DISSERTATION

SELECTIVE HALOGENATION OF PYRIDINES AND DIAZINES VIA UNCONVENTIONAL INTERMEDIATES

Submitted by

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ABSTRACT

SELECTIVE HALOGENATION OF PYRIDINES AND DIAZINES VIA UNCONVENTIONAL INTERMEDIATES

Pyridines and diazines are prevalent in pharmaceuticals, agrochemicals, ligands, and other organic materials, and it's vital that synthetic chemists can selectively functionalize these heterocycles. We have shown that heterocyclic phosphonium salts and Zincke imine intermediates can be used to regioselectively functionalize pyridine rings. This dissertation describes the development of these strategies with an emphasis on new approaches to selectively halogenate pyridines, which we view as a long-standing challenge in organic chemistry.

Chapter One introduces the importance of pyridines and diazines, as well as established methods and limitations in halogenating these azines. Chapter Two provides an overview of the synthesis and reactivity of heterocyclic phosphonium salts, and then describes a new strategy to access 4-halogenated pyridines via these reagents. Chapter Three examines further developments of heterocyclic phosphonium salts, including as how they can be used to selectively add amines and fluoroalkyl substituents to pyridines.

Chapter Four provides an overview of pyridine ring-opening reactions and then shows how this approach can be applied to selectively halogenate the 3-position of pyridines. Chapter Five describes how modifications to the ring-opening strategy can be used to change halogenation site-selectivity. This chapter also shows that the ring-opened intermediates can be used to form isotopically labeled pyridines and aniline derivatives.

ACKNOWLEDGEMENTS

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CHAPTER ONE

IMPORTANCE OF PYRIDINES AND HALOGENATION REACTIONS

1.1 Introduction to Pyridines and Diazines

Pyridines and diazines are prevalent in pharmaceuticals, agrochemicals, ligands, and other organic materials. A 2014 analysis of FDA-approved pharmaceuticals found that 59% of the 1086 small-molecule drugs examined contained a nitrogen heterocycle (*N*-heterocycle).[1,2] With 62 examples, pyridine was the second most common heterocycle, and its saturated counterpart, piperidine (72 examples), was the most common. Diazines such as pyrimidine and pyrazine were present in 16 and 5 examples, respectively. Figure 1.1 shows six pyridine-containing pharmaceuticals, spanning different levels of structural complexity and with different biological applications.

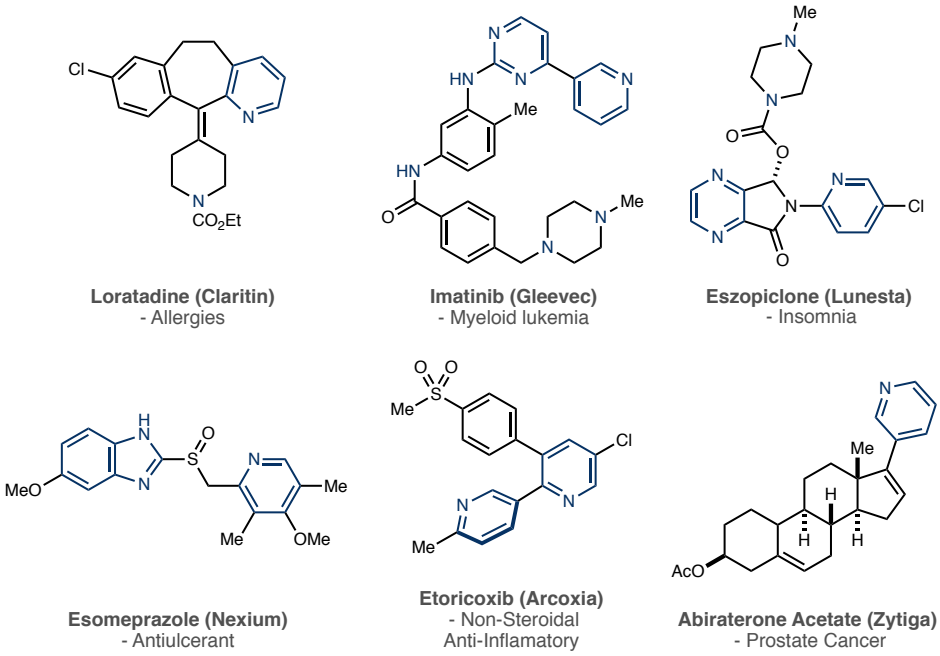

Figure 1.1. Examples of pyridine-containing pharmaceuticals.

The importance of the pyridine ring in pharmaceuticals is due to several factors.[3,4] The nitrogen atom's lone pair of electrons can engage in hydrogen-bonding interactions which can play a role in the binding between a pyridine-containing drug and its biological target. Compared to its piperidine, pyridine is more rigid, limiting the number of potential conformations a pyridine-containing drug can adopt, which in turn can lower the entropic cost of a drug binding to its target.[5] Compared to benzene, pyridine is more electron-deficient, making it more stable to oxidative metabolism by Cytochrome P-450 enzymes.[6] Additionally, it is more water-soluble than benzene rings, an important property for pharmaceuticals.[7]

1.2 Overview of Challenges in Pyridine Functionalization

Given the prevalence of azines in pharmaceuticals and agrochemicals, it's vital that synthetic chemists can access a variety of pyridine- and diazine-containing molecules. Many synthetic methods in the literature focus on making these heterocycles via *de novo* approaches, where the azine ring is built from acyclic non-azine starting materials.[8,9] Classical reactions in this category include the Hantzsch and Chichibabin pyridine syntheses, and while these approaches are important to the field of organic chemistry, they are sometimes impractical for medicinal chemists intending to rapidly derivatize an azine-containing lead compound.[10,11] For drug discovery applications, it's often most efficient to take an azine-containing starting material and diversify it into a variety of more complex molecules.[12] This approach to arene functionalization can be split into two categories: direct and indirect. Direct functionalization occurs on carbon-hydrogen (C-H) bonds, while indirect functionalization occurs from a prefunctiontionalized starting material, such as a carbon-halogen bond or an aryl boronic acid.

Direct functionalization of pyridines is often a challenge with existing methods. Many of the reactions that functionalize pyridine lack regiocontrol, giving mixtures of regioisomeric

products that can be a challenge to separate or characterize (**Figure 1.2**).[13,14] Metal-catalyzed reactions, which are fundamentally important to the field of organic chemistry, can often fail on pyridine-containing substrates due to an undesired ligation of the pyridine nitrogen atom to the metal center, which can deactivate the metal catalyst. Reactions that require strong oxidants can be problematic due to the potential oxidation of the pyridine's nitrogen to form the corresponding pyridine *N*-oxide.[15]

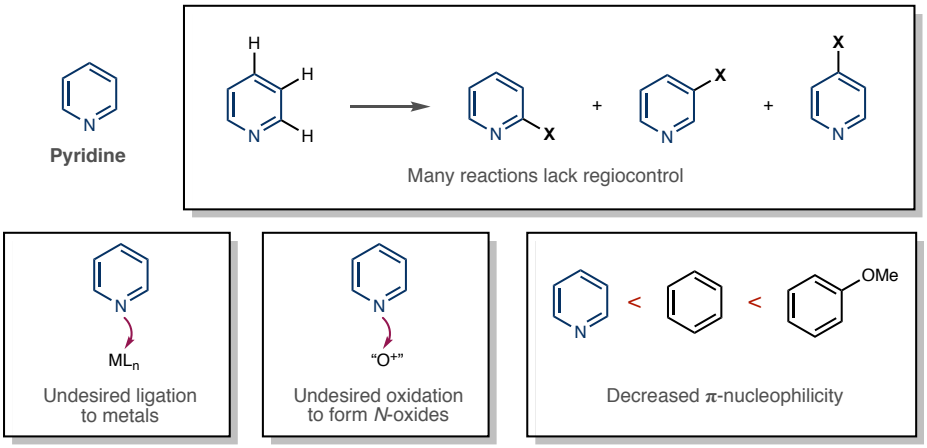

Figure 1.2. Overview of challenges in pyridine functionalization.

Perhaps most important to the content in this thesis is the decreased pi-nucleophilicity of pyridine compared to benzene and other electron-rich aromatics. The lone pair of electrons on the nitrogen atom is positioned perpendicular to the pi-system, rendering it incapable of donating into the aromatic ring. Additionally, electrophiles tend to react with the nitrogen atom first, forming a pyridinium cation that pulls electron density away from the aromatic ring. As a result, electrophilic aromatic substitution (EAS) reactions typically require harsh conditions on unbiased pyridine substrates, and these conditions are often incompatible with the more complex examples found in drug-like compounds. The intrinsic reactivity of unprotonated pyridine towards EAS has been estimated to be 10^7 less than benzene, comparable to nitrobenzene and anilinium salts (**Figure 1.3**).[15]

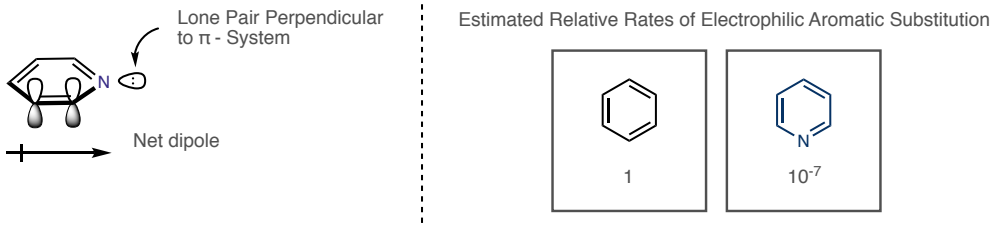

Figure 1.3. Reactivity of pyridine towards electrophilic aromatic substitution.

1.3 Existing Methods to Functionalize Pyridines

Classical approaches to functionalize pyridine include the Chichibabin amination and the Minisci reaction (**Figure 1.4**). In 1914, Chichibabin showed that pyridines react with sodium amide ($NaNH_2$) to form 2-aminopyridine products.[16] The harsh sodium amide reagent and the necessity for high temperatures limit the generality of this reaction significantly. In 1971, Minisci showed that alkyl radicals will add to pyridine rings, typically giving mixtures of 2- and 4-functionalized products.[17] Pyridines react with metalation reagents such as organolithiums to form organometallic intermediates that can then be trapped with various electrophiles. Without a directing group, this approach can be used to functionalize the 2-position of pyridines.[18] To functionalize the 3- or 4-position, a directing group is typically needed. The metalation reagents employed are strong bases that can react in other undesired ways, and the requirement for a preinstalled directing group can be impractical for the functionalization of many pyridine examples.[19]

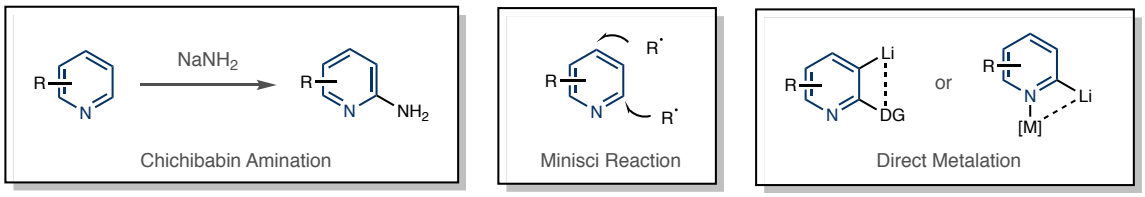

Figure 1.4. Classical approaches to pyridine functionalization.

In recent years, new reactions have been developed to functionalize pyridines and improve the scope and conditions for the classical approaches (**Figure 1.5**). Developments to the Minisci

reaction have been made, significantly improving the scope of available radical precursors. One example of an advance in this field is the methylation of pyridines and other azines using methanol and a methylation reagent under photoredox catalysis conditions.[20] Despite these advances, site-selectivity and difunctionalization is still a major issue for reactions in this class. Inspired by the classical Chichibabin reaction, the Hartwig lab developed a strategy to fluorinate the 2-position of pyridines and pyrimidines using an excess of silver(II) fluoride.[21] The 2-fluoropyridine products formed are active towards nucleophilic aromatic substitution (S_NAr), enabling a variety of further bond transformations. This approach was used to add alcohols, thiols, amines, and cyanide to the 2-position of pyridines and pyridine-containing pharmaceuticals.[22] The development of iridium-catalyzed borylation and silylation has significantly advanced the field of pyridine functionalization. Regioselectivity of these reactions are often determined by sterics, and on unsubstituted pyridine gives a statistical mixture of 3- and 4-substituted products (2:1 mixture). [14] The boryl and silyl functional groups installed can be converted into other functional groups, enabling the rapid diversification of a pyridine-containing molecule.[23] However, selective functionalization of one position with this approach is dependent on the specific substitution pattern of the pyridine.

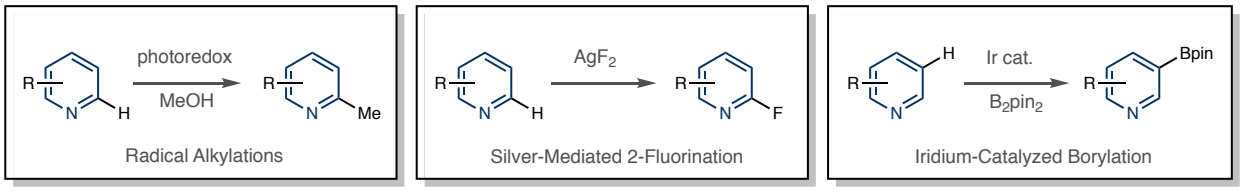

Figure 1.5. Modern developments in pyridine functionalization.

1.4 Introduction to Halogenated Arenes

For any class of aromatics, it's fundamental that synthetic chemists can access halogenated derivates. Haloarenes are vital to synthetic chemists for a variety of reasons. First, these motifs are inherently valuable in pharmaceuticals and agrochemicals (**Figure 1.6**).[24] Nearly 200 FDA-

approved pharmaceuticals contain an aryl chloride component, with Xanax, Spravato, and Abilify being famous examples.[25] Pharmaceuticals containing aryl bromide or aryl iodide components are less common but still present in examples such as Mirvaso and Nexterone. Incorporation of a halogen in place of a hydrogen atom can often increase the lipophilicity of a drug, which can improve cell permeability. Except for aryl fluorides, aryl halides can engage in halogen-bonding interactions, a noncovalent interaction arising from an electrophilic region (sigma-hole) on the halogen atom.[26–28]

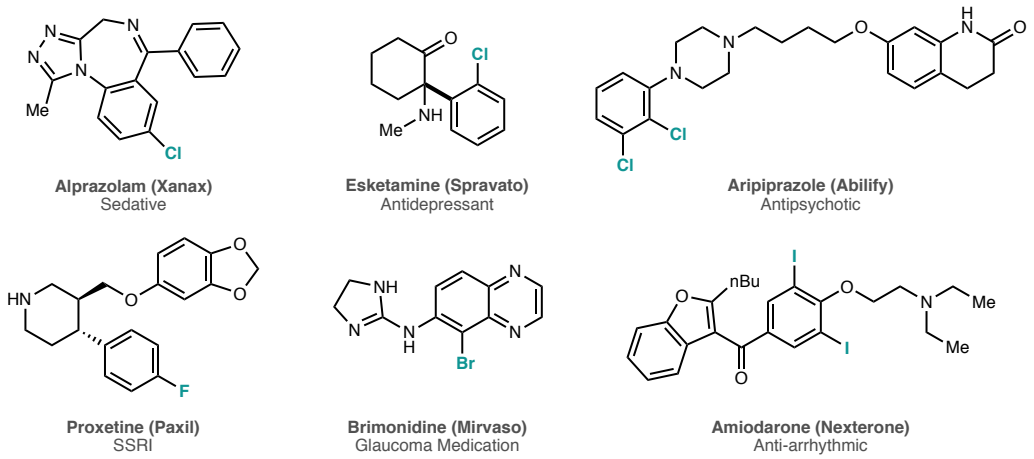

Figure 1.6. Examples of aryl halide pharmaceuticals.

Beyond being motifs found in pharmaceuticals and agrochemicals, aryl halides are useful synthetic intermediates in the synthesis of complex molecules (**Figure 1.7**). Aryl halides react in numerous ways and the halide atom can be replaced by a selection of other functional groups. They are often a fundamental component in metal-catalyzed cross coupling reactions, as metals can oxidatively insert into carbon-halogen bonds on aromatics.[29–31] The 2010 Nobel Prize in Chemistry was awarded to Suzuki, Negishi, and Heck for their pioneering work in developing this area.[32] Aryl halides undergo metal-halogen exchange to form organometallic intermediates (such as Grignard reagents and organolithiums) that can then react with an array of electrophiles.[33,34] Displacement of an aryl halide with a nucleophile can occur via S_NAr processes, although this is

typically performed on electron-deficient arenes.[35,36] Reaction conditions can promote the formation of aryl radical intermediates, enabling reactions with other aromatics, alkenes, and iminiums.[37] The prevalence of haloarene intermediates in medicinal chemistry journals was showcased in a 2014 publication which found that four of the top 20 most frequently published reactions in this field used an aryl halide precursor.[38] Additionally, installation of a halogen atom from an aromatic C-H bond was also included in this list.

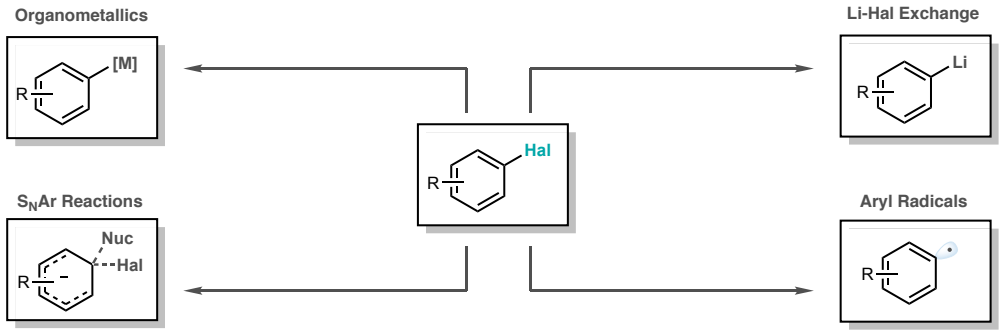

Figure 1.7. Reaction platforms for aryl halides.

1.5. Existing Strategies to Halogenate Arenes

Synthetic chemists have developed a variety of distinct approaches to access halogenated arenes (**Figure 1.8**). A classical strategy is electrophilic aromatic substitution (EAS), where nucleophilic arenes react with electrophilic halogenation reagents.[39–41] The strategy works best on electron-rich aromatics, and site-selectivity is often determined by inherent properties of the arene starting material. Organometallic intermediates derived from the stoichiometric metalation of aromatics can be trapped with electrophilic halogenation reagents.[42–44] Metal-catalyzed halogenation protocols have been developed that rely on functional groups to direct C-H insertion to a specific site on an aromatic ring.[45–48] These metal-catalyzed halogenations often rely on expensive palladium catalysts and require high temperatures due to the challenging C-H insertion step. A valuable multistep process is to first perform iridium- or rhodium-catalyzed borylation or silylation, as these functionalized arenes can then react further with copper halide salts or

electrophilic halogenation reagents to form aryl halide products.[49] As mentioned in Section 1.3, the substitution pattern of the substrate controls site-selectivity.[50,51]

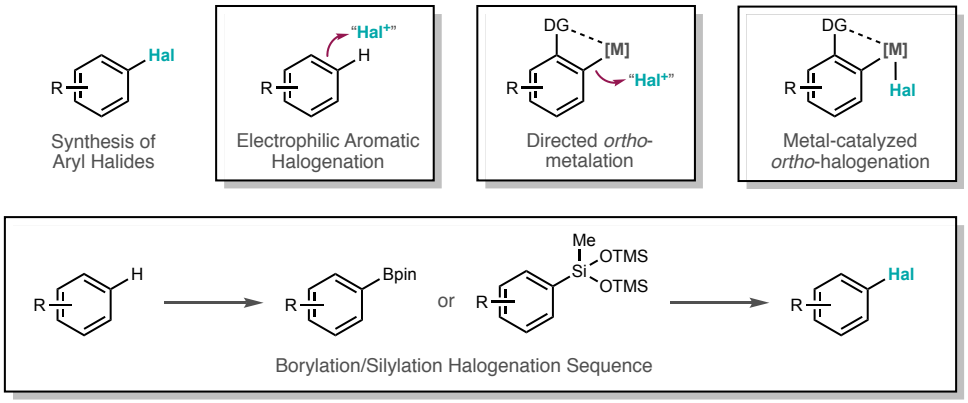

Figure 1.8. General strategies to halogenate arenes.

1.6 Existing Strategies to Halogenate Pyridines

Given the importance of pyridines and halogenated aromatics, it's fundamental that synthetic chemists can convert pyridines to halopyridines. Examples of pharmaceuticals and agrochemicals with halogenated azines are shown in Figure 1.9.[52] Despite all the above strategies being applicable to pyridines, it remains a synthetic challenge to selectively halogenate pyridines, particularly on complex molecules.

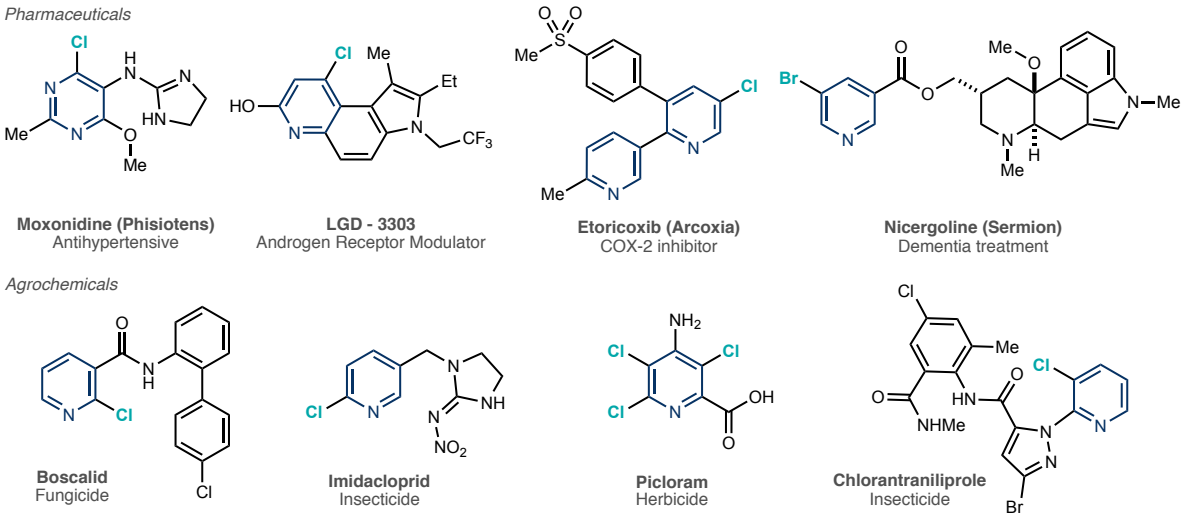

Figure 1.9. Examples of halogenated azine pharmaceuticals and agrochemicals.

The conditions to brominate pyridine via EAS conditions require heating pyridine with elemental bromine and fuming sulfuric acid at high temperatures (>130 °C).[53] This approach can be unselective between the 3- and 5-position on pyridines that are unsymmetrical, and significant amounts of dihalogenated products can be observed (**Figure 1.10**). On 2,4-dimethylpyridine, the observed ratio of 3-brominated pyridine **1.2** to 5-brominated pyridine **1.3** is 1.6:1.[54]

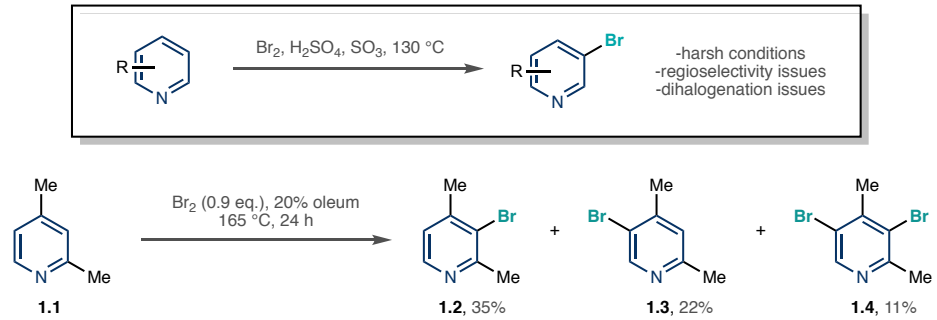

Figure 1.10. Conditions for electrophilic halogenation of pyridines.

Lithiation and electrophilic trapping of halogenation reagents at the 2-position of pyridines occurs when a mixture of *n*-butyllithium (*n*BuLi) and dimethylaminoethanol (DMAE) are used. Lithiated DMAE can coordinate to the pyridine nitrogen and then direct an equivalent of *n*Buli to the 2-position (**Figure 1.11, top**). This reaction is still *ortho* selective when there are directing groups present on the pyridine ring. Lithiating pyridines at the 3- or 4-position typically requires preinstalled directing groups and alternative metalation conditions.[18] These lithiation strategies have been used to access chlorinated derivatives of nicotine (**1.5, 1.7, 1.8**) (**Figure 1.11, bottom**).[55]

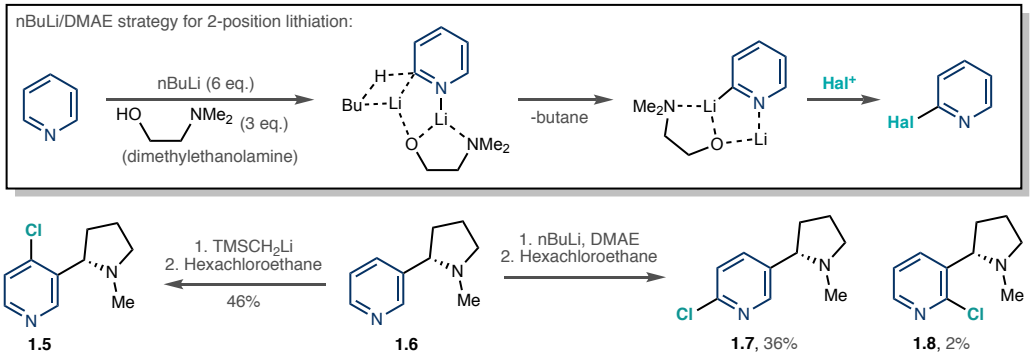

Figure 1.11. Halogenation of pyridines via lithiation/trapping sequences.

One pyridine-specific approach is to use pyridine *N*-oxides (**Figure 1.12**), which can be formed by reacting pyridines with strong oxidants such as MCPBA or dimethyldioxirane. Pyridine *N*-oxides are useful as these reagents can be both more nucleophilic and electrophilic than pyridine. The simple pyridine *N*-oxide **1.9** will react with phosphoryl chloride to give 2-chloropyridine **1.10**.[56] Accessing 4-halopyridines is even more challenging and relies on a multi-step sequence where a pyridine *N*-oxide is first nitrated at the 4-position under harsh electrophilic nitration conditions.[57,58] An example of this is shown on 2,2'-bipyridine, and the nitrated pyridine *N*-oxide **1.12** can be converted to the 4-bromo pyridine product **1.13** using phosphorus tribromide at reflux temperatures.

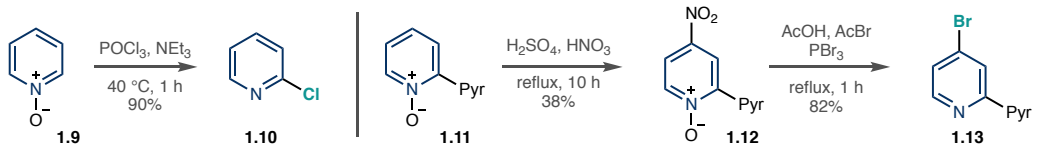

Figure 1.12. Halogenation of pyridine via pyridine *N*-oxide intermediates.

An additional reaction has been published that shows pyridine reacts with thionyl chloride at high temperatures to form 4-chloropyridine, but this reaction hasn't been shown on substituted pyridines (**Figure 1.13**).[59] The formation of 1,4'-bipyridinium **1.15** and **1.16** intermediates shows that an equivalent of pyridine is sacrificed in this protocol, and that it wouldn't be a viable strategy on complex pyridine examples.

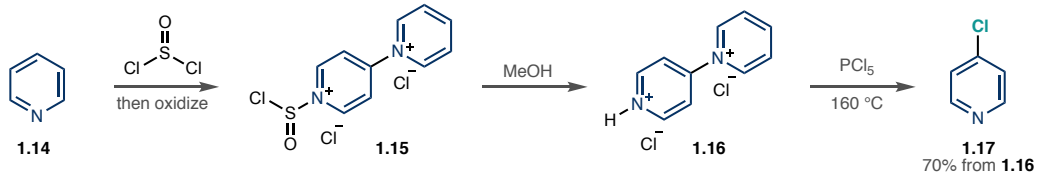

Figure 1.13. Halogenation of pyridine via 1,4'-bipyridinium salts.

Borylation/halogenation strategies have been shown to functionalize the 5-position of pyridines that already have a 3-position substituent, such as 3-methylpyridine **1.18** being converted

to the 5-chlorinated product **1.19** (**Figure 1.14**).[50] Additionally, 2,6-disubstituted pyridines can undergo selective borylation/halogenation at the 4-position, and this can be used to form chloropyridine **1.21** from 2,6-lutidine (**1.20**). Iridium-catalyzed borylation has been shown on more complex examples, such as the azine ring on Loratadine, although subsequent halogenation steps haven't been published.[60] Pyridines with a boryl substituent at the 2-position can undergo undesired protodeboronation strategies, making it a challenge to functionalize this position via a borylation strategy.[61]

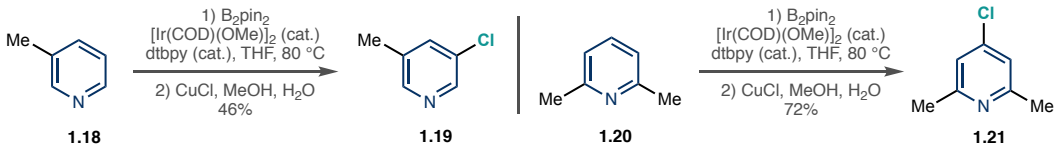

Figure 1.14. Halogenation of pyridine via pyridine *N*-oxides and iridium-catalyzed borylation sequences.

1.7 Conclusion

This chapter intends to establish the importance of pyridines and halogenated pyridines, as well as the strategies chemists use to synthesize and derivatize these compounds. The prevalence of azines in pharmaceuticals and the utility of halopyridines as synthetic intermediates is the basis of the work presented in the remaining chapters of this dissertation, which is focused on merging these two areas together in the development of new strategies to halogenate azines with high site-selectivity.

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CHAPTER TWO

HALOGENATION OF PYRIDINES VIA HETEROCYCLIC PHOSPHONIUM SALTS

2.1 Chapter Overview

This chapter will detail earlier work by the McNally lab to develop pyridyl phosphonium salts into useful reagents for pyridine 4-position functionalization, and then describe a novel method to synthesize 4-halogenated pyridines from C-H precursors using designed phosphine reagents. This two-step process is highly site-selective and enables access to many 4-chlorinated, brominated, and iodinated pyridines that otherwise might be a challenge to make. My coworker, Ren Rong Liu, assisted in the scope investigation. Juan Alegre-Requena and Rob Paton carried out computational analysis to better understand the reaction mechanism. Work presented in this chapter led to a publication in the Journal of the American Chemical Society.[1]

2.2 Introduction to Heterocyclic Phosphonium Salts

Due to limitations in existing methods to functionalize pyridines and other azines, the McNally group has been interesting in developing advancements in this area.[2] A major research program has been the development of pyridyl phosphonium salts as useful reagents for pyridine functionalization. This area is based on the exciting observation that triphenylphosphine reacts with *N*-Tf pyridiniums with excellent 4-position selectivity to form phosphonium salt products. The triphenylphosphine substituent can then be viewed as a versatile functional handle that enables a suite of subsequent transformations, allowing for the synthesis of functionalized pyridine and other azine products (**Figure 2.1**).

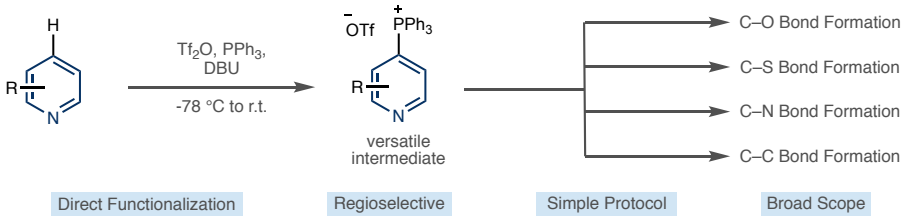


Figure 2.1. Pyridine 4-position functionalization strategy via pyridyl phosphonium salt intermediates.

The formation of these phosphonium salts is easy to run and uses reagents that are common in synthetic labs. Pyridine (**2.1**) is dissolved in dichloromethane, cooled to -78 °C, and then trifluoromethanesulfonic anhydride (Tf_2O), triphenylphosphine, and an organic base are sequentially added. Mechanistically, addition of the phosphine to *N*-Tf pyridinium **2.2** results in a 1,4-dihydropyridine intermediate (**2.3**), and the organic base, typically 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triethylamine (Et_3N), will eliminate a triflyl anion to rearomatize the pyridine ring, forming pyridyl phosphonium salt **2.4** (**Figure 2.2**). These salts are easy to isolate via precipitation in diethyl ether, making this reaction simple and quick to perform, and the products are bench-stable free-flowing powders. Pyridyl phosphonium salts were initially reported by Anders in the 1980s, but only on a limited set of examples and few derivatizations of these salts were examined.[3–6]

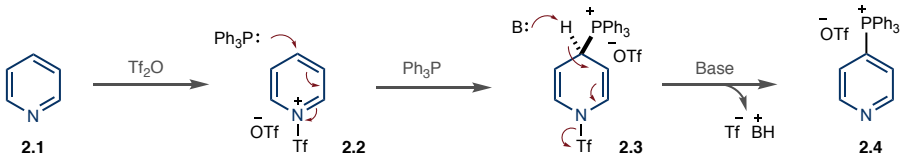
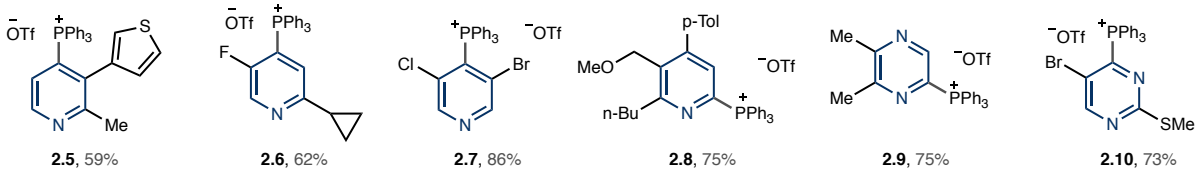


Figure 2.2. Mechanism for phosphonium salt formation.

Coworkers in the McNally group showed that these phosphonium salts could be formed on a variety of pyridine substrates with different substitution patterns (**Figure 2.3**). Even 3,5-disusbtituted pyridines will selectively react at the 4-position, such as in the formation of 3,4,5-trisubstituted pyridine **2.7**. When the 4-position is blocked by a carbon bearing substituent or a halide, then phosphonium salt formation can occur at the 2-position, and this has been shown to

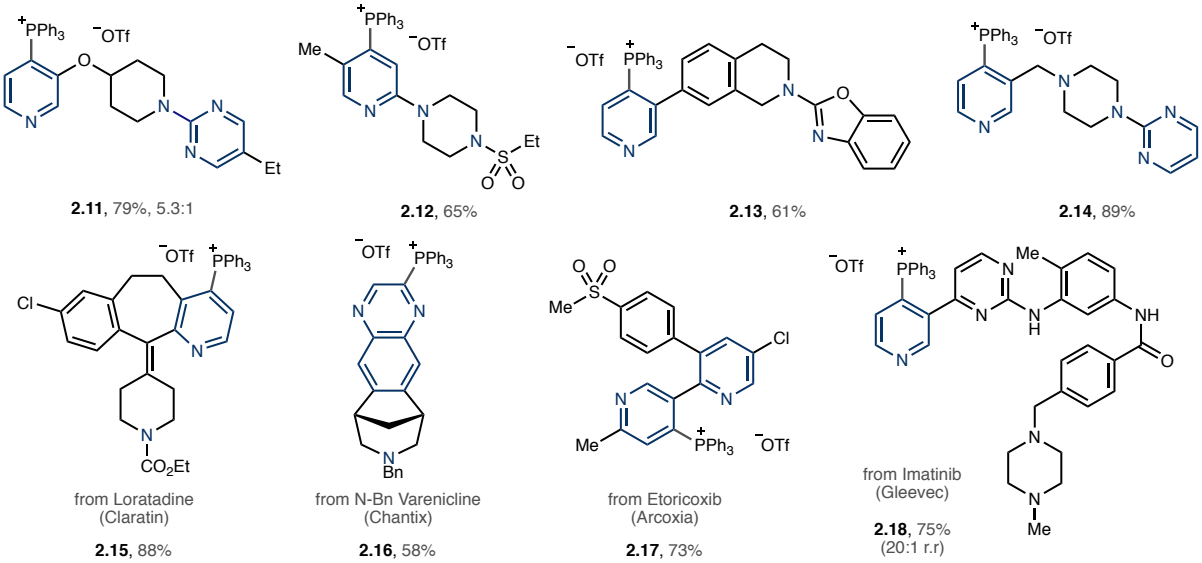
make tetrasubstituted pyridine products such as **2.8**. Additionally, the reaction works on other monoazines such as quinolines and isoquinolines, as well as diazines such as and pyrazines and pyrimidines to form phosphonium salts **2.9** and **2.10**.



2.5, 59% **2.6**, 62% **2.7**, 86% **2.8**, 75% **2.9**, 75% **2.10**, 73%

Figure 2.3. Selected scope of building block phosphonium salts.

Beyond simple building block azines, the reaction also works on a selection of complex drug-like fragments and pharmaceuticals (**Figure 2.4**). Substrates with multiple azines can still result in the selective phosphonium salt formation for one position, as seen in examples **2.11, 2.14,** and **2.17**. Selectivity here is due to selective triflic anhydride activation of the least sterically hindered pyridine nitrogen.[7] Notably, even the complex polyazine Gleevec still undergoes phosphonium salt formation to form **2.18** in high yield, and the reaction gives >20:1 site selectivity for the pyridine ring over the pyrimidine ring.



2.11, 79%, 5.3:1 **2.12**, 65% **2.13**, 61% **2.14**, 89%

2.15, 88% **2.16**, 58% **2.17**, 73% **2.18**, 75% (20:1 r.r)

Figure 2.4. Selected scope of complex phosphonium salts.

2.3 Reactions of Heterocyclic Phosphonium Salts

In the initial report by Hilton et al., the phosphonium salts were shown to react with alkoxide nucleophiles to form heteroaryl ether products such as **2.19** (**Figure 2.3, top**).[2] This reaction was performed using small building-block pyridines and also pharmaceuticals that contain azine rings. Two mechanisms were proposed for the nucleophilic displacement of the phosphine (**Figure 2.3, bottom**). One is a direct S_NAr pathway where the alkoxide attacks the pyridine initially, forming a dearomatized intermediate that rearomatizes by eliminating out triphenylphosphine as a leaving group. The other is a ligand-coupling mechanism where the alkoxide attacks the phosphorus atom to form a P(V) phosphorane, that then undergoes a reductive elimination-type step to migrate the alkoxide to the pyridine atom. Since the time of publication, experimental and computational evidence has been found that suggests the ligand-coupling mechanism to be operative for alkoxide addition.

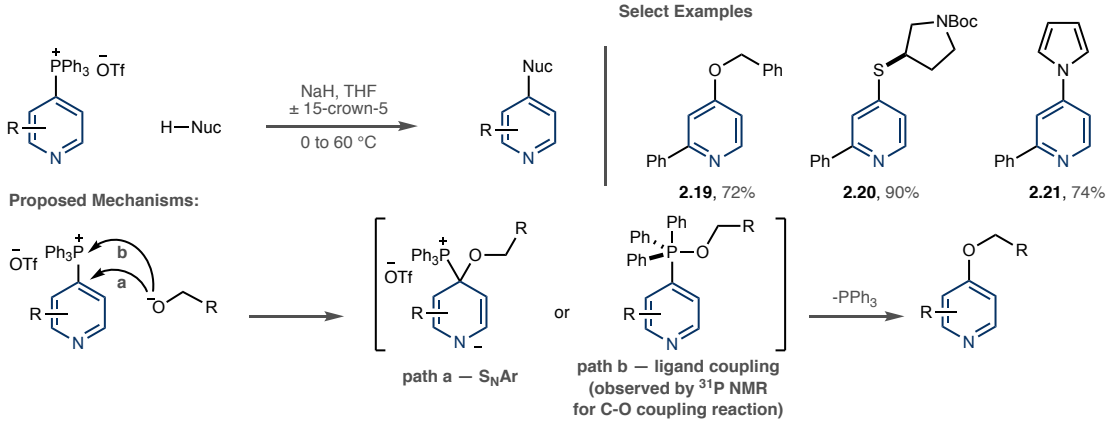


Figure 2.5. Nucleophilic reactions of pyridyl phosphonium salts and comparison of S_NAr and ligand coupling pathways.

Coworkers have found that other nucleophiles also react with pyridyl phosphonium salts. Anderson et al. showed that the original etherification conditions could be modified to install heteronucleophiles such as phenols, thiols , thiophenols, secondary anilines, and various endocyclic nucleophiles (**2.20, 2.21**).[8,9] Patel et al. showed that sodium azide will react with pyridyl

phosphonium salts to form 4-iminophosphorane products (**Figure 2.6**).[10] The azide first displaces the phosphine to form an organoazide intermediate that then reacts with the triphenylphosphine leaving group to form the iminophosphorane. In the case of tetrahydroquinoline phosphonium salt **2.22**, the resulting phosphonium salt **2.23** was converted to the corresponding 4-NH_2 (**2.24**), 4-(allyl)amino (**2.25**), and 4-isothiocyanate (**2.26**) pyridine via exposure to different sets of reaction conditions.

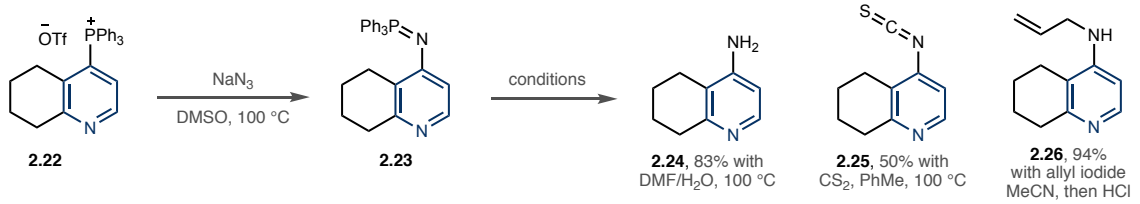


Figure 2.6. Reaction of azide nucleophile with pyridyl phosphonium salts and derivatizations of the iminophosphorane product.

Outside of nucleophilic additions, other reaction manifolds were explored for the phosphonium salts. Koniarczyk et al. showed that pyridylphosphonium salts react with carbonate bases to form a P(V) intermediate that behaves as a pyridyl-anion equivalent (**Figure 2.7**).[11] These intermediates can be trapped with electrophiles, and this approach was used to deuterate pyridines, forming product **2.27** and deuterated nicotine derivative **2.28**. Additionally, this strategy was applied to make tritiated pyridines using tritiated methanol precursor.

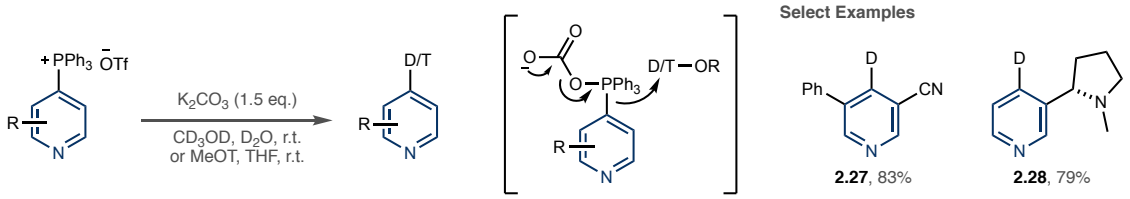


Figure 2.7. Deuteration of pyridines via carbonate-fragmentation pathway.

Xhang et al. showed that pyridyl phosphonium salts can be used as reagents for metal-catalyzed cross coupling reactions (**Figure 2.8**).[12,13] A nickel-catalyzed arylation with aryl boronic acids produces 4-aryl pyridines and a cobalt-catalyzed alkylation with alkyl zinc reagents produces

4-alkyl pyridines. Arylated pyridine **2.29** and alkylated pyridine **2.30** were synthesized with these strategies. Outside the McNally lab, the Feng group showed that these pyridyl phosphonium salts can be arylated with aryl iodides under palladium-catalyzed conditions, and the Shen group has since shown the arylation of phosphonium salts using aryl Grignard reagents as nucleophilic coupling partners.[14,15]

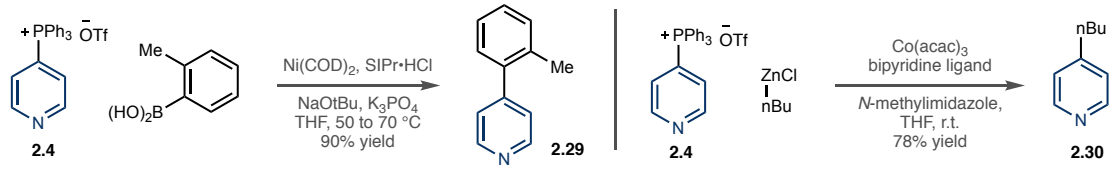


Figure 2.8. Arylation and alkylation of heterocyclic phosphonium salts.

Ligand-coupling reactions to form biaryls were developed by Hilton (**Figure 2.9**). In the initial publication, a three step protocol was used to couple two pyridines to form 4,4'-bipyridines from two corresponding C-H bonds.[16] The phosphonium salt forming conditions were modified to use a "fragmentable phosphine" in place of triphenylphosphine, and the resulting phosphonium salt undergoes base-elimination to form a 4-pyridyl phosphine with methyl acrylate as a byproduct. The 4-pyridyl phosphine is then reacted with a second pyridine to form a 4,4-bis-heterobiaryl phosphonium salt. In the presence of acid and a nucleophile (in this case, an alcohol solvent), P(V) ligand-coupling is triggered and a 4,4-bipyridine product forms. The importance of this discovery stems from the existing challenges in making bipyridine products and the lack of existing reactions that utilize P(V) ligand-coupling in productive ways.

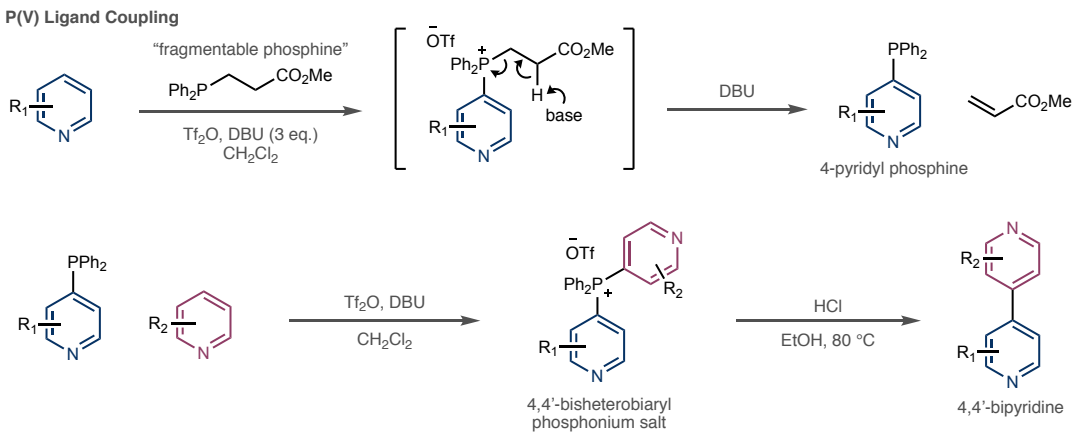


Figure 2.9. Ligand-coupling of phosphonium salts to form bipyridine products.

A follow-up to this work was published by Boyle et al., who showed that another way to form pyridyl phosphines or phosphonium salts is via S_NAr from chloropyridine precursors using either diphenylphosphine or a pyridyl phosphine, respectively, as the nucleophile (**Figure 2.10**).[17] Using this approach, a coupling between two different chloropyridines can be realized. While not having the advantage of starting from a pyridine's C-H bond, this work expands the ligand-coupling scope significantly. This approach tolerates functional groups that are typically incompatible with triflic anhydride activation, such as alcohols, alkyl amides, 2-trifluromethyl pyridines, and pyridines that are 2,6-disubstituted. Additionally, this approach enables the synthesis of 2,2'-bipyridines, 2,4'-bipyridines, as well as other bis-azine biaryls that are a challenge to make via existing cross-coupling methods.

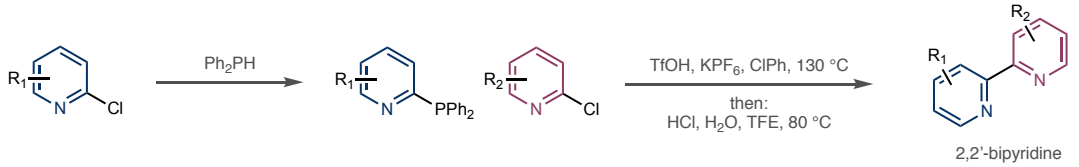


Figure 2.10. S_NAr ligand-coupling approach to synthesize 2,2-bipyridines.

2.4 Chlorination of Heterocyclic Phosphonium Salts

The conversion of pyridyl phosphonium salts into 4-halopyridine products was pursued due to the value of halopyridine products, as described in Chapter One. Initial approaches to this

involved reacting triphenylphosphonium salts with nucleophilic halide or metal halide reagents. These reactions were typically unsuccessful, giving trace amounts of the desired 4-halopyridine products and leading to decomposition of the starting material. Base-mediated electrophile trapping was also explored with various electrophilic halogenation reagents, but the reaction was never high yielding, and many simple substrates didn't work at all.

Halogenation of pyridyl phosphonium salts was unexpectedly observed by Hilton et al. while studying the bis-heterobiaryl phosphonium salt ligand-coupling reaction (**Figure 2.11**).[16] The ligand-coupling step was typically performed using by reacting the bis-heterobiaryl phosphonium salts with two equivalents of HCl at 80 °C in ethanol. In some cases, this procedure led to unwanted 4-chloropyridine byproducts instead of the desired 4,4'-bipyridine product. The chlorination was sometimes high yielding and also selective between the two pyridines bound to the phosphorus atom. Notably, Loratadine salt **2.31** selectively forming chloropyridine **2.33** in 58% yield instead of the desired bipyridine **2.32**.

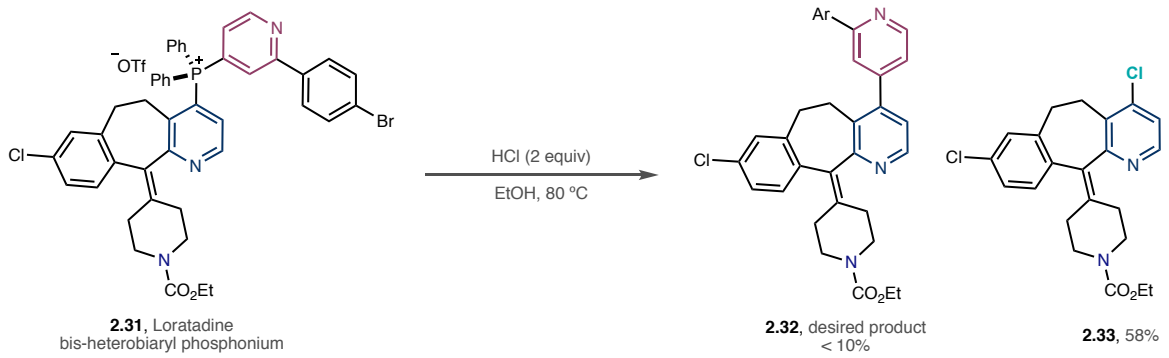


Figure 2.11. Initial discovery of phosphonium chlorination using Loratadine bis-heterobiaryl phosphonium salt.

To avoid these chloropyridine byproducts, Hilton et al. replaced HCl with TfOH in these cases, as the triflate anion is a worse nucleophile. This serendipitous discovery gave good insight into how to develop a more general halogenation of phosphonium salts: If triphenylphosphonium salts were unreactive towards the addition of halide nucleophiles, more electrophilic phosphonium

salts might work. It wasn't initially clear how the halogenation step was operating. As with the nucleophiles described in Chapter 2.3, both an S_NAr pathway and a ligand-coupling pathway were initially seen as viable mechanisms.

The initial strategy to make pyridyl phosphonium salts more electrophilic was to replace one of the phenyl substituents on the phosphorus atom with a more electron-deficient aromatic (**Figure 2.12**). Given our experience and success with pyridyl phosphines, we investigated replacing a phenyl substituent with a pyridine ring. Experience from the bipyridine reaction described above led us to initially use 4-pyridyl phosphines as nucleophiles. However, the resulting 4,4'-bisheterobiaryl phosphonium salts can react with halide nucleophiles to form two different chloropyridine products. This is due to competing S_NAr reactivities of the two pyridine substituents: the substrate (shown in blue) and the "dummy" phosphinyl pyridine (shown in red). To maximize chlorination yield of the substrate, no chlorination of the "dummy" pyridine should be observed. We found that this selectivity issue can be solved by making one of the pyridines excessively electron-rich, but the resulting halogenation conditions required an excess of acid at high temperatures (see Chapter 3 for an application of these phosphonium salts).

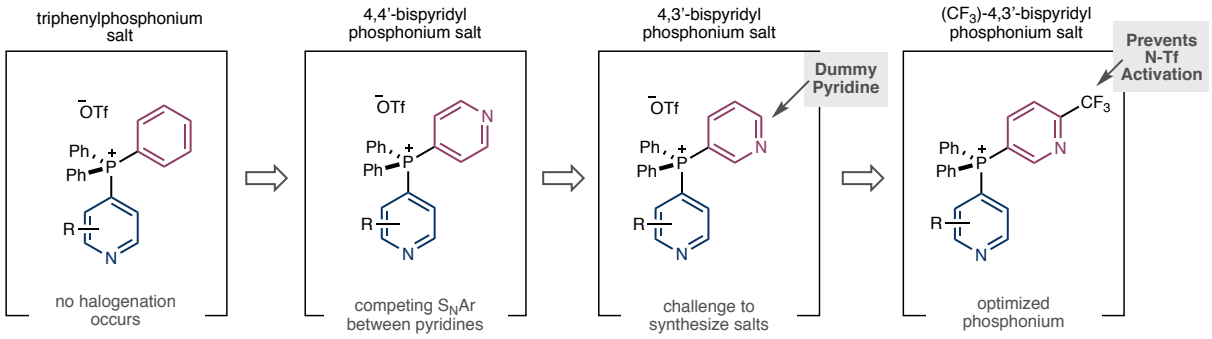


Figure 2.12. Optimization and design of a halogenation phosphine.

Another way to prevent the undesired halogenation of the "dummy" pyridine is to do an isomeric adjustment, putting the carbon-phosphorus bond at the 3-position of that pyridine ring instead of the 4-position (**Figure 2.12, third box**). However, it's a challenge to form the desired

phosphonium salt using 3-pyridyl diphenylphosphine (**2.34**). The pyridyl phosphine can react with triflic anhydride through the nitrogen atom, and then a molecule of unactivated 3-pyridyl diphenylphosphine can attack the undesired *N*-Tf pyridinium (**Figure 2.13**). This results in significant quantities of a "pseudo-dimer" product **2.35** and low yields for the desired phosphonium salts.

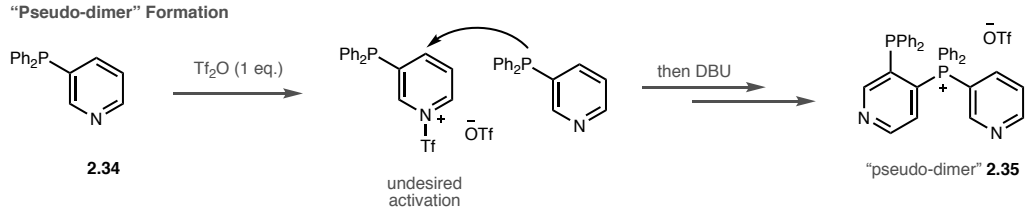


Figure 2.13. Formation of the "pseudo-dimer" product and the *ortho*-trifluoromethyl pyridyl phosphine solution.

The "pseudo-dimer" issue can be avoided by using a pyridyl phosphine that won't react with triflic anhydride. Several classes of pyridines are known to not react with triflic anhydride, including 2,6-disusbtituted pyridines and 2-trifluoromethyl pyridines for steric and electronic reasons. Phosphine **2.36** was synthesized in 82% yield by performing lithium/halogen exchange on 5-bromo-2-(trifluoromethyl)pyridine and then adding diphenylphosphine chloride. This pyridylphosphine was then reacted with 3-phenylpyridine **2.37** and triflic anhydride to form the corresponding phosphonium salt **2.38**, which was isolated in 76% yield (**Figure 2.14**). Despite using a more electron-deficient phosphine, the phosphonium salt formed in a high yield, comparable to the yield with triphenylphosphine.

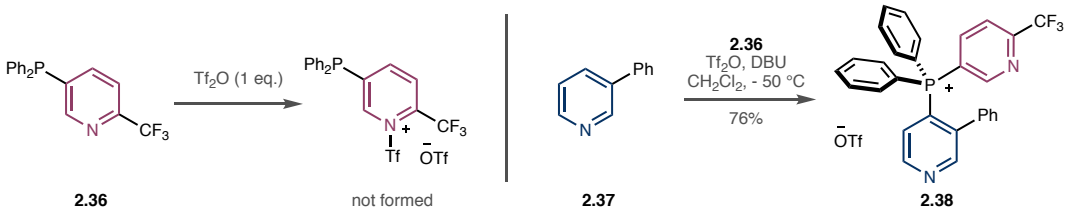


Figure 2.14. Development of a trifluoromethyl pyridyl phosphine.

From this 3,4'-bispyridyl phosphonium salt **2.38**, addition of four equivalents of lithium chloride and heating to 80 °C leads to 85% yield of the 4-chloropyridine product **2.39** (**Figure 2.15**). Using one equivalent of HCl in dioxane forms the 4-chloropyridine product in 95% yield. The non-acidic lithium chloride conditions were pursued because these conditions were much milder and would be more tolerant of acid-sensitive functional groups.

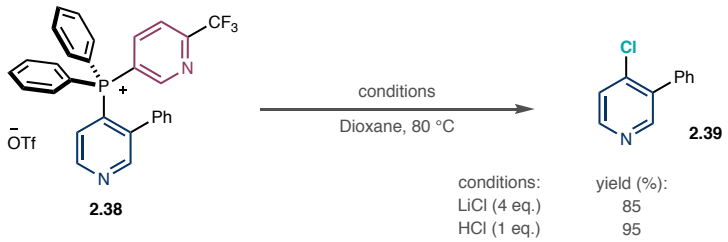


Figure 2.15. Initial results for halogenation of 3-phenyl phosphonium salt.

The scope of the reaction was explored, and we found that we could successfully chlorinate a variety of both simple and complex pyridines (**Figure 2.16**). Other azines such as isoquinoline, quinoxaline, pyridazine were shown to work, forming products **2.46**, **2.48**, and **2.49**. Chlorinated triazines **2.50** and **2.51** were also shown to form using the reaction protocol. One major limitation was that the pyridine scope was limited to pyridines with a substituent at the 3- or 5- position.

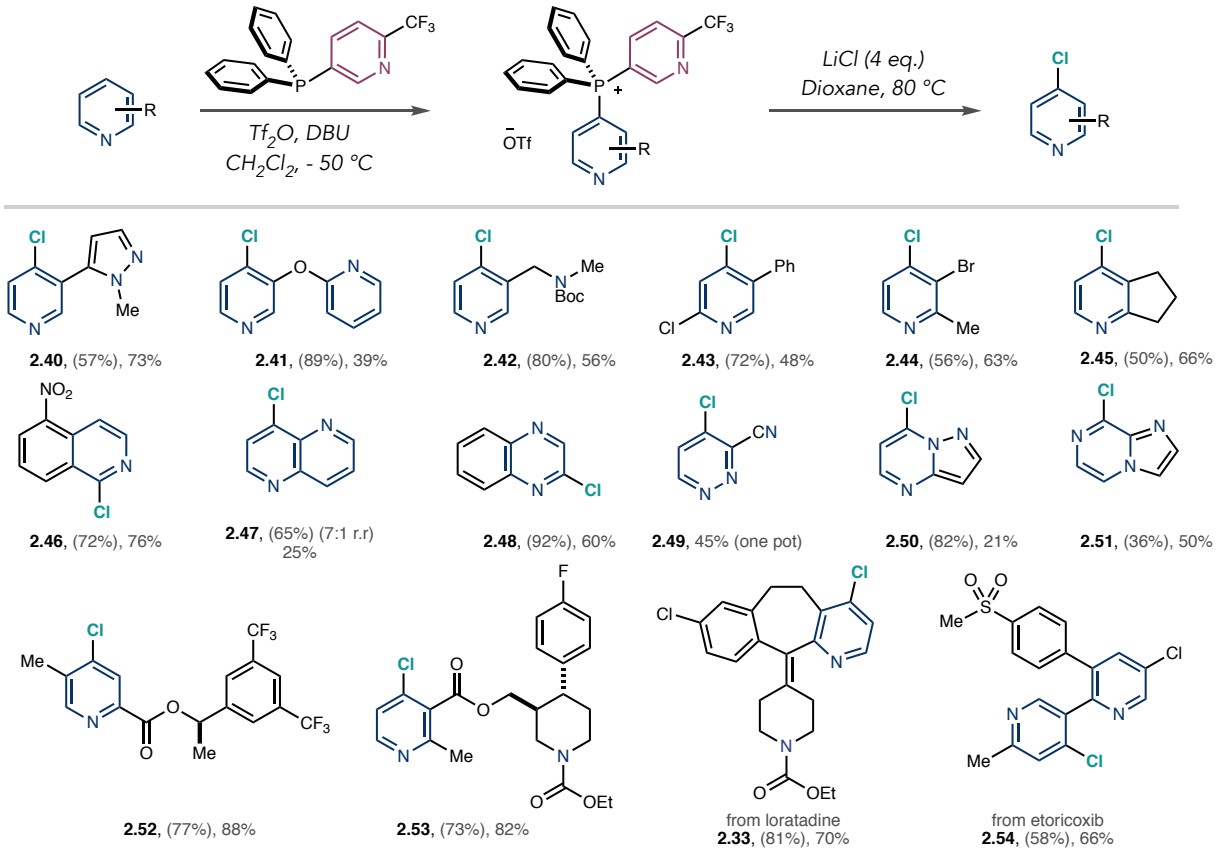


Figure 2.16. Select scope of pyridine 4-chlorination with monopyridyl phosphine. Numbers in parentheses refer to phosphonium salt yields.

Using 2-phenylpyridine, we were able to form the desired phosphonium salt, but the halogenation step proceeded in 3% yield with the LiCl conditions or 23% yield with the HCl conditions (**Figure 2.17**). Seemingly, these phosphonium salts behaved as though they were less electrophilic, and we proposed making the 2-substituted pyridyl phosphonium salts even more electrophilic by further modifying the phosphonium's substituents.

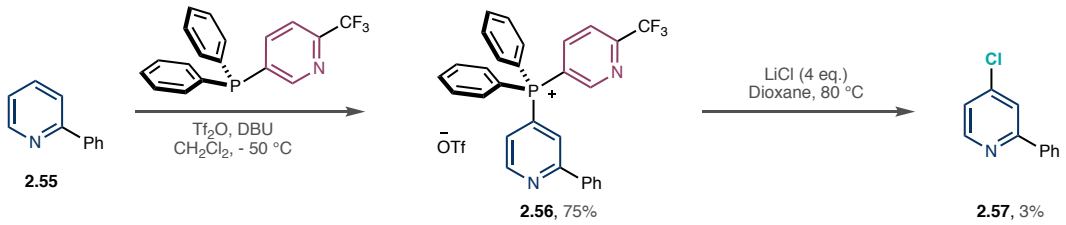


Figure 2.17. Low yielding chlorination reaction of 2-phenyl pyridine.

To do this, a second phenyl group on the phosphine was replaced with an *ortho*-CF_3 pyridine. The dipyridyl phosphine (**Phos II**) can be synthesized in 83% yield from the same pyridyl bromide starting material and replacing the diphenylphosphine chloride with dichlorophenyl phosphine. Using **Phos II**, both the salt-forming step and the halogenation step can proceed in good yield, forming products **2.58** and **2.57** in 81 and 70%, respectively, from 2-phenylpyridine. (**Figure 2.18**).

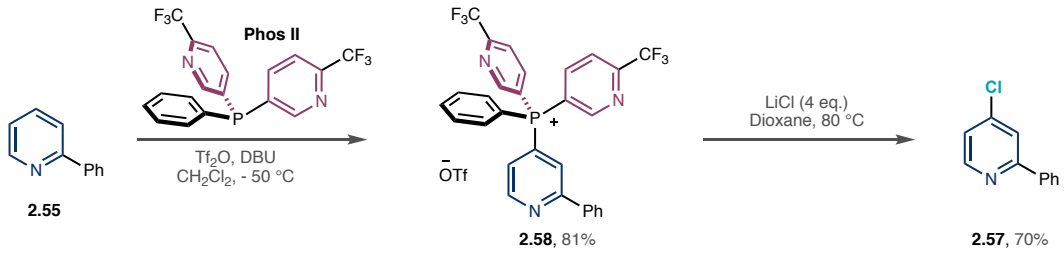


Figure 2.18. Redesigned phosphine for 2-substituted pyridines.

Beyond 2-phenyl pyridine, we found that a variety of simple and complex 2-aryl and 2-alkyl pyridines could be chlorinated using this phosphine (**2.59-2.63**) (**Figure 2.19**). From the experimental observation that 3-phenylpyridine and 2-phenylpyridine react differently, we hypothesized that a steric interaction from a 3-position substituent pushes on the bulky phosphonium ion, destabilizing the phosphonium salt to make it more reactive.

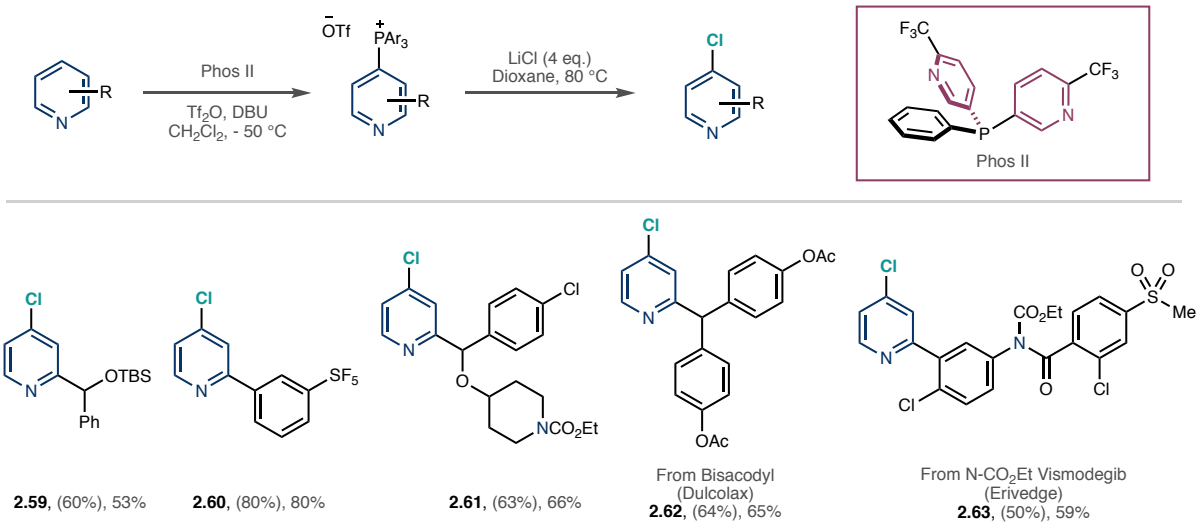


Figure 2.19. Select scope of pyridine 4-chlorination with Phos II. Numbers in parentheses refer to phosphonium salt yields.

Further probing this difference in reactivity, we hypothesized that 3,5-disubstituted pyridines could be halogenated from triphenylphosphonium salts. Having two group to sterically clash with the phosphine substituent should further elongate the carbon-phosphorus bond, increasing the reactivity of the salts. This strategy worked, and a selection of 3,5-disubstituted pyridines were halogenated directly from the triphenylphosphonium salts, forming products **2.64-2.66** (**Figure 2.20**). Pyrimidines were also able to undergo the chlorination using triphenylphosphonium salts, as these heterocycles are inherently very electrophilic, forming chloropyrimidines **2.67** and **2.68**. Highlights of the chlorination scope include substrates that have acid-sensitive functional groups, such as a TBS-protected alcohol (**2.59**) and a Boc-protected amine (**2.42**).

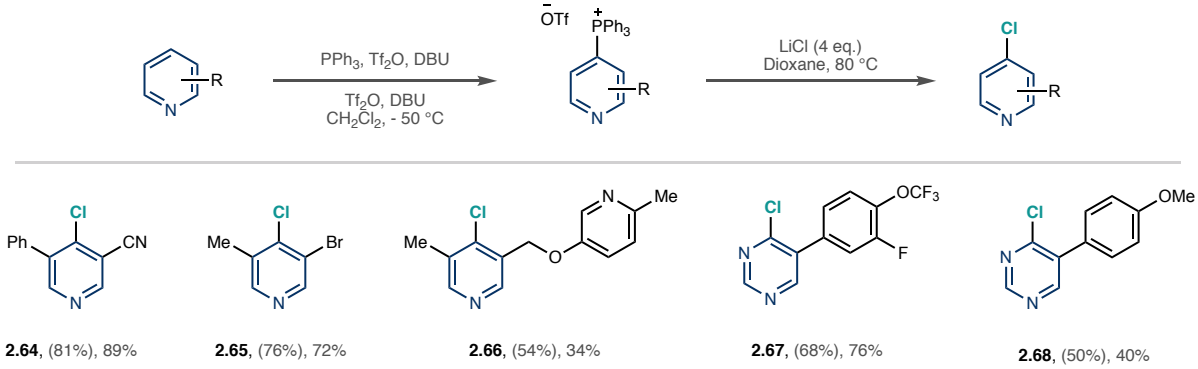


Figure 2.20. Select scope of pyridine 4-chlorination with triphenylphosphine. Numbers in parentheses refer to phosphonium salt yields.

2.5 Bromination and Iodination of Heterocyclic Phosphonium Salts

Given the success of the chlorination reaction, the addition of other halide nucleophiles was pursued. Switching from lithium chloride to lithium bromide or lithium iodide proved low yielding (**Figure 2.21**). Keeping solvent, time, and temperature the same as the chlorination protocol, using lithium bromide yielded 21% of 4-brominated pyridine **2.69** and using lithium iodide yielded 0% of the 4-iodinated pyridine **2.70**. This decrease in yield going from chloride to bromide to iodide follows the trend that the larger and more polarized halides are worse nucleophiles in polar aprotic solvents. It's also possible that the larger size of bromide and iodide make it more difficult to access the pyridine's 4-position.

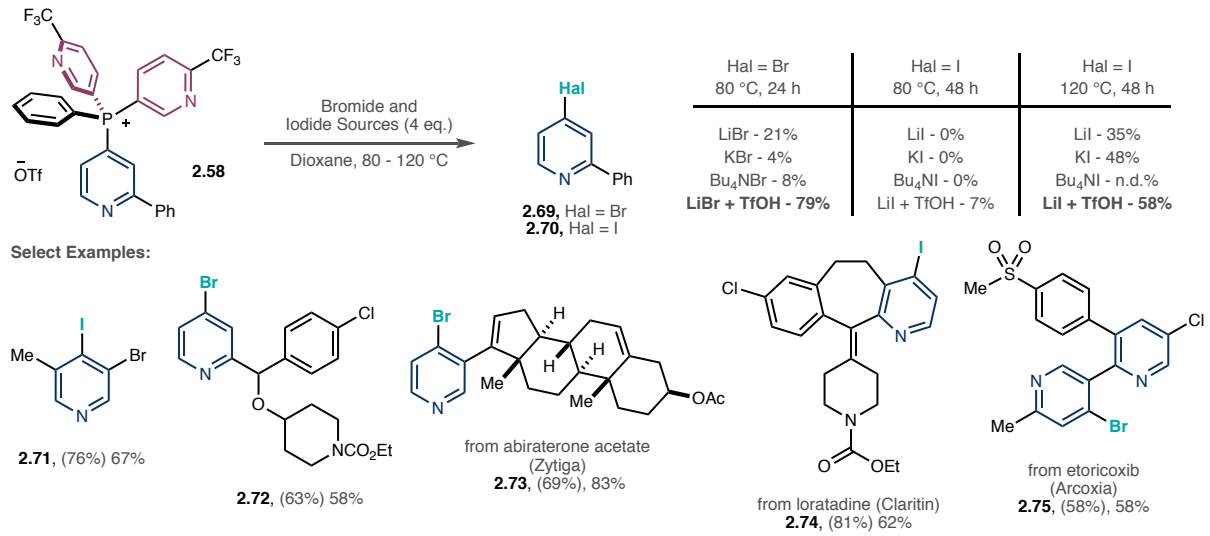


Figure 2.21. Select optimization and scope of pyridine 4-bromination and 4-iodination. Numbers in parentheses refer to phosphonium salt yields.

Given that HCl conditions work for the chlorination reaction, we pursued acidic activation conditions for the bromination and iodination. Hydrogen bromide and hydrogen iodide are inconvenient to use and difficult to obtain in an anhydrous solution. Alternatively, activating the pyridine ring with one equivalent of triflic acid and then adding lithium bromide yielded 4-bromo-2-phenylpyridine **2.69** in 79% yield. Triflic acid with lithium iodide only gave 7% of the desired iodinated product but heating the reaction to 120 °C for 48 hours gave 58% of iodinated pyridine **2.70**. We then showed that other pyridines could be brominated and iodinated under these optimized conditions, forming products **2.71-2.75**. We showed that phosphonium salts derived from all three of the phosphines used for the chlorination are amenable to the bromination and iodination conditions as well.

Next, a site-selective chlorination of a molecule with two pyridines was explored (**Figure 2.22, top**). Using **2.77**, a tripyridyl precursor to OX2R antagonist MK-1064, we showed that our standard set of conditions can be used to selectively chlorinate one of pyridine rings to form chloropyridine **2.76** with >20:1 site-selectively. Alternatively, "base-switch" conditions can be used, described in a previous report by Dolewski et al., to selectively form the phosphonium salt

on a different pyridine ring, leading to the formation of chloropyridine product **2.78** with >20:1 site-selectivity.[7] The selectivity for the standard phosphonium salt forming step is determined by sterics at the pyridine nitrogen affecting which pyridine is activated with triflic anhydride (**Figure 2.22, bottom left**). The switch in selectivity is controlled during the base-elimination step of the phosphonium salt forming reaction. Using *N*,*N*-dimethylcyclohexylamine as a base, the dihydropyridine intermediate that is less sterically hindered gets selectively deprotonated (**Figure 2.22, bottom right**).

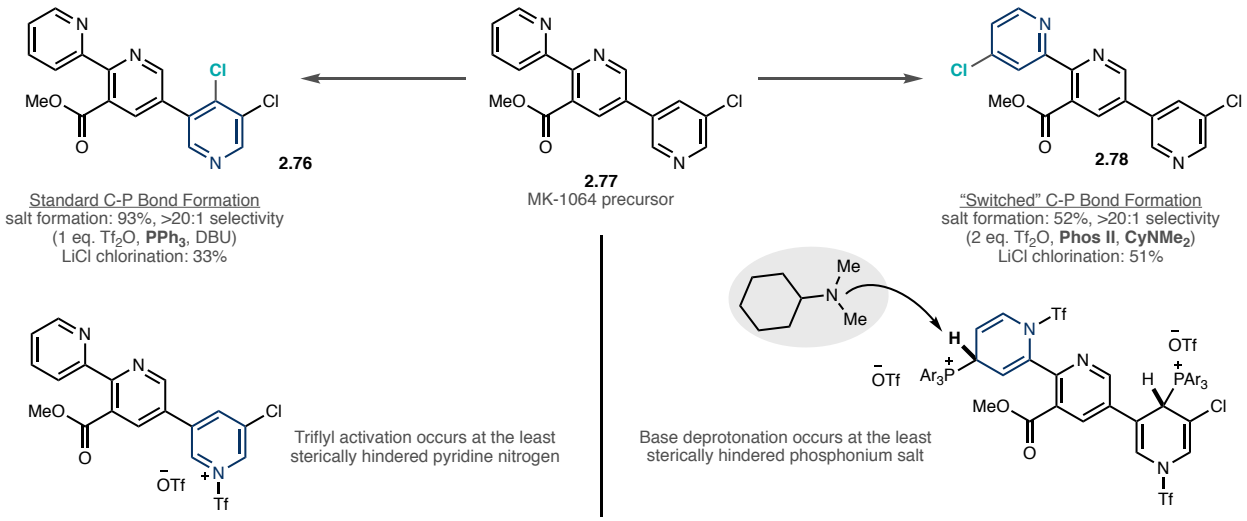


Figure 2.22. Two site-selective chlorination reactions of an MK-1064 precursor.

2.6 Computational Studies

Computational results from Juan Alegre-Requena and Rob Paton helped distinguish between the two initially proposed mechanisms of the reaction: S_NAr or P(V) ligand-coupling. Addition of halides to these phosphonium salt do not appear to form pentavalent species with chlorine, bromine, and iodine, as these P(V) intermediates would be too unstable (**Figure 2.23, top left**). This suggests that the direct S_NAr pathway is the mechanism of the halogenation.

Additionally, computations were able to support the theory that the sterics on the pyridine ring affect the reactivity of the phosphonium salts. Energy barriers were calculated for the

chlorinations of 2-phenylpyridine and 3-phenylpyridine using our monopyridyl phosphine (**Figure 2.23, right**). Chlorination of 2-phenylpyridine phosphonium salt had an energy barrier of 22.6 kcal/mol, while chlorination of 3-phenylpyridine phosphonium salt had an energy barrier of 19.7 kcal/mol. This suggests 3-phenylpyridine is approximately 50 times more reactive to this process than 2-phenylpyridine. Additionally, bond lengths were calculated for the transition states in the reaction. For the transition states for both the halide addition and phosphine elimination, the carbon-phosphorus bond is longer in the 3-phenyl cases than in the 2-phenyl cases.

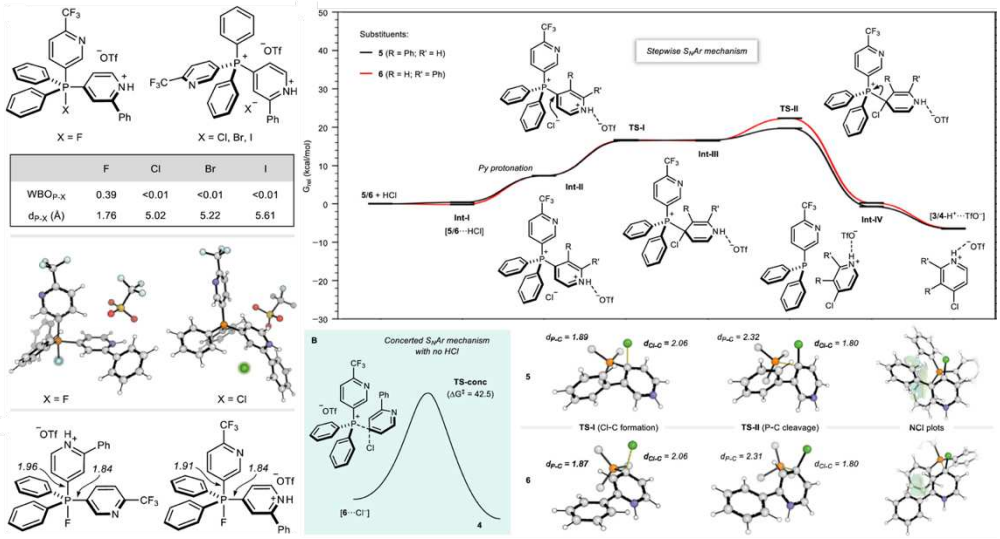


Figure 2.23. Computation experiments: Wiberg bond orders, bond lengths, and reaction profiles.

2.7 Fluorination of Heterocyclic Phosphonium Salts

Addition of fluoride anion to pyridyl phosphonium salts does not result in 4-fluoropyridine products. Using phosphonium salts derived from the pyridyl phosphines, multiple undesired decomposition products are observed when heated with fluoride anion. These products include the parent C-H starting material, 2-trifluoromethylpyridine, a variety of phosphine oxide products, and ligand-coupled bipyridine products. Using triphenylphosphonium salts, this reaction leads to the C-H starting material. Computations found that addition of fluoride anion leads to P(V) fluorophosphorane intermediates, likely due to the fluorophilic nature of the phosphorus atom.[18–

[20] Once these intermediates form, the axial carbon-phosphorus bond is elongated, allowing a pyridine substituent to react with an external proton source. This computational evidence supports our experimental observation that fluorination leads to different C-H pyridine products.

2.8 Conclusion

This chapter outlined previous work from the McNally lab in the field of pyridyl phosphonium salts, both in synthesizing these compounds and in derivatizing them through different reactivity platforms. This chapter then detailed the development of two new phosphines to achieve a 4-selective halogenation of pyridines. Chlorination, bromination, and iodination are amenable here, and the halogenation conditions are mild and easy to perform. Computational investigations suggest an S_NAr mechanism and support experimental observations in reactivity differences, such as the reactivity of 2- vs 3- substituted pyridines and different halide nucleophiles.

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CHAPTER THREE

FURTHER DEVELOPMENTS WITH HETEROCYCLIC PHOSPHONIUM SALTS

3.1 Chapter Overview

This chapter presents further developments in the 4-position functionalization of pyridines via phosphonium salt intermediates. Inspired by the halogenation strategy described in Chapter Two is a 4-selective amination of pyridines, and this chapter describes the development of a new phosphine reagent to accomplish this. My coworker, Ren Rong Liu, optimized the amination conditions and explored the substrate scope. The second reaction described in this chapter is a 4-selective fluoroalkylation of pyridines, which was discovered while developing the halogenation reaction. My coworker Xuan Zhang optimized the trifluoromethylation and synthesized most products in the trifluoromethylation scope. Coworkers Kyle Nottingham and Chirag Patel performed the optimization and scope of the difluoromethylation reaction. The fluoroalkylation reaction presented in the second part of this chapter was published in the journal *Nature*.[1]

3.2 Introduction to Pyridine Amination

Pyridyl amines are present in numerous pharmaceuticals and agrochemicals, and so methods to aminate C-H bonds on pyridines are sought after. Incorporation of these motifs can have significant effects on drug binding interactions and drug solubility.[2–4] Roflumilast and Torasemide are examples of bioactive 4-pyridyl anilines, and Sulfapyridine and Pyridinium are examples of 2-pyridyl anilines (**Figure 3.1**).[5] Additionally, aminoquinolines such as Chloroquine and Hydroxychloroquine are important treatments for malaria.[6]

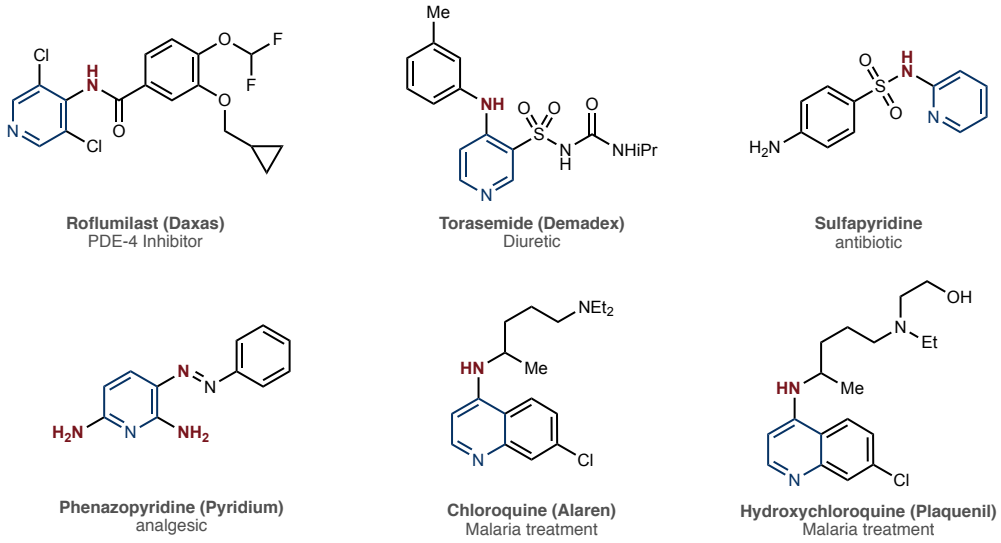

Figure 3.1. Example of aminopyridine pharmaceuticals.

General approaches to aminating aromatic rings include metal-catalyzed cross couplings, radical reactions with aminium radicals, reactions with nitrogen electrophiles, and nitroarene reduction processes.[7] Metal-catalyzed approaches typically require the corresponding aryl halide, such as in the Buchwald-Hartwig Reaction or Ullman Coupling, or they require aryl boronic acid coupling partners, such as in the Chan-Lam Coupling (**Figure 3.2, A,B**).[8–11] However, these prefunctionalized starting materials can be hard to access in many cases.

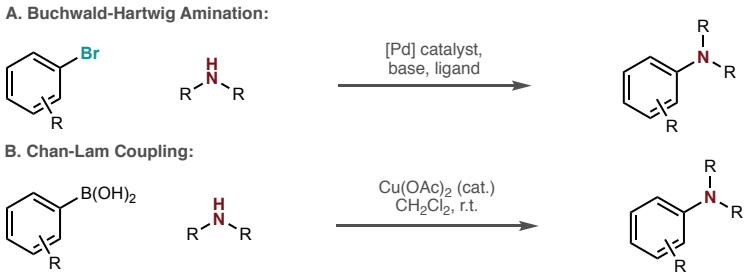

Figure 3.2. Metal-catalyzed amination reactions.

Electrophilic amination is a promising approach, but this strategy requires either electron-rich arenes or metalated arenes. The electrophiles used for these transformations, such as oxime esters and azo compounds, produce products that may require further transformations to be synthetically useful, such as the conversion of hydrazine dicarboxylate product **3.2** to carbamate

3.3 (**Figure 3.3, A**).[12–14] Radical amination with aminium radicals is a new and promising approach, although selectivity is often determined by the electronics of the arene starting material (**Figure 3.3, B**).[15] Regioisomers often form here, and the amination of toluene with piperidine forms **3.6** with a 5:1 ratio of para to ortho aminated toluene.

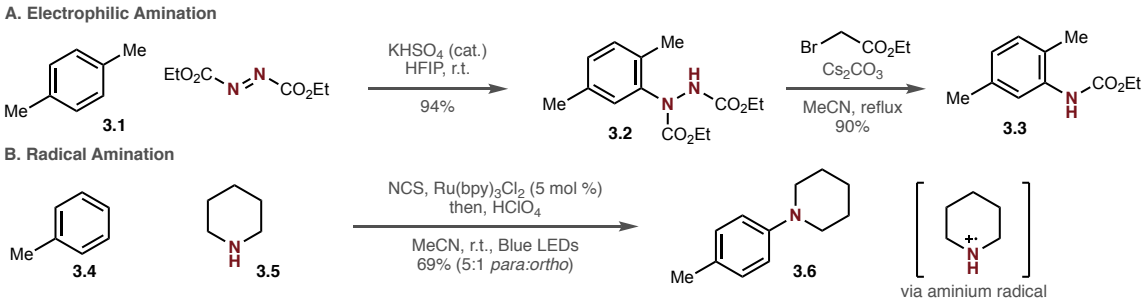

Figure 3.3. Electrophilic and radical amination strategies.

Many of these methods are not amenable to pyridines and azines, due to their poor π-nucleophilicity and the lack of prefunctionalized starting materials. For pyridines and other azines, S_NAr approaches are frequently employed to install amino substituents on the 2- or 4-positions of the ring, but this approach requires halogenated starting materials (**Figure 3.4**).[16]

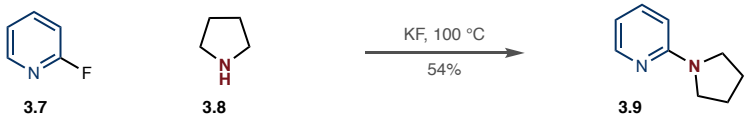

Figure 3.4. Amination of arenes via nucleophilic aromatic substitution.

As discussed in Chapter Two, earlier work from coworkers in the McNally group demonstrated that some nitrogen nucleophiles react with pyridyl phosphonium salts. Patel et al. showed that azide anion will add to pyridyl phosphonium salts to form iminophosphorane products that can then be transformed into other aniline derivates.[17] Anderson et al. showed that disubstituted anilines could add to phosphonium salts, forming tertiary diaryl aniline products.[18] Lacking in both published reactions is the ability to add aliphatic amines and primary anilines to

the 4-position of pyridines. Given the importance of these products, we hoped to develop a method to install these classes of amines.

3.3 Amination of Heterocyclic Phosphonium Salts

We were drawn to the polypyridyl phosphonium salts, such as **3.10**, used for the 4-halogenation reaction described in Chapter Two.[19] Because these phosphonium salts behave as more electrophilic variants of the triphenylphosphonium salts, we hypothesized that they should be more reactive towards S_NAr with an amine nucleophile. Unfortunately, reacting secondary amines such as pyrrolidine and piperidine with phosphonium salt **3.10** did not produce the desired aminated product (**Figure 3.5**). Instead, a mixture of decomposition products was observed, such as the C-H parent pyridines **3.13** and **3.14**, corresponding phosphine oxide byproducts, and bipyridine **3.15**. These products presumably resulted from the amine attacking the phosphorus atom to form an unstable P(V) intermediate. We envisioned an alternative approach would be to include lithium chloride in the reaction conditions and perform two sequential S_NAr steps: one to form a chloropyridine intermediate and another to convert that chloropyridine to the 4-aminated pyridine product. However, this approach yielded the same result, and it appeared that the phosphonium salt reacted with the amine faster than the chloride nucleophile.

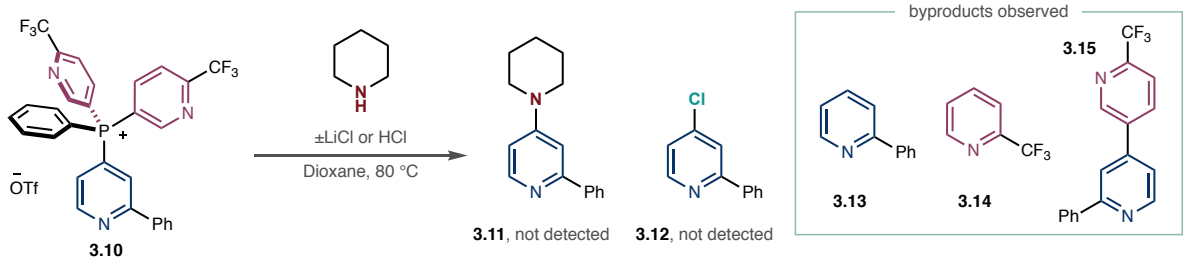

Figure 3.5. Failure of the chlorination phosphonium salts to undergo amination.

We then screened other modified phosphonium salts. An early strategy to achieve halogenation of phosphonium salts was to use 4,4'-bipyridyl phosphonium salts where the phosphinyl "dummy" pyridine (red) had an electron-donating substituent (**Figure 3.6**). The

purpose of the electron-donating substituent is to control chlorination selectivity between the two pyridines on the phosphonium salt: the substrate pyridine (blue) and the phosphinyl "dummy" pyridine (red) which we didn't want to be halogenated. When there is an electron difference between the two pyridine rings, the more electron deficient pyridine should undergo selective S_NAr. Using a phosphonium salt where the "dummy" pyridine had a 2-methoxy substituent, we observed formation of the desired 4-chloropyridine product, but also observed dealkylation to form the corresponding 2-pyridone. As a result, we investigated "dummy" pyridines with a 2-amino substituent. We synthesized phosphonium salt **3.15** from 2-phenyl pyridine and 2-piperidinyl pyridyl phosphine, and then observed that adding HCl at 100 °C led to formation of the 4-chloropyridine product **3.12** in 85% yield. No 2-piperidyl-4-chloropyridine **3.13** was observed, showing that the strategy to control halogenation selectivity was successful. Heating with lithium chloride results in no 4-chloropyridine **3.12**, and the halogenation conditions are harsher than the protocol described in Chapter Two. However, when phosphonium salt **3.10** unsuccessfully reacted with amines to form 4-aminated pyridines, phosphonium salt **3.15** was revisited.

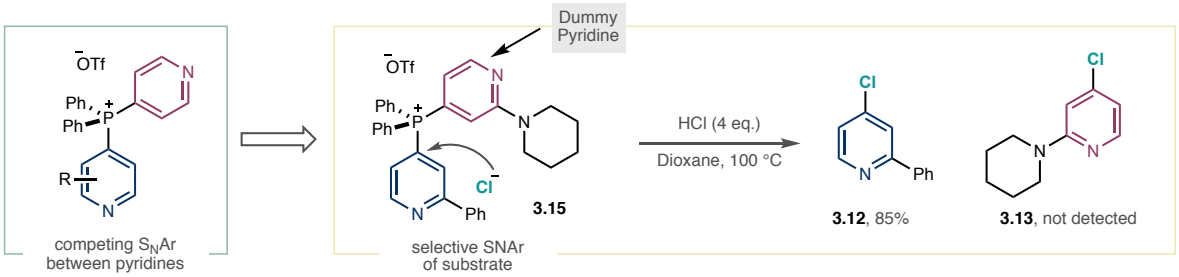

Figure 3.6. Development of an amination phosphonium salt.

Reacting piperidine with 4,4'-bisheterobiaryl phosphonium salt **3.15** yielded no desired aminated product. However, when 2 equivalents of piperidine and 4 equivalents of HCl were used at 120 °C, the desired aminated product **3.11** was formed in 58% yield (**Figure 3.7**). No aminated product forms when TfOH is used in place of HCl, suggesting that 4-chloropyridine **3.12** is an

intermediate in the reaction. Like the halogenation described in Chapter Two, we believe the chlorination of phosphonium salt **3.15** operates via an S_NAr mechanism instead of P(V) ligand-coupling.

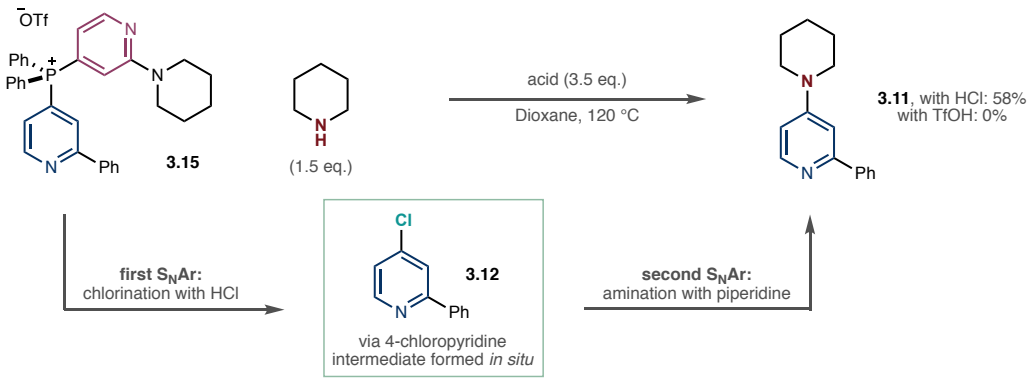

Figure 3.7. Initial hit for pyridine 4-amination.

With these conditions, my coworker Ren Rong Liu investigated the generality of the susbtrate scope. A selection of 31 amines were successfully coupled together with 2-phenylpyridine phosphonium salt **3.15** to form products **3.16-3.45**. (**Figure 3.8**). Many cyclic amines served as competent nucleophiles in the reaction to afford the corresponding 4-aminated products. Simple acyclic secondary amines such as dimethylamine and *N*-methylphenethylamine gave products **3.23** and **3.24** in reasonable yield, while other amines in this class such as diethylamine only gave trace amounts of product **3.25**. Butylamine was low yielding on pyridines, while phenylhydrazine and ethoxyamine worked well (**3.29, 3.30**). Additionally, various primary and secondary anilines were coupled successfully, and primary anilines will outcompete secondary amines, as seen in example **3.45**.

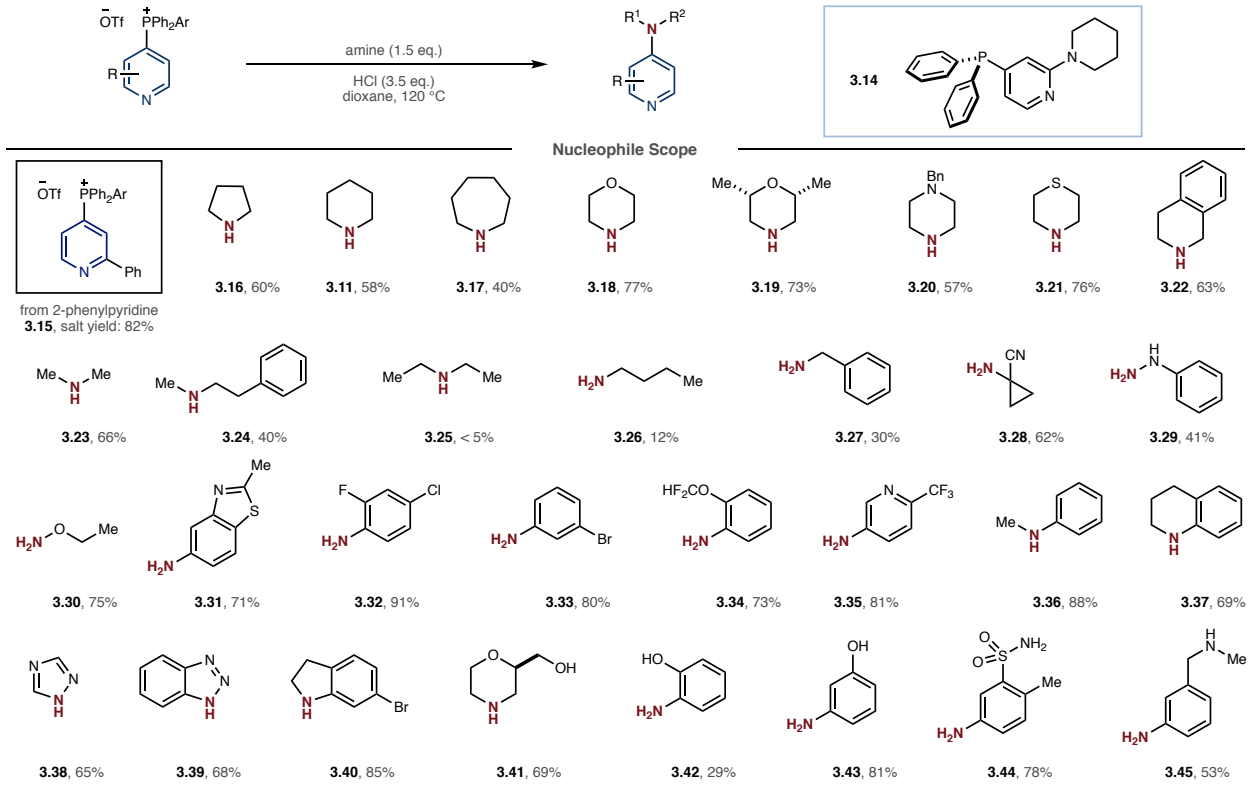

Figure 3.8. Scope of amination reaction on 2-phenyl pyridine. Numbers in parentheses refer to phosphonium salt yields.

The scope of heteroarenes was studied next, and fortunately the scope of this reaction matched the scope of previous phosphonium salt reactions. Figure 3.9 shows examples of bioactive molecules that were aminated with this strategy, as well as convergent couplings between structurally complex amine nucleophiles and complex pyridine substrates. Various disubstituted pyridines are tolerated here, including Loratadine and Etoricoxib, to form aminopyridines **2.47**, **2.48**, and **3.52**. Quinolines such as the fungicide quinoxyfen and OBn-Cinchonidine were successfully aminated at the 2-position to form aminoquinoline products **3.50** and **3.51**. Basic amines on both the pyridine substrate and amine substrate are tolerated, and representative examples of this include products **3.51** and **3.54**.

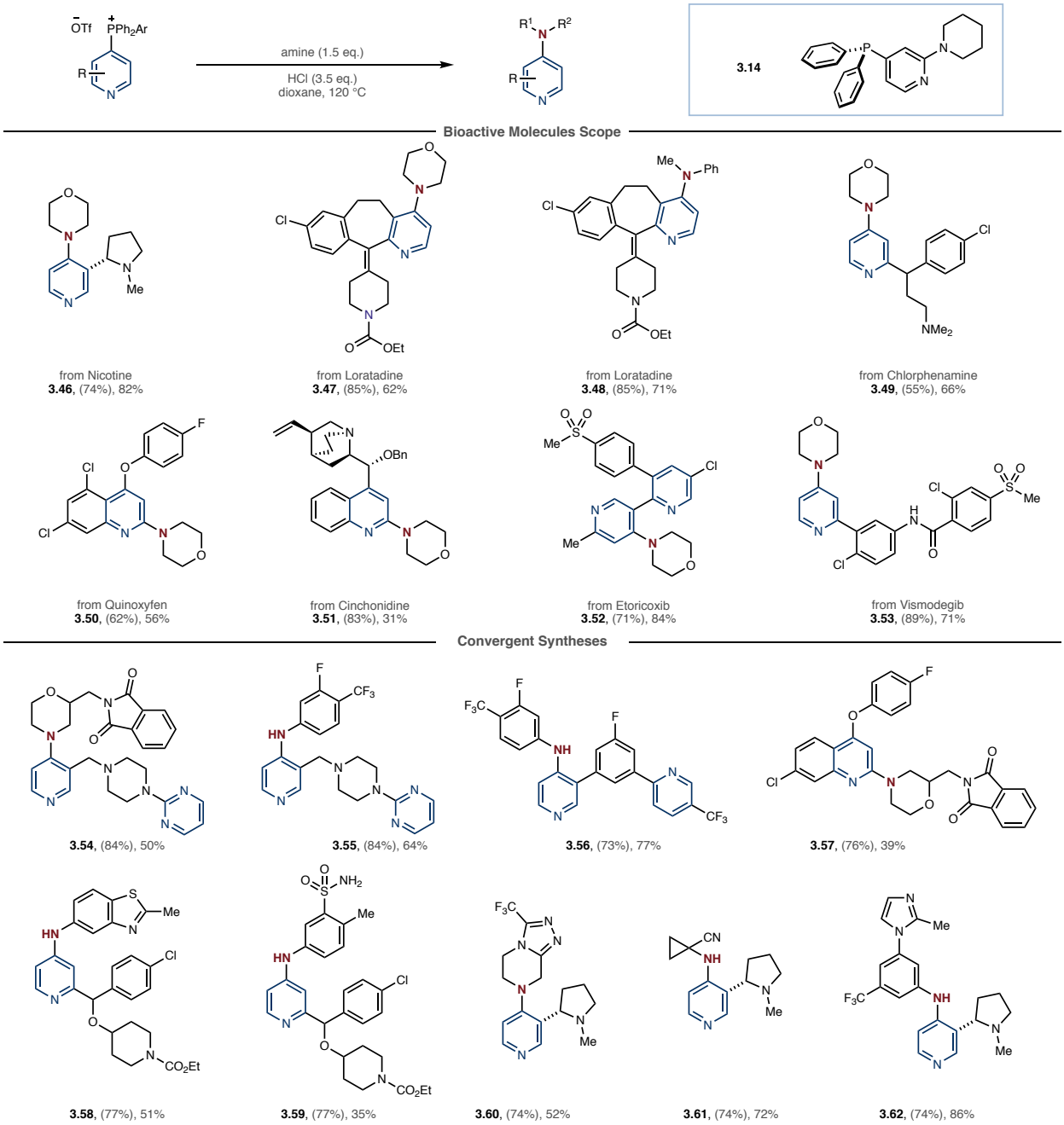

Figure 3.9. Bioactive molecules scope and convergent synthesis for 4-amination of pyridyl phosphonium salts. Numbers in parentheses refer to phosphonium salt yields.

3.4 Introduction to Pyridine Fluoroalkylation

Another sought after transformation in synthetic chemistry is the fluoroalkylation of arenes.[20] Fluoroalkyl groups can profoundly affect a pharmaceutical's pharmacokinetic and pharmacodynamic properties in a variety of ways.[21–24] Installation of trifluoromethyl and

difluoromethyl groups often increase the lipophilicity of a drug, which in turn increases its cell membrane permeability. Another potential benefit is improved metabolic stability, as C-H bonds are more susceptible to metabolic oxidation by Cytochrome P-450 enzymes than C-F bonds.[25] Additionally, the C-H of a difluoromethyl group can behave as a hydrogen-bond donor, and this interaction can be used to tune the binding ability of a pharmaceutical to an enzyme's active site.[26]

Existing methods to incorporate trifluoromethyl and difluoromethyl groups on pyridines are limited in scope and applicability. Hartwig and Chen have developed strategies to use Cu-CF_3 complexes to convert aryl iodides and bromides to trifluoromethylated products (**Figure 3.10**)[27,28]. Hartwig's method uses a phenanthroline-ligated Cu-CF_3 complex as the trifluoromethylating reagent, while Chen's method forms Cu-CF_3 in situ using methyl fluorosulfonyldifluoroacetate (Chen's reagent). However, the need for a halogenated precursor can limit the practicality of this reaction and so methods to install the fluoroalkyl group directly from the C-H bond are often required.

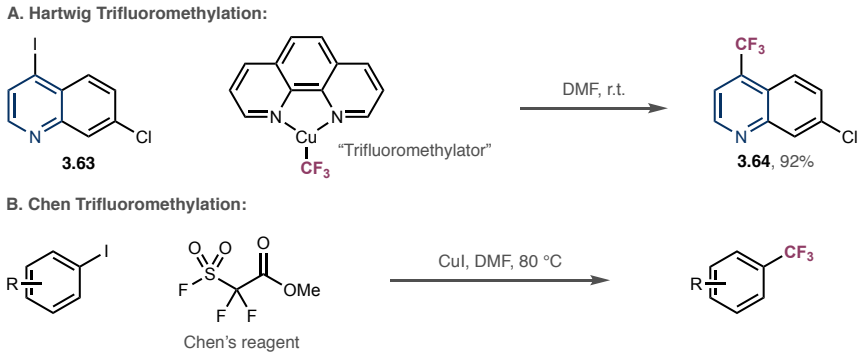

Figure 3.10. Literature approaches to trifluoromethylation of aryl halides.

Pyridine trifluoromethylation via a radical approach has been shown by the Baran and MacMillan labs. Baran and coworkers showed that the sodium trifluoromethylsulfinate (Langlois Reagent) can be oxidized to generate a trifluoromethyl radical that reacts with heteroarenes (**Figure 3.11, A**).[29] This approach was used to convert 4-cyanopyridine **3.65** into

trifluoromethylated pyridines **3.67** and **3.68** with a 2.4:1 regioisomeric ratio in preference of the 2-functionalized isomer. MacMillan and coworkers reported a similar reaction where the trifluoromethyl radical is formed by single-electron reduction of triflyl chloride using photoredox catalysis conditions (**Figure 3.11, B**).[30] Using this approach, the authors converted 2-methoxypyridine **3.69** into trifluoromethylated pyridines **3.71** and **3.72** with a 2.9:1 regioisomeric ratio in preference of the 3-functionalized isomer. Accessing multiple isomers can be beneficial for accessing a library of derivatized compounds. However, these regioisomers can be difficult to separate and isolate as pure compounds.

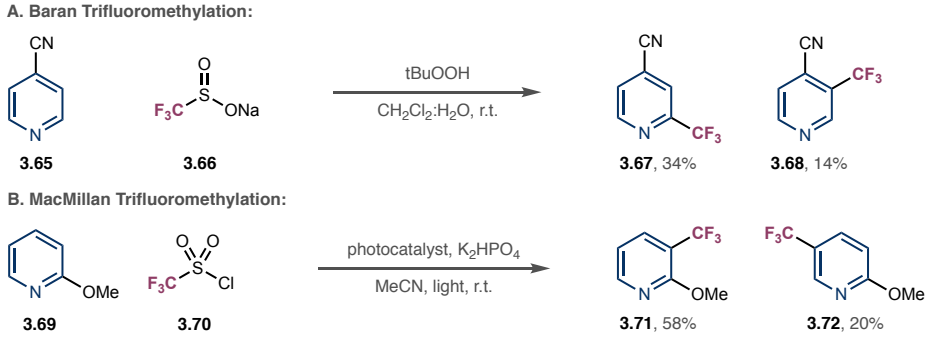

Figure 3.11. Literature approaches to radical trifluoromethylation of pyridines.

In 2014, Kanai and coworkers reported a 2-trifluoromethylation of pyridines using pyridine *N*-oxides that are further activated with trifluroomethyldifluoroborane (**Figure 3.12, A**).[31] Addition of Ruppert-Prakash ($TMSCF_3$) and a fluoride activator leads to formation of CF_3 anion which adds to the 2-position selectively. A subsequent publication in 2016 disclosed an approach to switch the selectivity to the 4-position (**Figure 3.12, B**).[32] Pyridines were first coordinated to a bulky borane Lewis acid that effectively blocked the 2-position from nucleophilic addition. Using 3-phenylpyridine **3.73**, addition of the boron Lewis acid gives adduct **3.74**. Generation of CF_3 anion then results in 4-position attack on the pyridinium, forming a dearomatized 1,4-dihydropyridine intermediate. The intermediate can then be oxidized with PIFA to yield 4-trifluoromethylated pyridine products **3.75** and **3.76**. The 4-selectivity is not perfect here, and due

to the bulky borane Lewis acid, the reaction is a challenge on 2-substituted pyridines; the only example of this shown is on a 2-alkynyl pyridine. The requirement for an oxidation step further limits the practicality of this method.

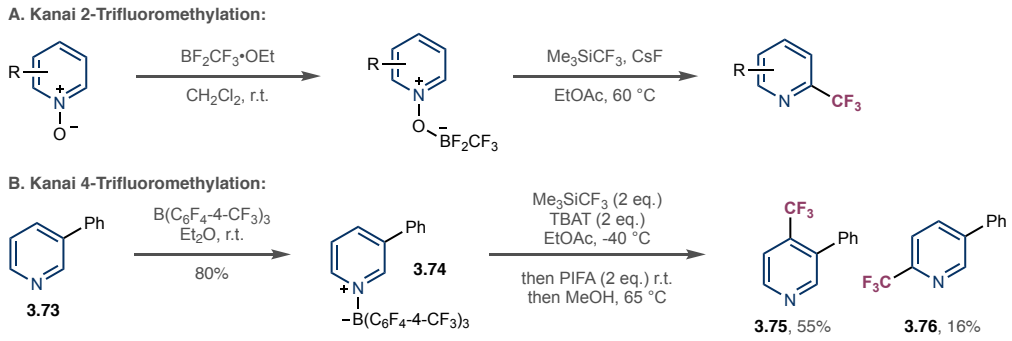

Figure 3.12. Kanai's trifluoromethylation of pyridine.

3.5 Trifluoromethylation of Pyridines via Phosphonium Salt Intermediates

The conversion of pyridyl phosphonium salts to 4-trifluromethylated pyridines was seen as an appealing strategy to access these fluoroalkylated products with high regioselectivity. Use of trifluoromethyl anion can be problematic due to decomposition into a difluoromethyl carbene and fluoride anion.[33] As a result, an alternative strategy was required. While developing more electrophilic phosphonium salts for the halogenation reaction, one class of phosphonium salts that was investigated was P-CF_3 phosphonium salts. This class of phosphonium salts had previously been studied for their behavior as Lewis acids (**Figure 3.13**).[34,35]

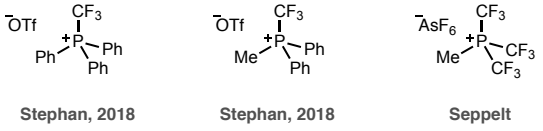

Figure 3.13. Literature examples of P-CF_3 phosphonium salts.

We hypothesized that the electron withdrawing CF_3 substituent on the phosphorus atom could facilitate S_NAr with a halide nucleophile. Trifluoromethylated phosphine Ph_2PCF_3 (**3.78**) is easily prepared by reacting diphenylphosphine chloride first with phenol and triethylamine to form

intermediate **3.77**, and then with $TMSCF_3$ and CsF to displace phenoxide with a trifluoromethyl anion (**Figure 3.14**).[36]

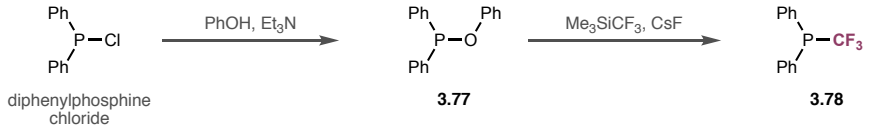

Figure 3.14. Synthesis of Ph_2PCF_3 from diphenylphosphine chloride.

Reaction this phosphine with 2-phenyl pyridine **3.13** under the standard phosphonium salt forming conditions yielded none of the desired product **3.79**, but trace amounts of the 4-trifluoromethylated pyridine product **3.80** (**Figure 3.15**).[37] We hypothesized that the phosphonium salt **3.79** initially formed in the reaction mixture, but then rapidly decomposed into the trifluoromethylated pyridine via a ligand-coupling step.[38]

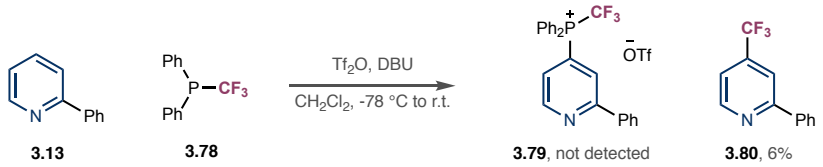

Figure 3.15. Initial result for pyridine trifluoromethylation.

Because of the low yield for the phosphonium salt formation, more electron-rich P-CF_3 phosphines were synthesized and used for the phosphonium salt forming reaction (**Figure 3.16**). Using *para*-OMe substituted phosphine **3.82**, the phosphonium salt formed in 54% yield, while *para*-NMe_2 substituted phosphine **3.83** formed the phosphonium salt in 81% yield. Further modifying the amino substituent from dimethylamine to pyrrolidine (**3.84**) improved the yield of the phosphonium salt to 85%.

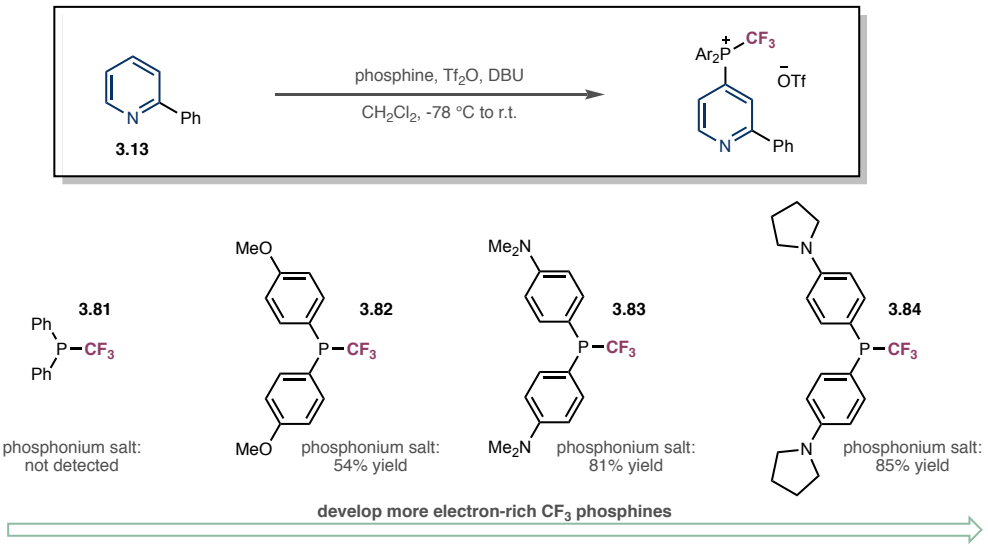

Figure 3.16. Development of more electron-rich trifluoromethyl phosphines.

Excitingly, the phosphonium salts that form using phosphine **3.84** be converted into the 4-trifluoromethylated pyridine simply by adding 1.5 equivalents of triflic acid and an excess of water and methanol (**Figure 3.17**). Once 2-phenyl pyridine **3.13** forms phosphonium salt **3.85**, these conditions gives trifluoromethylated pyridine **3.80** in 84% yield, suggesting nearly quantitative conversion from phosphonium salt **3.85**. The ability to run this reaction in a single pot makes this transformation simple and fast to perform.

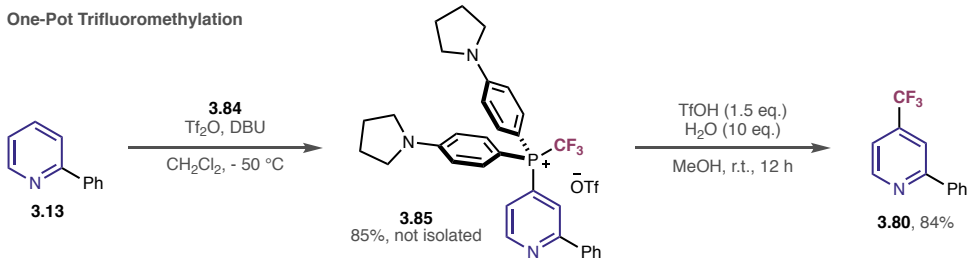

Figure 3.17. One-pot trifluoromethylation of 2-phenyl pyridine.

We next investigated the generality of the substrate scope, and it was found that a diverse selection of pyridines and other azines could be trifluoromethylated in this one-pot reaction sequence (**Figure 3.18**). A selection of more complex pyridines and pharmaceuticals can be trifluroomethylated with this strategy, including the drugs Gleevec and Etoricoxib to form products

3.99 and **3.101**. We found that in addition to the acidic conditions for ligand-coupling, basic conditions using sodium bicarbonate at room temperature could also be employed. In some cases, this alternative set of conditions gave superior yields for the trifluoromethylation step.

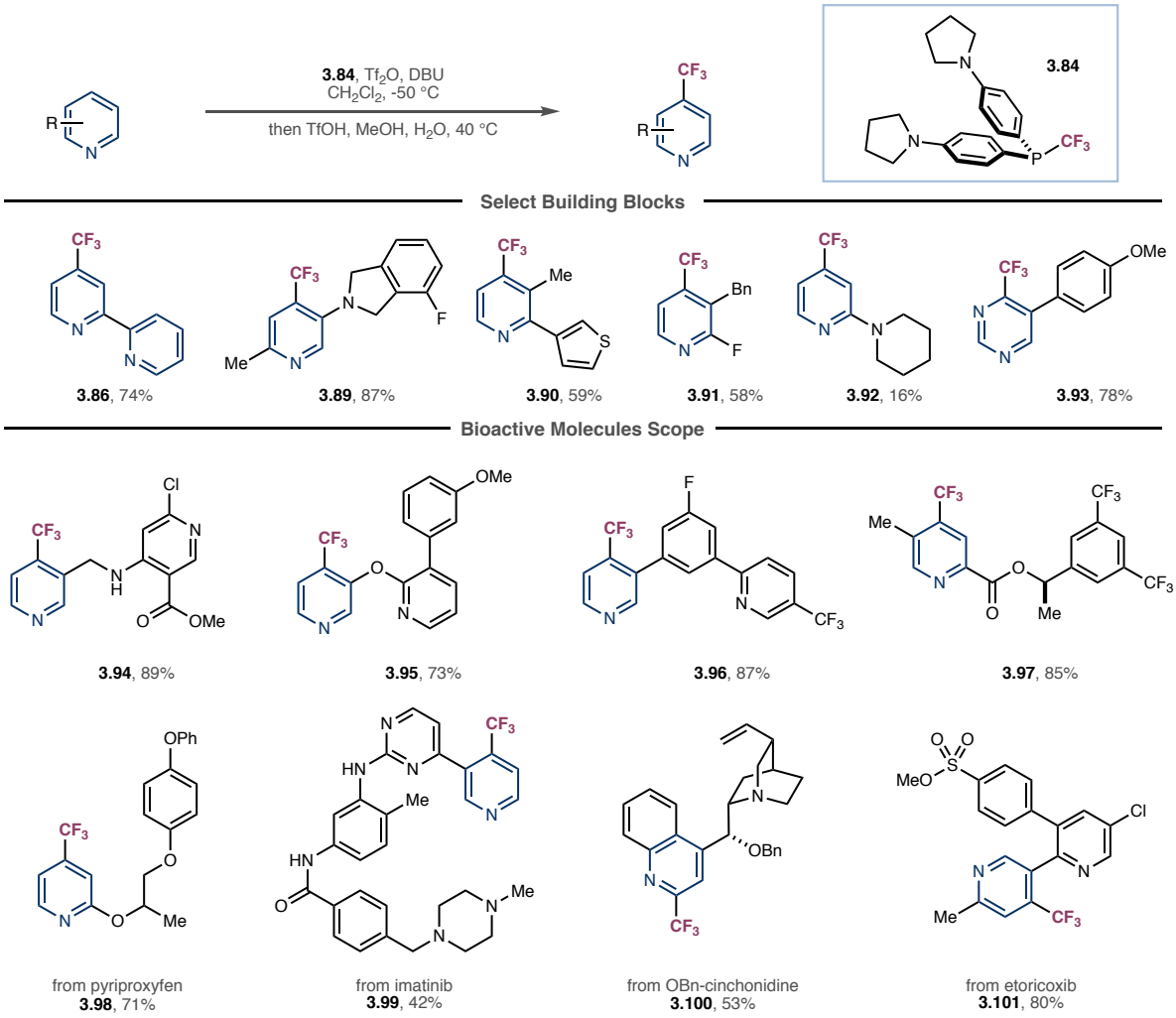

Figure 3.18. Select scope from the trifluoromethylation reaction.

In exploring the scope of trifluromethylation, we hoped to see if the trifluoromethyl protocol was amenable to our site-switching conditions (**Figure 3.19**).[39] Pleasingly, we were able to take MK-1064 precursor **3.103** and selectively install a trifluoromethyl group at two different positions using both our standard set of reaction conditions and our base-switching conditions (see Chapter 2.5 for an explanation of how the base-switching conditions work). The standard salt

forming conditions are used to trifluoromethylate the 3,5-disubstituted pyridine, forming product **3.102** in 31% yield, while the base switch conditions selectively functionalize the 2-substituted pyridine, forming product **3.104** in 67% yield.

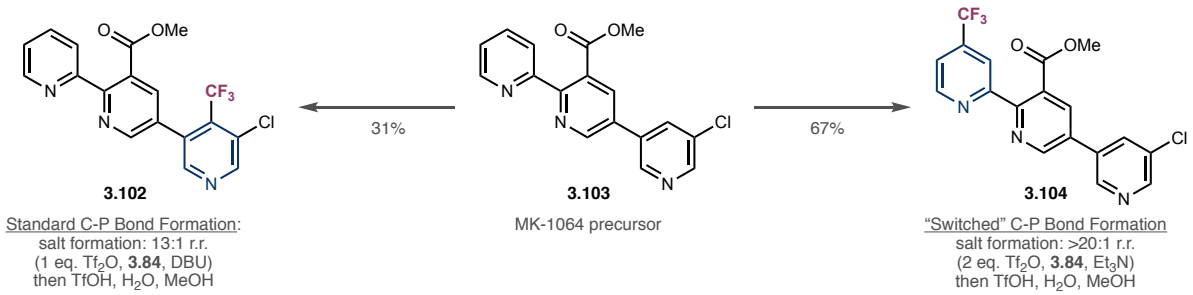

Figure 3.19. A selectivity-switching trifluoromethylation strategy on an MK-1064 precursor.

3.6 Difluoromethylation of Pyridines via Phosphonium Salt Intermediates

We next hypothesized that a similar strategy could be used to install a difluoromethyl group instead of a trifluoromethyl group. Coworker Kyle Nottingham and Chirag Patel developed a difluoromethyl phosphine reagent to install CF_2H groups at the 4-position of pyridines.[40] Because a CF_2H group is less electron-deficient than a CF_3 group, they could achieve high salt-forming yields using phosphine **3.105** with *para*-OMe aryl substituents.[41] A similar set of ligand-coupling conditions were employed. Here, HCl was added as the acid and EtOH as the solvent. The scope of the one-pot difluoromethylation was investigated and a large selection of simple and complex azine-containing substrates were converted the corresponding 4-difluoromethylated pyridines (**Figure 3.20**). Example **3.111** shows that this strategy can be used to access 4-difluoromethylated pyrimidines.

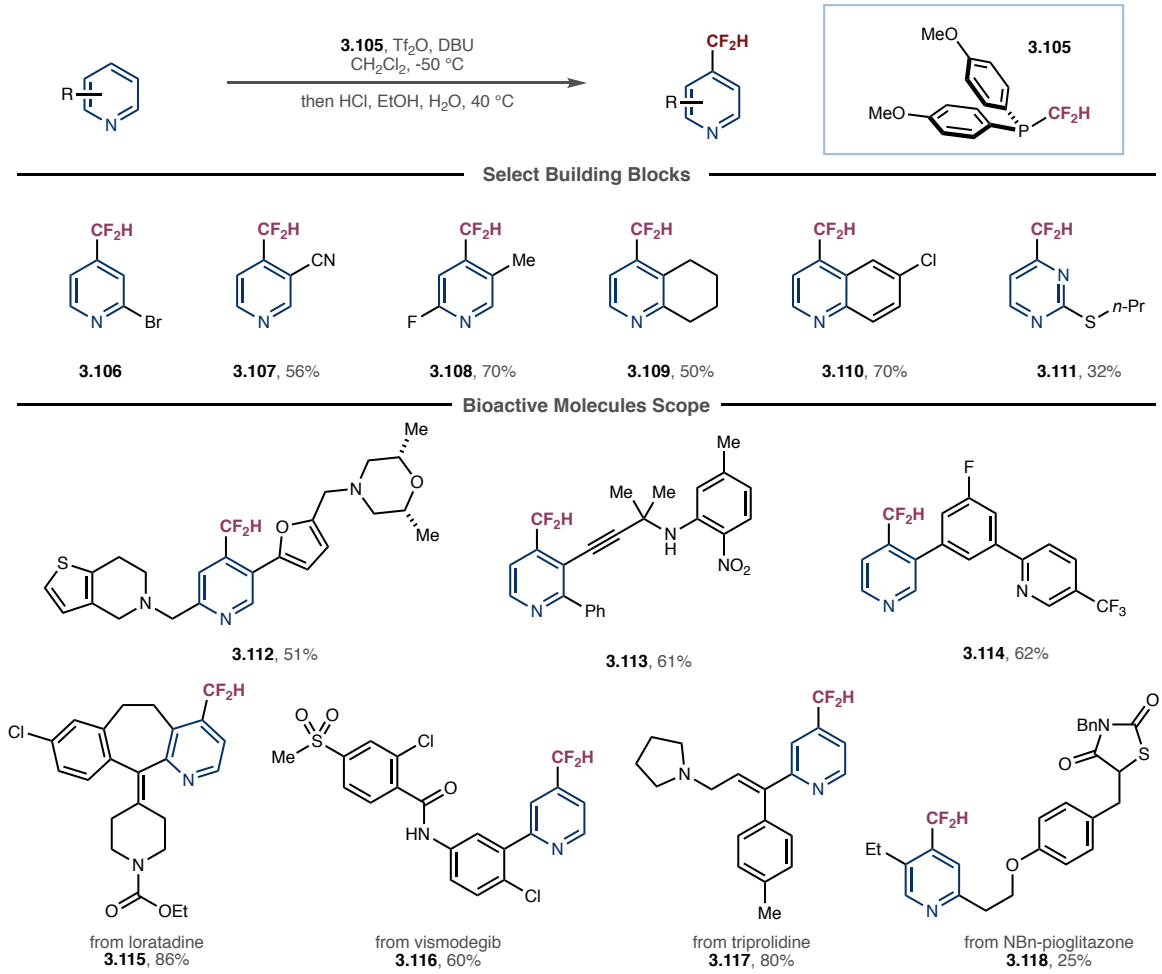

Figure 3.20. Select difluoromethylation scope via P(V) ligand-coupling.

The addition of perfluoroethylation and pentafluoroarylation to the 4-position of pyridines was also accomplished with this strategy (**Figure 3.21**). In both cases, novel phosphines were developed to use as reagents. Using phosphine **3.119** with 2-phenyl pyridine **3.13** gives perfluoroethylated pyridine **3.120** in 74% yield. Similarly, using phosphine **3.121** gives perfluorarylated pyridine **3.122** in 85% yield. Efforts are ongoing to explore the scope of fluoroalkylated and fluoroarylated coupling partners.

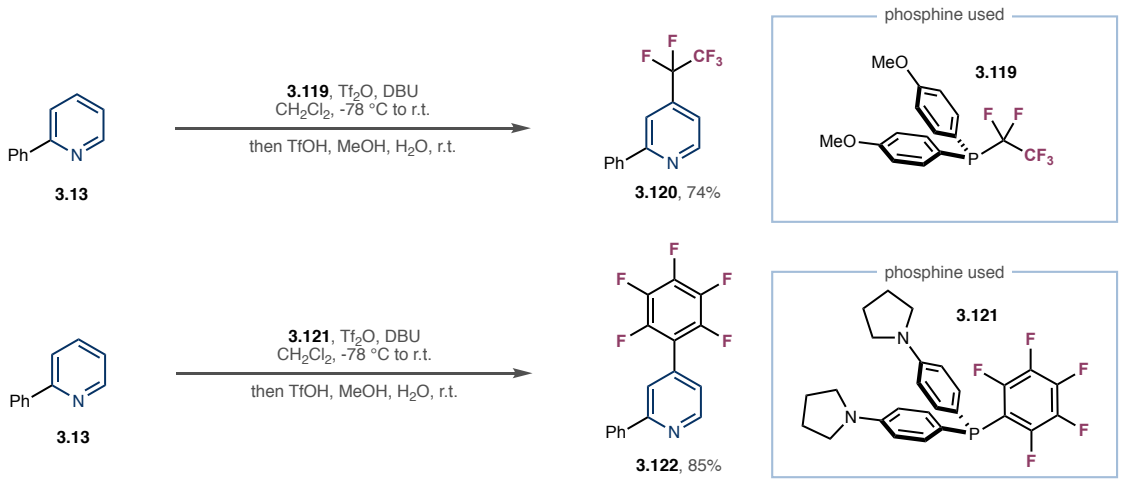

Figure 3.21. Perfluoroethylation and perfluoroarylation of 2-phenyl pyridine.

3.7 Fluoroalkylation Mechanism and Computational Studies

The fluoroalkylation proceeds through a ligand-coupling pathway as supported by computational studies. An alcohol nucleophile attacks the phosphonium to form a P(V) phosphorane, initiating a ligand-coupling step that forms the desired product. Ligand-coupling pathways on phosphorus are impacted by the geometry of the phosphorane. Phosphoranes adopt a trigonal bipyramidal geometry with two axial substituents and three equatorial substituents. During the trifluoromethylation ligand coupling step, the axial CF_3 substituent migrates onto the equatorial pyridinium, forming a dearomatized dihydropyridine intermediate that then rearomatizes to form the trifluoromethylated pyridine product and diphenylphoshine as a byproduct (**Figure 3.22**).[42]

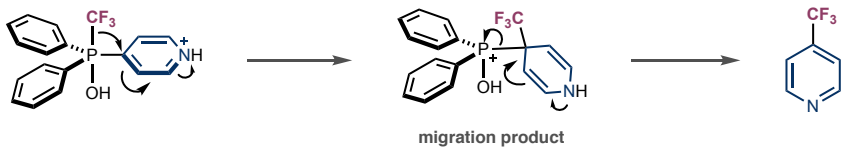

Figure 3.22. Mechanism of ligand-coupling step.

Due to the trans effect, a buildup of negative charge occurs on the axial substituent, and so the groups that can occupy that position must be able to stabilize the buildup of negative charge. As a result, electron withdrawing substituents like pyridines and fluoroalkyl groups can be used as

competent nucleophiles for the ligand coupling reaction, whereas groups such as phenyl and methyl typically can't.

The energy barriers for different transformations of the P(V) phosphorane were calculated, and the CF_3 migration step was calculated to be 19 kcal/mol (**3.123**) (**Figure 3.23**). Migration of a phenyl substituent onto the pyridine ring (**3.124**), which is not observed experimentally, was calculated to be 32 kcal/mol. Proteodephosphination via ejection of a pyridinium (**3.125**) or trifluoromethyl (**3.126**) substituent was calculated to be 27 and 40 kcal/mol, respectively.

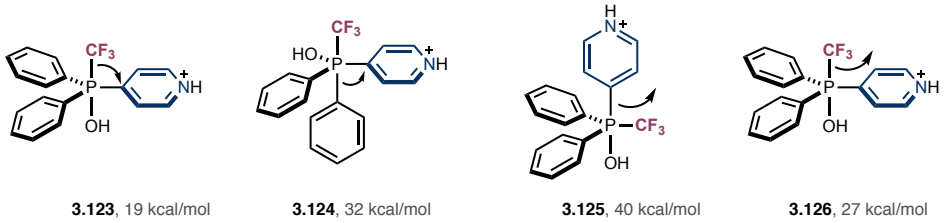

Figure 3.23. Comparison of reaction pathways from P(V) phosphorane intermediate. Numbers shown represent activation energy ($\Delta G^{\ddagger}$).

3.8 Conclusion

This chapter describes two reactions using pyridyl phosphonium salts that were discovered while studying the pyridine halogenation strategy described in Chapter Two. Using 4,4'-bis-heterobiaryl phosphonium salts, a 4-selective amination of pyridines can be achieved, greatly expanding the scope of amine nucleophiles amenable to phosphonium salt derivatization. Additionally, a discovery of trace amounts of trifluoromethylated pyridine when using a P-CF_3 phosphine led to the development of a one-pot trifluoromethylation and difluoromethylation reaction. Not only is this reaction useful for forming these products, but it represents a significant advancement in the field of phosphorus ligand-coupling.

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CHAPTER FOUR

HALOGENATION OF PYRIDINES VIA ZINCKE IMINE INTERMEDIATES

4.1 Chapter Overview

This chapter describes a novel strategy to halogenate the 3- and 5-position of pyridines. A historical background of pyridine ring-opening reactions will be presented, followed by a description of how these intermediates can be used to access functionalized pyridines. We show that pyridines can be temporarily converted to ring-opened *N*-Tf imine derivates, and that these intermediates can easily react with electrophilic halogenation reagents. A large selection of iodinated, brominated, and chlorinated pyridines can be formed in a one-pot approach, and dihalogenation is also possible. My coworker Ben Boyle optimized the ring-opening reaction and contributed to the scope. Louis de Lescure and Rob Paton carried out computational studies to better understand the mechanism of the reaction.

4.2 Introduction to Pyridine Ring-Opening Reactions

A handful of reactions are known that involve ring-opening pyridine into acyclic derivatives, with the most famous example being the Zincke reaction.[1,2] Initially published in 1904, the Zincke reaction is a two-step process to convert pyridines into *N*-functionalized pyridinium salts (**Figure 4.1**). Pyridine (**4.1**) reacts via S_NAr with 2,4-dinitrochlorobenzene (**4.2**) to form pyridinium salt **4.3** known as a Zincke salt. These salts are typically isolated by a precipitation or recrystallization.[3,4] In the second step, Zincke salt **4.3** reacts with a primary amine under basic conditions at elevated temperatures, and this forms an *N*-functionalized pyridinium. This approach has been used to install aryl, alkyl, and amino groups on the pyridine nitrogen.[5–7]

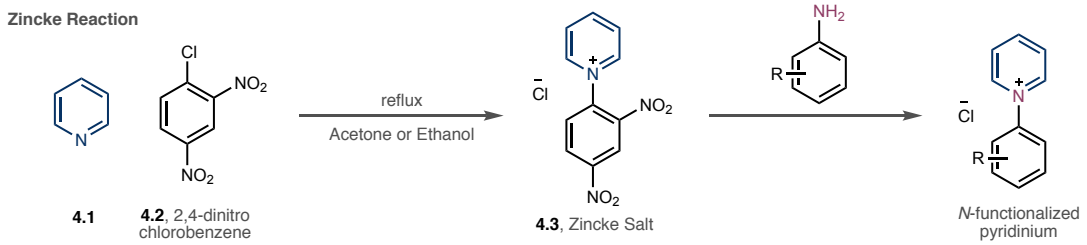


Figure 4.1. Overview of the Zincke reaction.

The conversion of Zincke salt **4.3** to pyridiniums **4.7** proceeds through ring-opened intermediates known as Konig salts. (**Figure 4.2**) In this reaction, aniline first adds to the 2-position of the pyridinium to make dearomatized 1,2-dihydropyridine intermediate **4.4**. This then undergoes ring-opening to construct 1,3,5-azatriene intermediate **4.5**. Aniline adds to the azatriene, displacing the less nucleophilic 2,4-dinitrobenzene aniline, and the resulting intermediate, **4.6**, then recyclizes to give *N*-phenyl pyridinium **4.7**.[8]

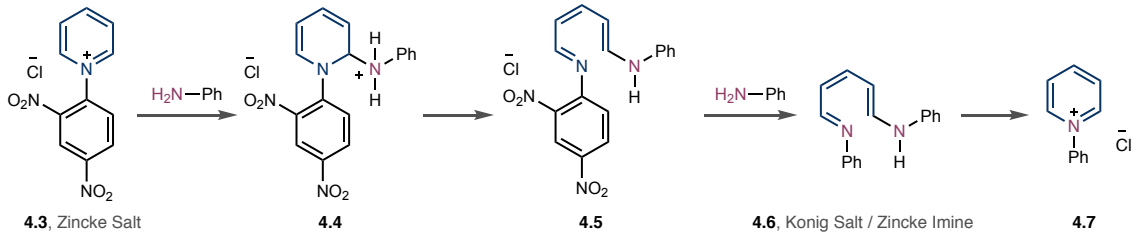


Figure 4.2. Mechanism of the Zincke reaction.

If a secondary amine is used instead of a primary amine, a Zincke iminium will form (**Figure 4.3**). These Zincke iminiums can be converted to Zincke aldehydes upon exposure to aqueous basic conditions.[8] Zincke aldehydes have been used as building blocks for the total synthesis of natural products, including the Vanderwal syntheses of Strychnine and Porothramycin A.[9,10] Alternatively, these iminiums have been used to produce cyanine dyes, azulenes, and benzene derivatives.[3,11,12]

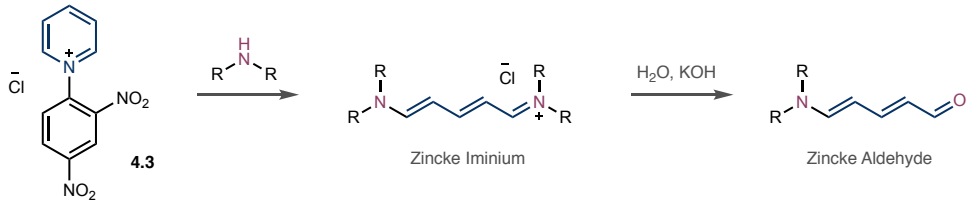


Figure 4.3. Synthesis of Zincke iminiums and Zincke aldehydes.

Pyridiniums other than Zincke salts have been shown to undergo ring-opening reactions as well. In the same year of Zincke's original publication, Konig published that *N*-cyano pyridinium salt **4.8** will react with anilines to make *N*-phenyl pyridinium salt **4.9** (**Figure 4.4, A**).[13] This observation was expanded upon by the Vanderwal group over a century later (**Figure 4.4, B**). They showed that this activation strategy could be used to ring-open pyridinyl anilines to form alpha, beta-unsaturated indole aldehydes, as shown in the conversion of **4.10** to **4.11.**[14]

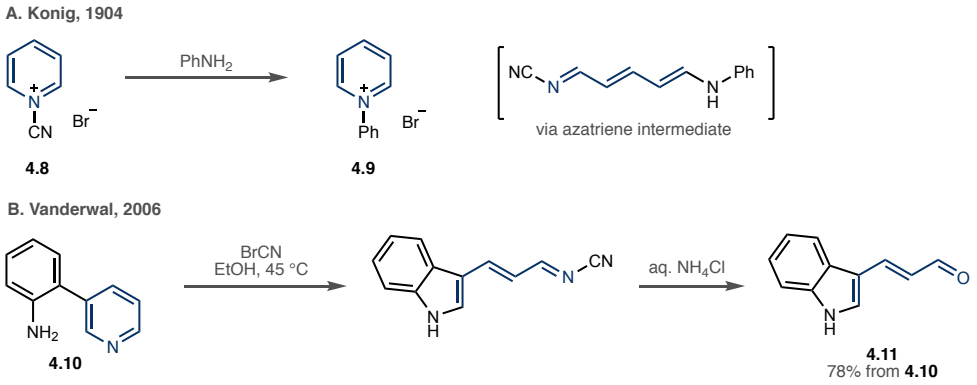


Figure 4.4. Ring-opening reactions of *N*-cyano pyridinium salts.

Other activating groups have also been used for pyridine ring-opening reactions. In 1926, Baumgarten showed that pyridinium sulfonate **4.12** will react in an aqueous sodium hydroxide solution to form glutaconaldehyde sodium salt **4.13** (**Figure 4.5, A**).[15] In 1965, Katritzky published that *N*-methoxy pyridinium salt **4.14** undergo ring-opening with hydroxide ions to produce glutaconic dialdehyde mono-O-methyloxime product **4.15** (**Figure 4.5, B**).[16]

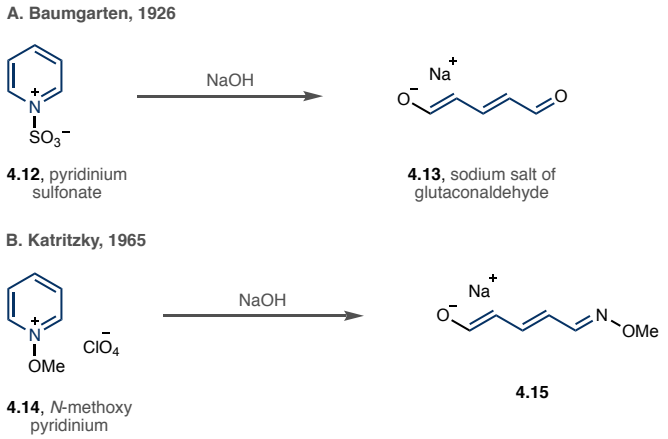


Figure 4.5. Baumgarten and Katritzky's pyridine ring-opening reactions.

In 1997, Toscano showed that *N*-triflyl (*N*-Tf) pyridinium salt **4.16** reacts with secondary amines to form *N*-Tf Zincke imine product **4.17** in 15% yield (**Figure 4.6**).[17,18] Additionally, dihydropyridine **4.18** forms as a byproduct, resulting from **4.17** reacting with the starting material **4.16**. He showed that both dimethylamine and diethylamine could be used as nucleophiles for this reaction, and they were able to isolate the resulting *N*-Tf imines in low yields. The linear trans-olefin structure they proposed is supported by ^{1}H NMR coupling constants and X-ray crystallography. In 1998, Toscano showed that these imines react with diiron nonacarbonyl to form novel organoiron compounds, although further uses of these organometallic products not published.[19] A 2005 publication from the Rivera group shows that aniline, *N*-methylaniline, and allylamine have also be used as nucleophiles to ring-open *N*-Tf pyridinium salts.[20] The *N*-Tf Zincke imines discovered by the Toscano lab are the basis of the pyridine halogenation reaction presented in this chapter.

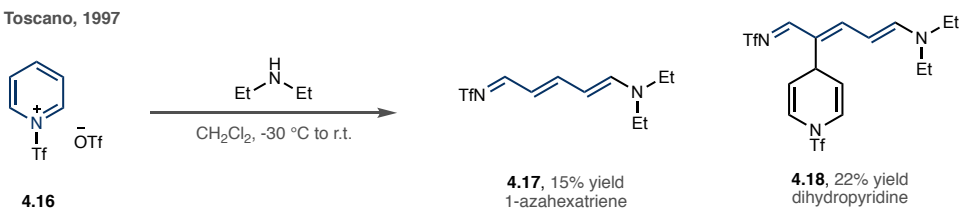


Figure 4.7. Toscano's ring-opening of *N*-Tf pyridinium salts.

4.3 A Ring-Opening Strategy for Pyridine Functionalization

Because of current limitations in 3-selective functionalization strategies on pyridines, the McNally group has been interested in developing new reactions in this area. An initial idea was to use the phosphonium salt-forming reaction to achieve 3-selective functionalization (**Figure 4.8**). We envisioned that the 1,4-dihydropyridine intermediate that forms could react with electrophiles at the 3-position, and subsequent loss of triphenylphosphine would form a 3-functionalized pyridine product.[21,22] Many attempts were made to develop this reaction, but the reaction was never general as loss of triphenylphosphine was always competitive with electrophile trapping.

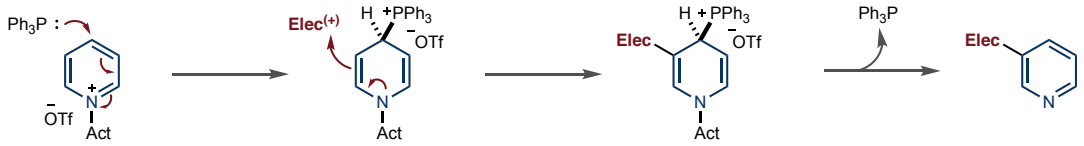


Figure 4.8. Pyridine 3-position functionalization via dihydropyridines.

An alternative approach was envisioned that used ring-opened derivatives of pyridine in place of the dihydropyridine. The goal was to develop a ring-opening/functionalization/ring-closing sequence (**Figure 4.9**). Early attempts were made to use Zincke imines, such as **4.5**, for this reaction. However, there are significant issues with this approach. First, the conditions to make Zincke salts such as **4.3** are harsh and fail on pyridines with a 2-position substituent. This would be a major limitation, as many pyridines we would want to functionalize have a 2-position substituent. Second, the conditions to perform the ring-opening step are also harsh and the imines are often not observed, as the ring-closing to form pyridinium products occurs rapidly.

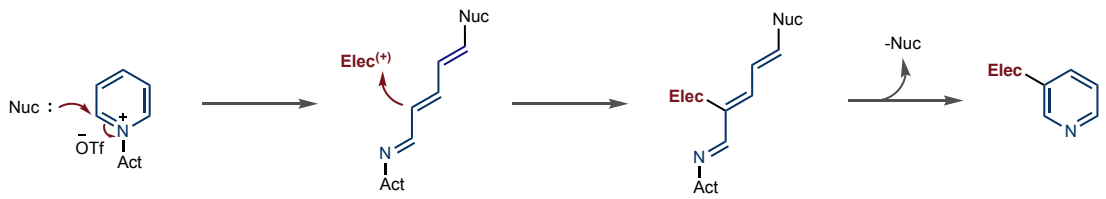


Figure 4.9. Pyridine 3-position functionalization via ring-opening/ring-closing sequence.

Alternatively, the *N*-Tf imines originally reported by Toscano form at low temperatures and are isolatable. Triflic anhydride activation is compatible with a range of different pyridine classes, including 2-substituted pyridines and a variety of complex drug-like fragments and pharmaceuticals.[23] The major limitation is that triflic anhydride does not activate 2,6-disubstituted pyridines or 2-trifluoromethyl pyridines. Our investigation began by sequentially reacting pyridine with triflic anhydride and piperidine. We found that two different products formed: 52% of the desired Zincke imine **4.18** and 20% of iminium byproduct **4.19**, obtained from product **4.18** reacting further with excess equivalents of piperidine (**Figure 4.10**).

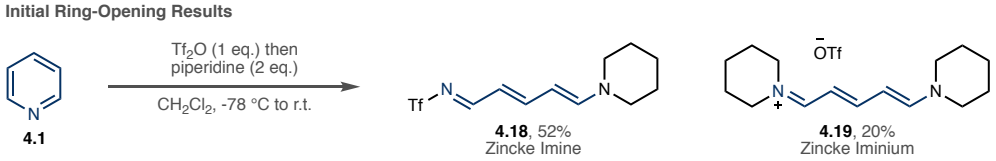


Figure 4.10. Initial result for *N*-Tf imine formation.

Further optimization showed that using dibenzylamine as a nucleophile and collidine as a base in EtOAc gave 97% of desired Zincke imine **4.20** and none of the undesired iminium product **4.21** (**Figure 4.11, top**). We believe that using a less nucleophilic amine like dibenzylamine prevents further reaction to form the Zincke iminium byproduct. In addition to optimizing on pyridine, we also looked at conditions to ring-open 2-phenylpyridine (**4.23-4.27)**. Using cyclic amines, such as pyrrolidine, piperidine, and morpholine, as well as acyclic amines, such as diisobutylamine and dibenzylamine, we found optimal ring-opening yields with dibenzylamine (**Figure 4.11, top**). For the cyclic amines that gave lower imine yields, we tend to observe higher yields of the undesired triflamidated amine, resulting from the amine attacking the triflyl's sulfur atom instead of the pyridinium's 2-position carbon atom.[24]

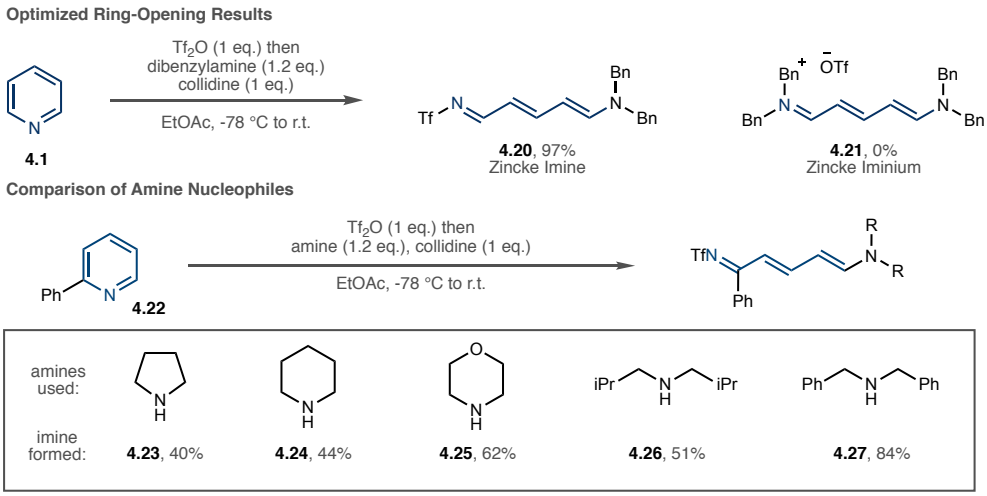


Figure 4.11. Further results for *N*-Tf imine formation.

After finding that the ring-opening reaction was high yielding on both pyridine and 2-phenyl pyridine, a series of other pyridine-containing substrates was tested. We found that pyridines with a variety of substitution patterns and functional groups could be ring-opened. Pyridines disubstituted at the 2,3- or 2,5- positions work well, as seen in examples **4.31, 4.32**, and **4.39**, and boronic ester substrate **4.33** can be ring-opened in reasonable yield. More complex examples were examined next, and we were able to ring-open a 3,3'-bipyridine to form **4.35** as well as a bis-azine to form **4.36**. Imines **4.38**, **4.39**, and **4.40** were derived from pharmaceuticals Vismodegib, Etoricoxib, and Loratadine, respectively, and all formed in reasonable yields.

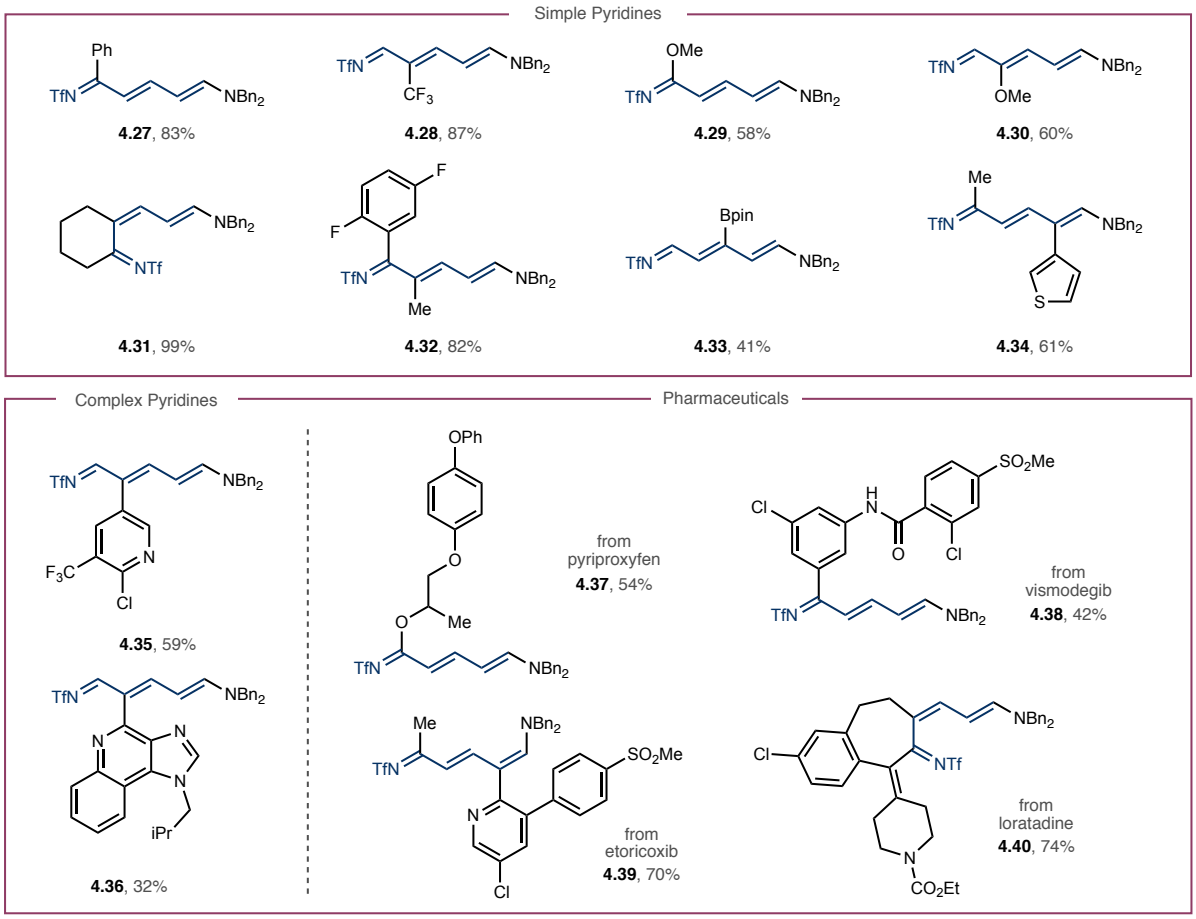


Figure 4.12. Select scope of Zincke imine formation from pyridine precursors.

We then investigated strategies to convert the ring-opened imines to the pyridines that they are derived from. Ammonium salts such as ammonium acetate and ammonium chloride are inexpensive and easy to handle. Adding ten equivalents of ammonium acetate and heating 2-phenyl Zincke imine **4.27** to 60 °C for 2 hours yields 2-phenyl pyridine **4.22** in 90% yield (**Figure 4.13, top**)[25,26] Alternatively, some of the imines will recyclize in the presence of trifluoroacetic acid (TFA) (**Figure 4.13, bottom**).[27] This is typically dependent on the substituent pattern on the imine, as 3-substituted imines such as **4.41** will recyclize within one hour with two equivalents of TFA, while the 2-phenyl imine **4.27** recyclizes very slowly under these conditions.

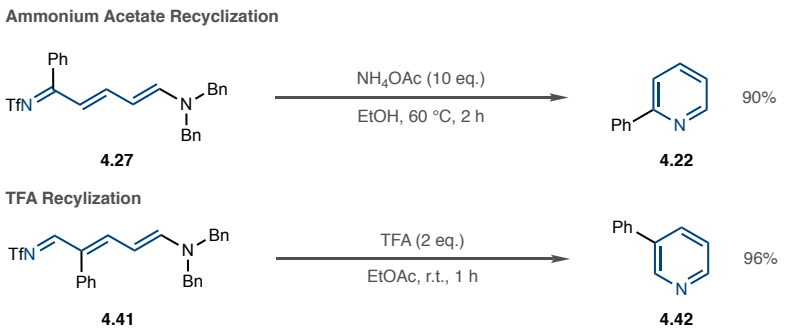
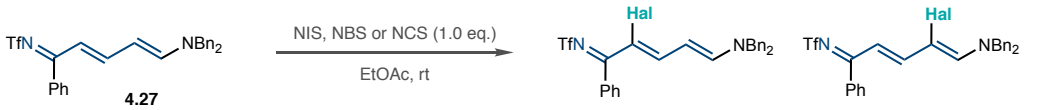


Figure 4.13. Conversion of Zincke imines to pyridines using ammonium acetate or trifluoroacetic acid.

4.4 Electrophilic Halogenation of Zincke Imines

After finding that we could convert first pyridines to Zincke imines and then Zincke imines to pyridines, we looked to explore the reactivity of imines. We hypothesized that the polarized alkenes should behave similarly to enamines, and therefore react easily with electrophiles.[28,29] We were drawn to halide electrophiles, as accessing 3-halogenated pyridines would be a major advancement in the field of pyridine functionalization.[30]

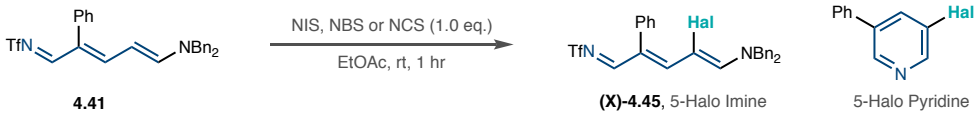
Because *N*-Tf Zincke imines appear to have two nucleophilic carbon atoms, we expected to see a mixture of halogenated products when reacting them with electrophilic halogenation reagents. When we reacted imine **4.27** with one equivalent of NIS in EtOAc, we were surprised to exclusively observe 3-iodinated imine **I-4.43** in nearly quantitative yield (**Figure 4.14**). Bromination with NBS in EtOAc yielded a 4:1 mixture of 3- and 5-brominated products (**Br-4.43** and **Br-4.44)**, but we found that switching the solvent to CH_2Cl_2 improved the 3-position selectivity to >20:1 in favor of the 3-brominated product. Chlorination with NCS was low yielding and gave the 5-chlorinated product as the major product.



NXS / conditions	3-Halo Imine (%)	5-Halo Imine (%)
NIS	92	0
NBS	75	17
NBS, –78 °C, CH_2Cl_2	92	1
NCS	6	21

Figure 4.14. Reaction of 2-phenyl Zincke imine with electrophilic halogenation reagents.

Upon finding that the 3-position was preferentially halogenated in the presence of NIS and NBS, we questioned what would happen if we used an imine where the 3-position was substituted (**Figure 4.15**). Reacting imine **4.41**, derived from 3-phenyl pyridine, with NIS results in none of the desired 5-iodinated product **(I-4.45)**. The starting material decomposes into an unidentified byproduct when the reaction was heated to 50 °C. We proposed that we needed a more electrophilic halogenation reagent, and there is literature precedent for using TFA to make NIS more reactive.[31,32] Reacting imine **4.41** with NIS and two equivalents of TFA, we observed none of the iodinated imine product, but instead saw 90% of the 5-iodinated pyridine product. Under these conditions, the imine is rapidly iodinated at the 5-position and then the resulting imine intermediate ring-closes in situ to produce the iodinated pyridine. The TFA promoted ring-closing of the halogenated imine is faster than the starting material imine, likely due to 1,3-allylic strain between the large iodine atom and the 3-position substituent. This results in minimal background cyclization, as only minor amounts of 3-phenyl pyridine are observed.



NXS / conditions	5-Halo Imine (%)	5-Halo Pyridine (%)
NIS	0	0
NIS + TFA (2.0 eq)	0	90
NBS + TFA (2.0 eq)	0	76
NCS (1.2 eq) + HCl (4.0 eq), CH_2Cl_2	0	76

Figure 4.15. Reaction of 3-phenyl Zincke imine with electrophilic halogenation reagents.

Bromination of the 3-phenyl adduct with NBS does proceed without acid, but we found addition of TFA to be higher yielding and a quicker reaction. Chlorination with NCS is low yielding with TFA, as the background cyclization outcompetes the chlorination, returning 3-phenyl pyridine **4.42**. However, using NCS, HCl as the acid, and CH_2Cl_2 as the solvent was found to form the 5-chlorinated product in 76% yield.[33] Fluorination of both the 2-phenyl and 3-phenyl imines proved challenging, and these results will be discussed in more depth in Chapter 5.5.

4.5 One-Pot Halogenation of Pyridines and Diazines via Zincke Imine Intermediates

Upon finding conditions to ring-open, functionalize, and then ring-close the pyridines, we hoped to sequence the steps together to achieve a one-pot reaction (**Figure 4.16**). We were able to iodinate and brominate the 3-position of 2-phenylpyridine using the neutral *N*-halosuccinimide conditions, forming products **4.46** and **4.47** in 68% and 58% yield, respectively. 3-Phenyl pyridine was converted to iodopyridine **4.48** in 82% yield, bromopyridine **4.49** in 81% yield, and chloropyridine **4.50** in 79% yield, all in one-pot reactions using the acidic conditions. We were excited to find that sequencing these steps together into a one-pot reaction provided the halogenated products in high yields.

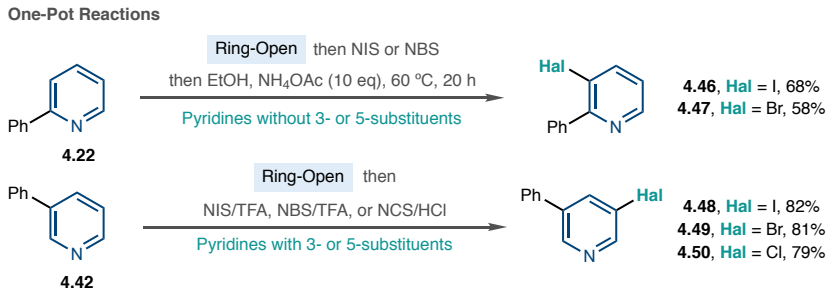


Figure 4.16. One-pot halogenation protocols for 2- and 3-phenyl pyridine.

The next step was to explore the substrate scope of the reaction (**Figure 4.17**). We selected iodination for most substrates as the reaction conditions were the simplest and the yields were often the best. We picked 32 building block azines to halogenate and found that the scope is very

general. Pyridines with different substitution patterns are tolerated, and notably 2,4-disubstituted pyridines are still iodinated at the 3-position to form products **4.68** and **4.69** with >20:1 selectivity. In a couple cases, the reaction was higher yielding when done in two separate stages, and that was performed when forming halopyridines **4.58**, **4.66**, and **4.80**. Select examples of bromination and chlorination are additionally shown here, including on 2,5-disubstituted pyridines to form products **4.71** and **4.72**. Trihalogenated pyridines **4.74** and **4.75** can be made with this method, and azines other than pyridines work too. Notably, 4-phenylpyrimidine undergoes the ring-opening reaction to form the iodinated, brominated, and chlorinated derivatives **4.76-4.78**.

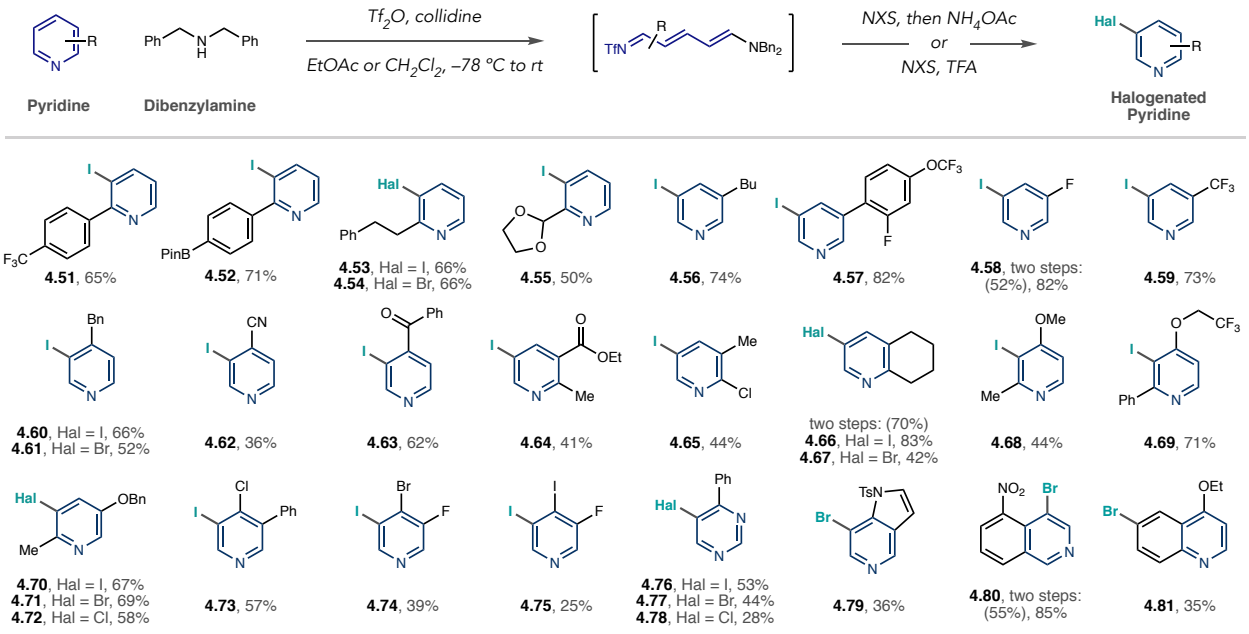


Figure 4.17. One-pot halogenation scope for building block pyridines.

Quinoline and isoquinoline substrates did not undergo the ring-opening reaction, but instead formed a dearomatized cyclic intermediate that was still able to undergo bromination with NBS. In the case of 5-nitroisoquinoline, the dearomatized intermediate **4.83** was isolated and characterized (**Figure 4.18**). Halogenation of these intermediates via a modified procedure is possible. Using NBS in CH_2Cl_2, brominated intermediate **4.84** forms, and addition of TFA at room temperature leads to rearomatization of the azine.

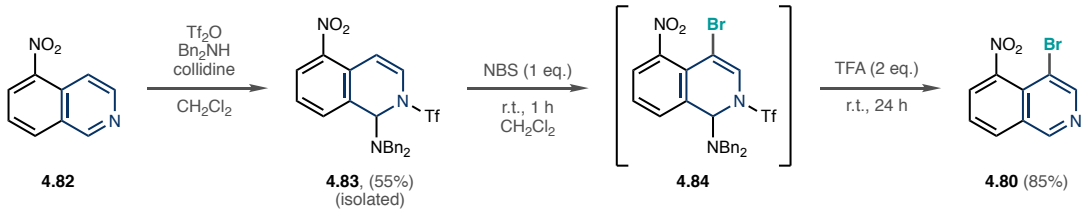


Figure 4.18. Details of ring-closed bromination protocol.

Subsequently, a series of substrates with electron-rich aromatics was studied (**Figure 4.19**). Iodination of the Zincke imine outcompetes many electron-rich aromatics, such as thiophenes, furans, and anisoles to form iodopyridines **4.85**, **4.86**, and **4.87**. Furopyridines, azaindoles, and thienopyridines were also amenable to the reaction conditions, and iodinated derivatives **4.98-4.92** all formed in high yield. In all cases here, no undesired iodination of the electron-rich aromatics was observed.

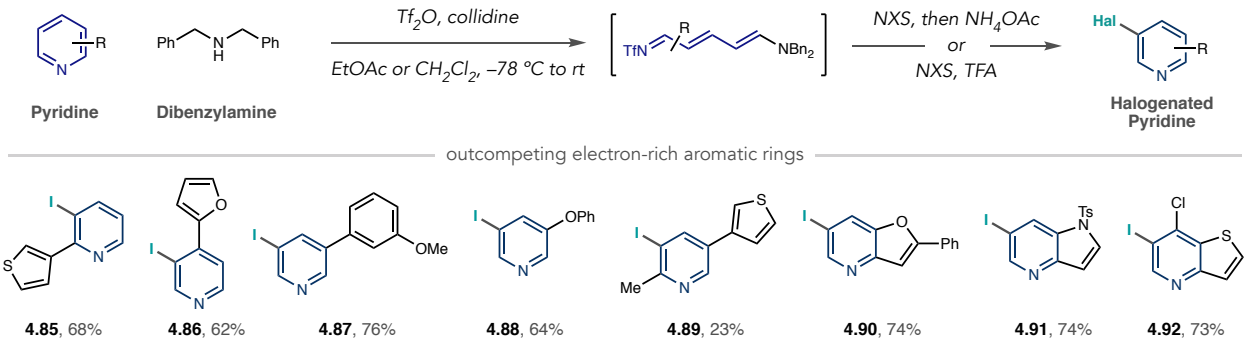


Figure 4.19. Iodinating pyridine substrates that contain electron-rich aromatics.

Next, a series of more complex azine-containing substrates were halogenated, including nine drug-like fragments and 8 bioactive molecules (**Figure 4.20**). Many examples of both iodination and bromination are shown, and in the case of Loratadine, chlorination is shown as well (**4.110-4.102**). Pyridines **4.105** and **4.106** formed atropisomers, suggesting an asymmetric halogenation is possible. Haloquinolines **4.100**, **4.116**, and **4.117**) were formed from quinoline precursors, and isoquinoline **4.99** was synthesized with this strategy. This reaction proved to be

general on late-stage compounds and accessing many of these products via other late-stage methods could be challenging or impossible.

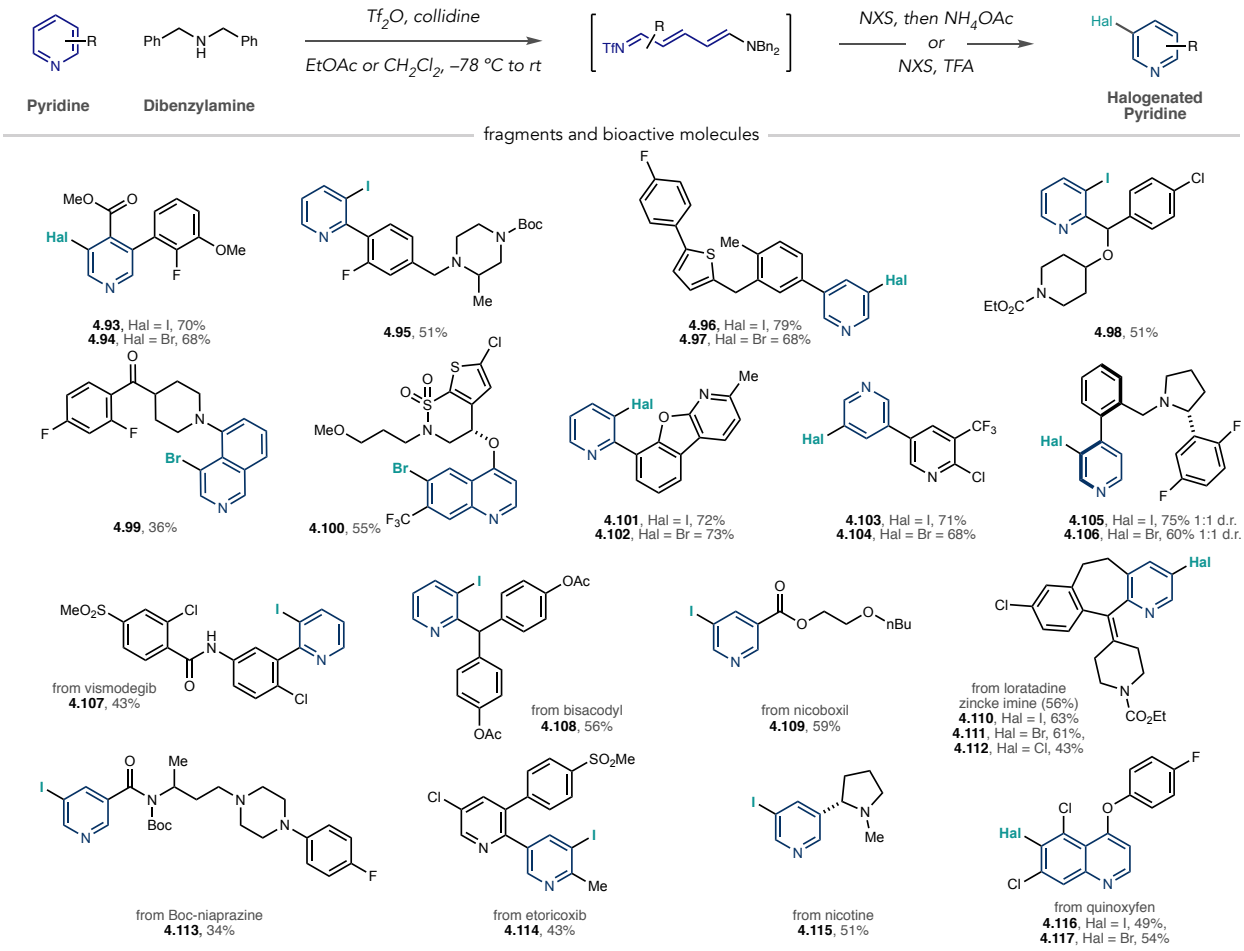


Figure 4.20. One-pot halogenation scope for fragments and bioactive molecules.

4.6 Dihalogenation of Pyridines via Zincke Imine Intermediates

Beyond accessing singly halogenated azines, we questioned whether we could combine the neutral and acidic halogenation conditions to achieve a dihalogenation of pyridine. Installing two halide atoms on the same pyridine ring is desirable, as now there are two functional handles to further derivatize.[34–36] Dihalogenation is a significant challenge via existing methods, as many existing halogenation reactions have selectivity issues.

The dihalogenation was successfully achieved in a two-pot sequence (**Figure 4.21**). 2-phenyl imine **4.27** was formed in situ and directly halogenated directly with either NIS or NBS. The iodinated and brominated imines (**X-4.43**) were then purified via precipitation, and both were isolated in 80% yield. Those imines were subjected to the NXS/TFA conditions and dihalogenated pyridines **4.118-4.123** were formed. To make dichloropyridine **4.114**, 2-phenyl imine **4.27** was reacted with two equivalents of *N*-chlorosuccinimide and four equivalents of HCl. This approach allowed us to rapidly make seven different dihalogenated derivatives of 2-phenyl pyridine.

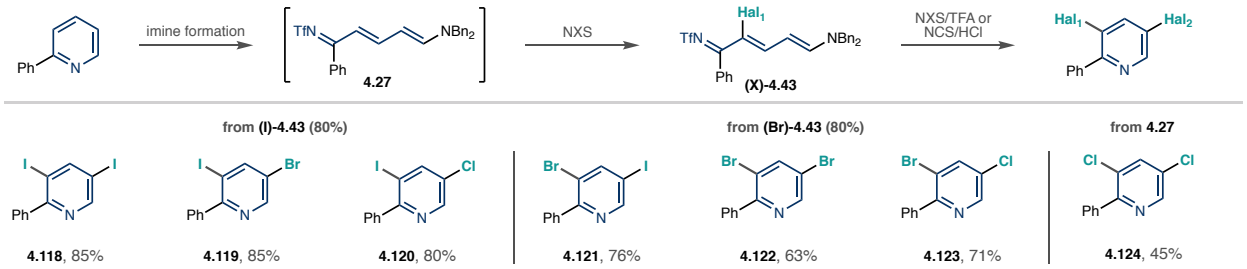


Figure 4.21. Dihalogenation of 2-phenyl pyridine.

Additionally, this dihalogenation method works on the pharmaceutical Vismodegib (**Figure 4.22**). Imine formation and iodination yields iodinated Vismodegib imine product **4.113** in 50% yield, and subsequent chlorination of the 5-position with NCS and TFA gives dihalogenated Vismodegib derivative **4.114** in 74% yield.

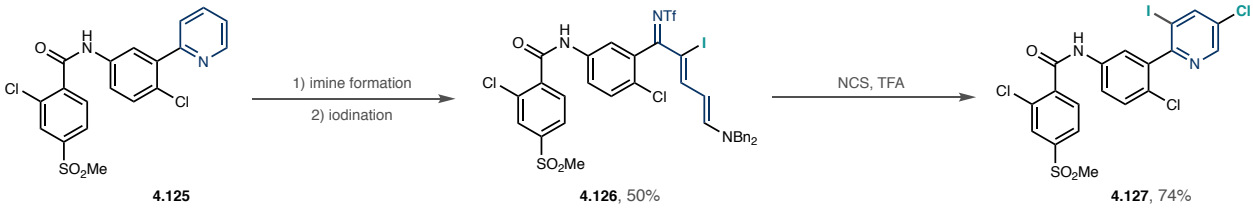


Figure 4.22. Dihalogenation Vismodegib.

4.7 Mechanism and Computational Studies

We were interested in studying the source of 3-position selectivity for the neutral *N*-iodosuccinimide and *N*-bromosuccinimide reactions. Computations were performed by Louis de

Lescure, a coworker who is co-advised by Professor Rob Paton. Fukui indices were calculated for the Zincke imine, and the values for the 3- and 5-position were very similar.[37] This suggests that there is not an inherent electronic difference between positions on the imine responsible for the observed selectivity. The reaction profiles for the halogenation reaction were then studied. We believe the halogenation operates via a simple two-electron pathway, where succinimide first transfer the halogen atom to the imine to form **Int-1**, then the succinimide anion deprotonates the resulting iminium, thereby reconjugating the molecule to form the halogenated imine product (**Figure 4.23**).

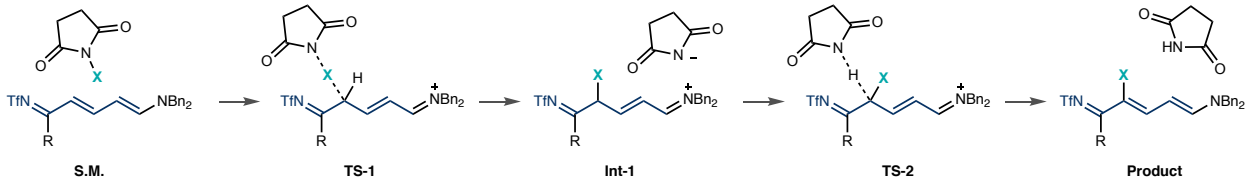


Figure 4.23. Mechanism for Zincke halogenation.

Reaction profiles for NCS, NBS, and NIS halogenating the 3- and 5-positions were computed (**Figure 4.24**). Computations predict that the rate-limiting step of the chlorination and bromination reactions is the halogen-transfer step. Chlorination with NCS has a very early transition state which resembles the starting material **S.M.** more than **Int-1**.[38] As a result, the poor selectivity of the chlorination reaction is due to the lack of inherent reactivity in the starting material. The bromination transition state is later, and so the transition state resembles **Int-1** more than the starting material **S.M**. The energy barrier for the 5-position bromination is 2.6 kcal/mol higher than the 3-position bromination. We believe the source of selectivity is the preference to have a conjugated imine rather than a conjugated iminium in the transition state.

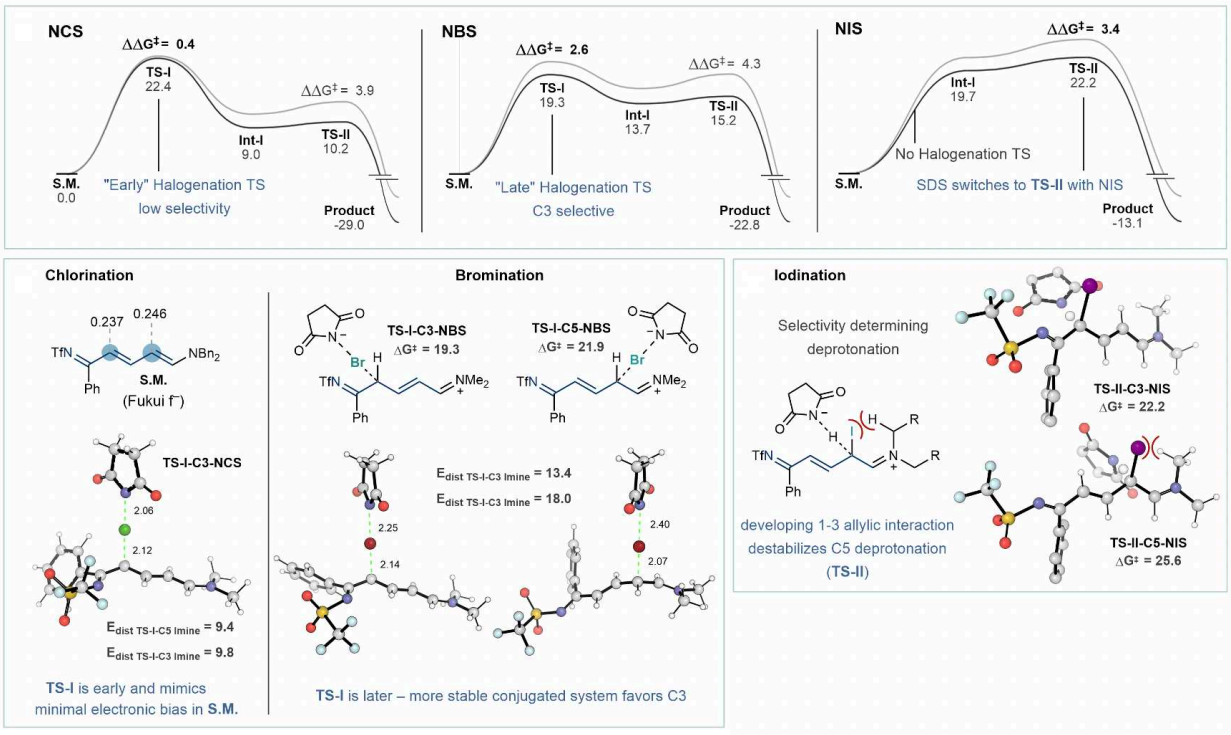


Figure 4.24. Computational studies for Zincke halogenation.

Computations predicted that the rate-limiting step of the iodination reaction is the deprotonation step, and no transition state was found for the halogen-transfer step. Deprotonation of the 5-iodinated iminium intermediate was calculated to be 3.4 kcal/mol higher in energy than the 3-position iodination. We believe the source of selectivity is an unfavorable 1,3-allylic interaction that would need to develop for the 5-iodinated iminium to be deprotonated.[39] The specific interaction is between the large iodine atom at the 5-position and the methylene group on the dibenzylamine side. This steric interaction is avoided when the iodine is at the 3-position, and the reversibility of the halogen-transfer step enables the 5-iodinated intermediate to be converted to the 3-iodinated intermediate.

Experimentally, this difference in rate-determining steps can be supported with a KIE study.[40] Because the reaction is very fast at room temperature and heterogenous at low temperatures, performing a rate-study was challenging. Instead, we ran an intermolecular

competition study. We synthesized a deuterated isotopolog of the 2-phenyl imine **4.129** by deuterating 2-phenyl-3-iodopyridine **4.46** and then performing the standard ring-opening reaction **(Figure 4.25)**.

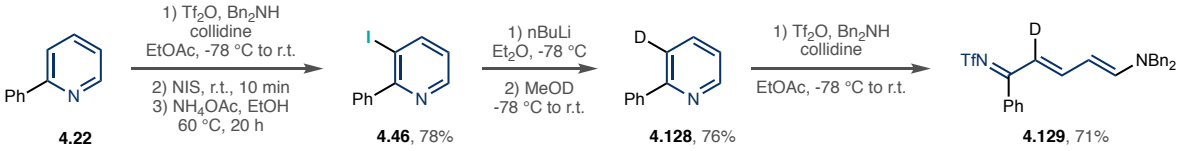


Figure 4.25. Synthesis of deuterated isotopolog of 2-phenyl imine.

One equivalent of both protonated imine **4.27** and deuterated isotopolog **4.129** were added to a reaction vial, and one equivalent of either NBS or NIS was added (**Figure 2.26**). After 10 minutes, both reactions had consumed all the *N*-halosuccinimide reagent, and the deuteration content of the remaining starting material was analyzed. In the NIS case, we observed a significant enrichment of deuterated imine (**4.129** / **4.27** = 2.70) suggesting that the deprotonation step could be the rate-limiting step. Alternatively, in the NBS case, we observed similar amounts of protonated and deuterated starting material remaining (**4.129** / **4.27** = 1.06). The lack of significant bias towards bromination suggests that deprotonation is not the rate-limiting step here.

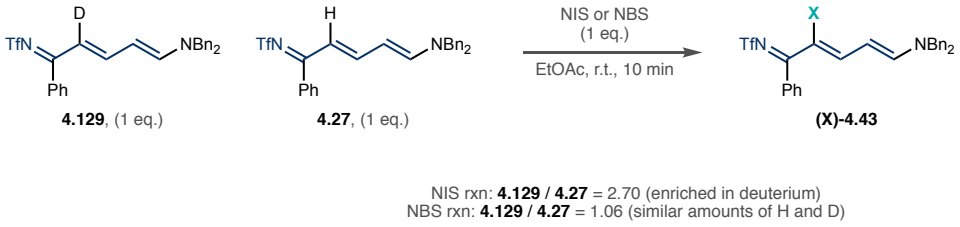


Figure 4.26. Intermolecular competition experiment.

4.8 Conclusion

The chapter shows that pyridines can be easily halogenated at the 3- and 5-position using a ring-opening/functionalization/ring-closing sequence. The imine intermediates that are formed are much more nucleophilic than pyridine itself, enabling a mild halogenation at room temperature. The reaction is simple and fast to perform, and the iodination and bromination proceed with

notably high regioselectivity. Computational and experimental mechanistic studies help explain the source of selectivity for these reactions.

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CHAPTER FIVE

FURTHER DEVELOPMENTS WITH ZINCKE IMINES AND IMINIUMS

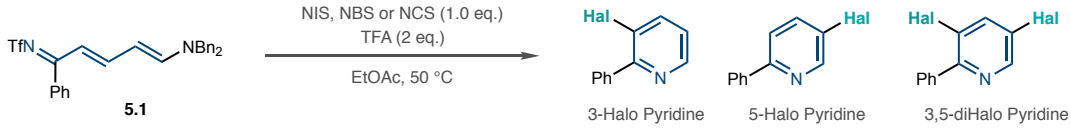
5.1 Chapter Overview

This chapter presents further developments of the Zincke imine chemistry described in Chapter Four. Strategies are described that expand the scope of the halogenation reaction to achieve 5-selective iodination, 5-selective chlorination, and 3-selective chlorination of 2-substituted pyridines. The reactions of Zincke imines with electrophilic fluorination reagents is described here as well. Beyond halogenation, this chapter shows that pyridines can be isotopically labeled with deuterium and nitrogen-15 atoms via Zincke imine intermediates. Finally, strategies to modify the ring-closing step and form rearranged pyridine or benzene products are presented. Ben Boyle optimized the ring-opening reaction that forms Zincke imines and iminiums, Ben Uhlenbruck discovered and explored the scope of the *N*-phenyl imine chlorination strategy, and Marie Anderson worked on the optimization of the fluorination reaction.

5.2 Switching Halogenation Site-Selectivity with Zincke Iminium Intermediates

As described in Chapter Four, the reaction of *N*-Tf imines with *N*-iodosuccinimide and *N*-bromosuccinimide is highly selective for halogenating the 3-position, and we questioned if there was a way to switch halogenation selectivity to the 5-position. Accessing differently halogenated products could be useful for chemists hoping to make libraries of pyridine derivatives.[1] The initial strategy to access 5-halogenated pyridines was to react *N*-Tf imines with *N*-halosuccinimide reagents in the presence of trifluoroacetic acid (TFA). We had previously established that this combination of reagents can halogenate the 5-position, but it had only been applied on substrates where the 3-position was substituted.

Reacting 2-phenyl imine **5.1** with one equivalent of *N*-halosuccinimide reagents and two equivalents of TFA led to a mixture of halogenated pyridine products (**Figure 5.1**). In all cases, both monohalogenated pyridines and the dihalogenated pyridine were observed. However, we were excited to observe the 5-halogenated pyridine as the major product in all three cases. This might be caused by a difference in the rates of the acid-promoted recyclization step. Previously, we had observed that 2,5-disubstituted imines recyclize faster than 2,3-disubstituted imines, potentially due to 1,3-allyl strain between the 5-position substituent and the benzyl group of the dibenzylamine moiety. This was a promising first result, and we hypothesized that screening acids and solvents might improve the yield and selectivity of this reaction.



NXS / conditions	3-Halo Pyridine (%)	5-Halo Pyridine (%)	3,5-diHalo Pyridine (%)
NIS-TFA	8	20	8
NBS-TFA	8	24	17
NCS-TFA	6	36	10

Figure 5.1. Reaction of Zincke imine with *N*-halosuccinimides in the presence of trifluoroacetic acid (TFA).

As an alternative approach, we questioned if other Zincke-type structures would lead to different regioselectivity outcomes when reacted with electrophilic halogenation reagents. We knew we could drastically change the reactivity by using two equivalents of an amine nucleophile to form an iminium cation. These Zincke iminium structures were sometimes observed during the ring-opening optimization studies, and we questioned how these would react under the halogenation conditions. These iminium cations are known in the literature as intermediates in the reaction to form Zincke aldehydes.[2] They are sometimes referred to as streptocyanine dyes, which differ from traditional cyanine dyes in that their amino and imino groups are open-chain instead of closed-chain (**Figure 5.2**).[3–5] They are also similar to vinamidinium salts, which have been used

for *de novo* syntheses of pyridines and pyrimidines.[6,7] Unsubstituted Zincke iminiums have previously been reported to react with carbon electrophiles, and so decided to investigate their reaction with halogen electrophiles. [8]

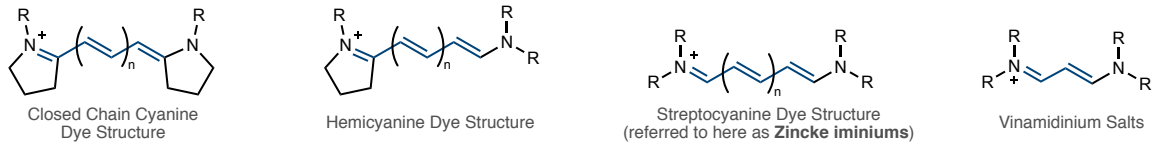


Figure 5.2. Classification of cyanine dyes and structure of Zincke iminium.

We found that the addition of three equivalents of pyrrolidine to *N*-Tf dibenzylamine imines formed Zincke iminiums in quantitative yield (**Figure 5.3, A**). Dipyrrolidine iminium **5.4** was synthesized in one-pot from 2-phenyl pyridine **5.3** by performing the standard dibenzylamine ring-opening reaction and then adding an excess of pyrrolidine (**Figure 5.3, B**). While direct addition of pyrrolidine to *N*-Tf 2-phenyl pyridinium does form the desired product, we found these dibenzylamine conditions to be higher yielding. Iminium **5.4** was isolated in 50% yield by performing a basic workup and then precipitating out the iminium in hexanes. These iminiums could be isolated as solids and no decomposition was observed after storage under air at room temperature for several months.

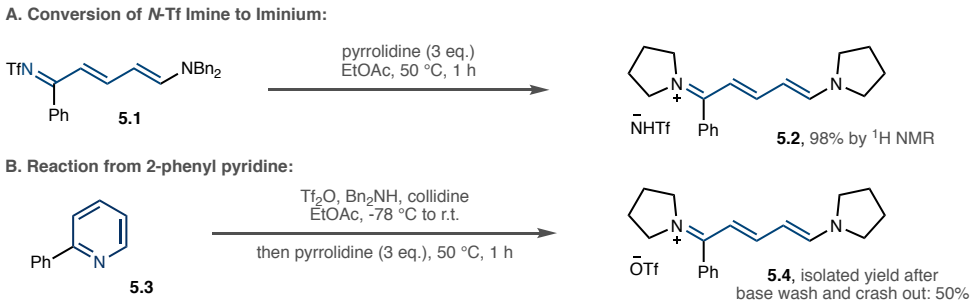
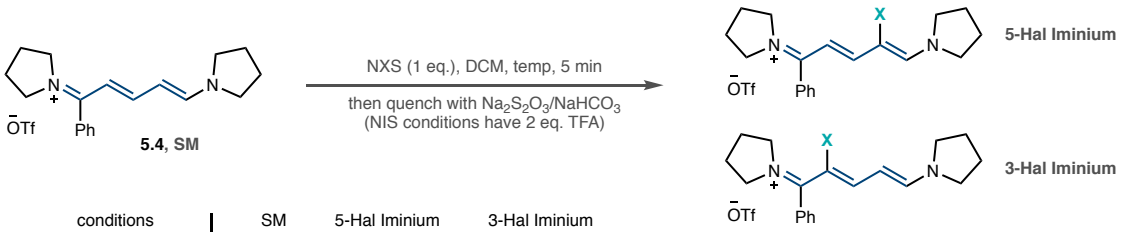


Figure 5.3. Synthesis of Zincke iminium from *N*-Tf imine or 2-phenyl pyridine.

The reactions of iminium **5.4** with electrophilic halogenation reagents was then investigated (**Figure 5.4**). Reacting with one equivalent of NIS leads to decomposition and no desired iodination. Instead, reacting **5.4** with one equivalent of NIS and two equivalents of TFA

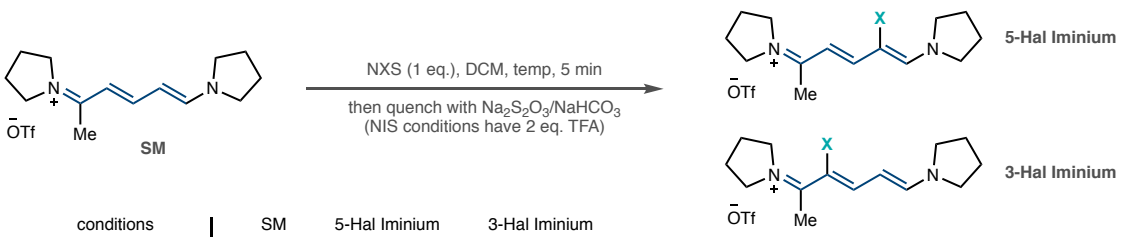
leads to productive iodination of the imine. Not only did the reaction work in 77% yield, but it was highly selective (>20:1) for the 5-position. Reacting **5.4** with NBS gives the corresponding brominated iminium in 73% yield with a 5:1 regioisomeric ratio in preference of the 5-position. Interestingly, selectivity is worsened when the reaction was run at -78 °C, and so we believe the bromination is reversible and the 5-brominated iminium ion is the thermodynamic product. Chlorination with NCS was lower yielding (50% combined) and gives a preference for the 3-chlorinated product (r.r = 2.3:1). After halogenation, the iminium ions can be recyclized to the pyridine by heating to 60 °C with ammonium acetate in ethanol overnight. The acid-promoted recyclization strategy employed for the Zincke imines is not applicable to these iminiums.



conditions	SM	5-Hal Iminium	3-Hal Iminium
NIS/TFA, r.t.	15	77	tr
NBS, r.t.	16	61	12
NBS, -78 °C	17	29	32
NCS, r.t.	35	15	35
NCS, 0 °C	59	9	20

Figure 5.4. Reactions of 2-phenyl Zincke iminium with electrophilic halogenation reagents.

It was unexpected that we would achieve any selectivity on these iminiums as are almost electronically symmetrical. We questioned if we would still observe a selective reaction if the 2-position substituent was different, such as an alkyl group instead of an aryl group. A Zincke iminium derived from 2-methyl pyridine was synthesized and the same screen of halogenation reagents was performed (**Figure 5.5**). We were pleased to see similar yields, selectivity, and reaction trends.



conditions	SM	5-Hal Iminium	3-Hal Iminium
NIS/TFA, r.t.	28	57	n.d.
NBS, r.t.	10	57	tr
NBS, -78 °C	34	25	4
NCS, r.t.	32	19	27
NCS, 0 °C	35	14	28

Figure 5.5. Reactions of 2-methyl Zincke iminium with electrophilic halogenation reagents.

We then wanted to see if we could perform the 5-halogenation reaction in a one-pot sequence and found the NIS iodination performs similarly when the iminium is formed *in situ* from 2-phenyl pyridine. In contrast, bromination using NBS with or without TFA was unsuccessful in these cases. Therefore, we opted to focus on iodination as a more promising strategy towards a one pot 5-position halogenation.

We found that using having DMF present as a co-solvent improved the yield of the iodination step. Additionally, adding one equivalent of dimethylsulfide five minutes into the iodination step also improved the yield, potentially due to a quenching of the active iodination reagent which could prevent decomposition of the iodinated iminium products.[9] The steps were able to be sequenced into a one pot reaction, and a selection of 2-substiuted pyridines were iodinated at the 5-position (**Figure 5.6**). Notably, electron-rich aromatic substituents such as 4-methoxyphenyl and 3-furyl were still compatible with the halogenation reaction, and no iodination of those rings was observed in the synthesis of iodopyridine **5.6** and **6.7**. Current efforts are ongoing to further improve the yield and to expand the substrate scope to more complex examples.

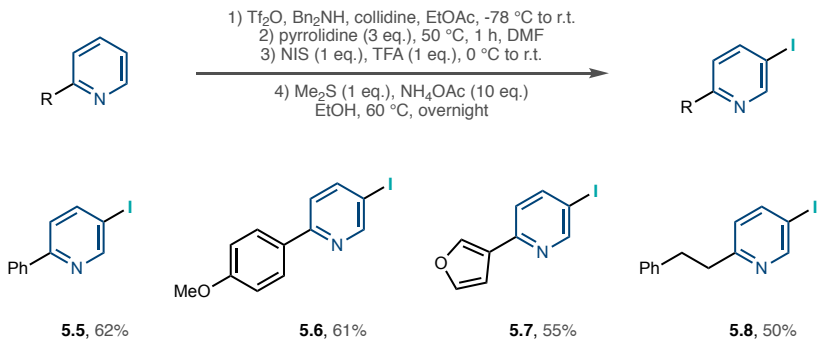


Figure 5.6. One-pot 5-iodination strategy for 2-substituted pyridines.

In studying the source of selectivity for this reaction, Louis de Lescure calculated the relative energies of brominated iminiums **5.9** and **5.10** (**Figure 5.7**). It was found that the 5-brominated iminium **5.10** was 2.3 kcal/mol lower in energy than 3-brominated iminium **5.9**. We believe that iminium **5.9** is destabilized due to two groups sterically clashing with the pyrrolidine substituent instead of just one.

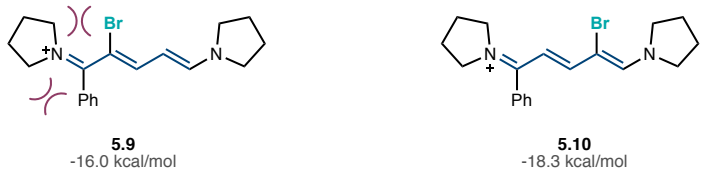


Figure 5.7. Relative energies of 3- and 5-brominated iminium products. Energy values are relative to the dehalogenated iminium and NBS.

5.3 Chlorination of Zincke Imines using Iodine Monochloride

Another modified halogenation strategy was discovered while developing ways to recyclize the halogenated Zincke imine intermediates formed in Chapter Four. When the 2-phenyl imine **5.1** is iodinated at the 3-position to form imine **5.11**, ammonium acetate works best for recyclization to iodopyridine **5.12**. However, adding TFA to the imine **5.11** results in minor amounts of 3,5-diiodinated pyridine **5.13** being formed, as well as imine **5.1**. Presumably, this resulted from a scrambling of the halide from the 3-position to the 5-position. Because this effectively destroys the selectivity achieved in the halogenation step, we questioned if other acids could promote the recyclization while avoiding the scrambling process.

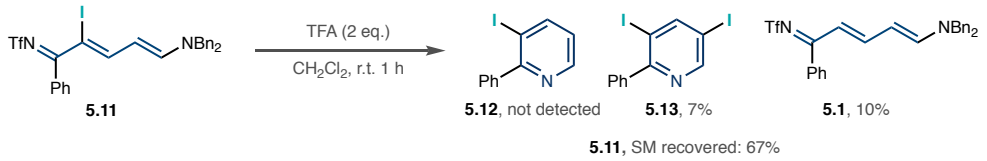


Figure 5.8. Reaction of iodinated *N*-Tf imine with TFA.

In a screen of acids, HCl was used to recyclize the 2-phenyl-3-iodo imine (formed *in situ* from imine **5.1**). After heating to 50 °C for 20 hours, we observed none of the desired 2-phenyl-3-iodo pyridine product. Instead, we observed formation of 2-phenyl-5-chloropyridine **5.14** in 78% yield. We were surprised to see this as the major product, as no electrophilic chlorination reagent had been added directly. This was seen as a promising approach to access 5-chloropyridine products. We found that other 2-substitued imines also produce 5-chlorinated pyridines under these conditions (**Figure 5.9**). 2-Ethylpyridine forms chloropyridine **5.16** in 29% yield, and despite the yield being low, the reaction is still highly selective for the 5-chloro product and none of the 3-chlorinated pyridine products were detected. We questioned if the reaction could be performed in a one-pot sequence, and this was shown on 2-phenyl pyridine to produce the 5-chloropyridine **5.14** in 45% yield. Using the isolated imine intermediate, the two steps (82% and 78%) produce an average yield of 64%, and it is currently unclear why the yield drops in the one-pot reaction.

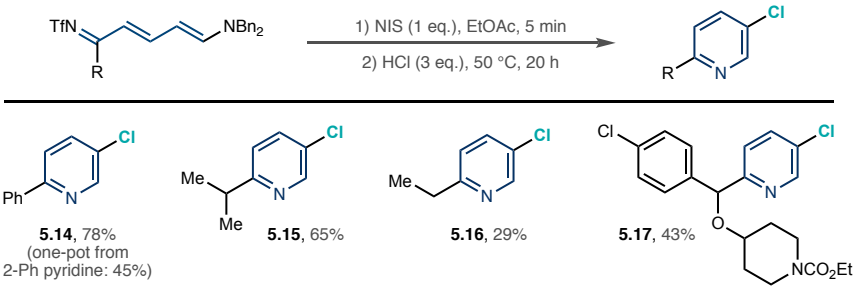


Figure 5.9. Select scope of pyridine 5-chlorination.

Mechanistically, we propose that iodine monochloride is formed in this reaction. NIS selectively iodinates the 3-position to form **5.11** and adding HCl will then deiodinate the iodinated intermediate to form Zincke imine **5.1** with iodine monochloride as a byproduct (**Figure 5.10**).

Iodine monochloride then chlorinates the 5-position to make imine **5.18** with hydrogen iodide as a byproduct. The hydrogen iodide that forms then promotes the recyclization step to form chloropyridine **5.14**. We believe that iodine monochloride, which is typically an electrophilic iodination reagent, chlorinates at both the 3- and 5-positions, but the halogenation is reversible and a faster ring-closing of the 5-chloro imine is responsible for the observed selectivity.[10,11]

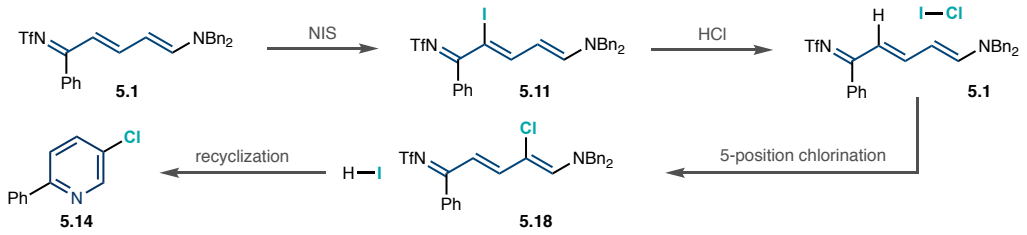


Figure 5.10. Proposed mechanism for 5-chlorination reaction.

As a mechanistic study, imine **5.1** was reacted with one equivalent of iodine monochloride and two equivalents of HCl (**Figure 5.11**). The yield of 2-phenyl-5-chloropyridine **5.14** was 78%, which is identical to the yield when NIS and HCl were used. Because the solid NIS reagent is easier to use in lab than the liquid and reactive iodine monochloride reagent, NIS conditions are being pursued, and current efforts are ongoing to improve the reaction yields.

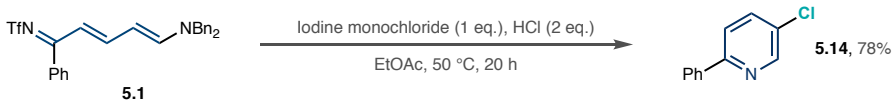


Figure 5.11. 5-Selective chlorination of Zincke imines using iodine monochloride and HCl.

5.4 Chlorination of *N*-Phenyl Imines

A third modification to the halogenation reaction was discovered by a coworker, Ben Uhlenbruck. An early approach to modify Zincke imine reactivity was to change the amine substituent on the *N*-Tf imine. As described in Chapter Four, amines other than dibenzylamine can add to *N*-Tf pyridiniums to form Zincke imines, and addition of aniline is high yielding and leads

to bench-stable solid products (**Figure 5.12**).[12] From 2-phenyl pyridine, the corresponding anilinyl imine **5.13** forms in 86% yield.

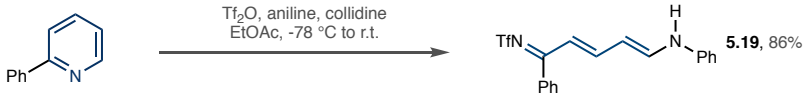
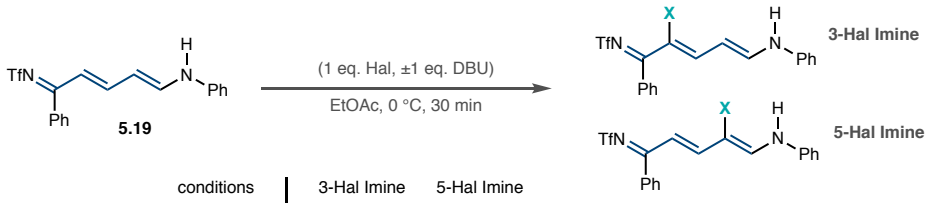


Figure 5.12. Synthesis of *N*-phenyl imines.

An interesting feature of the *N*-phenyl Zincke imines is that the N-H proton can be deprotonated to further modify the nucleophilicity of the imine. The reactivity of these imines with electrophilic halogenation reagents was tested under both neutral and basic conditions (**Figure 5.13**). When these imines are reacted with DBU and NCS, they are selectively chlorinated at the 3-position in 85% yield (>20:1 r.r.). Bromination under similar conditions is also 3-selective and forms 66% of the 3-brominated imine. Interestingly, the regioselectivity switches to the 5-position when NIS is used with DBU, and 89% of the 5-iodinated imine forms. These adduct can be ring-closed with ammonium acetate as well, although an acid-promoted recyclization using methanesulfonic acid at 40 °C is higher yielding.



conditions	3-Hal Imine	5-Hal Imine
NCS	48	9
NCS/DBU	85	1
NBS	67	4
NBS/DBU	66	8
NIS	4	1
NIS/DBU	0	89

Figure 5.13 Reaction of *N*-phenyl imines with electrophilic halogenation reagents.

The 3-chlorination reaction can be sequenced into a one-pot reaction. Because the imines decompose in the presence of excess NCS, special precautions are made to run the reaction at low temperature (-50 °C) and quench excess NCS with aqueous sodium thiosulfate before warming

the reaction to room temperature. Removing the aqueous layer and heating with methanesulfonic acid gives the 3-chlorinated pyridines in reasonable yield. Applying 2-phenyl pyridine to the one-pot reaction conditions gives 3-chloropyridine **5.20** in 71% yield (**Figure 5.14**). More pyridines were applied to the reaction conditions, and it was found that anisoles and alkyl groups at the 2-position were tolerated, as seen in examples **5.21** and **5.22**. 2,5-Disubstituted pyridines are competent here and chloropyridine **5.23** can be formed in 74% yield when *ortho*-toluidine is used in place of aniline. Complex examples like the Bepotastine precursor and Vismodegib were amenable to the reaction conditions, forming product **5.24** and **5.25** in 51% and 46% yield, respectively. Efforts are ongoing to extend the scope of the reaction to 4-substituted pyridines, where the ring-opening works but decomposition into *N*-aryl pyridiniums occurs before halogenation.

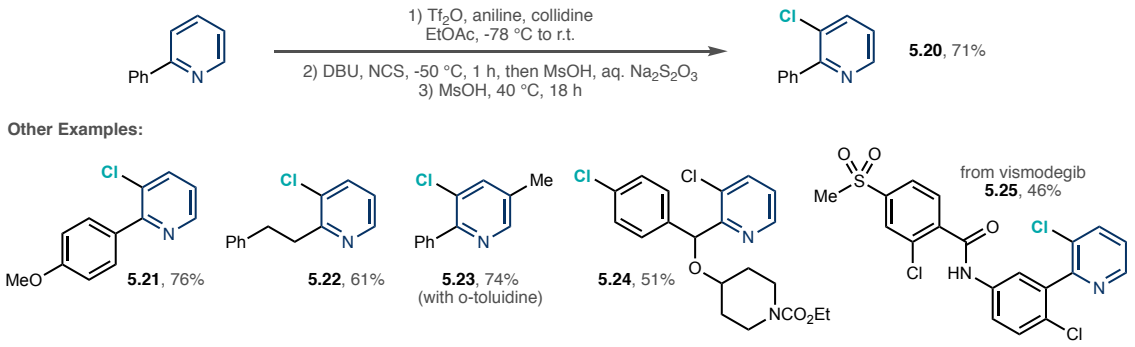


Figure 5.14. One-pot 3-position chlorination of pyridines via *N*-phenyl imines.

5.5 Fluorination of Pyridines via Zincke Imine Intermediates

Given the success of reacting the *N*-Tf Zincke imines with electrophilic halogenation reagents, we questioned whether they would react with electrophilic fluorination reagents. Fluorinated pyridines are present in a variety of approved drugs and other bioactive compounds (**Figure 5.15**).[13–15] Methods to install fluorine atoms on arenes are limited, and typically require prefunctionalized halide starting materials. A common method to access aryl fluorides is via the Balz-Schiemann reaction where an aniline nitrogen is oxidized to a diazonium salt, which can then

decompose in the presence of heat or light to form a reactive aryl cation species that abstracts fluoride from a tetrafluoroborate anion.[16,17] This approach is inconvenient as diazonium salts are known to be explosive.[18] The halogen-exchange (Halex) reaction can be used to displace an aromatic chloride with a fluoride anion, but this requires access to chlorinated precursors. Sanford has used this strategy to access 3-fluoropyridines although high temperatures are required on pyridines without electron-withdrawing substituents.[19,20] Buchwald and coworkers have reported the conversion of aryl triflates to aryl fluorides via palladium-catalysis, and the Hartwig lab has demonstrated this transformation using stoichiometric copper with aryl iodides. [21–23]

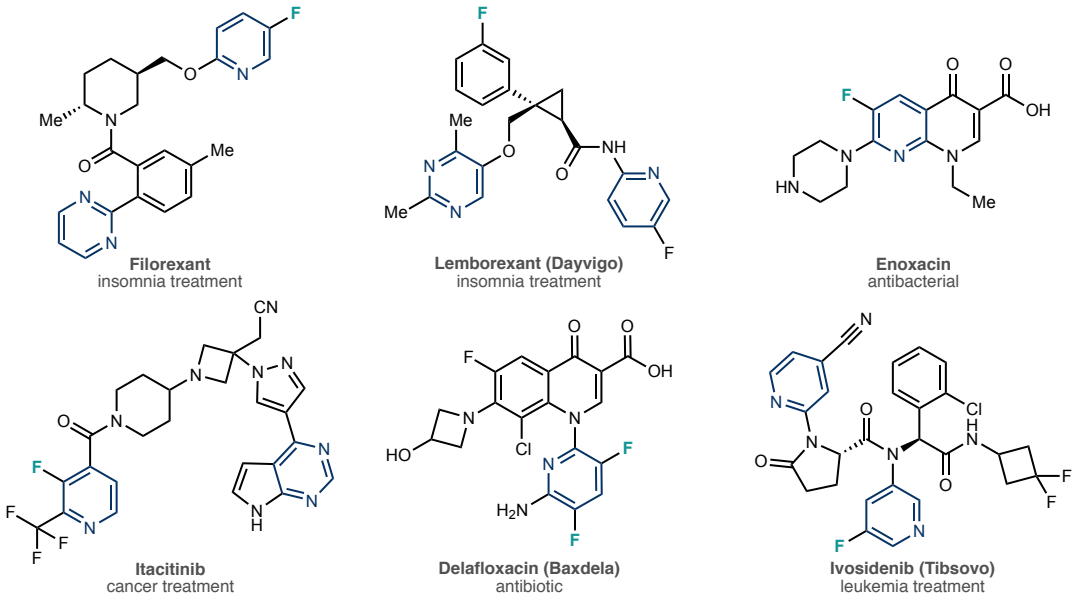


Figure 5.15. Examples of fluoropyridine pharmaceuticals.

Common electrophilic fluorination reagents include Selectfluor and NFSI.[24,25] Reacting these reagents with 2-phenyl Zincke imine **5.1**, we were pleased to see fluorination occurs in all cases, albeit in low yield. Using Selectfluor in MeOH and then recyclizing with ammonium acetate produces 35% of fluoropyridine **5.20**, with 3:1 site selectivity for the 3-position (**Figure 5.16**). Alternatively, using NFSI in iPrOAc and then recyclizing produces 31% fluorinated pyridine (**5.21**), with >20:1 site selectivity for the 5-position. Efforts are ongoing to understand the sources

of selectivity switching here. Yields for fluorinated pyridines are consistently low, and significant non-specific decomposition is observed.

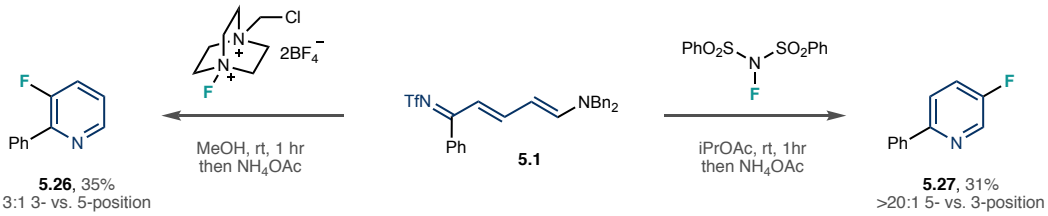


Figure 5.16. Fluorination of 2-phenyl Zincke imine with Selectfluor and NFSI.

The fluorination reaction was also tried on 3-substituted imines (**Figure 5.17**). Reacting imine **5.28** with NFSI in trifluoroethanol at room temperature yielded 70% of the desired 3-phenyl-5-fluoropyridine **5.29**. No ammonium acetate was required for recyclization, and we believe that the benzensulfonimide byproduct is acidic enough to promote recyclization. Other 3-substituted imines such as 3-butyl imine have also been shown to work in similar yields.

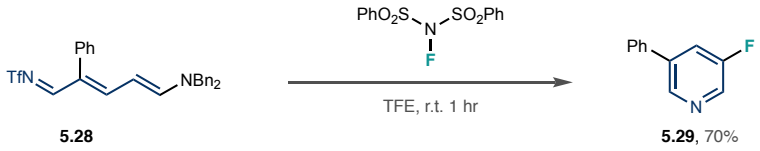


Figure 5.17. Fluorination of 3-phenyl Zincke imine with NFSI.

5.6 Isotopic Labelling of Pyridines via Zincke Imine Intermediates

We hypothesized that using ^{15}N-incorporated ammonium salts, Zincke imines could be recyclized to form ^{15}N-labeled pyridines. These products are used for NMR studies of biomolecules as ^{15}N NMR can help identify hydrogen-bonding interactions.[26,27] Methods to access these compounds either rely on the classical Zincke reaction, which is limited in scope, or rely on *de novo* pyridine syntheses.[28] The ring-opening reaction was performed on Loratadine and imine **5.31** was isolated in 74% yield. Imine **5.31** was then reacted with $^{15}NH_4Cl$ and silver acetate in EtOH at 80 °C, and ^{15}N-Loratadine **5.32** was formed in 75% yield (**Figure 5.18**). Mass spectrometry only showed the mass of the ^{15}N-incorporated product, and the NMR showed new

splitting from the pyridine's 2-position proton to the ^{15}N atom. Performing this reaction in two steps is essential to remove any of the ^{14}N-incorporated pyridine, and so a one-pot reaction is not practical here.

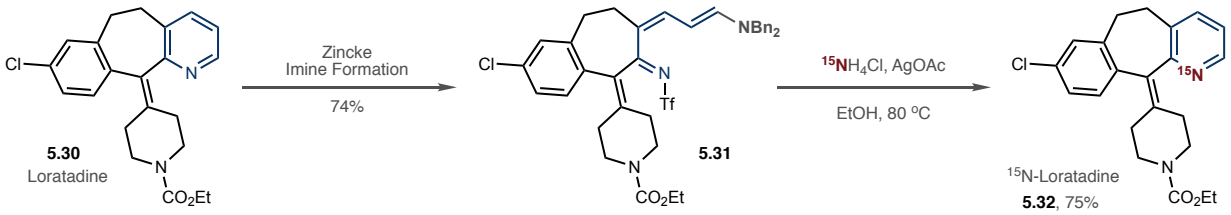


Figure 5.18. Nitrogen-15 labeling of Loratadine.

Another isotope we wished to install is deuterium.[29–31] Currently, a common approach to deuterate arenes is from aryl halide starting materials.[32,33] Previously published work from the McNally group showed that 4-pyridyl phosphonium salts could be transformed into 4-deuterated pyridines.[34] We hypothesized that Zincke imines could be deuterated at the 3- and 5-positions by adding an excess of deuterated acid.[35,36] We began by reacting 2-phenyl imine **5.1** with deuterated acetic acid in CH_2Cl_2 at 50 °C (**Figure 5.19**). After 4 hours, mass spectrometry analysis showed significant amounts of the deuterated imine, which was then recyclized with ammonium acetate. Deuterated 2-phenyl pyridine product **5.33** had 76% deuterium-incorporation at the 3-position and 56% deuterium-incorporation at the 5-position. However, some substrates produced significant amounts of background recyclization to form non-deuterated parent pyridines, and so efforts are ongoing to find other strategies that allow deuteration to occur but avoid recyclization.

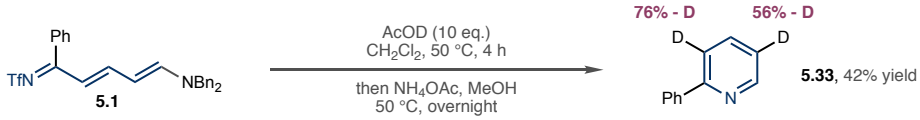


Fig. 5.19. Zincke imine deuteration with AcOD.

An alternative set of deuteration conditions were found to selectively deuterate the 5-position. Reacting 2-phenyl imine **5.1** with sodium bisulfite in a DCE:MeOD mixture at 80 °C led

to exclusive 5-position deuteration with 100% deuterium incorporation (**Figure 5.20**). We believe that sodium bisulfite adds to the imine, forming deconjugated intermediate **5.35** with two distinct enamine moieties.[37,38] Because only 5-position deuteration is observed, we believe that the dibenzylamine enamine is more nucleophilic than the *N*-Tf enamine, and only the dibenzylamine side of the molecule reacts. Alternatively, mixing sodium bisulfite and deuterated methanol can form deuterated sodium bisulfite, which could add across one of the double bonds to install the deuterium atom. If this is the case, the 5-position selectivity could result from steric accessibility of one double bond over another. Deconjugated imine **5.35** has not been observed experimentally, although it may only form transiently at higher temperatures.

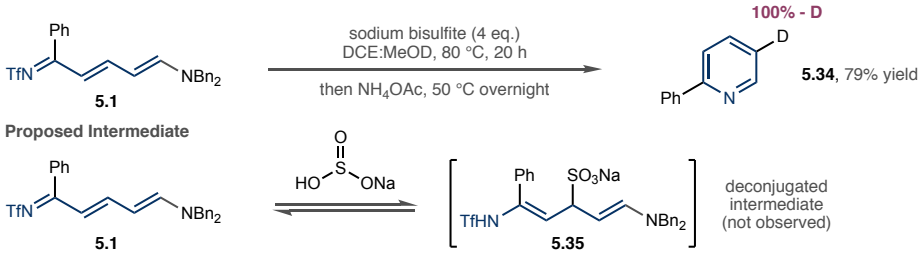


Fig. 5.20. Zincke imine deuteration with sodium bisulfite and deuterated methanol.

Combining the deuteration with the ^{15}N-labeling reaction could be used to form pyridines with two deuterium atoms and one ^{15}N atom. The net mass change here is 3 atomic units, and medicinal chemists often need to form "mass+3" analogs of drug compounds to use as internal standards for absorption, distribution, metabolism, and excretion (ADME) studies.[39–41] As such, we envisioned that our strategy be a useful approach for medicinal chemists intending to make "mass+3" analogs of pyridine-containing drugs. Our strategy was to first deuterate the imines with deuterated acid, and then recyclize using ^{15}N-ammonium chloride. We chose three complex pyridine-containing substrates on which to perform this transformation. Because of background rearomatization effects, none of the isotopes were installed with 100% abundance, but >80% incorporation was achieved in all cases (**Figure 5.21**). To synthesis mass+3 Vismodegib **5.37** and

mass+2 Loratadine **5.38**, we found that switching from AcOD to DCl (formed *in situ* by reacting acetyl chloride with deuterated ethanol) helped prevent background recyclization and improve the isotopic incorporation.

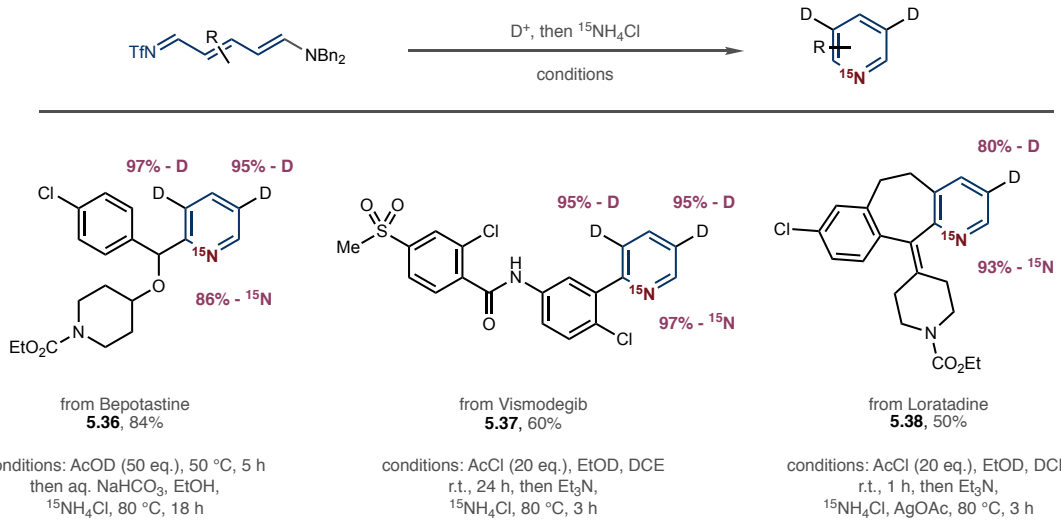


Figure 5.21. Complex examples of isotopically labeled pyridines.

5.7 Alternative Pathways for Zincke Imine Ring-Closure

In the processes of studying these *N*-Tf Zincke imines and iminiums, we discovered a selection of ring modification reactions. One interesting result came from performing a Vilsmeier-Hack formylation on the 2-phenyl Zincke imine **5.1** (**Figure 5.22**).[8] The 3-formylated imine **5.39** forms selectively and was isolated in 65% yield. When ammonium acetate was added to convert the imine back to a pyridine, two different pyridine products were observed. The minor product was 2-phenylnicotinaldehyde **5.40** which formed in 25% yield, and the major product was 3-benzoyl pyridine **5.41** which formed in 48% yield. While this rearomatization reaction was not fully selective for either pyridine product, this result is very exciting as the carbon that originates on the DMF molecule is later incorporated into the pyridine ring. Because ^{13}C DMF is commercially available, we propose that this could be a feasible strategy to synthesize ^{13}C-building block pyridines. Like deuterium and ^{15}N, ^{13}C-incorporation is important for stable isotope labelling

for ADME studies, and current methods to access ^{13}C-incorporated pyridines are very limited.[42,43] Similarly, ^{14}C-DMF has been used to synthesize radiolabeled pharmaceuticals and applying that reagent here will produce ^{14}C-incorporated pyridines.[44,45]

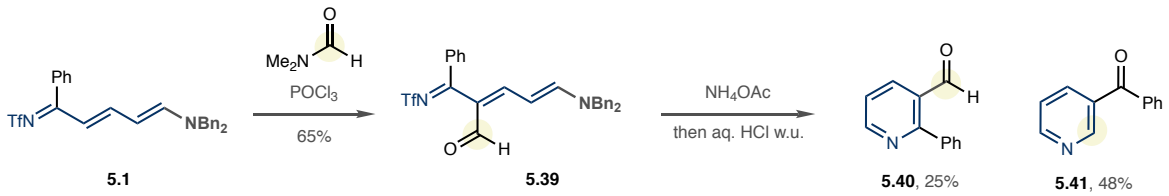


Figure 5.22. Zincke imine formylation and ammonium acetate recyclization.

This result inspired us to consider other recyclization pathways from Zincke imine intermediates, and we hypothesized that we could convert *N*-Tf Zincke imines to functionalized benzene products. We proposed a mechanism where *N*-Tf anilines could be produced from 2-alkyl imines (**Figure 5.23**). From 2-methyl imine **5.42**, cis-trans isomerization and tautomerization would form triene **5.43**, which could then undergo 6-pi electrocyclization to construct dearomatized benzene intermediate **5.44**. Elimination of dibenzylamine should yield *N*-Tf aniline product **5.45**.

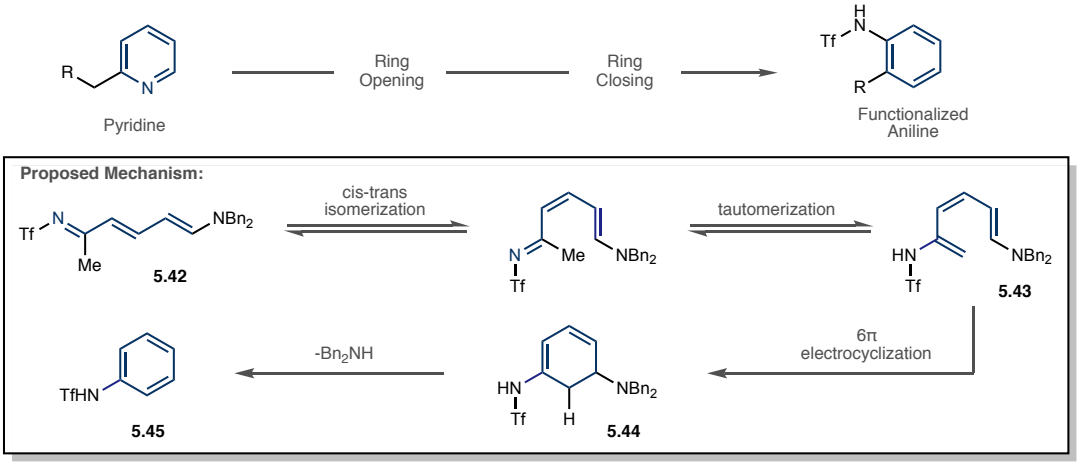


Figure 5.23. Proposed conversion of 2-alkyl Zincke imines to *N*-Tf anilines

A similar reaction was published by the Kano lab in 2021, where Zincke iminium **5.47** was first formed from the classical Zincke reaction (**Figure 5.24**).[46,47] Iminium **5.47** was treated with

trimethylsulfonium iodide under basic conditions to form sulfonium **5.48** which then undergoes 6π electrocyclization and forms aniline **5.49**. Because the iminiums are made via the classical Zincke reaction, the scope of available pyridine precursors is limited to substrates without a 2-position and accomplishing a similar reaction using *N*-Tf Zincke imines would give complementary products.

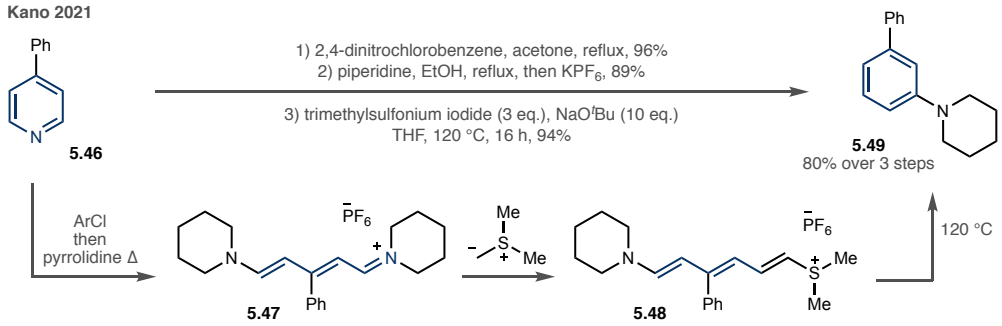


Figure 5.24. Kano's synthesis of meta-substituted anilines from 4-substituted pyridines.

We found that heating 2-alkyl Zincke imines at 120 °C in DMF for 2 hours yielded the *N*-Tf aniline products in high yield (**Figure 5.25**). 2-Ethyl imine **5.50** forms *ortho*-methyl aniline **5.51** in 91% yield, and no rearomatized 2-ethyl pyridine was observed under these reaction conditions. Complex pyridine **5.52** was then synthesized to use for this transformation, which was then ring-opened, and the imine intermediate was isolated. Heating the imine at 120 °C for 2 hours in DMF yielded novel trisubstituted aniline derivative **5.53** in 46% yield over two steps.

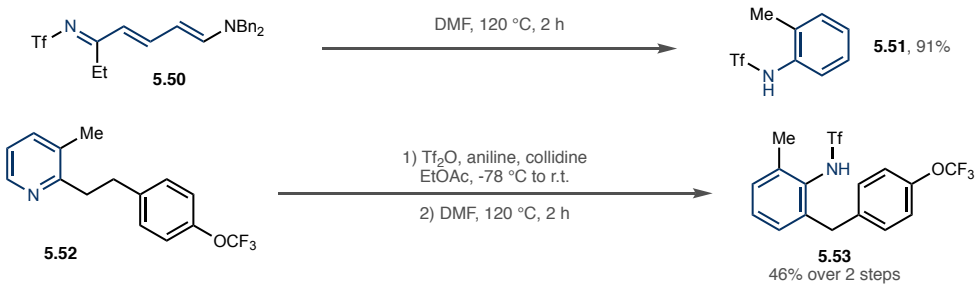


Figure 5.25. Examples of *N*-Tf anilines formed from 2-alkyl pyridines.

We then questioned if we could sequence this aniline formation with the iodination step. Using 2-benzyl Zincke imine **5.54**, addition of NIS at room temperature led to selective iodinate

the 3-position **5.55**, and then heating to 120 °C produces the trisubstituted iodoaniline **5.56** in 42% yield. This result is exciting as anilines and protected anilines are often *para*-selective for halogenation reactions, and this represents and approach to selectively accessing *ortho*-halogenated anilines. Methods to deprotect triflyl substituted amines have been reported.[48–50]

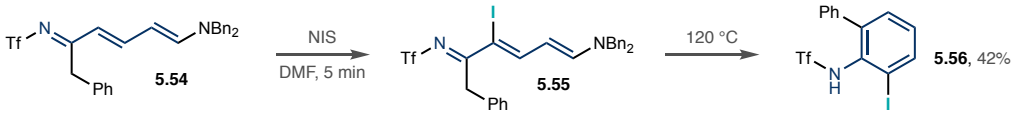


Figure 5.25. Sequential iodination and aniline formation to form iodobenzene.

5.8 Conclusion

This chapter presented further developments of Zincke imine chemistry. Sections 2-4 outlined modified halogenation strategies to access 5-iodinated pyridines, 5-chlorinated pyridines, and 3-chlorinated pyridines. The results presented here demonstrate that Zincke iminiums and *N*-phenyl imines can confer reactivity and selectivity advantages over the dibenzylamine imines presented in Chapter Four. The fluorination and isotope labelling reactions described here are currently being optimized and are promising methods to access useful products. Lastly, the section on ring-modification shows that this approach can be used to convert pyridines into anilines.

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APPENDIX ONE

HALOGENATION OF PYRIDINES VIA PHOSPHONIUM SALTS: EXPERIMENTAL

A 1.1 General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR (400 MHz) spectrometer or an Agilent Inova 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), $(CD_3)_2SO$ (2.50 ppm), CD_3OD (3.31 ppm) or CD_3CN (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants). 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 either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR spectrometer (100 MHz) or an Agilent Inova 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16 ppm), C_6D_6 (128.06 ppm), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or CD_3CN (1.32 ppm).

Low–resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 27 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 Merck glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Fluka or Material Harvest silica gel (230–400 mesh) under a positive pressure of air. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate.

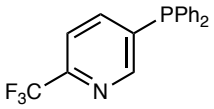
Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] Ethyl acetate (EtOAc), 1,2–Dichloroethane (DCE), chloroform, and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest 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, gas chromatography (GC) and gas chromatography–mass spectrometry (GCMS) using an Agilent 5977A fitted with an Agilent J&W HP–5ms Ultra Inert Column (30 m, 0.25 mm, 0.25 μm film) for MS analysis and an Agilent J&W VF–5ms column (10 m, 0.15 mm, 0.15 μm film) for FID analysis or liquid chromatography mass spectrometry (LCMS) using an Agilent 6310 Quadrupole Mass Spectrometer. Melting points (mp) were recorded using a Büchi B–450 melting point apparatus and are reported uncorrected.

Lithium halide salts were dried under vacuum at 120 °C before being stored in a glovebox. HCl (4.0 M in Dioxane) and trifluoromethanesulfonic acid (98%) were purchased from Sigma Aldrich chemical company and used without further purification but were routinely stored in a –20 ºC fridge. Anhydrous 1,4-Dioxane was purchased from EMD Millipore. Chlorodiphenylphosphine was purchased from Strem Chemicals and stored in a glovebox.

Dichlorophenylphosphine was purchased from BeanTown Chemical and stored in a glovebox. NEt_3 and DBU were distilled before use.

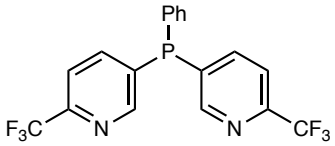
A 1.2 Preparation of Heterocyclic Phosphines

5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine



An oven-dried 250mL round bottom flask was charged with 2-trifluoromethyl-5-bromo pyridine (4.97 g, 22.00 mmol) and diethyl ether (80 mL). The colorless solution was cooled to –78 °C, and n-BuLi (1.6 M in Hexanes, 22.00 mmol 13.75 mL) was added dropwise. After 30 minutes, diphenylphosphine chloride (3.56 mL, 20.00 mmol) was added dropwise, and the flask was allowed to warm to room temperature. After 4 hours of stirring, the reaction was quenched with water (80 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 2.5% EtOAc in Hexanes) to provide the title compound as a white solid (5.63 g, 17.01 mmol, 85% yield). mp 67-70 ºC. IR ν_{max}/cm^{-1} (film): 3058, 3013, 1479, 1433, 1331, 1142, 1073, 746, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (1H, s), 7.72-7.66 (1H, m), 7.61 (1H, d, J = 8.0 Hz), 7.42-7.30 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.94 (d, J = 22.2 Hz), 147.84 (q, J = 34.8 Hz), 142.07 (d, J = 16.4 Hz), 138.68 (d, J = 20.1 Hz), 134.72 (d, J = 9.8 Hz), 134.05 (d, J = 20.5 Hz), 129.83, 129.15 (d, J = 7.2 Hz), 121.68 (q, J = 274.0 Hz), 120.20-120.05 (m); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.07; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –11.63; m/z LRMS (ESI + APCI) found $[M + H]^+$ 332.1, $C_{18}H_{14}F_3NP^+$ requires 332.1.

5,5'-(phenylphosphanediyl)bis(2-(trifluoromethyl)pyridine)



An oven-dried 250 mL round bottom flask was charged with 2-trifluoromethyl-5-bromo pyridine (16.65 g, 73.68 mmol) and diethyl ether (60 mL). The colorless solution was cooled to –78 °C, n-BuLi (2.5 M in hexanes, 73.68 mmol, 29.5 mL) was added dropwise. After 30 minutes, dichlorophenyphosphine (4.76 mL, 35.10 mmol) was added dropwise, and the flask was allowed to warm to room temperature. After 8 hours of stirring, the reaction was quenched with water (80 mL), organic layer separated, and aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 5% EtOAc in Hexanes) to provide the title compound as a white solid (12.06 g, 30.10 mmol, 86% yield). mp 65-66 ºC. IR ν_{max}/cm^{-1} (film): 3076, 1368, 1331, 1234, 1128, 1070, 834, 713; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.61 (2H, app t, *J* = 2.4 Hz), 7.75 (2H, ddd, *J* = 7.9, 6.1, 1.9 Hz), 7.68 (2H, d, *J* = 8.0 Hz), 7.52-7.43 (3H, m), 7.40-7.33 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.95 (d, *J* = 24.0 Hz), 148.79 (q, *J* = 35.3 Hz), 142.33 (d, *J* = 16.6 Hz), 136.10 (d, *J* = 19.0 Hz), 134.20 (d, *J* = 21.3 Hz), 132.05 (d, *J* = 9.1 Hz), 130.81, 129.67 (d, *J* = 8.0 Hz), 121.43 (q, *J* = 121.4 Hz), 120.62-120.45 (m); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –18.24; m/z LRMS (ESI + APCI) found $[M + H]^+$ 401.2, $C_{18}H_{12}F_6N_2P^+$ requires 401.1.

A 1.3 General Procedures

General Procedure A: Preparation of Heterocyclic Phosphonium Salts

An oven dried round bottom flask equipped with a stir bar was charged with the heterocycle (1.0 equiv), phosphine (1.1 equiv), and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –50 ºC and Tf_2O (1.0 equiv) was added dropwise. After stirring

for 1 hour, the reaction was cooled to –78 ºC and DBU (1.0 equiv) was added dropwise via syringe. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (approximately 20-30 minutes). The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O (3x). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to approximately 2-5 mL (depending on the scale of the reaction). The concentrated reaction mixture was added dropwise to an excess of a 50:50 Et_2O:Hexanes solution that was then placed in a –20 ºC refrigerator until the solid has settled to the bottom of the flask. The suspension was filtered on a frit, the solid washed with chilled Et_2O (0 ºC) and dried *in vacuo* to provide the pure product.

Notes.

1) To maximize the yield, vigorous stirring is required.

2) For long term storage (>2 weeks) it is best to keep the heteroaryl phosphonium salt product in a −20 °C fridge.

General Procedure B: Chlorination of Phosphonium Salts

An 8 mL screw-cap vial equipped with a stir bar was charged with the phosphonium salt (1.0 equiv), LiCl (4.0 equiv), and placed under a nitrogen atmosphere. Dioxane (0.1M) was added with a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 80 ºC. After the stated time, the reaction was cooled to room temperature, concentrated in *vacuo*, and purified by column chromatography under the stated conditions to provide the chlorinated heterocycle.

General Procedure C: Bromination of Phosphonium Salts

An 8 mL screw-cap vial equipped with a stir bar was charged with the phosphonium salt (1.0 equiv), LiBr (4.0 equiv), and placed under a nitrogen atmosphere. Dioxane (0.1M) was added, followed by a dropwise addition of TfOH (1.0 equiv). The septa cap was quickly replaced with an

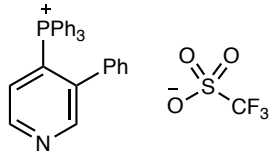
unpierced one and the reaction was heated to 80 ºC. After the stated time, the reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the brominated heterocycle.

General Procedure D: Iodination of Phosphonium Salts

An 8 mL screw-cap vial equipped with a stir bar was charged with the phosphonium salt (1.0 equiv), LiI (4.0 equiv), and placed under a nitrogen atmosphere. Dioxane (0.1M) was added, followed by a dropwise addition of TfOH (1.0 equiv). The septa cap was quickly replaced with an unpierced one and the reaction was heated to 120 ºC. After the stated time, the reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the iodinated heterocycle.

A 1.4 Synthesis of Phosphonium Salts and Halogenated Pyridines

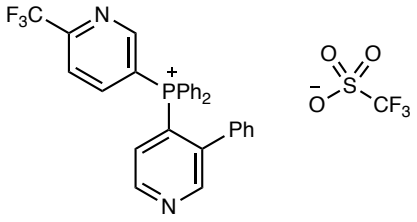
Triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate



Prepared according to our previous report.[1] ^{1}H NMR (400 MHz, $CDCl_3$): 8.95 (1H, app t, J = 4.7 Hz), 8.74 (1H, d, J = 6.8 Hz), 7.85- 7.73 (3H, m), 7.73-7.40 (13H, m), 7.11 (1H, t, J = 7.6 Hz), 6.91 (2H, app t, J = 7.6 Hz), 6.71 (2H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 153.63 (d, J = 8.0 Hz), 149.97 (d, J = 10.4 Hz), 141.68 (d, J = 7.3 Hz), 135.43 (d, J = 3.0 Hz), 134.41 (d, J = 4.5 Hz), 134.18 (d, J = 10.3 Hz), 130.59 (d, J = 13.0 Hz), 129.21, 128.89, 128.30, 128.20,

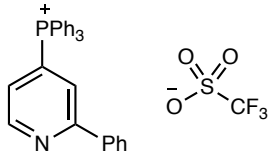
126.35 (d, J = 83.4 Hz), 120.82 (q, J = 321.2 Hz), 116.89 (d, J = 89.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$): –77.68; ^{31}P NMR (162 MHz, $CDCl_3$): 21.73. The spectroscopic data is in agreement with our reported synthesis.

Diphenyl(3-phenylpyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



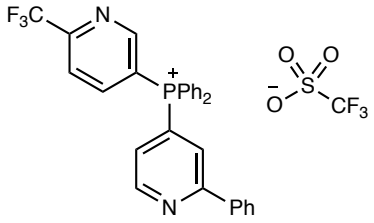
Prepared according to general procedure A, using 3-phenylpyridine (282 µL, 2.00 mmol), Tf_2O (336 µL, 2.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (728 mg, 2.20 mmol), DBU (298 µL, 2.00 mmol), and CH_2Cl_2 (20 mL). After purification by the standard procedure (except that two crash-outs were required), the title compound was isolated as a white solid (964 mg, 1.52 mmol, 76% yield). mp 54-57 ºC. IR ν_{max}/cm^{-1} (film): 3064, 1440, 1336, 1258, 1140, 1029, 722, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, app t, J = 4.0 Hz), 8.89-8.70 (2H, m), 8.38 (1H, dd, J = 5.9 Hz, 2.1 Hz), 7.97-7.87 (3H, m), 7.82-7.70 (8H, m), 7.49 (1H, d, J = 15.4, 5.2 Hz), 7.17 (1H, app t, J = 7.5 Hz), 6.96 (2H, app t, J = 8.0 Hz), 6.80 (2H, dd, J= 8.3, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.70 (d, J = 7.9 Hz), 152.74 (d, J = 12.6 Hz), 151.94 (qd, J = 35.8, 2.4 Hz), 150.22 (d, J = 10.6 Hz), 145.12 (d, J = 9.3 Hz), 141.69 (d, J = 7.0 Hz), 136.38 (d, J = 3.1 Hz), 134.63 (d, J = 10.7 Hz), 134.33 (d, J = 4.6 Hz), 131.20 (d, J = 13.4 Hz), 129.55, 129.41, 128.64, 128.30 (d, J = 3.1 Hz), 124.81 (d, J = 84.7 Hz), 122.00-121.78 (m), 120.72 (q, J = 321.0 Hz), 120.44 (qd, J = 275.3, 1.7 Hz), 119.15 (d, J = 86.4 Hz), 115.33 (d, J = 89.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.89, –78.29; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.31; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 485.2, $C_{27}H_{21}F_3N_4P^+$ requires 485.1.

Triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate



Prepared according to our previous report.[1] ^{1}H NMR (400 MHz, CDCl3): 9.01 (1H, app t, *J* = 5.1 Hz), 7.93–7.54 (18H, m), 7.50 (1H, ddd, *J* = 17.8, 5.1, 1.1 Hz), 7.42–7.36 (3H, m); ^{13}C NMR (100 MHz, CDCl3): 159.09 (d, *J* = 9.9 Hz), 151.63 (d, *J* = 10.7 Hz), 136.74 (d, *J* = 1.5 Hz), 136.14 (d, *J* = 3.2 Hz), 134.30 (d, *J* = 9.8 Hz), 130.91 (d, *J* = 13.0 Hz), 130.35, 129.23 (d, *J* = 84.1 Hz), 128.98, 127.00, 125.25 (d, *J* = 7.8 Hz), 123.08, (d, *J* = 8.4 Hz), 120.68 (q, *J* = 321.1 Hz), 115.49 (d, *J* = 89.1 Hz); ^{19}F NMR (365 MHz, CDCl3): –78.1; ^{31}P NMR (162 MHz, CDCl3): 22.7. The spectroscopic data is in agreement with our reported synthesis.

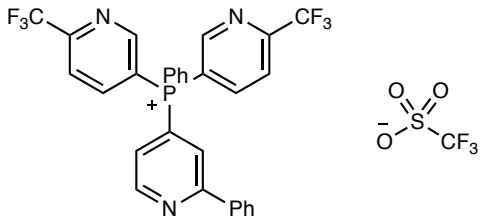
Diphenyl(2-phenylpyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using 2-phenylpyridine (571 μL, 4.00 mmol), Tf_2O (676 μL, 4.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (1.460 g, 4.40 mmol), DBU (598 μL, 4.00 mmol), and CH_2Cl_2 (40 mL). After purification by the standard procedure (except that two crash-outs were required), the title compound was isolated as a white solid (1.906 g, 3.00 mmol, 75% yield). mp 68-72 ºC. IR ν_{max}/cm^{-1} (film): 3063, 1573, 1440, 1258, 1141, 1029, 724, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.07 (1H, app t, *J* = 5.3 Hz), 8.83 (1H, dd, *J* = 6.1, 1.5 Hz), 8.68 (1H, ddd, *J* = 12.7, 8.5, 2.2 Hz), 8.18 (1H, dd, *J* = 8.3, 1.2 Hz), 7.98-7.68

(13H, m), 7.56 (1H, ddd, J = 13.3, 5.1, 1.1 Hz), 7.47-7.42 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.40 (d, J = 10.8 Hz), 153.29 (d, J = 13.0 Hz), 153.11 (qd, J = 36.1, 2.7 Hz), 151.90 (d, J = 11.0 Hz), 145.70 (d, J = 9.4 Hz), 136.71 (d, J = 2.0 Hz), 134.57 (d, J = 11.0 Hz), 131.25 (d, J = 13.4 Hz), 130.45, 129.01, 127.97, 127.13, 125.36 (d, J = 8.5 Hz), 123.24 (d, J = 9.2 Hz), 122.57-122.35 (m), 120.51 (q, J = 321.2 Hz), 120.42 (qd, J = 275.2, 1.7 Hz), 118.00 (d, J = 87.4 Hz), 113.83 (d, J = 89.9 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: −68.53, −78.34; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.38; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 485.2, $C_{27}H_{21}F_3N_4P^+$ requires 485.1.

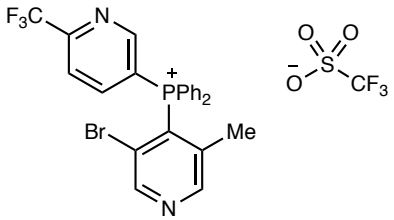
Phenyl(2-phenylpyridin-4-yl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using 2-phenylpyridine (282 μL, 2.00 mmol), Tf_2O (336 μL, 2.00 mmol), 5,5'-(phenylphosphanediyl)bis(2-(trifluoromethyl)pyridine (881 mg, 2.20 mmol), DBU (299 μL, 2.00 mmol), and CH_2Cl_2 (20 mL). After purification by the standard procedure (except that two crash-outs were required), the title compound was isolated as a white solid (1.146 g, 1.64 mmol, 81% yield). mp 85-88 ºC. IR ν_{max}/cm^{-1} (film): 3063, 1573, 1333, 1139, 1075, 1029, 725, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.05 (1H, app t, J = 5.3 Hz), 8.90 (2H, dd, J = 6.1, 1.7 Hz), 8.60 (2H, ddd, J = 13.2, 8.4, 2.1 Hz), 8.09 (2H, dd, J = 8.3, 1.9 Hz), 7.99-7.90 (4H, m), 7.85-7.71 (4H, m), 7.55 (1H, ddd, J = 13.7, 5.0, 1.3 Hz), 7.45-7.38 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.82 (d, J = 11.0 Hz), 153.69 (d, J = 13.4 Hz), 153.62 (qd, J = 35.8, 2.4 Hz), 152.16 (d, J = 11.5 Hz), 145.95 (d, J = 9.9 Hz), 137.34 (d, J = 2.9 Hz), 136.64 (d, J = 1.7 Hz), 134.89 (d, J = 11.2 Hz), 131.61 (d, J = 13.6 Hz), 130.75, 129.15, 127.45, 126.09 (d, J = 85.4 Hz),

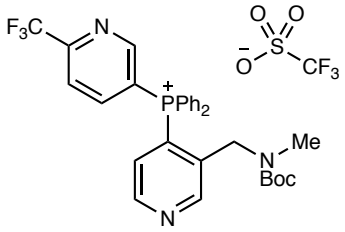
125.43 (d, J = 8.9 Hz), 123.47 (d, J = 9.4 Hz), 122.62-122.35 (m), 120.47 (qd, J = 275.7, 2.1 Hz), 120.32 (q, J = 320.7 Hz), 116.62 (d, J = 88.4 Hz), 112.45 (d, J = 90.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.74, –78.74; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.52; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 554.2, $C_{27}H_{21}F_3N_4P^+$ requires 554.1.

(3-Bromo-5-methylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



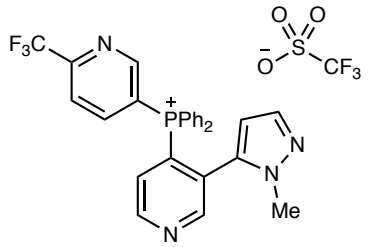
Prepared according to general procedure A, using 3-bromo-5-methylpyridine (116 μL, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification by the standard procedure (except that two crash-outs were required), the title compound was isolated at 95% purity as a white solid (172 mg, 0.26 mmol, 26% yield). IR ν_{max}/cm^{-1} (film): 3065, 1336, 1258, 1138, 1075, 1029, 720, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.97-8.87 (2H, m), 8.84 (1H, d, J = 5.7 Hz), 8.67 (1H, d, J = 6.0 Hz), 8.19-8.15 (1H, m), 7.96-7.77 (10H, m), 1.92 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.17 (d, J = 8.6 Hz), 153.18 (d, J = 6.1 Hz), 152.86 (d, J = 12.7 Hz), 152.84 (qd, J = 36.0, 2.7 Hz), 145.69 (d, J = 9.3 Hz), 142.66 (d, J = 7.4 Hz), 136.56 (d, J = 3.3 Hz), 134.80 (d, J = 11.0 Hz), 131.47 (d, J = 13.7 Hz), 125.06 (d, J= 8.5 Hz), 124.60 (d, J = 94.1 Hz), 122.70-122.46 (m), 121.06 (d, J = 87.7 Hz), 120.75 (q, J = 321.0 Hz), 120.60 (qd, J = 275.6, 2.2 Hz), 116.62 (d, J = 89.1 Hz), 20.85 (d, J = 4.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.55, –78.39; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.35; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 501.1, $C_{27}H_{21}F_3N_4P^+$ requires 501.0.

(3-(((*Tert*-butoxycarbonyl)(methyl)amino)methyl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



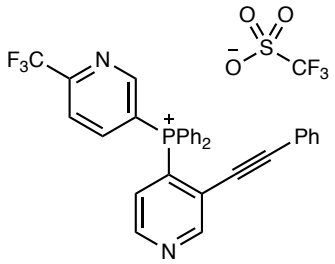
Prepared according to general procedure A, using *tert*-butyl methyl(pyridin-3-ylmethyl)carbamate (222 mg, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a brown solid (560 mg, 0.80 mmol, 80% yield). mp 83-87 ºC. IR ν_{max}/cm^{-1} (film): 2978, 2932, 1690, 1260, 1140, 1029, 723, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.88-8.70 (3H, m), 8.62 (1H, ddd, *J* = 12.8, 8.4, 2.1 Hz), 8.12 (1H, d, *J* = 7.6 Hz), 7.95-7.88 (2H, m), 7.85-7.76 (8H, m), 7.23 (1H, d, *J* = 15.3 Hz), 3.90 (2H, s), 2.61 (3H, s), 1.34 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.57, 153.43 (d, *J* = 12.7 Hz), 153.33 (qd, *J* = 36.1, 2.3 Hz), 150.84, 150.35, 146.04 (d, *J* = 9.6 Hz), 137.30-136.55 (2C, m), 134.47 (d, *J* = 11.0 Hz), 131.66 (d, *J* = 13.4 Hz), 128.78, 124.12 (d, *J* = 82.5 Hz), 122.90-122.52 (m), 120.64 (q, *J* = 321.0 Hz), 120.49 (qd, *J* = 275.6, 1.7 Hz), 118.30 (d, *J* = 86.8 Hz), 114.14 (d, *J* = 88.3 Hz), 81.09, 50.42, 35.62, 28.17; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.63, –78.40; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.92; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 552.2, $C_{30}H_{30}F_3N_3O_2P^+$ requires 552.2.

(3-(1-Methyl-1*H*-pyrazol-5-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



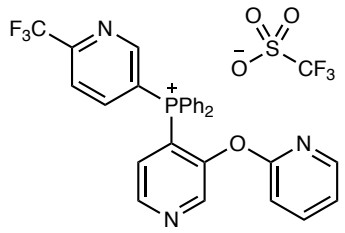
Prepared according to general procedure A, using 3-(1-methyl-1*H*-pyrazol-5-yl)pyridine (159 mg, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification by the standard procedure (except that two crash-outs were required), the title compound was isolated as a white solid (362 mg, 0.57 mmol, 57% yield). mp 154-149 ºC. IR ν_{max}/cm^{-1} (film): 3066, 1440, 1259, 1142, 1029, 722, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.06 (1H, app t, *J* = 4.6 Hz), 8.89-8.76 (2H, m), 8.64 (1H, d, *J* = 5.8 Hz), 8.08 (1H, d, *J* = 8.2 Hz), 7.96-7.66 (10H, m), 7.57 (1H, dd, *J* = 15.4, 4.8 Hz), 7.11 (1H, s), 5.68 (1H, s), 3.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.54 (d, *J* = 7.4 Hz), 153.04 (d, *J* = 12.8 Hz), 152.58 (qd, *J* = 36.1, 2.2 Hz), 152.11 (d, *J* = 10.5 Hz), 145.11 (d, *J* = 9.2 Hz), 138.58, 136.50 (d, *J* = 2.7 Hz), 134.51 (d, *J* = 10.7 Hz), 134.29 (d, *J* = 4.9 Hz), 131.13 (d, *J* = 13.4 Hz), 130.10 (d, *J* = 6.2 Hz), 129.37 (d, *J* = 9.3 Hz), 127.33 (d, *J* = 85.8 Hz), 121.90-121.60 (m), 120.59 (q, *J* = 320.7 Hz), 120.45 (q, *J* = 275.0 Hz), 118.59 (d, *J* = 87.0 Hz), 114.53 (d, *J* = 89.3 Hz), 110.88, 37.03; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.69, –78.36; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.01; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 489.2, $C_{27}H_{21}F_3N_4P^+$ requires 489.1.

Diphenyl(3-(phenylethynyl)pyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



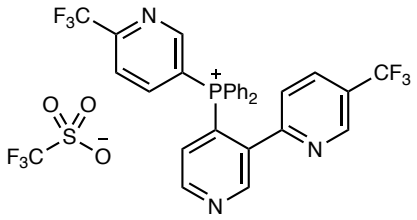
Prepared according to general procedure A, using 3-(phenylethynyl)pyridine (179 mg, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a brown solid (444 mg, 0.67 mmol, 67% yield). mp 69-72 ºC. IR ν_{max}/cm^{-1} (film): 3062, 2361, 2213, 1439, 1335, 1259, 1142, 722, 563; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.10 (1H, d, *J* = 6.2 Hz), 8.93 (1H, app t, *J* = 4.8 Hz), 8.85 (1H, dd, *J* = 6.1, 2.1 Hz), 8.79 (1H, ddd, *J* = 12.9, 4.5, 2.0 Hz), 8.11 (1H, dd, *J* = 7.7, 1.5 Hz), 7.95-7.87 (2H, m), 7.84-7.76 (8H, m), 7.42-7.30 (2H, m), 7.22-7.17 (2H, m), 6.69-6.65 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.64 (d, *J* = 6.7 Hz), 153.20 (d, *J* = 12.9 Hz), 153.00 (qd, *J* = 35.9, 2.5 Hz), 150.62 (d, *J* = 10.5 Hz), 145.73 (d, *J* = 9.5 Hz), 136.54 (d, *J* = 3.1 Hz), 134.65 (d, *J* = 11.0 Hz), 131.23 (d, *J* = 13.5 Hz), 131.01, 130.58, 129.06 (d, *J* = 9.1 Hz), 128.68, 127.07 (d, *J* = 87.6 Hz), 123.39 (d, *J* = 4.6 Hz), 122.50 – 122.30 (m), 120.68 (q, *J* = 321.0 Hz), 120.49 (qd, *J* = 275.4, 2.0 Hz), 119.38, 118.24 (d, *J* = 88.3 Hz), 114.00 (d, *J* = 90.8 Hz), 105.23, 84.14 (d, *J* = 6.5 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: −68.68, −78.31; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.23; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 509.2, $C_{31}H_{21}F_3N_2P^+$ requires 509.1.

Diphenyl(3-(pyridin-2-yloxy)pyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



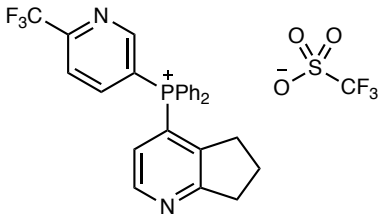
Prepared according to general procedure A, using 2-(pyridin-3-yloxy)pyridine (258 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (547 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol), and CH_2Cl_2 (15 mL). After purification by the standard procedure, the title compound was isolated as a white solid (870 mg, 1.34 mmol, 89% yield). mp 50-55 ºC. IR ν_{max}/cm^{-1} (film): 3064, 2248, 1430, 1529, 1140, 1029, 723, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.79-8.74 (2H, m), 8.68 (1H, app t, *J* = 4.3 Hz), 8.51 (1H, ddd, *J* = 13.1, 8.2, 2.2 Hz), 7.97 (1H, ddd, *J* = 8.3, 2.1, 0.7 Hz), 7.88 (1H, ddd, *J* = 5.0, 2.0, 0.7 Hz), 7.83-7.76 (2H, m), 7.72-7.64 (8H, m), 7.49 (1H, ddd, *J* = 8.2, 7.3, 2.0 Hz), 7.32 (1H, dd, *J* = 14.5, 5.1 Hz), 6.98 (1H, ddd, *J* = 7.3, 5.0, 0.8 Hz), 6.33 (1H, d, *J* = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.60, 153.01 (d, *J* = 13.2 Hz), 152.77 (qd, *J* = 34.7, 2.7 Hz), 151.17, 146.90, 146.89 (d, *J* = 10.8 Hz), 146.45 (d, *J* = 4.7 Hz), 145.22 (d, *J* = 9.7 Hz), 140.60, 136.34 (d, *J* = 3.1 Hz), 134.27 (d, *J* = 11.4 Hz), 131.07 (d, *J* = 13.6 Hz), 127.96 (d, *J* = 7.3 Hz), 122.31-122.10 (m), 121.17, 120.65 (q, *J* = 321.0 Hz), 120.37 (qd, *J* = 275.7 Hz, 2.2 Hz), 118.30 (d, *J* = 87.2 Hz), 118.19 (d, *J* = 89.3 Hz), 113.97 (d, *J* = 91.3 Hz), 111.22; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.57, –78.30; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.70; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 502.2, $C_{28}H_{20}F_3N_3OP^+$ requires 502.1.

Diphenyl(5-(trifluoromethyl)-[2,3'-bipyridin]-4'-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



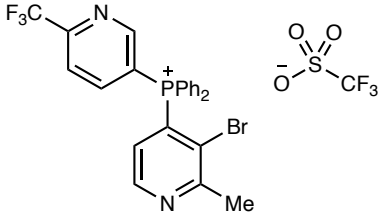
Prepared according to general procedure A using 5-(trifluoromethyl)-2,3'-bipyridine (336 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5-(diphenylphosphanyl)-2-(trifluoromethyl)pyridine (546 mg, 1.65 mmol), DBU (222 μL, 1.50 mmol) and CH_2Cl_2 (15 mL). After purification by the standard procedure, the title compound was isolated as a yellow solid (720 mg, 1.03 mmol, 69% yield). mp 72-76 ^oC; IR υ_{max}/cm^{-1} (film): 1606, 1581, 1440, 1329, 1259, 1134, 1076, 1029, 719, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.55 (1H, d, *J* = 7.1 Hz), 9.02 (1H, t, *J* = 4.9 Hz), 8.82 (1H, dd, *J* = 5.9, 2.2 Hz), 8.60 (1H, ddd, *J* = 12.8, 8.2, 2.3 Hz), 8.28 (1H, d, *J* = 8.4 Hz), 8.07-7.94 (2H, m), 7.79 (3H, qq, *J* = 4.3, 2.0 Hz), 7.73-7.61 (8H, m), 7.39 (1H, dd, *J* = 16.7, 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.87 (d, *J* = 11.8 Hz), 152.70, 151.79 (q, *J* = 35.8 Hz), 151.24 (d, *J* = 6.5 Hz), 144.60 (d, *J* = 8.8 Hz), 143.43, 135.80 (d, *J* = 3.7 Hz), 135.08 (d, *J* = 3.1 Hz), 135.01, 133.03 (dd, *J* = 10.4, 2.7 Hz), 131.45 (d, *J* = 10.6 Hz), 130.57 (d, *J* = 13.6 Hz), 126.97 (q, *J* = 33.8 Hz), 124.47, 123.28 (d, *J* = 57.7 Hz), 122.21 (d, *J* = 273.0 Hz), 122.14, 121.73 (d, *J* = 10.1 Hz), 120.85, 120.54 (q, *J* = 321.1 Hz), 120.43 (qd, *J* = 275.1, 1.9 Hz), 119.05 (d, *J* = 95.5 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –63.06, –68.64, –78.39; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 24.41; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 554.2, $C_{29}H_{19}F_6N_3P^+$ requires 554.1.

(6,7-Dihydro-5H-cyclopenta[b]pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



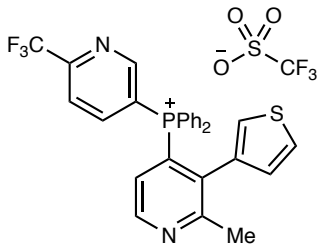
Prepared according to general procedure A using 6,7-dihydro-5H-cyclopenta[b]pyridine (119 mg, 1.00 mmol), Tf_2O (169 μL, 1.00 mmol), 5-(diphenylphosphanyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (147 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a white solid (300 mg, 0.50 mmol, 50% yield). mp 65-68 ^oC; IR υ_{max}/cm^{-1} (film): 1587, 1440, 1335, 1260, 1139, 1076, 1029, 724, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.87-8.64 (3H, m), 8.25 (1H, ddd, *J* = 8.0, 2.2, 1.1 Hz), 8.02-7.90 (2H, m), 7.84 (4H, td, *J* = 7.8, 3.9 Hz), 7.80-7.67 (4H, m), 7.02 (1H, dd, *J* = 14.5, 5.2 Hz), 3.17 (2H, t, *J* = 7.6 Hz), 2.37-2.23 (2H, m), 2.09 (2H, q, *J* = 7.5 Hz,); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.60 (d, *J* = 8.8 Hz), 153.22 (qd, *J* = 36.1, 2.5 Hz), 153.16 (d, *J* = 13.0 Hz), 150.00 (d, *J* = 9.9 Hz), 145.82 (d, *J* = 9.4 Hz), 140.92 (d, *J* = 7.5 Hz), 136.65 (d, *J* = 3.2 Hz), 134.32 (d, *J* = 10.9 Hz), 131.49 (d, *J* = 13.4 Hz), 124.64 (d, *J* = 9.8 Hz), 122.80 (dd, *J* = 10.1, 2.6 Hz), 121.87 (d, *J* = 83.9 Hz), 120.63 (q, *J* = 321.0 Hz), 120.47 (qd, *J* = 275.4, 1.9 Hz), 118.13 (d, *J* = 86.5 Hz), 113.93 (d, *J* = 89.1 Hz), 33.85 (d, *J* = 1.6 Hz), 32.39 (d, *J* = 2.5 Hz), 22.87; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.60, –78.37; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.86; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 449.2, $C_{26}H_{21}F_3N_2P^+$ requires 449.1.

(3-Bromo-2-methylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 3-bromo-2-methylpyridine (172 mg, 1.0 mmol), Tf_2O (169 μL, 1.00 mmol), 5-(diphenylphosphanyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (147 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a yellow solid (360 mg, 0.56 mmol, 56% yield). mp 56-60 °C; IR υ_{max}/cm^{-1} (film): 3064, 1440, 1335, 1185, 1142, 1076, 1028, 722, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.93-8.78 (3H, m), 8.27-8.17 (1H, m), 7.99-7.90 (2H, m), 7.86-7.72 (8H, m), 7.12 (1H, dd, *J* = 15.0, 4.9 Hz), 2.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.86 (d, *J* = 6.1 Hz), 153.18 (d, *J* = 12.9 Hz), 152.88 (qd, *J* = 36.1, 2.5 Hz), 149.86 (d, *J* = 11.6 Hz), 145.70 (d, *J* = 9.4 Hz), 136.41 (d, *J* = 3.2 Hz), 134.45 (d, *J* = 10.9 Hz), 131.25 (d, *J* = 13.7 Hz), 129.34 (d, *J* = 9.9 Hz), 127.96 (d, *J* = 91.4 Hz), 124.75 (d, *J* = 3.4 Hz), 122.51 (dd, *J* = 10.4, 2.9 Hz), 120.54 (q, *J* = 321.1 Hz), 120.44 (qd, *J* = 275.2, 1.6 Hz), 118.20 (d, *J* = 88.6 Hz), 114.04 (d, *J* = 91.0 Hz), 25.76 (d, *J* = 2.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.60, –78.36; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.10; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 501.1, $C_{24}H_{28}BrF_3N_2P^+$ requires 501.0.

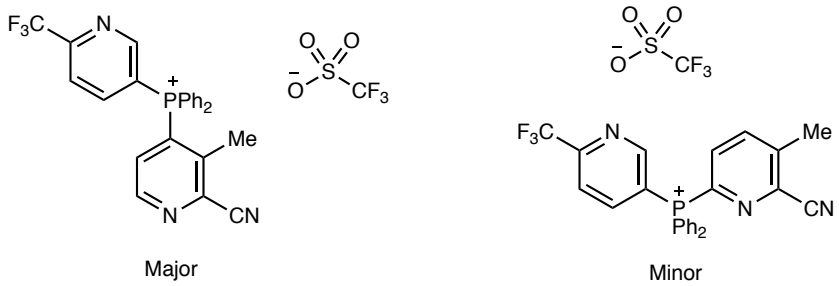
(2-Methyl-3-(thiophen-3-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using 2-methyl-3-(thiophen-3-yl)pyridine (263 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (547 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol), and CH_2Cl_2 (15 mL). After purification by the standard procedure (except that two crash-outs were done), the title compound was isolated as a white solid (489 mg, 0.75 mmol, 50% yield). mp 66-71 °C. IR ν_{max}/cm^{-1} (film): 3066, 3013, 2248,

1439, 1260, 1144, 1029, 721, 663; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78 (1H, app t, *J* = 5.1 Hz), 8.57 (1H, ddd, *J* = 12.5, 8.5, 2.0 Hz), 8.49 (1H, d, *J* = 5.7 Hz), 8.01-7.96 (1H, m), 7.91-7.82 (2H, m) 7.81-7.70 (4H, m), 7.70-7.61 (4H, m), 7.20 (1H, dd, *J* = 15.1, 5.2 Hz), 6.84 (1H, ddd, *J* = 4.9, 2.9, 0.4 Hz), 6.69-6.66 (1H, m), 6.27 (1H, d, *J* = 5.0 Hz), 2.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.36 (d, *J* = 8.0 Hz), 152.31 (d, *J* = 12.5 Hz), 151.86 (qd, *J* = 35.7, 2.4 Hz), 149.81 (d, *J* = 11.9 Hz), 144.77 (d, *J* = 9.2 Hz), 136.24 (d, *J* = 5.1 Hz), 135.92 (d, *J* = 7.1 Hz), 134.94 (d, *J* = 5.5 Hz), 134.39 (d, *J* = 10.5 Hz), 131.15 (d, *J* = 13.2 Hz), 128.36, 126.95 (d, *J* = 66.1 Hz), 126.14 (d, *J* = 86.2 Hz), 126.02 (d, *J* = 10.7 Hz), 122.14-121.92 (m), 120.72 (q, *J* = 321.0 Hz), 120.51 (qd, *J* = 275.2, 2.2 Hz), 119.61 (d, *J* = 87.0 Hz), 116.15 (d, *J* = 83.1 Hz), 115.26 (d, *J* = 83.9 Hz), 23.70 (d, *J* =2.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.73, –78.30; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.25; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 505.2, $C_{28}H_{21}F_3N_2PS^+$ requires 515.1.

(2-Cyano-3-methylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate

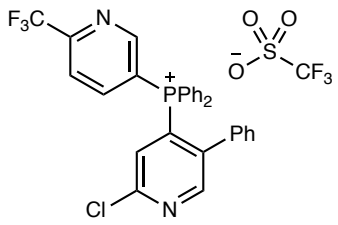


Major : Minor = 17:1

Prepared according to general procedure A, using 3-methylpicolinonitrile (118 mg, 1.00 mmol), Tf_2O (168 µL, 1.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (149 µL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a yellow solid (490 mg, 0.82 mmol, 82% yield); Major Isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86-8.80 (2H, m), 8.69 (1H, ddd, *J* = 13.0,

8.4, 2.2 Hz), 8.17 (1H, dd, *J* = 8.3, 1.8 Hz), 8.00-7.93 (2H, m), 7.87-7.75 (8H, m), 7.51 (1H, dd, *J* = 15.7, 5.0 Hz), 2.23 (3H, s); ^{13}C NMR (100 MHz, CD_3CN) δ: 155.16 (d, *J* = 13.2 hz), 153.48 (d, *J* = 35.6, 2.4 Hz), 150.93 (d, *J* = 11.7 Hz), 146.62 (d, *J* = 9.6 Hz), 142.65 (d, *J* = 8.2 Hz), 138.83 (d, *J* = 11.1 Hz), 137.53 (d, *J* = 3.2 Hz), 135.81 (d, *J* = 11.2 Hz), 134.32 (d, *J* = 10.4 Hz), 132.05 (d, *J* = 13.9 Hz), 128.52 (d, *J* = 86.3 Hz), 123.22-123.30 (m), 122.00 (q, *J* = 321.0 Hz), 121.89 (qd, *J* = 276.0, 3.2 Hz), 119.14 (d, *J* = 87.89 Hz), 116.41 (d, *J* = 7.6 Hz), 115.94 (d, *J* = 86.0 Hz), 21.14 (d, *J* = 5.3 Hz); ^{19}F NMR (365 MHz, CD_3CN) δ: –69.19, –79.20; ^{31}P NMR (162 MHz, CD_3CN) δ: 20.21 (Major Isomer), 14.58 (Minor Isomer); m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 448.2, $C_{25}H_{18}F_3N_3P^+$ requires 448.1.

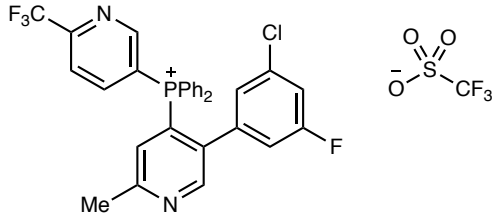
(2-Chloro-5-phenylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using 2-chloro-5-phenylpyridine (114 mg, 0.60 mmol), Tf_2O (101 μL, 0.60 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (219 mg, 0.66 mmol), DBU (90 μL, 0.60 mmol), and CH_2Cl_2 (6 mL). After purification by the standard procedure, the title compound was isolated as an amorphous solid (292 mg, 0.44 mmol, 73% yield). IR ν_{max}/cm^{-1} (film): 3604, 3013, 1560, 1441, 1259, 1029, 722, 666; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (1H, ddd , *J* = 12.8, 8.2, 2.1 Hz), 8.54 (1H, d, *J* = 7.1 Hz), 8.35 (1H, dd, *J* = 5.9, 1.9 Hz), 7.97-7.91 (3H, m), 7.86-7.74 (8H, m), 7.38 (1H, d, *J* = 15.2 Hz), 7.16 (1H, app td, *J* = 7.5, 1.0 Hz), 6.96 (2H, app t, *J* = 7.6 Hz), 6.81 (2H, dd, *J* = 8.0, 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.88 (d, *J* = 9.1 Hz), 152.63 (d, *J* = 12.8 Hz), 152.36 (d, *J* = 15.7 Hz), 152.09 (qd, *J* = 36.4, 2.7 Hz),

145.49 (d, J = 9.5 Hz), 140.46 (d, J = 7.2 Hz), 136.61 (d, J = 3.1 Hz), 134.73 (d, J = 10.6 Hz), 133.24 (d, J = 3.9 Hz), 131.90 (d, J = 10.2 Hz), 131.32 (d, J = 13.4 Hz), 129.80, 129.10 (d, J = 80.9 Hz), 128.69 (d, J = 11.7 Hz), 128.15 (d, J = 84.9 Hz), 122.07-121.82 (m), 120.70 (q, J = 320.9 Hz), 120.37 (qd, J = 275.5, 2.3 Hz), 118.39 (d, J = 87.4 Hz), 114.86 (d, J = 89.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.97, –78.33; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.20; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 519.2, $C_{29}H_{20}ClF_3N_2P^+$ requires 519.1.

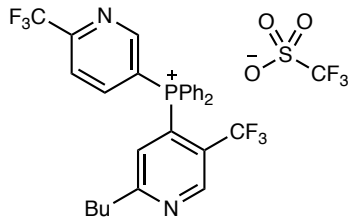
(5-(3-Chloro-5-fluorophenyl)-2-methylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A using (3-chloro-5-fluorophenyl)-2-methylpyridine (221 mg, 1.00 mmol), Tf_2O (169 μL, 1.00 mmol), 5-(diphenylphosphanyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (147 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a white solid (434 mg, 0.62 mmol, 62% yield). mp 100-102 °C; IR υ_{max}/cm^{-1} (film): 1581, 1439, 1335, 1259, 1143, 1075, 1029, 722, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00-8.83 (1H, m), 8.63 (1H, d, J = 7.5 Hz), 8.52 (1H, dd, J = 6.0, 1.9 Hz), 8.10 (1H, dd, J = 8.2, 2.1 Hz), 7.98-7.86 (2H, m), 7.86-7.69 (8H, m), 7.32 (1H, d, J = 16.2 Hz), 6.85 (1H, dt, J = 8.2, 2.0 Hz), 6.54 (1H, t, J = 1.7 Hz), 6.44 (1H, dt, J = 8.3, 1.9 Hz), 2.72 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.68 (d, J = 254.1 Hz), 161.34 (d, J = 10.5 Hz), 153.16-152.26 (m), 152.55 (qd, J = 36.0, 2.4 Hz), 145.68 (d, J = 9.3 Hz), 137.60 (dd, J = 8.9, 4.4 Hz), 136.49 (d, J = 3.2 Hz), 135.85-135.18 (m), 134.63 (d, J = 10.7 Hz), 131.90 (d, J = 10.3 Hz), 131.22 (d, J = 13.3 Hz), 129.04 (d, J = 12.5 Hz), 128.10 (d, J = 9.7 Hz), 126.19 (d, J

= 3.3 Hz), 124.95 (d, *J* = 84.2 Hz), 122.06 (d, *J* = 10.1 Hz), 120.69 (q, *J* = 320.8 Hz, 1H), 120.46 (qd, *J* = 275.2, 1.9 Hz), 119.42 (d, *J* = 65.1 Hz), 117.08 (d, *J* = 24.3 Hz), 115.58 (d, *J* = 22.6 Hz), 114.98 (d, *J* = 89.0 Hz), 24.62 (d, *J* = 1.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.80, –78.37, –108.46; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.93; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 551.2, $C_{30}H_{21}ClF_4N_2P^+$ requires 551.1.

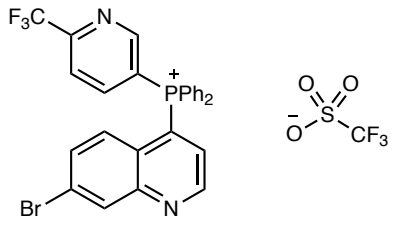
(2-Butyl-5-(trifluoromethyl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using 2-butyl-5-(trifluoromethyl)pyridine (305 mg, 1.50 mmol), Tf_2O (252 µL, 1.50 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (547 mg, 1.65 mmol), DBU (224 µL, 1.50 mmol), and CH_2Cl_2 (15 mL). After purification by the standard procedure (except that two crash-outs were required), the title compound was isolated as a white solid (723 mg, 1.06 mmol, 71% yield). mp 58-60 ºC. IR ν_{max}/cm^{-1} (film): 2962, 2874, 1578, 1259, 1137, 1029, 722, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.19 (1H, d, *J* = 7.4 Hz), 8.83-8.76 (2H, m), 8.21-8.16 (1H, m), 7.97-7.91 (2H, m), 7.85-7.69 (8H, m), 7.22 (1H, d, *J* = 17.6 Hz), 2.95 (2H, t, *J* = 7.8 Hz), 1.72-1.63 (2H, m), 1.37-1.27 (2H, m), 0.87 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.61 (d, *J* = 9.9 Hz), 153.23 (qd, *J* = 35.5, 2.5 Hz), 153.16 (d, *J* = 13.1 Hz), 150.35-150.11 (m), 146.26 (d, *J* = 9.5 Hz), 136.69 (d, *J* = 3.0 Hz), 134.74 (d, *J* = 11.0 Hz), 131.21 (d, *J* = 13.7 Hz), 130.34 (d, *J* = 8.7 Hz), 124.06 (d, *J* = 80.8 Hz), 124.05 (qd, *J* = 33.2, 3.9 Hz), 122.64 (qd, *J* = 274.8, 2.5 Hz), 122.57-122.35 (m), 120.65 (q, *J* = 321.0 Hz), 120.54 (qd, *J* = 273.2, 2.1 Hz), 118.87 (d, *J* = 88.1 Hz), 114.85 (d, *J* = 90.5 Hz), 38.10, 30.37, 22.29, 13.73; ^{19}F NMR

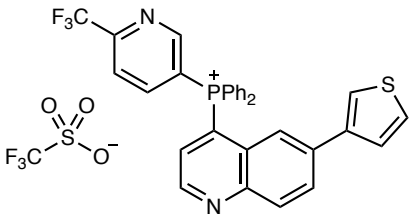
(365 MHz, $CDCl_3$) δ: –53,49, –68.68, –78.48; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 25.06; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 533.2, $C_{28}H_{24}F_6N_2P^+$ requires 533.2.

(7-Bromoquinolin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



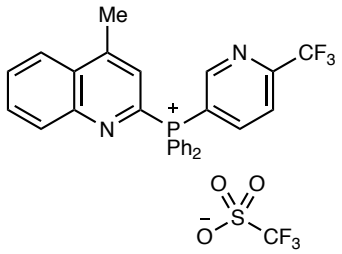
Prepared according to general procedure A (except that the reaction mixture was stirred for 60 min at –30 °C instead of –50 °C) using 7-bromoquinoline (208 mg, 1.0 mmol), Tf_2O (169 μL, 1.0 mmol), 5-(diphenylphosphanyl)-2-(trifluoromethyl)pyridine (364 mg, 1.1 mmol), DBU (147 μL, 1.0 mmol) and CH_2Cl_2 (10 mL). After the purification procedure, the title compound was isolated as a white solid (560 mg, 0.82 mmol, 82% yield). mp 134-137 ºC; IR υ_{max}/cm^{-1} (film): 1488, 1439, 1135, 1260, 1141, 1076, 1029, 723, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.22 (1H, t, *J* = 4.4 Hz), 8.82-8.70 (2H, m), 8.56 (1H, t, *J* = 2.0 Hz), 8.23-8.15 (1H, m), 7.98-7.89 (2H, m), 7.86-7.70 (8H, m), 7.61-7.50 (2H, m), 7.20 (1H, d, *J* = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.39 (qd, *J* = 36.2, 2.4 Hz), 153.37 (d, *J* = 13.1 Hz), 151.65 (d, *J* = 12.3 Hz), 149.27 (d, *J* = 7.2 Hz), 145.97 (d, *J* = 9.6 Hz), 136.79 (d, *J* = 3.2 Hz), 134.57 (d, *J* = 11.0 Hz), 134.34 (d, *J* = 2.3 Hz), 133.16, 131.78 (d, *J* = 9.1 Hz), 131.55 (d, *J* = 13.5 Hz), 126.39 (d, *J* = 6.5 Hz), 125.71, 124.33 (d, *J* = 6.7 Hz), 122.76 (dd, *J* = 10.3, 2.7 Hz), 122.33 (d, *J* = 29.9 Hz), 120.59 (q, *J* = 321.0 Hz), 120.49 (qd, *J* = 275.3, 1.8 Hz), 118.54 (d, *J* = 87.2 Hz), 114.58 (d, *J* = 89.1 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.63, –78.39; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.40; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 537.1, $C_{27}H_{28}BrF_3N_2P^+$ requires 537.0.

Diphenyl(6-(thiophen-3-yl)quinolin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



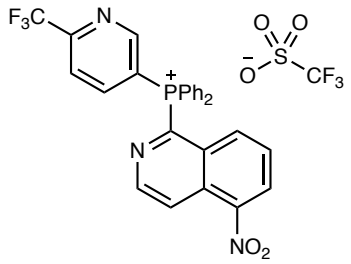
Prepared according to general procedure A using 6-(thiophen-3-yl)quinoline (211 mg, 1.00 mmol), Tf_2O (169 μL, 1.00 mmol), 5-(diphenylphosphanyl)-2-(trifluoromethyl)pyridine (382 mg, 1.10 mmol), DBU (147 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a yellow solid (418 mg, 0.61 mmol, 61% yield). mp 95-99 ^oC; IR υ_{max}/cm^{-1} (film): 1616, 1439, 1334, 1260, 1140, 1075, 1029, 723, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.16 (1H, t, *J* = 4.5 Hz), 8.86-8.72 (2H, m), 8.38 (1H, dd, *J* = 8.8, 2.2 Hz), 8.21 (1H, dd, *J* = 8.7, 2.3 Hz), 8.10 (1H, dd, *J* = 8.8, 1.9 Hz), 7.95 (2H, ddt, *J* = 11.2, 6.1, 2.8 Hz), 7.88-7.76 (8H, m), 7.53 (1H, dd, *J* = 17.6, 4.4 Hz), 7.39 (1H, d, *J* = 1.9 Hz), 7.30 (1H, dd, *J* = 5.1, 2.9 Hz), 7.12 (1H, dd, *J* = 2.9, 1.4 Hz), 6.68 (1H, dd, *J* = 5.1, 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.47 (d, *J* = 13.0 Hz), 153.36 (d, *J* = 35.5 Hz), 149.91 (d, *J* = 12.4 Hz), 148.01 (d, *J* = 7.1 Hz), 146.09 (d, *J* = 9.5 Hz), 139.43, 136.78, 136.73 (d, *J* = 3.1 Hz), 134.42 (d, *J* = 11.0 Hz), 132.63 (d, *J* = 2.3 Hz), 131.72, 131.56 (d, *J* = 13.3 Hz), 130.47, 127.80, 126.27 (d, *J* = 6.5 Hz), 125.29, 123.23, 122.79 (d, *J* = 10.4 Hz), 121.38, 121.29 (d, *J* = 4.0 Hz), 120.65 (q, *J* = 321.1 Hz), 120.48 (q, *J* = 275.6 Hz), 118.71 (d, *J* = 68.3 Hz), 114.88 (d, *J* = 88.9 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.62, –78.35; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.32; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 541.2, $C_{31}H_{21}F_3N_2PS^+$ requires 541.1.

(4-Methylquinolin-2-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



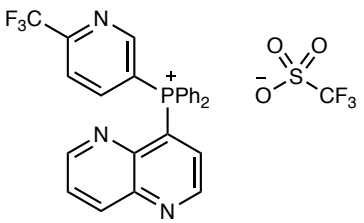
Prepared according to general procedure A, using 4-methylquinoline (132 μL, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a yellow solid (510 mg, 0.82 mmol, 82% yield). mp 64-67 ºC. IR ν_{max}/cm^{-1} (film): 3065, 1576, 1334, 1259, 1140, 1029, 724, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.08 (1H, dd, *J* = 5.5, 1.7 Hz), 8.63 (1H, ddd, *J* = 12.4, 8.5, 2.1 Hz), 8.19-8.15 (2H, m), 8.13 (1H, dd, *J* = 8.3, 1.9 Hz), 7.95-7.87 (3H, m), 7.85-7.71 (9H, m), 7.65 (1H, d, *J* = 4.9 Hz), 2.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.16 (d, *J* = 11.7 Hz), 152.97 (qd, *J* = 36.2, 2.4), 149.47 (d, *J* = 11.1 Hz), 148.71 (d, *J* = 23.0), 145.90 (d, *J* = 8.8 Hz), 143.45, 142.27, 136.46 (d, *J* = 3.0 Hz), 134.89 (d, *J* = 10.6 Hz), 132.05, 131.16 (d, *J* = 13.1 Hz), 130.81 (d, *J* = 12.6 Hz), 129.22 (d, *J* = 3.1 Hz), 125.20 (d, *J* = 109.5 Hz), 125.08 (d, *J* = 82.0 Hz), 122.23-122.00 (m), 120.82 (q, *J* = 321.0), 120.71 (qd, *J* = 274.7, 1.7 Hz), 119.79 (d, *J* = 87.3 Hz), 115.53 (d, *J* = 88.3 Hz), 19.34; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.71, –78.51; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 12.41; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 473.3, $C_{28}H_{21}F_3N_3P^+$ requires 473.1.

(5-Nitroisoquinolin-1-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate

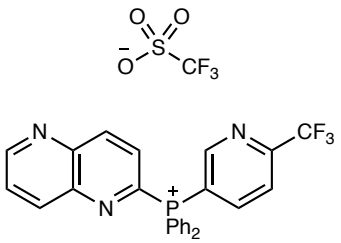


Prepared according to general procedure A, using 5-nitroisoquinoline (174 mg, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as an amorphous solid (471 mg, 0.72 mmol, 72% yield). IR ν_{max}/cm^{-1} (film): 3067, 3013, 1530, 1335, 1262, 1029, 747, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, d, *J* = 5.9 Hz), 8.89 (1H, dd, *J* = 5.6, 2.4 Hz), 8.83 (1H, d, *J* = 4.7 Hz), 8.57 (1H, d, *J* = 7.7 Hz), 8.44 (1H, app t, *J* = 9.7 Hz), 8.05 (1H, d, *J* = 8.1 Hz), 7.89-7.88 (3H, m), 7.82-7.74 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.48 (d, *J* = 12.1 Hz), 152.75 (qd, *J* = 35.6, 2.4 Hz), 146.28 (d, *J* = 42.7 Hz), 146.18 (d, *J* = 3.3 Hz), 146.13 (d, *J* = 29.4 Hz), 143.64 (d, *J* = 121.2 Hz), 136.81 (d, *J* = 3.1 Hz), 134.61 (d, *J* = 10.8 Hz), 131.66 (d, *J* = 13.3 Hz), 131.30 (d, *J* = 25.9 Hz), 130.84 (d, *J* = 2.2 Hz), 130.01-129.85 (2C, m), 129.11 (d, *J* = 12.6 Hz), 122.33 (d, *J* = 3.8 Hz), 121.97-121.73 (m), 120.71 (qd, *J* = 272.9, 2.3 Hz), 120.69 (q, *J* = 321.7 Hz), 120.43 (d, *J* = 92.7 Hz), 115.16 (d, *J* = 85.7 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.58, –78.37; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.30; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 504.2, $C_{27}H_{18}F_3N_3O_2P^+$ requires 504.1.

(1,5-Naphthyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Major

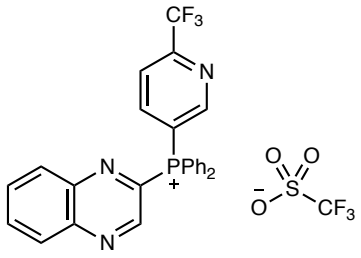


Minor

Major : Minor = 7:1

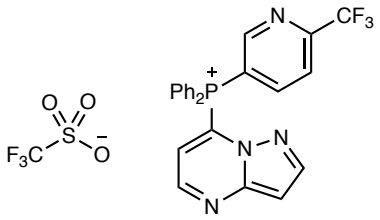
Prepared according to general procedure A using 1,5-naphthyridine (130 mg, 1.0 mmol), Tf_2O (169 µL, 1.0 mmol), 5-(diphenylphosphanyl)-2-(trifluoromethyl)pyridine (382 mg, 1.1 mmol), DBU (147 µL, 1.0 mmol) and CH_2Cl_2 (10 mL). After the purification procedure, the title compound was isolated as a yellow solid (440 mg, 0.73 mmol, 73% yield, combined yield). mp 95-99 ^oC; Both isomers, IR υ_{max}/cm^{-1} (film): 1622, 1519, 1324, 1265, 1240, 1175, 942, 729, 636; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.36 (1H, t, *J* = 4.6 Hz), 8.88 (1H, dd, *J* = 6.4, 2.1 Hz), 8.74- 8.62 (3H, m), 7.89 (3H, dq, *J* = 14.3, 3.3, 2.2 Hz), 7.84-7.64 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.16 (d, *J* = 13.2 Hz), 152.04, 151.73 (d, *J* = 12.2 Hz), 145.06 (d, *J* = 9.6 Hz), 144.54 (d, *J* = 5.8 Hz), 141.02 (d, *J* = 3.6 Hz), 138.63 (d, *J* = 2.4 Hz), 135.77 (d, *J* = 3.3 Hz), 134.24 (d, *J* = 11.0 Hz), 133.24 (d, *J* = 7.7 Hz), 131.05 (d, *J* = 13.3 Hz), 130.70 (d, *J* = 13.6 Hz), 126.71, 126.14 (d, *J* = 86.6 Hz), 123.18-121.21 (m), 120.56 (qd, *J* = 275.5, 2.0 Hz), 120.47 (q, *J* = 321.1 Hz), 119.95 (d, *J* = 90.1 Hz), 115.65 (d, *J* = 91.9 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.59, –78.40; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.96, 13.58; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 460.2, $C_{26}H_{18}F_3N_3P^+$ requires 460.1.

Diphenyl(quinoxalin-2-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using quinoxaline (130 mg, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a white solid (562 mg, 0.92 mmol, 92% yield). mp 172-175 °C. IR ν_{max}/cm^{-1} (film): 3065, 2922, 1440, 1260, 1141, 1029, 724, 634; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.11-9.04 (2H, m), 8.74 (1H, ddd, *J* = 12.3, 8.6, 1.4 Hz), 8.28-8.22 (2H, m), 8.17-8.11 (1H, dd, *J* = 8.2, 1.1 Hz), 8.11-7.90 (4H, m), 7.87-7.75 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.97 (d, *J* = 12.1 Hz, 153.28 (qd, *J* = 35.7, 2.4 Hz), 146.44 (d, *J* = 7.3 Hz), 146.30 (d, *J* = 10.0 Hz), 143.85 (d, *J* = 2.9 Hz), 142.88 (d, *J* = 17.5 Hz) 139.52 (d, *J* = 114.1 Hz), 136.86 (d, *J* = 3.1 Hz), 135.37, 135.05 (d, *J* = 10.9 Hz), 133.29, 131.42 (d, *J* = 13.4 Hz), 130.30 (d, *J* = 1.0 Hz), 130.16 (d, *J* = 2.6 Hz), 122.48-122.26 (m), 120.68 (qd, *J* = 275.2, 1.7 Hz), 120.65 (q, *J* = 321.0 Hz), 118.75 (d, *J* = 88.0 Hz), 114.55 (d, *J* = 88.6 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.62, –78.46; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 11.78; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 460.2, $C_{26}H_{18}F_3N_3P^+$ requires 460.1.

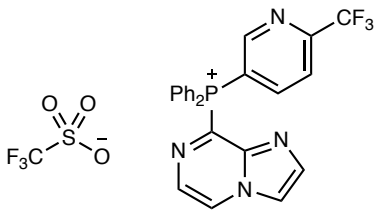
Diphenyl(pyrazolo[1,5-*a*]pyrimidin-7-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



>20:1 (Major:Unidentified Phosphonium) Mixture of Isomers

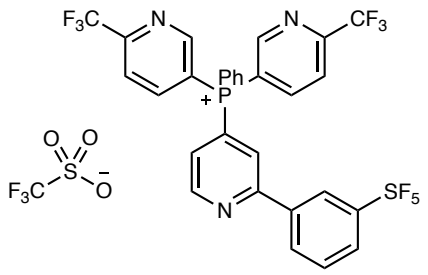
Prepared according to general procedure A using pyrazolo[1,5-a]pyrimidine (179 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (546 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol), and CH_2Cl_2 (15 mL). After purification by the standard procedure, the title compound was isolated as a yellow solid (739 mg, 1.23 mmol, 82% yield). Both Isomers, IR ν_{max}/cm^{-1} (film): 3066, 2925, 1726, 1603, 1260, 1121, 840, 766; Major Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, d, J = 6.4, 2.1 Hz), 8.78-8.70 (2H, m), 8.07 (1H, ddd, J = 8.3, 6.1, 0.7 Hz), 7.98-7.91 (3H, m), 7.82-7.74 (8H, m), 7.29 (1H, dd, J = 12.1, 4.2 Hz), 6.93 (1H, app t, J = 2.4 Hz); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.78 (d, J = 14.1 Hz), 153.51 (qd, J = 36.4, 2.8 Hz), 149.19 (d, J = 8.6 Hz), 148.85 (d, J = 1.4 Hz), 146.03 (d, J = 9.8 Hz), 145.42, 137.03 (d, J = 3.2 Hz), 134.77 (d, J = 11.3 Hz), 131.39 (d, J = 14.2 Hz), 126.70 (d, J = 99.5 Hz), 122.42-122.20 (m), 121.31 (d, J = 8.8 Hz), 120.66 (q, J = 320.7 Hz), 120.61 (qd, J = 275.7, 2.3 Hz), 116.83 (d, J = 90.9 Hz), 112.77 (d, J = 92.7 Hz), 100.2; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.65, –78.43; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.10 (Major Isomer), 14.6 (Minor Isomer); m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 449.3, $C_{24}H_{17}F_3N_4P^+$ requires 449.1.

Imidazo[1,5-*a*]pyrazin-8-yldiphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



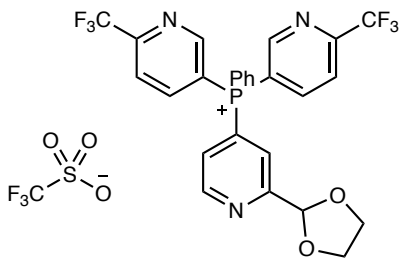
Prepared according to general procedure A, using imidazo[1,2-a]pyrazine (179 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (547 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol), and CH_2Cl_2 (15 mL). After purification by the standard procedure (except that two crash-outs were done), the title compound was isolated as an amorphous solid (321 mg, 0.54 mmol, 36% yield). IR ν_{max}/cm^{-1} (film): 3101, 3064, 2249, 1588, 1439, 1259, 1142, 1029, 724; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.04 (1H, app t, *J* = 4.3 Hz), 8.99 (1H, dd, *J* = 5.9, 2.1 Hz), 8.60 (1H, ddd, *J* = 12.5, 8.1, 2.2 Hz), 8.35 (1H, dd, *J* = 1.7, 1.2 Hz), 8.24 (1H, dd, *J* = 4.4, 1.0 Hz), 8.06 (1H, ddd, *J* = 8.3, 2.1, 0.8 Hz), 7.93-7.87 (2H, m), 7.87-7.70 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.61 (d, *J* = 12.5 Hz), 153.09 (qd, *J* = 36.2, 2.4 Hz), 146.05 (d, *J* = 9.3 Hz), 140.46 (d, *J* = 33.9 Hz), 137.89, 136.46 (d, *J* = 3.1 Hz), 134.96 (d, *J* = 11.1 Hz), 133.77, 130.85 (d, *J* = 13.7 Hz), 130.58 (d, *J* = 22.1 Hz), 125.67 (d, *J* = 3.3 Hz), 121.73-121.52 (m), 120.80 (q, *J* = 320.7 Hz), 120.69 (qd, *J* = 275.2, 1.6 Hz), 118.55 (d, *J* = 89.3 Hz), 116.90, 114.82 (d, *J* = 90.6 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.62, –78.39; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.40; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 449.2, $C_{24}H_{17}F_3N_4P^+$ requires 449.1.

(2-(3-(Pentafluoro-λ^6-sulfaneyl)phenyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



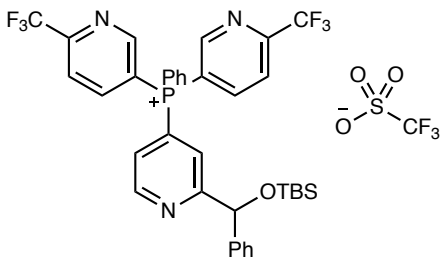
Prepared according to general procedure A (except that Et_3N was used as the base), using, 2-(3-(pentafluoro-λ6-sulfaneyl)phenyl)pyridine (422 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5,5'-(phenylphosphanediyl)bis(2-(trifluoromethyl)pyridine (660 mg, 1.65 mmol), Et_3N (209 μL, 1.50 mmol), and CH_2Cl_2 (15 mL). After purification by the standard procedure (except that a second crash-out using 100% diethyl ether was required), the title compound was isolated as a white solid (1.01 g, 1.22 mmol, 80% yield). mp 82-86 ºC. IR ν_{max}/cm^{-1} (film): 3066, 1586, 1441, 1334, 1075, 1029, 839, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.09 (1H, app t, *J* = 5.4 Hz), 8.92 (2H, dd, *J* = 6.1, 1.7 Hz), 8.60 (2H, ddd, *J* = 13.1, 4.8, 2.0 Hz), 8.47 (1H, app t, *J* = 1.6 Hz), 8.13-8.06 (4H, m), 8.01-7.94 (1H, m), 7.87-7.72 (5H, m), 7.60 (1H, ddd, *J* = 13.7, 8.7, 1.4 Hz), 7.52 (1H, app t, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.14 (d, *J* = 12.0 Hz), 155.06 – 154.40 (m), 154.07 (qd, *J* = 36.3, 2.4 Hz), 153.75 (d, *J* = 13.5 Hz), 152.34 (d, *J* = 11.3 Hz), 146.14 (d, *J* = 10.0 Hz), 137.67, 137.55 (d, *J* = 3.0 Hz), 134.98 (d, *J* = 11.1 Hz), 131.77 (d, *J* = 13.7 Hz), 130.69, 129.92, 128.00-127.80 (m), 126.76 (d, *J* = 86.1 Hz), 126.26 (d, *J* = 8.9 Hz), 125.38-125.16 (m) 124.11 (d, *J* = 9.5 Hz), 122.75-122.50 (m), 120.50 (qd, *J* = 275.8, 2.2 Hz), 120.36 (q, *J* = 320.3 Hz), 116.48 (d, *J* = 88.5 Hz), 112.61 (d, *J* = 86.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: 83.61 (1F, qn, *J* = 150.6 Hz), 62.55 (4F, d, *J* = 150.0 Hz), –68.78, –78.80; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.64; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 680.2, $C_{29}H_{18}F_{11}N_3PS^+$ requires 680.1.

(2-(1,3-Dioxolan-2-yl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



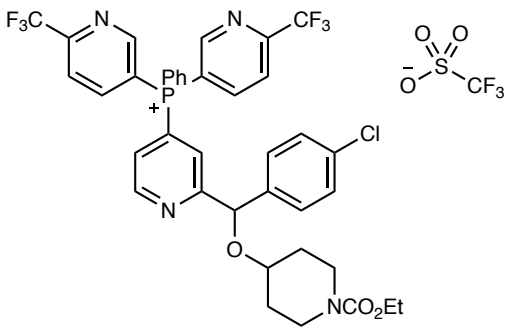
Prepared according to general procedure A, using 2-(1,3-dioxolan-2-yl)pyridine (151 mg, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), 5,5'-(phenylphosphanediyl)bis(2-(trifluoromethyl)pyridine (440 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification by the standard procedure (except that two crash-outs were done), the title compound was isolated as a brown solid (330 mg, 0.47 mmol, 47% yield). mp 67-72 °C. IR ν_{max}/cm^{-1} (film): 3066, 2900, 1334, 1258, 1138, 1074, 725, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, app t, *J* = 4.9 Hz), 8.87 (2H, d, *J* = 5.0 Hz), 8.57 (2H, ddd, *J* = 13.1, 8.4, 1.7 Hz), 8.10 (2H, dd, *J* = 8.3, 1.3 Hz), 7.98 (1H, app t, *J* = 7.7 Hz), 7.86-7.78 (2H, m), 7.77-7.69 (4H, m), 5.86 (1H, s), 4.07-3.95 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.37 (d, *J* = 10.1 Hz), 153.94 (qd, *J* = 36.2, 2.6 Hz), 153.72 (d, *J* = 13.5 Hz), 152.12 (d, *J* = 10.7 Hz), 146.14 (d, *J* = 9.8 Hz), 137.52 (d, *J* = 3.1 Hz), 135.00 (d, *J* = 11.3 Hz), 131.74 (d, *J* = 13.6 Hz), 128.06 (d, *J* = 9.0 Hz), 126.33 (d, *J* = 85.5 Hz), 123.90 (d, *J* = 9.6 Hz), 122.57-122.55 (m), 122.55 (qd, *J* = 275.3, 2.2 Hz), 120.39 (q, *J* = 320.8 Hz), 116.48 (d, *J* = 88.5 Hz), 112.44 (d, *J* = 90.2 Hz), 101.23 (d, *J* = 1.9 Hz), 65.85; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.78, –78.78; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.42; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 550.2, $C_{26}H_{19}F_6N_3O_2P^+$ requires 550.1.

(2-(((Tert-butyldimethylsilyl)oxy)(phenyl)methyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



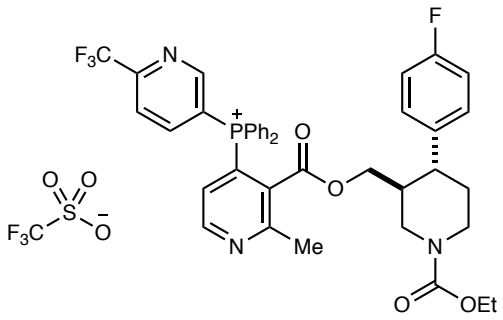
Prepared according to general procedure A using 2-(((tert-butyldimethylsilyl)oxy) (phenyl)methyl)pyridine (300 mg, 1.00 mmol), Tf_2O (169 μL, 1.00 mmol), 5,5'-(phenylphosphanediyl) bis(2-(trifluoromethyl)pyridine) (440 mg, 1.10 mmol), DBU (147 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a yellow solid (510 mg, 0.60 mmol, 60% yield). mp 70-74 ^oC; IR υ_{max}/cm^{-1} (film): 2954, 2932, 2859, 1373, 1333, 1257, 1142, 1075, 1029, 838, 725, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: ^1H NMR (400 MHz,) δ 9.07 (1H, t, *J* = 5.2 Hz), 8.94 (2H, ddd, *J* = 8.3, 6.1, 2.0 Hz), 8.87-8.74 (2H, m), 8.28 (2H, dt, *J* = 8.4, 2.7 Hz), 8.18-8.06 (1H, m), 8.00-7.77 (5H, m), 7.71 (1H, ddd, *J* = 13.5, 5.1, 1.9 Hz), 7.52-7.39 (5H, m), 6.08 (1H, s), 0.84 (9H, s), 0.07 (3H, s), 0.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.44 (d, *J* = 9.7 Hz), 153.77 (*J* = 35.8, 1.8 Hz), 153.58 (d, *J* = 13.4 Hz), 151.68 (d, *J* = 10.9 Hz), 145.97 (dd, *J* = 9.8, 1.9 Hz), 142.05, 137.31 (d, *J* = 3.2 Hz), 134.85 (d, *J* = 11.3 Hz), 131.62 (d, *J* = 13.8 Hz), 128.66, 128.10, 126.47, 126.01 (d, *J* = 84.9 Hz), 125.94 (d, *J* = 9.0 Hz), 122.53 (d, *J* = 10.1 Hz), 120.45 (qd, *J* = 275.4, 1.8 Hz), 120.36 (q, *J* = 320.7 Hz), 116.54 (dd, *J* = 88.3, 5.3 Hz), 112.43 (d, *J* = 90.2 Hz), 77.23 (d, *J* = 1.7 Hz), 25.55, 17.94, –5.06 (d, *J* = 39.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.70, –78.64; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.49; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 698.3, $C_{36}H_{35}F_6N_3OPSi^+$ requires 698.2.

(2-((4-Chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A using ethyl 4-((4-chlorophenyl) (pyridin-2-yl)methoxy)piperidine-1-carboxylate (450 mg, 1.20 mmol), Tf_2O (202 µL, 1.20 mmol), 5,5'-(phenylphosphanediyl)bis(2-(trifluoromethyl)pyridine) (528 mg, 1.44 mmol), DBU (176 µL, 1.20 mmol) and CH_2Cl_2 (12 mL). After purification by the standard procedure, the title compound was isolated as a yellow solid (700 mg, 0.94 mmol, 63% yield). mp 103-105 ^oC; IR υ_{max}/cm^{-1} (film): 3063, 2930, 1682, 1439, 1334, 1259, 1142, 1075, 1029, 725, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.01-8.80 (3H, m), 8.73-8.59 (2H, m), 8.14 (2H, dt, *J* = 8.6, 2.2 Hz), 8.07-7.93 (1H, m), 7.92-7.64 (5H, m), 7.57 (1H, ddd, *J* = 13.5, 5.1, 1.7 Hz), 7.36-7.28 (4H, m), 5.73 (1H, s), 4.10 (2H, q, *J* = 7.1 Hz), 3.72-3.44 (3H, m), 3.14 (2H, ddt, *J* = 12.3, 7.6, 3.7 Hz), 1.78-1.56 (3H, m), 1.45 (2H, dtd, *J* = 12.4, 7.9, 3.8 Hz), 1.24 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.12 (d, *J* = 10.1 Hz), 155.46, 153.89 (qd, *J* = 36.3, 2.5 Hz), 153.73 (d, *J* = 13.4 Hz), 151.68 (d, *J* = 10.8 Hz), 146.05 (d, *J* = 9.7 Hz), 138.51, 137.40 (d, *J* = 3.2 Hz), 134.95 (d, *J* = 11.3 Hz), 134.21, 131.61 (d, *J* = 13.6 Hz), 128.85 (d, *J* = 26.9 Hz), 126.31 (d, *J* = 38.4 Hz), 125.85 (d, *J* = 38.0 Hz), 123.73 (d, *J* = 10.0 Hz), 122.51 (d, *J* = 10.5 Hz), 120.48 (qd, *J* = 275.6, 2.1 Hz), 120.39 (q, *J* = 320.8 Hz), 116.53 (dd, *J* = 88.3, 3.8 Hz), 112.58 (d, *J* = 90.3 Hz), 79.95, 73.08, 61.37, 40.81 (d, *J* = 6.0 Hz), 30.91 (d, *J* = 94.6 Hz), 14.66; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.74, –78.68; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.51; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 773.2, $C_{38}H_{33}ClF_6N_4O_3P^+$ requires 773.2.

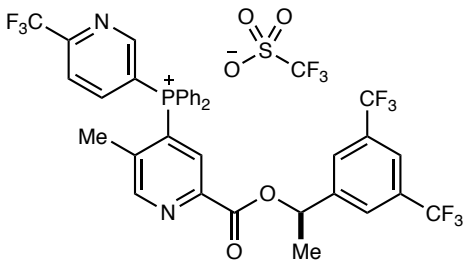
(3-((((3*S*,4*R*)-1-(Ethoxycarbonyl)-4-(4-fluorophenyl)piperidin-3-yl)methoxy)carbonyl)-2-methylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using ((3S,4R)-1-(ethoxycarbonyl)-4-(4-fluorophenyl)piperidin-3-yl)methyl 2-methylnicotinate (401 mg, 1.00 mmol), Tf_2O (169 µL, 1.00 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (364 mg, 1.10 mmol), DBU (149 µL, 1.00 mmol), and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a white solid (1st run: 525 mg, 0.60 mmol, 60% yield, 2nd run: 772 mg, 0.88 mmol, 88% yield, Average = 74%). mp 106-110 ºC. IR ν_{max}/cm^{-1} (film): 3068, 2985, 1688, 1439, 1261, 1139, 1030, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, app t, *J* = 4.9 Hz), 8.69 (1H, dd, *J* = 5.7, 1.7 Hz), 8.59 (1H, app t, *J* = 10.6 Hz), 8.09 (1H, dd, *J* = 8.1, 1.7 Hz), 7.83-7.55 (10H, m), 7.30-7.22 (1H, m), 7.05-6.95 (4H, m), 4.33-4.16 (4H, m), 3.53-3.08 (2H, m), 2.97 (3H, s), 2.79 (1H, br s), 2.55-2.28 (2H, m), 1.92-1.50 (3H, m), 1.30 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.64, 166.61, 161.73 (d, *J* = 245.5 Hz), 161.65-161.43 (m), 155.43-155.14 (m), 153.45 (dd, *J* = 40.4, 12.2 Hz), 152.47 (qd, *J* = 35.3, 2.2 Hz), 145.88 (d, *J* = 9.1 Hz), 137.98 (d, *J* = 2.7 Hz), 135.69 (d, *J* = 10.6 Hz), 133.86 (dd, *J* = 26.3, 10.5 Hz), 130.97-130.53 (2C, m), 128.65 (d, *J* = 7.8 Hz), 127.50 (d, *J* = 4.4 Hz), 122.15-121.92 (m), 120.69 (q, *J* = 321.0 Hz), 120.69 (d, *J* = 91.8 Hz), 120.59 (qd, *J* = 275.9, 1.6 Hz), 116.98 (d, *J* = 92.0), 116.66 (d, *J* = 92.9 Hz), 115.75 (d, *J* = 21.2 Hz), 67.98, 61.54, 46.98, 44.10, 44.02, 40.36, 34.00, 26.16, 14.62; ^{19}F NMR (365

MHz, $CDCl_3$) δ: –68.55, –78.33, –115.40; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 26.58; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 730.3, $C_{40}H_{37}F_4N_3O_4P^+$ requires 730.2.

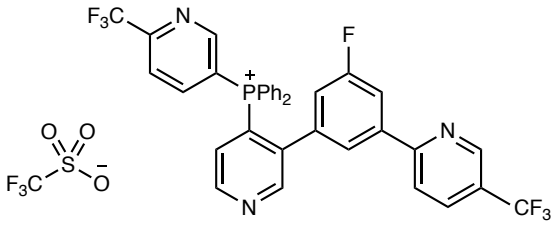
(*R*)-(2-((1-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)carbonyl)-5-methylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using (R)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl 5-methylpicolinate (596 mg, 1.58 mmol), Tf_2O (266 μL, 1.58 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (576 mg, 1.74 mmol), DBU (233 μL, 1.58 mmol), and CH_2Cl_2 (16 mL). After purification by the standard procedure (except that two crash-outs were required), the title compound was isolated as a white solid (1.04 g, 1.21 mmol, 77% yield). mp 106-108 ºC. IR ν_{max}/cm^{-1} (film): 3064, 1743, 1441, 1277, 1130, 1076, 724, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.93 (1H, d, *J* = 6.6 Hz), 8.83 (1H, d, *J* = 5.1 Hz), 8.69 (1H, app t, *J* = 9.2 Hz), 8.17 (1H, d, *J* = 7.9 Hz), 7.97-7.70 (14H, m), 6.10 (1H, q, *J* = 6.5 Hz), 2.15 (3H, s), 1.64 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.45, 154.56 (d, *J* = 8.5 Hz), 153.28 (q, *J* = 35.4 Hz), 153.23 (d, *J* = 12.9 Hz), 147.43 (d, *J* = 11.1 Hz), 145.89 (d, *J* = 9.5 Hz), 143.32, 141.39 (d, *J* = 7.1 Hz), 136.76 (d, *J* = 1.8 Hz), 134.39 (d, *J* = 11.0 Hz), 131.82 (q, *J* = 33.3 Hz), 131.56 (d, *J* = 13.7 Hz), 129.55 (d, *J* = 11.3 Hz), 126.64, 126.22 (d, *J* = 84.6 Hz), 123.05 (q, *J* = 272.7 Hz), 122.90-122.60 (m), 122.25-122.20 (m), 120.53 (q, *J* = 321.3 Hz), 120.42 (q, *J* = 275.1 Hz), 117.89 (d, *J* = 86.7 Hz), 113.78 (d, *J* = 89.1 Hz), 73.21, 21.46, 20.55 (d, *J* = 4.7 Hz); ^{19}F NMR

(365 MHz, $CDCl_3$) δ: –62.68, –68.69, –78.50; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.53; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 707.2, $C_{35}H_{25}F_9N_2O_2P^+$ requires 707.2.

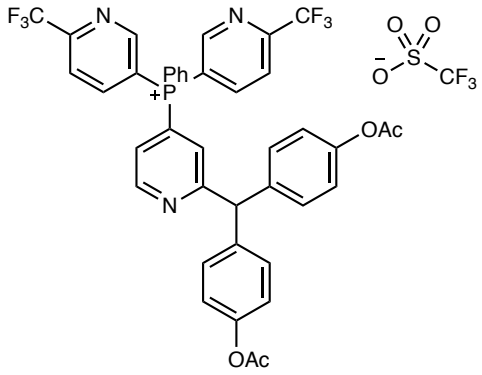
(3-(3-Fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using 3-(3-fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)pyridine (318 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (547 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol), and CH_2Cl_2 (15 mL). After purification by the standard procedure (except that two crash-outs were required), the title compound was isolated as a white solid (1.04 g, 1.30 mmol, 87% yield). mp 106-110 ºC. IR ν_{max}/cm^{-1} (film): 3066, 1604, 1330, 1260, 1134, 1029, 722, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.93 (1H, app t, *J* = 4.8 Hz), 8.74 (1H, d, *J* = 7.1 Hz), 8.69-8.57 (3H, m), 7.97-7.67 (12H, m), 7.62 (1H, d, *J* = 8.4 Hz), 7.57-7.44 (3H, m), 6.64 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.37 (d, *J* = 250.7 Hz), 156.66, 153.26 (d, *J* = 7.8 Hz), 152.96 (d, J = 12.5 Hz), 152.14 (qd, *J* = 36.1, 2.4 Hz), 150.71 (d, *J* = 10.6 Hz), 146.26 (q, *J* = 3.9 Hz), 145.33 (d, *J* = 9.3 Hz), 140.13 (d, *J* = 8.1 Hz), 139.6 (dd, *J* = 6.8, 1.8 Hz), 137.02 (dd, *J* = 8.1, 4.5 Hz), 136.22 (d, *J* = 2.9 Hz), 134.45-134.80 (2C, m), 131.13 (d, *J* = 13.3 Hz), 128.54 (d, *J* = 9.8 Hz), 125.80 (q, *J* = 33.2 Hz), 125.54, 124.78-124.60 (m), 123.35 (q, *J* = 272.4 Hz), 121.90-121.62 (m), 120.65 (q, *J* = 320.9 Hz), 120.33, 120.30 (qd, *J* = 275.3, 2.2 Hz), 119.20 (d, *J* = 86.6 Hz), 117.57 (d, *J* = 23.1 Hz), 115.07 (d, *J* = 89.3 Hz), 115.00 (d, *J* = 22.9 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ:

–62.49, –69.08, –78.38, –110.01 (1F, t, J = 8.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.24; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 648.2, $C_{35}H_{22}F_7N_3P^+$ requires 648.1.

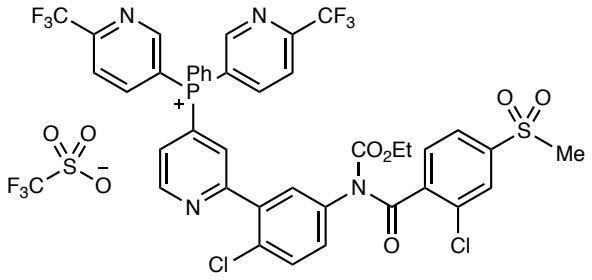
(2-(Bis(4-acetoxyphenyl)methyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A using (pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate (362 mg, 1.00 mmol), Tf_2O (169 μL, 1.00 mmol), 5,5'-(phenylphosphanediyl)bis (2-(trifluoromethyl)pyridine) (440 mg, 1.10 mmol), DBU (147 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a white solid (610 mg, 0.64 mmol, 64% yield). mp 125-130 ^oC; IR υ_{max}/cm^{-1} (film): 1751, 1505, 1372, 1335, 1260, 1194, 1076, 725, 637; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.93 (1H, s), 8.75 (2H, d, J = 6.1 Hz), 8.57 (2H, s), 8.09 (2H, s), 7.94 (1H, d, J = 7.4 Hz), 7.77 (2H, s), 7.61 (2H, dd, J = 13.4, 7.2 Hz), 7.52 (1H, s), 7.24 (1H, s), 7.17 (4H, d, J = 8.0 Hz), 6.96 (4H, d, J = 8.0 Hz), 5.78 (1H, s), 2.25 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.54, 165.87 (d, J = 10.3 Hz), 153.72 (d, J = 13.6 Hz), 153.61 (qd, J = 36.0, 2.3 Hz), 151.89 (d, J = 11.0 Hz), 149.65, 145.81 (d, J = 9.7 Hz), 138.73, 137.29, 134.80 (d, J = 11.3 Hz), 131.53 (d, J = 13.7 Hz), 130.34 , 126.89 (d, J = 9.4 Hz), 125.32 (d, J = 15.5 Hz), 122.37 (d, J = 10.5 Hz), 121.88, 120.57 (qd, J = 275.1, 1.9 Hz), 120.46 (d, J = 320.8 Hz), 119.88-118.09 (m), 116.46 (d, J = 88.4 Hz), 112.25 (d, J = 90.1

Hz), 57.54, 20.98; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.70, –78.58; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.19; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 760.2, $C_{40}H_{29}F_6N_3O_4P^+$ requires 760.2.

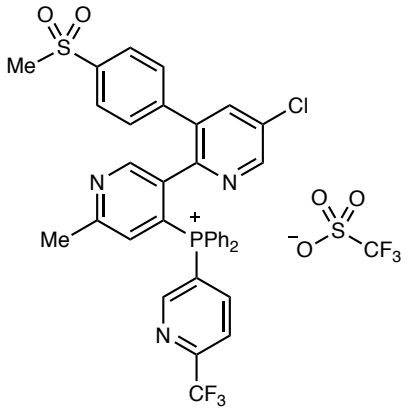
(2-(2-Chloro-5-(2-chloro-N-(ethoxycarbonyl)-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A using ethyl (4-chloro-3-(pyridin-2-yl)phenyl) (2-chloro-4-(methylsulfonyl)benzoyl)carbamate (492 mg, 1.00 mmol), Tf_2O (169 μL, 1.00 mmol), 5,5'-(phenylphosphanediyl)bis(2-(trifluoromethyl)pyridine) (440 mg, 1.10 mmol), DBU (147 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a white solid (500 mg, 0.49 mmol, 49% yield). mp 155-160 °C; IR υ_{max}/cm^{-1} (film): 1750, 1689, 1373, 1335, 1259, 1148, 1075, 1030, 725, 637; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15 (1H, t, *J* = 5.4 Hz), 8.92 (2H, dd, *J* = 6.3, 2.2 Hz), 8.68 (2H, ddd, *J* = 13.4, 8.3, 2.3 Hz), 8.13 (2H, dd, *J* = 8.4, 2.2 Hz), 8.05-7.47 (12H, m), 7.35 (1H, dd, *J* = 8.5, 2.6 Hz), 4.09 (2H, q, *J* = 7.1 Hz), 3.06 (3H, s), 1.04 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.91, 157.40 (d, *J* = 11.5 Hz), 153.96 (dd, *J* = 36.4, 2.3 Hz), 153.85 (d, *J* = 13.9 Hz), 152.56 (d, *J* = 11.3 Hz), 152.45, 145.99 (d, *J* = 9.9 Hz), 142.26 (d, *J* = 47.1 Hz), 136.96 (d, *J* = 114.0 Hz), 135.03 (d, *J* = 11.3 Hz), 132.28 (d, *J* = 5.4 Hz), 131.72 (d, *J* = 13.8 Hz), 131.49, 131.31, 131.01 (d, *J* = 14.5 Hz), 129.62 (d, *J* = 13.0 Hz), 129.37 , 128.98, 128.14, 127.99 (d, *J* = 9.8 Hz), 126.61 (d, *J* = 8.5 Hz), 126.10 (d, *J* = 9.7 Hz), 125.20, 122.60 (d, *J* = 10.3 Hz), 122.06, 121.89 (d, *J* = 2.0 Hz), 120.52 (qd, *J* = 275.5, 2.0 Hz), 120.47 (q, *J* = 320.7 Hz), 119.02 (d, *J* = 29.4 Hz), 116.48 (d, *J* = 88.5 Hz), 112.40 (d, *J* =

90.3 Hz), 64.43, 44.37, 13.77; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.67, –78.62; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.58; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 891.1, $C_{40}H_{28}Cl_2F_6N_4O_5PS^+$ requires 891.1.

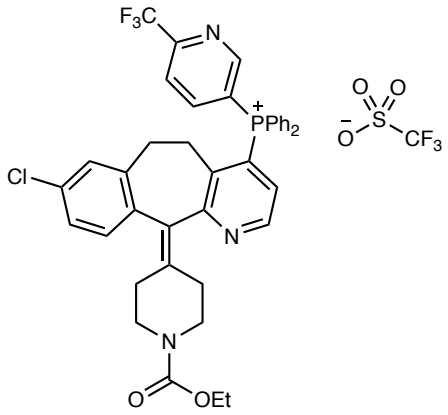
(5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 5-chloro-6'-methyl-3-(4-(methylsulfonyl) phenyl)-2,3'-bipyridine (538 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5-(diphenylphosphanyl)-2-(trifluoromethyl)pyridine (546 mg, 1.65 mmol), DBU (147 μL, 1.50 mmol) and CH_2Cl_2 (15 mL). After purification by the standard procedure, the title compound was isolated as a white solid (620 mg, 0.75 mmol, 50% yield). mp 160-164 ^oC; IR υ_{max}/cm^{-1} (film): 1576, 1437, 1336, 1260, 1068, 1030, 772, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (2H, d, J = 5.6 Hz), 8.33 (1H, d, J = 7.5 Hz), 8.09 (3H, d, J = 8.0 Hz), 7.83 (6H, ddd, J = 27.8, 10.5, 6.8 Hz), 7.74-7.61 (5H, m), 7.60-7.44 (3H, m), 7.21 (1H, d, J = 17.1 Hz), 3.11 (3H, s), 2.55 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.53 (d, J = 11.5 Hz), 153.68 (d, J = 12.1 Hz), 152.53 (d, J = 7.4 Hz), 152.24 (q, J = 35.8 Hz), 147.18 (d, J = 2.3 Hz), 146.13, 145.59 (d, J = 8.8 Hz), 141.39 (d, J = 38.5 Hz), 139.46, 136.06, 135.50 (d, J = 3.1 Hz), 134.05 (d, J = 10.3 Hz), 133.09 (d, J = 3.5 Hz), 132.59, 131.19 (d, J = 10.3 Hz), 130.57 (d, J = 13.5 Hz), 130.14, 128.80, 126.37 (d, J = 88.2 Hz), 122.66,

121.77, 120.78 (q, J = 321.1 Hz), 120.64 (q, J = 275.2 Hz), 118.07 (d, J = 93.3 Hz), 44.17, 24.67; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.54, –78.27; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.98; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 688.2, $C_{36}H_{27}ClF_3N_3O_2PS^+$ requires 688.1.

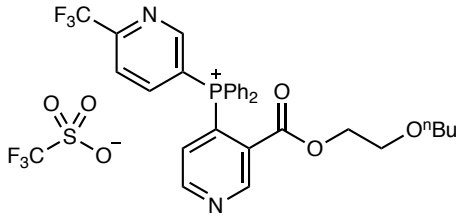
(8-Chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A using ethyl 4-(8-chloro-5,6-dihydro-11H-benzo- [5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (574.5 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5-(diphenylphosphanyl)-2-(trifluoromethyl)pyridine (546 mg, 1.65 mmol), DBU (222 μL, 1.50 mmol) and CH_2Cl_2 (15 mL). After purification by the standard procedure, the title compound was isolated as a yellow solid (1.05 g, 1.21 mmol, 81% yield). mp 150-153 ^oC; IR υ_{max}/cm^{-1} (film): 2922, 1688, 1479, 1438, 1336, 1260, 1223, 1143, 1030,724, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94-8.69 (3H, m), 8.24 (1H, d, J = 7.6 Hz), 7.98 (2H, q, J = 8.0 Hz), 7.92-7.61 (8H, m), 7.19-7.07 (3H, m), 6.72 (1H, d, J = 2.0 Hz), 4.15 (2H, q, J = 7.1 Hz), 3.75 (2H, dd, J = 12.5, 6.1 Hz), 3.46-3.27 (3H, m), 2.81 (1H, d, J = 17.5 Hz), 2.61-2.32 (4H, m), 2.25 (1H, s), 1.53 (1H, ddd, J = 17.0, 11.7, 4.9 Hz), 1.26 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.79 (d, J = 8.5 Hz), 155.42, 153.35 (d, J = 13.2 Hz), 153.26 (q, J = 36.2 Hz), 149.47

(d, J = 11.7 Hz), 145.99 (d, J = 9.5 Hz), 139.68, 136.92-136.39 (m), 134.49 (d, J = 10.9 Hz), 134.30 (d, J = 10.8 Hz), 133.85 (d, J = 33.8 Hz), 132.24, 131.73, 131.54 (dd, J = 13.3, 7.4 Hz), 129.90, 127.53 (d, J = 10.4 Hz), 126.59, 125.27 (d, J = 82.9 Hz), 122.81 (d, J = 10.2 Hz), 120.64 (q, J = 321.0 Hz), 120.50 (qd, J = 275.5, 2.1 Hz), 118.76 (d, J = 86.8 Hz), 115.32 (d, J = 55.2 Hz), 114.44 (d, J = 55.1 Hz), 61.44 , 44.72, 44.61, 30.55 (dd, J = 15.1, 9.6 Hz), 29.51, 14.64; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.61, –78.38; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.14; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 712.3, $C_{40}H_{35}ClF_3N_3O_2P^+$ requires 712.2.

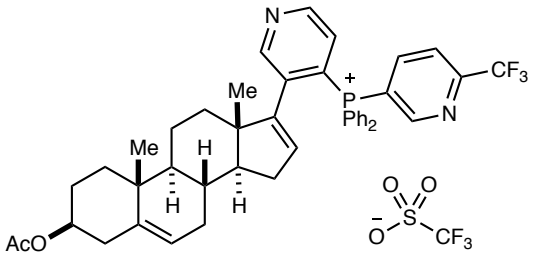
(3-((2-Butoxyethoxy)carbonyl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 2-butoxyethyl nicotinate (223 mg, 1.00 mmol), Tf_2O (169 µL, 1.00 mmol), 5-(diphenylphosphanyl)-2-(trifluoromethyl)pyridine (382 mg, 1.10 mmol), DBU (147 µL, 1.00 mmol) and CH_2Cl_2 (10 mL). After purification by the standard procedure, the title compound was isolated as a yellow solid (430 mg, 0.62 mmol, 62% yield). mp 54-56 °C; IR υ_{max}/cm^{-1} (film): 2960, 2872, 1712, 1440, 1336, 1259, 1142, 1076, 1029, 721, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.57 (1H, d, J = 6.4 Hz), 9.11 (1H, s), 8.77 (1H, dd, J = 6.1, 2.1 Hz), 8.48 (1H, ddd, J = 13.2, 8.2, 2.2 Hz), 8.05 (1H, dd, J = 8.3, 2.1 Hz), 7.93-7.51 (10H, m), 7.41 (1H, dd, J = 16.2, 5.0 Hz), 4.15-3.96 (2H, m), 3.50-3.39 (2H, m), 3.33 (2H, t, J = 6.6 Hz), 1.46 (2H, dq, J = 8.4, 6.7 Hz), 1.37-1.21 (2H, m), 0.85 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.38 (d, J = 1.8 Hz), 156.25 (d, J = 10.9 Hz), 153.24 (d, J = 5.7 Hz), 152.73 (d, J = 12.8 Hz), 152.23 (qd, J = 35.9, 2.5 Hz), 145.07 (d, J = 9.3 Hz), 135.61 (d, J = 3.2 Hz), 133.84 (d, J = 10.7

Hz), 131.54 (d, J = 9.4 Hz), 130.74 (d, J = 13.6 Hz), 127.88 (d, J = 84.7 Hz), 126.67, 121.95 (d, J = 2.3 Hz), 120.72 (d, J = 92.9 Hz), 120.62 (qd, J = 283.1, 2.3 Hz), 120.60 (q, J = 321.0 Hz), 116.98 (d, J = 93.5 Hz), 71.10, 67.51, 66.54, 31.45, 19.10, 13.78; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.53, –78.36; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 26.70; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 553.3, $C_{30}H_{29}F_3N_2O_3P^+$ requires 553.2.

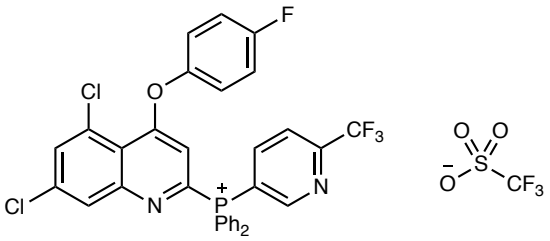
(3-((3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using (3*S*,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-1H-cyclopenta[a]phenanthren-3-yl acetate (587 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (547 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol), and CH_2Cl_2 (15 mL). After purification by the standard procedure (except that two crash-outs were required), the title compound was isolated as a white solid (898 mg, 1.03 mmol, 69% yield). mp 154-158 ºC. IR ν_{max}/cm^{-1} (film): 3503, 2940, 1726, 1258, 1144, 1030, 721, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.04 (1H, d, J = 7.4 Hz), 8.82-8.70 (3H, m), 8.18 (1H, d, J = 6.9 Hz), 7.94-7.87 (2H, m), 7.87-7.77 (6H, m), 7.73-7.68 (2H, m), 7.32 (1H, dd, J = 16.3, 5.1 Hz), 5.54 (1H, s), 5.28 (1H, d, J = 4.6 Hz), 4.57 (1H, m), 2.33-2.20 (2H, m), 2.00 (3H, s), 1.87-1.68 (5H, m), 1.63-1.32 (5H, m), 1.23-1.01 (5H, m), 0.95 (3H, s), 0.77 (1H, td, J = 12.6, 4.1 Hz), 0.59 (1H, td, J = 11.3, 4.1 Hz), -0.29 (1H,

m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.56, 152.90 (qd, *J* = 36.2, 2.3 Hz), 152.82 (d, *J* = 12.3 Hz), 150.97 (d, *J* = 7.6 Hz), 149.67 (d, *J* = 4.1 Hz), 149.23 (d, *J* = 11.0 Hz), 145.67 (d, *J* = 8.8 Hz), 139.86 (d, *J* = 20.9 Hz), 137.54 (d, *J* = 6.2 Hz), 136.40 (dd, *J* = 6.9, 3.1 Hz), 134.65 (dd, *J* = 28.9, 10.5 Hz), 131.45 (dd, *J* = 13.4, 8.8 Hz), 130.28 (d, *J* = 10.7 Hz), 123.79 (d, *J* = 84.9 Hz), 123.02-122.75 (m), 121.65, 120.77 (q, *J* = 321.0 Hz), 120.62 (d, *J* = 86.9 Hz), 120.54 (qd, *J* = 273.7, 1.8 Hz), 116.96 (d, *J* = 89.8 Hz), 115.98 (d, *J* = 90.0 Hz), 73.73, 56.05, 49.70, 49.12, 38.06, 36.91, 36.59, 33.64, 32.64, 30.99, 22.90, 27.68, 21.47, 20.43, 19.14, 18.87 ; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.33, –78.29; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.59; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 721.4, $C_{44}H_{45}F_3N_2O_2P^+$ requires 721.3.

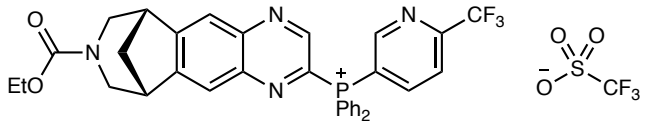
(5,7-Dichloro-4-(4-fluorophenoxy)quinolin-2-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A (except that EtOAc was used instead of CH_2Cl_2), using 5,7-dichloro-4-(4-fluorophenoxy)quinoline (308 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (547 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol), and EtOAc (15 mL). After purification by the standard procedure, the title compound was isolated as a white solid (811 mg, 1.03 mmol, 69% yield). mp 143-145 ºC. IR ν_{max}/cm^{-1} (film): 3070, 2360, 1559, 1263, 1139, 1030, 930, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98 (1H, d, *J* = 5.0 Hz), 8.64 (1H, ddd, *J* = 12.5, 8.6, 1.8 Hz), 8.08-8.02 (2H, m), 7.88-7.81 (2H, m), 7.75 (1H, d, *J* = 1.9 Hz), 7.72-7.65 (8H, m), 7.17-7.12 (2H, m), 7.05 (2H, app t, *J* = 8.1 Hz), 6.56 (1H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.23 (d, *J* = 14.2 Hz), 160.71 (d, *J* =

246.5 Hz), 153.84 (d, *J* = 12.1 Hz), 153.16 (qd, *J* = 35.8, 2.3 Hz), 152.28 (d, *J* = 25.3 Hz), 148.23 (d, *J* = 2.9 Hz), 146.80 (d, *J* = 120.3 Hz), 145.97 (d, *J* = 9.1 Hz), 137.85, 136.47 (d, *J* = 8.6 Hz), 134.87 (d, *J* = 10.8 Hz), 132.91, 131.53 (d, *J* = 1.5 Hz), 131.08 (d, *J* = 13.1 Hz), 128.22, 123.07 (d, *J* = 8.6 Hz), 122.15-121.92 (m), 120.68 (q, *J* = 321.1 Hz), 120.64 (qd, *J* = 274.4, 1.7 Hz), 118.97 (d, *J* = 87.4 Hz), 118.42 (d, *J* = 2.3 Hz), 117.49 (d, *J* = 23.7 Hz), 114.66 (d, *J* = 88.4 Hz), 110.68 (d, *J* = 30.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.69, –78.49, –115.18 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 12.91; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 637.1, $C_{33}H_{20}Cl_2F_4N_2OP^+$ requires 637.1.

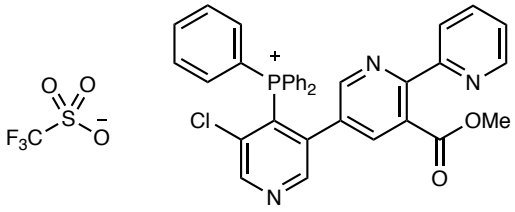
((6S,10R)-8-(Ethoxycarbonyl)-7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxalin-2-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A, using ethyl (6R,10S)-6,7,9,10-tetrahydro-8H-6,10-methanoazepino[4,5-g]quinoxaline-8-carboxylate (185 mg, 0.65 mmol), Tf_2O (109 μL, 0.65 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (237 mg, 0.72 mmol), DBU (98 μL, 0.65 mmol), and CH_2Cl_2 (7 mL). After purification by the standard procedure (except that two crash-outs were required), the title compound was isolated as a yellow solid (413 mg, 0.54 mmol, 83% yield). mp 133 - 137 ºC. IR ν_{max}/cm^{-1} (film): 2958, 2870, 1683, 1260, 1142, 1029, 754, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.12-8.90 (2H, m), 8.86-8.68 (1H, m), 8.26-7.90 (5H, m), 7.88-7.70 (8H, m), 4.19-3.74 (4H, m), 3.60-3.30 (4H, m), 2.52-2.43 (1H, m), 2.07 (1H, d, *J* = 11.4 Hz), 1.06 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.44, 155.35, 153.79 (d, *J* = 12.1 Hz), 152.94 (qd, *J* = 36.1, 2.5 Hz), 152.80 (d, *J* = 15.3 Hz), 145.96 (dd, *J* = 12.7, 9.1 Hz), 145.42 (dd,

J = 27.2, 7.6 Hz), 144.34 (d, J = 2.7 Hz), 143.29 (dd, J = 17.4, 3.8 Hz), 137.92, 136.85-136.57 (m), 134.95-134.65 (m), 131.22 (dd, J = 13.3, 3.7 Hz), 122.53-122.10 (2C, m), 120.56 (q, J = 321.0 Hz), 120.52 (qd, J = 275.2, 1.9 Hz), 118.80 (d, J = 87.8 Hz), 114.59 (d, J = 89.0 Hz), 114.30 (dd, J = 88.9, 7.6 Hz), 61.20 (d, J = 4.5 Hz), 49.72, 49.41 (d, J = 10.6 Hz), 40.65-39.80 (3C, m), 14.30; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.57, –78.34; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 11.45 (d, J = 7.2 Hz); m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 613.3, $C_{34}H_{29}F_3N_4O_2P^+$ requires 613.2.

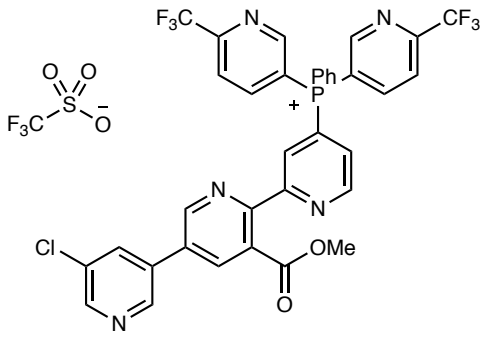
(5''–chloro–3'–(methoxycarbonyl)–[2,2':5',3''–terpyridin]–4''–yl)triphenylphosphonium trifluoromethanesulfonate



>20:1 (Major:Unidentified Phosphonium) Mixture of Isomers

Prepared according to our previous report.[2] Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, d, J = 4.5 Hz), 8.70 (1H, d, J = 3.1 Hz), 8.61 (1H, s), 8.28 (1H, s), 8.06–7.46 (18H, m), 7.40–7.29 (1H, m), 3.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 155.3 (d, J = 2.2 Hz), 154.7, 152.4 (d, J = 7.2 Hz), 151.9 (d, J = 4.8 Hz), 149.6, 148.6, 140.7 (d, J = 5.7 Hz), 136.9 (d, J = 10.9 Hz), 136.8, 136.1 (d, J = 2.3 Hz), 135.4 (d, J = 2.7 Hz), 134.0 (d, J = 10.6 Hz), 130.7 (d, J = 13.6 Hz), 130.0, 127.5, 125.5 (d, J = 88.0 Hz), 124.1, 122.6, 120.8 (q, J = 321.4 Hz), 116.9 (d, J = 89.1 Hz), 52.3; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.17, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.78.

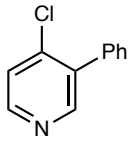
(5''-Chloro-3'-(methoxycarbonyl)-[2,2':5',3''-terpyridin]-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



A 25 mL round bottom flask was charged with methyl 5"-chloro-[2,2':5',3"-terpyridine]-3'-carboxylate (260 mg, 0.80 mmol), 5,5'-(phenylphosphanediyl)bis(2-(trifluoromethyl)pyridine (641 mg, 1.60 mmol, 2.0 equiv), and CH_2Cl_2 (8 mL). After being cooled to –50 °C, Tf_2O (269 µL, 1.60 mmol, 2.0 equiv) was added dropwise. After stirring for 90 minutes, the reaction was cooled to -78 °C and N,N-Dimethylcyclohexylamine (240 µL, 1.60 mmol, 2 equiv) was added dropwise. The reaction was warmed to room temperature before being quenched with H_2O. The organic layer was washed with H_2O (8 x 20 mL), dried over $MgSO_4$, concentrated in *vacuo*, and added dropwise to a 50/50 mixture of Et_2O/Hexanes before being placed in a –20 °C fridge. The mixture was filtered, redisolved in CH_2Cl_2, and the crash-out procedure was repeated a second and third time before affording the title compound as a yellow solid (362 mg, 0.41 mmol, 52% yield). mp 115 – 119 ºC. IR ν_{max}/cm^{-1} (film): 3061, 2955, 1726, 1440, 1334, 1258, 1029, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, app t, *J* = 4.9 Hz), 8.96 (2H, d, *J* = 5.3 Hz), 8.86 (1H, d, *J* = 1.5 Hz), 8.72 (1H, s), 8.67-8.59 (3H, m), 8.47 (1H, d, *J* = 14.4 Hz), 8.15-8.09 (3H, m), 7.99 (1H, app t, *J* = 6.5 Hz), 7.91 (1H, s), 7.87-7.77 (5H, m), 3.82 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.13, 157.52 (d, *J* = 11.0 Hz), 153.93 (qd, *J* = 36.0, 2.5 Hz), 153.81 (d, *J* = 13.5 Hz), 152.00 (d, *J* = 2.2 Hz), 151.42 (d, *J* = 11.0 Hz), 149.05, 148.73, 146.19 (d, *J* = 9.9 Hz), 145.81, 137.51 (d, *J* = 3.0 Hz), 135.77, 135.06 (d, *J* = 11.3 Hz), 134.24, 132.91, 132.79, 131.82, 131.69, 129.27, 127.82 (d, *J* = 9.0 Hz), 126.42 (d, *J* = 86.1 Hz), 125.82 (d, *J* = 9.8 Hz), 122.78-122.55 (m), 120.49 (qd, *J* = 275.5,

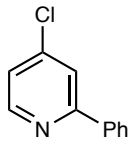
2.0 Hz), 120.40 (q, J = 320.8 Hz), 116.50 (d, J = 88.5 Hz), 112.45 (d, J = 90.2 Hz), 53.05; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –68.72, –78.70; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.51; m/z LRMS (ESI + APCI) found $[M - OTf]^+$ 724.2, $C_{35}H_{22}ClF_6N_5O_2P^+$ requires 724.1.

4-Chloro-2-phenylpyridine



Prepared according to general procedure B, using diphenyl(3-phenylpyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (32 mg, 0.05 mmol), LiCl (9 mg, 0.20 mmol), and Dioxane (0.5 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 10% EtOAc in Hexanes) was used to isolate a pure sample of the product (NMR Yield = 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (1H, s), 8.48 (1H, d, J = 5.3 Hz), 7.52-7.41 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.55, 149.30, 142.41, 136.55, 135.58, 129.63, 128.59, 128.56, 124.94. The spectroscopic data is in agreement with the literature.

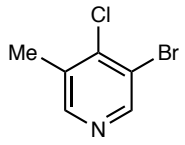
4-Chloro-2-phenylpyridine



Prepared according to general procedure B, using phenyl(2-phenylpyridin-4-yl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (35 mg, 0.05 mmol), LiCl (9 mg, 0.20 mmol), and Dioxane (0.5 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 7.5% EtOAc in Hexanes) was used to isolate a pure sample of the product (GC Yield: 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, J = 5.3 Hz), 8.00-7.96 (2H, m), 7.74 (1H, d, J = 1.9 Hz), 7.52-7.42 (3H, m), 7.25 (1H, dd, J = 5.4, 1.9 Hz); ^{13}C

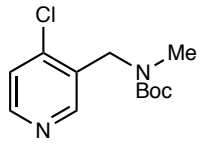
NMR (100 MHz, $CDCl_3$) δ: 159.17, 150.64, 144.89, 138.29, 129.75, 129.01, 127.13, 122.43, 121.03. The spectroscopic data is in agreement with the literature.

3-Bromo-4-chloro-5-methylpyridine



Prepared according to general procedure B using (3-bromo-5-methylpyridin-4-yl) triphenylphosphonium trifluoromethanesulfonate (175 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated at 80 °C for 24 hours. Flash column chromatography (silica gel: 33% EtOAc in Hexanes) afforded the title compound as a colorless oil (42 mg, 0.20 mmol, 68% yield). IR υ_{max}/cm^{-1} (film): 2921, 1584, 1458, 1422, 1146, 876; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.58 (1H, s), 8.33 (1H, s), 2.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.38, 149.46, 143.87, 134.05, 121.53, 18.00; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 206.0, $C_6H_6BrClN^+$ requires 205.9.

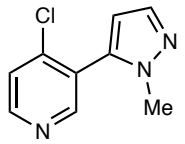
***Tert*-butyl ((4-chloropyridin-3-yl)methyl)(methyl)carbamate**



Prepared according to general procedure B, using (3-(((tert-butoxycarbonyl)(methyl)amino)methyl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (211 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 40% EtOAc in Hexanes) afforded the title compound as a colorless oil (43 mg, 0.17 mmol, 56% yield). IR ν_{max}/cm^{-1} (film): 2976, 2930, 1690, 1390, 1143, 729, 646; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.41 (1H, s), 8.38 (1H, d, J = 5.0 Hz), 7.27 (1H, d, J = 5.7 Hz), 4.53 (2H, d, J =

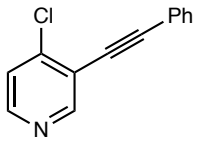
10.6 Hz) 2.86 (3H, s), 1.42 (9H, d, J = 14.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.73 (d, J = 45.7 Hz), 150.08, 149.40, 143.30 (d, J = 12.6 Hz) 131.52, 124.50, 80.33, 48.02 (d, J = 71.8 Hz), 34.68, 28.43; m/z LRMS (ESI + APCI) found $[M + H]^+$ 257.1, $C_{12}H_{18}ClN_2O_2^+$ requires 257.1.

4-Chloro-3-(1-methyl-1*H*-pyrazol-5-yl)pyridine



Prepared according to general procedure B, using (3-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (192 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 80% Et_2O in Hexanes) afforded the title compound as a clear oil (42 mg, 0.22 mmol, 73% yield). IR ν_{max}/cm^{-1} (film): 3038, 2920, 2231, 1551, 1391, 1095, 927, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (1H, d, J = 4.4 Hz), 8.55 (1H, s), 7.59 (1H, s), 7.48 (1H, d, J = 5.0 Hz), 6.36 (1H, s), 3.76 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.90, 151.03, 144.15, 138.78, 136.74, 126.73, 124.75, 108.13, 37.25; m/z LRMS (ESI + APCI) found $[M + H]^+$ 194.1, $C_9H_9ClN_3^+$ requires 194.0.

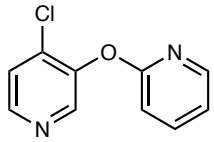
4-Chloro-3-(phenylethynyl)pyridine



Prepared according to general procedure B, using diphenyl(3-(phenylethynyl)pyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (198 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 48 hours. Flash column chromatography (silica gel: 2% Et_2O in Hexanes) afforded the title compound as a clear oil (41 mg, 0.19 mmol, 64% yield). IR ν_{max}/cm^{-1} (film): 3057, 2922, 2219, 1492, 1261,

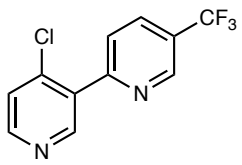
851, 688, 564; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (1H, s), 8.42 (1H, d, *J* = 5.3 Hz), 7.61-7.56 (2H, m), 7.43-7.34 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.45, 149.03, 145.16, 131.95, 129.29, 128.59, 124.13, 122.31, 120.94, 97.78, 83.02; m/z LRMS (ESI + APCI) found $[M + H]^+$ 214.1, $C_{13}H_9ClN^+$ requires 214.0.

4-Chloro-3-(pyridin-2-yloxy)pyridine



Prepared according to general procedure B, using diphenyl(3-(pyridin-2-yloxy)pyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (195 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 48 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes) afforded the title compound as a clear oil (24 mg, 0.12 mmol, 39% yield). IR ν_{max}/cm^{-1} (film): 3060, 2924, 2360, 2342, 1478, 1243, 776, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, s), 8.39 (1H, d, *J* = 5.2 Hz), 8.11 (1H, dd, *J* = 4.9, 1.8 Hz), 7.78- 7.72 (1H, m), 7.43 (1H, d, *J* = 5.2 Hz), 7.08-7.02 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.54, 147.44, 147.18, 146.82, 146.00, 139.93, 137.08, 125.36, 119.28, 111.26; m/z LRMS (ESI + APCI) found $[M + H]^+$ 207.1, $C_{10}H_8ClN_2O^+$ requires 207.0.

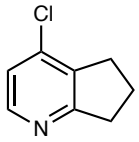
4'-Chloro-5-(trifluoromethyl)-2,3'-bipyridine



Prepared according to general procedure B using diphenyl(5-(trifluoromethyl)-[2,3'-bipyridin]-4'-yl) (6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (141 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated at 80 °C

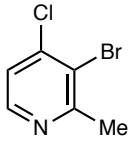
for 24 hours. Flash column chromatography (silica gel: 33% EtOAc in Hexanes) afforded the title compound as a white solid (32 mg, 0.13 mmol, 63% yield). mp 155-157 ºC; IR υ_{max}/cm^{-1} (film): 1625, 1604, 1575, 1484, 1323, 1126, 1083, 1015, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, d, *J* = 2.2 Hz), 8.83 (1H, s), 8.73-8.47 (1H, m), 8.05 (1H, dd, *J* = 8.3, 2.4 Hz), 7.83 (1H, d, *J* = 8.3 Hz), 7.46 (1H, d, *J* = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.24, 152.00, 150.86, 146.95 (q, *J* = 4.0 Hz), 142.14, 133.86, 133.61 (q, *J* = 3.5 Hz), 126.06 (q, *J* = 33.2 Hz), 125.15, 124.83, 123.52 (q, *J* = 272.6 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.46; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 259.1, $C_{11}H_7ClF_3N_2^+$ requires 259.0.

4-Chloro-6,7-dihydro-5H-cyclopenta[b]pyridine



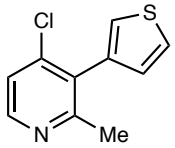
Prepared according to general procedure B using (6,7-dihydro-5H-cyclopenta [b]pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (120 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated at 80 °C for 40 hours. Flash column chromatography (silica gel: 33% EtOAc in Hexanes) afforded the title compound as a colorless oil (12 mg, 0.08 mmol, 41% yield, NMR yield is 66%). IR υ_{max}/cm^{-1} (film): 2961, 2924, 2853, 1559, 1457, 1259, 1088, 798; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (1H, d, *J* = 5.4 Hz), 7.04 (1H, d, *J* = 5.4 Hz), 3.08 (2H, t, *J* = 7.8 Hz), 2.99 (2H, t, *J* = 7.5 Hz), 2.14 (2H, p, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.39, 148.63, 140.84, 135.96, 121.55, 35.15, 30.06, 22.14; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 154.1, $C_8H_9ClN^+$ requires 154.0.

3-Bromo-4-chloro-2-methylpyridine



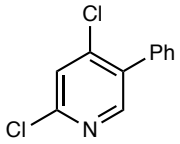
Prepared according to general procedure B using (3-bromo-2-methylpyridin-4-yl) diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (130 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated at 80 °C for 40 hours. Flash column chromatography (silica gel: 33% EtOAc in Hexanes) afforded the title compound as a colorless oil (26 mg, 0.13 mmol, 63% yield). IR υ_{max}/cm^{-1} (film): 2921, 1547, 1424, 1384, 1182, 854, 706; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (1H, d, *J* = 5.3 Hz), 7.23 (1H, d, *J* = 5.2 Hz), 2.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.11, 147.58, 144.62, 123.09, 122.01, 26.52; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 206.0, $C_6H_6BrClN^+$ requires 205.9.

4-Chloro-2-methyl-3-(thiophen-3-yl)pyridine



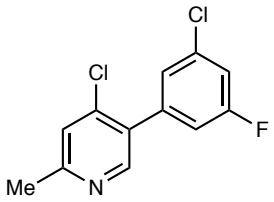
Prepared according to general procedure B, using (2-methyl-3-(thiophen-3-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (196 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 28 hours. Flash column chromatography (silica gel: 20% EtOAc in Hexanes) afforded the title compound as a yellow oil (54 mg, 0.26 mmol, 86% yield). IR ν_{max}/cm^{-1} (film): 3105, 2925, 2217, 1550, 1418, 907, 726, 656; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (1H, d, *J* = 5.4 Hz), 7.44 (1H, dd, *J* = 4.9, 3.0 Hz), 7.25 (1H, d, *J* = 5.6 Hz), 7.22 (1H, dd, *J* = 3.0, 1.3 Hz), 7.02 (1H, dd, *J* = 5.0, 1.3 Hz), 2.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.37, 148.49, 144.11, 136.12, 131.37, 128.54, 125.93, 124.59, 122.33, 24.20; m/z LRMS (ESI + APCI) found $[M + H]^+$ 210.1, $C_{10}H_8ClNS^+$ requires 210.1.

2,4-Dichloro-5-phenylpyridine



Prepared according to general procedure B, using (2-chloro-5-phenylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (196 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 72 hours. Flash column chromatography (silica gel gradient elution: 2% Et_2O in Hexanes to 10% Et_2O in Hexanes) afforded the title compound as a white solid (32 mg, 0.14 mmol, 48% yield). mp 74-78 ºC. IR ν_{max}/cm^{-1} (film): 3085, 2923, 1732, 1539, 1441, 1127, 826, 696; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.34 (1H, s), 7.52-7.40 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.77, 150.69, 144.25, 135.58, 134.42, 129.53, 128.89, 128.68, 124.87; m/z LRMS (ESI + APCI) found $[M + H]^+$ 224.0, $C_{11}H_8Cl_2N^+$ requires 224.0.

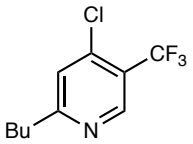
4-Chloro-5-(3-chloro-5-fluorophenyl)-2-methylpyridine



Prepared according to general procedure B using (5-(3-chloro-5-fluorophenyl)- 2-methylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethane sulfonate (140 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated at 80 °C for 24 hours. Flash column chromatography (silica gel: 15% EtOAc in Hexanes) afforded the title compound as a white solid (33 mg, 0.13 mmol, 65% yield). mp 108-110 ºC; IR υ_{max}/cm^{-1} (film): 3027, 1608, 1577, 1449, 1407, 1335, 1220, 873, 794; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.39 (1H, s), 7.29 (1H, s), 7.21 (1H, q, J = 1.2, 0.7 Hz), 7.15 (1H, dt, J = 8.4, 2.1 Hz), 7.06 (1H, ddd, J = 9.0, 2.4, 1.5 Hz), 2.58 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.48 (d, J = 250.2 Hz),

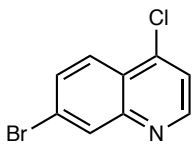
159.79, 150.28, 142.28, 138.68 (d, J = 9.1 Hz), 135.22 (d, J = 10.9 Hz), 131.38 (d, J = 2.3 Hz), 125.76 (d, J = 3.3 Hz), 124.34, 116.19 (d, J = 24.6 Hz), 115.42 (d, J = 22.3 Hz), 24.12; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –110.53; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 256.1, $C_{12}H_9Cl_2FN^+$ requires 256.0.

2-Butyl-4-chloro-5-(trifluoromethyl)pyridine



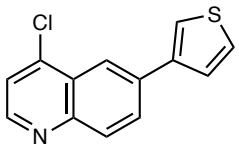
Prepared according to general procedure B, using (2-butyl-5-(trifluoromethyl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (205 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 24 hours. The ^{1}H NMR yield was measured using triphenylmethane (73 mg, 0.30 mmol, 1.0 equiv) as an internal standard (83% NMR yield). PTLC (2% Et_2O in Hexanes) was used to obtain approximately 25 mg of product (with solvent impurities) for characterization. IR ν_{max}/cm^{-1} (film): 2956, 2921, 1724, 1591, 1463, 1148, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (1H, s), 7.31 (1H, s), 2.83 (2H, t, J = 7.7 Hz), 1.77-1.67 (2H, m), 1.44-1.33 (2H, m), 0.95 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.15, 147.84 (q, J = 5.7 Hz), 142.64 (q, J = 1.6 Hz), 124.83, 122.70 (d, J = 273.0 Hz), 122.28 (q, J = 31.7 Hz), 37.95, 31.56, 22.50, 13.98; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.15; m/z LRMS (ESI + APCI) found $[M + H]^+$ 238.1, $C_{10}H_{12}ClF_3N^+$ requires 238.1.

7-Bromo-4-chloroquinoline



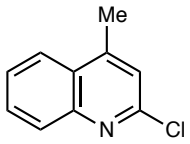
Prepared according to general procedure B using (7-bromoquinolin-4-yl)diphenyl(6-(trifluoromethyl) pyridin-3-yl)phosphonium trifluoromethanesulfonate (137.6 mg, 0.20 mmol), LiCl (34 mg, 0.8 mmol), and Dioxane (2.0 mL). The reaction was heated to 80 °C for 14 hours. Flash column chromatography (silica gel: 20% EtOAc in Hexanes) afforded the title compound as a white solid (36 mg, 0.15 mmol, 75% yield). mp 100-102 ºC; IR υ_{max}/cm^{-1} (film): 3080, 1602, 1551, 1483, 1059, 971, 812; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (1H, d, *J* = 4.7 Hz), 8.29 (1H, d, *J* = 1.9 Hz), 8.07 (1H, d, *J* = 9.0 Hz), 7.70 (1H, dd, *J* = 8.9, 2.0 Hz), 7.48 (1H, d, *J* = 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.03, 149.77, 142.86, 132.23, 131.26, 125.70, 125.40, 124.89, 121.67; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 242.0, $C_9H_6BrClN^+$ requires 241.9.

4-Chloro-6-(thiophen-3-yl)quinoline



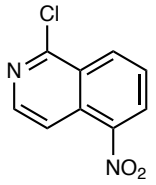
Prepared according to general procedure B using diphenyl(6- (thiophen-3-yl)quinolin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (138 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated at 80 °C for 17 hours. Flash column chromatography (silica gel: 33% EtOAc in Hexanes) afforded the title compound as a white solid (35 mg, 0.14 mmol, 72% yield). mp 114-116 ºC; IR υ_{max}/cm^{-1} (film): 3064, 1581, 1556, 1500, 1432, 1366, 834, 821; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, d, *J* = 4.7 Hz), 8.36 (1H, d, *J* = 2.0 Hz), 8.12 (1H, d, *J* = 8.7 Hz), 8.01 (1H, dd, *J* = 8.8, 2.0 Hz), 7.64 (1H, dd, *J* = 3.0, 1.4 Hz), 7.54 (1H, dd, *J* = 5.0, 1.4 Hz), 7.50-7.38 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.61, 148.50, 142.59, 141.26, 135.07, 130.47, 129.62, 126.98, 126.88, 126.49, 122.06, 121.76, 120.72; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 246.0, $C_{13}H_9ClNS^+$ requires 246.0.

2-Chloro-4-methylquinoline



Prepared according to general procedure B, using (4-methylquinolin-2-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (187 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 72 hours. Flash column chromatography (silica gel: 2% Et_2O in Hexanes) afforded the title compound as a white solid (17 mg, 0.10 mmol, 32% yield). IR ν_{max}/cm^{-1} (film): 2924, 2853, 1730, 1558, 1291, 1099, 844, 756; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.01 (1H, d, *J* = 8.4 Hz), 7.95 (1H, d, *J* = 8.3 Hz), 7.75-7.69 (1H, m), 7.60-7.54 (1H, m), 7.23 (1H, s), 2.68 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.65, 147.84, 147.78, 130.36, 129.27, 127.08, 126.81, 123.94, 122.62, 18.73; m/z LRMS (ESI + APCI) found $[M + H]^+$ 178.1, $C_{10}H_9ClN^+$ requires 178.0.

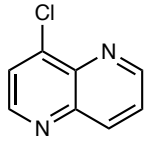
1-Chloro-5-nitroisoquinoline



Prepared according to general procedure B, using (5-nitroisoquinolin-1-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (196 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 12 hours. Flash column chromatography (silica gel: 10% EtOAc in Hexanes) afforded the title compound as a yellow solid (48 mg, 0.23 mmol, 76% yield). mp 183 - 185 ºC. IR ν_{max}/cm^{-1} (film): 3055, 2923, 1622, 1519, 1315, 1048, 813, 725; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, d, *J* = 8.5 Hz), 8.55 (1H, d, *J* = 7.7 Hz), 8.48 (1H, d, *J* = 6.1 Hz), 8.39 (1H, d, *J* = 6.1 Hz), 7.81 (1H, app t, *J* = 8.0 Hz);

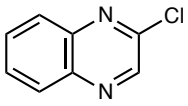
^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.72, 145.45, 144,89, 133.40, 130.43, 129.03, 127.60, 127.12, 115.93; m/z LRMS (ESI + APCI) found $[M + H]^+$ 209.0, $C_9H_6ClN_2O_2^+$ requires 209.0.

4-Chloro-1,5-naphthyridine



Prepared according to general procedure B using (1,5-naphthyridin-4-yl)diphenyl (6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (122 mg, 0.20 mmol), LiCl (34 mg, 0.8 mmol), and Dioxane (2.0). The reaction was heated at 80 °C for 34 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes) afforded the title compound as a colorless oil (8 mg, 0.05 mmol, 25% yield). IR υ_{max}/cm^{-1} (film): 2961, 2855, 1560, 1457, 1160, 1088, 942, 796; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.10 (1H, dd, *J* = 4.2, 1.6 Hz), 8.86 (1H, d, *J* = 4.7 Hz), 8.45 (1H, dd, *J* = 8.5, 1.7 Hz), 7.82-7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.77, 150.85, 145.13, 144.29, 141.09, 138.18, 125.47, 124.67; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 164.1, $C_8H_5ClN_2^+$ requires 164.0.

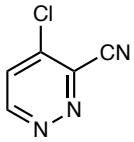
2-Chloroquinoxaline



Prepared according to general procedure B, using diphenyl(quinoxalin-2-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (244 mg, 0.40 mmol), LiCl (68 mg, 1.60 mmol), and Dioxane (4 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 2% Et_2O in Hexanes) afforded the title compound as a white solid (36 mg, 0.24 mmol, 60% yield). mp 43-45 ºC IR ν_{max}/cm^{-1} (film): 3048, 2920, 1542, 1153, 1092, 957, 758, 592; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (1H, s), 8.13-8.08 (1H, m), 8.04-7.98

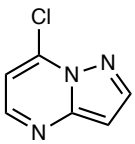
(1H, m) 7.83-7.74 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.47, 145.05, 142.11, 141.12, 131.35, 130.30, 129.43, 128.67; m/z LRMS (ESI + APCI) found $[M + H]^+$ 165.1, $C_8H_6ClN_2^+$ requires 165.0.

4-Chloropyridazine-3-carbonitrile



A 50 mL pressure tube was charged with pyridazine-3-carbonitrile (53 mg, 0.50 mmol), 5-(diphenylphosphaneyl)-2-(trifluoromethyl)pyridine (182 mg, 0.55 mmol), and EtOAc (5 mL). The pressure tube was cooled to –50 °C and Tf_2O (84 μL, 0.50 mmol) was added dropwise. After stirring for 1 hour, the flask was cooled to –78 °C, DBU (75 μL, 0.50 mmol) was added dropwise, and the flask was allowed to warm to room temperature. After 30 minutes, LiCl (85 mg, 2.00 mmol) was added, and the pressure tube was heated to 80 °C. After 5 hours, the reaction was cooled to room temperature, concentrated *in vacuo*, and purified by flash column chromatography (silica gel: 60% Et_2O in Hexanes) to afford the title compound as a an amorphous solid (32 mg, 0.23 mmol, 45% yield). IR ν_{max}/cm^{-1} (film): 3101, 2921, 1531, 1081, 852, 818, 756, 732; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.27 (1H, d, J = 5.6 Hz), 7.74 (1H, d, J = 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.97, 141.34, 140.36, 126.88, 112.93; m/z LRMS (ESI + APCI) found $[M + H]^+$ 140.1, $C_5H_3ClN_3^+$ requires 140.0.

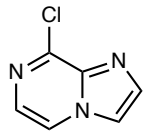
7-Chloropyrazolo[1,5-*a*]pyrimidine



Prepared according to general procedure B, using diphenyl(pyrazolo[1,5-a]pyrimidin-7-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (180 mg, 0.30

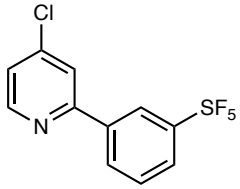
mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 48 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes) afforded the title compound as a yellow solid (23 mg, 0.06 mmol, 21% yield). The NMR spectra obtained match the reported literature values.[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (1H, d, *J* = 4.5 Hz), 8.25 (1H, d, *J* = 2.3 Hz), 6.99 (1H, d, *J* = 4.5 Hz), 6.84 (d, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.15, 148.33, 145.61, 139.14, 108.16, 98.84; m/z LRMS (ESI + APCI) found $[M + H]^+$ 154.1, $C_6H_5ClN_3^+$ requires 154.0.

8-Chloroimidazo[1,5-*a*]pyrazine



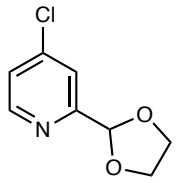
Prepared according to general procedure B, using imidazo[1,5-a]pyrazin-8-yldiphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (180 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 48 hours. Flash column chromatography (silica gel: 2% CH_3OH, 49% EtOAc, 49% Hexanes) afforded the title compound as a white solid (23 mg, 0.15 mmol, 50% yield). mp 175-176 ºC. IR ν_{max}/cm^{-1} (film): 3120, 2922, 1613, 1431, 1329, 1197, 905, 738, 592; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (1H, d, *J* = 4.6 Hz), 7.82 (1H, d, *J* = 1.0 Hz), 7.77 (1H, d, *J* = 1.1 Hz), 7.67 (1H, d, *J* = 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.13, 138.17, 135.89, 128.08, 118.94, 115.72; m/z LRMS (ESI + APCI) found $[M + H]^+$ 154.1, $C_6H_5ClN_3^+$ requires 154.0.

4-Chloro-2-(3-(pentafluoro-λ^6-sulfaneyl)phenyl)pyridine



Prepared according to general procedure B, using (2-(3-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (249 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 48 hours. Flash column chromatography (silica gel: 20% CH_2Cl_2 in Hexanes, ran twice) afforded the title compound as an amorphous solid (76 mg, 0.24 mmol, 80% yield). IR ν_{max}/cm^{-1} (film): 3081, 2926, 1572, 1459, 1099, 827, 713, 595; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.61 (1H, d, *J* = 5.2 Hz), 8.43 (1H, s), 8.10 (1H, d, *J* = 7.8 Hz), 7.82 (1H, d, *J* = 8.2 Hz), 7.72 (1H, s), 7.58 (1H, app t, *J* = 8.0 Hz), 7.33-7.29 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.92, 154.76 (m), 150.93, 145.30, 139.25, 129.89, 129.36, 126.95 (qn, *J* = 4.7 Hz), 124.88 (qn, *J* = 4.7 Hz), 123.37, 121.11; ^{19}F NMR (365 MHz, $CDCl_3$) δ: 83.96 (1F, qn, *J* = 152.1 Hz), 62.70 (4F, d, *J* = 150.1 Hz); m/z LRMS (ESI + APCI) found $[M + H]^+$ 316.0, $C_{11}H_8ClF_5NS^+$ requires 316.0.

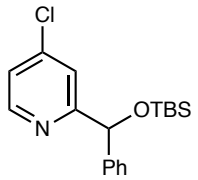
4-chloro-2-(1,3-dioxolan-2-yl)pyridine



Prepared according to general procedure B, using (2-(1,3-dioxolan-2-yl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (210 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 30% EtOAc in Hexanes) afforded the title compound as a yellow oil (34 mg, 0.18 mmol, 61% yield). IR ν_{max}/cm^{-1} (film): 2956, 2889, 1578, 1382, 1227, 1113, 831, 670; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, d, *J* = 5.3 Hz), 7.55 (1H, d, *J* = 1.8 Hz), 7.29 (1H, dd, *J* = 5.3, 2.0 Hz), 5.84 (1H, s), 4.19-4.04 (4H, m); ^{13}C NMR (100 MHz,

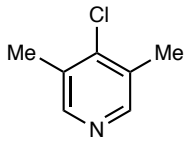
$CDCl_3$) δ: 158.94, 150.43, 145.07, 124.41, 121.38, 103.08, 65.77; m/z LRMS (ESI + APCI) found $[M + H]^+$ 186.1, $C_8H_9ClNO_2^+$ requires 186.0.

2-(((Tert-butyldimethylsilyl)oxy)(phenyl)methyl)-4-chloropyridine



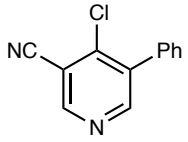
Prepared according to general procedure B using (2-(((tert-butyldimethylsilyl)oxy) (phenyl)methyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (85 mg, 0.10 mmol), LiCl (17 mg, 0.40 mmol), and Dioxane (1 mL). The reaction was heated at 80 °C for 44 hours. Flash column chromatography (silica gel: 15% EtOAc in Hexanes) afforded the title compound as a colorless oil (18 mg, 0.12 mmol, 62% yield). IR υ_{max}/cm^{-1} (film): 2954, 2928, 2856, 1973, 1556, 1462, 1390, 1252, 1112, 1068, 863, 835, 702; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.34 (1H, d, *J* = 5.3 Hz), 7.60 (1H, d, *J* = 2.1 Hz), 7.47-7.37 (2H, m), 7.31-7.25 (2H, m), 7.21 (1H, d, *J* = 7.3 Hz), 7.10 (1H, dd, *J* = 5.3, 2.1 Hz), 5.83 (1H, s), 0.91 (10H, s), –0.01 (6H, d, *J* = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.33, 149.65, 144.97, 143.32, 128.46, 127.59, 126.36, 122.54, 120.57, 77.64, 25.97, 18.41, –4.71, –4.83; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 334.2, $C_{18}H_{25}ClONSi^+$ requires 334.1.

4-Chloro-3,5-dimethylpyridine



A 25 mL round bottom flask was charged with 3,5-dimethylpyridine (57 µL, 0.50 mmol), triphenylphosphine (131 mg, 0.55 mmol), and CH_2Cl_2 (5 mL). The flask was cooled to –50 °C and Tf_2O (84 µL, 0.50 mmol) was added dropwise. After 1 hour, the flask was cooled to –78 °C, DBU (75 µL, 0.50 mmol) was added dropwise, and the flask was allowed to warm to room temperature. After 30 minutes, the reaction was quenched with H_2O and the organic layer was washed (3 x 10 mL). The organic layer was dried over $MgSO_4$, concentrated in *vacuo*, and dried under high-vacuum for 20 minutes. Dioxane (5 mL) was added, followed by the dropwise addition of HCl (4M in Dioxanes, 125 µL, 0.50 mmol). The reaction was heated at 80 °C for 24 hours before being cooled to room temperature and quenched with aqueous $NaHCO_3$. The aqueous layer was extracted from with CH_2Cl_2 (3 x 10 mL), and the organic extracts were dried with $MgSO_4$ and concentrated in *vacuo*. The ^1H NMR yield was measured using triphenylmethane (122 mg, 0.50 mmol, 1.0 equiv) as an internal standard (33% NMR yield). IR ν_{max}/cm^{-1} (film): 3021, 2954, 1562, 1408, 1078, 880, 762; ^1H NMR (400 MHz, CD_3OD) δ: 8.23 (2H, s), 2.38 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.87, 144.15, 131.58, 17.13; m/z LRMS (ESI + APCI) found $[M + H]^+$ 142.1, $C_7H_9ClN^+$ requires 142.0.

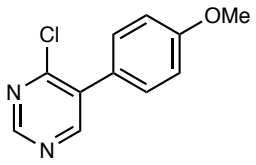
4-Chloro-5-phenylnicotinonitrile



Prepared according to general procedure B, using (3-cyano-5-phenylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (177 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 40 hours. Flash column chromatography (silica gel: 20% EtOAc in Hexanes) afforded the title compound as a white solid (57 mg, 0.27 mmol, 89% yield). mp 64-66 ºC; IR ν_{max}/cm^{-1} (film): 3035, 2921, 2360, 2236, 1544,

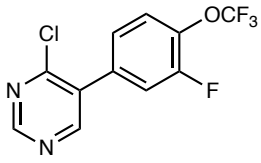
1422, 1095, 764, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, s), 8.72 (1H, s), 7.55-7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.15, 152.38, 144.48, 137.20, 133.66, 129.43, 129.35, 128.87, 114.28, 111.95; m/z LRMS (ESI + APCI) found $[M + H]^+$ 215.0, $C_{12}H_8ClN_2^+$ requires 215.0.

4-Chloro-5-(4-methoxyphenyl)pyrimidine



Prepared according to general procedure B using (5-(4-methoxyphenyl)pyrimidin-4-yl) triphenylphosphonium trifluoromethanesulfonate (119 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated at 80 °C for 40 hours. Flash column chromatography (silica gel: 15% EtOAc in Hexanes) afforded the title compound as a white solid (17 mg, 0.08 mmol, 40% yield). mp 90-91 ºC; IR υ_{max}/cm^{-1} (film): 2934, 1608, 1531, 1514, 1246, 1189, 1111, 1031, 824, 764, 885; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94 (1H, s), 8.64 (1H, s), 7.48-7.35 (2H, m), 7.10-6.93 (2H, m), 3.87 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.47, 159.36, 158.11, 157.02, 134.67, 130.69, 125.75, 114.35, 55.52; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 221.1, $C_{11}H_{10}ClN_2O^+$ requires 221.0.

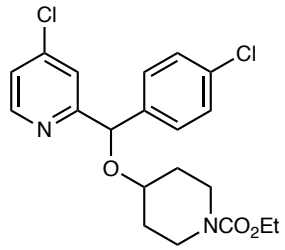
4-Chloro-5-(3-fluoro-4-(trifluoromethoxy)phenyl)pyrimidine



Prepared according to general procedure B using (5-(3-fluoro-4-(trifluoromethoxy) phenyl)pyrimidin-4-yl)triphenylphosphonium (134 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated at 80 °C for 24 hours. Flash column chromatography

(silica gel: 15% EtOAc in Hexanes) afforded the title compound as a colorless oil (44 mg, 0.15 mmol, 76% yield). IR υ_{max}/cm^{-1} (film): 1625, 1567, 1530, 1506, 1396, 1249, 1210, 1169, 1101, 788, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, s), 8.64 (1H, s), 7.41 (1H, t, *J* = 8.2 Hz), 7.28-7.00 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.77 (d, *J* = 68.5 Hz), 158.70 (d, *J* = 1.7 Hz), 158.60, 158.52, 150.93 (dd, *J* = 11.1, 1.7 Hz), 132.26 (d, *J* = 1.7 Hz), 128.74, 120.39 (q, *J* = 259.3 Hz), 120.13 (d, *J* = 15.5 Hz), 116.85 (d, *J* = 3.3 Hz), 109.54 (d, *J* = 25.7 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –57.99, –109.03; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 293.1, $C_{11}H_6ClF_4N_2O^+$ requires 293.0.

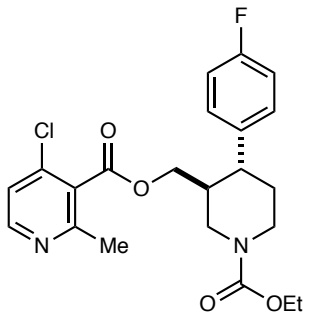
Ethyl 4-((4-chlorophenyl)(4-chloropyridin-2-yl)methoxy)piperidine-1-carboxylate



Prepared according to general procedure B using (2-((4-chlorophenyl)((1-(ethoxycarbonyl) piperidin-4-yl)oxy)methyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (185 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated at 80 °C for 24 hours. Flash column chromatography (silica gel: 33% EtOAc in Hexanes) afforded the title compound as a colorless oil (54 mg, 0.13 mmol, 66% yield). IR υ_{max}/cm^{-1} (film): 2929, 2867, 1692, 1572, 1431, 1383, 1227, 1085, 1029, 823, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (1H, d, *J* = 5.3 Hz), 7.54 (1H, d, *J* = 2.0 Hz), 7.44-7.23 (4H, m), 7.15 (1H, dd, *J* = 5.3, 2.1 Hz), 5.57 (1H, s), 4.10 (2H, q, *J* = 7.1 Hz), 3.75 (2H, dt, *J* = 11.6, 4.6 Hz), 3.60 (1H, tt, *J* = 7.6, 3.6 Hz), 3.22-3.10 (2H, m), 1.81 (2H, ddd, *J* = 11.6, 6.8, 3.4 Hz), 1.63 (2H, ddd, *J* = 13.1, 8.5, 4.3 Hz), 1.23 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.72, 155.58, 149.97, 145.14, 139.50, 133.79, 128.80, 128.25, 123.00, 120.89, 80.51, 72.89,

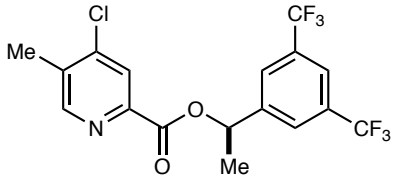
61.38, 41.14, 41.08, 31.27, 30.96, 14.78; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 409.2, $C_{20}H_{23}Cl_2N_2O_3^+$ requires 409.1.

((3*S*,4*R*)-1-(Ethoxycarbonyl)-4-(4-fluorophenyl)piperidin-3-yl)methyl 4-chloro-2-methylnicotinate



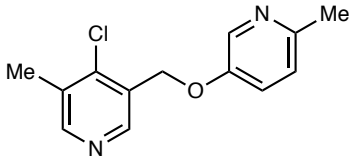
Prepared according to general procedure B, using (3-((((3S,4R)-1-(ethoxycarbonyl)-4-(4-fluorophenyl)piperidin-3-yl)methoxy)carbonyl)-2-methylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (176 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel gradient elution: 40% EtOAc in Hexanes to 50% EtOAc in Hexanes) afforded the title compound as an amorphous solid (71 mg, 0.16 mmol, 82% yield). IR ν_{max}/cm^{-1} (film): 2920, 2864, 1689, 1438, 1273, 1222, 832, 726; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.42 (1H, d, *J* = 5.3 Hz), 7.21 (1H, d, *J* = 5.4 Hz), 7.15 (2H, dd, *J* = 13.8 Hz, 5.5 Hz), 7.01 (2H, app t, *J* = 8.6 Hz), 4.49 (1H, br s), 4.27 (1H, br s), 4.19-4.09 (3H, m), 3.96 (1H, dd, *J* = 11.4, 7.3 Hz), 2.88-2.67 (2H, m), 2.60-2.44 (4H, m), 2.19-2.07 (1H, m), 1.81 (1H, m), 1.69 (1H, qd, *J* = 12.7, 4.2 Hz), 1.26 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.01, 161.89 (d, *J* = 245.7 Hz), 156.93, 155.50, 150.38, 141.12, 138.43 (d, *J* = 3.2 Hz), 129.08, 128.80 (d, *J* = 7.8 Hz), 122.02, 115.87 (d, *J* = 21.3 Hz), 66.25, 61.64, 47.09, 44.47, 41.02, 41.00, 34.23, 23.07, 14.84; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –115.60 (m); m/z LRMS (ESI + APCI) found $[M + H]^+$ 435.2, $C_{22}H_{25}ClFN_2O_4^+$ requires 435.1.

(*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl 4-chloro-5-methylpicolinate



Prepared according to general procedure B, using (R)-(2-((1-(3,5-bis(trifluoromethyl)phenyl)ethoxy)carbonyl)-5-methylpyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (257 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 48 hours. Flash column chromatography (silica gel: 15% EtOAc in Hexanes) afforded the title compound as a clear oil (71 mg, 0.16 mmol, 82% yield). IR ν_{max}/cm^{-1} (film): 3469, 2976, 1724, 1276, 1130, 899, 754, 637; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (1H, s), 8.07 (1H, s), 7.91 (2H, s), 7.81 (1H, s), 6.24 (1H, q, *J* = 6.7 Hz), 2.43 (3H, s), 1.77 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.63, 151.69, 146.57, 145.15, 143.83, 136.51, 133.16 (q, *J* = 33.6 Hz), 126.70 (d, *J* = 3.7 Hz), 125.91, 123.27 (q, *J* = 272.7 Hz), 122.28 (m), 72.72, 22.07, 17.12; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.93; m/z LRMS (ESI + APCI) found $[M + H]^+$ 412.1, $C_{17}H_{13}ClF_6NO_2^+$ requires 412.1.

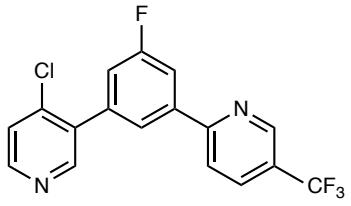
4-Chloro-3-methyl-5-(((6-methylpyridin-3-yl)oxy)methyl)pyridine



Prepared according to general procedure B using (3-methyl-5-(((6-methylpyridin-3-yl)oxy) methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (125 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 33% EtOAc in Hexanes) afforded the title compound as a white solid (17 mg, 0.07 mmol, 34% yield). mp 88-90 ºC; IR υ_{max}/cm^{-1} (film):

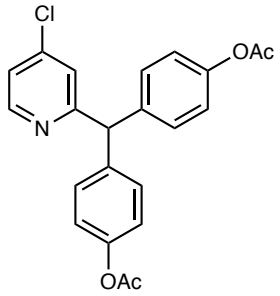
2922, 2854, 1742, 1697, 1574, 1484, 1455, 1368, 1271, 1243, 1065, 814, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (s, 1H), 8.44 (s, 1H), 8.29 (d, *J* = 3.0 Hz, 1H), 7.21 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 2H), 2.50 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.74, 151.39, 151.10, 147.83, 143.45, 136.73, 132.34, 129.81, 123.78, 123.03, 66.29, 23.31, 17.06; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 249.1, $C_{13}H_{14}ClN_2O^+$ requires 249.1.

4-Chloro-3-(3-fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)pyridine



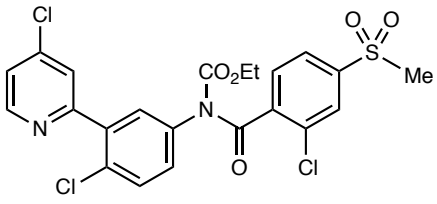
Prepared according to general procedure B, using (3-(3-fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (239 mg, 0.30 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 15% EtOAc in Hexanes) afforded the title compound as a white solid (82 mg, 0.23 mmol, 78% yield). mp 112-113 ºC. IR ν_{max}/cm^{-1} (film): 3044, 2924, 1596, 1328, 1114, 1082, 920, 838; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, s), 8.62 (1H, s), 8.53 (1H, d, *J* = 5.3 Hz), 8.02 (1H, dd, *J* = 8.3, 2.2 Hz), 7.92 (1H, app t, *J* = 8.3 Hz), 7.89-7.83 (2H, m), 7.46 (1H, d, *J* = 5.3 Hz), 7.29 (1H, ddd, *J* = 8.8, 6.4, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.14 (d, *J* = 247.5 Hz), 158.73 (m), 151.28, 150.11, 146.94 (q, *J* = 4.1 Hz), 142.40, 140.48 (d, *J* = 8.2 Hz), 138.18 (d, *J* = 8.1 Hz), 135.06 (d, *J* = 2.2 Hz), 134.38 (q, *J* = 3.6 Hz), 125.84 (q, *J* = 33.2 Hz), 125.04, 124.26 (d, *J* = 2.6 Hz), 123.67 (q, *J* = 274.3 Hz), 120.23, 118.24 (d, *J* = 22.9 Hz), 114.44 (d, *J* = 23.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.36, –111.67 (t, *J* = 9.5 Hz); m/z LRMS (ESI + APCI) found $[M + H]^+$ 353.1, $C_{17}H_{10}ClF_4N_2^+$ requires 353.0.

((4-Chloropyridin-2-yl)methylene)bis(4,1-phenylene) diacetate



Prepared according to general procedure B using (2-(bis(4-acetoxyphenyl)methyl) pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (190 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 33% EtOAc in Hexanes) afforded the title compound as a colorless oil (51 mg, 0.13 mmol, 65% yield). IR υ_{max}/cm^{-1} (film): 1754, 1572, 1555, 1503, 1368, 1191, 1164, 1016, 910, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (1H, d, J = 5.3 Hz), 7.23-7.10 (6H, m), 7.10-6.96 (4H, m), 5.62 (1H, s), 2.27 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.46, 164.40, 150.58, 149.58, 144.76, 139.33, 130.31, 124.14, 122.21, 121.72, 57.95, 21.22; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 396.2, $C_{22}H_{19}ClNO_4^+$ requires 396.1.

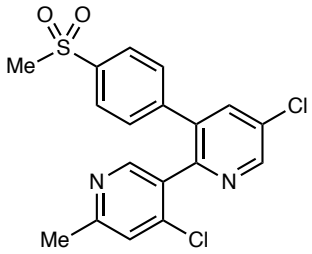
Ethyl (4-chloro-3-(4-chloropyridin-2-yl)phenyl)(2-chloro-4-(methylsulfonyl)benzoyl)carbamate



Prepared according to general procedure B using (2-(3-(2-chloro-N-(ethoxycarbonyl)-4-(methylsulfonyl)benz amido)phenyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (208 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and

Dioxane (2 mL). The reaction was heated at 80 °C for 26 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes) afforded the title compound as a white solid (62 mg, 0.12 mmol, 59% yield). mp 104-105 ºC; IR υ_{max}/cm^{-1} (film): 2980, 2929, 1744, 1697, 1572, 1453, 1312, 1259, 1152, 1074, 919, 726, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, d, *J* = 5.4 Hz), 8.09-7.85 (2H, m), 7.76 (1H, s), 7.68-7.51 (3H, m), 7.38-7.28 (2H, m), 4.10 (2H, q, *J* = 7.1 Hz), 3.08 (3H, s), 1.07 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.85, 156.98, 152.76, 150.60, 144.18, 142.59, 142.11, 139.13, 135.77, 132.75, 131.45, 131.42, 131.08, 129.87, 128.94, 128.46, 126.15, 125.36, 123.29, 64.28, 44.55, 13.91; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 527.1, $C_{22}H_{18}Cl_3N_2O_5S^+$ requires 527.0.

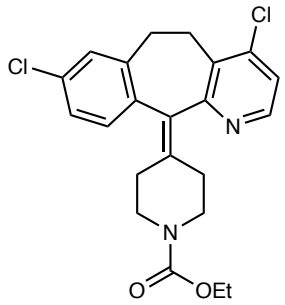
4',5-Dichloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine



Prepared according to general procedure B using (5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)- [2,3'-bipyridin]-4'-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (168 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 70% EtOAc in Hexanes) afforded the title compound as a colorless oil (52 mg, 0.13 mmol, 66% yield). IR υ_{max}/cm^{-1} (film): 2923, 2852, 1587, 1538, 1431, 1311, 1149, 1088, 1011, 836, 785, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, d, *J* = 2.4 Hz), 8.34 (1H, s), 7.88-7.72 (3H, m), 7.38-7.30 (2H, m), 7.12 (1H, s), 3.03 (3H, s), 2.52 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.20, 150.97, 150.71, 148.31, 142.95, 142.70, 140.29, 137.40, 137.20, 132.20, 131.21, 130.07,

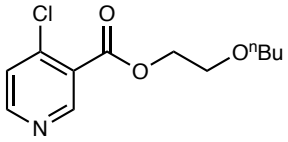
127.71, 123.97, 44.50, 24.19; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 393.1, $C_{18}H_{15}Cl_2N_2O_2S^+$ requires 393.0.

Ethyl 4-(4,8-dichloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine- 1-carboxylate



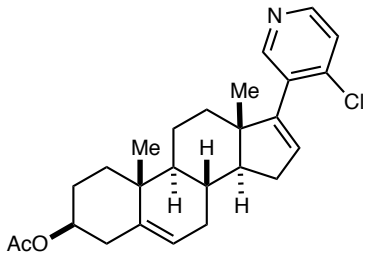
Prepared according to general procedure B using (8-chloro-11-(1-(ethoxycarbonyl) piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (172 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes) afforded the title compound as a white solid (59 mg, 0.14 mmol, 70% yield). mp 140-142 ºC; IR υ_{max}/cm^{-1} (film): 2977, 2907, 1695, 1542, 1423, 1384, 1215, 1118, 1057, 836, 766; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (1H, d, *J* = 5.3 Hz), 7.25-6.93 (4H, m), 4.12 (2H, q, *J* = 7.1 Hz), 3.78 (2H, t, *J* = 16.5 Hz), 3.38 (1H, ddd, *J* = 14.9, 10.3, 4.4 Hz), 3.20 (3H, dddt, *J* = 32.4, 13.4, 8.7, 4.4 Hz), 3.03 (1H, ddd, *J* = 16.7, 10.3, 4.5 Hz), 2.82 (1H, ddd, *J* = 15.0, 7.4, 4.5 Hz), 2.48 (1H, ddd, *J* = 14.0, 9.3, 4.6 Hz), 2.31 (3H, pt, *J* = 5.4, 2.9 Hz), 1.23 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.53, 155.53, 147.03, 144.78, 139.46, 138.42, 137.60, 133.66, 133.31, 131.75, 130.35, 128.85, 126.48, 123.36, 61.43, 44.80, 30.80, 30.69, 29.34, 14.76; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 417.2, $C_{22}H_{23}Cl_2N_2O_2^+$ requires 417.1.

2-Butoxyethyl 4-chloronicotinate



Prepared according to general procedure B using (3-((2-butoxyethoxy)carbonyl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (140 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 33% EtOAc in Hexanes) afforded the title compound as a colorless oil (34 mg, 0.13 mmol, 66% yield). IR υ_{max}/cm^{-1} (film): 2933, 2862, 1711, 1640, 1600, 1465, 1292, 1203, 1092, 819; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.05 (1H, s), 8.58 (1H, s), 7.40 (1H, d, *J* = 5.3 Hz), 4.55-4.42 (2H, m), 3.83-3.69 (2H, m), 3.49 (2H, t, *J* = 6.6 Hz), 1.56 (2H, tt, *J* = 8.5, 6.4 Hz), 1.43-1.30 (2H, m), 0.89 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.95, 152.79, 152.50, 144.27, 126.25, 126.01, 71.33, 68.38, 65.12, 31.78, 19.35, 13.97; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 258.1, $C_{12}H_{17}ClNO_3^+$ requires 258.1.

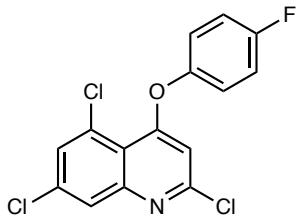
(3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-(4-Chloropyridin-3-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate



Prepared according to general procedure B, using (3-((3S,8R,9S,10R,13S,14S)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (218 mg, 0.25 mmol), LiCl (42 mg, 1.00 mmol), and Dioxane (2.5 mL). The reaction was heated

to 80 °C for 24 hours. Flash column chromatography (silica gel: 15% EtOAc in Hexanes) afforded the title compound as a white solid (78 mg, 0.18 mmol, 73% yield). mp 188 - 190 ºC. IR ν_{max}/cm^{-1} (film): 2942, 2911, 1730, 1367, 1235, 1036, 816, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36-8.33 (2H, m), 7.32 (1H, d, *J* = 5.2 Hz), 5.83 (1H, s), 5.40 (1H, d, *J* = 3.3 Hz), 4.65-4.55 (1H, m), 2.38-2.26 (3H, m), 2.15-1.98 (5H, m), 1.89-1.79 (2H, m), 1.77-1.43 (8H, m), 1.25-0.84 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.56, 150.70, 148.68, 148.43, 143.49, 140.11, 133.07, 132.53, 124.73, 122.37, 73.95, 56.92, 50.47, 49.82, 38.23, 37.02, 36.92, 34.81, 32.43, 31.68, 30.80, 27.83, 21.52, 20.80, 19.34, 16.38; m/z LRMS (ESI + APCI) found $[M + H]^+$ 426.3, $C_{26}H_{32}ClNO_2^+$ requires 426.2.

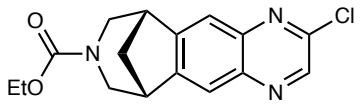
2,5,7-Trichloro-4-(4-fluorophenoxy)quinolone



Prepared according to general procedure B, using (5,7-dichloro-4-(4-fluorophenoxy)quinolin-2-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (236 mg, 0.3 mmol), LiCl (51 mg, 1.20 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 48 hours. Flash column chromatography (silica gel: 2% EtOAc in Hexanes) afforded the title compound as a white solid (42 mg, 0.12 mmol, 41% yield). Mp 143-145 °C. IR ν_{max}/cm^{-1} (film): 3095, 2923, 1560, 1365, 1189, 917, 767, 620; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (1H, d, *J* = 2.0 Hz), 7.58 (1H, d, *J* = 2.0 Hz), 7.23-7.10 (4H, m), 6.52 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.16, 166.60 (d, *J* = 248.0 Hz), 153.02, 150.08, 149.16 (d, *J* = 2.9 Hz), 136.43, 130.78, 130.08, 127.15, 122.67 (d, *J* = 8.7 Hz), 117.55 (d, *J* = 23.7 Hz), 117.04,

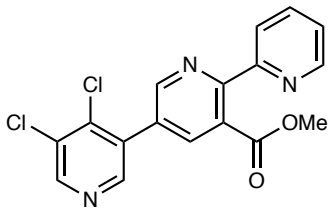
106.97; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –155.57-(–155.65); m/z LRMS (ESI + APCI) found [M + H]$^+$ 342.0, $C_{15}H_8Cl_3FNO^+$ requires 342.0.

Ethyl (6R,10S)-2-chloro-6,7,9,10-tetrahydro-8H-6,10-methanoazepino[4,5-g]quinoxaline-8-carboxylate



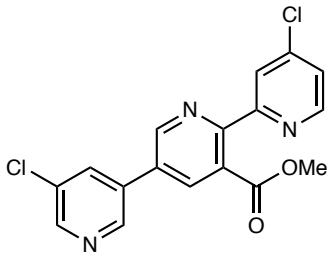
Prepared according to general procedure B, using ((6S,10R)-8-(ethoxycarbonyl)-7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxalin-2-yl)diphenyl(6-(trifluoromethyl)-1l4-pyridin-3-yl)phosphonium trifluoromethanesulfonate (191 mg, 0.25 mmol), LiCl (42 mg, 1.00 mmol), and Dioxane (2.5 mL). The reaction was heated to 80 °C for 72 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes) afforded the title compound as a yellow oil (36 mg, 0.11 mmol, 46% yield). IR ν_{max}/cm^{-1} (film): 2955, 2867, 2245, 1686, 1213, 1094, 910, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, d, *J* = 3.8 Hz), 7.87 (1H, d, *J* = 6.3 Hz), 7.77 (1H, d, *J* = 6.5 Hz), 4.15-3.76 (4H, m), 3.48-3.25 (4H, m), 2.45-2.38 (1H, m), 2.00 (1H, d, *J* = 11.1 Hz), 1.04 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.63, 150.04, 148.86, 146.48 (d, *J* = 1.9 Hz), 143.69, 142.41 (d, *J* = 7.2 Hz), 141.38 (d, *J* = 5.3 Hz), 122.17 (d, *J* = 43.9 Hz), 141.43 (d, *J* = 42.6 Hz), 61.28, 49.74, 49.44, 41.22, 40.05, 39.37, 14.53; m/z LRMS (ESI + APCI) found [M + H]$^+$ 318.2, $C_{16}H_{17}ClN_3O_2^+$ requires 318.1.

Methyl 4'',5''-dichloro-[2,2':5',3''-terpyridine]-3'-carboxylate



Prepared according to general procedure B, using (5"–chloro–3'–(methoxycarbonyl)–[2,2':5',3"–terpyridin]–4"–yl)triphenylphosphonium trifluoromethanesulfonate (147 mg, 0.20 mmol), LiCl (34 mg, 0.80 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 72 hours. Flash column chromatography (silica gel: 70% EtOAc in Hexanes, run twice) afforded the title compound as an amorphous solid (24 mg, 0.07 mmol, 33% yield). IR ν_{max}/cm^{-1} (film): 2948, 2853, 1728, 1421, 1269, 1118, 908, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (1H, d, *J* = 2.2 Hz), 8.71 (1H, s), 8.65 (1H, ddd, *J* = 4.8, 3.1, 0.9 Hz), 8.48 (1H, s), 8.23 (1H app dt, *J* = 7.9, 1.0 Hz), 8.06 (1H, d, *J* = 2.2 Hz), 7.88 (1H, app td, *J* = 7.8, 1.8 Hz), 7.36 (1H, ddd, *J* = 7.6, 2.8, 1.1 Hz), 3.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.99, 155.60, 155.50, 150.29, 150.20, 148.78, 148.65, 141.04, 137.79, 137.07, 133.63, 131.99, 130.27, 128.40, 124.21, 122.95, 52.77; m/z LRMS (ESI + APCI) found $[M + H]^+$ 360.1, $C_{17}H_{12}Cl_2N_3O_2^+$ requires 360.0.

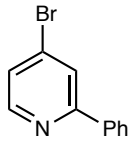
Methyl 4,5''-dichloro-[2,2':5',3''-terpyridine]-3'-carboxylate



Prepared according to general procedure B, using (5"-chloro-3'-(methoxycarbonyl)-[2,2':5',3"-terpyridin]-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (131 mg, 0.15 mmol), LiCl (25 mg, 0.60 mmol), and Dioxane (1.5 mL). The reaction was heated to 80 °C for 72 hours. Flash column chromatography (silica gel: 30% EtOAc in Hexanes) afforded the title compound as a white solid (28 mg, 0.08 mmol, 51% yield). mp 140-144 °C. IR ν_{max}/cm^{-1} (film): 2919, 2850, 1732, 1376, 1265, 1129, 891, 632; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, d, *J* = 2.3 Hz), 8.80 (1H, d, *J* = 2.0 Hz), 8.67 (1H, d, *J* = 2.3 Hz), 8.52

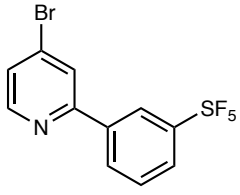
(1H, d, J = 5.3 Hz), 8.28 (1H, d, J = 1.9 Hz), 8.13 (1H, d, J = 2.3 Hz), 7.95 (1H, app t, J = 2.1 Hz), 7.36 (1H, dd, J = 5.3, 2.0 Hz), 3.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.85, 156.80, 153.91, 149.51, 148.92, 148.43, 145.93, 145.24, 135.49, 134.23, 133.39, 132.80, 131.90, 129.20, 124.38, 123.39, 52.83; m/z LRMS (ESI + APCI) found $[M + H]^+$ 360.1, $C_{17}H_{12}Cl_2N_3O_2^+$ requires 360.0.

4-Bromo-2-phenylpyridine



Prepared according to general procedure C, using phenyl(2-phenylpyridin-4-yl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (35 mg, 0.05 mmol), LiBr (17 mg, 0.20 mmol), TfOH (4 µL, 0.05 mmol) and Dioxane (0.5 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 3% EtOAc in Hexanes) was used to isolate a pure sample of the product (NMR Yield: 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, dd, J = 5.3, 0.4 Hz), 7.99-7.95 (2H, m), 7.90 (2H, dd, J = 1.8, 0.5 Hz), 7.51-7.38 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.05, 150.49, 138.20, 133.59, 129.73, 128.99, 127.14, 125.35, 124.02. The spectroscopic data is in agreement with the literature.

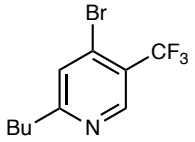
4-Bromo-2-(3-(pentafluoro-λ^6-sulfaneyl)phenyl)pyridine



Prepared according to general procedure C, using (2-(3-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (166 mg, 0.20 mmol), LiBr (69 mg, 0.80 mmol), TfOH (18 µL, 0.20 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 48 hours. Flash column

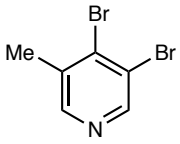
chromatography (silica gel: 20% CH_2Cl_2 in Hexanes, ran twice) afforded the title compound as an amorphous solid (62 mg, 0.17 mmol, 86% yield). IR ν_{max}/cm^{-1} (film): 3084, 2927, 1566, 1369, 1100, 834, 694, 596; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.53 (1H, d, *J* = 5.2 Hz), 8.42 (1H, app t, *J* = 1.9 Hz), 8.09 (1H, d, *J* = 7.9 Hz), 7.91 (1H, d, *J* = 1.4 Hz), 7.82 (1H, ddd, *J* = 8.3, 2.2, 0.8 Hz), 7.85 (1H, app t, *J* = 8.0 Hz), 7.47 (1H, dd, *J* = 7.0, 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.79, 154.75 (m), 150.76, 139.14, 133.95, 129.91, 129.36, 126.95 (qn, *J* = 4.6 Hz), 126.36, 124.89 (qn, *J* = 4.7 Hz), 124.12; ^{19}F NMR (365 MHz, $CDCl_3$) δ: 83.99 (1F, qn, *J* = 151.7 Hz), 62.73 (4F, d, *J* = 150.0 Hz); m/z LRMS (ESI + APCI) found $[M + H]^+$ 360.0, $C_{11}H_8BrF_5NS^+$ requires 359.9.

4-Bromo-2-butyl-5-(trifluoromethyl)pyridine



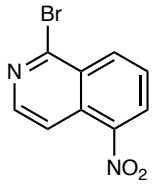
Prepared according to general procedure C, using (2-butyl-5-(trifluoromethyl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (137 mg, 0.20 mmol), LiBr (69 mg, 0.80 mmol), TfOH (18 μL, 0.20 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 24 hours. The ^1H NMR yield was measured using triphenylmethane (49 mg, 0.20 mmol, 1.0 equiv) as an internal standard (90% NMR yield). PTLC (4% Et_2O in Hexanes) was used to obtain approximately 10 mg of product for characterization. IR ν_{max}/cm^{-1} (film): 2959, 2861, 1583, 1321, 1137, 1019, 870, 690; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, s), 7.51 (1H, s), 2.82 (2H, t, *J* = 7.7 Hz), 1.76-1.67 (2H, m), 1.39 (2H, m, *J* = 7.5 Hz), 0.95 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.79, 147.70 (q, *J* = 5.9 Hz), 131.10 (q, *J* = 2.0 Hz), 128.37, 124.10 (q, *J* = 31.5 Hz), 122.90 (q, *J* = 273.1 Hz), 37.82, 31.59, 22.51, 13.97; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.29; m/z LRMS (ESI + APCI) found $[M + H]^+$ 282.0, $C_{10}H_{12}BrF_3N^+$ requires 282.0.

3,4-Dibromo-5-methylpyridine



Prepared according to general procedure C using (3-bromo-5-methylpyridin-4-yl) triphenylphosphonium trifluoromethanesulfonate (175 mg, 0.30 mmol), LiBr (104 mg, 1.20 mmol), TfOH (26 µL, 0.3 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 40 hours. Flash column chromatography (silica gel: 10% EtOAc in Hexanes) afforded the title compound as a colorless oil (60 mg, 0.24 mmol, 80% yield). IR υ_{max}/cm^{-1} (film): 2924, 1461, 1268, 1120, 1071, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (1H, s), 8.28 (1H, s), 2.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.88, 148.66, 137.07, 136.38, 124.17, 21.21; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 249.9, $C_6H_6Br_2N^+$ requires 249.9.

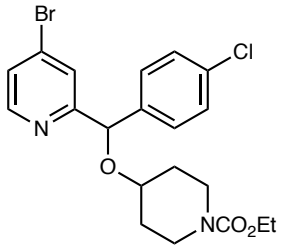
1-Bromo-5-nitroisoquinoline



Prepared according to general procedure C, using (5-nitroisoquinolin-1-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (131 mg, 0.20 mmol), LiBr (69 mg, 0.80 mmol), TfOH (18 µL, 0.20 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 20% CH_2Cl_2 in Hexanes, ran twice) afforded the title compound as a white solid (37 mg, 0.15 mmol, 70% yield). IR ν_{max}/cm^{-1} (film): 3050, 2923, 1622, 1522, 1311, 1037, 812, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, app dt, *J* = 8.5, 0.9 Hz), 8.55 (1H, dd, *J* = 7.7, 1.1 Hz), 8.46 (1H, d, *J* = 6.1 Hz), 8.40 (1H, dd, *J* = 6.1, 0.8 Hz), 7.81 (1H, app t, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.34, 145.45, 145.36, 135.78,

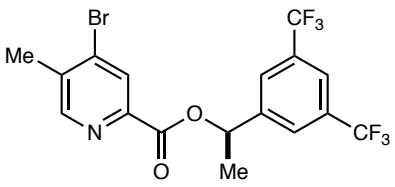
130.05, 129.40, 128.95, 127.26, 116.16; m/z LRMS (ESI + APCI) found $[M + H]^+$ 253.0, $C_9H_6Br_2N_2O_2^+$ requires 253.0.

Ethyl 4-((4-bromopyridin-2-yl)(4-chlorophenyl)methoxy)piperidine-1-carboxylate



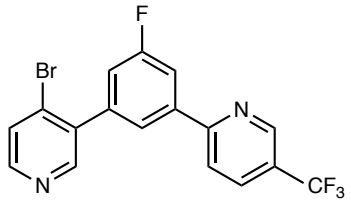
Prepared according to general procedure C using (2-((4-chlorophenyl) ((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (185 mg, 0.20 mmol), LiBr (70 mg, 0.80 mmol), TfOH (18 μL, 0.20 mmol), and Dioxane (2 mL). The reaction was heated at 80 °C for 40 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes) afforded the title compound as a colorless oil (52 mg, 0.12 mmol, 58% yield). IR υ_{max}/cm^{-1} (film): 2929, 2866, 1691, 1566, 1431, 1381, 1226, 1085, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (1H, d, *J* = 5.3 Hz), 7.69 (1H, d, *J* = 1.9 Hz), 7.41-7.18 (5H, m), 5.56 (1H, s), 4.10 (2H, q, *J* = 7.1 Hz), 3.75 (2H, t, *J* = 9.1 Hz), 3.60 (1H, dq, *J* = 7.9, 3.8 Hz), 3.17 (2H, ddd, *J* = 12.9, 8.5, 3.7 Hz), 1.81 (2H, ddd, *J* = 14.4, 7.1, 3.5 Hz), 1.63 (2H, ddt, *J* = 17.0, 12.9, 6.1 Hz), 1.23 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.54, 155.61, 149.85, 139.52, 133.91, 133.83, 128.84, 128.27, 126.02, 123.94, 80.51, 72.94, 61.42, 41.18, 41.11, 31.30, 31.00, 14.81; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 453.1, $C_{20}H_{23}BrClN_2O_3^+$ requires 453.1.

(*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl 4-bromo-5-methylpicolinate



Prepared according to general procedure C, using (R)-(2-((1-(3,5-bis(trifluoromethyl)phenyl)ethoxy)carbonyl)-5-methylpyridin-4-yl)diphenyl(6-(trifluoromethyl) pyridin-3-yl)phosphonium trifluoromethanesulfonate (171 mg, 0.20 mmol), LiBr (69 mg, 0.80 mmol), TfOH (18 µL, 0.20 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 15% EtOAc in Hexanes) afforded the title compound as a clear oil (72 mg, 0.16 mmol, 79% yield). IR ν_{max}/cm^{-1} (film): 2999, 2926, 1717, 1280, 1196, 1112, 900, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, s), 8.26 (1H, s), 7.91 (2H, s), 7.82 (1H, s), 6.25 (1H, q, *J* = 6.7 Hz), 2.45 (3H, s), 1.77 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.49, 151.13, 146.32, 143.82, 138.63, 135.93, 132.20 (q, *J* = 33.3 Hz), 129.22, 126.74 (d, *J* = 2.6 Hz), 123.29 (q, *J* = 272.9 Hz), 122.32 (qn, *J* = 3.6 Hz), 72.75, 22.11, 19.95; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -62.88; m/z LRMS (ESI + APCI) found $[M + H]^+$ 456.1, $C_{17}H_{13}BrF_6NO_2^+$ requires 456.0.

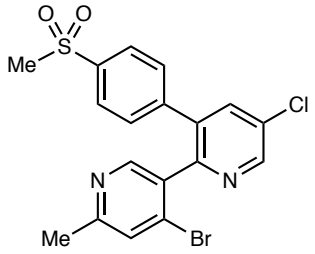
4-Bromo-3-(3-fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)pyridine



Prepared according to general procedure C, using (3-(3-fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (239 mg, 0.30 mmol), LiBr (104 mg, 1.20 mmol), TfOH (27 µL, 0.30 mmol), and Dioxane (3 mL). The reaction was heated to 80 °C for 48 hours. Flash column chromatography (silica gel: 20% EtOAc in Hexanes) afforded the title compound as a yellow solid (37 mg, 0.15 mmol, 70% yield). mp 115-118 °C. IR ν_{max}/cm^{-1} (film): 3038, 2924, 1603, 1329, 1109, 922, 840, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, s), 8.58 (1H, s), 8.43

(1H, d, J = 4.9 Hz), 8.03 (1H, d, J = 8.3 Hz), 7.92-7.84 (3H, m), 7.66 (1H, d, J = 4.9 Hz), 7.27 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.07 (d, J = 247.7 Hz), 158.71 (m), 150.80, 149.81, 146.94 (d, J = 4.0 Hz), 140.40 (d, J = 8.1 Hz), 139.80 (d, J = 8.4 Hz), 137.23 (d, J = 1.4 Hz), 134.38 (q, J = 3.4 Hz), 132.92, 128.30, 125.83 (q, J = 33.2 Hz), 124.20 (d, J = 2.6 Hz), 123.66 (q, J = 272.1 Hz), 120.23, 118.22 (d, J = 22.7 Hz), 114.4 (d, J = 23.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.36 (3F, s), –111.63 (1F, t, J = 9.3 Hz); m/z LRMS (ESI + APCI) found $[M + H]^+$ 397.1, $C_{17}H_{10}BrF_4N_2^+$ requires 397.0.

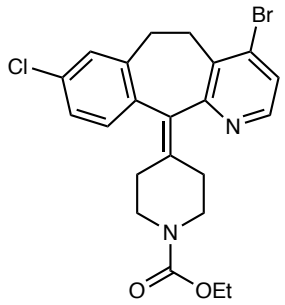
4'-Bromo-5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine



Prepared according to general procedure C using (5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (168 mg, 0.20 mmol), LiBr (70 mg, 0.80 mmol), and Dioxane (2.0 mL). The reaction was heated at 80 °C for 36 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes) afforded the title compound as a colorless oil (51 mg, 0.12 mmol, 58% yield). IR υ_{max}/cm^{-1} (film): 2924, 1581, 1431, 1399, 1311, 1284, 1149, 1090, 789, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, d, J = 2.3 Hz), 8.27 (1H, s), 7.89-7.75 (3H, m), 7.40-7.32 (3H, m), 3.04 (3H, s), 2.53 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.91, 152.09, 150.58,

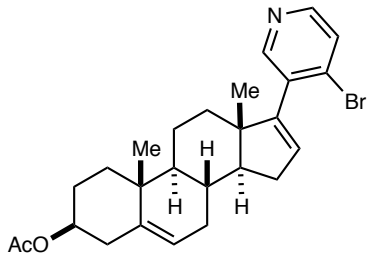
148.32, 142.91, 140.34, 137.49, 136.96, 133.26, 133.24, 132.23, 130.26, 127.75, 127.29, 44.55, 24.09; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 437.1, $C_{18}H_{15}BrClO_2N_2S^+$ requires 437.0.

Ethyl 4-(4-bromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene) piperidine-1-carboxylate



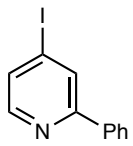
Prepared according to general procedure C using 8-chloro-11-(1-(ethoxycarbonyl) piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (172 mg, 0.20 mmol), LiBr (69 mg, 0.80 mmol), TfOH (18 µL, 0.20 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 36 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes) afforded the title compound as a white solid (76 mg, 0.17 mmol, 83% yield). mp 143-144 ºC; IR υ_{max}/cm^{-1} (film): 2976, 2907, 1695, 1541, 1422, 1383, 1215, 1120, 995, 835, 767; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.15 (1H, d, *J* = 5.3 Hz), 7.35 (1H, d, *J* = 5.2 Hz), 7.20-7.02 (3H, m), 4.11 (2H, q, *J* = 7.1 Hz), 3.86-3.70 (2H, m), 3.44-3.10 (4H, m), 3.02 (1H, ddd, *J* = 16.3, 9.6, 4.5 Hz), 2.82 (1H, ddd, *J* = 15.3, 8.0, 4.5 Hz), 2.46 (1H, ddd, *J* = 14.0, 9.0, 4.4 Hz), 2.39-2.22 (3H, m), 1.22 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.55, 155.49, 146.97, 139.22, 138.18, 137.20, 135.99, 133.70, 133.42, 133.28, 130.49, 128.99, 126.82, 126.39, 61.41, 44.77, 44.74, 32.07, 30.96, 30.76, 30.66, 14.73; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 461.2, $C_{22}H_{23}ClBrN_2O_2^+$ requires 461.1.

(3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-(4-Bromopyridin-3-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate



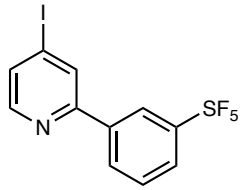
Prepared according to general procedure C, using using (3-((3S,8R,9S,10R,13S,14S)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl)pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (174 mg, 0.20 mmol), LiBr (69 mg, 0.80 mmol), TfOH (18 μL, 0.20 mmol), and Dioxane (2 mL). The reaction was heated to 80 °C for 24 hours. Flash column chromatography (silica gel: 15% EtOAc in Hexanes) afforded the title compound as a white solid (78 mg, 0.17 mmol, 83% yield). IR ν_{max}/cm^{-1} (film): 2951, 2854, 1729, 1366, 1234, 1036, 815, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (1H, s), 8.25 (1H, d, *J* = 5.0 Hz), 7.52 (1H, d, *J* = 5.2 Hz), 5.82 (1H, s), 5.41 (1H, d, *J* = 4.8 Hz), 4.66-4.56 (1H, m), 2.40-2.29 (3H, m), 2.15-2.00 (5H, m), 1.90-1.80 (2H, m), 1.77-1.45 (8H, m), 1.28-0.90 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.59, 150.14, 149.95, 148.46, 140.13, 135.34, 134.47, 132.42, 128.05, 122.38, 73.95, 56.97, 50.47, 49.92, 38.24, 37.03, 36.94, 34.75, 32.38, 31.68, 30.83, 27.84, 21.54, 20.79, 19.35, 16.42; m/z LRMS (ESI + APCI) found $[M + H]^+$ 470.3, $C_{26}H_{32}BrNO_2^+$ requires 470.2.

4-Iodo-2-phenylpyridine



Prepared according to general procedure B, using phenyl(2-phenylpyridin-4-yl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (1.06 g, 1.50 mmol), LiI (803 mg, 6.00 mmol), and Dioxane (15 mL). The reaction was heated to 120 °C for 63 hours. Flash column chromatography (silica gel: 5% EtOAc in Hexanes, then 3% EtOAc in Hexanes) afforded the title compound as a clear oil (320 mg, 1.14 mmol, 76% yield). IR ν_{max}/cm^{-1} (film): 3036, 2921, 1558, 1442, 1374, 1049, 771, 691, 632; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (1H, d, *J* = 5.1 Hz), 8.11 (1H, s), 7.59 (2H, d, *J* = 8.0 Hz), 7.60 (1H, d, *J* = 5.2 Hz), 7.50-7.41 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.52, 150.05, 138.07, 131.25, 130.06, 129.67, 128.97, 127.12, 106.26; m/z LRMS (ESI + APCI) found $[M + H]^+$ 282.0, $C_{11}H_9IN^+$ requires 282.1.

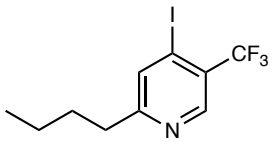
4-Iodo-2-(3-(pentafluoro-l6-sulfaneyl)phenyl)pyridine



Prepared according to general procedure D, using (2-(3-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-4-yl)(phenyl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (166 mg, 0.20 mmol), LiI (107 mg, 0.80 mmol), TfOH (18 μL, 0.20 mmol), and Dioxane (2 mL). The reaction was heated to 120 °C for 72 hours. Flash column chromatography (silica gel: 20% CH_2Cl_2 in Hexanes, ran twice) afforded the title compound as a white solid (50 mg, 0.12 mmol, 61% yield). mp 33-34 °C. IR ν_{max}/cm^{-1} (film): 3086, 2923, 1560, 1364, 1100, 823, 781, 593; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41-8.36 (2H, m), 8.13-8.07 (2H, m), 7.82 (1H, ddd, *J* = 8.3, 6.0, 0.8 Hz), 7.68 (1H, dd, *J* = 5.1, 1.5 Hz), 7.58 (1H, app t, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.30, 154.90-154.45 (m), 150.30, 139.04, 132.27, 130.07, 129.92, 129.34, 126.89 (qn, *J* = 4.6 Hz), 124.86 (qn, *J* = 4.7 Hz), 106.49; ^{19}F NMR (365 MHz,

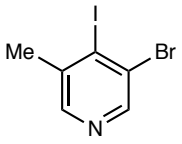
$CDCl_3$) δ: 84.00 (1F, qn, *J* = 150.8 Hz), 62.67 (4F, d, *J* = 150.0 Hz); m/z LRMS (ESI + APCI) found $[M + H]^+$ 408.0, $C_{11}H_8F_5INS^+$ requires 407.9.

2-Butyl-4-iodo-5-(trifluoromethyl)pyridine



Prepared according to general procedure D, using 2-butyl-5-(trifluoromethyl)pyridine (136 mg, 0.20 mmol), LiI (107 mg, 0.80 mmol), TfOH (18 µL, 0.20 mmol), and Dioxane (2 mL). The reaction was heated to 120 °C for 24 hours. Flash column chromatography (silica gel: 5% CH_2Cl_2 in Toluene) afforded the title compound as a white solid (47 mg, 0.14 mmol, 71% yield). mp 44-46 °C. IR ν_{max}/cm^{-1} (film): 2939, 2866, 1577, 1324, 1105, 1024, 937, 744; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.65 (1H, s), 7.83 (1H, s), 2.78 (2H, t, *J* = 7.7 Hz), 1.75-1.66 (2H, m), 1.44-1.33 (2H, m), 0.95 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.87, 146.92 (q, *J* = 6.2 Hz), 135.53, 127.57 (q, *J* = 31.0 Hz), 122.78 (q, *J* = 276.0 Hz), 103.41, 37.47, 31.63, 22.54, 13.99; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.61; m/z LRMS (ESI + APCI) found $[M + H]^+$ 330.1, $C_{11}H_8F_5INS^+$ requires 330.0.

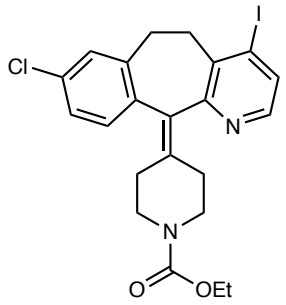
3-Bromo-4-iodo-5-methylpyridine



Prepared according to general procedure D using (3-bromo-5-methylpyridin-4-yl) triphenylphosphonium trifluoromethanesulfonate (175 mg, 0.30 mmol), LiI (160 mg, 1.20 mmol), TfOH (26 µL, 0.30 mmol), and Dioxane (3 mL). The reaction was heated at 120 °C for 3 hours. Flash column chromatography (silica gel: 10% EtOAc in Hexanes) afforded the title compound as a white solid (60 mg, 0.13 mmol, 67% yield). mp 110-112 ºC; IR υ_{max}/cm^{-1} (film): 2920, 1545,

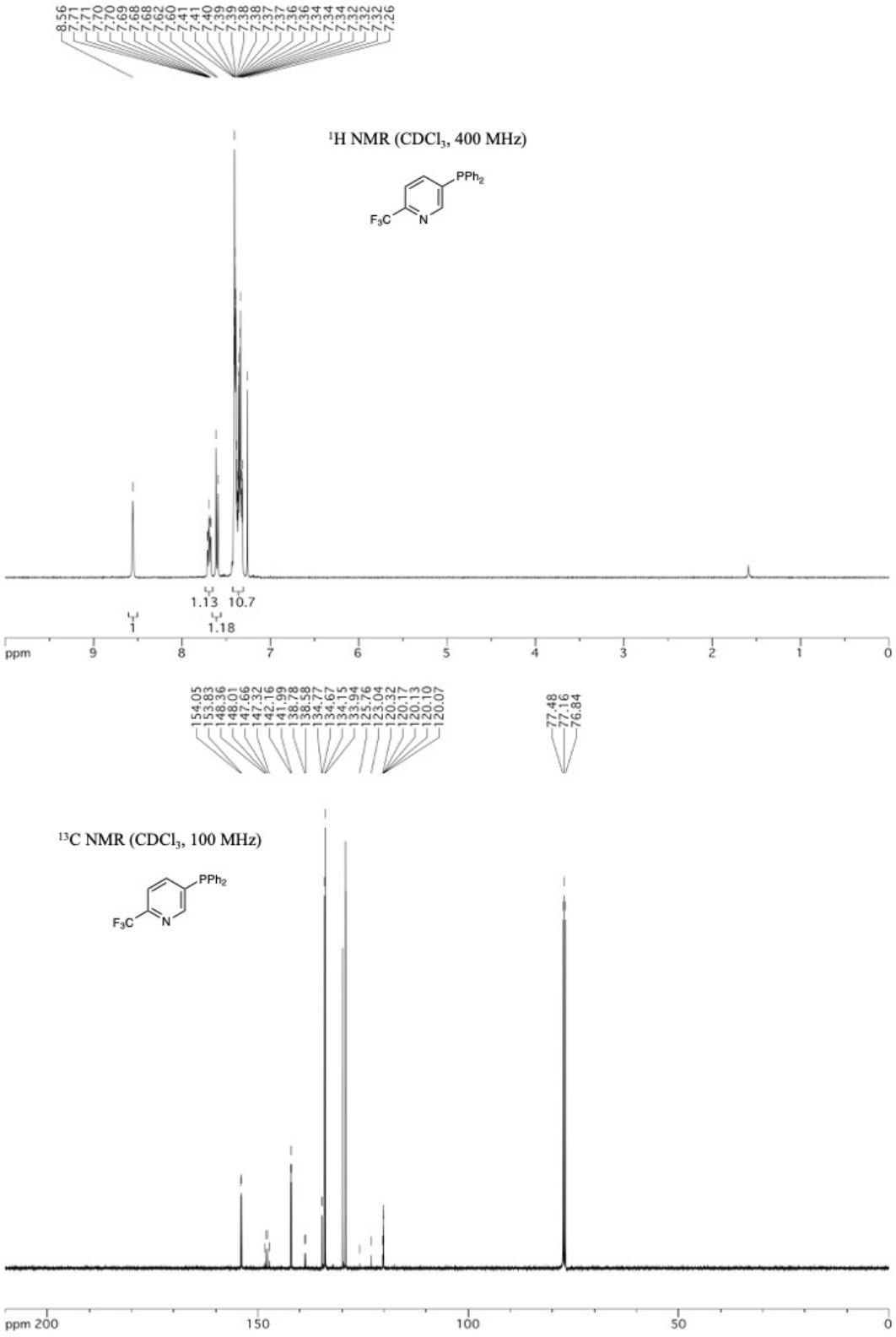
1414, 1374, 1182, 1134, 854, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (1H, s), 8.19 (1H, s), 2.49 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.26, 146.61, 140.65, 129.48, 119.21, 27.11; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 297.9, $C_6H_6BrIN^+$ requires 297.9.

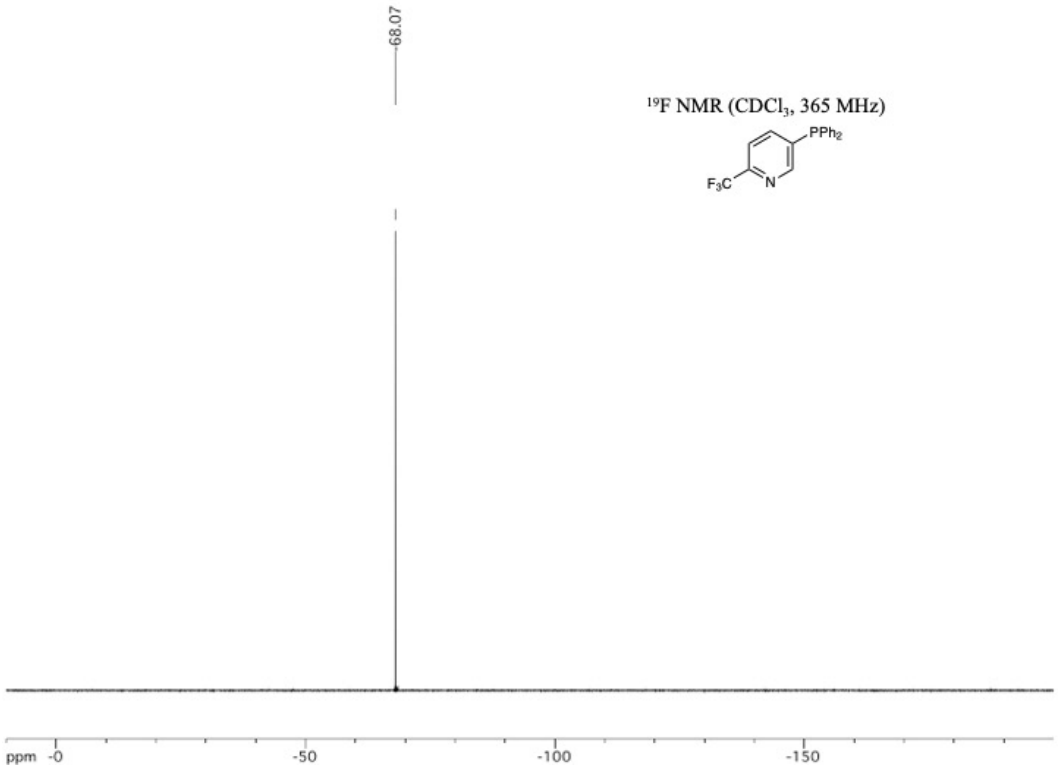
Ethyl 4-(8-chloro-4-iodo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene) piperidine-1-carboxylate



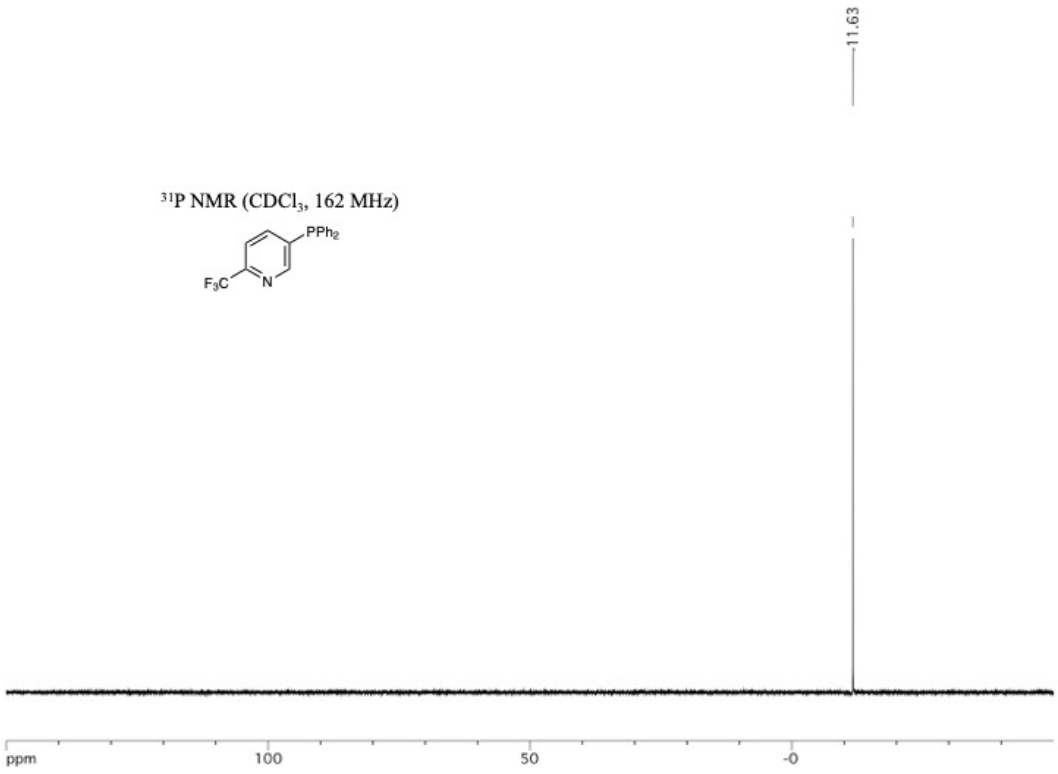
Prepared according to general procedure D using 8-chloro-11-(1-(ethoxycarbonyl) piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)diphenyl(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (172 mg, 0.20 mmol), LiI (107 mg, 0.80 mmol), TfOH (18 μL, 0.2 mmol), and Dioxane (2 mL). The reaction was heated at 120 °C for 16 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes) afforded the title compound as a white solid (64 mg, 0.13 mmol, 63% yield). mp 149-150 ºC; IR υ_{max}/cm^{-1} (film): 2920, 2855, 1688, 1534, 1471, 1431, 1227, 1114, 997, 832; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (1H, d , *J* = 5.2 Hz), 7.64 (1H, d, *J* = 5.2 Hz), 7.20-7.03 (3H, m), 4.13 (2H, q, *J* = 7.1 Hz), 3.77 (2H, dd, *J* = 19.7, 9.9 Hz), 3.32 (2H, tdd, *J* = 18.9, 8.6, 5.3 Hz), 3.17 (tt, *J* = 2H, 9.1, 4.6 Hz), 3.01-2.76 (2H, m), 2.52-2.21 (4H, m), 1.24 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.68, 155.55, 146.89, 138.96, 137.83, 136.82, 136.57, 133.94, 133.66, 133.34, 130.78, 129.29, 126.39, 113.56, 61.46, 44.83, 44.76, 37.35, 31.33, 30.72, 14.79; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 509.1, $C_{22}H_{23}ClIN_2O_2^+$ requires 509.0.

A 1.5 NMR Spectra

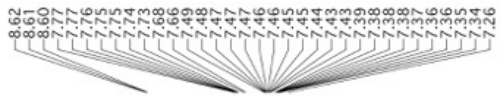




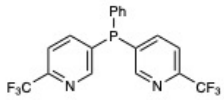
^{19}F NMR ($CDCl_3$, 365 MHz)

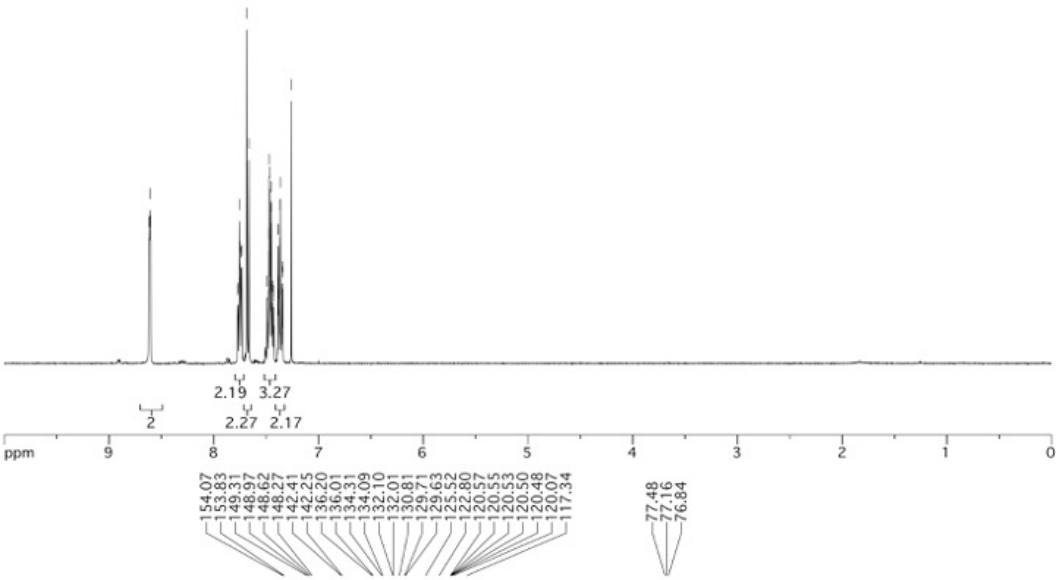


^{31}P NMR ($CDCl_3$, 162 MHz)

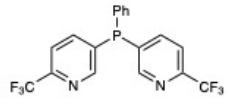


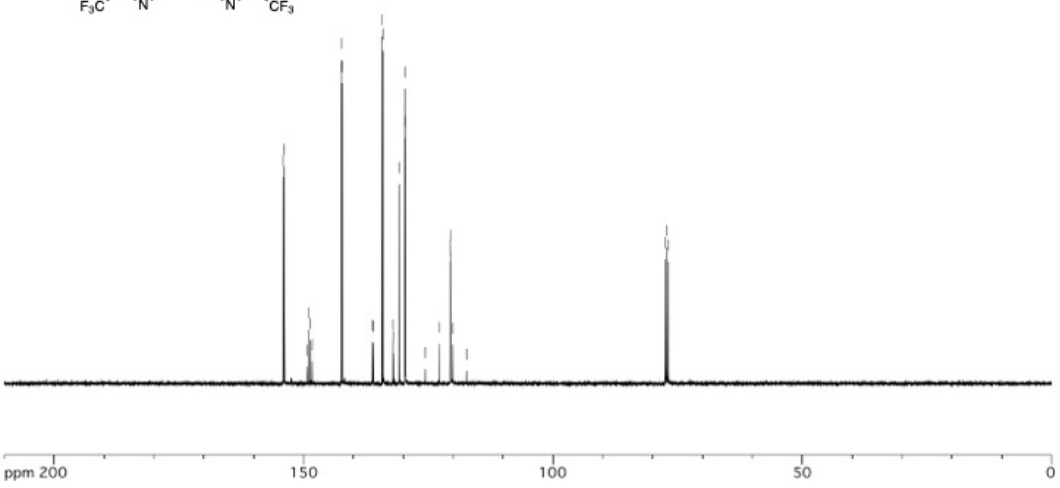
^{1}H NMR ($CDCl_3$, 400 MHz)



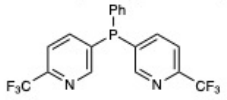


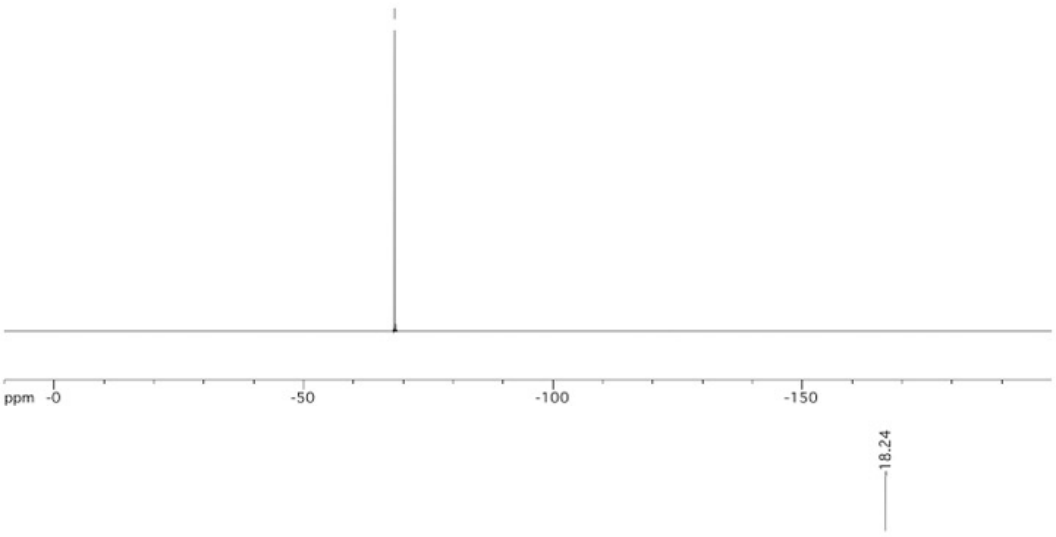
^{13}C NMR ($CDCl_3$, 100 MHz)



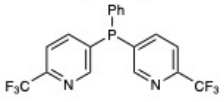


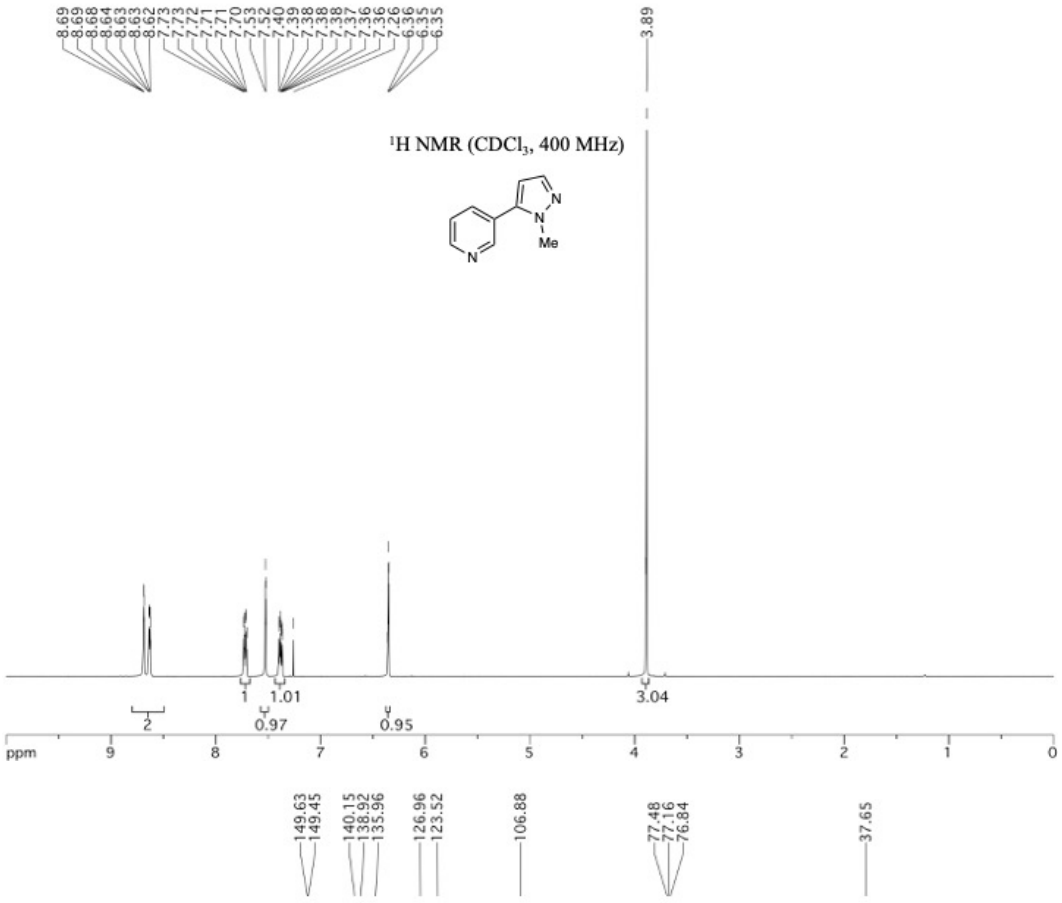
^{19}F NMR ($CDCl_3$, 365 MHz)



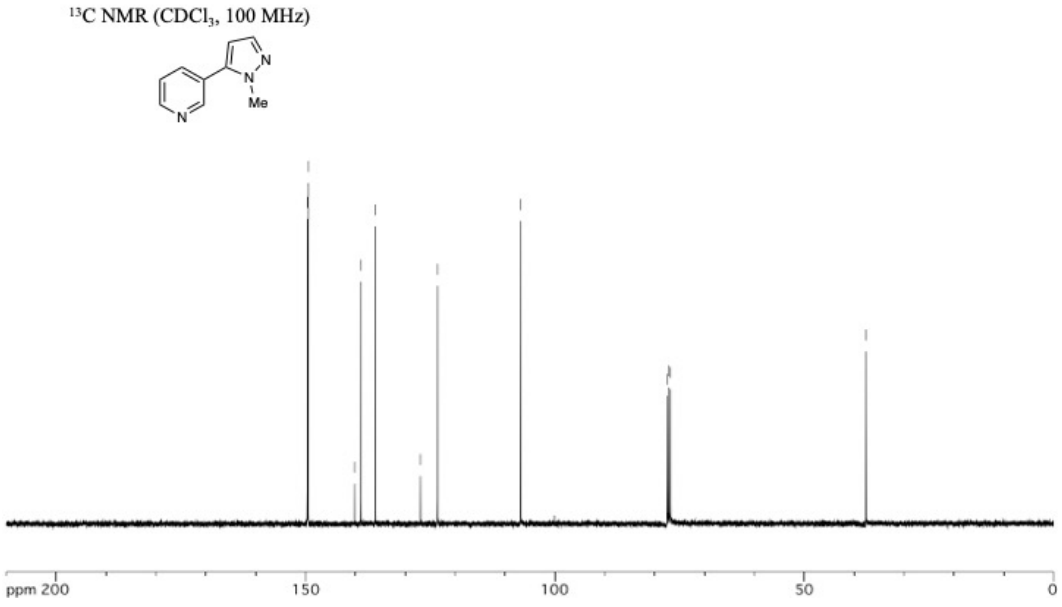


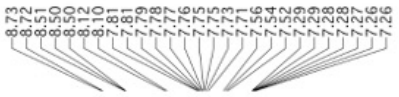
^{31}P NMR ($CDCl_3$, 162 MHz)



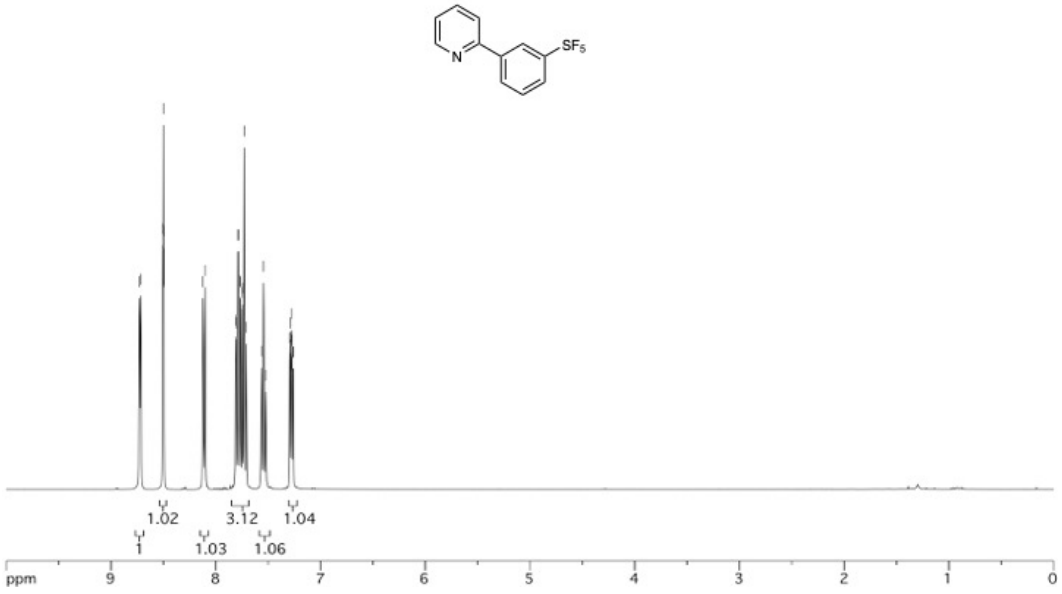

8.69
8.69
8.68
8.64
8.63
8.63
8.62
7.73
7.72
7.71
7.71
7.70
7.53
7.52
7.40
7.39
7.38
7.38
7.37
7.36
7.26
6.36
6.35
6.35
3.89
1H NMR (CDCl3, 400 MHz)
N
N
Me
N
1
1.01
3.04
2
0.97
0.95
ppm
9
8
7
6
5
4
3
2
1
0

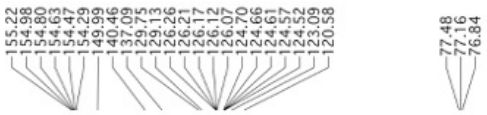
149.63
149.45
140.15
138.92
135.96
126.96
123.52
106.88
77.48
77.16
76.84
37.65


13C NMR (CDCl3, 100 MHz)
N
N
Me
N
ppm 200
150
100
50
0

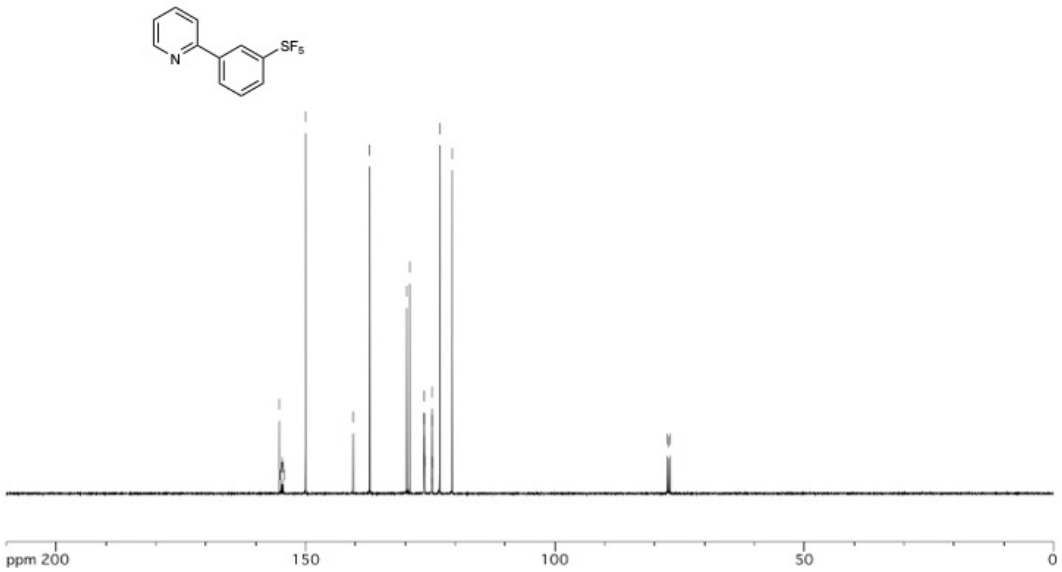


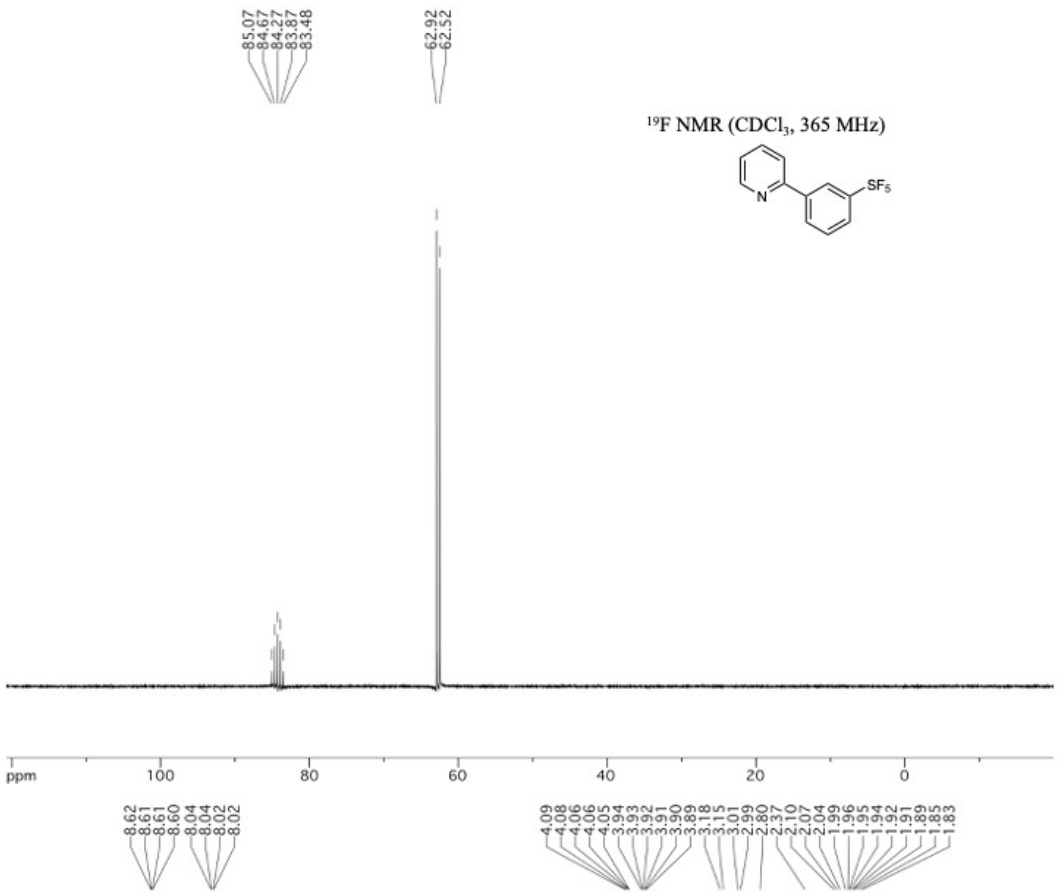
^{1}H NMR ($CDCl_3$, 400 MHz)



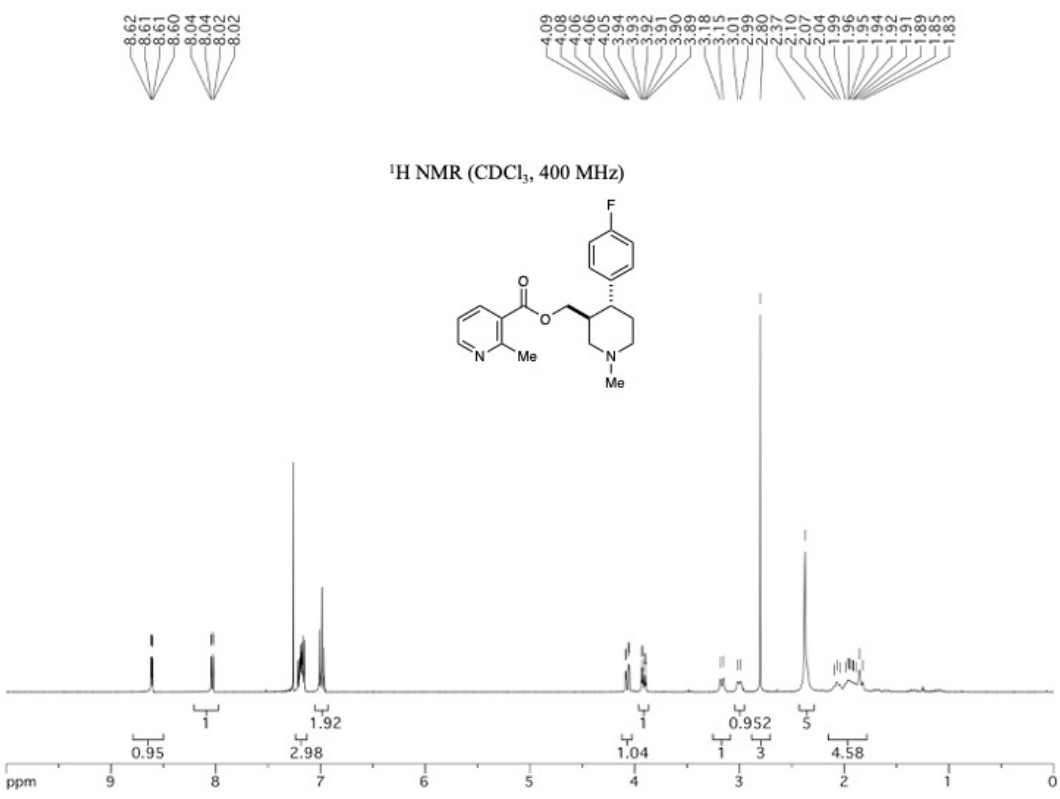


^{13}C NMR ($CDCl_3$, 100 MHz)



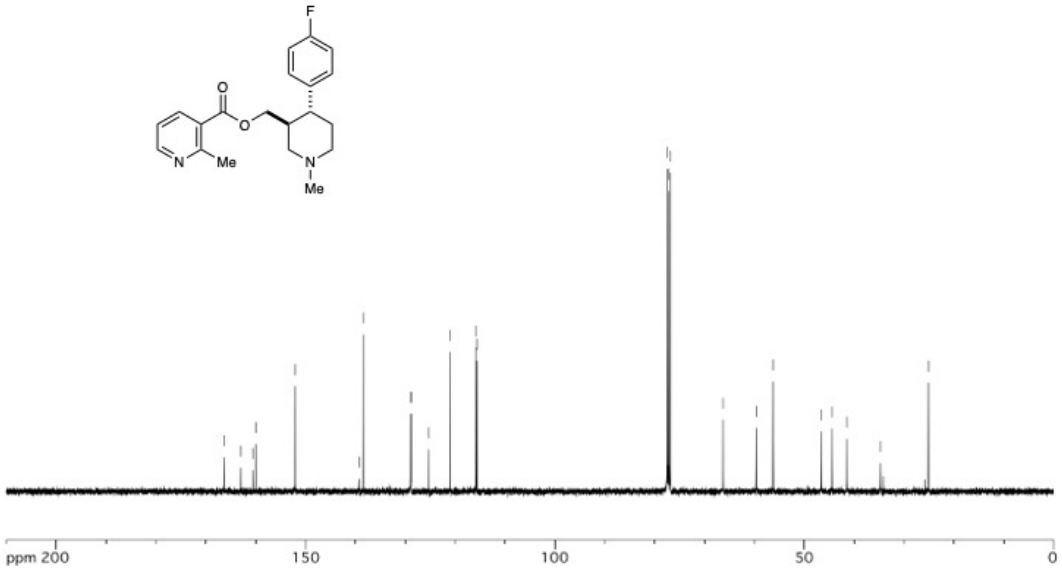


^{19}F NMR ($CDCl_3$, 365 MHz)

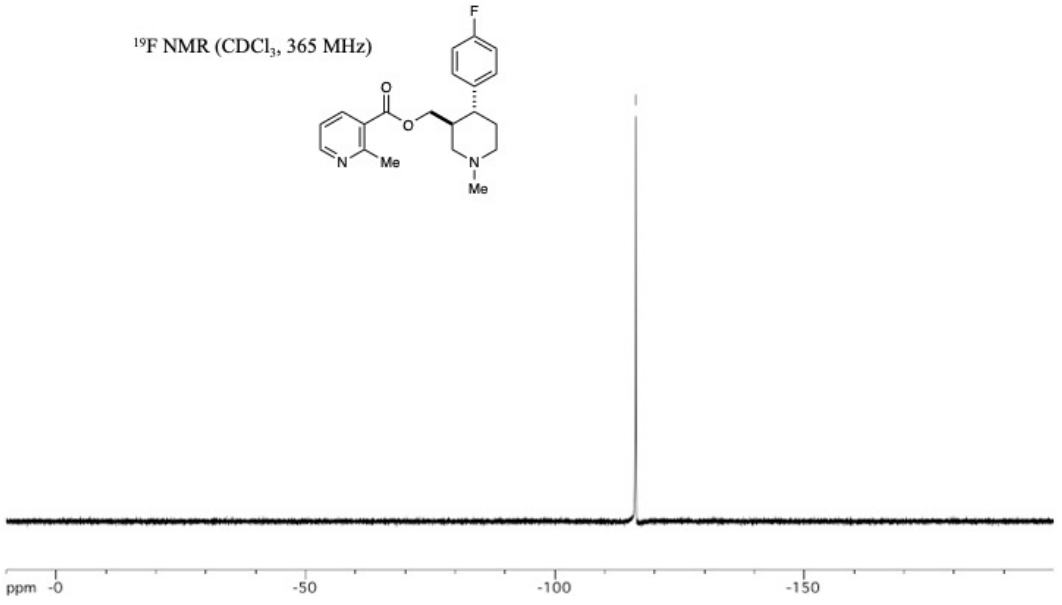


^{1}H NMR ($CDCl_3$, 400 MHz)

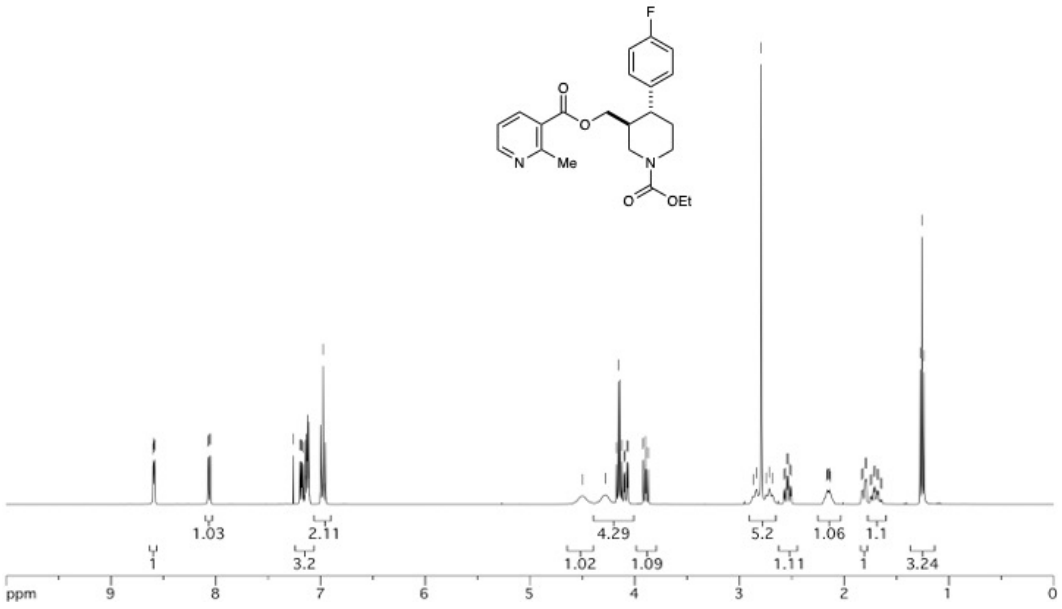
^{13}C NMR ($CDCl_3$, 100 MHz)

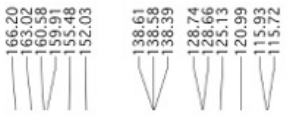


^{19}F NMR ($CDCl_3$, 365 MHz)

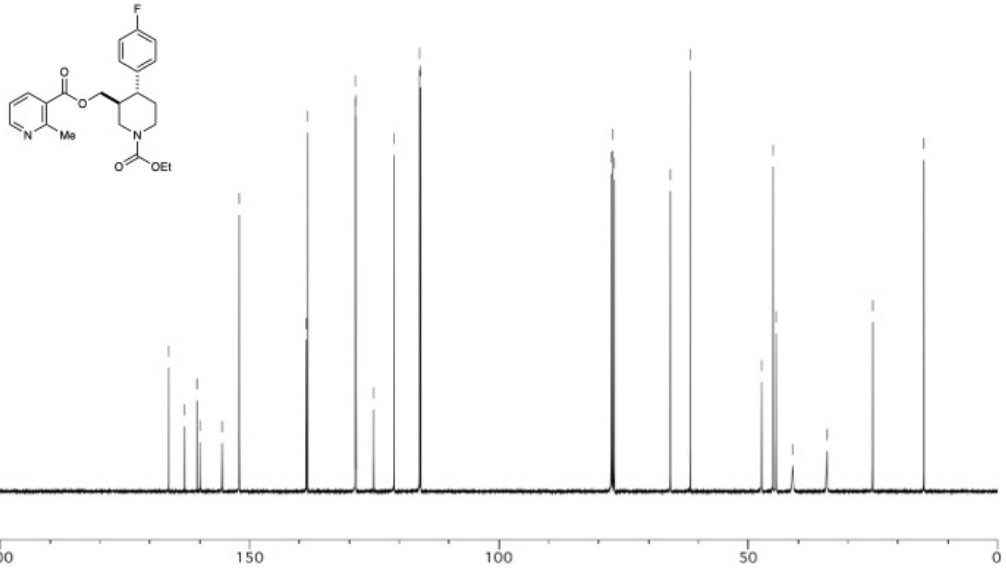


^{1}H NMR ($CDCl_3$, 400 MHz)

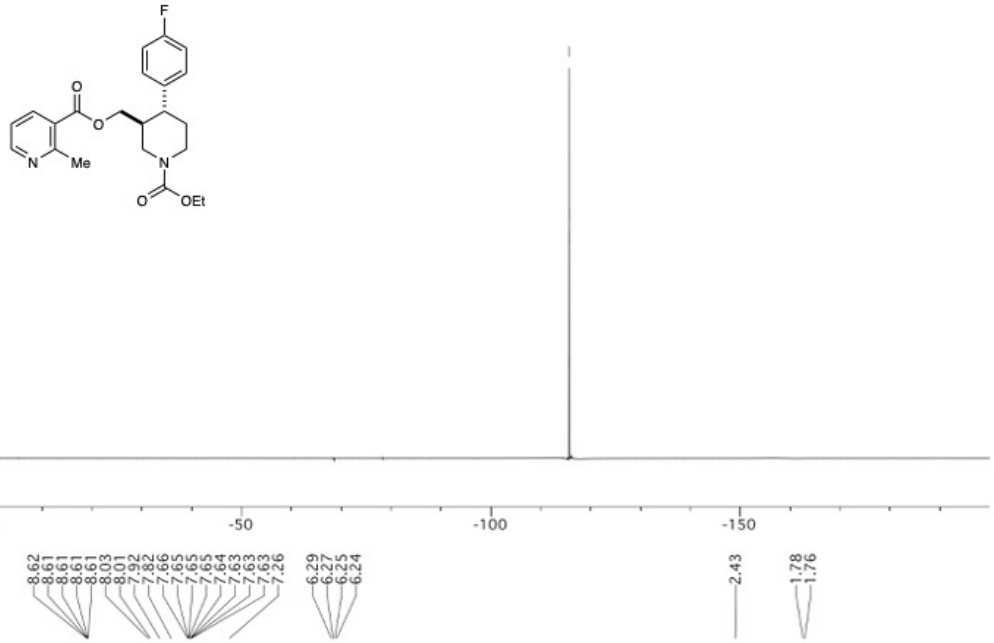




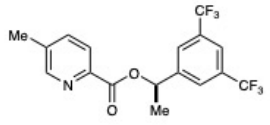
^{13}C NMR ($CDCl_3$, 100 MHz)

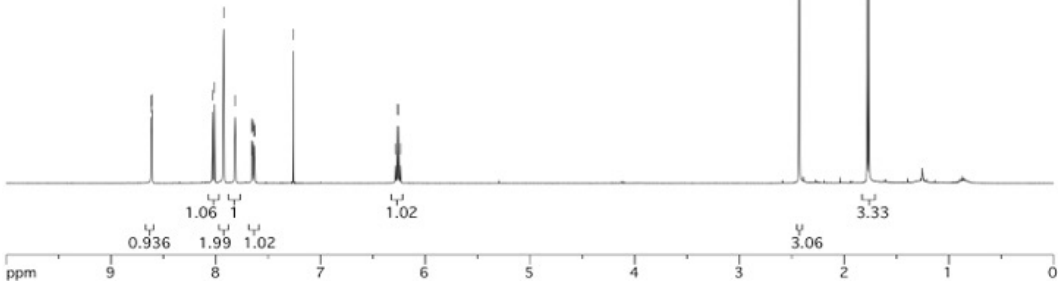


^{19}F NMR ($CDCl_3$, 365 MHz)

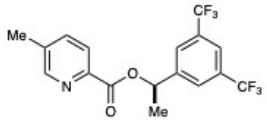


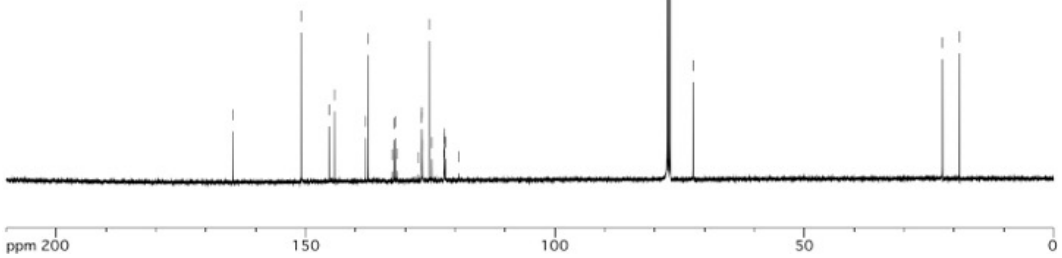
^{1}H NMR ($CDCl_3$, 400 MHz)



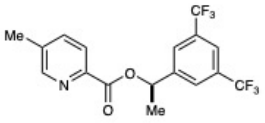


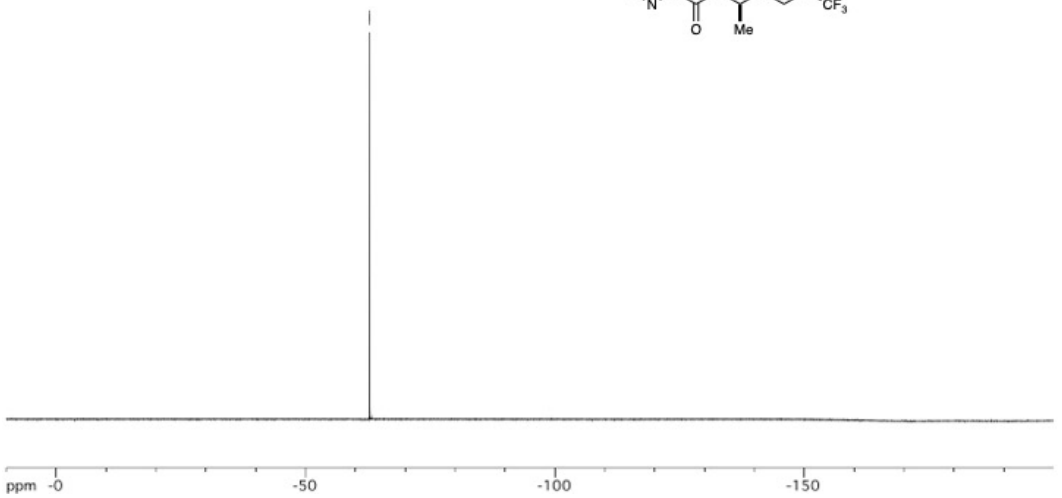
^{13}C NMR ($CDCl_3$, 100 MHz)



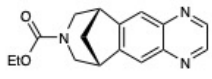


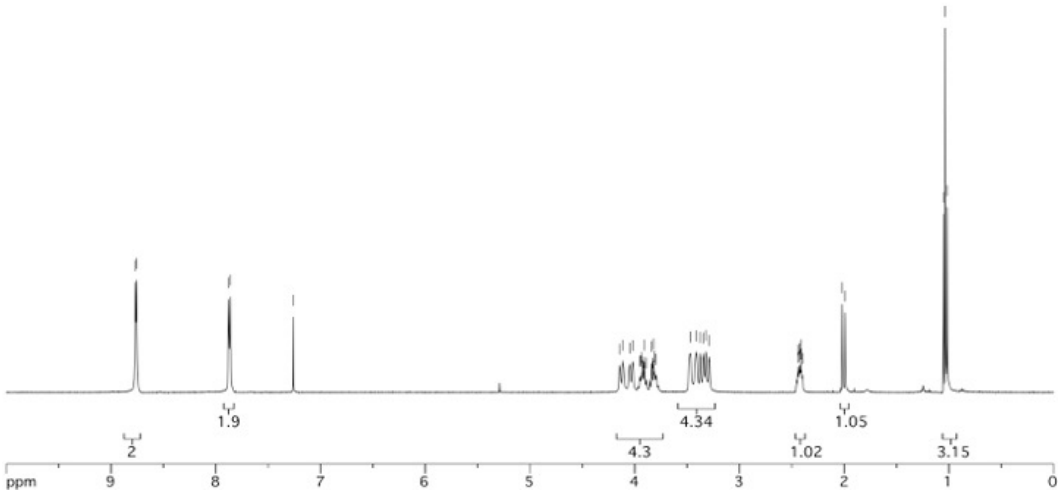
^{19}F NMR ($CDCl_3$, 365 MHz)

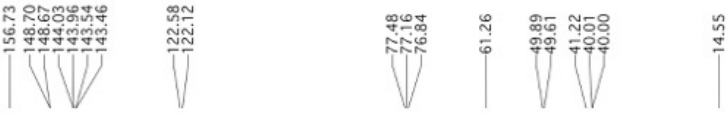




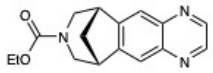
^{1}H NMR ($CDCl_3$, 400 MHz)

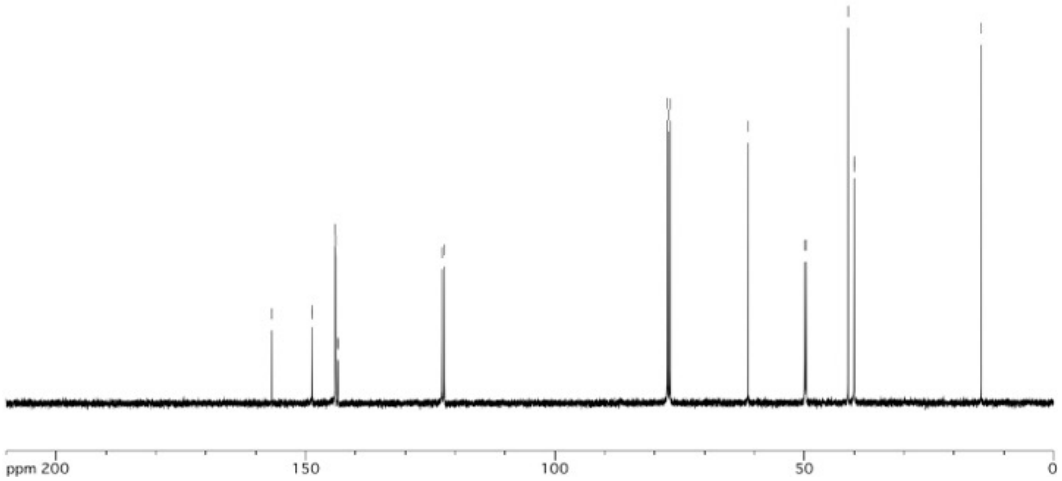


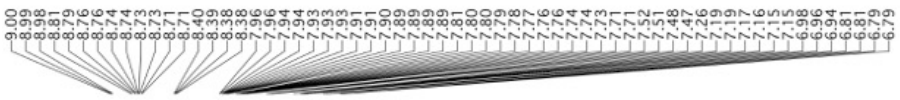




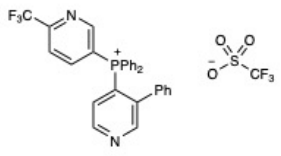
^{13}C NMR ($CDCl_3$, 100 MHz)



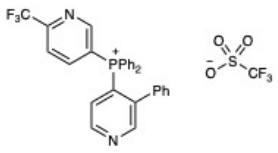


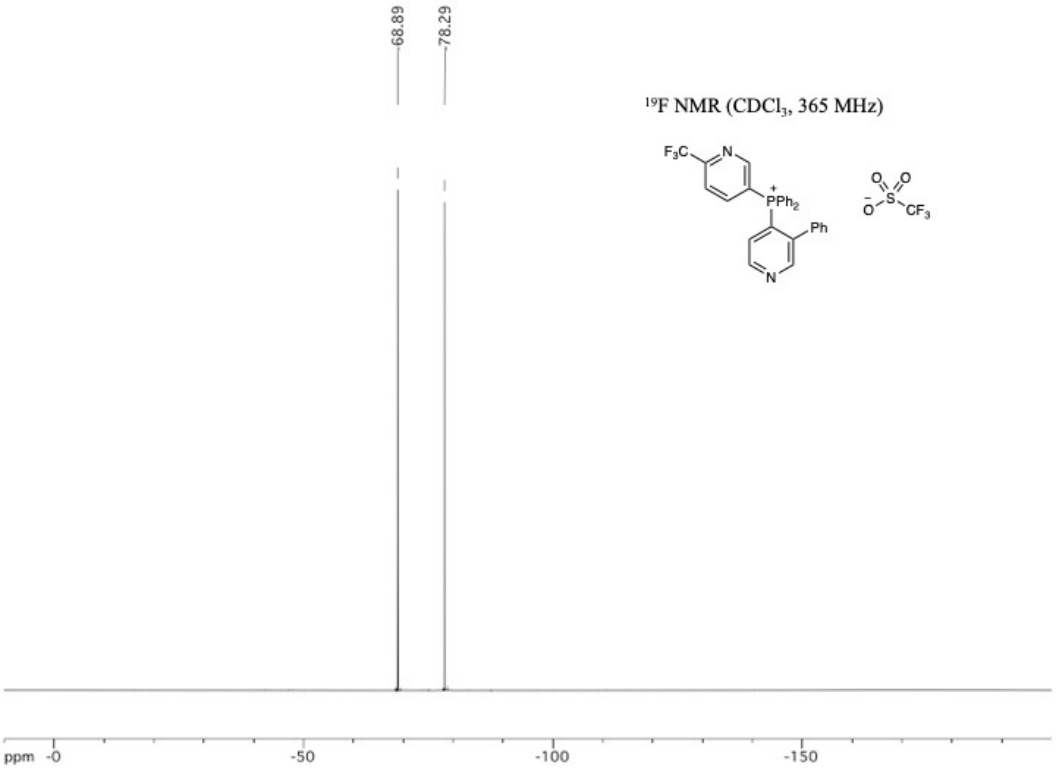


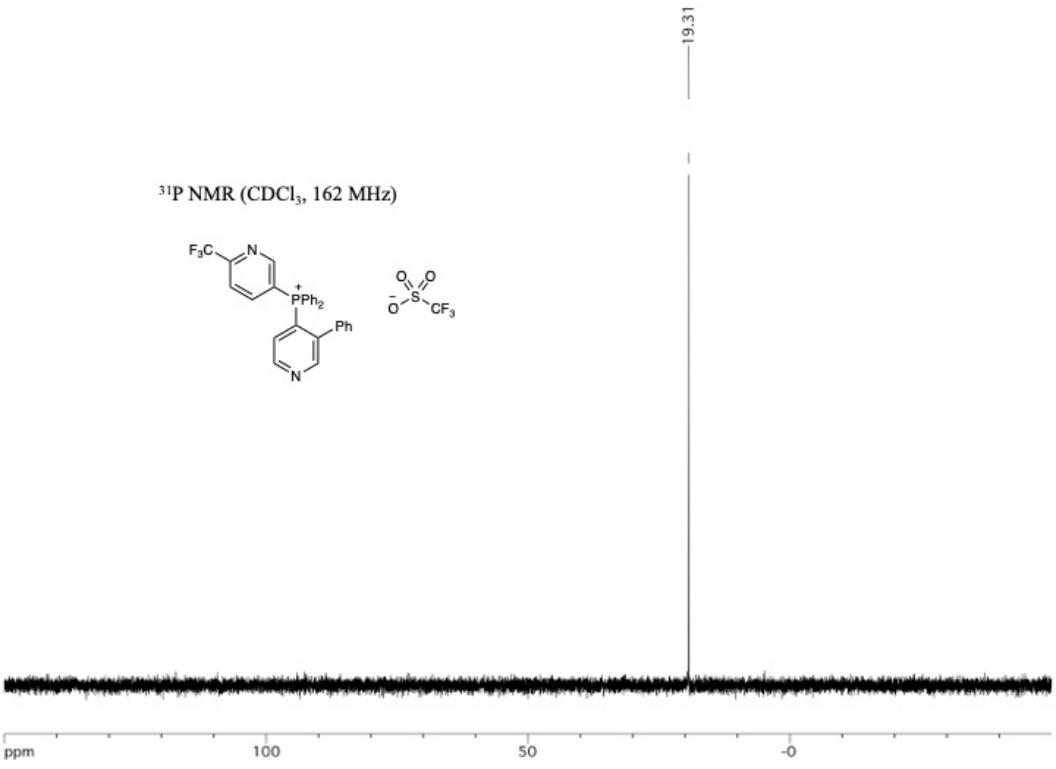
^{1}H NMR ($CDCl_3$, 400 MHz)

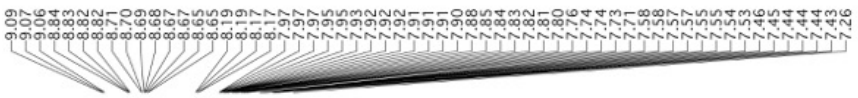


^{13}C NMR ($CDCl_3$, 100 MHz)

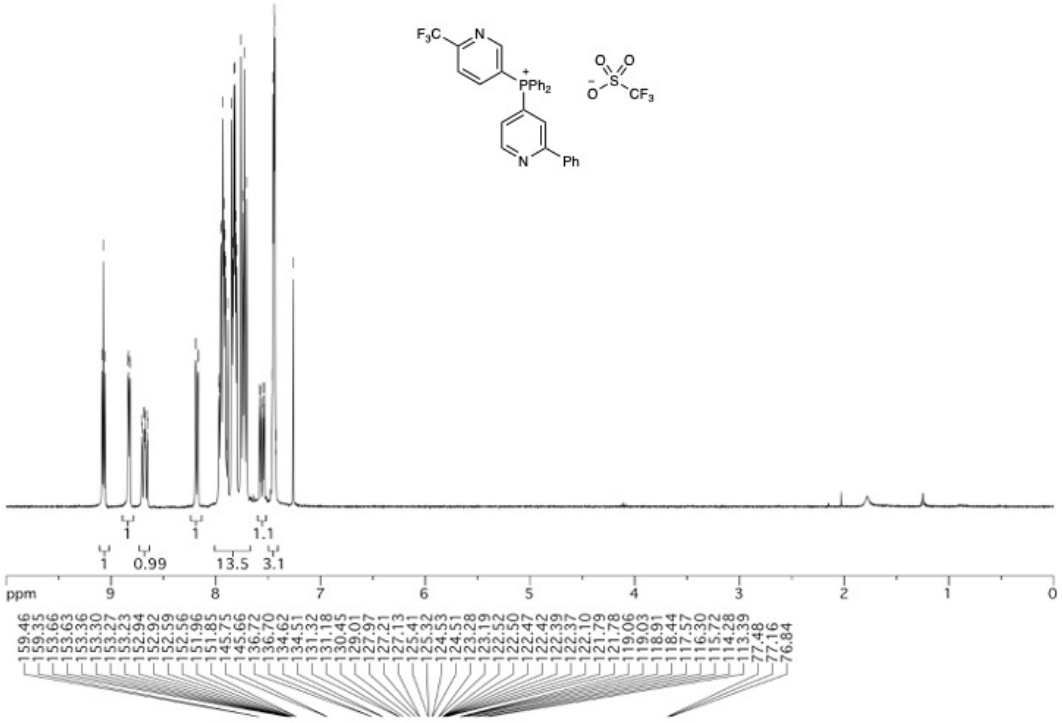



68.89
78.29
^{19}F NMR ($CDCl_3$, 365 MHz)
ppm -0
-50
-100
-150

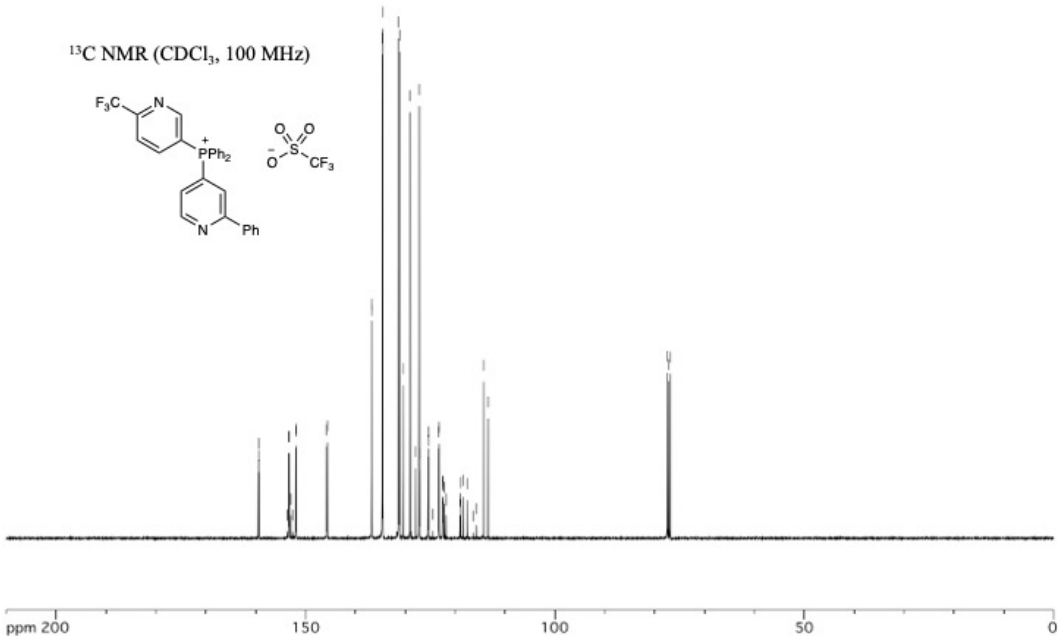

19.31
^{31}P NMR ($CDCl_3$, 162 MHz)
ppm
100
50
-0

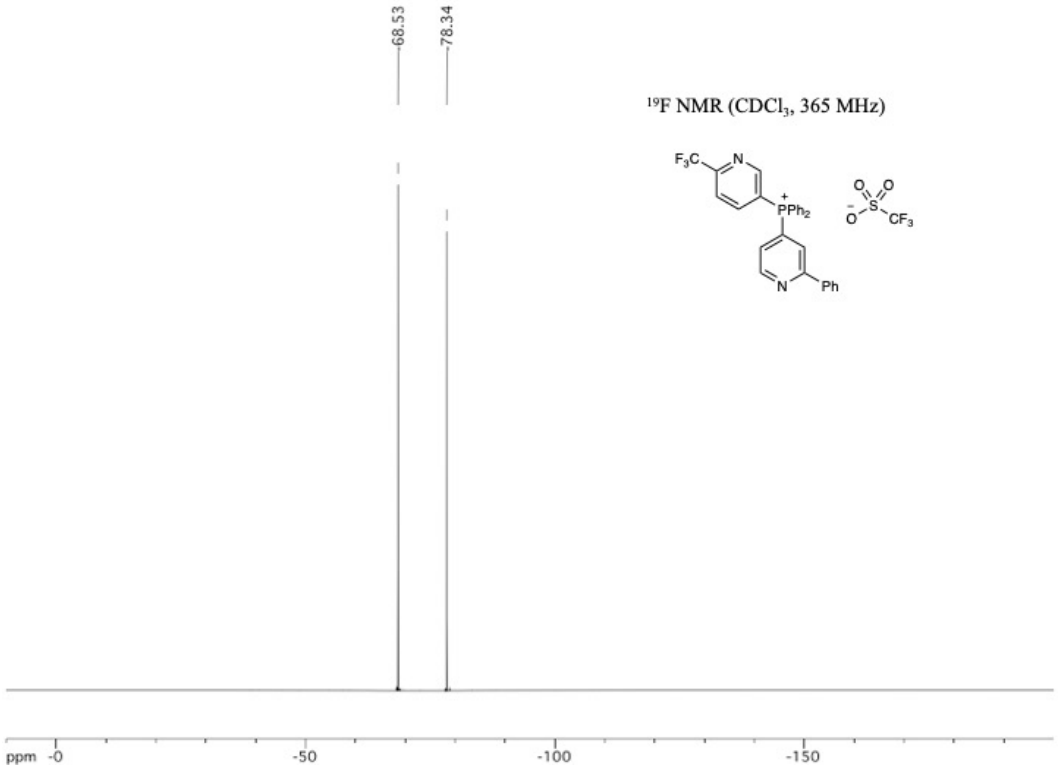


^{1}H NMR ($CDCl_3$, 400 MHz)

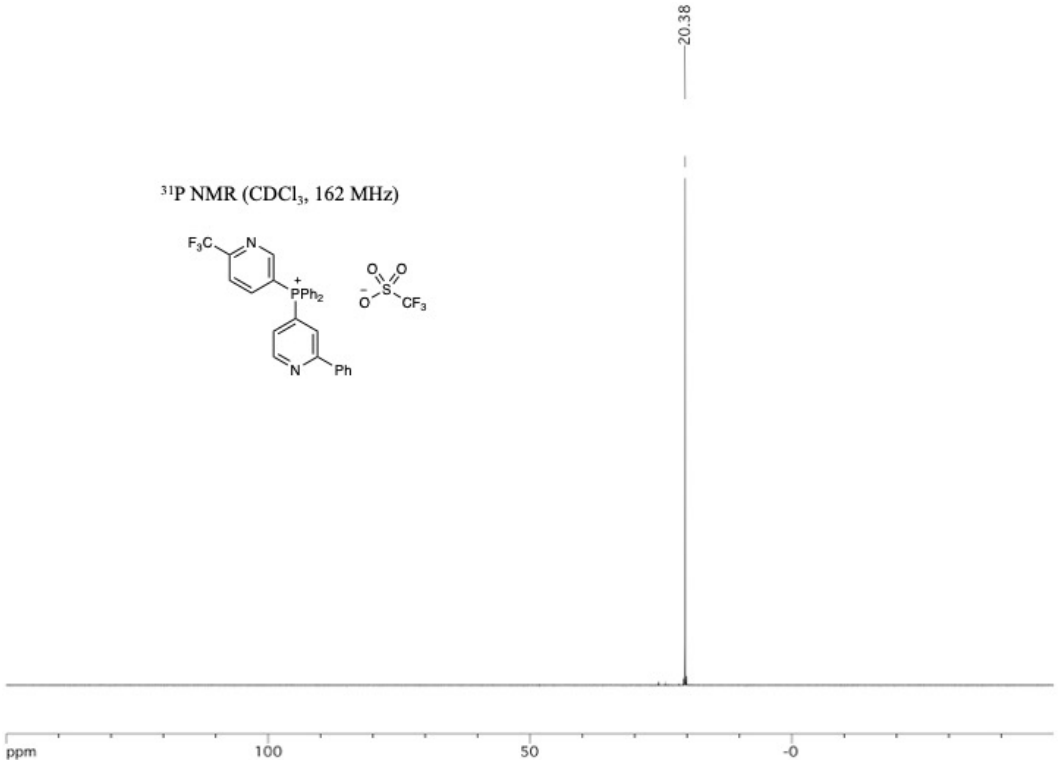


^{13}C NMR ($CDCl_3$, 100 MHz)

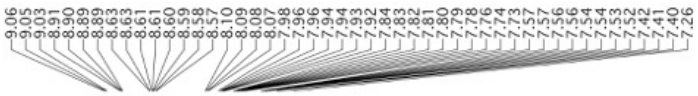




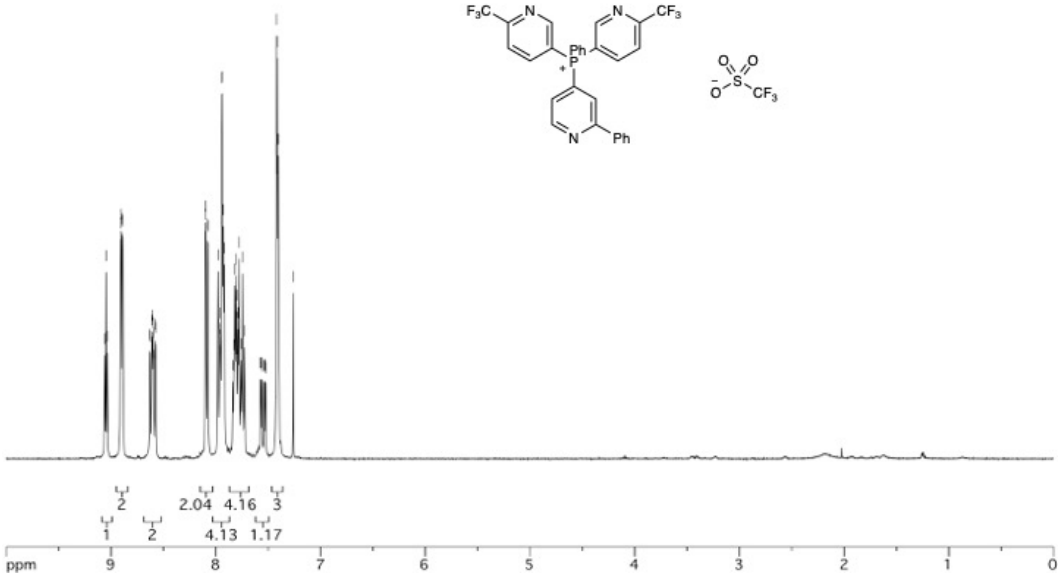
^{19}F NMR ($CDCl_3$, 365 MHz)



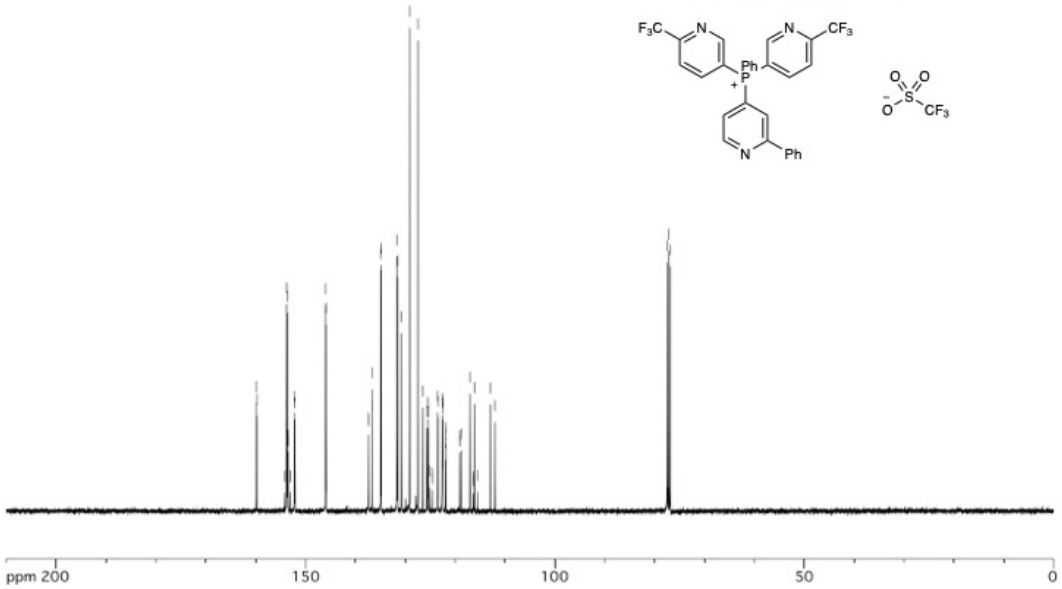
^{31}P NMR ($CDCl_3$, 162 MHz)

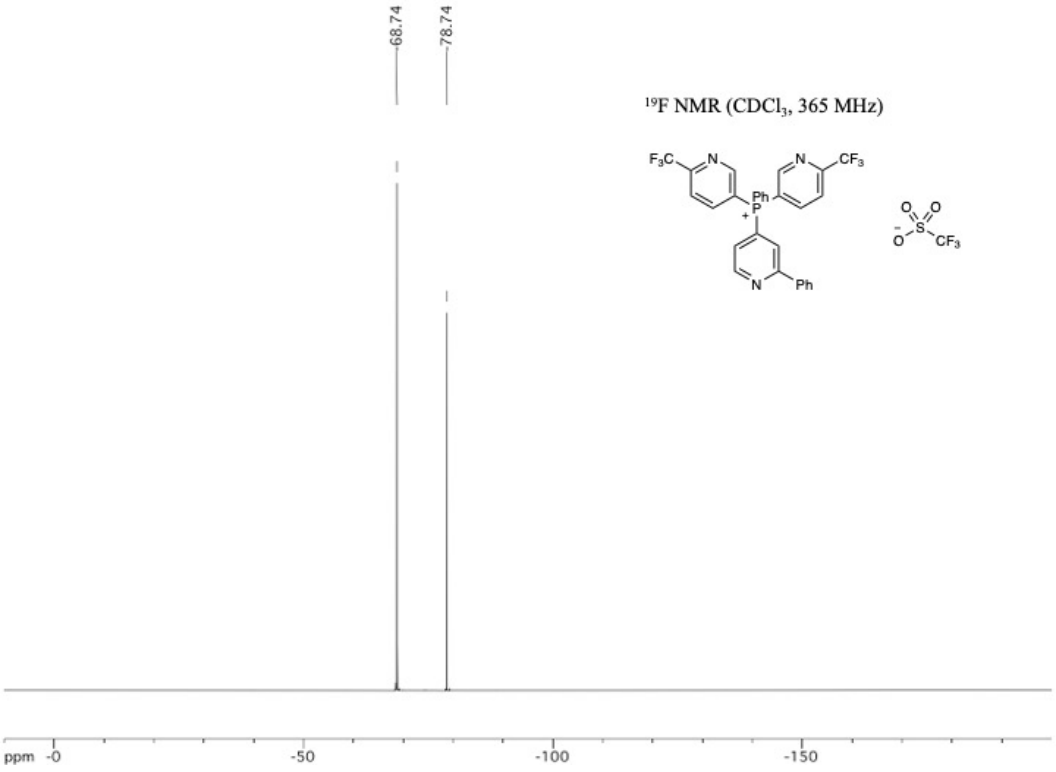


^{1}H NMR ($CDCl_3$, 400 MHz)

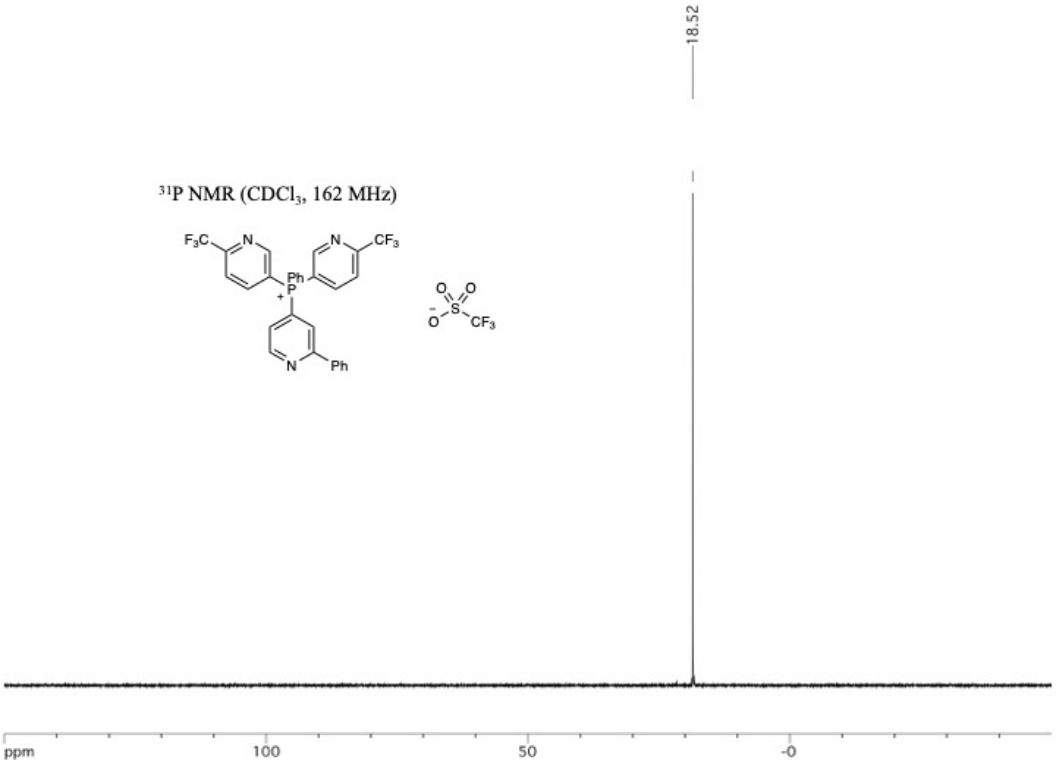


^{13}C NMR ($CDCl_3$, 100 MHz)

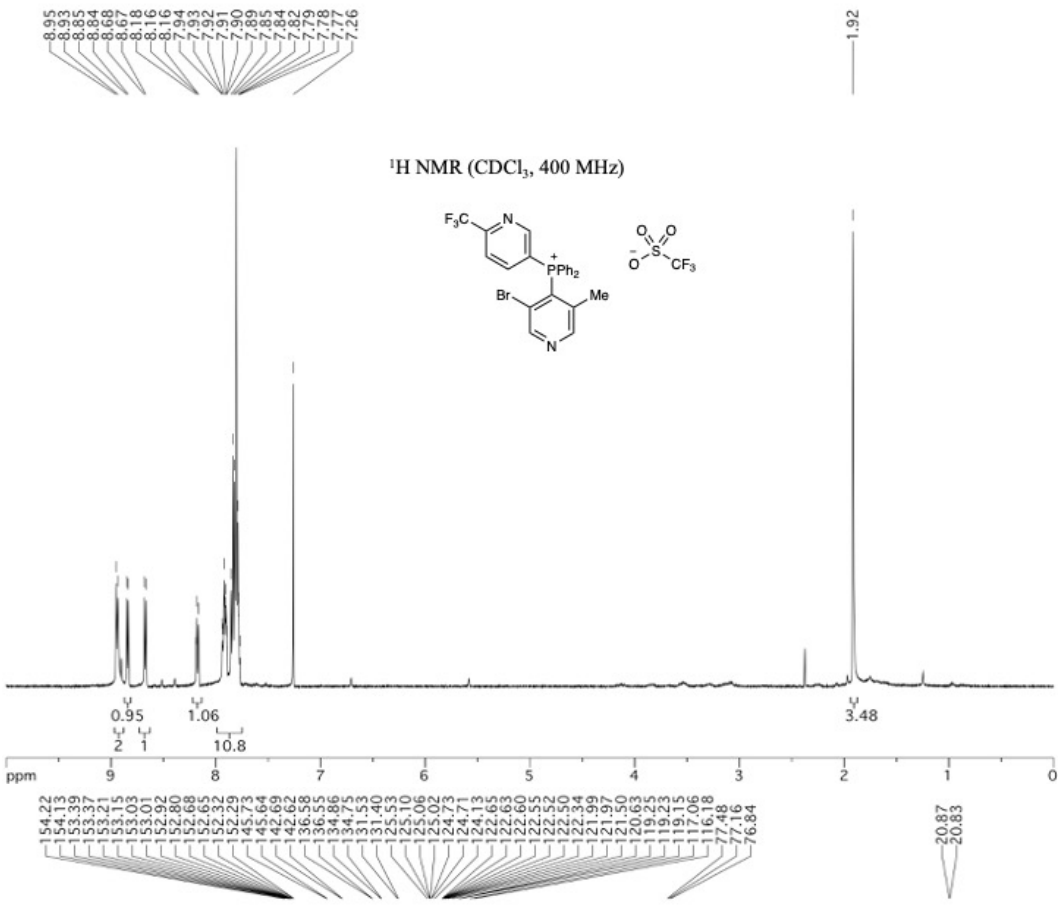




^{19}F NMR ($CDCl_3$, 365 MHz)

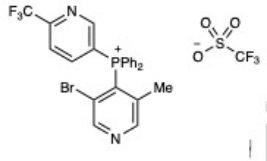


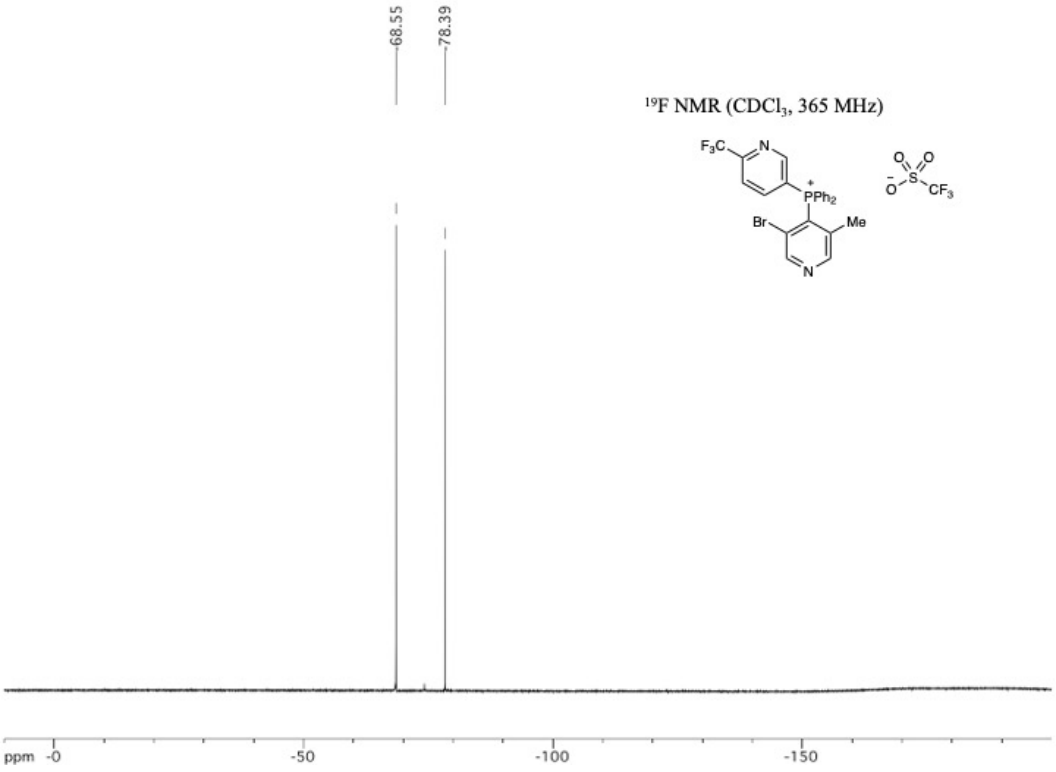
^{31}P NMR ($CDCl_3$, 162 MHz)



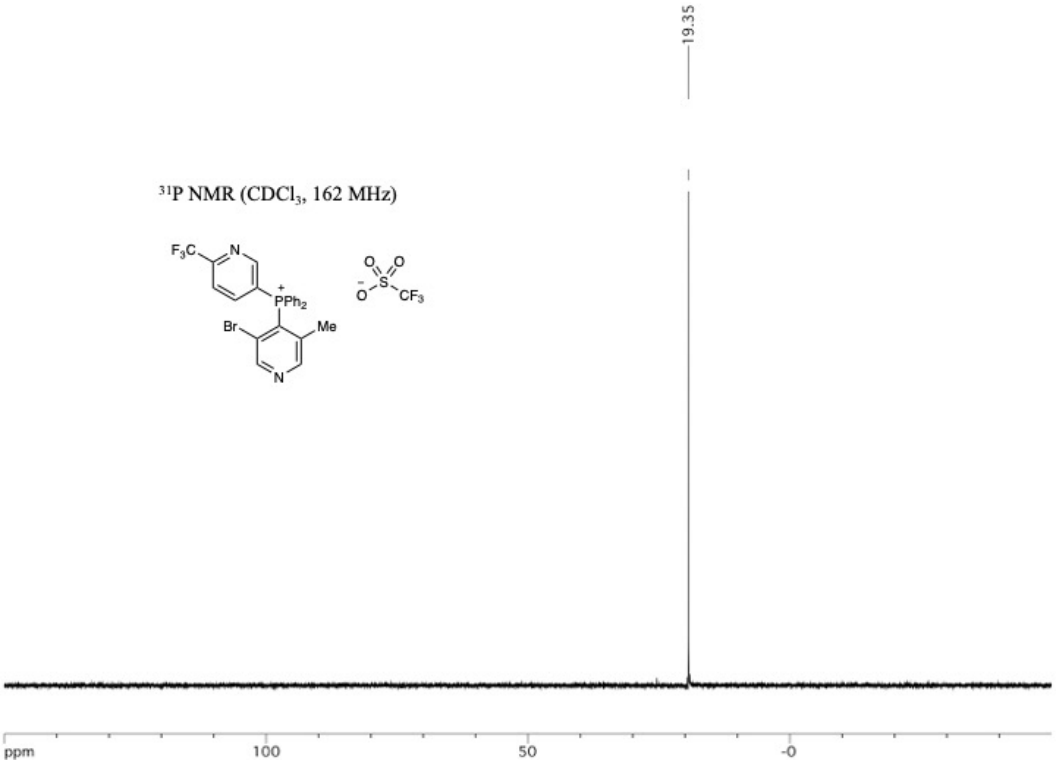
^{1}H NMR ($CDCl_3$, 400 MHz)

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

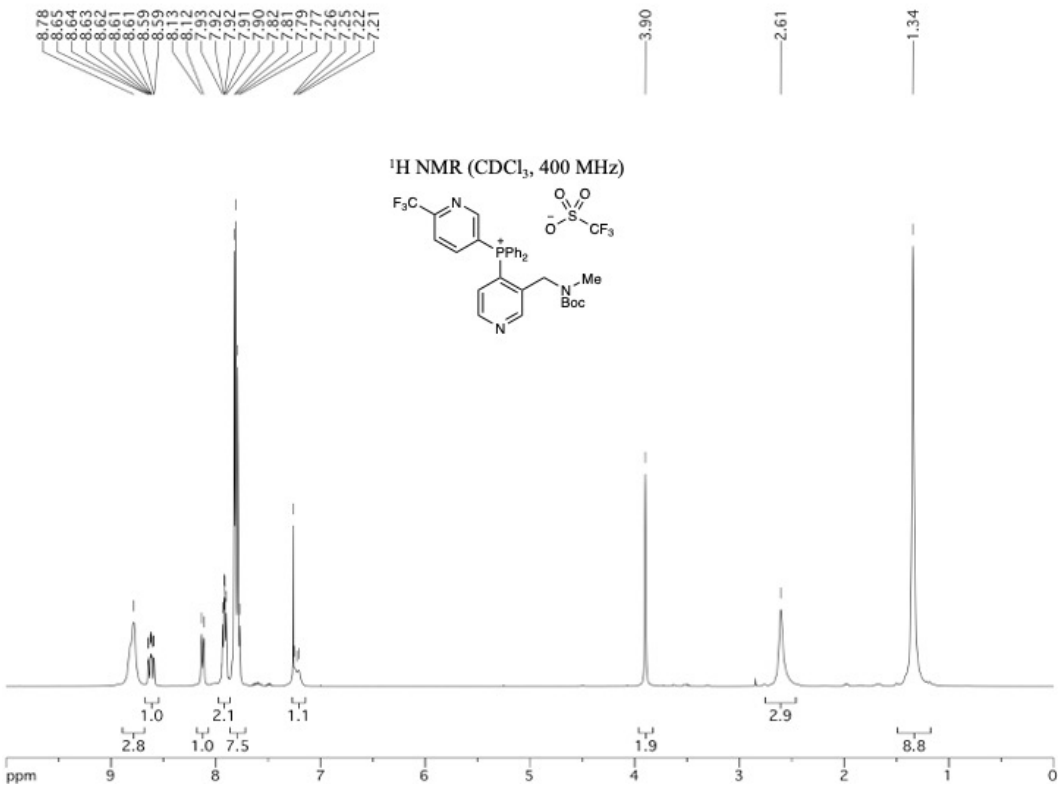


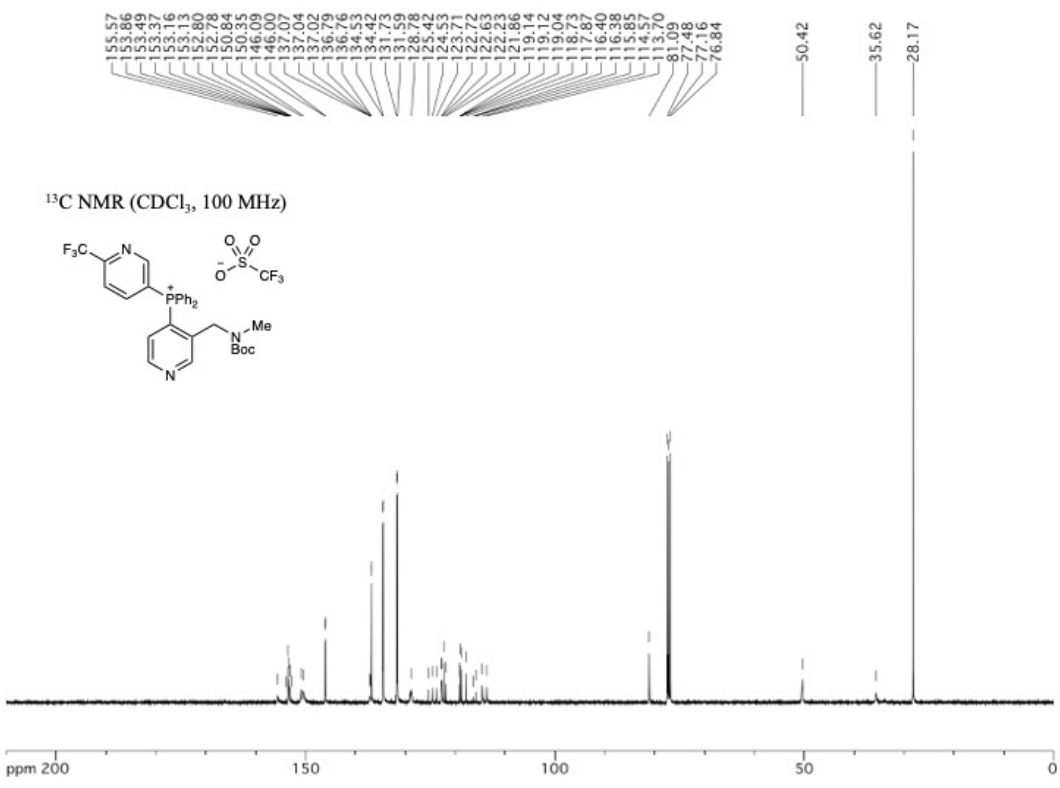


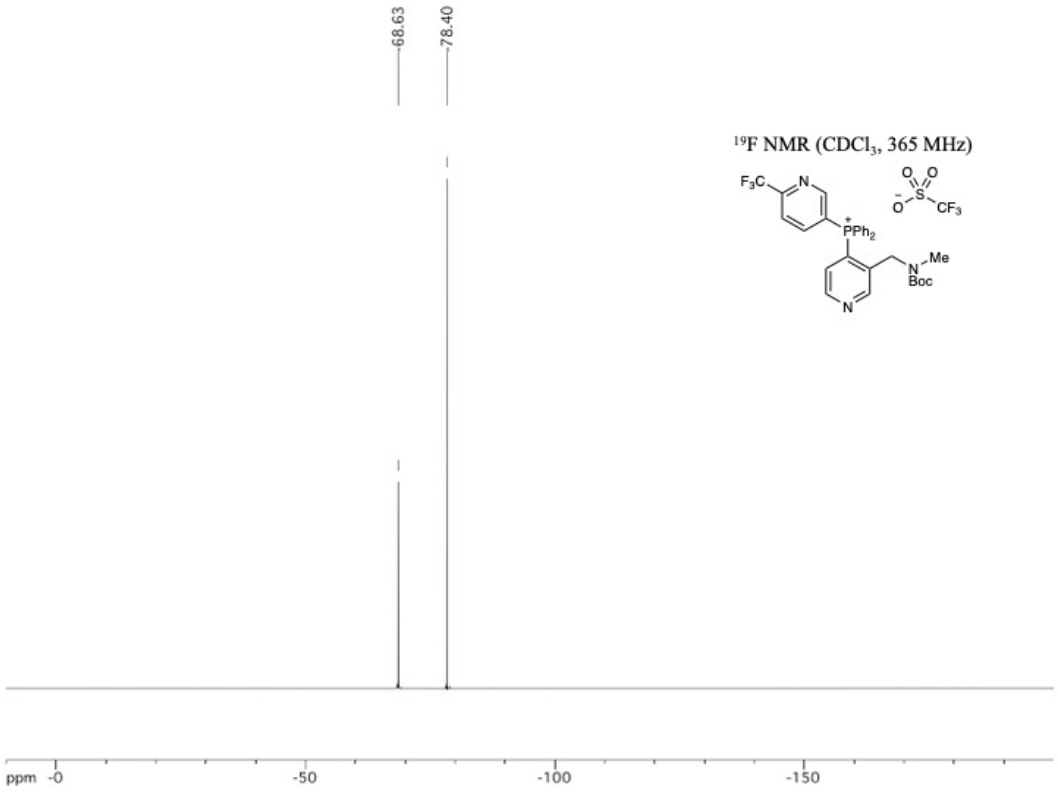
^{19}F NMR ($CDCl_3$, 365 MHz)



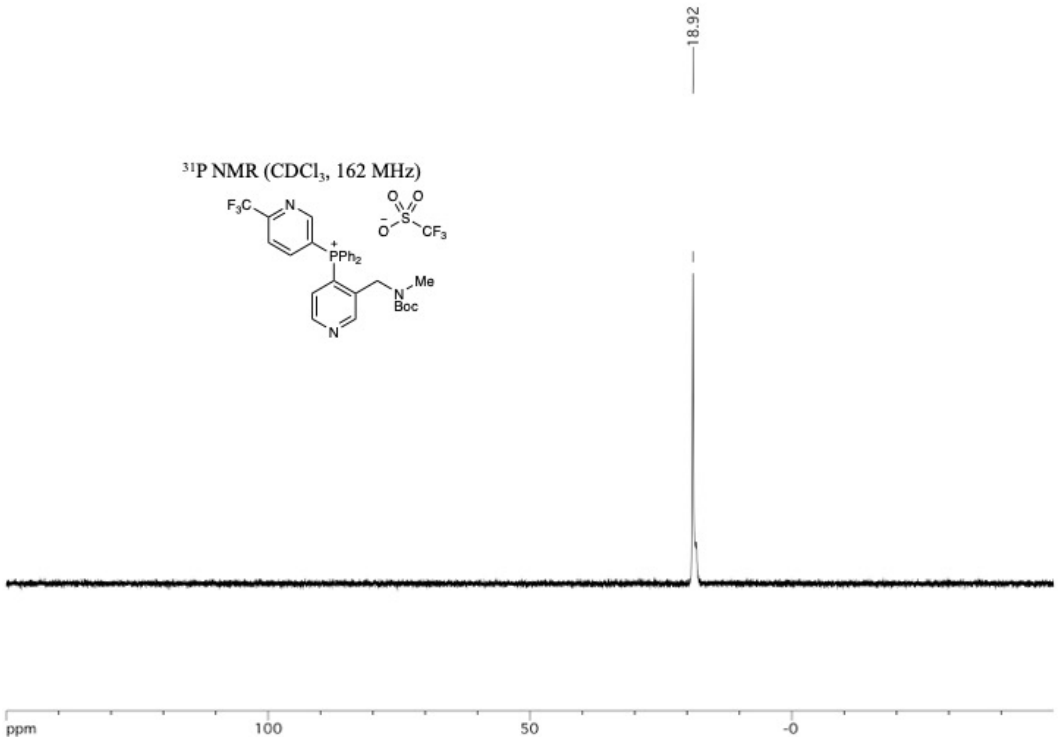
^{31}P NMR ($CDCl_3$, 162 MHz)


8.78
8.65
8.64
8.63
8.62
8.61
8.61
8.59
8.59
8.13
8.12
7.93
7.92
7.91
7.90
7.82
7.81
7.79
7.77
7.26
7.25
7.22
7.21
3.90
2.61
1.34
1H NMR (CDCl3, 400 MHz)
F3C
N
PPh2
CF3
Me
Boc
1.0
2.1
1.1
2.9
2.8
1.0
7.5
1.9
8.8
ppm
9
8
7
6
5
4
3
2
1
0

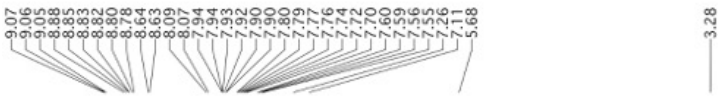

155.57
153.86
153.49
153.37
153.16
153.13
152.80
152.78
150.84
150.35
146.09
146.00
137.07
137.04
137.02
136.79
136.76
134.53
134.42
131.73
131.59
128.78
125.42
124.53
123.71
122.72
122.63
122.23
121.86
119.14
119.12
119.04
118.73
117.87
116.40
116.38
115.85
114.57
113.70
81.09
77.48
77.16
76.84
50.42
35.62
28.17
13C NMR (CDCl3, 100 MHz)
F3C
N
PPh2
CF3
Me
Boc
ppm 200
150
100
50
0



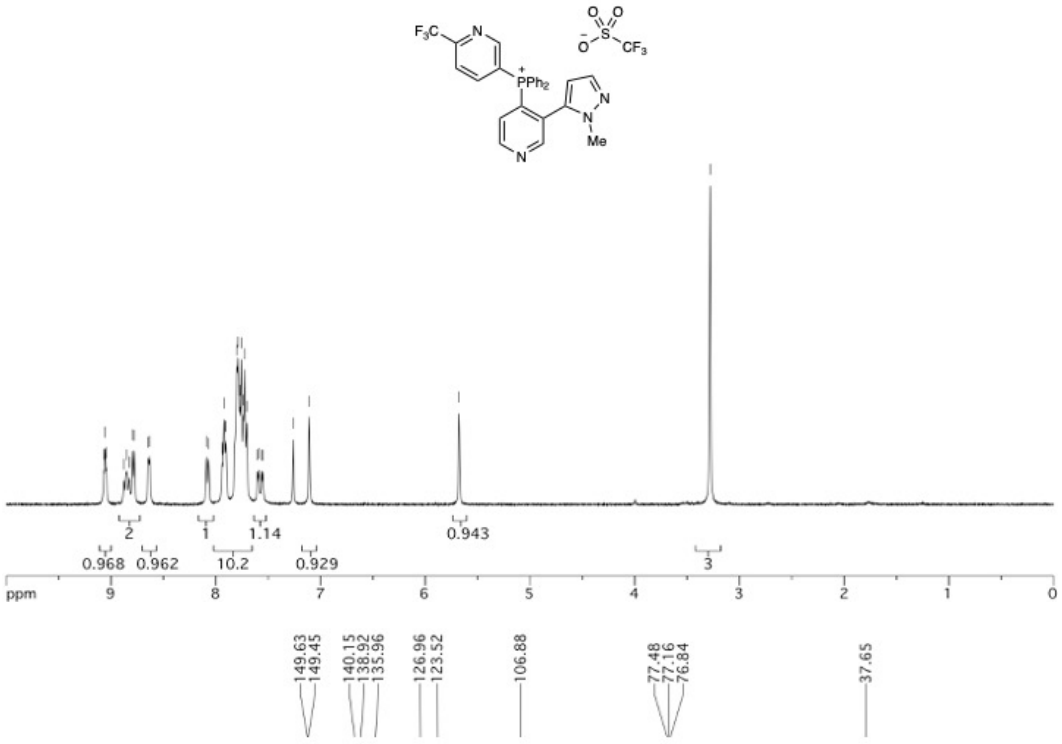
^{19}F NMR ($CDCl_3$, 365 MHz)



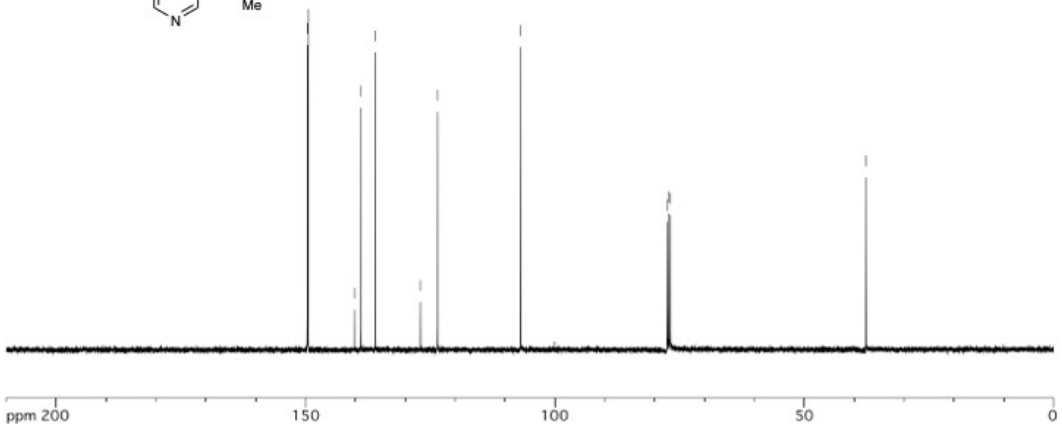
^{31}P NMR ($CDCl_3$, 162 MHz)

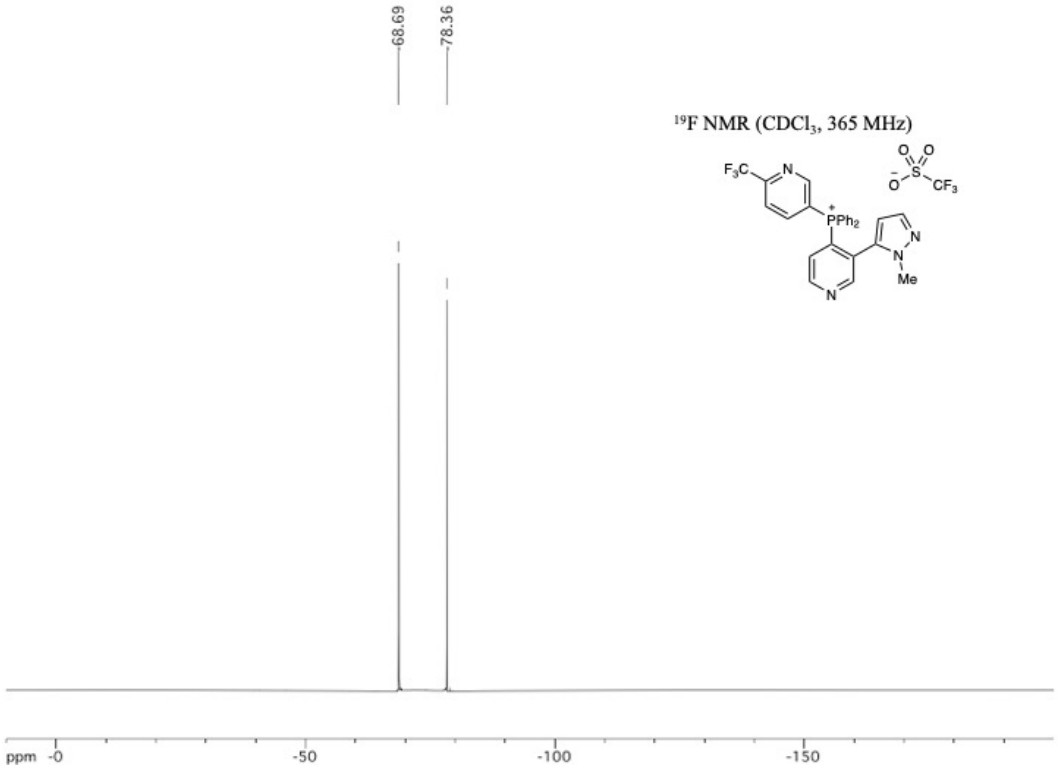


^{1}H NMR ($CDCl_3$, 400 MHz)

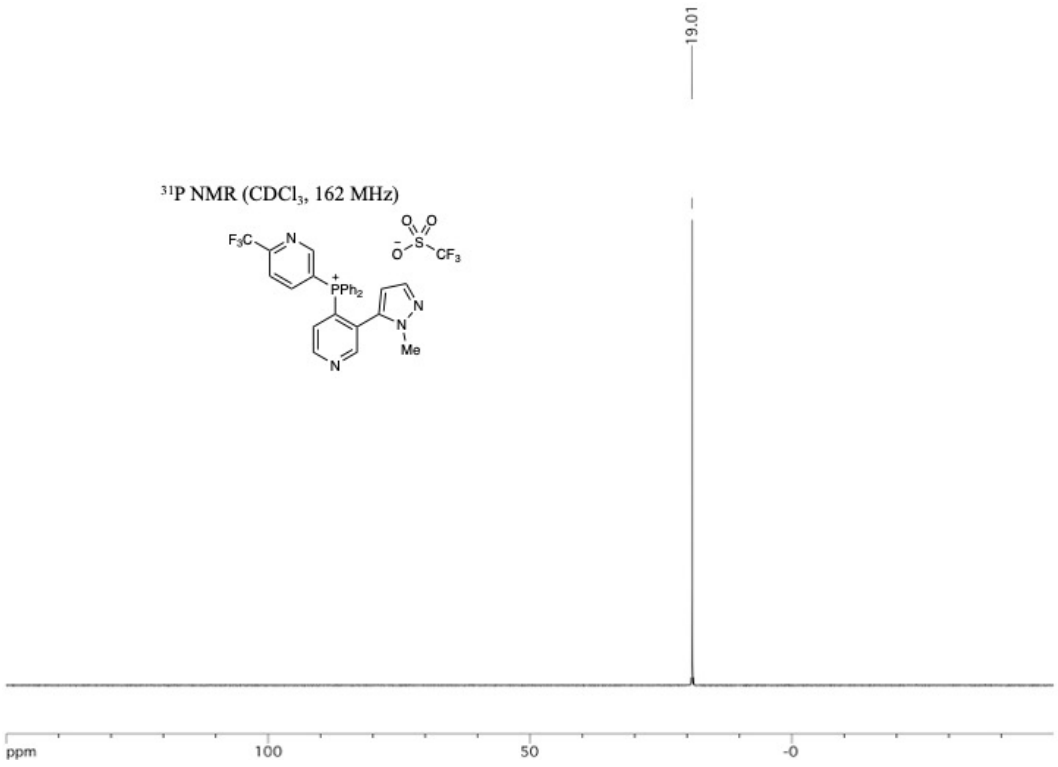


^{13}C NMR ($CDCl_3$, 100 MHz)



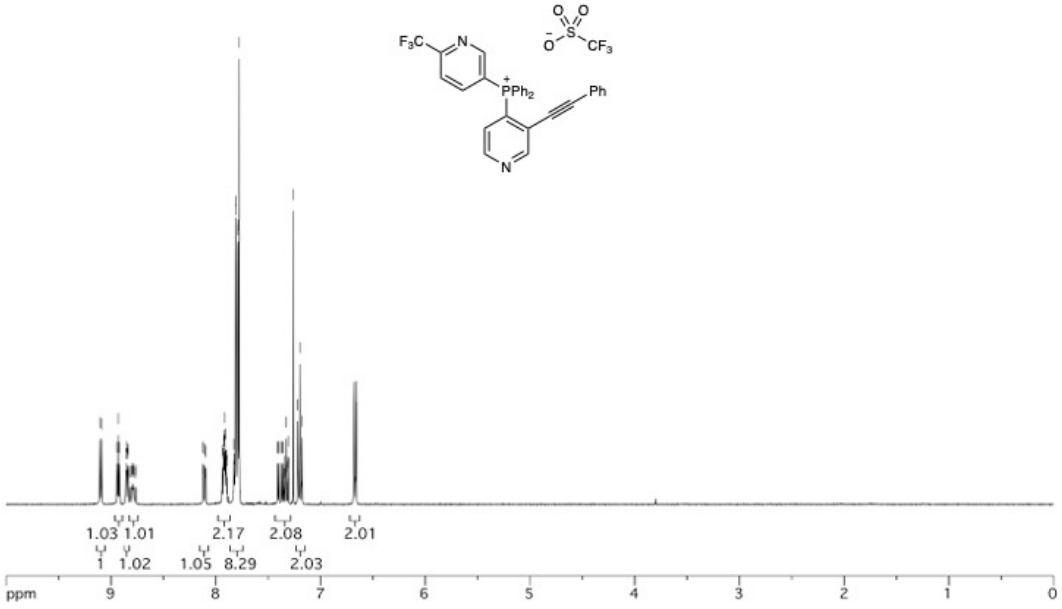


^{19}F NMR ($CDCl_3$, 365 MHz)

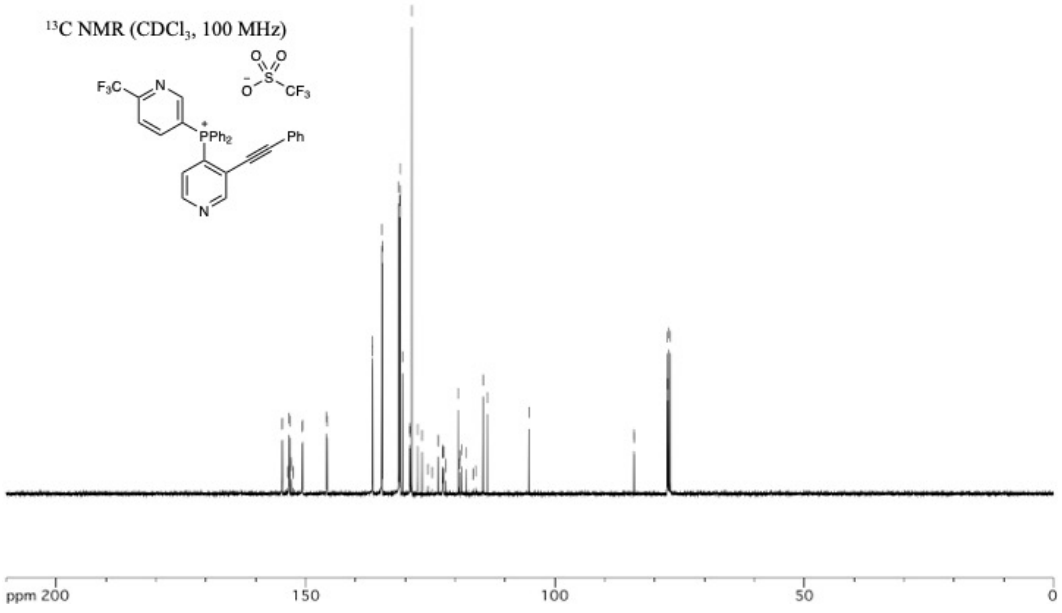


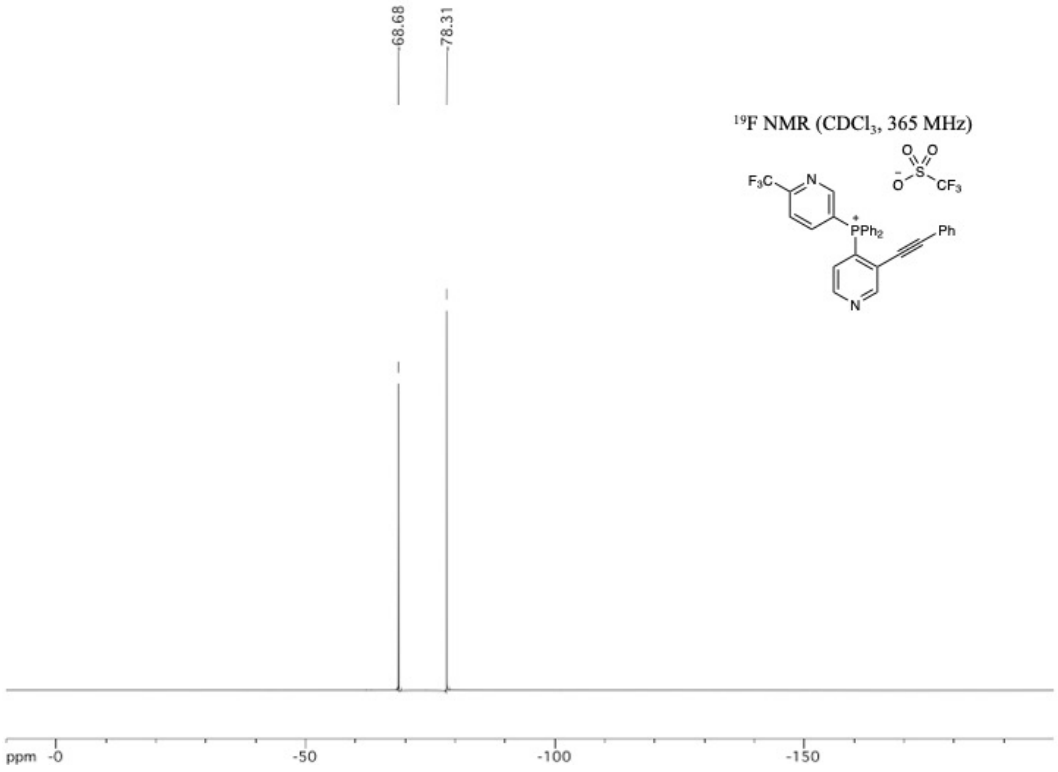
^{31}P NMR ($CDCl_3$, 162 MHz)

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

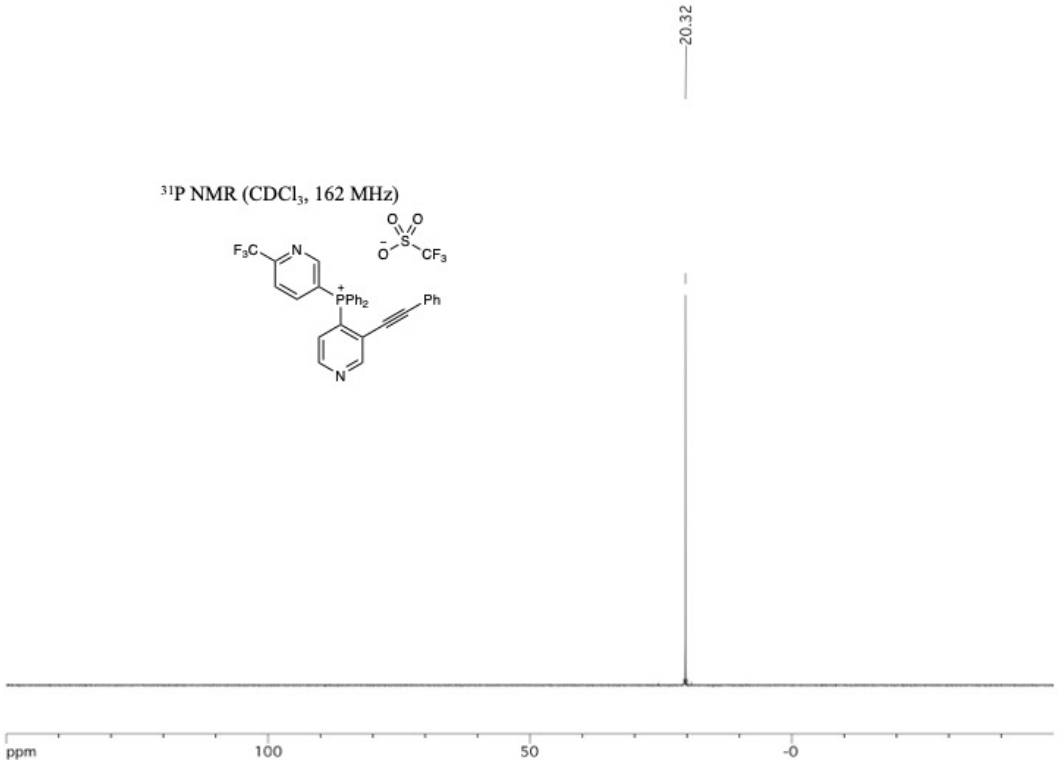


^{13}C NMR ($CDCl_3$, 100 MHz)

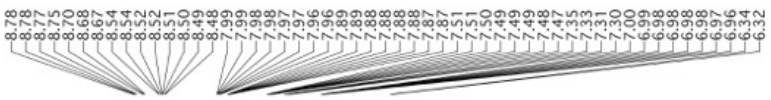




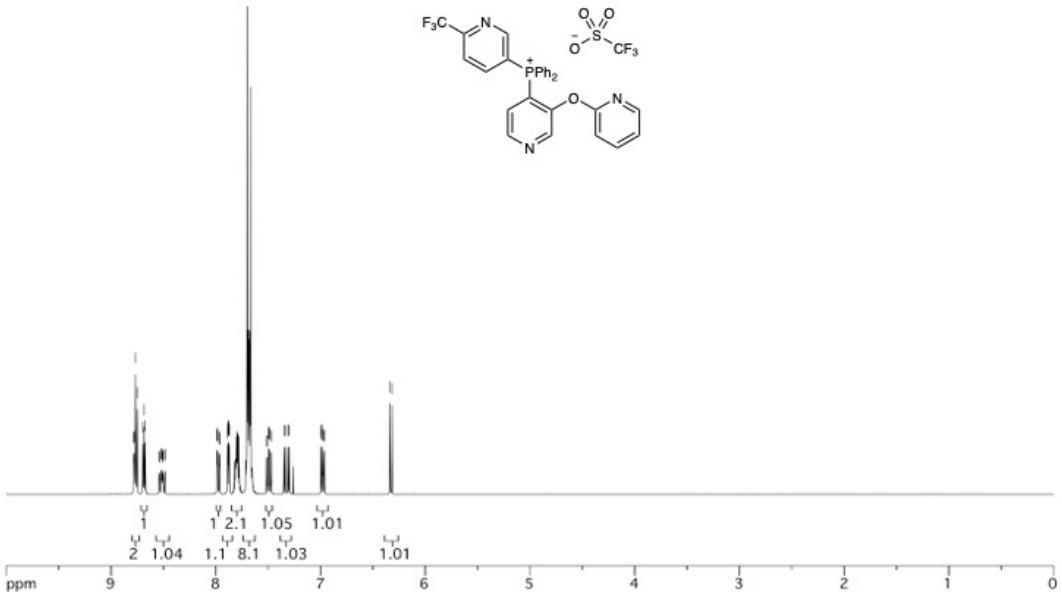
^{19}F NMR ($CDCl_3$, 365 MHz)



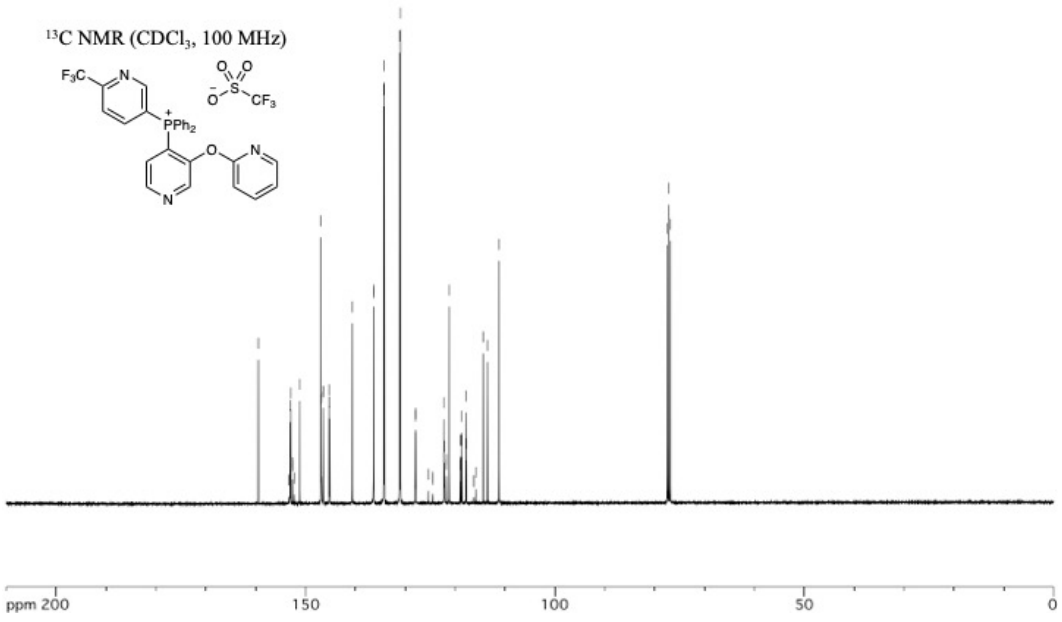
^{31}P NMR ($CDCl_3$, 162 MHz)

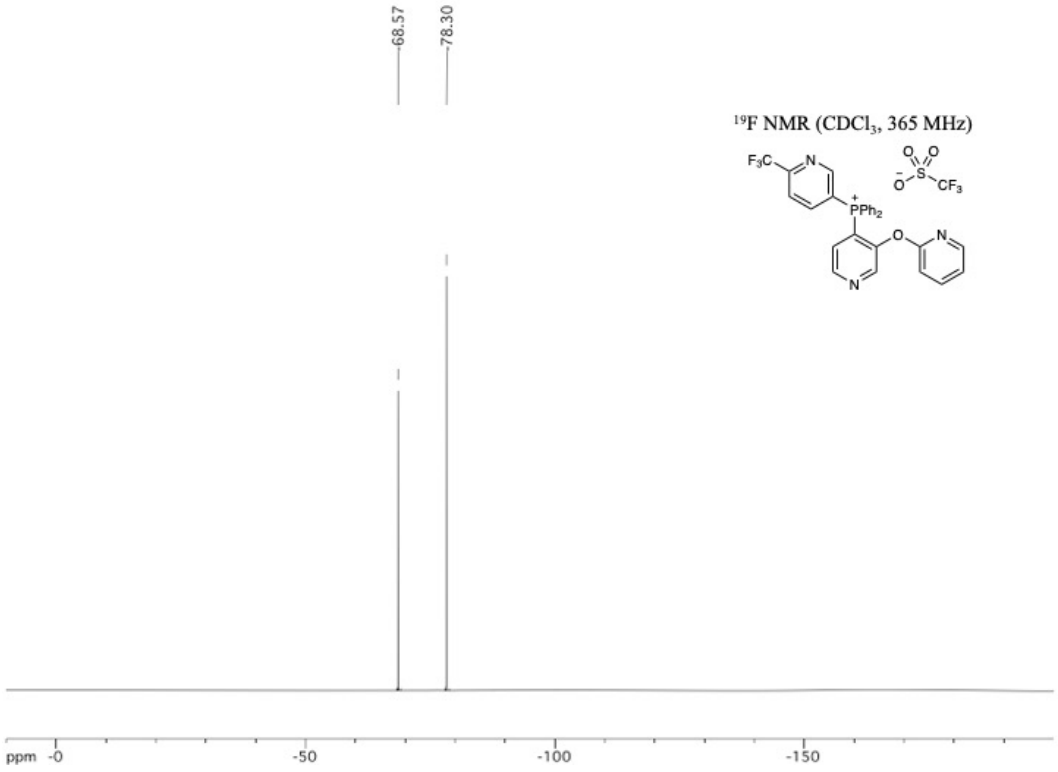


^{1}H NMR ($CDCl_3$, 400 MHz)

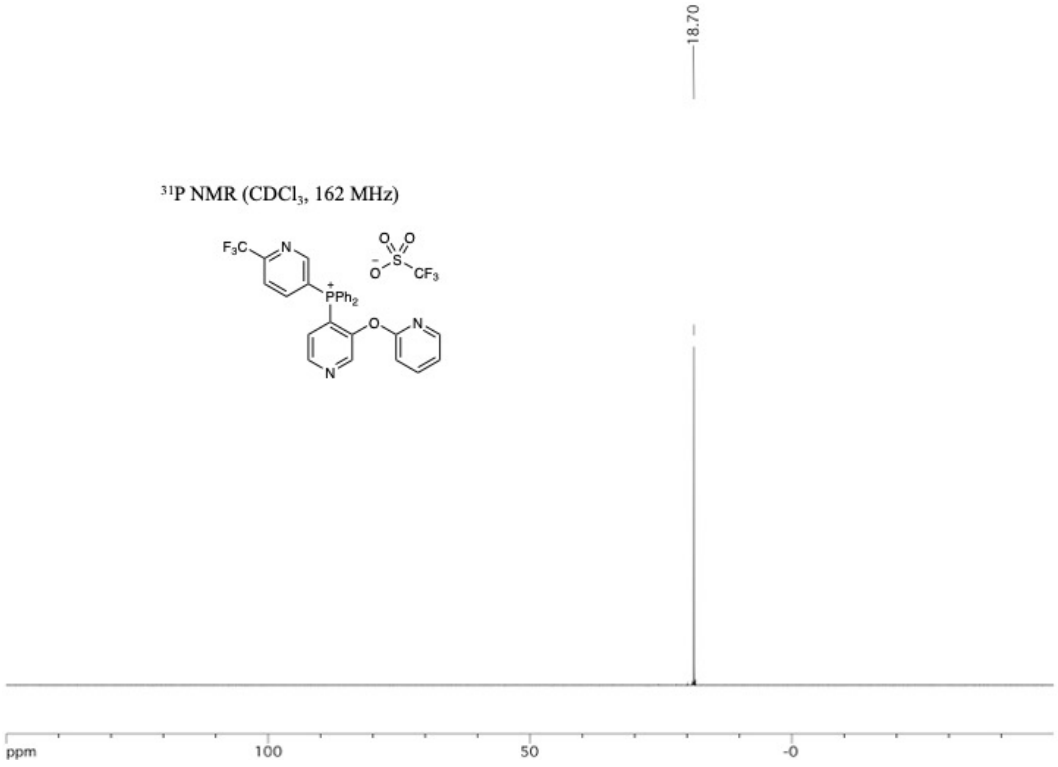


^{13}C NMR ($CDCl_3$, 100 MHz)

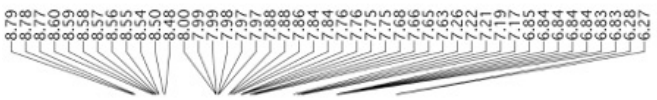




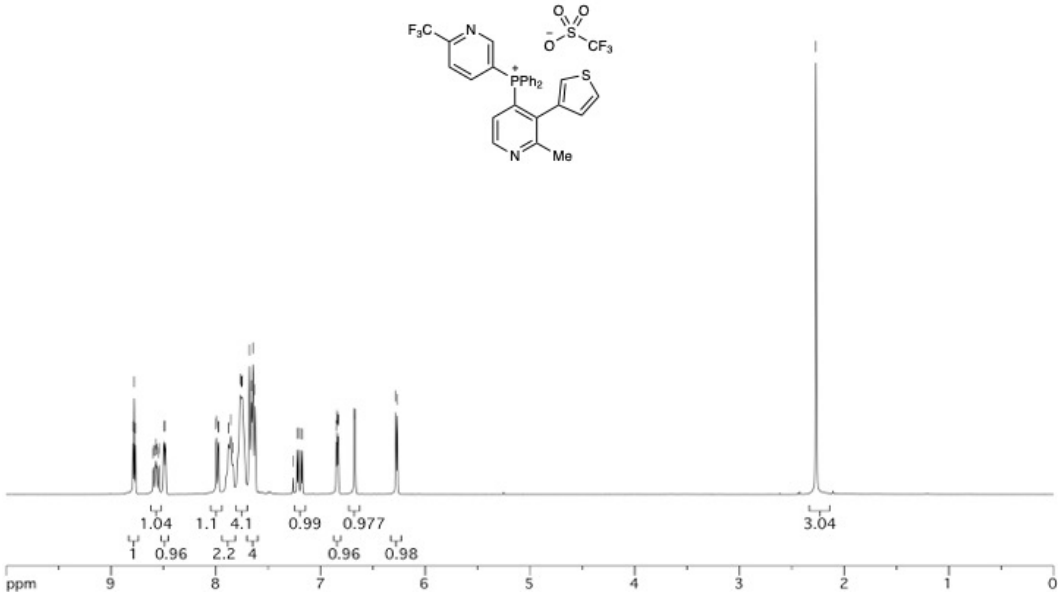
^{19}F NMR ($CDCl_3$, 365 MHz)



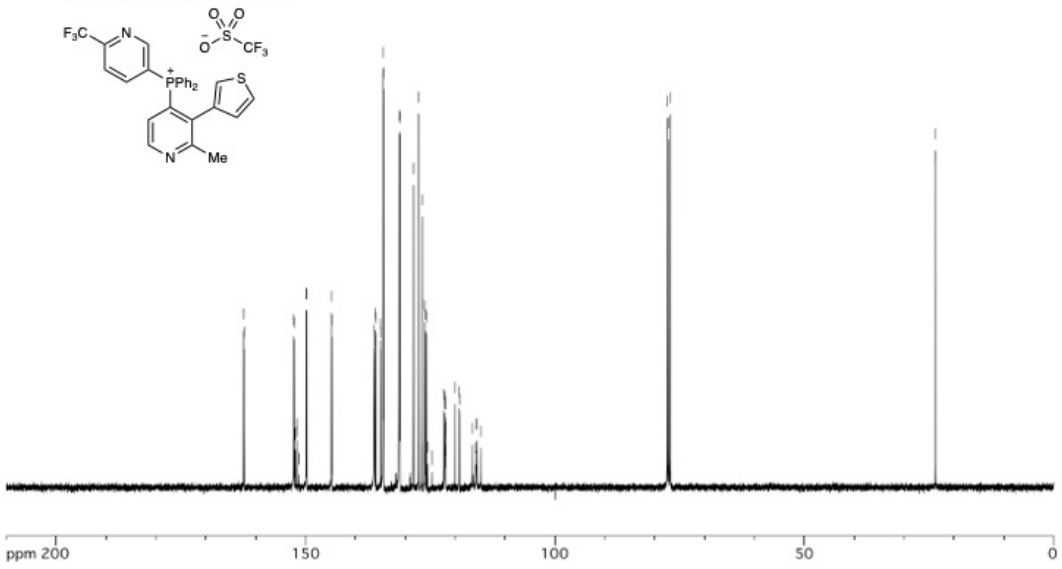
^{31}P NMR ($CDCl_3$, 162 MHz)

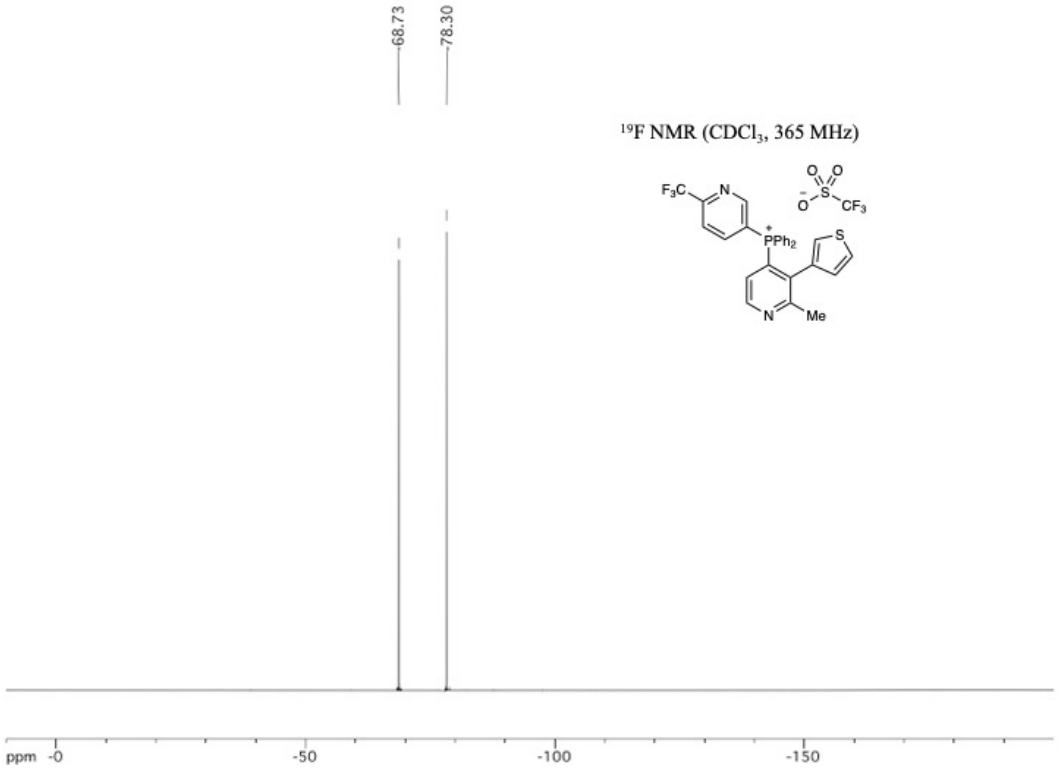


^{1}H NMR ($CDCl_3$, 400 MHz)

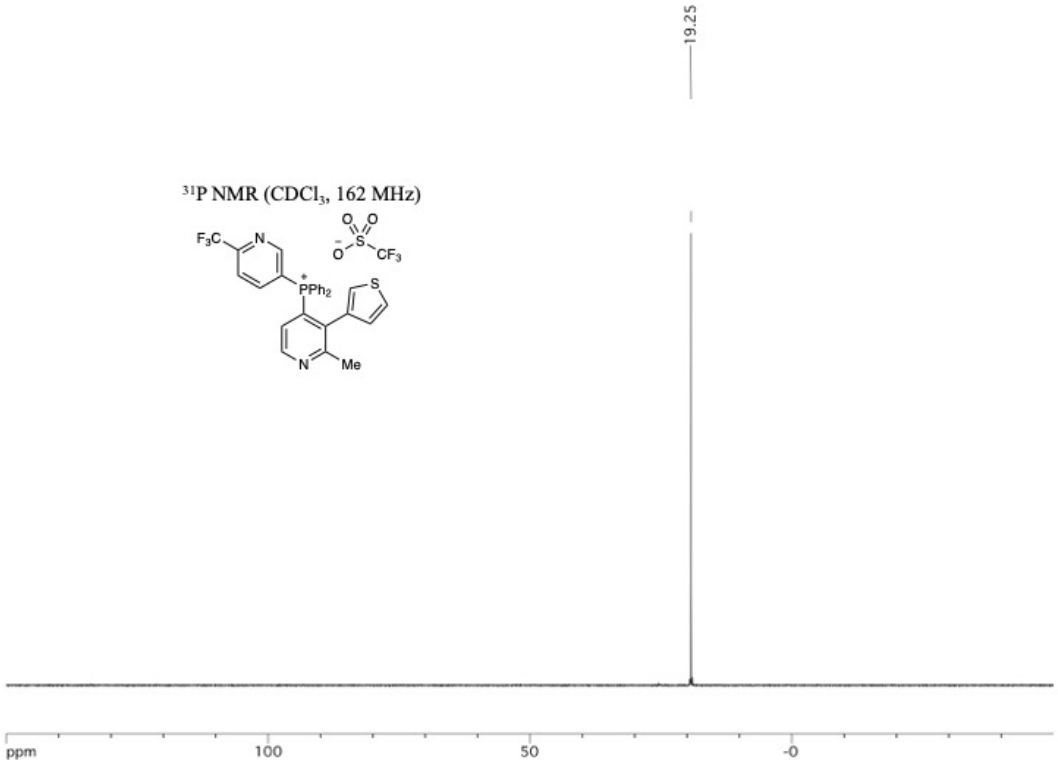


^{13}C NMR ($CDCl_3$, 100 MHz)

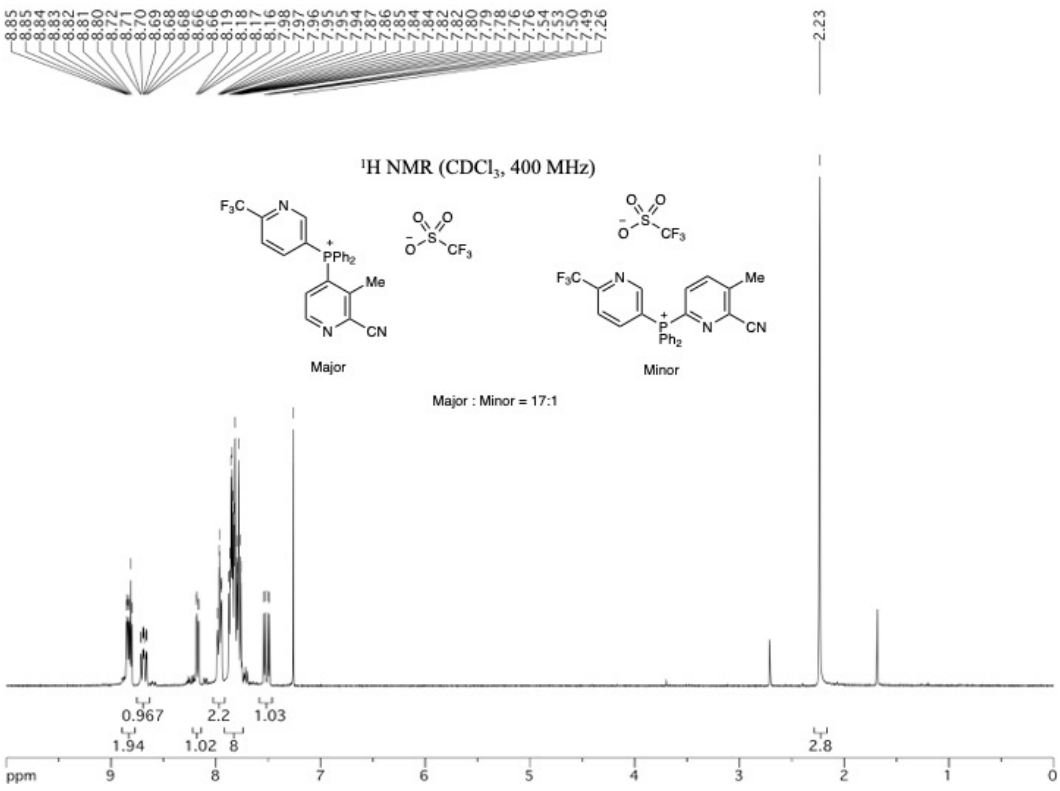


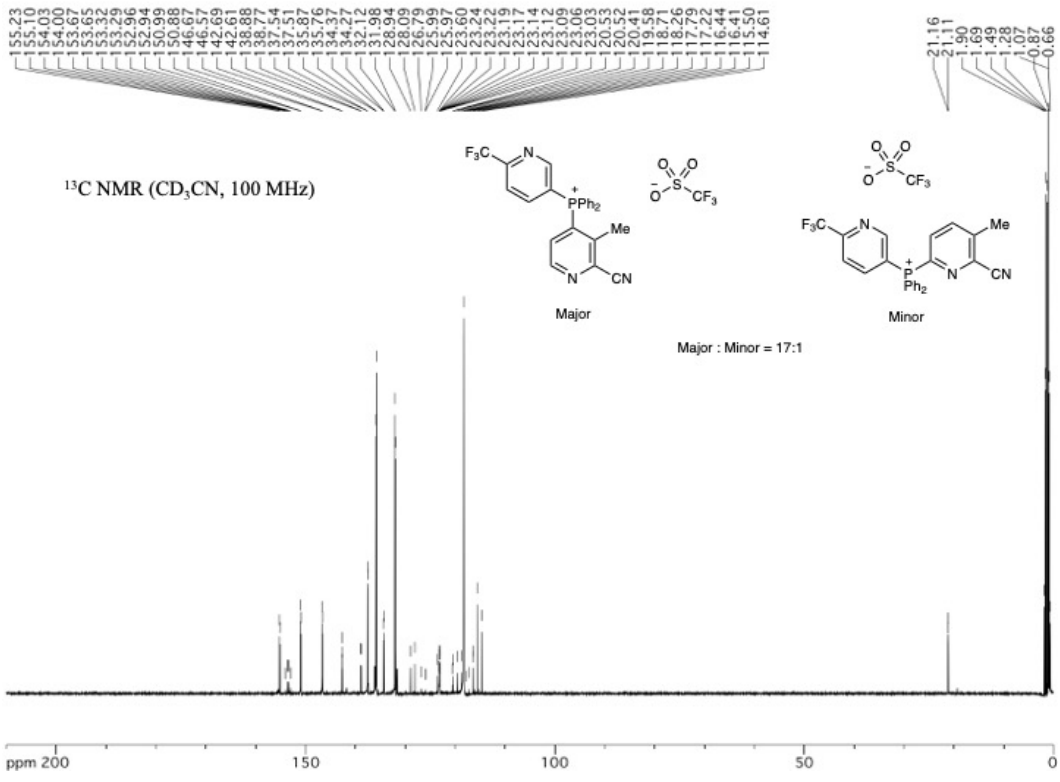


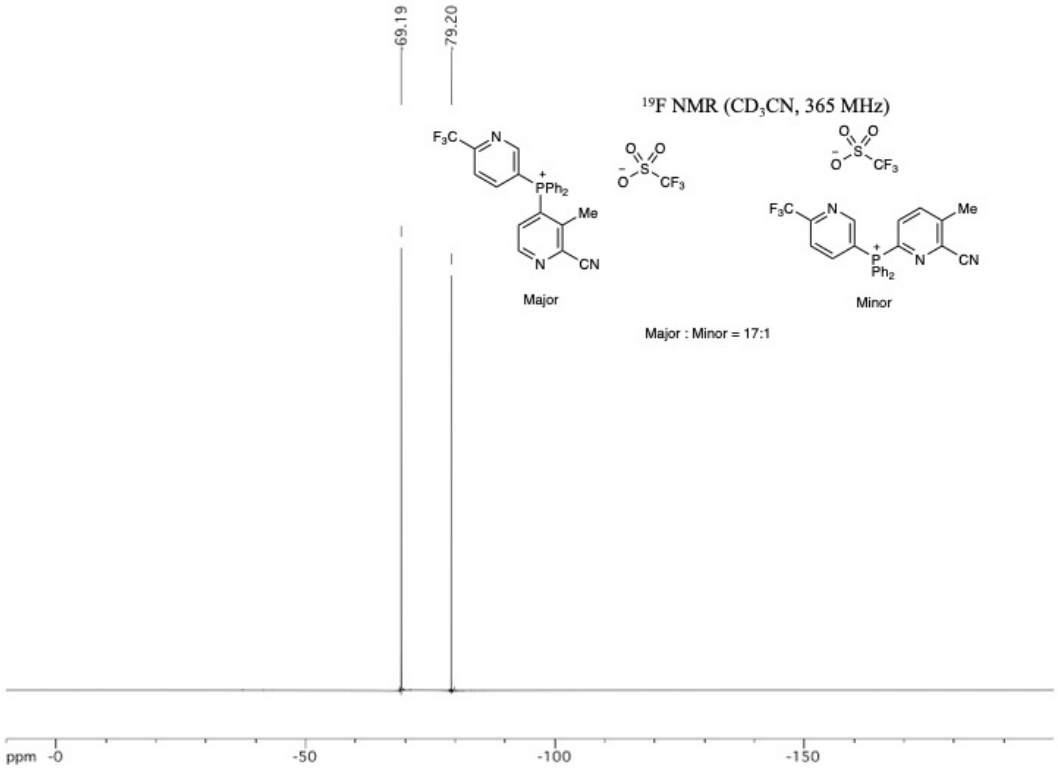
^{19}F NMR ($CDCl_3$, 365 MHz)

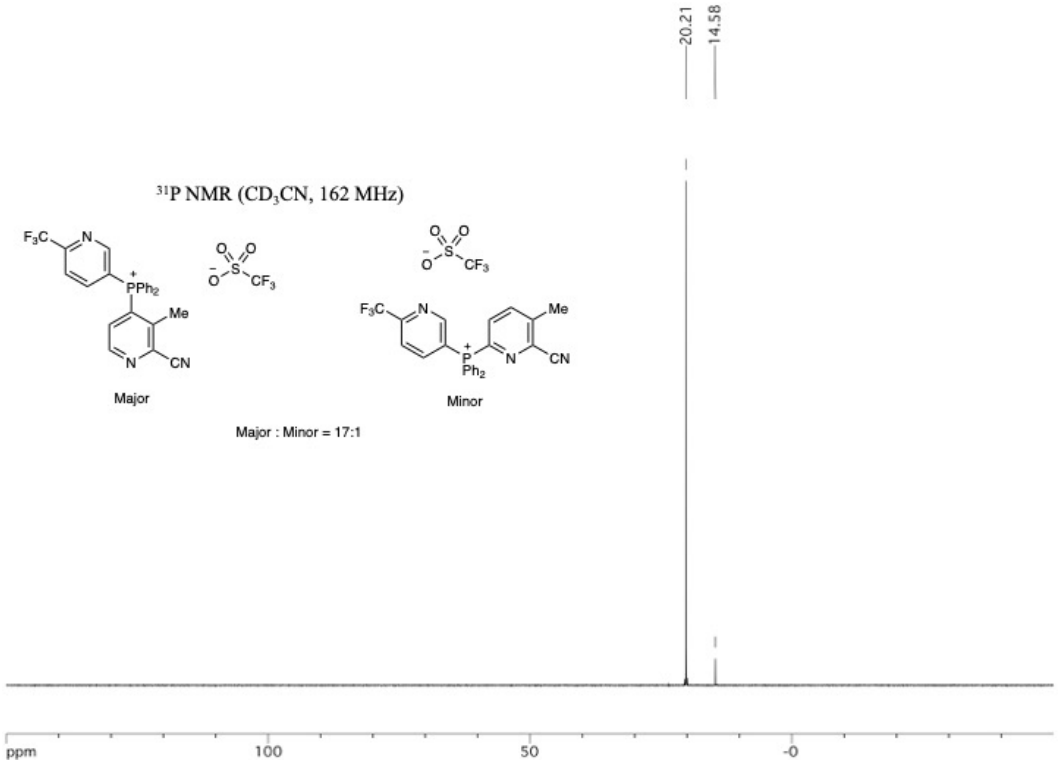


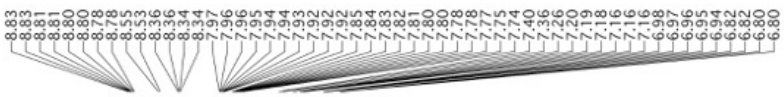
^{31}P NMR ($CDCl_3$, 162 MHz)


8.85 8.85 8.84 8.83 8.82 8.81 8.80 8.72 8.71 8.70 8.69 8.68 8.68 8.66 8.66 8.19 8.18 8.17 8.16 7.98 7.97 7.96 7.95 7.95 7.94 7.87 7.86 7.85 7.84 7.84 7.82 7.82 7.80 7.79 7.78 7.76 7.76 7.54 7.53 7.50 7.49 7.26
2.23
¹H NMR (CDCl₃, 400 MHz)
Major
Minor
Major : Minor = 17:1
0.967
2.2
1.03
1.94
1.02
8
2.8
ppm

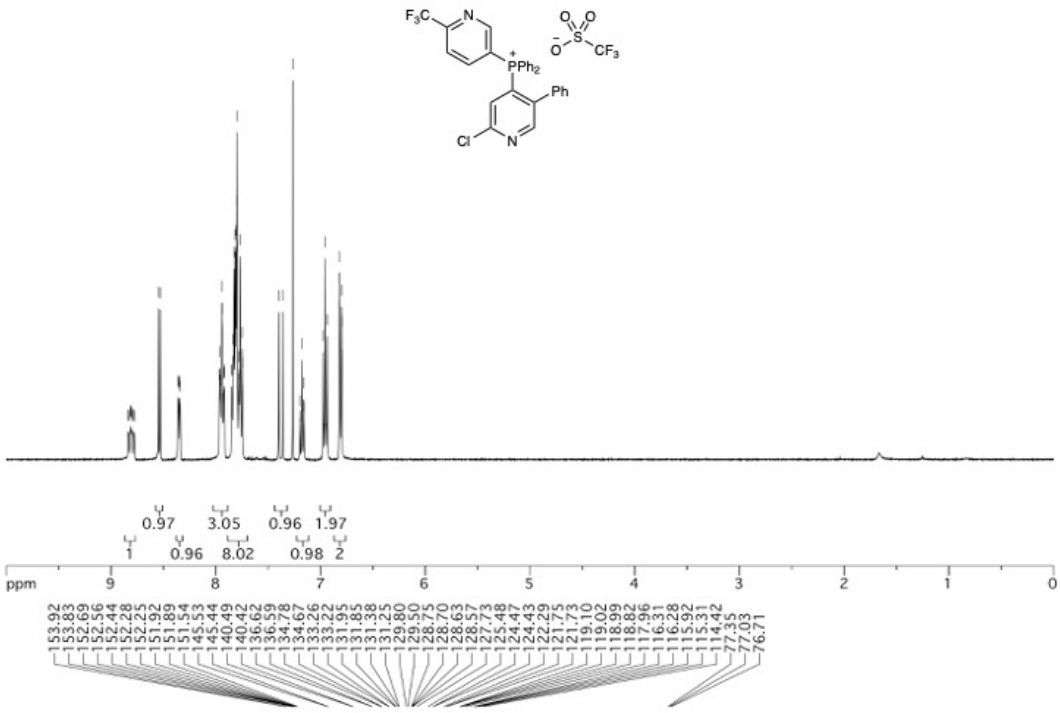

155.23 155.10 154.03 154.00 153.67 153.65 153.32 153.29 152.96 152.94 150.99 150.88 146.67 146.57 142.69 142.61 138.88 138.77 137.54 137.51 135.87 135.76 134.37 134.27 132.12 131.98 128.94 128.09 126.79 125.99 125.97 123.60 123.24 123.22 123.19 123.17 123.14 123.12 123.09 123.06 123.03 120.53 120.52 120.41 119.58 118.71 118.26 117.79 117.22 116.44 116.41 115.50 114.61
21.16 21.11 1.90 1.69 1.49 1.28 1.07 0.87 0.66
¹³C NMR (CD₃CN, 100 MHz)
Major
Minor
Major : Minor = 17:1
ppm 200
150
100
50
0


69.19
79.20
^{19}F NMR (CD_3CN, 365 MHz)
Major
Minor
Major : Minor = 17:1
ppm -0
-50
-100
-150

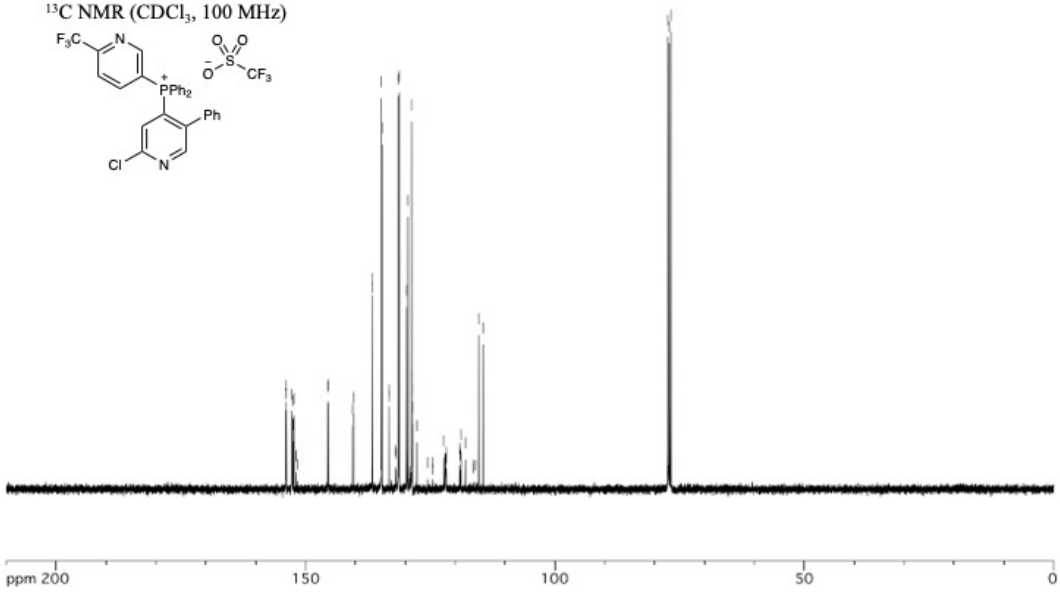

20.21
14.58
^{31}P NMR (CD_3CN, 162 MHz)
Major
Minor
Major : Minor = 17:1
ppm
100
50
-0

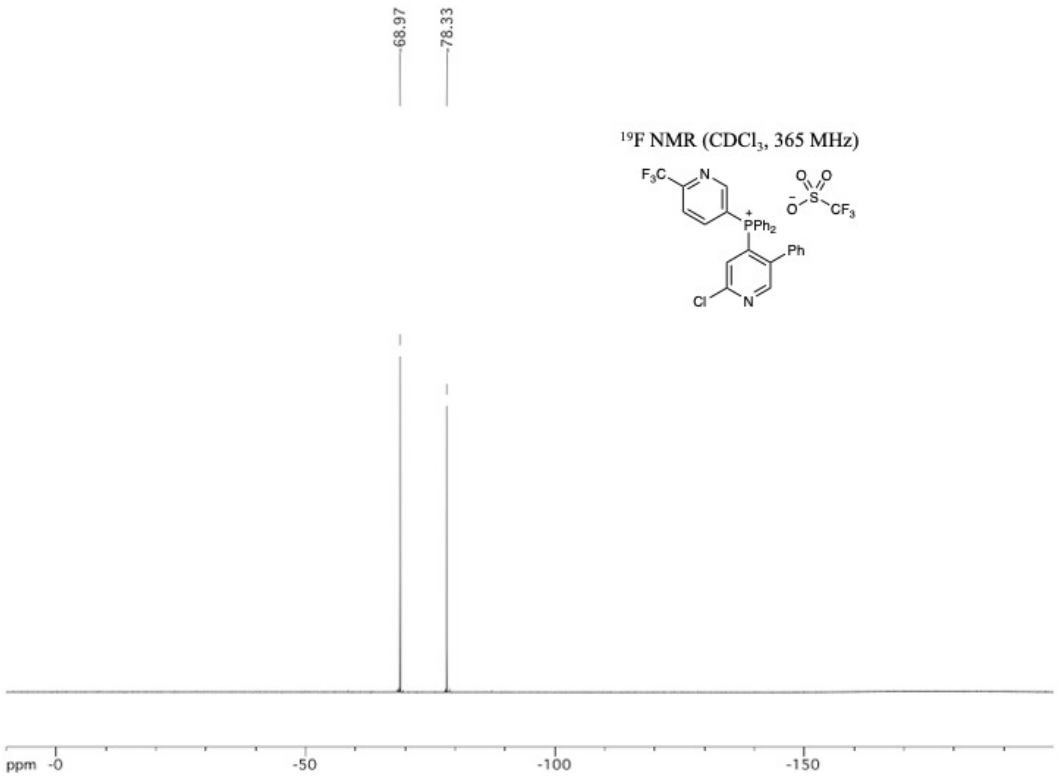


^{1}H NMR ($CDCl_3$, 400 MHz)

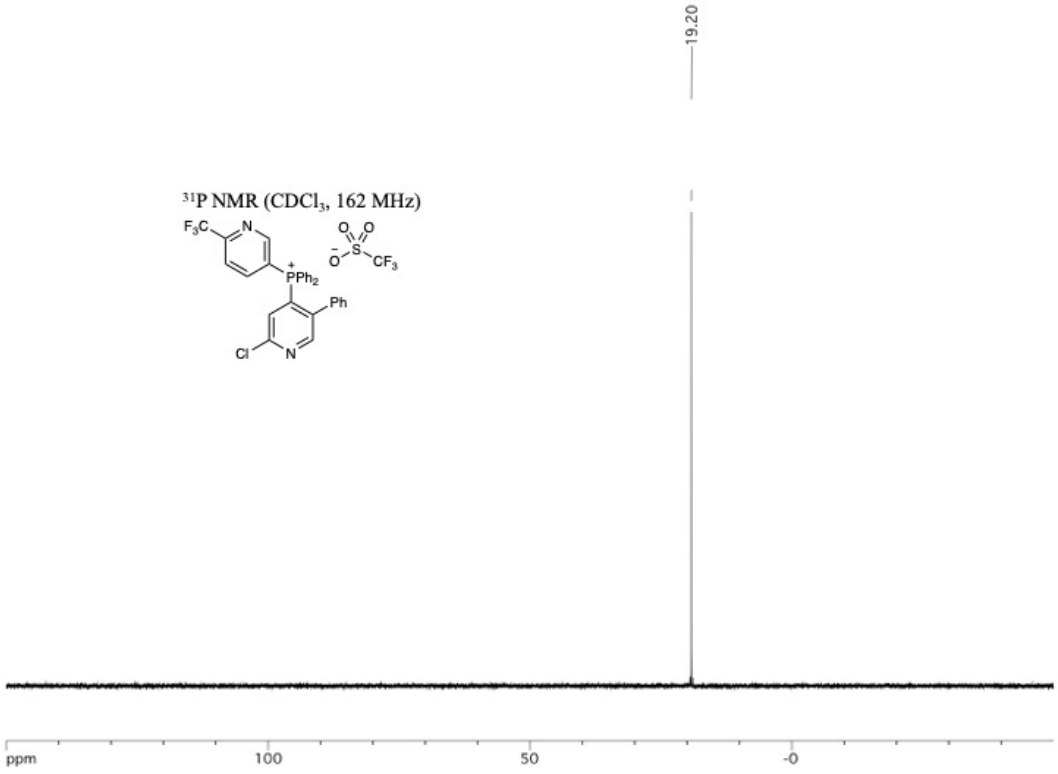


^{13}C NMR ($CDCl_3$, 100 MHz)

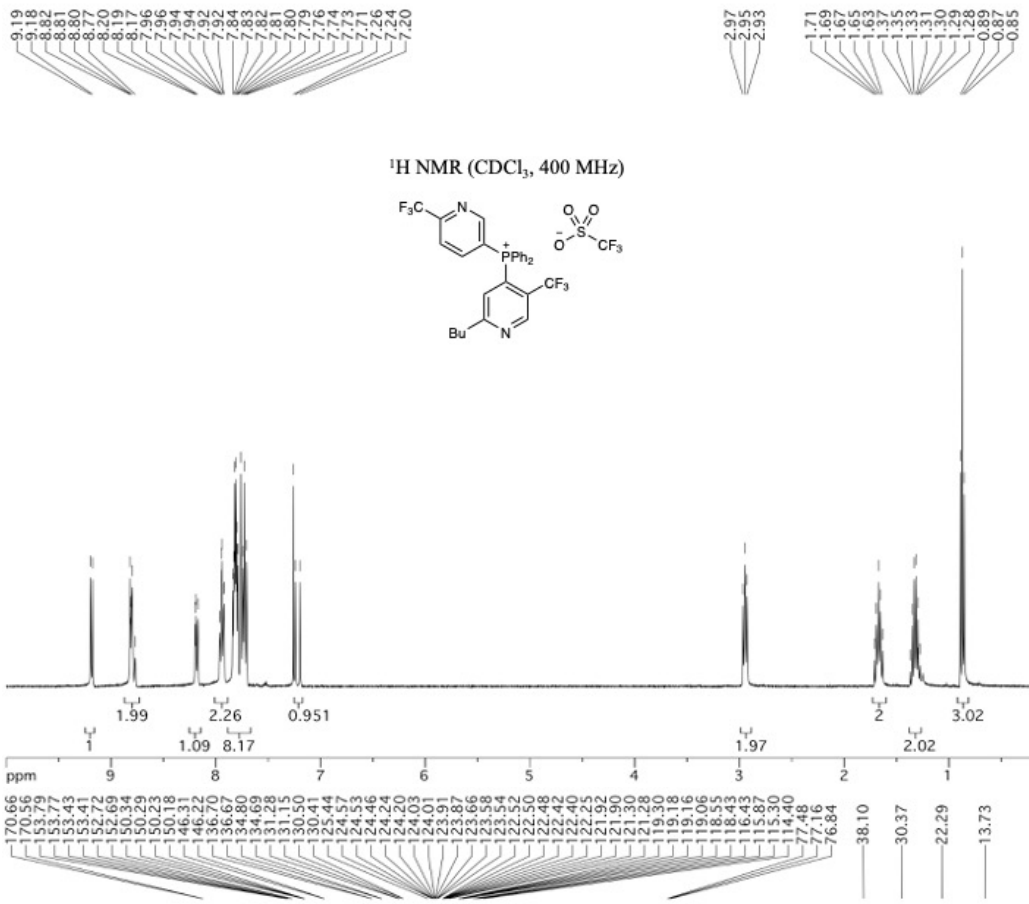


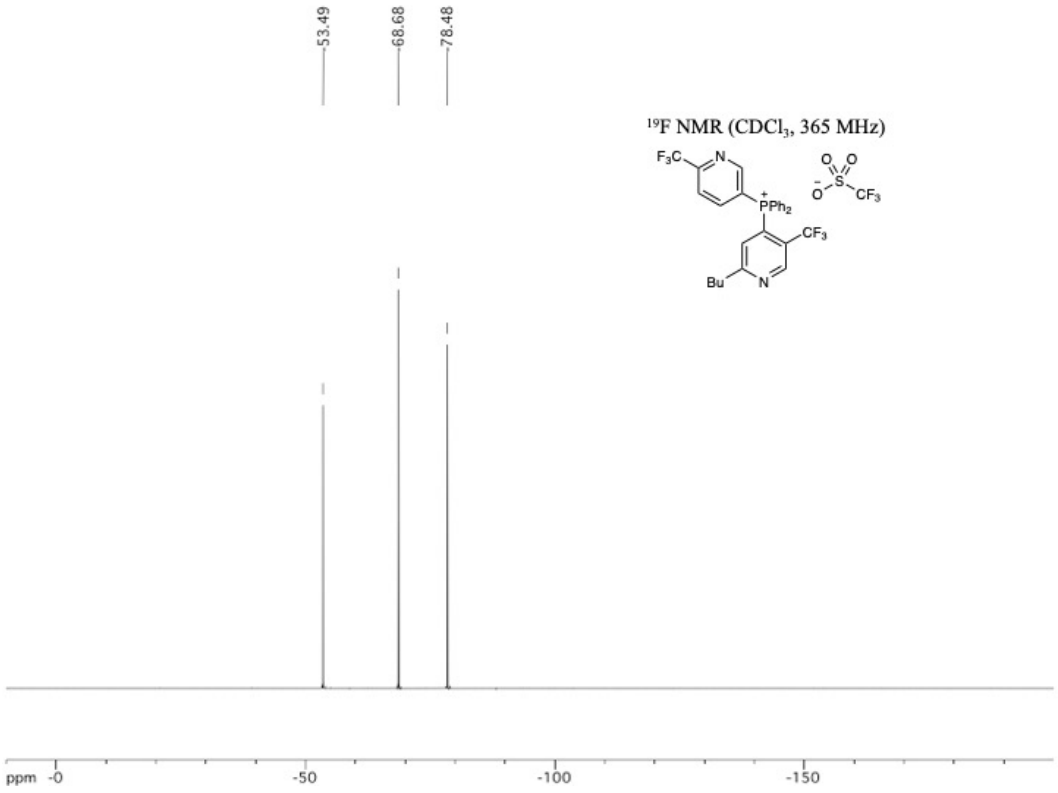


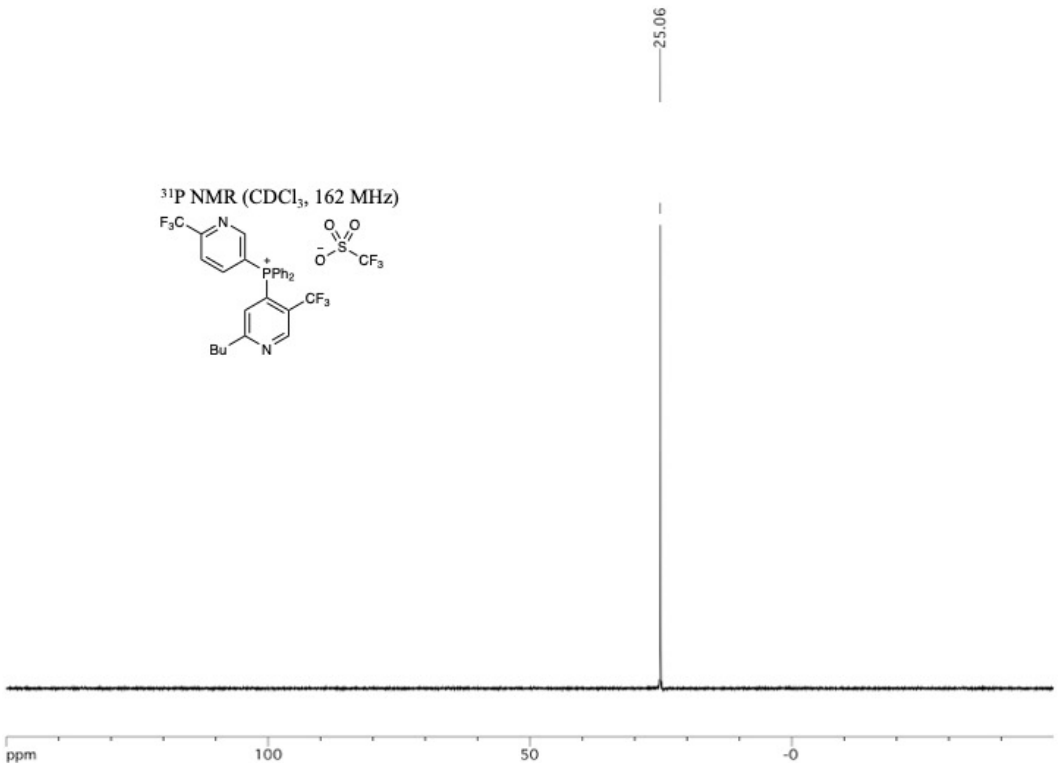
^{19}F NMR ($CDCl_3$, 365 MHz)

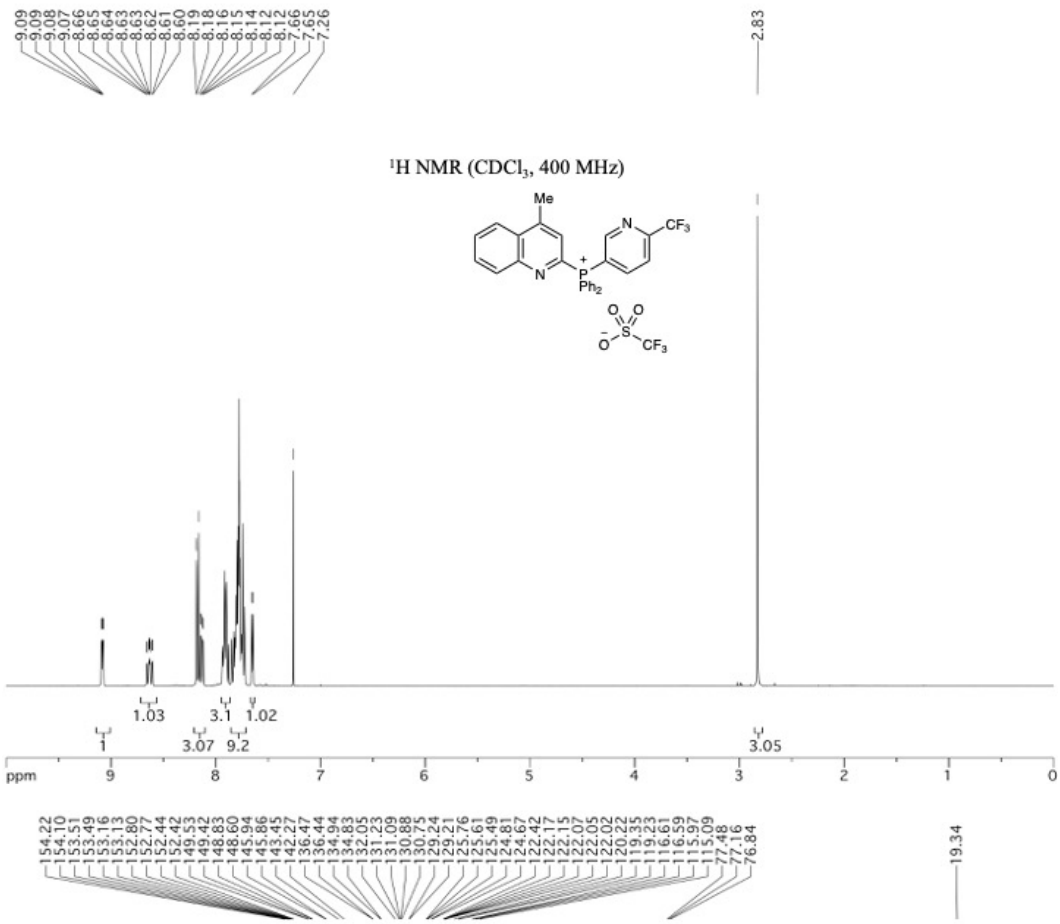


^{31}P NMR ($CDCl_3$, 162 MHz)

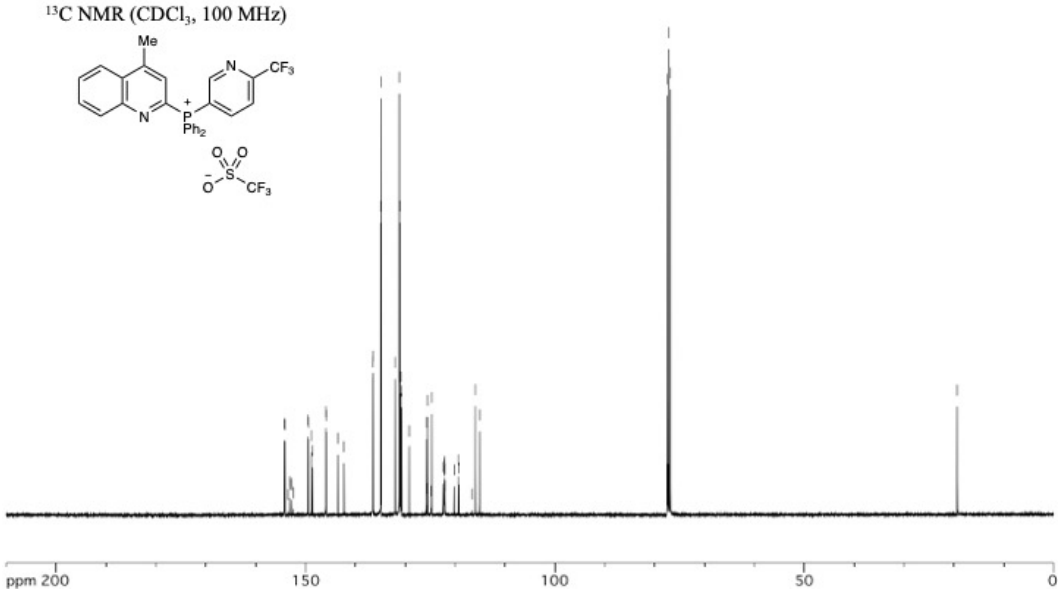

9.19
9.18
8.82
8.81
8.80
8.77
8.20
8.19
8.17
8.17
7.96
7.96
7.94
7.94
7.92
7.92
7.84
7.83
7.82
7.81
7.80
7.79
7.76
7.74
7.73
7.71
7.26
7.24
7.20
2.97
2.95
2.93
1.71
1.69
1.67
1.65
1.63
1.37
1.35
1.33
1.31
1.30
1.29
1.28
0.89
0.87
0.85
1H NMR (CDCl3, 400 MHz)
F3C
N
PPh2
CF3
Bu
N
O
O
O
S
CF3
1.99
2.26
0.951
2
3.02
1
1.09
8.17
1.97
2.02
ppm
9
8
7
6
5
4
3
2
1
0
170.66
170.56
153.79
153.77
153.43
153.41
152.72
152.69
150.34
150.29
150.23
150.18
146.31
146.22
136.70
136.67
134.80
134.69
131.28
131.15
130.50
130.41
124.44
124.57
124.53
124.46
124.24
124.20
124.01
124.03
123.91
123.87
123.66
123.58
123.54
122.52
122.50
122.48
122.42
122.40
122.25
121.92
121.90
121.30
121.28
119.30
119.18
119.16
119.06
118.55
118.43
116.43
115.87
115.30
114.40
77.48
77.16
76.84
38.10
30.37
22.29
13.73
13C NMR (CDCl3, 100 MHz)
F3C
N
PPh2
CF3
Bu
N
O
O
O
S
CF3
ppm 200
150
100
50
0

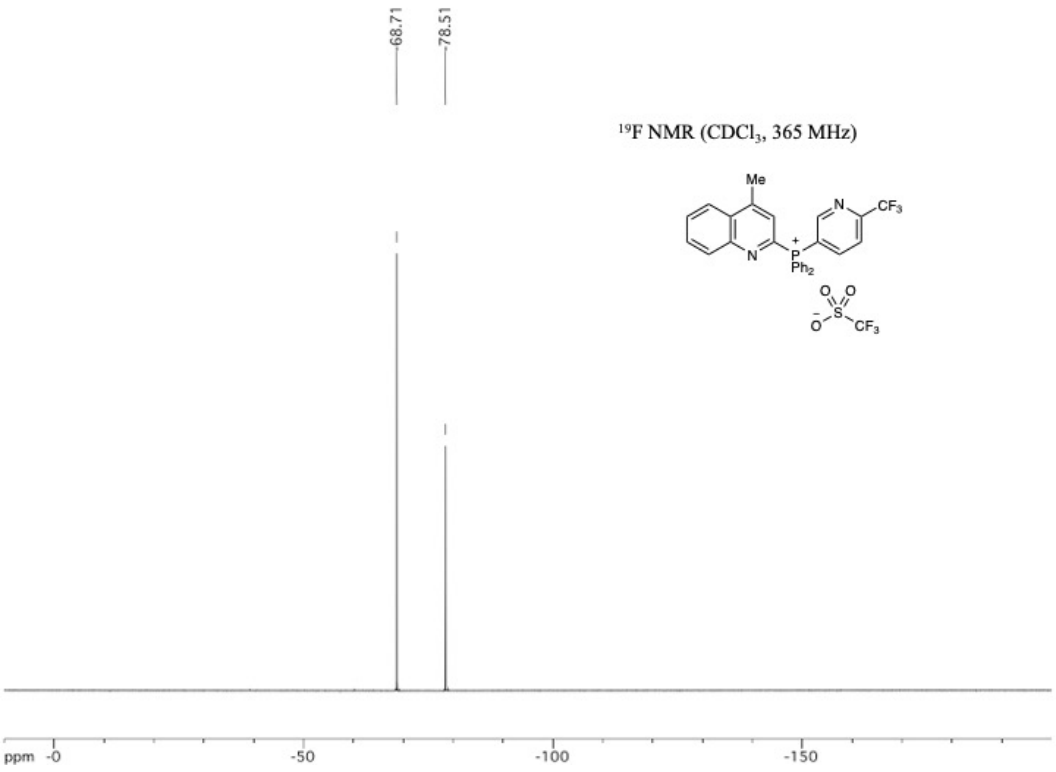

53.49
68.68
78.48
^{19}F NMR ($CDCl_3$, 365 MHz)
ppm -0
-50
-100
-150


25.06
^{31}P NMR ($CDCl_3$, 162 MHz)
ppm
100
50
-0

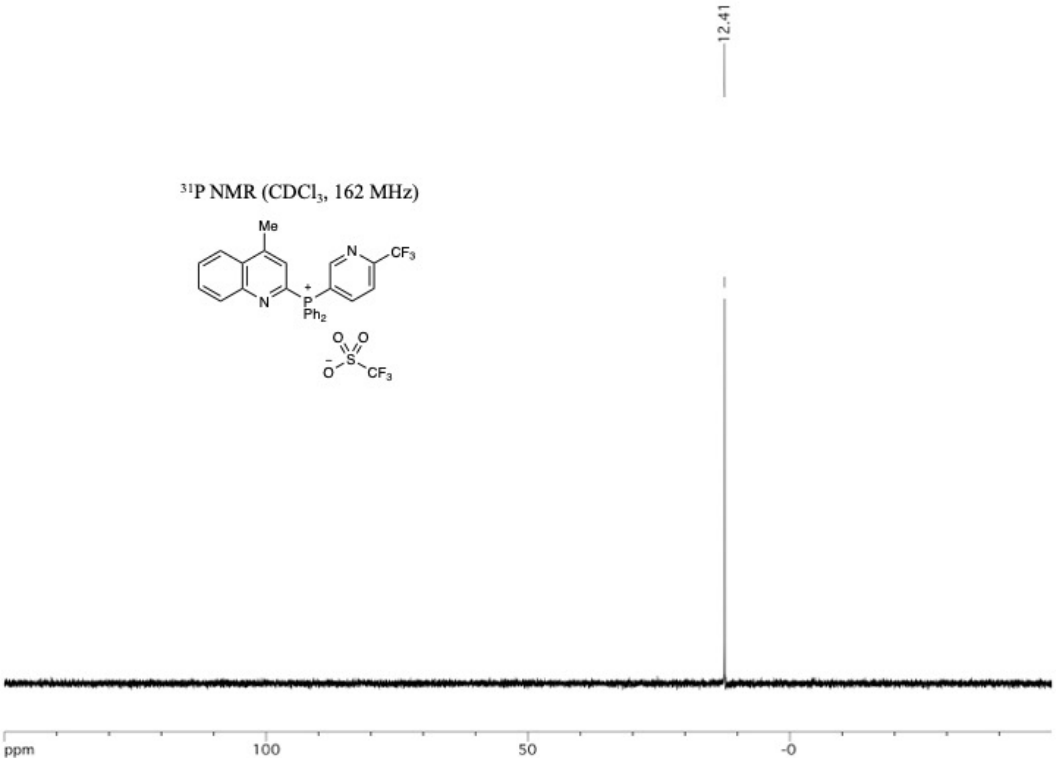

9.09
9.09
9.08
9.07
8.66
8.65
8.64
8.63
8.63
8.62
8.61
8.60
8.19
8.18
8.16
8.15
8.14
8.12
8.12
7.66
7.65
7.26
2.83
1H NMR (CDCl3, 400 MHz)
Me
N
CF3
P
Ph2
O
O
O
S
CF3
1.03
3.1
1.02
1
3.07
9.2
3.05
ppm
9
8
7
6
5
4
3
2
1
0

154.22
154.10
153.51
153.49
153.16
153.13
152.80
152.77
152.44
152.42
149.53
149.42
148.83
148.60
145.94
145.86
143.45
142.27
136.47
136.44
134.94
134.83
132.05
131.23
131.09
130.88
130.75
129.24
129.21
125.76
125.61
125.49
124.81
124.67
122.42
122.17
122.15
122.07
122.05
122.02
122.02
119.35
119.23
116.61
116.59
115.97
115.09
77.48
77.16
76.84
19.34

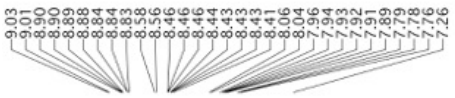

13C NMR (CDCl3, 100 MHz)
Me
N
CF3
P
Ph2
O
O
O
S
CF3
ppm 200
150
100
50
0



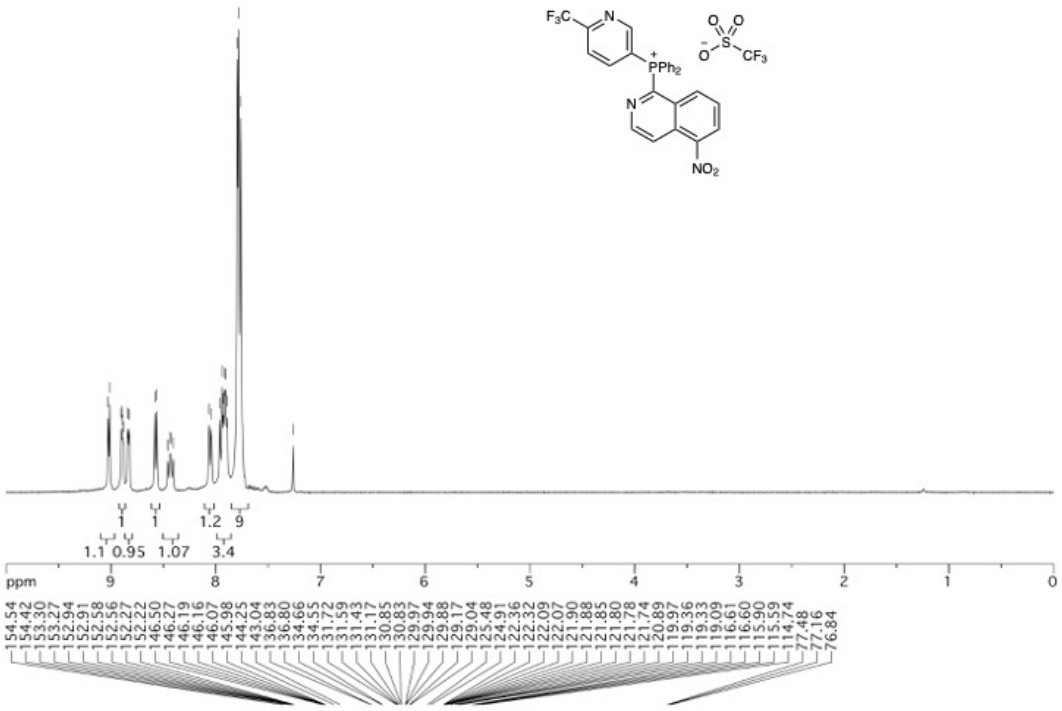
^{19}F NMR ($CDCl_3$, 365 MHz)



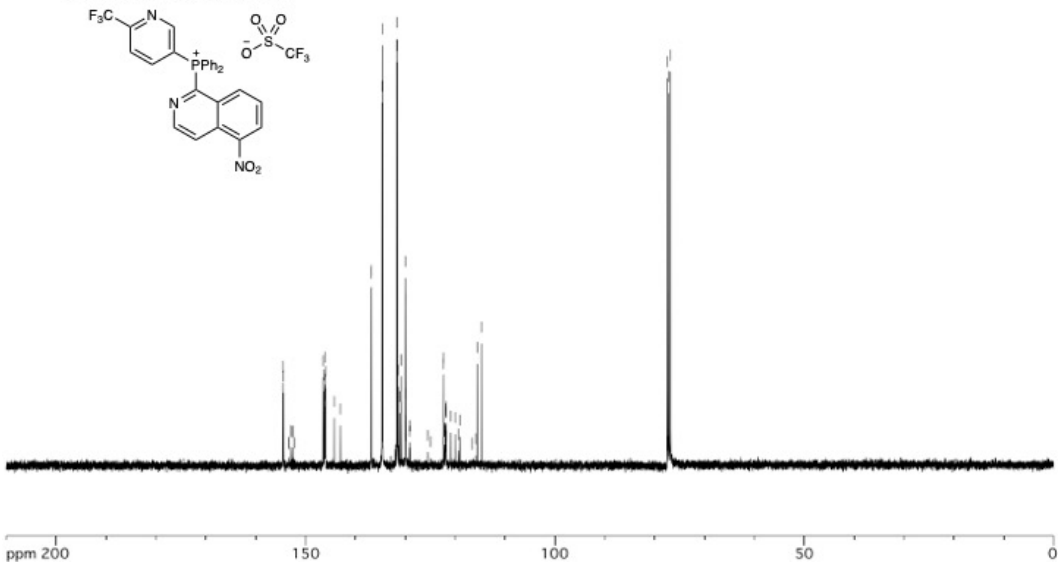
^{31}P NMR ($CDCl_3$, 162 MHz)

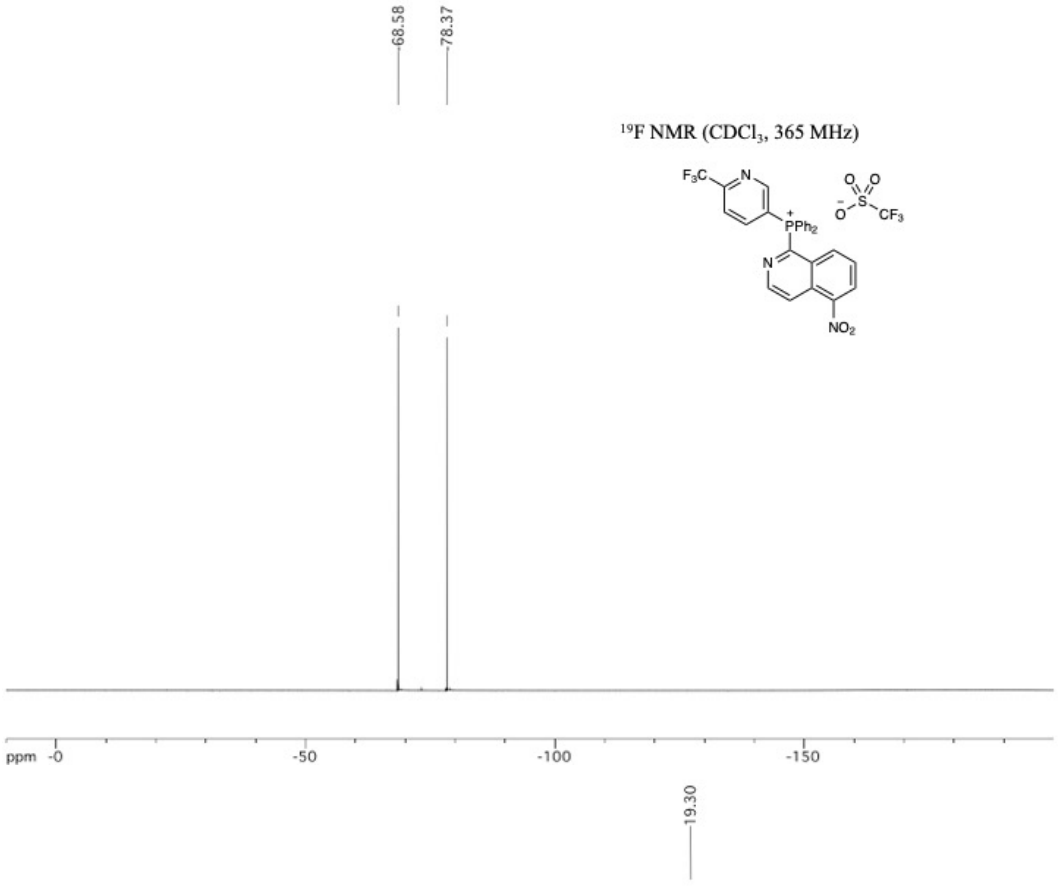


^{1}H NMR ($CDCl_3$, 400 MHz)

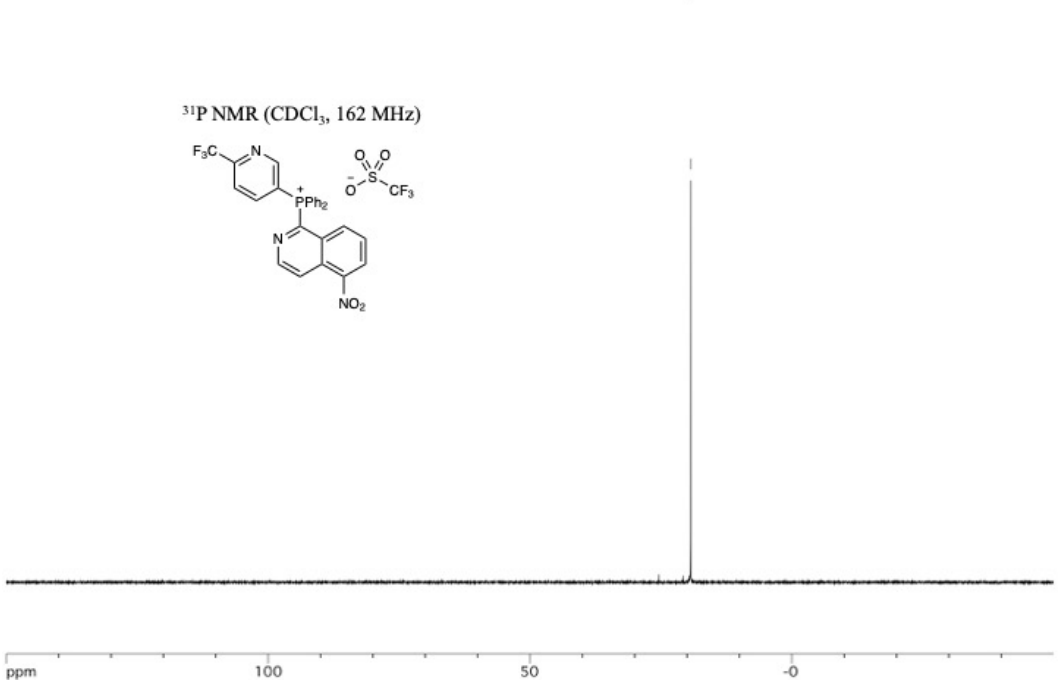


^{13}C NMR ($CDCl_3$, 100 MHz)



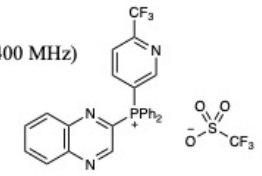


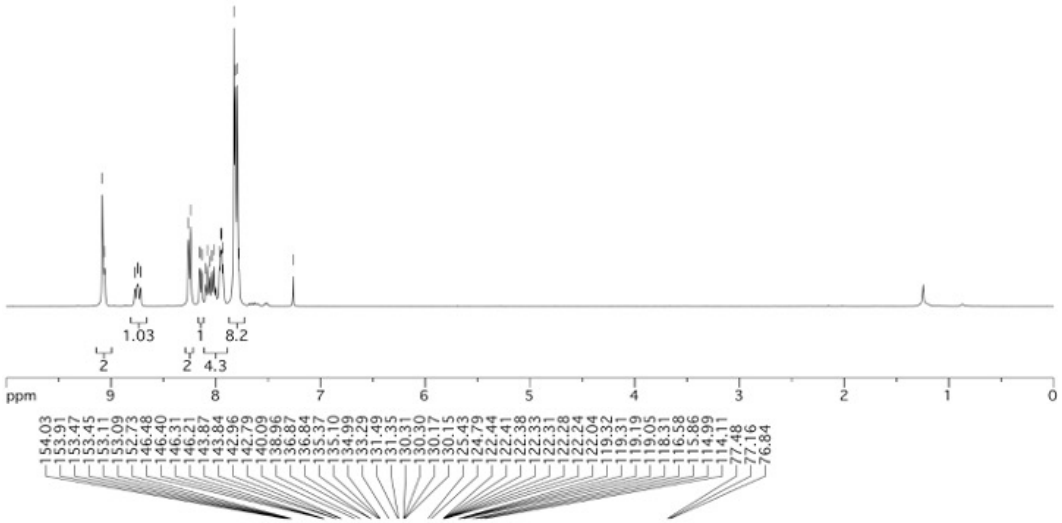
^{19}F NMR ($CDCl_3$, 365 MHz)



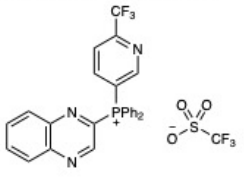
^{31}P NMR ($CDCl_3$, 162 MHz)

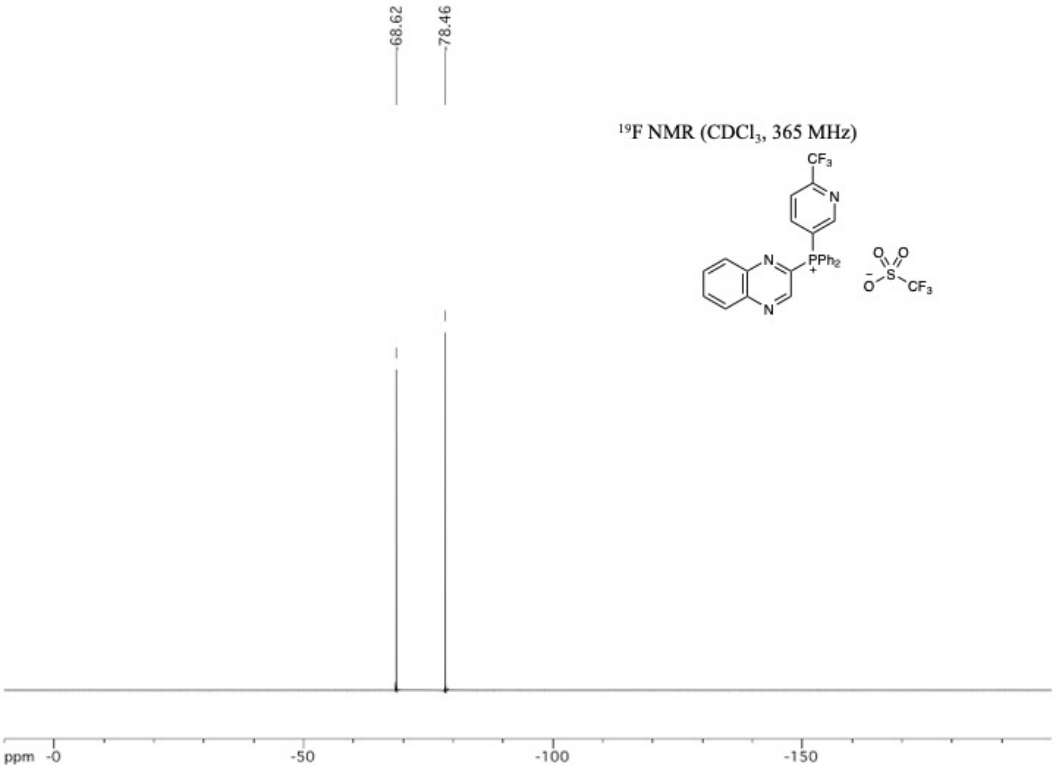
^{1}H NMR ($CDCl_3$, 400 MHz)



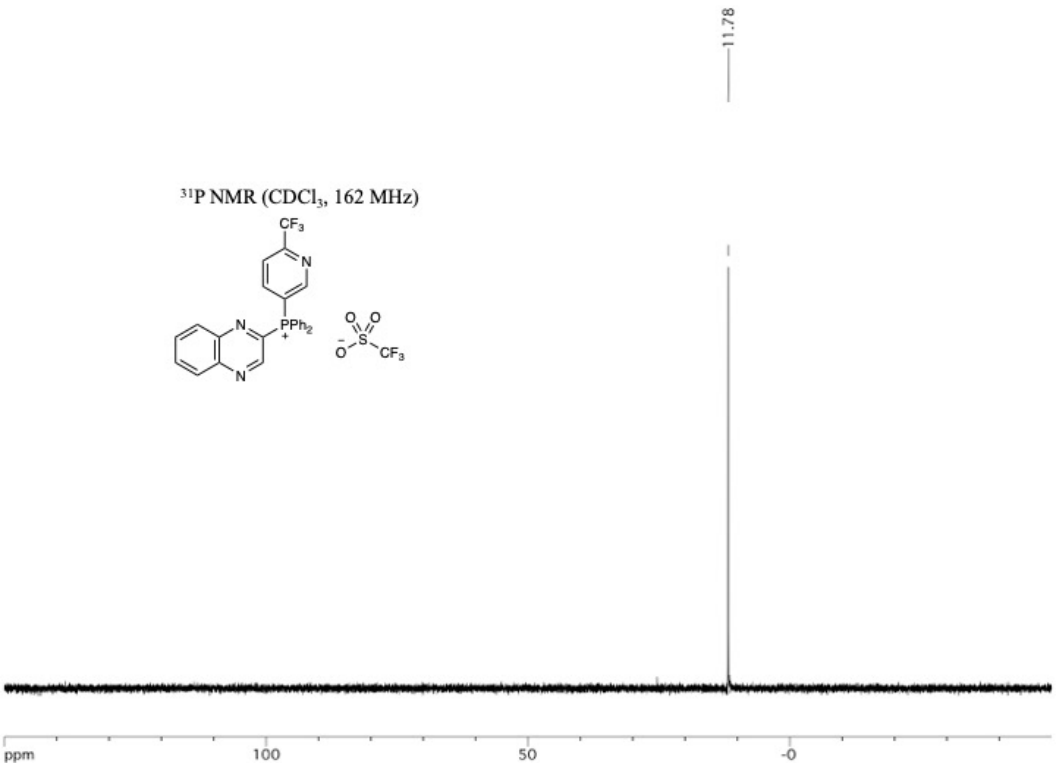


^{13}C NMR ($CDCl_3$, 100 MHz)

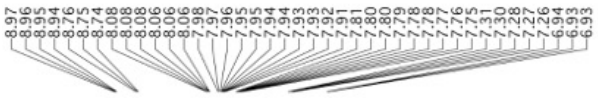




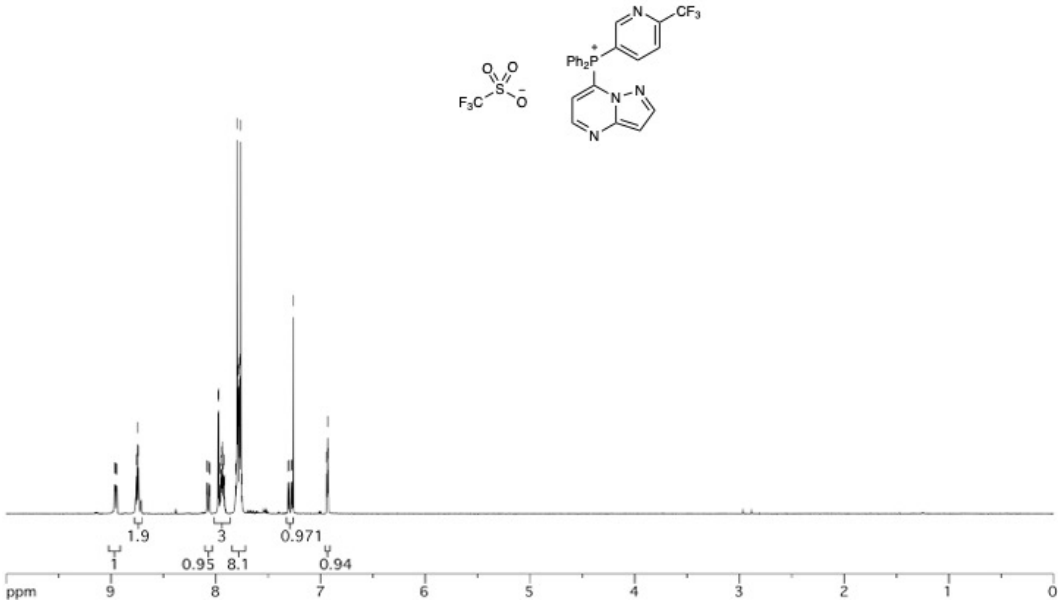
^{19}F NMR ($CDCl_3$, 365 MHz)



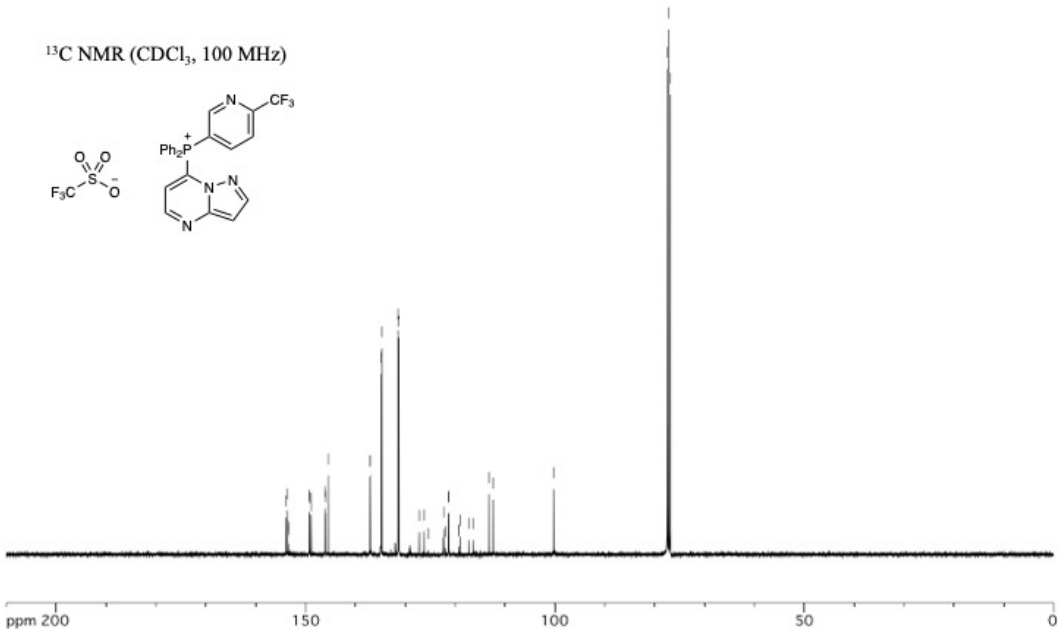
^{31}P NMR ($CDCl_3$, 162 MHz)

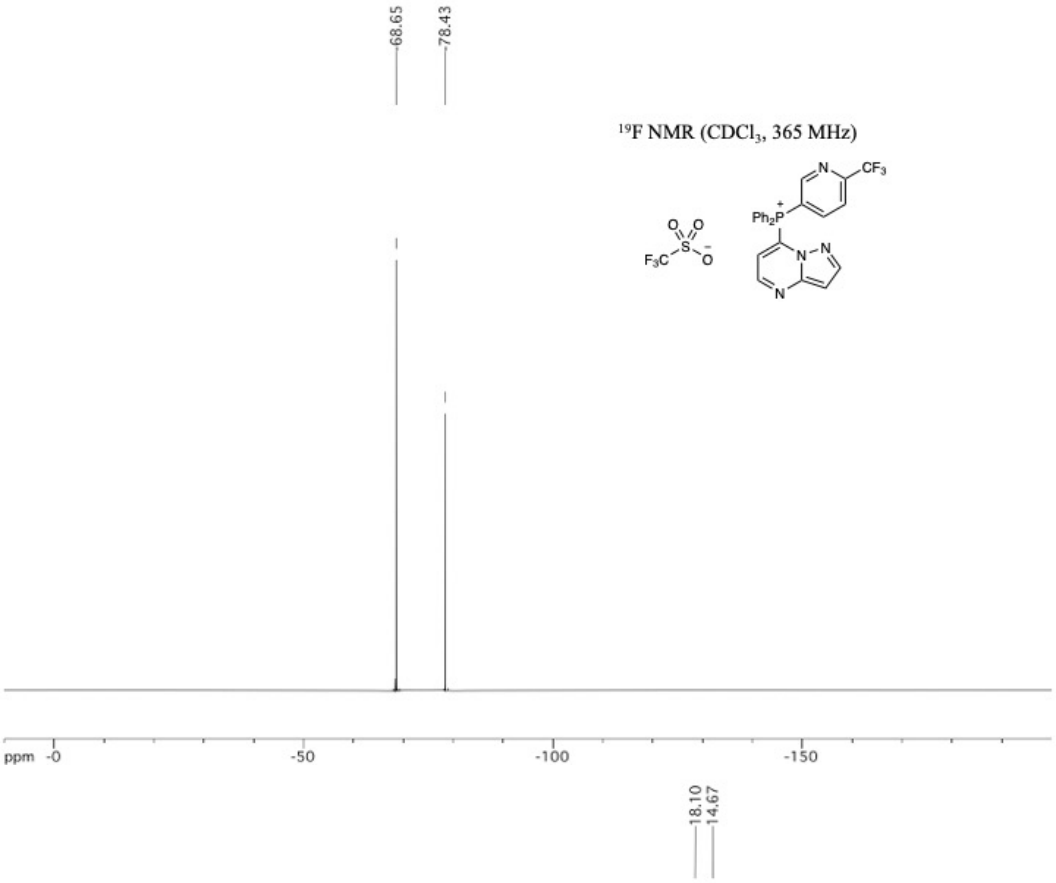


^{1}H NMR ($CDCl_3$, 400 MHz)

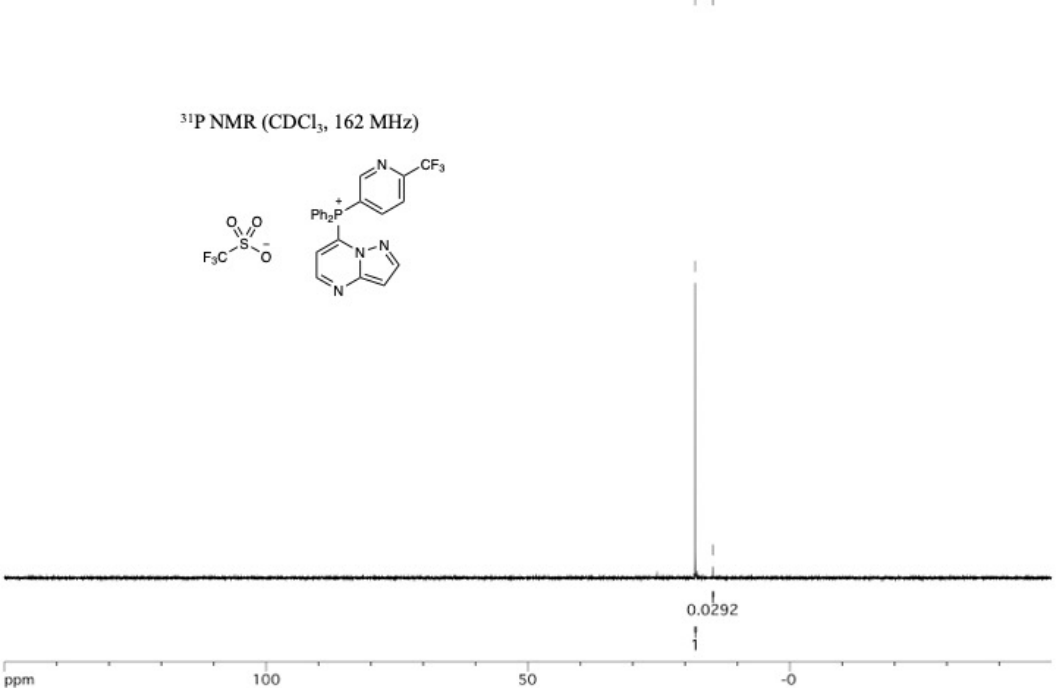


^{13}C NMR ($CDCl_3$, 100 MHz)

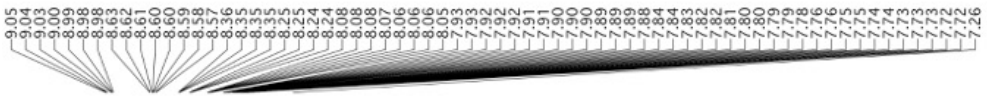




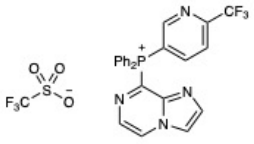
^{19}F NMR ($CDCl_3$, 365 MHz)

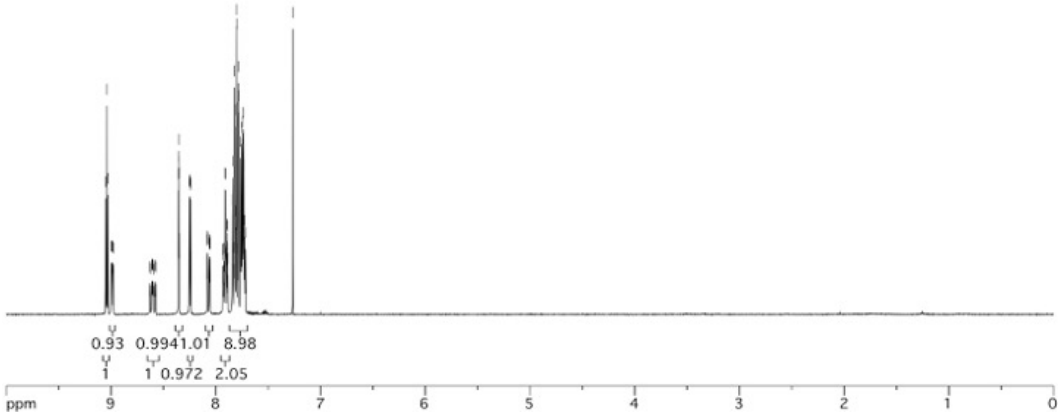


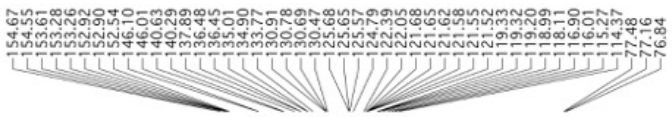
^{31}P NMR ($CDCl_3$, 162 MHz)



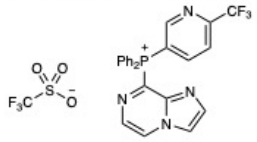
^{1}H NMR ($CDCl_3$, 400 MHz)



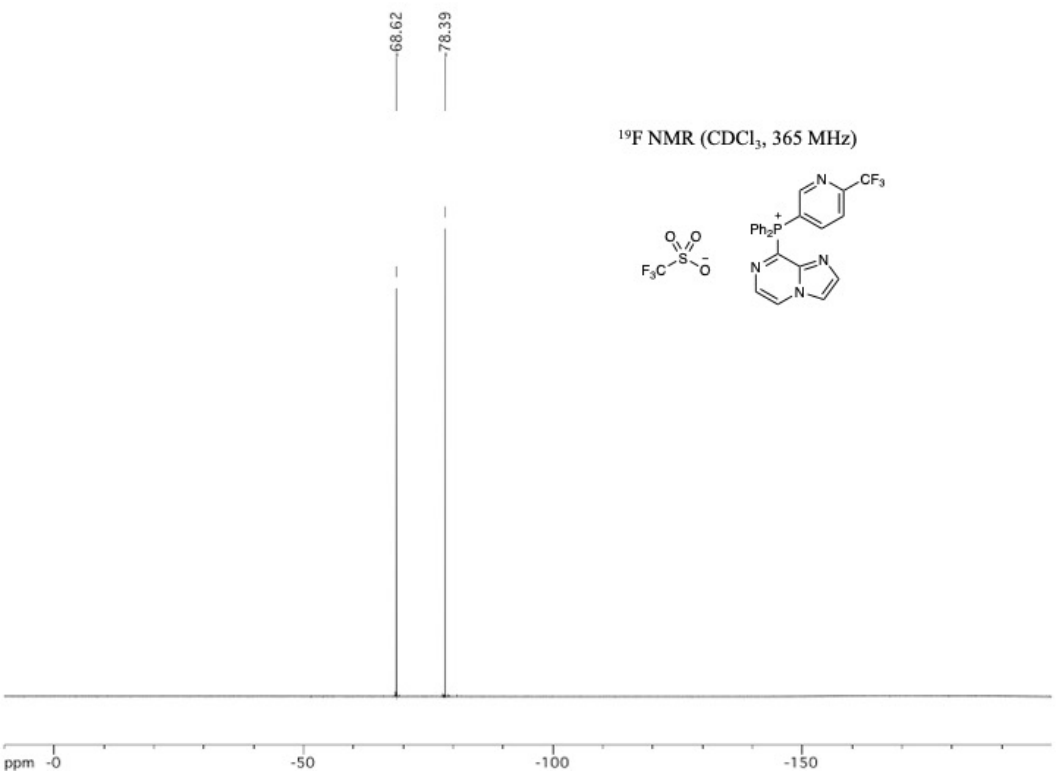




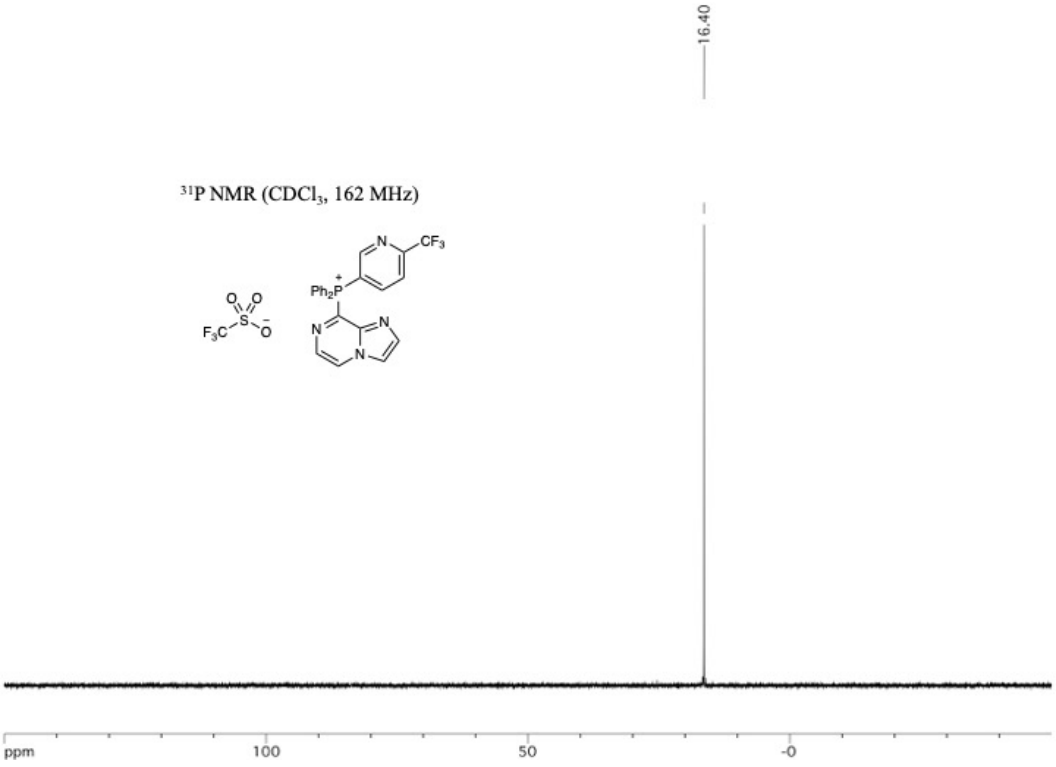
^{13}C NMR ($CDCl_3$, 100 MHz)

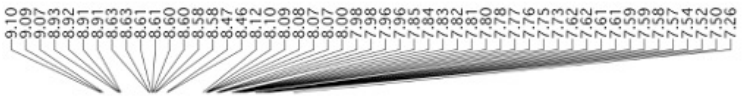


^{19}F NMR ($CDCl_3$, 365 MHz)

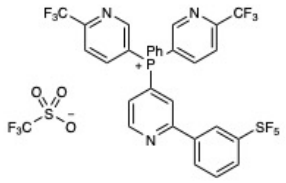


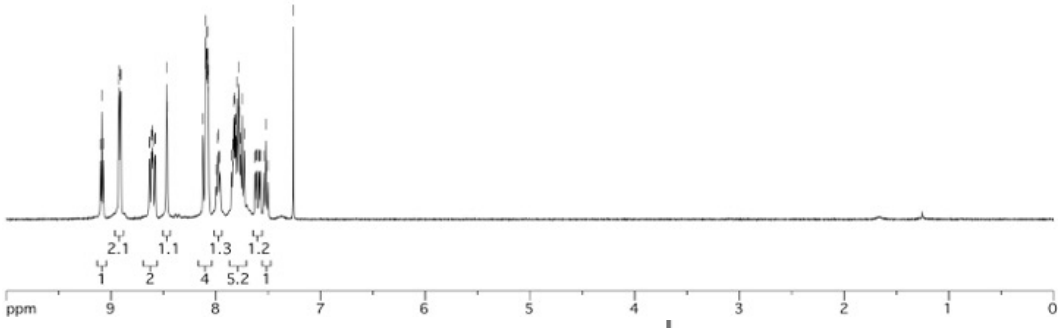
^{31}P NMR ($CDCl_3$, 162 MHz)

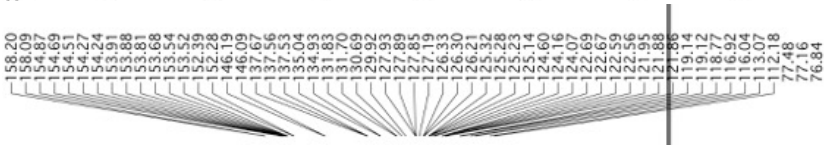




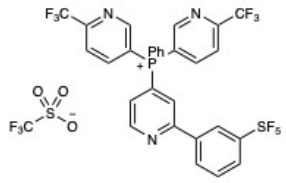
^{1}H NMR ($CDCl_3$, 400 MHz)

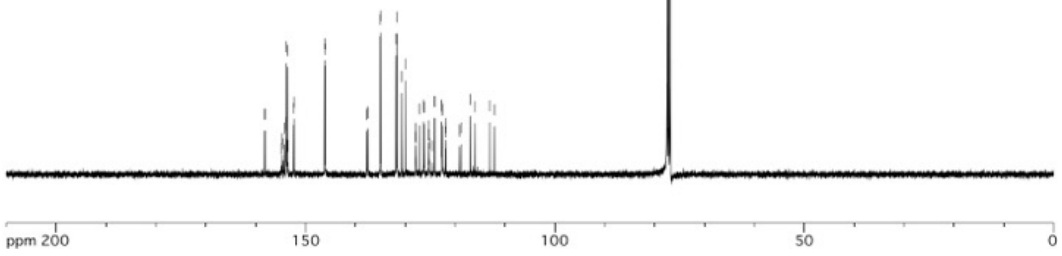


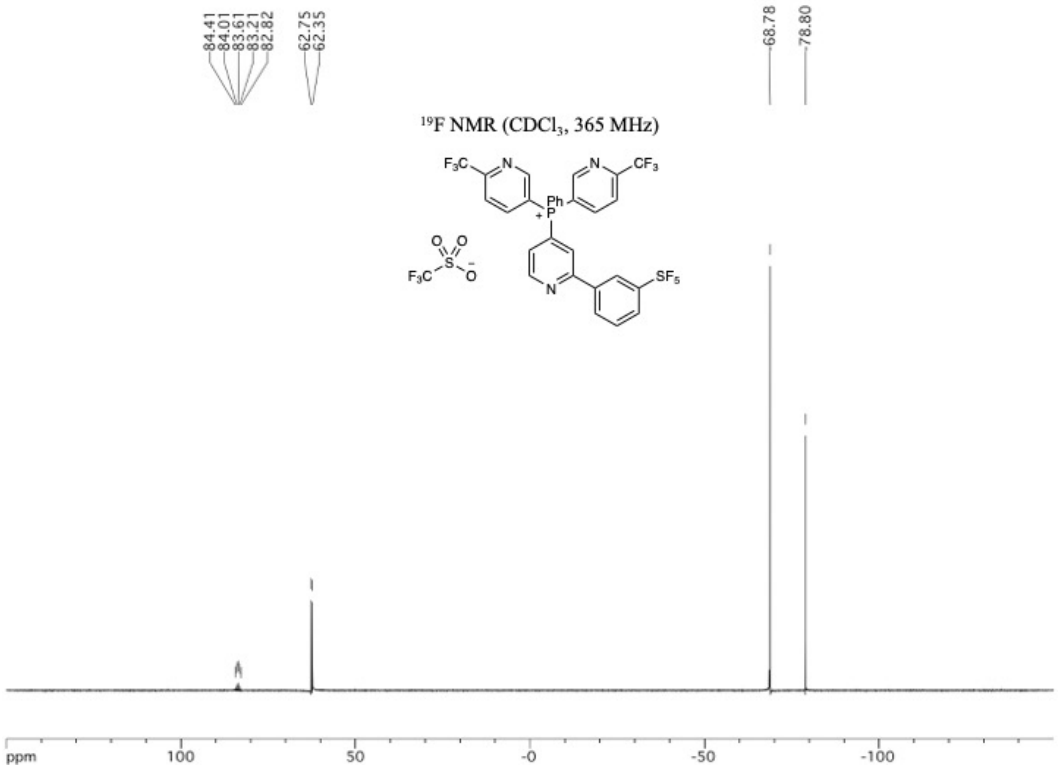


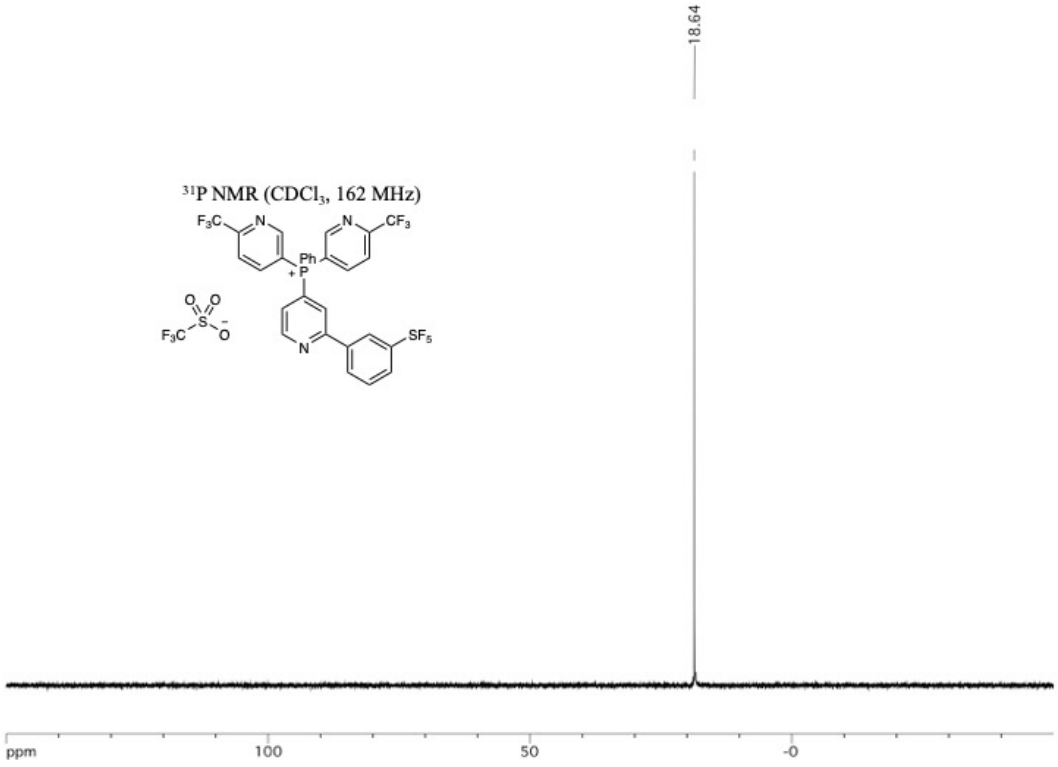


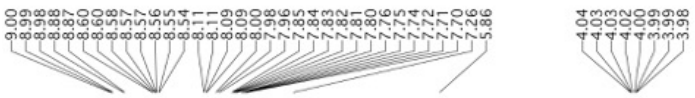
^{13}C NMR ($CDCl_3$, 100 MHz)



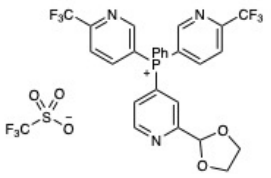


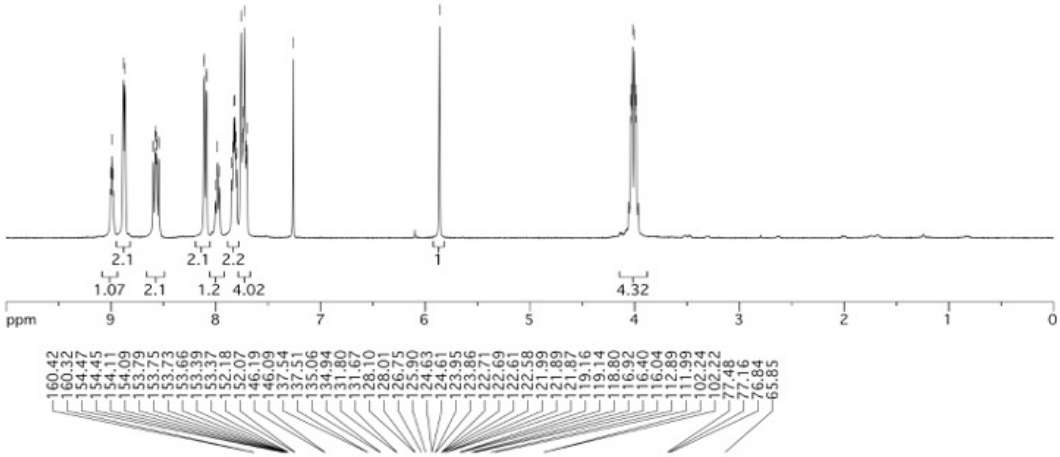

84.41
84.01
83.61
83.21
82.82
62.75
62.35
68.78
78.80
19F NMR (CDCl3, 365 MHz)
F3C
N
CF3
Ph
P
O
S
F3C
SF5
ppm
100
50
-0
-50
-100


18.64
31P NMR (CDCl3, 162 MHz)
F3C
N
CF3
Ph
P
O
S
F3C
SF5
ppm
100
50
-0

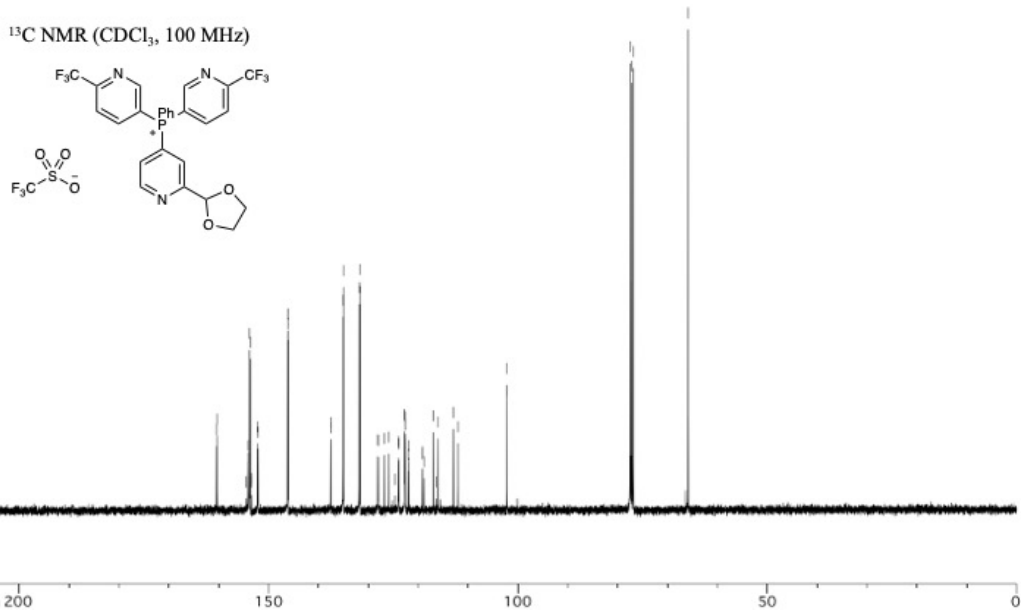


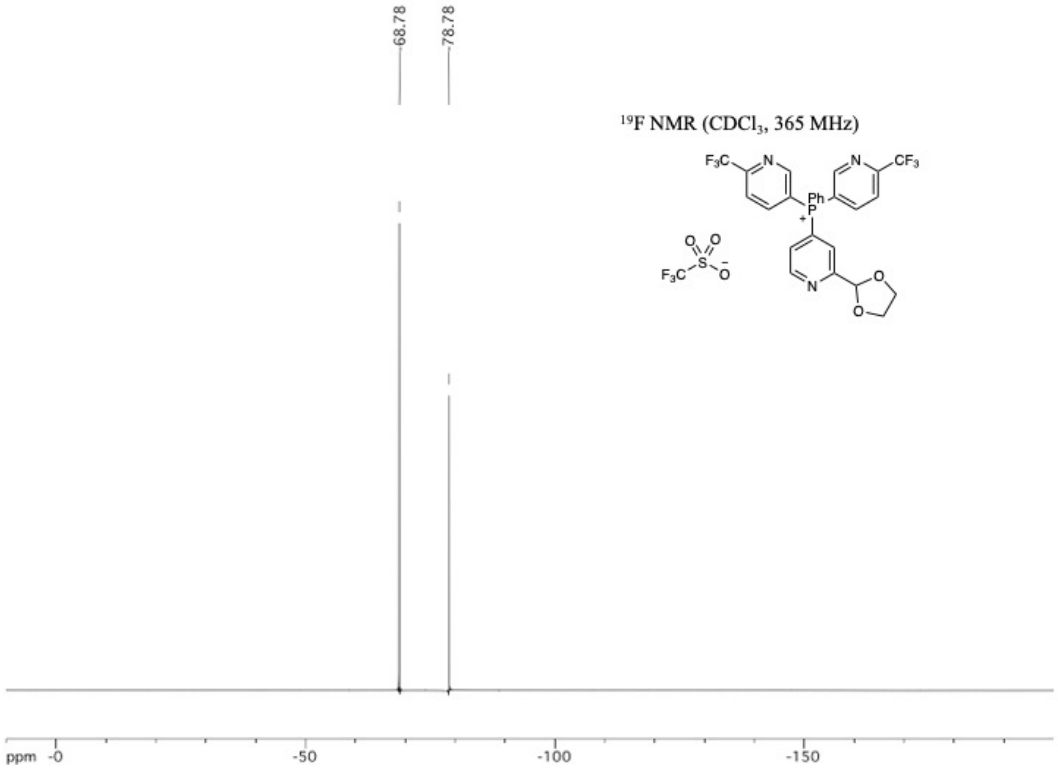
^{1}H NMR ($CDCl_3$, 400 MHz)



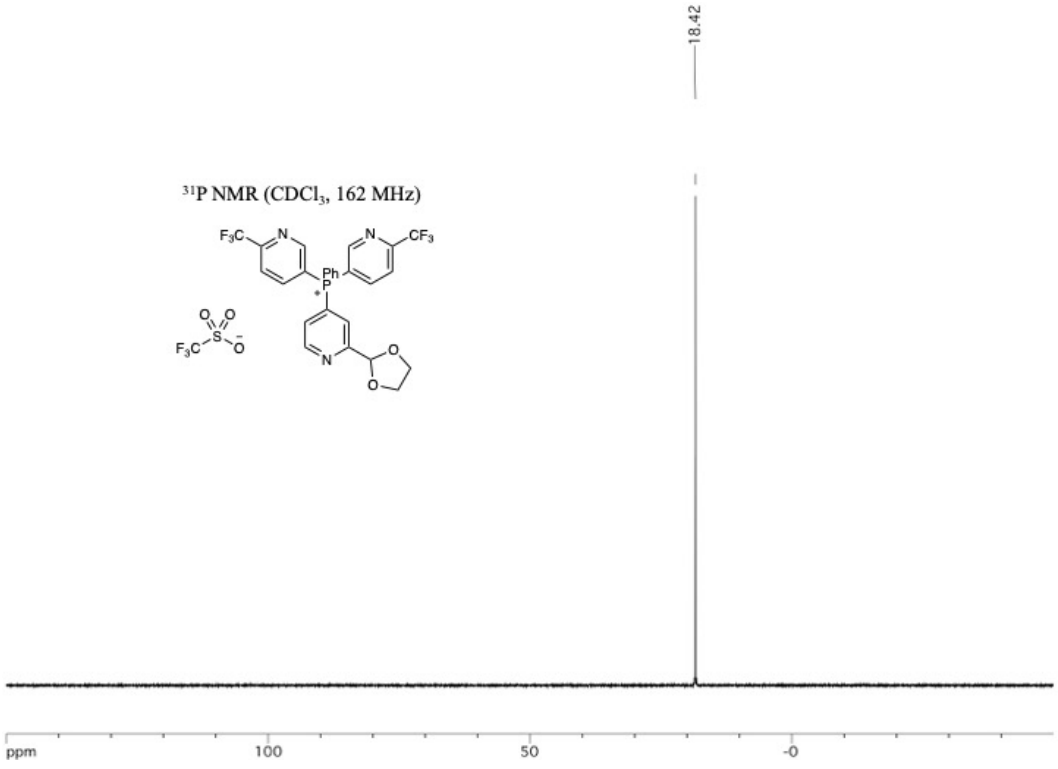


^{13}C NMR ($CDCl_3$, 100 MHz)

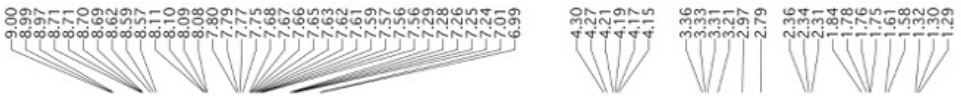




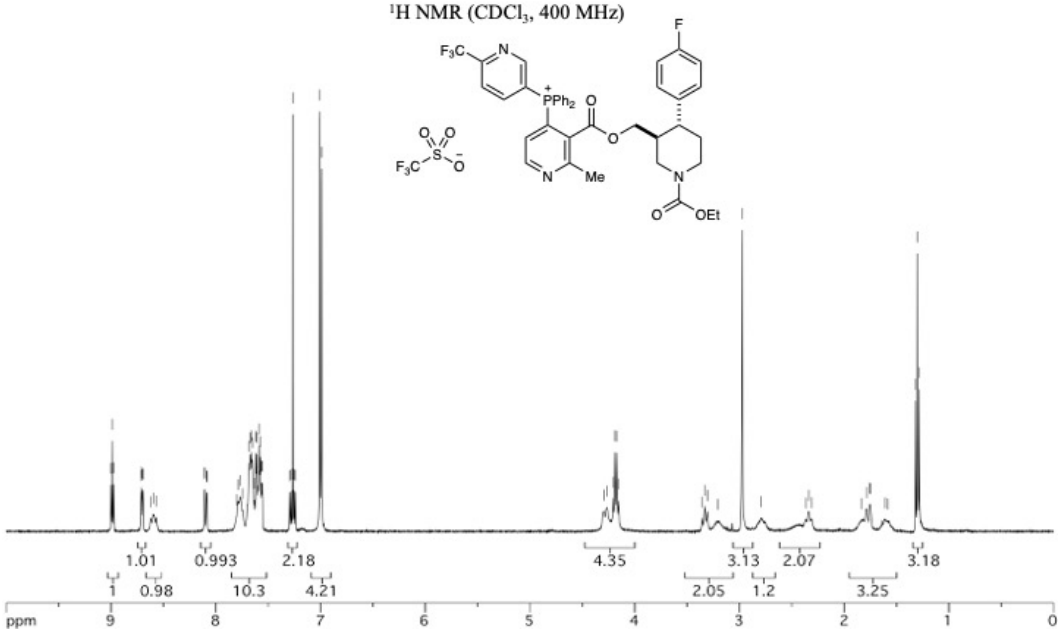
^{19}F NMR ($CDCl_3$, 365 MHz)

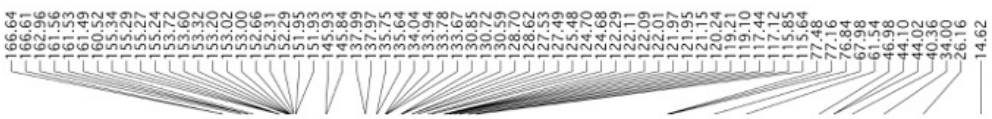


^{31}P NMR ($CDCl_3$, 162 MHz)

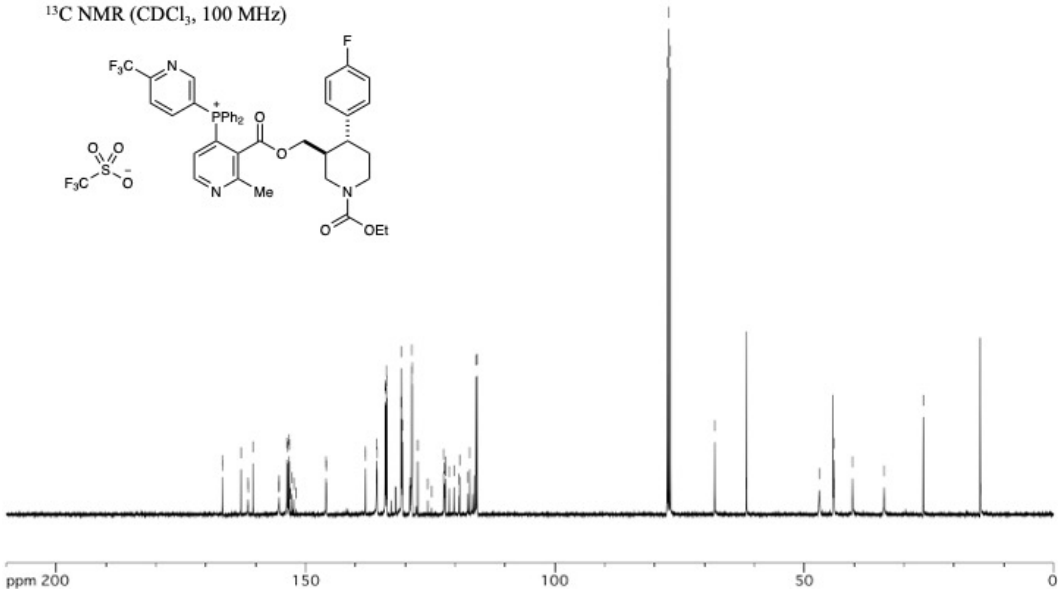


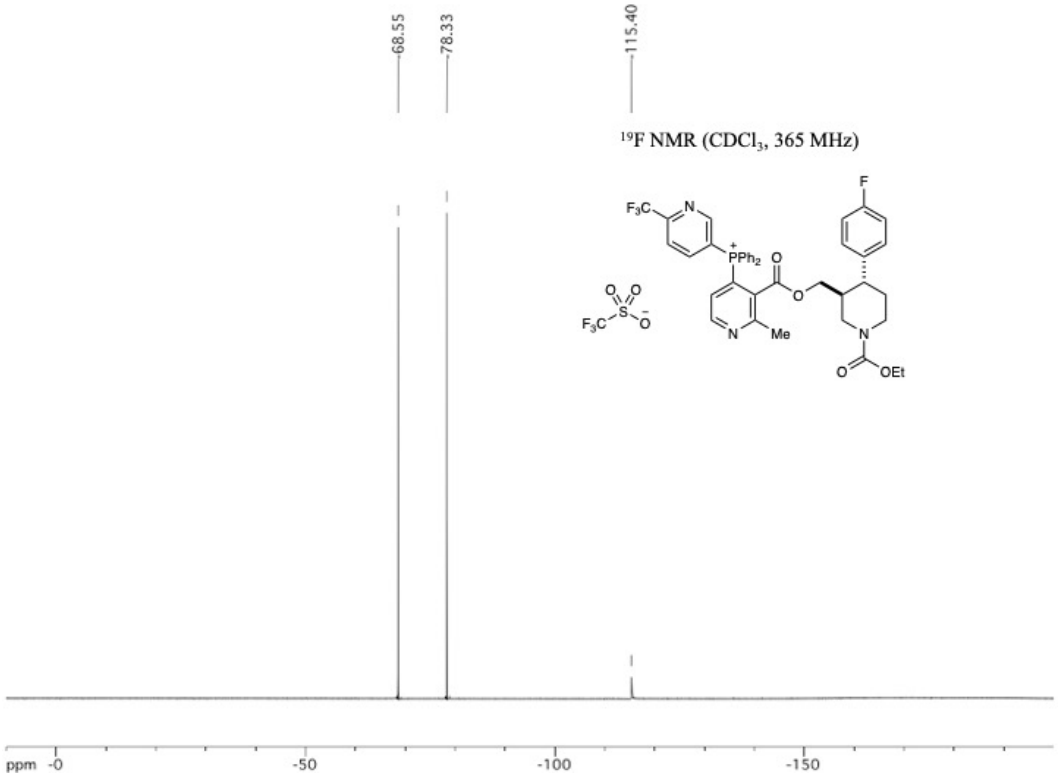
^{1}H NMR ($CDCl_3$, 400 MHz)



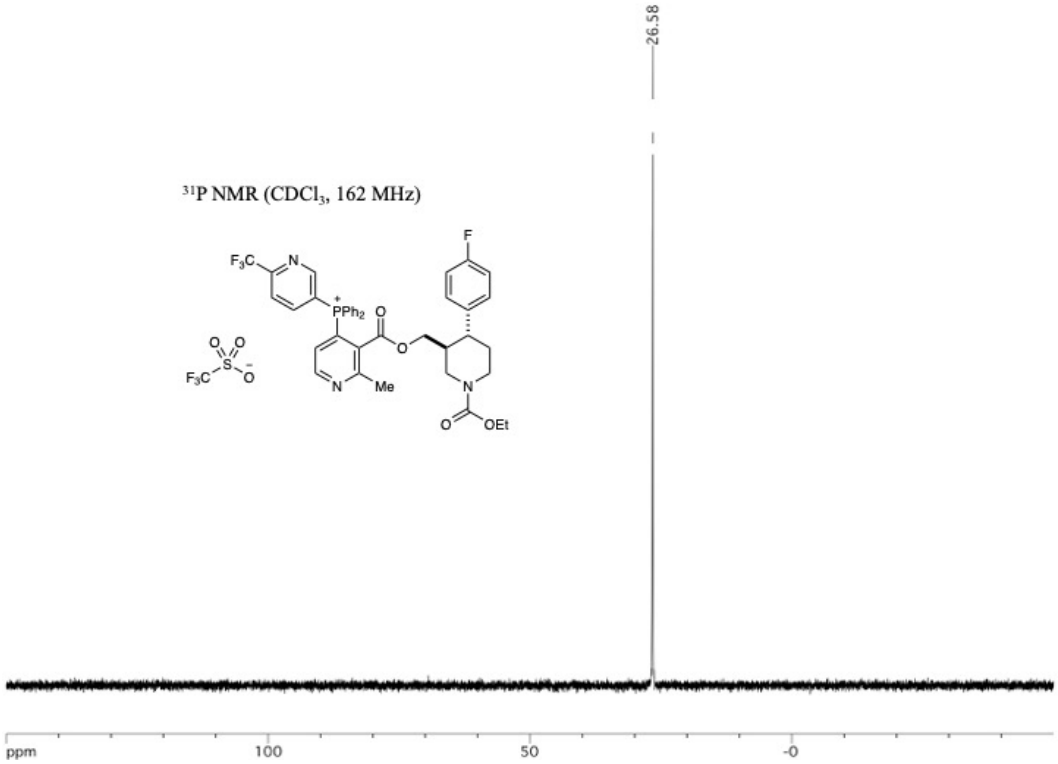


^{13}C NMR ($CDCl_3$, 100 MHz)

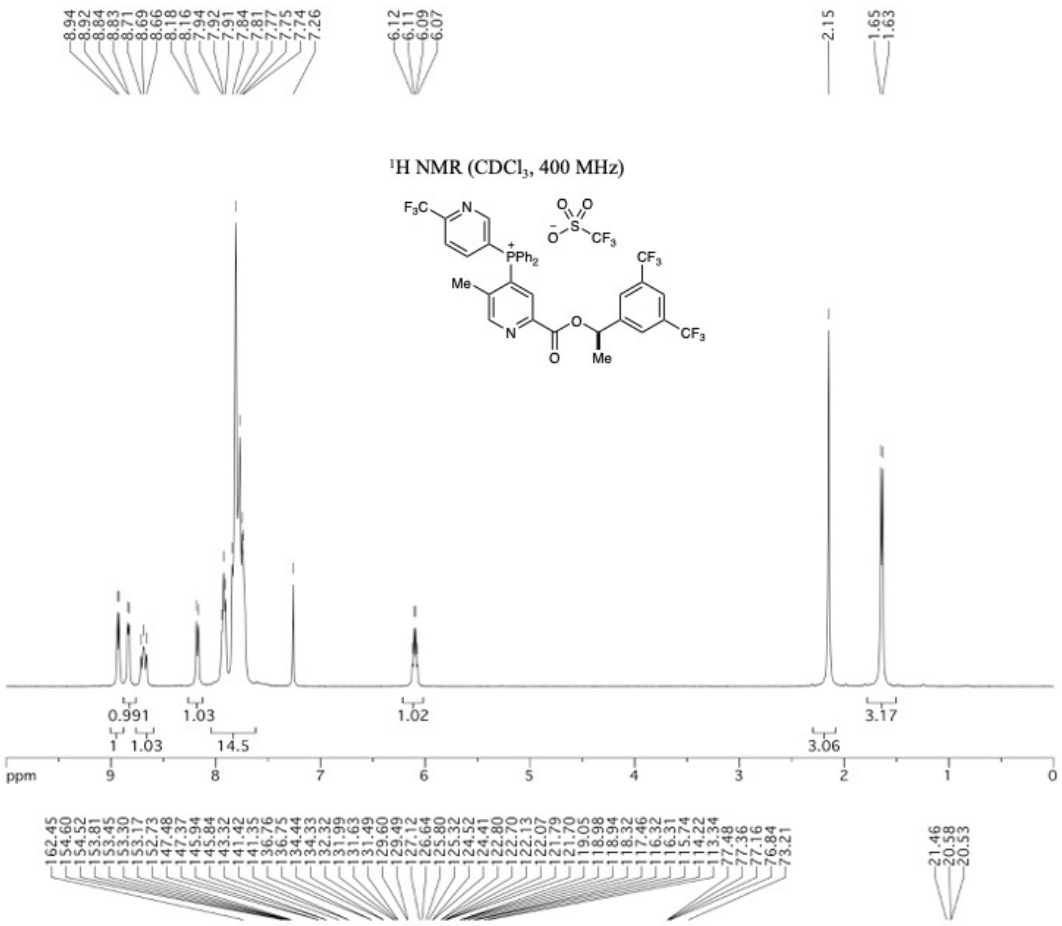




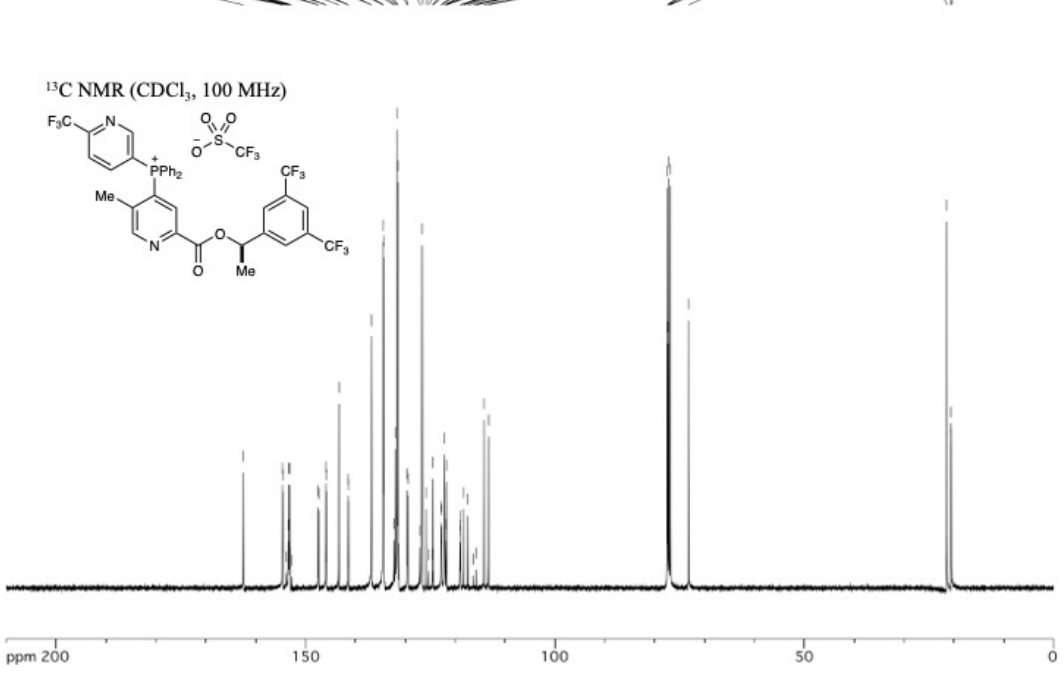
^{19}F NMR ($CDCl_3$, 365 MHz)



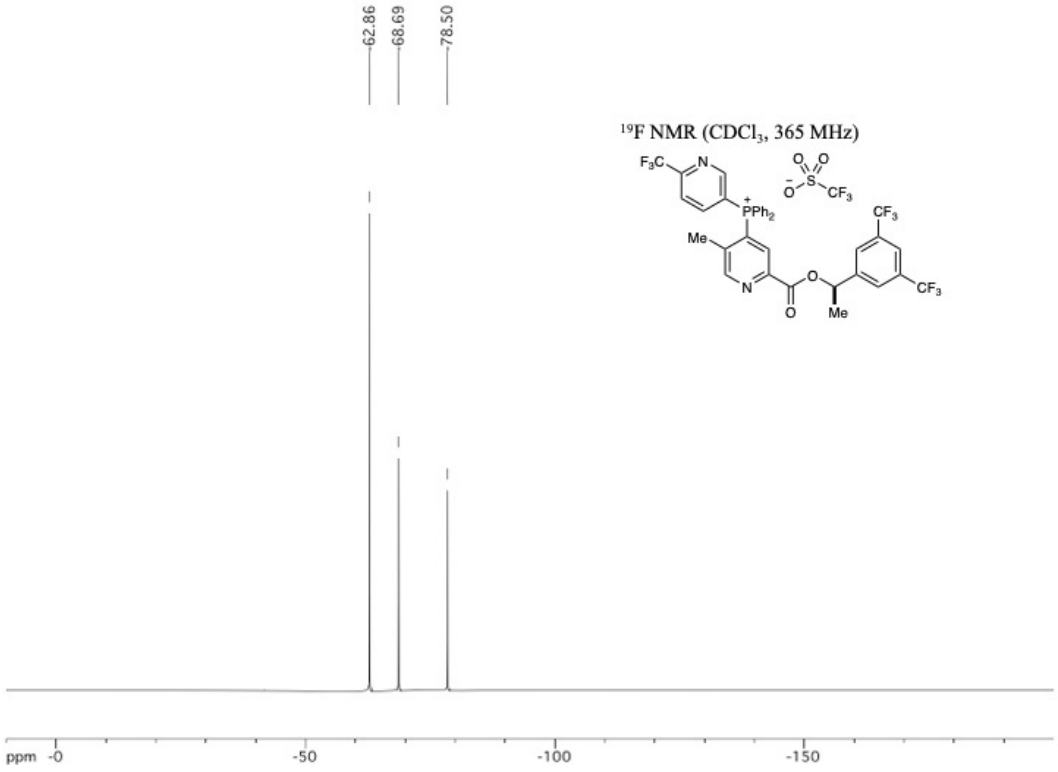
^{31}P NMR ($CDCl_3$, 162 MHz)



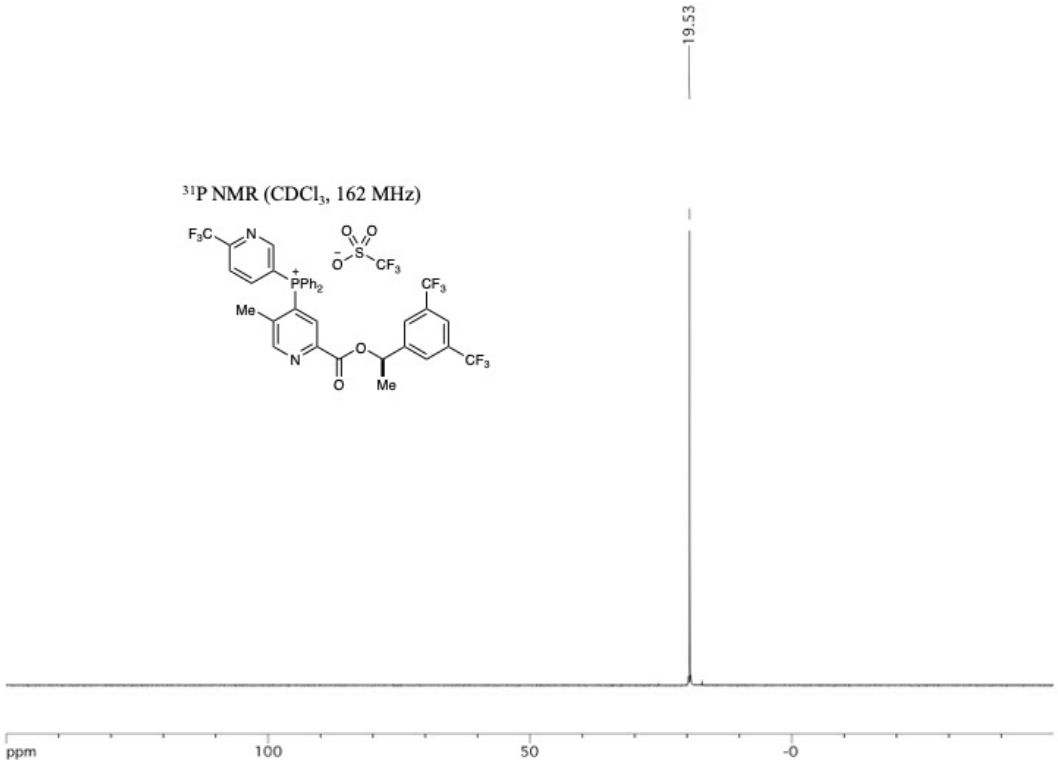
^{1}H NMR ($CDCl_3$, 400 MHz)



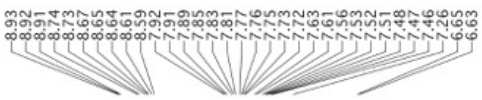
^{13}C NMR ($CDCl_3$, 100 MHz)



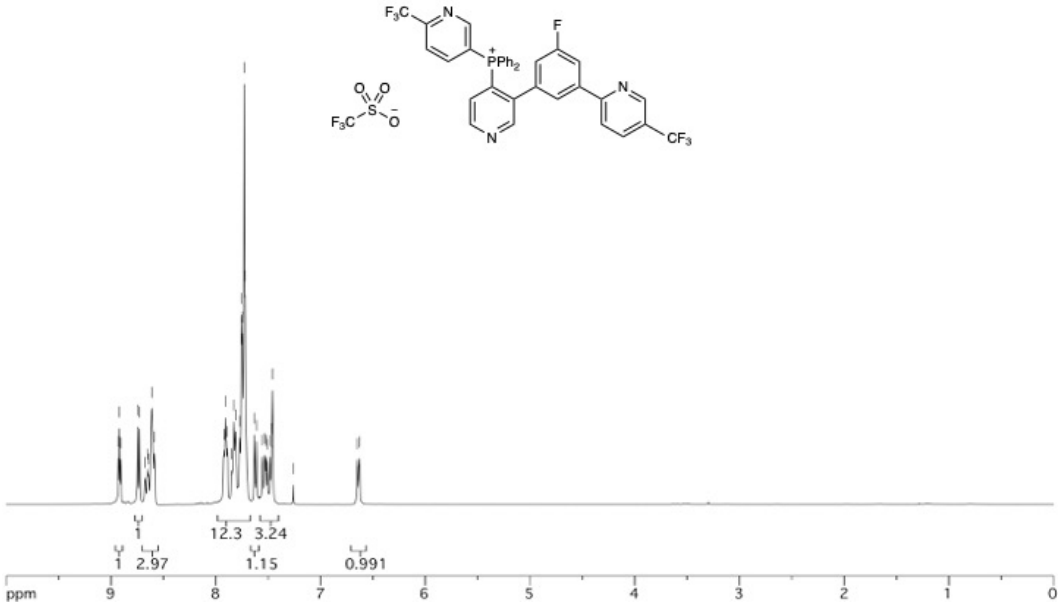
^{19}F NMR ($CDCl_3$, 365 MHz)

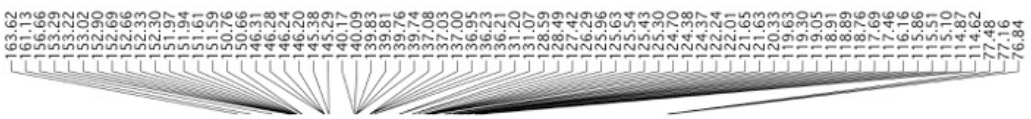


^{31}P NMR ($CDCl_3$, 162 MHz)

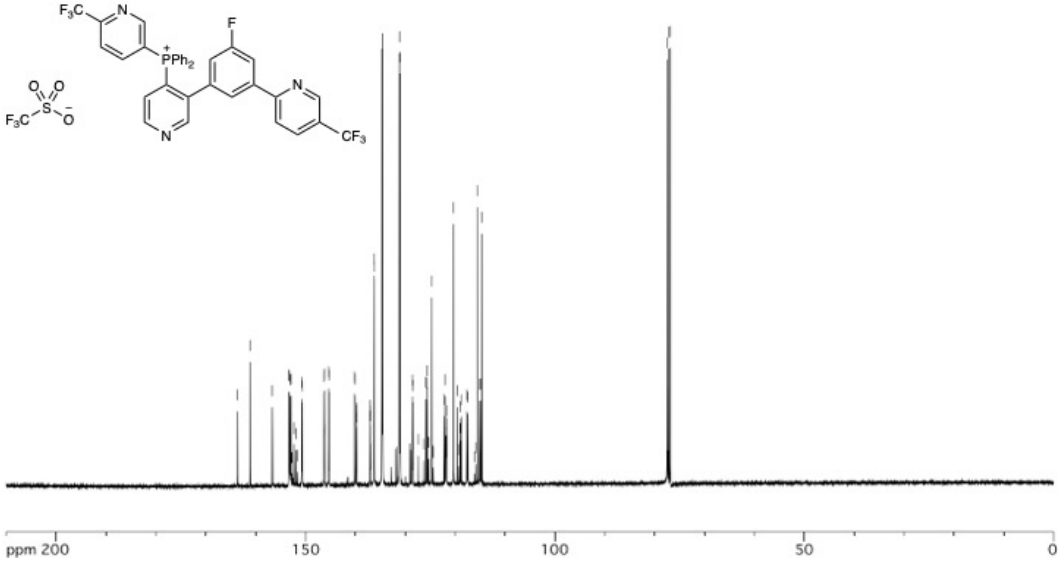


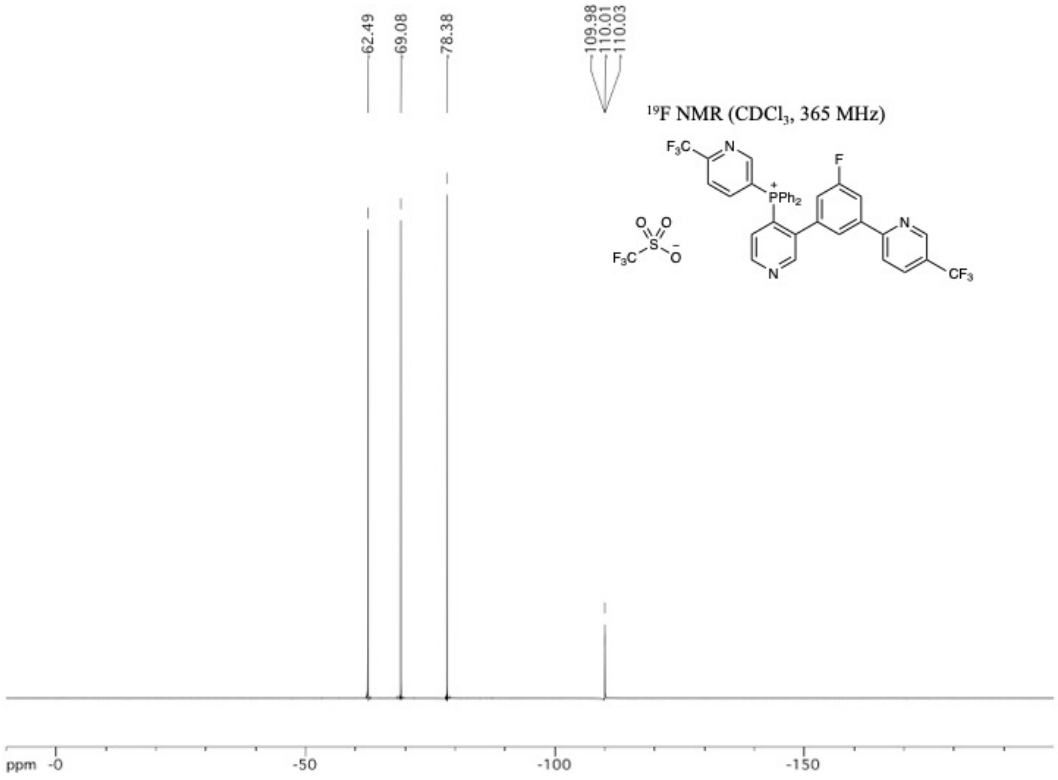
^{1}H NMR ($CDCl_3$, 400 MHz)



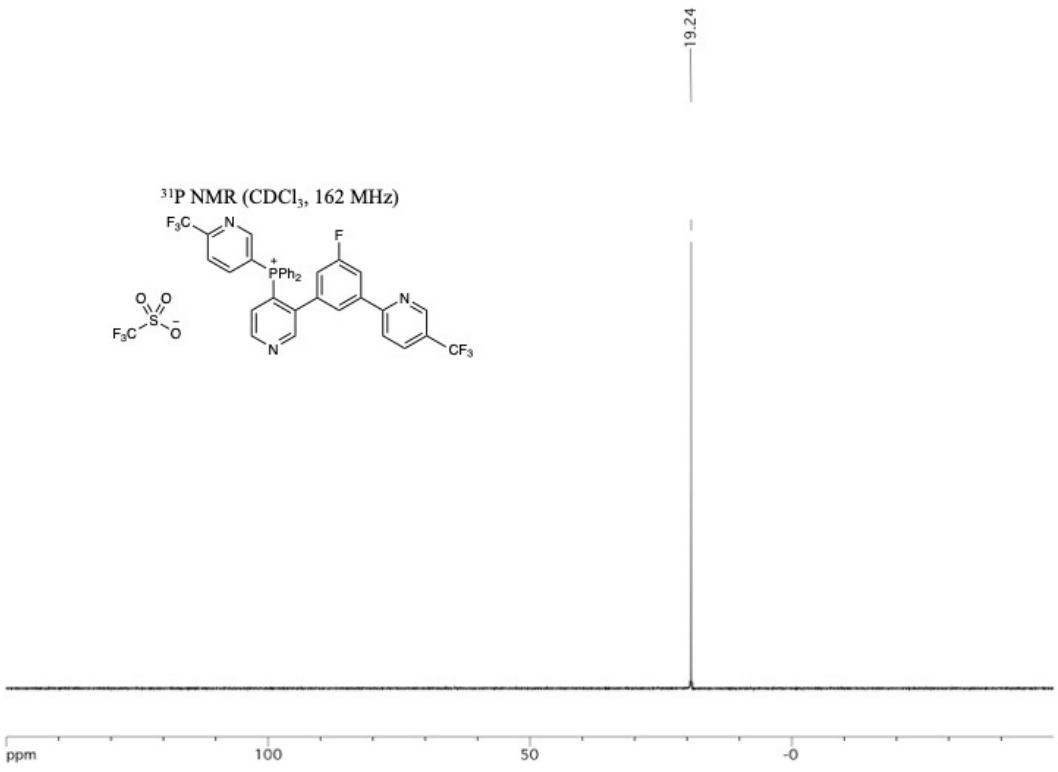


^{13}C NMR ($CDCl_3$, 100 MHz)

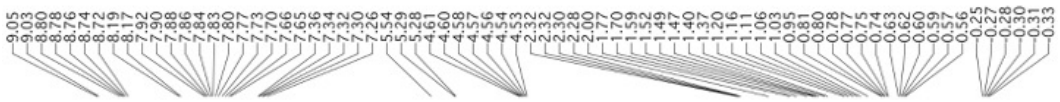




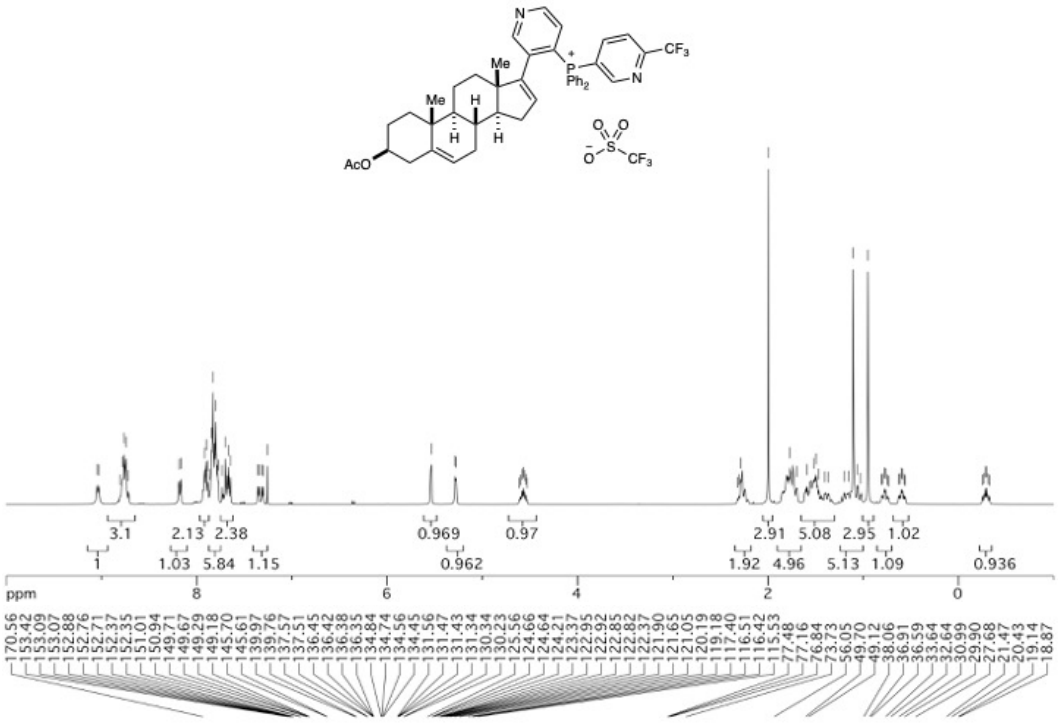
^{19}F NMR ($CDCl_3$, 365 MHz)



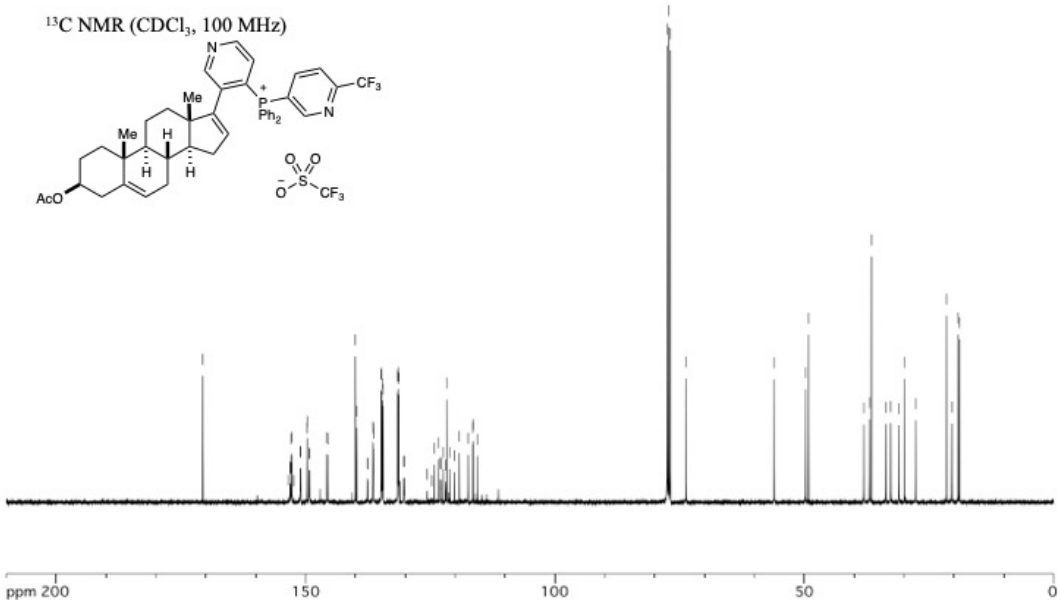
^{31}P NMR ($CDCl_3$, 162 MHz)

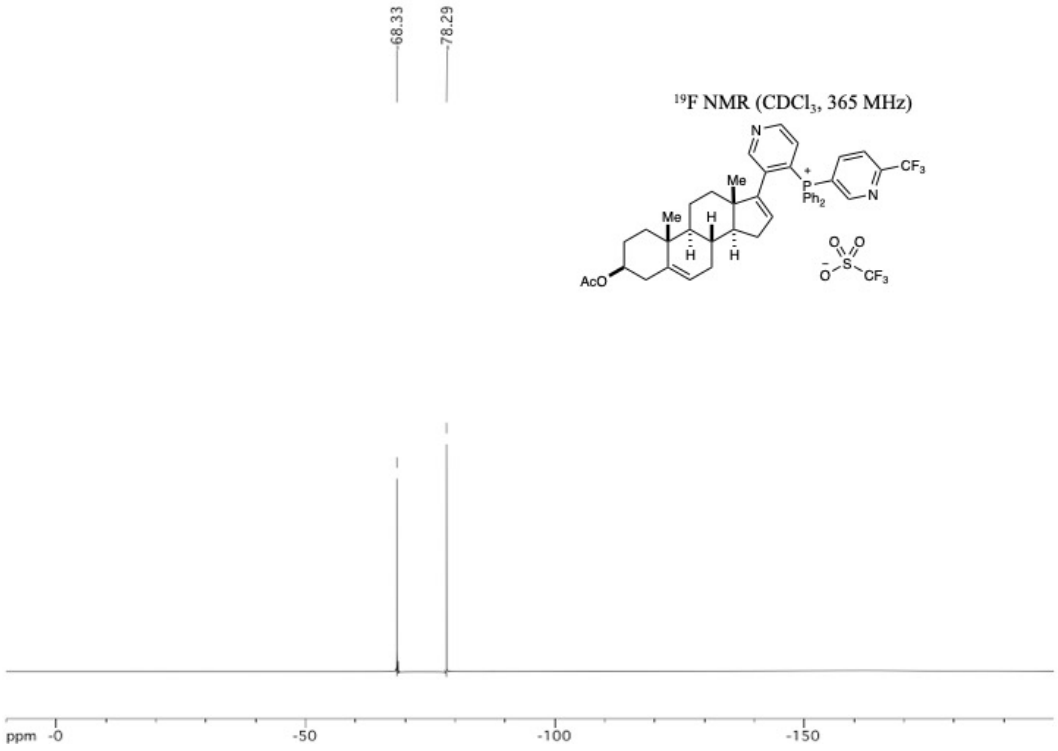


^{1}H NMR ($CDCl_3$, 400 MHz)

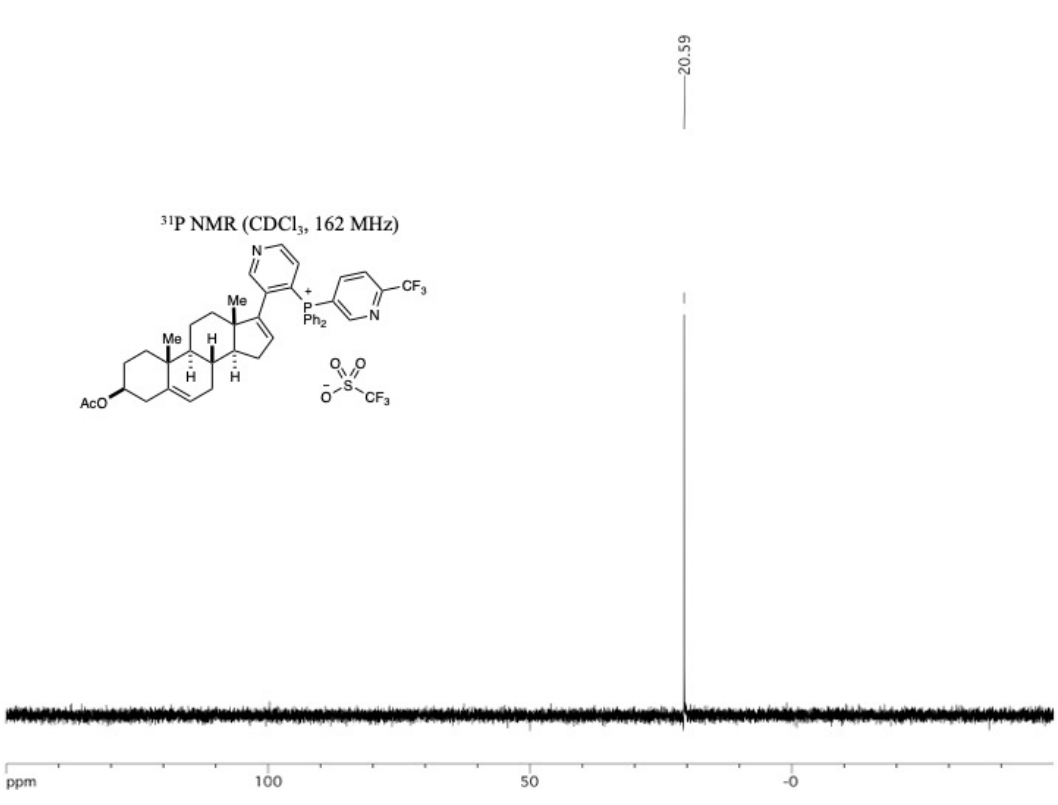


^{13}C NMR ($CDCl_3$, 100 MHz)

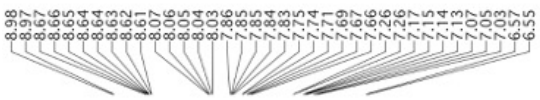




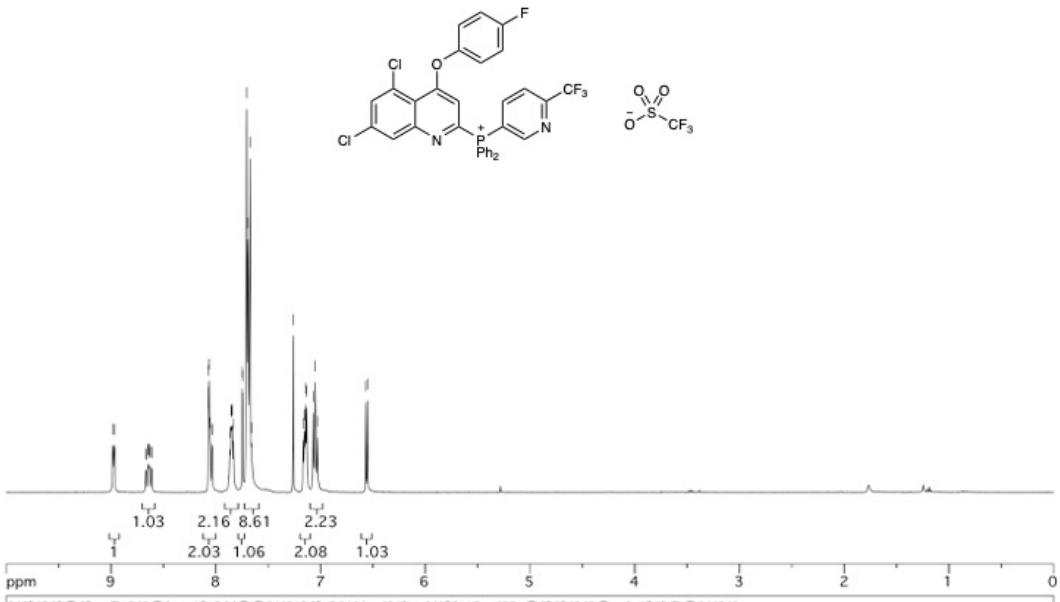
^{19}F NMR ($CDCl_3$, 365 MHz)

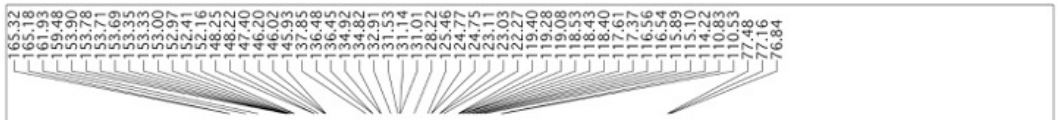


^{31}P NMR ($CDCl_3$, 162 MHz)

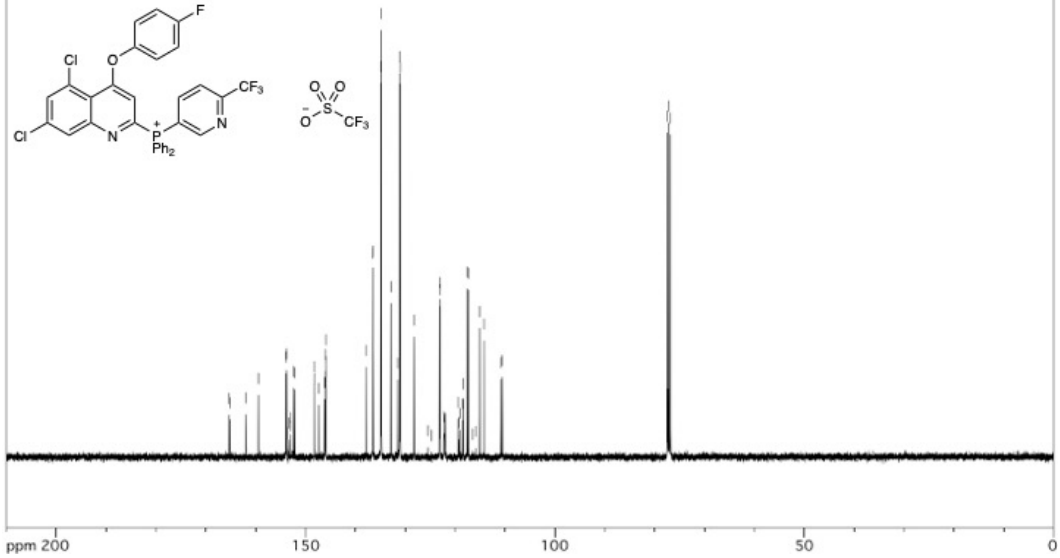


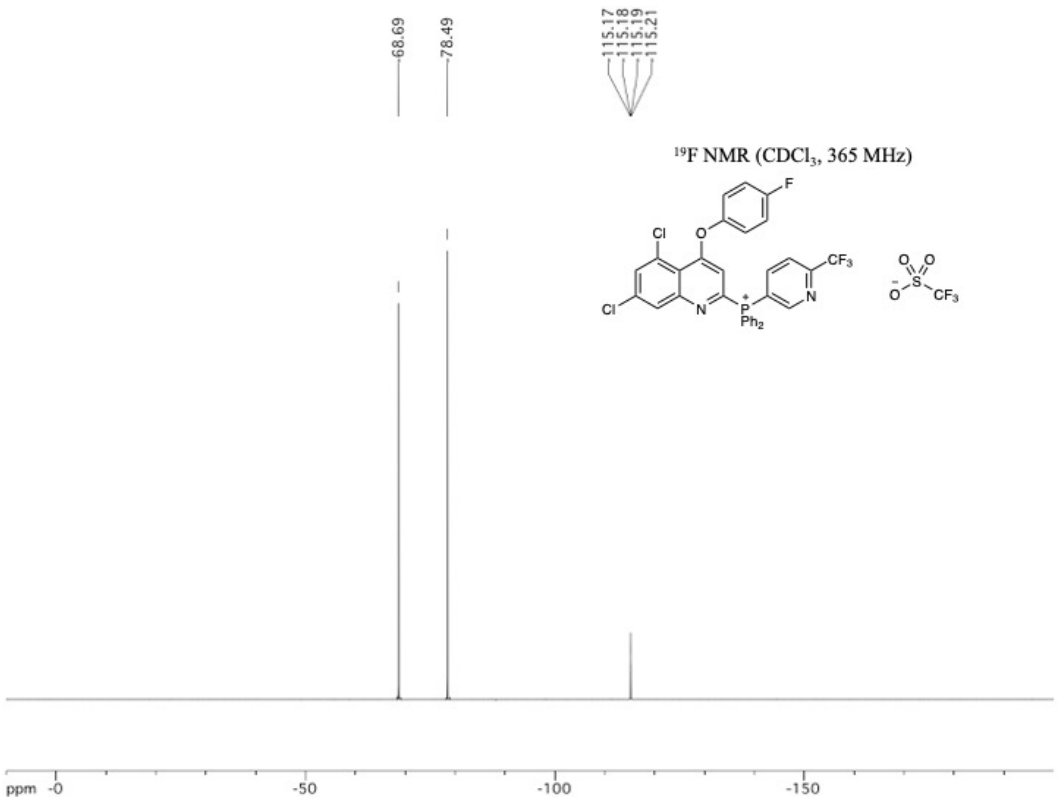
^{1}H NMR ($CDCl_3$, 400 MHz)



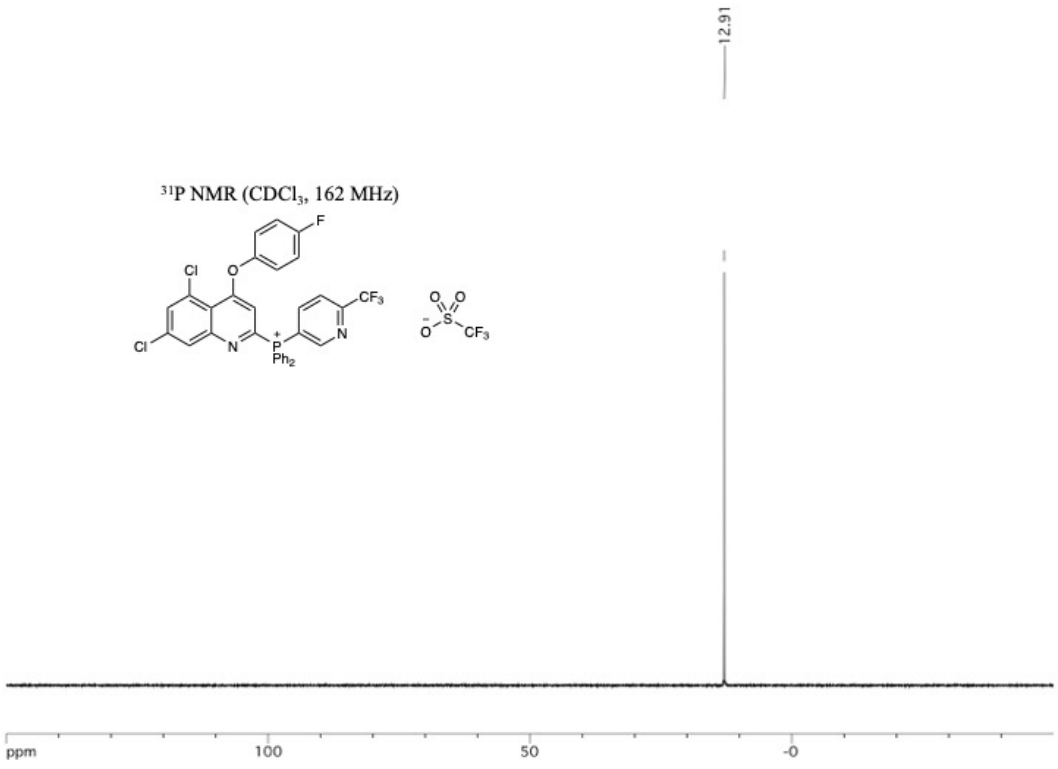


^{13}C NMR ($CDCl_3$, 100 MHz)



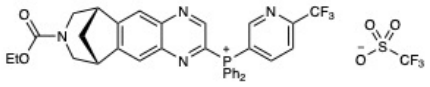


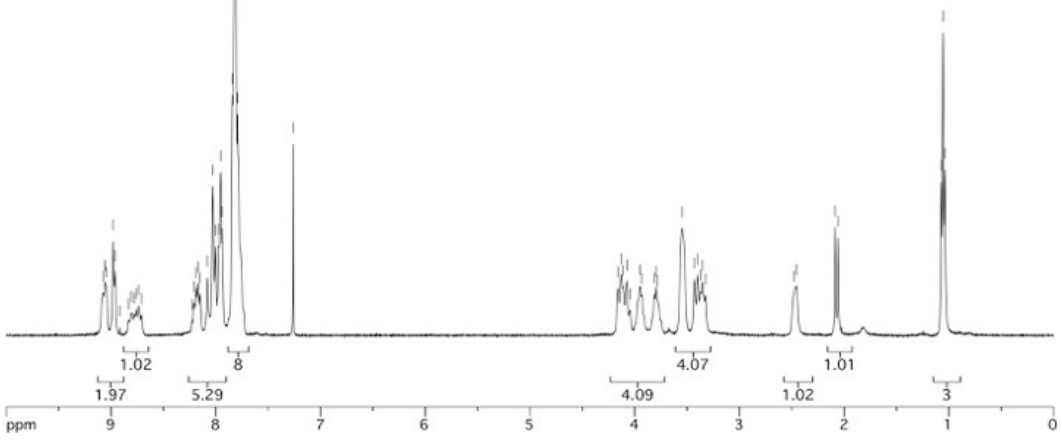
^{19}F NMR ($CDCl_3$, 365 MHz)

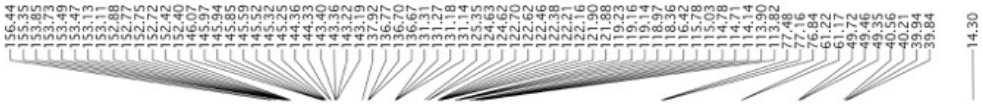


^{31}P NMR ($CDCl_3$, 162 MHz)

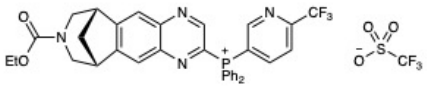
^{1}H NMR ($CDCl_3$, 400 MHz)

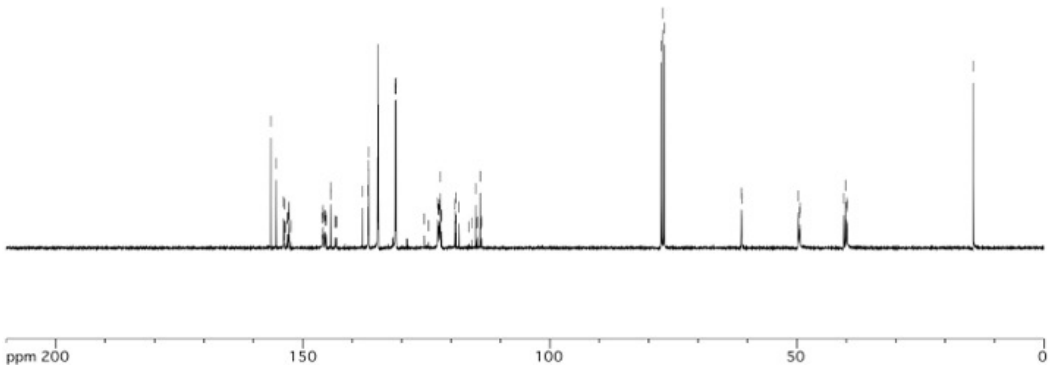


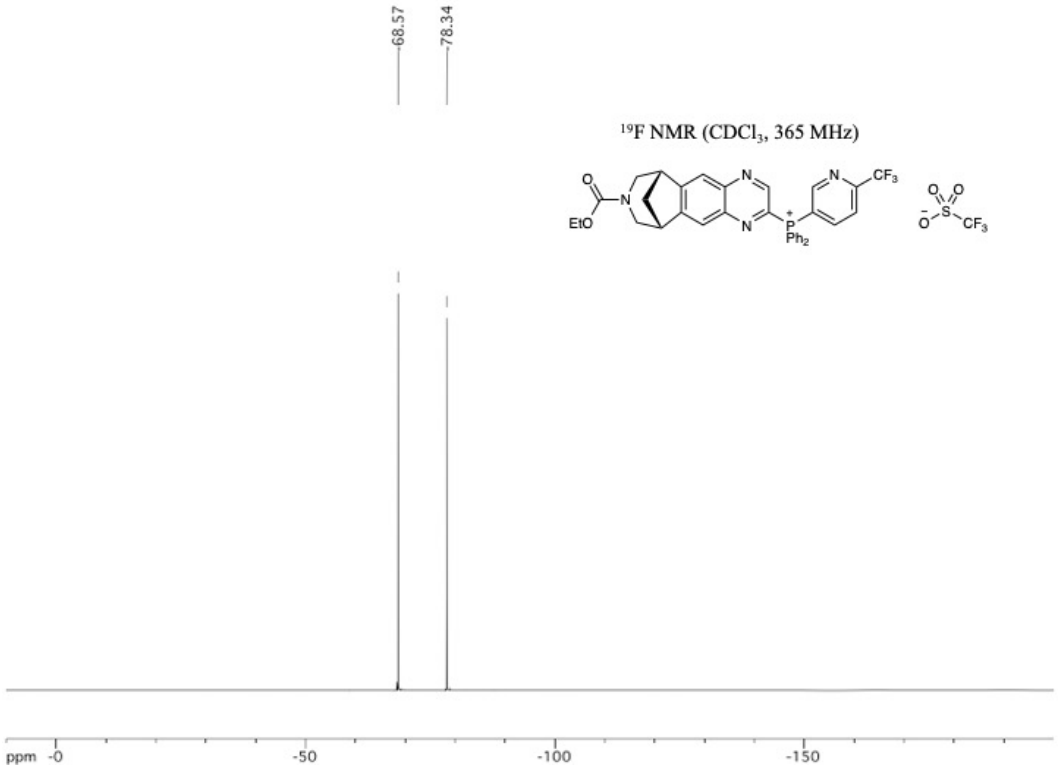




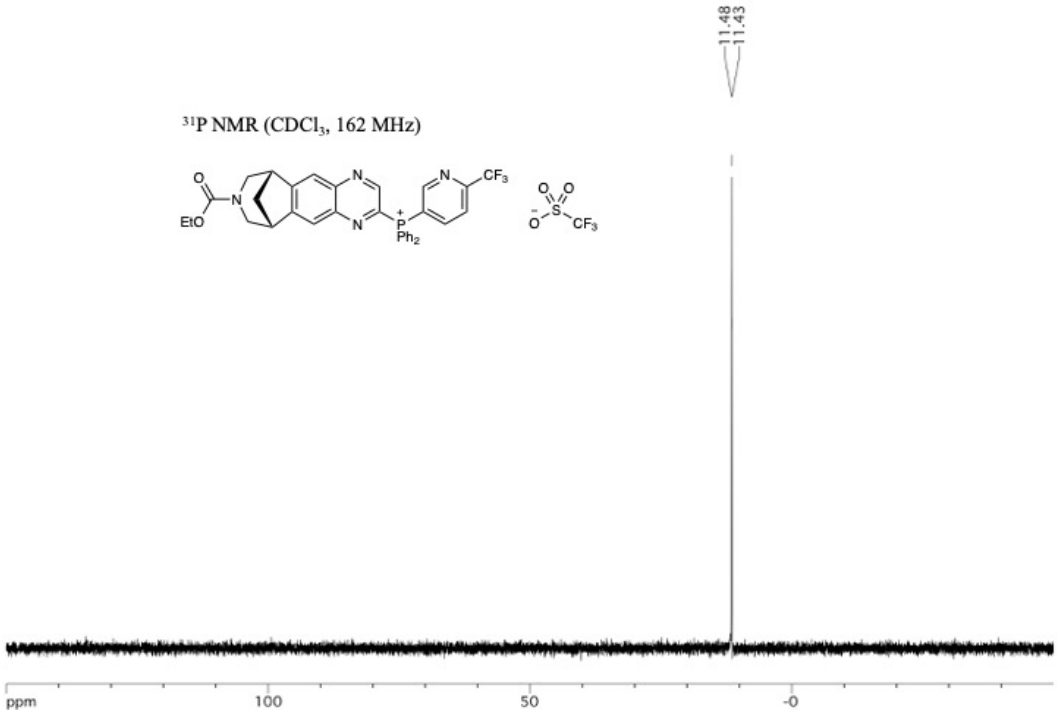
^{13}C NMR ($CDCl_3$, 100 MHz)



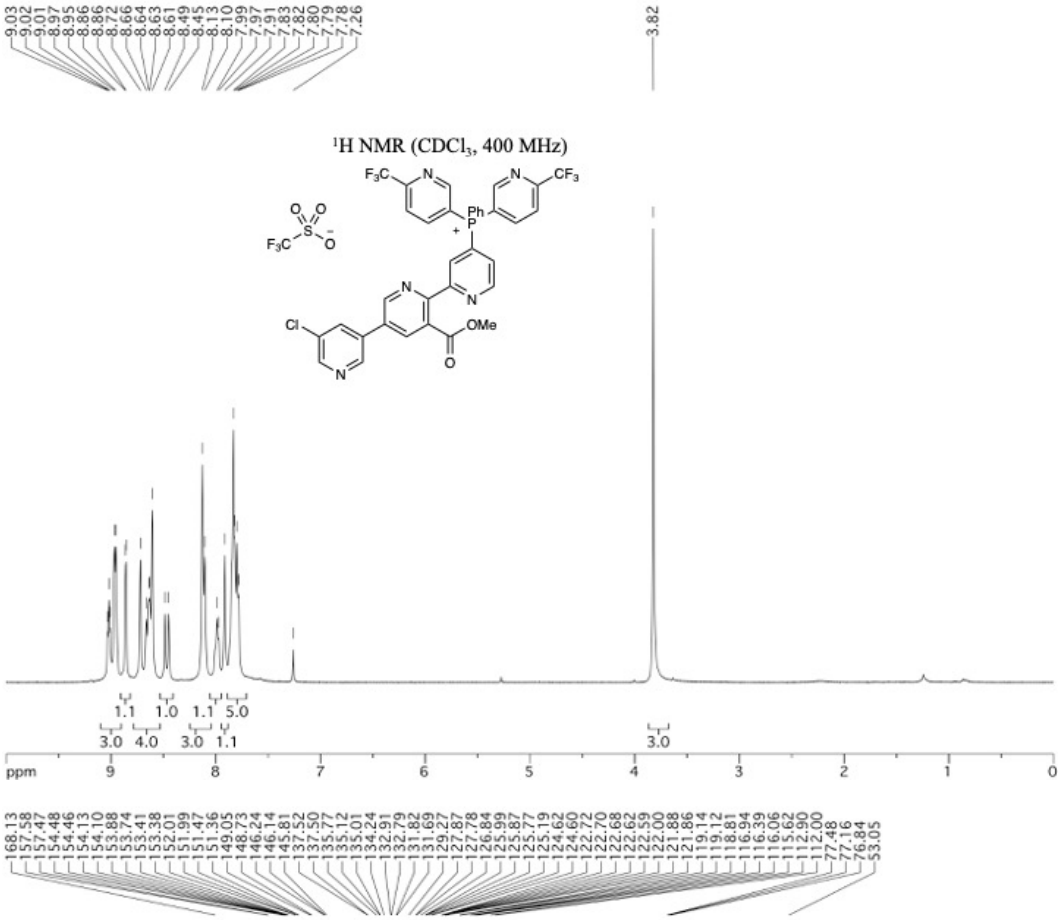




^{19}F NMR ($CDCl_3$, 365 MHz)



^{31}P NMR ($CDCl_3$, 162 MHz)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9.02
9.01
8.97
8.95
8.86
8.86
8.72
8.66
8.64
8.63
8.61
8.49
8.45
8.13
8.10
7.99
7.97
7.91
7.83
7.82
7.80
7.79
7.78
7.26
3.82
1H NMR (CDCl3, 400 MHz)
F3C
N
CF3
Ph
P
+
O
S
F3C
Cl
OMe
1.1
1.0
1.1
5.0
3.0
4.0
3.0
1.1
3.0
ppm
9
8
7
6
5
4
3
2
1
0

168.13
157.58
157.47
154.48
154.46
154.13
154.10
153.88
153.74
153.41
153.38
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122.62
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121.88
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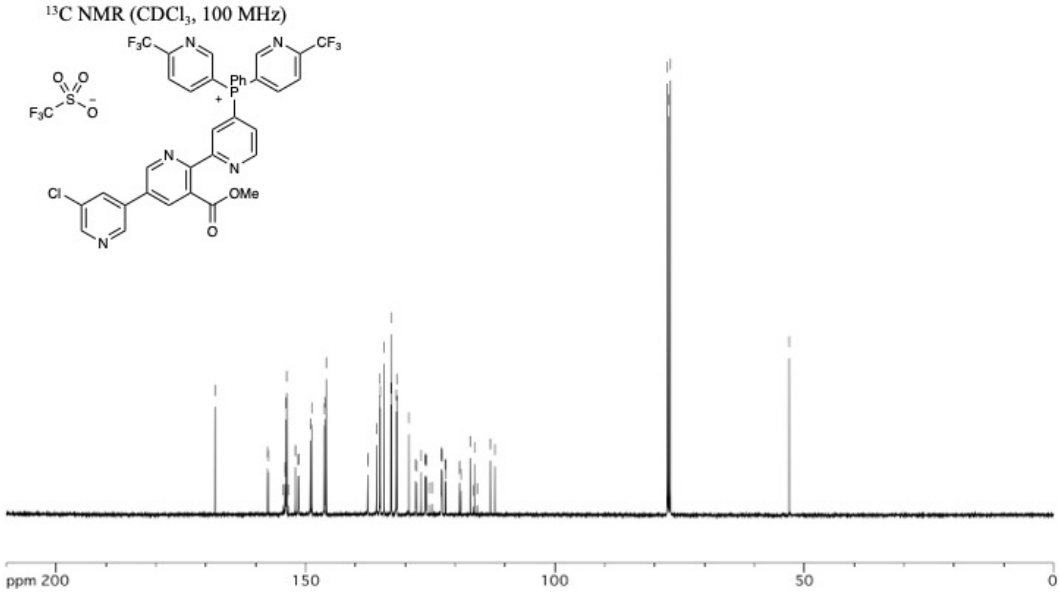
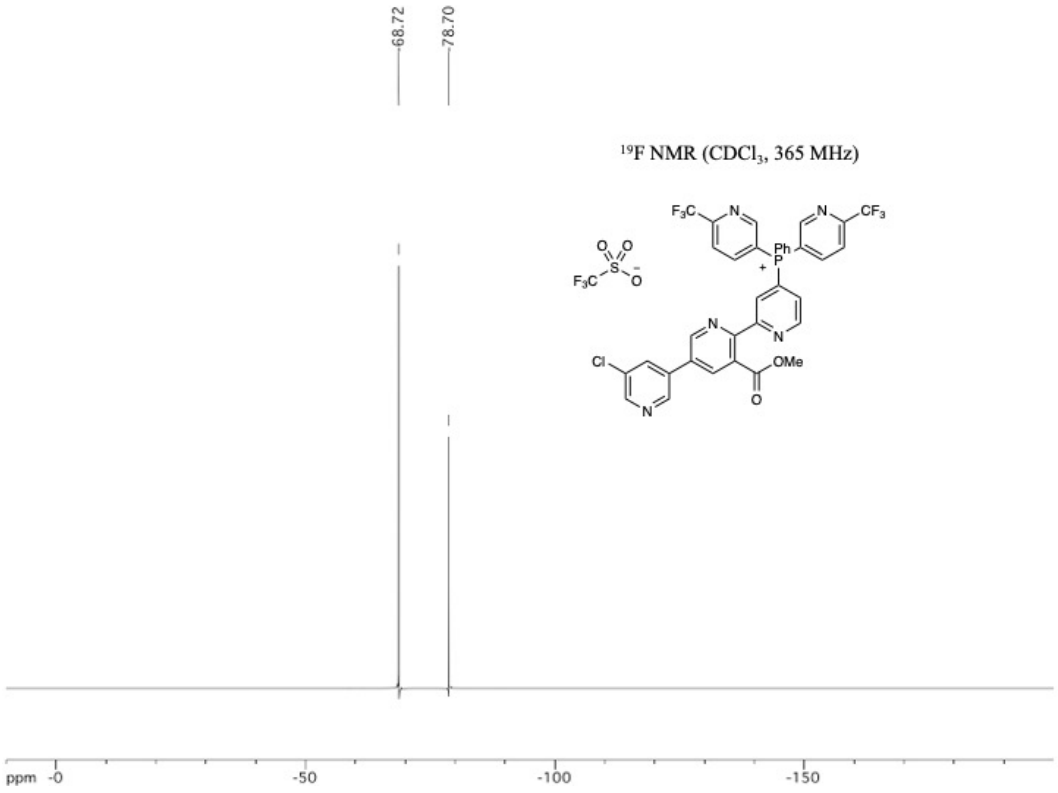
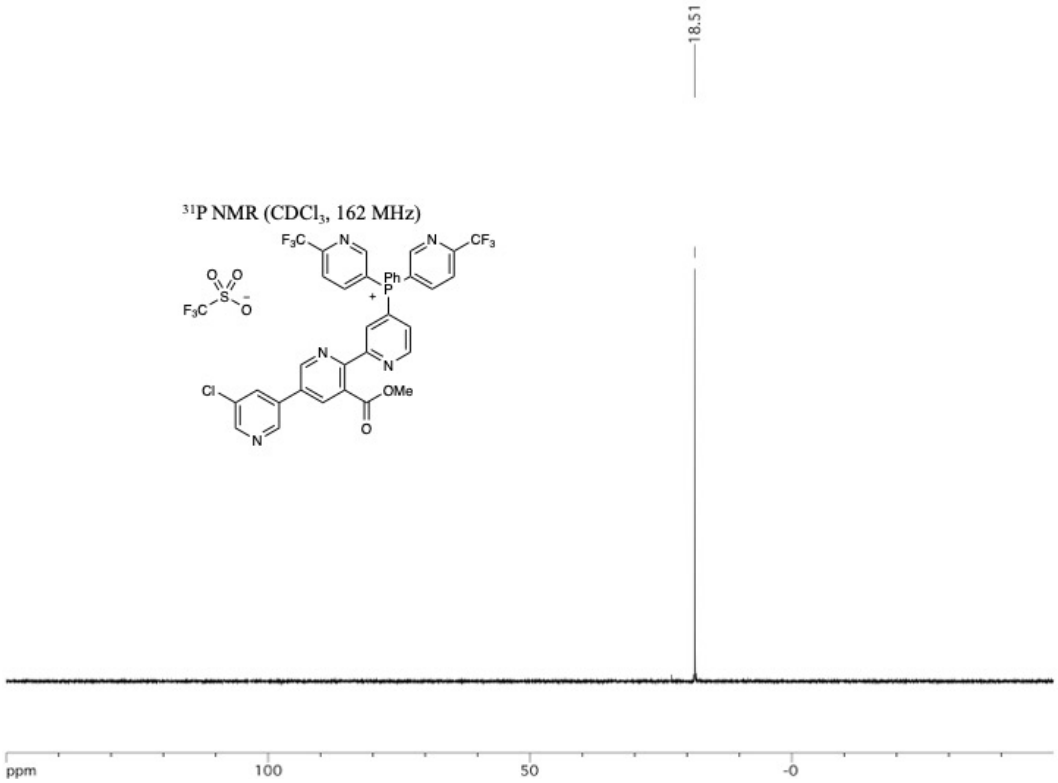
53.05

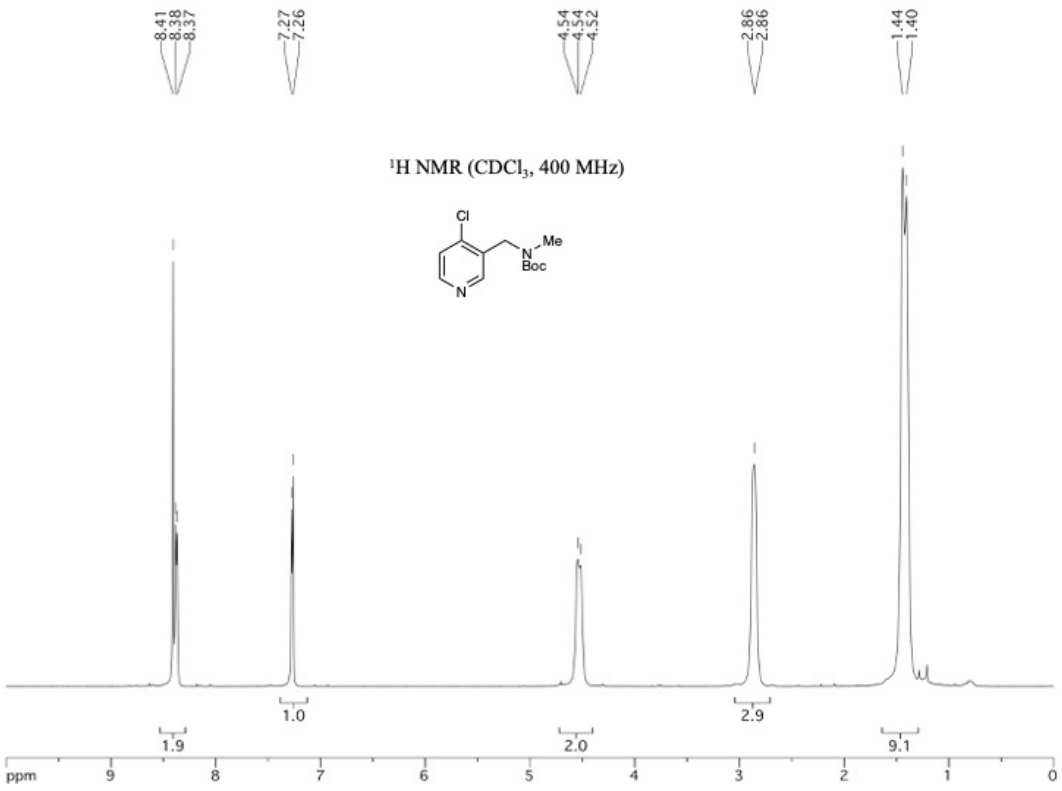

13C NMR (CDCl3, 100 MHz)
F3C
N
CF3
Ph
P
+
O
S
F3C
Cl
OMe
ppm 200
150
100
50
0

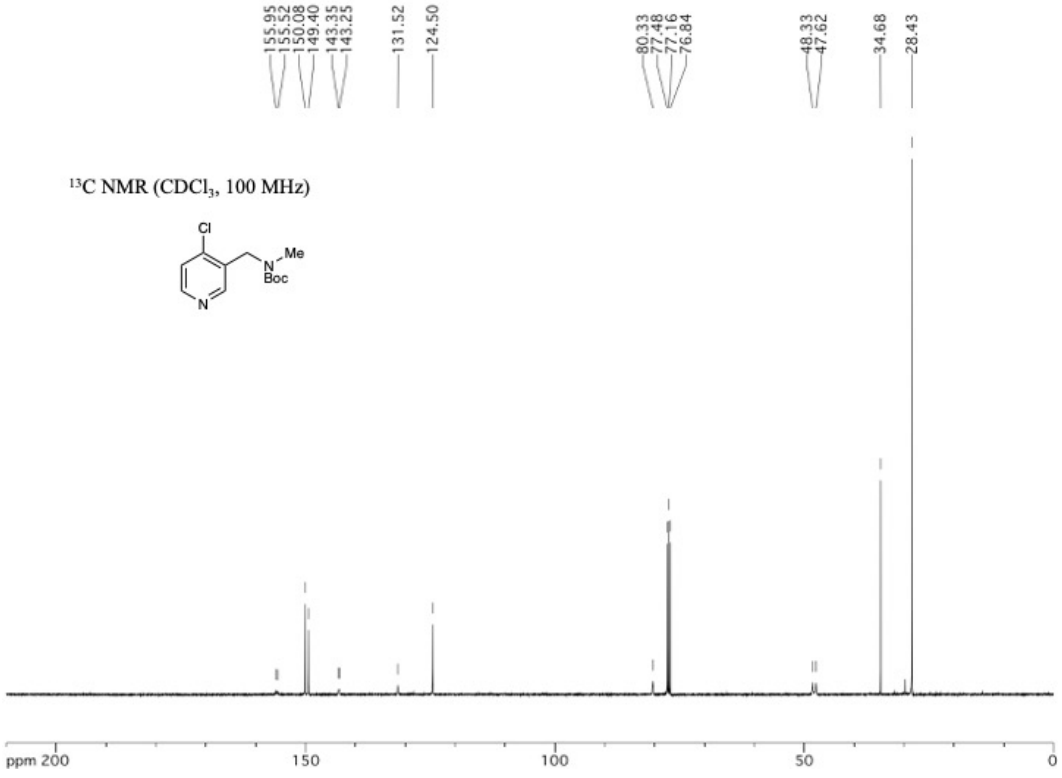


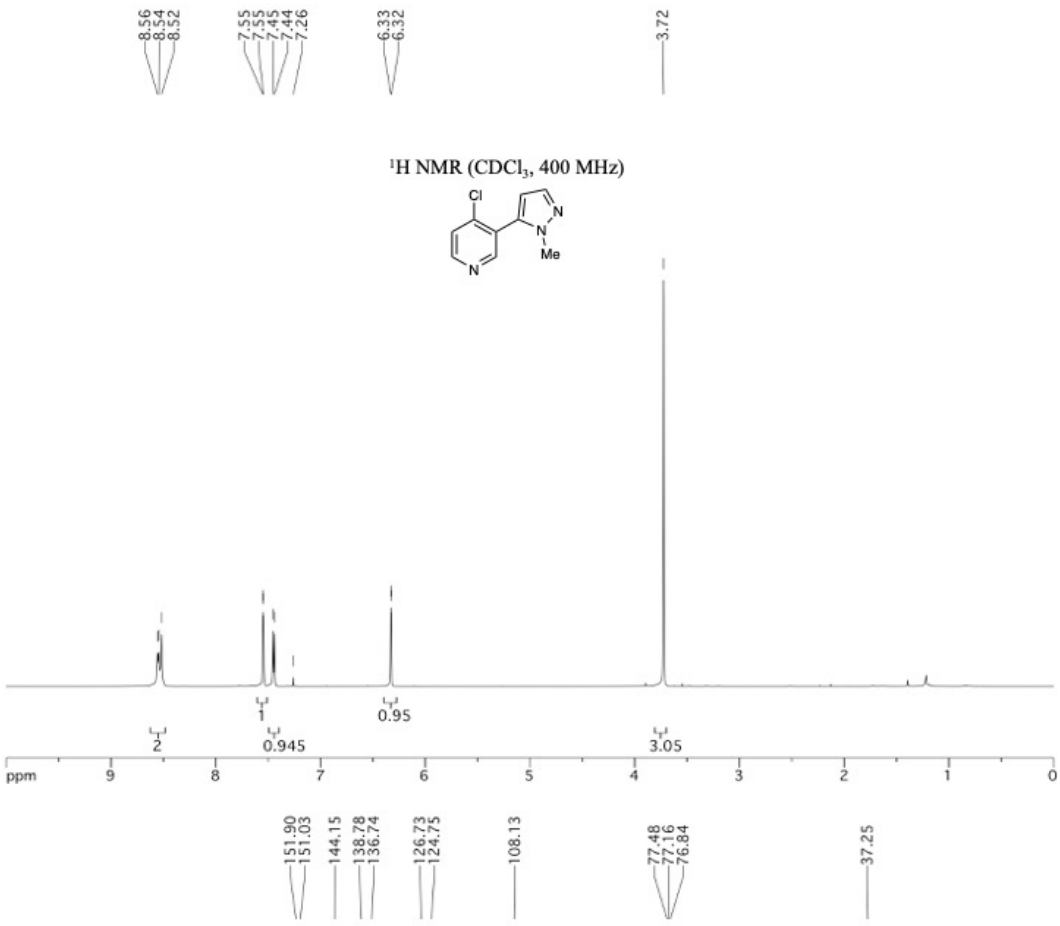
^{19}F NMR ($CDCl_3$, 365 MHz)



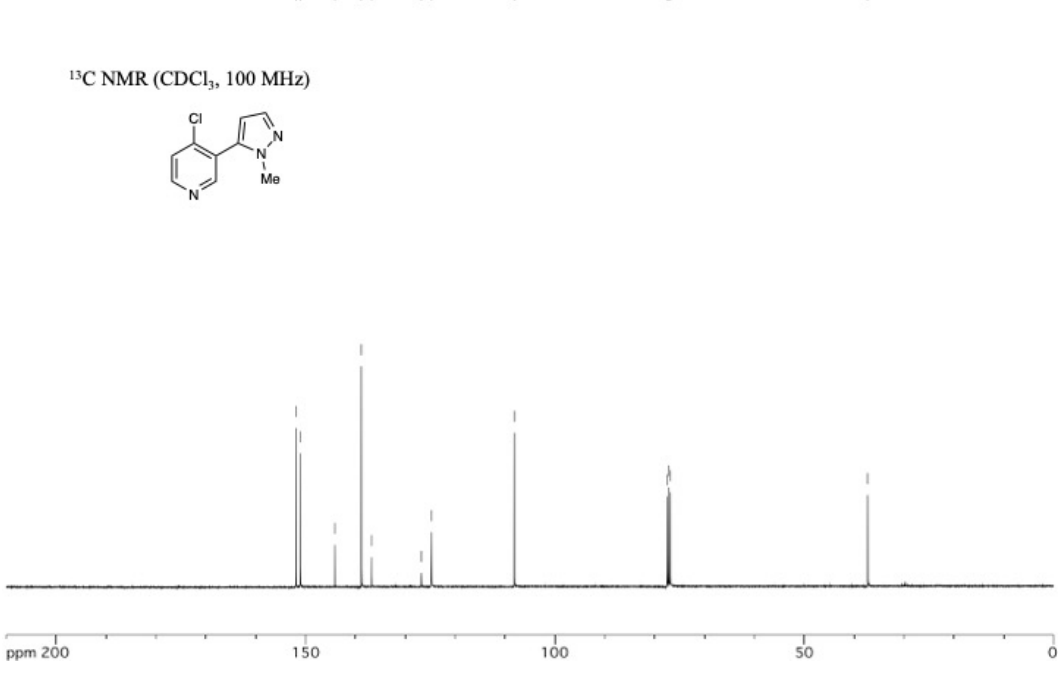
^{31}P NMR ($CDCl_3$, 162 MHz)


8.41
8.38
8.37
7.27
7.26
4.54
4.54
4.52
2.86
2.86
1.44
1.40
1H NMR (CDCl3, 400 MHz)
Cl
N
Me
Boc
1.9
1.0
2.0
2.9
9.1
ppm
9
8
7
6
5
4
3
2
1
0

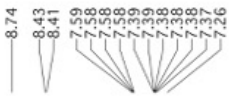

155.95
155.52
150.08
149.40
143.35
143.25
131.52
124.50
80.33
77.48
77.16
76.84
48.33
47.62
34.68
28.43
13C NMR (CDCl3, 100 MHz)
Cl
N
Me
Boc
ppm 200
150
100
50
0



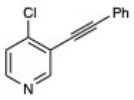
^{1}H NMR ($CDCl_3$, 400 MHz)

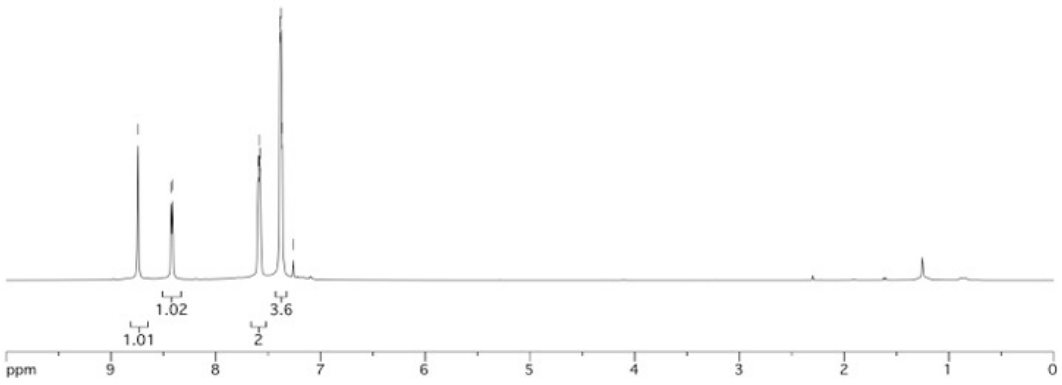


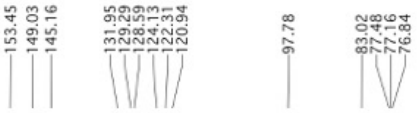
^{13}C NMR ($CDCl_3$, 100 MHz)



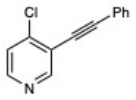
^{1}H NMR ($CDCl_3$, 400 MHz)

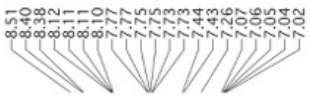




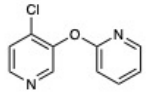


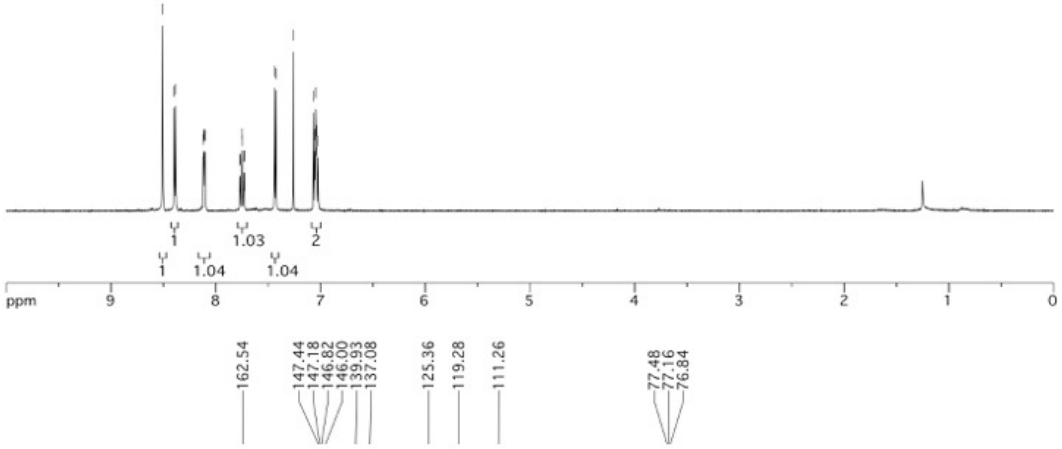
^{13}C NMR ($CDCl_3$, 100 MHz)



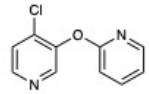


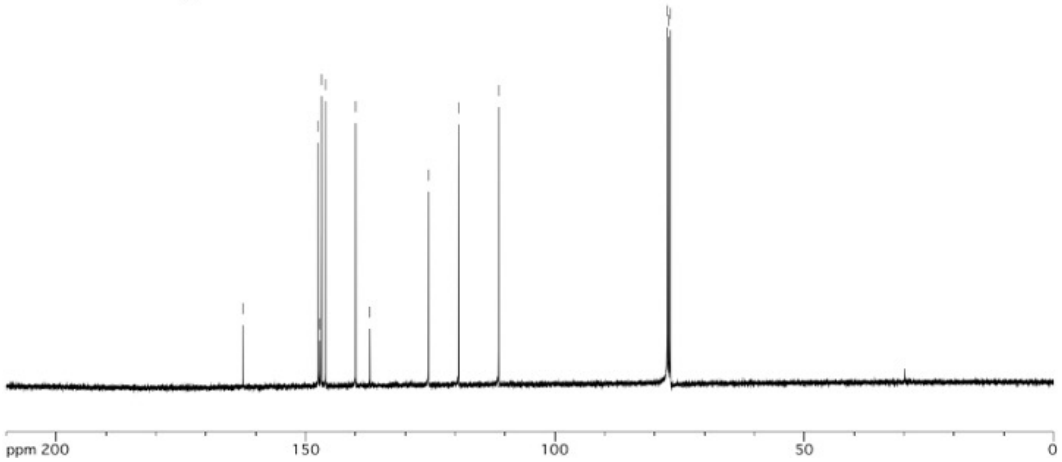
^{1}H NMR ($CDCl_3$, 400 MHz)

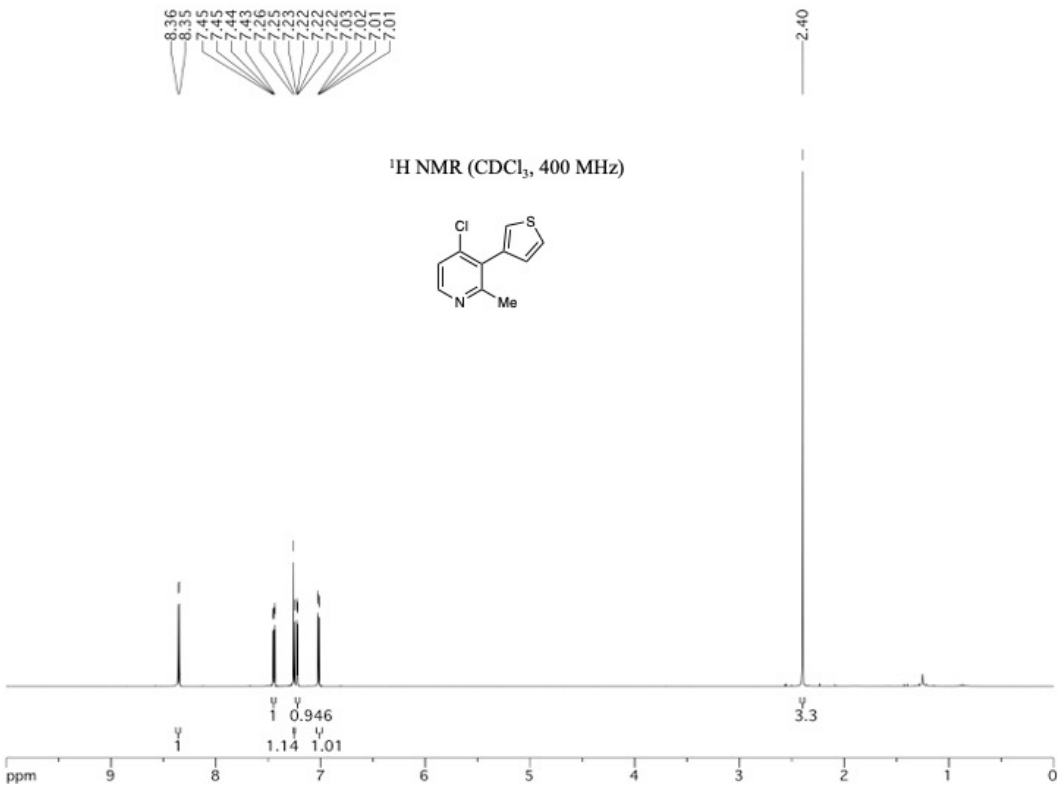




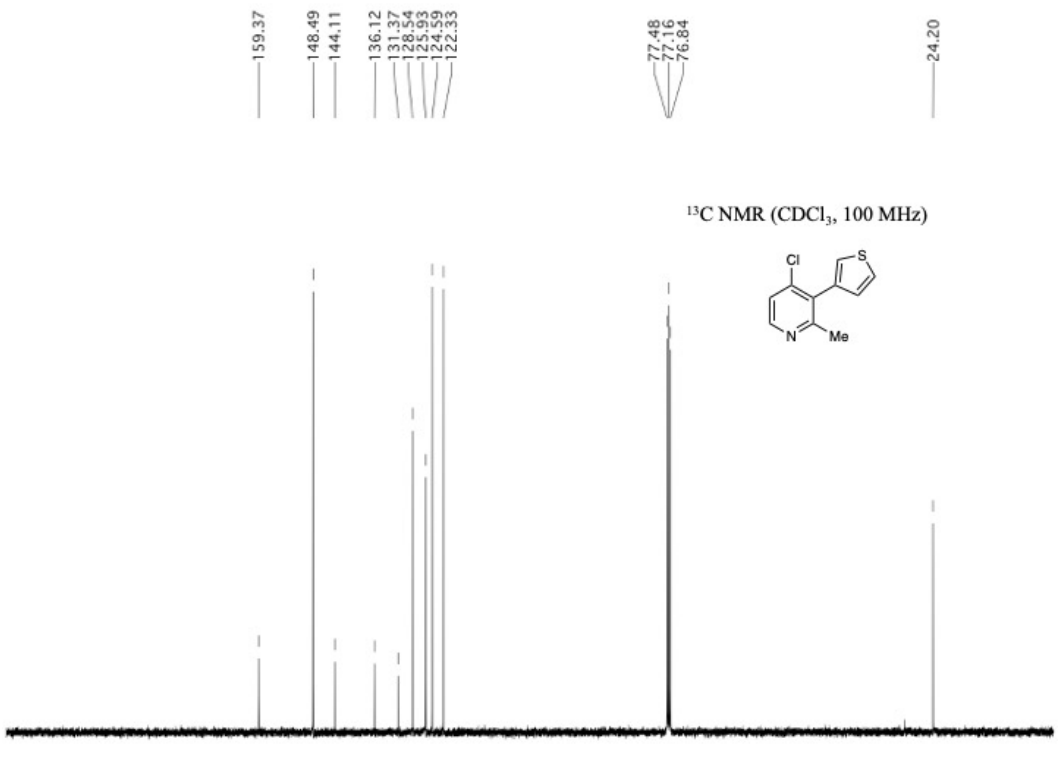
^{13}C NMR ($CDCl_3$, 100 MHz)



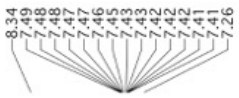




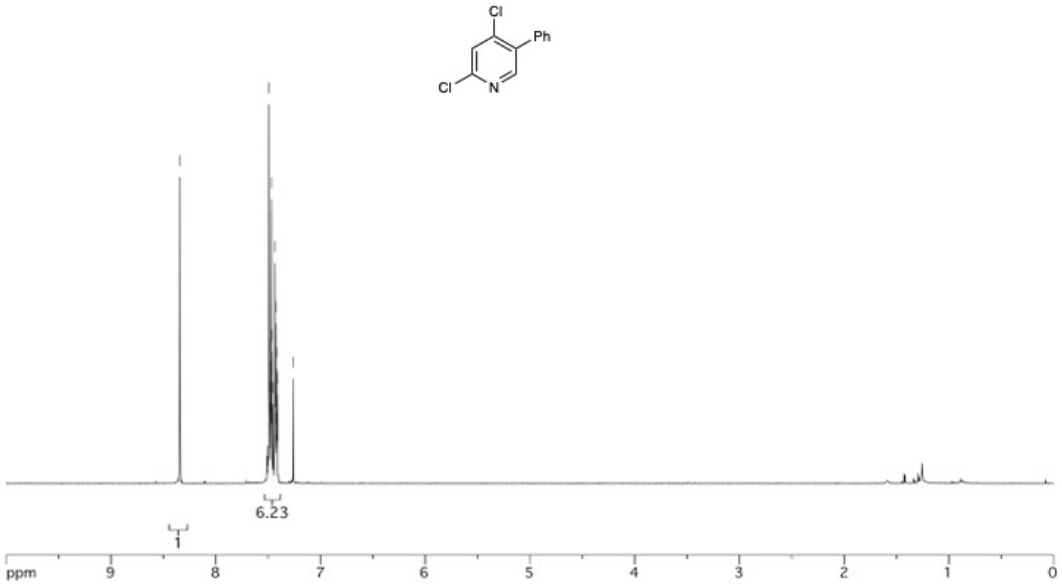
^{1}H NMR ($CDCl_3$, 400 MHz)



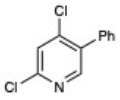
^{13}C NMR ($CDCl_3$, 100 MHz)

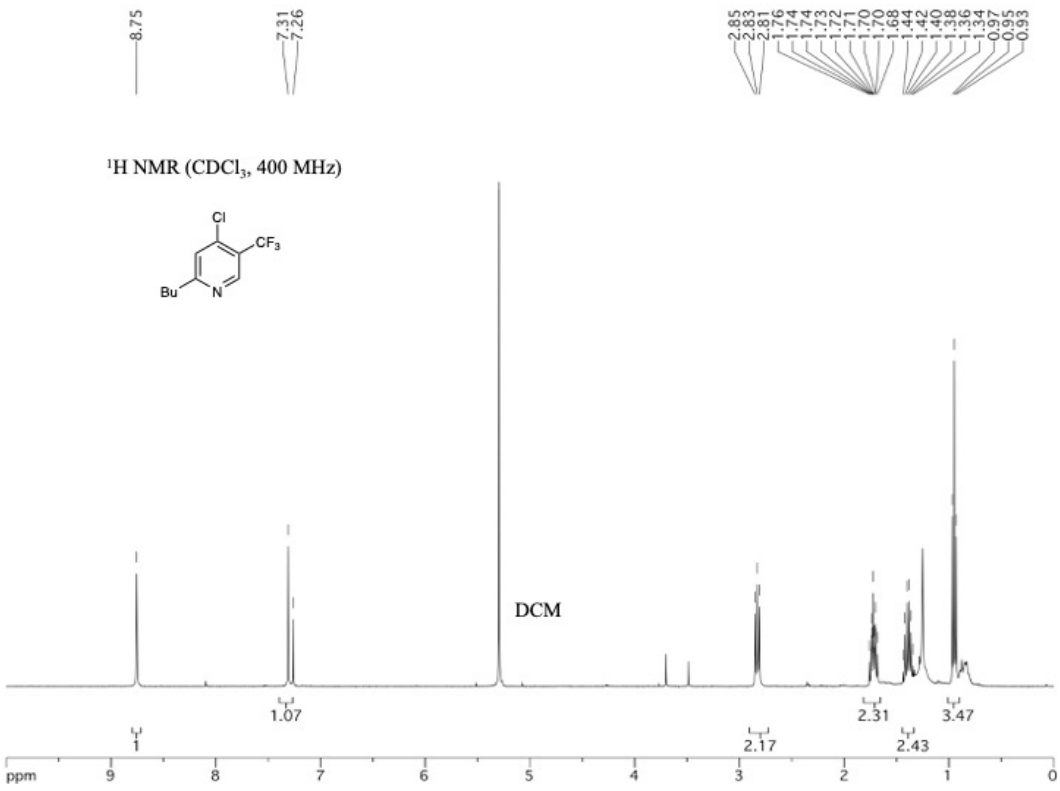


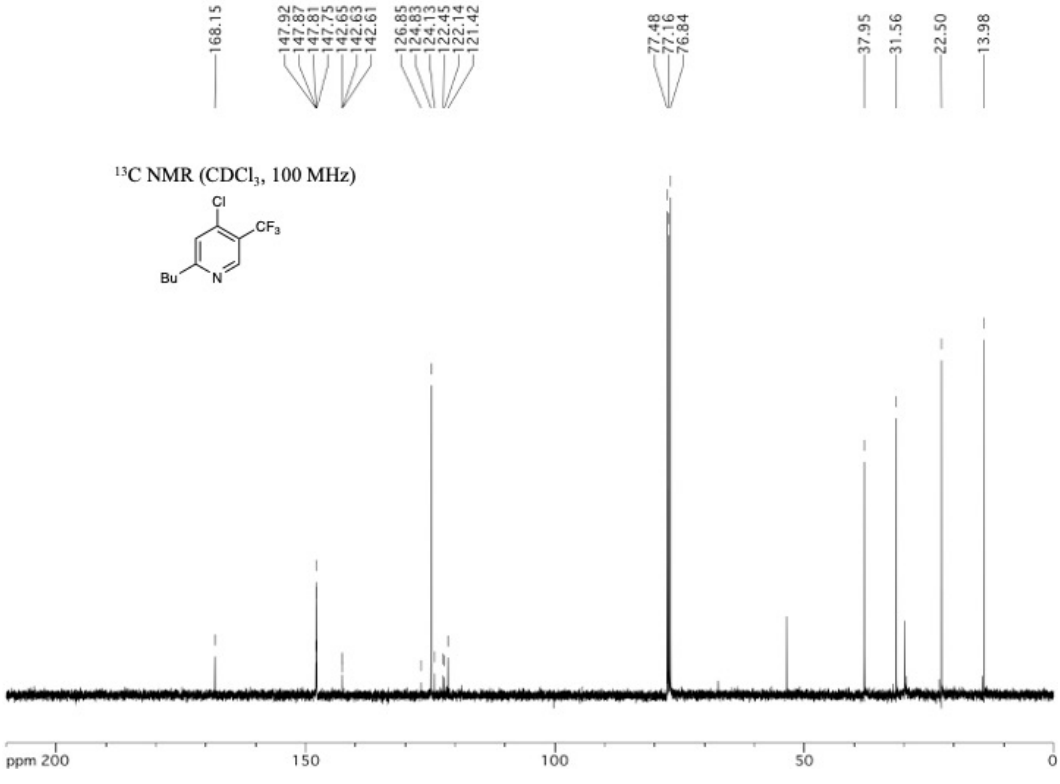
^{1}H NMR ($CDCl_3$, 400 MHz)



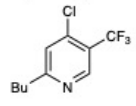
^{13}C NMR ($CDCl_3$, 100 MHz)



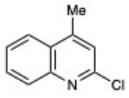

8.75
7.31
7.26
2.85
2.83
2.81
1.76
1.74
1.74
1.73
1.72
1.71
1.70
1.70
1.68
1.44
1.42
1.40
1.38
1.36
1.34
0.97
0.95
0.93
^{1}H NMR ($CDCl_3$, 400 MHz)
Cl
CF_3
Bu
N
DCM
1.07
2.31
3.47
1
2.17
2.43
ppm
9
8
7
6
5
4
3
2
1
0


168.15
147.92
147.87
147.81
147.75
142.65
142.63
142.61
126.85
124.83
124.13
122.45
122.14
121.42
77.48
77.16
76.84
37.95
31.56
22.50
13.98
^{13}C NMR ($CDCl_3$, 100 MHz)
Cl
CF_3
Bu
N
ppm 200
150
100
50
0

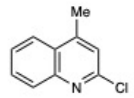
^{19}F NMR ($CDCl_3$, 365 MHz)

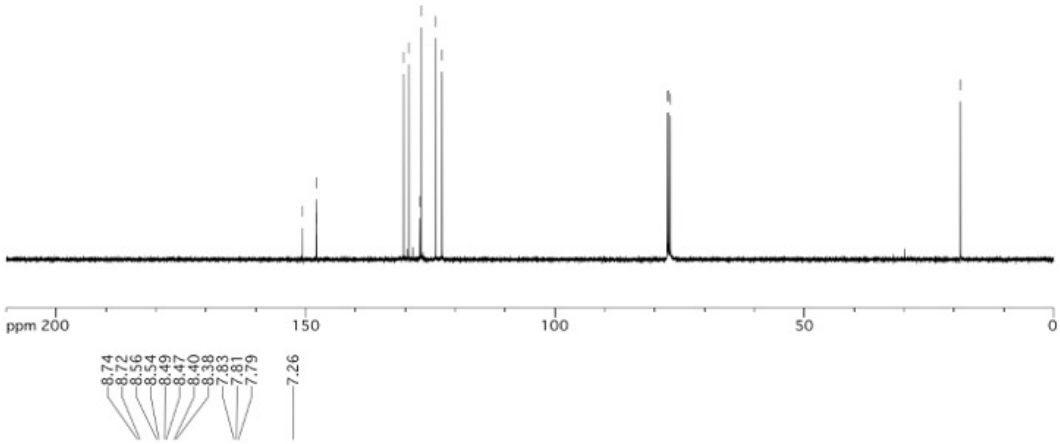


^{1}H NMR ($CDCl_3$, 400 MHz)

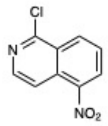


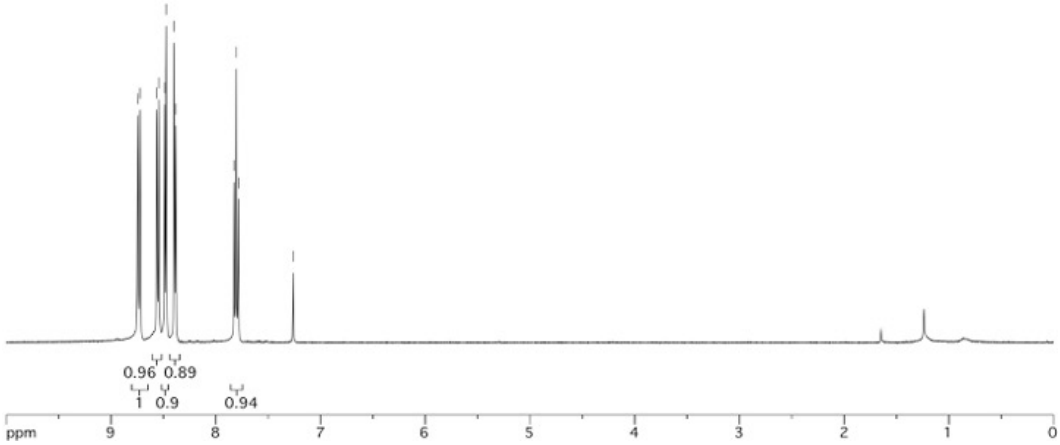
^{13}C NMR ($CDCl_3$, 100 MHz)



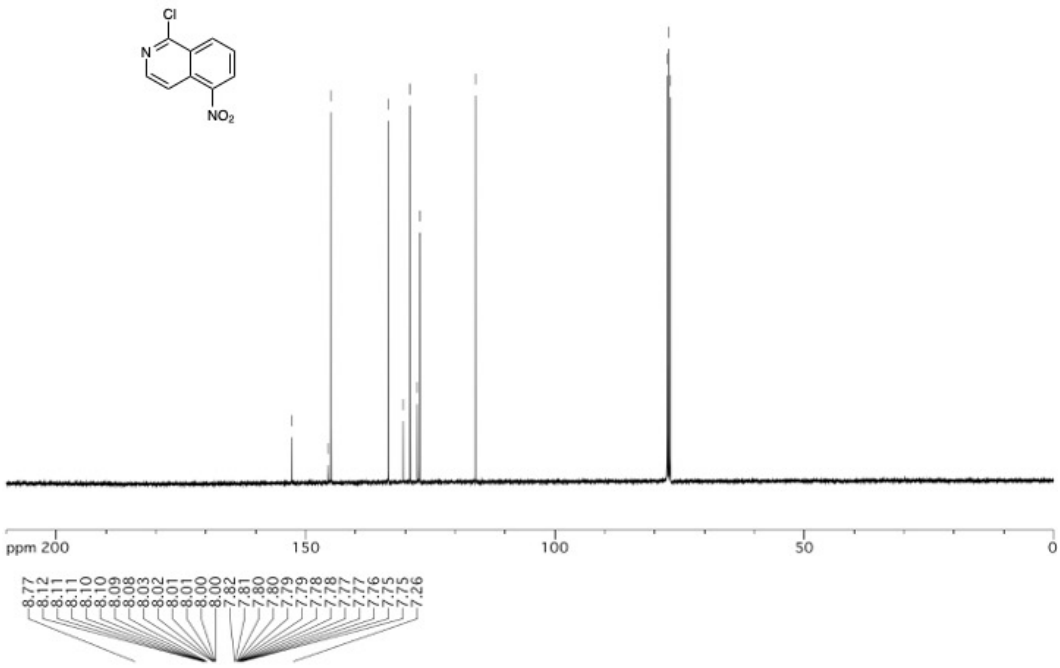


^{1}H NMR ($CDCl_3$, 400 MHz)

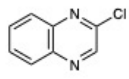


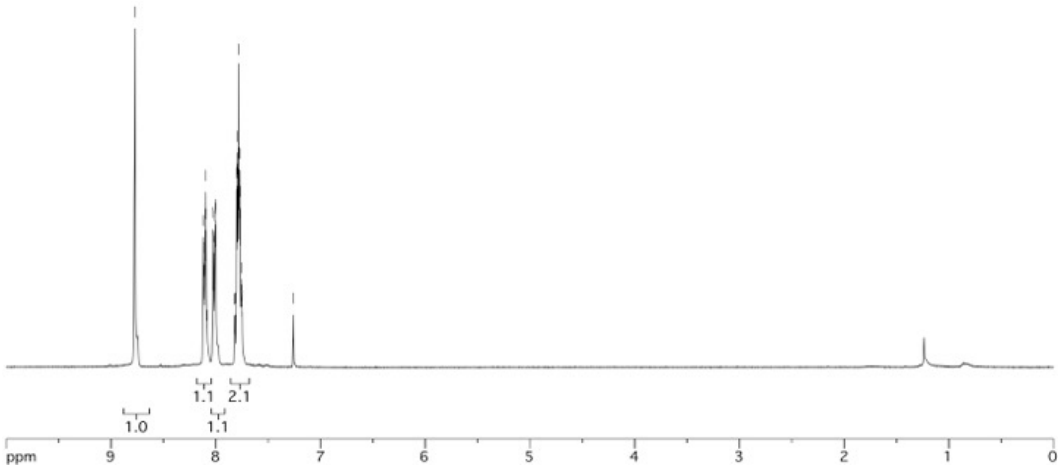


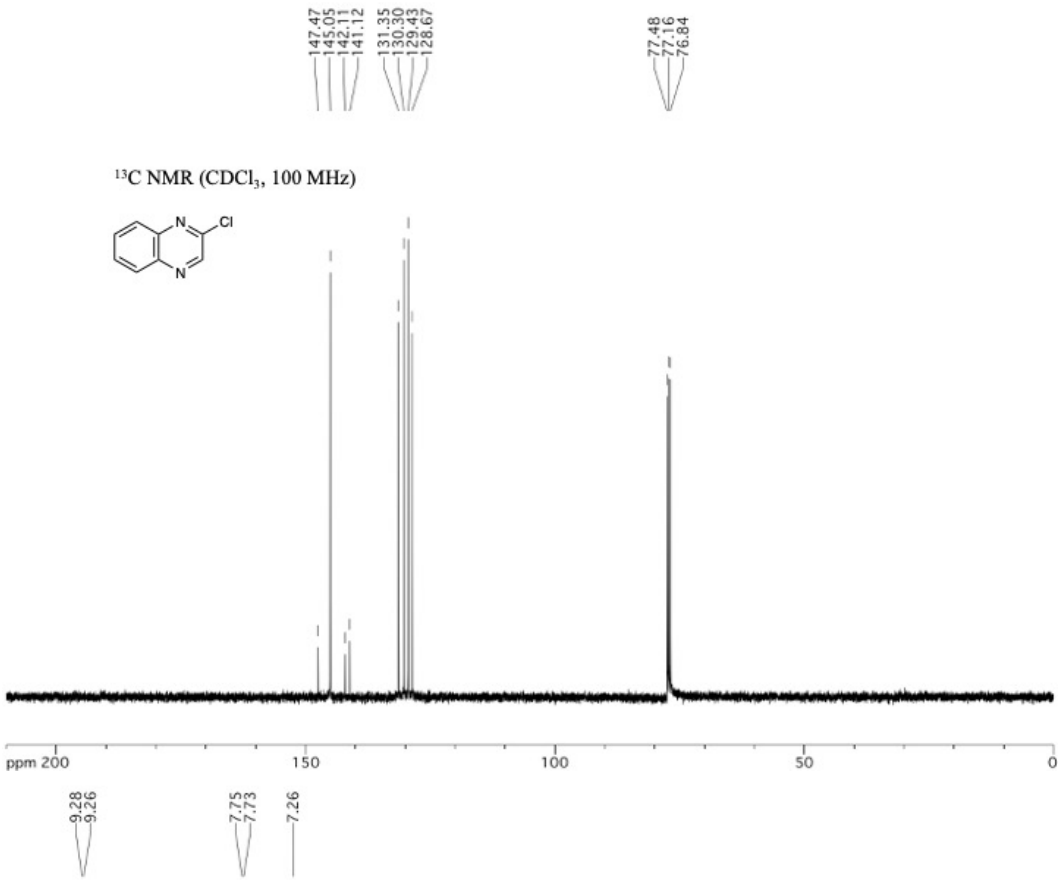
^{13}C NMR ($CDCl_3$, 100 MHz)



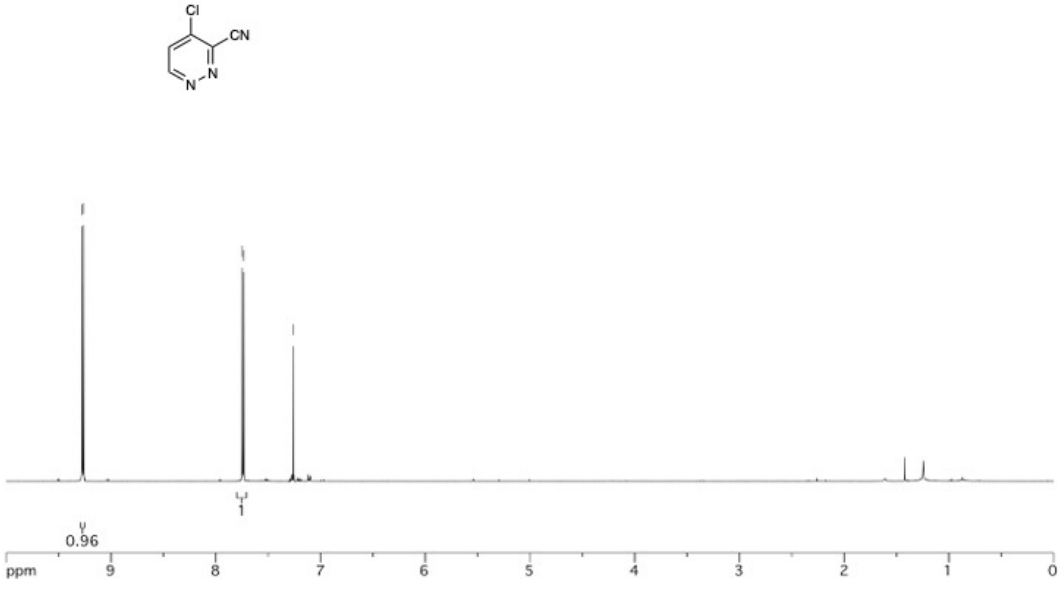
^{1}H NMR ($CDCl_3$, 400 MHz)



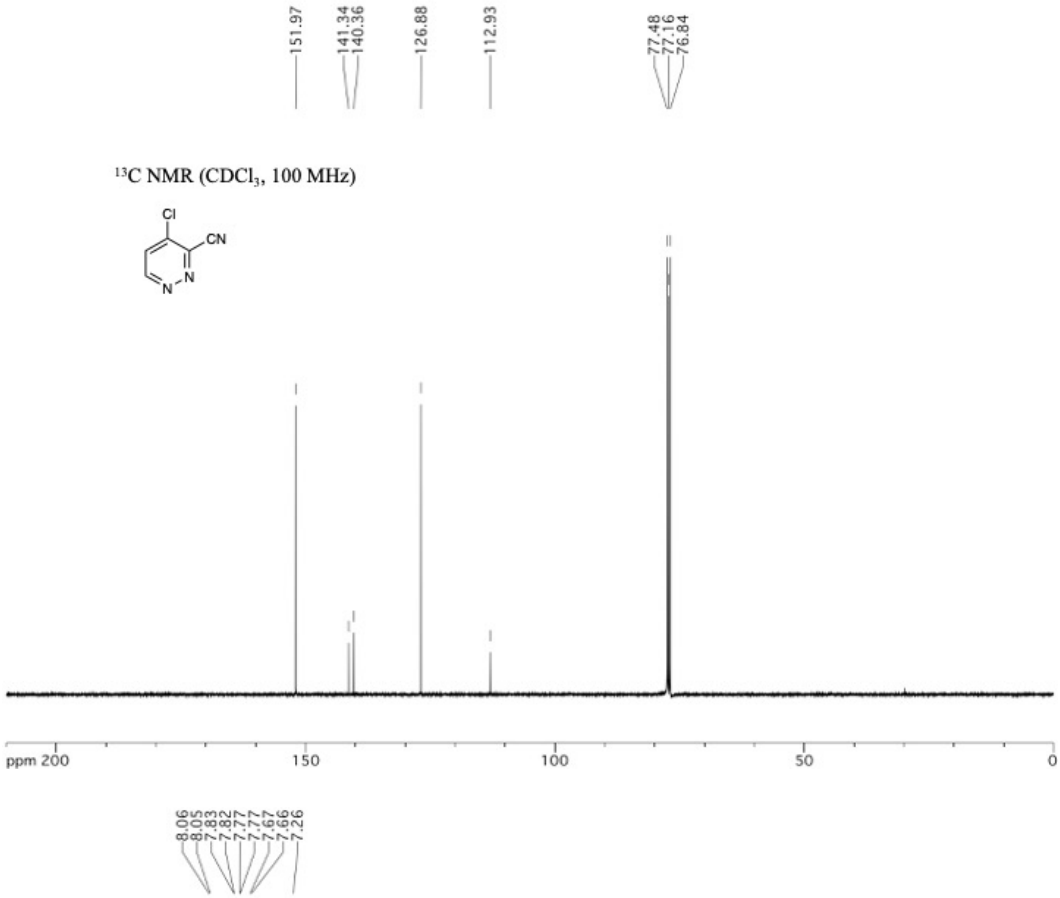




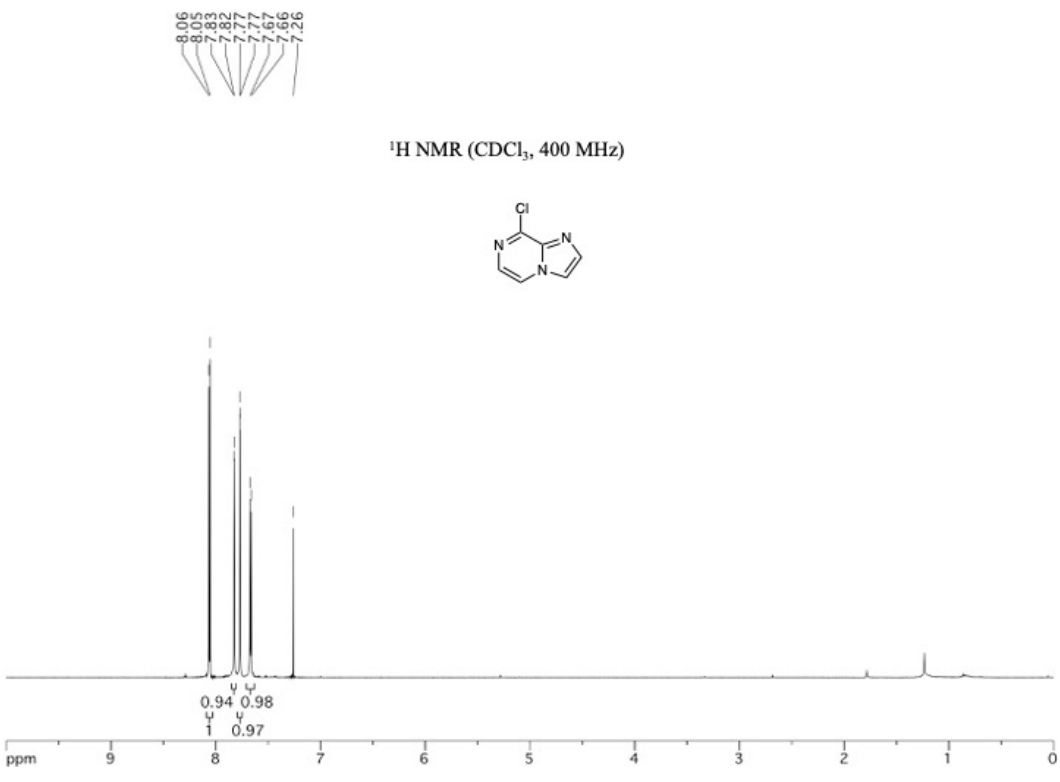
^{13}C NMR ($CDCl_3$, 100 MHz)



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

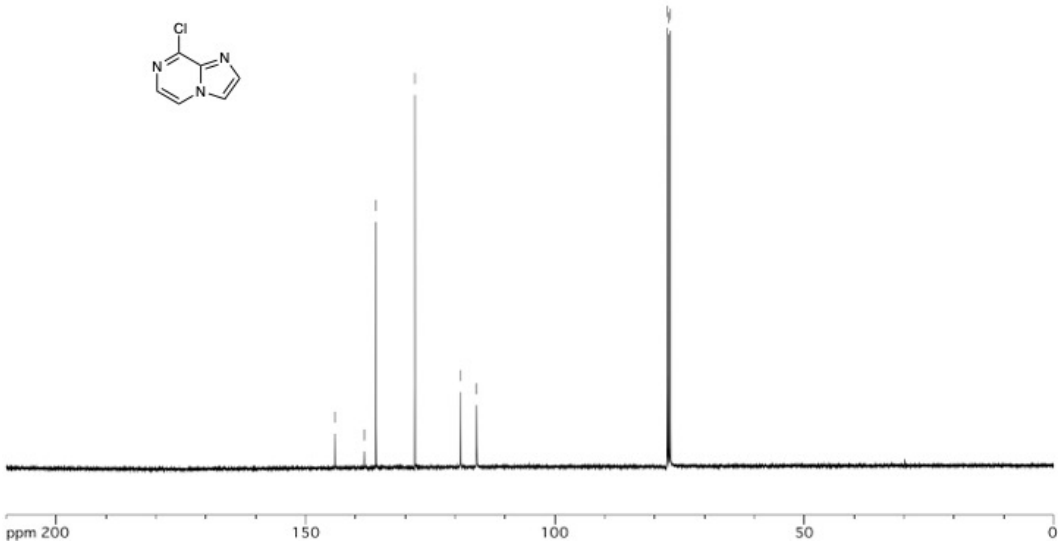


^{13}C NMR ($CDCl_3$, 100 MHz)

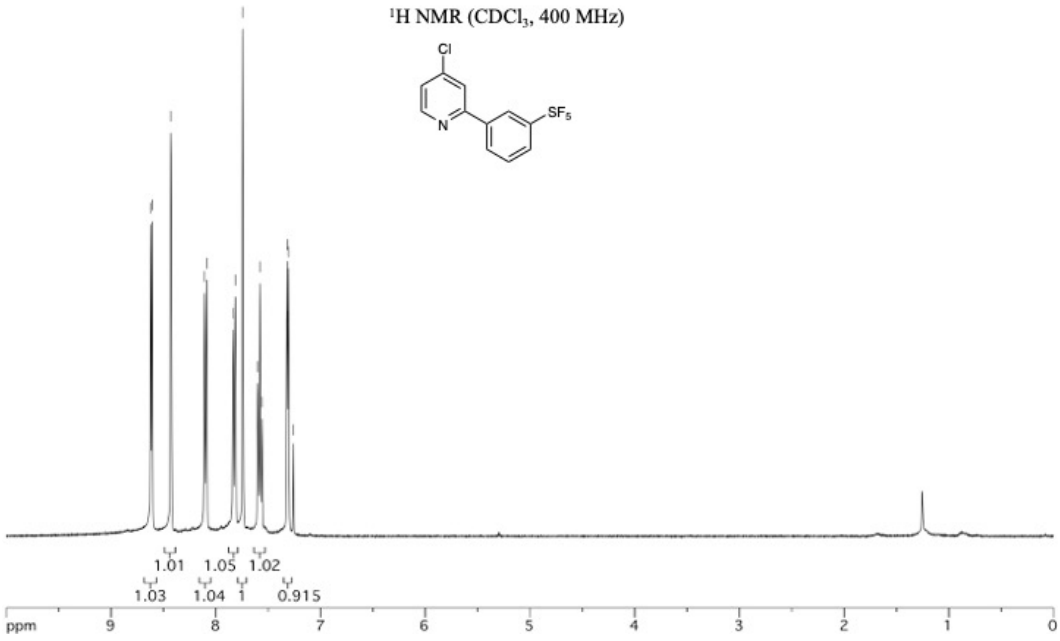


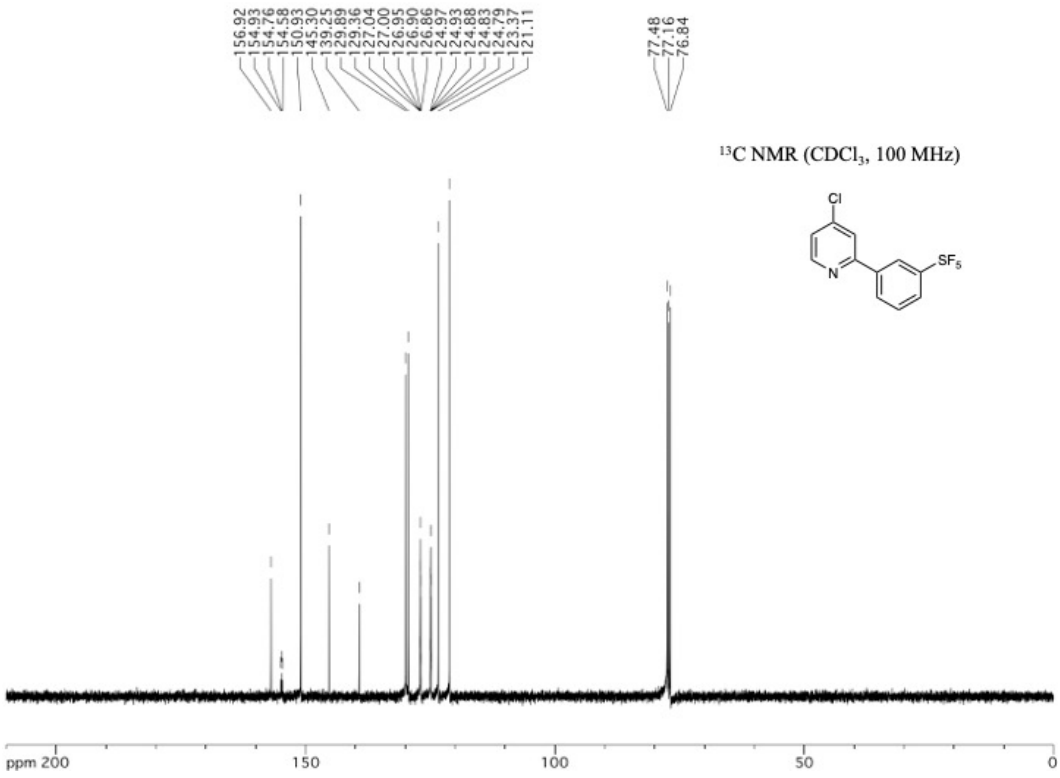
^{1}H NMR ($CDCl_3$, 400 MHz)

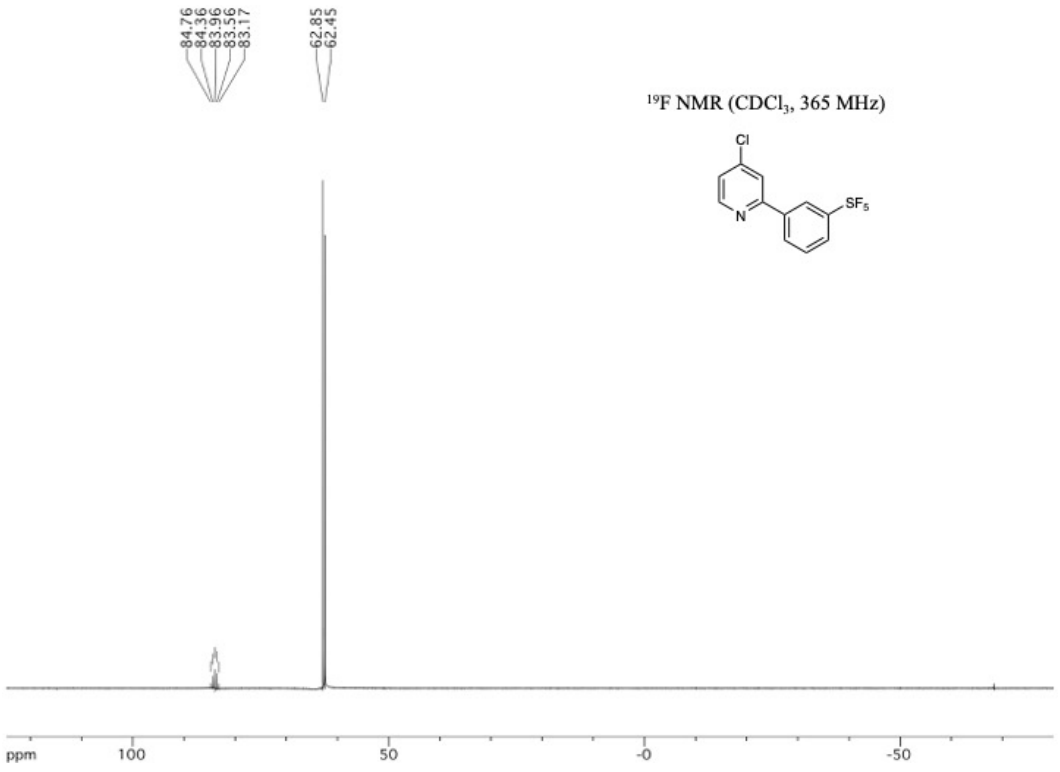
^{13}C NMR ($CDCl_3$, 100 MHz)

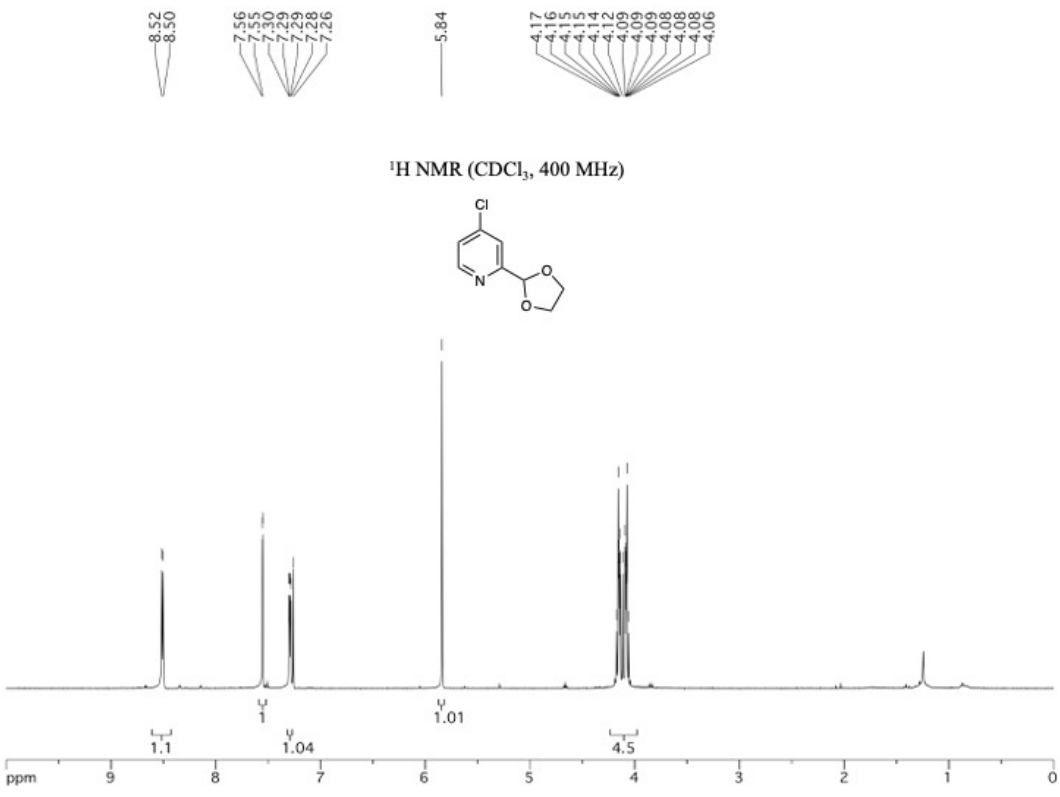


^{1}H NMR ($CDCl_3$, 400 MHz)

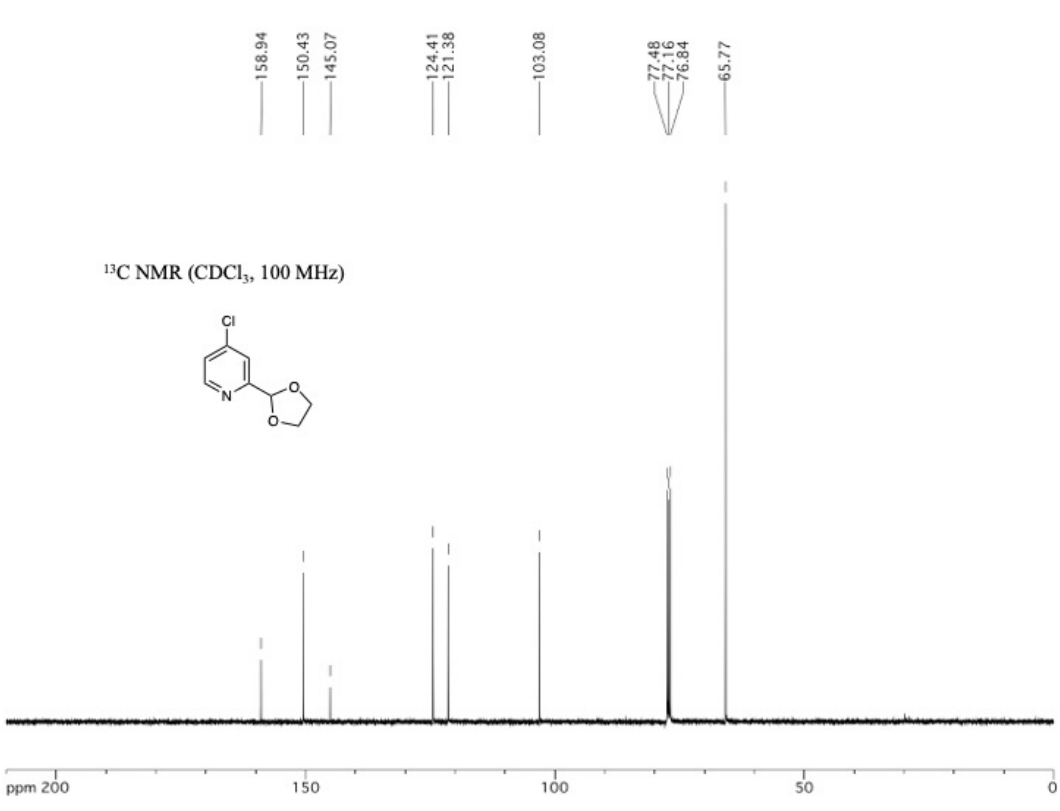



156.92
154.93
154.76
154.58
150.93
145.30
139.25
129.69
129.36
127.04
127.00
126.95
126.90
126.86
124.97
124.93
124.88
124.83
124.79
123.37
121.11
77.48
77.16
76.84
13C NMR (CDCl3, 100 MHz)
Cl
N
SF5
ppm 200
150
100
50
0

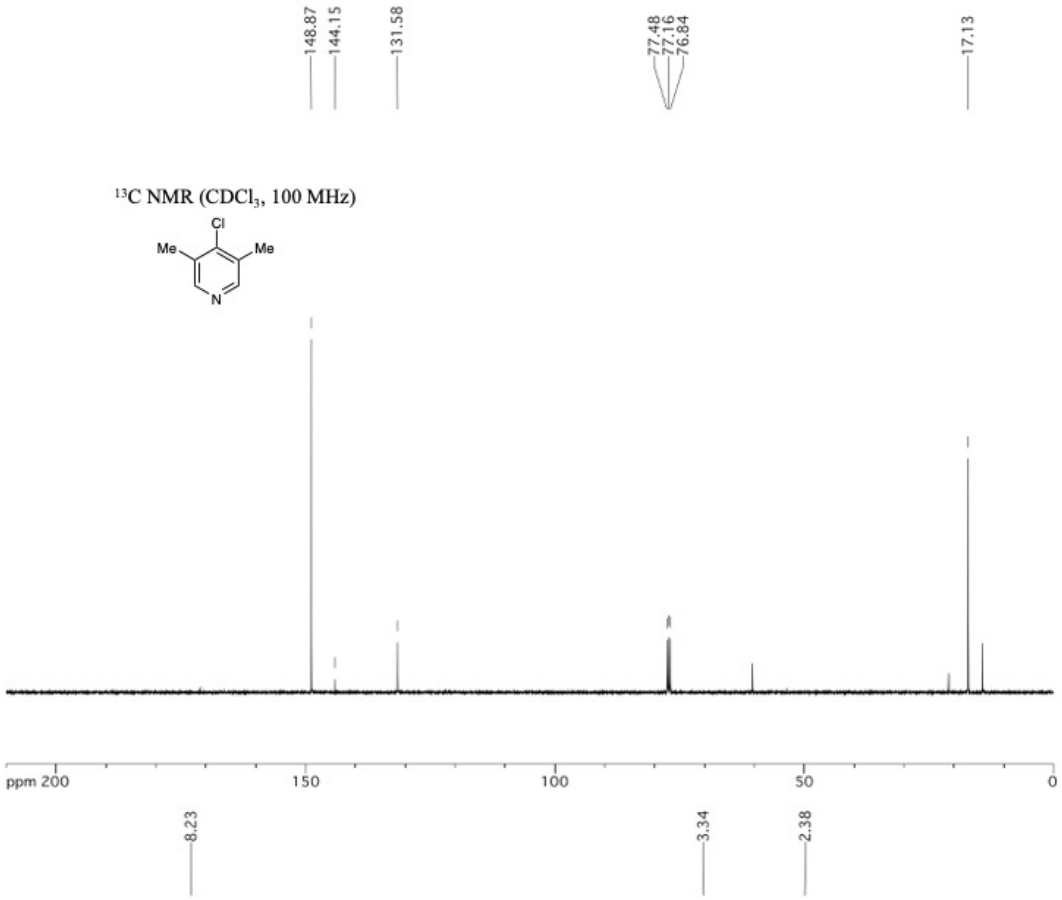

84.76
84.36
83.96
83.56
83.17
62.85
62.45
19F NMR (CDCl3, 365 MHz)
Cl
N
SF5
ppm
100
50
-0
-50



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

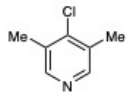


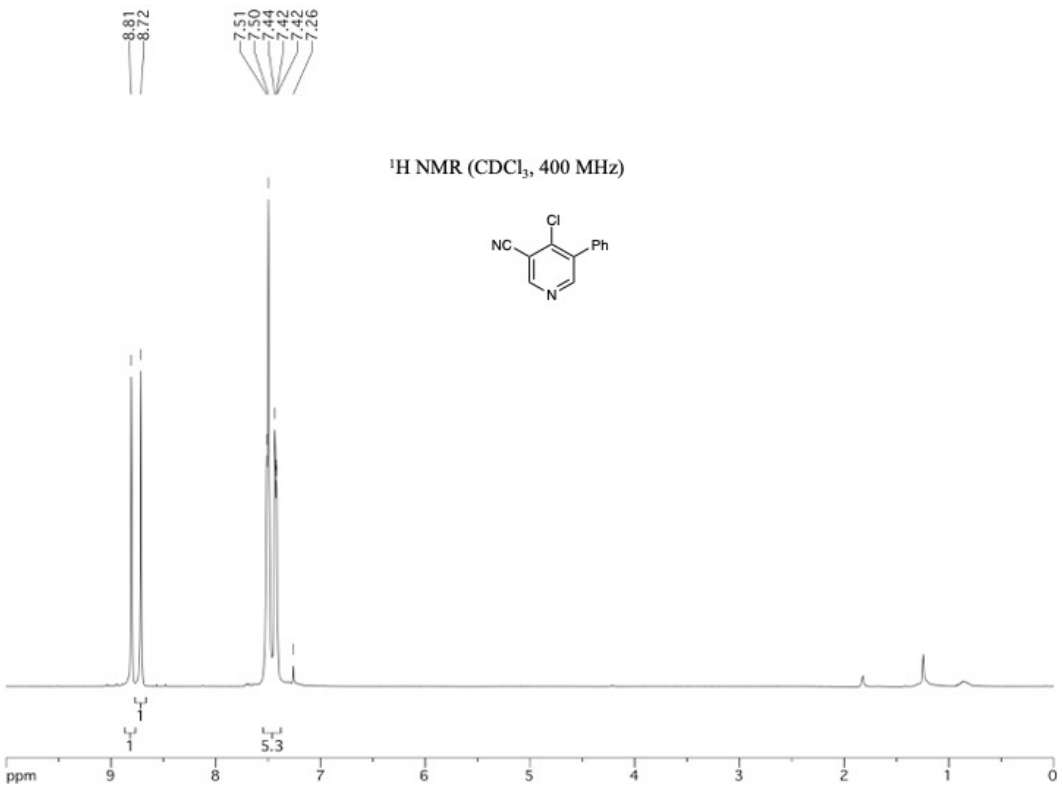
^{13}C NMR ($CDCl_3$, 100 MHz)

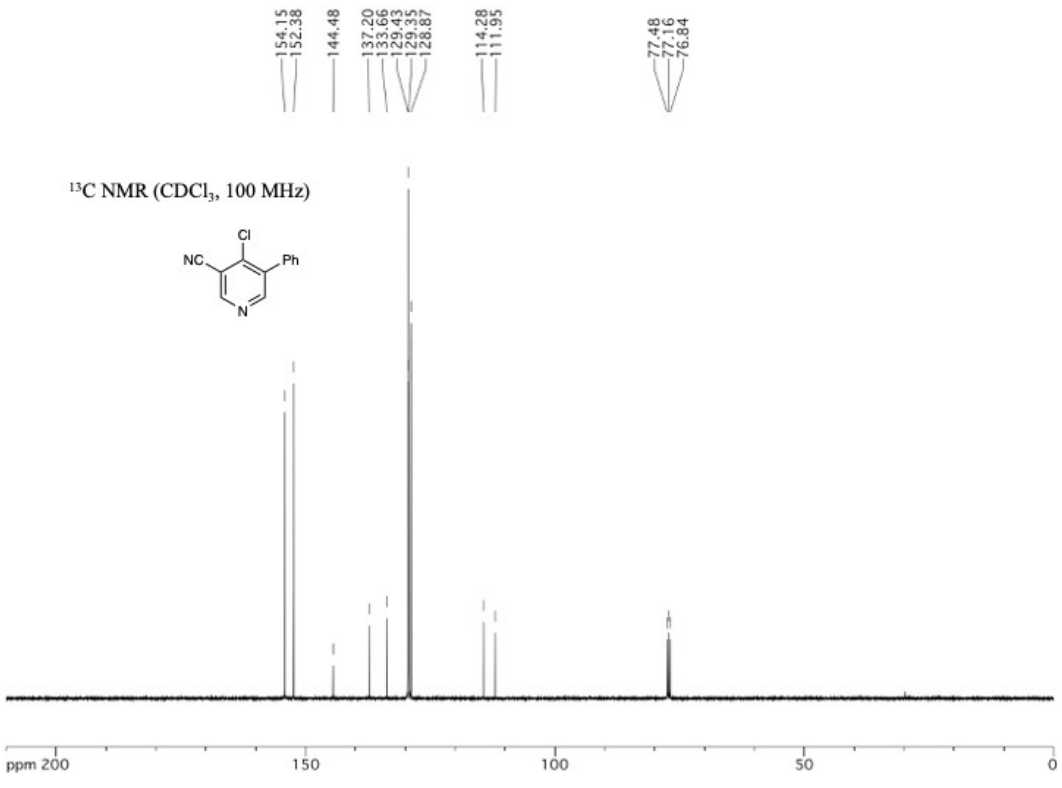


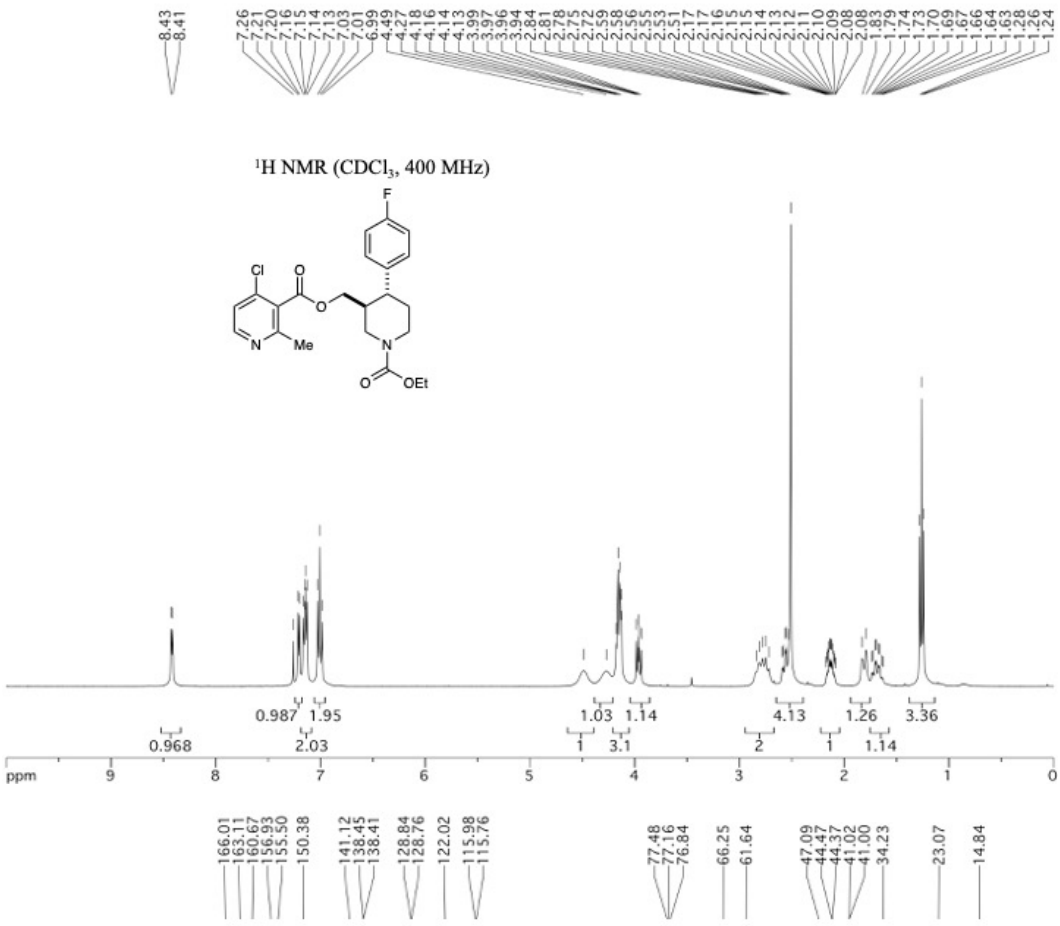
^{13}C NMR ($CDCl_3$, 100 MHz)

^{1}H NMR (CD_3OD, 400 MHz)



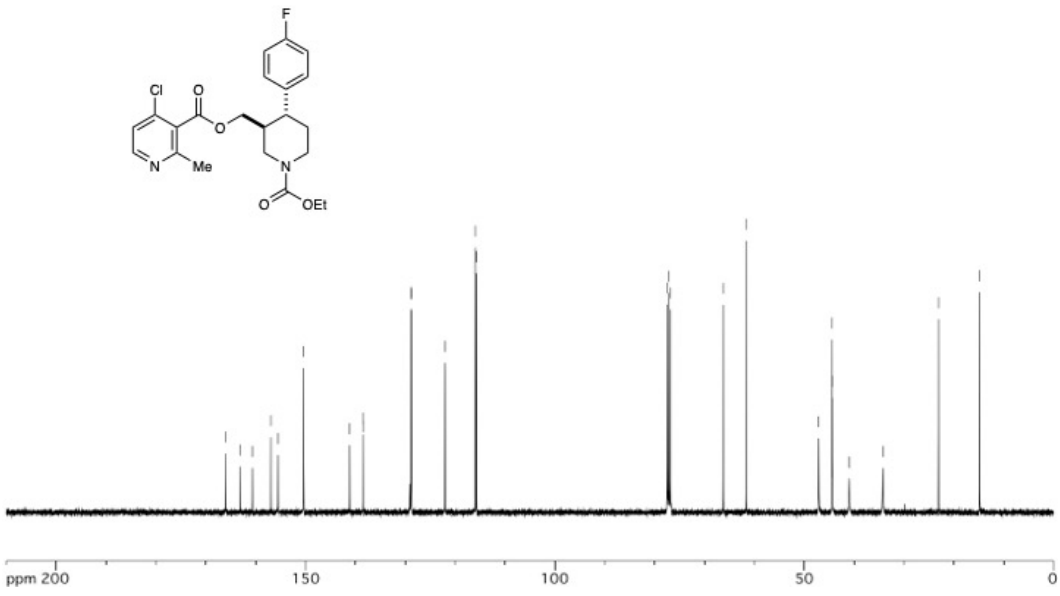

8.81
8.72
7.51
7.50
7.44
7.42
7.42
7.26
1H NMR (CDCl3, 400 MHz)
Cl
NC
Ph
N
1
1
1
5.3
ppm
9
8
7
6
5
4
3
2
1
0

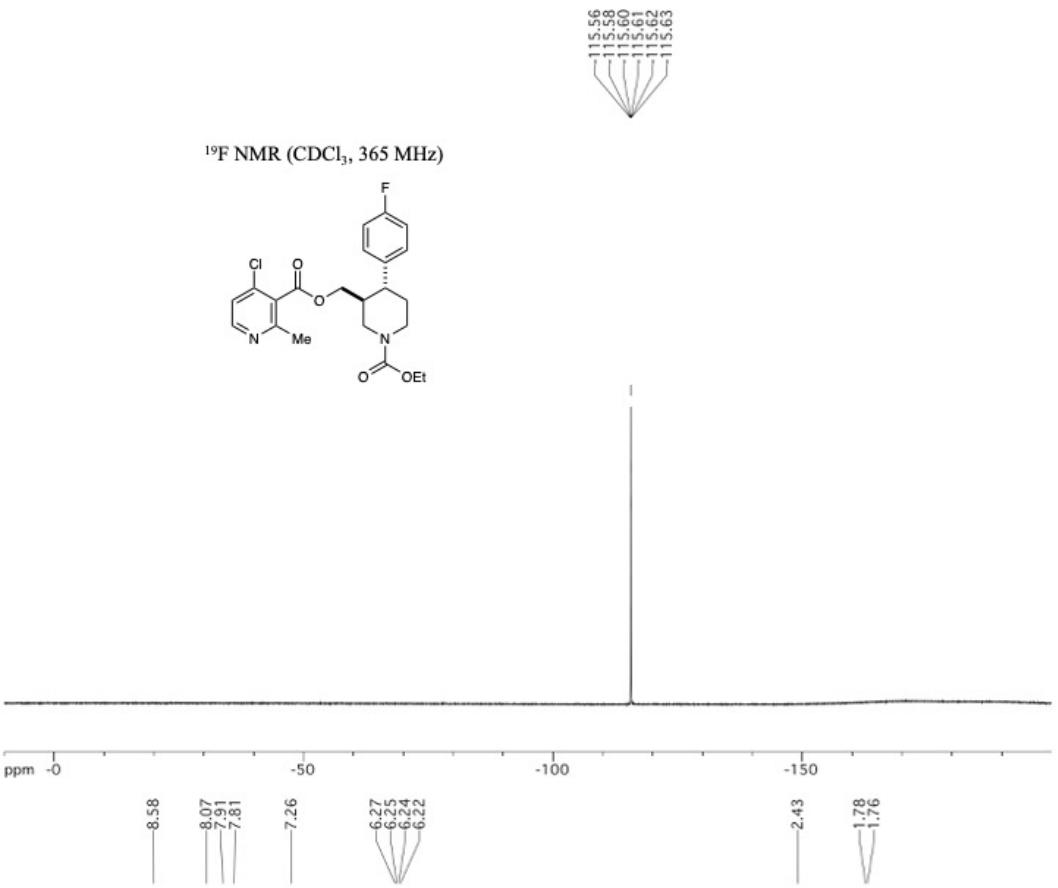

154.15
152.38
144.48
137.20
133.66
129.43
129.35
128.87
114.28
111.95
77.48
77.16
76.84
13C NMR (CDCl3, 100 MHz)
Cl
NC
Ph
N
ppm 200
150
100
50
0



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

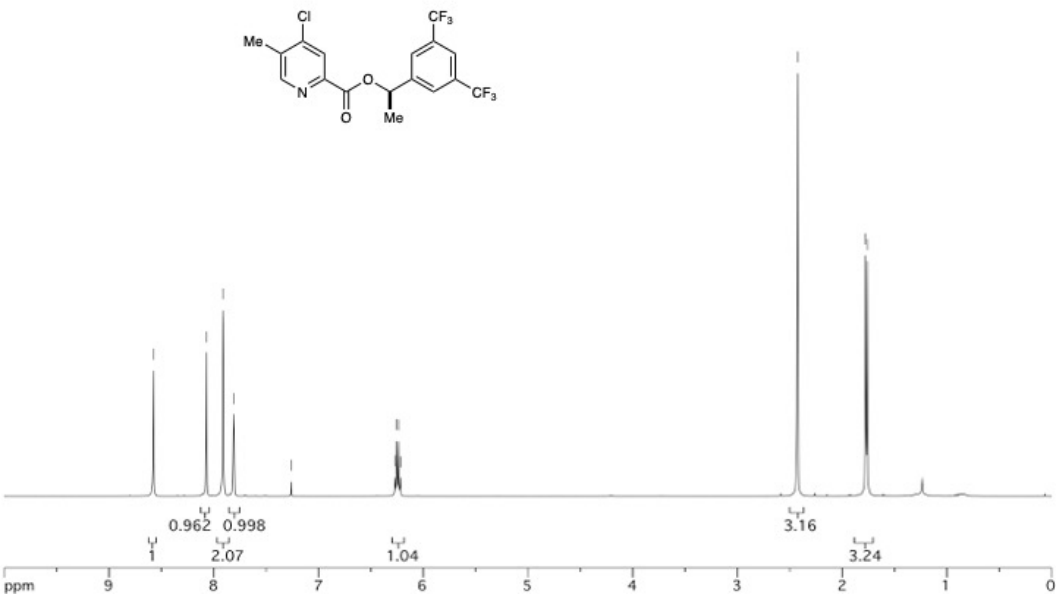
^{13}C NMR ($CDCl_3$, 100 MHz)

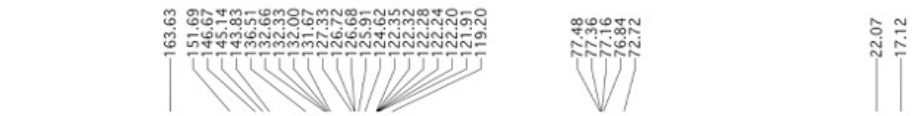




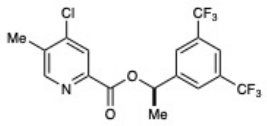
^{19}F NMR ($CDCl_3$, 365 MHz)

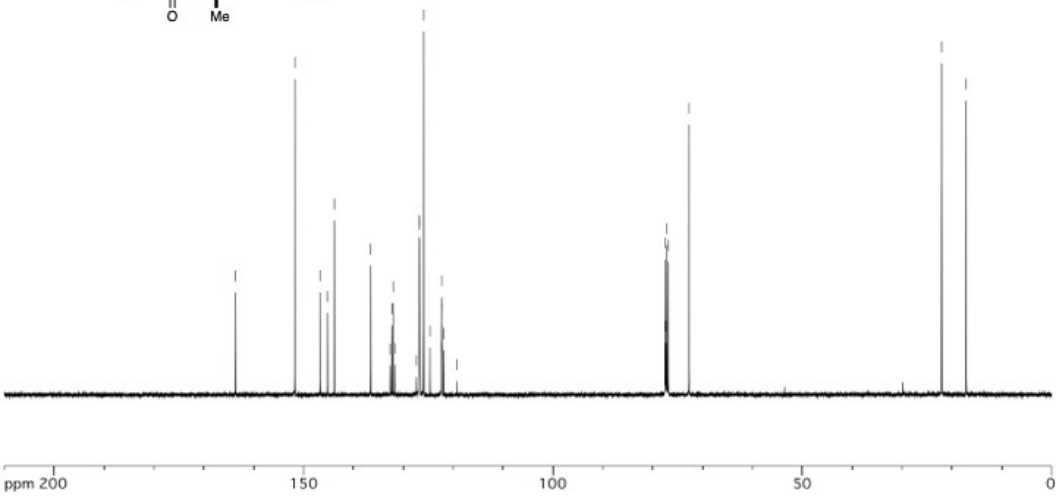
^{1}H NMR ($CDCl_3$, 400 MHz)



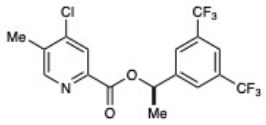


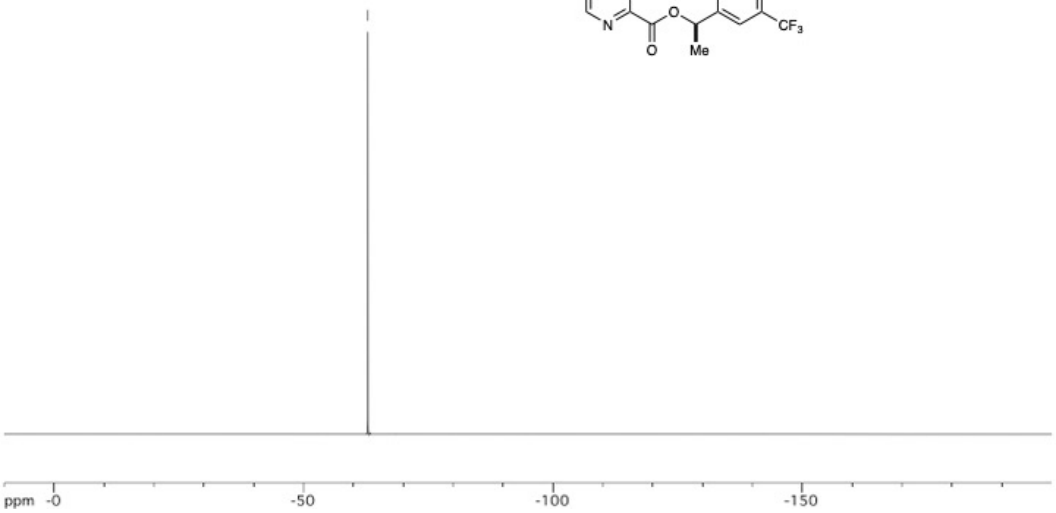
^{13}C NMR ($CDCl_3$, 100 MHz)

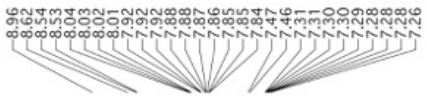




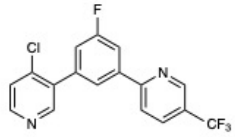
^{19}F NMR ($CDCl_3$, 365 MHz)

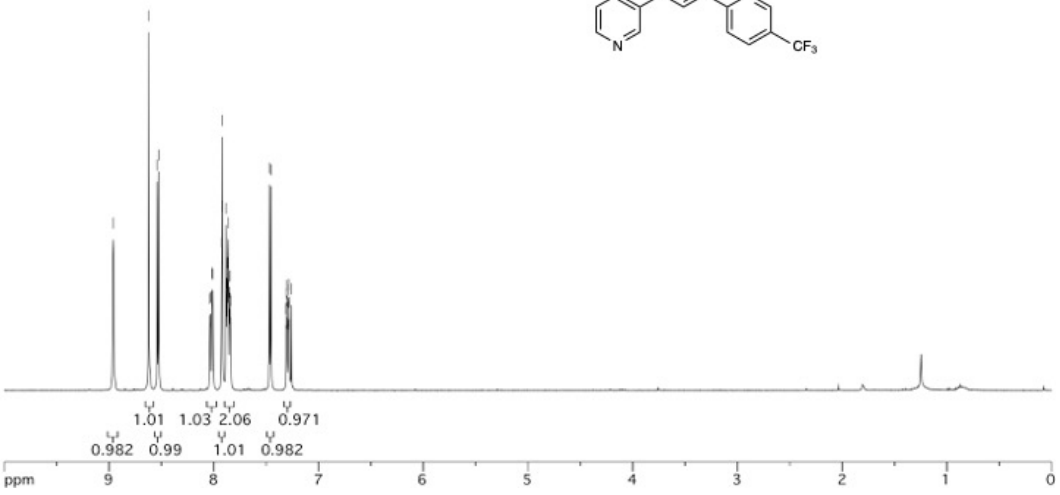


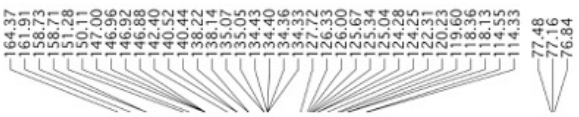




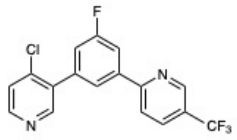
^{1}H NMR ($CDCl_3$, 400 MHz)

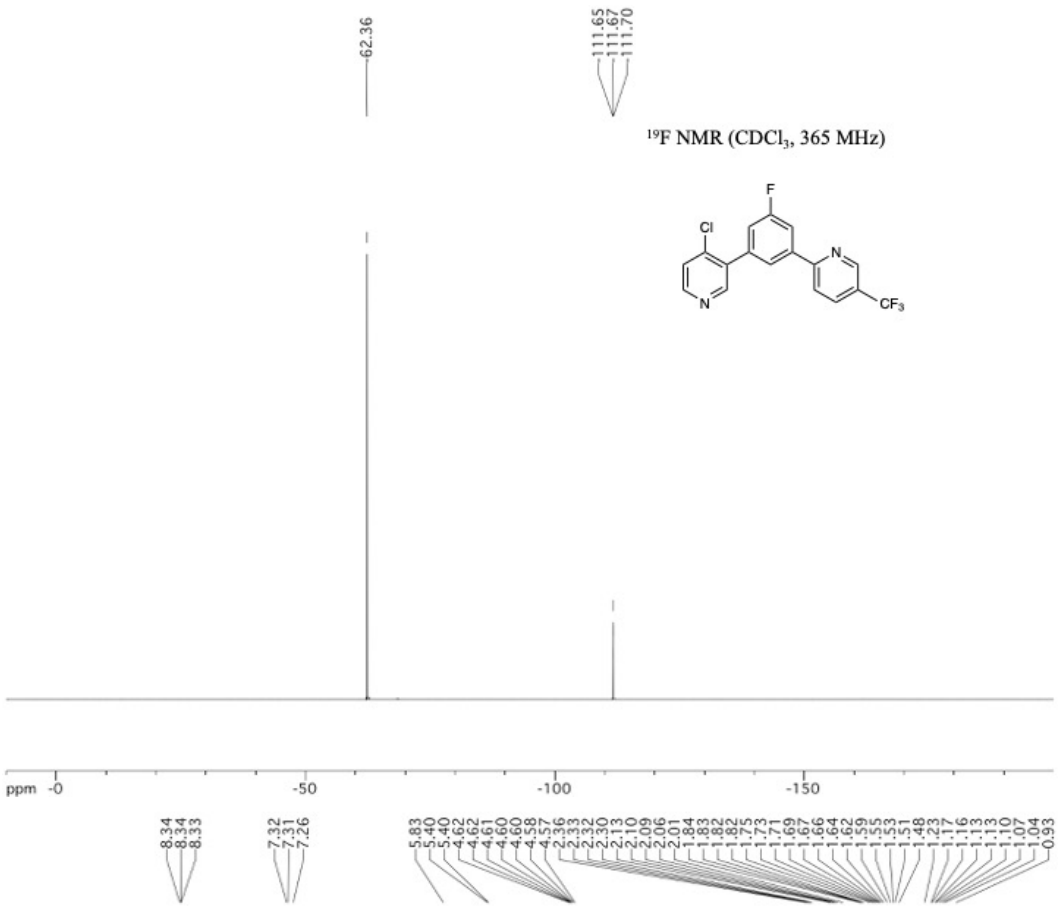




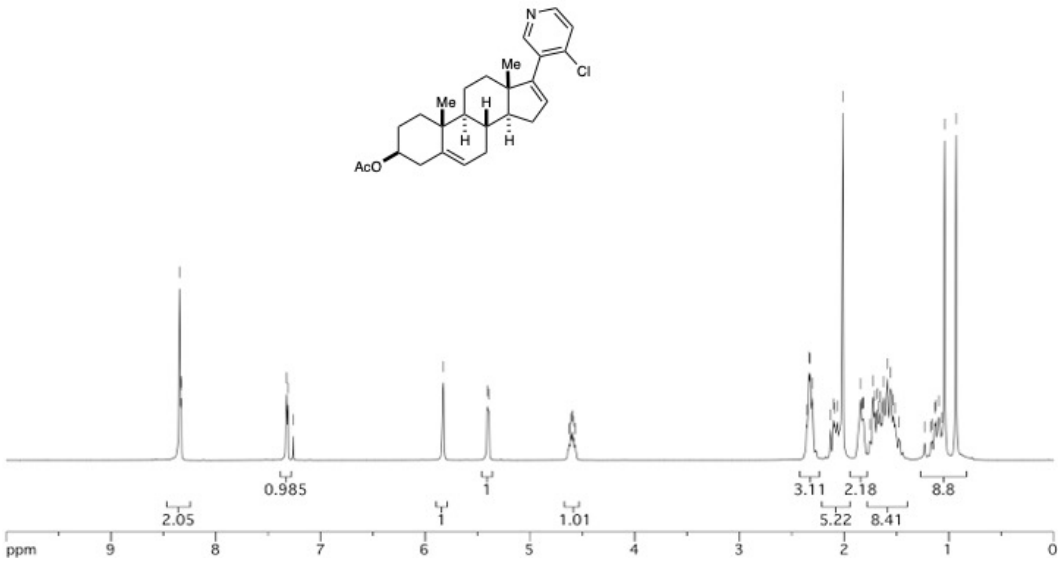


^{13}C NMR ($CDCl_3$, 100 MHz)



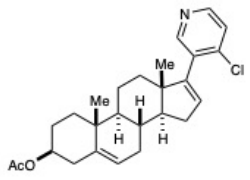


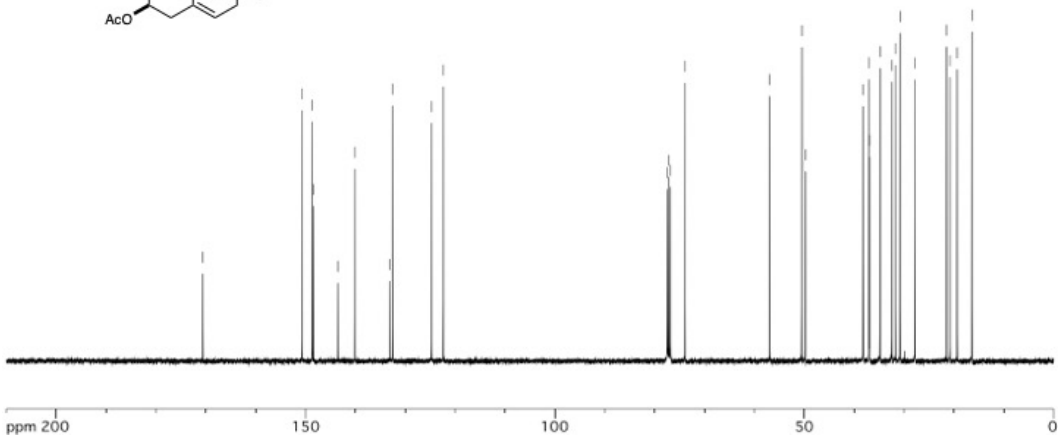
^{19}F NMR ($CDCl_3$, 365 MHz)

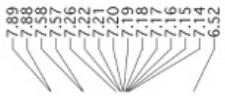


^{1}H NMR ($CDCl_3$, 400 MHz)

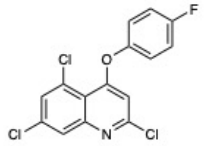
^{13}C NMR ($CDCl_3$, 100 MHz)

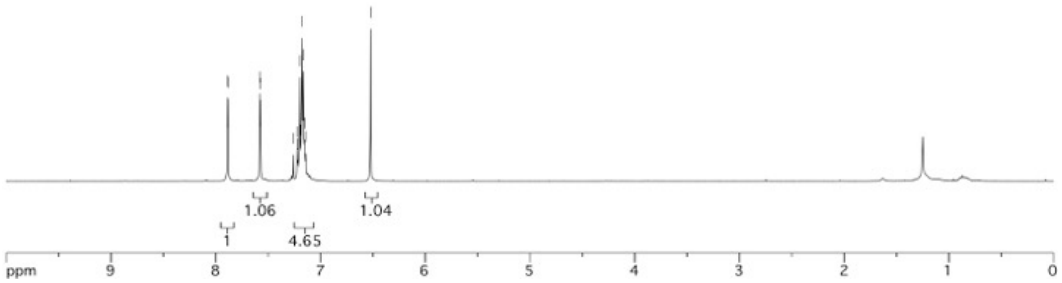


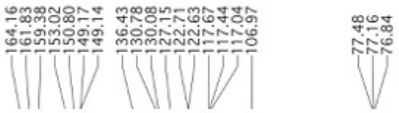




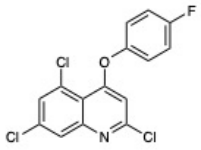
^{1}H NMR ($CDCl_3$, 400 MHz)

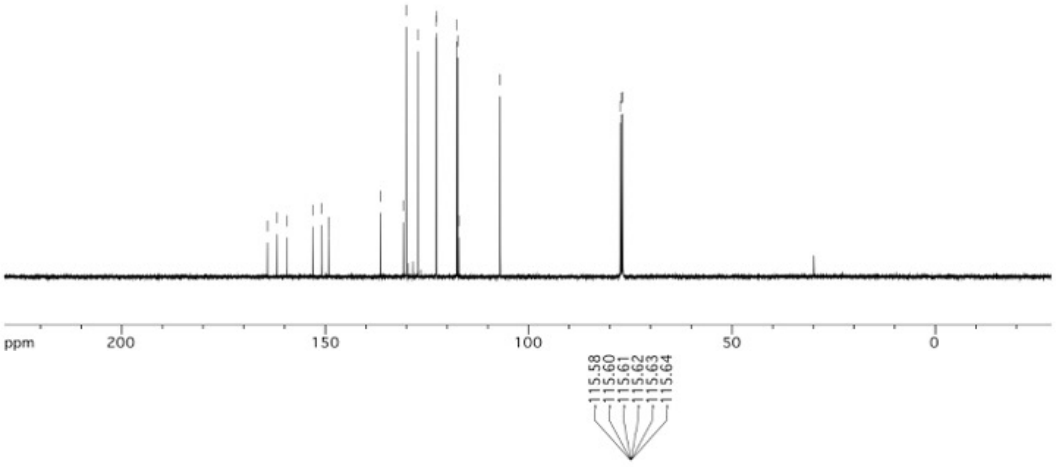




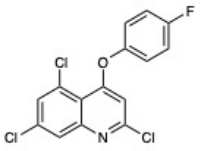


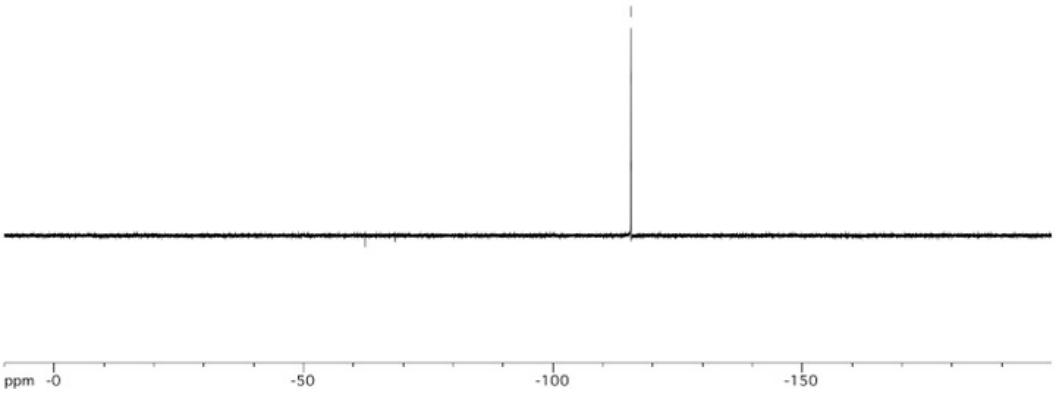
^{13}C NMR ($CDCl_3$, 100 MHz)

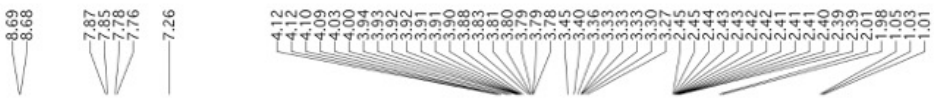




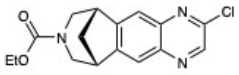
^{19}F NMR ($CDCl_3$, 365 MHz)



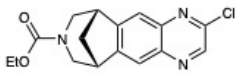


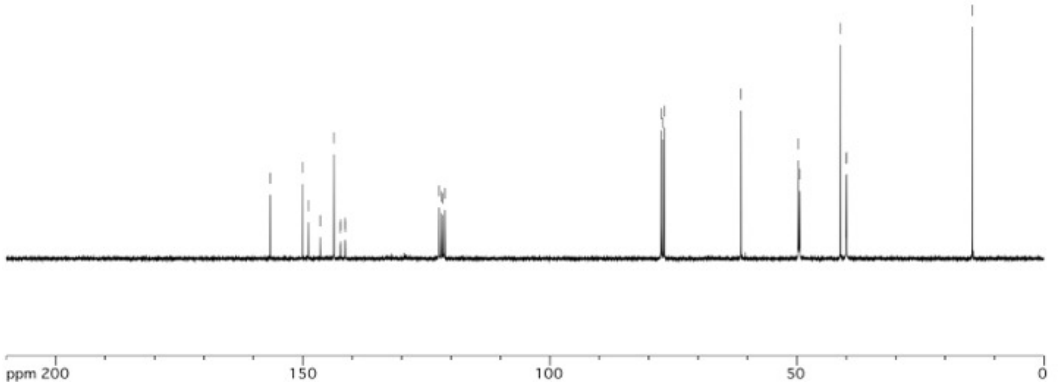


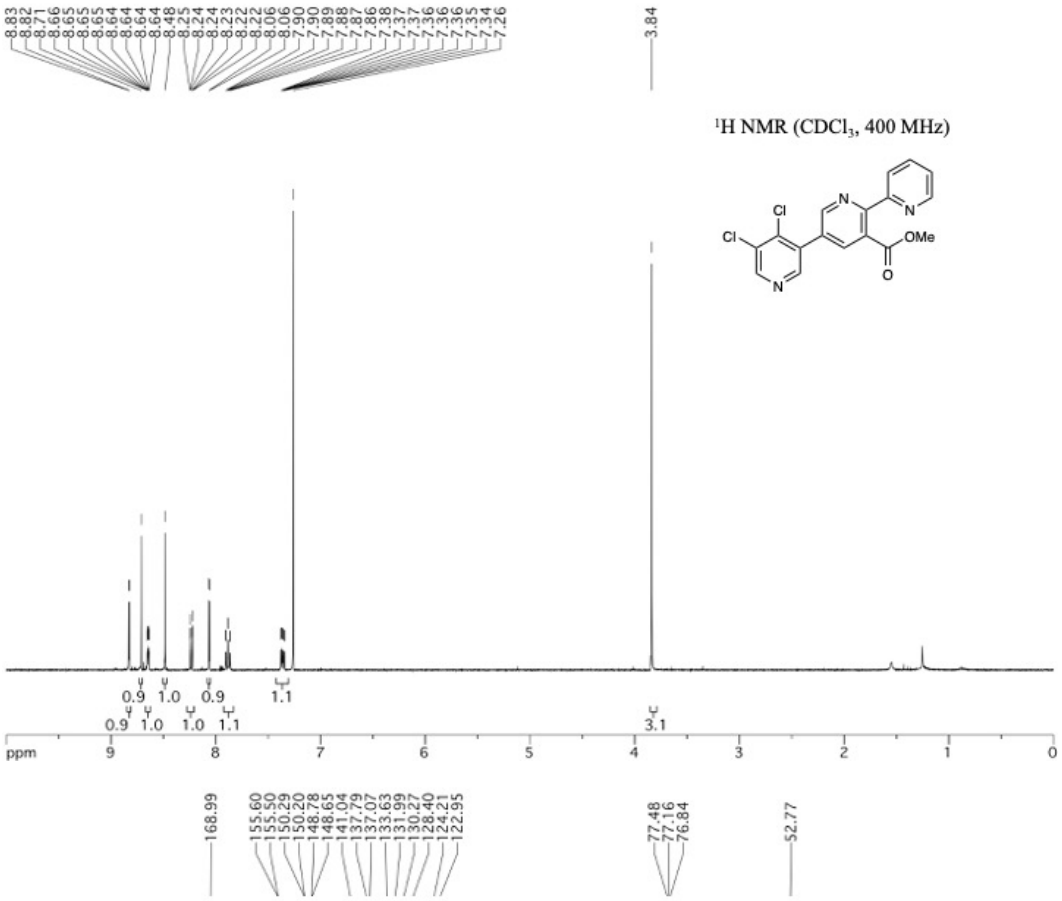
^{1}H NMR ($CDCl_3$, 400 MHz)



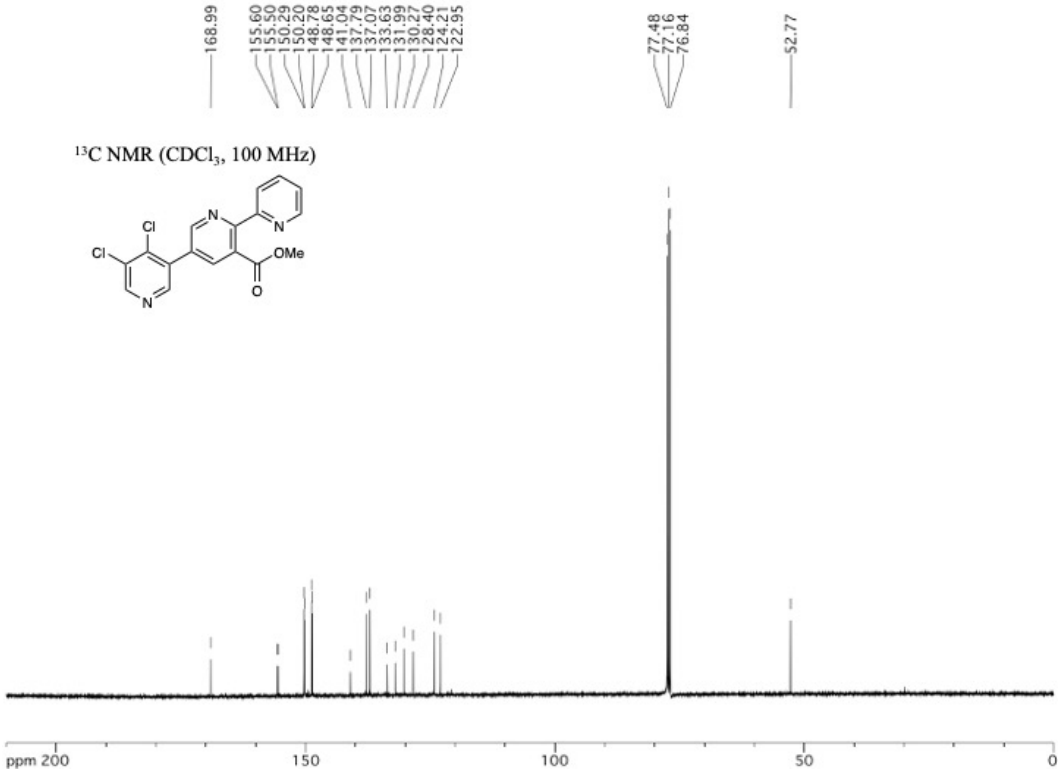
^{13}C NMR ($CDCl_3$, 100 MHz)



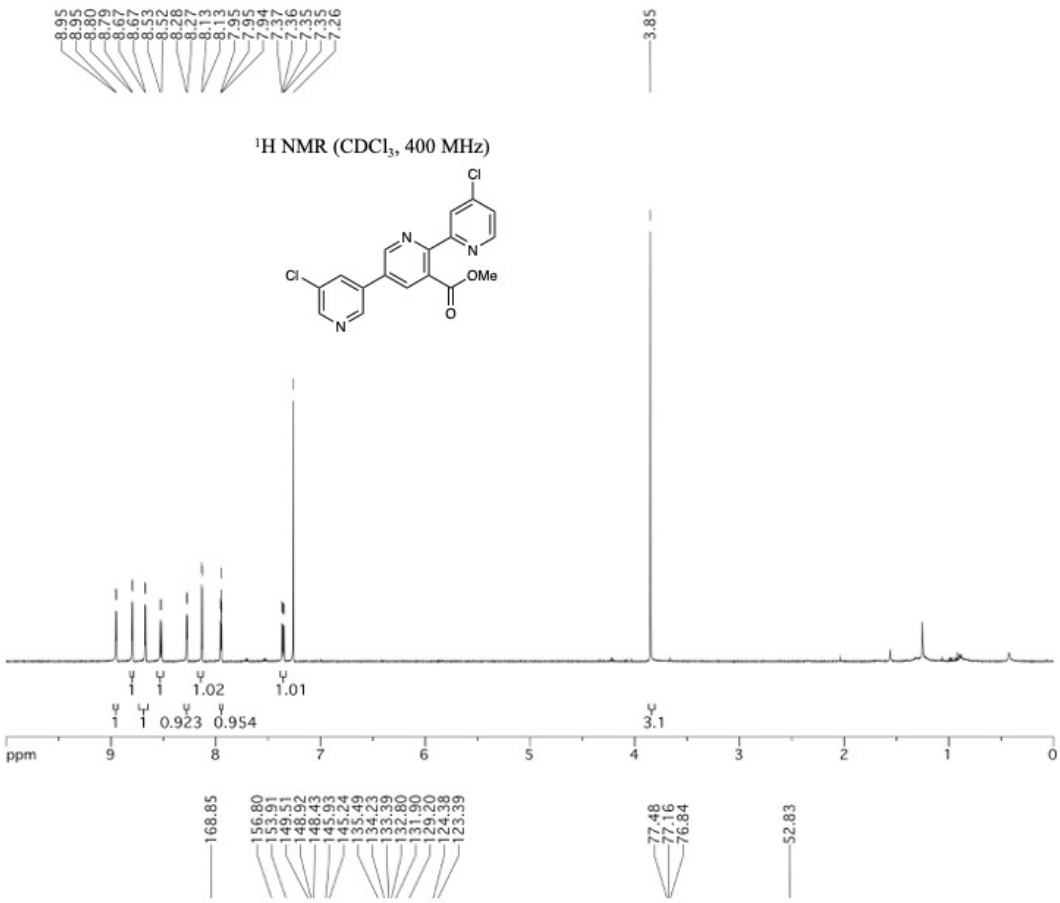




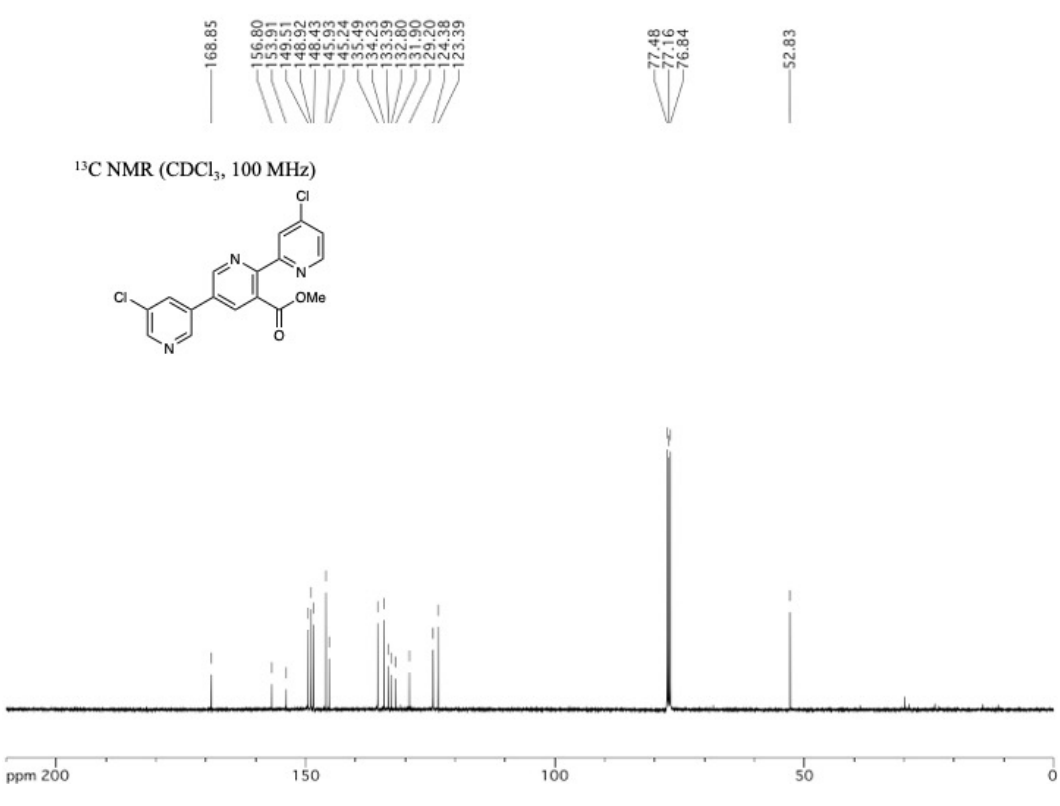
^{1}H NMR ($CDCl_3$, 400 MHz)



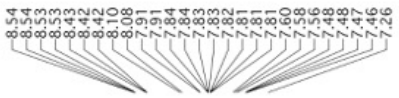
^{13}C NMR ($CDCl_3$, 100 MHz)



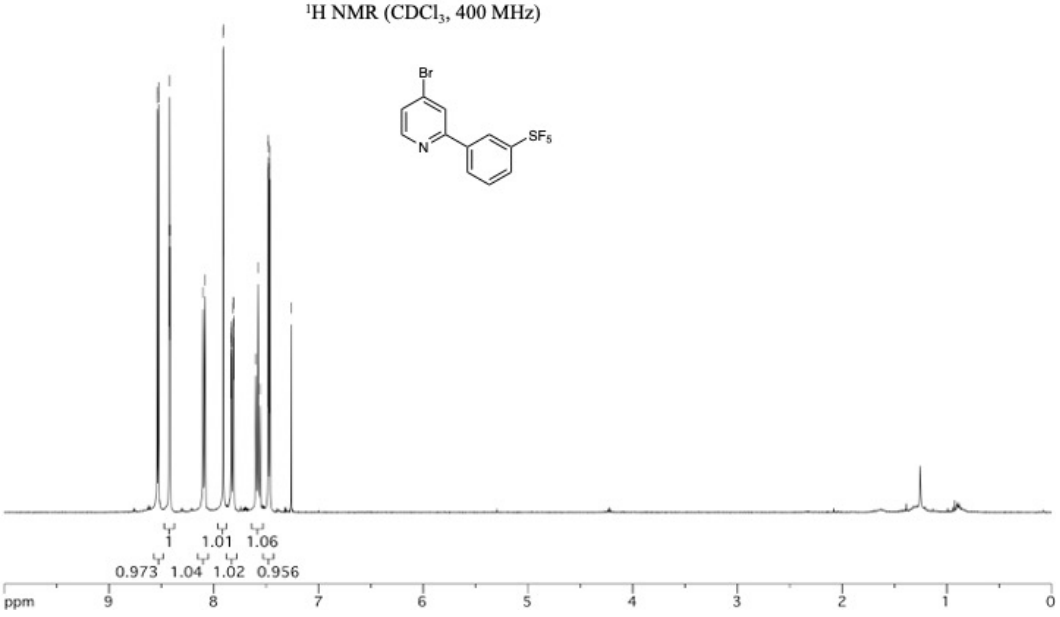
^{1}H NMR ($CDCl_3$, 400 MHz)

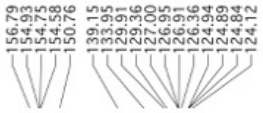


^{13}C NMR ($CDCl_3$, 100 MHz)

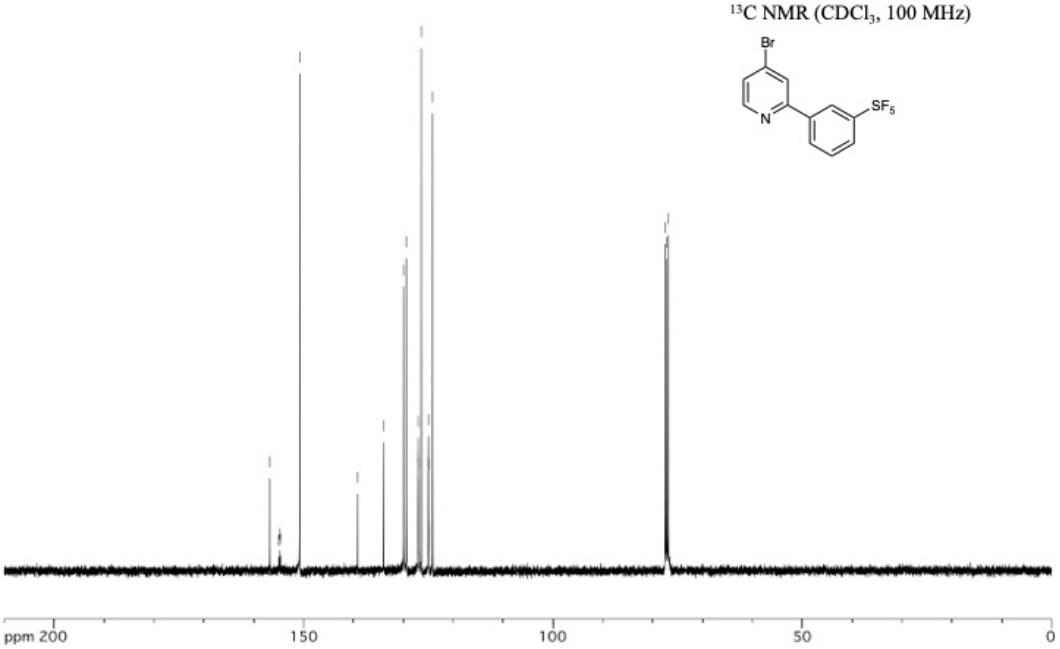


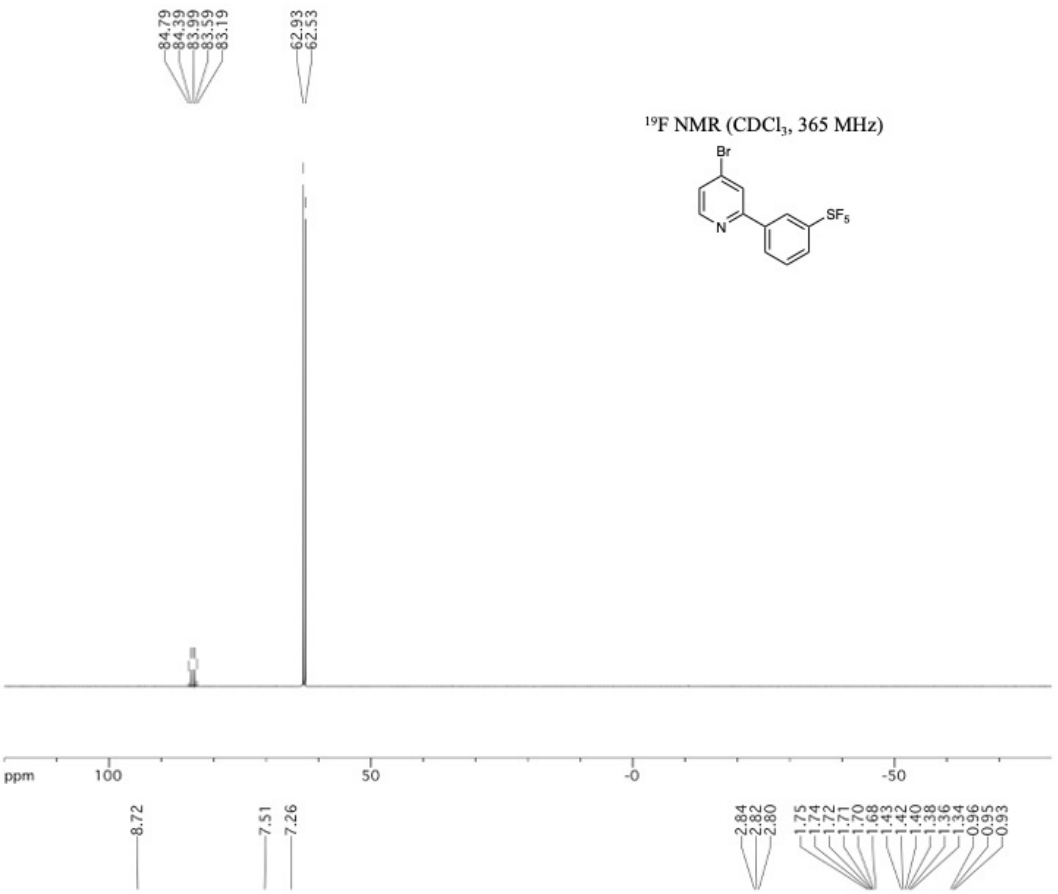
^{1}H NMR ($CDCl_3$, 400 MHz)



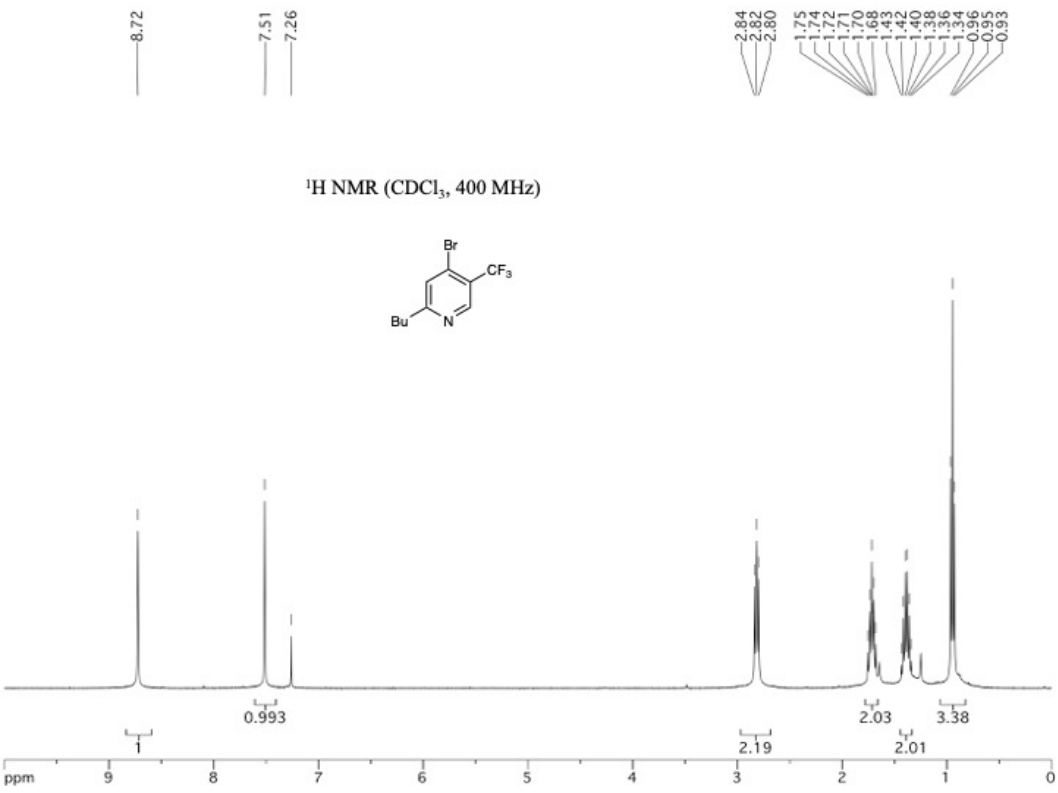


^{13}C NMR ($CDCl_3$, 100 MHz)

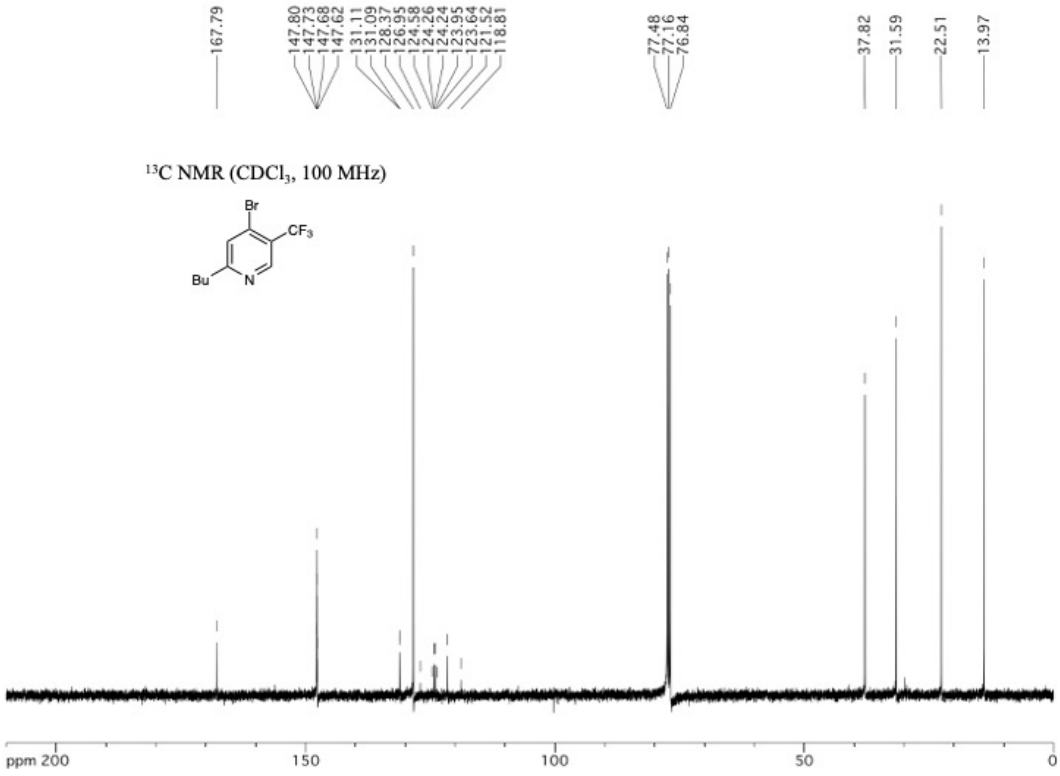


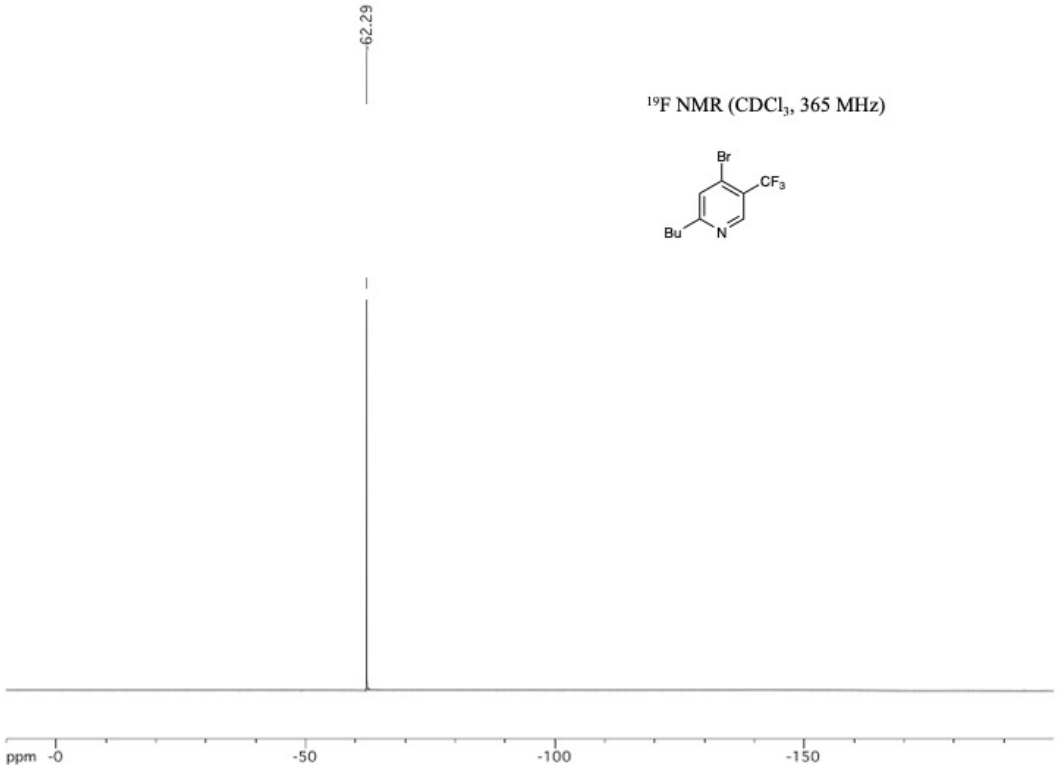


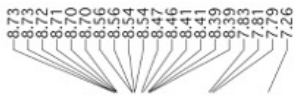
^{19}F NMR ($CDCl_3$, 365 MHz)



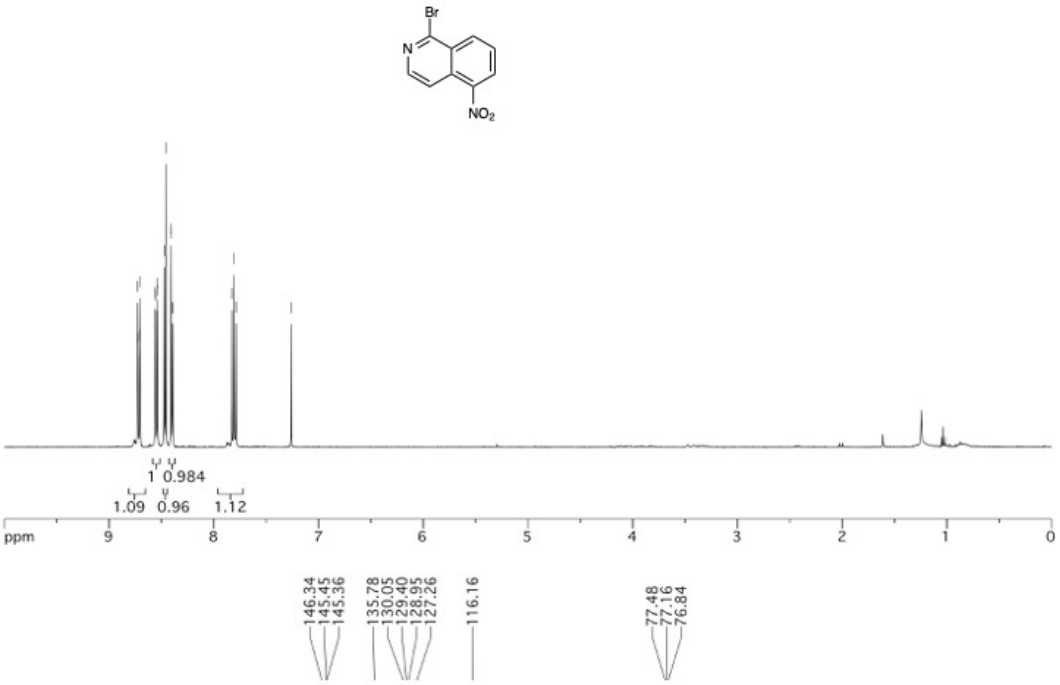
^{1}H NMR ($CDCl_3$, 400 MHz)


167.79
147.80
147.73
147.68
147.62
131.11
131.09
128.37
126.95
124.58
124.26
124.24
123.95
123.64
121.52
118.81
77.48
77.16
76.84
37.82
31.59
22.51
13.97
^{13}C NMR ($CDCl_3$, 100 MHz)
Br
CF_3
Bu
N
ppm 200
150
100
50
0

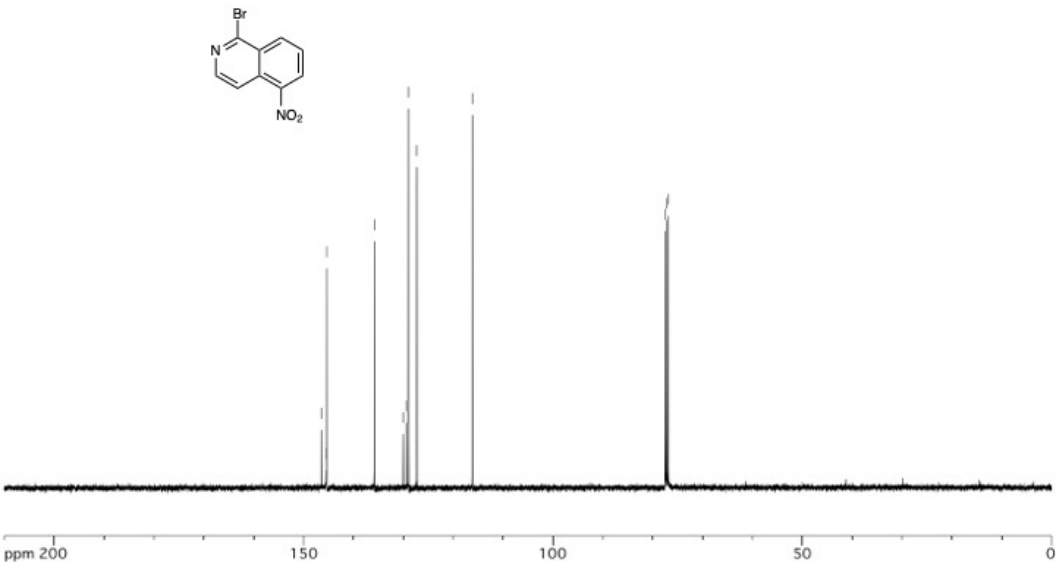

62.29
^{19}F NMR ($CDCl_3$, 365 MHz)
Br
CF_3
Bu
N
ppm -0
-50
-100
-150

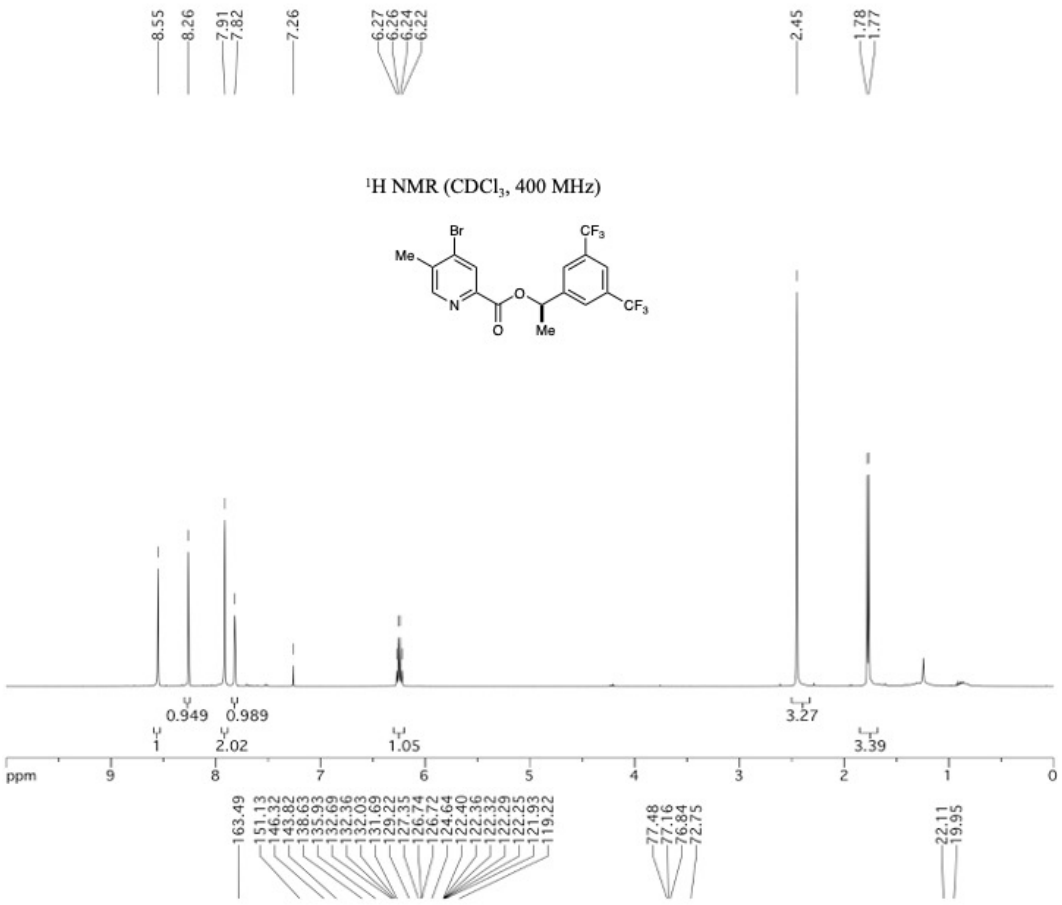


^{1}H NMR ($CDCl_3$, 400 MHz)

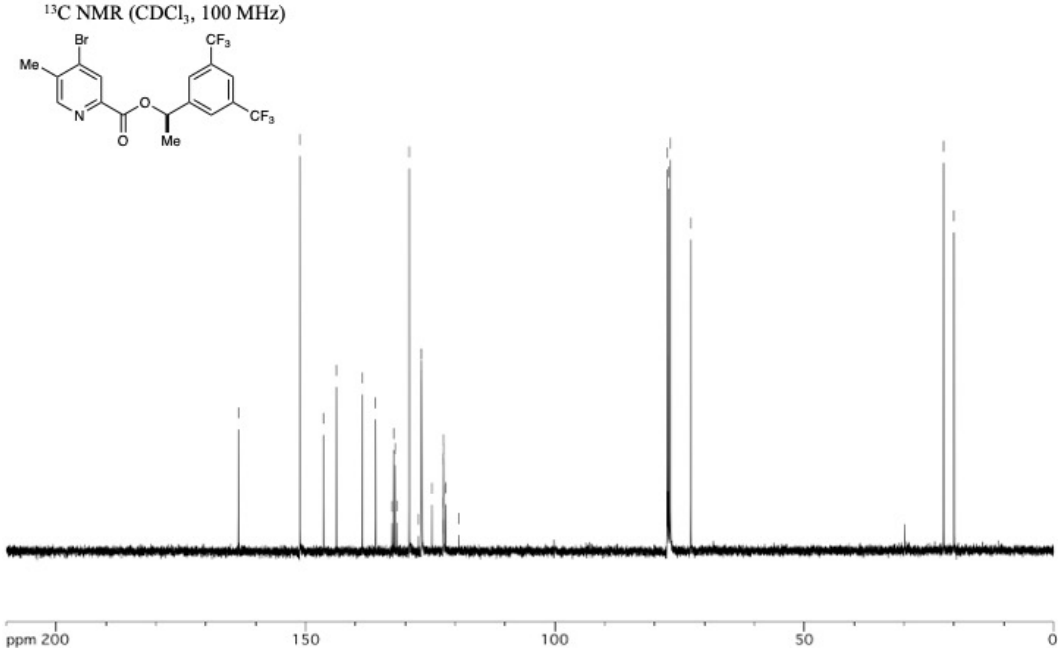


^{13}C NMR ($CDCl_3$, 100 MHz)



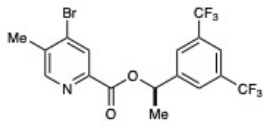


^{1}H NMR ($CDCl_3$, 400 MHz)

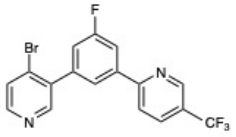


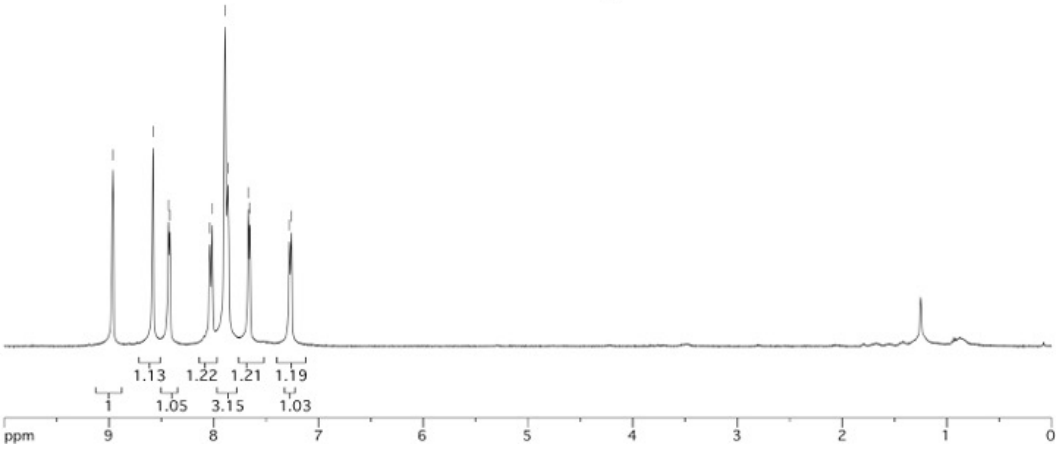
^{13}C NMR ($CDCl_3$, 100 MHz)

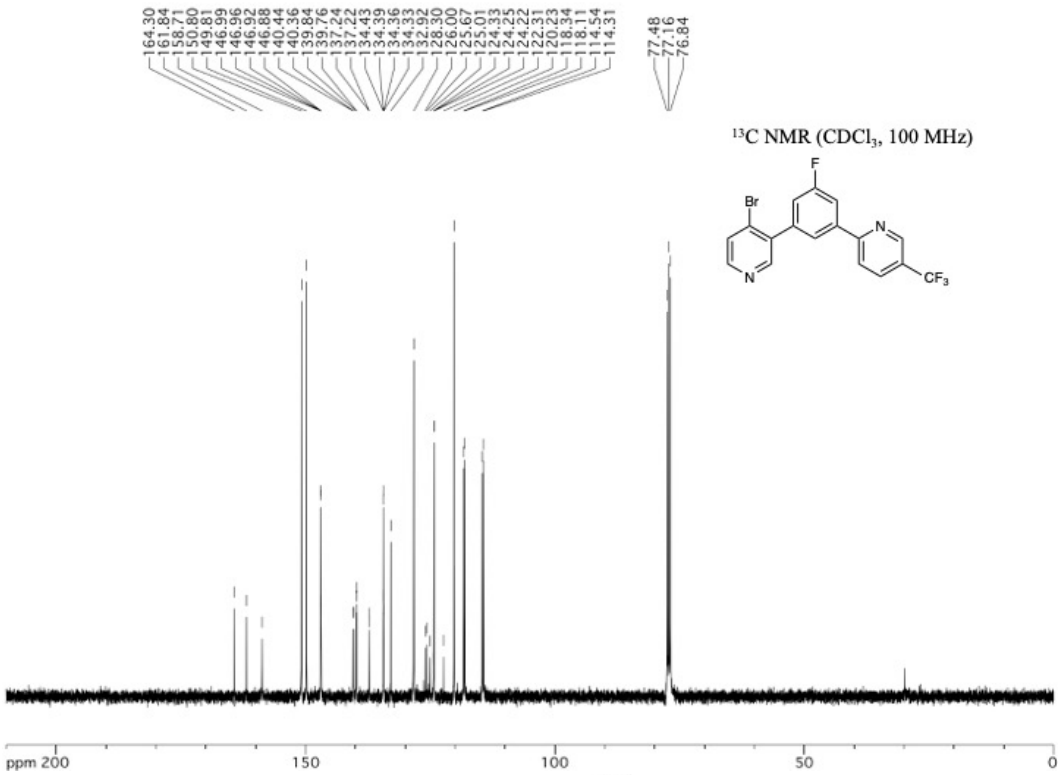
^{19}F NMR ($CDCl_3$, 365 MHz)

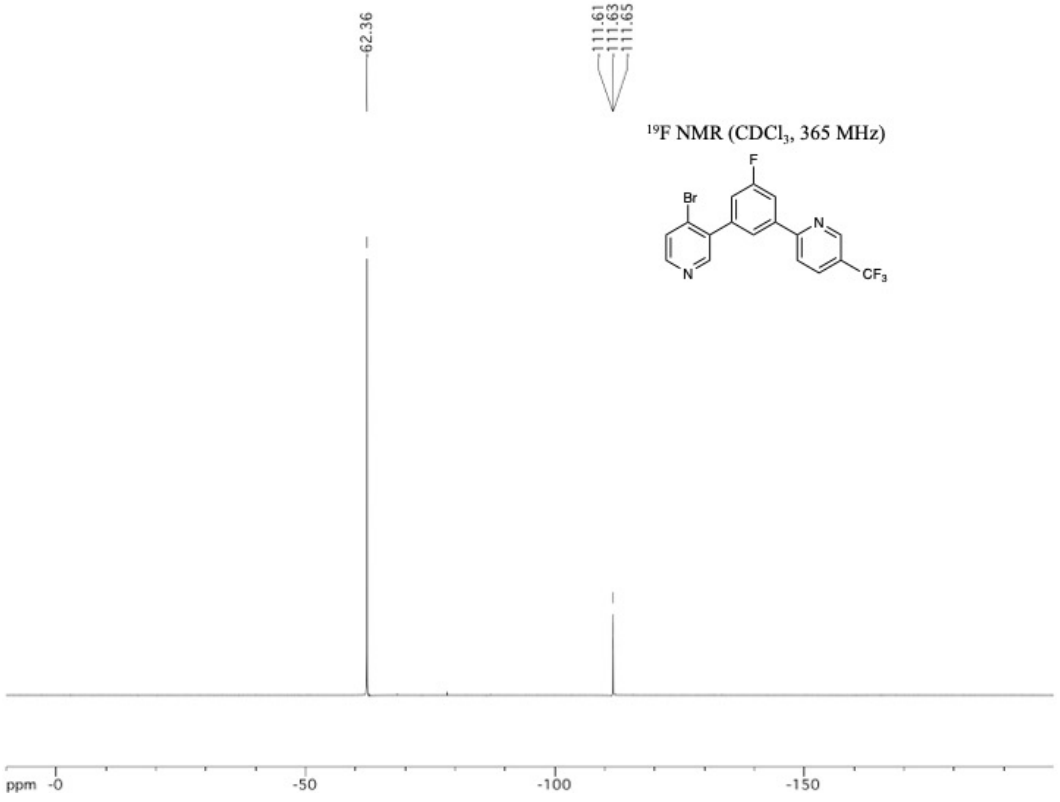


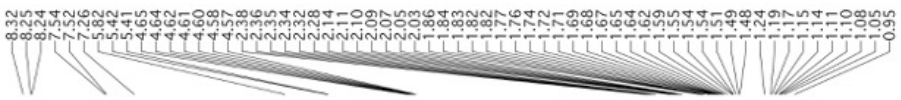
^{1}H NMR ($CDCl_3$, 400 MHz)



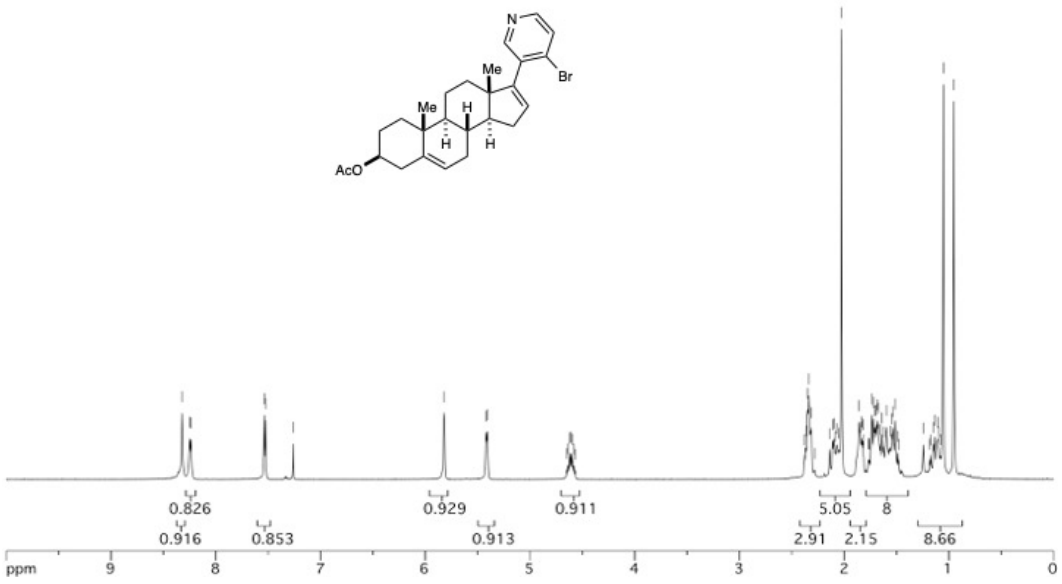



164.30
161.84
158.71
150.80
149.81
146.99
146.96
146.92
146.88
140.44
140.36
139.84
139.76
137.24
137.22
134.43
134.39
134.36
134.33
132.92
128.30
126.00
125.67
125.01
124.33
124.25
124.22
122.31
120.23
118.34
118.11
114.54
114.31
77.48
77.16
76.84
13C NMR (CDCl3, 100 MHz)
F
Br
N
N
CF3
ppm 200
150
100
50
0

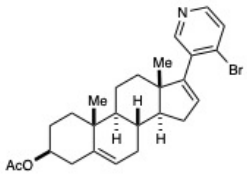

62.36
111.61
111.63
111.65
19F NMR (CDCl3, 365 MHz)
F
Br
N
N
CF3
ppm -0
-50
-100
-150

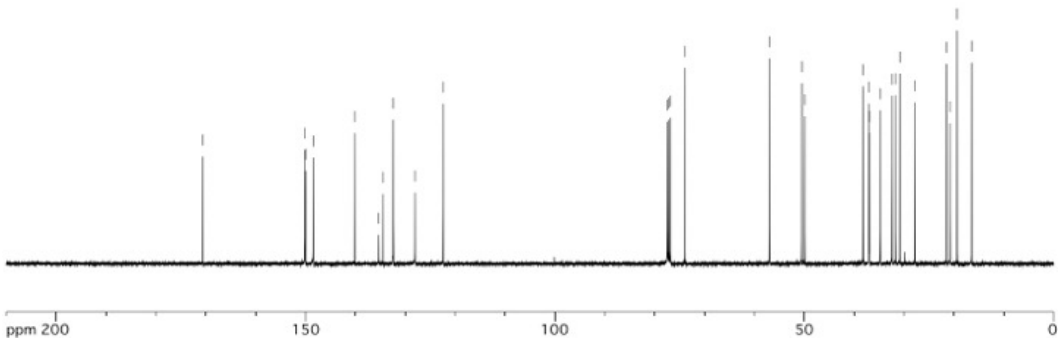


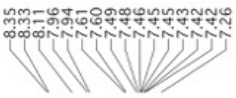
^{1}H NMR ($CDCl_3$, 400 MHz)



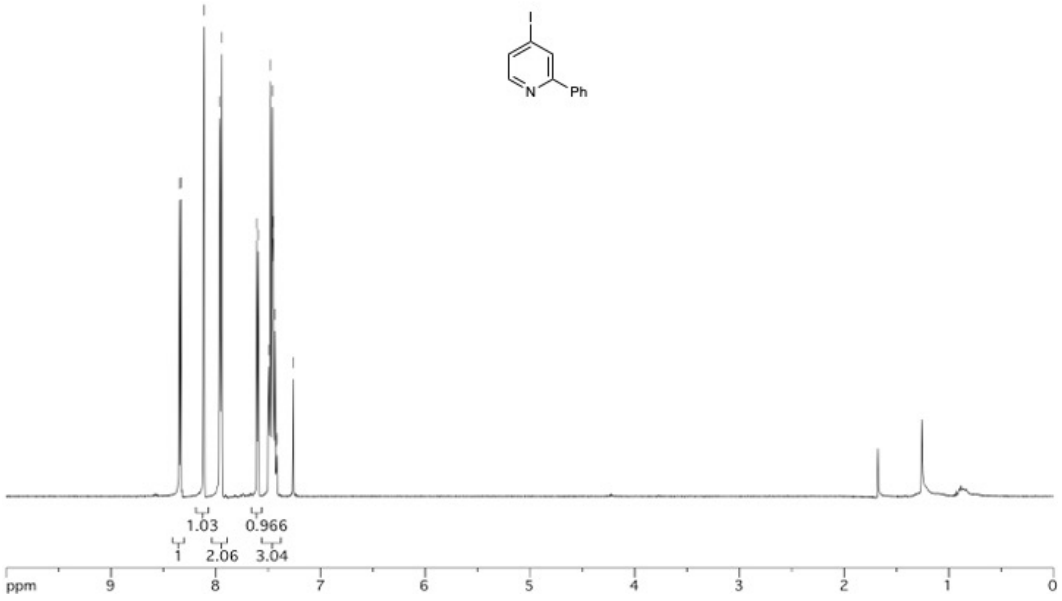
^{13}C NMR ($CDCl_3$, 100 MHz)



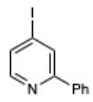


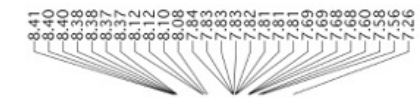


^{1}H NMR ($CDCl_3$, 400 MHz)

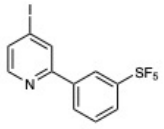


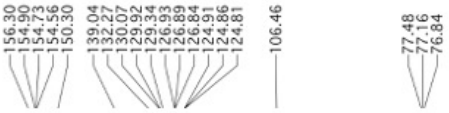
^{13}C NMR ($CDCl_3$, 100 MHz)



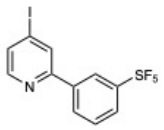


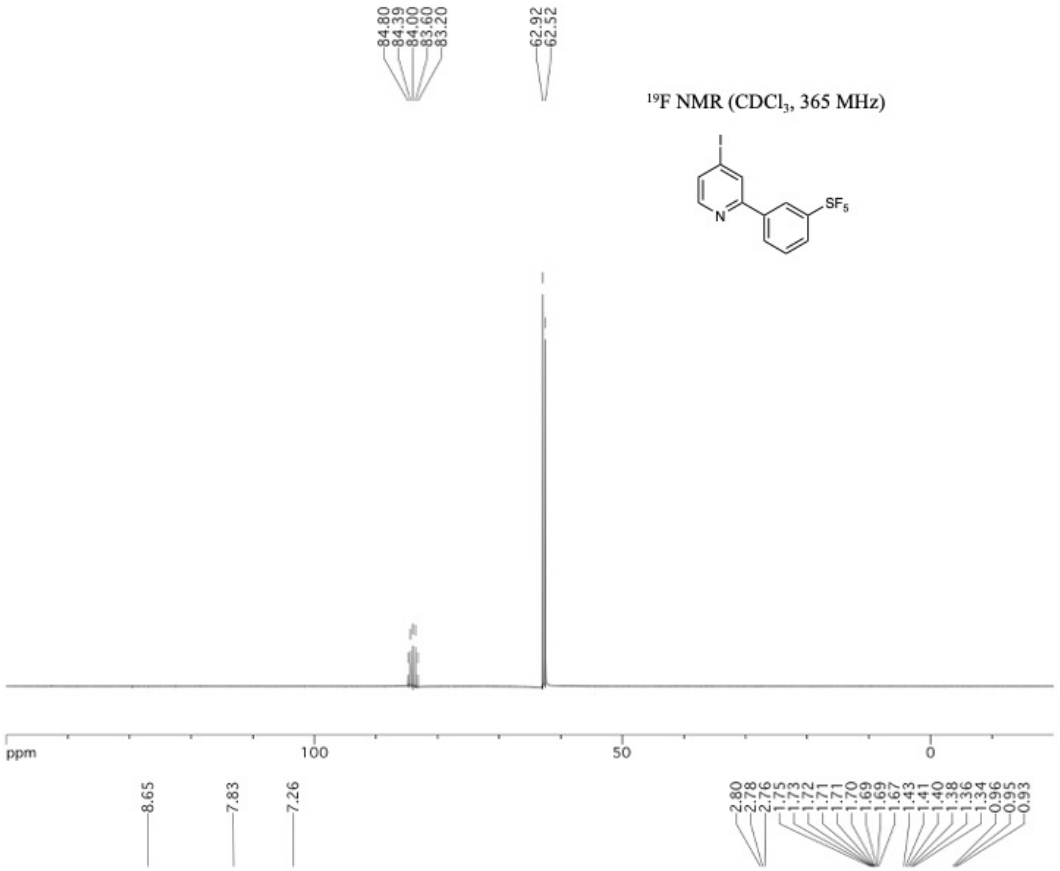
^{1}H NMR ($CDCl_3$, 400 MHz)

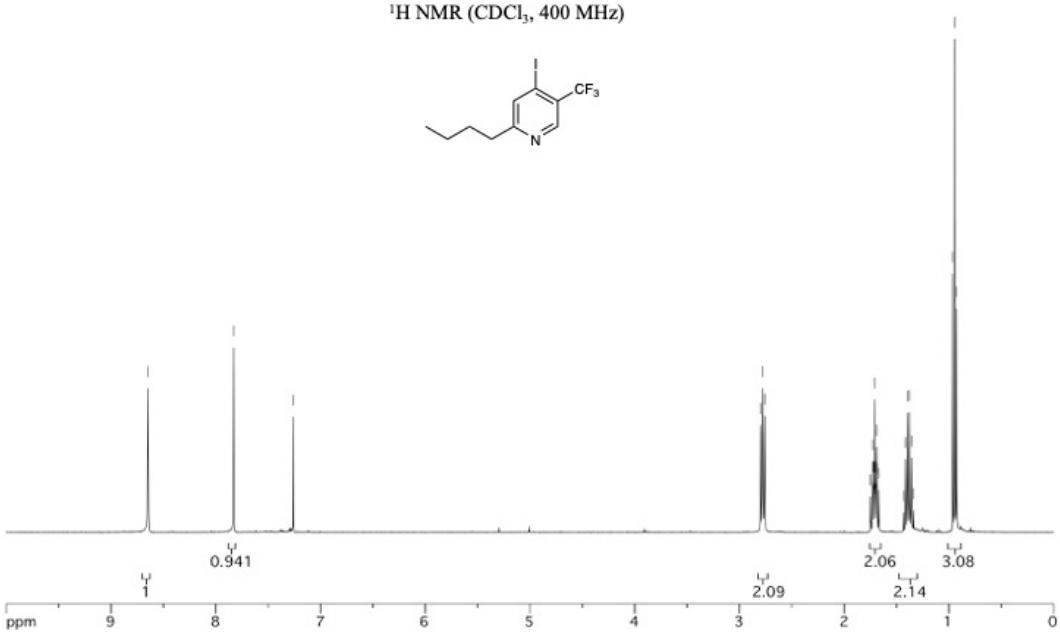


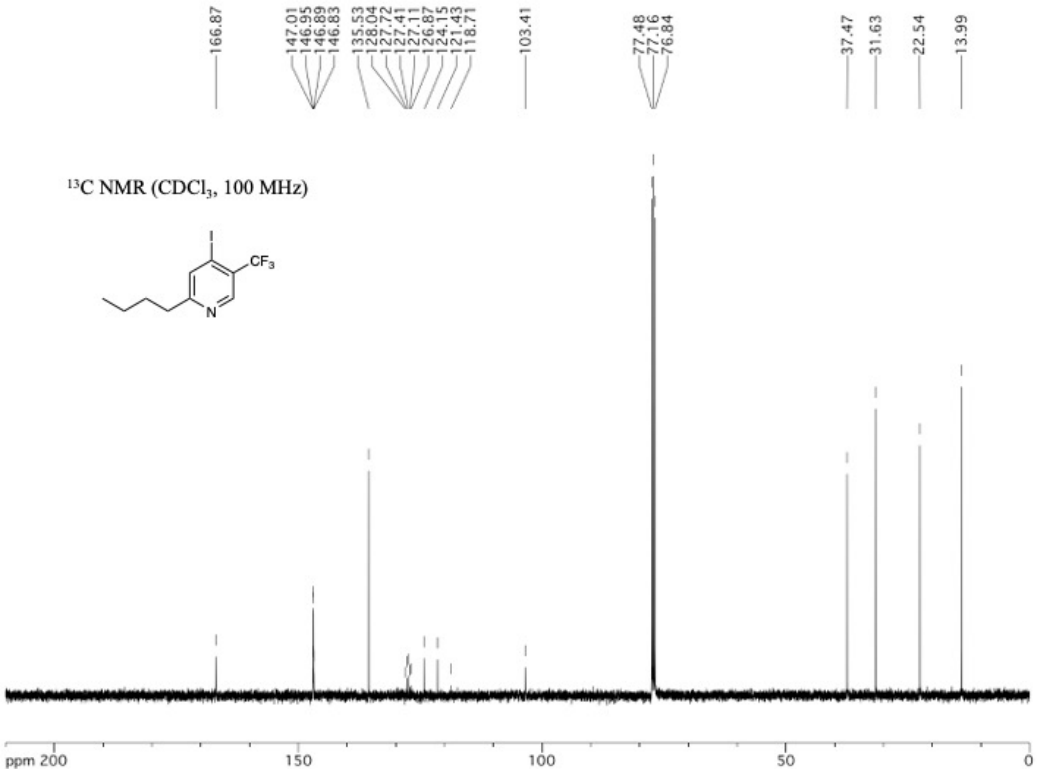


^{13}C NMR ($CDCl_3$, 100 MHz)

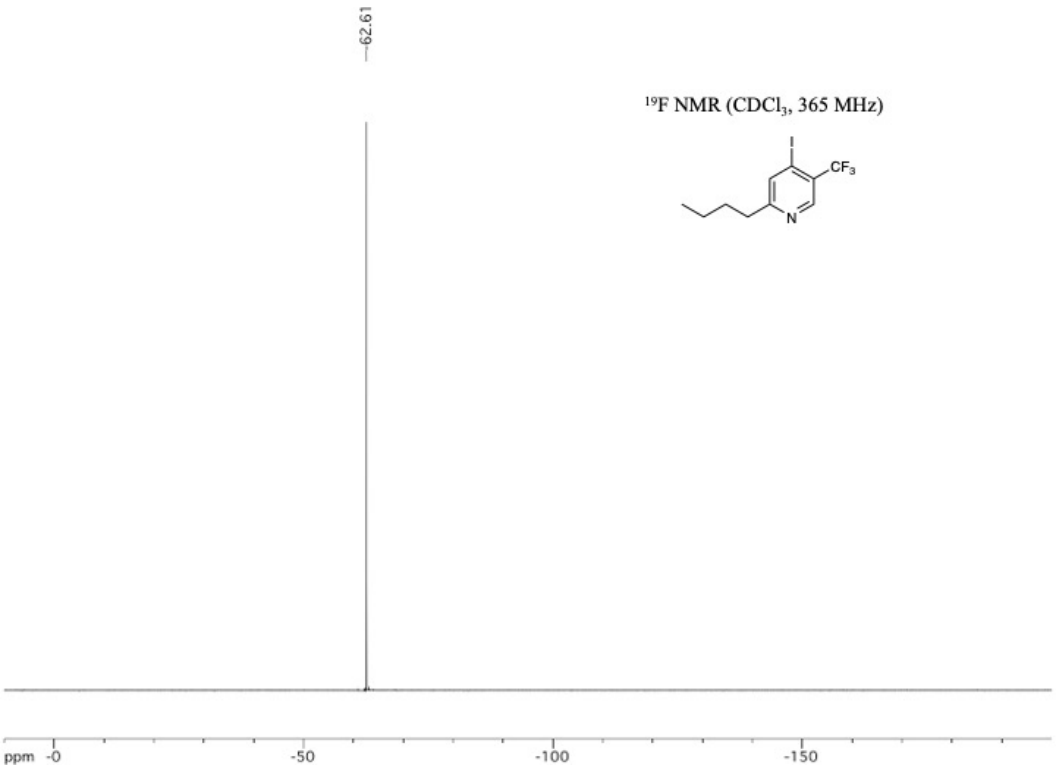



84.80
84.39
84.00
83.60
83.20
62.92
62.52
^{19}F NMR ($CDCl_3$, 365 MHz)
I
N
SF_5
ppm
100
50
0
8.65
7.83
7.26
2.80
2.78
2.76
1.75
1.73
1.72
1.71
1.71
1.70
1.69
1.69
1.67
1.43
1.41
1.40
1.38
1.36
1.34
0.96
0.95
0.93


^{1}H NMR ($CDCl_3$, 400 MHz)
I
CF_3
N
0.941
2.06
3.08
1
2.09
2.14
ppm
9
8
7
6
5
4
3
2
1
0



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



^{19}F NMR ($CDCl_3$, 365 MHz)

APPENDIX TWO

HALOGENATION OF PYRIDINES VIA ZINCKE IMINES: EXPERIMENTAL

A 2.1 General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR (400 MHz) spectrometer or an Agilent Inova 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), $(CD_3)_2SO$ (2.50 ppm), CD_3OD (3.31 ppm) or CD_3CN (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants). 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 either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR spectrometer (100 MHz) or an Agilent Inova 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16 ppm), C_6D_6 (128.06 ppm), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or CD_3CN (1.32 ppm).

Low–resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 27 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 Merck glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Fluka or Material Harvest silica gel (230–400 mesh) under a positive pressure of air. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate.

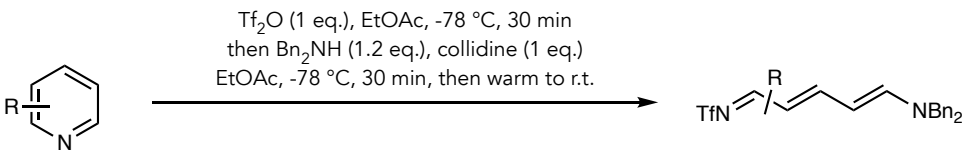
Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] 1,2–Dichloroethane (DCE), chloroform, and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest commercial quality and 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, gas chromatography (GC) and gas chromatography–mass spectrometry (GCMS) using an Agilent 5977A fitted with an Agilent J&W HP–5ms Ultra Inert Column (30 m, 0.25 mm, 0.25 μm film) for MS analysis and an Agilent J&W VF–5ms column (10 m, 0.15 mm, 0.15 μm film) for FID analysis or liquid chromatography mass spectrometry (LCMS) using an Agilent 6310 Quadrupole Mass Spectrometer. Melting points (mp) were recorded using a Büchi B–450 melting point apparatus and are reported uncorrected.

N-iodosuccinimide (NIS) was purchased from Combi-Blocks and used without further purification. *N*-bromosuccinimide (NBS) was purchased from Oakwood and recrystallized in water. *N*-chlorosuccinimide (NCS) was purchased from Oakwood and recrystallized in acetic acid. *N*-halosuccinimide reagents were kept in a -20 °C fridge and vials of repurified material were wrapped in aluminum foil. Trifluoroacetic acid (TFA) and HCl (4M in dioxanes) were purchased

form Sigma Aldrich and used without further purification, and were routinely stored in a -20 °C fridge. Trifluoromethanesulfonic anhydride (Tf_2O), dibenzylamine ($HNBn_2$), collidine (2,4,6-trimethylpyridine) were purchased from Oakwood and used without further purification, and were routinely stored in a -20 °C fridge. Trimethoxybenzene (TMB) was purchased from Oakwood and used without further purification. Anhydrous Ethyl Acetate was purchased from Acros Organics. Ammonium Acetate (NH_4OAc) was purchased from Fisher Chemical and used without further purification.

A 2.2 General Procedures:

General Procedure A (Zincke Imine Formation)



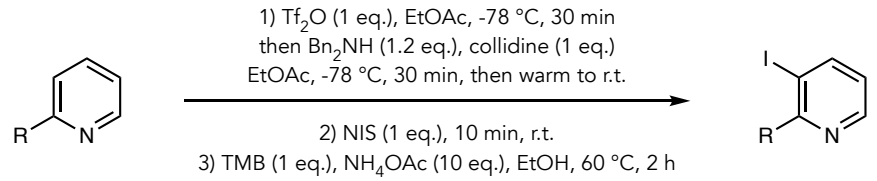
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before dibenzylamine (1.2 equiv) was added dropwise as a solution (1.0 M in EtOAc) followed by collidine (1.0 eq). 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 for approximately 30 minutes. The reaction was diluted with EtOAc then washed with H_2O (3x). The organic extract was dried ($MgSO_4$) and filtered. After filtration, 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 has settled, the hexanes was decanted off and the residual oil was washed with

hexanes and then dissolved in CH_2Cl_2 and concentrated *in vacuo* to provide the pure "Zincke imine" product.

Reaction Notes:

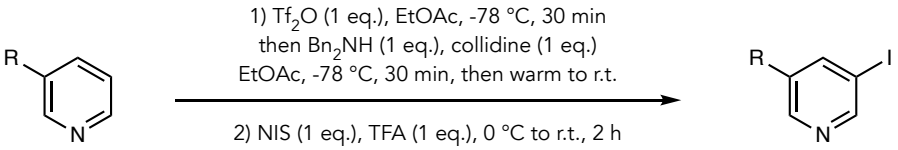
- Reaction is sensitive to excess of Tf_2O added (use of 1.2 eq results in substantial yield loss).
- Majority of substrates comparably with 1.0 equiv. and 2.0 equiv. collidine, 1.0 equiv. can be used regardless of substrate (Yields in scope table below denote how many equivalents were used for that specific yield, but were within 5% when repeated with the other collidine amount).
- 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 "bis-adduct" formation and care should be taken prior to crash out. Vaccing down prior to crash out results in significant (>20%) yield loss to bis-addition.
- If "bis-adduct" is observed, a short plug of silica (2-3 inches) and appropriate solvent eluent will remove it.
- Substrates with a 4-substituent (and unsubstituted pyridine) can be run with 1.0 eq Bn_2NH to minimize potential for bis-addition product formation.
- For substrates with a 2-R substituent, the organic extract can be concentrated *in vacuo* then redissolved in 2-10 mL CH_2Cl_2 prior to addition to the hexanes. This will provide higher yields.

General Procedure B (3-Position Iodination)



An oven dried 16 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.1 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 dibenzylamine (1.2 equiv) was added dropwise as a solution (1.0 M in EtOAc) followed by collidine (1.0 eq). 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 for approximately 30 minutes. *N*-iodosuccinimide (1 equiv.) was added as a solid, and the reaction was allowed to stir at room temperature for 10 minutes. Trimethoxybenzene (1 equiv.), Ammonium Acetate (10 equiv.) and EtOH (twice the volume of EtOAc used in step 1) was added and the reaction was stirred at 60 °C for 2 hours. After cooling to room temperature, the reaction was diluted with EtOAc and H_2O, then extracted into EtOAc (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

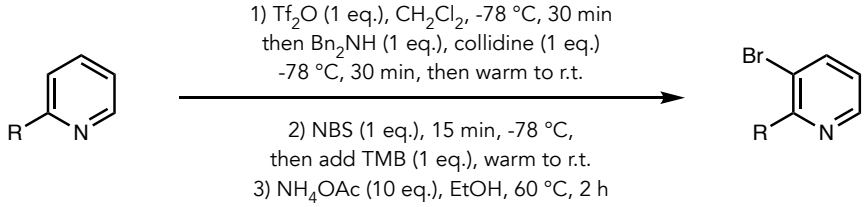
General Procedure C (5-Position Iodination)



An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen

atmosphere. EtOAc (0.1 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 dibenzylamine (1 equiv) was added dropwise as a solution (1.0 M in EtOAc) followed by collidine (1.0 eq). 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 for approximately 30 minutes. The reaction vessel was then placed in a 0 °C ice bath, and *N*-iodosuccinimide (1 equiv.) and trifluoroacetic acid (1 equiv.) were subsequently added. The reaction vessel was removed from the ice bath and allowed to stir at room temperature for 2 hours, before being quenched with aqueous sodium thiosulfate and aqueous sodium bicarbonate. The reaction was diluted with EtOAc and H_2O, then extracted into EtOAc (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

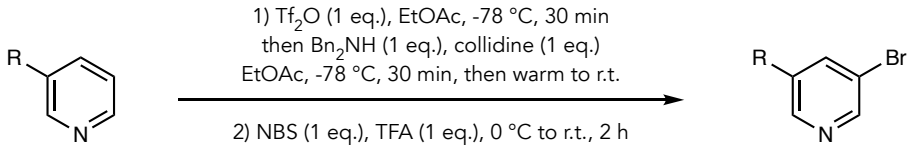
General Procedure D (3-Position Bromination)



An oven dried 16 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 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 dibenzylamine (1.0 equiv) was added dropwise as a solution (1.0 M in CH_2Cl_2) followed by collidine (1.0 eq). 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 for approximately 30 minutes. After reaching room temperature, the reaction vessel was cooled to –78 °C again and *N*-bromosuccinimide (1 eq.) was added as a solid. After stirring the reaction at –78 °C for 15 minutes, trimethoxybenzene (1 eq.) was added and the reaction was allowed to warm to room temperature. Ammonium Acetate (10 equiv.) and EtOH (twice the volume of CH_2Cl_2 used in step 1) was added and the reaction was stirred at 60 °C for 20 hours. After cooling to room temperature, the reaction was diluted with CH_2Cl_2 and H_2O, then extracted into CH_2Cl_2 (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

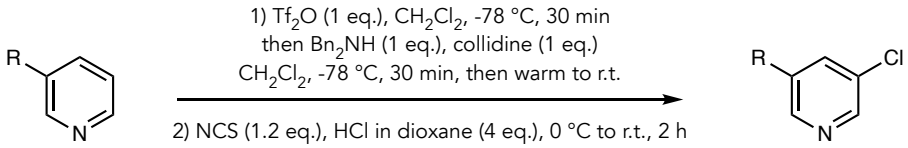
General Procedure E (5-Position Bromination)



An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.1 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 dibenzylamine (1 equiv) was added dropwise as a solution (1.0 M in EtOAc) followed by collidine (1.0 eq). 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 for approximately 30 minutes. The reaction vessel was then placed in a 0 °C ice bath, and *N*-bromosuccinimide (1 equiv.) and trifluoroacetic acid (1 equiv.) were subsequently added. The reaction vessel was removed from the ice bath and

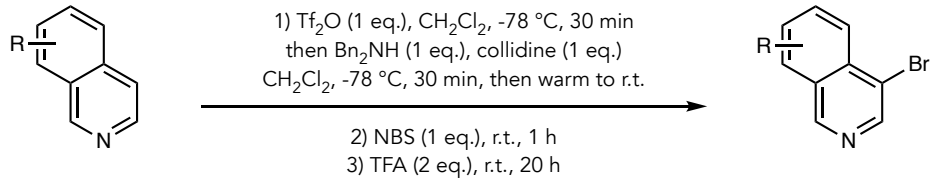
allowed to stir at room temperature for 2 hours, before being quenched with aqueous sodium thiosulfate and aqueous sodium bicarbonate. The reaction was diluted with EtOAc and H_2O, then extracted into EtOAc (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

General Procedure F (5-Position Chlorination)



An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 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 dibenzylamine (1 equiv) was added dropwise as a solution (1.0 M in CH_2Cl_2) followed by collidine (1.0 eq). 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 for approximately 30 minutes. The reaction vessel was then placed in a 0 °C ice bath, and *N*-chlorosuccinimide (1.2 equiv.) and HCl (4 M in dioxanes, 4 equiv.) were subsequently added. The reaction vessel was removed from the ice bath and allowed to stir at room temperature for 2 hours, before being quenched with aqueous sodium thiosulfate and aqueous sodium bicarbonate. The reaction was diluted with CH_2Cl_2 and H_2O, then extracted into CH_2Cl_2 (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

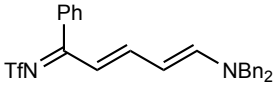
General Procedure G (Bromination of Isoquinolines)



An oven dried 8 mL vial equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 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 dibenzylamine (1 equiv) was added dropwise as a solution (1.0 M in CH_2Cl_2) followed by collidine (1.0 eq). 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 for approximately 30 minutes. *N*-bromosuccinimide (1 equiv) was added and the reaction was allowed to stir at room temperature for 1 hour. Then trifluoroacetic acid (2 equiv) was added and the reaction was left to stir at room temperature overnight. The reaction was quenched with aqueous sodium thiosulfate and aqueous sodium bicarbonate. The reaction was diluted with CH_2Cl_2 and H_2O, then extracted into CH_2Cl_2 (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

A 2.3 Synthesis of Imines and Halogenated Pyridines:

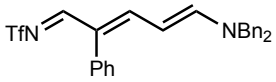
***N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



Prepared according to general procedure A using 2-phenylpyridine (4.29 mL, 30.0 mmol), EtOAc (300 mL, 0.1 M), Tf_2O (5.04 mL, 30.0 mmol), dibenzylamine (6.35 mL, 33.0 mmol, 1.0 M in EtOAc), and collidine (3.96 mL, 30.0 mmol). Washing 3x with H_2O and crashing out in hexanes afforded the title compound (12.44 g, 25.7 mmol , 86% yield) as a red solid. mp 68 – 70

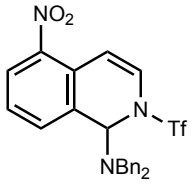
°C; IR ν_{max}/cm^{-1} (film): 1615, 1558, 1430, 1312, 1154, 1092, 997, 842, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (2H, d, *J* = 7.8 Hz), 7.50 (1H, t, *J* = 7.8 Hz), 7.45 – 7.25 (10H, m), 7.15 (4H, d, *J* = 7.4 Hz), 6.71 (1H, d, *J* = 13.7 Hz), 5.81 (1H, t, *J* = 12.2 Hz), 4.47 – 4.39 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.27, 160.32, 157.82, 138.10, 134.39, 133.86, 131.21, 129.79, 129.36, 128.97, 128.55, 128.35, 127.95, 127.34, 119.69 (q, *J* = 320.1 Hz), 114.59, 102.83, 59.89, 51.53; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -79.10; *m/z* HRMS (DART) found $[M+H]^+$ 485.1506, $C_{26}H_{24}F_3N_2O_2S^+$ requires 485.1511.

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



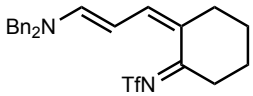
Prepared according to general procedure A using 3-phenylpyridine (1.43 mL, 10.0 mmol), EtOAc (100 mL, 0.1 M), Tf_2O (1.68 mL, 10.0 mmol), dibenzylamine (1.92 mL, 10.0 mmol, 1.0 M in EtOAc), and collidine (1.32 mL, 10.0 mmol). Washing 2x with H_2O and 1x with aqueous sodium bicarbonate, and then crashing out in hexanes afforded the title compound (3.98 g, 8.21 mmol, 82% yield) as a yellow solid. mp 136 – 139 °C; IR ν_{max}/cm^{-1} (film): 3027, 1617, 1485, 1305, 1167, 1100, 843, 734, 687; ^{1}H NMR (400 MHz, CD_3CN) δ: 8.21 (1H, s), 7.91 (1H, d, *J* = 11.9 Hz), 7.67 (1H, d, *J* = 13.0 Hz), 7.45 – 7.22 (11H, m), 7.16 – 7.00 (4H, m), 5.73 (1H, d, *J* = 12.5 Hz), 4.71 (2H, s), 4.40 (2H, s); ^{13}C NMR (100 MHz, CD_3CN) δ: 171.69, 167.27, 163.39, 135.51, 135.46, 135.25, 130.85, 130.04, 129.87, 129.70, 129.48, 129.28, 128.99, 128.30, 128.23, 128.14, 126.55, 121.20 (q, *J* = 323.1 Hz), 104.89, 62.12, 53.44; ^{19}F NMR (365 MHz, CD_3CN) δ: -79.16; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 485.2, $C_{26}H_{24}F_3N_2O_2S^+$ requires 485.2.

***N*,*N*-Dibenzyl-5-nitro-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinolin-1-amine**



Prepared according to general procedure A using 5-nitroisoquinoline (348 mg, 2.00 mmol), CH_2Cl_2 (20 mL, 0.1 M), Tf_2O (336 µL, 2.00 mmol), dibenzylamine (461 µL, 2.40 mmol, 1.0 M in CH_2Cl_2), and collidine (264 µL, 2.00 mmol). Flash column chromatography (silica gel gradient elution: 20 to 40% Toluene in Hexanes) afforded the title compound (550 mg, 1.10 mmol , 55% yield) as a yellow solid. mp 52 – 56 ˚C; IR ν_{max}/cm^{-1} (film): 2161, 1528, 1227, 1141, 1027, 923, 737, 654; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (1H, d, *J* = 7.9 Hz), 7.54 (1H, app t, *J* = 8.0 Hz), 7.48 (1H, d, *J* = 7.5 Hz), 7.38 – 7.23 (10H, m), 7.15 (1H, d, *J* = 8.0 Hz), 7.05 (1H, d, *J* = 8.0 Hz), 6.02 (1H, s), 3.74 (4H, app q, *J* = 13.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 114.72, 137.99, 133.46, 132.67, 129.01, 128.50, 128.37, 127.65, 126.90, 125.76, 124.18, 119.84 (q, *J* = 325.0 Hz), 110.32, 73.43, 51.78; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -74.36; *m/z* HRMS (DART) found $[M+H]^+$ 504.1248, $C_{24}H_{21}F_3N_3O_4S^+$ requires 504.1205.

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



Prepared according to general procedure A using 5,6,7,8-tetrahydroquinoline (647 µL, 5.00 mmol), EtOAc (50 mL, 0.1 M), Tf_2O (840 µL, 5.00 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), and collidine (640 µL, 5.00 mmol). Washing 3x with H_2O and crashing out in hexanes afforded the title compound (1.86 g, 4.01 mmol , 80% yield) as a yellow solid. mp 160 – 165 ˚C; IR ν_{max}/cm^{-1} (film): 1611, 1407, 1151, 1099, 852, 813, 667, 605; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 8.52 (1H, d, *J* = 11.6 Hz), 8.34 (1H, d, *J* = 13.5 Hz), 7.50 – 7.27 (8H, m), 7.26 – 7.20

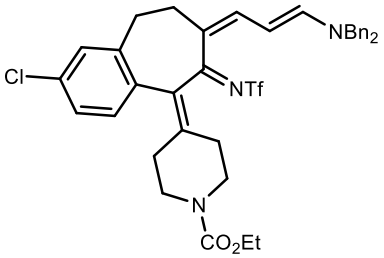
(2H, m), 5.98 (1H, t, J = 12.6 Hz), 4.80 (2H, s), 4.72 (2H, s), 2.77 (2H, t, J = 5.9 Hz), 2.19 (2H, t, J = 5.2 Hz), 1.66 – 1.52 (4H, m); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 174.18, 164.80, 156.00, 134.82, 134.35, 129.96, 128.88, 128.76, 128.44, 127.85, 127.36, 119.97 (q, J = 325.8 Hz), 115.20, 103.48, 59.86, 51.60, 32.71, 24.44, 21.84, 21.49; ^{19}F NMR (365 MHz, $(CD_3)_2SO$) δ: -78.11; *m/z* HRMS (DART) found $[M+H]^+$ 463.1642, $C_{24}H_{26}F_3N_2O_2S^+$ requires 463.1667.

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

2.6 1.0

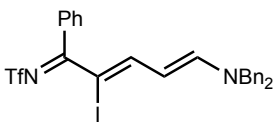
Prepared according to general procedure A using 3-fluoropyridine (172 µL, 2.00 mmol), Tf_2O (340 µL, 2.00 mmol), dibenzylamine (400 µL, 2.00 mmol, 1.0 M in EtOAc), collidine (240 µL, 2.00 mmol), and EtOAc (20 mL, 0.1 M). Purification procedure provided the title compound in a mixture of regioisomers (2.6:1) as a dark green solid (443 mg, 1.04 mmol, 52% yield). ^{1}H NMR (major, 400 MHz, $CDCl_3$) δ: 7.94 – 7.80 (1H, m), 7.60 (1H, d, J = 12.2 Hz), 7.44 (6H, dtd, J = 7.6, 5.6, 2.8 Hz), 7.28 – 7.16 (4H, m), 6.99 – 6.85 (1H, m), 6.09 (1H, t, J = 12.4 Hz), 4.57 (4H, d, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.49, 159.56, 157.31 (d, J = 9.1 Hz), 148.38 (d, J = 10.7 Hz), 148.14, 145.74, 141.43, 133.17 (d, J = 32.8 Hz), 129.68-129.36 (m, 3C), 128.92, 128.71, 128.49, 128.19, 127.61, 127.43, 119.98 (d, J = 322.9 Hz), 110.96, 98.67 (d, J = 4.5 Hz), 60.33, 52.08; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -77.50 (major), -77.67 (minor), -139.18 (major, dd, J = 27.8, 22.1 Hz), -145.65 (minor, t, J = 27.4 Hz ; *m/z* HRMS (DART) found $[M+H]^+$ 427.1102, $C_{20}H_{19}F_4N_2O_2S^+$ requires 427.1103.

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



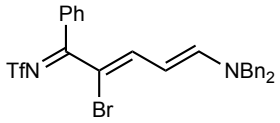
Prepared according to general procedure A using ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta [1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (1.914 g, 5.00 mmol), Tf_2O (840 μL, 5.00 mmol), dibenzylamine (1.149 mL, 6.00 mmol, 1.0 M in EtOAc), collidine (659 μL, 5.00 mmol), and EtOAc (50 mL, 0.1 M). Purification procedure provided the title compound as a bright orange solid (1.85 g, 2.60 mmol, 52% yield). mp 118 – 121 ˚C; IR ν_{max}/cm^{-1} (film): 3035, 2923, 2032, 1747, 1594, 1563, 1547, 1501, 1457, 1345, 1277, 1100, 1069, 1040, 961, 942, 874, 773, 700, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (1H, d, *J* = 12.7 Hz), 7.55 (1H, d, *J* = 12.0 Hz), 7.49 – 7.33 (6H, m), 7.24 – 6.97 (7H, m), 5.77 (1H, t, *J* = 12.4 Hz), 4.50 (4H, m), 4.12 (2H, q, *J* = 7.1 Hz), 3.89 – 3.64 (2H, m), 3.29 (2H, dddd, *J* = 16.6, 12.7, 8.4, 4.1 Hz), 3.12 (1H, dt, *J* = 16.8, 3.8 Hz), 2.90 – 2.63 (2H, m), 2.58 (2H, dq, *J* = 13.7, 4.2 Hz), 2.45 – 2.05 (3H, m), 1.24 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.46, 158.82, 155.52, 151.39, 138.98, 138.12, 134.35, 133.96, 133.70, 133.46, 133.28, 132.01, 129.89, 129.34, 129.11, 128.99, 128.51, 127.29, 125.94, 120.51, 119.62 (q, *J* = 320.4 Hz), 99.79, 61.40, 60.11, 51.59, 44.27, 44.06, 32.84, 32.00, 30.09, 24.35, 14.7; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -79.03; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 712.3, $C_{37}H_{38}ClF_3N_3O_4S^+$ requires 712.2.

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



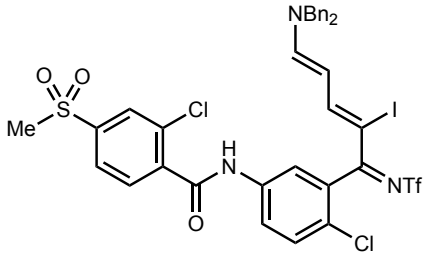
A 500 mL round bottom flask was charged with 2-phenylpyridine (715 μL, 5.00 mmol), EtOAc (50 mL), and cooled to -78 °C. Tf_2O (840 μL, 5.00 mmol) was added dropwise, and the reaction was left to stir for 30 mins. Then, dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc) and collidine (661 μL, 5.00 mmol), 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 (1.12 g, 5.00 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 H_2O, and the organic layer was washed with H_2O and then aqueous NaCl. The organic layer was collected and the separatory funnel was rinsed with CH_2Cl_2 (this is because the product partially crashes out of EtOAc). The organic extracts were dried ($MgSO_4$), filtered, and concentrated. Approximately 10 mL of CH_2Cl_2 was added to dissolve the solid residue, and the resulting solution was added dropwise to a flask containing 500 mL of hexanes. After sitting in a -20 °C fridge for 16 hours, the hexane was decanted and the solid product was collected on a frit and washed with hexanes to yield the pure compound (2.44 g, 4.00 mmol, 80 % yield) as a red solid. mp 201 – 204 °C; IR ν_{max}/cm^{-1} (film): 1604, 1557, 1312, 1158, 1095, 851, 696, 620; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ: 8.38 (1H, d, J = 11.7 Hz), 7.55 – 7.45 (3H, m), 7.43 – 7.28 (10H, m), 7.26 – 7.18 (2H, d, J = 7.4 Hz), 7.10 (1H, d, J = 12.0 Hz), 6.06 (1H, t, J = 11.9 Hz), 4.76 (2H, s), 4.65 (2H, s); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 175.39, 163.37, 162.37, 136.32, 134.66, 134.16, 130.00, 128.83, 128.43, 128.40 (2C), 128.18, 127.87, 127.25, 119.08 (q, J = 320.34 Hz), 110.88, 60.43, 51.94; ^{19}F NMR (365 MHz, $(CD_3)_2SO$) δ: -79.16; *m/z* HRMS (DART) found $[M+H]^+$ 611.0467, $C_{26}H_{23}F_3IN_2O_2S^+$ requires 611.0477

_N_-((1_E_,2_Z_,4_E_)-2-Bromo-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



A 500 mL round bottom flask was charged with 2-phenylpyridine (715 µL, 5.00 mmol), CH_2Cl_2 (50 mL), and cooled to -78 °C. Tf_2O (840 µL, 5.00 mmol) was added dropwise, and the reaction was left to stir for 30 mins. Then, dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in CH_2Cl_2) and collidine (661 µL, 5.00 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. After reaching room temperature, the reaction flask was then cooled to -78 °C where *N*-bromosuccinimide (890 mg, 5.00 mmol) was added and the reaction was allowed to stir for 15 minutes. Trimethoxybenzene (841 mg, 5.00 mmol) was added and the flask was allowed to warm to room temperature, where it was quenched with aqueous sodium thiosulfate. The reaction was diluted with $CH_2Cl_2$and H_2O, and the organic layer was washed with H_2O and then aqueous NaCl. The organic extracts were dried ($MgSO_4$), filtered, and concentrated. Approximately 10 mL of $CH_2Cl_2$was added to dissolve the oil residue, and the resulting solution was added dropwise to a flask containing 500 mL of hexanes. After sitting in a -20 °C fridge for 16 hours, the hexane was decanted and the solid product was collected on a frit and washed with hexanes to yield the pure compound (2.25 g, 4.00 mmol, 80 % yield) as a yellow solid. mp 179 – 182 °C; IR ν_{max}/cm^{-1} (film): 1607, 1417, 1311, 1165, 1093, 992, 874, 800, 745, 675; ^{1}H NMR (400 MHz, CD_3CN) δ: 7.77 (1H, d, *J* = 11.9 Hz), 7.62 – 7.30 (12H, m), 7.28 – 7.18 (4H, m), 6.12 (1H, t, *J* = 12.0 Hz), 4.61 – 4.58 (4H, m); ^{13}C NMR (100 MHz, CD_3CN) δ: 174.96, 163.31, 159.82, 137.81, 135.34, 135.09, 131.43, 131.13, 129.99, 129.92, 129.82, 129.64, 129.42, 129.13, 129.11, 128.41, 120.48 (q, *J* = 322.1 Hz), 108.41, 106.41, 106.42, 61.71, 53.15; ^{19}F NMR (365 MHz, CD_3CN) δ: -80.71; *m/z* HRMS (DART) found $[M+H]^+$ 611.0467, $C_{26}H_{23}F_3IN_2O_2S^+$ requires 611.0477

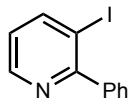
2-Chloro-*N*-(4-chloro-3-((1*E*,2*Z*,4*E*)-5-(dibenzylamino)-2-iodo-1-(((trifluoromethyl)sulfonyl)imino)penta-2,4-dien-1-yl)phenyl)-4-(methylsulfonyl)benzamide



A 100 mL round bottom flask was charged with 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (421 mg, 1.00 mmol) and EtOAc (20 mL). The flask was heated to 60 °C for about 10 minutes to fully dissolve the starting material, and then cooled to -78 °C. Tf_2O (168 µL, 1.00 mmol) was added dropwise, and the reaction was left to stir for 30 mins. Then, dibenzylamine (192 µL, 1.00 mmol, 1.0 M in EtOAc) and collidine (132 µL, 1.00 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 (225.0 mg, 1.00 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 H_2O, and the organic layer was washed 2x with H_2O and 1x with $NaHCO_3$. The organic extracts were dried ($MgSO_4$), filtered, and concentrated. Approximately 10 mL of CH_2Cl_2 was added to dissolve the solid residue, and the resulting solution was added dropwise to a flask containing 500 mL of hexanes. After sitting in a -20 °C fridge for 2 hours, the hexane was decanted and the solid residue was collected on a frit and washed with hexanes. The material was then further purified by flash column chromatography (silica gel: 50% Acetone in Hexanes) to yield the pure compound (443 g, 0.50 mmol, 50 % yield) as a yellow solid (note: column chromatography was used here because the Vismodegib starting material is insoluble in hexanes,

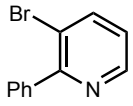
and so wasn't removed during the crash-out step). mp 215 – 218 °C; IR ν_{max}/cm^{-1} (film): 3312, 1559, 1417, 1155, 1094, 958, 851, 697, 672; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 11.01 (1H, s), 8.53 (1H, d, *J* = 11.5 Hz), 8.16 (1H, s), 8.03 (1H, d, *J* = 8.1 Hz), 7.95 – 7.87 (2H, m), 7.62 (1H, s), 7.57 (1H, d, *J* = 8.8 Hz), 7.44 – 7.28 (8H, m), 7.25 – 7.19 (2H, m), 7.05 (1H, d, *J* = 12.1 Hz), 6.15 (1H, t, *J* = 11.9 Hz), 4.81 (2H, s), 4.76 – 4.65 (2H, m), 3.36 (3H, s); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 170.02, 164.36, 163.83, 161.29, 143.19, 140.63, 137.25, 135.49, 134.43, 134.03, 130.96, 130.01, 129.89, 128.89, 128.82, 128.53, 128.42, 128.17, 127.97, 127.31, 125.94, 125.73, 121.69, 120.14, 119.14 (q, *J* = 326.8 Hz), 112.08, 86.05, 60.76, 52.20, 43.08; ^{19}F NMR (365 MHz, $(CD_3)_2SO$) δ: -78.95; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 876.1, $C_{34}H_{28}Cl_2F_3IN_3O_5S_2^+$ requires 876.0.

3-Iodo-2-phenylpyridine



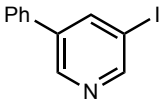
Prepared according to general procedure B using 2-phenylpyridine (1.43 mL, 10.00 mmol), EtOAc (100 mL, 0.1 M), Tf_2O (1.68 mL, 10.00 mmol), dibenzylamine (2.31 µL, 12.00 mmol, 1.0 M in EtOAc), collidine (1.32 mL, 10.00 mmol), *N*-iodosuccinimide (2.25 g, 10.00 mmol), trimethoxybenzene (1.68 g, 10.00 mmol), ammonium acetate (7.71 g, 100.0 mmol), and EtOH (100 mL). The crude material was purified by flash chromatography (silica gel: 2% Acetone in Hexanes, ran twice, then silica gel plug: 0 to 100% CH_2Cl_2 in Hexanes) to afford the title compound as a yellow oil (1.921 g, 6.83 mmol, 68% yield); IR ν_{max}/cm^{-1} (film): 3034, 1561, 1417, 1089, 1004, 915, 781, 740, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (1H, dd, *J* = 4.7, 1.5 Hz), 8.22 (1H, dd, *J* = 8.0, 1.5 Hz), 7.63 – 7.56 (2H, m), 7.48 – 7.39 (3H, m), 6.93 (1H, dd, *J* = 8.0, 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.47, 148.58, 147.55, 141.91, 128.18, 128.63, 127.92, 123.23, 94.26; *m/z* HRMS (DART) found $[M+H]^+$ 281.9790, $C_{11}H_9IN^+$ requires 281.9780.

3-Bromo-2-phenylpyridine



Prepared according to general procedure D (except that the ammonium acetate step was let run for 20 hours) using 2-phenylpyridine (57 μL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL) (Note: the brominated imine crashes out of CH_2Cl_2 at -78 °C, and the reaction vial was physically shaken after adding trimethoxybenzene and while warming to room temperature). The crude material was purified by flash chromatography (silica gel: 0 to 100% CH_2Cl_2 in Hexanes) to provide the title compound as a clear oil (54.7 mg, 0.23 mmol, 58% yield); IR ν_{max}/cm^{-1} (film): 3040, 1616, 1426, 1300, 1179, 1009, 738, 695, 611; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, d, J = 4.5 Hz), 7.99 (1H, d, J = 8.0 Hz), 7.69 (2H, d, J = 7.3 Hz), 7.51 – 7.40 (3H, m), 7.13 (1H, dd, J = 7.6, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.28, 148.16, 141.37, 139.66, 129.37, 128.83, 128.06, 123.32, 119.90; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 234.0, $C_{11}H_9BrN^+$ requires 234.0.

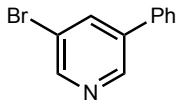
3-Iodo-5-phenylpyridine



Prepared according to general procedure C using 3-phenylpyridine (1.43 mL, 10.00 mmol), EtOAc (100 mL, 0.1 M), Tf_2O (1.68 mL, 10.00 mmol), dibenzylamine (2.31 μL, 12.00 mmol, 1.0 M in EtOAc), collidine (1.32 mL, 10.00 mmol), *N*-iodosuccinimide (2.25 g, 10.00 mmol), and trifluoroacetic acid (765 μL, 10.00 mmol). The crude material was purified by flash chromatography (silica gel: 10% Et_2O in Hexanes) to provide the title compound as a white solid (2.30 g, 8.19 mmol, 82% yield). mp 79 – 81 °C; IR ν_{max}/cm^{-1} (film): 3014, 1496, 1423, 1103, 1005,

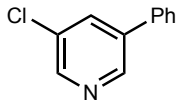
881, 785, 699, 663; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (1H, s), 8.77 (1H, s), 8.21 (1H, d, *J* = 1.4 Hz), 7.57 – 7.53 (2H, m), 7.51 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.35, 146.83, 142.63, 138.68, 136.44, 129.30, 128.77, 127.26, 93.76; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 282.0, $C_{11}H_9IN^+$ requires 282.0.

3-Bromo-5-phenylpyridine



Prepared according to general procedure E using 3-phenylpyridine (57 μL, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), and trifluoroacetic acid (31 μL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 10% Ether in Hexanes) to provide the title compound as a clear oil (76 mg, 0.32 mmol, 81% yield); IR ν_{max}/cm^{-1} (film): 3037, 1580, 1428, 1101, 1010, 881, 758, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (1H, d, *J* = 1.4 Hz), 8.65 (1H, d, *J* = 1.8 Hz), 8.00 (1H, app t, *J* = 1.8 Hz), 7.57 – 7.52 (2H, m), 7.50 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.31, 146.16, 137.92, 136.43, 134.12, 132.26, 129.32, 128.80, 127.28; *m/z* HRMS (DART) found $[M+H]^+$ 233.9921, $C_{11}H_9BrN^+$ requires 233.9918.

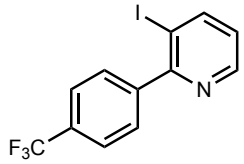
3-Chloro-5-phenylpyridine



Prepared according to general procedure F using 3-phenylpyridine (57 μL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in

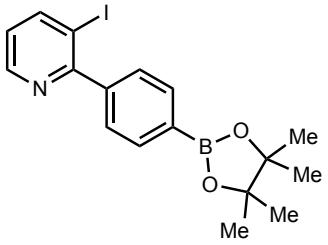
CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-chlorosuccinimide (53 mg, 0.40 mmol), and HCl (400 µL, 1.60 mmol, 4 M in dioxane). The crude material was purified by flash chromatography (silica gel: 10% Ether in Hexanes) to provide the title compound as a clear oil (60 mg, 0.32 mmol, 79% yield); IR ν_{max}/cm^{-1} (film): 1674, 1431, 1108, 1016, 906, 727, 697, 640; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, s), 8.55 (1H, s), 7.85 (1H, m), 7.58 – 7.53 (2H, m), 7.52 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.31, 146.16, 137.92, 136.43, 134.12, 132.26, 129.32, 128.80, 127.28; *m/z* HRMS (DART) found $[M+H]^+$ 190.0433, $C_{11}H_9ClN^+$ requires 190.0424

3-Iodo-2-(4-(trifluoromethyl)phenyl)pyridine



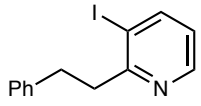
Prepared according to general procedure B using 2-(4-(trifluoromethyl)phenyl)pyridine (80 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 3:1:96 EtOH:MeOH:Hexanes, run twice) to provide the title compound as a white solid (91 mg, 0.26 mmol, 65% yield). mp 34 – 35 °C; IR ν_{max}/cm^{-1} (film): 1564, 1423, 1322, 1161, 1104, 1015, 846, 736; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.65 (1H, dd, J = 4.6, 1.3 Hz), 8.28 (1H, dd, J = 8.0, 1.4 Hz), 7.73 (4H, s), 7.02 (1H, dd, J = 8.0, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.98, 148.74, 147.80, 125.34, 104.79, 93.26, 65.93; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -62.67; *m/z* HRMS (DART) found $[M+H]^+$ 349.9654, $C_{12}H_8F_3IN^+$ requires 349.9654.

3-Iodo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine



Prepared according to general procedure B using 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine (112 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). Crude NMR showed 68% of the title compound relative to triphenylmethane internal standard. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes, run four times) to provide 20 mg of the title compound as an amorphous solid. IR ν_{max}/cm^{-1} (film): 2977, 1563, 1357, 1267, 1142, 1002, 730, 657; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.64 (1H, d, *J* = 4.5 Hz), 8.26 (1H, d, *J* = 8.0 Hz), 7.90 (2H, d, *J* = 7.5 Hz), 7.60 (2H, d, *J* = 7.5 Hz), 6.98 (1H, dd, *J* = 7.9, 4.6 Hz), 1.37 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.58, 148.69, 147.85, 144.51, 134.53, 128.61, 123.50, 94.29, 84.06, 25.07; *m/z* HRMS (DART) found $[M+H]^+$ 408.0680, $C_{17}H_{20}BINO_2^+$ requires 408.0632

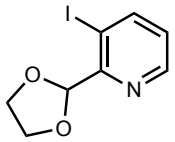
3-Iodo-2-phenethylpyridine



Prepared according to general procedure B using 2-phenethylpyridine (73 µL, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). Flash column chromatography (silica gel: 10% EtOAc in Hexanes, second column: 60% to

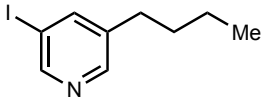
100% CH_2Cl_2 in Hexanes) afforded the title compound (82 mg, 0.26 mmol, 66% yield) as a yellow oil. IR ν_{max}/cm^{-1} (film): 1566, 1419, 1114, 1007, 908, 755, 697; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, dd, *J* = 4.6, 1.2 Hz), 8.10 (1H, dd, *J* = 7.9, 1.3 Hz), 7.36 – 7.32 (4H, m), 7.28 – 7.22 (1H, m), 6.87 (1H, dd, *J* = 7.9, 4.7 Hz) 3.35 – 3.29 (2H, m), 3.10 – 3.04 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.18, 148.70, 146.92, 141,48, 128.60, 128.52, 126.16, 122.72, 96.42, 43.42, 35.09; *m/z* HRMS (DART) found $[M+H]^+$ 310.0136, $C_{13}H_{13}IN^+$ requires 310.0093.

2-(1,3-Dioxolan-2-yl)-3-iodopyridine



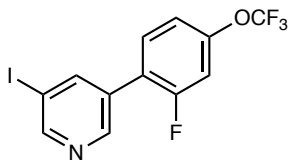
Prepared according to general procedure B using 2-(1,3-dioxolan-2-yl)pyridine (61 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 μL, 0.40 mmol), dibenzylamine (92 μL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 μL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel gradient elution: 35 to 50% EtOAc in Hexanes, run twice) to provide the title compound as a green oil (56 mg, 0.20 mmol, 50% yield); IR ν_{max}/cm^{-1} (film): 2890, 1379, 1028, 1008, 941, 793, 757, 627; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.61 (1H, d, *J* = 4.6 Hz), 8.16 (1H, dd, *J*= 8.0, 0.8 Hz), 7.02 (1H, dd, *J* = 8.0, 4.6 Hz), 6.19 (1H, s), 4.36 – 4.23 (2H, m), 4.17 – 4.02 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.98, 148.74, 147.80, 125.34, 104.79, 93.26, 65.93; *m/z* HRMS (DART) found $[M+H]^+$ 277.9669, $C_8H_9INO_2^+$ requires 277.9678.

3-Butyl-5-iodopyridine



Prepared according to general procedure C using 3-butylpyridinepyridine (59 µL, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 5% EtOAc in Hexanes) to provide the title compound as a clear oil (78 mg, 0.30, 74% yield); IR ν_{max}/cm^{-1} (film): 2955, 2927, 2857, 1548, 1419, 1018, 895, 703; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.65 (1H, s), 8.38 (1H, s), 7.84 (1H, s), 2.56 (2H, t, J = 7.8 Hz), 1.64 – 1.55 (2H, m), 1.42 – 1.30 (2H, m), 0.94 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.20, 148.50, 144.09, 140.24, 93.53, 31.11, 32.42, 22.27, 13.90; *m/z* HRMS (DART) found $[M+H]^+$ 262.0098, $C_9H_{13}IN^+$ requires 262.0093.

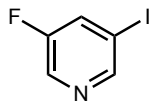
3-(2-Fluoro-4-(trifluoromethoxy)phenyl)-5-iodopyridine



Prepared according to general procedure C using 3-(2-fluoro-4-(trifluoromethoxy)phenyl)pyridine (103 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). Flash column chromatography (silica gel: 10% EtOAc in Hexanes) afforded the title compound (126 mg, 0.33 mmol, 82% yield) as a white solid. mp 68 – 71 °C; IR ν_{max}/cm^{-1} (film): 2924, 1623, 1507, 1401, 1166, 1009, 885, 723, 697; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.83 (1H, s), 8.69 (1H, s), 8.16 (1H, s), 7.44 (1H, app t, J = 8.5 Hz), 7.15 – 7.08 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.73 (d, J = 249.7 Hz), 155.21, 150.10 (dq, J = 11.0, 2.1 Hz), 147.99 (d, J = 3.6 Hz), 144.25 (d, J = 3.2 Hz), 132.26, 131.29 (d, J = 4.1 Hz), 123.13 (d, J = 14.0 Hz), 120.39 (q, J = 259.0 Hz), 117.23 (d, J =

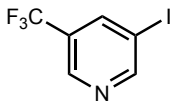
3.8 Hz), 109.77 (d, J = 32.8 Hz), 93.31; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -58.0 (3F, s), -113.05 (1F, app t, J = 9.6 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 383.9549, $C_{12}H_7F_4INO^+$ requires 383.9508.

3-Fluoro-5-iodopyridine



A 2.6:1 mixture of *N*-((1Z,2Z,4E)-5-(Dibenzylamino)-2-fluoropenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethane sulfonamide and *N*-((1Z,2E,4Z)-5-(dibenzylamino)-4-fluoropenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfon- amide (128 mg, 0.30 mmol) and CH_2Cl_2 (3 mL, 0.1 M) were added to an 8 mL vial which was subsequently cooled to 0 °C. *N*-iodosuccinimide (71 mg, 0.32 mmol) and trifluoroacetic acid (24 µL, 0.32 mmol) were added, the cooling bath was removed, and the reaction was allowed to stir for 2 hours. The reaction was quenched with aqueous sodium thiosulfate and sodium bicarbonate, triphenylmethane (internal standard) was added, and an aliquot was concentrated down. Crude NMR showed 82% of the title compound relative to triphenylmethane internal standard. Flash column chromatography yielded a mixture of the product and other non-pyridine byproducts. Spectra matched an authentic sample purchased from Oakwood.

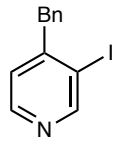
3-Iodo-5-(trifluoromethyl)pyridine



Prepared according to general procedure B (except that 0.9 equivalents of collidine was used and after addition of *N*-iodosuccinimide and TFA, the reaction was heated to 50 °C for 3 hours) using 3-(trifluoromethyl)pyridine (35 µL, 0.30 mmol), EtOAc (3 mL, 0.1 M), Tf_2O (50 µL, 0.30 mmol), dibenzylamine (58 µL, 0.30 mmol, 1.0M in EtOAc), collidine (36 µL, 0.27 mmol), *N*-iodosuccinimide (68 mg, 0.30 mmol), and trifluoroacetic acid (23 µL, 0.30 mmol). Crude NMR

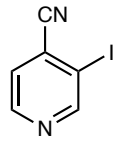
showed 65% of the title compound relative to triphenylmethane internal standard. Flash column chromatography yielded a mixture of the product and other non-pyridine byproducts. Spectra matched literature values.

4-Benzyl-3-iodopyridine



Prepared according to general procedure B using 4-benzylpyridine (64 µL, 0.40 mmol), EtOAc (4 mL), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). Flash column chromatography (silica gel: 15% EtOAc in Hexanes) afforded the title compound (92 mg, 0.26 mmol, 66% yield) as a brown oil. IR ν_{max}/cm^{-1} (film): 3028, 1576, 1394, 1083, 1011, 796, 618; ^1H NMR (400 MHz, CD_3CN) δ: 8.93 (1H, br s), 8.42 (1H, br s), 7.32 (2H, app t, J = 7.6 Hz), 7.27 – 7.19 (3H, m), 7.15 (1H, d, J = 3.0 Hz); ^{13}C NMR (100 MHz, CD_3CN) δ: 158.39, 153.45, 150.04, 138.98, 130.03, 129.61, 127.63, 118.24, 101.37, 45.99; *m/z* HRMS (DART) found $[M+H]^+$ 293.9931, $C_{12}H_{11}IN_2^+$ requires 295.9936.

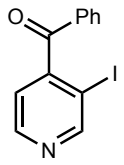
3-Iodoisonicotinonitrile



Prepared according to general procedure B (except that the NIS step was ran for 30 minutes instead of 10 minutes) using 4-cyanopyridine (42 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol),

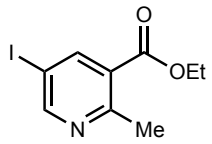
ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). Flash column chromatography (silica gel gradient elution: 5 to 15% EtOAc in Hexanes) afforded the title compound (33 mg, 0.14 mmol, 36% yield) as a brown solid. mp 115 – 118 °C; IR ν_{max}/cm^{-1} (film): 2922, 2852, 1215, 1082, 1018, 836, 613; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.11 (1H, s), 8.72 (1H, d, *J* = 4.9 Hz), 7.52 (1H, d, *J* = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.18, 149.09, 128.12, 127.26, 117.18, 95.07; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 231.0, $C_6H_4IN_2^+$ requires 230.9.

(3-Iodopyridin-4-yl)(phenyl)methanone



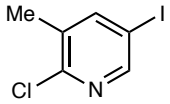
Prepared according to a modified version of general procedure B using phenyl(pyridin-4-yl)methanone)pyridine (73 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trimethoxybenzene (67 mg, 0.40 mmol). Instead of adding ammonium acetate, trifluoroacetic acid (92 μL, 1.20 mmol) was added and the reaction was left to stir at room temperature for 2 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in Hexanes) to provide the title compound as a yellow solid (76 mg, 0.25 mmol, 62% yield). mp 79 – 82 °C; IR ν_{max}/cm^{-1} (film): 1670, 1449, 1289, 1174, 979, 702, 638; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, s), 8.67 (1H, d, *J* = 4.7 Hz), 7.78 (2H, d, *J* = 7.8 Hz), 7.65 (1H, d, *J* = 7.4 Hz), 7.50 (2H, d, *J* = 7.6 Hz), 7.23 (1H, d, *J* = 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.95, 157.99, 151.62, 148.81, 134.63, 134.26, 130.46, 129.20, 122.47, 91.04; *m/z* HRMS (DART) found $[M+H]^+$ 309.9741, $C_{12}H_9INO^+$ requires 309.9729.

Ethyl 5-iodo-2-methylnicotinate



Prepared according to general procedure C (except that CH_2Cl_2 was the solvent and two equivalents of TFA were used) using ethyl 2-methylnicotinate (62 μL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 μL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (61 μL, 0.80 mmol). The crude material was purified by flash chromatography (silica gel: 5% EtOAc in Hexanes, run twice) to provide the title compound as a white solid (48 mg, 0.16 mmol, 41% yield). mp 83 – 86 °C; IR ν_{max}/cm^{-1} (film): 2922, 2850, 1724, 1372, 1268, 1247, 1082, 795; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, J = 2.2 Hz), 8.48 (1H, d, J = 2.2 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.78 (3H, s), 1.41 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.35, 158.77, 157.68, 146.16, 127.44, 89.19, 61.80, 24.46, 14.38; *m/z* HRMS (DART) found $[M+H]^+$ 291.9826, $C_9H_{11}INO_2^+$ requires 291.9834.

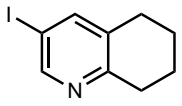
2-Chloro-5-iodo-3-methylpyridine



Prepared according to a modificiation of procedure C (where *N*-benzylaniline was used instead of dibenzylamine and two equivalents of TFA were used) using 2-chloro-3-methylpyridine (44 μL, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 μL, 0.40 mmol), *N*-benzylaniline (73 mg, 0.40 mmol, 1.0 M in EtOAc), collidine (53 μL, 0.40 mmol), *N*-iodosuccinimide (180 mg, 0.80 mmol), and trifluoroacetic acid (61 μL, 0.80 mmol) were added, the ice bath was removed, and the reaction was stirred at room temperature for 24 hours. Flash column chromatography (silica gel: 1% Ether in Hexanes; second column: 50% Toluene in Hexanes) afforded the title compound

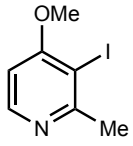
(44 mg, 0.18 mmol, 44% yield) as a clear oil. IR ν_{max}/cm^{-1} (film): 2923, 2237, 1397, 1184, 1076, 906, 724, 646; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.43 (1H, d, *J* = 1.9 Hz), 7.86 (1H, d, *J* = 1.5 Hz), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.99, 151.34, 147.16, 134.91, 90.89, 19.59; *m/z* HRMS (DART) found $[M+H]^+$ 253.9229, $C_6H_6ClIN^+$ requires 253.9233.

3-Iodo-5,6,7,8-tetrahydroquinoline



N-((1*E*,2*Z*)-2-((*E*)-3-(dibenzylamino)allylidene)cyclohexylidene)-1,1,1-trifluoromethanesulfonamide (185 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) were added to an 8 mL vial which was subsequently cooled to 0 °C. *N*-iodosuccinimide (94 mg, 0.42 mmol) and trifluoroacetic acid (32 μL, 0.42 mmol) were added, the cooling bath was removed, and the reaction was allowed to stir for 2 hours. After the workup for general procedure C, the crude material was purified by flash chromatography (silica gel: 5% EtOAc in Hexanes) to provide the title compound as a white solid (86 mg, 0.33 mmol, 83% yield). mp 96 – 100 °C; IR ν_{max}/cm^{-1} (film): 2924, 1689, 1433, 1228, 1085, 1014, 799, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, d, *J* = 1.2 Hz), 7.65 (1H, s), 2.83 (2H, t, *J* = 6.5 Hz), 2.70 (2H, t, *J* = 6.2 Hz), 1.90 – 1.80 (2H, m), 1.80 – 1.71 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.44, 152.59, 144.60, 134.80, 89.61, 32.10, 28.63, 22.82, 22.33; *m/z* HRMS (DART) found $[M+H]^+$ 259.9965, $C_9H_{11}IN^+$ requires 259.9936.

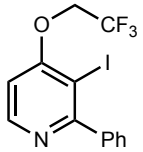
3-Iodo-4-methoxy-2-methylpyridine



Prepared according to a modified version of general procedure B using 4-methoxy-2-methylpyridine (49 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol),

dibenzylamine (77 μL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), and *N*-iodosuccinimide (90 mg, 0.40 mmol). After stirring with *N*-iodosuccinimide at room temperature for 1 hour, trifluoroacetic acid (61 μL, 0.80 mmol) was added and the reaction was left to stir at room temperature for an additional 2 hours. The crude material was purified by flash chromatography (silica gel: 40% EtOAc in Hexanes) to provide the title compound as a brown solid (47 mg, 0.18 mmol, 44% yield). mp 104 – 106 °C. IR ν_{max}/cm^{-1} (film): 2941, 1574, 1426, 1288, 1074, 981, 822, 737; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.25 (1H, d, *J* = 5.6 Hz), 6.53 (1H, d, *J* = 5.6 Hz), 3.92 (3H, s), 2.75 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.37, 162.20, 149.87, 104.07, 88.09, 56.48, 29.62; *m/z* HRMS (DART) found $[M+H]^+$ 249.9750, $C_7H_9INO^+$ requires 249.9729.

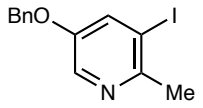
3-Iodo-2-phenyl-4-(2,2,2-trifluoroethoxy)pyridine



Prepared according to a modified version of general procedure B using 2-phenyl-4-(2,2,2-trifluoroethoxy)pyridine (101 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), and *N*-iodosuccinimide (90 mg, 0.40 mmol). After stirring with *N*-iodosuccinimide at room temperature for 1 hour, trifluoroacetic acid (61 μL, 0.80 mmol) was added and the reaction was left to stir at room temperature for an additional 2 hours. The crude material was purified by flash chromatography (silica gel gradient elution: 20 to 30% EtOAc in Hexanes) to provide the title compound as a white solid (108 mg, 0.28 mmol, 71% yield). mp 152 – 155 °C; IR ν_{max}/cm^{-1} (film): 1568, 1450, 1252, 1073, 978, 892, 856, 754; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.46 (1H, d, *J* = 5.5 Hz), 7.58 – 7.53 (2H, m), 7.49 – 7.40 (3H, m), 6.65 (1H, d, *J* = 5.5 Hz), 4.51 (2H, q, *J* = 7.8 Hz);

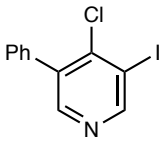
^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.87, 162.83, 150.37, 142.21, 129.21, 128.83, 128.04, 122.74 (q, *J* = 278.2 Hz), 105.52, 86.99, 66.21 (q, *J* = 36.7 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -73.43; *m/z* HRMS (DART) found $[M+H]^+$ 379.9764, $C_{13}H_{10}F_3INO^+$ requires 379.9759.

5-(Benzyloxy)-3-iodo-2-methylpyridine



Prepared according to a modified version of general procedure C using 5-(benzyloxy)-2-methylpyridine (80 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), and collidine (53 µL, 0.40 mmol). After *N*-iodosuccinimide (90 mg, 0.40 mmol) and trifluoroacetic acid (31 µL, 0.40 mmol) were added, the reaction was stirred at room temperature for 90 minutes. Then ammonium acetate (308 mg, 4.00 mmol) was added, and the reaction was heated to 50 °C for 22 hours. Flash column chromatography (silica gel 10% EtOAc in Hexanes) afforded the title compound (87 mg, 0.27 mmol, 67% yield) as a brown oil. IR ν_{max}/cm^{-1} (film): 2919, 2218, 1449, 1272, 1221, 1007, 907, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (1H, d, *J* = 2.6 Hz), 7.68 (1H, d, *J* = 2.6 Hz), 7.43 – 7.35 (5H, m), 5.05 (2H, s), 2.68 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.81, 152.36, 136.63, 135.88, 132.29, 128.86, 128.54, 127.68, 95.54, 70.85, 27.71; *m/z* HRMS (DART) found $[M+H]^+$ 326.0094, $C_{13}H_{13}INO^+$ requires 326.0042.

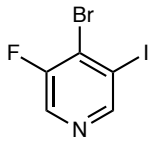
4-Chloro-3-iodo-5-phenylpyridine



Prepared according to general procedure C using 4-chloro-3-phenylpyridine (76 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0

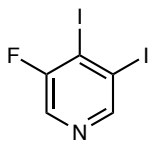
M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). Flash column chromatography (silica gel: 5% EtOAc in Hexanes) afforded the title compound (72 mg, 0.23 mmol, 57% yield) as a white solid. mp 74 – 77 °C; IR ν_{max}/cm^{-1} (film): 2923, 1534, 1389, 1242, 1076, 892, 765, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (1H, s), 8.42 (1H, s), 7.50 – 7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.12, 150.23, 146.04, 137.98, 135.96, 129.44, 128.86, 128.56, 99.36; *m/z* HRMS (DART) found $[M+H]^+$ 315.9383, $C_{11}H_8ClIN^+$ requires 315.9390.

4-Bromo-3-fluoro-5-iodopyridine



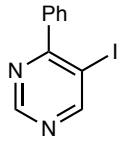
Prepared according to general procedure C using 4-bromo-3-fluoropyridine (70 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). Flash column chromatography (silica gel: 100% Toluene, run twice) afforded the title compound (47 mg, 0.16 mmol, 39% yield) as a white solid. mp 125 – 127 °C; IR ν_{max}/cm^{-1} (film): 1542, 1397, 1268, 1125, 867, 698, 628; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, s), 8.37 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.65 (d, J = 263 Hz), 153.32 (d, J = 4.9 Hz), 137.11 (d, J = 25.3 Hz), 127.36 (d, J = 19.0 Hz), 101.68 (d, J = 4.6 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -112.16; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 301.9, $C_5H_3BrFIN^+$ requires 301.8.

3-Fluoro-4,5-diiodopyridine



Prepared according to general procedure C using 3-fluoro-4-iodopyridine (89 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). Flash column chromatography (silica gel gradient elution: 2 to 3% EtOAc in Hexanes) afforded the title compound (35 mg, 0.10 mmol, 25% yield) as a white solid. mp 118 – 120 °C; IR ν_{max}/cm^{-1} (film): 1526, 1396, 1266, 1128, 866, 617, 611; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, s), 8.25 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.40 (d, J = 260 Hz), 152.27 (d, J = 4.8 Hz), 135.36 (d, J = 27 Hz), 108.29 (d, J = 3.9 Hz), 107.62 (d, J = 23 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -95.79; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 349.9, $C_5H_3FI_2N^+$ requires 349.8.

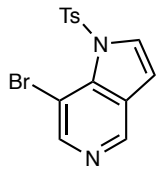
5-Iodo-4-phenylpyrimidine



Prepared according to a modified version of general procedure C using 4-phenylpyrimidine (63 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), and collidine (53 µL, 0.40 mmol). After *N*-iodosuccinimide (90 mg, 0.40 mmol) and trifluoroacetic acid (31 µL, 0.40 mmol) were added, the reaction was stirred at room temperature for 1 hour. Then ammonium acetate (308 mg, 4.00 mmol) and EtOH (8 mL) was added, and the reaction was heated to 60 °C for 2 hours. Flash column chromatography (silica gel: 10% EtOAc in Hexanes) afforded the title compound (60 mg, 0.21 mmol, 53% yield) as a white solid. mp 59 – 62 °C; IR ν_{max}/cm^{-1} (film): 1546, 1430, 1303, 1151, 1007, 741, 696, 621; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.15 – 9.13 (2H, m), 7.72 – 7.69 (2H, m), 7.50 – 7.47 (3H, m); ^{13}C

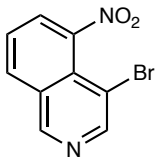
NMR (100 MHz, $CDCl_3$) δ: 167.80, 165.68, 157.49, 139.12, 130.21, 129.18, 128.36, 94.25; *m/z* HRMS (DART) found $[M+H]^+$ 282.9390, $C_{10}H_8IN_2^+$ requires 282.9732.

7-Bromo-1-tosyl-1*H*-pyrrolo[3,2-*c*]pyridine



Prepared according to modified version of general procedure E using 1-tosyl-1*H*-pyrrolo[3,2-*c*]pyridine (109 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in CH_2Cl_2), and collidine (53 µL, 0.40 mmol). After warming to room temperature, *N*-bromosuccinimide (71 mg, 0.40 mmol) was added and the reaction was stirred at room temperature for 1 h. Then, trifluoroacetic acid (61 µL, 0.80 mmol) as added and the reaction was stirred at room temperature for 2 hours. Flash column chromatography (silica gel: 30% EtOAc in Hexanes) afforded the title compound (50 mg, 0.14 mmol, 36% yield) as a brown solid. mp 152 – 158 ˚C; IR ν_{max}/cm^{-1} (film): 1405, 1360, 1170, 1120, 988, 922, 820, 703; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.80 (1H, s), 8.51 (1H, s), 7.94 (1H, d, J = 3.8 Hz), 7.71 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.1 Hz), 6.80 (1H, d, J = 3.8 Hz), 2.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.99, 145.57, 142.98, 137.43, 136.60, 131.19, 130.46, 130.06, 127.46, 105.66, 104.05, 21.82; *m/z* HRMS (DART) found $[M+H]^+$ 350.9850, $C_{14}H_{12}BrN_2O_2S^+$ requires 350.9803.

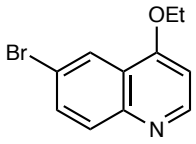
4-Bromo-5-nitroisoquinoline



In an 8 mL vial, *N*,*N*-dibenzyl-5-nitro-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinolin-1-amine (201 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (4 mL, 0.1 M). *N*-

bromosuccinimide (71 mg, 0.40 mmol) was added, and the reaction was stirred at room temperature for one hour. Then trifluoroacetic acid (61 μL, 0.80 mmol) was added and the reaction was stirred for 24 hours. Flash column chromatography (silica gel: 30% EtOAc in Hexanes) afforded the title compound (86 mg, 0.34 mmol, 85% yield) as an amorphous solid. IR ν_{max}/cm^{-1} (film): 1526, 1401, 1227, 1193, 1141, 1027, 772, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.27 (1H, s), 8.87 (1H, s), 8.21 (1H, d, *J* = 8.2 Hz), 7.96 (1H, d, *J* = 7.5 Hz), 7.74 (1H, app t, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.10, 149.62, 147.20, 132.22, 130.54, 127.21, 127.13, 125.54, 113.39; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 253.0, $C_9H_6BrN_2O_2^+$ requires 253.0.

6-Bromo-4-ethoxyquinoline



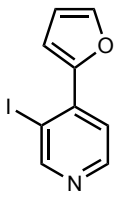
Prepared according to a modified version of general procedure G using 4-ethoxyquinoline (69 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 μL, 0.40 mmol), dibenzylamine (92 μL, 0.48 mmol, 1.0 M in CH_2Cl_2), and collidine (53 μL, 0.40 mmol). After warming to room temperature, *N*-bromosuccinimide (71 mg, 0.40 mmol) was added and the reaction was stirred at room temperature for 1 h. Then, trifluoroacetic acid (61 μL, 0.80 mmol) as added and the reaction was stirred at room temperature for 2 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes, second column: 2% MeOH in CH_2Cl_2) afforded the title compound (35 mg, 0.14 mmol, 35% yield) as a white solid. mp 83 – 83 °C; IR ν_{max}/cm^{-1} (film): 2921, 2851, 1570, 1350, 1302, 1153, 839, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (1H, br s), 8.36 (1H, d, *J* = 1.7 Hz), 7.88 (1H, d, *J* = 8.9 Hz), 7.74 (1H, dd, *J* = 8.9, 2.1 Hz), 6.71 (1H, d, *J* = 5.0 Hz), 4.24 (2H, q, *J* = 7.0 Hz), 1.57 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.74, 151.83, 148.00, 133.21,

130.85, 124.61, 122.85, 119.55, 101.40, 64.52, 14.58; *m/z* HRMS (DART) found $[M+H]^+$ 252.0077, $C_{11}H_{11}BrNO^+$ requires 252.0024.

3-Iodo-2-(thiophen-3-yl)pyridine

Prepared according to general procedure B using 2-(thiophen-3-yl)pyridine (65 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (92 μL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 90% CH_2Cl_2 in Hexanes) to provide the title compound as a brown oil (79 mg, 0.27 mmol, 68% yield). IR ν_{max}/cm^{-1} (film): 3037, 2220, 1563, 1436, 1186, 1002, 863, 786, 749, 644; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, *J* = 3.8 Hz), 8.23 (1H, d, *J* = 7.9 Hz), 7.81 (1H, d, *J* = 1.6 Hz), 7.52 (1H, d, *J* = 4.8 Hz), 7.37 (1H, dd, *J* = 4.7, 3.0 Hz), 6.91 (1H, dd, *J* = 7.9, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.79, 148.60, 148.05, 142.51, 128.91, 126.58, 124.99, 123.12, 93.71; *m/z* HRMS (DART) found $[M+H]^+$ 287.9387, $C_9H_7INS^+$ requires 287.9344.

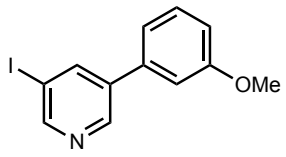
4-(Furan-2-yl)-3-iodopyridine



Prepared according to general procedure B using ethyl 4-(furan-2-yl)pyridine (58 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 μL, 0.40 mmol), dibenzylamine (92 μL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 μL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol),

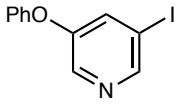
trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes) to provide the title compound as a brown amorphous solid (68 mg, 0.25 mmol, 62% yield); IR ν_{max}/cm^{-1} (film): 2924, 1581, 1393, 1093, 1003, 839, 742, 663; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, s), 8.52 (1H, d, *J* = 5.1 Hz), 7.66 (1H, d, *J* = 5.0 Hz), 7.61 (1H, d), 7.57 (1H, d, *J* = 3.5 Hz), 6.59 (1H, d, *J* = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.49, 148.75, 144.00, 141.00, 122.23, 112.77, 111.82, 91.06; *m/z* HRMS (DART) found $[M+H]^+$ 271.9596, $C_9H_7INO^+$ requires 271.9572.

3-Iodo-5-(3-methoxyphenyl)pyridine



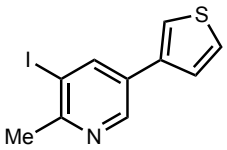
Prepared according to general procedure C using 3-(3-methoxyphenyl)pyridine (74 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 mL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes) to provide the title compound as a white solid (95 mg, 0.30 mmol, 76% yield). mp 66 – 69 ˚C; IR ν_{max}/cm^{-1} (film): 2927, 1691, 1421, 1294, 1219, 1087, 1011, 710, 664; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, s), 8.77 (1H, s), 8.21 (1H, s), 7.40 (1H, app t, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 7.7 Hz), 7.06 (1H, s), 6.97 (1H, dd, *J* = 8.2, 2.4 Hz), 3.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.23, 154.44, 146.81, 142.59, 138.49, 137.79, 130.32, 119.61, 114.04, 112.99, 93.71, 55.47; *m/z* HRMS (DART) found $[M+H]^+$ 311.9869, $C_{12}H_{11}INO^+$ requires 311.9885.

3-Iodo-5-phenoxypyridine



Prepared according to general procedure C (except that the solvent was CH_2Cl_2 and two equivalents of NIS and TFA were used) using 3-phenoxypyridine (69 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), and collidine (53 µL, 0.40 mmol) After *N*-iodosuccinimide (180 mg, 0.80 mmol) and trifluoroacetic acid (61 µL, 0.80 mmol) were added, the reaction was stirred at room temperature for 21 hours. Flash column chromatography (silica gel: 10% EtOAc in Hexanes) afforded the title compound (76 mg, 0.26 mmol, 64% yield) as a light yellow solid. mp 43 – 45 °C; IR ν_{max}/cm^{-1} (film): 2923, 1550, 1417, 1241, 1196, 1009, 881, 690; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, s), 8.35 (1H, s), 7.59 (1H, app t, J = 2.0 Hz), 7.42 – 7.32 (2H, m), 7.20 (1H, t, J = 7.5 Hz), 7.06 – 7.01 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.58, 154.47, 150.08, 139.76, 133.24, 130.34, 124.89, 119.49, 92.81; *m/z* HRMS (DART) found $[M+H]^+$ 297.9718, $C_{11}H_9INO^+$ requires 297.9729.

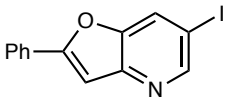
3-Iodo-2-methyl-5-(thiophen-3-yl)pyridine



Prepared according to general procedure B using 2-methyl-5-(thiophen-3-yl)pyridine (70 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes) to provide the title compound as a brown solid (48 mg, 0.09 mmol, 23% yield). mp 67 – 70 °C; IR ν_{max}/cm^{-1} (film): 3061, 2921, 2852, 1461, 1029, 816, 778, 640; ^1H NMR (400 MHz, $CDCl_3$) δ:

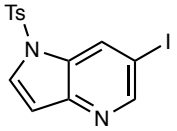
8.70 (1H, d, *J* = 1.9 Hz), 8.26 (1H, d, *J* = 1.9 Hz), 7.50 (1H, dd, *J* = 2.9, 1.2 Hz), 7.45 (1H, dd, *J* = 5.0, 2.9 Hz), 7.36 (1H, dd, *J* = 5.0, 1.2 Hz), 2.77 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.59, 146.17, 143.85, 137.19, 130.69, 127.25, 125.89, 121.75, 96.67, 28.69; *m/z* HRMS (DART) found $[M+H]^+$ 301.9538, $C_{10}H_9INS^+$ requires 301.9500.

6-Iodo-2-phenylfuro[3,2-*b*]pyridine



Prepared according to general procedure C (except that CH_2Cl_2 was the solvent) using 2-phenylfuro[3,2-*b*]pyridine (78 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in CH_2Cl_2), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol).. Flash column chromatography (silica gel gradient elution: 5 to 7.5% EtOAc in Hexanes) afforded the title compound (96 mg, 0.34 mmol, 74% yield) as a yellow solid. mp 190 – 194 °C; IR ν_{max}/cm^{-1} (film): 1527, 1402, 1227, 1142, 1028, 753, 698, 637; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, s), 8.10 (1H, s), 7.87 (2H, d, *J* = 7.1 Hz), 7.50 – 7.41 (3H, m), 7.17 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.17, 151.96, 148.52, 148.06, 139.06, 129.32, 129.14, 126.25, 125.55, 102.39, 85.78; *m/z* HRMS (DART) found $[M+H]^+$ 321.9749, $C_{13}H_9INO^+$ requires 321.9729.

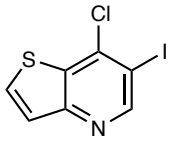
6-Iodo-1-tosyl-1*H*-pyrrolo[3,2-*b*]pyridine



Prepared according to general procedure C using 1-tosyl-1*H*-pyrrolo[3,2-*b*]pyridine (109 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), and collidine (53 µL, 0.40 mmol), After *N*-iodosuccinimide (90 mg, 0.40

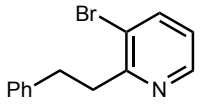
mmol) and trifluoroacetic acid (31 μL, 0.40 mmol) were added, the reaction was stirred at room temperature for 24 hours. Flash column chromatography (silica gel gradient elution: 10 to 15% EtOAc in Hexanes) afforded the title compound (118 mg, 0.30 mmol, 74% yield) as a white solid. mp 120 – 122 °C; IR ν_{max}/cm^{-1} (film): 1577, 1377, 1132, 1006, 894, 706, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, s), 8.61 (1H, s), 7.77 (2H, d, *J* = 8.4 Hz) 8.82 (1H, d, *J* = 3.8 Hz), 7.29 (2H, d, *J* = 8.1 Hz), 6.82 (1H, d, *J* = 3.7 Hz), 2.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.03, 147.36, 145.95, 134.79, 139.35, 129.78, 128.81, 126.91, 110.03, 87.13, 21.73; *m/z* HRMS (DART) found $[M+H]^+$ 398.9683, $C_{14}H_{12}IN_2O_2S^+$ requires 398.9664.

7-Chloro-6-iodothieno[3,2-*b*]pyridine



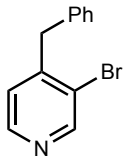
Prepared according to general procedure C (except that two equivalents of NIS and TFA were used) using 1 7-chlorothieno[3,2-*b*]pyridine (68 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 μL, 0.40 mmol), dibenzylamine (92 μL, 0.48 mmol, 1.0M in EtOAc), and collidine (53 μL, 0.40 mmol). After *N*-iodosuccinimide (180 mg, 0.80 mmol) and trifluoroacetic acid (61 μL, 0.80 mmol) were added, the reaction was stirred at room temperature for 22 hours. Flash column chromatography (silica gel: 7.5% EtOAc in Hexanes) afforded the title compound (89 mg, 0.29 mmol, 73% yield) as a white solid. mp 104 – 106 °C; IR ν_{max}/cm^{-1} (film): 3065, 1562, 1467, 1241, 1196, 1009, 882, 785, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (1H, s), 7.69 (1H, d, *J* = 5.5 Hz), 7.53 (1H, d, *J* = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.37, 155.29, 141.55, 134.14, 132.02, 125.83, 91.46; *m/z* HRMS (DART) found $[M+H]^+$ 295.8803, $C_7H_4ClINS^+$ requires 295.8798.

3-Bromo-2-phenethylpyridine



Prepared according to general procedure D using 2-phenethylpyridine (73 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). ^{1}H NMR of the crude material showed >20:1 selectivity for the desired product over the 5-bromo isomer. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes, second column: 100% CH_2Cl_2 in Hexanes) to provide the title compound as a yellow oil (69 mg, 0.26 mmol, 66% yield); IR ν_{max}/cm^{-1} (film): 2928, 1574, 1424, 1118, 1022, 791, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (1H, dd, *J* = 4.7, 1.2 Hz), 7.85 (1H, dd, *J* = 8.0, 1.3 Hz), 7.36 – 7.22 (5H, m), 7.05 (1H, dd, *J* = 8.0, 4.7 Hz), 3.33 – 3.22 (2H, m), 3.12 – 3.05 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.70, 147.95, 141.58, 140.34, 128.59, 128.53, 126.15, 122.72, 121.51, 39.74, 34.64; *m/z* HRMS (DART) found $[M+H]^+$ 262.0239, $C_{13}H_{13}BrN^+$ requires 262.0231.

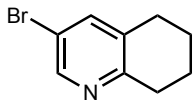
4-Benzyl-3-bromopyridine



Prepared according to general procedure D using 4-benzylpyridinepyridine (64 μL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel gradient elution: 15 to 20% Ether in Hexanes) to provide the title compound as a brown oil (52 mg, 0.21 mmol, 52%

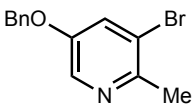
yield); IR ν_{max}/cm^{-1} (film): 1670, 1569, 1254, 1175, 1073, 934, 701, 638; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (1H, s), 8.38 (1H, d, *J* = 4.9 Hz), 7.33 (2H, t, *J* = 7.6 Hz), 7.27 (1H, t, *J* = 7.1 Hz), 7.19 (2H, d, *J* = 7.3 Hz), 7.00 1H, d, *J* = 4.9 Hz), 4.08 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.99, 149.39, 148.42, 137.42, 129.28, 128.90, 127.01, 125.70, 123.45, 41.19; *m/z* HRMS (DART) found $[M+H]^+$ 248.0083, $C_{12}H_{11}BrN^+$ requires 248.0075.

3-Bromo-5,6,7,8-tetrahydroquinoline



N-((1*E*,2*Z*)-2-((*E*)-3-(dibenzylamino)allylidene)cyclohexylidene)-1,1,1-trifluoromethane sulfonamide (185 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) were added to an 8 mL vial which was subsequently cooled to 0 °C. *N*-bromosuccinimide (75 mg, 0.42 mmol) and trifluoroacetic acid (32 μL, 0.42 mmol) were added, the cooling bath was removed, and the reaction was allowed to stir at room temperature for 2 hours. The crude material was purified by flash chromatography (silica gel: 10% Ether in Hexanes) to provide the title compound as a yellow oil (36 mg, 0.17 mmol, 42% yield); IR ν_{max}/cm^{-1} (film): 2928, 1557, 1436, 1394, 1157, 1017, 744, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (1H, d, *J* = 2.0 Hz), 7.49 (1H, d, *J* = 1.7 Hz), 2.85 (2H, t, *J* = 6.5 Hz), 2.75 (2H, t, *J* = 6.3 Hz), 1.92 – 1.84 (2H, m), 1.82 – 1.75 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.12, 147.74, 139.03, 134.31, 117.35, 32.13, 28.78, 22.95, 22.42; *m/z* HRMS (DART) found $[M+H]^+$ 212.0071, $C_9H_{11}BrN^+$ requires 212.0075.

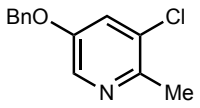
5-(Benzyloxy)-3-bromo-2-methylpyridine



Prepared according to a modified version of general procedure D using 5-(benzyloxy)-2-methylpyridine (80 μL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol),

dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), and collidine (53 mL, 0.40 mmol). After *N*-bromosuccinimide (71 mg, 0.40 mmol) and trifluoroacetic acid (31 µL, 0.40 mmol) were added, the reaction was stirred at room temperature for 1 hour. Then, ammonium acetate (308 mg, 4.00 mmol) was added and the reaction was heated to 50 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% Ether in Hexanes) to provide the title compound as a yellow oil (79 mg, 0.28 mmol, 69% yield); IR ν_{max}/cm^{-1} (film): 1670, 1569, 1289, 1254, 1174, 1012, 837, 701; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.21 (1H, d, J = 2.6 Hz), 7.44 (1H, d, J = 2.6 Hz), 7.42 – 7.32 (5H, m), 5.06 (2H, s), 2.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.37, 149.42, 136.00, 135.84, 128.84, 128.52, 127.64, 125.88, 120.86, 70.86, 23.94; *m/z* HRMS (DART) found $[M+H]^+$ 278.0171, $C_{13}H_{13}BrNO^+$ requires 278.0181.

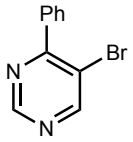
5-(Benzyloxy)-3-chloro-2-methylpyridine



Prepared according to modified version of general procedure F using 5-(benzyloxy)-2-methylpyridine (80 µL, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), and collidine (53 mL, 0.40 mmol). After *N*-chlorosuccinimide (53 mg, 0.40 mmol) and HCl (400 µL, 1.60 mmol, 4.0 M in dioxanes solution) were added, the reaction was stirred at room temperature for 1 hour. Then, ammonium acetate (308 mg, 4.00 mmol) was added and the reaction was heated to 50 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% Ether in Hexanes) to provide the title compound as a yellow oil (54 mg, 0.23 mmol, 58% yield); IR ν_{max}/cm^{-1} (film): 1670, 1149, 1288, 1264, 1174, 1012, 837, 701; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.18 (1H, d, J = 2.6 Hz), 7.45 – 7.33 (5H, m), 7.27 (1H, d, J = 2.6 Hz), 5.07 (2H, s), 2.55 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ:

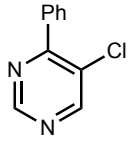
153.60, 148.16, 135.88, 135.51, 131.01, 128.86, 128.52, 127.64, 122.74, 70.87, 21.79; *m/z* HRMS (DART) found $[M+H]^+$ 234.0693, $C_{13}H_{13}ClNO^+$ requires 234.0686.

5-Bromo-4-phenylpyrimidine



Prepared according to a modified version of general procedure E using 4-phenylpyrimidine (63 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in CH_2Cl_2), and collidine (53 mL, 0.40 mmol). After *N*-bromosuccinimide (71 mg, 0.40 mmol) and trifluoroacetic acid (31 μL, 0.40 mmol) were added, the reaction was stirred at room temperature for 1 hour. Then, ammonium acetate (308 mg, 4.00 mmol) and EtOH (8 mL) were added and the reaction was heated to 60 °C for 2 hours. The crude material was purified by flash chromatography (silica gel: 15% Ether in Hexanes) to provide the title compound as a white solid (41 mg, 0.18 mmol, 44% yield). mp 90 – 92 ˚C; IR ν_{max}/cm^{-1} (film): 1559, 1437, 1395, 1172, 1017, 787, 743, 694; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.17 (1H, s), 8.93 (1H, s), 7.85 – 7.79 (2H, m), 7.54 – 7.43 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.42, 160.26, 157.02, 136.88, 130.45, 129.39, 128.41, 119.29; *m/z* HRMS (DART) found $[M+H]^+$ 234.9875, $C_{10}H_8BrN_2^+$ requires 234.9871.

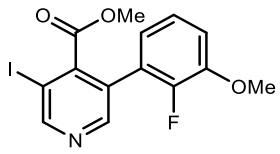
5-Chloro-4-phenylpyrimidine



Prepared according to a modified version of general procedure F using 4-phenylpyrimidine (63 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 μL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in EtOAc), and collidine (53 mL, 0.40 mmol). After *N*-chlorosuccinimide (53 mg,

0.40 mmol) and trifluoroacetic acid (61 µL, 0.80 mmol) were added, the reaction was stirred at 50 °C for 3 hours. Then, ammonium acetate (308 mg, 4.00 mmol) and EtOH (8 mL) were added and the reaction was heated to 60 °C for 2 hours. The crude material was purified by flash chromatography (silica gel: 15% Ether in Hexanes) to provide the title compound as a white solid (21 mg, 0.11 mmol, 28% yield). mp 84 – 86 ˚C; IR ν_{max}/cm^{-1} (film): 1558, 1514, 1437, 1395, 1157, 1017, 743, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.14 (1H, s), 8.78 (1H, s), 7.92 – 7.85 (2H, m), 7.55 – 7.49 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.71, 157.77, 156.57, 135.63, 130.63, 129.50, 129.33, 128.50; *m/z* HRMS (DART) found $[M+H]^+$ 191.0368, $C_{10}H_8ClN_2^+$ requires 191.0376.

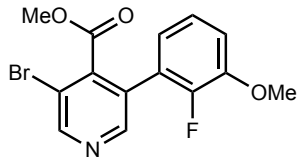
Methyl 3-(2-fluoro-3-methoxyphenyl)-5-iodoisonicotinate



Prepared according to general procedure C using methyl 3-(2-fluoro-3-methoxyphenyl)isonicotinate (105 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 30% Et_2O in hexanes) to provide the title compound as faint yellow amorphous solid (108 mg, 0.28 mmol, 70% yield); IR ν_{max}/cm^{-1} (film): 2950, 2840, 2360, 1735, 1618, 1581, 1527, 1477, 1401, 1325, 1220, 1195, 1176, 877; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.97 (1H, s), 8.57 (1H, d, *J* = 1.5 Hz), 7.11 (1H, td, *J* = 8.0, 1.4 Hz), 7.02 (1H, td, *J* = 8.1, 1.6 Hz), 6.82 (1H, ddd, *J* = 7.9, 6.1, 1.6 Hz), 3.91 (3H, s), 3.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.69, 156.90, 150.14 (d, *J* = 2.4 Hz), 149.50 (d, *J* = 248.4 Hz), 148.17, 148.06, 146.22, 130.09, 124.24 (d, *J* = 4.9 Hz), 122.05 (d, *J* = 1.4 Hz), 114.15 (d, *J* = 2.1

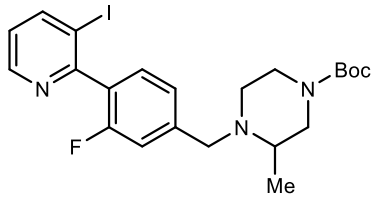
Hz), 91.22, 56.44, 52.93; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -137.98; *m/z* HRMS (DART) found $[M+H]^+$ 387.9873, $C_{14}H_{12}FINO_3^+$ requires 387.9846.

Methyl 3-bromo-5-(2-fluoro-3-methoxyphenyl)isonicotinate



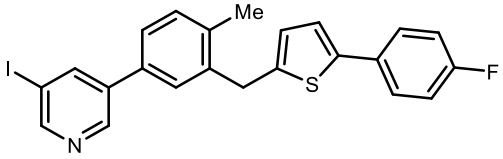
Prepared according to general procedure D using methyl 3-(2-fluoro-3-methoxyphenyl)isonicotinate (105 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 μL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The reaction was stirred at 60 °C for 3 hours before quenching. The crude material was purified by flash chromatography (silica gel gradient elution: 0 to 50% EtOAc in Hexanes) to provide the title compound as a clear oil (92 mg, 0.27 mmol, 68% yield); IR ν_{max}/cm^{-1} (film): 2917, 1699, 1430, 1275, 1113, 993, 892, 723, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.79 (1H, s), 8.59 (1H, s), 7.13 (1H, td, *J* = 8.0, 1.2 Hz), 7.03 (1H, td, *J* = 7.9, 1.4 Hz), 6.84 (1H, ddd, *J* = 7.8, 6.4, 1.5 Hz), 3.92 (3H, s), 3.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.65, 151.48, 149.67 (d, *J* = 2.3 Hz), 149.56 (d, *J* = 248.7 Hz), 148.16 (d, *J* = 10.5 Hz), 142.20, 130.13, 124.33, 124.28, 123.83 (d, *J* = 13.3 Hz), 122.06 (d, *J* = 1.3 Hz), 117.46, 114.21 (d, *J* = 2.2 Hz), 56.46, 52.95; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -138.09 (t, *J* = 7.0 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 339.9994, $C_{14}H_{12}BrFNO_3^+$ requires 339.9985.

Tert-butyl 4-(3-fluoro-4-(3-iodopyridin-2-yl)benzyl)-3-methylpiperazine-1-carboxylate



Prepared according to general procedure B using tert-butyl 4-(3-fluoro-4-(pyridin-2-yl)benzyl)-3-methylpiperazine-1-carboxylate (154 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (93 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a faint yellow oil (104 mg, 0.20 mmol, 51% yield); IR ν_{max}/cm^{-1} (film): 2976, 2360, 1679, 1626, 1565, 1426, 1391, 1365, 1080, 1052, 792, 768; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.65 (1H, dd, *J* = 4.7, 1.5 Hz), 8.24 (1H, dd, *J* = 8.0, 1.5 Hz), 7.31 (1H, t, *J* = 7.6 Hz), 7.19 (2H, t, *J* = 8.4 Hz), 7.03 (1H, dd, *J* = 8.0, 4.7 Hz), 4.03 (1H, d, *J* = 13.8 Hz), 3.65 (1H, dd, *J* = 13.2, 4.2 Hz), 3.25 (1H, d, *J* = 13.8 Hz), 3.11 (1H, s), 2.89 (1H, s), 2.68 (1H, d, *J* = 11.6 Hz), 2.47 (1H, ddd, *J* = 9.1, 6.2, 3.2 Hz), 2.12 (1H, s), 1.46 (9H, s), 1.12 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.89, 160.32 (d, *J* = 245.0 Hz), 152.68, 149.97, 149.94, 136.92, 131.14, 129.24, 125.37, 122.56, 122.46 (d, *J* = 8.4 Hz), 117.35 (d, *J* = 23.6 Hz), 107.57; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -114.18; *m/z* HRMS (DART) found $[M+H]^+$ 512.1207, $C_{22}H_{28}FIN_3O_2^+$ requires 512.1210.

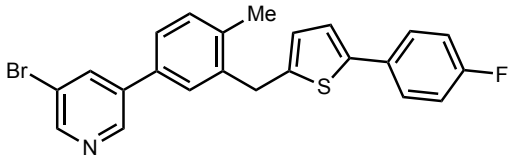
3-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-5-iodopyridine



Prepared according to general procedure B using 3-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyridine (144 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL,

0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a brown crystalline solid (153 mg, 0.32 mmol, 79% yield). mp 130 – 131 °C; IR ν_{max}/cm^{-1} (film): 3073, 3037, 2916, 1882, 1599, 1566, 1546, 1507, 1466, 1385, 1253, 1052, 952, 903, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83–8.63 (2H, m), 8.15 (1H, t, *J* = 2.0 Hz), 7.49 – 7.30 (4H, m), 7.28 – 7.19 (1H, m), 7.03 – 6.93 (3H, m), 6.67 (1H, d, *J* = 3.5 Hz), 4.15 (2H, s), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.24 (d, *J* = 246.8 Hz), 154.12, 146.71, 142.84, 142.39, 141.91, 139.33, 138.52, 137.34, 134.40, 131.51, 130.85, 130.81, 128.27, 127.26 (d, *J* = 7.9 Hz), 125.98 (d, *J* = 49.0 Hz), 122.83, 115.84 (d, *J* = 21.8 Hz), 93.85, 34.30, 19.4; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -114.93; *m/z* HRMS (DART) found $[M+H]^+$ 486.0199, $C_{23}H_{18}FINS^+$ requires 486.0189.

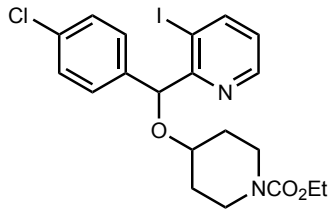
3-Bromo-5-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyridine



Prepared according to general procedure E using 3-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyridine (144 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes) to provide the title compound as a white solid (120 mg, 0.27 mmol, 68% yield). mp 115 – 117 °C; IR ν_{max}/cm^{-1} (film): 1508, 1422, 1228, 1098, 877, 802, 697, 653; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (1H, d, *J* = 1.8 Hz), 8.63 (1H, d, *J* = 2.1 Hz), 8.00 (1H, app t, *J* = 2.1 Hz), 7.50 – 7.45 (2H, m), 7.43 (1H, d, *J* = 1.6 Hz), 7.39 (1H, dd, *J* = 7.8, 1.9 Hz), 7.30 (1H, d, *J* = 7.8 Hz), 7.06 – 6.98 (3H, m), 6.72 (1H,

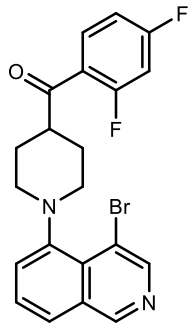
d, J = 3.6 Hz), 4.20 (2H, s), 2.39 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.21 (d, J = 246.7 Hz), 149.20, 146.37, 142.78, 141.90, 139.34, 138.13, 137.37, 136.73, 134.33, 131.51, 130.79 (d, J = 1.7 Hz), 128.26, 127.23 (d, J = 7.9 Hz), 126.22, 125.74, 122.82 (d, J = 1.1 Hz), 121.01, 115.82 (d, J = 22.0 Hz), 34.28, 19.39; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -114.85 – -114.95 (m); *m/z* HRMS (DART) found $[M+H]^+$ 438.0342, $C_{23}H_{18}BrFNS^+$ requires 438.0327.

Ethyl 4-((4-chlorophenyl)(3-iodopyridin-2-yl)methoxy)piperidine-1-carboxylate



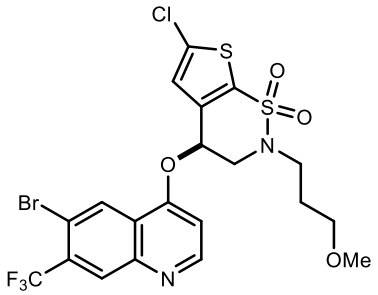
Prepared according to general procedure B using ethyl 4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (150 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 25% EtOAc in Hexanes) to provide the title compound as a brown oil (105 mg, 0.21 mmol, 53% yield); IR ν_{max}/cm^{-1} (film): 2928, 1687, 1433, 1228, 1085, 1006, 908, 794, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, J = 4.5 Hz), 8.10 (1H, d, J = 8.0 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.4 Hz), 6.91 (1H, dd, J = 8.0, 4.6 Hz), 6.06 (1H, s), 7.10 (2H, q, J = 7.1 Hz), 3.85 – 3.70 (2H, m), 3.60 – 3.53 (1H, m), 3.20 – 3.05 (2H, m), 1.90 – 1.60 (4H, m), 1.23 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.09, 155.56, 149.36, 147.60, 138.83, 133.55, 128.54, 128.54, 124.20, 95.31, 81.31, 73.33, 61.31, 41.27, 31.50, 31.04, 14.77; *m/z* HRMS (DART) found $[M+H]^+$ 501.0424, $C_{20}H_{23}ClIN_2O_3^+$ requires 501.0442.

3-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-5-iodopyridine



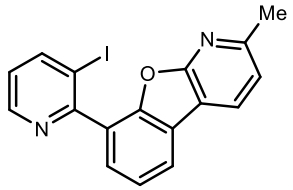
Prepared according to a procedure G usings (2,4-difluorophenyl)(1-(isoquinolin-5-yl)piperidin-4-yl)methanone (141 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 μL, 0.40 mmol), dibenzylamine (92 μL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 μL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), and trifluoroacetic acid (64 μL, 0.80 mmol). The crude material was purified by flash chromatography (silica gel: 5% acetone in hexanes) to provide the title compound as a faint brown oil (62 mg, 0.14 mmol, 36% yield); IR ν_{max}/cm^{-1} (film): 2951, 2803, 2360, 1738, 1680, 1607, 1572, 1557, 1494, 1422, 1298, 1171, 996, 787, 662; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.07 (1H, s), 8.68 (1H, s), 7.96 – 7.81 (1H, m), 7.69 (1H, dd, *J* = 8.1, 1.3 Hz), 7.61 – 7.44 (2H, m), 7.04 – 6.94 (1H, m), 6.89 (1H, ddd, *J* = 11.1, 8.6, 2.4 Hz), 3.40 (2H, d, *J* = 12.2 Hz), 3.31 – 3.20 (1H, m), 2.77 (2H, td, *J* = 12.0, 2.3 Hz), 2.39 – 2.16 (2H, m), 2.00 (2H, dt, *J* = 12.9, 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.88 (d, *J* = 4.9 Hz), 152.48, 149.88, 147.83, 133.23 (dd, *J* = 10.4, 4.6 Hz), 132.27, 129.82, 128.02, 124.02, 122.06, 115.37, 112.87 – 112.36 (m), 105.85 – 104.13 (m); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -102.23 (dq, *J* = 11.9, 7.7 Hz), -106.62 (q, *J* = 10.8 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 431.0550, $C_{21}H_{18}BrF_2N_2O^+$ requires 431.0571.

(S)-4-((6-Bromo-7-(trifluoromethyl)quinolin-4-yl)oxy)-6-chloro-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine 1,1-dioxide



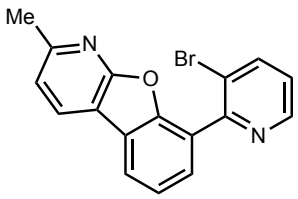
Prepared according to a modified version of general procedure G using (S)-6-chloro-2-(3-methoxypropyl)-4-((7-(trifluoromethyl)quinolin-4-yl)oxy)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine 1,1-dioxide (203 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 µL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel gradient elution: 3% MeOH in CHCl2 to 6% MeOH in CH_2Cl_2 followed silica gel gradient elution: 4% acetone in CH_2Cl_2 to 10% acetone in CH_2Cl_2) to provide the title compound as amorphous white solid (129 mg, 0.21 mmol, 53% yield); IR ν_{max}/cm^{-1} (film): 3022, 2360, 1591, 1565, 1484, 1339, 1238, 1198, 1090, 1068, 1047, 966 932, 907, 816; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.92 (1H, d, *J* = 5.1 Hz), 8.44 (1H, s), 8.38 (1H, s), 7.00 – 6.88 (2H, m), 5.57 (1H, d, *J* = 3.4 Hz), 4.43 (1H, dd, *J* = 16.0, 4.2 Hz), 4.14 (1H, dd, *J* = 16.1, 2.8 Hz), 3.67 (1H, dt, *J* = 13.9, 7.1 Hz), 3.44 – 3.29 (3H, m), 3.14 (3H, s), 1.81 (2H, ddd, *J* = 11.7, 5.8, 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.08, 152.85, 147.67, 137.55, 137.05, 134.87, 131.68 (q, *J* = 31.7 Hz), 130.15 (q, *J* = 5.7 Hz), 128.21, 125.71, 123.79, 122.29 (d, *J* = 203.1 Hz), 115.93, 102.93, 69.05, 66.61, 58.73, 49.73, 47.87, 29.30; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -62.88; *m/z* HRMS (DART) found $[M+H]^+$ 586.9505, $C_{20}H_{18}BrClF_3N_2O_4S_2^+$ requires 586.9512.

8-(3-Iodopyridin-2-yl)-2-methylbenzofuro[2,3-b]pyridine



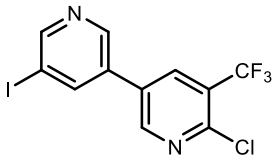
Prepared according to general procedure B using 2-methyl-8-(pyridin-2-yl)benzofuro[2,3-b]pyridine (104 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel gradient elution: 10% EtOAc in hexanes to 25% EtOAc in hexanes) to provide the title compound as an off-white solid (107 mg, 0.29 mmol, 72% yield). mp 198 – 200 °C; IR ν_{max}/cm^{-1} (film): 3053, 2920, 2360, 1942, 1628, 1596, 1578, 1562, 1493, 1360, 1307, 1221, 1145, 1033, 935, 903, 843; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, dd, *J* = 4.7, 1.5 Hz), 8.27 (1H, dd, *J* = 8.0, 1.5 Hz), 8.16 (1H, d, *J* = 7.7 Hz), 7.96 (1H, dd, *J* = 7.7, 1.4 Hz), 7.55 (1H, dd, *J* = 7.6, 1.3 Hz), 7.46 (1H, t, *J* = 7.6 Hz), 7.19 (1H, d, *J* = 7.8 Hz), 7.06 (1H, dd, *J* = 8.0, 4.7 Hz), 2.65 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.14, 158.27, 156.77, 151.26, 148.76, 147.08, 130.08, 128.27, 127.58, 124.08, 123.30, 123.18, 121.53, 119.00, 113.83, 96.55, 24.61; *m/z* HRMS (DART) found $[M+H]^+$ 387.0002, $C_{17}H_{12}IN_2O^+$ requires 386.9994.

8-(3-Bromopyridin-2-yl)-2-methylbenzofuro[2,3-*b*]pyridine



Prepared according to general procedure D using 2-methyl-8-(pyridin-2-yl)benzofuro[2,3-*b*]pyridine (104 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The reaction was stirred at 60 °C for 24 hours before quenching. ^{1}H NMR of the crude material showed >20:1 selectivity for the desired product over the 5-bromo isomer. The crude material was purified by flash chromatography (silica gel gradient elution: 20 to 30% EtOAc in Hexanes) to provide the title compound as an off-white solid (99 mg, 0.29 mmol, 73% yield). mp 175 – 178 ˚C; IR ν_{max}/cm^{-1} (film): 1572, 1416, 1177, 1013, 934, 761, 745, 643; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (1H, dd, *J* = 4.7, 1.4 Hz), 8.13 (1H, d, *J* = 7.7 Hz), 8.02 (1H, dd, *J* = 8.1, 1.4 Hz), 7.95 (1H, dd, *J* = 7.7, 1.1 Hz), 7.59 (1H, dd, *J* = 7.6, 1.1 Hz), 7.45 (1H, app t, *J* = 7.6 Hz), 7.22 (1H, dd, *J* = 8.1, 4.7 Hz), 7.17 (1H, d, *J* = 7.8 Hz), 2.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.10, 156.70, 154.71, 151.48, 148.13, 140.82, 130.02, 128.39, 125.09, 124.11, 123.25, 123.11, 121.87, 121.57, 118.94, 113.73, 24.57; *m/z* HRMS (DART) found $[M+H]^+$ 339.0121, $C_{17}H_{12}BrN_2O^+$ requires 339.0133.

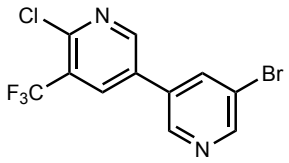
6-Chloro-5'-iodo-5-(trifluoromethyl)-3,3'-bipyridine



Prepared according to general procedure C using 6-chloro-5-(trifluoromethyl)-3,3'-bipyridine (103 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a white solid

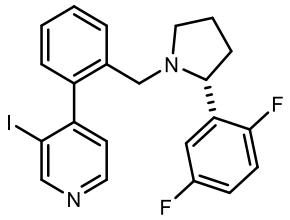
(109 mg, 0.28 mmol, 71% yield). mp 161 – 162 °C; IR ν_{max}/cm^{-1} (film): 3074, 3038, 1885, 1601, 1565, 1546, 1465, 1378, 1236, 1224, 1052, 869; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.93 (1H, d, *J* = 2.0 Hz), 8.78 – 8.73 (1H, m), 8.22 (1H t, *J* = 2.1 Hz), 8.15 (1H, d, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.44, 150.30, 149.28 (d, *J* = 1.6 Hz), 146.51, 142.67, 135.12 (q, *J* = 4.8 Hz), 132.90, 131.35, 127.91 – 124.83 (m), 122.03 (q, *J* = 273.3 Hz), 93.99; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -63.70; *m/z* HRMS (DART) found $[M+H]^+$ 384.9242, $C_{11}H_6ClF_3IN_2^+$ requires 384.9216.

5'-Bromo-6-chloro-5-(trifluoromethyl)-3,3'-bipyridine



Prepared according to general procedure E using 6-chloro-5-(trifluoromethyl)-3,3'-bipyridine (103 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 μL, 0.40 mmol), dibenzylamine (77 μL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), and trifluoroacetic acid (31 μL, 0.40 mmol). The reaction was stirred at room temperature for 4 hours before quenching. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in Hexanes) to provide the title compound as a white solid (92 mg, 0.27 mmol, 68% yield). mp 140 – 143 °C; IR ν_{max}/cm^{-1} (film): 3044, 1566, 1431, 1341, 1135, 1054, 893, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 – 8.72 (3H, m), 8.16 (1H, d, *J* = 2.0 Hz), 8.03 (1H, app t, *J* = 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.51, 150.31 (q, *J* = 0.9 Hz), 149.29 (q, *J* = 1.3 Hz), 146.14, 137.05, 135.14 (q, *J* = 4.8 Hz), 132.58, 131.30, 125.88 (q, *J* = 33.3 Hz), 121.97 (q, *J* = 269.1 Hz), 121.49; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -63.74; *m/z* HRMS (DART) found $[M+H]^+$ 338.9357, $C_{11}H_6BrClF_3N_2^+$ requires 338.9335.

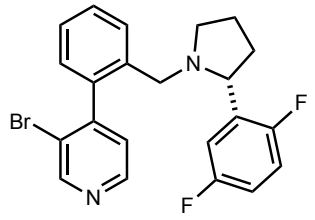
(R)-4-(2-((2-(2,5-Difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)-3-iodopyridine



Prepared according to general procedure B using (R)-4-(2-((2-(2,5-difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)pyridine (140 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a colorless oil as a 1:1 mixture of diastereomers (143 mg, 0.30 mmol, 75% yield); IR ν_{max}/cm^{-1} (film):, 2360, 1572, 1489, 1461, 1426, 1395, 1025, 840, 762; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, s), 8.97 (1H, s), 8.51 (1H, d, *J* = 4.8 Hz), 8.44 (1H, d, *J* = 4.9 Hz), 7.68 (1H, d, *J* = 7.8 Hz), 7.56 (1H, dd, *J* = 7.7, 1.4 Hz), 7.43 (2H, dtd, *J* = 9.2, 7.6, 1.4 Hz), 7.32 (3H, tdd, *J* = 7.5, 3.0, 1.3 Hz), 7.11 (1H, dd, *J* = 4.8, 0.7 Hz), 7.07 (1H, d, *J* = 4.8 Hz), 7.03 – 6.95 (3H, m), 6.93 – 6.77 (6H, m), 3.71 (1H, d, *J* = 13.1 Hz), 3.65 – 3.51 (4H, m), 3.11 (1H, ddd, *J* = 9.8, 7.4, 2.7 Hz), 2.99 (1H, ddd, *J* = 9.3, 7.4, 2.1 Hz), 2.95 – 2.82 (2H, m), 2.27 – 2.11 (4H, m), 2.02 (1H, td, *J* = 9.3, 7.8 Hz), 1.91 – 1.63 (3H, m), 1.56 (2H, dddd, *J* = 13.1, 10.2, 8.0, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.13 (ddd, *J* = 241.7, 7.2, 2.1 Hz), 157.20 (d, *J* = 6.0 Hz), 157.06 (ddd, *J* = 241.0, 6.5, 2.4 Hz), 154.30 (d, *J* = 15.6 Hz), 148.36, 141.55, 141.06, 132.79 (dd, *J* = 15.3, 6.9 Hz), 129.43, 129.03 (d, *J* = 4.1 Hz), 128.90 (d, *J* = 5.2 Hz), 127.22, 127.05, 125.82, 124.90, 116.33 (dd, *J* = 8.5, 5.9 Hz), 116.08 (dd, *J* = 8.6, 6.0 Hz), 114.97 – 114.01 (m, 2C), 100.49, 99.29, 61.66, 61.56, 56.40, 56.14, 54.02, 53.94, 33.63, 33.57, 23.02, 22.95; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -118.00 (ddtd, *J* = 138.2,

17.3, 8.4, 4.7 Hz), -126.20 (dddt, J = 79.9, 18.6, 9.6, 4.9 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 477.0654, $C_{22}H_{20}F_2IN_2^+$ requires 477.0639.

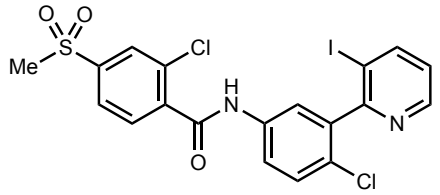
(*R*)-3-Bromo-4-(2-((2-(2,5-difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)pyridine



Prepared according to general procedure D using (*R*)-4-(2-((2-(2,5-difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)pyridine (140 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The reaction was stirred at 60 °C for 24 hours before quenching. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes, second plug: 0 to 5% MeOH in CH_2Cl_2) to provide the title compound as a yellow oil as a 1:1 mixture of diastereomers (104 mg, 0.24 mmol, 60% yield); IR ν_{max}/cm^{-1} (film): 2907, 1699, 1431, 1343, 1214, 1135, 892, 732; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H,s), 8.75 (1H, s), 8.51 (1H, d, J = 4.8 Hz), 8.46 (1H, d, J = 4.8 Hz), 7.66 (1H, d, J = 7.7 Hz), 7.57 (1H, d, J = 7.7 Hz), 7.42 (2H, qd, J = 7.5, 1.1 Hz), 7.31 (2H, app t, J = 7.5 Hz), 7.11 (1H d, J = 4.8 Hz), 7.08 (1H, d, J = 4.8 Hz), 7.04 (2H, app t, J = 7.6 Hz), 7.01 – 6.78 (6H, m), 3.75 (1H, d, J = 13.1 Hz), 3.65 – 3.55 (3H, m), 3.07 (1H, ddd, J = 9.5, 7.1, 2.4 Hz), 2.99 – 2.93 (2H, m), 2.89 (1H, d, J = 13.3 Hz), 2.25 – 2.08 (3H, m), 2.01 (1H, q, J = 8.2 Hz), 1.87 – 1.63 (4H, m), 1.62 – 1.50 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.05 (qt, J = 241.4, 2.3 Hz), 156.94 (qdd, J = 241.1, 4.7, 2.3 Hz), 151.97 (q, J = 6.6 Hz), 150.03 (d, J = 18.9 Hz), 147.88 (d, J = 4.6 Hz), 138.07 (d, J = 32.5 Hz), 136.87 (d, J = 10.0 Hz), 132.76 (ddd, J = 15.1, 6.9, 5.7 Hz), 129.88,

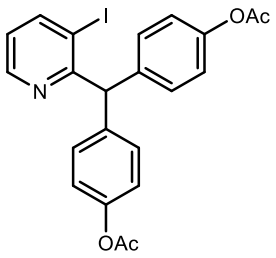
129.38, 128.94 (d, J = 8.7 Hz), 128.84 (d, J = 4.1 Hz), 126.95 (d, J = 11.9 Hz), 126.16, 125.33, 123.07, 121.80, 116.09 (ddd, J = 25.2, 8.6, 2.3 Hz), 114.44 (dd, J = 24.5, 8.7 Hz), 114.32 (ddd, J = 24.5, 5.2, 2.1 Hz), 61.65, 61.45, 56.23, 55.92, 53.76, 53.62, 33.95, 33.53, 22.90, 22.85; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -118.00 – -118.35 (m), -126.10 – -126.43 (m); *m/z* HRMS (DART) found $[M+H]^+$ 429.0784, $C_{22}H_{20}BrF_2N_2^+$ requires 429.0778.

2-Chloro-*N*-(4-chloro-3-(3-iodopyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide



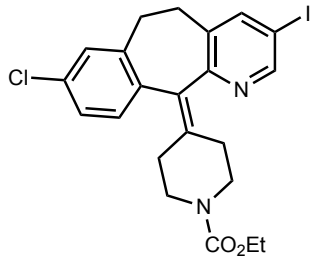
Prepared according to general procedure B using 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (126 mg, 0.30 mmol), EtOAc (6 mL, 0.05 M), Tf_2O (50 µL, 0.30 mmol), dibenzylamine (69 µL, 0.36 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (67 mg, 0.30 mmol), and trimethoxybenzene (51 mg, 0.30 mmol) ammonium acetate (231 mg, 3.00 mmol), and EtOH (6 mL). The crude material was purified by flash chromatography (silica gel: 5% Acetone in CH_2Cl_2) to provide the title compound as a white solid (71 mg, 0.13 mmol, 43% yield). mp 210 – 213 °C; IR ν_{max}/cm^{-1} (film): 2923, 1669, 1444, 1311, 1154, 1017, 804, 678; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 10.95 (1H, s), 8.66 (1H, d, J = 4.5 Hz), 8.41 (1H, d, J = 7.9 Hz), 8.13 (1H, s), 8.01 (1H, d, J = 8.1 Hz), 7.94 (1H, d, J = 8.0 Hz), 7.78 – 7.70 (2H, m), 7.58 (1H, d, J = 8.4 Hz), 7.24 (1H, dd, J = 7.9, 4.7 Hz), 3.35 (3H, s); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 163.86, 159.51, 148.52, 146.55, 143.13, 141.63, 140.80, 137.45, 130.95, 129.97, 129.73, 128.09, 126.35, 125.91, 124.73, 121.04, 120.94, 96.80, 43.08; *m/z* HRMS (DART) found $[M+H]^+$ 546.9145, $C_{19}H_{14}Cl_2IN_2O_3S^+$ requires 546.9147

((3-Iodopyridin-2-yl)methylene)bis(4,1-phenylene) diacetate



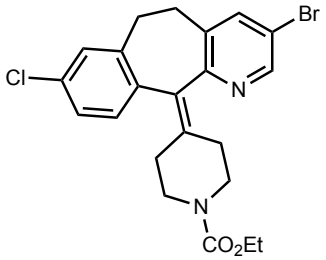
Prepared according to general procedure B (except after addition of NH_4OAc, the reaction was stirred for 1 hour at room temperature and washed 3x with H_2O (10 mL), the organic layer was then diluted with EtOH and heated to 60 °C for 1 hour) using pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate (145 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and ethanol (8 mL). The crude material was purified by flash chromatography (silica gel: 30 to 45% Et_2O in hexanes) followed by a second flash chromatography (silica gel: 2% Et_2O in CH_2Cl_2) to provide the title compound as a faint yellow solid (109 mg, 0.22 mmol, 56% yield). mp 63 – 65 °C; IR ν_{max}/cm^{-1} (film): 3035, 2923, 2852, 2032, 1747, 1672, 1594, 1563, 1547, 1501, 1458, 1406, 1345, 1313, 1100, 1068, 1058, 942, 874, 773, 747, 719, 687; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, dd, *J* = 4.6, 1.5 Hz), 8.11 (1H, dd, *J* = 8.0, 1.6 Hz), 7.26 (4H, d, *J* = 8.4 Hz), 7.06 – 6.97 (4H, m), 6.85 (1H, dd, *J* = 8.0, 4.6 Hz), 6.09 (1H, s), 2.28 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.59, 162.81, 149.47, 149.09, 147.42, 139.51, 130.57, 123.10, 121.42, 98.10, 58.74, 21.31; *m/z* HRMS (DART) found $[M+H]^+$ 488.0369, $C_{22}H_{19}INO_4^+$ requires 488.0359.

Ethyl 4-(8-chloro-3-iodo-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate



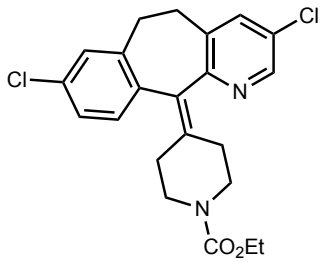
Ethyl 4-((6*Z*,7*Z*)-2-chloro-7-((*E*)-3-(dibenzylamino)allylidene)-6-(((trifluoromethyl) sulfonyl)imino)-6,7,8,9-tetra hydro-5*H*-benzo[7]annulen-5-ylidene)piperidine-1-carboxylate (213 mg, 0.30 mmol) and CH_2Cl_2 (3 mL, 0.1 M) were added to an 8 mL vial and subsequently cooled to 0 °C. *N*-iodosuccinimide (74 mg, 0.33 mmol) and trifluoroacetic acid (25 µL, 0.33 mmol) were added, the cooling bath was removed, and the reaction was allowed to stir at room temperature for 2 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in Hexanes, second column: 15% Ether in Hexanes) to provide the title compound as a white solid (96 mg, 0.19 mmol, 63% yield). mp 165 – 167 ˚C; IR ν_{max}/cm^{-1} (film): 2906, 1702, 1431, 1215, 993, 890, 820, 664; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, *J* = 1.2 Hz), 7.77 (1H, d, *J* = 1.0 Hz), 7.18 – 7.12 (2H, m), 7.08 (1H, d, *J* = 8.0 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.90 – 3.70 (2H, m), 3.41 – 3.23 (2H, m), 3.19 – 3.10 (2H, m), 2.85 – 2.73 (2H, m), 2.47 (1H, ddd, *J* = 14.0, 9.4, 4.6 Hz), 2.39 – 2.25 (3H, m), 1.25 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.83, 155.57, 152.60, 145.66, 139.38, 138.48, 137.47, 135.75, 133.28, 130.60, 129.05, 126.50, 91.47, 61.49, 44.87, 44.85, 31.51, 31.40, 30.92, 30.69, 14.81; *m/z* HRMS (DART) found $[M+H]^+$ 509.0491, $C_{22}H_{23}ClIN_2O_2^+$ requires 509.0493.

Ethyl 4-(3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate



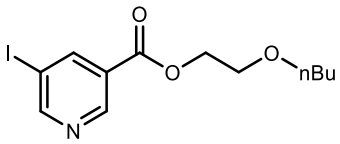
Ethyl 4-((6*Z*,7*Z*)-2-chloro-7-((*E*)-3-(dibenzylamino)allylidene)-6-(((trifluoromethyl) sulfonyl)imino)-6,7,8,9-tetra hydro-5*H*-benzo[7]annulen-5-ylidene)piperidine-1-carboxylate (213 mg, 0.30 mmol) and CH_2Cl_2 (3 mL, 0.1 M) were added to an 8 mL vial and subsequently cooled to 0 °C. *N*-bromosuccinimide (59 mg, 0.33 mmol) and trifluoroacetic acid (25 µL, 0.33 mmol) were added, the cooling bath was removed, and the reaction was allowed to stir at room temperature for 2 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in Hexanes, second column: 30% Ether in Hexanes with 1% Et_3N) to provide the title compound as a white solid (85 mg, 0.18 mmol, 61% yield). mp 140 – 144 ˚C; IR ν_{max}/cm^{-1} (film): 2906, 1701, 1432, 1215, 1109, 993, 891, 732; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.44 (1H, d, *J* = 2.0 Hz), 7.58 (1H, d, *J* = 2.0 Hz), 7.18 – 7.12 (2H, m), 7.08 (1H, d, *J* = 8.1 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.85 – 3.70 (2H, m), 3.42 – 3.24 (2H, m), 3.20 – 3.10 (2H, m), 2.88 – 2.73 (2H, m), 2.47 (1H, ddd, *J* = 13.9, 9.3, 4.5 Hz), 2.39 – 2.23 (3H, m), 1.24 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.54, 155.48, 147.65, 140.01, 139.35, 138.49, 137.48, 135.32, 133.25, 133.23, 130.57, 129.04, 126.48, 118.93, 61.46, 44.86, 44.83, 31.58, 31.39, 30.90, 30.67, 14.79; *m/z* HRMS (DART) found $[M+H]^+$ 463.0611, $C_{22}H_{23}BrClN_2O_2^+$ requires 463.0611.

Ethyl 4-(3,8-dichloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate



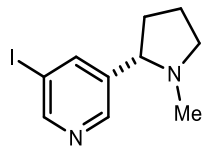
Ethyl 4-((6*Z*,7*Z*)-2-chloro-7-((*E*)-3-(dibenzylamino)allylidene)-6-(((trifluoromethyl) sulfonyl)imino)-6,7,8,9-tetra hydro-5*H*-benzo[7]annulen-5-ylidene)piperidine-1-carboxylate (213 mg, 0.30 mmol) and CH_2Cl_2 (3 mL, 0.1 M) were added to an 8 mL vial and subsequently cooled to 0 °C. *N*-chlorosuccinimide (44 mg, 0.33 mmol) and trifluoroacetic acid (25 μL, 0.33 mmol) were added, the cooling bath was removed, and the reaction was stirred at room temperature for 24 hours before quenching. The crude material was purified by flash chromatography (silica gel gradient elution: 0 to 50% EtOAc in Hexanes) to provide the title compound as a slightly yellow solid (54 mg, 0.13 mmol, 43% yield). mp 134 – 136 °C; IR ν_{max}/cm^{-1} (film): 2907, 1700, 1430, 1215, 1100, 993, 893, 732; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.35 (1H, d, *J* = 2.2 Hz), 7.43 (1H, d, *J* = 2.2 Hz), 7.18 – 7.12 (2H, m), 7.11 (1H, d, *J* = 8.1 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.88 – 3.70 (2H, m), 3.43 – 3.25 (2H, m), 3.20 – 3.10 (2H, m), 2.90 – 2.73 (2H, m), 2.47 (1H, ddd, *J* = 13.9, 9.3, 4.5 Hz), 2.40 – 2.23 (3H, m), 1.25 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.56, 155.12, 145.48, 139.37, 138.53, 137.57, 137.24, 134.84, 134.84, 133.26, 133.22, 130.58, 130.32, 129.05, 126.49, 61.48, 44.88, 44.83, 31.61, 31.40, 30.91, 30.67, 14.80; *m/z* HRMS (DART) found $[M+H]^+$ 417.1141, $C_{22}H_{23}Cl_2N_2O_2^+$ requires 417.1137.

2-Butoxyethyl 5-iodonicotinate



Prepared according to general procedure C (except after addition of *N*-iodosuccinimide and TFA, the reaction was heated to 50 °C) using 2-butoxyethyl nicotinate (89 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (32 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 20% Et_2O in hexanes) to provide the title compound as a colorless oil (82 mg, 0.24 mmol, 59% yield); IR ν_{max}/cm^{-1} (film): 3973, 3037, 2956, 2866, 2360, 1882, 1724, 1599, 1565, 1546, 1507, 1466, 1385, 1310, 1035, 952, 932, 783, 665; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.16 (1H, d, J = 1.9 Hz), 8.99 (1H, d, J = 2.2 Hz), 8.62 (1H, t, J = 2.0 Hz), 4.53 – 4.46 (2H, m), 3.79 – 3.72 (2H, m), 3.51 (2H, t, J = 6.6 Hz), 1.58 (2H, dq, J = 8.5, 6.7 Hz), 1.45 – 1.31 (2H, m), 0.92 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.13, 159.54, 149.43, 145.34, 127.74, 92.87, 71.38, 68.46, 65.08, 31.77, 19.39, 14.02; *m/z* HRMS (DART) found $[M+H]^+$ 350.0270, $C_{12}H_{17}INO_3^+$ requires 350.0253.

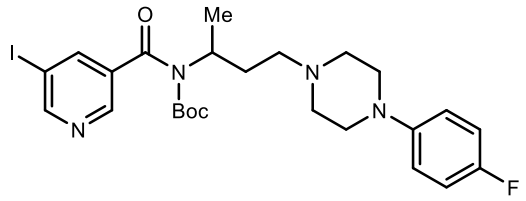
(S)-3-Iodo-5-(1-methylpyrrolidin-2-yl)pyridine



Prepared according to general procedure C (except using CH_2Cl_2 as the solvent and 3 eq TFA instead of 1 eq) using (s)-3-(1-methylpyrrolidin-2-yl)pyridine (64 mL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (96 µL, 1.20 mmol). The crude material was purified by flash chromatography (silica gel: 3% MeOH in CH_2Cl_2) followed by a second flash chromatography (2% Et_3N and 40% EtOAc in hexanes) to provide the title compound as a colorless oil (58 mg, 0.20 mmol, 51% yield); IR ν_{max}/cm^{-1} (film): 2924, 2257, 1720, 1667, 1594, 1566, 1547, 1502, 1455, 1428, 1313, 1266, 1177, 1105, 1072, 961,

918, 874, 774, 666; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (1H, d, *J* = 2.1 Hz), 8.39 (1H, d, *J* = 1.9 Hz), 7.99 (1H, t, *J* = 2.0 Hz), 3.17 (1H, ddd, *J* = 9.6, 7.8, 2.2 Hz), 2.99 (1H, t, *J* = 8.3 Hz), 2.26 (1H, q, *J* = 9.1 Hz), 2.12 (3H, s), 1.99 – 1.56 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.76, 148.12, 143.19, 141.44, 93.98, 68.35, 57.08, 40.57, 35.47, 22.85; *m/z* HRMS (DART) found $[M+H]^+$ 289.0215, $C_{10}H_{14}IN_2^+$ requires 289.0202.

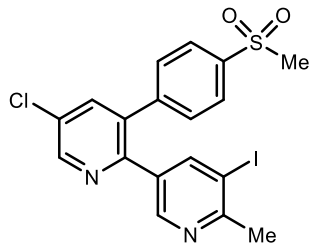
Tert-butyl (4-(4-(4-fluorophenyl)piperazin-1-yl)butan-2-yl)(5-iodonicotinoyl)carbamate



Prepared according to general procedure C (except using 2 eq TFA instead of 1 eq) using tert-butyl (4-(4-(4-fluorophenyl)piperazin-1-yl)butan-2-yl)(nicotinoyl)carbamate (184 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (64 µL, 0.80 mmol). The crude material was purified by flash chromatography (silica gel: 70% Et_2O in hexanes) to provide the title compound as a white solid (79 mg, 0.14 mmol, 34% yield). mp 63 – 65 °C; IR ν_{max}/cm^{-1} (film): 3037, 2924, 2360, 2257, 2031, 1720, 1667, 1594, 1566, 1547, 1502, 1455, 1369, 1266, 1117, 1057, 1036, 918, 903, 893, 773, 666; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, d, *J* = 2.1 Hz), 8.67 (1H, d, *J* = 2.0 Hz), 8.14 (1H, t, *J* = 2.1 Hz), 7.15 – 6.78 (4H, m), 4.65 (1H, dt, *J* = 8.3, 6.5 Hz), 3.10 (4H, t, *J* = 5.0 Hz), 2.60 (4H, q, *J* = 3.8 Hz), 2.56 – 2.35 (2H, m), 2.24 (1H, ddd, *J* = 17.1, 8.7, 4.4 Hz), 1.92 (1H, dt, *J* = 13.9, 7.5 Hz), 1.43 (3H, d, *J* = 6.8 Hz), 1.22 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.79, 157.86, 157.52, 157.31 (d, *J* = 238.7 Hz), 152.93, 148.07, 146.67, 142.97, 135.75, 117.95 (d, *J* = 7.6 Hz), 115.62 (d, *J* = 22.0 Hz), 92.62, 84.12, 55.86, 53.41, 52.00, 50.20, 31.57, 29.85, 27.74, 19.04; ^{19}F NMR

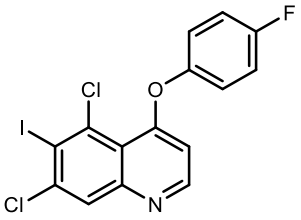
(365 MHz, $CDCl_3$) δ: -124.66; *m/z* HRMS (DART) found $[M+H]^+$ 583.1583, $C_{25}H_{33}FIN_4O_3^+$ requires 583.1581.

5-Chloro-5'-iodo-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine



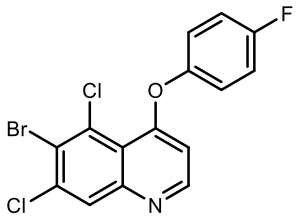
Prepared according to general procedure B (except no trimethoxybenzene was added prior to addition of NH_4OAc and the reaction was heated for 18 hours at 60 °C after the addition) using 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (143 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 μL, 0.40 mmol), dibenzylamine (92 μL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 μL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and ethanol (8 mL). The crude material was purified by flash chromatography (silica gel: 3% acetone in CH_2Cl_2) to provide the title compound as an amorphous colorless solid (83 mg, 0.17 mmol, 43% yield); IR ν_{max}/cm^{-1} (film): 2924, 1581, 1423, 1312, 1150, 956, 905, 767, 727, 647; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, d, *J* = 2.3 Hz), 8.23 (1H, d, *J* = 1.6 Hz), 8.14 (1H, d, *J* = 1.8 Hz), 7.95 (2H, d, *J* = 8.3 Hz), 7.75 (1H, d, *J* = 2.3 Hz), 7.42 (2H, d, *J* = 8.3 Hz), 3.10 (3H, s), 2.71 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.26, 150.43, 148.89, 148.74, 147.43, 143.50, 140.69, 138.15, 135.59, 132.99, 131.76, 130.49, 128.26, 95.94, 44.76, 28.83; *m/z* HRMS (DART) found $[M+H]^+$ 484.9538, $C_{18}H_{15}ClIN_2O_2S^+$ requires 484.9587

5,7-Dichloro-4-(4-fluorophenoxy)-6-iodoquinoline



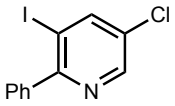
Prepared according to a modified version of general procedure G (except using using trimethoxybenzene to quench the *N*-iodosuccinimide, 3 eq trifluoroacetic acid, and heating to 80 °C overnight for the rearomatization step) using 5,7-dichloro-4-(4-fluorophenoxy)quinoline (123 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), and trifluoroacetic acid (96 µL, 1.20 mmol). The crude material was purified by flash chromatography (silica gel: 10% Et_2O in hexanes) to provide the title compound as white crystalline solid (85 mg, 0.20 mmol, 49% yield). mp 140 – 143 °C; IR ν_{max}/cm^{-1} (film): 3065, 2923, 2029, 1593, 1543, 1496, 1453, 1365, 1230, 1150, 1084, 1036, 780, 692, 657; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.67 (1H, d, J = 5.1 Hz), 8.18 (1H, s), 7.22 – 7.06 (4H, m), 6.66 (1H, d, J = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.30 (d, J = 244.8 Hz), 152.82, 150.87, 150.00, 149.97, 140.52, 129.82, 127.99, 122.56, 122.44 (d, J = 8.5 Hz), 117.34 (d, J = 23.6 Hz), 107.75, 107.43; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -116.60; *m/z* HRMS (DART) found $[M+H]^+$ 433.9029, $C_{15}H_8Cl_2FINO^+$ requires 433.9012.

5,7-Dichloro-4-(4-fluorophenoxy)-6-bromoquinoline



Prepared according to a modified version of general procedure G (except using trimethoxybenzene to quench the *N*-bromosuccinimide, and 3 eq trifluoroacetic acid instead of 2 eq, and heating to 80 °C overnight for the rearomatization step) using 5,7-dichloro-4-(4-fluorophenoxy)quinoline (123 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), and trifluoroacetic acid (96 µL, 1.20 mmol). The crude material was purified by flash chromatography (silica gel: 10% Et_2O in hexanes) to provide the title compound as white crystalline solid (84 mg, 0.22 mmol, 54% yield). mp 128 – 131 °C; IR ν_{max}/cm^{-1} (film): 3039, 2922, 2360, 2031, 1746, 1594, 1547, 1497, 1458, 1370, 1276, 1227, 1036, 952, 904, 893, 782, 666; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.67 (1H, s), 8.18 (1H, s), 7.23 – 7.07 (4H, m), 6.66 (1H, d, J = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.89, 160.32 (d, J = 245.0 Hz), 152.68, 149.97, 149.94, 136.92, 131.14, 129.24, 125.37, 122.56, 122.46 (d, J = 8.4 Hz), 117.35 (d, J = 23.6 Hz), 107.57; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -116.56; *m/z* HRMS (DART) found $[M+H]^+$ 387.9124, $C_{15}H_8BrCl_2FNO^+$ requires 387.9130.

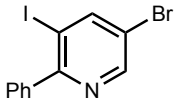
5-Chloro-3-iodo-2-phenylpyridine



An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-5-(dibenzylamino)-2-iodo-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (244 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-chlorosuccinimide (59 mg, 0.44 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was purified by flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes) to provide the title compound as a clear oil (101

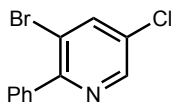
mg, 0.32 mmol, 80% yield); IR ν_{max}/cm^{-1} (film): 1508, 1422, 1228, 1161, 1013, 906, 827, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, *J* = 2.2 Hz), 8.26 (1H, d, *J* = 2.2 Hz), 7.60 – 7.56 (2H, m) 7.44 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.83, 147.53, 146.60, 140.84, 130.30, 129.28, 129.06, 128.14, 93.59; *m/z* HRMS (DART) found $[M+H]^+$ 315.9403, $C_{11}H_8ClIN^+$ requires 315.9390.

5-Bromo-3-iodo-2-phenylpyridine



An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-5-(dibenzylamino)-2-iodo-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (244 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-bromosuccinimide (71 mg, 0.44 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was purified by flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes) to provide the title compound as a white solid (123 mg, 0.34 mmol, 85% yield). mp 76 – 79 ˚C; IR ν_{max}/cm^{-1} (film): 1692, 1418, 1104, 1000, 891, 775, 692, 637; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, d, *J* = 1.9 Hz), 8.41 (1H, d, *J* = 2.0 Hz), 7.61 – 7.55 (2H, m) 7.44 – 7.41 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.09, 149.65, 149.13, 140.80, 129.21, 129.05, 128.12, 118.80, 94.18; *m/z* HRMS (DART) found $[M+H]^+$ 359.8897, $C_{11}H_8BrIN^+$ requires 359.8885.

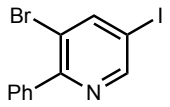
3-Bromo-5-chloro-2-phenylpyridine



An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-2-bromo-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (225 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1

M) was cooled to 0 °C. *N*-chlorosuccinimide (59 mg, 0.44 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was first subjected to flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes). The resulting mixture was then dissolved in Et_2O and 1.0 mmol of TfOH was added to precipitate out the TfOH salt at -78 °C. After filtration, the solid was dissolved in CH_2Cl_2 and washed 3 times with a saturated aqueous Na_2CO_3 solution. Drying with $MgSO_4$ and concentrating in vacuo provided the title compound as a white solid (76 mg, 0.28 mmol, 71% yield). mp 60 – 62 °C; IR ν_{max}/cm^{-1} (film): 3026, 1424, 1199, 1112, 1009, 889, 814, 693; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.60 (1H, d, *J* = 2.0 Hz), 8.02 (1H, d, *J* = 2.0 Hz), 7.69 – 7.64 (2H, m) 7.50 – 7.42 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.36, 146.91, 140.74, 138.37, 130.60, 129.36, 129.22, 128.19, 119.58; *m/z* HRMS (DART) found $[M+H]^+$ 269.9534, $C_{11}H_8BrClN^+$ requires 269.9508.

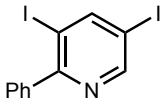
3-Bromo-5-iodo-2-phenylpyridine



An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-2-bromo-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (225 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-iodosuccinimide (90 mg, 0.40 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was first subjected to flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes). The resulting mixture was then dissolved in Et_2O and 1.0 mmol of TfOH was added to precipitate out the TfOH salt at -78 °C. After filtration, the solid was dissolved in CH_2Cl_2 and washed 3 times with a saturated aqueous Na_2CO_3 solution. Drying with $MgSO_4$ and concentrating in vacuo provided the title compound as a white solid (109

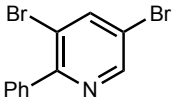
mg, 0.30 mmol, 76% yield). mp 93 – 95 ˚C; IR ν_{max}/cm^{-1} (film): 3023, 1422, 1103, 1002, 891, 789, 734, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, *J* = 1.7 Hz), 8.33 (1H, d, *J* = 1.8 Hz), 7.70 – 7.64 (2H, m) 7.50 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.79, 153.66, 149.04, 138.00, 129.39, 129.28, 128.24, 120.52, 91.16; *m/z* HRMS (DART) found $[M+H]^+$ 359.8880, $C_{11}H_8BrIN^+$ requires 359.8885.

3,5-Diiodo-2-phenylpyridine



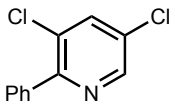
An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-5-(dibenzylamino)-2-iodo-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (244 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-iodosuccinimide (99 mg, 0.44 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was first subjected to flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes). The resulting mixture was then dissolved in Et_2O and 1.0 mmol of TfOH was added to precipitate out the TfOH salt at -78 °C. After filtration, the solid was dissolved in CH_2Cl_2 and washed 3 times with a saturated aqueous Na_2CO_3 solution. Drying with $MgSO_4$ and concentrating in vacuo provided the title compound as a white solid (138 mg, 0.34 mmol, 85% yield). mp 100 – 103 ˚C; IR ν_{max}/cm^{-1} (film): 3060, 1420, 1354, 1102, 998, 892, 781, 735, 633; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, *J* = 1.7 Hz), 8.58 (1H, d, *J* = 1.7 Hz), 7.60 – 7.55 (2H, m) 7.50 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.44, 154.62, 154.45, 140.90, 129.20, 129.11, 128.19, 95.02, 91.48; *m/z* HRMS (DART) found $[M+H]^+$ 407.8746, $C_{11}H_8I_2N^+$ requires 407.8746.

3,5-Dibromo-2-phenylpyridine



An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-2-bromo-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (225 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-bromosuccinimide (71 mg, 0.40 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was first subjected to flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes). The resulting mixture was then dissolved in Et_2O and 1.0 mmol of TfOH was added to precipitate out the TfOH salt at -78 °C. After filtration, the solid was dissolved in CH_2Cl_2 and washed 3 times with a saturated aqueous Na_2CO_3 solution. Drying with $MgSO_4$ and concentrating in vacuo provided the title compound as a white solid (79 mg, 0.25 mmol, 63% yield). mp 87 – 89 °C; IR ν_{max}/cm^{-1} (film): 3060, 1421, 1362, 1097, 1030, 913, 798, 775, 691; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, d, J = 2.0 Hz), 8.16 (1H, d, J = 2.0 Hz), 7.69 – 7.65 (2H, m) 7.50 – 7.42 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.76, 149.18, 143.20, 138.57, 129.31, 129.18, 128.19, 119.92, 118.87; *m/z* HRMS (DART) found $[M+H]^+$ 313.9010, $C_{11}H_8Br_2N^+$ requires 313.9003.

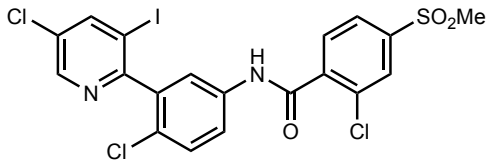
3,5-Dichloro-2-phenylpyridine



An 8 mL vial charged with *N*-((1*E*,2*E*,4*E*)-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (194 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-chlorosuccinimide (110 mg, 0.82 mmol) and HCl (400 µL, 1.60 mmol, 4 M in dioxane) were added and the reaction was warmed to room temperature and allowed to stir for 14 hours. The crude material was subjected to flash chromatography (Combiflash Autocolumn, silica

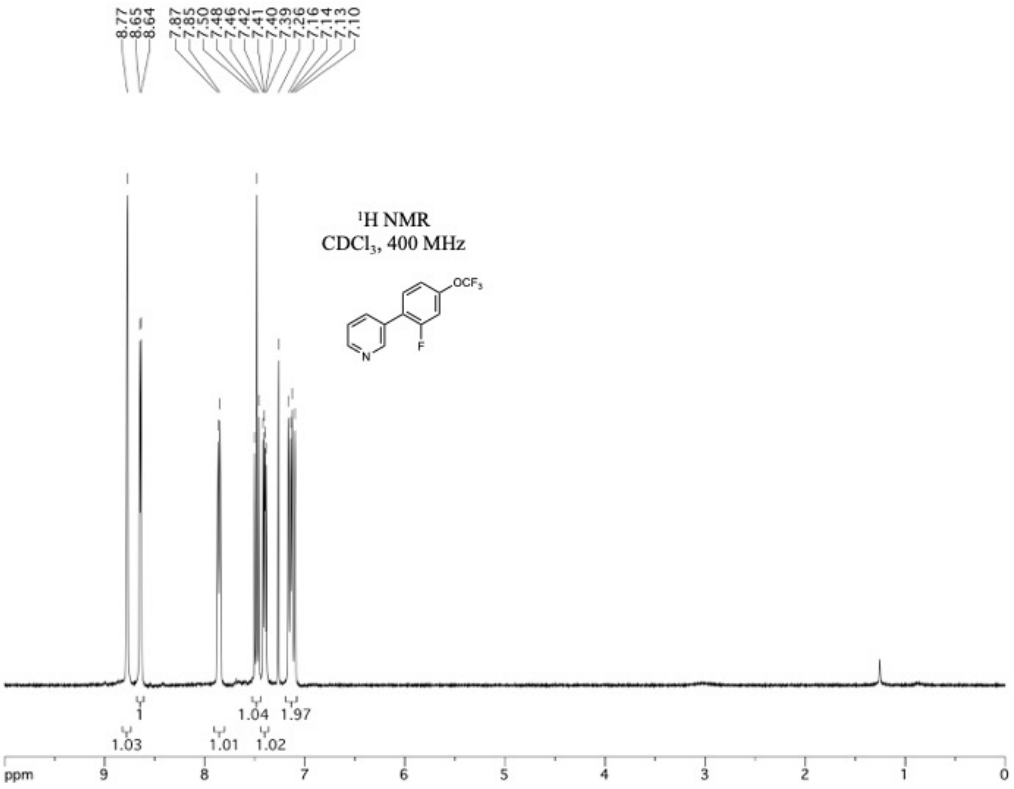
gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes) to provide the title compound as a clear oil (41 mg, 0.18 mmol, 45% yield); IR ν_{max}/cm^{-1} (film): 3060, 1422, 1353, 1199, 1102, 1001, 889, 776, 733, 690; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.57 (1H, d, *J* = 2.1 Hz), 7.83 (1H, d, *J* = 2.1 Hz), 7.74 – 7.69 (2H, m) 7.53 – 7.43 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.85, 146.62, 137.55, 137.28, 137.57, 130.57, 130.29, 129.40, 129.25, 128.26; *m/z* HRMS (DART) found $[M+H]^+$ 224.0044, $C_{11}H_8Cl_2N^+$ requires 224.0034.

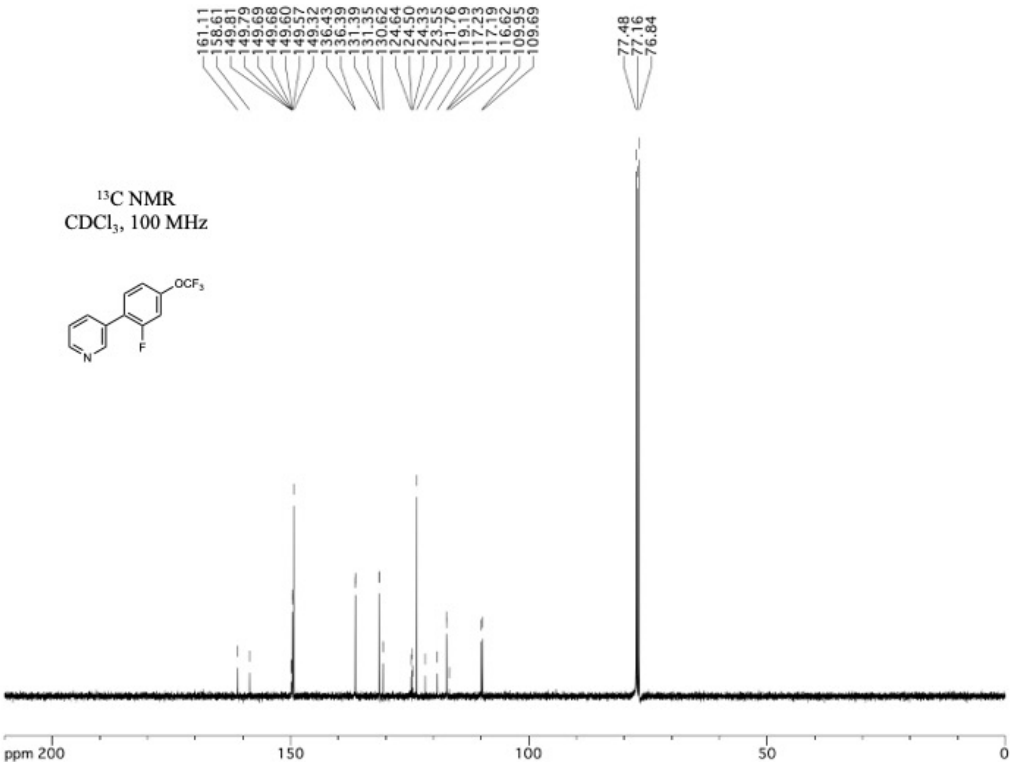
2-Chloro-*N*-(4-chloro-3-(5-chloro-3-iodopyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide

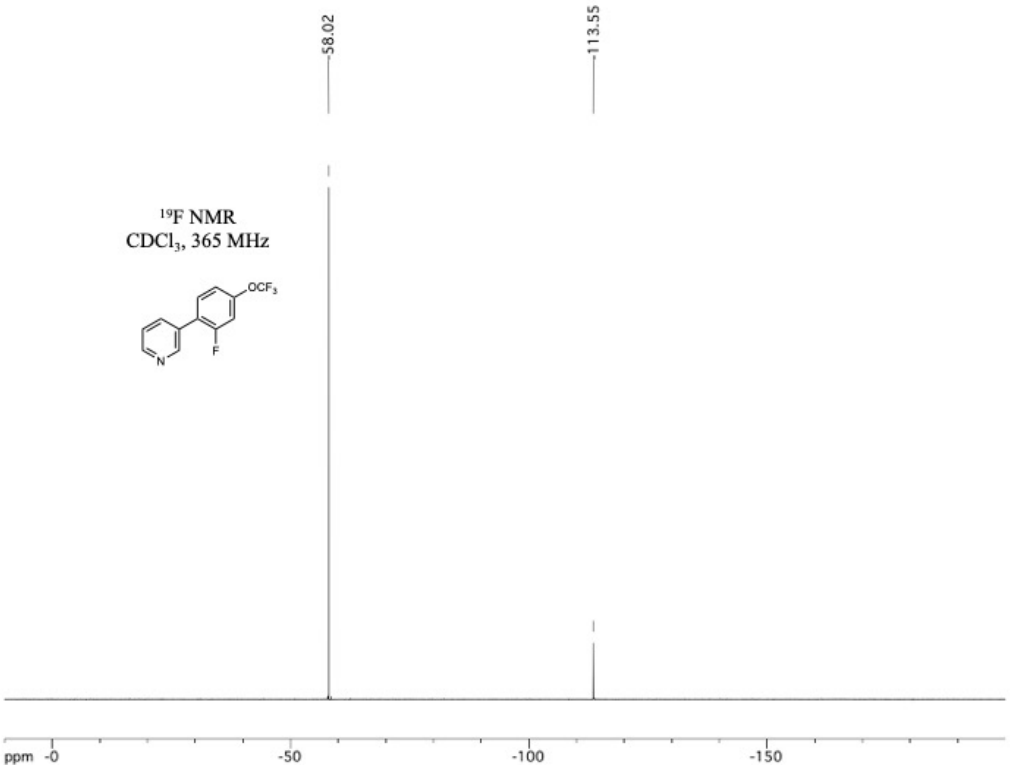


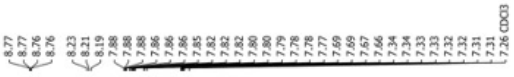
An 8 mL vial charged with 2-chloro-*N*-(4-chloro-3-((1*E*,2*Z*,4*E*)-5-(dibenzylamino)-2-iodo-1-(((trifluoromethyl) sulfonyl)imino)penta-2,4-dien-1-yl)phenyl)-4-(methylsulfonyl)benzamide (1785 mg, 0.20 mmol) and CH_2Cl_2 (12 mL, 0.017 M) was cooled to 0 °C. *N*-chlorosuccinimide (29 mg, 0.22 mmol) and trifluoroacetic acid (17 µL, 0.22 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 15 hours. The crude material was purified by flash chromatography (silica gel: 30% Acetone in Hexanes) to provide the title compound as a white solid (86 mg, 0.15 mmol, 74% yield). mp 256 – 259 °C; IR ν_{max}/cm^{-1} (film): 3263, 2923, 1658, 1538, 1422, 1306, 1094, 961, 890, 734, 692, 639; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ: 10.98 (1H, s), 8.74 (1H, d, *J* = 2.0 Hz), 8.62 (1h, d, *J* = 2.0 Hz), 8.15 (1H, s), 8.02 (1H, d, *J* = 8.0 Hz), 7.95 (1H, d, *J* = 8.0 Hz), 7.80 – 7.74 (2H, m), 7.61 (1H, d, *J* = 8.5 Hz), 3.36 (3H, s); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 163.88, 158.16, 147.09, 145.34, 143.14, 140.78, 140.53, 137.51, 130.97, 130.42, 129.98, 129.81, 128.10, 126.35, 125.92, 121.33, 120.93, 97.17, 43.09; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 581.0, $C_{19}H_{13}Cl_3IN_2O_3S^+$ requires 580.9.

A 2.4 NMR Spectra






58.02
113.55
19F NMR
CDCl3, 365 MHz
OCF3
F
N
ppm -0
-50
-100
-150


8.77
8.77
8.76
8.76
8.23
8.21
8.19
7.88
7.88
7.86
7.86
7.86
7.85
7.82
7.82
7.80
7.80
7.79
7.78
7.77
7.69
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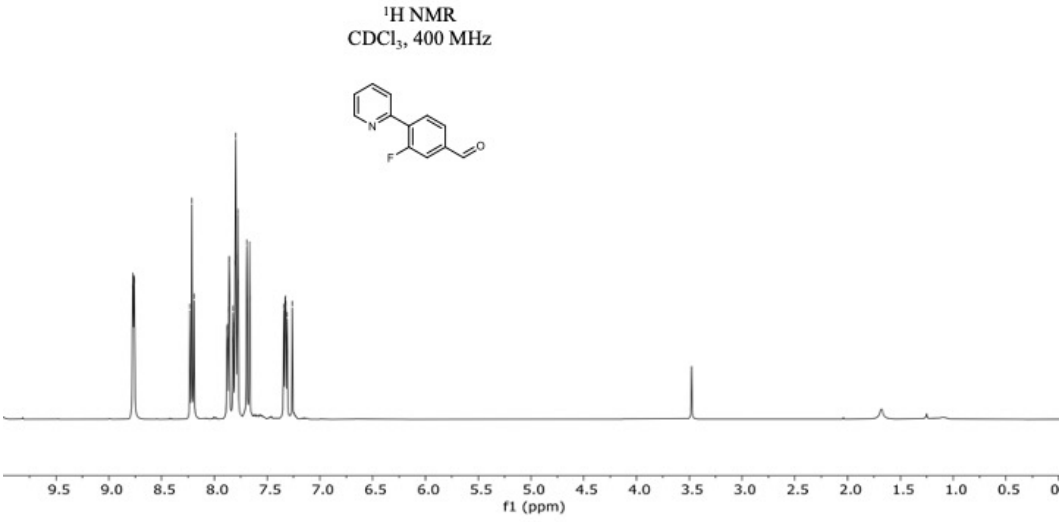
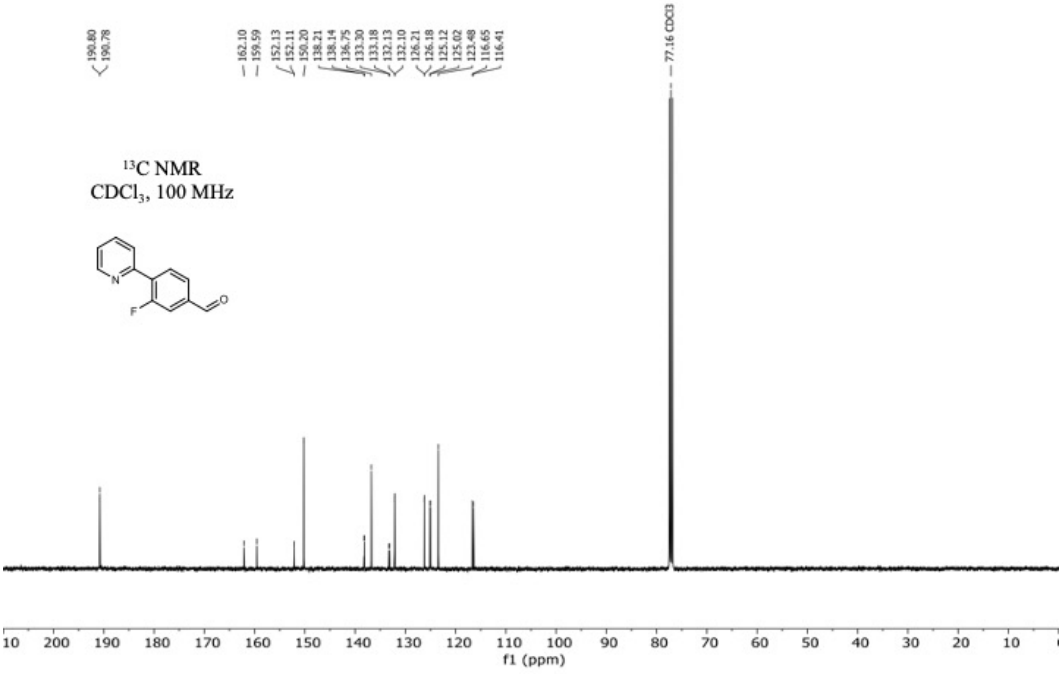
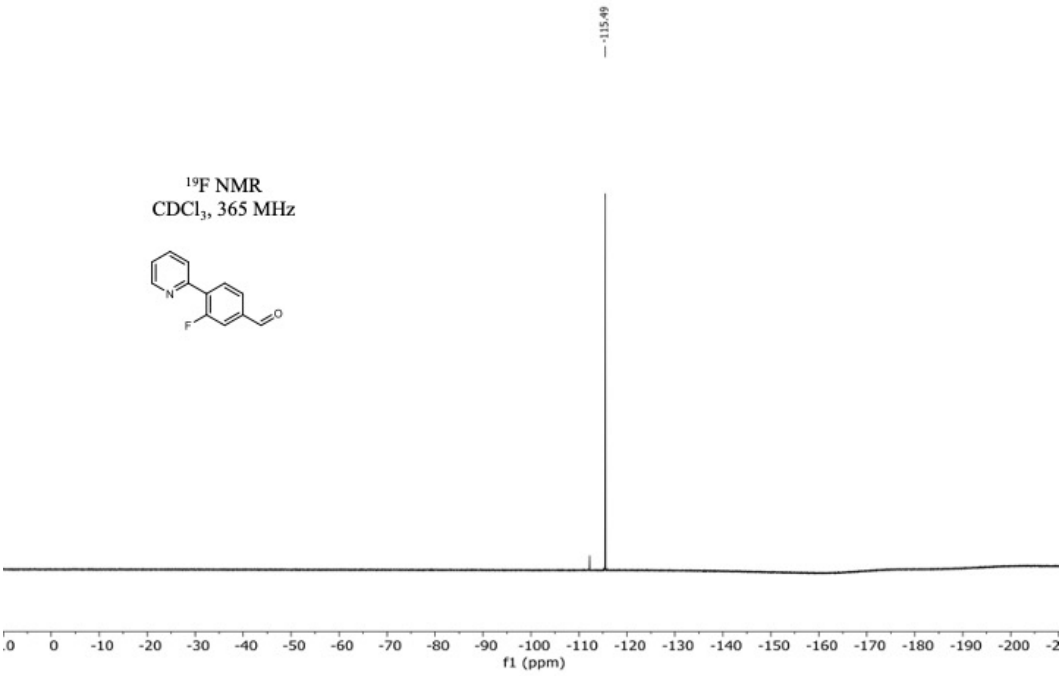
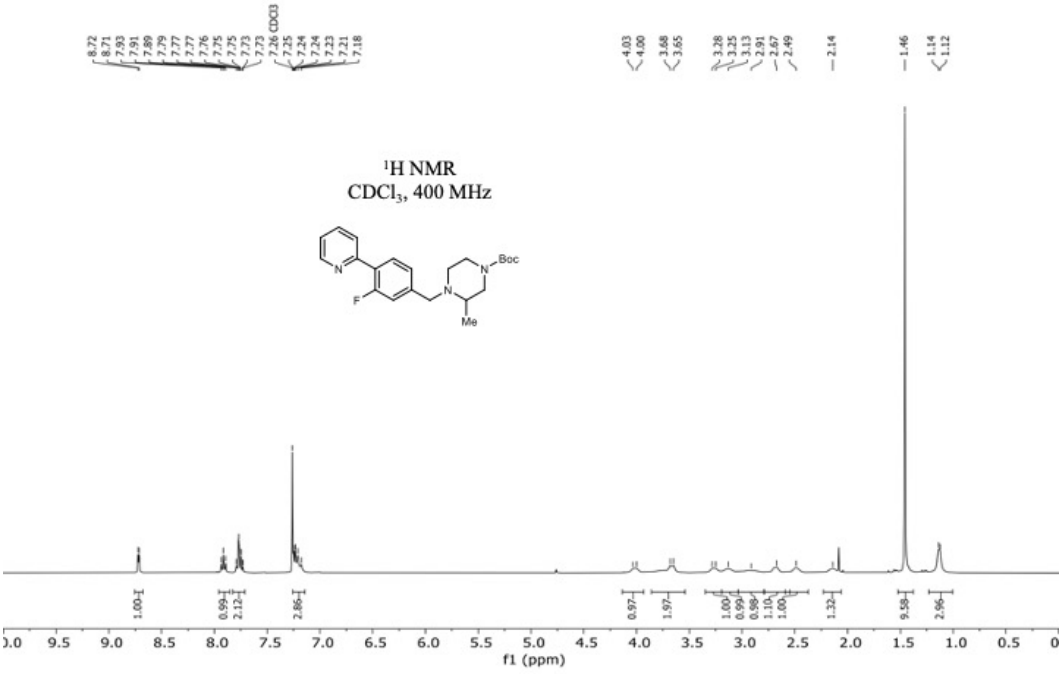
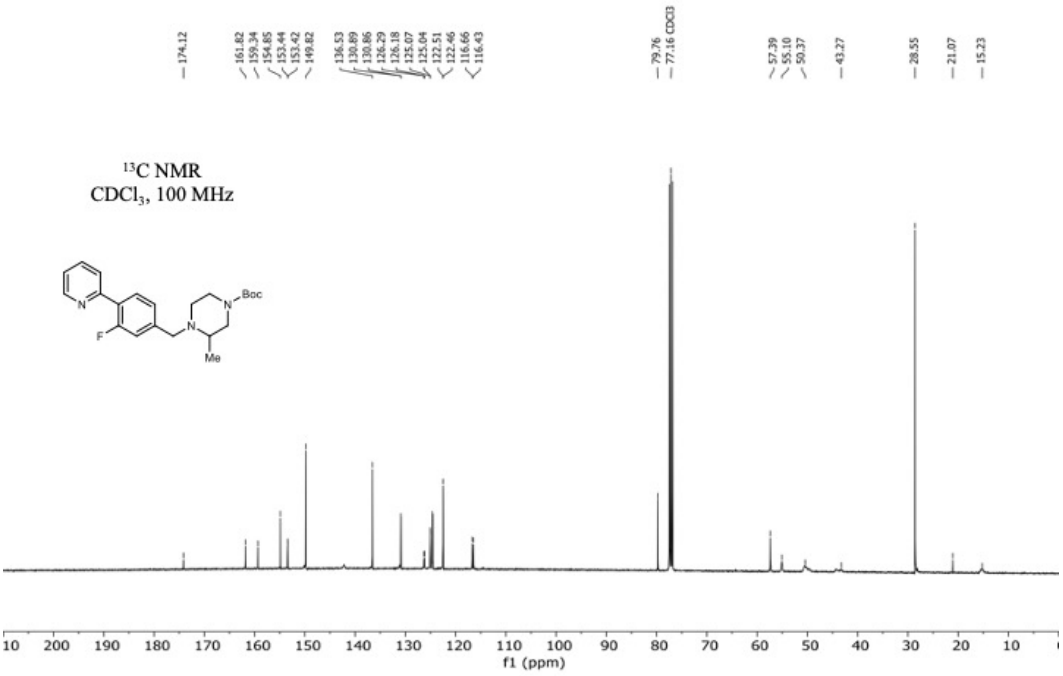
7.33
7.33
7.32
7.32
7.31
7.31
7.26 CDCl3

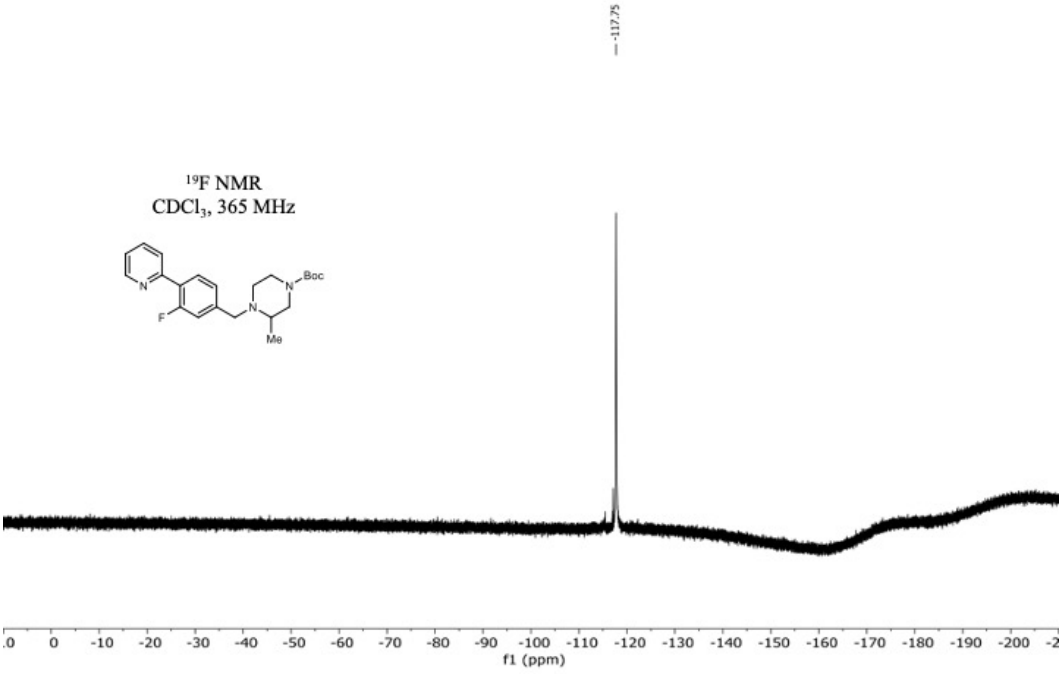

1H NMR
CDCl3, 400 MHz
N
F
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

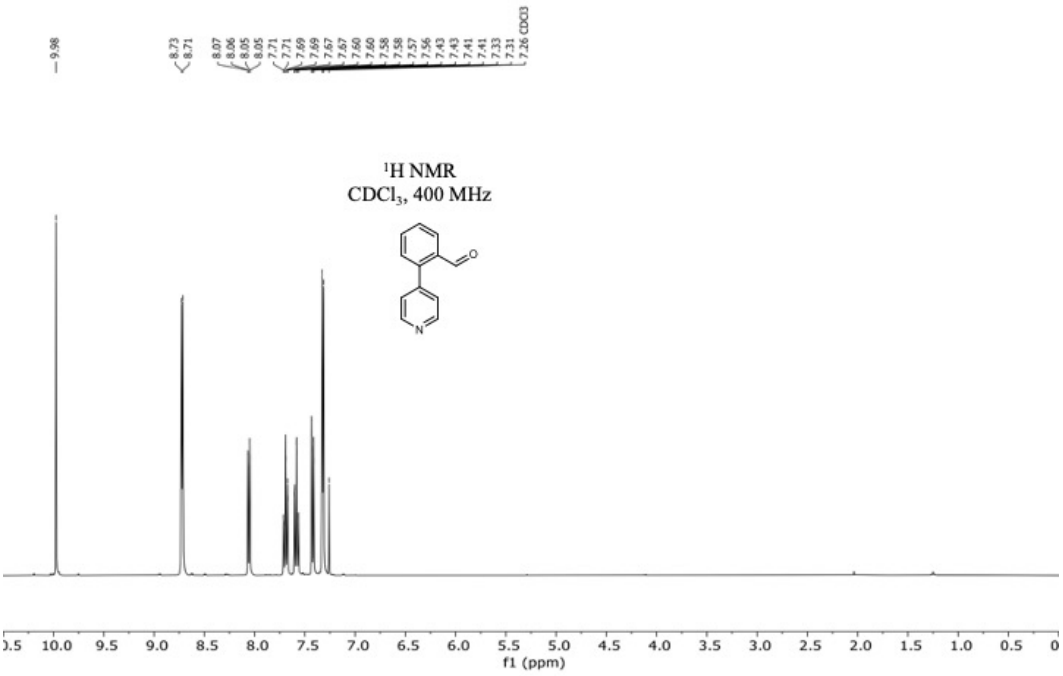

190.80
190.78
162.10
159.59
152.13
152.11
150.20
138.21
138.14
136.75
133.30
133.18
132.13
132.10
126.21
126.18
125.12
125.02
123.48
116.65
116.41
77.16 CDCl3
13C NMR
CDCl3, 100 MHz
N
F
O
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

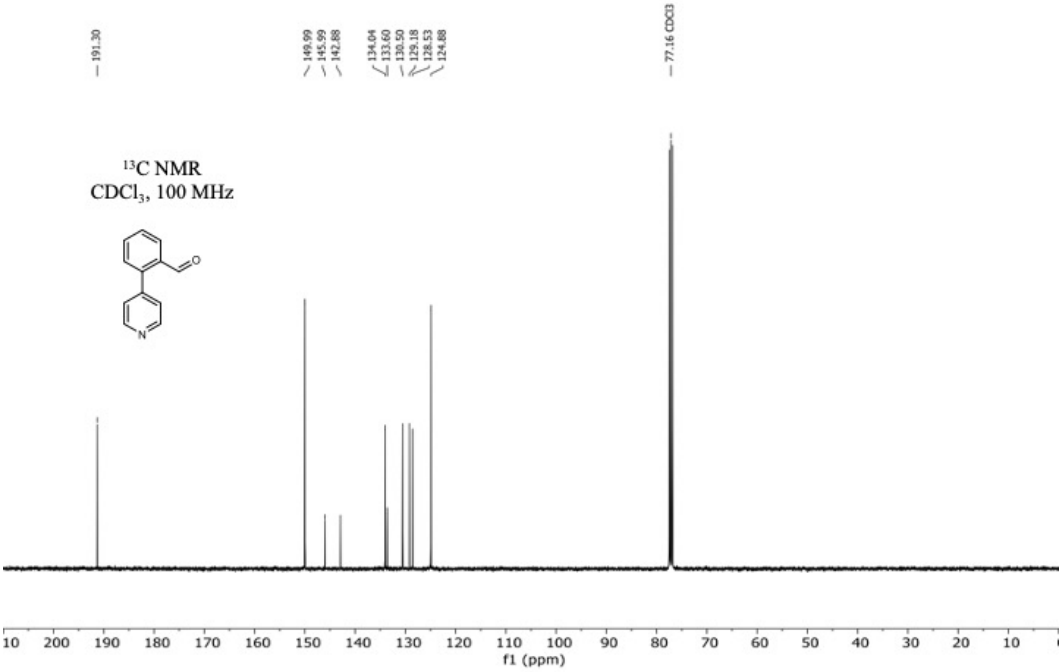

-115.49
19F NMR
CDCl3, 365 MHz
N
F
O
.0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -2
f1 (ppm)

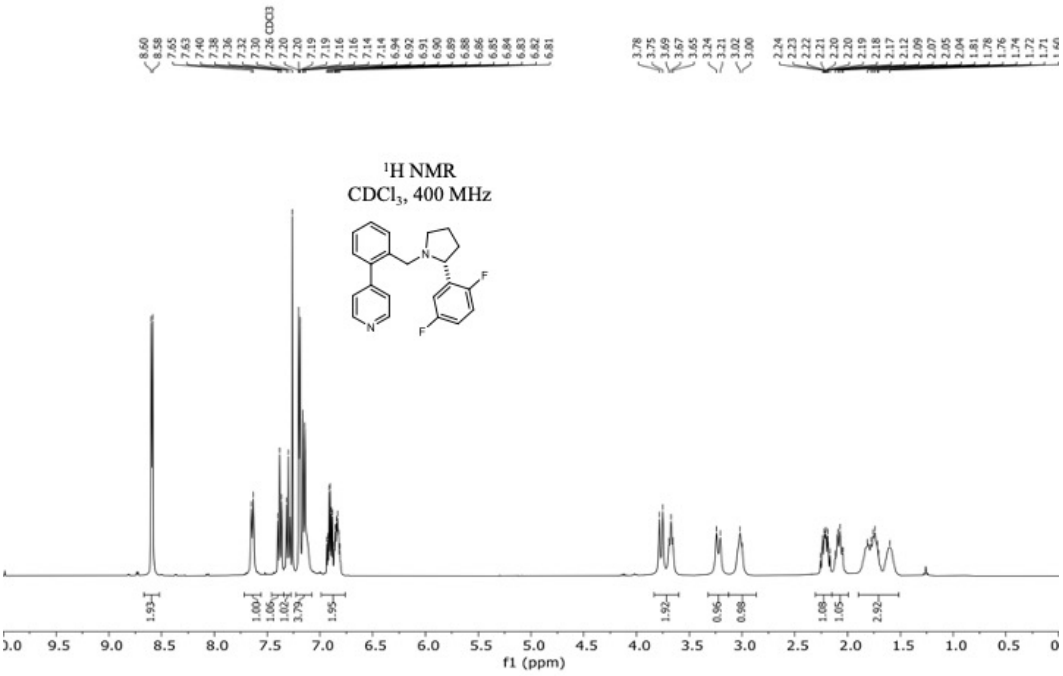

8.72
8.71
7.93
7.91
7.89
7.79
7.77
7.77
7.76
7.75
7.75
7.73
7.73
7.26 CDCl3
7.25
7.24
7.24
7.23
7.21
7.18
4.03
4.00
3.68
3.65
3.28
3.25
3.13
2.91
2.67
2.49
2.14
1.46
1.14
1.12
1H NMR
CDCl3, 400 MHz
Boc
N
F
Me
1.00
0.99
2.12
2.86
0.97
1.97
1.00
0.99
0.98
1.10
1.00
1.32
9.58
2.96
f1 (ppm)

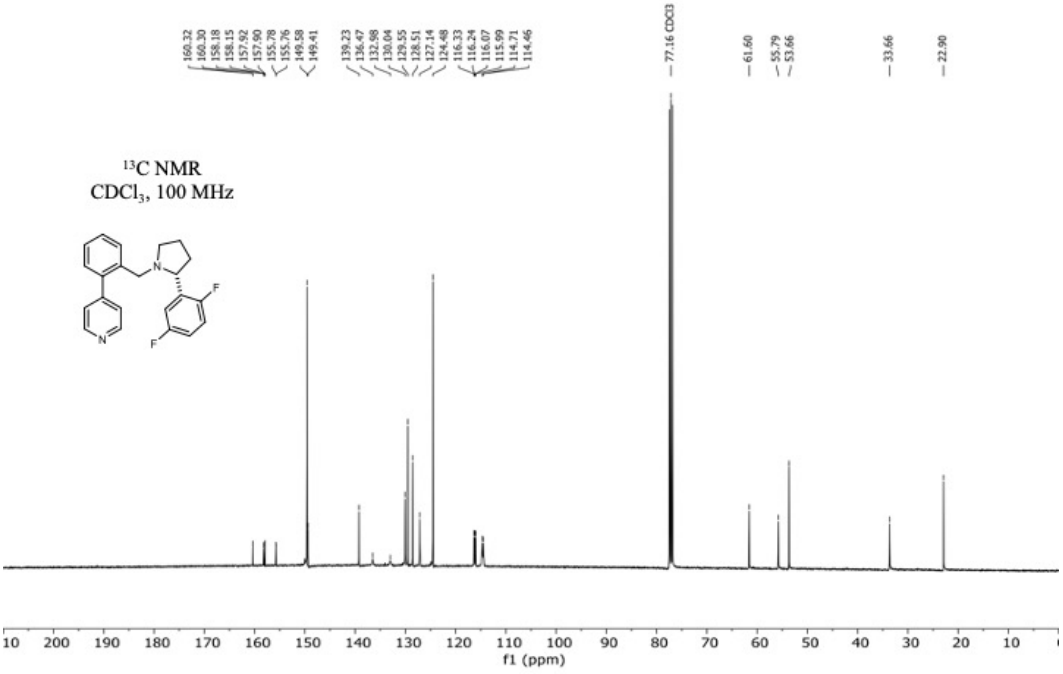

174.12
161.82
159.34
154.85
153.44
153.42
149.82
136.53
130.89
130.86
126.29
126.18
125.07
125.04
122.51
122.46
116.66
116.43
79.76
77.16 CDCl3
57.39
55.10
50.37
43.27
28.55
21.07
15.23
13C NMR
CDCl3, 100 MHz
Boc
N
F
Me
f1 (ppm)

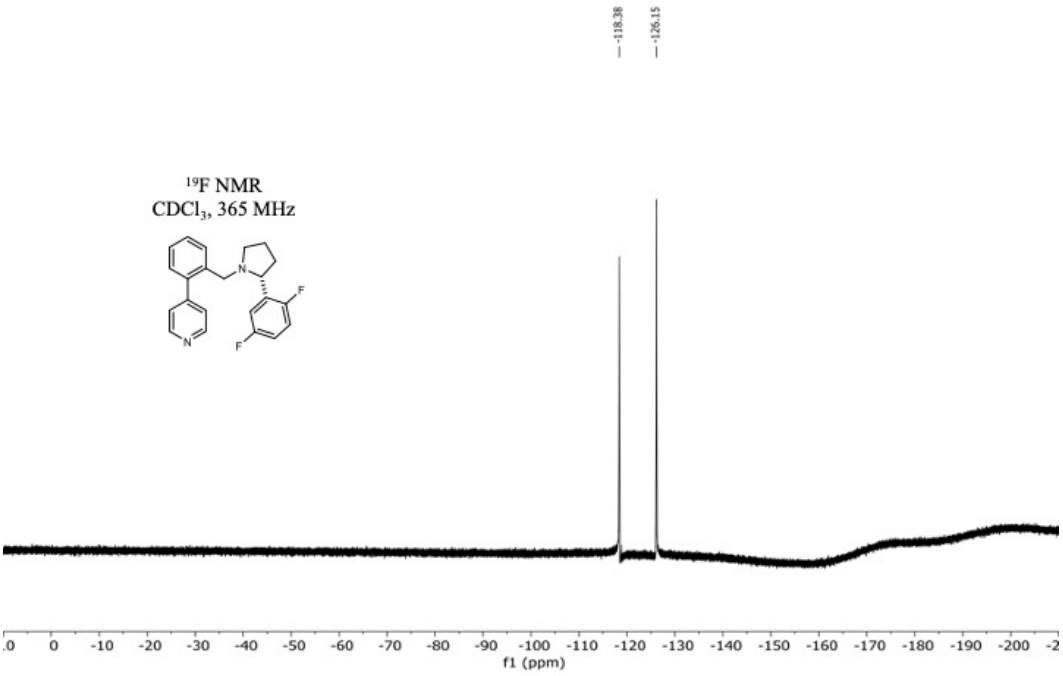

-117.75
^{19}F NMR
$CDCl_3$, 365 MHz
Boc
Me
f1 (ppm)

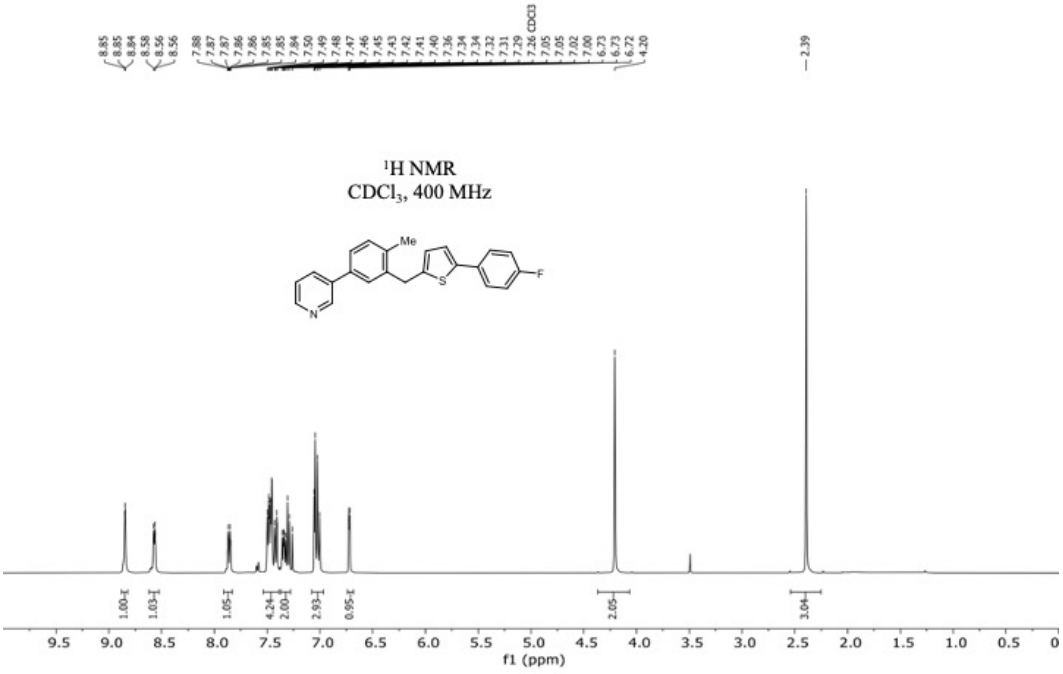

9.98
8.73
8.71
7.26 CDCl3
^{1}H NMR
$CDCl_3$, 400 MHz
f1 (ppm)

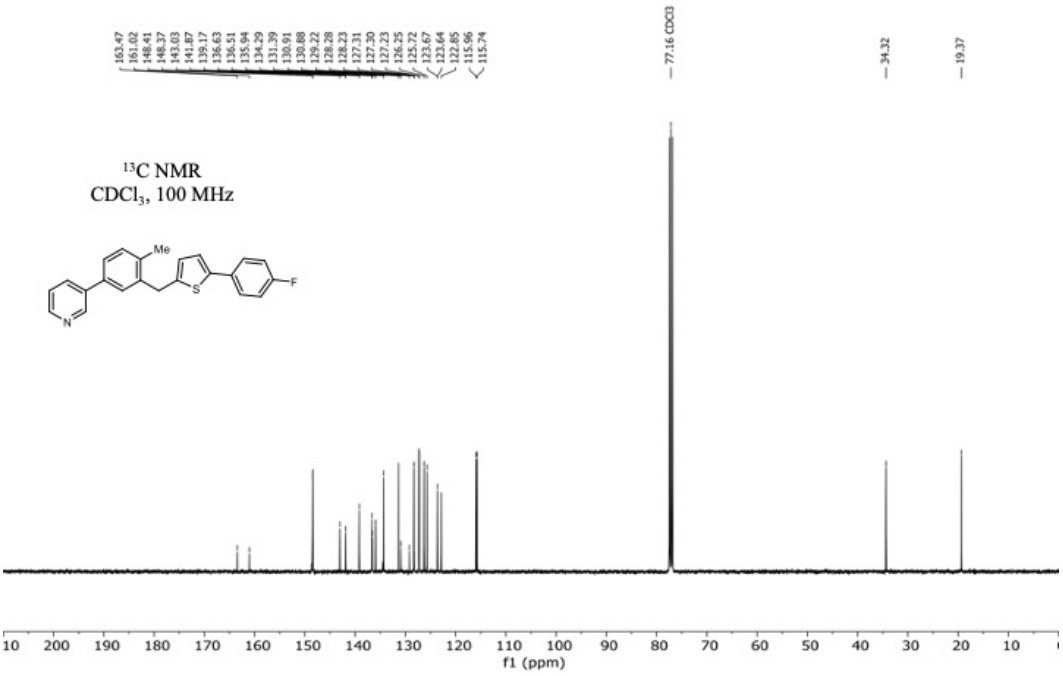

191.30
149.99
145.99
142.88
134.04
133.60
130.50
129.18
128.53
124.88
77.16 CDCl3
13C NMR
CDCl3, 100 MHz
f1 (ppm)

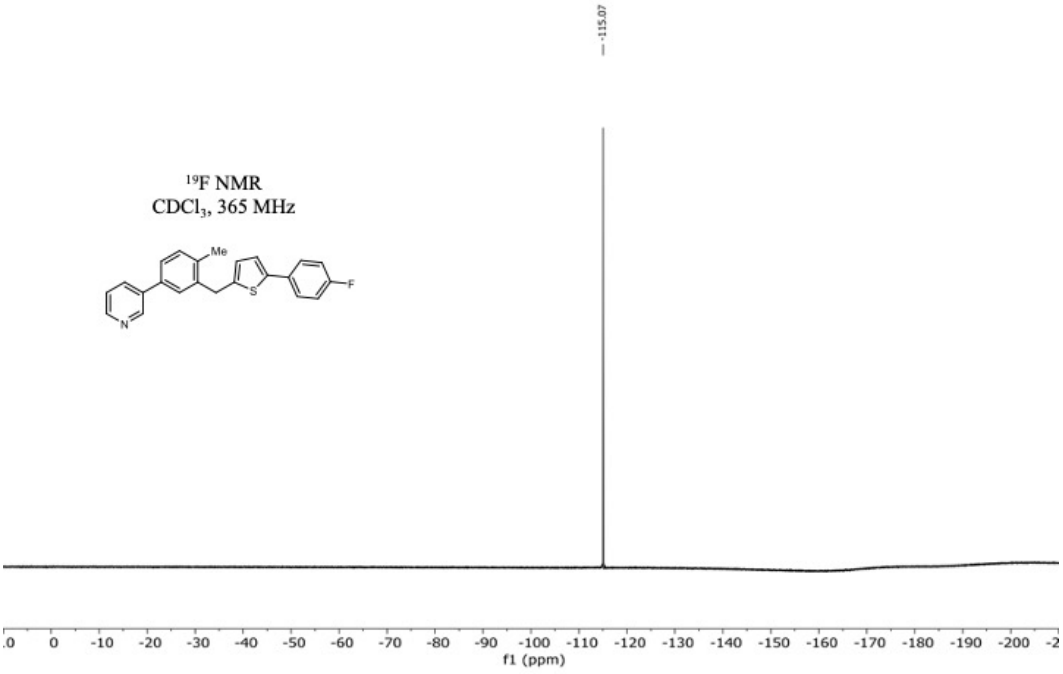

1H NMR
CDCl3, 400 MHz
f1 (ppm)

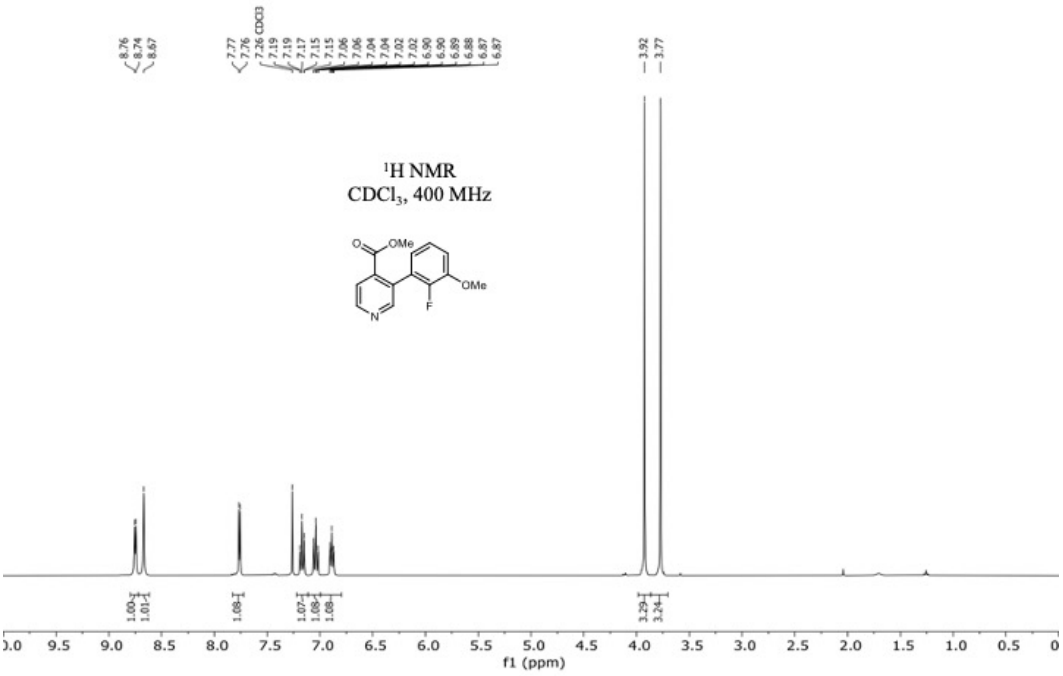

160.32
160.30
158.18
158.15
157.92
157.90
155.78
155.76
149.58
149.41
139.23
136.47
132.98
130.04
129.55
128.51
127.14
124.48
116.33
116.24
116.07
115.99
114.71
114.46
77.16 CDCl3
61.60
55.79
53.66
33.66
22.90
13C NMR
CDCl3, 100 MHz
f1 (ppm)

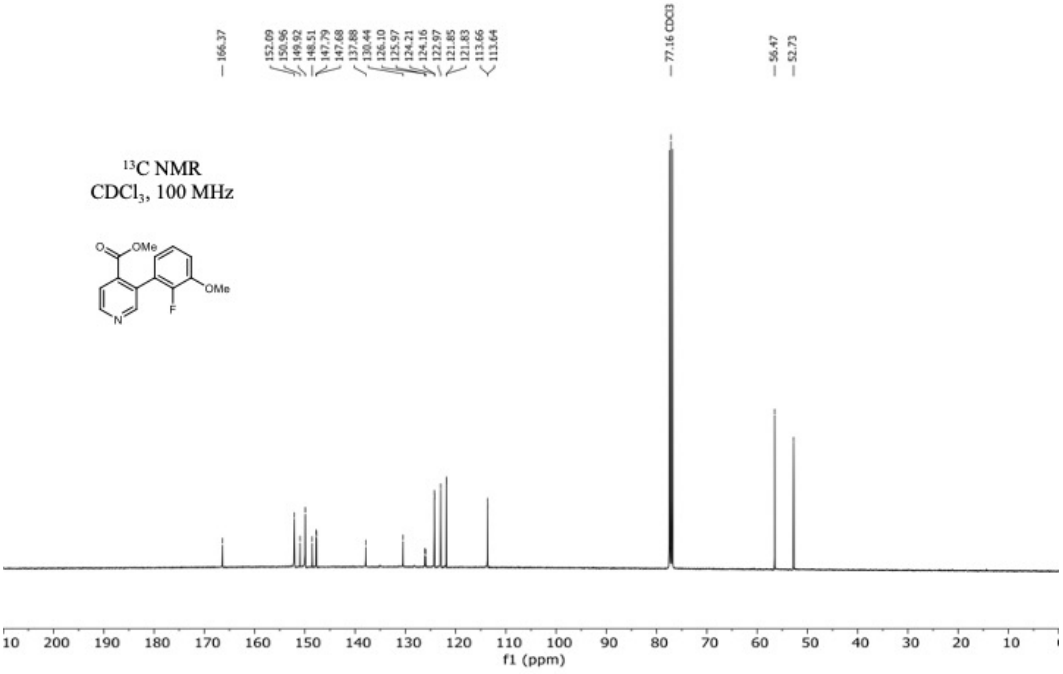

-118.38
-126.15
19F NMR
CDCl3, 365 MHz
f1 (ppm)

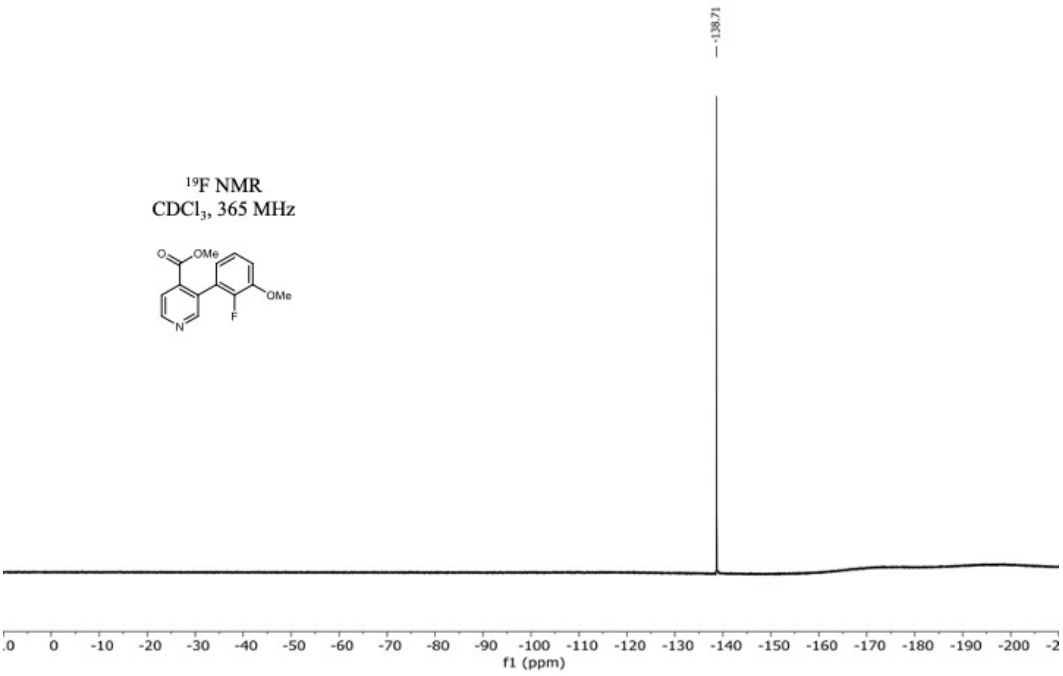

^{1}H NMR
$CDCl_3$, 400 MHz
Me
F
S
N
f1 (ppm)

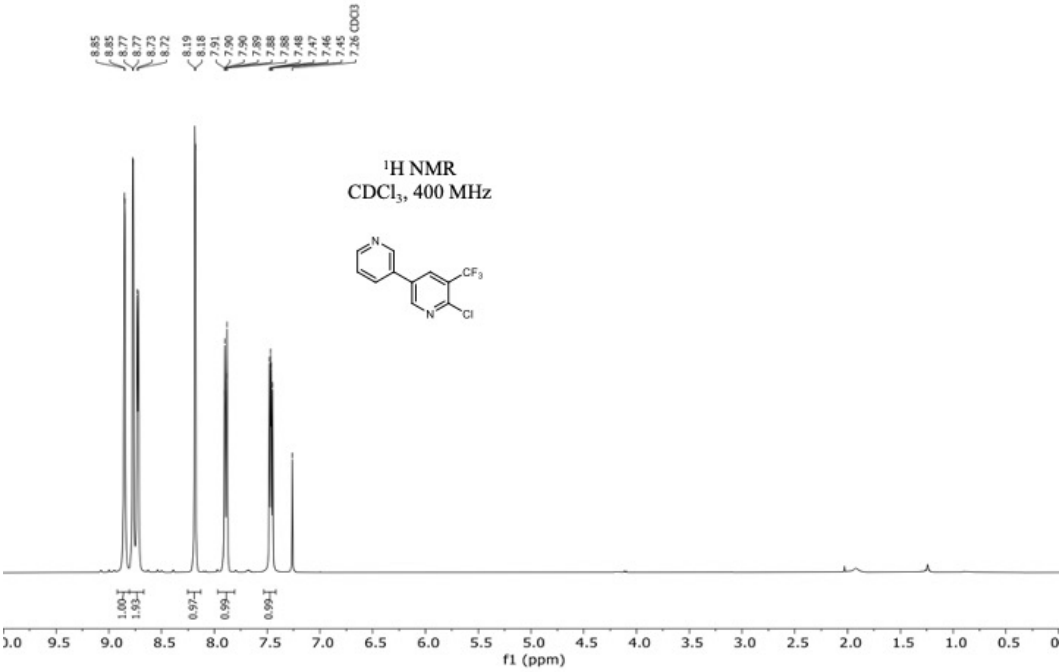

^{13}C NMR
$CDCl_3$, 100 MHz
Me
F
S
N
f1 (ppm)

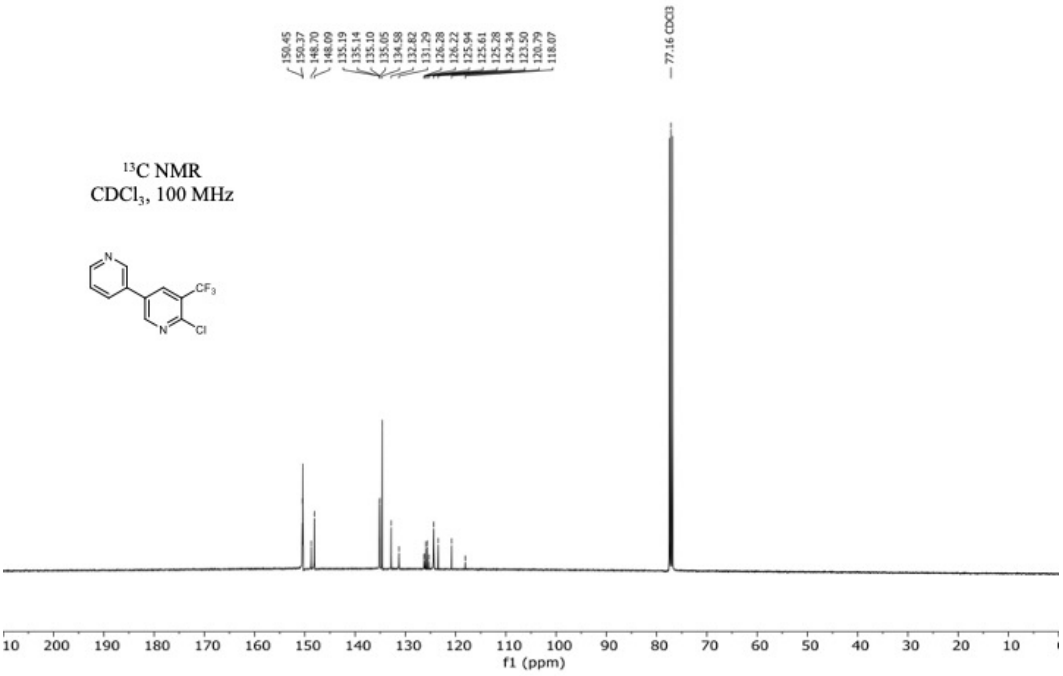

-115.07
19F NMR
CDCl3, 365 MHz
Me
S
F
N
f1 (ppm)

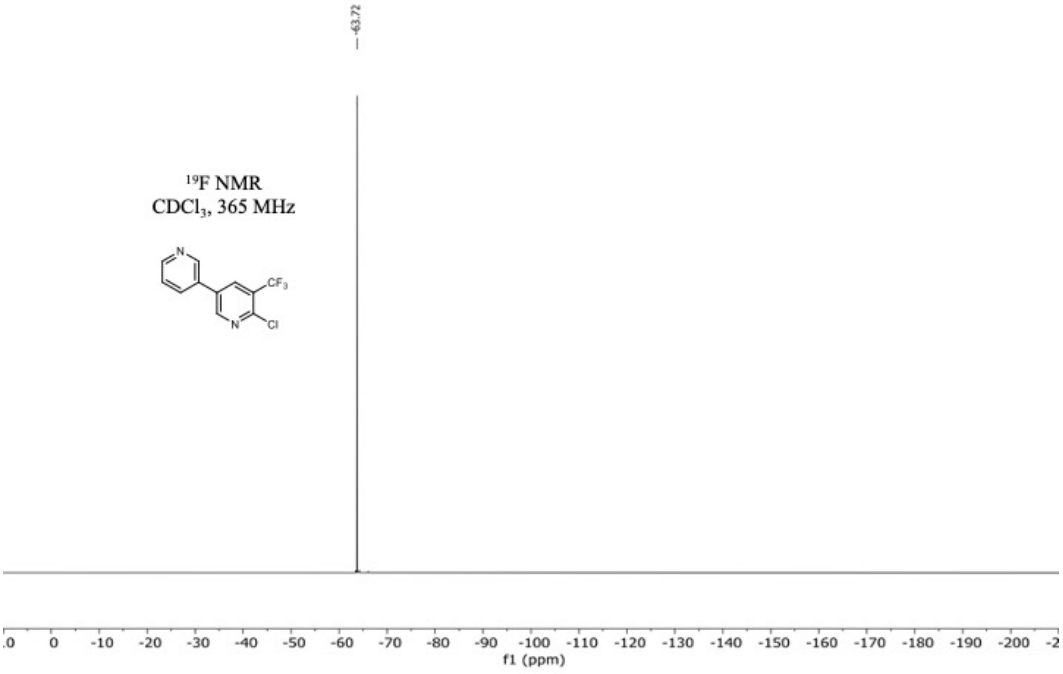

8.76
8.74
8.67
7.77
7.76
CDCl3
7.26
7.19
7.17
7.15
7.06
7.04
7.02
6.90
6.89
6.88
6.87
6.87
3.92
3.77
1H NMR
CDCl3, 400 MHz
O
OMe
OMe
F
N
1.00
1.01
1.08
1.07
1.08
1.08
3.29
3.24
f1 (ppm)

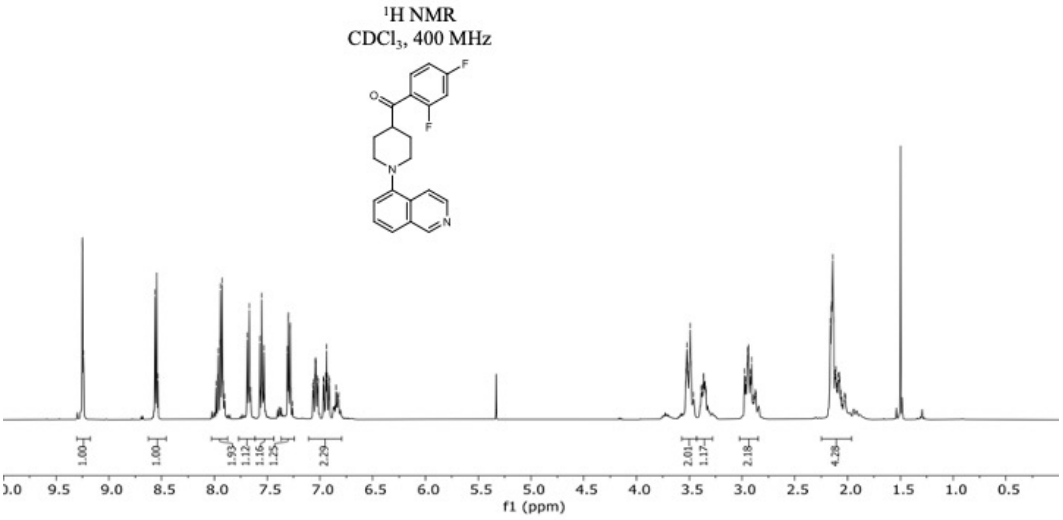

166.37
152.09
150.96
149.92
148.51
147.79
147.68
137.88
130.44
126.10
125.97
124.21
124.16
122.97
121.85
121.83
113.66
113.64
77.16 CDCl3
56.47
52.73
13C NMR
CDCl3, 100 MHz
OMe
OMe
F
N
f1 (ppm)


-138.71
19F NMR
CDCl3, 365 MHz
OMe
OMe
F
N
f1 (ppm)

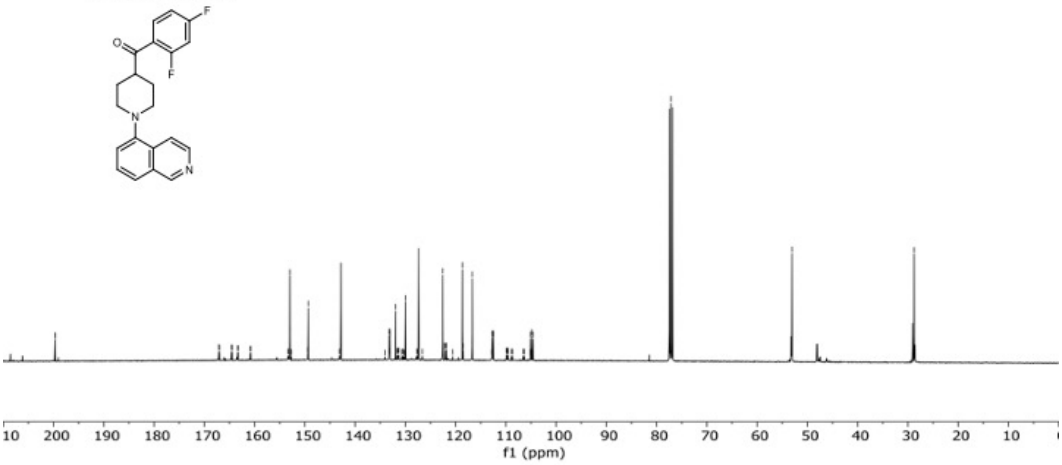

8.85
8.85
8.77
8.77
8.73
8.72
8.19
8.18
7.91
7.90
7.90
7.89
7.88
7.88
7.48
7.47
7.46
7.45
7.26 CDCl3
1H NMR
CDCl3, 400 MHz
N
CF3
N
Cl
1.00
1.93
0.97
0.99
0.99
f1 (ppm)

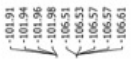

150.45
150.37
148.70
148.69
135.19
135.14
135.10
135.05
134.98
132.82
131.29
126.28
126.22
125.94
125.61
125.28
124.34
123.50
120.79
118.07
77.16 CDCl3
13C NMR
CDCl3, 100 MHz
N
CF3
N
Cl
f1 (ppm)


-63.72
19F NMR
CDCl3, 365 MHz
CF3
Cl
f1 (ppm)

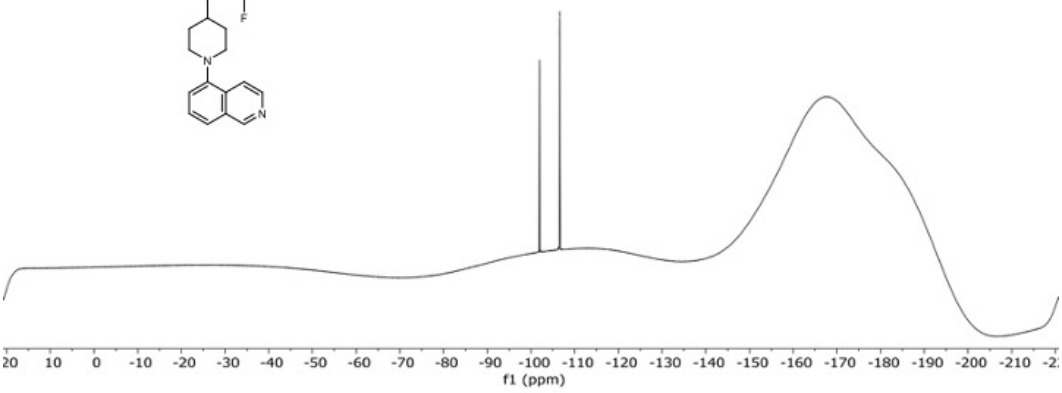

1H NMR
CDCl3, 400 MHz
F
F
O
N
f1 (ppm)

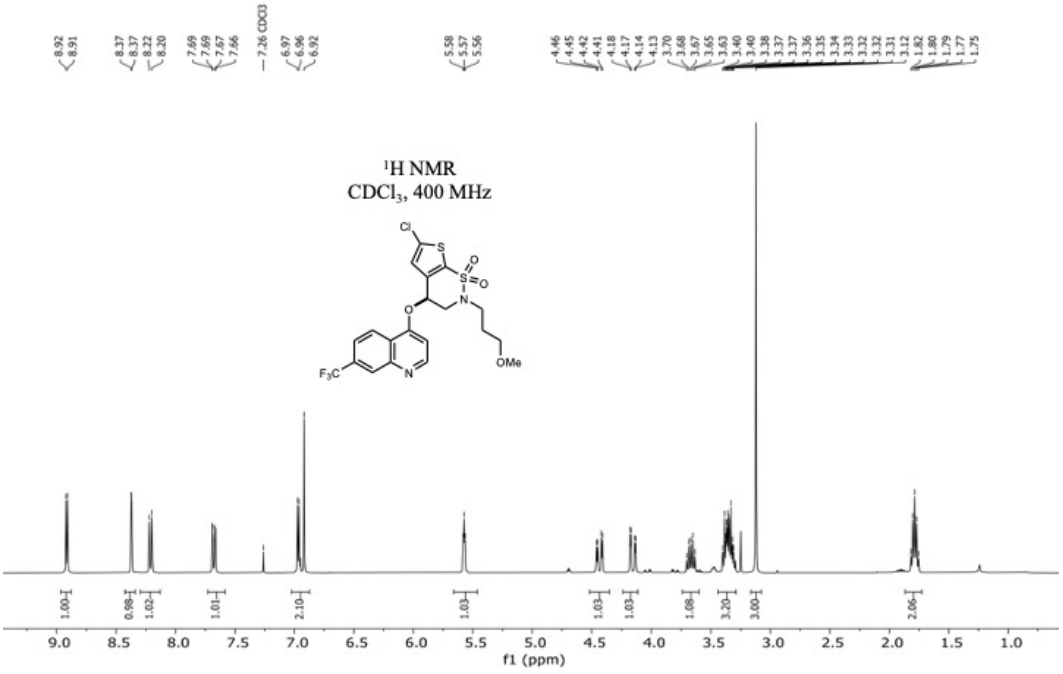
^{13}C NMR
$CDCl_3$, 100 MHz





^{19}F NMR
$CDCl_3$, 365 MHz




8.92
8.91
8.37
8.37
8.22
8.20
7.69
7.69
7.67
7.66
7.26 CDCl3
6.97
6.96
6.92
5.58
5.57
5.56
4.46
4.45
4.42
4.41
4.18
4.17
4.14
4.13
3.70
3.68
3.67
3.65
3.63
3.40
3.40
3.38
3.37
3.37
3.36
3.35
3.34
3.33
3.32
3.32
3.31
3.12
1.82
1.80
1.79
1.77
1.75
1H NMR
CDCl3, 400 MHz
Cl
S
O
O
N
O
F3C
N
OMe
1.00
0.98
1.02
1.01
2.10
1.03
1.03
1.03
1.08
3.20
3.00
2.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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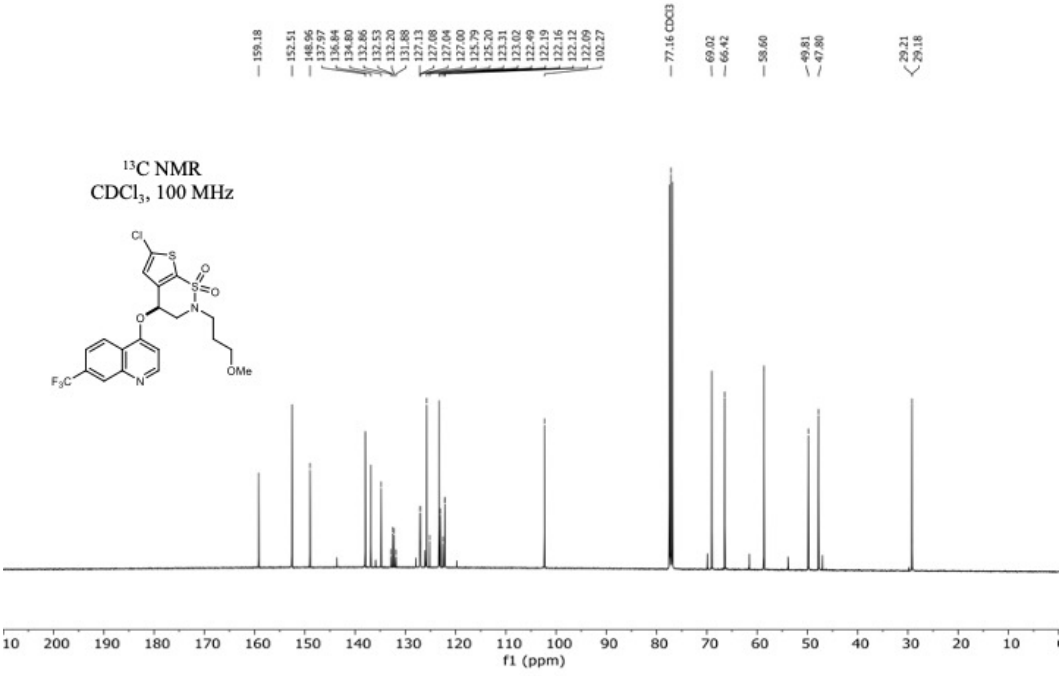
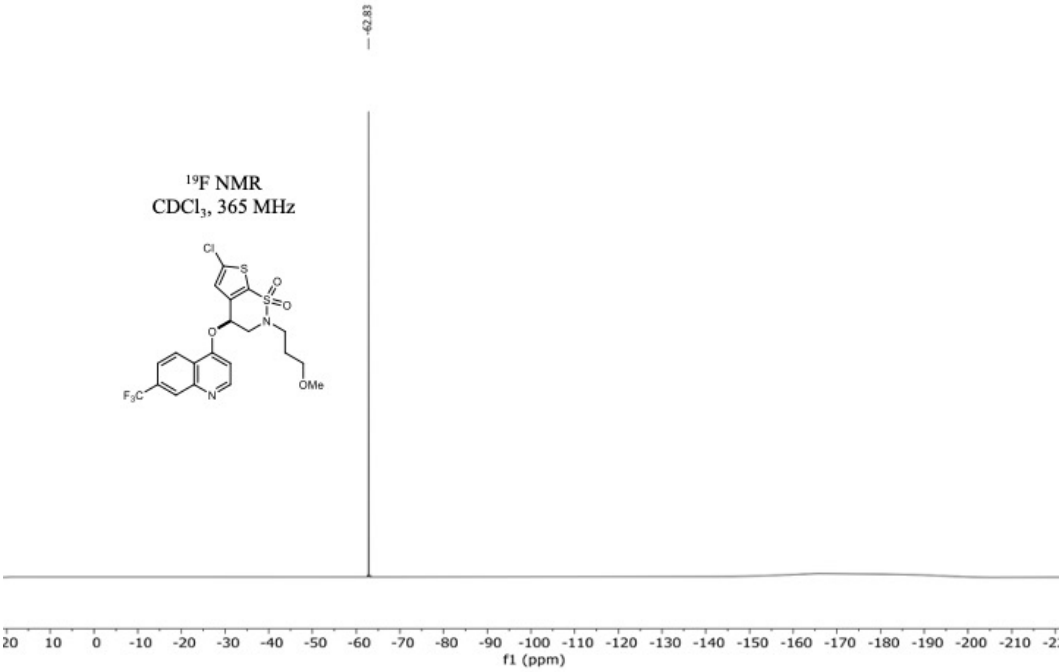
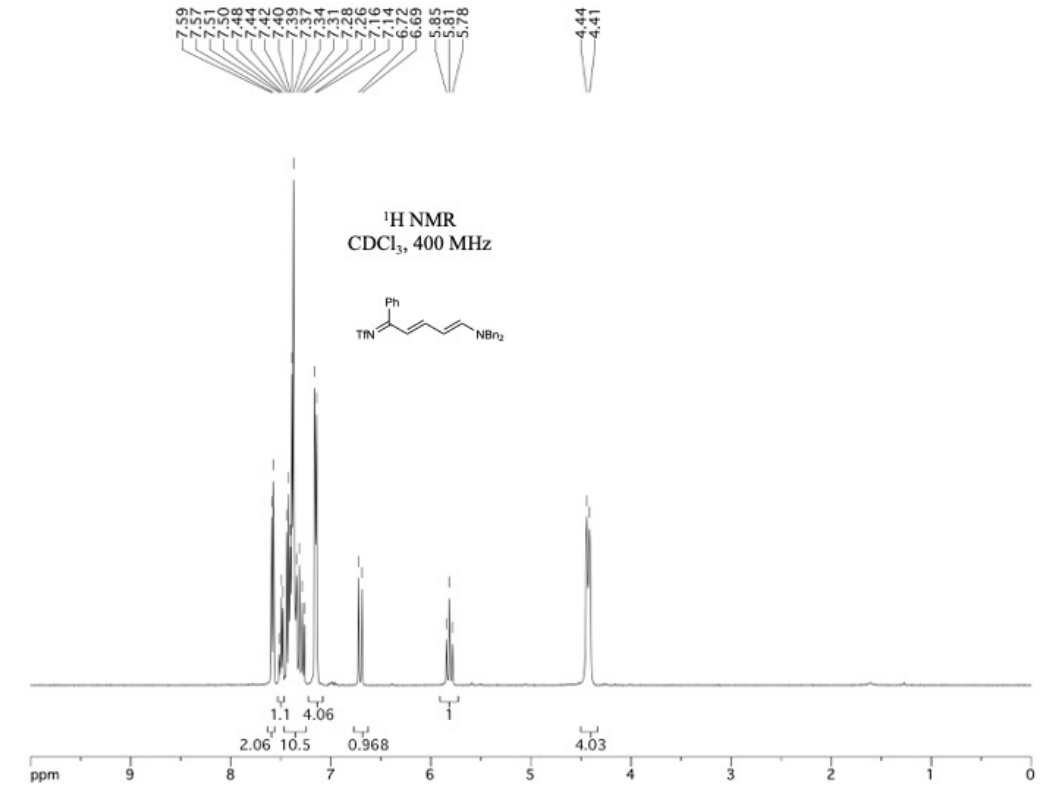
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


159.18
152.51
148.96
137.97
136.84
134.80
132.86
132.53
132.20
131.88
127.13
127.08
127.04
127.00
125.79
125.20
123.31
123.02
122.49
122.19
122.16
122.12
122.09
102.27
77.16 CDCl3
69.02
66.42
58.60
49.81
47.80
29.21
29.18
13C NMR
CDCl3, 100 MHz
Cl
S
O
O
N
O
F3C
N
OMe
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


-62.83
^{19}F NMR
$CDCl_3$, 365 MHz
f1 (ppm)


7.59
7.57
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7.44
7.42
7.40
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7.34
7.31
7.28
7.26
7.16
7.14
6.72
6.69
5.85
5.81
5.78
4.44
4.41
^{1}H NMR
$CDCl_3$, 400 MHz
Ph
TfN
NBn$_2$
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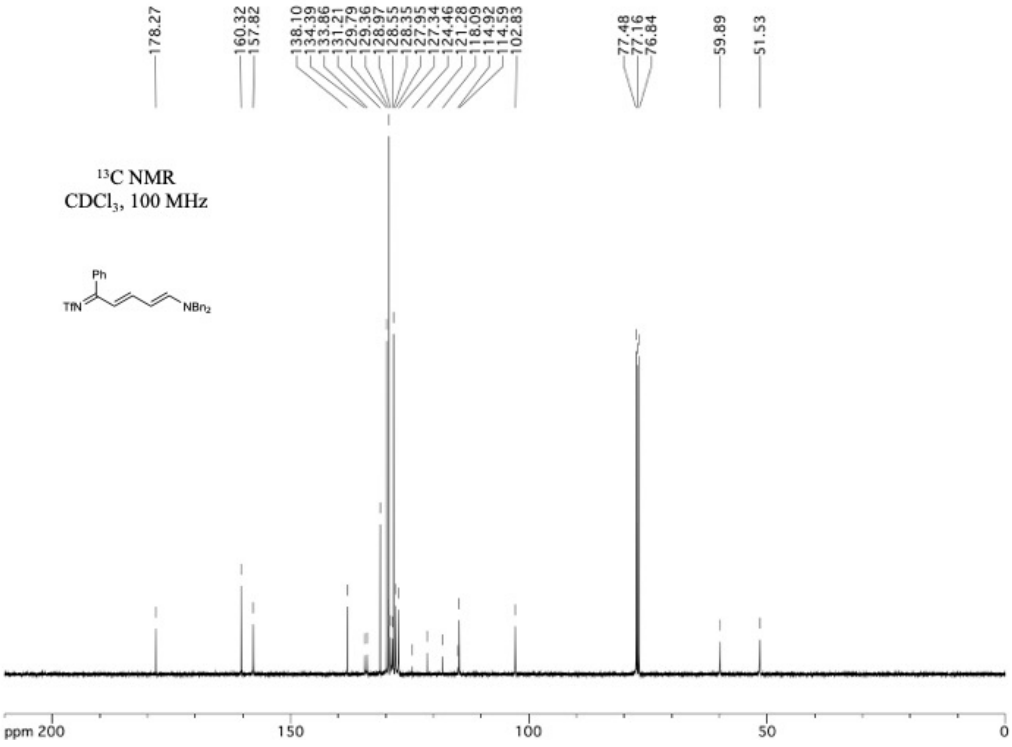
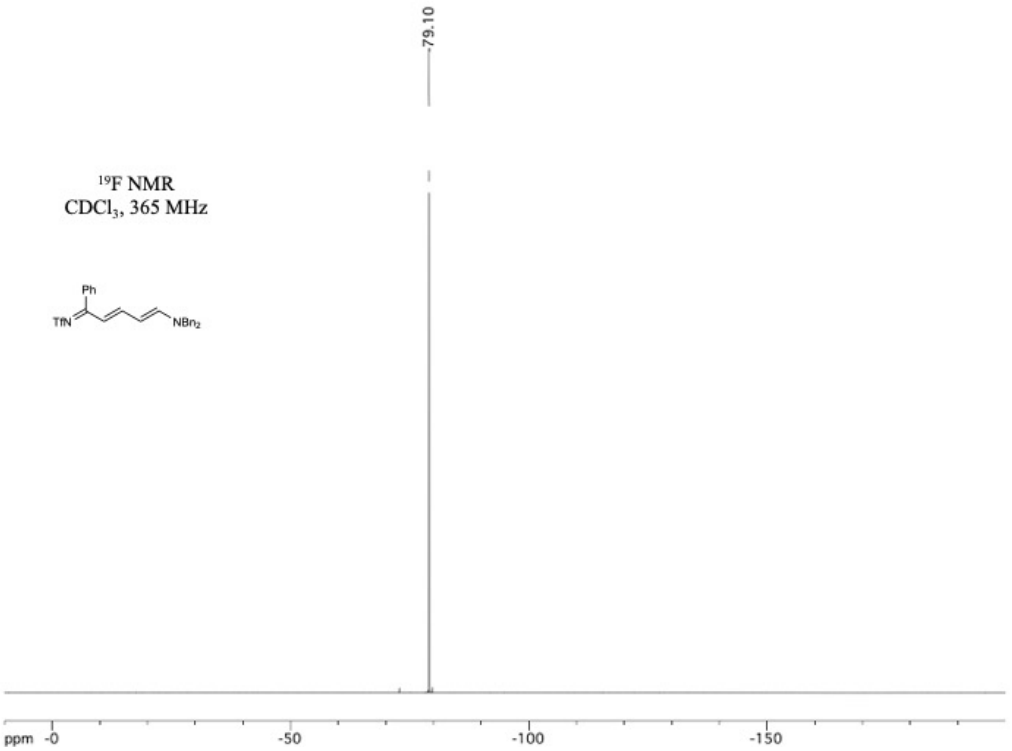
4.06
1
2.06
10.5
0.968
4.03
ppm


178.27
160.32
157.82
138.10
134.39
133.86
131.21
129.79
129.36
128.97
128.55
128.35
127.95
127.34
124.46
121.28
118.09
114.92
114.59
102.83
77.48
77.16
76.84
59.89
51.53
13C NMR
CDCl3, 100 MHz
Ph
TfN
NBn2
ppm 200
150
100
50
0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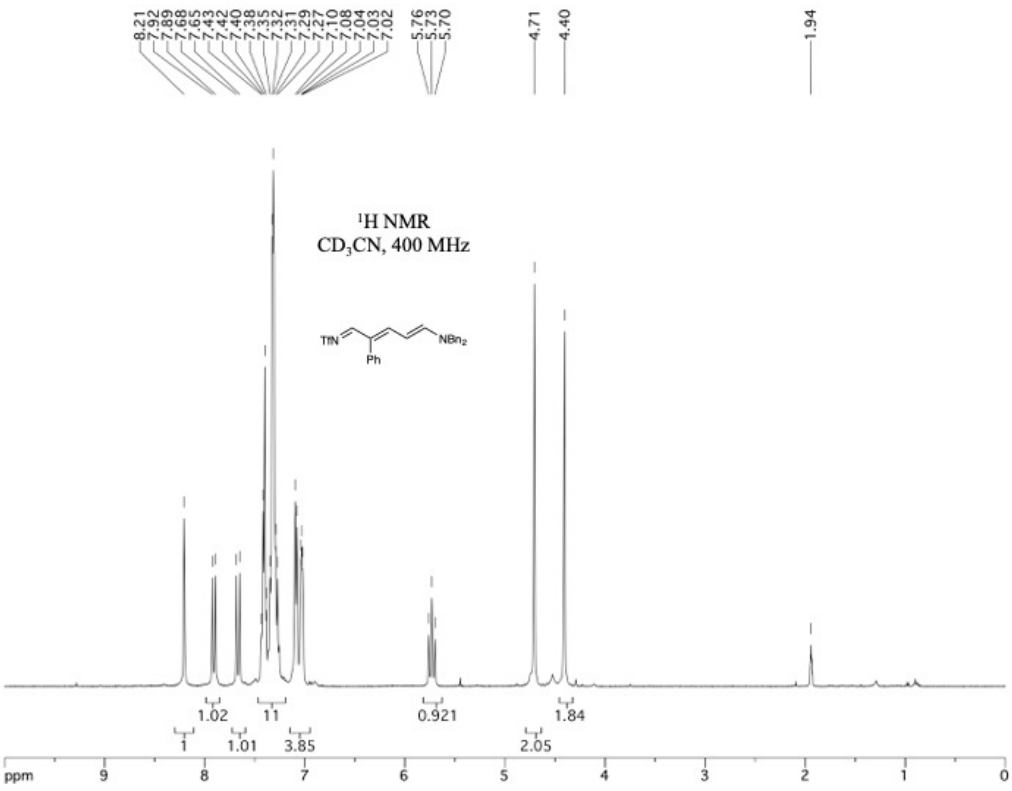
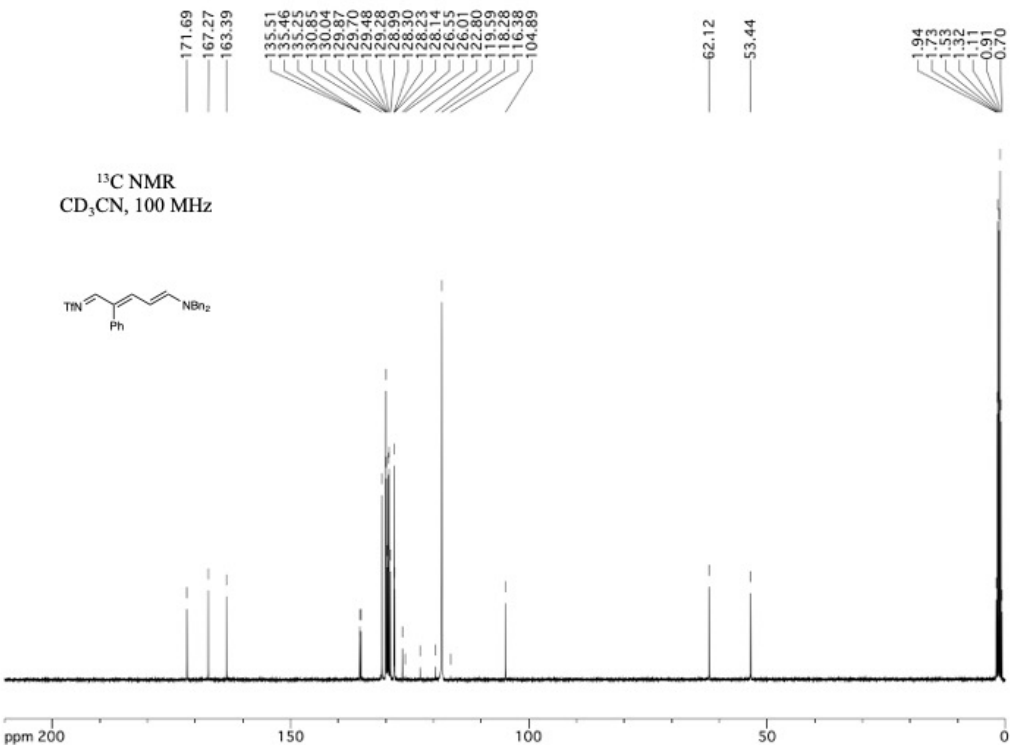
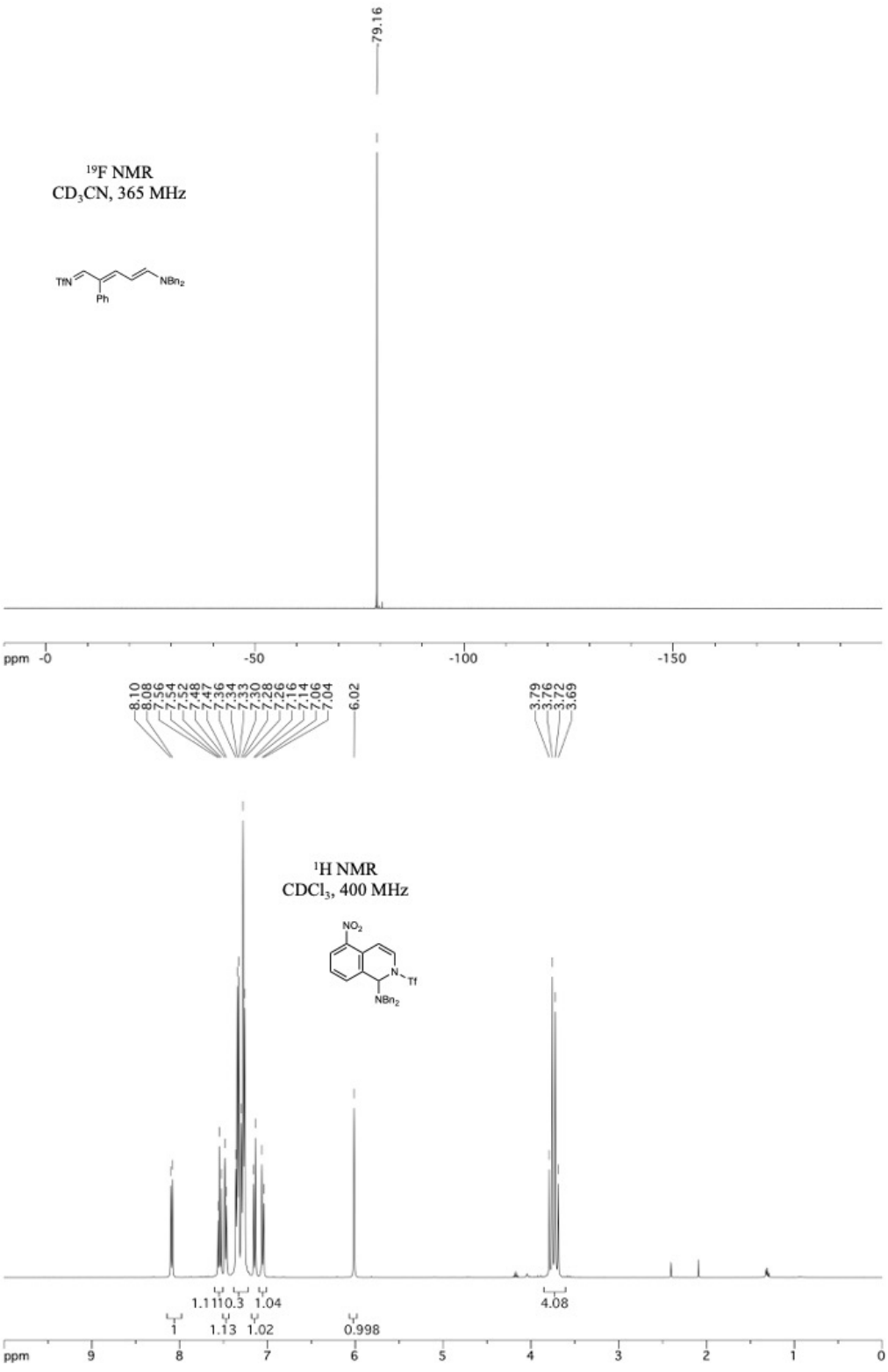
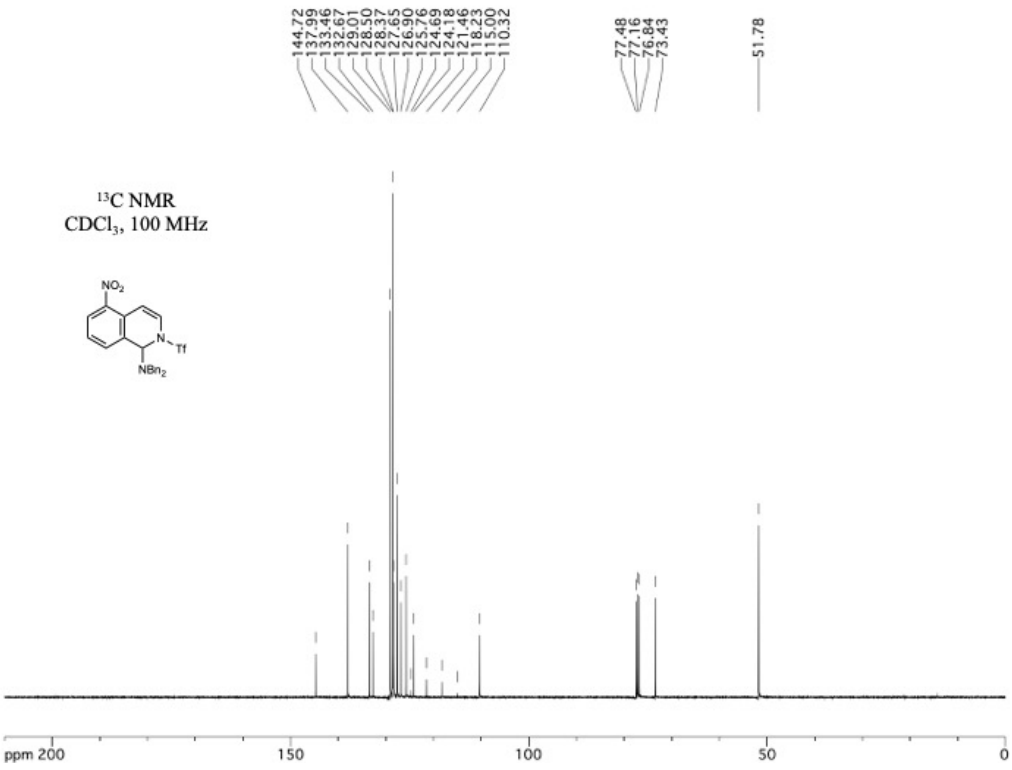
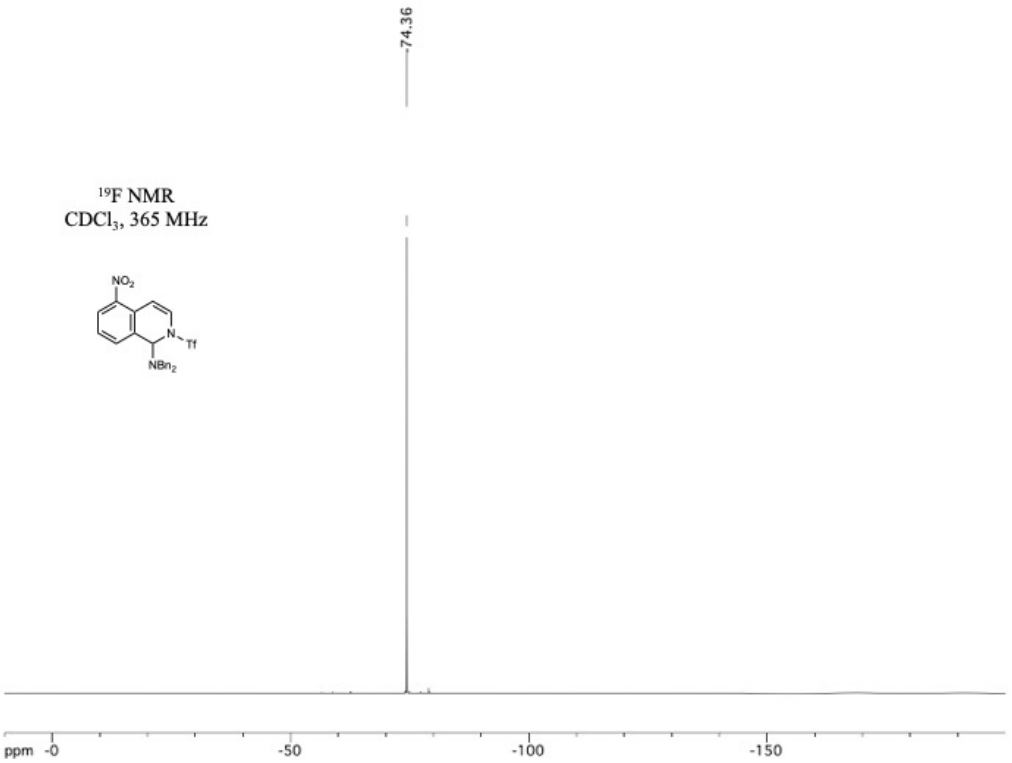
19F NMR
CDCl3, 365 MHz
Ph
TfN
NBn2
ppm -0
-50
-100
-150

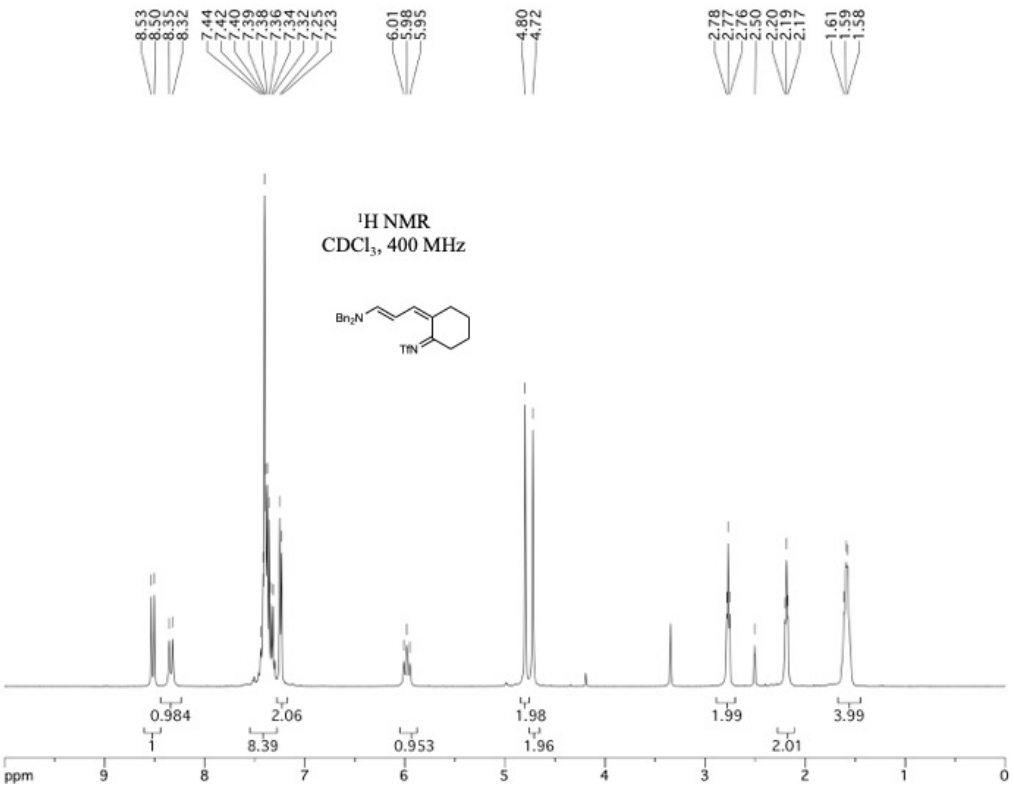

8.21
7.92
7.89
7.68
7.65
7.43
7.42
7.40
7.38
7.35
7.32
7.31
7.29
7.27
7.10
7.08
7.04
7.03
7.02
5.76
5.73
5.70
4.71
4.40
1.94
1H NMR
CD3CN, 400 MHz
TfN
NBn2
Ph
1.02
11
0.921
1.84
1
1.01
3.85
2.05
ppm
9
8
7
6
5
4
3
2
1
0

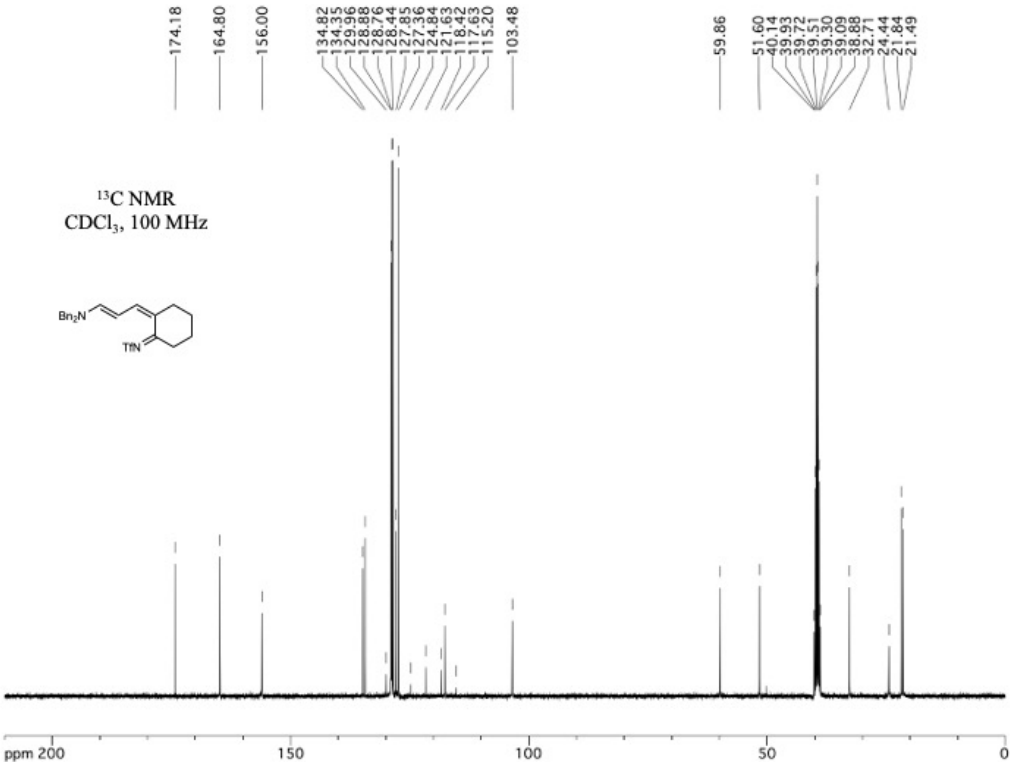

171.69
167.27
163.39
135.51
135.46
135.25
130.85
130.04
129.87
129.70
129.48
129.28
128.99
128.30
128.23
128.14
126.55
126.01
122.80
119.59
118.28
116.38
104.89
62.12
53.44
1.94
1.73
1.53
1.32
1.11
0.91
0.70
13C NMR
CD3CN, 100 MHz
TfN
NBn2
Ph
ppm 200
150
100
50
0


79.16
19F NMR
CD3CN, 365 MHz
TfN
NBn2
Ph
ppm -0
-50
-100
-150
8.10
8.08
7.56
7.54
7.52
7.48
7.47
7.36
7.34
7.33
7.30
7.28
7.26
7.16
7.14
7.06
7.04
6.02
3.79
3.76
3.72
3.69
1H NMR
CDCl3, 400 MHz
NO2
N
Tf
NBn2
1.11
10.3
1.04
4.08
1
1.13
1.02
0.998
ppm 9 8 7 6 5 4 3 2 1 0

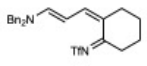

144.72
137.99
133.46
132.67
129.01
128.50
128.37
127.65
126.90
125.76
124.69
124.18
121.46
118.23
115.00
110.32
77.48
77.16
76.84
73.43
51.78
^{13}C NMR
$CDCl_3$, 100 MHz
NO_2
Tf
NBn_2
ppm 200
150
100
50
0


-74.36
^{19}F NMR
$CDCl_3$, 365 MHz
NO_2
Tf
NBn_2
ppm -0
-50
-100
-150

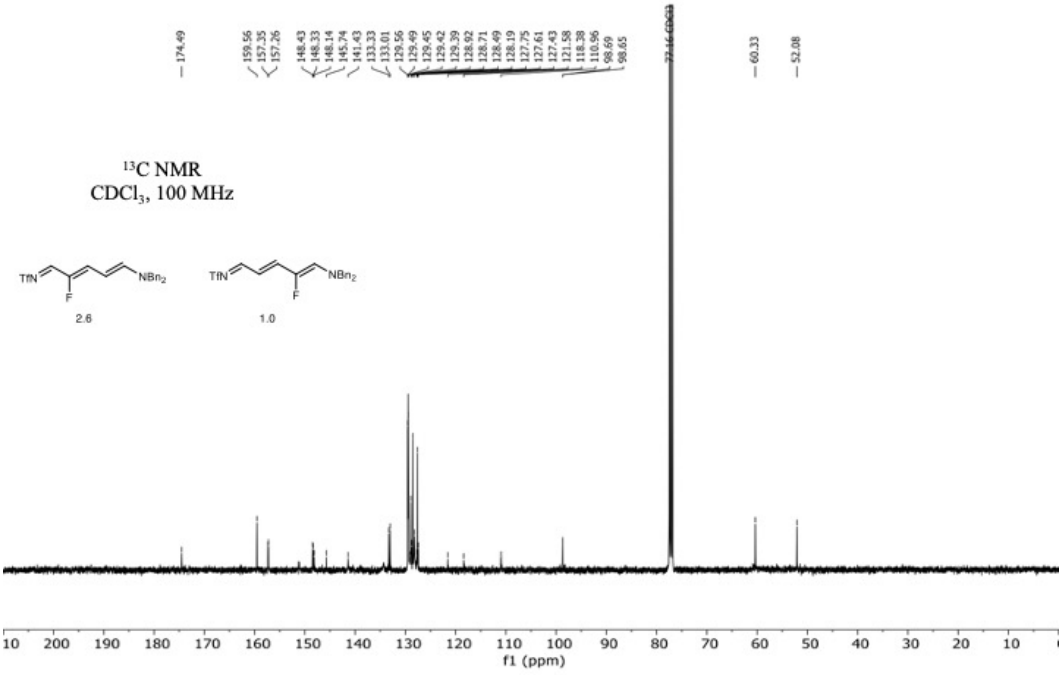

8.53
8.50
8.35
8.32
7.44
7.42
7.40
7.39
7.38
7.36
7.34
7.32
7.25
7.23
6.01
5.98
5.95
4.80
4.72
2.78
2.77
2.76
2.50
2.20
2.19
2.17
1.61
1.59
1.58
^{1}H NMR
$CDCl_3$, 400 MHz
Bn_2N
TfN
0.984
2.06
1.98
1.99
3.99
1
8.39
0.953
1.96
2.01
ppm
9
8
7
6
5
4
3
2
1
0

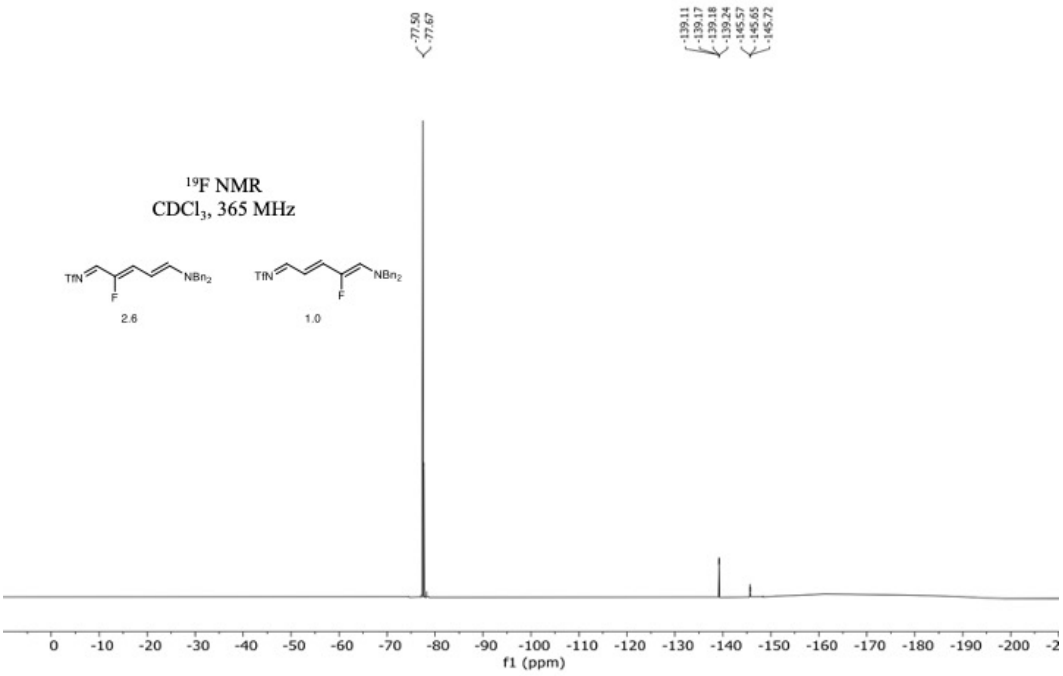

174.18
164.80
156.00
134.82
134.35
129.96
128.88
128.76
128.44
127.85
127.36
124.84
121.63
118.42
117.63
115.20
103.48
59.86
51.60
40.14
39.93
39.72
39.51
39.30
39.09
38.88
32.71
24.44
21.84
21.49
^{13}C NMR
$CDCl_3$, 100 MHz
Bn_2N
TfN
ppm 200
150
100
50
0

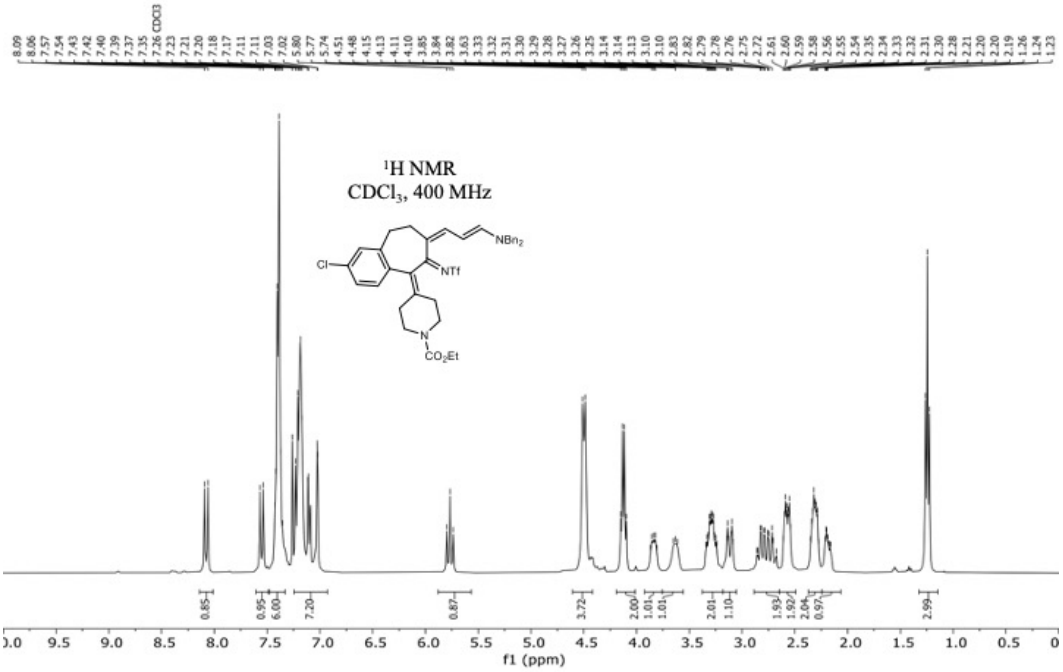
^{19}F NMR
$CDCl_3$, 365 MHz

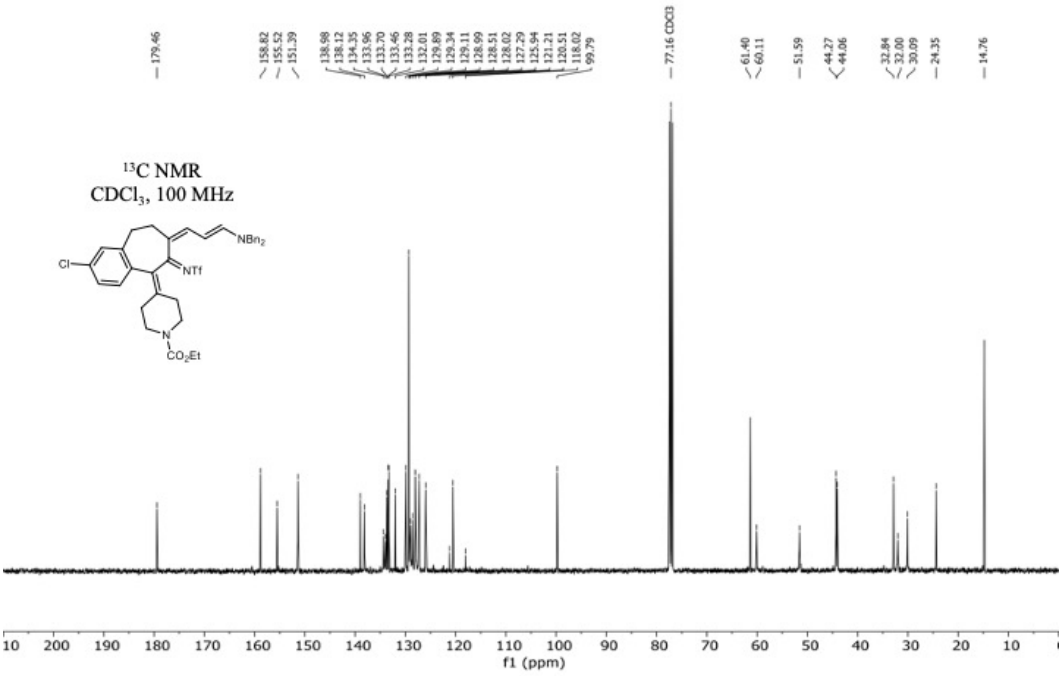


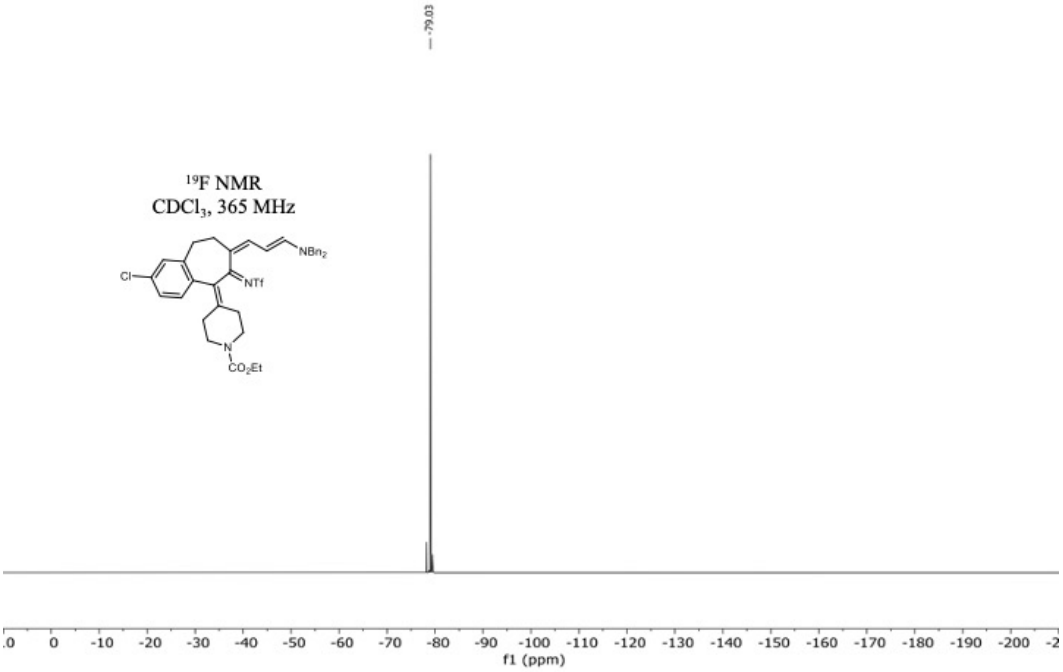
^{1}H NMR
$CDCl_3$, 400 MHz

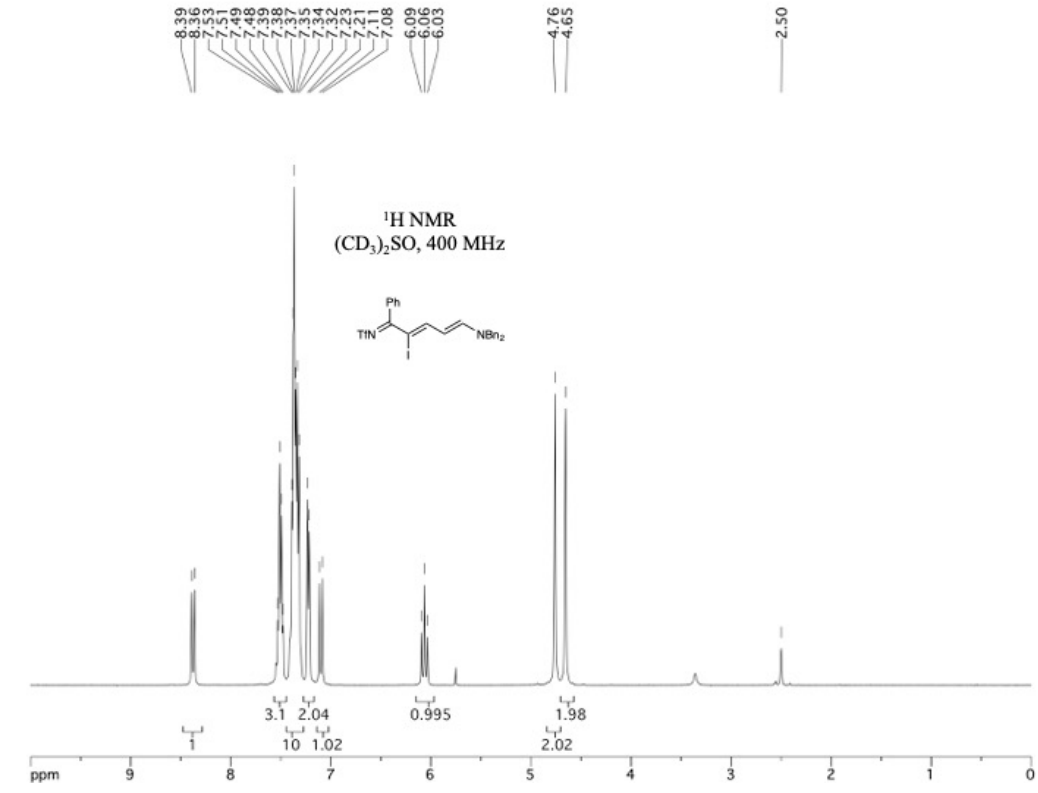

174.49
159.56
157.35
157.26
148.43
148.33
148.14
145.74
141.43
133.33
133.01
129.56
129.49
129.45
129.42
129.39
128.92
128.71
128.49
128.19
127.75
127.61
127.43
127.38
111.38
110.96
98.69
98.65
77.16
60.33
52.08
^{13}C NMR
$CDCl_3$, 100 MHz
TfN
NBn$_2$
F
2.6
1.0
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

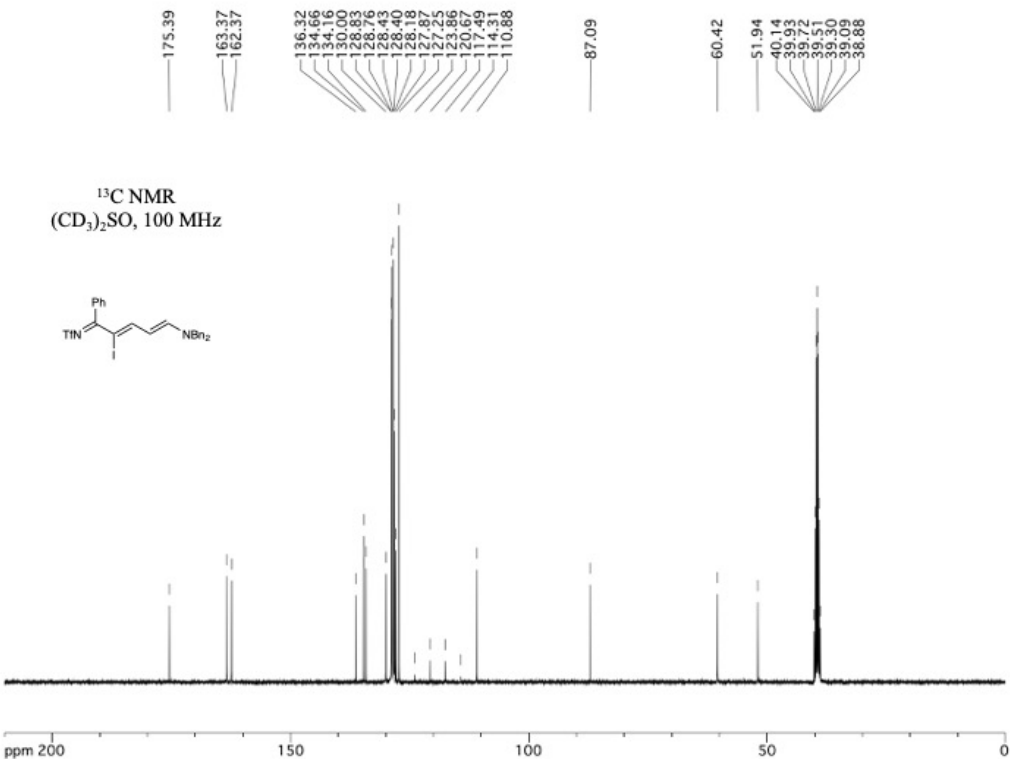

77.50
77.67
139.11
139.17
139.18
139.24
145.57
145.65
145.72
^{19}F NMR
$CDCl_3$, 365 MHz
TfN
NBn$_2$
F
2.6
1.0
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

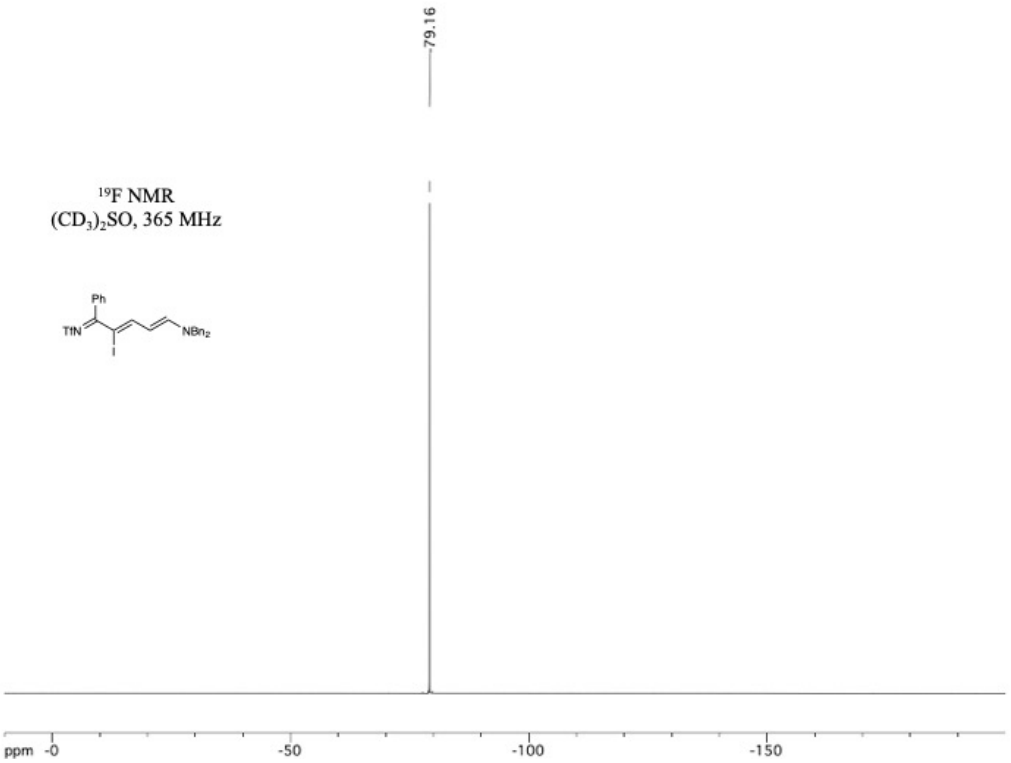

^{1}H NMR
$CDCl_3$, 400 MHz
NBn$_2$
NTf
Cl
N
CO$_2$Et
f1 (ppm)

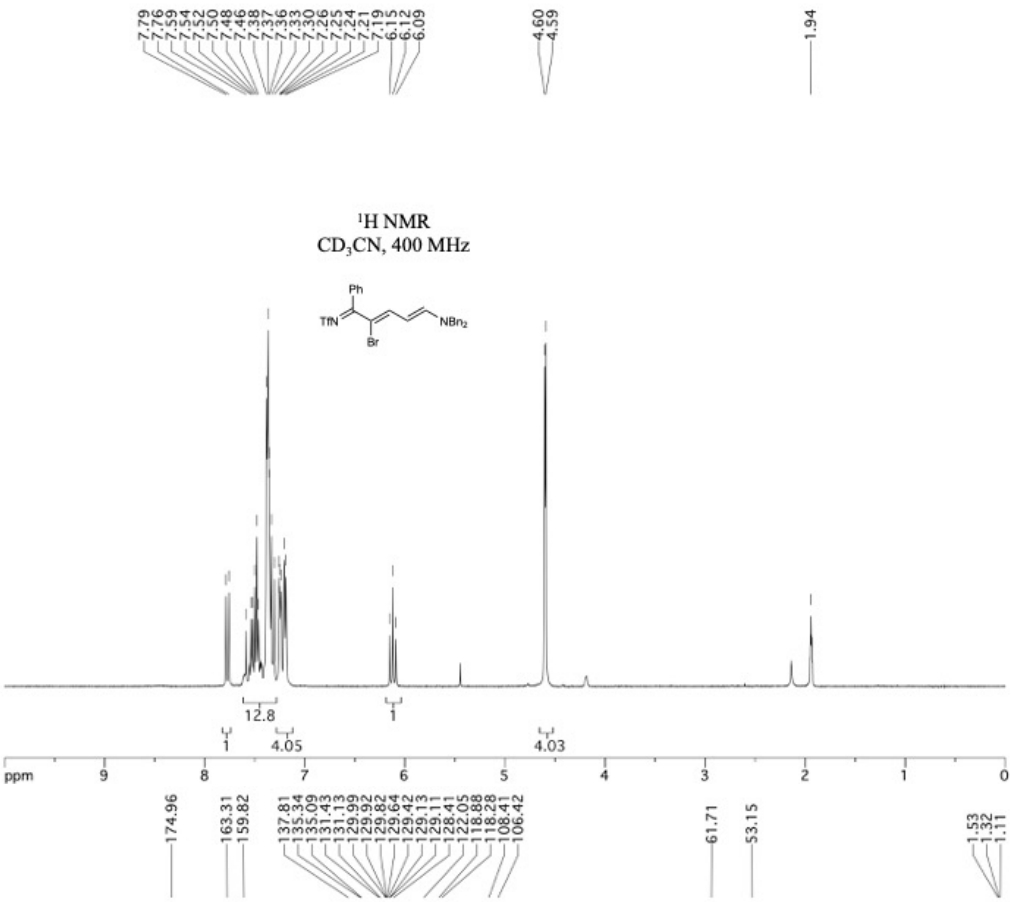

^{13}C NMR
$CDCl_3$, 100 MHz
NBn$_2$
NTf
Cl
N
CO$_2$Et
f1 (ppm)


-79.03
^{19}F NMR
$CDCl_3$, 365 MHz
Cl
NTf
NBn_2
N
CO_2Et
f1 (ppm)

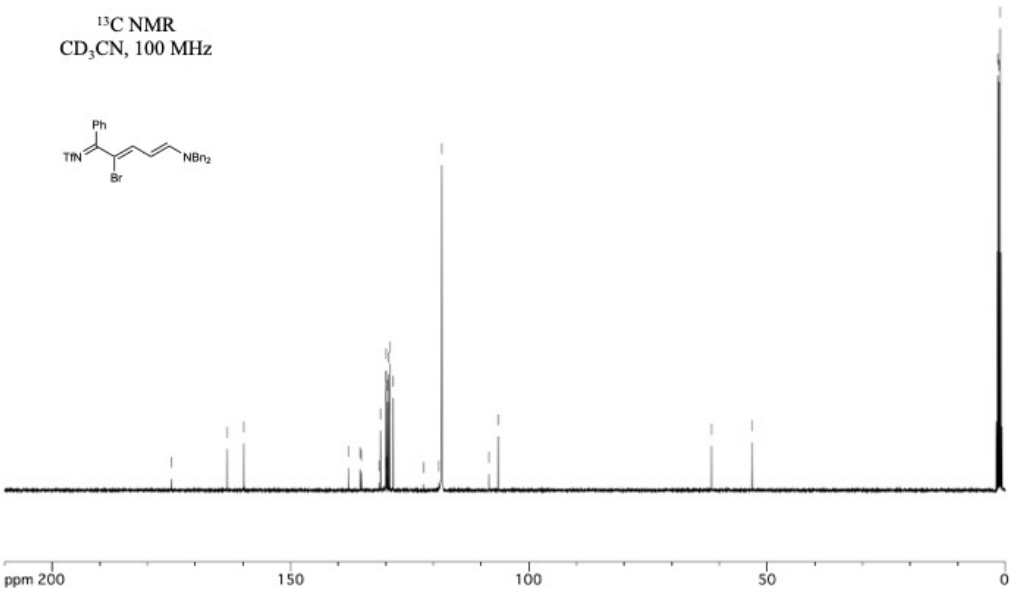

8.39
8.36
7.53
7.51
7.49
7.48
7.39
7.38
7.37
7.35
7.34
7.32
7.23
7.21
7.11
7.08
6.09
6.06
6.03
4.76
4.65
2.50
^{1}H NMR
$(CD_3)_2SO$, 400 MHz
Ph
TfN
I
NBn_2
3.1
2.04
0.995
1.98
1
10
1.02
2.02
ppm


175.39
163.37
162.37
136.32
134.66
134.16
130.00
128.83
128.76
128.43
128.40
128.18
127.87
127.25
123.86
120.67
117.49
114.31
110.88
87.09
60.42
51.94
40.14
39.93
39.72
39.51
39.30
39.09
38.88
13C NMR
(CD3)2SO, 100 MHz
Ph
TfN
I
NBn2
ppm 200
150
100
50
0

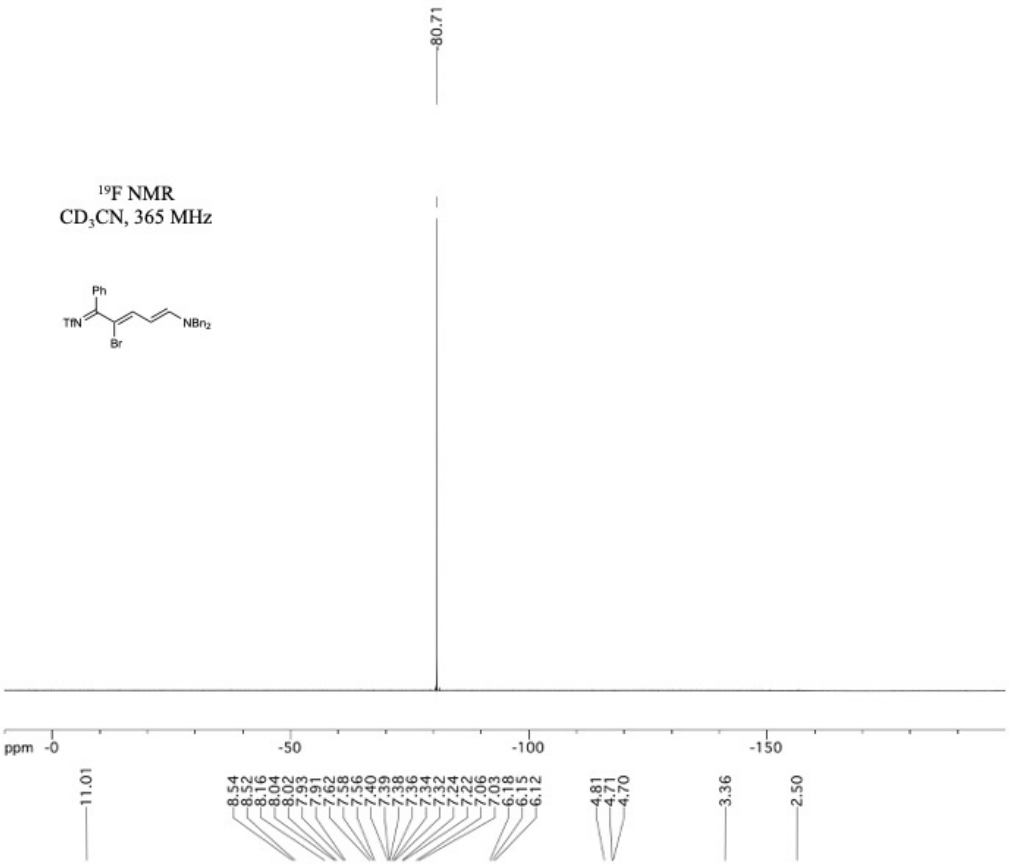

79.16
19F NMR
(CD3)2SO, 365 MHz
Ph
TfN
I
NBn2
ppm -0
-50
-100
-150



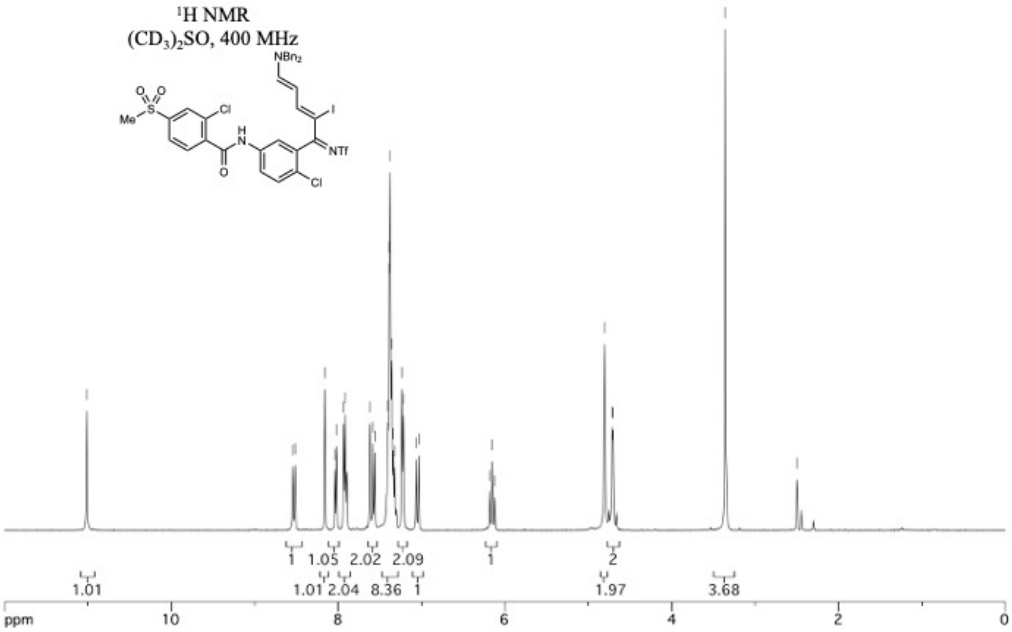
^{1}H NMR
CD_3CN, 400 MHz

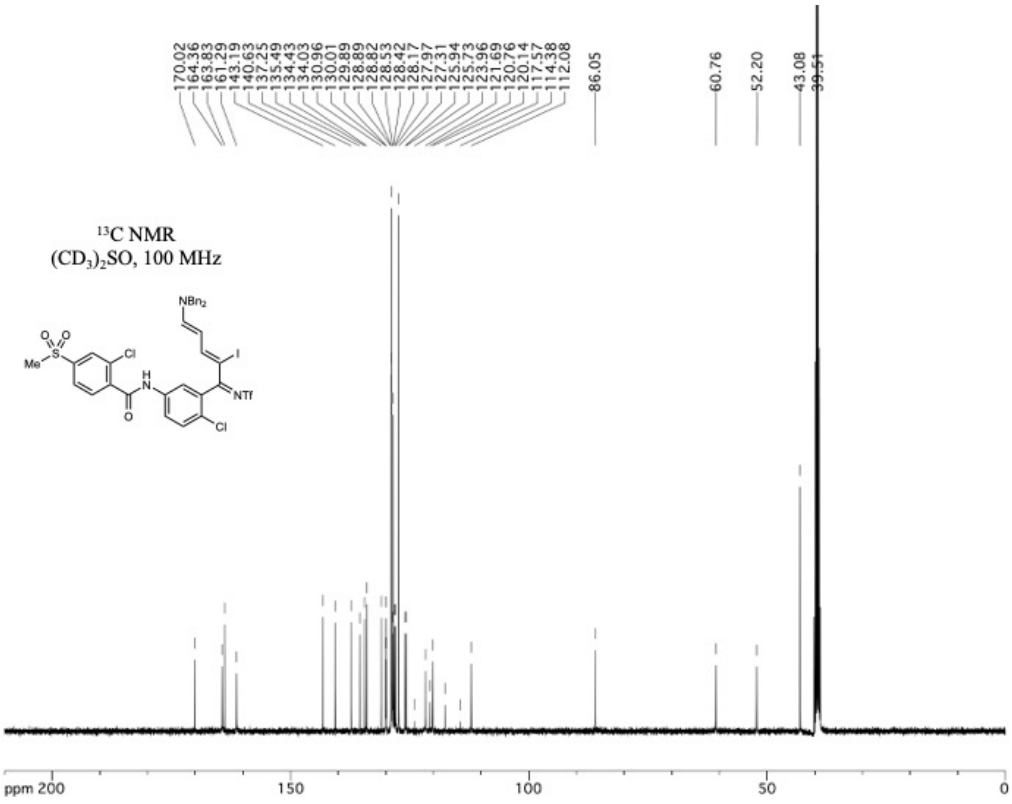


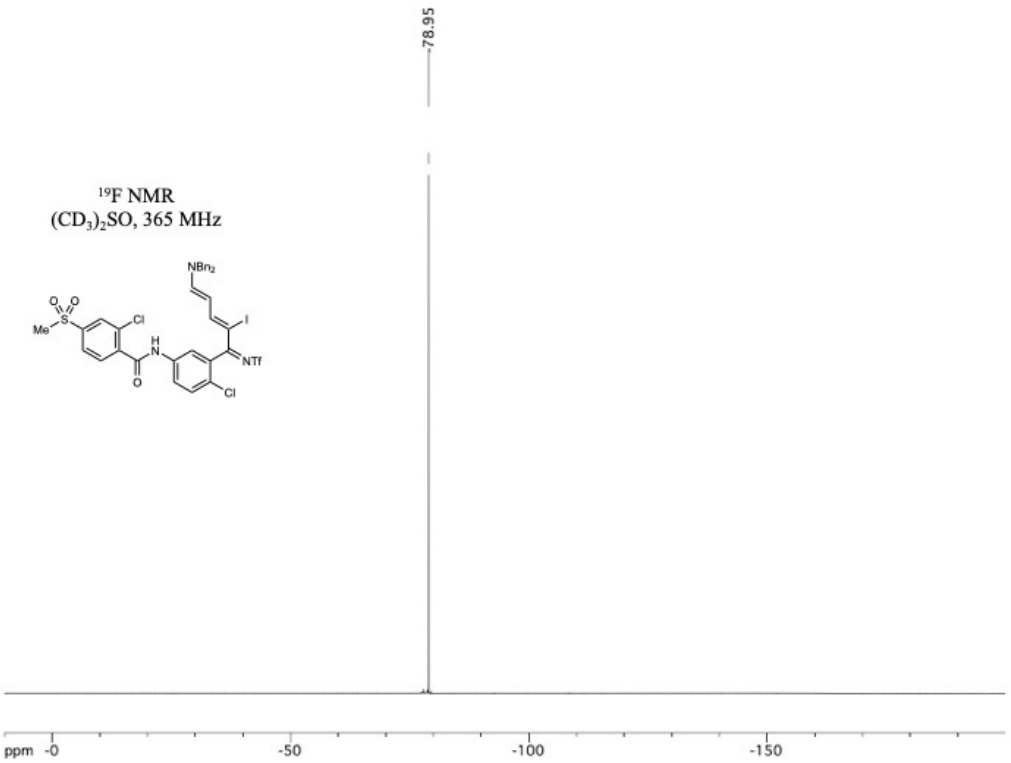
^{13}C NMR
CD_3CN, 100 MHz

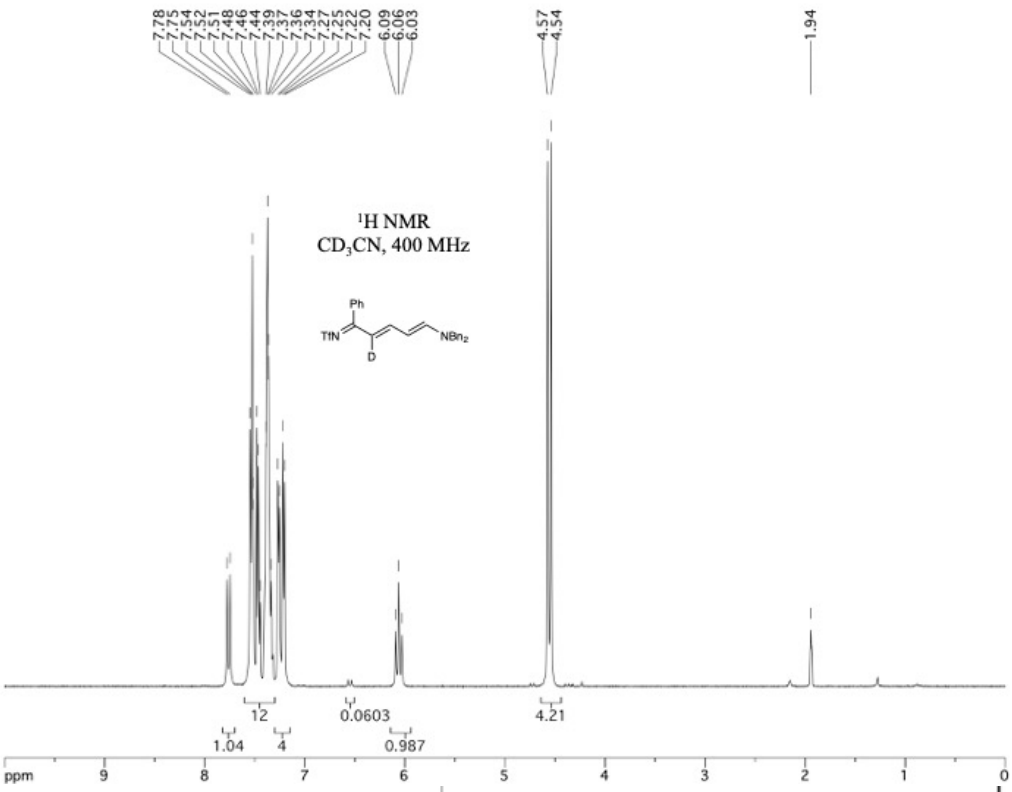

-80.71
19F NMR
CD3CN, 365 MHz
Ph
TfN
NBn2
Br
ppm -0
-50
-100
-150

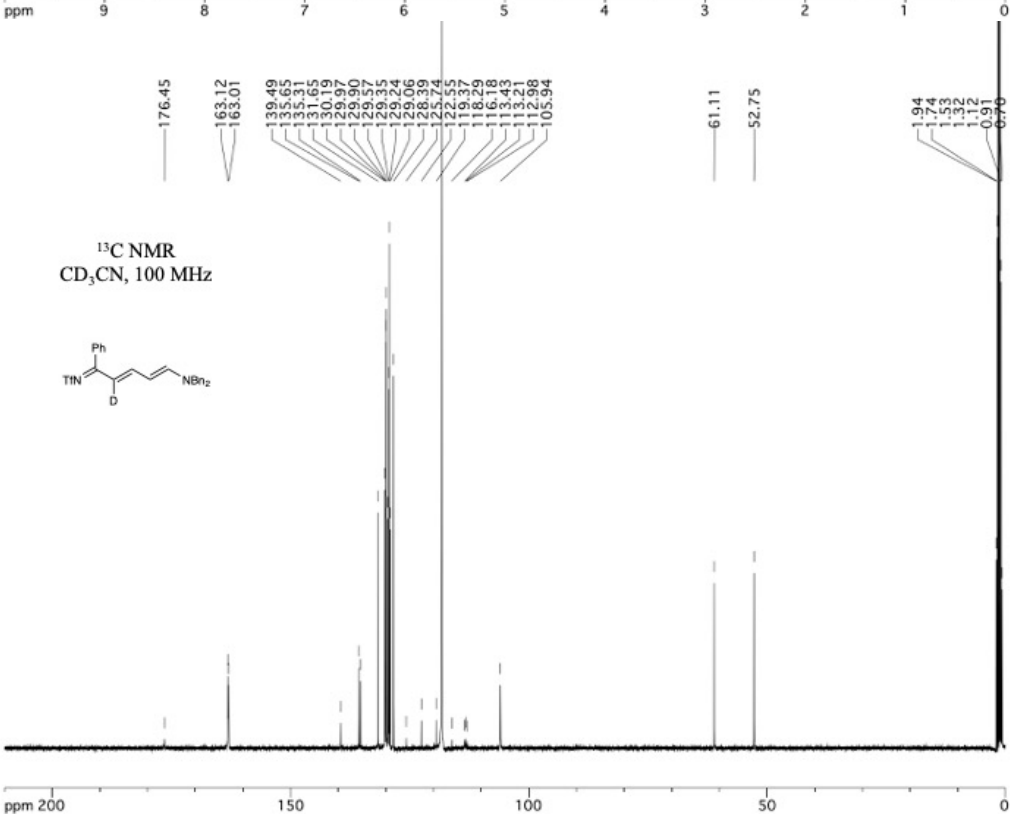
11.01
8.54
8.52
8.16
8.04
8.02
7.93
7.91
7.62
7.58
7.56
7.46
7.39
7.38
7.36
7.34
7.32
7.24
7.22
7.06
7.03
6.18
6.15
6.12
4.81
4.71
4.70
3.36
2.50

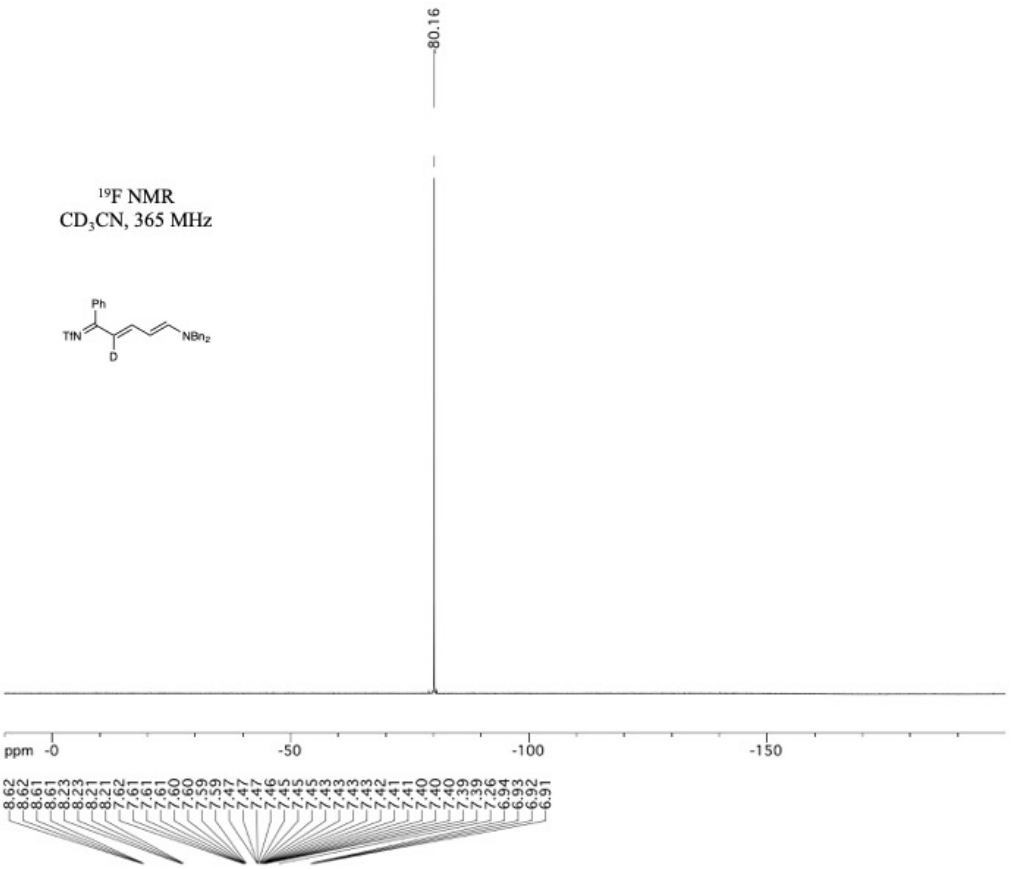

1H NMR
(CD3)2SO, 400 MHz
NBn2
Me
Cl
I
NTf
Cl
1 1.05 2.02 2.09 1 2
1.01 1.01 2.04 8.36 1 1.97 3.68
ppm 10 8 6 4 2 0

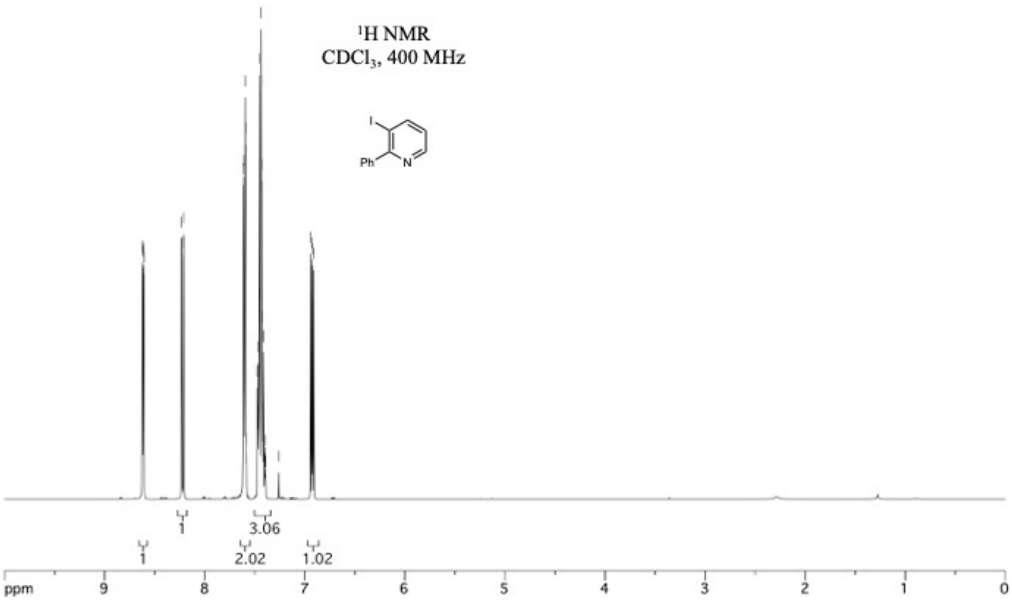

170.02
164.36
163.83
161.29
143.19
140.63
137.25
135.49
134.43
134.03
130.96
130.01
129.89
128.89
128.82
128.53
128.42
128.17
127.97
127.31
125.94
125.73
123.96
121.69
120.76
120.14
117.57
114.38
112.08
86.05
60.76
52.20
43.08
39.51
^{13}C NMR
$(CD_3)_2SO$, 100 MHz
NBn2
Me
Cl
I
NTf
Cl
ppm 200
150
100
50
0

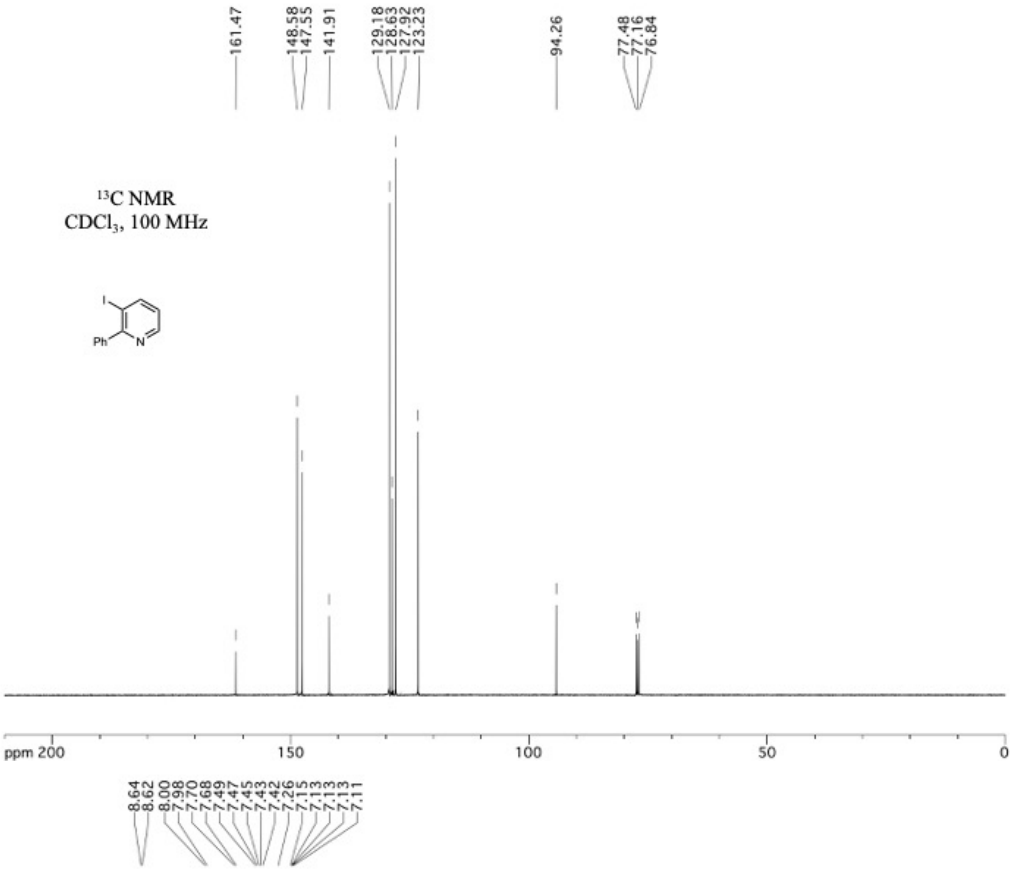

78.95
^{19}F NMR
$(CD_3)_2SO$, 365 MHz
NBn2
Me
Cl
I
NTf
Cl
ppm -0
-50
-100
-150

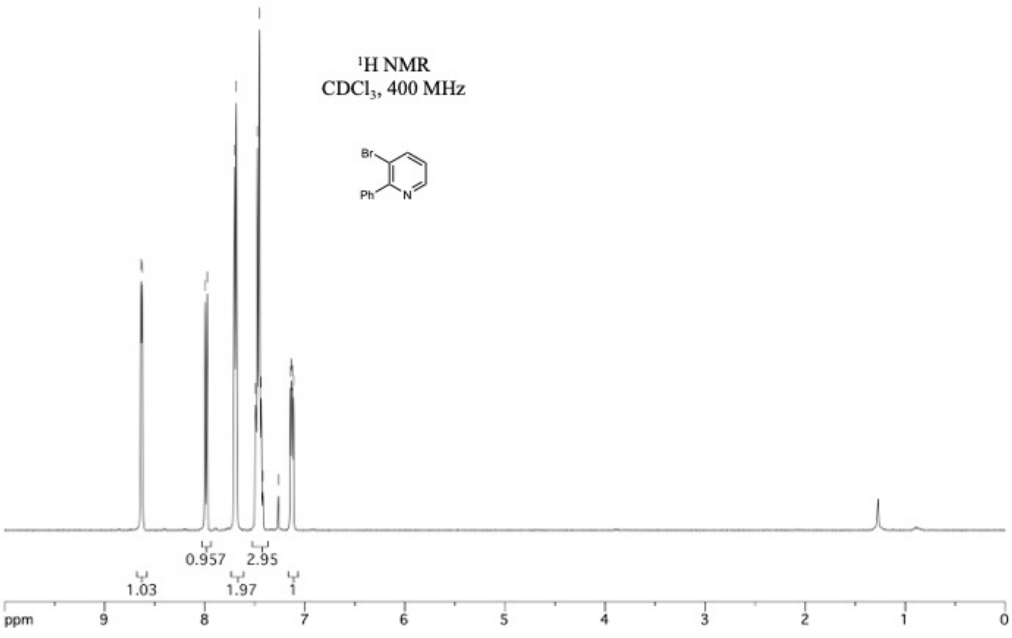

7.78
7.75
7.54
7.52
7.51
7.48
7.46
7.44
7.39
7.37
7.36
7.34
7.27
7.25
7.22
7.20
6.09
6.06
6.03
4.57
4.54
1.94
^{1}H NMR
CD_3CN, 400 MHz
Ph
TfN
D
NBn$_2$
12
0.0603
4.21
1.04
4
0.987
ppm

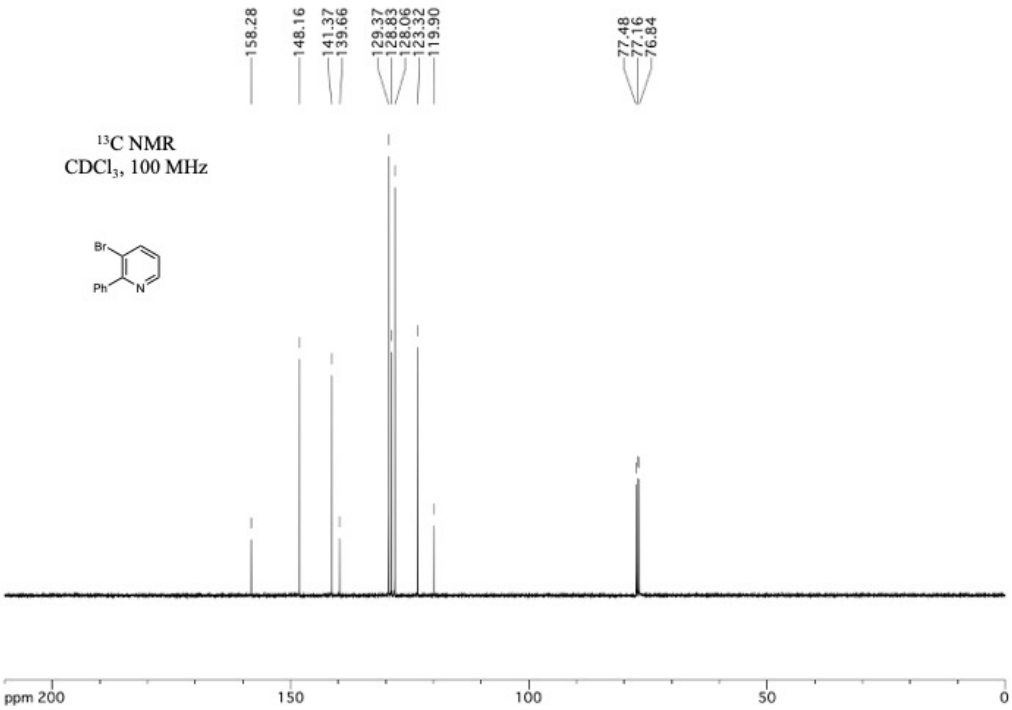

176.45
163.12
163.01
139.49
135.65
135.31
131.65
130.19
129.97
129.90
129.57
129.35
129.24
129.06
128.39
125.74
122.55
119.37
118.29
116.18
113.43
113.21
112.98
105.94
61.11
52.75
1.94
1.74
1.53
1.32
1.12
0.91
0.76
^{13}C NMR
CD_3CN, 100 MHz
Ph
TfN
D
NBn$_2$
ppm

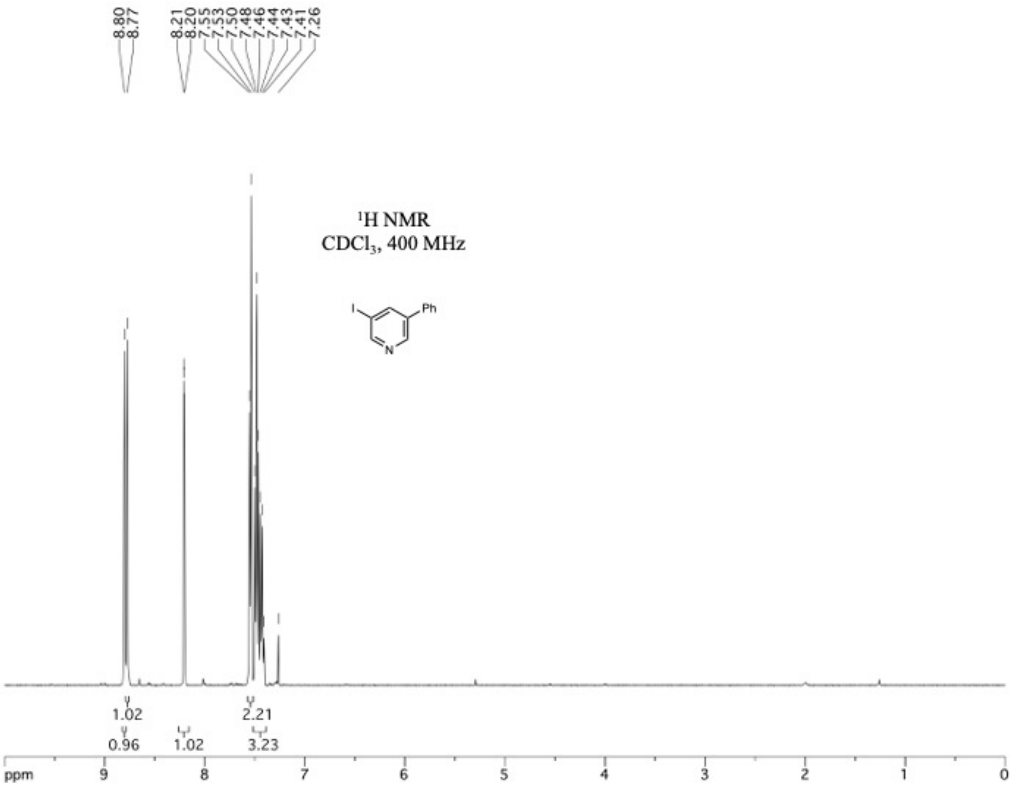

^{19}F NMR
CD_3CN, 365 MHz
Ph
TfN
D
NBn$_2$
-80.16
ppm -0
-50
-100
-150
8.62
8.62
8.61
8.61
8.23
8.23
8.21
7.62
7.61
7.61
7.60
7.60
7.59
7.59
7.47
7.47
7.46
7.45
7.45
7.45
7.43
7.43
7.43
7.42
7.41
7.40
7.40
7.40
7.39
7.26
6.94
6.93
6.92
6.91

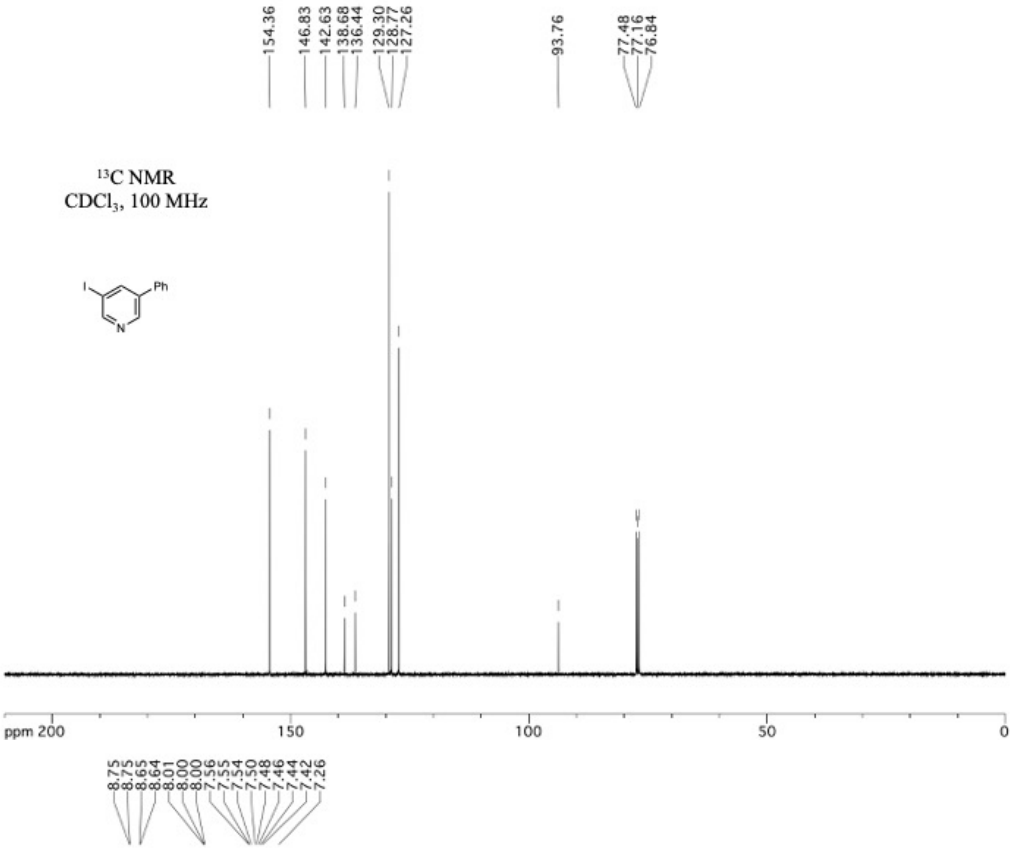

^{1}H NMR
$CDCl_3$, 400 MHz
I
Ph
N
1
3.06
1
2.02
1.02
ppm 9
8
7
6
5
4
3
2
1
0

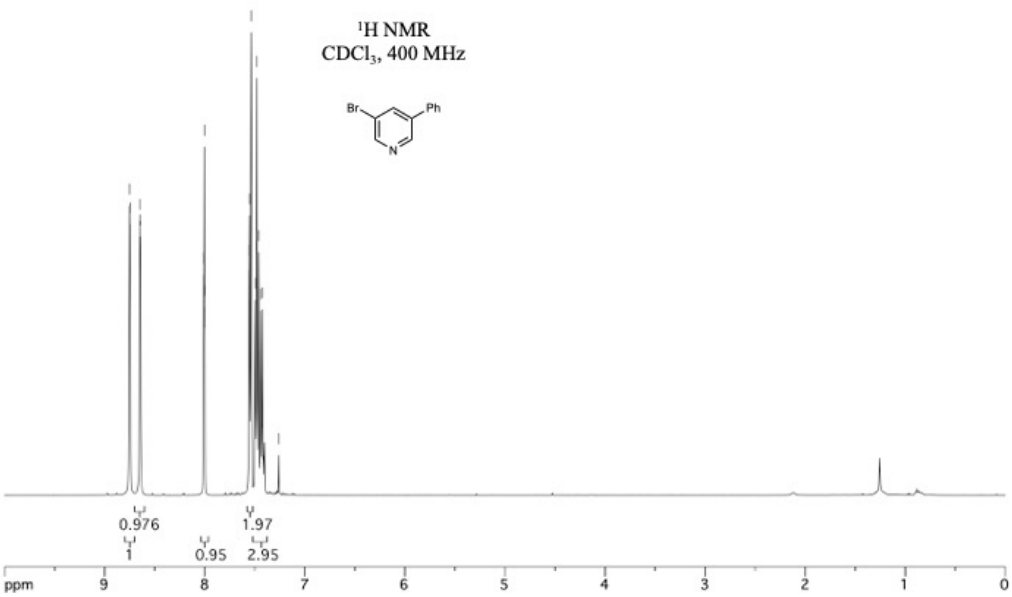

161.47
148.58
147.55
141.91
129.18
128.63
127.92
123.23
94.26
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
I
Ph
N
ppm 200
150
100
50
0

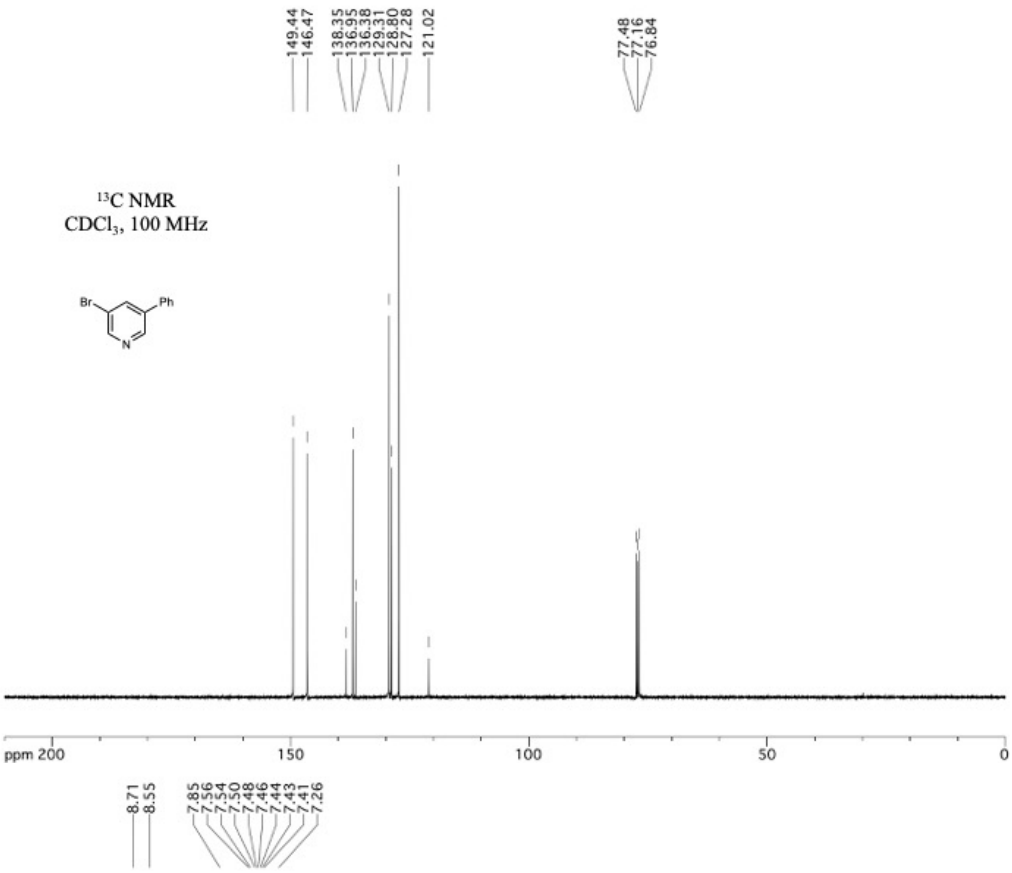

8.64
8.62
8.00
7.98
7.70
7.68
7.49
7.47
7.45
7.43
7.42
7.26
7.15
7.13
7.13
7.11
^{1}H NMR
$CDCl_3$, 400 MHz
Br
Ph
N
0.957
2.95
1.03
1.97
1
ppm
9
8
7
6
5
4
3
2
1
0

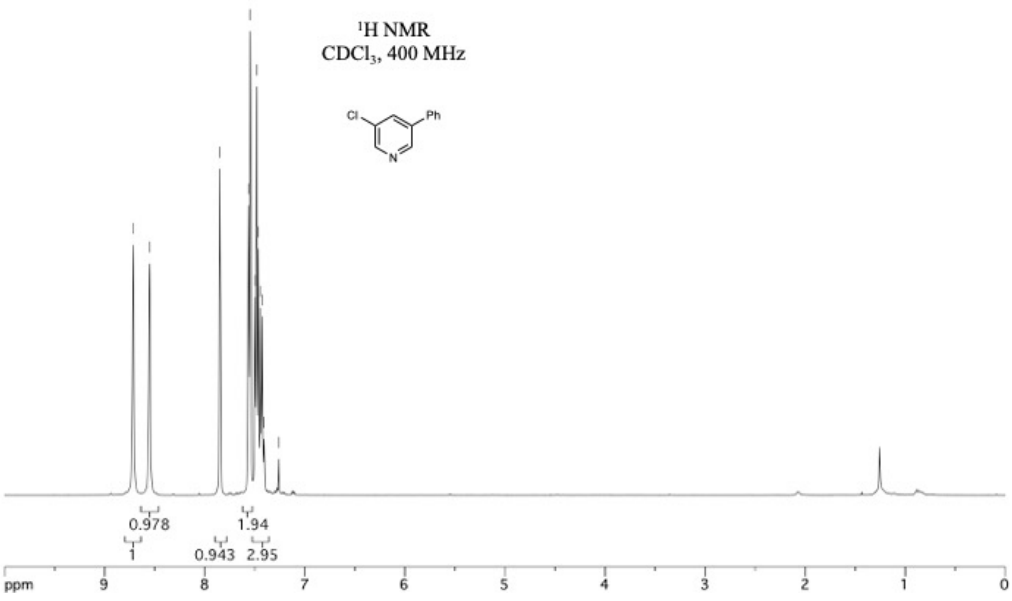

158.28
148.16
141.37
139.66
129.37
128.83
128.06
123.32
119.90
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Br
Ph
N
ppm 200
150
100
50
0

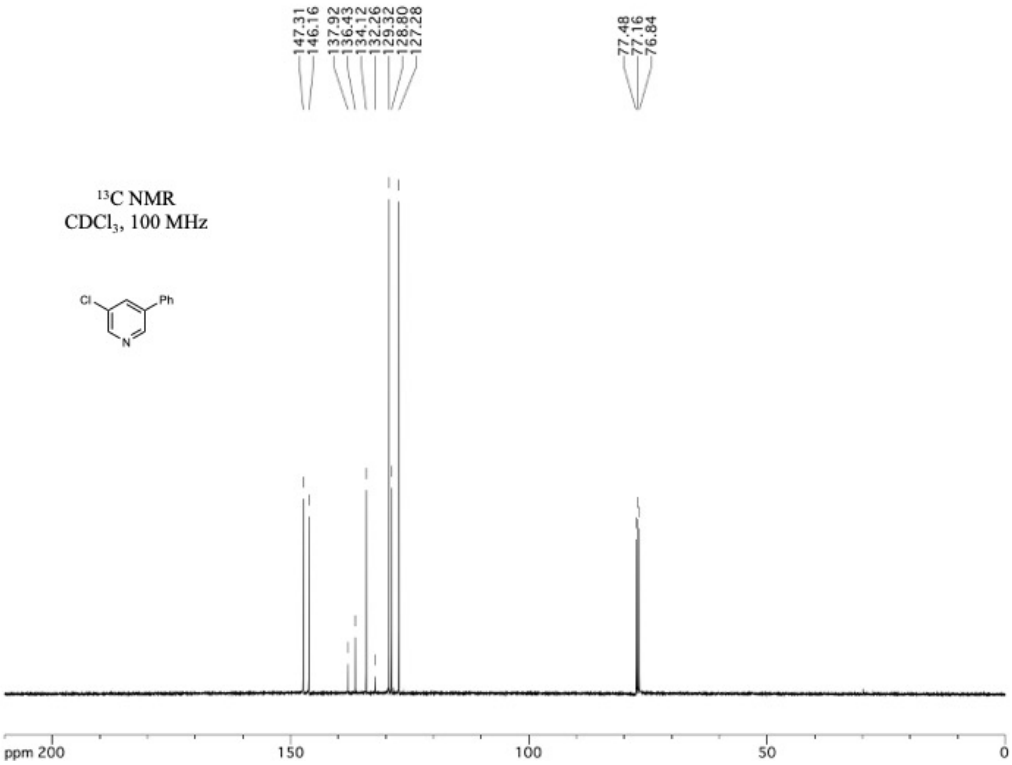

8.80
8.77
8.21
8.20
7.55
7.53
7.50
7.48
7.46
7.46
7.43
7.41
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
I
Ph
N
1.02
0.96
1.02
2.21
3.23
ppm
9
8
7
6
5
4
3
2
1
0

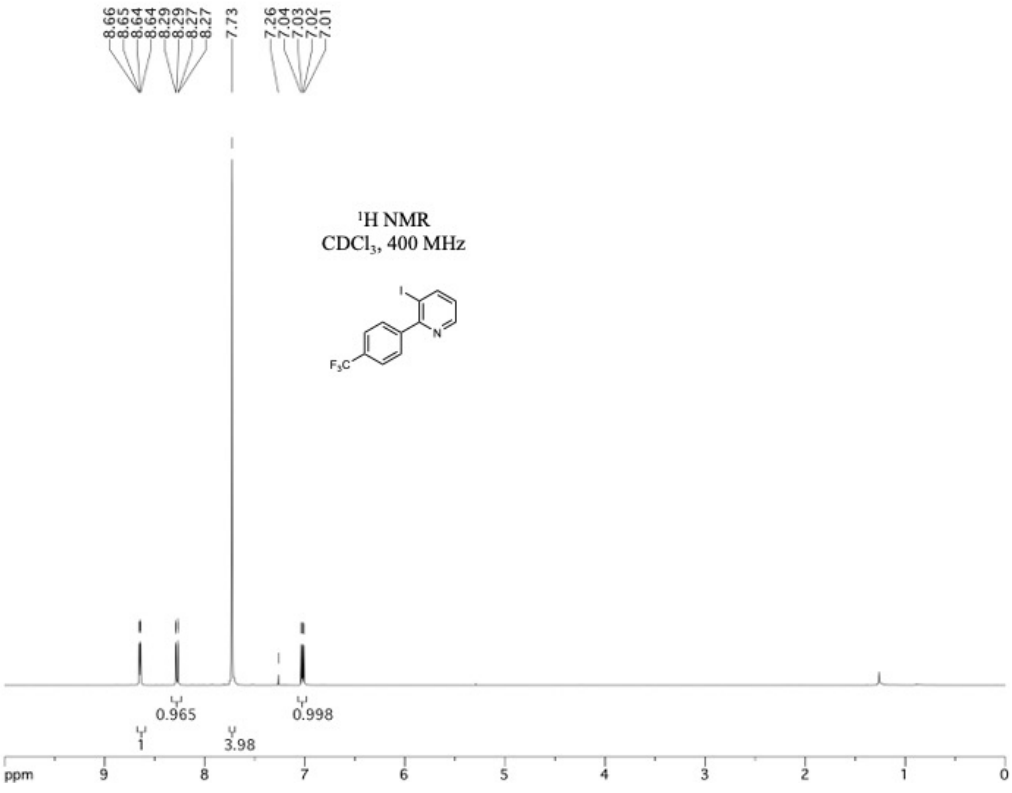

154.36
146.83
142.63
138.68
136.44
129.30
128.77
127.26
93.76
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
I
Ph
N
ppm 200
150
100
50
0
8.75
8.75
8.65
8.64
8.01
8.00
8.00
7.56
7.55
7.54
7.50
7.48
7.46
7.44
7.42
7.26

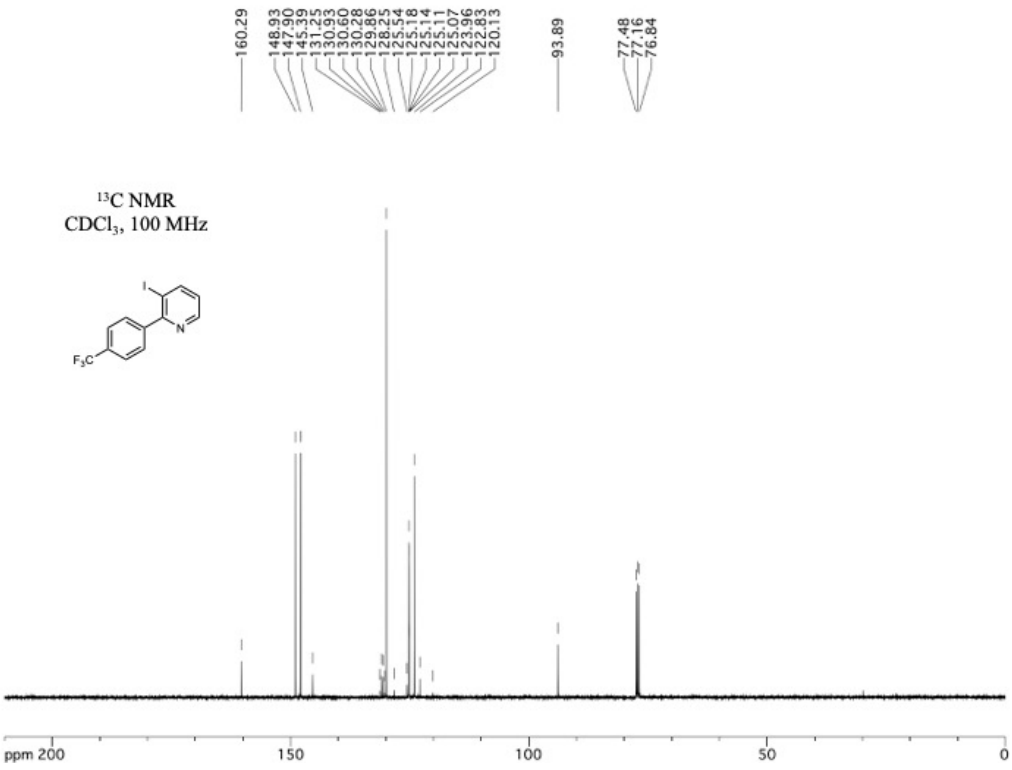

^{1}H NMR
$CDCl_3$, 400 MHz
Br
Ph
N
0.976
1
0.95
1.97
2.95
ppm
9
8
7
6
5
4
3
2
1
0

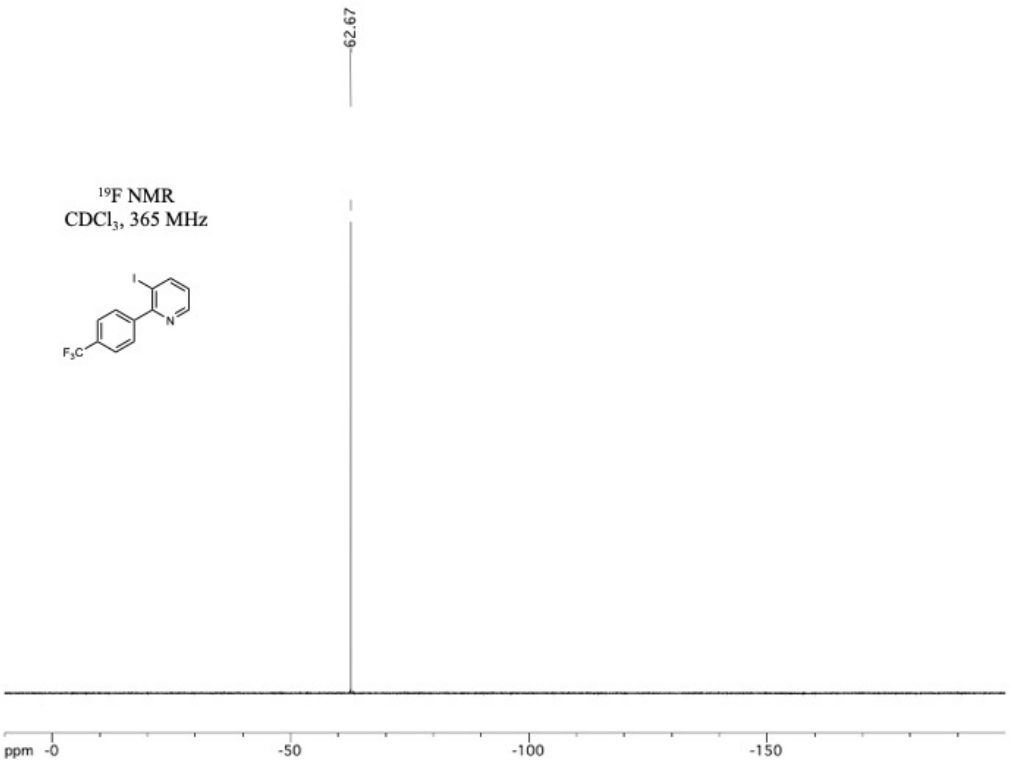

149.44
146.47
138.35
136.95
136.38
129.31
128.80
127.28
121.02
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Br
Ph
N
ppm 200
150
100
50
0

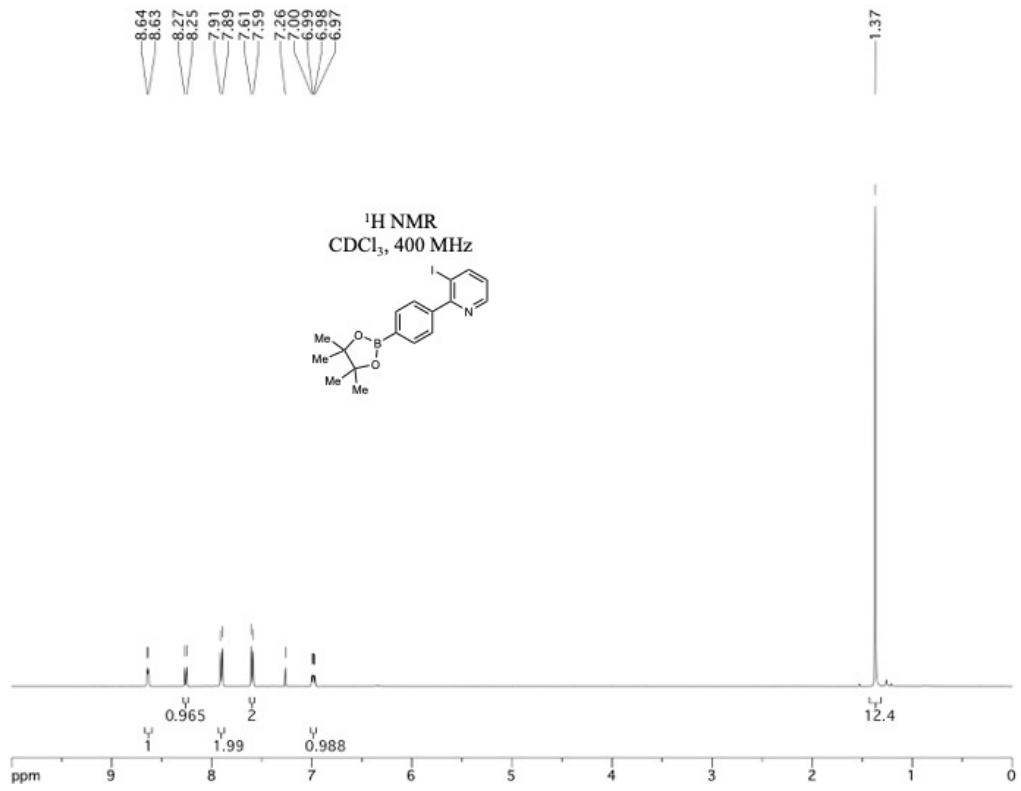

8.71
8.55
7.85
7.56
7.54
7.50
7.48
7.46
7.44
7.43
7.41
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Cl
Ph
N
0.978
1
1.94
0.943
2.95
ppm
9
8
7
6
5
4
3
2
1
0

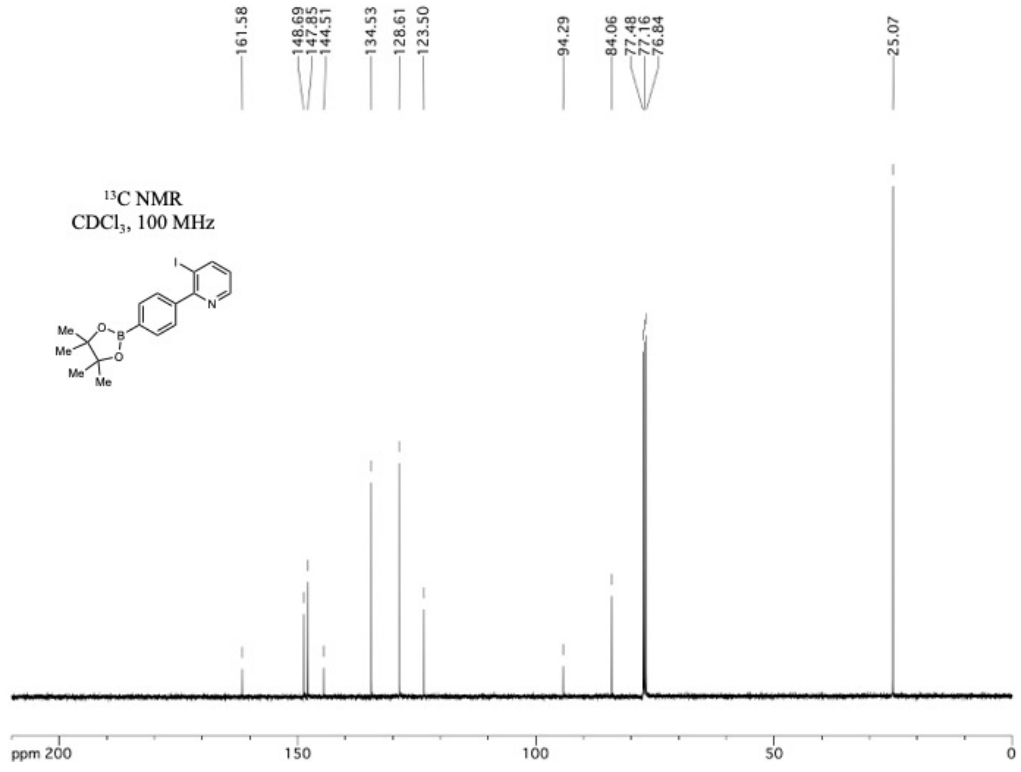

147.31
146.16
137.92
136.43
134.12
132.26
129.32
128.80
127.28
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
Cl
Ph
N
ppm 200
150
100
50
0

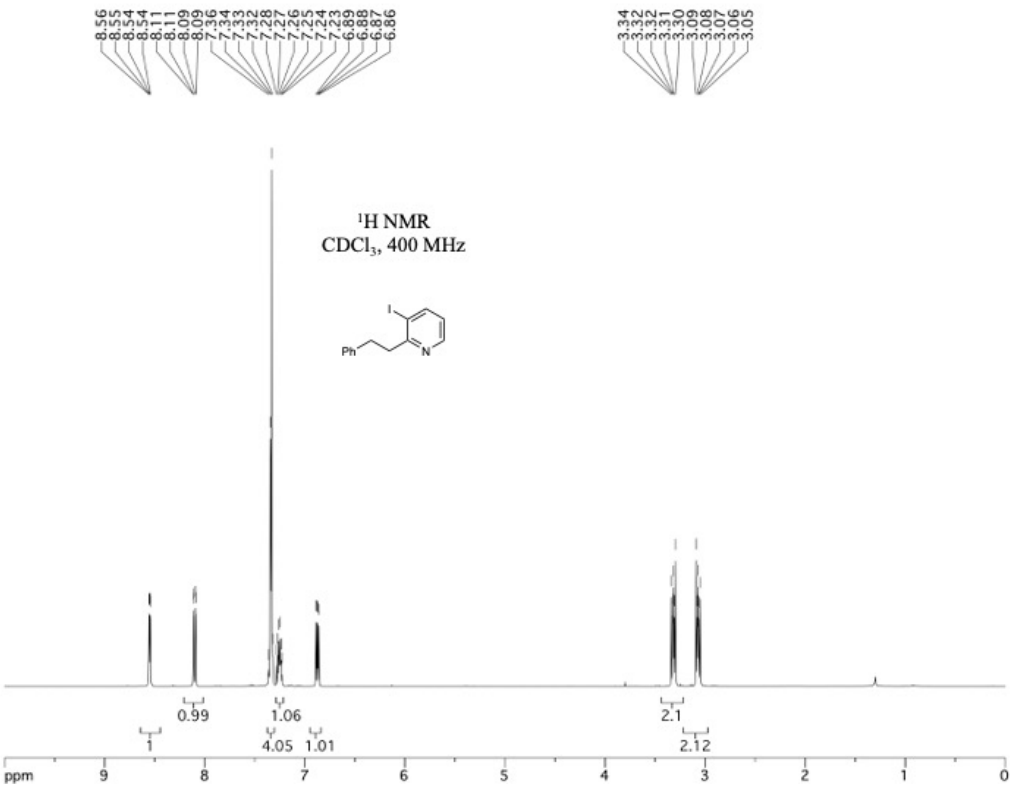

8.66
8.65
8.64
8.64
8.29
8.29
8.27
8.27
7.73
7.26
7.04
7.03
7.02
7.01
1H NMR
CDCl3, 400 MHz
I
N
F3C
0.965
0.998
1
3.98
ppm
9
8
7
6
5
4
3
2
1
0

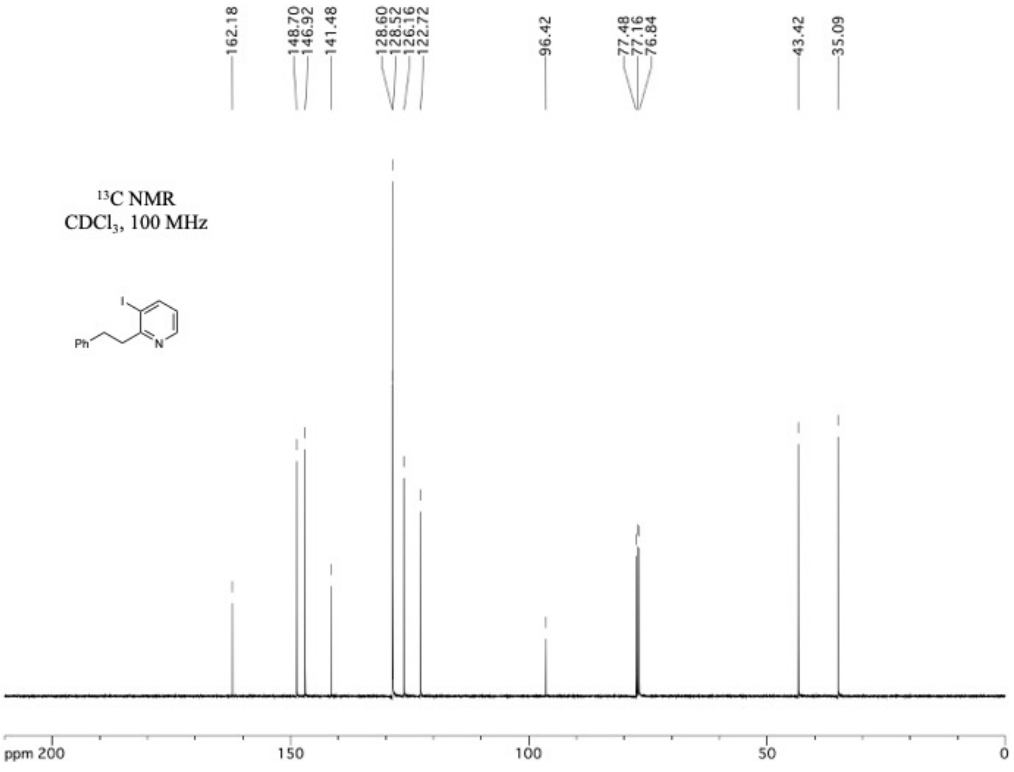

160.29
148.93
147.90
145.39
131.25
130.93
130.60
130.28
129.86
128.25
125.54
125.18
125.14
125.11
125.07
123.96
122.83
120.13
93.89
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
I
N
F3C
ppm 200
150
100
50
0

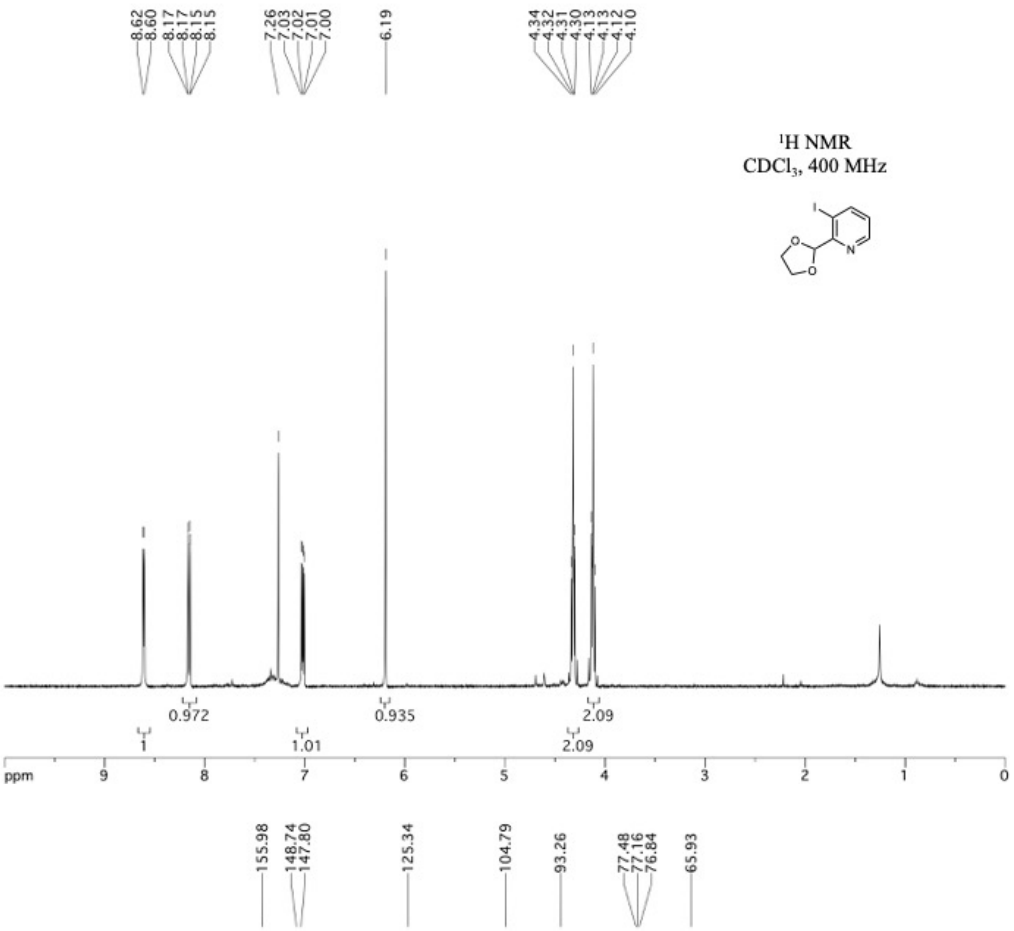

62.67
19F NMR
CDCl3, 365 MHz
I
N
F3C
ppm -0
-50
-100
-150


8.64
8.63
8.27
8.25
7.91
7.89
7.61
7.59
7.26
7.00
6.99
6.98
6.97
1.37
^{1}H NMR
$CDCl_3$, 400 MHz
0.965
2
12.4
1
1.99
0.988
ppm

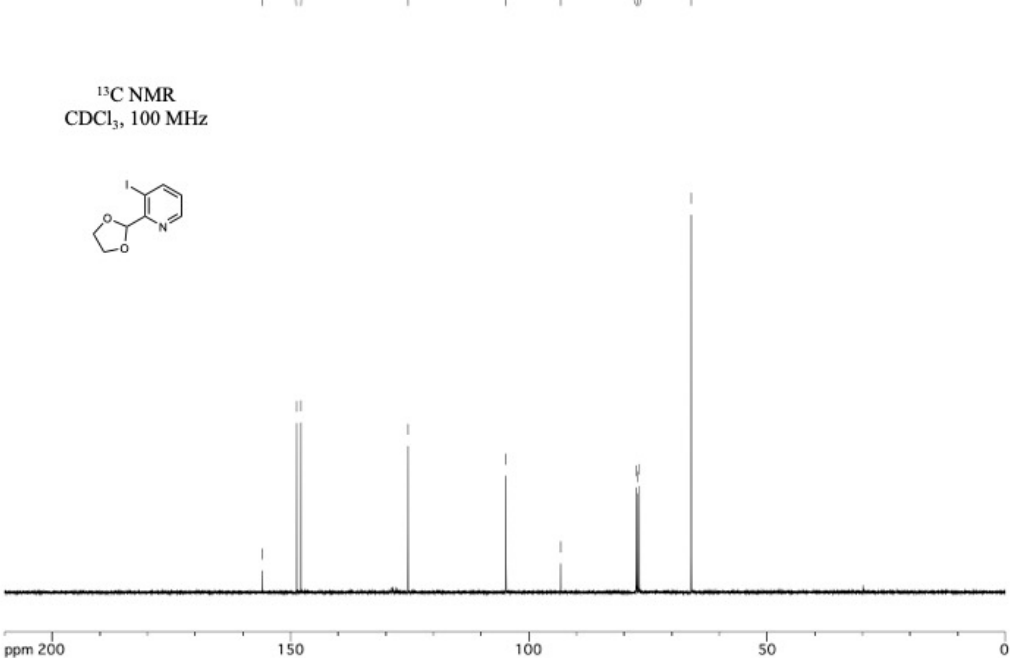

161.58
148.69
147.85
144.51
134.53
128.61
123.50
94.29
84.06
77.48
77.16
76.84
25.07
^{13}C NMR
$CDCl_3$, 100 MHz
ppm 200
150
100
50
0


8.56
8.55
8.54
8.54
8.11
8.11
8.09
8.09
7.36
7.34
7.33
7.32
7.28
7.27
7.26
7.25
7.24
7.23
6.89
6.88
6.87
6.86
3.34
3.32
3.32
3.31
3.30
3.09
3.08
3.07
3.06
3.05
^{1}H NMR
$CDCl_3$, 400 MHz
I
Ph
N
0.99
1.06
2.1
1
4.05
1.01
2.12
ppm
9
8
7
6
5
4
3
2
1
0

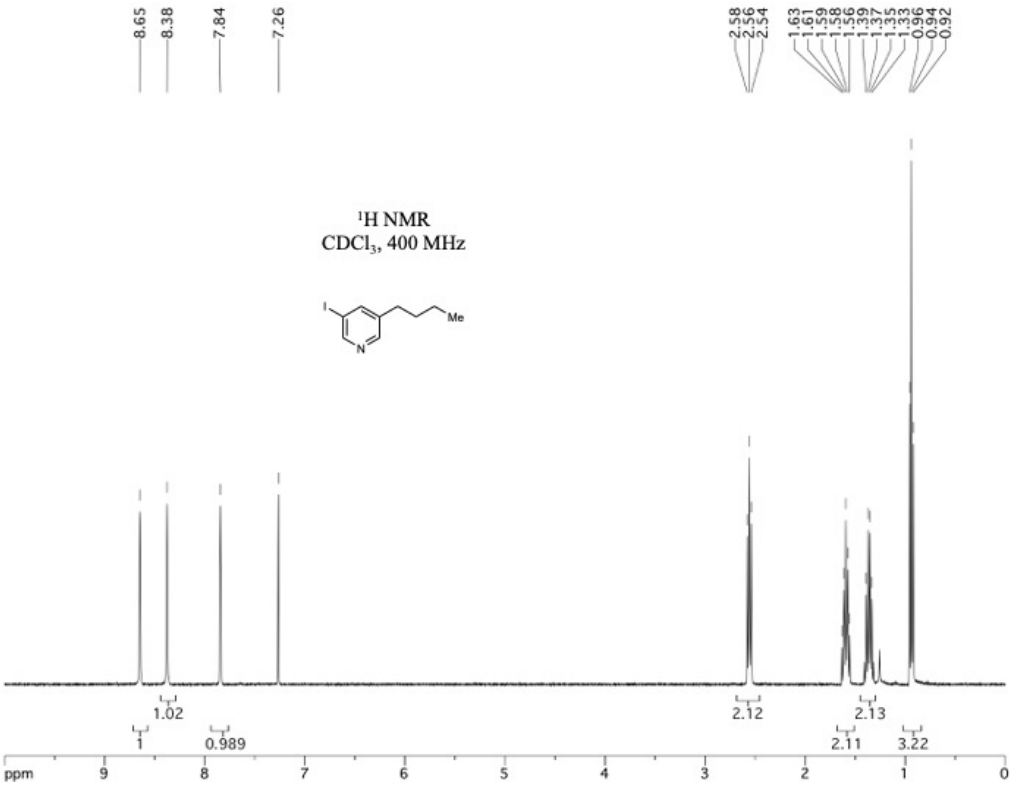

162.18
148.70
146.92
141.48
128.60
128.52
126.16
122.72
96.42
77.48
77.16
76.84
43.42
35.09
^{13}C NMR
$CDCl_3$, 100 MHz
I
Ph
N
ppm 200
150
100
50
0

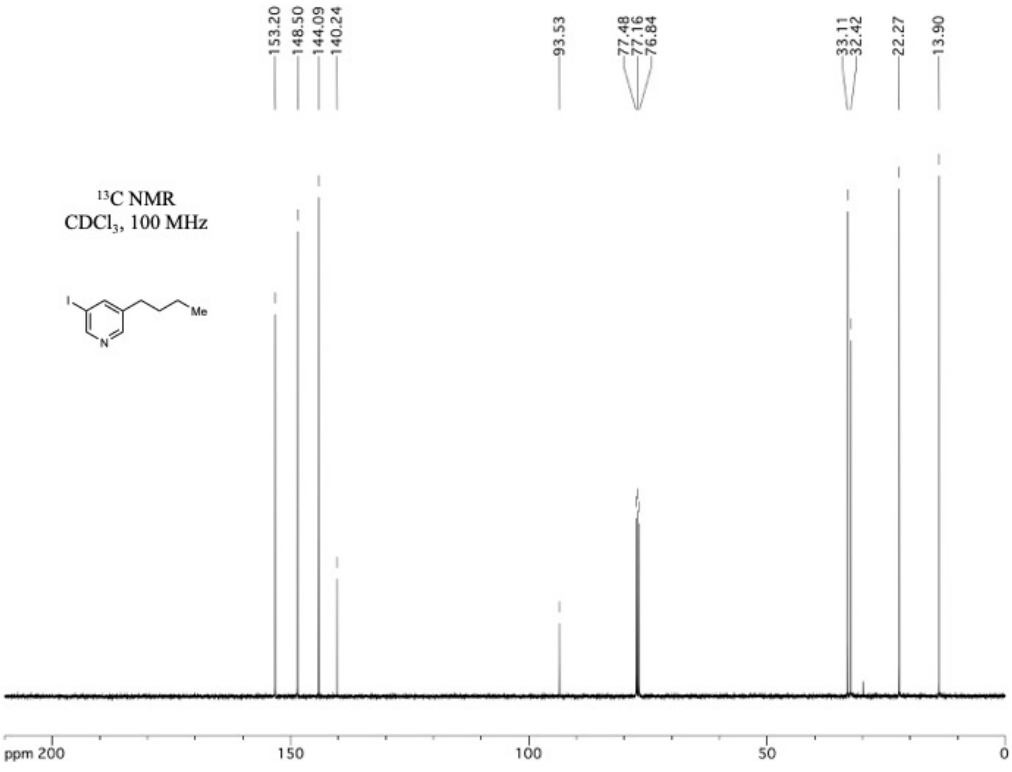


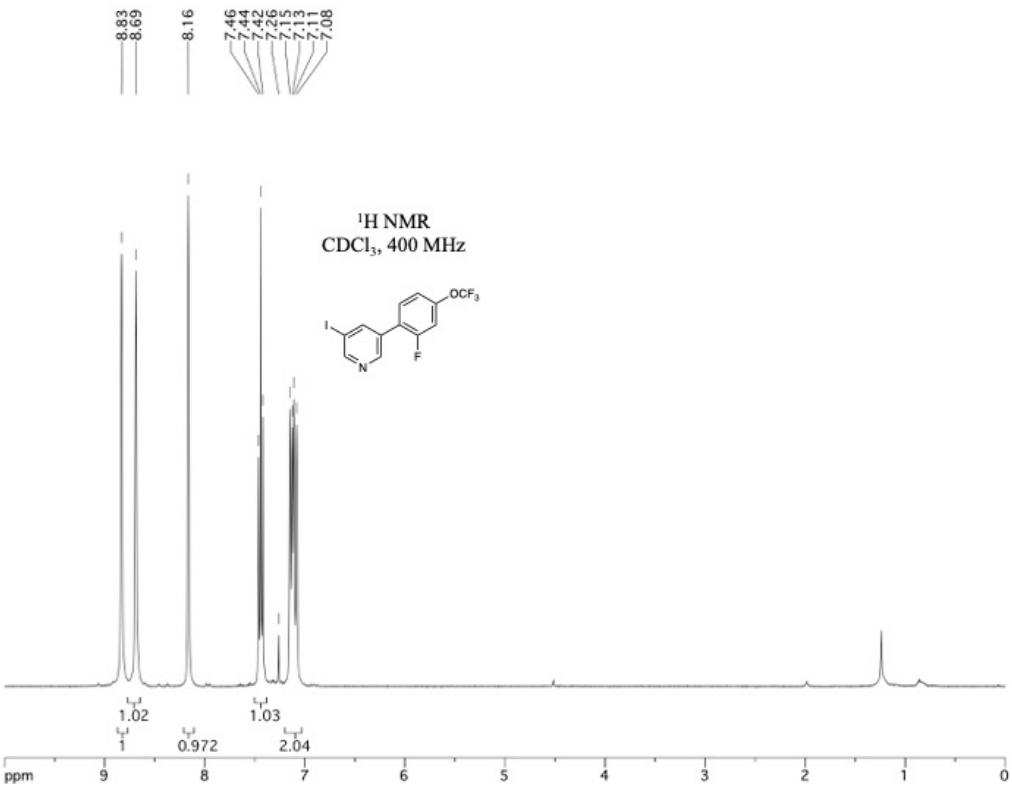
^{1}H NMR
$CDCl_3$, 400 MHz

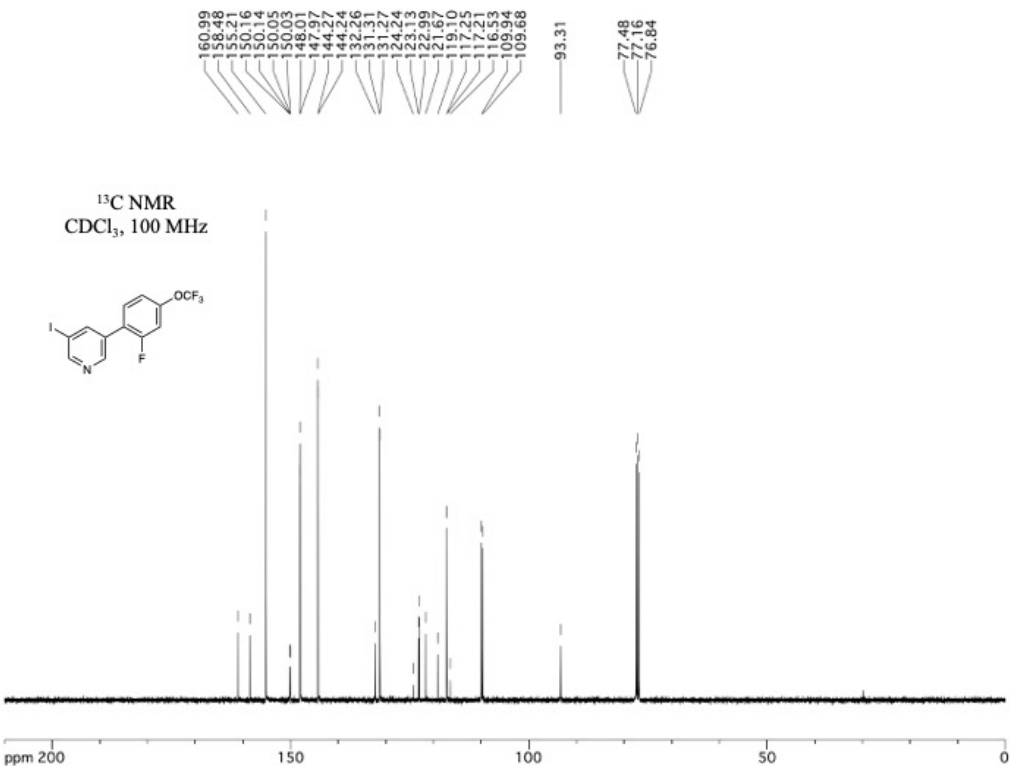


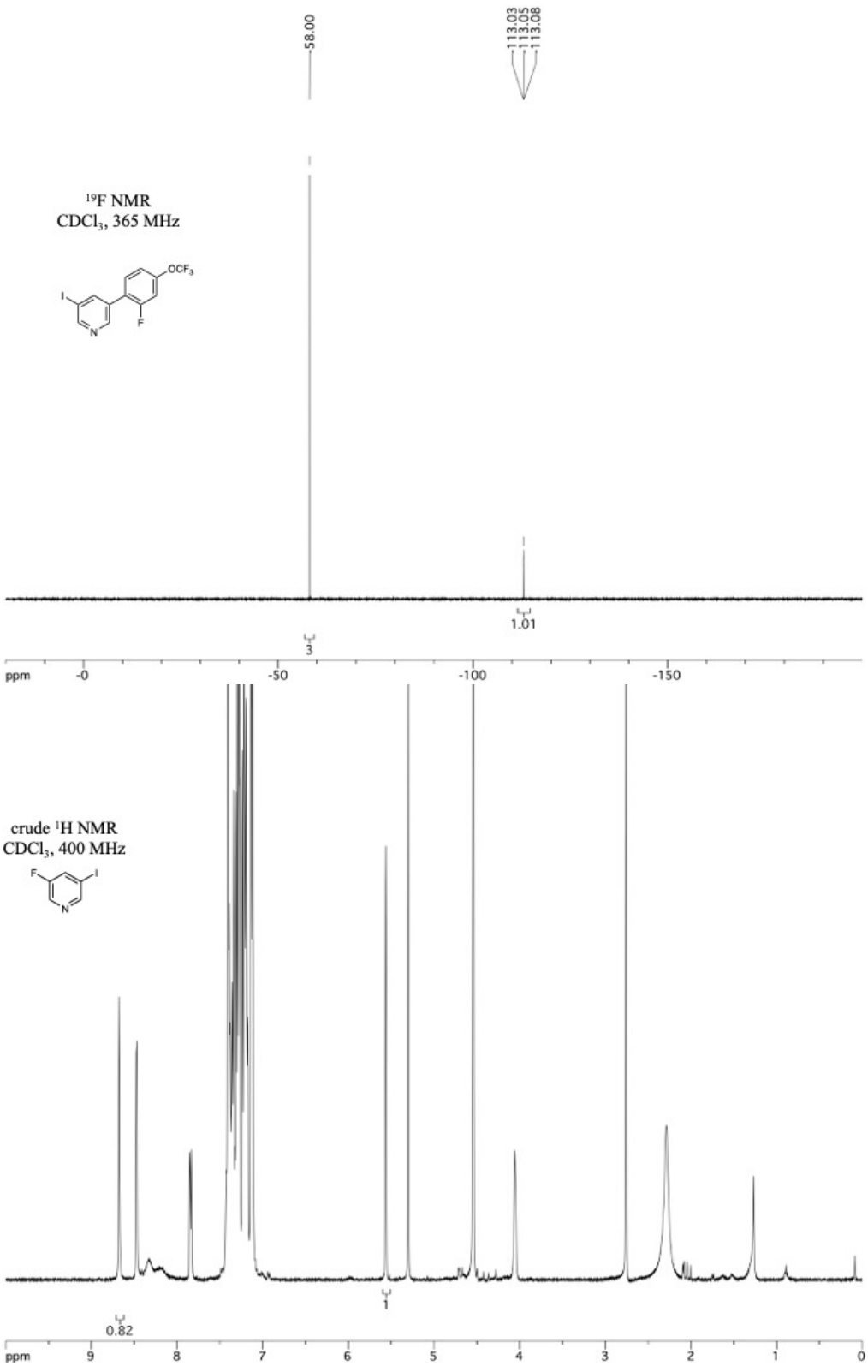
^{13}C NMR
$CDCl_3$, 100 MHz

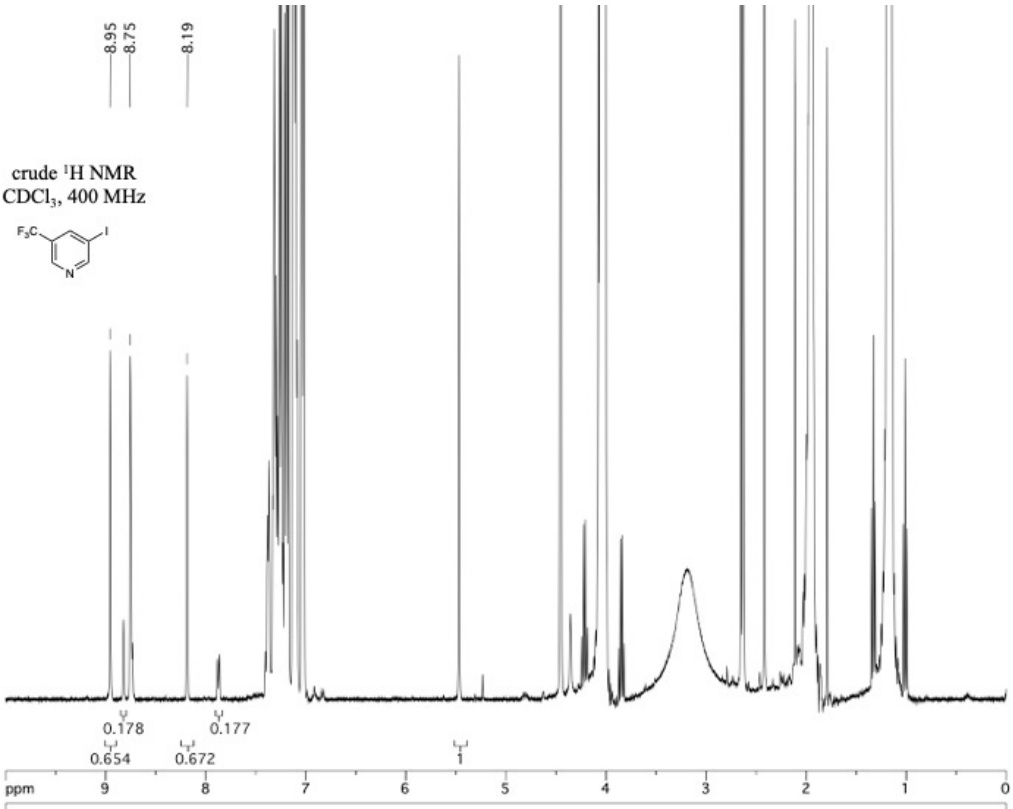

8.65
8.38
7.84
7.26
2.58
2.56
2.54
1.63
1.61
1.59
1.58
1.56
1.39
1.37
1.35
1.33
0.96
0.94
0.92
^{1}H NMR
$CDCl_3$, 400 MHz
I
Me
N
1.02
1
0.989
2.12
2.13
2.11
3.22
ppm
9
8
7
6
5
4
3
2
1
0

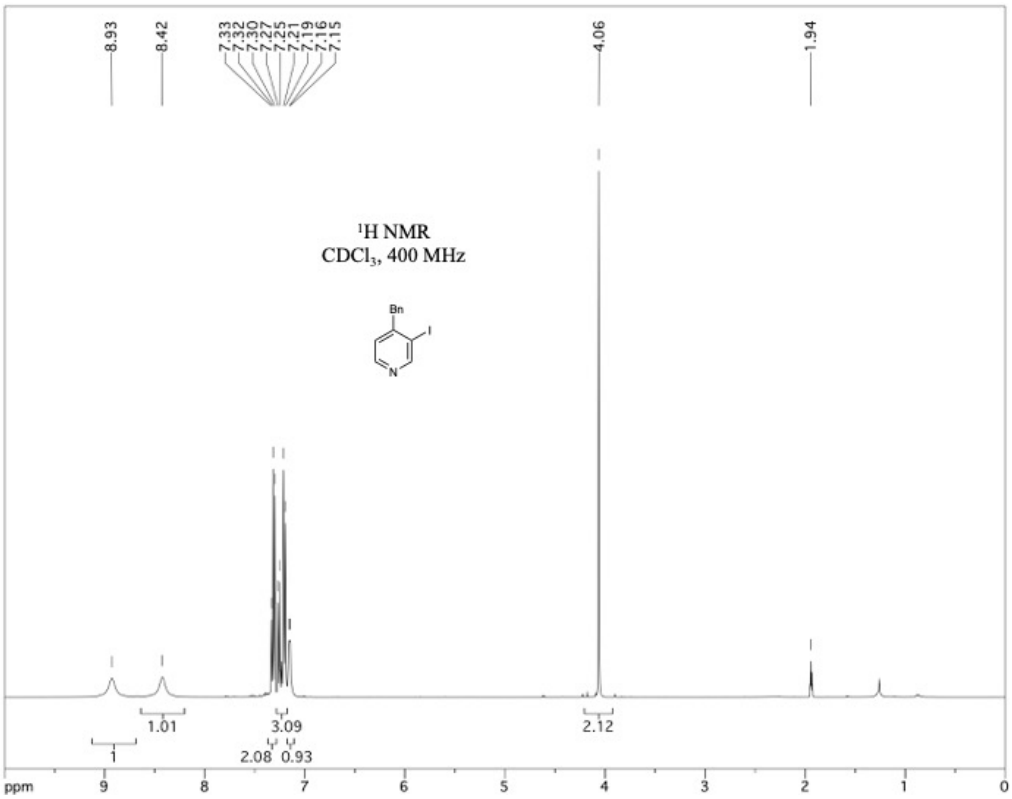

153.20
148.50
144.09
140.24
93.53
77.48
77.16
76.84
33.11
32.42
22.27
13.90
^{13}C NMR
$CDCl_3$, 100 MHz
I
Me
N
ppm 200
150
100
50
0

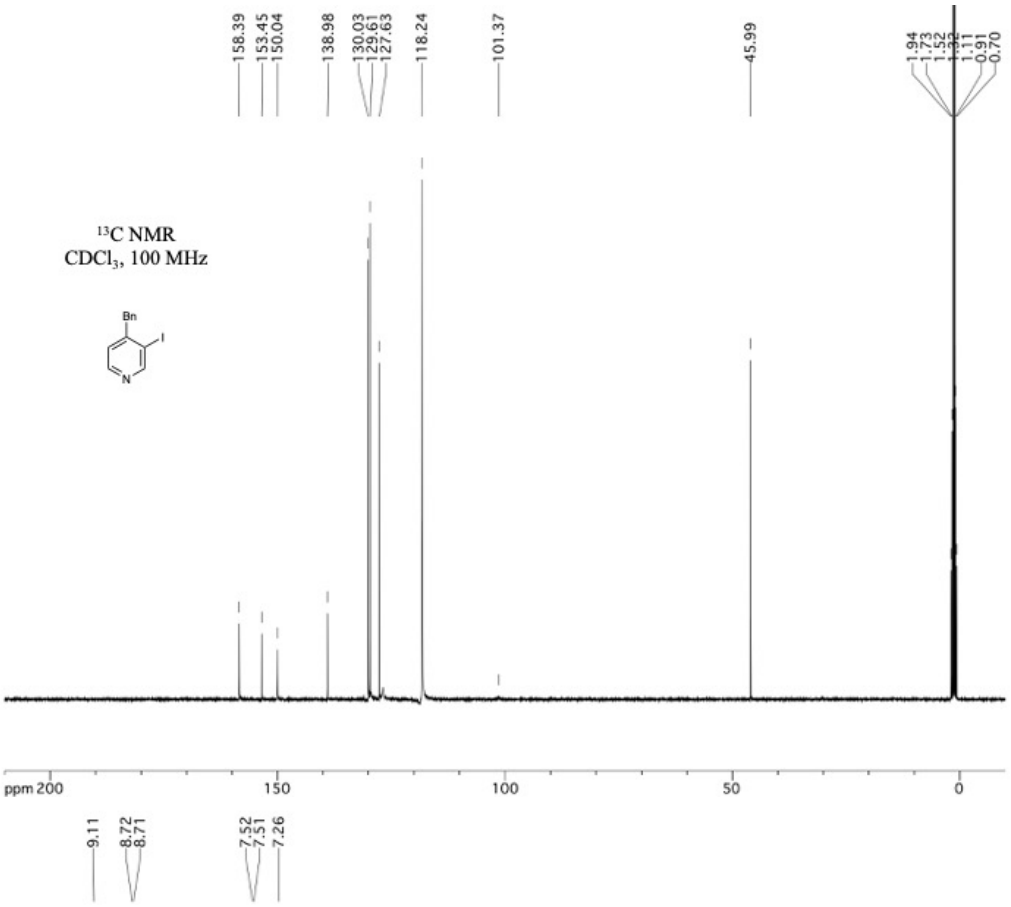

8.83
8.69
8.16
7.46
7.44
7.42
7.26
7.15
7.13
7.11
7.08
^{1}H NMR
$CDCl_3$, 400 MHz
OCF_3
I
N
F
1.02
1.03
1
0.972
2.04
ppm
9
8
7
6
5
4
3
2
1
0

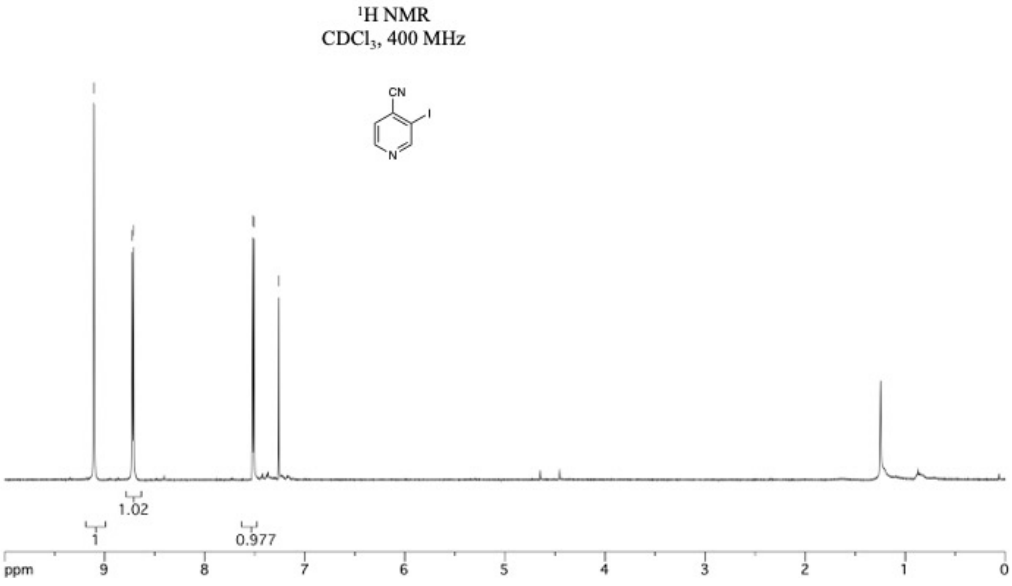

160.99
158.48
155.21
150.16
150.14
150.05
150.03
148.01
147.97
144.27
144.24
132.26
131.31
131.27
124.24
123.13
122.99
121.67
119.10
117.25
117.21
116.53
109.94
109.68
93.31
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
OCF_3
I
N
F
ppm 200
150
100
50
0

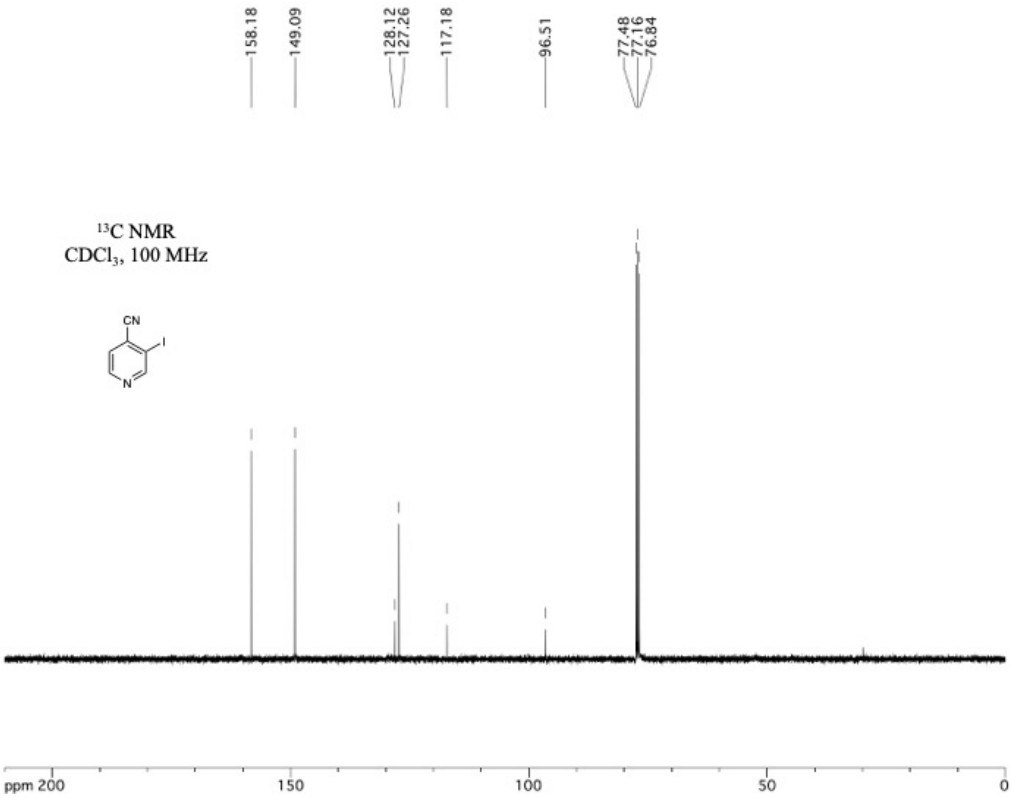

58.00
113.03
113.05
113.08
19F NMR
CDCl3, 365 MHz
OCF3
I
F
N
1.01
3
ppm
-0
-50
-100
-150
crude 1H NMR
CDCl3, 400 MHz
F
I
N
0.82
1
ppm
9
8
7
6
5
4
3
2
1
0

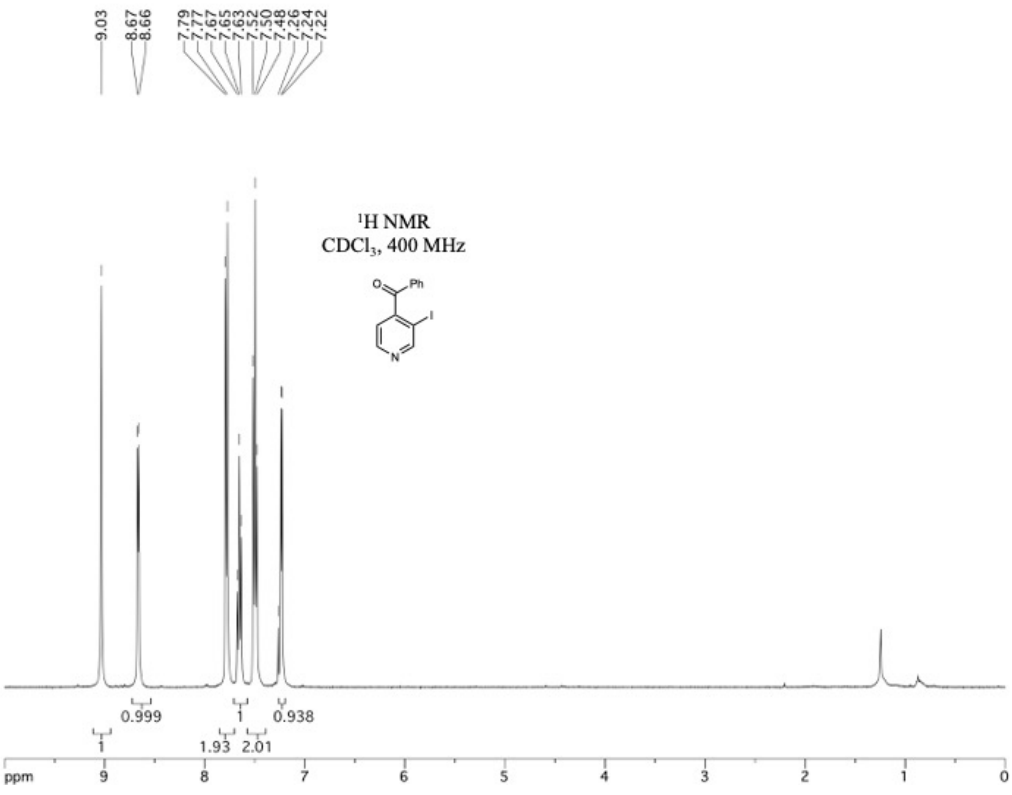

crude ^{1}H NMR
$CDCl_3$, 400 MHz
8.95
8.75
8.19
0.178
0.654
0.177
0.672
1
ppm

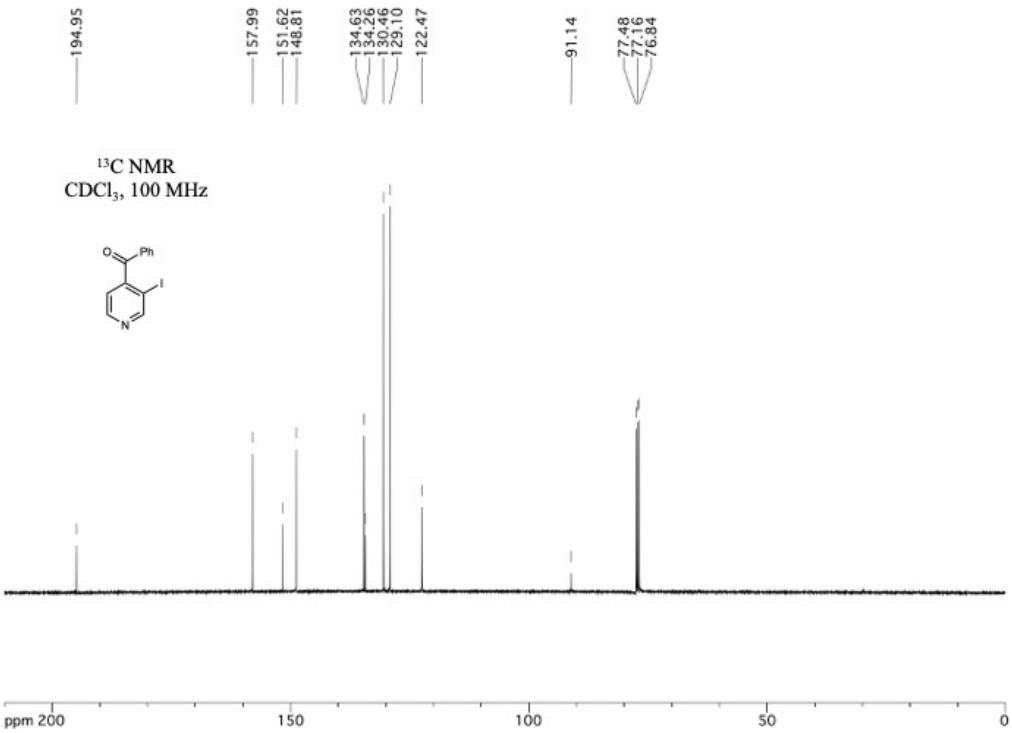

^{1}H NMR
$CDCl_3$, 400 MHz
8.93
8.42
7.33
7.32
7.30
7.27
7.25
7.21
7.19
7.16
7.15
4.06
1.94
Bn
1
1.01
3.09
2.08
0.93
2.12
ppm

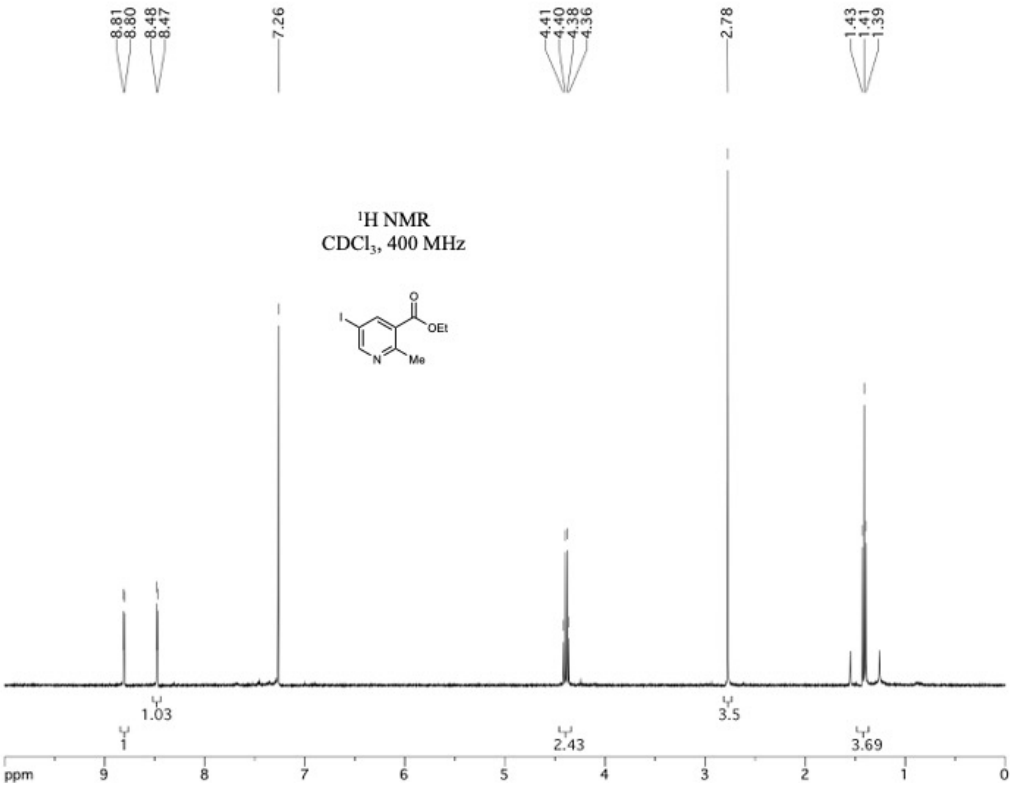

158.39
153.45
150.04
138.98
130.03
129.61
127.63
118.24
101.37
45.99
1.94
1.73
1.52
1.32
1.11
0.91
0.70
^{13}C NMR
$CDCl_3$, 100 MHz
Bn
I
N
ppm 200
150
100
50
0
9.11
8.72
8.71
7.52
7.51
7.26

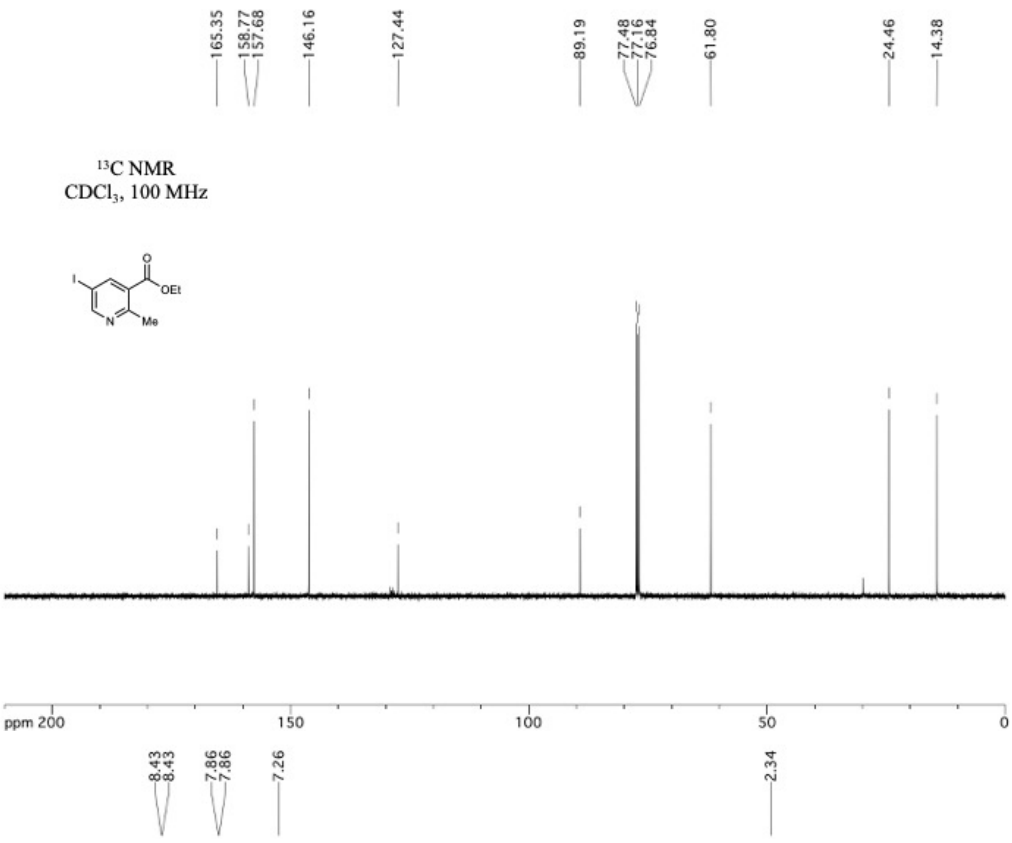

^{1}H NMR
$CDCl_3$, 400 MHz
CN
I
N
1.02
1
0.977
ppm
9
8
7
6
5
4
3
2
1
0

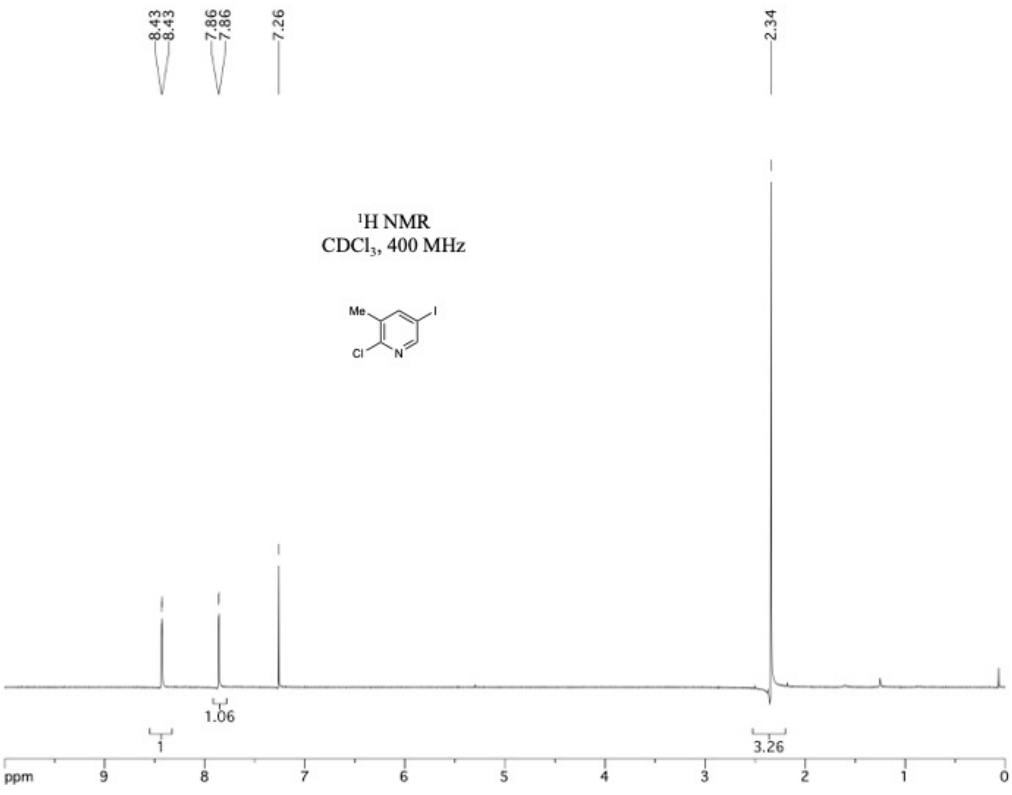

158.18
149.09
128.12
127.26
117.18
96.51
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
CN
I
N
ppm 200
150
100
50
0

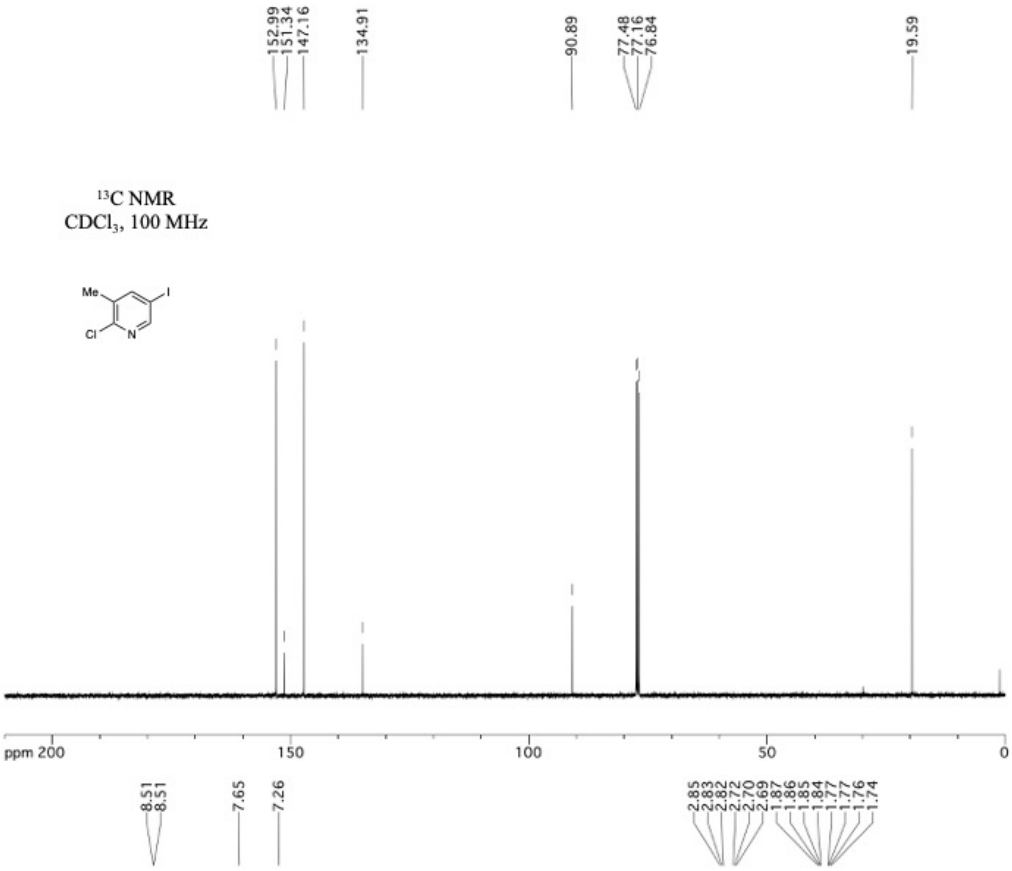

9.03
8.67
8.66
7.79
7.77
7.67
7.65
7.63
7.52
7.50
7.48
7.26
7.24
7.22
^{1}H NMR
$CDCl_3$, 400 MHz
O
Ph
I
N
0.999
1
0.938
1
1.93
2.01
ppm
9
8
7
6
5
4
3
2
1
0

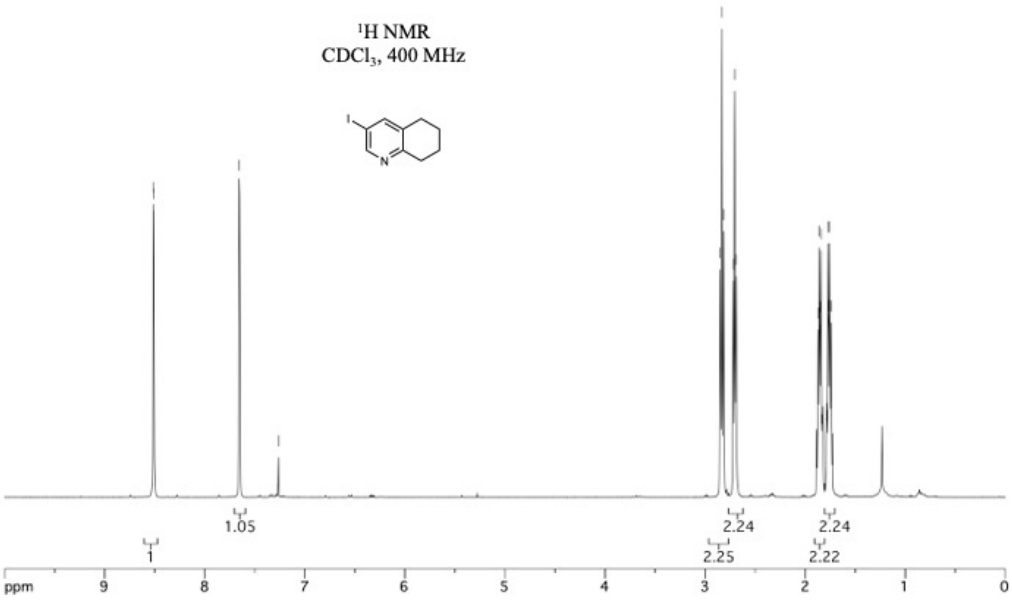

194.95
157.99
151.62
148.81
134.63
134.26
130.46
129.10
122.47
91.14
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
O
Ph
I
N
ppm 200
150
100
50
0

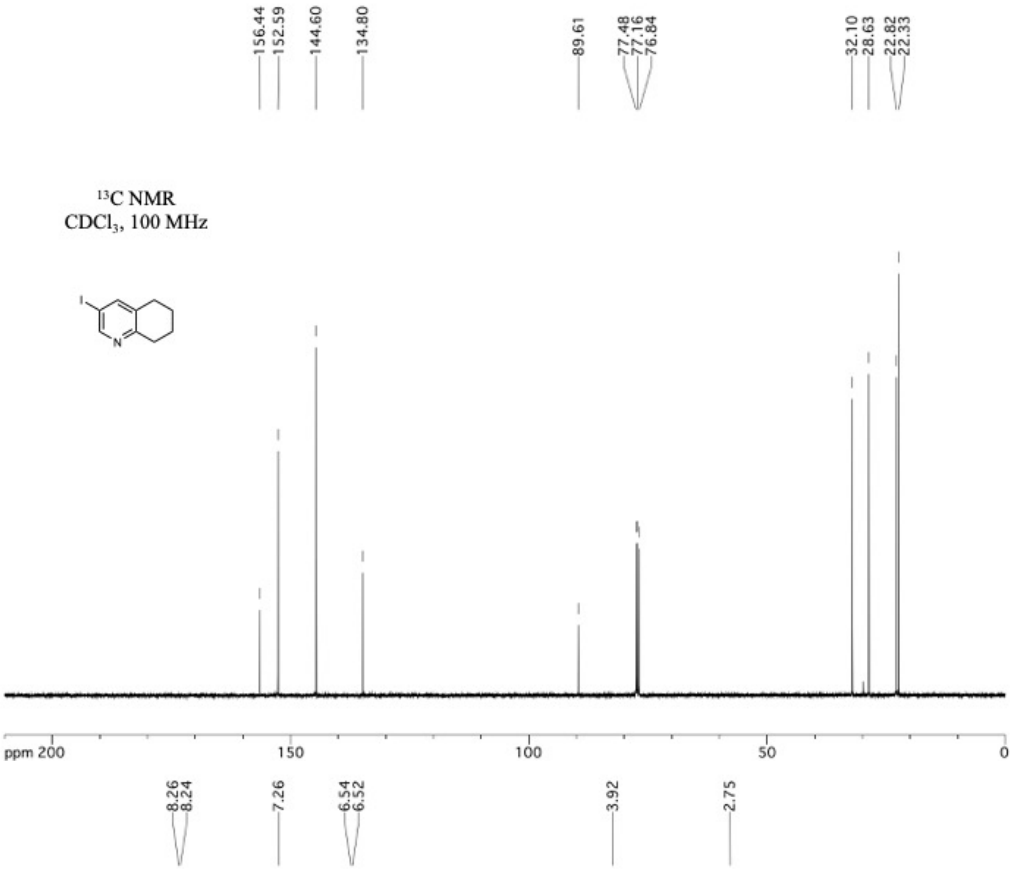

8.81
8.80
8.48
8.47
7.26
4.41
4.40
4.38
4.36
2.78
1.43
1.41
1.39
1H NMR
CDCl3, 400 MHz
I
O
OEt
N
Me
1.03
3.5
1
2.43
3.69
ppm
9
8
7
6
5
4
3
2
1
0

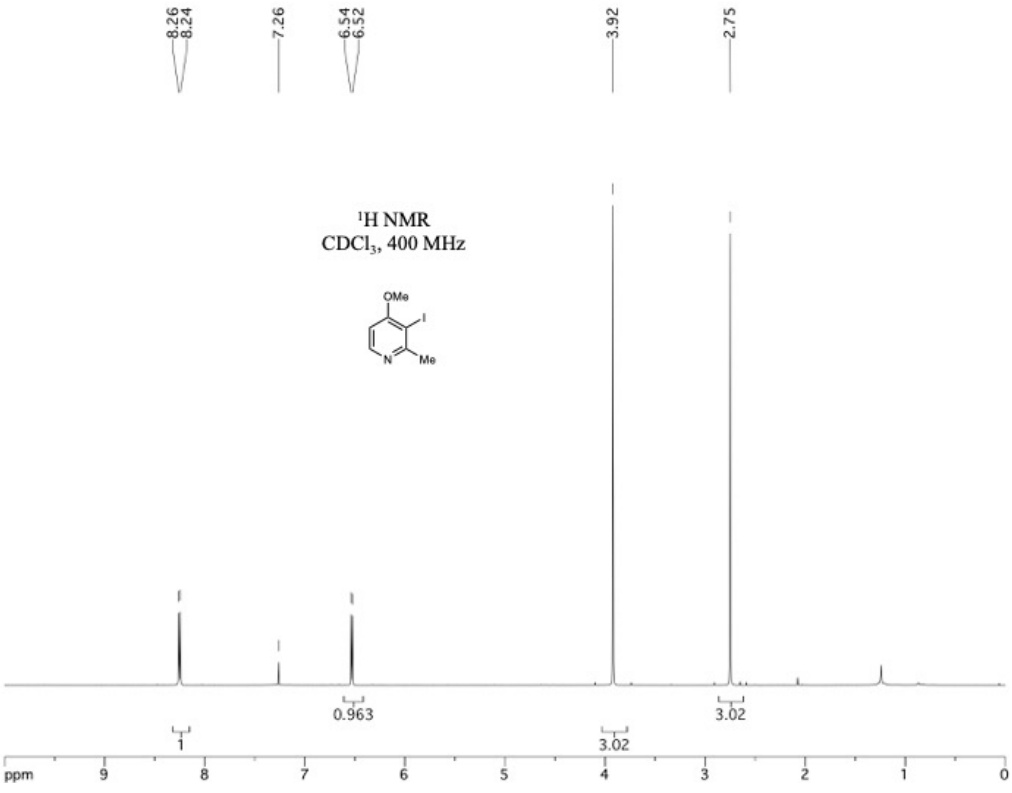

165.35
158.77
157.68
146.16
127.44
89.19
77.48
77.16
76.84
61.80
24.46
14.38
13C NMR
CDCl3, 100 MHz
O
OEt
I
N
Me
ppm 200
150
100
50
0


8.43
8.43
7.86
7.86
7.26
2.34
1H NMR
CDCl3, 400 MHz
Me
I
Cl
N
1.06
1
3.26
ppm
9
8
7
6
5
4
3
2
1
0


152.99
151.34
147.16
134.91
90.89
77.48
77.16
76.84
19.59
^{13}C NMR
$CDCl_3$, 100 MHz
Me
I
Cl
N
ppm 200
150
100
50
0
8.51
8.51
7.65
7.26
2.85
2.83
2.82
2.72
2.70
2.69
1.87
1.86
1.85
1.84
1.77
1.77
1.76
1.74


^{1}H NMR
$CDCl_3$, 400 MHz
I
N
1
1.05
2.24
2.24
2.25
2.22
ppm
9
8
7
6
5
4
3
2
1
0


156.44
152.59
144.60
134.80
89.61
77.48
77.16
76.84
32.10
28.63
22.82
22.33
13C NMR
CDCl3, 100 MHz
I
N
ppm 200
150
100
50
0


8.26
8.24
7.26
6.54
6.52
3.92
2.75
1H NMR
CDCl3, 400 MHz
OMe
I
N
Me
0.963
3.02
1
3.02
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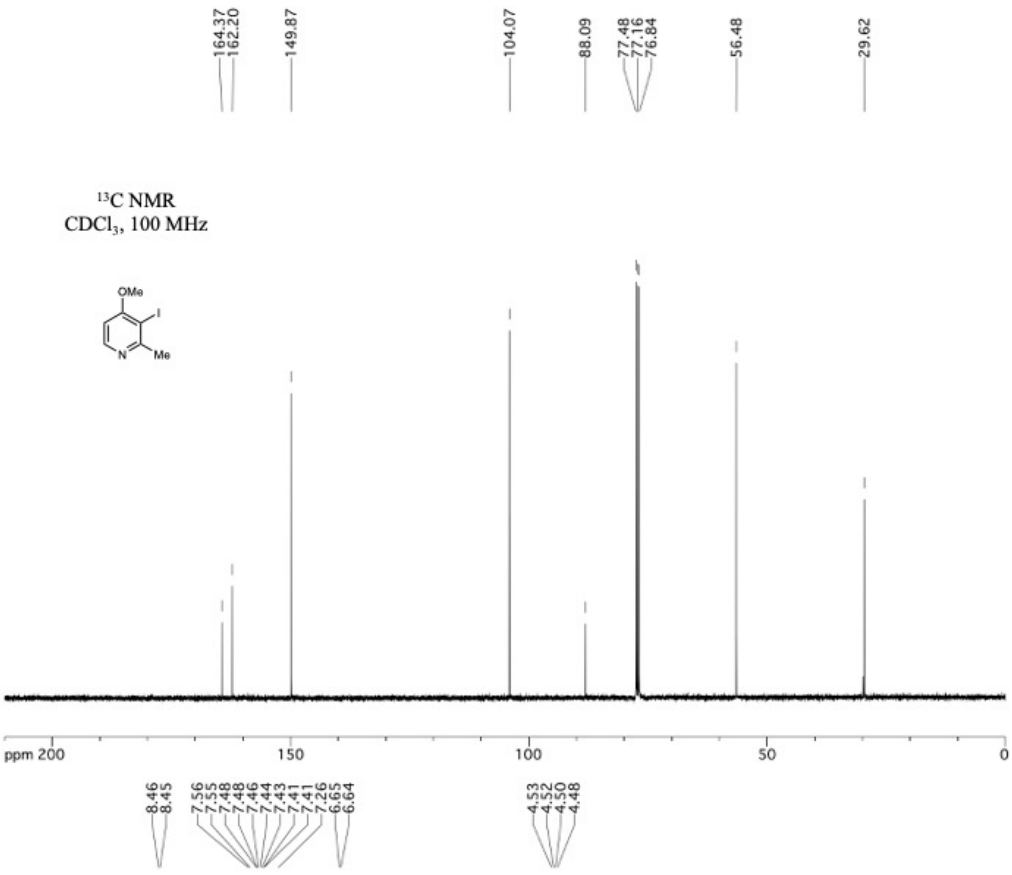
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162.20
149.87
104.07
88.09
77.48
77.16
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29.62
13C NMR
CDCl3, 100 MHz
OMe
I
N
Me
ppm 200
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50
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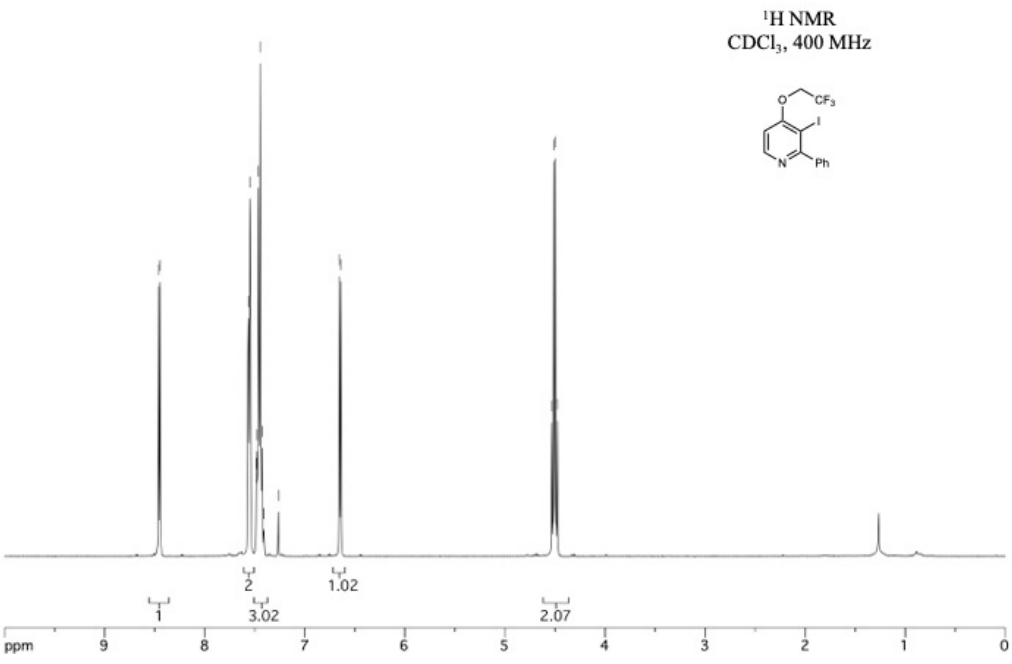
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8.45
7.56
7.55
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7.46
7.44
7.43
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7.41
7.26
6.65
6.64
4.53
4.52
4.50
4.48
1H NMR
CDCl3, 400 MHz
O
CF3
I
N
Ph
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2
3.02
1.02
2.07
ppm
9
8
7
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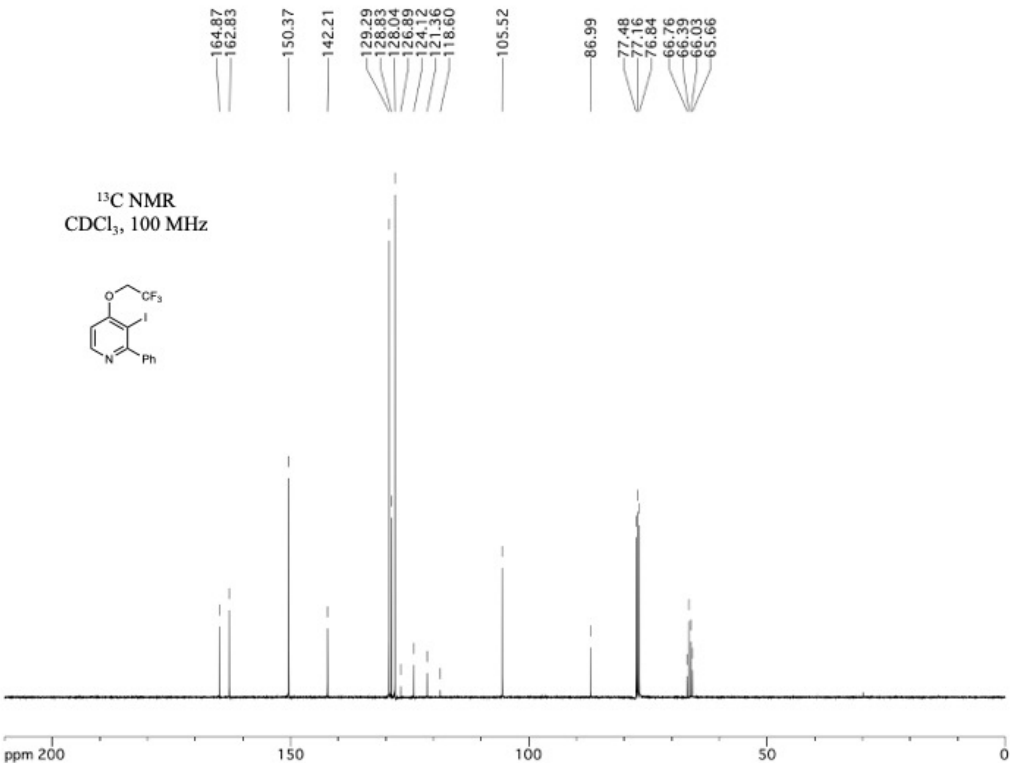
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126.89
124.12
121.36
118.60
105.52
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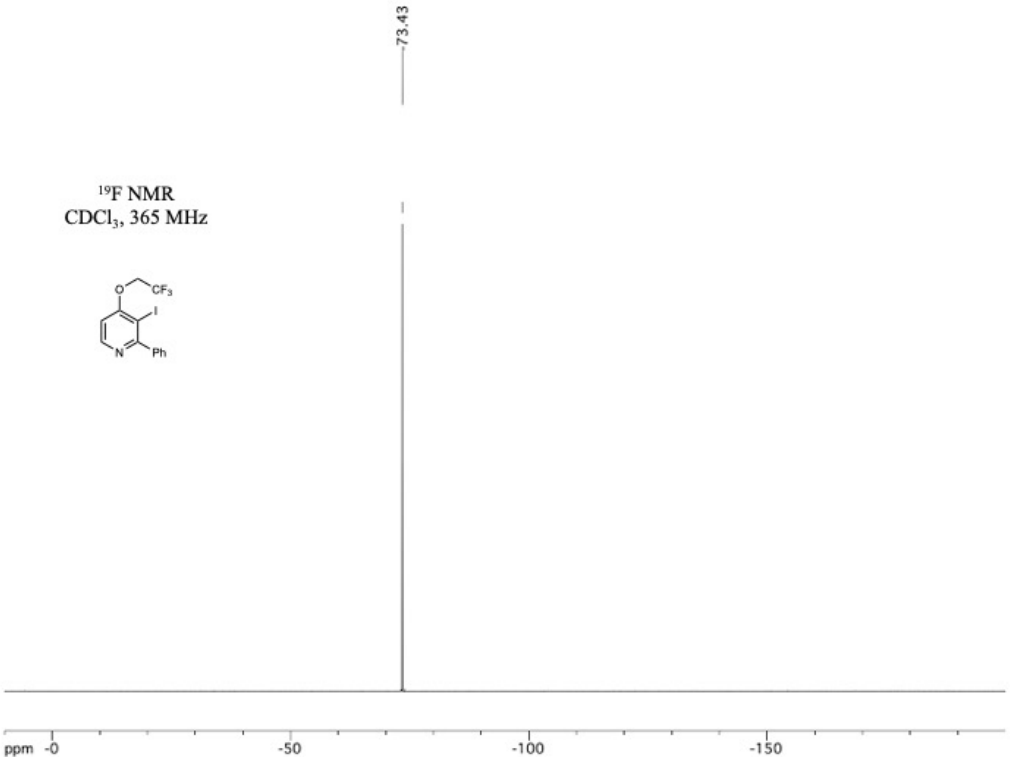
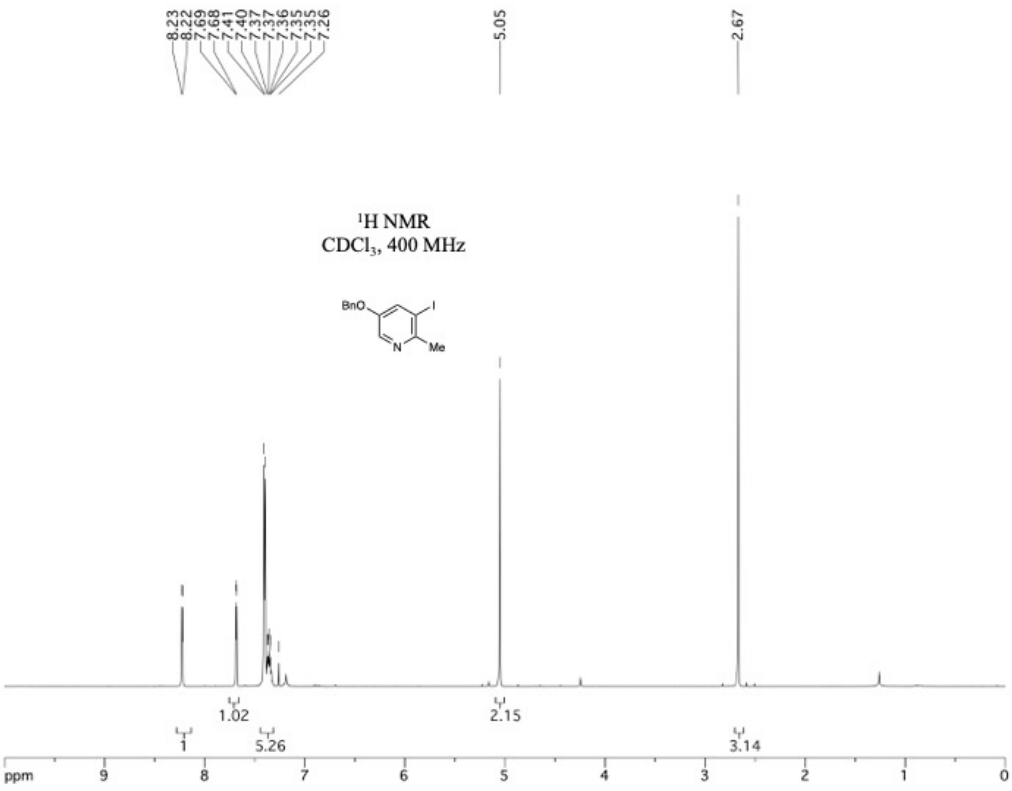
77.48
77.16
76.84
66.76
66.39
66.03
65.66
13C NMR
CDCl3, 100 MHz
CF3
O
I
N
Ph
ppm 200
150
100
50
0


73.43
19F NMR
CDCl3, 365 MHz
CF3
O
I
N
Ph
ppm -0
-50
-100
-150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8.22
7.69
7.68
7.41
7.40
7.37
7.37
7.36
7.35
7.35
7.26
5.05
2.67
1H NMR
CDCl3, 400 MHz
BnO
I
N
Me
1.02
2.15
1
5.26
3.14
ppm
9
8
7
6
5
4
3
2
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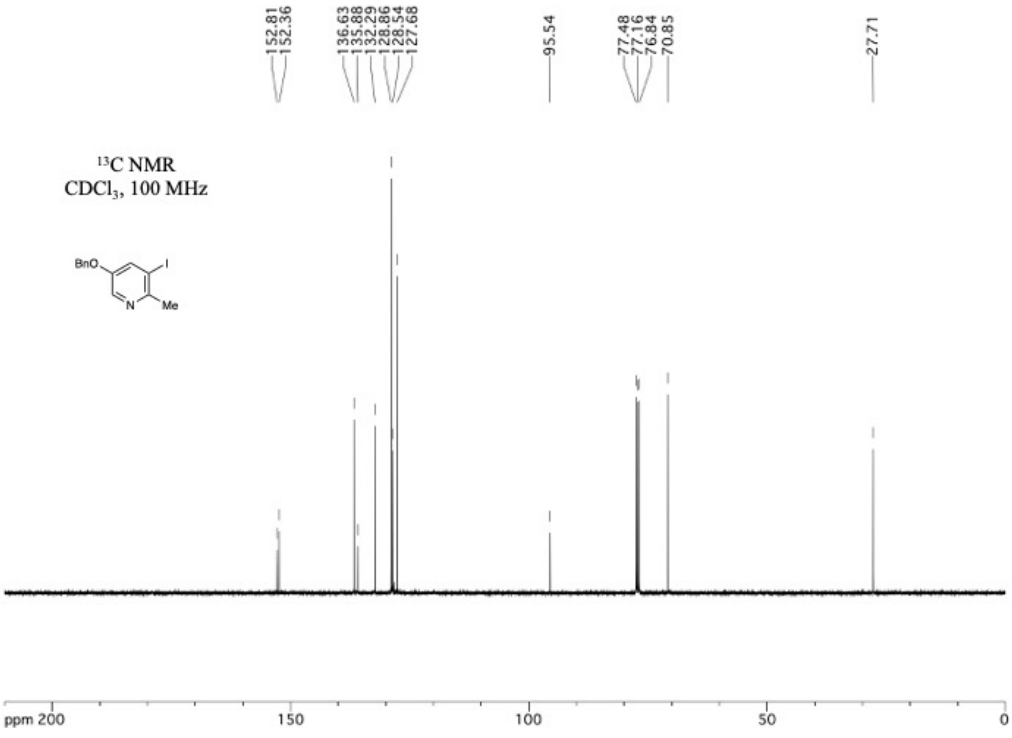
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152.36
136.63
135.88
132.29
128.86
128.54
127.68
95.54
77.48
77.16
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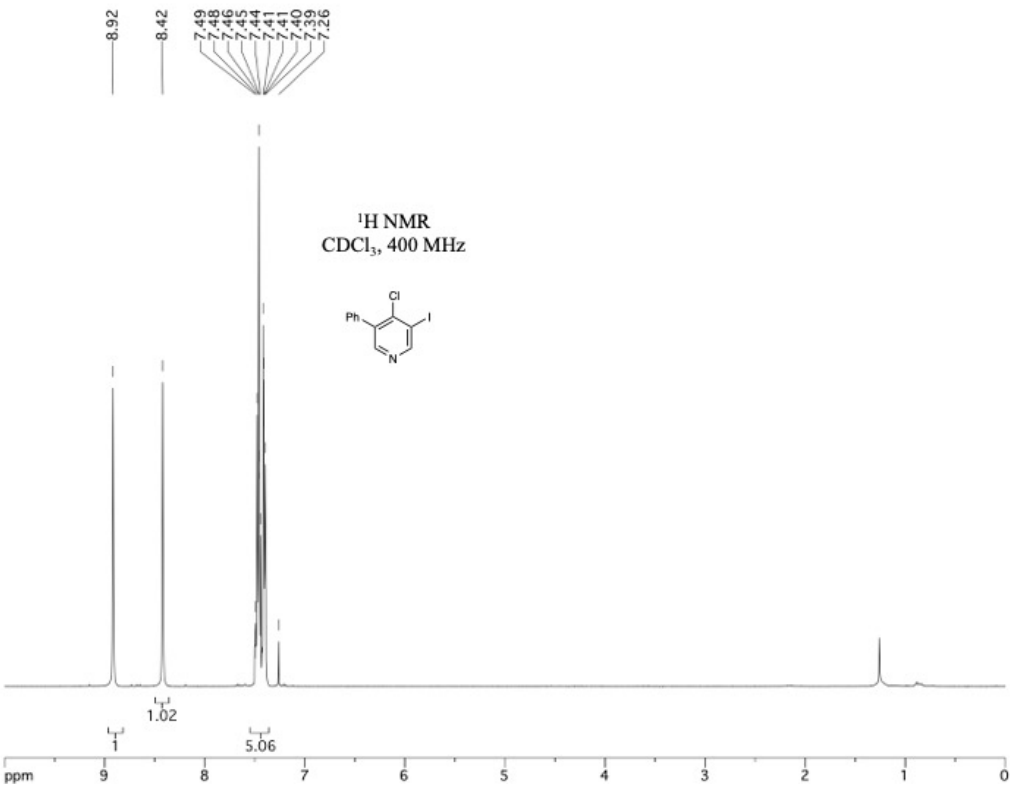
70.85
27.71
13C NMR
CDCl3, 100 MHz
BnO
I
N
Me
ppm 200
150
100
50
0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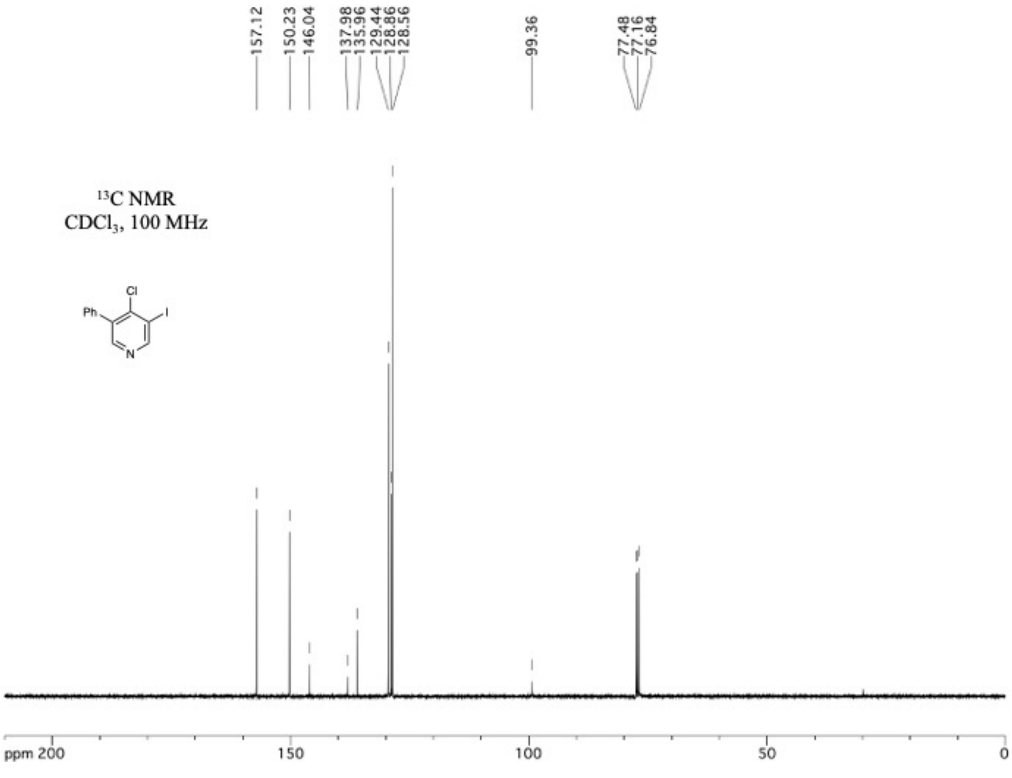
8.42
7.49
7.48
7.46
7.45
7.44
7.41
7.41
7.40
7.39
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Cl
Ph
I
N
1.02
1
5.06
ppm
9
8
7
6
5
4
3
2
1
0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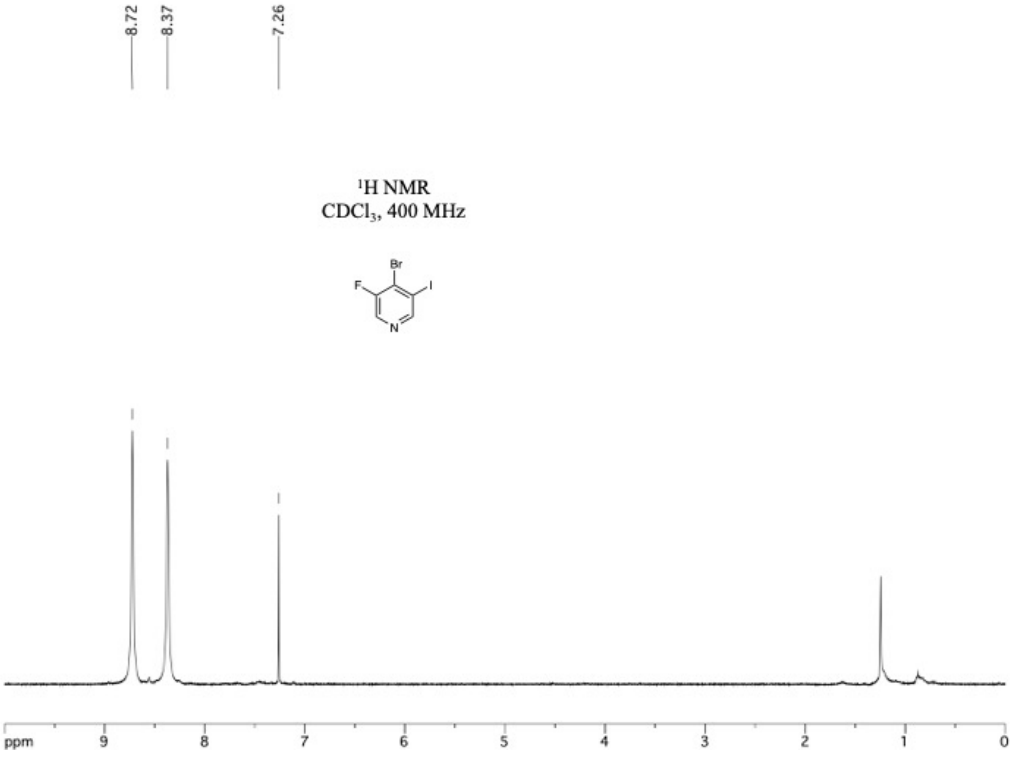
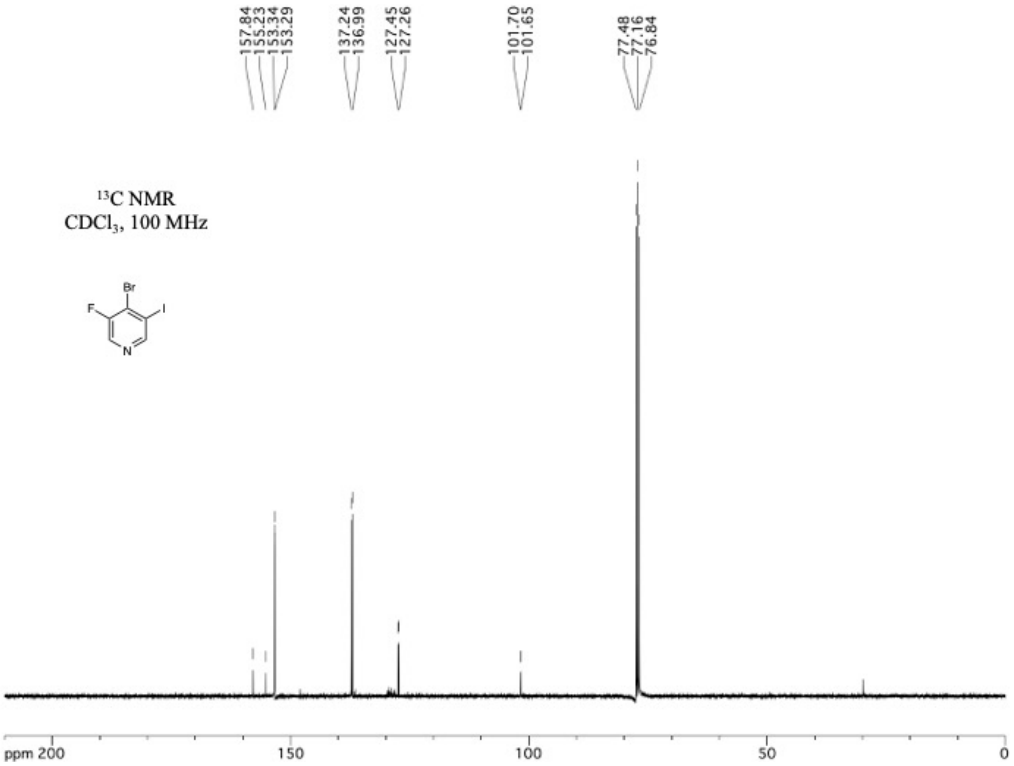
150.23
146.04
137.98
135.96
129.44
128.86
128.56
99.36
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
Ph
I
N
ppm 200
150
100
50
0


8.72
8.37
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Br
F
I
N
ppm
9
8
7
6
5
4
3
2
1
0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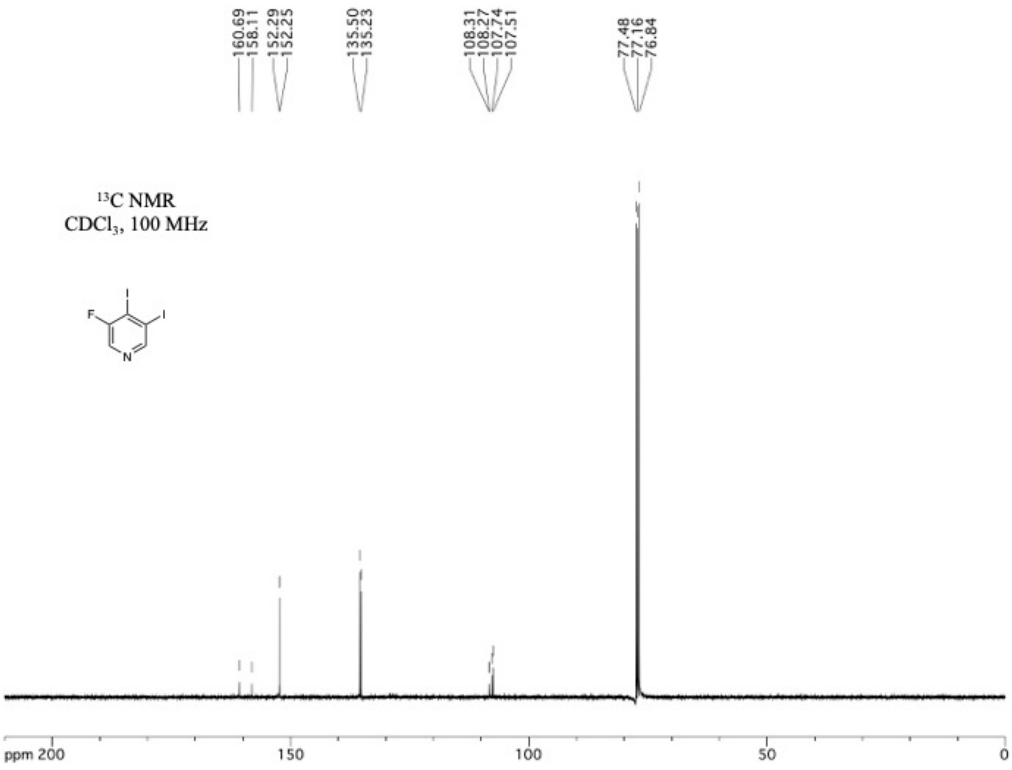
153.34
153.29
137.24
136.99
127.45
127.26
101.70
101.65
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Br
F
I
N
ppm 200
150
100
50
0

^{19}F NMR
$CDCl_3$, 365 MHz

^{1}H NMR
$CDCl_3$, 400 MHz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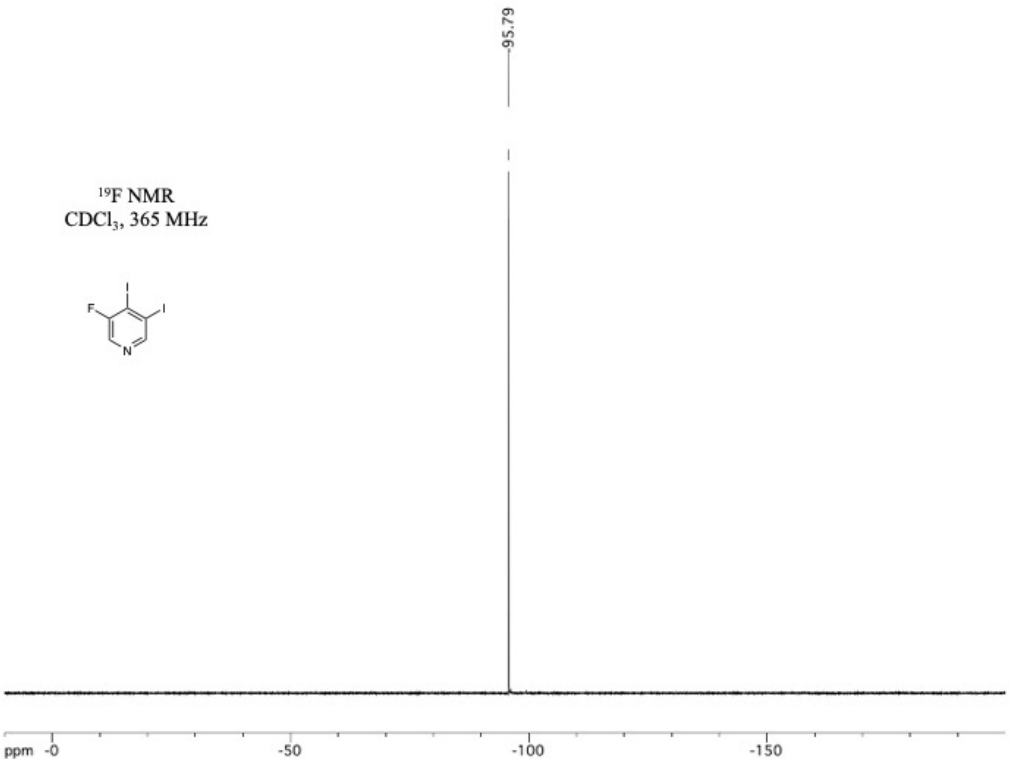
158.11
152.29
152.25
135.50
135.23
108.31
108.27
107.74
107.51
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
F
I
I
N
ppm 200
150
100
50
0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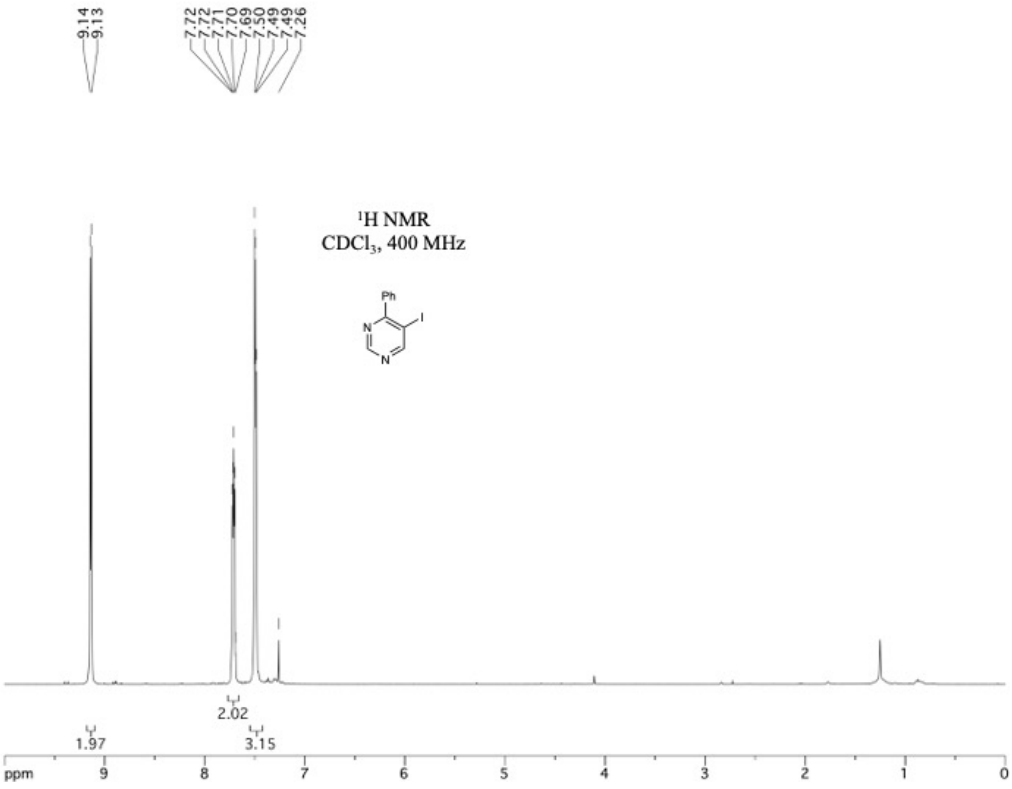
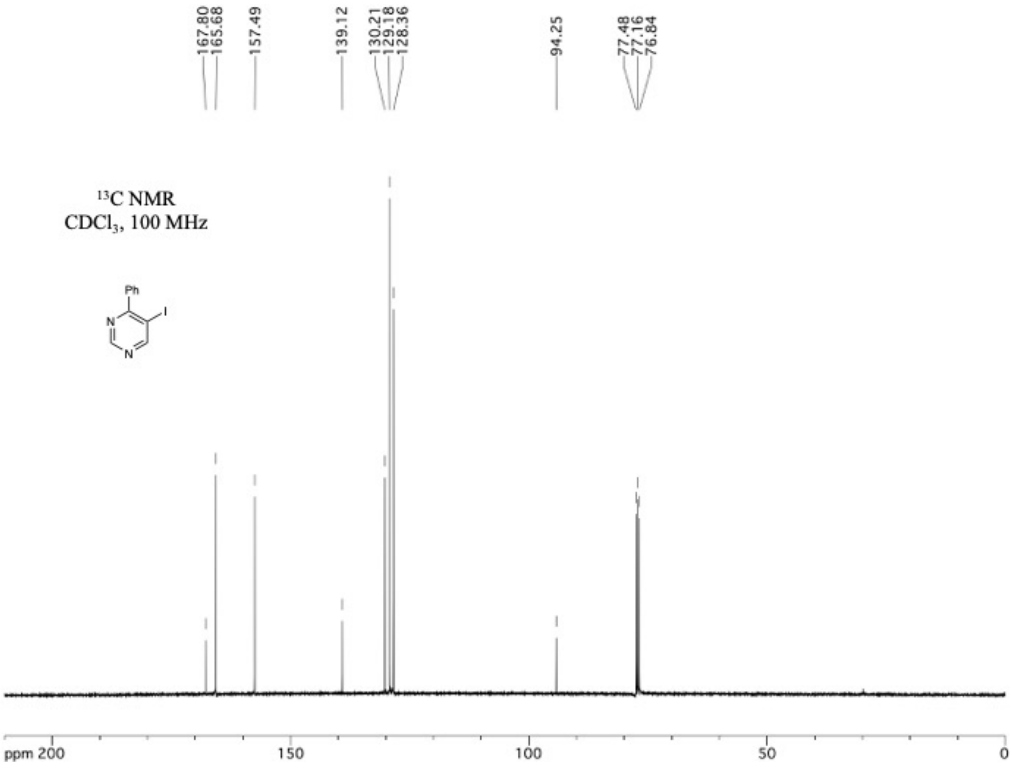
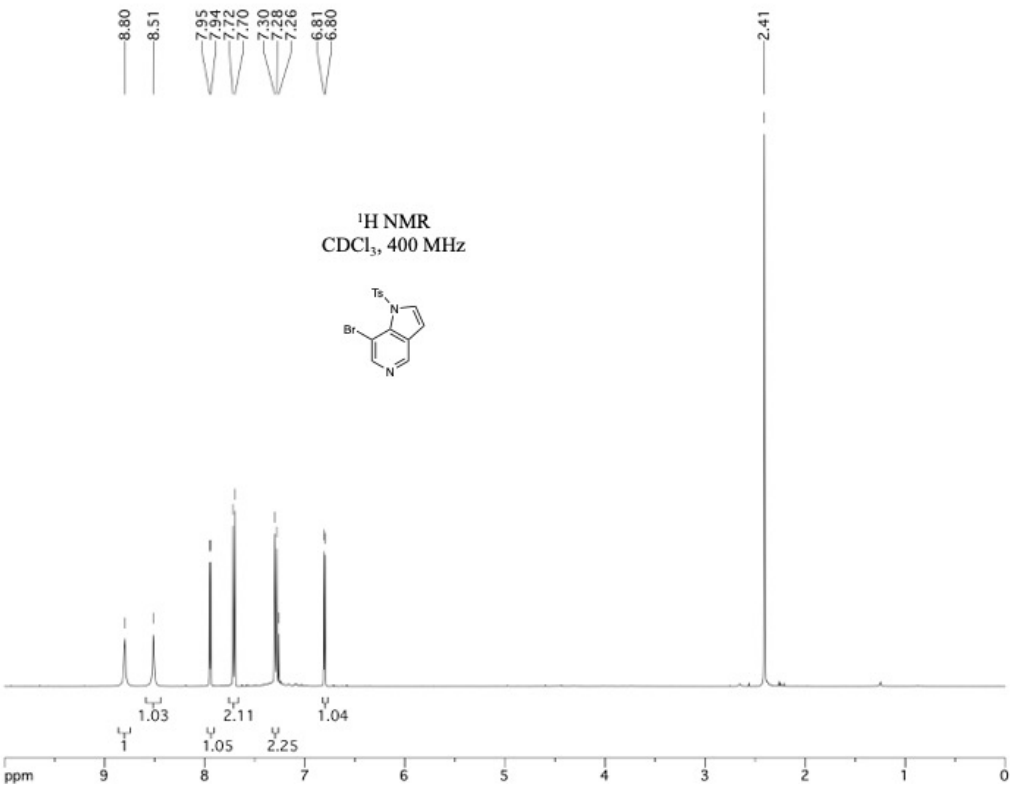
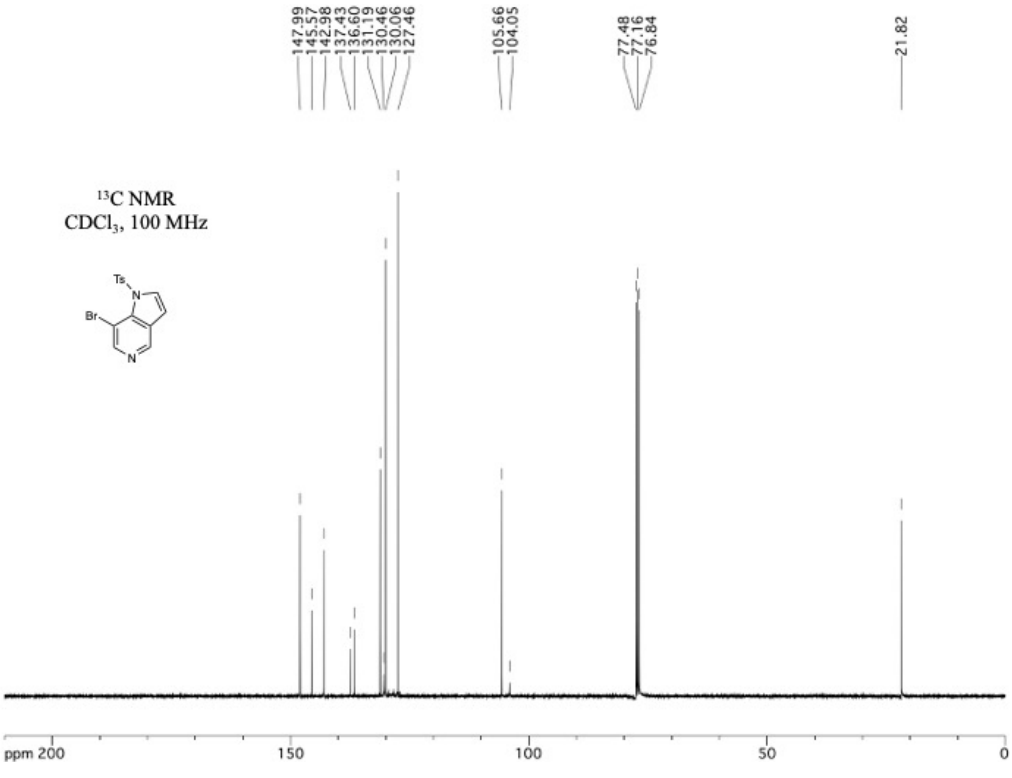
$CDCl_3$, 365 MHz
F
I
I
N
ppm -0
-50
-100
-150


9.14
9.13
7.72
7.72
7.71
7.70
7.69
7.50
7.49
7.49
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Ph
N
I
N
2.02
1.97
3.15
ppm
9
8
7
6
5
4
3
2
1
0


167.80
165.68
157.49
139.12
130.21
129.18
128.36
94.25
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Ph
N
I
N
ppm 200
150
100
50
0


8.80
8.51
7.95
7.94
7.72
7.70
7.30
7.28
7.26
6.81
6.80
2.41
^{1}H NMR
$CDCl_3$, 400 MHz
Ts
N
Br
N
1.03
2.11
1.04
1
1.05
2.25
ppm
9
8
7
6
5
4
3
2
1
0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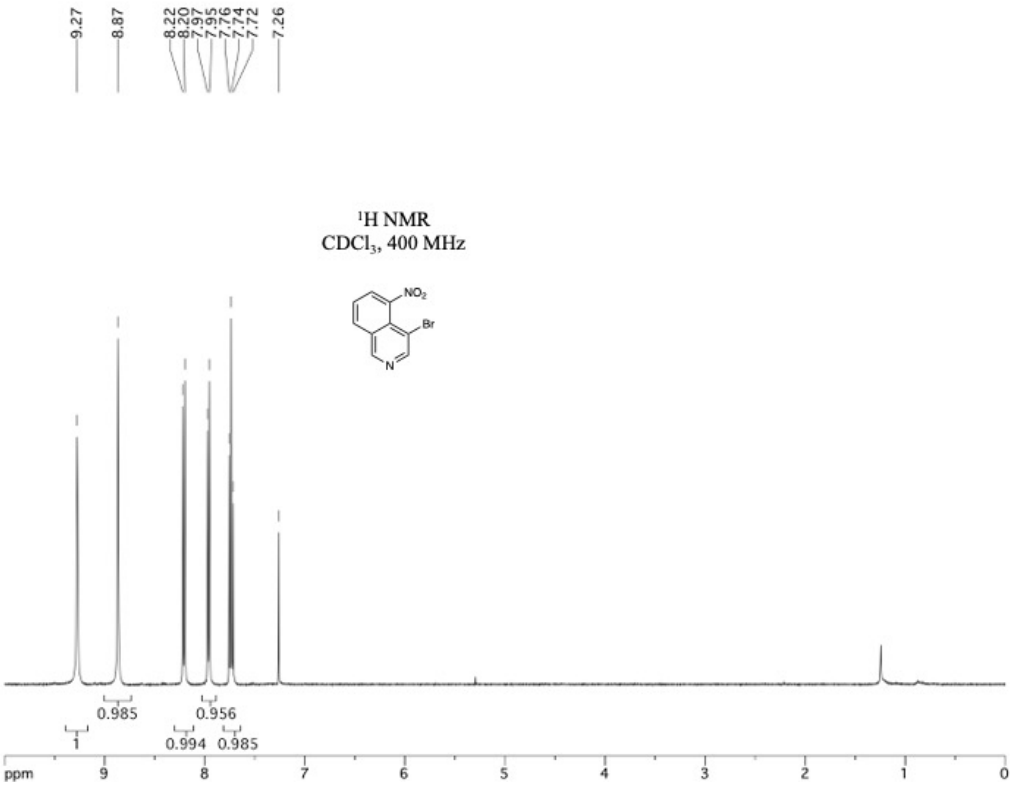
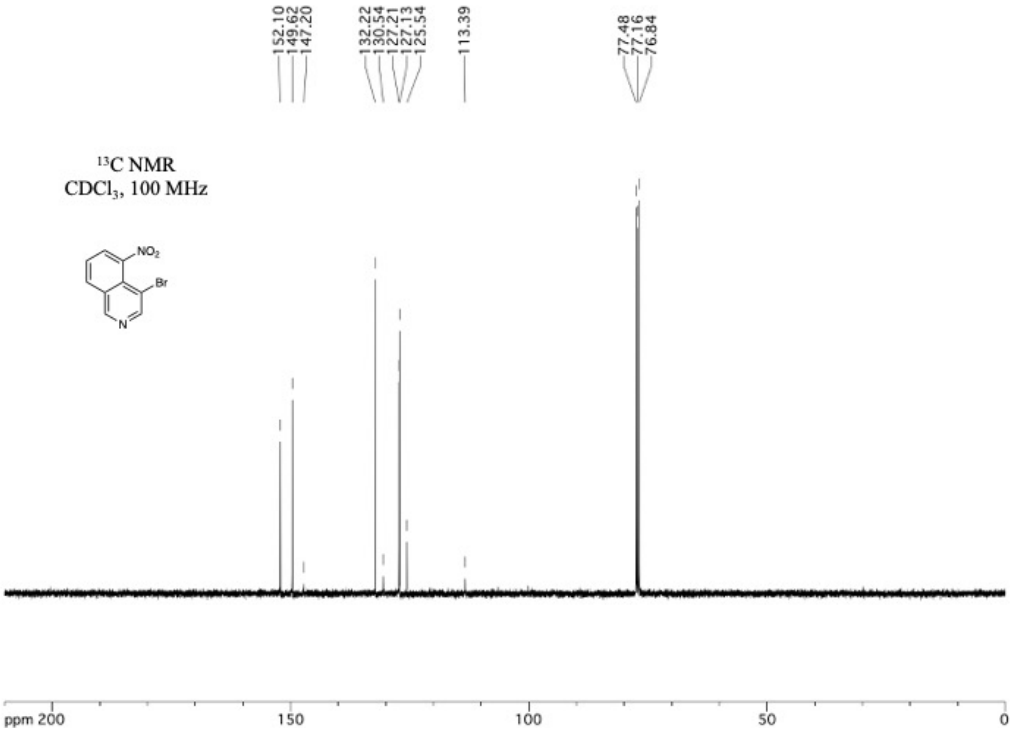
145.57
142.98
137.43
136.60
131.19
130.46
130.06
127.46
105.66
104.05
77.48
77.16
76.84
21.82
^{13}C NMR
$CDCl_3$, 100 MHz
Ts
N
Br
N
ppm 200
150
100
50
0


9.27
8.87
8.22
8.20
7.97
7.95
7.76
7.74
7.72
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
NO_2
Br
N
0.985
0.956
1
0.994
0.985
ppm
9
8
7
6
5
4
3
2
1
0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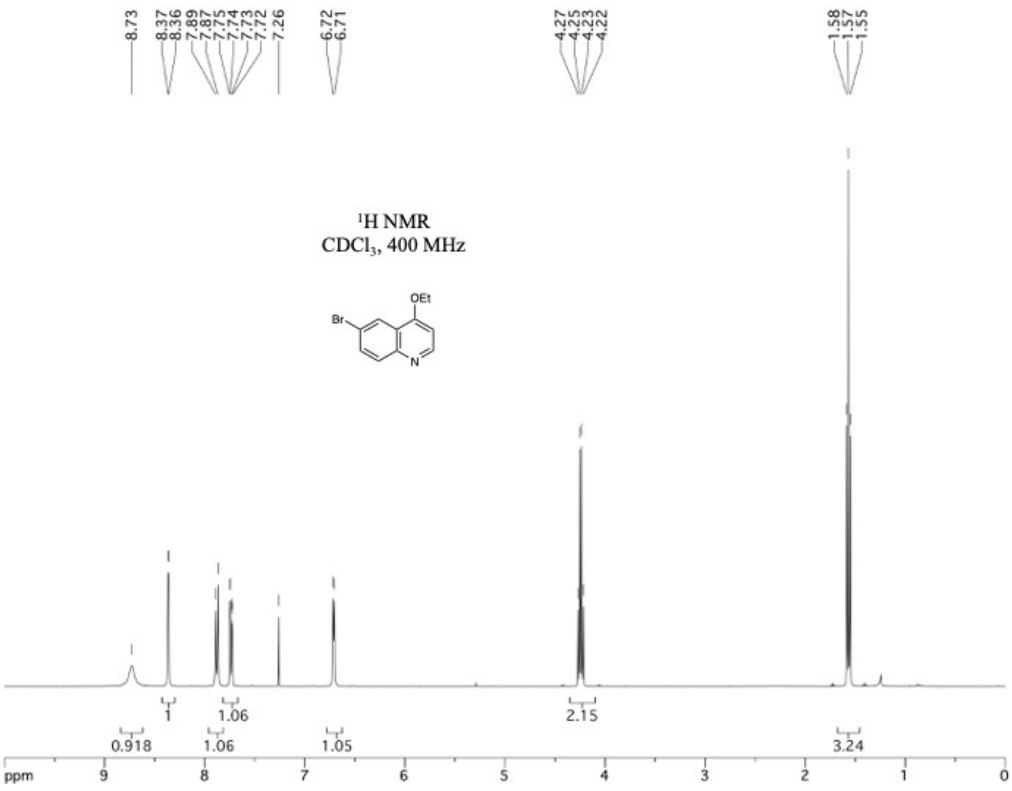
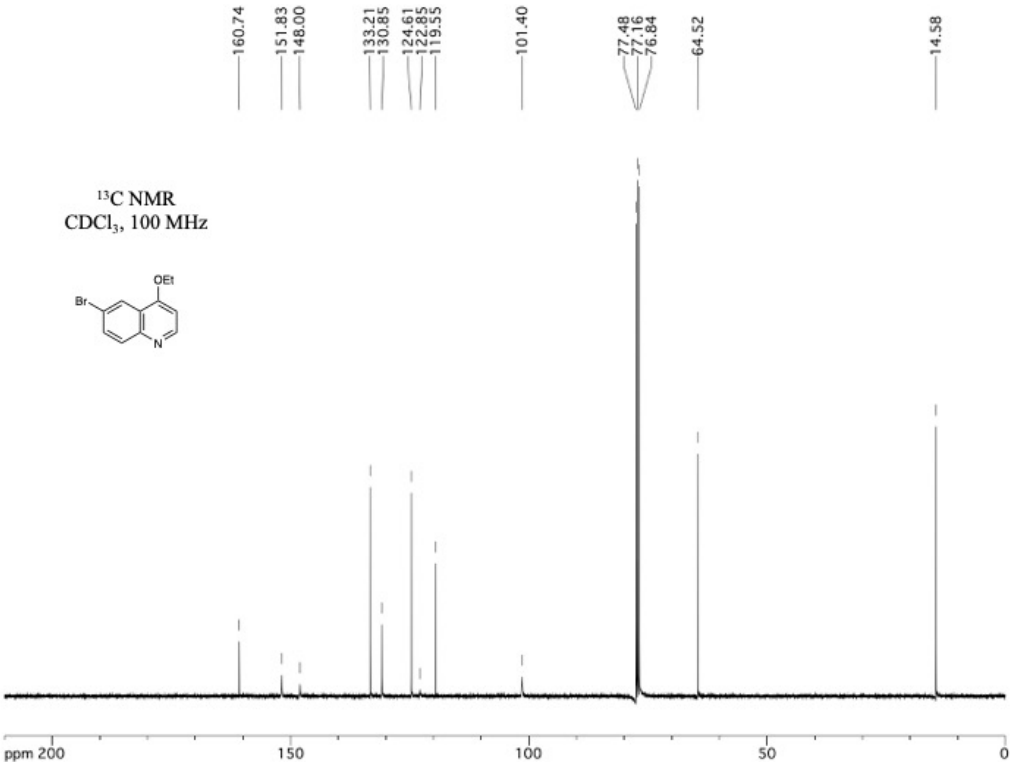
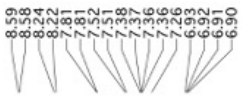
149.62
147.20
132.22
130.54
127.21
127.13
125.54
113.39
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
NO_2
Br
N
ppm 200
150
100
50
0



^{1}H NMR
$CDCl_3$, 400 MHz



^{13}C NMR
$CDCl_3$, 100 MHz



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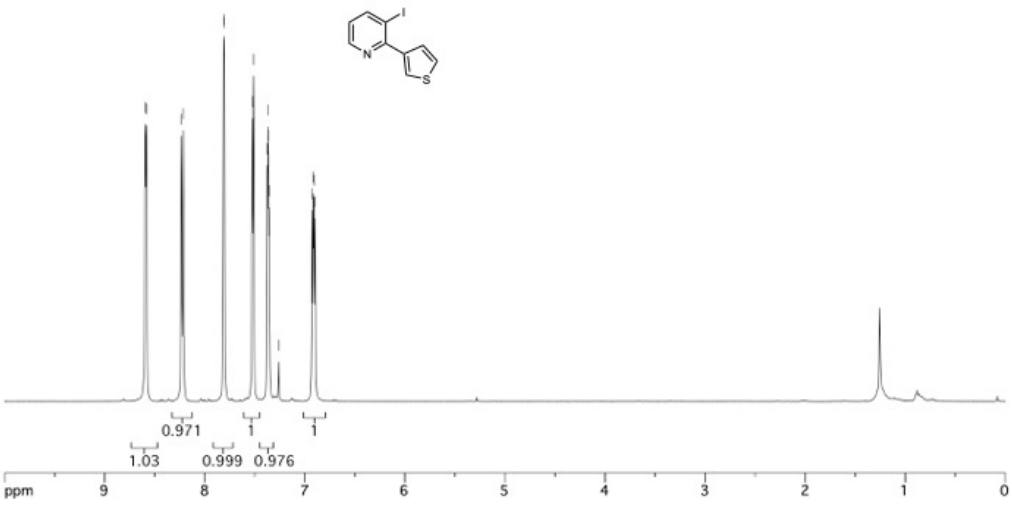
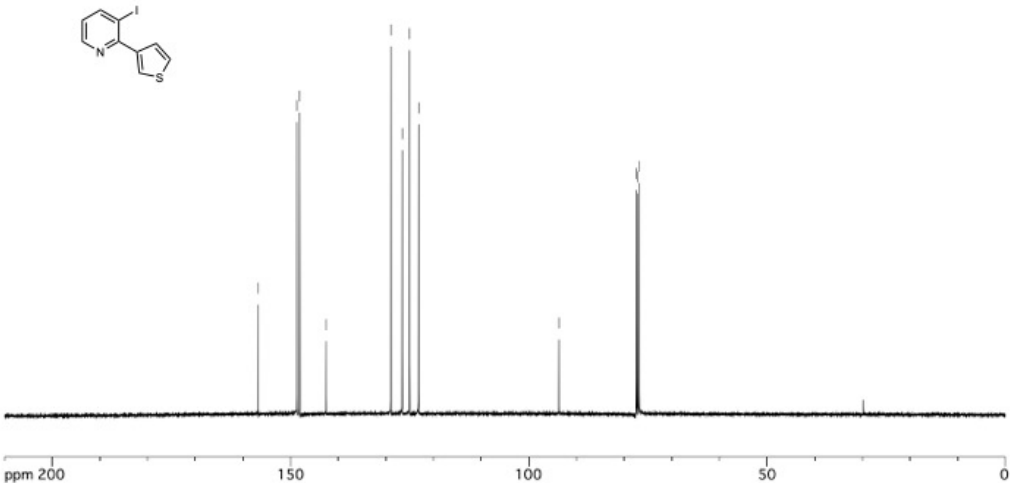
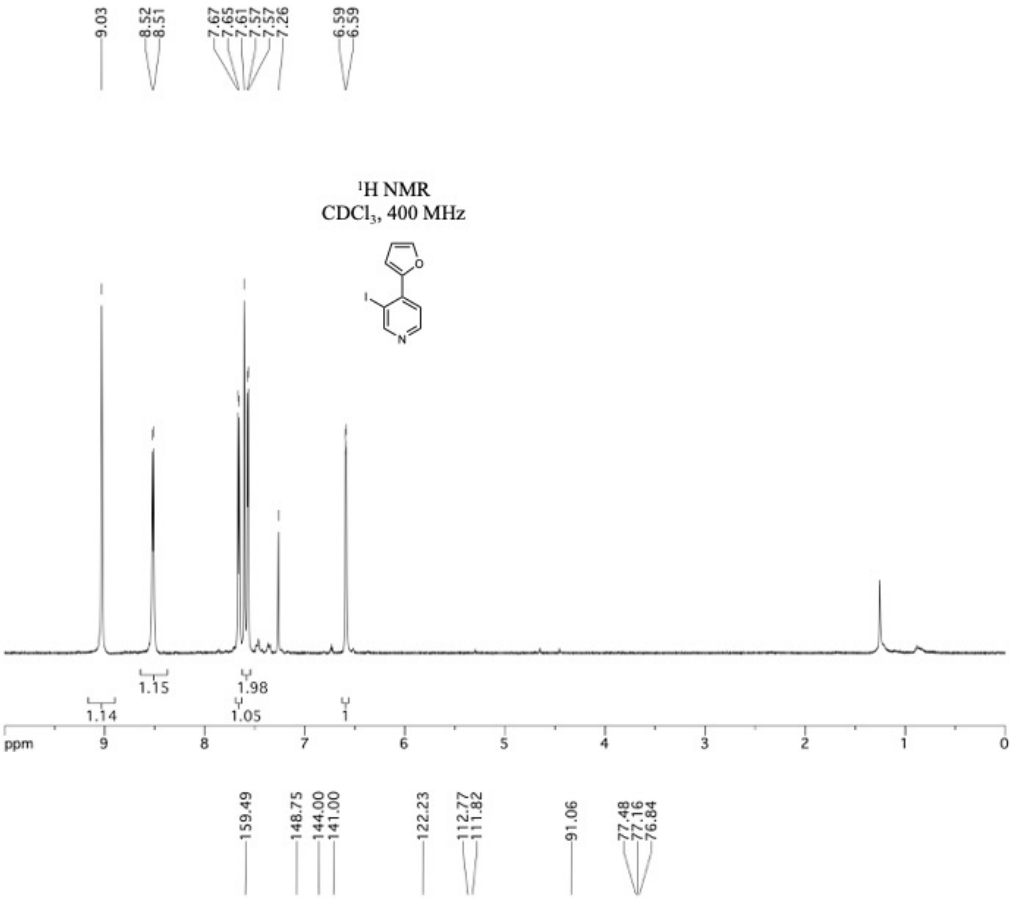
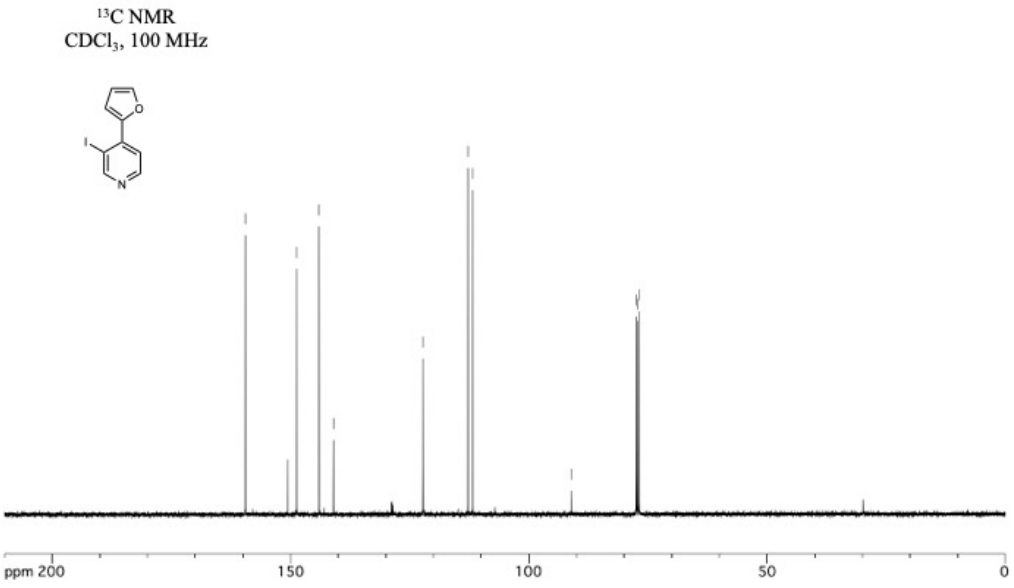
$CDCl_3$, 400 MHz



^{13}C NMR
$CDCl_3$, 100 MHz




9.03
8.52
8.51
7.67
7.65
7.61
7.57
7.57
7.26
6.59
6.59
1H NMR
CDCl3, 400 MHz
1.15
1.98
1.14
1.05
1
ppm
9
8
7
6
5
4
3
2
1
0
159.49
148.75
144.00
141.00
122.23
112.77
111.82
91.06
77.48
77.16
76.84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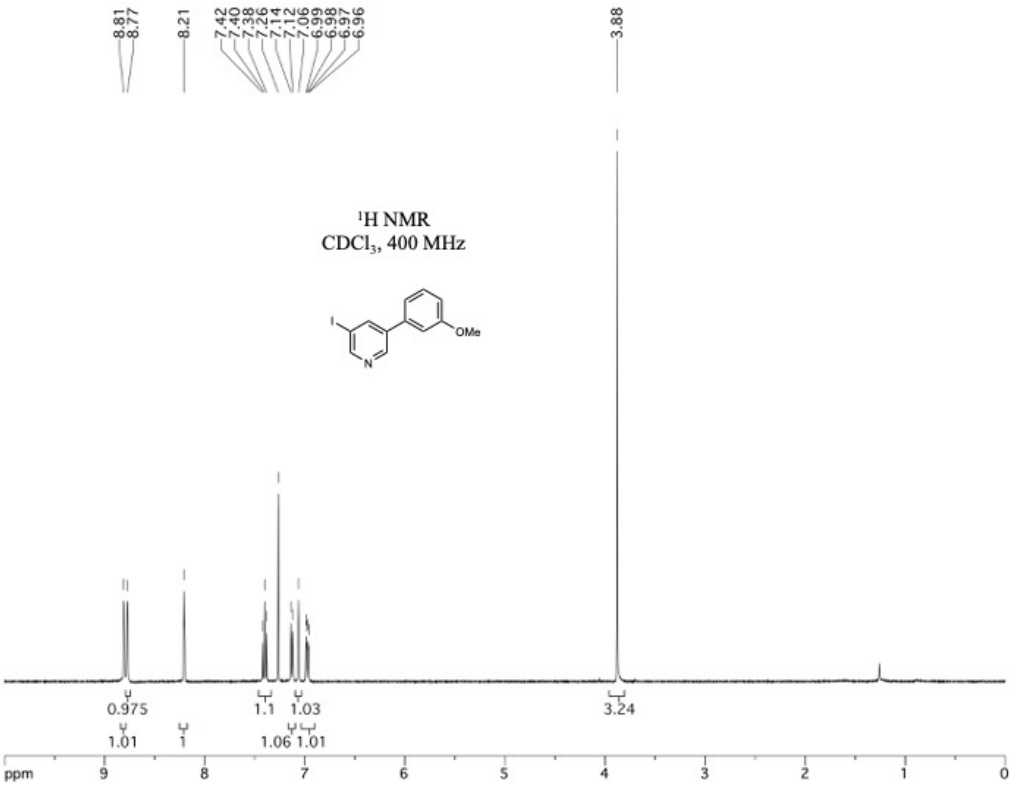
CDCl3, 100 MHz
ppm 200
150
100
50
0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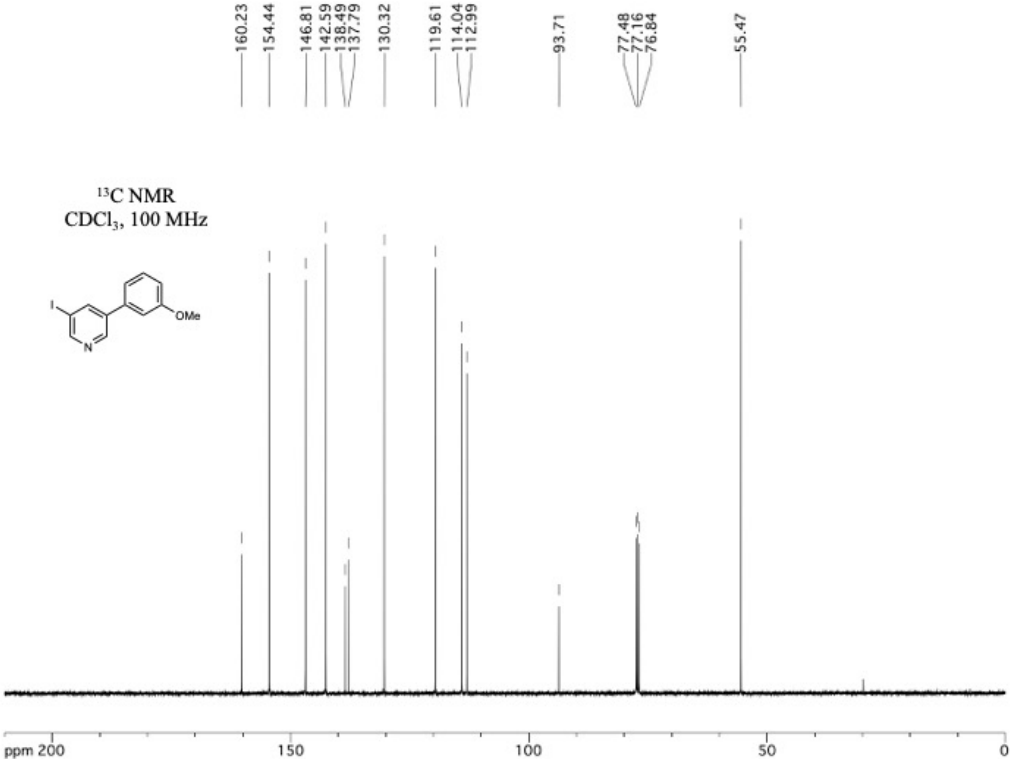
8.77
8.21
7.42
7.40
7.38
7.26
7.14
7.12
7.06
6.99
6.98
6.97
6.96
3.88
^{1}H NMR
$CDCl_3$, 400 MHz
I
OMe
N
0.975
1.1
1.03
3.24
1.01
1
1.06
1.01
ppm
9
8
7
6
5
4
3
2
1
0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154.44
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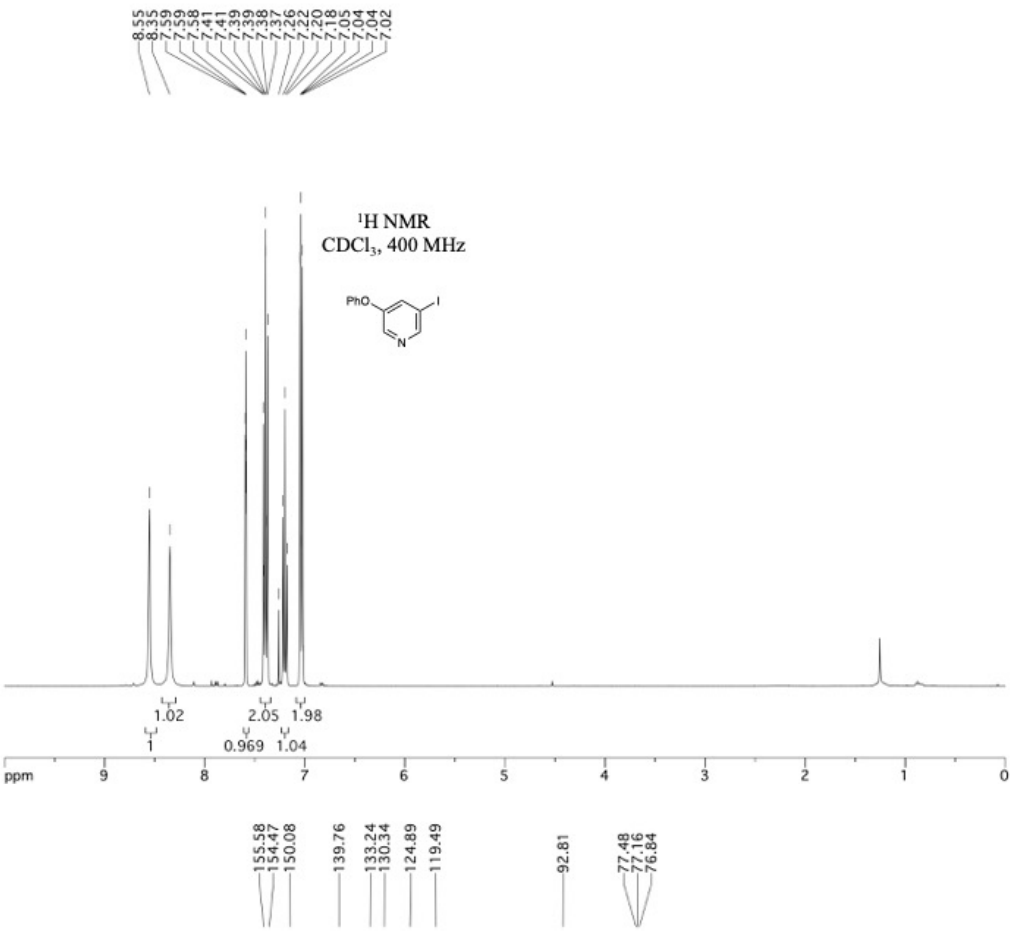
142.59
138.49
137.79
130.32
119.61
114.04
112.99
93.71
77.48
77.16
76.84
55.47
^{13}C NMR
$CDCl_3$, 100 MHz
I
OMe
N
ppm 200
150
100
50
0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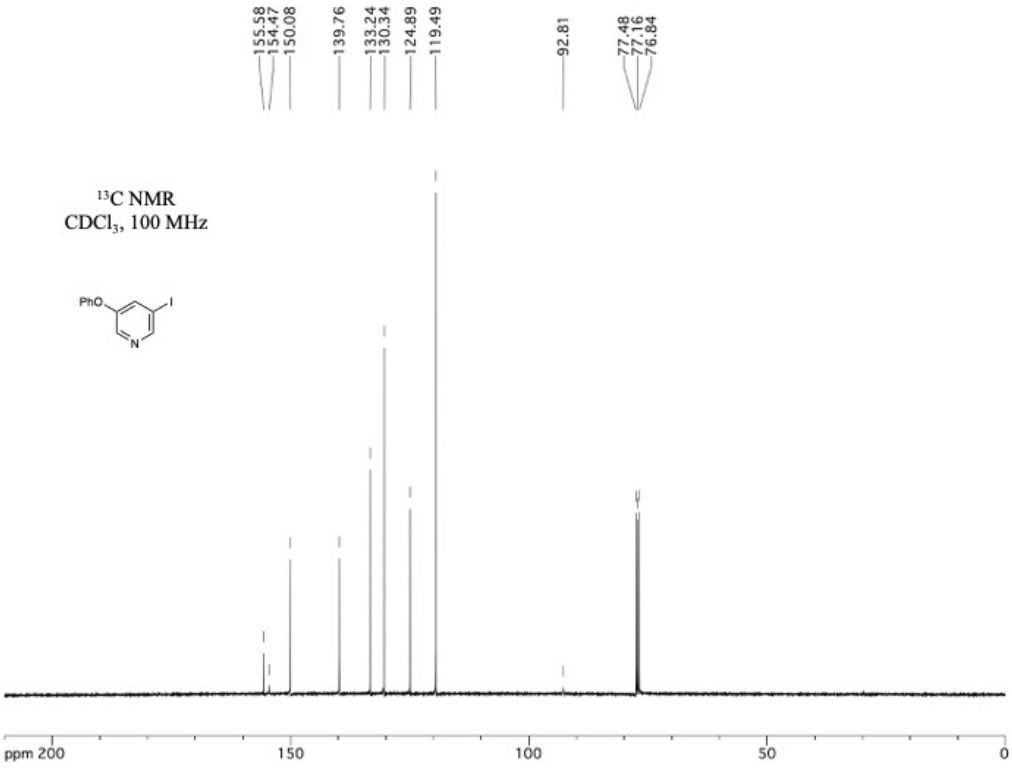
7.59
7.58
7.41
7.41
7.39
7.39
7.38
7.37
7.26
7.22
7.20
7.18
7.05
7.04
7.04
7.02
^{1}H NMR
$CDCl_3$, 400 MHz
PhO
I
N
1.02
2.05
1.98
1
0.969
1.04
ppm
9
8
7
6
5
4
3
2
1
0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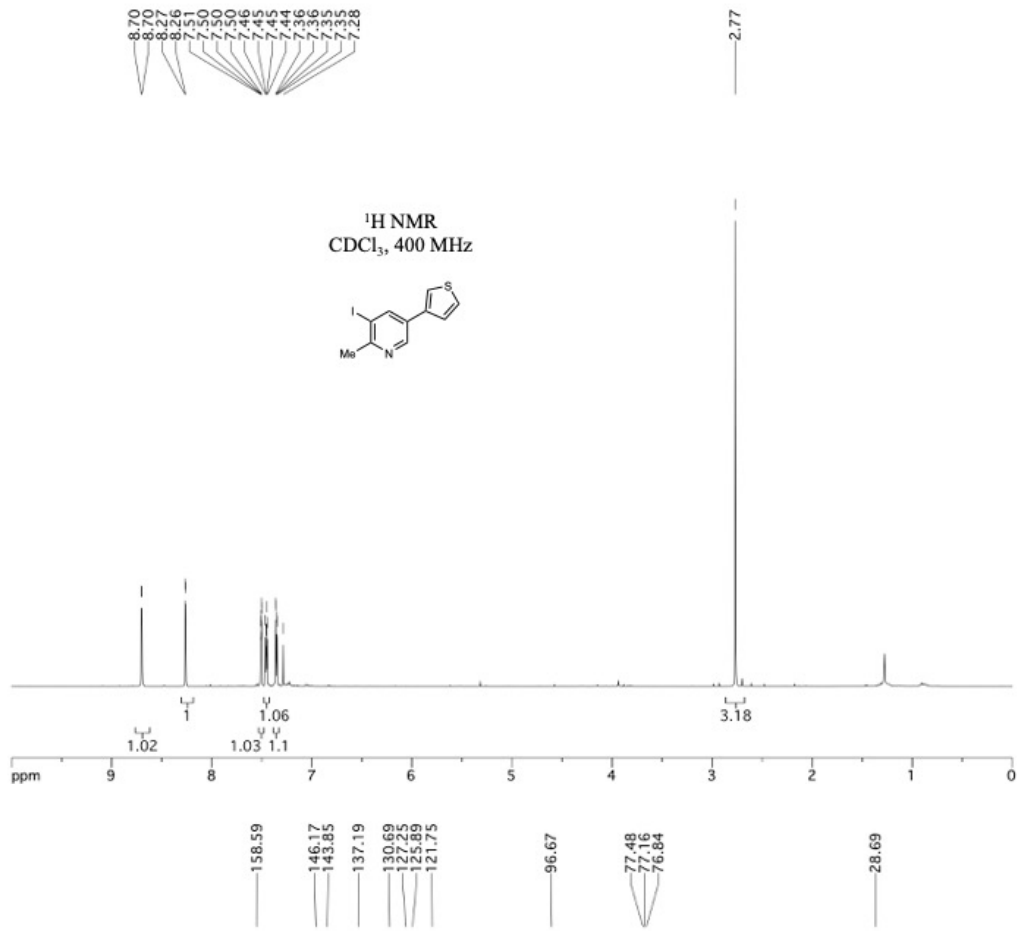
133.24
130.34
124.89
119.49
92.81
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
PhO
I
N
ppm 200
150
100
50
0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8.70
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8.26
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7.50
7.50
7.46
7.45
7.44
7.36
7.36
7.35
7.35
7.28
2.77
1H NMR
CDCl3, 400 MHz
I
Me
N
S
1
1.06
3.18
1.02
1.03
1.1
ppm
9
8
7
6
5
4
3
2
1
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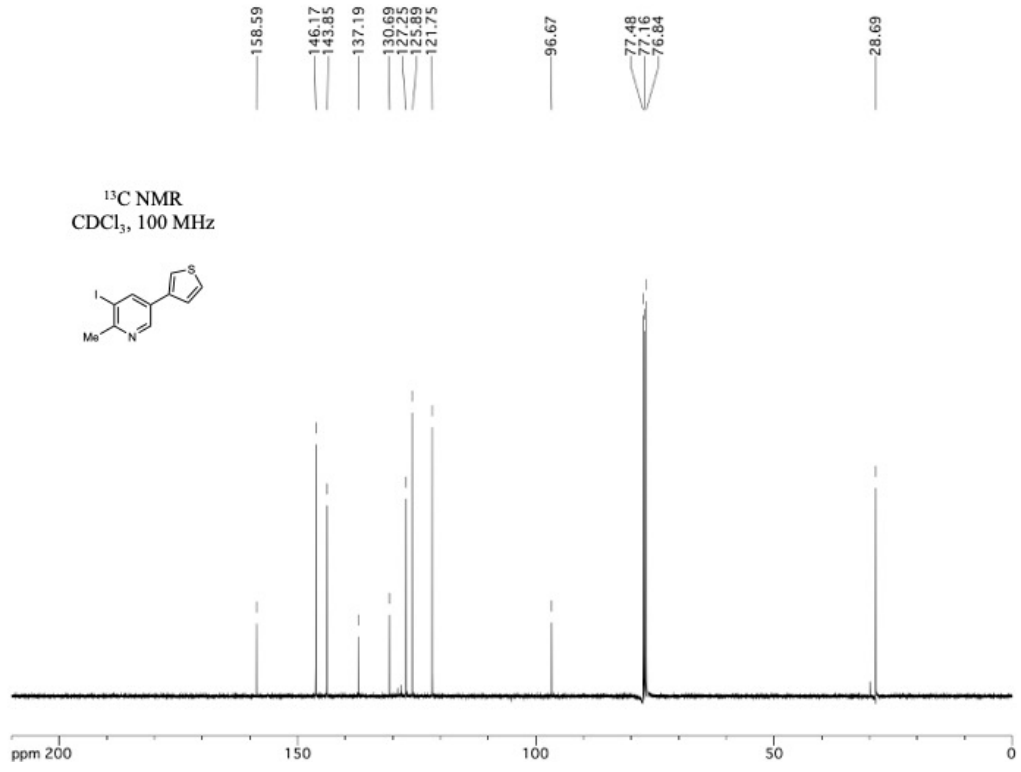
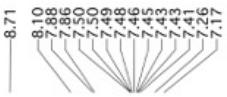
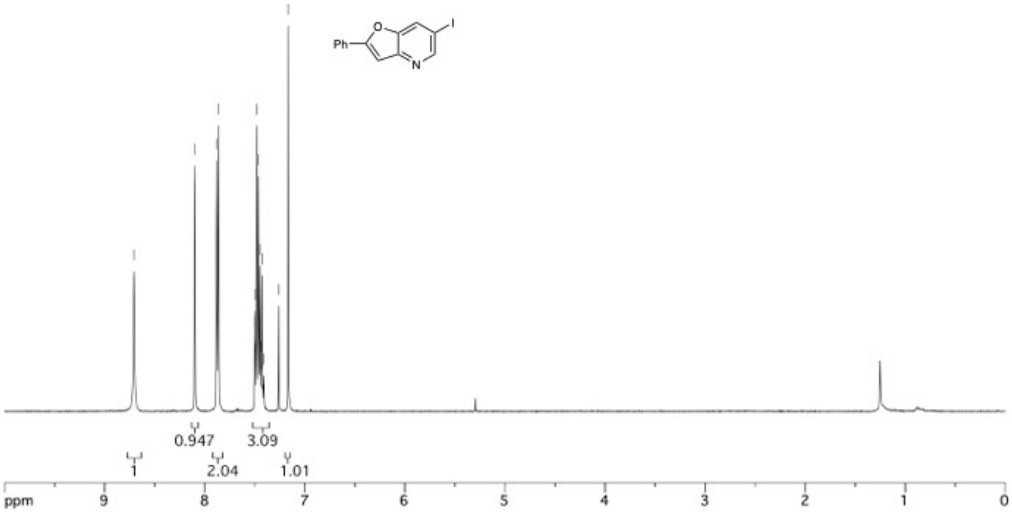
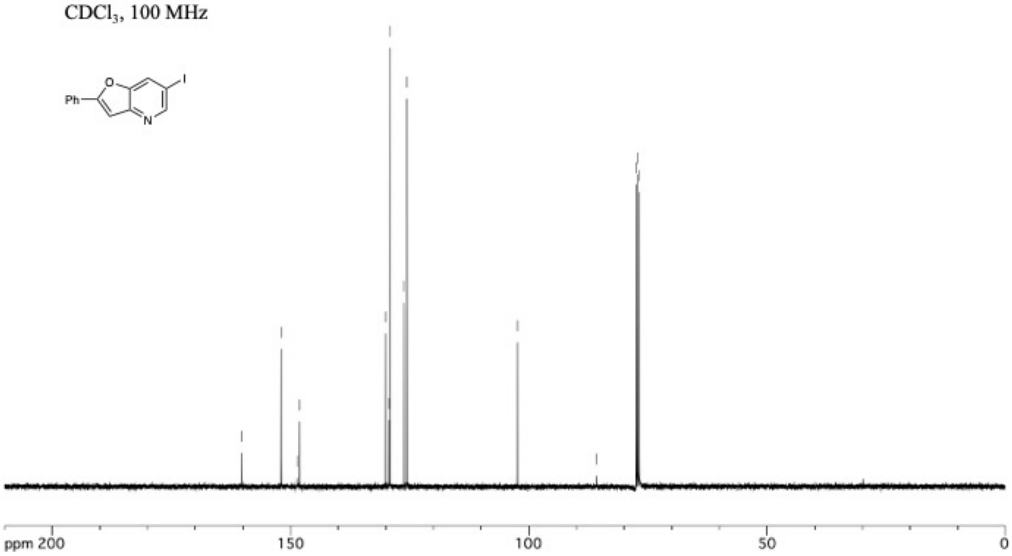

158.59
146.17
143.85
137.19
130.69
127.25
125.89
121.75
96.67
77.48
77.16
76.84
28.69
13C NMR
CDCl3, 100 MHz
I
Me
N
S
ppm 200
150
100
50
0

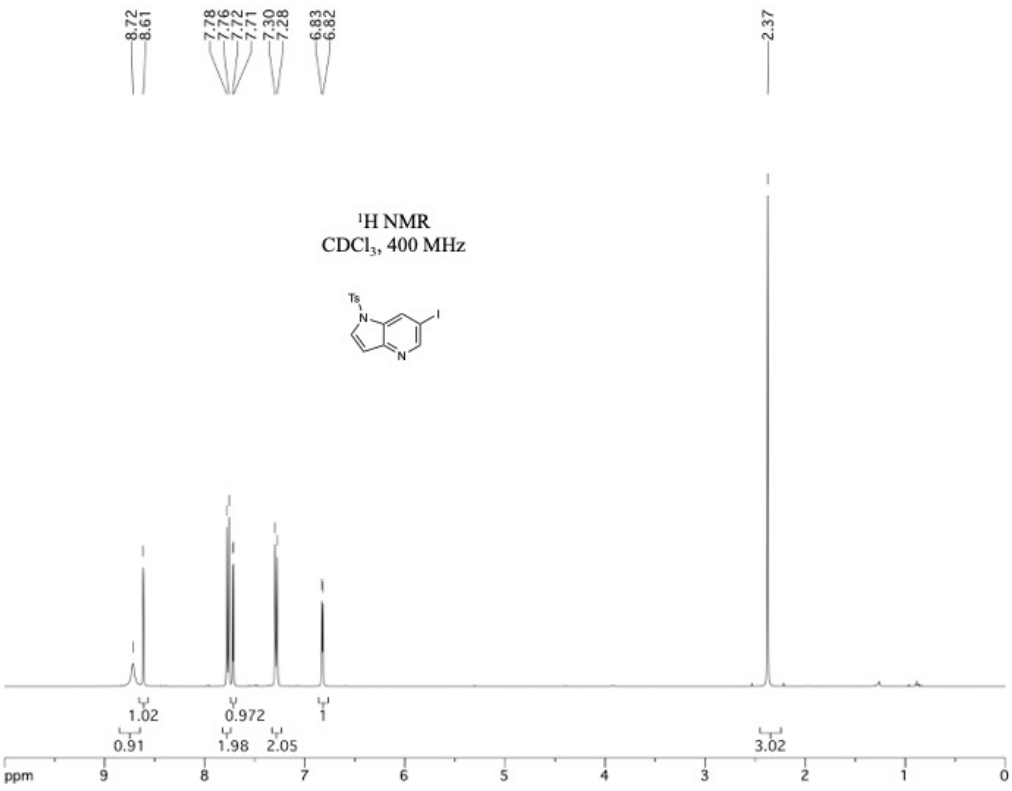


^{1}H NMR
$CDCl_3$, 400 MHz

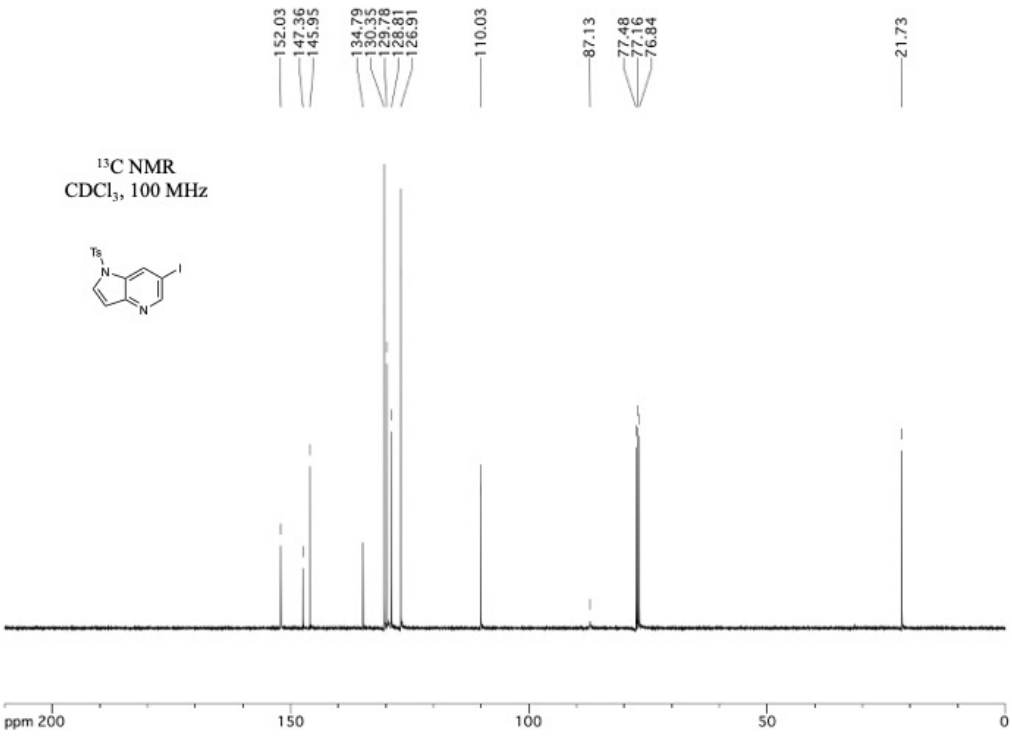


^{13}C NMR
$CDCl_3$, 100 MHz

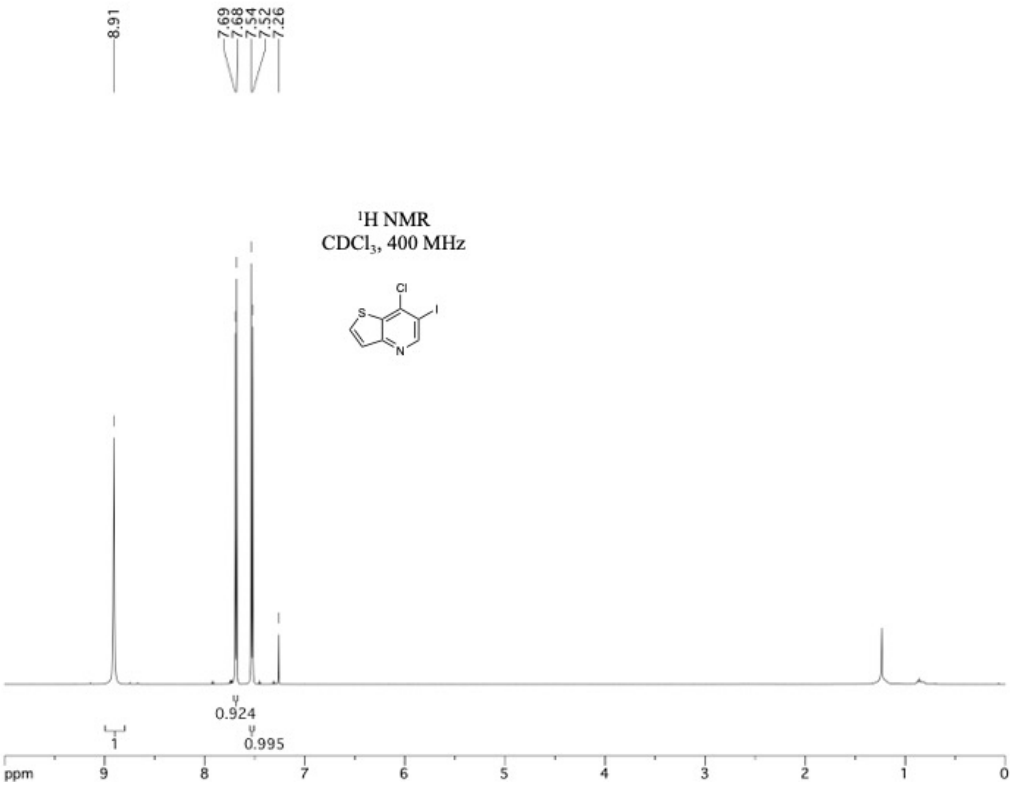


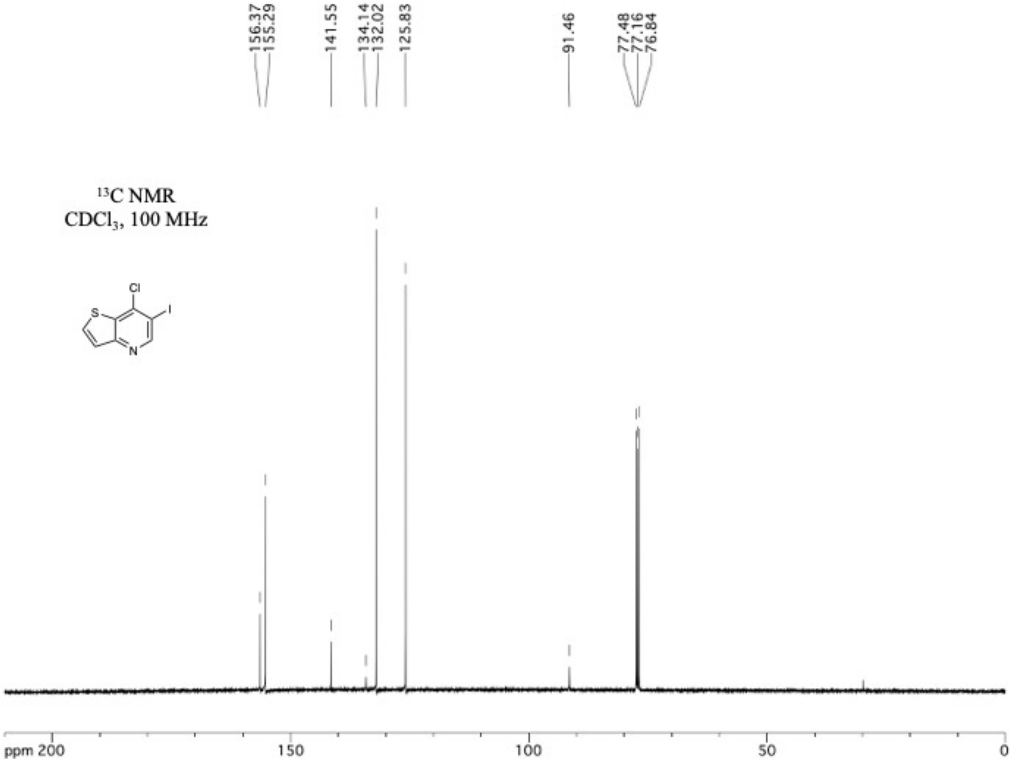


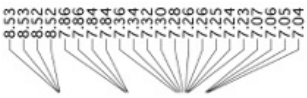
^{1}H NMR
$CDCl_3$, 400 MHz

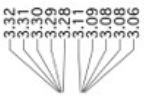


^{13}C NMR
$CDCl_3$, 100 MHz

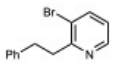

8.91
7.69
7.68
7.54
7.52
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Cl
S
I
N
0.924
1
0.995
ppm
9
8
7
6
5
4
3
2
1
0


156.37
155.29
141.55
134.14
132.02
125.83
91.46
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
S
I
N
ppm 200
150
100
50
0

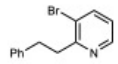


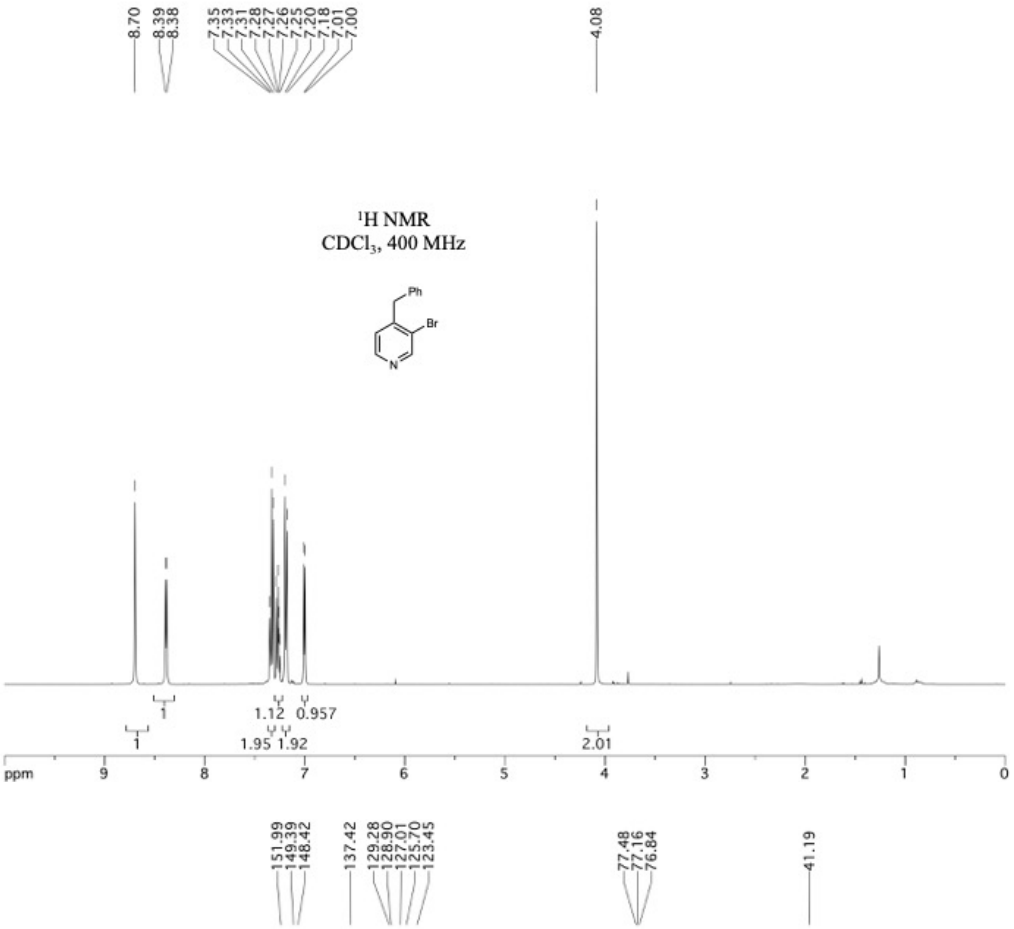


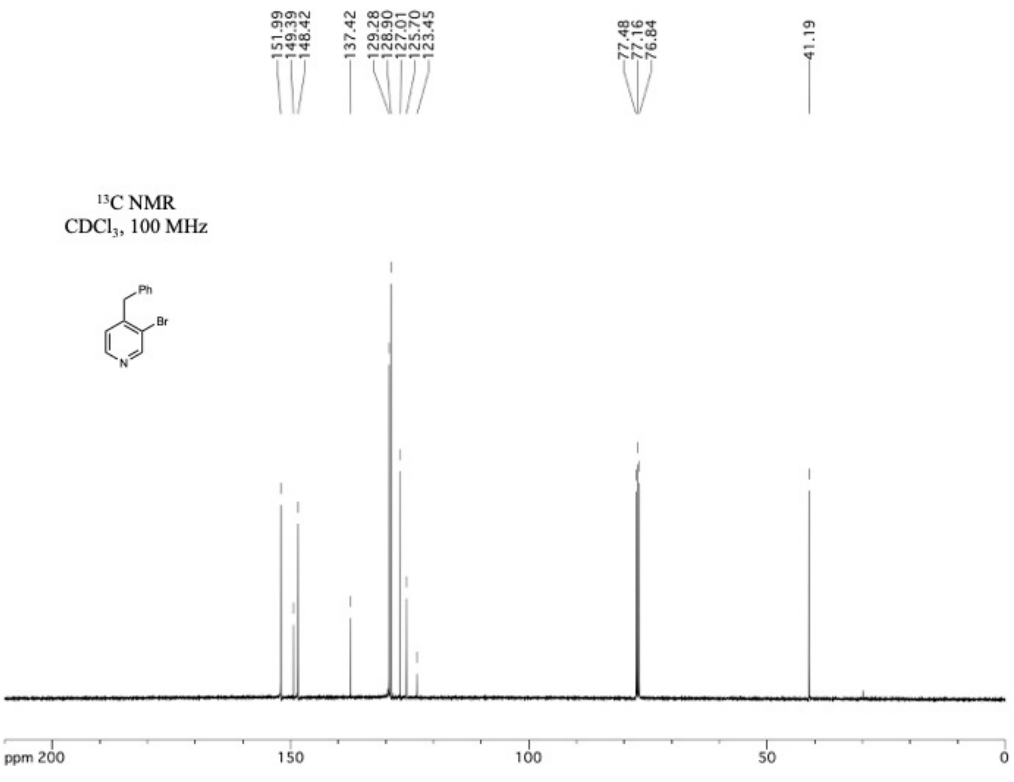
^{1}H NMR
$CDCl_3$, 400 MHz

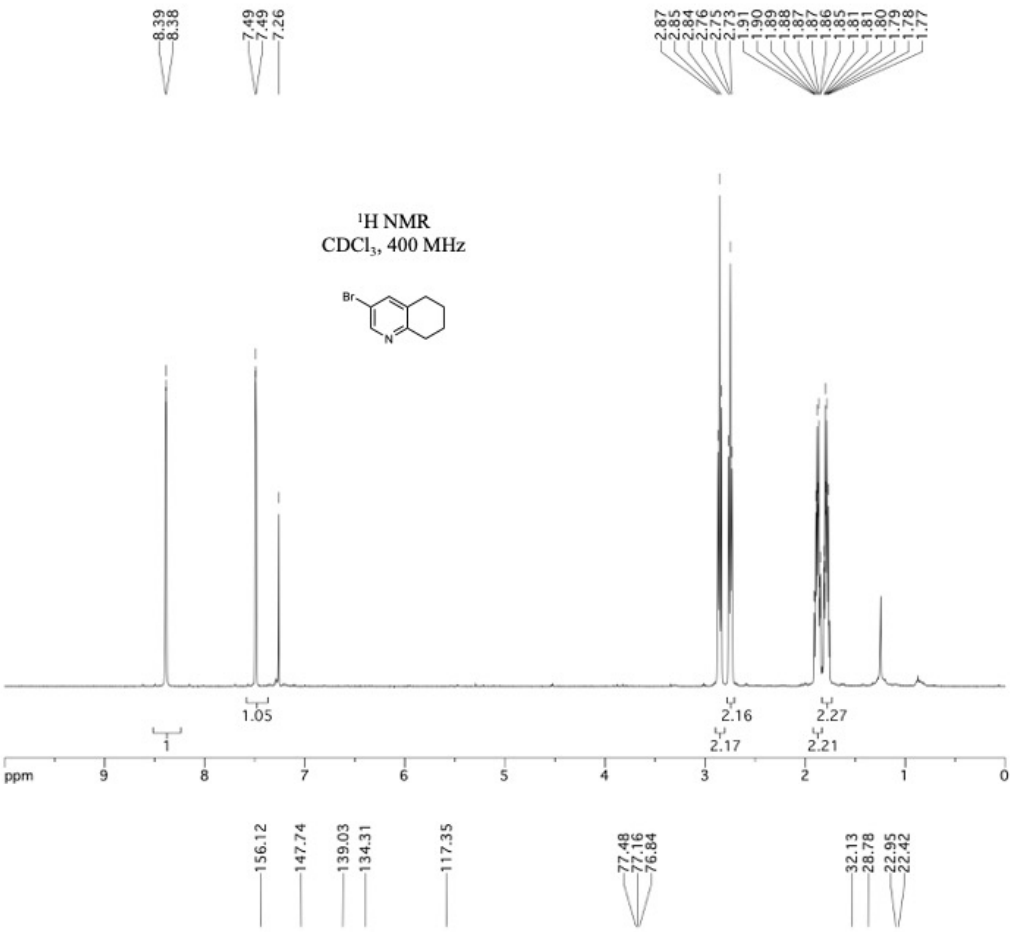


^{13}C NMR
$CDCl_3$, 100 MHz

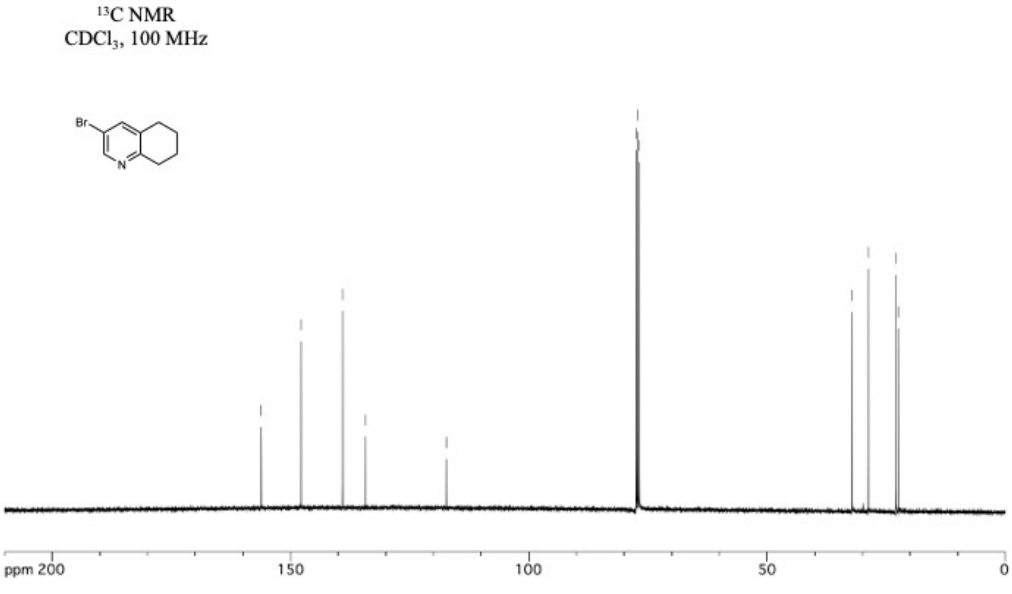


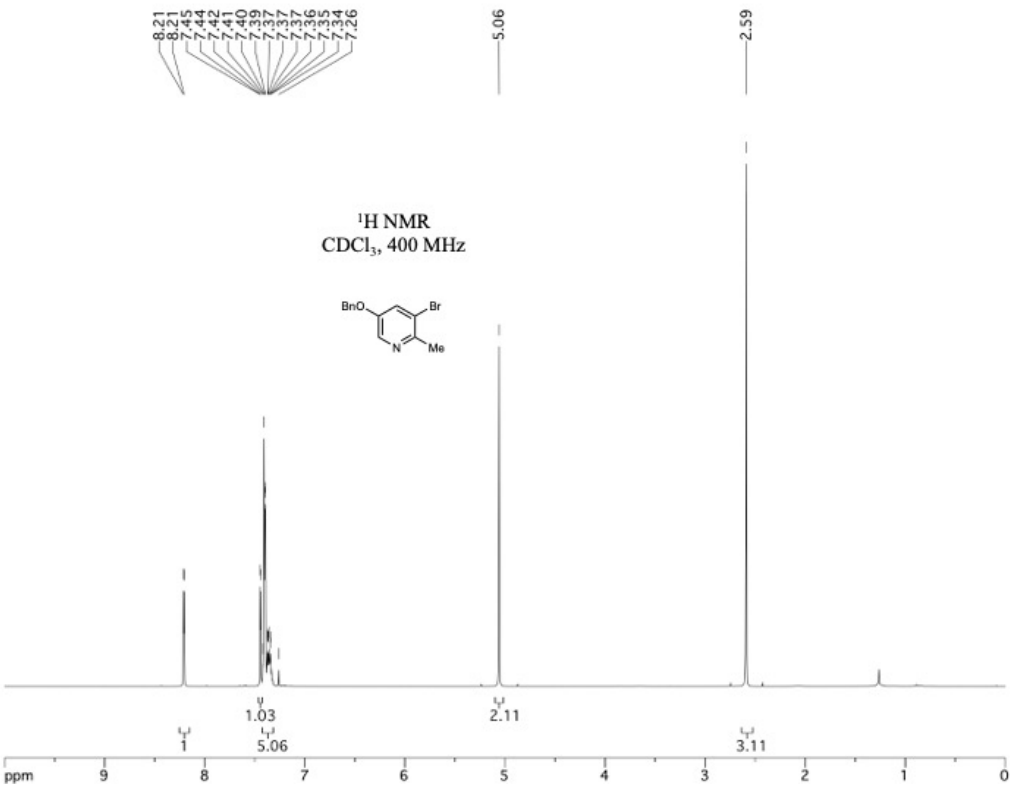

8.70
8.39
8.38
7.35
7.33
7.31
7.28
7.27
7.26
7.25
7.20
7.18
7.01
7.00
4.08
1H NMR
CDCl3, 400 MHz
Ph
Br
N
1
1.12
0.957
1
1.95
1.92
2.01
ppm
9
8
7
6
5
4
3
2
1
0

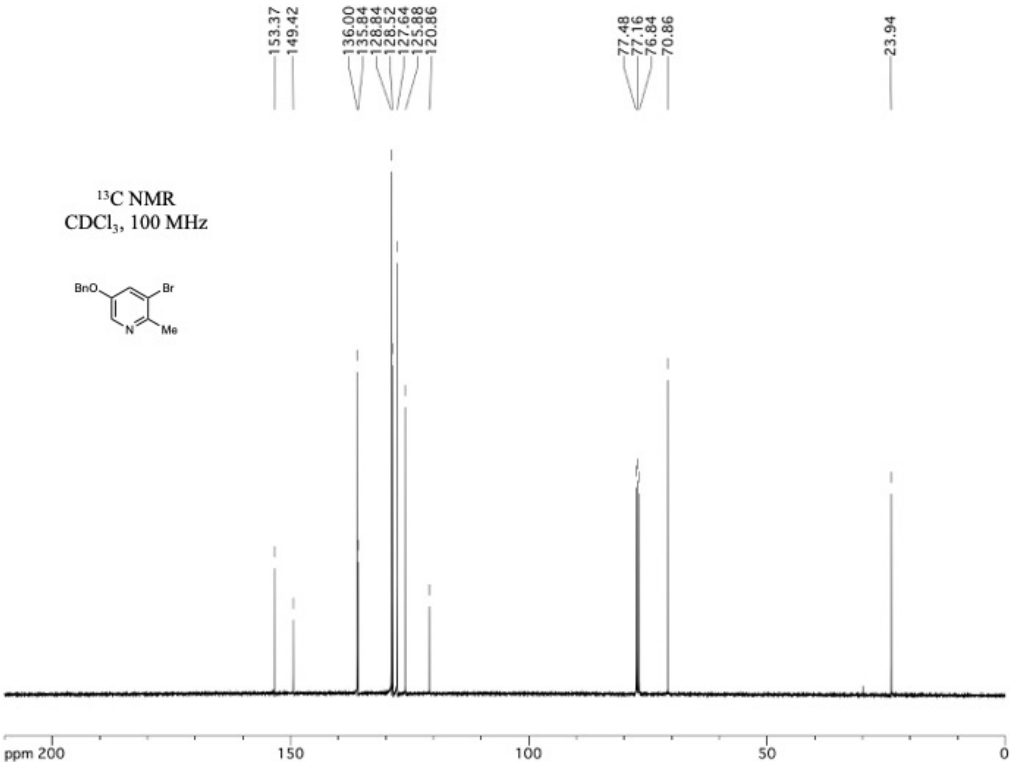

151.99
149.39
148.42
137.42
129.28
128.50
125.01
123.70
123.45
77.48
77.16
76.84
41.19
13C NMR
CDCl3, 100 MHz
Ph
Br
N
ppm 200
150
100
50
0


8.39
8.38
7.49
7.49
7.26
2.87
2.85
2.84
2.76
2.75
2.73
1.91
1.90
1.89
1.88
1.87
1.87
1.86
1.85
1.81
1.81
1.80
1.79
1.78
1.77
1H NMR
CDCl3, 400 MHz
Br
N
1.05
1
2.16
2.17
2.27
2.21
ppm
9
8
7
6
5
4
3
2
1
0

156.12
147.74
139.03
134.31
117.35
77.48
77.16
76.84
32.13
28.78
22.95
22.42


13C NMR
CDCl3, 100 MHz
Br
N
ppm 200
150
100
50
0


8.21
8.21
7.45
7.44
7.42
7.41
7.40
7.39
7.37
7.37
7.37
7.36
7.35
7.34
7.26
5.06
2.59
1H NMR
CDCl3, 400 MHz
BnO
Br
N
Me
1.03
2.11
1
5.06
3.11
ppm
9
8
7
6
5
4
3
2
1
0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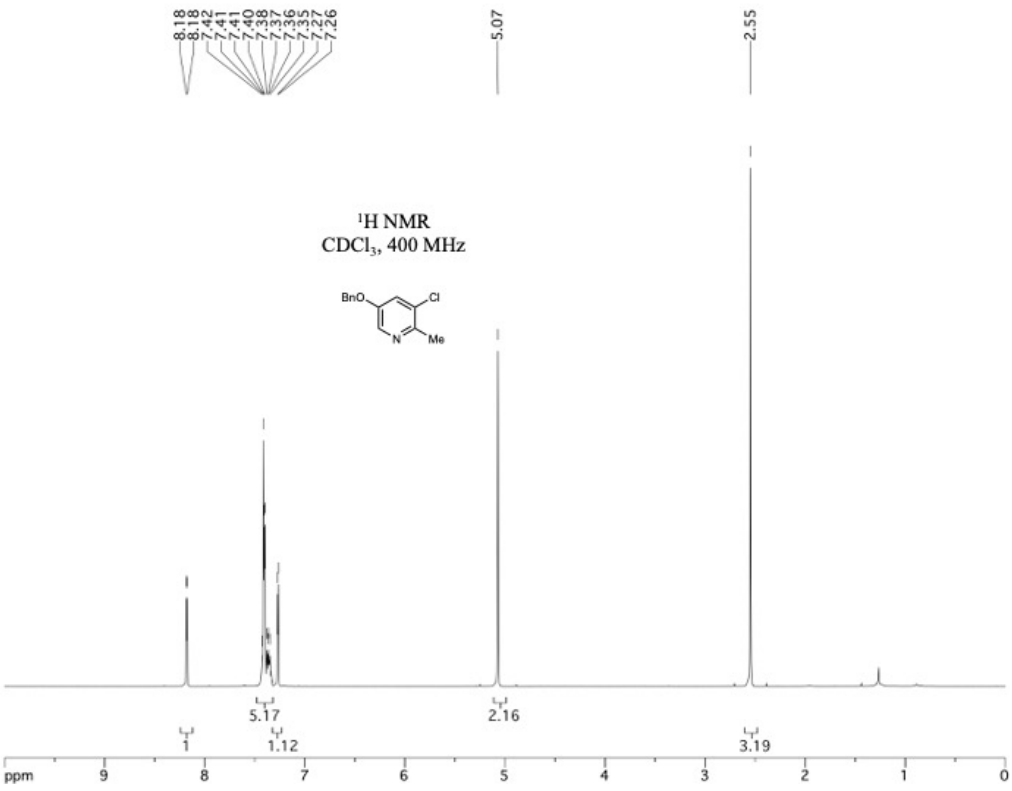
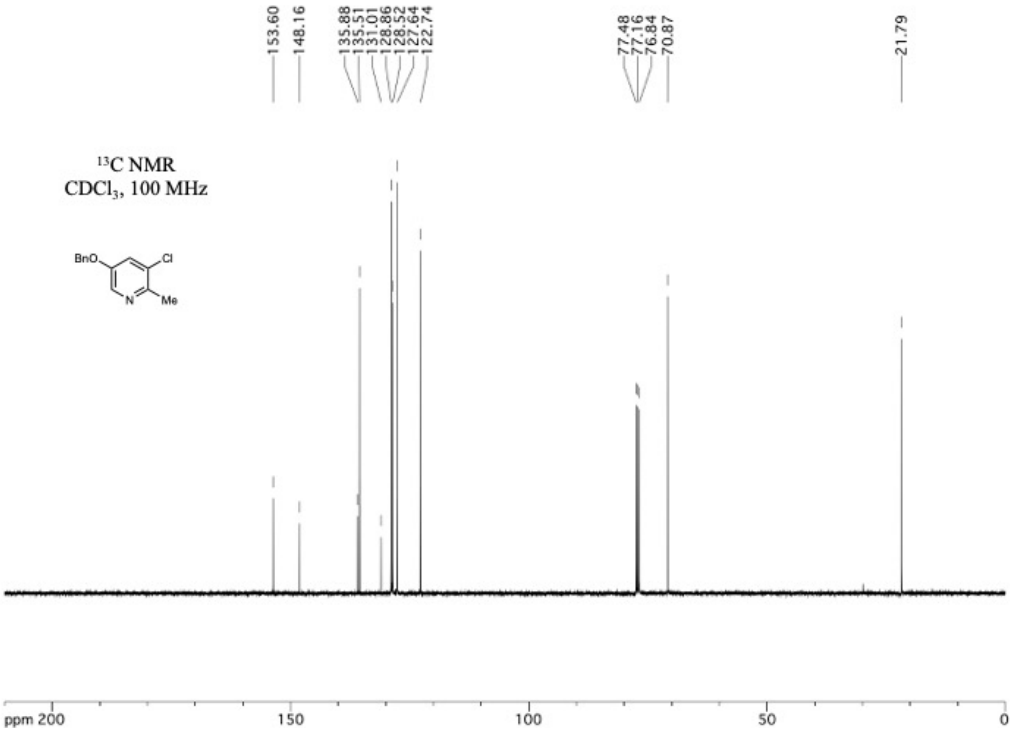
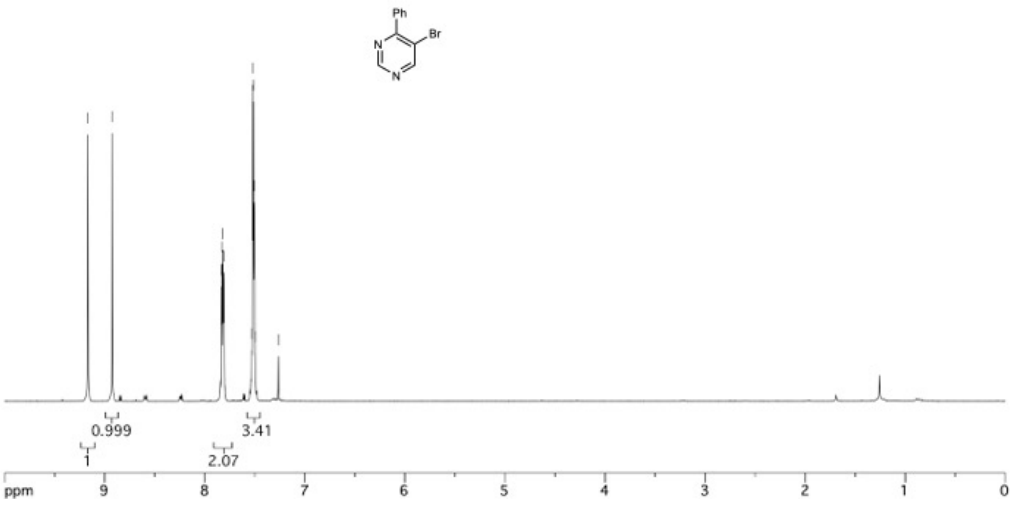
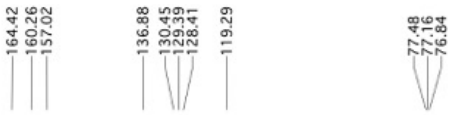
149.42
136.00
135.84
128.84
128.52
127.64
125.88
120.86
77.48
77.16
76.84
70.86
23.94
13C NMR
CDCl3, 100 MHz
BnO
Br
N
Me
ppm 200
150
100
50
0


8.18
8.18
7.42
7.41
7.40
7.38
7.37
7.36
7.35
7.27
7.26
5.07
2.55
^{1}H NMR
$CDCl_3$, 400 MHz
BnO
Cl
N
Me
5.17
2.16
1
1.12
3.19
ppm
9
8
7
6
5
4
3
2
1
0

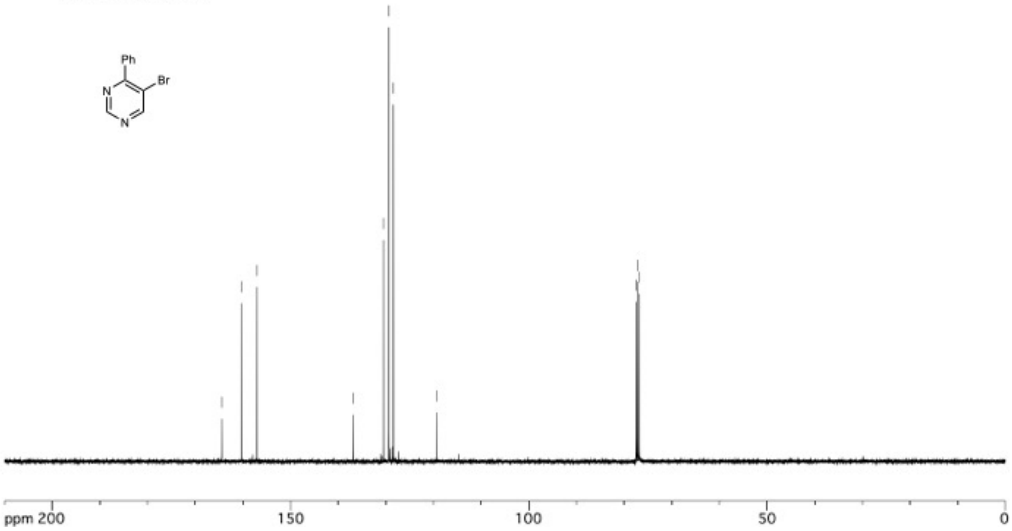

153.60
148.16
135.88
135.51
131.01
128.86
128.52
127.64
122.74
77.48
77.16
76.84
70.87
21.79
^{13}C NMR
$CDCl_3$, 100 MHz
BnO
Cl
N
Me
ppm 200
150
100
50
0

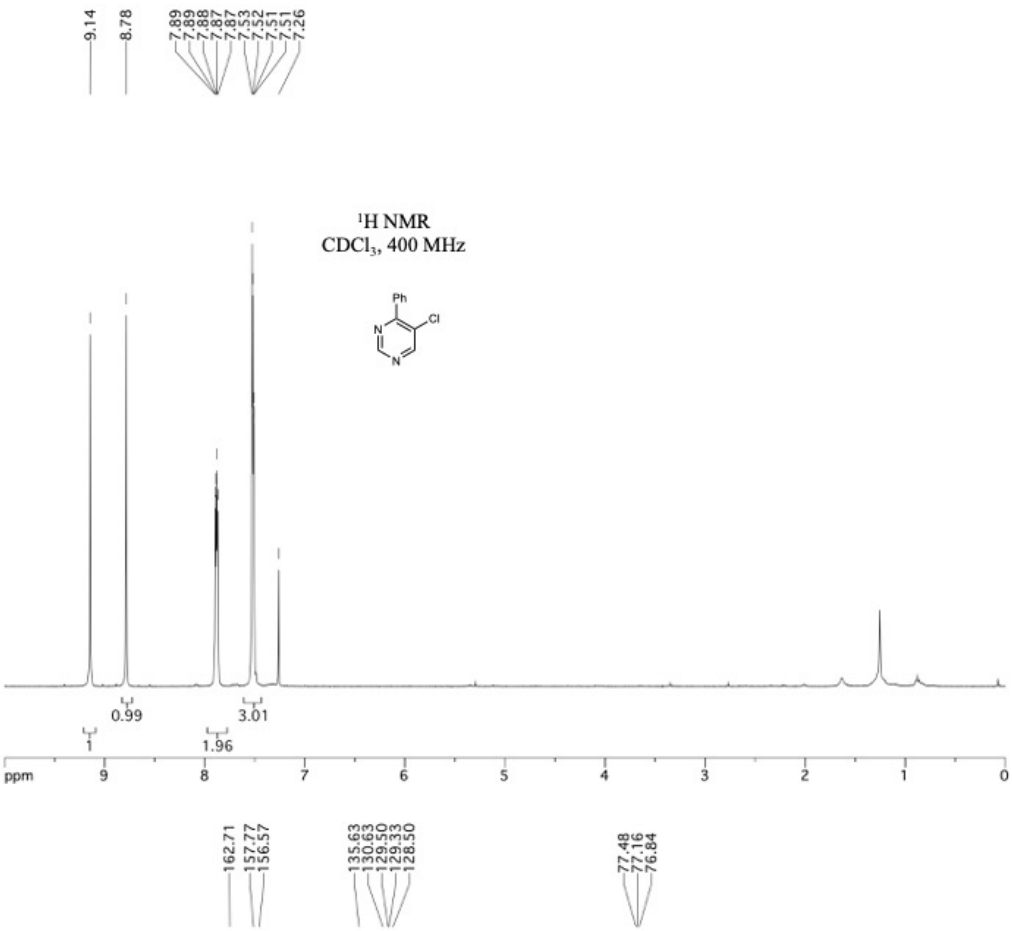
^{1}H NMR
$CDCl_3$, 400 MHz

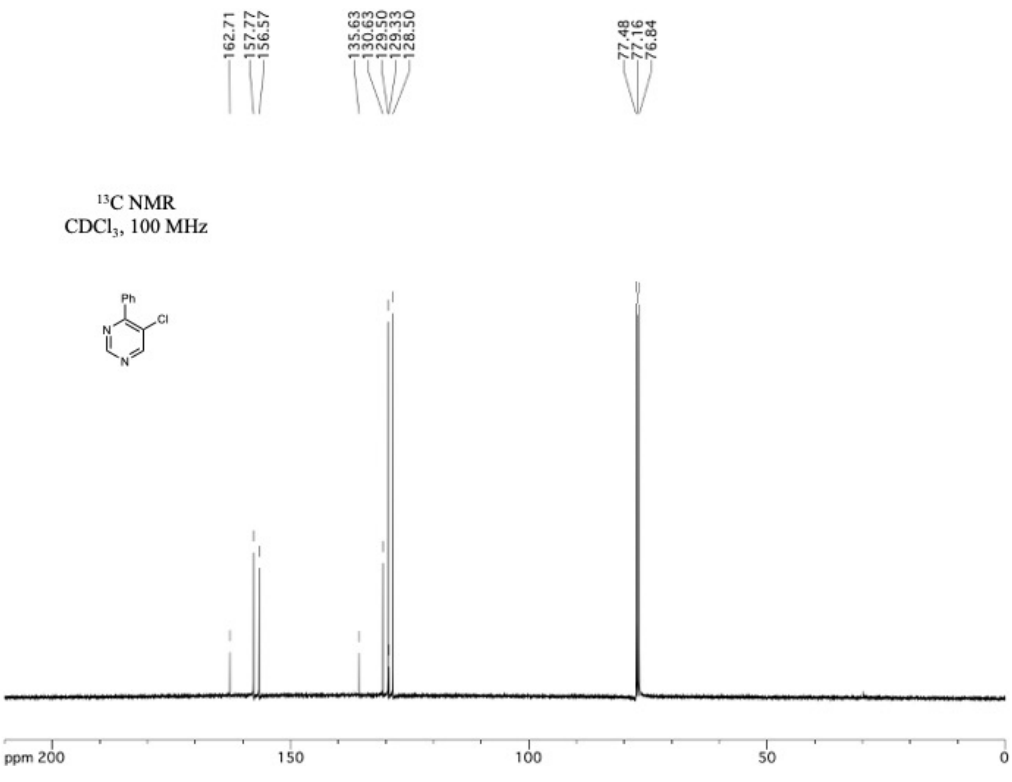


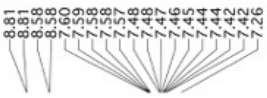


^{13}C NMR
$CDCl_3$, 100 MHz



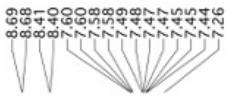

9.14
8.78
7.89
7.89
7.88
7.87
7.87
7.53
7.52
7.51
7.51
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Ph
Cl
N
N
0.99
3.01
1
1.96
ppm
9
8
7
6
5
4
3
2
1
0


162.71
157.77
156.57
135.63
130.63
129.50
129.33
128.50
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Ph
Cl
N
N
ppm 200
150
100
50
0

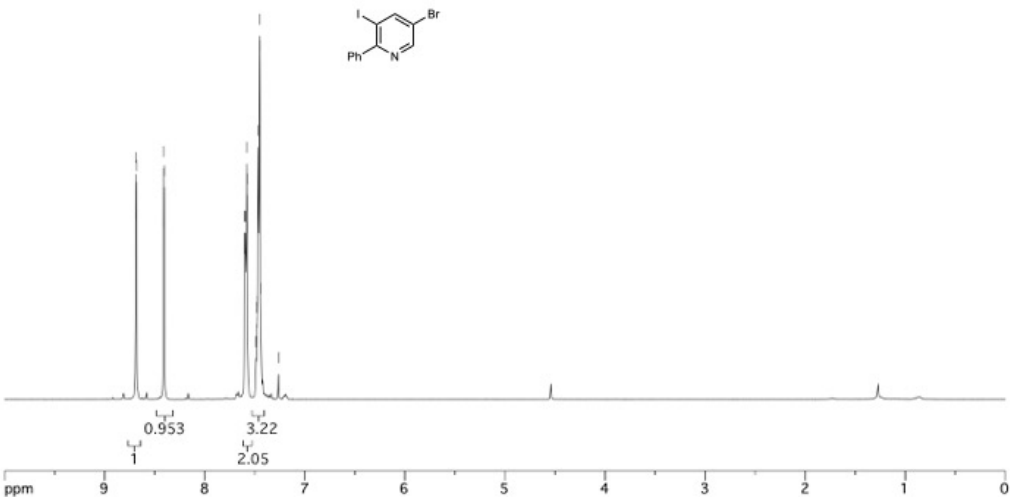


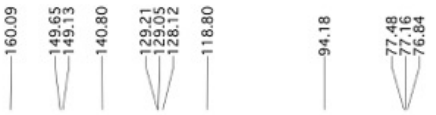
^{1}H NMR
$CDCl_3$, 400 MHz

^{13}C NMR
$CDCl_3$, 100 MHz

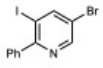


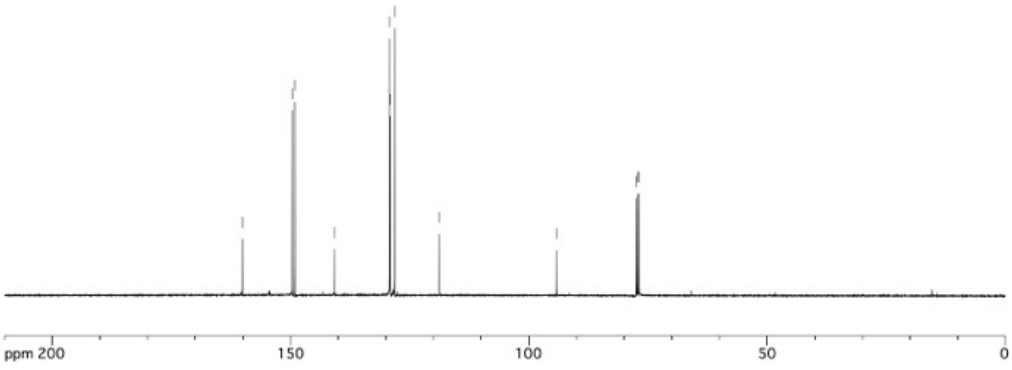
^{1}H NMR
$CDCl_3$, 400 MHz

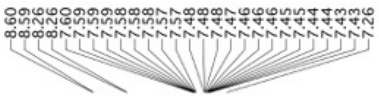




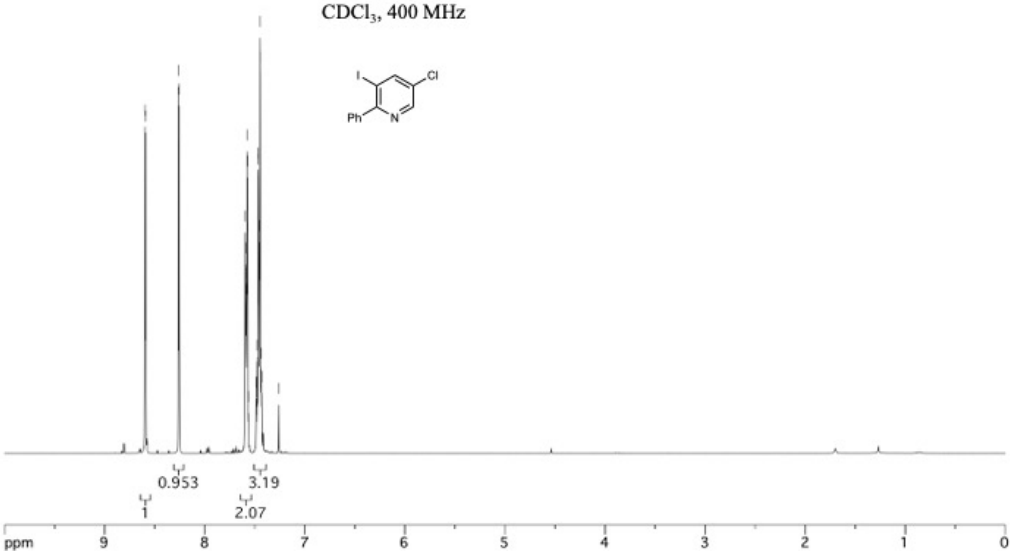
^{13}C NMR
$CDCl_3$, 100 MHz



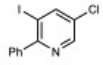




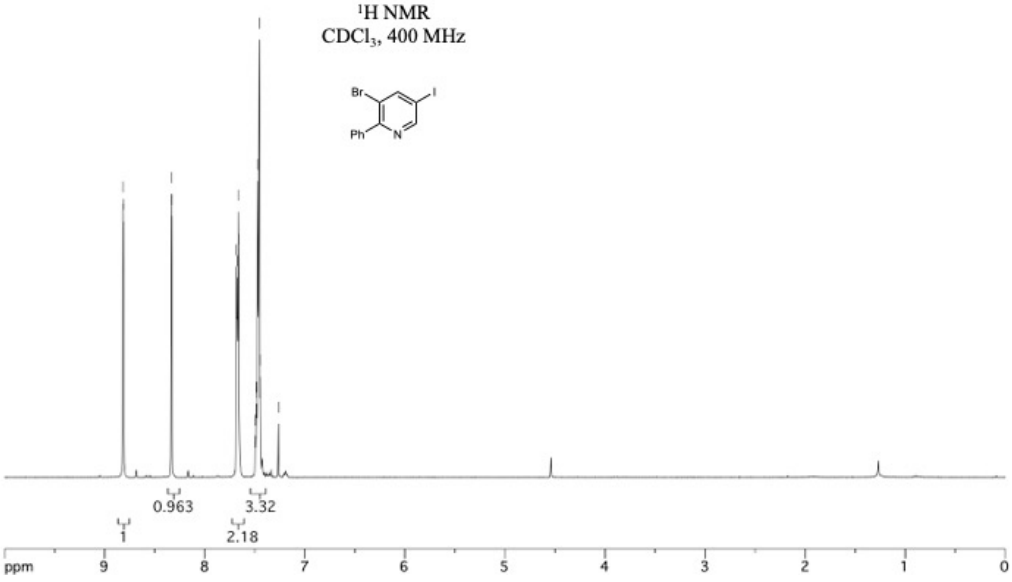
^{1}H NMR
$CDCl_3$, 400 MHz



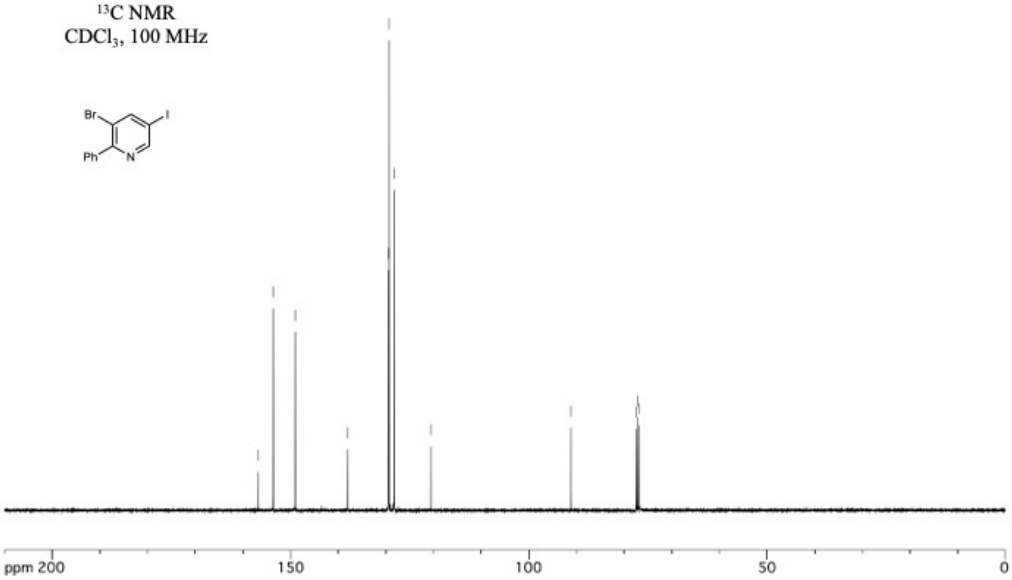
^{13}C NMR
$CDCl_3$, 100 MHz

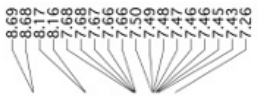


^{1}H NMR
$CDCl_3$, 400 MHz

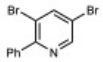


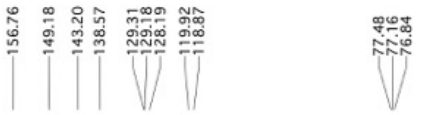
^{13}C NMR
$CDCl_3$, 100 MHz



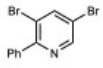


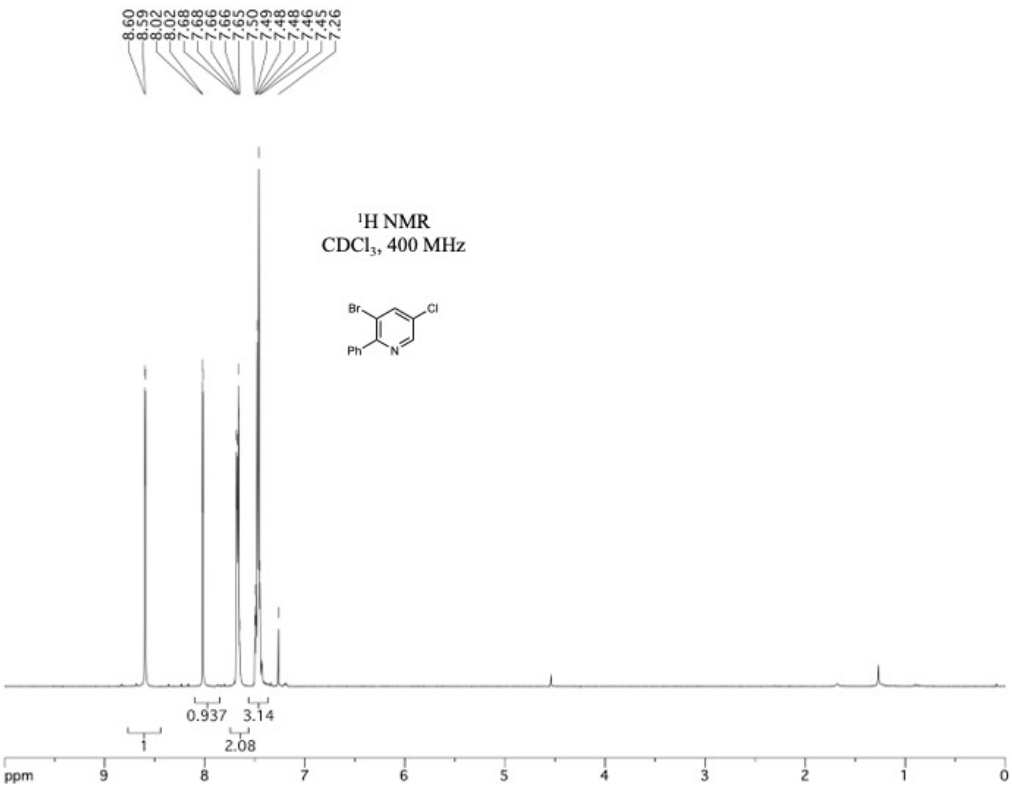
^{1}H NMR
$CDCl_3$, 400 MHz

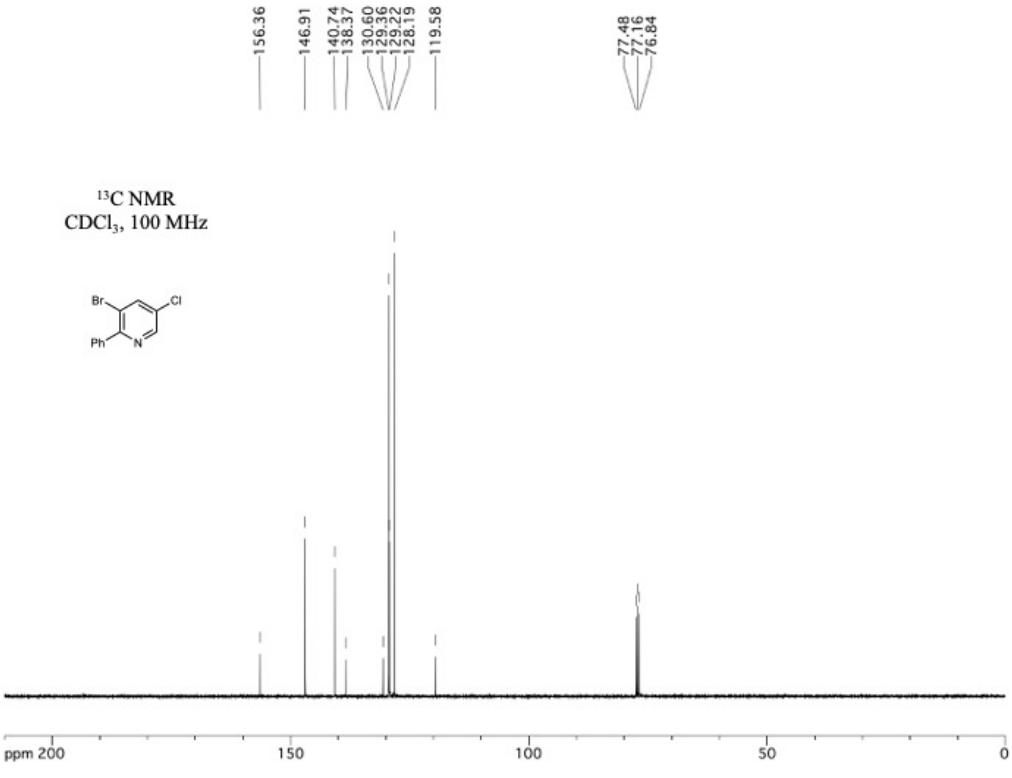


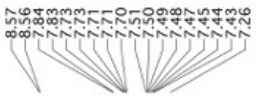


^{13}C NMR
$CDCl_3$, 100 MHz

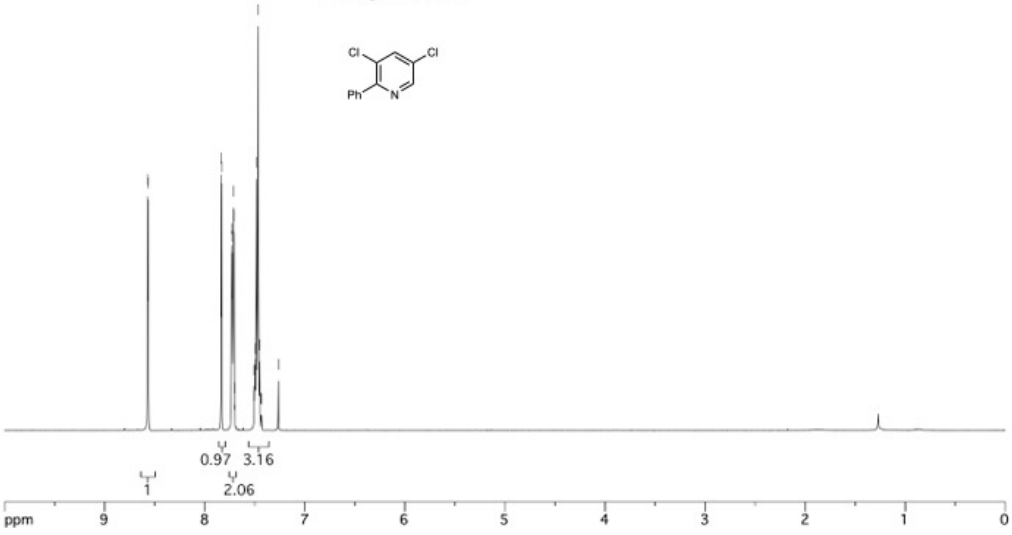



8.60
8.59
8.02
8.02
7.68
7.68
7.66
7.66
7.65
7.50
7.49
7.48
7.48
7.46
7.45
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Br
Cl
Ph
N
0.937
3.14
1
2.08
ppm
9
8
7
6
5
4
3
2
1
0

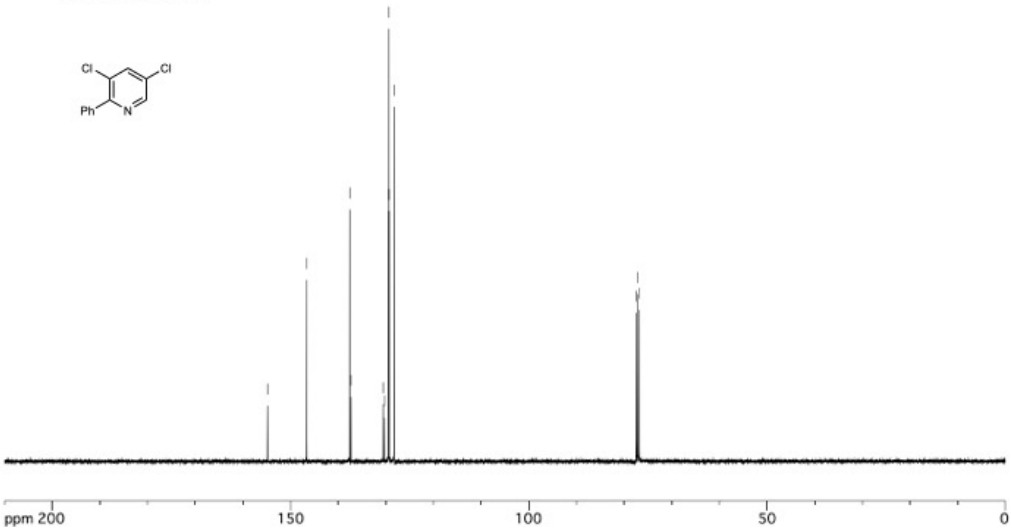

156.36
146.91
140.74
138.37
130.60
129.36
129.22
128.19
119.58
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Br
Cl
Ph
N
ppm 200
150
100
50
0

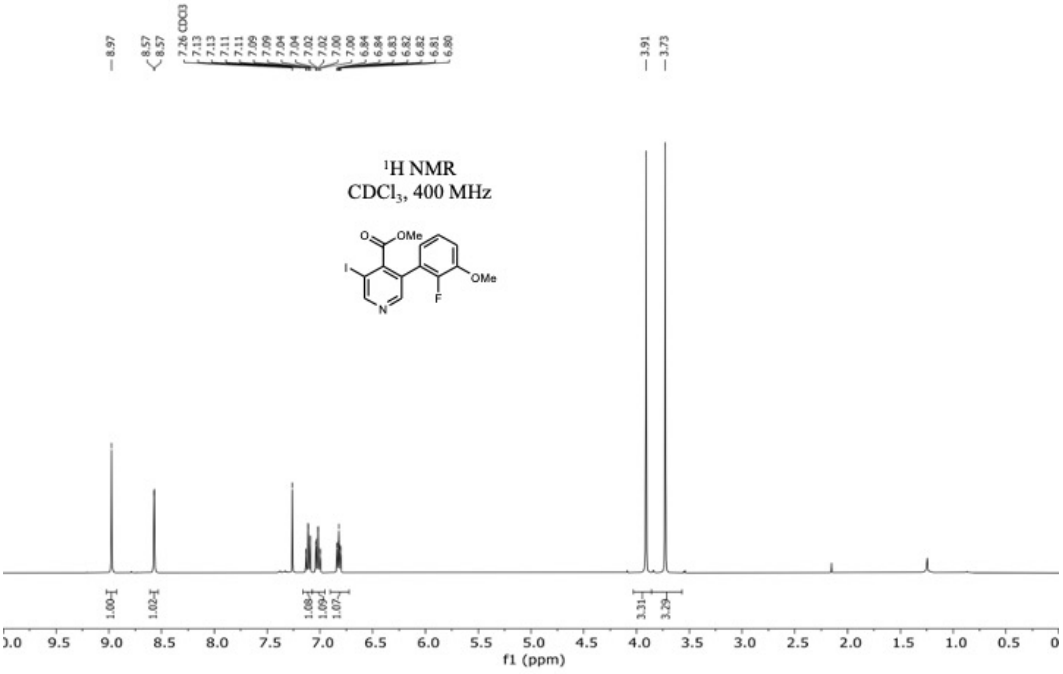


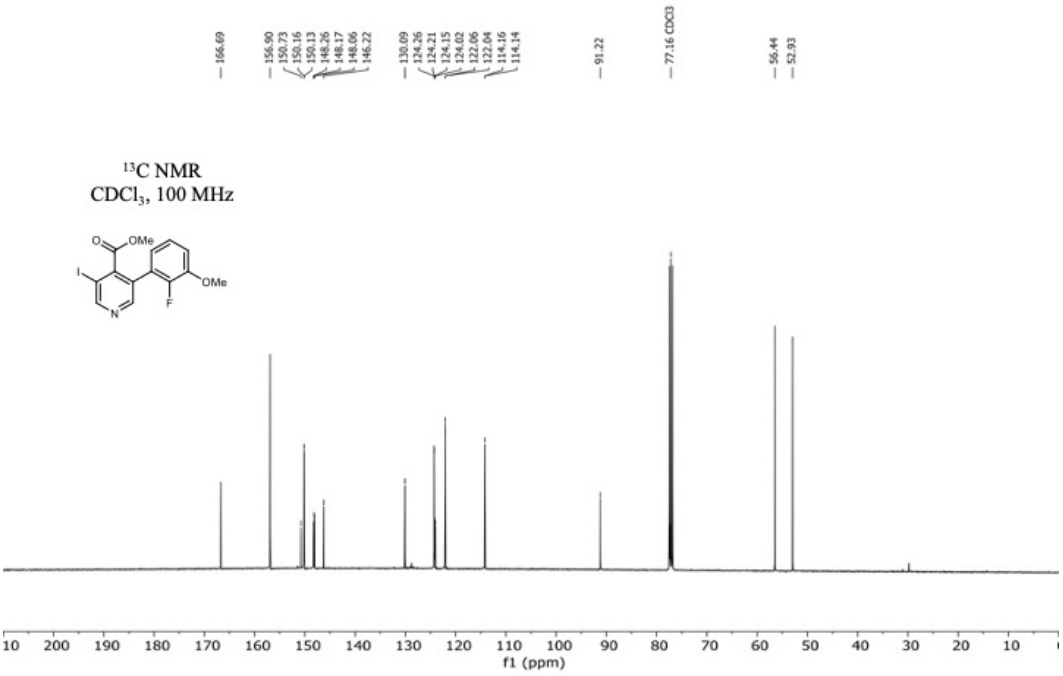
^{1}H NMR
$CDCl_3$, 400 MHz



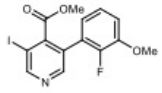
^{13}C NMR
$CDCl_3$, 100 MHz

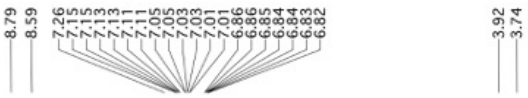



8.97
8.57
8.57
7.26 CDCl3
7.13
7.13
7.11
7.11
7.09
7.09
7.04
7.04
7.02
7.02
7.00
7.00
6.84
6.84
6.83
6.82
6.82
6.81
6.80
3.91
3.73
1H NMR
CDCl3, 400 MHz
OMe
I
OMe
F
N
1.00
1.02
1.08
1.09
1.07
3.31
3.29
f1 (ppm)

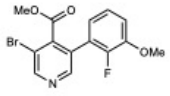

166.69
156.90
150.73
150.16
150.13
148.26
148.17
148.06
146.22
130.09
124.26
124.21
124.15
124.02
122.06
122.04
114.16
114.14
91.22
77.16 CDCl3
56.44
52.93
13C NMR
CDCl3, 100 MHz
OMe
I
OMe
F
N
f1 (ppm)

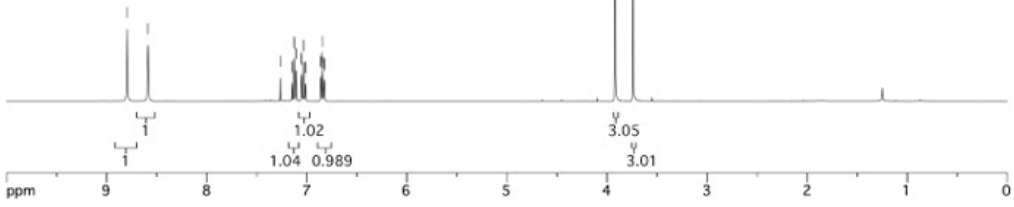
^{19}F NMR
$CDCl_3$, 365 MHz

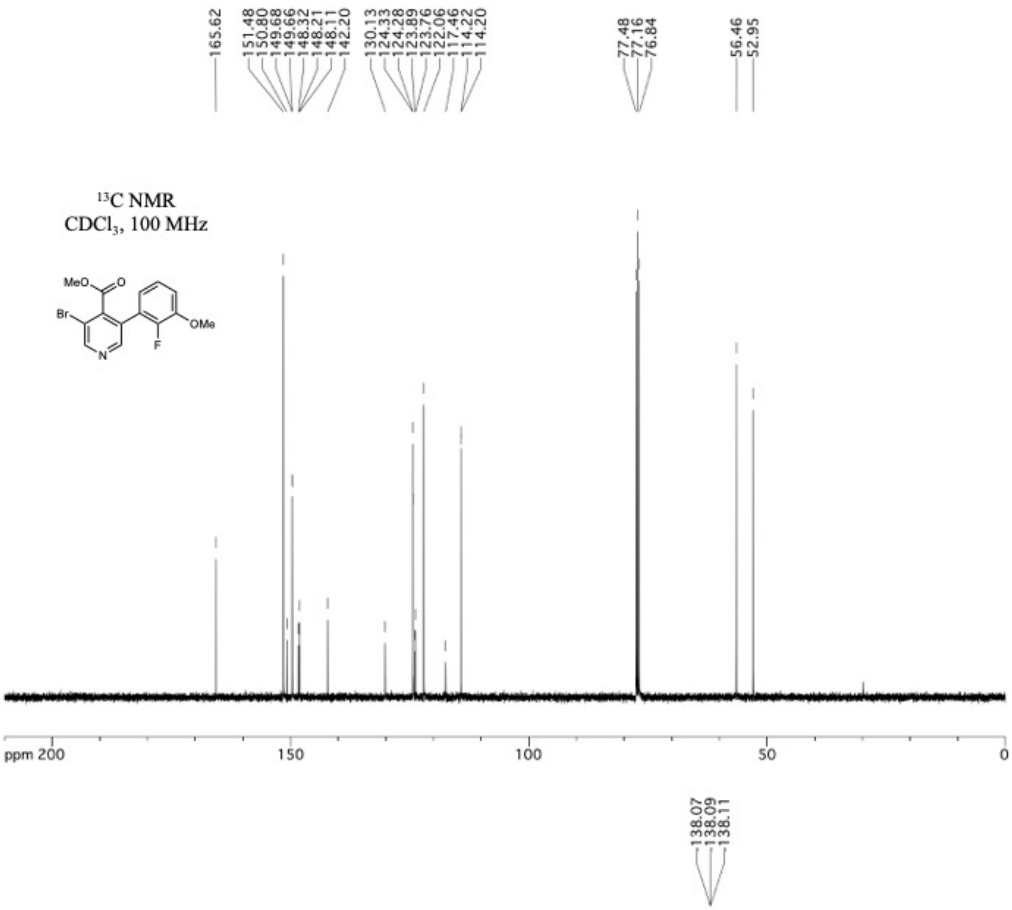


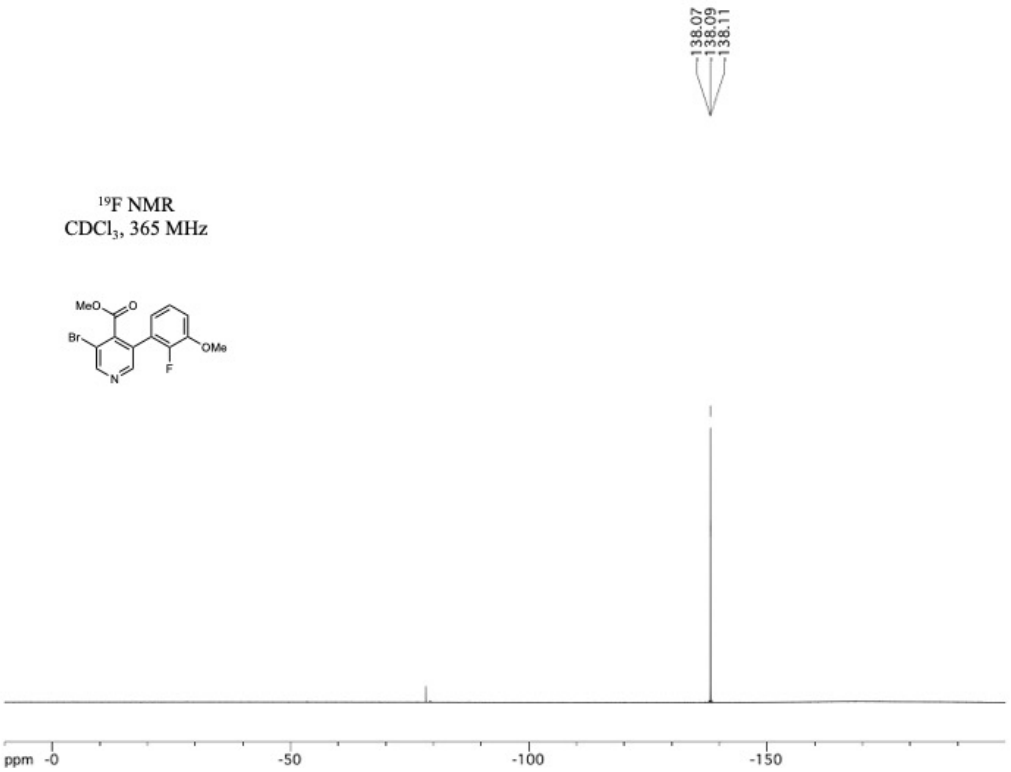


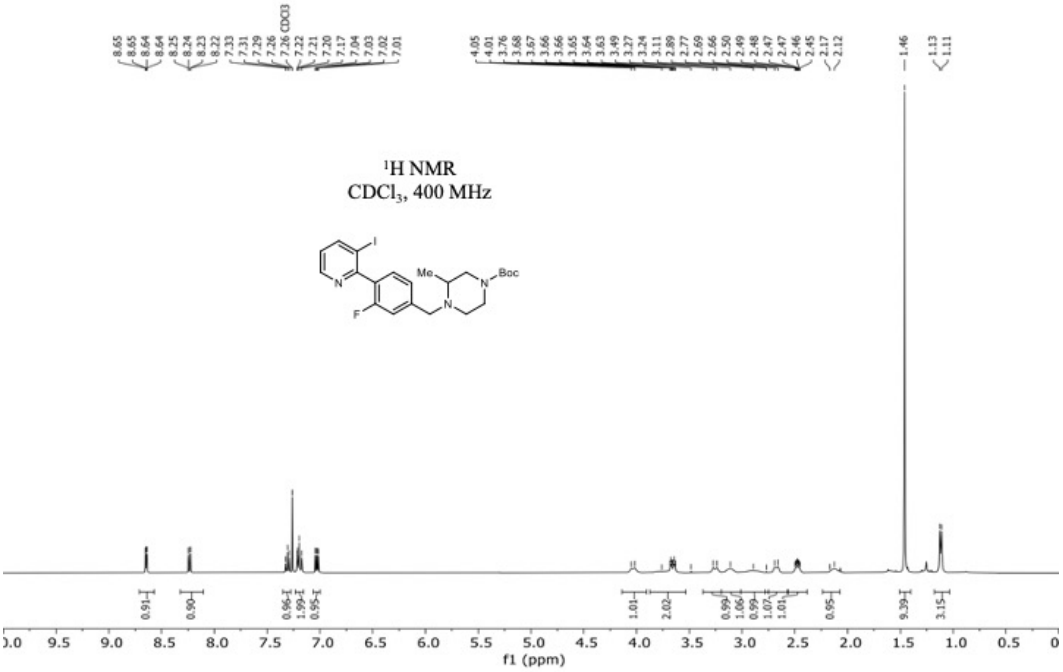
^{1}H NMR
$CDCl_3$, 400 MHz



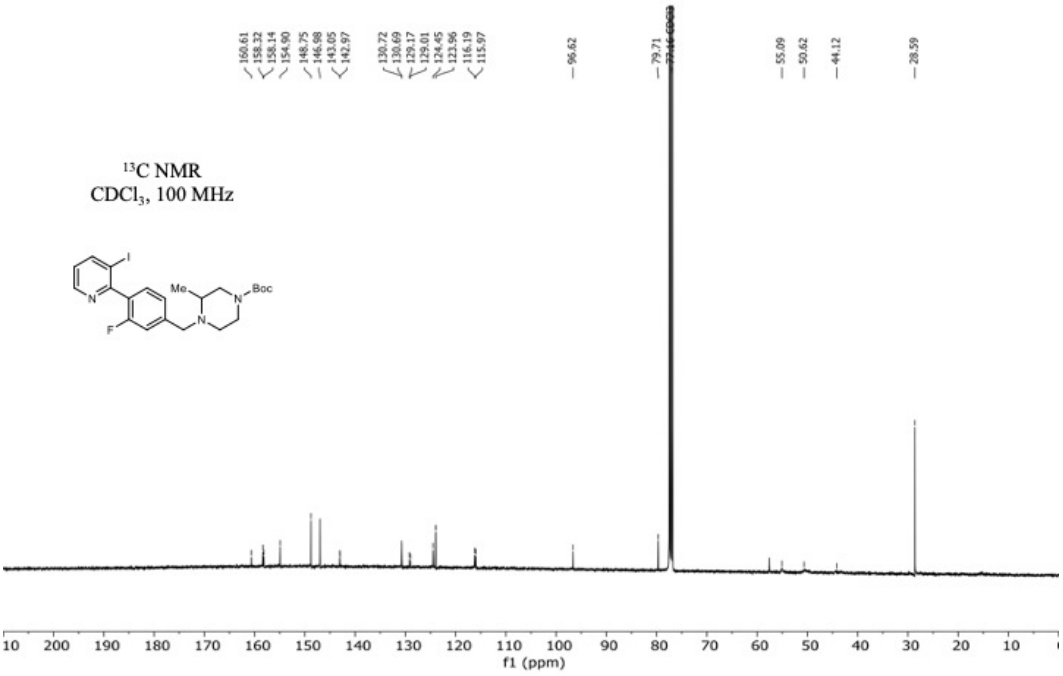



165.62
151.48
150.80
149.68
149.66
148.32
148.21
146.11
142.20
130.13
124.33
124.28
123.89
123.76
122.06
117.46
114.22
114.20
77.48
77.16
76.84
56.46
52.95
13C NMR
CDCl3, 100 MHz
MeO
O
Br
OMe
F
N
ppm 200
150
100
50
0

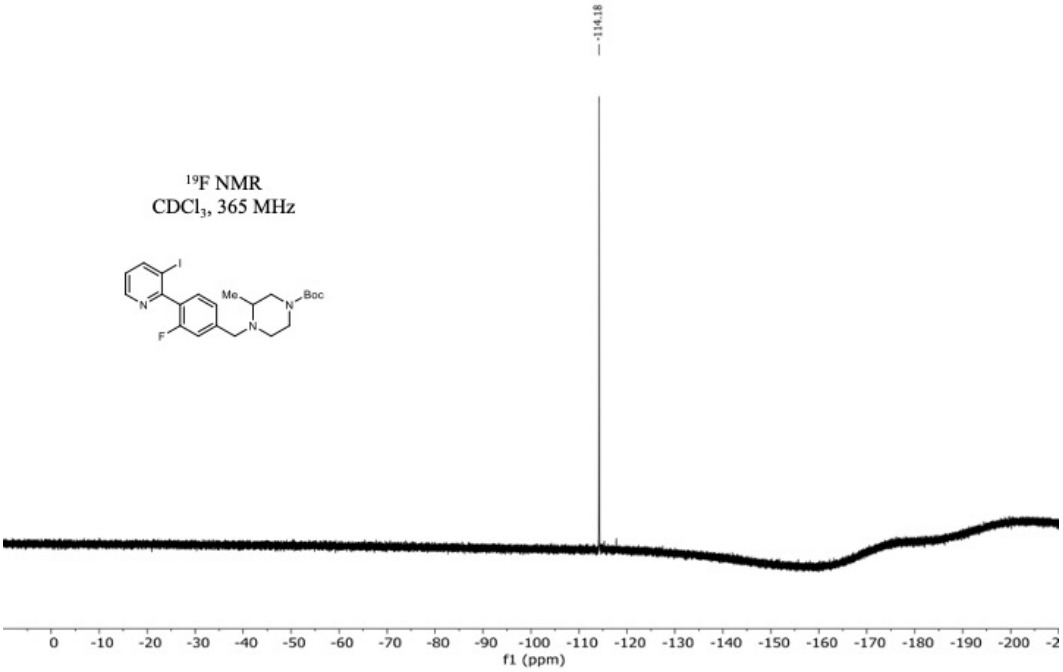

138.07
138.09
138.11
19F NMR
CDCl3, 365 MHz
MeO
O
Br
OMe
F
N
ppm -0
-50
-100
-150

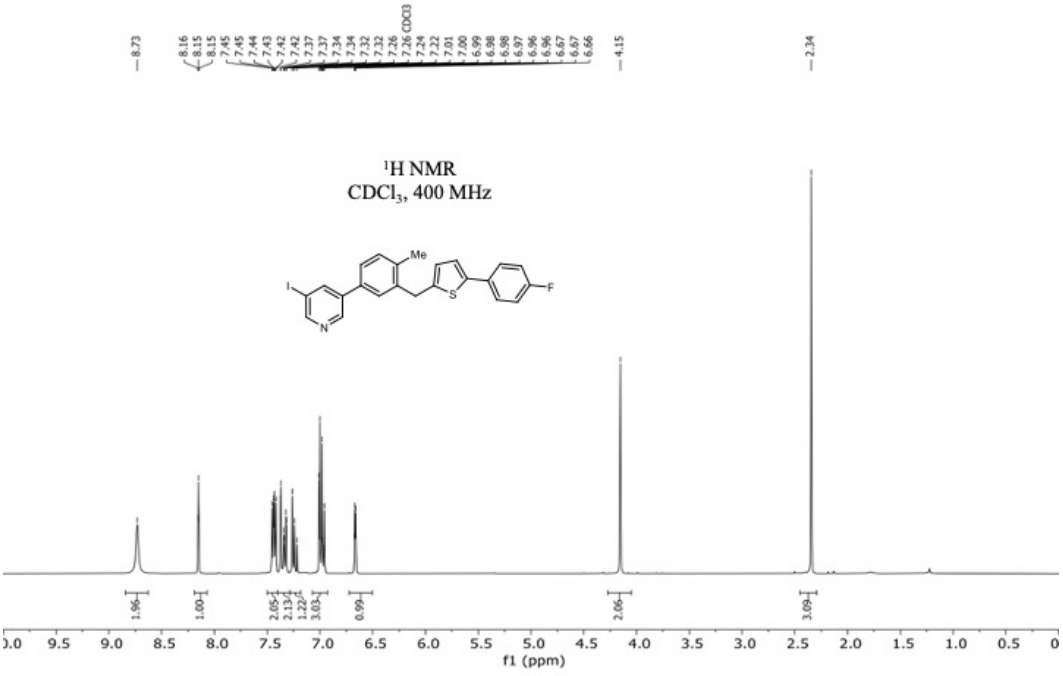


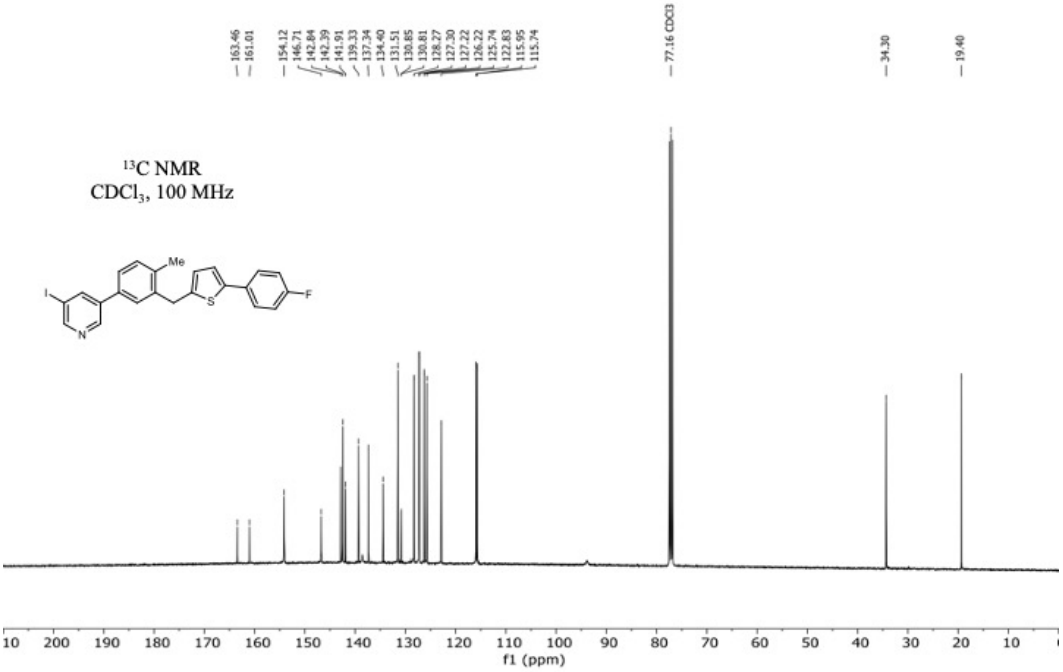
^{1}H NMR
$CDCl_3$, 400 MHz

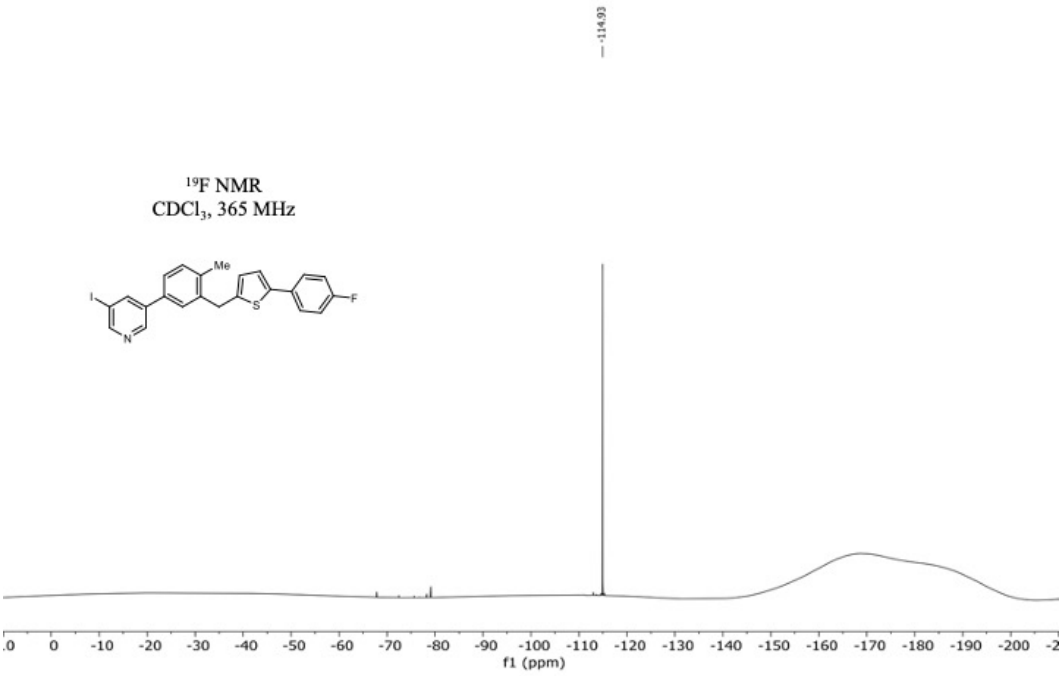


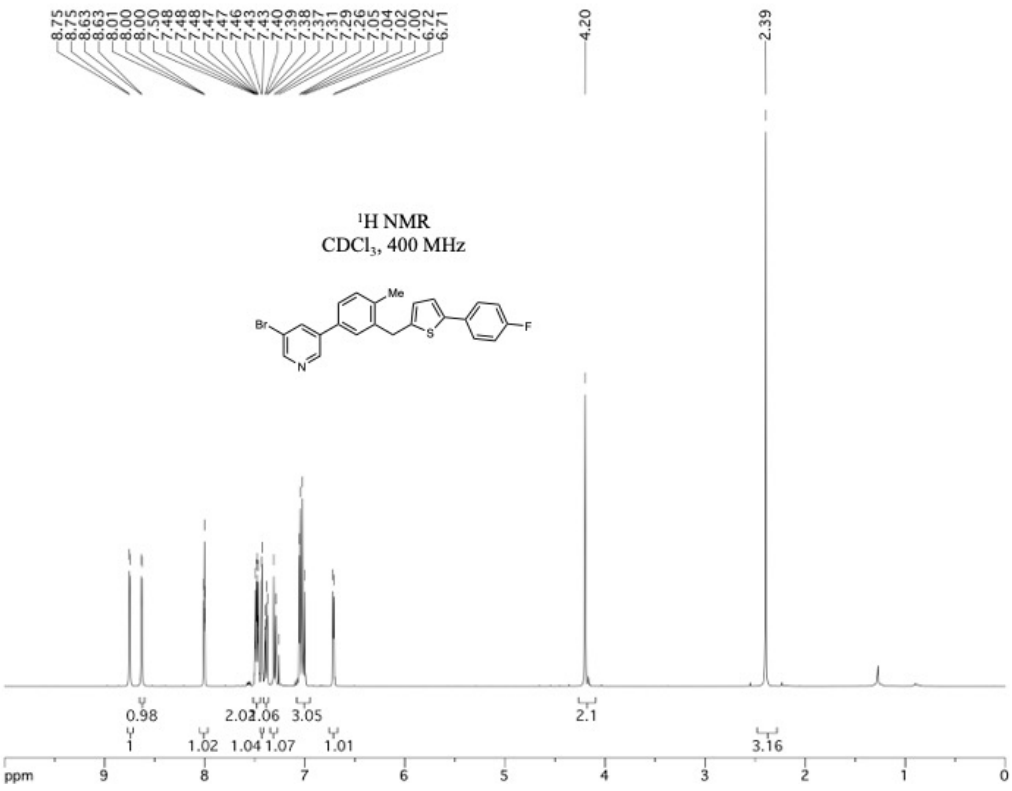
^{13}C NMR
$CDCl_3$, 100 MHz


-114.18
19F NMR
CDCl3, 365 MHz
I
N
Me
N
Boc
N
F
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

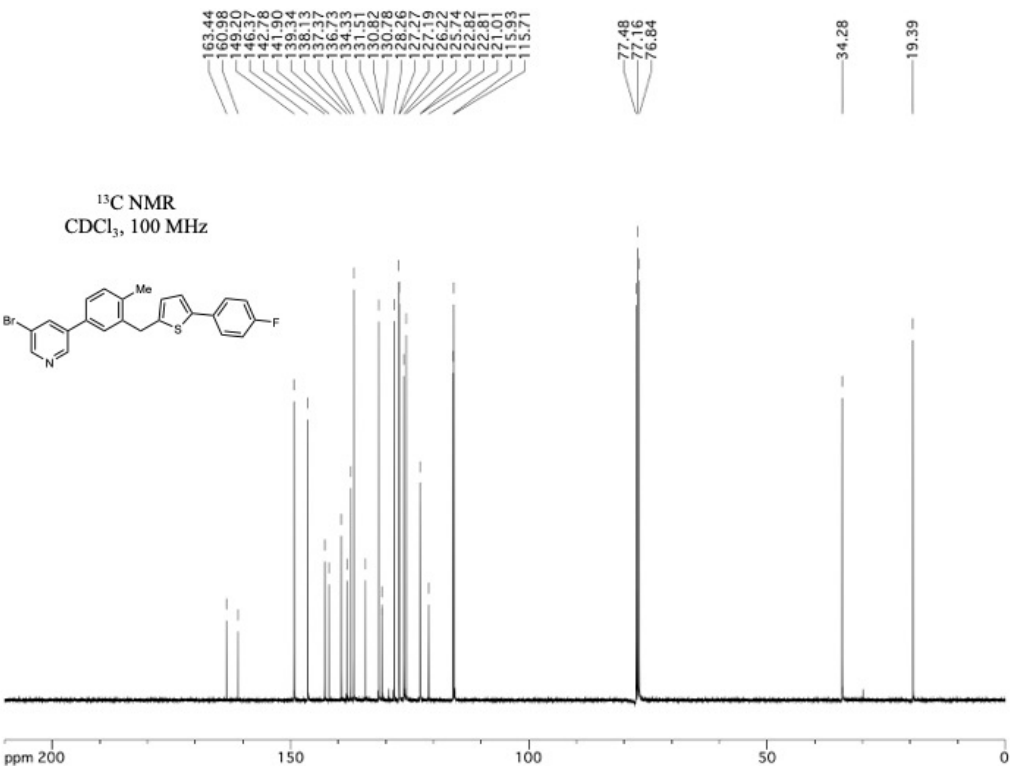

8.73
8.16
8.15
8.15
7.45
7.45
7.44
7.43
7.42
7.42
7.37
7.37
7.34
7.34
7.32
7.32
7.26
7.26 CDCl3
7.24
7.22
7.01
7.00
6.99
6.98
6.98
6.97
6.96
6.96
6.67
6.67
6.66
4.15
2.34
1H NMR
CDCl3, 400 MHz
Me
I
N
S
F
1.96
1.00
2.05
2.13
1.22
3.05
0.99
2.06
3.09
f1 (ppm)


163.46
161.01
154.12
146.71
142.84
142.39
141.91
139.33
137.34
134.40
131.51
130.85
130.81
128.27
127.30
127.22
126.22
125.74
122.83
115.95
115.74
77.16 CDCl3
34.30
19.40
13C NMR
CDCl3, 100 MHz
Me
I
N
S
F
f1 (ppm)

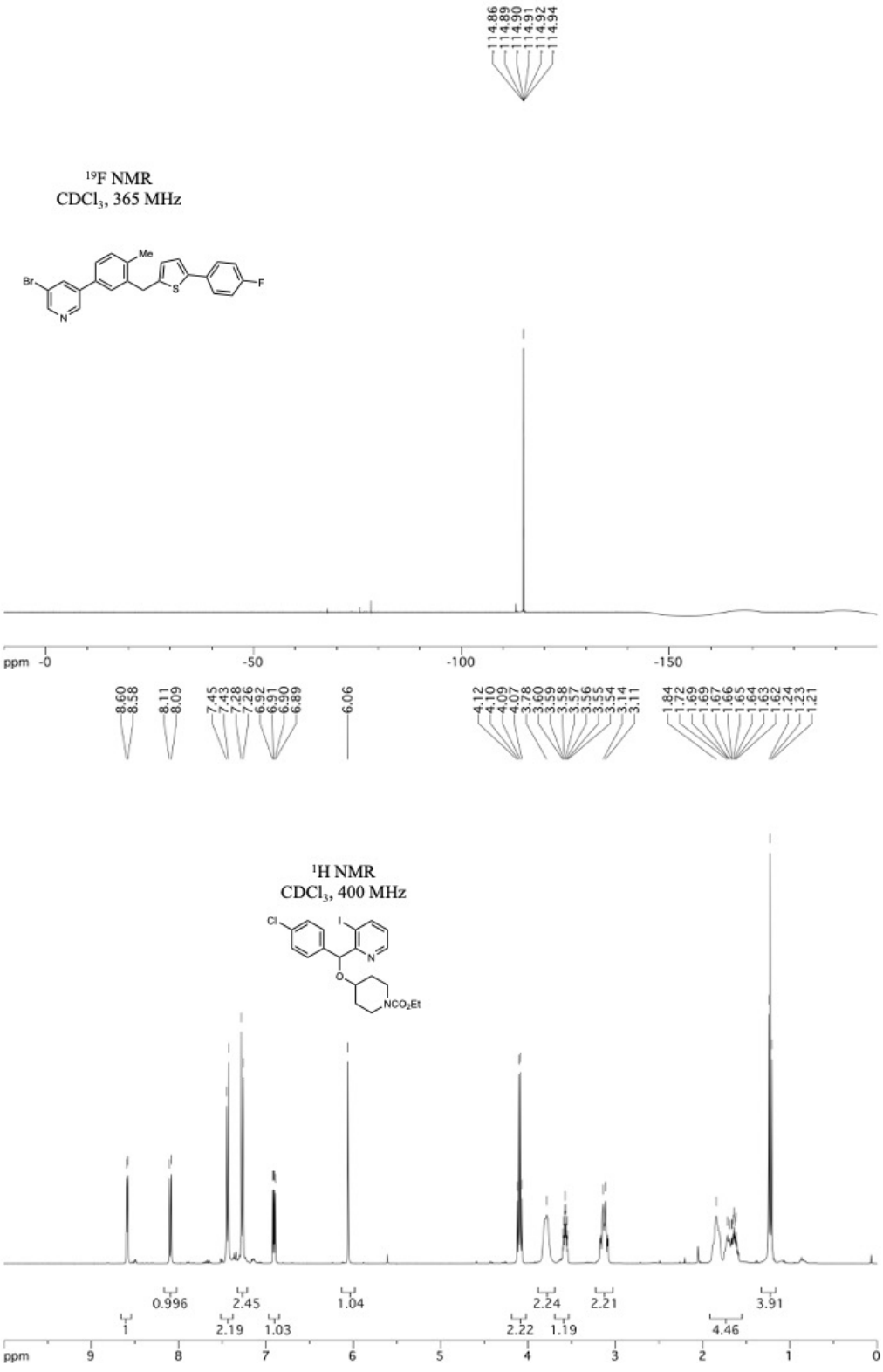

-114.93
19F NMR
CDCl3, 365 MHz
Me
I
N
S
F
f1 (ppm)

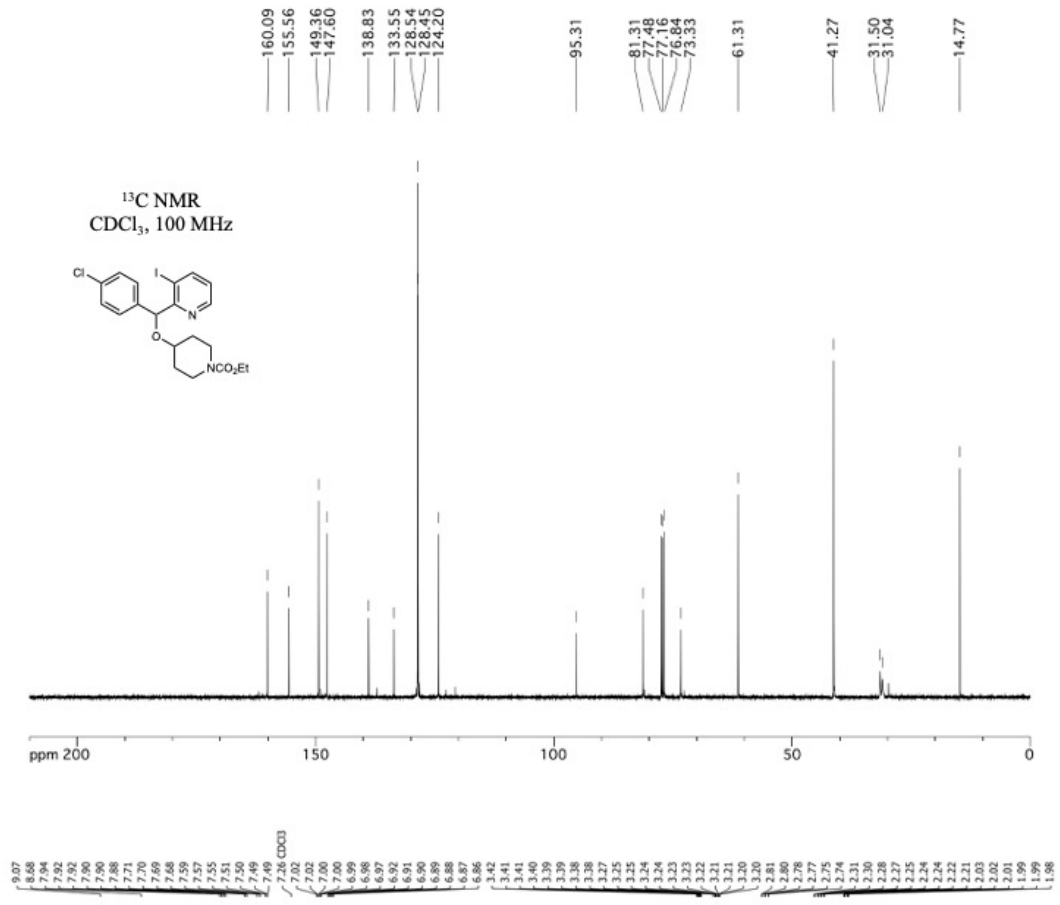


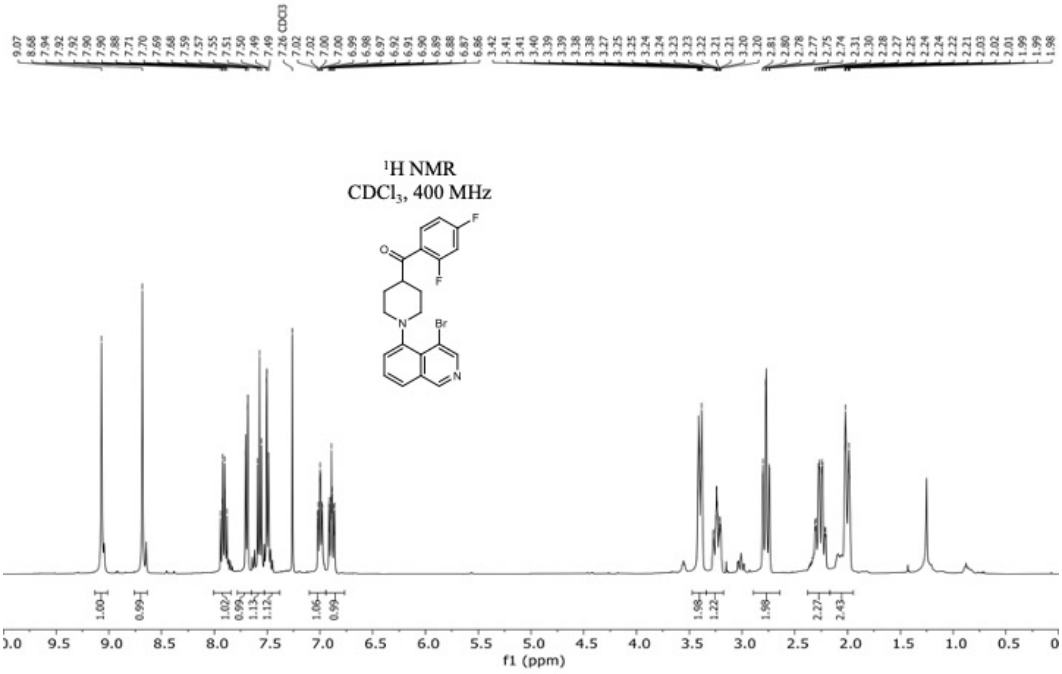
^{1}H NMR
$CDCl_3$, 400 MHz

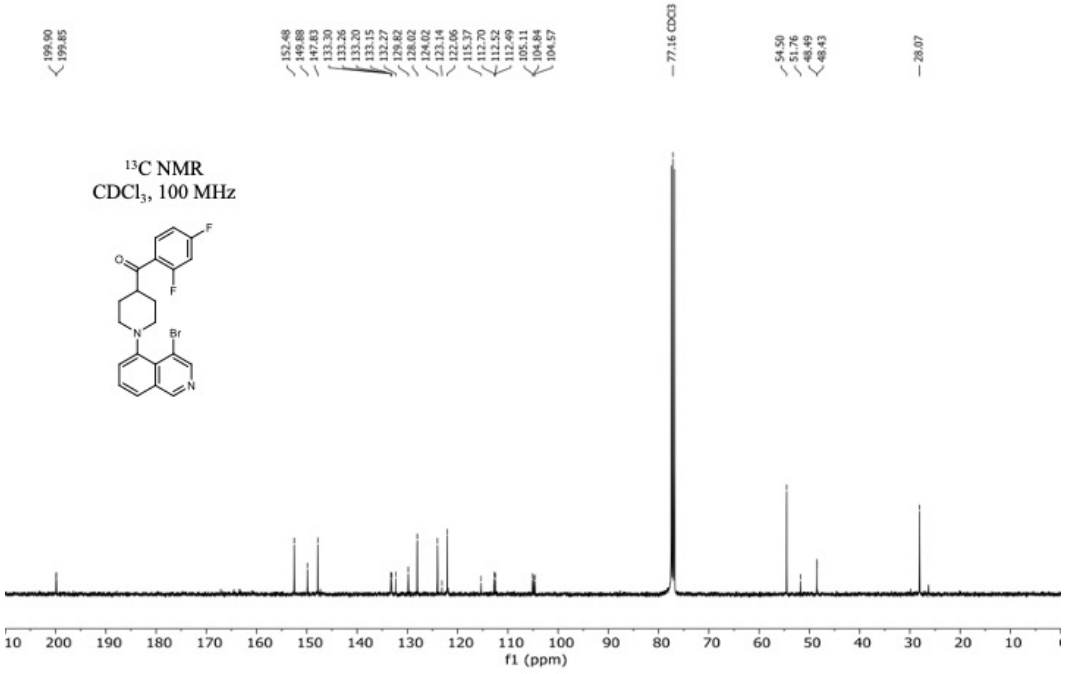


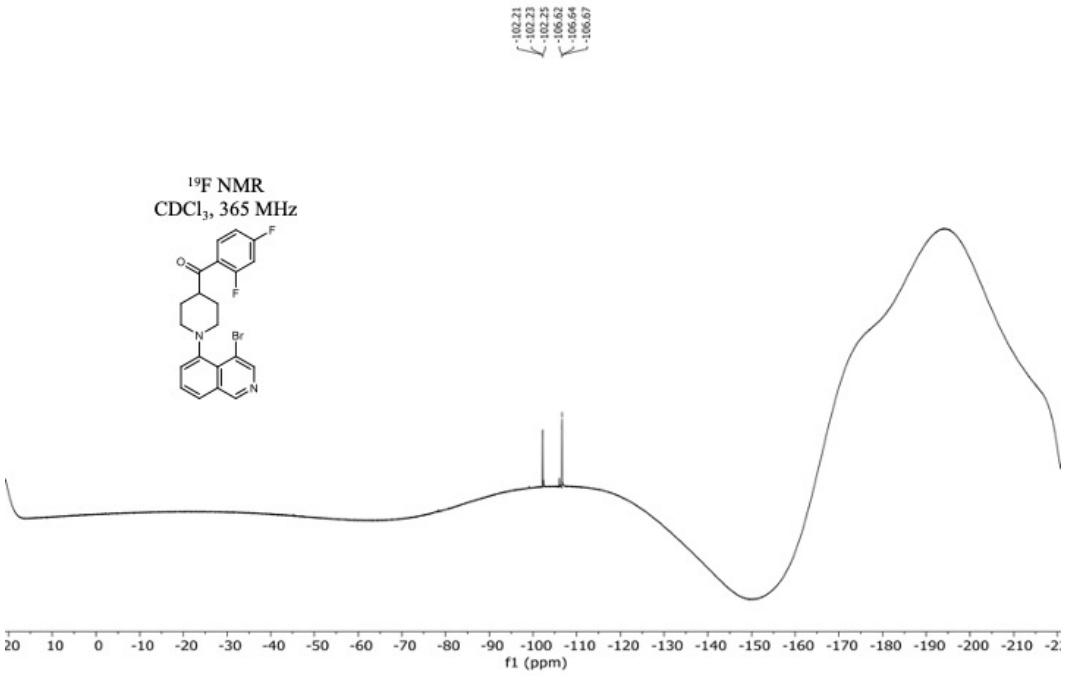
^{13}C NMR
$CDCl_3$, 100 MHz

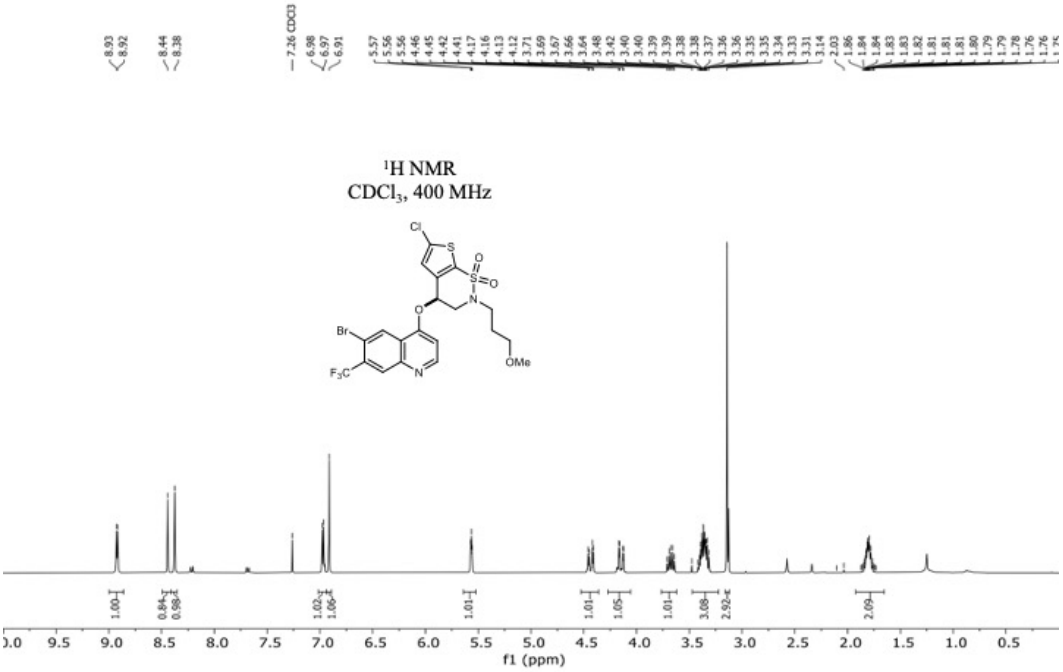

114.86
114.89
114.90
114.91
114.92
114.94
19F NMR
CDCl3, 365 MHz
Me
Br
S
F
N
ppm -0
-50
-100
-150
8.60
8.58
8.11
8.09
7.45
7.43
7.28
7.26
6.92
6.91
6.90
6.89
6.06
4.12
4.10
4.09
4.07
3.78
3.60
3.59
3.58
3.57
3.56
3.55
3.54
3.14
3.11
1.84
1.72
1.69
1.69
1.67
1.66
1.65
1.64
1.63
1.62
1.24
1.23
1.21
1H NMR
CDCl3, 400 MHz
Cl
I
N
O
NCO2Et
0.996
2.45
1.04
2.24
2.21
3.91
1
2.19
1.03
2.22
1.19
4.46
ppm
9
8
7
6
5
4
3
2
1
0

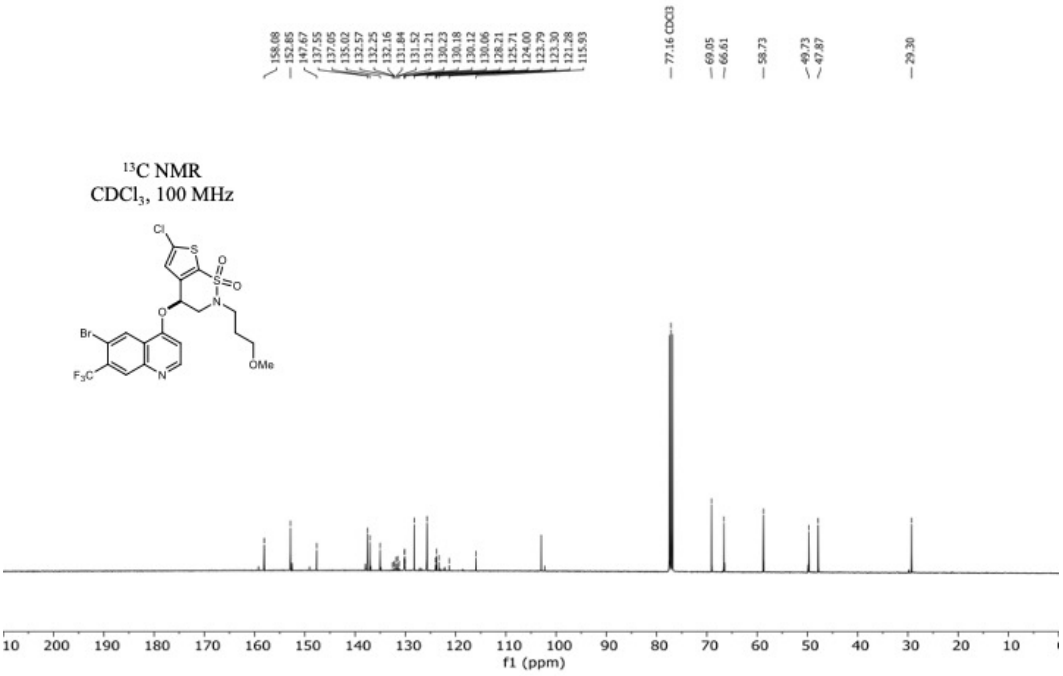

160.09
155.56
149.36
147.60
138.83
133.55
128.54
128.45
124.20
95.31
81.31
77.48
77.16
76.84
73.33
61.31
41.27
31.50
31.04
14.77
13C NMR
CDCl3, 100 MHz
Cl
I
N
O
NCO2Et
ppm 200
150
100
50
0

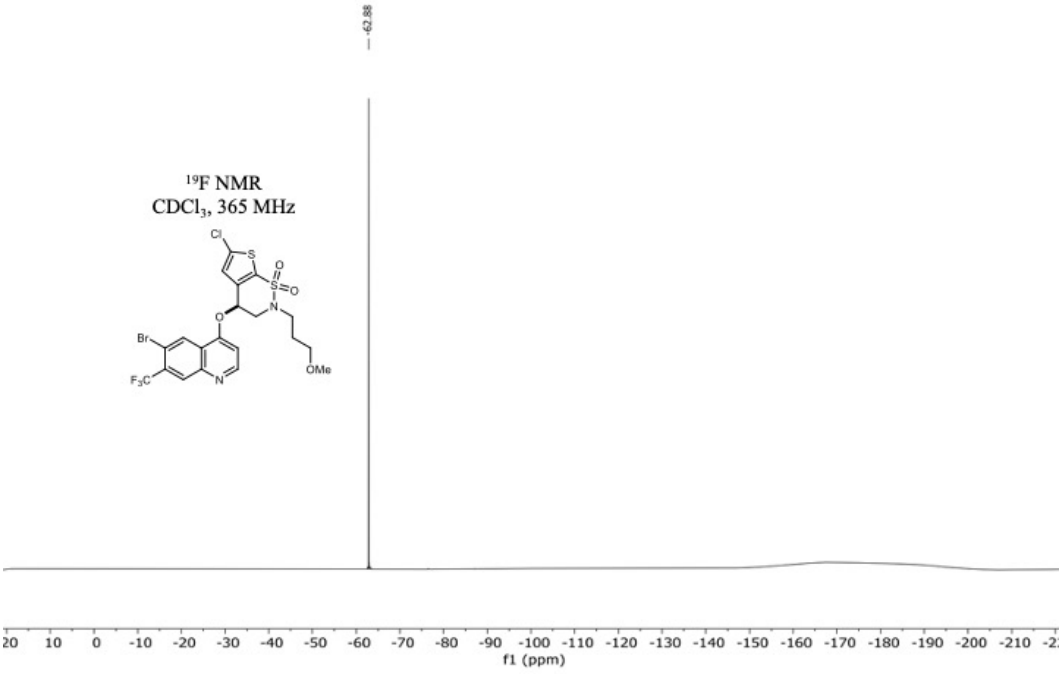

1H NMR
CDCl3, 400 MHz
F
O
F
N
Br
N
1.00
0.99
1.02
0.99
1.13
1.12
1.06
0.99
1.98
1.22
1.98
2.27
2.43
f1 (ppm)

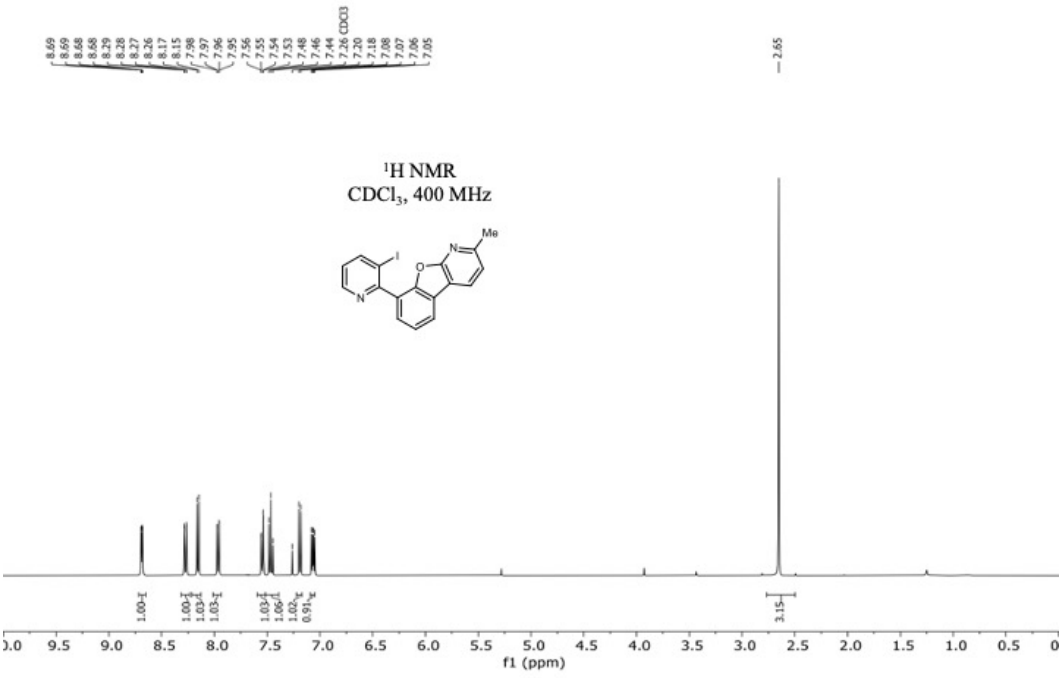

199.90
199.85
152.48
149.88
147.83
133.30
133.26
133.20
133.15
132.27
129.82
128.02
124.02
123.14
122.06
115.37
112.70
112.52
112.49
105.11
104.84
104.57
77.16 CDCl3
54.50
51.76
48.49
48.43
28.07
13C NMR
CDCl3, 100 MHz
F
O
F
N
Br
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

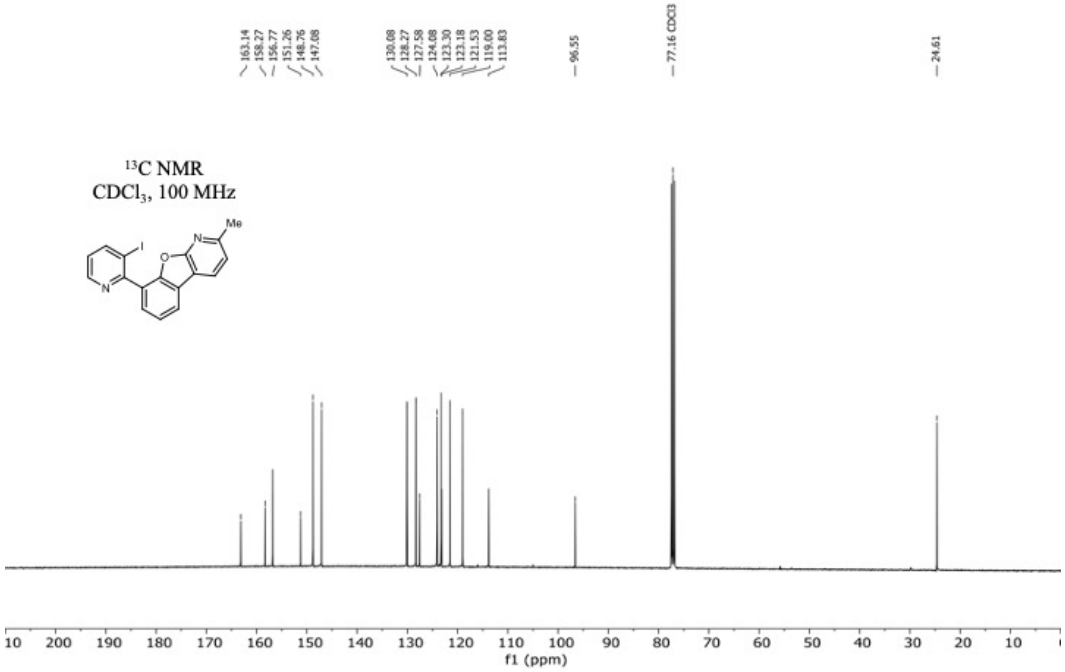

-102.21
-102.23
-102.25
-106.62
-106.64
-106.67
19F NMR
CDCl3, 365 MHz
F
O
F
N
Br
N
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

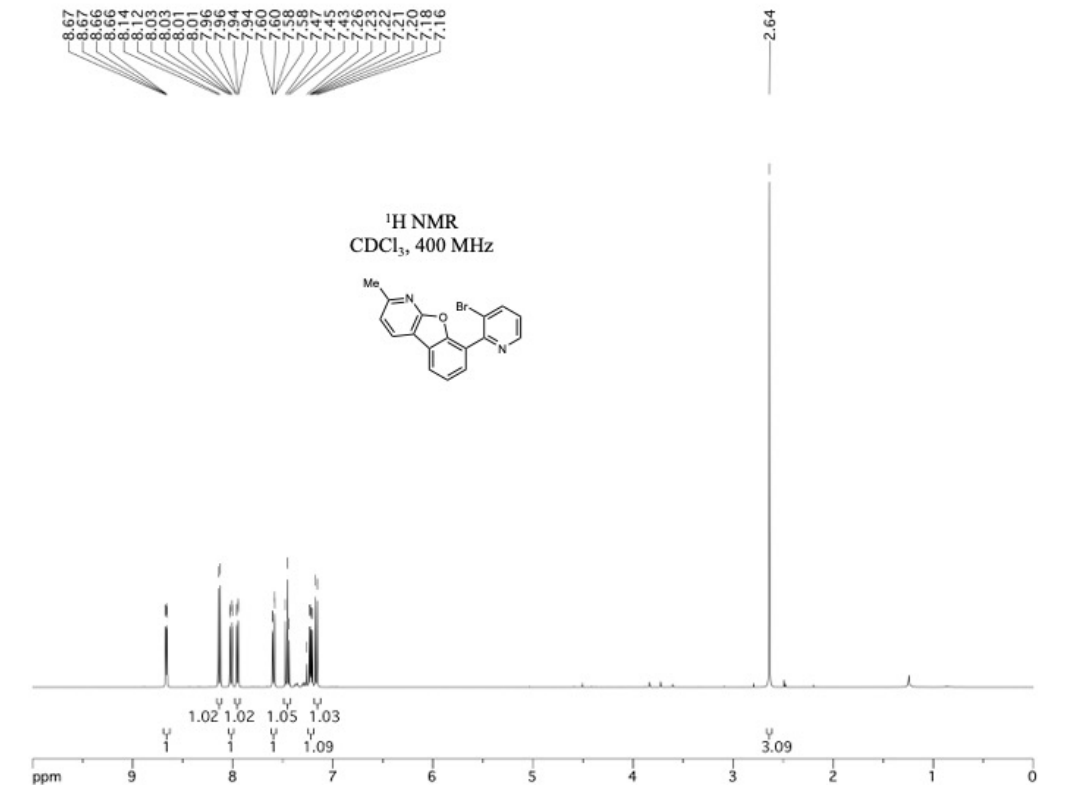

8.93
8.92
8.44
8.38
7.26 CDCl3
6.98
6.97
6.91
5.57
5.56
5.56
5.46
4.45
4.42
4.41
4.17
4.16
4.13
4.12
3.71
3.69
3.67
3.66
3.64
3.48
3.42
3.40
3.40
3.39
3.39
3.38
3.38
3.37
3.36
3.35
3.35
3.34
3.33
3.31
3.14
2.03
1.86
1.84
1.84
1.83
1.83
1.82
1.81
1.81
1.80
1.79
1.79
1.78
1.76
1.76
1H NMR
CDCl3, 400 MHz
Cl
S
O
S
O
N
O
Br
F3C
N
OMe
1.00
0.84
0.98
1.02
1.06
1.01
1.01
1.05
1.01
3.08
2.92
2.09
f1 (ppm)


158.08
152.85
147.67
137.55
137.05
135.02
132.57
132.25
132.16
131.84
131.52
131.21
130.23
130.18
130.12
130.06
128.21
125.71
124.00
123.79
123.30
121.28
115.93
77.16 CDCl3
69.05
66.61
58.73
49.73
47.87
29.30
13C NMR
CDCl3, 100 MHz
Cl
S
O
S
O
N
O
Br
F3C
N
OMe
f1 (ppm)


-62.88
19F NMR
CDCl3, 365 MHz
Cl
S
O
O
S
N
O
Br
F3C
N
OMe
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


8.69
8.69
8.68
8.68
8.29
8.28
8.27
8.26
8.17
8.15
7.98
7.97
7.96
7.95
7.56
7.55
7.54
7.53
7.48
7.46
7.44
7.26 CDCl3
7.20
7.18
7.08
7.07
7.06
7.05
2.65
1H NMR
CDCl3, 400 MHz
Me
I
N
O
N
1.00
1.00
1.03
1.03
1.03
1.06
1.02
0.91
3.15
0.0 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
f1 (ppm)


163.14
158.27
156.77
151.26
148.76
147.08
130.08
128.27
127.58
124.68
123.30
123.18
121.53
119.00
113.83
96.55
77.16 CDCl3
24.61
13C NMR
CDCl3, 100 MHz
Me
I
N
O
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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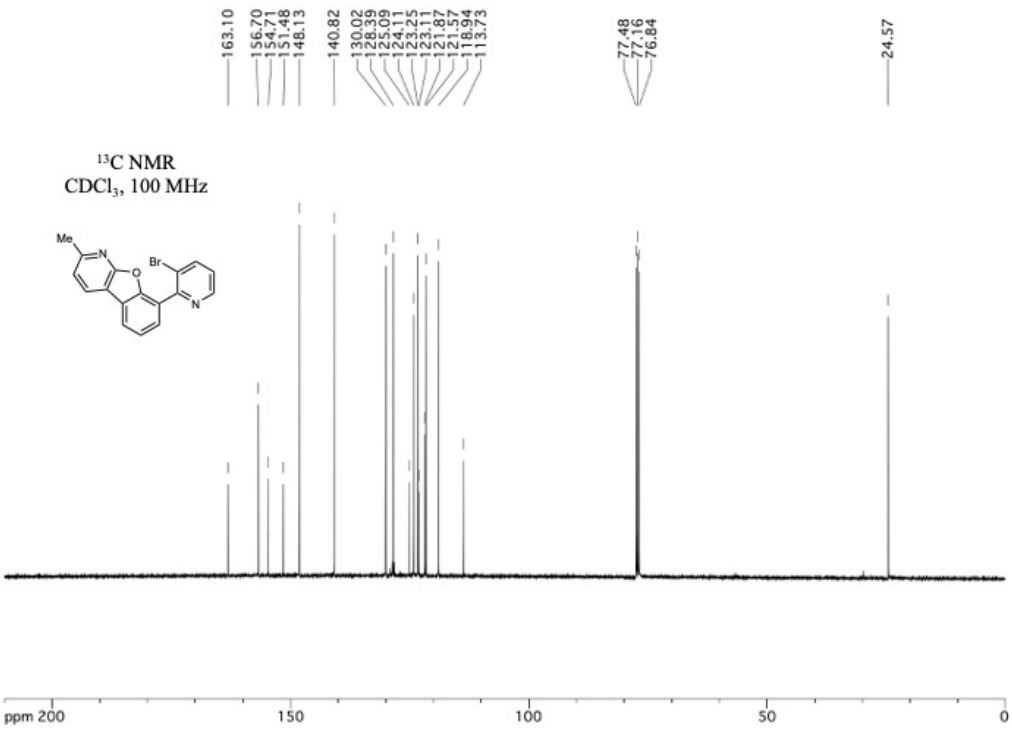
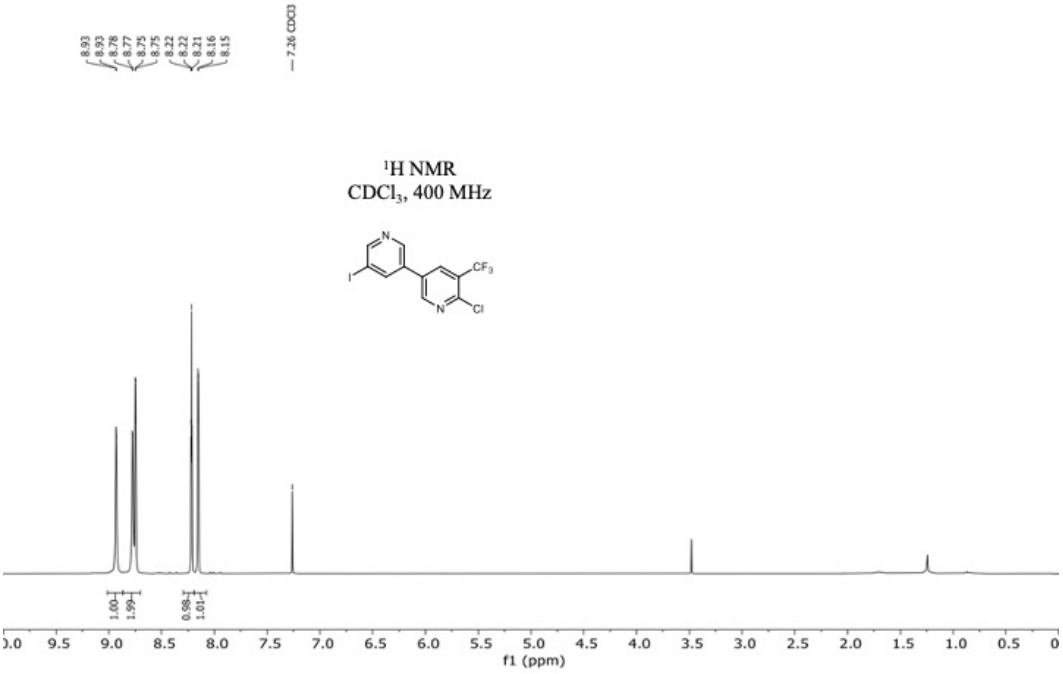
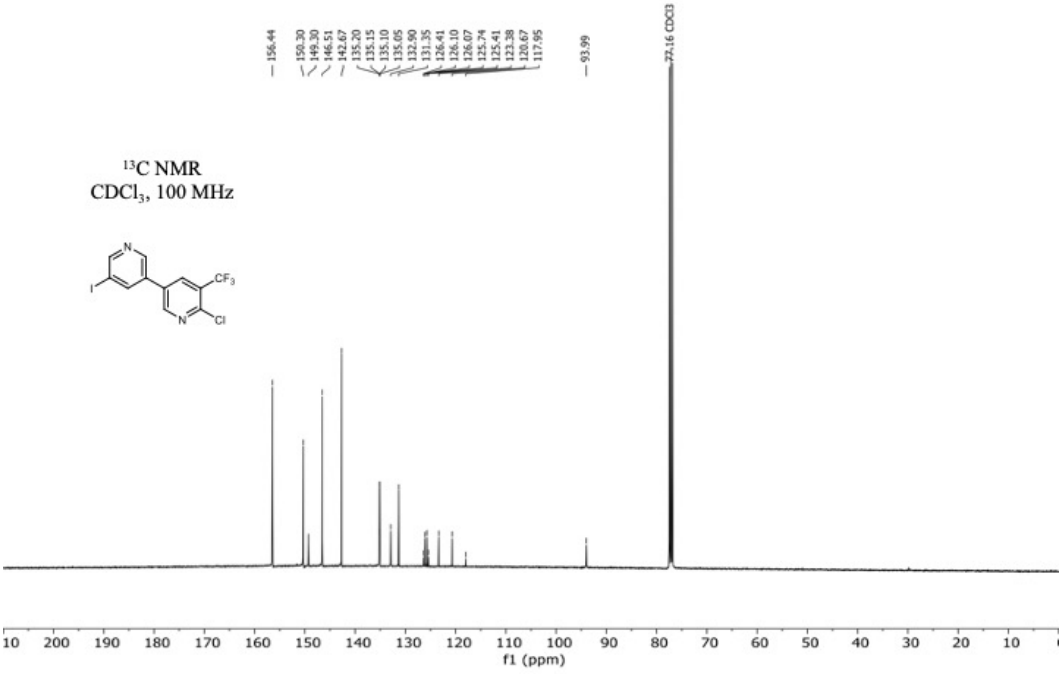
8.67
8.66
8.66
8.14
8.12
8.03
8.03
8.01
8.01
7.96
7.96
7.94
7.94
7.60
7.60
7.58
7.58
7.47
7.45
7.43
7.26
7.23
7.22
7.21
7.20
7.18
7.16
2.64
1H NMR
CDCl3, 400 MHz
Me
N
O
Br
N
1.02 1.02 1.05 1.03
1 1 1 1.09
3.09
ppm 9 8 7 6 5 4 3 2 1 0


163.10
156.70
154.71
151.48
148.13
140.82
130.02
128.39
125.09
124.11
123.25
123.11
121.87
121.57
118.94
113.73
77.48
77.16
76.84
24.57
^{13}C NMR
$CDCl_3$, 100 MHz
Me
N
O
Br
N
ppm 200
150
100
50
0


8.93
8.93
8.78
8.77
8.75
8.75
8.22
8.22
8.21
8.16
8.15
7.26 CDCl3
^{1}H NMR
$CDCl_3$, 400 MHz
N
I
CF_3
N
Cl
1.00
1.99
0.98
1.01
f1 (ppm)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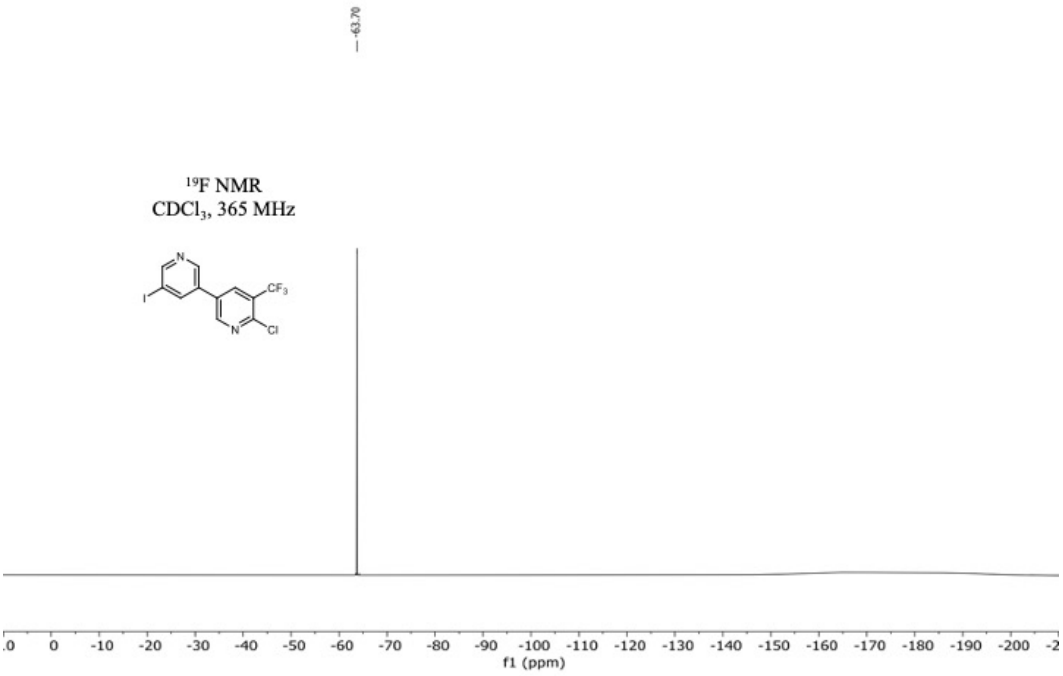
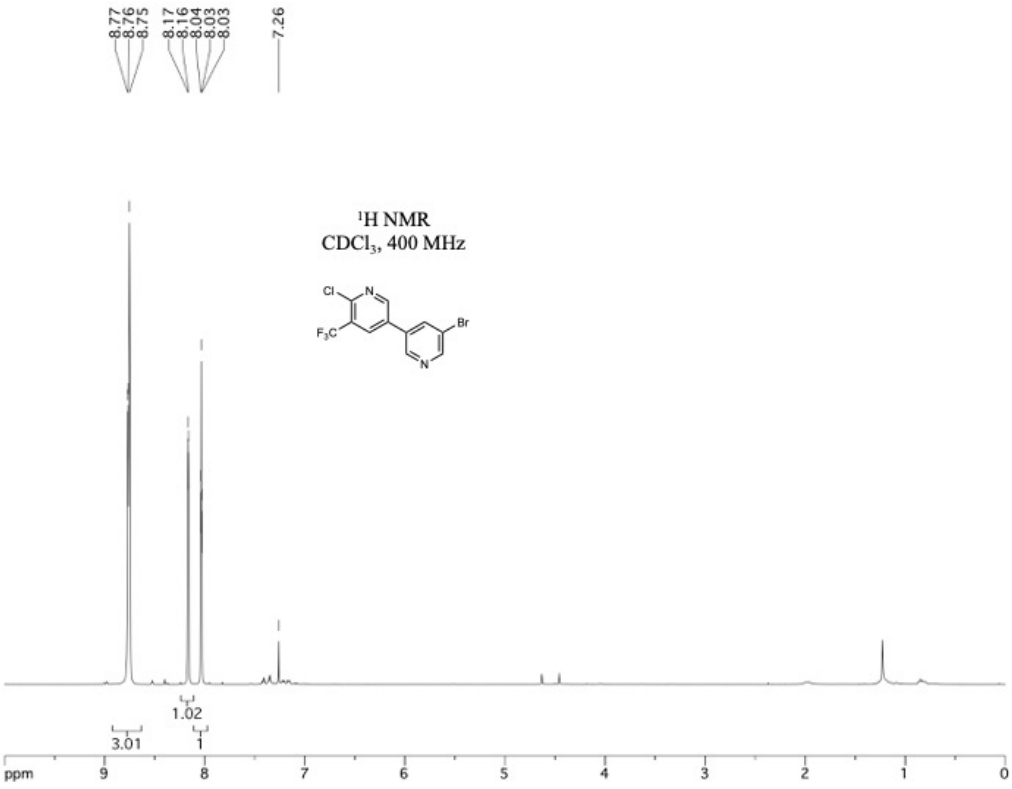
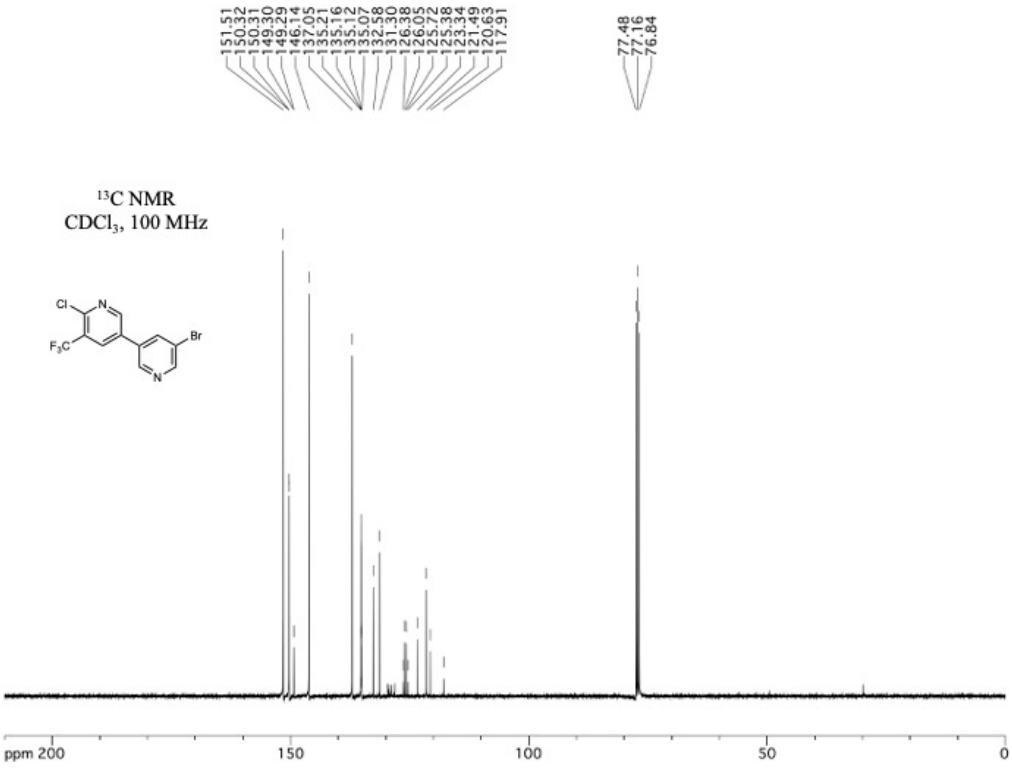
150.30
149.30
146.51
142.67
135.20
135.15
135.10
135.05
132.90
131.35
126.41
126.10
126.07
125.74
125.41
123.38
120.67
117.95
93.99
77.16 CDCl3
13C NMR
CDCl3, 100 MHz
N
I
CF3
Cl
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


63.70
19F NMR
CDCl3, 365 MHz
N
I
CF3
Cl
N
.0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -2
f1 (ppm)


8.77
8.76
8.75
8.17
8.16
8.04
8.03
8.03
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Cl
N
F_3C
Br
N
1.02
3.01
1
ppm
9
8
7
6
5
4
3
2
1
0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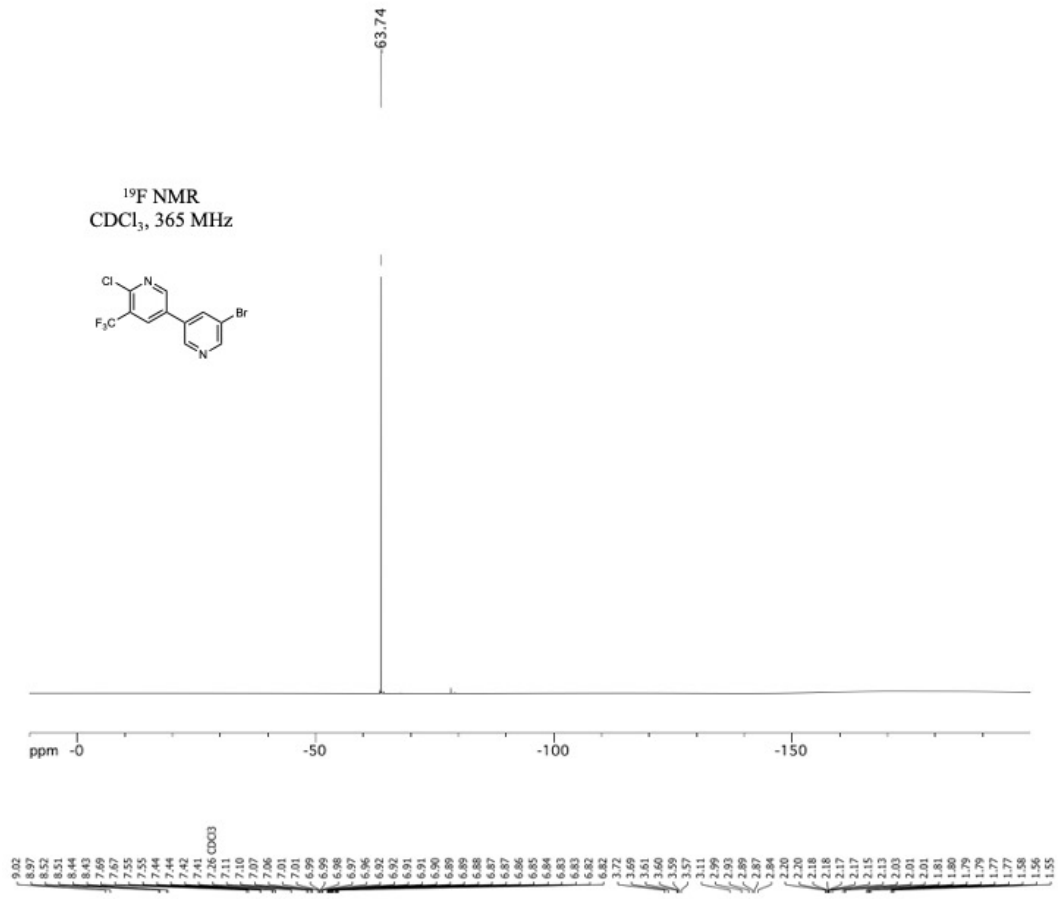
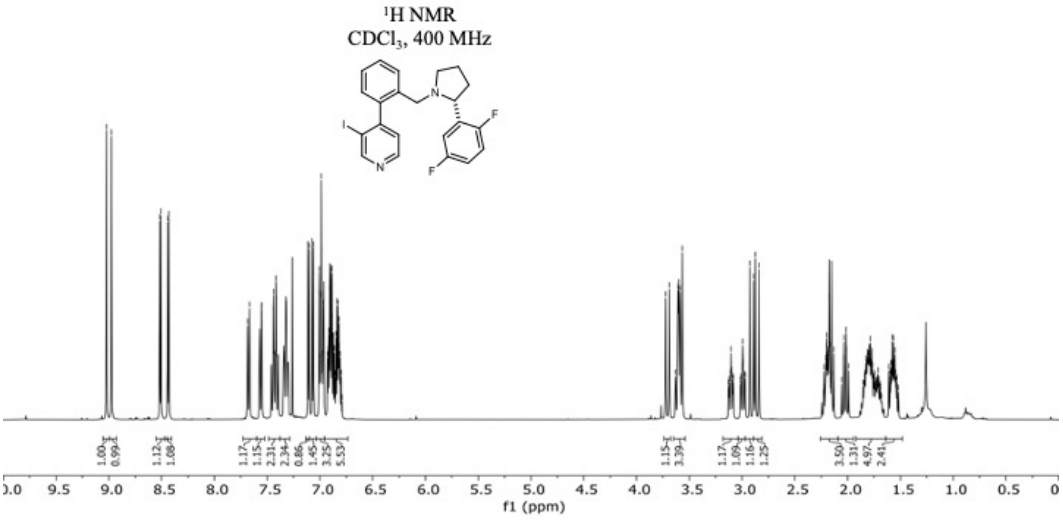
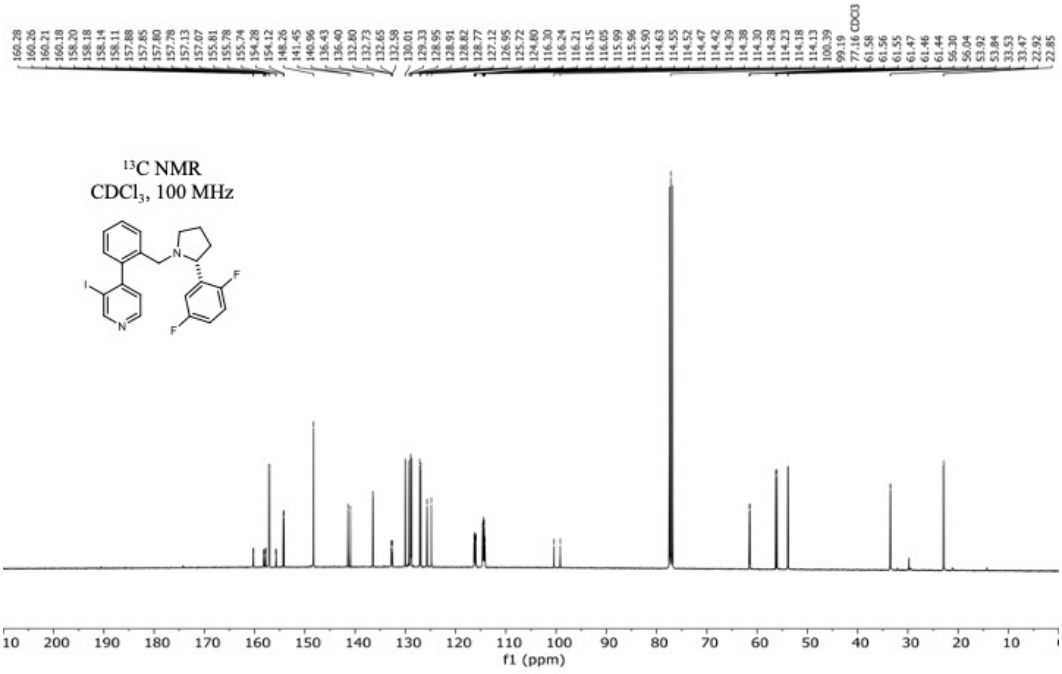
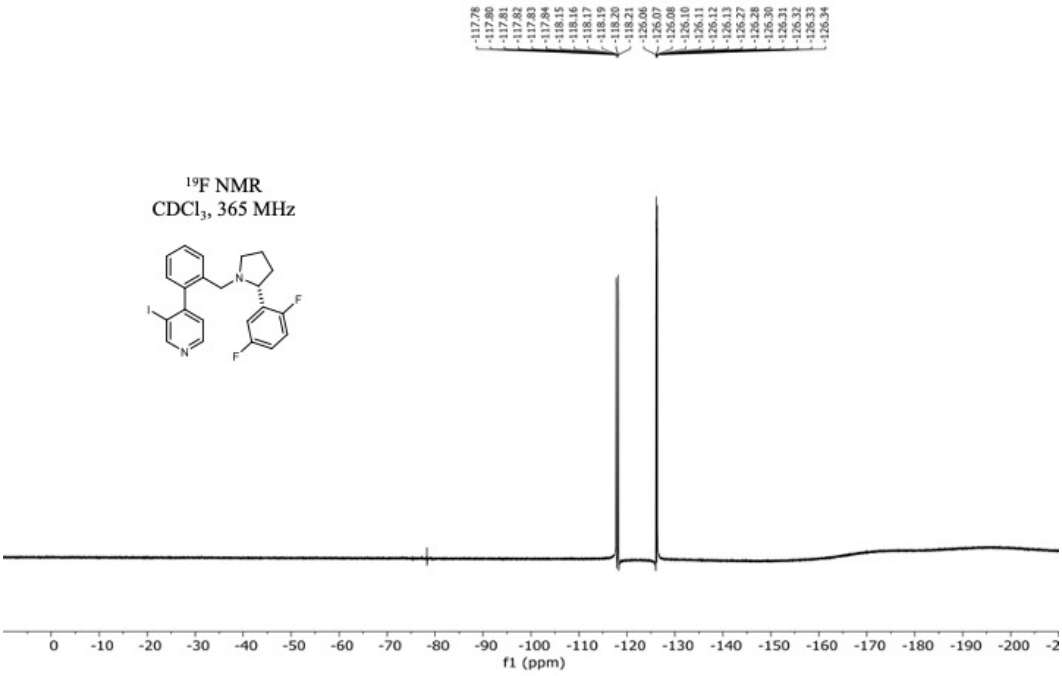
150.32
150.31
149.30
149.29
146.14
137.05
135.21
135.16
135.12
135.07
132.58
131.30
126.38
126.05
125.72
125.38
123.34
121.49
120.63
117.91
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
N
F_3C
Br
N
ppm 200
150
100
50
0


-63.74
19F NMR
CDCl3, 365 MHz
Cl
N
F3C
Br
N
ppm -0
-50
-100
-150
CDCl3


1H NMR
CDCl3, 400 MHz
N
I
N
F
F
f1 (ppm)


160.28
160.26
160.21
160.18
158.20
158.18
158.14
158.11
157.88
157.85
157.80
157.78
157.13
157.07
155.81
155.78
155.74
154.28
154.12
148.26
141.45
140.96
136.43
136.40
132.80
132.73
132.65
132.58
130.01
129.33
128.95
128.91
128.82
128.77
127.12
126.95
125.72
124.80
116.30
116.24
116.21
116.15
116.05
115.99
115.96
115.90
114.63
114.55
114.52
114.47
114.42
114.39
114.38
114.30
114.28
114.23
114.18
114.13
100.39
99.19
77.16 CDCl3
61.58
61.56
61.55
61.47
61.46
61.44
56.30
56.04
53.92
53.84
33.53
33.47
22.92
22.85
13C NMR
CDCl3, 100 MHz
I
N
N
F
F
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-117.78
-117.80
-117.81
-117.82
-117.83
-117.84
-118.15
-118.16
-118.17
-118.19
-118.20
-118.21
-126.06
-126.07
-126.08
-126.10
-126.11
-126.12
-126.13
-126.27
-126.28
-126.30
-126.31
-126.32
-126.33
-126.34
19F NMR
CDCl3, 365 MHz
I
N
N
F
F
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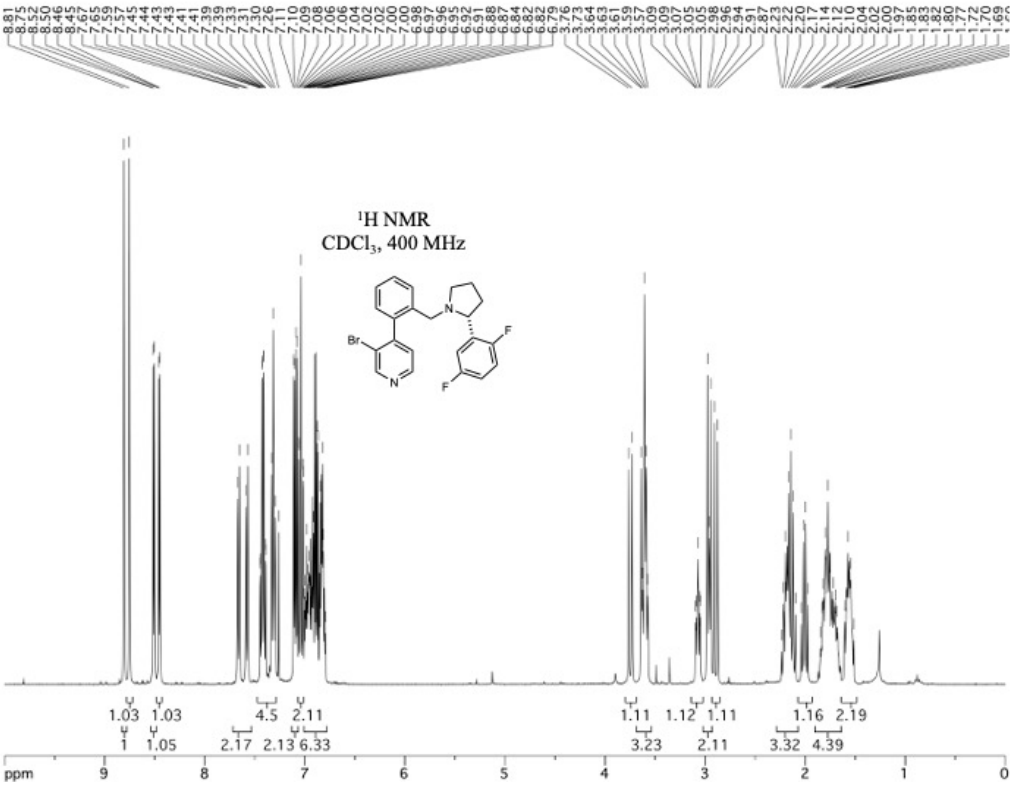
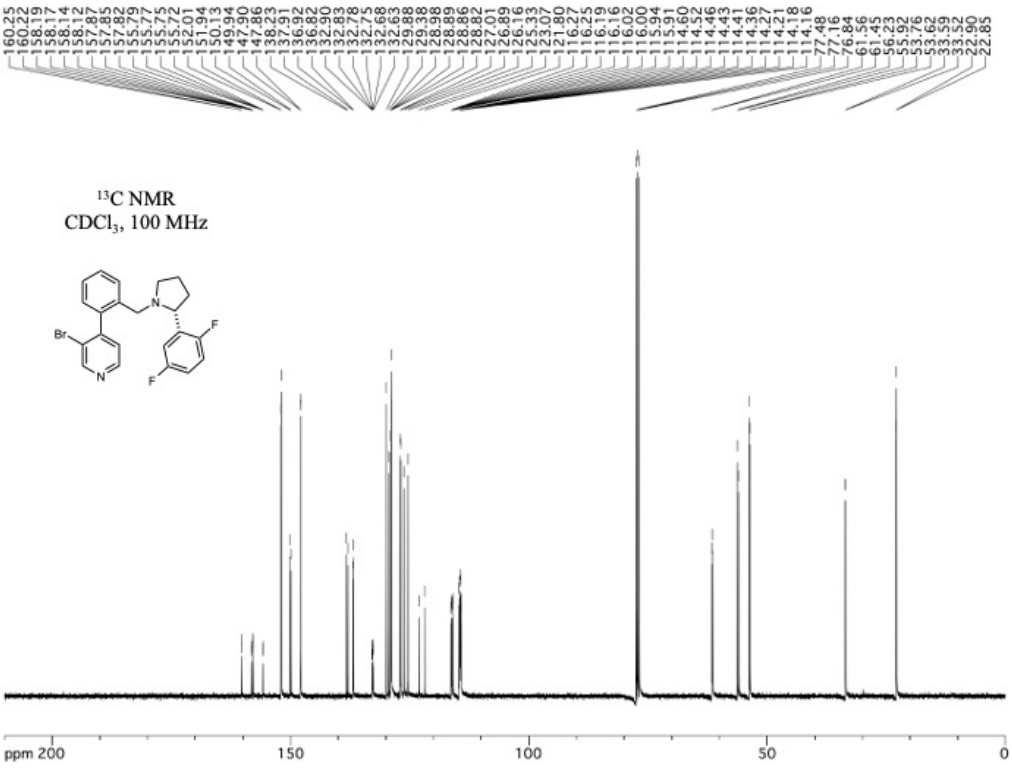
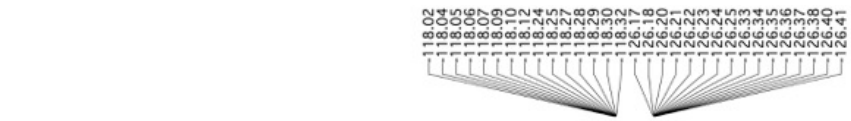
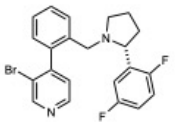
f1 (ppm)


^{1}H NMR
$CDCl_3$, 400 MHz
Br
N
F
F
1.03 1.03 4.5 2.11 1.11 1.12 1.11 1.16 2.19
1 1.05 2.17 2.13 6.33 3.23 2.11 3.32 4.39
ppm 9 8 7 6 5 4 3 2 1 0

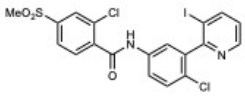

^{13}C NMR
$CDCl_3$, 100 MHz
Br
N
F
F
ppm 200 150 100 50 0

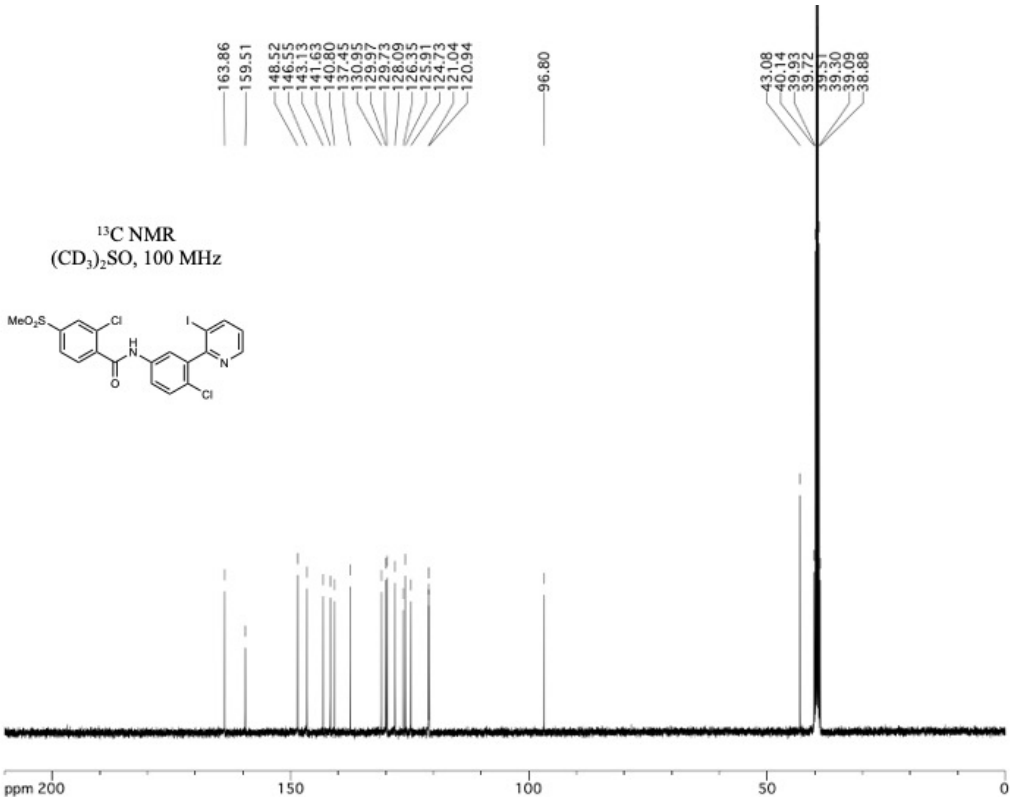


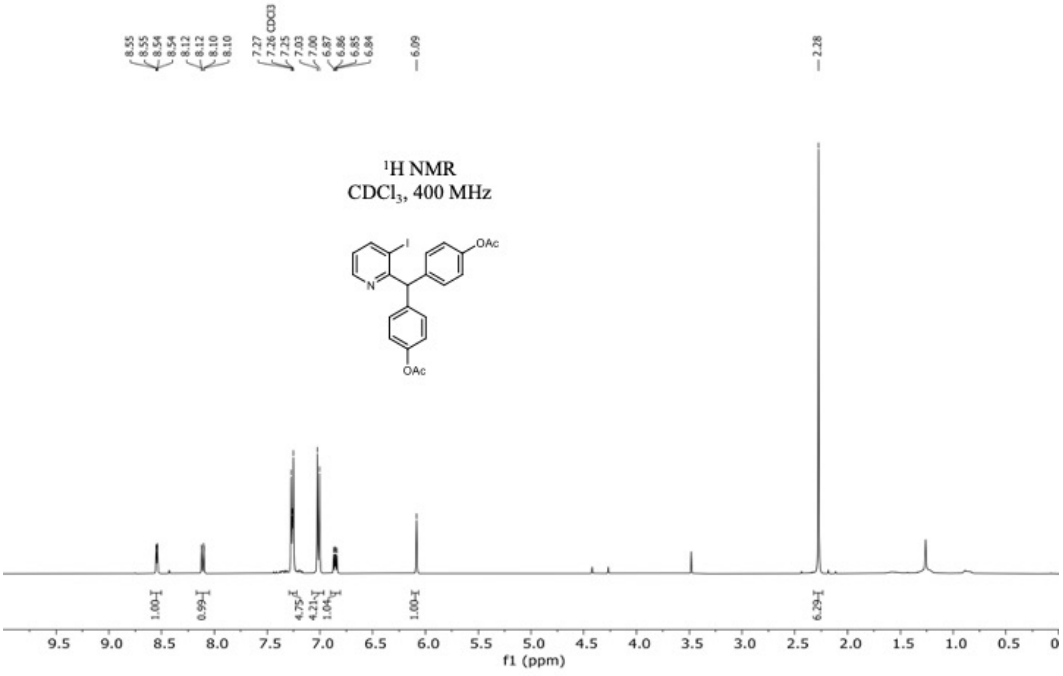
^{19}F NMR
$CDCl_3$, 365 MHz

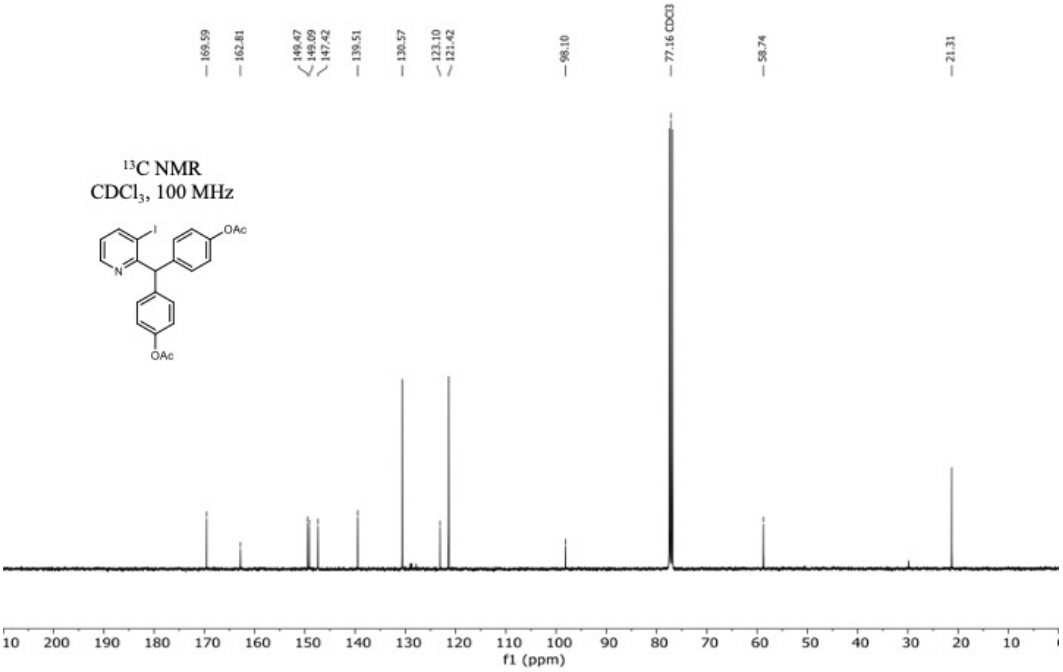


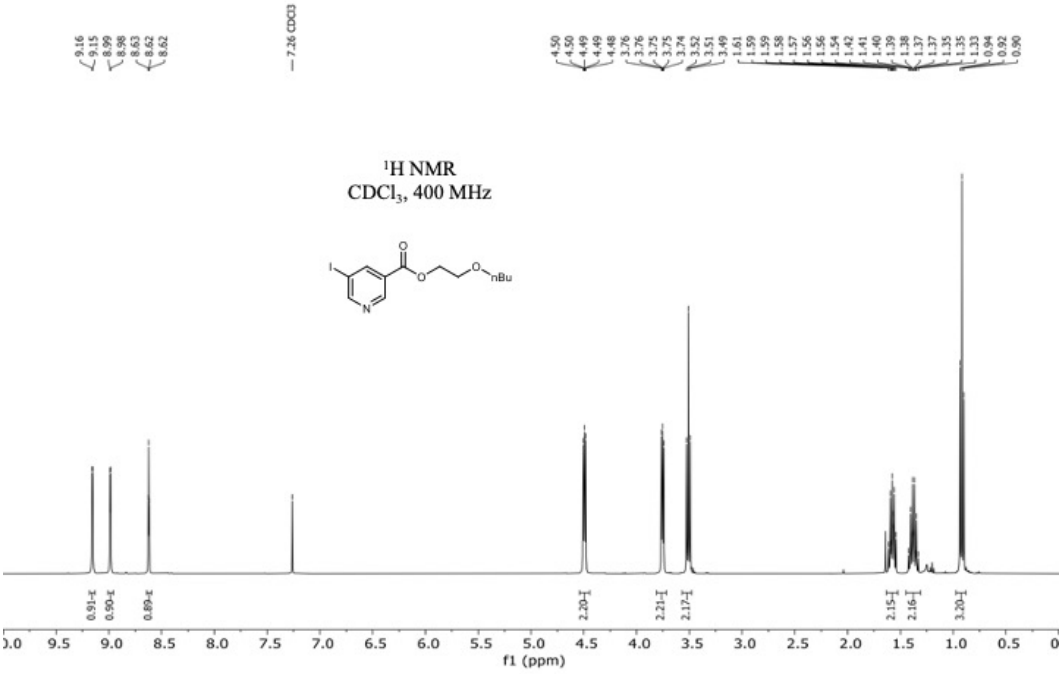
^{1}H NMR
$(CD_3)_2SO$, 400 MHz




163.86
159.51
148.52
146.55
143.13
141.63
140.80
137.45
130.95
129.97
129.73
128.09
126.35
125.91
124.73
121.04
120.94
96.80
43.08
40.14
39.93
39.72
39.51
39.30
39.09
38.88
^{13}C NMR
$(CD_3)_2SO$, 100 MHz
MeO2S
Cl
I
N
H
O
Cl
ppm 200
150
100
50
0


8.55
8.55
8.54
8.54
8.12
8.12
8.10
8.10
7.27
7.26 CDCl3
7.25
7.03
7.00
6.87
6.86
6.85
6.84
6.09
2.28
^{1}H NMR
$CDCl_3$, 400 MHz
I
N
OAc
OAc
1.00
0.99
4.75
4.21
1.04
1.00
6.29
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)


169.59
162.81
149.47
149.09
147.42
139.51
130.57
123.10
121.42
98.10
77.16 CDCl3
59.74
21.31
13C NMR
CDCl3, 100 MHz
I
OAc
OAc
N
f1 (ppm)


9.16
9.15
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8.98
8.63
8.62
8.62
7.26 CDCl3
4.50
4.50
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4.48
3.76
3.76
3.75
3.75
3.74
3.52
3.51
3.49
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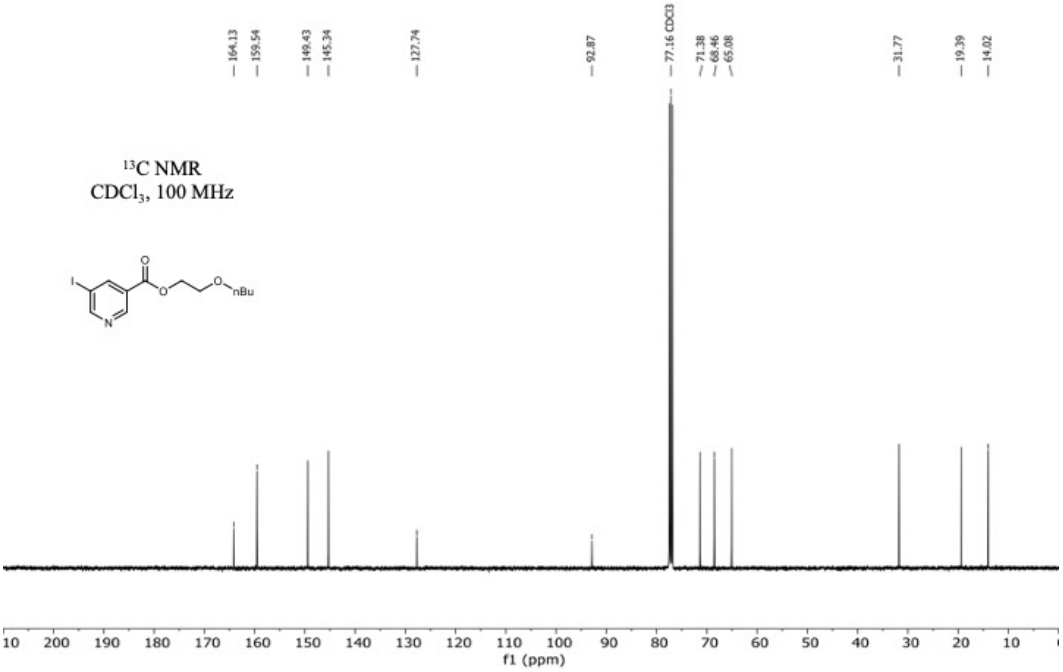
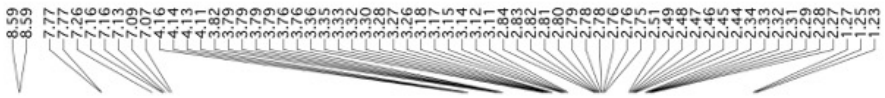
1.59
1.59
1.58
1.57
1.56
1.56
1.54
1.42
1.41
1.40
1.39
1.38
1.37
1.37
1.35
1.35
1.33
0.94
0.92
0.90
1H NMR
CDCl3, 400 MHz
I
O
O
O
nBu
N
0.91
0.90
0.89
2.20
2.21
2.17
2.15
2.16
3.20
f1 (ppm)


164.13
159.54
149.43
145.34
127.74
92.87
77.16 CDCl3
71.38
68.46
65.08
31.77
19.39
14.02
13C NMR
CDCl3, 100 MHz
I
O
O
O
nBu
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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7.77
7.26
7.16
7.13
7.09
7.07
4.16
4.14
4.13
4.11
3.82
3.79
3.79
3.79
3.79
3.76
3.76
3.36
3.35
3.33
3.32
3.30
3.28
3.27
3.26
3.18
3.17
3.15
3.14
3.12
3.11
2.84
2.83
2.82
2.81
2.80
2.79
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2.78
2.76
2.76
2.75
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2.49
2.48
2.47
2.46
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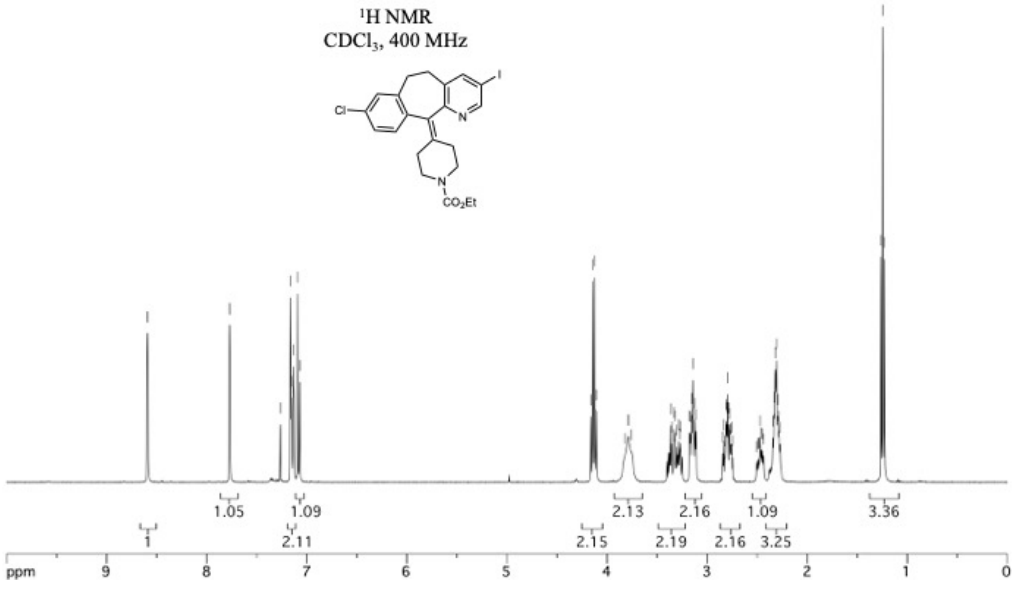
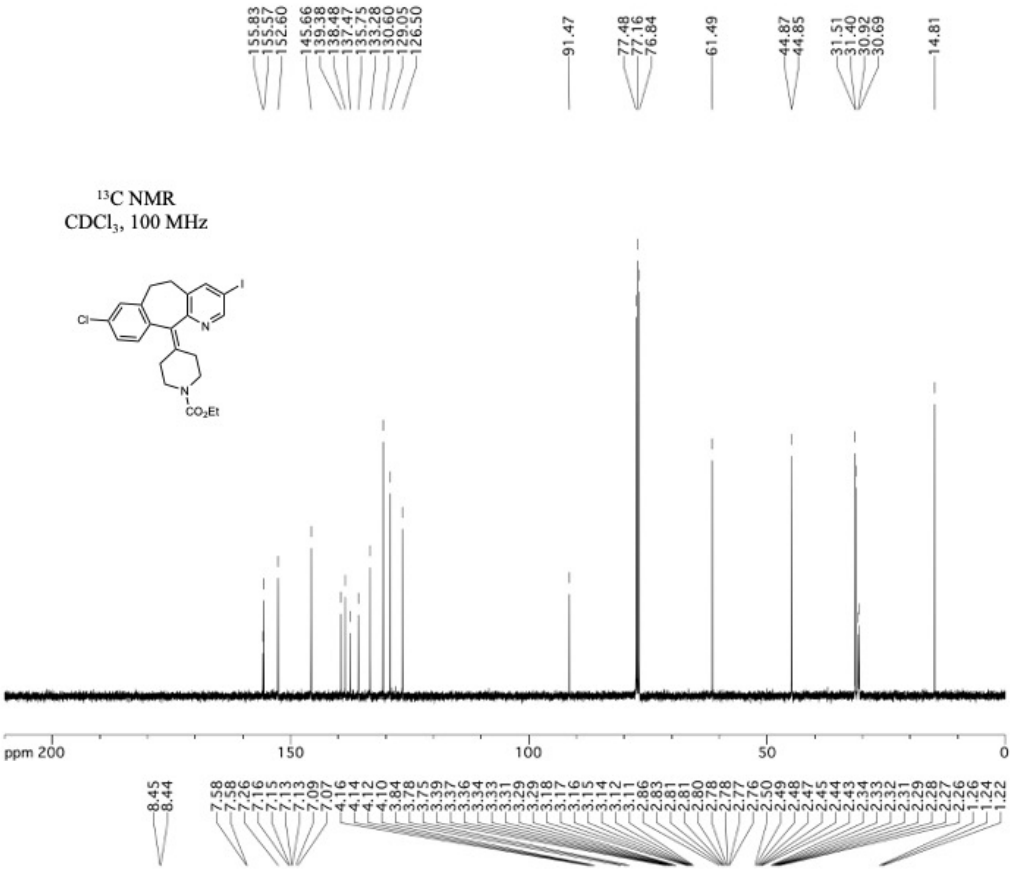
2.29
2.28
2.27
1.25
1.23


1H NMR
CDCl3, 400 MHz
Cl
I
N
N
CO2Et
1.05
1.09
2.13
2.16
1.09
3.36
1
2.11
2.15
2.19
2.16
3.25
ppm 9 8 7 6 5 4 3 2 1 0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155.57
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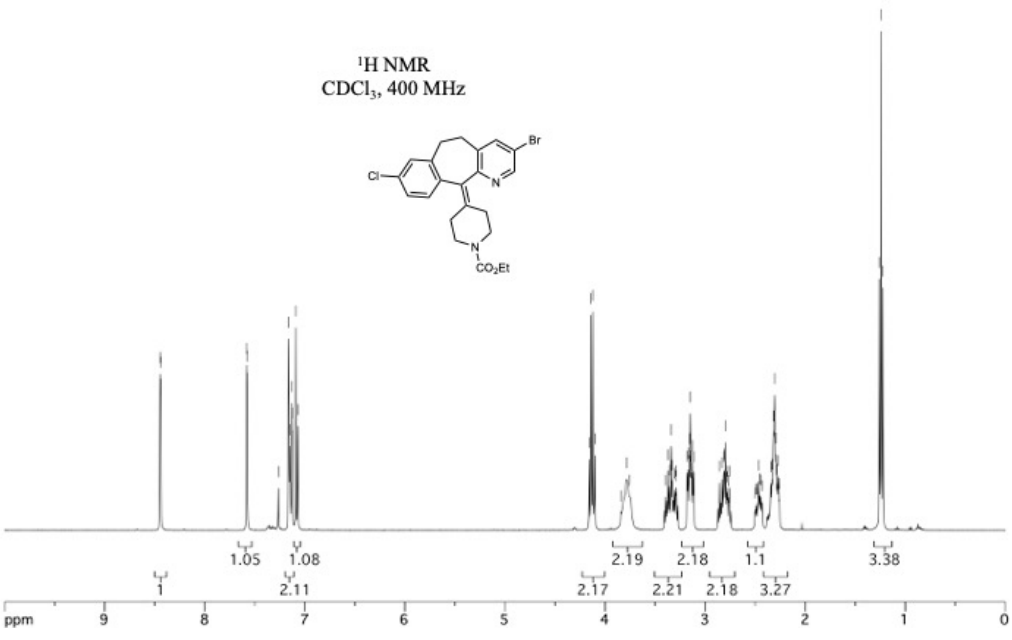
145.66
139.38
138.48
137.47
135.75
133.28
130.60
129.05
126.50
91.47
77.48
77.16
76.84
61.49
44.87
44.85
31.51
31.40
30.92
30.69
14.81
13C NMR
CDCl3, 100 MHz
Cl
I
N
N
CO2Et
ppm 200
150
100
50
0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8.44
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7.16
7.15
7.13
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7.09
7.07
4.16
4.14
4.12
4.10
3.84
3.78
3.75
3.39
3.37
3.36
3.34
3.33
3.31
3.29
3.29
3.18
3.17
3.16
3.15
3.14
3.12
3.11
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2.81
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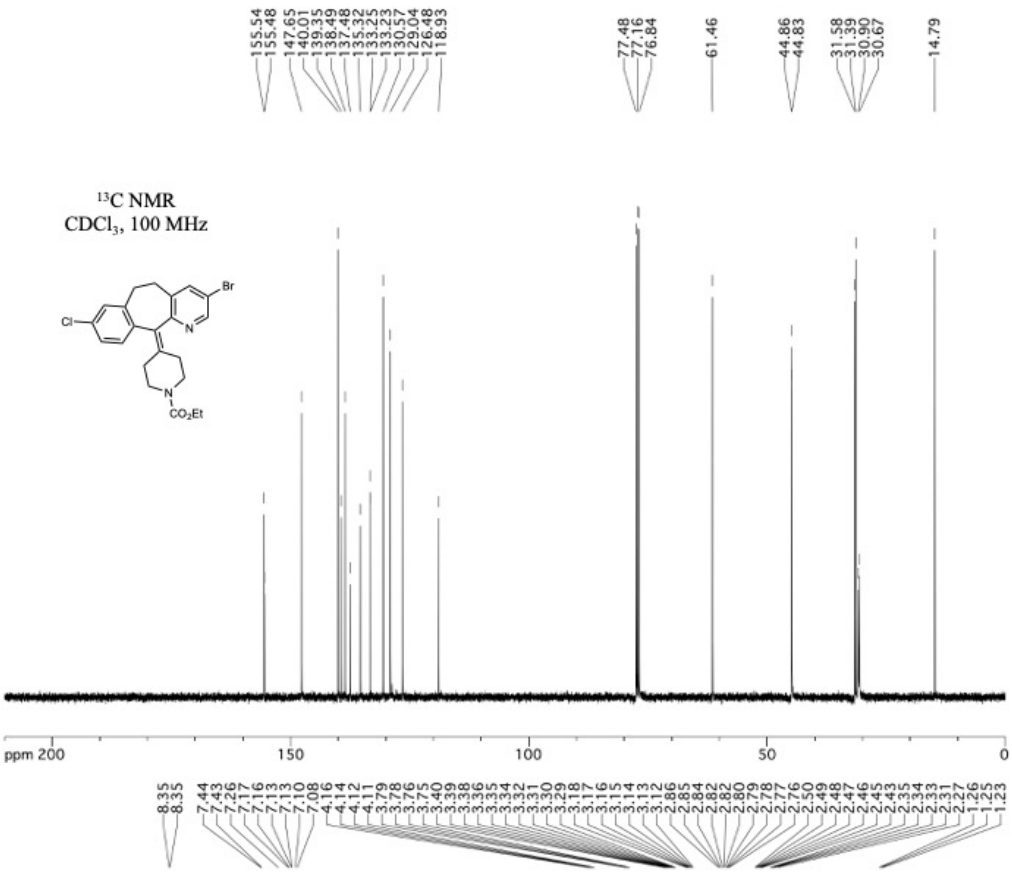
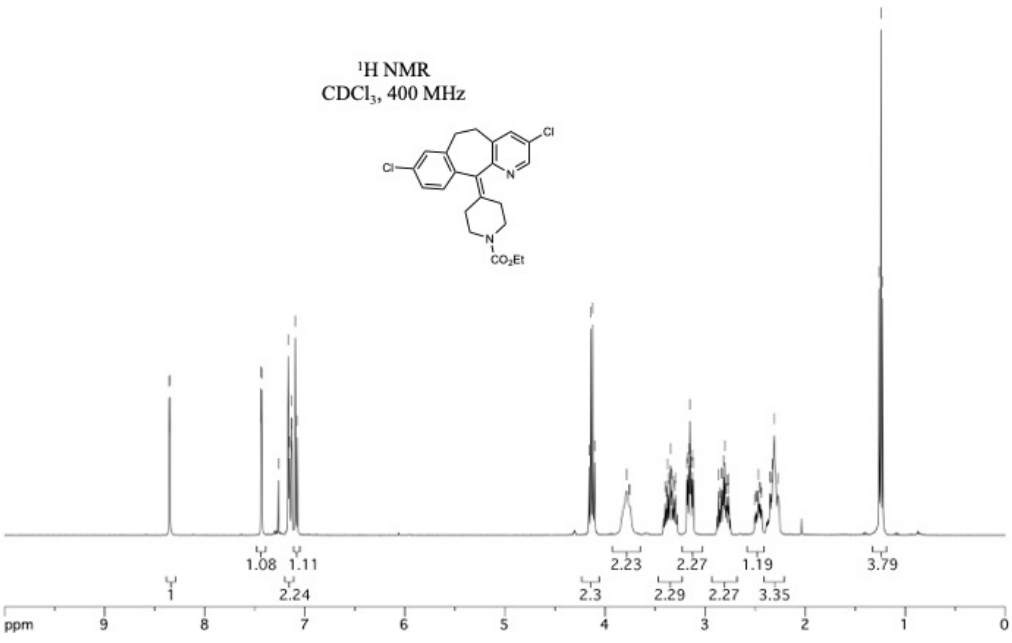
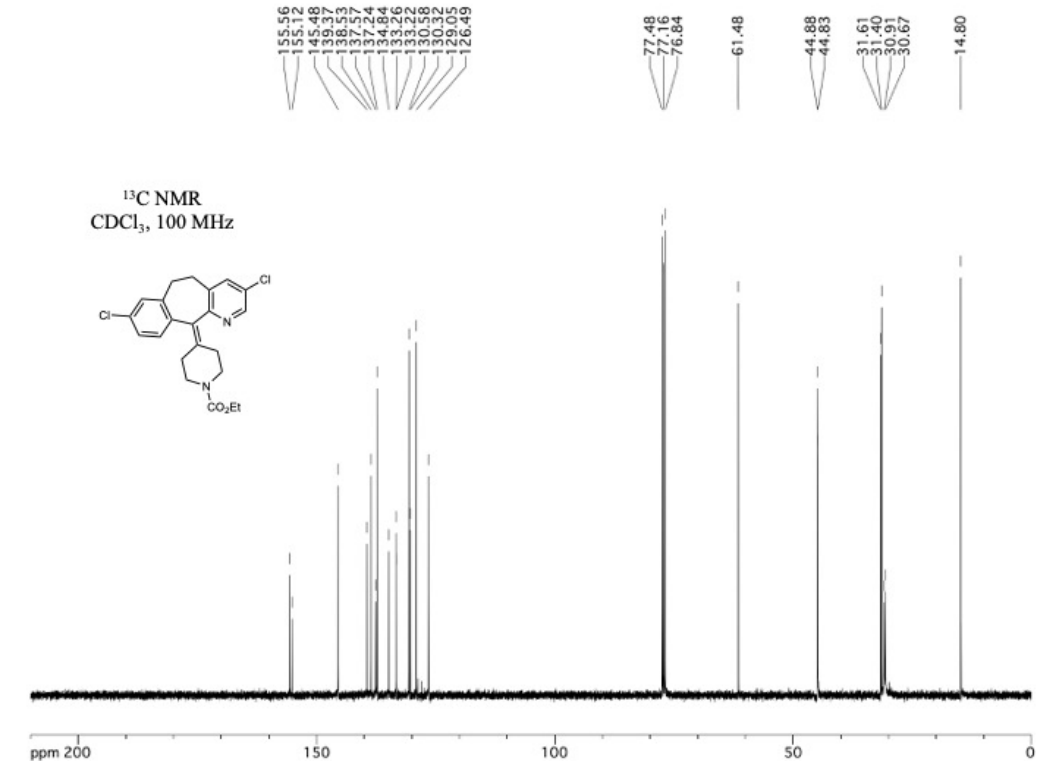
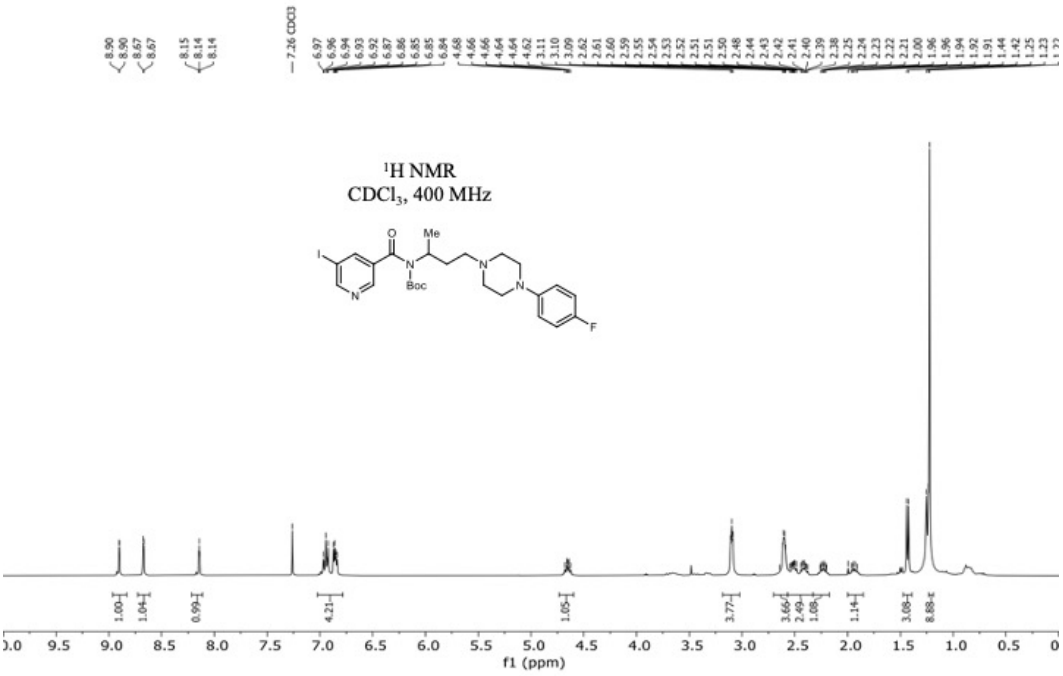
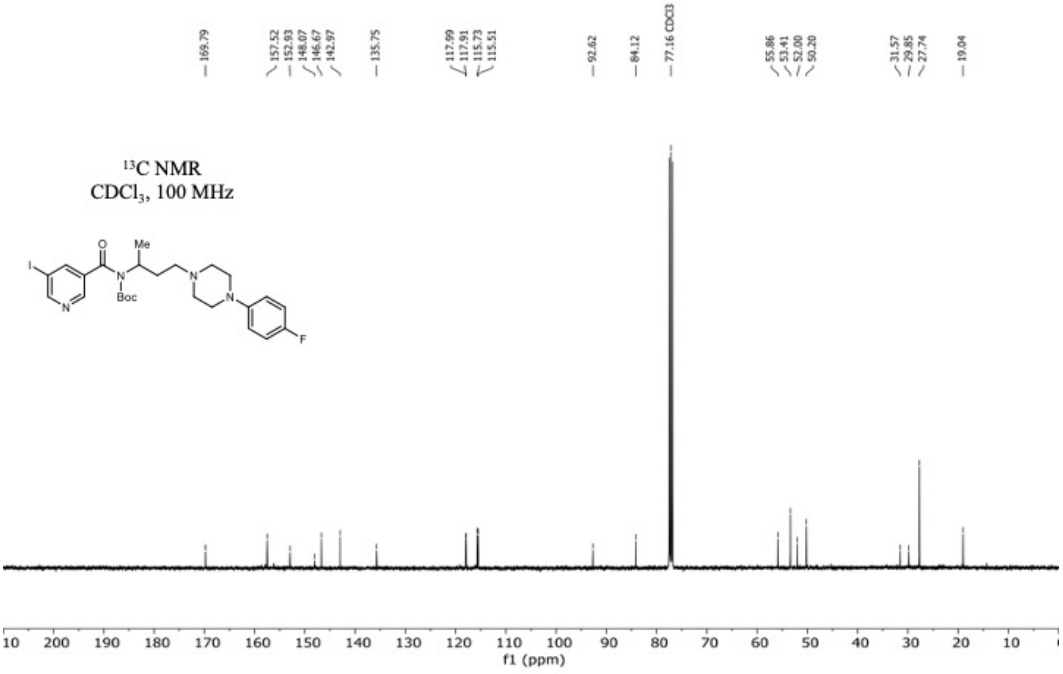
2.76
2.50
2.49
2.48
2.47
2.45
2.44
2.43
2.34
2.33
2.32
2.31
2.29
2.28
2.26
2.26
1.24
1.22
1H NMR
CDCl3, 400 MHz
Br
Cl
N
N
CO2Et
1.05
1.08
2.19
2.18
1.1
3.38
1
2.11
2.17
2.21
2.18
3.27
ppm 9
8
7
6
5
4
3
2
1
0

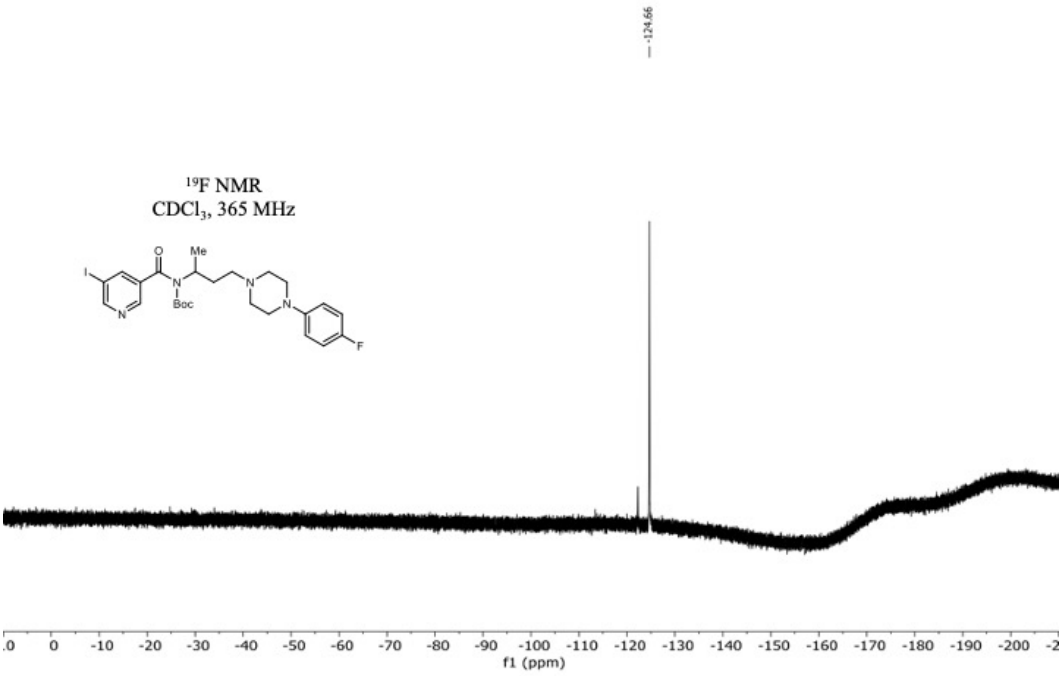

155.54
155.48
147.65
140.01
139.35
139.49
137.48
133.32
133.23
130.57
129.04
126.48
118.93
77.48
77.16
76.84
61.46
44.86
44.83
31.58
31.39
30.90
30.67
14.79
13C NMR
CDCl3, 100 MHz
Br
Cl
N
N
CO2Et
ppm 200
150
100
50
0

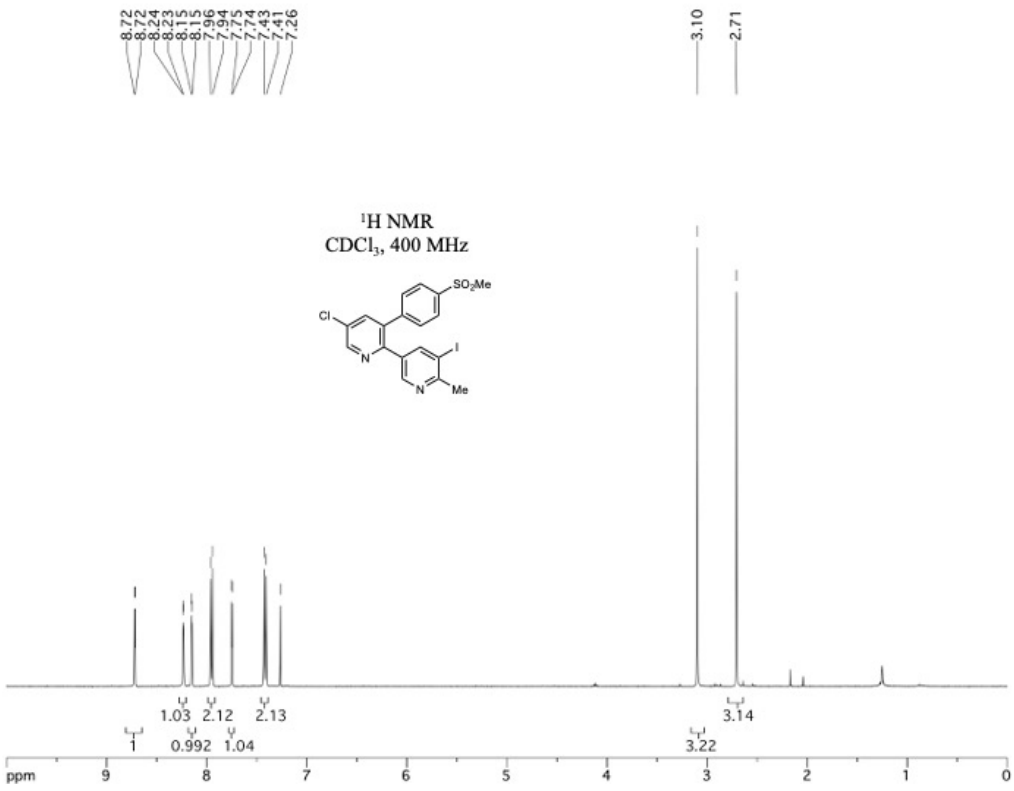

1H NMR
CDCl3, 400 MHz
Cl
Cl
N
N
CO2Et
1.08
1.11
2.24
1
2.3
2.23
2.27
2.29
2.27
1.19
3.35
3.79
ppm
9
8
7
6
5
4
3
2
1
0

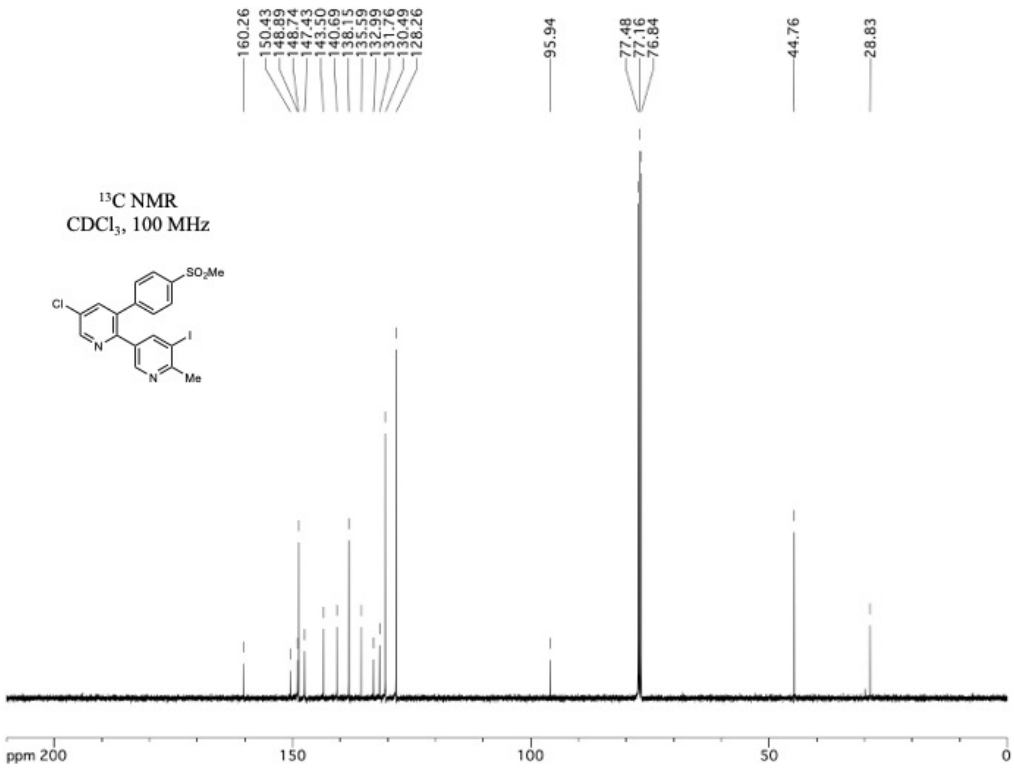

155.56
155.12
145.48
139.37
138.53
137.57
137.24
134.84
133.26
133.22
130.58
130.32
129.05
126.49
77.48
77.16
76.84
61.48
44.88
44.83
31.61
31.40
30.91
30.67
14.80
13C NMR
CDCl3, 100 MHz
Cl
Cl
N
N
CO2Et
ppm 200
150
100
50
0

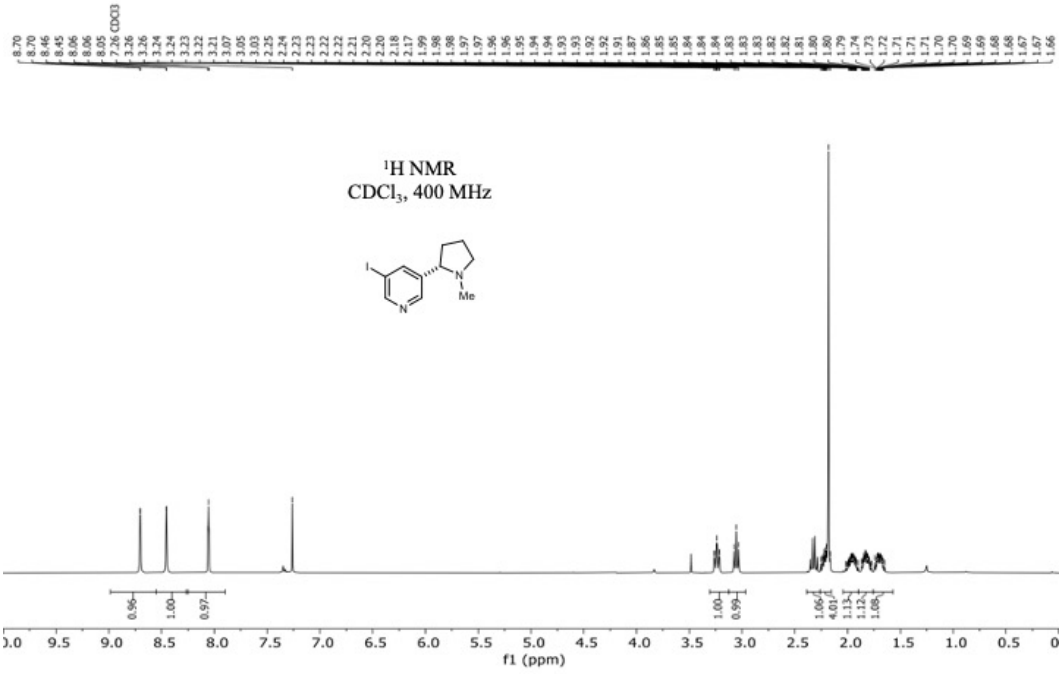

8.90
8.90
8.67
8.67
8.15
8.14
8.14
7.26 CDCl3
6.97
6.96
6.94
6.93
6.92
6.87
6.86
6.85
6.85
6.84
1H NMR
CDCl3, 400 MHz
O
Me
I
N
N
Boc
N
F
1.00
1.04
0.99
4.21
1.05
3.77
3.66
2.49
1.08
1.14
3.08
8.88
f1 (ppm)

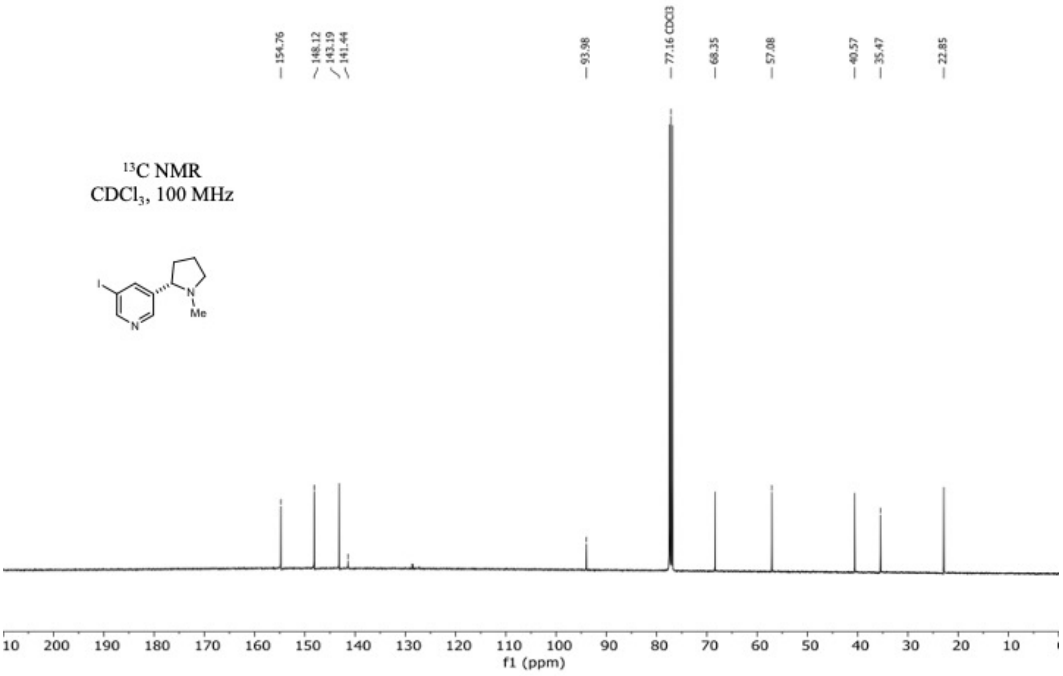

169.79
157.52
152.93
148.07
146.67
142.97
135.75
117.99
117.91
115.73
115.51
92.62
84.12
77.16 CDCl3
55.86
53.41
52.00
50.20
31.57
29.85
27.74
19.04
13C NMR
CDCl3, 100 MHz
Me
Boc
f1 (ppm)


-124.66
19F NMR
CDCl3, 365 MHz
Me
Boc
f1 (ppm)

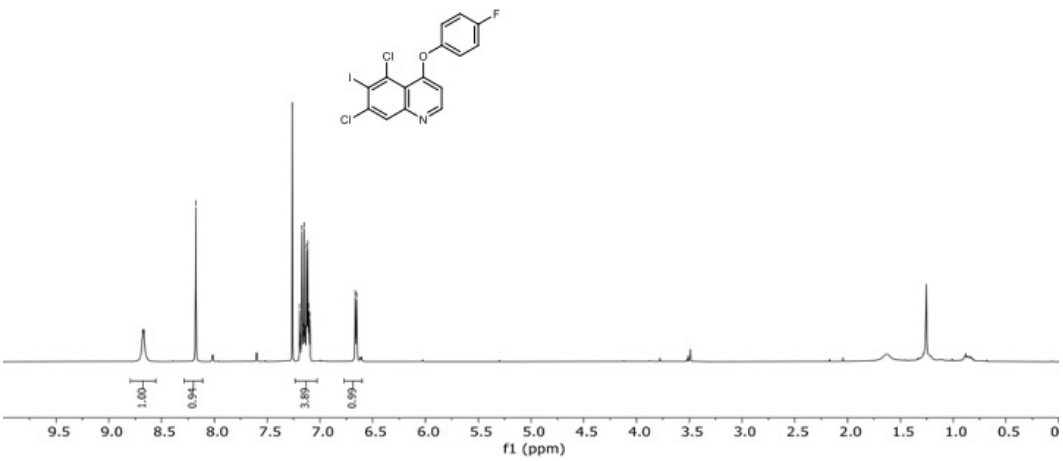

8.72
8.72
8.24
8.23
8.15
8.15
7.96
7.94
7.75
7.74
7.43
7.41
7.26
3.10
2.71
1H NMR
CDCl3, 400 MHz
SO2Me
Cl
I
N
N
Me
1.03
2.12
2.13
3.14
1
0.992
1.04
3.22
ppm
9
8
7
6
5
4
3
2
1
0


160.26
150.43
148.89
148.74
147.43
143.50
140.69
138.15
135.59
132.99
131.76
130.49
128.26
95.94
77.48
77.16
76.84
44.76
28.83
13C NMR
CDCl3, 100 MHz
SO2Me
Cl
I
N
N
Me
ppm 200
150
100
50
0

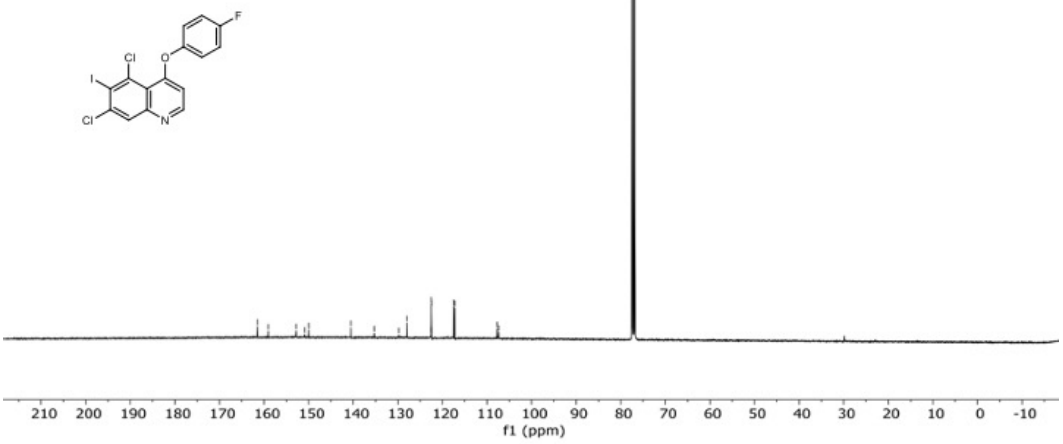

^{1}H NMR
$CDCl_3$, 400 MHz
f1 (ppm)

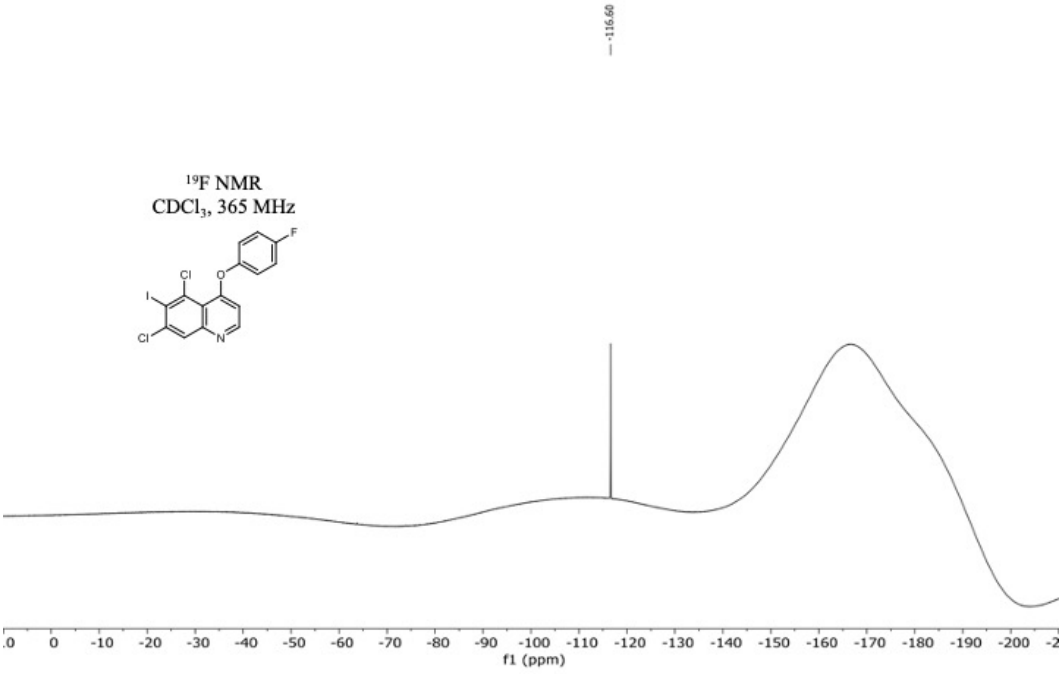

^{13}C NMR
$CDCl_3$, 100 MHz
f1 (ppm)

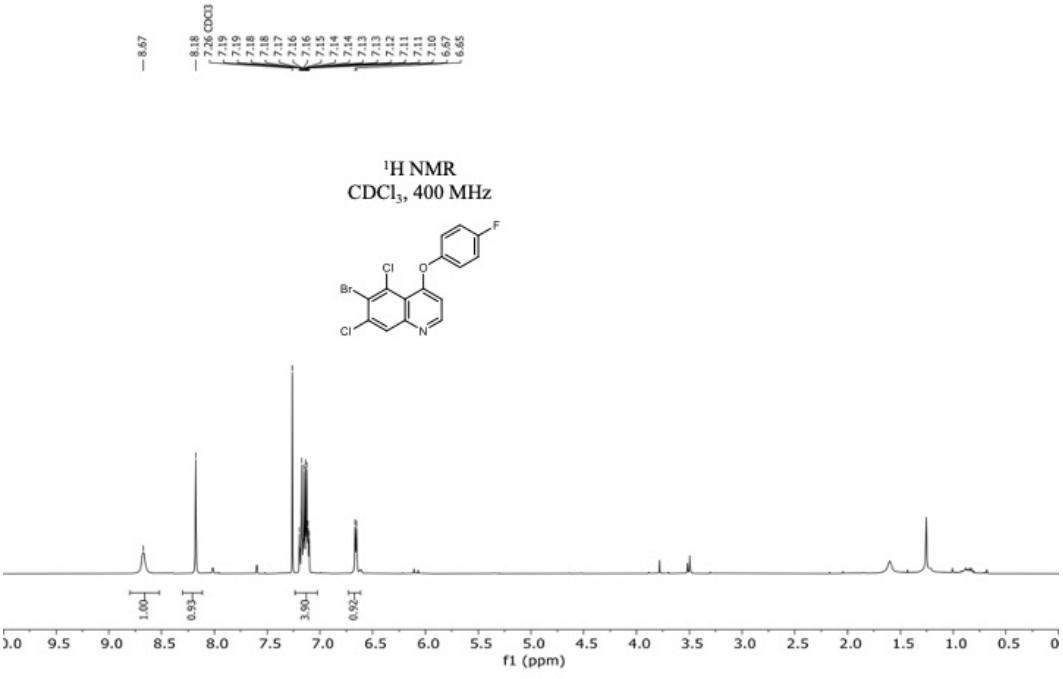
^{1}H NMR
$CDCl_3$, 400 MHz

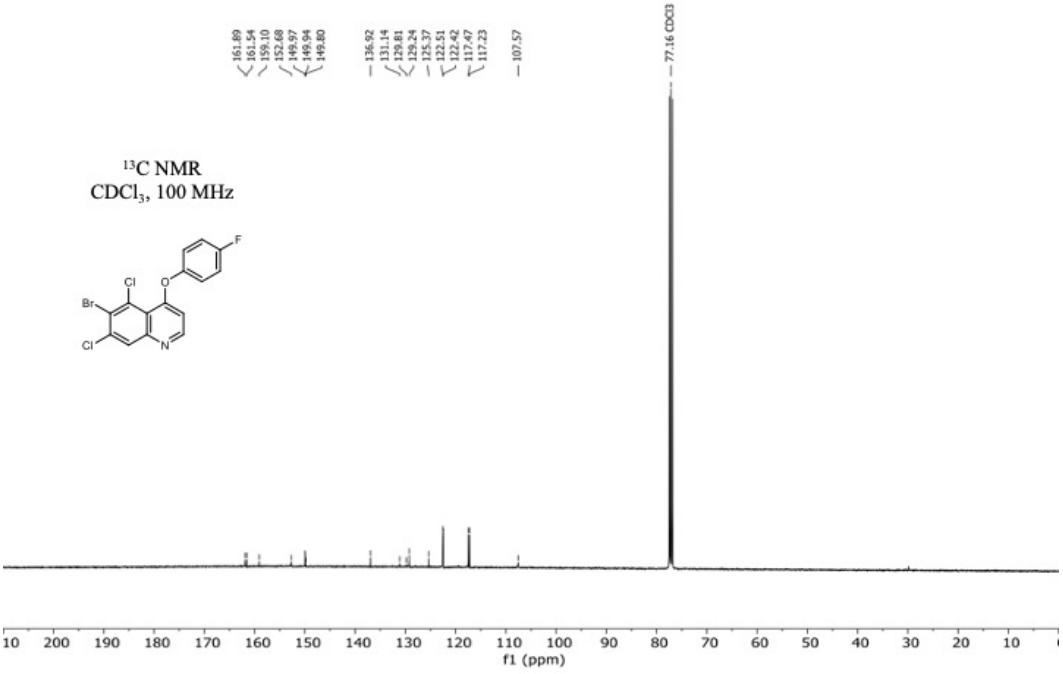


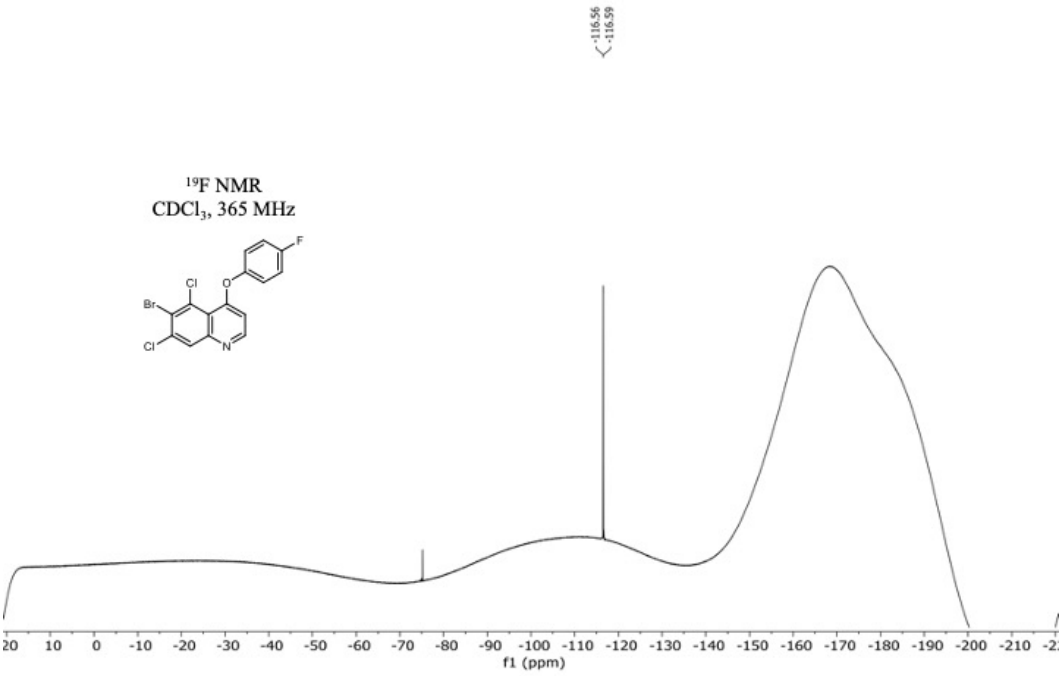
^{13}C NMR
$CDCl_3$, 100 MHz

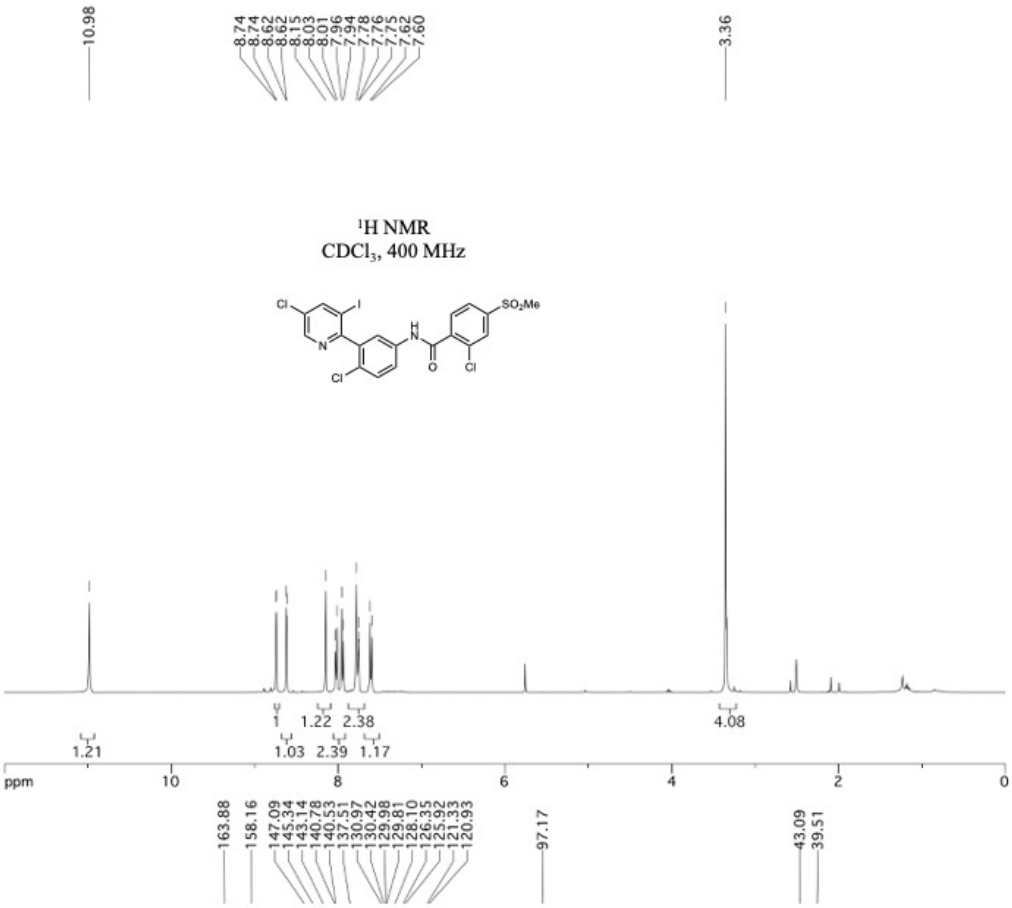



-116.60
19F NMR
CDCl3, 365 MHz
F
Cl
O
I
Cl
N
.0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -2
f1 (ppm)

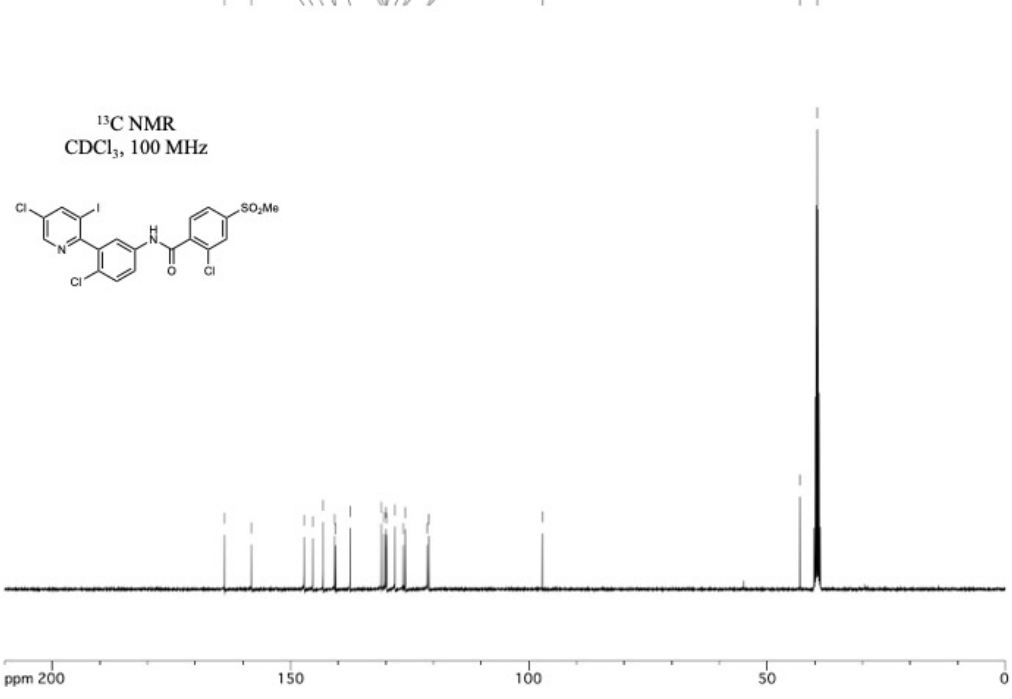

8.67
8.18
7.26 CDCl3
7.19
7.19
7.18
7.18
7.17
7.16
7.16
7.15
7.14
7.14
7.13
7.13
7.12
7.11
7.11
7.10
6.67
6.65
1H NMR
CDCl3, 400 MHz
F
Cl
O
Br
Cl
N
1.00
0.93
3.90
0.92
.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)


161.89
161.54
159.10
152.68
149.97
149.94
149.80
136.92
131.14
129.81
129.24
125.37
122.51
122.42
117.47
117.23
107.57
77.16 CDCl3
13C NMR
CDCl3, 100 MHz
F
O
Cl
Br
Cl
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-116.56
-116.59
19F NMR
CDCl3, 365 MHz
F
O
Cl
Br
Cl
N
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)



^{1}H NMR
$CDCl_3$, 400 MHz



^{13}C NMR
$CDCl_3$, 100 MHz