DISSERTATION

SITE-SELECTIVE PYRIDINE FUNCTIONALIZATION VIA NUCLEOPHILIC ADDITIONS TO ACTIVATED PYRIDINIUMS

Submitted by

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ABSTRACT

SITE-SELECTIVE PYRIDINE FUNCTIONALIZATION VIA NUCLEOPHILIC ADDITIONS TO ACTIVATED PYRIDINIUMS

Pyridines and diazines are important heterocycles commonly found in pharmaceuticals, agrochemicals, ligands, and various other organic molecules. Pyridines existing in these molecules usually have multiple bonds connected to them that contribute to their reactivity and characteristics. Therefore, there are ongoing efforts l to find new methods to functionalize these heterocycles. Our lab has contributed to this field by developing methods to functionalize pyridines directly from the C–H bond through phosphonium salts or Zincke imines.

Chapter One gives an overview of the current methods for pyridine functionalization and their limitations. Chapter Two describes the synthesis of *N*-Tf Zincke imines and their use for regioselective 3-position pyridine functionalization. Bipyridines and pyridine-piperidine coupled products are accessed through this method. Chapter Three discusses using *N*-Tf Zincke imines to form ^{15}N pyridines and coupled with deuteration forms higher mass isotopologues. Chapter Four describes the formation of *N*-alkyl pyridinium salts from *N*-Tf Zincke imines. This chapter focuses on optimizing the ring-opening of 2-ester pyridines and ring-closing them with amino esters to access pipecolic esters for macrocyclization.

Chapter Five highlights direct nucleophile additions to the 4-position of *N*-Tf pyridinium salts for pyridine functionalization. 4-aminated pyridines are formed with both aliphatic amines and anilines from the C–H bond. The regioselectivity of this amination is controlled by the basicity of the reaction. In addition, 4-NH_2 pyridines are achieved through this method by adding benzophenone imine, an ammonia surrogate. This reaction extends to adding in heteroatom nucleophiles including alcohols, thioesters, amides, and sulfonamides.

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Chapter 1. Introduction and Background of Pyridines

1.1 Importance of Nitrogen-containing Heterocyclic Compounds in Pharmaceuticals

Pharmaceuticals play a vital role in modern medicine to treat and prevent diseases. A recent 2014 report showed that 59% of FDA-approved small molecule pharmaceutical drugs contain an aromatic nitrogen heterocycle (*N*-heterocycle).[1] These *N*-heterocycles include pyridine, piperidine, pyrimidine, and pyrazine. Due to the prevalence of these motifs in pharmaceuticals and agrochemicals, methods to derivatize them are in high demand. Figure 1.1 depicts some of the top-selling drugs and agrochemicals containing *N*-heterocycles and pyridine.

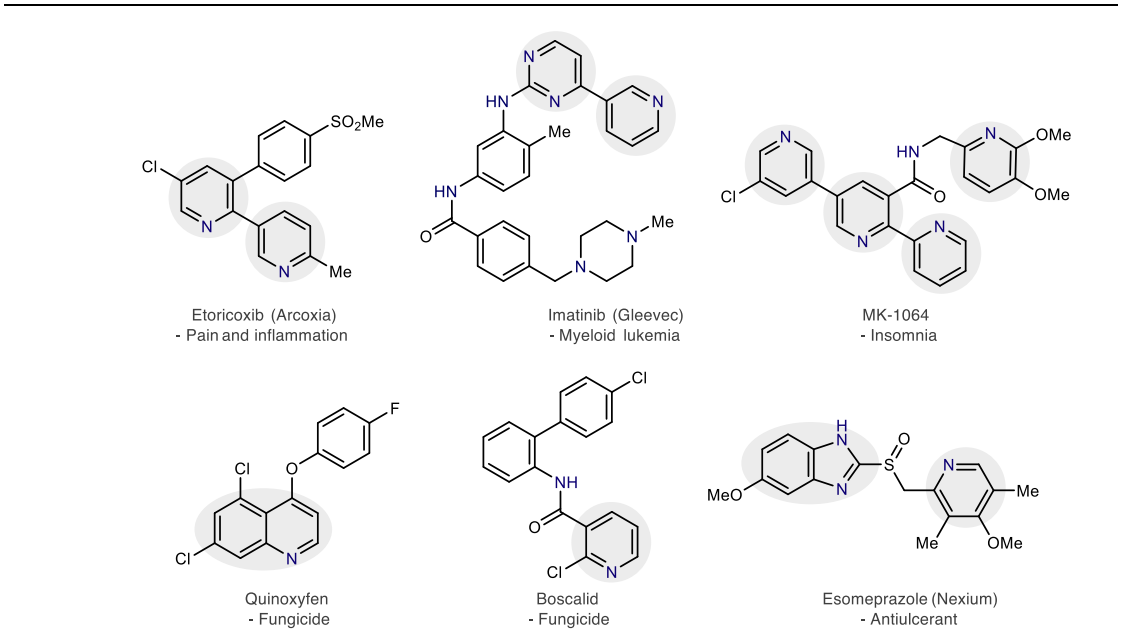

Figure 1.1. Aromatic nitrogen heterocycles in pharmaceuticals and agrochemicals

N-heterocycles are structurally similar to benzene; however, at least one methine group is replaced with a nitrogen atom. Because nitrogen is more electronegative than carbon, the switch to a nitrogen atom induces a net dipole in the aromatic ring that causes the arene to become electron-deficient (Figure 1.2). The electron deficiency increases as additional methine groups on benzene are replaced with nitrogen

atoms, such as in the case of diazines like pyrimidines and pyrazines. The lone pairs of the sp^2-nitrogen atom contribute significantly to the reactivity of the *N*-heterocycle. The *N*-lone pair is unable to donate into the ring because it is perpendicular to the π-system, which makes it challenging to perform classical Friedel-Crafts electrophilic aromatic substitution reactions (EAS) on azines.[2] Alternatively, the lone pair serves as a Brønsted or Lewis acid, coordinates to protons and transition metals, and also reacts with electrophiles.[3,4] Due to the electron deficiency of the *N*-heterocycle, nucleophilic aromatic substitutions reactions (S_NAr) are more facile compared to benzene and can occur without the need of an electron-withdrawing group. [2]

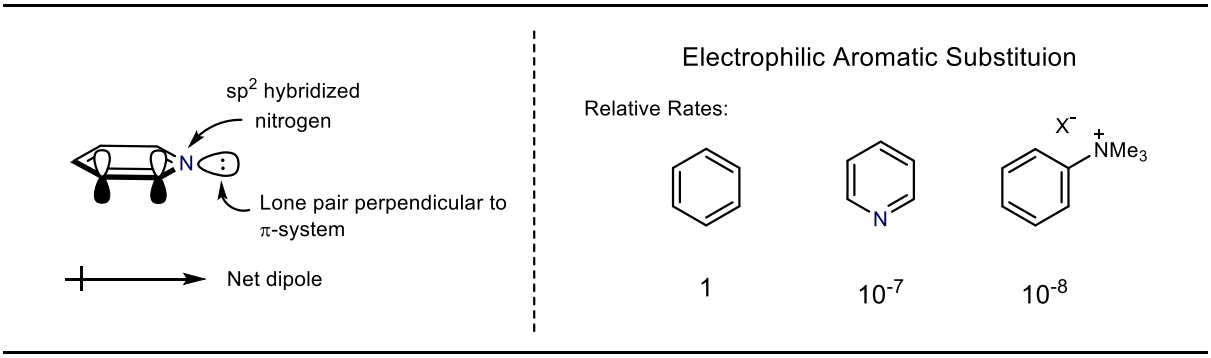

Figure 1.2. Electronic properties of aromatic *N*-heterocycles.

N-heterocycles are appealing to medicinal chemists for a variety of reasons. The incorporation of a pyridine ring can improve the bioavailability and pharmacokinetics of a pharmaceutical drug.[5] The induced dipole implemented by the nitrogen improves the aqueous solubility of the compound, which is important because it is desirable for drugs to be water-soluble in a biological system. [6,7] Additionally, the lone pair on the pyridine's nitrogen assists in a drug-protein interaction through hydrogen bonding.[5,7,8] The rigidity of aromatic *N*-heterocyclic rings, in contrast to piperidines and acyclic structures with rotatable bonds, is also beneficial for drugs.[9] The rigidity keeps the drug in its needed conformation, which improves its chances of reaching the target binding site.

1.2 Direct Functionalization of Pyridines

1.2.1 Classical Methods to Functionalization Pyridines

Despite a high demand for methods to selectively functionalize *N*-heterocycles, there is a shortage of viable approaches to accomplish these transformations selectively and from the corresponding C–H bonds. Direct functionalization on *N*-heterocycles is a challenging process and classical EAS reactions require harsh conditions to achieve productive reactivity due to pyridine's electron deficiency and Lewis basicity.[2,10] For example, electrophilic halogenation on pyridines requires elemental bromine, fuming sulfuric acid, and high temperatures which limits its applicability on complex systems (Figure 1.3). The Chichibabin reaction provides 2-selective amination on pyridines to occur but requires sodium amide ($NaNH_2$), a highly basic and nucleophilic reagent.[11] Directed metalation requires strong, reactive lithium and Grignard bases, and suffers from poor regioselectivity.[12,13] Minisci-type reactions form carbon-carbon bonds via a radical pathway, but the selection of nucleophiles is limited and mixtures of 2- and 4-position functionalized products are commonly observed.[14–16] These classical methods to directly functionalize simple *N*-heterocycles commonly result in possible side reactions and decomposition of late-stage compounds. Thus, mild conditions and selective reactions are prioritized to avoid complications during the derivatization phase.

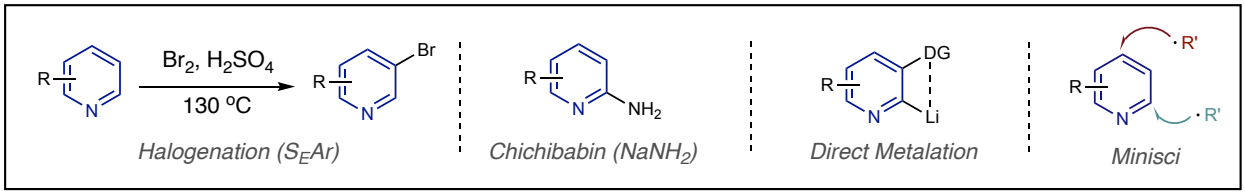

Figure 1.3. Classical methods to functionalize pyridines.

1.2.2 Modern Methods for Pyridine Derivatization

In recent years, milder methods to functionalize azines have been developed and shown to be applicable on complex drug-like molecules (Figure 1.4). Merck and Fier have addressed the limitations of the Chichibabin reaction by using a bifunctional chloropyrazine reagent to install a NH_2Boc group at the 2-position of pyridines through an addition and elimination process.[11,17] Additionally, the Hartwig group has

developed a 2-position fluorination protocol of Ag-pyridiniums to generate useful products for S_NAr.[11,18,19] They have also studied the selectivity and reactivity of pinacol boronic ester installation at the 3-position of pyridines, and these products engage readily in various reactions.[20] Perfluoroalkylation and perfluoroarylation of pyridines has been shown by the Kanai lab through a sequence that includes boron activation, addition, and oxidation.[21] Although these methods have broadened the selection of conditions and allowed for medicinal chemists to acquire valuable functionalized products that previously were unobtainable, new developments are still needed to achieve functionalization at different positions on an *N*-heterocycle and overcome the limitations in current methods.

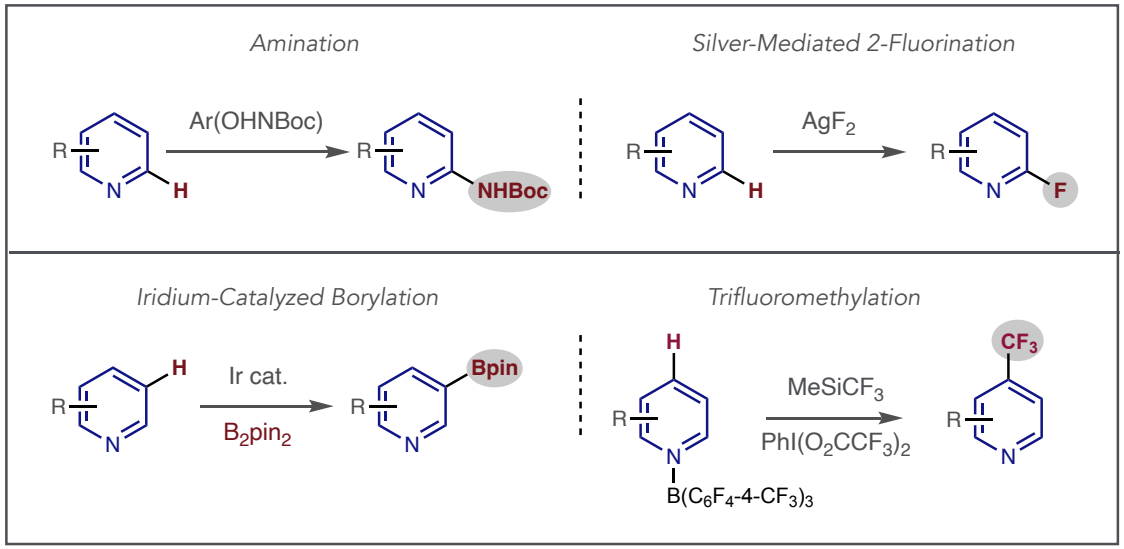

Figure 1.4. Recent developments to functionalize pyridines.

1.2.3 Nucleophile Addition to *N*-Triflyl Pyridiniums

Triflic anhydride (Tf_2O) is known to activate pyridines to form electrophilic *N*-Tf pyridiniums, and various groups have explored different nucleophiles that can add to these intermediates. Adding cyanide nucleophile to *N*-Tf-pyridiniums formed regioisomeric mixtures of cyanated pyridine products at the 2- and 4- positions after rearomatization.[22] The Anders group first showed that phosphines can add at the 4-position of pyridine without a directing group. However, the *N*-Tf dihydropyridine intermediate was too unstable to isolate, so only 4-substituted

pyridines were observed.[23] Using phosphonates instead of phosphines improved the stability of the dihydropyridine intermediates, making isolation possible. The McNally lab further explored the addition of phosphines to *N*-Tf pyridiniums and showed that this reaction was successful and selective on a range of more complex and sterically hindered pyridine examples.[23–35] With this platform, valuable bonds, such as carbon-carbon, carbon-oxygen, carbon-nitrogen, carbon-sulfur, and carbon-halogen bonds, were formed at the 4-position of pyridines via the pyridyl phosphonium salts.[23–35]

Enol triflates add selectively to the 4-position of *N*-Tf-pyridiniums to form ketone products, and the resulting dihydropyridine intermediate rearomatizes with potassium tert-butoxide (KO*t*Bu) in DMSO (Figure 1.5).[38] Similarly, using silyl ketene acetals as nucleophiles produces polycyclic γ- and δ-lactones.[39] The Corey lab demonstrated that electron-rich aromatics can be used as nucleophiles to form biaryl products, and an intramolecular version that results in spirocyclic products has been shown by the Clayden group. [40, 41] With literature precedent on nucleophile addition on *N*-Tf-pyridiniums, we saw this as an opportunity to study these activated pyridines for other reactivity.

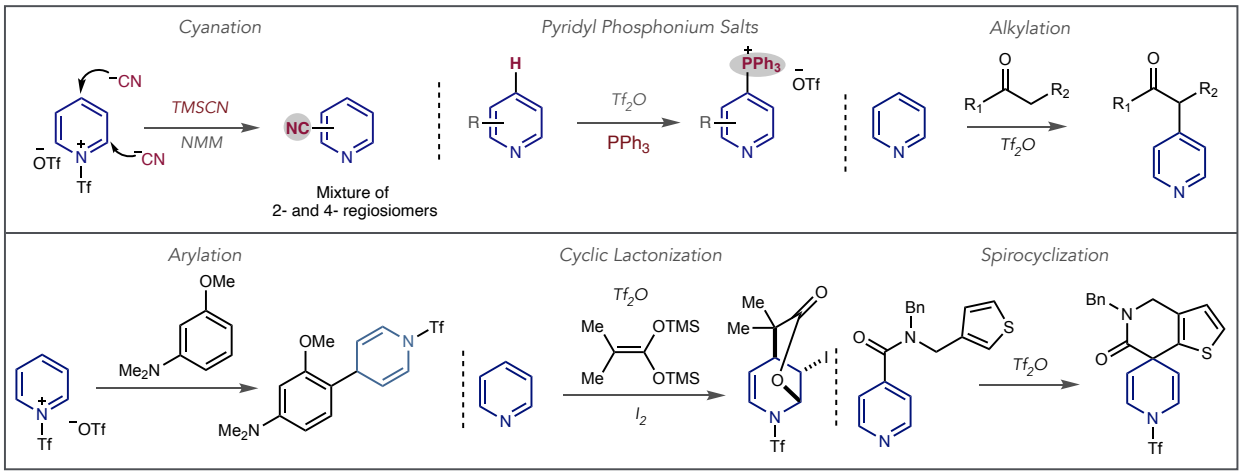

Figure 1.5. Methods to add nucleophiles to *N*-Tf pyridiniums.

1.3 Conclusion

This chapter discusses the background and importance of pyridine in existing organic molecules. The challenges to functionalize pyridine directly from the C–H bond and the limitations of classical and current methods were highlighted. The following chapters in this dissertation will focus on developing methods to functionalize pyridines through triflic anhydride activation and addition of different nucleophiles

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Chapter 2. 3-Selective Pyridine Functionalization via Electrophile Trapping with Zincke Imines

2.1 Overview

This chapter describes a new method to achieve 3,4-bipyridines through Zincke imine coupling with *N*-Tf pyridinium salts. This reaction occurs by transforming one pyridine to a π-electron rich Zincke imine intermediate that can add into electrophilic *N*-Tf pyridinium salts. After ring-closure of the Zincke imine with an ammonia salt, 3,4-pyridine-dihydropyridine products are formed. These products subsequently can undergo rearomatization with a base to form 3,4-bipyridines, or isolated and subjected to metal-catalyzed hydrogenation conditions to make pyridine-tetrahydropyridine and pyridine-piperidine coupled products. This method is the first example of directly forming these bipyridine products and regioselectivity from the C–H bond of each substrate using Zincke imine intermediates. Ben Boyle optimized the Zincke imine formation and ran the initial addition to *N*-Tf pyridinium salts. Professor Rob Paton (CSU) and Louis de Lescure carried out computational studies. This work is undergoing preparation for publication.

2.2 Background

2.2.1 Current Methods for 3-Position Functionalization of Pyridine

Direct, site-selective functionalization of *N*-heterocycles from the C–H bond is important for medicinal chemists to efficiently make libraries of derivatized lead compounds. The McNally lab has discovered new ways to functionalize pyridines using pyridyl phosphonium salts intermediates.[1–9] These intermediates are made by reacting pyridines sequentially with triflic anhydride, phosphines, and an organic base. This method is regioselective for the 4-position of pyridines, leaving the other sites unfunctionalized under the reaction conditions.

The functionalization at the 3-positon of pyridines is challenging due to the electronics of the ring preventing from undergoing classical reactions such as electrophilic aromatic substitution (EAS). For example, the traditional method to access 3-halogenated pyridines require elemental bromine and fuming sulfuric acid to non-activated pyridines. Recently, there has been some development in this field including iridium-catalyzed borylation developed by Ishiyama, Miyara, and Hartwig. Although the regioselectivity of the borylation is still being studied, the 3-position is reasonably favored for unsubstituted pyridine (2:1 for 3- vs 4-position) (Figure 2.1A).[10] The Hartwig group demonstrated that this Ir-catalyzed C–H functionalization protocol can extend to 5-silylation of 3-methylpyridine; however, potential regioselectivity challenges may occur on other substituted pyridines (Figure 2.1B).[11]

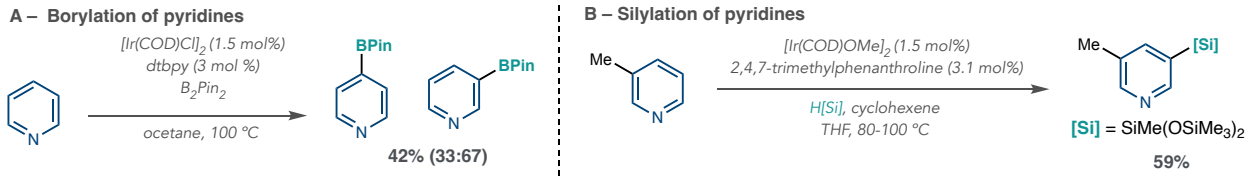


Figure 2.1. Iridium-catalyzed C–H functionalization of pyridines

To overcome the limitations of 3-position direct functionalization of pyridines, we envisioned changing the inherent reactivity and electronics of pyridine by breaking its aromaticity to enable new transformations. Our approach centers around the idea that ring-opening a pyridine will reveal a polar conjugated π-system. The ring-opening step will invert the polarity of pyridines from a π-deficient electrophile to a π-rich nucleophile.

2.2.2 The Classic Zincke Reaction and Limitations

We were inspired by the Zincke ring-opening reaction of pyridines discovered in 1904 using 2,4-dinitrochlorobenzene, a secondary amine, and an aqueous base to achieve Zincke aldehydes.[12,13] First, the pyridine is activated via an S_NAr reaction with 2,4-dinitrochlorobenzene to form a Zincke salt (Figure 2.2a). Second, nucleophilic addition of a secondary amine results in a ring-opened conjugated iminium product. An aqueous base in the reaction mixture then converts the iminium intermediate to the Zincke aldehyde product. The overall limitations include that the Zincke reaction requires high temperatures, and the activation of 2-substituted pyridines does not proceed with aryl activation, which severely limits the scope and application of this reaction on complex systems such as drugs and drug-like fragments (Figure 2.2b).

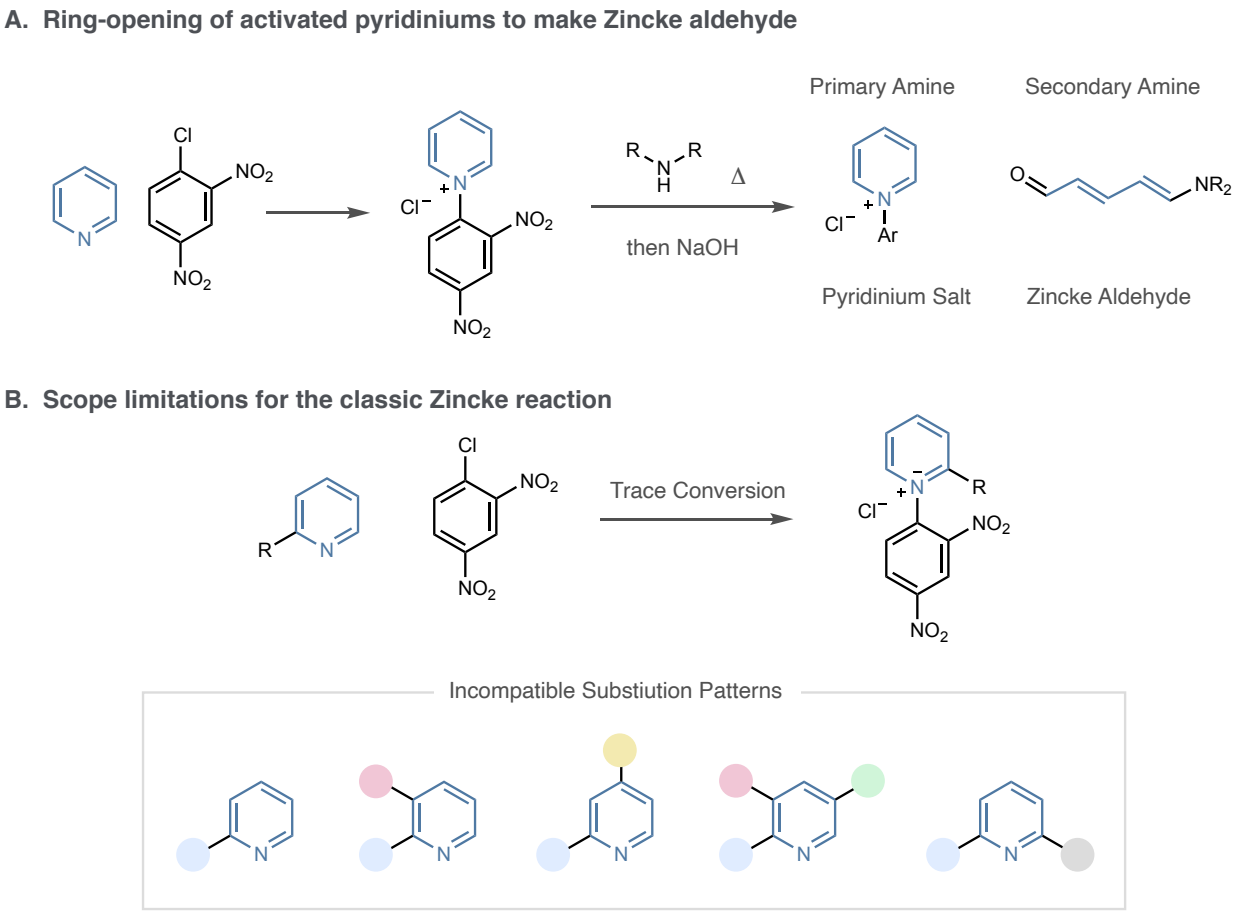


Figure 2.2. Conditions and limitations of the Zincke reaction

The Zincke reaction has been mostly used to make natural products by the Vanderwal group, such as in the synthesis of gelsemine and strychnine.[14,15] In these examples, the Zincke aldehyde is an intermediate for an intramolecular Diels-Alder to make the fused *N*-heterocycle core of the natural product molecule. Despite the use of the reaction in natural product synthesis, the Zincke reaction for new carbon-atom bond for pyridine functionalization is underexploited. The McNally group demonstrated its versatility in a recent publication for selective 3-halogenation of pyridines via *N*-Tf Zincke imines.[16]

2.2.3 *N*-Tf Zincke Imine Reaction Design and Optimization

The ring-opening of *N*-Tf pyridinium salts by an amine (diethylamine) was reported by the Toledano group in 1998 as they were interested in the ligation of the azatriene with iron(0) complexes. They also observed low yields of the ring-opened product adding to their *N*-Tf pyridinium salts but since then, no further explorations have been published on these azatrienes.[17] We saw the *N*-Tf Zincke imine potential as a useful intermediate for pyridine functionalization since the lone pair on the amine nitrogen could donate into a conjugated system. The Zincke imine can behave as both an electron donor and acceptor due to the flow of electrons within the molecule, with specifically the 3- and 5- positions on the Zincke imine being nucleophilic, and the 2-, 4-, and 6-positions being electrophilic (Figure 2.3). After functionalizing the Zincke imine, ring-closing conditions are implemented to regenerate the pyridine. Our lab anticipated that this dearomatized, conjugated system will open new reaction pathways and bond formations that are not possible with pyridines.

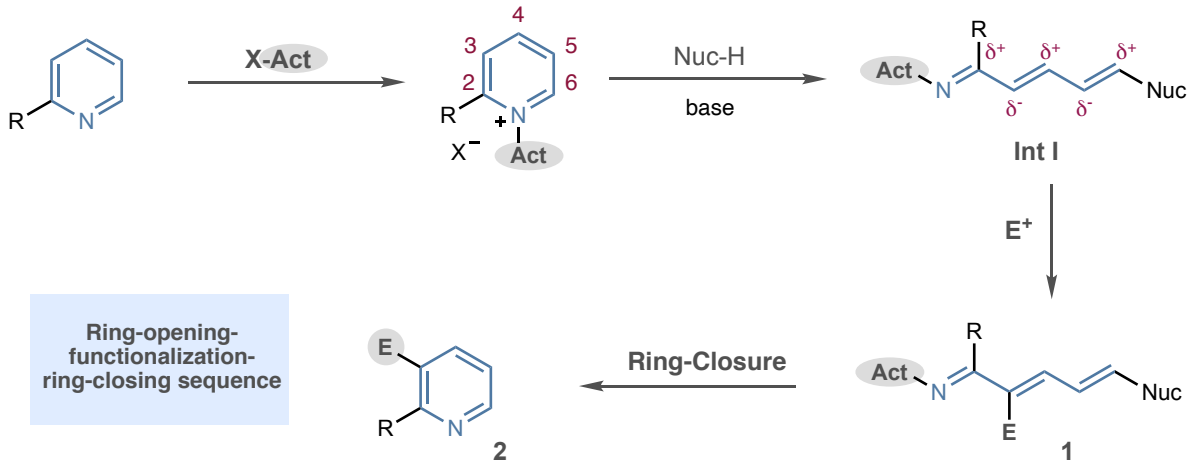
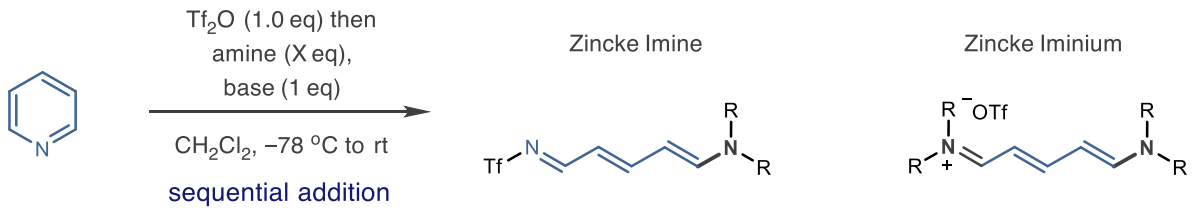


Figure 2.3. Sequence to functionalize pyridines via Zincke imines.

Using pyridine as our test substrate, we studied the reactivity and the selectivity of the amine addition on *N*-Tf pyridinium salts (Table 2.1). Initially, a mixture of Zincke imine and iminium was observed when two equivalents of piperidine were added to the *N*-Tf pyridinium. We wanted to optimize the reaction so the amine could selectively add once to the pyridine to ring-open without displacing the *N*-Tf side of the Zincke imine. When switching to acyclic amines, complete formation of the Zincke imine was achieved using dibenzylamine even at higher equivalents. With further optimization, we found that 1.2 equivalents of dibenzylamine and 1 equivalent of a base, collidine, produced high yields of our desired *N*-Tf Zincke imine. Next, we found that switching solvents from dichloromethane (CH_2Cl_2) to ethyl acetate (EtOAc) was more general on a wider range of pyridines. With the optimized conditions to form the Zincke imine, we wanted to explore its reactivity for selective C–H functionalization.

Table 2.1. Optimization of *N*-Tf Zincke imine formation. *Yield determined by ^{1}H NMR using triphenylmethane as an internal standard.



Entry	Amine (eq)	Base eq.	Zincke Imine%	Zincke Iminium%
1	piperidine (2)	none	52	20
2	piperidine (1)	NEt_3 (2)	51	15
3	piperidine (1)	lutidine (1)	75	6
4	piperidine (3)	none	-	78
5	pyrrolidine (2)	none	28	57
6	*N*-benzylmethylamine (2)	none	52	6
7	dibenzylamine (2)	none	99	-
8	dibenzylamine (1.2)	none	98	-
9	**dibenzylamine (1.2)**	**collidine (1)**	**97**	-

2.3 Bipyridine Synthesis from Zincke Imines

2.3.1 Significance and Approaches to Make Bipyridine

Bis-heterobiaryls are common motifs found in pharmaceuticals and lead treatments for diseases (Figure 2.4). The polarity and structure of bis-heterobiaryls are useful physical properties for drug discovery. The additional *N*-heterocycle increases the number of sites for hydrogen bonding that can improve a drug's uptake and metabolization. The rigidity of bis-heterobiaryls allows them to retain correct confirmation in an enzyme pocket.

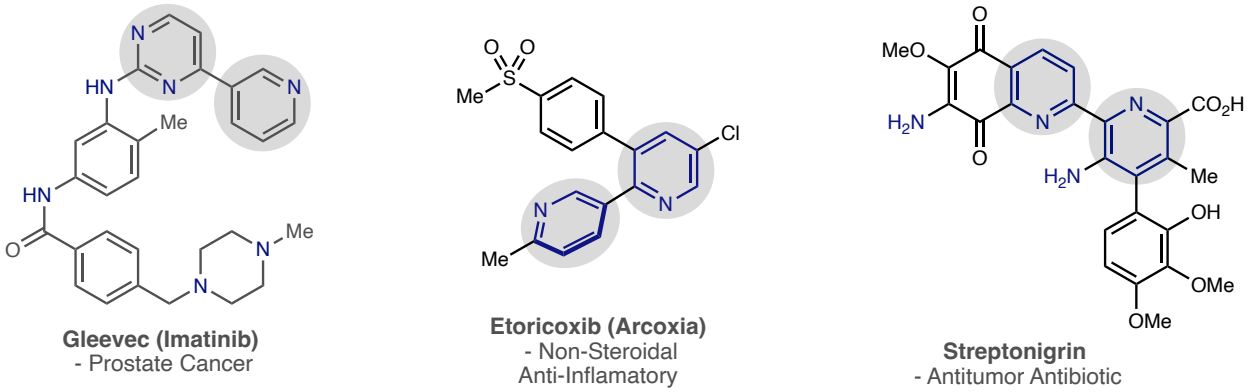


Figure 2.4. Pharmaceutical drugs containing bis-heterobiaryls

Aryl-aryl coupling commonly occurs through transition metal catalysis to synthesize biaryl products; however, these metal-catalyzed processes typically require preinstalled halide or boronic acid functional handles (Figure 2.5A).[18–20] The limited commercial and synthetic availability of

these reagents, particularly on azine rings, makes it a challenge to form bis-heterobiaryls. [21] Additionally, even when the reagents are available, multiple functionalities and polar sites on the starting materials may lead to catalyst poisoning and unproductive coupling yields. Due to the limited available methods to couple *N*-heterocycles directly from their corresponding C–H bonds, we wanted to investigate reacting the Zincke imines with *N*-Tf pyridiniums for bis-heterobiaryl coupling.

More recently, pyridylsulfinates have been developed by the Willis group as nucleophilic Suzuki cross-coupling partners (Figure 2.5B).[22] Although the sulfinates are more stable than 2-boronic acids on pyridine, the pyridylsulfinate is made for a halopyridine which limits its applicability on complex pharmaceuticals and fragments. The Yu lab reported a 3-position pyridine dimerization directly from the C–H bond using a Pd (II) catalyst (Figure 2.5C).[23] However, they required forcing reaction conditions to obtain the 3,3'-bipyridine with limited scope. The McNally has found a method to make bis-heterobiaryls directly from a C–H bond using pyridyl phosphonium salts (Figure 2.5D). The phosphonium salts are formed on pyridines without a need for a leaving group at the ipso-position which widens the scope for this protocol to make 4,4'-bipyridines on complex systems containing various functionalities.[2] Although bipyridine formation has been targeted, 3,4'-bipyridine synthesis remains underdeveloped.

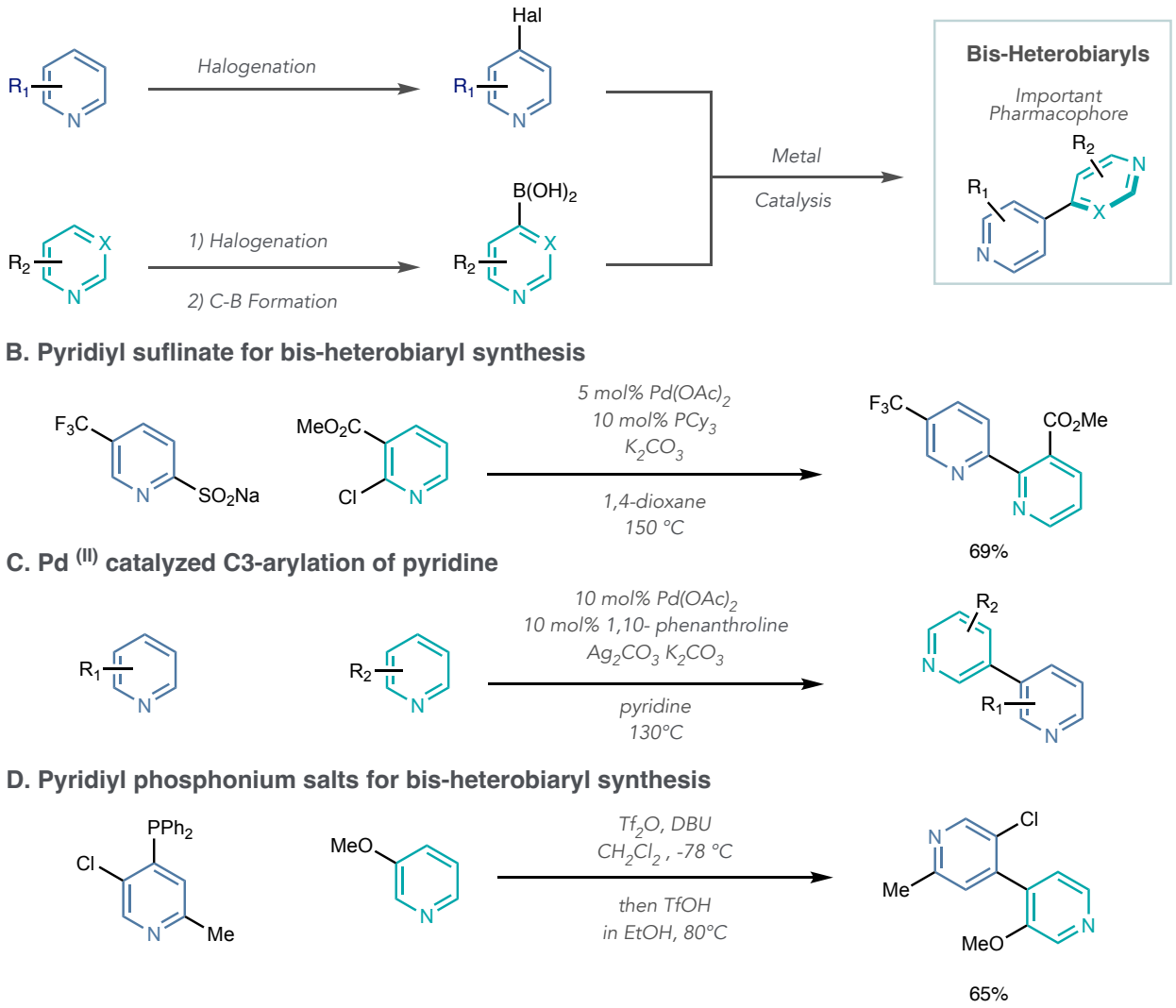


Figure 2.5. Common methods to make bis-heterobiaryls.

2.3.2 Zincke Imines for 3,4-Bipyridine Coupling

To generate 3,4'-bipyrdines, a different approach is needed; thus, we hypothesize that Zincke imines would be a suitable nucleophilic coupling partner to *N*-Tf-pyridiniums. In 2007, the Corey lab showed that electron-rich aryls can react with *N*-Tf-pyridiniums to form dihydropyridine intermediates (Figure 2.6A).[24] Although biaryl products can be produced under their conditions, the aryl nucleophile was limited to 3-methoxy-*N*,*N*-dimethylaniline. Poor selectivity was observed when other electron-rich heterocycles such as pyrroles were used as nucleophiles. For Zincke

imines, each position is polarized due to the push-pull π-system and reactivity with electrophiles is possible at the 3- or 5-position. Thus, reaction with an *N*-Tf pyridinium and a base was proposed to form a functionalized imine product (Figure 2.6B). This will allow for electronically and sterically distinct pyridines to serve both as the nucleophile and electrophile to make valuable bipyridine products (Figure 2.6C).

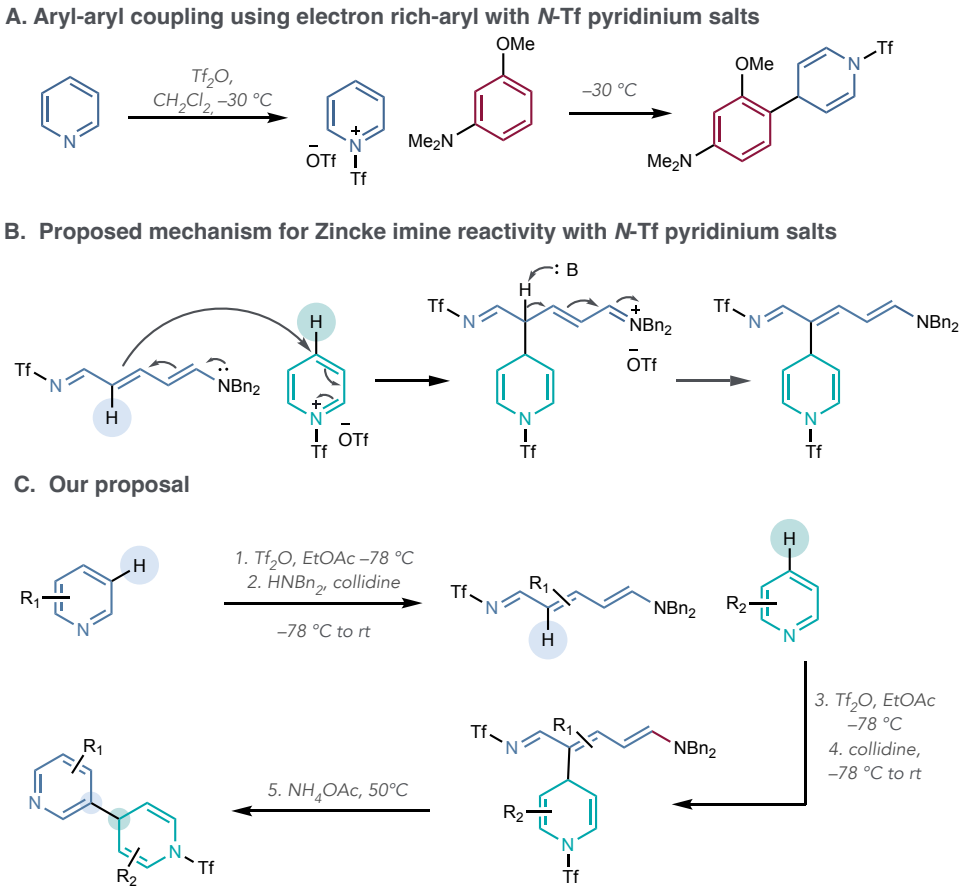


Figure 2.6. Addition of π-nucleophiles into *N*-Tf pyridiniums.

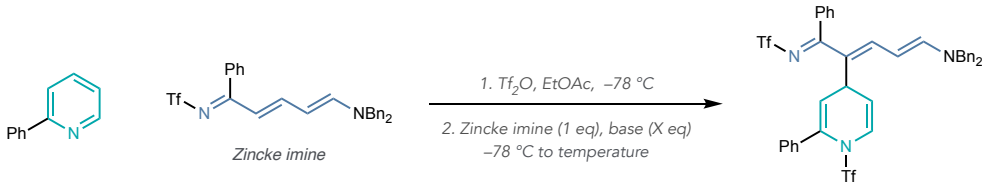
2.4 Results and Discussion

2.4.1 Optimization for Zincke Imine Addition into *N*-Tf-Pyridiniums

Because the nucleophilic Zincke imine and electrophilic *N*-Tf pyridinium salts are both derived from pyridines, interconversion between the roles can give mixtures of coupled products if the reaction is done in a one-pot sequence. To avoid a mixture of products, the Zincke imine is

purified and isolated to remove any remaining pyridine starting material before it is added to the *N*-Tf pyridinium. We used the 2-phenyl Zincke imine and 2-phenyl *N*-Tf-pyridinium as our test substrates for optimization (Table 2.2). Various organic and inorganic bases were screened, and collidine was determined to be the optimal base. EtOAc was the best solvent and yields were further improved when the reaction was allowed to warm to room temperature after adding the Zincke imine and base. When using 2-phenylpyridine as the acceptor, the highest yield observed was 52%, but higher yields were observed when an electron-withdrawing group was at the 3-position on the acceptor pyridine due to increased electrophilicity of the 4-position on the *N*-Tf-pyridinium.

Table 2.2. Optimization of Zincke Imine and *N*-Tf-pyridinium cross-coupling.



Entry	Solvent	Base eq.	Temperature	Pdt%
1	EtOAc	collidine (1 eq)	-78°C[a]	31
2	EtOAc	none	rt	17
3	**EtOAc**	**collidine (1 eq)**	**rt**	**52**
4	EtOAc	NEt_3 (1 eq)	rt	33
5	EtOAc	Cs_2CO_3 (1 eq)	rt	27
6	EtOAc	Hunig's base (1 eq)	rt	36
7	DCM	collidine (1 eq)	rt	30
8	MeCN	collidine (1 eq)	rt	35

2.4.2 Scope of Pyridine-Dihydropyridine Coupled Products

To test the versatility of our strategy and see how comparable it was to transition-metal approaches, simple pyridine building blocks were subjected to the reaction (Figure 2.7). Halogenated pyridines prone to undergo oxidative addition in metal-catalyzed reactions were not displaced under our reaction conditions. Mono- and disubstituted Zincke imines with varied sterics

and electronics coupled with our *N*-Tf-pyridiniums. We found that methyl groups at the 2- or 4-position on the Zincke imine showed issues in chemoselectivity. Under the reaction conditions, deprotonation of the methyl group would occur, leading to benzylic functionalization instead of 3,4'-bipyridines (Figure 2.8). Other alkyl groups, such as 2-ethyl and 2-isopropyl, at the 2-position avoided this side pathway and favored reactivity through the Zincke imine. Different substitution patterns and electronics on our *N*-Tf-pyridiniums were suitable to form the pyridine-dihydropyridine products. Fused-heteroaryls can be activated and used to couple with Zincke imines in high yields.

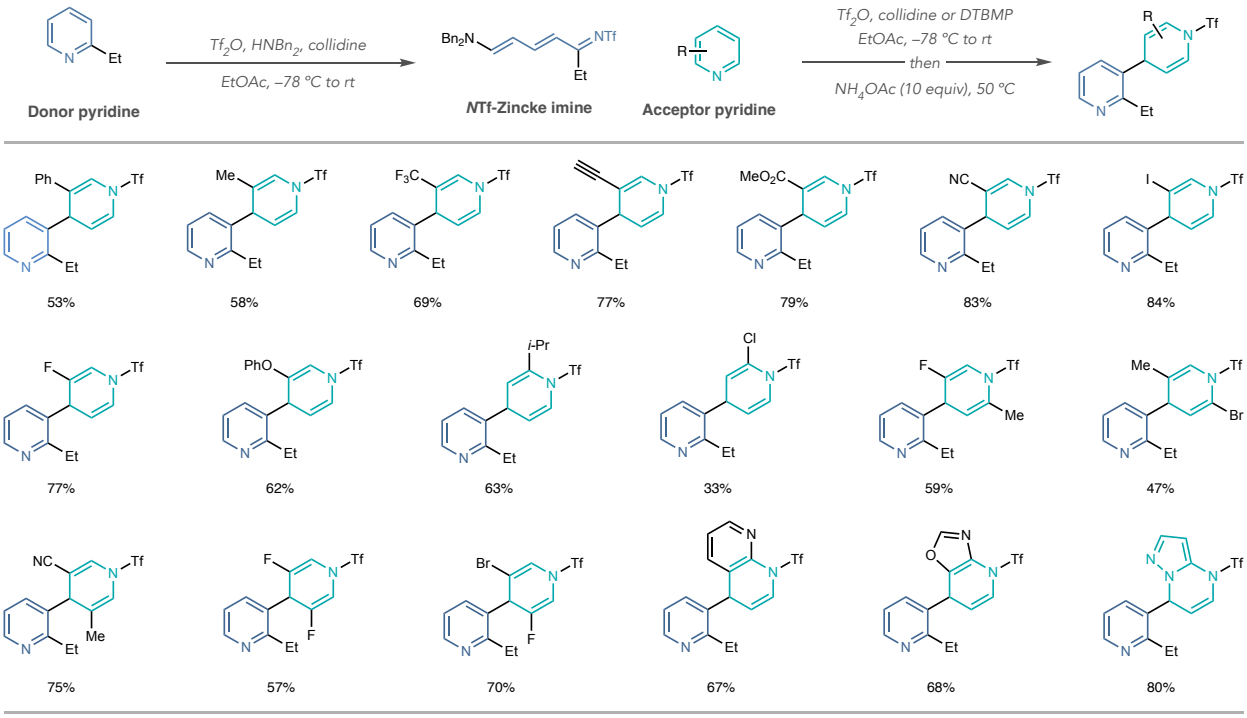


Figure 2.7. Simple pyridine-dihydropyridine coupling with isolated 2-ethyl Zincke imine

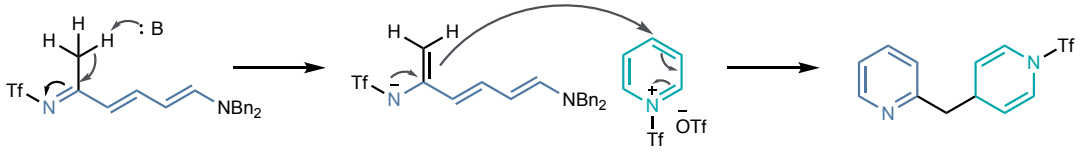


Figure 2.8. Favored chemoselectivity of 2-methyl Zincke imine with *N*-Tf-pyridiniums.

2.5 Accessing to 3,4-Bipyridines

2.5.1 Rearomatization Conditions to Form 3,4-Bipyridines

In order to form 3,4-bipyridines from the pyridine-dihydropyridines, a base is required to facilitate the elimination of the triflyl group. Initially using reported conditions by the Corey lab with KO*t*Bu as the base in DMSO resulted in some rearomatization, but significant yield was lost.[24] After screening different bases, it was found that switching the base to DBU in EtOAc was key to fully rearomatize the 2-phenyl dihydropyridine to form the 3,4'-bipyrdine product at room temperature (Figure 2.9.1)

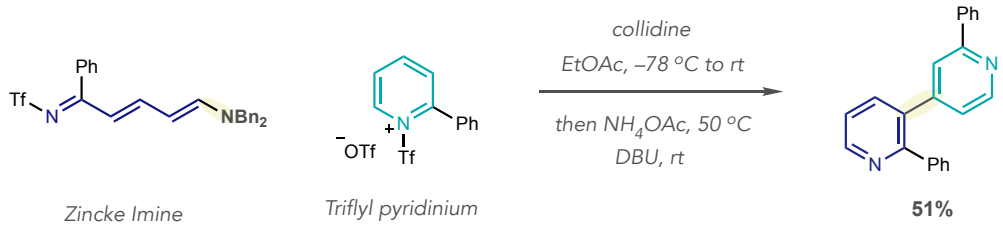
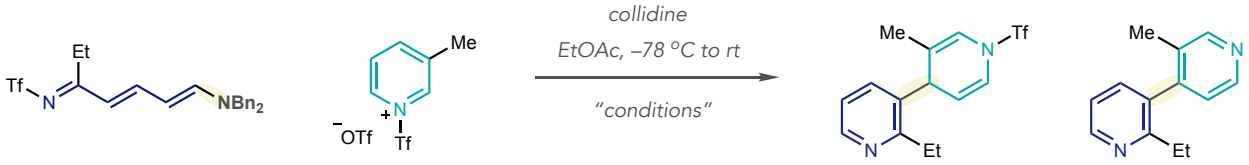


Figure 2.9.1. Rearomatization to form 3,4-bipyridines

However, when other dihydropyridines such as 3-methyl were tested using DBU for rearomatization at room temperature, trace amounts of product were observed (Table 2.3). I discovered that a crucial part for the rearomatization to occur successfully was the counterion in the ammonium salt used for the recyclization of the Zincke imine. When using NH_4OAc, the acetate counterion (–OAc) can become acetic acid (HOAc), which protonates the DBU and prevents it from deprotonating the dihydropyridine for rearomatization. To test this hypothesis, I initially added an inorganic base, $NaHCO_3$, to react with any acetic acid that may be present in the reaction. A minor increase in yield to 21% of the desired product was observed, but the majority remained as the pyridine-dihydropyridine. Switching to the ammonium salt to NH_4CO_3H allowed

for complete rearomatization of the dihydropyridine to form 3,4-bipyridine. Different simple building blocks were able to couple and form the 3,4-bipyridines under these optimized conditions.

Table 2.3. Optimized conditions for rearomatization to achieve 3,4-bipyridines



Zincke Imine | *Triflyl pyridinium*

NH_4OAc then DBU	**52%**	**9%**
NH_4OAc then $NaHCO_3$, DBU	**47%**	**21%**
NH_4CO_3H then DBU	**0%**	**61%**

2.5.2 Scope of 3,4-Bipyridine via Zincke Imine Coupling

The generality of this reaction is highlighted by different substituted pyridines and azines that could undergo this coupling reaction (Figure 2.9.2). 2- and 3- substituted alkyl, aryl, and heteroaryl pyridines behaved as acceptors to give moderate to high yields of the coupled product. In the case when 3-methoxy Zincke imine was used where its most reactive site is substituted, reactivity occurred at the 5-position adding into 6-bromopyridine for a 56% yield. This reaction protocol extends to fused heterocycles to form bisazines. Zincke imine can also add into *N*-Tf-pyridazinium salts. NH_3 in MeOH allowed for full recyclization of the Zincke imine as well as rearomatization of the pyridazine to achieve a pyridine-pyridazine coupled product. 4-substituted and 2-, 4-dibsutituted Zincke imine donors can add into 3-halopyridines to form bipyridines. In addition, 3-,5-disubstituted pyridine acceptor can also undergo the coupling reaction even when there is steric around the reactive axis. Over the course of this reaction, it was found that the 2,6-di-tert-butyl-4-methylpyridine (DTBMP) gave higher yields compared to collidine in some cases. The convergent coupling of complex pyridines can be achieved in this way. This highlights the advantage of this method over metal-catalyzed reactions by avoiding the need to have prefunctinalized the precursors.

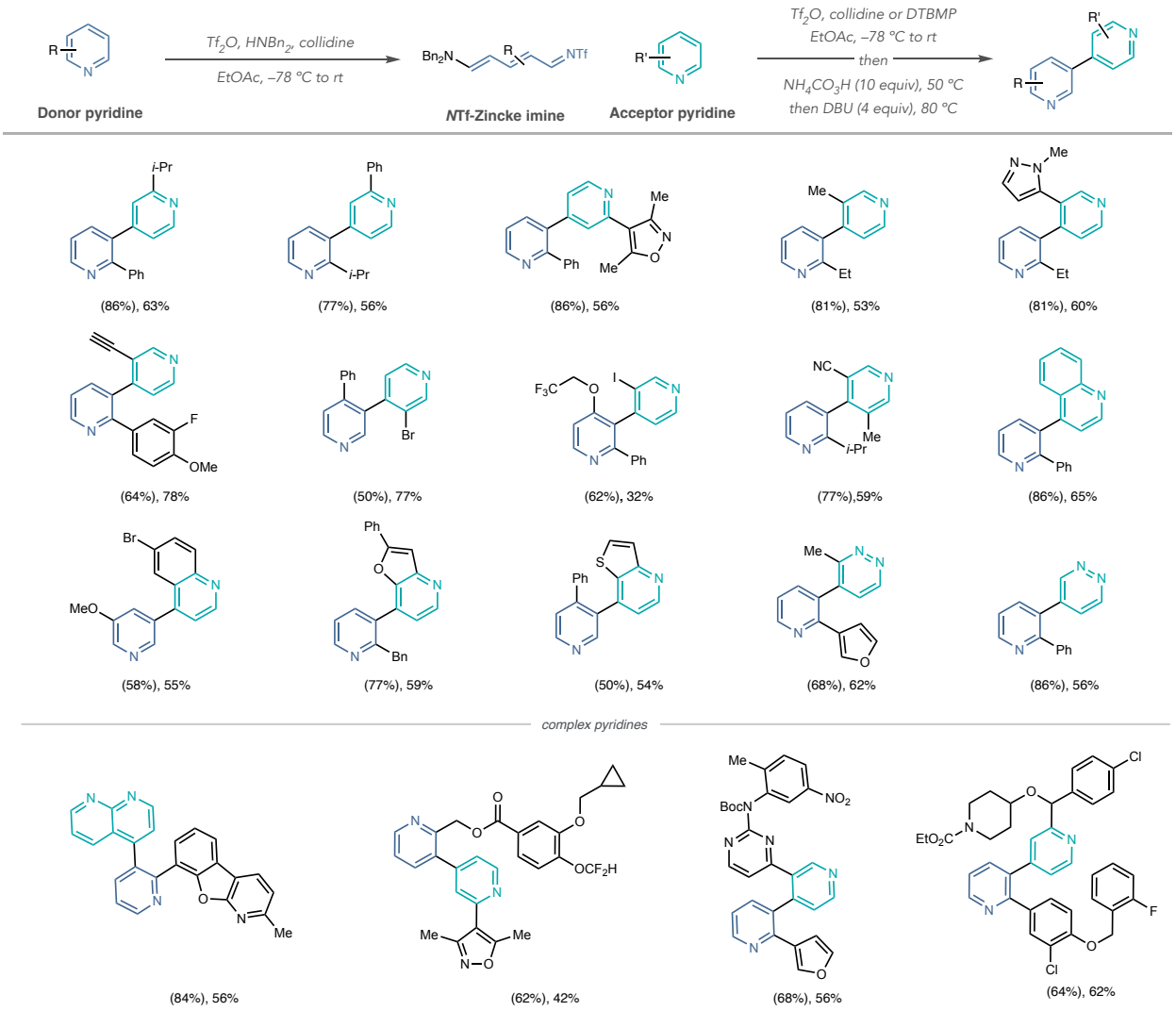


Figure 2.9.2. Scope of simple pyridines and convergent examples of 3,4-bipyridines

2.5.3 Computational Studies Explanation for Regioselectivity

There are two sites, 3- and 5-position, on the Zincke imine that hold most of the electron density and are reactive toward electrophiles. The NBO charge and Fukui (f +) indices calculated for the Zincke imine favored the 5-position which contradicts the observed regioisomer since only the 3-position reacts with *N*-Tf pyridinium salts and not the 5-position. To explain the regioselectivity of this reaction, it was studied computationally with density functional theory (DFT) where the free energy of each possible transition state for each regioisomer was calculated

(Figure 2.9.3). Dimethylamine was modeled to simplify the calculations, but it is representative of the dibenzylamine Zincke imines.

The calculation indicated that the initial addition into *N*-Tf pyridinium is reversible where the Zincke imine can add at both the 3- and 5-position. The regioselectivity is determined during the reconjugation step done by collidine. The calculations highlighted that deprotonation of the 5-position proton of the Zincke imine created higher distortion due to the induced sterics compared to the proton at the 3-position. This result aligns with our computational studies done on halogenation where the $A^{1,3}$ allylic interactions at the imine control the regioselectivity. Ultimately, the calculation supports experimental observation for the regioselectivity of the product where the Zincke imine reacts at the 3-position and adds to the 4-position of the *N*-Tf-pyridinium salts to give the lowest distortion energy compared to the other calculated transition states.

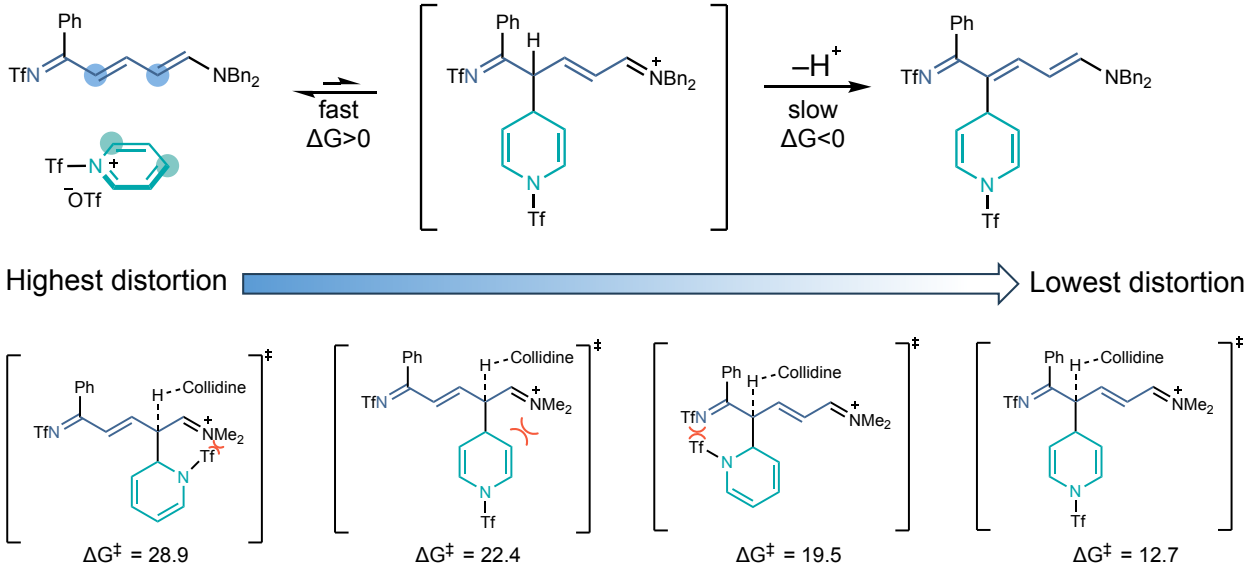


Figure 2.9.3. Distortion energy calculated with DFT to explain regioselectivity of Zincke imine

2.5.4 Regioselectivity Switch Mediate by Zincke Iminiums

The switch in regioselectivity was achieved by subjecting Zincke iminiums, where the *N*-Tf side of the Zincke imine has been displaced by the amine, to the reaction conditions. Since both sides of the ring-opened Zincke iminium are the same, the regioselectivity switches to the 5-

position. This occurs since the regioselectivity for the Zincke iminium system is dictated by the stability of the product since every step in the reaction is reversible. This is demonstrated in the case of 2-phenyl Zincke iminium reacting with 5-chloroquinoline and 2-ethyl Zincke iminium with 3-cyanopyridines to form the 4,5-bisazine product (Figure 2.9.4).

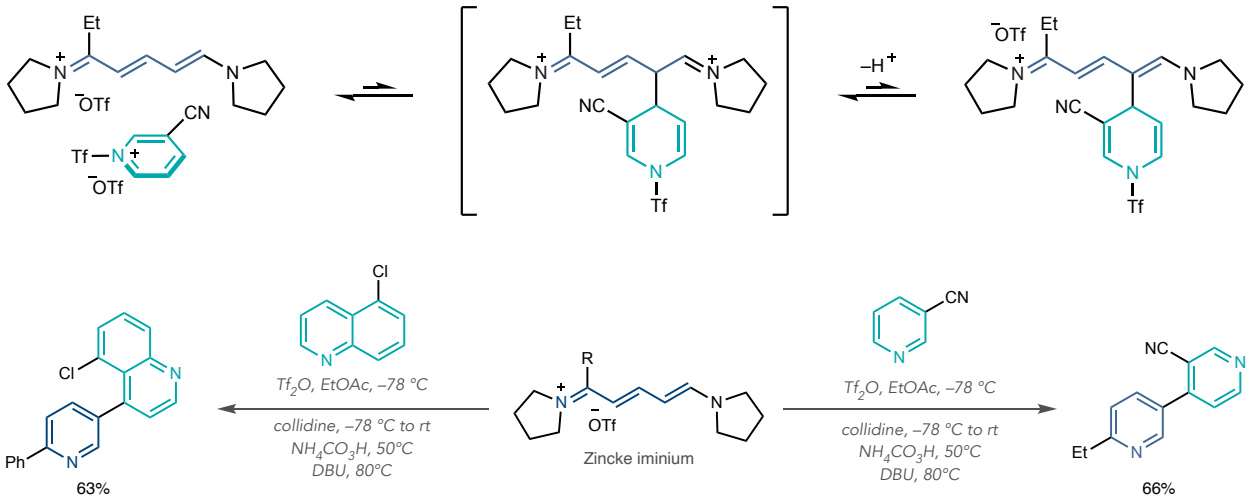


Figure 2.9.4. Switching regioselectivity using Zincke iminium

2.6 Reduction of Pyridine-Dihydropyridine Products

In addition to rearomatization, the pyridine-dihydropyridine is a valuable intermediate that can be further derivatized to achieve saturated *N*-heterocycles (Figure 2.9.5). Since the pyridine is no longer stabilized by aromaticity, we can selectively hydrogenate the *N*-Tf-dihydropyridines with Pd/C and H_2 under acidic conditions. At 500 psi and in the presence of a 3-subsitutent, on the dihydropyridine, the isolated pyridine-dihydropyridine is converted to the pyridine-tetrahydropyridine at 92% yield. Increasing the pressure to 1000 psi and one equivalent Pd/C resulted in full saturation of the dihydropyridine to achieve the pyridine-piperidine product in one step. I investigated lower pressures, but the results of the hydrogenation became inconsistent. This hydrogenation method can be useful for in drug synthesis since piperidines are the most common *N*-heterocycles in FDA-approved pharmaceutical drugs.[1]

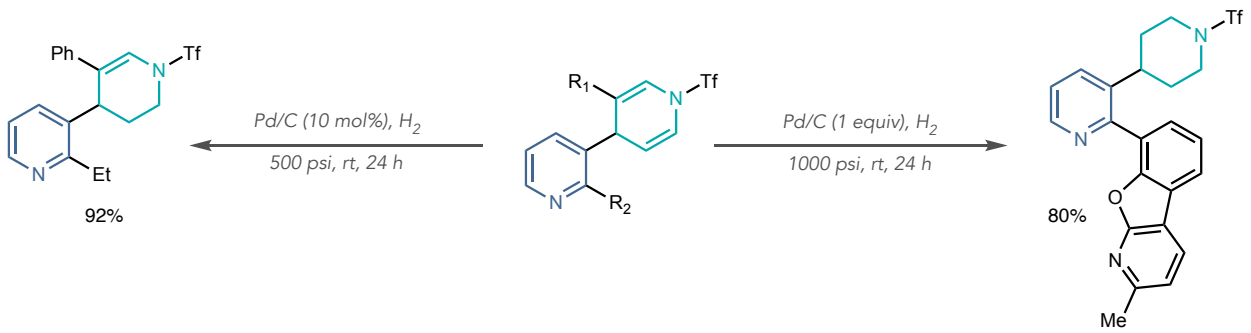


Figure 2.9.5. Reduction of *N*-Tf-dihydropyridine under hydrogenation conditions

2.7 Acylation of Zincke Imine

2.7.1 Importance of Acylation

Acylation is a classical EAS reaction performed on benzenes. Acyl groups are inherently valuable in drugs and agrochemicals, and they are synthetically useful as they can be transformed into other functional groups such as carboxylic acids and alcohols.[25] As a result, chemists are in search of acylation methods on *N*-heterocycles. To install an acyl group on an *N*-heterocycle, chemists typically use a pre-installed functional handle such as a methylene or cyano group to perform oxidation or hydrolysis, respectively.[26,27] Both methods require high temperatures and harsh reagents to undergo the necessary conversion to form the acyl group. We presumed that our Zincke imine will overcome these limitations and bridge this gap.

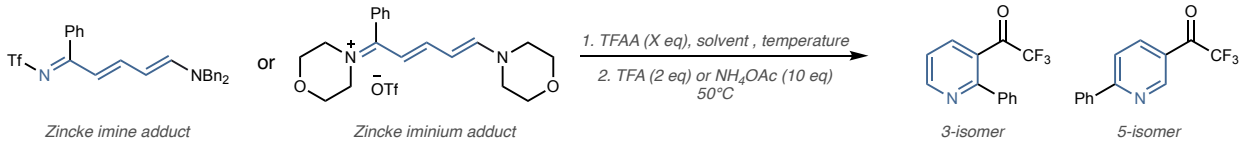
2.7.2 Reaction Optimization

Since we know that our Zincke imines are nucleophilic, we decided to react them with trifluoroacetic anhydride (TFAA) for the acylation (Table 2.4). Initially, I tested 2-phenyl Zincke imine with two equivalents of TFAA in acetonitrile (MeCN), then rearomatized the product under acidic conditions with two equivalents of trifluoroacetic acid (TFA) at 50 °C overnight to achieve the acylated pyridine. In MeCN, a mixture of 3- and 5-acylated products were formed under the reaction conditions. The ratio of the two products became more prominent when CH_2Cl_2 was used as a solvent, but complete selectivity for the 5-position was observed with ethyl acetate. Although

the reaction is completely selective in ethyl acetate, the overall yield is low, maxing out at mid-30%.

When one nucleophilic site on the Zincke imine substituted, such as in the case of 3-butyl which left only the 5-position available for reactivity, I saw the acylated yield nearly doubled. From that result, I hypothesized that the acylation reaction occurred too quickly, and the Zincke imine was too reactive with excess TFAA present which resulted in other side reaction pathways and unselective acylation. Thus, Zincke iminiums were tested next to study the impact of changing the electronics of imine to be less electron-rich, to observe if it can increase the yield and maintain the acylation regioselectivity. After reacting 2-phenyl Zincke iminiums with TFAA, complete 5-position acylation occurred in high yields. Since Zincke iminiums are unable to rearomatize with TFA, neutral conditions using ammonium acetate (NH_4OAc) were implemented instead. At 50 °C overnight, the ring-closing occurred to produce the acylated pyridine without any ammonia incorporation to the trifluoroacetate group. Other Zincke iminiums will be tested to examine the scope of this reaction.

Table 2.4: Optimization for acylation with Zincke imine. *Yield determined by ^1H NMR using triphenylmethane as an internal standard



Zincke imine adduct *Zincke iminium adduct* *3-isomer* *5-isomer*

Entry	Adduct	Solvent	TFAA eq.	Temperature	TFA 2 eq or NH_4OAc 10 eq	3-isomer%	5-isomer%
1	imine	MeCN	2	rt	TFA	3	32
2	imine	CH_2Cl_2	2	rt	TFA	14	39
3	imine	EtOAc	2	rt	TFA	ND	34
4	iminium	CH_2Cl_2	1	rt	NH_4OAc	ND	22
5	**iminium**	**CH_2Cl_2**	**2**	**rt**	**NH_4OAc**	**2**	**86**
6	iminium	CH_2Cl_2	2	50°C	NH_4OAc	2	84

2.8 Conclusion

Zincke imines enable chemists to address challenges in pyridine functionalization by changing from electron deficient pyridine to an electron rich conjugated system. Bipyridines are formed using this platform directly from their C–H precursors. The computational studies highlighted that the regioselectivity of this reaction was based on the reconjugation step after the addition to reform the Zincke imine. The regioselectivity can be switched to the 5-position when using the Zincke iminium where the regioselectivity is observed based on the stability of the product. This coupling reaction works beyond pyridines where quinolines, fused heterocycles, and pyridazines can also behave as acceptors. Convergent coupling scope shown demonstrates the importance of this method and its advantages over metal-catalyzed methods. This reaction can extend to making pyridine-tetrahydropyridine or pyridine-piperidine coupled products by hydrogenating isolated pyridine-dihydropyridine products using Pd/C and H_2 gas.

Finally, other carbon-based electrophiles such as acyl groups can react with Zincke iminiums. TFAA can selectively acylate the 5-position of the Zincke iminiums in high yields. Further investigation is needed to determine the scope of this reaction.

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Chapter 3. Synthesis of ^{15}N-Pyridines and Higher Mass Isotopologues

3.1 Overview

This chapter discusses an alternative approach to obtaining ^{15}N-pyridines from Zincke imines. First, pyridines undergo ring-opening conditions to form the *N*-Tf Zincke imine. Then, the *N*-Tf Zincke imine ring closes after the addition of $^{15}NH_4Cl$, NaOAc, and heat to obtain ^{15}N-pyridine products. Higher mass isotopologues were achieved by deuteration of the 3- and 5-positions of the Zincke imine before ring closure. This method allows chemists to access ^{15}N pyridines from the parent ^{14}N pyridine and commercially available $^{15}NH_4Cl$ salt. David Thomas developed the ring-closure conditions, synthesized *N*-Tf Zincke imines on building blocks, and preformed subsequent ring-closure to access ^{15}N pyridines. Marie Hart formed *N*-Tf Zincke imines on complex pyridines and made their ^{15}N isotopologue. Kaila Steenback helped synthesized ^{15}N pyridines and developed conditions for deuteration. Jeff Levy ran the initial reaction and found the first results for ^{15}N isotopologue and deuteration on *N*-Tf Zincke imines. This work was published in the *Journal of the American Chemical Society* in 2024.[1]

3.2 Background

3.2.1 Importance of ^{15}N-Pyridines

The incorporation of isotopes into pharmaceuticals and agrochemicals allows chemists to study the candidate compounds in various stages of development.[2–4] The higher mass isotopes are used in mechanistic probes with NMR and mass spectrometry.[5–7] Modern techniques are emerging to use ^{15}N azines as a SABRE-SHETH approach to study the spin hyperpolarization for bioimaging.[8–10] Two common ways to achieve pyridine isotopes are by de novo synthesis by

combining simpler precursors and exchanging C–H bonds or functional groups on molecules.[11–15] However, there are limited approaches to incorporate ^{15}N in pyridines within the ring.

3.2.2 Methods to form ^{15}N pyridines

Until recently, there were limited ways in incorporate ^{15}N into pyridines. The de novo synthesis approach allows tetrahydropyran derivatives as glutaraldehyde surrogates under oxidative conditions to form ^{15}N pyridine (Figure 3.1A).[16] However, it would be challenging to access other ^{15}N substituted pyridines since they must append to the tetrahydropyran. Chukanov and Chekmenev used the classic Zincke reaction on a limited number of pyridines to form ^{15}N pyridine isotopologues with incomplete ^{15}N incorporation (Figure 3.1B).[17,18] As mentioned in chapter 2, to form the *N*-aryl Zincke salts for the reaction, forcing conditions are required to react dinitrochlorobenzene with pyridines. A major limitation to this activation step is that it does not extend to pyridines with substituents. These constraints prevent this method from being applied during late-stage functionalization. During the final stages of this work, we became aware of three other approaches to form ^{15}N pyridine isotopologues using the ring-opened Zincke imine intermediates.[19–21]

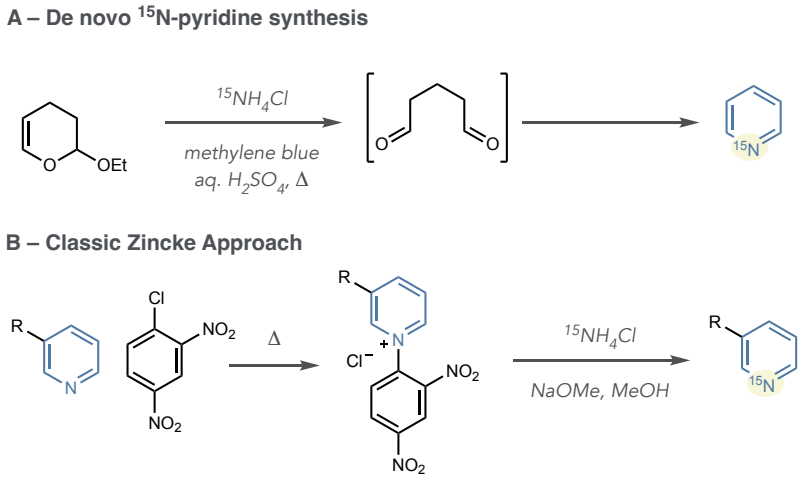


Figure 3.1. Methods to form ^{15}N-pyridines

3.3 Results and Discussion

3.3.1 Zincke Imine Strategy

The *N*-Tf-Zincke imines have addressed the issues of the classic Zincke reactions. Both simple building blocks ranging in substituent patterns and complex pyridines can undergo the activation step. Since *N*-Tf-Zincke imines can undergo ring-closure with a variety of $^{14}NH_4X$ salts, switching to commercially available and relatively inexpensive $^{15}NH_4X$ salts is an appealing way to access ^{15}N pyridine isotopologues. In addition, deuterium incorporation can occur at the nucleophilic sites, the 3- and 5-position, on the *N*-Tf-Zincke imines before ring closure to achieve higher-mass isotopologues that can used for in vivo ADMET studies.

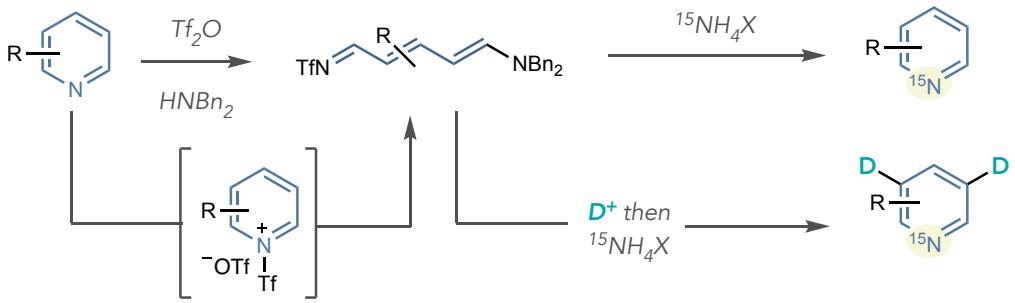
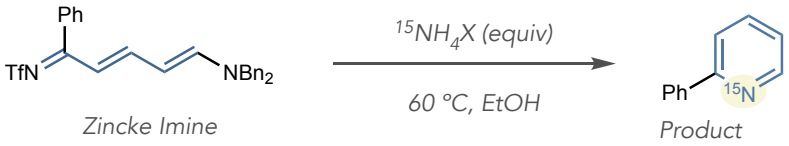


Figure 3.2. Formation of ^{15}N-pyridine and higher mass isotopologues via Zincke imines

3.3.2 Optimization for ^{15}N Isotopologues

The ring-opening of pyridines to form Zincke imines still requires sequential addition of Tf_2O, dibenzylamine, and collidine.[22,23] Our reported protocol to ring-close *N*-Tf Zincke imines in our halogenation paper required 10 equivalents of NH_4OAc in EtOH (Table 3.1).[22] Here, we found that we can lower to two equivalents of $^{15}NH_4Cl$, the least expensive $^{15}NH_4X$ salt commercially available, with equimolar of NaOAc present in the reaction to achieve high ^{15}N incorporation in pyridines. We found that NaOAc was necessary in the reaction since no ring closure occurred with having just $^{15}NH_4Cl$.

Table 3.1. Development of a general protocol for pyridine ^{15}N-labeling



Zincke Imine *Product*

$^{15}NH_4Cl$ (equiv)	Additive (equiv)	% Zincke Imine	% Product
$^{15}NH_4Cl$ (10)	NaOAc (10)	83	6
$^{15}NH_4Cl$ (10)	NaOAc (10)	0	98
$^{15}NH_4Cl$ (5)	NaOAc (5)	0	99
$^{15}NH_4Cl$ (2)	NaOAc (2)	0	98

High ^{15}N incorporation of pyridines is achieved through this method by taking advantage of the different physical properties between Zincke imines and ^{14}N pyridines. Washing the crude reaction mixture with saturated $NaHCO_3$ followed by aqueous $CuSO_4$ removes excess dibenzylamine; adding this to hexanes allows for precipitation of pure Zincke imines. In most cases, the unreacted ^{14}N pyridine starting material is soluble in hexanes; however, when the pyridine also precipitates out of hexanes, an acidic aqueous work up is preformed to protonate the pyridine before subjecting the reaction to hexanes. This isolation procedure avoids the need for column chromatography and achieves high ^{15}N incorporation in the final product.

We occasionally observed the formation of both Zincke imine and iminium in cases of mono 3- and 4-substitution especially if it is an electron-withdrawing group. For 3-substituted pyridines, we isolated the mixture of Zincke imine and iminium and added 2 equivalents of $^{15}NH_4Cl$ and NaOAc relative to the amount of pyridine starting material. We increased the amount of dibenzylamine from 1.2 to 2.0 equivalents for 4-substituted pyridines to selectively form Zincke iminiums.

3.3.3 Scope of ^{15}N labelled Pyridines and Deuteration

With the optimized conditions and isolation procedure, we examined the scope of the building block pyridines that can undergo this isotope exchange (Figure 3.3). We found that in the majority of cases, there were a >95%^{15}N incorporation in the pyridine products with a significant amount measuring at >99%. This reaction tolerated 2-substituted pyridines including methyl and phenethyl substituents, acetal, and protected pyrrolidine. Other groups such as furan, thiophene, methoxy, and morpholine were also viable at this position. This reaction extends to 3-substituted pyridines including trifluoromethyl, (hetero)aryl groups, and halides. Mono 4-substituted pyridines converted to Zincke iminiums underwent ring-closure to give >99% ^{15}N pyridines. We found that disubstituted pyridines with 2,3-, 2,4-, 2,5-, and 3,4-substitution patterns containing a range of useful functional handles and carbon-bearing groups were tolerated under the reaction

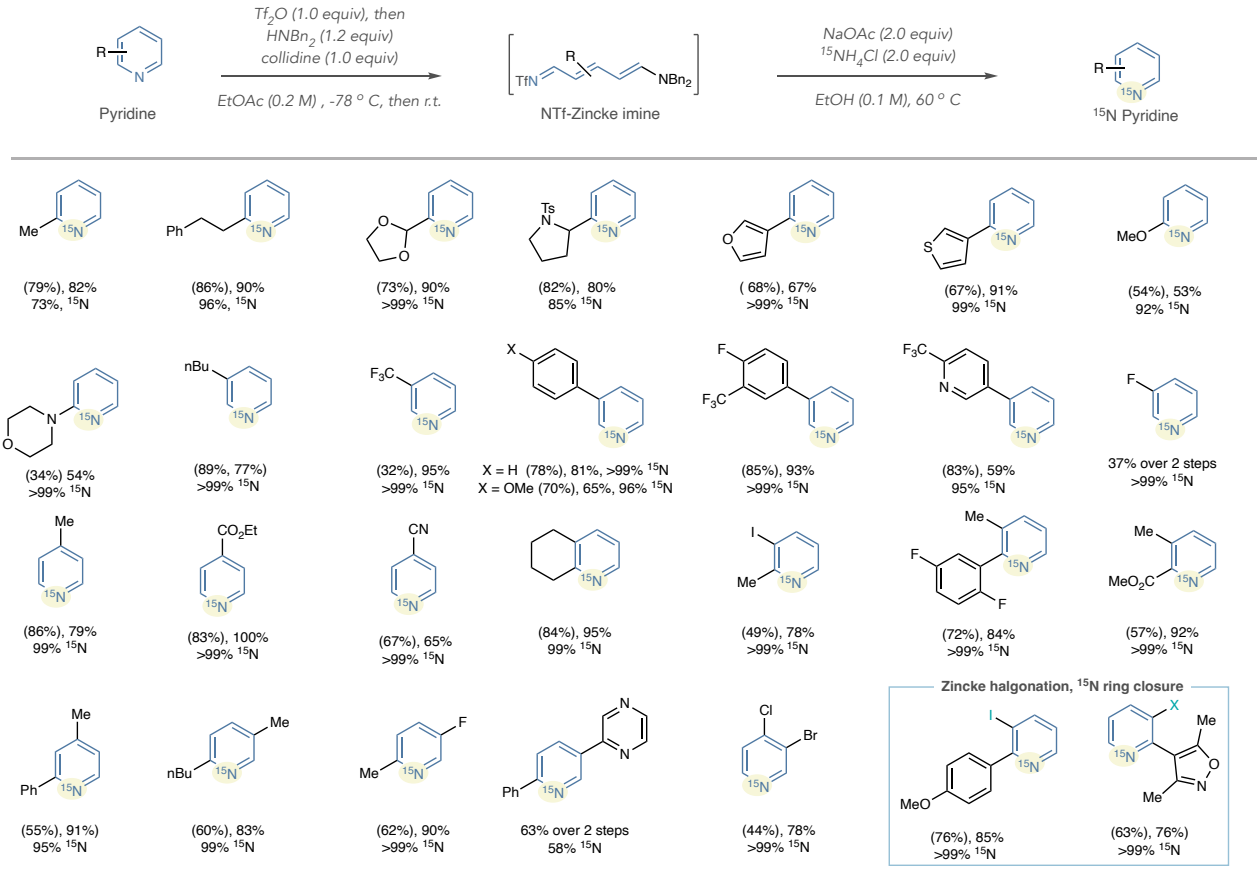


Figure 3.3. ^{15}N labeling of building block-type pyridines via Zincke imine

conditions. Additional ^{15}N 2,3-disubstituted pyridines were accessed by preforming selective C3-halogenation of Zincke imine intermediates followed by ring closure.

This labeling process extends to drug-like molecules and pharmaceutical compounds where they are generally more complex and can possess multiple heterocycles and reactive sites (Figure 3.4). With the current available methods, multistep sequences are typically required to achieve ^{15}N-labeled pyridines for these advanced molecules and are potentially unfeasible if the appropriate ^{15}N-pyridine is not readily available. 2-, 3-, 4-substituted and 2,3-disubstituted pyridines resembling drug fragments were formed and successfully labeled from their ^{14}N pyridine. This reaction also extends to a series of drug compounds to form ^{15}N-isotopologues of vismodegib, bisacodyl, zytiga, etoricoxib, and loratadine.

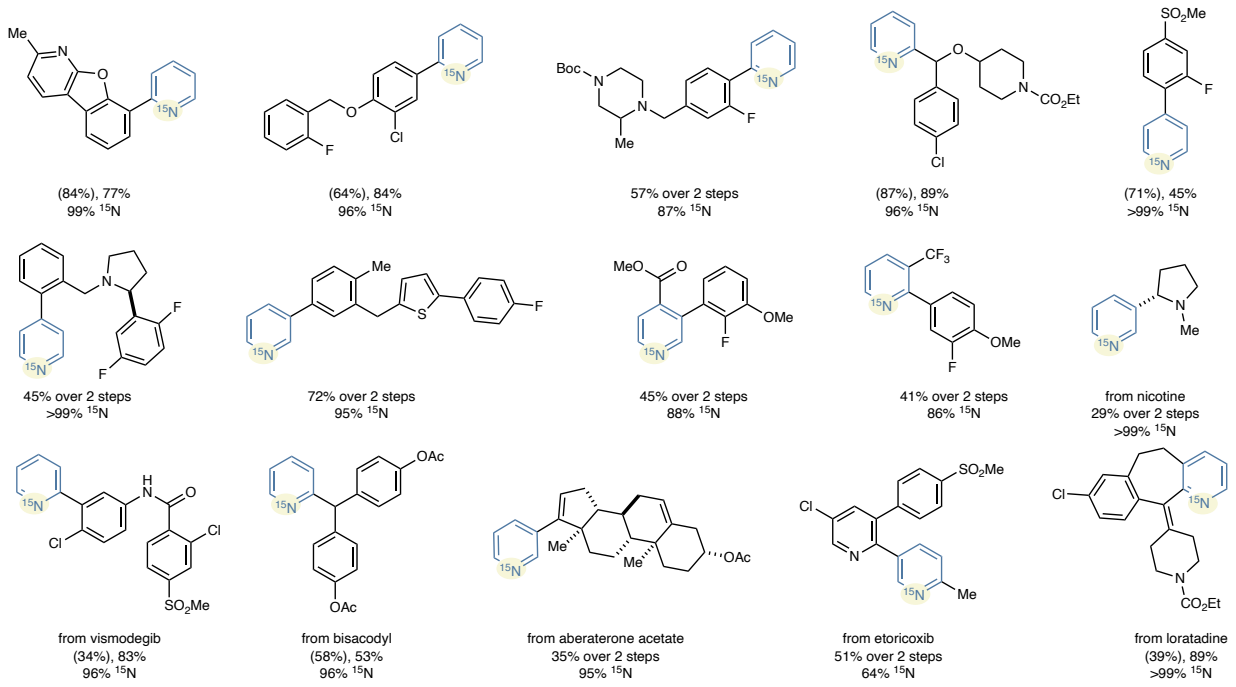


Figure 3.4. ^{15}N Labeling of Drug-Like Fragments and Pharmaceuticals

3.3.4 Considerations for Lower Incorporation of ^{15}N

Competing mechanisms potentially occurred in cases where there were low ^{15}N incorporation resulting in incomplete replacement of the initial ^{14}N atom. The control experiments we conducted highlighted that acid-mediated background premature ring-closure was unlikely; we instead observed the formation of $^{15}NH_2Tf$ in these reactions (Figure 3.5A). This outcome implies that $^{15}NH_3$ can react with the Tf-portion of Zincke imines, instead of displacing the *N*-Tf to form ^{14}N-pyridines cyclization (Figure 3.5B).

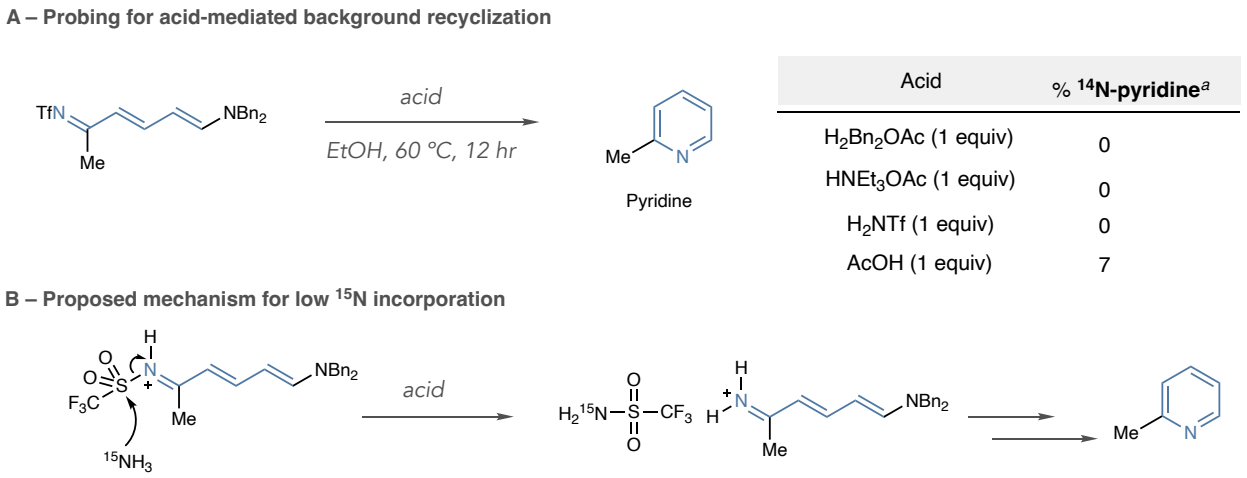


Figure 3.5. Control experiments to investigate low ^{15}N incorporation

We found an alternative route to increase the ^{15}N incorporation in cases where it was low by forming and ring-closing the Zincke iminium salts. We selected 2-methylpyridine as our substrate to study this protocol (Figure 3.6). To form these intermediates, we performed the standard ring-opening protocol, then added 4 equivalents of pyrrolidine, and heated the reaction mixture to 50 °C for an hour to fully transform the *N*-Tf Zincke imine into Zincke iminium. Similar to Zincke imines, we isolated the Zincke iminium by performing aqueous washings and subjecting it to hexanes. We added the isolated Zincke iminium to the ring-closing conditions and observed an improvement from 72% to >99% ^{15}N incorporation for 2-methypyridine.

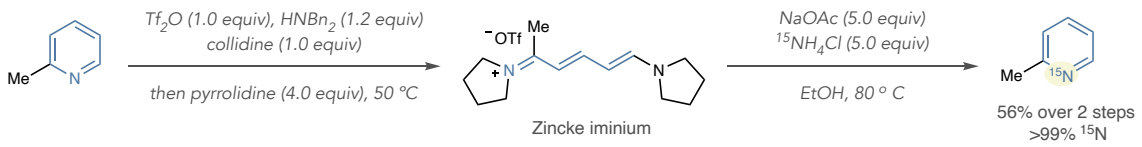


Figure 3.6. Increasing percentage ^{15}N incorporation using Zincke iminium intermediates

3.3.5 Development for Deuteriation of Zincke Imines

For in vivo ADMET studies in blood plasma, blood plasma ion suppression can occur that can introduce substantial inaccuracies that limit quantitative analysis. [4,24,25] Thus, using higher mass isotopes ion traces which do not overlap with the parent compounds are preferred. To demonstrate this, we deuterated the Zincke imines before ring-closure to obtain M+2 and M+3 pyridine isotopologues. Additional mass units could be introduced into different parts of a candidate's structure for +4 or higher isotopologues by combining with other labeling methods.

We developed two reaction protocols for the deuteration of 2- and 3-substituted pyridines. Deuteration occurred at the C3- and C5-positions of the 2-phenyl Zincke imine with AcOD at 50 °C after 24 hours (Figure 3.7A). Minor amounts of recyclization to 2-phenylpyridine occurred with incomplete deuterium incorporation under these conditions. A precipitation was done to separate the deuterium labeled Zincke imine from the partially unlabeled 2-phenylpyridine. Then, the crude Zincke imine was subjected to standard ring closure conditions to form d_2-product with reasonable levels of D- and ^{15}N-incorporation in 42% yield.

Mono 3-substituted pyridines needed a modified deuteration procedure to avoid premature ring closure and incomplete deuterium incorporation (Figure 3.7B). 3-substituted adduct was stirred in an EtOD/DCE solution of DCl at 0 °C for complete deuteration at C5. The deuterated intermediate underwent precipitation to remove minor amounts of partially deuterated pyridine in the reaction mixture, and recyclization with $^{15}NH_4Cl$ formed M+2 product with excellent isotopic purity. We applied these labeling protocols to vismodegib and 3-subsittuted complex pyridine-

containing compounds to convert them into M+3 and M+2 higher-mass isotopologues, respectively (Figure 3.7C).

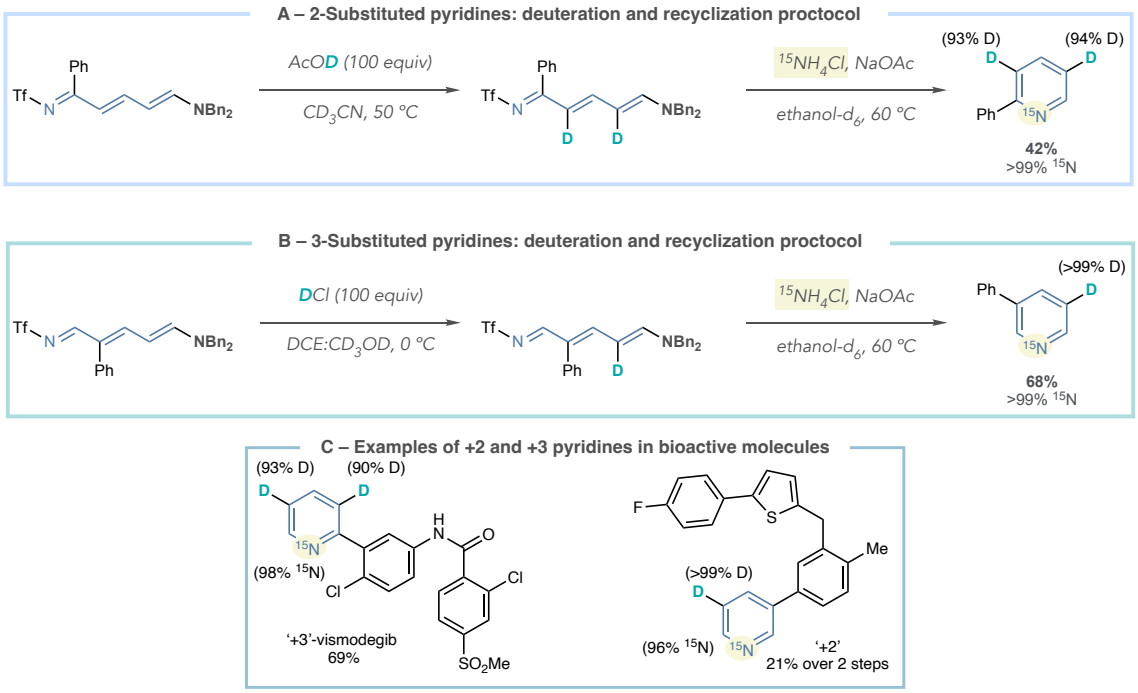


Figure 3.7. Deuterium and ^{15}N labeling sequences for [M+2] and [M+3] pyridine

3.4 Conclusion

We have developed a strategy to exchange ^{14}N for ^{15}N in pyridines in a two-step process and have extended this to form higher mass isotopes for M+2 and M+3 by adding deuterium to the *N*-Tf Zincke imines. Compared to the existing methods, this method allows chemists to convert a variety of pyridines with different substitution patterns and functional groups to undergo the exchange. This isotopic labeling strategy for ^{15}N and deuterium incorporation can be used at later stages of drug development and avoid the recourse to extensive synthesis from simpler precursors. Limitations from classical Zincke reactions are addressed in this process and the incorporation is shown >95% in most cases. Lower incorporation can be addressed by switching to Zincke iminium systems to avoid undesired side reactivity.

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Chapter 4. *N*-Alkyl Pyridinium Formation with Amino Esters from Zincke Imines

4.1 Overview

The drug-like physicochemical and pharmacokinetic properties in the bioactivity shown by macrocycles found in nature have made scientists interested in developing new approaches to synthesize these molecules for therapeutic treatments. We hope to access *N*-alkyl pipecolic esters that can be used in macrocyclization. Preliminary results show promise in this approach to achieve *N*-alkyl pyridinium salts with amino esters that can be converted to *N*-alkyl pipecolic esters for macrocyclization. This is an ongoing collaboration with Merck & Co., Inc. and further investigations will continue to be performed in the McNally lab to identify the scope of this reaction.

4.2 Background

4.2.1 Macrocycles in Pharmaceuticals

Macrocycles have been found in natural products to serve various biochemical functions and have been incorporated in pharmaceuticals for drug discovery.[1,2] The functional and stereochemical complexity of macrocycles cause it to have a specific confirmation. This allows them to engage in protein targets with high selectivity and affinity. With these characteristics, macrocycles can address certain illnesses that small molecules are incapable of treating. The prevalence of piperidine in macrocycles are highlighted in rapamycin, an antitumor drug, and CAL inhibitor prodrug, treatment for cystic fibrosis (Figure 4.1).[3,4] Studies have shown that the addition of piperidine in the CAL inhibitor prodrug cause it to have a well-defined confirmation and increased its potency and selectivity for the target.[4]

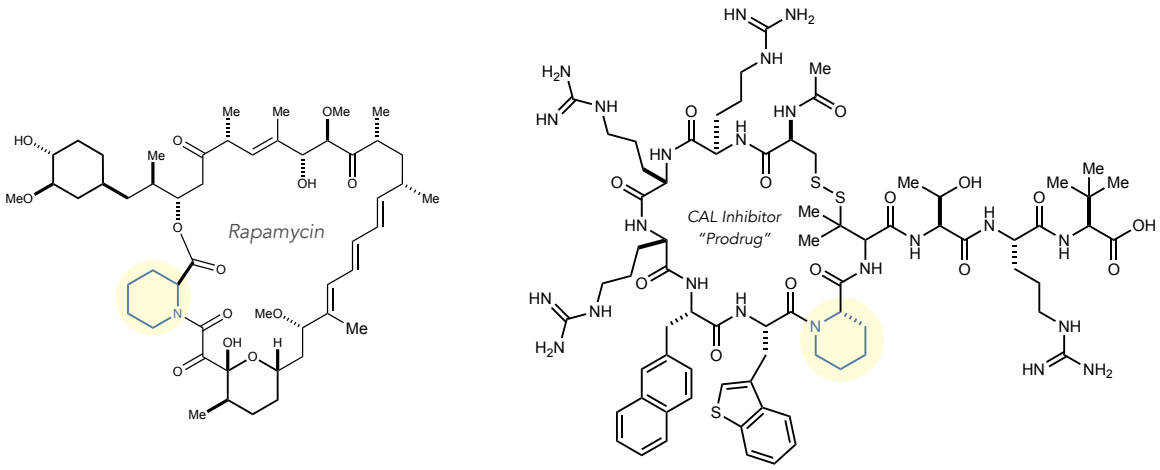


Figure 4.1. Examples of piperidine in macrocycles

Macrocycles are generally linked by amide bonds between different amino acids. Although including piperidine in a macrocycle has shown benefits, it is challenging to access different substituted pipecolic esters to incorporate in a macrocycle. We thought a of strategy to address this limitation by forming different pipecolic esters derived from 2-ester pyridines that are commercially and easily accessible. This method combines *N*-Tf Zincke imine synthesis and ring-closure with amino esters to form *N*-alkyl pyridinium salts that would undergo hydrogenation to give the pipecolic ester product.

4.2.2 Methods to Form *N*-alkyl Pyridinium Salts and Access Piperidines

Adding substituents to the *N*-terminus of a pyridine typically requires harsh conditions and becomes increasingly challenging to do when there are other substituents present on the pyridine ring. Most reports of alkylating pyridine salts involve methylation or benzylation; however, the pyridine scope for these methods is limited which highlights their incompatibility to complex pyridines (Figure 4.2A).[5,6] The challenge remains to have a method that efficiently and broadly forms these pyridinium salts beyond primary alkyl groups. Amino acid-derived pyridinium salts made from triphenylpyran salts have been used to form α-aryl esters and amides (Figure 4.2B).

The pyridine motif in the salts accessed through this method is limited to triphenyl which prevents them being used broadly as way to access other useful *N*-heterocycles.[7,8]

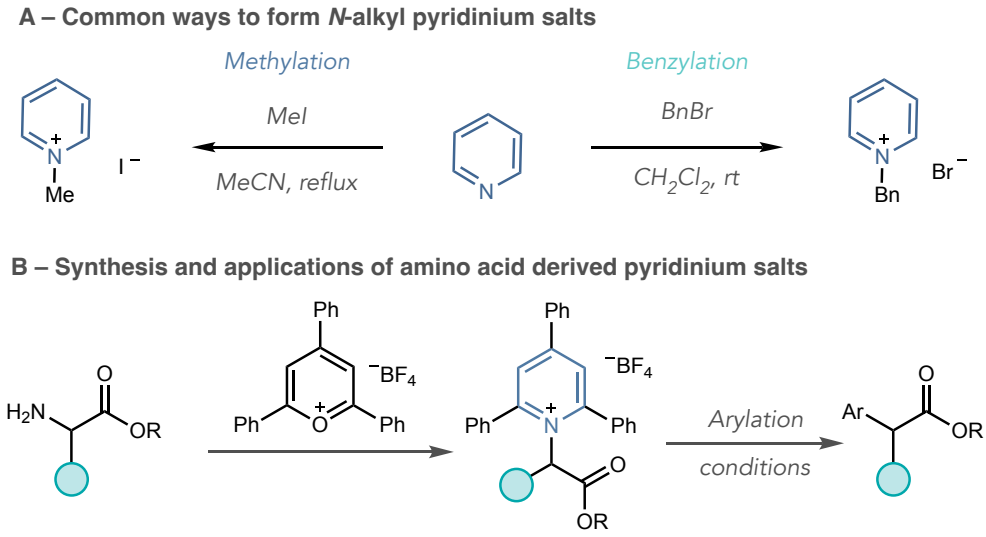


Figure 4.2. Methods to form *N*-alkyl pyridinium salts

It has been shown in literature that these *N*-alkyl pyridiniums can be reduced enantioselectivity to access piperidine via metal-catalysis and hydrogen gas. Using $[Ir(COD)Cl]_2$, *N*-benzyl-2-phenyl pyridinium salt can undergo asymmetric hydrogenation to achieve highly enantioselective *N*-benzyl α-substituted piperidines (Figure 4.3A).[9] This reaction recently has

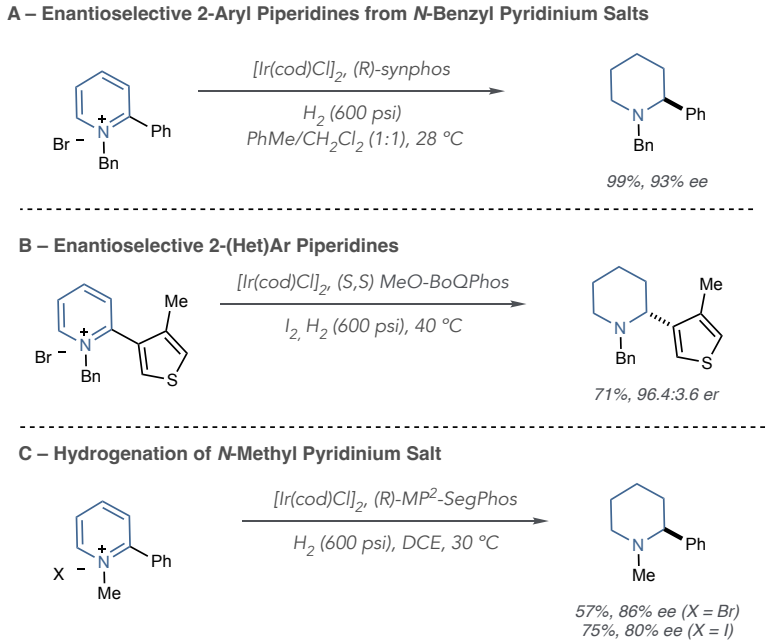


Figure 4.3. Enantioselective hydrogenation of *N*-alkyl pyridinium salts

expanded beyond 2-phenyl pyridines to access enantioselective 2-aryl and heteroaryl piperidines from the *N*-benzyl pyridinium salts by changing the ligand (Figure 4.3B).[10] In addition, a collaboration between Zhang group and Merck found that other 2-phenyl *N*-alkyl pyridinium salts, including methyl, ethyl, and isopropyl, can also undergo hydrogenation (Figure 4.3C).[11] This method highlighted that the counterion of the pyridinium salt was important for the reactivity and enantioselectivity.

The McNally group recently reported using these Zincke imine intermediates to form *N*-(hetero)aryl pyridinium salts by adding various (heteroaryl)anilines in the ring-closure step on a wide range of pyridines including complex systems (Figure 4.4A).[12] They demonstrated that these *N*-(hetero)aryl pyridinium salts can be asymmetrically hydrogenated into *N*-(hetero)arylpiperidines under metal-catalyzed conditions. We hope to apply this ring-opening ring-closing approach to add alkylamines, specifically amino esters, into 2-ester Zincke imine intermediates to form *N*-alkyl pyridinium salts (Figure 4.4B). Then, subjecting them to hydrogenation conditions will achieve enantioselective *N*-alkyl pipecolic esters for macrocycle synthesis.

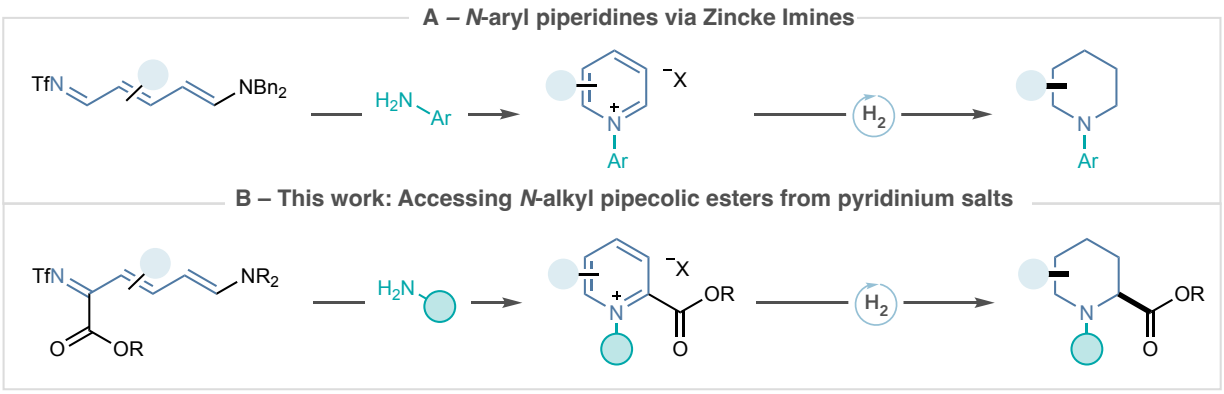


Figure 4.4. Accessing different classes pyridinium salts via Zincke imines

Not only does this Zincke imine approach solve the scope limitations of *N*-alkyl pyridinium salt formation, but it also allows for a different connectivity between piperidines and amino ester

to be achieved. Traditionally, piperidines will add to amino esters at the carbonyl center to form the amide bond; whereas, in this method, the reactivity of amino esters switches to behaving as an amine nucleophile that adds into the Zincke imines to achieve the *N*-alkyl bond resulting in pyridinium salts to access *N*-alkyl piperidines (Figure 4.5). [13]

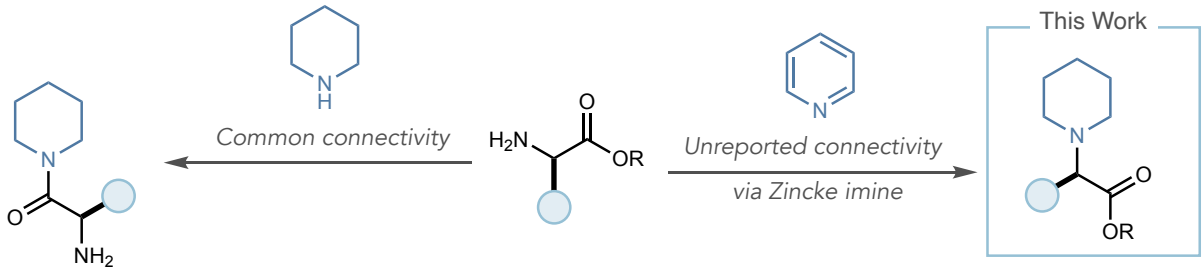


Figure 4.5. New connectivity accessed on N-alkyl pyridinium salts with amino esters via Zincke imines

4.3 Results and Discussion

4.3.1 Optimization to Form Zincke Imine on 2-Ester Pyridines

Our goal was to find conditions to allow for the formation of *N*-alkyl pyridinium salts from 2-ester pyridines with amino esters. The first step was to improve the yield of forming 2-ester Zincke imines. Using general Zincke imine reaction conditions with dibenzylamine as the amine, I saw only 40% yield of the ring-opened product was observed for 2-isopropyl ester pyridine in the reaction (Figure 4.6). A possible side reaction occurring is triflylation of the amine through either reacting with unreacted Tf_2O or detriflylation with the *N*-Tf pyridinium salts to Tf-NR_2 side product, which prevents the 2-ester pyridine from undergoing the ring-opening reaction. I found that 23% of the Tf-NBn_2 by product was generated in this reaction so next I examined less nucleophilic amines such as anilines and secondary amines such as *N*-substituted anilines and diarylamines to see if this side reaction can be avoided.

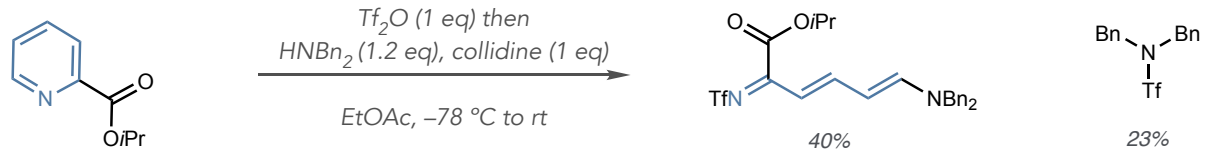
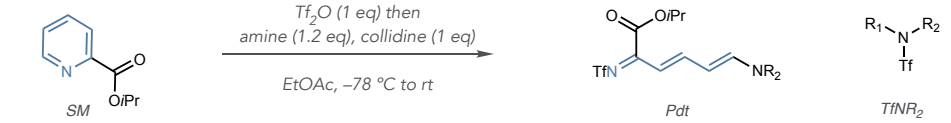


Figure 4.6. General Zincke imine conditions on 2-isoproylester pyridine

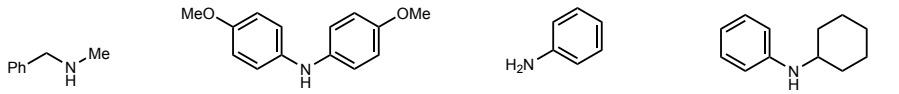
The formation of the Zincke imine product and Tf-NR_2 by-product was monitored and highlighted the correlation between the two yields of the two products (Table 4.1). In cases where the product yield was low, the amount of Tf-NR_2 was high. This supported that these amines are not compatible in this reaction since it prevented the pyridine from being activated for the ring-opening step. For example, *N*-methyl benzyl amine gave lower yields of the ring-opened product with higher amounts of the Tf-NBnMe. Electron rich diarylamines gave similar yields to dibenzylamine, but aniline did not make any of the Zincke imine product and showed high amounts of Tf-HNPh. N-cyclohexyl aniline gave the highest yield and Tf-NCyPh was not observed in the reaction. Additionally, indolines and tetrahydroquinolines worked efficiently for the ring-opening step. Adding a methoxy group to these amines on the phenyl ring proved to be important to increase the yield of the Zincke imine from 29% to 76% for 5-methoxyindoline, and 49% to 79% for 6-methoxytetrahydroquinoline while giving trace amounts of Tf-NR_2. After testing *N*-cyclohexyl aniline, 5-methoxyindoline, and 6-methoxytetrahydroquinoline on different disubstituted 2-ester pyridines, 6-methoxytetrahydroquinoline showed to be the most general at giving the highest yields for the Zincke imine product.

4.3.2 *N*-alkyl Pyridiniums Formation with Amino Esters

Table 4.1. Examination of different amines to form Zincke imines on 2-isopropyl ester pyridine



Other Amines:



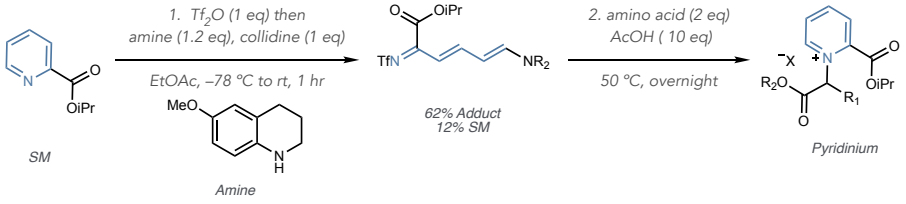
SM%	$TfNR_2$%	Pdt%	SM%	$TfNR_2$%	Pdt%	SM%	$TfNR_2$%	Pdt%	SM%	$TfNR_2$%	Pdt%
62	44	25	33	9	45	53	42	-	10	-	79

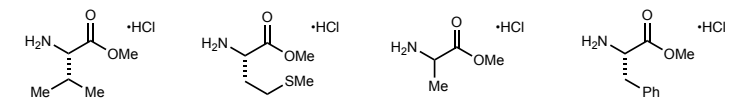
Indolines & Tetrahydroquinolines

SM%	$TfNR_2$%	Pdt%	SM%	$TfNR_2$%	Pdt%	SM%	$TfNR_2$%	Pdt%	SM%	$TfNR_2$%	Pdt%
16	-	29	10	2	76	11	3	49	13	8	78

With the optimized conditions to form ring-opened 2-ester Zincke imines, we next examined the ring-closing conditions with different amino ester to form the *N*-alkyl pyridinium salts. A few amino ester HCl salts were added to the crude reaction mixture containing 2-isopropyl ester pyridine Zincke imine (Table 4.2). After adding acetic acid (AcOH) with the amino esters and heating the reaction to 50 ºC overnight, L-valine-OMe, and methyl L-methionine gave the highest yields of 67% and 60% of the pyridinium salt product, respectively. Other amino esters also worked but gave lower yields.

Table 4.2: Formation of *N*-alkyl pyridiniums with amino esters via Zincke imines

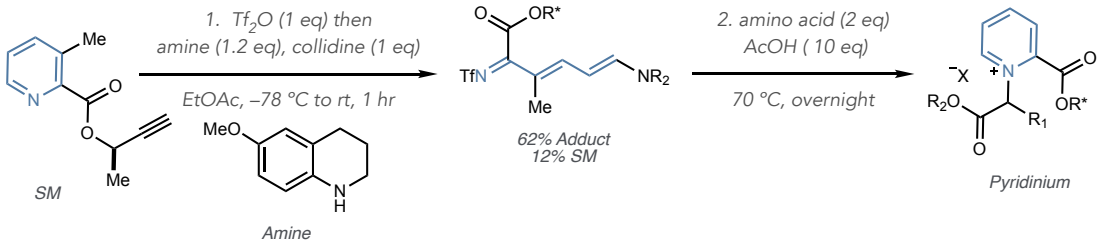


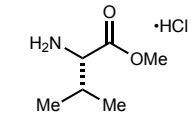


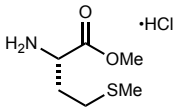
SM%	Pyridinium%	SM%	Pyridinium%	SM%	Pyridinium%	SM%	Pyridinium%
11	67	17	60	13	37	10	38

We realized that racemization or epimerization was likely to occur due to the increased acidity of α-carbon on the amino ester in the pyridinium salt. Additionally, the presence of freed dibenzylamine from the Zincke imine after ring closure or unreacted amino ester may perform the deprotonation for the racemization or epimerization. To monitor the amino acid stereocenter by ^{1}H NMR, an enantiopure 2-ester 3-methyl pyridine, (R)-2-(but-3-yn-2-yloxy)-3-methylpyridine, was tested by Jake Selingo, and he found that indeed epimerization was happening in the case of L-valine OMe HCl salt, which resulted in a 3:1 dr. L-methionine HCl salt gave a 4:1 dr (Table 4.3).

Table 4.3. Epimerization of α-carbon to amino ester in *N*-alkyl pyridinium salt







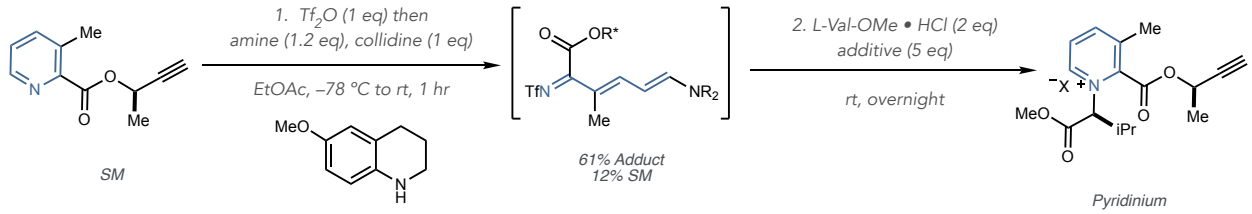
SM%	Pyridinium%	dr
22	52	3:1

SM%	Pyridinium%	dr
20	68	4:1

I initially thought this epimerization may be avoided if we performed the ring-closing step at lower temperatures such as room temperature. I switched to using free based L-valine-OMe to ensure the amino ester would be fully soluble in the reaction (Table 4.4). After testing a variety of inorganic bases with either sodium and potassium counterions, trace amounts of the pyridinium salts and poor mass balance with epimerization occurred in most cases.

On the contrary, acids were more compatible and gave moderate to high yields of the *N*-alkyl pyridinium product (Table 4.5). However, in all cases where pyridinium salts were formed,

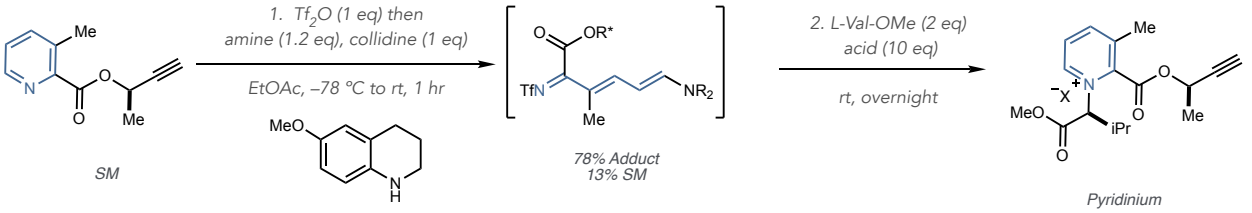
Table 4.4. Different inorganic bases tested for ring closure with L-Val-OMe



Entry	additive	SM%	adduct%	Pyridinium%	d.r.
1	NaOAc	15	-	8	2:1
2	$NaHSO_3$	11	27	5	1:1
3	Na_2SO_3	10	23	5	>20:1
4	KOAc	16	-	-	-
5	K_2HPO_4	16	-	6	1:1
6	K_2O_3S	14	-	-	-
7	$K_2S_2O_5$	7	-	-	-

the epimerization occurred. Formic acid gave the highest yield of 78%, and the best dr of 8:1 compared to other acids tested varying in different pKa's in a one-pot reaction.

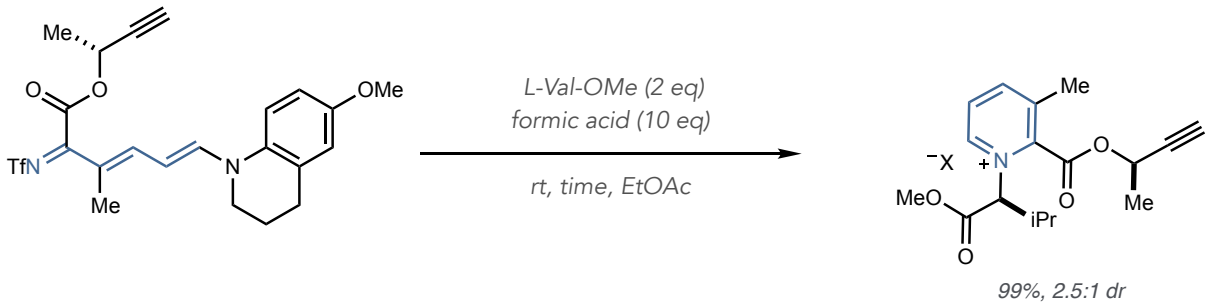
Table 4.5. Ring closure under acidic conditions with L-Val-OMe



Entry	acids	SM%	adduct%	Pyridinium%	d.r.
1	AcOH	19	22	**41**	4:1
2	benzoic acid	15	24	**45**	3:1
3	tosic acid	95	-	**-**	-
4	malonic acid	19	-	**-**	-
5	pivolic acid	12	-	**17**	4:1
6	formic acid	14	-	**79**	7.88:1
7	phophoric acid	36	-	**-**	-
8	HCl	28	-	**-**	-

I also examined this reaction from the isolated (R)-2-(but-3-yn-2-yloxy)-3-methyl Zincke imine, the yield of the pyridinium salt was 99%, but greater epimerization occurred to give a 2.5:1 dr in this two-pot reaction (Figure 4.6). This highlighted that the epimerization occurred much quicker in the case of using purified Zincke imine.

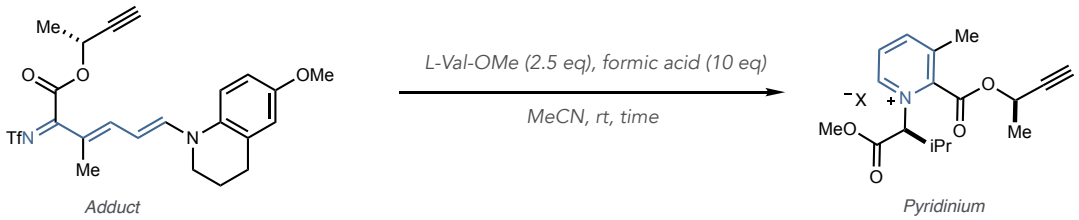
Figure 4.6. Two-pot reaction to form *N*-alkyl pyridinium salt with L-Val-OMe



To test this hypothesis, I conducted a time study to determine when the epimerization began in the reaction. Starting with the one-pot reaction where the Zincke imine is generated in situ, the epimerization occurred after eight hours. Whereas, using the purified, isolated Zincke imine, epimerization occurred within five hours where the dr dropped to 15:1 with more product forming sooner in the reaction. Increasing the equivalents of formic acid in the reaction decreased the yield by slowing down the reaction, which resulted in lowered amounts of epimerization. Attempts to add in hydrides to the pyridinium salts to break aromaticity and change the electronics of the pyridine ring to avoid acidifying the α–proton were unsuccessful.

Next, testing different solvents with isolated Zincke imine showed that acetonitrile was the best at forming pyridinium salt and preventing epimerization to give 93% yield of the pyridinium salt with a 22:1 dr. The concentration of formic acid in water also made a significant impact on the epimerization where 75% formic acid in water gave the highest dr of 37.5:1, when compared to 50% and 25% concentrations, while still retaining high yields of the product (Table 4.6).

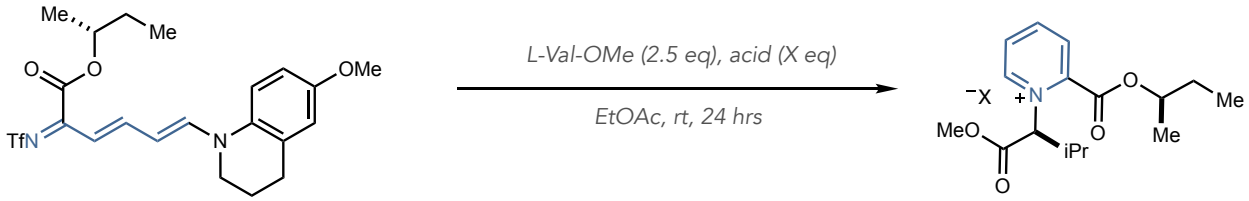
Table 4.6. Formic acid concentration effects on epimerization



Entry	formic acid concentration	adduct%	Pyridinium%	d.r.
1	75% in H_2O	-	**86**	37.5:1
2	50% in H_2O	-	**91**	22:1
3	25% in H_2O	-	**85**	15:1

Testing these optimized conditions on enantiopure monosubstituted 2-ester pyridine resulted in 15% yield of the pyridinium salt with 84% of unreacted Zincke imine remaining. This result highlighted that the added substitution pattern on the Zincke imine affected the rate of ring-closure where 2,3-dibustituted occurred much faster compared to monosubstituted 2-ester pyridine. To increase the rate of ring-closure, the equivalent of 88% formic acid in the reaction was lowered from ten to five (Table 4.7). As a result, more product formed in high dr after stirring for 24 hours. Switching to AcOH increased the yield to 72% and retained >20:1 dr in EtOAc.

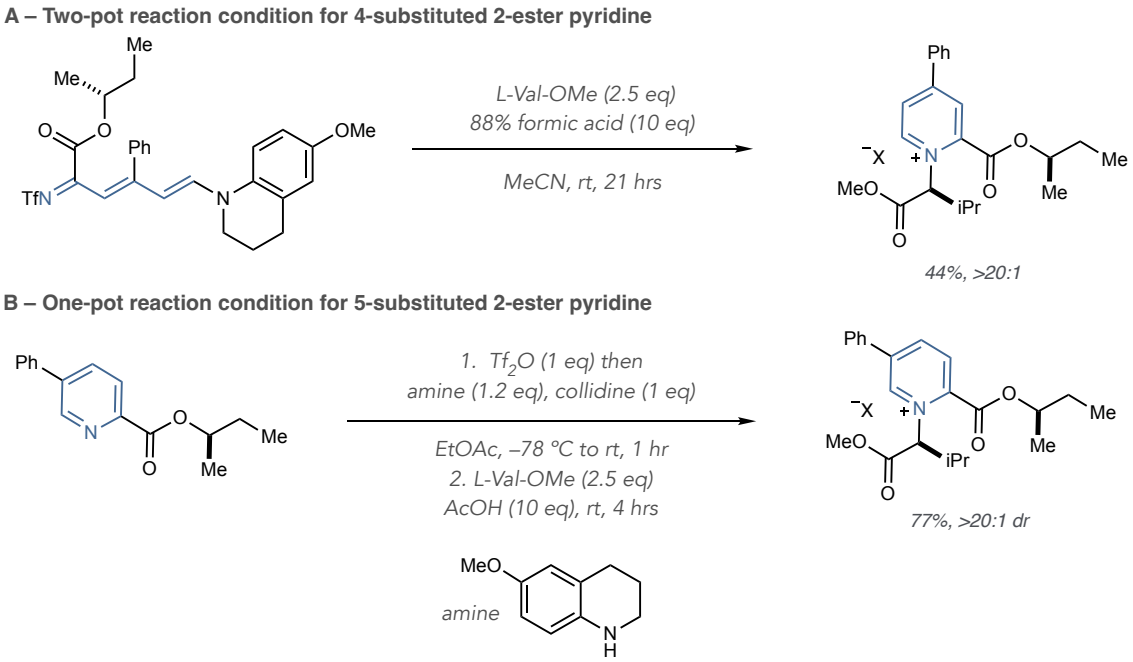
Table 4.7. Epimerization comparison between acids for monosubstituted 2-ester pyridine



Entry	acid (X eq)	Pyridinium%	d.r.
1	88% formic acid (5 eq)	**66**	23.4:1
2	AcOH (15 eq)	**72**	>20:1

With these two conditions in hand, other disubstituted 2-esterpyridine were tested. 4-phenyl-2-ester pyridine required 10 equivalents of 88% formic acid to give 44% yield and >20:1 dr (Figure 4.7A). 5-phenyl-2-ester pyridine was carried as a one-pot reaction since dihydropyridine intermediate was observed in the reaction (Figure 4.7B). This showed that after four hours with 10 equivalents AcOH, pyridinium salt was formed in 77% yield with >20:1 dr. Further investigation is needed to determine conditions needed for each type of 2-ester pyridine and amino ester to form the *N*-alkyl pyridinium salts. Hydrogenation conditions also need to be developed to achieve pipecolic esters for macrocyclization.

Figure 4.7. Conditions for one- and two-pot reaction for disubstituted 2-ester pyridines



4.4 Conclusion

N-alkyl pyridinium salts are formed by opening 2-ester pyridines to their Zinke imines and ring-closing with amino esters. This method addresses issues of steric hinderance affecting the formation of the pyridinium salts. Additionally, the connectivity of the pyridine to the amino esters has not been achieved from existing methods. A challenge of this reaction is allowing the formation

of the pyridinium salt while preserving the amino ester's stereocenter that is prone to racemization and epimerization. Certain acids and solvents have been shown to avoid this side reaction from occurring and more studies need to be done to test the broadness of this reaction and to find hydrogenation conditions to make pipecolic esters for macrocyclization.

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Chapter 5. Amination of Pyridines and Addition of Other Nucleophiles

5.1 Overview

This chapter describes an approach for amination of pyridines directly from the C–H bond at the 4-position. It will start with the background and current methods to form these products along with their limitations. Here, we demonstrated that amines could add directly into *N*-Tf pyridinium salts to form dihydropyridine intermediates that can be rearomatized with a base to form 4-aminated pyridines. This reaction is applicable to a variety of aliphatic amines and anilines on a range of different mono- and disubstituted pyridines. The strength of this reaction is highlighted in its compatibility with complex amines and pyridines. My coworker, Marie Hart, worked on the scope of adding a variety of amines to different pyridines. Dr. Benjamin Jones worked on the amine scope for 2-phenylpyridine and helped with the complex pyridine and amine scope. Additionally, this reaction platform can access 4-NH_2 pyridines using benzophenone imine as an ammonia surrogate. Both amination works are completed and under preparation to be submitted for publication.

Alcohols, thioesters, amides, and sulfonamides can also add selectively to the 4-position of *N*-Tf pyridinium salts. These developments will allow chemists to efficiently access functionalized pyridine in one step from the C–H bond. Amanda Melanese is currently optimizing and investigating the scope for heteroatom nucleophile addition into *N*-Tf pyridinium salts.

5.2 Background

5.2.1 Strategies for Amination of Pyridines

Many pharmaceutical drugs today contain carbon-nitrogen bonds, but installing these bonds on to pyridines can be challenging. This is due to the electron deficient nature of pyridines making them 10^6 times less reactive, compared to benzene, to undergo nitration reactions. [1]

S_NAr and transition-metal catalysis are the most common methods to aminate arenes, and both require aryl halides as starting materials (Figure 5.1). [2,3] Over 25 years ago, Buchwald and Hartwig developed a method using Pd(0) to aminate halogenated arenes.[3,4] To this day, it is one of the most used reactions to make aminated products in the pharmaceutical industry.[5] Although the Buchwald-Hartwig cross-coupling reaction is the most reliable way to make aminated products, yields significantly drop when substituents are near the nitrogen of the amine. This issue was highlighted by Merck in 2019 where they showed diminished yields for amination as the methyl group was closer to the nitrogen on piperidine.[5] Their finding highlighted that even the modest hindrance around the amine can depreciate the efficiency of the reaction. Furthermore, a preexisting aryl-halogen, aryl-triflate, or aryl-mesylate bond is required in the arene starting material, and installing these functional groups onto pyridines selectively is challenging.

The Chichibabin reaction and *N*-oxides are the two main approaches for direct amination at the 2-position of pyridines, but both require harsh conditions to activate the pyridine and install the amine.[6,7]

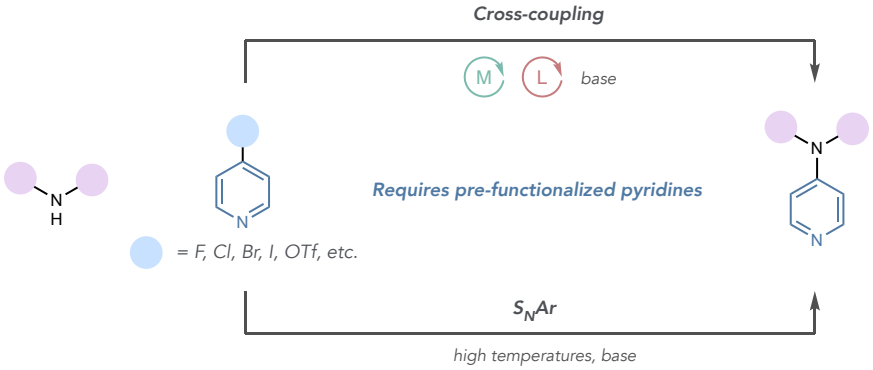


Figure 5.1. Classical methods for amination of pyridines

Photoredox-catalysis approaches have been developed to aminate from the C–H bond; however these methods are limited in scope, and suffer from scalability issues.[8,9]

5.2.2 Developments for Direct 4-Position Amination of Pyridine

Methods to directly install an amine at the 4-position of pyridines from the C–H bond are less precedented. It has been demonstrated by the Krayushkin lab that activation of pyridine occurs with 1-trichloromethylbenzene, and subsequent addition of piperidine or morpholine leads to 4-aminated products

(Figure 5.2A).[10] The exact intermediate that the amine reacts with is unclear. They proposed that the chloride counterion can add into the pyridinium and form a 4-chloropyridine in situ that can be activated again to make 4-chloropyridinium that allows for the amine to add in through a S_NAr pathway.

The McNally lab has reported a 4-amination protocol using pyridyl phosphonium salts (Figure 5.2B).[11] This is a stepwise functionalization method that involves using high heat and the extremely toxic and pyrophoric sodium azide (NaN_3) for the reaction to occur to form their iminophosphoranes. From the iminophosphoranes, further derivatization with harsh conditions is required to get to the aminated product via hydrolysis or alkylation. The risks of using NaN_3 and the required stepwise sequence discourage chemists from using this method. We wanted to find an alternative with milder conditions to directly aminate from the C–H bond of pyridines.

Recently, Leonori and coworkers reported a 4-amination of pyridines via desaturative catalysis where they reacted 4-piperdones with amines under photoredox conditions (Figure 5.2C).[1] Although the reaction works on a variety of amines, the scope of this method is limited to the availability of 4-piperidones. Therefore, direct C–H 4-amination of pyridines remain underdeveloped.

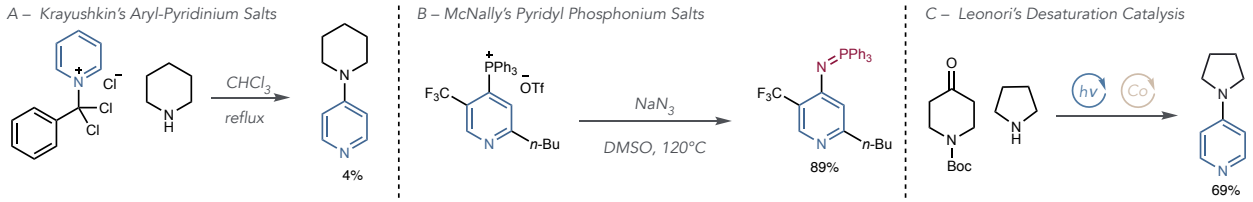


Figure 5.2: Methods to directly aminate the 4-position of pyridines

5.3 Reaction and Discussion

5.3.1 Amination of Pyridines through Triflic Anhydride Activation

Knowing that nucleophiles such as amines can add into *N*-Tf pyridinium salts to make Zincke imines, we were interested in seeing whether we could control the regioselectivity of the amine addition for pyridine amination. I found that adding three equivalents of piperidine to *N*-Tf pyridinium salts formed the 4-piperidine dihydropyridine instead of Zincke imine.

Low temperature NMR studies were conducted and showed that the amine initially adds to the 4-position of the *N*-Tf pyridinium salt to form the dihydropyridine intermediate instead of the 6-position observed for Zinck imines. This highlighted that the regioselectivity of the amine addition to *N*-Tf pyridinium salt is dependent on the basicity of the reaction. We hypothesized that the amine kinetically adds to the 4-position of the *N*-Tf pyridinium salts first, and in the presence of a strong base such as triethylamine, the proton on the amine gets deprotonated (Figure 5.3). However, in the presence of a weaker base such as collidine before the amine is deprotonated, it can equilibrate out of the 4-position and add to the 6-position to irreversibly ring-open to the *N*-Tf Zincke imine.

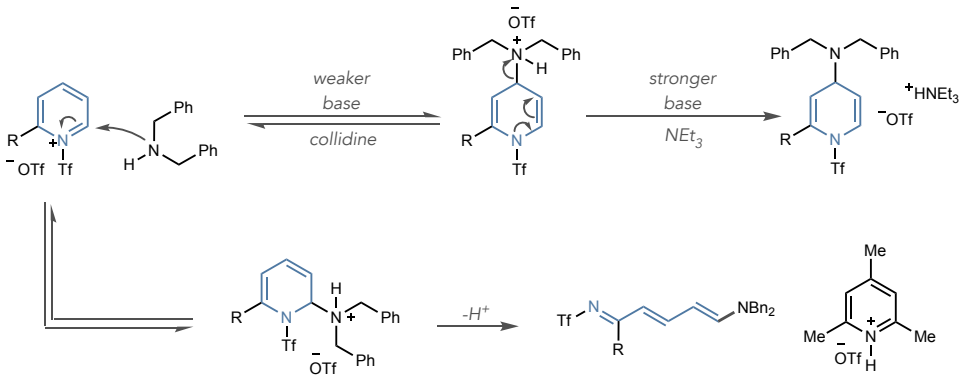


Figure 5.3. Base-mediated regioselectivity of amine addition into N-Tf pyridinium salts

This hypothesis is further supported by computational studies done by Louis de Lescure. The energy barrier to add to the 4-position is slightly lower than adding to the 6-position of 2-phenyl pyridine *N*-Tf pyridinium salt (Figure 5.4). However, over time if the reaction is not basic enough, the amine can equilibrate out the 4-positon and attack the 6-position to form the more stable intermediate, followed by a low energy barrier to make the Zincke imine. Therefore, the amine kinetically prefers to add to the 4-position of *N*-Tf pyridinium salts, but the formation of the

Zincke imine is thermodynamically favored.

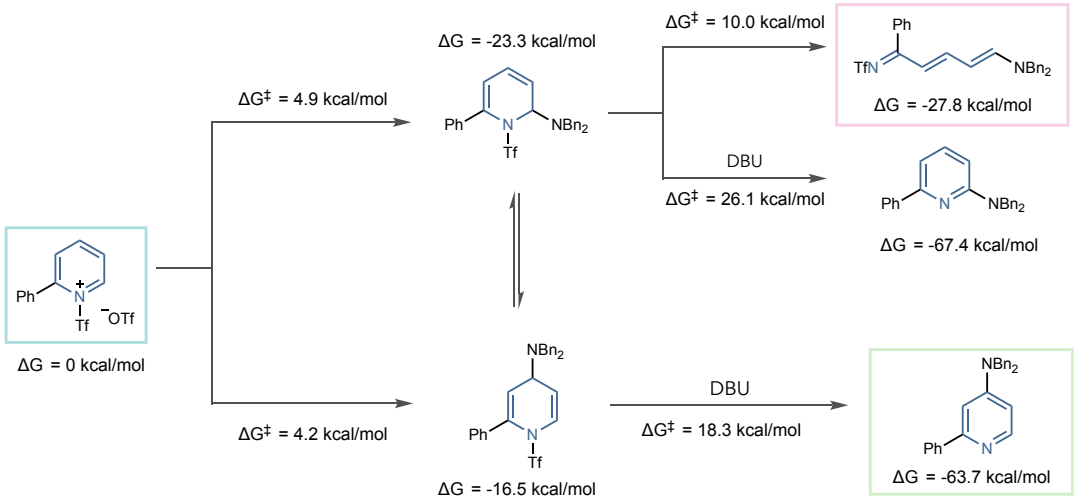
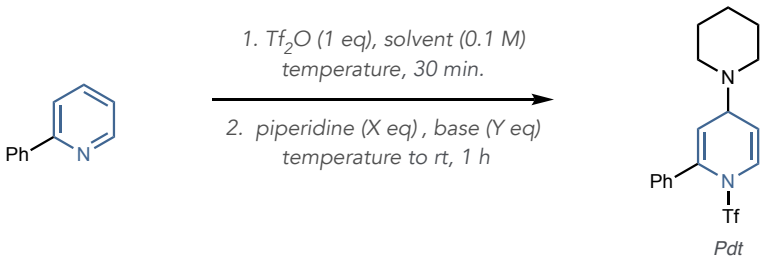


Figure 5.4. Calculated energy barriers for amine addition at the 4- vs 6-position on 2-phenylpyridine

Next, I began the optimization process and looked at the optimal amine equivalency. Due to the nucleophilic nature of amines, they can react with either triflic anhydride or by attacking the triflyl group of the *N*-Tf pyridinium salt which would deactivate the pyridine and prevent subsequent amine addition as mentioned in Chapter 4.

Additionally, the amines can also ring-open *N*-Tf pyridinium salts instead of the desired dihydropyridine intermediate. With 2-phenylpyridine as our model substrate with piperidine, solvents and higher temperatures did not affect the yield of the dihydropyridine intermediate (Table 5.1). The addition of DBU to the reaction with 1.5 equivalents of piperidine showed significant drop in yield. This is likely due to DBU's ability to react with triflyl groups to form Tf-DBU adducts. However, switching to three equivalents triethylamine and lowering the equivalents of piperidine to one allowed for comparable yields to using three equivalents of piperidine. Further investigation showed that triethylamine can be lowered to two equivalents and proved successful on a variety of aliphatic amines. Achieving high yields of the dihydropyridine intermediate with triethylamine highlights the importance of the base's pKa in the reaction.

Table 5.1 Conditions for piperidine addition into 2-phenyl *N*-Tf pyridinium salt



Pdt

Entry	Solvent	Piperidine eq.	Temperature	Base (eq)	Pdt%
1	MeCN	3	–30°C	-	54
2	CH_2Cl_2	3	–78°C	-	50
3	**EtOAc**	**3**	**–78°C**	**-**	**60**
4	EtOAc	3	–30°C	-	54
5	EtOAc	1.5	–78°C	DBU (3 eq)	34
6	**EtOAc**	**1**	**–78°C**	**NEt_3 (3 eq)**	**68**

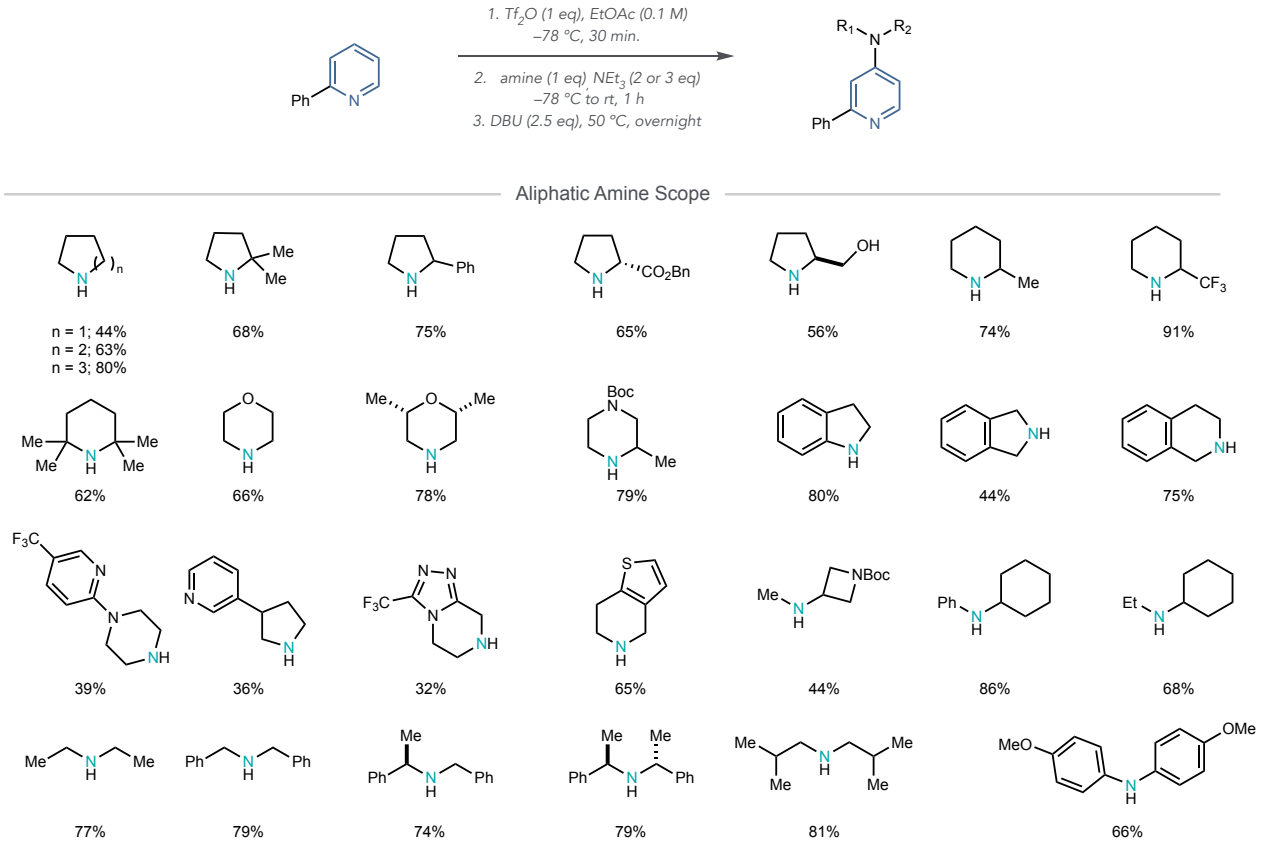
Next, I studied the rearomatization of the dihydropyridine intermediate to form the desired 4-aminated pyridine product. I found that the combination of 2.5 equivalents of DBU and heating the reaction to 50 °C can successfully produce the fully rearomatized 4-aminated 2-phenylpyridine product overnight.

5.3.2 Addition of Amine to 2-Phenyl Pyridine

With the optimized conditions, a wide variety of amines are tolerated in the reaction conditions (Figure 5.5). The first set of amines I tested were cyclic aliphatic amines such as derivatives of pyrrolidine, piperidine, and morpholine. This reaction also extended to symmetric and asymmetric acyclic aliphatic amines. Although dibenzylamine was the optimal amine to form *N*-Tf Zincke imines, under these reaction conditions with triethylamine as the base, the regioselectivity of the amine addition switches to obtain the 4-aminated pyridine product.

Increasing the steric encumbrance near the nitrogen on secondary amines gave the best yield by disfavoring the detriflylation of the pyridinium salt and allowing for attack at the 4-position of *N*-Tf pyridinium salts. This became apparent when the yield of 2-methylpiperidine (74%) was higher compared to unsubstituted piperidine (63%). Amination still occurred for 2,2,6,6-tetramethylpiperidine (TMP) where the α-carbons to the nitrogen reactive center were fully

methylated to produce 62% of the product. This highlights the advantage of this method compared to transition-metal catalysis where sterics around the amine nitrogen would result in low to no reactivity. This also applies to acyclic secondary amines including α-enantiopure methylated dibenzylamine and diisobutylamine. Notably, bis(4-methoxyphenyl)amine sufficiently reacted to form the product. Primary amines and amino esters also are amenable to the reaction with moderate to high yields. Anilines and (hetero) anilines efficiently added to 2-phenyl pyridinium salts to give 4-aminated 2-phenylpyridine.



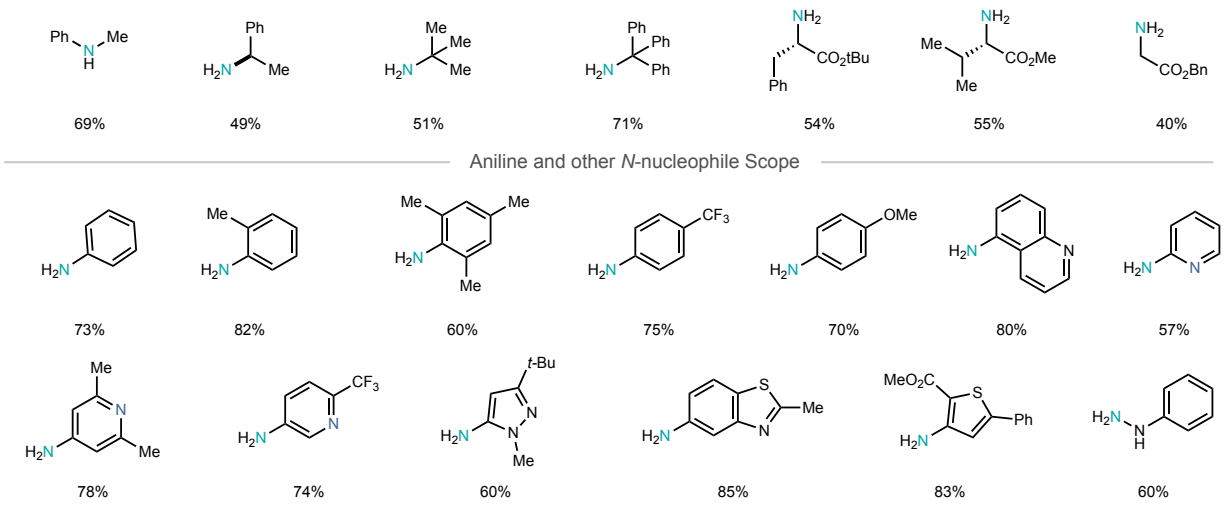


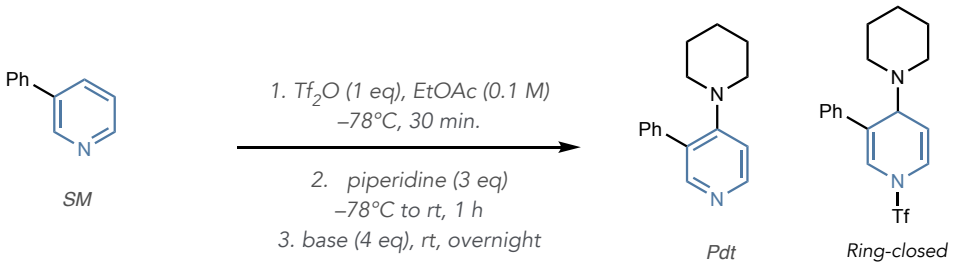
Figure 5.5: Amines and anilines addition into 2-phenypyridine

5.3.2 Rearomatization Challenge with Other Pyridines

The next challenge was adding amines to other substituted pyridines. Although the amination occurred with 3-substituted pyridines to form the dihydropyridine intermediate, the rearomatization did not occur with DBU. 3-phenyl dihydropyridine with piperidine was used as a model substrate to find conditions for the rearomatization process. Other bases with pKa's ranging from 12-35 in water were tested, but none were successful to produce a 3-substituted aminated pyridine. Oxidation approaches using ammonium cerium (IV) nitrate (CAN), 2,3-dichloro-5,6-Dicyanobenzoquinone (DDQ), and [bis(trifluoroacetoxy)iodo]benzene (PIFA) as oxidants were unable to rearomatize the pyridine after the amine addition. Decomposition of the aminated dihydropyridine was observed under these oxidative conditions instead. Phosphazene bases were the next class of bases that I tested. The dihydropyridine intermediate remained for most of these bases (Table 5.2). However, rearomatization did occur when P4-*t*-bu-phosphazene was used, but

the majority of the dihydropyridine intermediate converted back to 3-phenylpyridine to result in only 21% of the product.

Table 5.2. Examination of phosphazene bases to rearomatize 3-phenyl dihydropyridine



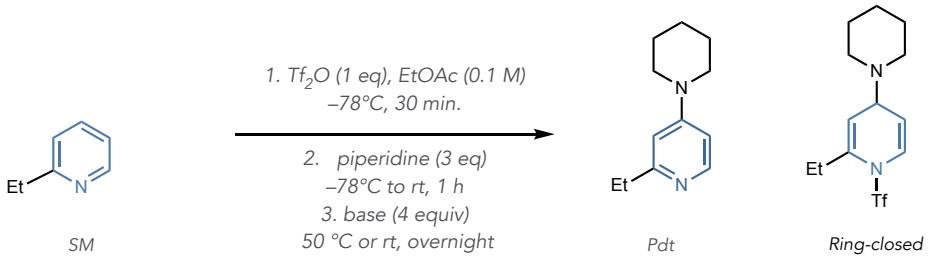
Entry	Base	SM%	Ring-closed%	Pdt%
1	P_1-phosphazene (BTPP)	11	67	-
2	P_2-*t*-Bu-phosphazene	7	58	-
3	**P_4-*t*-Bu-phosphazene**	**48**	**-**	**21**
4	BEMP	9	56	-
5	BTMG	11	67	-

Similarly, when the 2-position is an alkyl or non-electron withdrawing group, the rearomatization to the pyridine does not occur. This rearomatization challenge exposed a possible mechanism for the triflyl elimination step. We believe that after the base deprotonates the proton at the 4-position of the dihydropyridine, the anion prefers to stabilize itself before eliminating the triflyl group to make the aminated pyridine product. In the case of 2-phenylpyridine, the anion resonates into the phenyl and is stabilized after the deprotonation step. As a result, we hypothesize that the rearomatization may undergo an E1cB (conjugate base) type mechanism to eliminate the triflyl group.

After testing a variety of different bases to rearomatize 2-ethyl dihydropyridine intermediate, I observed the aminated pyridine product in the case of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) at 50 ºC and NaH at room temperature overnight (Table 5.3). This highlighted that the pKa and counterion for this rearomatization is critical for this substrate class. The pKa of TBD is slightly higher than DBU in acetonitrile, 25.98 versus 24.33. Although the pKa's of LDA and

NaH are similar in water, the sodium counterion might be important to allow the rearomatization to occur. We decided to use TBD as the base to rearomatize the challenging 2-substitueted dihydropyridine since it is safer to handle compared to NaH.

Table 5.3. Bases for rearomatization of 2-alkyl dihydropyridine

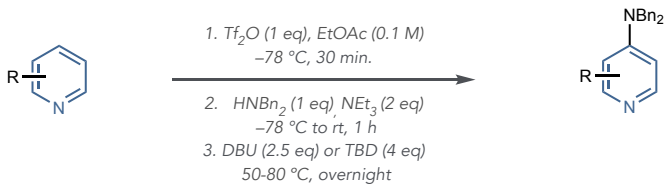


Entry	Base	Temp.	SM%	Ring-closed%	Pdt%
1	DBU	50°C	18	68	5
2	**TBD**	**50°C**	**16**	**7**	**67**
3	MTBD	50°C	15	66	8
6	LiHMDS	rt	19	68	-
7	LDA	rt	11	64	-
8	**NaH**	**rt**	**16**	**-**	**64**

5.3.3 Scope of Pyridines with Dibenzylamine

With the two optimized rearomatization conditions, we looked at the pyridine scope for this reaction with dibenzylamine (Figure 5.6). A variety of 2-substituted pyridines including 2-alkyl, pyridyl, acetyl, and ester worked in this reaction. Notably, dibenzylamine selectively adds to the 4-position of 2-chloropyridine where under other amination conditions the S_NAr would likely occur at the C–Cl bond. 3-halogenated pyridines are compatible to obtain the 4-aminated pyridines. This reaction extends to 2,3-, 2,5-, and 3,5-disubstituted pyridines containing a range of functional groups and carbon-bearing groups. Dibenzylamine can also selectively added to the 4-position of quinoline and fused heterocycles.

3.3.4 4-Amination of Simple and Complex Pyridines and Amines



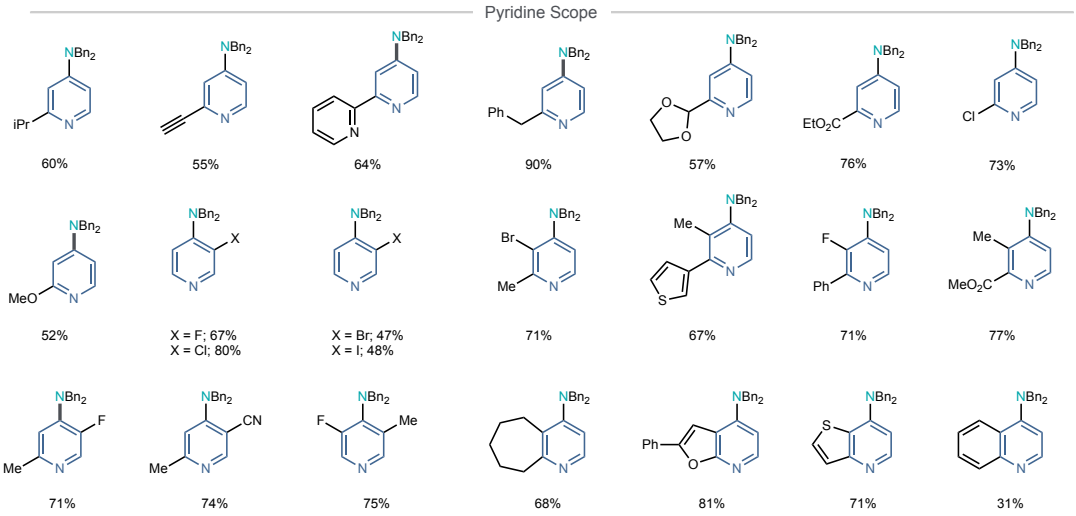


Figure 5.6. Dibenzylamine addition to pyridine building blocks

Next, we wanted to determine the generality of this amination reaction by testing different amines and pyridines (Figure 5.7). 2-trifluoromethylpiperidine successfully added to 2-methyl-3-iodopyridine and rearomatization occurred for monosubstituted in 3-phenyl and 3-alkyl pyridines to form the 4-aminated product with anilines as the amine. This further supports that the aromatization is undergoing an E1cb type mechanism since after deprotonation the electron density can be stabilized by the aromatic ring of the aniline. In addition, the aniline may increase the acidity of 4-position proton of the dihydropyridine to allow for deprotonation.

In addition, we preformed this reaction on complex substrates to highlight its potential application for drug discovery. We successfully applied this amination reaction to pharmaceuticals such as loratadine and vismodegib with dibenzylamine. Nicotine also underwent this amination reaction with p-trifluoromethylaniline. FDA-approved amine containing the drugs, fluoxetine and amoxapine, effectively added to pyridines to give the 4-aminated product.

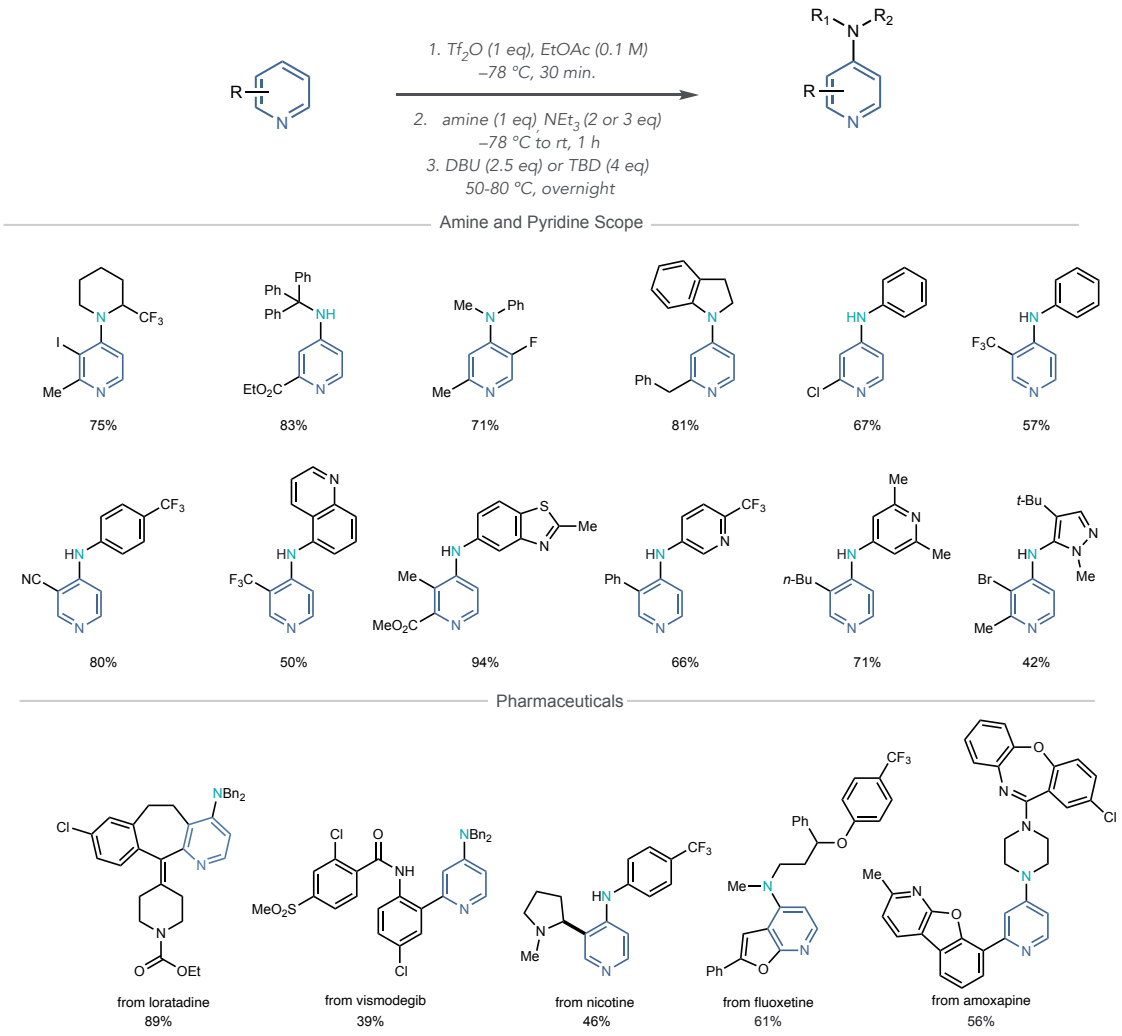


Figure 5.7. Amination with different amine and pyridine coupling partners and extending to complex and pharmaceutical examples

5.4 Achieving 4-NH_2 Pyridines and Addition of Other Nucleophiles

Another valuable group to have on a pyridine ring is -NH_2. We thought of accessing these products by adding in ammonia surrogates in *N*-Tf pyridinium salts. Different from the aminated product achieved previously with direct addition, these aminopyridines products behave as substrates for subsequent amination or electrophilic aromatic reactions.[12,13] The most common way to achieve these 4-NH_2 pyridine products is by reduction of the 4-nitropyridine (Figure 5.8).[14] An example is shown for 2,2-bipyridine where oxidation of the pyridine is required to form the *N*-oxide followed by nitric acid and sulfuric acid to install

the nitro group at the 4-position. Lastly, reduction of the nitro group with $NaBH_4$ and 10%/C will form the 4-NH_2. This highlights how the current method to obtain these 4-NH_2 pyridine products require harsh conditions and multiple steps to conduct from the C–H bond. Alternatively, our method will allow access to these 4-NH_2 directly from the pyridine C–H bond all in one step.

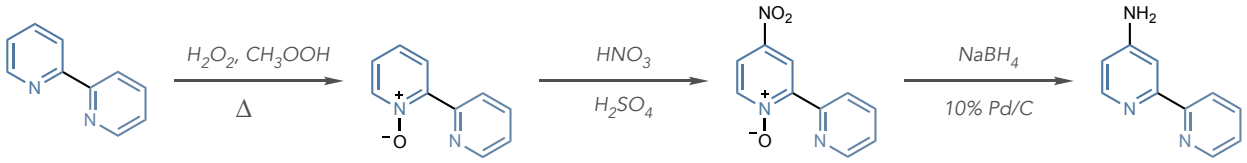


Figure 5.8. Classical method to add –NH_2 at the 4-position of pyridines

5.4.1 Conditions to Access -NH_2 with Benzophenone Imine

We thought of testing benzophenone imine as an ammonia surrogate since there has been literature precedent of achieving -NH_2 from benzophenone imine for transition metal-catalyzed amination reaction simply from an aqueous workup.[15,16] I added benzophenone imines to 2-phenyl *N*-Tf pyridinium salts in the presence of triethylamine and rearomatization with DBU and observed the formation of the addition product. Then, the addition of 1 M aqueous HCl revealed the 4-NH_2 2-phenylpyridine product. This highlights how sp^2 hybridized amines can also add to *N*-Tf pyridinium salts.

5.3.2 Scope of 4-NH_2 Pyridines

The scope of this reaction complements the scope of what has been shown for the amination reaction in this chapter for 2- and 3-substituted pyridines, but benzophenone imines can also add to 4-substituted and 2,4- and 3,4- disubstituted pyridines to form the -NH_2 at the 2- or 6-position which are sites for ring-opening (Figure 5.9). Unlike the aliphatic amines, benzophenone imine avoids opening these pyridines and forming Zincke imines since it is a sp^2 hybridized amine. It can also add to 2,3-, 3,5-, and 2,5-disubstituted pyridines containing different functional groups. Beyond pyridines, benzophenone imine can add into 2-phenyl pyridazine, quinolines, and fused heterocycles to form their -NH_2 product.

Since this reaction is a one-step process without requiring harsh conditions to install the -NH_2 group, we envision this reaction to be used for late-stage functionalization. Not only does this reaction work

on pharmaceuticals such as vismodegib and quinoxyfen, but it also can be applied to drug-like fragments that contain different functional groups. This will allow chemists to install the -NH_2 group directly from the C–H bond of a lead compound and avoid having to start over from pyridine precursors.

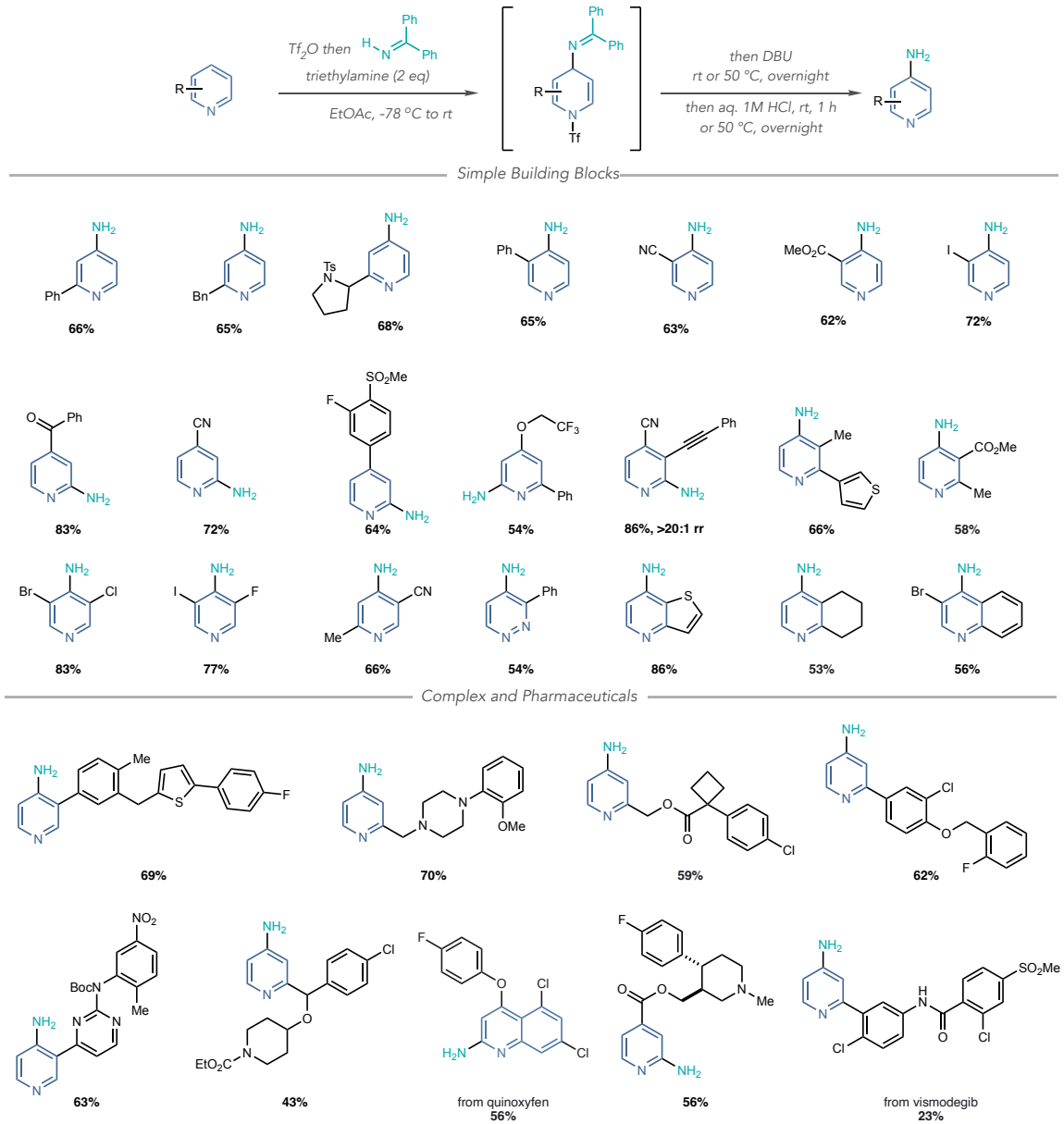


Figure 5.9. Scope for 4-NH_2 pyridine products on simple and complex examples

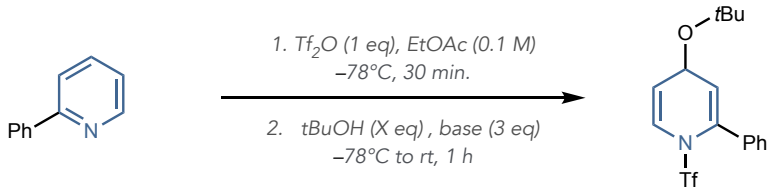
5.4.2 Addition of Other Nucleophiles to *N*-Tf Pyridiniums

Other carbon-heteroatom formations on pyridines are highly desired due to the value of

these new bonds in the drug discovery process. We questioned whether other nucleophiles can potentially add into our *N*-Tf pyridiniums to form the dihydropyridine intermediates. I initially investigated adding *t*BuOH (*tert*-butanol) in the presence of different bases. When I screened triethylamine and other organic bases, the dihydropyridine intermediate were not observed. Next, I tested different alkali metal bases and found that LiO*t*Bu showed a modest yield of a dihydropyridine intermediate (Table 5.4). The lithium counterion is critical to achieving the dihydropyridine since product was not observed in the case of NaO*t*Bu and KO*t*Bu.

To test whether it was the alcohol (*t*BuOH) or the base (LiO*t*Bu) that added into the *N*-Tf pyridinium salt, a control experiment with no alcohol was tested. A comparable yield of the product was observed from the control which suggests that the alkoxide in LiO*t*Bu is doing the addition. From this result, I concluded that in order for alcohols to add to the *N*-Tf pyridinium salts, they must first be fully deprotonated and become the alkoxide.

Table 5.4. Bases tested for alcohol addition into 2-phenyl *N*-Tf pyridinium



Base/Nucleophile	*n*BuOH (X eq)	SM%	Pdt%
NEt_3	2	54	0
NaO*t*Bu	2	72	0
KO*t*Bu	2	71	0
LiO*t*Bu	2	28	42
LiO*t*Bu	0	17	47

In attempts to form the alkoxide, strong bases including NaH and *n*BuLi were tested. The importance of lithium counterion for the alkoxide was highlighted in these reactions since *n*BuLi and other lithium bases worked most efficiently and broadly against other alcohols. In addition, *n*BuLi is also the key base to allow other heteroatom nucleophiles including thioesters, amides, and sulfonamides to also add into *N*-Tf pyridinium salts. These dihydropyridines can be rearomatized with DBU to form pyridine products (Figure 5.9.1).

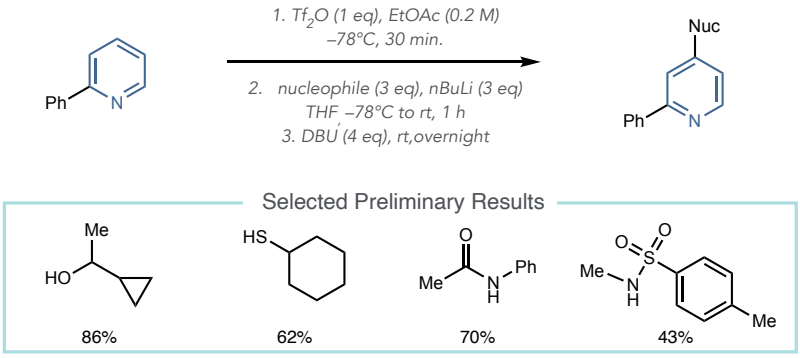


Figure 5.9.1 Functionalization of pyridines with other heteroatom nucleophiles

Amanda Melanese is currently optimizing these nucleophile additions into *N*-Tf pyridinium salts reaction and investigating the scope of this reaction. She saw optimal yields of the dihydropyridine intermediates when 1.5 equivalents of *n*BuOH reacted with equal molar of *n*BuLi in the presence of DBU. For thioesters, DTBMP as the base gave comparable yields to *n*BuLi. Preliminary studies done by Amanda showed different secondary amides and sulfonamides can add into 2-phenyl *N*-Tf-pyridinium salt. Primary amides and sulfonamides can also add at lower yields. Efforts towards optimizing and determining the scope of these reactions are ongoing in the lab.

5.5 Conclusion

The power of activating pyridines with Tf_2O for pyridine functionalization is highlighted in this chapter. Through this activation mode, multiple heteroatom nucleophiles can add directly to the C–H bond of pyridines selectively at the 4-position. In the presence of triethylamine, aliphatic amines and anilines can add to simple and complex pyridines. The regioselectivity of the amine addition is found experimentally and is computationally dependent on the basicity of the reaction. In addition, 4-NH_2 pyridines can also be

accessed through the addition of benzophenone imines. This reaction extends to 4-subsituted pyridines and pyridazine. Alcohols, amides, and sulfonamides can add to *N*-Tf pyridinium salts with *n*BuLi, and thioesters can also react with DTBMP as the base. Direct nucleophile addition to *N*-Tf pyridinium salts is advantageous for chemists since it avoids exposure to harsh conditions that can lead to decomposition and needing to perform multiple steps before achieving the desired functional group. Therefore, these reactions can be implemented for late-stage functionalization due to their simplicity.

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Appendix
Synthesis of ^{15}N-Pyridines and Higher Mass Isotopologs via Zincke Imine Intermediates

A 1.1 General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz), an Agilent Inova 400 (400 MHz) spectrometer, an Agilent Inova 500 (500 MHz) spectrometer, or a Bruker AV-111 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.1 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm), $(CD_3)_2CO$ (2.05 ppm), CD_3CN (1.94 ppm), D_2O (4.79 ppm), or $(CD_3)_2SO$ (2.50 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz), an Agilent Inova 400 (100 MHz) spectrometer, an Agilent Inova 500 spectrometer (125 MHz) or a Bruker AV-111 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.01 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16 ppm), CD_3OD (49.00 ppm), $(CD_3)_2CO$ (29.84 ppm), CD_3CN (1.32 ppm), D_2O, or $(CD_3)_2SO$ (39.52 ppm).

High–resolution mass spectra (HRMS) were measured on an Agilent 6224 TOF LC/MS ("Q-TOF") interfaced to an

Agilent 1200 HPLC with multi-mode (combined ESI and APCI).

Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared (IR) spectra were recorded on a Nicolet IS-50 FT-IR spectrometer as either solids or neat films, either through direct application or deposited in $CHCl_3$, with absorptions reported in wavenumbers (cm^{-1}).

Analytical thin layer chromatography (TLC) was performed using pre-coated Silicycle glass backed silica gel plates (Silicagel 60 F254). Manual flash column chromatography was undertaken on Silicycle silica gel Siliaflash P60 40-63 μm (230-400 mesh) under a positive pressure of air unless otherwise stated. Automated flash column chromatography was undertaken using a Teledyne Isco CombiFlash NextGen 300+ using 12 g, 24 g, or 40 g RediSep Normal-Phase Silica cartridges. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with a chamber of I_2 in SiO_2, ceric ammonium molybdate, or basic potassium permanganate solutions as appropriate. Melting points (mp) were recorded using a Büchi B-450 melting point apparatus and are reported uncorrected.

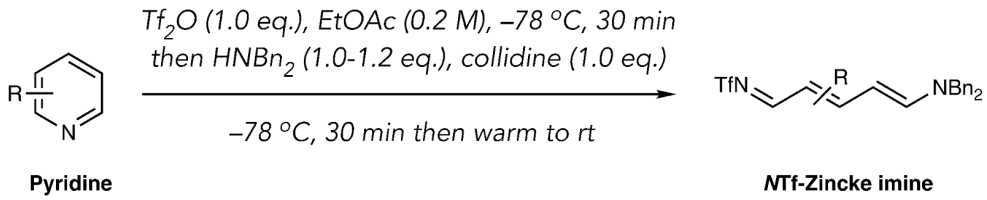
All reagents were purchased at the highest commercial quality and used without further purification. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated. All reactions were monitored by TLC, ^1H NMR spectra taken from reaction samples, and liquid chromatography mass spectrometry (LCMS) using an Agilent 6310 Quadrupole Mass Spectrometer for MS analysis.

Trifluoromethanesulfonic anhydride (Tf_2O, 99%), dibenzylamine (Bn_2NH), and collidine (2,4,6-trimethylpyridine) were purchased from Oakwood Chemical and used without further purification but routinely stored in a –20 °C freezer. Anhydrous Ethyl Acetate was purchased from Acros Organics. NaOAc was purchased from Fischer Scientific and used without further purification.

EtOH (200 proof) was purchased from Pharmaco and used without further purification. 1,2-dichloroethane (DCE), acetyl chloride (AcCl), and *d*-acetic acid (AcOD) were purchased from Sigma Adlrich and used without further purification. $CDCl_3$, CD_3CN, CD_3OD, ethanol-d_6, $^{15}NH_4OAc$ (98% ^{15}N), $^{15}NH_4Cl$ (99% ^{15}N) were purchased from Cambridge Isotopes and used without further purification.

A 1.2. Preparation of *N*Tf-Zincke Imines

General Procedure A (Pyridine Ring-Opening to Zincke imines).



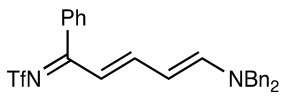
An oven dried round bottom flask with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.10 or 0.20 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before 1.0 M solution of Bn_2NH (1.0 or 1.2 equiv) was added dropwise followed by collidine (1.0 equiv). The reaction was stirred for a further 30 minutes at –78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (30 min for 0.50 mmol scale). The reaction was diluted with EtOAc and washed with aqueous sodium bicarbonate (3x) followed by a brine wash and 10% wt. aqueous $CuSO_4$ (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. After filtration, the organic extract was diluted with minimal EtOAc or CH_2Cl_2 (approximately 1.0 mL per 1.0 mmol) and added dropwise to excess hexanes (approx. 100 mL per 1.0 mmol) and the resulting oil was allowed to settle overnight in a –20 ºC fridge. After

the oil/precipitate settled, the hexanes were decanted off and the oil/precipitate was washed with hexanes. If the product was an oil, it was dissolved with EtOAc or CH_2Cl_2, concentrated *in vacuo*, and dried on high vacuum to provide the pure "Zincke imine." If the product was a precipitate, it was collected and dried *in vacuo* to provide the pure "Zincke imine."

Reaction Notes:

- Reaction is sensitive to excess of Tf_2O added (use of 1.2 equiv. results in substantial yield loss).
- Majority of substrates comparably with 1.0 equiv. and 2.0 equiv. collidine, 1.0 equiv. can be used regardless of substrate
- Stirring is critical to achieve consistent yields; recommended stirring 500-750 rpm.
- For larger scales, it is recommended to allow the reaction to warm fully to room temperature, the 30 minutes was based on initial smaller scale reactions.
- Substrates with a 4-substituent (and unsubstituted pyridine) are susceptible to "iminium" formation and care should be taken prior to crash out. Concentration in vacuo prior to crash out results in significant (>20%) yield of "iminium"
- Reaction works comparably in most cases in 0.10 M vs 0.20 M EtOAc but yields improve with 0.20 M in some cases

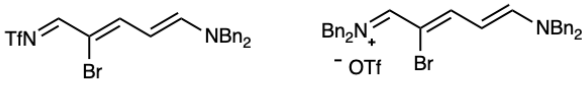
***N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



Prepared according to general procedure A using 2-phenylpyridine (1.78 mL, 12.5 mmol), Tf_2O (2.10 mL, 12.5 mmol), dibenzylamine (2.90 mL, 15.0 mmol, 1.0 M in EtOAc), collidine (1.70 mL, 12.5 mmol), EtOAc (125 mL, 0.10 M). The crude material was purified by precipitation in hexanes (1.2 L) to afford the title compound as a red-brown solid (5.20 g, 10.8 mmol, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ:7.64 – 7.56 (m, 2H), 7.55 – 7.31 (m, 10H), 7.31 – 7.27 (m, 1H), 7.21 – 7.09 (m, 4H), 6.71 (d, *J* = 13.7 Hz, 1H), 5.83 (t, *J* = 12.2 Hz, 1H), 4.46 – 4.39 (m, 4H) ; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 485.2, $C_{26}H_{24}F_2N_2O_2S^+$ requires 485.15.236.

These data are consistent with those previously reported in the literature.[1,2]

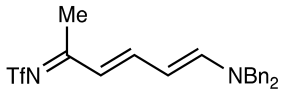
85:15 *N*-((1*Z*,2*Z*,4*E*)-2-Bromo-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide & *N*-benzyl-*N*-((2*Z*,4*E*)-2-bromo-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1-phenylmethanaminium trifluoromethanesulfonate



Prepared according to general procedure A using 3-bromopyridine (1.20 mL, 12.5 mmol), Tf_2O (2.10 mL, 12.5 mmol), dibenzylamine (2.90 mL, 15.0 mmol, 1.0 M in EtOAc), collidine (1.70 mL, 12.5 mmol), EtOAc (125 mL, 0.10 M). The reaction was stirred overnight at room temperature prior to the work-up steps. The crude material was purified by precipitation in hexanes (1.2 L) to afford the title compound as a yellow solid 85:15 mixture of imine and iminium. ^{1}H NMR (major, 400 MHz, $CDCl_3$) δ: 8.22 (s, 1H), 8.06 (d, *J* = 11.8 Hz, 1H), 7.83 (d, *J* = 12.5 Hz, 1H), 7.47 – 7.29 (m, 8H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.24 (t, *J* = 12.1 Hz, 1H), 4.75 (s, 2H), 4.71 (s, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 167.37, 164.48, 163.48, 134.34, 134.21, 129.68, 129.57, 129.47, 129.24,

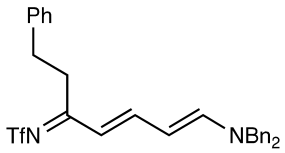
128.89, 128.12, 120.69 (q, J = 322.7 Hz), 106.58, 104.75, 61.63, 53.26; ^{19}F NMR (375 MHz, $CDCl_3$) δ: -79.19, -79.22.

_N_-((2_E_,3_E_,5_E_)-6-(Dibenzylamino)hexa-3,5-dien-2-ylidene)-1,1,1-trifluoromethanesulfonamide



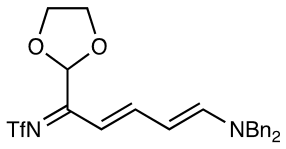
Prepared according to general procedure A using 2-methylpyridine (1.23 mL,12.5 mmol), Tf_2O (2.10 mL, 12.5 mmol), dibenzylamine (2.90 mL, 15.0 mmol, 1.0 M in EtOAc), collidine (1.70 mL, 12.5 mmol), EtOAc (125 mL, 0.10 M). The crude material was purified by precipitation in hexanes (1.2 L) to afford the title compound as a yellow solid (4.17 g, 9.75 mmol, 78% yield); mp: 128 – 131 °C; IR ν_{max}/cm^{-1} (film): 3028, 2929, 1624, 1570, 1488, 1444, 1369, 1330, 1304, 1262; ^{1}H NMR (400 MHz, CD_3CN) δ: 7.98 – 7.67 (m, 2H), 7.62 – 6.98 (m, 10H), 6.07 (s, 1H), 5.85 (t, J = 12.2 Hz, 1H), 4.59 (s, 2H), 4.51 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 178.90, 161.11, 158.81, 158.80, 135.69, 135.22, 129.56, 129.45, 129.07, 128.88, 128.53, 127.92, 120.32 (q, J = 320.0 Hz), 114.61, 103.66, 60.48, 52.24; ^{19}F NMR (375 MHz, CD_3CN) δ: –80.46; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 423.1, $C_{21}H_{22}F_3N_2O_2S^+$ requires 423.13.

_N_-((3_E_,4_E_,6_E_)-7-(Dibenzylamino)-1-phenylhepta-4,6-dien-3-ylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure A (except with 1.0 equiv of dibenzylamine) using 2-phenethylpyridine (1.83 g, 10.0 mmol), Tf_2O (1.68 mL, 10.0 mmol), dibenzylamine (1.92 mL, 10.0 mmol, 1.0 M in EtOAc), collidine (1.32 mL, 10.0 mmol), EtOAc (50 mL, 0.20 M). The crude material was purified by precipitation in hexanes (1.0 L) to afford the title compound as a yellow solid (4.42 mg, 8.60 mmol, 86% yield); mp: 149 – 151 °C; IR ν_{max}/cm^{-1} (film): 3028, 2929, 1617, 1566, 1473, 1441, 1371, 1352, 1309, 1257; ^1H NMR (400 MHz, CD_3CN) δ: 7.70 (d, *J* = 12.4 Hz, 2H), 7.54 – 6.95 (m, 15H), 6.16 (d, *J* = 13.6 Hz, 1H), 5.83 (t, *J* = 12.2 Hz, 1H), 4.56 (d, *J* = 31.4 Hz, 4H), 2.91 (d, *J* = 1.9 Hz, 4H); ^{13}C NMR (100 MHz, CD_3CN) δ: 180.52, 161.53, 161.51, 159.01, 141.61, 135.61, 135.16, 129.58, 129.45, 129.14, 129.11, 128.97, 128.90, 128.56, 127.93, 126.72, 120.35 (q, *J* = 320.2 Hz), 113.42, 104.08, 60.53, 52.35, 34.96; ^{19}F NMR (375 MHz, CD_3CN) δ: –80.38; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 513.2, $C_{16}H_{19}N_2^+$ requires 513.18.

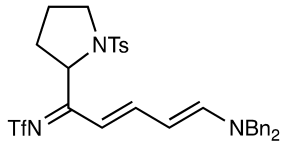
_N_-((1_Z_,2_E_,4_E_)-5-(Dibenzylamino)-1-(1,3-dioxolan-2-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure A using 2-(1,3-dioxolan-2-yl)pyridine (76.3 mg, 0.50 mmol), Tf_2O (82.5 µL, 0.50 mmol), dibenzylamine (115 µL, 0.60 mmol), collidine (66.0 µL, 0.50 mmol), EtOAc (2.5 mL, 0.2 M). The crude material was purified by precipitation in hexanes (50 mL) to afford the title compound as a yellow solid (175 mg, 0.36 mmol, 73% yield); mp: 120 – 122 °C; IR ν_{max}/cm^{-1} (film): 3031, 2360, 1568, 1491, 1430, 1152, 1088, 951; ^1H NMR (400 MHz, CD_3CN) δ: 8.03 (d, *J* = 16.3 Hz, 2H), 7.45 – 7.35 (m, 5H), 7.35 – 7.26 (m, 3H), 7.26 – 7.14 (m, 2H), 6.18 (s, 2H), 5.79 (s, 1H), 4.63 (d, *J* = 24.3 Hz, 4H), 4.17 – 3.84 (m, 4H); ^{13}C NMR (small

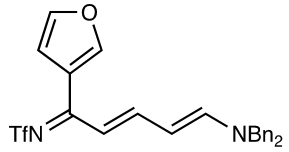
iminium impurity, 100 MHz, $CDCl_3$) δ: 192.97, 171.87, 160.38, 154.76, 150.10, 135.19, 134.89, 129.99, 129.89, 129.68, 129.46, 129.13, 128.42, 122.43 (q, *J* = 318.1 Hz), 101.55, 66.24, 61.34, 53.01; ^{19}F NMR (375 MHz, CD_3CN) δ: –80.47; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 481.2, $C_{23}H_{23}F_3N_2O_4S^+$ requires 481.50.

_N_-((1_Z_,2_E_,4_E_)-5-(Dibenzylamino)-1-(1-tosylpyrrolidin-2-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



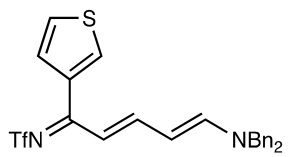
Prepared according to general procedure A (except with 1.0 equiv of diebenzylamine) using 2-(1-tosylpyrrolidin-2-yl)pyridine (650 mg, 2.15 mmol), Tf_2O (360 μL, 2.15 mmol), dibenzylamine (420 μL, 2.15 mmol, 1.0 M in EtOAc), collidine (280 μL, 2.15 mmol), EtOAc (22 mL, 0.10 M). The crude material was purified by precipitation in hexanes (200 mL) to afford the title compound as a yellow-orange solid (1.11 g, 1.76 mmol, 82% yield); mp: 85 – 88 °C; IR ν_{max}/cm^{-1} (film): 2972, 2360, 1617, 1568, 1490, 1426, 1401, 1315, 1234, 1153; ^1H NMR (400 MHz, CD_3CN) δ: 8.11 – 7.89 (m, 2H), 7.72 (d, *J* = 7.9 Hz, 2H), 7.57 – 7.26 (m, 11H), 7.24 (d, *J* = 7.4 Hz, 1H), 6.24 (d, *J* = 13.2 Hz, 1H), 6.08 (d, *J* = 12.7 Hz, 1H), 4.93 (s, 1H), 4.67 (s, 2H), 4.60 (s, 2H), 3.45 (s, 1H), 3.37 – 3.22 (m, 1H), 2.42 (s, 3H), 2.09 – 1.95 (m, 1H), 1.89 – 1.74 (m, 2H), 1.56 – 1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:179.29, 159.07, 144.68, 135.12, 134.79, 130.40, 129.61, 129.53, 129.24, 129.05, 128.70, 128.06, 127.97, 107.79 (q, *J* = 297.5 Hz), 60.92, 52.54, 50.10, 34.22, 24.94, 21.12; ^{19}F NMR (375 MHz, CD_3CN) δ: –74.88; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 632.3, $C_{31}H_{33}F_3N_3O_4S^+$ requires 632.18.

***N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-(furan-3-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



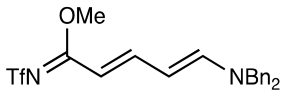
Prepared according to general procedure A using 2-(furan-3-yl)pyridine (1.45 g, 10.0 mmol), Tf_2O (1.68 mL, 10.0 mmol), dibenzylamine (2.31 mL, 12.0 mmol, 1.0 M in EtOAc), collidine (1.30 mL, 10.0 mmol), EtOAc (100 mL, 0.10 M). The crude material was purified by precipitation in hexanes (1.0 L) to afford the title compound as a red solid (3.25 g, 6.80 mmol, 68% yield); mp: 63 – 66 ºC; IR ν_{max}/cm^{-1} (film): 3031, 1548, 1469, 1433, 1308, 1146, 1092, 989, 837, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (s, 1H), 7.72 (dd, *J* = 13.6, 12.0 Hz, 1H), 7.47 – 7.31 (m, 8H), 7.17 (d, *J* = 6.9 Hz, 4H), 6.71 (d, *J* = 1.9 Hz, 1H), 6.56 (d, *J*= 13.6 Hz, 1H), 5.81 (t, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 19.4 Hz, 4H); ^{13}C NMR (100 MHz, CD_3CN) δ: 167.00, 163.19, 161.30, 147.10, 144.99, 135.60, 135.24, 129.95, 129.86, 129.55, 129.33, 129.02, 128.32, 126.59, 121.01 (d, *J* = 320.3 Hz), 113.43, 111.53, 105.97, 61.14, 52.72; ^{19}F NMR (375 MHz, $CDCl_3$) δ: –79.18; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 475.2, $C_{24}H_{21}F_3N_2O_3S^+$ requires 475.13.

***N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-(thiophen-3-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



Prepared according to general procedure A from 2-(thiophen-3-yl)pyridine[2] (806 mg, 5.00 mmol), EtOAc (25 mL, 0.2 M), Tf_2O (840 mL, 5.00 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), and collidine (660 mL, 5.00 mmol). The crude material was purified by precipitation in hexanes (500 mL) to afford the title compound as a red solid (1.64 g, 3.34 mmol, 67% yield); mp: 56 – 60 ºC; IR ν_{max}/cm^{-1} (film): 3082, 1617, 1557, 1438, 1354, 1348, 1149, 1095, 844; ^1H NMR (400 MHz, CD_3CN) δ: 7.91 – 7.74 (m, 3H), 7.47 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.42 – 7.33 (m, 7H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 2H), 6.54 (d, *J* = 13.2 Hz, 1H), 6.09 (t, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 22.3 Hz, 4H); ^{13}C NMR (100 MHz, CD_3CN) δ: 169.02, 163.25, 162.24, 141.37, 135.67, 135.31, 131.21, 129.99, 129.92, 129.60, 129.38, 129.32, 129.08, 128.39, 127.39, 121.08 (q, *J* = 320.3 Hz), 113.65, 106.21, 61.18, 52.78; ^{19}F NMR (375 MHz, CD_3CN) δ: –80.04; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 491.2, $C_{24}H_{22}F_3N_2O_2S_2^+$ requires 491.1.

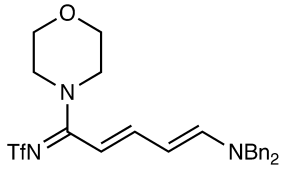
Methyl (1*Z*,2*E*,4*E*)-5-(dibenzylamino)-*N*-((trifluoromethyl)sulfonyl)penta-2,4-dienimidate



Prepared according to general procedure A using 2-methoxypyridine (1.31 mL, 12.5 mmol), Tf_2O (2.10 mL, 12.5 mmol), dibenzylamine (2.90 mL, 15.0 mmol, 1.0 M in EtOAc), collidine (1.70 mL, 12.5 mmol), EtOAc (125 mL, 0.10 M). The crude material was purified by precipitation in hexanes (1.2 L) to afford the title compound as a yellow solid (2.97 g, 6.75 mmol, 54% yield); mp: 140 – 142 ºC; IR ν_{max}/cm^{-1} (film): 3031, 2941, 1625, 1587, 1573, 1501, 1444, 1429, 1362, 1320; ^1H NMR (400 MHz, CD_3CN) δ 7.71 (t, *J* = 13.2 Hz, 1H), 7.53 (d, *J* = 12.5 Hz, 1H), 7.43 – 7.11 (m, 10H), 5.90 (d, *J* = 13.8 Hz, 1H), 5.64 (t, *J* = 12.3 Hz, 1H), 4.47 (d, *J* = 35.1 Hz, 4H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 171.92, 158.10, 155.29, 136.54, 136.52, 135.94, 130.56, 129.40, 128.66, 128.30, 127.86, 120.18 (q, *J* = 319.4 Hz), 100.94, 100.33, 59.93, 55.86, 51.73; ^{19}F NMR

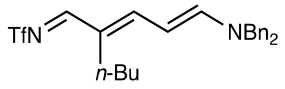
(375 MHz, CD_3CN) δ: –80.47; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 439.2, $C_{21}H_{22}F_3N_2O_3S^+$ requires 439.12.

_N_-((1_Z_,2_E_,4_E_)-5-(Dibenzylamino)-1-morpholinopenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



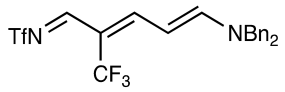
Prepared according to general procedure A using 4-(pyridin-2-yl)morpholine (82.0 mg, 0.50 mmol), Tf_2O (82.5 μL, 0.50 mmol), dibenzylamine (115 μL, 0.60 mmol, 1.0 M in EtOAc), collidine (66.0 μL, 0.50 mmol), EtOAc (5.0 mL, 0.10 M). The crude material was purified by precipitation in hexanes (50 mL) to afford the title compound as a yellow solid (84.2 mg, 0.17 mmol, 34% yield). mp: 149 – 153 ºC; IR ν_{max}/cm^{-1} (film): 2848, 1620, 1581, 1506, 1420, 1169, 1006, 701; ^1H NMR (400 MHz, CD_3CN) δ: 7.49 – 7.28 (m, 8H), 7.24 (d, J = 7.5 Hz, 4H), 5.83 (d, J = 13.8 Hz, 1H), 5.48 (t, J = 12.1 Hz, 1H), 4.45 (s, 4H), 3.65 (s, 8H); ^{13}C NMR (100 MHz, CD_3CN) δ: 166.10, 155.46, 155.18, 137.43, 129.75, 128.73, 128.54, 121.42 (q, J = 321.0 Hz), 105.40, 99.76, 66.99, 52.84, 48.49; ^{19}F NMR (375 MHz, CD_3CN) δ: –80.01; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 494.3, $C_{24}H_{27}F_3N_3O_3S^+$ requires 494.2.

_N_-((1_E_,2_E_)-2-((_E_)-3-(Dibenzylamino)allylidene)hexylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure A using 3-butylpyridine (1.48 mL, 10.0 mmol), Tf_2O (1.65 mL, 10.0 mmol), dibenzylamine (2.31 mL, 12.0 mmol, 1.0 M in EtOAc), collidine (1.32 mL, 10.0 mmol), EtOAc (100.0 mL, 0.10 M). The crude material was purified by precipitation in hexanes (1.0 L) to afford the title compound as a yellow solid (4.13 g, 8.9 mmol, 89% yield); mp: 105 – 107 °C; IR ν_{max}/cm^{-1} (film): 3027, 2947, 1613, 1500, 1447, 1284, 1177, 1118, 1090, 886; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 7.55 (d, *J* = 12.1 Hz, 1H), 7.47 – 7.35 (m, 6H), 7.29 – 7.16 (m, 5H), 5.81 (t, *J* = 12.3 Hz, 1H), 4.60 (s, 2H), 4.52 (s, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.37 – 1.16 (m, 4H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:175.05, 164.64, 158.26, 134.12, 133.81, 129.02, 128.48, 128.22, 127.82, 127.19, 119.96 (q, *J* = 322.9 Hz), 100.57, 60.45, 52.00, 30.13, 24.73, 22.48, 13.99; ^{19}F NMR (375 MHz, $CDCl_3$)) δ: –77.92; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 465.3, $C_{24}H_{28}F_3N_2O_2S^+$ requires 465.17.

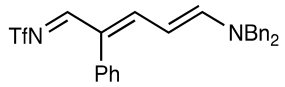
_N_-((1_E_,2_Z_,4_E_)-5-(Dibenzylamino)-2-(trifluoromethyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure A using 3-(trifluoromethyl)pyridine (1.44 mL, 12.5 mmol), Tf_2O (2.10 mL, 12.5 mmol), dibenzylamine (2.90 mL, 15.0 mmol, 1.0 M in EtOAc), collidine (1.70 mL, 12.5 mmol), EtOAc (125 mL, 0.10 M). The crude material was purified by precipitation in hexanes (1.2 L). The mixture required stirring overnight at room temperature to afford the title compound as an orange solid (1.95 g, 4.00 mmol, 32% yield); mp: 111 – 113 °C; IR ν_{max}/cm^{-1} (film): 3035, 2360, 2341, 1624, 1517, 1451, 1440, 1306, 1326, 1263; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ: 8.64 (d, *J* = 11.5 Hz, 1H), 8.09 (s, 1H), 7.52 – 7.14 (m, 12H), 4.94 (s, 2H), 4.78 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ: 179.28, 136.07, 135.60, 129.88 (d, *J* = 10.7 Hz),

129.45, 129.26, 128.91, 128.30, 120.70 (q, J = 320.4 Hz), 104.04, 60.87, 52.62.; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ: –60.73, –79.23; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 477.2, $C_{21}H_{19}F_6N_2O_2S^+$ requires 477.1.

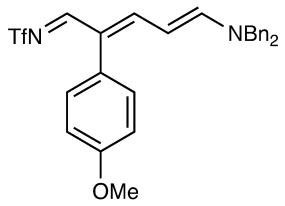
***N*-((1*E*,2*E*,4*E*)-5-(Dibenzylamino)-2-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



Prepared according to general procedure A using 3-phenylpyridine (2.87 mL, 20.0 mmol), Tf_2O (3.36 mL, 20.0 mmol), dibenzylamine (3.84 mL, 20.0 mmol, 1.0 M in EtOAc), collidine (2.64 mL, 20.0 mmol), EtOAc (200 mL, 0.10 M). The crude material was not concentratepurified by precipitation in hexanes (2.0 L) to afford the title compound as a yellow solid (7.54g, 15.6 mmol, 78% yield); mp: 139 – 142 °C; ^{1}H NMR (400 MHz, CD_3CN) δ: 8.14 (s, 1H), 7.87 (d, J = 11.9 Hz, 1H), 7.63 (d, J = 13.0 Hz, 1H), 7.36 (d, J = 7.1 Hz, 3H), 7.32 – 7.19 (m, 8H), 7.00 (dd, J = 18.3, 6.1 Hz, 4H), 5.67 (t, J = 12.5 Hz, 1H), 4.67 (s, 2H), 4.38 (s, 2H); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 485.2, $C_{26}H_{23}F_3N_2O_2S^+$ requires 485.15.

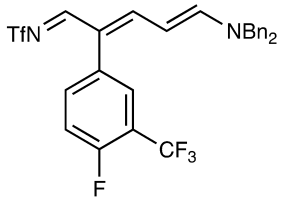
These data are consistent with those previously reported in the literature.[1]

***N*-((1*E*,2*E*,4*E*)-5-(Dibenzylamino)-2-(4-methoxyphenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



Prepared according to general procedure A using 2-(4-methoxyphenyl)pyridine (926 mg, 5.00 mmol), Tf_2O (830 μL, 5.0 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), collidine (66.0 μL, 5.00 mmol), EtOAc (50 mL, 0.10 M). The crude material was purified by precipitation in hexanes (500 mL) to afford the title compound as an orange solid (1.80 g, 3.50 mmol, 70% yield); mp: 69 – 71 °C; IR ν_{max}/cm^{-1} (film): 1615, 1485, 1169, 1105, 856, 548, 533; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.37 (s, 1H), 7.58 (d, *J* = 12.1 Hz, 1H), 7.48 – 7.30 (m, 7H), 7.19 (qd, *J* = 6.6, 2.5 Hz, 3H), 7.05 (dd, *J* = 6.7, 2.8 Hz, 2H), 6.79 (d, *J* = 7.2 Hz, 2H), 6.72 (dt, *J* = 7.6, 1.3 Hz, 1H), 5.85 (t, *J* = 12.4 Hz, 1H), 4.53 (s, 2H), 4.31 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.23, 159.60, 159.54, 135.25, 133.94, 133.68, 129.49, 129.36, 129.20, 128.64, 128.31, 127.54, 126.63, 122.29, 116.82 (q, *J* = 319.4 Hz), 115.27, 113.69, 102.04, 60.52, 55.19, 52.01; ^{19}F NMR (375 MHz, $CDCl_3$) δ: –77.78; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 515.2, $C_{27}H_{25}F_3N_2O_3S^+$ requires 515.16.

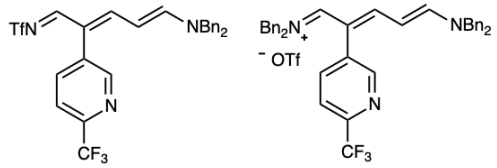
_N_-((1_E_,2_E_,4_E_)-5-(Dibenzylamino)-2-(4-fluoro-3-(trifluoromethyl)phenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure A (except with 1.0 equiv of dibenzylamine) using 3-(4-fluoro-3-(trifluoromethyl)phenyl)pyridine (2.41 g, 10.0 mmol), EtOAc (50 mL, 0.20 M), Tf_2O (1.68 mL, 10.0 mmol), dibenzylamine (1.92 mL, 10.0 mmol, 1.0 M in EtOAc), and collidine (1.32 mL, 10.0 mmol). The crude material was purified by precipitation in hexanes (2.0 L) to afford the title compound as a yellow solid (4.85 g, 8.50 mmol, 85% yield); mp: 70 – 74 °C; IR ν_{max}/cm^{-1}

(film): 3055, 1620, 1486, 1441, 1312, 1167, 1109, 856; ^{1}H NMR (400 MHz, CD_3CN) δ: 8.22 (s, 1H), 7.95 (d, *J* = 11.8 Hz, 1H), 7.72 (d, *J* = 13.2 Hz, 1H), 7.48 (d, *J* = 6.5 Hz, 1H), 7.44-7.39 (m 3H), 7.37 – 7.21 (m, 7H), 7.06 (dd, *J* = 6.4, 3.3 Hz, 2H), 5.71 (t, *J* = 12.5 Hz, 1H), 4.72 (s, 2H), 4.47 (s, 2H); ^{13}C NMR (101 MHz, CD_3CN) δ: 171.14, 166.92, 164.19, 159.44 (dq, *J* = 253.0, 2.0 Hz), 137.32 (d, *J* = 8.6 Hz), 135.25, 135.12, 132.54 (q, *J* = 3.0 Hz), 130.09, 129.88, 129.80, 129.57, 129.12, 128.29, 123.84 (q, *J* = 271.4 Hz), 123.46, 121.17 (q, *J* = 322.6), 118.59 (q, *J* = 5.1 Hz), 118.17, 117.97, 104.71, 62.08, 53.54; ^{19}F NMR (376 MHz, CD_3CN) δ: –61.85 (d, *J* = 12.8 Hz), –79.34, –118.74 (tt, *J* = 11.9, 6.3 Hz); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 571.2, $C_{27}H_{22}F_7N_2O_2S^+$ requires 571.1.

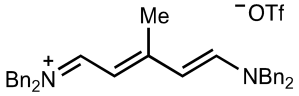
_N_-((1_E_,2_E_,4_E_)-5-(Dibenzylamino)-2-(6-(trifluoromethyl)pyridin-3-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure A using 6-(trifluoromethyl)-3,3'-bipyridine (112 mg, 0.50 mmol), EtOAc (2.5 mL, 0.20 M), Tf_2O (82.5 mL, 0.50 mmol), dibenzylamine (115 μL, 0.60 mmol), and collidine (66 μL, 0.50 mmol). The crude material was purified by precipitation in hexanes (50 mL) to afford the title compound in a mixture of regioisomers (14.3:1) as an orange solid (230 mg, 0.42 mmol, 83% yield). mp: 61 – 65 ºC; IR ν_{max}/cm^{-1} (film): 3028, 1617, 1483, 1332, 1163, 1105, 839, 701; ^{1}H NMR (major, 400 MHz, CD_3CN) δ: 8.50 (s, 1H), 8.28 (s, 1H), 7.99 (d, *J* = 11.6 Hz, 1H), 7.88 – 7.60 (m, 3H), 7.45 – 7.38 (m, *J* = 6.8 Hz, 3H), 7.36 – 7.29 (m, 5H), 7.09 – 7.01 (m, 2H), 5.76 (t, *J* = 12.5 Hz, 1H), 4.72 (s, 2H), 4.50 (s, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ: 171.20, 166.68, 164.67, 152.25, 146.59 (q, *J* = 35.4 Hz), 140.12, 139.42, 135.40,

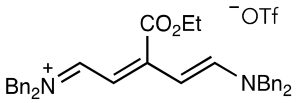
135.13, 135.08, 130.11, 129.91, 129.85, 129.61, 129.17, 128.37, 122.50 (q, J = 364.6 Hz), 121.15 (q, J = 324.2 Hz), 121.38 (q, J = 3.1 Hz), 104.79, 62.13, 53.62; ^{19}F NMR (375 MHz, CD_3CN) δ: –68.20 (minor), –68.31 (major), –79.15 (minor), –79.23 (major); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 554.2, $C_{26}H_{22}F_6N_3O_2S^+$ requires 554.17.

_N_-Benzyl-_N_-((2_E_,4_E_)-5-(dibenzylamino)-3-methylpenta-2,4-dien-1-ylidene)-1-phenylmethanaminium trifluoromethanesulfonate



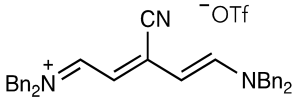
Prepared according to general procedure A (except with 2.0 equiv dibenzylamine and 2.0 equiv collidine) using 4-methylpyridine (1.49 mL, 5.0 mmol), EtOAc (50 mL, 0.10 M), Tf_2O (841 µL, 5.0 mmol), dibenzylamine (2.12 mL, 11.0 mmol, 1.0 M in EtOAc), and collidine (1.11 mL, 10.0 mmol). The 10% wt. aqueous $CuSO_4$ washings were done prior to washings with sat. $NaHCO_3$. The crude material was purified by precipitation in hexanes (500 mL) to afford the title compound as a green solid (2.67 g, 4.30 mmol, 86% yield); mp: 130 – 132° C; IR ν_{max}/cm^{-1} (film): 2360, 2341, 1588, 1547, 1244, 1163, 1032, 668, 555; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (d, J = 12.4 Hz, 2H), 7.40 – 7.26 (m, 13H), 7.21 (dd, J = 7.4, 2.1 Hz, 4H), 7.12 (d, J = 7.2 Hz, 3H), 5.83 (d, J = 12.4 Hz, 1H), 4.68 (s, 4H), 4.48 (s, 4H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.62, 172.31, 172.26, 156.95, 134.01, 133.35, 129.28, 128.96, 128.59, 128.50, 128.42, 127.22, 120.99 (q, J = 320.9 Hz), 106.93, 60.66, 51.50, 14.40; ^{19}F NMR (375 MHz, $CDCl_3$) δ: –78.08; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 471.4, $C_{34}H_{35}N_2^+$ requires 471.28.

_N_-Benzyl-_N_-((2_Z_,4_E_)-5-(dibenzylamino)-3-(ethoxycarbonyl)penta-2,4-dien-1-ylidene)-1-phenylmethanaminium trifluoromethanesulfonate



Prepared according to general procedure A (except with 2.0 equiv dibenzylamine and 2.0 equiv collidine) using ethyl isonicotinate (749.0 µL, 5.0 mmol), EtOAc (50 mL, 0.1 M), Tf_2O (841 µL, 5.0 mmol), dibenzylamine (1.92 mL, 10.0 mmol, 1.0 M in EtOAc), and collidine (1.11 mL, 10.0 mmol). The 10% wt. aqueous $CuSO_4$ washings were done prior to washings with sat. $NaHCO_3$. The crude material was purified by precipitation in hexanes (500 mL) to afford the title compound as a red solid (2.82 g, 4.15 mmol, 83% yield); mp: 59 – 61 °C; IR ν_{max}/cm^{-1} (film): 3031, 2360, 1720, 1587, 1517, 1408, 1257, 1173, 1028, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 12.5 Hz, 1H), 7.47 – 6.95 (m, 28H), 6.16 (d, J = 12.5 Hz, 1H), 4.23 (p, J = 7.0 Hz, 3H), 1.29 – 1.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.43, 162.27, 157.57, 133.48, 132.99, 129.44, 129.27, 129.06, 128.83, 128.66, 128.50, 127.77, 120.83 (q, J = 320.6 Hz), 103.49, 63.09, 62.47, 60.62, 52.76, 14.06; ^{19}F NMR (375 MHz, $CDCl_3$) δ: –78.17; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 529.4, $C_{36}H_{37}N_2O_2^+$ requires 529.29.

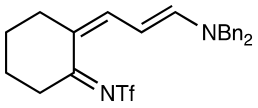
_N_-Benzyl-_N_-((2_Z_,4_E_)-3-cyano-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1-phenylmethanaminium trifluoromethanesulfonate



Prepared according to general procedure A (except with 2.0 equiv dibenzylamine and 2.0 equiv collidine) using isonicotinonitrile (520 mg, 5.00 mmol), EtOAc (50 mL, 0.10 M), Tf_2O (841 µL, 5.00 mmol), dibenzylamine (1.92 mL, 10.0 mmol, 1.0 M in EtOAc), and collidine (1.11 mL, 10.0 mmol). The 10% wt. aqueous $CuSO_4$ washings were done prior to washings with sat. $NaHCO_3$. The crude material was purified by precipitation in hexanes (500 mL) to afford the title compound

as a reddish-brown solid (2.11 g, 3.35 mmol, 67% yield); mp: 77 – 80 °C; IR ν_{max}/cm^{-1} (film): 3062, 1731, 1562, 1522, 1439, 1218, 1026, 863, 753, 635;^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 12.3 Hz, 2H), 7.41 (dd, *J* = 5.1, 1.9 Hz, 6H), 7.38 – 7.31 (m, 7H), 7.22 (dd, *J* = 7.7, 1.8 Hz, 3H), 7.19 – 7.14 (m, 4H), 7.01 (d, *J* = 12.3 Hz, 2H), 4.74 (s, 4H), 4.63 (s, 4H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.06, 139.22, 132.81, 132.48, 129.69, 129.63, 129.39, 128.95, 128.56, 128.37, 127.13, 126.43, 120.79 (q, *J* = 320.1 Hz), 113.36, 108.47, 60.97, 53.46; ^{19}F NMR (375 MHz, $CDCl_3$) δ: –78.24; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 482.3, $C_{34}H_{32}N_3^+$ requires 482.26.

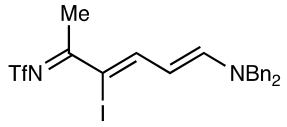
_N_-((1_E_,2_Z_)-2-((_E_)-3-(Dibenzylamino)allylidene)cyclohexylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure A 5,6,7,8-tetrahydroquinoline (2.47 mL, 20.0 mmol), EtOAc (100 mL, 0.20 M), Tf_2O (3.36 mL, 20.0 mmol), dibenzylamine (4.61 mL, 24.0 mmol, 1.0 M in EtOAc), and collidine (2.64 mL, 20.0 mmol). Washing with H_2O (x2), saturated aqueous $NaHCO_3$, and precipitating dropwise from hexanes (1.5 L) afforded the title compound (7.81 g, 16.9 mmol, 84% yield) as a red–pink solid. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.33 (d, *J* = 13.2 Hz, 1H), 7.97 (d, *J* = 11.8 Hz, 1H), 7.51 – 7.27 (m, 8H), 7.21 (d, *J* = 7.2 Hz, 2H), 5.82 (t, *J* = 12.5 Hz, 1H), 4.64 (s, 2H), 4.59 (s, 2H), 2.86 (t, *J* = 6.0 Hz, 2H), 2.23 (t, *J* = 6.0 Hz, 2H), 1.65 (ttd, *J* = 12.9, 6.1, 3.2 Hz, 4H); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 463.3, $C_{24}H_{26}F_3N_2O_2S^+$ requires 463.2.

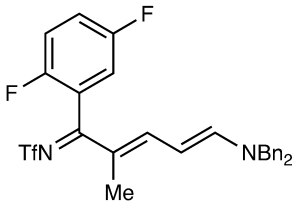
These data are consistent with those previously reported in the literature.[1,2]

***N*-((2*E*,3*Z*,5*E*)-6-(Dibenzylamino)-3-iodohexa-3,5-dien-2-ylidene)-1,1,1-trifluoromethanesulfonamide 2**



Prepared according to general procedure A using 2-methyl-3-iodopyridine (1.10 g, 5.00 mmol), Tf_2O (841 μL, 5.00 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), collidine (660 μL, 5.00 mmol) and EtOAc (50 mL, 0.10 M). The crude material was purified by precipitation in hexanes (500 mL) to afford the title compound as a yellow solid (1.34 g, 2.45 mmol, 49% yield); mp: 132 – 135 °C; IR ν_{max}/cm^{-1} (film): 3675, 2969, 2917, 2849, 2358, 1407, 1066; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.63 (dd, *J* = 11.8, 1.8 Hz, 2H), 7.47 – 7.31 (m, 6H), 7.21 (ddd, *J* = 7.1, 3.6, 1.8 Hz, 4H), 6.09 (t, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 13.0 Hz, 4H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.50, 157.83, 156.48, 133.86, 133.50, 129.64, 129.13, 129.08, 129.03, 128.78, 128.37, 127.86, 127.52, 118.97 (q, *J* = 319.4 Hz), 107.72, 59.77, 51.67l; ^{19}F NMR (375 MHz, $CDCl_3$) δ: –79.23; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 549.1 $C_{21}H_{20}F_3IN_2O_2S^+$ requires 549.03.

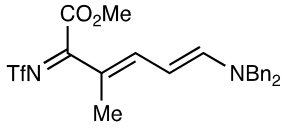
***N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-(2,5-difluorophenyl)-2-methylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



Prepared according to general procedure A using 2-(2,5-difluorophenyl)-3-methylpyridine (1.03 g, 5.00 mmol), Tf_2O (840 μL, 5.00 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc),

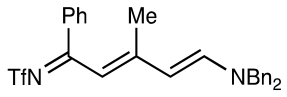
collidine (660 μL, 5.00 mmol), EtOAc (50 mL, 0.10 M). The crude material was purified by precipitation in hexanes (500 mL) to afford the title compound as an orange solid (2.24 g, 4.20 mmol, 84% yield); mp: 134 – 136 °C; IR ν_{max}/cm^{-1} (film): 2988, 1409, 1176, 1101, 893, 617, 597; ^{1}H NMR (400 MHz, CD_3CN) δ 7.76 (d, *J* = 11.8 Hz, 1H), 7.46 – 7.33 (m, 6H), 7.33 – 7.18 (m, 7H), 7.07 (ddd, *J* = 8.3, 5.4, 3.1 Hz, 1H), 6.03 (t, *J* = 12.3 Hz, 1H), 4.62 (d, *J* = 16.4 Hz, 4H), 1.95 (d, *J* = 8.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 168.43, 163.25, 162.17, 159.01 (d, *J* = 239.2 Hz), 157.10, 154.72, 135.52, 135.25, 129.91 (d, *J* = 8.9 Hz), 129.33 (t, *J* = 26.0 Hz), 128.48, 120.68 (q, *J* = 320.4 Hz), 117.66 (dd, *J* = 25.1, 9.0 Hz), 104.56, 61.29, 52.90, 12.04; ^{19}F NMR (375 MHz, CD_3CN) δ –80.60, –120.94 (dtd, *J* = 16.7, 8.2, 4.7 Hz), –121.31 (dq, *J* = 17.2, 4.8 Hz); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 535.2, $C_{27}H_{23}F_5N_2O_2S^+$ requires 535.14.

Methyl (2*Z*,3*E*,5*E*)-6-(dibenzylamino)-3-methyl-2-(((trifluoromethyl)sulfonyl)imino)hexa-3,5-dienoate



Prepared according to general procedure A (except with 1.0 equiv dibenzylamine) using methyl 3-methylpicolinate (1.35 mL, 10.0 mmol), Tf_2O (1.68 mL, 10.0 mmol), dibenzylamine (1.92 mL, 10.0 mmol, 1.0 M in EtOAc), collidine (1.32 mL, 10.0 mmol), EtOAc (50 mL, 0.20 M). The crude material was purified by precipitation in hexanes (1.0 L) to afford the title compound as a yellow solid (2.72 g, 5.70 mmol, 57% yield); mp 186 – 189 °C; IR ν_{max}/cm^{-1} (film): 1726, 1610, 1573, 1480, 1433, 1398, 1311, 1247; ^1H NMR (400 MHz, CD_3CN) δ: 8.12 (d, *J* = 11.5 Hz, 1H), 7.54 (d, *J* = 12.9 Hz, 1H), 7.48 – 7.27 (m, 8H), 7.25 – 7.21 (m, 2H), 6.19 (dd, *J* = 12.9, 11.5 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 4H), 3.86 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 167.11, 165.36, 164.58, 162.54, 134.40, 134.23, 129.68, 129.57, 129.46, 129.19, 128.91, 128.26, 120.71 (q, *J* = 322.1 Hz), 118.18, 106.68, 61.39, 53.19, 52.97, 11.03; ^{19}F NMR (375 MHz, CD_3CN) δ: –79.81; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 481.2, $C_{23}H_{24}F_3N_2O_4S^+$ requires 481.13.

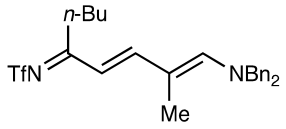
***N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-3-methyl-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



Prepared according to general procedure A using 4-methyl-2-phenylpyridine (930 mg, 5.50 mmol), EtOAc (55 mL, 0.10 M), Tf_2O (924 µL, 5.50 mmol), dibenzylamine (1.27 mL, 6.60 mmol, 1.0 M in EtOAc), and collidine (727 µL, 5.50 mmol). Washing with H_2O (x2), saturated aqueous $NaHCO_3$, and precipitating dropwise from hexanes (550 mL) afforded the title compound (1.64 g,

3.29 mmol, 60% yield) as a red solid. mp: 58 – 61 ºC; IR ν_{max}/cm^{-1} (film): 3035, 1599, 1453, 1388, 1247, 1169, 1092, 1011, 722; ^{1}H NMR (400 MHz, CD_3CN) δ: 8.21 (d, *J* = 12.6 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.46 – 7.32 (m, 10H), 7.26 (br s., 4H), 5.71 (s, 1H), 4.58 (br s., 4H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 173.27, 169.35, 159.38, 143.67, 136.67, 135.76, 131.05, 130.78, 129.96, 129.91, 129.58, 129.20, 129.05, 128.90, 128.69, 120.82 (q, *J* = 319.9 Hz), 115.36, 107.20, 60.94, 52.12, 21.24; ^{19}F NMR (376 MHz, CD_3CN) δ: –80.65; *m/z* LRMS (ESI + APCI) found [M + H]$^+$ 499.3, $C_{27}H_{26}F_3N_2O_2S^+$ requires 499.2.

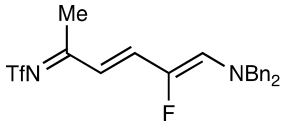
_N_-((1_E_,3_E_,5_E_)-1-(Dibenzylamino)-2-methylnona-1,3-dien-5-ylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure A using 2-butyl-5-methylpyridine (894 mg, 6.00 mmol), EtOAc (30 mL, 0.20 M), Tf_2O (1.00 mL, 6.00 mmol), dibenzylamine (1.40 mL, 7.20 mmol, 1.0 M in EtOAc), and collidine (793 mL, 6.00 mmol). Washing with H_2O (x2), saturated aqueous $NaHCO_3$, and precipitating dropwise from hexanes (600 mL) afforded the title compound (1.71 g, 3.57 mmol, 60% yield) as a yellow solid. mp: 103 – 106 ºC; IR ν_{max}/cm^{-1} (film): 2969, 1548, 1482, 1311, 1174, 1100, 1021, 943; ^{1}H NMR (400 MHz, CD_3CN) δ: 7.80 (d, *J* = 13.6 Hz, 1H), 7.67 (s, 1H), 7.47 – 7.31 (m, 6H), 7.27 (d, *J* = 7.4 Hz, 4H), 6.17 (d, *J* = 13.6 Hz, 1H), 4.68 (s, 4H), 2.68 (t, *J* = 7.7 Hz, 2H), 1.85 (s, 3H), 1.63 (p, *J* = 7.6 Hz, 2H), 1.39 (h, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 182.96, 162.82, 162.35, 136.70, 130.78, 129.98, 129.14,

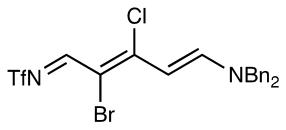
128.32, 120.85 (q, J = 320.3 Hz), 110.73, 57.94, 37.11, 32.23, 23.33, 14.16, 12.20; ^{19}F NMR (376 MHz, CD_3CN) δ: –80.37; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 479.3, $C_{25}H_{30}F_3N_2O_2S^+$ requires 479.2.

_N_-((2_E_,3_E_,5_Z_)-6-(Dibenzylamino)-5-fluorohexa-3,5-dien-2-ylidene)-1,1,1-trifluoromethanesulfonamide



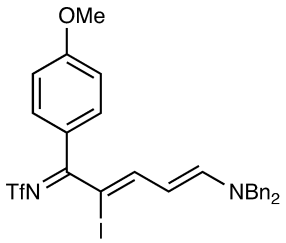
Prepared according to general procedure A using 2-methyl-5-fluoropyridine (556 mg, 5.00 mmol), Tf_2O (840 µL, 5.00 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), collidine (660 µL, 5.0 mmol), EtOAc (50 mL, 0.10 M). The crude material was purified by precipitation in hexanes (500 mL) to afford the title compound as an orange solid (1.36 g, 3.10 mmol, 62% yield); mp: 106 – 108 °C; IR ν_{max}/cm^{-1} (film): 3675, 2988, 2900, 2358, 1495, 1102, 794; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 – 7.19 (m, 6H), 7.09 (dd, J = 7.8, 1.7 Hz, 5H), 6.41 (d, J = 26.3 Hz, 1H), 6.02 (d, J = 13.9 Hz, 1H), 4.40 (s, 4H), 2.36 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 181.07, 141.25 (d, J = 13.8 Hz), 140.51 (d, J = 234.9 Hz), 138.41 (d, J = 2.8 Hz), 135.03, 129.33, 128.74, 128.00, 119.50 (q, J = 319.9 Hz), 112.12 (d, J = 4.2 Hz), 50.72, 24.42; ^{19}F NMR (375 MHz, $CDCl_3$) δ: –79.11, –146.56-146.92 (m); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 441.2, $C_{21}H_{20}F_4N_2O_2S^+$ requires 441.13.

_N_-((1_E_,2_E_,4_E_)-2-Bromo-3-chloro-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure A using 3-bromo-4-chloropyridine (962 mg, 5.00 mmol), Tf_2O (840 µL, 5.00 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), collidine (660 µL, 5.00 mmol), EtOAc (50 mL, 0.10 M). The crude material was purified by precipitation in hexanes (500 mL) to afford the title compound as a red solid (2.16 g, 4.15 mmol, 83% yield); mp: 58 – 61 °C; IR ν_{max}/cm^{-1} (film): 2987, 2359, 1610, 1480, 1174, 1106, 852; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.03 (s, 1H), 8.31 (d, *J* = 11.7 Hz, 1H), 7.57 – 7.34 (m, 6H), 7.31 – 7.26 (m, 2H), 7.24 (dd, *J* = 7.6, 1.9 Hz, 2H), 6.68 (d, *J* = 11.7 Hz, 1H), 4.75 (s, 2H), 4.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.83, 157.97, 156.02, 132.99, 132.72, 129.60, 129.53, 129.51, 129.05, 128.57, 127.77, 119.83 (q, *J* = 322.5 Hz), 102.88, 102.36, 61.71, 53.23; ^{19}F NMR (375 MHz, $CDCl_3$) δ: –77.53; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 521.2, $C_{20}H_{17}BrClF_3N_2O_2S^+$ requires 520.98.

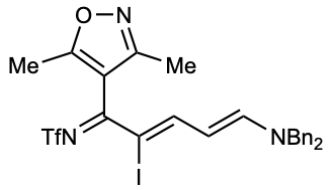
_N_-((1_E_,2_Z_,4_E_)-5-(Dibenzylamino)-2-iodo-1-(4-methoxyphenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide 2



A 500 mL round bottom flask was charged with 2-(4-methoxyphenyl)pyridine (1.30 g, 7.00 mmol), EtOAc (70 mL, 0.10 M), and cooled to –78 °C. Tf_2O (1.18 mL, 7.00 mmol) was added dropwise, and the reaction was left to stir for 30 mins. Then, dibenzylamine (1.62 mL, 8.40 mmol, 1.0 M in EtOAc) and collidine (930 µL, 7.00 mmol), were added and the reaction continued to stir at –78 °C. After 30 mins, the –78 °C bath was removed, and the reaction was allowed to warm to

room temperature. Then, *N*-iodosuccinimide (1.57 g, 7.00 mmol) was added, the reaction stirred at room temperature for 10 minutes, and then the reaction was quenched with aqueous sodium thiosulfate. The reaction was diluted with EtOAc and washed with aqueous sodium bicarbonate (3x) followed by a brine wash and 10% wt. aqueous $CuSO_4$ (3x). The organic layer was collected and the separatory funnel was rinsed with CH_2Cl_2 (this is because the product partially precipitates out of EtOAc). The organic extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. After filtration, the organic extract was diluted with minimal CH_2Cl_2 (approximately 1.0 mL per 1.0 mmol) and added dropwise to excess hexanes (approximately 100 mL per 1.0 mmol) and the resulting oil was allowed to settle overnight in a –20 ºC fridge. After the oil/precipitate had settled, the hexanes were decanted off and oil/precipitate was washed with hexanes. Precipitation afforded the compound as a green powder (3.40 g, 5.30 mmol, 76% yield); mp: 174 – 176 °C; IR ν_{max}/cm^{-1} (film): 1610, 1562, 1418, 1230, 1176, 884, 842, 616; ^{1}H NMR (400 MHz, CD_3CN) δ: 7.78 (d, *J* = 11.9 Hz, 1H), 7.38 (ddd, *J* = 7.2, 5.2, 3.9 Hz, 8H), 7.29 – 7.18 (m, 4H), 7.11 (d, *J* = 11.8 Hz, 1H), 7.05 – 6.97 (m, 2H), 6.05 (t, *J* = 11.9 Hz, 1H), 4.60 (d, *J* = 10.8 Hz, 4H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 178.39, 164.12, 162.62, 162.45, 135.53, 135.25, 131.65, 129.96, 129.87, 129.74, 129.60, 129.36, 129.07, 128.44, 120.48 (q, *J* = 319.0 Hz), 114.47, 110.72, 87.85, 61.76, 56.19, 53.22; ^{19}F NMR (375 MHz, CD_3CN) δ: –80.49; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 641.1, $C_{27}H_{24}F_3IN_2O_3S^+$ requires 641.05.

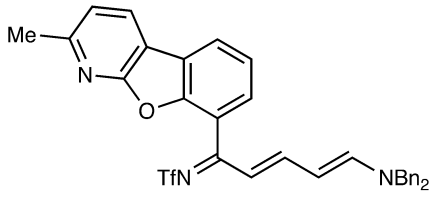
_N_-((1_E_,2_Z_)-5-(Dibenzylamino)-1-(3,5-dimethylisoxazol-4-yl)-2-iodopent-2-en-1-ylidene)-1,1,1-trifluoromethanesulfonamide



A 8 mL scintillation vial was charged with 3,5-dimethyl-4-(pyridin-2-yl)isoxazole (87 mg, 0.50 mmol), EtOAc (5.0 mL, 0.10 M), and cooled to –78 °C. Tf_2O (84.0 µL, 0.50 mmol) was added dropwise, and the reaction was left to stir for 30 mins. Then, dibenzylamine (115 µL, 0.60 mmol, 1.0 M in EtOAc) and collidine (66.0 µL, 0.50 mmol), were added and the reaction continued to stir at –78 °C. After 30 mins, the –78 °C bath was removed, and the reaction was allowed to warm to room temperature. Then, *N*-iodosuccinimide (113 mg, 0.50 mmol) was added, the reaction stirred at room temperature for 10 minutes, and then the reaction was quenched with aqueous sodium thiosulfate. The reaction was diluted with EtOAc and washed with aqueous sodium bicarbonate (3x) followed by a brine wash and 10% wt. aqueous $CuSO_4$ (3x). The organic layer was collected and the separatory funnel was rinsed with CH_2Cl_2 (this is because the product partially precipitates out of EtOAc). The organic extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. After filtration, the organic extract was diluted with minimal CH_2Cl_2 (approximately 1.0 mL per 1.0 mmol) and added dropwise to excess hexanes (approximately 100 mL per 1.0 mmol) and the resulting oil was allowed to settle overnight in a –20 ºC fridge. Precipitation afford the compound as a yellow powder (185 mg, 0.29 mmol, 63% yield); mp: 168 – 170 °C; IR ν_{max}/cm^{-1} (film): 3209, 2262, 1610, 1562, 1408, 1172, 1105, 860, 698; ^1H NMR (400 MHz, CD_3CN) δ: 8.03 (d, J = 11.7 Hz, 1H), 7.45 – 7.33 (m, 6H), 7.29 (dd, J = 7.8, 2.9 Hz, 3H), 7.27 – 7.16 (m, 3H), 6.20 (t, J = 11.9 Hz, 1H), 4.67 (d, J = 6.7 Hz, 4H), 2.26 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 168.17, 165.67, 164.70, 163.07, 159.28, 134.89, 134.82, 130.05, 129.96, 129.82, 129.59, 129.27, 128.55, 120.41 (q, J = 319.3 Hz), 113.39, 112.50, 87.04, 62.22,

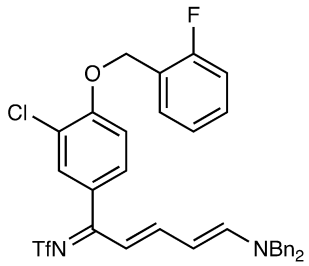
53.65, 12.01, 10.57; ^{19}F NMR (375 MHz, CD_3CN) δ –80.49; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 630.1, $C_{25}H_{23}F_3IN_3O_3S^+$ requires 630.05.

_N_-((1_Z_,2_E_,4_E_)-5-(Dibenzylamino)-1-(2-methylbenzofuro[2,3-_b_]pyridin-8-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



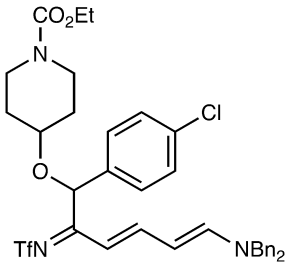
Prepared according to general procedure A using 2-methyl-8-(pyridin-2-yl)benzofuro[2,3-b]pyridine (972 mg, 3.73 mmol), EtOAc (19 mL, 0.2 M), Tf_2O (626 µL, 3.73 mmol), dibenzylamine (861 µL, 4.48 mmol, 1.0 M in EtOAc), and collidine (493 µL, 3.73 mmol). Washing with H_2O (x2), saturated aqueous $NaHCO_3$, and precipitating dropwise from hexanes (400 mL) afforded the title compound as a green solid (1.14 g, 1.93 mmol, 52% yield); mp: 138 – 141 ºC; IR ν_{max}/cm^{-1} (film): 3024, 1566, 1474, 1442, 1348, 1165, 1098, 893, 809; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, *J* = 11.9 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.79 – 7.68 (m, 2H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.24 (s, 2H), 7.06 (d, *J* = 6.0 Hz, 3H), 7.00 – 6.85 (m, 4H), 5.88 (t, *J* = 12.1 Hz, 1H), 4.54 (s, 4H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.06, 162.51, 161.69, 161.32, 156.76, 150.92, 133.89, 133.78, 129.97, 129.45, 128.87, 128.52, 127.96, 123.80, 123.04, 122.58, 119.95 (q, *J* = 320.6 Hz), 118.85, 112.87, 105.53, 60.42, 52.78, 23.97; ^{19}F NMR (375 MHz, $CDCl_3$) δ: –78.77; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 590.3, $C_{32}H_{27}F_3N_3O_3S^+$ requires 590.2.

_N_-((1_Z_,2_E_,4_E_)-1-(3-Chloro-4-((2-fluorobenzyl)oxy)phenyl)-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



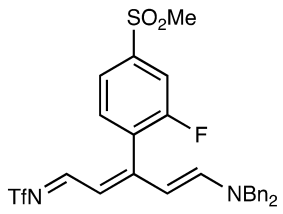
Prepared according to general procedure A using 3-chloro-4-((2-fluorobenzyl)oxy)phenylpyridine (2.20 g, 7.00 mmol), Tf_2O (1.18 mL, 7.00 mmol), dibenzylamine (1.62 mL 8.40 mmol, 1.0 M in EtOAc), collidine (925 μL, 7.00 mmol), EtOAc (70 mL, 0.10 M). The crude material was purified by precipitation in hexanes (700 mL) to afford the title compound as a red solid (2.88 g, 4.48 mmol, 64% yield); mp: 70 – 73 °C; IR ν_{max}/cm^{-1} (film): 3071, 2357, 1557, 1437, 1168, 992, 832, 695, 551, 533; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 2.2 Hz, 1H), 7.58 (td, *J* = 7.5, 1.8 Hz, 1H), 7.53 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.46 – 7.27 (m, 9H), 7.23 – 7.14 (m, 5H), 7.10 (ddd, *J* = 9.7, 8.2, 1.2 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.64 (d, *J* = 13.6 Hz, 1H), 5.84 (t, *J* = 12.1 Hz, 1H), 5.27 (s, 2H), 4.42 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.49, 160.33 (d, *J* = 247.1 Hz), 158.25 (d, *J* = 330.4 Hz), 158.08, 134.07 (d, *J* = 51.1 Hz), 131.82 (d, *J* = 3.2 Hz), 130.11 (d, *J* = 8.1 Hz), 129.43 (d, *J* = 3.9 Hz), 128.83 (d, *J* = 43.4 Hz), 128.01, 127.39, 124.62 (d, *J* = 3.6 Hz), 123.46 – 122.92 (m), 119.74 (q, *J* = 320.1 Hz), 115.49 (d, *J* = 20.9 Hz), 113.97, 112.96, 103.06, 64.75 (d, *J* = 4.7 Hz), 59.98, 51.57; ^{19}F NMR (375 MHz, $CDCl_3$) δ: –78.97, –118.61 (dt, *J* = 12.1, 6.1 Hz); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 643.2, $C_{33}H_{27}ClF_4N_2O_3S^+$ requires 643.14.

Ethyl-4-(((2*Z*,3*E*,5*E*)-1-(4-chlorophenyl)-6-(dibenzylamino)-2-(((trifluoromethyl)sulfonyl)imino)hexa-3,5-dien-1-yl)oxy)piperidine-1-carboxylate



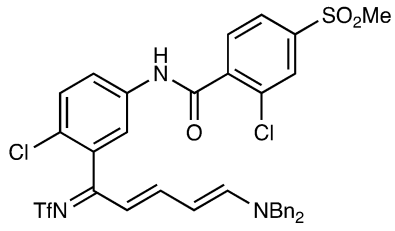
Prepared according to general procedure A using ethyl 4-((4-chlorophenyl)(pyridin-2-yl)methoxy)- piperidine-1-carboxylate (1.87 g, 5.00 mmol), EtOAc (25 mL, 0.20 M), Tf_2O (840 µL, 5.00 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), and collidine (661 µL, 5.00 mmol). Washing with H_2O (x2), saturated aqueous $NaHCO_3$, and precipitating dropwise from hexanes (500 mL) afforded the title compound as a yellow solid (3.06 g, 4.34 mmol, 87% yield); mp: 74 – 77 ºC; IR ν_{max}/cm^{-1} (film): 2934, 1690, 1567, 1482, 1431, 1155, 1095, 784; ^1H NMR (400 MHz, CD_3CN) δ: 8.16 (t, *J* = 13.2 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.42 – 7.32 (m, 8H), 7.29 (d, *J* = 5.4 Hz, 2H), 7.20 (d, *J* = 6.1 Hz, 2H), 6.30 (d, *J* = 13.2 Hz, 1H), 6.07 (s, 1H), 5.64 (s, 1H), 4.65 (s, 2H), 4.57 (s, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.78 – 3.58 (m, 3H), 3.15 (tt, *J* = 9.4, 3.9 Hz, 2H), 1.88 – 1.78 (m, 2H), 1.54 (dp, *J* = 13.0, 4.3 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 177.05, 160.52, 156.17, 140.04, 135.35, 135.03, 134.15, 130.04, 129.94, 129.71, 129.48, 129.45, 129.32, 129.17, 128.46, 120.95 (q, *J* = 319.8 Hz), 79.91, 74.69, 61.88, 61.34, 53.03, 41.93, 41.89, 32.23, 31.42, 15.03; ^{19}F NMR (375 MHz, CD_3CN) δ: –80.07; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 704.3, $C_{35}H_{38}ClF_3N_3O_5S^+$ requires 704.2.

_N_-((1_E_,2_Z_,4_E_)-5-(Dibenzylamino)-3-(2-fluoro-4-(methylsulfonyl)phenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide 2d



Prepared according to general procedure A (except using 1.0 equiv of dibenzylamine) using 4-(2-fluoro-4-(methylsulfonyl)phenyl)pyridine (1.26 g, 5.00 mmol), Tf_2O (840 µL, 5.00 mmol), dibenzylamine (960 µL, 5.00 mmol, 1.0 M in EtOAc), collidine (660 µL, 5.00 mmol), EtOAc (5.0 mL, 0.10 M). The crude material was purified by precipitation in hexanes (500 mL) followed by automated flash column chromatography (silica gel: gradient 5% to 20% EtOAc in CH_2Cl_2) to afford the compound as an orange solid (2.05 g, 3.55 mmol, 71% yield); mp: 88 – 92 °C; IR ν_{max}/cm^{-1} (film): 3675, 2987, 2900, 2361, 2341, 1506, 1077, 562; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 11.3 Hz, 1H), 7.76 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.69 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.47 – 7.31 (m, 8H), 7.18 (d, *J* = 7.1 Hz, 2H), 7.01 (d, *J* = 7.3 Hz, 2H), 6.69 (d, *J* = 12.6 Hz, 1H), 6.37 (d, *J* = 11.4 Hz, 1H), 6.02 (d, *J* = 12.7 Hz, 1H), 4.56 (s, 2H), 4.36 (s, 2H), 3.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.85, 164.51, 160.20, 157.68, 154.87, 144.18 – 143.41 (m), 133.36, 132.88, 132.62, 129.62, 129.56, 128.90, 128.55, 127.38, 123.59 (d, *J* = 4.1 Hz), 119.86 (q, *J* = 319.4 Hz), 116.05, 115.80, 104.58, 60.14, 52.80, 44.49;^{19}F NMR (375 MHz, $CDCl_3$) δ: –77.75, –109.93; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 704.3, $C_{35}H_{37}ClF_3N_3O_5S^+$ requires 704.22.

2-Chloro-*N*-(4-chloro-3-((1*Z*,2*E*,4*E*)-5-(dibenzylamino)-1-(((trifluoromethyl)sulfonyl)imino)penta-2,4-dien-1-yl)phenyl)-4-(methylsulfonyl)benzamide

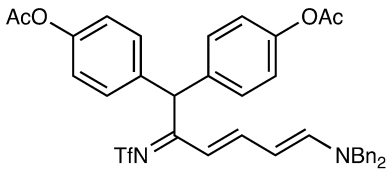


A 100 mL round bottom flask was charged with 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)- benzamide (1.26g, 3.00 mmol) and EtOAc (50 mL, 0.60 M). The flask was heated to 70 °C for 1 hour to fully dissolve the starting material, and then cooled to –78 °C. Tf_2O

(500 μL, 3.00 mmol) was added dropwise, and the reaction was left to stir for 30 mins. Then, dibenzylamine (700 μL, 3.60 mmol, 1.0 M in EtOAc) and collidine (400 μL, 3.00 mmol), were added and the reaction continued to stir at –78 °C. After 30 mins, the –78 °C bath was removed, and the reaction was allowed to warm to room temperature. The crude material was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ (3x), then brine (1x), then 1.0 M HCl (9x), then sat. aq. $NaHCO_3$ and dried with Mg_2SO_4. The organic layer was concentrated then precipitated in hexanes (300 mL) to afford the title compound as a yellow solid (765 mg, 1.02 mmol, 34% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (s, 1H), 7.95 (d, *J* = 1.7 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 11.9 Hz, 1H), 7.43 – 7.29 (m, 8H), 7.18 – 7.09 (m, 4H), 7.05 (s, 1H), 6.67 (s, 1H), 5.93 (t, *J* = 12.2 Hz, 1H), 4.46 (d, *J* = 13.5 Hz, 4H), 3.05 (s, 3H); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 750.2, $C_{34}H_{28}Cl_2F_3N_3O_5S_2^+$ requires 750.09.

These data are consistent with those previously reported in the literature.[1]

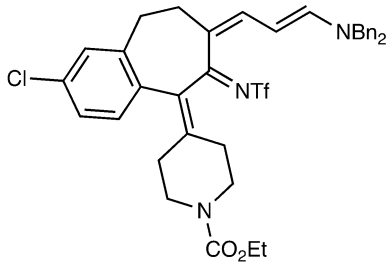
((2*Z*,3*E*,5*E*)-6-(Dibenzylamino)-2-(((trifluoromethyl)sulfonyl)imino)hexa-3,5-diene-1,1-diyl)bis(4,1-phenylene) diacetate



Prepared according to general procedure A using (pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate (1.81 g, 5.00 mmol), Tf_2O (840 μL, 5.0 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), collidine (660 μL, 5.00 mmol), EtOAc (25 mL, 0.20 M). The crude material was purified by precipitation in hexanes (50 mL), then washed with 1.0 M HCl (x3) to afford the title compound as a yellow solid (2.01 g, 2.90 mmol, 58% yield); mp: 75 – 78 °C; IR ν_{max}/cm^{-1}

(film): 2928, 2360, 1754, 1619, 1565, 1480; ^{1}H NMR (400 MHz, CD_3CN) δ: 7.93 (t, *J* = 12.7 Hz, 1H), 7.73 (d, *J* = 11.8 Hz, 1H), 7.43 – 7.00 (m, 15H), 6.94 (d, *J* = 8.1 Hz, 4H), 5.88 (t, *J* = 12.1 Hz, 1H), 5.77 (s, 1H), 4.51 (s, 2H), 4.43 (s, 2H), 2.13 (s, 6H); ^{13}C NMR (101 MHz, CD_3CN) δ 178.26, 170.46, 162.74, 159.16, 150.80, 145.06, 139.74, 135.66, 135.28, 131.19, 130.93, 130.15, 130.00, 129.87, 129.62, 129.57, 129.52, 129.34, 129.04, 128.39, 127.30, 122.94, 122.63, 122.10, 118.92, 113.40, 105.71, 61.08, 57.42, 56.40, 52.93, 36.91, 35.30, 29.76, 25.89, 21.23, 20.92, 19.05, 11.72; ^{19}F NMR (375 MHz, CD_3CN) δ: –80.10; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 691.3,$C_{37}H_{34}F_3N_2O_6S^+$ requires 691.2.

Ethyl 4-((6*Z*,7*Z*)-2-chloro-7-((*E*)-3-(dibenzylamino)allylidene)-6-(((trifluoromethyl)sulfonyl)imino)-6,7,8,9 -tetrahydro-5*H*-benzo[7]annulen-5-ylidene)piperidine-1-carboxylate



Prepared according to general procedure A using ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta [1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (1.15 g, 3.00 mmol), Tf_2O (500 μL, 3.00 mmol), dibenzylamine (700 μL, 3.60 mmol, 1.0 M in EtOAc), collidine (400 μL, 3.00 mmol), and EtOAc (30 mL, 0.1 M). The crude material was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ (3x), then brine, then 1.0 M HCl (3x), then sat. aq. $NaHCO_3$ and dried with Mg_2SO_4. The crude material was purified by precipitation in hexanes (300 mL) to afford the title compound as

an orange solid (830 mg, 1.17 mmol, 39% yield);[1]H NMR (400 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 12.7 Hz, 1H), 7.53 (d, *J* = 12.0 Hz, 1H), 7.45 – 7.30 (m, 6H), 7.29 – 7.09 (m, 6H), 7.03 (d, *J* = 2.2 Hz, 1H), 5.75 (t, *J*= 12.4 Hz, 1H), 4.49 (d, *J* = 12.2 Hz, 4H), 4.23 – 4.04 (m, 2H), 3.84 (dt, *J* = 13.0, 5.1 Hz, 1H), 3.64 (s, 1H), 3.29 (dddd, *J* = 16.8, 12.6, 8.3, 4.0 Hz, 2H), 3.12 (dt, *J*= 16.9, 3.8 Hz, 1H), 2.91 – 2.64 (m, 2H), 2.58 (ddd, *J* = 13.8, 9.1, 4.3 Hz, 2H), 2.32 (ddt, *J* = 13.7, 9.8, 4.9 Hz, 2H), 2.18 (ddd, *J* = 14.1, 6.6, 4.2 Hz, 1H), 1.25 (td, *J* = 7.1, 4.8 Hz, 3H); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 712.3, $C_{37}H_{37}ClF_3N_3O_4^+$ requires 711.21.

These data are consistent with those previously reported in the literature.[1]

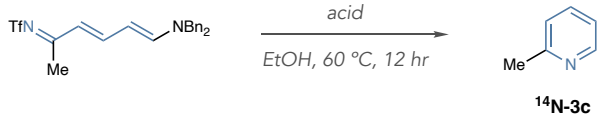
A 1.3. Control Studies for Recyclization

We considered three potential reaction pathways that could result in incomplete ^{15}N incorporation during the recyclization of Zincke imines. To probe these pathways, we chose the imine derived from 2-methylpyridine (**2c**) as it results in pyridine **3c** with 72% ^{15}N-incorporation.

a) Acid-mediated background recycyclizations.

As the reaction progresses, H_2BnNOAc and H_2NTf form in the reaction that potentially serve as acids for a background recyclization process. We conducted the following control reactions in Table S1 where an oven dried 8 mL vial equipped with a stir bar was charged with the described acid (1.0 equiv, premixed in EtOH, 0.1M) and imine **2c** (1.0 equiv) which was then stirred at 60 ºC for 12 hours. As seen from these results, such background reactions are not occurring. An equivalent of AcOH does promote a small amount of background recyclization, as amines are present during and after the recyclization, no free AcOH is present and we can eliminate this possibility.

Table S1. Controls for Probing the Background Acid Promoted Recyclization of Zincke Imines [a]



14N-3c

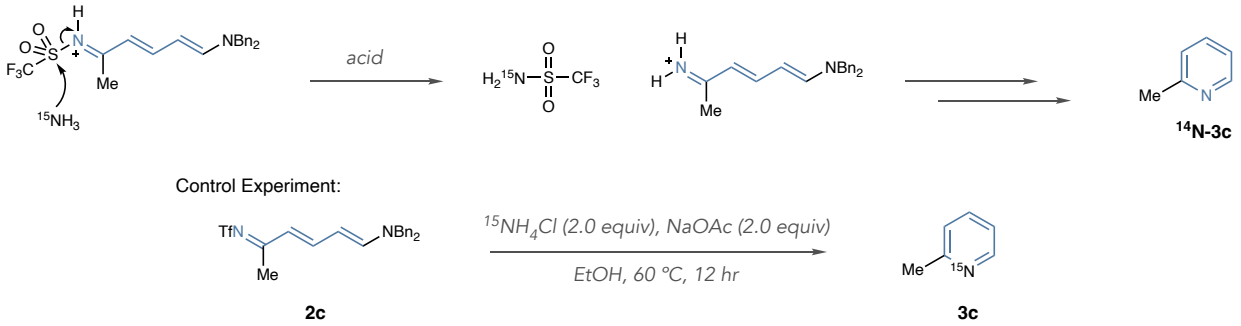
Acid	% **14N-3c**[a]
H_2Bn_2OAc (1 equiv)	0
$HNEt_3OAc$ (1 equiv)	0
H_2NTf (1 equiv)	0
AcOH (1 equiv)	7

[a]Yields obtained by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard

b) Recyclization via a de-triflylation pathway.

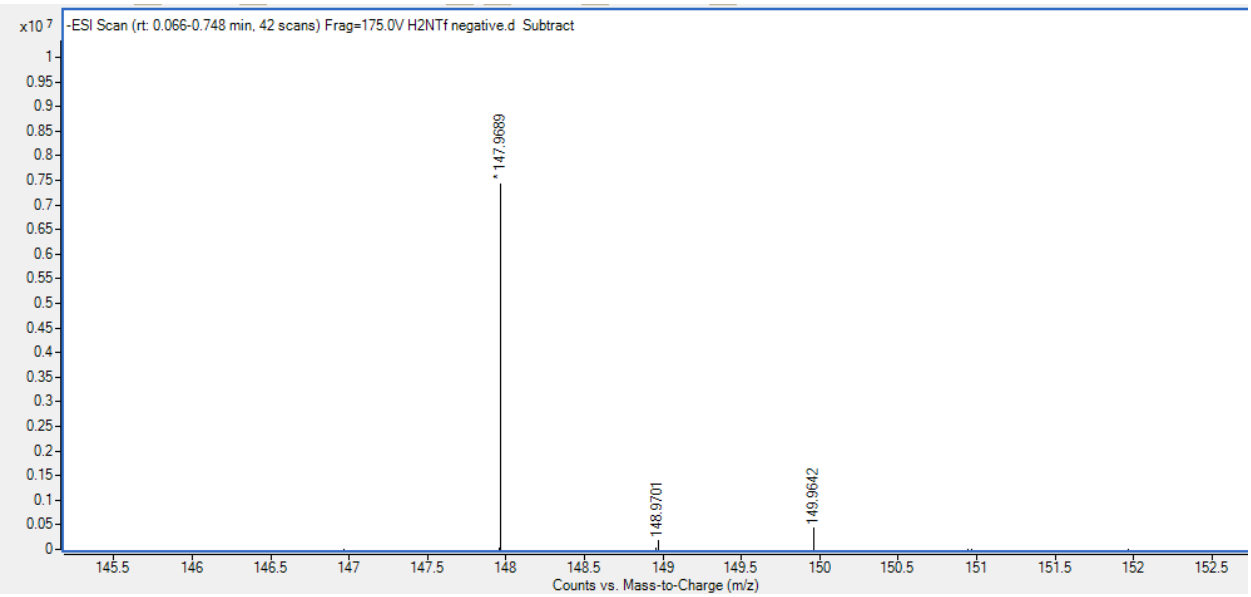
Scheme S1 shows a reaction pathway involving a de-triflylation step that would result in ^{14}N-pyridines and $H_2{}^{15}NTf$ as a reaction byproduct. To probe this scenario, we performed a control reaction with imine **2c** (1.0 equiv) under the general ^{15}N recyclization conditions (2.0 equiv $^{15}NH_4Cl$, 2.0 equiv NaOAc, 0.10 M EtOH, 60 °C, overnight) was set up to determine if any $H_2{}^{15}NTf$ was produced and the crude reaction mixture analyzed using HRMS. The following data indicates that $H_2{}^{15}NTf$ is forming in the reaction and that this pathway could account for incomplete incorporation of ^{15}N during the recyclization process.

Scheme S1. Probing the Possible Recyclization Pathways Resulting in ^{15}N-triflamide Formation



2c **3c**

HRMS spectra of H_2NTf

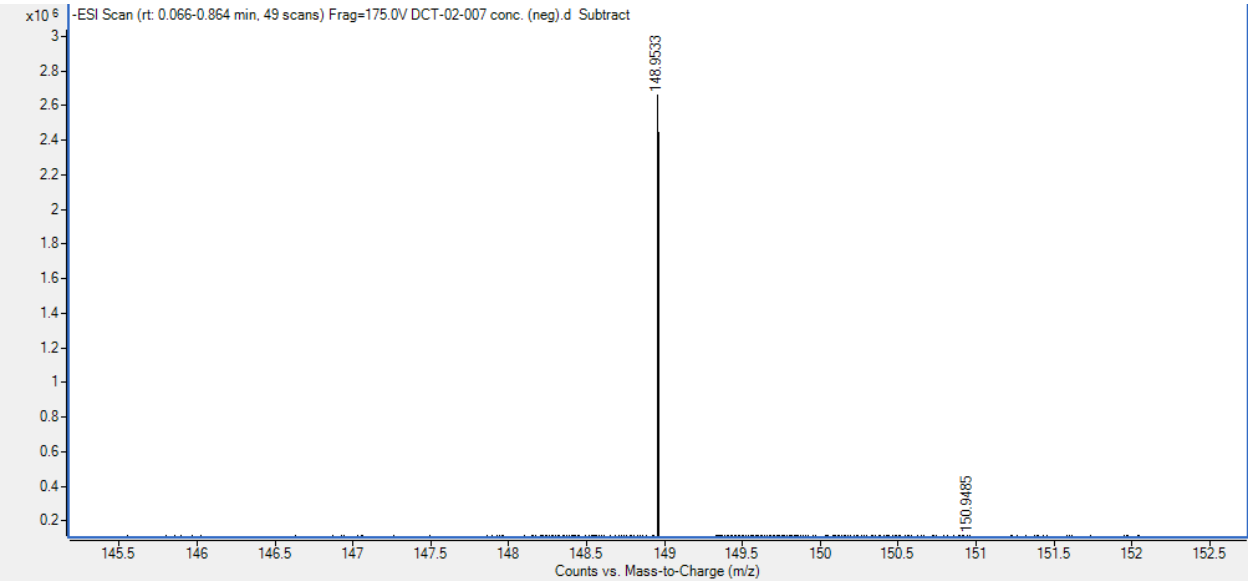


$$\text{Ratio of } [H_2NTf]/[M+1] = \frac{[H_2NTf]}{[M+1]}$$

$$39.96 = \frac{7446406.5}{186339.19}$$

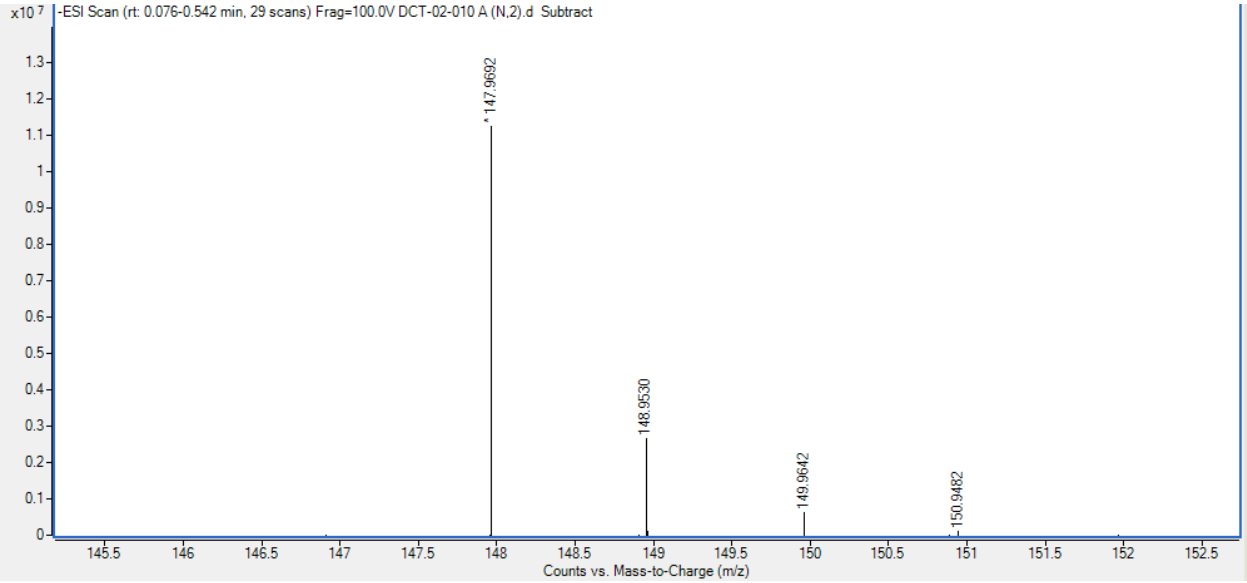
We synthesized an authentic sample of $H_2{}^{15}NTf$ using the method of Bosnidou and Muñiz.[3]

HRMS spectra of $H_2{}^{15}NTf$



To detect if $H_2{}^{15}NTf$ was generated in the reaction, the crude mixture was filtered to remove inorganic salts and then diluted in MeCN and filtered again before running the sample on HRMS.

HRMS of crude reaction mixture of **3c**



$$\text{Ratio of } [H_2NTf]/[M+1] = \frac{[H_2NTf]}{[M+1]}$$

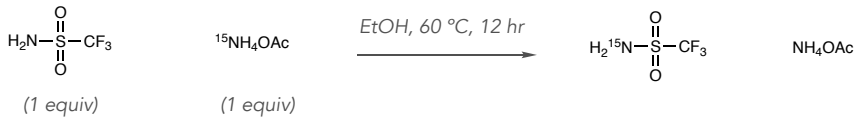
$$4.21 = \frac{11250735}{2675328.75}$$

This corresponds to 18% $H_2{}^{15}NTf$ generated in the ring closing of **2c**, 27% ^{14}N-**3c** is observed.

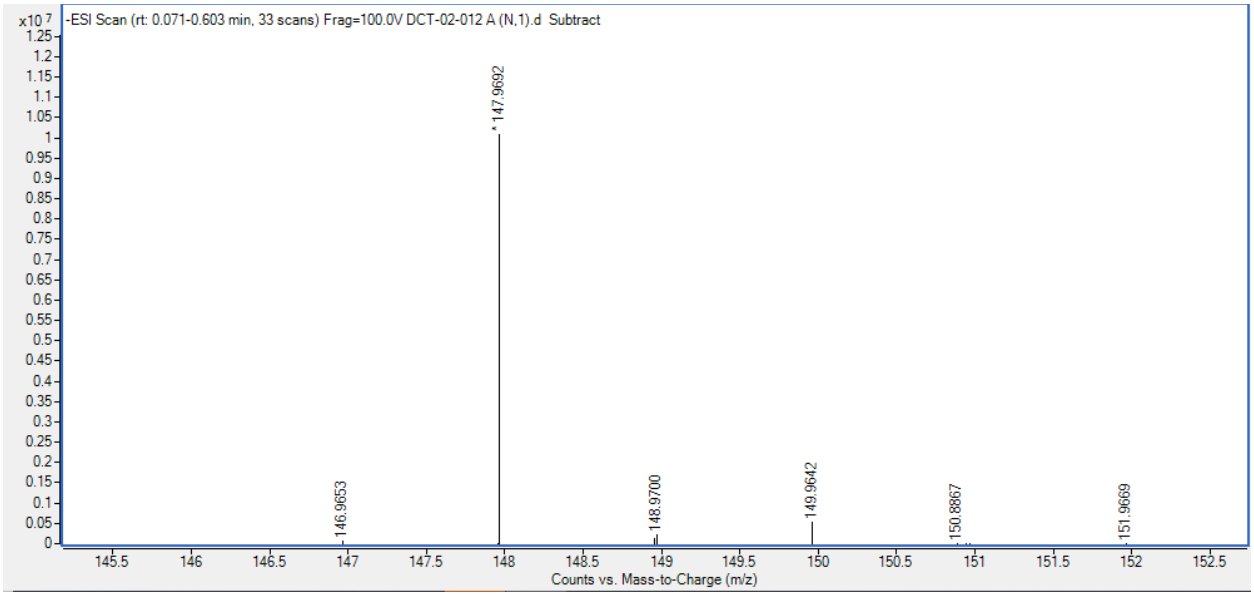
c) Reaction of $H_4{}^{15}NOAc$ with H_2NTf to generate $H_2{}^{15}NTf$.

We considered that the reaction pathway in Scheme S2 could be operative, which would generate *$H_2{}^{15}NTf$* during the course of the reaction and potentially account for incomplete ^{15}N incorporation. We performed the following control reaction and analyzed the crude reaction mixture by HRMS:

Scheme S1. Probing the Possible Recyclization Pathways Resulting in ^{15}N-triflamide Formation



To an oven dried 8 mL vial equipped with stir bar was charged H_2NTf (1.0 equiv), $^{15}NH_4Cl$ (1.0 equiv), NaOAc (1.0 equiv), and EtOH (0.1M). The reaction mixture was heated to 60 °C and let stir for 12 hours. The crude was filtered to remove inorganic salts then diluted with MeCN and filtered again before running the sample on HRMS.



$$\text{Ratio of } [H_2NTf]/[M+1] = \frac{[H_2NTf]}{[M+1]}$$

$$43.01 = \frac{10089815}{234590.05}$$

The ratio of [H_2NTf]/[M+1] in this control is comparable to that of the authentic H_2NTf. On the basis of this control reaction, we exclude a pathway that generates $^{14}NH_4OAc$ from H_2NTf and $^{15}NH_4OAc$ accounts for incomplete ^{15}N incorporation, and prefer the de-triflylation pathway in part b) as the most likely cause of this phenomenon.

A 1.4. Calculation of ^{15}N-incorporation

We obtained %^{15}N incorporation values via HRMS using an Agilent 6224 TOF LC/MS ("OTOF") interfaced to an

Agilent 1200 HPLC with using ESI in positive mode for pyridine product and negative mode for when studying NH_2Tf and $^{15}NH_2Tf$. Our formulas for calculated values are shown below:

Abbreviations used in formulas for ^{15}N incorporation:

0.0107 = natural abundance of ^{13}C
0.4931 = natural abundance of ^{81}Br
0.2423 = natural abundance of ^{37}Cl

N_C = number of carbons in the molecule
N_{Br} = number of bromides in the molecule
N_{Cl} = number of chlorides in the molecule

A_{14N} = abundance of ^{14}N pyridine mass **[M+1]** peak

A_{15N} = abundance of ^{15}N pyridine mass **[M+2]** peak

A_{15N13C} = abundance of $^{15}N^{13}C$ pyridine mass **[M+3]** peak

When applicable, ^{35}Cl is accounted for in A_{14N} , A_{15N} , A_{14N13C} , A_{15N13C}
When applicable, ^{79}Br is accounted for in A_{14N} , A_{15N} , A_{14N13C} , A_{15N13C}

$A_{15N37Cl}$ = abundance of $^{15}N^{37}Cl$ pyridine mass **[M+4]** peak
$A_{15N81Br}$ = abundance of $^{15}N^{81}Br$ pyridine mass **[M+4]** peak

$A_{15N13C37Cl}$ = abundance of $^{15}N^{13}C^{37}Cl$ pyridine mass **[M+5]** peak
$A_{15N13C81Br}$ = abundance of $^{15}N^{13}C^{81}Br$ pyridine mass **[M+5]** peak

$A_{15N37Cl37Cl}$ = abundance of $^{15}N^{37}Cl^{37}Cl$ pyridine mass **[M+6]** peak
$A_{15N37Cl81Br}$ = abundance of $^{15}N^{37}Cl^{81}Br$ pyridine mass **[M+6]** peak

$A_{15N13C37Cl37Cl}$ = abundance of $^{15}N^{13}C^{37}Cl^{37}Cl$ pyridine mass **[M+7]** peak
$A_{15N13C37Cl81Br}$ = abundance of $^{15}N^{13}C^{37}Cl^{81}Br$ pyridine mass **[M+7]** peak

Formula 1- used to calculate ^{15}N incorporation:

$$\%^{15}\text{N incorporation} = \frac{(A_{15N} - ((0.0107 \times N_C) \times A_{14N})) + (A_{15N13C})}{A_{14N} + A_{15N} + A_{15N13C}} \times 100\%$$

accounting for the natural abundance of ^{13}C

$A_{14N} + A_{15N} + A_{15N13C}$: [M+1 peak] [M+2 peak] [M+3 peak]

Formula 2- used to calculate ^{15}N incorporation for substrates containing one bromide:

$$\%^{15}\text{N incorporation} = \frac{(A_{15N} - ((0.0107 \times N_C) \times A_{14N})) + (A_{15N13C} - ((0.4931 \times A_{14N})) + (A_{15N81Br} - ((0.0107 \times N_C) \times (0.4931 \times A_{14N})) + (A_{15N13C81Br})}{A_{14N} + A_{15N} + A_{15N13C} + A_{15N81Br} + A_{15N13C81Br}} \times 100\%$$

accounting for the natural abundance of ^{81}Br
accounting for the natural abundance of ^{13}C
accounting for the natural abundance of ^{13}C with ^{81}Br

$A_{14N} + A_{15N} + A_{15N13C} + A_{15N81Br} + A_{15N13C81Br}$: [M+1 peak] [M+2 peak] [M+3 peak] [M+4 peak] [M+5 peak]

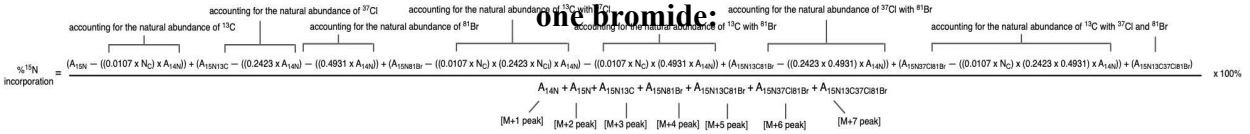
Formula 3- used to calculate ^{15}N incorporation for substrates containing one chloride:

$$\%^{15}\text{N incorporation} = \frac{(A_{15N} - ((0.0107 \times N_C) \times A_{14N})) + (A_{15N13C} - ((0.2423 \times A_{14N})) + (A_{15N37Cl} - ((0.0107 \times N_C) \times (0.2423 \times A_{14N})) + (A_{15N13C37Cl})}{A_{14N} + A_{15N} + A_{15N13C} + A_{15N37Cl} + A_{15N13C37Cl}} \times 100\%$$

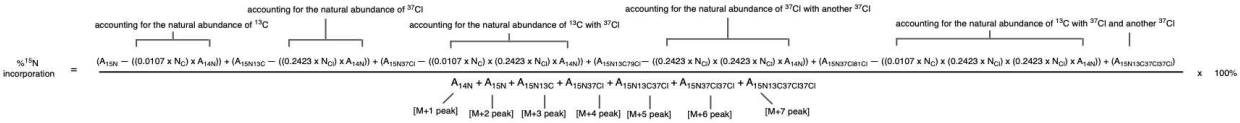
accounting for the natural abundance of ^{37}Cl
accounting for the natural abundance of ^{13}C
accounting for the natural abundance of ^{13}C with ^{37}Cl

$A_{14N} + A_{15N} + A_{15N13C} + A_{15N37Cl} + A_{15N13C37Cl}$: [M+1 peak] [M+2 peak] [M+3 peak] [M+4 peak] [M+5 peak]

Formula 4- used to calculate ^{15}N incorporation for substrates containing one chloride and one bromide:

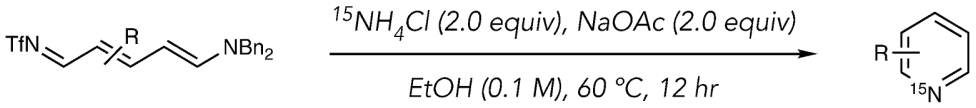


Formula 5- used to calculate ^{15}N incorporation for substrates containing two chlorides:



5. Synthesis of ^{15}N-Pyridines

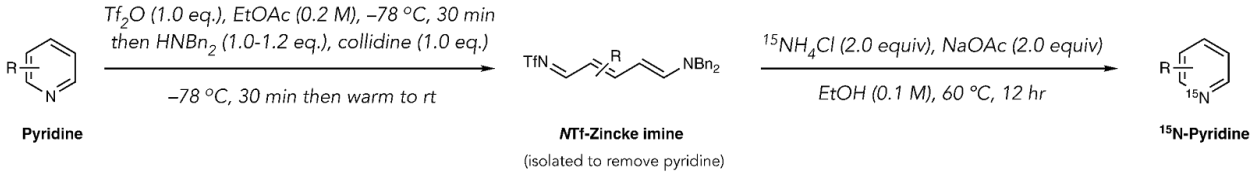
General Procedure B (^{15}N-pyridine formation from isolated *N*Tf-Zincke imines)



***N*Tf-Zincke imine** **^{15}N-Pyridine**

An oven dried 8 mL vial equipped with a stir bar was charged with the *N*Tf Zincke imine (1.0 equiv), $^{15}NH_4Cl$ (2.0 equiv) and NaOAc (2.0 equiv) with EtOH (0.10 M) was stirred at 60 ºC overnight. The reaction was diluted with EtOAc and washed with sodium bicarbonate (3x) followed by a brine wash. The combined organic extract was washed with 10% wt. $CuSO_4$ (3x), and then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography.

General Procedure C (^{15}N-pyridine formation when isolated *N*Tf-Zincke imines have minor impurities)

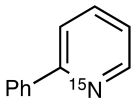


An oven dried round bottom flask with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.10 or 0.20 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before a 1.0 M solution of Bn_2NH (1.0 or 1.2 equiv) was added dropwise followed by collidine (1.0 equiv). The reaction was stirred for a further 30 minutes at –78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring. The reaction was diluted with EtOAc and washed with aqueous sodium bicarbonate (3x) followed by a brine wash. The combined organic extract was washed with 10% wt. $CuSO_4$ (3x), and then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The organic extract was added dropwise to excess hexanes (approx. 100 mL per 1.0 mmol) and the resulting oil was allowed to settle overnight in a –20 ºC fridge. After the oil/precipitate had settled, the hexanes was decanted off and the oil/precipitate washed with hexanes. If the product was an oil, it was dissolved with EtOAc, concentrated *in vacuo*, and dried under vacuum to provide the "Zincke imine" mixture. If the product was a precipitate, it was collected and dried under strong vacuum to provide the "Zincke imine" mixture.

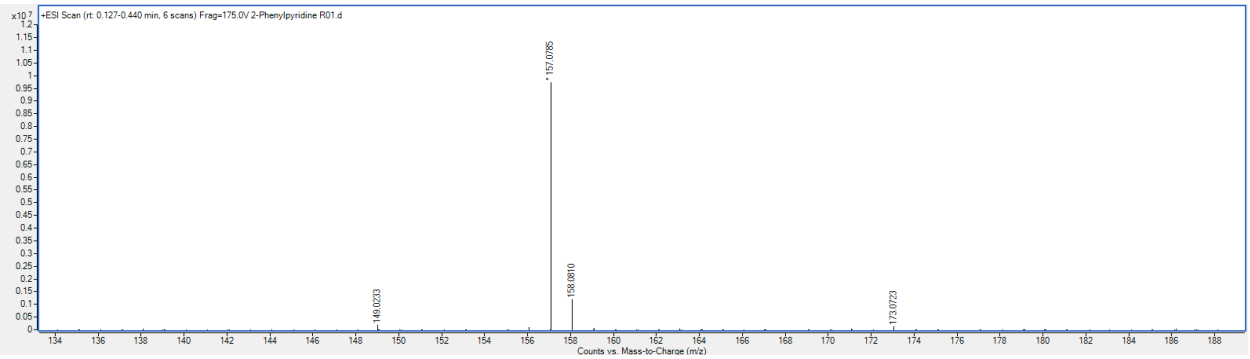
The crude imine mixture was added to an oven dried 8 mL vial and concentrated to remove excess solvent. The vial was charged with a stir bar and diluted with EtOH (0.10 M). $^{15}NH_4Cl$ (2.0 equiv relative to starting heterocycle) and NaOAc (2.0 equiv relative to starting heterocycle) were added

and the reaction mixture allowed to stir at 60 ºC overnight. The reaction was diluted with EtOAc and washed with sodium bicarbonate (3x), followed by a brine wash. The combined organic extract was washed with 10% wt. $CuSO_4$ (3x), and then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography.

2-Phenylpyridine-1-^{15}*N*



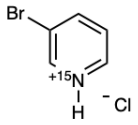
Prepared according to general procedure B using *N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (242 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.0 mmol), NaOAc (82.0 mg, 1.0 mmol). The crude material was purified by automated flash chromatography (silica gel: 0% to 20% EtOAc in hexanes) to afford the title compound as a colorless oil (64.5 mg, 0.42 mmol, 83% yield); IR ν_{max}/cm^{-1} (film): 3060, 2836, 1589, 1561, 1465, 1447, 1024, 1149, 1068, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (ddt, *J* = 11.1, 4.9, 1.4 Hz, 1H), 8.03 – 7.95 (m, 2H), 7.80 – 7.69 (m, 2H), 7.53 – 7.39 (m, 3H), 7.23 (ddt, *J* = 6.7, 4.8, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.21 (d, *J* = 2.3 Hz), 148.35 (d, *J* = 1.2 Hz), 138.51 (d, *J* = 7.1 Hz), 137.11 (d, *J* = 3.2 Hz), 128.47, 128.11, 126.42 (d, *J* = 2.2 Hz), 121.89 (d, *J* = 2.5 Hz), 121.00 (d, *J* = 2.4 Hz), 128.87, 127.05, 122.22, 120.70, 93.03, 55.44; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 306.58 (d, *J* = 11.1 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 157.0785, $C_{11}H_{10}N^{15}N^+$ requires 157.0778, >99% ^{15}N incorporation determined by HRMS.



3a

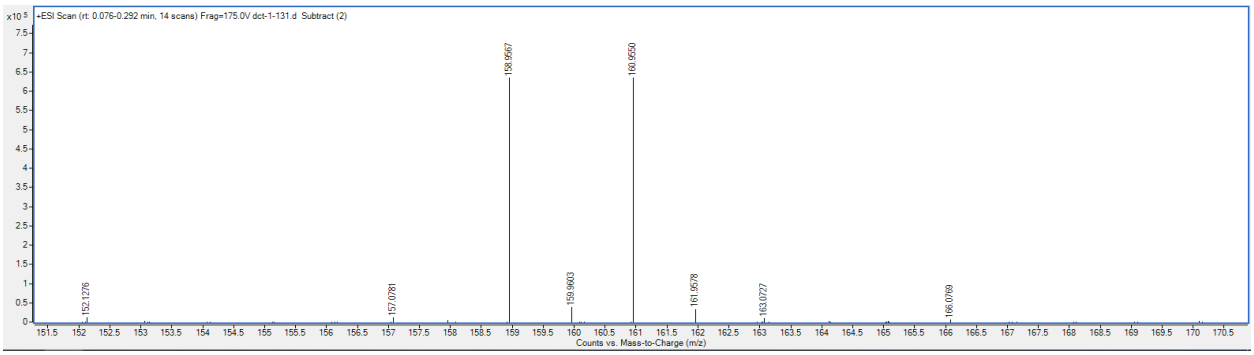
$$\textbf{>99\%}\ ^{15}\text{N incorporation} = \frac{(9736621 - ((0.0107 \times 11) \times 0)) + 1193459.38}{0 + 9736621 + 1193459.38} \times 100\%$$

3-Bromopyridine-1-^{15}N



Prepared according to general procedure C using 3-bromopyridine (48.0 µL, 0.50 mmol), Tf_2O (84.0 µL, 0.50 mmol), dibenzylamine (115 µL, 0.60 mmol), collidine (66.0 µL, 0.50 mmol), EtOAc (2.5 mL, 0.20 M), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 20% EtOAc in hexanes) then treated with 5.0 equiv. of HCl (4.0 M in dioxane) after isolation to afford the title compound as a white solid (44.0 mg, 0.23 mmol, 45% yield); mp: 165 – 166 °C; IR ν_{max}/cm^{-1} (film): 3098, 3008, 2090, 1525, 1357, 1332, 1111, 802, 668; ^{1}H NMR (400 MHz, CD_3OD) δ: 8.83 (s, 1H), 8.71 – 8.34 (m, 2H), 7.68 (dq, J = 9.4, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ: 150.44 (d, J = 4.1 Hz), 145.08 (d, J = 10.9 Hz), 142.25 (d, J = 11.5 Hz), 129.55, 123.74; ^{15}N NMR (40 MHz, $CDCl_3$): ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI)

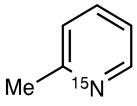
found $[M + H]^+$ 158.9567, $C_5H_5Br^{15}N^+$ requires 158.9570, 99% ^{15}N incorporation determined by HRMS.



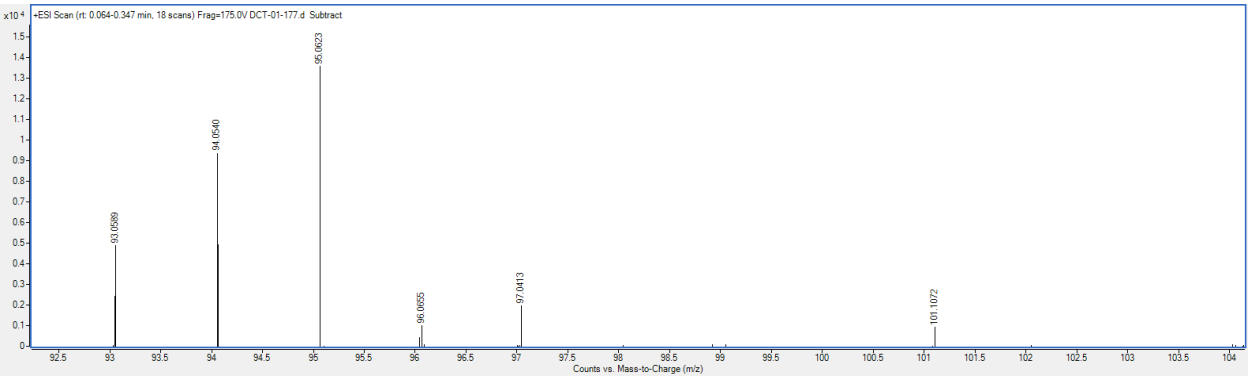
3b

$$\textbf{99\%}\ ^{15}\text{N incorporation} = \frac{(635086.06 - ((0.0107 \times 5) \times 10880.29)) + (38617.27 - (0.4931 \times 10880.29)) + (634874.56 - ((0.0107 \times 5) \times (0.4931 \times 10880.29)) + (33971.88)}{10880.29 + 635086.06 + 38617.27 + 634874.56 + 33971.88} \times 100\%$$

2-Methylpyridine-1-^{15}N



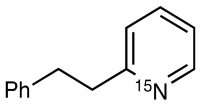
Prepared according to general procedure B using *N*-((2*E*,3*E*,5*E*)-6-(Dibenzylamino)hexa-3,5-dien-2-ylidene)-1,1,1-trifluoromethanesulfonamide (211 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). Yield was determined by ^1H NMR in duplicate due to volatility of the desired product. 1,3,5-Trimethoxybenzene (84.10 mg, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (82% yield - average of two trials: 82% yield and 81% yield); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 95.0623, $C_6H_8{}^{15}N^+$ requires 95.0622, 73% ^{15}N incorporation determined by HRMS.



3c

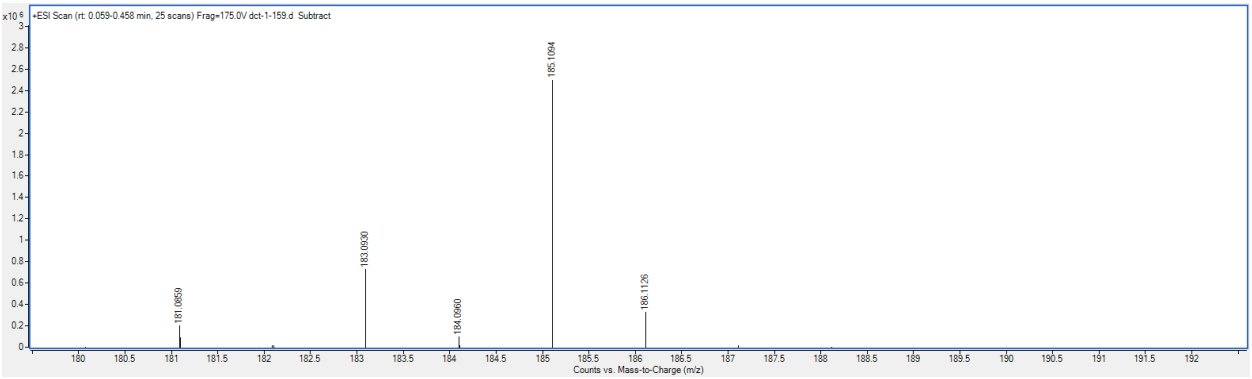
$$\textbf{73\% } ^{15}\text{N incorporation} = \frac{(13595.49 - ((0.0107 \times 6) \times 4931.67)) + 1015.47}{4931.67 + 13595.49 + 1015.47} \times 100\%$$

2-Phenethylpyridine-1-^{15}N



Prepared according to general procedure B using *N*-((3*E*,4*E*,6*E*)-7-(Dibenzylamino)-1-phenylhepta-4,6-dien-3-ylidene)-1,1,1-trifluoromethanesulfonamide (256 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 20% EtOAc in hexanes) to afford the title compound as a yellow oil (82.9 mg, 0.45 mmol, 90% yield); IR ν_{max}/cm^{-1} (film): 3027, 2926,1594, 1475, 1377, 1230, 1184, 1152, 698, 603; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (dd, *J* = 10.4, 5.0 Hz, 1H), 7.69 (td, *J* = 7.7, 1.8 Hz, 1H), 7.40 – 7.16 (m, 7H), 3.33 – 2.86 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.95 (d, *J* = 1.7 Hz), 148.57, 141.28, 137.05 (d, *J* = 3.4 Hz), 128.58, 128.49, 126.15, 123.42 (d, *J* = 2.5 Hz), 121.60 (d, *J* = 2.6 Hz), 39.78 (d, *J* =

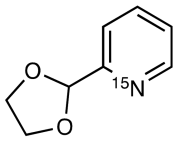
7.9 Hz), 36.22 (d, J = 1.1 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ: 302.92 (d, J = 7.0 Hz); HRMS (ESI + APCI) found $[M + H]^+$ 185.1094, $C_{13}H_{14}{}^{15}N^+$ requires 185.1091, 96% ^{15}N incorporation determined by HRMS.



3d

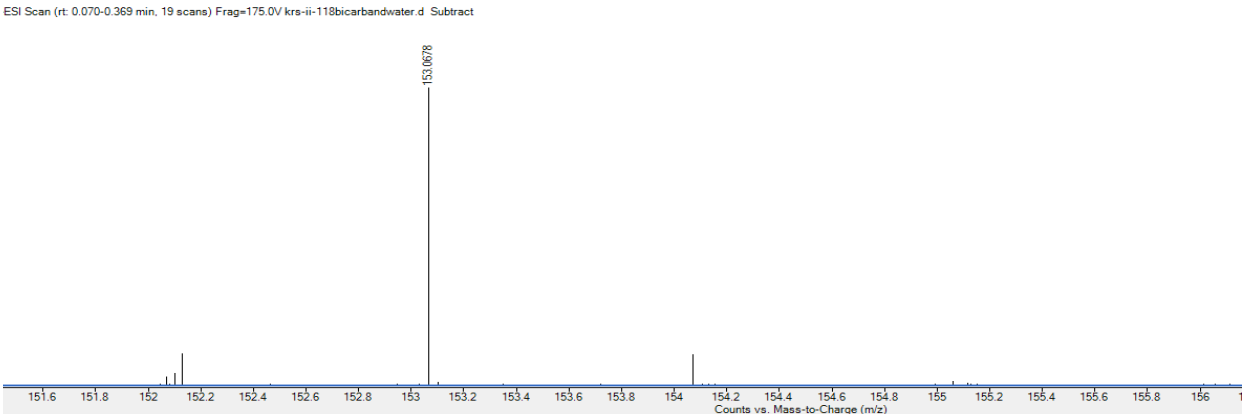
$$\textbf{96\% } ^{15}\text{N incorporation} = \frac{(2500629.25 - ((0.0107 \times 13) \times 99076.64)) + 324850.88}{99076.64 + 2500629.25 + 324850.88} \times 100\%$$

2-(1,3-Dioxolan-2-yl)pyridine -1-^{15}*N*



Prepared according to general procedure B using *N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-(1,3-dioxolan-2-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (240 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.1 mg, 1.00 mmol). Yield was determined by ^{1}H NMR in duplicate due to volatility of the desired product. Mesitylene (70.0 µL, 0.50 mmol, 1.00 equiv) was added as the internal standard for ^{1}H NMR analysis (90%

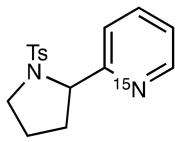
yield - average of two trials: 90% yield and 91% yield). *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 153.0678, $C_8H_9{}^{15}NO_2^+$ requires 153.06, >99% ^{15}N incorporation determined by HRMS.



3e

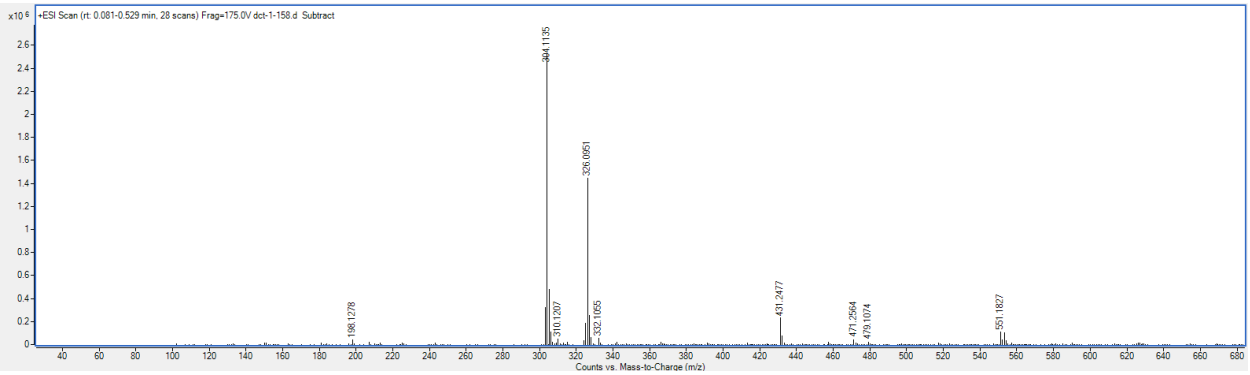
$$\textbf{>99\% } {}^{15}\text{N incorporation} = \frac{(72058.25 - ((0.0107 \times 8) \times 0)) + 5996.89}{0 + 72058.25 + 5996.89} \times 100\%$$

2-(1-Tosylpyrrolidin-2-yl)pyridine-1-^{15}N



Prepared according to general procedure B using *N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-(1-tosylpyrrolidin-2-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (323 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: 40% EtOAc in hexanes) to afford the title compound as a cream solid (121.9 mg, 0.40 mmol, 80% yield); mp:

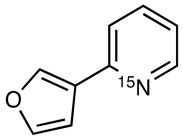
114 – 119 °C; IR ν_{max}/cm^{-1} (film): 3048, 2940, 1585, 1464, 1333, 1160, 1090, 1005, 819, 666, 587; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (dd, *J* = 10.3, 4.9 Hz, 1H), 7.64 – 7.54 (m, 3H), 7.51 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 3H), 7.11 – 6.99 (m, 1H), 4.74 (ddd, *J* = 8.3, 3.8, 1.4 Hz, 1H), 3.57 (ddd, *J* = 9.9, 7.2, 4.4 Hz, 1H), 3.26 (ddd, *J* = 10.0, 8.1, 7.0 Hz, 1H), 2.00 – 1.80 (m, 2H), 1.78 – 1.65 (m, 1H), 1.54 (dtt, *J* = 11.5, 6.9, 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.00 (d, *J* = 1.7 Hz), 148.89, 143.54, 136.64 (d, *J* = 3.1 Hz), 134.30, 129.68, 127.58, 122.04 (d, *J* = 2.5 Hz), 121.09 (d, *J* = 2.2 Hz), 64.54 (d, *J* = 10.9 Hz), 49.66, 33.75, 23.93, 21.51; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 306.20 (d, *J* = 10.9 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 304.1135; $C_{16}H_{19}N^{15}NO_2S^+$ requires 304.1132, 85% ^{15}N incorporation determined by HRMS.



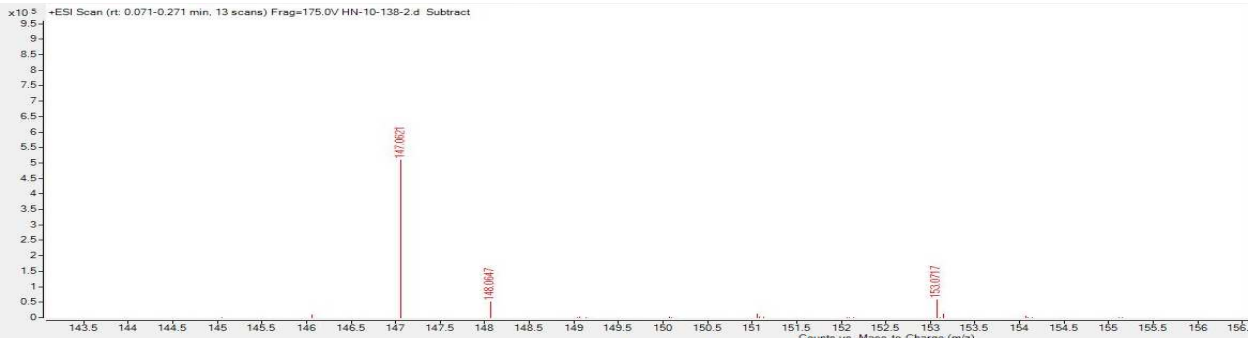
3f

$$\textbf{85\% } ^{15}\text{N incorporation} = \frac{(16265822 - ((0.0107 \times 16) \times 3096453.5)) + 4519571.5}{3096453.5 + 16265822 + 4519571.5} \times 100\%$$

2-(Furan-3-yl)pyridine-1-^{15}N



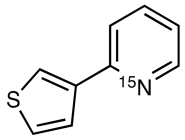
Prepared according to general procedure B using *N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-(furan-3-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (237 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 20% EtOAc in hexanes) to afford the title compound as a brown oil (49.0 mg, 0.34 mmol, 67% yield); IR ν_{max}/cm^{-1} (film): 3061, 2921, 1744, 1604, 1508, 1469, 1187, 1159, 871, 774; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.60 (dddd, *J* = 11.0, 4.9, 1.8, 1.0 Hz, 1H), 8.04 (t, *J* = 1.2 Hz, 1H), 7.68 (td, *J* = 7.7, 1.9 Hz, 1H), 7.51 (t, *J* = 1.8 Hz, 1H), 7.47 (dq, *J* = 7.9, 1.1 Hz, 1H), 7.16 (ddt, *J* = 7.7, 4.9, 1.4 Hz, 1H), 6.91 (dd, *J* = 1.9, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.87 (d, *J* = 1.9 Hz), 149.71, 143.98, 141.31 (d, *J* = 2.9 Hz), 136.74 (d, *J* = 3.1 Hz), 127.15 (d, *J* = 8.4 Hz), 121.84 (d, *J* = 2.6 Hz), 120.24 (d, *J* = 2.2 Hz), 108.70 (d, *J* = 1.9 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ: 302.78 (d, *J* = 10.4 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 147.0621, $C_9H_8{}^{15}NO^+$ requires 147.0571, >99% ^{15}N incorporation determined by HRMS.



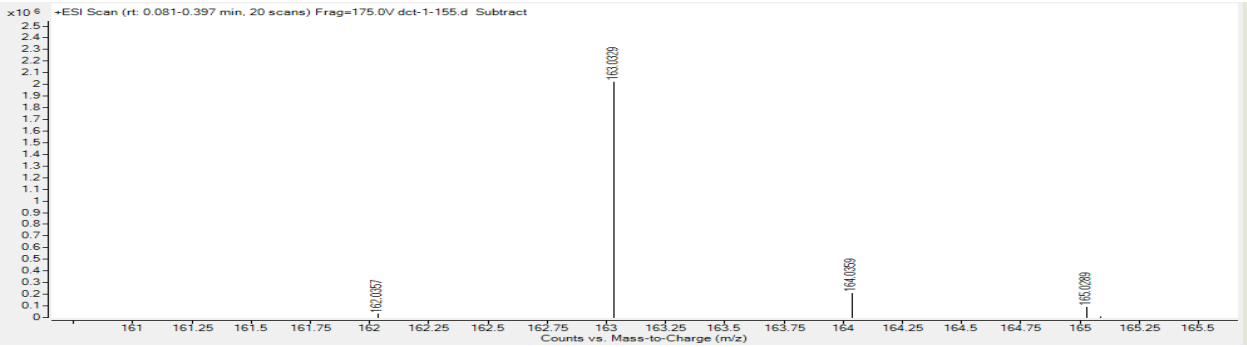
3g

$$\textbf{>99\%}\ ^{15}\text{N incorporation} = \frac{(510364.75 - ((0.0107 \times 9) \times 0)) + 52150.52}{0 + 510364.75 + 52150.52} \times 100\%$$

2-(Thiophen-3-yl)pyridine-1-^{15}N



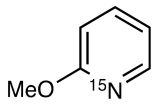
Prepared according to general procedure B using *N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-(thiophen-3-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (245 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 10% EtOAc in hexanes) to afford the title compound as a brown oil (74.2 mg, 0.46 mmol, 91% yield); IR ν_{max}/cm^{-1} (film): 3079, 2923, 1591, 1562, 1462, 1432, 1279, 862, 761; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.62 (ddd, *J* = 12.4, 3.6, 1.4 Hz, 1H), 7.90 (dd, *J* = 3.1, 1.3 Hz, 1H), 7.73 – 7.63 (m, 2H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.39 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.15 (t, *J* = 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.61 (d, *J* = 1.8 Hz), 149.70, 142.28 (d, *J* = 8.2 Hz), 136.81 (d, *J* = 3.0 Hz), 126.41, 126.27 (d, *J* = 2.1 Hz), 123.59 (d, *J* = 2.9 Hz), 121.91 (d, *J* = 2.5 Hz), 120.38 (d, *J* = 2.2 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ: 304.63 (d, *J* = 11.1 Hz); HRMS (ESI + APCI) found $[M + H]^+$ 163.0329, $C_9H_8{}^{15}NS^+$ requires 163.0342, 99% ^{15}N incorporation determined by HRMS.



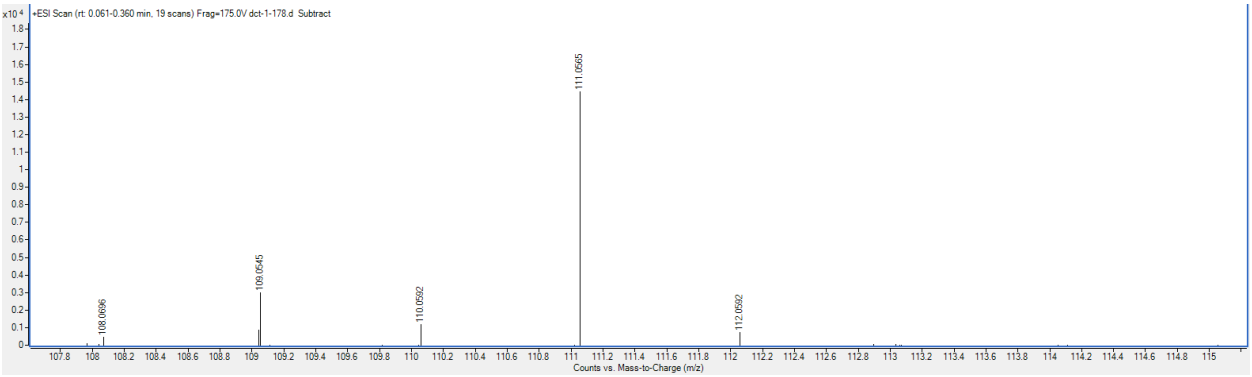
3h

$$\textbf{99\%}\ ^{15}\text{N incorporation} = \frac{(2022638.62 - ((0.0107 \times 9) \times 28534.13)) + 88108.52}{28534.13 + 2022638.62 + 88108.52} \times 100\%$$

2-Methoxypyridine-1-^{15}N



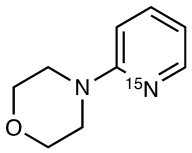
Prepared according to a modified general procedure B, using methyl (1*Z*,2*E*,4*E*)-5-(dibenzylamino)-*N*-((trifluoromethyl)sulfonyl)penta-2,4-dienimidate (219 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol) and stirred at 80 ºC. Yield was determined by ^1H NMR in duplicate due to volatility of the desired product. 1,3,5-Trimethoxybenzene (84.10 mg, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (53% yield - average of two trials: 53% yield and 53% yield). *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 111.0555, $C_5H_8{}^{15}NO^+$ requires 111.0571, 92% ^{15}N incorporation determined by HRMS.



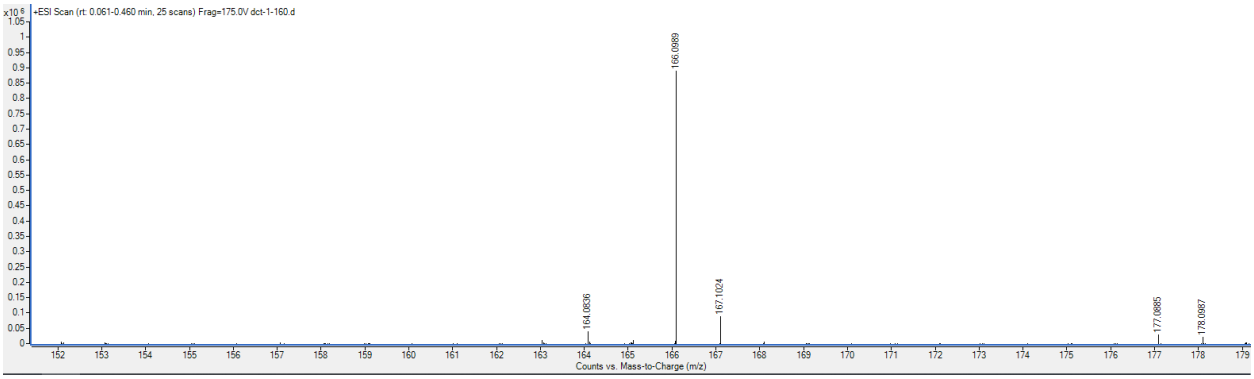
3i

$$\textbf{92\% } {}^{15}\text{N incorporation} = \frac{(14435.71 - ((0.0107 \times 6) \times 1188.9)) + 742.53}{1188.9 + 14435.71 + 742.53} \times 100\%$$

4-(Pyridin-2-yl-^{15}N)morpholine



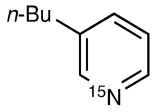
Prepared according to a modified general procedure B using *N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-morpholinopenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (247 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol), and heated to 80 °C for 48 hours. The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 30% EtOAc in hexanes) to afford the title compound as an orange oil (45.0 mg, 0.27 mmol, 54% yield); IR ν_{max}/cm^{-1} (film): 3369, 2971, 2856, 1636, 1594, 1433, 1265, 1241, 1116, 1045, 937, 767; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.20 (td, *J* = 6.8, 1.9 Hz, 1H), 7.64 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 6.79 – 6.70 (m, 2H), 3.83 (t, *J* = 5.2 Hz, 4H), 3.65 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.73, 162.76, 159.66, 144.30 (d, *J* = 4.0 Hz), 140.21, 113.59 (d, *J* = 2.3 Hz), 108.70, 66.52, 46.21 (d, *J* = 1.9 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ: ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 166.0989, $C_9H_{13}N^{15}NO^+$ requires 166.0993, >99% ^{15}N incorporation determined by HRMS.



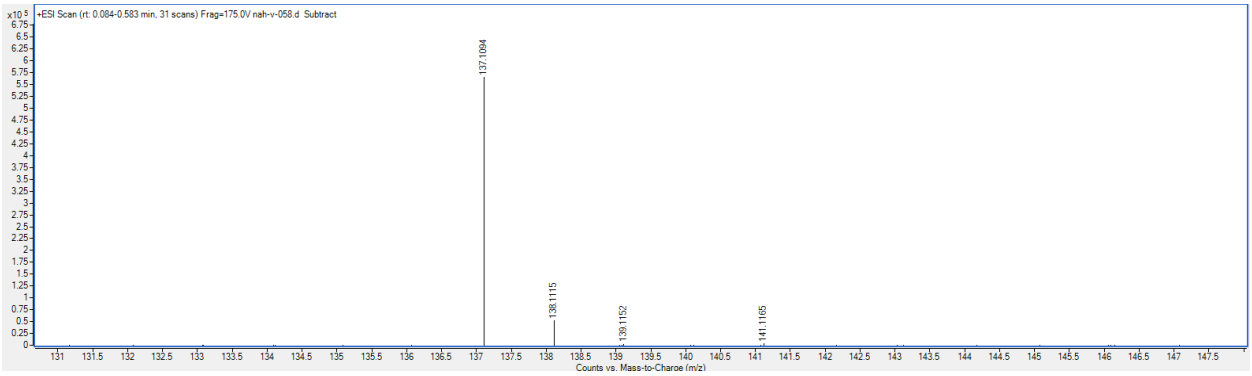
3j

$$\textbf{>99\%}\ ^{15}\text{N incorporation} = \frac{(841516.75 - ((0.0107 \times 9) \times 0)) + 85223.86}{0 + 841516.75 + 85223.86} \times 100\%$$

3-Butylpyridine-1-^{15}N



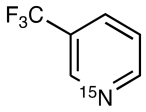
Prepared according to general procedure B using *N*-((1*E*,2*E*)-2-((*E*)-3-(Dibenzylamino)allylidene)hexylidene)-1,1,1-trifluoromethanesulfonamide (232.3 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.1 mg, 1.00 mmol). Yield was determined by ^1H NMR in duplicate due to volatility of the desired product. Mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (78% yield - average of two trials: 77% yield and 78% yield). *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 137.1094, $C_9H_{14}{}^{15}N^+$ requires 137.1091, >99% ^{15}N incorporation determined by HRMS.



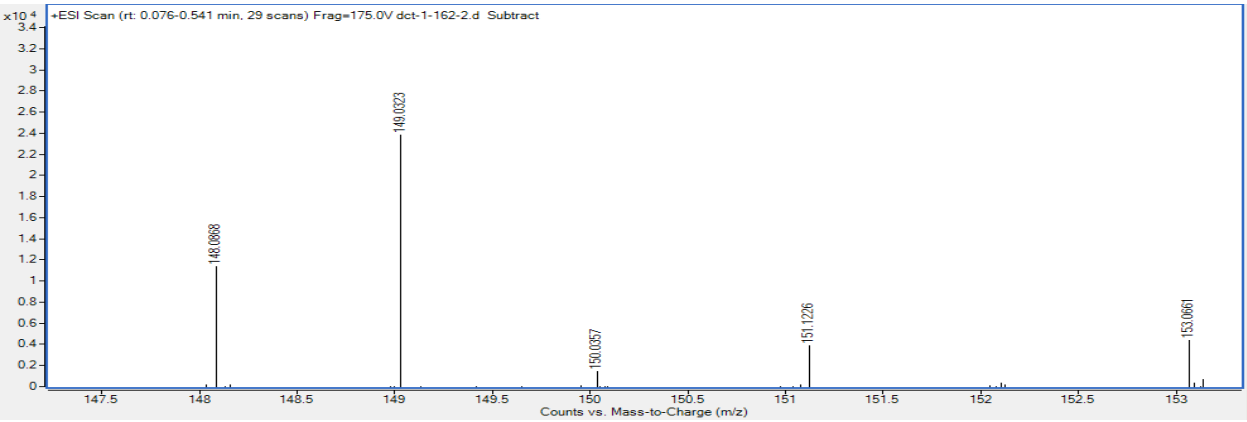
3k

$$\textbf{>99\% } ^{15}\text{N incorporation} = \frac{(855165.88 - ((0.0107 \times 9) \times 0)) + 85331}{0 + 855165.88 + 85331} \times 100\%$$

3-(Trifluoromethyl)pyridine-1-^{15}N



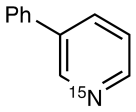
Prepared according to general procedure B using *N*-((1*E*,2*Z*,4*E*)-5-(Dibenzylamino)-2-(trifluoromethyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (238 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.1 mg, 1.00 mmol). Yield was determined by ^1H NMR due to volatility of the desired product. Mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (95% yield). *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 149.0323, $C_6H_5F_3{}^{15}N^+$ requires 149.0339, 87% ^{15}N incorporation determined by HRMS.



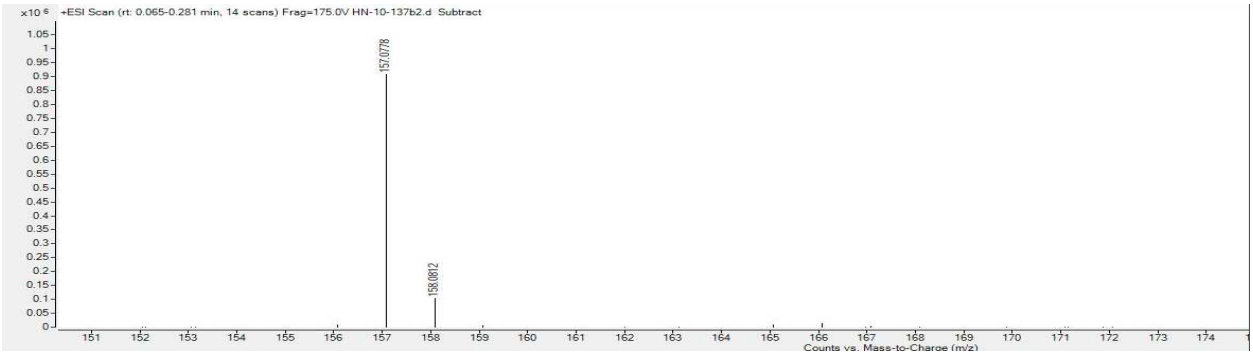
3l

$$\textbf{87\%}\ ^{15}\text{N incorporation} = \frac{(14336.14 - ((0.0107 \times 6) \times 2232.33)) + 1460.4}{2232.33 + 14336.14 + 1460.4} \times 100\%$$

3-Phenylpyridine-1-^{15}N



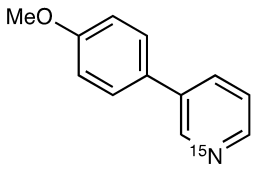
Prepared according to general procedure B using *N*-((1*E*,2*E*,4*E*)-5-(Dibenzylamino)-2-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (484 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 20% EtOAc in hexanes) to afford the title compound as a brown solid (55.8 mg, 0.41 mmol, 81% yield); IR ν_{max}/cm^{-1} (film): 3028, 2919, 2849, 1580, 1470, 1448, 1399, 1002, 751, 696; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.86 (d, *J* = 10.4 Hz, 1H), 8.59 (dd, *J* = 11.0, 4.9 Hz, 1H), 7.87 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.48 (dd, *J* = 8.5, 6.7 Hz, 2H), 7.45 – 7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.45, 148.32, 137.91, 136.81, 134.52 (d, *J* = 3.3 Hz), 129.19, 128.63 (d, *J* = 1.8 Hz), 128.22, 127.26, 123.71, 29.80; ^{15}N NMR (40 MHz, $CDCl_3$) δ: ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 157.0778, $C_{11}H_{10}{}^{15}N^+$ requires 157.0778, >99% ^{15}N incorporation determined by HRMS.



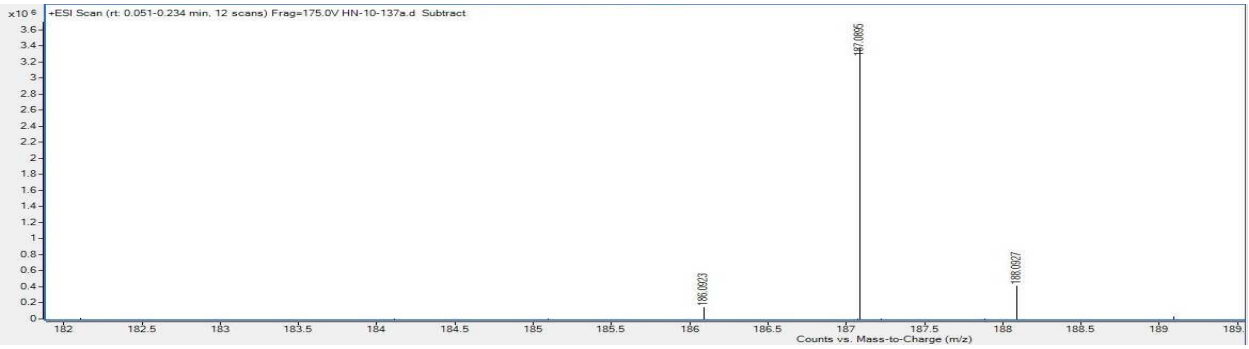
3m

$$\textbf{>99\%}\ {}^{15}\text{N incorporation} = \frac{(907964.75 - ((0.0107 \times 11) \times 0)) + 104337.88}{0 + 907964.75 + 104337.88} \times 100\%$$

3-(4-Methoxyphenyl)pyridine-1-^{15}N



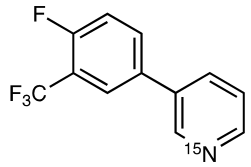
Prepared according to general procedure B using *N*-((1*E*,2*E*,4*E*)-5-(Dibenzylamino)-2-(4-methoxyphenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (514 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 10 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 20% EtOAc in hexanes) to afford the title compound as a brown solid (60.0 mg, 0.33 mmol, 65% yield); mp: 55 – 58 °C; IR ν_{max}/cm^{-1} (film): 3013, 2936, 1604, 1516, 1429, 1280, 1248, 1179, 1027, 800, 720; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.89 – 8.75 (m, 1H), 8.54 (dd, *J* = 10.9, 4.8 Hz, 1H), 7.82 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.56 – 7.45 (m, 2H), 7.41 – 7.29 (m, 1H), 7.09 – 6.84 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.87, 148.07, 147.95, 136.35 (d, *J* = 2.5 Hz), 133.96, 133.93, 130.35, 128.62, 128.32, 123.60 (d, *J* = 2.5 Hz), 114.66, 55.47; ^{15}N NMR (40 MHz, $CDCl_3$) δ: ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 187.0895, $C_{12}H_{12}{}^{15}NO^+$ requires 187.0884, 96% ^{15}N incorporation determined by HRMS.



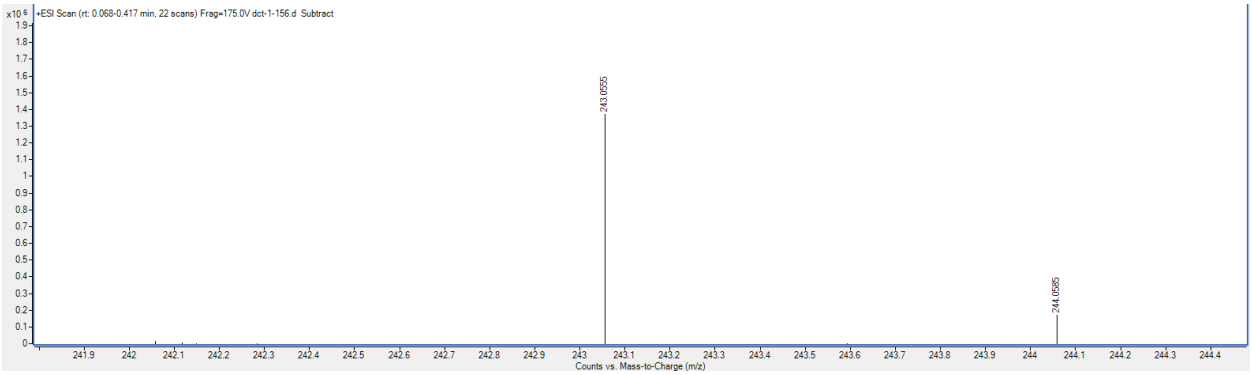
3n

$$\textbf{96\%}\ {}^{15}\text{N incorporation} = \frac{(3369996 - ((0.0107 \times 12) \times 142583.09)) + 414349.94}{142583.09 + 3369996 + 414349.94} \times 100\%$$

3-(4-Fluoro-3-(trifluoromethyl)phenyl)pyridine-1-^{15}N



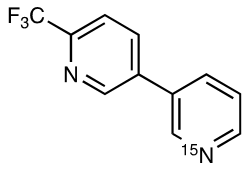
Prepared according to general procedure B using *N*-((1*E*,2*E*,4*E*)-5-(Dibenzylamino)-2-(4-fluoro-3-(trifluoromethyl)phenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (228 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 40% EtOAc in hexanes) to afford the title compound as a brown oil (113 mg, 0.25 mmol, 93% yield); IR ν_{max}/cm^{-1} (film): 3034, 2926, 1507, 1332, 1260, 1246, 1129, 1056, 905, 731, 606; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (d, *J* = 9.8 Hz, 1H), 8.55 (d, *J* = 6.6 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.75 – 7.63 (m, 2H), 7.45 (s, 1H), 7.37 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.30 – 7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.18 (d, *J* = 2.1 Hz), 158.62 (d, *J* = 2.2 Hz), 148.78, 147.65, 134.94 (d, *J* = 3.2 Hz), 134.26 (d, *J* = 4.0 Hz), 132.68 (d, *J* = 8.6 Hz), 128.93 (d, *J* = 6.5 Hz), 126.04 (dd, *J* = 4.7, 1.8 Hz), 124.12, 118.06, 117.85; ^{19}F NMR (375 MHz) δ: –56.59 (d, *J* = 13.2 Hz), –75.32; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 250.08; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 243.0555, $C_{12}H_8F_4{}^{15}N^+$ requires 243.0558, >99% ^{15}N incorporation determined by HRMS.



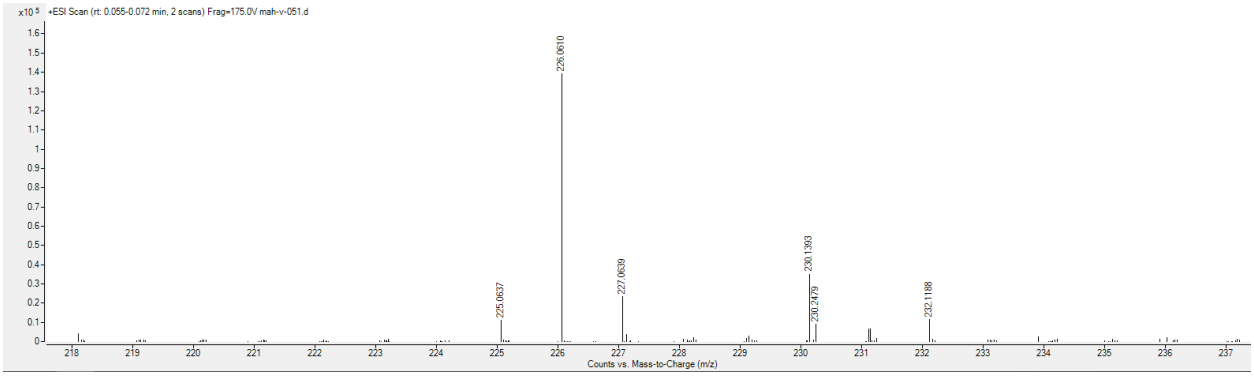
3o

$$\textbf{>99\%}\ ^{15}\text{N incorporation} = \frac{(1372250.12 - ((0.0107 \times 12) \times 0)) + 2581.63}{0 + 1372250.12 + 2581.63} \times 100\%$$

5-(Pyridin-3-yl-^{15}N)-2-(trifluoromethyl)pyridine



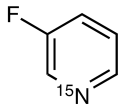
Prepared according to general procedure B using *N*-((1*E*,2*E*,4*E*)-5-(Dibenzylamino)-2-(6-(trifluoromethyl)pyridin-3-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (229.8 mg, 0.42 mmol), EtOH (4.2 mL, 0.10 M),$^{15}NH_4Cl$ (45.2 mg, 0.84 mmol), NaOAc (68.0 mg, 0.84 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 20% to 50% EtOAc in hexanes) to afford the title compound as a cream solid (55.8 mg, 0.25 mmol, 59% yield); mp: 145 – 146 °C; IR ν_{max}/cm^{-1} (film): 3030, 2926, 1339, 1242, 1173, 1088, 1029, 993, 860, 808; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.87 (s, 1H), 8.80 (d, *J* = 10.4 Hz, 1H), 8.69 – 8.60 (m, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.85 (dt, *J* = 6.4, 2.2 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.44 – 7.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.18, 148.36, 148.27, 136.40, 135.72, 134.63 (d, *J* = 3.2 Hz), 132.16, 123.97, 122.87, 120.68 (q, *J* = 2.6, 2.9, 8.2 Hz), 120.15; ^{19}F NMR (375 MHz) δ: –67.84; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 314.05; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 226.0610, $C_{11}H_8F_3N^{15}N^+$ requires 226.0604, 95% ^{15}N incorporation determined by HRMS.



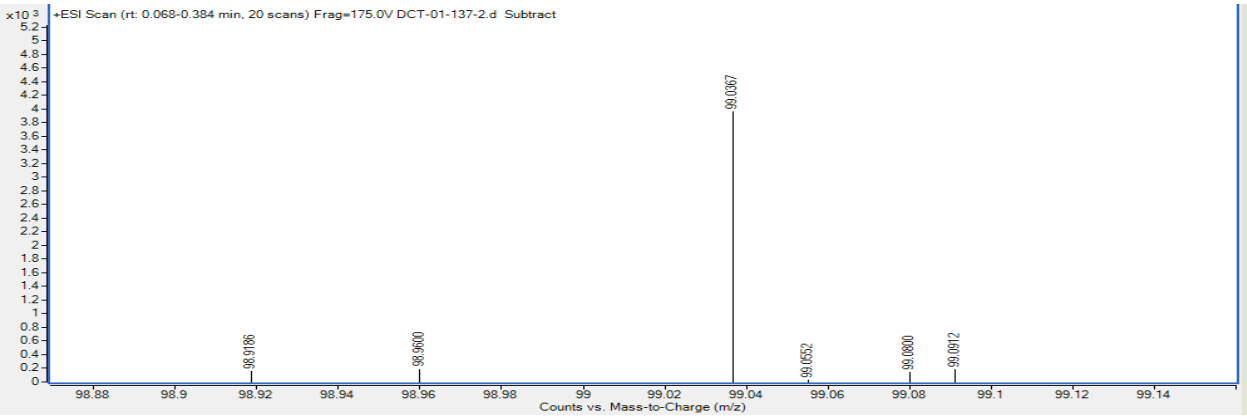
3p

$$\text{95\% } ^{15}\text{N incorporation} = \frac{(4534793.5 - ((0.0107 \times 11) \times 218384.34)) + 431245.16}{218384.34 + 4534793.5 + 431245.16} \times 100\%$$

3-Fluoropyridine-1-^{15}N



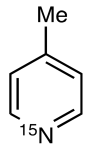
Prepared according to general procedure C (except with 1.0 equiv of dibenzylamine) using 3-fluoropyridine (430 µL, 5.00 mmol), Tf_2O (840 µL, 5.00 mmol), dibenzylamine (943 µL, 5.00 mmol), collidine (660 µL, 5.00 mmol), EtOAc (25 mL, 0.20 M), EtOH (50 mL, 0.10 M),$^{15}NH_4Cl$ (545 mg, 10.0 mmol), NaOAc (820 mg, 10.0 mmol). Yield was determined by ^1H NMR in duplicate due to volatility of the desired product. Mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (38% yield - average of two trials: 37% yield and 39% yield); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 99.0367, $C_5H_5F^{15}N^+$ requires 99.0371, >99% ^{15}N incorporation determined by HRMS.



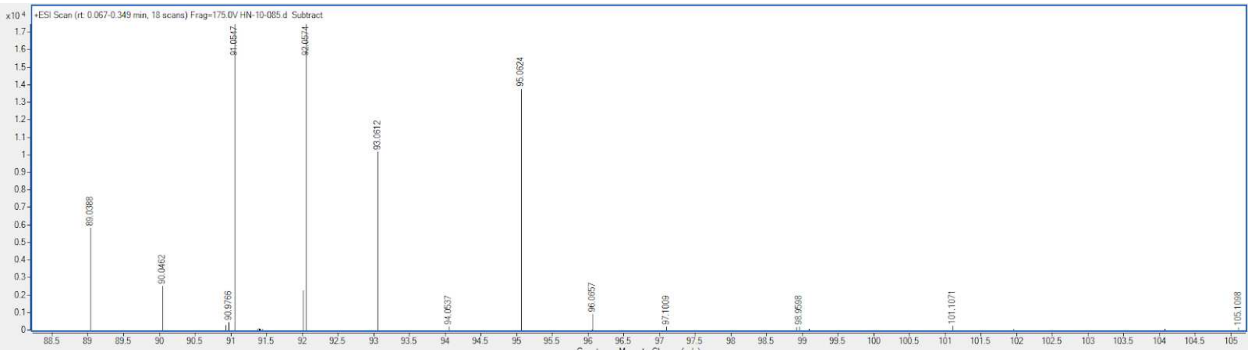
3q

$$\textbf{>99\%}\ ^{15}\text{N incorporation} = \frac{(3962.67 - ((0.0107 \times 5) \times 0)) + 35.54}{0 + 3962.67 + 35.54} \times 100\%$$

4-Methylpyridine-1-^{15}N



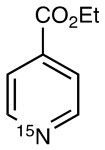
Prepared according to general procedure B using *N*-Benzyl-*N*-((2*E*,4*E*)-5-(dibenzylamino)-3-methylpenta-2,4-dien-1-ylidene)-1-phenylmethanaminium trifluoromethanesulfonate (310 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). Yield was determined by ^1H NMR in duplicate due to volatility of the desired product. 1,3,5-Tristrifluoromethylbenzene (93.2 µL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (78% yield - average of two trials: 79% yield and 77% yield); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 95.0624, $C_6H_8{}^{15}N^+$ requires 95.0622, 99% ^{15}N incorporation determined by HRMS.



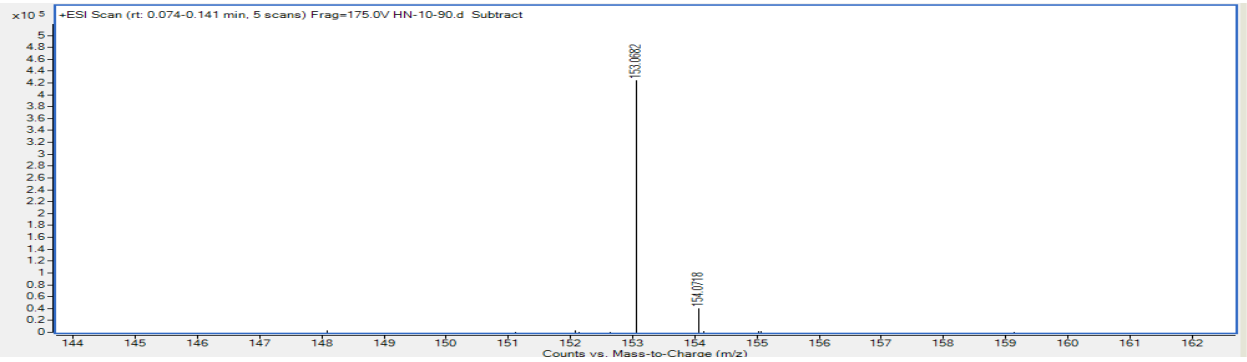
3r

$$\textbf{99\%}\ {}^{15}\text{N incorporation} = \frac{(15387.57 - ((0.0107 \times 6) \times 172.15)) + 350.3}{172.15 + 15387.57 + 350.3} \times 100\%$$

Ethyl isonicotinate-1-^{15}N



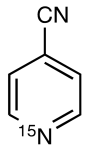
Prepared according to a modified general procedure B using *N*-Benzyl-*N*-((2*Z*,4*E*)-5-(dibenzylamino)-3-(ethoxycarbonyl)penta-2,4-dien-1-ylidene)-1-phenylmethanaminium trifluoromethanesulfonate (339 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M), $^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol), heated to 60 °C for 1 hour. Yield was determined by ^1H NMR in duplicate due to volatility of the desired product. 1,3,5-tristrifluoromethylbenzene (93.2 µL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (99.5% yield - average of two trials: 99% yield and 100% yield); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 153.0682, $C_8H_{10}{}^{15}NO_2{}^+$ requires 153.0676, >99% ^{15}N incorporation determined by HRMS.



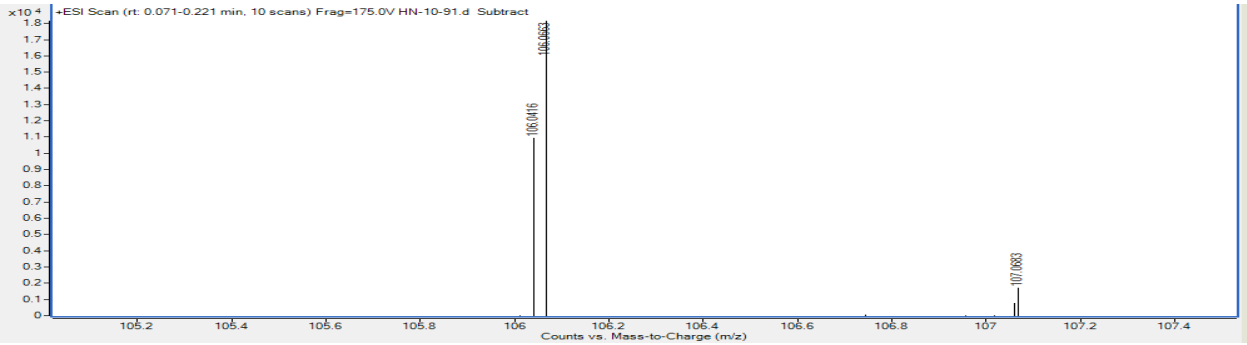
3s

$$\text{>99\% } ^{15}\text{N incorporation} = \frac{(424396.25 - ((0.0107 \times 8) \times 0)) + 40320.82}{0 + 424396.25 + 40320.82} \times 100\%$$

Isonicotinonitrile-1-^{15}N



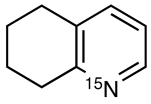
Prepared according to a modified general procedure B using *N*-Benzyl-*N*-((2*Z*,4*E*)-3-cyano-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1-phenylmethanaminium trifluoromethanesulfonate (316 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol), heated to 60 ºC for 1 hour. Yield was determined by ^1H NMR in duplicate due to volatility of the desired product. 1,3,5-Tristrifluoromethylbenzene (93.2 µL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (68% yield - average of two trials: 65% yield and 70% yield); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 106.0416, $C_6H_5N^{15}N^+$ requires 106.0418, >99% ^{15}N incorporation determined by HRMS.



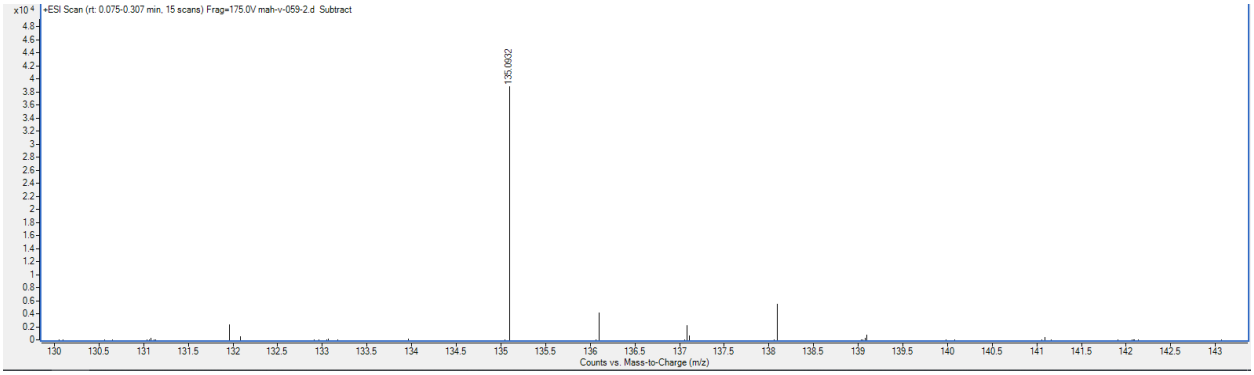
3t

>99% ^{15}N incorporation = $\frac{(36086.81 - ((0.0107 \times 6) \times 0)) + 1706.64}{0 + 36086.81 + 1706.64}$ x 100%

5,6,7,8-Tetrahydroquinoline-1-^{15}N



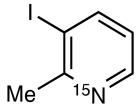
Prepared according to general procedure B using *N*-((1*E*,2*Z*)-2-((*E*)-3-(Dibenzylamino)allylidene)cyclohexylidene)-1,1,1-trifluoromethanesulfonamide (231.1 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.1 mg, 1.00 mmol). Yield was determined by ^1H NMR in duplicate due to volatility of the desired product. Mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (94.5% yield - average of two trials: 94% yield and 95% yield). *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 135.0932, $C_9H_{12}{}^{15}N^+$ requires 135.0935, 99% ^{15}N incorporation determined by HRMS.



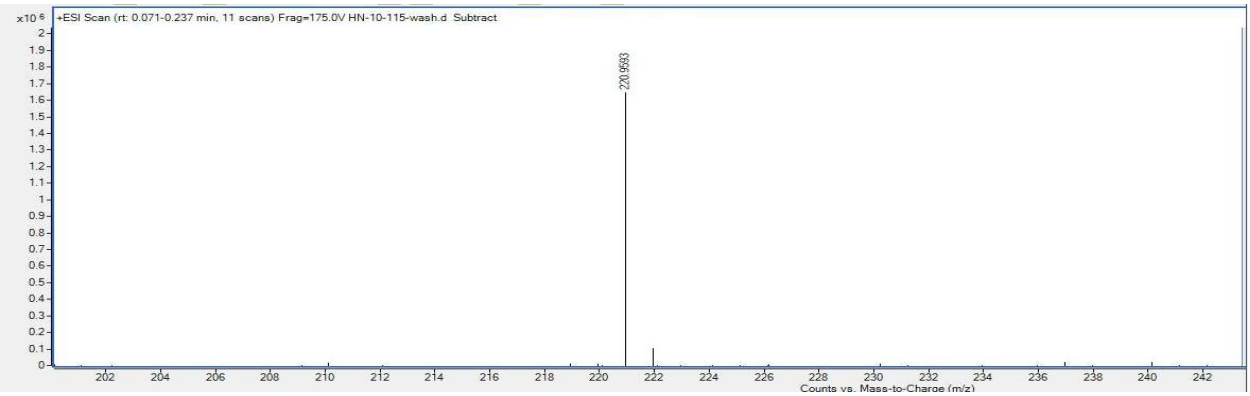
3u

$$\textbf{99\% } {}^{15}\text{N incorporation} = \frac{(72552.34 - ((0.0107 \times 9) \times 883.07)) + 3762.85}{883.07 + 72552.34 + 3762.85} \times 100\%$$

3-Iodo-2-methylpyridine-1-^{15}N



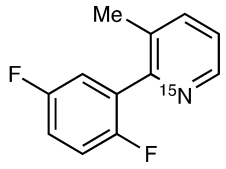
Prepared according to general procedure B using *N*-((2*E*,3*Z*,5*E*)-6-(Dibenzylamino)-3-iodohexa-3,5-dien-2-ylidene)-1,1,1-trifluoromethanesulfonamide (274 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.0 mmol), NaOAc (82.0 mg, 1.0 mmol). Yield was determined by ^1H NMR due to volatility of the desired product. 1,3,5-Tristrifluoromethylbenzene (93.2 µL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (78% yield); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 220.9593, $C_6H_7I^{15}N^+$ requires 220.9588, >99% ^{15}N incorporation determined by HRMS.



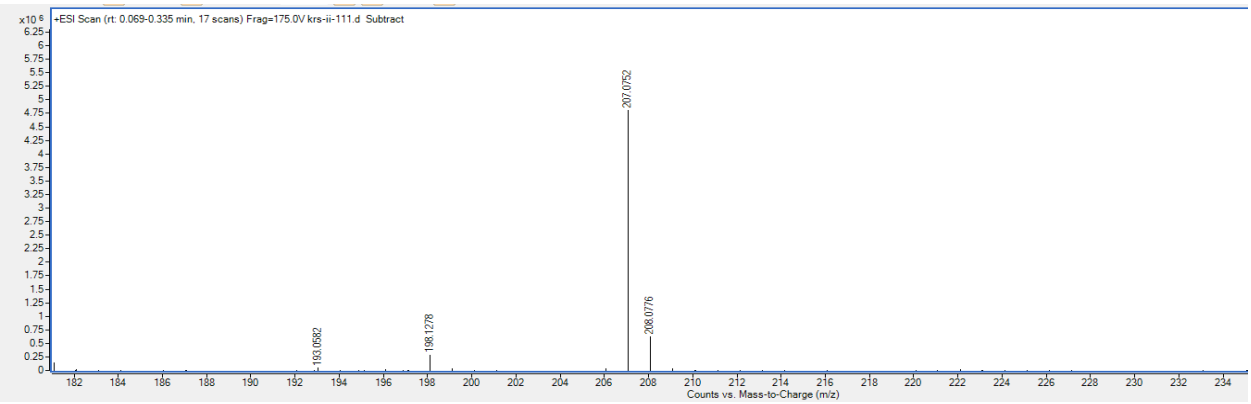
3v

$$\textbf{>99\% } ^{15}\text{N incorporation} = \frac{(1648700.62 - ((0.0107 \times 6) \times 0)) + 104685.4}{0 + 1648700.62 + 104685.4} \times 100\%$$

2-(2,5-Difluorophenyl)-3-methylpyridine-1-^{15}N



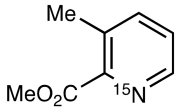
Prepared according to general procedure B using *N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-(2,5-difluorophenyl)-2-methylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (267 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.0 mmol), NaOAc (82.0 mg, 1.0 mmol). The crude material was purified by automated flash chromatography (silica gel: 20% EtOAc in hexanes) to afford the title compound as a brown oil (87.0 mg, 0.42 mmol, 84% yield); IR ν_{max}/cm^{-1} (film): 3049, 2927, 1568, 1496, 1436, 1245, 1182, 1171, 780, 629; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.53 (dd, *J* = 11.1, 4.8 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.28 – 7.19 (m, 1H), 7.11 (dddd, *J* = 21.5, 9.6, 4.9, 2.8 Hz, 3H), 2.25 (d, *J* = 1.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.99 (d, *J* = 2.4 Hz), 157.58 (d, *J* = 2.4 Hz), 155.79 (d, *J* = 243.1 Hz), 152.99 (t, *J* = 1.8 Hz), 147.17, 138.20 (d, *J* = 3.1 Hz), 132.77, 130.17 – 127.03 (m), 123.25 (d, *J* = 2.5 Hz), 117.83 (ddd, *J* = 24.3, 4.3, 1.4 Hz), 116.73 (td, *J* = 24.3, 8.6 Hz), 18.91 (d, *J* = 4.\5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.30, -118.90 – -119.18 (m), -121.44 (dq, *J* = 18.8, 6.4 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ: 313.64; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 207.0752, $C_{12}H_9F_2{}^{15}N^+$ requires 207.0746, >99% ^{15}N incorporation determined by HRMS.



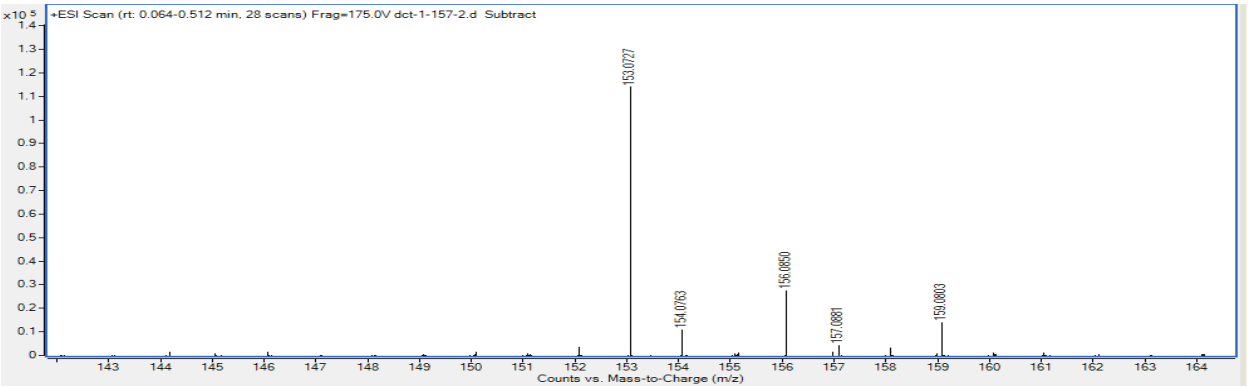
3w

$$\textbf{>99\%}\ ^{15}\text{N incorporation} = \frac{(5125385.5 - ((0.0107 \times 12) \times 0)) + 1770}{0 + 5125385.5 + 1770} \times 100\%$$

Methyl 3-methylpicolinate-1-^{15}N



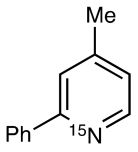
Prepared according to general procedure B using methyl (2*Z*,3*E*,5*E*)-6-(dibenzylamino)-3-methyl-2-(((trifluoromethyl)sulfonyl)imino)hexa-3,5-dienoate (240 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.1 mg, 1.00 mmol). Yield was determined by ^1H NMR due to volatility of the desired product. 1,3,5-Trimethoxybenzene (84.10 mg, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (92%) *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 153.0727, $C_8H_{10}{}^{15}NO_2^+$ requires 153.0676, >99% ^{15}N incorporation determined by HRMS.



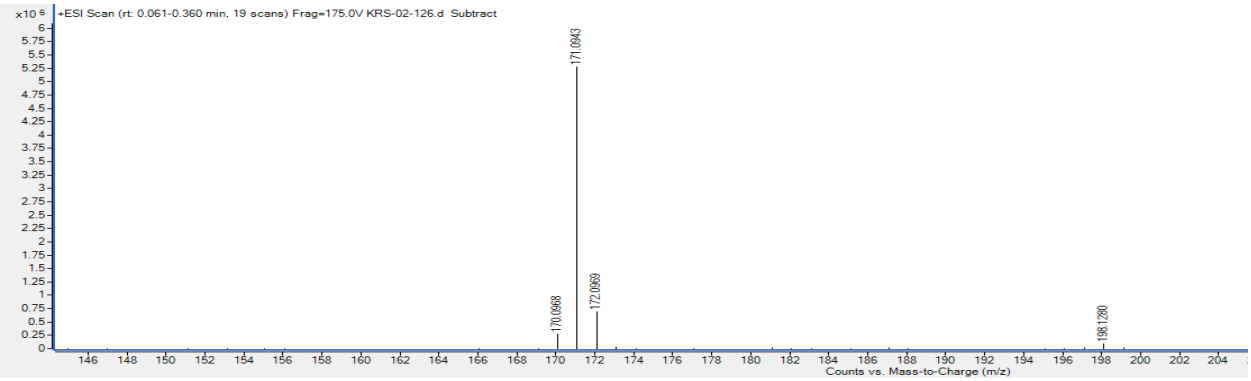
3x

$$\textbf{>99\%}\ ^{15}\text{N incorporation} = \frac{(113914.59 - ((0.0107 \times 8) \times 0)) + 10778.46}{0 + 113914.59 + 10778.46} \times 100\%$$

4-Methyl-2-phenylpyridine-1-^{15}N



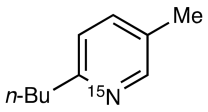
Prepared according to general procedure B using *N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-3-methyl-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (249 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 10% EtOAc in hexanes) to afford the title compound as a brown oil (78.2 mg, 0.46 mmol, 91% yield); IR ν_{max}/cm^{-1} (film): 3057, 2921, 2211, 1599, 1444, 907, 773, 729, 692, 588; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (dd, *J* = 11.0, 5.1 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.35 – 7.13 (m, 4H), 6.83 (dtd, *J* = 5.1, 1.6, 0.8 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.33 (d, *J* = 1.6 Hz), 149.40, 147.82, 147.79, 139.56, 139.48, 128.86, 128.72, 126.97 (d, *J* = 2.4 Hz), 123.17 (d, *J* = 2.6 Hz), 121.56 (d, *J* = 2.4 Hz), 21.24; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 297.92 (d, *J* = 11.0 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 171.0943, $C_{12}H_{11}{}^{15}N^+$ requires 171.0935, 95% ^{15}N incorporation determined by HRMS.



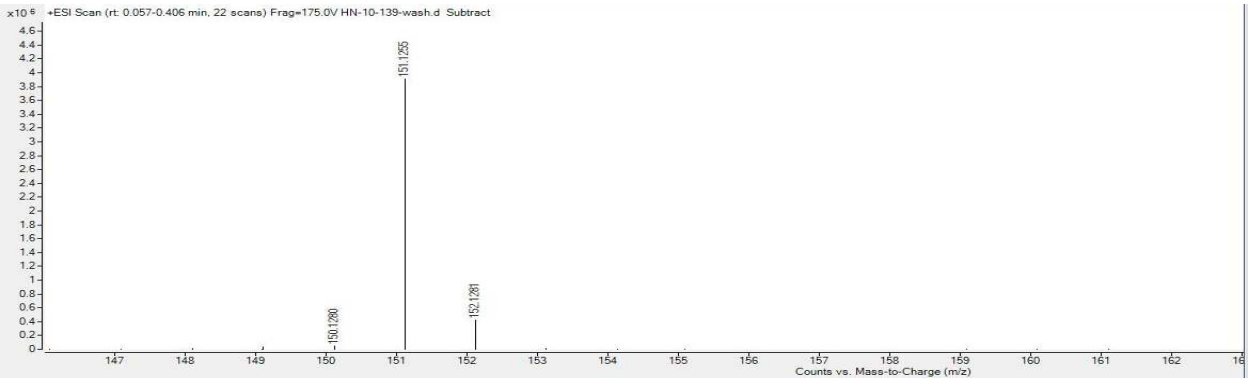
3y

$$\textbf{95\%}\ ^{15}\text{N incorporation} = \frac{(6773756 - ((0.0107 \times 12) \times 343723.75)) + 785811.31}{343723.75 + 6773756 + 785811.31} \times 100\%$$

2-Butyl-5-methylpyridine-1-^{15}N



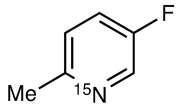
Prepared according to general procedure B using *N*-((1*E*,3*E*,5*E*)-1-(Dibenzylamino)-2-methylnona-1,3-dien-5-ylidene)-1,1,1-trifluoromethanesulfonamide (478 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). Yield was determined by ^1H NMR due to volatility of the desired product. 1,3,5-Tristrifluoromethylbenzene (93.2 μL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (83% yield); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 151.1255, $C_{10}H_{16}{}^{15}N^+$ requires 151.1248, 99% ^{15}N incorporation determined by HRMS.



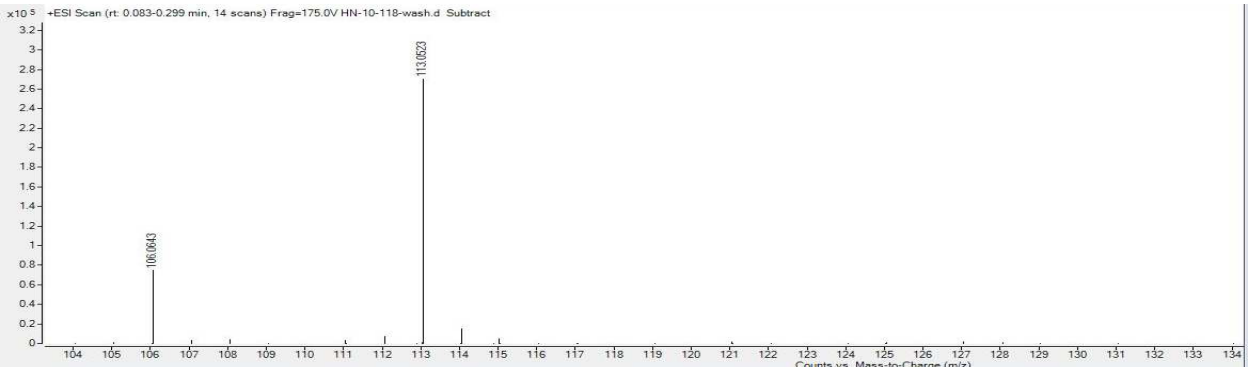
3z

$$\textbf{99\%}\ ^{15}\text{N incorporation} = \frac{(3907158 - ((0.0107 \times 10) \times 52164.77)) + 417680.41}{52164.77 + 3907158 + 417680.41} \times 100\%$$

5-Fluoro-2-methylpyridine-1-^{15}N



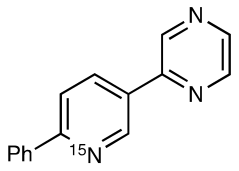
Prepared according to general procedure B using *N*-((2*E*,3*E*,5*Z*)-6-(Dibenzylamino)-5-fluorohexa-3,5-dien-2-ylidene)-1,1,1-trifluoromethanesulfonamide (220 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). Yield was determined by ^1H NMR due to volatility of the desired product. 1,3,5-Tristrifluoromethylbenzene (93.2 μL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (90% yield); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 113.0523, $C_6H_7F^{15}N^+$ requires 113.0527, >99% ^{15}N incorporation determined by HRMS.



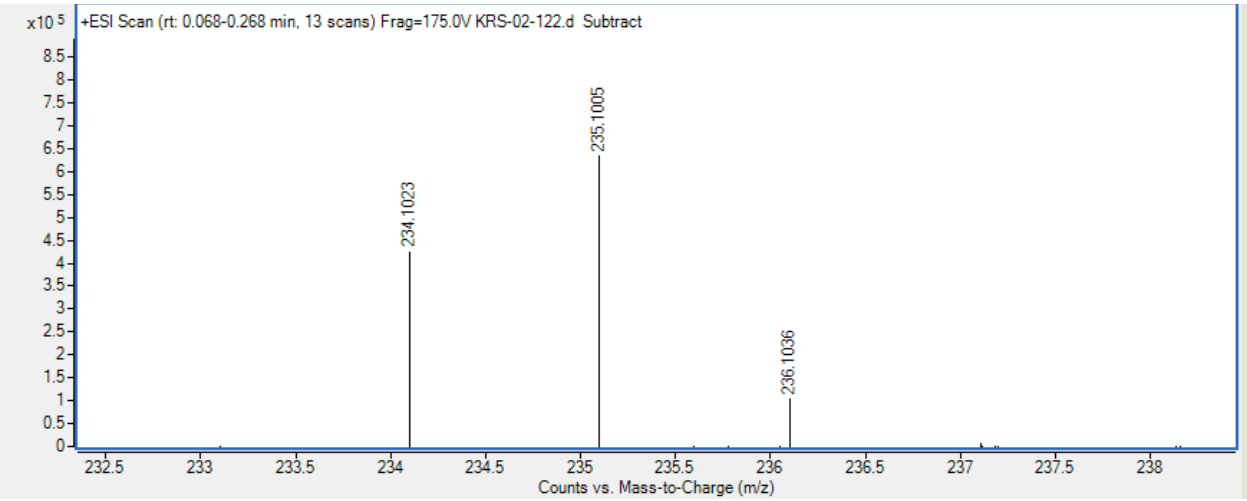
3aa

>99% ^{15}N incorporation = $\frac{(17087.53 - ((0.0107 \times 6) \times 0)) + 1593.69}{0 + 17087.53 + 1593.69}$ x 100%

2-(6-Phenylpyridin-3-yl-1-15*N*)pyrazine



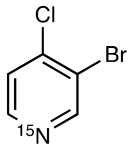
Prepared according to general procedure C using 2-(6-phenylpyridin-3-yl)pyrazine (117 mg, 0.50 mmol), Tf_2O (83.8 µL, 0.50 mmol), dibenzylamine (115 µL, 0.60 mmol), collidine (66.0 µL, 0.50 mmol), EtOAc (2.5 mL, 0.20 M), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 50% to 70% EtOAc in hexanes) to afford the title compound as a yellow solid (74.9 mg, 0.32 mmol, 63% yield); mp: 146 – 149 ^{o}C; IR ν_{max}/cm^{-1} (film): 3054.90, 2361.10, 1954.22, 1591.60, 1465.32, 1011.84, 837.43, 733.51, 688.79; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.11 – 9.06 (m, 1H), 8.86 (s, 1H), 8.43 (s, 1H), 8.32 (s, 1H), 8.14 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.87 – 7.79 (m, 2H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.30 – 7.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.41, 150.40, 148.00, 144.59, 143.60, 141.93, 138.59, 135.11, 130.34, 129.56, 128.92, 127.09, 120.50; ^{15}N NMR (40 MHz, $CDCl_3$): ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 235.1005, $C_{15}H_{11}N_2{}^{15}N^+$ requires 235.0996, 58% ^{15}N incorporation determined by HRMS.



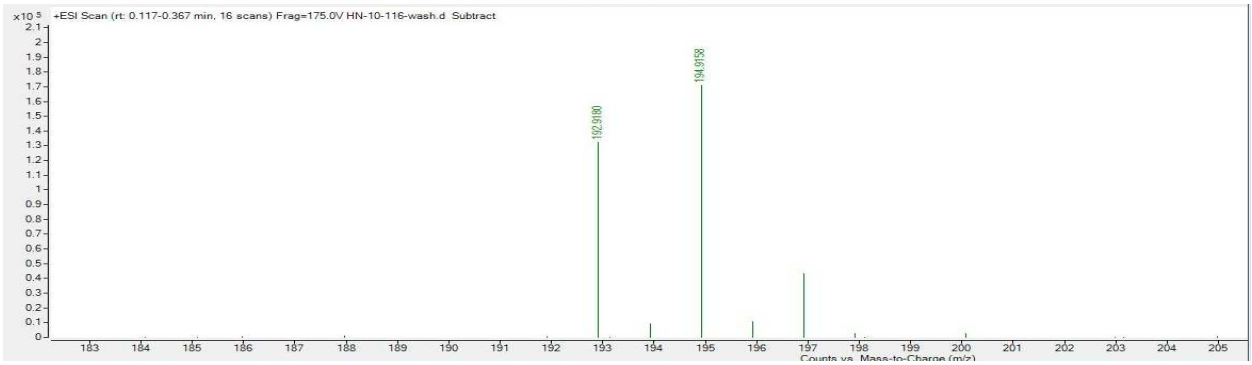
3ab

$$\textbf{58\%}\ ^{15}\text{N incorporation} = \frac{(393024.34 - ((0.0107 \times 15) \times 264125.72)) + 65615.12}{264125.72 + 393024.34 + 65615.12} \times 100\%$$

3-Bromo-4-chloropyridine-1-^{15}N



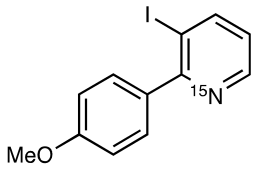
Prepared according to general procedure B using *N*-((1*E*,2*E*,4*E*)-2-Bromo-3-chloro-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (520 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). Yield was determined by ^1H NMR due to volatility of the desired product. 1,3,5-Tristrifluoromethylbenzene (93.2 µL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^1H NMR analysis (78% yield); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 192.9180, $C_5H_4BrCl^{15}N^+$ requires 192.9181, >99% ^{15}N incorporation determined by HRMS.



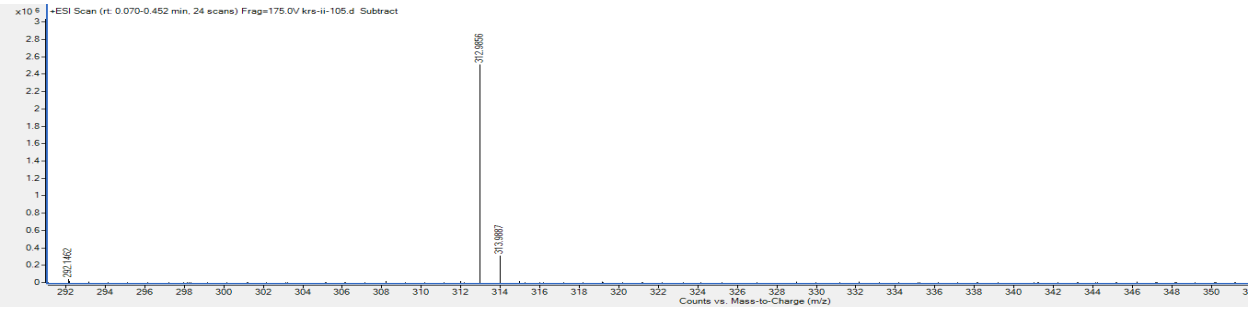
3ac

>99% ^{15}N incorporation $= \frac{(113946.95 - ((0.0107 \times 5) \times 704.06)) + (8205.17 - (0.2423 \times 704.06) - (0.4931 \times 704.06)) + (147408.41 - ((0.0107 \times 5) \times (0.2423 \times 704.06)) - ((0.0107 \times 5) \times (0.4931 \times 704.06)) + (9337.13 - ((0.2423 \times 0.4931) \times 704.06) + (37429.77 - ((0.0107 \times 5) \times (0.2423 \times 0.4931) \times 704.06) + (2093.77)}{704.06 + 113946.95 + 8205.17 + 147408.41 + 9337.13 + 37429.77 + 2093.77} \times 100\%$

3-Iodo-2-(4-methoxyphenyl)pyridine-1-^{15}N



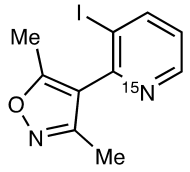
Prepared according to general procedure B using *N*-((1*E*,2*Z*,4*E*)-5-(Dibenzylamino)-2-iodo-1-(4-methoxyphenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (320 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: 60% EtOAc in hexanes) to afford the title compound as a yellow oil (133 mg, 0.43 mmol, 85% yield); IR ν_{max}/cm^{-1} (film): 3034, 2956, 2834, 1608, 1514, 1415, 1246, 1174, 1023, 832, 789, 580; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (dd, *J* = 11.9, 4.6 Hz, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 6.94 (dd, *J* = 18.2, 7.1 Hz, 3H), 3.84 (d, *J* = 1.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.06, 159.94, 148.52, 147.81 (d, *J* = 2.9 Hz), 134.34 (d, *J* = 7.3 Hz), 130.74 (d, *J* = 1.4 Hz), 122.97, 113.32, 94.36, 55.35; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 316.03; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 312.9856, $C_{12}H_{10}I^{15}NO^+$ requires 312.98, >99% ^{15}N incorporation determined by HRMS.



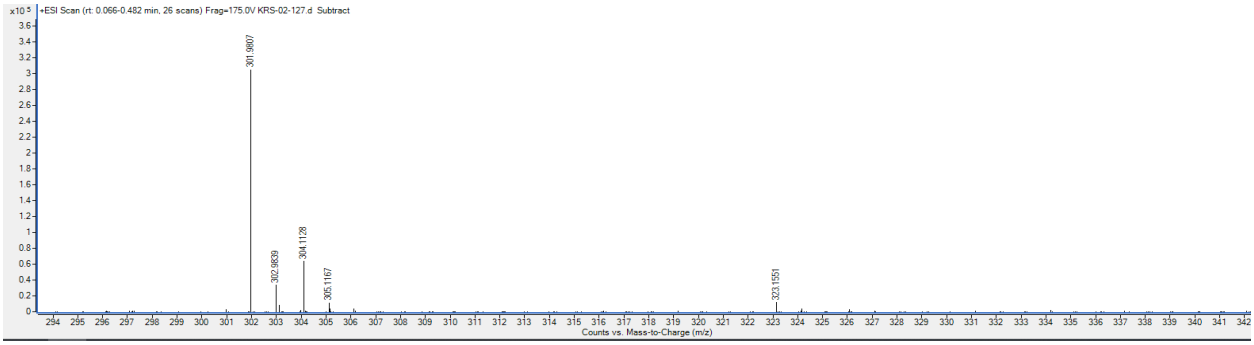
3ad

$$\textbf{>99\%}\ ^{15}\text{N incorporation} = \frac{(2166145.5 - ((0.0107 \times 12) \times 0)) + 260968.98}{0 + 2166145.5 + 260968.98} \times 100\%$$

4-(3-Iodopyridin-2-yl-1-^{15}N)-3,5-dimethylisoxazole



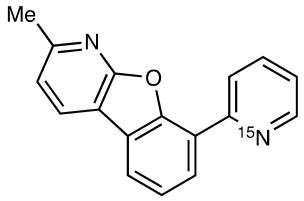
Prepared according to a modified general procedure B (except using 4.0 equiv of $^{15}NH_4Cl$, 4.0 equiv of NaOAc, and heated to 60 ºC for 48 hours). Used *N*-((1*E*,2*Z*)-5-(Dibenzylamino)-1-(3,5-dimethylisoxazol-4-yl)-2-iodopent-2-en-1-ylidene)-1,1,1-trifluoromethanesulfonamide (314 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (109 mg, 2.00 mmol), NaOAc (164 mg, 2.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 30% to 50% EtOAc in hexanes) to afford the title compound as a brown oil (114 mg, 0.38 mmol, 76% yield); IR ν_{max}/cm^{-1} (film): 3039, 2963, 2924, 1634, 1558, 1455, 1430, 1399, 1247, 990, 793, 729; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.60 (ddd, *J* = 11.4, 4.7, 1.6 Hz, 1H), 8.20 (dd, *J*= 8.0, 1.6 Hz, 1H), 7.00 (ddd, *J* = 8.1, 4.6, 1.5 Hz, 1H), 2.28 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.65 (d, *J* = 1.4 Hz), 158.70, 153.51, 149.04, 147.16 (d, *J* = 2.9 Hz), 124.16 (d, *J* = 2.5 Hz), 118.94, 97.69 (d, *J* = 3.2 Hz), 12.40, 10.74; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 322.17 (d, *J* = 11.2 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 301.9807, $C_{10}H_9IN^{15}NO^+$ requires 301.97, >99% ^{15}N incorporation determined by HRMS.



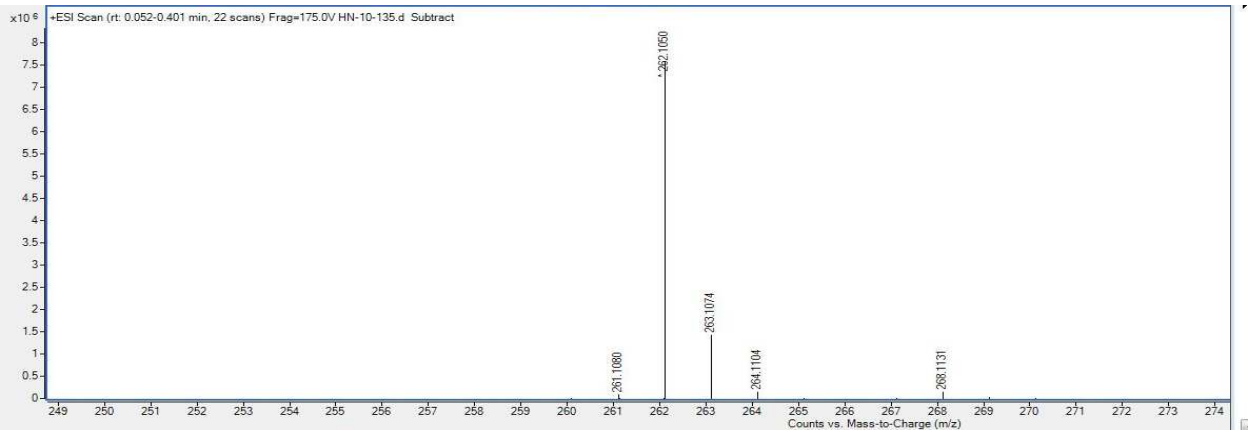
3ae

$$\textbf{>99\%}\ ^{15}\text{N incorporation} = \frac{(613210 - ((0.0107 \times 10) \times 0)) + 68670.08}{0 + 613210 + 68670.08} \times 100\%$$

2-Methyl-8-(pyridin-2-yl-^{15}N)benzofuro[2,3-*b*]pyridine



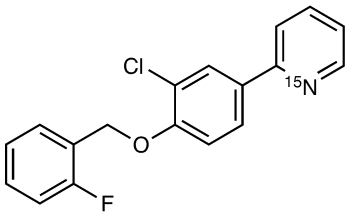
Prepared according to general procedure B using *N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-(2-methylbenzofuro[2,3-*b*]pyridin-8-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (295 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 20% EtOAc in hexanes) to afford the title compound as a white solid (100 mg, 0.39 mmol, 77% yield); mp: 104 – 107 °C; IR ν_{max}/cm^{-1} (film): 3053, 2919, 1590, 1576, 1409, 1389, 1178, 1162, 1059, 776, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (dddd, *J* = 11.2, 4.8, 1.9, 1.0 Hz, 1H), 8.54 (dq, *J* = 8.0, 1.1 Hz, 1H), 8.38 (dd, *J* = 7.9, 1.3 Hz, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.93 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.85 (td, *J* = 7.7, 1.9 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.30 (ddt, *J* = 7.9, 5.2, 1.6 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.02, 156.61, 153.05 (d, *J* = 2.0 Hz), 151.88 (d, *J* = 1.8 Hz), 149.74, 136.87 (d, *J* = 3.0 Hz), 130.07, 127.84 (d, *J* = 3.6 Hz), 124.76 (d, *J* = 2.2 Hz), 124.44 (d, *J* = 8.2 Hz), 123.88, 123.60, 122.78 (d, *J* = 2.5 Hz), 121.49, 119.16, 113.74, 24.60; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 307.80 (d, *J* = 11.1 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 262.1050, $C_{17}H_{13}N^{15}NO^+$ requires 262.0993, 99% ^{15}N incorporation determined by HRMS.



3af

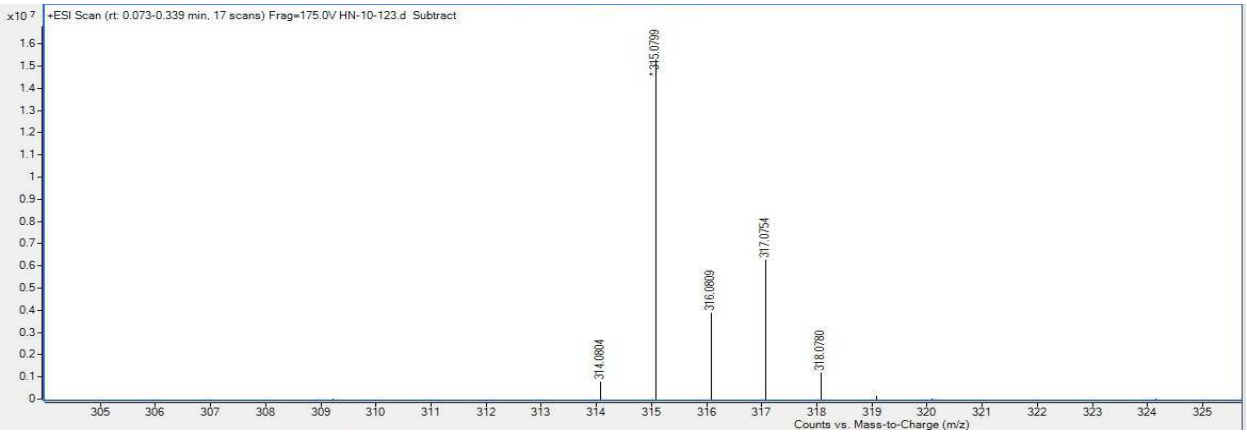
$$\textbf{99\%}\ ^{15}\text{N incorporation} = \frac{(7587363 - ((0.0107 \times 17) \times 76175.01)) + 1430622}{76175.01 + 7587363 + 1430622} \times 100\%$$

2-(3-Chloro-4-((2-fluorobenzyl)oxy)phenyl)pyridine-1-^{15}N



Prepared according to general procedure B using *N*-((1*Z*,2*E*,4*E*)-1-(3-Chloro-4-((2-fluorobenzyl)oxy)phenyl)-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (321 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 50% EtOAc in hexanes) to afford the title compound as a white solid (132.5 mg, 0.42 mmol, 84% yield); mp: 75 – 77 ºC ; IR νmax/cm-1 (film): 3072, 2885, 1588, 1507, 1454, 1280, 1252, 1229, 1055, 1101, 771, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (dddd, *J* = 11.1, 4.9, 1.8, 0.9 Hz, 1H), 8.09 (d, *J* = 2.2 Hz, 1H), 7.85 (dd, *J* = 8.6, 2.2 Hz, 1H),

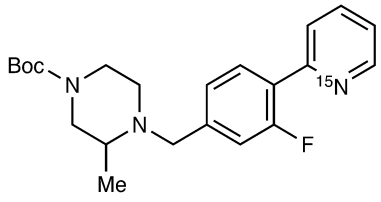
7.72 (td, *J* = 7.7, 1.9 Hz, 1H), 7.62 (ddd, *J* = 13.9, 7.8, 1.4 Hz, 2H), 7.32 (tdd, *J* = 7.5, 5.3, 1.8 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.14 – 7.04 (m, 2H), 5.28 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.29 (d, *J* = 246.6 Hz), 155.78 (d, *J* = 1.8 Hz), 154.68, 149.72, 136.97 (d, *J* = 3.1 Hz), 133.50, 129.83 (d, *J* = 8.1 Hz), 129.40 (d, *J* = 3.8 Hz), 129.01 (d, *J* = 2.6 Hz), 126.30 (d, *J* = 2.6 Hz), 124.53 (d, *J* = 3.6 Hz), 123.87, 123.68 (d, *J* = 13.9 Hz), 122.12 (d, *J* = 2.5 Hz), 120.00 (d, *J*= 2.4 Hz), 115.36 (d, *J* = 21.0 Hz), 113.89, 64.66 (d, *J* = 4.7 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ: -118.74 (dt, *J* = 12.3, 6.2 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ: 304.81 (d, *J* = 11.2 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 315.0799, $C_{18}H_{14}ClF^{15}NO^+$ requires 315.0713, 96% ^{15}N incorporation determined by HRMS.



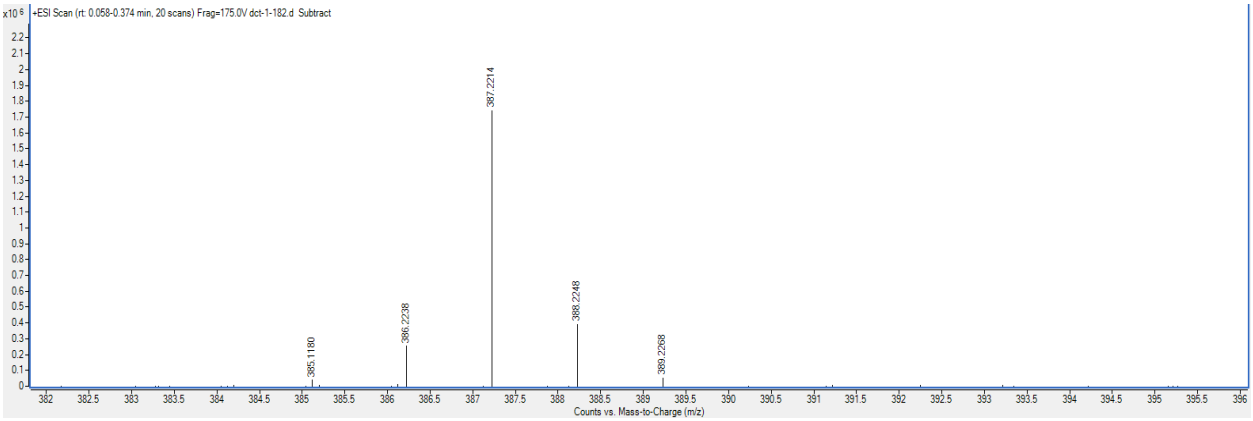
3ag

96% ^{15}N incorporation = $\frac{(15284552 - ((0.0107 \times 18) \times 785404)) + (3893708.25 - (0.2423 \times 785404)) + (6270661 - ((0.0107 \times 18) \times (0.2423 \times 785404)) + (1167442.62)}{785404 + 15284552 + 3893708.25 + 6270661 + 1167442.62} \times 100\%$

***tert*-Butyl 4-(3-fluoro-4-(pyridin-2-yl-^{15}*N*)benzyl)-3-methylpiperazine-1-carboxylate**



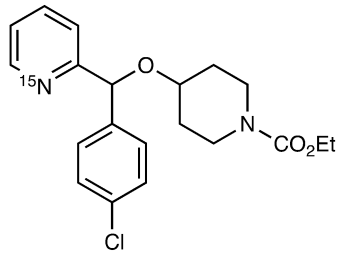
Prepared according to general procedure C with 1.0 equiv dibenzylamine, using *tert*-butyl4-(3-fluoro-4-(pyridin-2- yl)benzyl)-3-methylpiperazine-1-carboxylate[3] (77.0 mg, 0.20 mmol), Tf_2O (34.0 μL, 0.20 mmol), dibenzylamine (38.0 μL, 0.20 mmol), collidine (26.0 μL, 0.20 mmol), EtOAc (2.0 mL, 0.10 M), EtOH (2.0 mL, 0.10 M),$^{15}NH_4Cl$ (22.0 mg, 0.40 mmol), NaOAc (33.0 mg, 0.40 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 40% EtOAc in hexanes) to afford the title compound as a yellow oil (110 mg, 0.29 mmol, 57% yield); IR ν_{max}/cm^{-1} (film): 2973, 2927, 2852, 2808, 1693, 1624, 1585, 1460, 1435, 1416; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (ddd, *J* = 11.2, 4.7, 1.6 Hz, 1H), 7.91 (t, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 9.5, 2.6 Hz, 2H), 7.47 – 7.05 (m, 4H), 4.00 (d, *J* = 13.8 Hz, 1H), 3.65 (d, *J* = 13.1 Hz, 1H), 3.25 (d, *J* = 13.8 Hz, 1H), 3.13 (d, *J* = 10.2 Hz, 1H), 2.90 (s, 1H), 2.74 – 2.63 (m, 1H), 2.47 (dt, *J* = 6.3, 3.1 Hz, 1H), 2.13 (s, 1H), 1.46 (s, 9H), 1.12 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.87, 159.39 (d, *J* = 1.3 Hz), 154.89, 153.52 (d, *J* = 2.5 Hz), 149.86, 142.65 (d, *J* = 6.1 Hz), 136.48 (d, *J* = 2.9 Hz), 130.85 (t, *J* = 3.1 Hz), 128.72, 124.96 (d, *J* = 3.0 Hz), 124.58 (d, *J* = 2.2 Hz), 124.49 (d, *J* = 2.1 Hz), 122.43 (d, *J* = 2.3 Hz), 116.56, 116.32, 79.71, 57.50, 55.08, 29.84, 28.58; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 310.36 (d, *J* = 11.1 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 387.2214, $C_{22}H_{29}FN_2{}^{15}NO^+$ requires 387.2209, 87% ^{15}N incorporation determined by HRMS.



3ah

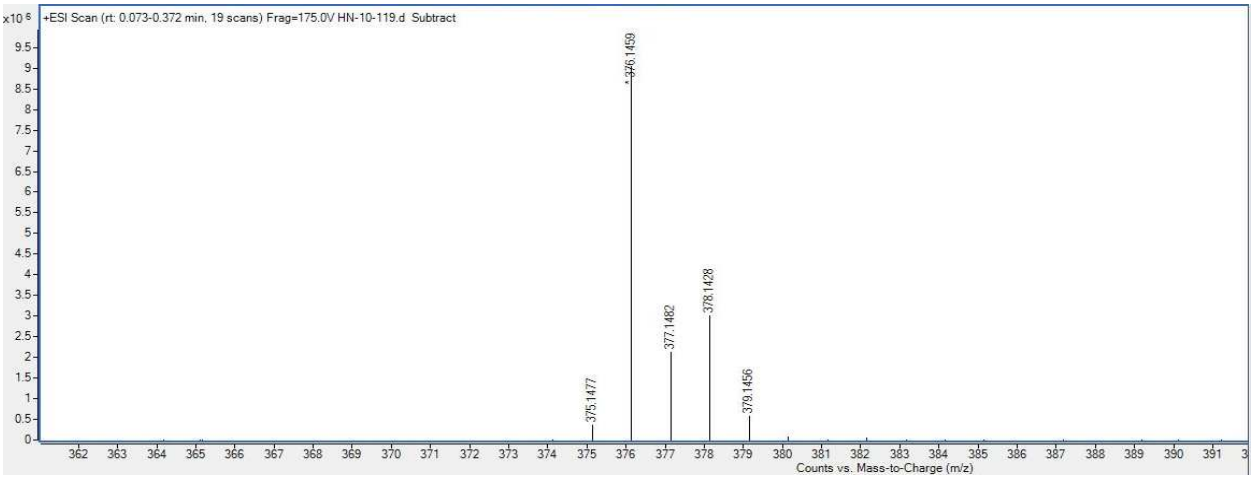
$$\textbf{87\% } ^{15}\text{N incorporation} = \frac{(1777462.5 - ((0.0107 \times 22) \times 263737.72)) + 401589.91}{263737.72 + 1777462.5 + 401589.91} \times 100\%$$

Ethyl 4-((4-chlorophenyl)(pyridin-2-yl-15*N*)methoxy)piperidine-1-carboxylate



Prepared according to general procedure B using ethyl-4-(((2*Z*,3*E*,5*E*)-1-(4-chlorophenyl)-6-(dibenzylamino)-2-(((trifluoromethyl)sulfonyl)imino)hexa-3,5-dien-1-yl)oxy)piperidine-1-carboxylate (352 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M), $^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 100% EtOAc in hexanes) to afford the title compound as a yellow oil (175 mg, 0.45 mmol, 89% yield); IR ν_{max}/cm^{-1} (film): 2928, 2867, 1691, 1430, 1272, 1226, 1083, 1028, 1014, 764; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.67 – 8.37 (m, 1H), 7.63 (td, J = 7.7, 1.8 Hz, 1H), 7.47

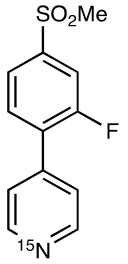
(dd, J = 7.8, 1.3 Hz, 1H), 7.38 – 7.25 (m, 2H), 7.25 – 7.19 (m, 2H), 7.11 (ddt, J = 7.6, 5.0, 1.5 Hz, 1H), 5.57 (d, J = 1.6 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.72 (dt, J = 13.7, 5.8 Hz, 2H), 3.58 (tt, J = 7.5, 3.6 Hz, 1H), 3.21 – 3.08 (m, 2H), 1.85 – 1.70 (m, 2H), 1.60 (ttd, J = 11.9, 7.4, 3.5 Hz, 2H), 1.19 (t, J = 7.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.89 (d, J = 1.4 Hz), 155.57, 148.99, 140.19, 137.02 (d, J = 3.1 Hz), 133.42, 128.62, 128.19, 122.62, 122.59, 120.64, 120.62, 81.13, 81.02, 72.65, 61.31, 41.12, 41.08, 31.12, 14.76; ^{15}N NMR (40 MHz, CD_3CN) δ: 303.25 (d, J = 11.0 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 376.1459, $C_{20}H_{24}ClN^{15}NO_3^+$ requires 376.1440, 96% ^{15}N incorporation determined by HRMS.



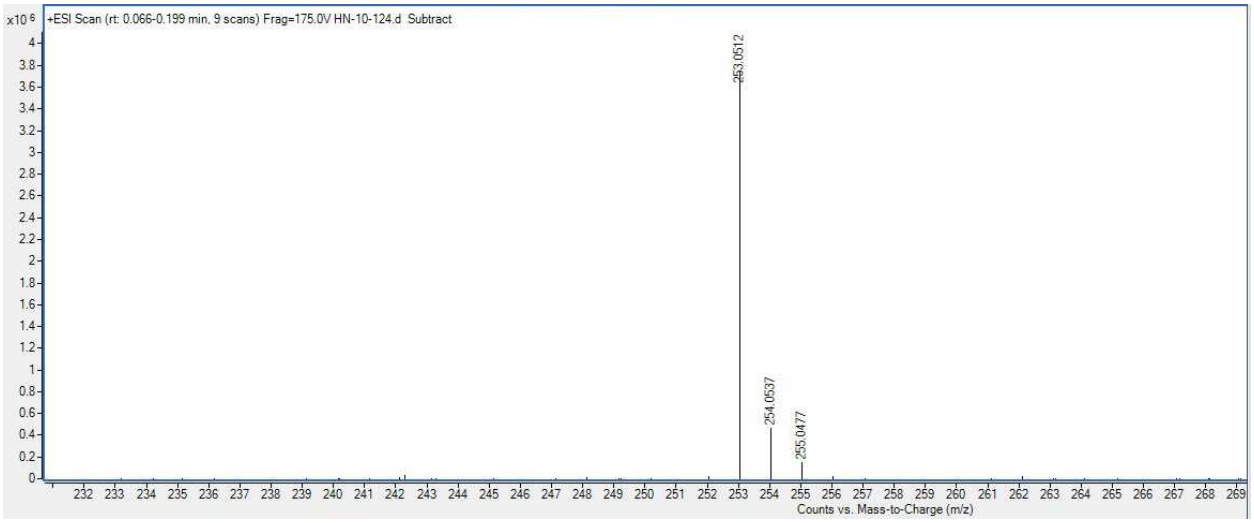
3ai

96% ^{15}N incorporation = $\frac{(9044847 - ((0.0107 \times 20) \times 372291.72)) + (2107856.605 - (0.2423 \times 372291.72)) + (3009843.25 - ((0.0107 \times 20) \times (0.2423 \times 372291.72)) + (584794.75)}{372291.72 + 9044847 + 2107856.605 + 3009843.25 + 584794.75} \times 100\%$

4-(2-Fluoro-4-(methylsulfonyl)phenyl)pyridine-1-^{15}N



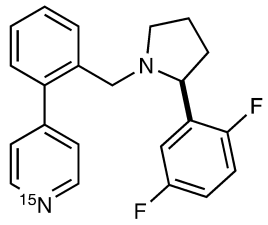
Prepared according to general procedure B using *N*-((1*E*,2*Z*,4*E*)-5-(Dibenzylamino)-3-(2-fluoro-4-(methylsulfonyl)phenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (290 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 100% EtOAc in hexanes) to afford the title compound as a brown solid (57.0 mg, 0.23 mmol, 45% yield); mp: 139 – 140 ^{o}C; IR ν_{max}/cm^{-1} (film): 3062, 2993, 2901, 1596, 1397, 1294, 1217, 1144, 1130, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85 (s, 2H), 7.85 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.79 (dd, *J* = 9.4, 1.8 Hz, 1H), 7.69 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.52 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.45 (d, *J* = 256.1 Hz), 150.10, 142.62, 142.55, 141.49, 131.93, 131.80, 131.68 (d, *J* = 2.9 Hz), 123.72 (d, *J* = 2.3 Hz), 116.11, 115.86, 44.38; ^{19}F NMR (375 MHz, $CDCl_3$) δ: -112.81 (t, *J* = 8.3 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ; ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 253.0512, $C_{12}H_{11}F^{15}NO_2S^+$ requires 253.0459, >99% ^{15}N incorporation determined by HRMS.



3aj

>99% ^{15}N incorporation = $\frac{(3739818.5 - ((0.0107 \times 12) \times 0)) + 466499.66}{0 + 3739818.5 + 466499.66}$ x 100%

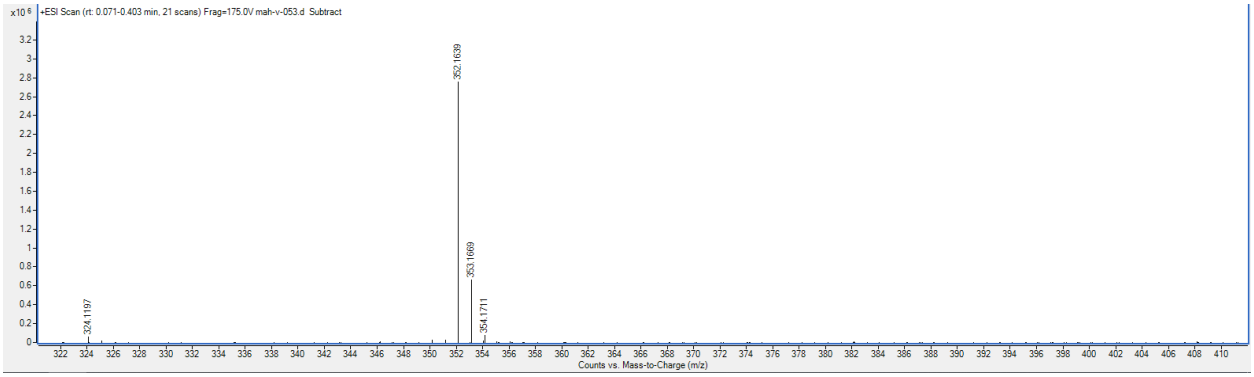
(*S*)-4-(2-((2-(2,5-Difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)pyridine-1-^{15}*N*



Prepared according to general procedure C using (*S*)-4-(2-((2-(2,5-difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)- pyridine.[1] (420 µL, 1.20 mmol), Tf_2O (198 µL, 1.20 mmol), dibenzylamine (276 µL, 1.44 mmol, 1.0 M in EtOAc), collidine (158 µL, 1.20 mmol), EtOAc (6.0 mL, 0.20 M), EtOH (12.0 mL, 0.10 M),$^{15}NH_4Cl$ (131 mg, 2.40 mmol), NaOAc (197 mg, 2.40 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 20% to 40% EtOAc

in hexanes) to afford the title compound as a yellow oil (190 mg, 0.54 mmol, 45% yield); IR ν_{max}/cm^{-1} (film): 3063, 2966, 1595, 1495, 1402, 1240, 1168, 1140, 813, 760;

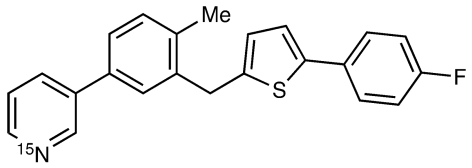
Due to broadening of peaks, the doublets for the ortho and meta protons (each 2H) are broadened underneath the aryl peaks. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (dd, *J* = 7.7, 1.3 Hz, 2H), 7.31 (td, *J* = 7.6, 1.3 Hz, 2H), 7.24 – 7.17 (m, 2H), 7.06 (ddd, *J* = 10.1, 6.8, 2.0 Hz, 3H), 6.83 (td, *J* = 9.1, 4.2 Hz, 1H), 6.76 (tt, *J* = 7.3, 3.5 Hz, 1H), 3.68 (d, *J* = 13.4 Hz, 2H), 3.59 (t, *J* = 8.1 Hz, 1H), 3.14 (d, *J* = 13.5 Hz, 2H), 2.94 (ddd, *J* = 9.5, 7.4, 2.5 Hz, 3H), 2.14 (dtd, *J* = 12.5, 8.7, 6.4 Hz, 1H), 2.06 – 1.95 (m, 1H), 1.82 – 1.58 (m, 2H), 1.52 (dddd, *J* = 12.8, 10.1, 7.8, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.71, 160.07 (d, *J* = 2.0 Hz), 157.93 (d, *J* = 1.9 Hz), 155.53 (d, *J* = 1.8 Hz), 139.38, 136.09, 132.89 (d, *J* = 6.8 Hz), 132.74 (d, *J* = 6.7 Hz), 129.83, 129.01, 128.21, 126.87, 116.06 (d, *J* = 8.4 Hz), 115.81 (d, *J*= 8.4 Hz), 114.41 (d, *J* = 25.8 Hz), 114.32 (d, *J* = 8.7 Hz), 114.17 (d, *J* = 39.0 Hz), 61.33, 55.65, 53.43, 33.48, 22.71; ^{15}N NMR (40 MHz, $CDCl_3$): ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 352.1639, $C_{22}H_{21}F_2N^{15}N^+$ requires 352.1638, >99% ^{15}N incorporation determined by HRMS.



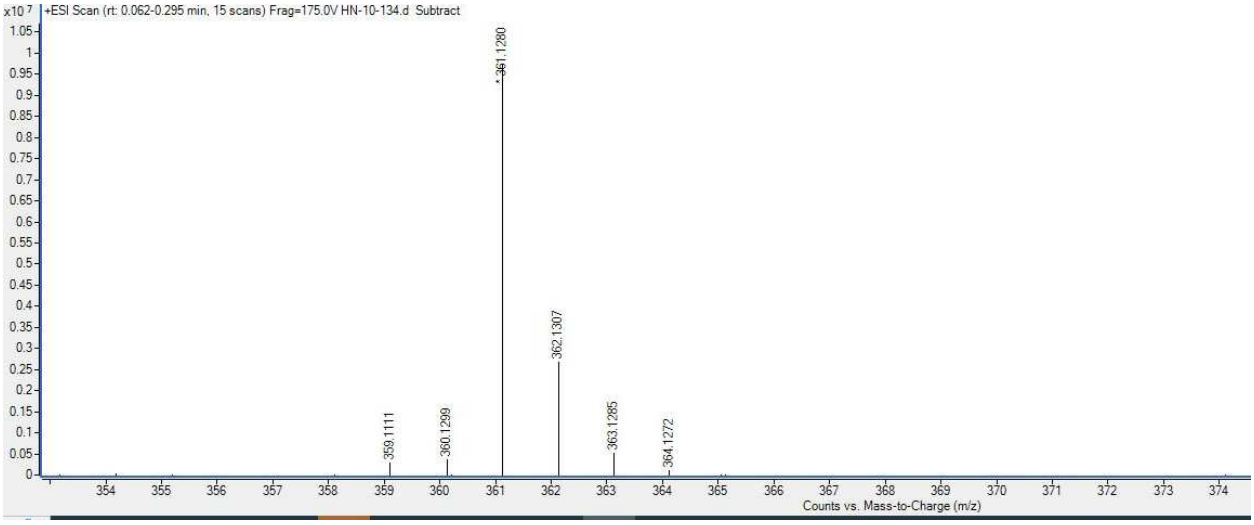
3ak

$$\text{>99\% } ^{15}\text{N incorporation} = \frac{(1865173 - ((0.0107 \times 22) \times 0)) + 443547.31}{0 + 1865173 + 443547.31} \times 100\%$$

3-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyridine-1-^{15}N



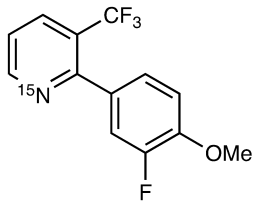
Prepared according to general procedure C (except with 1.0 equiv dibenzylamine) using 3-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-pyridine[1] (180 mg, 0.50 mmol), Tf_2O (84.0 μL, 0.50 mmol), dibenzylamine (96.0 μL, 0.50 mmol), collidine (66.0 μL, 0.50 mmol), EtOAc (5.0 mL, 0.10 M), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 20% EtOAc in hexanes) to afford the title compound as an pink solid (128 mg, 0.36 mmol, 72% yield);mp: 52 – 60 °C; IR ν_{max}/cm^{-1} (film): 3030, 2918, 1508, 1475, 1424, 1229, 1161, 826, 796, 705; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.86 (d, J = 10.0 Hz, 1H), 8.57 (dd, J = 11.1, 4.9 Hz, 1H), 7.86 (dt, J = 8.0, 2.0 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.42 (dd, J = 7.8, 2.1 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.08 – 6.98 (m, 3H), 6.72 (d, J = 3.5 Hz, 1H), 4.20 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.44, 160.99, 148.28 (d, J = 4.3 Hz), 143.00, 141.84, 139.15, 136.62, 136.51, 135.88, 134.31 (d, J = 3.4 Hz), 131.37, 130.87 (d, J = 3.3 Hz), 128.25, 127.28, 127.20, 126.23, 125.69, 123.64, 122.82 (d, J = 1.3 Hz), 115.93, 115.72, 34.29, 19.34; ^{19}F NMR (375 MHz, $CDCl_3$) δ: -114.92 – -115.18 (m); ^{15}N NMR (40 MHz, $CDCl_3$) δ: ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 361.1280, $C_{23}H_{19}F^{15}NS^+$ requires 361.1187, 96% ^{15}N incorporation determined by HRMS.



3al

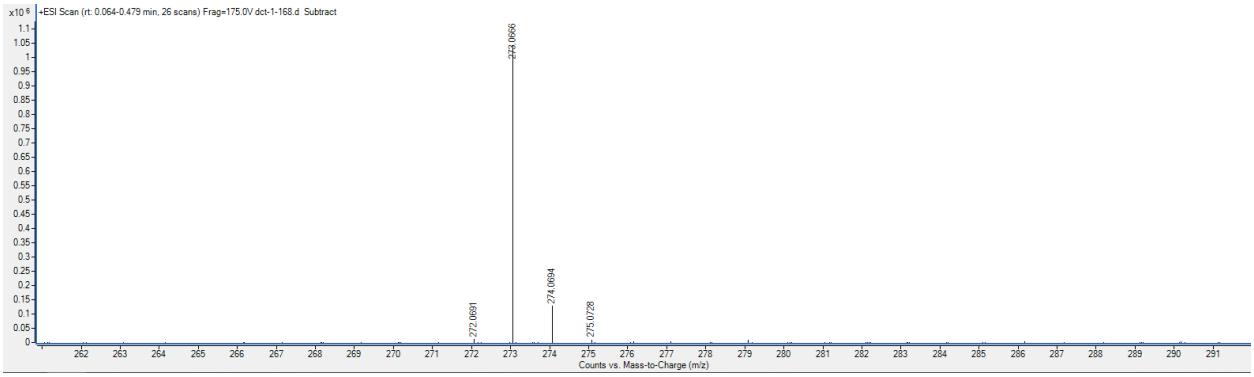
$$\textbf{96\% } ^{15}\text{N incorporation} = \frac{(9743218 - ((0.0107 \times 23) \times 360932.19)) + 2683987.75}{360932.19 + 9743218 + 2683987.75} \times 100\%$$

2-(3-Fluoro-4-methoxyphenyl)-3-(trifluoromethyl)pyridine-1-^{15}N



Prepared according to general procedure C using 2-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)pyridine (136 mg, 0.50 mmol), Tf_2O (84.0 µL, 0.50 mmol), dibenzylamine (115 µL, 0.60 mmol), collidine (66.0 µL, 0.50 mmol), EtOAc (2.5 mL, 0.20 M), EtOH (5.0 mL, 0.10 M), $^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 15% EtOAc in hexanes) to afford the title compound as a yellow oil (55.5 mg, 0.21 mmol, 41% yield); IR ν_{max}/cm^{-1}

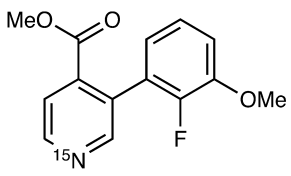
(film): 2938, 2843, 1566, 1518, 1437, 1321, 1302, 1272, 1129, 1115, 1019; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (dd, *J* = 11.4, 4.4 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.30 (m, 1H), 7.24 – 7.16 (m, 2H), 6.96 (t, *J* = 8.5 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.95, 153.11, 152.01, 150.66, 148.47 (d, *J* = 10.7 Hz), 135.11 (dd, *J* = 5.1, 2.7 Hz), 132.14, 125.15 (d, *J* = 2.0 Hz), 122.78 (dd, *J* = 272.7, 269.6 Hz), 121.90 (d, *J* = 2.7 Hz), 117.02 (d, *J* = 19.7 Hz), 112.84 (d, *J* = 2.2 Hz), 56.36; ^{19}F NMR (375 MHz) δ: -57.45, -135.55 (dd, *J* = 11.9, 8.5 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ: 320.06 (d, *J* = 11.4 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 273.0666, $C_{13}H_{10}F_4{}^{15}NO^+$ requires 273.0663, 99% ^{15}N incorporation determined by HRMS.



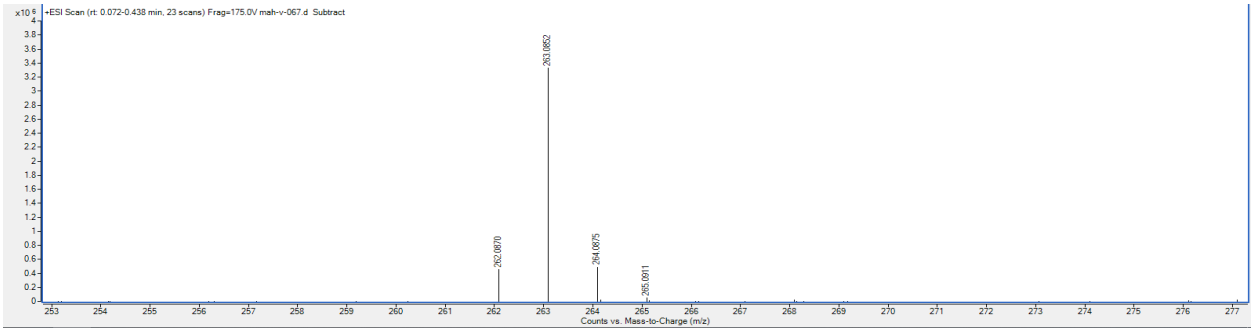
3am

$$\textbf{99\% } {}^{15}\text{N incorporation} = \frac{(1042071.06 - ((0.0107 \times 13) \times 12034.07)) + 128795.36}{12034.07 + 1042071.06 + 128795.36} \times 100\%$$

Methyl 3-(2-fluoro-3-methoxyphenyl)isonicotinate-^{15}*N*



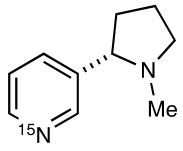
Prepared according to general procedure C using methyl 3-(2-fluoro-3-methoxyphenyl)isonicotinate[1] (130 mg, 0.50 mmol), Tf_2O (84.0 µL, 0.50 mmol), dibenzylamine (96.0 µL, 0.50 mmol), collidine (66.0 µL, 0.50 mmol), EtOAc (5.0 mL, 0.10 M), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 20% to 40% EtOAc in hexanes) to afford the title compound as a brown oil (59.3 mg, 0.23 mmol, 45% yield); IR ν_{max}/cm^{-1} (film): 2954, 2844, 1734, 1482, 1470, 1436, 1295, 1103, 1012, 779 ; ^1H NMR (400 MHz, CD_3CN) δ: 8.65 (dd, *J* = 10.9, 5.1 Hz, 1H), 8.56 (d, *J* = 10.9 Hz, 1H), 7.65 (ddd, *J* = 5.0, 1.6, 0.7 Hz, 1H), 7.17 – 7.01 (m, 2H), 6.83 (ddd, *J* = 7.6, 6.4, 1.8 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ:166.81, 152.33, 150.58, 149.99 (d, *J* = 244.1 Hz), 148.15 (d, *J* = 10.9 Hz), 138.53 – 138.44 (m), 126.33 (d, *J* = 13.1 Hz), 124.93 (d, *J* = 4.7 Hz), 123.16 (d, *J* = 2.1 Hz), 122.26 (d, *J* = 1.9 Hz), 117.89, 114.31 (d, *J* = 2.1 Hz), 56.57, 52.78; ^{19}F NMR (375 MHz, CD_3CN) δ: -140.56 (t, *J* = 7.0 Hz); ^{15}N NMR (40 MHz, $CDCl_3$): ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 263.0852, $C_{14}H_{13}F^{15}NO_3^+$ requires 263.0844, 88% ^{15}N incorporation determined by HRMS.



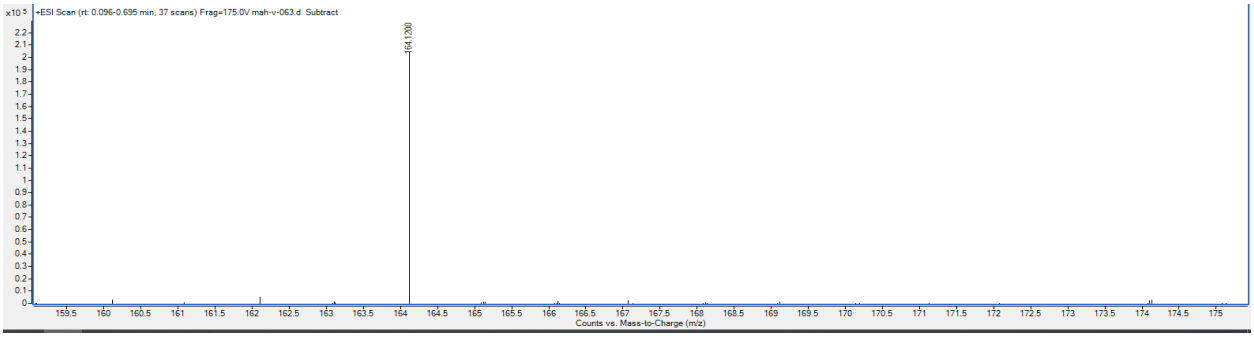
3an

$$\textbf{88\%}\ ^{15}\text{N incorporation} = \frac{(3556261 - ((0.0107 \times 14) \times 483823.53)) + 493577.25}{483823.53 + 3556261 + 493577.25} \times 100\%$$

(*S*)-3-(1-Methylpyrrolidin-2-yl)pyridine-1-^{15}*N*



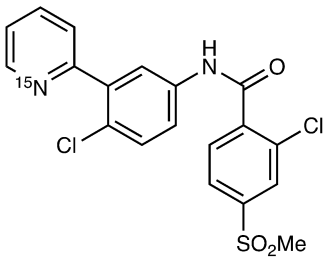
Prepared according to general procedure C using (*S*)-3-(1-methylpyrrolidin-2-yl)pyridine (80.3 µL, 0.50 mmol), Tf_2O (82.5 µL, 0.50 mmol), dibenzylamine (115 µL, 0.60 mmol), collidine (66.0 µL, 0.50 mmol), EtOAc (2.5 mL, 0.20 M), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.1 mg, 1.00 mmol). Yield was determined by ^{1}H NMR in duplicate due to volatility of the desired product. Mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv) was added as the internal standard for ^{1}H NMR analysis (34% yield - average of two trials: 29% yield and 39% yield). *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 164.1200, $C_{10}H_{15}N^{15}N^+$ requires 164.1200, >99% ^{15}N incorporation determined by HRMS.



3ao

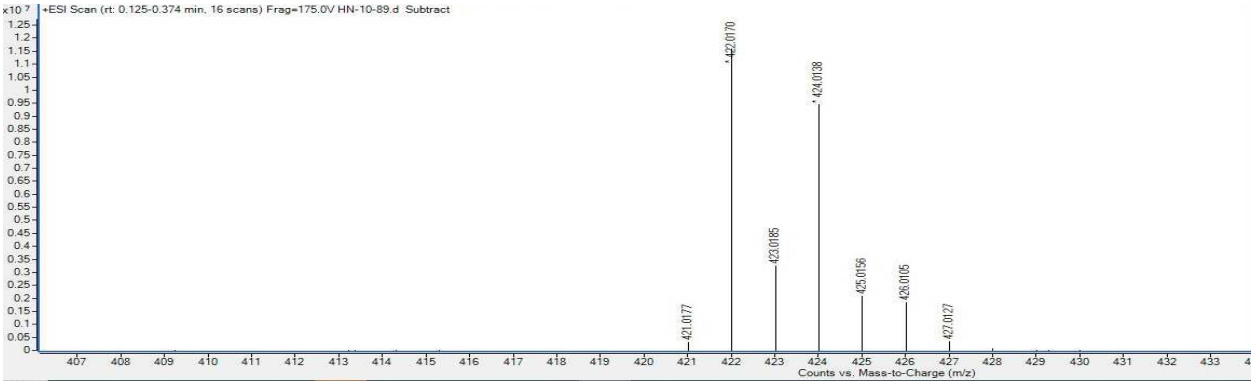
$$\text{>99\% } ^{15}\text{N incorporation} = \frac{(140954.81 - ((0.0107 \times 10) \times 0)) + 17986.52}{0 + 140954.81 + 17986.52} \times 100\%$$

2-Chloro-*N*-(4-chloro-3-(pyridin-2-yl-^{15}*N*)phenyl)-4-(methylsulfonyl)benzamide



Prepared according to a modified general procedure B (except with 4.0 equiv of $^{15}NH_4Cl$, 4.0 equiv of NaOAc, and heating to 80 °C) using 2-Chloro-*N*-(4-chloro-3-((1*Z*,2*E*,4*E*)-5-(dibenzylamino)-1-(((trifluoromethyl)sulfonyl)imino)penta-2,4-dien-1-yl)phenyl)-4-(methylsulfonyl)benzamide (375 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (109 mg, 2.00 mmol), NaOAc (164 mg, 2.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 20% to 100% EtOAc in hexanes) to afford the title compound as a cream solid (178 mg, 0.42 mmol, 83% yield); mp: 60 – 62 °C; IR ν_{max}/cm^{-1} (film): 3298, 3065, 2901, 1680, 1533, 1457, 1303, 1281, 1150, 1099; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (dd, *J* = 11.4, 4.7 Hz, 1H), 7.39 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.14 – 6.98 (m, 4H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.76 (d, *J* = 13.1 Hz, 2H), 3.33 (dddd, *J* = 22.9, 14.0, 9.8, 5.9 Hz, 2H), 3.11 (ddt, *J* = 13.0, 9.2, 4.2 Hz, 2H), 2.88 – 2.66 (m, 2H), 2.45 (ddd, *J* = 14.2, 9.3, 4.6 Hz, 1H), 2.29 (td, *J* = 13.4, 6.0 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.05, 155.47, 146.63, 139.54, 137.64, 137.50 (d), 134.22, 134.15, 133.67 – 133.15 (m), 132.90, 130.54, 129.00, 126.13, 122.28 (d, *J* = 2.5 Hz), 61.30, 44.80, 44.76, 31.69, 31.45, 30.73, 30.53,

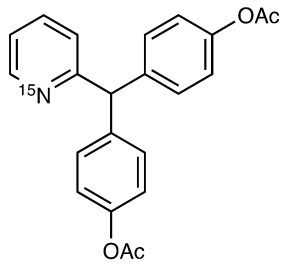
14.68; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 309.92 (d, J = 10.8 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 422.0170, $C_{19}H_{15}Cl_2N^{15}NO_3S^+$ requires 422.0145, 98% ^{15}N incorporation determined by HRMS.



3ap

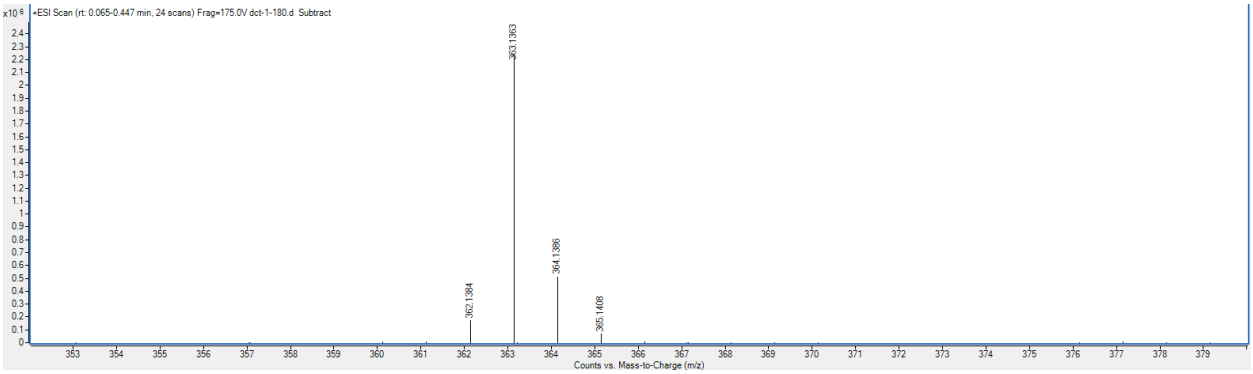
98% ^{15}N incorporation = $\frac{(11591100 - ((0.0107 \times 19) \times 314263.44)) + (3248189 - ((0.2423 \times 2) \times 314263.44)) + (9435477 - ((0.0107 \times 19) \times (0.2423 \times 2) \times 314263.44)) + (2092150.88 - ((0.2423 \times 2) \times (0.2423 \times 2) \times 314263.44)) + (1839268.75 - ((0.0107 \times 19) \times (0.2423 \times 2) \times (0.2423 \times 2) \times 314263.44)) + (349443.41)}{314263.44 + 11591100 + 3248189 + 9435477 + 2092150.88 + 1839268.75 + 349443.41} \times 100\%$

((Pyridin-2-yl-^{15}*N*)methylene)bis(4,1-phenylene) diacetate



Prepared according to a modified general procedure B using ((2*Z*,3*E*,5*E*)-6-(Dibenzylamino)-2-(((trifluoromethyl)sulfonyl)imino)hexa-3,5-diene-1,1-diyl)bis(4,1-phenylene) diacetate (345 mg,

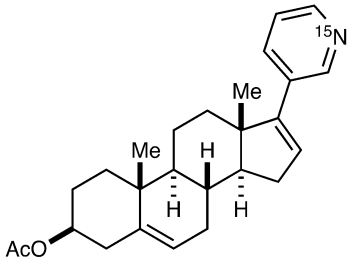
0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol), and heating to 60 °C for 1 hour. The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 50% EtOAc in hexanes) to afford the title compound as a yellow oil (96.0 mg, 0.27 mmol, 53% yield); IR ν_{max}/cm^{-1} (film): 3048, 2254, 1752, 1584, 1565, 1502, 1465, 1430, 1368, 1190; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (dd, *J* = 11.0, 4.6 Hz, 1H), 7.61 (td, *J* = 7.7, 1.9 Hz, 1H), 7.21 – 7.08 (m, 6H), 7.06 – 6.96 (m, 4H), 5.66 (d, *J* = 2.6 Hz, 1H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.61, 162.63, 149.60, 149.39, 140.05, 136.77 (d, *J* = 3.0 Hz), 130.39, 123.96 (d, *J* = 2.3 Hz), 121.78 (d, *J* = 2.4 Hz), 121.60, 58.07 (d, *J* = 8.2 Hz), 21.19; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 312.58 (d, *J* = 11.0 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 363.1363, $C_{22}H_{20}{}^{15}NO_4^+$ requires 363.1357, 93% ^{15}N incorporation determined by HRMS.



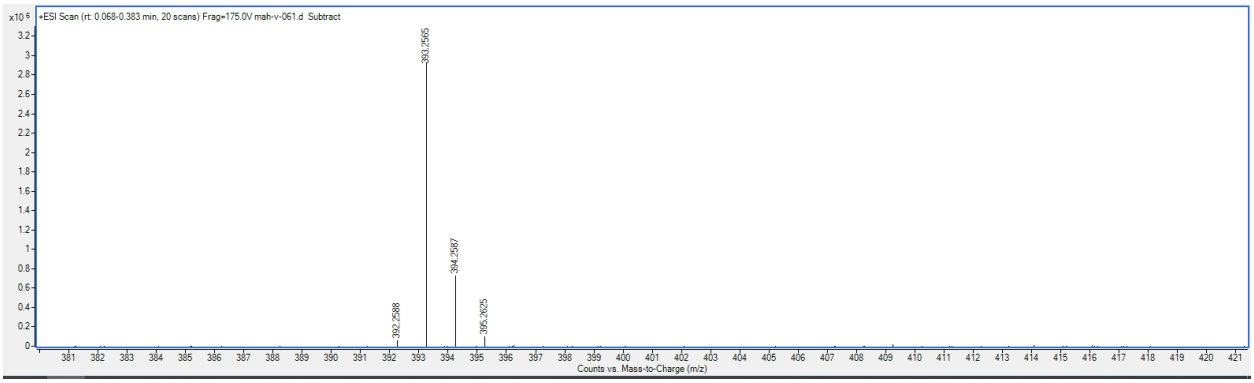
3aq

$$\textbf{93\% } ^{15}\text{N incorporation} = \frac{(2240059 - ((0.0107 \times 22) \times 174843.81)) + 514335.94}{174843.81 + 2240059 + 514335.94} \times 100\%$$

(3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-10,13-Dimethyl-17-(pyridin-3-yl-^{15}*N*)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate



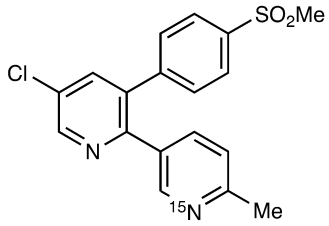
Prepared according to general procedure C using (3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4, 7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (196 mg 0.50 mmol), Tf_2O (82.5 μL, 0.50 mmol), dibenzylamine (115 μL, 0.60 mmol), collidine (66.0 μL, 0.50 mmol), EtOAc (2.5 mL, 0.20 M), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: gradient 20% to 40% EtOAc in hexanes) to afford the title compound as a brown oil (68.7 mg, 0.18 mmol, 35% yield); IR ν_{max}/cm^{-1} (film): 2933, 2852, 1720, 1373, 1250, 1194, 1032, 910, 795, 731 ; ^1H NMR (400 MHz, CD_3CN) δ: 8.56 (s, 1H), 8.51 – 8.10 (m, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.21 – 7.04 (m, 1H), 5.92 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.34 (d, *J* = 5.1 Hz, 1H), 4.61 – 4.48 (m, 1H), 2.34 – 2.25 (m, 3H), 2.19 (ddd, *J* = 15.8, 6.5, 3.2 Hz, 1H), 2.07 – 1.97 (m, 3H), 1.86 – 1.73 (m, 3H), 1.73 – 1.32 (m, 10H), 1.20 – 1.07 (m, 3H), 1.07 – 1.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.52, 151.63, 147.66, 140.03, 133.79, 129.32, 129.20 – 128.27 (m), 127.72, 122.29, 73.85, 57.47, 50.25, 47.33, 38.14, 36.85, 36.79, 35.20, 31.80, 31.51, 30.41, 29.70, 27.74, 21.43, 20.82, 19.26, 16.57; ^{15}N NMR (40 MHz, $CDCl_3$): ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 393.2565, $C_{26}H_{34}{}^{15}NO_2^+$ requires 393.2554, 98% ^{15}N incorporation determined by HRMS.



3ar

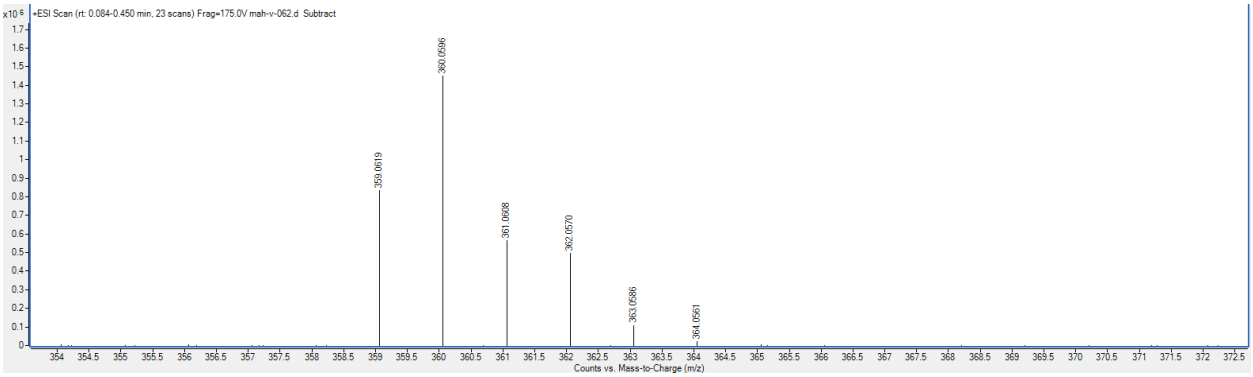
$$\textbf{98\%}\ ^{15}\text{N incorporation} = \frac{(3602646.5 - ((0.0107 \times 26) \times 76058.43)) + 898711.81}{76058.43 + 3602646.5 + 898711.81} \times 100\%$$

5-Chloro-2-(6-methylpyridin-3-yl-1-^{15}*N*)-3-(4-(methylsulfonyl)phenyl)pyridine



Prepared according to general procedure C using 5-chloro-2-(6-methylpyridin-3-yl)-3-(4-(methylsulfonyl)phenyl)- pyridine (197 mg, 0.50 mmol), Tf_2O (82.5 µL, 0.50 mmol), dibenzylamine (115 µL, 0.60 mmol), collidine (66.0 µL, 0.50 mmol), EtOAc (2.5 mL, 0.20 M), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (54.5 mg, 1.00 mmol), NaOAc (82.0 mg, 1.00 mmol). The crude material was purified by automated flash chromatography (silica gel: 80% EtOAc in hexanes) to afford the title compound as a brown oil (91.8 mg, 0.26 mmol, 51% yield); IR ν_{max}/cm^{-1} (film): 2926, 1598, 1430, 1312, 1150, 1123, 956, 905, 779, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ:

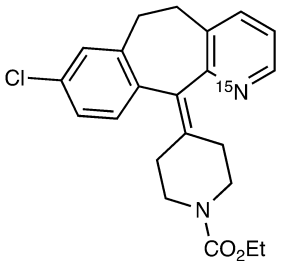
8.61 (d, J = 2.3 Hz, 1H), 8.32 (s, 1H), 7.82 (d, J = 7.9 Hz, 2H), 7.66 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.03 (s, 1H), 3.00 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.38, 152.29, 149.55, 148.36, 143.67, 140.21, 137.98, 137.43, 135.34, 131.12, 130.38, 127.92, 122.95, 44.54, 24.14; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 303.59; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 360.0596, $C_{18}H_{16}ClN^{15}NO_2S^+$ requires 360.0586, 64% ^{15}N incorporation determined by HRMS.



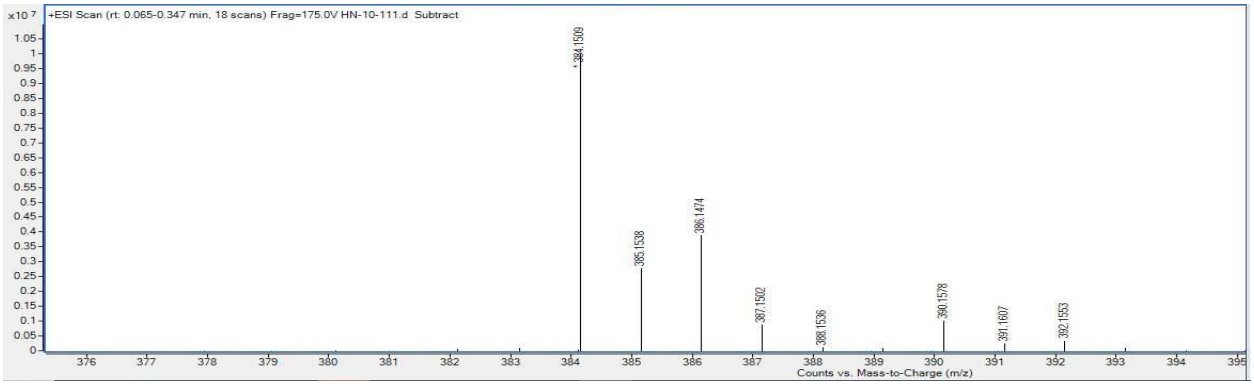
3as

64% ^{15}N incorporation = $\frac{(1450467 - ((0.0107 \times 18) \times 835136.31)) + (565208.75 - (0.2423 \times 835136.31)) + (495914.62 - ((0.0107 \times 18) \times (0.2423 \times 835136.31)) + (110641.4)}{835136.31 + 1450467 + 565208.75 + 495914.62 + 110641.4} \times 100\%$

Ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene-1-15*N*)piperidine-1-carbox- ylate



Prepared according to a modified general procedure B (except using 10.0 equiv of $^{15}NH_4Cl$, 10.0 equiv AgOAc and heating to 80 °C for 48 hours) using ethyl 4-((6*Z*,7*Z*)-2-chloro-7-((*E*)-3-(dibenzylamino)allylidene)-6-(((trifluoromethyl)sulfonyl)imino)-6,7,8,9 -tetrahydro-5*H*-benzo[7]annulen-5-ylidene)piperidine-1-carboxylate (356 mg, 0.50 mmol), EtOH (5.0 mL, 0.10 M),$^{15}NH_4Cl$ (272 mg, 5.00 mmol), AgOAc (833 mg, 5.00 mmol).The crude material was purified by automated flash chromatography (silica gel: gradient 0% to 100% EtOAc in hexanes) to afford the title compound as a brown solid (171 mg, 0.45 mmol, 89% yield); mp: 121-127°C ; IR ν_{max}/cm^{-1} (film): 2982, 2863, 1698, 1472, 1430, 1219, 1168, 1115, 995, 829, 762; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 12.7 Hz, 1H), 7.53 (d, *J* = 12.0 Hz, 1H), 7.45 – 7.30 (m, 6H), 7.29 – 7.09 (m, 6H), 7.03 (d, *J* = 2.2 Hz, 1H), 5.75 (t, *J*= 12.4 Hz, 1H), 4.49 (d, *J* = 12.2 Hz, 4H), 4.23 – 4.04 (m, 2H), 3.84 (dt, *J* = 13.0, 5.1 Hz, 1H), 3.64 (s, 1H), 3.29 (dddd, *J* = 16.8, 12.6, 8.3, 4.0 Hz, 2H), 3.12 (dt, *J*= 16.9, 3.8 Hz, 1H), 2.91 – 2.64 (m, 2H), 2.58 (ddd, *J* = 13.8, 9.1, 4.3 Hz, 2H), 2.32 (ddt, *J* = 13.7, 9.8, 4.9 Hz, 2H), 2.18 (ddd, *J* = 14.1, 6.6, 4.2 Hz, 1H), 1.25 (td, *J* = 7.1, 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.07, 155.81 (d, *J* = 2.2 Hz), 148.76, 142.48, 140.83, 138.56, 138.48, 137.31, 136.56, 136.53, 132.30, 131.03, 129.83, 128.78, 127.24, 125.75, 125.52 (d, *J* = 2.2 Hz), 125.50, 122.92 (d, *J* = 2.5 Hz), 122.82, 121.82, 44.39; ^{15}N NMR (40 MHz, $CDCl_3$): ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 384.1509, $C_{22}H_{24}ClN^{15}NO_2^+$ requires 384.1491, >99% ^{15}N incorporation determined by HRMS.



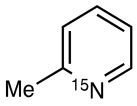
3at

>99% ^{15}N incorporation = $\frac{(10004291 - ((0.0107 \times 22) \times 0)) + (2774385.5 - (0.2423 \times 0)) + (3880406.25 - ((0.0107 \times 22) \times (0.2423 \times 0)) + (886408.88)}{0 + 10004291 + 2774385.5 + 3880406.25 + 886408.88} \times 100\%$

A 1.6. Preparation of ^{15}N Pyridines via Zincke Iminiums

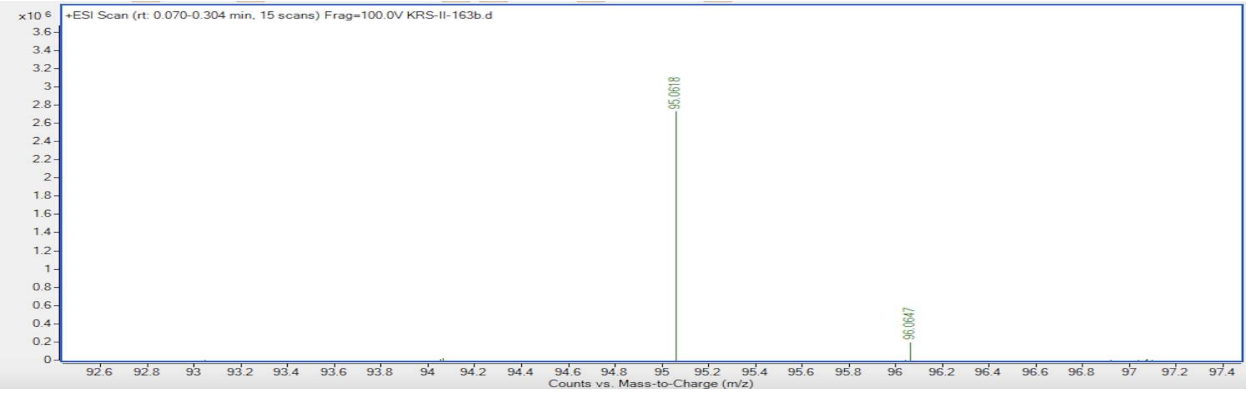
Here we show a procedure (over two steps) for isolating a ^{15}N pyridine via a Zincke iminium intermediate as well as a method for the synthesis and isolation of Zincke iminiums.

2-Methylpyridine-1-^{15}*N*



An oven dried round bottom flask with a stir bar was charged with 2-methylpyridine (9.9 µL, 0.10 mmol) and placed under a nitrogen atmosphere. EtOAc (0.20 M) was added, the reaction vessel cooled to –78 ºC, and Tf_2O (16.8 µL, 0.10 mmol) was added dropwise. The reaction was stirred for 30 minutes before 1.0 M solution of dibenzylamine (23.0 µL, 0.12 mmol) was added dropwise, followed by collidine (13.2 µL, 0.10 mmol). The reaction was stirred for a further 30 minutes at –

78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (15 min for 0.10 mmol scale). Pyrrolidine (33.4 μL, 0.40 mmol) was added and the reaction was heated to 50 ºC for 1 hour. The reaction was removed from the heat and allowed to stir until it cooled to room temperature (15 min). The reaction was quenched with aqueous sodium carbonate (Na_2CO_3) and allowed to stir at room temp for 30 minutes. The organic layer was diluted with EtOAc, removed, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. After filtration, the organic extract was diluted with minimal EtOAc (approximately 1.0 mL per 1.0 mmol) and added dropwise to excess hexanes (approx. 100 mL per 1.0 mmol) and the resulting oil was allowed to settle overnight in a –20 ºC fridge. After the oil/precipitate settled, the hexanes were decanted off and the oil/precipitate was washed with hexanes. The product was collected and dried *in vacuo* to provide the "Zincke pyrrolidine iminium." The crude iminium was added to an oven dried 8 mL vial and concentrated to remove excess solvent. The vial was charged with a stir bar and diluted with EtOH (1.0 mL, 0.10 M). $^{15}NH_4Cl$ (27.3 mg, 0.50 mmol, 5.0 equiv relative to starting heterocycle) and NaOAc (41.0 mg, 0.50 mmol, 5.0 equiv relative to starting heterocycle) were added and the reaction mixture allowed to stir at 80 ºC overnight. Yield was determined by ^1H NMR in duplicate due to volatility of the desired product. 1,3,5-Trimethoxybenzene (33.64 mg, 0.10 mmol, 2.0 equiv) was added as the internal standard for ^1H NMR analysis (56% yield - average of two trials: 56% yield and 56% yield); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 95.0618, $C_6H_8{}^{15}N^+$ requires 95.0622, >99% ^{15}N incorporation determined by HRMS.

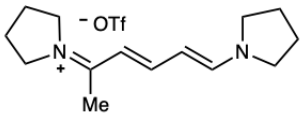


3c'

$$\textbf{>99\% } ^{15}\text{N incorporation} = \frac{(22971728 - ((0.0107 \times 6) \times 0)) + 213327.52}{0 + 22971728 + 213327.52} \times 100\%$$

Preparation and Characterization of the Zincke Iminium synthesized from 2-methylpyridine

1-((3*E*,5*E*)-6-(pyrrolidin-1-yl)hexa-3,5-dien-2-ylidene)pyrrolidin-1-ium trifluoromethanesulfonate

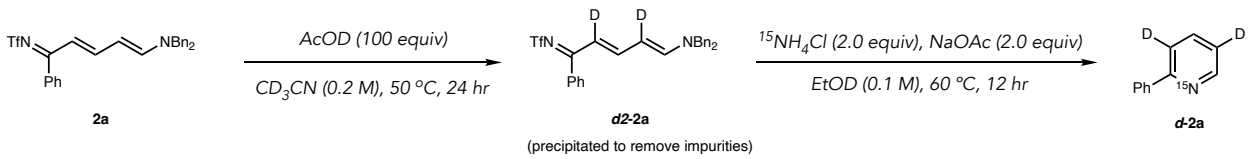


An oven dried round bottom flask with a stir bar was charged with 2-methylpyridine (0.99 mL, 10.0 mmol) and placed under a nitrogen atmosphere. EtOAc (0.20 M) was added, the reaction vessel cooled to –78 ºC, and Tf_2O (1.68 mL, 10.0 mmol) was added dropwise. The reaction was stirred for 30 minutes before 1.0 M solution of dibenzylamine (2.31 mL, 12 mmol) was added dropwise, followed by collidine (1.32, 10.0 mmol). The reaction was stirred for a further 30 minutes at –78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (1 hour for 10.0 mmol scale). Pyrrolidine (3.31 mL, 40 mmol) was added and the reaction was heated to 50 ºC for 1 hour. The reaction was removed from the heat

and allowed to stir until it cooled to room temperature (1 hour). The reaction was quenched with aqueous sodium carbonate (Na_2CO_3) and allowed to stir at room temp for 30 minutes. The organic layer was diluted with EtOAc, removed, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. After filtration, the organic extract was diluted with minimal EtOAc (approximately 1.0 mL per 1.0 mmol) and added dropwise to excess ether:hexanes (1:1) (approx. 100 mL per 1.0 mmol) and the resulting oil was allowed to settle overnight in a –20 ºC fridge. After the oil/precipitate settled, the hexanes were decanted off and the oil/precipitate was collected and purified by automated flash chromatography (silica gel: gradient 5% to 10% MeOH in CH_2Cl_2), then collected and added added dropwise to excess hexanes (approx. 100 mL per 1.0 mmol) and the resulting oil was allowed to settle overnight in a –20 ºC fridge. After the oil/precipitate settled, the hexanes were decanted off and the oil/precipitate was washed with hexanes to afford the "Zincke pyrrolidine iminium" as a purple solid (2.6705 g, 7.25 mmol, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, J = 11.8 Hz, 1H), 7.75 (t, J = 12.8 Hz, 1H), 5.73 (d, J = 13.3 Hz, 1H), 5.61 (t, J = 12.1 Hz, 1H), 3.70 (dt, J = 12.9, 6.6 Hz, 4H), 3.59 – 3.52 (m, 2H), 3.40 (t, J = 7.2 Hz, 2H), 2.35 (s, 3H), 2.07 (t, J = 7.4 Hz, 6H), 1.98 (q, J = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.84, 157.99, 157.18, 121.05 (q, J = 320.8 Hz), 105.44, 104.09, 53.59, 51.02, 50.19, 48.00, 25.14, 25.08, 25.04, 24.88, 17.34; ^{19}F NMR (375 MHz, $CDCl_3$) δ: -78.19; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 219.2, $C_{14}H_{23}N_2^+$ requires 219.19.

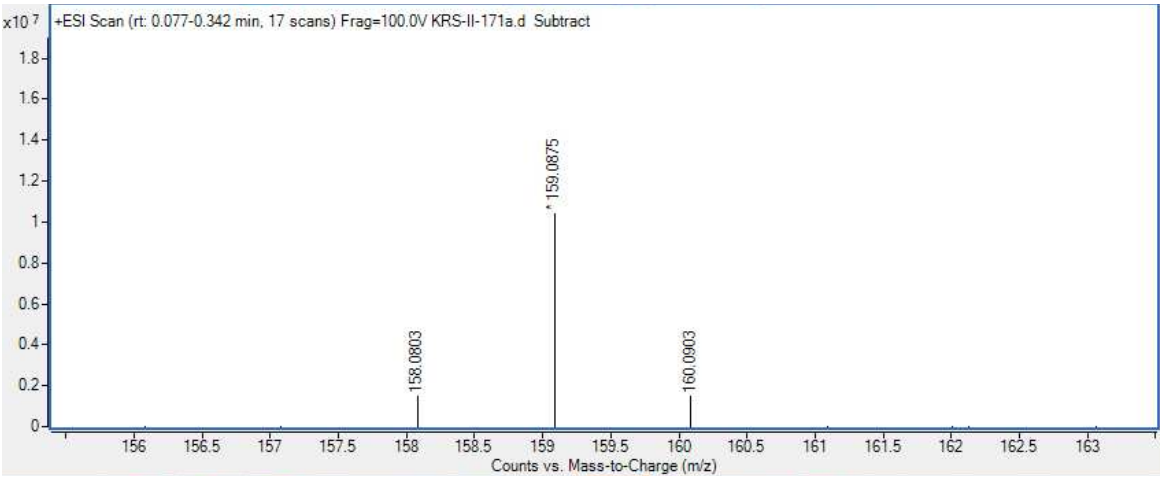
A 1.7. Synthesis of Higher Mass Isotopologs

Deuteration Procedure for 2-phenylpyridine-3,5-d_2-1-^{15}N



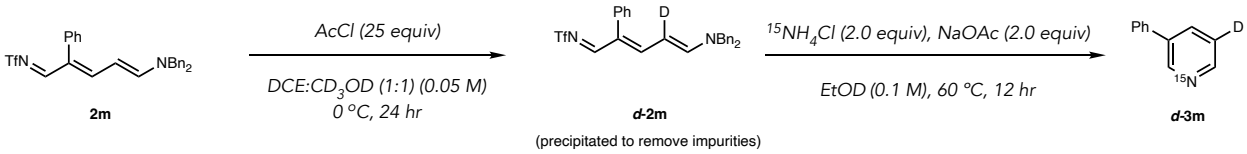
An oven dried 8 mL vial equipped with a stir bar was charged with the **2a** (121 mg, 0.25 mmol, 1.0 equiv), AcOD (1.44 mL, 25 mmol, 100 equiv), CD_3CN (1.25 mL, 0.20 M) and stirred at 50 ºC for 24 hours. The reaction was quenched at 0 ºC with 110 equiv. of Et_3N and stirred for 30 minutes at 0 ºC then warmed to room temperature and stirred for 30 minutes. The reaction was concentrated down, dissolved in minimal CH_2Cl_2, and precipitated from 25 mL of hexanes, then stored for an hour in a –20 ºC fridge. Then, the hexanes were decanted and the D-**2m** imine was collected (using CH_2Cl_2) and concentrated into an 8 mL vial. The vial was charged with $^{15}NH_4Cl$ (27.3 mg, 0.50 mmol, 2.0 equiv relative to **2a**) and NaOAc (41.1 mg, 0.50 mmol, 2.0 equiv relative to **2a**) with EtOD (2.5 mL, 0.10 M) and stirred at 60 ºC overnight. The reaction was diluted with EtOAc and washed with sodium bicarbonate (3x) followed by a brine wash. The combined organic extract was washed with 10% wt. $CuSO_4$ (3x), and then dried ($MgSO_4$), filtered, and concentrated down. The crude material was purified by flash chromatography (silica gel: gradient 0% to 20% EtOAc in hexanes) after isolation to afford the title compound as a red oil (33 mg, 0.21 mmol, 42% yield); IR νmax/cm-1 (film): 3037, 2924, 1566, 1541, 1428, 1371, 739, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (dd, J = 10.9, 1.9 Hz, 1H), 8.01 – 7.93 (m, 2H), 7.77 (s, 1H), 7.73 (dt, J = 8.0, 1.0 Hz, 0.07H (deuterium incorporated site)), 7.54 – 7.39 (m, 3H), 7.17 (dd, J = 7.1, 2.5 Hz, 0.06H (deuterium incorporated site)); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.68 (d, J = 1.4 Hz), 150.46 (d, J = 2.6 Hz), 140.24, 140.16, 137.86 (d, J = 3.2 Hz), 137.75 (d, J = 2.8 Hz), 129.92, 129.68, 129.35 (d, J = 25.4 Hz), 127.63 (d, J = 2.7 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ: 313.98 (d, J = 11.4 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 159.0875, $C_{11}H_7D_2{}^{15}N^+$ requires 159.0909;

^{15}N incorporation: >99% extrapolated value from **3a**. Deuterium incorporation: 93% at C3 94% at C5 measured by ^{1}H NMR.



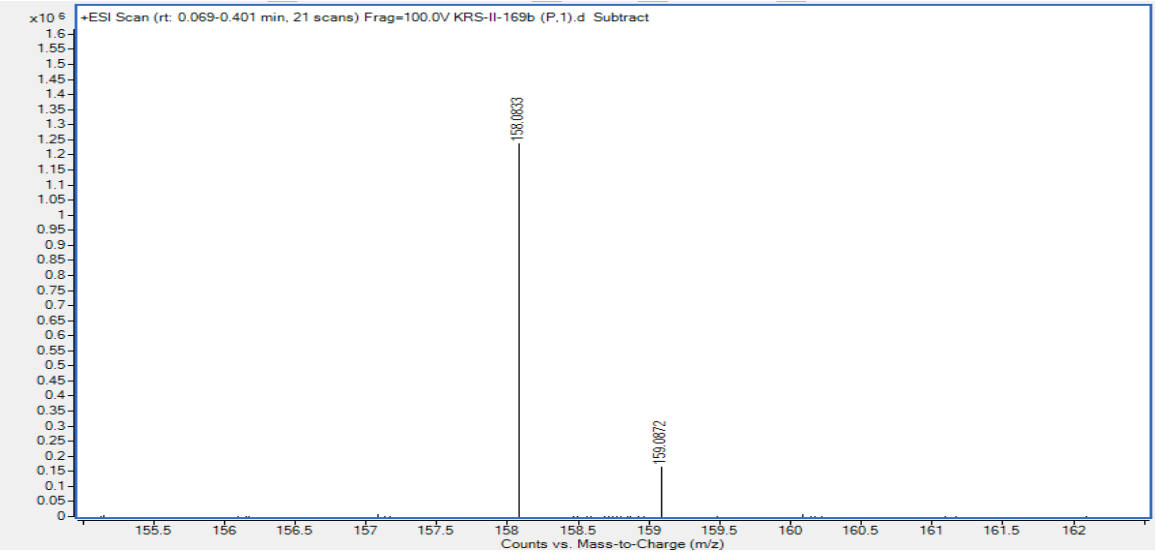
Z	Abund % (Norm)	Max Abund	Formula & Ion Species	Diff (ppm)	m/z	Abund	Sat	Species
		1797302.75			158.081	1797302.75		
1		12011902			159.0882	12011902	S	
1		1756421.12			160.0909	1756421.12		

Deuteration Procedure for 3-phenylpyridine-5-*d*-1-^{15}*N*



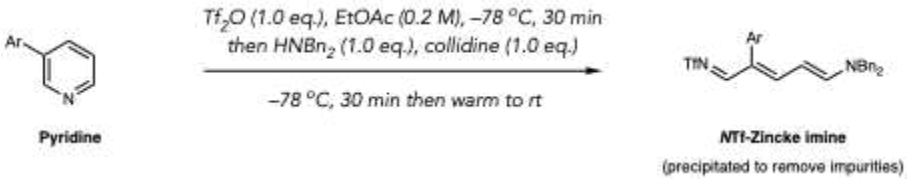
An oven dried 8 mL vial equipped with a stir bar was charged with the **2a** (121 mg, 0.25 mmol, 1.0 equiv), AcCl (446 µL, 6.25 mmol, 25 equiv) was added at –78 ºC dropwise, DCE (5 mL): CD_3OD (5 mL) and stirred at 0 ºC for 24 hours. The reaction was quenched at 0 ºC with 35 equiv. of Et_3N and stirred for 30 minutes at 0 ºC then warmed to room temperature and stirred for 30 minutes. The reaction was concentrated down, dissolved in minimal CH_2Cl_2, and precipitated

from 25 mL of hexanes, then stored for an hour in a –20 ºC fridge. Then, the hexanes were decanted and the D-**2m** imine was collected (using CH_2Cl_2) and concentrated into an 8 mL vial. The vial was charged with $^{15}NH_4Cl$ (27.3 mg, 0.50 mmol, 2.0 equiv. relative to **2m**) and NaOAc (41.1 mg, 0.50 mmol, 2.0 equiv. relative to **2m**) with EtOD (2.5 mL, 0.10 M) and stirred at 60 ºC overnight. The reaction was diluted with EtOAc and washed with sodium bicarbonate (3x) followed by a brine wash. The combined organic extract was washed with 10% wt. $CuSO_4$ (3x), and then dried ($MgSO_4$), filtered, and concentrated down. The crude material was purified by flash chromatography (silica gel: gradient 0% to 20% EtOAc in hexanes) after isolation to afford the title compound as a slightly pink oil (53.4 mg, 0.34 mmol, 68% yield); IR νmax/cm-1 (film): 3034, 2922, 2851, 1455, 1431, 1274, 1161, 1030, 763, 696; ^{1}H NMR (400 MHz, CD_3CN) δ: 8.89 (s, 1H), 8.60 (s, 1H), 7.92 (s, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.35 (dd, *J* = 8.3, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.45 (d, *J* = 4.8 Hz), 137.99, 136.84, 134.40 (d, *J* = 3.3 Hz), 129.21, 128.24, 127.29, 29.83; ^{15}N NMR (40 MHz, $CDCl_3$): ^{15}N peak was unresolved; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 158.0833, $C_{11}H_8D^{15}N^+$ requires 158.0846.^{15}N incorporation: >99% extrapolated value from **3m**. Deuterium incorporation: >99% at C5, measured by ^{1}H NMR.

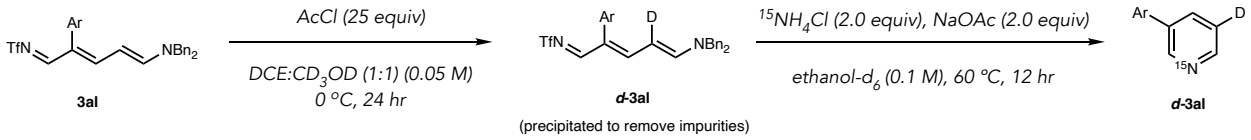


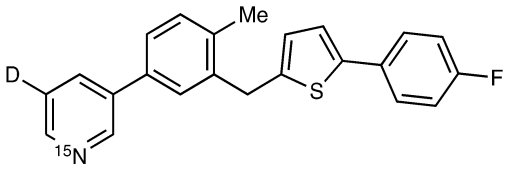
Z	Abund % (Norm)	Max Abund	Formula & Ion Species	Diff (ppm)	m/z	Abund	Sat	Species
1		1993657.62			158.0836	1993657.62		
1		170723.94			159.0877	170723.94		

Deuteration Procedure for 3-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyridine-5-*d*-1-^{15}N



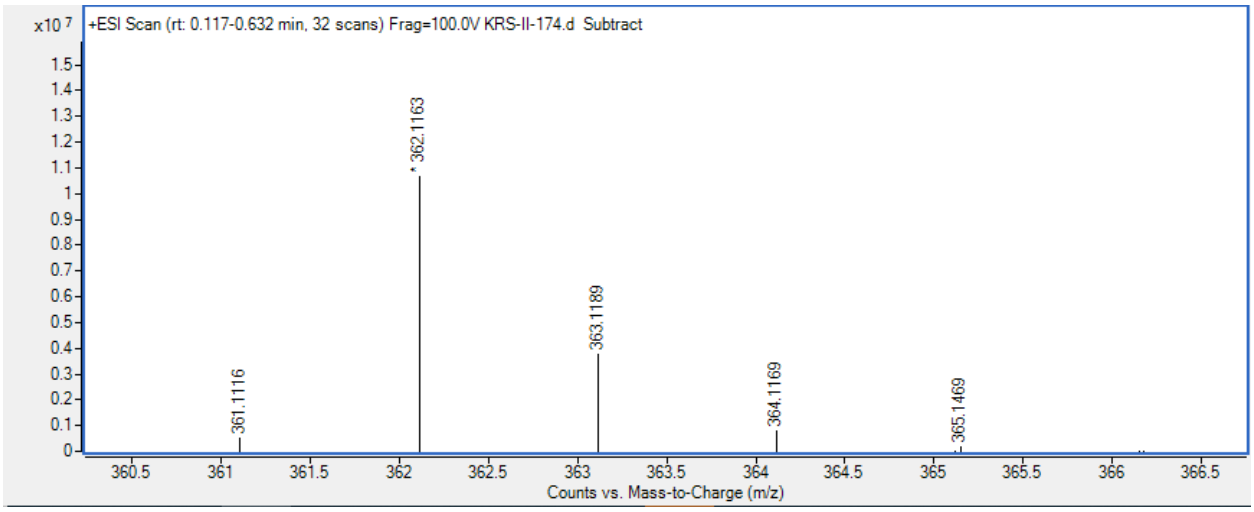
Prepared using 3-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)- pyridine (180 mg, 0.50 mmol), Tf_2O (84 µL, 0.50 mmol), dibenzylamine (96.0 µL, 0.50 mmol), collidine (66.0 µL, 0.50 mmol), EtOAc (5.0 mL, 0.10 M). Washed reaction mixture 3x with 1.0 M HCl, 3x with saturated aqueous solution of sodium bicarbonate, and 3x 10% wt. aqueous $CuSO_4$ and dried ($MgSO_4$) and concentrated followed by precipitation in 50 mL of hexanes and was left in the fridge for an overnight.





An oven dried 50 mL equipped with a stir bar was charged with the decanted ***N*Tf-Zincke imine**, AcCl (892 µL, 12.5 mmol, 25 equiv), DCE (10 mL): CD_3OD (10 mL) and stirred at 0 ºC for 24

hours. The reaction was quenched at 0 ºC with 35 equiv. of Et_3N and stirred for 30 minutes at 0 ºC then warmed to room temperature and stirred for 30 minutes. The reaction was concentrated down, dissolved in minimal CH_2Cl_2, and precipitated from 25 mL of hexanes, then stored for an hour in a –20 ºC fridge. Then, the hexanes were decanted and the D-**2m** imine was collected (using CH_2Cl_2) and concentrated into an 8 mL vial. The vial was charged with $^{15}NH_4Cl$ (54.5 mg, 1.0 mmol, 2.0 equiv relative to starting pyridine) and NaOAc (82.0 mg, 1.00 mmol, 2.0 equiv relative to starting pyridine) with EtOD (5.0 mL, 0.10 M) and stirred at 60 ºC overnight. The reaction was diluted with EtOAc and washed with sodium bicarbonate (3x) followed by a brine wash. The combined organic extract was washed with 10% wt. $CuSO_4$ (3x), and then dried ($MgSO_4$), filtered, and concentrated down. The crude material was purified by flash chromatography (silica gel: gradient 0% to 20% EtOAc in hexanes) after isolation to afford the title compound as a slight yellow oil (74 mg, 0.11 mmol, 21% yield); IR νmax/cm-1 (film): 3033, 2851, 1507, 1437, 1229, 1158, 831, 799, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86 (d, *J* = 9.3 Hz, 1H), 8.58 (d, *J* = 9.6 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.53 – 7.38 (m, 4H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.08 – 6.98 (m, 3H), 6.72 (dt, *J* = 3.7, 1.0 Hz, 1H), 4.21 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ :162.18 (d, *J* = 246.7 Hz), 148.14 (d, *J* = 3.1 Hz), 142.97, 141.80, 139.13, 136.60, 135.81, 134.23 (d, *J* = 3.2 Hz), 131.35, 130.84 (d, *J* = 3.3 Hz), 128.21, 127.24, 127.16, 126.20, 125.66, 123.61, 123.35, 123.10, 122.80 (d, *J* = 1.2 Hz), 115.90, 115.68, 34.26, 19.31; ^{15}N NMR (40 MHz, $CDCl_3$) δ: 310.86;^{19}F NMR (375 MHz, $CDCl_3$) δ: -114.98; *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 362.1163, $C_{23}H_{17}DF^{15}NS^+$ requires 362.1255. ^{15}N incorporation: 96% extrapolated value from **3al**. Deuterium incorporation: >99% at C5, measured by ^{1}H NMR.



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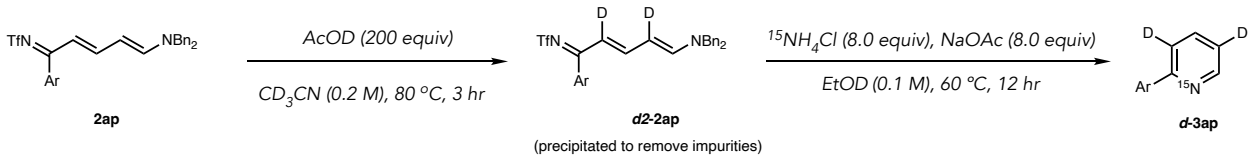
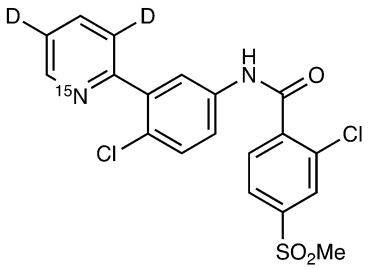
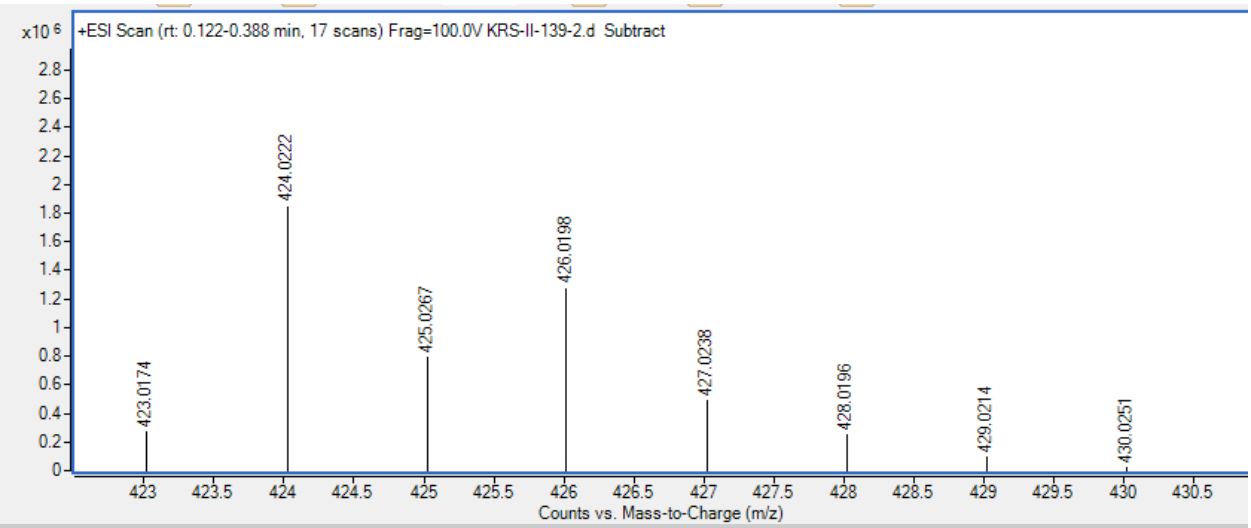
1		12619311			362.1195	12619311	S	
1		4598661.5			363.122	4598661.5		
1		991808.06			364.1199	991808.06		
1		135702.22			365.1192	135702.22		
		185300.2			365.1497	185300.2		

Deuteration Procedure for 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl-3,5-d_2-1-^{15}N)phenyl)-4-(methylsulfonyl)benzamide





An oven dried 8 mL vial equipped with a stir bar was charged with the **2ap** (75 mg, 0.10 mmol, 1.0 equiv), AcOD (573 µL, 10 mmol, 100 equiv), CD_3CN (0.5 mL, 0.20 M) and stirred at 80 ºC for 3 hours. The reaction was diluted with EtOAc and washed with 1.0 M aqueous HCl (3x) then saturated aqueous sodium bicarbonate (3x) followed by a brine wash and then dried ($MgSO_4$), filtered, and concentrated down and precipitated from 10 mL of hexanes stored for an hour in a –20 ºC fridge. Then, the D-**2ap** imine was decanted and charged with $^{15}NH_4Cl$ (43.6 mg, 0.80 mmol, 2.0 equiv relative to **2ap**) and NaOAc (41.1 mg, 0.80 mmol, 8.0 equiv relative to **2ap**) with EtOD (1.0 mL, 0.10 M) and stirred at 60 ºC overnight. The reaction was diluted with EtOAc and washed with sodium bicarbonate (3x) followed by a brine wash. The combined organic extract was washed with 10% wt. $CuSO_4$ (3x), and then dried ($MgSO_4$), filtered, and concentrated down. The crude material was purified by flash chromatography (silica gel: gradient 100% Hexanes to 100% EtOAc) after isolation to afford the title compound as a slightly yellow solid (29.3 mg, 0.07 mmol, 69% yield); mp: 162-169 ºC; IR νmax/cm-1 (film): 3017, 2923, 1672, 1582, 1538, 1440, 1309, 1152, 1139, 801; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ: 9.84 (s, 1H), 8.60 (dd, *J* = 11.5, 1.9 Hz, 1H), 8.00 (d, *J* = 2.7 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.84 – 7.75 (m, 3H), 7.63 (d, *J* = 7.9 Hz, 0.07H (deuterium incorporated site)), 7.45 (d, *J* = 8.7 Hz, 1H), 7.30 (ddd, *J* = 7.6, 4.8, 1.5 Hz, 0.10H (deuterium incorporated site)), 3.14 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 164.97, 157.03, 150.41, 144.29, 141.67, 140.63 (d, *J* = 7.9 Hz), 138.20 (d, *J* = 9.1 Hz), 136.96 (d, *J* = 2.6 Hz), 132.72, 131.50, 130.85, 129.95, 129.63 (d, *J* = 10.1 Hz), 128.45, 127.86, 127.02, 123.62 (d, *J* = 8.7 Hz), 121.98 (d, *J* = 9.4 Hz), 44.27; ^{15}N NMR (40 MHz, CD_3CN) δ: 244.76 (d, J = 10.3 Hz); *m/z* HRMS (ESI + APCI) found $[M + H]^+$ 424.0267, $C_{19}H_{12}D_2Cl_2N^{15}NO_3S^+$ requires 424.0276. ^{15}N incorporation: 97% extrapolated value from **3ap**. Deuterium incorporation: 93% at C3 at 90% C5, measured by ^{1}H NMR.



Z	Abund % (Norm)	Max Abund	Formula & Ion Species	Diff (ppm)	m/z	Abund	Sat	Species
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1		788252.25			425.0267	788252.25		
1		1279730.75			426.0198	1279730.75		
1		491973.16			427.0238	491973.16		
1		255809.17			428.0196	255809.17		
1		95682.46			429.0214	95682.46		
1		24089.42			430.0251	24089.42		

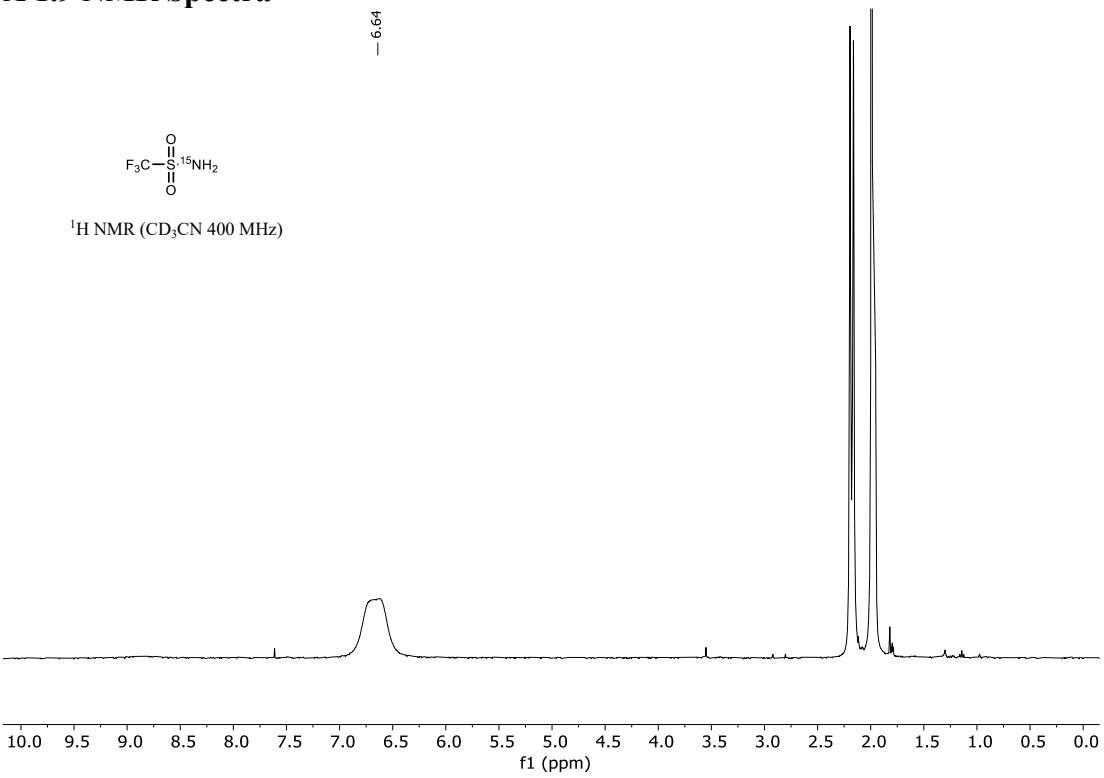
A 1.8. References

(1) Boyle, B. T.; Levy, J. N.; de Lescure, L.; Paton, R. S.; McNally, A. Halogenation of the 3-Position of Pyridines Through Zincke Imine Intermediates. *Science* **2022**, *378*, 773-779. DOI:10.1126/science.add8980

(2) Selingo, J. D.; Greenwood, J. W.; Andrews, M. K.; Patel, C.; J., N. A; Pio, B.; Shevlin, M.; Phillips, E. M.; Maddess, M. L.; J., N. A.; Pio, B.; Shevlin, M.; Phillips, E. M.; Maddess, M. L.;; McNally, A. A General Strategy for N–(Hetero)Aryl Piperidine Synthesis Using Zincke Imine Intermediates. **2023**. https://doi.org/DOI:10.26434/chemrxiv-2023-68575.

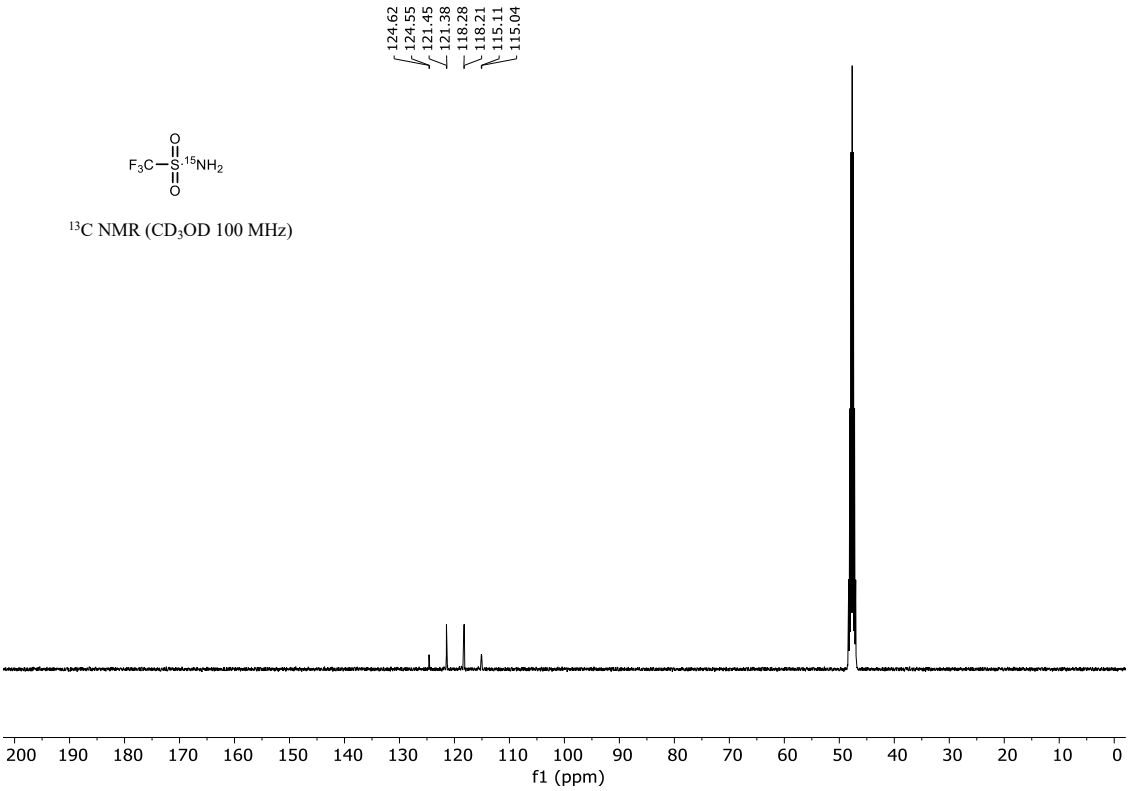
(3) Bosnidou, A. E.; Muñiz, K. Intermolecular Radical C(Sp3)−H Amination under Iodine Catalysis. *Angewandte Chemie International Edition* **2019**, *58* (22), 7485–7489. https://doi.org/10.1002/anie.201901673.

A 1.9 NMR Spectra

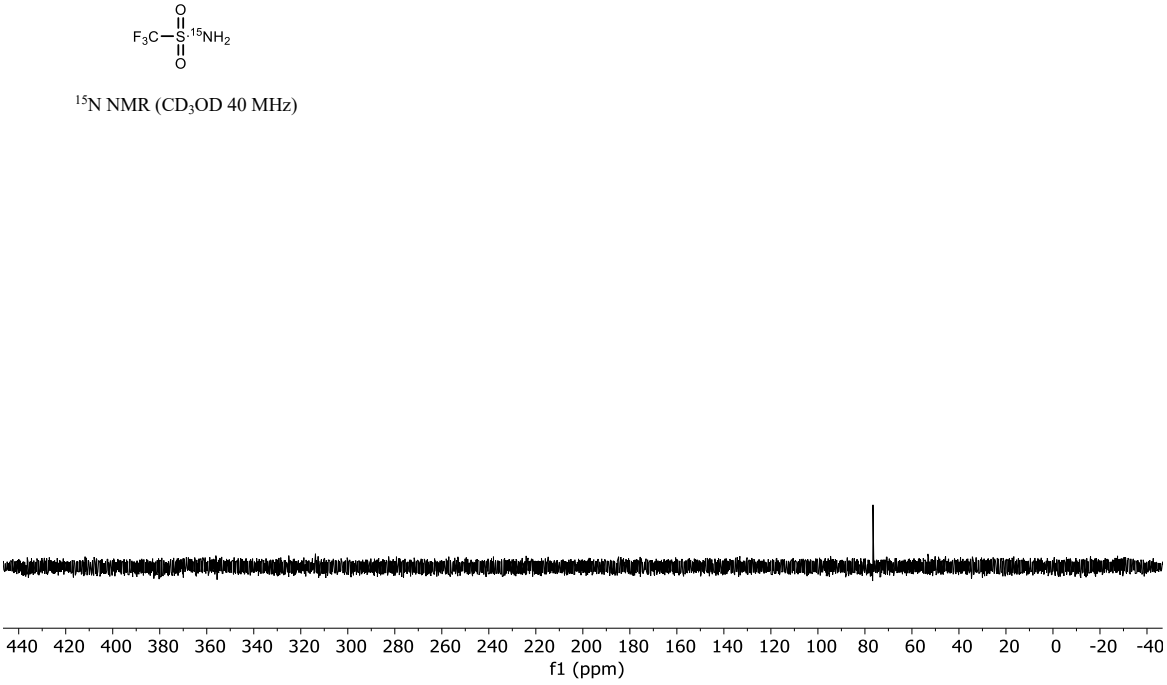


$F_3C-S(=O)(=O)-{}^{15}NH_2$

^1H NMR (CD_3CN 400 MHz)

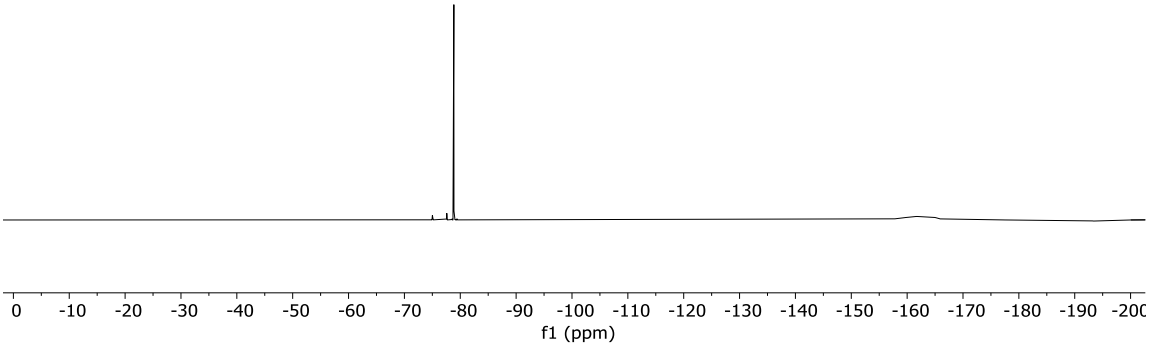


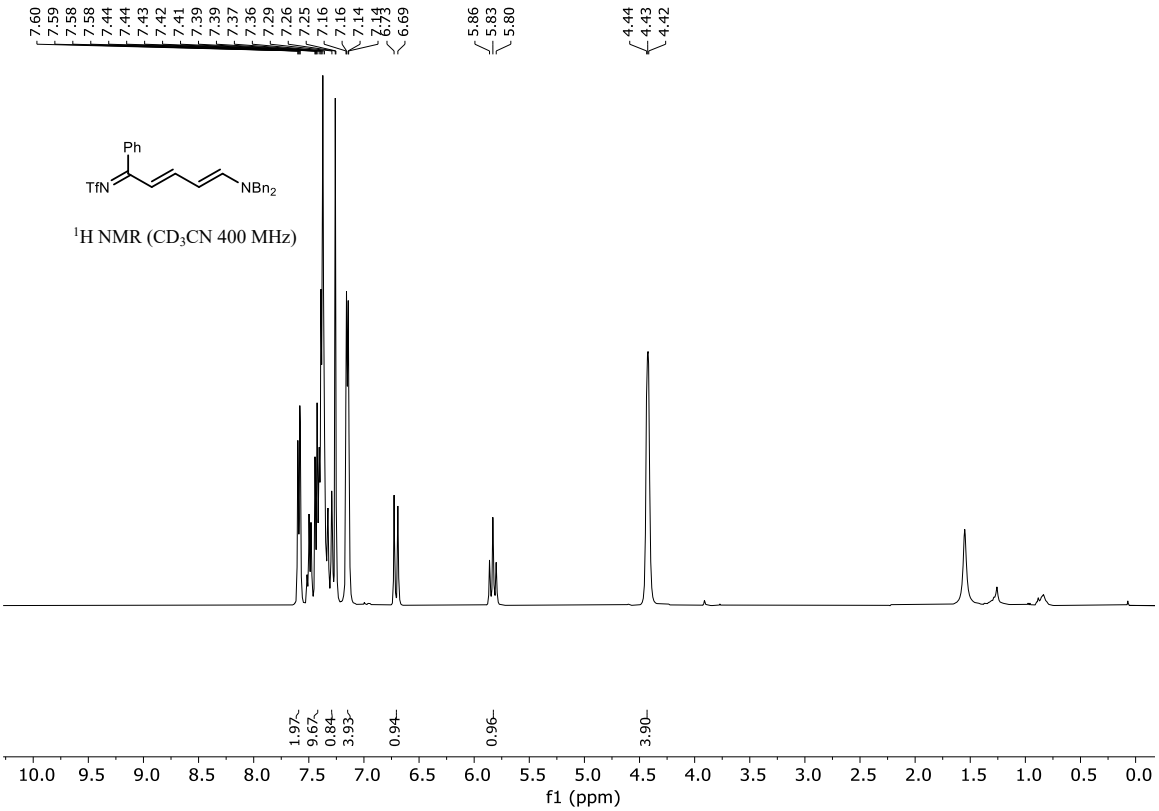
^{13}C NMR (CD_3OD 100 MHz)



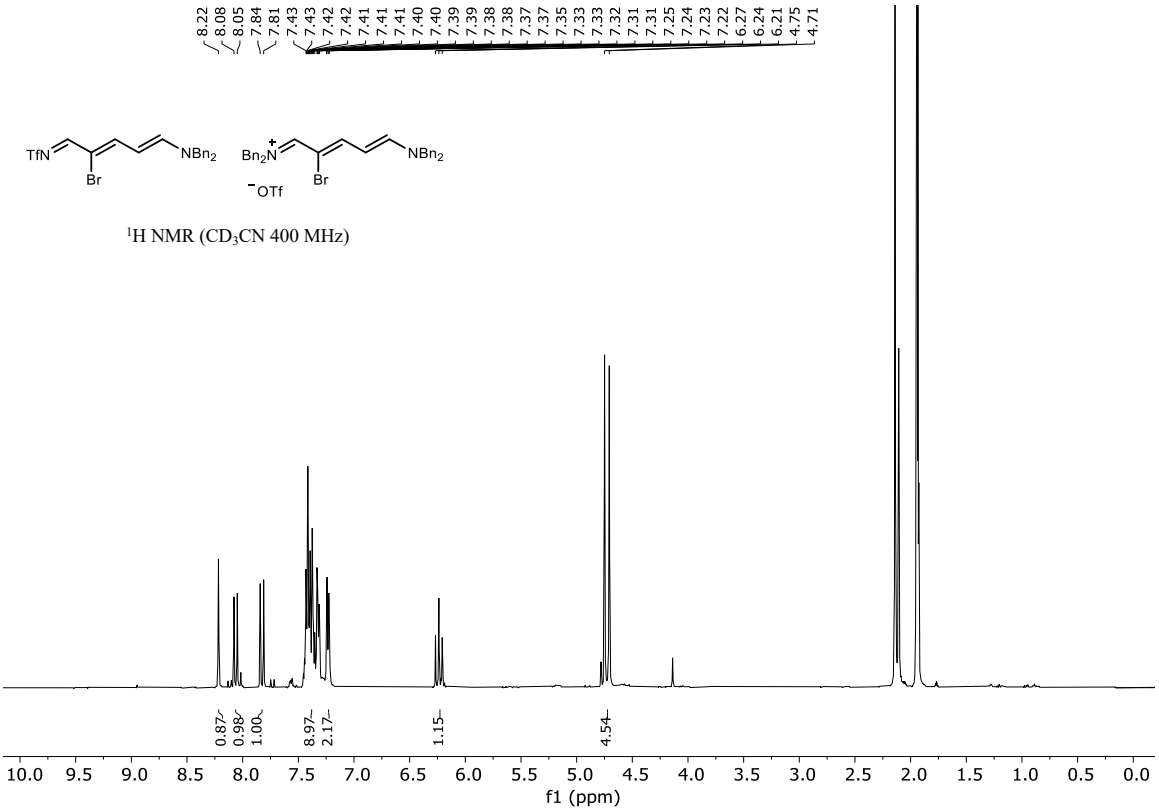
^{15}N NMR (CD_3OD 40 MHz)

^{19}F NMR (CD_3OD 100 MHz)

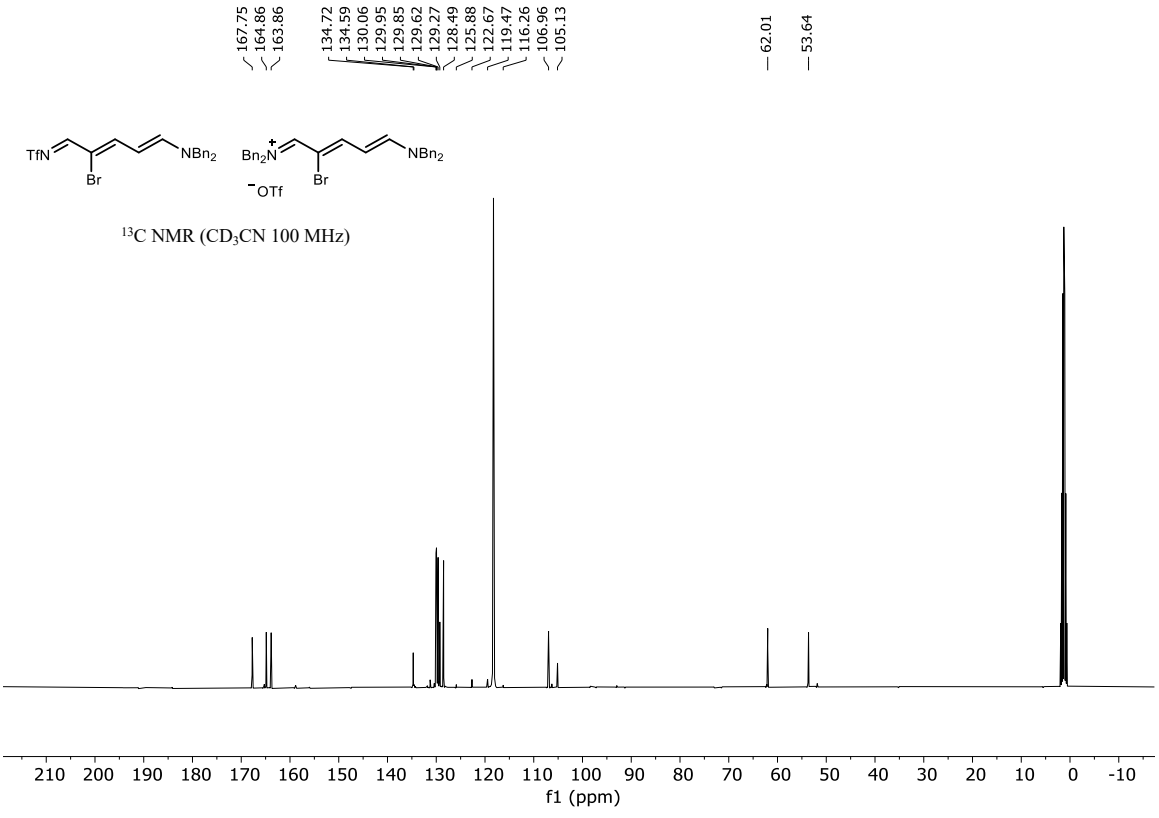




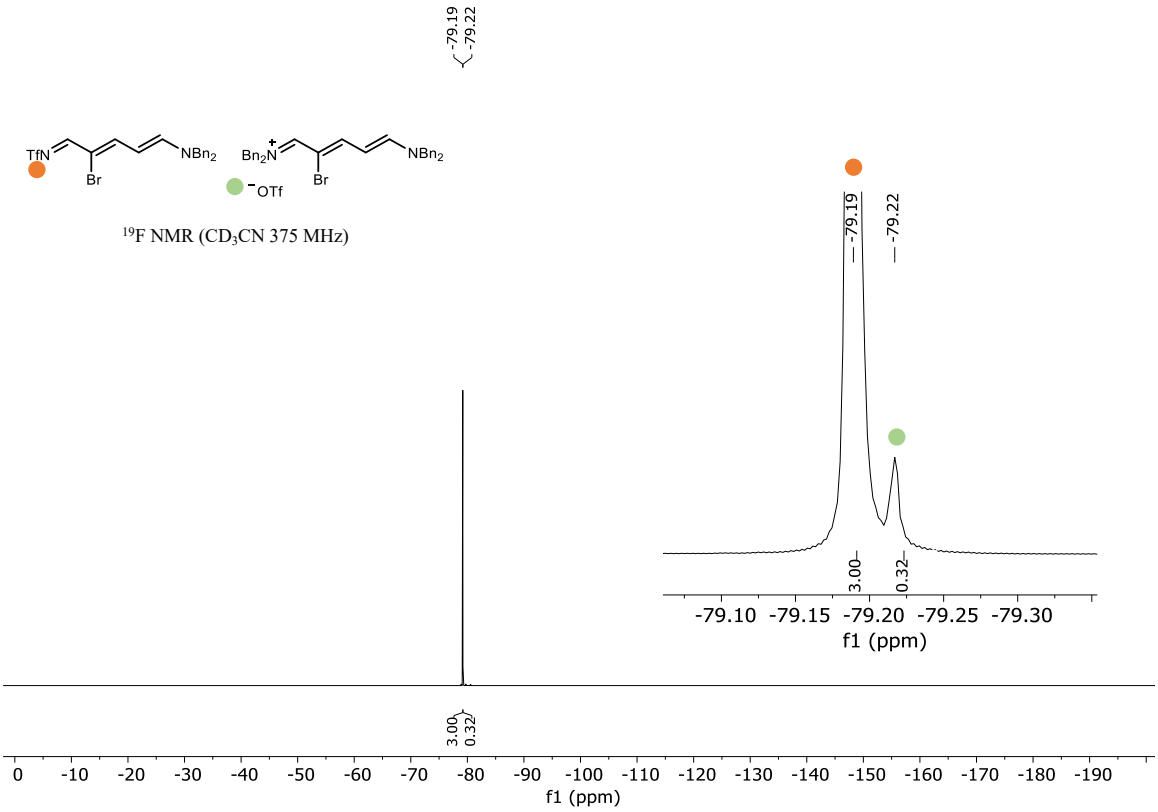
^{1}H NMR (CD_3CN 400 MHz)



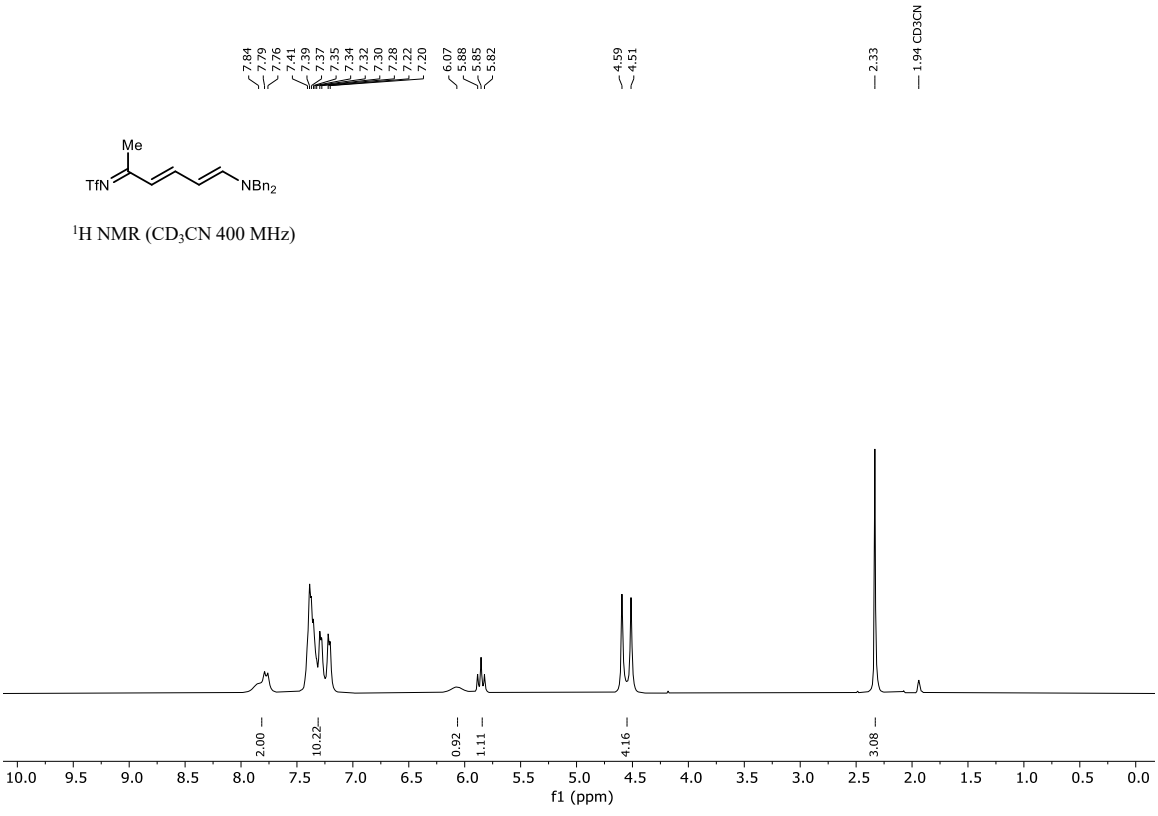
^{1}H NMR (CD_3CN 400 MHz)



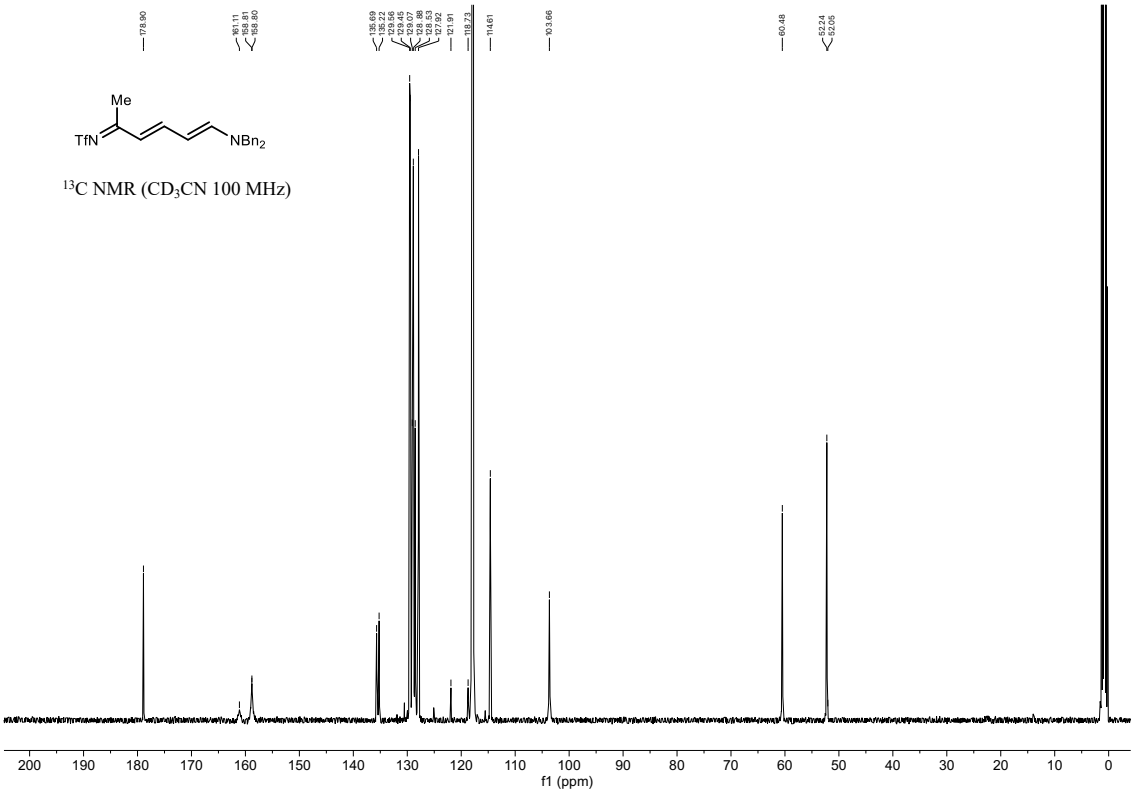
^{13}C NMR (CD_3CN 100 MHz)



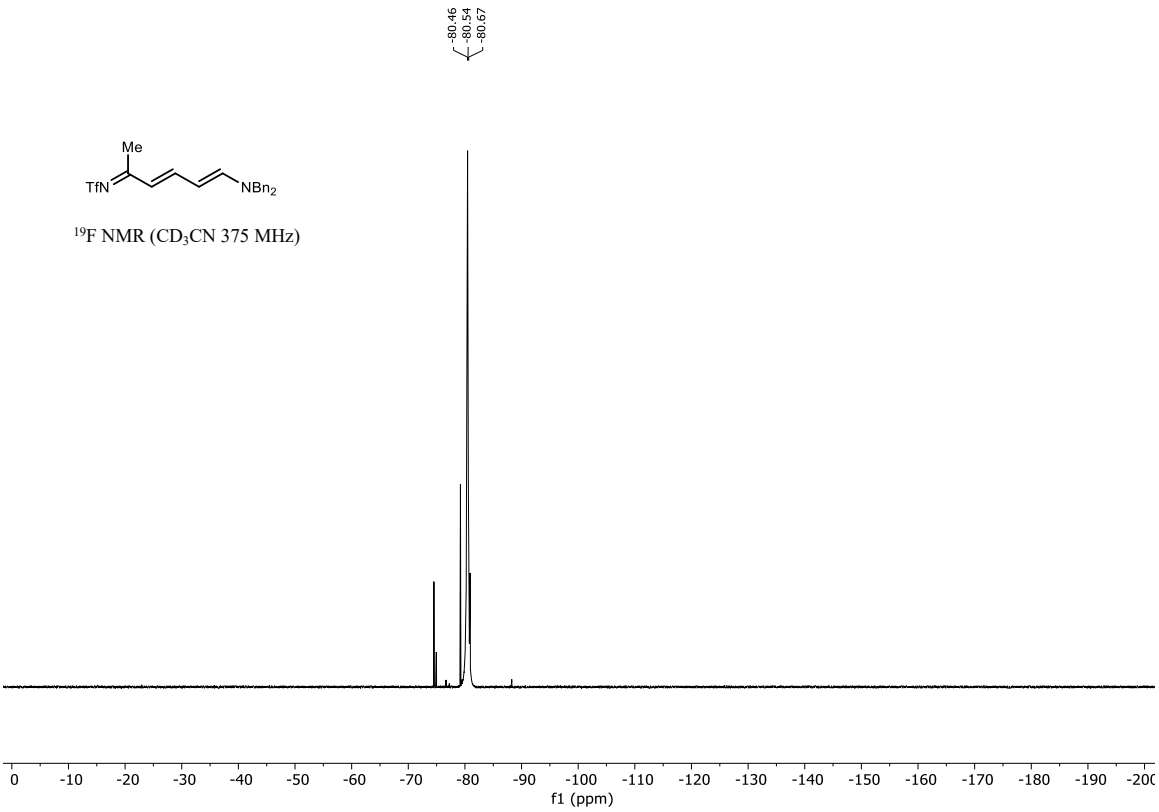
^{19}F NMR (CD_3CN 375 MHz)



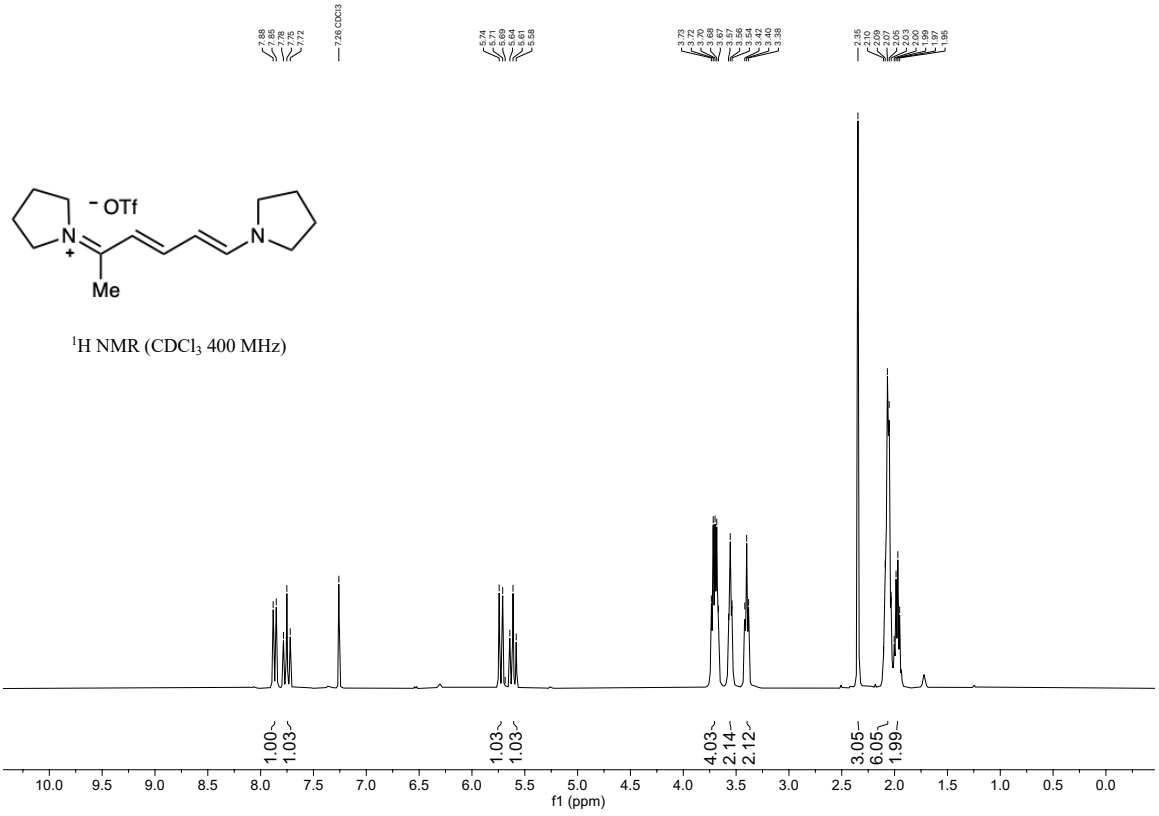
^{1}H NMR (CD_3CN 400 MHz)



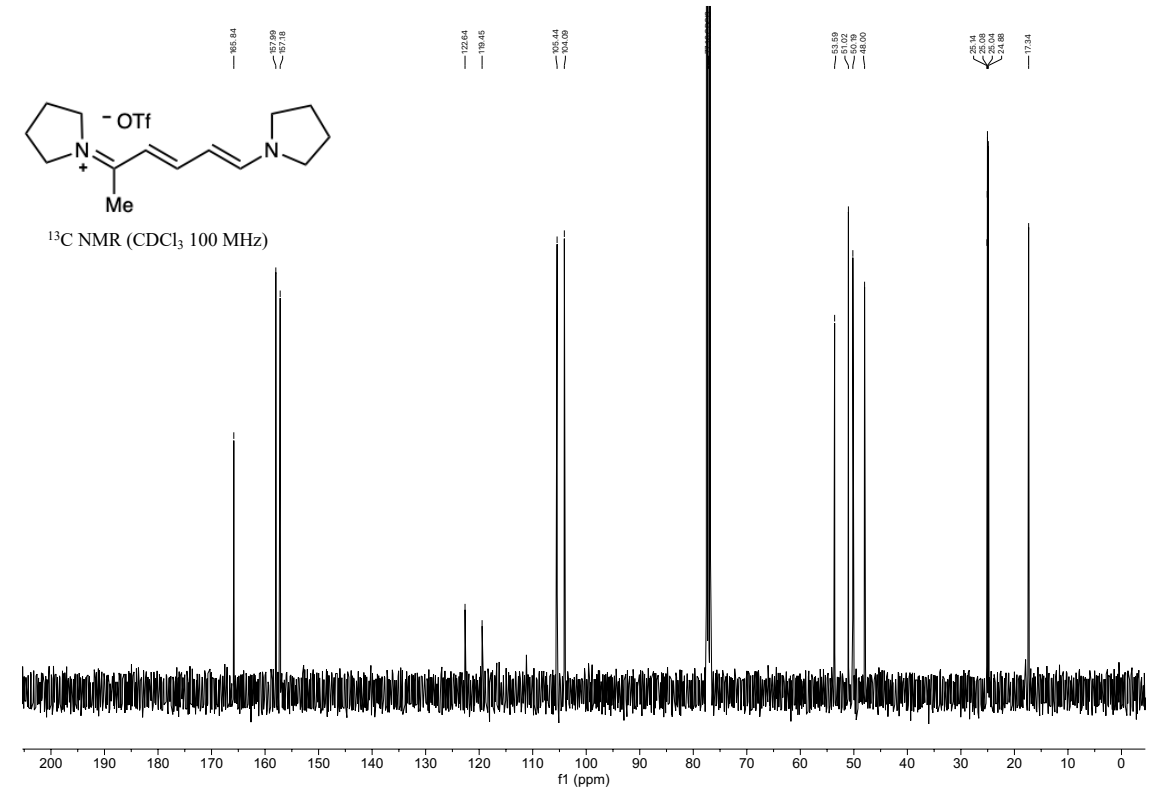
^{13}C NMR (CD_3CN 100 MHz)



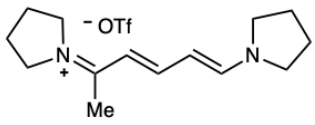
^{19}F NMR (CD_3CN 375 MHz)



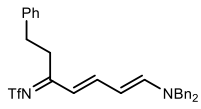
^{1}H NMR ($CDCl_3$ 400 MHz)



^{13}C NMR ($CDCl_3$ 100 MHz)



^{19}F NMR ($CDCl_3$ 375 MHz)



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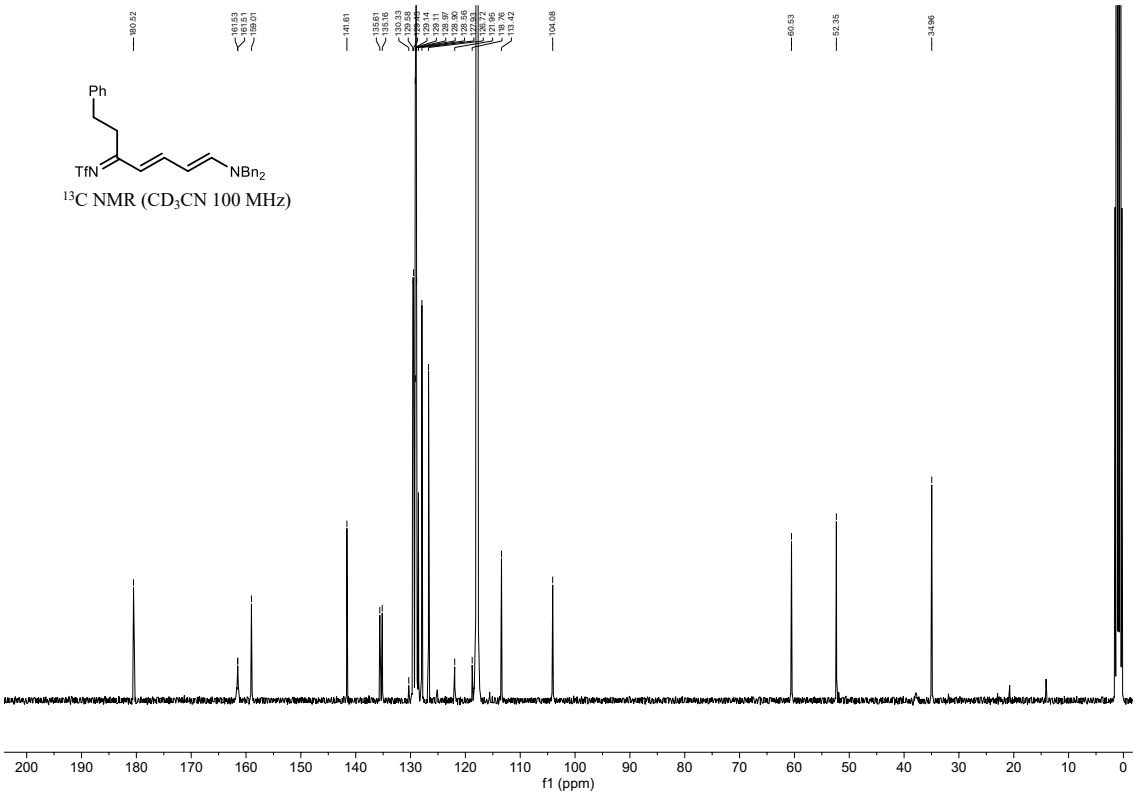

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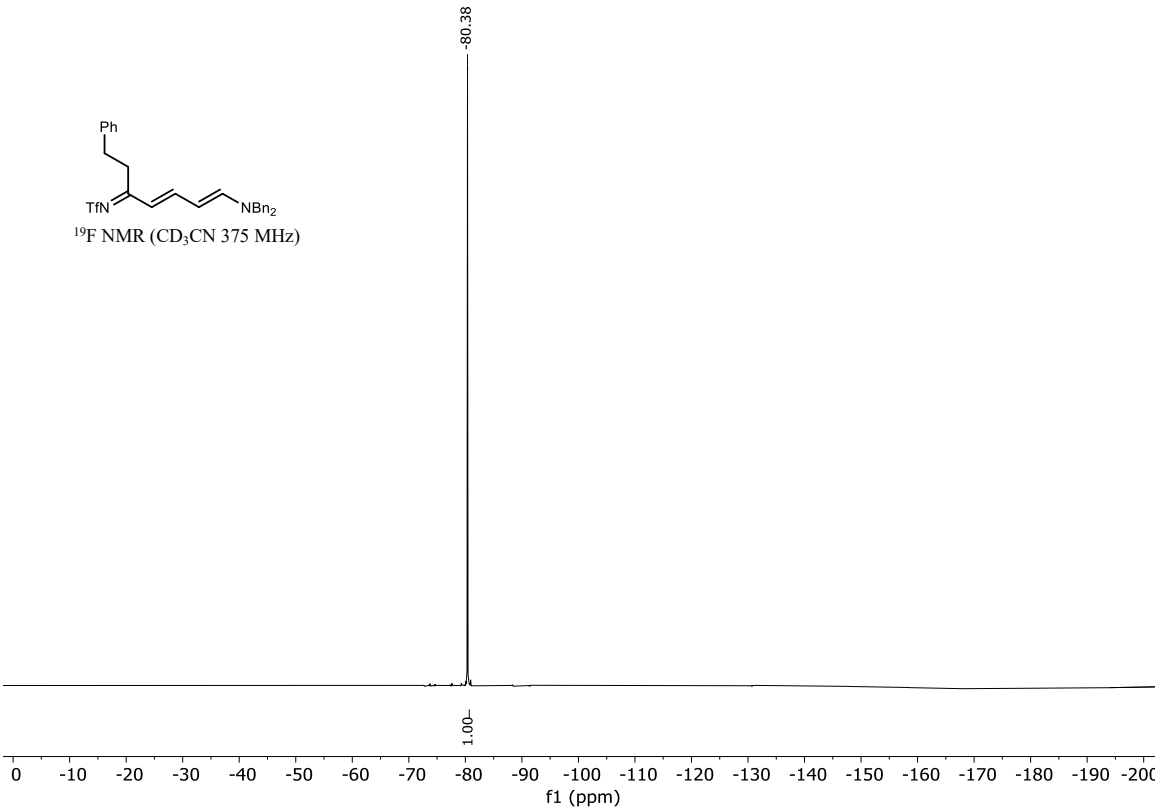

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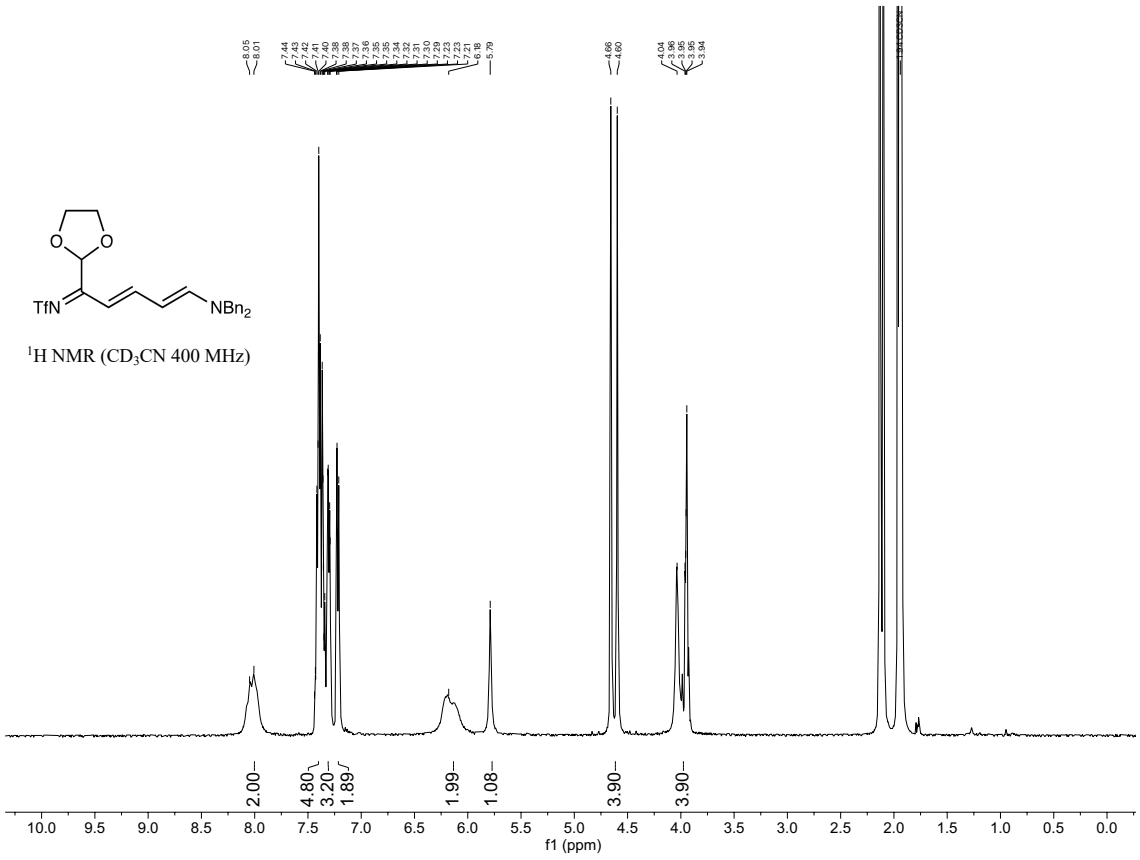

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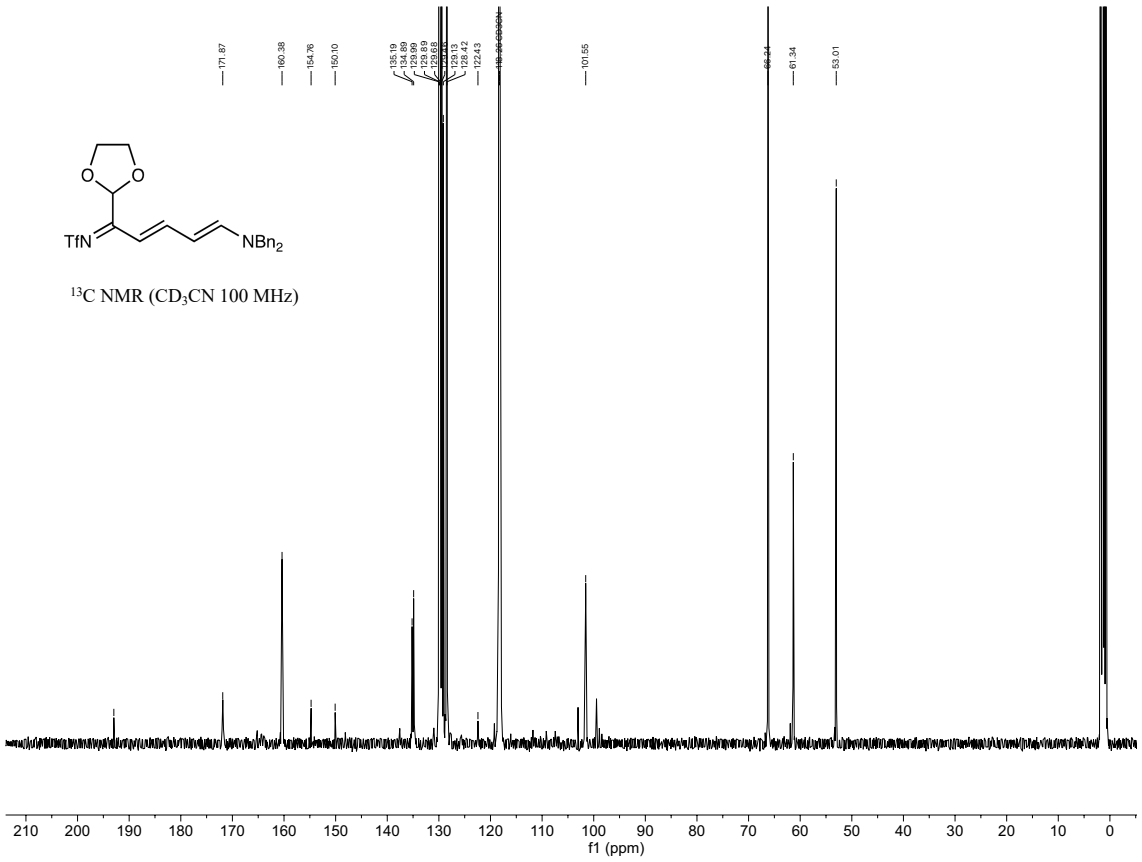

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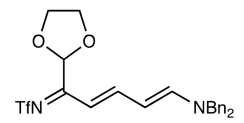

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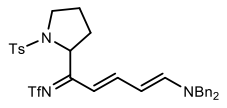

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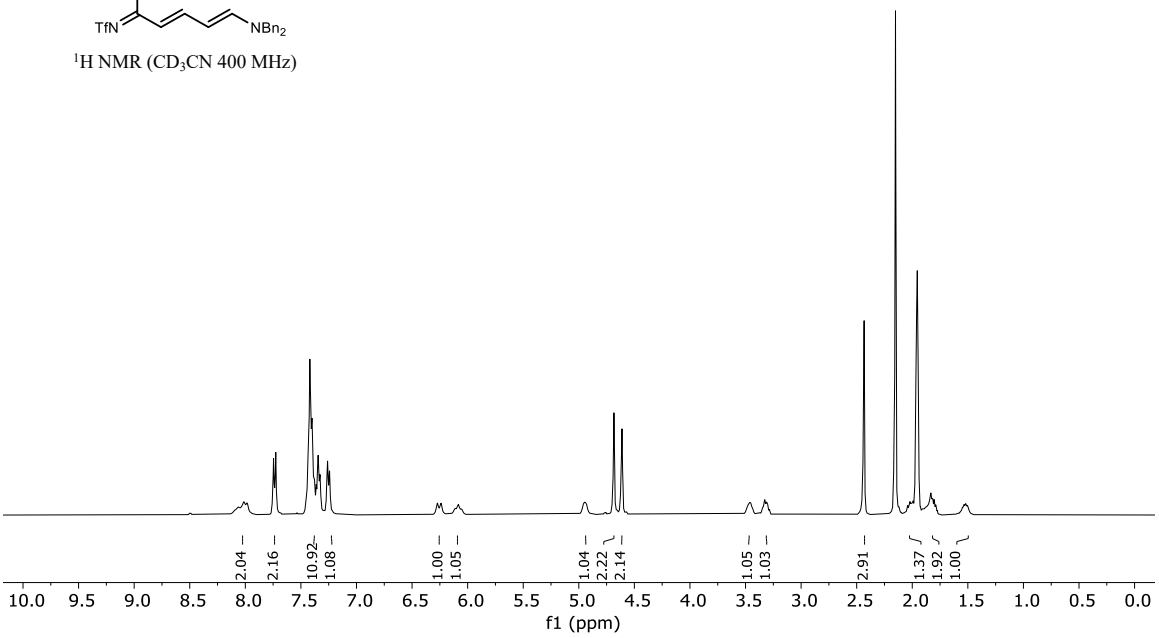
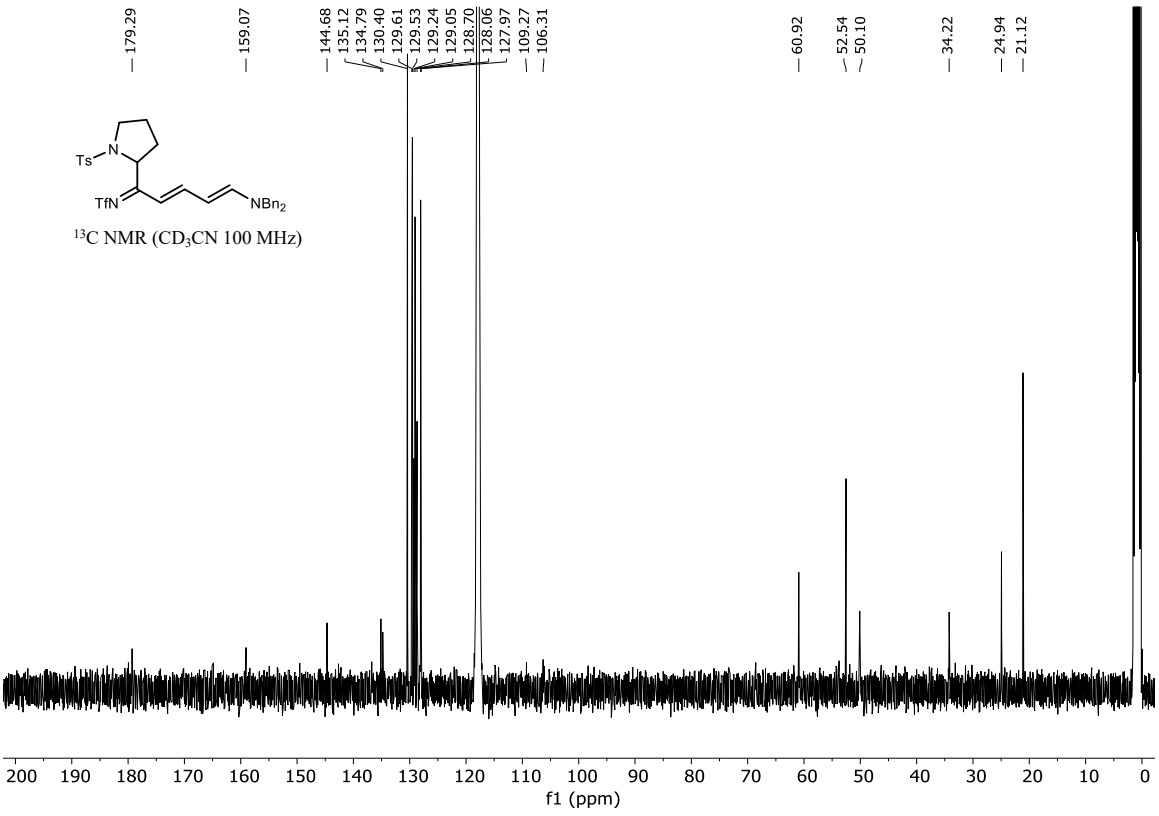
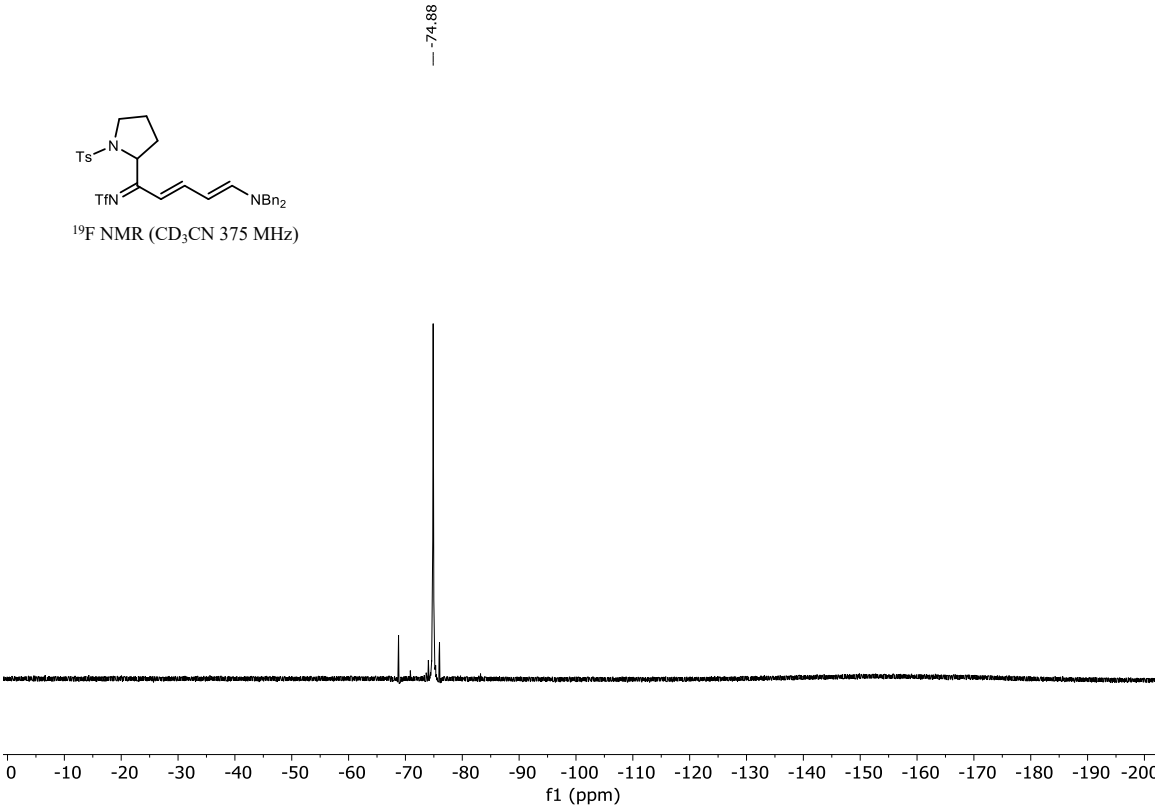




^{13}C NMR (CD_3CN 100 MHz)



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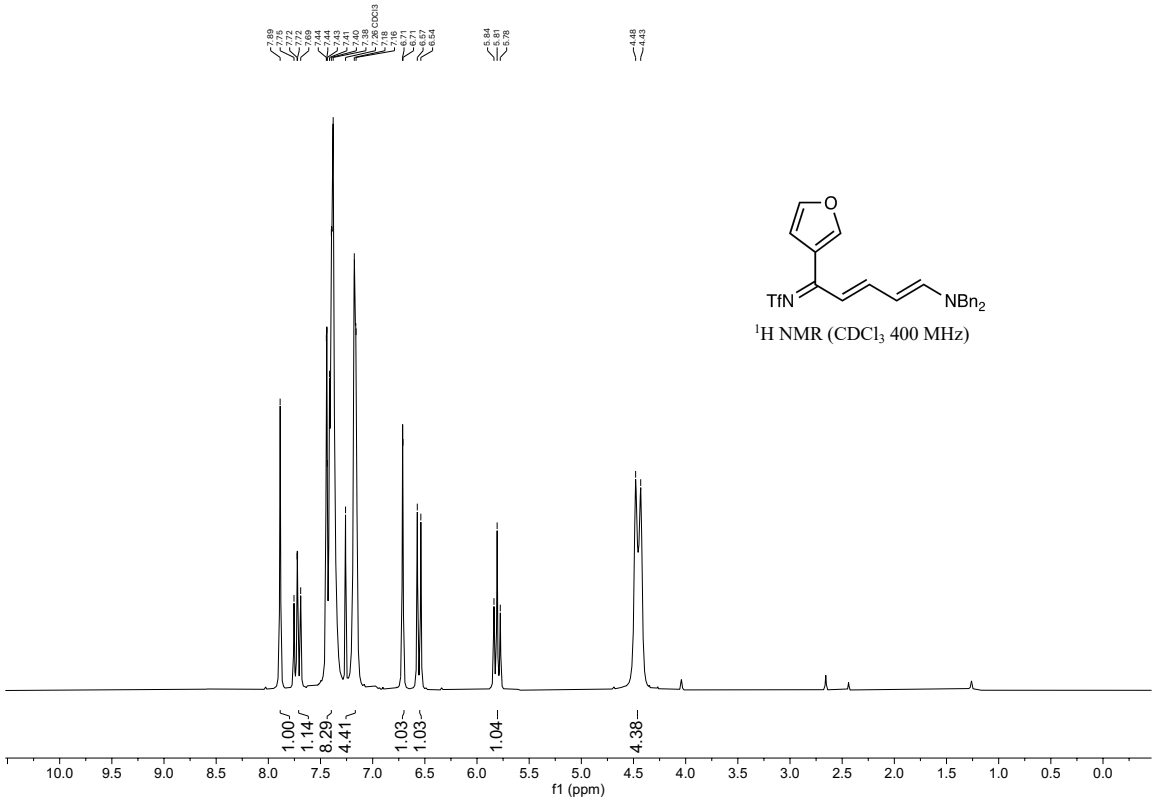
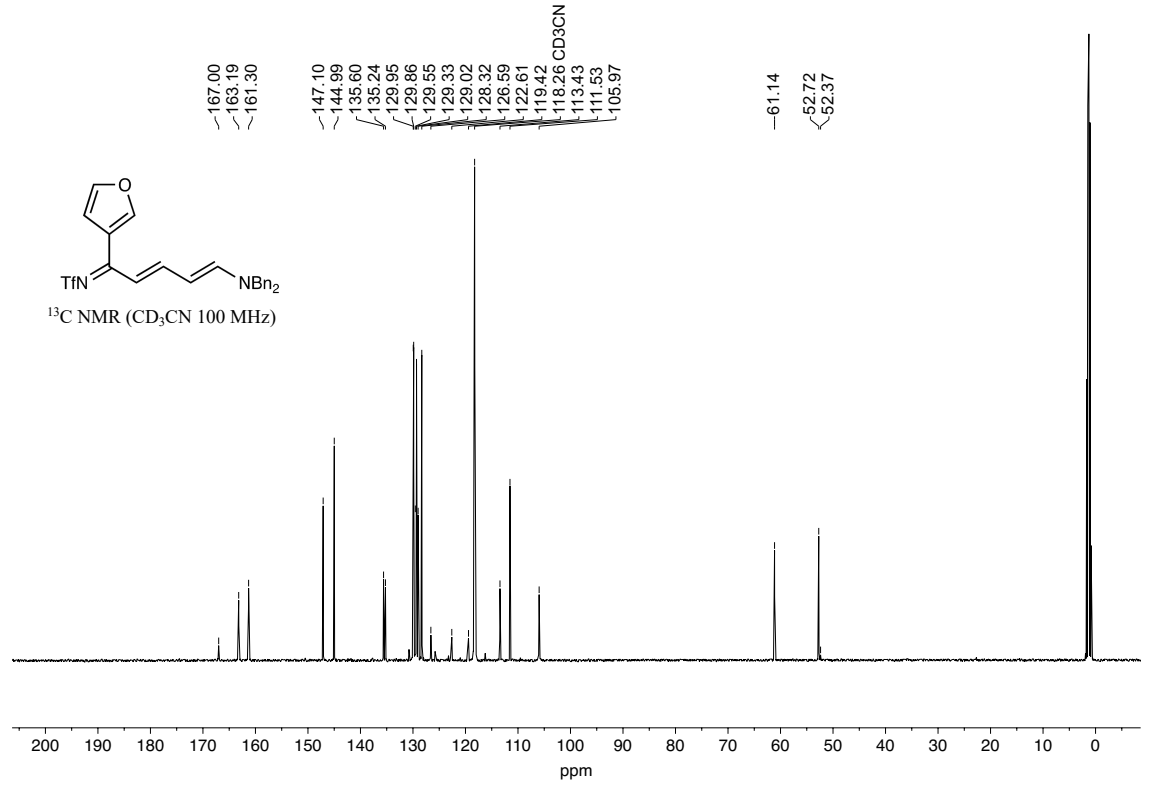
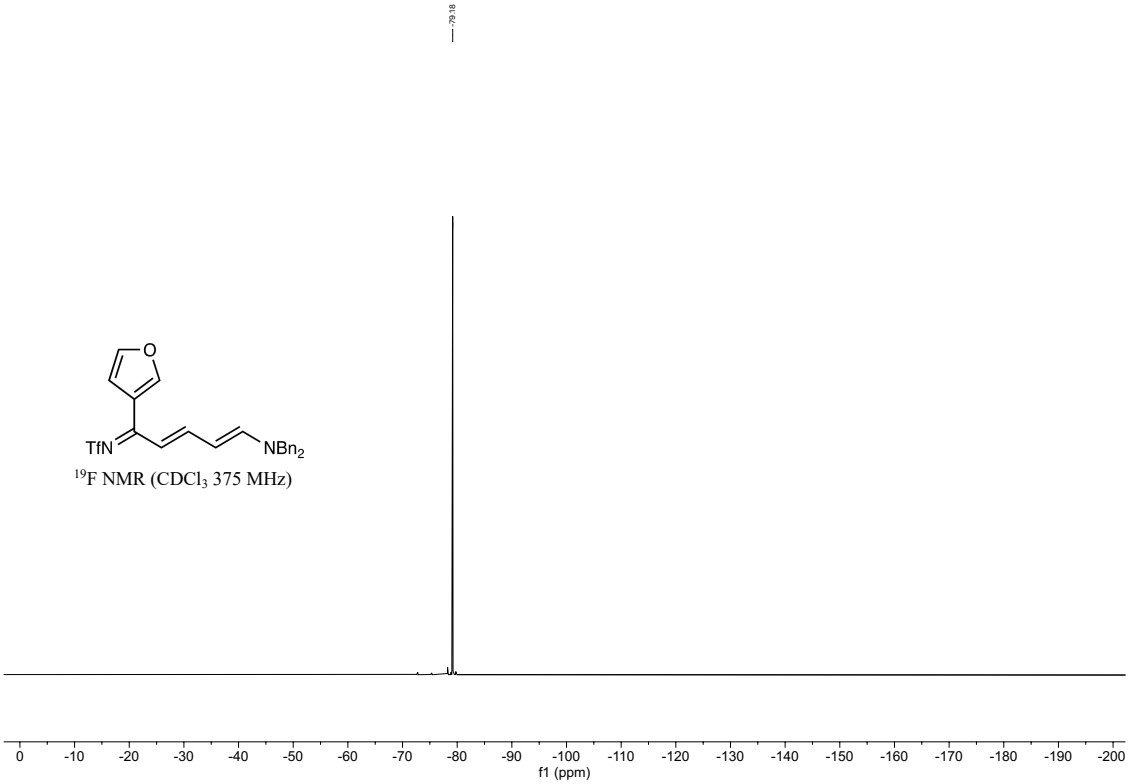


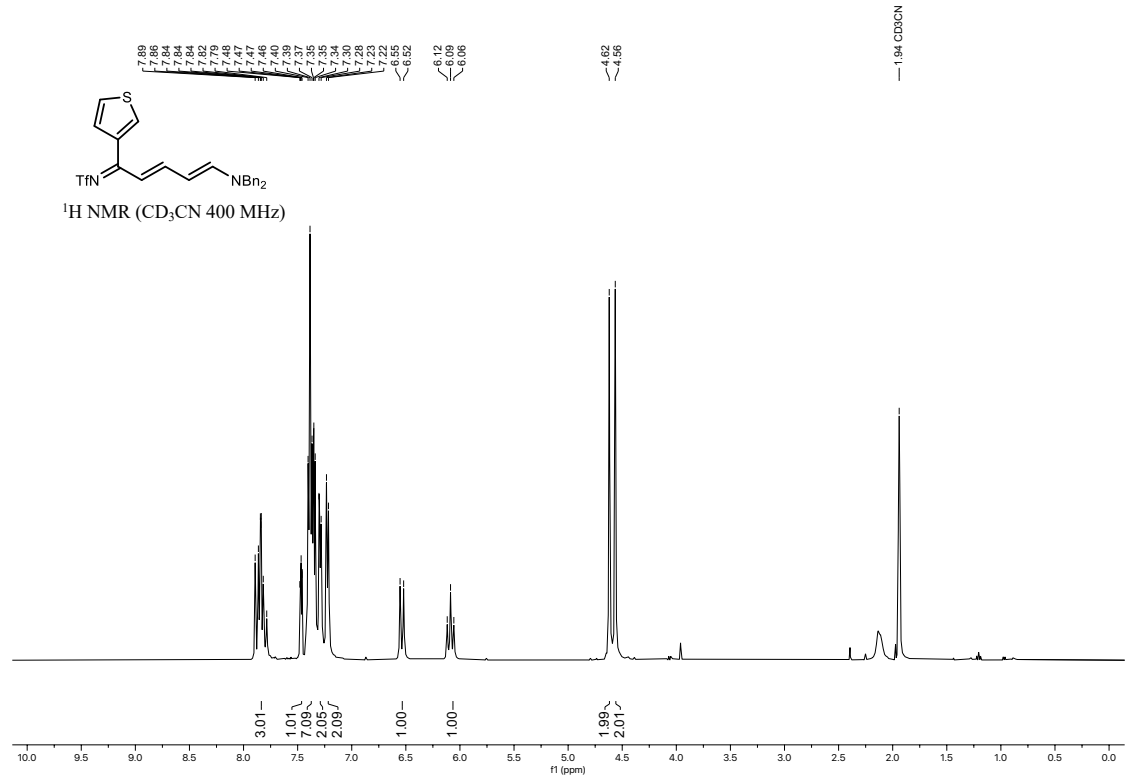
^{1}H NMR ($CDCl_3$ 400 MHz)



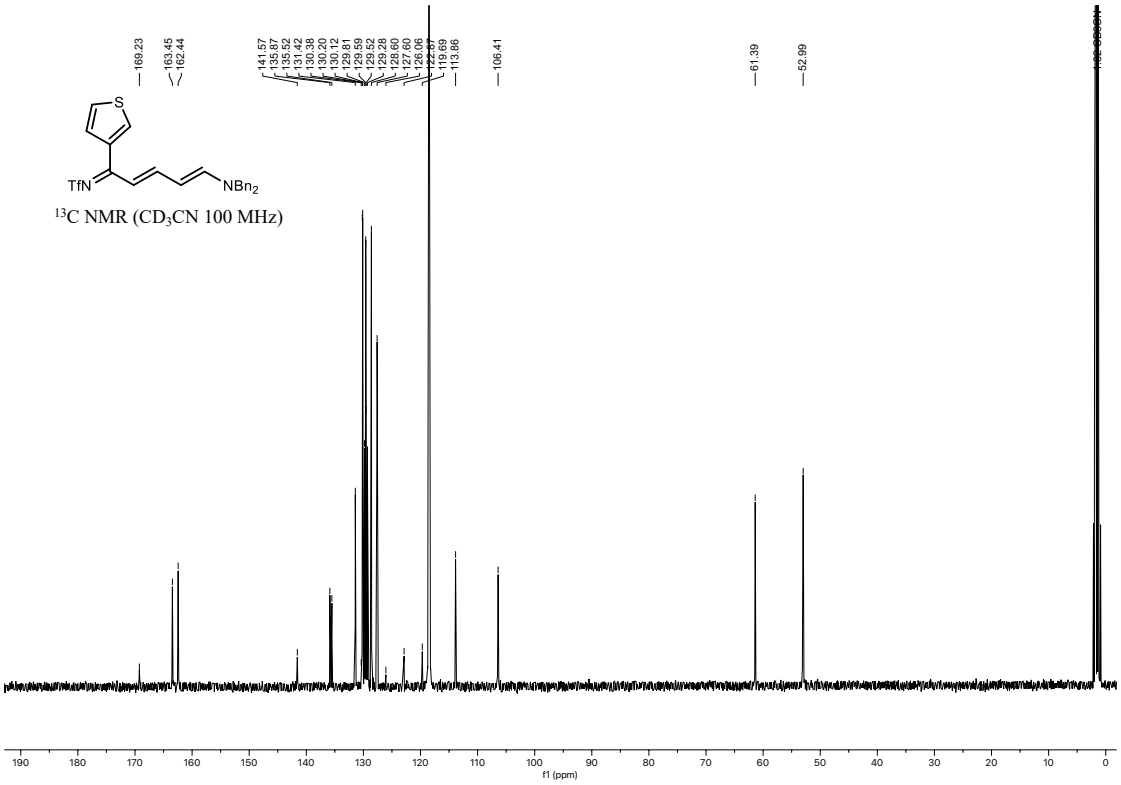
^{13}C NMR (CD_3CN 100 MHz)



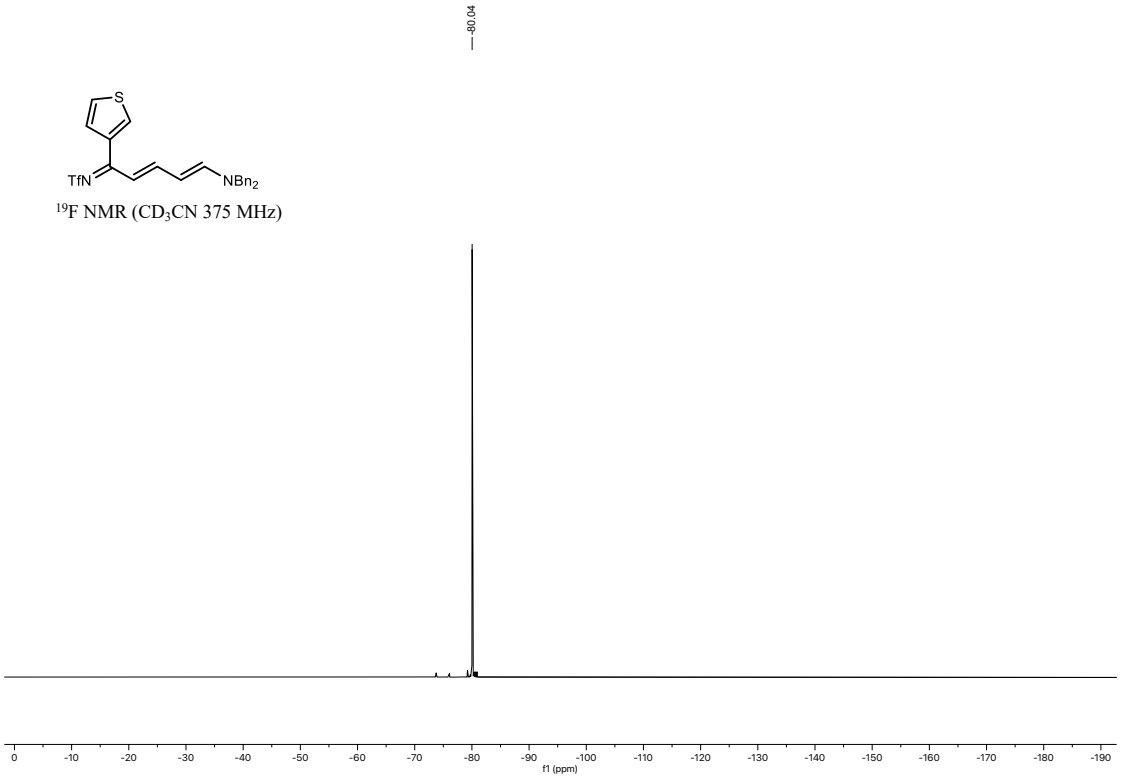
^{19}F NMR ($CDCl_3$ 375 MHz)



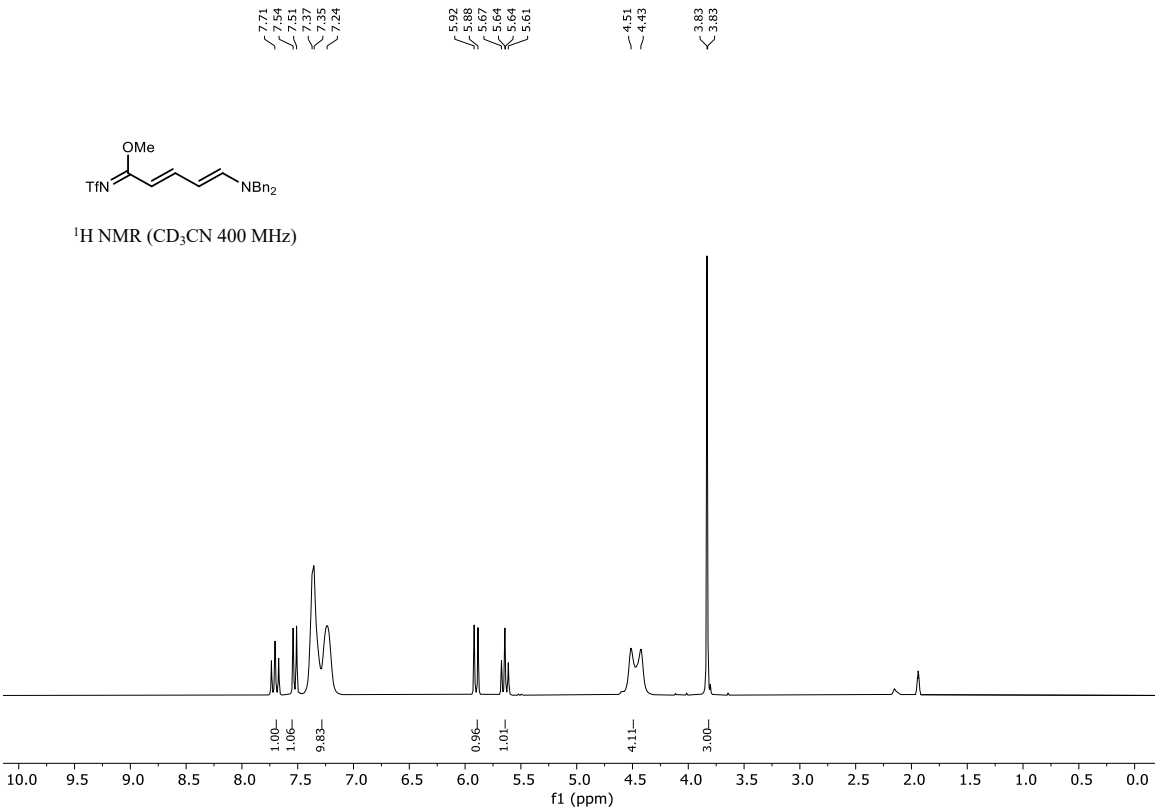
^{1}H NMR (CD_3CN 400 MHz)



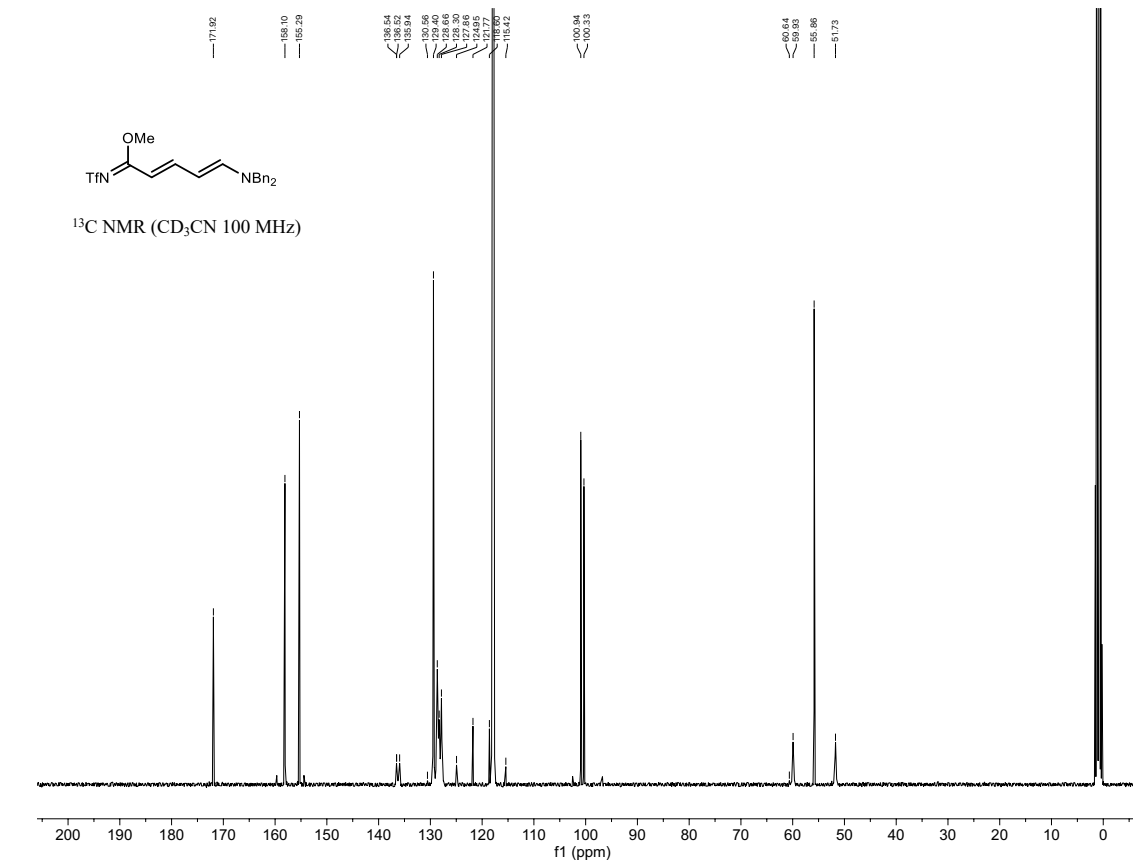
^{13}C NMR (CD_3CN 100 MHz)



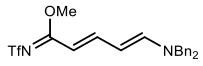
^{19}F NMR (CD_3CN 375 MHz)



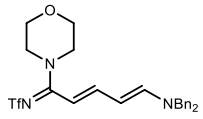
^{1}H NMR (CD_3CN 400 MHz)



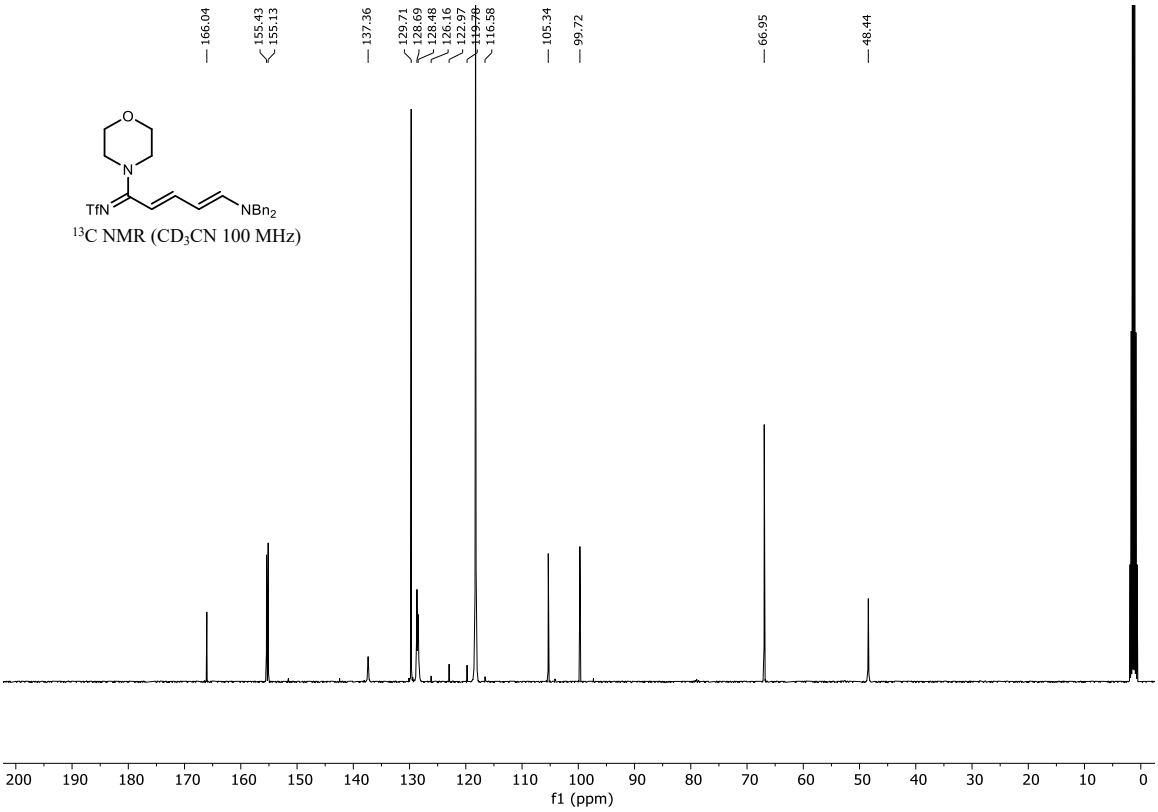
^{13}C NMR (CD_3CN 100 MHz)



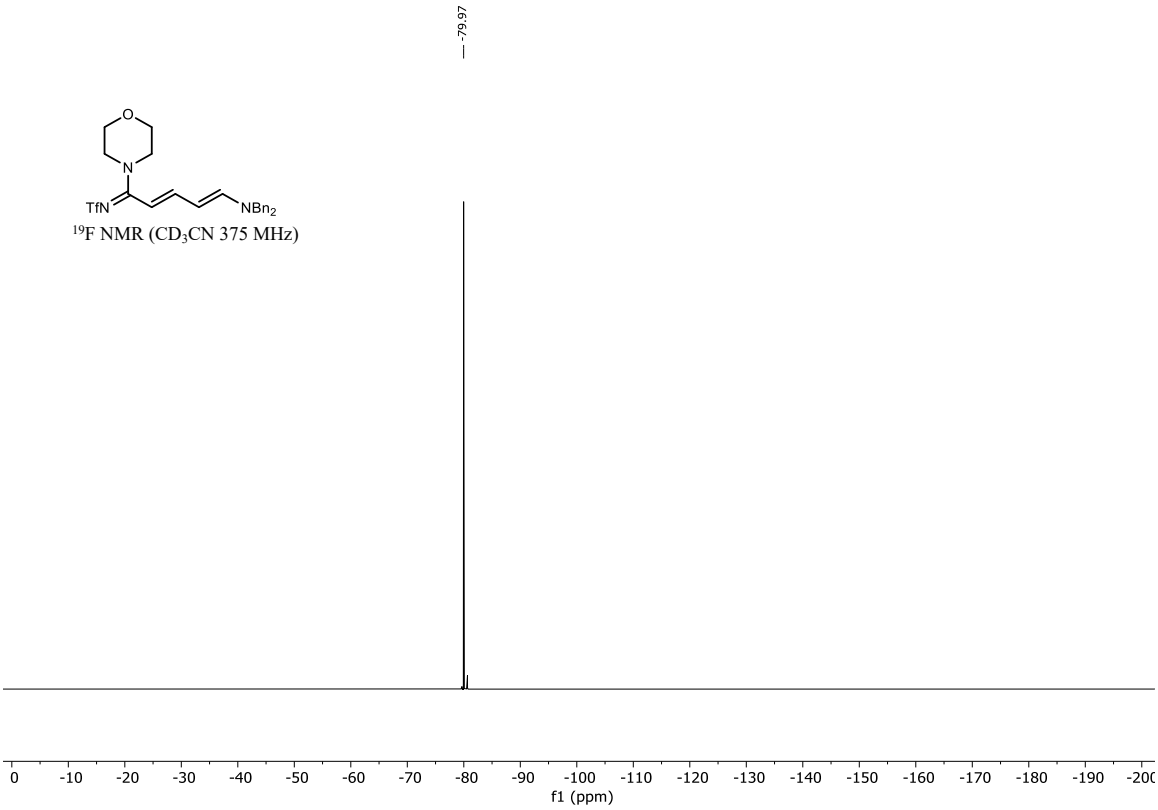
^{19}F NMR (CD_3CN 375 MHz)



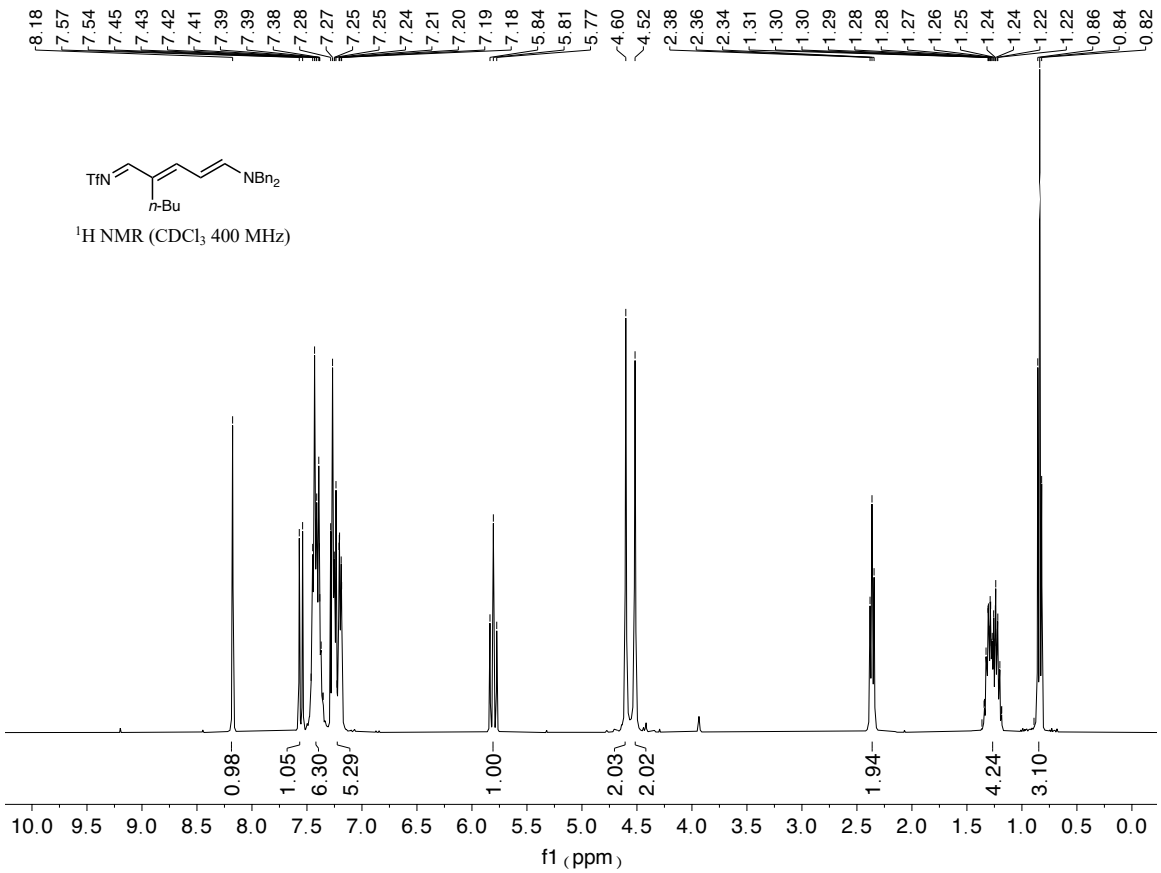
^{1}H NMR (CD_3CN 400 MHz)



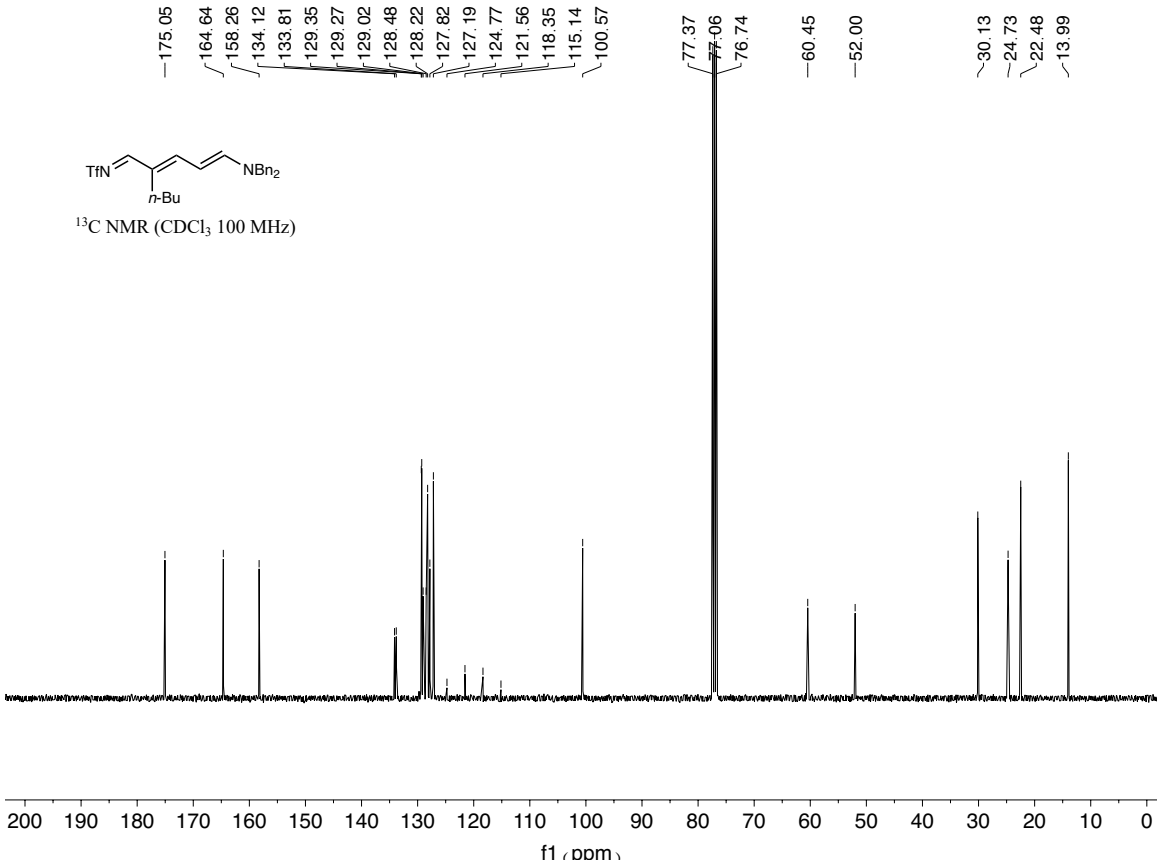
^{13}C NMR (CD_3CN 100 MHz)



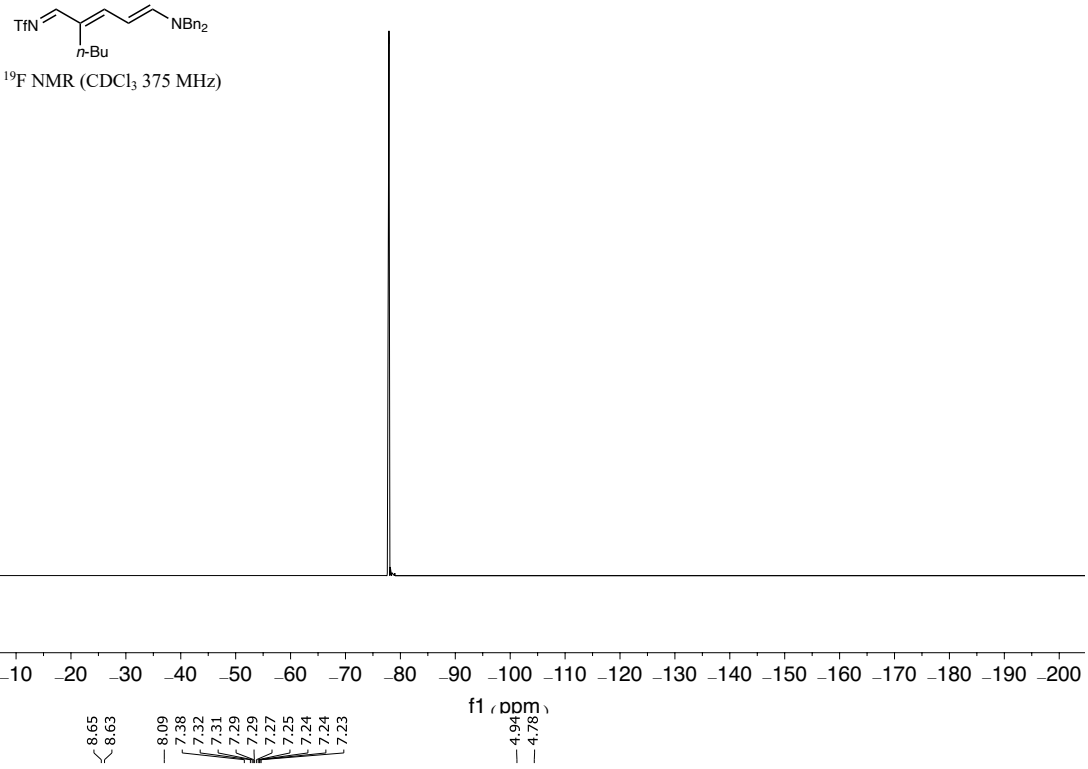
^{19}F NMR (CD_3CN 375 MHz)



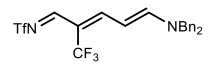
^{1}H NMR ($CDCl_3$ 400 MHz)



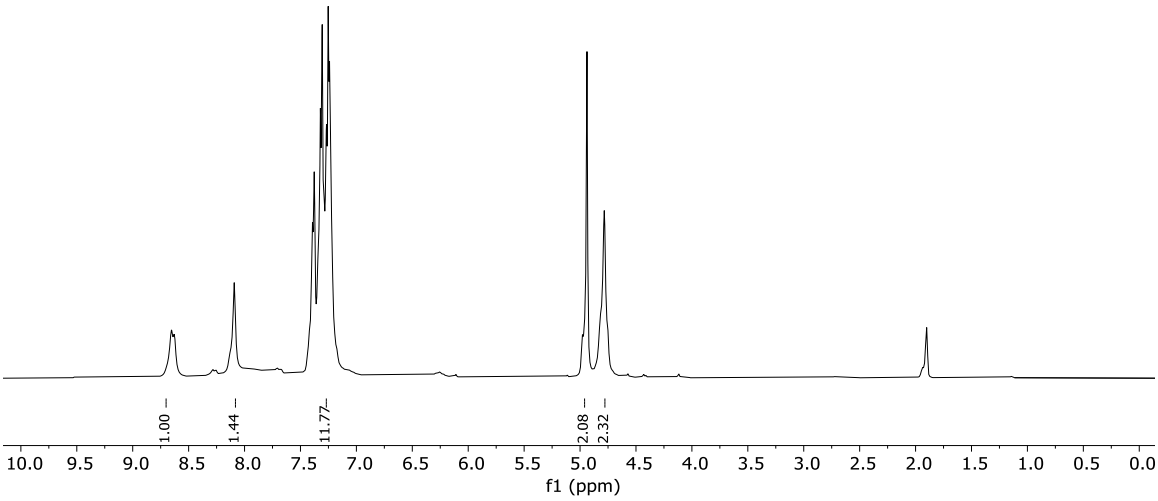
^{13}C NMR ($CDCl_3$ 100 MHz)

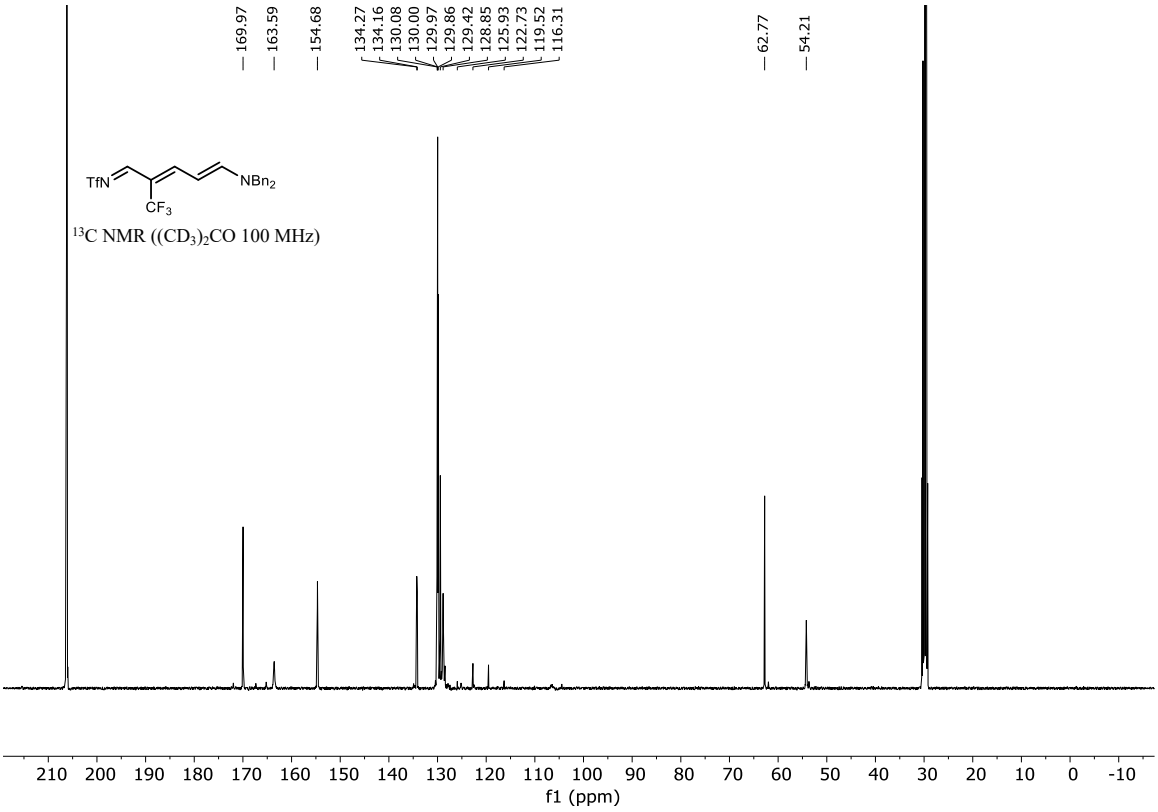


^{19}F NMR ($CDCl_3$ 375 MHz)

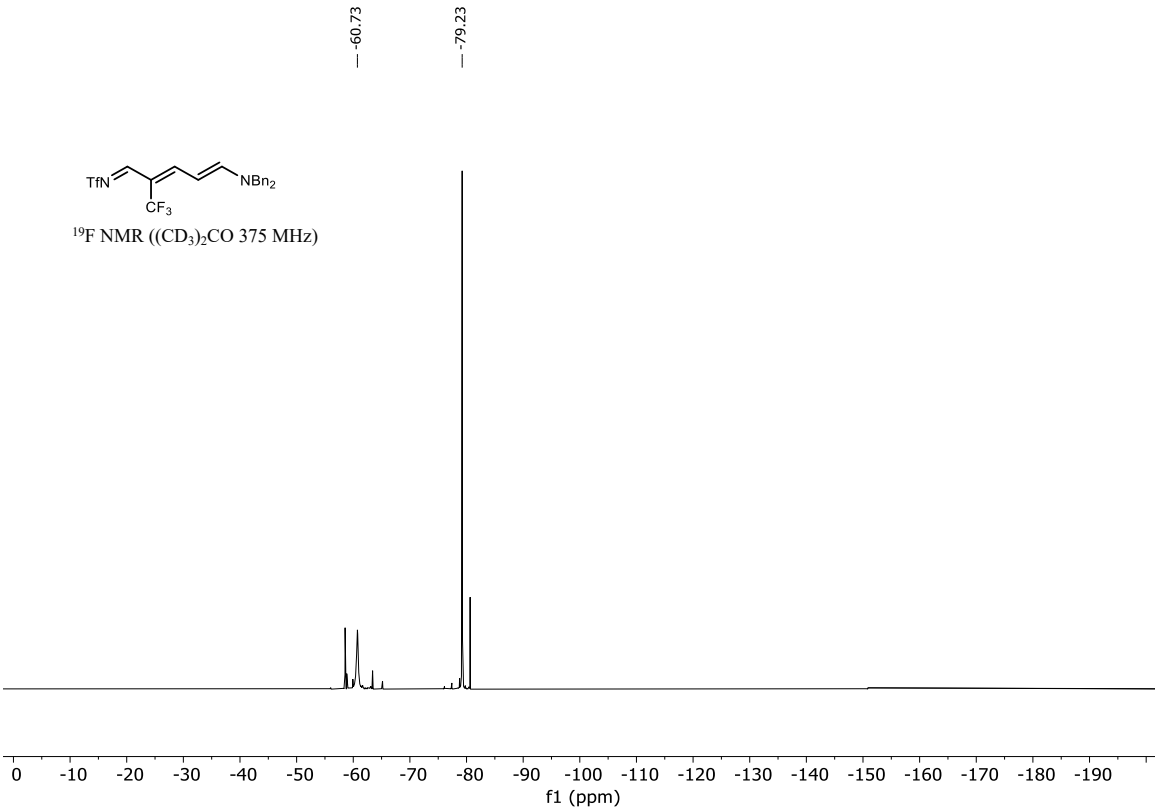


^{1}H NMR ($(CD_3)_2CO$ 400 MHz)

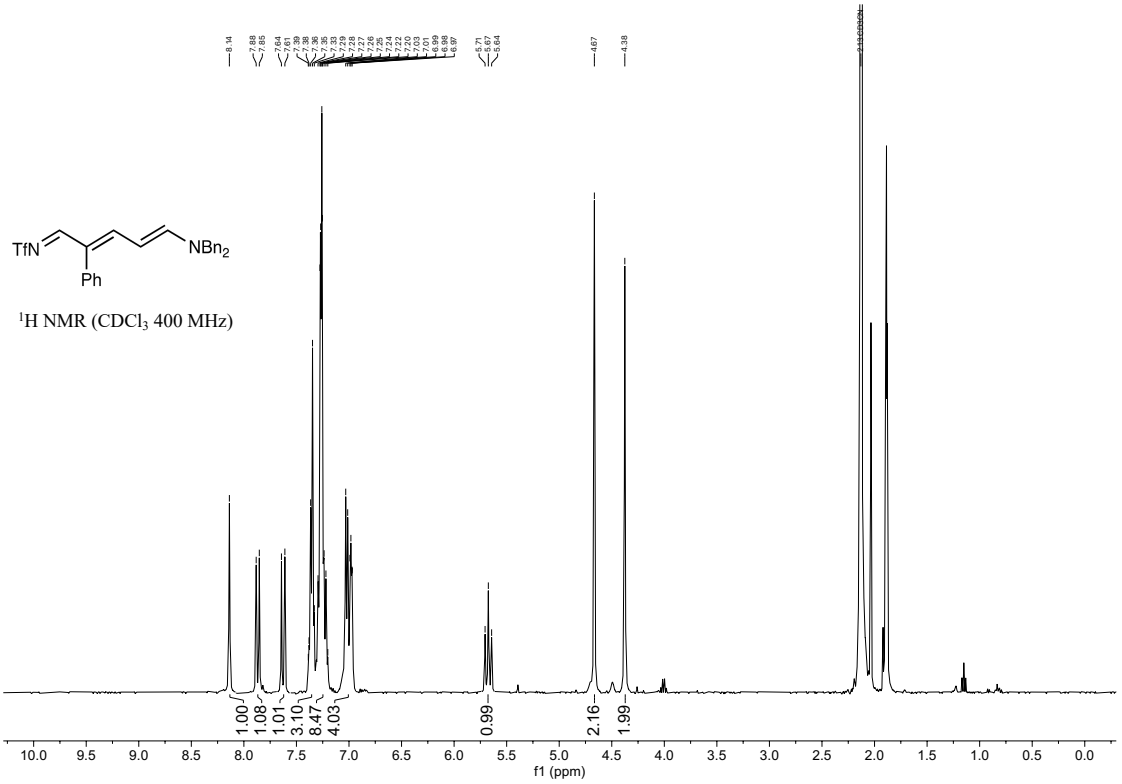




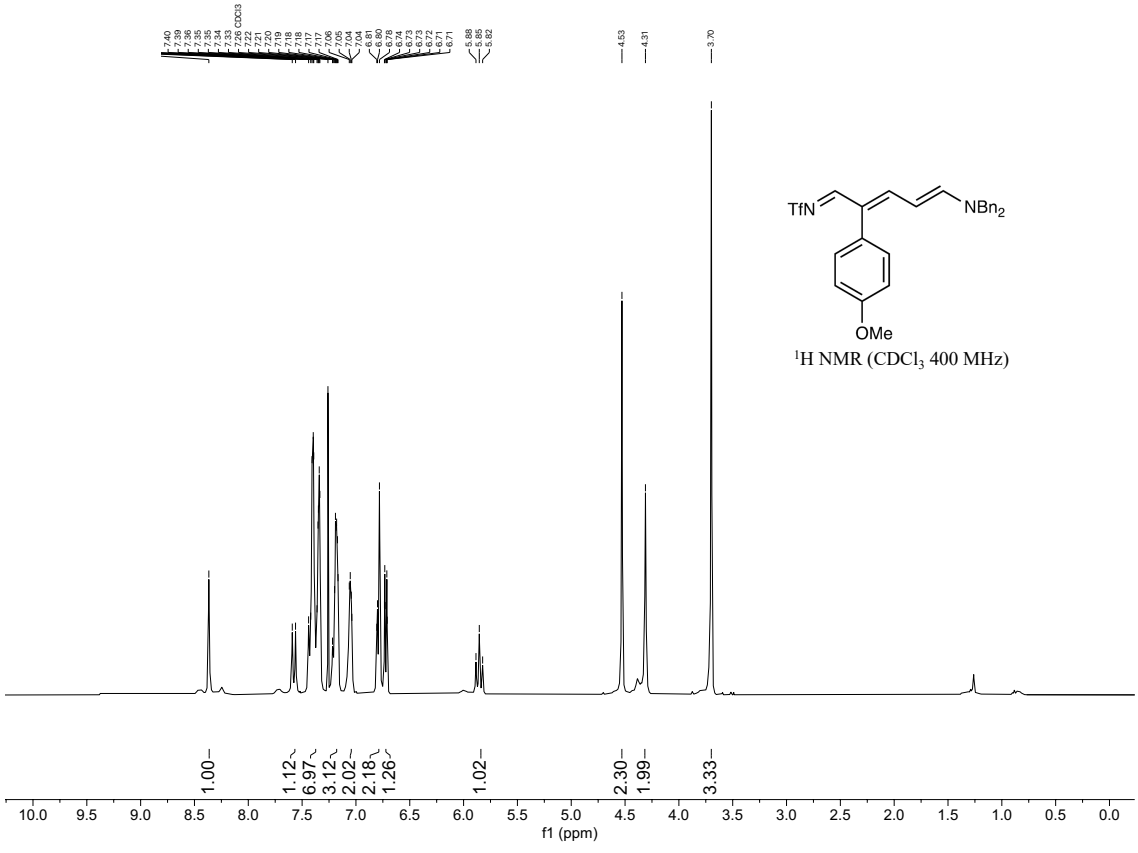
^{13}C NMR ($(CD_3)_2CO$ 100 MHz)



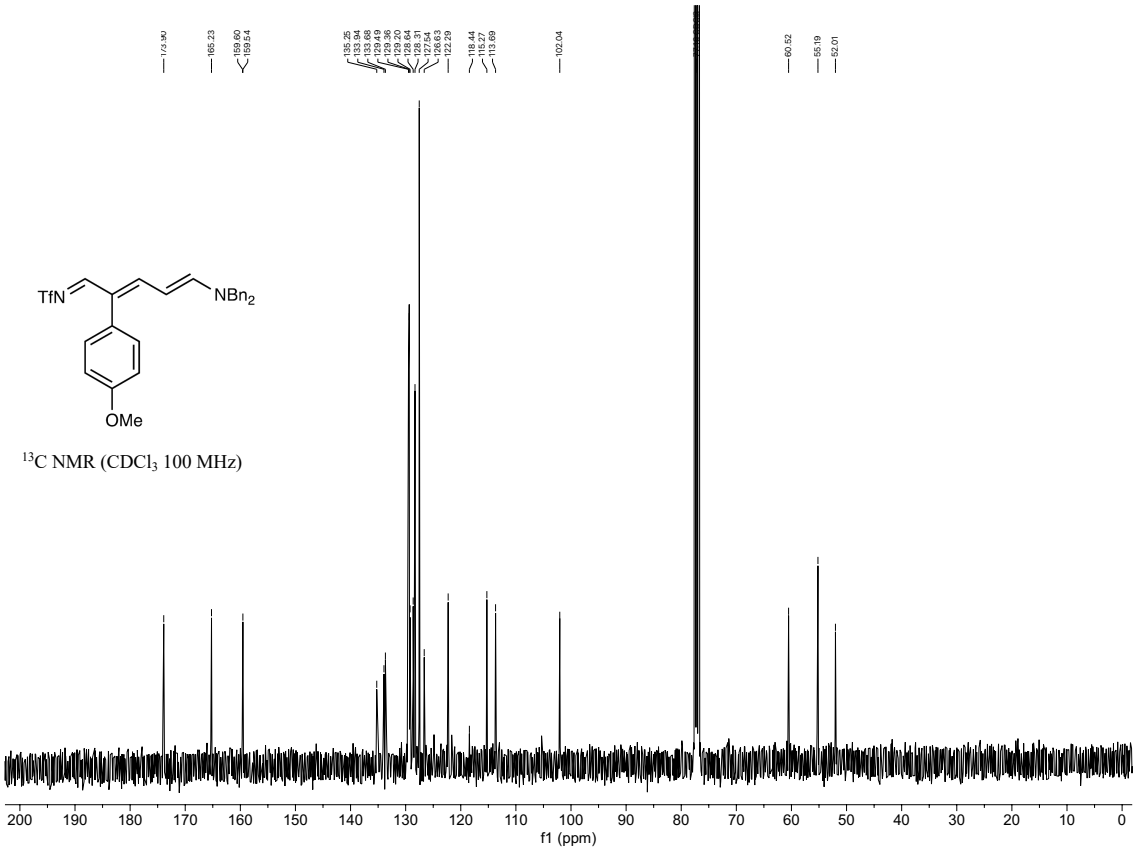
^{19}F NMR ($(CD_3)_2CO$ 375 MHz)



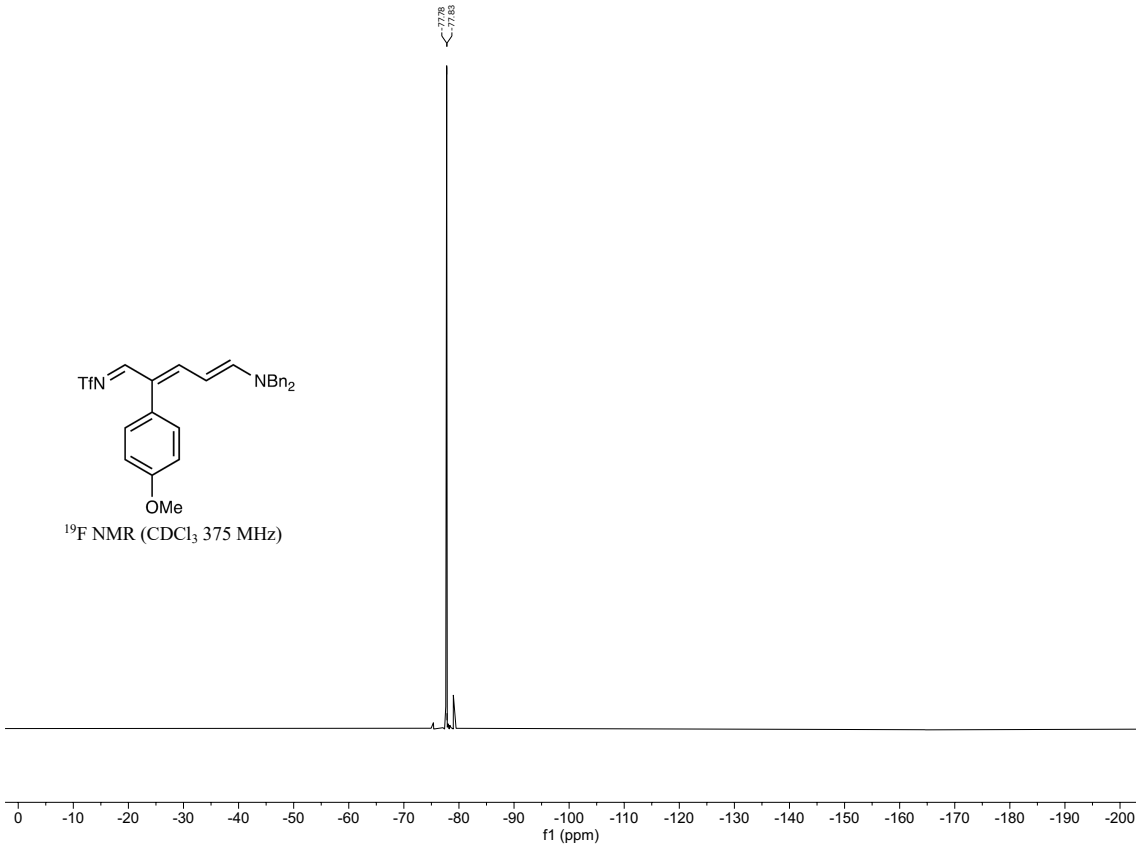
^{1}H NMR ($CDCl_3$ 400 MHz)



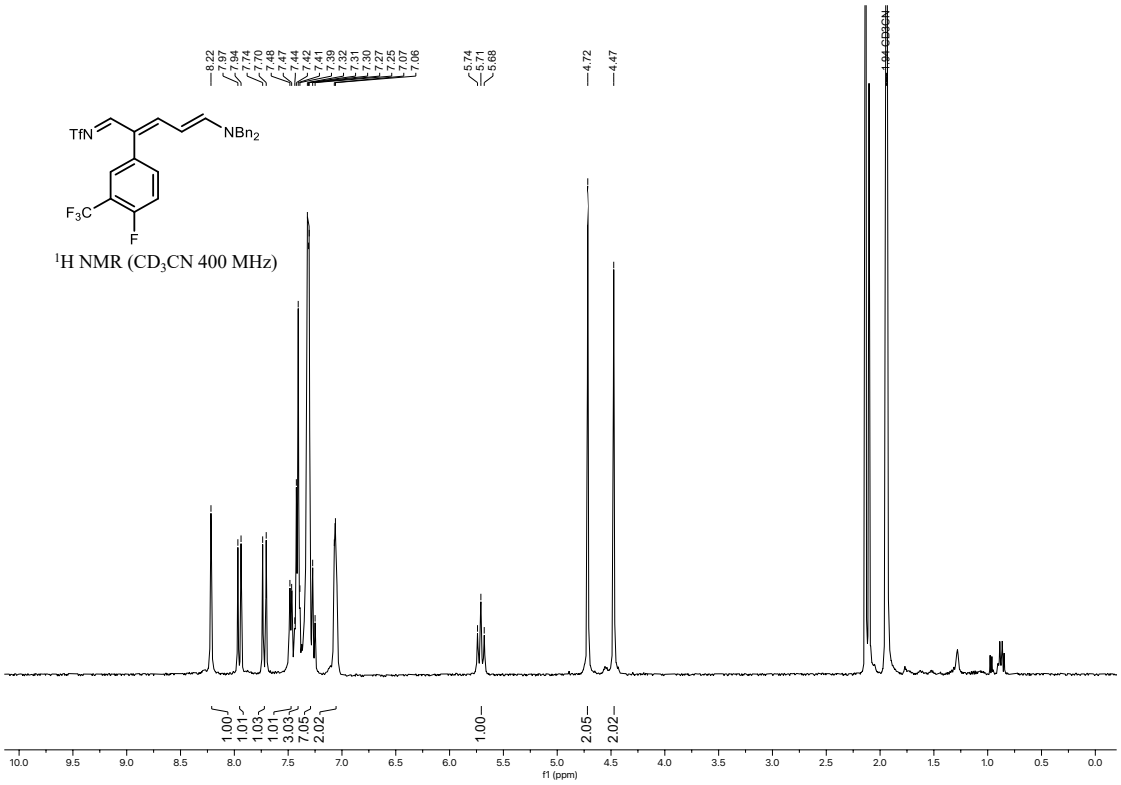
^{1}H NMR ($CDCl_3$ 400 MHz)



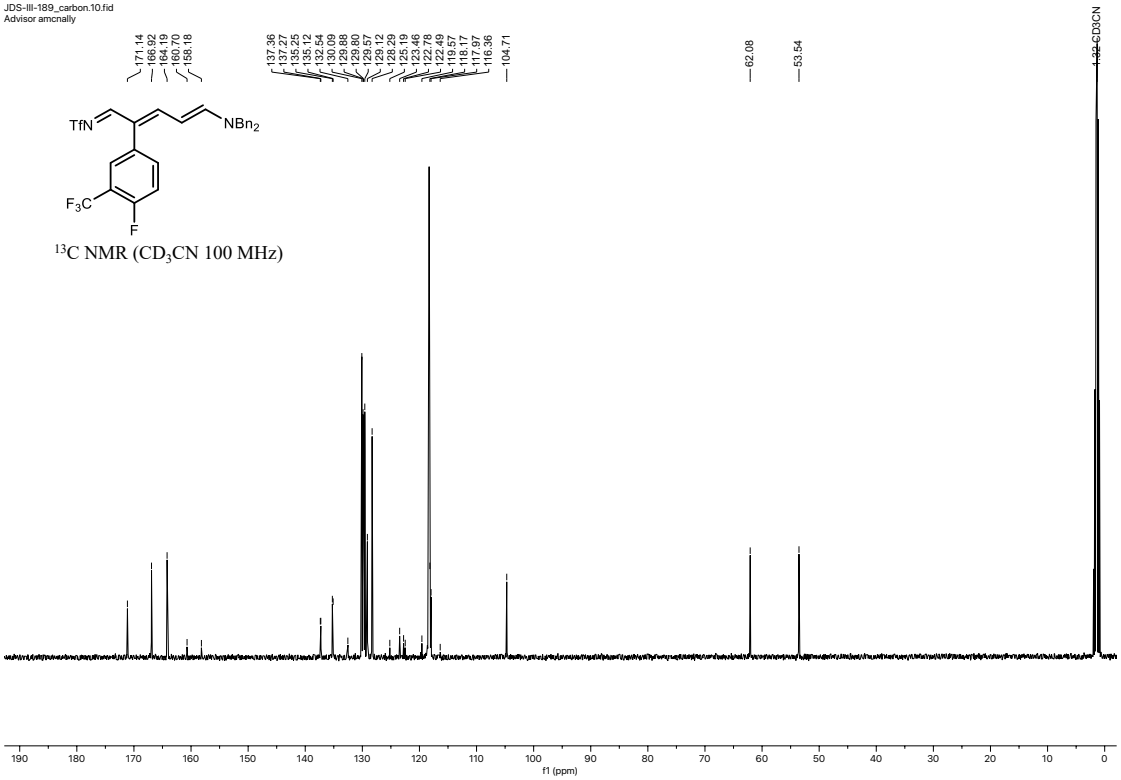
^{13}C NMR ($CDCl_3$ 100 MHz)



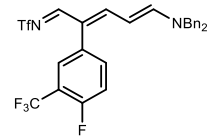
^{19}F NMR ($CDCl_3$ 375 MHz)



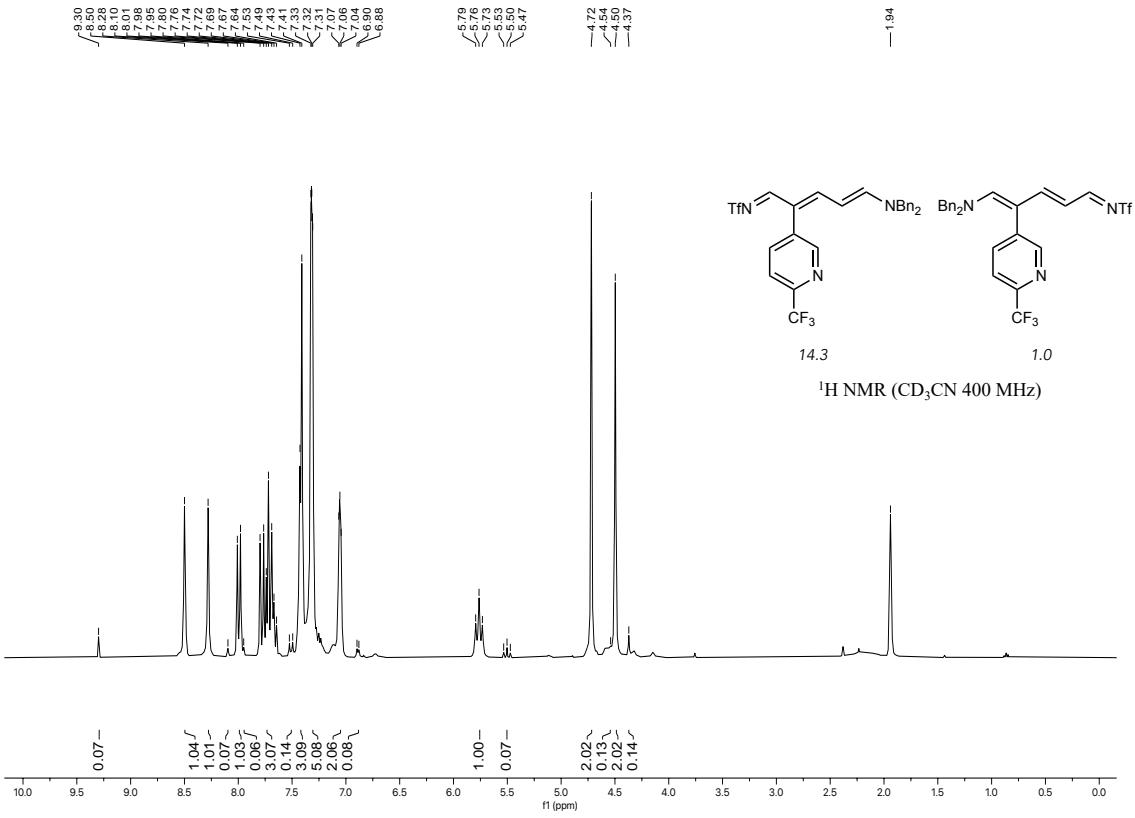
^{1}H NMR (CD_3CN 400 MHz)



^{13}C NMR (CD_3CN 100 MHz)

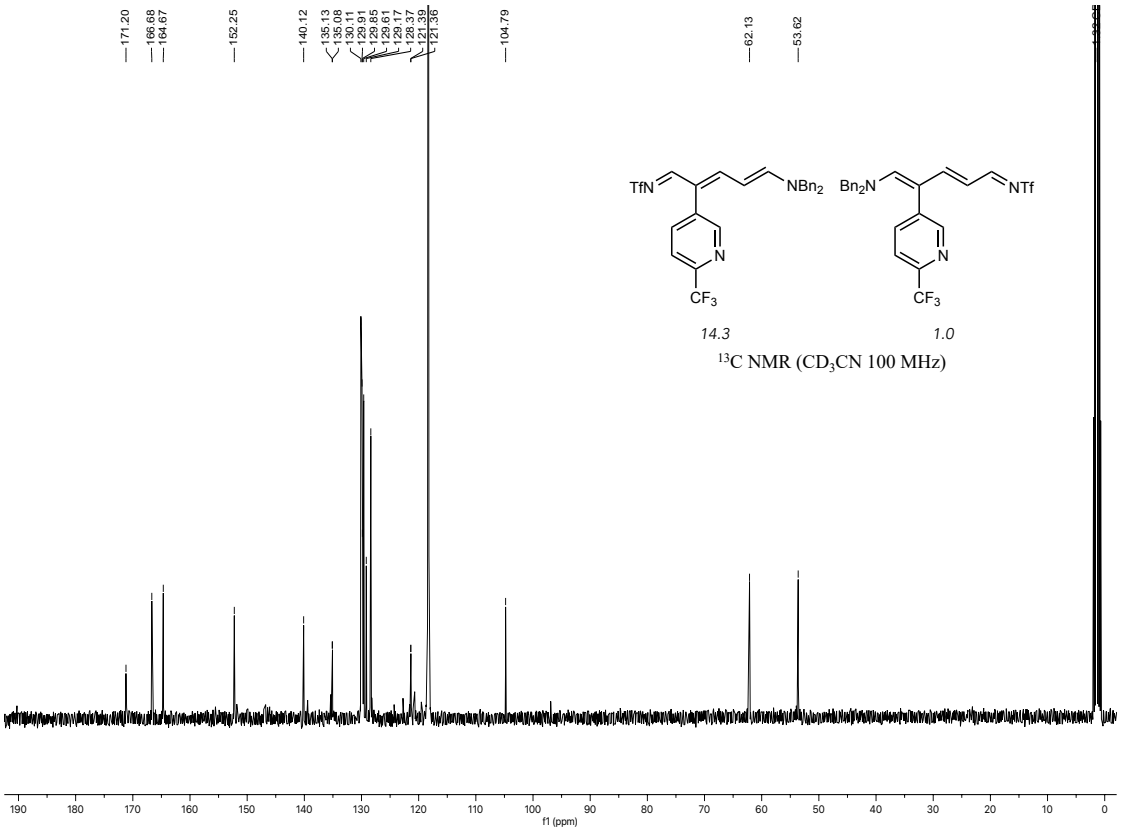


^{19}F NMR (CD_3CN 375 MHz)

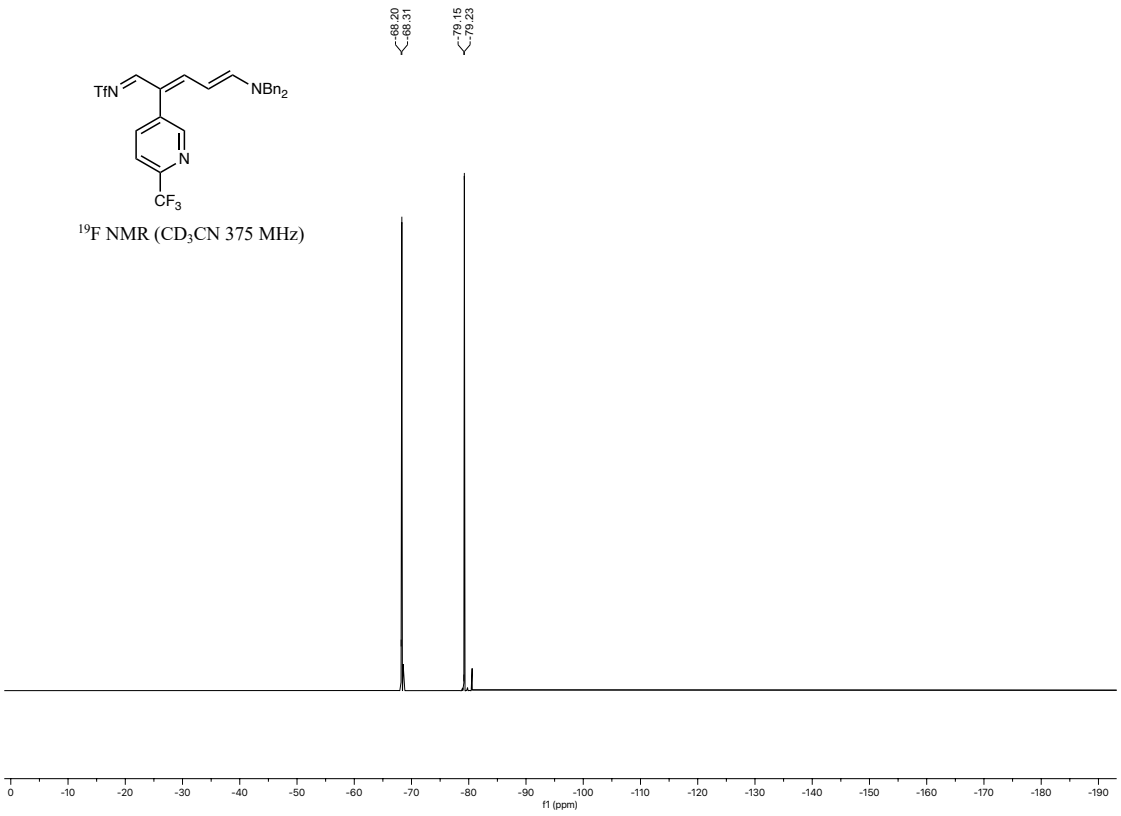


14.3 *1.0*

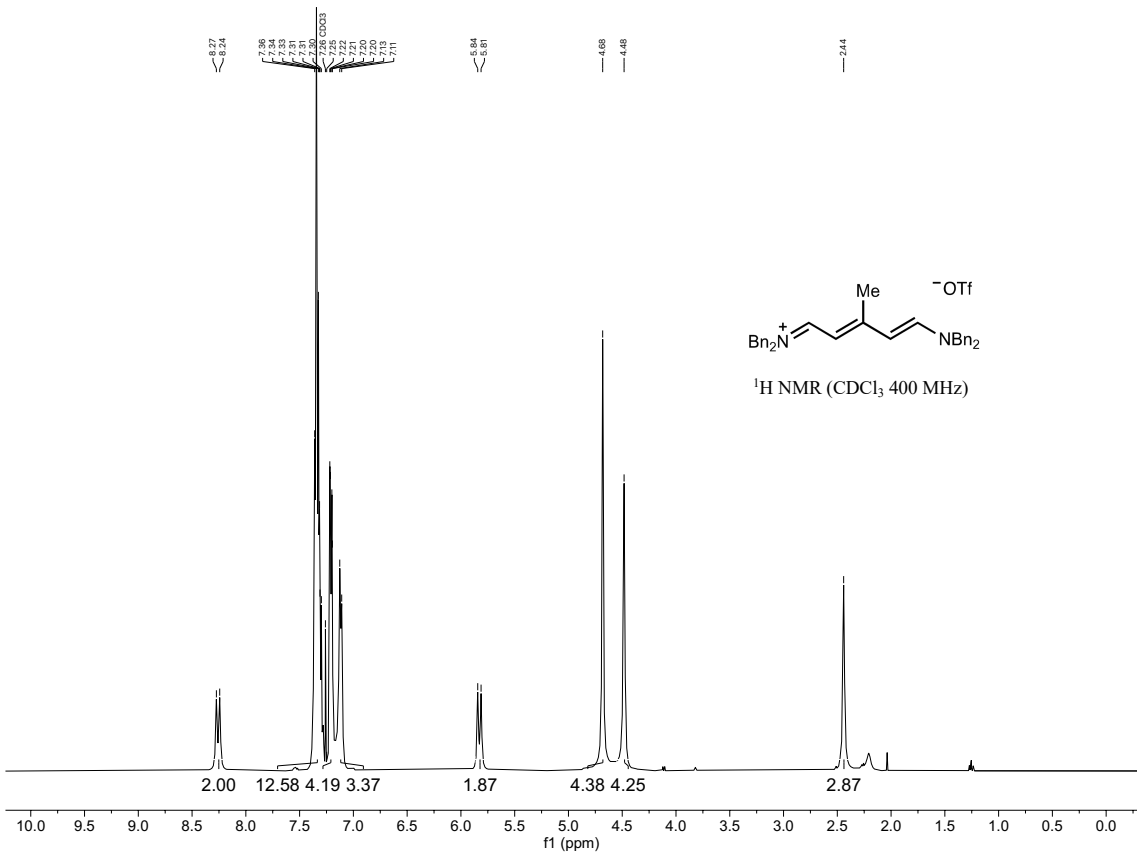
^{1}H NMR (CD_3CN 400 MHz)



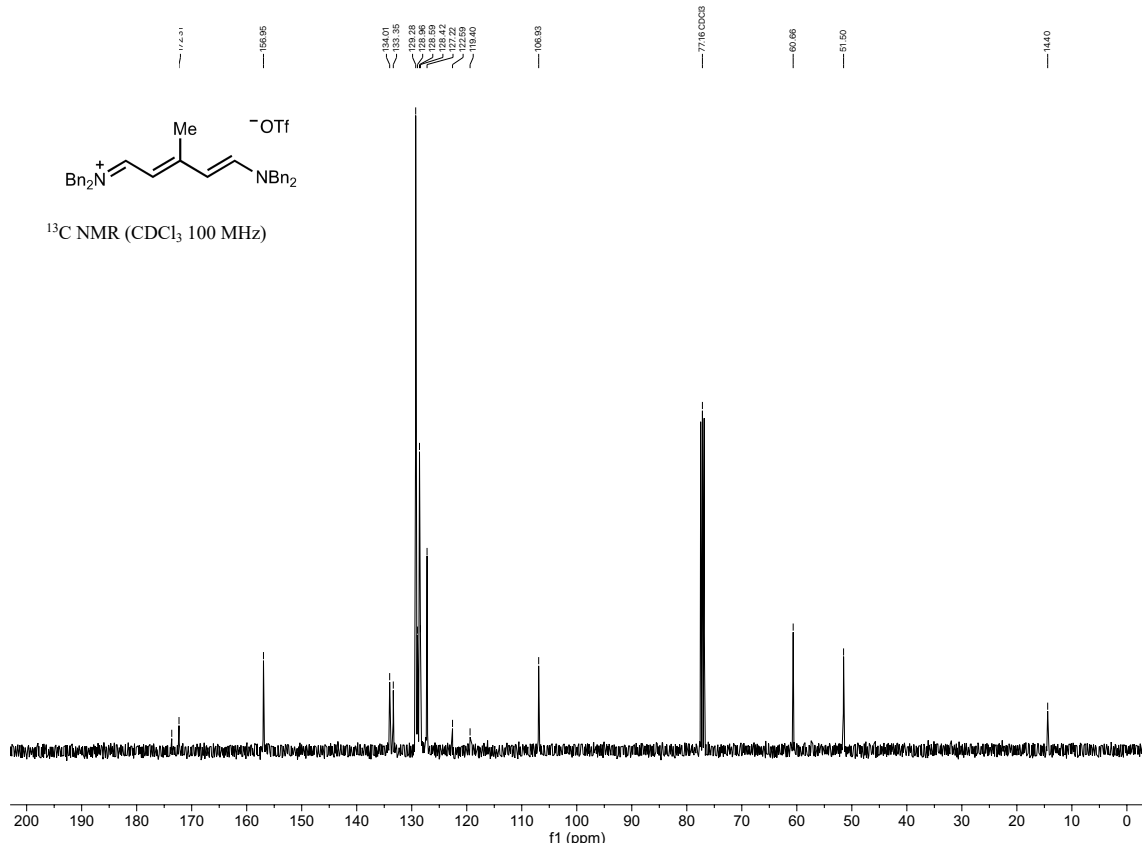
^{13}C NMR (CD_3CN 100 MHz)



^{19}F NMR (CD_3CN 375 MHz)



^{1}H NMR ($CDCl_3$ 400 MHz)



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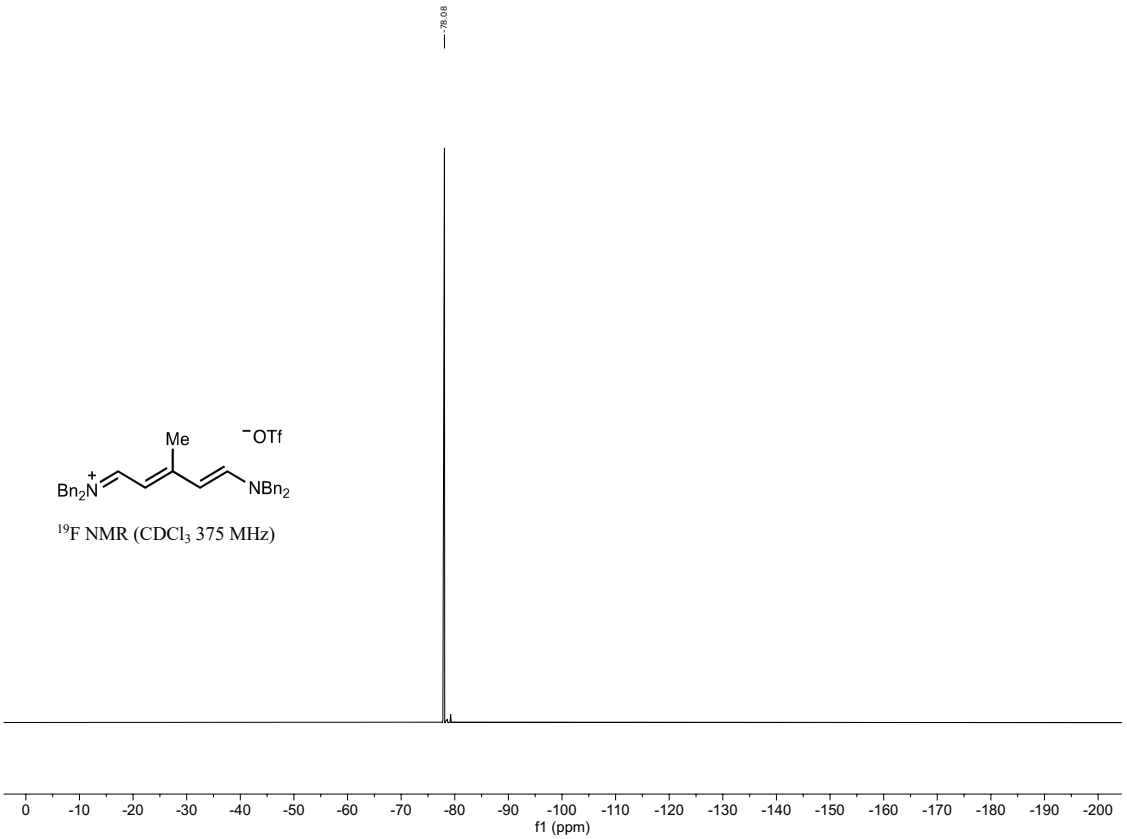
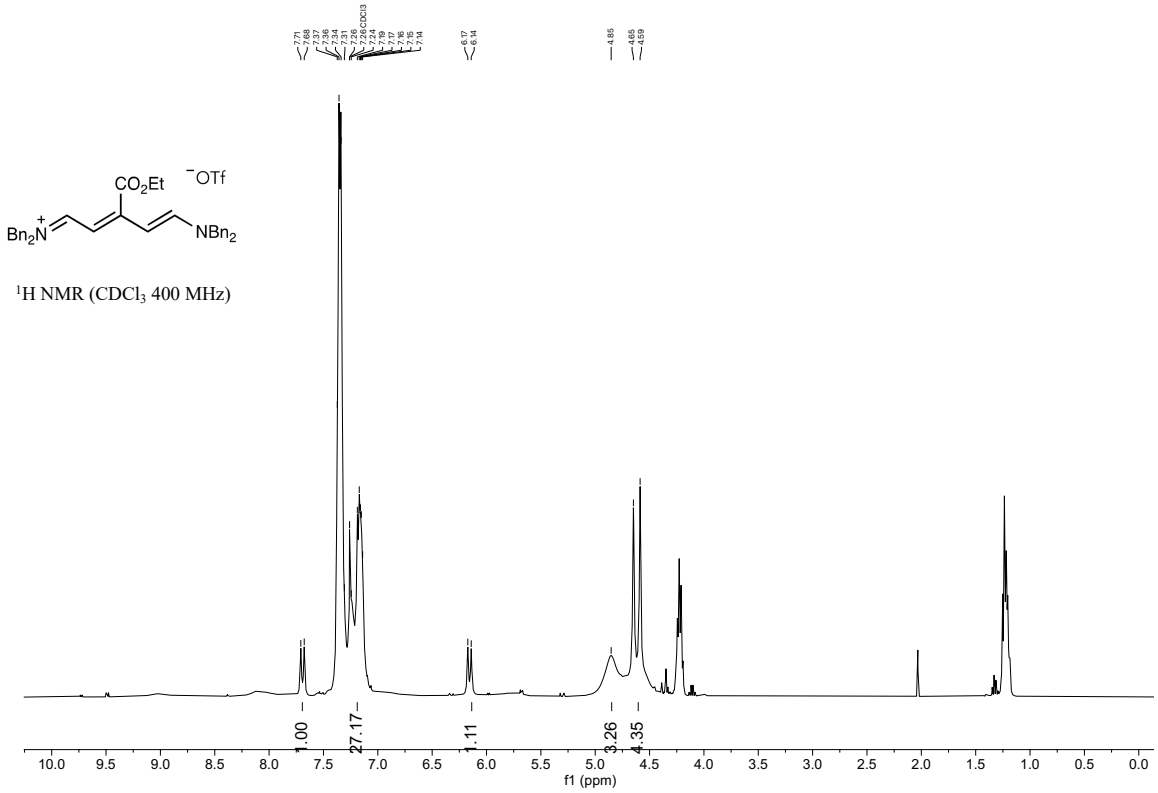
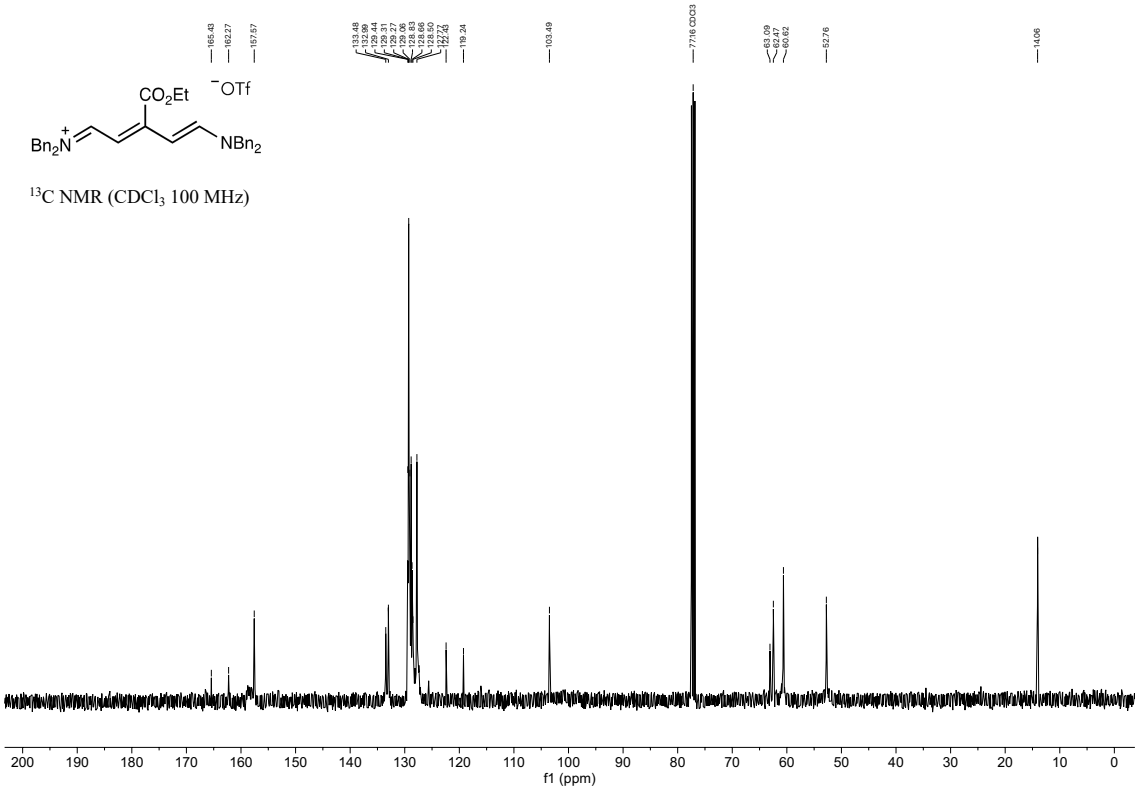


^{19}F NMR ($CDCl_3$ 375 MHz)



^{1}H NMR ($CDCl_3$ 400 MHz)



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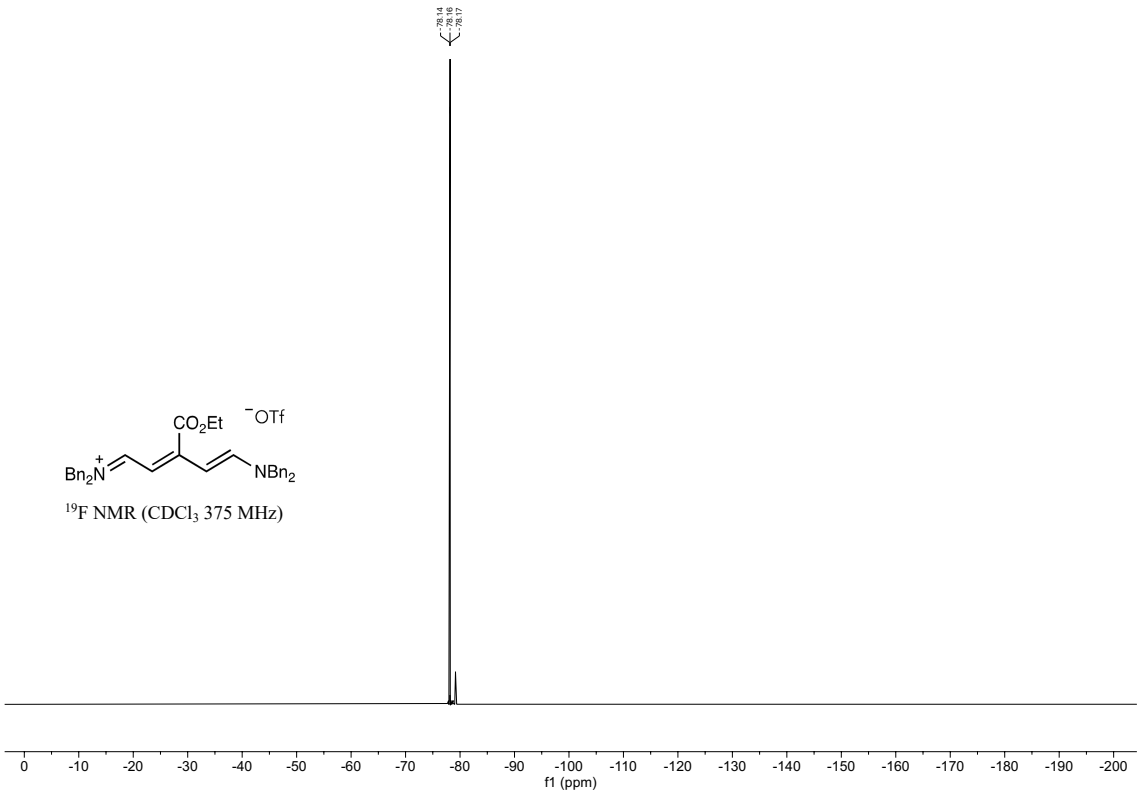
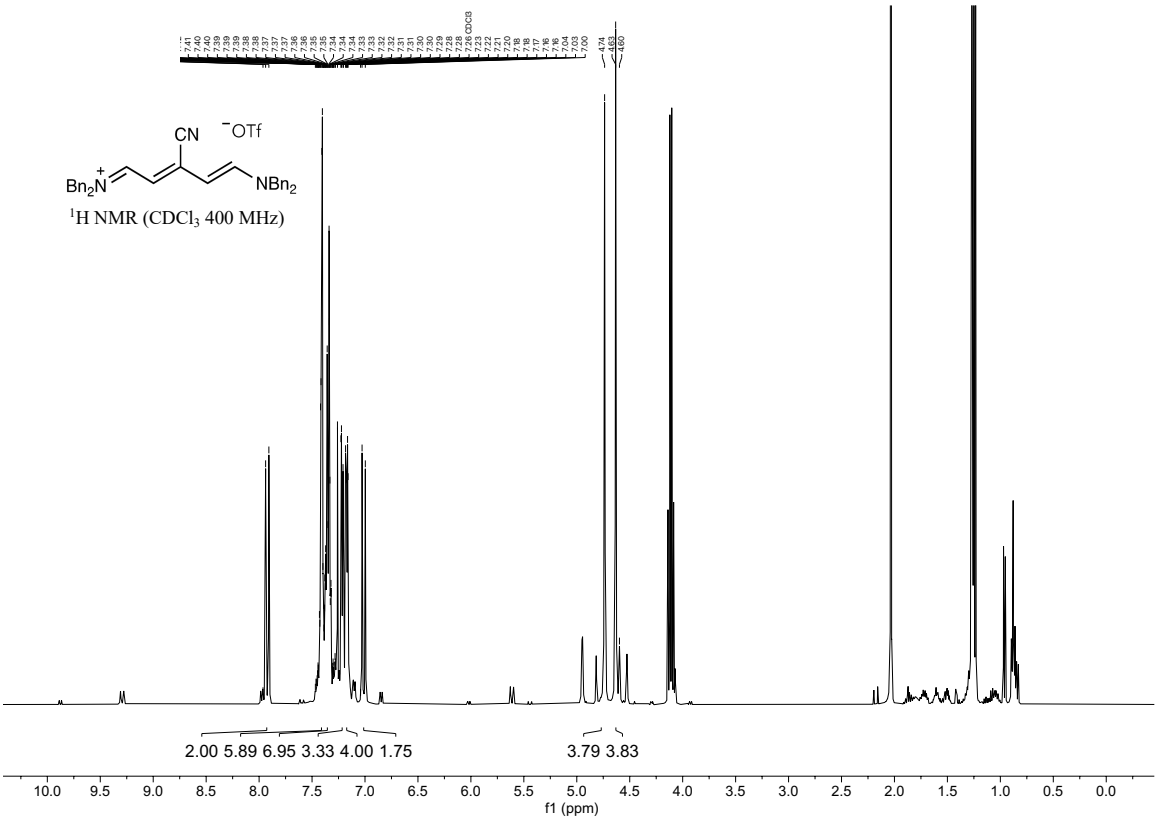


^{19}F NMR ($CDCl_3$ 375 MHz)



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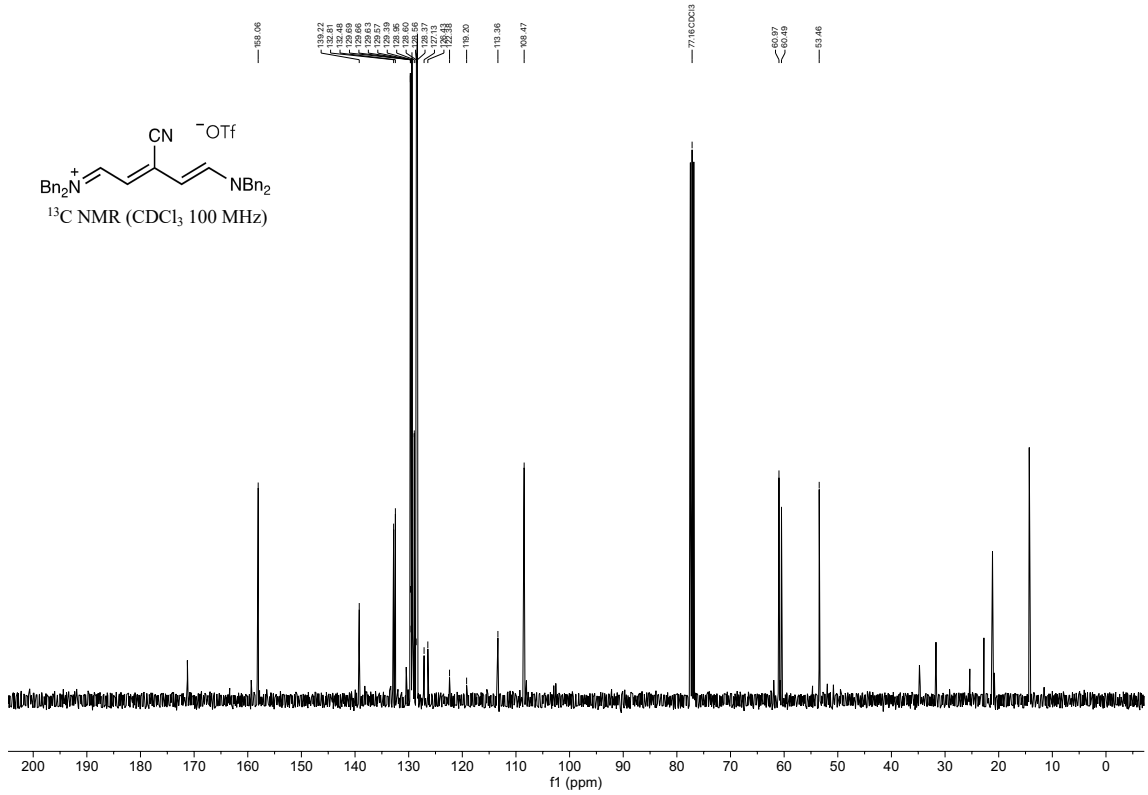

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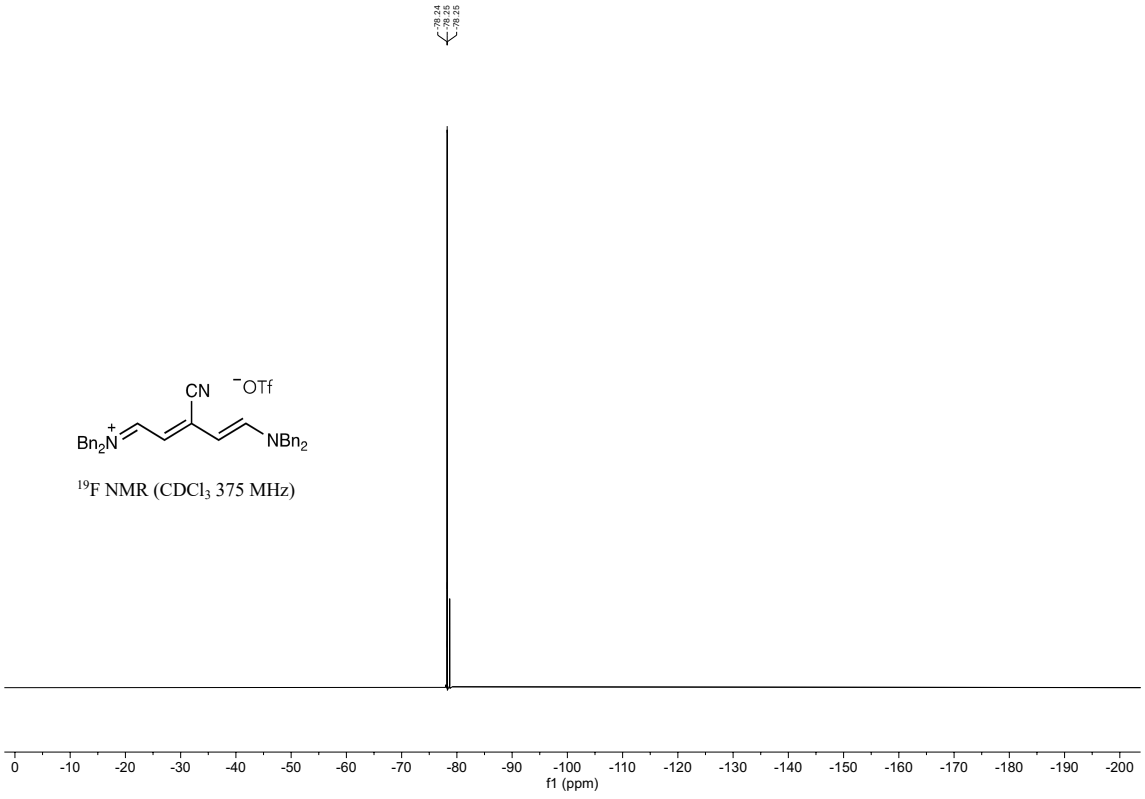

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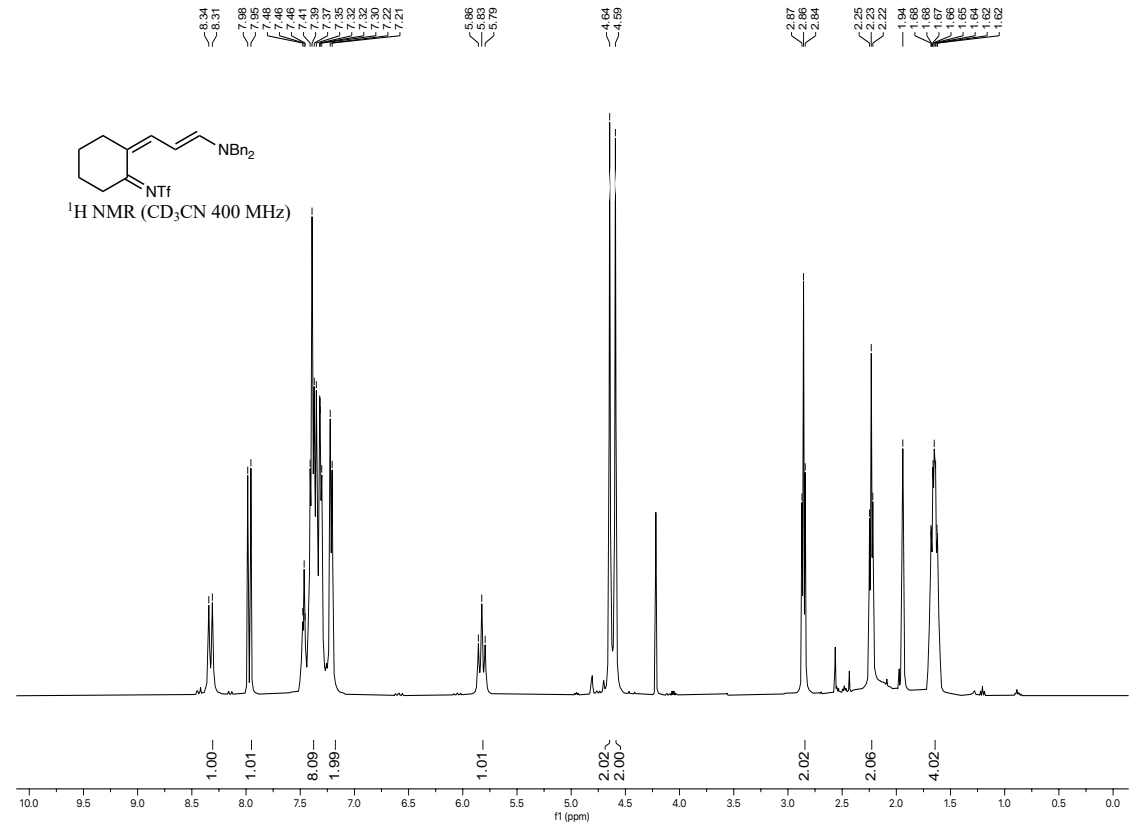
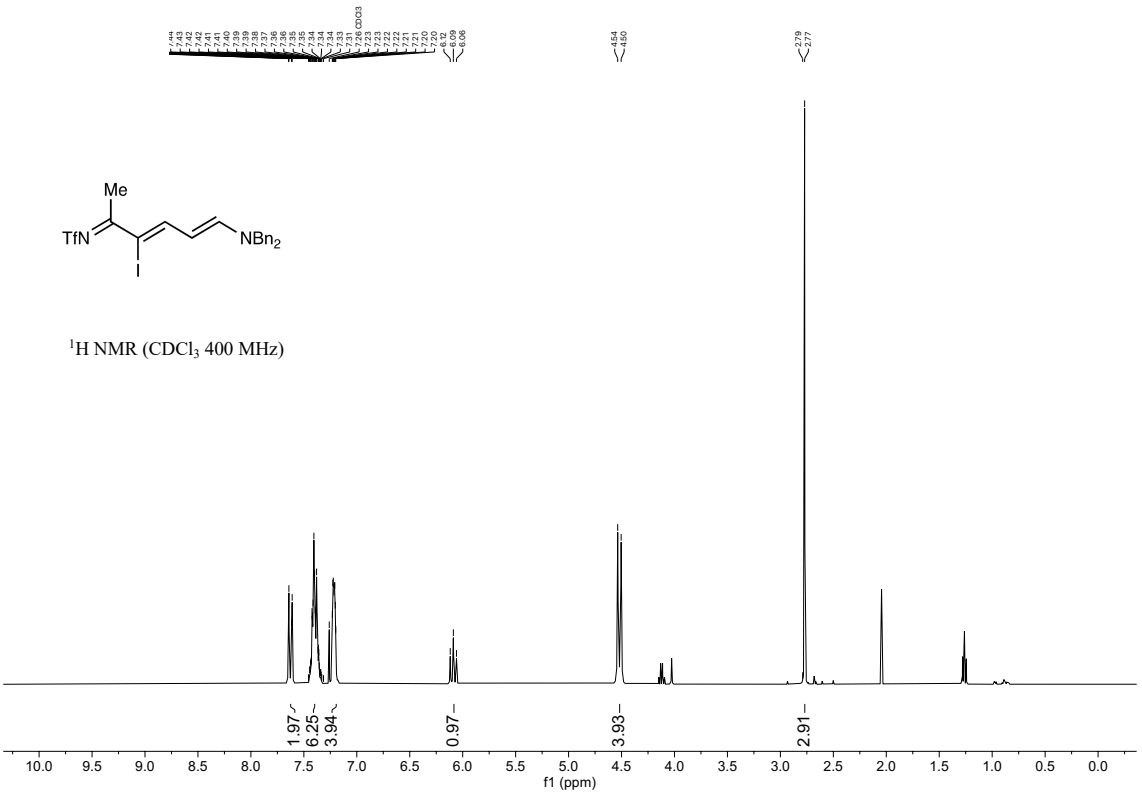
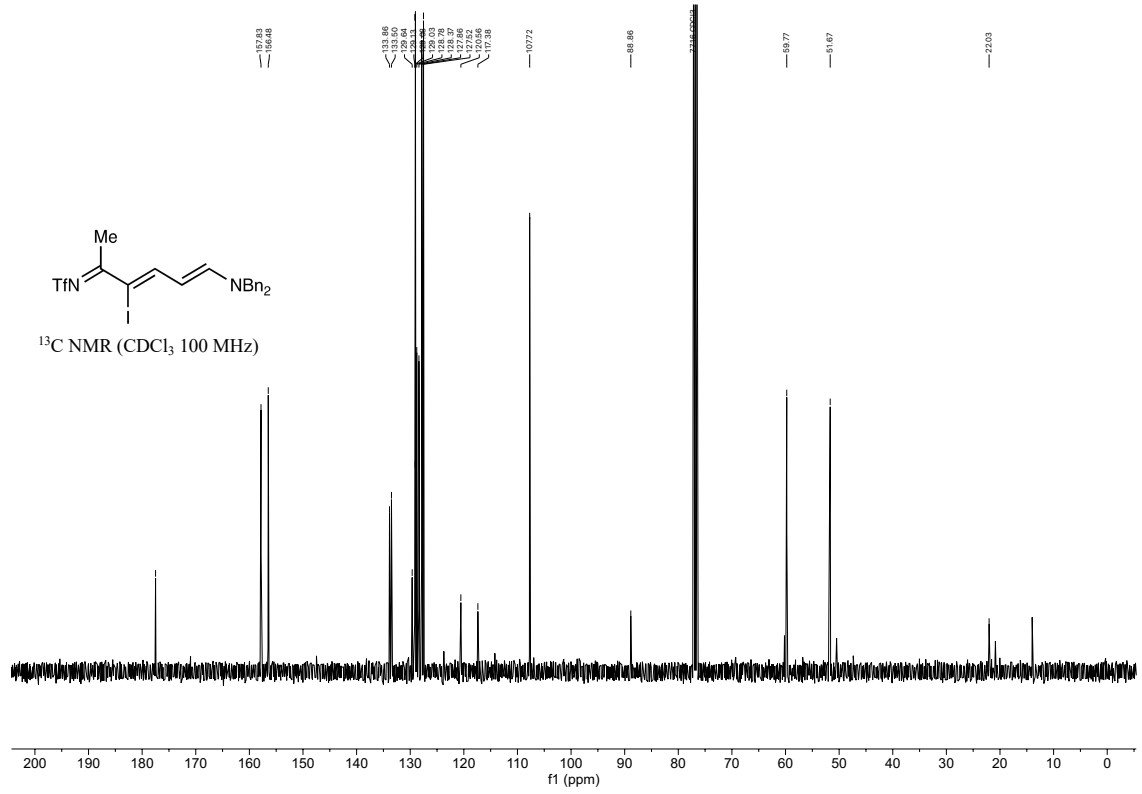


^{1}H NMR (CD_3CN 400 MHz)


Me
TfN
NBn2
I
1H NMR (CDCl3 400 MHz)
1.97
6.25
3.94
0.97
3.93
2.91
f1 (ppm)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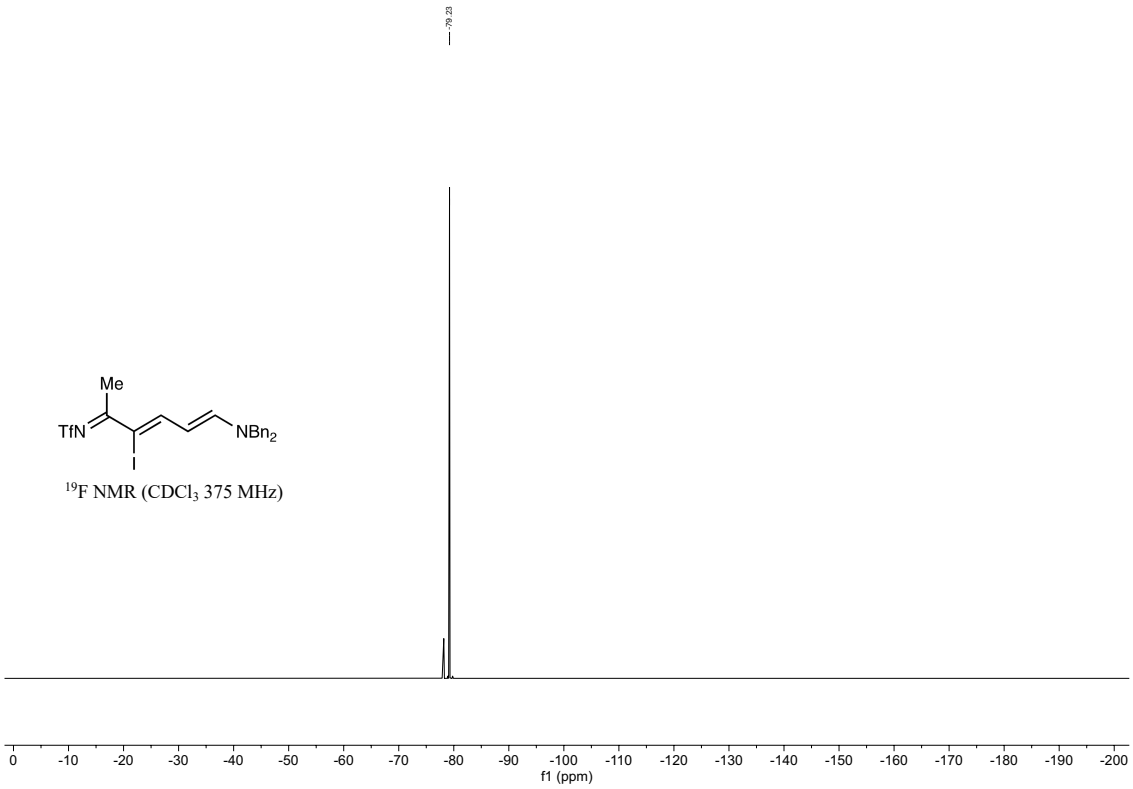
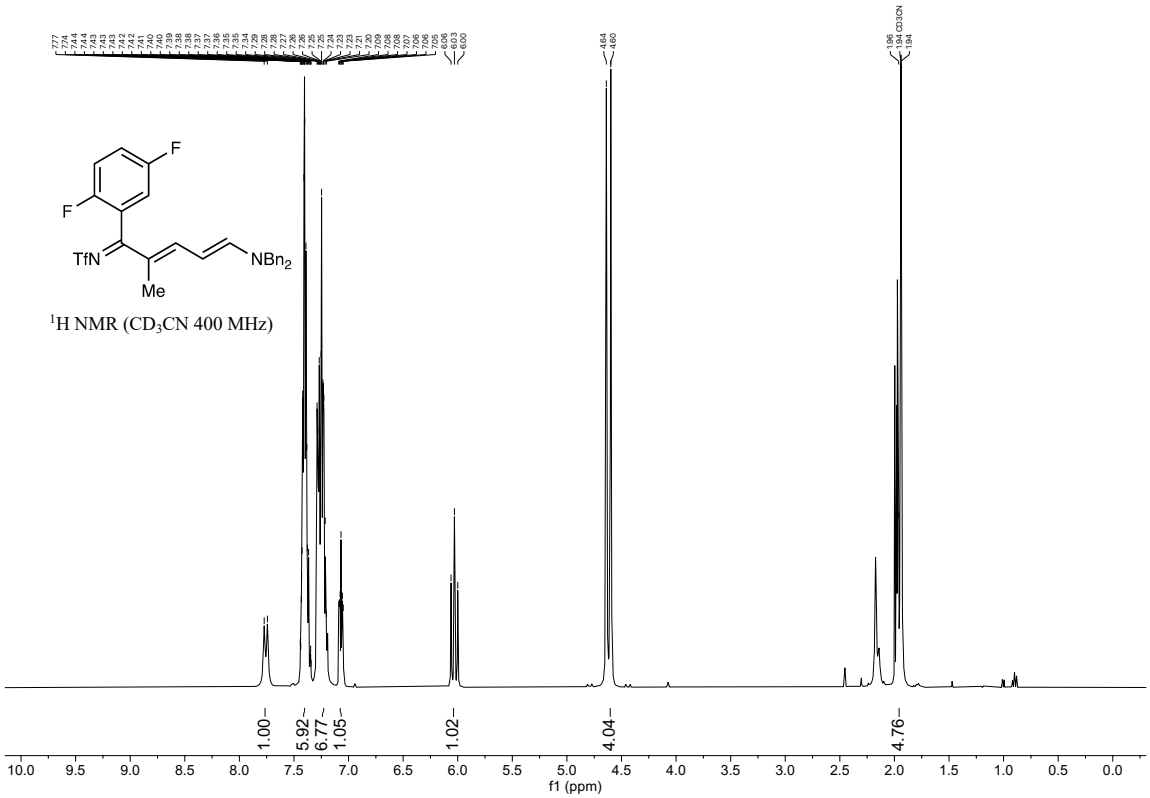
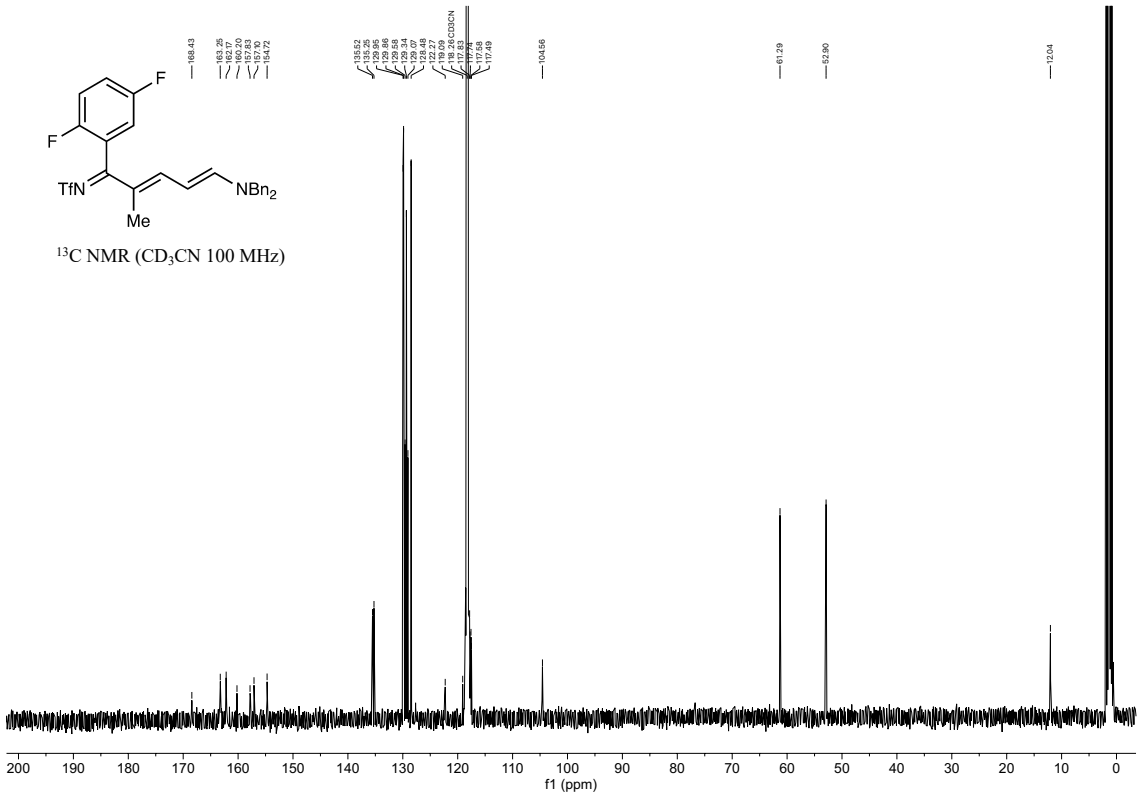
TfN
NBn2
I
13C NMR (CDCl3 100 MHz)
f1 (ppm)



^{19}F NMR ($CDCl_3$ 375 MHz)

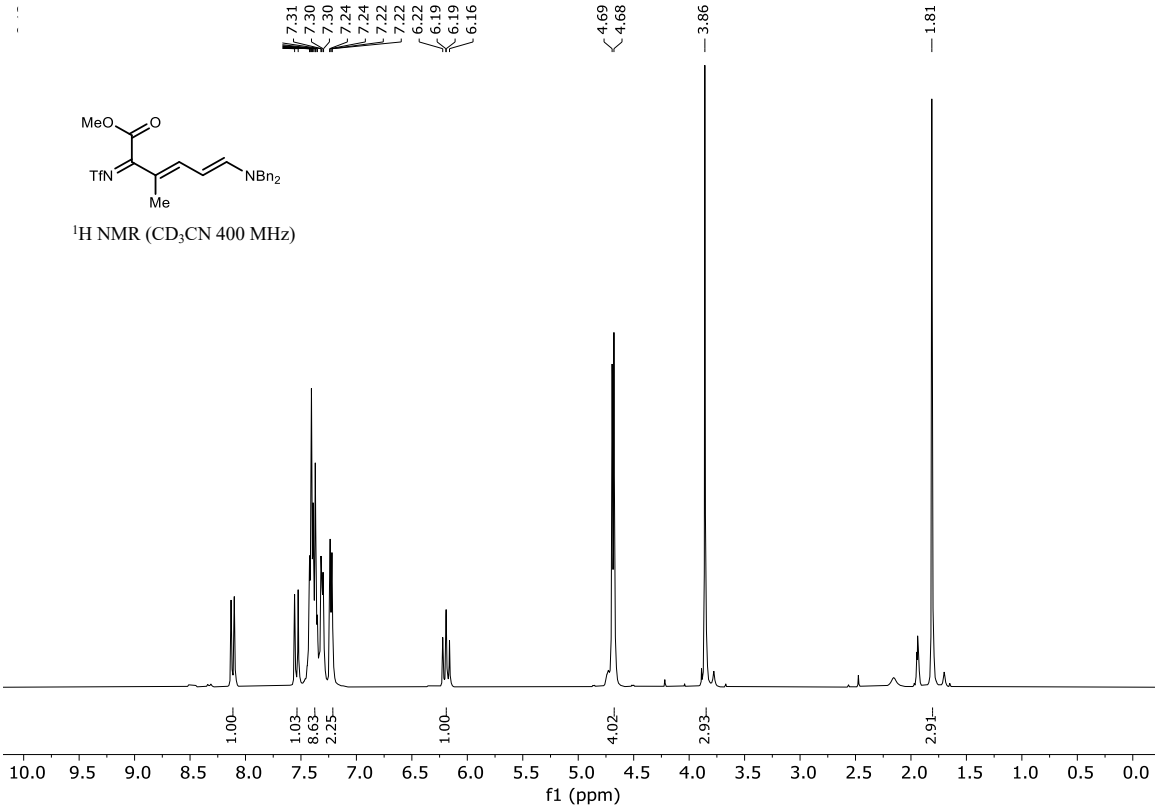


^{1}H NMR (CD_3CN 400 MHz)



^{13}C NMR (CD_3CN 100 MHz)

^{19}F NMR (CD_3CN 375 MHz)



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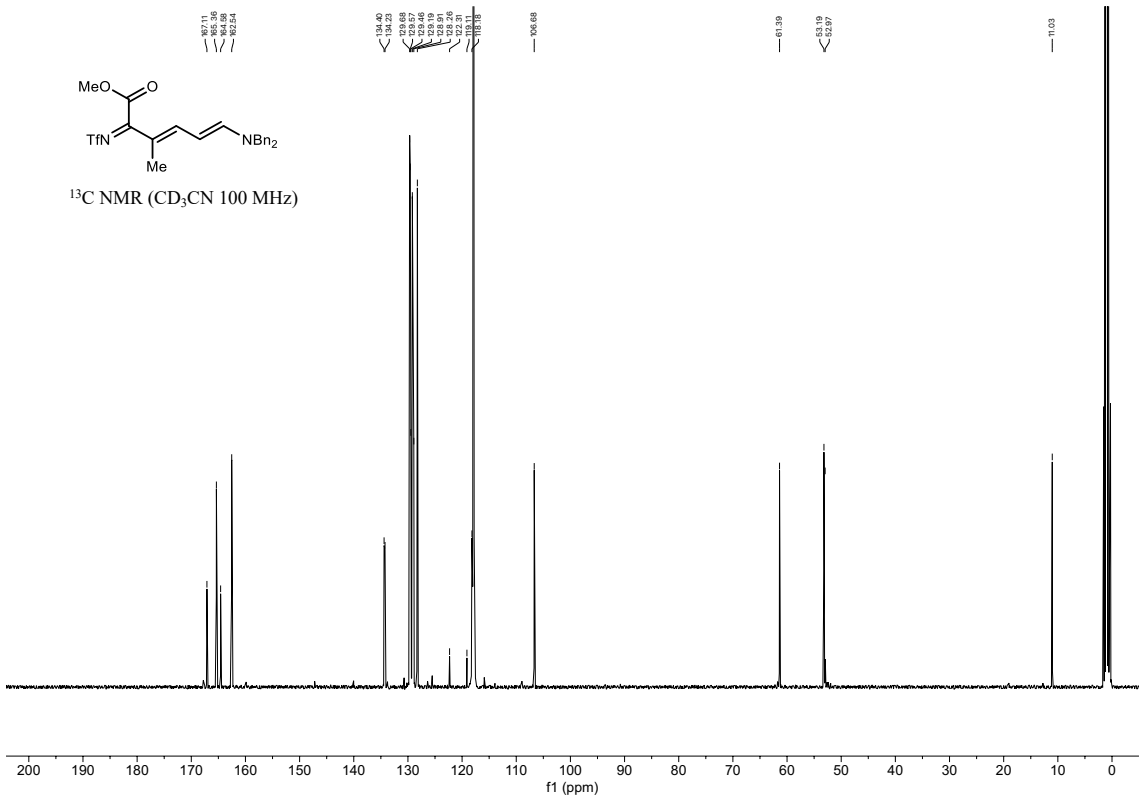

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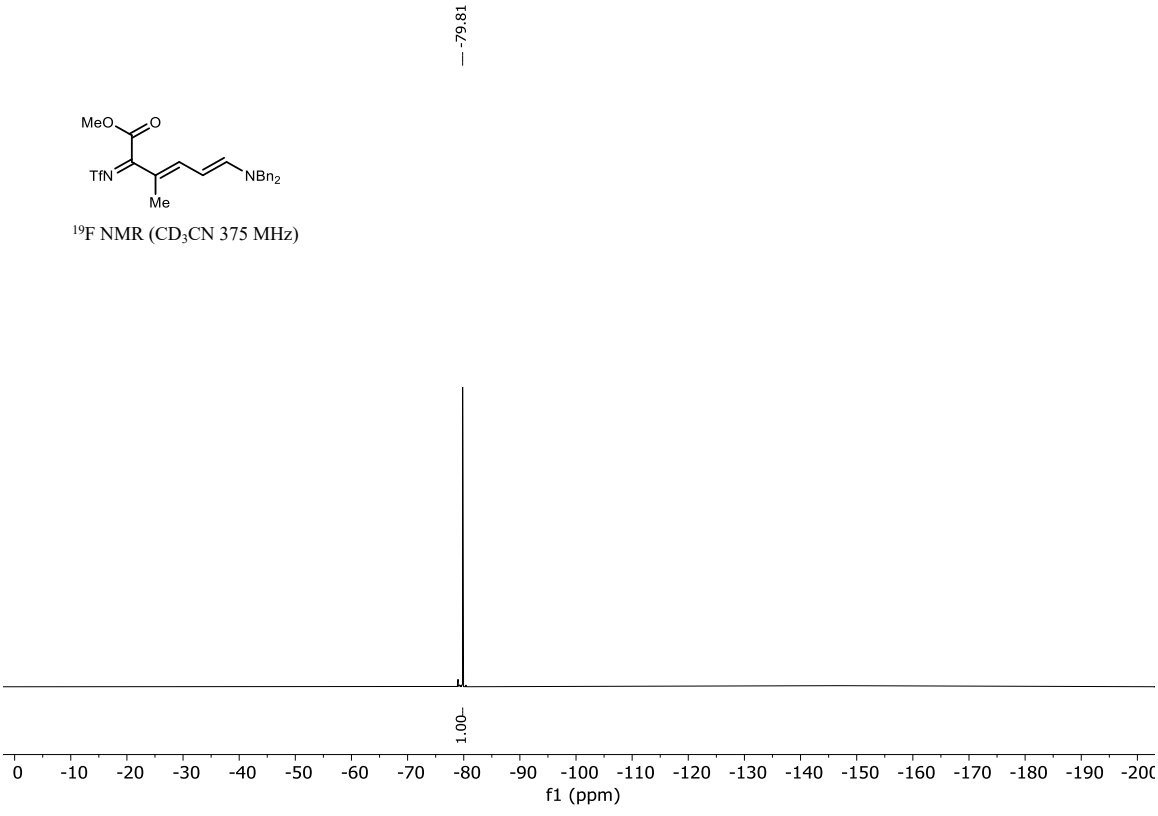
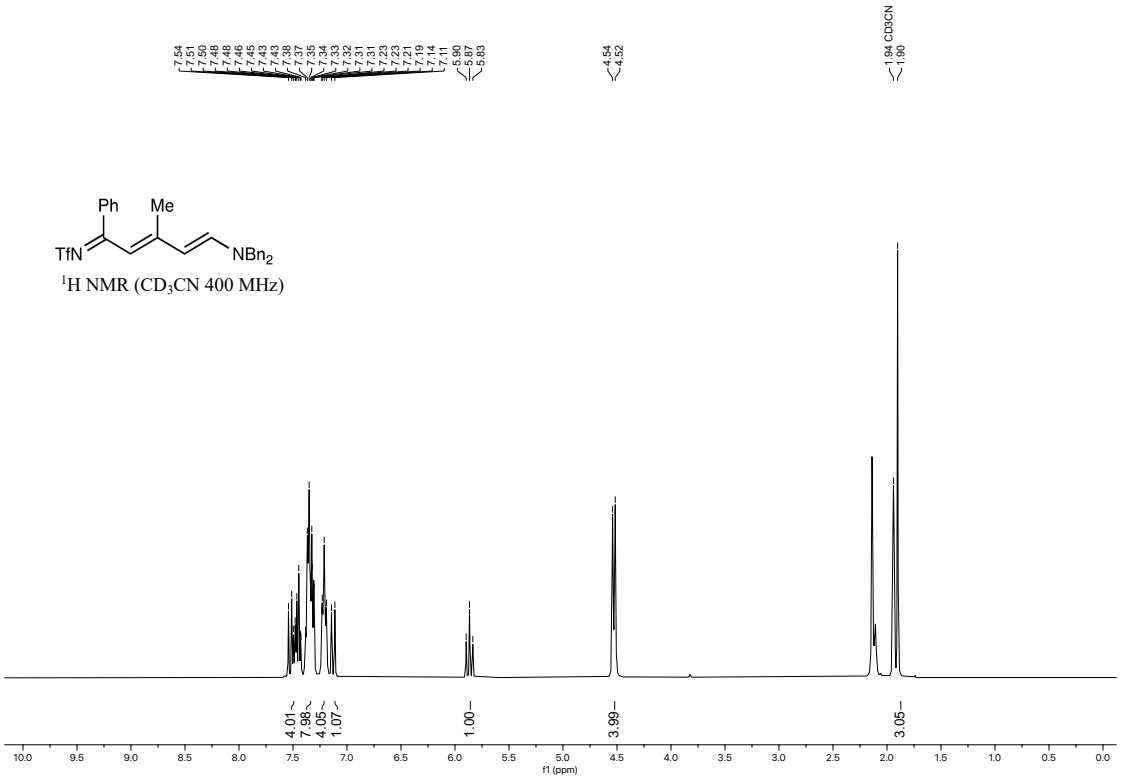
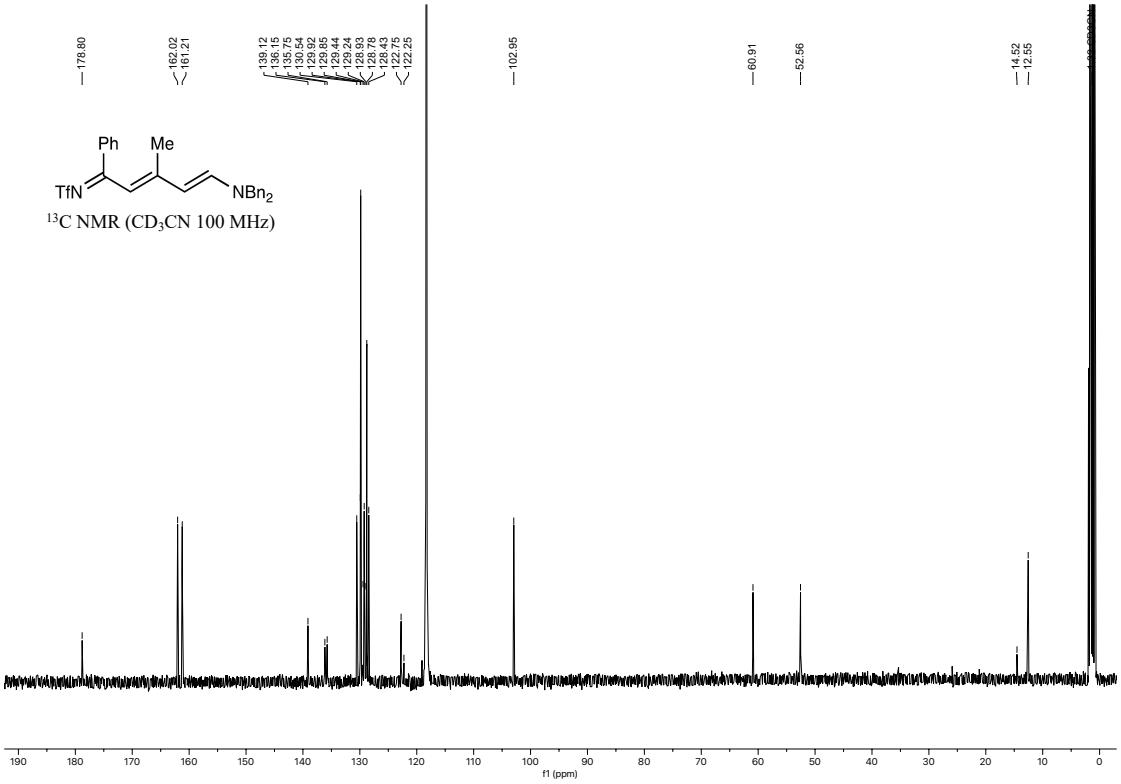


^{19}F NMR (CD_3CN 375 MHz)

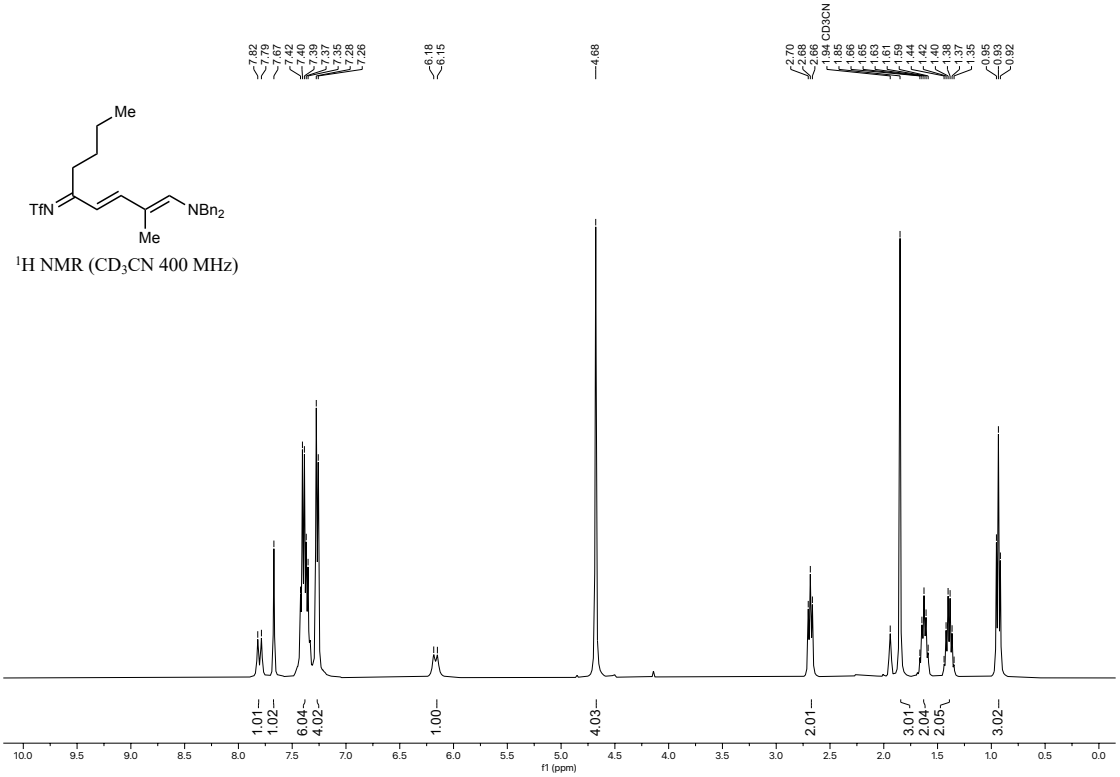


^{1}H NMR (CD_3CN 400 MHz)

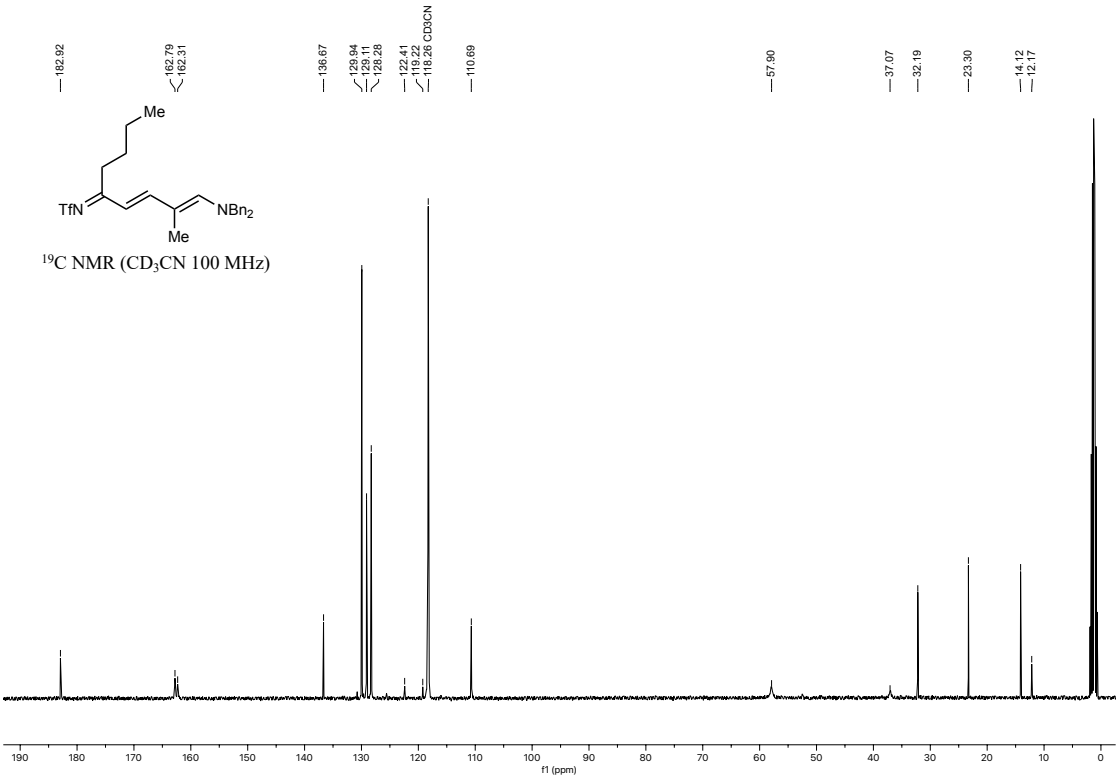


^{13}C NMR (CD_3CN 100 MHz)

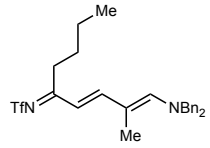
^{19}F NMR (CD_3CN 375 MHz)



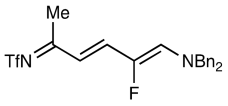
^{1}H NMR (CD_3CN 400 MHz)



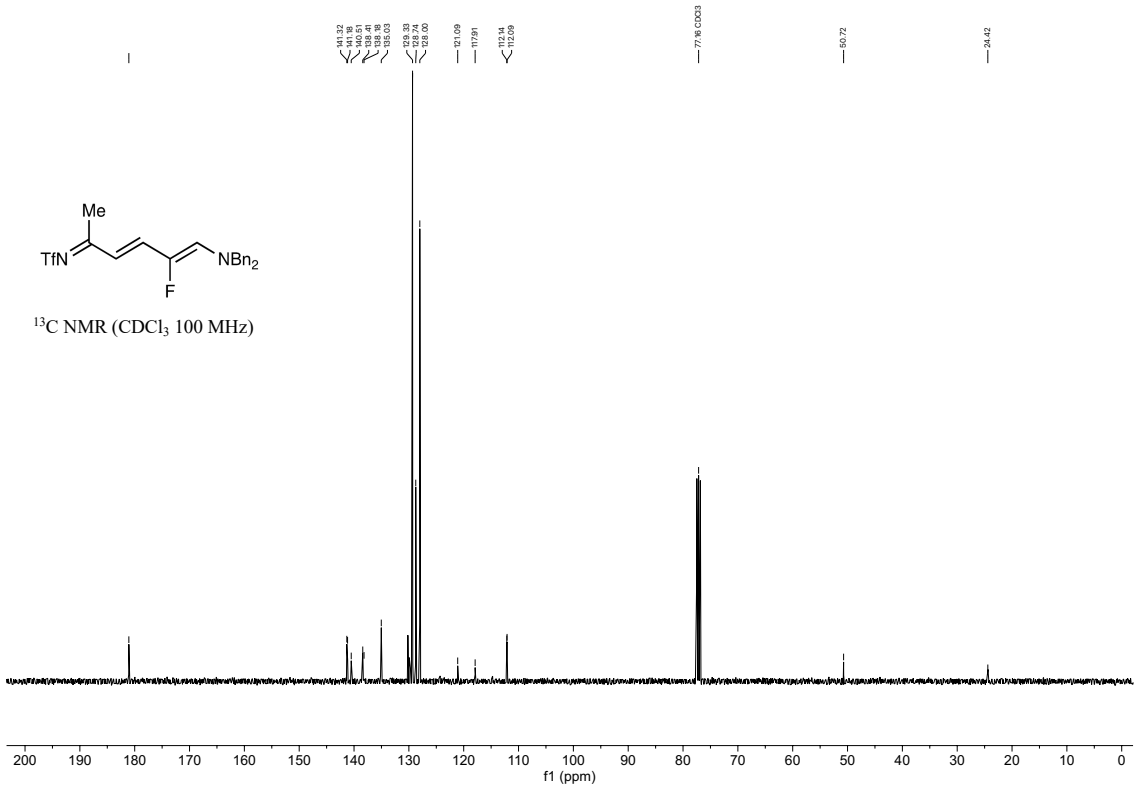
^{19}C NMR (CD_3CN 100 MHz)



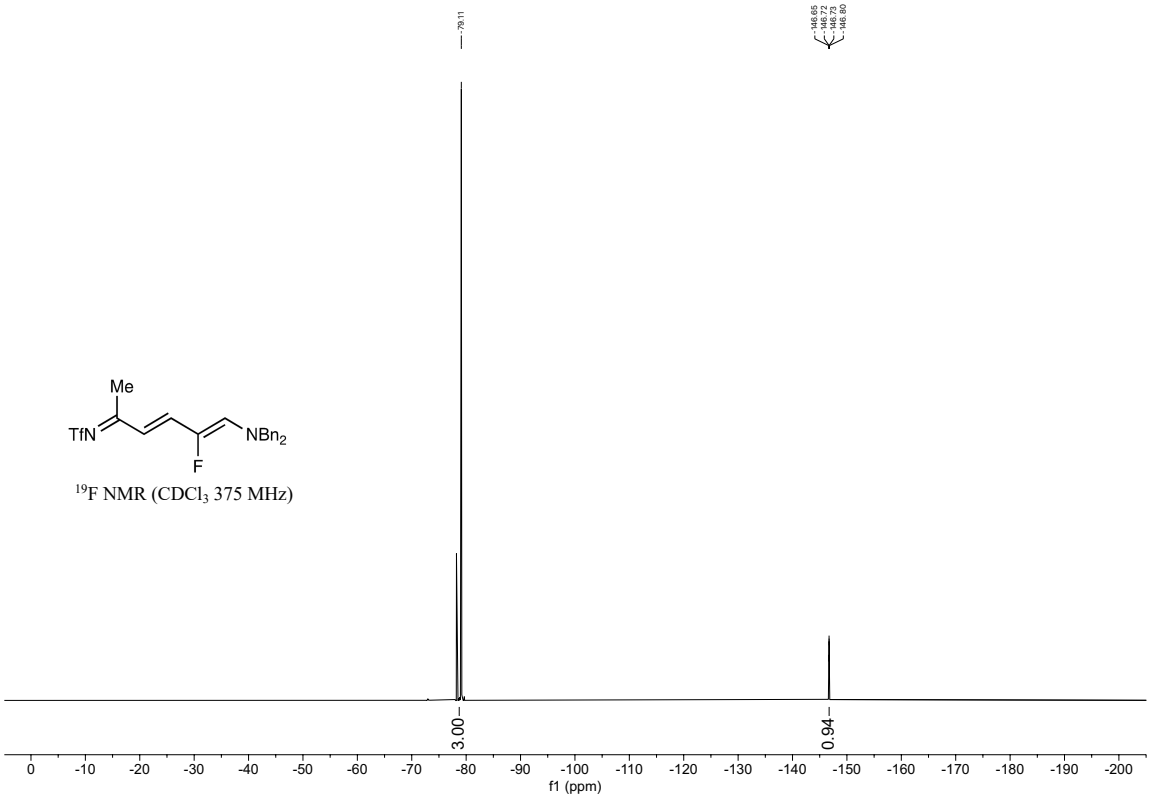
^{19}F NMR (CD_3CN 375 MHz)



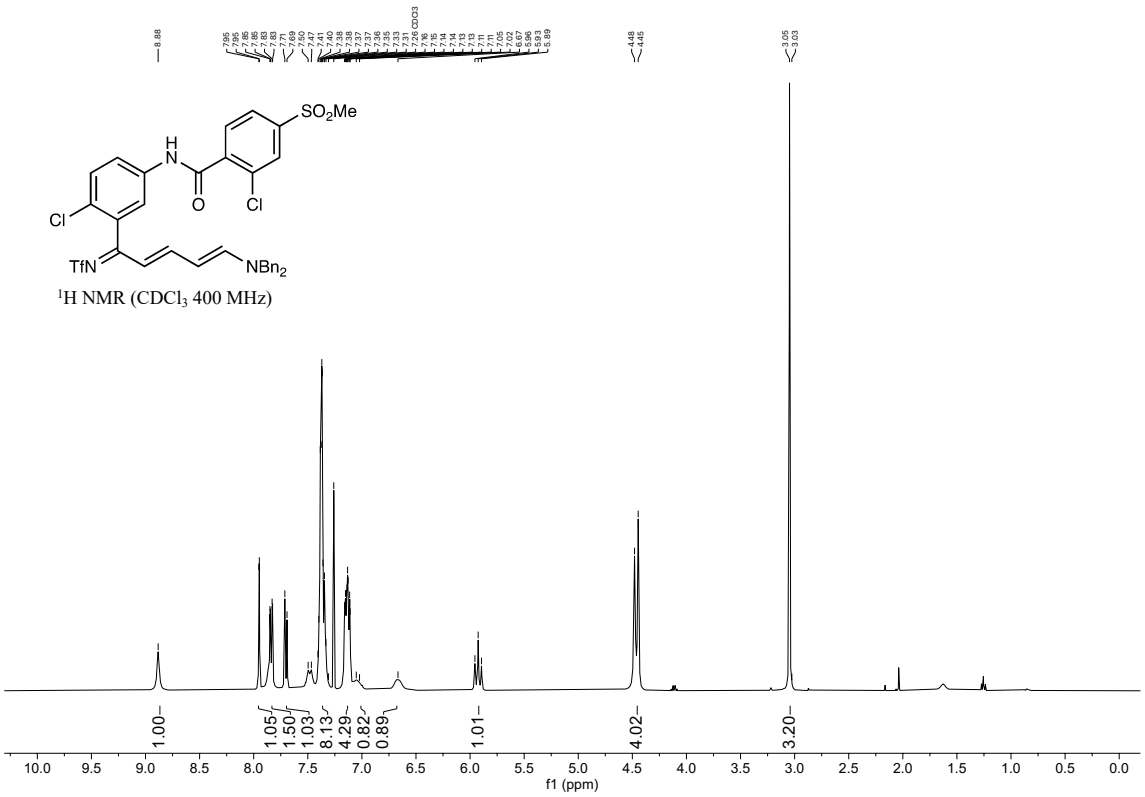
^{1}H NMR ($CDCl_3$ 400 MHz)



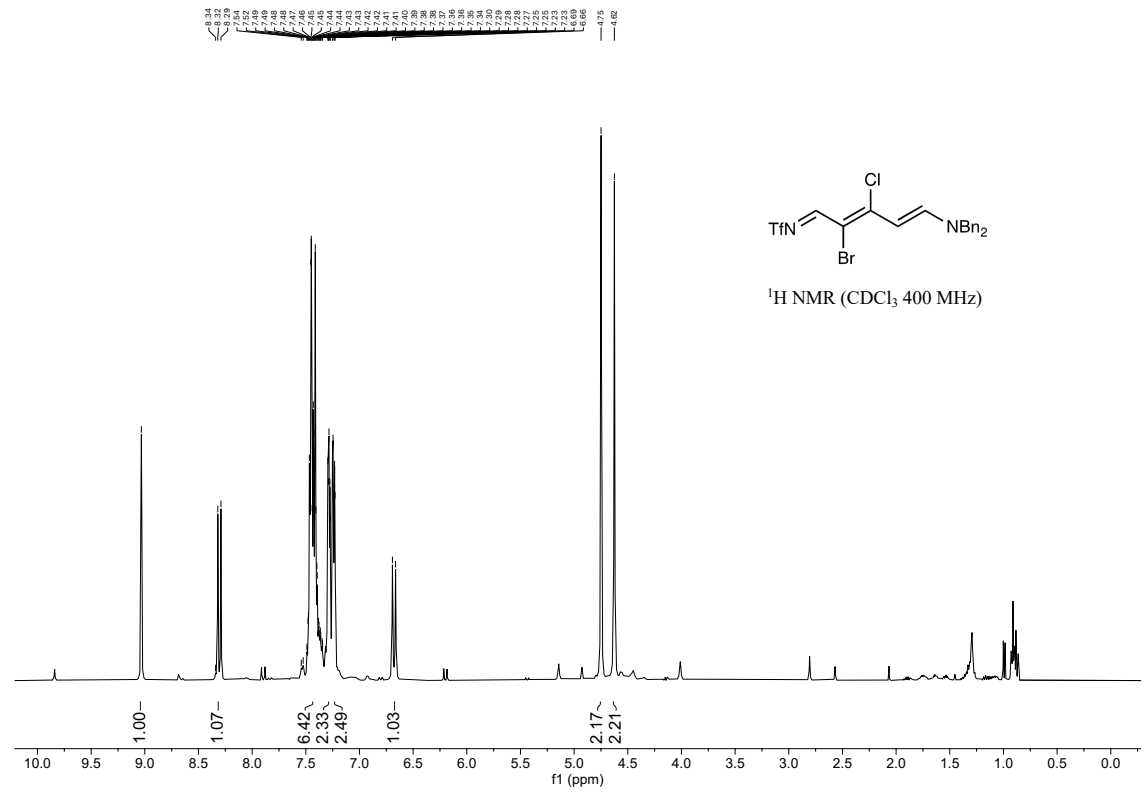
^{13}C NMR ($CDCl_3$ 100 MHz)



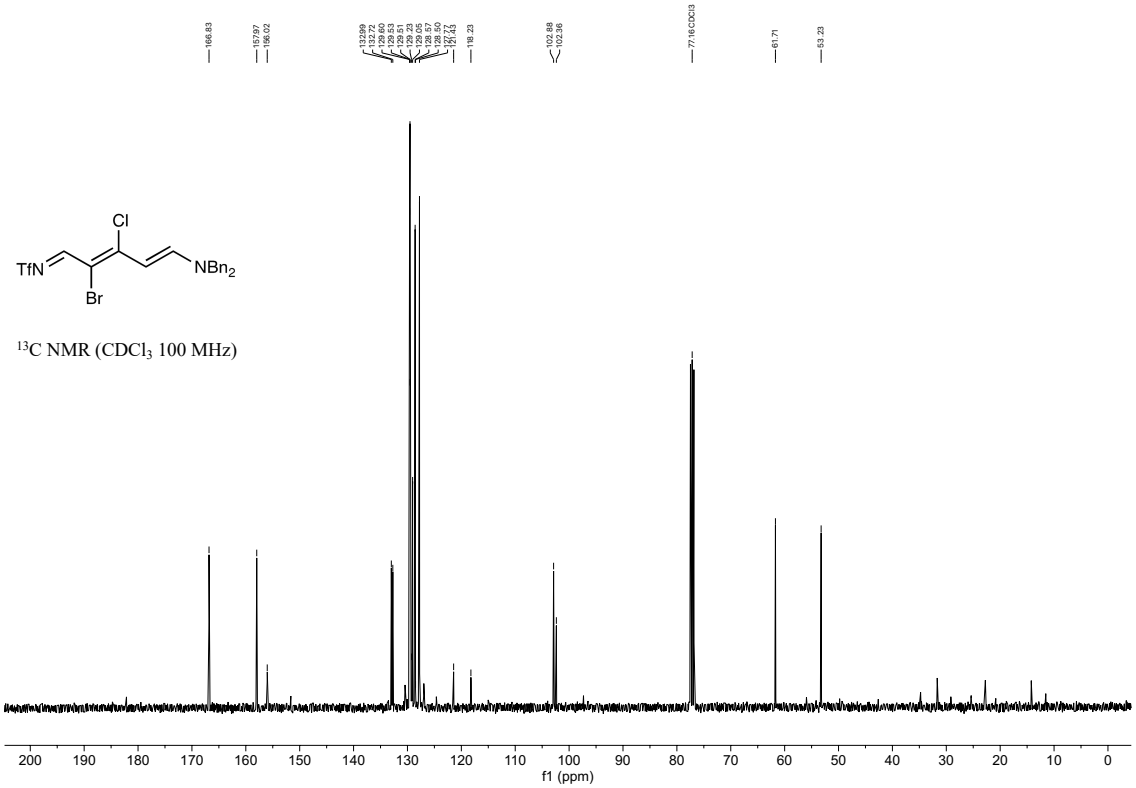
^{19}F NMR ($CDCl_3$ 375 MHz)



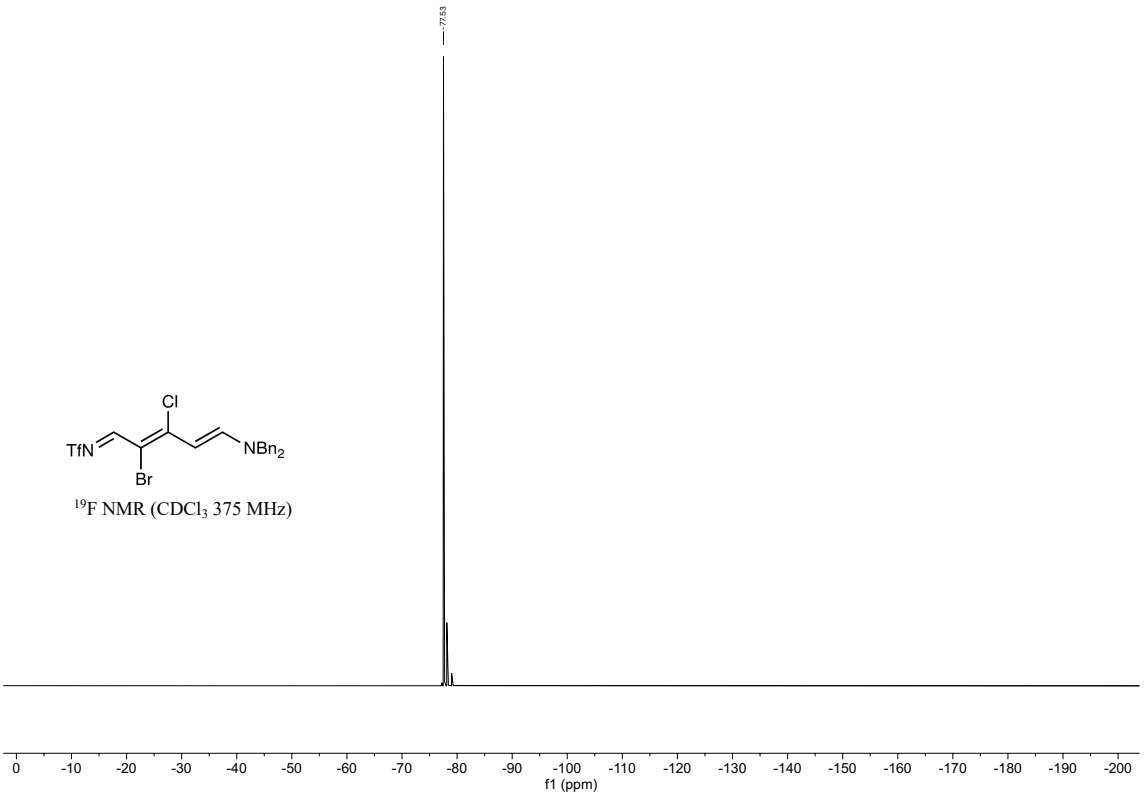
^{1}H NMR ($CDCl_3$ 400 MHz)



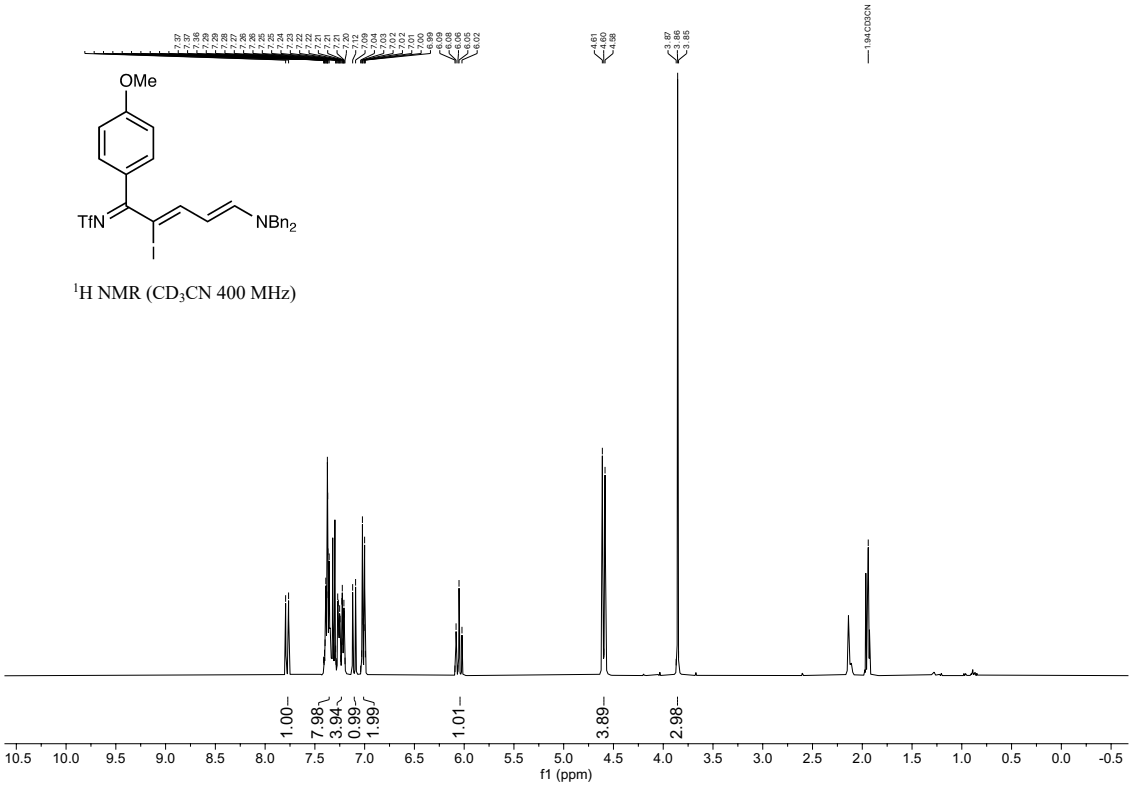
^{1}H NMR ($CDCl_3$ 400 MHz)



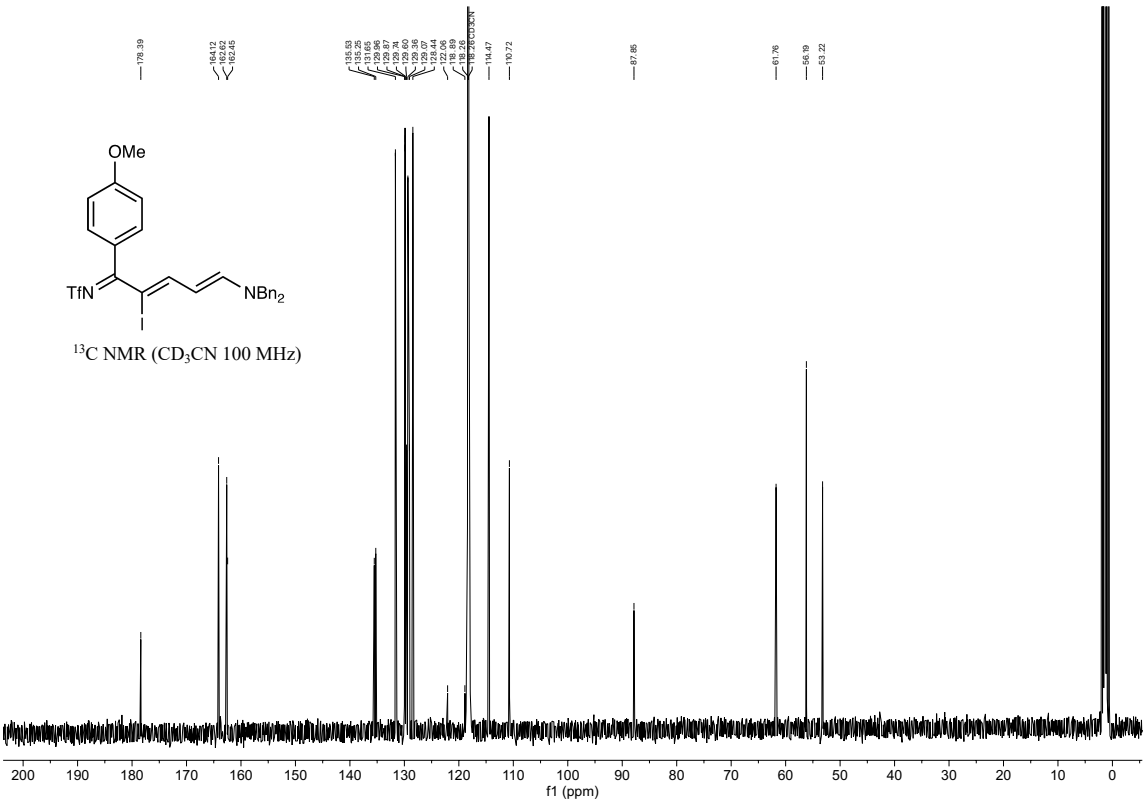
^{13}C NMR ($CDCl_3$ 100 MHz)



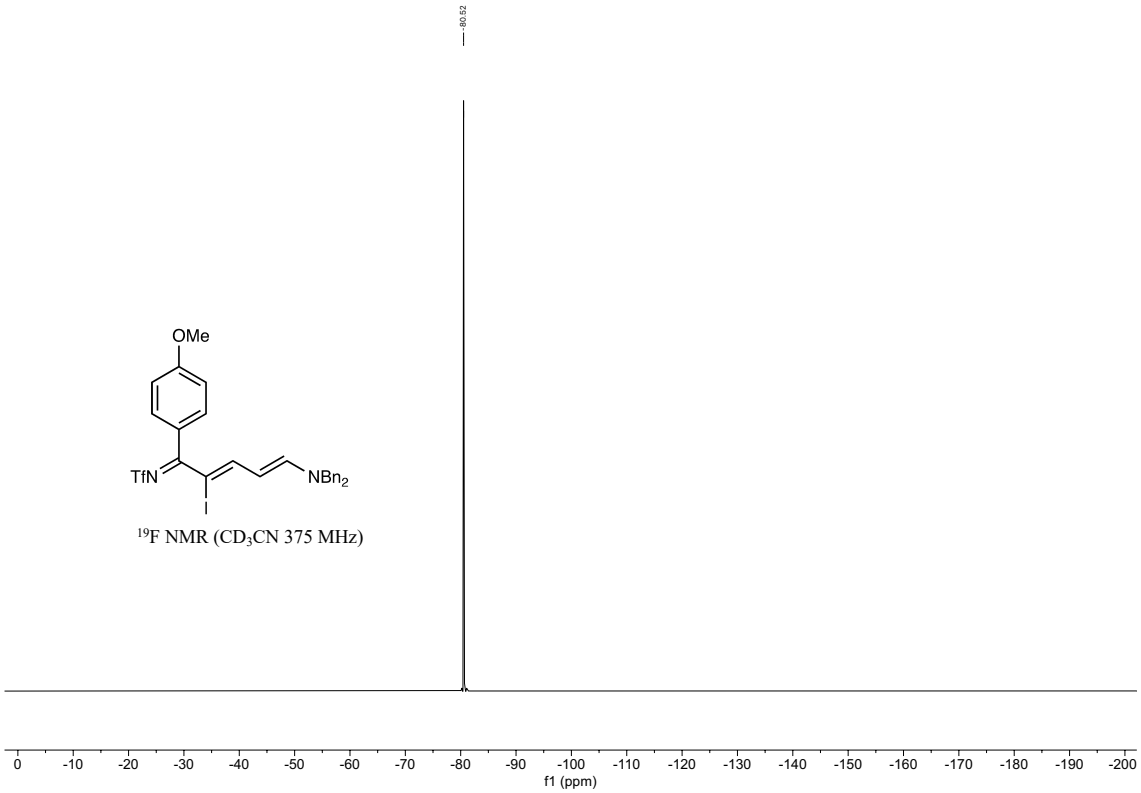
^{19}F NMR ($CDCl_3$ 375 MHz)



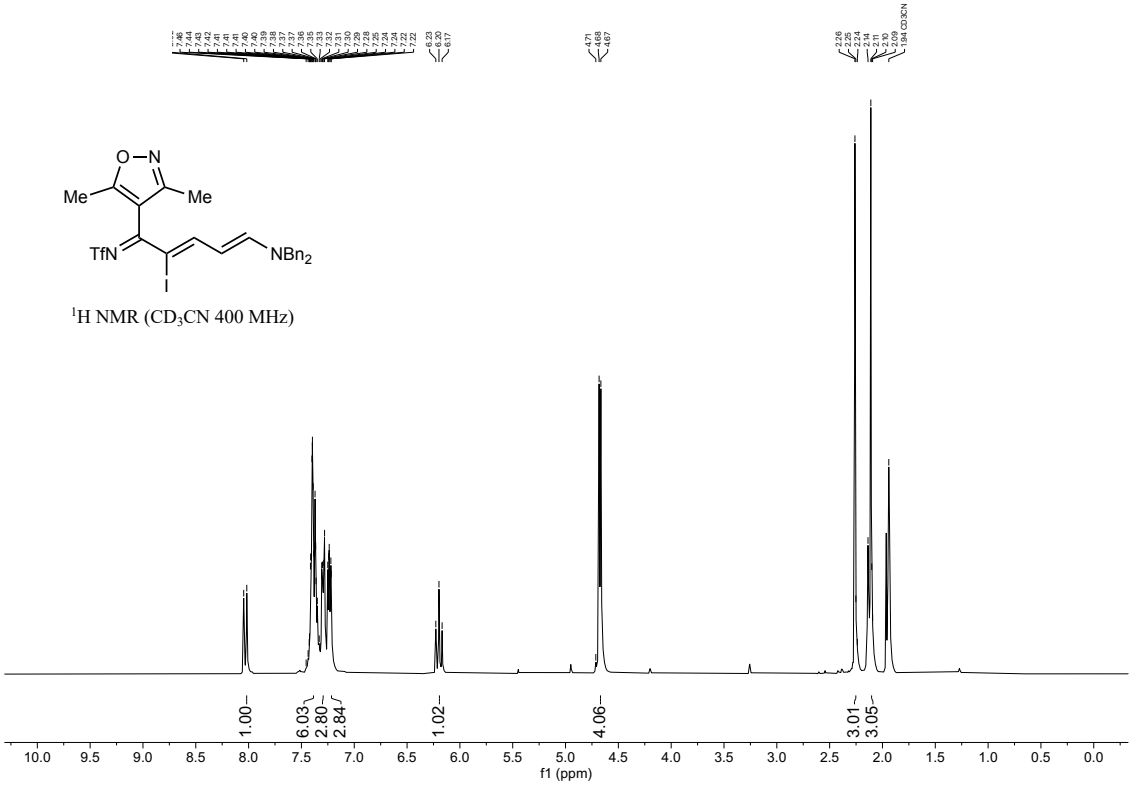
^{1}H NMR (CD_3CN 400 MHz)



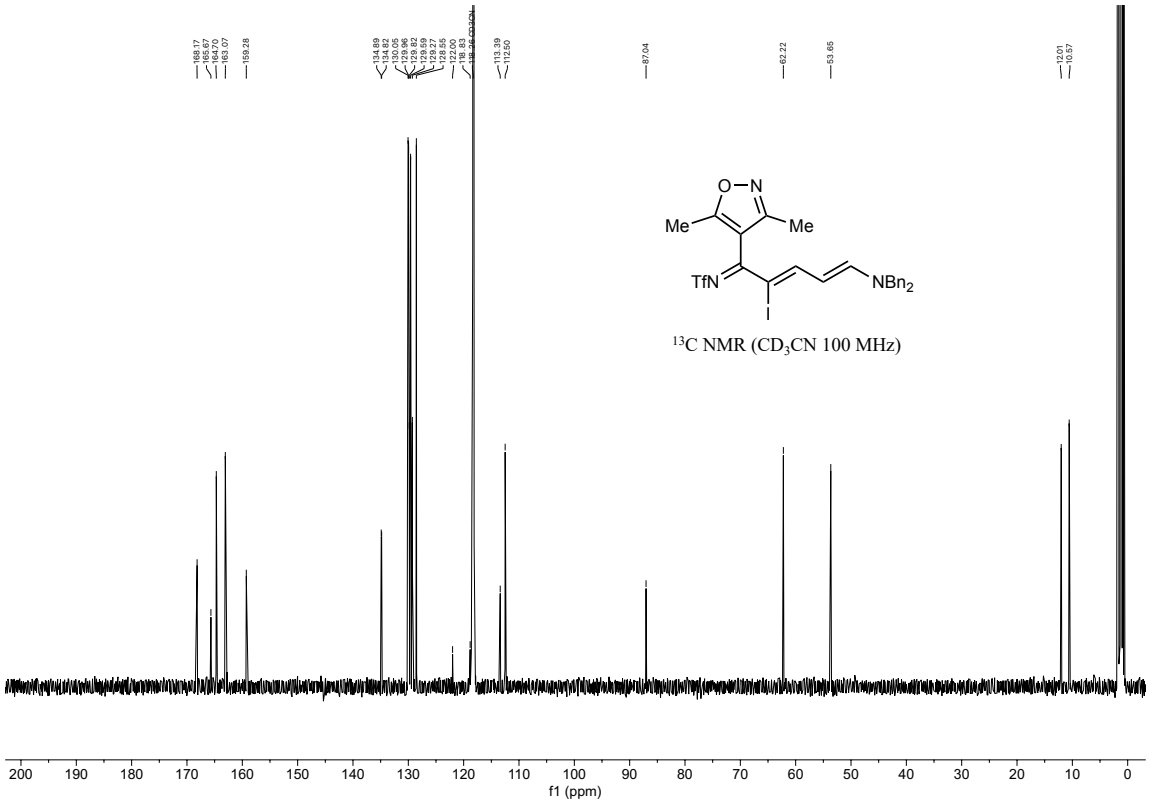
^{13}C NMR (CD_3CN 100 MHz)



^{19}F NMR (CD_3CN 375 MHz)

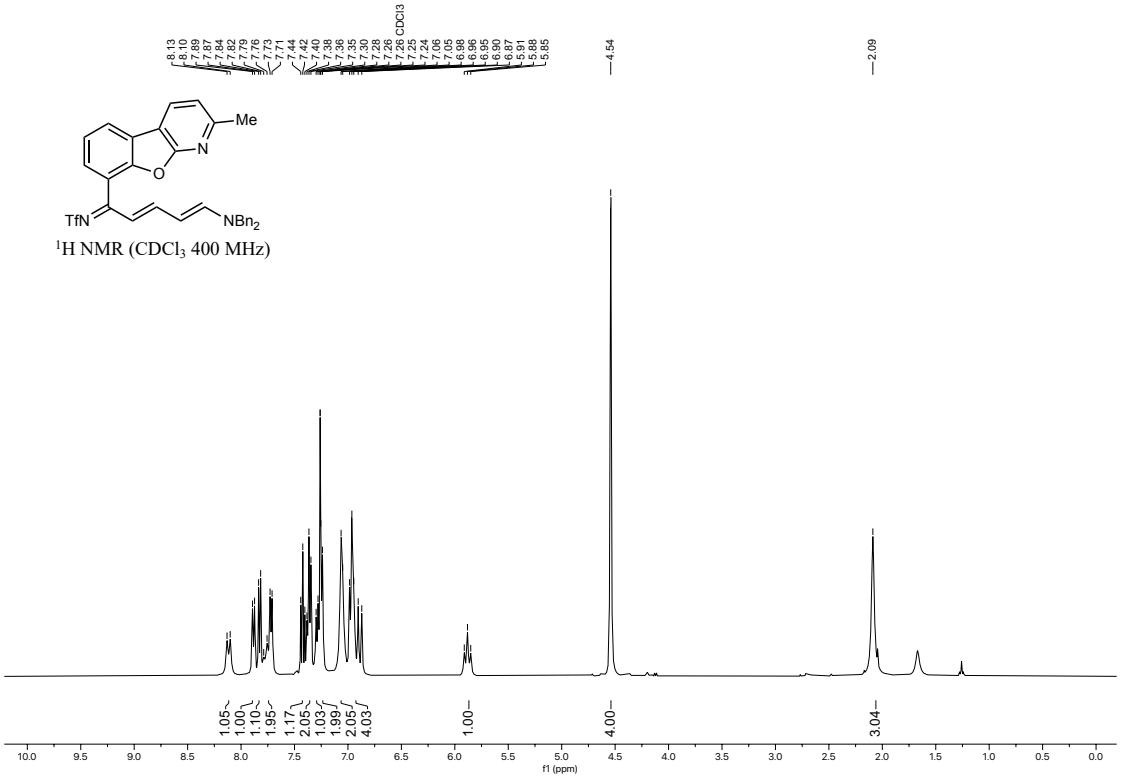


^{1}H NMR (CD_3CN 400 MHz)

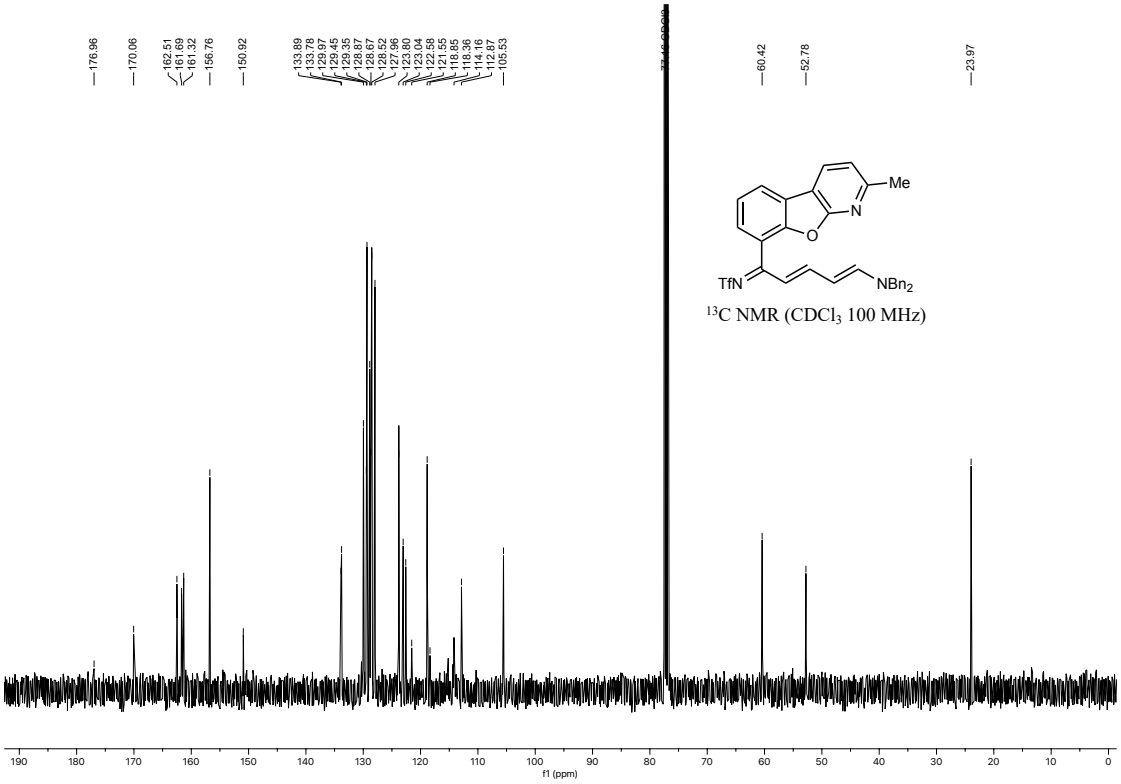


^{13}C NMR (CD_3CN 100 MHz)

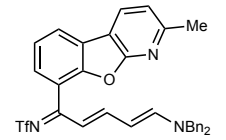
^{19}F NMR (CD_3CN 375 MHz)



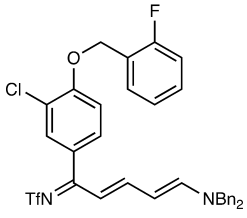
^{1}H NMR ($CDCl_3$ 400 MHz)



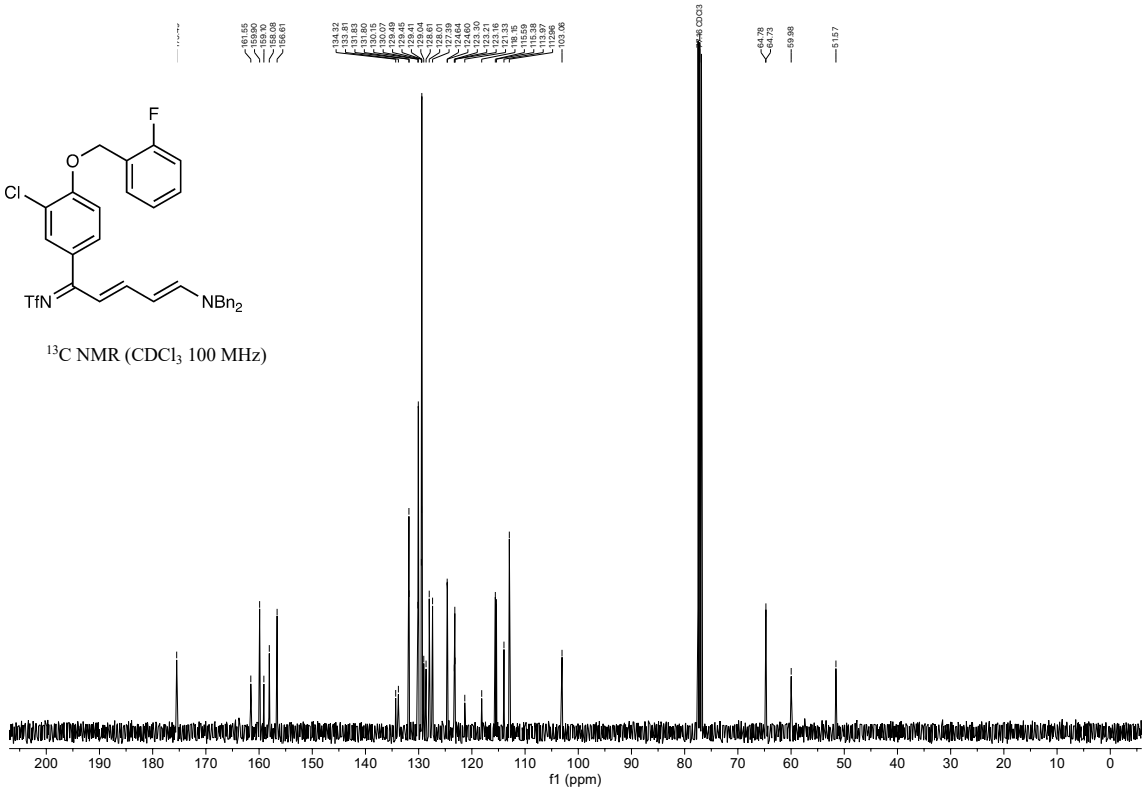
^{13}C NMR ($CDCl_3$ 100 MHz)



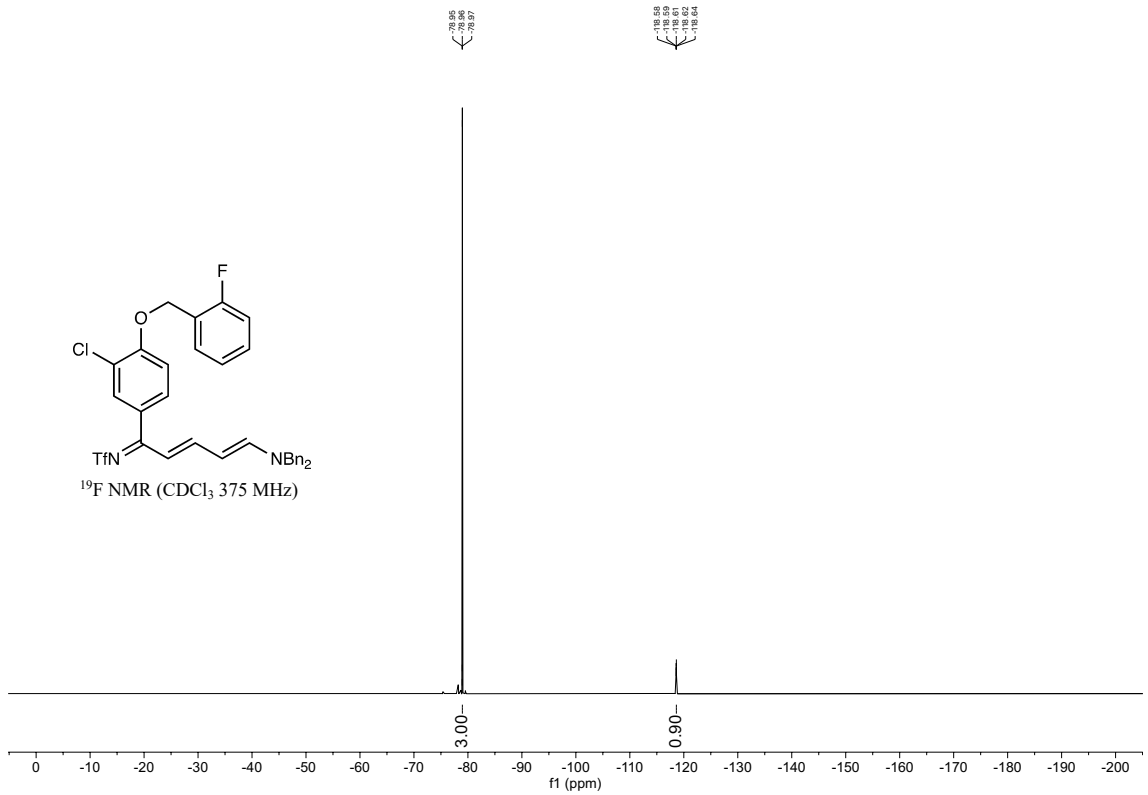
^{19}F NMR ($CDCl_3$ 100 MHz)



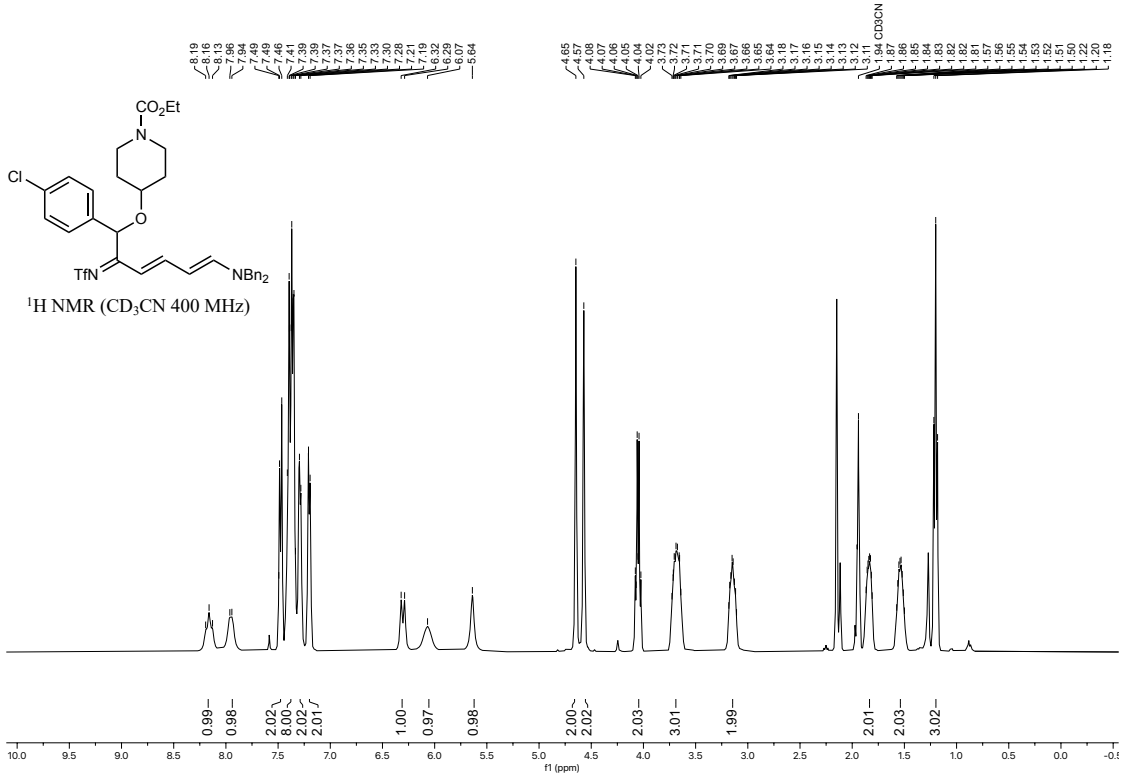
^{1}H NMR ($CDCl_3$ 400 MHz)

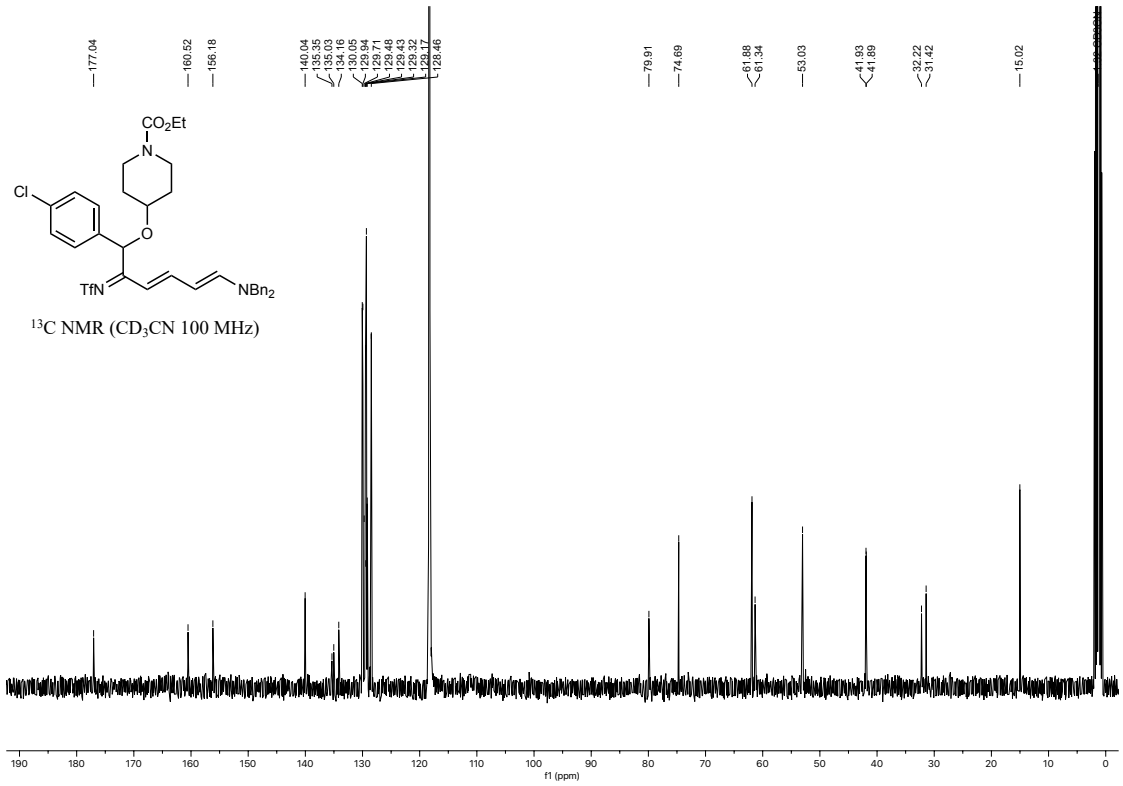


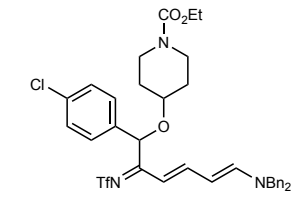
^{13}C NMR ($CDCl_3$ 100 MHz)



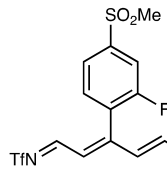
^{19}F NMR ($CDCl_3$ 375 MHz)


CO2Et
N
Cl
O
TfN
NBn2
1H NMR (CD3CN 400 MHz)
f1 (ppm)

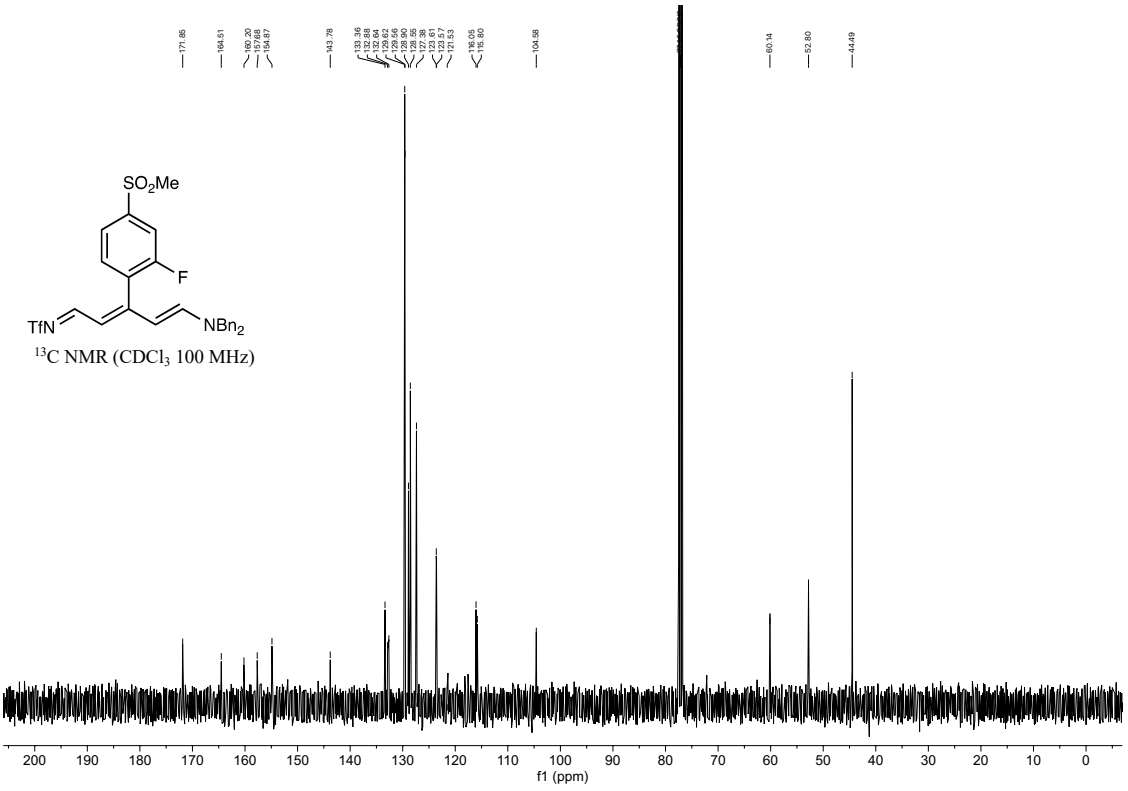

CO2Et
N
Cl
O
TfN
NBn2
13C NMR (CD3CN 100 MHz)
f1 (ppm)



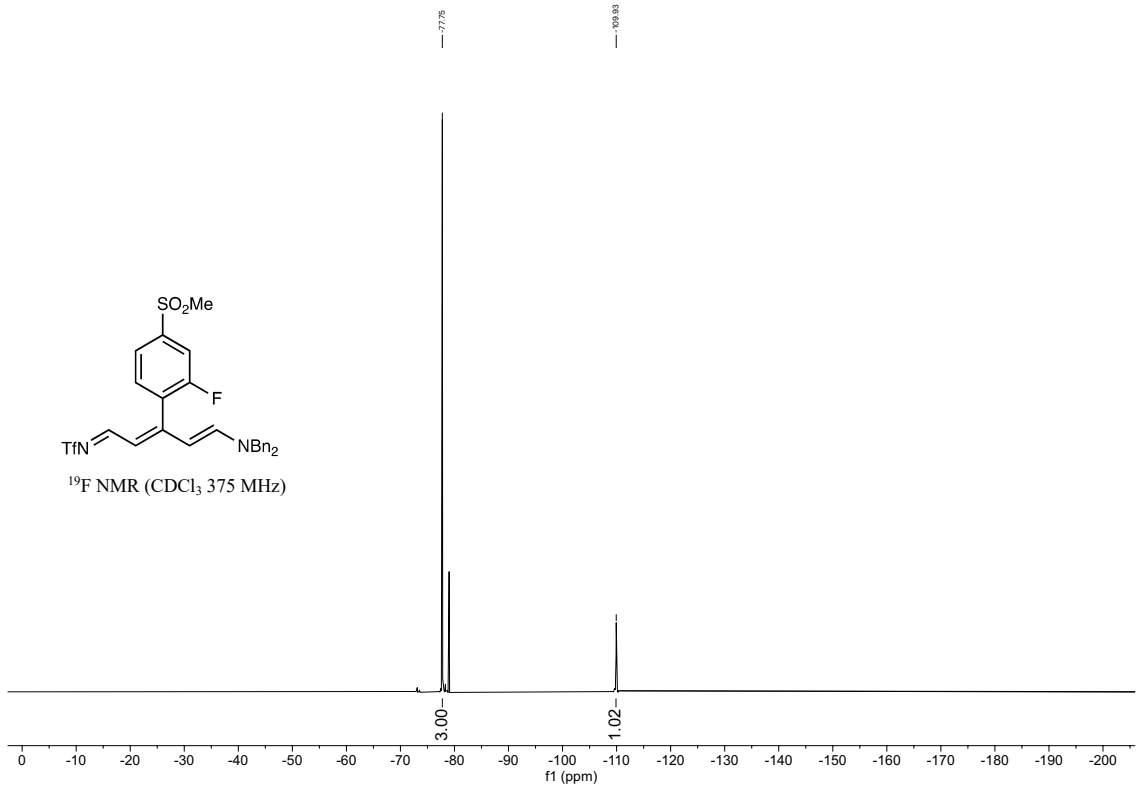
^{19}F NMR (CD_3CN 375 MHz)



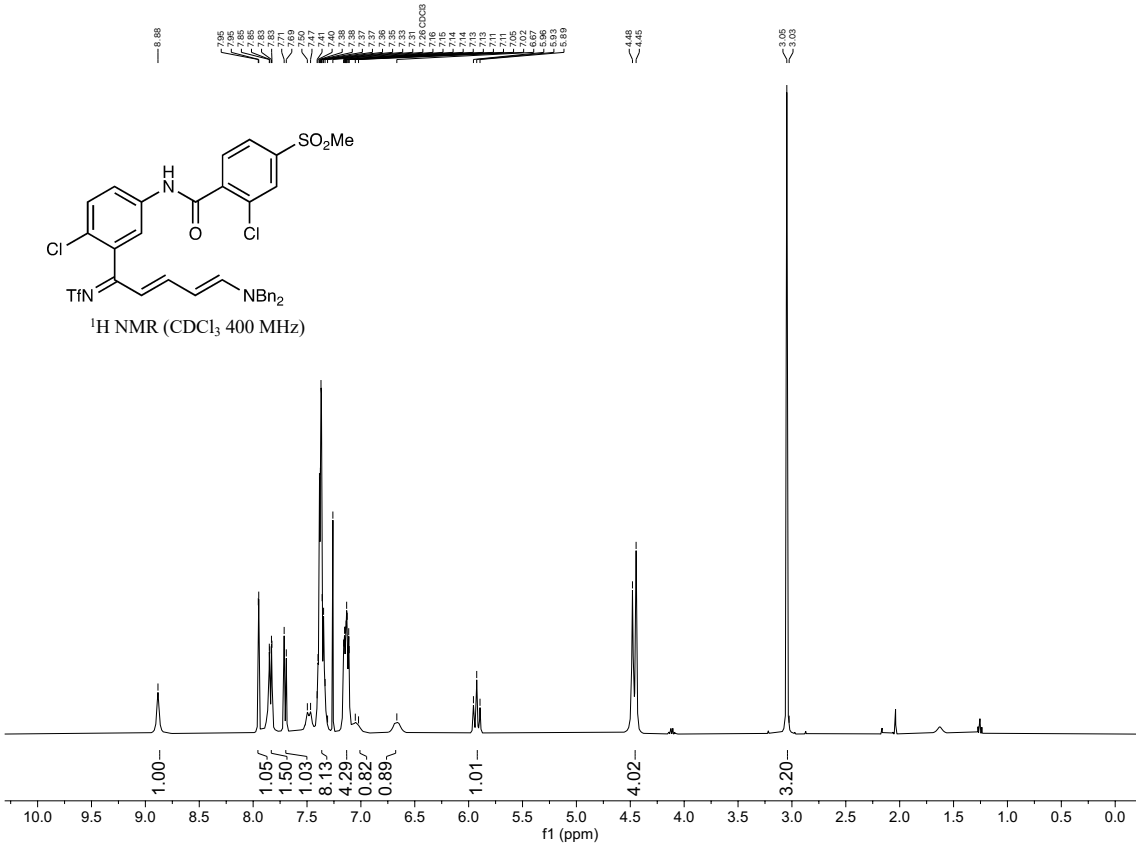
^{1}H NMR ($CDCl_3$ 400 MHz)



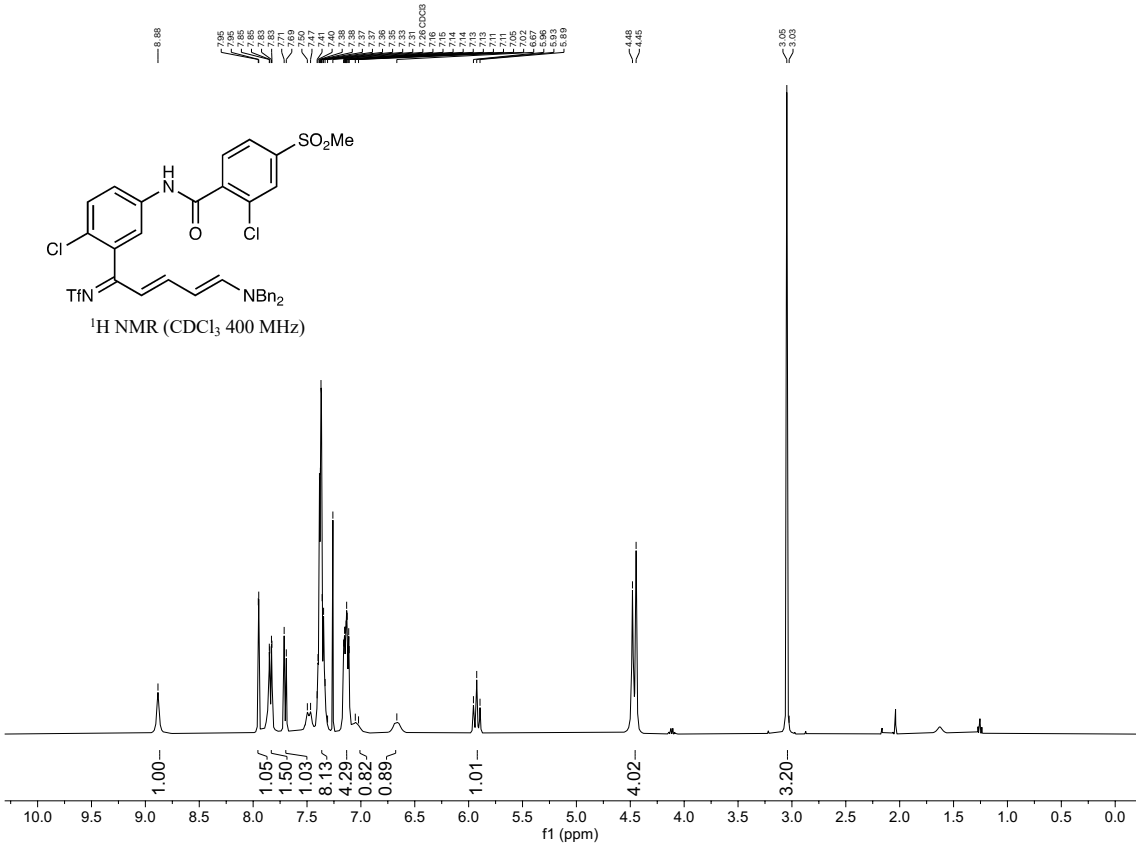
^{13}C NMR ($CDCl_3$ 100 MHz)



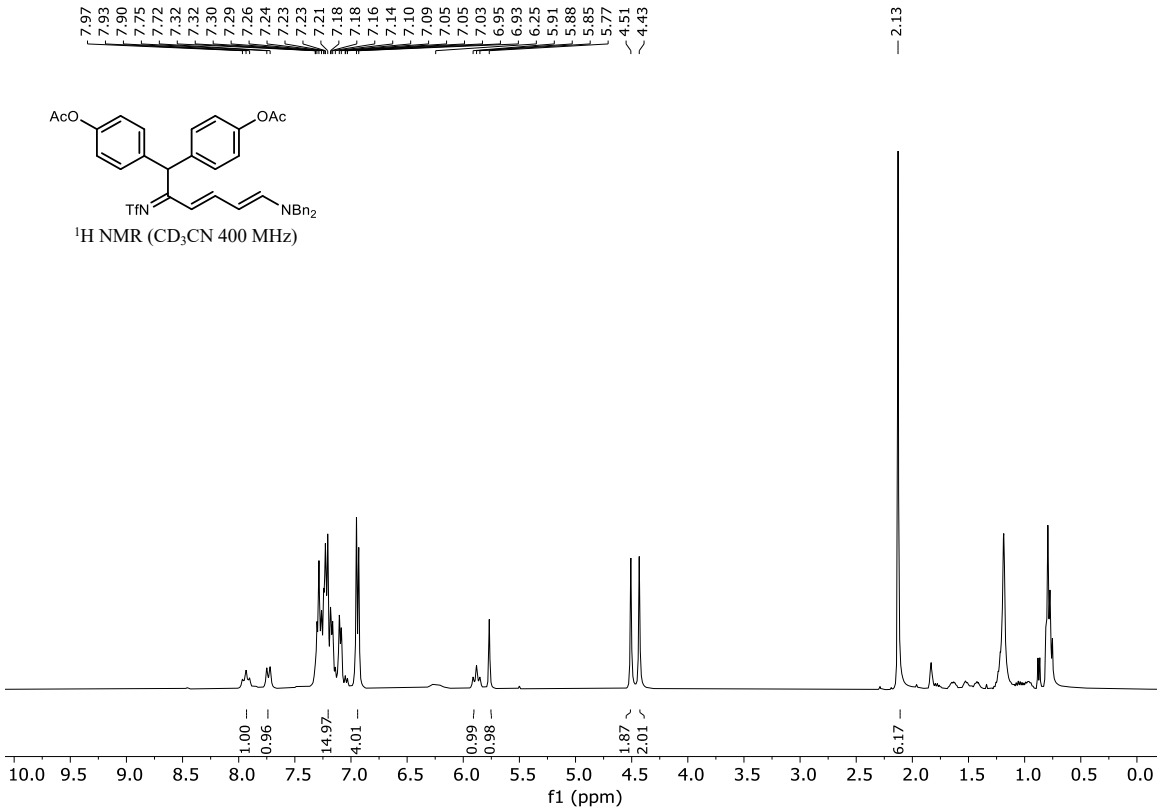
^{19}F NMR ($CDCl_3$ 375 MHz)



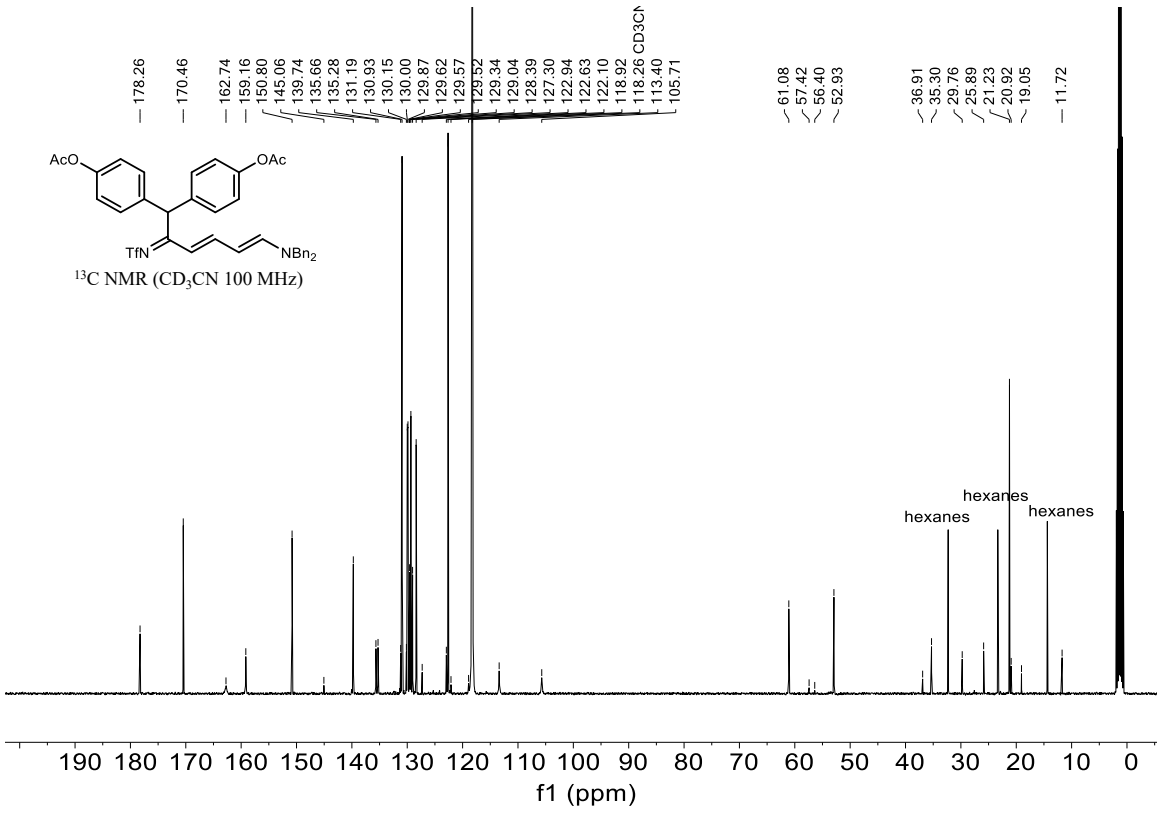
^{1}H NMR ($CDCl_3$ 400 MHz)



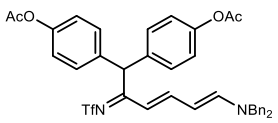
^{1}H NMR ($CDCl_3$ 400 MHz)



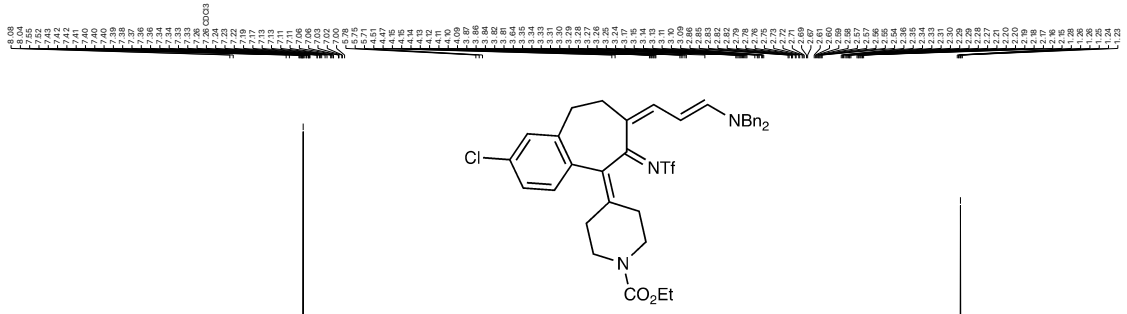
^{1}H NMR (CD_3CN 400 MHz)



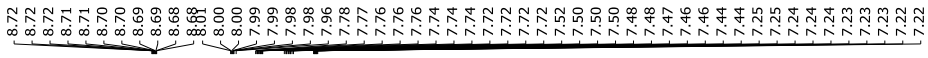
^{13}C NMR (CD_3CN 100 MHz)



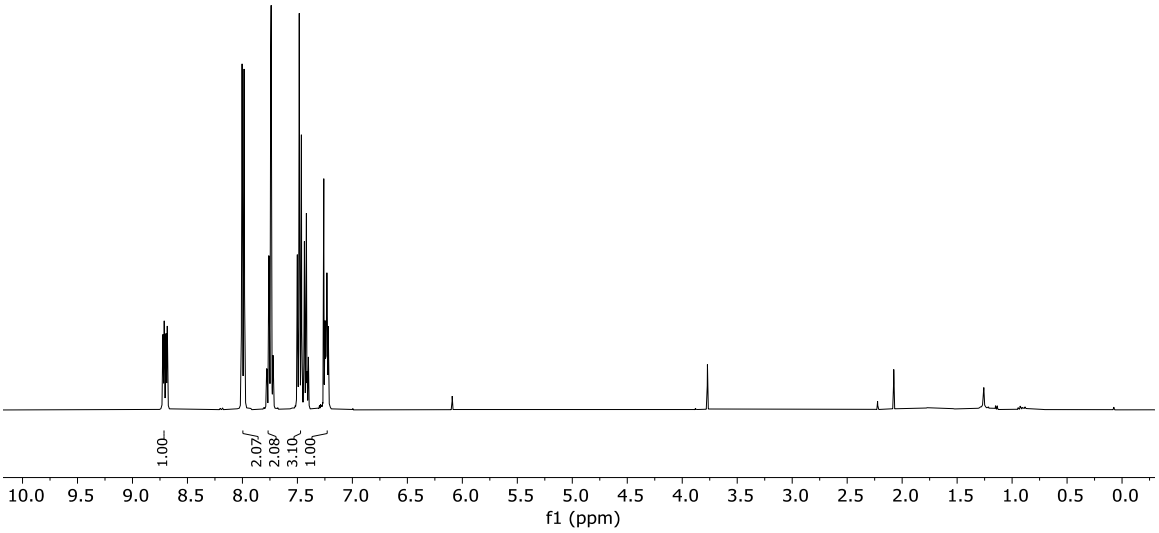
^{19}F NMR (CD_3CN 375 MHz)

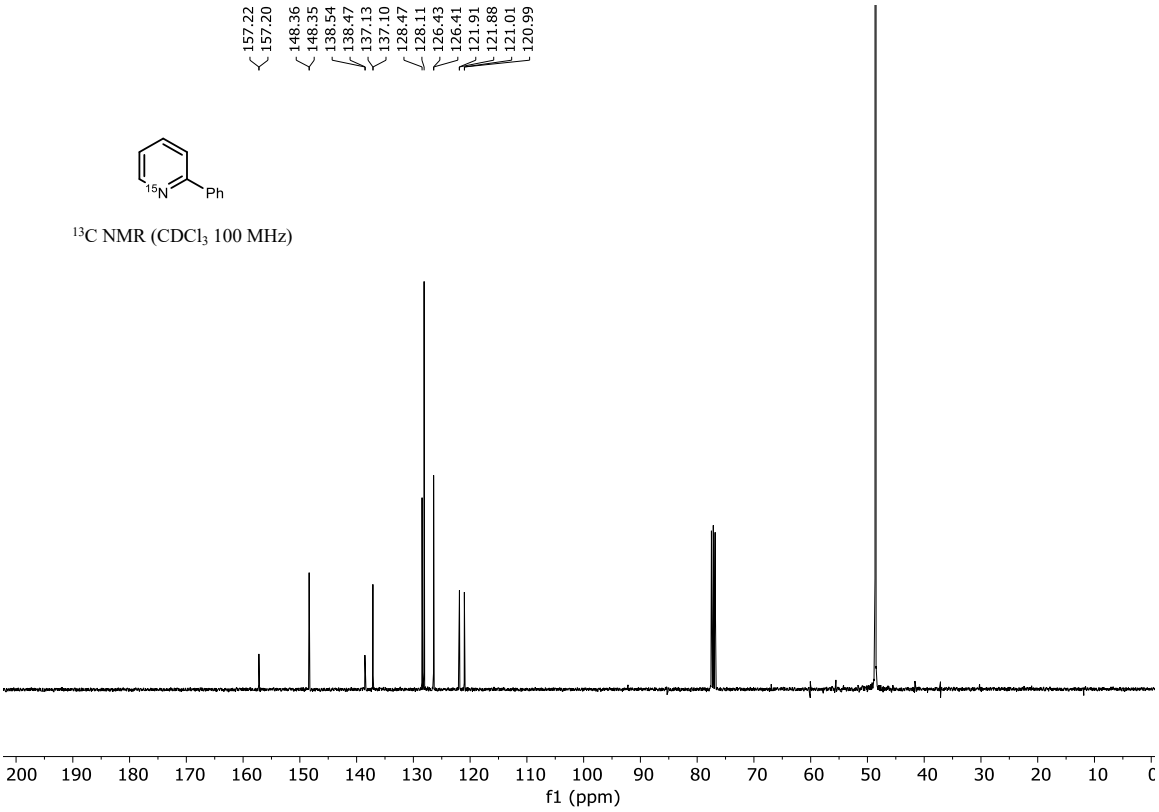


^{1}H NMR ($CDCl_3$ 400 MHz)

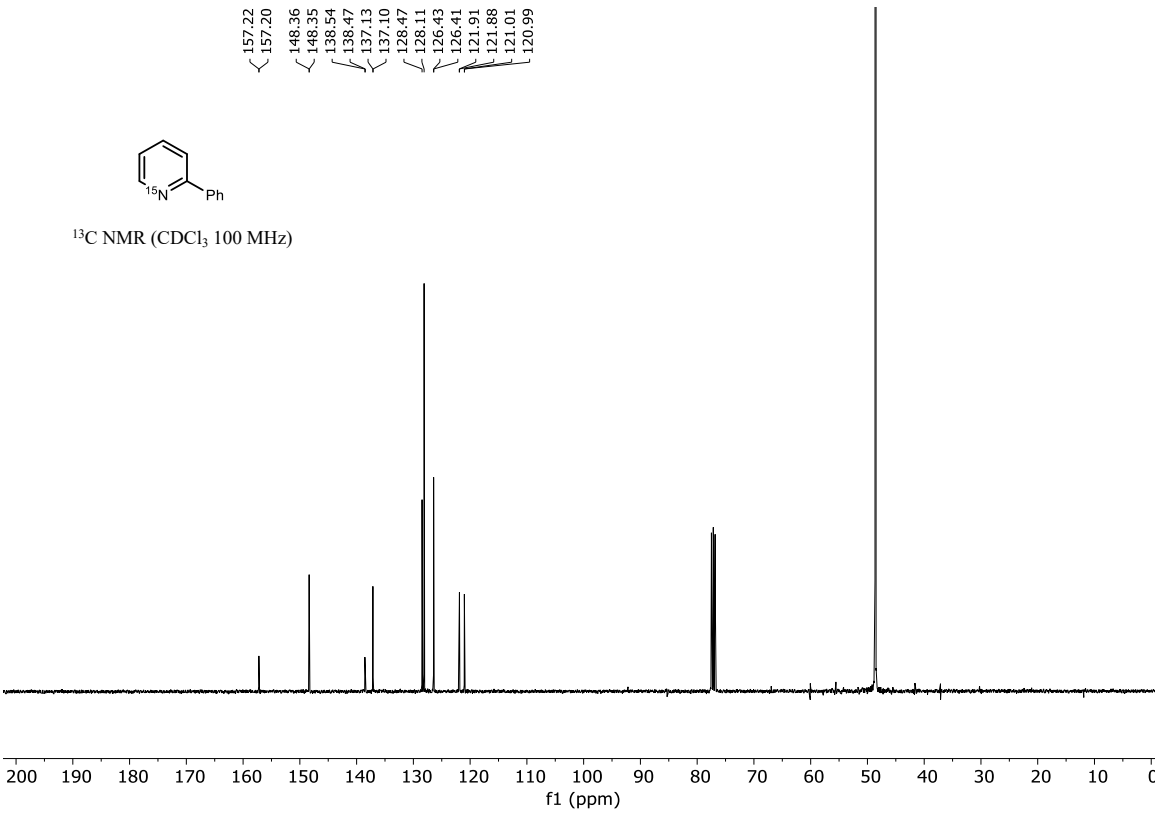


^{1}H NMR ($CDCl_3$ 400 MHz)

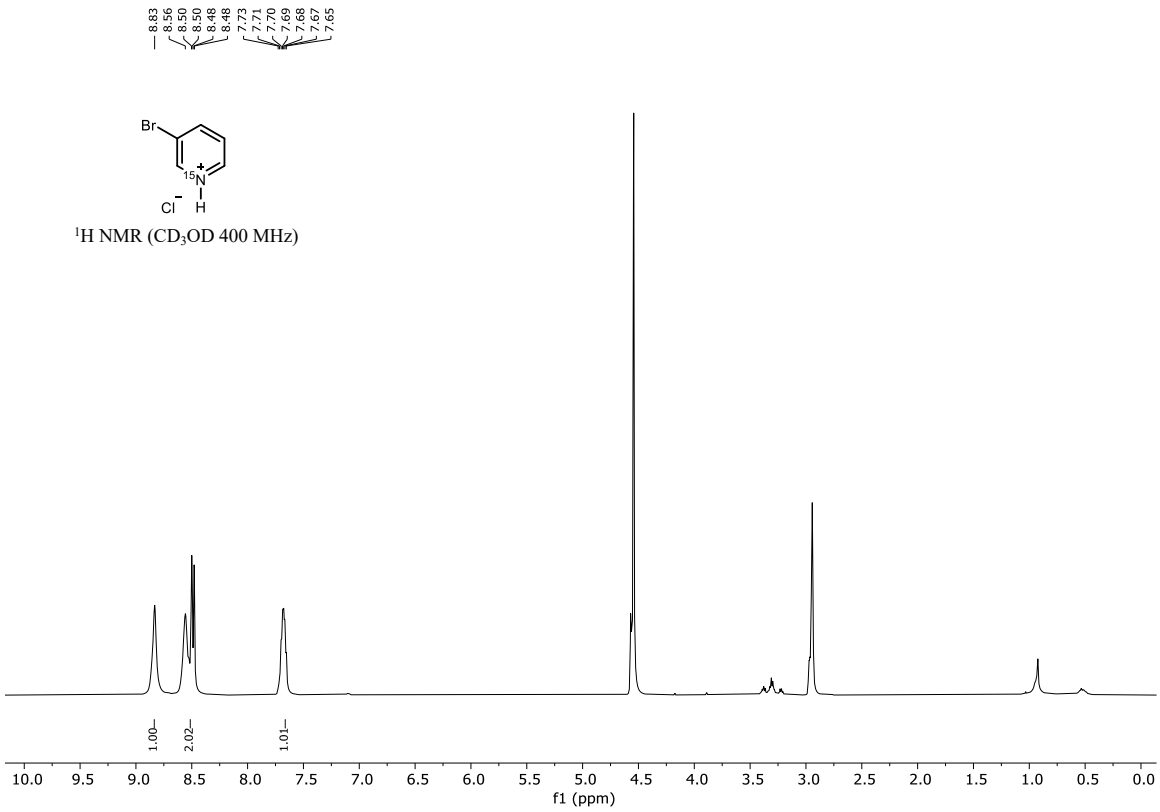




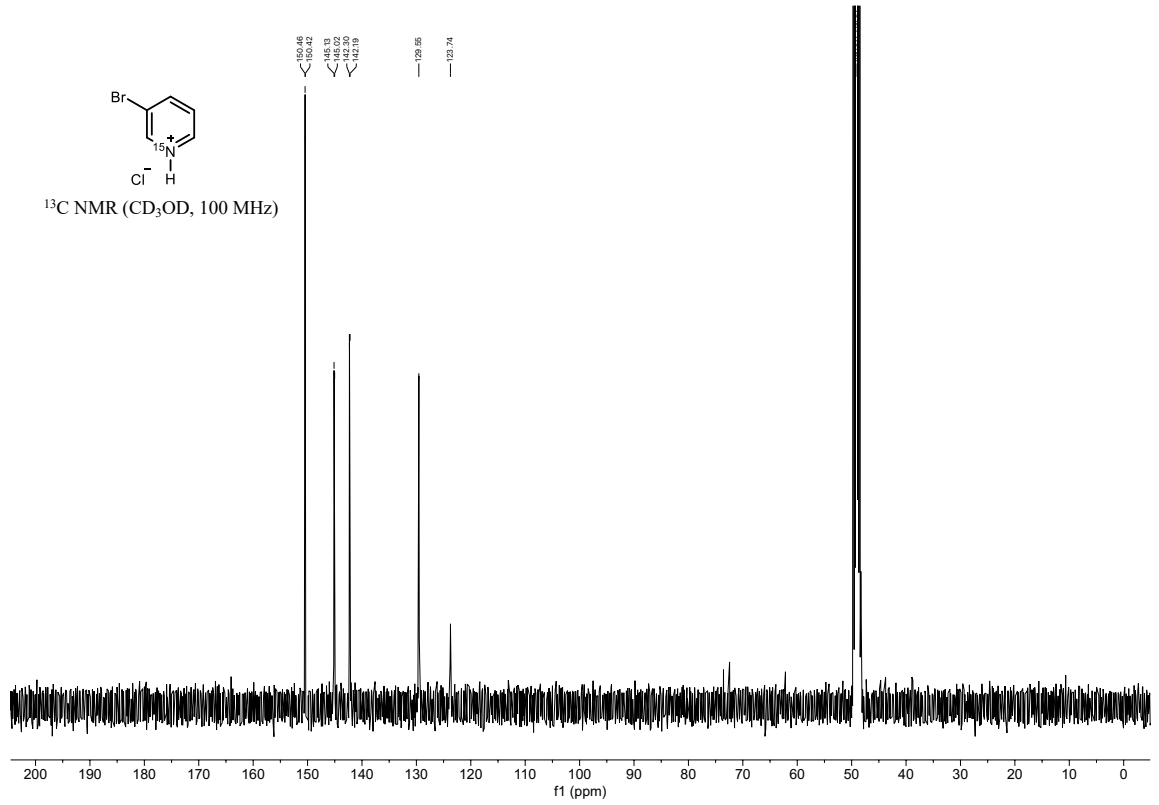
^{13}C NMR ($CDCl_3$ 100 MHz)



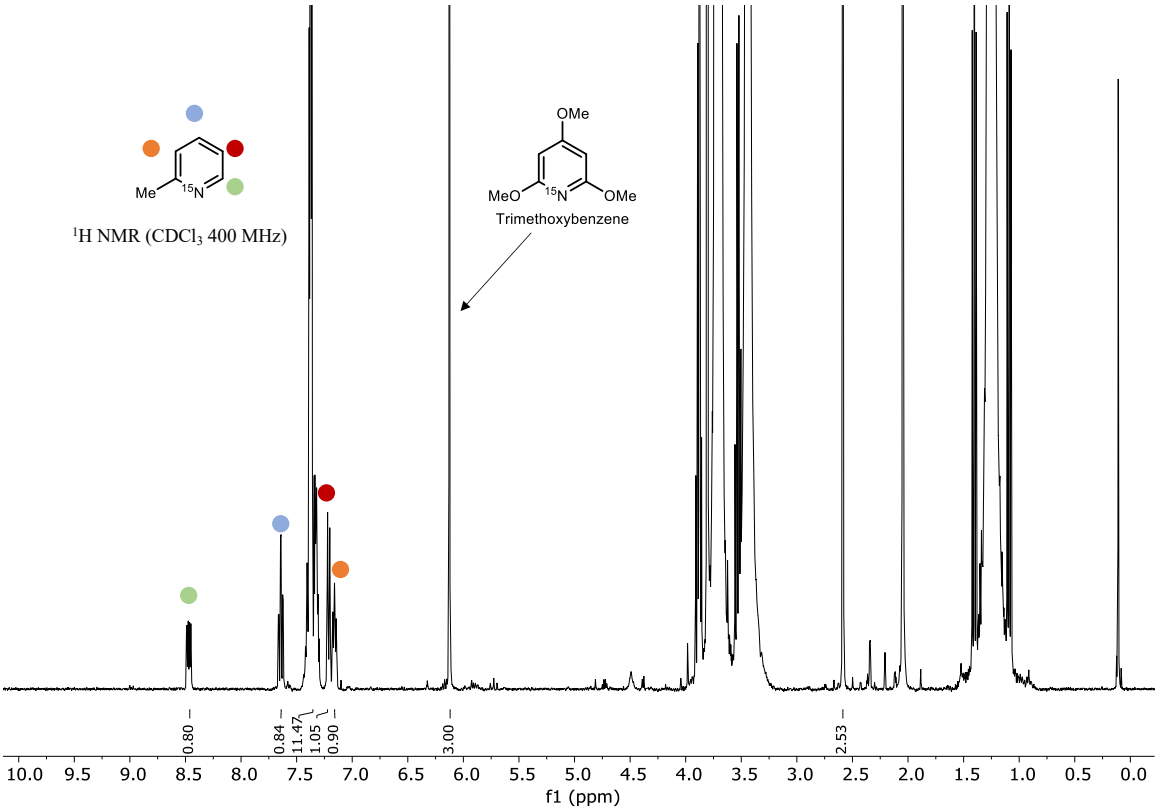
^{13}C NMR ($CDCl_3$ 100 MHz)

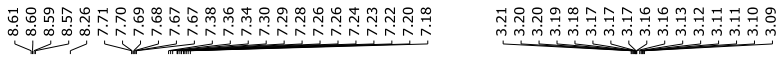


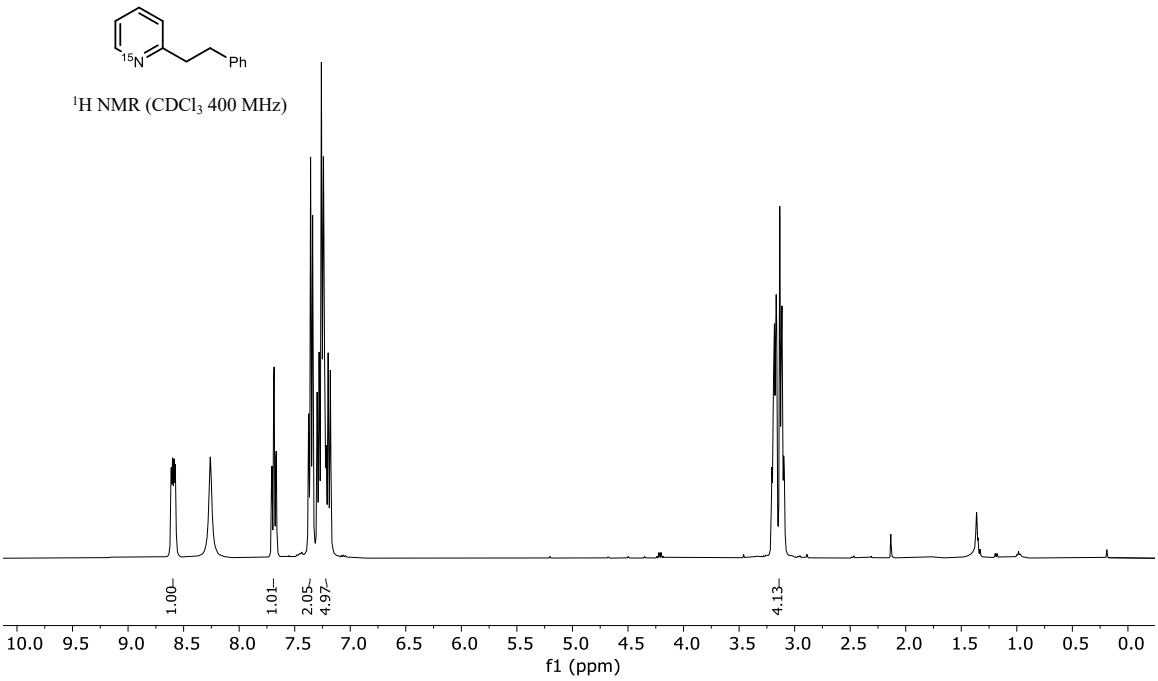
^{1}H NMR (CD_3OD 400 MHz)

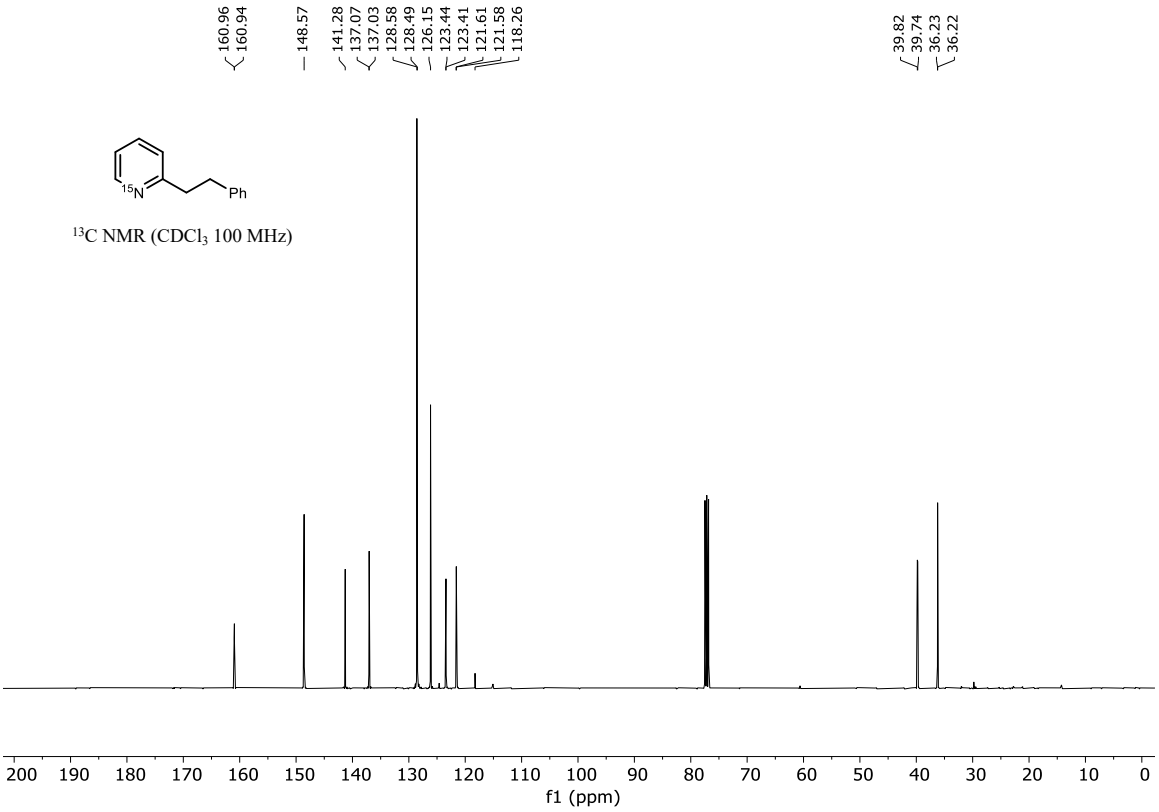


^{13}C NMR (CD_3OD, 100 MHz)

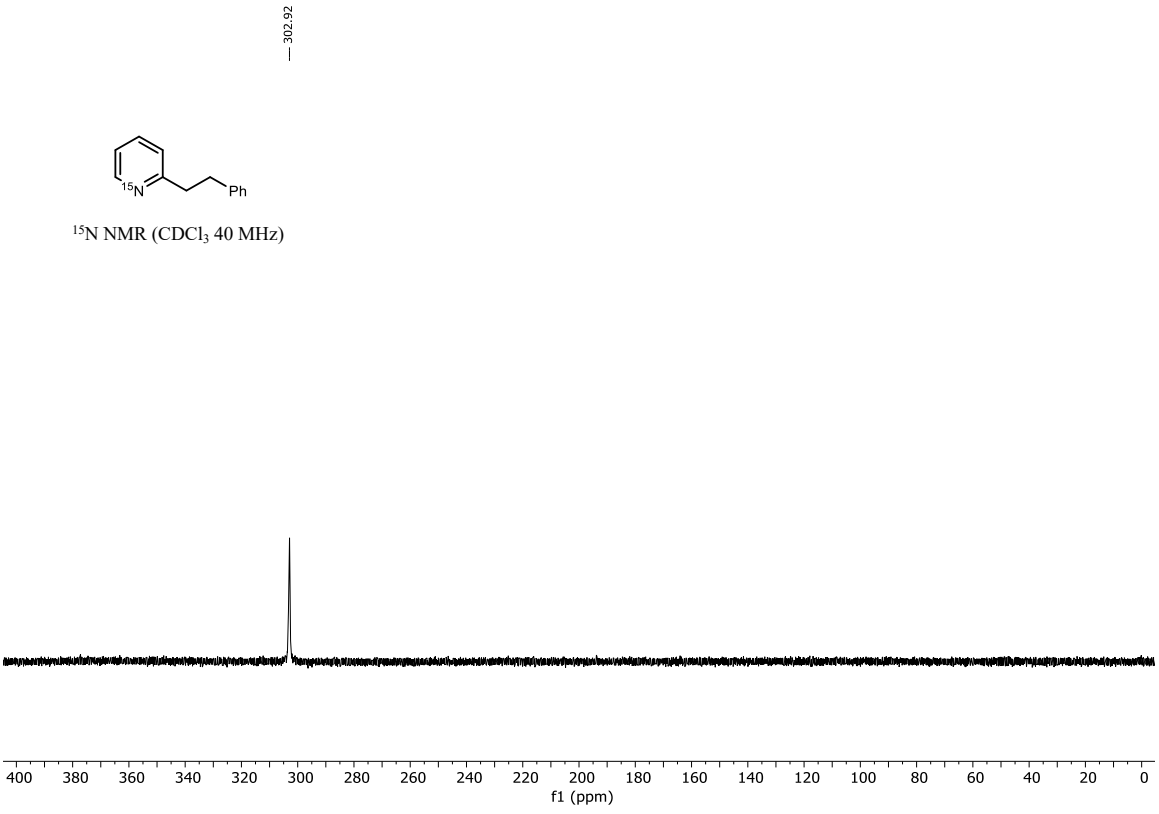

Me
15N
1H NMR (CDCl3 400 MHz)
OMe
MeO
15N
OMe
Trimethoxybenzene
0.80
0.84
11.47
1.05
0.90
3.00
2.53
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


8.61 8.60 8.59 8.57 8.26 7.71 7.70 7.69 7.68 7.67 7.67 7.38 7.36 7.34 7.30 7.29 7.28 7.26 7.26 7.24 7.23 7.22 7.20 7.18
3.21 3.20 3.20 3.19 3.18 3.17 3.17 3.17 3.16 3.16 3.13 3.12 3.11 3.11 3.10 3.09

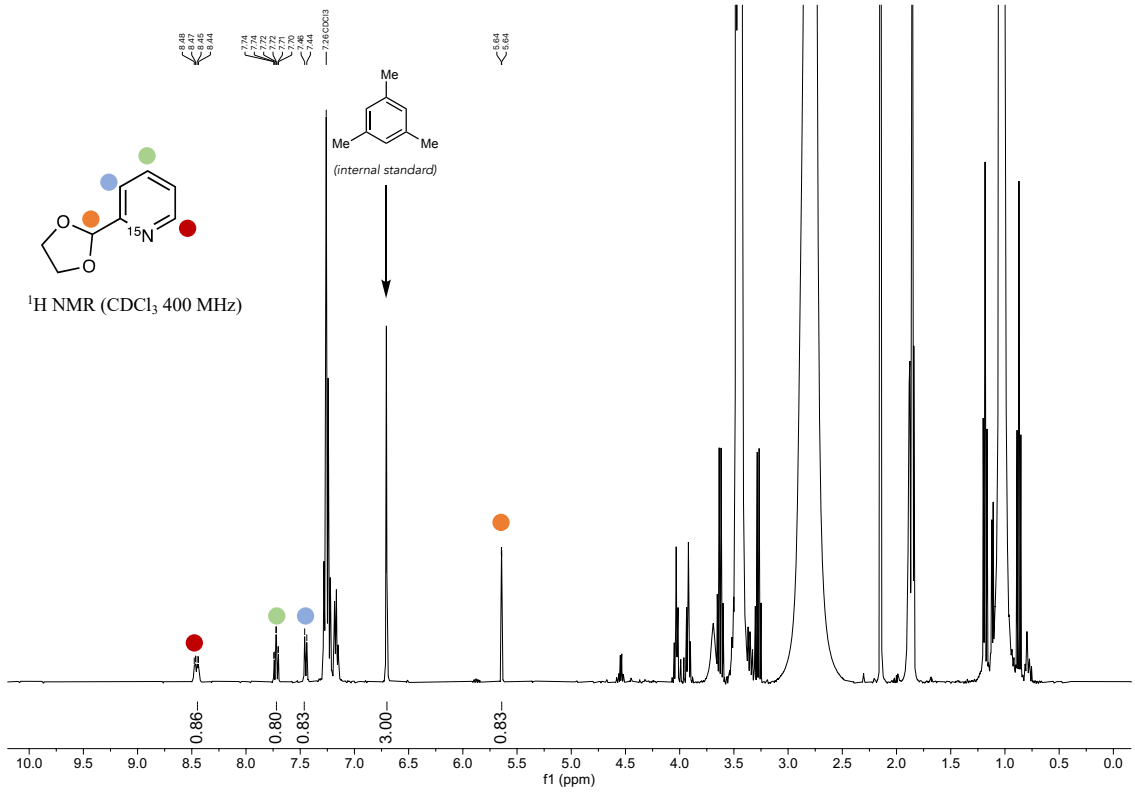

15N
Ph
1H NMR (CDCl3 400 MHz)
1.00
1.01
2.05
4.97
4.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



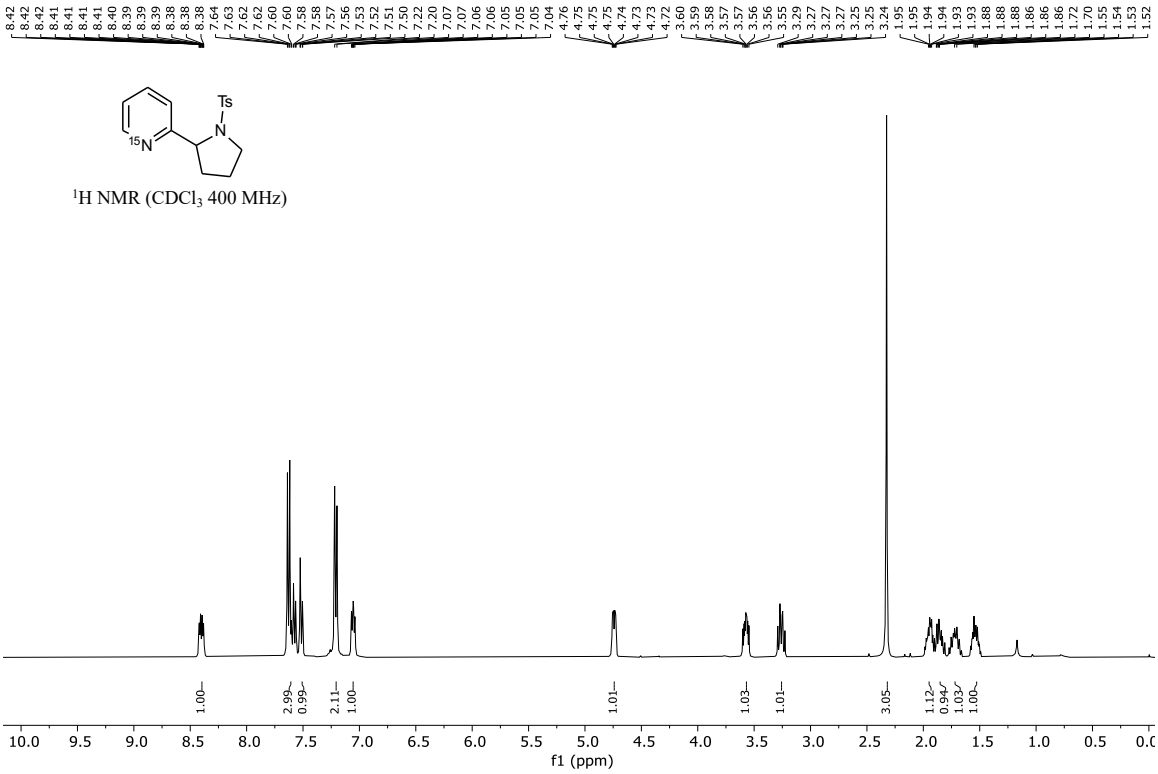
^{13}C NMR ($CDCl_3$ 100 MHz)



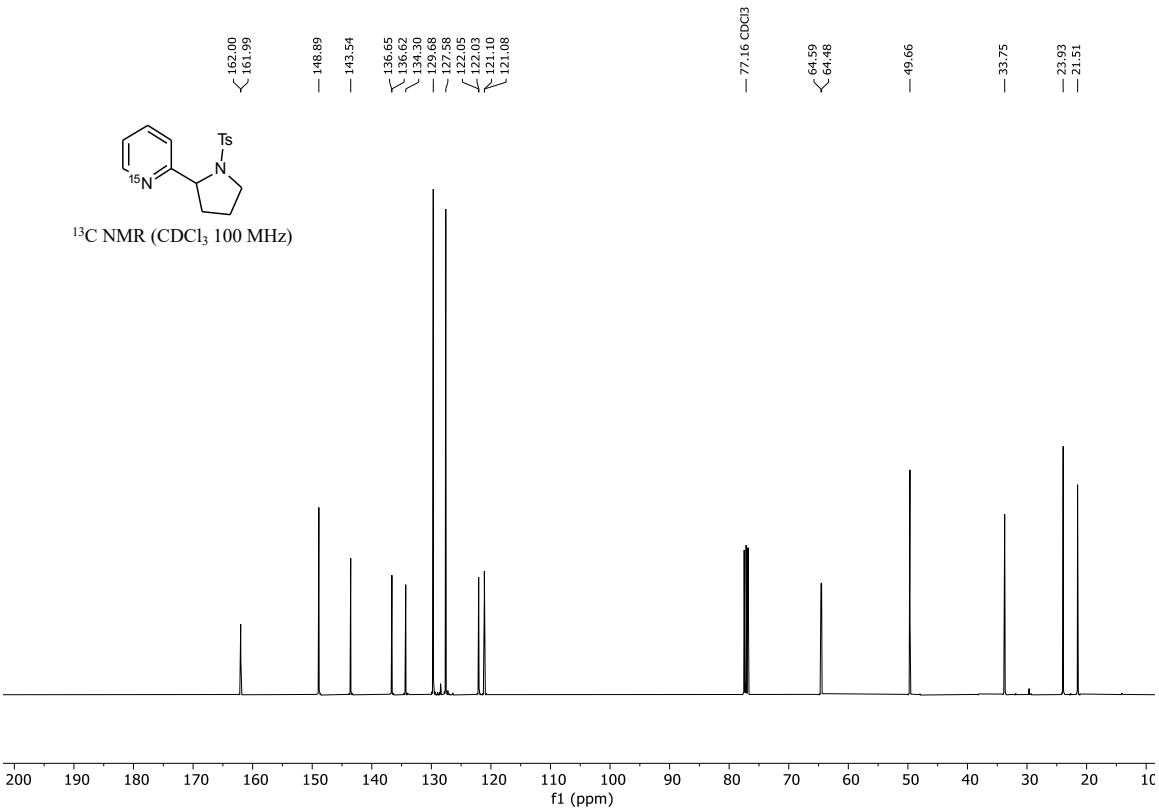
^{15}N NMR ($CDCl_3$ 40 MHz)



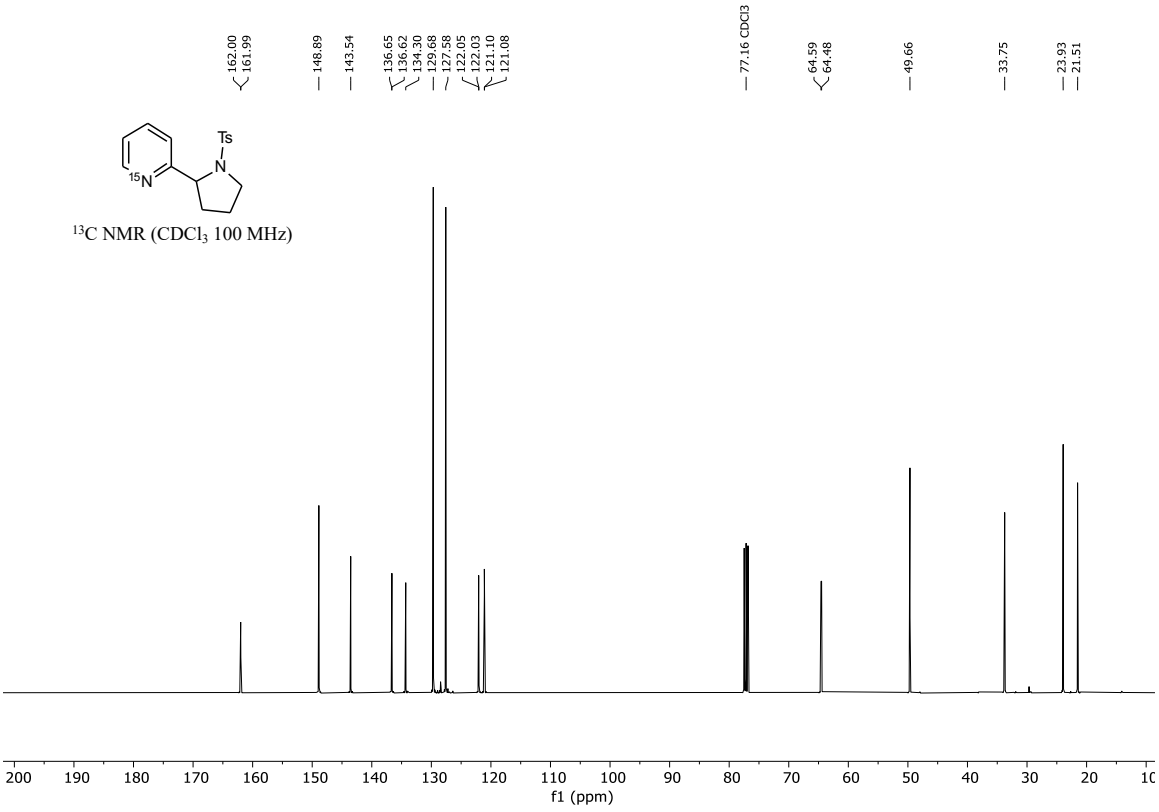
^{1}H NMR ($CDCl_3$ 400 MHz)



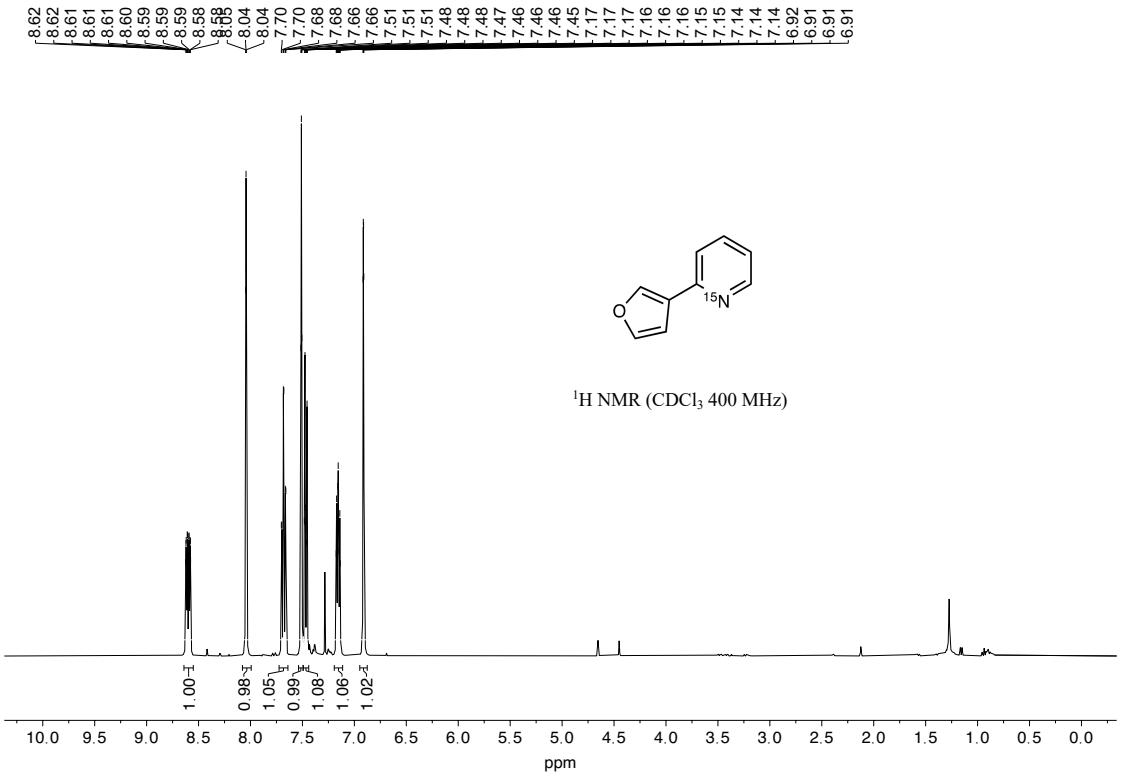
^{1}H NMR ($CDCl_3$ 400 MHz)



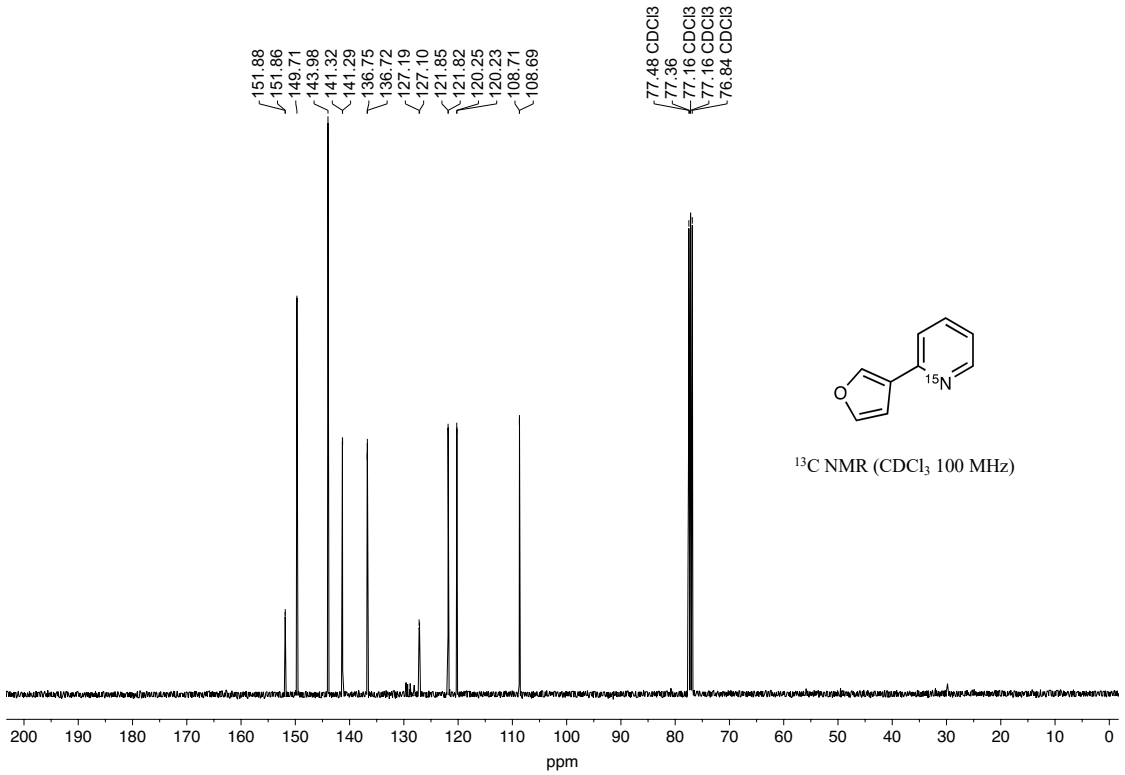
^{13}C NMR ($CDCl_3$ 100 MHz)



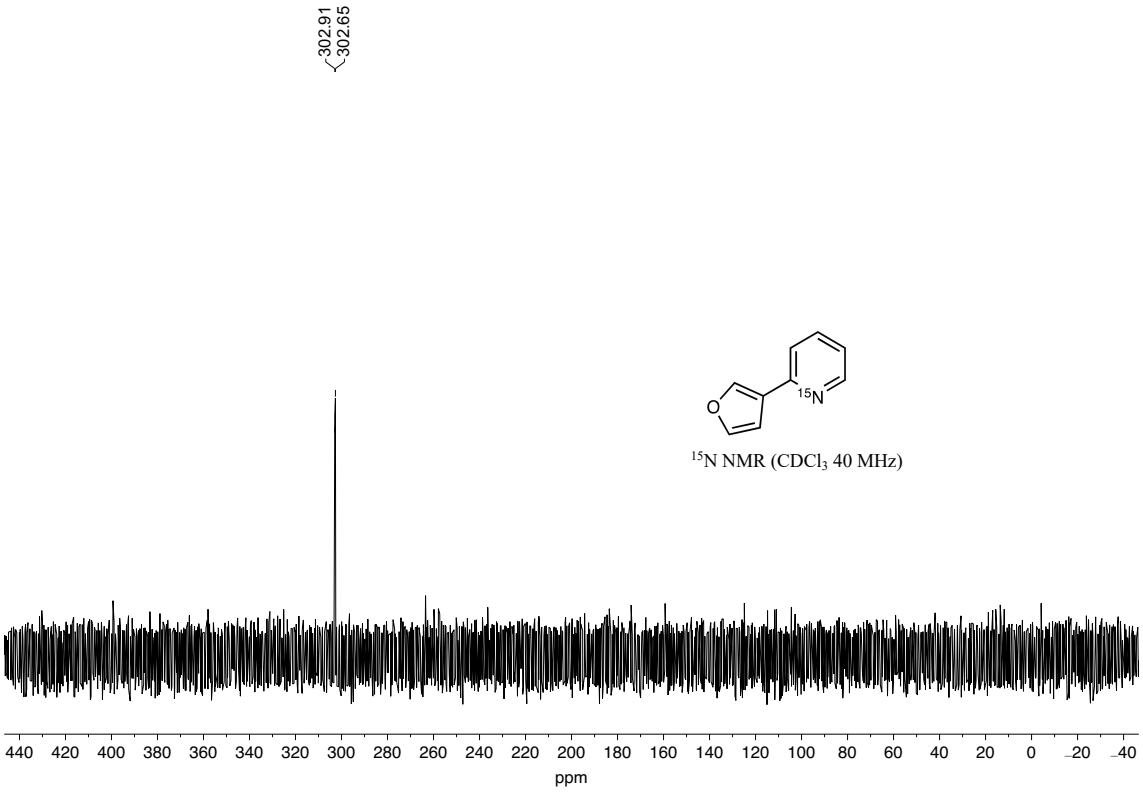
^{13}C NMR ($CDCl_3$ 100 MHz)



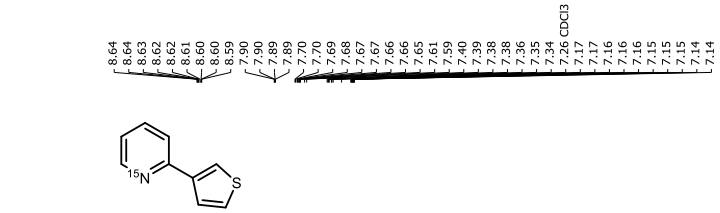
^{1}H NMR ($CDCl_3$ 400 MHz)



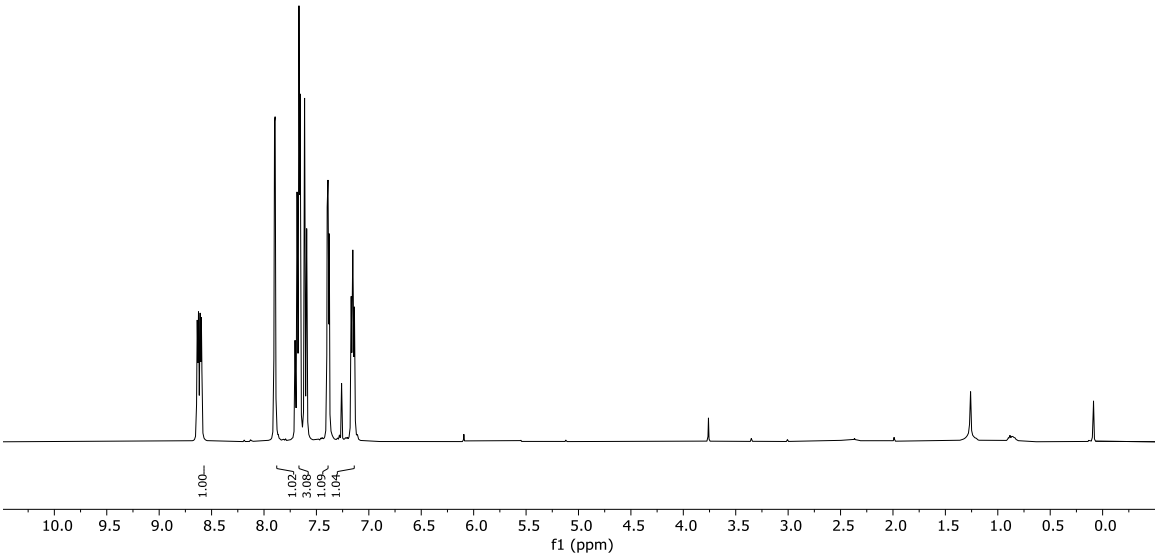
^{13}C NMR ($CDCl_3$ 100 MHz)

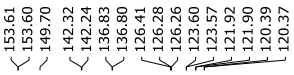


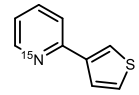
^{15}N NMR ($CDCl_3$ 40 MHz)



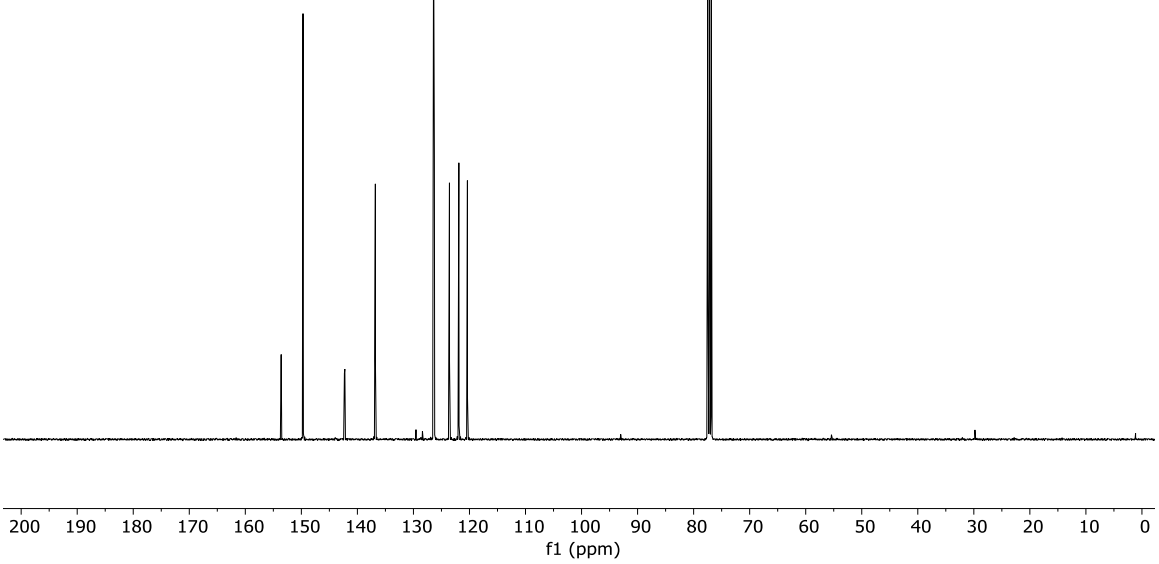
^{1}H NMR ($CDCl_3$ 400 MHz)



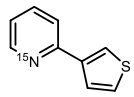




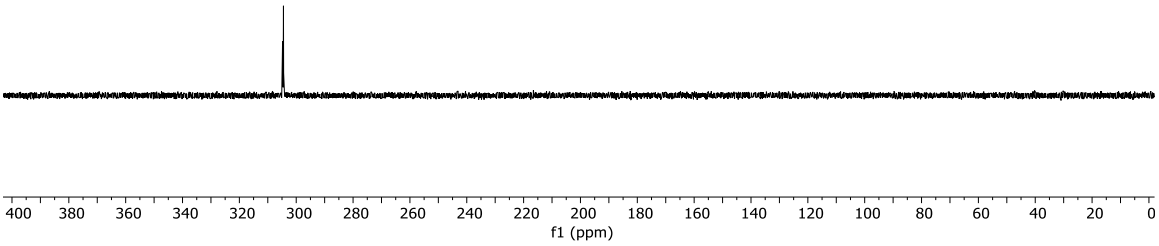
^{13}C NMR ($CDCl_3$ 100 MHz)

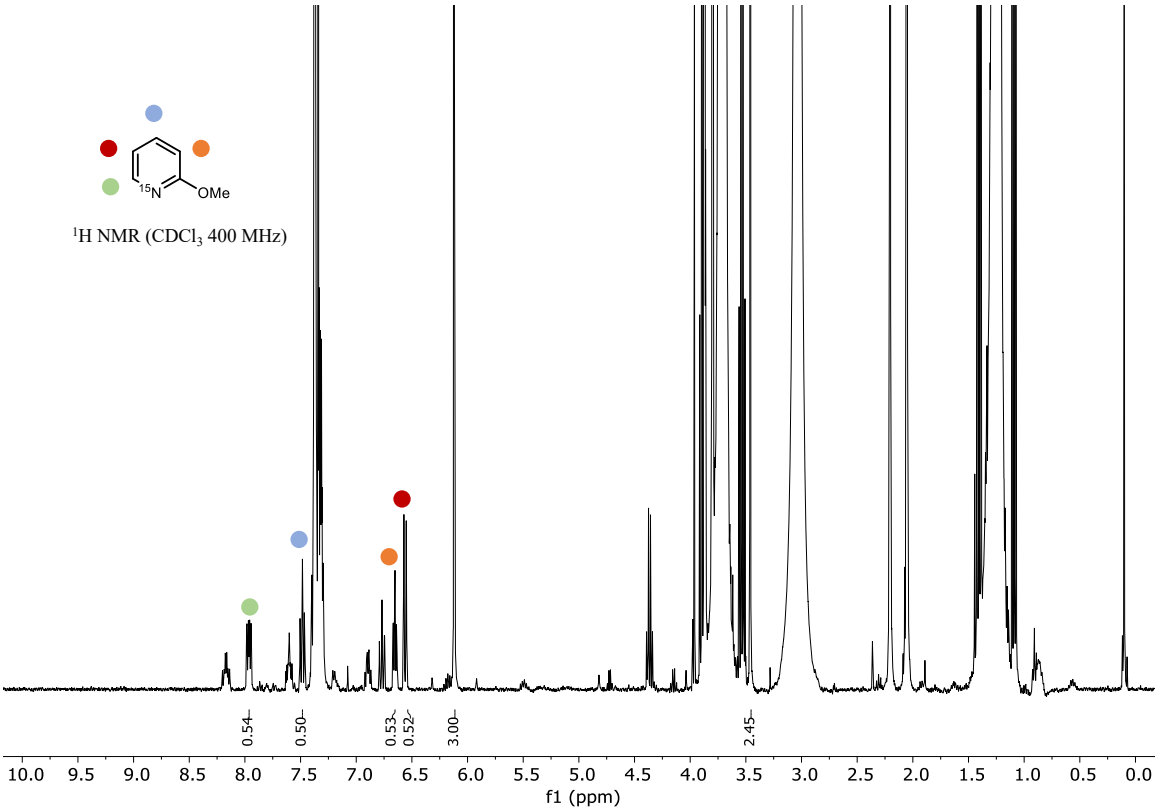


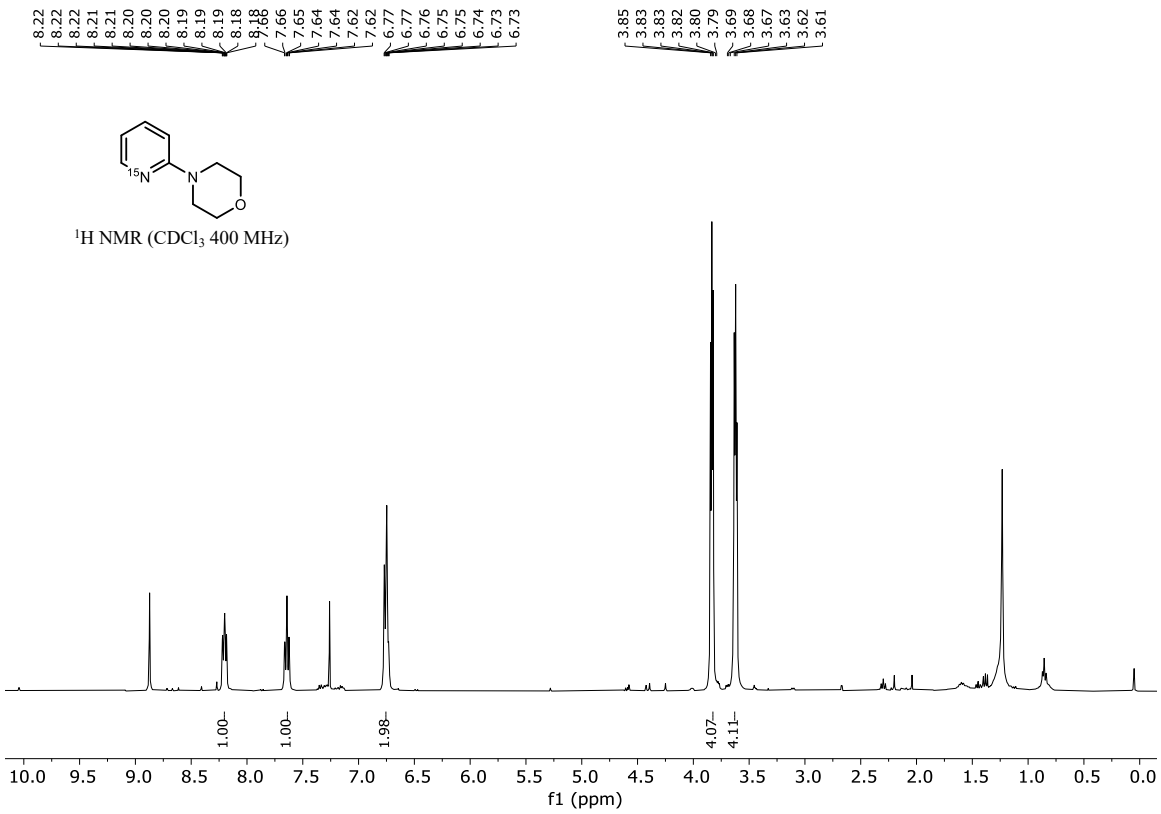
304.77
304.50



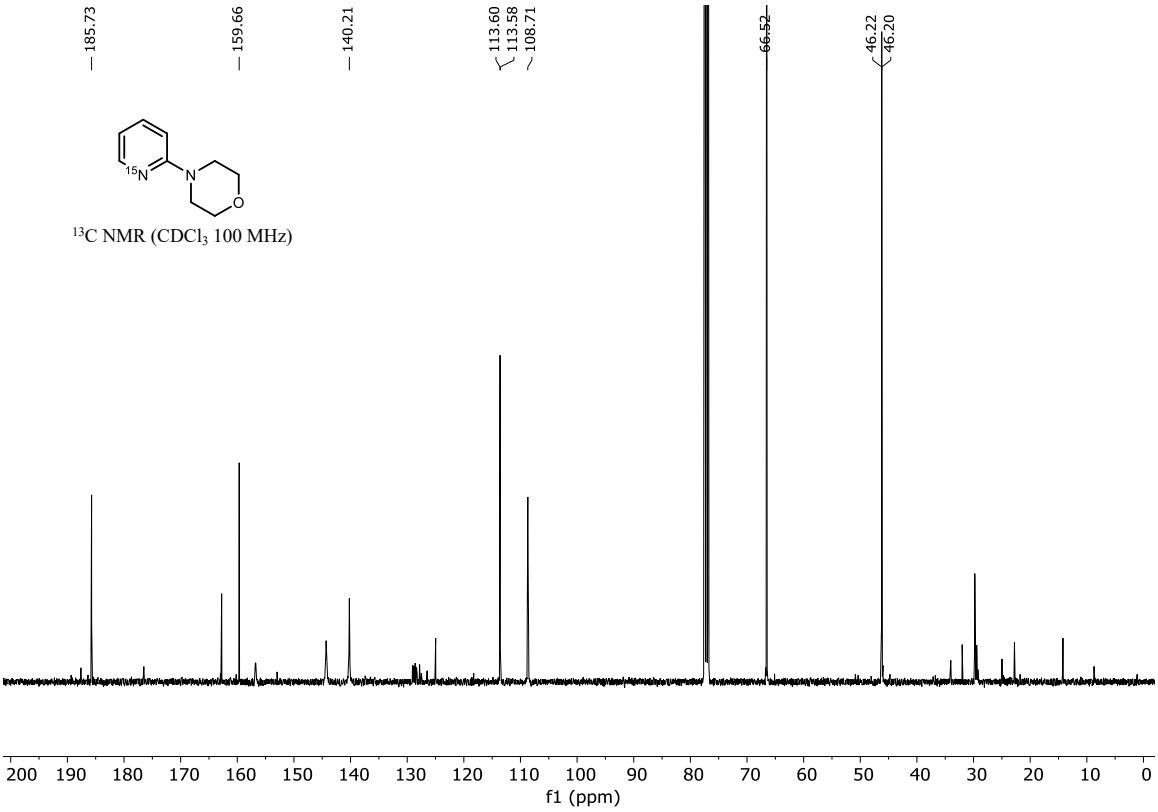
^{15}N NMR ($CDCl_3$ 40 MHz)



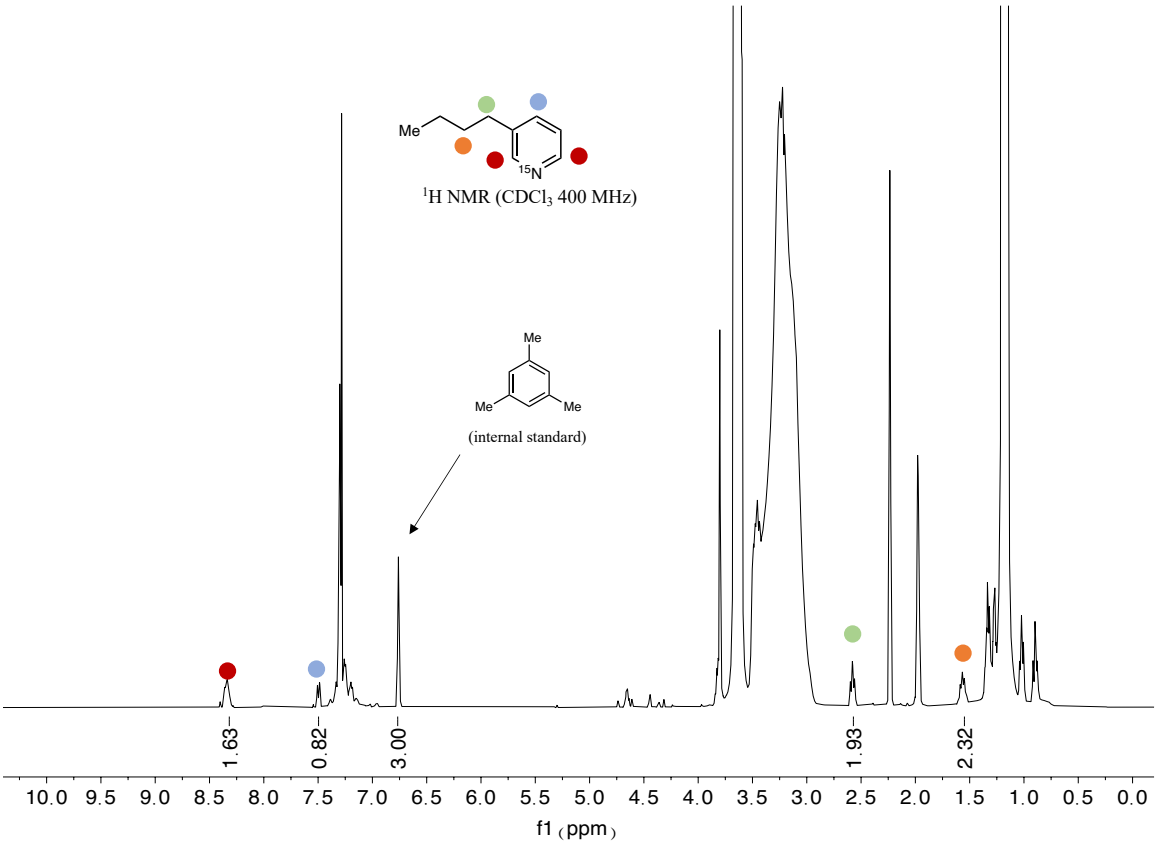

^{15}N
OMe
^{1}H NMR ($CDCl_3$ 400 MHz)
0.54
0.50
0.53
0.52
3.00
2.45
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

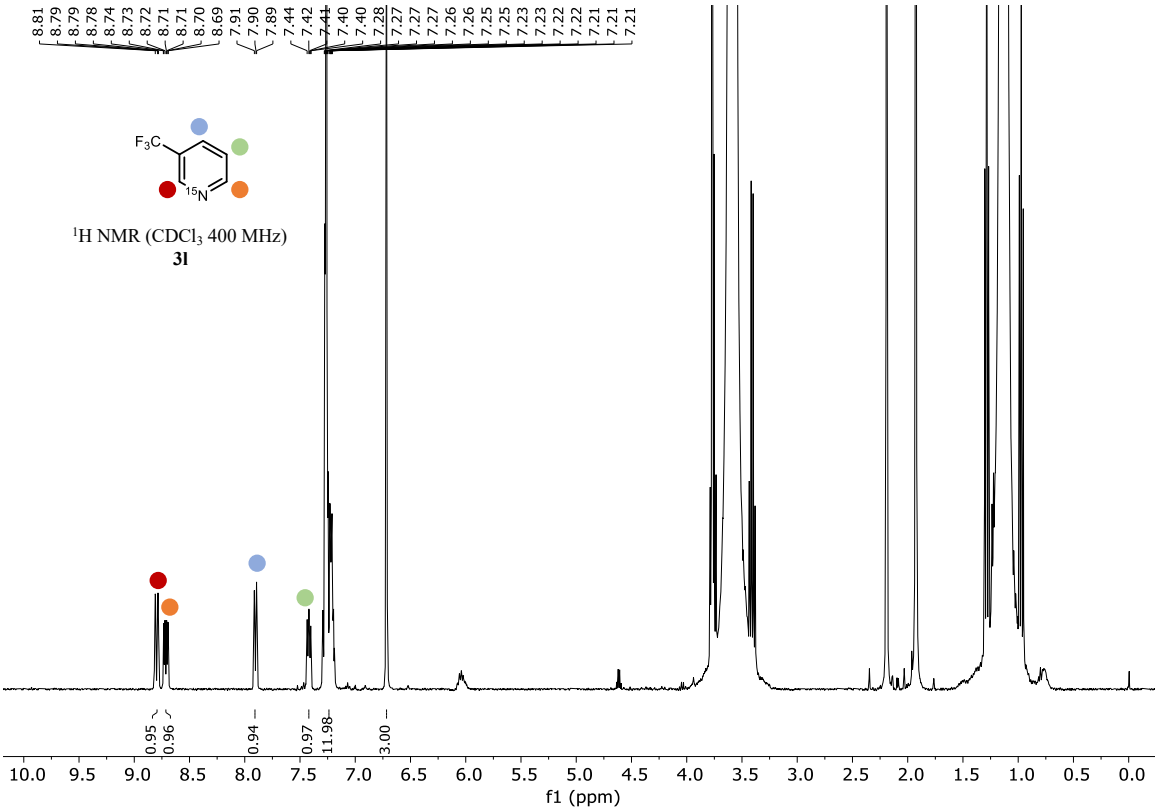


^{1}H NMR ($CDCl_3$ 400 MHz)

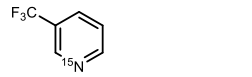


^{13}C NMR ($CDCl_3$ 100 MHz)

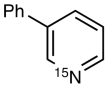

Me
15N
1H NMR (CDCl3 400 MHz)
Me
Me
Me
(internal standard)
1.63
0.82
3.00
1.93
2.32
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



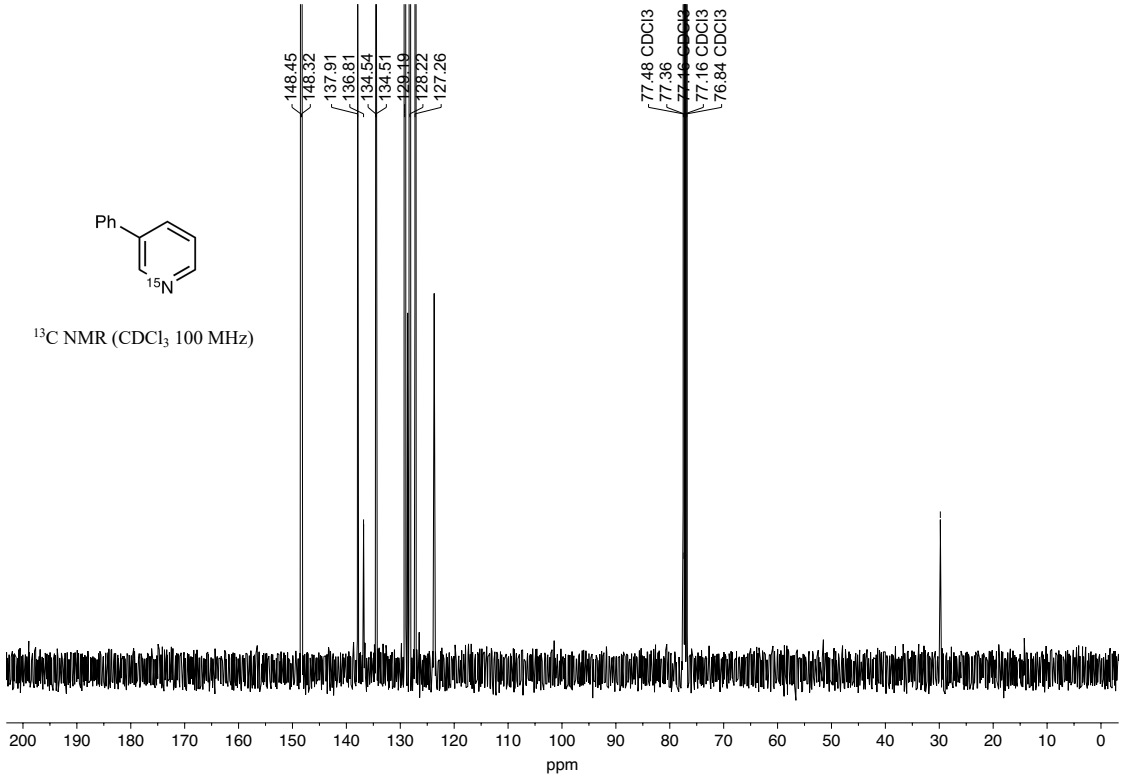
^{1}H NMR ($CDCl_3$ 400 MHz)
3l



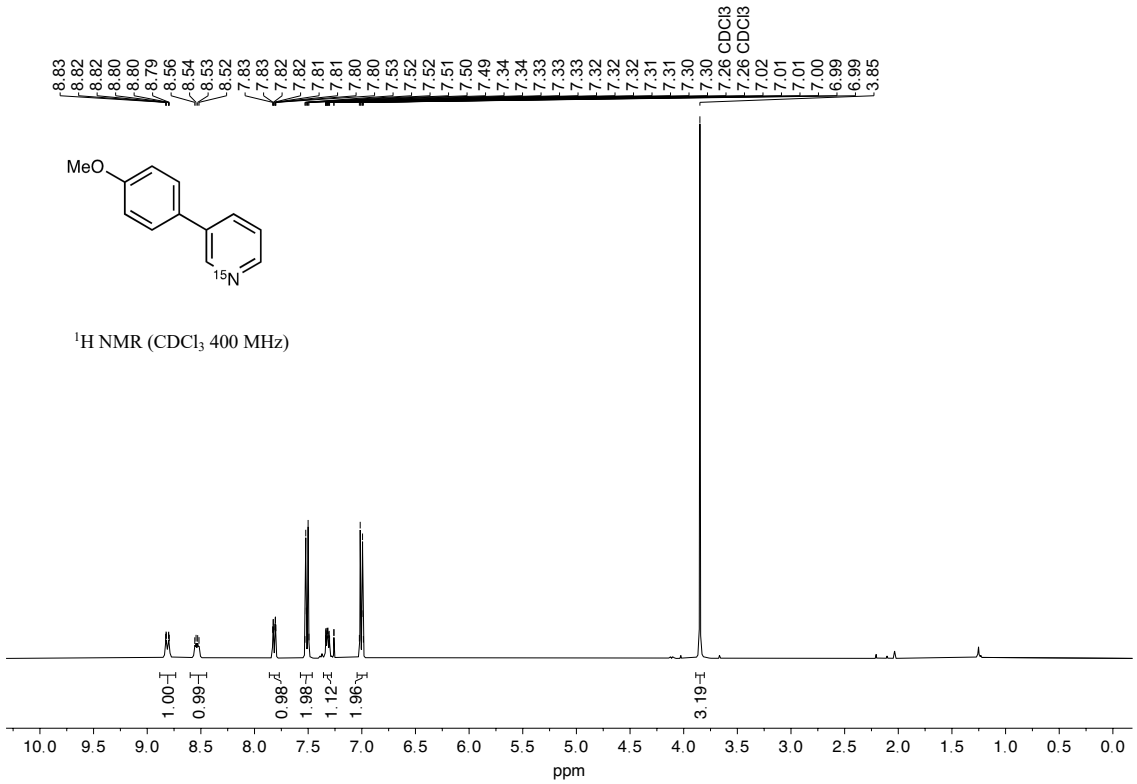
^{19}F NMR ($CDCl_3$ 375 MHz)



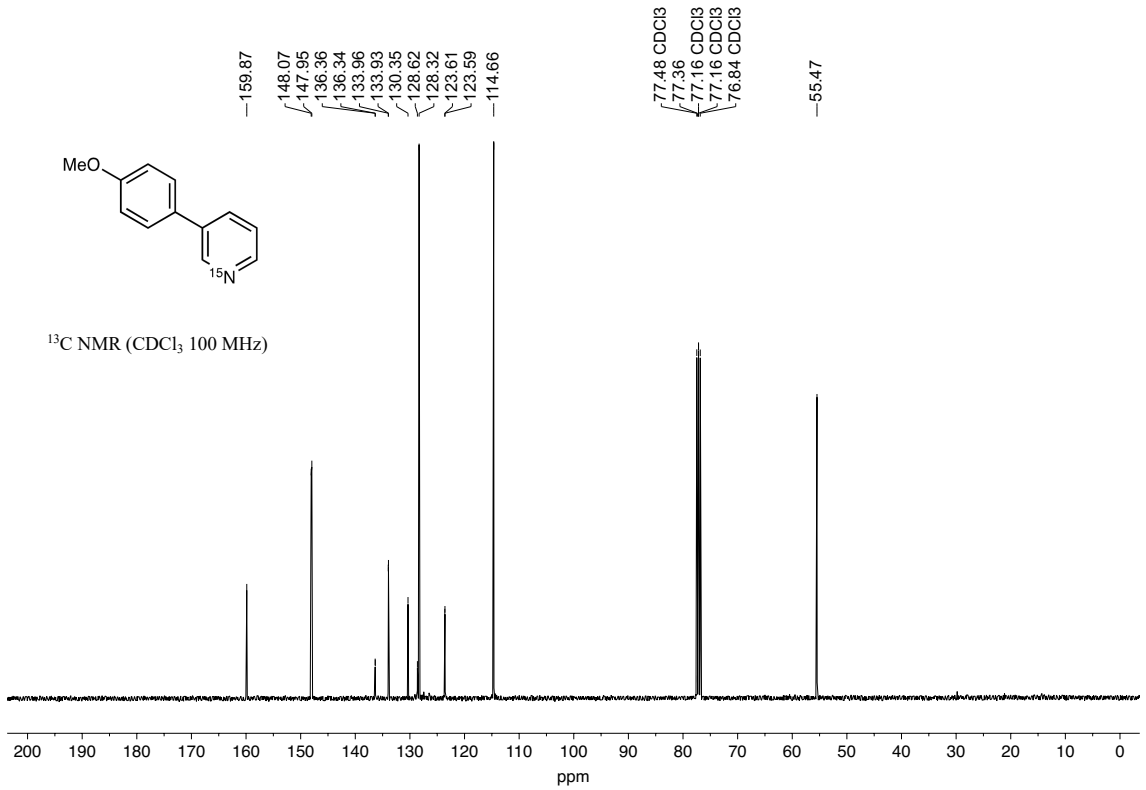
^{1}H NMR ($CDCl_3$ 400 MHz)



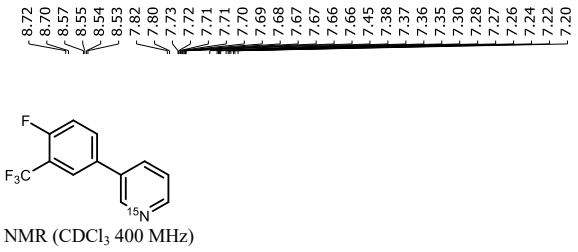
^{13}C NMR ($CDCl_3$ 100 MHz)



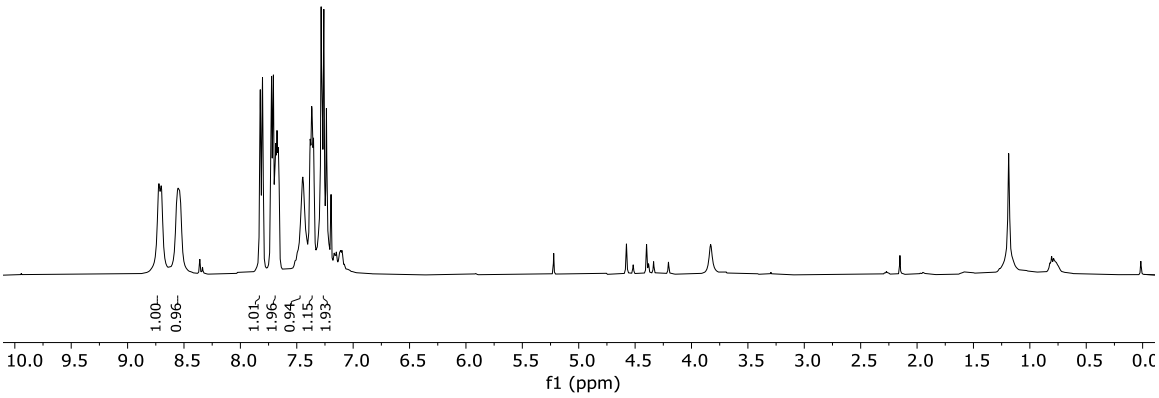
^{1}H NMR ($CDCl_3$ 400 MHz)

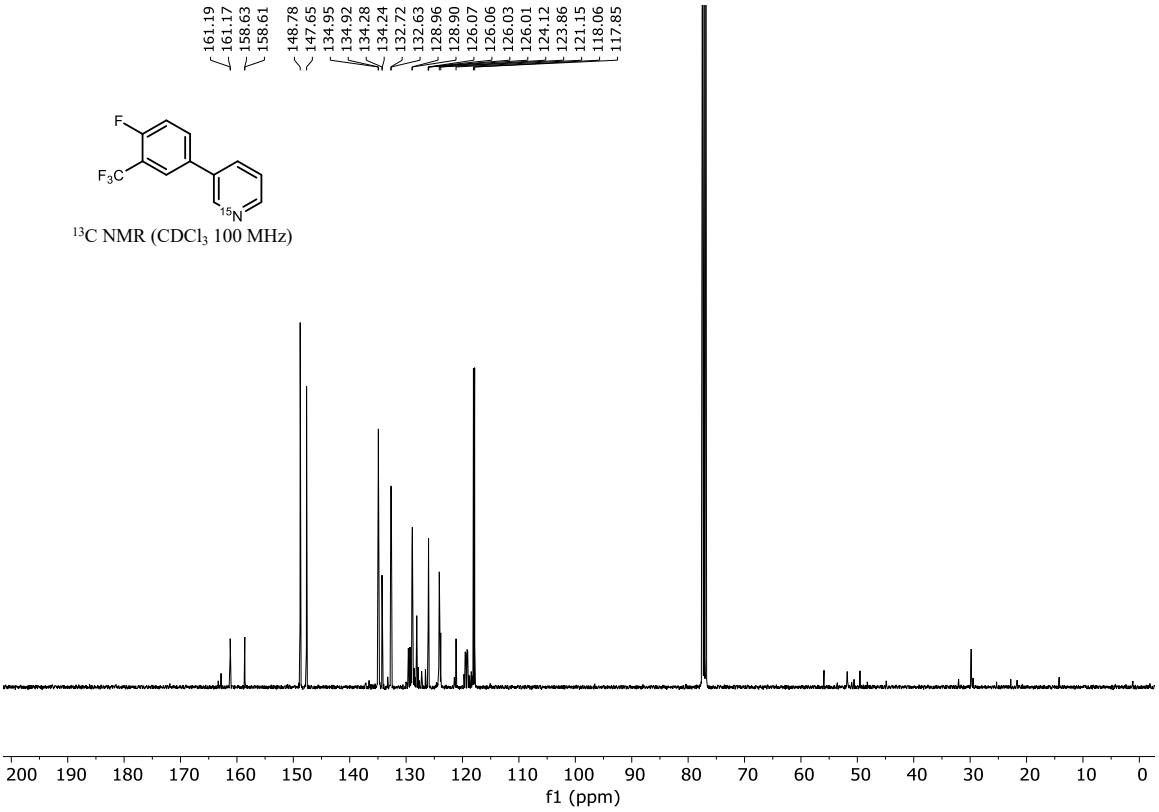


^{13}C NMR ($CDCl_3$ 100 MHz)

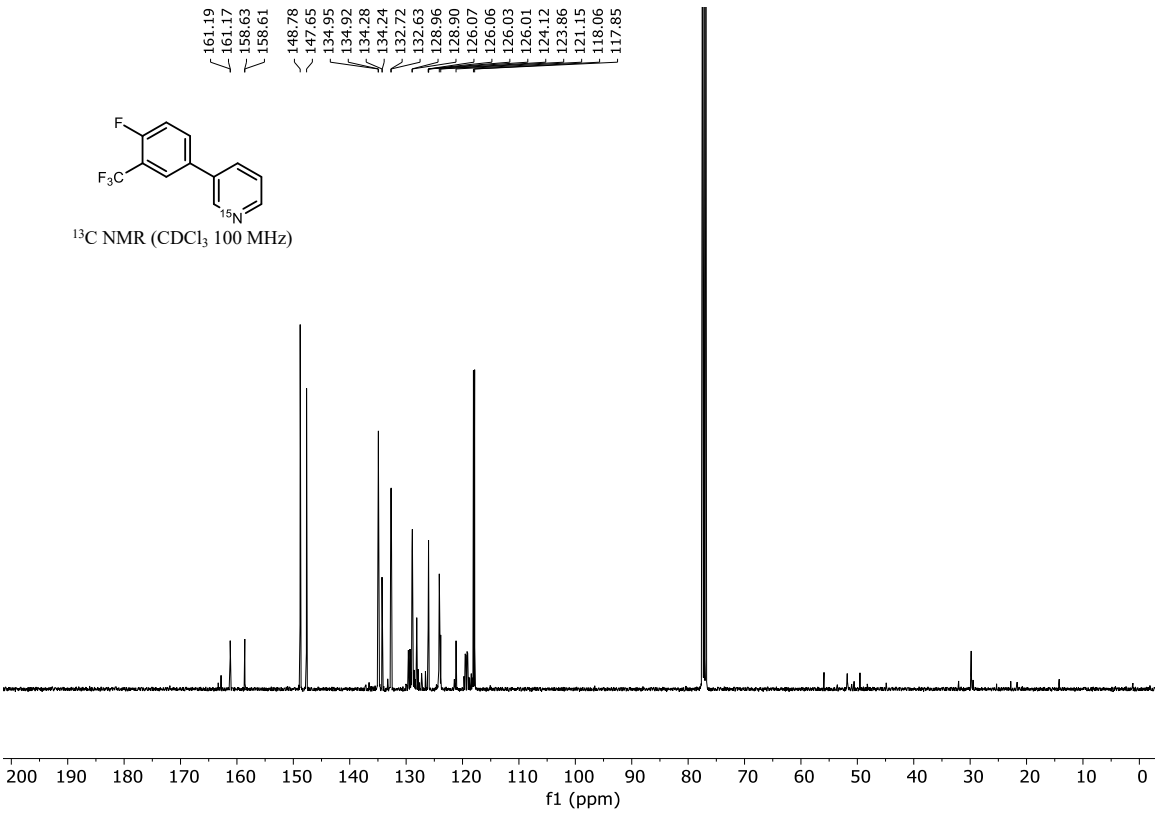


^{1}H NMR ($CDCl_3$ 400 MHz)

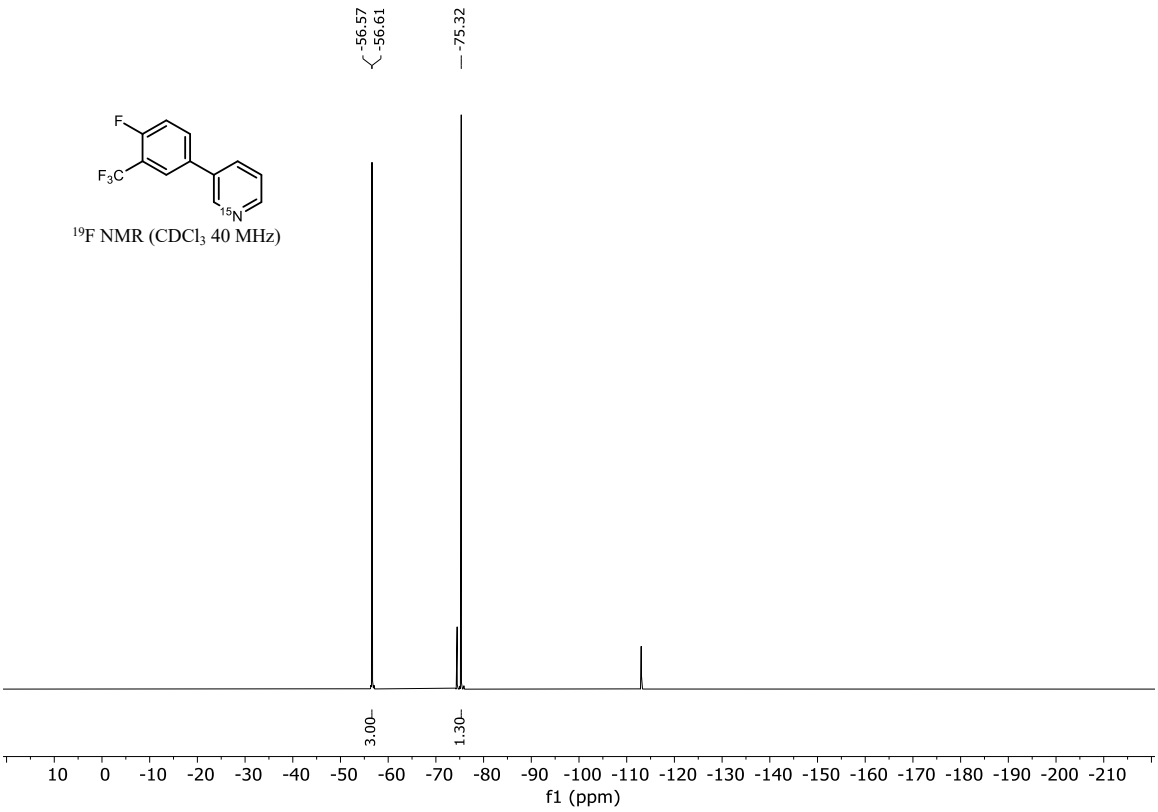




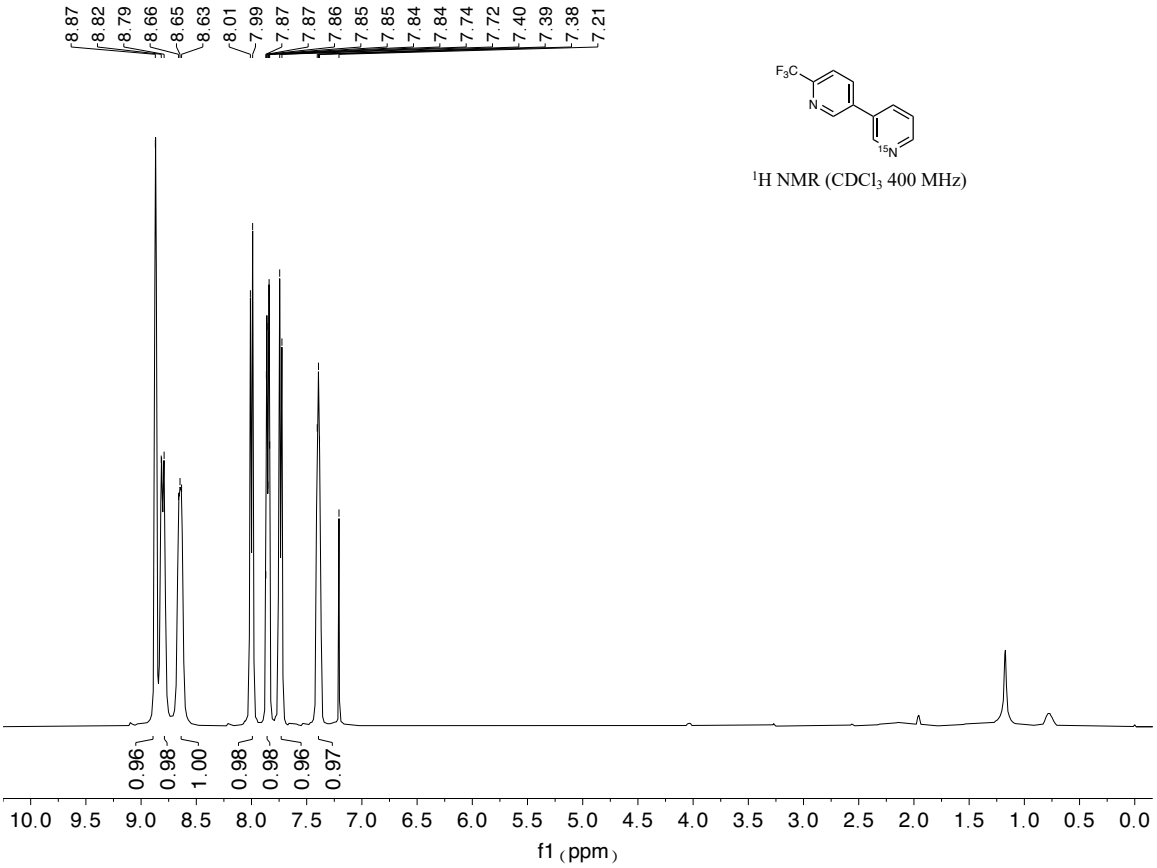
^{13}C NMR ($CDCl_3$ 100 MHz)



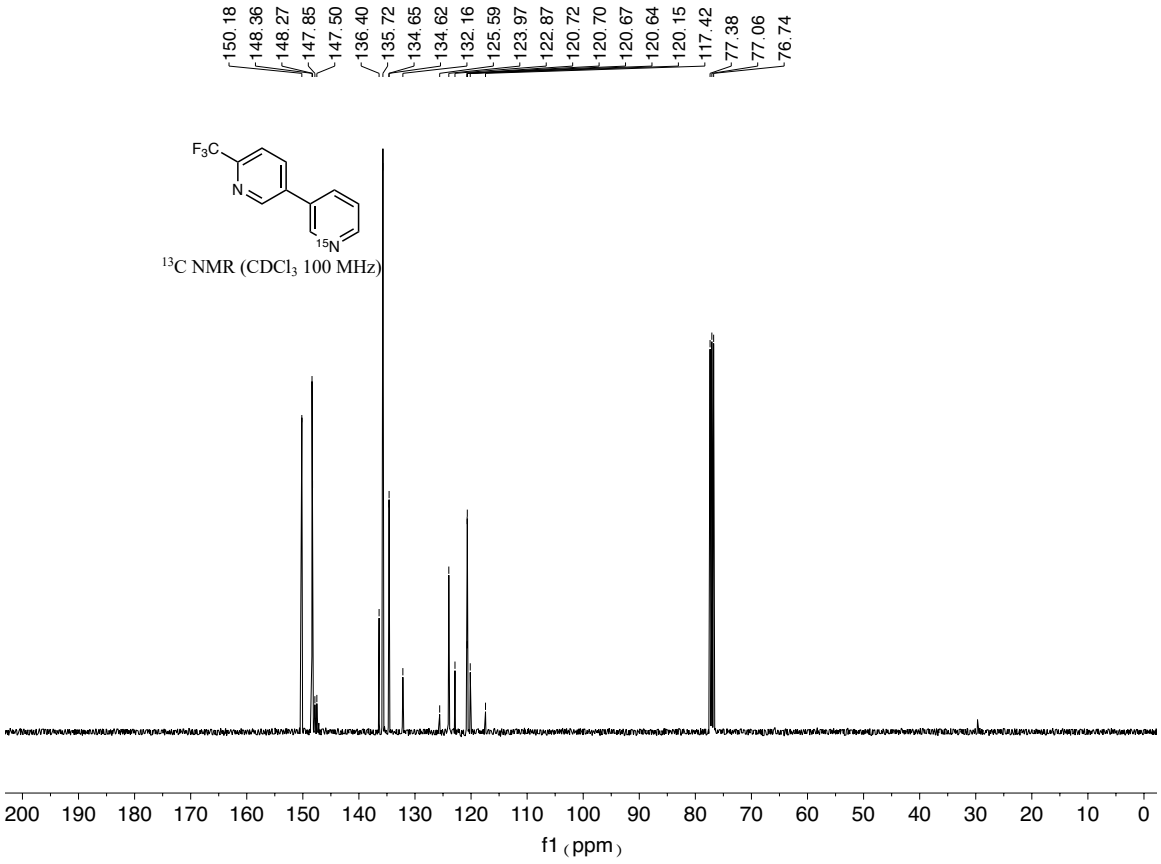
^{13}C NMR ($CDCl_3$ 100 MHz)



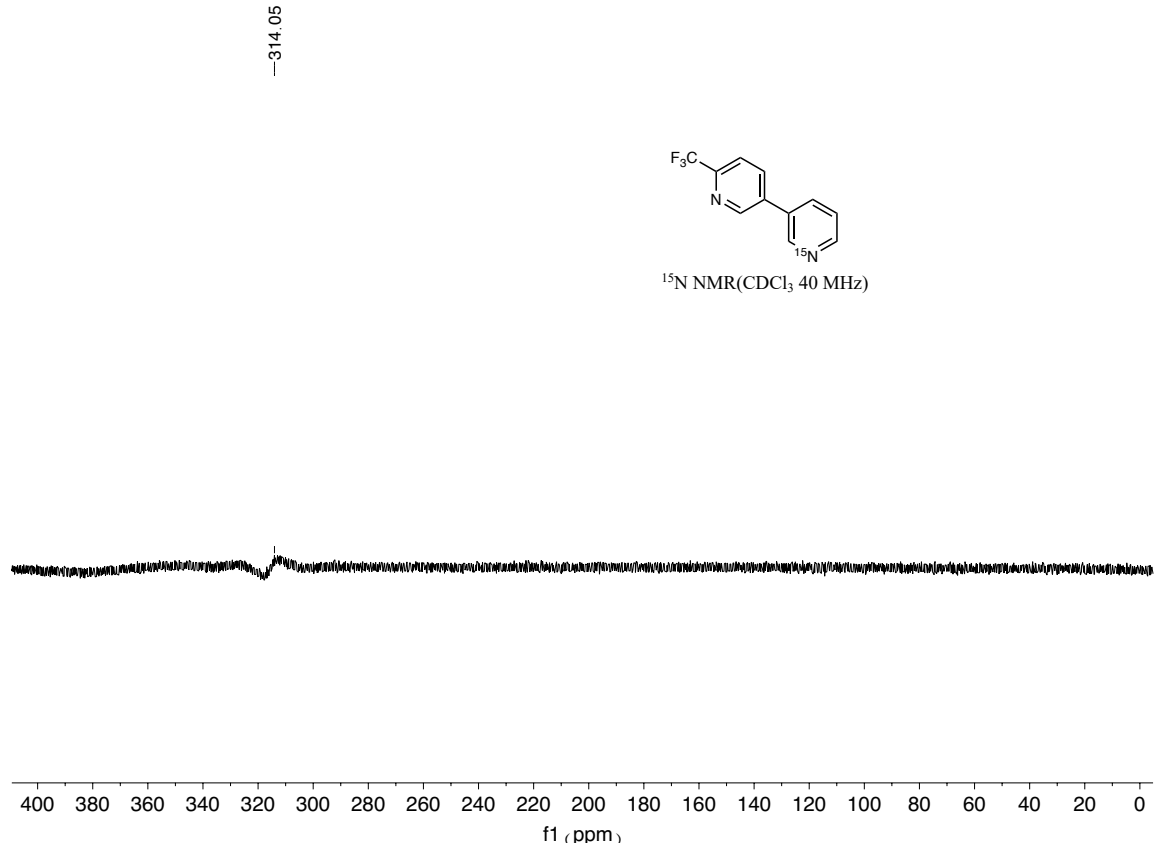
^{19}F NMR ($CDCl_3$ 40 MHz)



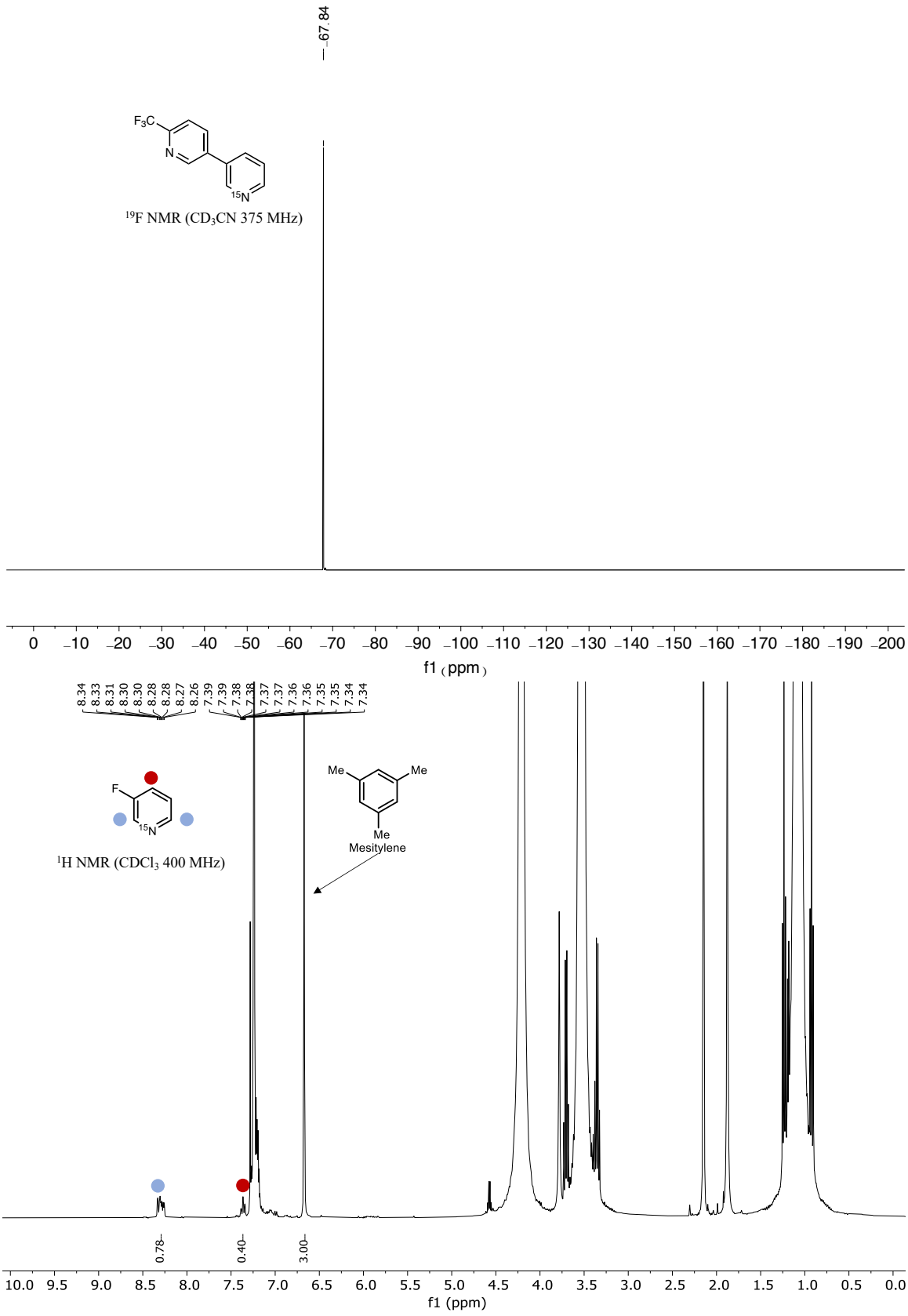
^{1}H NMR ($CDCl_3$ 400 MHz)

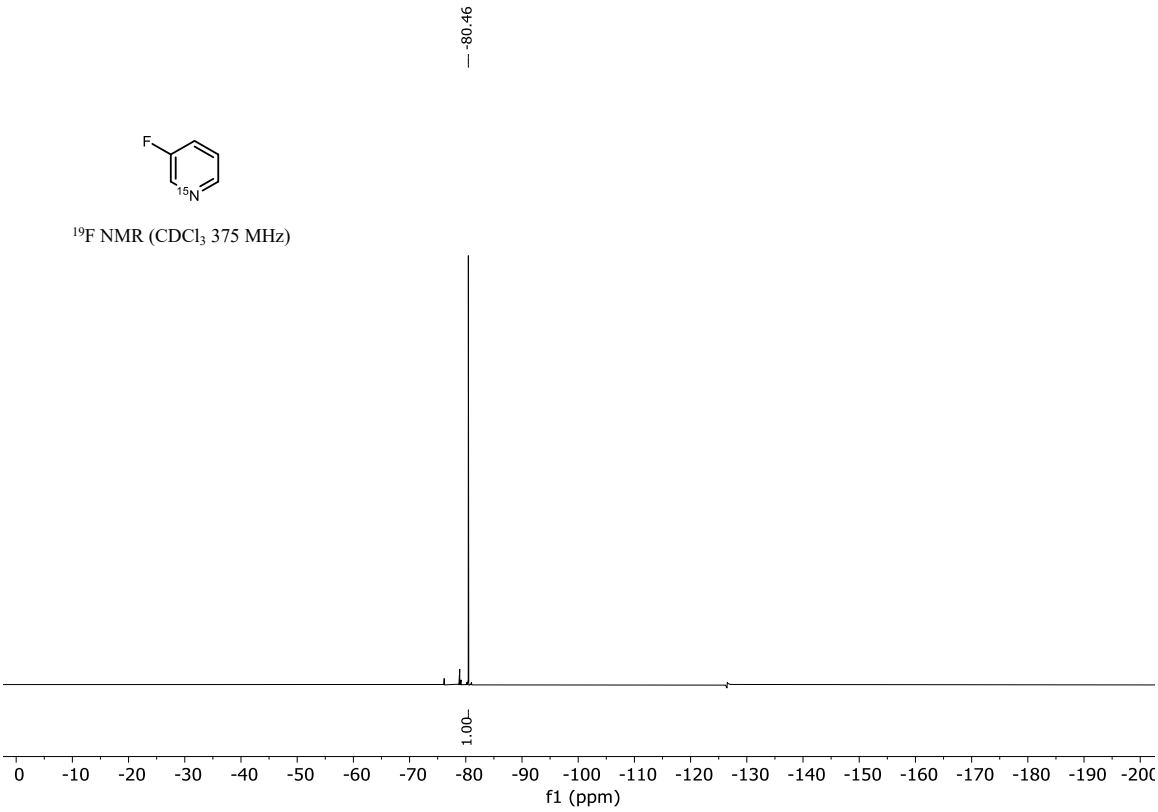


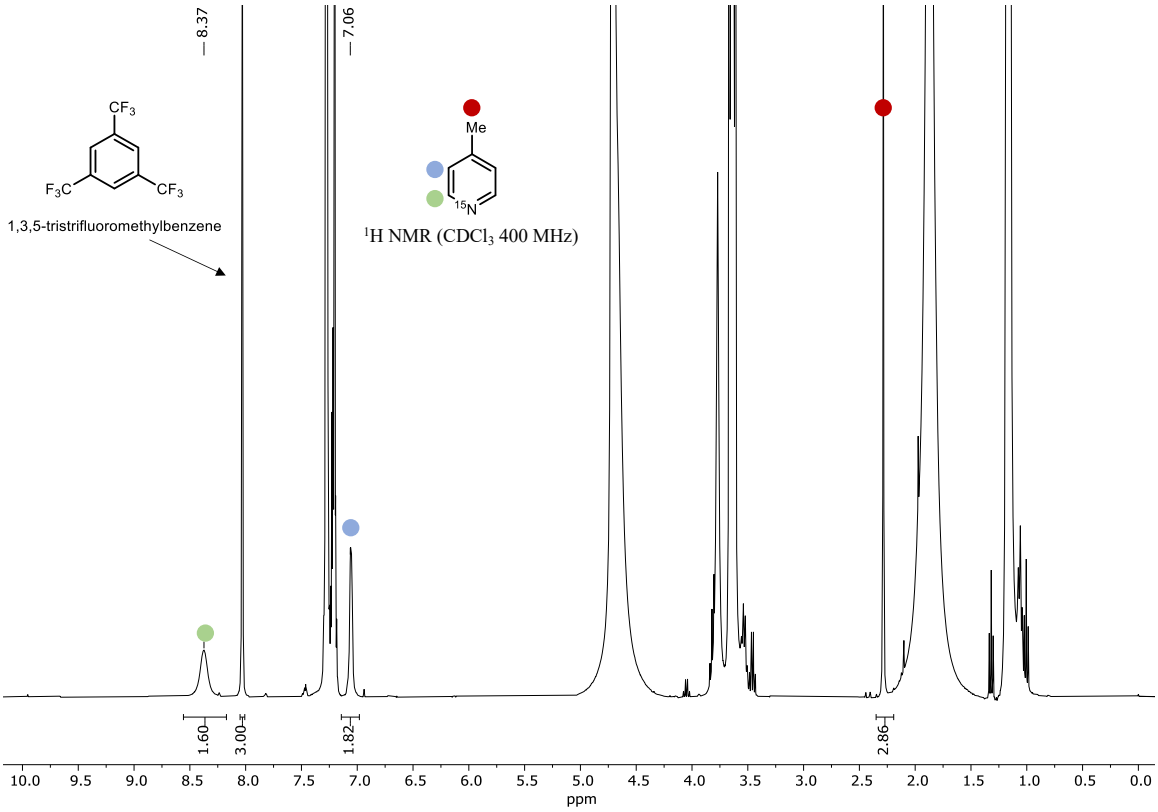
^{13}C NMR ($CDCl_3$ 100 MHz)

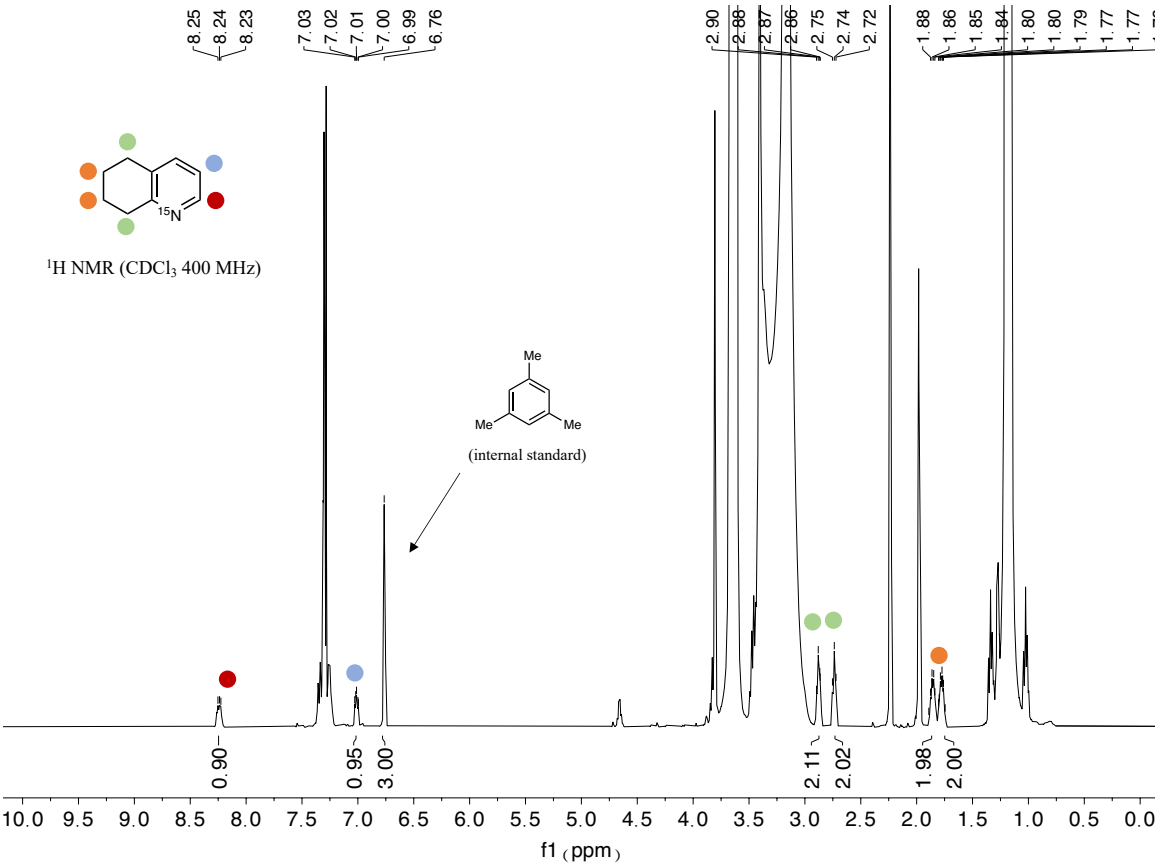


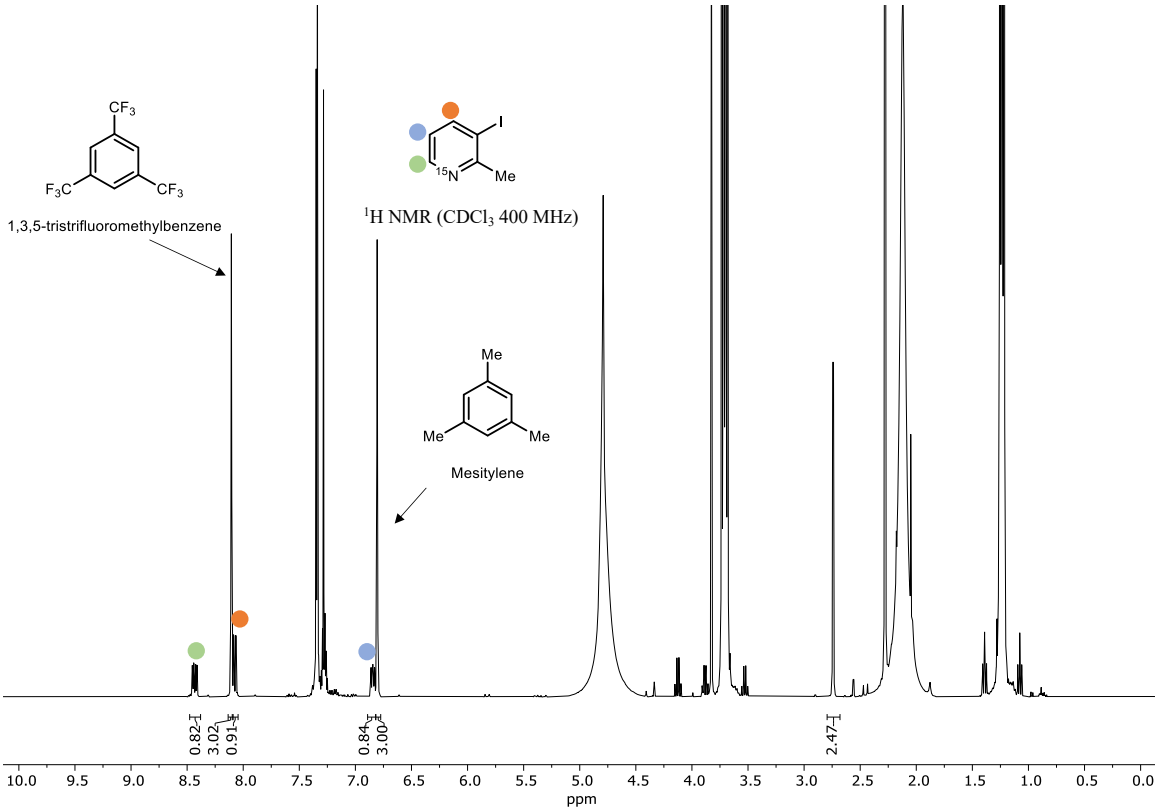
^{15}N NMR($CDCl_3$ 40 MHz)

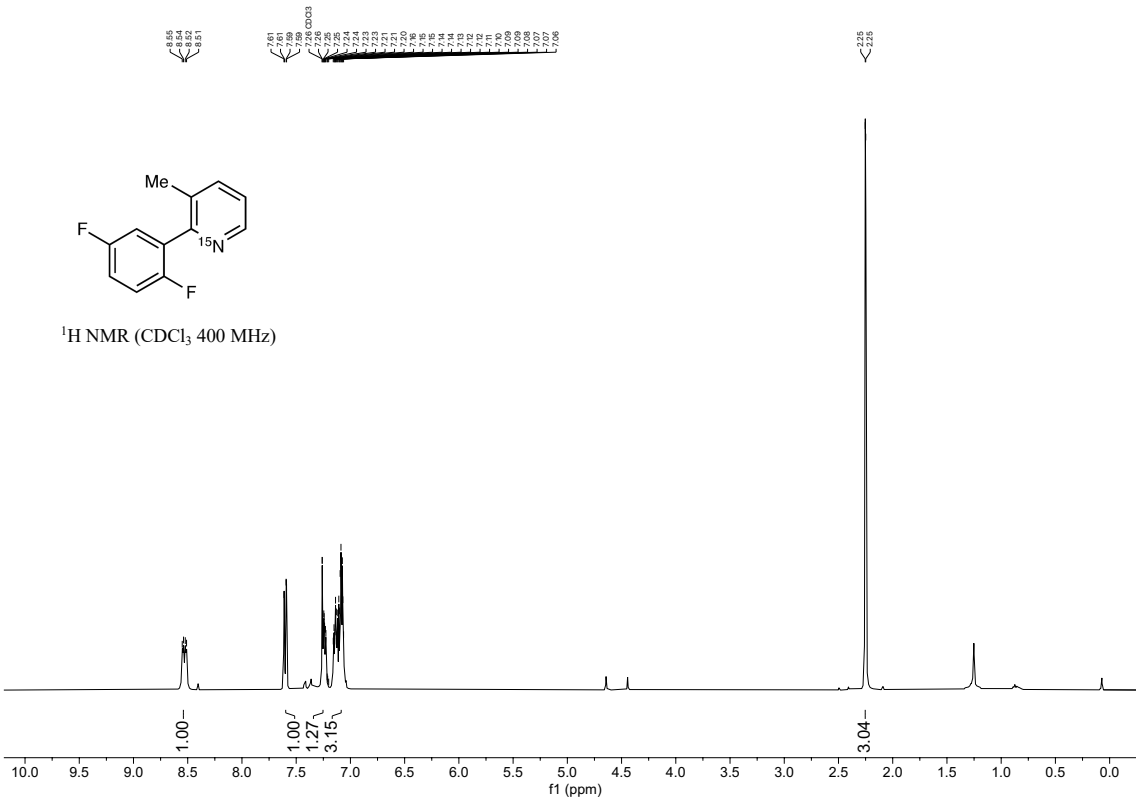

-67.84
F3C
N
15N
19F NMR (CD3CN 375 MHz)
f1 (ppm)
8.34
8.33
8.31
8.30
8.30
8.28
8.28
8.27
8.26
7.39
7.39
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.34
F
15N
1H NMR (CDCl3 400 MHz)
Me
Me
Me
Mesitylene
0.78
0.40
3.00
f1 (ppm)


-80.46
F
15N
19F NMR (CDCl3 375 MHz)
1.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

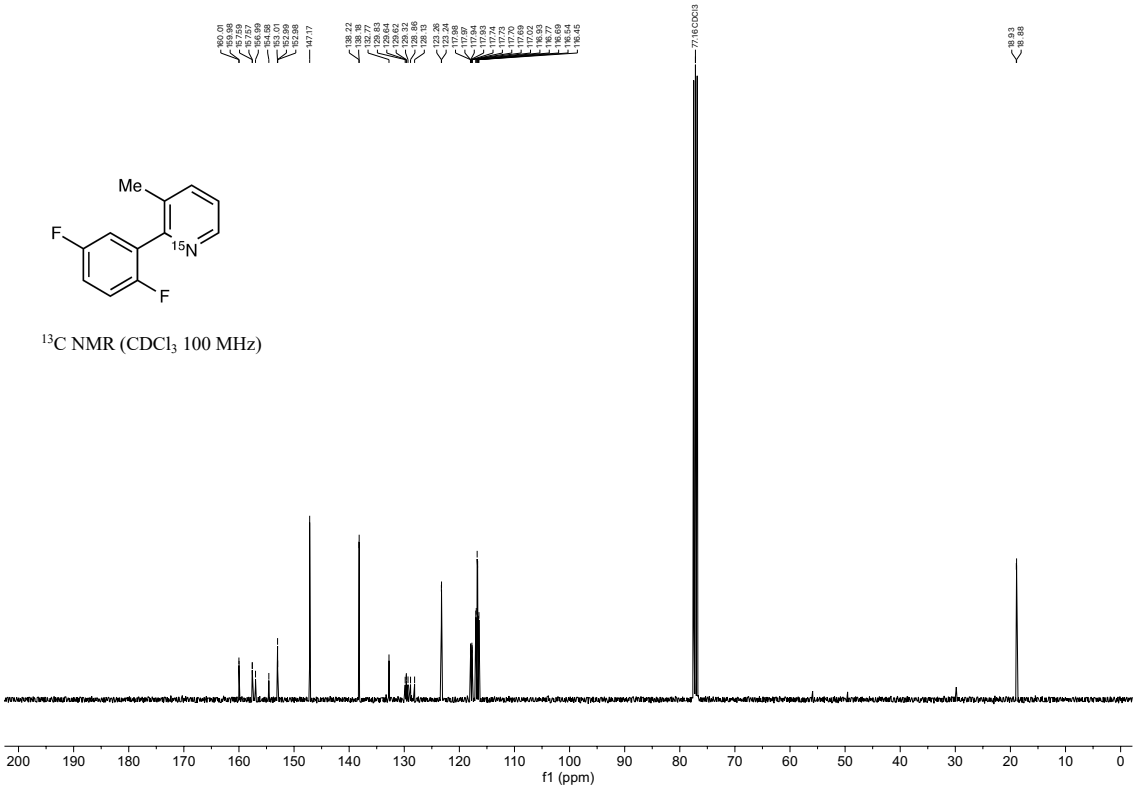

8.37
7.06
CF3
F3C
CF3
1,3,5-tristrifluoromethylbenzene
Me
15N
1H NMR (CDCl3 400 MHz)
1.60
3.00
1.82
2.86
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


8.25
8.24
8.23
7.03
7.02
7.01
7.00
6.99
6.76
2.90
2.88
2.87
2.86
2.75
2.74
2.72
1.88
1.86
1.85
1.84
1.80
1.80
1.79
1.77
1.77
15N
1H NMR (CDCl3 400 MHz)
Me
Me
Me
(internal standard)
0.90
0.95
3.00
2.11
2.02
1.98
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

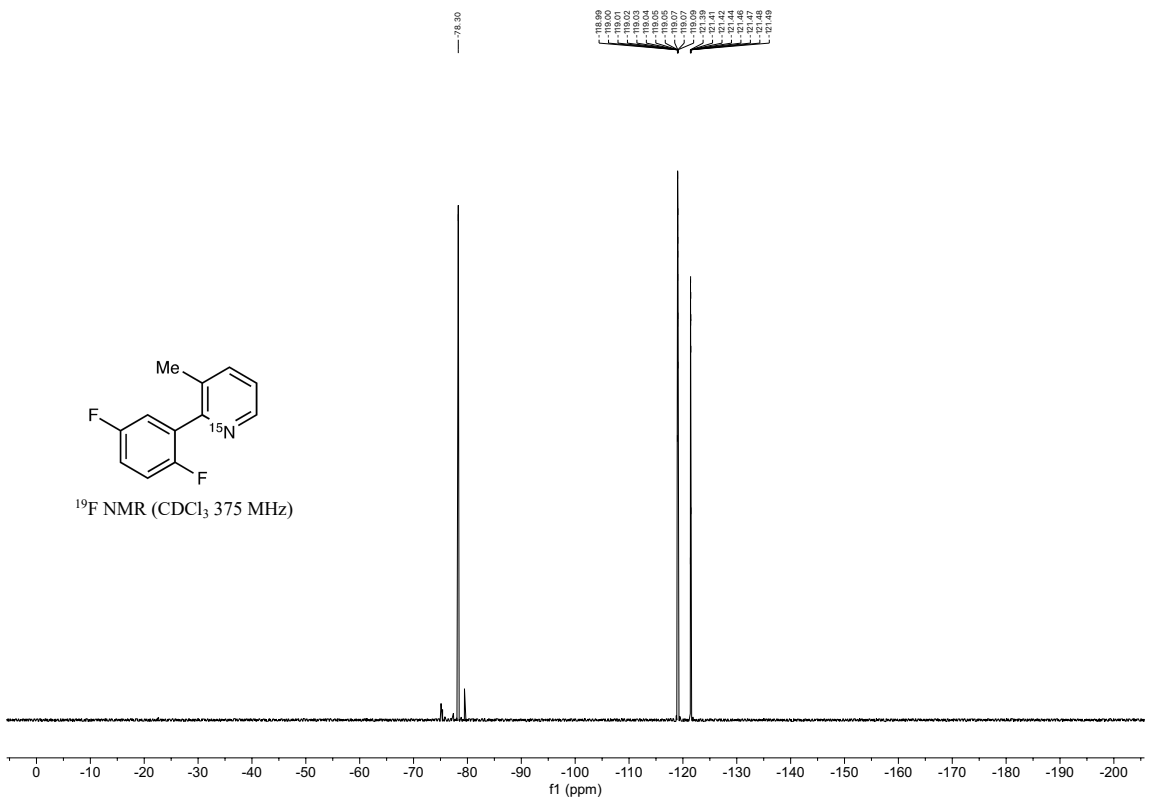

CF3
F3C
CF3
1,3,5-tristrifluoromethylbenzene
I
15N
Me
1H NMR (CDCl3 400 MHz)
Me
Me
Me
Mesitylene
0.82
3.02
0.91
0.84
3.00
2.47
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm



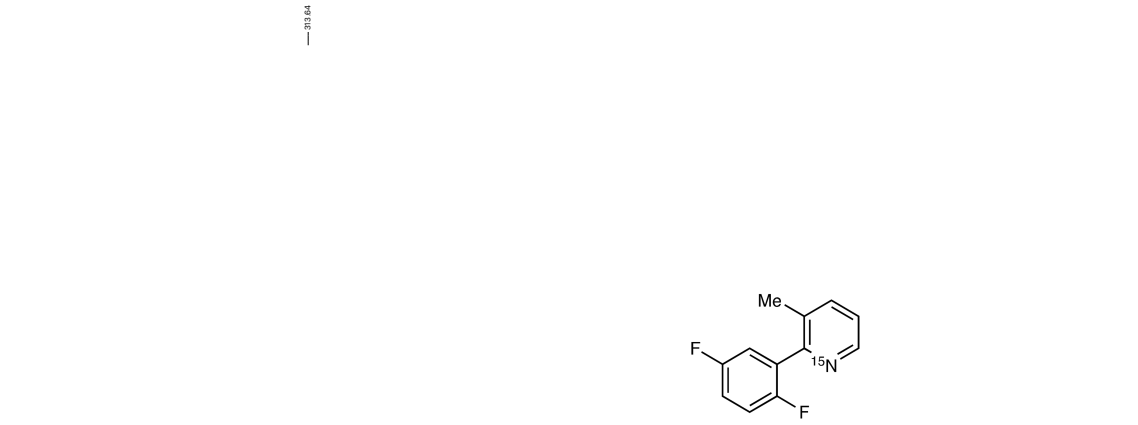
^{1}H NMR ($CDCl_3$ 400 MHz)



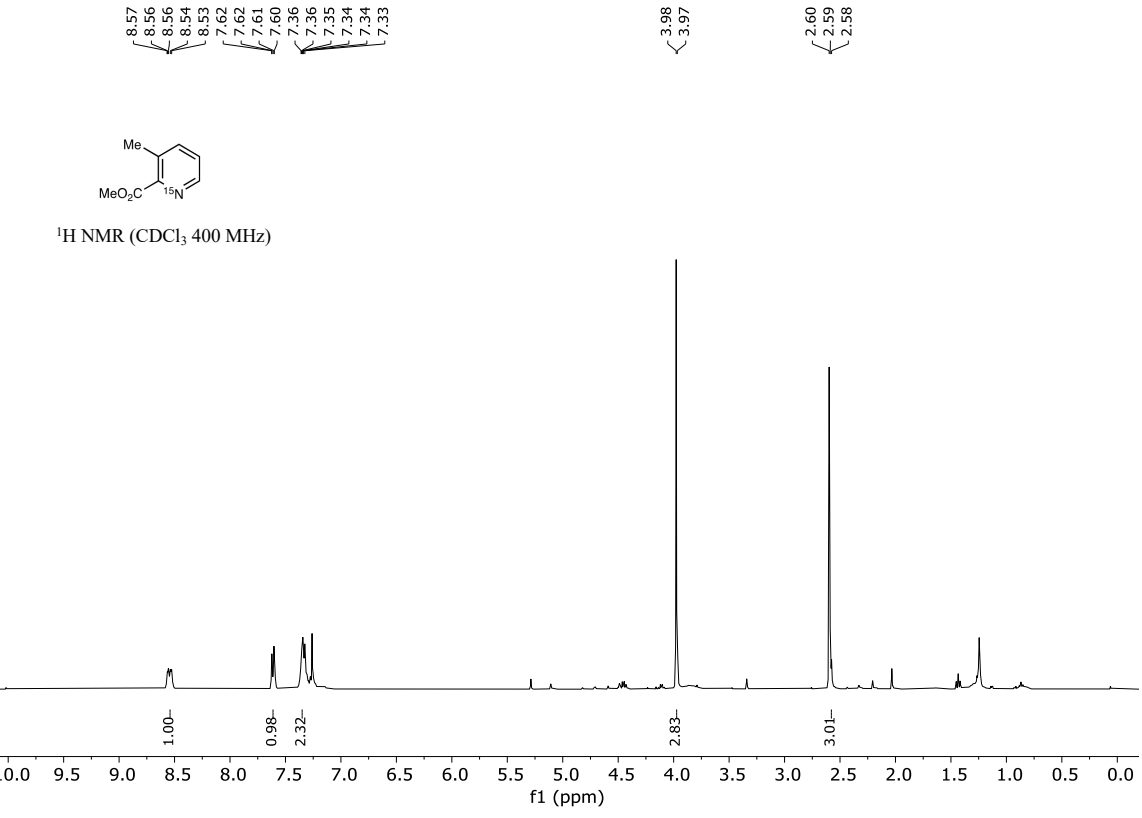
^{13}C NMR ($CDCl_3$ 100 MHz)



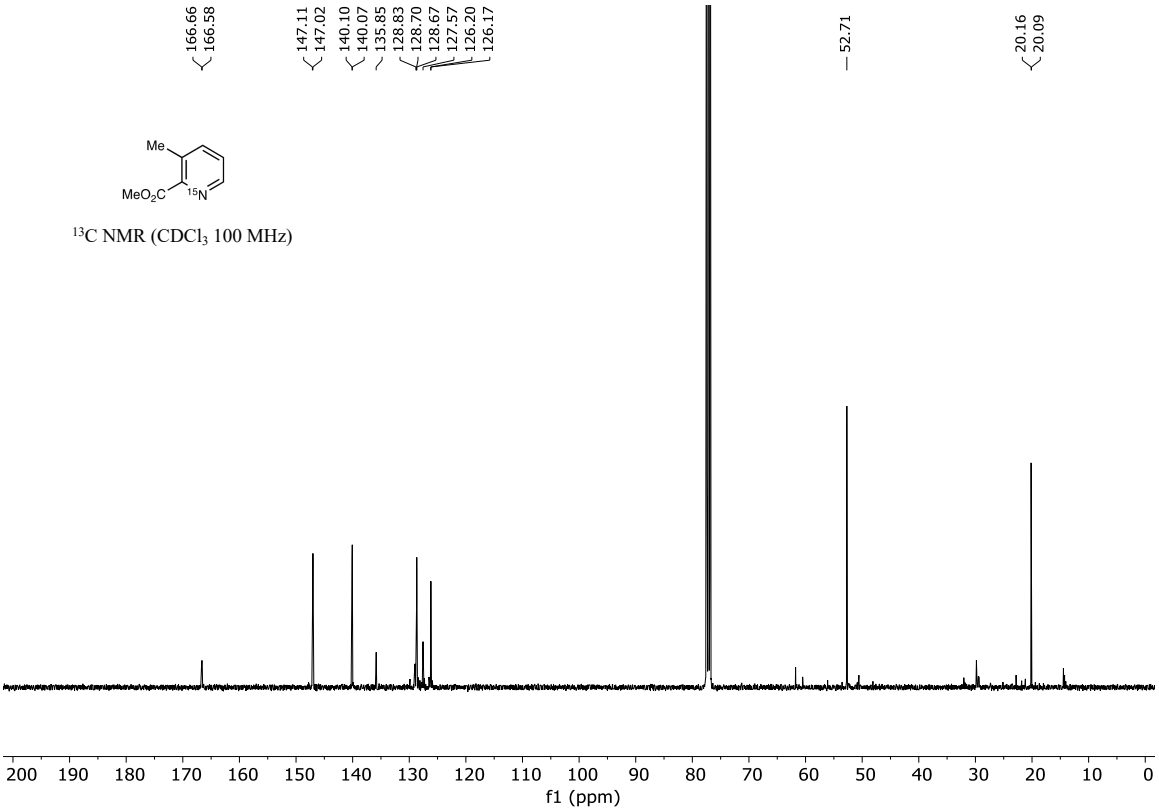
^{19}F NMR ($CDCl_3$ 375 MHz)



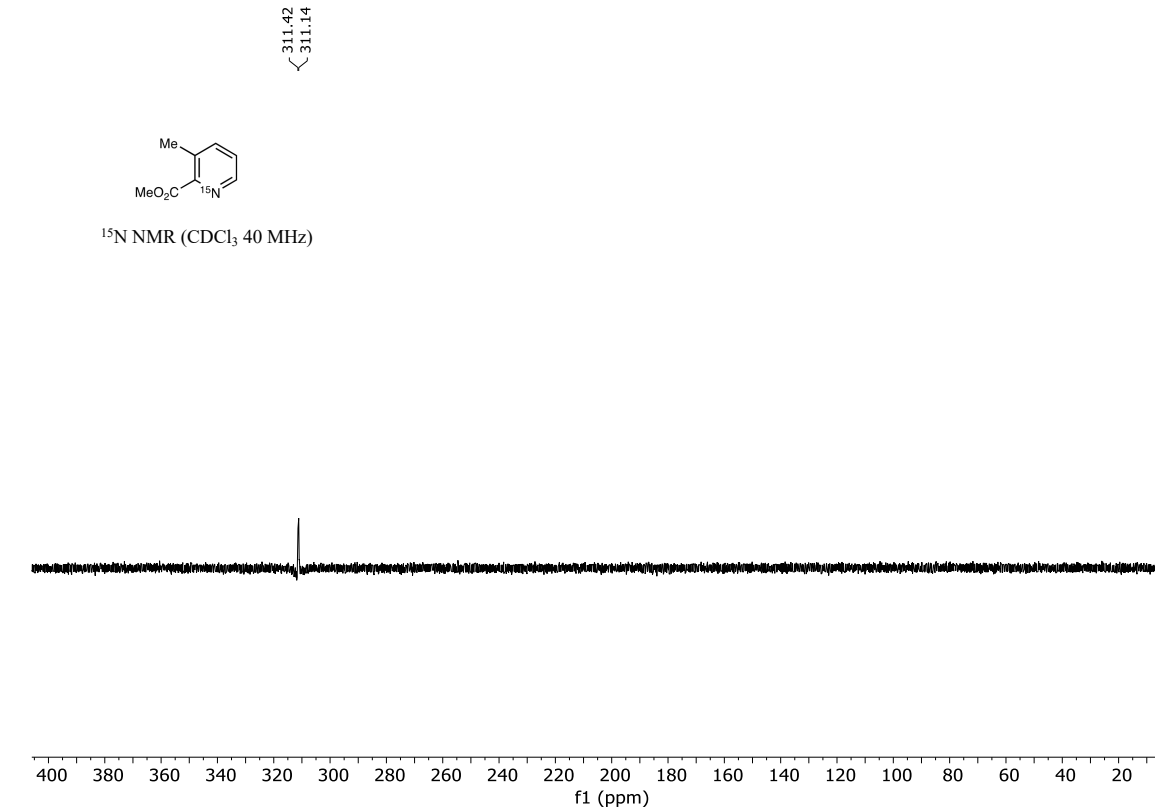
^{15}N NMR ($CDCl_3$ 40 MHz)



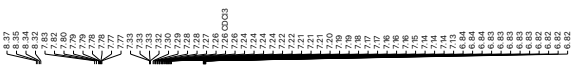
^{1}H NMR ($CDCl_3$ 400 MHz)

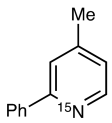


^{13}C NMR ($CDCl_3$ 100 MHz)

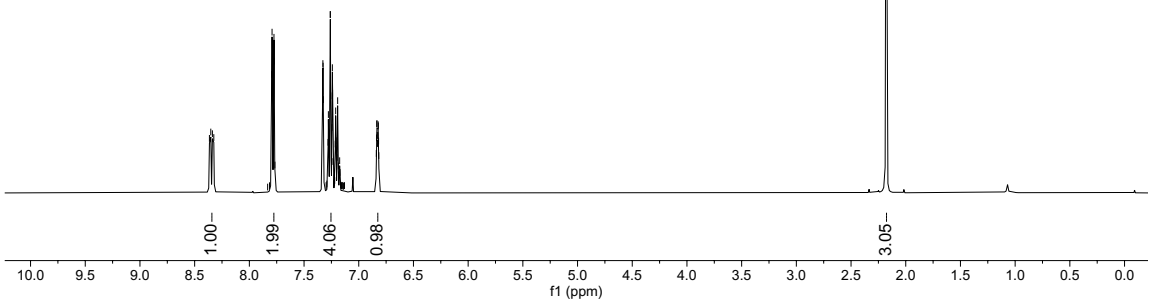


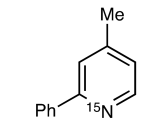
^{15}N NMR ($CDCl_3$ 40 MHz)



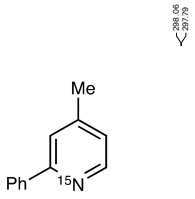


^{1}H NMR ($CDCl_3$ 400 MHz)

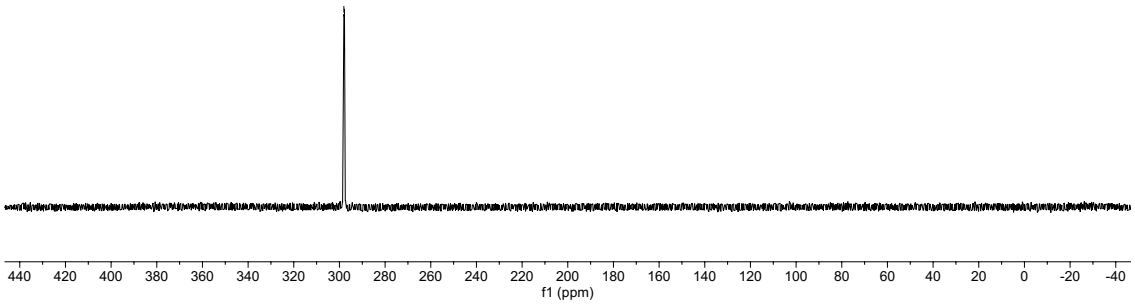




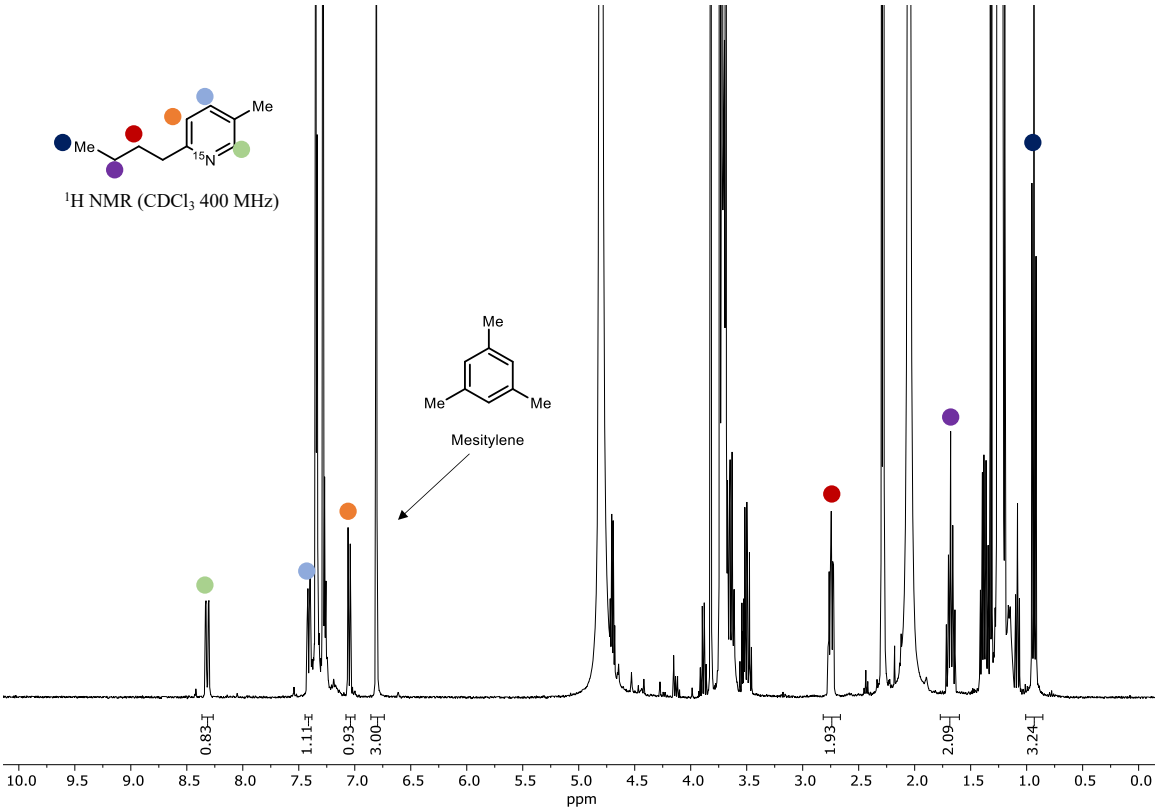
^{13}C NMR ($CDCl_3$ 100 MHz)

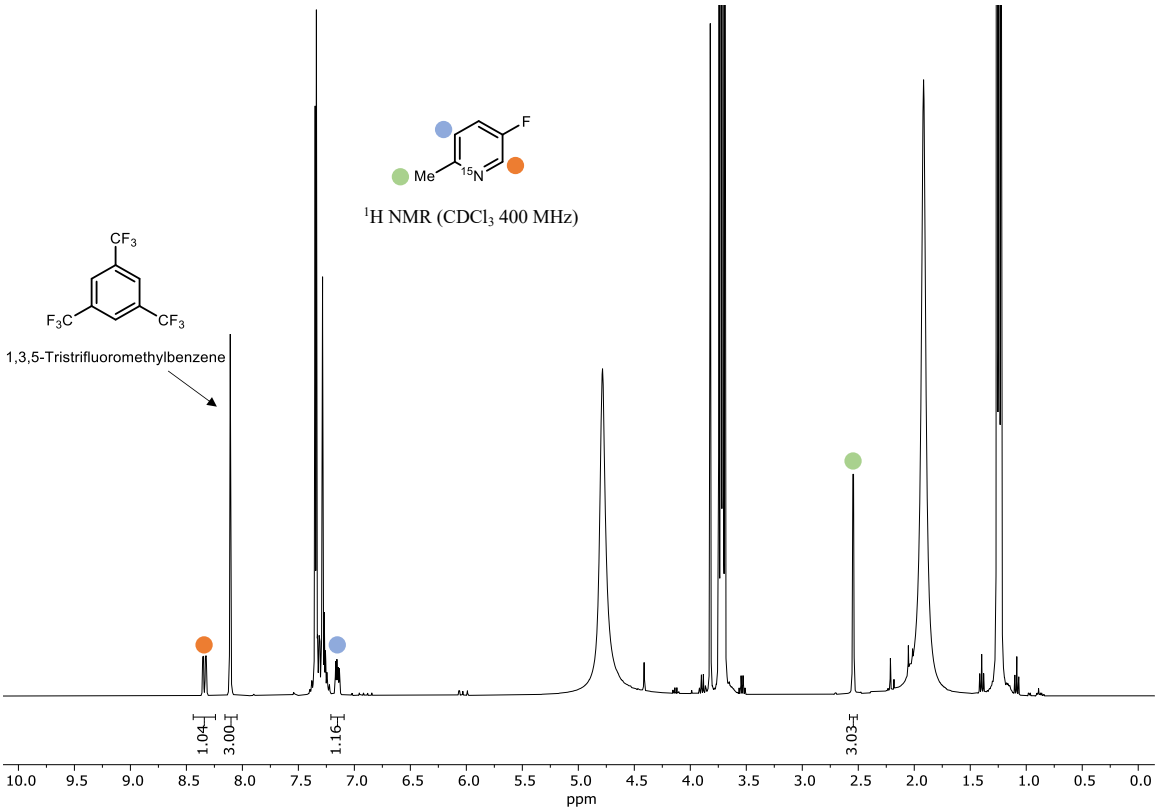


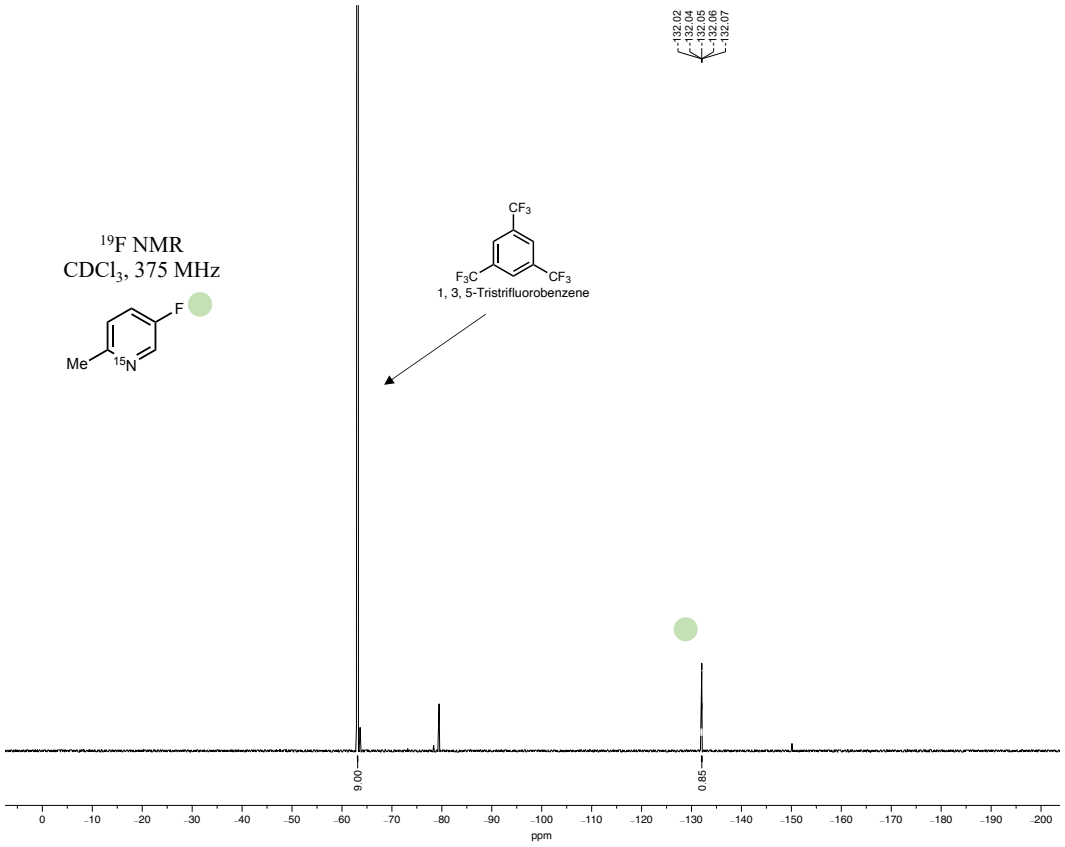
^{15}N NMR ($CDCl_3$ 40 MHz)

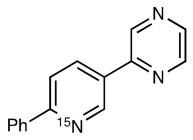


^{1}H NMR ($CDCl_3$ 400 MHz)

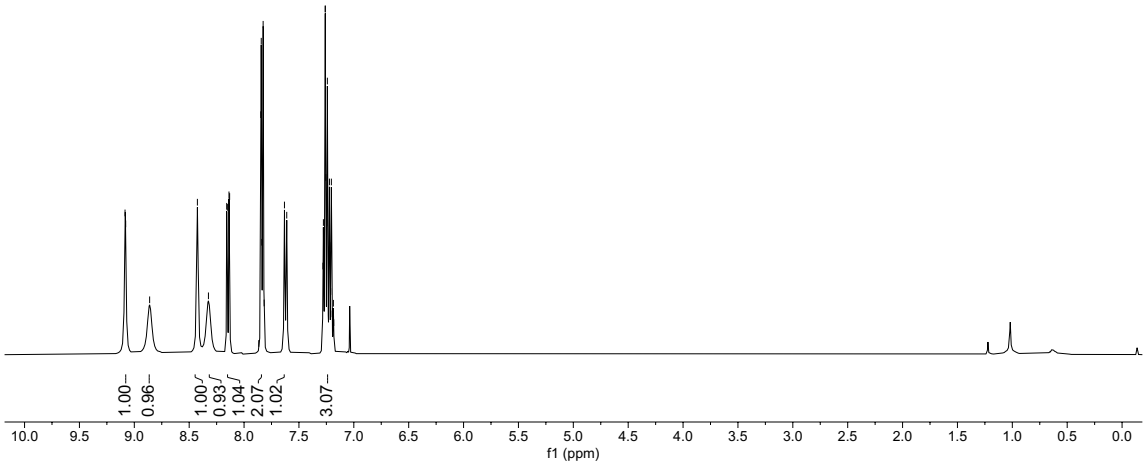


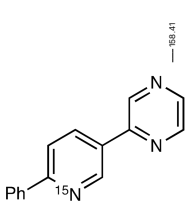

F
Me
15N
1H NMR (CDCl3 400 MHz)
CF3
F3C
CF3
1,3,5-Tristrifluoromethylbenzene
1.04
3.00
1.16
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


19F NMR
CDCl3, 375 MHz
F
Me
15N
CF3
F3C
CF3
1, 3, 5-Tristrifluorobenzene
-132.02
-132.04
-132.05
-132.06
-132.07
9.00
0.85
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
ppm

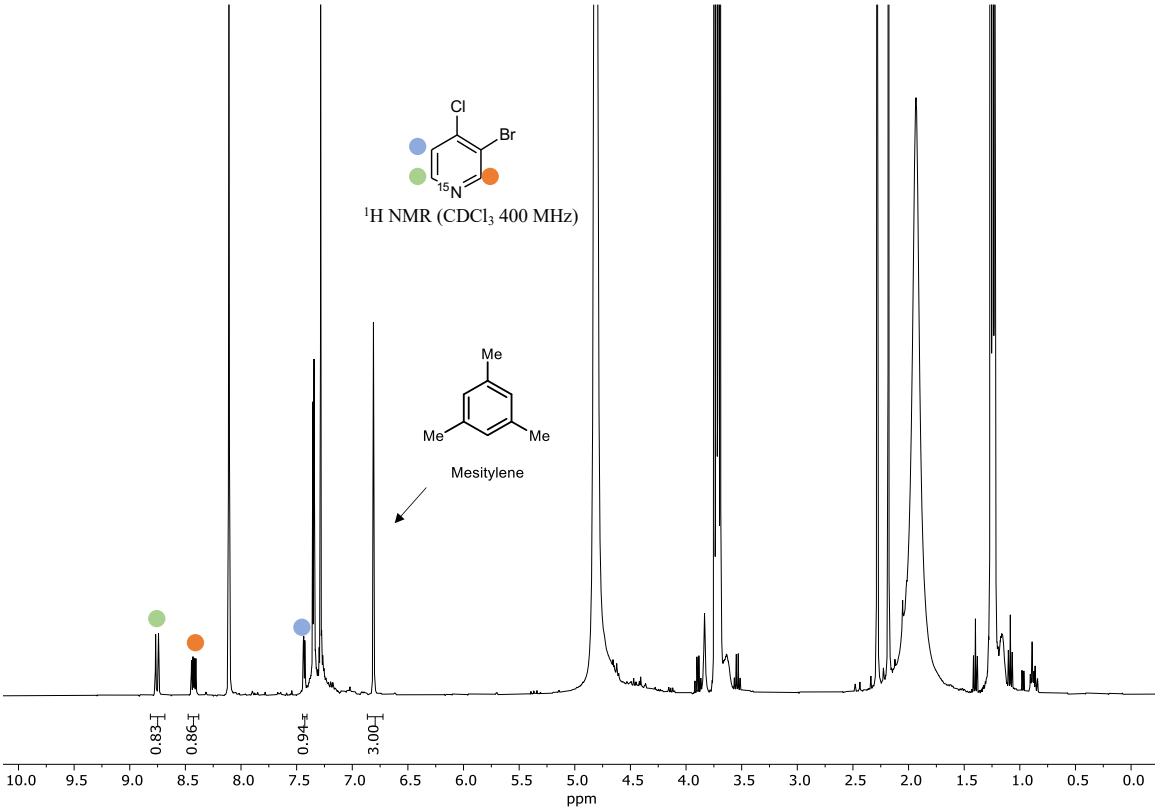


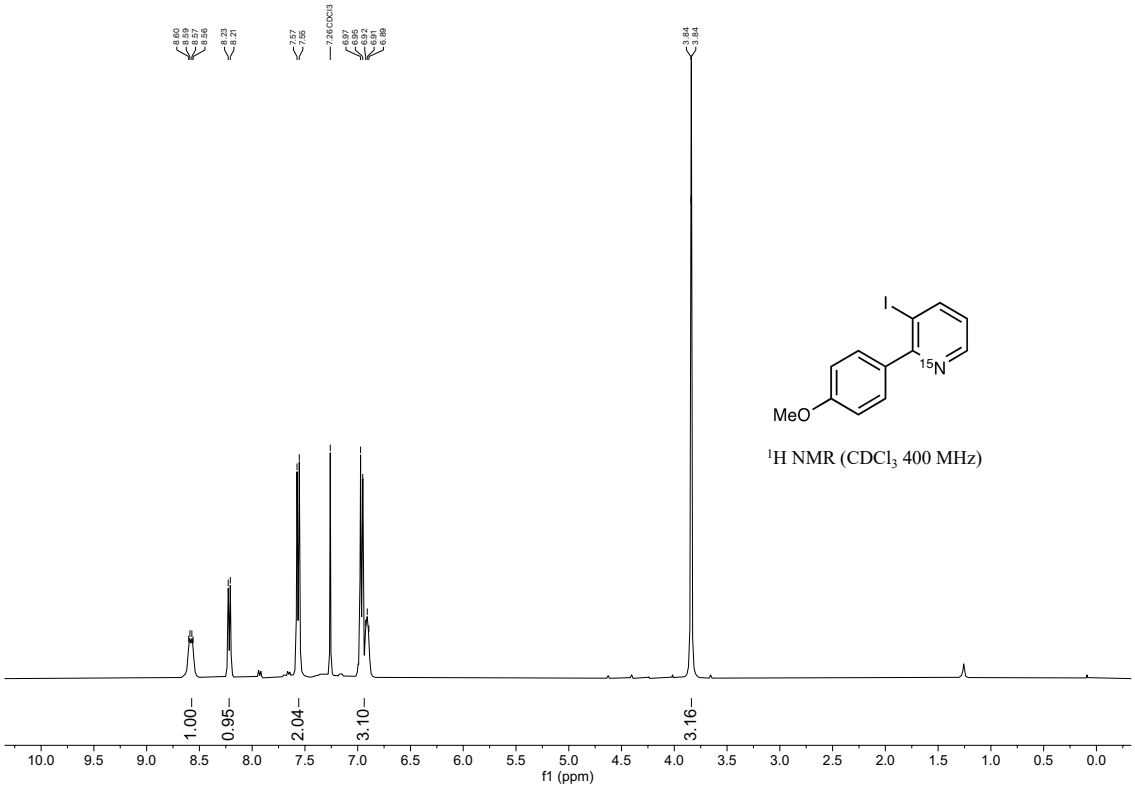
^{1}H NMR ($CDCl_3$ 400 MHz)

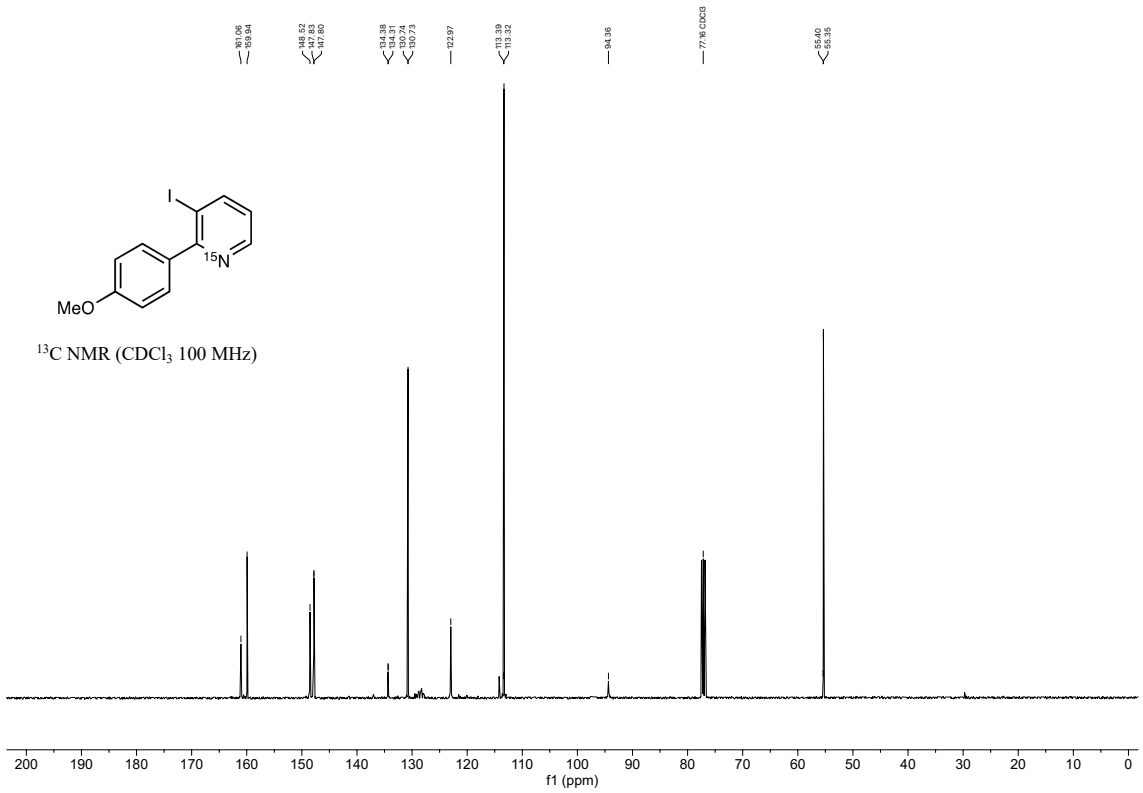




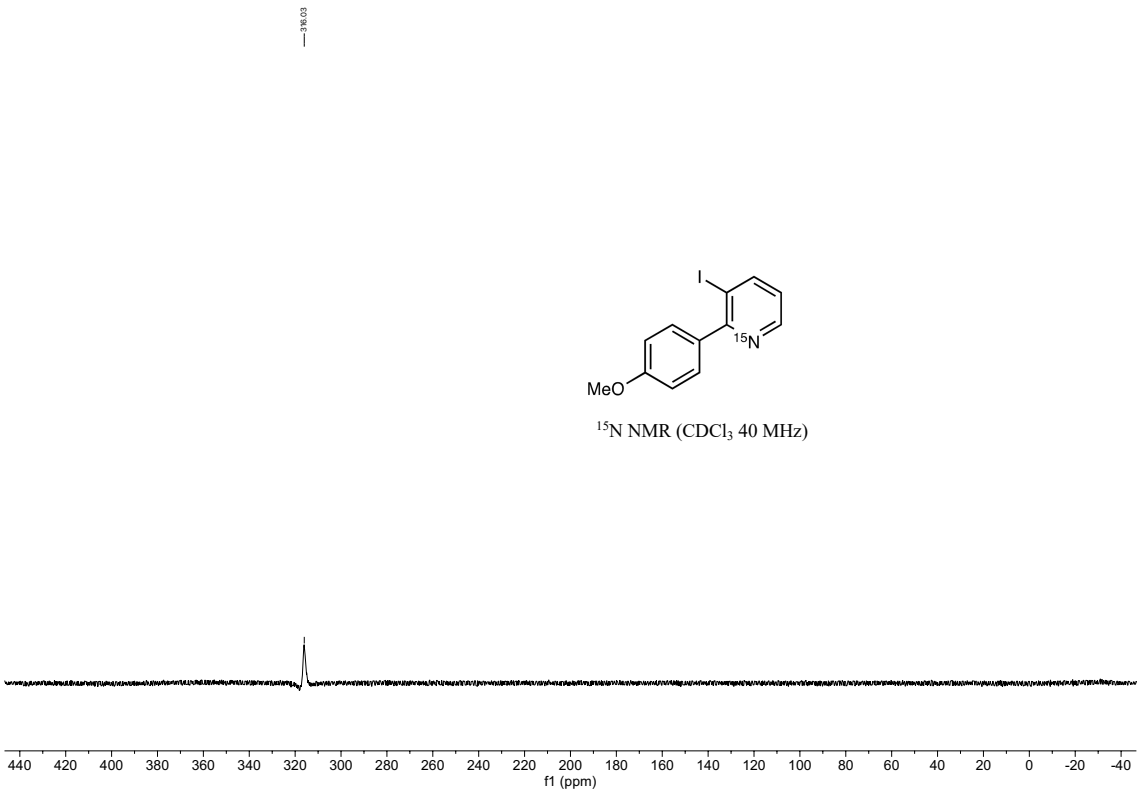
^{13}C NMR ($CDCl_3$ 100 MHz)


Cl
Br
15N
1H NMR (CDCl3 400 MHz)
Me
Me
Me
Mesitylene
0.83
0.86
0.94
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

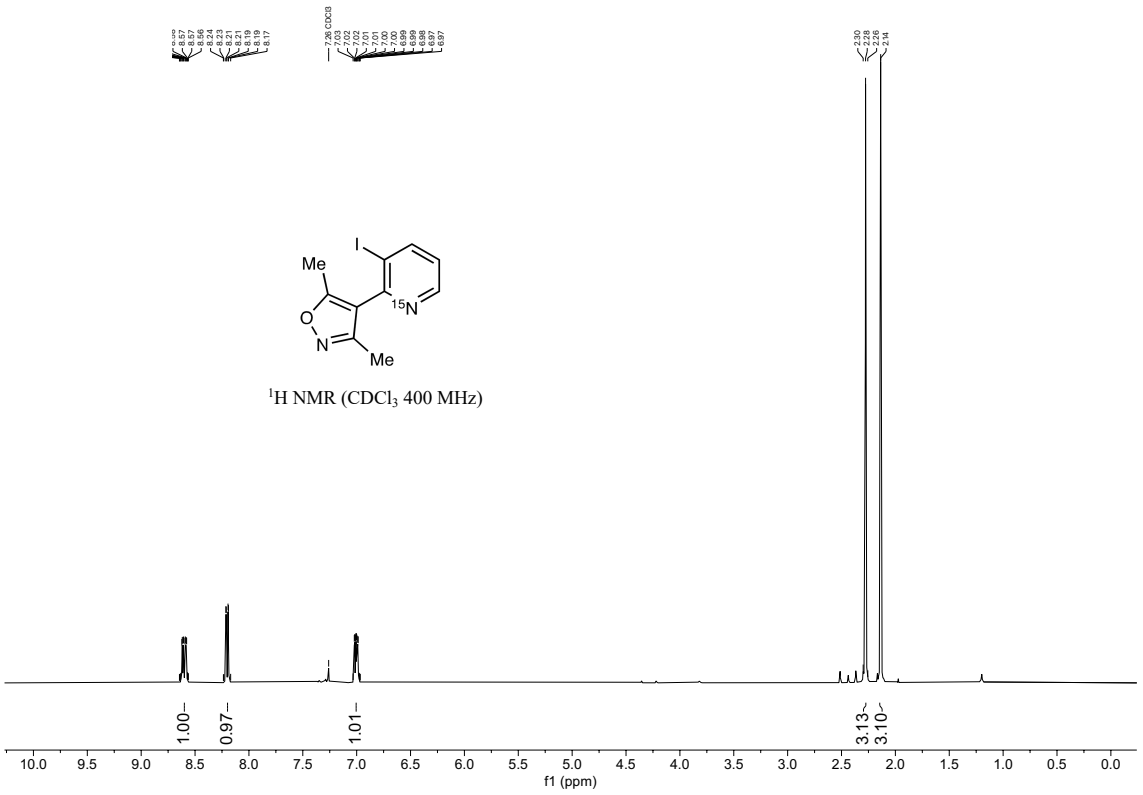

I
15N
MeO
1H NMR (CDCl3 400 MHz)
1.00
0.95
2.04
3.10
3.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



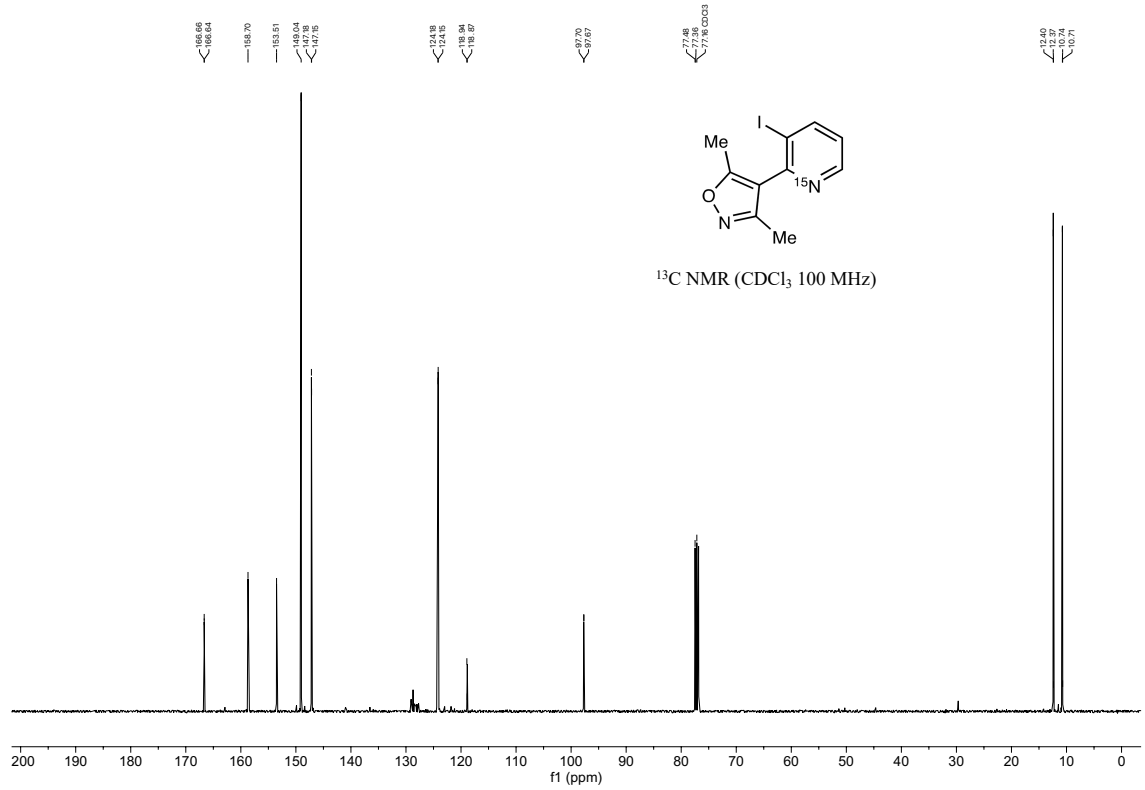
^{13}C NMR ($CDCl_3$ 100 MHz)



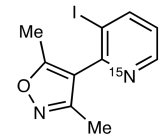
^{15}N NMR ($CDCl_3$ 40 MHz)



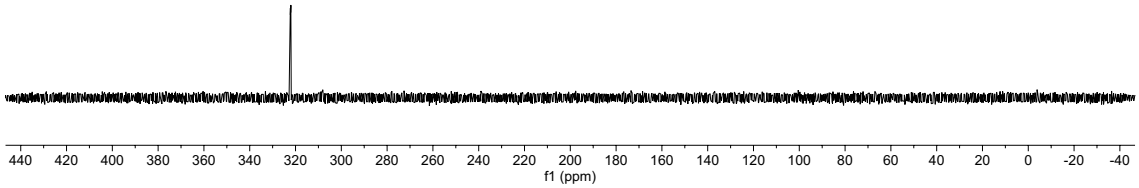
^{1}H NMR ($CDCl_3$ 400 MHz)

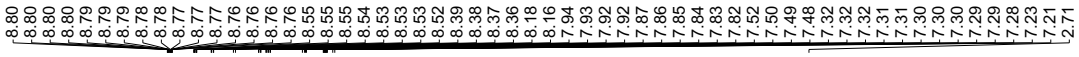


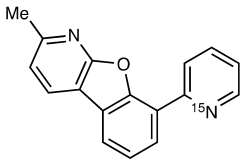
^{13}C NMR ($CDCl_3$ 100 MHz)



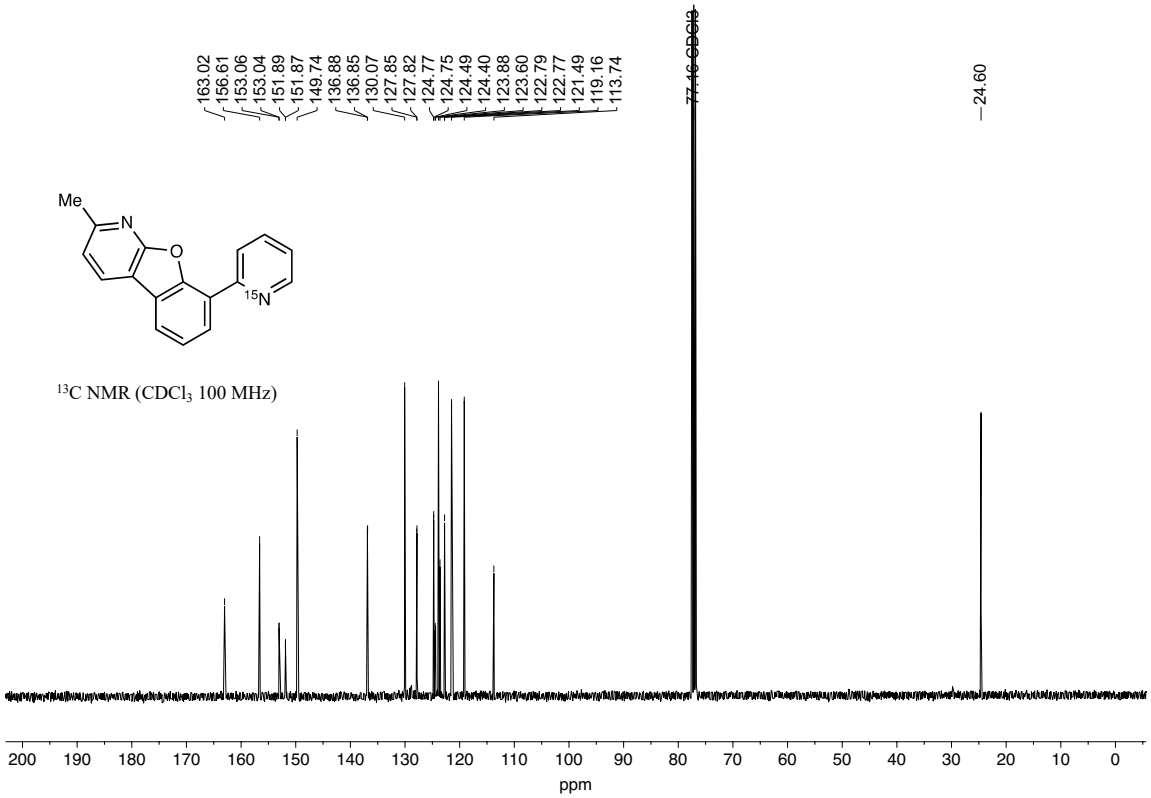
^{15}N NMR ($CDCl_3$ 40 MHz)



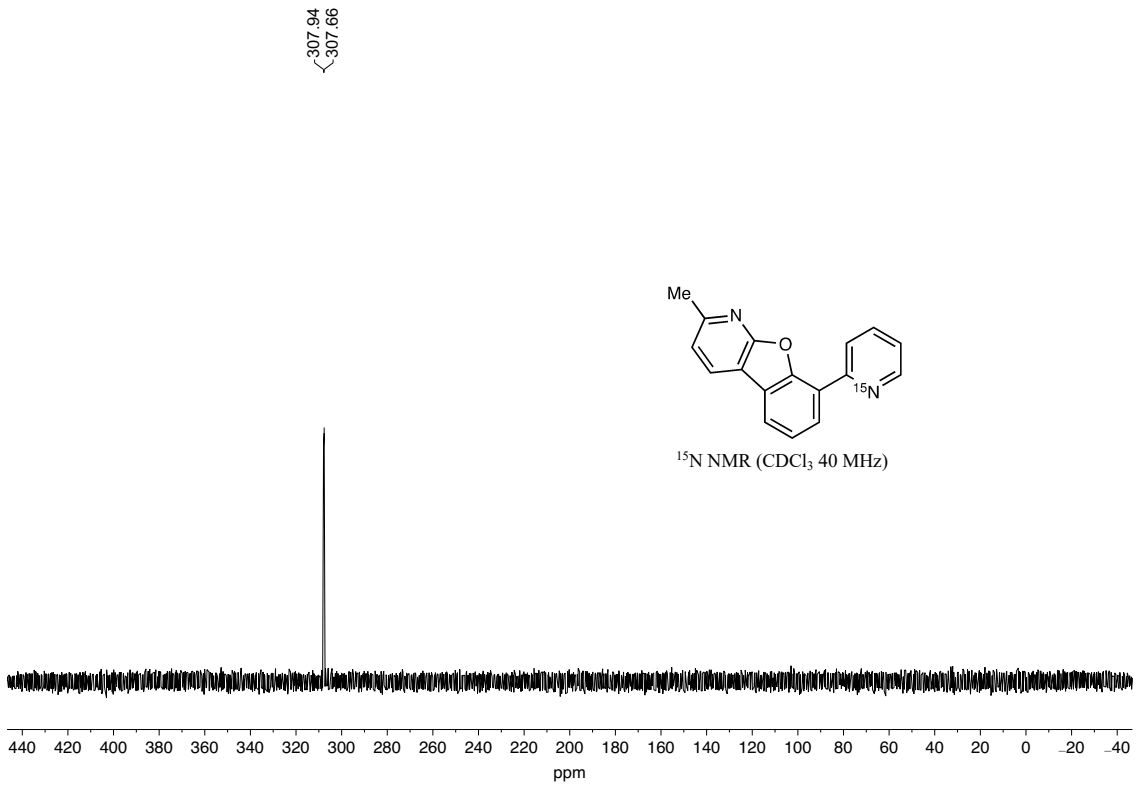




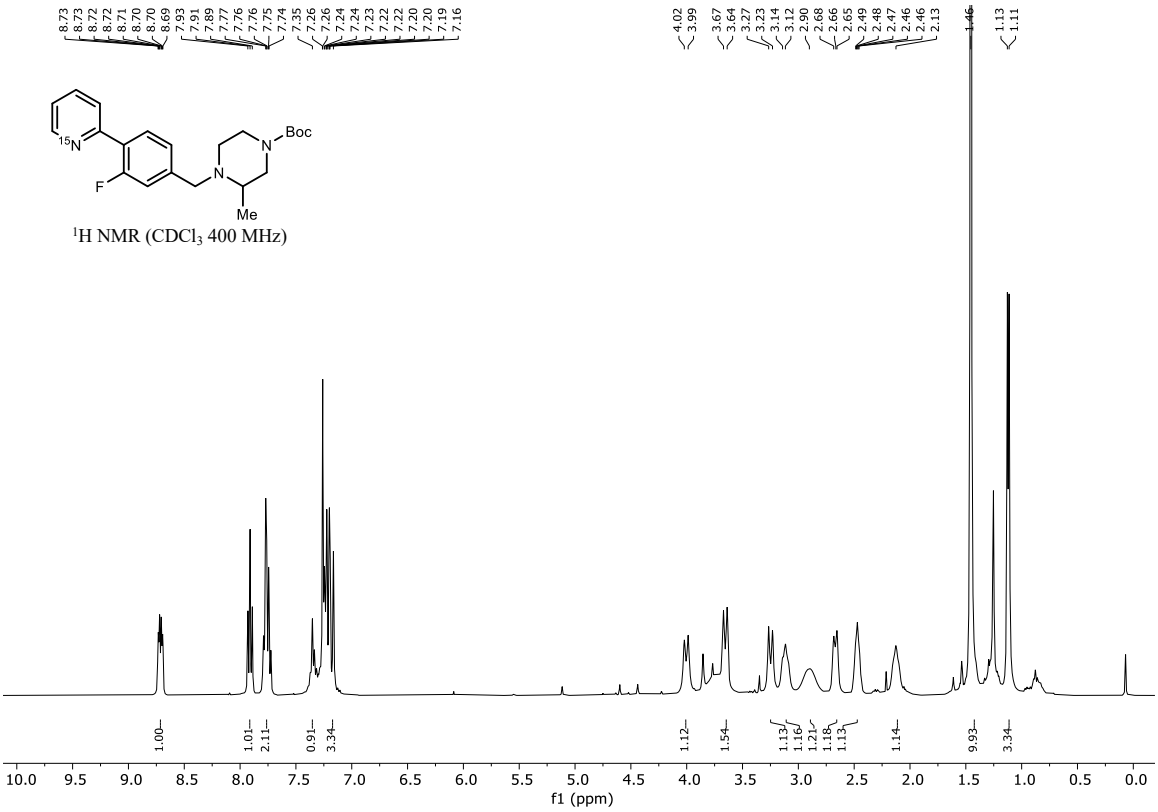
^{1}H NMR ($CDCl_3$ 400 MHz)



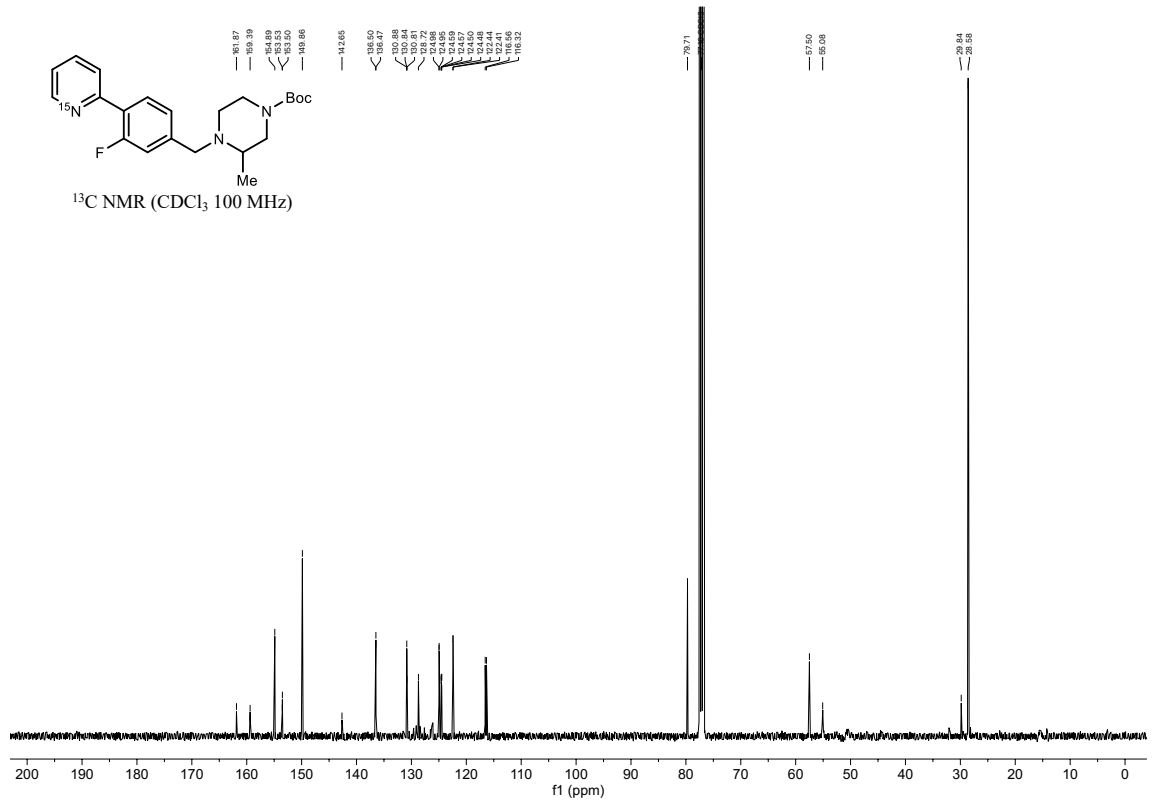
^{13}C NMR ($CDCl_3$ 100 MHz)



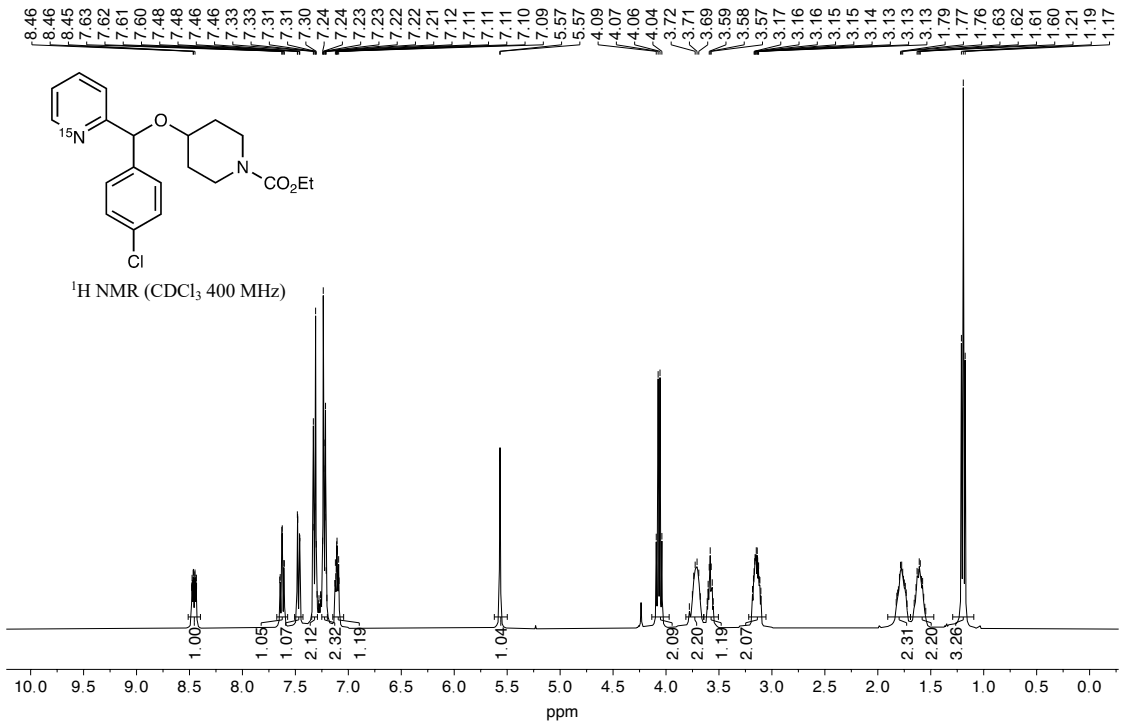
^{15}N NMR ($CDCl_3$ 40 MHz)

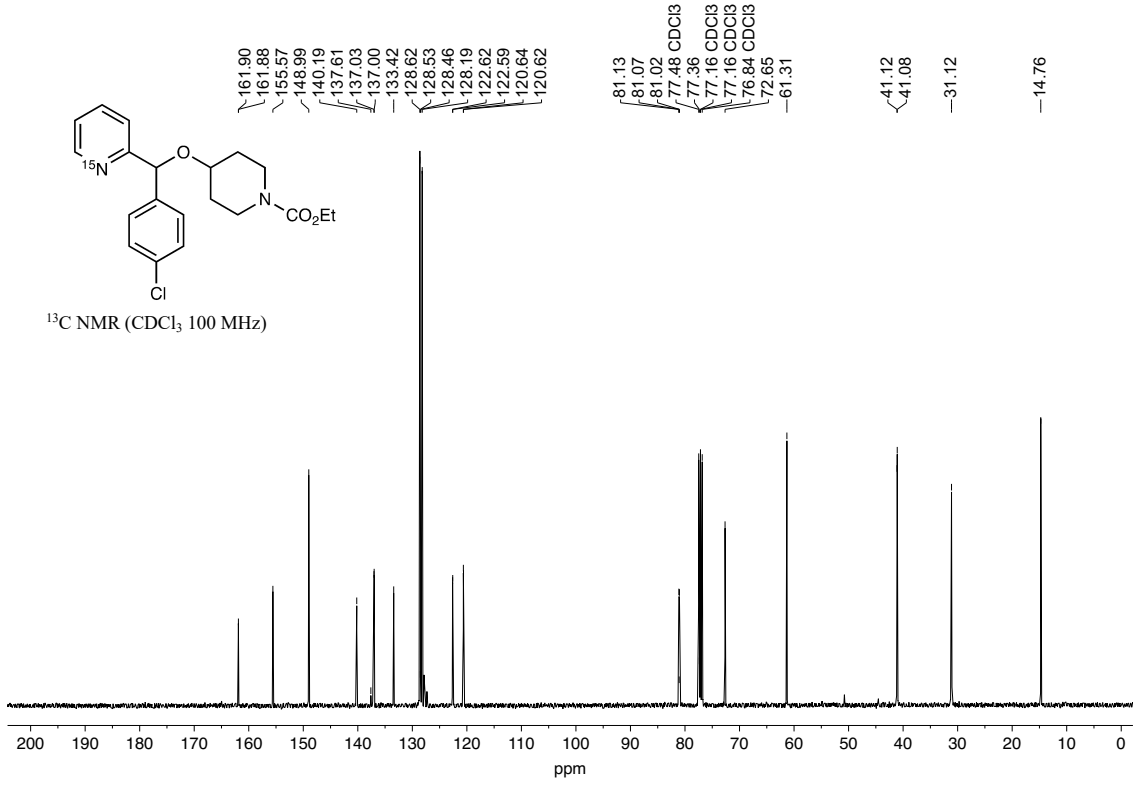


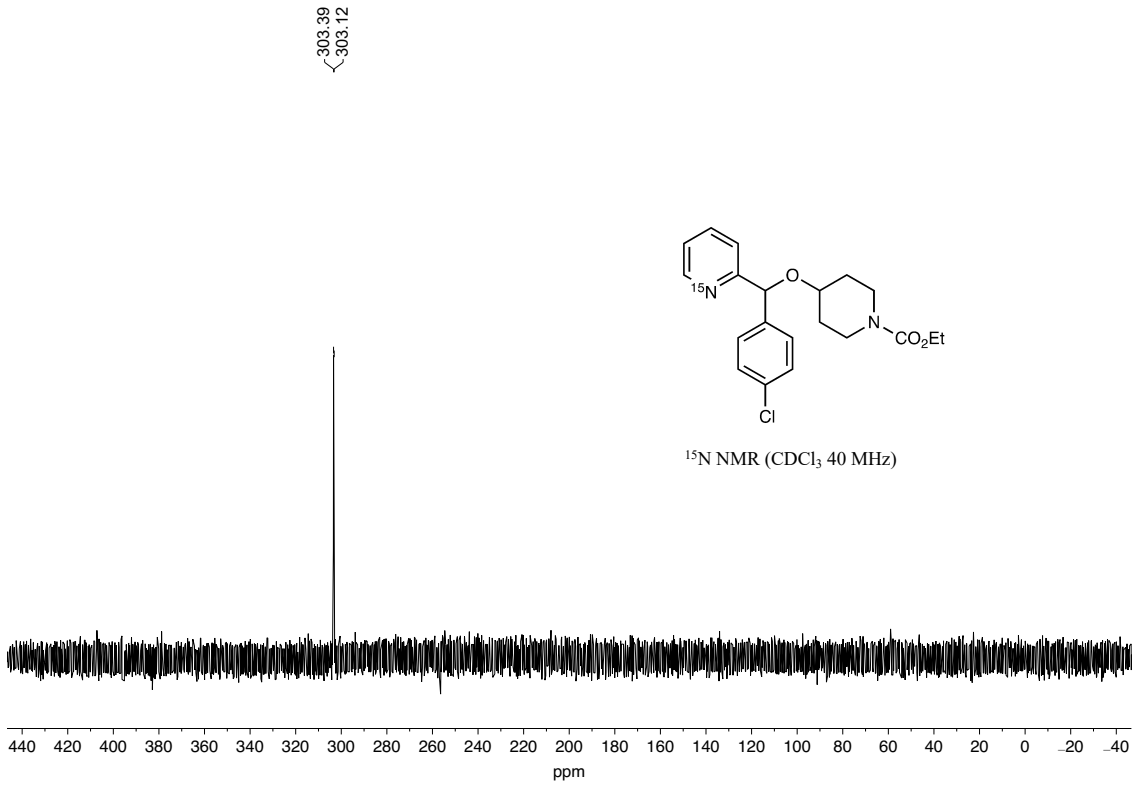
^{1}H NMR ($CDCl_3$ 400 MHz)



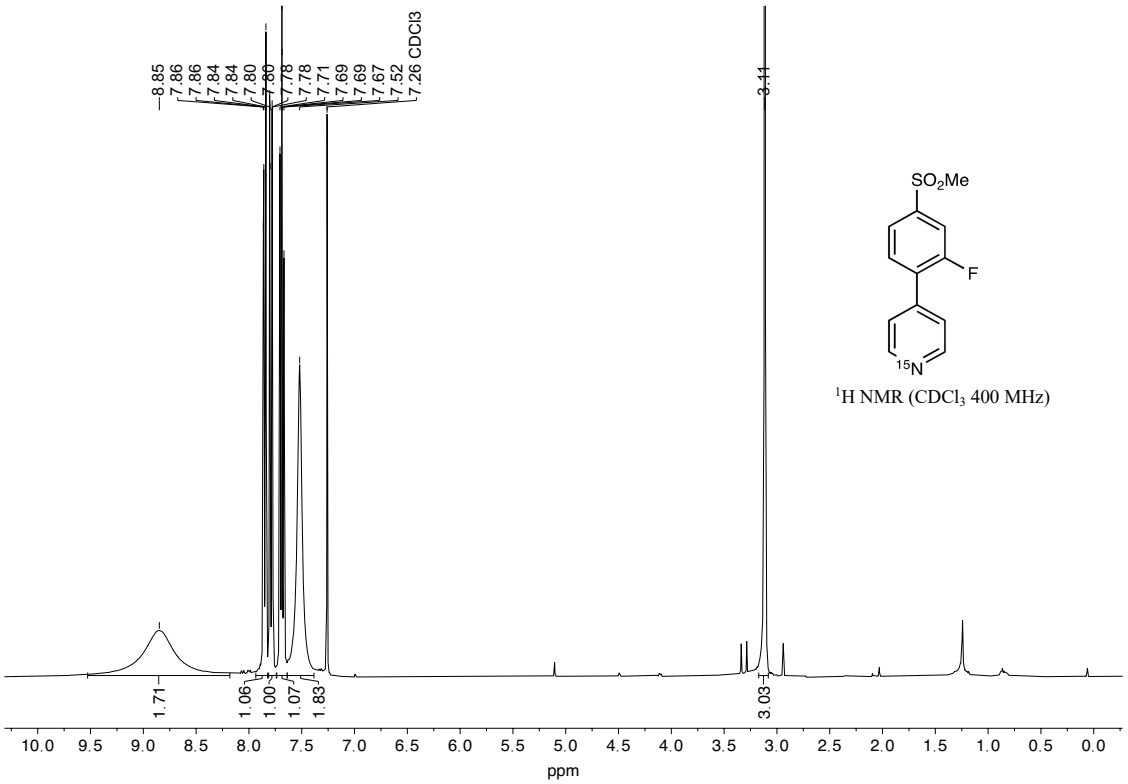
^{13}C NMR ($CDCl_3$ 100 MHz)


8.46 8.46 8.45 7.63 7.62 7.61 7.60 7.48 7.48 7.46 7.46 7.33 7.31 7.31 7.30 7.24 7.24 7.23 7.23 7.22 7.22 7.21 7.12 7.11 7.11 7.11 7.10 7.09 5.57 5.57 4.09 4.07 4.06 4.04 3.72 3.71 3.69 3.59 3.58 3.57 3.17 3.16 3.16 3.15 3.15 3.14 3.13 3.13 3.13 1.79 1.77 1.76 1.63 1.62 1.61 1.60 1.21 1.19 1.17
15N
O
N
CO2Et
Cl
1H NMR (CDCl3 400 MHz)
1.00 1.05 1.07 2.12 2.32 1.19 1.04 2.09 2.20 1.19 2.07 2.31 2.20 3.26
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

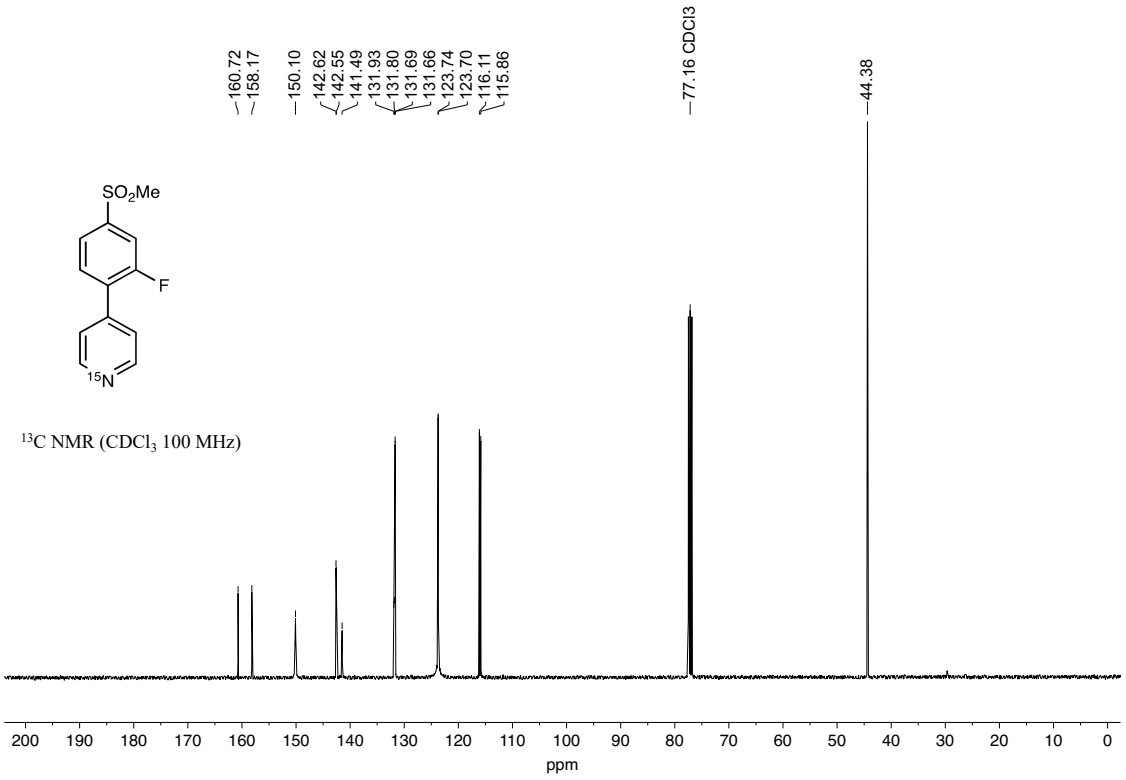

161.90 161.88 155.57 148.99 140.19 137.61 137.03 137.00 133.42 128.62 128.53 128.46 128.19 122.62 122.59 120.64 120.62
81.13 81.07 81.02 77.48 CDCl3 77.36 77.16 CDCl3 77.16 CDCl3 76.84 CDCl3 72.65 61.31
41.12 41.08 31.12 14.76
15N
O
N
CO2Et
Cl
13C NMR (CDCl3 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

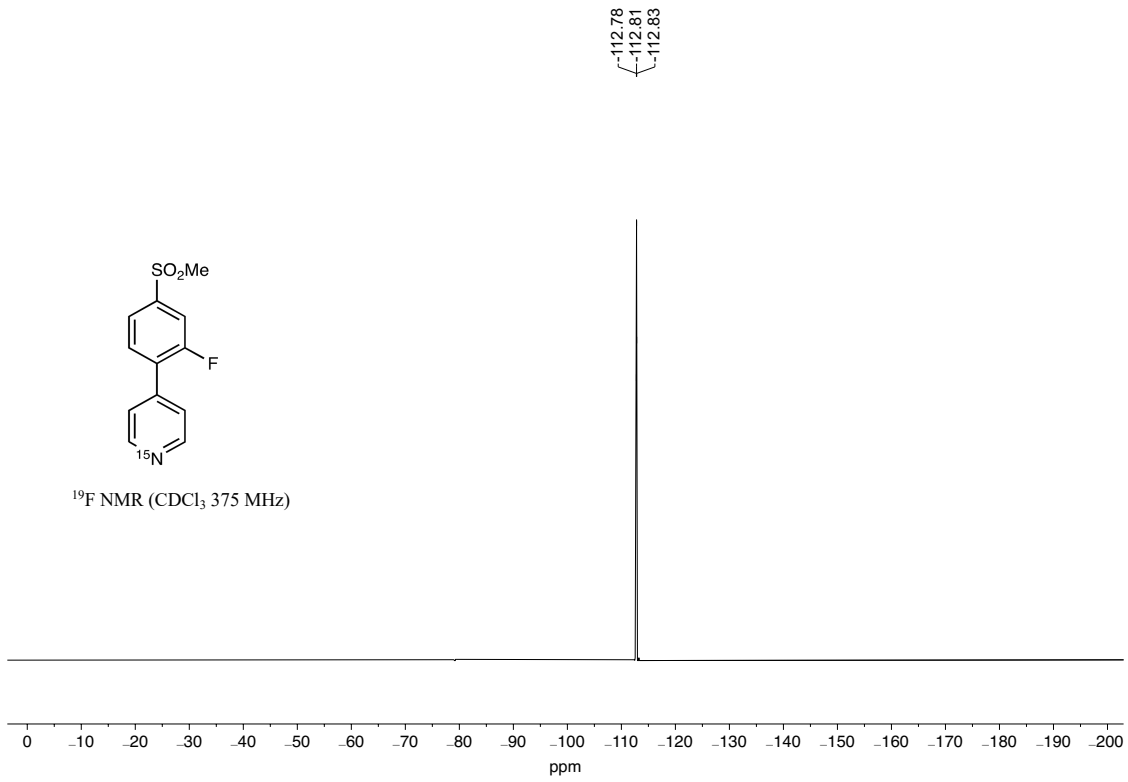


^{15}N NMR ($CDCl_3$ 40 MHz)

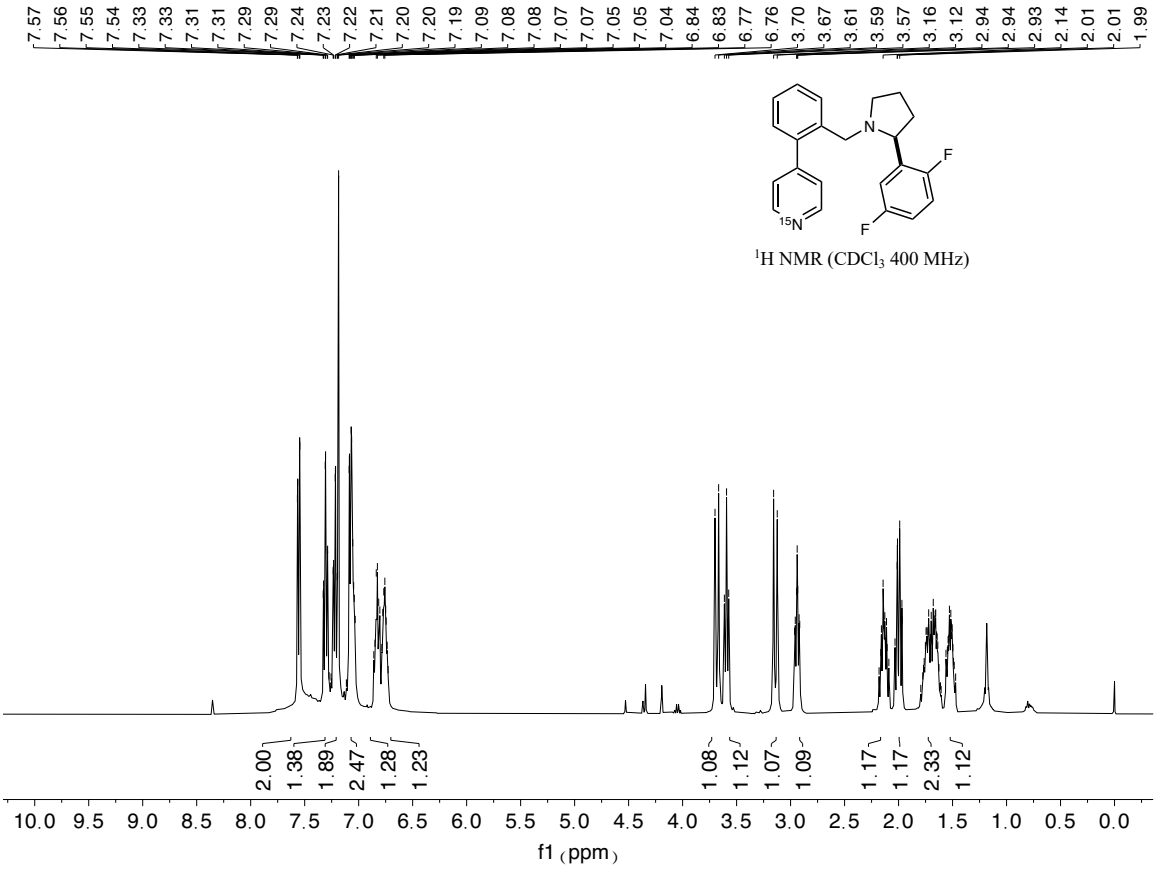


^{1}H NMR ($CDCl_3$ 400 MHz)

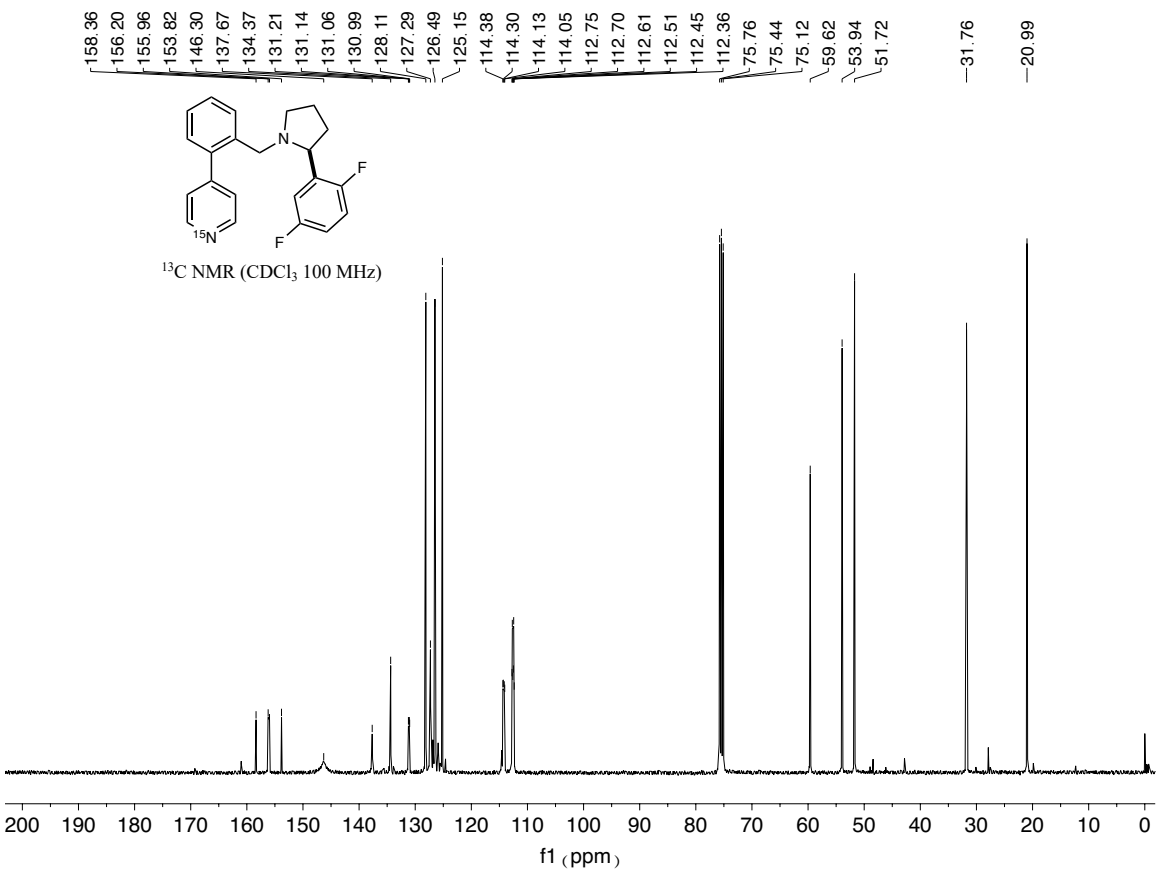

160.72
158.17
150.10
142.62
142.55
141.49
131.93
131.80
131.69
131.66
123.74
123.70
116.11
115.86
77.16 CDCl3
44.38
SO2Me
F
15N
13C NMR (CDCl3 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

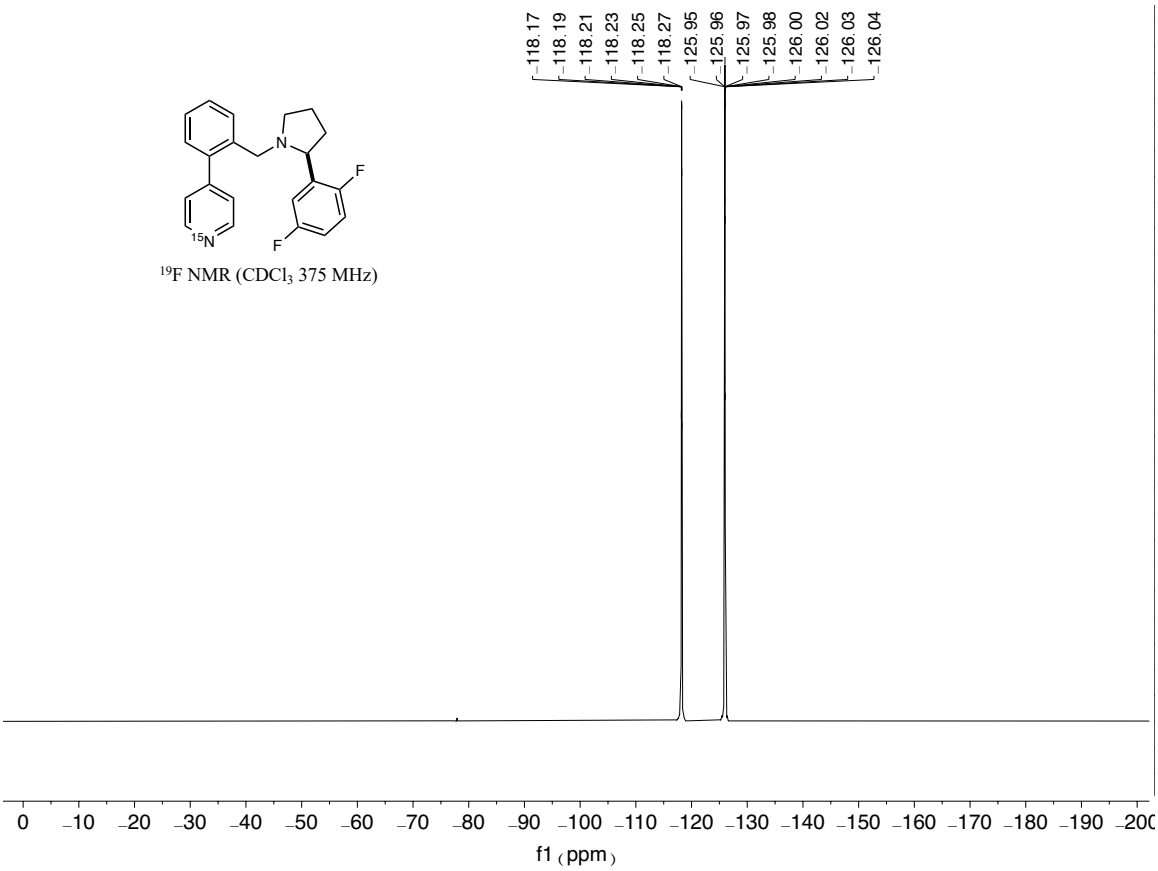


^{19}F NMR ($CDCl_3$ 375 MHz)

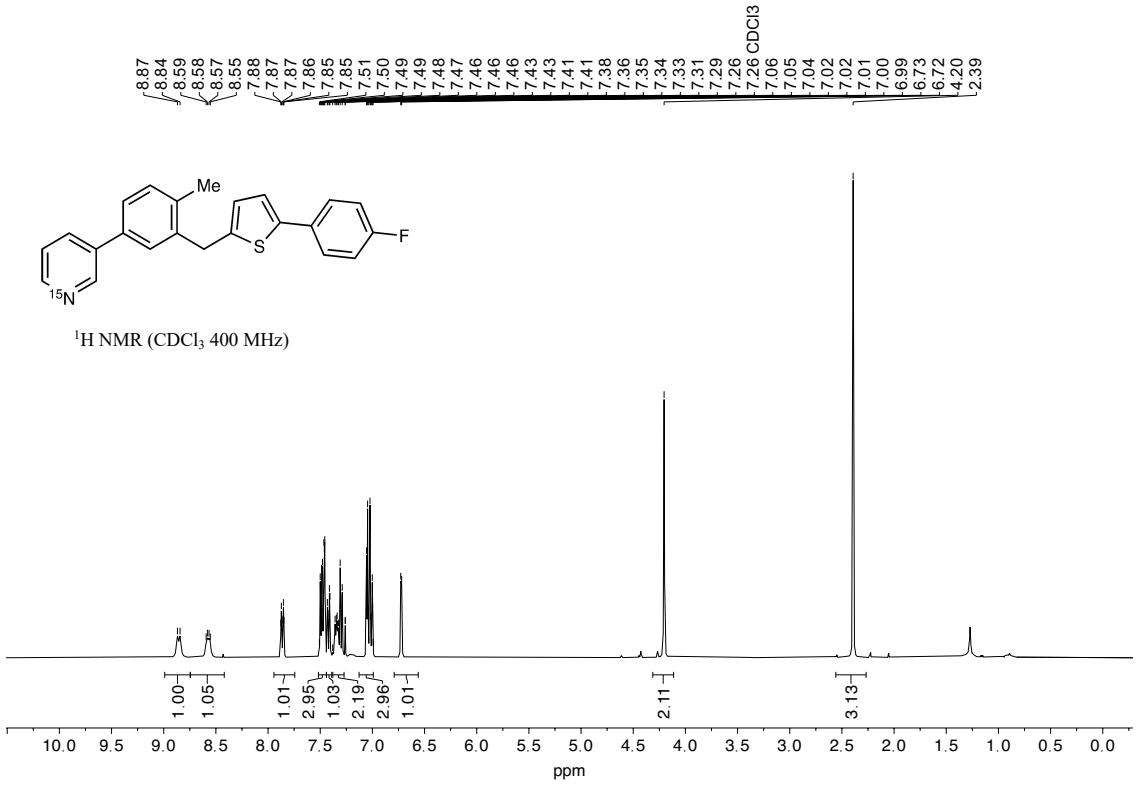


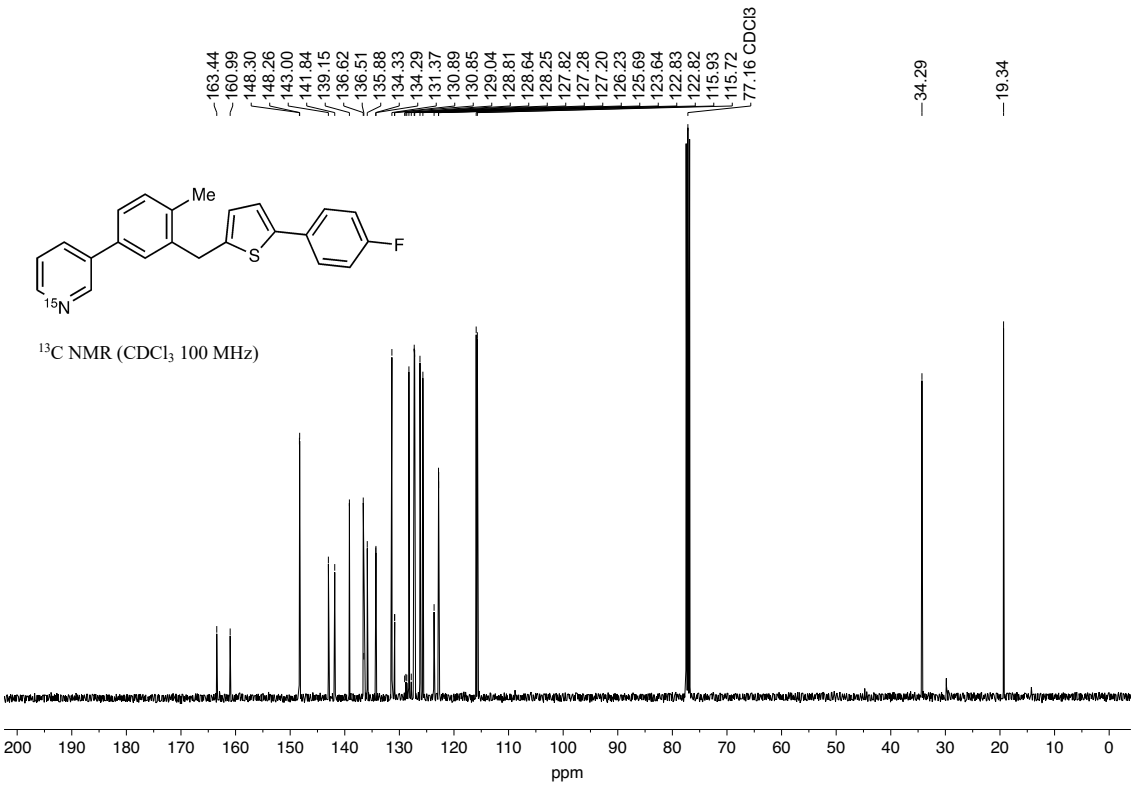
^{1}H NMR ($CDCl_3$ 400 MHz)


158.36
156.20
155.96
153.82
146.30
137.67
134.37
131.21
131.14
131.06
130.99
128.11
127.29
126.49
125.15
114.38
114.30
114.13
114.05
112.75
112.70
112.61
112.51
112.45
112.36
75.76
75.44
75.12
59.62
53.94
51.72
31.76
20.99
N
F
F
15N
13C NMR (CDCl3 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

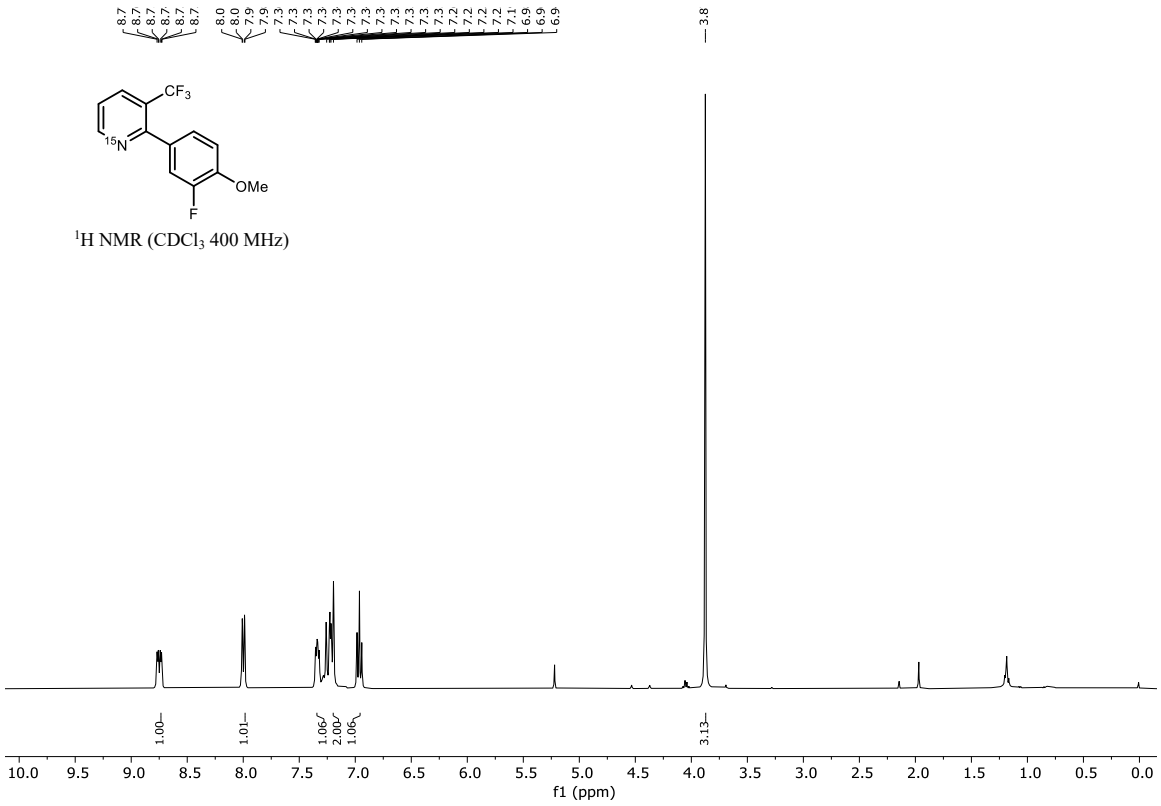


^{19}F NMR ($CDCl_3$ 375 MHz)

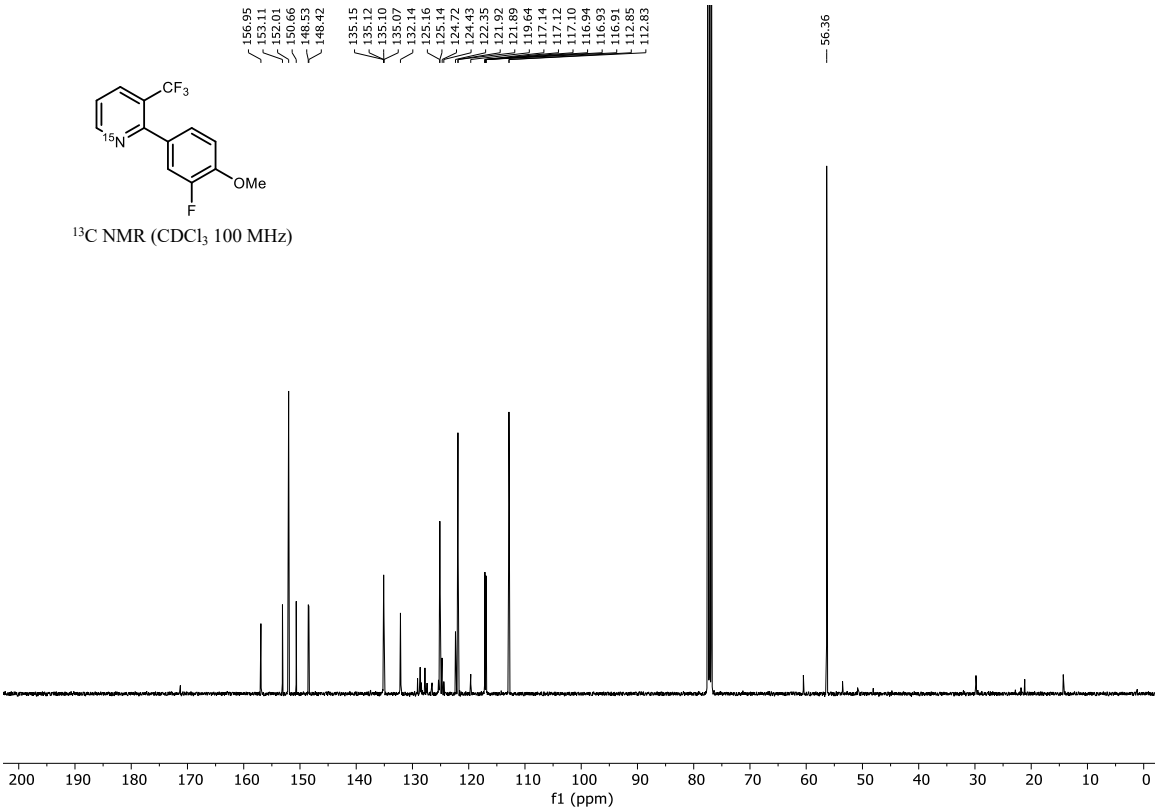

8.87
8.84
8.59
8.58
8.57
8.55
7.88
7.87
7.87
7.86
7.85
7.85
7.51
7.50
7.49
7.49
7.48
7.47
7.46
7.46
7.46
7.43
7.43
7.41
7.41
7.38
7.36
7.35
7.34
7.33
7.31
7.29
7.26
7.26 CDCl3
7.06
7.05
7.04
7.02
7.02
7.01
7.00
6.99
6.73
6.72
4.20
2.39
Me
F
S
15N
1H NMR (CDCl3 400 MHz)
1.00
1.05
1.01
2.95
1.03
2.19
2.96
1.01
2.11
3.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


163.44
160.99
148.30
148.26
143.00
141.84
139.15
136.62
136.51
135.88
134.33
134.29
131.37
130.89
130.85
129.04
128.81
128.64
128.25
127.82
127.28
127.20
126.23
125.69
123.64
122.83
122.82
115.93
115.72
77.16 CDCl3
34.29
19.34
Me
S
F
15N
13C NMR (CDCl3 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

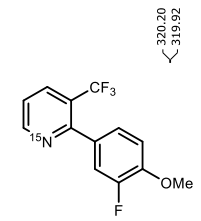
^{19}F NMR ($CDCl_3$ 375 MHz)



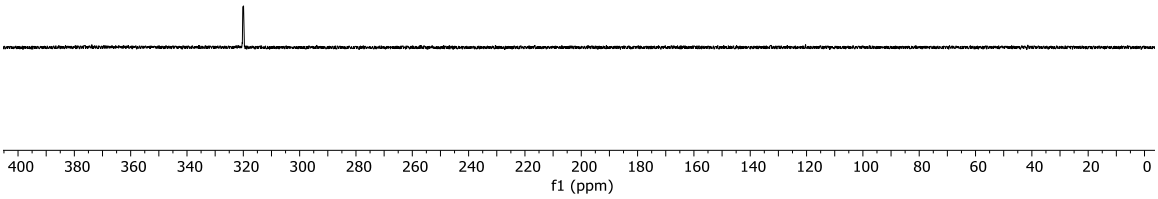
^{1}H NMR ($CDCl_3$ 400 MHz)

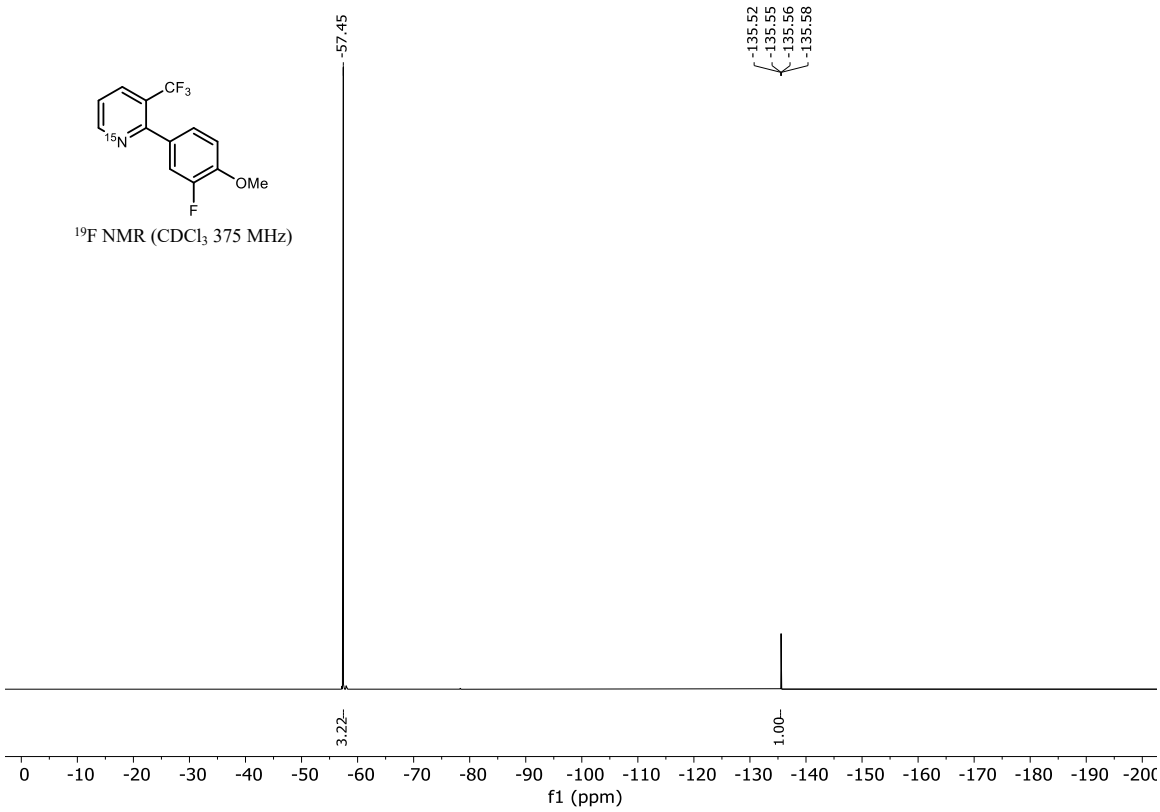


^{13}C NMR ($CDCl_3$ 100 MHz)

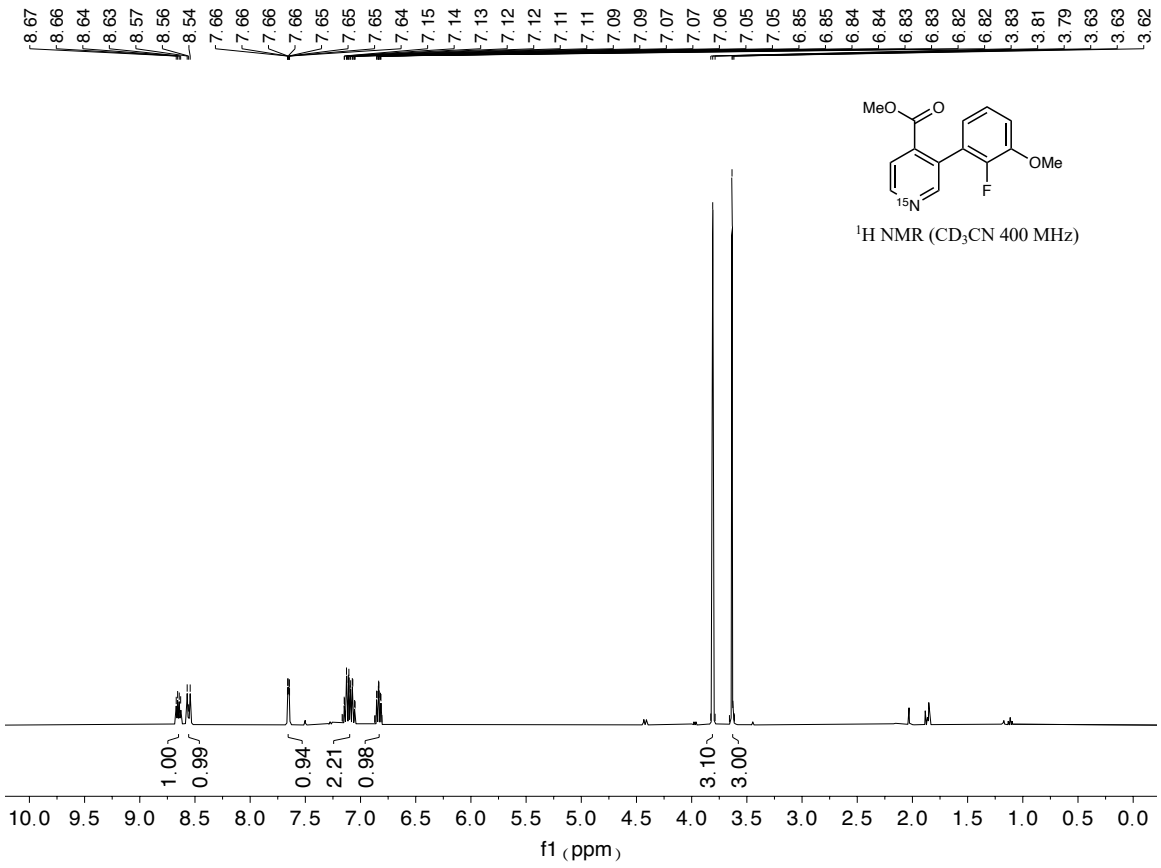


^{15}N NMR ($CDCl_3$ 40 MHz)

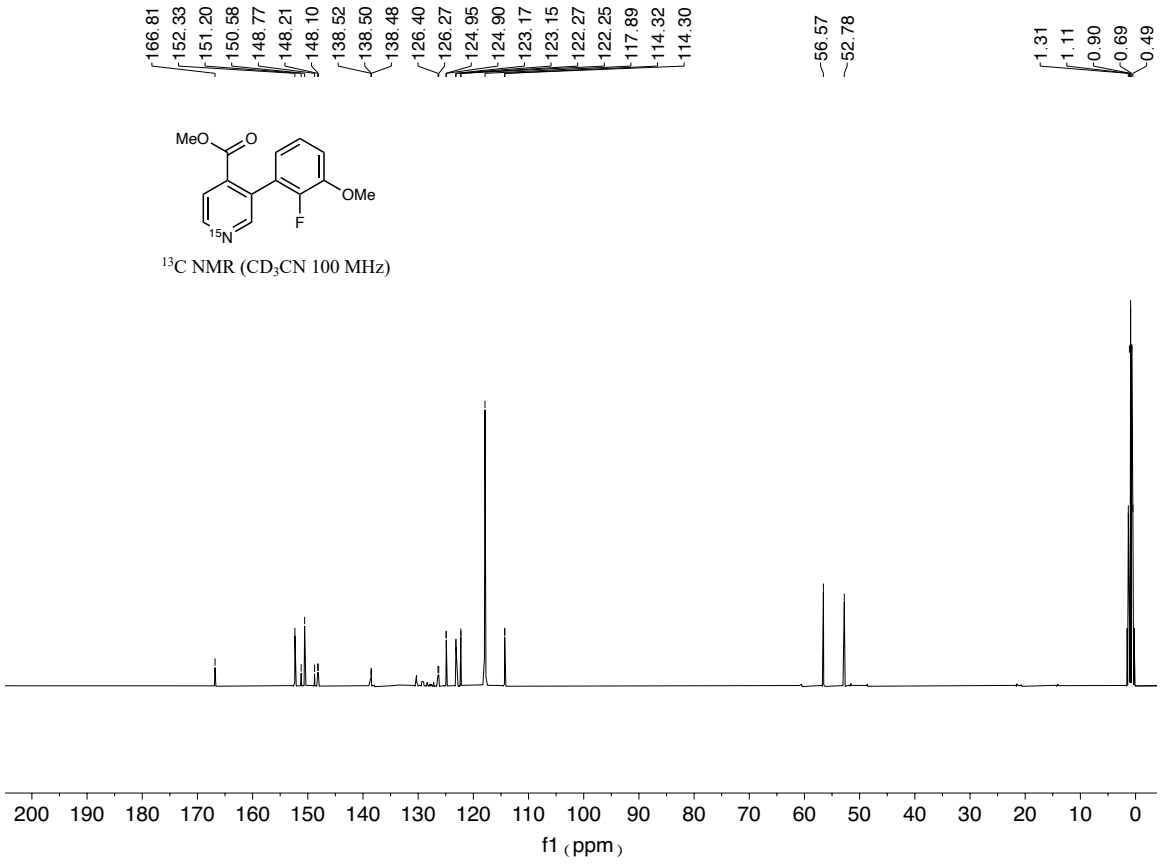




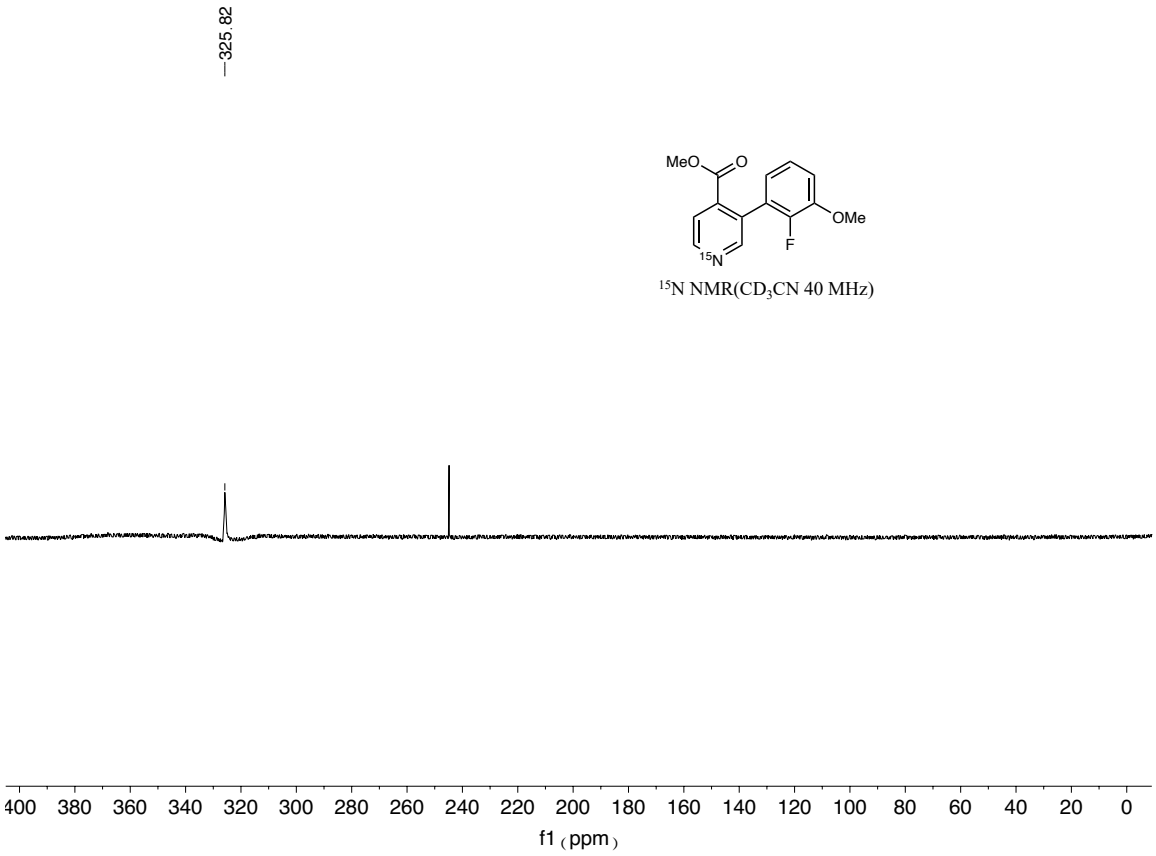
^{19}F NMR ($CDCl_3$ 375 MHz)



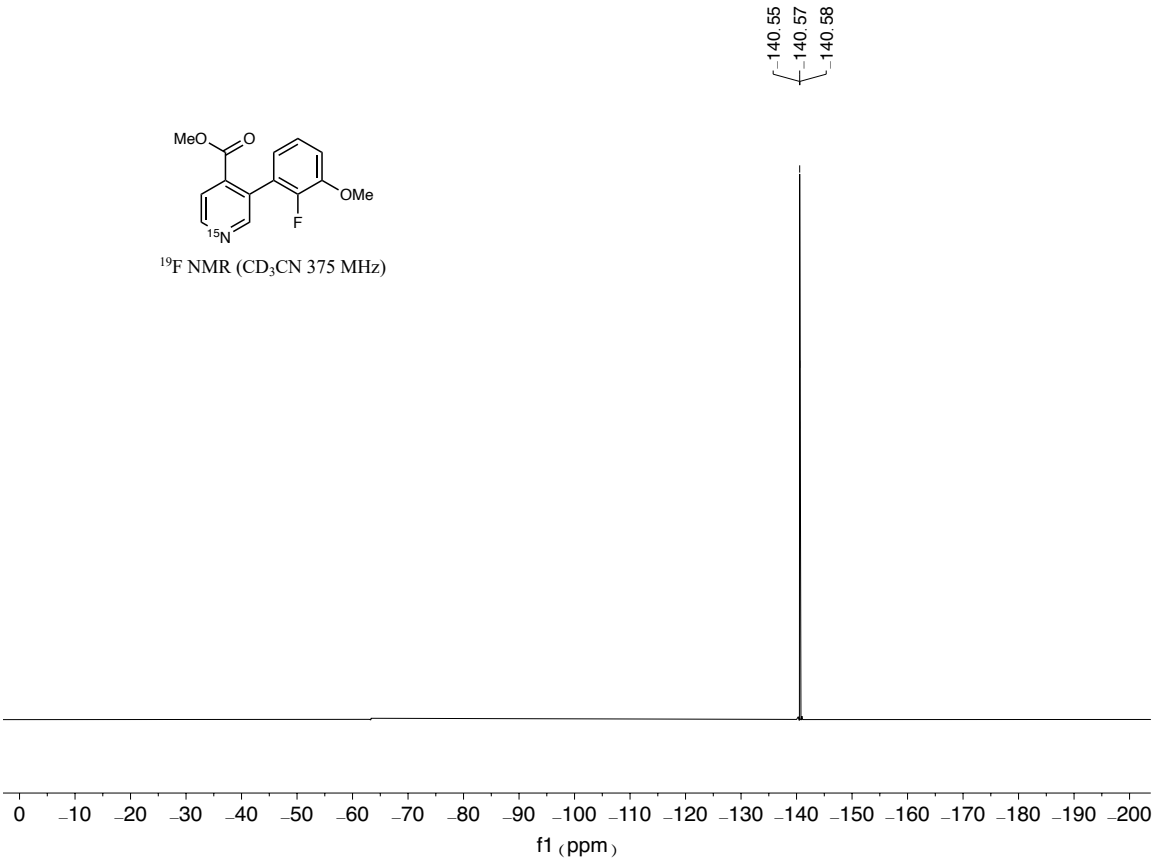
^{1}H NMR (CD_3CN 400 MHz)



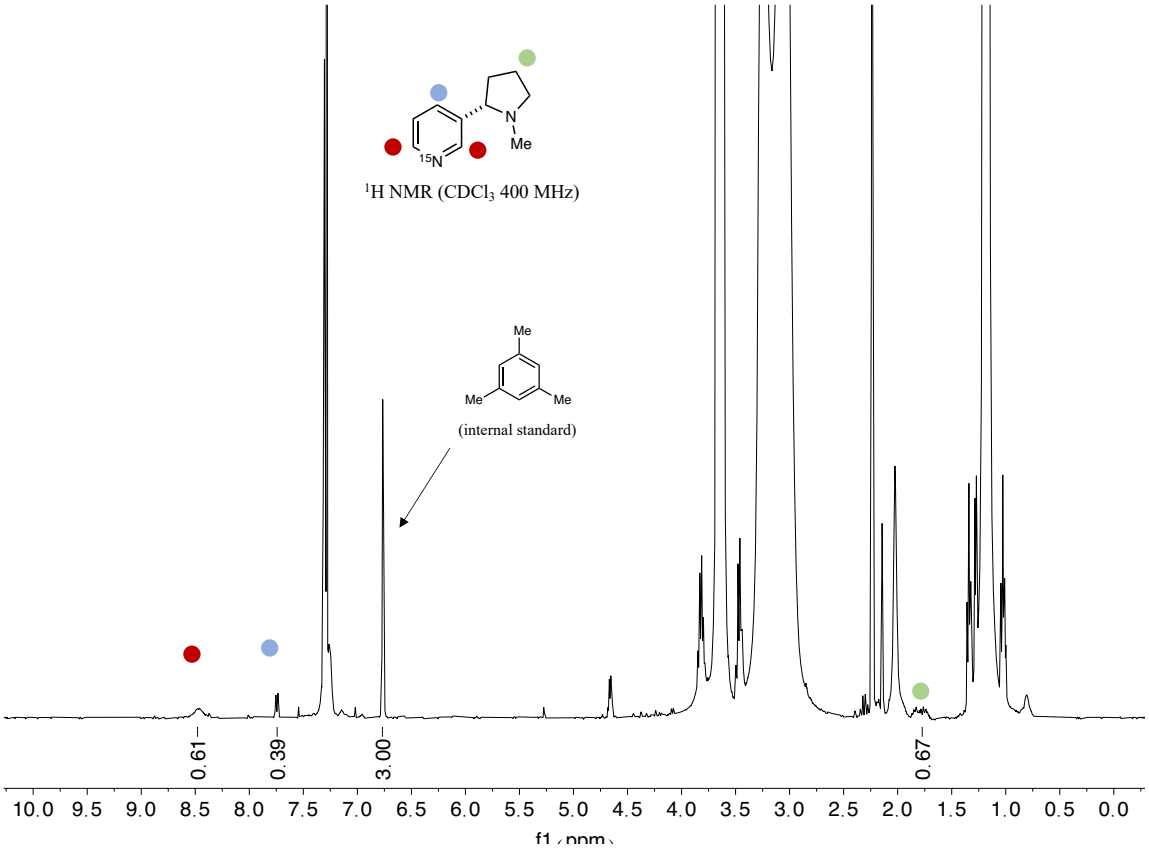
^{13}C NMR (CD_3CN 100 MHz)

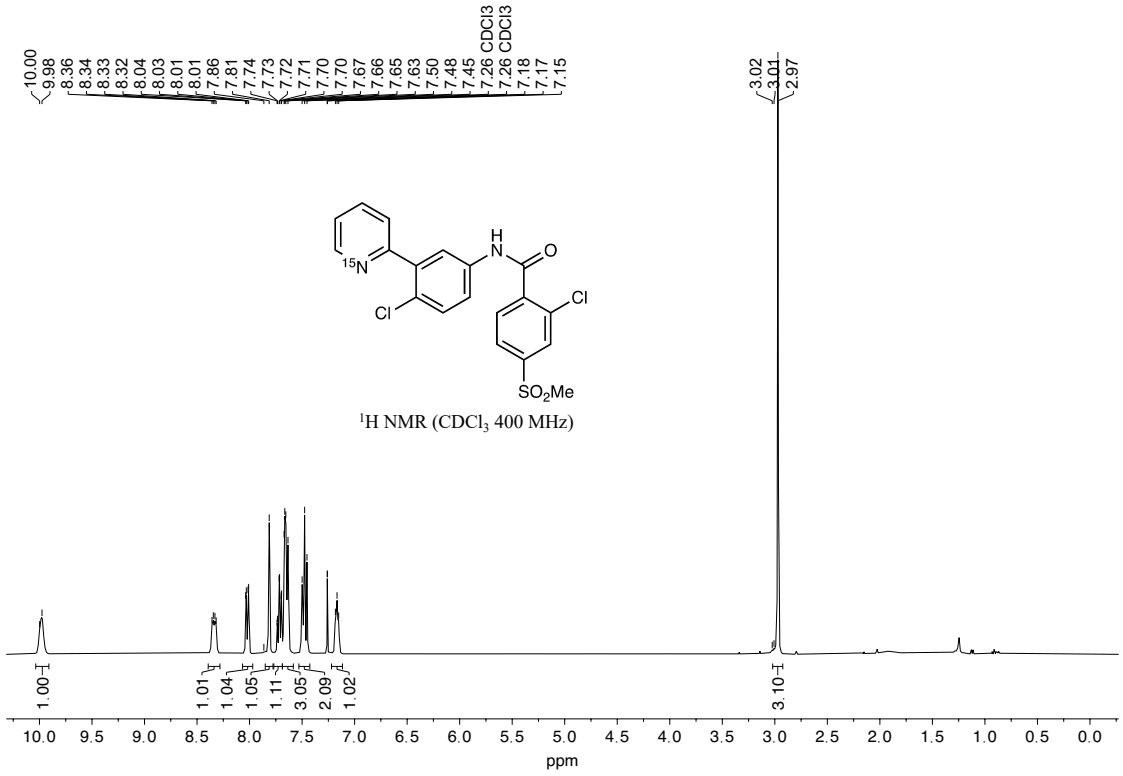


^{15}N NMR(CD_3CN 40 MHz)

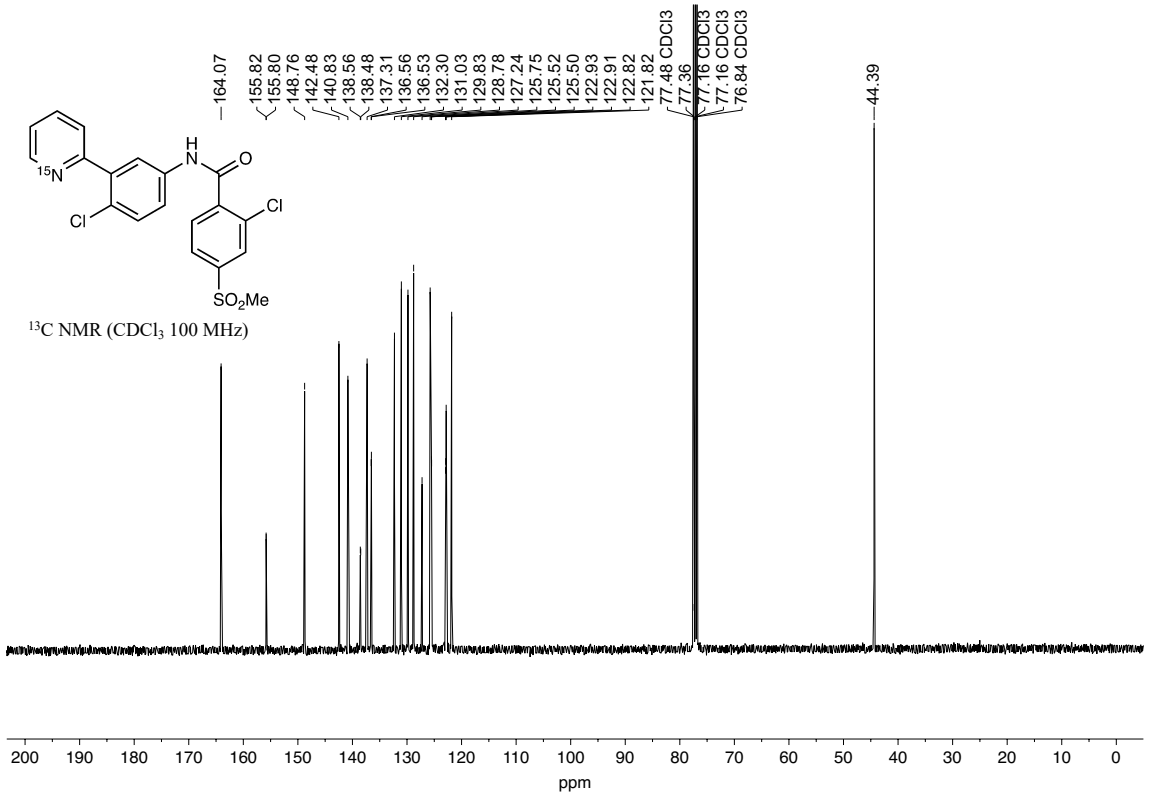


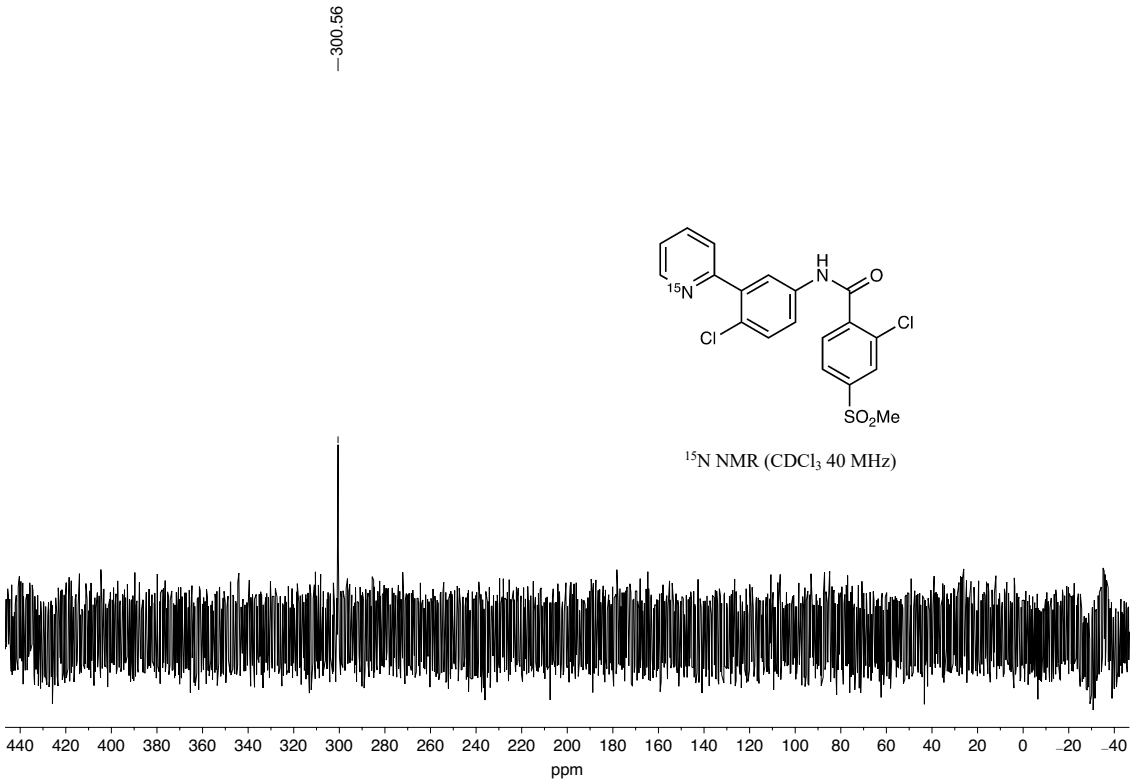
^{19}F NMR (CD_3CN 375 MHz)


^{1}H NMR ($CDCl_3$ 400 MHz)
Me
Me
Me
(internal standard)
0.61
0.39
3.00
0.67
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

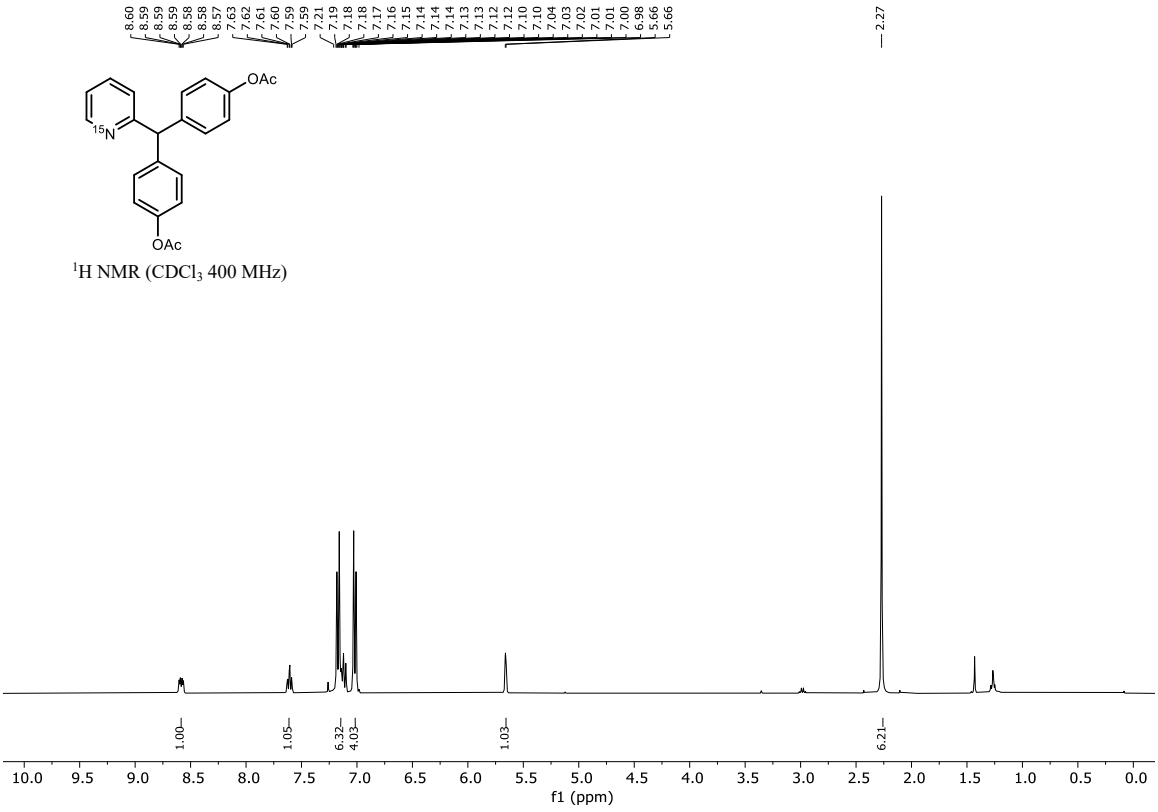


^{1}H NMR ($CDCl_3$ 400 MHz)

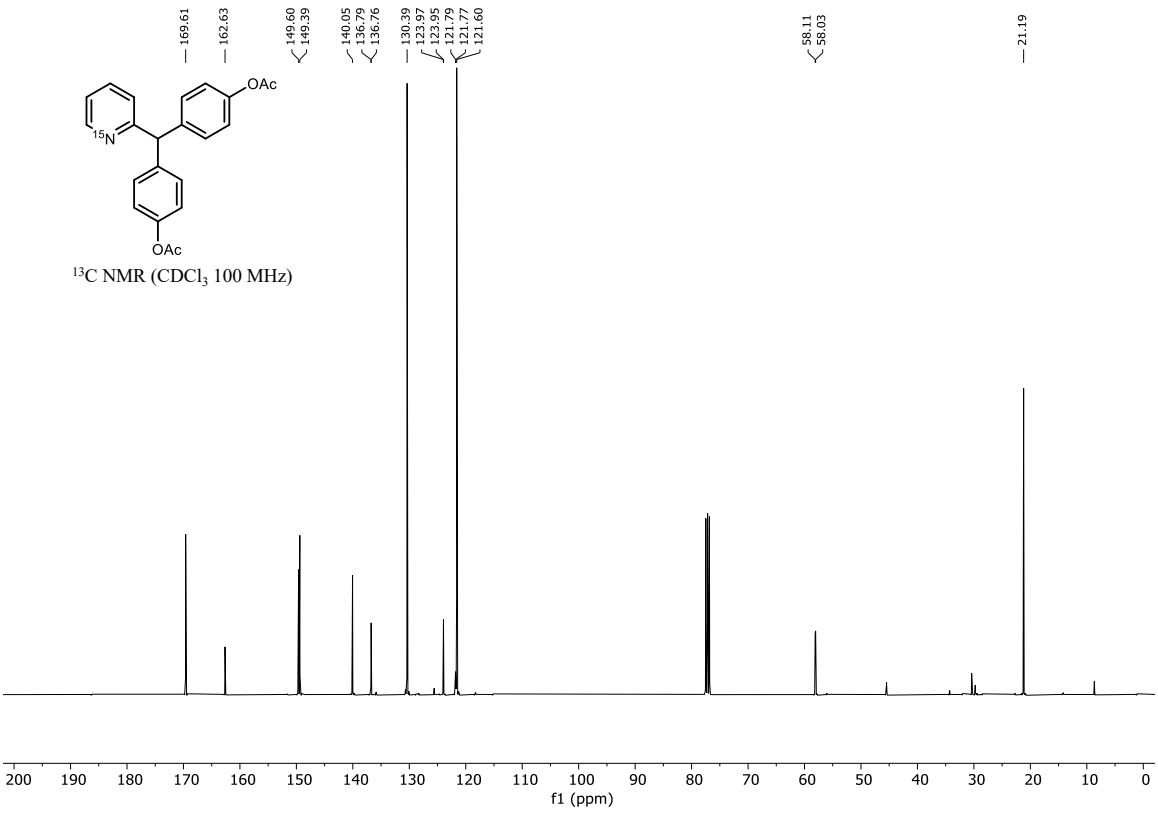

164.07
155.82
155.80
148.76
142.48
140.83
138.56
138.48
137.31
136.56
136.53
132.30
131.03
129.83
128.78
127.24
125.75
125.52
125.50
122.93
122.91
122.82
121.82
77.48 CDCl3
77.36
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3
44.39
15N
H
N
O
Cl
Cl
SO2Me
13C NMR (CDCl3 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm



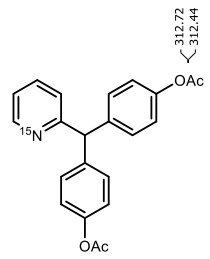
^{15}N NMR ($CDCl_3$ 40 MHz)



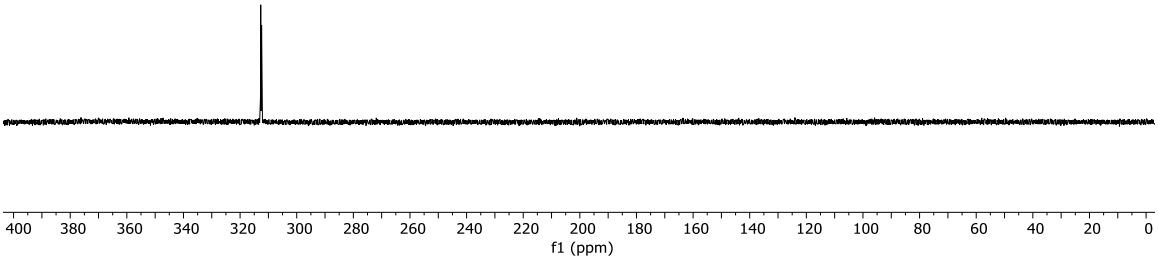
^{1}H NMR ($CDCl_3$ 400 MHz)

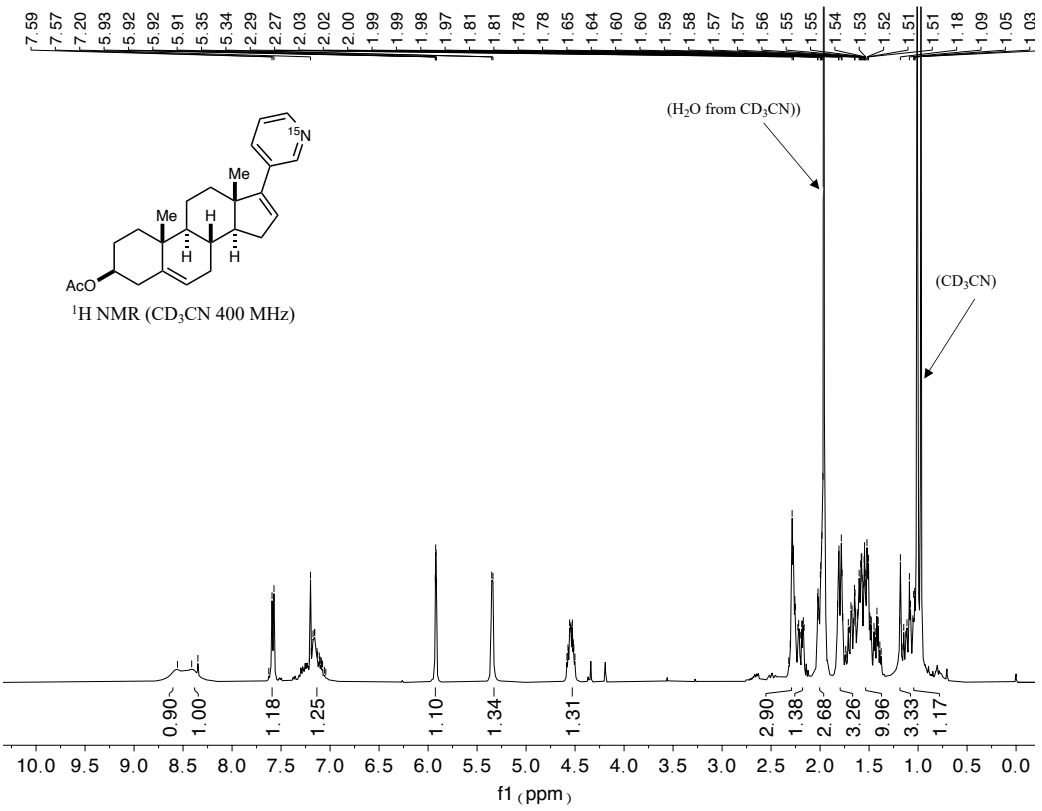


^{13}C NMR ($CDCl_3$ 100 MHz)

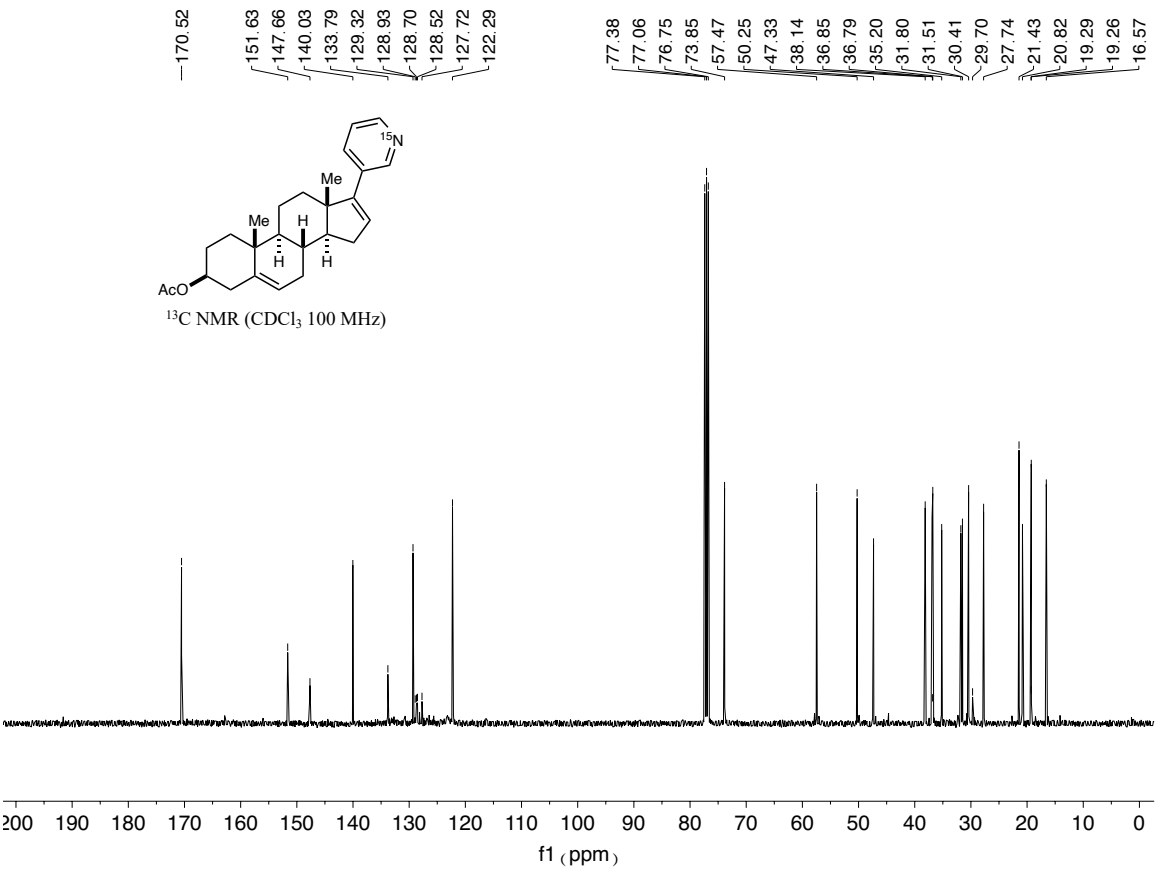


^{15}N NMR ($CDCl_3$ 40 MHz)

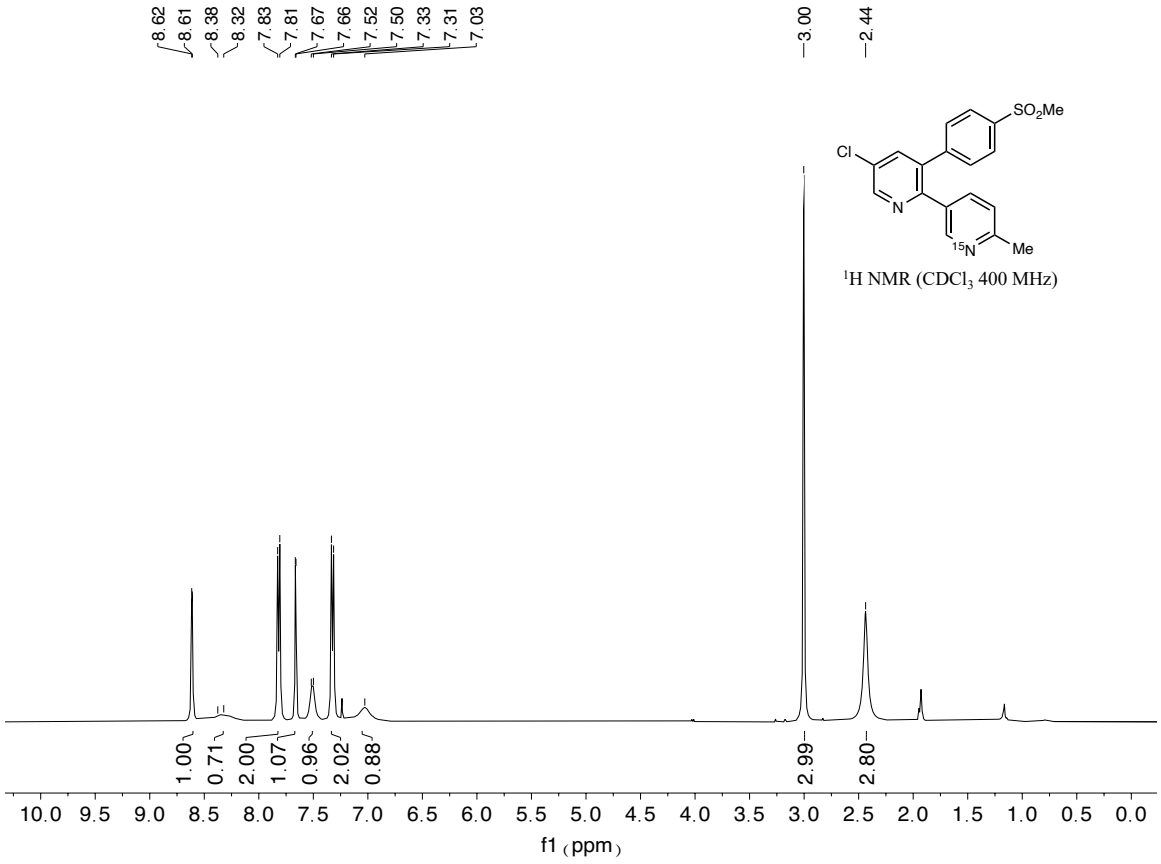


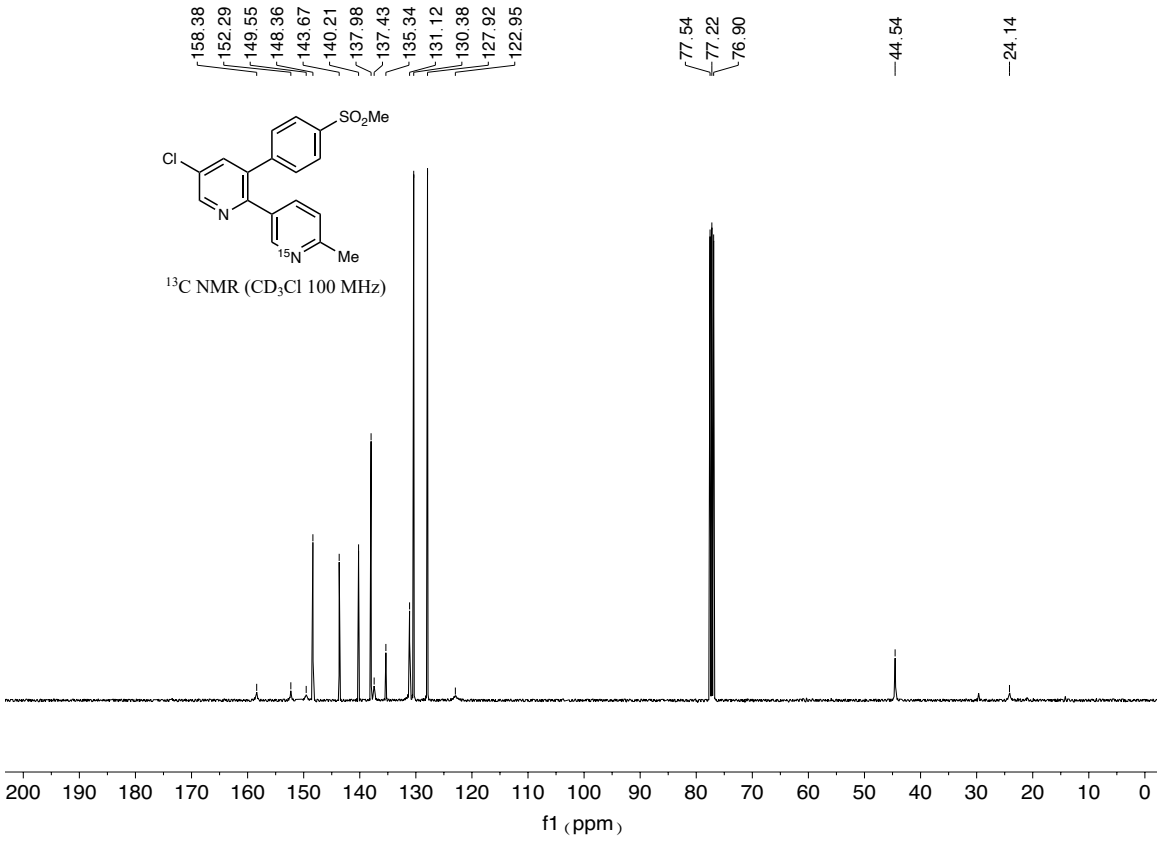


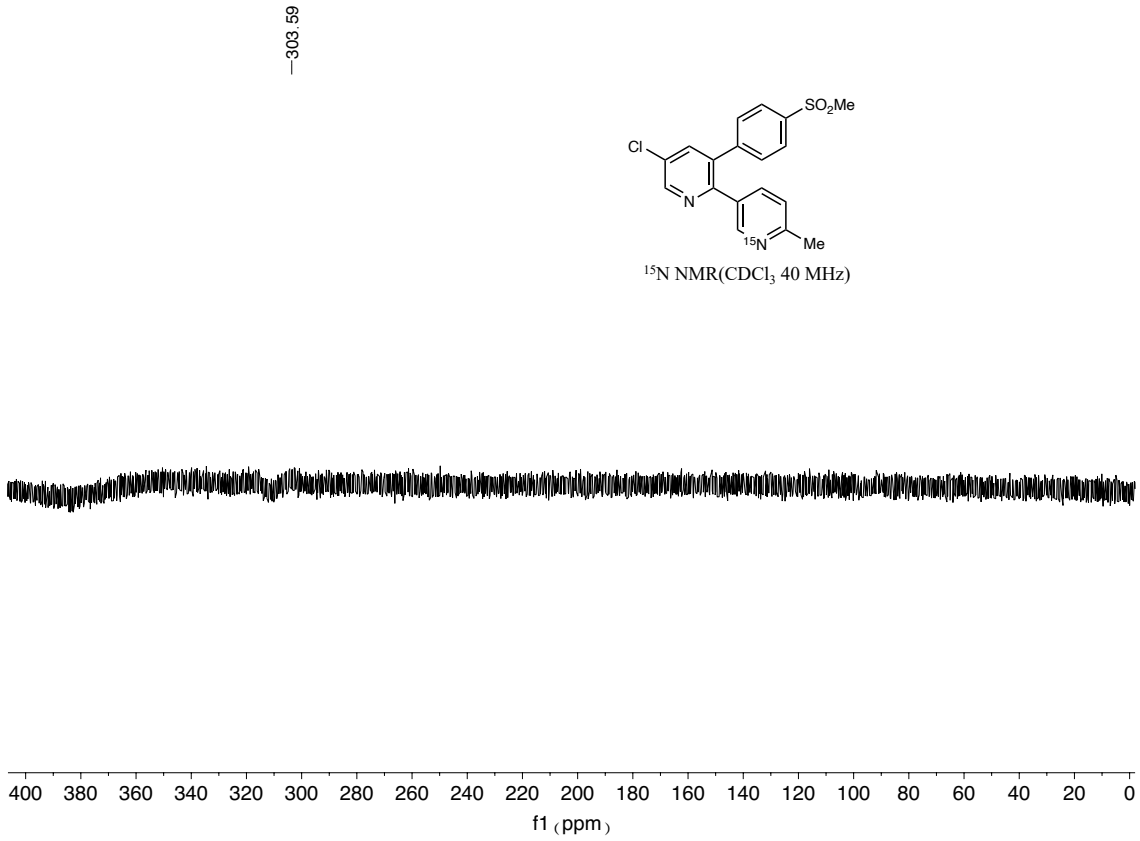
^{1}H NMR (CD_3CN 400 MHz)



^{13}C NMR ($CDCl_3$ 100 MHz)

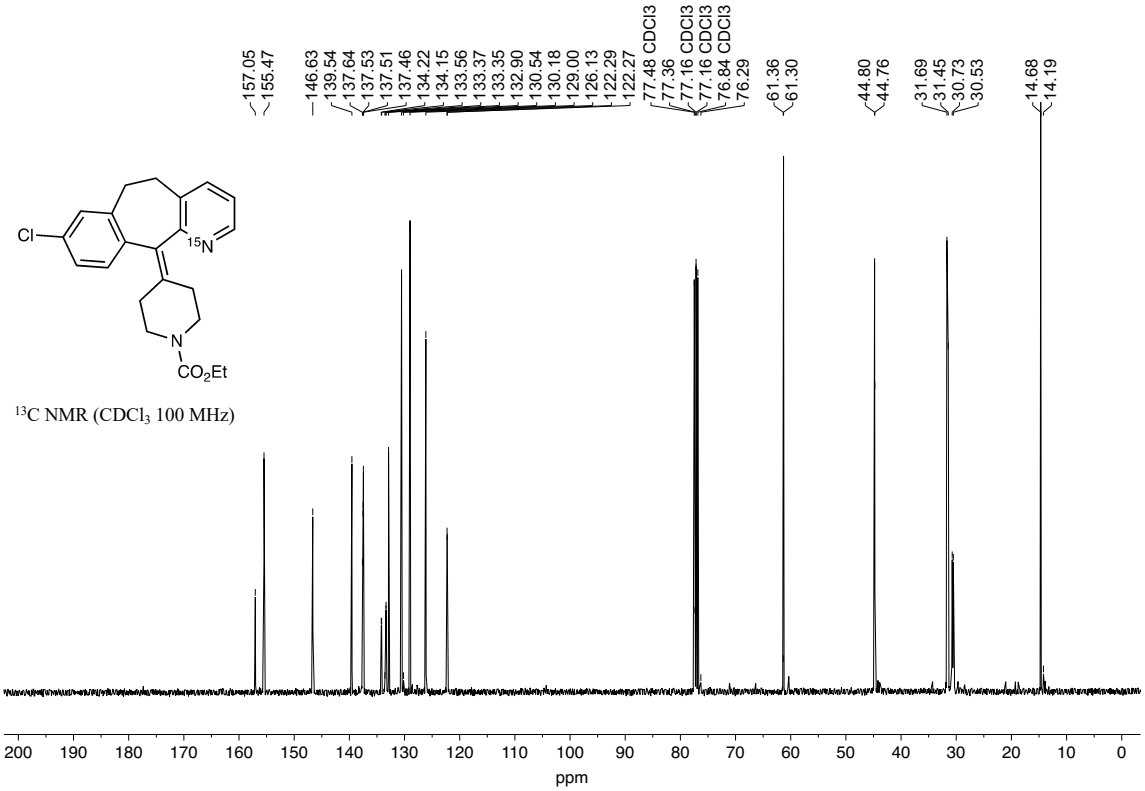

8.62
8.61
8.38
8.32
7.83
7.81
7.67
7.66
7.52
7.50
7.33
7.31
7.03
3.00
2.44
SO2Me
Cl
N
15N
Me
1H NMR (CDCl3 400 MHz)
1.00
0.71
2.00
1.07
0.96
2.02
0.88
2.99
2.80
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


158.38
152.29
149.55
148.36
143.67
140.21
137.98
137.43
135.34
131.12
130.38
127.92
122.95
77.54
77.22
76.90
44.54
24.14
SO2Me
Cl
N
15N
Me
13C NMR (CD3Cl 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

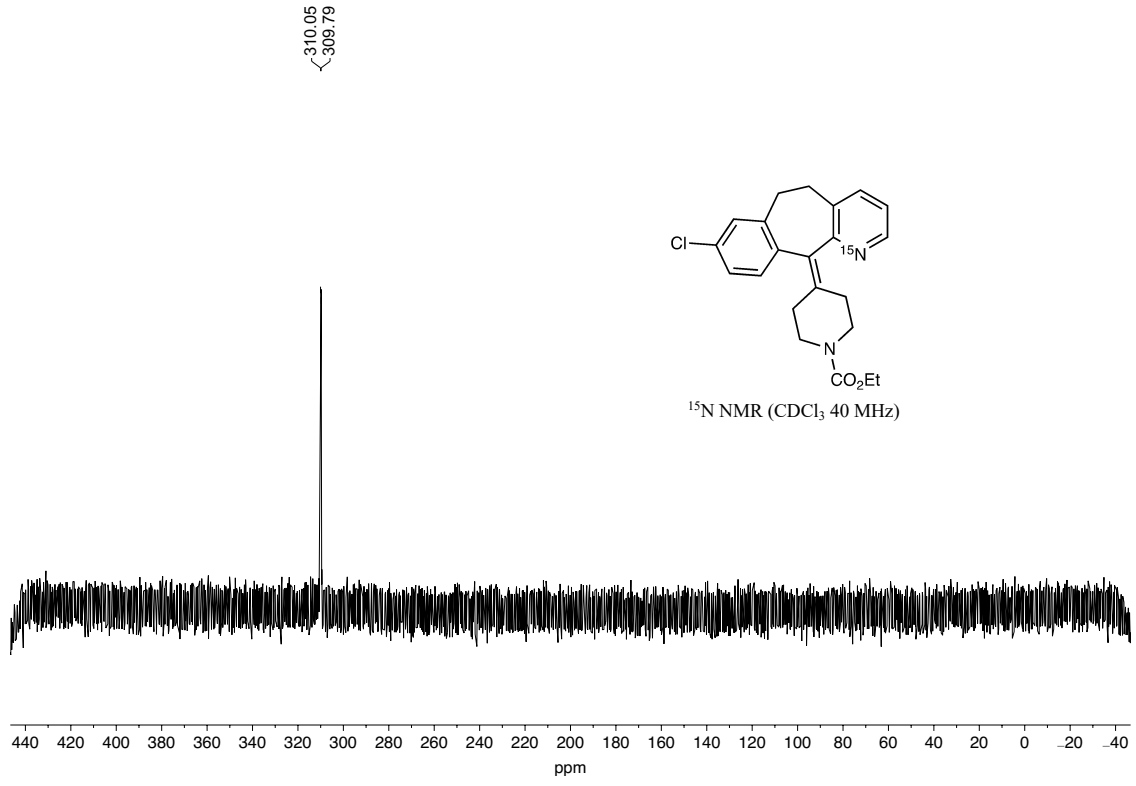


^{15}N NMR($CDCl_3$ 40 MHz)

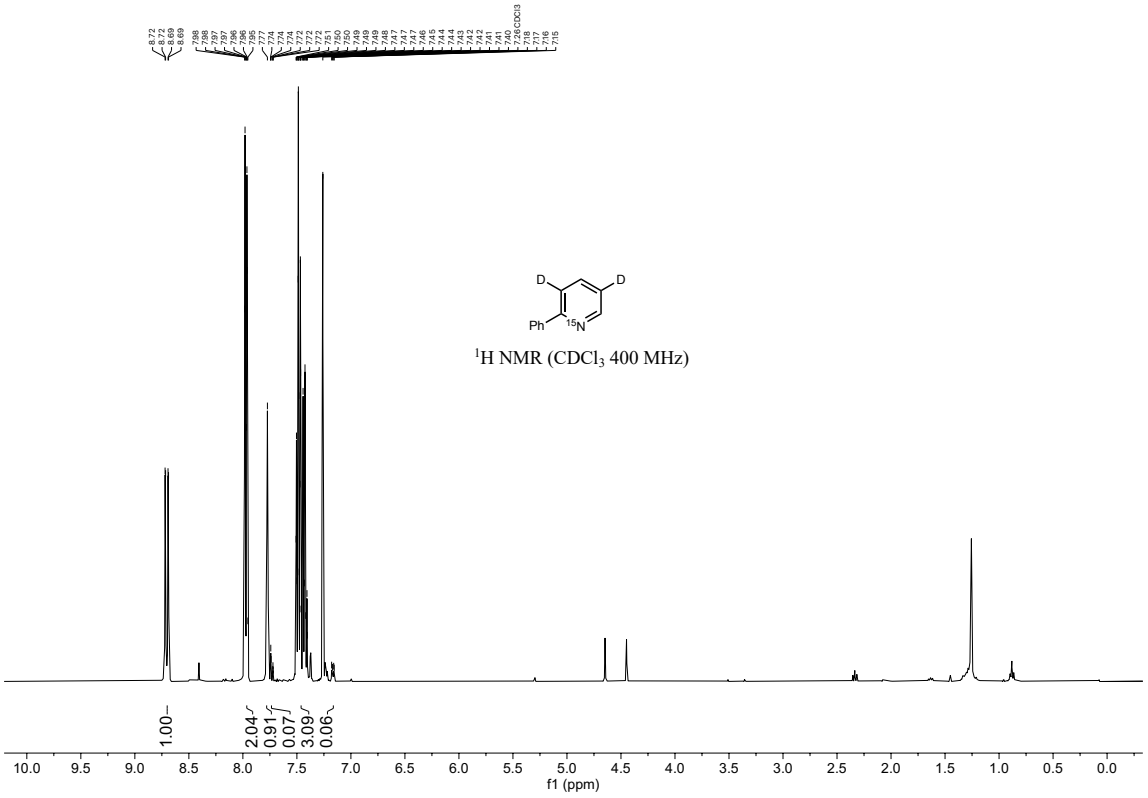
^{1}H NMR ($CDCl_3$ 400 MHz)



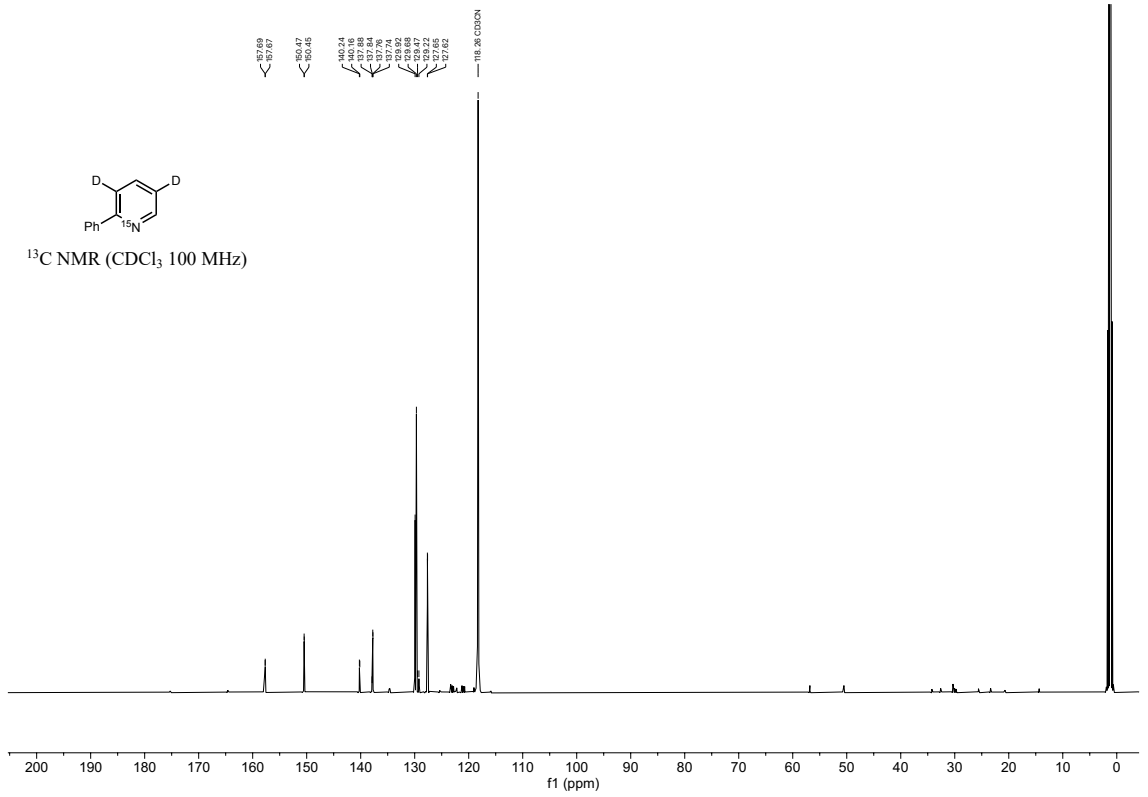
^{13}C NMR ($CDCl_3$ 100 MHz)



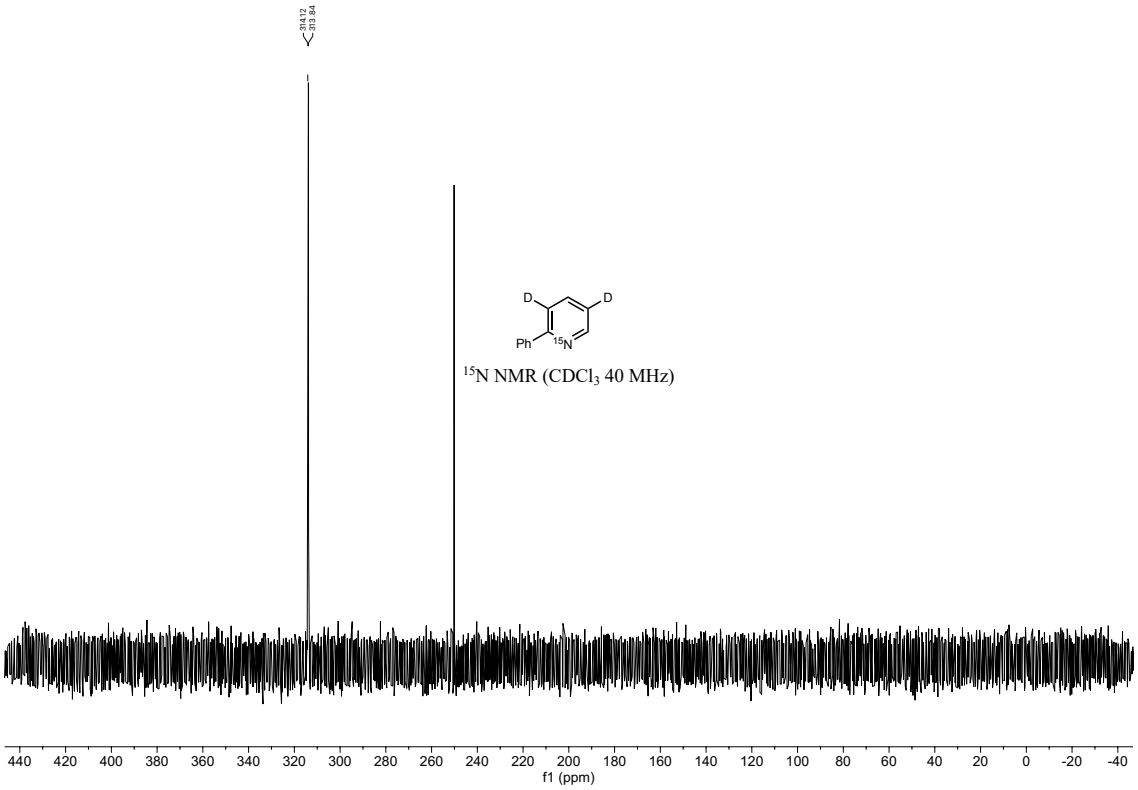
^{15}N NMR ($CDCl_3$ 40 MHz)



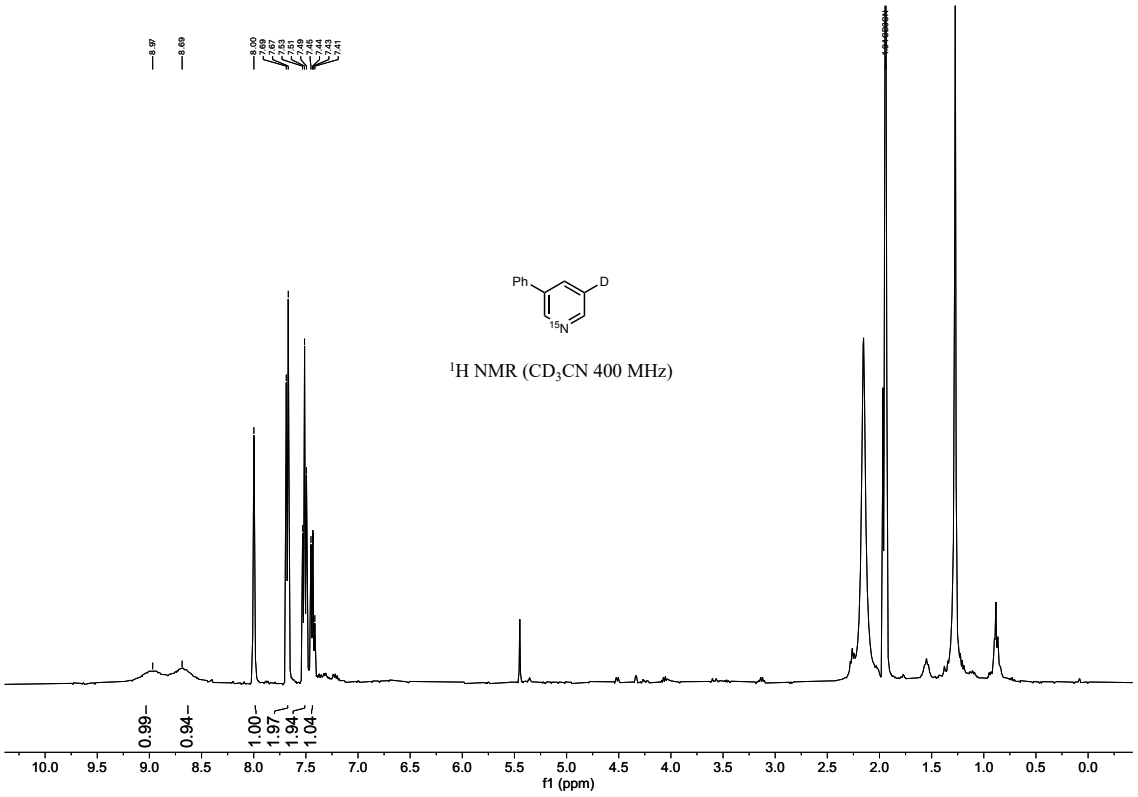
^{1}H NMR ($CDCl_3$ 400 MHz)



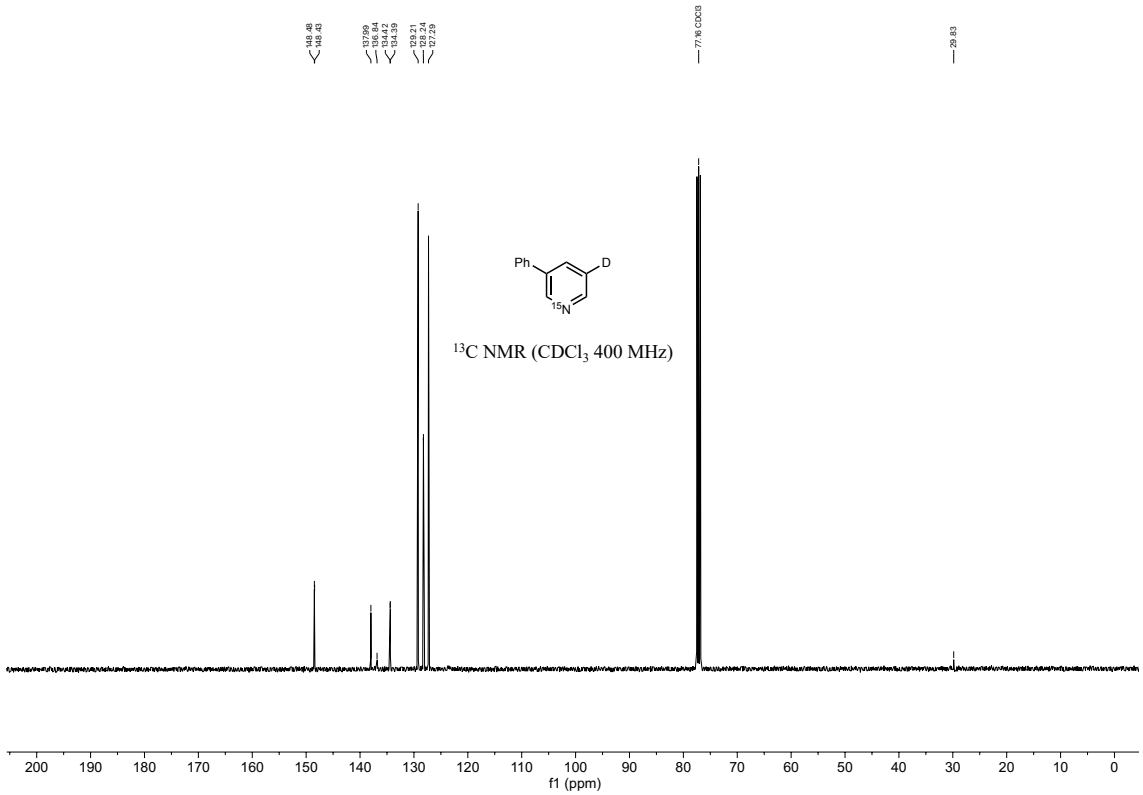
^{13}C NMR ($CDCl_3$ 100 MHz)



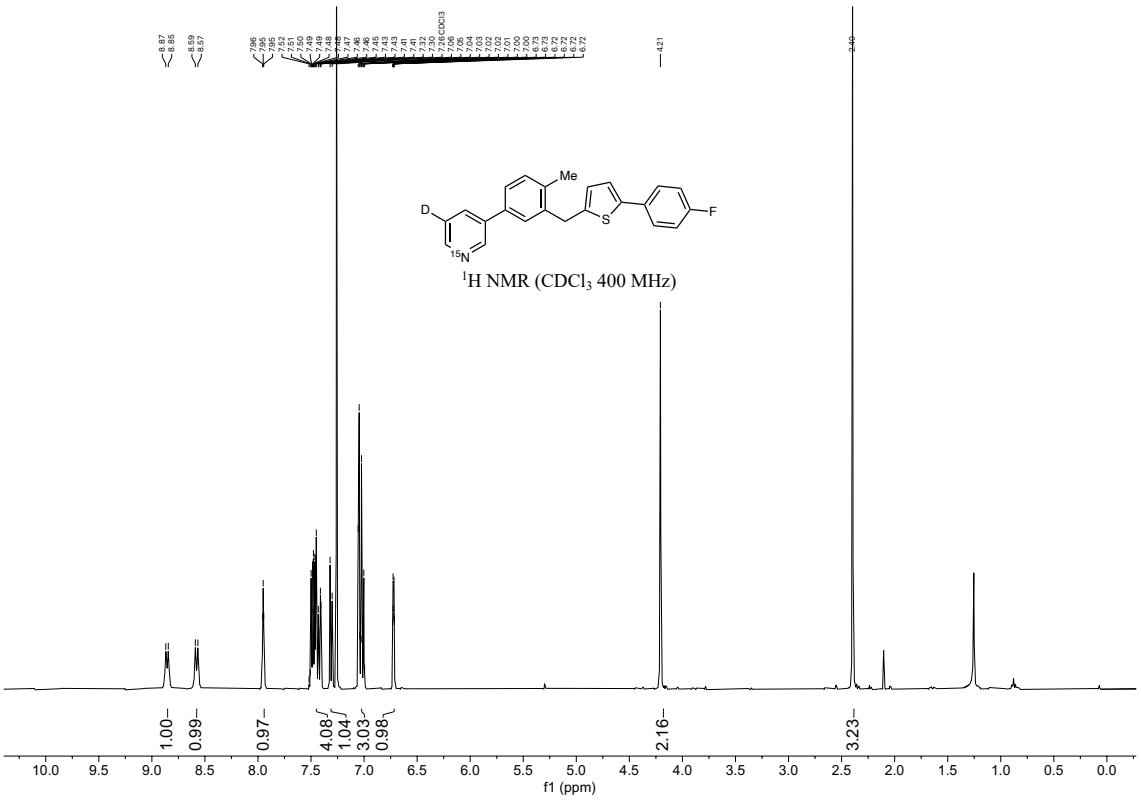
^{15}N NMR ($CDCl_3$ 40 MHz)



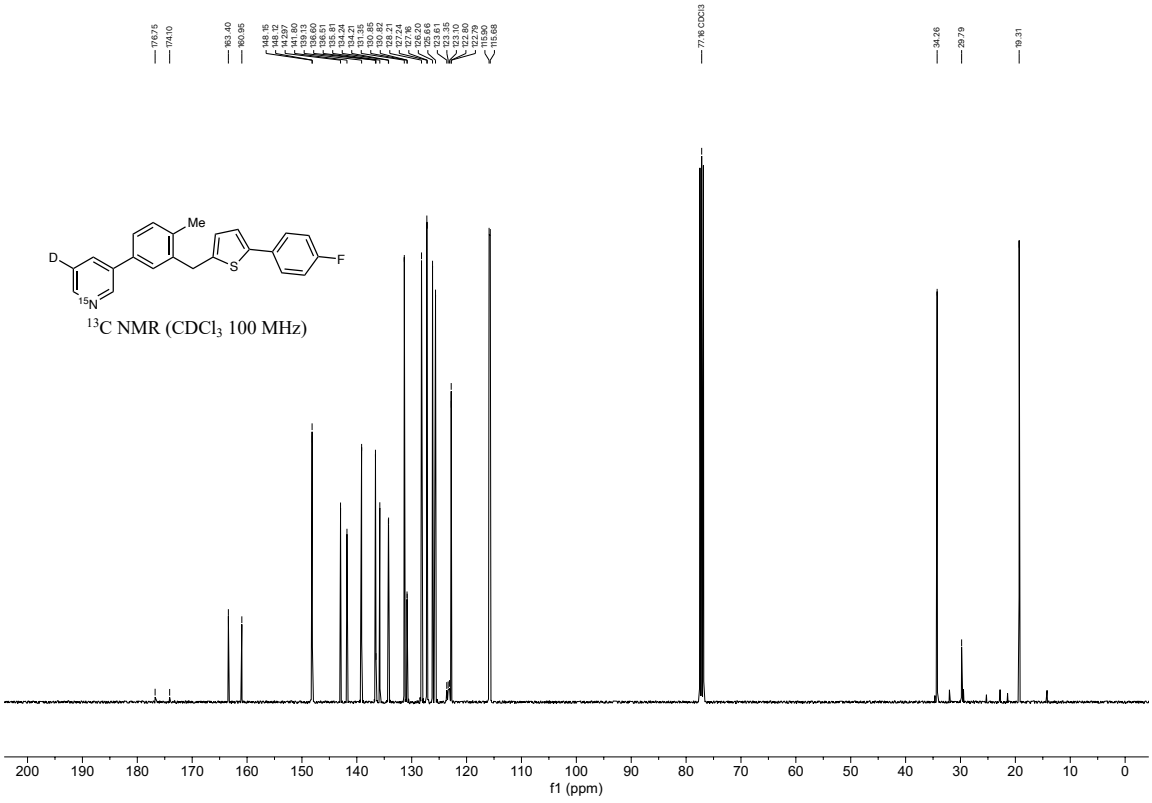
^{1}H NMR (CD_3CN 400 MHz)



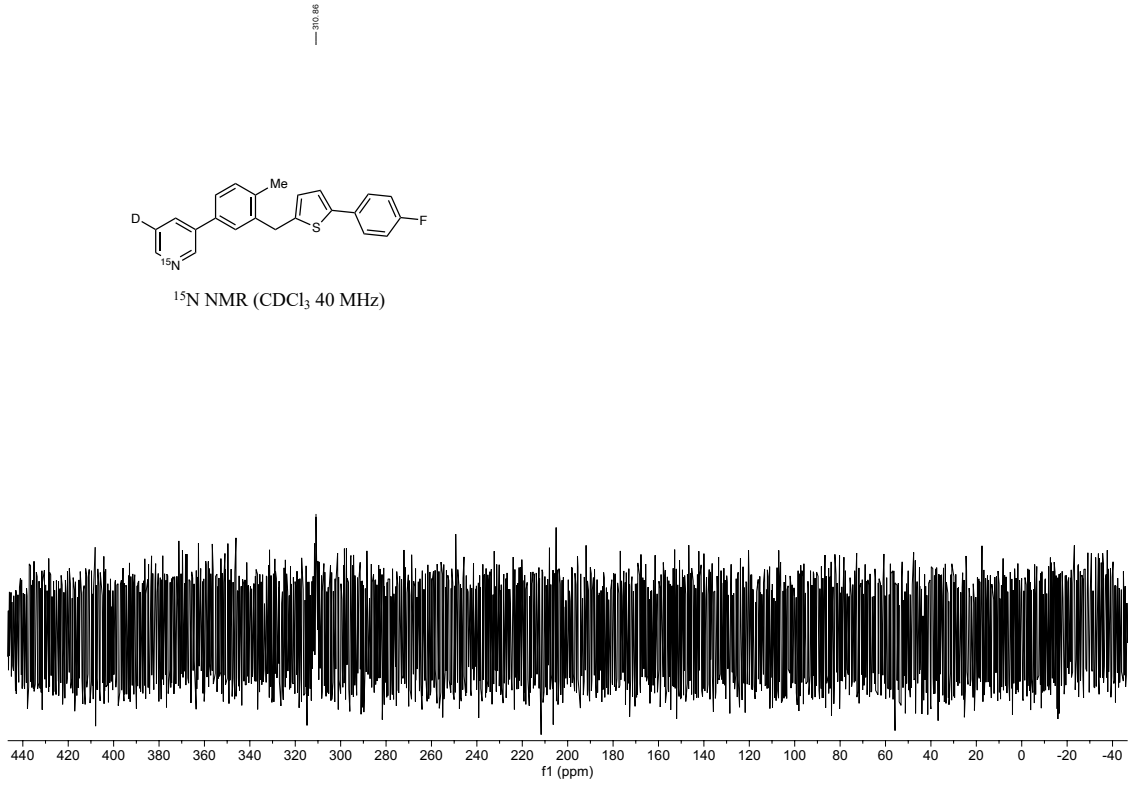
^{13}C NMR ($CDCl_3$ 400 MHz)



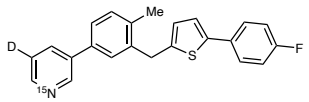
^{1}H NMR ($CDCl_3$ 400 MHz)



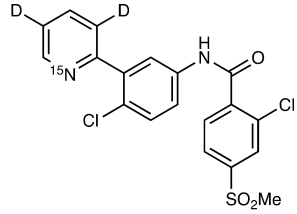
^{13}C NMR ($CDCl_3$ 100 MHz)



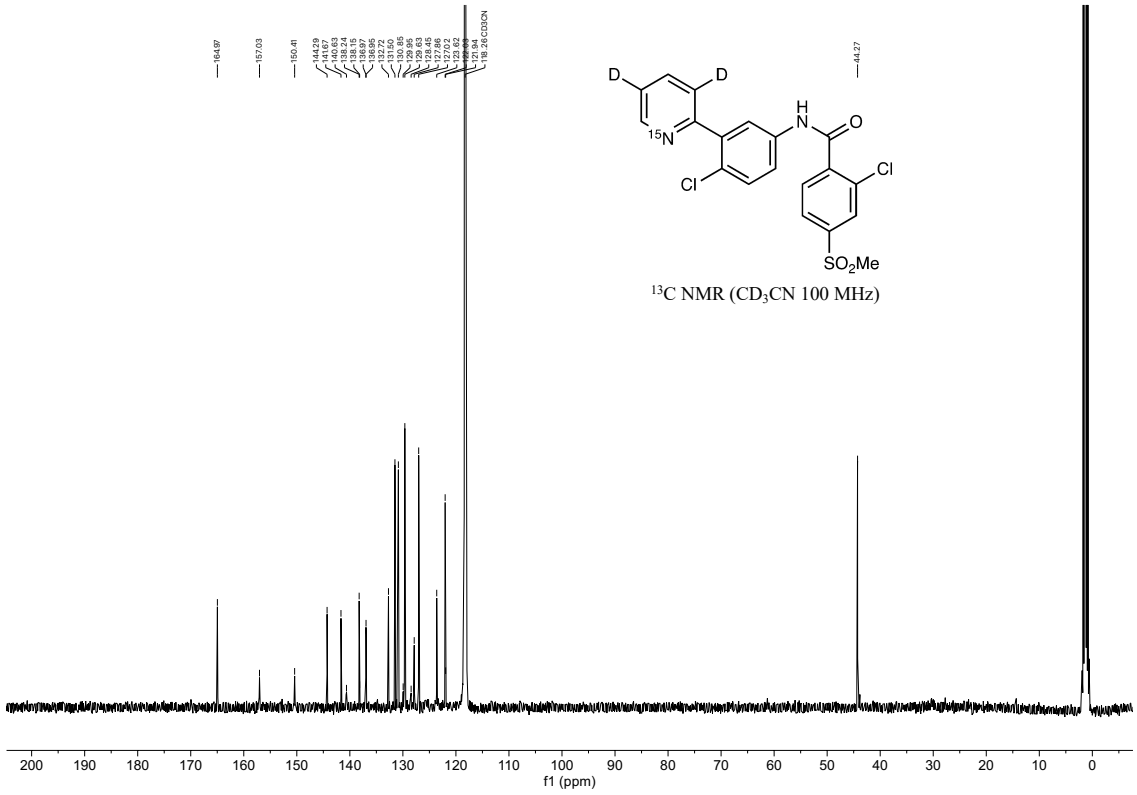
^{15}N NMR ($CDCl_3$ 40 MHz)



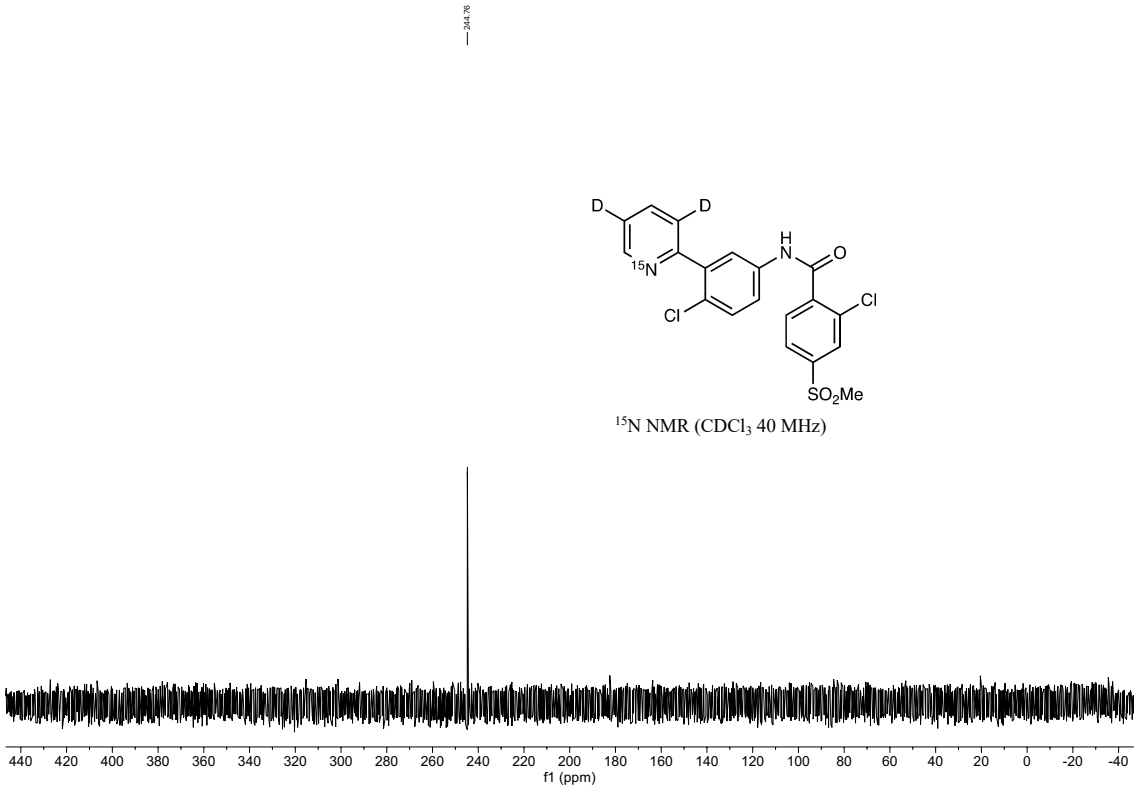
^{19}F NMR ($CDCl_3$ 375 MHz)



^{1}H NMR ($(CD_3)_2CO$ 400 MHz)



^{13}C NMR (CD_3CN 100 MHz)



^{15}N NMR ($CDCl_3$ 40 MHz)