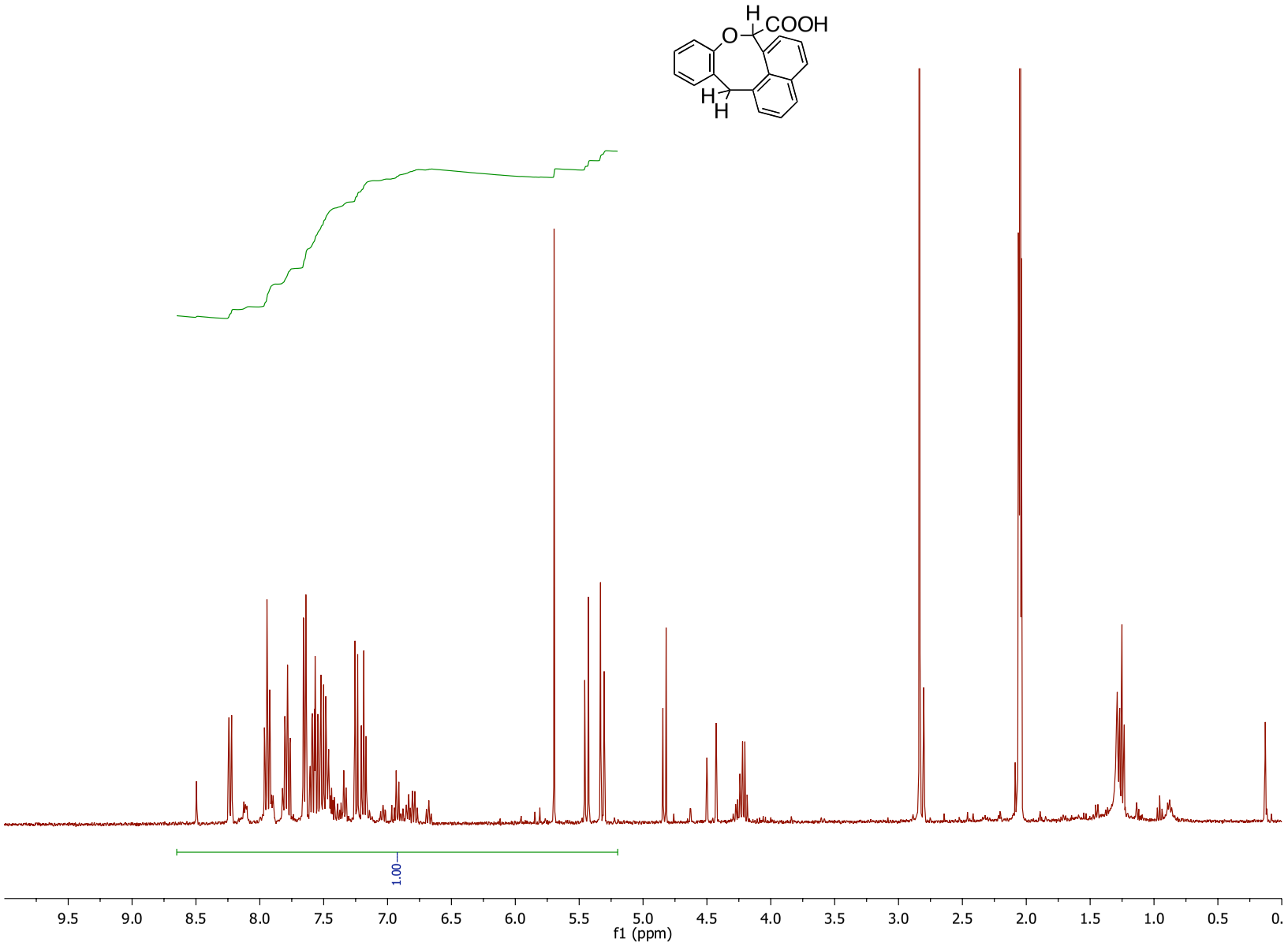
^{13}C NMR (500 MHz, $CDCl_3$, 25°C)



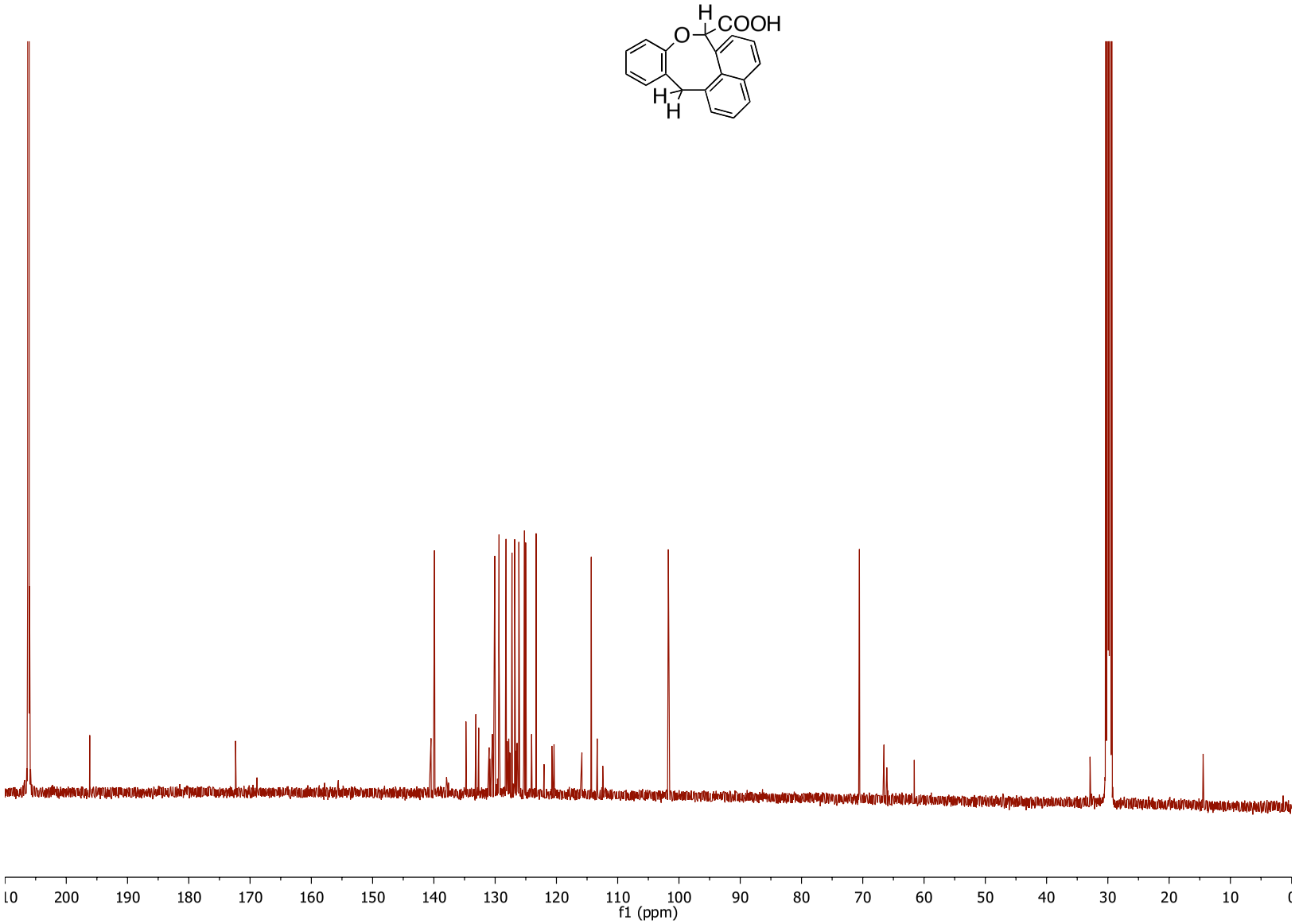
^{1}H NMR (500 MHz, $CDCl_3$, -10°C)
detected in solution



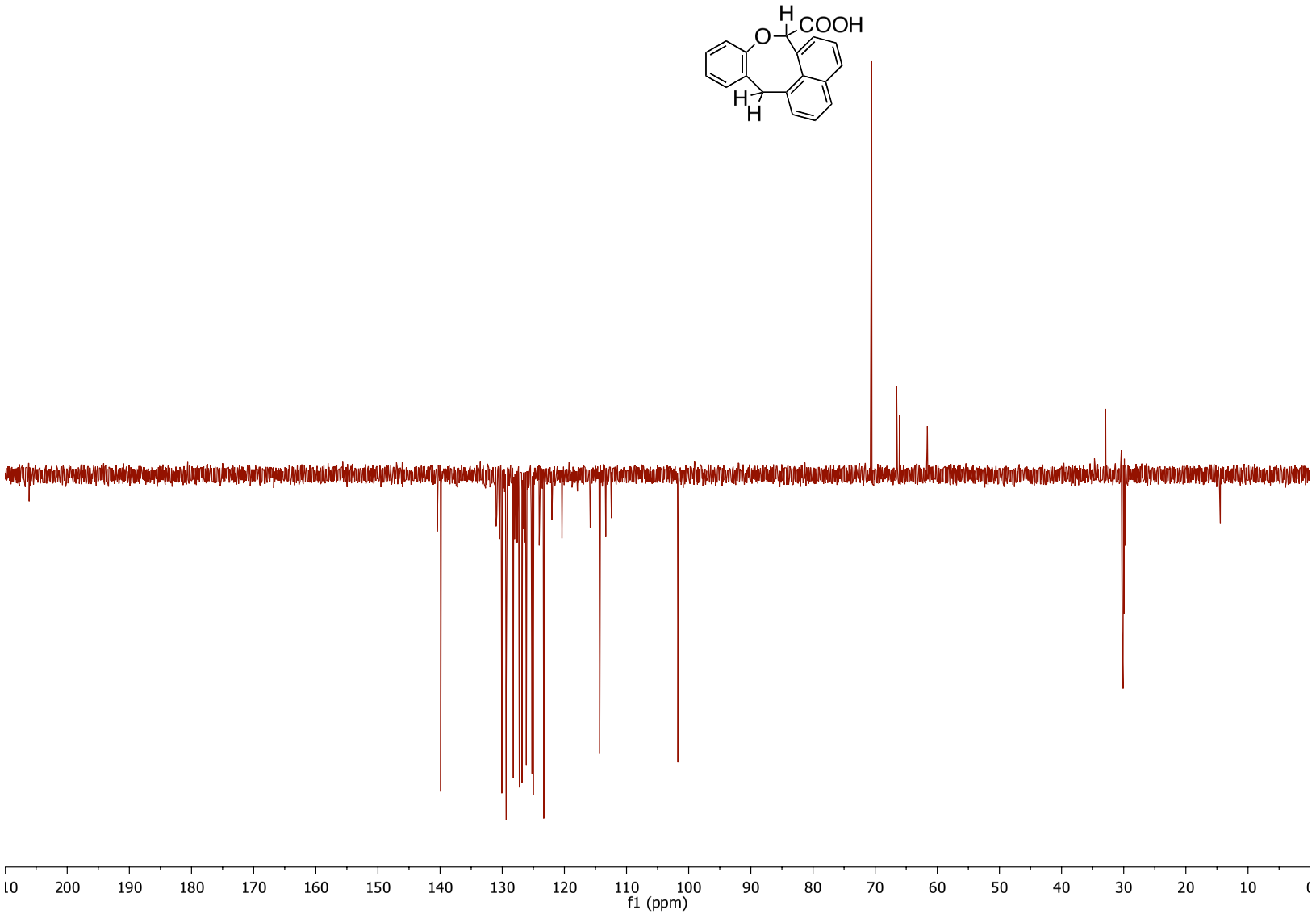
^{1}H (500 MHz, acetone-d_6, -10°C)
detected in solution



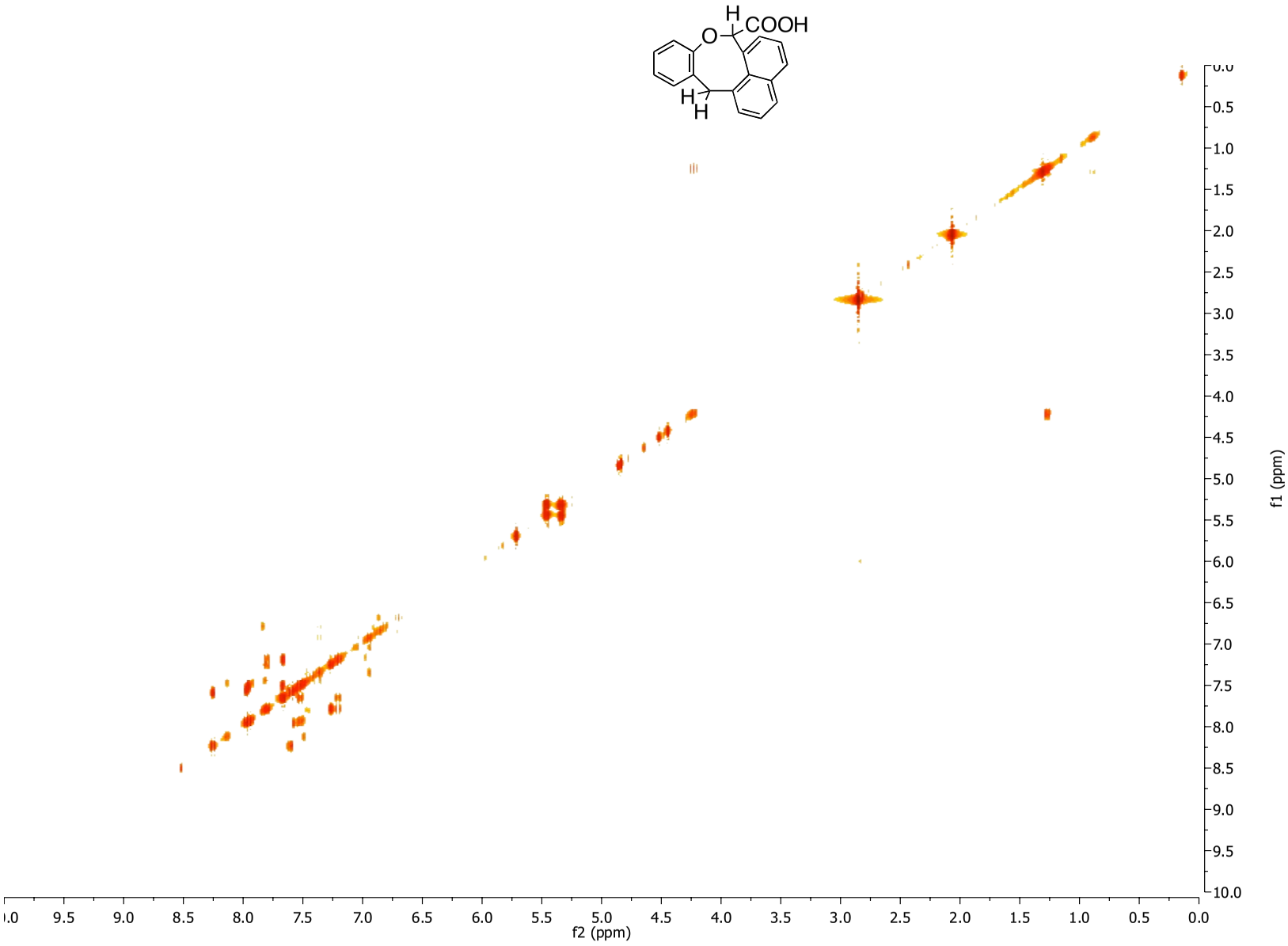
^{1}H NMR (500 MHz, acetone-d_6, 25°C)



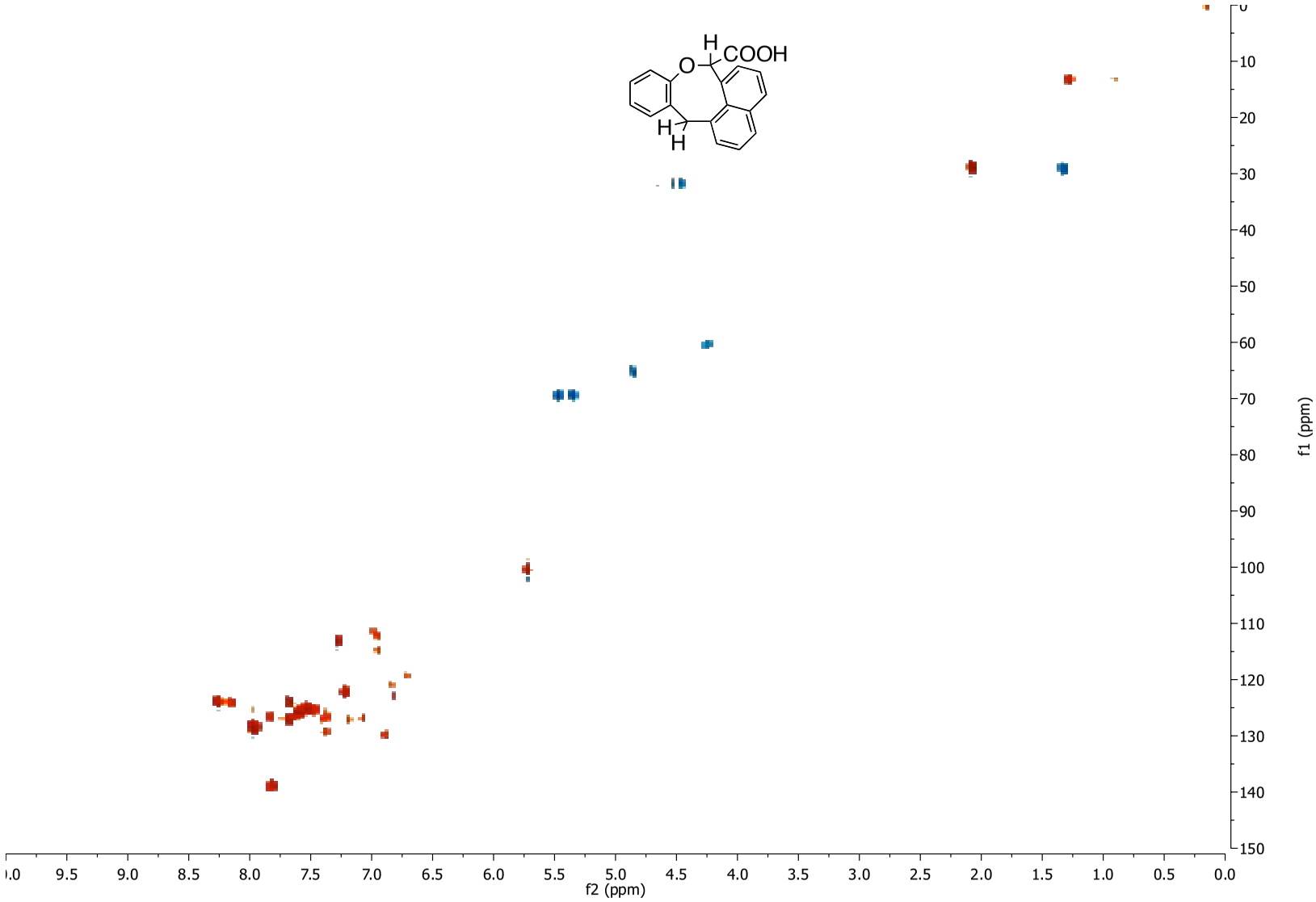
^{13}C NMR (500 MHz, $CDCl_3$, 25°C)



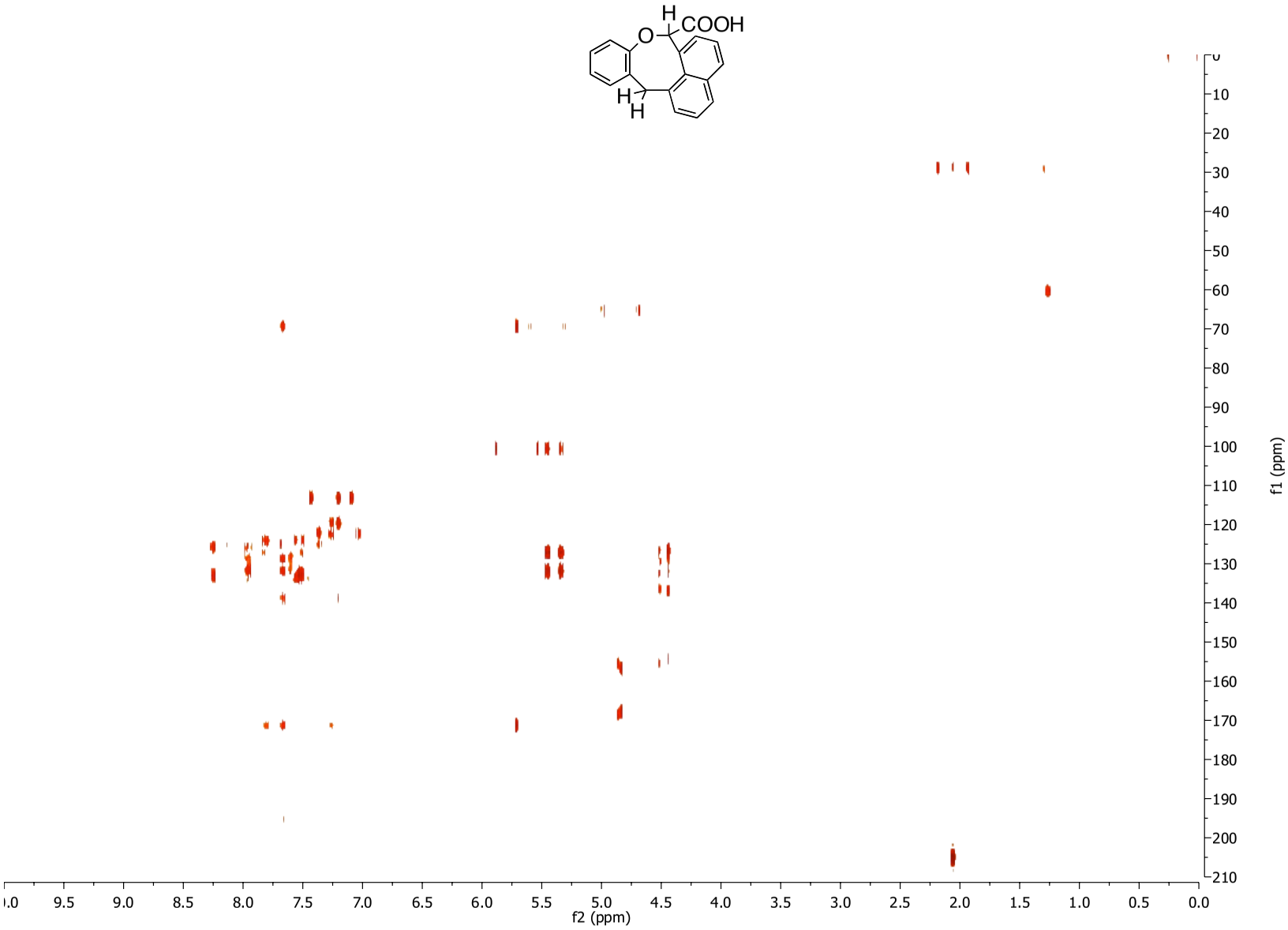
DEPT NMR (500 MHz, acetone-d_6, 25°C)



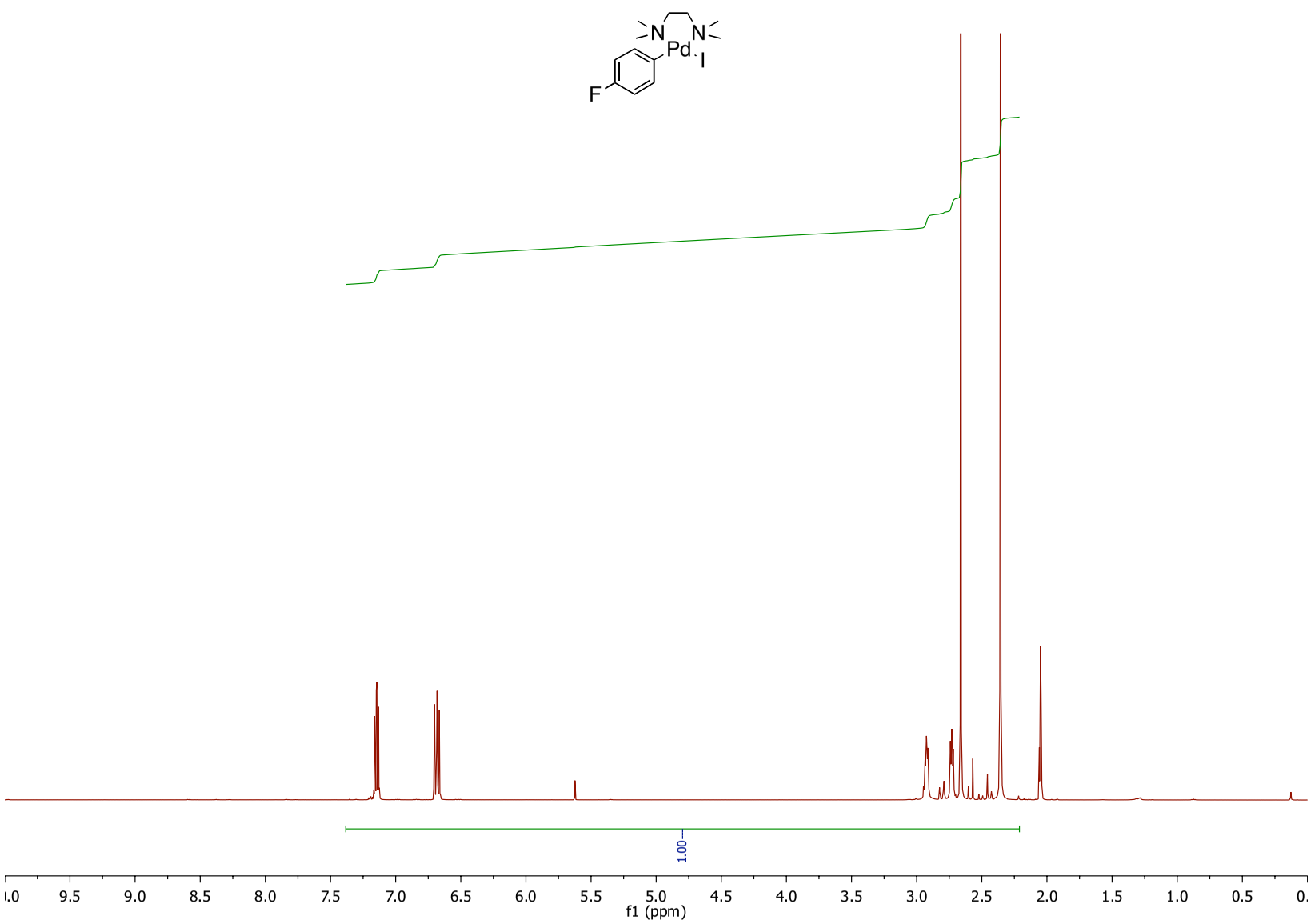
COSY NMR (500 MHz, acetone-d_6, 25°C)



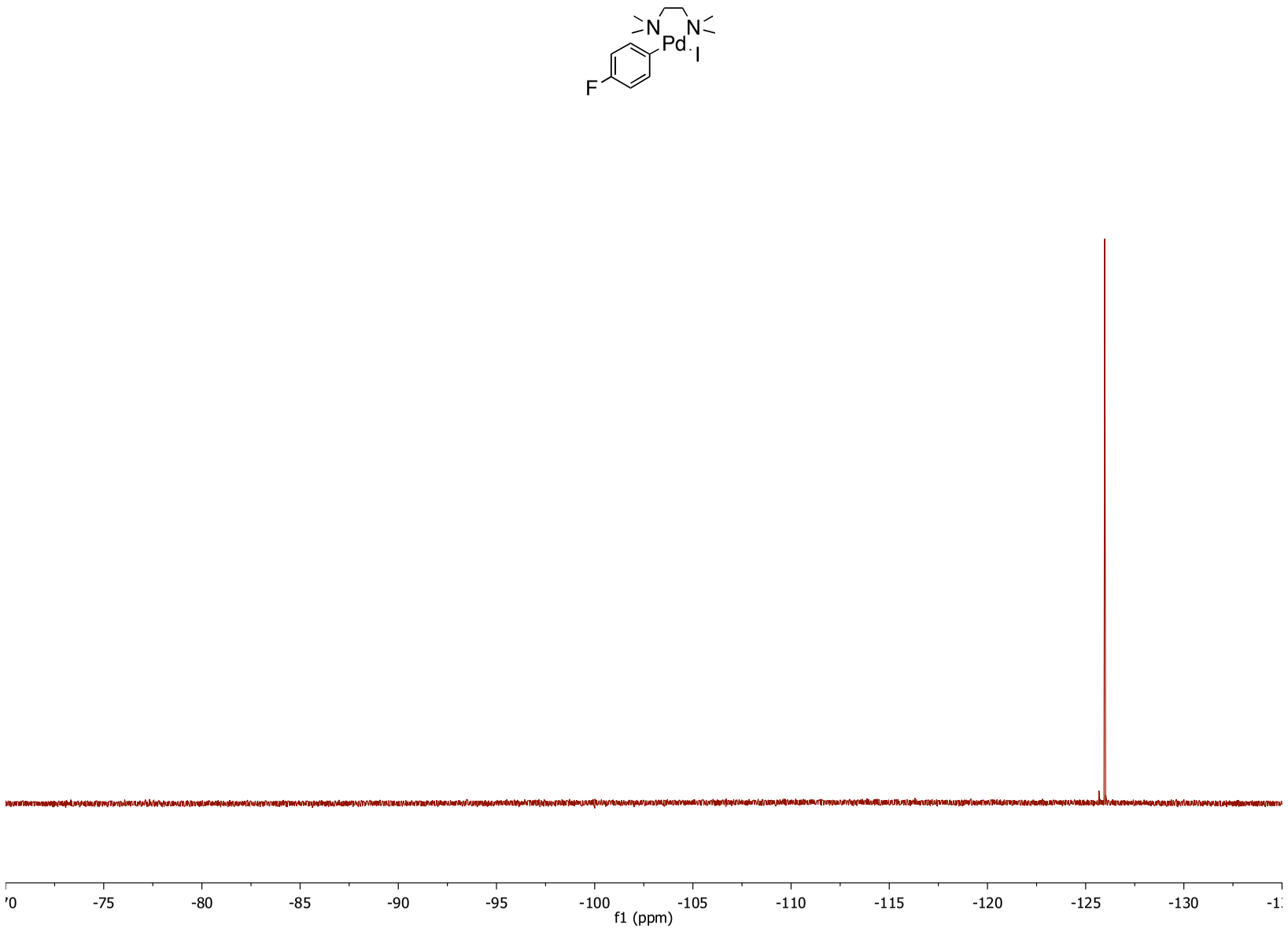
HSQC NMR (500 MHz, acetone-d_6, 25°C)



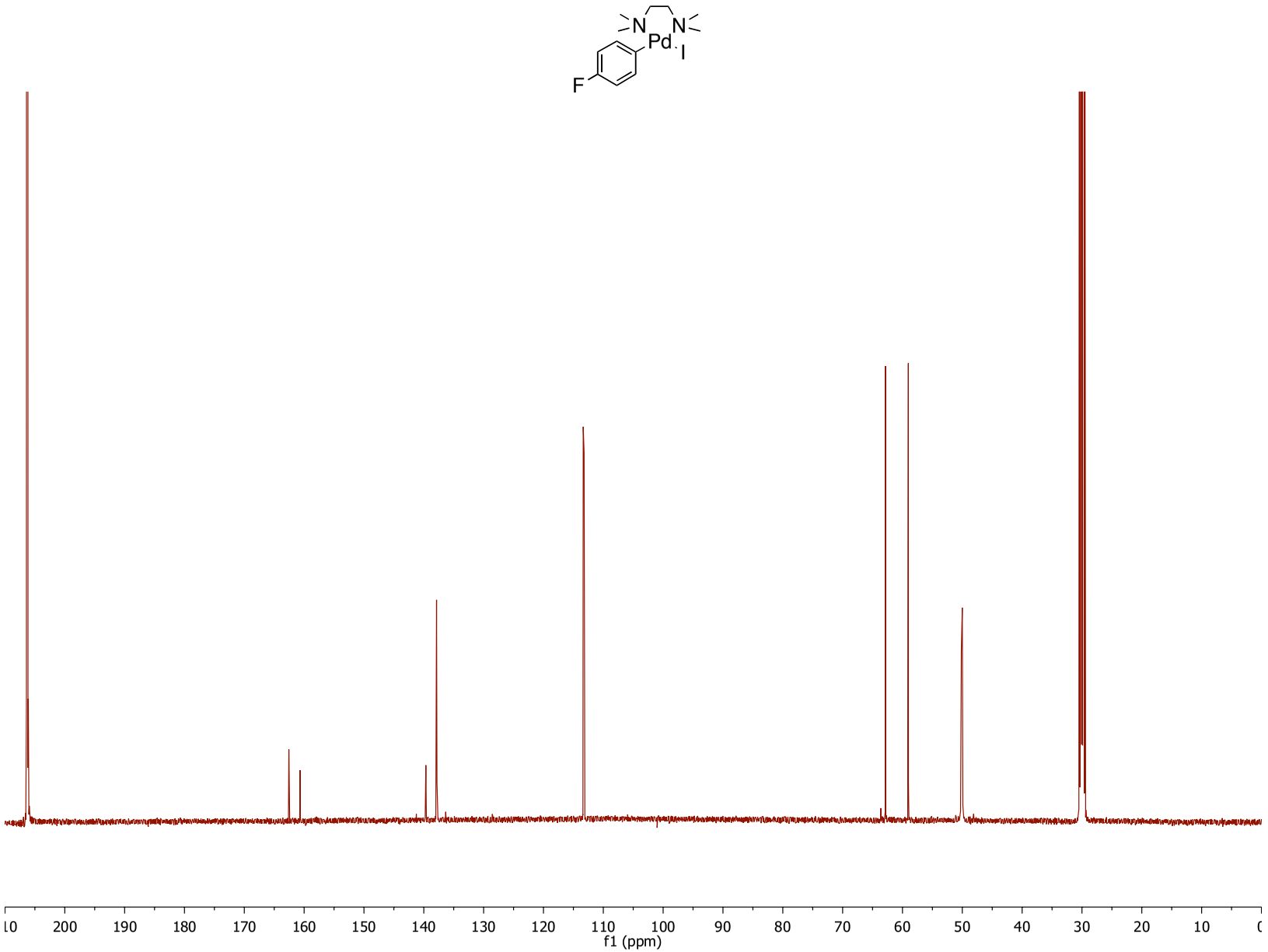
HMBC NMR (500 MHz, acetone-d_6, 25°C)



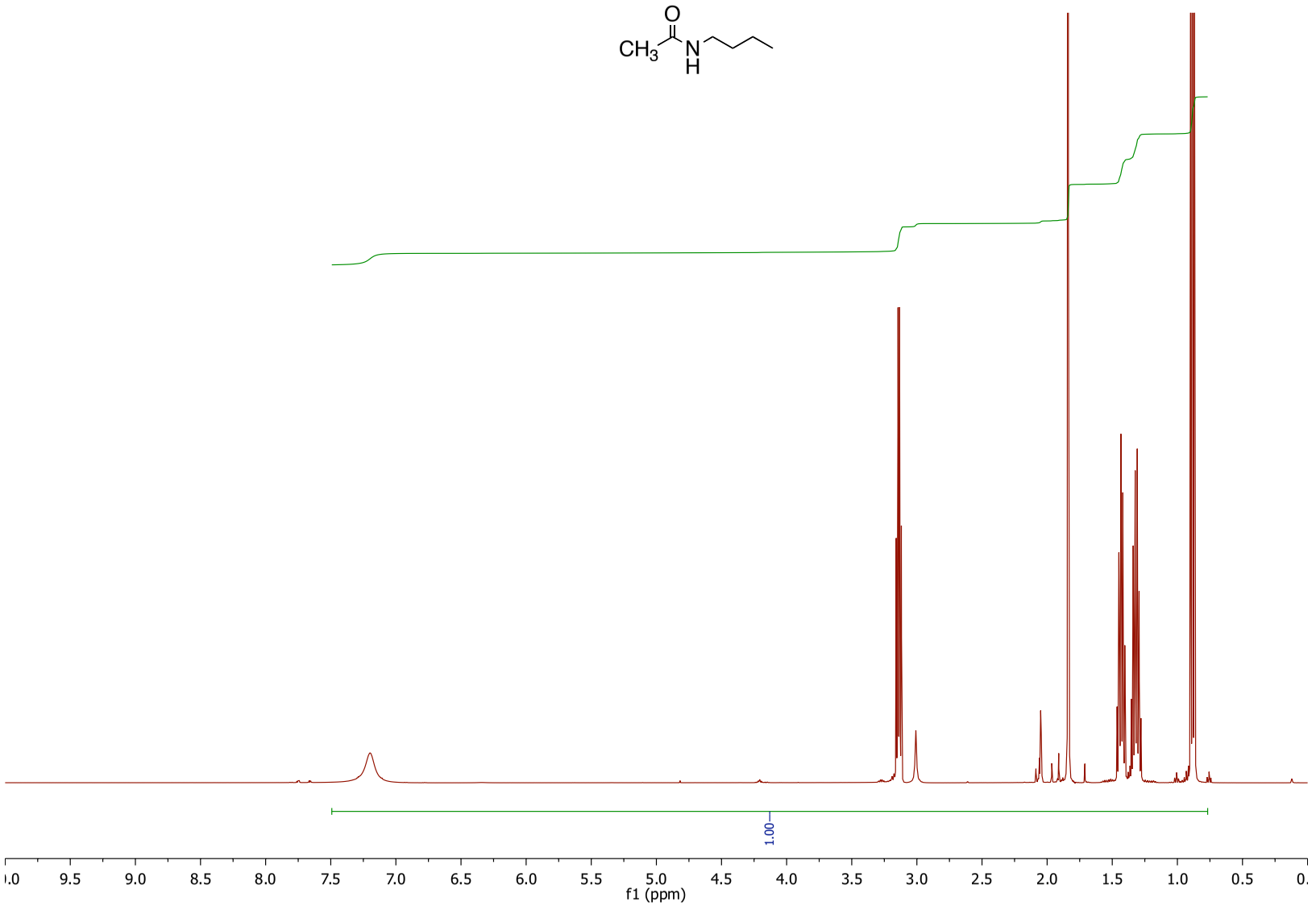
^{1}H NMR (400 MHz, acetone-d_6, 25°C)



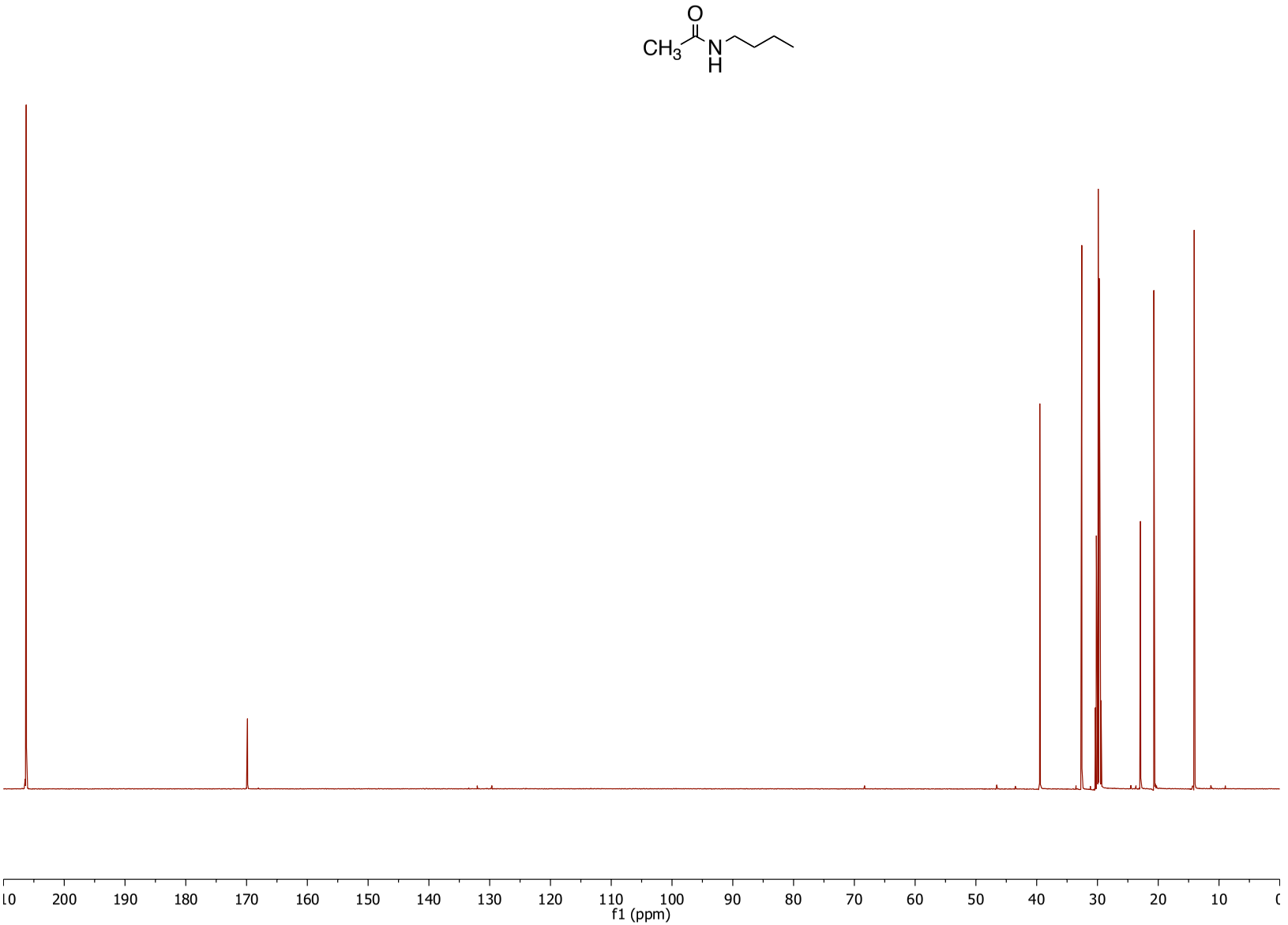
^{19}F NMR (400 MHz, acetone-d_6, 25°C)



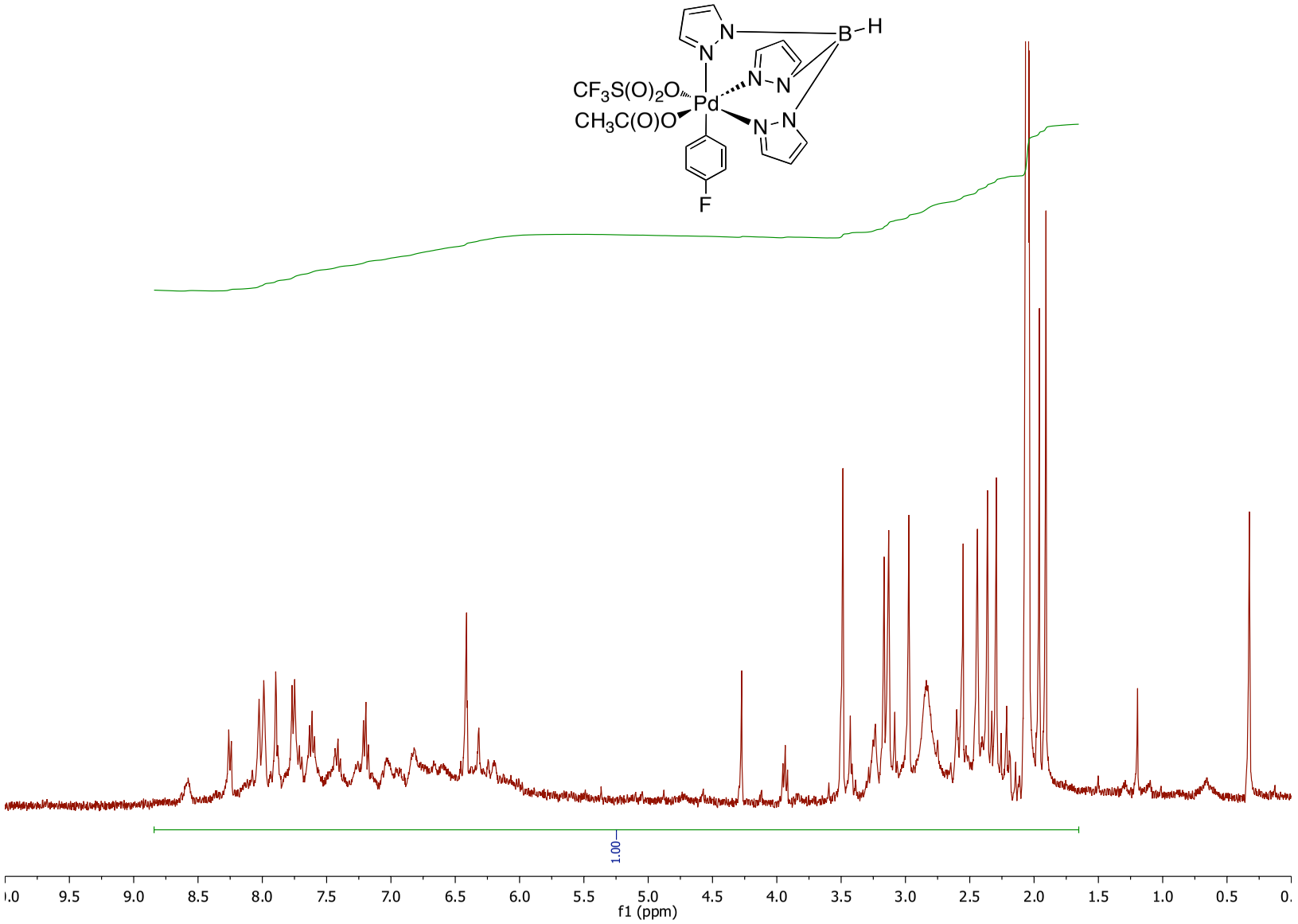
^{13}C NMR (500 MHz, acetone-d_6, 25°C)



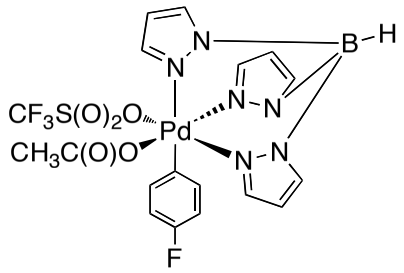
^{1}H NMR (400 MHz, acetone-d_6, 25°C)

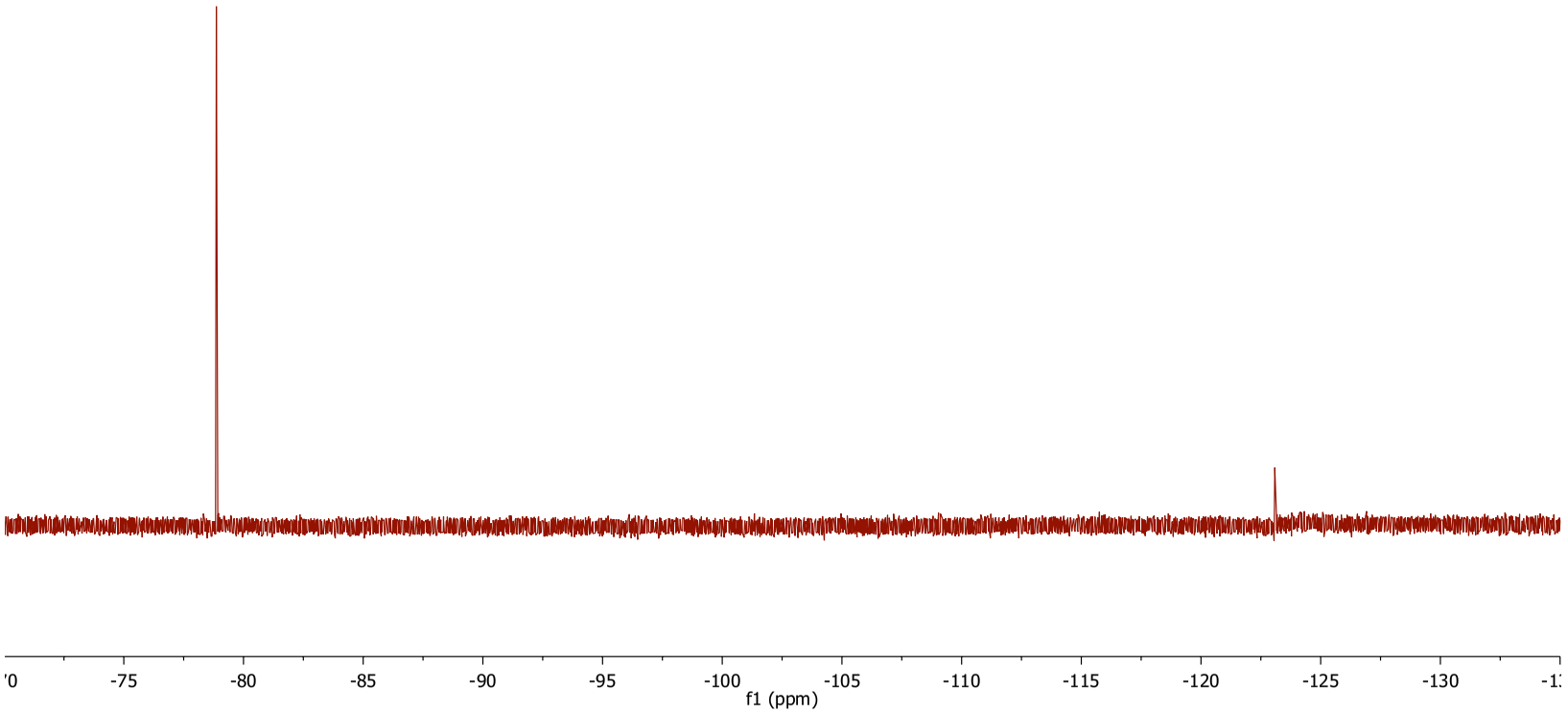


^{13}C NMR (500 MHz, acetone-d_6, 25°C)

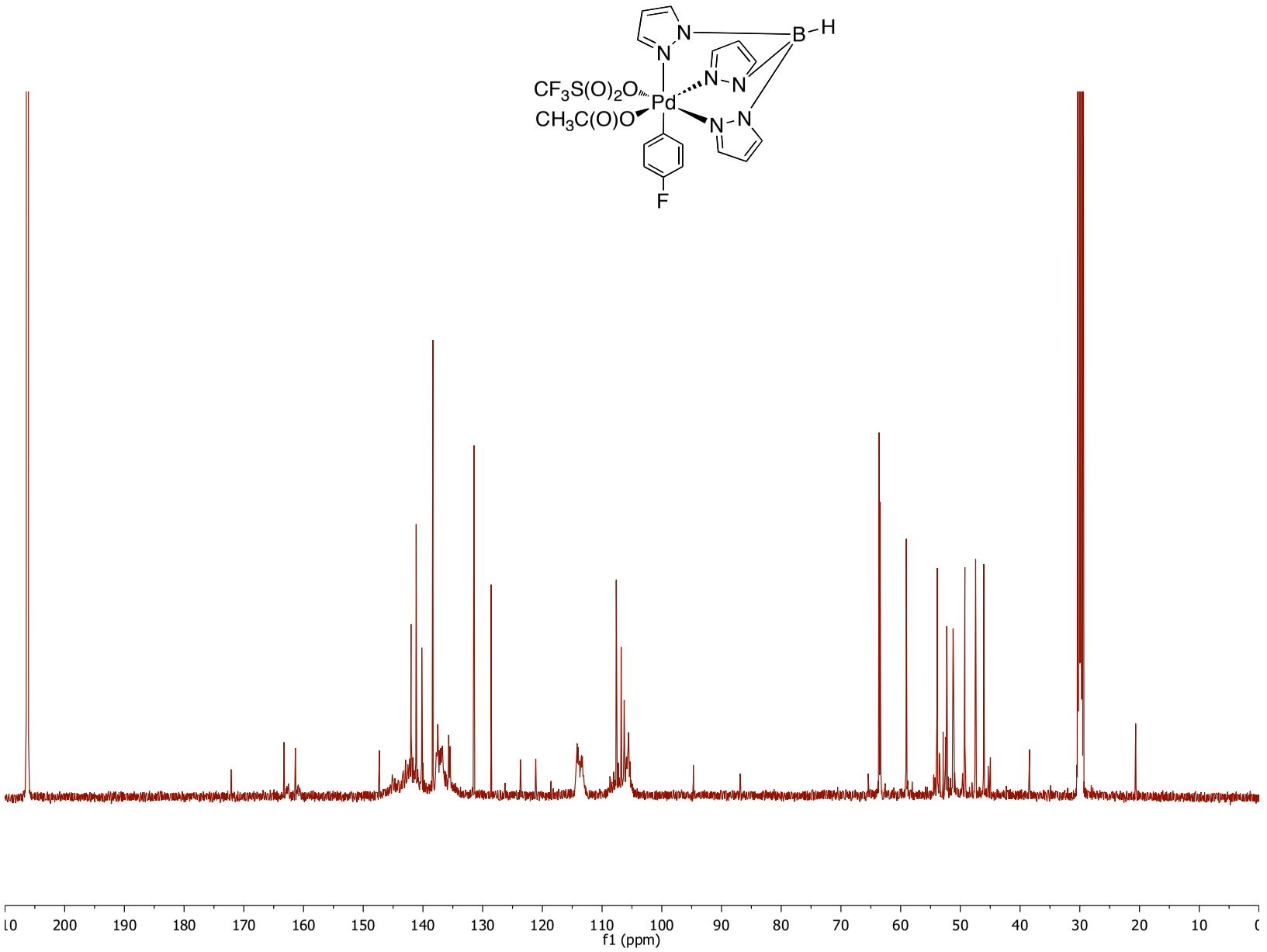


^{1}H NMR (400 MHz, acetone-d_6, 25°C)

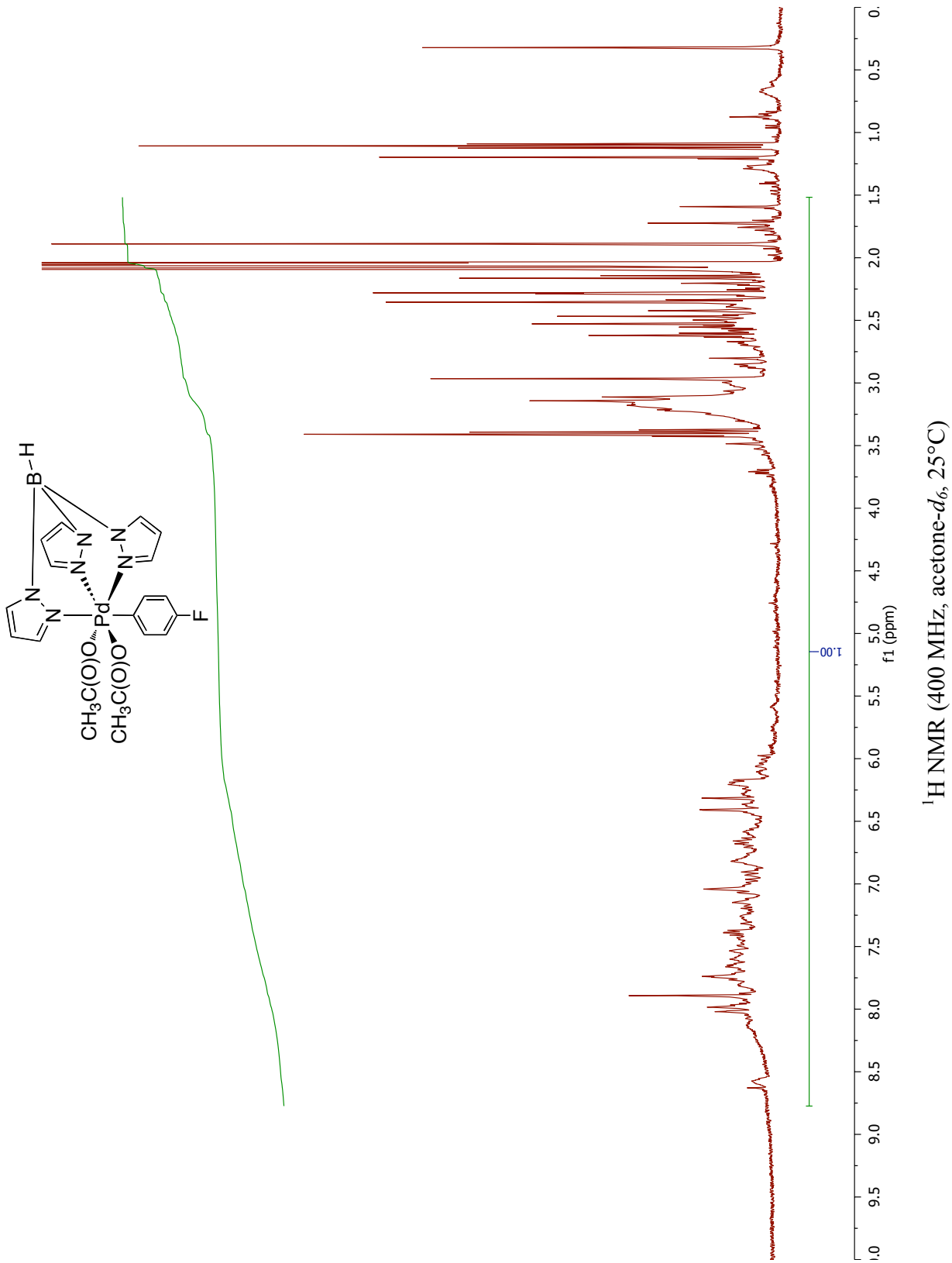




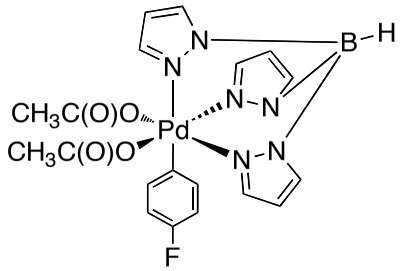
^{19}F NMR (400 MHz, acetone-d_6, 25°C)

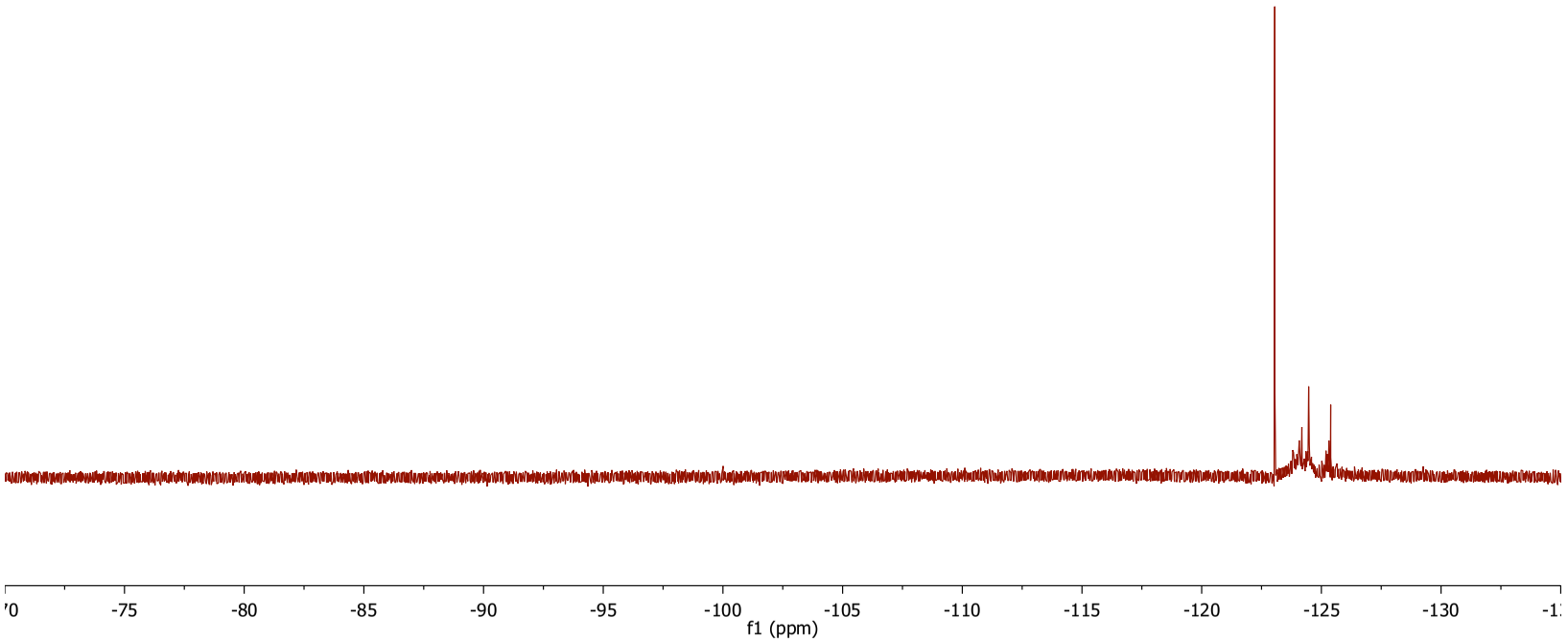


^{13}C NMR (500 MHz, acetone-d_6, 25°C)

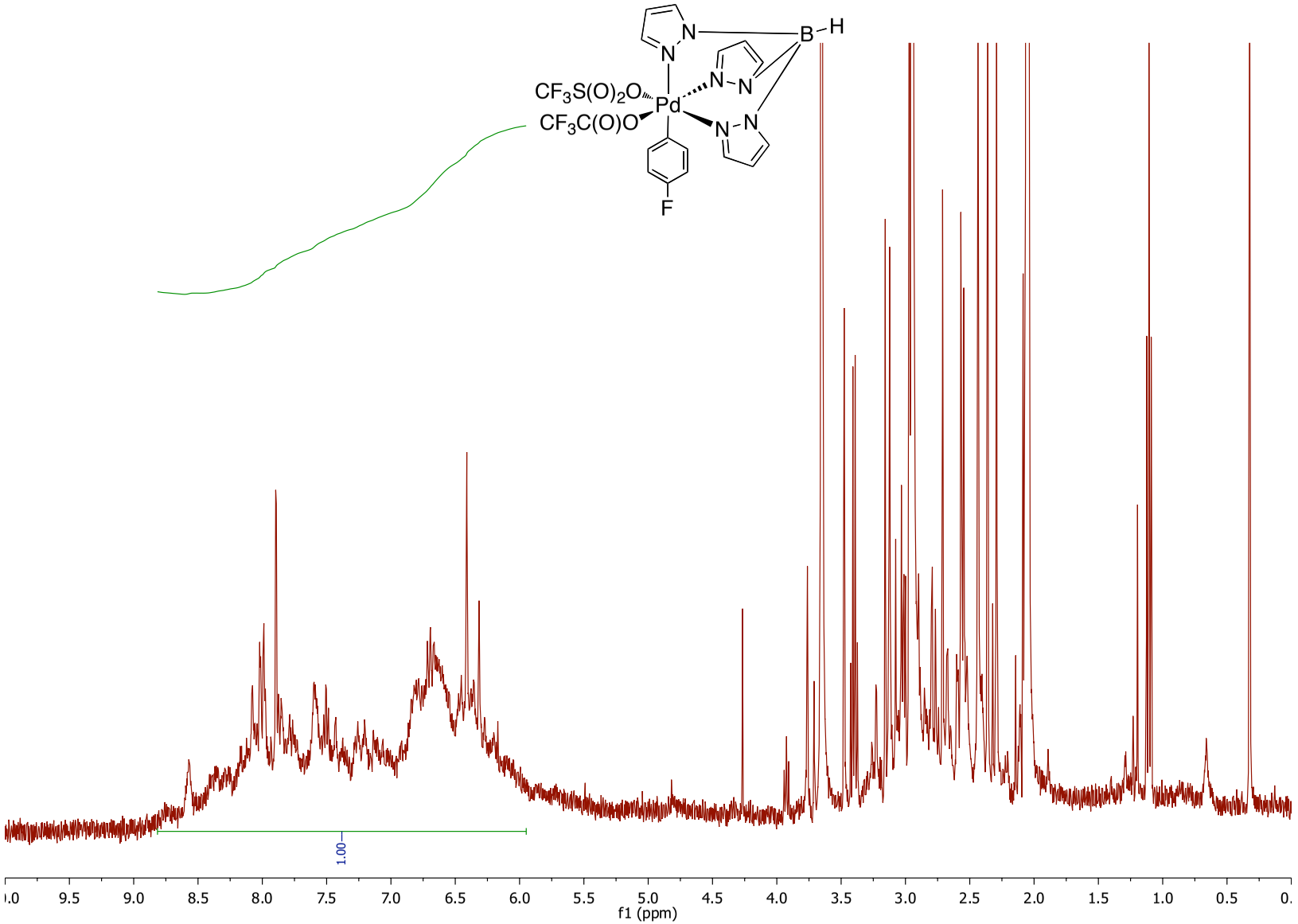


^{1}H NMR (400 MHz, acetone-d_6, 25°C)

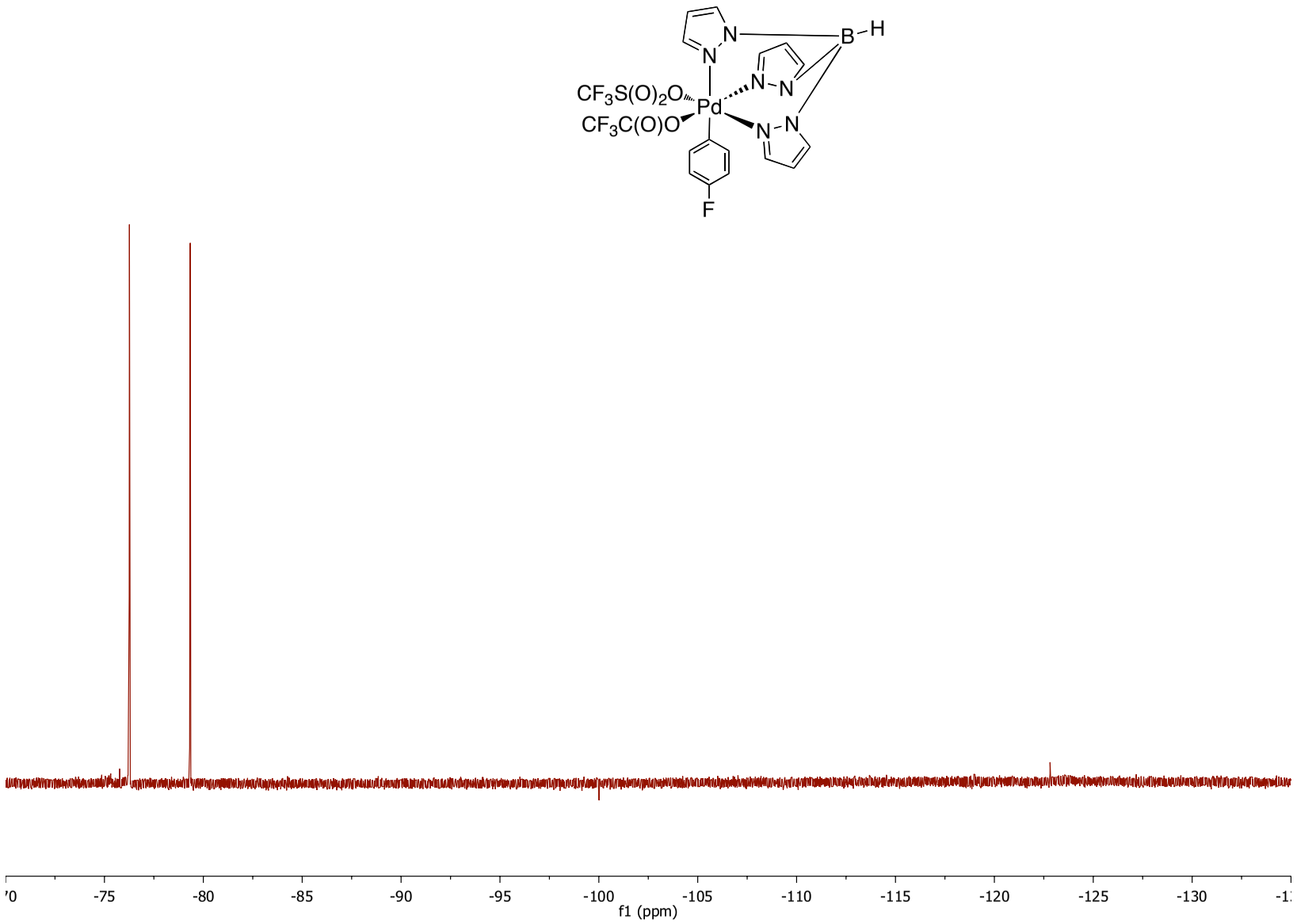




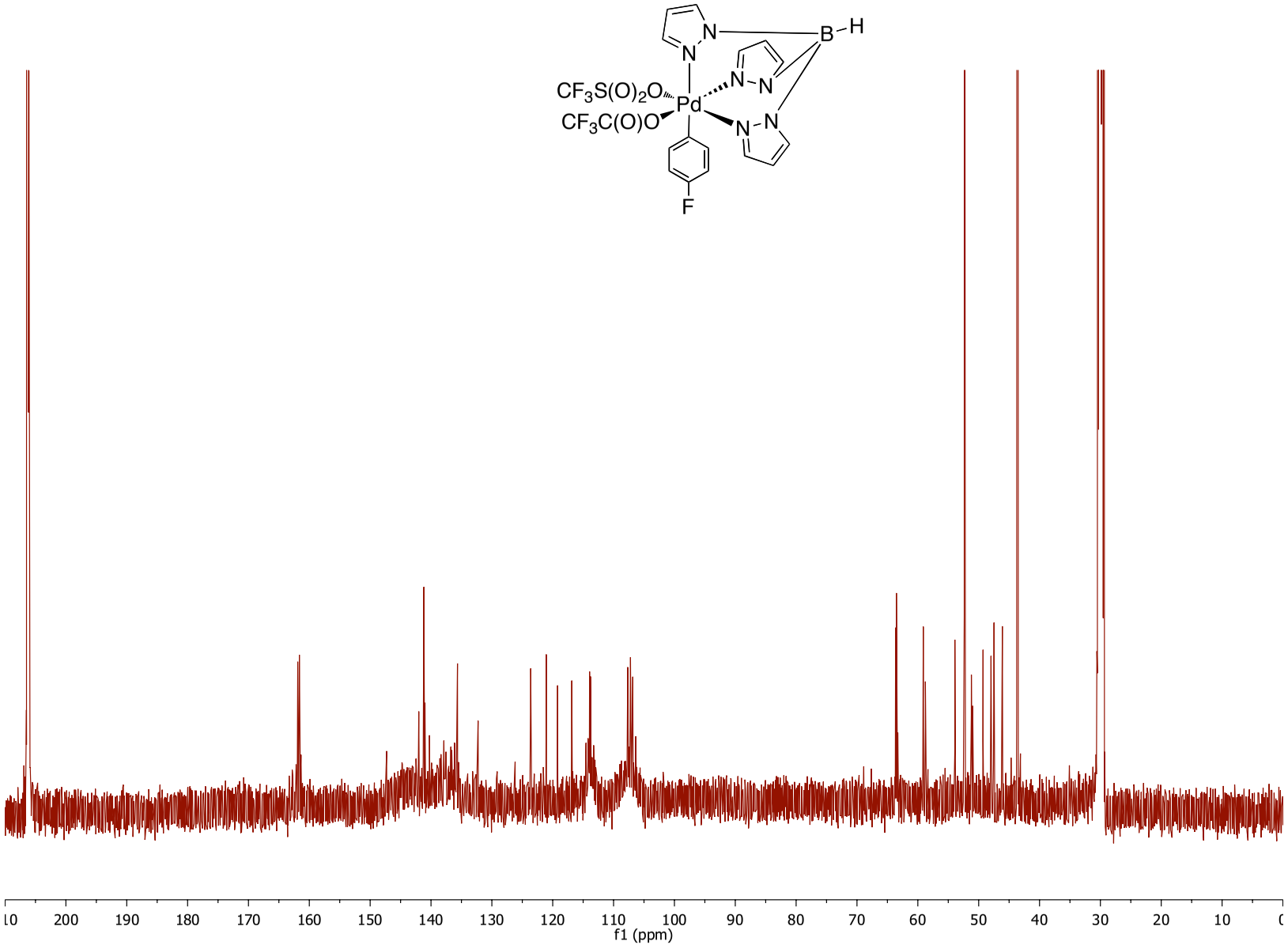
^{19}F NMR (400 MHz, acetone-d_6, 25°C)



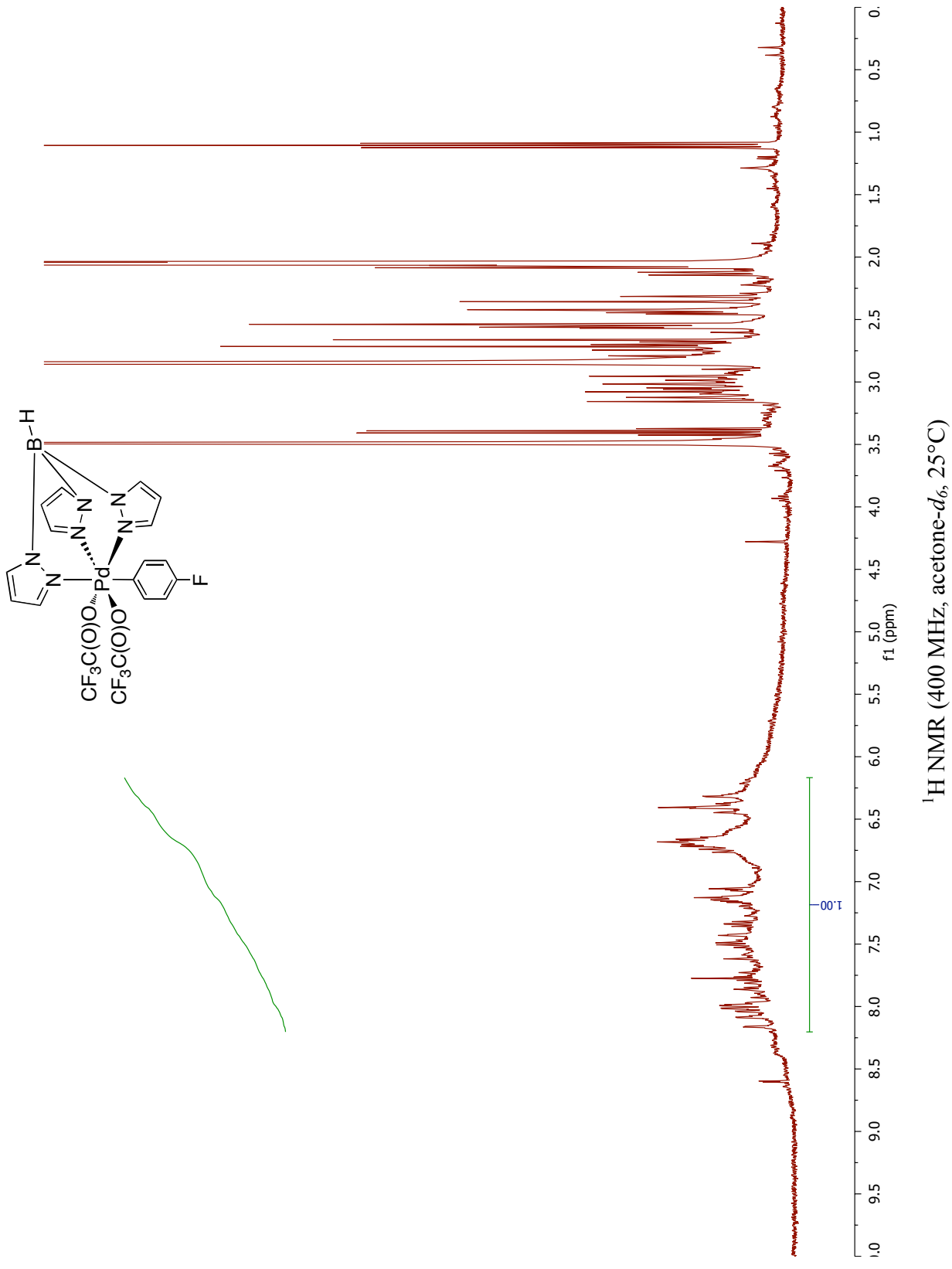
^{1}H NMR (400 MHz, acetone-d_6, 25°C)



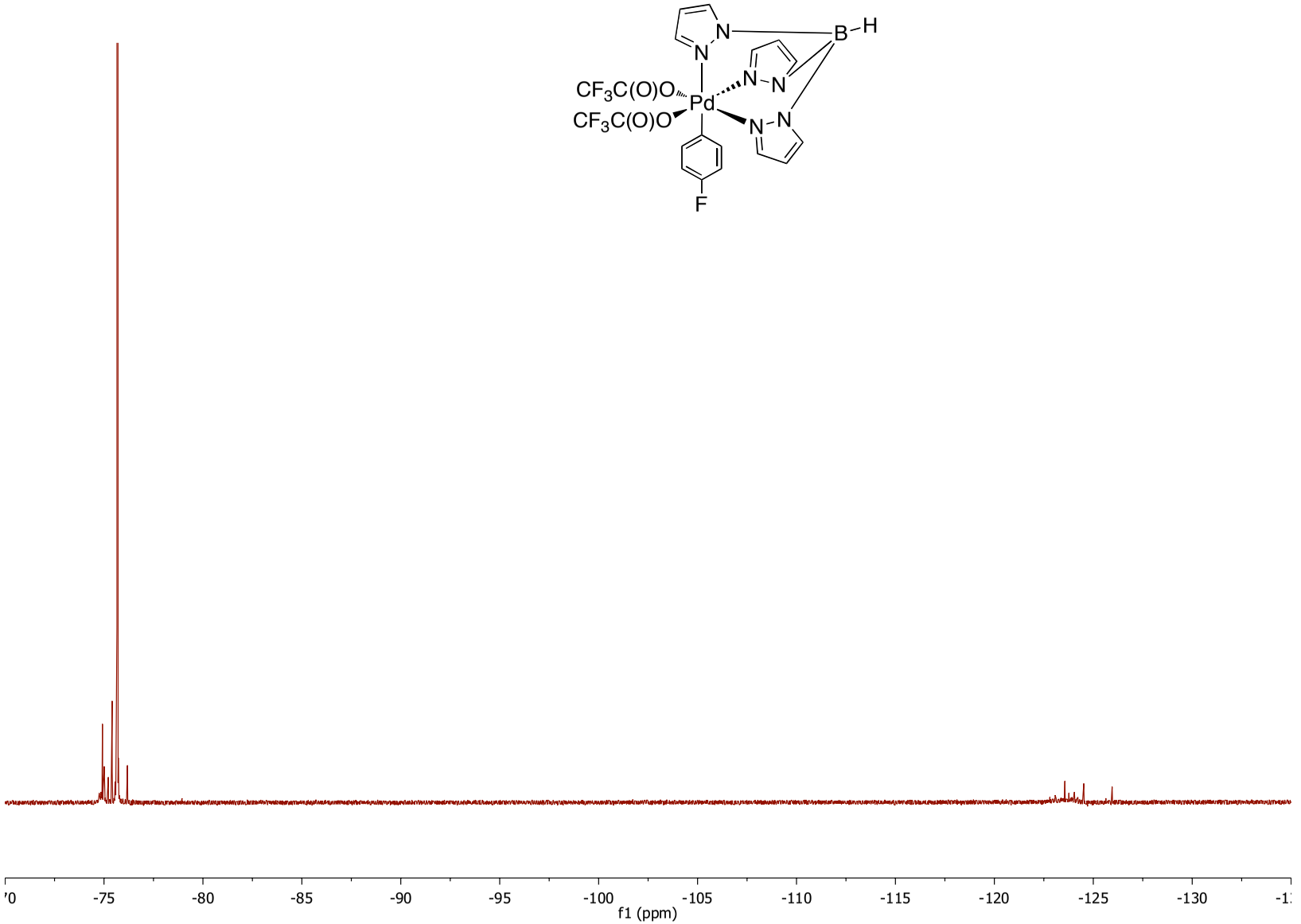
^{19}F NMR (400 MHz, acetone-d_6, 25°C)



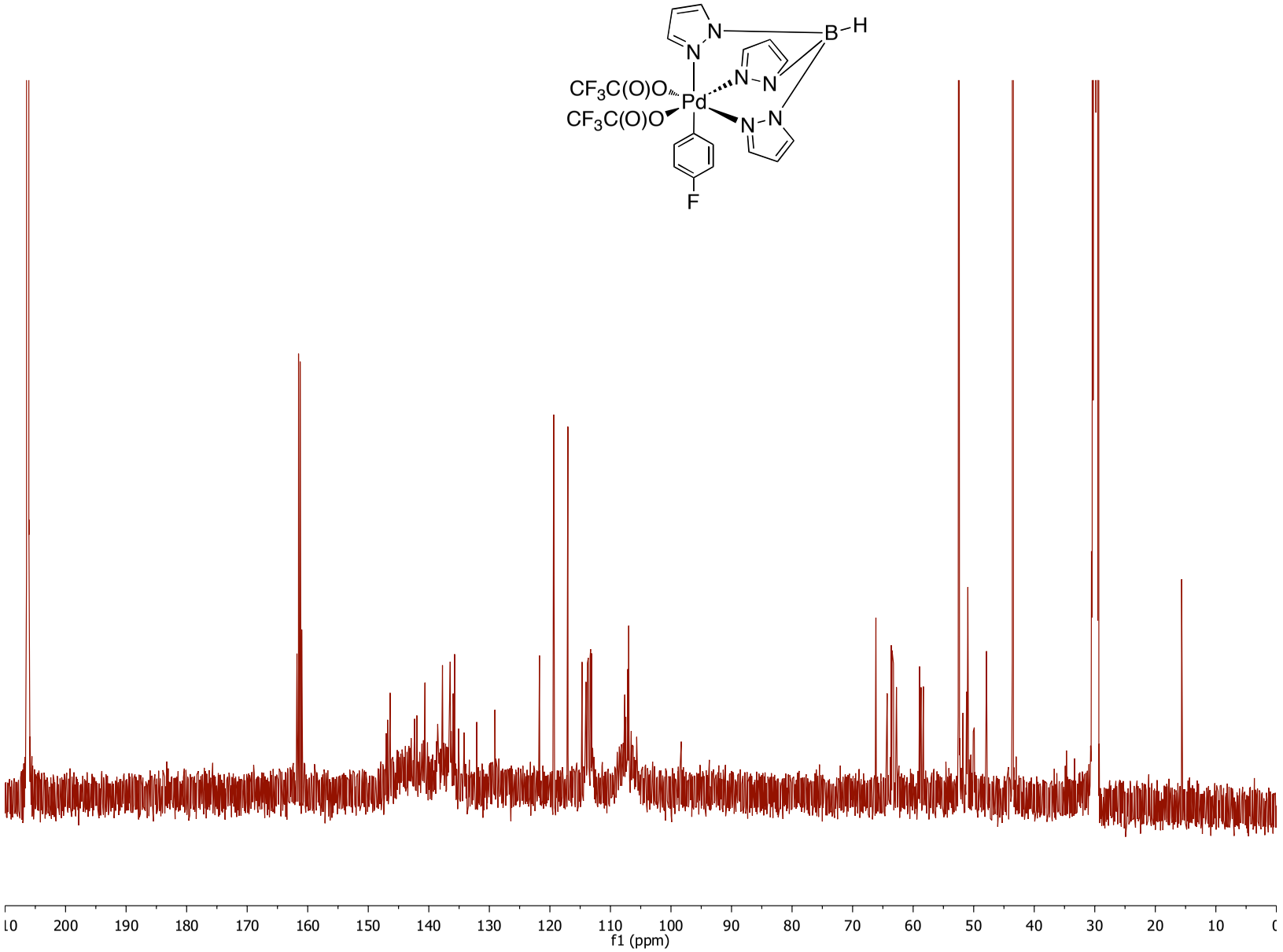
^{13}C NMR (500 MHz, acetone-d_6, 25°C)



^{1}H NMR (400 MHz, acetone-d_6, 25°C)



^{19}F NMR (400 MHz, acetone-d_6, 25°C)



^{13}C NMR (500 MHz, acetone-d_6, 25°C)